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Ruthenium-Catalyzed Hydration of Nitriles and Transformation of δ-Ketonitriles to Ene-lactams: Total Synthesis of (–)-Pumiliotoxin C

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Abstract: Hydration of nitriles with 1–2 equivalents of water can be performed efficiently by using $RuH_2(PPh_3)_4$ catalyst to give the corresponding amides. Under the similar reaction conditions, δ-ketonitriles can be converted into the corresponding ene-lactams, which are versatile synthetic intermediates. The efficiency of the reaction is demonstrated by the short-step synthesis of (–)-pumiliotoxin C.

INTRODUCTION

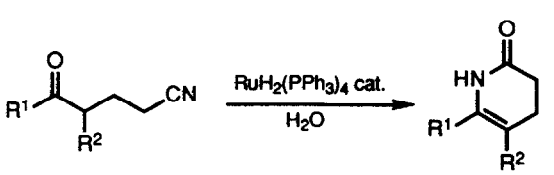
The activation of nitriles under mild and neutral conditions is of importance in view of enzymatic[1] and synthetic points.[2] Although there are many methods for hydration of nitriles, they require acidic or basic conditions usually.[2,3] Hydration of nitriles under neutral conditions has been explored by using heterogeneous[4] and homogeneous[5] catalysts; however, the problems of these methods are that the reactions require large excess of water and extremely high reaction temperatures. Therefore, development of an effective method for hydration of nitriles by using an equivalent of water under mild and neutral conditions is waited to be explored.

During the course of our systematic study on the activation of nitriles with homogeneous catalysts,[6] we found that hydration of nitriles proceeds smoothly upon treatment with only 1–2 equivalents of water in the presence of $RuH_2(PPh_3)_4$ catalyst under neutral conditions to give the corresponding amides (eq 1).[7] The present

$$R\text{–}CN \xrightarrow[H_2O]{RuH_2(PPh_3)_4\ cat} RCONH_2 \qquad (1)$$

hydration is advantageous over the previous methods[2–5] because of its simple operation, high efficiency, neutral reaction conditions, and freedom from need of excess water.

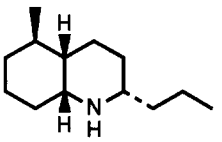
The principle of the hydration can be extended for the catalytic transformation of δ-ketonitriles to ene-lactams (eq 2),[7] which are highly useful intermediates for synthesis of piperidine[8] and hydroquinoline[9] ring systems.



(2)

Although ene-lactams have been prepared, the reported methods require strong acidic or basic conditions and lack the generality of applicable substrates.[10] The present reaction is advantageous over the previous methods because i) the reaction proceeds generally and highly efficiently under neutral conditions; ii) various functional groups tolerate the reaction; iii) δ-ketonitriles can be easily prepared from ketones *via* Michael addition to acrylonitriles.[11]

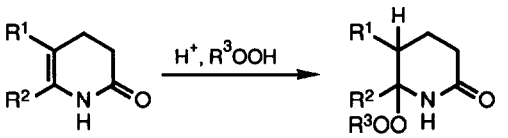
The effectiveness of the present reaction is illustrated by the synthesis of (–)-pumiliotoxin C (**1**), which is an interesting toxic skin alkaloid produced by Central American frogs *Dendrobates pumilio* and *D. auratus*.[12]



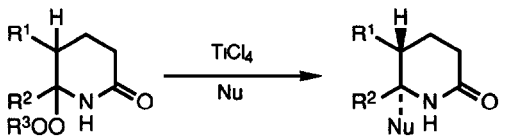
(–)-pumiliotoxin C (**1**)

Interest in the synthesis of pumiliotoxin C is increasing not only due to its unusual *cis*-decahydroquinoline structure but also the significant neurological activities.[13] A limited amount of the toxin available from the frogs makes it an attractive target for total synthesis.[9] Although racemic pumiliotoxin C has been synthesized by various methods,[14] natural (–)-**1** has been synthesized only by two methods; intramolecular Diels-Alder reaction[14c] and cyclization of piperidine enamines.[14f]

As a consequence of exploring synthetic utility of ene-lactams, we developed novel method for preparation of δ-substituted δ-lactams from ene-lactams *via* δ-dioxylactams. Thus, we disclosed that ene-lactams can be converted into δ-dioxylactams by acid catalyzed reactions with alkyl hydroperoxides or hydrogen peroxide (eq 3).



(3)



(4)

δ-Dioxylactams thus obtained can be transformed to *trans* δ-substituted lactams upon treatment with various nucleophiles in the presence of $TiCl_4$ (eq 4). Since lactams are versatile synthetic intermediates of cyclic amine derivatives,[15] the present reaction provides a useful method for the stereoselective synthesis of a variety of cyclic amines.

RESULTS AND DISCUSSIONS

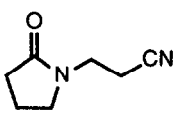
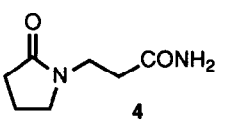
Hydration of Nitriles to Amides

The catalytic activity of various metal complexes has been examined for the hydration of acetonitrile. The reaction of acetonitrile with water (2 equiv.) was carried out in the presence of a catalyst (3 mol%) in 1,2-

dimethoxyethane (DME, 0.5 mL) at 120 °C for 24 h in a sealed tube under argon. The conversion of the starting material and the yield of acetamide were determined by GLC analysis using an internal standard (pentadecane). $RuH_2(PPh_3)_4$ is the best catalyst for the formation of acetamide (conv. 100%, yield 95%). The results with $Ru(OH)(CO)(PPh_3)_2$,[5b] or $PdCl_2$[5c] are not satisfactory (conv. 76%, yield 78%; 35%, 7%, respectively). The known hydration catalysts, such as $Ni(piaH)_2Cl_2 \cdot 2H_2O$,[5a] $[Ru(NH_3)_5Cl]Cl_2$,[5d] $Pd(OH)_2(bipy)(H_2O)$,[5f] and Cu(0)[4a] showed no catalytic activity. The use of a polar solvent such as DME and THF gave satisfactory results. A reaction temperature higher than 100 °C was required.

The representative results of the catalytic hydration of nitriles are summarized in Table 1. Various aromatic and aliphatic nitriles can be converted into the corresponding amides in excellent yields. The reaction proceeds efficiently in the presence of only 1–2 equivalents of water. Other functional groups, which are readily hydrolyzed under acidic and basic conditions, tolerate the reaction.

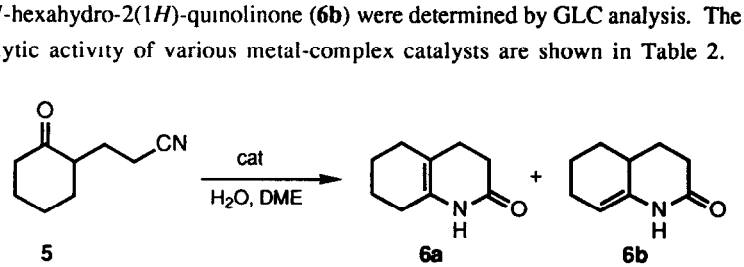
Table 1. Ruthenium-Catalyzed Hydration of Nitriles[a]

entry	nitrile	amide	yield,[b] %
1	CH_3CN	CH_3CONH_2	92
2	PhCN	$PhCONH_2$	92
3	$C_5H_{11}CN$	$C_5H_{11}CONH_2$	94
4	$PhCH_2CN$	$PhCH_2CONH_2$	77
5	$H_3COCO(CH_2)_2CN$	$H_3COCO(CH_2)_2CONH_2$ **2**	93
6	$NC(CH_2)_4CN$	$H_2NCO(CH_2)_4CONH_2$ **3**	91
7		 **4**	94

[a] A mixture of acetonitrile (2.0 mmol), water (4.0 mmol), and $RuH_2(PPh_3)_4$ (0.06 mmol) in DME (0.5 mL) was heated at 120 °C for 24 h in a sealed tube under argon. [b] Isolated yield.

Transformation of δ-Ketonitriles to Ene-lactams

The ruthenium-catalyzed reaction of δ-ketonitriles, which are obtained readily by cyanoethylation of ketones, with two equivalents of water in the presence of 3 mol% of $RuH_2(PPh_3)_4$ at 120 °C proceeds highly efficiently. The catalytic activity of various metal complexes was examined for the transformation of 2-(2-cyanoethyl)cyclohexanone (**5**). The conversion of **5** and the yields of 3,4,5,6,7,8-hexahydro-2(*1H*)-quinolinone (**6a**) and 3,4,4a,5,6,7-hexahydro-2(1*H*)-quinolinone (**6b**) were determined by GLC analysis. The representative results for the catalytic activity of various metal-complex catalysts are shown in Table 2. $RuH_2(PPh_3)_4$



5 **6a** **6b**

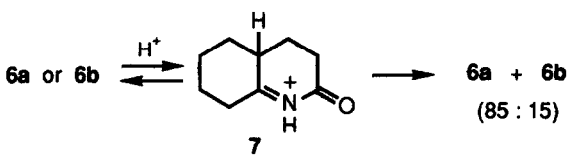
is the best catalyst among the catalysts examined. HPLC and ^{1}H NMR analysis showed that the isomeric ratio of **6a** and **6b** was approximately 90 / 10, irrespective of the metal catalysts. Separation of **6a** and **6b** was performed easily by column chromatography.

Table 2. Catalytic Activity of Various Metal Complexes for the Reaction of 2-(2-Cyanoethyl)cyclohexanone (**5**)[a]

entry	catalyst	conv.,[b] %	yield of **6**,[c] %
1	$RuH_2(PPh_3)_4$	100	94
2	$IrH_3(PPh_3)_2$	88	89
3	$RhH(CO)(PPh_3)_3$	61	98
4	$ReH_5(PPh_3)_2$	16	63
5	$RhCl(PPh_3)_3$	29	98
6	$RuCl_2(PPh_3)_3$	23	70
7	$Cu(OAc)_2$	23	53

[a] A mixture of **5** (2.0 mmol), water (4.0 mmol), and catalyst (0.06 mmol) in DME (0.5 mL) was heated at 120 °C for 24 h in a sealed tube under argon. [b] Determined by GLC analysis based on **5**. [c] Determined by GLC analysis based on the converted **5**.

Ene-lactams can be isomerized easily under acidic conditions. Typically, isomerically pure **6a** was converted into a mixture of **6a** and **6b** by stirring in DME in the presence of a catalytic amount of HCl at room temperature. HPLC analysis showed that the isomeric ratio of **6a** and **6b** was 85 / 15. Similar treatment of isomerically pure **6b** gave a mixture of **6a** and **6b** (85 / 15). This isomerization can be rationalized by assuming protonation of **6a** or **6b** to give *N*-acyliminium ion **7**.



7

Using two equivalents of water the best result was obtained. The reaction temperature of 120–160 °C is required. In general, the reaction proceeds efficiently in a polar solvent. The excellent yields of the ene-lactams (**6a** + **6b**) were obtained by using DME, DMF, and acetone. The reactions in DMSO or THF gave moderate yields. The reaction did not proceed in a halogenated solvent such as CH_2Cl_2 and $CHCl_3$. The representative results of the transformation of δ-ketonitriles to ene-lactams are shown in Table 3. Irrespective of cyclic and aliphatic ketones, δ-ketonitriles can be converted into the corresponding ene-lactams with high efficiency. Ketonitriles bearing ester groups were converted into the corresponding ene-lactams without hydrolysis of the esters (entry 8). The reaction of ketonitriles derived from 1,3-diketones gave the corresponding keto ene-lactams, which are highly useful synthetic intermediates for lycopodium alkaloid (entry 9).[10e,f,16] Similar treatment of ε-ketonitriles gave the corresponding ene-lactams bearing azacycloheptane skeleton (entry 11).

Table 3. Ruthenium-Catalyzed Transformation of Ketonitriles to Ene-lactams[a]

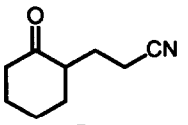
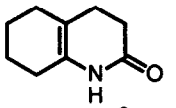
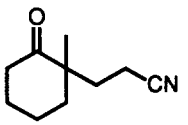
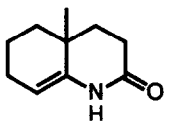
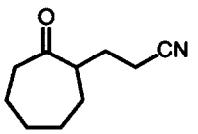
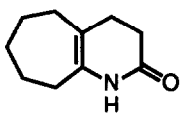
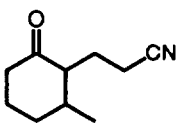
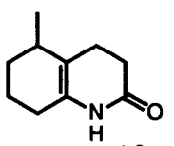
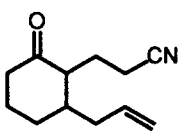
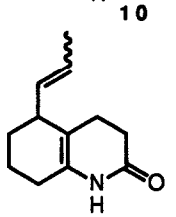
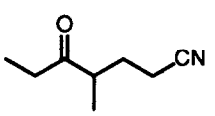
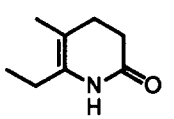
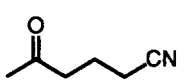
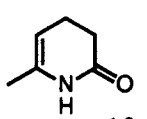
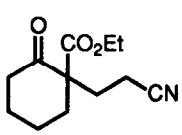
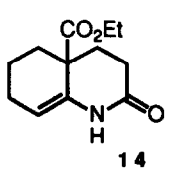
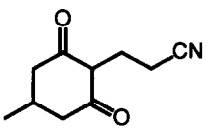
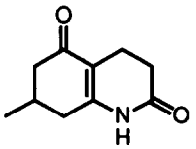
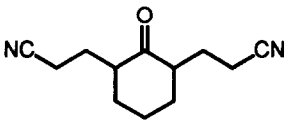
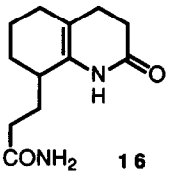
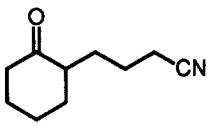
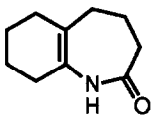
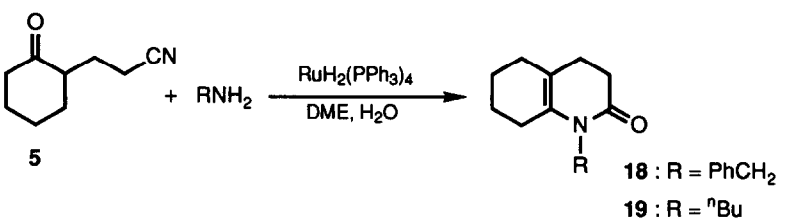
entry	ketonitrile	product	yield,[b] %
1	 5	 6a	72
2		 8	79
3		 9	65
4		 10	80
5		 11	85[c]
6		 12	51
7		 13	43
8		 14	85

Table 3 (continued)

entry	ketonitrile	product	yield,[b] %
9		 **15**	97
10		 **16**	85
11		 **17**	41

[a] A mixture of nitrile (2.0 mmol), water (4.0 mmol) and $RuH_2(PPh_3)_4$ (0.06 mmol) in DME (0.5 mL) was reacted at 120 °C for 24 h in a sealed tube under argon. [b] Isolated yield. [c] *cis* / *trans* = 16 / 84.

N-Protected ene-lactams are useful intermediates for the synthesis of a variety of alkaloids. However, *N*-protection of ene-lactams generally requires strong basic conditions as well as *N*-substitution of lactams and amides.[15] Recently we found that $RuH_2(PPh_3)_4$-catalyzed reaction of nitriles with amines gives the corresponding *N*-substituted amides highly efficiently.[6] The principle of the amide synthesis has been extended to the catalytic transformation of δ-ketonitriles to *N*-substituted ene-lactams. Thus, the ruthenium-catalyzed reaction of δ-ketonitriles with primary amines gives the corresponding *N*-substituted ene-lactams in moderate yields. Typically, 1-benzyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (**18**) was prepared upon treatment of δ-ketonitrile **5** with benzylamine (1.2 equiv.) and two equivalents of water in the presence of 3 mol% of $RuH_2(PPh_3)_4$ in DME at 160 °C (41% yield). Similar treatment of **5** with butylamine gave 1-butyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (**19**) in 35% yield.



5

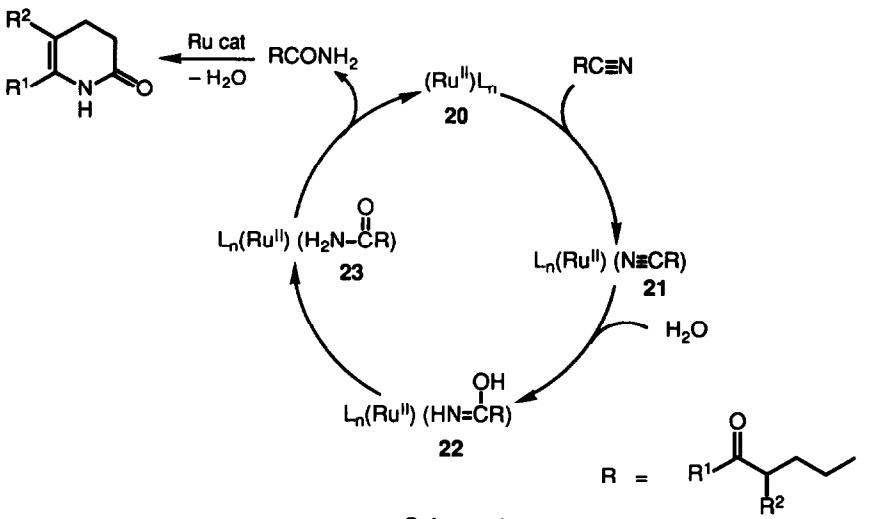
18 : R = $PhCH_2$

19 : R = ^nBu

Reaction Mechanism

The present reaction can be rationalized by assuming the mechanism as shown in Scheme 1. The catalytically active species seems to be coordinatively unsaturated Ru(II) complex **20**, which undergoes

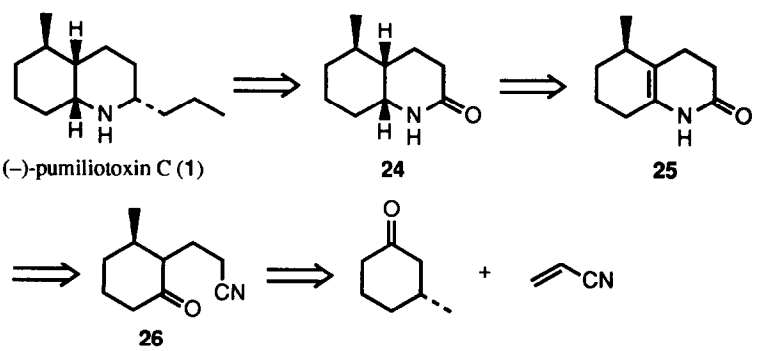
coordination of nitriles to give nitrile complex **21**. Nucleophilic attack of water to **21** provides hydroxyimino complex **22**, which undergoes isomerization to give amido complex **23**. Dissociation of ketoamide gives **20** to complete catalytic cycle. Further, ruthenium-induced intramolecular cyclization of ketoamide would give ene-lactam. An alternative pathway which involves oxidative addition of water to ruthenium (II) complex to give hydroxy ruthenium complex (RuOH), and subsequent insertion into carbon–nitrogen triple bond of ketonitriles seems unlikely. Kinetic studies on the hydration of nitriles with transition metal catalysts revealed that the hydration reactions proceed via external nucleophilic attack of water to coordinated nitriles.[5k]



Scheme 1

Total Synthesis of (–)-Pumiliotoxin C

The strategy for short step synthesis of (–)-pumiliotoxin C (**1**) is shown in Scheme 2, in which the ruthenium-catalyzed cyclization of δ-ketonitrile **26** and diastereoselective catalytic hydrogenation of ene-lactam **25** are key steps. We chose (R)-(+)-pulegone (**27**) as a starting material. Unfortunately, the optical purity of commercially available sample is not satisfactory, and purification is very difficult.[17] Optically pure (+)-pulegone



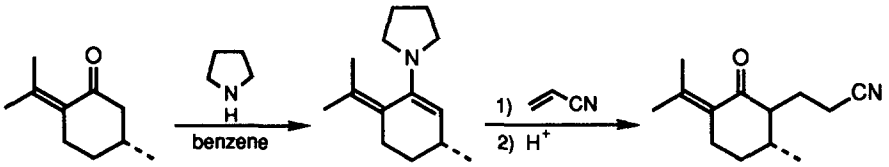
(–)-pumiliotoxin C (1) **24** **25**

26

Scheme 2

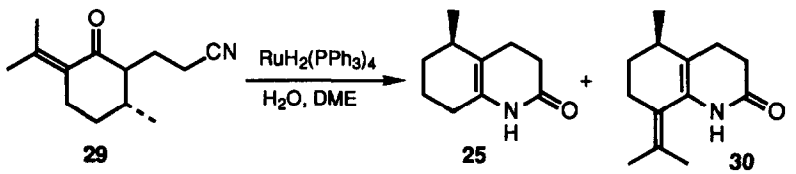
was obtained by using Corey's method.[18] Thus, treatment of commercial (+)-pulegone with semicarbazide hydrochloride and sodium acetate trihydrate in EtOH-water afforded the corresponding semicarbazone. Recrystallization from EtOH three times gave optically pure semicarbazone ($[\alpha]_D^{24}$ +67.5° (*c* 2.00, $CHCl_3$); lit. $[\alpha]_D^{23}$ +66° (*c* 2.05, $CHCl_3$)[18]). Hydrolysis of the optically pure semicarbazone thus obtained with 2 N HCl aqueous solution gave optically pure **27** ($[\alpha]_D^{23}$ +23.2° (neat), lit. $[\alpha]_D^{25.5}$ +22.47° (neat)[19a], $[\alpha]_D^{27}$ +23.6° (neat)[19b]).[20]

Optically pure **27** thus obtained was converted into the corresponding enamine **28** by the reaction with pyrrolidine in the presence of *p*-toluenesulfonic acid catalyst in benzene at reflux temperature (58% yield). Cyanoethylation of **28** with acrylonitrile followed by treatment with a buffer solution of sodium acetate–acetic acid gave **29** as a *cis* and *trans* mixture (61% yield). GLC analysis showed that *cis* / *trans* ratio of **29** was 2 / 3.



27 **28** **29**

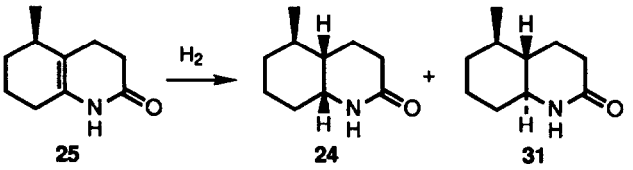
Extrusion of isopropylidene group is performed by conjugate addition of water to pulegone and subsequent retro-aldol reaction, giving 3-methylcyclohexanone and acetone.[22] If $RuH_2(PPh_3)_4$ acts as Lewis acid to accelerate conjugate addition of water, one can expect that deisopropylidenation and cyclization of δ-ketonitrile **29** can be performed at the same time to give the desire ene-lactam. The treatment of **29** with water in the



29 **25** **30**

presence of $RuH_2(PPh_3)_4$ (3 mol%) in DME in a sealed tube under argon gave ene-lactam **25** along with isopropylidene ene-lactam **30**. The effects of the amount of water and reaction time for the transformation of **29** have been examined. The standard conditions for the formation of ene-lactams (120 °C) is not enough for the formation of **25**. The excess amount of water (15 equiv.) and high reaction temperature (160 °C) gave **25** selectively (**25** / **30** = 90 / 10). Ene-lactam **25** was isolated in 56% yield by means of medium pressure liquid chromatography. Recrystallization of **25** from hexane–EtOAc gave colorless needles (mp 127.5–128.5 °C, $[\alpha]_D^{26}$ +45.2° (*c* 1.01, $CHCl_3$)).

Diastereoselective hydrogenation of **25** was investigated under various conditions. Hydrogenation of **25** gave (4a*S*,5*R*,8a*R*)-5-methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**24**) along with (4a*S*,5*R*,8a*S*)-5-methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**31**). The stereochemistry of optically active lactam **24** was confirmed by comparing its ^1H and ^{13}C NMR spectral data with those of racemic **24**.[14a] The effects of catalysts on the diastereoselectivity have been investigated for the hydrogenation of **25** in EtOH (containing



catalytic amount of HCl) at room temperature under hydrogen atmosphere (1 atm). The combined yields and the diastereomeric ratio of lactams **24** and **31** were determined by GLC and ^{1}H NMR (270 MHz) analysis. The results are shown in Table 4. By using 5% palladium on charcoal (K-type), purchased from Engelhard Co. Ltd., a mixture of lactams **24** and **31** was obtained quantitatively, and the *cis* / *trans* ratio (**24** / **31**) was 93 / 7 (entry 1). In contrast, the yield decreased to 28% by using standard grade 5% Pd-C (entry 2). In the case of using homogeneous catalyst such as $RhCl(PPh_3)_3$, the lactams were not obtained. Hydrogenation of **25** in EtOH–acetic acid (5 / 1, containing conc. HCl) in the presence of 5% Pd-C (K-type) under hydrogen atmosphere (1 atm) at room temperature for 5 h gave **24** with higher selectivity (98 / 2), although the yield was low (entry 7). The reaction of **25** under H_2 pressure (85 kg/cm^2) at 60 °C gave good yield (90%) and high selectivity (98 / 2) (entry 8). Recrystallization of the product from hexane–EtOAc gave **24** as colorless needles (mp 146.5–147.5 °C, $[\alpha]_D^{25}$ –60.4° (*c* 1.00, $CHCl_3$)).

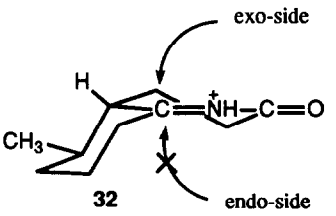
Table 4. Hydrogenation of **25** with Various Catalysts[a]

entry	catalyst	yield,[b] %	**24** : **31**[c]
1	5% Pd-C (K-type)[d]	99	93 : 7
2	5% Pd-C[e]	28	89 : 11
3	Pd-Black	98	90 : 10
4	5% Pd-$BaSO_4$	37	87 : 13
5	5% Pd-$BaCO_3$	90	84 : 16
6	5% Pd-$SrCO_3$	75	84 : 16
7[f]	5% Pd-C (K-type)[d]	34	98 : 2
8[g]	5% Pd-C (K-type)[d]	90	98 : 2

[a]Reaction was carried out by using ene-lactam **25** (0.5 mmol), catalyst (15 mg) and conc. HCl (0.02 mL) in EtOH (2 mL) at room temperature for 5 h under H_2 (1 atm). [b]Determined by ^{1}H NMR (270 MHz) analysis based on the starting material. [c]Determined by ^{1}H NMR (270 MHz) and GLC analysis. [d]Purchased from Engelhard Co. Ltd. [e]Purchased from Nacalai Tesque, Inc. [f]In EtOH-acetic acid (5 : 1 containing conc. HCl (1 drop)). [g]In EtOH-acetic acid (5 : 1 containing conc. HCl (1 drop)) under H_2 (85 kg/cm^2) at 60 °C for 24 h.

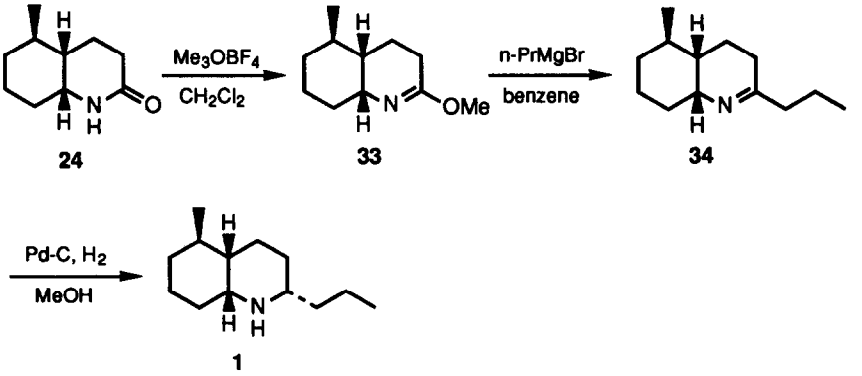
The high diastereoselectivity obtained in the hydrogenation of **25** can be rationalized by assuming the formation of *N*-acyliminium ion **32** by protonation of **25**. Attack of metal hydride to the stable conformer of **32** occurs from less hindered exo-side to give the lactam **24**.

The *cis*-fused lactam **24** thus obtained can be converted into (–)-pumiliotoxin C (**1**) by the Oppolzer's procedures.[14i] Lactam **24** was converted into (4a*S*,5*R*,8a*R*)-2-methoxy-3,4,4a,5,6,7,8,8a-octahydroquinoline (**33**, 62%) upon treatment with trimethyloxonium tetrafluoroborate in the presence of an equivalent of *N*,*N*-diiso-



32

propylethylamine in CH_2Cl_2 at 0 °C. Lactim ether **33** thus obtained was allowed to react with n-propyl magnesium bromide in benzene at reflux temperature to give (4a*S*,5*R*,8a*R*)-2-propyl-3,4,4a,5,6,7,8,8a-octahydroquinoline (**34**). Hydrogenation of crude imine **34** proceeds selectively from sterically less hindered

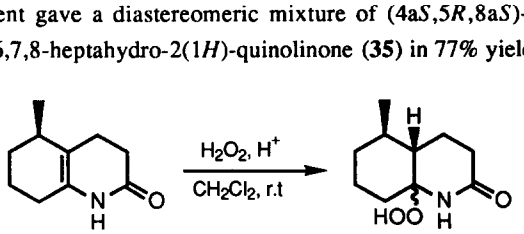


24 **33** **34** **1**

exo-side to give natural (–)-pumiliotoxin C (**1**). Treatment with HCl followed by recrystallization from 2-propanol gave optically pure **1**•HCl ($[\alpha]_D^{21}$ –16.2° (*c* 1.00, CH_3OH), lit. $[\alpha]_D^{20}$ –14.5° (*c* 1.00, CH_3OH),[14c] $[\alpha]_D^{20}$ –13.1° (*c* 1.0, CH_3OH),[14f] (+)-isomer: $[\alpha]_D^{20}$ +16.4° (*c* 1.00, CH_3OH),[14c] $[\alpha]_D^{25}$ +16.2° (*c* 1.00, CH_3OH),[14b] $[\alpha]_D^{24}$ +16.1° (*c* 1.00, CH_3OH);[14h] mp 286–288 °C (sealed capillary under Ar), lit.[14c] mp 288–290 °C (sealed capillary)). ^1H and ^{13}C NMR (**1**•HCl) and mass (**1**•free base) spectral data were consistent with those reported in the literature.[14a,i]

Synthesis of trans-δ-Substituted Lactams from Ene-lactams via δ-Dioxylactams

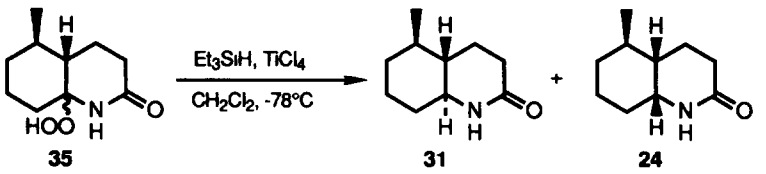
Treatment of ene-lactams with alkyl hydroperoxides or hydrogen peroxide in the presence of an acid catalyst gave the corresponding δ-dioxylactams generally and efficiently. Typically, to a solution of **25** (2.0 mmol) and *p*-toluenesulfonic acid (0.2 mmol) in CH_2Cl_2 (6 mL) was added a 30% hydrogen peroxide solution slowly at room temperature. The resulting mixture was stirred at room temperature for 3 h. Separation of the aqueous layer and removal of the solvent gave a diastereomeric mixture of (4a*S*,5*R*,8a*S*)- and (4a*S*,5*R*,8a*R*)-8a-hydrodioxy-5-methyl-3,4,4a,5,6,7,8-heptahydro-2(1*H*)-quinolinone (**35**) in 77% yield. ^1H NMR (270 MHz)



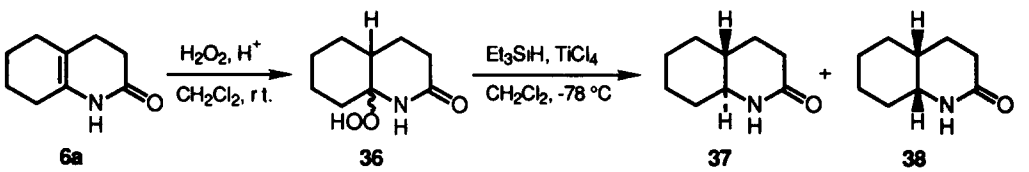
25 **35**

analysis showed that the diastereomeric ratio of **35** was 67 / 33.

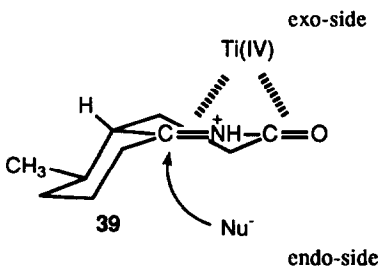
The reaction of δ-dioxylactams with various nucleophiles in the presence of $TiCl_4$ provides a novel and convenient method for stereoselective synthesis of *trans*-δ-substituted lactams. Typical reaction procedure for the preparation of *trans*-δ-substituted lactams is exemplified by the reaction of **35** with Et_3SiH. Thus, the reaction of **35** with Et_3SiH (3.0 equiv.) in the presence of $TiCl_4$ (2.0 equiv.) in CH_2Cl_2 (4 mL) at –78 °C gave **31** along



with **24** (**31** / **24** = 90 / 10) in 72% yield. Recrystallization from EtOAc gave pure *trans*-fused lactam **31**. Similarly, *trans*-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**37**) can be prepared selectively by using our method. Thus, the acid-catalyzed reaction of **6a** with hydrogen peroxide gave 3,4,4a,5,6,7,8-heptahydro-8a-hydrodioxy-2(1*H*)-quinolinone (**36**, diastereomer ratio 50 / 50) which was treated with Et_3SiH in the presence of $TiCl_4$ to afford **37** along with *cis*-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**38**) (93 / 7) in 91% yield. $TiCl_4$ has been proven to be an effective Lewis acid for these reactions. $SnCl_4$ gave moderate results, although other Lewis acids such as $AlCl_3$ and BF_3•OEt_2 gave unsatisfactory results.

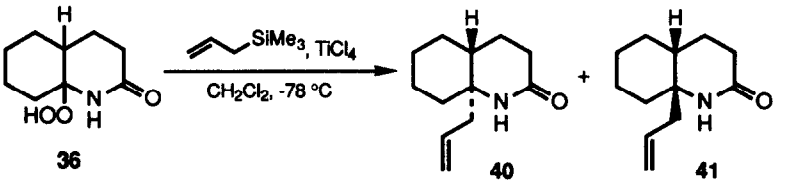


These reactions can be rationalized by assuming the formation of *N*-acyliminium ion intermediate **39**.[23] The reaction of δ-dioxylactam **35** with $TiCl_4$ gives iminium ion intermediate **39** where the carbonyl group and the double bond coordinate to the titanium (IV) species from the sterically less hindered exo-side. Nucleophilic attack occurs from the opposite side of titanium(IV) (endo-side) to give *trans*-isomer **31** stereoselectively.



Similar treatment of δ-dioxylactams with carbon nucleophiles such as allylsilanes and cyanosilanes gave δ-allyl- and δ-cyanolactams stereoselectively. Typically, $TiCl_4$-induced reaction of **36** with allyltrimethylsilane

gave *trans*-8a-allyl-3,4,4a,5,6,7,8-heptahydro-2(1*H*)-quinolinone (**40**) along with *cis*-8a-allyl-3,4,4a,5,6,7,8-heptahydro-2(1*H*)-quinolinone (**41**) (93 / 7) in 81% yield.



It is in contrast that hydrogenations of ene-lactam **25** and **6a** with Pd/C catalyst gave *cis*-fused lactam **24** and **38**, respectively. Thus, we are in a position to be able to prepare either *cis*- or *trans*- fused decahydroquinolines selectively by the catalytic hydrogenation of ene-lactams or the acid-catalyzed reaction of ene-lactams with hydrogen peroxide followed by treatment with Et_3SiH in the presence of $TiCl_4$.

EXPERIMENTAL SECTION

General. NMR spectra were obtained on JEOL JNM-PMX-60 SI (^1H, 60 MHz), JEOL JNM-GSX-270 (^1H, 270 MHz; ^{13}C, 67.9 MHz), and JEOL JNM-GX-270 (^1H, 500 MHz; ^{13}C, 125.7 MHz) spectrometers. IR spectra were recorded on Hitachi 215 and Shimadzu FTIR-4100 spectrometers. Analytical GLC evaluations were carried out on JEOL JGC-20-KFP and Shimadzu GC-9A flame ionization chromatographs by using a 0.5 m x 4 mm analytical column (10% silicone SE-30 on 60–80 mesh Uniport HP and 10% PEG-20M on 60–80 mesh Uniport HP). Mass spectra were obtained on Hitachi RMS-4 mass spectrometer. Elemental analyses were carried out on Yanagimoto MT-2 CHN and MT-3 CHN corder. Medium pressure liquid chromatography was performed on Yamazen model FMI-C.

Materials. 1,2-Dimethoxyethane (DME) was distilled over calcium hydride. $RuH_2(PPh_3)_4$ was prepared by the literature procedure.[24] 2-(3-Cyanopropyl)cyclohexanone was prepared by the reaction of pyrrolidine enamine of cyclohexanone with 4-iodobutanenitrile.[11] 2-(2-Cyanoethyl)-3-methylcyclohexanone and 2-(2-cyanoethyl)-3-allylcyclohexanone were prepared by the reactions of 2-(2-cyanoethyl)-2-cyclohexenone[25] with Me_2CuLi in ether[26] and with allyltrimethylsilane in the presence of $TiCl_4$,[27] respectively. 2-(2-Cyanoethyl)-2-methylcyclohexanone,[28] 2-(2-cyanoethyl)-2-ethoxycarbonylcyclohexanone,[29] 2-(2-cyanoethyl)-5-methyl-1,3-cyclohexanedione[30] were prepared according to the literature procedures. (R)-(+)-Pulegone ($[\alpha]_D$ +22° (neat)) was purchased from Aldrich Chemical Company, Inc.

Preparation of δ-Ketonitriles. δ-Ketonitriles were prepared readily by cyanoethylation of the enamines of the corresponding ketones.[11] Preparation of 2-(2-cyanoethyl)cyclohexanone (**5**) is representative. In a dry 300 mL three-necked round-bottomed flask equipped with a magnetic stirrer and a reflux condenser were placed *N*-(1-cyclohexenyl)pyrrolidine (21.3 g, 0.141 mol), acrylonitrile (9.10 g, 0.172 mol), and 1,4-dioxane (75 mL). The mixture was refluxed for 14 h. Water (37.5 mL) was added to the resulting yellow solution, and the mixture was heated at reflux for 1 h. After removal of the solvent, the residual oil was poured into water (100 mL) and extracted with ether (50 mL x 3). The combined organic layers were washed successively with 1 N hydrochloric acid (50 mL) and water (50 mL), and dried over $MgSO_4$. After removal of the solvent, the residue

was distilled under reduced pressure to give **5** (13.1 g, 62%) as a colorless oil: bp 105–108 °C (1 mmHg); IR (neat) 2940, 2865, 2245, 1709, 1451, 1431, 1377, 1314, 1231, 1132, 1076, 1044, 976, 889, 840, 830, 718 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.34–1.92 (m, 5 H), 2.04–2.20 (m, 3 H), 2.27–2.42 (m, 1 H), 2.47 (t, J = 6.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 15.1, 25.0, 25.5, 27.9, 34.2, 42.1, 48.7, 119.7, 211.7.

General Procedure for Ruthenium-Catalyzed Hydration of Nitriles and Cyclization of Ketonitriles. A mixture of nitrile (2.0 mmol), water (4.0 mmol), and $RuH_2(PPh_3)_4$ (0.06 mmol) in DME (0.5 mL) was reacted at 120 °C for 24 h in a sealed tube under argon. After removal of the solvent, the residue was purified by column chromatography (Florisil or SiO_2) or thin layer chromatography (SiO_2). The structures of acetamide, benzamide, hexanamide, and phenylacetamide were determined by comparison with the authentic samples.

3-Methoxycarbonylpropanamide (2). IR (Nujol) 3370, 3200, 1745, 1665, 1630, 1175, 1030, 920, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.53–2.86 (m, 4 H, CH_2), 3.71 (s, 3 H, CH_3), 6.30 (br-s, 2 H, $CONH_2$).

Hexanediamide (3). IR (Nujol) 3375, 3175, 1645, 1415, 1330, 1215, 1120, 910, 870, 805 cm^{-1}; ^1H NMR (DMSO-d^6, 60 MHz) δ 1.56–2.14 (m, 4 H, $COCH_2$), 2.18–2.57 (m, 4 H, CH_2), 6.22–7.22 (br-s, 2 H, CONH), 7.22–8.22 (br-s, 2 H, CONH).

***N*-(2-Carbamoylethyl)-2-pyrrolidone (4).** IR (Nujol) 3350, 3160, 1660, 1470, 1420, 1380, 1295 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.66–2.70 (m, 6 H, CH_2), 3.45 (t, J = 6 Hz, 2 H, NCH_2), 3.57 (t, J = 7 Hz, 2 H, NCH_2), 5.67–6.50 (br-s, 2 H, CONH), 6.50–7.27 (br-s, 1 H, CONH).

Catalytic Activities of Metal Complexes for the Cyclization of δ-Ketonitrile 5. A mixture of **5** (0.302 g, 2.00 mmol), water (0.072 g, 4.00 mmol), and catalyst (3 mol%) in DME (0.5 mL) was reacted at 120 °C for 24 h in a sealed tube under argon. The conversion of the starting material and the combined yields of 3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (**6a**) and 3,4,4a,5,6,7-hexahydro-2(1*H*)-quinolinone (**6b**) were determined by GLC analysis (10% PEG-20M, 100–220 °C) using an internal standard (n-hexadecane). The results are summarized in Table 2.

3,4,5,6,7,8-Hexahydro-2(1*H*)-quinolinone (6a). A mixture of **5** (0.302 g, 2.00 mmol), water (0.072 g, 4.0 mmol), and $RuH_2(PPh_3)_4$ (0.069 g, 0.06 mmol) in DME (0.5 mL) was reacted at 120 °C for 24 h in a sealed tube under argon. Removal of the solvent gave a brown solid. ^1H NMR analysis showed that an isomeric ratio of **6a** and **6b** was 90 / 10. The mixture was subjected to column chromatography (SiO_2, hexane–EtOAc = 2 / 1) to give **6a** (0.216 g, 72%) and **6b** (0.014 g, 5%). **6a:** mp 142 °C; IR (KBr) 3220, 3177, 3094, 2932, 2862, 1669, 1489, 1441, 1391, 1318, 1235, 1202, 1134, 976, 828, 818, 733, 542, 522 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.57–1.73 (m, 4 H, H^6, H^7), 1.96–2.05 (m, 4 H, H^5, H^8), 2.19 (tm, J = 8.3 Hz, 2 H, H^4), 2.48 (dd, J = 8.3 and 8.3 Hz, 1 H, H^3), 2.48 (dd, J = 7.3 and 8.3 Hz, 1 H, H^3), 7.53 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 22.2, 22.7, 25.8, 26.2, 27.8, 30.7, 109.6, 128.3, 171.6; mass spectrum m/e (relative intensity %) 151 (M^+, 100), 123 (72), 94 (57), 80 (20), 67 (18), 53 (17). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.62; H, 8.75; N, 9.21. **6b:** IR (KBr) 3200, 3085, 2938, 1678, 1663, 1624, 1476, 1389, 1329, 1302, 1215, 1188, 1169, 1020, 999, 884, 835, 718, 608, 509, 474, 436, 405 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.27 (dddd, J = 2.7, 11.0, 12.7 and 12.7 Hz, 1 H), 1.37–1.59 (m, 3 H), 1.75–2.00 (m, 4 H), 2.02–2.13 (m, 2 H), 2.18–2.34 (m, 1 H), 2.42 (ddd, J = 5.6, 12.5, and 17.6 Hz, 1 H, H^3ax), 2.53 (ddd, J = 2.4, 5.9, and 17.6 Hz, 1 H, H^3eq), 4.93 (dd, J = 3.5 and 5.5 Hz, 1 H, C=CH), 8.11 (br-

s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 22.1, 23.5, 27.3, 29.5, 32.0, 33.5, 103.9, 136.2, 171.0. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.66; N, 9.26. Found: C, 71.72; H, 8.73; N, 9.23.

4a-Methyl-3,4,4a,5,6,7-hexahydro-2(1*H*)-quinolinone (8). mp 156–157 °C; IR (KBr) 3179, 3079, 2930, 2885, 2839, 1688, 1667, 1615, 1476, 1460, 1383, 1335, 1315, 1211, 1080, 978, 922, 889, 858, 781, 719, 523, 503, 455, 420 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.16 (s, 3 H, CH_3), 1.40 (ddd, J = 5.4, 12.0, and 12.0 Hz, 1 H), 1.56–1.75 (m, 6 H), 2.00–2.11 (m, 2 H), 2.49 (dd, J = 2.9 and 5.4 Hz, 1 H, CHC=O), 2.54 (dd, J = 8.8 and 10.0 Hz, 1 H, CHC=O), 8.45 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 18.2, 22.7, 23.5, 28.7, 31.2, 34.1, 36.8, 104.0, 139.3, 170.2. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.79; H, 9.16; N, 8.50.

8-Azabicyclo[5.4.0]undec-1(7)-en-9-one (9). mp 112–113 °C; IR (KBr) 3206, 3158, 3094, 2926, 2830, 1694, 1672, 1487, 1449, 1418, 1391, 1356, 1321, 1285, 1263, 1245, 1233, 1192, 1172, 1159, 1140, 1082, 1022, 990, 951, 916, 878, 826, 775, 729, 675, 635, 556, 530, 476, 465 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.48–1.64 (m, 4 H), 1.64–1.75 (m, 2 H), 2.11–2.22 (m, 4 H), 2.25–2.34 (m, 2 H), 2.40 (dd, J = 1.2 and 6.9 Hz, 1 H, H^3ax), 2.43 (dd, J = 2.7 and 6.9 Hz, 1 H, H^3eq), 7.81 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 25.8, 26.7, 28.3, 30.5, 31.2, 32.6, 32.8, 114.2, 132.9, 171.7. Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 71.62; H, 8.75; N, 9.21.

5-Methyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (10). IR (KBr) 3208, 3164, 3106, 2932, 2863, 1701, 1682, 1636, 1483, 1445, 1385, 1315, 1240, 1221, 1202, 1094, 957, 907, 802, 779, 741, 720, 625, 600, 529, 486, 457, 444, 430 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.01 (d, J = 6.9 Hz, 3 H, CH_3), 1.37 (ddd, J = 5.5, 8.3, and 10.1 Hz, 1 H, H^6ax), 1.58–1.65 (m, 1 H), 1.69–1.78 (m, 2 H), 1.97–2.03 (m, 2 H), 2.10 (ddd, J = 7.9, 7.9, and 7.9 Hz, 1 H), 2.15–2.25 (m, 1 H), 2.32–2.40 (m, 1 H), 2.44 (ddd, J = 6.6, 16.0, and 16.0 Hz, 1 H, H^3ax), 2.47 (ddd, J = 7.3, 10.3, and 16.0 Hz, 1 H, H^3eq), 7.50 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 19.3, 23.7, 26.7, 30.9, 31.6, 114.4, 128.4, 171.6; mass spectrum m/e (relative intensity %) 165 (15), 150 (73), 122 (75), 94 (100), 80 (61). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.70; H, 9.15; N, 8.48. Found: C, 72.66; H, 9.13; N, 8.49.

5-(2-Propenyl)-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (11). ^1H NMR ($CDCl_3$, 60 MHz) δ 1.33-2.85 (m, 11 H), 1.66 (d, J = 5 Hz, 3 H, $=CCH_3$), 5.23–5.60 (m, 2 H, CH=CH), 7.76 (br-s, 1 H, NH). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.17; H, 8.71; N, 7.16.

3,4-Dihydro-6-ethyl-5-methyl-2(1*H*)-pyridinone (12). mp 77–78 °C; IR (KBr) 3220, 3094, 2967, 2934, 2878, 1695, 1680, 1464, 1391, 1367, 1312, 1281, 1246, 1217, 1181, 1163, 1138, 1063, 1028, 968, 941, 889, 814, 775, 727, 673, 630, 559, 530, 480, 455 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.05 (t, J = 7.6 Hz, 3 H, CH_3CH_2), 1.70 (br-s, 3 H, CH_3C=), 2.12 (q, J = 7.6 Hz, 2 H, CH_3CH_2C=), 2.23 (tm, J = 8.6 Hz, 2 H, H^4), 2.44 (dd, J = 8.6 and 8.6 Hz, 1 H, H^3), 2.44 (dd, J = 8.6 and 10,0 Hz, 1 H, H^3), 6.99 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 12.4, 16.8, 23.1, 27.1, 30.6, 107.0, 131.2, 171.9; mass spectrum m/e (relative intensity %) 139 (M^+, 100), 124 (82), 110 (66), 96 (68), 82 (40), 68 (40), 56 (44). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.95; H, 9.30; N, 10.09.

3,4-Dihydro-6-methyl-2(1*H*)-pyridinone (13). ^1H NMR (270 MHz, $CDCl_3$) δ 1.81 (ddd, J = 1.7, 1.7, and 1.7 Hz, 3 H, CH_3), 2.18–2.33 (m, 2 H, C=C–CH_2), 2.38–2.47 (m, 2 H, CH_2C=O), 4.79 (qdd, J = 1.7, 4.0, and 8.0 Hz, 1 H, =CH), 8.23 (br-s, 1 H, NH); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 18.8, 20.1, 30.1, 100.1, 133.0, 172.2.

4a-Ethoxycarbonyl-3,4,5,6,7-pentahydro-2(1*H*)-quinolinone (14). mp 136–137 °C; IR (KBr) 3181, 3132, 3054, 2977, 2938, 2909, 1720, 1678, 1660, 1618, 1451, 1427, 1394, 1345, 1298, 1240, 1217, 1192, 1159, 1098, 1015, 980, 935, 901, 845, 790, 760, 725, 644, 623, 571, 548, 511, 491, 434 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.26 (t, J = 7.1 Hz, 3 H, CH_3), 1.42–1.51 (m, 2 H), 1.60–1.78 (m, 2 H), 2.06–2.18 (m, 2 H), 2.18–2.39 (m, 3 H), 2.41–2.54 (m, 1 H), 4.20 (q, J = 7.1 Hz, 2 H, OCH_2), 5.12 (dd, J = 3.7 and 3.7 Hz, 1 H, =CH), 8.20 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 14.2, 19.2, 23.3, 29.4, 30.6, 33.8, 45.2, 61.4, 106.4, 133.7, 169.4, 173.9. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.26; H, 7.58; N, 6.28.

7-Methyl-1,2,3,4,5,6,7,8-octahydroquinoline-2,5-dione (15). mp 200–201 °C; IR ($CHCl_3$) 3400, 2960, 1700, 1635, 1455, 1365, 1290, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.10 (d, J = 6 Hz, 3 H, CH_3), 1.67–2.50 (m, 5 H), 2.50–2.73 (m, 4 H), 8.67 (br-s, 1 H, NH). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.01; H, 7.31; N, 7.82. Found: C, 66.63; H, 7.28; N, 7.75.

8-(2-Carbamoylethyl)-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (16). mp 278–279 °C (dec.); IR (Nujol) 3200, 1670, 1640, 1160, 810, 720 cm^{-1}; ^1H NMR (DMSO-d_6, 60 MHz) δ 1.67–2.03 (m, 6 H, CH_2), 2.20 (t, J = 4 Hz, 2 H, $=CCH_2$), 2.00–2.40 (m, 1 H, CH), 2.55 (t, J = 4 Hz, 2 H, $COCH_2$), 2.57 (t, J = 4 Hz, 2 H, CH_2CO), 8.28 (br-s, 3 H, NH); mass spectrum m/e (relative intensity %) 222 (M^+, 40), 205 (16), 166 (21), 151 (100), 123 (33), 112 (38), 55 (40). Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H,8.16; N, 12.60. Found: C, 64.85; H, 8.17; N, 12.32.

2-Azabicyclo[5.4.0]undec-1(7)-en-3-one (17). IR (Nujol) 3150, 1700, 1680, 850, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.00–1.85 (m, 6 H), 1.85–2.47 (m, 8 H), 7.52 (br-s, 1 H, NH).

1-Benzyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (18). A mixture of **5** (0.302 g, 2.00 mmol), benzylamine (0.247 g, 2.30 mmol), water (0.080 g, 4.44 mmol), and $RuH_2(PPh_3)_4$ (0.069 g, 0.06 mmol) in DME (0.5 mL) was reacted at 160 °C for 24 h in a sealed tube under argon. After removal of the solvent, the residue was purified by MPLC (SiO_2, hexane–EtOAc = 3 / 1) to give **18** (0.198 g, 41%) as a yellow liquid: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.46–1.64 (m, 4 H), 2.00–2.08 (m, 4 H), 2.16 (t, 2 H, J = 7.3 Hz), 2.57 (t, 2 H, J = 7.3 Hz), 4.86 (s, 2 H), 7.13–7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 21.9, 22.8, 25.3, 25.4, 28.9, 31.7, 43.7, 105.3, 115.2, 126.2, 126.6, 128.4, 131.4, 138.6, 170.4.

1-Butyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (19). A mixture of **5** (0.302 g, 2.00 mmol), butylamine (0.158 g, 2.16 mmol), water (0.080 g, 4.44 mmol), and $RuH_2(PPh_3)_4$ (0.069 g, 0.06 mmol) in DME (0.5 mL) was reacted at 160 °C for 24 h in a sealed tube under argon. After removal of the solvent, the residue was purified by preparative TLC (SiO_2, $CHCl_3$–ether = 10 / 1, R_f = 0.41–0.68) to give **19** (0.147 g, 35%) as a yellow liquid: IR (neat) 2925, 1650, 1440, 1400, 1195, 1130 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.92 (t, J = 6 Hz, 3 H, CH_3), 1.10–1.90 (m, 8 H), 1.90–2.74 (m, 8 H), 3.56 (t, J = 7 Hz, 2 H, NCH_2).

Preparation of (R)-(+)-Pulegone Semicarbazone.[18] In a 3 L round-bottomed flask equipped with a mechanical stirrer were placed (+)-pulegone (**27**, $[\alpha]_D$ +22° (neat), Aldrich Chemical Company, Inc.) (263 g, 1.73 mol), EtOH (1500 mL) and water (750 mL). The flask was cooled to 0 °C, and sodium acetate trihydrate (600 g, 6.09 mol) and semicarbazide hydrochloride (300 g, 2.70 mol) were added to the mixture. The solution was stirred at 0 °C for 2 h and then at room temperature for 45 h. The precipitated solid was separated by filtration and dissolved with $CHCl_3$ (800 mL x 3). Evaporation of the $CHCl_3$ gave a colorless solid. This solid was recrystallized three times from EtOH to afford optically pure (R)-(+)-pulegone semicarbazone (272 g, 75%) as colorless needles: $[\alpha]_D^{24}$ +67.5° ($CHCl_3$, c 2 00), lit. $[\alpha]_D^{23}$ +66° (c 2.05, $CHCl_3$);[18] IR (KBr) 3461, 3180,

3000, 2951, 2930, 2909, 2851, 1695, 1665, 1618, 1572, 1528, 1468, 1457, 1443, 1427, 1380, 1370, 1323 1302, 1283, 1248, 1221, 1138, 1088, 1028, 1011, 988, 938, 916, 862, 766, 743, 691, 606, 583, 532, 488, 440 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.01 (d, J = 6.1 Hz, 3 H, CH_3), 1.09–1.27 (m, 1 H), 1.67–1.83 (m, 3 H), 1.75 (s, 3 H, $=CCH_3$), 1.88 (s, 3 H, $=CCH_3$), 2.08–2.27 (m, 1 H), 2.50–2.63 (m, 2 H), 5.77 (br-s, 2 H, NH_2), 8.39 (br-s, 1 H, NH).

Preparation of Optically Pure 27. In a 2 L round-bottomed flask equipped with a mechanical stirrer was placed optically pure (R)-(+)-pulegone semicarbazone (232 g, 1.11 mol) dissolved in dioxane (600 mL) and 2 N hydrochloric acid (1.1 L, 2.20 mol). The solution was stirred for 8 h at room temperature. Ether (700 mL) was added to the mixture, and the organic layer was separated. The aqueous layer was extracted with ether (500 mL x 3). The combined organic layers were washed successively with saturated $NaHCO_3$ aqueous solution (400 mL x 3) and water (500 mL x 2), and dried over Na_2SO_4. After removal of the solvent, the residue (250 g) was distilled under reduced pressure to give optically pure **27** (109 g, 64%): bp 95–97 °C (15 mmHg); $[\alpha]_D^{23}$ +23.2° (neat), lit. $[\alpha]_D^{25.5}$ +22.47° (neat),[19a] $[\alpha]_D^{27}$ +23.6° (neat);[19b] ^1H NMR ($CDCl_3$, 60 MHz) δ 0.98 (d, J = 5 Hz, 3 H, CH_3), 1.18–1.53 (m, 2 H), 1.70–1.96 (m, 2 H), 1.78 (s, 3 H, $=CCH_3$), 1.97 (s, 3 H, $=CCH_3$), 2.06–2.96 (m, 4 H).

Preparation of *N*-((3*R*)-6-Isopropylidene-3-methyl-1-cyclohexenyl)pyrrolidine (28). In a 100 mL round-bottomed flask equipped with a magnetic stirrer and a Dean-Stark trap connected to a reflux condenser were placed **27** (21.7 g, 0.143 mol), pyrrolidine (12.0 mL, 0.143 mol), *p*-toluenesulfonic acid (0.5 g), and benzene (60 mL). After stirring at reflux for 14.5 h, pyrrolidine (12.0 mL) was added, and the mixture was stirred for 9.5 h at reflux. After removal of the solvent, the residue was distilled under reduced pressure to give **28** (16.8 g, 58%) as a colorless oil: bp 97–103 °C (1.5 mmHg); IR (neat) 3050, 2920, 1635, 1450, 1390, 1370, 1290, 1185, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.97 (dd, J = 6 and 1.5 Hz, 3 H, CH_3), 1.46–2.37 (m, 9 H), 1.67 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 2.58–3.13 (m, 4 H, NCH_2), 4.20 (dd, J = 3 and 13.5 Hz, 1 H, =CH).

Preparation of (3*R*)-2-(2-Cyanoethyl)-6-isopropylidene-3-methylcyclohexanone (29). In a 200 mL three-necked round bottomed flask equipped with a magnetic stirrer and a reflux condenser were placed **28** (14.4 g, 0.070 mol), acrylonitrile (14.0 mL, 0.21 mol), and absolute EtOH (70 mL). The solution was refluxed for 17 h. After removal of the solvent, a mixture of anhydrous sodium acetate (10 g), acetic acid (20 mL), water (20 mL), and dioxane (60 mL) was added, and the mixture was refluxed for 3 h. The solution was poured into water (200 mL) and extracted with ether (100 mL x 5). The combined extracts were washed successively with 5% NaOH (50 mL x 3), 2 N hydrochloric acid (50 mL x 3), and water (100 mL x 3), and dried over $MgSO_4$. After removal of the solvent, the residual oil was distilled under reduced pressure to give **29** (8.72 g, 61%) as a colorless liquid. GLC analysis (30 m glass capillary column packed with SCOT PEG-20M) of the product showed that *cis* / *trans* ratio of **29** was 2 / 3: bp 105–107 °C (0.03 mmHg); IR (neat) 2930, 2860, 2250, 1715, 1680, 1450, 1380, 1285 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.83–1.16 (m, 3 H, CH_3), 1.14–2.12 (m, 7 H), 1.76 (s, 3 H, $=CCH_3$), 1.90 (s, 3 H, $=CCH_3$), 2.12–2.83 (m, 3 H).

Preparation of (5*R*)-5-Methyl-3,4,5,6,7,8-hexahydro-2(1*H*)-quinolinone (25). A mixture of **29** (1.54 g, 7.50 mmol), water (2.0 mL, 0.11 mol), and $RuH_2(PPh_3)_4$ (0.260 g, 0.225 mmol) in DME (2 mL) was reacted at 160 °C for 48 h in a sealed tube (240 x 24 mm) under argon. The reaction mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layers were dried over Na_2SO_4. After removal of the solvent, the residue was

purified by MPLC (SiO_2, EtOAc–hexane = 1 / 3) to give **25** (0.624 g, 56%) as a colorless solid. Recrystallization from hexane–EtOAc (9 / 1) gave colorless needles: mp 127.5–128.5 °C; $[\alpha]_D^{26}$ +45.2° (*c* 1.01, $CHCl_3$). IR (KBr) 3208, 3164, 3106, 2932, 2863, 1701, 1682, 1636, 1483, 1445, 1385, 1315, 1240, 1221, 1202, 1094, 957, 907, 802, 779, 741, 720, 625, 600, 529, 486, 457, 444, 430 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.01 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.37 (ddd, *J* = 5.5, 8.3, and 10.1 Hz, 1 H, H^6ax), 1.58–1.65 (m, 1 H), 1.69–1.78 (m, 2 H), 1.97–2.03 (m, 2 H), 2.10 (ddd, *J* = 7.9, 7.9, and 7.9 Hz, 1 H), 2.15–2.25 (m, 1 H), 2.32–2.40 (m, 1 H), 2.44 (ddd, *J* = 6.6, 16.0, and 16.0 Hz, 1 H, H^3ax), 2.47 (ddd, *J* = 7.3, 10.3, and 16.0 Hz, 1 H, H^3eq), 7.50 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 19.3, 23.7, 26.7, 30.9, 31.6, 114.4, 128.4, 171.6; mass spectrum m/e (relative intensity %) 165 (15), 150 (73), 122 (75), 94 (100), 80 (61). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.70; H, 9.15; N, 8.48. Found: C, 72.66; H, 9.13; N, 8.49.

Hydrogenation of 25 with Various Catalysts. A mixture of **25** (81 mg, 0.5 mmol), catalyst (15 mg), conc. hydrochloric acid (0.02 mL) in EtOH (2 mL) was stirred at room temperature for 5 h under hydrogen atmosphere (1 atm). After filtration of the catalyst through a pad of Celite and removal of the solvent under reduced pressure, CH_2Cl_2 (15 mL) and saturated $NaHCO_3$ aqueous solution (2 mL) were added to the residue. The organic layer was separated, washed successively with saturated $NaHCO_3$ aqueous solution (2 mL) and brine (2 mL), and dried over Na_2SO_4. Removal of the solvent gave (4a*S*,5*R*,8a*R*)-5-methyl-2,3,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**24**) along with (4a*S*,5*R*,8a*S*)-5-methyl-2,3,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**31**). The yield and the diastereomeric ratio of **24** and **31** were determined by ^1H NMR (270 MHz) and GLC analysis (PEG-20M, 0.25 mm x 30 m). The results with various catalysts were shown in Table 4.

Preparation of (4a*S*,5*R*,8a*R*)-5-Methyl-2,3,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (24). In a 30 mL round-bottomed flask equipped with a magnetic stirrer and a hydrogen balloon were placed **25** (1.63 g, 9.88 mmol), 5% Pd-C (K-type, 0.81 g), EtOH (8 mL), acetic acid (1.6 mL), and conc. hydrochloric acid (5 drops). The mixture was stirred at 60 °C under hydrogen pressure (85 kg/cm^2) for 24 h. After filtration of the catalyst through a pad of Celite and removal of the solvent under reduced pressure, CH_2Cl_2 (70 mL) and saturated Na_2CO_3 aqueous solution (10 mL) were added to the residue. The organic layer was separated, washed with a saturated aqueous Na_2CO_3 solution (10 mL x 2), and dried over Na_2SO_4. Removal of the solvent gave a mixture of **24** and **31** (1.49 g, 90 %). ^1H NMR (270 MHz) and GLC analysis (30 m glass capillary column packed with SCOT PEG-20M) of the product showed that the diastereomeric ratio of **24** and (4a*S*,5*R*,8a*S*)-5-Methyl-2,3,4a,5,6,7,8,8a-octahydro-2(1H)-quinolinone (**31**) was 98 / 2. Recrystallization from EtOAc gave pure **24** as a colorless needles: mp 146.5–147.5 °C; $[\alpha]_D^{25}$ –60.4° (*c* 1.00, $CHCl_3$); IR (KBr) 3179, 2951, 2924, 2896, 2855, 1669, 1605, 1480, 1455, 1402, 1362, 1364, 1331, 1316, 1248, 1213, 1200, 1163, 1138, 1127, 1082, 1019, 974, 955, 932, 891, 868, 822, 774, 708, 637, 548, 517, 494, 473 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.91–1.12 (m, 1 H, H^7ax), 1.43 (dddd, *J* = 3.7, 3.7, 3.7, and 10.5 Hz, 1 H, H^{4a}), 1.48–1.54 (m, 2 H, H^6ax, H^6eq), 1.54–1.72 (m, 5 H, H^4ax, H^5ax, H^7eq, H^8ax, H^8eq), 2.05 (dddd, *J* = 5.0, 5.0, 5.0, and 13.8 Hz, 1 H, H^4eq), 2.28 (ddd, *J* = 5.0, 10.7, and 16.0 Hz, 1 H, H^3ax), 2.29 (ddd, *J* = 5.0, 7.7, and 16.0 Hz, 1 H, H^3eq), 3.62 (ddd, *J* = 3.7, 3.7, and 3.7 Hz, 1 H, H^{8a}), 6.00 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 19.4, 20.1, 23.2, 27.4, 27.8, 31.7, 33.8, 39.8, 52.1. Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.24; N, 8.33. Found: C, 71.76; H, 10.14; N, 8.33.

Preparation of (4a*S*,5*R*,8a*R*)-2-Methoxy-5-methyl-3,4,4a,5,6,7,8,8a-octahydroquinoline (33). A solution of **24** (0.775 g, 4.63 mmol) in dry CH_2Cl_2 (5 mL) was added to a mixture of Me_3OBF_4 (1.39 g, 9.39 mmol), *N*,*N*-diisopylethylamine (0.83 mL, 4.76 mmol) in CH_2Cl_2 (5 mL) at 10 °C under argon. The

mixture was stirred for 2 h at room temperature. CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ aqueous solution (15 mL) were added to the mixture at 0 °C. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The combined organic layers were dried over Na_2SO_4. After removal of the solvent, the residual oil was subjected to short column chromatography (Al_2O_3, hexane) to give **33** (0.520 g, 62%) as a pale yellow oil; IR (neat) 2930, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (d, J = 6.4 Hz, 3 H, CH_3), 1.01 (dddd, J = 4.6, 9.8, 9.8, and 12.0 Hz, 1 H), 1.25–1.53 (m, 5 H), 1.53–1.66 (m, 3 H), 1.83 (dddd, J = 1.6, 4.6, 9.8, and 11.5 Hz, 1 H), 2.04–2.12 (m, 2 H), 3.52 (ddd, J = 2.0, 4.0, and 8.0 Hz, 1 H, CH–N), 3.63 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 19.8, 20.9, 22.6, 23.0, 28.7, 33.4, 33.7, 51.7, 54.8, 162.4.

Preparation of (–)-Pumiliotoxin C (1). A solution of n-propyl bromide (2.8 mL, 30 mmol) in dry ether (15 mL) was added to a suspension of magnesium turnings (0.80 g, 33 mmol) in dry ether (8 mL). After stirring for 30 min at room temperature, the molarity of the Grignard solution was determined to be 1.3 mol/L by Gilman titration.[31] The freshly prepared Grignard solution (6.0 mL, 7.8 mmol) was placed in a 30 mL side-armed flask. After removal of ether under reduced pressure, dry benzene (8 mL) was added to the residue to replace ether with benzene. A solution of **33** (0.465 g, 2.56 mmol) in benzene (5 mL) was added to the Grignard solution in benzene prepared above. The mixture was refluxed for 4 h. After cooling to room temperature, the mixture was quenched by pouring into a mixture of ether (20 mL) and saturated $NaHCO_3$ aqueous solution (10 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with ether (10 mL x 2). The combined organic layers were dried over $MgSO_4$. Removal of the solvent under reduced pressure gave crude (4a*S*,5*R*,8a*R*)-5-methyl-2-propyl-3,4,4a,5,6,7,8,8a-octahydroquinoline (**34**) (0.514 g) which was immediately used without further purification. In a 30 mL side-armed flask fitted with hydrogen balloon were placed the crude imine prepared above (0.496 g), 5% Pd-C (K-type, 0.128 g), and MeOH (20 mL). The mixture was stirred at room temperature under hydrogen atmosphere (1 atm) for 48 h. After filtration through a pad of Celite, the mother liquor was treated with conc. hydrochloric acid. Removal of the solvent gave **1**•HCl (0.502 g, 49% from lactam **24**) as a colorless solid. Recrystallization from 2-propanol gave colorless needles: mp 286–288 °C (sealed capillary) (lit.[14c] mp 288–290 °C (sealed capillary)); $[\alpha]_D^{21}$ –16.2° (*c* 1.00, CH_3OH) (lit. $[\alpha]_D^{20}$ –14.5° (*c* 1.00, CH_3OH),[14c] $[\alpha]_D^{20}$ –13.1° (*c* 1.0, CH_3OH),[14f] (+)-isomer: $[\alpha]_D^{20}$ +16.4° (*c* 1.00, CH_3OH),[14c] $[\alpha]_D^{25}$ +16.2° (*c* 1.00, CH_3OH),[14b] $[\alpha]_D^{24}$ +16.1° (*c* 1.00, CH_3OH)[14h]); IR (KBr) 3100–2500, 2965, 2955, 2930, 2872, 2816, 2708, 2602, 1580, 1472, 1456, 1443, 1431, 1420, 1404, 1373, 1356, 1315, 1283, 1180, 1117, 1059, 1026, 997, 970, 951, 916, 883, 833, 804, 783, 745, 656, 613, 544, 502, 486 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (d, J = 6.4 Hz, 3 H, C^5-CH_3), 0.92 (t, J = 7.4 Hz, 3 H, CH_2CH_3), 0.95–1.01 (m, 1 H, H-6ax), 1.27 (dddd, J = 2.2, 7.4, 15.0, and 30.0 Hz, 1 H, $CHCH_3$ in propyl group), 1.36–1.52 (m, 4 H, H^3ax, H^{4a}, H^7ax, $CHCH_3$ in propyl group), 1.52–1.64 (m, 2 H, H^4ax, H^8ax), 1.77 (br-d, J = 14.0 Hz, 1 H, H^3eq), 1.86 (br.d, J = 13.0 Hz, 1 H, H^6eq), 2.03–2.11 (m, 2 H, H-5, H^4eq), 2.11–2.24 (m, 2 H, $CH_2CH_2CH_3$), 2.40 (tq, J = 3.7 and 13.8 Hz, 1 H, H^7eq), 2.49 (br-d, J = 15.0 Hz, 1 H, H^8eq), 2.97 (br-ddd, J = 10.3, 10.3, and 10.3 Hz, 1 H, H^2), 3.31 (br-d, J = 10.5 Hz, 1 H, H^{8a}), 8.44 (br-s, 1 H, NH), 9.54 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.8 (CH_2CH_3), 19.2 (CH_2CH_3), 19.8 ($CHCH_3$), 20.5 (C^7), 23.3 (C^4), 25.3 (C^3), 27.2 (C^5), 29.2 (C^8), 34.4 ($CH_2CH_2CH_3$), 35.0 (C^6), 41.0 (C^{4a}), 58.2 (C^{8a}), 60.2 (C^2). The assignments of signals were determined by H-H and C-H COSY experiments. Mass spectrum (free base) (relative intensity %) m/e 195 (M^+, 2), 152 (100). Anal. Calcd for $C_{13}H_{26}ClN$: C, 67.36; H, 11.31; N, 6.04; Cl, 15.29. Found: C, 67.27; H, 11.00; N., 6.33; Cl, 15.10.

(4a*S*,5*R*)-8a-Hydrodioxy-5-methyl-3,4,4a,5,6,7,8-heptahydro-2(1*H*)-quinolinone (35). In a 30 mL round-bottomed flask equipped with a magnetic stirrer were placed **25** (0.330 g, 2.00 mmol), *p*-toluenesulfonic acid (0.038 g, 0.200 mmol), and CH_2Cl_2 (4 mL). To the stirred solution was added 30% H_2O_2 aqueous solution (0.454 g, 4.00 mmol) dropwise over a period of 3 min. After the addition was complete, the reaction mixture was stirred for 3 h. The mixture was washed with water to remove excess hydrogen peroxide. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give **35** (0.306 g, 77%): ^1H NMR (270 MHz) analysis of the product showed that the diastereomeric ratio of **35** was 67 / 33: IR (KBr) 3305, 2953, 2936, 2870, 1665, 1458, 1387, 1346, 1300, 1277, 1223, 1148, 1036, 1007, 986, 926, 920, 880, 831, 816, 739, 690, 567, 521 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.90 (d, J = 6.4 Hz, 0.67 x 3 H, *trans*-CH_3), 0.90–1.15 (m, 1 H), 1.00 (d, J = 6.4 Hz, 0.33 x 3 H, *cis*-CH_3), 1.27–1.45 (m, 2 H), 1.45–1.95 (m, 6 H), 2.03–2.90 (m, 3 H), 7.81 (br-s, 0.67 x 1 H, NH), 8.44 (br-s, 0.67 x 1 H, NH), 10.9 (br-s, 1 H, OOH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 17.7,* 19.4,* 19.5, 19.8, 21.1, 21.9,* 26.8,* 30.3,* 30.9, 31.6, 33.0, 33.9,* 34.1, 35.2, 41.9,* 46.9, 89.3, 91.6,* 175.6,* 175.7. An asterisk indicates that the signals are due to the minor product.

(4a*S*,5*R*,8a*S*)-5-Methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (31). In a 30 mL round-bottomed flask equipped with a magnetic stirrer were placed **35** (0.199 g, 1.00 mmol) and dry CH_2Cl_2 (4 mL). $TiCl_4$ (0.22 mL, 2.00 mmol) was added dropwise at –78 °C, and the mixture was stirred for 1 h. Et_3SiH (0.342 g, 3.00 mmol) was added dropwise at –78 °C for 5 min. After stirring for 6 h, the reaction was quenched by pouring into ice water (10 mL). The mixture was extracted with CH_2Cl_2 (10 mL x 2) and dried over Na_2SO_4. Removal of the solvent gave a mixture of **31** and **24** (0.120 g, 72%). ^1H NMR (270 MHz) analysis of the product showed that the diastereomeric ratio of **31** and **24** was 90 / 10. Recrystallization from EtOAc gave pure **31** as colorless needles: mp 180–180.5 °C; $[\alpha]_D^{25}$ +14.7° (c 1 06, $CHCl_3$); IR (KBr) 3191, 3090, 2960, 2940, 2936, 2899, 2867, 2860, 2845, 1661, 1480, 1456, 1448, 1438, 1408, 1368, 1343, 1318, 1291,1264, 1250, 1217, 1171, 1132, 1121, 1078, 1003, 980, 957, 930, 903, 874, 843, 804, 691, 581, 548, 527, 490, 475, 436 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (d, J = 7.8 Hz, 3 H, CH_3), 0.92–1.00 (m, 1 H, H^{4a}), 1.01–1.10 (m, 1 H, H^6ax), 1.17–1.27 (m, 1 H, H^5), 1.27–1.44 (m, 3 H, H^4ax, H^7ax, H^8ax), 1.68–1.84 (m, 3 H, H^6eq, H^7eq, H^8eq), 2.07 (dddd, J = 1.6, 2.2, 7.1, and 13.3 Hz, 1 H, H^4eq), 2.34 (ddd, J = 7.1, 12.7, and 18.2 Hz, 1 H, H^3ax), 2.47 (ddd, J = 1.8, 6 4, and 18.2 Hz, 1 H, H^3eq), 2.96 (ddd, J = 3.2, 10.0, and 10.0 Hz, 1 H, H^{8a}), 6.44 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 19.1, 24.0, 24.8, 31.6, 33.4, 35.1, 46.1, 57.4, 172.6. Anal. Calcd for $C_{10}H_{17}NO$; C, 71.81; H, 10.24, N, 8.33 Found: C, 71.99; H, 10.23; N, 8.43.

3,4,4a,5,6,7,8-Heptahydro-8a-hydrodioxy-2(1*H*)-quinolinone (36). In a 30 mL side-armed round-bottomed flask equipped with a magnetic stirrer were placed **6a** (0.302 g, 2.00 mmol), *p*-toluenesulfonic acid (0.038 g, 0.200 mmol), and CH_2Cl_2 (4 mL). To the stirred solution was added 30% hydrogen peroxide aqueous solution (0.454 g, 4.00 mmol) dropwise over a period of 5 min at room temperature. After the addition was complete, the reaction mixture was stirred for 4 h. The mixture was washed with water to remove excess hydrogen peroxide. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give **36** (0.318 g, 86%) as a colorless oil. ^1H NMR (270 MHz) analysis showed that the diastereomeric ratio of **36** was 50 / 50: IR (KBr) 3220, 2938, 2861, 1680, 1460, 1449, 1395, 1343, 1330, 1281, 1258, 1215, 1157, 1141, 1092, 1040, 993, 959, 938, 922, 870, 853, 824, 793, 739, 689, 613, 567, 517, 465 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.23–1.45 (m, 2 H), 1.45–2.02 (m, 7 H), 2.11–2.30 (m, 1 H), 2.30–2.55 (m, 3 H), 8.21 (br-s, 0.5 x 1 H, NH), 8.46 (br-s, 0 5 x 1 H, NH), 11.1 (br-s, 0.5 x 1 H, OOH), 11.2 (br-s, 0.5 x 1 H, OOH); ^{13}C

NMR ($CDCl_3$, 67.9 MHz) δ 21.2, 22.3, 22.5, 23.0, 24.3, 25.6, 27.4, 27.6, 27.7, 31.0, 32.8, 33.5, 35.3, 41.0, 88.9, 91.6, 175.7, 175.9.

***trans*-3,4,4a,5,6,7,8,8a-Octahydro-2(1*H*)-quinolinone (37).** In a 30 mL side-armed flask equipped with a magnetic stirrer were placed **36** (0.185 g, 1.00 mmol) and dry CH_2Cl_2 (4 mL). $TiCl_4$ (0.22 mL, 2.0 mmol) was added dropwise at –78 °C, and the mixture was stirred for 1 h at –78 °C. Et_3SiH (0.342 g, 3.00 mmol) was added dropwise at –78 °C over a period of 4 min. After stirring for 8 h at –78 °C, the reaction was quenched by pouring into ice water (10 mL). The mixture was extracted with CH_2Cl_2 (10 mL x 2) and the combined organic layers were dried over Na_2SO_4. Removal of the solvent gave **37** along with *cis*-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinolinone (**38**) as a pale yellow solid (0.139 g, 91%). ^1H NMR (270 MHz) analysis showed that the ratio of **37** and **38** was 93 / 7. Recrystallization from EtOAc gave pure **37** as colorless needles: IR (KBr) 3191, 3090, 2932, 2899, 2853, 1659, 1624, 1480, 1450, 1433, 1404, 1372, 1358, 1344, 1318, 1302, 1244, 1198, 1127, 1084, 1046, 978, 874, 806, 791, 700, 546, 502, 451, 419 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.99–1.16 (m, 1 H), 1.21–1.39 (m, 4 H), 1.47 (dddd, J = 7.3, 11.8, 11.8, and 12.3 Hz, 1 H), 1.70–1.86 (m, 5 H), 2.39 (ddd, J = 6.5, 11.5, and 17.5 Hz, 1 H, H^3ax), 2.42 (ddd, J = 2.5, 7.0, and 17.5 Hz, 1 H, H^3eq), 2.90 (ddd, J = 3.8, 9.9, and 9.9 Hz, 1 H, H^{8a}), 6.71 (br-s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 24.3, 25.7, 28.0, 30.9, 31.5, 33.2, 40.1 (C^{4a}), 57.7 (C^{8a}), 172.4 (C=O).

***trans*-8a-Allyl-3,4,4a,5,6,7,8-heptahydro-2(1*H*)-quinolinone (40).** In a 30 mL side-armed flask equipped with a magnetic stirrer were placed **36** (0.185 g, 1.00 mmol) and dry CH_2Cl_2 (4 mL). $TiCl_4$ (0.22 mL, 2.0 mmol) was added dropwise at –78 °C, and the mixture was stirred for 1 h at –78 °C. Allyltrimethylsilane (0.348 g, 3.00 mmol) was added dropwise at –78 °C over a period of 5 min. After stirring for additional 5 h at –78 °C, the reaction was quenched by pouring into ice water (10 mL). The mixture was extracted with CH_2Cl_2 (10 mL x 2) and dried over Na_2SO_4. Removal of the solvent gave **40** along with *cis*-8a-allyl-3,4,4a,5,6,7,8-heptahydro-2(1*H*)-quinolinone (**41**) as a pale yellow solid (0.156 g, 81%). ^1H NMR (270 MHz) analysis showed that the ratio of **40** and **41** was 93 / 7: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.22–1.35 (m, 2 H), 1.35–1.61 (m, 5 H), 1.61–1.75 (m, 2 H), 1.75–1.94 (m, 2 H), 2.20–2.42 (m, 2 H, CH_2C=O), 2.27 (d, J = 11.0 Hz, 2 H, =CCH_2), 5.01–5.14 (m, 2 H, =CH_2), 5.63–5.82 (m, 1 H, –CH=), 6.58 (br-s, 0.93 x 1 H, NH), 6.75 (br-s, 0.07 x 1 H, NH); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 21.1,* 21.9, 22.5, 22.9, 25.8,* 26.8, 28.4, 30.7,* 35.2, 35.5, 36.5,* 43.1,* 45.5, 55.8,* 56.4, 119.3, 132.3,* 132.6, 172.5. An asterisk indicates that the signals are due to **41**. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.20; H, 9.81; N, 7.28.

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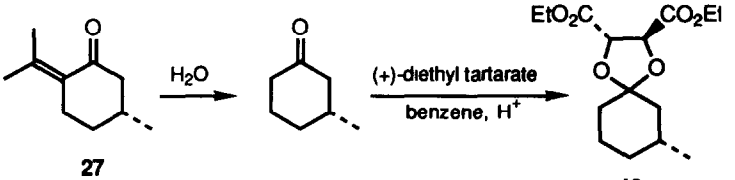
20. Optical purity of **27** obtained was determined by the following route.[21] Deisopropylidenation of pulegone[22] gave (+)-3-methylcyclohexanone, which was converted to acetal **42** by acid catalyzed acetalization with (+)-diethyl tartarate. ^{13}C NMR analysis showed that acetal **42** was obtained as a single diastereomer.



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