SYNTHESIS OF *trans*-4a-ARYL-6-OXODECAHYDROISOQUINOLINES

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Abstract—General and short synthesis of *trans*-4a-aryl-6-oxodecahydroisoquinolines was described. In particular, the synthesis of 2-cyclopropylmethyl-4a-(3-hydroxyphenyl)-*trans*-6-oxodecahydroisoquinoline (**1 2**), one of the remarkably useful molecule as an opioid message structural part, was attained in only seven steps. The key step in this synthetic approach was 1,4-conjugate addition of aryl moiety to sterically hindered enones (**2**).

Classification of opioid receptors into three different types (μ, δ, and κ) has been established by not only pharmacological but also molecular biological study.[1] And many opioid ligands highly selective and potent for each opioid receptor type were reported.[2] Some of them were rationally designed on the basis of "message-address concept"[3] (message structural part in the opioid ligand: essential moiety for elicitation of intrinsic activity on opioid receptors, and address structural part in the opioid ligand: necessary moiety for selectivity on each opioid receptor type) in opioid area, and the resultant receptor type selective agonists and antagonists were proved to be useful tools for pharmacological studies to elucidate the properties of each opioid receptor type.[2,4]

In the strategy for design of opioid ligands employing the above concept, the first task is to select the message structure and to establish its general synthetic method for execution of medicinal chemistry. The requisite properties of the message structure should be to have high opioid activity on its own molecule and to have functional group at suitable position in its structure in order to construct an address moiety. Although 4,5-epoxymorphinans, morphinans, benzomorphans, and so on have been well known structures[5] as message moiety (Figure 1), we were especially interested in *trans*-4a-aryl-6-oxodecahydroisoquinolines as a target message since the system has *trans*-fused ring structure which includes angular axial phenol group mimic the C-D ring system of morphine. And it has a ketone group at suitable position for introduction of address moiety. Moreover the presence of rotationable phenol ring in this message

molecule let us expect that the affinity and agonistic potency for opioid receptor could become higher than those of classical message molecules in which the corresponding phenol groups were fixed by 4,5-epoxy and methylene bridge (Figure 1).[6-8]

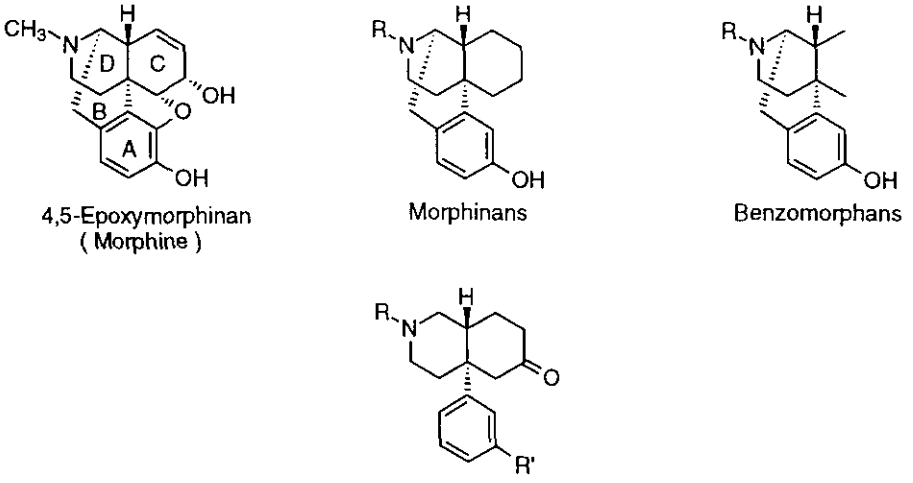
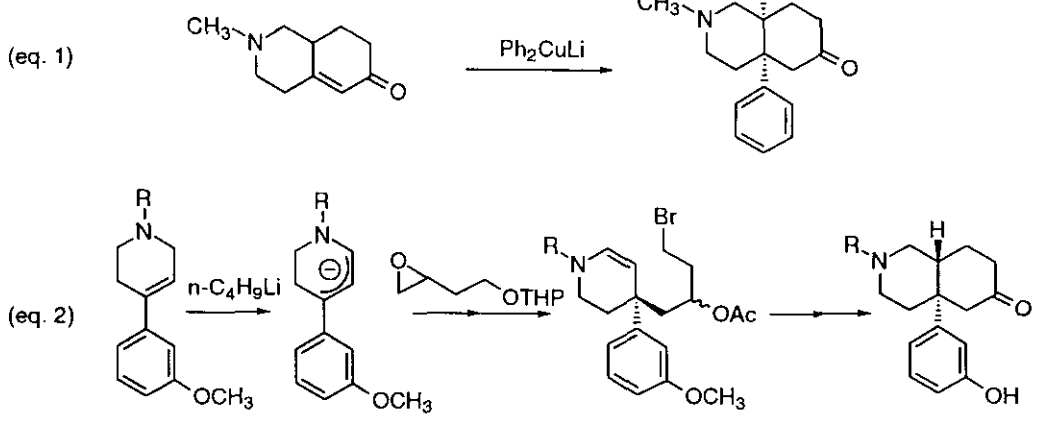


Figure 1. Opioid ligans as message structural part.

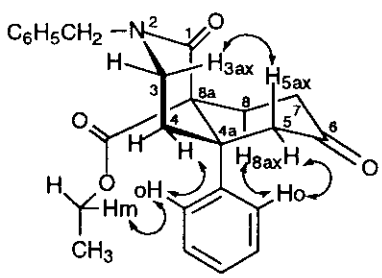
There have been several reports on the synthesis of *trans*-4a-aryl-6-oxodecahydroisoquinolines.[8-10] And the common synthetic challenge of this system is the construction of quaternary carbon bearing angular aryl group. This angular aryl group cannot be incorporated in an intramolecular fashion as is the case for benzomorphans and morphinans.[5] Finch *et al.*[11] disclosed a direct synthetic route for the preparation of 4a-aryl-6-oxodecahydroisoquinolines which involved the 1,4-conjugate addition of phenyl group to the readily available α , β -unsaturated ketone, giving exclusively the *cis*-fused compound but not the *trans*-isomer (Scheme 1, eq. 1). Zimmermann *et al.*[10] and Judd *et al.*[8] described synthetic routes to the *trans*-4a-aryl-6-



Scheme 1

oxodecahydroisoquinolines, employing metalated enamines for the construction of quaternary carbon as a key step (Scheme 1, eq. 2). Though the above syntheses are efficient and general, in this paper we wish to describe a shorter new synthetic route to *trans*-4a-aryl-6-oxodecahydroisoquinolines which is corresponding to Finch's synthetic strategy[11] starting from the structurally modified enones.

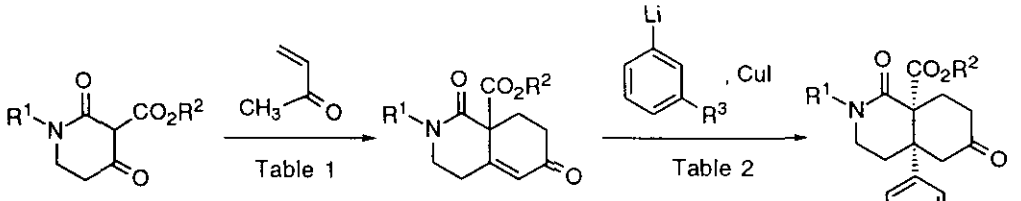
The starting enones (**2**) were prepared from 2,4-piperidinedione derivatives[12] (**1**) in accordance with literature[13] for **2a** or by our modified procedure for **2b,c** (Scheme 2). The results of the annelation for preparation of **2** were summarized in Table 1. Compound (**1a**) was transformed into enone (**2a**) by Schultz's[13] conditions in 50% isolated yield. On the other hand, annelation of compound (**1b**) by using methyl vinyl ketone (MVK) under modified basic conditions (KOH (0.1 eq.) and 18-crown-6 (0.1 eq.) in MeOH at room temperature) gave on workup enone (**2b**) in excellent isolated yield (95%). Also good isolated yield (70%) of enone (**2c**) was attained by annelation of **1c** with MVK in the presence of NaOEt (0.12 eq.) in corresponding alcohol. The next step is the 1,4-conjugate addition of aryl moiety on the sterically hindered enones to construct all carbon core of the target messages (Scheme 2). The results of the 1,4-conjugate addition reaction were summarized in Table 2. As a model study, lithium diphenylcuprate[14] prepared from phenyllithium and CuI was reacted with enone (**2a**) in Et_2O at 0℃ for 1 h to give exclusively 1,4-adduct (**3a**) in 51% isolated yield. In case of enone (**2b**), since it has been well-known that chlorotrimethylsilane as additive accelerates the reaction rate and chemoselectivity on cuprate-enone conjugate addition,[15] the reaction of enone (**2b**) and lithium diphenylcuprate was performed in the presence of chlorotrimethylsilane in Et_2O / THF (1:2) at -75℃ to room temperature. However the desired 1,4-adduct (**3b**) was obtained in 30% isolated yield. The stereochemistry of product (**3a**) was assigned to be structure of (**3a'**) by ^{1}H-NMR, COSY, and NOESY spectra, and NOE experimental study (Figure 2). In particular, observation of positive NOE enhancement on the hydrogen combinations of H_o-H_m .



3a'

Figure 2. Assignment of stereochemistry of product (**3a**)

H_o-H_{8ax} , and H_{3ax}-H_{5ax} indicated that the 1,4-adduct should be *cis*-fused decahydroisoquinoline structure bearing axial 4a-phenyl group. In the above 1,4-conjugate additon reaction, no *trans*-fused isomers were detected. This 1,4-conjugate addition could also be applied to the introduction of an aryl



1a R^1=$CH_2C_6H_5$, R^2=C_2H_5
1b R^1=$CH_2C_3H_5$, R^2=CH_3
1c R^1=$CH_2C_3H_5$, R^2=C_2H_5

2a R^1=$CH_2C_6H_5$, R^2=C_2H_5
2b R^1=$CH_2C_3H_5$, R^2=CH_3
2c R^1=$CH_2C_3H_5$, R^2=C_2H_5

3a R^1=$CH_2C_6H_5$, R^2=C_2H_5, R^3=H
3b R^1=$CH_2C_3H_5$, R^2=CH_3, R^3=H
3c R^1=$CH_2C_6H_5$, R^2=C_2H_5, R^3=OCH_3
3d R^1=$CH_2C_3H_5$, R^2=C_2H_5, R^3=OCH_3

Scheme 2

Table 1. The results of annelation reaction of 2,4-piperidinedione derivatives.

Entry	substrate	Condition of the reaction with MVK[a]	Product	Yield(%)[b]
1	**1a**	MVK (1.7 eq.), *tert*-C_4H_9OK (0.12 eq.), PhH / *tert*-C_4H_9OH (2/1), 80℃, 5 h	**2a**	50
2	**1b**	MVK (2.3 eq.), KOH (0.1 eq.), 18-crown-6 (0.1 eq.), CH_3OH, rt, 22 h	**2b**	95
3	**1c**	MVK (2.3 eq.), $NaOC_2H_5$ (0.12 eq.), C_2H_5OH, rt, 7.5 h	**2c**	70

a) After the reaction of **1** with methyl vinyl ketone (MVK) under above conditions, the resultant intermediates were subjected to the common procedure as follows : i) cyclization and dehydration (pyrrolidine in benzene at 80℃). ii) hydrolysis of the resultant dienamines (AcOH / H_2O / NaOAc 2:2:1, △).

b) The isolated yield of the corresponding enones (**2**).

Table 2. The results of 1,4-conjugate addition of arylcuprates to enones

Entry	ArLi	Condition of cuprate formation	Substrate	1,4-Conjugate addition condition	Product	Yield (%)[a]
1	PhLi (cyclohexane / Et_2O 1.0 M sol., 4.0 eq.)	CuI (2.0 eq.), Et_2O, 0℃, 1 h	**2a**	Et_2O, 0℃～rt, 1 h	**3a**	51
2	PhLi (cyclohexane / Et_2O 1.0 M sol., 4.0 eq.)	CuI (2.0 eq.), Et_2O, -20℃, then -75℃, TMSCl (4.0 eq.)	**2b**	Et_2O / THF 1/2, -75℃～rt, 2 h	**3b**	30
3	*m*-bromoanisole (4.0 eq.), *tert*-BuLi (pentane 1.3 M sol. , 8.0 eq.), THF, -70～-25℃, then THF→Et_2O[b] at -20℃	CuI (2.0 eq.), Et_2O, 0℃, 10 min	**2a**	Et_2O, 0℃～rt, 30 min	**3c**	40
4	*m*-bromoanisole (4.0 eq.), *tert*-BuLi (pentane 1.6 M sol. , 8.0 eq.), THF, -70～-25℃, then THF→Et_2O[b] at -20℃	CuI (2.0 eq.), Et_2O, 0℃, 10 min	**2c**	Et_2O, 0℃～rt, 1 h	**3d**	50

a) The isolated yield of the corresponding 1,4-adducts (**3**).

b) THF was removed under reduced pressure and substituted by Et_2O.

moiety having oxygen function at meta position (Scheme 2). Thus, enone (**2a, c**) were individually treated in Et_2O at 0℃ with lithium di(*m*-methoxyphenyl)cuprate prepared by transmetalation of *m*-bromoanisole by using *t*-BuLi followed by addition of CuI to give on workup exclusively desired 1,4-adducts [**3c** (40%), **3d** (50 %)], respectively. Again no *trans*-fused isomer was detected in each case.

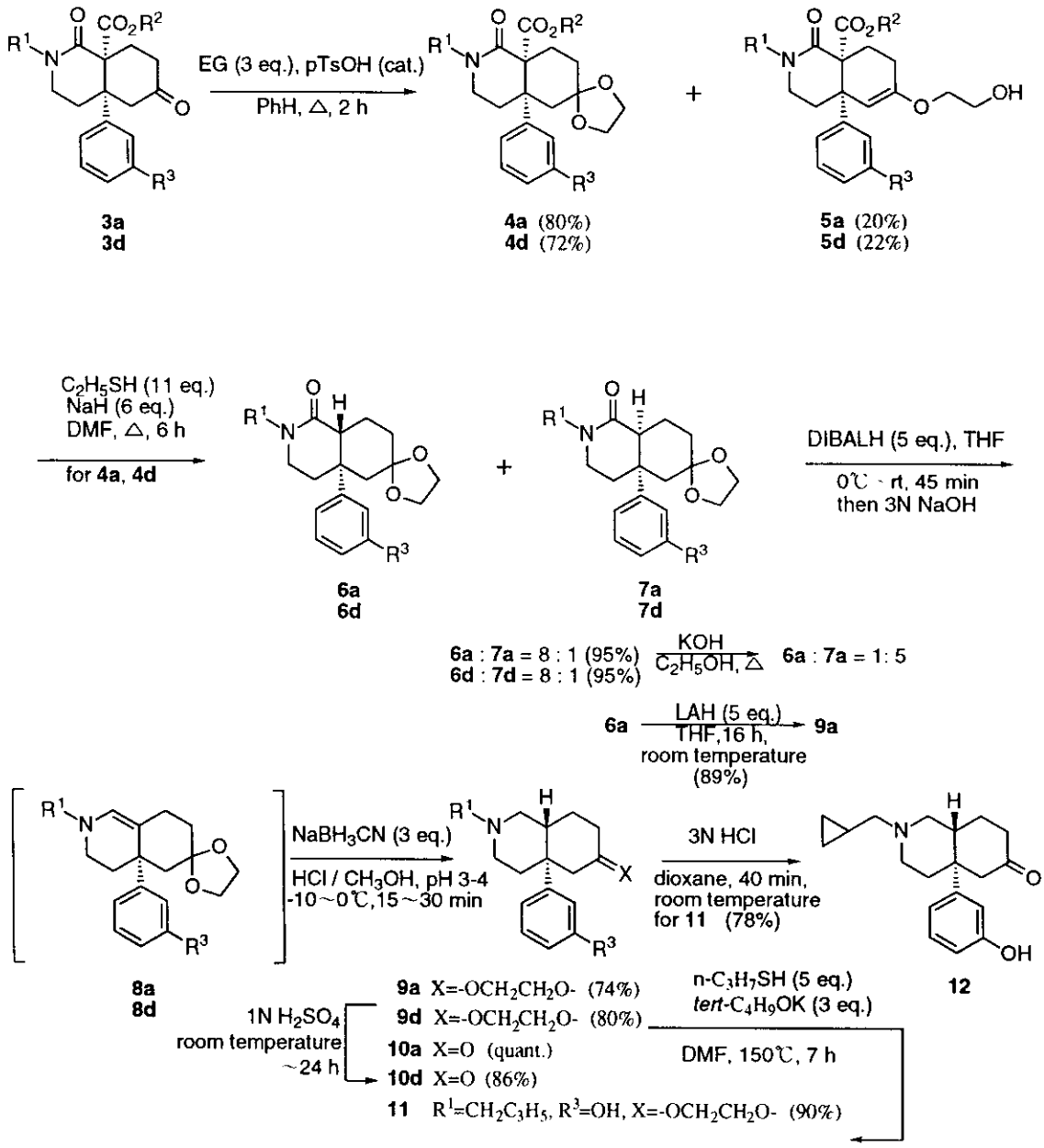
As mentioned above, we succeeded in the 1,4-conjugate addition on such a sterically hindered enone system. Our next attention is to transform the *cis*-fused 1,4-adducts to *trans*-4a-aryldecahydroisoquinoline systems and to synthesize 2-cyclopropylmethyl-4a-(3-hydroxyphenyl)-*trans*-6-oxodecahydroisoqinoline (**12**) which is remarkably unique molecule as an opioid message because of its opioid κ receptor selectivity and potent agonistic property with antinociceptive activity [8] (Scheme 3).

Protection of keto group of adducts (**3a, d**) by using ethylene glycol furnished compounds [**4a** (80%), **4d** (72%)] accompanied with vinyl ethers [**5a** (20%), **5d** (22%)], respectively. Compounds (**4a, d**) were purified by silica gel column chromatography and individually heated with EtSNa in DMF[16] to afford *trans*-lactams (**6a, d**) and *cis*-lactams (**7a, d**) as **6**:**7** = *ca.* 8:1 mixture in 95% combined yield, respectively. *Trans* stereochemistry of major isomer (**6a**) was confirmed by treatment of a 8:1 mixture of **6a** and **7a** by KOH in refluxing EtOH. This produced 1:5 mixture of **6a** and **7a**. This result is consistent with that of Rapoport and co-workers; they showed that *cis*-4a-aryldecahydroisoquinoline is thermodynamically more stable than the *trans* isomer.[9] Reduction of a 8:1 mixture of **6d** and **7d** with diisobutylaluminum hydride (5.0 eq.)[13,17] followed by treatment with NaOH furnished enamine intermediate, and sequential reduction of this intermediate with $NaBH_3CN$ in MeOH at pH 3-4 brought about kinetic protonation[18] and hydride reduction of the resulting iminium salt to give a desired *trans*-4a-aryldecahydroisoquinoline (**9d**) in excellent overall yield. Deprotection of ethylene ketal of compound (**9d**) gave ketone (**10d**). The stereochemistry of **9d** and **10d** was confirmed to be *trans* by comparison of ^{1}H-NMR, IR, and MS spectra and TLC analysis with those of authentic samples independently synthesized according to literature.[10,19] Similarly, a 8:1 mixture of **6a** and **7a** was converted into **10a** in more than 70% overall yield. The stereochemistry of **9a** was suggested to be *trans* by the fact that the isolated *trans*-lactam isomer (**6a**) was converted into compound (**9a**) in 89% yield by direct reduction using lithium aluminum hydride.

Finally, one of the target message molecule, compound (**12**), was synthesized in 70% overall yield by the following sequence: (1) cleavage of phenol methyl ether of compound (**9d**) by heating with *n*-PrSK in DMF, and (2) deprotection of ethylene ketal of resulting phenol (**11**) under acidic conditions and recrystallization from MeOH / EtOAc. The obtained 2-cyclopropylmethyl-4a-(3-hydroxyphenyl)-*trans*-6-oxodecahydroisoquinoline (**12**) was identical with an authentic sample independently synthesized according to literature[10,19] by comparison of ^{1}H-NMR, IR, and MS spectra and TLC analysis (Scheme 3).

In summary, we have shown general short syntheses of *trans*-4a-aryl-6-oxodecahydroisoquinoline systems. In particular, 2-cyclopropylmethyl-4a-(3-hydroxyphenyl)-*trans*-6-oxodecahydroisoquinoline (**12**), a remarkably useful molecule as an opioid message moiety, was synthesized in only seven steps in

19% total yield. This new synthetic approach could be applied to the synthesis of the target message having a variety of nitrogen substituent groups and aryl groups.



a : R^1=$CH_2C_6H_5$, R^2=C_2H_5, R^3=H
d : R^1=$CH_2C_3H_5$, R^2=C_2H_5, R^3=OCH_3

Scheme 3

Experimental Section

General. Melting points were determined on a Yanaco MP-500D melting point apparatus and are uncorrected. NMR data were taken on JEOL JNM-EX-90 (90 MHz) or JEOL GX-400 (400 MHz) spectrometers in $CDCl_3$ solution and reported in δ (ppm) downfield from tetramethylsilane (TMS). IR spectra were determined on a JASCO FT / IR-5000 spectrophotometer. MS specta were obtained on a JEOL JES-D-300 or JEOL JMS-D-303 instruments using an electric ionization method (EI). Elemental analysis were determined with a Heraeus CHN-O RAPID for carbon, hydrogen, and nitrogen. Reaction progress and purity of final products were determined on Merck Silica Gel Art. 5715. Column chromatography was carried out using Merck Silica Gel (70-230 mesh) with the indicated eluents.

Ether and THF were distilled from benzophenone ketyl just prior to use. Anhydrous benzene was prepared by distillation after drying over phosphorus pentoxide. Anhydrous *tert*-butanol was prepared by distillation after treatment with sodium. Anhydrous dimetylformamide (DMF) was prepared by distillation under reduced pressure after drying with magnesium sulfate. Unless otherwise stated, all reagents and other solvents were reagent grade and used without subsequent purification.

2-Benzyl-8a-carboethoxy-1,6-dioxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (2a)

To a stirred solution of 1-benzyl-3-carboethoxy-2,4-piperidinedione (**1a**) (8.73 g, 31.75 mmol) in anhydrous benzene (30 mL) and anhydrous *tert*-butanol (15 mL) at rt was added potassium *tert*-butoxide (428 mg, 3.81 mmol) under argon, and the mixture was heated to 70℃ over 2 h. After cooling to rt, to the mixture was added dropwise methyl vinyl ketone (4.44 mL, 53.97 mmol), and the mixture was gradually heated to 80℃, and stirring was continued for 5 h. The reaction mixture was cooled to rt, and treated with saturated ammonium chloride solution, then the mixture was extracted with a mixture of ether / ethyl acetate (9 : 1 v/v). The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave an oily residue (9.64 g) which was used for next reaction without further purification.

To a stirred solution of the above residue (9.64 g) in anhydrous benzene (38 mL) was added pyrrolidine (4 mL, 47.62 mmol) , and the mixture was refluxed for 4 h using Dean-Stark apparatus. After cooling to rt, the reaction mixture was treated with a mixture of acetic acid / water / sodium acetate (2:2:1 w/w) (15 mL) at 100℃ for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid solution, saturated sodium bicarbonate solution, and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue (5.8 g) which was subjected to column chromatography (80 g) (eluted with n-hexane / ethyl acetate 3:2 v/v) to afford 3.9 g (50%) of enone (**2a**) as a solid: mp 72～74℃ (ether); IR ($CHCl_3$) 1734, 1680, 1653, 1600 cm^{-1}; ^{1}H-NMR (90 MHz) δ 1.29 (3H, t, J = 7.0 Hz), 1.55～3.20 (6H, m), 3.28～3.47 (2H, m), 4.26 (2H, q, J = 7.0 Hz), 4.34 (1H, d, J = 14.5 Hz), 4.97 (1H, d, J = 14.5 Hz), 5.98 (1H, br s), 7.30 (5H, s); MS m/z 327 (M^+).

8a-Carbomethoxy-2-cyclopropylmethyl-1,6-dioxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (2b)

To a stirred solution of 1-cyclopropylmethyl-3-carbomethoxy-2,4-piperidinedione (**1b**) (300 mg, 1.3 mmol) in methanol (1 mL) at rt was added 1N potassium hydroxide-methanol solution (0.13 mL, 0.13 mmol) and 18-crown-6 (34 mg, 0.13 mmol) under argon. After stirring for 10 min, to the mixture at rt was added methyl vinyl ketone (0.1 mL, 1.2 mmol / 0.1 mL, 1.2 mmol / 0.05 mL, 0.6 mmol) intermittently, and stirring was continued for 22 h. The reaction mixture was concentrated under reduced pressure, and resulting residue was treated with saturated potassium chloride solution, then the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily residue (653 mg) which was used for next reaction without further purification.

To a stirred solution of the above residue (653 mg) in anhydrous benzene (10 mL) was added pyrrolidine (0.28 mL, 3.41 mmol) , and the mixture was refluxed for 6 h using Dean-Stark apparatus. After cooling to rt, the reaction mixture was treated with a mixture of acetic acid / water / sodium acetate (2:2:1 w/w) (5 mL) at 100℃ for 3 h. The reaction mixture was treated with water, then the mixture was extracted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue (892 mg) which was subjected to column chromatography (18 g) (eluted with n-hexane / ethyl acetate 1:1～1:2 v/v) to afford 342 mg (95%) of enone (**2b**) as a solid: mp 95.5～96.5℃ (ether); IR ($CHCl_3$) 1744, 1680, 1657, 1628 cm^{-1}; ^{1}H-NMR (90 MHz) δ 0.22～0.38 (2H, m), 0.42～0.65 (2H, m), 1.00 (1H, m), 1.89～3.60 (10H, m), 3.78 (3H, s), 5.98 (1H, br s); MS m/z 277 (M^+); Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found : C, 64.93; H6.91, N, 5.11.

8a-Carboethoxy-2-cyclopropylmethyl-1,6-dioxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (2c)

To a stirred solution of 1-cyclopropylmethyl-3-carboethoxy-2,4-piperidinedione (**1c**) (6.25 g, 26.15 mmol) in ethanol (30 mL) at rt was added sodium ethoxide (213 mg, 3.14 mmol) follwed by methyl vinyl ketone (4.84 mL, 58.84 mmol) under argon, and the mixture was stirred for 7.5 h. The reaction mixture was treated with saturated ammonium chloride solution, and extracted with a mixture of ether / ethyl acetate (9:1 v/v). The organic layer was washed with saturated ammonium chloride solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave an oily residue which was used for next reaction without further purification.

To a stirred solution of the above residue in anhydrous benzene (80 mL) was added pyrrolidine (5.46 mL, 65.38 mmol) , and the mixture was refluxed for 16 h using Dean-Stark apparatus. After cooling to rt, the reaction mixture was treated with a mixture of acetic acid / water / sodium acetate (2:2:1 w/w) (65 mL) at 100℃ for 1 h. The reaction mixture was extracted with ethy acetate, and the organic layer was washed with 1N hydrochloric acid solution, 1N sodium carbonate solution, and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (200 g) (eluted with n-hexane / ethyl acetate 1:1, 3:4 v/v) to afford 5.34 g (70%) of enone

(**2c**) as a solid: mp 50~52℃ (ether); IR ($CHCl_3$) 1740, 1680, 1653, 1628 cm^{-1}; ^{1}H-NMR (90 MHz) δ 0.19~0.38 (2H, m), 0.42~0.65 (2H, m), 1.01 (1H, m), 1.30 (3H, t, J = 7.5 Hz), 1.91~3.65 (10H, m), 4.25 (2H, q, J = 7.5 Hz), 6.00(1H, br s); MS m/z 291(M^+); Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found : C, 65.83; H, 7.11, N, 4.88.

2-Benzyl-8a-carboethoxy-4a-phenyl-*cis*-1,6-dioxodecahydroisoquinoline (3a)

To a stirred suspension of copper(I) iodide (1.17 g, 6.12 mmol) in anhydrous ether (10 mL) at 0℃ was added 1.0M phenyllithium cyclohexane / ether solution (12.3 mL, 12.23 mmol) dropwise under argon, and stirring was continued for 1 h. To a resulting mixture was added a solution of 2-benzyl-8a-carboethoxy-1,6-dioxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (**2a**) (1 g, 3.06 mmol) in anhydrous ether (40 mL) dropwise, and the mixture was reacted at 0℃ for 1 h and at rt for 1 h. The reaction mixure was treated with saturated ammonium chloride solution for 30 min under vigorous stirring, and extracted with ethyl acetate. The water layer was alkalified with 28% ammonia solution (80 mL), and extracted with ethyl acetate. The combined organic layer was washed with 28% ammonia solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue (1.19 g) which was subjected to column chromatography (35 g) (eluted with n-hexane / ethyl acetate 2:1 v/v) to afford 631 mg (51%) of 1,4-adduct (**3a**) as a white solid: mp 132~135℃ (ether / n-hexane); IR (KBr) 1729, 1630 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.01 (3H, t, J = 7.2 Hz), 1.61 (1H, dd, J = 5.2 and 13.7 Hz), 2.20 (1H, dt, J = 4.3 and 14.1 Hz), 2.40 (1H, dt, J = 5.8 and 14.1 Hz), 2.52 (1H, dm, J = 16.5 Hz), 2.60 (1H, d, J = 16.2 Hz), 2.70 (1H, dd, J = 1.5 and 16.2 Hz), 2.78 (1H, ddd, J = 2.4, 5.8 and 14.1 Hz), 3.34 (1H, ddd, J = 7.0, 13.4 and 13.7 Hz), 3.45 (1H, dt, J = 5.2 and 13.4 Hz), 3.59 (1H, dd, J = 7.0 and 13.4 Hz), 3.87 (1H, dq, J = 7.2 and 10.5 Hz), 4.02 (1H, dq, J = 7.2 and 10.5 Hz), 4.54 (1H, d, J = 14.7 Hz), 4.94 (1H, d, J = 14.7 Hz), 7.21 (2H, d, J = 7.0 Hz), 7.22~7.33 (6H, m), 7.36 (2H, d, J = 2.7 Hz); MS m/z 405 (M^+); Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found : C, 74.06; H, 6.70, N, 3.62.

8a-Carbomethoxy-2-cyclopropylmethyl-4a-phenyl-*cis*-1,6-dioxodecahydroisoquinoline (3b)

To a stirred suspension of copper(I) iodide (138 mg, 0.72 mmol) in anhydrous ether (2 mL) at -20℃ was added 1.0M phenyllithium cyclohexane / ether solution (1.52 mL, 1.44 mmol) dropwise under argon, and stirring was continued for 30 min. After cooling to -75℃, to the mixture was added chlorotrimethylsilane (0.18 mL, 1.44 mmol) followed by a solution of 8a-carbomethoxy-2-cyclopropylmethyl-1,6-dioxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (**2b**) (100 mg, 0.36 mmol) in anhydrous THF (3 mL) / ether (1.5 mL) dropwise, and the mixture was warmed to rt for 2 h. The reaction mixture was treated with 1N hydrochloric acid solution, and extracted with ethyl acetate. The organic layer was washed with saturated ammonium chloride solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (10 g) (eluted with n-hexane / ethyl acetate 4:3 v/v) and recrystallization from ether / n-hexane to afford 40 mg (30%) of 1,4-adduct (**3b**) as a white solid: mp 76~80℃ (ether / n-hexane); IR ($CHCl_3$) 1742, 1717, 1636, 1502, 1446 cm^{-1}; ^{1}H-

NMR (400 MHz) δ 0.30 (1H, m), 0.34 (1H, m), 0.51~0.62 (2H, m), 1.09 (1H, m), 1.68 (1H, dm), 2.14 (1H, dt, J = 3.4 and 14.2 Hz), 2.36 (1H, dt, J = 5.9 and 14.2 Hz), 2.50 (1H, dm), 2.71 (1H, ddd, J = 3.4, 5.9 and 13.9 Hz), 2.76 (2H, br s), 3.23 (1H, dd, J = 6.8 and 14.2 Hz), 3.37 (1H, dt, J = 9.3 and 14.2 Hz), 3.47 (3H, s), 3.63 (1H, dd, J = 6.8 and 13.9 Hz), 3.69~3.74 (2H, m), 7.20~7.34 (5H, m); HRMS Calcd for $C_{21}H_{25}NO_4$ (M^+): 355.1784. Found : 355.1783.

2-Benzyl-8a-carboethoxy-4a-(3-methoxyphenyl)-*cis*-1,6-dioxodecahydroisoquinoline (3c)

To a stirred solution of *m*-bromoanisole (115 mg, 0.61 mmol) in anhydrous THF (1.5 mL) at -70℃ was added 1.3M *tert*-butyllithium pentane solution (0.94 mL, 1.2 mmol) dropwise under argon, and the resulting white suspension was warmed to -25℃, and then the solvent was removed under reduced pressure. To the residue at -20℃ was added anhydrous ether (1 mL), and the mixture was warmed to rt. The resulting red solution was added dropwise to a stirred suspension of copper(I) iodide (58.3 mg, 0.31 mmol) in anhydrous ether (2 mL) at 0℃. After stirring for 10 min, a solution of 2-benzyl-8a-carboethoxy-1,6-dioxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (**2a**) (50 mg, 0.15 mmol) in anhydrous ether (3 mL) was added dropwise at the same temperature, and the reaction was continued for 30 min at 0℃~rt. The reaction mixture was treated with saturated ammonium chloride solution followed by 28% ammonia solution, and extracted with ethyl acetate. The organic layer was washed with saturated ammonium chloride solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (10 g) (eluted with n-hexane / ethyl acetate 2:1, 4:3 v/v) and recrystallization from ether / n-hexane to afford 27 mg (40%) of 1,4-adduct (**3c**) as a white solid: mp 76~80℃ (ether / n-hexane); IR ($CHCl_3$) 1738, 1715, 1642, 1607, 1584 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.04 (3H, t, J = 7.9 Hz), 1.60 (1H, dd, J = 5.4 and 13.7 Hz), 2.21 (1H, dt, J = 5.4 and 14.9 Hz), 2.39 (1H, dt, J = 5.4 and 14.9 Hz), 2.52 (1H, dm), 2.62 (1H, d, J = 16.1 Hz), 2.68 (1H, dd, J = 1.5 and 16.1 Hz), 2.78 (1H, ddd, J = 2.4, 5.4 and 13.9 Hz), 3.31 (1H, ddd, J = 6.8, 11.7 and 13.7 Hz), 3.44 (1H, dt, J = 5.4 and 11.7 Hz), 3.58 (1H, dd, J = 6.8 and 13.7 Hz), 3.76 (3H, s), 3.93 (1H, dq, J = 7.3 and 10.7 Hz), 4.04 (1H, dq, J = 7.3 and 10.7 Hz), 4.54 (1H, d, J = 14.7 Hz), 4.94 (1H, d, J = 14.7 Hz), 6.75~6.83 (3H, m), 7.21 (1H, t, J = 7.8 Hz), 7.28~7.40 (5H, m); HRMS Calcd for $C_{26}H_{29}NO_5$ (M^+): 435.2046. Found : 435.2025.

8a-Carboethoxy-2-cyclopropylmethyl-4a-(3-methoxyphenyl)-*cis*-1,6-dioxodecahydroisoquinoline (3d)

To a stirred solution of *m*-bromoanisole (0.7 mL, 5.5 mmol) in anhydrous THF (15 mL) at -70℃ was added 1.55M *tert*-butyllithium pentane solution (7.1 mL, 11.0 mmol) dropwise under argon, and the resulting white suspension was warmed to -25℃, and then the solvent was removed under reduced pressure. To the residue at -20℃ was added anhydrous ether (10 mL), and the mixture was warmed to rt. The resulting red solution was added dropwise to a stirred suspension of copper(I) iodide (524 mg, 2.75 mmol) in anhydrous ether (15 mL) at 0℃. After stirring for 10 min, a solution of 8a-carboethoxy-2-

cyclopropylmethyl-1,6-dioxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (**2c**) (400 mg, 1.38 mmol) in anhydrous ether (10 mL) was added dropwise at the same temperature, and the reaction was continued for 1 h at 0℃～rt. The reaction mixture was treated with saturated ammonium chloride solution followed by 28% ammonia solution, and extracted with ethyl acetate. The organic layer was washed with saturated ammonium chloride solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (41 g) (eluted with n-hexane / ethyl acetate 3:2 v/v) to afford 274 mg (50%) of 1,4-adducts (**3d**) as a colorless oil: IR (neat) 1738, 1715, 1634, 1607, 1584, 1493, 1448 cm^{-1}; ^{1}H-NMR (400 MHz) δ 0.26～0.38 (2H, m), 0.51～0.62 (2H, m), 1.04 and 1.26 (3H, each t, each J = 7.3 Hz), 1.18 (1H, m), 1.68 (2H, dd, J = 4.4 and 13.2 Hz), 2.18 (1H, dt, J = 4.4 and 13.7 Hz), 2.36 (1H, dt, J = 5.9 and 14.2 Hz), 2.48 (1H, br d, J = 15.6 Hz), 2.74 (2H, s), 3.29 (1H, dd, J = 6.8 and 13.7 Hz), 3.36 (1H, m), 3.54 (1H, dd, J = 7.3 and 13.7 Hz), 3.63～3.76 (2H, m), 3.77 (3H, s), 3.89, 3.91, 3.99 and 4.02 (2H, each q, each J = 7.3 Hz), 6.80～6.82 (3H, m), 7.22 (1H, t, J = 7.3 Hz); HRMS Calcd for $C_{23}H_{29}NO_5$ (M^+): 399.2046. Found : 399.2033.

2-Benzyl-8a-carboethoxy-6,6-ethylenedioxy-4a-phenyl-*cis*-1-oxodecahydroisoquinoline (4a)

A stirred solution of 2-benzyl-8a-carboethoxy-4a-phenyl-*cis*-1,6-dioxodecahydroisoquinoline (**3a**) (117 mg, 0.29 mmol), ethylene glycol (52 μL, 0.86 mmol) and *p*-toluenesulfonic acid (11 mg, 0.06 mmol) in benzene (4 mL) was refluxed for 2 h with Dean-Stark apparatus. The reaction mixture was cooled to rt, and diluted with ethly acetate. The resulting mixture was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (8 g) (eluted with n-hexane / ethyl acetate 1:1 v/v) to afford 104 mg (80%) of the ketal (**4a**) as a colorless amorphous and 25 mg (20%) of vinyl ether (**5a**) as a white solid. Compound (**4a**): IR ($CHCl_3$) 1725, 1638, 1499, 1448 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.03 (3H, t, J = 7.3 Hz), 1.64 (1H, m), 1.83 (1H, m), 2.20 (2H, d, J = 2.9 Hz), 2.49 (1H, m), 2.65 (2H, m), 3.24 (1H, m), 3.38 (1H, m), 3.82～3.99 (6H, m), 4.45 (1H, d, J = 14.7 Hz), 4.87 (1H, d, J = 14.7 Hz), 7.16～7.36 (8H, m), 7.54 (2H, d, J = 7.8 Hz); MS m/z 449 (M^+). Compound (**5a**): mp 114～116℃ (ether): IR (KBr) 3450, 1715, 1669, 1632, 1495, 1454 cm^{-1}; ^{1}H-NMR (400 MHz,) δ 0.96 (3H, t, J = 7.3 Hz), 1.57 (1H, m), 1.93 (1H, m), 2.20 (3H, m), 2.47 (1H, m), 3.23～3.43 (3H, m), 3.62～3.78 (2H, m), 3.82～3.98 (4H, m), 4.36 (1H, s), 4.64 (1H, d, J = 15.1 Hz), 4.74 (1H, d, J = 15.1 Hz), 7.21～7.40 (10H, m): MS m/z 449 (M^+).

8a-Carboethoxy-2-cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-methoxyphenyl)-*cis*-1-oxodecahydroisoquinoline (4d)

A stirred solution of 8a-carboethoxy-2-cyclopropylmethyl-4a-(3-methoxyphenyl)-*cis*-1,6-dioxodecahydroisoquinoline (**3d**) (90 mg, 0.23 mmol), ethylene glycol (70 μL, 1.13 mmol) and *p*-toluenesulfonic acid (8.6 mg, 0.045 mmol) in benzene (6 mL) was refluxed for 2 h with Dean-Stark apparatus. The reaction mixture was cooled to rt, and diluted with ethly acetate. The resulting mixtre was washed with saturated

sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (6 g) (eluted with n-hexane / ethyl acetate 3:1, 1:2 v/v) to afford 72 mg (72%) of ketal (**4 d**) as a colorless oil in lower polar fraction and 22 mg (22%) of vinyl ether (**5 d**) as a colorless oil in higher polar fraction. Compound (**4 d**): IR (neat) 1730, 1636, 1584, 1495 cm^{-1}; ^{1}H-NMR (400 MHz) δ 0.21~0.36 (2H, m), 0.46~0.59 (2H, m), 0.96 and 1.05 (3H, each t, each J = 7.3 Hz), 1.06 (1H, m), 1.56 (1H, m), 1.81 (1H, m), 2.11 (1H, m), 2.21 (2H, s), 2.43 (1H, m), 2.60 (1H, m), 2.77 (1H, m), 3.28~3.42 (2H, m), 3.43 (1H, m), 3.58 (1H, m), 3.78 and 3.79 (3H, each s), 3.86~4.02 (6H, m), 6.74 (1H, dd, J = 2.0 and 7.8 Hz), 7.07 (1H, dd, J = 2.0 and 7.8 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.32 (1H, t, J = 2.0 Hz); HRMS Calcd for $C_{25}H_{33}NO_6$ (M^+): 443.2308. Found : 443.2330.

2-Benzyl-6,6-ethylenedioxy-4a-phenyl-1-oxodecahydroisoquinoline (6a, 7a)

To a stirred suspension of sodium hydride (60% dispersion in mineral oil) (170 mg, 4.25 mmol) in anhydrous DMF (7 mL) at room temperature was added ethanethiol (0.58 mL, 7.79 mmol) dropwise under argon. After stirring for 10 minutes, a solution of 2-benzyl-8a-carboethoxy-6,6-ethylene-dioxy-4a-phenyl-*cis*-1-oxodecahydroisoquinoline (**4 a**) (318 mg, 0.71 mmol) in anhydrous DMF (5 mL) was added to the above mixture, and the resulting mixture was heated at 80℃ for 6 h. The reaction mixture was concentrated under reduced puressure below 50℃ to give residue which was diluted with ethyl acetate. The resulting solution was washed with saturated ammonium chloride solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (12 g) (eluted with n-hexane / ethyl acetate 2:1, 1:1, 1:2 v/v) to afford 245 mg (95.2%) of *trans*-lactam (**6 a**) and *cis*-lactam (**7 a**) (**6 a**:**7 a**=*ca.* 8:1 mixture) as white solid. The obtained mixture was recrystallized from ether / n-hexane to give pure *trans* isomer (**6 a**). Compund (**6 a**): mp 148~150℃ (ether / n-hexane): IR (KBr) 1634, 1495, 1452 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.68 (2H, d, J = 13.2 Hz), 1.84~1.97 (3H, m), 2.10 (1H, m), 2.40~2.61 (4H, m), 2.99 (1H, m), 3.49 (1H, dt, J = 6.8 and 8.3 Hz), 3.61 (1H, ddd, J = 5.4, 6.8 and 8.3 Hz), 3.79 (1H, dd, J = 6.8 and 14.2 Hz), 3.85 (1H, m), 4.24 (1H, d, J = 14.7 Hz), 4.71 (1H, d, J = 14.7 Hz), 7.12~7.32 (10H, m): MS m/z 377 (M^+); Anal. Calcd for $C_{24}H_{27}NO_3$: C, 76.37; H, 7.21; N, 3.71. Found : C, 76.24; H, 7.27, N, 3.64. Compund (**7 a**): ^{1}H-NMR (400 MHz) δ 1.55~1.70 (2H, m), 1.80~2.10 (5H, m), 2.36~2.55 (3H, m), 2.82 (1H, m), 2.94 (1H, m), 3.90~3.94 (2H, m), 3.97~4.04 (2H, m), 4.29 (1H, d, J = 14.7 Hz), 4.58 (1H, d, J = 14.7 Hz), 7.00 (2H, m), 7.15~7.34 (8H, m).

2-Cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-methoxyphenyl)-1-oxodecahydroisoquinoline (6d, 7d)

To a stirred suspension of sodium hydride (60% dispersion in mineral oil) (22.6 mg, 0.564 mmol) in anhydrous DMF (1 mL) at rt was added ethanethiol (84 μL, 1.13 mmol) dropwise under argon. After stirring for 10 min, a solution of 8a-carboethoxy-2-cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-

methoxyphenyl)-*cis*-1-oxodecahydroisoquinoline (**4 d**) (50 mg, 0.113 mmol) in anhydrous DMF (1 mL) was added to the above mixture, and the resulting mixture was heated at 80℃ for 3 h. The reaction mixture was concentrated under reduced puressure below 50℃ to give residue which was diluted with ethyl acetate. The resulting solution was washed with saturated ammonium chloride solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (5 g) (eluted with n-hexane / ethyl acetate 2:1, 3:2, 1:1, 1:2 v/v) to afford 40 mg (95%) of *trans*-lactam (**6 d**) and *cis*-lactam (**7 d**) (**6d:7d** = *ca.* 8:1 mixture) as colorless oil. Compund (**6 d+7 d**): IR (neat) 1634, 1584, 1491, 1452, 1435 cm^{-1}: Compound (**6 d**): ^{1}H-NMR (400 MHz) δ 0.11 (1H, m), 0.21 (1H, m), 0.30~0.46 (2H, m), 0.84 (1H, m), 1.64 (1H, m), 1.84 (1H, m), 1.97~2.03 (2H, m), 2.10 (1H, dq, J = 3.9 and 13.2 Hz), 2.36 (1H, dd, J = 3.2 and 12.5 Hz), 2.51 (1H, d, J = 2.4 Hz), 2.55 (1H, d, J = 2.4 Hz), 2.70 (1H, m), 2.99 (1H, dd, J = 6.8 and 13.7 Hz), 3.11 (1H, m), 3.32 (2H, dd, J = 6.8 and 13.7 Hz), 3.55 (1H, t, J = 6.8 Hz), 3.65 (1H, m), 3.77 (3H, s), 3.81 (1H, m), 3.87 (1H, m), 6.72 (1H, dd, J = 2.4 and 8.3 Hz), 6.80 (1H, t, J = 2.4 Hz), 6.82 (1H, d, J = 8.3 Hz), 7.18 (1H, t, J = 8.3 Hz): Compound (**7 d**): ^{1}H-NMR (400 MHz) δ 4.00 (0.37H, s): Compund (**6 d+7 d**): MS m/z 371 (M^+).

2-Benzyl-6,6-ethylenedioxy-4a-phenyl-*trans*-decahydroisoquinoline (9a)

Procedure A: To a stirred solution of 2-benzyl-6,6-ethylenedioxy-4a-phenyl-1-oxodecahydroisoquinoline (**6 a+7 a** : *ca.* 8:1 mixtuire) (52 mg, 0.14 mmol) in anhydrous THF (1.5 mL) at 0℃ was added 0.9M diisobutylalminum hydride n-hexane solution (0.81 mL, 0.73 mmol) dropwise under argon, and the mixture was continued to stir at rt for 30 min. The reaction mixture was carefully treated with methanol (3 mL), and stirred for 20 min, and then concentrated under reduced puressure to give a residue. The resulting residue was treated with 3N sodium hydroxide solution (10 mL), and extracted with chloroform three times. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 42.5 mg of the enamine (**8 a**), which was used for next reaction without further purification.

To a stirred mixture of the enamine (**8 a**) (42.5 mg) and sodium cyanoborohydride (26 mg, 0.41 mmol) in methanol (2 mL) at -10℃ was added saturated hydrochloric acid-methanol solution dropwise until the mixture indicated pH 3-4, and stirring was continued for 30 min. The reaction mixture was concentrated under reduced puressure to give a residue which was dissolved in chloroform. The resulting organic layer was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (5 g) (eluted with chloroform / methanol 60:1 v/v) to afford 37 mg (74%) of 4a-aryldecahydroisoquinoline (**9 a**) as a colorless oil.

Procedure B: To a stirred suspension of lithium aluminum hydride (5.3 mg, 0.133 mmol) in anhydrous THF (1 mL) at rt was added 2-benzyl-6,6-ethylenedioxy-4a-phenyl-*trans*-1-oxodecahydroisoquinoline

(**6a**) (10 mg, 0.027 mmol) under argon, and the mixture was stirred for 16 h at rt. The reaction mixture was diluted with ether (10 mL), and treated with saturated sodium potassium tartarate solution for 1 h with stirring. The resulting white suspension was filtered througth celite by suction, and the filtrate was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (400 mg) (eluted with chloroform / methanol 50:1 v/v) to afford 8.7 mg (89%) of 4a-aryldecahydroisoquinoline (**9a**) as a colorless oil. Compound (**8a**): IR (neat) 1659, 1493, 1448 cm^{-1}. Compoun (**9a**): IR (neat) 1497, 1448 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.57～1.64 (2H, m), 1.69～1.80 (4H, m), 1.98～2.07 (2H, m), 2.27 (1H, dq, J = 4.9 and 13.2 Hz), 2.39 (1H, dd, J = 2.4 and 13.7 Hz), 2.54 (1H, m), 2.75～2.88 (2H, m), 3.30 (1H, dd, J = 7.3 and 15.1 Hz), 3.40～3.50 (1H, m), 3.52 (1H, m), 3.73 (1H, dd, J = 7.3 and 14.2 Hz), 3.81 (1H, dt, J = 4.9 and 7.3 Hz), 7.13 (1H, t, J = 7.3 Hz), 7.24～7.32 (7H, m), 7.41 (2H, d, J = 7.3 Hz); MS m/z 363 (M^+).

2-Cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (9d)

To a stirred solution of 2-cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-methoxyphenyl)-1-oxodecahydroisoquinoline (**6d+7d** : *ca.* 8:1 mixtuire) (13 mg, 0.035 mmol) in anhydrous THF (0.5 mL) at 0℃ was added 0.9M diisobutylaluminum hydride n-hexane solution (0.2 mL, 0.18 mmol) dropwise under argon, and the mixture was continued to stir at 0℃ for 15 min and at rt for 30 min. The reaction mixture was carefully treated with methanol (3 mL), and stirred for 15 min, and then concentrated under reduced puressure to give a residue. The resulting residue was treated with 3N sodium hydroxide solution (4 mL), and extracted with chloroform three times. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 13.7 mg of the enamine (**8d**), which was used for next reaction without further purification.

To a stirred mixture of the enamine (**8d**) (13.7 mg) and sodium cyanoborohydride (6.6 mg, 0.105 mmol) in methanol (0.5 mL) at 0℃ was added saturated hydrochloric acid-methanol solution dropwise until the mixture indicated pH 3-4, and stirring was continued for 15 min. The reaction mixture was concentrated under reduced puressure to give a residue which was dissolved in chloroform. The resulting organic layer was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (4 g) (eluted with chloroform / methanol 10:1 v/v) to afford 10 mg (80%) of 4a-aryldecahydroisoquinoline (**9d**) as a colorless oil. Compound (**8d**): IR (neat) 1659, 1605, 1582, 1487 cm^{-1}; ^{1}H-NMR (90 MHz) δ 0.02～0.17 (2H, m), 0.39～0.60 (2H, m), 0.91 (1H, m), 1.51～2.80 (12H, m), 3.55～3.94 (4H, m), 3.80 (3H, s), 4.09 (1H, br s), 6.70 (1H, m), 6.92～7.32 (3H, m); MS m/z 355 (M^+). Compund (**9d**): IR (neat) 1607, 1582, 1491, 1458 cm^{-1}; ^{1}H-NMR (400 MHz) δ 0.02～0.11 (2H, m), 0.43～0.52 (2H, m), 0.78～0.88 (1H, m), 1.56 (1H, d, J = 13.7 Hz), 1.63～1.73 (1H, m), 1.73～1.83 (4H, m), 1.98～2.08 (2H, m), 2.17 (1H, dd, J = 6.6 and 12.5 Hz), 2.23～2.36 (2H, m), 2.39 (1H, dd, J = 2.2 and 13.5 Hz), 2.71～2.76 (1H, m), 2.79 (1H, dd, J = 12.0 and 12.0 Hz), 2.95 (1H, br dd, J = 3.4 and 11.2 Hz), 3.36

(1H, ddd, J = 7.3, 7.3 and 7.8 Hz), 3.57 (1H, ddd, J = 5.4, 6.8 and 7.8 Hz), 3.75 (1H, ddd, J = 6.8, 7.3 and 7.3 Hz), 3.80 (3H, s), 3.82 (1H, ddd, J = 5.4, 7.3 and 7.3 Hz), 6.66 (1H, dd, J = 2.2 and 8.1 Hz), 6.97 (1H, br s), 7.02 (1H, br d, J = 8.1 Hz), 7.19 (1H, dd, J = 8.1 and 8.1 Hz): HRMS Calcd for $C_{22}H_{31}NO_3$ (M^+): 357.2304. Found : 357.2302.

2-Benzyl-4a-phenyl-*trans*-6-oxodecahydroisoquinoline (10a)

A solution of 2-benzyl-6,6-ethylenedioxy-4a-phenyl-*trans*-decahydroisoquinoline (**9a**) (57 mg, 0.16 mmol) in 1N sulfuric acid (4.5 mL) was stirred at 25℃ for 24 h. The reaction mixture was alkalified by treatment with 5% sodium hydroxide solution, and extracted with chloroform three times. The combined organic layer was washed with brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 51 mg (quantitative yield) of ketone (**10a**) as a colorless oil : IR (neat) 1713 cm^{-1}; ^{1}H-NMR (400 MHz) δ 1.89～2.00 (3H, m), 2.03 (1H, m), 2.23～2.56 (5H, m), 2.63 (1H, m), 2.72 (1H, t, J = 11.5 Hz), 2.87 (1H, dd, J = 3.4 and 11.5 Hz), 2.95 (1H, dd, J = 1.5 and 13.7 Hz), 3.53 (2H, s), 7.17 (1H, t, J = 7.3 Hz), 7.27～7.34 (7H, m), 7.41 (2H, d, J = 7.3 Hz); MS m/z 319 (M^+), 228 (M^+-$C_6H_5CH_2$).

2-Cyclopropylmethyl-4a-(3-methoxyphenyl)-*trans*-6-oxodecahydroisoquinoline (10d)

A solution of 2-cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (**9d**) (10 mg, 0.028 mmol) in 1N sulfuric acid (1 mL) was stirred at 25℃ for 10 h. The reaction mixture was alkalified by treatment with saturated sodium bicarbonate solution, and extracted with ethyl acetate two times. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude residue which was subjected to column chromatography (3 g) (eluted with chloroform / methanol 10:1 v/v) to afford 7.5 mg (86%) of ketone (**10d**) as a colorless oil: IR (neat) 1717, 1605, 1582 cm^{-1}; ^{1}H-NMR (400 MHz) δ 0.05～0.11 (2H, m), 0.47～0.53 (2H, m), 0.89 (1H, m), 1.90～2.07 (4H, m), 2.19～2.44 (6H, m), 2.56 (1H, m), 2.74 (1H, t, J = 11.7 Hz), 2.84 (1H, dd, J = 1.5 and 14.2 Hz), 2.91 (1H, m), 3.11 (1H, br dd), 3.71 (3H, s), 6.65 (1H, m), 6.87～6.92 (2H, m), 7.15 (1H, t, J = 8.3 Hz): HRMS Calcd for $C_{20}H_{27}NO_2$ (M^+): 313.2042. Found : 313.2061.

2-Cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-hydroxyphenyl)-*trans*-decahydroisoquinoline (11)

To a stirred solution of 2-cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (**9d**) (916 mg, 2.56 mmol) in anhydrous DMF (20 mL) at rt was added 1-propanethiol (1.16 mL, 12.8 mmol) and potassium *tert*-butoxide (865 mg, 7.71 mmol) under argon, the mixture was heated at 150℃ for 7 h. After cooling to rt, the reaction solvent was removed under reduced pressure. The resulting residue was treated with saturated sodium bicarbonate solution (25 mL), and extracted with a mixture of chloroform / ethanol (3:1 v/v) (25 mL) three times. The combined organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave 792 mg (90%) of almost pure phenol (**11**) as a solid which was further purified by recrystallization from methanol to afford 547 mg of the phenol (**11**): mp 197.5～199.0℃ (methanol); IR (KBr) 3400, 3028, 1620, 1580, 1499, 1367, 1274, 1089, 913, 777 cm^{-1};

^{1}H-NMR (400 MHz) δ 0.02~0.11 (2H, m), 0.43~0.51 (2H, m), 0.81~0.89 (1H, m), 1.55 (1H, d, J = 13.4 Hz), 1.60~1.90 (1H, br s, OH), 1.63~1.68 (1H, m), 1.68~1.83 (4H, m), 1.97~2.08 (2H, m), 2.20 (1H, dd, J = 6.7 and 12.5 Hz), 2.24~2.34 (2H, m), 2.35 (1H, dd, J = 2.3 and 13.6 Hz), 2.73~2.77 (1H, m), 2.81 (1H, dd, J = 11.9 and 11.9 Hz), 2.97 (1H, br dd, J = 3.3 and 11.3 Hz), 3.38 (1H, ddd, J = 7.0, 7.3 and 7.6 Hz), 3.58 (1H, ddd, J = 5.2, 7.0 and 7.6 Hz), 3.75 (1H, ddd, J = 7.0, 7.0 and 7.0 Hz), 3.81 (1H, ddd, J = 5.2, 7.0 and 7.3 Hz), 6.57 (1H, dd, J = 2.1 and 7.9 Hz), 6.88 (1H, br s), 6.94 (1H, br d, J = 7.9 Hz), 7.12 (1H, dd, J = 7.9 and 7.9 Hz); MS m/z 343 (M^+); Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.04. Found : C, 73.26; H, 8.44, N, 4.13.

2-Cyclopropylmethyl-4a-(3-hydroxyphenyl)-*trans*-6-oxodecahydroisoquinoline (12)

To a stirred solution of 2-cyclopropylmethyl-6,6-ethylenedioxy-4a-(3-hydroxyphenyl)-*trans*-decahydroisoquinoline (**11**) (508 mg, 1.48 mmol) in 1,4-dioxane (7.5 mL) at rt was added 3N hydrochloric acid solution (2.5 mL), and the mixture was continued to stir for 40 min. The reaction mixture was treated with saturated sodium bicarbonate solution (30 mL), and extracted with a mixture of chloroform / ethanol (3:1 v/v) (30 mL) three times. The combined organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave a solid residue which was recrystallized from methanol / ethyl acetate two times to afford 346 mg (78%) of ketone (**12**) as white needle crystals: mp 201.5~204.0℃ (methanol / ethyl acetate); IR (KBr) 3400, 3028, 1711, 1584, 1491, 1354, 1232, 1214, 1056, 874, 791, 731 cm^{-1}; ^{1}H-NMR (400 MHz) δ 0.07~0.14 (2H, m), 0.47~0.55 (2H, m), 0.83~0.93 (1H, m), 1.92~2.08 (4H, m), 2.27~2.59 (7H, m), 2.72 (1H, dd, J = 11.7 and 11.7 Hz), 2.85~2.93 (2H, m), 3.07 (1H, br dd, J = 3.9 and 11.7 Hz), 3.20~4.50 (1H, br s, OH), 6.61 (1H, dd, J = 2.0 and 7.8 Hz), 6.88 (1H, br s), 6.95 (1H, br d, J = 7.8 Hz), 7.12 (1H, dd, J = 7.8 and 7.8 Hz); MS m/z 299 (M^+); Anal. Calcd for $C_{19}H_{25}NO_2 \cdot 0.1H_2O$: C, 75.76; H, 8.48; N, 4.65. Found : C, 75.67; H, 8.38, N, 4.68.

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