ESTABLISHMENT OF EFFICIENT HYDROXYLATION AT ANGULAR POSITION OF 4a-ARYL-*trans*-DECAHYDRO-ISOQUINOLINES

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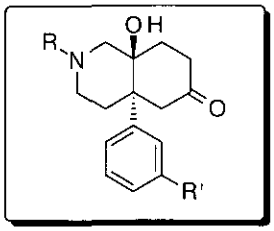
Abstract—Efficient hydroxylation method at angular 8a position of 4a-aryl-*trans*-decahydroisoquinolines was described. By utilizing the transformation process, syntheses of 2-methyl- and 2-cyclopropylmethyl-8a-hydroxy-4a-(3-methoxy-phenyl)-6-oxo-*trans*-decahydroisoquinolines (**13** and **17**), the useful molecules as an opioid message substructure, were attained. The key step in this transformation was *N*-protection of enamine intermediate by 2,2,2-trichloroethoxycarbonyl chloride and subsequent epoxidation and hydride reduction.

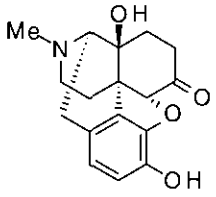
Classification of opioid receptors into three different types (μ, δ, and κ) has been established by not only pharmacological but also molecular biological study.[1] And many opioid ligands, highly selective and potent for each opioid receptor type, have been reported.[2] Some of them were rationally 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 sufficient pharmacophores to bind to opioid receptors on its own molecule and to have functional group at suitable position in its structure in order to construct an address moiety. As one of the target compound of this message moiety, we have recently reported the effective synthesis of 4a-aryl-6-oxo-*trans*-decahydroisoquinolines (Figure 1).[5] Moreover, there have been many reports suggesting the importance of angular (8a position of decahydroisoquinolines) hydroxy group to set ligands pharmacology in the opioid field.[6] For example, dihydrooxymorphone

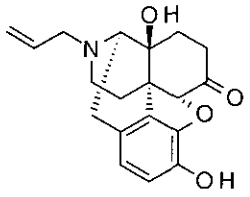
showed higher analgesic activity than morphine, and naloxone which has hydroxy group at the angular position was a pure antagonist but nalorphine was a partial agonist. Therefore, 6-oxo-*trans*-decahydroisoquinolines having 8a-hydroxy substituent would be attractive as the message substructure.



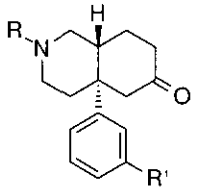
4a-aryl-8a-hydroxy-6-oxo-*trans*-decahydroisoquinolines



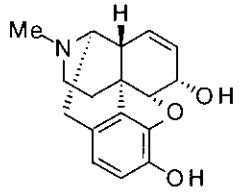
dihydrooxymorphone



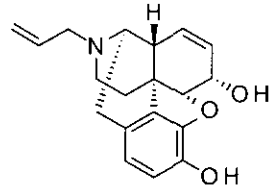
naloxone



4a-aryl-6-oxo-*trans*-decahydroisoquinolines



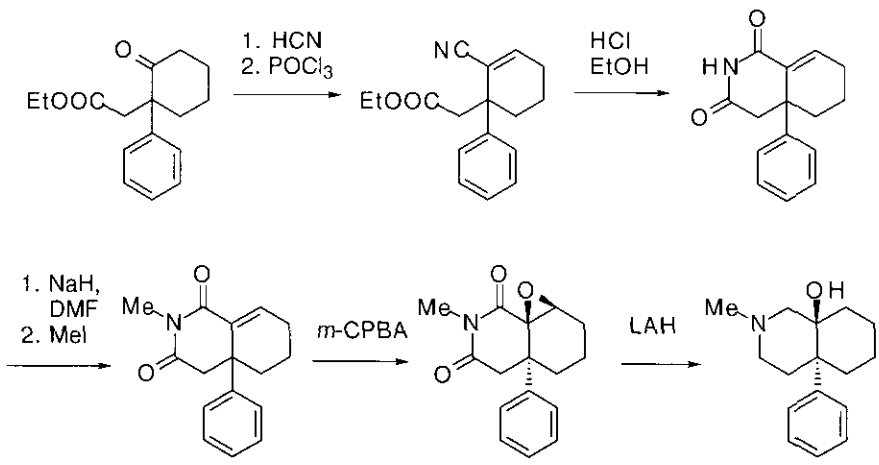
morphine



nalorphine

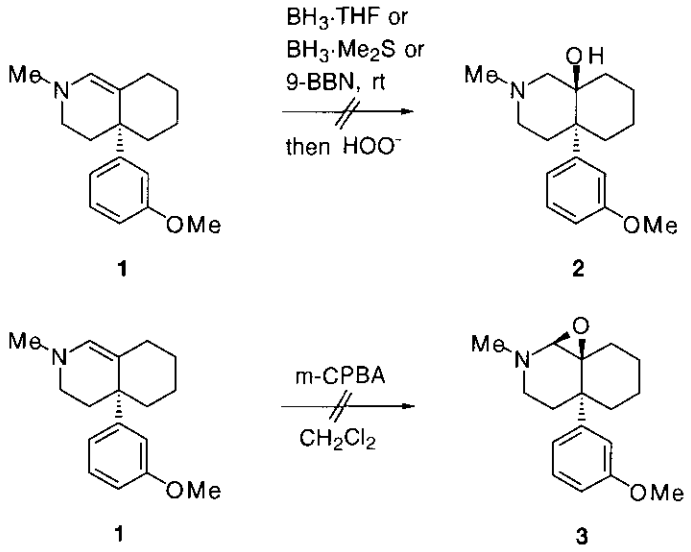
Figure 1. Structural comparison of opioid ligands

There has been only one patent on the synthesis of *trans*-4a-aryl-8a-hydroxydecahydroisoquinolines.[7] This patent showed brief information of the synthetic route and conditions to 4a-aryl-8a-hydroxy-*trans*-decahydroisoquinolines (Scheme 1), but no way to the corresponding 6-oxo derivatives. In this paper, we wish to describe a general and short synthetic transformation from enamine intermediate to 4a-aryl-8a-hydroxy-6-oxo-*trans*-decahydroisoquinolines by introduction of hydroxy group at angular 8a position.



Scheme 1. Reported patent method to synthesize a 4a-aryl-8a-hydroxy-*trans*-decahydroisoquinoline

Our starting material was enamine intermediate (Scheme 2) which was conveniently obtained by our's[5] and Zimmermann's method.[8] Previous reports showed that β-hydroxylation of enamines was attained by sequential hydroboration-oxidation reaction.[9] At first, we applied the similar conditions to perform 4a-(3-methoxyphenyl)-2-methyl-2,3,4,4a,5,6,7,8-octahydroisoquinoline (**1**) as a model case.



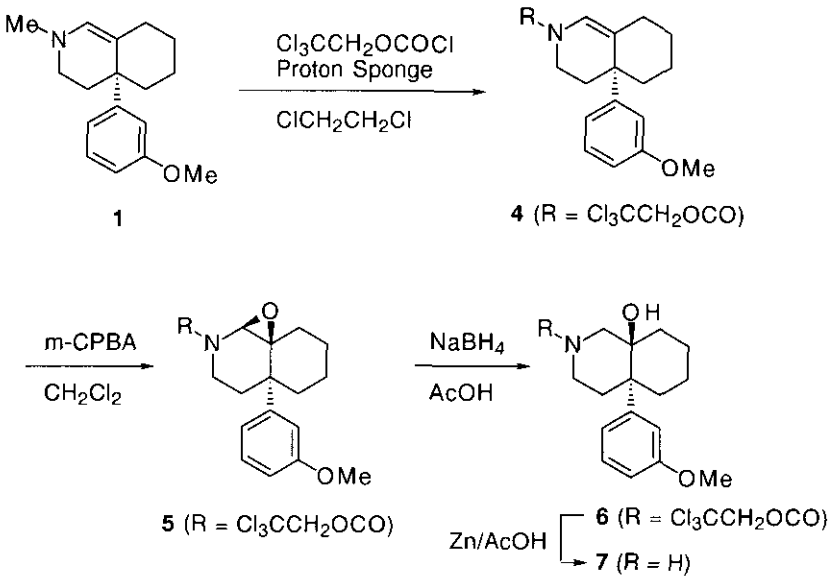
Scheme 2. Synthetic approach of β-hydroxylation of enamine (**1**)

Thus, enamine (**1**) was treated with boran reagent, e.g. boran THF complex, boran dimethyl sulfide complex or 9-BBN in THF at room temperature, followed by alkaline hydrogen peroxide to give only a starting material but no hydroxylated desired compound (**2**). This result may come from the steric hindrance of β-position of the enamine (**1**), because there has been scarcely report of β-hydroxylation of β,β-disubstituted enamines. Then, direct epoxidation of enamine (**1**) was attempted (Scheme 2). In this case, the reaction afforded unidentified highly polar byproducts that might be caused by *N*-oxidation of electron rich enamine system.

Finally, we succeeded the β-hydroxylation of enamine (**1**) by use of epoxidation-reduction route after *N*-protection as below (Scheme 3).

There have been many reports of *N*-protection of ordinary tertially amines by deriving to carbamates using alkoxycarbonyl chloride,[10] but it has not been reported whether this method can be applied to enamine moiety or not. After some trials to set the suitable conditions, we found that enamine (**1**) was transformed into carbamate (**4**) (almost 100% yield) by treatment with 2,2,2-trichloroethoxycarbonyl chloride and 1,8-bis(dimethylamino)naphthalene (Proton Sponge) in 1,2-dichloroethane at room temperature. This intermediate was very useful for its higher stability than corresponding enamine (**1**) and for its convenience to derive message substructure having various *N*-substitution group. The next step is the epoxidation of olefin and subsequent reduction to give target hydroxylated compound at the angular position. This

transformation was achieved by the following method: epoxidation of **4** with *m*-CPBA in dichloromethane and reduction of **5** with sodium borohydride in acetic acid to give desired compound (**6**) (74%, two steps).



Scheme 3. Synthetic route of 4a-aryl-8a-hydroxy-*trans*-decahydroisoquinoline

The product (**6**) was converted into secondary amine (**7**) (83%), and the stereochemistry of compound (**7**) was assigned by NOESY spectrum. Figure 2 shows possible stereostructures of compound (**7**) marked with alphabetical character in order of the proton peak from upfield to downfield on the ^{1}H-NMR spectrum ((H_c, H_d) and (H_h, H_i) were observed at almost the same chemical shift on the spectrum, so they are expressed H_{cd} and H_{hi}), and Table 1 shows hydrogen combinations which were observed as cross peaks on NOESY spectrum.

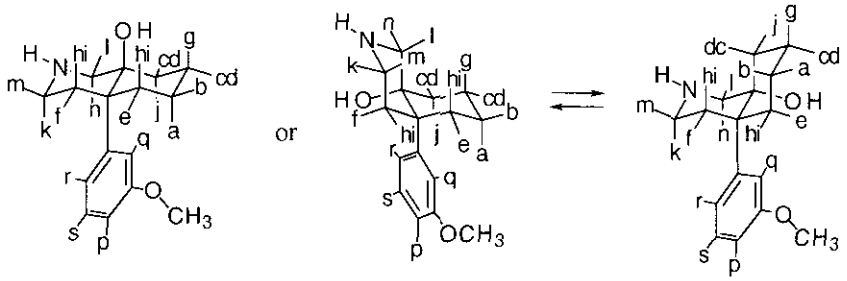


Figure 2. Possible stereostructures of compound (**7**)

Table 1. Cross peaks on the NOESY spectrum of compound (7).

Peak (ppm)	cross peaks	Peak (ppm)	cross peaks	Peak (ppm)	cross peaks
a (0.92)	b,cd,e	h (2.11)	b,e,f,m	o (3.81)	p,q
b (1.34)	a,cd,e,g,hi	i (2.16)	b,e,f,m	p (6.69)	o
c (1.50)	g,j,l	j (2.27)	cd,q,r	q (7.06)	e,f,j,n,o
d (1.51)	g,j,l	k (2.34)	f,m,n	r (7.08)	e,f,j,n
e (1.65)	f,hi,q,r	l (2.53)	cd,n	s (7.21)	r,q
f (1.69)	e,hi,k,m,q,r	m (2.63)	f,hi,k		
g (1.87)	b,cd	n (2.57)	k,l,q,r		

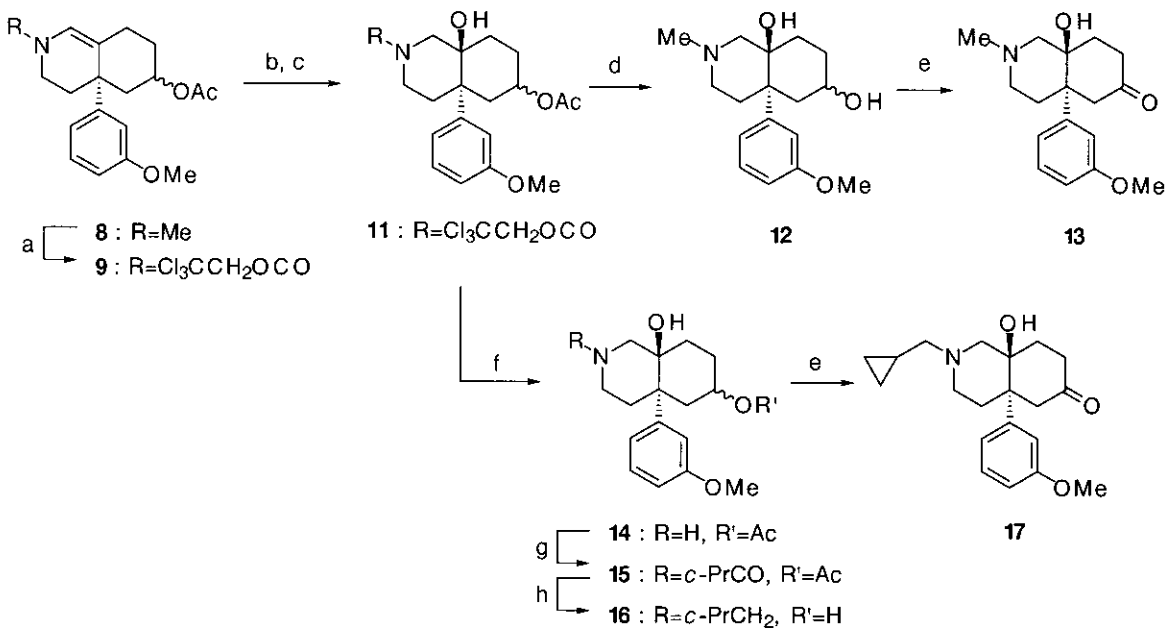
For example, observations of positive NOE on the hydrogen combinations of H_a - H_e, H_b - (H_e, H_{hi}) but of no NOE on the hydrogen combinations of H_a - H_{hi} in the adjacent methylene peaks of (H_a, H_b) and (H_e, H_{hi}) indicated that the hydrogen combinations of H_a - H_{hi} should be *trans*-diaxial conformation. Similarly, H_g, H_j, H_k, and another H_{hi} should be axial conformation. These observations lead us to determine that the ring juncture of compound (**7**) is *trans*, because assuming that the ring juncture of compound (**7**) is *cis*, conformations of these hydrogens should be inter convertible between axial and equatorial, and positive NOE should be observed all of the hydrogen combinations in the adjacent methylene peaks. Observations of positive NOE on the hydrogen combinations of (H_q, H_s) - (H_e, H_f, H_j, H_n) are consistent with above estimation. In the course of above epoxidation-reduction reaction, no *cis*-fused isomer was detected.

The hydroxylation method described above could also be applied to the 6-substituted enamine (**8**),[8] and the synthesis of desired message molecule was achieved (Scheme 4). Thus, 6-acetoxy-4a-(3-methoxyphenyl)-2-methyl-2,3,4,4a,5,6,7,8-octahydroisoquinoline (**8**) and 2,2,2-trichloroethoxycarbonyl chloride were stirred in 1,2-dichloroethane with Proton Sponge to give carbamate (**9**) (72%). Epoxidation with *m*-CPBA and reduction with sodium borohydride were similarly conducted to afford hydroxylated compound (**11**) (63%, two steps). *N*-Methyl derivative (**13**) of 8a-hydroxy-6-oxo-*trans*-decahydroisoquinoline was obtained by hydride reduction with lithium aluminum hydride and Swern oxidation using oxalyl chloride, DMSO, and triethylamine (71%, 77% respectively).

On the other hand, *N*-cyclopropylmethyl derivative (**17**) was synthesized by following method: 1) deprotection of 2,2,2-trichloroethoxycarbonyl group of compound (**11**) under zinc/acetic acid condition (72%), 2) amide formation of the resulting secondary amine (**14**) by using cyclopropanecarbonyl chloride and Proton Sponge (91%), 3) reduction of the amide (**15**) with lithium aluminum hydride, 4) oxidation of the resulting alcohol (**16**) using Swern method to furnish desired 8a-hydroxy-6-oxo compound (**17**).

In summary, we have established efficient hydroxylation method at angular 8a position of 4a-aryl-*trans*-decahydroisoquinolines. By using the transformation process, 2-methyl- and 2-cyclopropylmethyl-8a-hydroxy-4a-(3-methoxyphenyl)-6-oxo-*trans*-decahydroisoquinolines (**13** and **17**), remarkably useful

molecules as an opioid message moiety, were synthesized from the conveniently available enamine intermediates. This new regioselective hydroxylation method disclosed above could be applicable to the syntheses of the variety of pharmacologically unique opioid ligands. Moreover, introduction of hydroxyl group to the β-position of β,β-disubstituted enamines could be attained using disclosed method.



(a) Cl_3CH_2OCOCl, Proton Sponge, $ClCH_2CH_2Cl$, rt, 15 h (b) *m*-CPBA, 0 °C, 15 min
(c) $NaBH_4$, AcOH, 0 °C - rt, 15 min (d) $LiAlH_4$, THF, rt, 30 min
(e) $(COCl)_2$, DMSO,CH_2Cl_2, -55 °C, 30 min; then Et_3N, -55 °C - rt (f) Zn, AcOH, rt, 4 h
(g) *c*-PrCOCl, Proton Sponge, $ClCH_2CH_2Cl$, 5 min (h) $LiAlH_4$, THF, 0 °C - rt, 3 h

Scheme 4. Syntheses of 4a-aryl-6-oxo-*trans*-decahydroisoquinolines

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) spectrometer or JEOL GX-400 (400 MHz) spectrometer or JEOL GSX-500 (500 MHz) spectrometer and reported in δ (ppm) downfield from tetramethylsilane (TMS). IR were determined on a JASCO FT/IR-5000 as KBr pellets or neat. MS spectra were obtained on a JEOL JES-D-300 or JEOL JMS-D-303 or VG ZAB-HF instrument applying an electric ionization method (EI). 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) or Merck Lobar column (Art. 10401). CH_2Cl_2 and DMSO were distilled from CaH_2, and THF was distilled from benzophenone ketyl just prior to use.

2-(2,2,2-Trichloroethoxycarbonyl)-4a-(3-methoxyphenyl)-2,3,4,4a,5,6,7,8-octahydroisoquinoline (4).

To a solution of **1** (1.41 g, 5.47 mmol) and Proton Sponge (0.50 g, 2.40 mmol) in 1,2-dichloroethane (15 mL) at 0 ℃ under an argon atmosphere was added 2,2,2-trichloroethyl chloroformate (1.13 mL, 8.21 mmol). After stirring at rt for 24 h, the solvent was removed *in vacuo* and ether (15 mL) was added. The mixture was washed with 1N HCl (10 and 6 mL) and saturated NaCl solution (10 mL), dried (Na_2SO_4), and the organic solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with cyclohexane-ethyl acetate (5:1) to give 2.30 g (100%) of **4** as a pale yellow oil. IR (neat) 2936, 1763, 1717, 1667, 1607, 1582, 1412, 1125, 1054, 820, 706 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.15-1.25 (1H, m), 1.26-1.27 (1H, m), 1.40-1.49 (1H, m), 1.52-1.60 (1H, m), 1.66-1.72 (1H, m), 1.80-1.93 (2H, m), 2.15-2.21 (2H, m), 2.56 (1H, d, J = 13.4 Hz), 2.90-3.01 (1H, m), 3.80 (3H, s), 3.83-3.90 (1H, m), 4.79-4.88 (2H, m), 6.75 (1H, dd, J = 7.9, 2.5 Hz), 6.87 (1H, s), 6.92 (2H, d, J = 8.5 Hz), 7.26 (1H, t, J = 7.9 Hz); HRMS (EI) Calcd for $C_{19}H_{22}NO_3Cl_3$: 417.0668. Found : 417.0643.

2-(2,2,2-Trichloroethoxycarbonyl)-8a-hydroxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (6).

To a solution of **4** (0.94 g, 2.24 mmol) in CH_2Cl_2 (20 mL) at 0 ℃ under an argon atmosphere was added *m*-chloroperbenzoic acid (0.55 g, 3.19 mmol). After stirring at rt for 15 min, the solvent was removed *in vacuo*. To a solution of the residue in acetic acid (20 mL) at 0 ℃ was slowly added $NaBH_4$ (0.42g, 6.73 mmol). After stirring at rt for 5 min, the solvent was removed *in vacuo*. The residue was quenched with saturated $NaHCO_3$ solution (20 mL), extracted with EtOAc (2 x 20 mL), dried (Na_2SO_4), and the organic solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with $CHCl_3$ to give 10.8 g (63%) of **6** as a colorless oil: IR (neat) 3460, 2934, 1705, 1607, 1582, 1444, 1245, 1127, 994, 882, 758 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.90-1.01 (1H, m), 1.33-1.40 (1H, m), 1.52-1.60 (2H, m), 1.67-1.76 (2H, m), 1.80-1.90 (1H, m), 2.05-2.12 (1H, m), 2.20-2.40 (2H, m), 2.48-2.63 (1H, m), 3.81 (3H, s), 3.86-4.00 (3H, m), 4.73 (2H, s), 6.73 (1H, dd, J = 8.6, 2.5 Hz), 7.03 (1H, s), 7.06 (1H, d, J = 7.9 Hz), 7.24 (1H, t, J = 7.9 Hz); HRMS (EI) Calcd for $C_{19}H_{24}NO_4Cl_3$: 435.0773. Found : 435.0760.

8a-Hydroxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (7).

A solution of **6** (330 mg, 0.76 mmol) in 90% aqueous acetic acid (12 mL) was treated with Zn (0.37 g, 5.67 mmol) and stirred at rt for 3 h. The insoluble material was filtered off through Celite pad by washing with acetic acid and the filtrate was evaporated *in vacuo*. To the residue was added saturated $NaHCO_3$ solution and the mixture was extracted with $CHCl_3$ (3 x 15 mL). The organic layer was washed with saturated NaCl solution (15 mL), dried ($MgSO_4$), and evaporated *in vacuo* . The residue was chromatographed on silica gel eluting with $CHCl_3$ then 5% MeOH/$CHCl_3$ to give 164 mg (83%) of **7** as a colorless oil: IR (neat) 3358, 2938, 1607, 1582, 1452, 1249, 1054, 886, 712 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.87-0.98 (1H, m), 1.31-1.37 (1H, m), 1.48-1.55 (2H, m), 1.63-1.71 (2H, m), 1.80-1.92 (1H,,m), 2.10-2.19 (2H, m), 2.27 (1H, dt, J = 13.4, 5.5 Hz), 2.35 (1H, dt, J = 12.8, 1.8 Hz), 2.54 (1H, d, J = 11.0 Hz), 2.64 (1H, d, J = 11.6 Hz), 3.59 (1H, d, J = 11.0 Hz), 3.81 (3H, s), 6.69 (1H, dd, J =

7.9, 2.4 Hz), 7.06-7.09 (2H, m), 7.21 (1H, t, J = 7.9 Hz); HRMS (EI) Calcd for $C_{16}H_{23}NO_2$: 261.1730. Found : 261.1756.

6-Acetoxy-2-(2,2,2-trichloroethoxycarbonyl)-4a-(3-methoxyphenyl)-2,3,4,4a,5,6,7,8-octahydroisoquinoline (9).

To a solution of **8** (19.5 g, 61.8 mmol) and Proton Sponge (6.6 g, 30.8 mmol) in 1,2-dichloroethane (100 mL) at 0 ℃ under an argon atmosphere was added 2,2,2-trichloroethyl chloroformate (12.8 mL, 93.0 mmol). After stirring at rt for 15 h, the solvent was removed *in vacuo* and ether (400 mL) was added. The mixture was washed with 1N HCl (2 x 150 mL) and saturated NaCl solution (100 mL), dried (Na_2SO_4), and the organic solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with cyclohexane-ethyl acetate (10:1-5:1) to give 21.2 g (72%) of **15** as a pale yellow oil of diastereomeric mixture at C-6. A more polar fraction (6α-acetoxy isomer, pale yellow oil); IR (neat) 3024, 1717, 1415, 1255, 1216, 758 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.31 (3H, d, J = 4.8 Hz), 1.57-1.65 (2H, m), 1.75-1.86 (2H, m), 1.98-2.06 (1H, m), 2.14-2.23 (1H, m), 2.63-2.74 (1H, m), 2.77-2.88 (1H, m), 3.08 (1H, d, J = 15.1 Hz), 3.80 (3H, s), 3.82-3.89 (1H, m), 4.67-4.85 (2H, m), 4,98 (1H, s), 6.70 (1H, dd, J = 6.3, 2.0 Hz), 6.80 (1H, dd, J = 2.5, 1.9 Hz), 6.85 (1H, d, J = 7.8 Hz), 7.01 (1H, d, J = 7.8 Hz), 7.22 (1H, t, J = 7.8 Hz); HRMS calcd for $C_{21}H_{24}NO_5Cl_3$ 475.0720, found 475.0716. A less polar fraction (6β-acetoxy isomer, pale yellow oil); IR (neat) 2954, 1725, 1410, 1251, 1141, 1046, 754 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.39-1.53 (2H, m), 1.83-2.09 (3H, m), 2.02 (3H, s), 2.25-2.30 (2H, m), 2.83-3.07 (2H, m), 3.82 (3H, s), 3.85-3.95 (1H, m), 4.54-4.61 (1H, m), 4.70-4.88 (2H, m), 6.77 (1H, dd, J = 7.8, 2.4 Hz), 6.91-6.95 (2H, m), 6.98 (1H, d, J = 9.3 Hz), 7.27 (1H, t, J = 7.8 Hz); HRMS calcd for $C_{21}H_{24}NO_5Cl_3$ 475.0720, found 475.0718.

6-Acetoxy-2-(2,2,2-trichloroethoxycarbonyl)-8a-hydroxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (11).

To a solution of **9** (16.5 g, 34.6 mmol) in CH_2Cl_2 (200 mL) at 0 ℃ under an argon atmosphere was added *m*-chloroperbenzoic acid (16.5 g, 95.6 mmol). After stirring at rt for 1.5 h, the solvent was removed *in vacuo*. To a solution of the residue in acetic acid (150 mL) at 0 ℃ was slowly added $NaBH_4$. After stirring at rt for 15 min, the solvent was removed *in vacuo*. The residue was quenched with saturated $NaHCO_3$ solution (300 mL), extracted with EtOAc (3 x 200 mL), dried (Na_2SO_4), and the organic solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$ to give 10.8 g (63%) of **11** as a colorless oil of diastereomeric mixture at C-6. An analytical sample was prepared for only a less polar fraction by chromatography (colorless oil): IR (neat) 3462, 2958, 1715, 1605, 1582, 1437, 1249, 1033, 758 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.55-1.65 (2H, m), 1.65-1.85 (2H, m), 1.92 (3H, s), 1.97-2.18 (2H, m), 2.20-2.57 (3H, m), 3.50 (1H, t, J = 7.8 Hz), 3.79 (3H, s), 3.80-3.95 (2H, m), 4.78 (2H, d, J = 6.5 Hz), 6.68-6.84 (2H, m), 6.92-7.25 (2H, m); HRMS calcd for $C_{21}H_{26}NO_6Cl_3$ 493.0828, found 493.0816.

6,8a-Dihydroxy-4a-(3-methoxyphenyl)-2-methyl-*trans*-decahydroisoquinoline (12).

To a solution of **11** (1.5 g, 3.03 mmol) in dry THF (20 mL) was added $LiAlH_4$ (0.35 g, 9.22 mmol). After stirring at rt for 0.5 h, the mixture was cooled to 0 ℃ and slowly treated with aqueous solution of rochelle salt (potassium sodium tartrate, tetrahydrate). After addition of $CHCl_3$ (20 mL), the insoluble material was filtered through Celite pad washing with $CHCl_3$. The filtrate was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with $CHCl_3$-NH_4OH saturated $CHCl_3$-5% MeOH/NH_4OH saturated $CHCl_3$ to give 0.63 g (71%) of **12** as a solid of diastereomeric mixture at C-6: IR (KBr) 3412, 1599, 1493, 1236, 1071, 893, 795, 723, 540 cm^{-1}; MS (El) m/z 291 (M^+).

8a-Hydroxy-4a-(3-methoxyphenyl)-2-methyl-6-oxo-*trans*-decahydroisoquinoline (13).

A solution of DMSO (330 mg, 4.36 mmol) in dry CH_2Cl_2 (1.5 mL) was added to oxalyl chloride (0.19 mL, 2.18 mmol) in dry CH_2Cl_2 (12 mL) at -55 ℃ under an argon atmosphere. After stirring at -55 ℃ for 2 min, a solution of **12** (0.5 g, 1.72 mmol) in dry CH_2Cl_2 (4 mL) was added and the solution was stirred at -55 ℃ for 0.5 h. Then Et_3N (1.2 mL, 6.09 mmol) was added and the mixture was allowed to warm to rt. The mixture was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 12 mL). The organic layer was washed with saturated NaCl solution (10 mL), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$-2-5% MeOH/$CHCl_3$ to give 0.45 g (91%) of **13**. The obtained solid was recrystallized from n-hexane-EtOAc to give 0.38 g (77%) of **13**: mp 96-97 ℃; IR (KBr) 3406, 2944, 1711, 1605, 1578, 1452, 1257, 1114, 1038, 895, 774, 708 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 1.85-1.93 (2H, m), 2.15-2.32 (3H, m), 2.33 (3H, s), 2.39-2.46, 2.55 (2H, t, J = 11.0 Hz), 2.62-2.66 (1H, m), 2.77 (1H, d, J = 11.0 Hz), 2.79-2.86 (2H, m), 3.13 (1H, d, J = 14.6 Hz), 3.78 (3H, s), 6.72 (1H, dd, J = 7.4, 3.0 Hz), 6.96-6.97 (2H, m), 7.21 (1H, t, J = 8.5Hz); MS (El) m/z 289 (M^+); Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found : C, 70.51; H, 8.05, N, 4.93.

6-Acetoxy-8a-hydroxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (14).

A solution of **11** (2.04 g, 4.12 mmol) in acetic acid (50 mL) was treated with Zn (2.70 g, 41.2 mmol) and stirred at rt for 4 h. The insoluble material was filtered off through Celite pad by washing with acetic acid and the filtrate was evaporated *in vacuo*. To the residue was added saturated $NaHCO_3$ solution (50 mL) and the mixture was extracted with $CHCl_3$ (3 x 50 mL). The organic layer was washed with saturated NaCl solution (50 mL), dried ($MgSO_4$), and evaporated *in vacuo* . The residue was chromatographed on silica gel eluting with $CHCl_3$ then 5% MeOH/NH_4OH saturated $CHCl_3$ to give 0.95 g (72%) of **14** as as a colorless oil of diastereomeric mixture at C-6: IR (neat) 3360, 2936, 1712, 1607, 1582, 1455, 1248, 1053, 888, 713 cm^{-1}; MS (El) m/z 319 (M^+).

6-Acetoxy-2-cyclopropanecarbonyl-8a-hydroxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (15).

A solution of **14** (0.68 g, 2.13 mmol) in dry 1,2-dichloroethane (15 mL) was treated with Proton Sponge (0.46 g, 2.13 mmol) and cyclopropanecarbonyl chloride (0.29 mL, 3.19 mmol) at rt for 30 min. After the concentration of a reaction mixture, the residue was treated with 1N HCl (20 mL) and extracted with ether (2 x 20 mL). The organic layer was washed with saturated NaCl solution (10 mL), dried (Na_2SO_4), and

evaporated *in vacuo* to give 0.75 g of the crude oily product **15** (91%). This material was used for the next step without further purification: IR (neat) 3430, 2944, 1702, 1605, 1582, 1453, 1240, 1029, 750 cm^{-1}; MS (EI) m/z 387 (M^+).

2-Cyclopropylmethyl-6,8a-dihydroxy-4a-(3-methoxyphenyl)-*trans*-decahydroisoquinoline (16).

To a solution of **15** (0.75 g; crude) in dry THF (20 mL) at 0 ℃ was added lithium aluminum hydride (0.24 g, 6.39 mmol) under an argon atmosphere. The mixture was stirred at 0 ℃ for 2 h and at rt for 1 h. The reaction mixture was treated with saturated potassium sodium tartrate (Rochelle salt) solution (5 mL). After addition of $CHCl_3$ (50 mL), the insoluble material was filtered off through Celite pad by washing with $CHCl_3$ and the filtrate was evaporated *in vacuo* to give 0.52 g of the crude oily product **16** (85%). This compound was used for the next step without further purification: IR (neat) 3425, 2940, 1607, 1582, 1444, 1292, 1091, 880, 753 cm^{-1}; MS (EI) m/z 331 (M^+).

2-Cyclopropylmethyl-8a-hydroxy-4a-(3-methoxyphenyl)-6-oxo-*trans*-decahydroisoquinoline (17).

A solution of DMSO (0.24 mL, 3.45 mmol) in dry CH_2Cl_2 (1.0 mL) was added to oxalyl chloride (0.15 mL, 1.73 mmol) in dry CH_2Cl_2 (10 mL) at -55 ℃ under an argon atmosphere. After stirring at -55 ℃ for 2 min, a solution of **16** (0.52 g, 1.57 mmol) in dry CH_2Cl_2 (4 mL) was added and the solution was stirred at -55 ℃ for 30 min. Then Et_3N (1.09 mL, 7.84 mmol) was added and the mixture was allowed to warm to rt. The mixture was treated with H_2O (15 mL) and extracted with CH_2Cl_2 (10 mL). The organic layer was washed with saturated NaCl solution (10 mL), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with $CHCl_3$-2% MeOH/$CHCl_3$ to give 0.32 g (62%, 3 steps) of **17** as a pale yellow oil: IR (neat) 3404, 2940, 1711, 1605, 1582, 1493, 1429, 1241, 1038, 897, 756 cm^{-1}; NMR ($CDCl_3$, 400 MHz) δ 0.11 (2H, d, J = 5.9 Hz), 0.50-0.55 (2H, m), 0.81-0.89 (1H, m), 1.86-1.90 (2H, m), 2.25-2.28 (2H, m), 2.32-2.37 (3H, m), 2.39-2.46 (1H, m), 2.53 (1H, d, J = 14.3 Hz), 2.75-2.87 (4H, m), 3.14 (1H, d, J = 14.3 Hz), 3.77 (3H, s), 6.70-6.72 (1H, m), 6.97-6.98 (2H, m), 7.20 (1H, t, J = 8.8 Hz); HRMS (EI) Calcd for $C_{20}H_{27}NO_3$: 329.1992. Found : 329.1955.

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