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Synthesis of an Enantiomerically Pure Aminoisoquinocarbazole with Antiarrhythmic Activity *via* Lipase-catalyzed Enantioselective Transesterification

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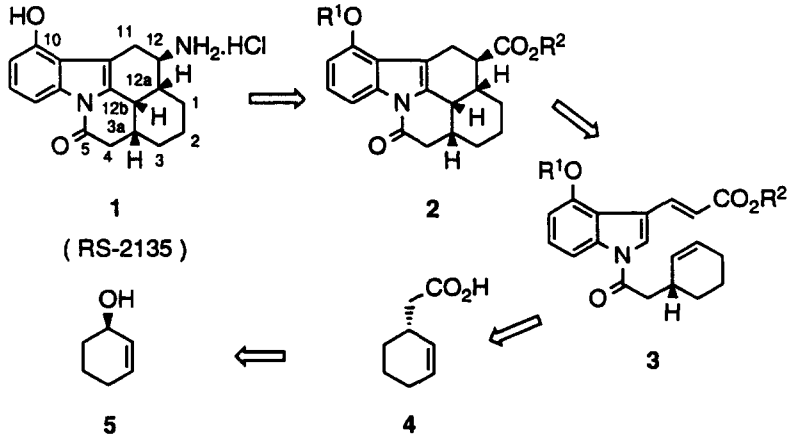
Abstract: Enantiomerically pure (*R*)-2-cyclohexen-1-ol **5** was prepared *via* lipase-catalyzed enantioselective transesterification of 2-substituted cyclohexanol, and stereospecifically converted to (-)-(2-cyclohexenyl)acetic acid **4**. Enantiomerically pure aminoisoquinocarbazole **1** (RS-2135) was synthesized stereoselectively from **4**, using an intramolecular Diels-Alder reaction and Curtius rearrangement.

We disclosed in 1992 that the aminohydroisoquinocarbazoles have potent class 1c antiarrhythmic activity. In particular, the compound (+)-**1** (RS-2135) had the most potent antiarrhythmic activity and relatively low toxicity.[1] As the optically active compound is generally preferable to the racemic one to develop the compound as a medicine which has stereogenic atoms, the practical and economical synthetic method for the optically active compound (+)-**1** was an important consideration.



Scheme 1

Originally the compound (+)-1 was synthesized by the separation of the diastereomeric mixture, which was prepared from the racemic 1 and L-Boc-proline.[1a] However, the synthetic route was not feasible in industrial production because the antipode must be discarded and the large scale separation of the diastereomeric mixture was impractical. Therefore, a more efficient and concise route for the synthesis of (+)-1 was sought. Retro-synthesis of RS-2135 is shown in Scheme 1. As the racemic 2 was stereoselectively synthesized by the intramolecular Diels-Alder reaction of the racemic 3,[2] the optically active 2 bearing the four requisite stereogenic centers was expected to be prepared from optically active 3. Since Claisen rearrangement of 5 to 4 was likely to proceed stereospecifically in view of the reaction mechanism, the optically active cyclohexenylacetic acid was expected to be prepared from the optically active 2-cyclohexenol.

A practical and economical synthetic method to provide (+) or (-)-2-cycloalken-1-ol in high enantiomeric excess has not been established until recently, although several synthetic attempts have been reported.[3-8] In our previous paper, we solved these problems by performing a lipase-catalyzed enantioselective transesterification which afforded 5 in good chemical and optical yield.[9] Here we wish to report on the synthesis of the enantiomerically pure aminoisoquinocarbazole (+)-1 (RS-2135) using (+)-2-cyclohexen-1-ol as a starting material and the detail of the lipase-catalyzed enantioselective transesterification reaction leading to the practical synthesis of (+)-2-cyclohexen-1-ol.

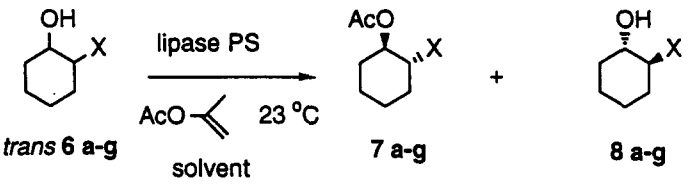
Lipase-catalyzed enantioselective transesterification of 2-substituted cycloalkanol

Although there are many reports on the enzymatic kinetic resolution of secondary alcohols,[10] we chose substrate, enzyme and experimental conditions as follows. *trans*-2-Substituted cycloalkanols were chosen as substrates in enzymatic reaction instead of 2-cycloalkenol since bulky substituents such as a phenylthio or a iodo group were expected to enhance the enantioselection and its ready conversion to cycloalkenol. All 2-substituted cycloalkanols were prepared from cycloalkene oxides according to a literature method.[11]

Lipase PS from *pseudomonas fluorescence* (Amano pharmaceutical) was selected after screening several commercially available lipases (lipase A(Amano pharmaceutical), lipase M(Amano pharmaceutical), lipase F(Amano pharmaceutical)) in the reaction with **6a**. Although a variety of solvents, such as diisopropyl ether, n-hexane, acetonitrile and tetrahydrofuran were available, generally diisopropyl ether was most suitable for reasons of solubility and reaction rate. In the case of **6e**, acetonitrile was chosen because of poor solubility in diisopropyl ether. Isopropenyl acetate was used as an acylation agent. The reaction was usually conducted at room temperature and monitored by HPLC (CHIRAL CELL OD Daisel, n-hexane-iPr_2O=97-3). The reaction of **6b** at low reaction temperature did not influence the enantioselectivity.

In the case of **6a**, the conversion of the reaction reached 50 % in 9 h at room temperature and remained unchanged even after 24 h. Enantiomeric purity of the acetylated product **7a** was almost 100 %

Table 1 Lipase-catalyzed enantioselective transesterification of *trans*-2-substituted cyclohexan-1-ol



trans **6 a-g** **7 a-g** **8 a-g**

Substrate	X	Reaction time (h)	Solvent	7 Yield (%)[a]	7 %e.e.	8 Yield (%)[a]	8 %e.e.
6a	SPh	24	iPr_2O	50	>99[b]	45	>99[b]
6b	I	6.5	iPr_2O	47	97[c]	46	96[d]
6c	Br	6.5	iPr_2O	39	93[c]	32	89[d]
6d	Cl	6.5	iPr_2O	46	84[c]	41	79[d]
6e	OTs	24	CH_3CN	49[e]	>99[c]	51[e]	92[d]
6f	NHPh	24	iPr_2O	44	>99[b]	45	>99[b]
6g	CH_2SPh	24	iPr_2O	46	>99[b]	44	>99[b]

a) Isolated yield. b) Optical purity was determined by HPLC (CHIRAL CELL OD). c) Optical purity was determined by HPLC after conversion to **10**. (see scheme 2) d) Optical purity was determined by the specific rotation of the corresponding acetate comparing with the enantiomer **7**. e) HPLC yield.

Table 2 Specific rotations and absolute configulations of **7** and **8**

Substrate	7 Specific rotation $[\alpha]_D^{23}$ (c , $CHCl_3$)	7 abs. config.[a]	8 Specific rotation $[\alpha]_D^{23}$ (c , $CHCl_3$)	8 abs. config.
6a	+6.9 (1.25)	(1R , 2R)	+71.9 (1.21)	(1S , 2S)
6b	-47.1 (2.15)	(1R , 2R)	+33.1 (2.50)	(1S , 2S)
6c	-46.0 (2.01)	(1R , 2R)	+31.3 (2.05)	(1S , 2S)
6d	-51.2 (2.51)	(1R , 2R)	+32.9 (2.18)	(1S , 2S)
6e	-22.2 (1.74)	(1R , 2R)	+13.7 (5.38)	(1S , 2S)
6f	+32.2 (1.47)	(1R , 2R)	+73.9 (2.44)	(1S , 2S)
6g	-34.2 (1.00)	(1R , 2R)	+80.6 (1.04)	(1S , 2S)

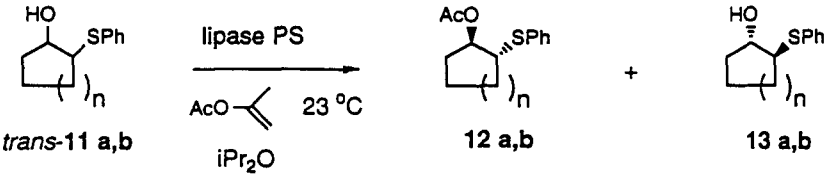
a) Absolute configulation was determined after conversion to **5** (see scheme 2) and comparison of its specific rotation with the reported value.[3]

and, to our surprise, it did not decrease after a prolonged reaction period. The unreacted alcohol **8a** also showed virtually 100 % e.e.. The same results were obtained from the other hexanols which were substituted at 2-position by a phenyl containing group (**6f**, **6g**). In the case of **6e**, the reaction was slow and incomplete after 24 h. As the results, enantiomeric purity of **8e** was 92 % e.e. although the acetylated product **7e** was virtually 100 % e.e..

It was found that the ring size of the cycloalkanol did not influence the enantioselectivity and that both of the 2-phenylthiocyclopentanol **11a** and 2-phenylthiocycloheptanol **11b** gave the same result as 2-phenylthiohexanol **6a**. 2-Halogenated cyclohexanols gave some what different results from the above mentioned cycloalkanols which contained a phenyl group in their substituent. The reaction of 2-iodocyclohexanol **6b** gave the acetylated product **7b** in 97 % e.e. after 6.5 h, but enantiomeric purity of **7b** decreased gradually (85 % e.e., after 24 h) if the reaction time was extended. Interestingly, enantioselectivity decreased as the size of the halogen atom became smaller (**6b**, **6c**, **6d**).

Absolute configurations and enantiomeric purities of **7**, **8**, **12**, and **13** were determined by their conversion to 2-cyclohexen-1-ol, of which specific rotation values were compared to the authentic one.[3]

Table 3 Lipase-catalyzed enantioselective transesterification of *trans*-2-phenylthiocycloalkanol



trans-**11 a,b** **12 a,b** **13 a,b**

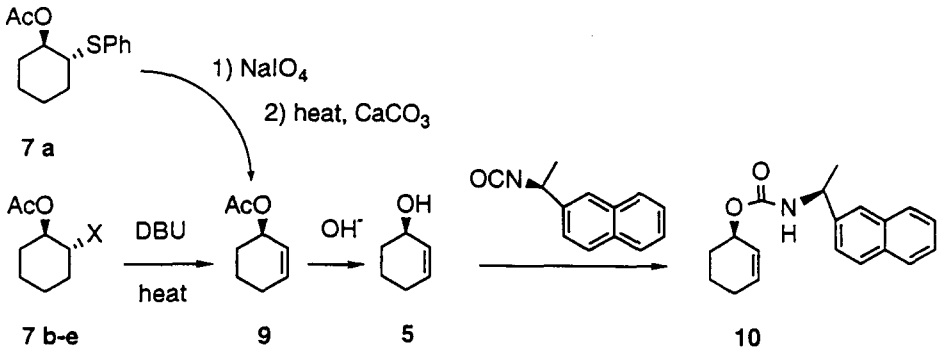
Substrate	n	Reaction time (h)	**12** Yield (%)[a]	**12** %e.e.	**13** Yield (%)[a]	**13** %e.e.
11a	1	24	50	>99[b]	50	>99[b]
11b	3	24	47	>99[c]	50	>99[b]

a) Isolated yield. b) Determined by HPLC (CHIRAL CELL OD). c) Hydrolized to the alcohol and determined by HPLC (CHIRAL CELL OD).

As these enzymatic reactions were conducted in relatively high concentrations in organic media and furthermore a 100 g scale reaction were successfully performed without undue difficulty, foreseeably industrial scale up should be possible.

Preparation of (+)-2-cyclohexen-1-ol 5 and (+)-2-cyclohexenylacetic acid 4

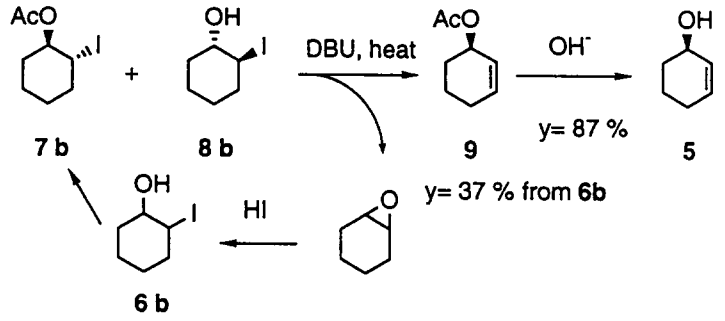
Cyclohexenol **5** was prepared through two routes shown in scheme 2. In the first of these, enantiomerically pure acetate **7a** was oxidized by sodium periodate and heated in the presence of $CaCO_3$ followed by hydrolysis, to give an enantiomerically pure (*R*)-2-cyclohexen-1-ol **5**, $[\alpha]_D^{23}$ +130(c=1.87, $CHCl_3$) in 47 % yield from **7a**. The enantiomeric excess was determined to be more than 99 % e.e. by the HPLC analysis after derivatization to the carbamate with (*S*) (+)-1-(1-naphthyl)ethyl isocyanate. Its specific rotation was +130 (c=1.21, $CHCl_3$), exceeding that of the highest one of the antipode reported (-112 (c=0.60, $CHCl_3$)).[12] This route can accomplish high enantiomeric excess in cyclohexenol **5**. However, it is not satisfactory because pyrolysis of the sulfoxide is not always reproducible and the antipode **8a** must be discarded. (scheme 2)



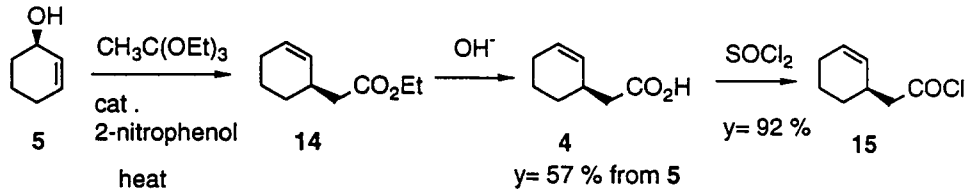
Scheme 2

In the second route, 2-cyclohexenol was prepared by an elimination reaction. Heating of the 2-iodohexyl acetate **7b** in DBU at 120 °C followed by hydrolysis gave (*R*)-2-cyclohexenol **5** (95 % e.e.) in 45 % yield. (scheme 2) When the mixture of the enzymatic reaction products (**7b+8b**) was heated in DBU, a mixture of (*R*)-2-cyclohexenyl acetate **9** and cyclohexene oxide was obtained, and separated readily by fractional distillation. Since the regeneration of the racemic 2-iodocyclohexanol as a substrate from cyclohexene oxide could be successfully implemented, this route can provide a practical means to synthesize enantiomerically pure (*R*)-2-cyclohexen-1-ol **5**. (scheme 3)

(+)-Cyclohexenol **5** was stereospecifically converted to (-)-2-cyclohexenyl acetic acid **4** by Claisen rearrangement and hydrolysis without loss of enantiomeric purity, which was determined as follows. The carboxylic acid **4** was converted to the amide of (*S*) (-)-naphthylethylamine using diethylphosphoryl cyanide, and then analyzed by HPLC.



Scheme 3

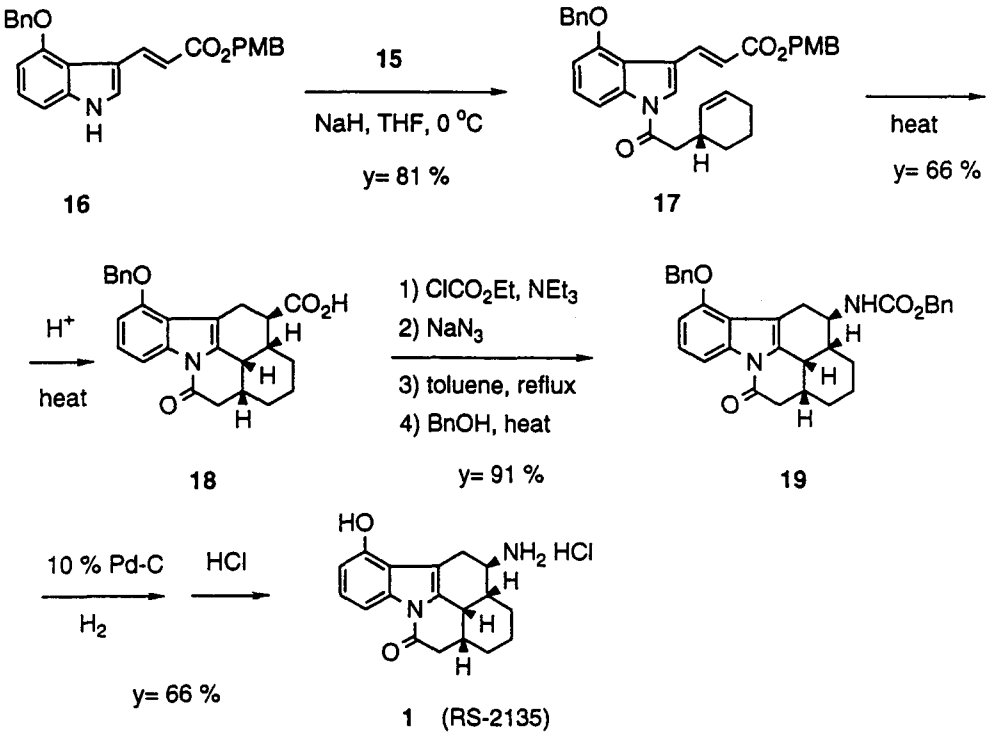


Scheme 4

Synthesis of RS-2135

(-)-(2-Cyclohexenyl)acetic acid **4** of 97 % e.e. was converted to the acid chloride **15** with thionyl chloride. Sodium salt of indolyl propenoate **16**, which was prepared from 4-benzyloxyindol-3-carboxaldehyde, was acylated by **15** to give **17** in high yield. Intramolecular Diels-Alder reaction of **17** was conducted by heating at 160 °C for 24 h in mesitylene. Subsequent acid treatment simultaneously caused the double bond migration and ester hydrolysis to give the pentacyclic carboxylic acid **18** stereoselectively, which precipitated in the reaction mixture and could be isolated easily by filtration. This three steps conversion installed the requisite four stereogenic centers in the fused tricyclic framework of **18**. After one recrystallization from EtOH-CH_2Cl_2, almost enantiomerically pure **18** ($[\alpha]_D^{23}$ +108.4(c=1.34,DMF))was obtained. Azidation of a mixed anhydride of **18** and Curtius rearrangement followed by alcoholysis gave the carbamate **19**. Deprotection of **19** by hydrogenolysis afforded enantiomerically pure (>99 % e.e.) RS-2135 in good yield. Its enantiomeric excess was determined by HPLC after conversion to the L-Boc-prolylamide

In summary, enantiomerically pure (*R*)-2-cyclohexen-1-ol **5** was prepared *via* lipase-catalyzed enantioselective transesterification of 2-substituted cyclohexanol, and stereospecifically converted to (-)-(2-cyclohexenyl)acetic acid **4**. Enantiomerically pure pentacyclic aminoisoquinocarbazole **1** (RS-2135), which contains four stereogenic centers, was synthesized stereoselectively from **4** using intramolecular Diels-Alder reaction and Curtius rearrangement.



Scheme 5

EXPERIMENTAL SECTION

Melting points were measured on a Yanaco micro melting apparatus and uncorrected. IR spectra were recorded on a Nic.5SXC or a ASCO A-302 spectrometer.. ^{1}H-NMR spectra were recorded with a Varian T-60 (60MHz) or a JEOL JNM-GX 270 (270MHz) spectrometer, and the chemical shifts are expressed in ppm from tetramethylsilane as an internal standard. Mass spectra were obtained with a JEOL JMS-D300 mass spectrometer. Optical rotations were recorded with a Perkin-Elmer model 241 polarimeter. Organic extracts were dried over anhydrous $MgSO_4$. Merck silica gel (kieselgel 60 Art . 9385) was employed for a flash chromatography.

General procedure of lipase catalyzed transesterification A mixture of substrate (0.5 mmol), isopropenyl acetate (1 mmol), and lipase PS (Amano) (250 mg) in the appropriate solvent (2.5 ml) was stirred at 23 °C. A ratio of substrate and acetylated product was monitored by HPLC (CHIRAL CELL OD was used for **6a** and **6f** with n-hexane-isopropanol=97-3 as the eluent.) or the reaction was quenched after appropriate time for **6b**, **6c**, **6d**, **6e**. When about a half of the substrate was acetylated, the mixture was

filtered and evaporated. The residue was chromatographed on silica gel with a mixed solvent of n-hexane and AcOEt to afford both an optically active cyclohexanol and an acetylated product.

(*R*)-2-Cyclohexenyl acetate 9 (scheme 3) A mixture of **6b** (25.0 g, 111 mmol), isopropenyl acetate (24.4 ml), and lipase PS (50 g) in isopropyl ether (550 ml) was stirred for 6.5 h at 23 °C. The reaction mixture was filtered and evaporated. The residual oil was dissolved in DBU (50 ml) and distilled under reduced pressure. After cyclohexene oxide was recovered (50 °C / 15 mmHg), **9** was obtained (5.69 g, 36.6 %) as a colorless oil (57-58 °C / 8 mmHg). IR ($CHCl_3$) : 1720, 1370, 1245 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270MHz) δ : 5.99-5.92 (m, 1H), 5.73-5.67 (m, 1H), 5.28-5.23 (m, 1H), 2.29-1.63 (m, 6H), 2.02 (s, 3H). MS m/z : 140 (M^+). $[\alpha]_D^{23}$ +199.0 (c=2.40, $CHCl_3$).

(*R*)-2-Cyclohexen-1-ol 5 To a solution of **9** (5.69 g, 40.6 mmol) in MeOH (2 ml) was added 1N NaOH (81 ml). The mixture was stirred overnight at r.t. and was extracted with CH_2Cl_2. The extract was dried and distilled under reduced pressure to afford **5** (3.46 g, 86.9 %) as a colorless oil. (96-97 °C / 75 mmHg) ^{1}H-NMR ($CDCl_3$, 60 MHz) δ : 5.97-5.58 (m, 2H), 4.29-4.03 (m, 1H), 2.11-1.39 (m, 7H). $[\alpha]_D^{23}$ +123.4 (c=1.81, $CHCl_3$).

(*R*)-(2-Cyclohexen-1-yl)acetic acid 4 A mixture of **5** (3.46 g, 35.3 mmol) and *o*-nitrophenol (150 mg) in triethylorthoacetate (18.2 ml) was heated at 170 °C removing EtOH continuously. After 9 h, the mixture was distilled to give the ethyl ester of **4** (90-95 °C / 10mmHg), which was dissolved in a mixture of 1N NaOH (50 ml) and MeOH (5 ml). The solution was stirred for 12 h at r.t. and evaporated to remove MeOH. After washing with ether, the aqueous layer was acidified to pH 1 with conc.HCl and extracted with AcOEt. The extract was dried, evaporated, and distilled under reduced pressure to give **4** (2.83 g, 57 %) as a colorless oil (97 °C / 1.2 mmHg). IR (neat) : 2940, 1705, 1295 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ : 5.90-5.47 (m, 2H), 2.75-1.20 (m, 10H). $[\alpha]_D^{23}$ -67.2 (c=1.60, MeOH).

(*R*)-*p*-Methoxybenzyl (E)-3-[4-benzyloxy-1-[2-(2-cyclohexen-1-yl)acetyl]-1H-indol-3-yl]2-propionate 17 A solution of thionyl chloride (2.1 ml) and **4** (2.64 g, 18.8 mmol) in benzene (8 ml) was refluxed for 1.5 h and distilled under reduced pressure to afford (*R*)-(2-cyclohexen-1-yl)acetyl chloride **15** (2.74 g, 91.9 %) as a colorless oil (72 °C / 7 mmHg). To a solution of *p*-methoxybenzyl (E)-3-(4-benzyloxy-1H-indol-3-yl)-2-propenoate (6.20 g, 15 mmol) in THF (30 ml) was added NaH (663 mg, 55% in mineral oil) at 0 °C under N_2. After stirring for 0.5 h, a solution of **15** (2.34 g) in THF (8 ml) was added dropwise at 0 °C to this mixture. The solution was stirred for 1h, poured onto ice, and extracted with AcOEt. The extract was washed with brine, dried, and evaporated. The residue was recrystallized from AcOEt-CH_2Cl_2 to afford **17**

(6.50 g, 80.9 %). m.p. 165-166 °C. IR (KBr) : 2931, 1711, 1697, 1432, 1268 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ : 8.35 (d, 1H, J=16Hz), 8.12 (d, 1H, J=8Hz), 7.69(s, 1H), 7.51 (d, 2H, J=7Hz), 7.41-7.30(m, 6H), 6.91-6.83 (m, 3H), 6.45 (d, 1H, J=16Hz), 5.82-5.79 (m, 1H), 5.66-5.62 (m, 1H), 5.26 (s, 2H), 3.82 (s, 3H), 2.95-2.85 (m, 3H), 2.03-1.27 (m, 6H). MS m/z : 535 (M^+). *Anal.* Calcd for : $C_{34}H_{33}NO_5$; C,76.24;H, 6.21;N,2.62. Found ; C,76.36;H,6.24;N,2.58. $[\alpha]_D^{23}$ -49.3 (c=1.08, $CHCl_3$).

[3a*R*-(3aα,12α,12aα,12bα)]-10-Benzyloxy-1,2,3,3a,4,5,11,12,12a,12b-decahydro-5-oxoisoquino[2,1,8-*lma*]carbazole-12-carboxylic acid 18 A suspension of **17** (6.50 g, 12.1 mmol) in mesitylene (40 ml) was heated at 70 °C until it became a clear solution and refluxed for 24 h under N_2. Then a solution of 4N HCl in dioxane (4.4 ml) was added to the mixture at 60 °C and the reaction mixture was stirred at 85 °C for 6 h. After cooling to 0 °C, the precipitated crystal was collected, washed with AcOEt, and recrystallized from EtOH-CH_2Cl_2 to afford **18** (3.19 g, 65.7 %) as an optically pure stereoisomer. m.p. 270-271 °C. IR (KBr) : 3410, 1712, 1500, 1440, 1255 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 270 MHz) δ : 12.35 (bs, 1H), 7.85 (d, 1H, J=8Hz), 7.54-7.31 (m, 5H), 7.18 and 7.15 (each d, 1H, J=8Hz), 6.91 (d, 1H, J=8Hz), 5.21 (s, 2H) , 3.35-3.28(m, 2H), 3.18-3.10 (m, 2H), 2.86-2.74 (m, 2H), 2.50-2.44 (m, 2H), 2.21-2.16 (m, 1H), 1.63-1.50 (m, 2H), 1.33-1.29 (m, 1H), 1.07-1.01 (m, 1H), 0.73-0.67 (m, 1H). MS m/z : 415 (M^+). *Anal.* Calcd for : $C_{26}H_{25}NO_4$; C,75.16;H,6.07;N,3.37. Found ; C,75.07;H,6.20;N,3..20. $[\alpha]_D^{23}$ +108.4 (c=1.34, DMF)

[3a*R*-(3aα,12α,12aα,12bα)]-(10-Benzyloxy-1,2,3,3a,4,5,11,12,12a,12b-decahydro-5-oxoisoquino [2,1,8-*lma*]carbazol-12-yl)carbamic acid benzylester 19 To a suspension of **18** (1.0 g , 2.4 mmol) in dry acetone (6.4 ml), were added NEt_3 (402 μl) and ethyl chloroformate (346 μl) at 0 °C under N_2. After stirring for 0.5 h, a solution of NaN_3 (234 mg) in H_2O (1.4 ml) was added to the mixture, which was stirred at 0 °C for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 . The extract was washed with brine, dried, and evaporated. The residue was dissolved in toluene (7.4 ml) and the solution was refluxed for 1.5 h under N_2. After addition of benzyl alcohol (0.8 ml), the mixture was refluxed for 5 h. The reaction mixture was evaporated and purified by chromatography on silica gel (n-hexane-AcOEt=3-1) to give **19** (1.14 g, 90.9 %) as a colorless solid. m.p. 140-141 °C. IR (KBr) : 3410, 2912, 1712, 1500, 1440, 1368, 1256 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz) δ : 8.02 (d, 1H, J=8Hz), 7.47-7.17 (m, 11H), 6.77 (d, 1H, J=8Hz), 5.14-5.02 (m, 5H), 4.07 (bs, 1H), 3.21-3.13 (m, 2H), 3.00-2.90 (m, 2H), 2.69 (d, 1H, J=2Hz), 2.34-2.16 (m, 2H), 1.70-1.58 (m, 3H), 1.31-1.26 (m, 1H),1.03-0.91 (m, 1H). MS m/z : 520 (M^+). *Anal.* Calcd for : $C_{33}H_{32}N_2O_4$; C,76.13;H,6.20;N,5.38. Found : C, 75.98; H,6.32;N,5.25. $[\alpha]_D^{23}$ +85.3 (c=1.21, $CHCl_3$).

[3a*R*-(3aα,12α,12aα,12bα)]-12-Amino-2,3,3a,4,11,12,12a,12b-octahydro-10-hydroxyisoquino[2,1,8-*lma*]carbazol-5(1H)-one hydrochloride 1 A solution of **19** (1.0 g, 1.9 mmol) and conc. HCl (0.62 ml) in

a mixture of EtOH (25 ml), H_2O (25 ml), and CH_2Cl_2 (5 ml) was hydrogenated on 10% Pd-C (1.0 g) at 0 °C for 6 h. After removal of the catalyst, the solution was evaporated and the residue was reprecipitated from MeOH-AcOEt to afford **1** (0.42 g, 65.7 %) as a colorless solid. m.p. 232-234 °C. IR (KBr) : 3404, 3306, 2959, 1692, 1653, 1534, 1266 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 270 MHz) δ : 9.80 (bs, 1H), 8.23 (bs, 3H), 7.71(d, 1H, J=8Hz), 7.06 and 7.02 (each d, 1H, J=8Hz), 6.68 (d, 1H, J=8Hz), 3.30-3.00 (m, 4H), 2.60-2.49 (m, 2H), 2.35-2.18 (m, 2H), 1.65-1.56 (m, 3H), 1.35-1.25 (m, 1H), 1.01-0.68 (m, 2H). MS m/z : 296 (M^+-HCl). *Anal.* Calcd for : $C_{18}H_{20}N_2O_2$ HCl 1.5 H_2O ;C,60.08;H,6.72;N,7.78;Cl,9.85. Found :C, 60.03;H, 6.58;N,7.62;Cl,9.77. $[\alpha]_D^{23}$ +66.4 (c=0.45, MeOH).

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