

Asymmetric Synthesis of Functionalized Benzo[*a*]quinolizine Derivatives *via* a Diastereoselective *N*-Acyliminium Ion Cyclization

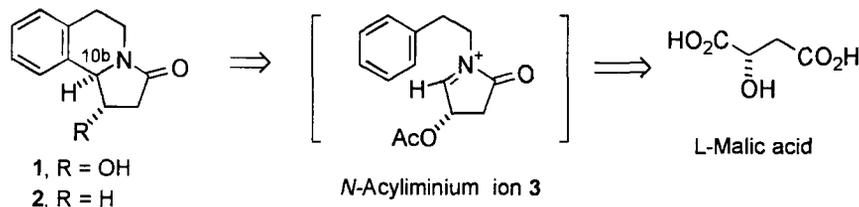
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Abstract : A chiral synthesis of functionalized benzo[*a*]quinolizine derivative (**5**) has been accomplished starting from a chiral lactone **7**. The key feature is the efficient control of the stereochemistry of ring juncture of the functionalized benzo[*a*]quinolizine derivative **5** by the *N*-acyliminium ion cyclization of chiral lactam **11b**. © 1997 Elsevier Science Ltd. All rights reserved.

Recently, there has been considerable interest in the development of synthetic approaches which allow the synthesis of alkaloids in optically pure form.¹ The *N*-acyliminium ion cyclization has proven to be a potential tool for the construction of complex polycyclic heterocycles.² The utilization of chiral lactams in the *N*-acyliminium ion cyclization can result in a stereoselective synthesis of various alkaloids. During our continuing studies on *N*-acyliminium ion cyclizations leading to nitrogen-containing heterocycles,³ we have recently shown that the asymmetric synthesis of optically pure pyrrolidinoisoquinoline derivatives (**1**, **2**) could be achieved by a diastereoselective cyclization of the chiral *N*-acyliminium ion (**3**), which was derived from L-malic acid (Scheme 1).⁴

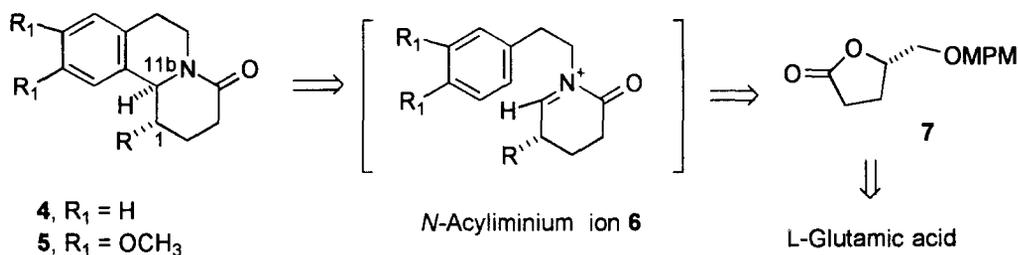


Scheme 1

As an extension of this protocol, we envisioned that this strategy could be applied for the synthesis of functionalized benzo[*a*]quinolizines (**4**, **5**) in optically pure form (Scheme 2). The benzo[*a*]quinolizines are key intermediates for the synthesis of *Ipecac* alkaloid emetine^{5c} and they possess interesting biological activities.⁶ Syntheses of racemic benzo[*a*]quinolizines have appeared in the literature.⁵ However, methods for the chiral

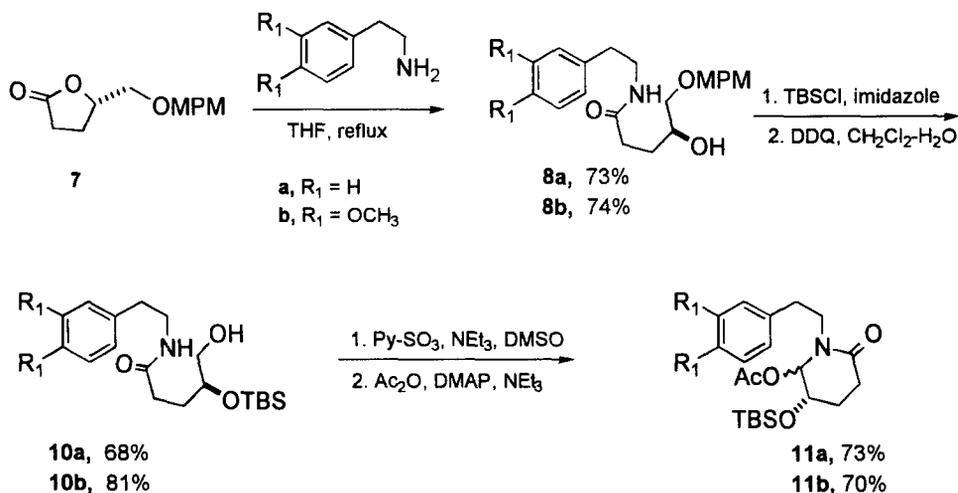
Dedicated to Prof. Sang Chul Shim on the occasion of his 60th birthday.

synthesis of benzo[*a*]quinolizines are scarce and have only recently been reported by the employment of chiral auxiliaries.⁷



Scheme 2

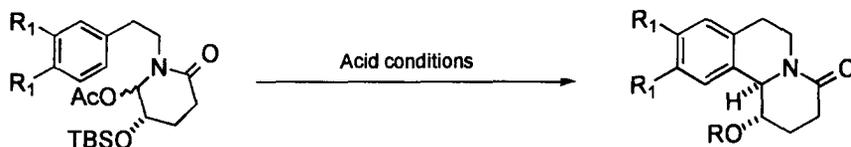
Herein we describe an asymmetric synthesis of functionalized benzo[*a*]quinolizines (**4**, **5**) using a diastereoselective cyclization of the chiral *N*-acyliminium ion (**6**). The benzo[*a*]quinolizines (**4**, **5**) may be versatile intermediates for the synthesis of several pyridoisoquinoline alkaloids since they already have hydroxyl and amide groups for further transformations. The key feature of our approach is based on earlier findings⁴ that the stereochemistry of ring juncture (C-11b) can be controlled by the nucleophilic attack of aromatic rings at the side opposite to the proximate substituent (-OR) in *N*-acyliminium ion (**6**).



Scheme 3

The requisite chiral *N*-acyliminium ion precursors (**11a**, **11b**) were prepared as shown in Scheme 3. Our synthesis starts from the chiral lactone (**7**), readily available in high enantiomeric purity from an inexpensive L-glutamic acid.⁸ We selected phenyl and 3,4-dimethoxyphenyl rings as aromatic π -nucleophiles to examine the reactivity of the *N*-acyliminium ion (**6**). Aminolysis of **7** with phenethylamine and 3,4-dimethoxyphenethylamine in THF gave amides **8a** and **8b**. The secondary hydroxyl group in **8a** and **8b** was protected as TBS group and MPM protecting group was removed by DDQ⁹ to afford **10a** and **10b**. Parikh oxidation¹⁰ of the primary alcohol

in **10a** and **10b** followed by acetylation of the resulting hydroxylactams afforded chiral acetoxy lactams (**11a**, **11b**) as mixtures of epimers.



11a, R₁=H

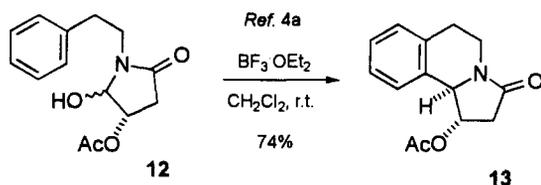
11b, R₁=OCH₃

4, R₁=H, R=H, 20%, 1. HCO₂H, reflux; 2. AcCl, EtOH.

5, R₁=OCH₃, R=H, 83%, BF₃·OEt₂, r.t.

14, R₁=OCH₃, R=TBS, 86%, BF₃·OEt₂, -30 °C

Scheme 4



Scheme 5

These chiral lactams **11a** and **11b** were subjected to the *N*-acyliminium ion cyclization conditions to obtain functionalized benzo[*a*]quinolizines (**4**, **5**) as shown in Scheme 4. However, attempts to cyclize **11a** in various conditions such as BF₃·OEt₂,^{4a} TsOH,^{5c,5d} CH₃SO₃H^{4b} were unsuccessful. Significant decomposition of **11a** was observed.

Upon using formic acid^{4b} as an activating agent, the *N*-acyliminium ion cyclization of **11a** proceeded to afford the desired benzo[*a*]quinolizines (**4**) in 20 % yield. The hydrolysis step (AcCl/EtOH) was required since the hydroxyl group in the cyclized product **4** was formylated in the reaction condition. The poor reactivity of **11a** is unexpected since the high reactivity of *N*-acyliminium ions owing to the electron-withdrawing influence of *N*-acyl group has been well known² and the cyclization of *N*-acyliminium ion derived from 5-membered lactam (**12**) proceed easily with BF₃·OEt₂ at room temperature (Scheme 5) from our previous result.^{4a} On the other hand, the acetoxy lactam **11b**, which has more reactive 3,4-dimethoxyphenyl ring as a π -nucleophile, cyclized smoothly with BF₃·OEt₂ at -30 °C to provide a silylated benzo[*a*]quinolizine (**14**) in 86 % yield. These results show that *N*-acyliminium ion (**6**) derived from the 6-membered lactam seems less reactive than *N*-acyliminium ion (**3**) from the 5-membered lactam toward the same π -nucleophile.¹¹ Thus, more activation of aromatic rings by substitution of electron releasing group is necessary for the 6-membered lactams to proceed *N*-acyliminium ion cyclization efficiently. Finally, TBS group in **14** was removed by treatment of TBAF to afford 1-hydroxybenzo[*a*]quinolizine (**5**) in quantitative yield. 1-Hydroxybenzo[*a*]quinolizine (**5**) could be obtained directly in 83 % yield when the acetoxy lactam **11b** was treated with BF₃·OEt₂ at room temperature. The TBS group was simultaneously removed during the cyclization process which simplified further transformations. The stereochemistry of newly formed asymmetric center (C11b) in **5** was assigned to be *R* by analogy of our previous results⁴ and unambiguously confirmed by X-ray analysis (Fig. 1). The *trans* relationship between angular hydrogen (C11b-H) and C1-H in **5** proves that the nucleophilic attack of 3,4-dimethoxyphenyl ring

occurs from the opposite site of the silyloxy substituent on the lactam (**11b**) during the cyclization step.

The enantiomeric purity of **5** was ascertained after conversion to (*R*)-*N*-(α -methylbenzyl)carbamate derivative (**15**).¹² 1-Hydroxy-benzo[*a*]quinolizine (**5**) was acylated with (*R*)- α -methylbenzyl isocyanate in THF-DMF with

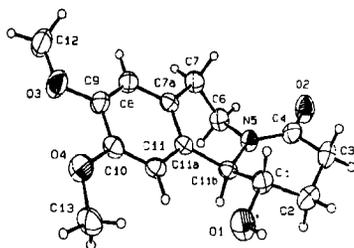
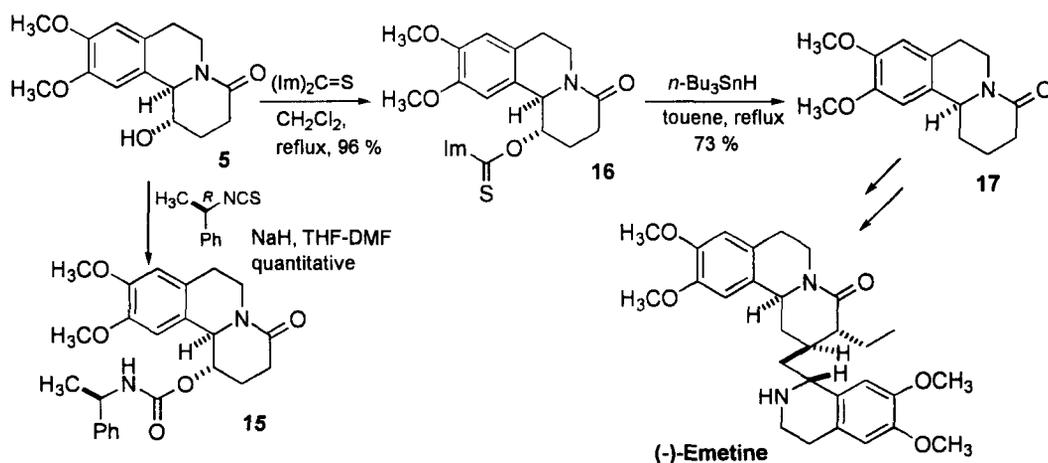


Fig 1. The X-Ray structure of **5**

a catalytic amount of NaH to provide **15** in a diastereomeric form. To the limits of detection by 300 MHz ¹NMR spectroscopy and chiral HPLC analysis of **15**, only a single diastereomer was formed to demonstrate **15** to be of >99 % de. Accordingly, 1-hydroxy-benzo[*a*]quinolizine (**5**), obtained in this synthesis, is presumed to be of >99 % enantiomeric purity.

To further illustrate the synthetic utility of this strategy, 1-hydroxy-benzo[*a*]quinolizine (**5**) was converted to benzo[*a*]quinolizine derivative **17** by the removal of hydroxyl group. The racemic form of benzo[*a*]quinolizine derivative **17** has been used as a key intermediate for the synthesis of *Ipecac* alkaloid (\pm)-emetine.^{5c} Treatment of **5** with *N,N*-thiocarbonyldiimidazole in CH₂Cl₂ afforded thiocarbonylimidazolidine **16** in 96 % yield. Compound **16** was transformed to benzo[*a*]quinolizine derivative **17** ($[\alpha]_D^{26} -212.5^\circ$ (*c* 2.93, CHCl₃)) by the radical cleavage of carbon-oxygen bond with tributyltin hydride. 1-Hydroxy-benzo[*a*]quinolizine (**5**) also can be used as a potential intermediate for the synthesis of (-)-emetine¹³ and related alkaloids in optically pure form.



Scheme 6

In conclusion, we have achieved a chiral synthesis of functionalized benzo[*a*]quinolizine derivative (**5**) by employment of the diastereoselective *N*-acyliminium ion cyclization of chiral lactam (**11b**). A chiral lactone (**7**), readily available from L-glutamic acid, was used as a convenient chiral source. This procedure can be extended to asymmetric synthesis of more complex isoquinoline alkaloids by the further chemical transformation of the

existing hydroxyl and an amide functions in benzo[*a*]quinolizine derivative (**5**).

EXPERIMENTAL

General Methods: Melting points (mp) were determined on a Thomas-Hoover capillary melting apparatus and uncorrected. ¹H NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer. ¹³C NMR spectra were recorded on a Gemini Varian-300 (75 MHz) spectrometer. Infrared (IR) spectra were obtained on a Perkin Elmer 16F-PC FT-IR and MIDAC 101025 using a potassium bromide pellet or sodium chloride cell. Optical rotations were determined on a Autopol III polarimeter (Rudolph Research Co.) using sodium D line. Analytical GC-MS work was performed with Hewlett-Packard 5988A GC-Mass. High (EI) resolution mass spectra were determined on VG70-VSEQ (VG ANALITICAL, UK) at 70eV. Elemental analysis was performed by Elementar Analysensysteme GmbH Vario EL. Analytical thin layer chromatography (TLC) were carried out on E. Merck precoated silica gel 60 F₂₅₄ plates.

***N*-2-Phenylethyl (4*S*)-4-hydroxy-5-(4-methoxybenzyloxy)pentanamide (8a).** A solution of lactone (**7**, 4.08 g, 17.3 mmol) and phenethylamine (3.6 ml, 25.9 mmol) in THF (40 ml) was refluxed for 90 h. The reaction mixture was concentrated and purified by flash column chromatography (EtOAc : hexane = 1 : 1 ~ EtOAc only) to give **8a** as a pale yellow solid (4.59 g, 74 %): mp 64-66 °C; [α]_D²⁴ -2.32° (*c* 2.98, CHCl₃); IR (KBr) 3306, 2933, 1645 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.84-7.29 (9H, m, Ar), 6.38 (1H, br s, NH), 4.43 (2H, s, OCH₂Ar), 3.75 (4H, br s, CH₃O, CHOH), 3.47-3.30 (4H, m, MPMOCH₂, NHCH₂), 2.76 (2H, t, *J*=7.1 Hz, Ph-CH₂), 2.27 (2H, t, *J*=7.0 Hz, COCH₂), 1.79 (1H, m, CH₂CHOH), 1.65 (1H, m, CH₂CHOH); ¹³C-NMR (75 MHz, CDCl₃) δ 173.56, 159.31, 139.02, 130.19, 129.49, 129.42, 128.76, 127.66, 127.49, 126.48, 113.88, 74.17, 73.00, 69.91, 55.36, 40.79, 35.66, 32.78, 29.15; Anal. Calcd for C₂₁H₂₇NO₄: C 70.56, H 7.61, N 3.92. Found: C 70.74, H 7.58, N 3.74.

***N*-2-(3,4-Dimethoxyphenyl)ethyl (4*S*)-4-hydroxy-5-(4-methoxybenzyloxy)pentanamide (8b).** Compound **8b** was prepared from lactone (**7**, 13 g, 0.055 mol) and 3,4-dimethoxyphenethylamine (18.6 ml, 0.11 mol) following a procedure similar to that of **8a** in 73 % yield (16.64 g) as a white solid: mp 84-85 °C; [α]_D²⁴ -0.51 (*c* 3.13, CHCl₃); IR (KBr) 3296, 2898, 1636 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.22 (2H, d, *J*=8.4 Hz, MPM), 6.84 (2H, d, *J*=8.4 Hz, MPM), 6.69-6.78 (3H, m, Ar), 5.99 (1H, br s, NH), 4.43 (2H, s, OCH₂Ar), 3.83 (3H, s, CH₃O), 3.82 (3H, s, CH₃O), 3.76 (3H, s, CH₃O), 3.31-3.47 (4H, m, MPMOCH₂ and NHCH₂), 2.71 (2H, t, *J*=7.1 Hz, ArCH₂CH₂), 2.27 (2H, t, *J*=6.9 Hz, COCH₂), 1.75-1.83 (1H, m, CH₂CHOH), 1.60-1.70 (1H, m, CH₂CHOH); ¹³C-NMR (75 MHz, CDCl₃) δ 173.48, 159.26, 149.00, 147.64, 131.54, 130.12, 129.37 (2C), 120.67, 113.82 (2C), 112.04, 111.46, 74.12, 72.96, 69.90, 55.97, 55.82, 55.31, 40.88, 35.21, 32.75, 29.14; Anal. Calcd for C₂₃H₃₁NO₆: C 66.17, H 7.48, N, 3.35. Found: C 66.07, H 7.38, N 3.34.

***N*-2-Phenylethyl (4*S*)-4-(*t*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pentanamide (9a).** To a solution of alcohol (**8a**, 2.39 g, 6.69 mmol) in DMF (10 ml) was added *t*-butyldimethylsilyl chloride (1.41 g, 9.36 mmol) and imidazole (0.73 g, 10.7 mmol) at 0 °C. After stirring at room temperature for 1 h, the mixture was diluted with EtOAc (100 ml). The EtOAc solution was washed with H₂O (100 ml), brine (100 ml × 3), dried over

MgSO₄, and concentrated to afford **9a** an oil (3.12 g, 99 %): $[\alpha]_D^{24}$ -9.36° (*c* 4.06, CHCl₃); IR (neat) 2930, 1646 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.85-7.32 (9H, m, Ar), 5.65 (1H, br s, NH), 4.43 (2H, s, OCH₂Ar), 3.85 (1H, m, CHOH), 3.79 (3H, s, CH₃O), 3.29-3.52 (4H, m, MPMOCH₂, NHCH₂), 2.78 (2H, t, *J*=7.0 Hz, PhCH₂), 2.13-2.25 (2H, m, COCH₂), 1.72-1.93 (2H, m, CH₂CHOH), 0.89 (9H, s, *t*-butyl), 0.02 (6H, s, (CH₃)₂Si); ¹³C-NMR (75 MHz, CDCl₃) δ 173.05, 159.22, 139.08, 130.41, 130.03, 129.46, 129.30, 128.88, 128.76, 126.51, 113.83, 74.12, 72.97, 70.75, 55.30, 40.70, 35.76, 32.11, 30.58, 25.97 (3C), 18.17, -4.02, -4.67; MS, *m/z* (relative intensity, %): 415 (M⁺ - *t*-butyl, 0.4), 320 (3), 122 (10), 121 (100); HRMS (EI) Calcd for C₂₇H₄₁NO₄Si: 471.2808. Found 471.2805.

N-[2-(3,4-Dimethoxyphenyl)ethyl] (4*S*)-4-(*t*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pentanamide (**9b**). Compound **9b** was prepared from alcohol (**8b**, 15 g, 36 mmol), *t*-butyldimethylsilyl chloride (7.58 g, 50 mmol) and imidazole (4.15 g, 60 mmol) following a procedure similar to that of **8a** in 93 % yield (17.8 g) as an oil: $[\alpha]_D^{24}$ -7.25° (*c* 2.73, CHCl₃); IR (neat) 2930, 1646 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.17 (2H, d, *J*=8.3 Hz, MPM), 6.79 (2H, d, *J*=8.3 Hz, MPM), 6.65-6.73 (3H, m, Ph), 5.88 (1H, br s, NH), 4.36 (2H, s, OCH₂Ar), 3.77 (3H, s, CH₃O), 3.76 (3H, s, CH₃O), 3.71 (3H, s, CH₃O), 3.35-3.39 (2H, m, NHCH₂), 3.23-3.31 (2H, m, MPMOCH₂), 2.66 (2H, t, *J*=7.0 Hz, ArCH₂CH₂), 2.11-2.19 (2H, m, COCH₂), 1.80-1.85 (1H, m, CH₂CHOSi), 1.68-1.73 (1H, m, CH₂CHOSi), 0.82 (9H, s, *t*-butyl), 0.02 (6H, s, (CH₃)₂Si); ¹³C-NMR (75 MHz, CDCl₃) δ 173.2, 159.2, 149.0, 147.6, 131.6, 130.2, 129.3 (2C), 120.8, 113.7(2C), 111.9, 111.0, 74.0, 72.9, 70.0, 55.8 (3C), 40.7, 35.0, 32.1, 30.6, 25.8, 18.9, -4.9, -5.1; MS, *m/z* (relative intensity, %): 475 (M⁺ - *t*-butyl, 3), 278 (3), 164 (40), 121 (100), 73(9); HRMS (EI) Calcd for C₂₉H₄₅NO₆Si: 531.3007. Found: 531.3015.

N-2-Phenylethyl (4*S*)-4-(*t*-butyldimethylsilyloxy)-5-hydroxypentanamide (**10a**). To a stirred solution of MPM ether (**9a**, 0.3 g, 0.64 mmol) in CH₂Cl₂-H₂O (2 ml/0.1 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 0.17 g, 0.76 mmol) in an ice bath. After stirring at room temperature for 1 h, the mixture was filtered and extracted with CH₂Cl₂ (5 ml × 2). The combined organic layer was washed with saturated aqueous NaHCO₃ solution (15 ml), brine (15 ml), dried over MgSO₄, and concentrated. Flash column chromatography (EtOAc : hexane = 1 : 1) of the residue afforded **10a** as a white solid (0.17 g, 73 %): mp 114-116 °C; $[\alpha]_D^{24}$ +9.85° (*c* 2.58, CHCl₃); IR (KBr) 3268, 2932, 1640 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.17-7.32 (5H, m, Ar), 5.80 (1H, br s, NH), 3.79 (1H, m, CHOSi), 3.42-3.50 (4H, m, NHCH₂, CH₂OH), 2.80 (2H, t, *J*=7.0 Hz, ArCH₂CH₂), 2.09-2.31 (2H, m, COCH₂), 1.75-1.92 (2H, m, COCH₂CH₂), 0.88 (9H, s, *t*-butyl), 0.06 (6H, s, (CH₃)₂Si); ¹³C-NMR (75 MHz, CDCl₃) δ 173.17, 138.87, 128.64, 128.26 (2C), 126.52 (2C), 71.61, 65.38, 40.73, 35.62, 31.08, 28.74, 25.86 (3C), 18.09, -4.16, -4.51; MS, *m/z* (relative intensity, %): 322 (M⁺ - 2CH₃, 2), *320 (16), 294 (M⁺ - *t*-butyl, 71), 276 (12), 242 (49), 231 (17), 105 (100), 75 (65); Anal. Calcd for C₁₉H₃₃NO₃Si: C 64.91, H 9.46, N 3.98, Found: C 64.87, H 10.01, N 4.04.

N-[2-(3,4-Dimethoxyphenyl)ethyl] (4*S*)-4-(*t*-butyldimethylsilyloxy)-5-hydroxypentanamide (**10b**).

Compound **10b** was prepared from MPM ether (**9b**, 17 g, 0.032 mol) and DDQ (8.71 g, 0.038 mol) following a procedure similar to that of **9a** in 87 % yield (11.5 g) as a white solid: mp 88-90 °C; $[\alpha]_D^{26}$ + 9.15° (*c* 1.06,

CHCl₃); IR (KBr) 3286, 2932, 1644 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.68-6.78 (3H, m, Ar), 5.80 (1H, br s, NH), 3.82 (6H, s, 2 x CH₃O), 3.76 (1H, m, CHOSi), 3.39-3.45 (4H, m, COCH₂, CH₂OH), 2.72 (2H, t, *J*=6.9 Hz), 2.12-2.27 (2H, m, PhCH₂), 1.75-1.88 (2H, m, CH₂CHOSi), 0.85 (9H, s, *t*-butyl), 0.05 (6H, s, Si(CH₃)₂); ¹³C-NMR (75 MHz, CDCl₃) δ 173.23, 148.95, 147.70, 131.37, 120.60, 112.06, 111.54, 71.61, 65.38, 55.90 (2C), 40.81, 35.62, 31.08, 28.74, 25.86 (3C), 18.09, -4.15, -4.61; MS, *m/z* (relative intensity, %): 394 (M⁺-H₂O, 5), 355 (M⁺-*t*-butyl, 12), 171 (31), 165 (83), 164 (100), 151 (37), 73 (61); Anal. Calcd for C₂₁H₃₇NO₅Si: C 61.28, H 9.06, N 3.40. Found: C 61.13, H 9.01, N 3.33.

(5*S*)-6-Acetoxy-5-(*t*-butyldimethylsilyloxy)-1-(2-phenylethyl)piperidine-2-one (11a). To a solution of hydroxyamide (**10a**, 1.11 g, 3.15 mmol) and triethylamine (2.64 ml, 18.9 mmol) in DMSO (8 ml) was treated with a solution of pyridine-SO₃ complex (8.9 g, 0.056 mol) in DMSO (8 ml) *via* syringe under argon atmosphere while maintaining the temperature at about 20 °C. After stirring for 1.5 h, the reaction mixture was poured slowly into vigorously stirred ice water (50 ml) and the aqueous mixture was extracted with EtOAc (60 ml). The organic layer was washed with water (60 ml), brine (40 ml), dried over MgSO₄, and concentrated. The residue was diluted with CH₂Cl₂ (10 ml) and treated with triethylamine (1.32 ml, 9.5 mmol), acetic anhydride (0.9 ml, 9.5 mmol) and catalytic amount of 4-dimethylaminopyridine (DMAP) at 0 °C. After stirring at room temperature overnight, the reaction mixture was quenched by addition of water (10 ml). The separated organic layer was dried over MgSO₄, concentrated, and purified by flash column chromatography (EtOAc : hexane = 1 : 2) to give acetoxy lactam (**11a**, 0.91 g, 73 %) as an oil (ca. 2.3 : 1 mixture of epimers from ¹H-NMR analysis): IR (neat) 2930, 1743, 1664 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.16-7.26 (5H, m, Ar), 5.85 (1H, br s, AcOCH), 3.94 (1H, br s, CHOSi), 3.86 (1H, m, NCH₂), 3.12 (1H, m, NCH₂), 2.74-2.85 (2H, m, PhCH₂), 2.62 (1H, m, COCH₂), 2.37 (1H, m, COCH₂), 2.00 & 2.02 (3H, two s, CH₃CO), 1.73-1.78 (2H, m, COCH₂CH₂), 0.82 & 0.92 (9H, two s, *t*-butyl); ¹³C-NMR (75 MHz, CDCl₃) δ 170.72, 170.52, 139.23, 129.44, 129.26, 128.96, 127.02, 126.82, 84.86, 66.19, 48.28, 34.58, 27.54, 26.13 (3C), 26.06, 24.67, 18.41, -4.38, -4.53; MS, *m/z* (relative intensity, %): 333 (M⁺ - AcO, 6), 331 (M⁺ - *t*-butyl, 23), 240 (66), 212 (22), 105 (34), 73 (100); HRMS (EI) Calcd for C₂₁H₃₃NO₄Si: 391.2172. Found: 391.2179.

(5*S*)-6-Acetoxy-1-[2-(3,4-dimethoxyphenyl)ethyl]-5-(*t*-butyldimethylsilyloxy)piperidine-2-one (11b).

Compound **11b** was prepared from hydroxyamide **10b** following a procedure similar to that of **11a** in 70 % yield (ca. 7:1 mixture of epimers from ¹H-NMR analysis): mp 107 °C; IR (KBr) 2956, 1748, 1650 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.72 (3H, br s, Ar), 5.83 (1H, br s, AcOCH), 3.92 (1H, m, CHOSi), 3.82 (3H, s, CH₃O), 3.78 (3H, s, CH₃O), 3.08 (1H, m, NCH₂), 2.66-2.77 (2H, m, ArCH₂), 2.60 (1H, m, COCH₂), 2.34 (1H, dd, *J*=17.5, 5.5 Hz, COCH₂), 2.03 (3H, s, CH₃CO), 1.69-1.78 (2H, m, COCH₂CH₂), 0.83 & 0.76 (9H, two s, *t*-butyl); ¹³C-NMR (75 MHz, CDCl₃) δ 174.00, 170.16, 148.95, 147.60, 131.31, 120.96, 112.03, 111.34, 84.19, 65.54, 55.85 (2C), 47.89, 33.60, 27.05, 25.59 (3C), 24.12, 21.07, 17.88, -4.71, -5.10; MS, *m/z* (relative intensity, %): 393 (M⁺ -AcO, 3), 391 (42), 240 (51), 227 (100), 73 (56); Anal. Calcd for C₂₃H₃₇NO₆Si: C 61.17, H 8.26, N 3.10. Found: C 61.11, H 8.20, N 3.10.

(1*S*,11*bR*)-1-Hydroxy-1,2,3,6,7,11*b*-hexahydro-benzo[*a*]quinolizine-4-one (4). A solution of acetoxy lactam (**4a**, 156 mg, 0.4 mmol) in formic acid (5 ml) was refluxed for 22 h. Reaction mixture was concentrated and dried in vacuo. The residue was diluted with ethanol (5 ml) and treated with acetyl chloride (1.5 ml) in an ice bath and stirred at room temperature for 5 h. The reaction mixture was evaporated, diluted with EtOAc (10 ml), washed with saturated aqueous NaHCO₃ solution (10 ml), brine (10 ml), dried over MgSO₄, and concentrated. Flash column chromatography (EtOAc only) of the residue and recrystallization from CH₂Cl₂-ethyl acetate afforded **4** (17 mg, 20 %) as a needle: mp 143-144 °C; [α]_D²⁶ -141.4° (*c* 0.37, CHCl₃); IR (KBr) 3369, 2928, 1614 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.19-7.57 (4H, m, Ar), 4.61-4.66 (1H, m, H₆), 4.54 (1H, d, *J*=7.0 Hz, H_{11*b*}), 4.08 (1H, m, H₁), 2.87-2.96 (2H, m, 2 x H₇), 2.64-2.79 (2H, m, H₃, H₆), 2.41-2.48 (1H, m, H₃), 1.97-2.13 (2H, m, 2 x H₂); ¹³C-NMR (75 MHz, CDCl₃) δ 170.55, 136.51, 136.02, 129.54, 127.96, 127.16, 126.45, 70.05, 62.89, 41.48, 29.61, 29.53, 28.50; MS, *m/z* (relative intensity, %): 217 (M⁺, 35), 145 (100), 132 (20), 131 (46), 130 (68); HRMS (EI) Calcd for C₁₃H₁₃NO₂: 217.1103. Found: 217.1103.

(1*S*,11*bR*)-1-(*t*-Butyldimethylsilyloxy)-9,10-dimethoxy-1,2,3,6,7,11*b*-hexahydro-benzo[*a*]quinolizine-4-one (14). To a solution of acetoxy lactam (**11b**, 166 mg, 0.383 mmol) in dry CH₂Cl₂ (5 ml) was added BF₃·OEt₂ (0.14 ml, 1.15 mmol) *via* syringe under argon atmosphere at -78 °C. After stirring at -78 °C for 3 h, the reaction temperature was slowly elevated to -30 °C and stirred for 1 h. The reaction mixture was diluted with CH₂Cl₂ (50 ml) and quenched by addition of saturated aqueous NaHCO₃ solution (50 ml). The organic layer was separated, dried over MgSO₄ and concentrated. The residue was purified by flash column chromatography (EtOAc : hexane = 2 : 3) to give **14** as a colorless oil (124 mg, 86 %): [α]_D²⁷ -30.7° (*c* 4.00, CHCl₃); ¹H-NMR (300 MHz, CDCl₃) δ 6.75 (1H, s, Ar), 6.58 (1H, s, Ar), 4.68 (1H, m, H₁), 4.42 (1H, d, *J*=5.0 Hz, H_{11*b*}), 4.06 (1H, m, H₆), 3.80 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 2.83-2.63 (3H, m, H₆, 2 x H₇), 2.56 (1H, m, H₃), 2.36 (1H, m, H₃), 1.76-1.87 (2H, m, 2 x H₂), 0.83 (9H, s, *t*-butyl), -0.06 (6H, s, Si(CH₃)₂); MS, *m/z* (relative intensity, %): 392 (M⁺, 26), 334 (M⁺ - *t*-butyl, 39), 232 (23), 191(100), 176 (30).

(1*S*,11*bR*)-9,10-Dimethoxy-1-hydroxy-1,2,3,6,7,11*b*-hexahydro-benzo[*a*]quinolizine-4-one (5). To a solution of acetoxy lactam (**11b**, 173 mg, 0.383 mmol) in dry CH₂Cl₂ (5 ml) was added BF₃·OEt₂ (0.14 ml, 1.15 mmol) *via* syringe under argon atmosphere in an ice bath. After stirring at room temperature for 36 h, the reaction mixture was quenched by addition of saturated aqueous NaHCO₃ solution (10 ml). The mixture was extracted with CH₂Cl₂ (15 ml), dried over MgSO₄ and concentrated. Flash column chromatography (EtOAc : hexane = 1 : 1) of the residue and recrystallization from CH₂Cl₂-methanol afforded **5** as a needle (88 mg, 83 %): mp 194-195 °C; [α]_D²⁴ -152.6° (*c* 2.35, CHCl₃); IR (KBr) 3247, 2923, 1603 cm⁻¹; ¹H-NMR (300 MHz, DMSO-*d*₆) δ : 7.29 (1H, s, Ar), 6.71 (1H, s, Ar), 5.51 (1H, d, *J*=5.0 Hz, H_{11*b*}), 4.38 (1H, m, H₆), 3.97 (1H, m, H₁), 3.72 (6H, s, OCH₃), 2.50-2.82 (3H, m, H₆, 2 x H₇), 2.38 (1H, m, H₃), 2.21 (1H, m, H₃), 1.76-1.83 (2H, m, 2 x H₂); ¹³C-NMR (75 MHz, DMSO-*d*₆) δ 168.18, 147.56, 146.94, 128.67, 127.54, 111.85, 110.00, 68.71, 68.51, 61.56, 61.34, 55.48, 28.83, 28.05, 27.75; MS, *m/z* (relative intensity, %): 277 (M⁺, 39), 232 (19), 191 (100), 176 (29).
X-ray diffraction analysis of 5. The X-ray data were collected on an Enraf-Nonius CAD-4 automatic

diffractometer with graphite-monochromated Mo K α ($\lambda=0.71073$ Å) at ambient temperature. The unit cell parameters were determined by least-squares fitting of 25 well-centered reflections. During the data collection, three standard reflections monitored every hour did not show any significant intensity variation. The data were corrected for Lorentz and polarization effect, and empirically for absorption (azimuthal scans of 3 reflections). The structure was solved by the direct method (SHELX-86) and were refined by full-matrix least-squares techniques (SHELX-93).¹⁴ All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were determined on the basis of Flack parameter and chemical need. Crystal parameters and procedural information corresponding to data collection and structure refinement are given in Table 1.

Table 1. Details of Crystallographic Data for 5.¹⁵

Formula	C ₁₅ H ₁₉ NO ₄
FW	277.31
temperature, K	293(2)
wavelength, Å	0.71073
crystal system	orthorhombic
space group	P2 ₁ 2 ₁ 2 ₁ (No. 19)
<i>a</i> , Å	8.112(2)
<i>b</i> , Å	12.094(2)
<i>c</i> , Å	13.770(3)
<i>V</i> , Å ³	1351.0(5)
<i>Z</i>	4
<i>d</i> _{calcd} , g/cm ³	1.363
absorption coefficient, mm ⁻¹	0.099
F(000)	592
crystal size, mm	0.35 x 0.35 x 0.45
theta range, deg	2.24 - 24.97
index ranges	0 ≤ <i>h</i> ≤ 9, 0 ≤ <i>k</i> ≤ 14, 0 ≤ <i>l</i> ≤ 16
reflections collected	1172
independent reflections { <i>I</i> > 2 σ (<i>I</i>)}	1172
refinement method	full-matrix least-squares on F ²
data to parameter ratio	1172/183
GOF on F ²	1.059
final R indices { <i>I</i> > 2 σ (<i>I</i>)}	R ₁ = 0.0374, wR ₂ = 0.0960
R indices (all data)	R ₁ = 0.0377, wR ₂ = 0.0964
largest diff. peak and hole	0.177 and -0.185 e.Å ⁻³

$$R_1 = \frac{\sum F_o - F_c}{\sum F_o}$$

$$wR_2 = \left\{ \frac{\sum w(F_o^2 - F_c^2)}{\sum wF_o^4} \right\}^{1/2}, \text{ where } w = 1 / \{ \sigma^2 F_o^2 + (0.0712P)^2 + 0.09P \},$$

$$\text{where } P = \{ \text{Max}(F_o^2, 0) + 2F_c^2 \} / 3$$

(1*S*,11*B*R)-9,10-Dimethoxy-[(*R*)-*N*-(2-phenylethyl)carbonyloxy]-1,2,3,6,7,11*b*-hexahydro-benzo[*a*]

quinolizine-4-one (15). To a solution of 1-hydroxy-benzo[*a*]quinolizine (**5**, 50 mg, 0.18 mmol) and (*R*)- α -methylbenzyl isocyanate (52 mg, 0.36 mmol) in THF-DMF (3ml/3ml) was added catalytic amount of NaH and the mixture was stirred at room temperature overnight. The mixture was quenched by adding 4 drops of water and diluted with EtOAc (20 ml). The solution was washed with saturated aqueous NaHCO₃ solution (10 ml), brine, dried over MgSO₄, and concentrated. The residue was purified by flash column chromatography (EtOAc only) to give **15** in quantitative yield: mp 174-176 °C; ¹H-NMR (300 MHz, CDCl₃) δ 7.27-7.35 (5H, m, Ar), 6.84 (1H, s, Ar), 5.42 (1H, s, Ar), 5.42 (1H, m, H₁), 5.25 (1H, d, *J*=6.4 Hz, H_{11*b*}), 4.88 (1H, m, CH₃CH), 4.68 (1H, m, H₆), 3.84 (3H, s, CH₃O), 3.69 (3H, s, CH₃O), 2.92 (1H, m, H₇), 2.80 (1H, m, H₇), 2.56-2.62 (2H, m, H₃, H₆), 2.37 (1H, m, H₃), 1.94-1.99 (2H, m, 2 x H₂), 1.53 (3H, d, *J*=6.3 Hz, CH₃); ¹³C-NMR (75 MHz, CDCl₃) δ 169.66, 155.32, 148.99, 129.42, 128.87, 128.19, 127.08, 126.58, 112.68, 108.75, 71.84, 61.37, 56.60, 51.61, 42.13, 28.87, 28.66, 24.64, 23.15; Chiral phase HPLC analysis: Column; CSP (R, R) Whelk-01, 25 cm x 4.6 mm i.d., Flow rate; 1.0 ml / min, Mobile phase; EtOH : hexane : NEt₃ = 60 : 40 : 0.1, Detector; UV (280 nm), Retention time; 10.73 min.

(1*S*,11*B*R)-9,10-Dimethoxy-1-(1-imidazolethiocarbonyloxy)-1,2,3,6,7,11*b*-hexahydro-benzo[*a*]quinolizine

-4-one (16). To a solution of 1-hydroxybenzoquinolizine (**5**, 167 mg, 0.6 mmol) in CH₂Cl₂ (5 ml) was added thiocarbonyldiimidazole (0.22 g, 1.2 mmol) under argon atmosphere and refluxed for 12 h. The reaction mixture was cooled to room temperature and washed with water, dried over MgSO₄, and concentrated. The residue was purified by flash column chromatography (EtOAc only) to give **16** as a pale yellow oil (0.22 g, 96 %): [α]_D²⁴ -24.6° (*c* 3.15, CHCl₃); IR (neat) 2928, 1636 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 8.40 (1H, s), 7.66 (1H, s), 7.09 (1H, s), 6.90 (1H, s), 6.65 (1H, s), 6.26 (1H, br s, H₁), 5.00 (1H, br s, H_{11*b*}), 4.80 (1H, m, H₆), 3.86 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 2.80-3.03 (2H, m, 2 x H₇), 2.51-2.73 (3H, m, 2 x H₃, H₆), 2.03-2.19 (2H, m, 2 x H₂).

(11*B*R)-9,10-Dimethoxy-1,2,3,6,7,11*b*-hexahydro-benzo[*a*]quinolizine-4-one (17).

A solution of thiocarbonylimidazolide (**16**, 220 mg, 0.57 mmol) in dry toluene (10 ml) was added dropwise to a refluxing solution of tributyltin hydride (0.23 ml, 0.85 mmol) in toluene (40 ml) *via* syringe over 20 min under argon atmosphere. After refluxing for 4 h, the reaction mixture was concentrated and diluted with acetonitrile (40 ml). The acetonitrile solution was washed with hexane (10 ml x 2) to remove tin-containing compounds, concentrated, and purified by flash column chromatography (EtOAc only) to give **17** as a colorless oil (108 mg, 73 %): [α]_D²⁴ -212.5° (*c* 2.93, CHCl₃); IR (neat) 2980, 1636 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 6.65 (1H, s), 6.59 (1H, s), 4.83 (1H, m, H₆), 4.58 (1H, dd, *J*=4.4, 10.1 Hz, H_{11*b*}), 3.83 (6H, s, 2 x CH₃O), 2.74-2.94 (2H, m,

2 x H₇), 2.53-2.62 (3H, m, 2 x H₃, H₆), 2.36 (1H, m, H₂), 1.82-1.96 (2H, m, H₁, H₂), 1.66 (1H, m, H₁); ¹³C-NMR (75 MHz, CDCl₃) δ 169.83, 148.44 (2C), 129.82, 127.98, 112.37, 109.14, 57.28, 56.78, 56.51, 40.27, 32.80, 31.53, 29.07, 20.19; MS, m/z (relative intensity, %): 261 (M⁺, 72), 260 (54), 246 (31), 230 (31), 191 (100), 146 (68); HRMS (EI) Calcd for C₁₅H₁₉NO₃: 261.1362. Found: 261.1365.

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15. Complete data including atomic coordinates, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Center.

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