Pergamon

Tetrahedron, Vol. 53, No. 9, pp. 3045-3056, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00070-7

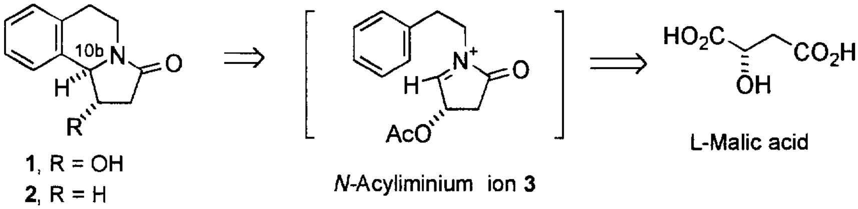
Asymmetric Synthesis of Functionalized Benzo[*a*]quinolizine Derivatives *via* a Diastereoselective *N*-Acyliminium Ion Cyclization

Yong Sup Lee*[a], Soo Sung Kang[a,b], Jung Hoon Choi[b] and Hokoon Park*[a]

[a]Division of Applied Science, Korea Institute of Science & Technology, P.O. Box 131 Cheongryang, Seoul 130-650, Korea
[b]Department of Chemistry, Hanyang University, Seoul 133-791, Korea

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 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]



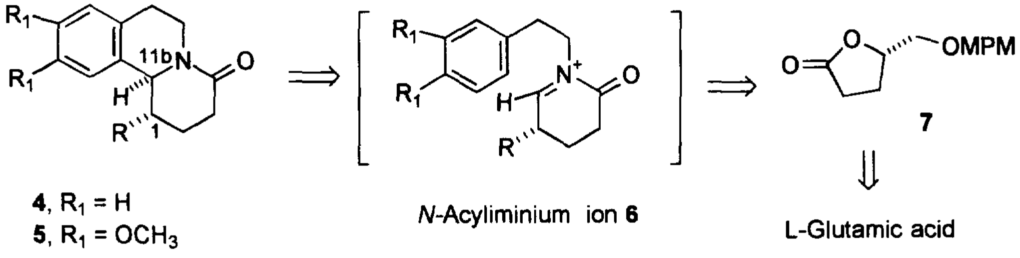
Scheme 1

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

---

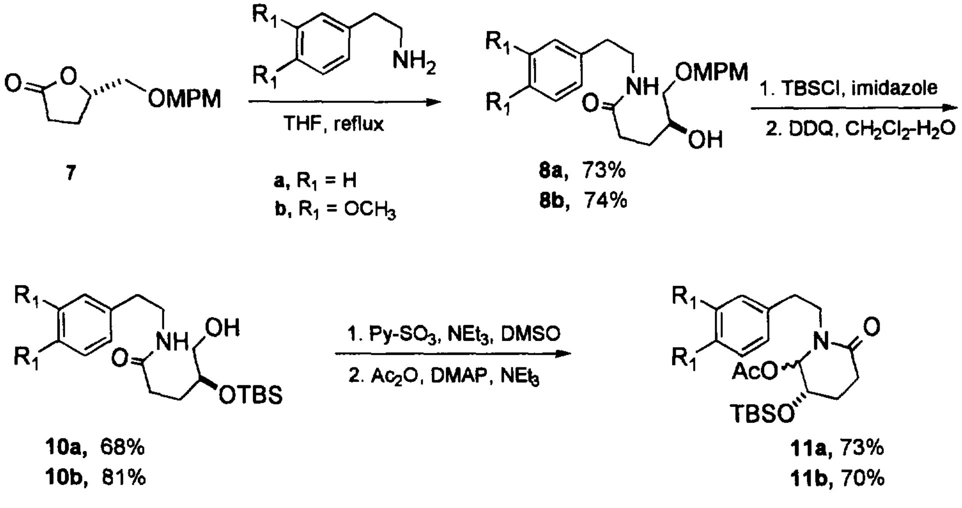
Dedicated to Prof. Sang Chul Shim on the occasion of his 60th birthday.

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



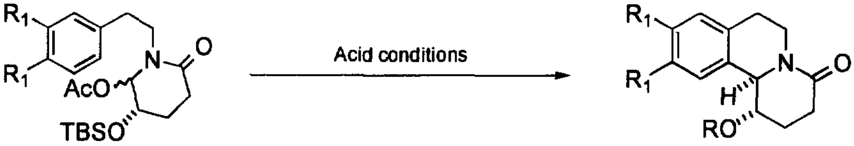
Scheme 2

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 findings[4] 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 DDQ[9] to afford **10a** and **10b**. Parikh oxidation[10] of the primary alcohol in **10a** and **10b** followed by acetylation of the resulting hydroxylactams afforded chiral acetoxylactams (**11a**, **11b**) as mixtures of epimers.

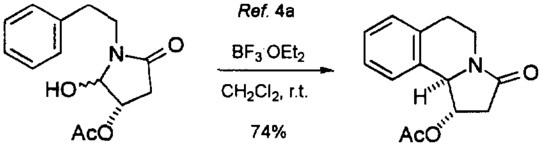


11a, R_1=H
11b, R_1=OCH_3

4, R_1=H, R=H, 20%, 1. HCO_2H, reflux; 2. AcCl, EtOH.
5, R_1=OCH_3, R=H, 83%, $BF_3 \cdot OEt_2$, r.t.
14, R_1=OCH_3, R=TBS, 86%, $BF_3 \cdot OEt_2$, -30 °C

Scheme 4

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 $BF_3 \cdot OEt_2$,[4a] TsOH,[5c,5d] CH_3SO_3H[4b] were unsuccessful. Significant decomposition of **11a** was observed.



12 **13**

Scheme 5

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 known[2] and the cyclization of *N*-acyliminium ion derived from 5-membered lactam (**12**) proceed easily with $BF_3 \cdot OEt_2$ at room temperature (Scheme 5) from our previous result.[4a] On the other hand, the acetoxylactam **11b**, which has more reactive 3,4-dimethoxyphenyl ring as a π-nucleophile, cyclized smoothly with $BF_3 \cdot OEt_2$ 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-hydroxy-benzo[*a*]quinolizine (**5**) in quantitative yield. 1-Hydroxy-benzo[*a*]quinolizine (**5**) could be obtained directly in 83 % yield when the acetoxylactam **11b** was treated with $BF_3 \cdot OEt_2$ 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 results[4] 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 silyoxy 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 a catalytic amount of NaH to provide **15** in a diastereomeric form. To the limits of detection by 300 MHz ^{1}NMR 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.

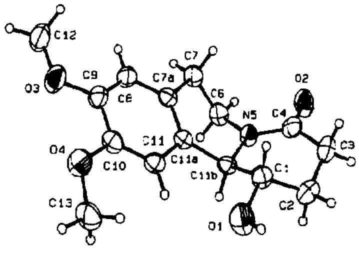
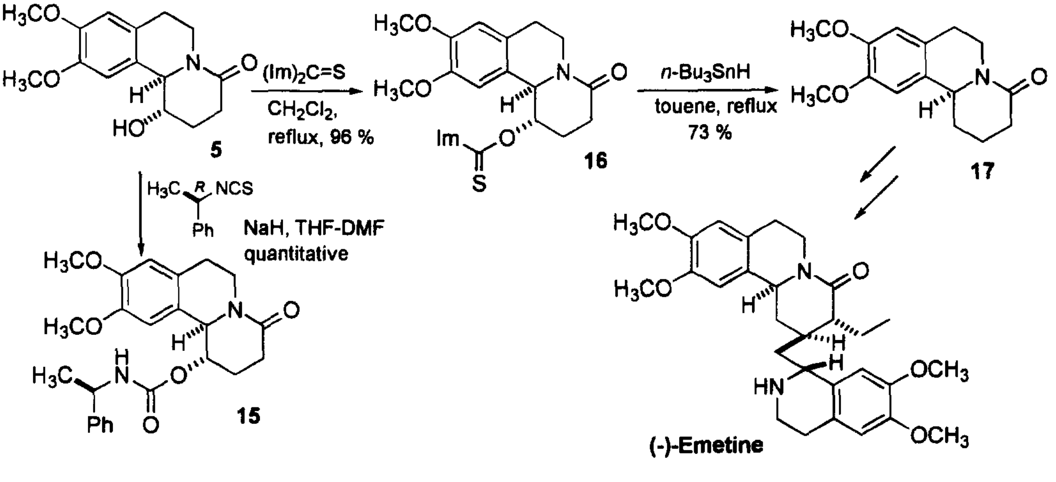


Fig 1. The X-Ray structure of **5**

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 (±)-emetine.[5c] Treatment of **5** with *N,N*-thiocarbonyldiimidazole in CH_2Cl_2 afforded thiocarbonylimidazolide **16** in 96 % yield. Compound **16** was transformed to benzo[*a*]quinolizine derivative **17** ($[\alpha]^{26}_D$ -212.5° (*c* 2.93, $CHCl_3$)) 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 (-)-emetine[13] 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. ^{1}H NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer. ^{13}C 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 F_{254} plates.

***N*-2-Phenylethyl (*4S*)-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; $[\alpha]^{24}_{D}$ -2.32° (*c* 2.98, $CHCl_3$); IR (KBr) 3306, 2933, 1645 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.84-7.29 (9H, m, Ar), 6.38 (1H, br s, $\underline{NH}$), 4.43 (2H, s, $O\underline{CH_2}Ar$), 3.75 (4H, br s, $\underline{CH_3}O$, $\underline{CH}OH$), 3.47-3.30 (4H, m, $MPMO\underline{CH_2}$, $NH\underline{CH_2}$), 2.76 (2H, t, *J*=7.1 Hz, Ph-$\underline{CH_2}$), 2.27 (2H, t, *J*=7.0 Hz, $CO\underline{CH_2}$), 1.79 (1H, m, $\underline{CH_2}CHOH$), 1.65 (1H, m, $\underline{CH_2}CHOH$); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{21}H_{27}NO_4$: 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 (*4S*)-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; $[\alpha]^{24}_{D}$-0.51 (*c* 3.13, $CHCl_3$); IR (KBr) 3296, 2898, 1636 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) 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, $\underline{NH}$), 4.43 (2H, s, $O\underline{CH_2}Ar$), 3.83 (3H, s, $\underline{CH_3}O$), 3.82 (3H, s, $\underline{CH_3}O$), 3.76 (3H, s, $\underline{CH_3}O$), 3.31-3.47 (4H, m, $MPMO\underline{CH_2}$ and $NH\underline{CH_2}$), 2.71 (2H, t, *J*=7.1 Hz, $Ar\underline{CH_2}CH_2$), 2.27 (2H, t, *J*=6.9 Hz, $CO\underline{CH_2}$), 1.75-1.83 (1H, m, $\underline{CH_2}CHOH$), 1.60-1.70 (1H, m, $\underline{CH_2}CHOH$); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{23}H_{31}NO_6$: C 66.17, H 7.48, N, 3.35. Found: C 66.07, H 7.38, N 3.34.

***N*-2-Phenylethyl (*4S*)-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 H_2O (100 ml), brine (100 ml × 3), dried over

$MgSO_4$, and concentrated to afford **9a** an oil (3.12 g, 99 %): $[\alpha]^{24}_D$ -9.36° (*c* 4.06, $CHCl_3$); IR (neat) 2930, 1646 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 6.85-7.32 (9H, m, Ar), 5.65 (1H, br s, NH), 4.43 (2H, s, OCH_2Ar), 3.85 (1H, m, CHOH), 3.79 (3H, s, CH_3O), 3.29-3.52 (4H, m, $MPMOCH_2$, $NHCH_2$), 2.78 (2H, t, *J*=7.0 Hz, $PhCH_2$), 2.13-2.25 (2H, m, $COCH_2$), 1.72-1.93 (2H, m, CH_2CHOH), 0.89 (9H, s, *t*-butyl), 0.02 (6H, s, $(CH_3)_2Si$); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{27}H_{41}NO_4Si$: 471.2808. Found 471.2805.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl] (*4S*)-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: $[\alpha]^{24}_D$ -7.25° (*c* 2.73, $CHCl_3$); IR (neat) 2930, 1646 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) 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, OCH_2Ar), 3.77 (3H, s, CH_3O), 3.76 (3H, s, CH_3O), 3.71 (3H, s, CH_3O), 3.35-3.39 (2H, m, $NHCH_2$), 3.23-3.31 (2H, m, $MPMOCH_2$), 2.66 (2H, t, *J*=7.0 Hz, $ArCH_2CH_2$), 2.11-2.19 (2H, m, $COCH_2$), 1.80-1.85 (1H, m, CH_2CHOSi), 1.68-1.73 (1H, m, CH_2CHOSi), 0.82 (9H, s, *t*-butyl), 0.02 (6H, s, $(CH_3)_2Si$); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{29}H_{45}NO_6Si$: 531.3007. Found: 531.3015.

***N*-2-Phenylethyl (*4S*)-4-(*t*-butyldimethylsilyloxy)-5-hydroxypentanamide (10a).** To a stirred solution of MPM ether (**9a**, 0.3 g, 0.64 mmol) in CH_2Cl_2-H_2O (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 CH_2Cl_2 (5 ml × 2). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution (15 ml), brine (15 ml), dried over $MgSO_4$, 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; $[\alpha]^{24}_D$ +9.85° (*c* 2.58, $CHCl_3$); IR (KBr) 3268, 2932, 1640 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) 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, $NHCH_2$, CH_2OH), 2.80 (2H, t, *J*=7.0 Hz, $ArCH_2CH_2$), 2.09-2.31 (2H, m, $COCH_2$), 1.75-1.92 (2H, m, $COCH_2CH_2$), 0.88 (9H, s, *t*-butyl), 0.06 (6H, s, $(CH_3)_2Si$); ^{13}C-NMR (75 MHz, $CDCl_3$) 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^+ - $2CH_3$, 2), 320 (16), 294 (M^+- *t*-butyl, 71), 276 (12), 242 (49), 231 (17), 105 (100), 75 (65); Anal. Calcd for $C_{19}H_{33}NO_3Si$: 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] (*4S*)-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 ; $[\alpha]^{26}_D$ + 9.15° (*c* 1.06, CHCl$_3$); IR (KBr) 3286, 2932, 1644 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 6.68-6.78 (3H, m, Ar), 5.80 (1H, br s, NH), 3.82 (6H, s, 2 x CH$_3$O), 3.76 (1H, m, CHOSi), 3.39-3.45 (4H, m, COCH$_2$, CH$_2$OH), 2.72 (2H, t, *J*=6.9 Hz), 2.12-2.27 (2H, m, PhCH$_2$), 1.75-1.88 (2H, m, CH$_2$CHOSi), 0.85 (9H, s, *t*-butyl), 0.05 (6H, s, Si(CH$_3$)$_2$); ^{13}C-NMR (75 MHz, CDCl$_3$) 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$^+$-H$_2$O, 5), 355 (M$^+$-*t*-butyl, 12), 171 (31), 165 (83), 164 (100), 151 (37), 73 (61); Anal. Calcd for C$_{21}$H$_{37}$NO$_5$Si: 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-SO$_3$ 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 MgSO$_4$, and concentrated. The residue was diluted with CH$_2$Cl$_2$ (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 MgSO$_4$, concentrated, and purified by flash column chromatography (EtOAc : hexane = 1 : 2) to give acetoxylactam (**11a**, 0.91 g, 73 %) as an oil (ca. 2.3 : 1 mixture of epimers from ^{1}H-NMR analysis): IR (neat) 2930, 1743, 1664 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.16-7.26 (5H, m, Ar), 5.85 (1H, br s, AcOCH), 3.94 (1H, br s, CHOSi), 3.86 (1H, m, NCH$_2$), 3.12 (1H, m, NCH$_2$), 2.74-2.85 (2H, m, PhCH$_2$), 2.62 (1H, m, COCH$_2$), 2.37 (1H, m, COCH$_2$), 2.00 & 2.02 (3H, two s, CH$_3$CO), 1.73-1.78 (2H, m, COCH$_2$CH$_2$), 0.82 & 0.92 (9H, two s, *t*-butyl); ^{13}C-NMR (75 MHz, CDCl$_3$) 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 C$_{21}$H$_{33}$NO$_4$Si: 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 ^{1}H-NMR analysis): mp 107 °C; IR (KBr) 2956, 1748, 1650 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 6.72 (3H, br s, Ar), 5.83 (1H, br s, AcOCH), 3.92 (1H, m, CHOSi), 3.82 (3H, s, CH$_3$O), 3.78 (3H, s, CH$_3$O), 3.08 (1H, m, NCH$_2$), 2.66-2.77 (2H, m, ArCH$_2$), 2.60 (1H, m, COCH$_2$), 2.34 (1H, dd, *J*=17.5, 5.5 Hz, COCH$_2$), 2.03 (3H, s, CH$_3$CO), 1.69-1.78 (2H, m, COCH$_2$CH$_2$), 0.83 & 0.76 (9H, two s, *t*-butyl); ^{13}C-NMR (75 MHz, CDCl$_3$) 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 C$_{23}$H$_{37}$NO$_6$Si: C 61.17, H 8.26, N 3.10. Found: C 61.11, H 8.20, N 3.10.

(*1S,11bR*)-1-Hydroxy-1,2,3,6,7,11b-hexahydro-benzo[*a*]quinolizine-4-one (4). A solution of acetoxylactam (**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 $NaHCO_3$ solution (10 ml), brine (10 ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (EtOAc only) of the residue and recrystallization from CH_2Cl_2-ethyl acetate afforded **4** (17 mg, 20 %) as a needle: mp 143-144 °C; $[\alpha]^{26}_D$ -141.4° (*c* 0.37, $CHCl_3$); IR (KBr) 3369, 2928, 1614 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.57 (4H, m, Ar), 4.61-4.66 (1H, m, H_6), 4.54 (1H, d, *J*=7.0 Hz, H_{11b}), 4.08 (1H, m, H_1), 2.87-2.96 (2H, m, 2 x H_7), 2.64-2.79 (2H, m, H_3, H_6), 2.41-2.48 (1H, m, H_3), 1.97-2.13 (2H, m, 2 x H_2); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{13}H_{15}NO_2$: 217.1103. Found: 217.1103.

(*1S,11bR*)-1-(*t*-Butyldimethylsilyloxy)-9,10-dimethoxy-1,2,3,6,7,11b-hexahydro-benzo[*a*]quinolizine-4-one (14). To a solution of acetoxylactam (**11b**, 166 mg, 0.383 mmol) in dry CH_2Cl_2 (5 ml) was added $BF_3 \cdot OEt_2$ (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 CH_2Cl_2 (50 ml) and quenched by addition of saturated aqueous $NaHCO_3$ solution (50 ml). The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (EtOAc : hexane = 2 : 3) to give **14** as a colorless oil (124 mg, 86 %): $[\alpha]^{27}_D$ -30.7° (*c* 4.00, $CHCl_3$); ^1H-NMR (300 MHz, $CDCl_3$) δ 6.75 (1H, s, Ar), 6.58 (1H, s, Ar), 4.68 (1H, m, H_1), 4.42 (1H, d, *J*=5.0 Hz, H_{11b}), 4.06 (1H, m, H_6), 3.80 (3H, s, $O\underline{CH_3}$), 3.79 (3H, s, $O\underline{CH_3}$), 2.83-2.63 (3H, m, H_6, 2 x H_7), 2.56 (1H, m, H_3), 2.36 (1H, m, H_3), 1.76-1.87 (2H, m, 2 x H_2), 0.83 (9H, s, *t*-butyl), -0.06 (6H, s, $Si(\underline{CH_3})_2$); MS, m/z (relative intensity, %): 392 (M^+, 26), 334 (M^+- *t*-butyl, 39), 232 (23), 191(100), 176 (30).

(*1S,11bR*)-9,10-Dimethoxy-1-hydroxy-1,2,3,6,7,11b-hexahydro-benzo[*a*]quinolizine-4-one (5). To a solution of acetoxylactam (**11b**, 173 mg, 0.383 mmol) in dry CH_2Cl_2 (5 ml) was added $BF_3 \cdot OEt_2$ (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 $NaHCO_3$ solution (10 ml). The mixture was extracted with CH_2Cl_2 (15 ml), dried over $MgSO_4$ and concentrated. Flash column chromatography (EtOAc : hexane = 1 : 1) of the residue and recrystallization from CH_2Cl_2-methanol afforded **5** as a needle (88 mg, 83 %): mp 194-195 °C; $[\alpha]^{24}_D$ -152.6° (*c* 2.35, $CHCl_3$); 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_{11b}), 4.38 (1H, m, H_6), 3.97 (1H, m, H_1), 3.72 (6H, s, $O\underline{CH_3}$), 2.50-2.82 (3H, m, H_6, 2 x H_7), 2.38 (1H, m, H_3), 2.21 (1H, m, H_3), 1.76-1.83 (2H, m, 2 x H_2); ^{13}C-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 Kα (λ=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	$P2_12_12_1$ (No. 19)
a, Å	8.112(2)
b, Å	12.094(2)
c, Å	13.770(3)
V, $Å^3$	1351.0(5)
Z	4
d_{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	$0 \leq h \leq 9$, $0 \leq k \leq 14$, $0 \leq l \leq 16$
reflections collected	1172
independent reflections{$I>2\sigma(I)$}	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 {$I>2\sigma(I)$}	$R_1 = 0.0374$, $wR_2 = 0.0960$
R indices (all data)	$R_1 = 0.0377$, $wR_2 = 0.0964$
largest diff. peak and hole	0.177 and -0.185 $e.A^{-3}$

$R_1 = \Sigma Fo\text{-}Fc/\Sigma Fo$

$wR_2 = \{\Sigma w(Fo^2\text{-}Fc^2)^2/\Sigma wFo^4\}^{1/2}$, where $w = 1/\{\sigma^2Fo^2+(0.0712P)^2 + 0.09P\}$,

where $P = \{Max(Fo^2,0)+2Fc^2\}/3$

(*1S,11bR*)-9,10-Dimethoxy-[(*R*)-*N*-(2-phenylethyl)carbonyloxy]-1,2,3,6,7,11b-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 $NaHCO_3$ solution (10 ml), brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (EtOAc only) to give **15** in quantitative yield: mp 174-176 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27-7.35 (5H, m, Ar), 6.84 (1H, s, Ar), 5.42 (1H, s, Ar), 5.42 (1H, m, H_1), 5.25 (1H, d, *J*=6.4 Hz, H_{11b}), 4.88 (1H, m, $CH_3\underline{CH}$), 4.68 (1H, m, H_6), 3.84 (3H, s, $\underline{CH_3}O$), 3.69 (3H, s, $\underline{CH_3}O$), 2.92 (1H, m, H_7), 2.80 (1H, m, H_7), 2.56-2.62 (2H, m, H_3, H_6), 2.37 (1H, m, H_3), 1.94-1.99 (2H, m, 2 x H_2), 1.53 (3H, d, *J*=6.3 Hz, $\underline{CH_3}$); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 : NEt_3 = 60 : 40 : 0.1, Detector; UV (280 nm), Retention time; 10.73 min.

(*1S,11bR*)-9,10-Dimethoxy-1-(1-imidazolethiocarbonyloxy)-1,2,3,6,7,11b-hexahydro-benzo[*a*]quinolizine -4-one (16). To a solution of 1-hydroxybenzoquinolizine (**5**, 167 mg, 0.6 mmol) in CH_2Cl_2 (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 $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (EtOAc only) to give **16** as a pale yellow oil (0.22 g, 96 %): $[\alpha]^{24}_D$ -24.6° (*c* 3.15, $CHCl_3$); IR (neat) 2928, 1636 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) 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, H_1), 5.00 (1H, br s, H_{11b}), 4.80 (1H, m, H_6), 3.86 (3H, s, $O\underline{CH_3}$), 3.78 (3H, s, $O\underline{CH_3}$), 2.80-3.03 (2H, m, 2 x H_7), 2.51-2.73 (3H, m, 2 x H_3, H_6), 2.03-2.19 (2H, m, 2 x H_2).

(*11bR*)-9,10-Dimethoxy-1,2,3,6,7,11b-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 %): $[\alpha]^{24}_D$ -212.5° (*c* 2.93, $CHCl_3$); IR (neat) 2980, 1636 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.65 (1H, s), 6.59 (1H, s), 4.83 (1H, m, H_6), 4.58 (1H, dd, *J*=4.4, 10.1 Hz, H_{11b}), 3.83 (6H, s, 2 x $\underline{CH_3}O$), 2.74-2.94 (2H, m, 2 x H_7), 2.53-2.62 (3H, m, 2 x H_3, H_6), 2.36 (1H, m, H_2), 1.82-1.96 (2H, m, H_1, H_2), 1.66 (1H, m, H_1); ^{13}C-NMR (75 MHz, $CDCl_3$) 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 $C_{15}H_{19}NO_3$: 261.1362. Found: 261.1365.

Acknowledgment. Financial support from the Korea Ministry of Science and Technology is gratefully acknowledged.

References and notes

1. (a) Ludwig, C.; Wistrand, L.-G. *Acta Chim. Scand.* **1994**, *48*, 367. (b) Mangeney, P.; Gosmini, R.; Raussou, S.; Commercon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*. 1877. (c) Zhang, P.; Cook, J.M. *Tetrahedron Lett.* **1995**, *36*, 6999.
2. (a) Hiemstra, H. and Speckamp, W.N. *Additions to N-Acyliminium ions.* In *Comprehensive Organic Synthesis;* Trost, B.M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 1047-1082. (b) Speckamp, W.N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
3. (a) Lee, Y.S.; Kim, S.H.; Jung, S.H.; Lee, S.J.; Park, H. *Heterocycles* **1994**, *37*, 303. (b) Lee, Y.S.; Kim, C.S.; Park, H. *Heterocycles* **1994**, *38*, 2605.
4. (a) Lee, Y.S.; Kang, D.W.; Lee, S.J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149. (b) Lee, Y.S.; Kang, D.W.; Lee, S.J.; Park, H. *Synth. Commun.* **1995**, *25*, 1947.
5. (a) Palasz, P.D.; Utley, J.H.P.; Hardstone, J.D. *Acta Chim. Scand.* **1984**, *38*, 281. (b) Bhattacharjya A.; Bhattacharya P.K.; Pakrashi, S.C. *Heterocycles* **1983**, *20*, 2397. (c) Kametani, T.; Surgenor, S.A.; Fukumoto, K. *Heterocycles* **1980**, *14*, 303. (d) Kametani, T.; Surgenor, S.A.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1*, **1980**, *14*, 303.
6. (a) Lee, L.C.; Borght, T.V.; Sherman, P.S.; Frey, K.A.; Kilbourn, M.R. *J. Med. Chem.* **1996**, *39*, 191. (b) Kobor, J.; Sohar, P.; Fulup, F. *Tetrahedron* **1994**, *50*, 4873.
7. (a) Meyer, A.I.; Du, B.; Gonzalez, M.A. *J. Org. Chem.* **1990**, *55*, 4218. (b) Takeuchi, Y.; Kamada, Y.; Nishimura, K.; Nishioka, H.; Nishikawa, M.; Hashigaki, K.; Yamamoto, M.; Harayama, T. *Chem. Pharm. Bull.* **1994**, *42*, 796.
8. (a) Huh, N.; Thompson, C.M. *Tetrahedron* **1995**, *51*, 5935. (b) Oishi T.; Iwakuma, T.; Hirama, M.; Ito, S. *Synlett* **1995**, 404. (c) Tse, A.; Mansour, T.S. *Tetrahedron Lett.* **1995**, *36*, 7807.
9. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
10. Parikh, J.R.; Doering, W.E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
11. (a) Tsuda, Y.; Sakai, A.; Kaneko, M.; Ishiguro, Y.; Isobe, K.; Taga, J.-I; Sano, T. *Chem. Pharm. Bull.* **1990**, 38, 1462. (b) Mondon, A. *Chem. Ber.* **1959**, *92*, 1461.
12. Wu, E.S.C.; Mack, R.A.; Kover, A., Loch III, J.T.; Mullen, G.; Murray, R.J.; Gordon, J.C.; Machulskis, A.C.; McCreedy, S.A.; Blosser, J.C. *Bioorg. Chem. Lett.* **1995**, *5*, 1813.

13. Ihara, M.; Yasui K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc. Perkin Trans 1* **1990**, 1469.
14. (a) Sheldrick, G.M. SHELXS-86: A program for structure determination. University of Gottingen, Germany, 1986. (b) Sheldrick, G.M. SHELXS-93: A program for structure determination. University of Gottingen, Germany, 1993.
15. Complete data including atomic coordinates, bond lengths and bond angles have been deposited at the Cambridge Crystallographic Data Center.

(*Received in Japan* 6 *December* 1996; *accepted* 16 *January* 1997)