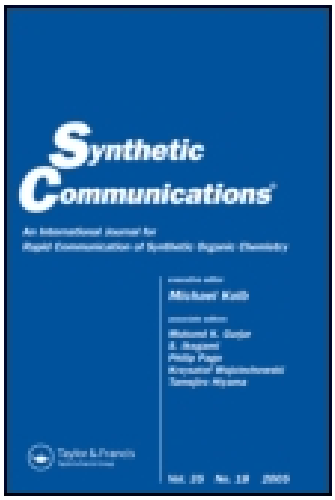

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SYNTHESIS OF CYCLOPENTENE-FUSED PYRROLOISOQUINOLINONE DERIVATIVE VIA N-ACYLIMINIUM ION CYCLIZATION

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SYNTHESIS OF CYCLOPENTENE-FUSED PYRROLOISOQUINOLINONE DERIVATIVE VIA *N*-ACYLIMINIUM ION CYCLIZATION

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ABSTRACT

In this research, a new class of pyrrolo[2,1-*a*]isoquinolinone derivative **7** was prepared. C-4 Hydroxylated 5-ethoxylactam **1b** gave 4,5-epoxylactam **2** in high yield instead of isoquinoline derivative **3b** under the *N*-acyliminium ion cyclization condition. The 4,5-epoxylactam **2** was converted to another *N*-acyliminium ion precursor **6** through base-promoted epoxide ring opening, silylation, and thermal Diels–Alder reaction with cyclopentadiene in high yield. Finally, compound **6** was cyclized in the presence of $TiCl_4$ to provide cyclopentene-fused pyrroloisoquinoline derivative **7**.

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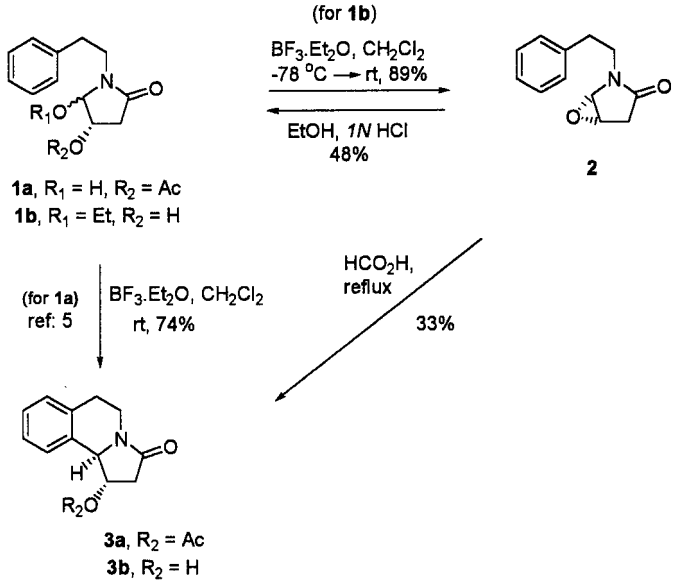
INTRODUCTION

For many researchers, the *N*-acyliminium ion has been used as a reactive intermediate for efficient synthetic method, in particular for carbon–carbon bond formation.[1] We also recently reported synthetic routes to several heterocyclic systems such as azepinoindole, quinolizidine and indolizidine rings through the *N*-acyliminium ion cyclization strategy.[2] In our previous synthesis of pyrroloisoquinoline derivatives via *N*-acyliminium ion cyclization of 5-ethoxy or 5-hydroxylactams (for example, **1a**) derived from L-malic acid and L-tartaric acid, the protection of C-4 hydroxyl group was important in getting high yields of cyclized products (Scheme 1).[3]

In case of refluxing 4-acetoxy-5-hydroxylactam **1a** in formic acid, the cyclized product **3a** was obtained in high yield (74%) whereas the cyclized product **3b** was obtained only in less than 20% yield when 4-hydroxy-5-ethoxylactam **1b** was used in the same reaction condition. We presumed that the low yield of the desired cyclized product was due to the formation of less reactive 4,5-epoxylactam **2** as an intermediate. Herein we wish to report the synthesis and potential utility of **2** by the synthesis of cyclopentene-fused pyrroloisoquinoline derivative **7**.

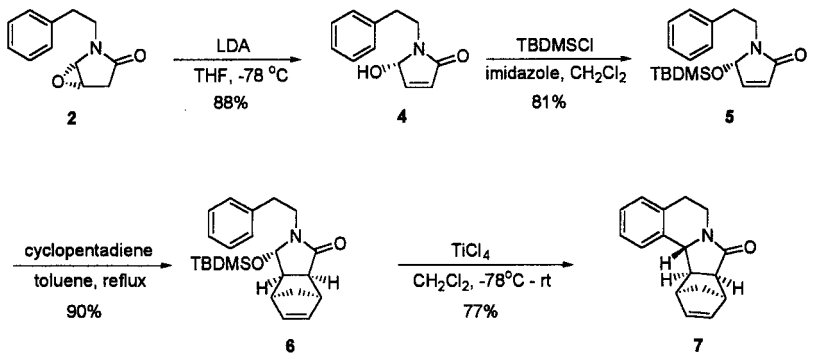


Scheme 1.

RESULTS AND DISCUSSION

During the investigation of cyclization of **1b**, we found that 4,5-epoxylactam **2** could be obtained in high yield by the treatment of **1b** with $BF_3 \cdot Et_2O$ at room temperature (Scheme 1). The presence of epoxide ring in **2** was proved by the ready conversion to the starting 5-ethoxylactam **1b** upon treatment of 1 N HCl in ethanol. The 4,5-epoxylactam **2** can also be transformed to the cyclized product **3b** in 33% yield when heated at reflux in formic acid. To examine the synthetic utility of **2**, the openings of epoxide ring by several nucelophiles were tried. However, the attempts to open the ring by using ethylmagnesium bromide, allyltrimethylsilane, or trimethylaluminum were unsuccessful. The less reactivity of epoxide ring was unexpected since the epoxide ring-opening reaction of 1-phenoxycarbonyl-2,3-epoxy-pyrrolidine with allyltrimethylsilane has been known in the literature.[4]

On the other hand, when **2** was treated with LiHDMS, unsaturated 5-hydroxy-enlactam **4** was obtained in 29% yield. The yield of **4** was improved to 88% yield by using LDA as a base (Scheme 2). Since the enantiomeric purity could not be checked by chiral HPLC or ^{1}H NMR using chiral shifting agent at this stage, compound **4** was converted to 5-silyloxy-enlactam **5** in 81% yield. The enantiomeric excess of **5** was determined to be 77% by ^{1}H NMR analysis using the chiral shifting agent $Eu(hfc)_3$.[5] The configuration of C-5 was assigned to *S* by comparison of the optical rotation of **5** with that of (5*S*)-1-benzyl-5-(*tert*-butyldimethylsilyloxy)-1,5-dihydro-pyrrol-2-one, which was prepared by Yoda group.[6] The moderate enantiomeric purity of **5** seems to be due to the slight equilibrium of 5-hydroxy-enlactam **4** to its ring-opened aldehydo–enamide structure during the formation of **4** or the silylation step.



Scheme 2.

The 5-silyloxy-enlactam **5** was used as a dienophile in the thermal Diels–Alder reaction with cyclopentadiene[7a] to gain a tricyclic lactam **6** in 90% yield. The thermal Diels–Alder reaction of **5** is expected to proceed with a high endoselectivity and diastereoselectivity as was previously reported.[7] The tricyclic lactam **6** was subjected to the *N*-acyliminium ion cyclization condition to form pentacyclic pyrrolo[2,1-*a*]isoquinolinone ring **7**. Interestingly, the tricyclic lactam **6** did not cyclize efficiency under the influence of $BF_3 \cdot Et_2O$ to give the cyclized product **7** only in 10% yield. On the other hand, the stronger Lewis acid, $TiCl_4$ was an efficient activator[8] for the cyclization to provide **7** in high yield (77%) and as a single diastereomer resulting from a diastereoselective attack of benzene ring *anti* to the cyclopentene ring during the cyclization. The chemical shifts of each protons and the stereochemistry of angular position in **7** could be fully assigned by using ^{1}H NMR, in particular ^{1}H-^{1}H COSY techniques.

In conclusion, we have found that C-4 hydroxylated 5-ethoxylactam **1b** gave 4,5-epoxylactam **2** in high yield instead of isoquinoline ring under the *N*-acyliminium ion cyclization condition. The 4,5-epoxylactam **2** was converted to another *N*-acyliminium ion precursor **6** through base-promoted epoxide ring opening, silylation, and thermal Diels–Alder reaction with cyclopentadiene in high yield. Finally, compound **6** was cyclized in the presence of $TiCl_4$ to provide cyclopentene-fused pyrroloisoquinoline derivative **7**. Although, we have shown one example on the utility of 4,5-epoxylactam by synthesizing cyclopentene-fused pyrroloisoquinoline derivative and the enantiomeric excess of 5-silyloxy-enlactam **5** was not high enough, it seems that 4,5-epoxylactam can be useful intermediate in the synthesis of several chiral or racemic form of isoquinoline or pyrrolidine derivatives by chemical transformation. We are now investigating to improve the enatiomeric excess of 5-silyloxy-enlactam **5**.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and uncorrected. IR spectra were obtained on a Perkin Elmer 16F PC FT-IR spectrometer. The NMR spectra were recorded on Varian Gemini 300 FT or Brucker Advance 300 spectrometers at 300 MHz (for ^{1}H NMR) and 75 MHz (for ^{13}C NMR). The chemical shifts are reported in ppm downfield relative to tetramethylsilane. Mass spectra were determined with a HP 590 GC/MS 5972 MSD spectrometer and high resolution mass spectra were recorded on a Jeol JMS-AX 505WA mass spectrometer by chemical ionization method (CI) using methane as a carrier gas. Optical rotations were measured on an AUTOPOL III automatic

polarimeter and all concentrations are given in g/mL. All starting materials were obtained from commercial supplies, and used without further purification. Analytical thin layer chromatography was carried out on pre-coated silica gel (Merck Kiesegel 60 F_{254} layer thickness 0.25 mm). Flash column chromatography was carried out using Kiesegel 60 (230 ~ 400 mesh, Merck).

(1*S*,5*S*)-2-Phenethyl-6-oxa-2-aza-bicyclo[3,1,0]hexan-3-one (2): To a solution of **1b**[3b] (1.65 g, 6.62 mmol) in CH_2Cl_2 was added dropwise $BF_3{\cdot}Et_2O$ at $-78^\circ C$ for 10 min under argon atmosphere. After 2 h, the mixture was allowed to warm to r.t. and further stirred for 30 min. The mixture was poured into ice-water containing Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (EtOAc/hexane=2 : 1) to afford **3** (1.20 g, 89%) as a white solid. $R_f = 0.34$ (EtOAc/hexane = 2 : 1) M.p. 112–114°C; MS *m/z*: 203(M^+); HRMS (Cl) Calcd. for $C_{12}H_{14}NO_2$ $(M+H)^+$: *m/z* 204.1025. Found: 204.1020; $[\alpha]_D^{20} + 52.6^\circ$ (*c* 1.48, $CHCl_3$): IR (KBr, cm^{-1}) 2930, 1704, 1448, 1382, 1284, 1242, 1072, 700; ^1H NMR ($CDCl_3$) δ 7.28–7.18 (5H, m, phenyl), 4.48 (1H, d, $J = 5.3$ Hz, H-5), 4.10–3.98 (1H, m, H-4), 3.71 (1H, m, $PhCH_2CH_2$–), 3.42 (1H, m, $PhCH_2CH_2$–), 2.96–2.78 (2H, m, $PhCH_2CH_2$–), 2.71 (1H, dd, $J = 17.6$, 8.3 Hz, H-3), 2.55 (1H, dd, $J = 17.6$, 4.9 Hz, H-3′); ^{13}C NMR ($CDCl_3$) δ 171.8, 138.6, 128.7, 128.6, 126.6, 84.3, 66.4, 42.5, 36.0, 34.1.

(5*S*)-5-Hydroxy-1-phenethyl-1,5-dihydropyrrol-2-one (4): To a stirred solution of freshly distilled diisopropylamine (0.26 mL, 1.86 mmol), in THF (10 mL) was added a solution of *n*-butyllithium (0.69 mL, 2.05 mmol, 2.5 M solution in hexane) $-78^\circ C$ under argon atmosphere. The solution of LDA was slowly warmed to 0°C and stirred for 10 min and cooled again to $-78^\circ C$. To the LDA solution was added dropwise a solution of **2** (315 mg, 1.55 mmol) in THF (10 mL) for 20 min. The reaction mixture was stirred at the same temperature for 30 min and quenched by addition of sat. NH_4Cl. The solution was dispersed into excess CH_2Cl_2 and dried over $MgSO_4$. The solution was concentrated and the resulting brownish solid was recrystallized from EtOAc/hexane to give **4** (229 mg) as a white solid. The mother liquor was concentrated and purified by flash column chromatography (EtOAc/hexane = 2 : 1) to give 49 mg of **4** additionally. Yield = 88%. $R_f = 0.33$ (EtOAc/hexane=2/1). M.p. 102–104°C; MS *m/z*: 203 (M^+); HRMS (CI) Calcd. for $C_{12}H_{14}NO_2$ $(M+H)^+$: *m/z* 204.1025. Found: 204.1030; $[\alpha]_D^{20} + 37.8^\circ$ (*c* 1.08, $CHCl_3$); IR (KBr, cm^{-1}) 3158, 2832, 1662, 1590, 1428, 1312, 1120, 1090, 694; ^1H NMR ($CDCl_3$) δ 7.30–7.17 (5H, m, phenyl), 6.85 (1H, d, $J = 6.0$ Hz, H-4), 6.05 (1H, d, $J = 6.0$ Hz, H-3), 5.12 (1H, br d, $J = 5.7$ Hz, H-5), 3.75 (1H, m, $PhCH_2CH_2$–), 3.51 (1H, m, $PhCH_2CH_2$–), 2.90 (2H, t, $J = 7.1$ Hz, $PhCH_2CH$–); ^{13}C NMR ($CDCl_3$) δ 170.1, 146.4, 139.2, 129.1, 129.0, 128.6, 126.3, 84.2, 41.1, 31.0.

(5*S*)-5-(*tert*-Butyldimethylsilyloxy)-1-phenethyl-1,5-dihydropyrrol-2-one (5): To a stirred solution of **4** (915 mg, 4.5 mmol) in CH_2Cl_2 (20 mL) was added portionwise TBDMSCl (882 mg, 5.9 mmol) and imidazole (460 mg, 6.8 mmol) at r.t. and stirred for 1 h. The mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (EtOAc/hexane = 1 : 5) to give **5** (1.15 g, 81%) as a white solid. $R_f = 0.23$ (EtOAc/hexane = 1/5). M.p. 96–98°C; MS *m/z*: 317(M^+); HRMS (CI) Calcd. for $C_{18}H_{28}NO_2Si$ $(M+H)^+$: *m/z* 318.1889. Found: 318.1881; $[\alpha]_D^{20} + 41.9°$ (*c* 1.40, $CHCl_3$); IR (KBr, cm^{-1}) 2932, 1690, 1444, 1422, 1362, 1252, 1082, 862; ^1H NMR ($CDCl_3$) δ 7.24–7.11 (5H, m, phenyl), 6.69 (1H, dd, $J = 6.0$, 1.2 Hz, H-4), 6.06 (1H, d, $J = 6.0$ Hz, H-3), 5.17 (1H, s, H-5), 3.75 (1H, m, $PhCH_2CH_2$–), 3.26 (1H, m, $PhCH_2CH_2$–), 2.79 (2H, m, $PhCH_2CH_2$–), 0.83 (9H, s, –Si($C(CH_3)_3$), 0.04 (3H, s, $SiCH_3$), 0.00 (3H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 169.5, 145.8, 139.4, 129.2, 129.0, 128.9, 126.9, 84.2, 41.1, 35.2, 26.0, 8.4, −3.8, −3.9.

(1*S*,2*S*,5*S*,6*R*,7*R*)-5-(*tert*-Butyldimethylsilyloxy)-4-phenethyl-4-aza-tricyclo [5,2,1,$0^{2,6}$]dec-8-en-3-one (6): To a dried 10 mL, round-bottom-flask was added **5** (779 mg, 2.45 mmol) and fresh distillated cyclopentadiene (0.6 mL, 7.36 mmol) in dry toluene (20 mL). The reaction solution was heated at reflux for 18 h. After cooling to r.t., the mixture was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/hexane = 1 : 5) to give **6** (842 mg, 90%) as a white solid. $R_f = 0.26$ (EtOAc/hexane = 1 : 5) M.p. 148–150°C; MS *m/z*: 383 (M^+); HRMS (CI) Calcd. for $C_{23}H_{34}NO_2Si$ $(M+H)^+$: *m/z* 384.2359. Found: 384.2368; $[\alpha]_D^{20} - 3.2°$ (*c* 0.43, $CHCl_3$); IR (KBr, cm^{-1}) 2956, 1674, 1454, 1388, 1252, 1054, 840; ^1H NMR ($CDCl_3$) δ 7.16–7.02 (5H, m, phenyl), 5.86 (1H, dd, $J = 5.6$, 2.8 Hz, H-7 or H-8), 5.69 (1H, dd, $J = 5.6$, 2.8 Hz, H-7 or H-8), 4.38 (1H, s, H-5), 3.49 (1H, m, $PhCH_2CH$–), 3.47–2.89 (5H, m, $PhCH_2CH$–, H-2, H-6 and H-9), 2.56 (2H, m, $PhCH_2CH_2$–), 2.42 (1H, m, H-1), 1.39 (1H, d, $J = 8.4$ Hz, H-10), 2.21 (1H, d, $J = 8.4$ Hz, H-10′), 0.78 (9H, s, −Si($C(CH_3)_3$), 0.00 (3H, s, $SiCH_3$), −0.01 (3H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 175.2, 139.2, 136.9, 133.5, 129.1, 128.8, 126.7, 85.6, 51.7, 49.8, 48.3, 45.2, 44.8, 41.2, 34.2, 26.1, 18.3, −3.8, −4.3.

(8a*S*,9*S*,12*R*,12a*R*,12b*R*)-5,8a,9,12,12a,12b-Hexahydro-6*H*-9,12-methanoindeno[1,2-*a*]isoquinolin-8-one (7): To a solution of **6** (295 mg, 0.77 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of $TiCl_4$ (2.31 mL, 2.31 mmol, 1 M solution in CH_2Cl_2) at −78°C for 10 min under argon atmosphere. After stirring for 2 h at the same temperature, the mixture was warmed to r.t. After 30 min, the mixture was poured into ice-water containing Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash column chromatography (EtOAc/hexane = 1 : 5)

to afford **7** (149 mg, 77%) as a white solid. $R_f = 0.21$ (EtOAc/hexane = 1 : 5). M.p. 96–98°C; MS *m*/*z*: 251 (M^+); HRMS (CI) Calcd for $C_{17}H_{18}NO$ $(M+H)^+$: *m*/*z* 252.1388. Found: 252.1394; $[\alpha]_D^{20} + 102.4°$ (*c* 0.81, $CHCl_3$); IR (KBr, cm^{-1}) 3454, 2926, 1680, 1458, 1300, 1250, 1044, 758; ^{1}H NMR ($CDCl_3$) δ 7.29–7.06 (4H, m, phenyl), 6.33 (1H, m, H-11), 6.26 (1H, m, H-10), 4.23 (1H, m, $PhCH_2CH$–), 4.11 (1H, d, $J = 2.9$ Hz, H-12b), 3.32–3.29 (2H, m, H-9 and H-12), 3.12 (1H, m, $PhCH_2CH_2$–), 2.98 (1H, m, H-8a), 2.66 (2H, m, $PhCH_2CH_2$–), 2.64 (1H, m, $PhCH_2CH_2$–), 1.69 (1H, d, $J = 8.5$ Hz, H-13), 1.47 (1H, d, $J = 8.5$ Hz, H-13′); ^{13}C NMR ($CDCl_3$) δ 173.5, 138.9, 137.3, 134.7, 134.0, 129.5, 127.1, 127.1, 125.2, 60.1, 51.8, 51.6, 46.9, 46.2, 44.9, 37.6, 28.6.

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