Lewis Acid-Catalyzed Ring-Opening Reactions of Semicyclic *N,O*-Acetals

Masaharu Sugiura and Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo
CREST, Japan Science and Technology Corporation (JST)
Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

Supporting Information

General Methods. Melting points were uncorrected. IR spectra were recorded on a Jasco FT/IR-610 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA300 or JNM-LA400 spectrometer in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (δ = 0) for ^{1}H NMR, and $CDCl_3$ was used as internal standard (δ = 77.0) for ^{13}C NMR. High-resolution mass spectra (HRMS) were measured with JEOL JMX-SX-102A Mass Spectrometer. Low-resolution mass spectra (EIMS) were measured with Shimazu GCMS-QP5050A Mass Spectrometer. Column chromatography was conducted on Silica gel 60 (Merck) and preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F. Dichloromethane was distilled from P_2O_5, then from CaH_2, and dried over MS 4A. Acetonitrile was distilled from CaH_2 and dried over MS 4A. All other solvents and chemical compounds were purified based on standard procedures.

Benzyl *N*-(tetrahydropyran-2-yl)carbamate (5a). To a solution of 3,4-dihydro-2*H*-pyran (273 μL, 3 mmol) and benzyl carbamate (453 mg, 1 equiv.) in dichloromethane (3 mL) was added *p*-toluenesulfonic acid monohydrate (5.7 mg, 1 mol%) at rt. The reaction proceeded exothermically and was stirred for 1 hour. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was recrystallized from diethyl ether/hexane (ca. 3:1) to give **5a** as colorless needles (first crop: 456 mg, second crop: 98 mg; total 79% yield).
M.p. 83-84 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.24-7.28 (m, 5H), 5.28 (brs, 1H), 5.15 (brd, *J* = 12.3 Hz, 1H), 5.09 (brd, *J* = 12.3 Hz, 1H), 4.90 (brt, *J* = 9.7 Hz, 1H), 3.98 (m, 1H), 3.60 (m, 1H), 1.95-1.75 (m, 2H), 1.60-1.45 (m, 3H), 1.45-1.27 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.3, 136.1, 128.4, 128.10, 128.06, 79.9, 66.9, 66.8, 31.3, 24.9, 22.7.

IR (film from $CDCl_3$ solution) 3345, 3029, 2930, 2890, 2856, 1703, 1533, 1440, 1308, 1281, 1247, 1060, 1040, 905, 728, 697 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.45; H, 7.32; N, 5.68.

3-Benzyloxycarbonylamino-7-hydroxy-1-phenylheptan-1-one (6a). To a solution of **5a** (47.0 mg, 0.2 mmol) and 1-phenyl-1-(trimethylsilyloxy)ethylene (46.0 mg, 1.2 equiv.) in dichloromethane (2 mL) was added trimethylsilyl trifluoromethanesulfonate (TMSOTf; 7.2 μL, 0.2 equiv.) at 0 °C. After being stirred for 15 min, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by PTLC (ethyl acetate) to give **6a** as colorless solid (63.7 mg, 90%).

M.p. 70-71 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ =7.93 (brd, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.44 (brt, *J* = 7.5 Hz, 2H), 7.38-7.25 (m, 5H), 5.44 (brd, *J* = 8.4 Hz, 1H), 5.07 (s, 2H), 4.12 (m, 1H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.34 (dd, *J* = 16.9, 4.4 Hz, 1H), 3.12 (dd, *J* = 16.9, 5.9 Hz, 1H), 1.82 (brs, 1H), 1.75-1.30 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.9, 156.0, 136.8, 136.5, 133.3, 128.6, 128.4, 128.03, 128.00, 127.95, 66.6, 62.4, 48.3, 42.6, 33.9, 32.2, 22.5.

IR (film from $CDCl_3$ solution) 3339, 3063, 3034, 2938, 2864, 1695, 1535, 1451, 1250, 1068, 1026, 753, 694 cm^{-1}.

Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.78; H, 7.28; N, 3.92.

5-(Benzyloxycarbonylamino)oct-7-en-1-ol (6b). According to the procedure for **6a**, the reaction of **5a** (47.3 mg, 0.2 mmol) with allyltrimethylsilane (64 μL, 2 equiv.) and TMSOTf (7.2 μL, 0.2 equiv.) in dichloromethane (1 mL) at 0 °C for 2 hours provided **6b** as a colorless syrup (PTLC, hexane/ethyl acetate 1:1; 50.5 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ =7.39-7.27 (m, 5H), 5.75 (m, 1H), 5.20-4.95 (m, 4H), 4.69 (brd, *J* = 8.8 Hz, 1H), 3.71 (m, 1H), 3.60 (brt, *J* = 6.1 Hz, 2H), 2.22 (m, 2H), 1.86 (brs, 1H),

1.53-1.26 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.1, 136.6, 134.1, 128.4, 128.0, 127.9, 117.9, 66.5, 62.4, 50.5, 39.4, 34.4, 32.3, 22.0.

IR (neat) 3405, 3324, 3069, 3034, 2938, 2863, 1697, 1642, 1537, 1454, 1253, 1071, 1026, 916, 738, 698 cm^{-1}.

2-Benzyloxycarbonylamino-6-hydroxyhexanenitrile (6c). According to the procedure for **6a**, the reaction of **5a** (47.3 mg, 0.2 mmol) with trimethylsilyl cyanide (54 μL, 2 equiv.) and TMSOTf (7.2 μL, 0.2 equiv.) in dichloromethane (1 mL) at 0 °C for 15 min. provided **6c** as a colorless syrup (PTLC, hexane/ethyl acetate 1:1; 52.2 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24-7.26 (m, 5H), 5.79 (brd, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 4.58 (m, 1H), 3.61 (t, *J* = 5.6 Hz, 2H), 2.28 (brs, 1H), 1.80 (m, 2H), 1.63-1.46 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.3, 135.6, 128.5, 128.4, 128.1, 118.6, 67.5, 61.9, 42.7, 32.7, 31.3, 21.6.

IR (neat) 3323, 3035, 2942, 2870, 2246, 1702, 1536, 1456, 1264, 1029, 741, 699 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.70; H, 7.10; N, 10.52.

5-Benzyloxycarbonylamino-2,2-dimethyl-9-hydroxynonan-3-one (6d). According to the procedure for **6a**, the reaction of **5a** (47.4 mg, 0.2 mmol) with 1-*t*-butyl-1-(trimethylsilyloxy)ethylene (52.0 mg, 1.5 equiv.) and TMSOTf (7.2 μL, 0.2 equiv.) in dichloromethane (1 mL) at 0 °C for 20 min. provided **6d** as a colorless solid (PTLC, hexane/ethyl acetate 1:1; 60.2 mg, 89%).

M.p. 47-48 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38-7.26 (m, 5H), 5.43 (brd, *J* = 8.4 Hz, 1H), 5.06 (s, 2H), 3.92 (m, 1H), 3.58 (brt, *J* = 6.2 Hz, 2H), 2.84 (dd, *J* = 17.4, 3.8 Hz, 1H), 2.63 (dd, *J* = 17.4, 5.6 Hz, 1H), 1.92 (brs, 1H), 1.70-1.20 (m, 6H), 1.09 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 215.1, 156.0, 136.6, 128.4, 127.95, 127.92, 66.4, 62.4, 48.0, 44.3, 40.4, 33.7, 32.2, 26.1, 22.5.

IR (film from $CDCl_3$ solution) 3351, 3064, 3034, 2938, 2869, 1701, 1536, 1457, 1252, 1062, 739, 698 cm^{-1}.

Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.77; H, 8.64; N, 4.04.

Methyl 3-benzyloxycarbonylamino-2,2-dimethyl-7-hydroxyheptanoate (6e). According to the procedure for **6a**, the reaction of **5a** (47.4 mg, 0.2 mmol) with 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (52.0 mg, 1.5 equiv.) and TMSOTf (7.2 μL, 0.2 equiv.) in dichloromethane (1 mL) at 0 °C for 20 min. provided **6e** as a colorless syrup (PTLC, hexane/ethyl acetate 1:1; 67.3 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.38-7.24 (m, 5H), 5.20 (brd, *J* = 10.6 Hz, 1H), 5.09 (s, 2H), 3.71 (ddd, *J* = 10.8, 10.6, 2.0 Hz, 1H), 3.64 (s, 3H), 3.57 (brt, *J* = 6.6 Hz, 2H), 1.91 (brs, 1H), 1.68-1.10 (m, 6H), 1.20 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.0, 156.8, 136.6, 128.4, 128.0, 127.9, 66.6, 62.5, 57.6, 51.8, 46.5, 32.2, 31.0, 23.1, 22.7, 22.6.

IR (neat) 3356, 3064, 3033, 2946, 2867, 1712, 1537, 1457, 1260, 1142, 1057, 740, 699 cm^{-1}.

HRMS calcd for $C_{18}H_{27}NO_5$ (M^+) 337.1889, found 337.1902.

Benzyl *N*-(tetrahydrofuran-2-yl)carbamate (5b). According to the procedure for **5a**, the reaction of 2,3-dihydrofuran (0.23 mL, 3 mmol) with benzyl carbamate (453 mg, 1 equiv.) and *p*-toluenesulfonic acid monohydrate (5.7 mg, 1 mol%) in dichloromethane (3 mL) at rt for 10 min. provided **6e** as a colorless solid (silica gel column chromatography, hexane/ethyl acetate 2:1; 407.7 mg, 61%).

M.p. 66-68 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40-7.28 (m, 5H), 5.57 (m, 1H), 5.25-5.03 (m, 3H), 3.90 (ddd, *J* = 8.4, 7.0, 6.7 Hz, 1H), 3.83 (ddd, *J* = 8.4, 7.0, 6.7 Hz, 1H), 2.19 (m, 1H), 1.93 (apparent quintet, *J* = 7.1 Hz, 2H), 1.68 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.4, 136.2, 128.5, 128.2 (br), 82.8, 67.1, 66.9, 31.8, 24.6 (one aromatic carbon is overlapped).

IR (KBr) 3311, 3051, 2975, 2943, 2871, 1729, 1697, 1547, 1257, 1043, 741, 701 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.07; H, 6.85; N, 6.33.

3-Benzyloxycarbonylamino-6-hydroxy-1-phenylheptan-1-one (6f). According to the procedure for **6a**, the reaction of **5b** (44.3 mg, 0.2 mmol) with 1-phenyl-1-(trimethylsilyloxy)ethylene (76.2 mg, 2 equiv.) and TMSOTf (7.2 μL, 0.2 equiv.) in dichloromethane (2 mL) at 0 °C for 15 min. provided **6f** as a colorless solid (PTLC, hexane/ethyl acetate 1:2; 61.6 mg, 90%).

M.p. 68-69 °C

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 (brd, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44 (brt, *J* = 7.5 Hz, 2H), 7.37-7.27 (m, 5H), 5.55 (brd, *J* = 8.4 Hz, 1H), 5.07 (s, 2H), 4.16 (m, 1H), 3.64 (m, 2H), 3.36 (dd, *J* = 17.1, 4.2 Hz, 1H), 3.12 (dd, *J* = 17.1, 6.0 Hz, 1H), 2.11 (brs, 1H), 1.85-1.70 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.9, 156.1, 136.7, 136.4, 133.4, 128.6, 128.4, 128.0, 127.9, 66.6, 62.2, 48.1, 42.7, 30.7, 29.1 (one aromatic carbon is overlapped).

IR (film from $CDCl_3$ solution) 3338, 3063, 3034, 2942, 1697, 1537, 1451, 1254, 1059, 1024, 753, 694 cm^{-1}.

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.08; H, 6.88; N, 4.06.

***trans*-3-Acetoxytetrahydropyran-2-yl 3-chlorobenzoate (7).** To a solution of *trans*-3-hydroxytetrahydropyran-2-yl 3-chlorobenzoate[1] (556.7 mg, 2.17 mmol), 4-dimethylaminopyridine (13 mg, 5 mol%), and triethylamine (0.36 mL, 1.2 equiv.) was added acetic anhydride (0.23 mL, 1.1 equiv.) at rt. After being stirred for 1 hour, the mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/ethyl acetate 6:1-3:1) to give **7** as a viscous syrup (558.1 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01 (brs, 1H), 7.94 (apparent d, *J* = 7.9 Hz, 1H), 7.56 (apparent d, *J* = 8.0 Hz, 1H), 7.40 (apparent t, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 3.3 Hz, 1H), 4.91 (ddd, *J* = 4.4, 3.6, 3.3 Hz, 1H), 3.96 (ddd, *J* = 11.3, 10.4, 3.2 Hz, 1H), 3.77 (dt, *J* = 11.3, 4.2 Hz, 1H), 2.25-1.80 (m, 3H), 2.11 (s, 3H), 1.60 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.0, 163.4, 134.6, 133.5, 131.2, 129.8, 129.7, 128.0, 92.2, 67.4, 62.9, 24.3, 21.0, 20.6.

IR (neat) 3073, 2960, 2884, 1737, 1575, 1427, 1369, 1285, 1239, 1071, 920, 748 cm^{-1}.

3-Acetoxy-2-(benzyloxycarbonylamino)tetrahydropyran (5c). To a suspension of **7**

(304.6 mg, 1.02 mmol), benzyl carbamate (169.5 mg, 1.1 equiv.), and 4Å molecular sieves powder (activated using a domestic microwave oven, 306 mg) in dichloromethane (5 mL) was added TMSOTf (185 μL, 1 equiv.) at rt. After being stirred for 10 min, the mixture was quenched with saturated aqueous $NaHCO_3$, diluted with ethyl acetate, and filtered through a Celite pad. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by PTLC (hexane/ethylacetate 1:1) to give **5c** as viscous syrup (260.7 mg, 87% yield, diastereomeric ratio = 54:46).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39-7.29 (m, 5H), 5.55 (brd, *J* = 9.9 Hz, 0.46H), 5.50 (brd, *J* = 9.4 Hz, 0.54H), 5.20-5.05 (m, 2H), 5.06 (dd, *J* = 9.9, 1.1 Hz, 0.46H), 4.85 (m, 0.46H), 4.79 (dd, *J* = 9.4, 9.2 Hz, 0.54H), 4.64 (ddd, *J* = 10.3, 9.4, 4.7 Hz, 0.54H), 4.05-3.89 (m, 1H), 3.72-3.47 (m, 1H), 2.20-2.00 (m, 1H), 2.13 (s, 1.38H), 2.02 (s, 1.62H), 1.90-1.53 (m, 2.54H), 1.40 (m, 0.46H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9, 170.3, 155.7, 155.3, 136.0, 135.8, 128.47, 128.42, 128.39, 128.24, 128.05, 128.00, 82.5, 79.1, 69.8, 69.3, 67.2, 66.7, 66.6, 66.5, 29.0, 27.2, 24.6, 21.0, 20.9, 19.8.

IR (neat) 3337, 3065, 3033, 2955, 2857, 1731, 1529, 1241, 1075, 1048, 742, 699 cm^{-1}.

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.13; H, 6.55; N, 4.71.

***syn*-4-Acetoxy-3-benzyloxycarbonylamino-7-hydroxy-1-phenylheptan-1-one (6g).** According to the procedure for **6a**, the reaction of **5c** (58.1 mg, 0.2 mmol) with 1-phenyl-1-(trimethylsilyloxy)ethylene (77.0 mg, 2 equiv.) and TMSOTf (7.2 μL, 0.2 equiv.) in acetonitrile (2 mL) at 0 °C for 2 hours provided **6g** as a colorless solid (PTLC, hexane/ethyl acetate 1:1; 62.1 mg, 76% yield). The diastereomeric ratio of **6g** was determined as 91:9 by ^{1}H NMR analysis.

M.p. 115-116 °C

^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ = 7.89 (brd, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44 (brt, *J* = 7.5 Hz, 2H), 7.45-7.25 (m, 5H), 5.30 (brd, *J* = 8.4 Hz, 1H), 5.23-5.00 (m, 3H), 4.49 (m, 1H), 3.75-3.48 (m, 2H), 3.30-3.03 (m, 2H), 2.00 (s, 3H), 1.77-1.50 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ = 197.3, 170.4, 156.1, 136.6, 136.3, 133.4, 128.7, 128.5, 128.1, 128.0, 74.7, 67.0, 62.1, 49.9, 40.7, 28.3, 27.8, 20.8 (one aromatic carbon is overlapped).

IR (film from $CDCl_3$ solution): 3351, 3063, 3034, 2948, 2875, 1712, 1536, 1451, 1373, 1238, 1044, 756, 694 cm^{-1}.

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.55; H, 6.58; N, 3.10.

***syn*-6-Acetoxy-5-benzyloxycarbonylamino-2,2-dimethyl-9-hydroxynonan-3-one (6h).** According to the procedure for **6a**, the reaction of **5c** (28.8 mg, 0.098 mmol) with 1-*t*-butyl-1-(trimethylsilyloxy)ethylene (34.0 mg, 2 equiv.), and TMSOTf (3.6 μL, 0.2 equiv.) in acetonitrile (1 mL) at 0 °C for 5 hours provided **6h** as a colorless syrup (PTLC, hexane/ethyl acetate 1:1; 23.8 mg, 61% yield). The diastereomeric ratio of **6h** was determined as 94:6 by ^{1}H NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ = 7.42-7.28 (m, 5H), 5.14 (brd, *J* = 10.5 Hz, 1H), 5.09 (s, 2H), 5.02 (m, 1H), 4.32 (m, 1H), 3.73-3.47 (m, 2H), 2.73 (dd, *J* = 17.9, 7.6 Hz, 1H), 2.65 (dd, *J* = 17.9, 5.3 Hz, 1H), 2.02 (s, 3H), 1.87 (brs, 1H), 1.75-1.45 (m, 4H), 1.09 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ = 213.1, 170.4, 156.0, 136.3, 128.5, 128.21, 128.18, 74.4, 70.0, 62.1, 49.3, 44.2, 38.3, 28.3, 27.8, 26.2, 20.9.

IR (neat) 3361, 2960, 2873, 1710, 1535, 1371, 1237, 1052, 742, 699 cm^{-1}.

***syn*-Methyl 4-acetoxy-3-benzyloxycarbonylamino-2,2-dimethyl-7-hydroxyheptanoate (6i).** According to the procedure for **6a**, the reaction of **5c** (31.3 mg, 0.106 mmol) with 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (37.0 mg, 2 equiv.) and TMSOTf (3.6 μL, 0.2 equiv.) in acetonitrile (1 mL) at 0 °C for 30 min. provided **6i** as a colorless syrup (PTLC, hexane/ethyl acetate 1:1; 36.7 mg, 87% yield). The diastereomeric ratio of **6i** was determined as 94:6 by ^{1}H NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ = 7.43-7.28 (m, 5H), 5.74 (brd, *J* = 10.6 Hz, 1H), 5.15 (d, *J* = 12.1 Hz, 1H), 5.11 (d, *J* = 12.1 Hz, 1H), 5.17-5.07 (m, 1H), 3.88 (dd, *J* = 10.6, 1.3 Hz, 1H), 3.65 (s, 3H), 3.64-3.55 (m, 2H), 1.96 (s, 3H), 1.91 (brs, 1H), 1.70-1.45 (m, 4H), 1.23 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ = 176.3, 170.0, 157.0, 136.4, 128.5, 128.2, 128.1, 72.1, 67.1, 62.1, 58.8, 51.9, 44.8, 28.7, 28.3, 24.1, 23.0, 20.9.

IR (neat) 3440, 2952, 2876, 1728, 1513, 1232, 1148, 1050, 750, 699 cm^{-1}.

HRMS calcd for $C_{20}H_{29}NO_7$ (M^+) 395.1944, found 395.1917.

***trans*-3-Benzyloxy-2-methoxytetrahydropyran (8).** To a refluxing suspension of *trans*-3-hydroxy-2-methoxytetrahydropyran[2] (661 mg, 5 mmol), powdered anhydrous KOH (1.403 g, 5 equiv.) in anhydrous 1,4-dioxane (2.5 mL), was added dropwise benzylbromide (1.44 mL, 2.4 equiv.). The mixture was stirred under refluxing for 30 min. After cooling to rt, the mixture was diluted with diethyl ether, washed with water. The aqueous layer was extracted twice with diethyl ether and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane/ethyl acetate 10:1-5:1) to give **8** as a colorless oil (1.006 g, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42-7.22 (m, 5H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.62 (d, *J* = 12.1 Hz, 1H), 4.42 (d, *J* = 3.8 Hz, 1H), 3.83 (ddd, *J* = 11.3, 8.4, 3.7 Hz, 1H), 3.51 (m, 1H), 3.45 (s, 3H), 3.31 (ddd, *J* = 6.6, 3.8, 3.8 Hz, 1H), 2.02-1.78 (m, 2H), 1.77-1.60 (m, 1H), 1.52-1.35 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.6, 128.3, 127.6, 127.5, 101.9, 74.2, 71.5, 61.9, 55.4, 25.3, 22.0.

IR (neat) 2849, 2873, 1452, 1192, 1146, 1124, 1080, 1041, 959, 739, 698 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.96; H, 8.11.

3-Benzyloxy-2-(benzyloxycarbonylamino)tetrahydropyran (5d). According to the procedure for **5c**, the reaction of **8** (600 mg, 2.70 mmol) with benzyl carbamate (450 mg, 1.1 equiv.) and TMSOTf (490 μL, 1 equiv.) using 4Å molecular sieves powder (810 mg) in dichloromethane (14 mL) at rt for 10 min. provided 5d as viscous syrup (PTLC, hexane/ethyl acetate 2:1; 633.9 mg, 68% yield, diastereomeric ratio = 74:26).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40-7.20 (m, 10H), 5.86 (brd, *J* = 8.3 Hz, 0.74H), 5.34 (brd, *J* = 9.3 Hz, 0.26H), 5.20-5.03 (m, 2H), 4.98 (dd, *J* = 9.3, 1.5 Hz, 0.74H), 4.79 (dd, *J* = 8.7, 8.3 Hz, 0.26H), 4.63 (d, *J* = 11.8 Hz, 0.74H), 4.60 (d, *J* = 11.9 Hz, 0.26H), 4.49 (d, *J* = 11.9 Hz, 0.26H), 4.41 (d, *J* = 11.8 Hz, 0.74H), 4.00-3.80 (m, 1H), 3.65-3.40 (m, 1.74H), 3.14 (m, 0.26H), 2.20 (m, 0.26H), 2.06 (m, 0.74H), 1.94-1.73 (m, 1H), 1.73-1.45 (m, 1.26H), 1.36 (m, 0.74H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.64, 155.56, 138.1, 137.7, 136.19, 136.16, 128.4, 128.36, 128.34, 127.99, 127.96, 127.8, 127.7, 127.63, 127.56, 83.2, 79.7, 75.5, 72.7, 70.8, 70.7, 66.81, 66.79, 66.3, 65.7.

IR (neat) 3436, 3332, 3062, 3032, 2947, 2863, 1729, 1502, 1455, 1214, 1073, 1040, 739, 696 cm^{-1}.

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.08; H, 6.88; N, 3.87.

***syn*-4-Benzyloxy-3-benzyloxycarbonylamino-7-hydroxy-1-phenylheptan-1-one (6j).** According to the procedure for **6a**, the reaction of **5d** (34.3 mg, 0.1 mmol) with 1-phenyl-1-(trimethylsilyloxy)ethylene (38.5 mg, 2 equiv.) and TMSOTf (3.6 μL, 0.2 equiv.) in acetonitrile (1 mL) at -23 °C for 1 hour provided **6j** as a colorless solid (PTLC, hexane/ethyl acetate 1:1; 31.2 mg, 67% yield) The diastereomeric ratio of **6j** was determined as 94:6 by ^{1}H NMR analysis.

M.p. 83-84 °C

^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ = 7.87 (brd, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.42 (brt, *J* = 7.5 Hz, 2H), 7.37-7.28 (m, 5H), 7.28-7.15 (m, 5H), 5.31 (brd, *J* = 9.2 Hz, 1H), 5.08 (s, 2H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.43 (m, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 3.75-3.48 (m, 3H), 3.26 (dd, *J* = 17.0, 8.1 Hz, 1H), 3.14 (dd, *J* = 17.0, 4.8 Hz, 1H), 1.90-1.50 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ = 198.2, 156.2, 138.0, 136.64, 136.44, 133.2, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 78.8, 72.2, 66.8, 62.6, 49.7, 40.8, 28.7, 26.9.

IR (film from $CDCl_3$ solution) 3431, 3363, 3062, 3032, 2943, 2871, 1711, 1597, 1503, 1451, 1219, 1059, 741, 696 cm^{-1}.

Anal. Calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77; N, 3.03. Found: C, 72.57; H, 6.90; N, 3.10.

***syn*-6-Benzyloxy-5-benzyloxycarbonylamino-2,2-dimethyl-9-hydroxynonan-3-one (6k).** According to the procedure for **6a**, the reaction of **5d** (34.2 mg, 0.1 mmol) with 1-*t*-butyl-1-(trimethylsilyloxy)ethylene (34.5 mg, 2 equiv.), and TMSOTf (3.6 μL, 0.2 equiv.) in acetonitrile (1 mL) at 0 °C for 3 hours provided **6k** as a colorless syrup (PTLC, hexane/ethyl acetate 1:1; 26.2 mg, 59% yield). The diastereomeric ratio of **6k** was determined as 94:6 by ^{1}H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ = 7.42-7.20 (m, 10H), 5.20 (brd, *J* = 9.3

Hz, 1H), 5.20-5.00 (m, 2H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.26 (m, 1H), 3.65 (t, *J* = 5.1 Hz, 2H), 3.53 (m, 1H), 2.84 (dd, *J* = 17.8, 8.3 Hz, 1H), 2.68 (dd, *J* = 17.8, 4.7 Hz, 1H), 1.87-1.48 (m, 5H), 1.07 (s, 9H).

^{13}C NMR (750 MHz, $CDCl_3$, major diastereomer) δ = 214.2, 156.1, 138.1, 136.4, 128.5, 128.4, 128.1, 127.9, 127.8, 78.9, 71.9, 66.8, 62.6, 49.0, 44.1, 38.8, 28.6, 26.6, 26.2.

IR (neat) 3436, 2954, 2871, 1708, 1502, 1454, 1333, 1255, 1059, 740, 698 cm^{-1}.

***syn*-Methyl 4-benzyloxy-3-benzyloxycarbonylamino-2,2-dimethyl-7-hydroxyheptanoate (6l).** According to the procedure for **6a**, the reaction of **5d** (34.5 mg, 0.1 mmol) with 1-methoxy-2-methyl-1-(trimethylsilyloxy)propene (35.0 mg, 2 equiv.) and TMSOTf (3.6 μL, 0.2 equiv.) in acetonitrile (1 mL) at -23 °C for 40 min. provided **6l** as a colorless syrup (PTLC, hexane/ethyl acetate 1:1; 42.3 mg, 94% yield). The diastereomeric ratio of **6l** was determined as 94:6 by ^{1}H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ = 7.42-7.20 (m, 10H), 5.74 (brd, *J* = 10.4 Hz, 1H), 5.12 (s, 2H), 4.54 (d, *J* = 10.8 Hz, 1H), 4.26 (d, *J* = 10.8 Hz, 1H), 3.83 (d, *J* = 10.4 Hz, 1H), 3.70-3.50 (m, 3H), 3.35 (s, 3H), 1.90 (brs, 1H), 1.77-1.27 (m, 4H), 1.25 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ = 176.5, 157.2, 137.8, 136.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.6, 77.4, 71.1, 66.9, 62.5, 59.4, 51.6, 44.8, 28.5, 26.6, 23.8, 23.5.

IR (neat) 3444, 2949, 2873, 1723, 1509, 1454, 1323, 1251, 1149, 1063, 1029, 741, 699 cm^{-1}.

PCC-oxidation / Reductive cyclization of 6g and 6j. To a suspension of **6g** (20.7 mg, 0.050 mmol) or **6j** (14.3 mg, 0.031 mmol) and 4Å molecular sieves powder (activated using a domestic microwave oven, 20 mg for **6g**, 15 mg for **6j**) in dichloromethane (0.5 mL) was added pyridinium chlorochromate (27 mg for **6g**, 17 mg for **6j**, 2.5 equiv.) at rt. After being stirred at rt for 20-30 min, Celite and ethyl acetate were added to the mixture. The resulting suspension was filtered through a short silica gel column washing with ethyl acetate and concentrated *in vacuo*. The residue was dissolved in dry acetonitrile (0.5 mL) and treated with triethylsilane (16 μL for **6g**, 10 μL for **6j**, 2 equiv.) and $BF_3{\cdot}OEt_2$ (13 μL for **6g**, 8 μL for **6j**, 2 equiv.) at 0 °C. After 15 min, the mixture was quenched with saturated aqueous

$NaHCO_3$ and diluted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by PTLC (THF/hexane 2:1) to give *cis*-**9** (14.9 mg, 75%) or *cis*-**10** (9.3 mg, 68%) respectively. The spectral data of *cis*-**9** and *cis*-**10** were identical to the data for *cis*-isomers.[3]

3-Benzyloxycarbonylamino-1-phenyl-7-(trimethylsilyoxy)heptan-1-one (11). The authentic sample **11** was prepared as follows. To a solution of **6a** (29 mg, 0.082 mmol), triethylamine (23 μL, 2 equiv.) in dichloromethane (1 mL) was added chlorotrimethylsilane (16 μL, 1.5 equiv.) at rt. After being stirred at rt for 10 min, the mixture was quenched with pH 7 buffer solution (Na_2HPO_4/citric acid system), and diluted with ethyl ether. The organic layer was separated, washed with brine, and dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a pure **11** (35 mg, quantitative yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.94 (brd, *J* = 7.5 Hz, 2H), 7.57 (apparent t, *J* = 7.2 Hz, 1H), 7.46 (brt, *J* = 7.5 Hz, 2H), 7.38-7.27 (m, 5H), 5.34 (brd, *J* = 8.4 Hz, 1H), 5.08 (s, 2H), 4.11 (m, 1H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.36 (dd, *J* = 16.8, 4.5 Hz, 1H), 3.12 (dd, *J* = 16.8, 5.4 Hz, 1H), 1.80-1.20 (m, 6H), 0.09 (s, 9H).

NMR Experiment: **TMSOTf-Catalyzed Reaction of 5a with 1-phenyl-1-(trimethylsilyloxy)ethylene in $CDCl_3$.** In a dry NMR tube with a septum, **5a** (14.3 mg, 0.06 mmol) was dissolved in $CDCl_3$ (dried over 4Å molecular sieves pellet, 0.6 mL). 1-phenyl-1-(trimethylsilyloxy)ethylene (12 mg, 1.0 equiv.) and TMSOTf (2.2 μL, 0.2 equiv.) were successively introduced to the solution. Then the reaction had been monitored by a NMR spectrometer. The gradual consumption of **5a** and the formation of **11** were observed and the reaction was almost completed after 45 min. Addition of water (5 μL) to this resultant showed an immediate formation of alcohol **6a**.

***syn*-3-(4-Benzyloxycarbonylamino-5-hydroxy-8-hydroxy-2-oxooctyl)-3*H*-quinazolin-4-one (6m).** According to the procedure for **6a**, the reaction of **5d** (33.9 mg, 0.099 mmol) with 3-[2-(trimethylsilyloxy)propen-3-yl]-3*H*-quinazolin-4-one[4] (54.5 mg, 2 equiv.) and TMSOTf (45 μL, 2.5 equiv.) in acetonitrile (1 mL) at rt for 3 hours provided **6m** as a colorless syrup (PTLC, THF/hexane 3:1; 27.4 mg, 51% yield). The diastereomeric ratio of **6m** was determined as 93:7 by ^{1}H NMR analysis.

^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ = 8.25 (brd, *J* = 8.1 Hz, 1H), 7.79 (brs, 1H), 7.80-7.68 (m, 2H), 7.50 (ddd, *J* = 8.1, 6.4, 1.7 Hz, 1H), 7.43-7.23 (m, 10H), 5.36 (brd, *J* = 9.0 Hz, 1H), 5.08 (s, 2H), 4.76 (d, *J* = 17.7 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.55 (d, *J* = 17.7 Hz, 1H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.32 (m, 1H), 3.63 (brt, *J* = 5.5 Hz, 2H), 3.54 (m, 1H), 2.93-2.70 (m, 2H), 2.00-1.50 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer) δ = 200.8, 160.8, 156.3, 147.9, 146.5, 137.9, 136.2, 134.5, 128.54, 128.51, 128.25, 128.16, 128.03, 128.00, 127.4, 126.7, 78.9, 72.0, 77.0, 62.3, 54.2, 49.4, 43.3, 28.5, 26.7 (two aromatic carbons are overlapped).

IR (neat) 3421, 2941, 2872, 1679, 1613, 1516, 1474, 1366, 1259, 1059, 774, 741, 698 cm^{-1}.

3-Benzyloxy-1-benzyloxycarbonyl-2-[2-oxo-3-(4-oxo-4*H*-quinazolin-3-yl)propyl] piperidine (12). To a solution of **6m** (32.0 mg, 0.059 mmol) and triethylamine (45 μL, 6.5 equiv.) in DMSO (147 μL) was added sulfur trioxide pyridine complex (28 mg, 3 equiv.) at rt. After being stirred at rt for 30 min, saturated aqueous $NaHCO_3$ was added and the mixture was diluted with ethyl acetate. The organic layer was separated and washed with water (twice) and brine (twice), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in dry acetonitrile (0.5 mL) and treated with triethylsilane (28 μL, 3 equiv.) and $BF_3{\cdot}OEt_2$ (22 μL, 3 equiv.) at 0 °C. After 10 min, the mixture was quenched with saturated aqueous $NaHCO_3$, diluted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by PTLC (THF/hexane 2:1) to give **12** as a viscous syrup (diastereomerically pure, 14.2 mg, 46%).

^{1}H NMR (300 MHz, DMSO-d_6, 50 °C) δ = 8.14 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.98 (s, 1H), 7.84 (ddd, *J* = 8.0, 7.1, 1.4 Hz, 1H), 7.69 (brd, *J* = 8.0 Hz, 1H), 7.55 (ddd, *J* = 8.0, 7.1, 1.3 Hz, 1H), 7.43-7.17 (m, 10H), 5.16-4.86 (m, 5H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 3.85 (dd, *J* = 13.5, 3.3 Hz, 1H), 3.48 (m, 1H), 3.05 (dd, *J* = 16.1, 5.5 Hz, 1H), 2.95-2.70 (m, 2H), 1.87 (m, 1H), 1.74-1.46 (m, 2H), 1.34 (m, 1H).

^{13}C NMR (75 MHz, DMSO-d_6, 50 °C) δ = 201.3, 159.7, 154.3, 147.8, 147.6, 138.2, 136.7, 134.2, 128.1, 128.0, 127.5, 127.3, 127.1, 127.06, 126.9, 125.9, 121.3, 74.6, 69.5, 66.2, 54.0, 49.5, 38.2, 35.7, 24.7, 23.4 (one aromatic carbon is overlapped).

IR (neat) 2930, 2870, 1731, 1684, 1473, 1421, 1362, 1257, 1161, 1089, 775, 738, 697.

EIMS (70 eV) 525 (M^+, 0.6) 417 (1.7), 390 (4.1), 282 (3.6), 202 (19.5), 187 (5.7), 159 (6.4),

147 (7.1), 130 (4.6), 91 (100).

Isofebrifugine. The mixture of **12** (9.3 mg, 0.018 mmol) in 6N hydrochloric acid (0.7 mL) was refluxed for 1 hour. After cooling to rt, the pH of the mixture was adjusted to ca. 9 by the careful addition of 20 wt % aqueous Na_2CO_3. The mixture was then extracted three times with chloroform. The combined organic layers were dried over anhydrous Na_2SO_4 and anhydrous Na_2CO_3 and concentrated *in vacuo* at under 30 °C to give isofebrifugine (4.8 mg, 90%) which ^{1}H NMR spectrum was identical to the reported data[5].

References

(1) This alcohol was prepared *via m*-CPBA oxidation of 3,4-dihydro-2*H*-pyran in dichloromethane.

(2) Frimer, A. A. *Synthesis* **1977**, 578.

(3) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989.

(4) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255.

(5) (a) Kobayashi, S; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H.-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833. (b) Takeuchi, Y.; Hattori, M.; Abe, H.; Harayama, T. *Synthesis* **1999**, 1814.