HETEROCYCLES, Vol. 66, 2005, pp. 341 – 346. © The Japan Institute of Heterocyclic Chemistry
Received, 29th August, 2005, Accepted, 7th October, 2005, Published online, 11th October, 2005. COM-05-S(K)29

ALTERNATIVE SYNTHESIS OF (-)-GEISSMAN-WAISS LACTONE, A KEY INTERMEDIATE OF NECINE BASES

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Abstract – A facile synthetic route to (-)-Geissman-Waiss lactone, a key intermediate of necine bases, was established by employing ring closing metathesis (RCM), followed by intramolecular Michael reaction of the resulting α,β-unsaturated lactone, as the key steps.

Pyrrolizidine alkaloids are widely distributed in nature with a variety of structural and stereochemical features.[1] These alkaloids are known to exhibit interesting biological activities, such as antitumor activity and carcinogenicity.[2] Due to the attractive biological activities, much attention has been paid to the synthesis of these alkaloids, particularly, necine base moieties.[3]

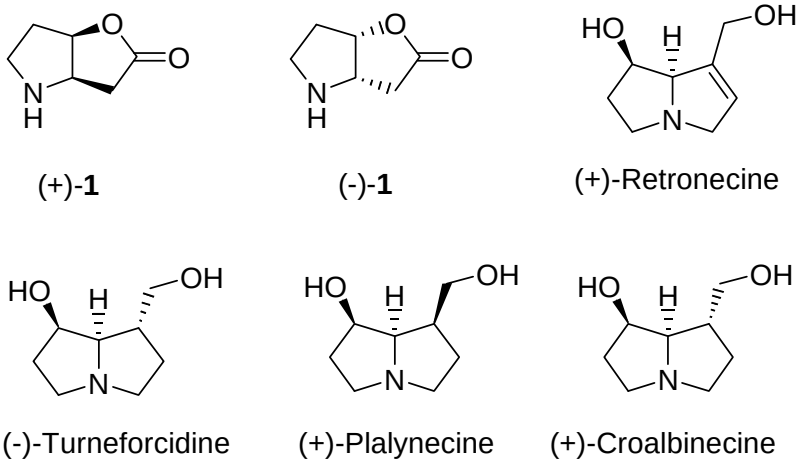


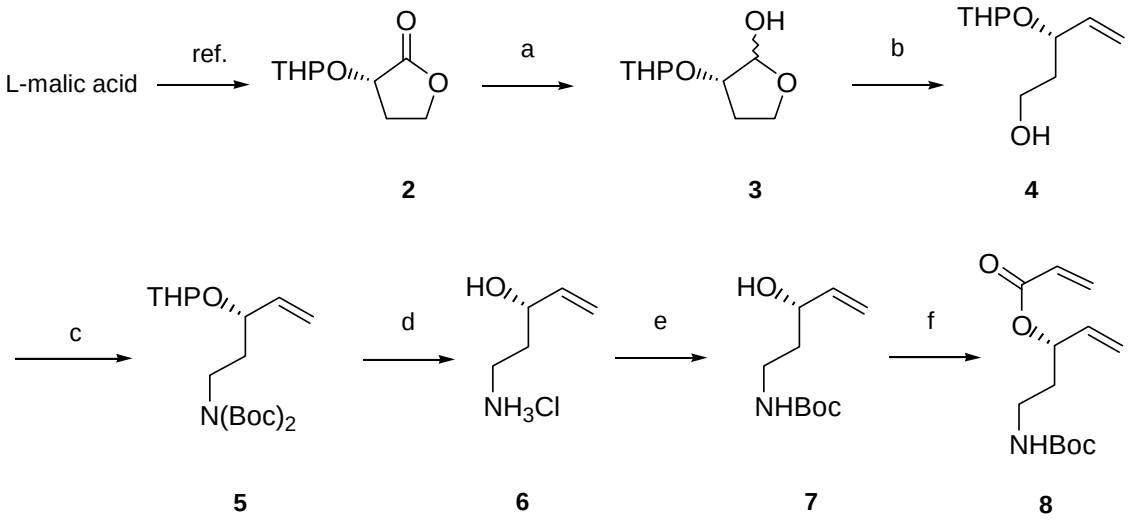
Figure 1. Structures of Geissmann-Waiss lactone **1** and typical pyrrolizidine alkaloids.

We have already reported the syntheses of necine bases and also the necic acids by application of our newly developed synthetic strategies.[4] As part of our continuing work on the synthesis of pyrrolizidine alkaloids, we are interested in further development of a new synthetic route to Geissman-Waiss lactone (**1**), since both (+)- and (-)-lactones (**1**) were recognized as key intermediates for the synthesis of various types of necine bases; such as (+)-retronecine,[5,6] (-)-turneforcidine,[7] (+)-platynecine,[8] and (+)-croalbinecine.[6b] although a number of approaches to chiral Geissman-Waiss lactone have been reported to date.[9]

Dedicated to the memory of the late Professor Kenji Koga.

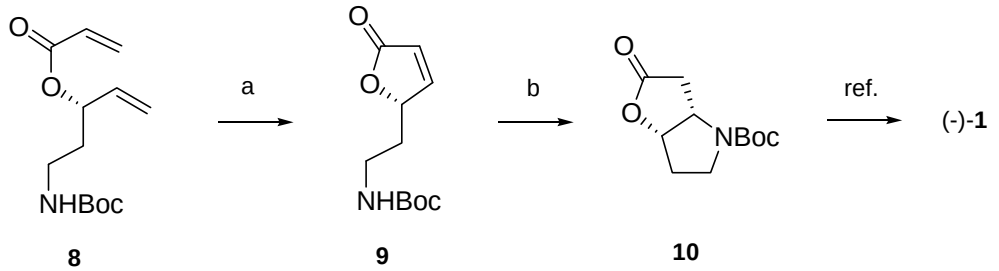
Our synthesis of (-)-**1** starts from the optically pure γ-lactone (**2**), a readily accessible from L-malic acid, according to the literature procedure.[10]

Reduction of **2** with diisobutylaluminum hydride (DIBAH) gave the lactol (**3**),[10] which on Wittig reaction with methyltriphenylphosphonium bromide in the presence of potassium hexamethyldisilazide (KHMDS) afforded the olefin (**4**). Introduction of an amino function was achieved by employing a modified Mitsunobu reaction conditions[11] to provide the protected amine (**5**) in 88% yield. Treatment of **5** with acetyl chloride in methanol under acidic reaction conditions at ambient temperature furnished the hydroxy-amine hydrochloride (**6**), which, on selective protection of the amino group with $(Boc)_2O$ gave *N*-Boc compound (**7**) in 81% yield from **5**. Acylation of **7** with acryloyl chloride was achieved by using ethylmagnesium bromide as the base in THF at room temperature to give the ester (**8**) in 87% yield.



Scheme 1. *Reagents and conditions*: (a) DIBAH, CH_2Cl_2, -78°C (90%); (b) $MePPh_3Br$, 0.5 M KHMDS in toluene, THF, 15°C (97%); (c) $NH(Boc)_2$, *n*-Bu_3P, ADDP, tol (88%); (d) AcCl, MeOH, rt; (e) $(Boc)_2O$, Et_3N, THF, rt (81% from **5**); (f) acryloyl chloride, EtMgBr, THF, rt (87%).

Since the requisite dienyl ester (**8**) for the key RCM reaction[12] was prepared in relatively short steps, we attempted the construction of an α,β-unsaturated γ-lactone moiety as follows.



Scheme 2. *Reagents and conditions*: (a) Grubbs' 2nd generation Ru catalyst, CH_2Cl_2, 40°C (85%); (b) NaH, DMF, 0°C (96%).

The ring-closing metathesis reaction of **8** was achieved by using 5 mol % of Grubbs' 2nd generation ruthenium catalyst {tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-

ylidene][benzylidene]ruthenium (IV) dichloride}in CH_2Cl_2 at 40°C to afford the desired lactone (**9**) in 85% yield.

Finally, treatment of **9** with sodium hydride in DMF brought about the intramolecular Michael reaction to afford the *N*-protected Geissmann-Waiss lactone (**10**) in 96% yield. The spectroscopic data of the synthesized compound including its specific optical rotation, were identical with those reported; mp 109-111°C, $[\alpha]_D$ +134.7° (c=1.04, $CHCl_3$); [lit.,[9j] mp 106-107°C, $[\alpha]_D$ +96.0° (*c* 0.43, CH_2Cl_2)], [lit.,[9g] mp 111°C, $[\alpha]_D$ –113.1° (*c* 1.00, $CHCl_3$) and lit.,[9i] mp 111-112°C, $[\alpha]_D$ –141.1° (*c* 0.44, $CHCl_3$) for the antipode of **10**].

Since deprotection of the *N*-Boc group of **10** was already achieved,[9j] this synthesis constitutes the synthesis of (-)-Geissman-Waiss lactone.

In summary, we were able to establish the concise synthesis of (-)-Geissman-Waiss lactone, a key intermediate for the synthesis of necine basess, by employing RCM, followed by an intramolecular Michael reaction of the resulting α,β-unsaturated lactone, as the key steps. The strategy developed here provides a further useful example of RCM in the synthesis of natural compounds.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL LAMBDA-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) instrument for solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

(3*S*)-Tetrahydropyranyloxypent-4-en-1-ol (**4**)**:** To a stirred solution of methyltriphenylphosphonium bromide (3.80 g, 10.64 mmol) in THF (42 mL) was added KHMDS (0.5 M in toluene, 16 mL, 7.98 mmol) at 0°C under argon, and the resulting solution was stirred for further 20 min at rt, and cooled to -78°C. To this solution was added a solution of the lactol (**3**) (500 mg, 2.66 mmol) in THF (3 mL), and the whole was stirred at 15°C for 12 h. After treatment with saturated NH_4Cl solution, the mixture was extracted with EtOAc. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane-EtOAc (2:1, v/v) gave the alcohol (**4**) (479 mg, 97 %) as a mixture of diastereomers: $[\alpha]_D^{27}$ -49.0° (*c* 1.02, $CHCl_3$); IR ν_{max} 3410 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.46-1.66 (6H, m), 1.66-1.94 (2H, m), 2.18 (0.4H, t, *J*=5.6 Hz) 2.88 (0.6H, t, *J*=6.3 Hz), 3.42-3.59 (1H, m), 3.65-4.00 (3H, m), 4.25-4.42 (1H, m), 4.54-4.60 (0.6H, m), 4.72-4.78 (0.4H, m), 5.10-5.33 (2H, m), 5.74 (0.6H, ddd, *J*=6.9, 10.4, 17.3 Hz), 5.93 (0.4H, ddd, *J*=6.8, 10.3, 17.3 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 19.7, 20.4, 25.2, 25,3, 30.8, 36.9, 37.6, 59.6, 59.7, 62.8, 63.7, 75.4, 76.5, 96.9, 98.2, 115.1, 116.6, 137.9, 139.2; MS (FAB): 187 $(M+H)^+$; Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.83; H, 9.47.

***N*,*N*-Bis(*tert*-butoxycarbonyl)-(3*S*)-tetrahydropyranyloxypent-4-enylamine** (**5**)**:** To a stirred solution of **4** (458 mg, 2.46 mmol) in dry toluene (10 mL) were added tributylphosphine (923 ml, 3.69 mmol) and di-*tert*-butyl iminodicarboxylate (1.07 g, 4.93 mmol) at rt, and the resulting mixture was cooled to 0°C.

After addition of 1,1'-(azodicarbonyl)dipiperidine (ADDP) (1.24 g, 4.93 mmol) to the mixture at the same temperature, the whole was stirred for further 6 h at rt. The mixture was treated with *n*-hexane, and the insoluble materials precipitated were removed off by filtration through a pad of Celite. The filtrate was concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane-EtOAc (15:1, v/v) gave the protected amine (**5**) (830 mg, 88 %) as a mixture of diastereomers: $[\alpha]_D^{34}$ -12.8° (*c* 1.04, $CHCl_3$); IR ν_{max} 1690 and 1750; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.50 (6H, s), 1.64-2.00 (2H, m), 3.38-3.94 (4H, m), 4.06-4.18 (1H, m), 4.62-4.75 (1H, m), 5.08-5.32 (2H, m), 5.56-5.98 (1H, m); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 19.3, 19.5, 25.4, 25.6, 30.6, 30.8, 33.2, 34.7, 42.8, 43.6, 62.0, 62.4, 74.3, 75.6, 82.0, 82.1, 94.7, 97.4, 115.2, 117.7, 137.8, 139.0, 152.3, 152.4; MS (CI): 329 $(M+H-57)^+$; HRMS (CI): Calcd for $C_{20}H_{36}NO_6$+H-Bu-*t* : 329.1838. Found: 329.1830.

***N-tert*-Butoxycarbonyl-(3*S*)-hydroxypent-4-enylamine (7):** To a stirred solution of **5** (200 mg, 0.52 mmol) in dry MeOH (5 mL) was added AcCl (1.07 mL, 15.00 mmol) at 0°C under argon, and the resulting solution was stirred for further 2 h at ambient temperature. After evaporation of the solvent, the residual hydrochloride (**6**) was dissolved in THF (2.5 mL), and triethylamine (0.15 mL, 1.10 mmol) was added to this solution. To this solution was added slowly a solution of di-*tert*-butyl dicarbonate (0.12 mL, 0.53 mmol) in THF (0.5 mL) at 0°C, and the mixture was stirred for further 12 h at rt. Evaporation of the solvent gave a residue, which was taken up with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Removal of the solvent left a residue, which was purified by column chromatography on silica gel using *n*-hexane-EtOAc (2:1, v/v) as eluent to afford the *N*-Boc amine (**7**) (85 mg, 81 %): $[\alpha]_D^{32}$ +8.62° (*c* 1.01, $CHCl_3$); IR ν_{max} 1520, 1690 and 3360; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.45 (9H, s), 1.57-1.78 (2H, m), 2.81 (1H, br s), 3.05-3.23 (1H, m), 3.25-3.55 (1H, m), 4.10-4.26 (1H, m), 4.82 (1H, br s), 5,11 (1H, br d, *J*=10.4 Hz), 5.26 (1H, br d, *J*=17.3 Hz), 5.89 (1H, ddd, *J*=5.9, 10.4, 17.3 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 28.3, 37.1, 37.2, 70.2, 79.5, 114.3, 140.5, 156.8; MS (EI): 201 (M^+); HRMS (EI): calcd for $C_{10}H_{19}NO_3$: 201.1365. Found: 201.1342.

***N-tert*-Butoxycarbonyl-(3*S*)-acryloyloxypent-4-enylamine (8):** To a stirred solution of **7** (325 mg, 1.62 mmol) in THF (8 mL) was added ethylmagnesium bromide (0.96 M, 1.85 mL, 1.78 mmol) at rt under argon, and the resulting solution was stirred for further 20 min. To this solution was added acryloyl chloride (0.26 mL, 3.23 mmol) at the same temperature, and the whole was stirred for 3 h. After treatment with saturated $NaHCO_3$ solution, the mixture was extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:1, v/v) as eluent to afford the ester (**8**) (360 mg, 87 %) as an oil; $[\alpha]_D^{33}$ –30.5° (*c* 1.01, $CHCl_3$); IR ν_{max} 1700, 1740 and 3380 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.44 (9H, s), 1.82-1.90 (2H, m), 2.99-3.12 (1H, m), 3.22-3.34 (1H, m), 4.74 (1H, br s), 5.20 (1H, br d, *J*=10.5 Hz), 5.28 (1H, br d, *J*=17.3 Hz), 5.41 (1H, br dd, *J*=6.0, 13.1 Hz), 5.75-5.92 (1H, m), 5.85 (1H, br dd, *J*=1.0, 10.5 Hz), 6.14 (1H, br dd, *J*=10.4, 17.3 Hz), 6.43 (1H, br dd, *J*=1.0, 17.3 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 28.3, 34.5, 36.6, 72.4, 79.20, 116.9, 128.4, 131.0. 135.7, 155.8, 165.5 ; MS (CI): 256 (M+H); HRMS (CI): calcd for $C_{13}H_{22}NO_4$: 256.1549. Found: 256.1575.

5-(2-*tert*-Butoxycarbonylaminoethyl)-2(5*H*)-furanone (9): A solution of the ester (**8**) (1.4 g, 5.49 mmol) in dry CH_2Cl_2 (550 mL) in the presence of Grubbs' 2nd generation Ru catalyst (233 mg, 0.275 mmol, 5%mol) was heated at 40°C for 5 h. Evaporation of the solvent gave a residue, which was

subjected to column chromatography on silica gel. Elution with *n*-hexane-EtOAc (1:1, v/v) gave the furanone (**9**) (1.1 g, 85 %) a colorless oil; $[\alpha]_D^{28}$ +33.9° (*c* 1.00, $CHCl_3$); IR ν_{max} 1520, 1680, 1760 and 3360 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.45 (9H, s), 1.65-1.83 (1H, m), 2.00-2.15 (1H, m), 3.20-3.42 (2H, m), 4.76 (1H, br s), 5.07-5.14 (1H, m), 6.12 (1H, dd, *J*=2.0, 5.8 Hz), 7.51 (1H, dd, *J*=1.3, 5.8 Hz); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 28.3, 33.6, 37.0, 79.6, 81.4, 121.5, 155.9, 156.1, 172.7; MS (EI): 228 $(M+1)^+$; HRMS (EI): calcd for $C_{11}H_{18}NO_4$ $(M+1)^+$: 228.1236. Found: 228.1248.

***N-tert*-Butoxycarbonyl (-)-Geissman-Waiss Lactone (10):** To a stirred suspension of NaH (60%, 282 mg, 7.05 mmol) in DMF (33 mL) was slowly added a solution of the furanone (**9**) (800 mg, 3.52 mmol) in DMF (2 mL) at 0°C under argon. After being stirred for 5 min, the mixture was treated with saturated NH_4Cl solution, and extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using *n*-hexane-EtOAc (1:1, v/v) as eluent to afford the desired compound (**10**) (767 mg, 96 %); mp 109-110 °C (from EtOAc-nexane); $[\alpha]_D^{28}$ +134.7° (*c* 1.02, $CHCl_3$); IR ν_{max} 1690 and 1780 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 270 MHz) δ 1.47 (9H, s), 1.95-2.38 (2H, m), 2.65-2.96 (2H, m), 3.25-3.95 (2H, m), 4.30-4.52 (1H, m), 5.00-5.12 (1H, m); ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ 28.4, 30.1, 30.6, 35.8, 36.6, 43.9, 44.2, 57.8, 80.4, 83.1, 84.1 ; MS (EI): 227 (M^+); HRMS (EI): calcd for $C_{11}H_{17}NO_4$: 227.1157. Found: 227.1144. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.92; H, 7.57; N, 6.14.

ACKNOWLEDGEMENT

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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