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A Streamlined Asymmetric Synthesis of Substituted Geissman-Waiss Lactones, Oseltamivir Precursors and Peptidyl Hydroxylactams from (–)-Azidocyclohexenol

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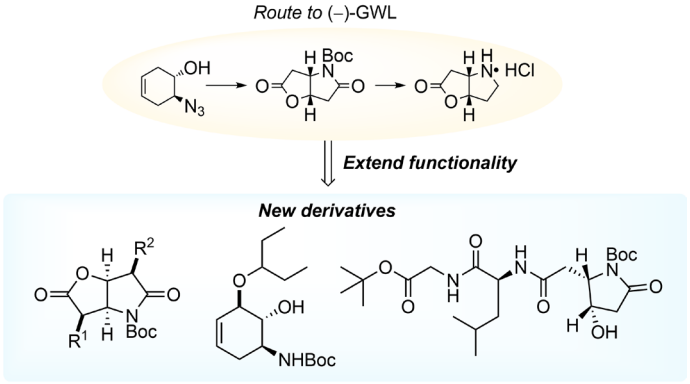
Graphical Abstract



Abstract

The asymmetric synthesis of methyl or pentyloxy *N*,*O*-bicyclic γ-butyrolactone lactams, 6-aminocyclohex-3-ene-1,2-diol (an oseltamivir precursor) and β-hydroxy lactam tripeptide, starting from (–)-(1*S*,2*S*)-1-azido-2-hydroxycyclohexene is hereby described. Synthetic transformations in the developed protocols include a linear relay of reduction/protection of the azide, allylic hydroxylation, alcoholysis, oxidative cleavage promoting lactonization/lactamization sequences and methylation. This route provides a simple synthetic pathway towards necine alkaloid derivatives, the antiviral drug oseltamivir (Tamiflu) and peptides incorporating rigid lactam units for foldamer synthesis thus extending the usefulness of our previously reported asymmetric synthetic methodology.

Keywords: Geissman-Waiss lactone, necine alkaloids, γ-butyrolactone, lactam, peptide, oseltamivir

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Introduction

Heterocycles are widely found in natural products, and the construction of these often complex ring structures remains an important and challenging subset of organic synthesis. For example, the necine alkaloids, natural products that have gained attention due to their reported anticancer and antimicrobial activities [1–4], feature the bicyclic pyrrolizidine motif. Synthetic access to the pyrrolizidine ring can be achieved through the Geissman-Waiss lactone (GWL, **3**, hexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one), known for its use in the synthesis of the necine alkaloid retronecine (**4**) [5] by Geissman and Waiss in 1962 (**Figure 1**). Since then, a number of synthetic methodologies have been developed towards the enantioselective synthesis of the GWL including from (*R*)-malic acid [6], keto-proline by yeast reduction [7], by dirhodium (II) carbenoid catalyzed reaction of diazoacetate and (*S*)-malimide [8], and cycloaddition reactions [9]. Additionally, *cis*-lactone lactam derivatives were also synthesized starting from *N*-protected amino acids [10].

A simple enantioselective methodology to access (–)-GWL through the synthesis pathway involving the intermediate γ-butyrolactone lactam **2** which can be synthesized in several steps from *meso*-cyclohexadiene epoxide has been previously developed [11,12]. Aside from necine alkaloids, intermediates along this synthetic pathway were also used to design and develop efficient methodologies for the synthesis of heterocyclic compounds based on γ-butyrolactone moieties [13,14]. Herein we report the enantioselective synthesis of *N*,*O*-bicyclic γ-butyrolactone lactam derivatives **5** and **6** as a precursor for the synthesis of retronecine base analogs starting from starting from (1*S*,2*S*)-1-azido-2-hydroxycyclohexene **1**. From intermediates along this synthetic pathway, a 6-aminocyclohex-3-ene-1,2-diol derivative **7** that can be further functionalized into oseltamivir-like molecules with potential antiviral properties [15] and a β-hydroxy lactam tripeptide **8**, were synthesized and characterized. These four new derivatives represent an extension of synthetic pathways toward retronecine, allowing the access of useful derivatives from the synthetic intermediates (**Figure 1**).

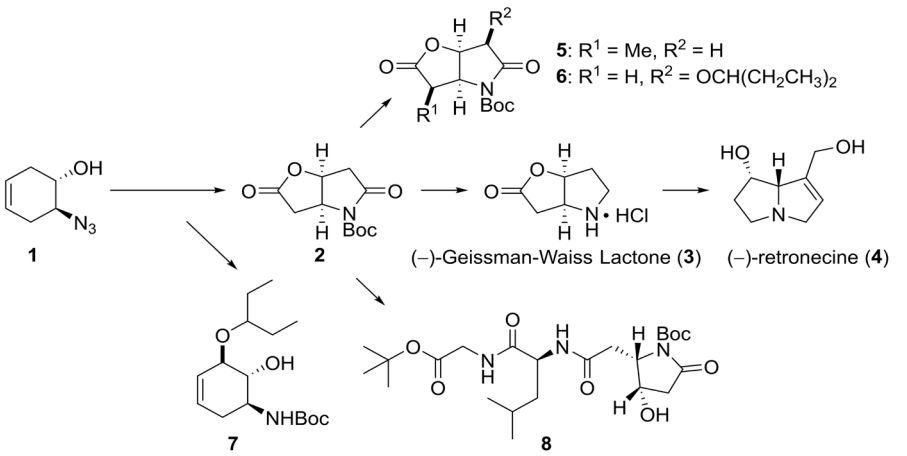


Figure 1. The synthesis pathway to (–)-retronecine (**4**) *via* the intermediate (–)-Geissman-Waiss lactone (GWL) (**3**). From starting material **1**, compounds **5** and **6** can be derived to extend the functionality of the synthesis pathway.

Materials and Methods

Reagents and instrumentations. All chemicals and solvents used in this study were of reagent grade, and no further purification was done unless specified. Thin layer chromatography (TLC) packed with silica gel 60 F254 (Merck KGaA) and visualised under UV light were performed to monitor all reactions. Nuclear magnetic resonance (NMR) spectra for ^{1}H and ^{13}C were acquired with a Bruker Ultra Shield 300 MHz and 400 MHz spectrometer at 300 K using tetramethylsilane (TMS) as an internal standard in chloroform solvent ($CDCl_3$) at ambient temperature. Parts per million (ppm, units) were recorded to express chemical shifts and the coupling constants were recorded in hertz (Hz). The multiplicity of the signals for the ^{1}H NMR spectra is indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). Fourier transformed infrared (FT-IR) spectra were obtained from an FT-IR spectrophotometer 1700X (Perkin Elmer, Waltham, MA) with neat or KBr pellets and wavenumber (ν) in cm^{-1}. MS spectra were recorded by Agilent GC–7890A MS 5975. The concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at a reduced pressure.

Synthesis of tert-butyl (1S,6S)-6 (hydroxy)cyclohex-3-enylcarbamate (9). To a solution of compound **1** (210 g, 1.02 mmol, 1 equiv) in ethanol (4 mL), di-*tert*-butyldicarbonate reagent (Boc_2O; 450 mg, 2.04 mmol, 2 equivs) was added followed by 20% $Pd(OH)_2/C$ (10.2 mg) at room temperature. The reaction proceeded with the addition of triethylsilane (0.33 mL, 2.04 mmol, 2 equivs). After stirring for 24 hrs, the resulting mixture was filtered through Celite™. After complete removal of ethanol, the residue was purified using column chromatography (petroleum ether/ EtOAc =15: 0.5) to give compound **9** (180 mg, 78%) as a white solid. R_f = 0.25 (SiO_2, hexane: EtOAc 21:7); m.p. 76-78 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.50-5.60 (m, 2H), 4.90 (brs, 1H), 3.60-3.70 (m, 1H), 3.20-3.30 (m, 1H), 2.30-2.50 (m, 1H), 2.00-2.10 (m, 1H), 1.80-1.90 (m, 1H), 1.60-1.70 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 124.9 (2C), 124.5 (2C), 80.1, 70.8, 52.4, 33.9, 31.6, 28.4 (3C); IR (Film-KBr): $\tilde{\nu}$ = 3362, 2928, 2854, 1679, 1524, 1445, 1303, 1237, 1167, 1057, 1011, 878 cm^{-1}. MS [CI, NH_3] m/z (%) = 213.1 (100) [M^+]; Calculated for [$C_{11}H_{19}NO_3$]: 213.14.

Synthesis of tert-butyl ((1S,6R)-5,6-dihydroxycyclohex-3-en-1-yl)carbamate (10). Selenium dioxide (SeO_2, 7.8 mg, 1.41 mmol, 1 equiv) was added to 3 mL dry ethanol containing compound **9** (100 mg, 0.47 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 5 mins. Then, *tert*- butylhydroperoxide (TBHP, 180 µL, 1.89 mmol, 2 equivs) was added to the reaction mixture, and refluxed for 24 hrs. The resulting products were concentrated under reduced pressure and purified using column chromatography on silica gel with hexane:EtOAc (21:7) to yield 50 mg (46%) compound **10** as a yellowish solid. R_f = 0.4 (SiO_2, hexane: EtOAc 21: 7); m.p. 73-75 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40-5.50 (m, 2H), 4.43-4.60 (brs, IH), 3.66-3.75 (m, 2H), 3.25-3.44 (m, 1H), 2.45-2.63 (d, 1H, J = 15.6), 2.15-2.25 (d, 1H, J = 12), 1.46 (s, 9H); 13C NMR (100 MHz, $CDCl_3$): δ 156.8, 124.5 (2C), 124.4 (2C), 79.3, 69.4, 56.4, 52.1, 31.3, 28.3 (2C); IR (film-KBr): $\tilde{\nu}$ = 3601, 3552, 2979, 2933, 1713, 1505, 1453, 1367, 1279, 1253, 1158, 985, 862, 791. MS [CI, NH_3] *m/z* (%) = 253.01 (75) [M + H^+ + Na^+], 252.9 (10) [M + Na^+]; calculated for $C_{11}H_{19}NO_4$: 229.1314 [M + Na]$^+$, found 252.1207 [M + Na]$^+$.

Synthesis of tert-butyl (5-hydroxy-6-(1-ethylpropoxy)cyclohex-3-en-1-yl)carbamate (7). $BF_3 \cdot Et_2O$ (90 µL, 2 equivs) was added dropwise to a solution of compound **10** (112 mg, 0.37 mmol, 1 equiv) in 3-pentanol (5 mL) and the resulting mixture was stirred at room temperature. After 24 hrs, saturated aqueous $NaHCO_3$ was added and the product was extracted with ethyl acetate (twice) and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ EtOAc, 6:4) to produce **7** (59 mg, 53%). R_f = 0.69 (SiO_2, hexanes: EtOAc, 5:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52-5.62 (m, 2H), 4.58 (brs, IH), 3.62-3.75 (m, 2H), 3.09-3.04(m, 1H), 2.50-2.52 (d, 2H, J = 15.4), 1.87-2.00 (d, 2H, J = 15.6), 1.58-1.63 (m, 2H), 1.45 (s, 9H), 0.7-1.4 (m, 6H); ^{13}C NMR (100 MHz, CDCl3): δ 156.9, 124.9 (2C), 124.3 (2C), 80.0, 74.9, 71.0, 56.5, 52.4, 31.5, 29.8, 28.3 (3C), 24.8, 24.1; IR (Film): $\tilde{\nu}$; = 3373, 3283, 2974, 1675, 1552, 1309, 1247, 1165, 1054, 871, 851, 743, 660. MS [CI, NH_3]: *m/z* (%) = 324.90 $[M + Na + 2H]^+$. calculated for $C_{16}H_{29}NO_4$: 299.2.

Synthesis of (3aS,6S,6aR)-tert-butyl 2,5-dioxo-6-(pentan-3-yloxy)tetrahydro-2H-furo[3,2-b]pyrrole-4(5H)-carboxylate (6). To a stirred solution of 7 (47 mg, 0.16 mmol, 1 equiv) in 5 mL biphasic solution of CCl_4:ACN:H_2O (1:1:2) was added $RuCl_3.3H_2O$ (3 mg, 8.3% mol) at 0 °C, followed by $NaIO_4$ (140 mg, 4.1 equiv) portion-wise. The reaction mixture was stirred for 8 hrs at 0 °C. The mixture was diluted with 5 mL water and extracted with DCM (5 mL x 3). The combined organic layer was dried ($MgSO_4$) and the solvent was evaporated to give a brownish solid, which was purified by column chromatography on silica (MeOH/ EtOAc, 0.5:9.5) to yield **6** (19 mg, 38%) as a brown solid. R_f = 0.51 (SiO_2, EtOAc/MeOH, 9:1); m.p. 168-170 °C. ^{1}H NMR (400 MHz, CDC_{l3}) δ 5.04−5.14 (m, 1H), 5.23−5.31 (m, 1H), 3.99−4.10 (m, 1H), 3.11−3.33 (m, 1H), 2.23−2.62 (m, 2H), 1.37−1.40 (m, 4H), 1.26 (s, 9H), 0.88−0.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 151.5, 86.7, 80.1, 70.1, 62.9, 59.4, 41.6, 28.0, 22.8, 14.2; IR (Film): $\tilde{\nu}$; = 2920, 2852, 1725, 1590, 1460, 1373, 1259, 860. MS [CI, NH_3]: m/z (%) = 328.1$[M+H]^+$; calculated for $C_{16}H_{25}NO_6$: 317.4

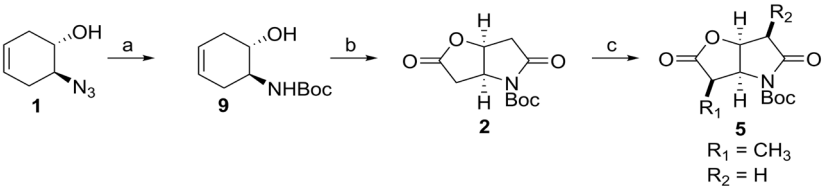
Synthesis of (3aS,6aS)-tert-butyl 2,5-dioxotetrahydro-2H-furo[3,2-b]pyrrole-4(5H)-carboxylate (3). To a stirred solution of **9** (530 mg, 1.8 mmol, 1 equiv) in 55 mL biphasic solution of CCl_4:ACN:H_2O (1:1:2) was added $RuCl_3.3H_2O$ (32 mg, 8.3% mol) at 0 °C, followed by $NaIO_4$ (1.58 g, 4.1 equivs) portion-wise. The reaction mixture was stirred for 8 hrs at 0 °C. The mixture was diluted with 30 mL water and extracted with DCM (15 mL x 3), followed by 1-butanol (15 mL x 3). The combined organic layer was dried ($MgSO_4$) and the solvent was evaporated to give a brownish solid, which was purified by column chromatography on silica (hexanes/EtOAc, 9:1) to yield **2** (268 mg, 61 %) as a white solid. R_f = 0.71 (SiO_2, EtOAc/MeOH 9:1); m.p. 162-164 °C. ^{1}H NMR (400 MHz, CDC_{l3}): δ 5.01-5.09 (ddd, J = 5.1, 5.5, 2.7, 1H), 4.74-4.81 (ddd, J = 4.8, 6.0, 2.2, 1H), 2.89-2.98 (m, 4H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 169.8, 149.8, 84.7, 73.5, 57.9, 38.6, 35.6, 28.0. ; IR (Film): $\tilde{\nu}$ = 1781, 1768, 1721, 1356, 1324, 1251, 1225, 1186, 1149, 1047, 1022, 933, 907, 836 cm^{-1} MS [CI, NH_3] : m/z (%) = 259.1 (44) $[M + NH_4]^+$; Elemental analysis calcd (%) for $C_{11}H_{15}NO_5$ (241.1): C 54.77, H 6.27, N 5.81; found C 54.99, H 6.36, N 5.44.

Synthesis of (3aS,6aS)-tert-butyl 3-methyl-2,5-dioxotetrahydro-2H-furo[3,2-b] pyrrole-4(5H)-carboxylate (5). To a solution of compound **2** (0.015 g, 0.058 mmol, 1 equiv) in THF (5 mL), lithium diisopropylamide (LDA; 0.007 mL, 0.056 mmol, 1 equiv) was added, followed by iodomethane (0.007 mL, 0.09 mmol, 1.5 equivs). The reaction mixture was stirred at –78 ℃ for 7 hrs under N_2 atmosphere. The mixture was diluted with DCM and washed with 10 mL of $NaHCO_3$ for two times and followed by brine, NaCl. Then the organic layers was dried using anhydrous $MgSO_4$. The solvent was removed under reduced pressure to obtain a yellowish crude compound, which was purified using the column chromatography on silica gel with the mobile phase hexane: EtOAc (4:6) to give the compound **5** in 0.010 g with 64% yield. R_f = 0.71 (SiO_2, hexane: EtOAc 4:6); melting point 162-164 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.02-5.07 (ddd, J = 2.7, 2.3, 2.4, 1H), 4.75-4.78 (ddd, J = 2.0 , 1.9, 2.0, 1H), 2.85-2.97 (m, 2H), 2.80-2.84 (m, 1H), 1.53 (s, 9H), 1.21- 1.31 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 169.9, 149.4, 84.7, 72.5, 58.4, 38.8, 35.3, 30.6, 28.9. IR (film-KBr): $\tilde{\nu}$ = 2926, 2359, 1771, 1386, 1364, 1330, 1295, 1252, 1167, 1086, 1054, 939, 801. MS [CI, NH_3] *m/z* (%) = 273.1 [M + NH_4^+]; calculated for $C_{12}H_{17}NO_5$: 255.1.

Synthesis of tert-butyl (2S,3S)-2-(2-(((S)-1-((2-(tert-butoxy)-2-oxoethyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)-3-hydroxy-5-oxopyrrolidine-1-carboxylate (8). To a stirred solution of lactone lactam **2** (28.0 mg, 0.12 mmol) in 2 ml solvent mixture of EtOH and water (3:1), was added NaOH (9.3 mg, 0.23 mmol, 2 equiv.). The reaction mixture was stirred for 1 hr. The solvent was then removed and the remaining mixture was diluted with 1 ml water, added with Amberlite IR-120 and stirred for 30 min. The mixture was filtered to afford the crude carboxylic acid which could be used without further purification. To a stirred solution of crude carboxylic acid (10.0 mg, 0.4 mmol, 1 equiv) in dry DMF (1 mL) was added EDC·HCl (11.2 mg, 1.5 equivs), HOBt (7.6 mg, 1.5 equivs), and DiPEA (0.76 ml, 1.1 equivs) at 0 ℃. The ice bath was removed, and the reaction mixture was stirred for 24 hrs at room temperature. The solvent was evaporated using a rotary evaporator and the reaction mixture was dissolved in DCM (5 mL), washed with 1 M $KHSO_4$ (5 mL), 5% $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over by $MgSO_4$ and the solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel (EtOAc:MeOH, 14:1) to yield 15.5 mg (38%) of **8** as colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): ™ = 7.62-7.51(d, *J* = 2.7, 1H,NH), 7.43-7.32 (t, *J* = 2.8,3.0, 2.2, 1H , NH), 4.53-4.42 (t, 1H,C*H*$_2$CON), 4.43-4.30 (M, 1H, CHCHOH), 3.98 -3.88 (d, 2H, *J* = 1.5), 3.71-3.66 (m, 1H, CHOH), 2.83-2.25 (m, 4H, $CH_{2)}$, 1.91-1.80 (m, 2H, $CH_2C(CH_3)_2$, 1.80-1.62 (m, 1H, $CHCH_3$), 0.96-0.88 (s, 6H, CH_3); 13C NMR (75.5 MHz, $CDCl_3$): ™ = 172.81, 170.3, 168.5, 157.3, 156.4, 82.1,81.7, 67.4, 59.1,56.3, 51.7, 42.5, 41.3, 23.6, 21.MS [CI, NH_3] : m/z (%) = 489.18 (56) [M + NH_4^+]; Elemental analysis calcd (%) for $C_{23}H_{41}N_3O_7$ (471.29): C 58.6, H 8.8, N 8.9 ; found C 57.9, H 8.36, N 8.9.

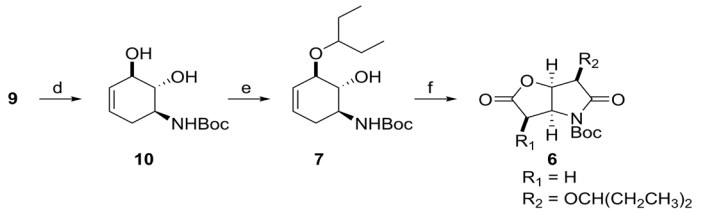
Results and Discussion

In detail, the asymmetric synthesis of *cis*-γ-butyrolactone lactam **5** commenced with the reduction and protection of the starting material **1** with $Pd(OH_2)$/C and triethylsilane in the presence of Boc_2O afforded *N*-Boc cyclohexene **9**. The olefinic group was cleaved oxidatively with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ in a biphasic solution of CCl_4, MeCN and water which underwent lactonisation followed by lactamisation by five membered-ring closing to give *cis*-*N*-Boc-γ-butyrolactone lactam **2** in 61% yield. The methylated product was synthesized from compound **2** via lithiation with LDA and the resulting enolate was alkylated with MeI at –78 °C to afford the alkylated product methyl-*N*,*O*-bicyclic γ-butyrolactone lactam **5** (**Scheme 1**).



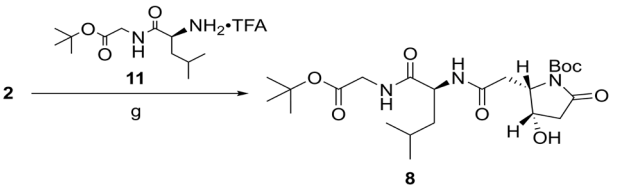
Scheme 1. Synthesis of *cis*-γ-butyrolactone lactam **5** from **1**. Reagents and conditions: (a) Boc_2O (1.5 equiv), $Pd(OH)_2$/C, Et_3SiH (1.5 equivs), EtOH, r.t., 20 h, 88% (b) $RuCl_3.3H_2O$ (8.3 %mol), $NaIO_4$ (4.1 equivs), CCl_4:CH_3CN:H_2O (1:1:2), 0 °C, 61%. (c) LDA (1 equiv), CH_3I (1.5 equiv.), THF, –78 °C, 7 h, 64%.

We also envisioned the synthesis of pentane-*N*,*O*-bicyclic γ-butyrolactone lactam **6** from *N*-Boc cyclohexene **9** (**Scheme 2**). Thus, compound **10** was prepared from **9** via allylic hydroxylation by treatment with using SeO_2 and *tert*-butyl hydroperoxide produced 56% yield of **10**. Alcoholysis reaction of **10** was performed next, with 3-pentanol and catalytic amount of Lewis acid $BF_3 \cdot OEt_2$ promoting the alcoholysis by lowering the LUMO of **10** to produce **7**. Derivative **7** contains a 6-aminocyclopent-3-en-1,2-diol motif that may prove useful as a scaffold for oseltamivir-like derivatives. Further, oxidative cleavage of the double bond in **7** using $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ in a biphasic solution of CCl_4, MeCN and water, directly afforded the final product pentan-*N*,*O*-bicyclic γ-butyrolactone lactam **6** via *in situ* intermediate formation of the corresponding diacid with concomitant lactonization and ring closing lactamization cascade. Considering the structure of oseltamivir, an antiviral drug used to treat influenza, analog **7** is useful precursor of related derivatives. Furthermore, as additional chemical values, compounds **5** and **6** may provide interesting complexity in the structure of necine alkaloids that is useful for structure-activity relationship and medicinal chemistry studies.



Scheme 2. Synthesis of *cis*-γ-butyrolactone lactam **6** from **9**. Reagents and conditions: (d) EtOH, SeO_2, TBHP, refluxed, 24 h, 56% (e) 3-pentanol, $BF_3.OEt_2$, rt, 24 h, 53%, (f) $RuCl_3.3H_2O$ (8.3 % mol), $NaIO_4$ (4.1 equivs), CCl_4:CH_3CN:H_2O (1:1:2), 0 °C, 38%.

Tripeptide **8**, could be synthesized through hydrolysis of lactone lactam **2**, followed by a peptide coupling reaction (**Scheme 3**). Prior to the synthesis of peptide **8**, the lactone ring in **2** would be initially hydrolysed using NaOH in ethanol and water mixture to give its corresponding amino acid. Subsequently, peptide **11** was coupled with preactivated carboxylic acid intermediate using HOBt/EDC in CH_2Cl_2 in the presence of DIPEA to afford **8** in 38%. Foldamers based on aliphatic oligoamide building blocks are homologs of α−peptides, where incremental addition of carbon atoms maybe incorportated into the side-chain, providing β−, γ−, δ−, and other types of peptide structures. So far, most explored foldamers have been mostly anchored on biologically active β-peptides. While constrained β-amino acid containing rigid cyclopentanes has been reported to induce stability on certain helical motifs, a limited knowledge is known for the synthesis of foldameric oligoamides linked by γ−butyrolactam units. The insertion of a lactam may presumably lead to more stabilized helical structures owing to additional H-bonding interaction of the carboxyl moiety and hydroxyl moieties in **8**. and rigidity conferred by a oxo-pyrrolidine unit.



Scheme 3. Synthesis of tripeptide γ-butyrolactam conjugate **8** from *cis*-γ-butyrolactone lactam **2** and peptide **11**. Reagents and conditions: (g) i. EtOH:H_2O (3:1), NaOH, 1 h, Amberlite. ii. HOBt, EDC.HCl, DiPEA, 38%.

Conclusion

In this study, we described the synthesis and characetrization of methyl-*N*,*O*-bicyclic γ-butyrolactone lactam **5** and pentane-*N*,*O*-bicyclic γ-butyrolactone lactam **6** starting from (1*S*,2*S*)-1-azido-2-hydroxycyclohexene. We also successfully explored the use of lactone lactam **2** as a valuble enantiomeric building block for the synthesis of β-hydroxy lactam tripeptide **8**, and the use of intermediate **9** as a building block for oseltamivir-like derivative **7**.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization, M.T.M.A.; methodology, N.S.S., N.P.S.H., and M.T.M.A.; data collection N.S.S., N.P.S.H., and M.T.M.A.; analysis and interpretation of data, N.S.S., N.P.S.H., G.L.L.N., A.P.G.M., and M.T.M.A.; original draft preparation, N.S.S., N.P.S.H., and M.T.M.A.; review and editing of the draft, G.L.L.N. and A.P.G.M. All authors have read and agreed to the final version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

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