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Asymmetric synthesis of ceramide sphingolipid based on (*2S,3S,4S*)-3,4-dihydroxy-5-(hydroxymethyl)pyrrolidine lactam

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ABSTRACT

A facile approach to the versatile chiral building block **2** was developed based on glutamic acid, whereby a new method for asymmetric synthesis of sex pheromone **1** was explored from cheap glutamic acid.

The skeleton of either pyrrolidine lactam **2** or its fragment **3** (see Fig. 1) is one common structural unit found in drugs, drug candidates, and numerous bioactive natural products including sphingolipids or ceramides, which possess diverse bioactivities such as controlling cell growth, maturity, survival, and death as well as inhibiting or activating certain enzymes, and lead to promising efficacies for the control of cancer and other cell proliferation.[1] Therefore, the chiral lactam **2** might be a potentially attractive building block for the natural products. Recently, ceramide sphingolipid **1**, a sex pheromone of hair crab, has been isolated by Fusetani and co-workers from the urine of the female hair crab defined as the species *Erimacrus isenbeckii*, which elicits pre-copulatory behavior in the male ones.[2] Additionally the relative analogues have been confirmed to exhibit cytotoxicity against tumors cells in mice or inhibition against phospholipase A2.[3] These natural products have become the synthetic targets of many chemists due to their biological activities and intriguing structures, and several approaches to the total synthesis of the crab sex pheromone **1** or its analogues have been reported.[4] Among these approaches, the most challenging work is the construction of optically active sphingosine unit bearing three chiral centers. In the recent years, we have been devoted to exploring some multifunctional building blocks and utilizing them in the asymmetric synthesis of some natural products including bioactive piperidine alkaloids, depsipeptides, and ceramides.[5] Herein, we describe a concise method for

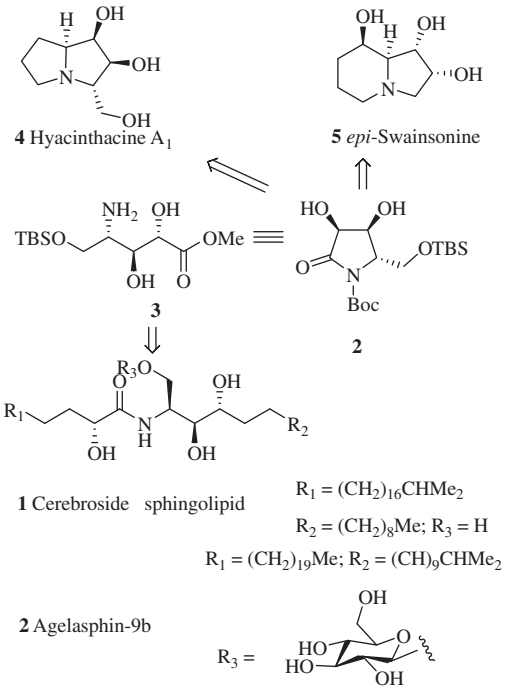

Figure 1. Examples of the natural products containing lactam **2** or its fragment **3** unit.

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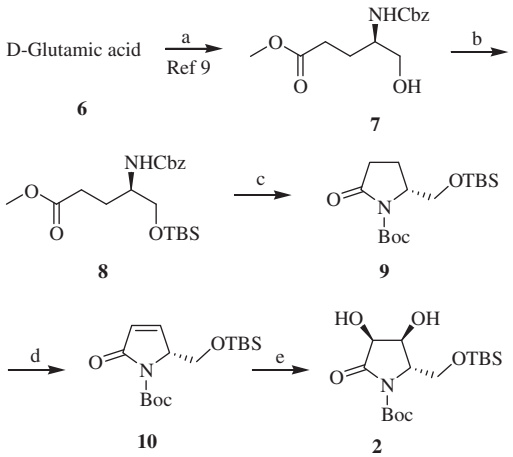
the preparation of the lactam **2** based on the glutamic acid and its utility in the total synthesis of the crab sex pheromone **1**.

Usually the optically active building block **2** could be obtained through (*R*)-pyroglutamic acid[6] derived from the natural glutamic acid as the chiral source,[7] or directly through the self-condensation of glutamic acid derivative in high temperature and low pressure,[8] and these approaches required many steps or inconvenience, and led to an unsatisfied overall yield despite its robust chemistry. Considering step-efficiency, condition-mildness, and overall yield, we started to explore a short approach to **2** from the cheap glutamic acid (Scheme 1). Initially, (*R*)-glutamic acid was conveniently converted to its derivative **7** in 57% yield according to the known method.[9] Next, protection of compound **7** as its TBS ether (TBSCl, imidazole) gave the compound **8** in 97% yield. Upon hydrogenation (10% Pd/C, MeOH) of compound **8** to remove the protective group (Cbz) of the amino, spontaneously intramolecular cyclization and subsequent amidation with Boc_2O in 'one pot' resulted in the known lactam **9** in 69% yield.[6c,10] Treatment of compound **9** with LDA/PhSeBr in tetrahydrofuran at −78 °C followed by elimination of the resulting phenylselenyl derivative with H_2O_2[11] smoothly gave the alkene **10** in 71% yield. Then the alkene **10** was oxidized with $K_2Os_2O_2(OH)_4$/NMO in *t*-BuOH/H_2O to give the dihydroxylative compound **2** as the single isomer {$[\alpha]_D^{25}$ +10.8 (*c* 0.8, $CHCl_3$); lit.[6c] the enantiomer $[\alpha]_D^{20}$ −10.6 (*c* 0.84, $CHCl_3$)} in 65% yield. The spectroscopic and physical data of the lactam **2** were identical with the reported data.[6c,12]

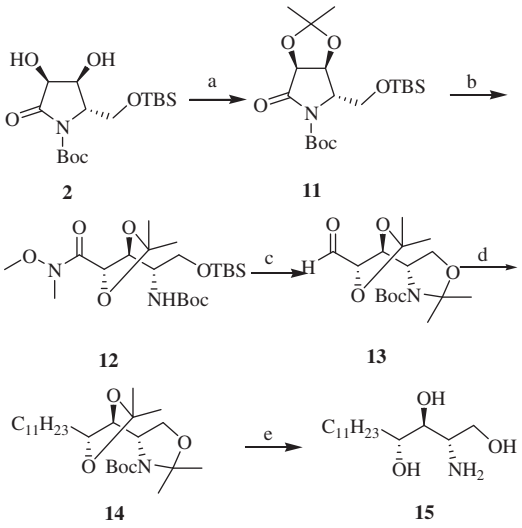
Encouraged by the convenient method for preparation of building block **2**, we then started to investigate the challenging synthesis of sphingosine unit based on the lactam **2** (Scheme 2). Protection of the two hydroxyl groups of **2** with 2,2-dimethoxypropane (DMP) afforded the compound **11** in 96% yield. Treatment of compound **11** with LiOH in THF/H_2O gave the corresponding carboxylic acid as a colorless foam without further purification due to its dehydrative reversion to lactam **11**.[13] Then immediate condensation of the crude carboxylic acid with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of HOBt and EDC afforded the desired product **12** in 67% overall yield. Next, **12** deprotected with TBAF in tetrahydrofuran, followed by protection (DMP, $BF_3{\cdot}Et_2O$)[14] and reduction with DIBAL-H[15] generated the aldehyde **13** in 43% overall yield (three steps).

The unpurified aldehyde **13** was directly subjected to the Wittig reaction with decanetriphenylphosphonium bromide in the presence of *n*-BuLi to afford the *E* and *Z* mixture of the olefin in 71% combined yield. Hydrogenation (10% Pd/C, MeOH) of the olefin mixture and removal of the protective groups (CF_3COOH, AcOH/H_2O) afforded the desired compound **15** in 53% overall yield.

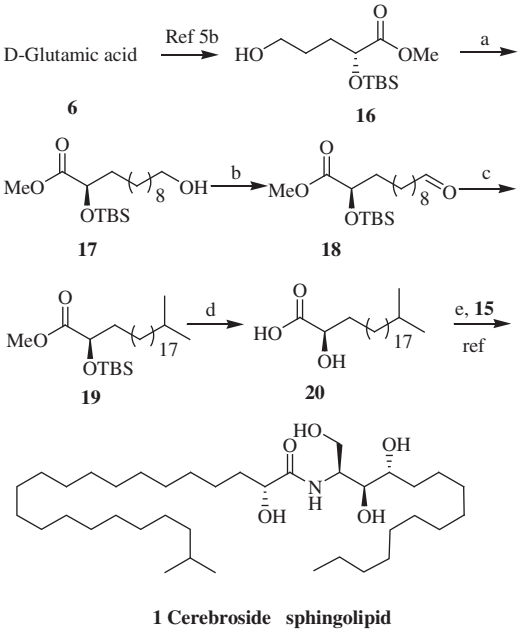
In order to prepare acid **20** for the total synthesis of sex pheromone **1**, we again selected D-glutamic acid **6** as a starting material



Scheme 1. The synthetic route of the important lactam **2**. Reagents and conditions: (a) (i) MeOH, $SOCl_2$, −20 °C to rt, 2 h, (ii) CbzCl, Na_2CO_3–$NaHCO_3$, 1,4-dioxione/H_2O (v/v = 1/1), 0 °C to rt, overnight, (iii) $NaBH_4$, MeOH, THF, 0 °C, 2 h, three steps 57%; (b) TBSCl, imidazole, DMAP, DMF, rt, overnight, 97%; (c) 10% Pd/C, H_2, TEA, Boc_2O, rt, 48 h, 69%; (d) (i) LDA, THF, PhSeBr, −78 °C, 6 h, (ii) H_2O_2, DCM, rt, 2 h, two steps 71%; (e) $K_2Os_2O_2(OH)_4$, NMO, *t*-BuOH/H_2O (v/v = 3/1), rt, overnight, 65%.



Scheme 2. The synthetic route of the compound **15**. Reagents and conditions: (a) DMP, TsOH, acetone, rt, overnight, 96%; (b) (i) LiOH, THF/H_2O (v/v = 3/1), rt, 1 h, (ii) NH(OMe)Me·HCl, HOBt, EDC, *i*-Pr_2NEt, DCM, 0 °C to rt, 12 h, two steps 67%; (c) (i) TBAF, THF, rt, 3 h, (ii) DMP, $BF_3{\cdot}Et_2O$, DCM, rt, 4 h, two steps 63%, (iii) DIBAL-H, DCM, −78 °C, 3 h, 69%; (d) (i) *n*-$C_{10}H_{21}PPPh_3Br$, *n*-BuLi, THF, 0 °C to rt, 4 h, 71%, (ii) 10% Pd/C, H_2, MeOH, rt, overnight, 86%; (e) (i) CF_3COOH, rt, 5 h, (ii) AcOH–H_2O (v/v = 4/1), 45 °C, 12 h, 62%.



Scheme 3. The synthesis of the Cerebroside sphingolipid **1**. Reagents and conditions: (a) (i) $(COCl)_2$, DMSO, TEA, DCM, −78 °C, 4 h, 85%, (ii) $BnOCH_2(CH_2)_5CH_2PPh_3Br$, *n*-BuLi, THF, rt, 3 h, 81%, (iii) 10% Pd/C–20% $Pd(OH)_2$/C, MeOH, overnight, 95%; (b) (i) $(COCl)_2$, DMSO, TEA, DCM, −78 °C, 4 h, 95%; (c) (i) $Me_2CH(CH_2)_7CH_2PPh_3Br$, *n*-BuLi, THF, 0 °C, 3 h, 85%, (ii) 10% Pd/C, MeOH, rt, 4 h, 92%; (d) (i) TBAF, THF, rt, 4 h, (ii) LiOH, THF–H_2O (v/v = 3/1), rt, 6 h, two steps 53%; (e) (i) [1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride] (WSCI), HOBt, DCM, rt, 24 h, (ii) TBAF, THF, rt, 6 h, two steps 46%.

for the preparation of the important intermediate **16** by our own method (Scheme 3).[5b]

Oxidization of alcohol **16** with DMSO/$(COCl)_2$ at −78 °C provided the unpurified aldehyde, which was directly subjected to the Wittig reaction and hydrogenation to afford alcohol **17** in 65% yield. Similarly, the alcohol **17** was easily converted to the compound **19** according to the above Wittig reaction conditions in 74% yield. Deprotection and hydrolysis of the compound **19** gave the corresponding acid **20** in 53% yield. By the known method[4a] the condensation of the acid **20** with the amino of the compound **15** in the presence of [1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride] (WSCI)[4a] and HOBt followed by the removal of the protective group afforded the sex pheromone **1** {$[\alpha]_D^{25}$ +12.3 (*c* 0.13, $CHCl_3$–MeOH, 1:1); lit.[4c] $[\alpha]_D^{22}$ +12.5 (*c* 0.16, $CHCl_3$–MeOH, 1:1); lit.[4b] $[\alpha]_D^{28}$ +14 (*c* 0.70, $CHCl_3$–MeOH, 1:1)} in 46% overall yield. The spectroscopic and physical data of the synthetic sex pheromone **1** were identical with the reported data.[4,16] Thus, a new method for the asymmetric synthesis of sex pheromone **1** was established based on the glutamic acid as the starting material.

In conclusion, sex pheromone **1** of the hair crab was synthesized based on the readily available building block **2** derived from the cheap starting material. Further application of this methodology in the asymmetric synthesis of other ceramides and natural products, through the versatile chiral building block **2**, is in progress and to be published elsewhere.

Acknowledgments

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12. Physical data for synthetic building block **2**. $[\alpha]_D^{20}$ +10.8, (*c* 0.8, $CHCl_3$), {lit.[6c] the enantiomer $[\alpha]_D^{20}$ −10.6 (*c* 0.84, $CHCl_3$)}. IR 3440, 2956, 1775, 1368, 1286, 1154, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.58 (dd, *J* = 5.1, 3.3 Hz, 1H), 4.35 (d, *J* = 4.8 Hz, 1H), 4.14–4.11 (m, 1H), 3.98 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.83 (dd, *J* = 11.1, 1.5 Hz, 1H), 3.33 (s, 1H), 3.08 (s, 1H), 1.54 (s, 9H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 149.6, 83.7, 71.5, 69.2, 64.6, 61.7, 27.9, 25.8, 18.1, −5.7, −5.6 ppm; MS (ESI): 384 ($M+Na^+$); HRESIMS calcd for $[C_{16}H_{31}NO_6Si+Na]^+$: 384.1820, found: 384.1835.
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16. Physical data for synthetic pheromone of hair crab **1**. $[\alpha]_D^{25}$ +12.3 (*c* 0.13, $CHCl_3$–MeOH, 1:1); {lit.[4c] $[\alpha]_D^{22}$ +12.5 (*c* 0.16, $CHCl_3$–MeOH, 1:1); lit.[4b] $[\alpha]_D^{28}$ +14 (*c* 0.70, $CHCl_3$–MeOH, 1:1)}. IR (film): ν_{max} 3379, 2915, 1642, 1472, 1084 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$–CD_3OD, 1:1): δ 4.12–4.07 (m, 1H), 4.02 (dd, *J* = 7.9, 3.8 Hz, 1H), 3.76 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.70 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.57–3.49 (m, 2H), 1.73–1.60 (m, 2H), 1.56–1.08 (br m, 59H), 0.87–0.83 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CHCl_3$–MeOH, 1:1): δ 176.21, 75.62, 72.68, 72.32, 61.34, 52.01, 51.92, 39.44, 34.83, 33.01, 32.31, 30.29, 30.17, 30.09, 30.03, 30.00, 29.95, 29.88, 29.72, 28.32, 27.83, 26.24, 25.62, 23.08, 22.82, 14.34, 13.72 ppm; MS (ESI): 650.5 ($M+Na^+$); HRMS(MALDI/DHB) calcd for ($C_{38}H_{77}NO_5+Na^+$): 650.5717, found: 650.5699.