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Studies toward a synthesis of C3-epimauritine D: construction of the macrocycle

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Abstract—We successfully synthesized a 14-membered cyclic enamide of C3-epimauritine D from the *cis*-2,3-pyrrolidinediol derivative. Treatment of the pyrrolidinediol with nitrobenzonitrile in an S_NAr reaction efficiently installed the desired aryl–alkyl ether linkage on the *N*-heterocyclic system. Macrocyclization was successfully achieved by the use of TFFH as the peptide coupling reagent in the presence of HOAt.

Over the past decades, considerable investigations into the total synthesis of cyclopeptide alkaloids were performed owing to their prominent biological activities as well as structural interests.[1] Numerous efforts have been specially concentrated on the macrocyclization.[2] Recently, the total synthesis of sanjoinine G1 was reported which utilized an intramolecular S_NAr reaction[3] and modified Schmidt protocol[4] for the construction of the macrocycle. Herein, we wish to report our newly developed procedure toward epimauritine D **1** (Fig. 1), which is the C3-epimer of 14-membered cyclopeptide alkaloid mauritine D that was isolated from *Zizyphus nummularia* by Tschesche.[5] We reasoned that unnatural epimer would provide biological activity relationship as well as synthetic methodology comparing with natural product. In this report, we described the preparation of the key intermediate **2** of C3-epimauritine D by macrocyclization at the C1–N14 site.

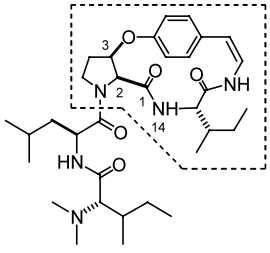
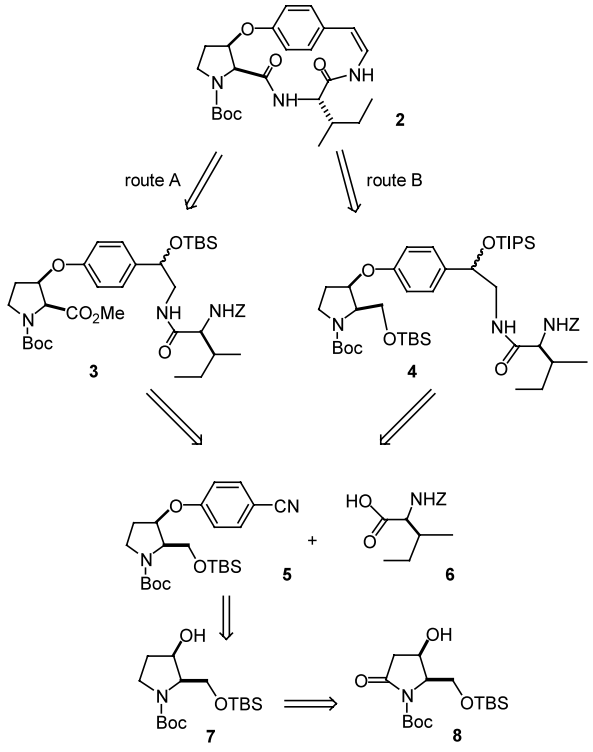


Figure 1. Structure of C3-epimauritine D **1**.

Our retrosynthetic analysis for the enamide **2** is illustrated in Scheme 1. We envisioned that macrocycle **2**



Scheme 1.

Keywords: cyclopeptide alkaloid; epimer; pyrrolidinone; macrocyclization; cyclic enamide; pfp ester; TFFH.

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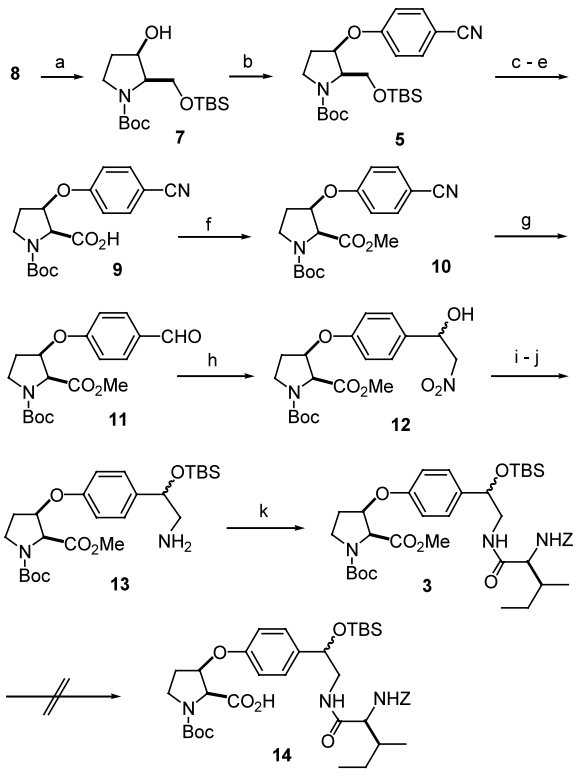


Scheme 2. *Reagents and conditions*: (a) reflux, BH_3SMe_2, THF, 5 h, 88%; (b) nitrobenzonitrile, NaH, DMF, −30°C, 4 h, 78%; (c) AcOH:THF:H_2O (3:1:1 v/v/v), 40–45°C, 15 h, 88%; (d) DMSO, TFAA, NEt_3, CH_2Cl_2, −78°C, 3 h; (e) 1 M $KMnO_4$, 1.25 M NaH_2PO_4 buffer (pH 4.12), *t*-BuOH, rt, 1 h, 81% for two steps; (f) DCC, DMAP, MeOH, CH_2Cl_2, 0°C–rt, 3 h, 96%; (g) Raney Ni, NaH_2PO_2, py:AcOH:H_2O (2:1:1 v/v/v), 40°C, 3 h, 93%; (h) Na, CH_3NO_2, MeOH, 0°C, 30 min, 93% with recovered starting material; (i) TBDMS–Cl, imidazole, DMF, 0–25°C, 24 h, 93%; (j) 10% Pd/C, HCO_2NH_4, MeOH, 0–25°C, 4 h, 82%; (k) *Z*-isoleucine **6**, DCC, HOBt, NMM, CH_2Cl_2, 0°C–rt, 3 h, 94%.

could be produced by an intramolecular cyclization of either intermediate **3** or **4**. Compounds **3** and **4** could be disconnected into **5** and **6**. Compound **5** could be prepared from pyrrolidine **7** and *p*-nitrobenzonitrile via an S_NAr reaction. Compound **7** could be obtained from the known pyrrolidinone **8**.

An attempted synthesis of linear precursor **14** is outlined in Scheme 2. Pyrrolidinone **8** was prepared in five steps from D-serine[6] and then reduced to compound **7** by using borane–dimethylsulfide complex. One of the key steps was the construction of aryl–alkyl ether linkage to set the C-3 stereocenter of compound **5**. We carried out the S_NAr reaction with compound **7** using various conditions (Table 1).[4a,7] Treatment of **7** with fluorobenzonitrile at room temperature afforded a desilylated by-product (entry 2). Compound **5** could be achieved in 78% yield by first generating the alkoxide of **7** via NaH which then displaced the nitro group of *p*-nitrobenzonitrile. Optimization of **5** required performing the reaction at −30°C (entry 7) since low yields were obtained at higher temperatures (entries 3 and 5). Furthermore, replacing NaH with the bases DBU, Et_3N, or LiH resulted in no product (entries 1, 4 and 6).

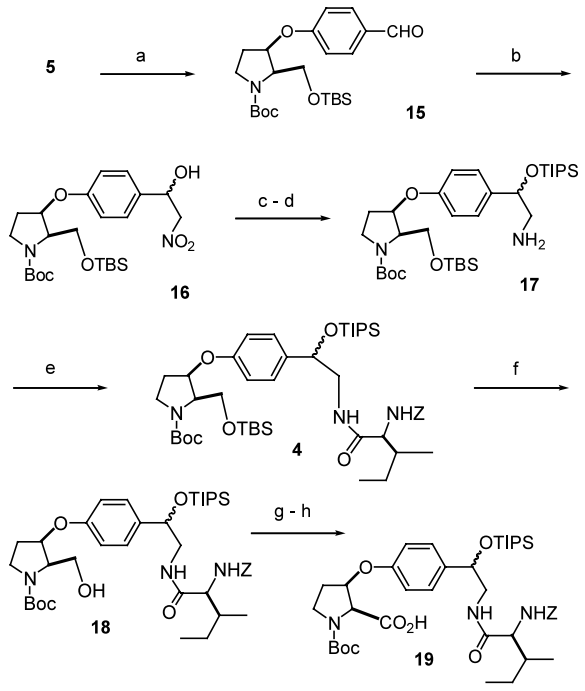
Compound **5** was converted to **9** by a Swern–Masamune oxidation, followed by protection to methyl ester **10**. The cyano group of **10** was treated with Raney Ni and NaH_2PO_2 to afford aldehyde **11**, which was then reacted with the anion of nitromethane to give the expected epimeric benzylic alcohol **12**. Treatment of compound **12** with TBS–Cl and imidazole followed by reduction of the nitro group using ammonium formate and Pd/C provided the amine **13** in good yield. Coupling reaction between the amine **13** and *Z*-isoleucine **6** was achieved by using standard DCC/HOBt methodology. We were unexpectedly confronted by the problem that the hydrolysis of compound **3** to carboxylic acid **14** was unsuccessful with aqueous solutions of bases such as LiOH, NaOH, and $Ba(OH)_2$. Thus, construction of macrocycle via route A was hampered due to the failure of the preparation of the linear precursor **14**.

Because of the difficulty encountered in the hydrolysis of **3**, we changed our strategy and planned a different route via the linear precursor **4** (Scheme 3). Compound **4** was prepared from compound **5** via a similar synthetic protocol as for compound **3**. The cyano group of **5** was converted to the aldehyde **15** in 73% yield, followed by a Henry reaction to produce **16**. In order to differentiate the protecting groups on the secondary alcohol from the primary alcohol, compound **16** was silylated with TIPSOTf in the presence of 2,6-lutidine[8] to yield, after reduction of the nitro group, amine **17**.

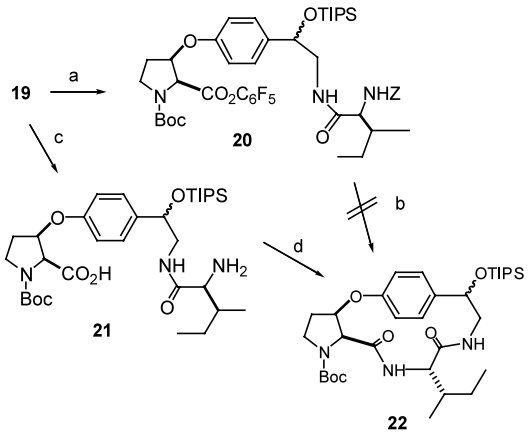
Table 1. S_NAr reaction under various conditions

Entry	Substrate[a]	Base	Solvent	Reaction time (h)	Reaction temp.	Yield[b]
1	A	DBU	CH_3CN	12	rt	n.r.[c]
2	A	NaH	HMPA	1	rt	Trace[d]
3	B	NaH	HMPA	1	rt	25%
4	B	Et_3N	HMPA	24	rt	n.r.
5	B	NaH	DMF	2	0°C	34%
6	B	LiH	DMF	12	rt	n.r.
7	B	NaH	DMF	4	−30°C	78%

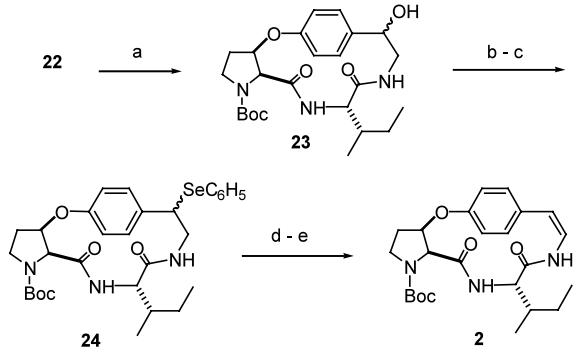
[a] A: fluorobenzonitrile; B: nitrobenzonitrile.
[b] Isolated yield.
[c] n.r.: no reaction.
[d] Trace: trace amount of product.



Scheme 3. *Reagents and conditions*: (a) Raney Ni, NaH_2PO_2, py:AcOH:H_2O (2:1:1 v/v/v), 40–45°C, 3 h, 73%; (b) Na, CH_3NO_2, MeOH, 0°C, 30 min, 85% with recovered starting material; (c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 3 h, 65%; (d) 10% Pd/C, HCO_2NH_4, MeOH, 40°C, 2 h, 81%; (e) *Z*-isoleucine **6**, DCC, HOBt, NMM, CH_2Cl_2, 0°C–rt, 3 h, 91%; (f) AcOH:THF:H_2O (3:1:1 v/v/v), 45–50°C, 3 h, 87%; (g) DMSO, TFAA, NEt_3, CH_2Cl_2, −78°C, 3 h; (h) 1 M $KMnO_4$, 1.25 M NaH_2PO_4 buffer (pH 4.12), *t*-BuOH, rt, 1 h, 65% for two steps.



Scheme 4. *Reagents and conditions*: (a) pentafluoro phenol, DCC, CH_2Cl_2, 0°C–rt, 3 h, 92%; (b) 10% Pd/C, cyclohexene, EtOH, 4-pyrrolidinopyridine, 1,4-dioxane, 95°C–rt, 4 h; (c) 10% Pd/C, MeOH, rt, 1 h, 87%; (d) TFFH, HOAt, DIEA, CH_2Cl_2, 0°C, 2 h, 75%.



Scheme 5. *Reagents and conditions*: (a) TBAF, THF, 0°C–rt, 2 h, 60%; (b) MsCl, NEt_3, CH_2Cl_2, −10°C, 30 min; (c) diphenyldiselenide, $NaBH_4$, EtOH, 80°C, 30 min, 50% for two steps; (d) $NaIO_4$, MeOH, 40 min; (e) benzene, 60°C, 40 min, 60% for two steps.

Acylation of amine **17** by Z-isoleucine **6** produced amide **4** which was then selectively deprotected to alcohol **18** by using a mixture of acetic acid:tetrahydrofuran:water. Subsequently, the Swern–Masamune oxidation of alcohol **18** afforded the carboxylic acid **19**.

As shown in Scheme 4, our initial investigation on the macrocyclization of carboxylic acid **19** was carried out under modified Schmidt protocol.[2f,9] Interestingly, our attempt to form the macrocycle **22** from the activated pentafluorophenyl (pfp) ester **20** afforded none of the desired product. After removal of the Z group of compound **19**, several attempts to cyclize compound **21** to lactam **22** failed using standard reagents such as BOP-Cl, DPPA, and BOP.[10] However, using methodology developed by Carpino,[11] compound **21** reacted with tetramethylfluoroformamidinium hexafluorophosphate (TFFH)/HOAt in CH_2Cl_2 to give the desired product **22** as a mixture of two diastereomers in 75% yield.

Completion of the synthesis of the cyclic enamide **2** is shown in Scheme 5. Desilylation of the macrocycle **22** using TBAF afforded the alcohol **23**, which was then converted to the selenide **24** by sequential mesylation and selenation. Oxidation of compound **24** with sodium periodate, followed by thermal elimination, afforded the enamide **2** in 60% yield with a rotation value of −274 (*c* 0.69, $CHCl_3$).

In conclusion, the cyclic enamide **2**[12] was efficiently synthesized from the known pyrrolidinone **8** in 17 steps and an overall yield of 1.4%. The structure was confirmed by ^1H, ^{13}C, ^1H–^1H COSY, and ^1H–^{13}C COSY NMR spectroscopy and HRMS spectrometry. Further investigations toward the total synthesis of C3-epi-mauritine D with **2** are now in progress.

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12. Data for **2**: R_f 0.62 (*n*-hexane:EtOAc, 1:1); mp 198–199°C; $[\alpha]_D^{25} = -274$ (*c* 0.69, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.69 (d, $J = 6.9$ Hz, 3H), 0.80 (m, 3H), 1.14 (m, 2H), 1.40 (s, 9H), 2.16 (m, 1H), 2.46 (m, 1H), 2.83 (m, 1H), 3.36 (m, 1H), 3.53 (m, 1H), 4.07 (dd, $J_1 = 10.1$ Hz, $J_2 = 3.1$ Hz, 1H), 4.54 (d, $J = 7.0$ Hz, 1H), 5.12 (m, 1H), 6.09 (m, 1H), 6.30 (m, 2H), 6.61 (dd, $J_1 = 10.3$ Hz, $J_2 = 7.5$ Hz, 1H), 6.97 (m, 1H), 7.05 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.95, 15.55, 23.00, 28.23, 30.64, 34.89, 43.49, 57.85, 59.29, 77.20, 80.97, 115.11, 115.42, 123.34, 126.05, 129.68, 131.83, 154.98, 157.37, 167.33, 168.04; FTIR (KBr, cm^{-1}): 3230, 2871, 2180, 1706, 1505, 1393, 1247; HRMS (EI) $[M]^+$ m/z calcd 443.2420 for $C_{21}H_{41}O_4N_3$, found 443.2417.