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Synthetic Studies of 14-Membered Cyclopeptide Alkaloids

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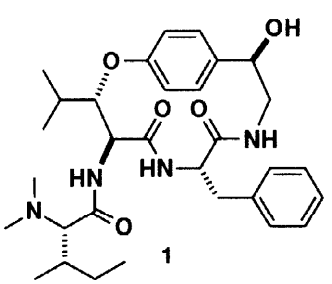
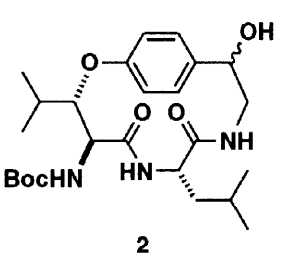
Abstract : A strained 14-membered cyclopeptide was prepared from the Garner aldehyde derived from D-serine. The key steps in the synthesis were the construction of the alkyl-aryl ether linkage via an S_NAr reaction involving 4-fluorobenzonitrile and the macrolactamization using a modification of the Schmidt protocol involving an activated pentafluorophenyl ester. © 1998 Elsevier Science Ltd. All rights reserved.

Cyclopeptide alkaloids are a family of closely related polyamide bases of plant origin.[1-4] The isolation and structural elucidation of pandamine (**1**) by Païs and co-workers[5] provided the first entry into this class of natural products. Since those pioneering studies over 200 cyclopeptide alkaloids containing either a 13-, 14-, or 15-membered macrocycle have been reported. They are particularly common to plants in the Rhamnaceae family, but have been isolated from more than 25 other species. Although the occurrence of the cyclopeptide alkaloids is widespread in nature, their low natural abundance has hindered a thorough evaluation of their biological activity. Consequently, the synthesis of cyclopeptide alkaloids has attracted the interest of a number research groups and a variety of approaches have been investigated to increase their availability.[6-10] These studies have culminated in the total synthesis of several natural products.[11-17]



1



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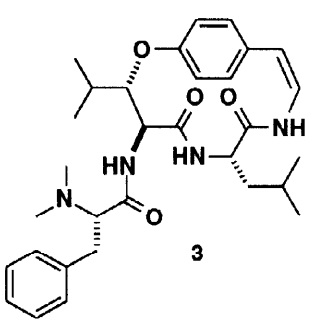

3

The 14-membered cyclopeptide alkaloids, in addition to being the largest group, are perhaps the most synthetically challenging as a result of the strain inherent in this ring size. Another synthetic obstacle of this subclass of cyclopeptide alkaloids is the presence of an alkyl-aryl ether. This group can be further distinguished according to the β-hydroxy-α-amino acid in the ring. We have chosen to target the natural products containing a β-hydroxyleucine unit and herein describe the synthesis of **2**. This synthesis potentially allows us to access some members of the frangulanine-type cyclopeptide alkaloids, such as sanjoinine A (**3**).

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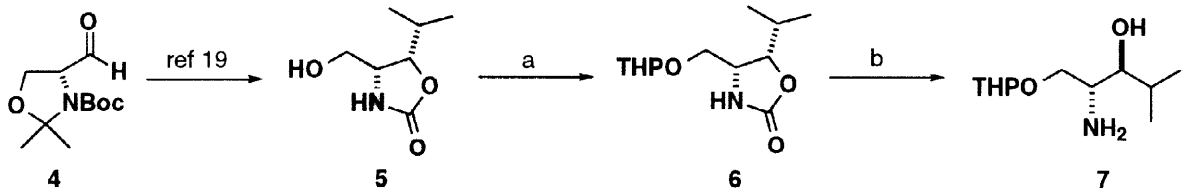
Our strategy for the synthesis of the 14-membered macrocycle containing β-hydroxyleucine begins with the Garner aldehyde **4** derived from D-serine.[18] We have reported previously that **4** could be converted into the oxazolidinone **5** in three steps and have demonstrated the use of this intermediate in our synthesis of (2S, 3S)-3-hydroxyleucine.[19] For the purpose of this study, the primary alcohol in **5** was protected as its THP ether **6** and subsequent treatment with potassium hydroxide afforded the amino alcohol **7** (**Scheme 1**).

Scheme 1

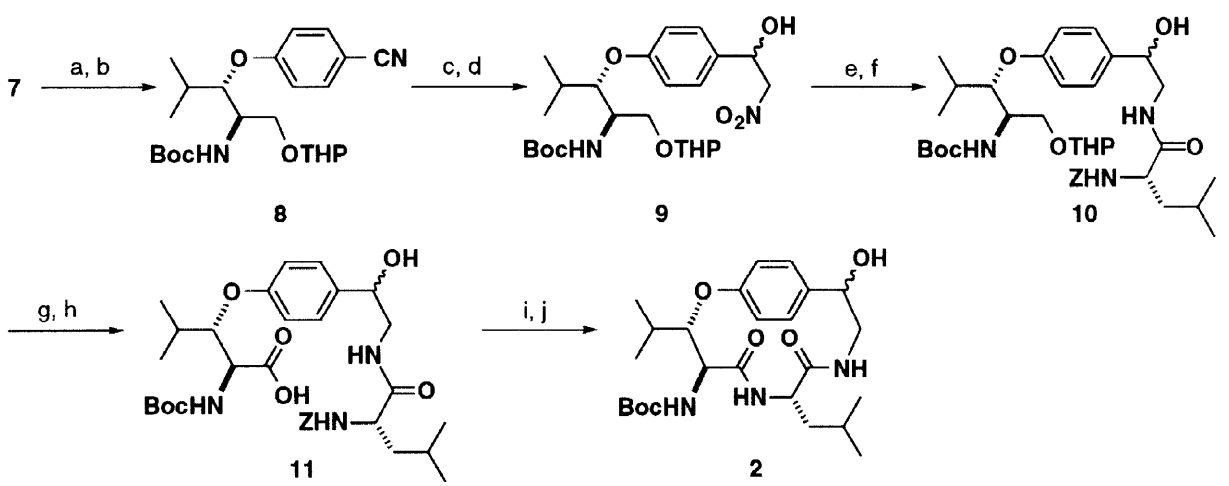


4 5 6 7

Reagents and Conditions : a) 3,4-Dihydro-2*H*-pyran, PPTS, CH_2Cl_2, 73%; b) KOH, MeOH:H_2O (4:1), reflux, 100%.

The alkyl-aryl ether linkage was installed with retention of configuration by deprotonation of the hydroxyl group in **7** using sodium hydride and subsequent reaction with 4-fluorobenzonitrile.[20] The amine was then protected as its Boc-derivative to give **8**. Reduction of the aromatic nitrile was accomplished using Raney nickel and sodium hypophosphite hydrate.[21] Treatment of the resulting aldehyde with the anion derived from nitromethane (Henry conditions[22]) gave **9** in excellent yield after recovery of starting material. The aliphatic nitro group in **9** was then reduced by transfer hydrogenation and the resulting amine was coupled effectively with *N*-Z-leucine using benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) to give **10**. Simultaneous removal of the THP protecting group and oxidation of the resulting primary alcohol and the benzylic alcohol was realized using Jones reagent. Selective reduction of the benzylic ketone was achieved using sodium borohydride and lithium chloride to give **11** in excellent yield.

Scheme 2



8 9 10 11 2

Reagents and Conditions : a) 4-Fluorobenzonitrile, NaH, DMSO, 85%; b) Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt, 92%; c) Raney Ni, $NaH_2PO_2.H_2O$, pyridine:AcOH:H_2O (2:1:1), 93%; d) CH_3NO_2, NaOMe, 0 °C, 96% (based on recovered starting material); e) 10% Pd/C, NH_4CO_2H, MeOH, 94%; f) *N*-Z-Leucine, BOP, DIPEA, CH_2Cl_2, 0 °C to rt, 81%; g) Jones reagent, acetone, 83%; h) $NaBH_4$, LiCl, THF, EtOH, 97%; i) Pentafluorophenol, EDAC, DMAP (cat.), 97%; j) Pd black, γ-terpinene, 1,4-dioxane, *t*-BuOH, 4-pyrrolidinopyridine, reflux, 49%.

The carboxylic acid in **11** was activated as its pentafluorophenyl ester by treatment with pentafluorophenol, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDAC) and a catalytic amount of 4-dimethylaminopyridine (DMAP). Cyclization was then accomplished using a modification of the Schmidt protocol.[23] Slow addition of the pentafluorophenyl ester to a refluxing suspension of palladium black in 1,4-dioxane containing *t*-BuOH, γ-terpinene (as the hydrogen source) and 4-pyrrolidinopyridine gave the cyclopeptide **2** as a mixture of diastereomers (ratio 1.3:1) in 49% yield. The two isomers were separated by flash chromatography on silica but the stereochemistry at the hydroxyl position has not been determined.

The high resolution mass spectra agreed with the calculated values and the ^{1}H-NMR spectra of both isomers[24] are consistent with the literature values.[15]

In conclusion, we have reported an efficient new synthesis (15 steps from the Garner aldehyde, 9% overall yield) of a 14-membered cyclopeptide that could serve as a potential precursor to some naturally occurring cyclopeptide alkaloids, such as **3**. The alkyl-aryl ether linkage and the strained 14-membered macrocycle have been formed.

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24. **2** (major isomer): mp 248-249 °C (decomp.); *Rf* 0.26 (ethyl acetate:petroleum ether 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (3H, d, J 6.7), 0.81 (3H, d, J 6.6), 1.00 (3H, d, J 6.7), 1.08 (3H, d, J 6.8), 1.22-1.35 (2H, m), 1.38 (9H, s), 1.41-1.45 (1H, m), 2.08-2.11 (1H, m), 3.07 (1H, d, J 14.0), 3.15 (1H, br s), 3.98-4.02 (2H, m), 4.23-4.29 (1H, m), 4.67 (1H, d, J 8.3), 5.13 (1H, d, J 10.5), 5.17 (1H, br s), 5.97 (1H, d, J 10.5), 6.13 (1H, d, J 9.3), 6.81 (1H, dd, J 8.3 2.3), 6.93 (1H, dd, J 8.5 2.1), 6.99 (1H, dd, J 8.5 2.1), 7.35 (1H, dd, J 8.6 2.0); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.42, 20.08, 22.39, 22.79, 24.50, 28.25, 28.67, 42.28, 47.52, 51.92, 57.31, 72.10, 79.73, 80.24, 114.50, 119.42, 125.97, 127.15, 133.54, 154.99, 156.80, 170.70, 171.07; IR (film) 3298 (s), 2960 (m), 2930 (m), 2869 (w), 1700 (m), 1646 (s), 1540 (m), 1508 (s) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{39}N_3O_6Na$ (M + Na): *m/z* 500.2737, found 500.2731; $[\alpha]_D^{20}$ -54.4 (*c* 0.16, MeOH), Lit.[17] $[\alpha]_D^{25}$ -33.3 (*c* 0.19, $CHCl_3$); **2** (minor isomer): mp 260-262 °C (decomp.); *Rf* 0.15 (ethyl acetate:petroleum ether 70:30); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75 (3H, d, J 6.3), 0.80 (3H, d, J 6.4), 0.99 (3H, d, J 6.7), 1.16 (3H, d, J 6.9), 1.26-1.46 (3H, m), 1.39 (9H, s), 2.05-2.09 (1H, m), 3.24-3.29 (1H, m), 3.66 (1H, d, J 7.1), 3.87-3.94 (2H, m), 4.00-4.03 (1H, m), 4.60 (1H, dd, J 8.5 1.7), 4.84 (1H, dd, J 12.2 6.0), 4.92 (1H, d, J 10.5), 5.60 (1H, br m), 5.75 (1H, d, J 8.2), 6.86 (1H, dd, J 8.4 1.9), 6.89 (1H, dd, J 8.2 2.1), 6.93 (1H, dd, J 8.4 2.2), 7.39 (1H, dd, J 8.4 1.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.36, 20.14, 22.00, 22.79, 24.18, 28.20, 28.82, 40.22, 47.99, 51.18, 57.26, 73.07, 80.44, 81.55, 117.90, 121.61, 126.57, 127.55, 135.53, 154.94, 156.63, 171.15, 171.58; IR (film) 3344 (m), 3273 (s), 2961 (w), 2931 (w), 2869 (w), 1675 (m), 1638 (s), 1542 (m), 1510 (w) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{39}N_3O_6Na$ (M + Na): *m/z* 500.2737, found 500.2739; $[\alpha]_D^{20}$ -51.4 (*c* 0.14, MeOH).