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Total Synthesis of Sanjoinine A (Frangufoline)

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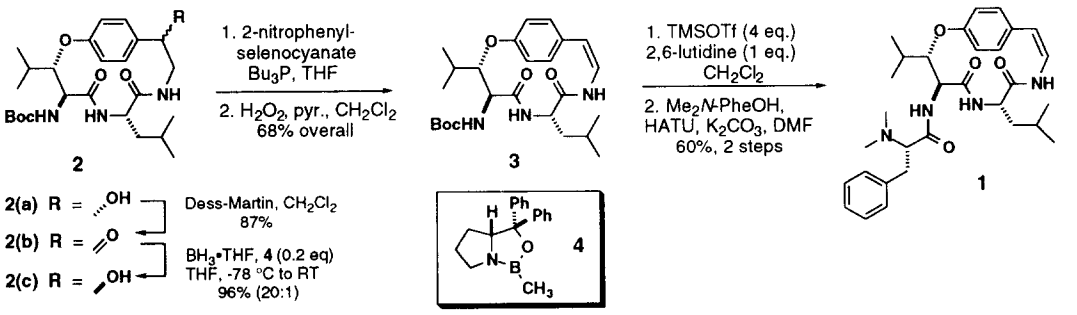
Abstract : Sanjoinine A (**1**) was synthesized from a 14-membered cyclopeptide prepared from a Garner aldehyde derived from D-serine. The key steps in the synthesis were the catalytic asymmetric reduction of ketone **2(b)** and the final removal of the Boc group.

Keywords : Alkaloids; Asymmetric Reactions; Macrocycles; Strained Compounds

Sanjoinine A (frangufoline)[1,2] (**1**) was isolated from sanjoin, the seeds of *Zizyphus vulgaris* var. *spinosus* Bunge, a member of the Rhamnaceae family.[3] Sanjoin has been used as a sedative herbal medicine in the Orient and has been the subject of several pharmacological studies.[4-6] These investigations and the synthetic challenges of 14-membered cyclopeptide alkaloids made **1** an attractive target. We have recently described the preparation of intermediate **2** (R = OH) as a pair of separable isomers and their stereochemistry was determined by correlating the β-isomer **2(c)** to the natural product, sanjoinine G1.[7a,b] We now report the first total synthesis of sanjoinine A (**1**, **Scheme**) which possesses the enamide double bond necessary for in vivo sedative activity.[5]

Scheme



The synthesis began with a difficult introduction of the enamide bond in **3** which probably increases the strain in this system. Additionally, there is no driving force for the formation of the double bond as it is not conjugated to the aromatic ring as shown in the X-ray of mauritine A, a similar 14-membered cyclopeptide alkaloid.[8] As treatment of **2** with Martin sulfurane or Burgess reagent did not effect the desired dehydration, the alcohols were converted to selenides in the presence of *n*-Bu_3P.[9] The selenides were directly oxidized with hydrogen peroxide and pyridine. The β-hydroxyl isomer **2(c)** gave **3**[10] in 75% (2 steps) while the α-isomer **2(a)** yielded less than 5% of the product (**Scheme**), an observation consistent with our previous experience,[11] and the results of Schmidt et al.[12] Fortunately, the unreactive α-isomer can be recycled by oxidation to its corresponding

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ketone by Dess-Martin reagent (87%) followed by reduction. Although reduction of ketone **2(b)** using $NaBH_4$ gave an undesired 1:3 (β:α) ratio of two alcohols, we found that reduction with BH_3•THF in the presence of 20% mol (R)-Me CBS catalyst **4**[13] afforded the desired β–alcohol (20:1; β:α) in 96% yield. This remarkable selectivity suggests an increased steric bulkiness of the aromatic ring which is probably orthogonal to the carbonyl group. This conversion of **2(a)** to **2(c)** improved the overall yield of the elimination steps to 68% yield.

The subsequent removal of the Boc group in **3** presented another problem. Standard conditions, using TFA with anisole as a cation scavenger, or HCl (g) in dioxane gave poor results. Under these reaction conditions, enamide cleavage is possible.[14] Therefore, different Lewis acids were tried. Treatment of **3** with BF_3•Et_2O decomposed the macrocycle. However, TMSOTf in the presence of 2,6-lutidine[15] cleanly removed the Boc group. The reaction mixture was then transferred to a DMF solution containing N,N-dimethylphenylalanine preactivated with *O*-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium PF_6 salt (HATU), followed by addition of anhydrous K_2CO_3. After aqueous work-up and column chromatography, we isolated synthetic **1** in 60% yield for two steps. The synthetic sample had similar physical data to the natural product: mp 248-249 °C; $[\alpha]_D^{20}$ -330 (lit.[16] mp 249 °C; lit.[16] $[\alpha]_D^{27}$ -316).

In conclusion, we achieved an efficient total synthesis (20 steps; 5% overall yield) of **1** from D-serine. This approach to 14-membered cyclopeptide alkaloids hopefully will facilitate the investigation of their biological properties and of their role in plants.

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10. **3**: mp 246-248 °C (decomp.); R_f 0.6 (50% ethyl acetate: petroleum ether); ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (3H, d, J 6.5), 0.83 (3H, d, J 6.5), 1.02 (3H, d, J 6.7), 1.26 (3H, d, J 6.8) 1.33-1.39 (1H, m), 1.74-1.79 (1H, m), 2.00-2.04 (1H, m), 4.11-4.18 (2H, m), 4.88-4.91 (2H, m), 5.61 (1H, d, J 7.7), 6.37 (1H, d, J 7.6), 6.43 (1H, d, J 9.7), 6.66 (1H, dd, J 9.8, 7.8), 7.03-7.06 (2H, m), 7.11 (1H, dd, J 7.9, 2.2), 7.16 (1H, dd, J 8.2, 2.2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.47, 20.34, 20.62, 23.23, 24.30, 28.22, 29.37, 39.35, 52.55, 56.93, 81.07, 81.92, 116.12, 122.26, 122.78, 125.69, 130.29, 131.71, 155.41, 156.16, 172.34; IR ($CHCl_3$) 3393.8 (s), 1690 (m), 1625.2 (s), 965.3 (s) cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{37}N_3O_5$: (M+H) 460.2806, found 460.2811; $[\alpha]_D^{20}$ -295.7 (*c* 0.47, $CHCl_3$)
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