

## TOTAL SYNTHESIS OF SANJOININE-G1

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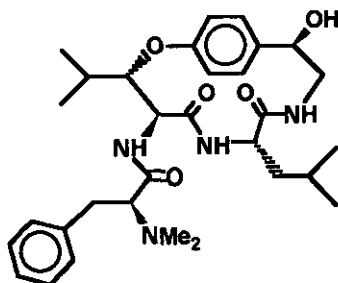
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**Abstract-** Sanjoinine-G1 (**1**), a 14-membered cyclopeptide, was synthesized with stereoselective reactions. Started from D-serine, a cyclic precursor for various frangulanine type 14-membered cyclopeptide alkaloids was synthesized and the side chain acylation product was identical with the natural sanjoinine-G1 (17 steps, overall yield 1.36%).

Cyclopeptide alkaloids have been isolated in several species of plants.<sup>1</sup> We had isolated sanjoinine-G1 (**1**), a frangulanine type 14-membered *p*-ansa cyclopeptide alkaloid as a sedative component<sup>2</sup> from Sanjoin (seed of *Zizyphus vulgaris*) which has been traditionally used for treatment of insomnia in East Asia.



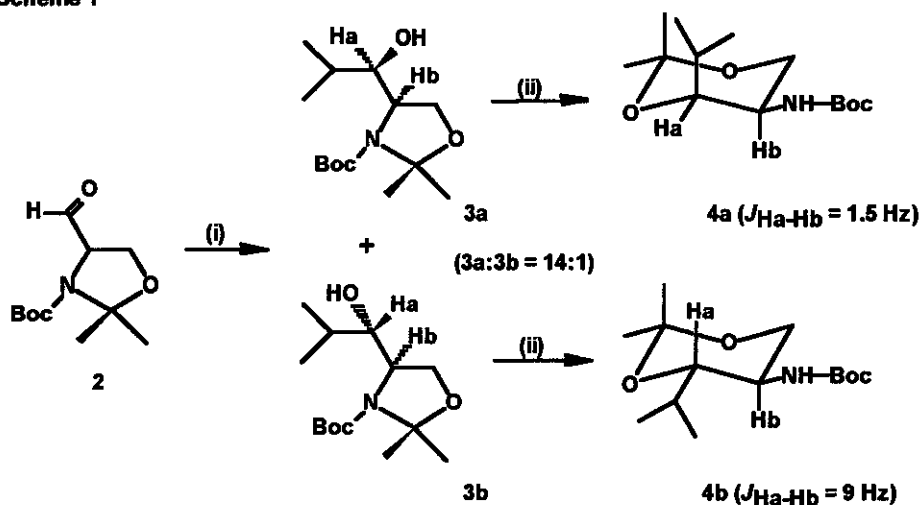
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Although several attempts<sup>3</sup> for the synthesis of cyclopeptide alkaloids have been made, only

Schmidt<sup>3d</sup> and Joullie<sup>3e</sup> groups succeeded in the total synthesis of natural 14-membered *p*-ansa cyclopeptide alkaloids, frangulanine (>26 steps) and nummularine-F (25 steps).

To establish an efficient stereoselective synthetic route to 14-membered cyclopeptide alkaloids, we devised a new process for the asymmetric synthesis of (*S,S*)- $\beta$ -phenoxy-leucine moiety. Starting from *D*-serine, (*R*)-serinal acetonide (**2**) was prepared according to the Garner's method.<sup>4</sup> The Grignard reaction of **2** with isopropylmagnesium chloride afforded predominantly syn product (**3a**) (syn/anti ratio:14/1, chemical yield:60%). The stereochemical assignment was done by the coupling constants ( $J_{\text{Ha-Hb}}$ ) of the derived acetonides (**4a**) and (**4b**)<sup>5</sup> (Scheme 1). On the other hand, the same reaction by chelation control with  $\text{TiCl}_4$  resulted in a higher diastereoselectivity (>99% d.e.) for **3a** but a low chemical yield (<40%).

Scheme 1



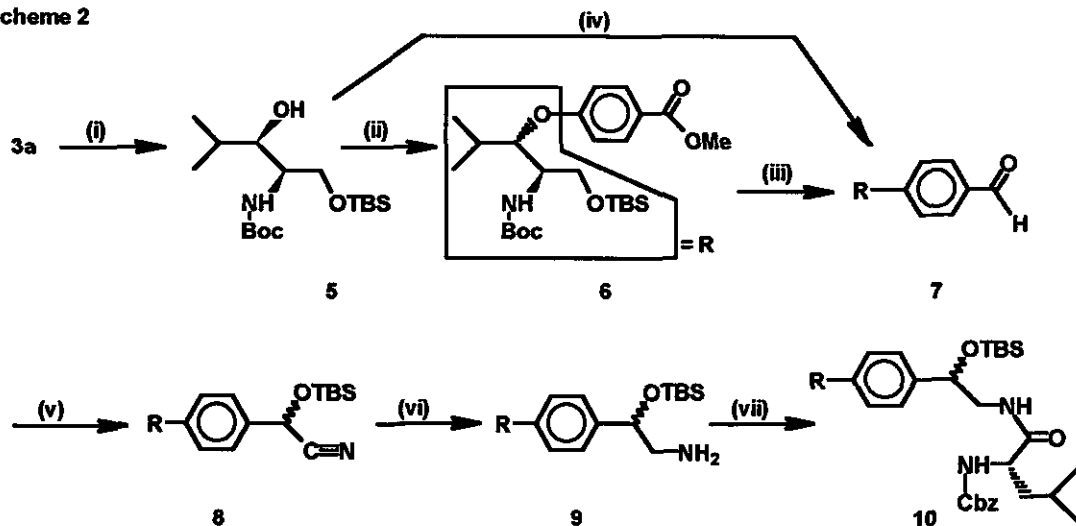
i. isopropylmagnesium chloride, THF, -30 °C  $\rightarrow$  0 °C; ii. a) TsOH, MeOH, 25 °C;

b) 2,2-dimethoxypropane, TsOH, 25 °C

Mitsunobu etherification<sup>6</sup> of **3a** with *N*-Cbz-tyramine or with methyl 4-hydroxybenzoate was not successful probably due to the difficulties of bulky phenolate ion to attack the sterically hindered C3-center in **3a**. Therefore, **3a** was converted to **5** by mild acid hydrolysis of the acetonide (oxazolidine) followed by the selective TBS protection<sup>7</sup> of the primary hydroxyl group (Scheme 2). Alcohol (**5**) was substituted with methyl 4-hydroxybenzoate (40% yield) or 4-hydroxybenzaldehyde (20% yield) by the Mitsunobu reaction in which the C3-stereocenter was inverted.<sup>8</sup> Compound (**7**), which was obtained by the sequential DIBAL-H reduction / PDC

oxidation of **6** or by the direct Mitsunobu reaction of **5** with 4-hydroxybenzaldehyde, was then converted to TBS protected cyanohydrin (**8**) (80% yield) by Cava process.<sup>9</sup>

Scheme 2



- i. a) TsOH, MeOH, 25 °C; b) TBS-Cl, DMAP, TEA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; ii. PPh<sub>3</sub>, DEAD, methyl 4-hydroxybenzoate, THF, 25 °C; iii. a) DIBAL-H, THF, 0 °C; b) PDC, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C; iv. PPh<sub>3</sub>, DEAD, 4-hydroxybenzaldehyde, THF, 25 °C; v. KCN, ZnI<sub>2</sub>, TBS-Cl, MeCN, 25 °C; vi. HCO<sub>2</sub>NH<sub>4</sub>, 10% Pd/C, MeOH, 70 °C; vii. isobutyl chloroformate, *N*-methylmorpholine, L-Cbz-leucine, THF, 0 °C

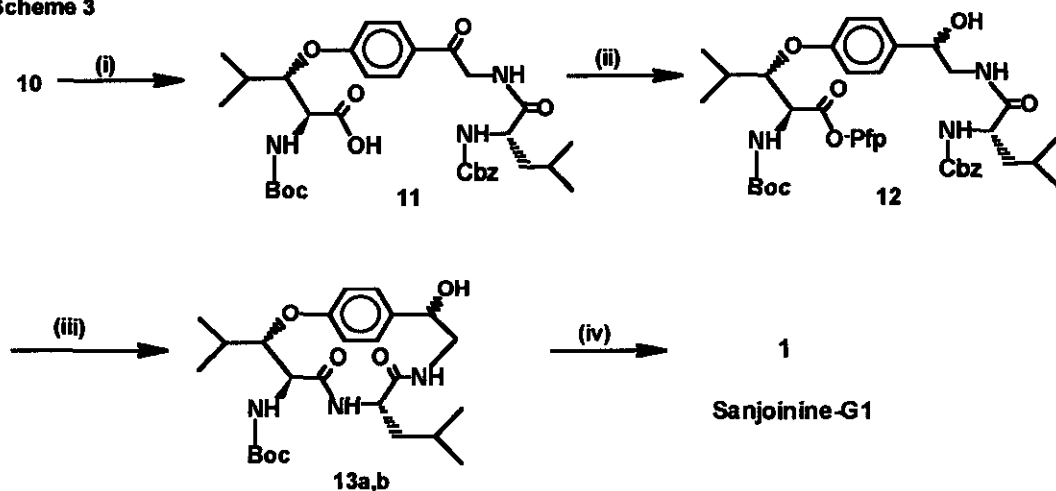
Reduction of the cyano group in **8** for the generation of primary amine without affecting other functionalities was not satisfactory with the known nitrile reducing agents.<sup>10</sup> Nitrile (**8**) was reduced successfully to primary amine (**9**) (70% yield) by catalytic transfer hydrogenation of the cyano function with ammonium formate and 10% Pd/C.<sup>11</sup> Amine (**9**) was smoothly coupled with *N*-Cbz-L-leucine to **10** (78% yield) by a mixed anhydride method.

Jones' reagent was successfully applied to the one-pot TBS deprotection and generation of keto-carboxylic acid (**11**) (76% yield) from **10** without affecting other functional groups<sup>12</sup> (Scheme 3).

Cyclization<sup>3d,e</sup> with pentafluorophenyl ester of **11** resulted in ether cleavage probably due to the electron-withdrawing bezophenone moiety and the high temperature employed. Therefore, the keto group in **11** was first reduced with NaBH<sub>4</sub> and the carboxyl group was then esterified with pentafluorophenol to give **12** (quantitative yield). The mixture of **12** was then applied into a cyclization process to yield the 14-membered cyclic peptide (**13a,b**) (45% yield) in ratio of

1.5/1 (**13a/13b**). FAB and high resolution mass spectroscopic data of these two diastereomers are consistent with calculated value of monomeric cyclopeptide.<sup>13</sup>  $^1\text{H}$ - $^1\text{H}$  COSY spectra of **13a,b** are completely assigned.<sup>14</sup> The optical rotation and ir spectrum of **13a** are also shown.<sup>15</sup>

Scheme 3



**i.** Jones' reagent, acetone, 0 °C; **ii.** a)  $\text{NaBH}_4$ , MeOH, 0 °C; b) pentafluorophenol, DCC,  $\text{CH}_2\text{Cl}_2$ , 0 °C; **iii.** 10% Pd/C, 4-pyrrolidinopyridine, EtOH, dioxane, 90 °C; **iv.** a) TFA, anisole, 25 °C; b) L-N,N-dimethylphenylalanine, DCC,  $\text{CH}_2\text{Cl}_2$ , 25 °C

The Boc group in (**13a**) was cleaved with TFA, and the resulting amino group was coupled with L-N,N-dimethylphenylalanine by using DCC to generate natural alkaloid sanjoinine-G1 (63% yield).

In conclusion, we developed a novel total synthetic protocol for sanjoinine-G1, a frangularine type 14-membered cyclopeptide alkaloid in 17 overall steps, 1.36% overall yields starting from D-serine. The protocol includes highly diastereoselective synthesis of the (S,S)- $\beta$ -phenoxy-leucine unit.

## ACKNOWLEDGEMENT

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10. We tried to reduce the nitrile moiety with the reagents such as  $\text{LiAlH}_4$ , DIBAL-H,  $\text{BH}_3$ -THF or  $\text{NaBH}_4/\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ .
11. In other cases, main products of this reaction were reported to be alkane. See: G. R. Brown, and A. J. Foubister, *Synthesis*, 1982, 1036.

12. In the TBS deprotection and subsequent oxidation with PDC-DMF from (10), only the secondary benzylic alcohol was oxidized. Oxidizing reagents such as Collins' reagent, activated DMSO or  $\text{KMnO}_4$  resulted in the formation of complex reaction products or amide cleavage.
13. HRms : calculated for  $\text{C}_{25}\text{H}_{39}\text{N}_3\text{O}_6$  : 477.2839. Found : 477.2829 (13a), 477.2812 (13b)
14. (13a)  $^1\text{H-Nmr}$  (300 MHz,  $\text{CDCl}_3$ , TMS) : 0.83(d,  $J = 5.6$  Hz, 6H), 1.02(d,  $J = 6.7$  Hz, 3H), 1.12(d,  $J = 6.7$  Hz, 3H), 1.26-1.35(m, 2H), 1.41(s, 9H), 1.42-1.46(m, 1H), 2.14-2.16(m, 1H), 2.66(br s, OH), 3.08(d,  $J = 14.1$  Hz, 1H), 3.97-4.03(m, 2H), 4.10-4.32(m, 1H), 4.69(d,  $J = 8.4$  Hz, 1H), 5.08(d,  $J = 10.6$  Hz, NH), 5.20(d,  $J = 3.2$  Hz, 1H), 5.76(d,  $J = 10.8$  Hz, NH), 6.00(d,  $J = 9.1$ Hz, NH), 6.84(dd,  $J = 8.3, 2.5$  Hz, 1H), 6.95(dd,  $J = 8.5, 1.9$  Hz, 1H), 7.00(dd,  $J = 8.4, 2.0$  Hz, 1H), 7.36(dd,  $J = 8.6, 1.9$  Hz, 1H)
- (13b)  $^1\text{H-Nmr}$  (300 MHz,  $\text{CDCl}_3$ , TMS) : 0.83(dd,  $J = 6.5, 6.4$  Hz, 6H), 1.02(d,  $J = 6.6$  Hz, 3H), 1.09(d,  $J = 6.7$  Hz, 3H), 1.29-1.36(m, 3H), 1.41(s, 9H), 2.07-2.12(m, 1H), 3.09(d,  $J = 13.7$  Hz, 1H), 3.87(s, OH), 4.03-4.09(m, 2H), 4.25-4.33(m, 1H), 4.68(d,  $J = 8.3$  Hz, 1H), 5.21(s, 1H), 5.23(d,  $J = 10.7$  Hz, NH), 6.34-6.41(m, 2NH), 6.83(dd,  $J = 8.4, 2.3$  Hz, 1H), 6.97(dd,  $J = 8.7, 1.9$  Hz, 1H), 7.02(dd,  $J = 8.5, 2.0$  Hz, 1H), 7.44(dd,  $J = 8.6, 1.8$  Hz, 1H)
15.  $[\alpha]_D^{25} -33.33^\circ$  ( $c=0.19$ ,  $\text{CHCl}_3$ ).  $\text{Ir}$  ( $\text{cm}^{-1}$ ) 3429, 3020, 2964, 1711, 1660, 1606, 1510, 1369, 1215, 1168, 1084

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