TOTAL SYNTHESIS OF SANJOININE-G1

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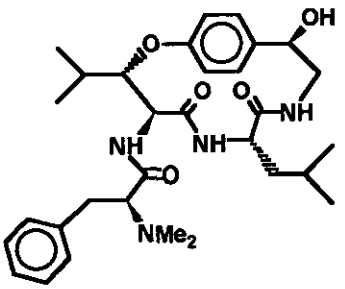
Abstract- Sanjoinine-G1 **(1)**, a 14-membered cyclopeptide, was synthesized with stereoselective reactions. Started from D-serine, a cyclic precursor for various frangulanine type 14-membered cyclopeptide alkaloids was synthesized and the side chain acylation product was identical with the natural sanjoinine-G1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

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



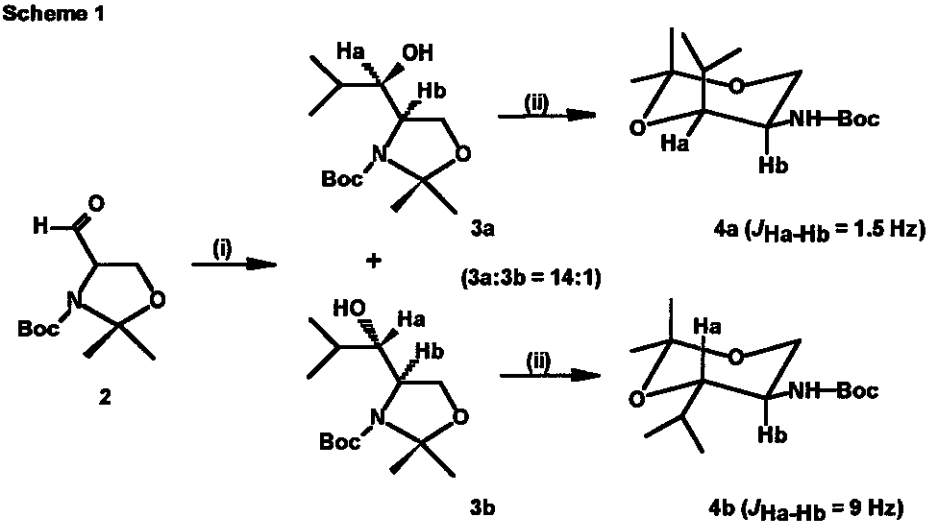
1

Although several attempts[3] for the synthesis of cyclopeptide alkaloids have been made, only

Schmidt[3d] and Joullie[3e] 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 stereoselctive synthetic route to 14-membered cyclopeptide alkaloids, we devised a new process for the asymmetric synthesis of (*S,S*)-β-phenoxyleucine moiety. Starting from D-serine, (*R*)-serinal acetonide **(2)** was prepared according to the Garner's method.[4] 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_{Ha-Hb}) of the derived acetonides **(4a)** and **(4b)**[5] (Scheme 1). On the other hand, the same reaction by chelation control with $TiCl_4$ resulted in a higher diastereoselectivity (>99% d.e.) for **3a** but a low chemical yield (<40%).

Scheme 1

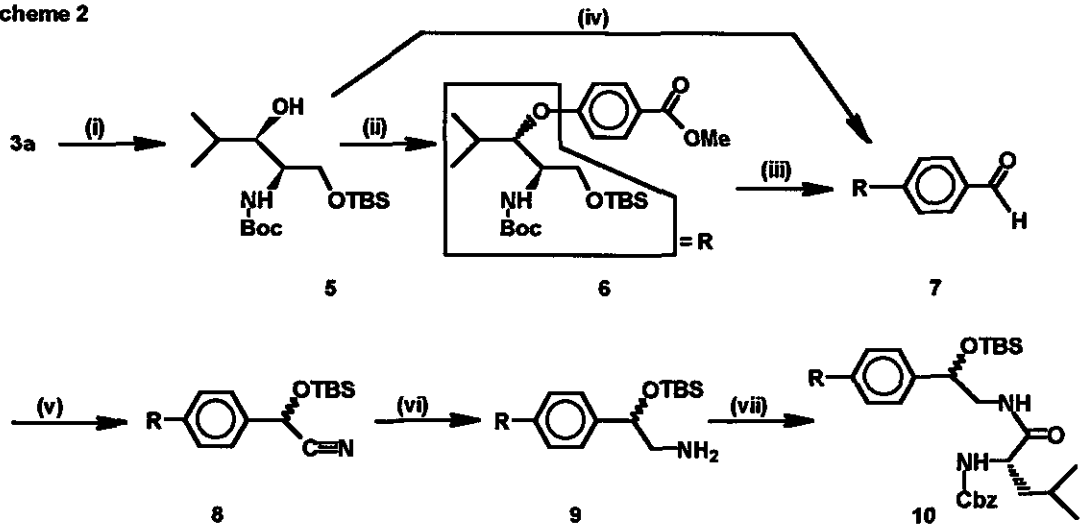


i. isopropylmagnesium chloride, THF, - 30 °C→0 °C; ii. a) TsOH, MeOH, 25 °C; b) 2,2-dimethoxypropane, TsOH, 25 °C

Mitsunobu etherification[6] 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[7] 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.[8] 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.[9]

Scheme 2



i. a) TsOH, MeOH, 25 °C; b) TBS-Cl, DMAP, TEA, CH_2Cl_2, 0 °C; ii. PPh_3, DEAD, methyl 4-hydroxybenzoate, THF, 25 °C; iii. a) DIBAL-H, THF, 0 °C; b) PDC, CH_2Cl_2, 25 °C; iv. PPh_3, DEAD, 4-hydroxybenzaldehyde, THF, 25 °C; v. KCN, ZnI_2, TBS-Cl, MeCN, 25 °C; vi. HCO_2NH_4, 10% Pd/C, MeOH, 70 °C; vii. isobutyl chloroformate, *N*-methylmorpholine, L-Cbz-leucine, THF, 0 °C

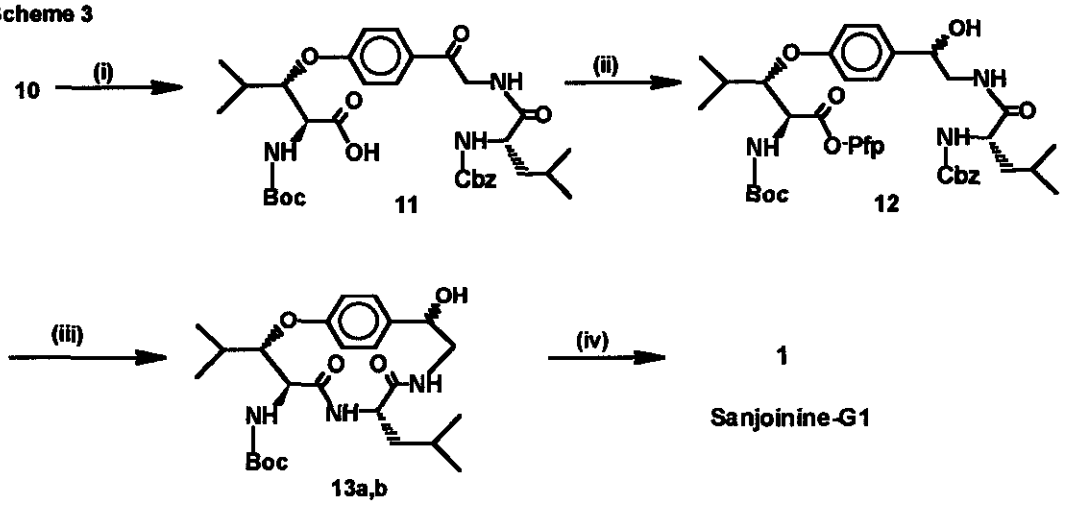
Reduction of the cyano group in **8** for the generation of primary amine without affecting other functionalities was not satisfactory with the known nitrile reducing agents.[10] Nitrile **(8)** was reduced successfully to primary amine **(9)** (70% yield) by catalytic transfer hydrogenation of the cyano function with ammonium formate and 10% Pd/C.[11] 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[12] (Scheme 3).

Cyclization[3d,e] 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 $NaBH_4$ 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 cycliopeptide.[13] ^1H-^1H COSY spectra of **13a,b** are completely assigned.[14] The optical rotation and ir spectrum of **13a** are also shown.[15]

Scheme 3



i. Jones' reagent, acetone, 0 °C; ii. a) $NaBH_4$, MeOH, 0 °C; b) pentafluorophenol, DCC, CH_2Cl_2, 0 °C; iii. 10% Pd/C, 4-pyrrolidinipyridine, EtOH, dioxane, 90 °C; iv. a) TFA, anisole, 25 °C; b) L-*N,N*-dimethylphenylalanine, DCC, CH_2Cl_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 frangulanine 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*)-β-phenoxyleucine unit.

ACKNOWLEDGEMENT

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10. We tried to reduce the nitrile moiety with the reagents such as $LiAlH_4$, DIBAL-H, BH_3-THF or $NaBH_4/CoCl_2 \cdot 6H_2O$.
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 $KMnO_4$ resulted in the formation of complex reaction products or amide cleavage.
13. HRms : calculated for $C_{25}H_{39}N_3O_6$: 477.2839. Found : 477.2829 (**13a**), 477.2812 (**13b**)
14. **(13a)** ^{1}H-Nmr (300 MHz, $CDCl_3$, 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 = 9.1Hz, 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}H-Nmr (300 MHz, $CDCl_3$, 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. $[\alpha]^{25}_D$ -33.33^0 (c=0.19, $CHCl_3$). Ir (cm^{-1}) 3429, 3020, 2964, 1711, 1660, 1606, 1510, 1369, 1215, 1168, 1084

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