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An Asymmetric Total Synthesis of Sanjoinine G1

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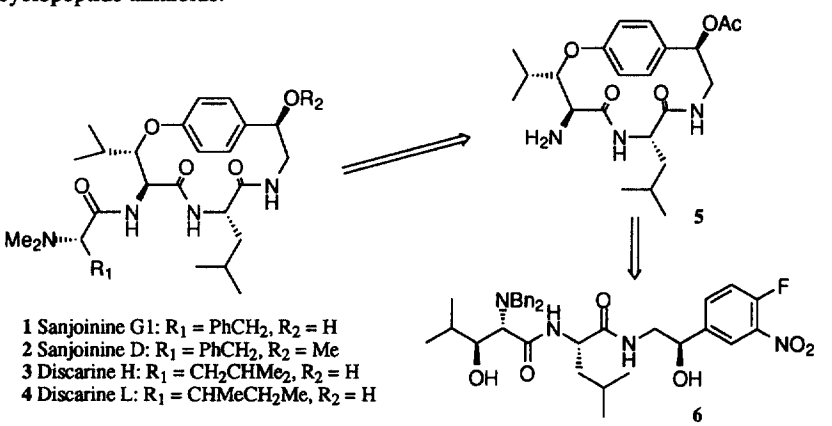
Abstract: A convergent total synthesis of sanjoinine G1, a 14-membered cyclopeptide alkaloid was described. Formation of aryl-alkyl ether bond with concomitant construction of macrocycle by way of an intramolecular SNAr reaction was the key step in this synthesis. Only two conventional peptide coupling steps were required for the preparation of the cyclization precursor. © 1998 Elsevier Science Ltd. All rights reserved.

Key words: Intramolecular SNAr reaction; Cyclopeptide alkaloid; Sanjoinine G1; Amino acid

Sanjoinine G1 (**1**) and sanjoinine D (**2**) (Scheme 1) have recently been isolated from sanjoin (seed of *Zizyphus vulgaris*) and were shown to possess interesting sedative effect.[1] In fact, sanjoin has been frequently used in the oriental traditional medicine as an important and reliable hypnotic or sedative agent for the treatment of insomnia. Related natural products such as discarine H (**3**), discarine L (**4**) have also been identified from the methanol extract of the root bark of *Discaria febrifuga* Mart. which is employed in folk medicine as a potent antithermic agent.[2] These 14-membered para ansa polyamide cyclophanes possessing a characteristic *endo aryl-alkyl ether* bond belong to a growing family of natural products known as cyclopeptide alkaloids.[3]



1 Sanjoinine G1: $R_1 = PhCH_2$, $R_2 = H$
2 Sanjoinine D: $R_1 = PhCH_2$, $R_2 = Me$
3 Discarine H: $R_1 = CH_2CHMe_2$, $R_2 = H$
4 Discarine L: $R_1 = CHMeCH_2Me$, $R_2 = H$

Scheme 1

Although potent biological activities such as hypnotic, sedative, antibacterial, antifungal and ion sequestering properties have been described for cyclopeptide alkaloids, almost nothing is known about their physiological role in plants.[4] The low natural abundance (e.g., the isolated yield of sanjoinine G1 from the alkaloidal fractions was only $3.5 \times 10^{-5}\%$)[1b] has hampered systematic bioactivity evaluations. The need of materials for detailed biological studies of this important class of natural products and the synthetic challenges posed by this strained para cyclophane have attracted the attention of number of synthetic groups and

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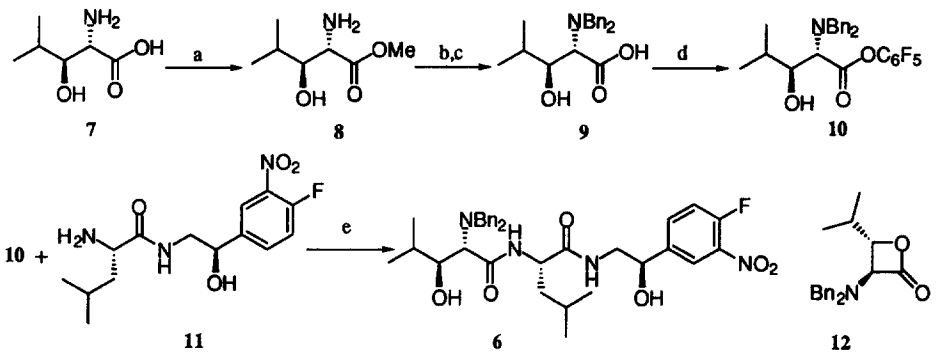
numerous new methodologies emerged from these studies. Among the different approaches investigated,[5-9] only macrolactamization strategy has led to total syntheses of this class of natural products,[10,11] thanks to an efficient carboxylic acid activating technology developed by Schmidt et al.. Synthesis of sanjonine G1 has recently been reported from Han[12] and Jouillé's[13] groups employing very similar synthetic scheme. Unfortunately, both syntheses required separation of diastereomers at their very later stage. We report herein a novel total asymmetric synthesis of sanjoinine G1 via a macrocyclic intermediate **5** which is also the common presursor of sanjoinine D (*O*-methyl sanjoinine G1 **2**), discarine H (**3**) and discarine L (**4**). As shown in Scheme 1, macrocyclization by formation of *endo aryl-alkyl ether bond* via intramolecular S_NAr reaction, developed in this laboratory,[14,15] was the key ring closure step in our synthesis.



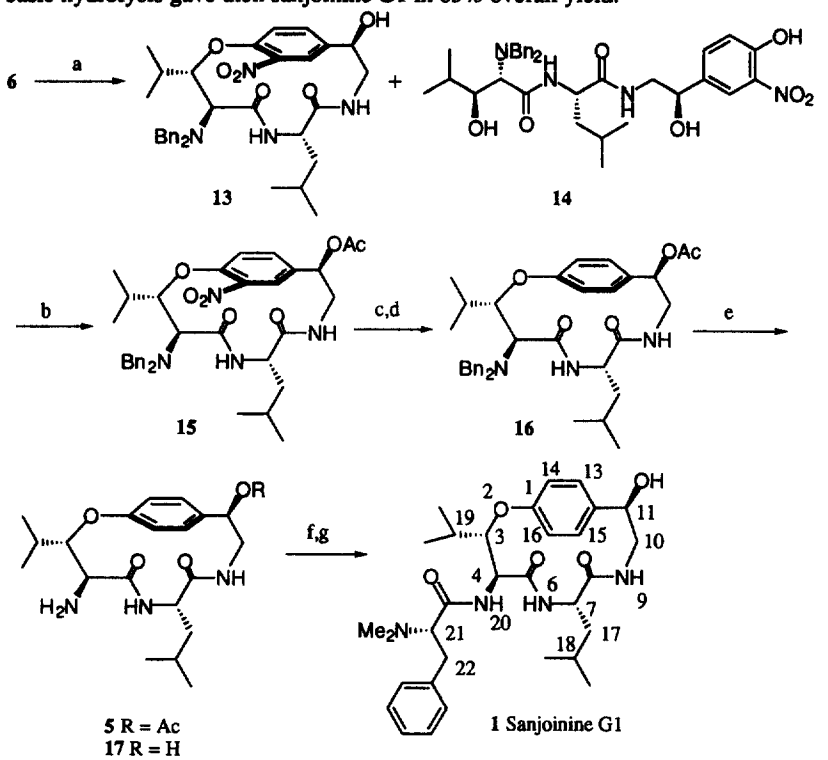
Reagents and Conditions: a) $SOCl_2$, MeOH; b) $NaHCO_3$, BnBr, DMSO-THF, 80°C; c) K_2CO_3, MeOH-H_2O, quantitative; d) EDC, C_6F_5OH, CH_2Cl_2; e) DMF, 60°C, 75%.

Scheme 2

The preparation of linear tripeptide **6** is shown in Scheme 2. The (2*S*,3*S*)-*N*,*N*-dibenzyl hydroxyleucine (**9**) was prepared by esterification of (2*S*,3*S*)-hydroxyleucine (**7**),[16] *N*,*N*-bisbenzylation followed by basic hydrolysis under classic conditions in excellent overall yield. The protection of amino group as its dibenzyl derivative was necessary in order to avoid undesired β-elimination process during the subsequent S_NAr based cyclization as found in our previous studies. It was quickly observed that the coupling between acid **9** and dipeptide **11**[15b] was much more difficult than one may expected. A primary side reaction is the formation of β-lactone (**12**) formed via intramolecular attack of β-hyroxyl group onto the activated carboxylic function. It is worth noting that the related coupling between dipeptide **11** and *L*-*N*,*N*-dibenzylserine went smoothly to afford the desired tripeptide without competitive formation of the (2*S*)-2-*N*,*N*-dibenzylamino β-lactone.[15] We hypothesized that the Thorpe-Ingold effect[17] may account for the facile formation of compound **12** in the present case. After much experimentation varying the coupling reagents (EDC, EDC-HOBt, PyBroP, etc), the solvent (CH_2Cl_2, DMF), the temperature and the stoichiometry of two coupling partners (**9** vs **11**), the best conditions we found were to activate the acid as its pentafluorophenol ester[18] followed by heating at 60° in DMF in the presence of 1 equivalent of dipeptide **11**. Under these optimized conditions, the desired tripeptide **6** was obtained reproducibly in 75% yield. Activation of **9** as its acyl fluoride by cyanuric acid[19] followed by coupling with **11** give low yield of **6**.

Treatment of the linear tripeptide **6** under our previous established conditions (TBAF, DMSO, 0.01M, 3Å molecular sieves, 85°C)[15] afforded the desired 14-membered ansa cyclophane **13** in 45% yield together with the hydroxylated compound **14**. Acylation of the crude product under standard conditions allowed facile separation of the desired acyl derivative **15** from the triacylated compound derived from **14**. It is interesting to note that only one atropoisomer was isolated in contrast to previous studies. Though no detailed stereochemistry assignment was made, a *P* configuration[20] was tentatively assigned for the newly created planar chirality since unfavorable steric interaction between nitro and isopropyl groups was minimized in this stereomer. Although this atropodiastereoselectivity was of no consequence in the present total synthesis as this

chirality will be destroyed in the subsequent synthetic manipulations. It is nevertheless pertinent to future studies concerning the synthesis of non-natural cyclophane with desired planar chirality.[21] Reduction of nitro to amino group ($SnCl_2$, DMF) followed by one-pot reductive-deamination provided compound **16**. Lalancette's conditions ($NaBH_4$, S_8)[22] were found to be inefficient for the reduction of nitro in contrast to our model studies. Hydrogenolysis of *N*-benzyl group was realized using Pearlman's catalyst in solvent mixture THF-^{t}BuOH to provide **5** in quantitative yield. When hydrogenolysis was carried out in methanol or ethanol, partial transesterification occurred to give deacetylated compound **17**, complicating thus the synthetic operations. Finally, coupling of the crude hydrogenolysis product with *L-N,N*-dimethyl phenylalanine followed by basic hydrolysis gave then sanjoinine G1 in 65% overall yield.[23]



Reagents and Conditions: a) TBAF, DMSO, 85°C, 45%; b) Ac_2O, Et_3N, DMAP, CH_2Cl_2; c) $SnCl_2$, DMF, 60°C; d) $NaNO_2$, H_3PO_2, Cu_2O, THF-H_2O, 70%; e) $Pd(OH)_2$, THF-tBuOH, quantitative; f) *L-N,N*-dimethyl phenylalanine, EDC, HOBt, 65%; g) K_2CO_3, MeOH-H_2O, quantitative.

Scheme 3

In conclusion, a novel synthetic strategy has been developed for the synthesis of cyclopepetide alkaloids as exemplified by a total synthesis of sanjoinine G1. The synthetic scheme is highly convergent as only two peptide coupling are required to reach the cyclization precursor and conditions for the post-manipulations of nitro group have also been firmly established. Furthermore, it is worth noting that the cyclization of **6** involves a very hindered secondary alcohol with an isopropyl and a *N,N*-dibenzylamino groups at the adjacent positions. We speculated that cycloetherification of tripeptide containing other β-hydroxy-α-amino acids such as phenylserine, β-hydroxyproline frequently found in cyclopeptide alkaloids would be even more efficient on the steric ground. Applications of this strategy to the synthesis of other members of this class of natural products are in progress.

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23 Physical data of synthetic sanjoinine G1: mp: 233°C, Lit[1b]: 236-238°C; $[\alpha]_D$ –55 ($CHCl_3$, *c* 0.15), Lit[1b]: $[\alpha]_D$ –68; IR ($CHCl_3$): 3231, 1662, 1606, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (d, *J* = 5.6 Hz, 6H, 2xMe), 0.94 (d, *J* = 6.7 Hz, 3H, Me), 1.12 (d, *J* = 6.8 Hz, 3H, Me), 1.30-1.70 (m, 3H, H17, H18), 1.89 (d of sept, *J* = 2.0, 6.7 Hz, 1H, H19), 2.26 (s, 6H, NMe_2), 2.93 (dd, *J* = 6.2, 14.3 Hz, 1H, H22), 3.08 (dd, *J* = 5.4, 14.3 Hz, 1H, H22'), 3.12 (d, *J* = 14.1 Hz, 1H, H10), 3.25 (t, *J* = 6.4 Hz, 1H, H21), 4.01 (m, 1H, H7), 4.27 (ddd, *J* = 3.8, 11.0, 14.1 Hz, 1H, H10'), 4.38 (dd, *J* = 9.0, 10.0 Hz, 1H, H4), 4.79 (dd, *J* = 2.0, 9.0 Hz, 1H, H3), 5.17 (d, *J* = 3.8 Hz, 1H, H11), 5.92 (d, *J* = 11.0 Hz, 1H, NH9), 6.36 (d, *J* = 9.0 Hz, 1H, NH6), 6.80 (dd, *J* = 2.5, 8.4 Hz, 1H, H14), 6.95 (dd, *J* = 2.4, 8.4 Hz, 1H, H13), 7.10-7.27 (m, 6H), 7.34 (dd, *J* = 2.4, 8.8 Hz, 1H, H15), 7.46 (d, *J* = 10.0 Hz, 1H, NH20); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 14.7, 20.3, 22.8, 24.7, 28.8, 29.8, 33.8, 42.5, 47.8, 52.1, 55.8, 71.1, 72.2, 79.7, 119.6, 126.0, 126.4, 127.2, 127.9, 128.5, 129.2, 133.7, 156.8, 170.0, 171.2; MS (CI) *m/z* 553 ($M+H^+$).