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STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF 14-MEMBERED CYCLOPEPTIDE ALKALOIDS: SYNTHESIS OF A CYCLIC PRECURSOR TO NUMMULARINE-F

Robert J. Heffner and Madeleine M. Joullié*
Department of Chemistry, University of Pennsylvania
Philadelphia, PA 19104-6323

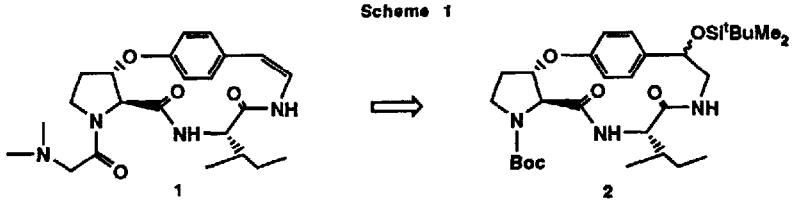
ABSTRACT: *A highly strained 14-membered para-ansa cyclopeptide, a potential precursor of the cyclopeptide alkaloid, nummularine-F, was made by cyclization of a pentafluorophenyl ester under catalytic hydrogenation conditions. This cyclization and the stereoselective synthesis of the acyclic activated ester from D-serine, are presented.*

Since 1966, when the structure of pandamine was confirmed,[1] more than 100 cyclopeptide alkaloids have been isolated and their structures elucidated. Cyclopeptide alkaloids are particularly common in plants of the Rhamnacea family, and have also been discovered in more than 25 other species of plants. Their widespread occurrence makes them an important class of natural products.

These alkaloids exhibit biological activity in a number of areas. Some cyclopeptides have been reported to show activity against gram-positive bacteria and some fungi.[2] Others have been found to inhibit energy transfer in plants by interrupting photophosphorylation in isolated spinach chloroplasts.[3] Frangulanine, a 14-membered para-ansa cyclopeptide, has exhibited selective ionophoric properties by inducing mitochondrial swelling in KCl and RbCl solutions, but not with NaCl, or LiCl.[4] The difficulty in isolating significant quantities of these alkaloids have hampered extensive pharmacological investigations of this class of compounds. Hence, the development of efficient strategies for their synthesis will make these interesting molecules available for further testing.

Since the initial work in 1972 by Païs,[5] a number of synthetic approaches to the cyclopeptide alkaloids have been recorded in the literature. The pioneering cyclization studies of Schmidt, Rapoport, Lipshutz, and those in our laboratory, have made some cyclopeptide alkaloids (13-, dihydro 14-, and 15-membered) accessible.[6] These investigations have demonstrated that cyclization to the 14-membered para-ansa cyclopeptide alkaloids are the most difficult, due to the competing dimerization process. As part of our continuing research efforts in the area of cyclopeptide alkaloid synthesis, we now report on progress made toward the total synthesis of a natural 14-membered cyclopeptide alkaloid, nummularine-F (**1, Scheme 1**). This compound was isolated from the root

Scheme 1

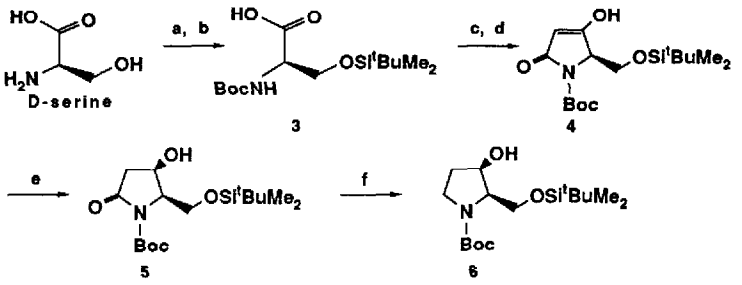


1 **2**

bark of *Zizyphus nummularia*, and its structure elucidated. However, its biological activity has yet to be determined.

Herein we report the synthesis of the 14-membered para-ansa cyclopeptide (**2**), a potential precursor of **1** starting from D-serine. The pivotal transformations of this strategy are: (in **Scheme 2**) a) stereoselective synthesis of the *cis*-3-hydroxypyrrolidine derivative (**6**); (in **Scheme 3**) b) the inversion of the *cis*-3-hydroxy function of **6** under Mitsunobu conditions to the desired β-aryl ether (**7**); and c) cyclization to a highly strained para-ansa 14-membered cyclopeptide (**2**).

Scheme 2



[a] Boc_2O, H_2O, NaOH, t-BuOH; [b] 1. $^tBuMe_2SiCl$, DMF, imidazole; 2. 1M K_2CO_3, THF, MeOH, H_2O; [c] isopropenyl chloroformate, CH_2Cl_2, DMAP, Meldrum's acid, 5° C; [d] EtOAc, reflux; [e] $NaBH_4$, CH_2Cl_2; [f] $BH_3 \cdot Me_2S$, THF, heat.

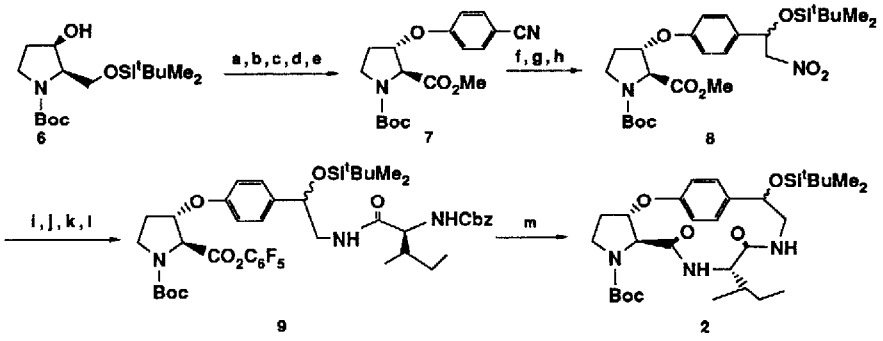
The preparation of *cis*-3-hydroxypyrrolidine **6** began with D-serine as the source of chirality (**Scheme 2**). D-Serine was protected as its Boc-derivative, under basic conditions, with di-*tert*-butyl dicarbonate. The hydroxy function was protected as its *tert*-butyldimethylsilyl ether, upon treatment with *tert*-butyldimethylsilyl chloride and imidazole, in DMF. Hydrolysis of the silyl ester was effected by stirring with 1M K_2CO_3, THF, and methanol, affording compound **3** in quantitative yield. The pyrrolidinone (**5**) was obtained by using a previously described protocol.[8] Homologation of acid **3**, along with concomitant lactamization, was accomplished with isopropenyl chloroformate and Meldrum's acid, in the presence of 4-dimethylaminopyridine. Decarboxylation of the intermediate in refluxing EtOAc gave the tetronic acid (**4**). This compound was selectively reduced to the *cis*-3-hydroxypyrrolidinone (**5**) with sodium borohydride, to afford an overall yield of 58% from D-serine. Reduction of compound **5** to the *cis*-3-hydroxypyrrolidine (**6**) utilized borane dimethyl sulfide complex in refluxing tetrahydrofuran, and afforded **6** in 87% yield.

The stereochemistry at the 3-hydroxy center of **6** could now be inverted to the desired *trans* aryloxy ether linkage under Mitsunobu conditions (**Scheme 3**), followed by silyl ether deprotection, oxidation, and methyl ester formation to give compound **7**. *Cis*-3-Hydroxypyrrolidine (**6**) was treated with triphenyl phosphine, p-cyanophenol, and diethyl azodicarboxylate (DEAD) in tetrahydrofuran at 5°C to form the *trans* p-cyano-β-aryloxy ether **7** in 75% yield.[9]

The silyl ether was cleaved in a mixture of acetic acid, H_2O, and tetrahydrofuran (3 : 1 : 1), at 45°C, to give the corresponding alcohol in 97% yield. The alcohol was first oxidized to the aldehyde under Swern conditions, using trifluoroacetic anhydride and DMSO.[10] The resulting aldehyde was immediately oxidized to the carboxylic acid utilizing potassium permanganate, *tert*-butyl alcohol, buffered with sodium dihydrogen phosphate, to afford the acid in an overall yield of 94% from the alcohol.[11] Esterification of the acid to the methyl ester (**7**) was accom-

plished in 87% yield using DCC and methanol.[12]

Scheme 3



[a] PPh_3, DEAD, C_7H_5NO, THF; [b] AcOH, H_2O, THF, 3:1:1, 45° C; [c] TFAA, DMSO, CH_2Cl_2, Et_3N, -78° C; [d] $KMnO_4$, NaH_2PO_4, *t*-BuOH, 5° C; [e] DCC, DMAP, MeOH, CH_2Cl_2; [f] Raney Nickel, NaH_2PO_2 . H_2O (pyridine: HOAc: H_2O 2:1:1), 45° C. [g] $MeNO_2$, MeONa, 25°C; [h] ^{t}BuMe$_2$SiCl, DMF, imidazole; [i] NH_4CO_2, MeOH, 10% Pd/C, 25° C; [j] L-Cbz-isoleucine, DCC, THF, MeOH, H_2O; [k] LiOH, H_2O, MeOH; [l] pentafluorophenol, DCC, CH_2Cl_2; [m] Pd/C, H_2 dioxane, EtOH, 3h.

The p-cyano aryloxy ether (**7**) was reduced to the aldehyde using Raney nickel and sodium hypophosphite hydrate,[13] followed by carbon chain extension under Henry conditions with the addition of nitromethane to the aldehyde.[14] This transformation gave an inseparable diastereomeric mixture of benzylic hydroxy products, along with a terminal nitro group that served as a latent amine function. The presence of diastereomers is not a problem, since both will be converted to the same styrylamine unit. The hydroxy function was protected as the *tert*-butyldimethylsilyl ether using *tert*-butyldimethylsilyl chloride and imidazole, in DMF, to afford **8** as a mixture of diastereomers, in 43% overall yield from **7**.

Reduction of the nitro group of compound **8** with ammonium formate over 10% palladium on carbon, in methanol, afforded the corresponding amine. The amine was coupled with the L-N-Cbz-isoleucine, using DCC, in 81% overall yield. Hydrolysis of the methyl ester with LiOH · H_2O in aqueous methanol, followed by formation of the pentafluorophenyl ester, using pentafluorophenol and DCC in CH_2Cl_2, gave compound **9** in 50% overall yield. Cyclization of the active ester **9** to the desired 14-membered para-ansa cyclopeptide **2** was effected using Schmidt's method[15] to afford a 50% yield of separable diastereomers in a ratio of 2:1. These isomers were separated on silica gel using petroleum ether : ethyl acetate (70:30); ; R_f 0.46 and 0.27 respectively for major and minor products.

High-resolution mass spectroscopy values for both diastereomers agree with the calculated values.[16] The 500 MHz ^{1}H-NMR spectra of both isomers are consistent with the proposed cyclic monomers.[17] The rotation and IR spectra of the major diastereomer are given.[18,19]

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REFERENCES

1. Païs, M.; Jarreau, F.-X.; Lusinchi, X.; Goutarel, R. *Ann. Chim.* (Paris) **1966**, 83.

2. Tschesche, R; Kaussmann, E.U., in *The Alkaloids*, Vol. 15, R.H. Manske, Ed. (New York, NY: Academic Press), **1975**, Chapter 4.

3. Ravizzini, R.A.; Andreo, C.S.; Vallejos, R.H. *Plant and Cell Physiol.* **1977**, 18, 701.

4. Kawai, K; Nozawa, Y.; Ogihara, Y. *Experientia* **1977**, 33, 1454.

5. Marchand, J.; Rocchiccioli, F.; Païs, M.; Jarreau, F.-X. *Bull. Soc. Chim. Fr.* **1972**, 12, 4699.

6. (a) Schmidt, U.; Lieberknecht, A.; Bökens, H.; Griesser, H. *J. Org. Chem.* **1983**, 48, 16, 2680. (b) Lagarias, J.C.; Houghten, R.A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, 100, 26, 8802. (c) Lipshutz, B.H.; Huff, B.E.; Siahaan, T.J.; Webb, H. Personal communication. (d) Nutt, R.F.; Chen, K.-M.; Joullié, M.M. *J. Org. Chem.* **1984**, 49, 6, 1013. (e) Bowers, M. M.; Carroll, P.; Joullié, M.M. *J. Chem. Soc. Perkin Trans. I* **1989**, 857. (f) Flanagan, D. M., Ph. D. Dissertation, University of Pennsylvania, **1988**.

7. Tschesche, R.; Elgamal, M.; Miana, G.A.; Eckhardt, G. *Tetrahedron* **1975**, 31, 2944.

8. Ewing, W.R.; Joullié, M.M. *Heterocycles* **1988**, 27, 2843.

9. Mitsunobu, O. *Synthesis*, **1981**, 1.

10. Mancuso, A.J.; Swern, D. *Synthesis*, **1981**, 1981, 165.

11. Abiko, A.; Roberts, J.C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, 27, 38, 4537.

12. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 46, 4475.

13. Staskun, B.; Backeberg, O.G. *J. Chem. Soc.* **1964**, 5880.

14. Henry, L.C. *R. Acad. Sci., Paris* **1895**, 120, 1265.

15. Schmidt, U.; Griesser, H.; Lieberknecht, A.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1981**, 20, 280.

16. HRMS of **2**: calcd. for $C_{30}H_{49}O_6SiN_3$ (M + H): 576.339. Found: 576.347 and 576.342 for major and minor diastereomers respectively.

17. ^{1}H-NMR (500 MHz, $CDCl_3$) of **2**: Major Isomer δ: 0.0815 (3H, s), 0.114 (3H, s), 0.761 (3H, s), 0.7751 (3H, s), 0.810-0.915 (2H, m), 0.954 (9H, s), 1.26 and 1.41 (9H, s) Boc rotational isomers, 1.53-1.57 (1H, m) 2.04-2.17 (1H, m), 2.36-2.41 (1H, m), 3.00 (1H, d), 3.42-4.29 (4H, m), 3.96 (1H, m), 5.07 (1H, d), 5.27 (1H, m), 5.39 (1H, m), 5.67 and 5.84 (1H, m) Boc rotational isomers, 6.86 (1H, s), 6.97 (1H, d), 7.11 (1H, d), 7.39 (1H, dd). Minor Isomer δ: -0.0543 (3H, s), 0.0608 (3H, s), 0.733 and 0.748 (6H, d), 0.763 to 0.846 (3H, m), 0.886 (9H, s), 1.26 and 1.41 (9H, s) Boc rotational isomers, 1.53 (1H, m) 2.10 (1H, m), 2.39 (1H, m), 3.21 and 4.04 (6H, m), 4.58 (1H, m), 4.94 (1H, d), 5.74 and 5.93 (1H, m) Boc rotational isomers, 6.87 (1H, d), 6.96 to 7.05 (2H, m), 7.49 (1H, d).

18. Major Isomer, oil: $[\alpha]_D^{25}$ -37.3° (0.625, $CHCl_3$).

19. IR ($CHCl_3$, cm^{-1}) of **2**: 3680 (w), 3440 (m), 2980 (s), 2950 (s), 2910 (s), 2870 (s), 1690 (s), 1670 (s), 1610 (w), 1510 (m), 1465 (w) 1405 (s), 1370 (m), 1330 (w), 1320 (w), 1290 (w), 1260 (m), 1235 (m), 1170 (m), 1145 (m), 1135 (m), 1115 (m), 1090(m), 1055 (w), 1010 (w), 935 (w), 910 (w), 895 (w), 860 (m), 835 (m).

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