Stereocontrolled Synthesis of 1,7a-Diepialexine

Nobuo Ikota

National Institute of Radiological Sciences, 9-1, Anagawa-4-chome, Chiba-shi 260, Japan

Key Words: (S)-pyroglutamic acid; chiral synthesis; pyrrolizidine alkaloid; 1,7a-diepialexine; diastereoselective allylation

Abstract: (2R,5R)-Dihydroxymethyl-(3R,4S)-dihydroxypyrrolidine derivative 15, 1,7a-diepialexine 1, and 1,7,7a-triepialexine 2 have been synthesized from (S)-pyroglutamic acid derivative 4.

Alexine^{1,2} is a new class of polyhydroxylated pyrrolizidine alkaloid with a hydroxymethyl group at C-3 and five contiguous asymmetric centers, and has been shown to possess inhibitory activity toward the fungal glucan 1,4- α -glucosidase. Recently, 1,7a-diepialexine (1-epiaustraline) 1^{3,4} has been isolated and its structure is related to (2*R*,5*R*)-dihydroxymethyl-(3*R*,4*S*)-dihydroxypyrrolidine derivative. In connection with our synthetic studies on the utility of optically active pyroglutamic acid derivatives for natural product synthesis, ⁵ we describe here a stereocontrolled synthesis of (2*R*,5*R*)-dihydroxymethyl-(3*R*,4*S*)-dihydroxypyrrolidine derivative 15 and 1,7a-diepialexine 1 *via* a none-carbohydrate based approach utilizing (*S*)pyroglutamic acid derivative 4.⁶



Addition of vinylmagnesium bromide⁷ in THF at -40- -50 °C to (3R,4R,5R)-1-(*tert*-butoxycarbonyl)-3,4-isopropylidenedioxy-5-trityloxymethyl-2-pyrrolidinone 4 ⁵c (m.p. 142-143 °C, $[\alpha]_D^{20}$ +43.2° (c 0.6, CHCl₃)), prepared from the unsaturated lactam 3 by *cis*-dihydroxylation with a catalytic amount of OsO₄ followed by isopropylidenation, yielded the enone 5⁸ in 93% yield. Reduction of 5 with NaBH₄ in the presence of CeCl₃ in MeOH⁹ gave the allylic alcohol 6 as a 1:2.4 mixture of inseparable diastereomers in 91% yield. Conversion of 6 to the mesylate followed by cyclization with *tert*-BuOK in THF provided the pyrrolidine 7 as the sole stereoisomer in 72% yield. The configurations of 7 were confirmed by the conversion of 7 into the hydrochloride of *meso*-2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine 910,11 (m.p. 99-101 °C) *via* the alcohol 8 in 77% yield. On the other hand, diols 10 and 12 were obtained by ozonolysis of 6 followed by workup with NaBH₄ and both were converted to *tert*-butyldimethylsilyl ethers 11 and 13 in 48% and 19% yields, respectively. Then, oxidation of 11 by the method of Swern¹² followed by reduction with NaBH₄ in EtOH at -78°C gave 13 with high diastereoselectivity (13:11=18:1) in 73% yield. The silyl



Reagents and conditions: (a) cat. OSO_4 , *N*-methylmorpholine *N*-oxide, acetone-H₂O, then 2,2-dimethoxypropane, cat. *p*-TsOH, acetone; (b) vinylmagnesium bromide, THF, -40 - -50 °C; (c) NaBH₄, CeCl₃·7H₂O, MeOH; (d) MsCl, TEA, CH₂Cl₂, then *tert*-BuOK, THF; (e) O₃, CH₂Cl₂, -78 °C, then NaBH₄, EtOH; (f) 10% HCl, MeOH, 60 °C; (g) *tert*-butyldimethylsilyl chloride, imidazole, DMF, 0 °C; (h) Swern oxidation, -20 °C, then NaBH₄, EtOH, -78 °C; (i) tetrabutylammonium fluoride, THF; (j) Swern oxidation, then allylation, -78 °C; (k) chloromethylmethyl ether, *N*,*N*-diethylaniline, CH₂Cl₂; (i) *tert*-butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH₂Cl₂, then (i), then BnBr, K₂CO₃, acetone; (m) MsCl, TEA, CH₂Cl₂ then 10% Pd-C, H₂, EtOH.

ether 13 was further converted to the mesvlate and treated with tert-BuOK in THF to provide the pyrrolidine 14 with intramolecular SN2 displacement in 75% yield. Acid hydrolysis of 14 gave the hydrochloride of (2R,5R)-dihydroxymethyl-(3R,4S)-dihydroxypyrrolidine 16¹³ (m.p. 190-192 °C, $[\alpha]_{D^{20}}$ +51.5° (c 1, H₂O)) in 78% yield. The carbon unit required for the pyrrolizidine skeleton was introduced using the dia stereoselective allylation previously reported 5a,d,14 After removal of the silvl ether from 14 with tetrabutylammonium fluoride in THF, Swern oxidation of the resulting alcohol 15 (m.p. 145 °C, $[\alpha]_D^{20}$ -49.1° (c 1.6, CHCl3)) gave the corresponding aldehyde, which was treated with either allylmagnesium chloride in THF or allyllithium in ether-THF at -78°C to afford 17 predominantly¹⁵ (allylmagnesium chloride: 17/20=2.5/1, yield 84%; allyllithium: 17/20=5.4/1, yield 81%; the ratio was determined by HPLC analysis). After protection of the hydroxy group of 17 as the methoxymethyl ether, selective transformation of N-tert-butoxycarbonyl group of 18 into N-benzyl group was effected by reaction with tert-butyldimethylsilvl trifluoromethanesulfonate 16 in the presence of 2.6-lutidine followed by successive treatments with tetrabutylammonium fluoride in THF and benzyl bromide in the presence of poassium carbonate in acetone to furnish 19 in 58% yield. Ozonolysis of 19 followed by reductive workup with NaBH4 gave the alcohol 21 in 58% yield. Mesylation of 21 followed by cleavage of the protecting groups afforded 1,7adiepialexine 1 ($[\alpha]_{D^{20}}$ +12.5°(c 0.6, H₂O), lit. $[\alpha]_{D^{20}}$ +12°(c 1.17, H₂O),³ $[\alpha]_{D^{20}}$ +8.5°(c 0.41, H₂O)⁴) in 52% yield after purification by ion exchange chromatography (Dowex 50W-X8, H⁺ form). Its spectral data (1 H and 13 C NMR) were identical with those reported for 1.⁴ By a parallel series of reactions, 20 was converted to 1,7,7a-triepialexine 2^{17} (oil, $[\alpha]_D^{20} + 4.7^{\circ}(c \ 0.5, H_2O)$).

Presently described synthesis is stereoselective and provides a new approach for the preparation of the polyhydroxylated pyrrolizidines and its stereoisomers.

Acknowledgment. We express our thanks to Professors T. Hino (Chiba University) and K. Koga (University of Tokyo) for spectral measurements. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, and was entrusted to NIRS by the Science and Technology Agency, using the Special Coordination Funds for Promoting Science and Technology.

References and Notes

- Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M; Watkin, D. J. *Tetrahedron Lett.* 1988, 29, 2487.
- 2. Fleet, G. W. J.; Haraldsson, M.; Nash, R. J.; Fellows, L. E. Tetrahedron Lett. 1988, 29, 5441.
- Harris, C. M.; Harris, T. M.; Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. Tetrahedron Lett. 1989, 30, 5685.
- Nash, R. J.; Fellows, L. F.; Dring, J. V.; Fleet, G. W. J.; Grigdhar, A.; Ramsden, N. G.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. Phytochemistry 1990, 29, 111.
- a. Ikota, N.; Hanaki, A. Chem. Pharm. Bull. 1987, 35, 2140.
 b. Ikota, N.; Hanaki, A. Heterocycles 1987, 26, 2369.
 c. Ikota, N.; Hanaki, A. Chem. Pharm. Bull. 1989, 37, 1087.
 d. Ikota, N. Chem. Pharm. Bull. 1990, 38, 2712.
- 6. Recently, the use of the related chiral 2-pyrrolidinone derivatives in natural product synthesis has been reported; Hamada, Y.; Kawai, A.; Kohno, Y.; Shioiri, T. J. Am. Chem. Soc. 1989, 111, 1524;

Smith, III, A. B.; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. Tetrahedron Lett. 1991, 32, 4859; Hamada, Y.; Tanada, Y.; Yokokawa, F.; Shioiri, T. Tetrahedron Lett. 1991, 32, 5983.

- 7. Ohta, T.; Hosoi, A.; Kimura, T.; Nozoe, S. Chem. Lett. 1987, 2091.
- 8. Satisfactory spectral and/or analytical data were obtained for all new compounds.
- 9. Luche, J. C.; Hahn, L. R.; Crabbe, P. J. Chem. Soc., Chem. Commun. 1978, 601.
- 10. ¹³C NMR spectral data: $\delta_C(D_2O, \text{ dioxane } \delta=67.40)$ 58.83(t), 64.87(d), 71.35(d).
- Synthesis of optically active 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidines has been reported: (2R, 3R,4R,5R)-derivative, Fleet, G. W. J.; Smith, P. W. Tetrahedron Lett. 1985, 26, 1469; Card, C. P.; Hittz, W. D.; J. Org. Chem. 1985, 50, 891; Hung, R. R.; Straub, J. A.; Whiteside, G. M. J. Org. Chem. 1991, 56, 3849, (2R,3R,4R,5S)-derivative, Shing, T. K. M. J. Chem. Soc., Chem. Commun. 1987, 262.
- 12. Mancus, A. J.; Huang, S. L.; Swern, D. J. Org. Chem. 1978, 43, 2480.
- 13. ¹³C NMR spectral data: $\delta_C(D_2O, \text{ dioxane } \delta = 67.40)$ 58.39(t), 58.97(t), 62.58(d), 63.07(d), 70.96 (d), 72.03(d).
- 14. Hamana, H.; Ikota, N.; Ganem, B. J. Org. Chem., 1987, 52, 5492.
- 15. Condensation of the aldehyde derived from 15 with allyltrimethylsilane in the presence of TiCl4 in methylene chloride at -78 °C gave only 17. However, the yield was at most 30% due to the instability of the aldehyde toward acidic condition.
- 16. Sakaitani, M.; Ofune, Y. Tetrahedron Lett. 1985, 26, 5543.
- 17. ¹H and ¹³C NMR spectral data: $\delta_{H}(270 \text{ MHz}, D_{2}O)$ 1.83(1H,m), 2.18(1H,m), 2.81(2H,m), 3.21 (1H,m), 3.34(1H,m), 3.61(1H,dd), 3.78(1H,dd), 3.88(1H,dd), 4.16(1H,dd), 4.53(1H,m); δ_{C} (D₂O, dioxane δ =67.40) 35.29(t), 53.81(t), 62.97(t), 69.30(d), 70.81(d), 70.91(d), 73.34(d), 74.90(d). HRMS (FAB): [M+1]⁺ m/z 190.1086 (calcd for C₈ H₁₆NO₄, 190.1080).

(Received in Japan 13 January 1992)