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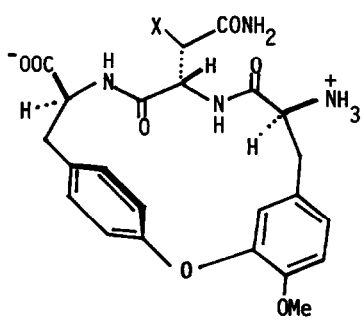
# TOTAL SYNTHESIS OF OF4949-III, A NOVEL INHIBITOR OF AMINOPEPTIDASE B

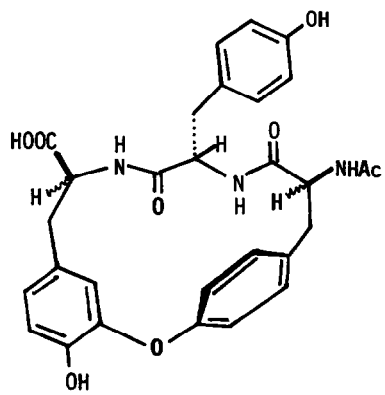
Shigeru Nishiyama, Yoshikazu Suzuki, and Shosuke Yamamura*
Department of Chemistry, Faculty of Science and Technology, Keio University,
Hiyoshi, Yokohama, Japan

Summary: A novel aminopeptidase B inhibitor (OF4949-III) has been synthesized from N-benzyloxycarbonyl-3,5-dibromo-L-tyrosyl-L-asparaginyl-3,4-dichloro-L-tyrosine methyl ester, whose oxidation with thallium trinitrate (TTN) as a key step followed by zinc reduction affords the corresponding diphenyl ether with the same heterocyclic skeleton as that of OF4949-III.

Four novel aminopeptidase B inhibitors represented by OF4949-I (1) have been isolated from the culture broth of a fungus, Penicillium rugulosum OF4949,[1] and their stereostructures have been also elucidated on the basis of some chemical evidence together with an X-ray crystallographic analysis of the monobromo derivative of OF4949-I.[2] Quite recently, a novel inhibitor of angiotensin-I converting enzyme (ACE), designated K-13, has been isolated from the culture broth of Micromonospara halophytica subsp. exilisia K-13,[3] and its structure (2) has been also determined by spectral and chemical studies of K-13 and its derivatives.[4] These two antibiotics, OF4949-I and K-13, are quite similar to each other in their structures. Interestingly, however, their cyclization modes are different around a diphenyl ether moiety. In connection with our synthetic study on tyrosine-derived metabolites,[5] we are interested in these antibiotics because of their unique structures and a variety of physiological activities.[3,6] We describe herein a total synthesis of OF4949-III (3).



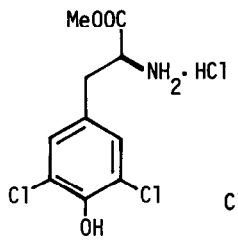
1 X = OH
3 X = H



2

L-Tyrosine was treated with $Cl_2$ in MeOH (0 °C - room temp., overnight) and then esterified with 2,2-dimethoxypropane (room temp., 4 days) to afford 3,5-dichloro-L-tyrosine methyl ester (4),[7] in almost quantitative yield, which was connected to N-t-butoxycarbonyl-L-asparagine using DCC (1.1 equiv.) - 1-hydroxybenzotriazole (1 equiv.) - N-methylmorpholine (1 equiv.) in DMF (0 °C - room temp., overnight) and then treated with HCl in dioxane (room temp., 1.5 h) to give rise to the corresponding dipeptide (5)[7] in 99% yield. According to essentially the same procedure as described above, the desired tripeptide (6)[7] was further produced, in ca. 60% yield, from 5 and N-benzyloxycarbonyl-3,5-dibromo-L-tyrosine.

In the next step, the tripeptide (6) so far obtained was oxidized with TTN (3 equiv.)[5] in MeOH (0 °C - room temp., overnight) to afford the desired cyclization product (7),[8] in ca. 25% yield,[9] which was subjected to zinc reduction in AcOH - THF (0 °C - room temp., overnight) followed by methylation with an excess amount of diazomethane in MeOH (room temp., 5 min) to give rise to the corresponding diphenyl ether (8)[7] in 72% yield. This diphenyl ether (8) was further subjected to catalytic hydrogenation [$H_2$/Pd-black in THF containing conc.HCl (room temp., overnight)][10] followed by reprotection using $(BOC)_2O$ (1.5 equiv.) - $Et_3N$ (1.5 equiv.) in dioxane (room temp., 3 h) to afford a N-t-butoxycarbonyl compound (9)[7] in 66% yield. Finally, this compound (9) was subjected to catalytic hydrogenation [$H_2$/Pd-black in MeOH containing NaOAc (3 equiv.) (room temp., 2 days)] to afford a diphenyl ether (10),[7] in 99% yield, which was hydrolyzed with 1N NaOH (1.2 equiv.) (room temp., 10 min), deprotected with HCl (30 equiv.) (room temp., overnight), and then neutralized with 1N NaOH to give rise to

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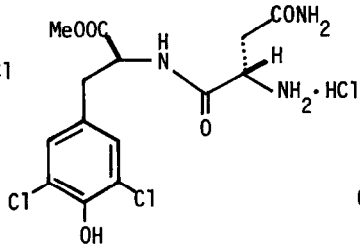
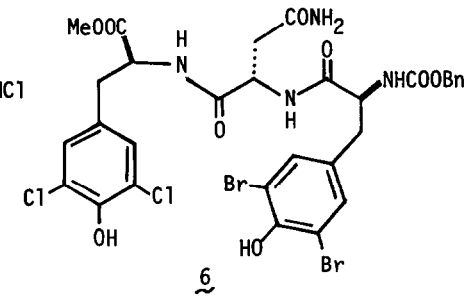



5

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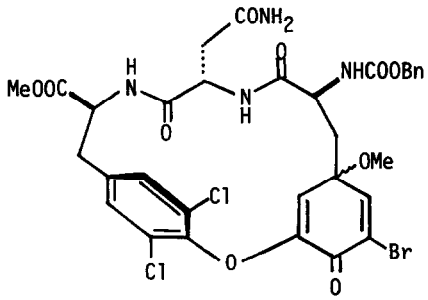


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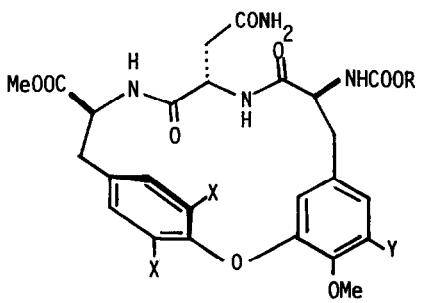


8 R = Bn, X = Cl, Y = Br
9 R = $Bu^t$, X = Cl, Y = Br
10 R = $Bu^t$, X = Y = H

the desired tripeptide,[11] in 77% overall yield, which was completely identical with natural OF4949-III (1) in all respects of spectral data (IR and $^1$H NMR). Further synthetic study on K-13 (2) is in progress.

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7. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: 4: mp 103.5 - 106.5 °C; $C_{10}H_{11}NO_3Cl_2 \cdot HCl$ [m/z 265($M^+$ - HCl)]; IR (Nujol) 1750 $cm^{-1}$; $\delta$($CD_3OD$) 3.80(3H, s) and 7.18(2H, s). 5 as amorphous powder: $C_{14}H_{17}N_3O_5Cl_2 \cdot HCl$ [m/z 378($M^+$ - Cl)]; IR (Nujol) 1725, 1670, 1620, and 1560 $cm^{-1}$; $\delta$($CD_3OD$) 3.68(3H, s) and 7.15(2H, s). 6: mp 214 - 217 °C; $[\alpha]_D^{24}$ +5.76° (c 1.03, DMSO); IR (Nujol) 3400, 3270, 1725, 1690, 1640, and 1525 $cm^{-1}$; $\delta$(DMSO-$d_6$) 2.87 - 3.00(4H, complex), 3.62(3H, s), 3.92 - 4.12(2H, complex), 4.97(2H, br.s), 7.15(2H, s), 7.27(5H, s), and 7.43(2H, s). The molecular ion peak has not been detected in its mass spectrum, but the structure is supported by the other spectral data. 8: mp 149 - 151 °C; $[\alpha]_D^{26}$ +39.1° (c 0.41, MeOH); $C_{32}H_{31}N_4O_9Cl_2Br$ [m/z 767($M^+$ + 1)]; IR (film) 3325, 3100, 1730, 1660, 1560, and 1490 $cm^{-1}$; $\delta$($CDCl_3$) 2.18 - 2.61(2H, complex), 2.83(1H, br.d, J = 13.7 Hz), 3.08(1H, br.d, J = 10.5 Hz), 3.33(1H, dd, J = 13.4, 3.9 Hz), 3.81(3H, s), 4.01(3H, s), 4.47(1H, br.s), 4.59(1H, br.s), 4.88 - 4.94(1H, m), 5.10(1H, d, J = 12.2 Hz), 5.19(1H, d, J = 12.2 Hz), 5.63 - 5.65(2H, complex), 5.72(1H, br.s), 6.89(1H, br.s), 7.16(1H, br.s), and 7.30 - 7.38(6H, complex). 9: mp 159 - 164 °C; $[\alpha]_D^{26}$ +43.4° (c 0.14, MeOH); IR (film) 1740 $cm^{-1}$; $\delta$($CD_3OD$) 1.48(9H, s), 3.77(3H, s), 3.95(3H, s), 5.70(1H, d, J = 2.1 Hz), 6.85(1H, d, J = 2.1 Hz), 7.27(1H, d, J = 2.7 Hz), and 7.57(1H, d, J = 2.7 Hz). These spectral data support the assigned structure, although the molecular ion peak has not

been detected in its mass spectrum. 10: mp 163 - 164 °C; $[\alpha]_D^{27}$ +50.8° (c 0.03, MeOH); $C_{29}H_{36}N_4O_9$ [m/z 585($M^+$ + 1)]; IR (film) 3300, 1730, 1660, 1540, and 1500 $cm^{-1}$; $\delta$ ($CD_3OD$) 5.88(1H, d, J = 2.4 Hz), 6.61(1H, dd, J = 8.5, 2.4 Hz), 6.87(1H, dd, J = 8.5, 2.4 Hz), 6.92(1H, d, J = 8.5 Hz), 6.99(1H, dd, J = 8.5, 2.4 Hz), 7.19(1H, dd, J = 8.5, 2.4 Hz), and 7.37(1H, dd, J = 8.5, 2.4 Hz).

8. Although the oxidation product (7) was unable to be purified completely, its structure was confirmed by its $^1H$ NMR spectrum: $\delta$ (acetone-$d_6$) 3.16(3H, s), 3.67(3H, s), 5.30(1H, br.s), 7.21 - 7.37(7H, complex), and 7.49(1H, br.s).
9. Such a cyclization product as K-13 (2) has not yet been obtained.
10. Although reductive removal of the three halogen atoms has been attempted together with the N-benzyloxycarbonyl group, any good result has not yet been obtained.
11. The optical rotation of natural OF4949-III has not been reported. The synthetic sample shows the negative optical rotation ($[\alpha]_D^{27}$ -38.2° (c 1.06, 0.1N HCl)) similar to that of OF4949-1 (1).

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