Tetrahedron Letters, Vol.30, No.3, pp 379-382, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

BIOMIMETIC SYNTHESIS AND STEREOSTRUCTURE OF K-13, A NOVEL INHIBITOR OF ANGIOTENSIN I CONVERTING ENZYME

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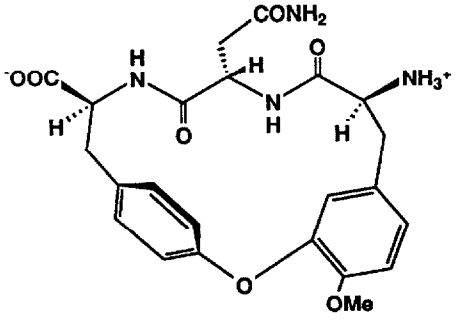
Summary: A novel inhibitor of angiotensin I converting enzyme (K-13) has been synthesized from N-acetyl-3,5-dichloro-L-tyrosyl-O-benzyl-L-tyrosyl-3,5-diiodo-L-tyrosine methyl ester, whose oxidation with thallium trinitrate (TTN) as a key step followed by zinc reduction affords the corresponding diphenyl ether with the same heterocyclic skelton as that of K-13, indicating that K-13 is biosynthesized from three molecules of L-tyrosine.

A novel inhibitor of angiotensin I converting enzyme, designated K-13, has been isolated from the culture broth of Micromonospora halophytica subsp. exilisia K-13,[1] and its structure has also been elucidated on the basis of the spectral data together with some chemical evidence.[2] However, the stereostructure of K-13 remains unsettled. In connection with OF 4949-III (**1**), an inhibitor of aminopeptidase B,[3,4] we are interested in the structure and physiological activity of K-13 (**2**), because their cyclization modes are different around a diphenyl ether moiety although their structures are similar to each other. We describe herein a total synthesis of K-13, indicating that its stereostructure is represented by **2**.

3,5-Dibromo-L-tyrosine methyl ester was connected to N-t-butyloxycarbonyl-O-benzyl-L-tyrosine using DCC (1.2 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., overnight) to afford the corresponding dipeptide (**3**),[5] in 70% overall yield. According to essentially the same procedure as described above, the desired tripeptide (**4**)[5] was further produced, in 78% yield, from **3** and N-t-butyloxycarbonyl-3,5-dichloro-L-tyrosine.

In the next step, the tripeptide (**4**) was oxidized with TTN (3 equiv.) in MeOH - dioxane



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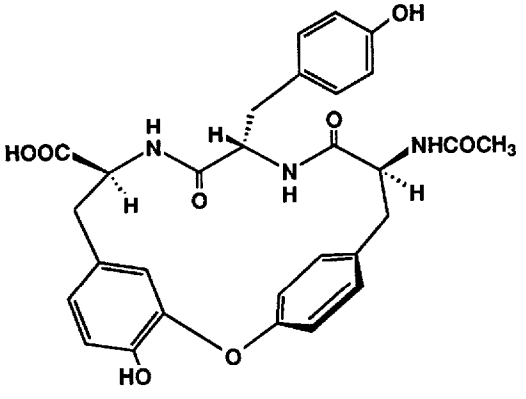

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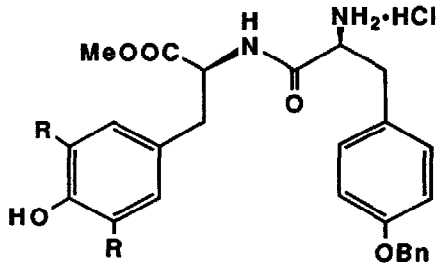
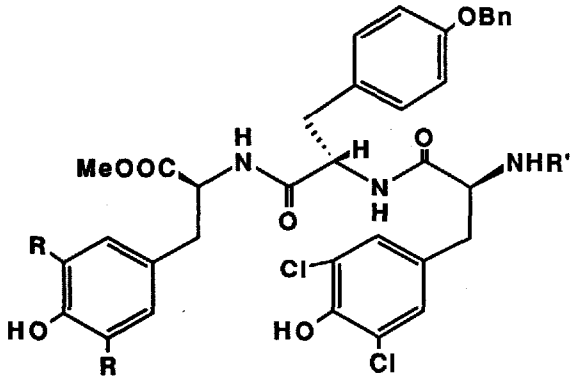
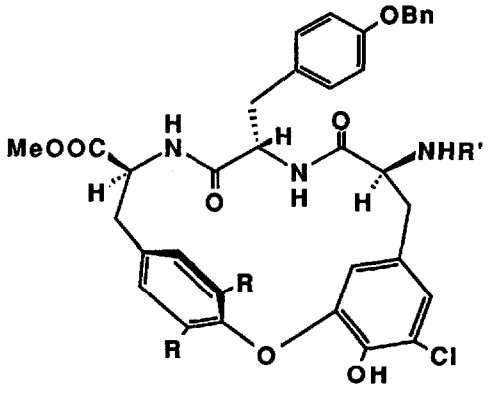


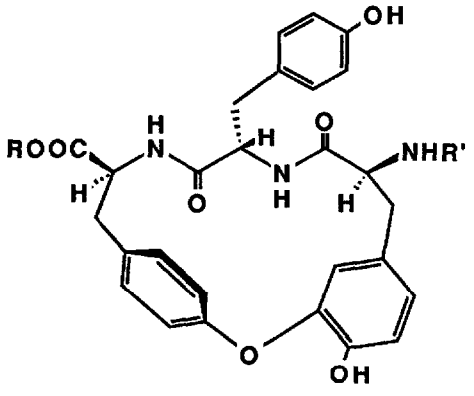
3 R = Br
9 R = I



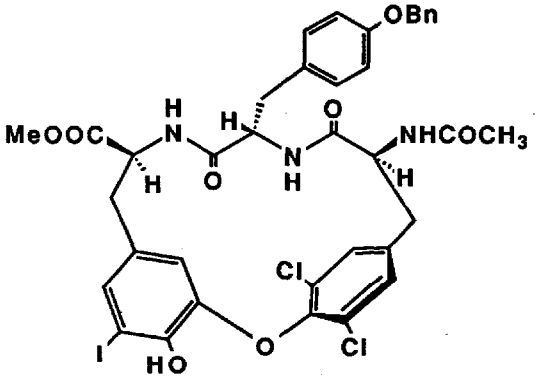
4 R = Br, R' = COO^tBu
10 R = I, R' = $COCH_3$



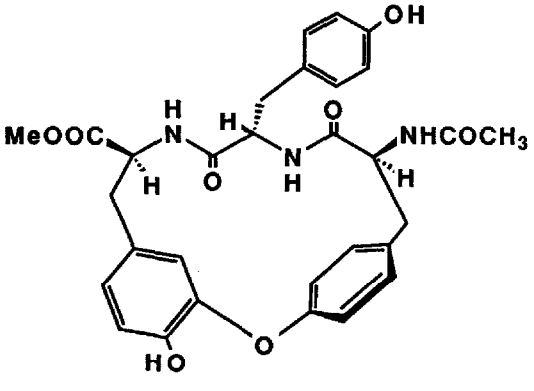
5 R = Br, R' = COO^tBu
12 R = I, R' = $COCH_3$



6 R = Me, R' = COO^tBu
7 R = Me, R' = $COCH_3$
8 R = H, R' = $COCH_3$



11



13

(2:1) (0 °C → room temp., overnight) and then treated with Zn in AcOH - THF (room temp., 3 h) to afford a cyclization product (**5**),[6] in 42% overall yield. Unfortunately, however, its cyclization mode is not identical with that of K-13 (**2**), but instead **5** has the same heterocyclic skelton as that of OF 4949-III (**1**). This macrocyclic compound (**5**) was subjected to catalytic hydrogenation [H_2/Pd-black, NaOAc/MeOH (room temp., 2 days)] to give a phenol (**6**),[6] in 96% yield, which was then converted into the corresponding N-acetyl compound (**7**)[6] in 2 steps [1) HCl /dioxane (room temp., overnight); 2) Ac_2O/pyr. (room temp., 5.5 h) (68% overall yield)]. Finally, **7** was hydrolyzed with 1N NaOH (3.1 equiv.) in MeOH (room temp., 25 min) and then treated with Amberlite IR-120 (H^+) to afford an isomer (**8**) of K-13, in 98% yield. Its physiological property will be examined in due course.

As judged from the above result, 3,5-diiodo-L-tyrosine methyl ester must be used instead of the corresponding 3,5-dibromo compound. Thus, according to the same procedure as described above, 3,5-diiodo-L-tyrosine methyl ester was connected to N-t-butyloxycarbonyl-O-benzyl-L-tyrosine to give rise to the corresponding dipeptide (**9**),[5] in 97% overall yield, which was further reacted with N-acetyl-3,5-dichloro-L-tyrosine using DCC (1.2 equiv.) - 1-hydroxybenzotriazole (1 equiv.) - N-methylmorpholine (1 equiv.) in DMF (0 °C → room temp., 18 h) to afford a tripeptide (**10**)[5] in quantitative yield.

This compound (**10**) was subjected to TTN oxidation in MeOH - THF (1:2.5) (-22 °C → room temp., 9 h) followed by Zn in AcOH (room temp., overnight) to give a desired diphenyl ether (**11**)[6] in 15% overall yield. In this case, another macrocyclic compound (**12**)[7] was also obtained in ca. 5% yield, which was readily converted into **7** on catalytic hydrogenation. Finally, the macrocyclic diphenyl ether (**11**) was subjected to catalytic hydrogenation [H_2/Pd-black, NaOAc/THF - MeOH (1:1) (room temp., 4 days)] to afford a desired phenol (**13**), in 20% yield. In this case, reductive dechlorination did not take place smoothly.[8] Furthermore, **13** was treated with 1N aq. NaOH (14 equiv.) and then with Amberlite IR-120 (H^+) to give rise to the seventeen-membered macrocyclic tripeptide in quantitative yield. The synthetic tripeptide was completely identical with natural K-13 (**1**) in all respects of spectral data (IR and ^1H NMR). Particularly, the optical rotation of the synthetic sample ($[\alpha]_D^{26}$ -7.4° (c 0.65, MeOH)) is quite similar to that of natural K-13 ($[\alpha]_D^{19}$ -3.4° (c 0.62, MeOH)). According to essentially the same procedure as described above, the remaining three stereoisomers have also been synthesized.[4,9] In connection with these tyrosine-derived antibiotics, further synthetic study on vancomycin and related compounds is in progress using our synthetic method demonstrated in the present paper.

The authors wish to thank Dr. Hiroshi Sano (Tokyo Research Laboratories, Kyowa Hakko Kogyo Co. Ltd.) for providing them an authentic sample of K-13 and its ^1H NMR spectrum. They are also indebted to Dr. Yutaka Hashimoto (Research Laboratories, Pharmaceutical Group, Nippon Kayaku, Co. Ltd.) for measurement of FAB-mass spectra. This research has been supported in part by grants from the Ministry of Education, Science and Culture as well as from the Kawakami Memorial Foundation, to which grateful acknowledgement is made.

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3. S. Sano, K. Ikai, H. Kuroda, T. Nakamura, A. Obayashi, Y. Ezure, and H. Enomoto, J. Antibiot., 39, 1674 (1986); S. Sano, K. Ikai, K. Katayama, K. Takesako, T. Nakamura, A. Obayashi, Y. Ezure, and H. Enomoto, ibid., 39, 1685 (1986).

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5. All new compounds described herein gave satisfactory spectral data consistent with the assigned structures.

6. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: **5**: mp 151 - 154 °C; $[\alpha]_D^{27}$ +53.0° (c 1.0, MeOH); IR (film) 3325, 2950, 1740, 1650, 1540, and 1500 cm^{-1}; δ ($CDCl_3$) 1.50 (9H, s), 2.37 (1H, t, J= 12.7 Hz), 2.67 (1H, br.d., J= 14.2 Hz), 2.80 (1H, dd, J= 9.8, 16.1 Hz), 2.98 (1H, dd, J= 4.4, 14.2 Hz), 3.02 (1H, dd, J= 5.4, 14.2 Hz), 3.32 (1H, dd, J= 3.9, 13.4 Hz), 3.83 (3H, s), 4.41 (1H, m), 4.50 (1H, m), 4.94 (1H, m), 5.05 (2H, s), 5.41 (1H, d, J= 6.8 Hz), 5.67 (1H, d, J= 2.0 Hz), 5.91 (1H, s), 6.01 (1H, d, J= 9.8 Hz), 6.40 (1H, d, J= 7.8 Hz), 6.74 (1H, d, J= 2.0 Hz), 6.93 (2H, d, J= 8.8 Hz), 7.06 (1H, d, J= 2.0 Hz), 7.14 (2H, d, J= 8.8 Hz), 7.32 - 7.44 (5H, complex), and 7.60 (1H, d, J= 2.0 Hz). **6** as amorphus powder: $C_{31}H_{37}N_3O_9$ [m/z 620 (M^++1)]; $[\alpha]_D^{28}$ +43.0° (c 1.25, MeOH); IR (Nujol) 3300, 1730, 1650, and 1500 cm^{-1}; δ (CD_3OD) 1.43 (9H,s), 2.64 - 2.76 (3H, complex), 2.93 (2H, br.dd, J= 5.9, 13.9 Hz), 3.81 (3H, s), 4.23 (1H, complex), 4.53 - 4.56 (1H, complex), 4.78 (1H, m), 5.34 (1H, d, J= 8.3 Hz), 5.84 (1H, br.s), 6.46 (1H, br.dd, J= 1.5, 7.8 Hz), 6.63 (2H, d, J= 8.3 Hz), 6.73 (1H, d, J= 7.8 Hz), 6.84 (1H, dd, J= 2.0, 8.1 Hz), 6.99 - 7.01 (3H, complex), 7.18 (1H, dd, J= 2.0, 8.3 Hz), 7.36 (1H, dd, J= 2.0, 8.1 Hz), 7.98 (1H, d, J= 8.8 Hz), and 8.52 (1H, d, J= 9.8 Hz). **7** as amorphus powder: $C_{30}H_{31}N_3O_8$ [m/z 562 (M^++1)]; $[\alpha]_D^{28}$ +20.9° (c 0.64, MeOH); IR (Nujol) 3300, 1730, 1640, and 1510 cm^{-1}; δ (CD_3OD) 1.90 (3H, s). **8**: mp 212 - 216 °C; $C_{29}H_{29}N_3O_8$ [m/z 548 (M^++1)]; $[\alpha]_D^{24}$ +30.0° (c 1.3, MeOH); IR (Nujol) 3300, 1720, 1640, and 1510 cm^{-1}; δ (CD3OD) 1.90 (3H, s), 2.62 - 2.74 (3H, complex), 2.94 - 3.00 (2H, complex), 3.42 (1H, dd, J= 3.4, 13.2 Hz), 4.52 - 4.59 (2H, complex), 4.77 (1H, dd, J= 3.9, 12.5 Hz), 5.90 (1H, d, J= 1.5 Hz), 6.44 (1H, dd, J= 1.5, 8.1 Hz), 6.62 (2H, d, J= 11.2 Hz), 6.80 (1H, dd, J= 2.5, 8.1 Hz), 7.00 (3H, d, J= 11.2 Hz, overlapped with one proton), 7.20 (1H, dd, J= 2.0, 8.3 Hz), 7.40 (1H, dd, J= 2.0, 8.3 Hz), and 7.97 (1H, d, J= 9.3 Hz). **11** as amorphus powder: $C_{37}H_{34}N_3O_8Cl_2I$ [m/z 846 (M^++1)]; $[\alpha]_D^{25}$ -2.2° (c 0.2, THF); IR (KBr) 3300, 2925, 1730, 1620, and 1510 cm^{-1}; δ (DMSOd-6) 1.89 (3H, s), 2.76 - 3.08 (6H, complex), 3.54 (3H, s), 4.20 - 4.26 (1H, complex), 4.29 - 4.36 (1H, complex), 4.70 - 4.78 (1H, complex), 5.02 (2H, s), 6.11 (1H, d, J= 2.4 Hz), 6.79 (2H, d, J= 8.2 Hz), 7.01 (2H, d, J= 8.2 Hz), 7.11 (1H, d, J= 2.4 Hz), 7.23 (1H, d, J= 2.4 Hz), 7.35 - 7.48 (5H, complex), 7.64 (1H, d, J= 2.4 Hz), 8.18 (1H, d, J= 7.1 Hz), and 8.50 (1H, d, J= 8.2 Hz). **13** as amorphus powder: IR (film) 3300, 1740, 1630, 1510 cm^{-1}; δ (CD_3OD) 2.07 (3H, s), 2.78 - 3.16 (6H, complex), 3.76 (3H, s), 4.20 (1H, t, J= 5.6 Hz), 4.50 (1H, dd, J= 5.4, 12.0 Hz), 4.60 (1H, dd, J= 2.9, 9.5 Hz), 6.41 (1H, d, J= 2.0 Hz), 6.64 (2H, d, J= 8.3 Hz), 6.69 - 6.74 (2H, complex), 6.85 (2H, d, J= 8.3 Hz), 6.97 (2H, d, J= 8.3 Hz), 7.01 (1H, dd, J= 2.4, 8.3 Hz), 7.07 (1H, dd, J= 2.4, 8.3 Hz), and 7.34 (1H, dd, J= 2.4, 8.3 Hz).

7. This compound has not been obtained in completely pure state, and directly used for the next experiment leading to the formation of **7**.

8. Other methods for reductive dechlorination are examined.

9. These results will be published elsewhere in detail.

(Received in Japan 2 November 1988)