TOTAL SYNTHESIS OF SEN-215 BY USE OF PALLADIUM CATALYZED CARBONYLATION

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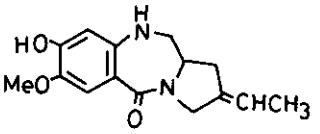
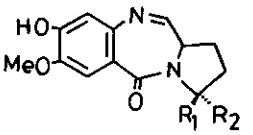
Abstract——The total synthesis of SEN-215 was achieved by use of palladium catalyzed carbonylation.

SEN-215(1) was isolated from the fermentation broth of Streptomyces cylindros Poros SEN-215 and its structure was elucidated by spectral data.[2] The fundamental pyrrolo-1,4-benzodiazepine part of SEN-215 is common to neothramycin(2) and tomaymycin(3) having antitumor activities, but the total synthesis of this antibiotic has not been achieved yet. In this communication, we report the total synthesis of SEN-215 by use of palladium catalyzed carbonylation, which method has been successfully introduced by us to synthesis of various heterocycles, including 1,4-benzodiazepinones(4)[3,4] and anthramycin(5)[5] itself. For the synthesis of SEN-215, the tetra-substituted aromatic compound 6 was required, which was prepared from guaiacol(10), and hydroxy-L-proline (7) was used as the starting amino acid.



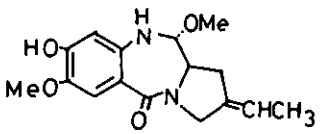
SEN-215(1)



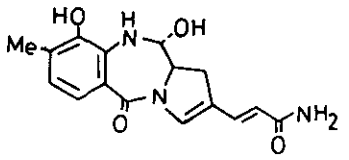
Neothramycin(2)

A: R_1=OH, R_2=H

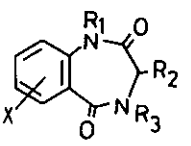
B: R_1=H, R_2=OH



Tomaymycin(3)



Anthramycin(5)



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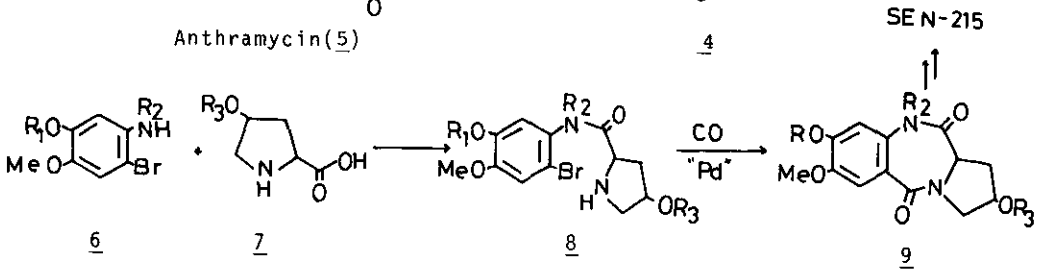
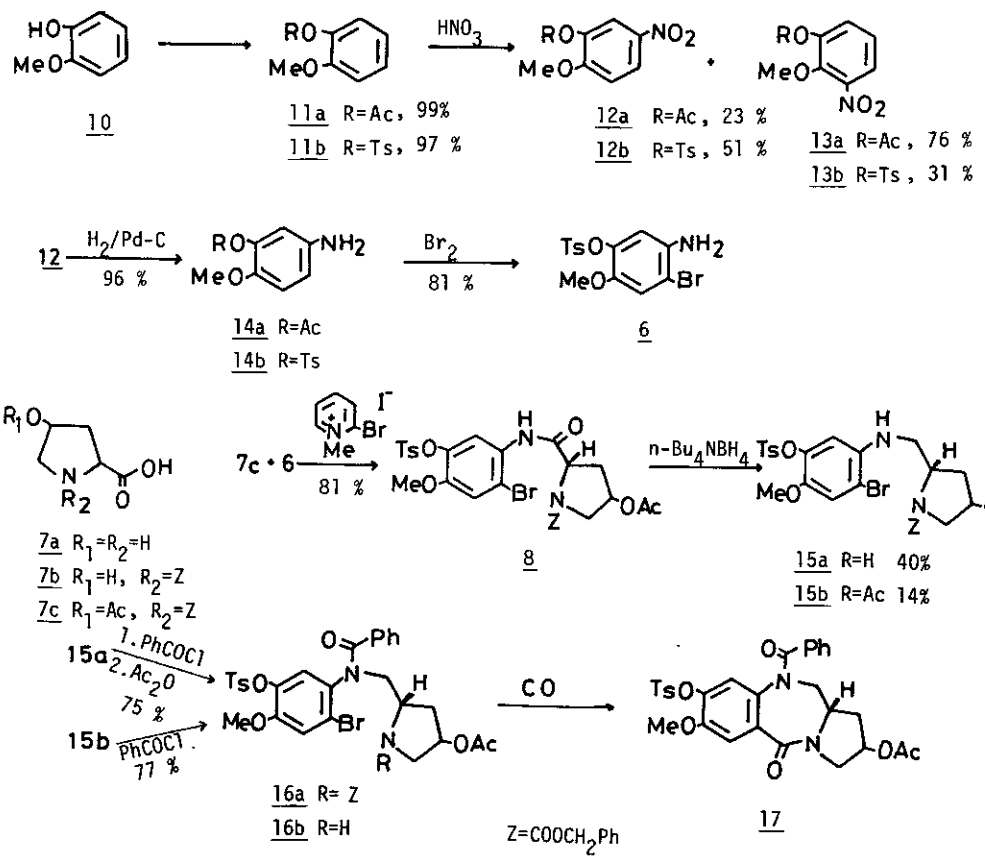
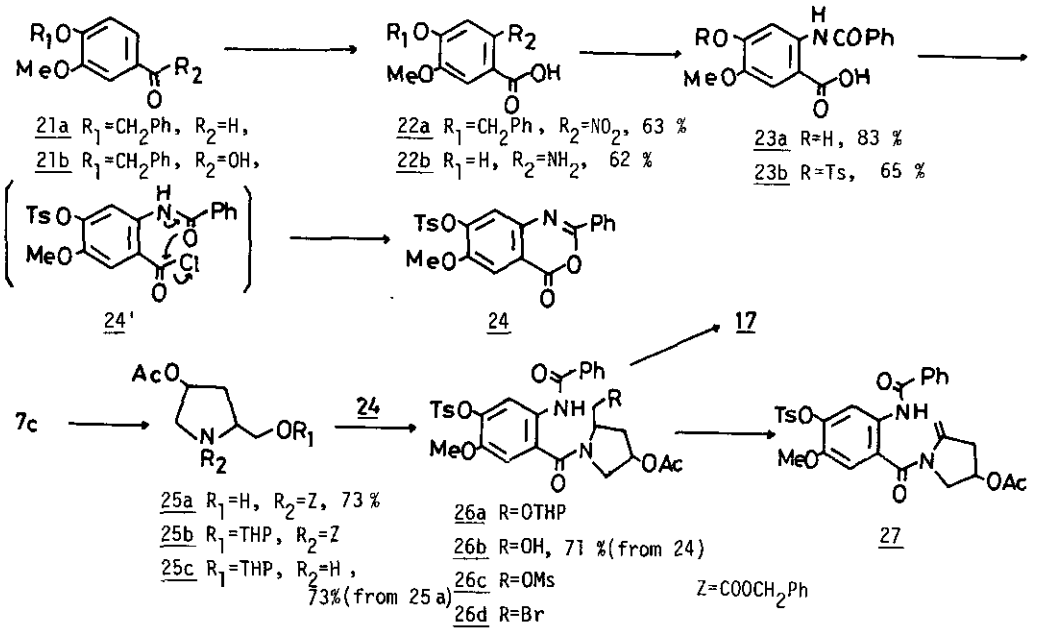


6 7 8 9

Protection for guaiacol with acetyl chloride followed by nitration afforded the ortho 13a and para nitrated compound 12a. Hydrogenolysis of the para nitrated compound 12a with 10 % Pd on charcoal was tried not to have afforded the anilino derivative 14a. Therefore, the protecting group of 10 was changed from the acetyl to tosyl group and then treatment of 11b in the same manner afforded 14b, which was brominated to produce the tetra-substituted aromatic compound 6. On the other hand, hydroxy-L-proline was converted to O-acetyl-N-benzyloxycarbonyl-hydroxy-L-proline(7c) in the usual manner, which was condensed with 6 in the presence of 2-bromo-1-methylpyrrolidinium iodide and n-Bu_3N[6] to give the compound 8. Reduction of the secondary amide of 8 with n-Bu_4NBH_4[7] in dichloroethane produced a mixture of 15a and 15b. Treatment of 15b with benzoyl chloride afforded the compound 16a, which was also obtained by the same treatment of 15a followed by acetylation. Deprotection of compound 16a with HBr-AcOH afforded the secondary amine 16b, which was treated in the presence of 2 mol % of $Pd(OAc)_2$, 4 mol % of PPh_3 and an equimolar amount of n-Bu_3N at 100°C under an atmosphere of

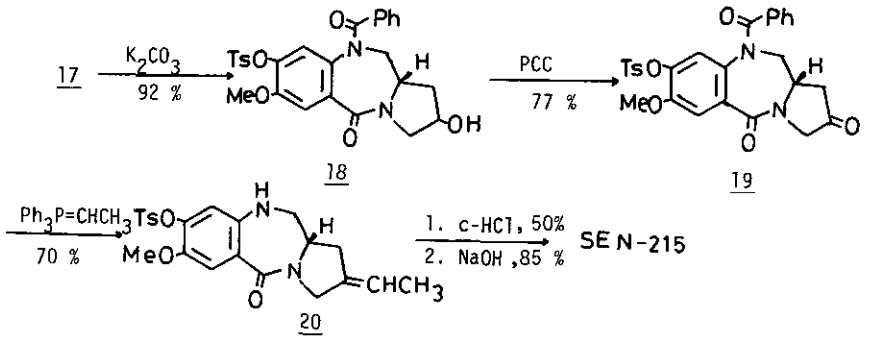


carbon monoxide to afford only 9 % yield of pyrrolo-1,4-benzodiazepine 17. However, 4 atm pressure of carbon monoxide at 100°C in the presence of 10 mol % of $Pd(OAc)_2$ for 40 h made to raise the yield (54 %) of 17, the structure of which was confirmed by IR, NMR and mass spectra. In addition, to establish its structure, the compound 17 was synthesized by another route as follows.



Protection for vanillin with benzyl bromide followed by oxidation with silver oxide and then nitration afforded the compound 22a, which was hydrogenated with 10 % Pd on charcoal to give the anthranilic acid derivative 22b. Benzoylation followed by tosylation gave the compound 23b, which was treated with oxalyl chloride or thionyl chloride to produce the anthranil derivative 24[83 %, mp 165-166°C, IR νmax(Nujol) 1745, 1626, 1610, 1590, 1580 cm^{-1}; MS m/e 423(M^+)] via the acid chloride 24'. For the synthesis of the pyrrolidine part, the compound 7c was converted to the alcohol 25a by reduction,[8] which was protected with dihydropyrane, followed by hydrogenolysis of benzyloxycarbonyl group with 10 % Pd on charcoal afforded the desired pyrrolidine derivative 25c. A benzene solution of 24 and 25c was refluxed for 12 h to give the compound 26a,[9] which was treated with p-TsOH to afford the alcohol 26b. Mesylation of 26b followed by substitution with KBr in DMSO gave the bromide 26d. To attempt the cyclization, 26d was treated with NaH in THF to give the elimination product 27. However, when the mesylate 26c was treated with KH in THF, the cyclization product 17 was obtained in the yield of 23 %. The spectral data of this compound were fully

identical with those of the carbonylation product previously obtained. Conversion of 17 to 19 was carried out in the usual manner and then treatment with ethyl triphenylphosphonium bromide in the presence of t-BuOK in THF afforded the compound 20 in the yield of 70 %. Though the nmr spectrum of the compound 20 supported this structure, the stereochemistry of the ethylidene group remains to be solved in the future. Treatment of 20 with conc.HCl in EtOH and then 10 % NaOH in MeOH produced SEN-215. The spectral data of this compound(NMR, IR and MS) were identical with those of the authentic sample kindly supplied by Dr. Murayama.[2] But the melting point of our sample(mp 246-248°C) did not agree with the described melting point(mp 205-206°C) for the natural antibiotic. Since the stereochemistry of natural product has not been determined yet on scarcity of the sample with its insufficient spectral data, the final conclusion as the structure of SEN-215 could not be obtained. Further study is in progress in our laboratory.



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REFERENCRES AND NOTES

1. Present address, Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University, Ishikari-tobetsu, 061-02 Japan
2. S. Matsumura, Y. Ezure, M. Ozaki, H. Watanabe and O. Tanabe, Japan Kokai, 78, 56693(1978); Chem. Abstr., 89, 161536p(1978).
3. M. Mori, M. Ishikura, T. Ikeda and Y. Ban, Heterocycles, 16, 1491(1981).
4. M. Ishikura, M. Mori, T. Ikeda, M. Terashima and Y. Ban, J. Org. Chem., 47, 2456(1982).
5. M. Ishikura, M. Mori, M. Terashima and Y. Ban, Chem. Comm., 741(1982).
6. E. Bald, K. Saigo and T. Mukaiyama, Chem. Lett., 1163(1975).
7. T. Wakamatsu, H. Inaki, A. Ogawa, M. Watanabe and Y. Ban, Heterocycles, 14, 1437, 1441(1980);
8. K. Ishizumi, K. Koga and S. Yamada, Chem. Pharm. Bull., 16, 492(1968).
9. L. A. Ereede, J. Org. Chem., 41, 1763(1976).

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