STRUCTURE AND SYNTHESES OF SEN-215 AND OXOTOMAYMYCIN

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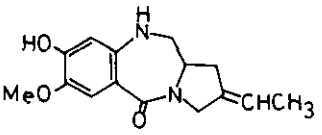
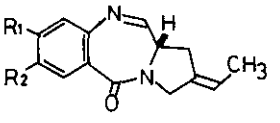
Abstract——The structure of SEN-215 was determined as (11aS)(E)-2-ethylidene-2,3,5,10,11,11a-hexahydro-8-hydroxy-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepine by conversion of (E)- and (Z)-pretomaymycin into (E)- and (Z)-SEN-215.

SEN-215 was isolated from the fermentation broth of Streptomyces cylindrosporus SEN-215 and its structure was elucidated by spectral data.[1] The basic carbon framework of SEN-215(1) is common to prothracarcin(2), pretomaymycin(3), tomaymycin(4) and oxotomaymycin(5), which are pyrrolo-1,4-benzodiazepine antibiotics having antitumor activities.[2] We have already reported the total synthesis of SEN-215 by use of palladium catalyzed carbonylation from guiacol(7) and 4-hydroxy-L-proline[3] as shown in Scheme 2. However, the melting point of the

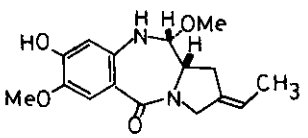
Scheme 1



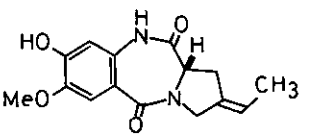
SEN-215(1)



Prothracarcin(2) $R_1=R_2=H$
Pretomaymycin(3) $R_1=OH, R_2=OMe$



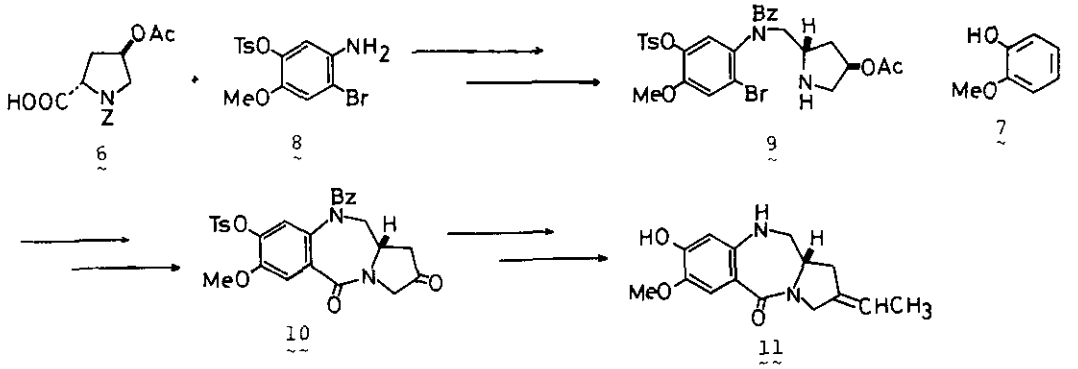
Tomaymycin(4)



Oxotomaymycin(5)

synthetic product (mp 246-248°C) did not agree with that (mp 205-206°C) of the natural antibiotic[1] though the spectral data of the compound (NMR, IR and Mass) were identical with those of the authentic sample. Thus, the final conclusion about the structure of the natural product (1) had to be reserved for further investigation. In this communication, we report that the complete structure of SEN-215 should be represented by formula (1a) in Scheme 4, through conversion of (E)- and (Z)-pretomaymycin into (E)- and (Z)-SEN-215, respectively, during which studies the synthesis of oxotomaymycin(5) was effected.

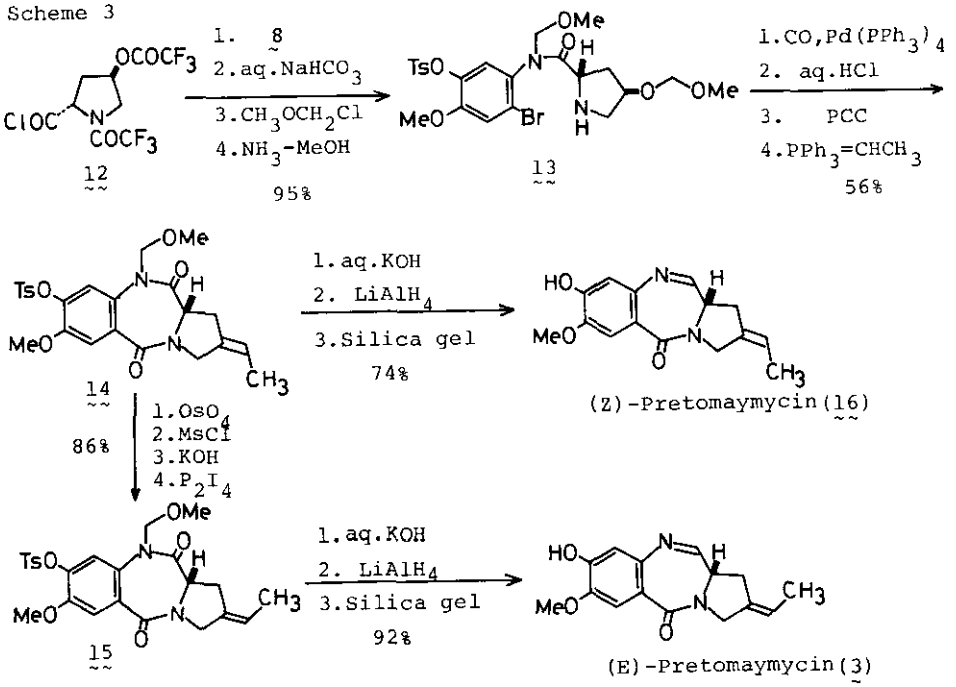
Scheme 2



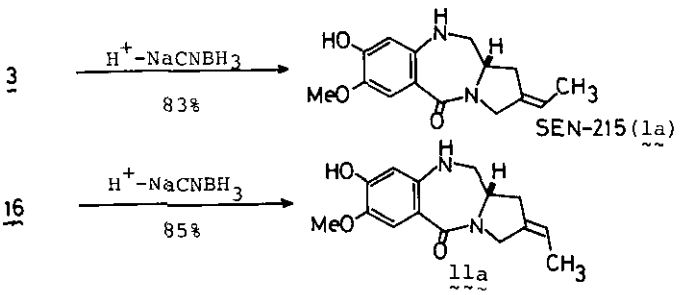
The total syntheses of (E)- and (Z)-pretomaymycins, (3) and (16), were achieved from o-haloaniline 8 and 4-hydroxy-L-proline derivative 12 in the optically active forms as shown in Scheme 3.[4] Since the interconversion of pretomaymycin to tomaymycin could be effected,[5] and the stereochemistry of tomaymycin was already determined to be in E-configuration at an olefinic part by X-ray analysis,[6] the ethylidene group of pretomaymycin(3) has confirmatively (E)-configuration. Moreover, by comparison with the ^{13}C-NMR spectra of compounds 14 and 15, the ethylidene group of the former compound 14 has (Z)-configuration and that of the latter one has (E)-configuration.[7] These results describe that the ethylidene group of compound 14 which was obtained by the Wittig reaction has (Z)-configuration. Therefore, the ethylidene group of compound 11 should have (Z)-configuration. Since SEN-215 was considered to be a reduced product of imino group of pretomaymycin, (E)-pretomaymycin(3) was treated with $NaCNBH_3$ in MeOH in the presence of acid to afford (E)-SEN-215 in an optically active form ($[\alpha]_D^{25}$ +150.2°(c=0.136, MeOH), lit.[1] $[\alpha]_D^{24}$ +158.1°(c=0.956, MeOH)) in high yield, whose

spectral data and the melting point (mp 205-207°C) were fully identical with those of the natural antibiotic, establishing the complete structure to be 1a (Scheme 4). (Z)-Pretomaymycin(16) was reduced in a similar manner to afford (Z)-SEN-215(11a) in high yield. The melting point of this compound 11a showed 246-249°C, which agreed with that of the compound 11 previously synthesized.[3] These results indicated that the ethylidene group of SEN-215 has (E)-configuration, in which the asymmetric carbon of C-11a is in S-configuration.

Scheme 3



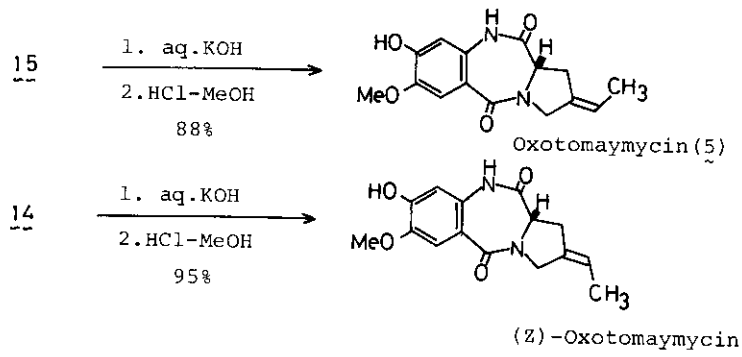
Scheme 4



Furthermore, oxotomaymycin(5)[8] of the establishing structure, which was isolated from Streptomyces achromogenes var. Tomaymycetics was also synthesized from compound 15 having E-ethylidene group. Namely, compound 15 was treated with KOH followed by treatment with HCl-MeOH to afford (E)-oxotomaymycin(5), whose melting point (mp 228-230°C) and the spectral data were fully identical with those of the natural product. Similar treatment of compound 14 afforded (Z)-oxotomaymycin (mp 299-300°C) in high yield.

Further studies are in progress.

Scheme 5



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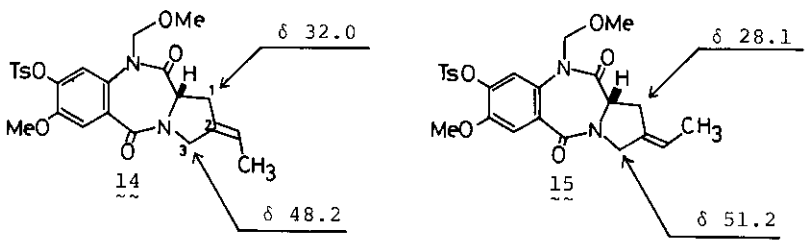
5. Z. Tozuka, H. Takasugi, and T. Takaya, J. Antibiotics, 36, 276 (1983).
6. S. K. Arora, J. Antibiotics, 34, 462 (1981).
7. The chemical shift(28.1 ppm) of the methylene group at C-1 of E-isomer 15, which is influenced by the steric compression effect of the methyl group in the ethylidene moiety, is 3.9 ppm in higher field than that of the Z-isomer 14. Moreover, the chemical shift (48.2 ppm) of methylene group at C-3 of the Z-isomer 14 is 3.00 ppm in higher field than that of the E-isomer 15 (51.2 ppm) due to the same steric compression.



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