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Studies directed towards the stereoselective synthesis of polyene macrolide antibiotics

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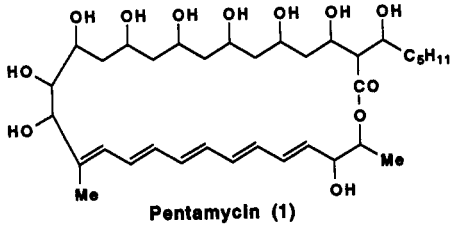
Abstract - A stereoselective method for a convergent synthesis of 1,3-polyhydroxyl functions and a reliable strategy for determining a stereostructure of 1,3-polyols have been developed. These methods have been effectively applied for the synthesis of naturally occurring all-syn-nonamethoxy-1-pentacosene 3 and the determination of the stereostructure of 1,3-polyol part in pentamycin (1), a polyene macrolide antibiotic.

INTRODUCTION

The polyene macrolide antibiotics, exemplified by pentamycin (1), involve a complex array of 1,3-polyhydroxyl functions and exhibit a strong antifungal activity. However, most of them, except amphotericin B, are too toxic to be used clinically. It is known that the permeability of the sterol-containing membranes is enhanced by these antibiotics and the antifungal activity as well as the toxicity is related to this function. In order to clarify the intrinsic antifungal properties involving exact nature of sterol complexation which may serve in the development of therapeutically important medicines, structure-activity relationship should be examined extensively. The primary obstacle for these studies is that except for a few cases (ref. 1) even relative configurations of 1,3-polyols contained in these antibiotics remains unknown. Thus, efforts were initially focused on the stereoselective synthesis of both syn- and anti-1,3-polyols aiming to determine the stereostructure of polyhydroxylated fragments by synthesizing the compounds having the likely stereostructure. Then, a direct method for determining a stereostructure of these functionalities was investigated with the recognition that such a method would be required essentially in the present studies.



Pentamycin (1)

CONVERGENT SYNTHESIS OF 1,3-POLYOLS

We have already reported a general synthetic method for 1,3-syn-tetrols and 1,3-anti-triols based on the biogenetic pathway (ref. 2). Recently, an effective and stereoselective method for combining two fragments could be developed, by which a facile construction of the higher homologues of 1,3-polyols became possible (Fig. 1). In this strategy, two additional chiral

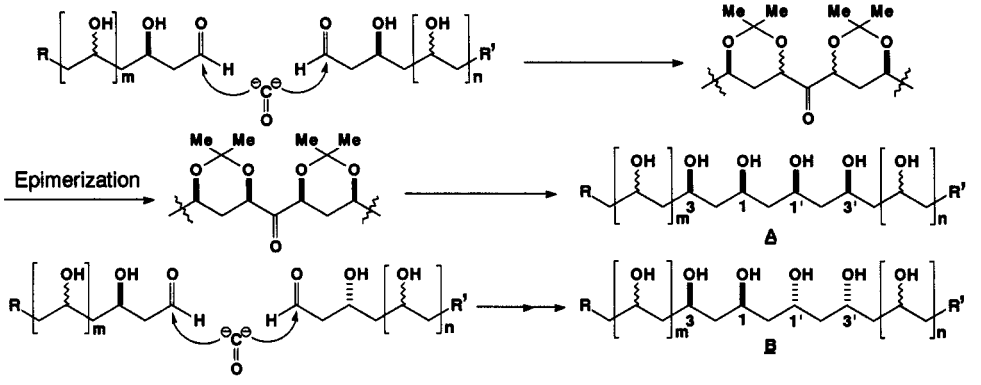


Fig. 1 Strategy for convergent synthesis of 1,3-polyols.

hydroxyl groups are produced. The newly introduced hydroxyl groups at the C-1 and C-1' positions should be syn to the C-3 and C-3'-hydroxyl groups, respectively, and thus, in principle, either 3,1,1',3'-all-syn-tetrol derivatives A or 3,1-syn-1,1'-anti-1',3'-syn tetrol derivatives B can be prepared.

For the purpose of demonstrating an availability of the present strategy, we synthesized naturally occurring α,β-unsaturated δ-lactone derivative 2 (ref. 3) and 1-pentacosene derivative 3 (ref. 4) involving nine methoxyl groups. Synthesis of 3 is shown in Fig. 2. The starting all-syn-tetrol 5 can be synthesized either by the present convergent method or by the previously reported stepwise method (see, ref. 2).

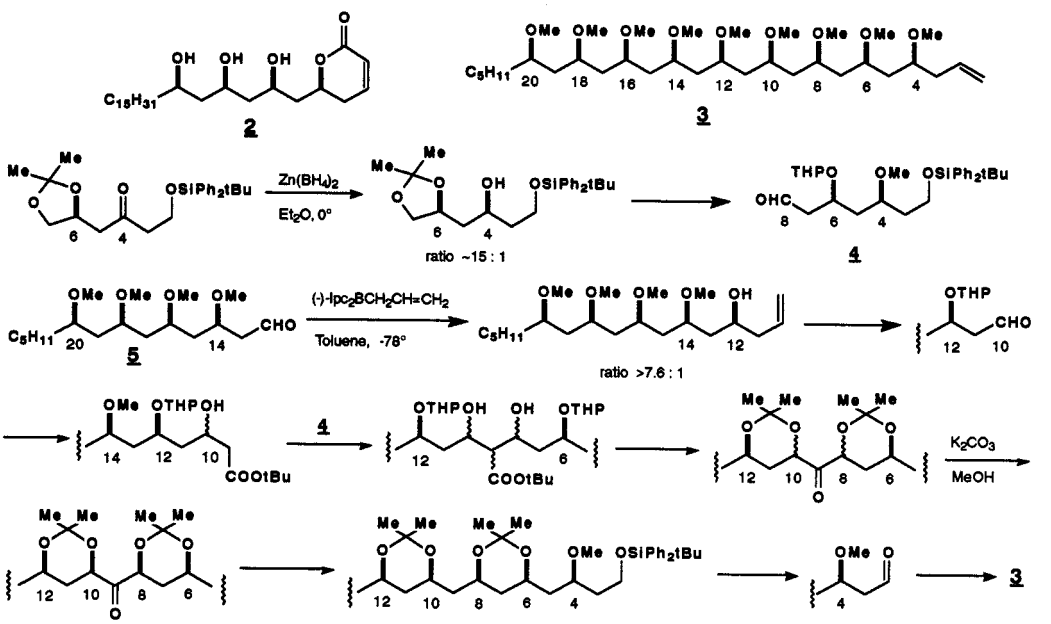


Fig.2 Convergent synthesis of acetogenine 3

DETERMINATION OF STEREOSTRUCTURE OF 1,3-POLYOLS

In the process of determining the stereostructure of (-)-tarchonanthuslactone, we synthesized both 5,7-syn-6 and 5,7-anti-7 stereoselectively. During the comparison studies using the ^{1}H NMR(400MHz) technique, we found that the splitting pattern of the C-4 protons

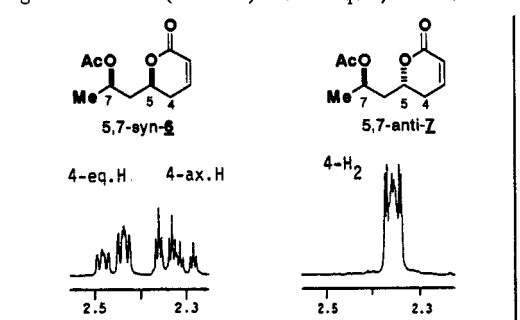


Fig. 3 ^{1}H NMR (400MHz) signals of the C_4 - protons of 6 and 7

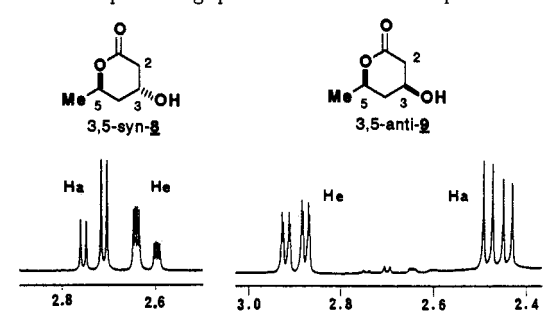


Fig. 4 ^{1}H NMR (400MHz) signals of the C_2 - protons of 8 and 9

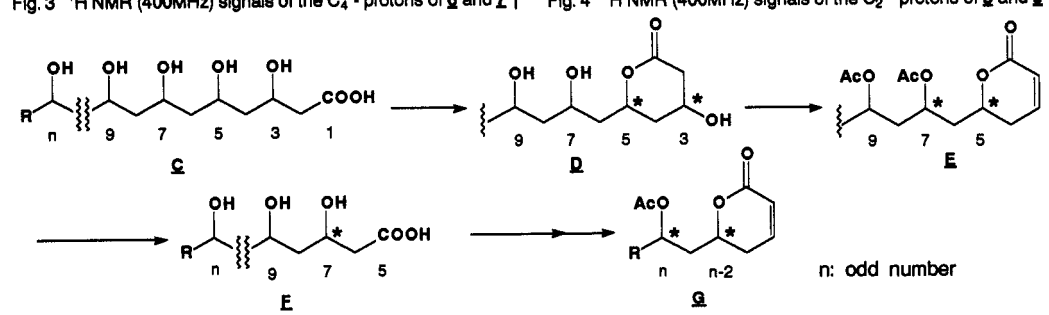
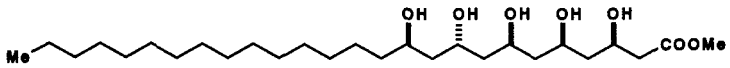


Fig.5 Strategy for determination of stereostructure of 1,3-polyols

of 6 was clearly different from that of 7 (Fig. 3) (ref. 5). This structure specific splitting pattern of C-4 protons was proved to be observed generally in this type of compounds provided the C-7 hydroxyl group was acylated. Based on the above important observation, a general strategy for determining the stereostructure of 1,3-polyol system could be established. The outline was shown in Fig. 5.

Polyhydroxy acid C derivable from natural antibiotics can be converted to lactone D. NMR signals of axH and eqH at the C-2 position of 3,5-syn-8 differ significantly from those of 3,5-anti-9 in every case we examined (cf. Fig. 4). Thus, differentiation of 3,5-syn and 3,5-anti isomers of D is possible from their NMR signals. Acetylation of D followed by elimination of acetic acid produces E, whose relative stereostructure at the C-5 and the C-7 positions can be determined by the splitting pattern of C-4 protons as mentioned above. Thus, it is possible to determine the configurations of three hydroxyl groups at the C-3, C-5, and C-7 positions by only three operations (i. lactonization ii. acetylation iii. elimination of acetic acid). Then, unsaturated lactone in E is oxidatively cleaved to carboxylic acid leading to F having the same β-hydroxy acid structure as that of the starting C. Therefore, by repeating the above procedures the relative configurations of all of the hydroxyl groups in C can eventually be determined unequivocally. The absolute structure can also be determined by measuring the $[\alpha]_D$ value or the CD spectrum of G.

The generality of the present method was firmly confirmed by using 3,5-syn-5,7-syn-7,9-anti-9,11-anti-pentol 10 prepared by the authenticated method (see, ref. 2).



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DETERMINATION OF STEREOSTRUCTURE AND SYNTHETIC STUDIES OF PENTAMYCIN (1)

Although pentamycin isolated from the mycelium of Streptomyces pentaticus, n. sp. (ref. 6) is presumed to have the same gross structure with fungichromin as shown in 1, the stereostructure is not known yet. Thus, we started our work from determining the stereostructure of 1,3-polyol part of 1.
Treatment of 1 with acetone dimethyl acetal-camphor sulfonic acid (CSA) followed by acetylation afforded three isomers, two(11, 12) of which were shown in Fig. 6 (hereafter, one of the enantiomers was shown). Large coupling constant of C-2 H (t, J = 10 Hz) in 11 show that C-2 H is axial with respect to the acetonide ring indicating relative configurations at 3',2,3 as shown in 11. C-13 H appears as doublet of doublets (J = 12, 3

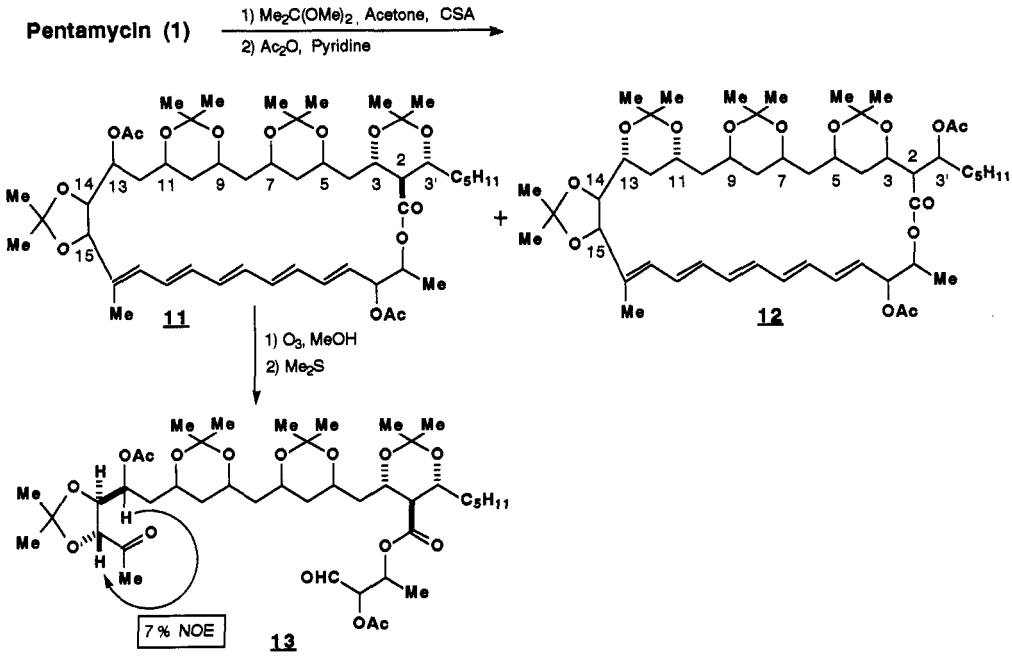

Fig.6 Modification of Pentamycin (1)

Hz) on irradiation of C-14 H in 12, which shows that C-13 OH and C-11 OH are in a syn-relationship. Ozonolysis of 11 followed by dimethyl sulfide treatment afforded 13. Enhancement of C-15 H signal (7%) upon irradiation of C-13 H in 13 shows the trans arrangement of C-15 H and C-14 H. However, a relation between the C-13 and C-14 positions is still not clear.

Pentamycin (1) was converted into 16 via 14, 15. Relative configurations at the C-7, C-9, and C-11 positions were confirmed as all-syn by applying the method discussed above (Fig. 5). α,β-Unsaturated lactone 16 was converted into 18 via 17. Conversion of 18 to 19 and 20 is now in progress. Pentamycin (1) can also be converted into 21, whose absolute configurations at the C-26 and C-27 positions can be assigned as shown in 21 from its $[\alpha]_D$ value. Anti-relationship between the C-26 and C-27 positions was determined by conversion into acetonide 22. Independently, in the process of synthetic studies of 1, we synthesized the optically active 14' from 23 and 24. The NMR spectrum (500MHz) of 14 obtained from 1 was found to be identical with that of 14'. Thus, the relative and absolute structure of 14 can be illustrated as 14'. By combining the data shown above, the absolute structure of 1 could be established as either 1' or 1''.

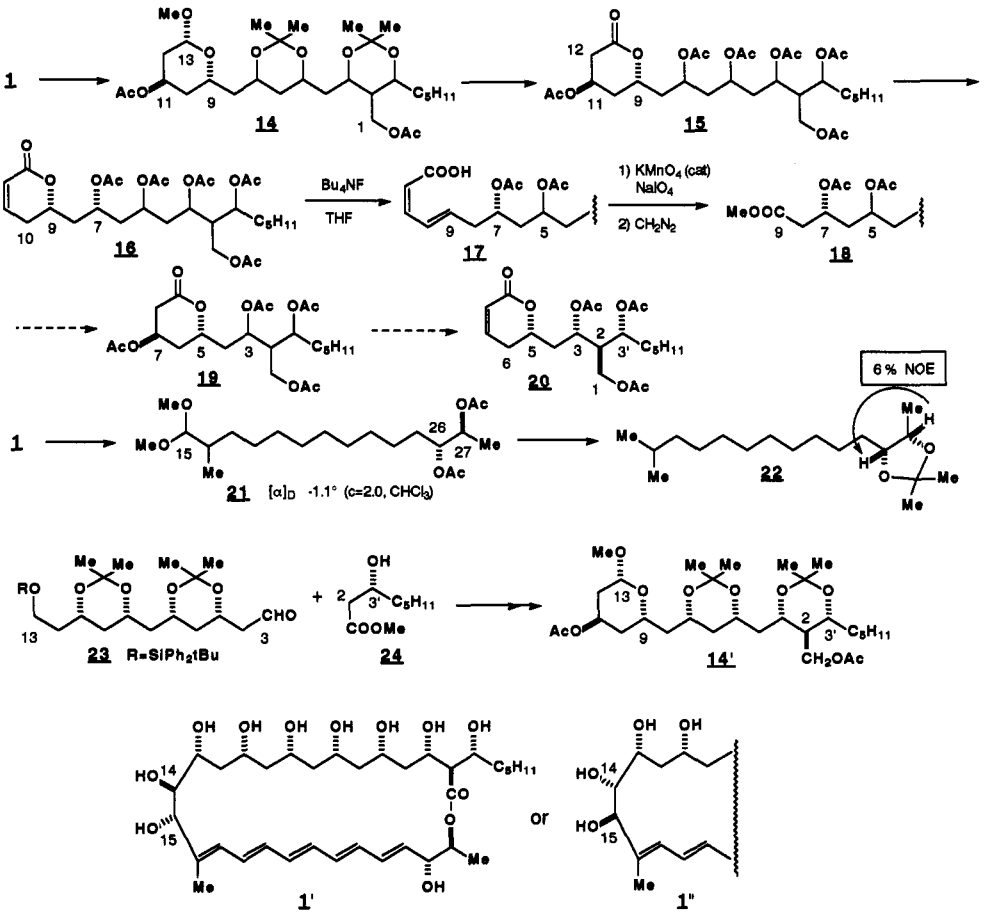

Fig. 7 Stereostructure of 1

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