

The Absolute Stereochemistry of Pamamycin-607, an Aerial Mycelium-inducing Substance of *Streptomyces alboniger*

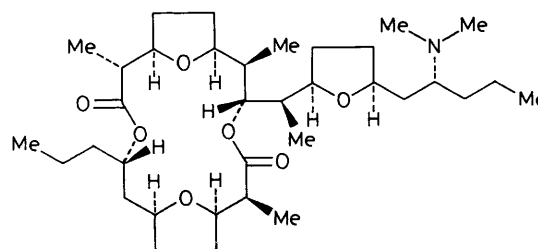
Masahiro Natsume, Satoru Kondo, and Shingo Marumo*

Department of Agricultural Chemistry, Nagoya University, Nagoya 464-01, Japan

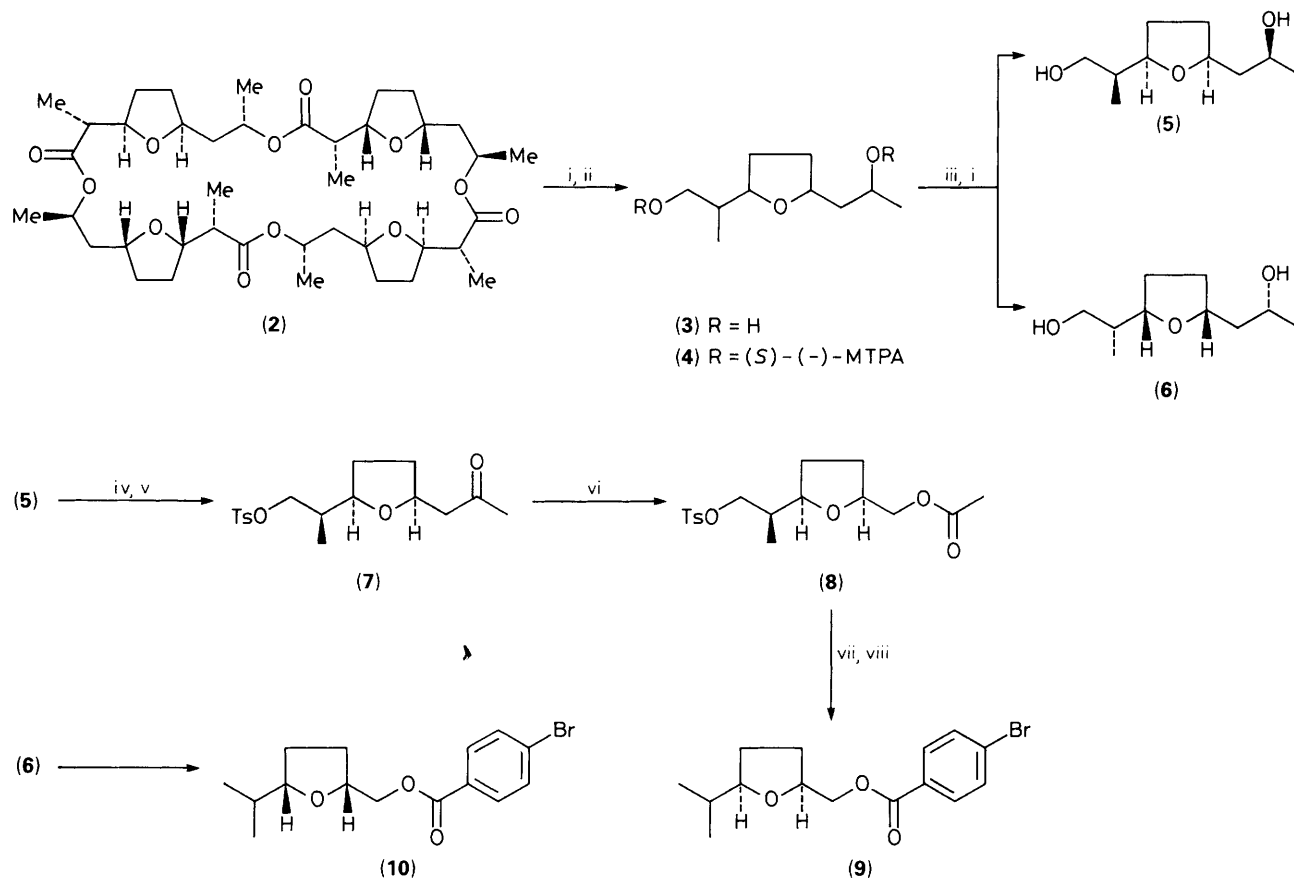
The absolute stereochemistry of pamamycin-607 has been determined as (**1**), by derivatizing it to a furfuryl compound (**14**), the optical rotation of which coincided with that of an authentic compound derived chemically from nonactin antibiotic.

Pamamycin-607 is an aerial mycelium-inducing substance isolated from *Streptomyces alboniger* IFO 12738.¹ It also acts as an antibiotic against certain fungi and bacteria. Pamamycin-607 has the unique ability to transfer only anions (e.g. MnO_4^-) from the aqueous to the benzene layer at neutral and acidic pH. The structure with relative stereochemistry was elucidated by use of 500 MHz 2D ^1H - ^1H and ^1H - ^{13}C correlation NMR and NOE difference spectroscopies.² Here we report that the absolute stereochemistry of pamamycin-607 has been determined as (**1**).

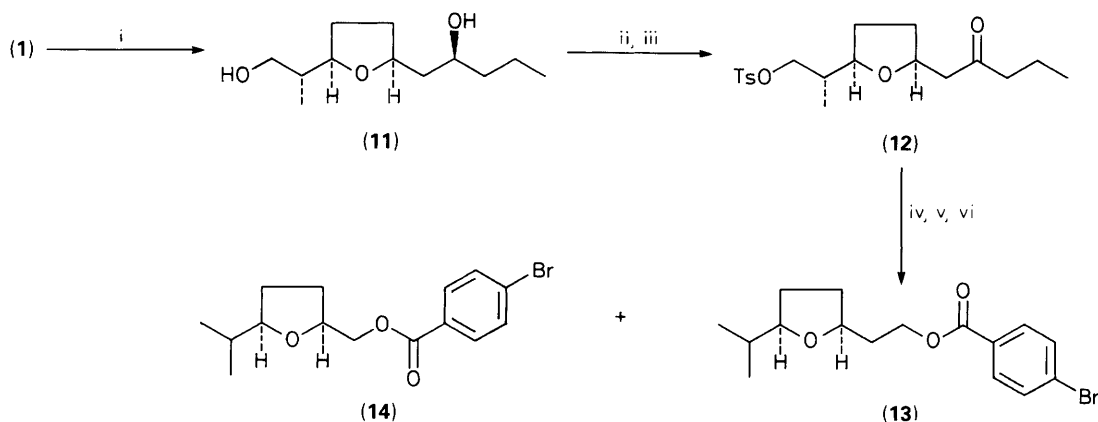
The smaller hydroxy-acid moiety composing one half of the macrodiolide molecule of pamamycin-607 is quite similar to



(**1**)



Scheme 1. Reagents: i, LiAlH_4 , Et_2O ; ii, (S)-(-)-MTPA-Cl, pyridine; iii, recycle HPLC; iv, TsOCl ($\text{Ts} = \text{SO}_2\text{C}_6\text{H}_4\text{Me-p}$); v, pyridinium dichromate (PDC), CH_2Cl_2 ; vi, $\text{CF}_3\text{CO}_3\text{H}$, K_2HPO_4 ; vii, LiAlH_4 , tetrahydrofuran (THF); viii, $p\text{-Br-C}_6\text{H}_4\text{COCl}$, pyridine.



Scheme 2. Reagents: i, LiAlH_4 , Et_2O ; ii, TsOCl , pyridine; iii, PDC, CH_2Cl_2 ; iv, $\text{CF}_3\text{CO}_3\text{H}$, K_2HPO_4 ; v, LiAlH_4 , THF; vi, $p\text{-Br-C}_6\text{H}_4\text{COCl}$, pyridine.

the hydroxy-acid unit of the nonactin molecule. Since the absolute stereochemistry of nonactin has already been established,³ we prepared the furfuryl compound (14) from both pamamycin-607 and nonactin through chemical degradation and derivatization, and their optical rotations were compared.

Nonactin (2) (200 mg) was degraded reductively with

lithium aluminium hydride (LiAlH_4) to give a racemic diol mixture (3). The racemic mixture was converted to a diastereoisomeric mixture of (S)-(-)- α -methoxy- α -trifluoromethylphenylacetate (MTPA) (4),⁴ and the latter mixture was separated by recycling HPLC (12 cycles; Develosil 60-10; 20×250 mm; Et_2O -n-hexane 2:8; 9.9 ml min^{-1}) to afford pure

diastereoisomers.[†] Each diastereoisomer was reduced with LiAlH_4 to recover optically pure enantiomers of diols (**5**) and (**6**). The absolute configurations of (**5**) and (**6**) could be assigned by comparing their optical rotations with the data reported by Beck *et al.*³ {(**5**): $[\alpha]_{\text{D}} + 36^\circ$ (*c* 1.0, benzene), lit. $+31^\circ$ (*c* 2.16); (**6**): $[\alpha] - 37^\circ$ (*c* 1.0, benzene)}; thus, their absolute stereochemistry was established as shown in Scheme 1.

Selective tosylation of the primary alcohol in diol (**5**) followed by oxidation of the secondary alcohol with pyridinium dichromate yielded methylketone (**7**) { $[\alpha]_{\text{D}} - 16^\circ$ (*c* 1.0, benzene)}.[‡] Baeyer–Villiger oxidation of (**7**) with trifluoroperacetic acid and K_2HPO_4 gave the sole product (**8**) { $[\alpha]_{\text{D}} - 23^\circ$ (*c* 1.0, benzene)}; no reaction took place with *m*-chloroperbenzoic acid (*m*CPBA) or peracetic acid. The product (**8**) was reduced with LiAlH_4 to give the furfuryl alcohol derivative which, without purification, was reacted with *p*-bromobenzoyl chloride to give a non-volatile benzoate (**9**) (17.1 mg). Diol (**6**) was reacted in a similar manner to (**5**), and the antipodal benzoate (**10**) was obtained.

Pamamycin-607 (**1**) was reduced with LiAlH_4 to give two diols, fragments *S* (**11**) and *L*, the structure of which may be deduced from (**1**), (Scheme 2). Fragment *S* (42 mg) { $[\alpha]_{\text{D}} + 7.2^\circ$ (*c* 2.0, benzene)} was tosylated and oxidized to give a ketone (**12**). Baeyer–Villiger oxidation of (**12**) with trifluoroperacetic acid and K_2HPO_4 gave two products. The two products were, without separation, subjected to reductive detosylation with LiAlH_4 followed by *p*-bromobenzoylation to give a benzoate mixture (**13**) and (**14**). The mixture was separated by HPLC (Develosil 60-5; 8×250 mm; EtOAc–*n*-hexane 7:93; 2.5 ml min^{-1}) to give a major benzoate (**13**) (11.5 mg) and a minor one (**14**) (0.66 mg) (Scheme 2).

[†] The diastereoisomeric purity was analysed by HPLC (Develosil 60-5; 8×250 mm \times 2; Et₂O–*n*-hexane 15:85; 2.5 ml min^{-1}), to be 96.7% for the less polar diastereoisomer and 96.3% for the more polar one.

[‡] All the new compounds gave satisfactory spectral data.

The minor benzoate (**14**) showed the positive optical rotation, $[\alpha]_{365} + 14^\circ$ (*c* 0.078, CHCl_3), which coincided with the rotation { $[\alpha]_{365} + 14^\circ$ (*c* 1.0, CHCl_3)} of the same benzoate (**9**) derived from nonactin and opposed to that of the antipodal benzoate (**10**) { $[\alpha]_{365} - 13^\circ$ (*c* 1.0, CHCl_3)}. This excellent agreement of the optical rotations between (**14**) and (**9**) provides the evidence that the absolute configuration of the tetrahydrofuran ring of fragment *S* is as shown in (**14**).

Since the relative stereochemistry of pamamycin-607 has already been established as (**1**) by extensively analysing the spatial relationships among all protons in the molecule by NOE difference and 2D-J resolved spectroscopies,² and that of fragment *S* was also confirmed by Walcup and Park's synthesis of its racemate,⁵ the absolute stereochemistry of pamamycin-607 has thus been elucidated as shown in (**1**).

To confirm this result, the optical rotation of the major benzoate (**13**) was measured. In this case, an extra CH_2 group inserted between the asymmetric tetrahydrofuran ring and the benzoyloxy group may effect little change in the optical rotation. Actually, the positive optical rotation of benzoate (**13**) { $[\alpha]_{365} + 9^\circ$ (*c* 0.10, CHCl_3)} was similar to those of (**14**) and (**9**).

S. K. is currently at Central Research Laboratories, Hokko Chemical Industry Co., Ltd., 2165 Toda, Atsugi, Kanagawa 243, Japan.

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