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

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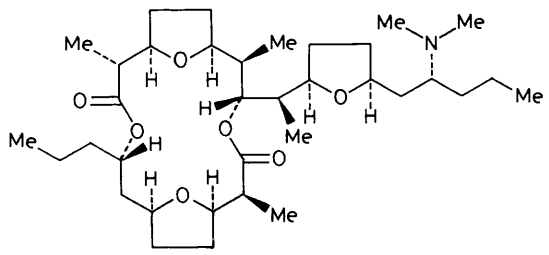
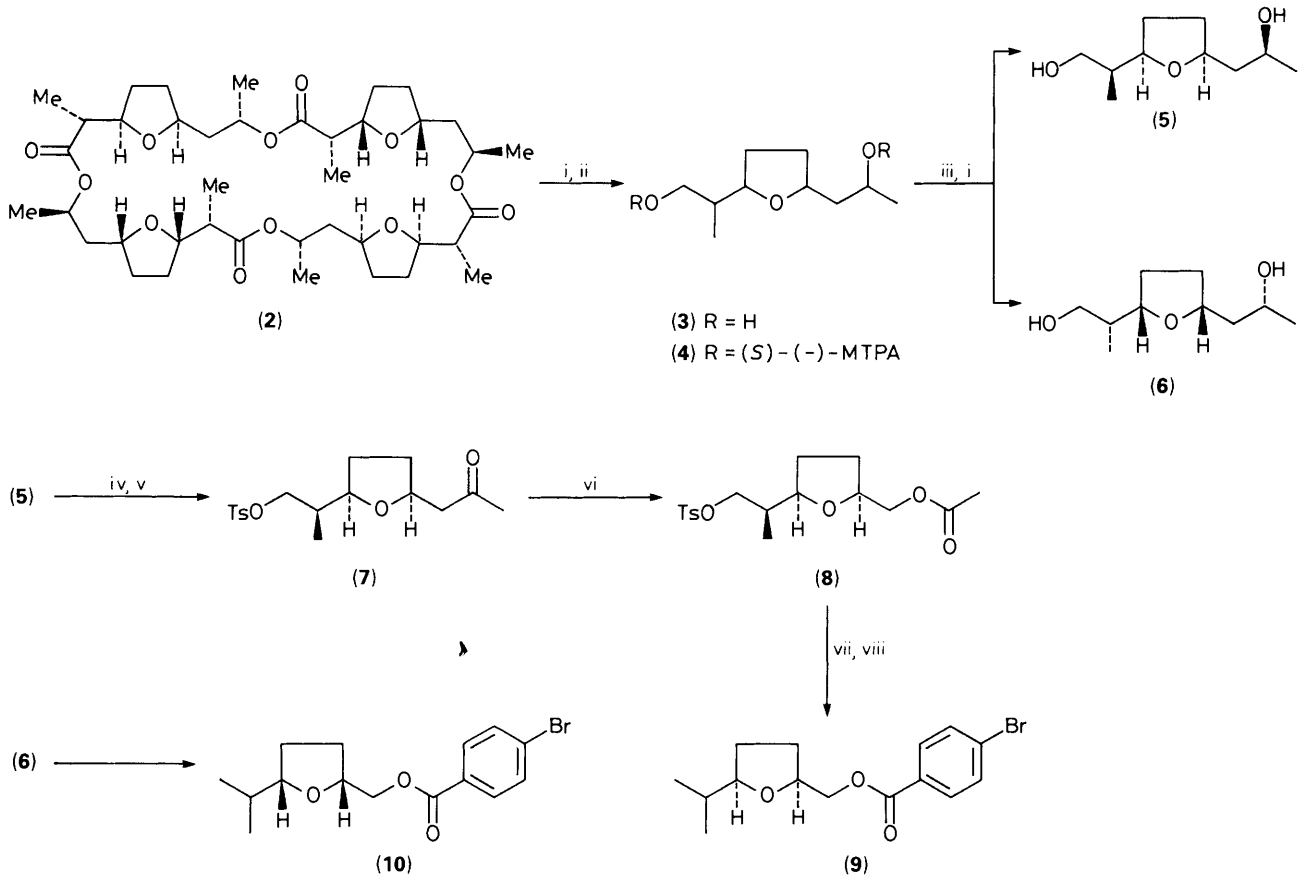
The absolute stereochemistry of pamamycin-607 has been determined as (**1**), by derivatizing it to a furfuryl compound (**14**), the optical rotation of which coincided with that of an authentic compound derived chemically from nonactin antibiotic.

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**).

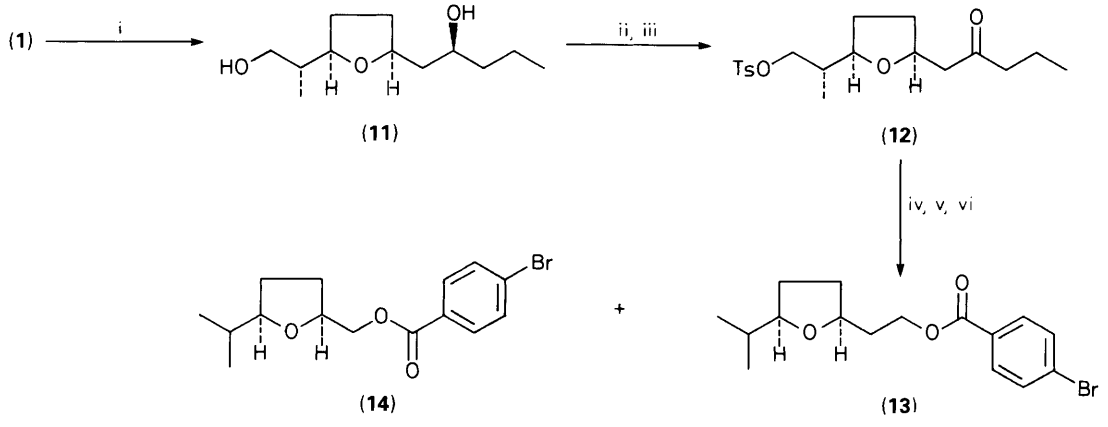
The smaller hydroxy-acid moiety composing one half of the macrodiolide molecule of pamamycin-607 is quite similar to



(**1**)



Scheme 1. *Reagents*: i, $LiAlH_4$, Et_2O; ii, (*S*)-(−)-MTPA-Cl, pyridine; iii, recycle HPLC; iv, TsOCl (Ts = $SO_2C_6H_4Me$-*p*); v, pyridinium dichromate (PDC), CH_2Cl_2; vi, CF_3CO_3H, K_2HPO_4; vii, $LiAlH_4$, tetrahydrofuran (THF); viii, *p*-Br-C_6H_4COCl, pyridine.



Scheme 2. *Reagents*: i, $LiAlH_4$, Et_2O; ii, TsOCl, pyridine; iii, PDC, CH_2Cl_2; iv, CF_3CO_3H, K_2HPO_4; v, $LiAlH_4$, THF; vi, *p*-Br-C_6H_4COCl, 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**): $[\alpha]_D$ +36° (*c* 1.0, benzene), lit. +31° (*c* 2.16); (**6**): $[\alpha]$ −37° (*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**) {$[\alpha]_D$ −16° (*c* 1.0, benzene)}.‡ Baeyer–Villiger oxidation of (**7**) with trifluoroperacetic acid and K_2HPO_4 gave the sole product (**8**) {$[\alpha]_D$ −23° (*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) {$[\alpha]_D$ +7.2° (*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 × 2; Et_2O–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° (*c* 0.078, $CHCl_3$), which coincided with the rotation {$[\alpha]_{365}$ +14° (*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° (*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° (*c* 0.10, $CHCl_3$)} was similar to those of (**14**) and (**9**).

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Received, 1st August 1989; Com. 9/03244D

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