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Enantioselective synthesis of the larger fragment of pamamycin-607†

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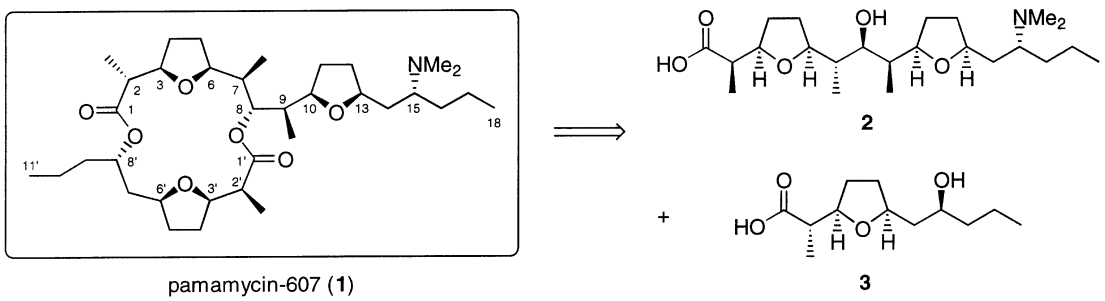
Abstract

The enantiomerically pure methyl ester of the complete larger hydroxy acid (C(1)–C(18)) of the macrodiolide antibiotic pamamycin-607 has been synthesized using a general sultone route to actic acids and analogs. The requisite *N*,*N*-dimethylamino moiety was introduced by Mitsunobu inversion with hydrazoic acid followed by a reaction cascade involving hydrogenation and double reductive methylation.

Keywords: antibiotics; sultones; desulfurization; Mitsunobu reaction.

Pamamycin-607 (**1**)[1,2] is a member of a group of 16-membered macrodiolides that have been isolated from *Streptomyces alboniger* and *Streptomyces aurantiacus*. Next to displaying autoregulatory and anionophoric activities,[3] the macrocycle **1** composed of the two hydroxy acids **2** and **3** (Scheme 1) is especially interesting for its potent antibiotic activity against Gram-positive



Scheme 1.

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† Dedicated to Professor A. Kleemann on the occasion of his 60th birthday.

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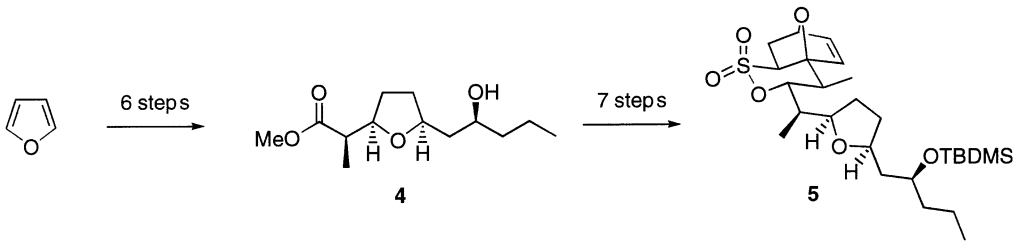
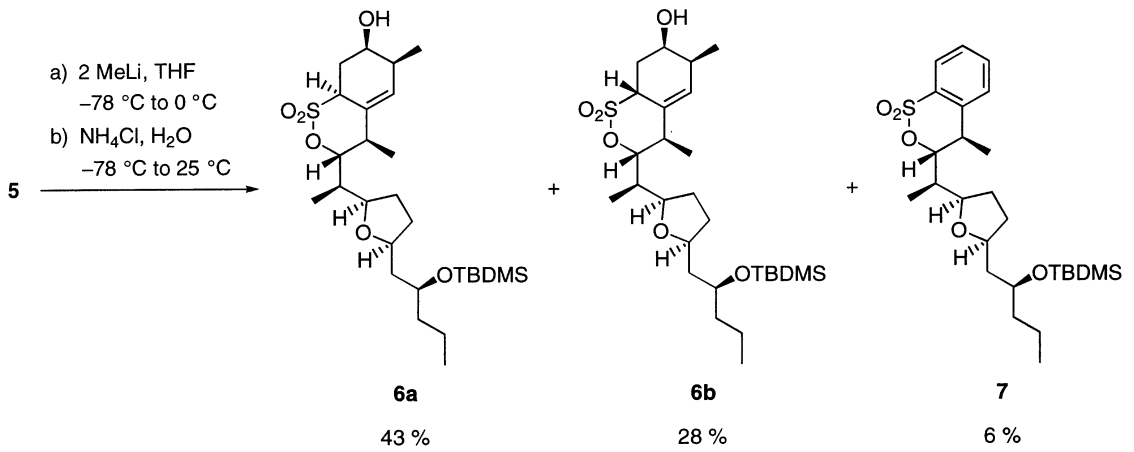
bacteria including multiple antibiotic-resistant strains of *Mycobacterium tuberculosis*[3a] as well as against phytopathogenic fungi.[1b,3a]

Whereas several groups have disclosed synthetic routes to different moieties of pamamycin-607 (**1**),[4–6] a total synthesis of **1** has not been published yet. Our approach to **1** relies on an iterative application of a methodology[7] developed for the synthesis of actic acids and analogs. Along these lines, we recently reported an efficient access to sultone **5**[5b] as a highly advanced intermediate for the larger fragment **2** via methyl ester **4** (Scheme 2) as well as to the methyl ester of the smaller fragment **3**.[5a] Here we communicate the straightforward conversion of sultone **5** to the methyl ester of the complete larger fragment **2** that is a building block of the pamamycin homologs 621A and 635B too.[3b]

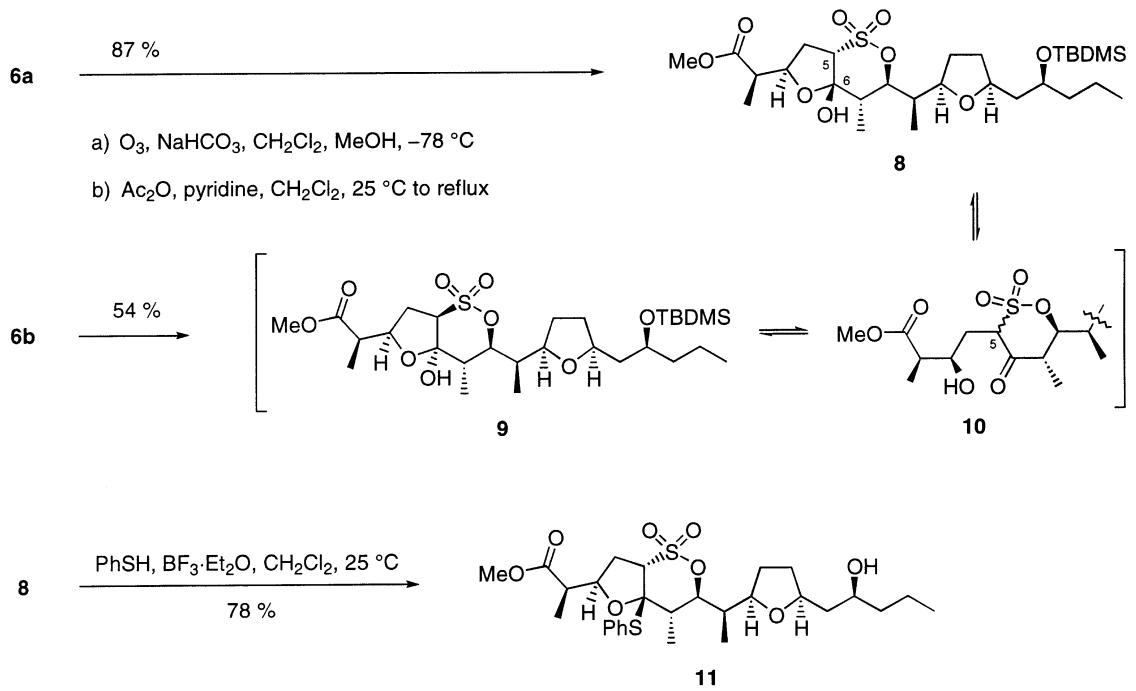


Scheme 2.

Treatment of sultone **5** with two equivalents of methyllithium cleanly introduced a methyl group only *syn* to the hydroxyl substituent via tandem elimination/alkoxide-directed 1,6-addition[8] (Scheme 3). In the resultant epimeric trisubstituted olefins **6a** and **6b**, all carbon atoms of the larger fragment's backbone had now been assembled. While only trace amounts of a tetrasubstituted alkene isomer[5a] were detected, a small quantity of the benzene derivative **7** could be isolated as a byproduct. The crude mixture was easily separated by flash chromatography to give the pure components in the yields listed in Scheme 3, and the two allylic sultones **6a** and **6b** were then separately subjected to an oxidative olefin cleavage (Scheme 4).



Scheme 3.

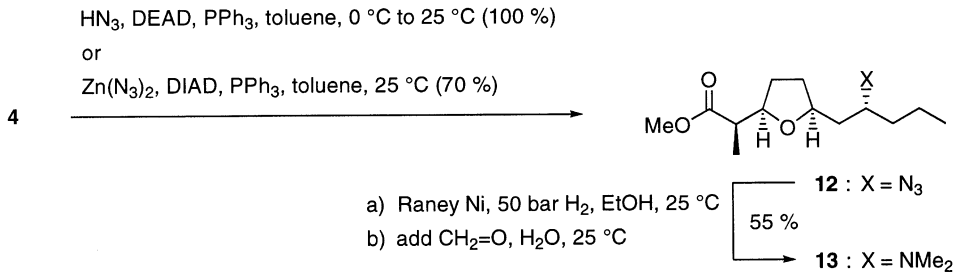


Scheme 4.

Ozonolysis of the major sultone **6a** followed by eliminative workup[5a] delivered the expected hemi-acetal **8** as a single stereoisomer in excellent yield (Scheme 4). Crucial to the successful execution of this transformation was to keep the ozonation time as short as possible and to conduct the acetylation/elimination of the intermediate peroxy hemi-acetal at reflux temperature. Remarkably, only the same stereoisomer **8** was obtained from the minor sultone **6b** under these conditions as well. This result is readily rationalized through an equilibration of the corresponding γ-hydroxy ketone **10**, which should be very prone to epimerization at C(5) (pamamycin numbering) due to the presence of two adjacent electron-withdrawing groups. Once an (*S*) configuration is set up at C(5), recyclization indeed should lead to hemi-acetal **8** with a *cis* fusion between five- and six-membered ring. In the diastereomer **8** isolated, all carbon substituents can occupy an equatorial position on a chair δ-sultone, whereas at least one carbon substituent would have to be axial in the alternative diastereomer **9**. While the relative configuration at C(5) and C(6) (pamamycin numbering) was irrelevant in view of the further synthetic elaboration, formation of a single product made characterization easier. Treatment of hemi-acetal **8** with thiophenol in the presence of trifluoroborane not only effected lactol *S*,*O*-acetal interchange, but simultaneously cleaved the silyl ether on the side chain[9] to give alcohol **11**.

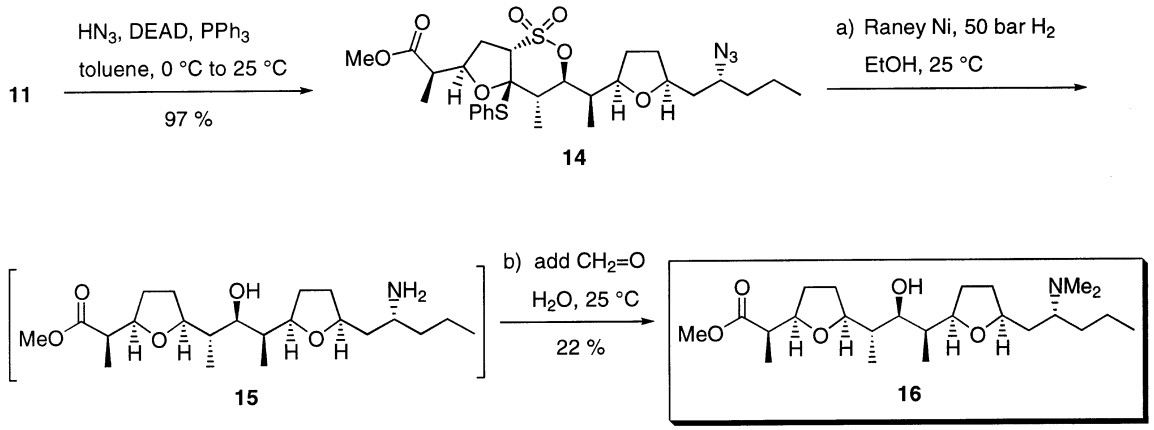
In order to find suitable conditions for the introduction of the requisite dimethylamino moiety with inversion of configuration that might be coupled in a tandem fashion with the reductive sultone cleavage, a model experiment was performed (Scheme 5). To this end, methyl ester **4**[5a] was first subjected to a Mitsunobu reaction[10] with either hydrazoic acid or zinc azide. Using hydrazoic acid as azide source turned out to be superior with respect to both yield and reaction time (1 h versus 2 days with zinc azide). Upon application of our standard conditions for

reductive sultone desulfurization[5a] to the resultant product **12** followed by addition of a 35% aqueous formaldehyde solution to the reaction mixture, a smooth azide reduction and subsequent double reductive alkylation[11] of the intermediate primary amine took place to deliver the dimethylamino product **13**.[4h]



Scheme 5.

Similarly, a Mitsunobu reaction of *S,O*-acetal **11** with hydrazoic acid efficiently introduced the nitrogen function of **14** with clean inversion of configuration (Scheme 6). Gratifyingly, treatment of azide **14** under the conditions used for **12** indeed directly provided the desired methyl ester **16**[1e,2b,12] ($[\alpha]_D^{30} = -33.4$ (*c* 0.99, CH_2Cl_2)) of the larger fragment of pamamycin-607 (**1**) as a single stereoisomer. Further optimization of this reaction cascade as well as coupling of fragments **2** and **3** to give pamamycin-607 (**1**) is currently being investigated and will be reported in due course.



Scheme 6.

Acknowledgements

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12. ^{1}H NMR and mass spectral data of synthetic **16** are identical to the data reported for **16** derived from natural pamamycin-607 (**1**) by chemical degradation (see Ref. 1e, 2b).