Pergamon

Tetrahedron Letters 41 (2000) 4347–4351

TETRAHEDRON LETTERS

A sultone approach to the C(1)–C(18) moiety of pamamycin-607†

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Received 17 March 2000; accepted 12 April 2000

Abstract

A highly advanced enantiomerically pure C(1)–C(18) precursor of the larger fragment of the macrodiolide pamamycin-607 has been synthesized. The stereotriad C(7)–C(9) between the two heterocyclic rings of the target was generated using a diastereoselective hydroboration controlled by minimization of allylic 1,3-strain.

Keywords: antibiotics; Diels–Alder reactions; sultones; hydroboration.

The pamamycins are a group of 16-membered macrodiolides that have been isolated from *Streptomyces alboniger* and *Streptomyces aurantiacus*. These compounds display interesting autoregulatory, antibiotic, and anionophoric activities.[1] Pamamycin-607 (**1**)[2,3] is especially intriguing for its potent activity against gram-positive bacteria including multiple antibiotic-resistant strains of *Mycobacterium tuberculosis*[1] as well as against phytopathogenic fungi.[1,2b]

Whereas several groups have disclosed synthetic routes to different moieties of pamamycin-607 (**1**),[4,5] a total synthesis of **1** has not been published yet. Our retrosynthetic analysis of **1** (Scheme 1) relies on an iterative application of a methodology[6] developed for the synthesis of actic acids and analogs. According to this plan, we have recently communicated a short and highly enantioselective access to the methyl ester **5** as an intermediate for the larger fragment **2** and the methyl ester of the complete smaller fragment **3** from furan and 2-bromo-4-methylfuran, respectively.[5] While the C(1)–C(8) portion of **2** should be available from hydroxyalkylfuran **4** using a reaction sequence similar to the one that was successful for the synthesis of **3** and **5**, the selective generation of the stereotriad C(7)–C(9) (pamamycin numbering) between the two heterocyclic rings of **4** presents an extra challenge.

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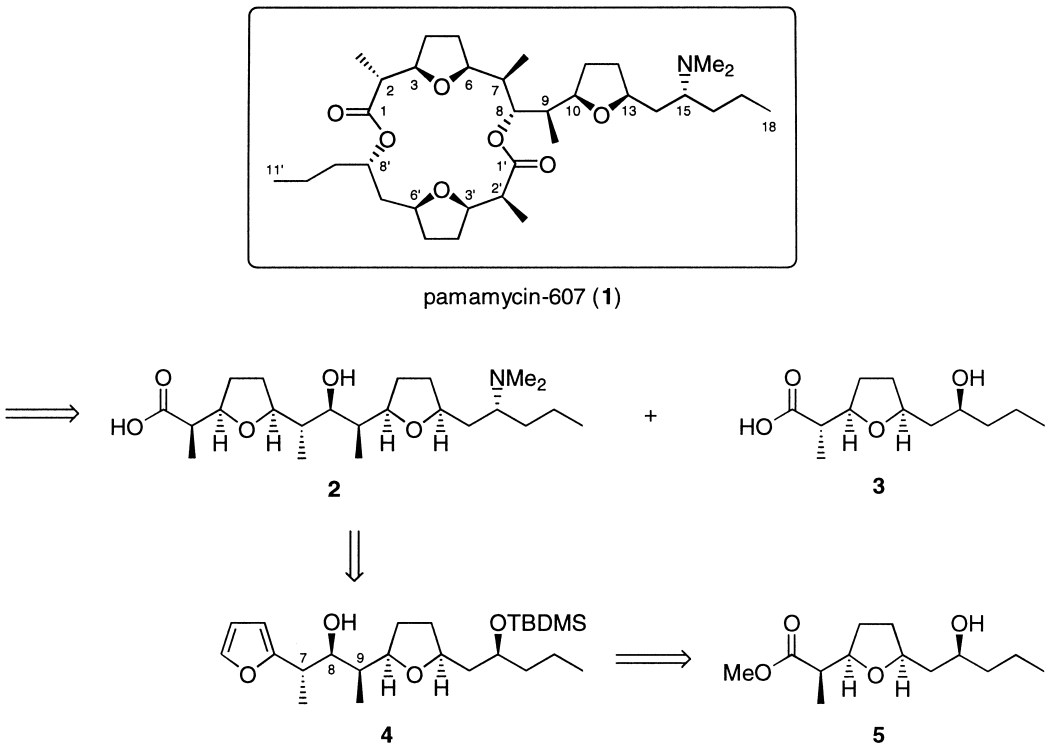
† In memoriam Professor Eberhard Steckhan.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00659-6

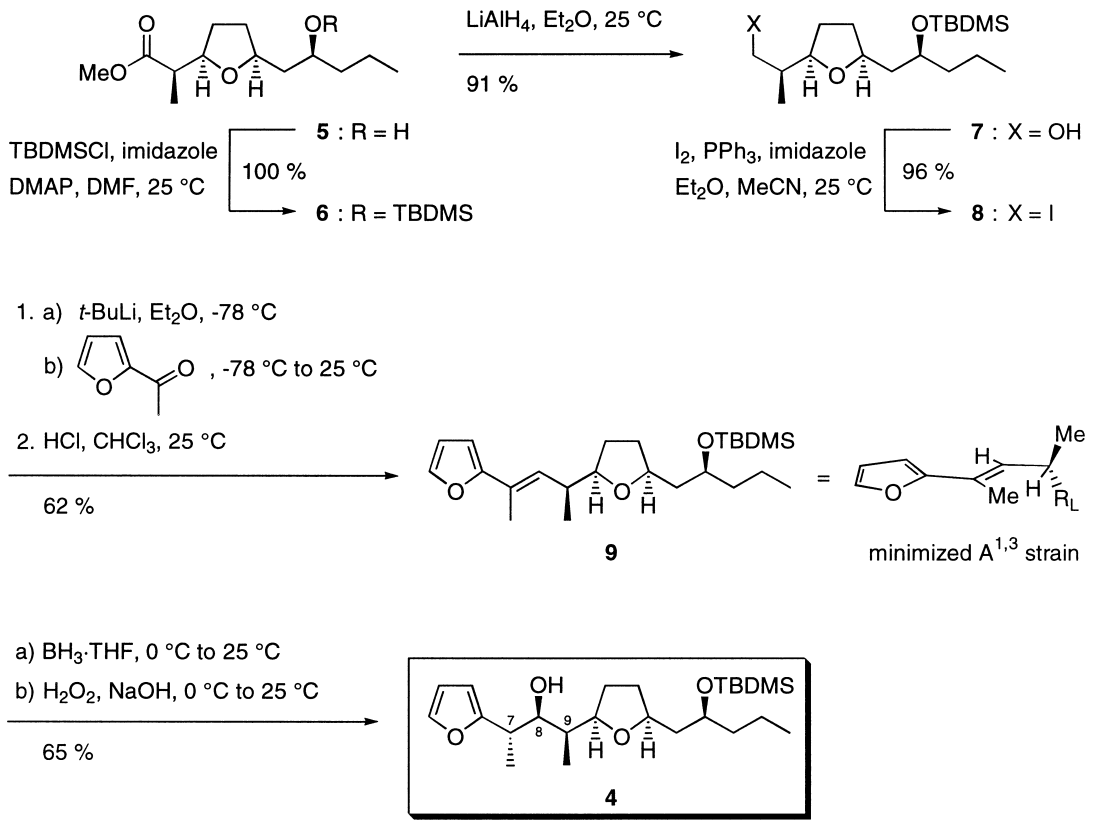


Scheme 1.

Here we report an efficient solution to this problem as well as the smooth intramolecular Diels–Alder reaction of the vinylsulfonate derived from the crucial hydroxyalkylfuran **4** to give a highly advanced C(1)–C(18) precursor of the larger fragment **2**.

As illustrated in Scheme 2, silylation of the hydroxyl group of **5** with *tert*-butyldimethylchlorosilane followed by reduction of the ester function in **6** delivered the mono-protected diol **7** in excellent yield. Conversion[7] of **7** to the iodide **8** followed by halogen–lithium exchange[8] and subsequent addition of 2-acetylfuran to the resultant organolithium intermediate yielded two diastereomeric tertiary alcohols (*dr* = 1:1). Upon stirring a chloroform solution of this mixture with catalytic amounts of concentrated aqueous hydrogen chloride for a few minutes at room temperature, the (*E*) olefin **9** was formed with complete diastereoselectivity.

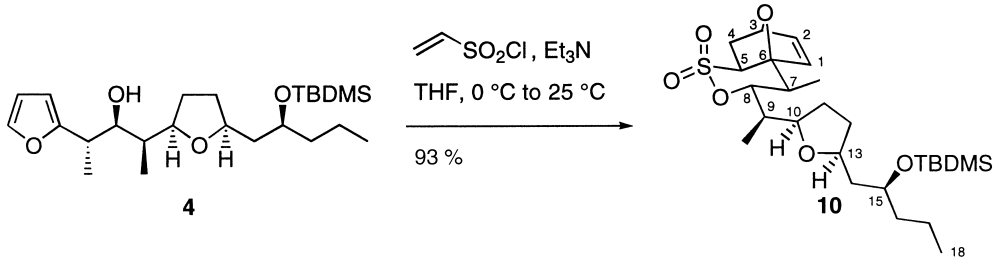
We envisioned to exploit the preferred conformation of this trisubstituted olefin dictated by minimization of allylic 1,3-strain[9,10] in order to effect a diastereoselective hydroboration/oxidation to the key hydroxyalkylfuran **4**. A strong NOE between the vinylic methyl group and the allylic hydrogen atom supported the assumption that **9** adopts the depicted conformation. Thus, a borane should preferentially approach the olefin from the top face in order to avoid non-bonding interactions with the larger tetrahydrofuranyl substituent R_L on the stereogenic allylic carbon. Indeed, hydroboration of **9** followed by standard oxidative workup delivered largely one stereoisomer that was isolated in good yield. Since the ^1H, ^1H coupling pattern within the stereotriad C(7)–C(9) (pamamycin numbering; **4**: H-8, δ 4.00, dd, $J_{8,9} = 1.9$ Hz, $J_{8,7} = 8.8$ Hz) fitted very well the corresponding couplings observed for pamamycin-607 (H-8, δ 4.99, dd, $J_{8,9} = 0.9$ Hz, $J_{8,7} = 10.8$ Hz) and the methyl ester of the larger fragment **2** (H-8, δ 3.76, dd, $J_{8,9} = 1.8$ Hz, $J_{8,7} = 9.7$ Hz),[2e] we tentatively



Scheme 2.

assigned the desired configuration to this major product **4**. Thus, we were ready to enter the second iterative cycle of our sultone route to actic acids and analogs.[5,6]

Treatment of hydroxyalkylfuran **4** with vinylsulfonyl chloride smoothly produced a single sultone **10** via tandem esterification/cycloaddition[5,6] in high yield (Scheme 3). Whereas the enantiomerically pure compound **10** ($[\alpha]_D^{25} = -9.2$ (*c* 0.95, CH_2Cl_2)) did not crystallize, *rac*-**10** prepared analogously from *rac*-1,2-epoxypentane[5] gave suitable crystals that allowed elucidation of its relative configuration by X-ray diffraction.



Scheme 3.

Next to proving the formation of an *exo* sultone with equatorial orientation of both alkyl substituents on a chair δ-sultone, this analysis (Fig. 1)[11,12] also unambiguously confirmed the anticipated stereochemical course of the preceding hydroboration/oxidation step. In sultone **10**, all carbon atoms of the backbone of the larger fragment **2** have been assembled (see pamamycin numbering of **10**) except for the C(2) methyl group, which is to be introduced during the following tandem elimination/alkoxide-directed 1,6-addition.[5,6] Since the requisite *N*,*N*-dimethylamino group will be attached with inversion of configuration, seven of the nine stereogenic centers present in **2** are already set up correctly. Further elaboration of sultone **10** to **2** according to our general access to actic acids and analogs is currently being investigated and will be reported in due course.

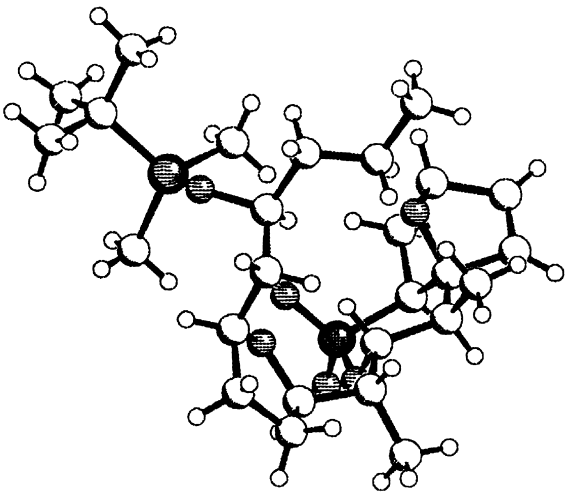


Figure 1. [11,12]

Acknowledgements

Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank the BASF AG and the ASTA Medica AG for generous gifts of chemicals.

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