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Toward the synthesis of pamamycin-607

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Abstract

Using sultone chemistry, a short and highly enantioselective synthesis of an advanced precursor for the larger hydroxy acid moiety and of the complete smaller hydroxy acid portion of the macrodiolide antibiotic pamamycin-607 has been accomplished.

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

Sultones derived from vinylsulfonates of hydroxyalkyl substituted 1,3-dienes via intramolecular Diels–Alder reaction have proven to be versatile intermediates for organic synthesis.[1] Using sultone chemistry, we have recently developed a highly stereoselective and flexible synthesis of actic acids **1** that is not only applicable to the naturally occurring macrotetrolide subunits[2] with R^1=Me, Et, *i*-Pr and R^2=Me, but allows a further variation of the substituents R^1 and R^2 in a straightforward manner. Scheme 1 illustrates how the hydroxy acids **1** can be assembled from four simple building blocks: furan, an epoxide, vinylsulfonyl chloride, and an organolithium reagent. Moreover, an enantioselective synthesis is at hand, since a large variety of the requisite enantiomerically pure epoxides is readily available in both enantiomeric forms.[3] Our sultone route to **1** was first exemplified for racemic nonactic acid (R^1, R^2=Me). Due to the extensive application of sequential transformations, only six steps were needed to secure methyl nonactate from furan.[4]

Here, we report a related approach toward pamamycin-607 (**2**).[5,6] The pamamycins are a group of 16-membered macrodiolides isolated from *Streptomyces alboniger* and *Streptomyces aurantiacus*, which display pronounced autoregulatory, antibiotic, and anionophoric activities.[7] Pamamycin-607 is especially interesting for its potent activity against Gram-positive bacteria including multiple antibiotic-resistant strains of *Mycobacterium tuberculosis*[7] as well as against some phytopathogenic fungi.[5b,7] Due to these biological properties and challenged by its unique structure, several groups have developed routes to different moieties of pamamycin-607,[8] while a total synthesis of **2** has not been reported yet.

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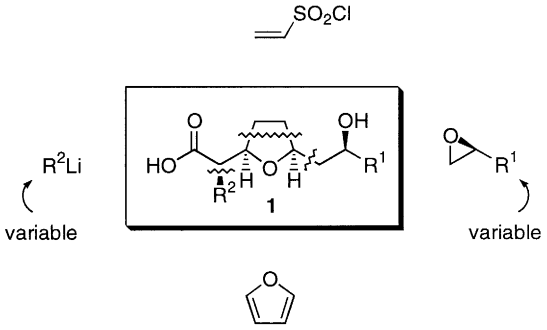
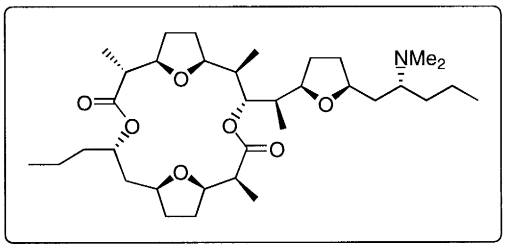
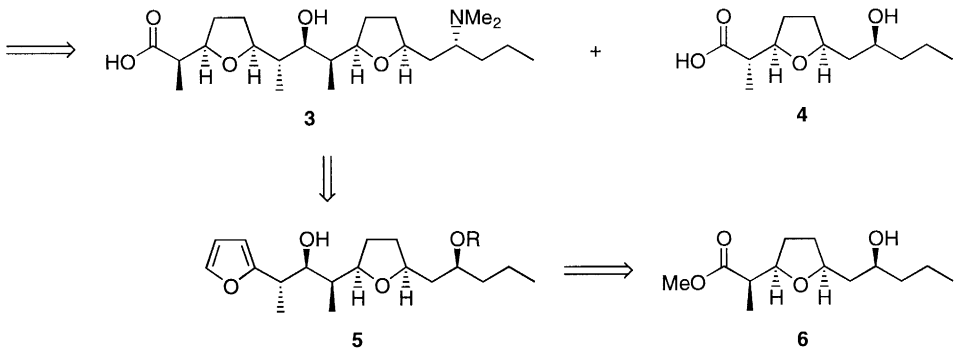


Scheme 1.

The macrocycle **2** is composed of two hydroxy acids, a larger fragment **3** and a smaller fragment **4** (Scheme 2). We view the larger fragment **3** as a substituted actic acid analog, which should be available by our general route to actic acids from hydroxyalkylfuran **5**. This precursor itself is disconnected retrosynthetically to the methyl ester **6** of yet another actic acid analog. Following the building block assembly depicted in Scheme 1, we have recently prepared the enantiomerically pure methyl ester **6** (Scheme 3).

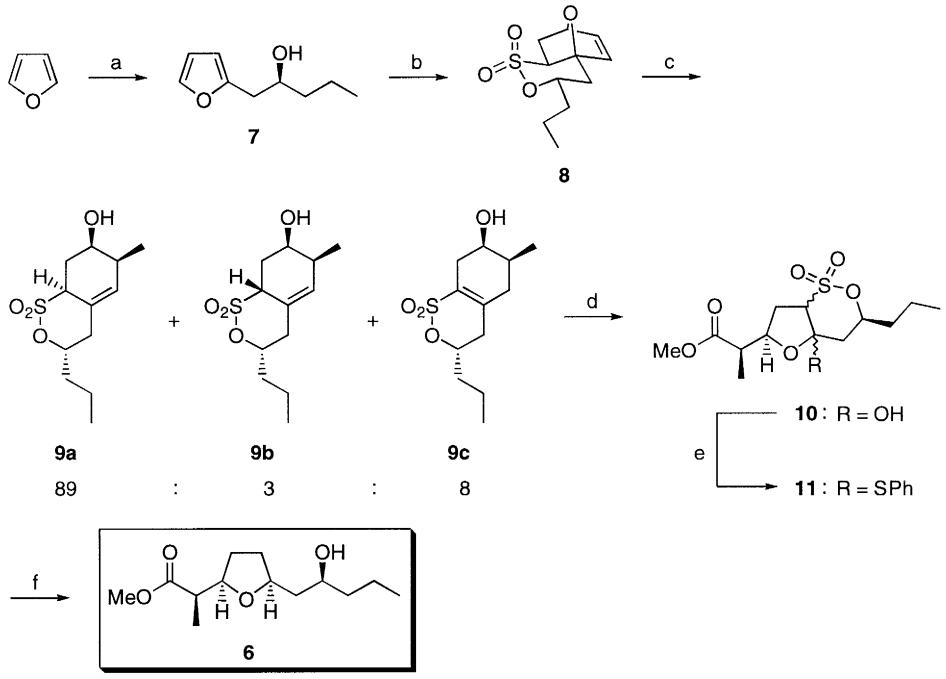


pamamycin-607 (**2**)



Scheme 2.

Alcohol **7**, readily available from furan and (*S*)-1,2-epoxypentane[9] reacted with vinylsulfonyl chloride to give sultone **8** by a tandem esterification/cycloaddition with complete diastereoselectivity. Subsequent treatment of **8** with 2 equivalents of methyllithium induced a tandem elimination/alkoxide-directed 1,6-addition[10] to yield the bicyclic compounds **9a**–**c**. Ozonolysis of this mixture, followed by eliminative workup afforded two diastereomeric hemi-acetals **10**. Only the trisubstituted olefins **9a** and **9b** are attacked by ozone, while the vinylic sultone **9c** can easily be separated. A Lewis acid-catalyzed exchange of the hydroxyl group in **10** against a phenylthio group in **11** then set the stage for a tandem reductive elimination/hydrogenation with Raney nickel to give **6** ($[\alpha]^{25}_{D}=-23.5$ (*c* 1.43, CH_2Cl_2)) via a single



Scheme 3. (a) (i) *n*-BuLi, THF, −78°C to −15°C, (ii) (*S*)-1,2-epoxypentane, −15°C to 25°C, 77%; (b) CH_2=$CHSO_2Cl$, NEt_3, THF, 0°C to 25°C, 81%; (c) (i) MeLi, THF, −78°C to 0°C; (ii) NH_4Cl, H_2O, −78°C to 25°C, 66%; (d) (i) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78°C; (ii) Ac_2O, pyridine, CH_2Cl_2, 25°C, 61%; (e) PhSH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 25°C, 82%; (f) Raney Ni (W2), 50 bar H_2, EtOH, 25°C, 54%

2,3-dihydrofuran. The conversion of **11** to **6** proceeds without adding hydrogen gas, too.[4] However, we recently found that conducting these desulfurizations under hydrogen pressure is superior in terms of reproducibility,[11] while the diastereoselectivity (**6**:6-*epi*-**6**=18:1) is not affected at all.

Using a similar strategy, we prepared the complete C-2 epimeric smaller fragment **4** as well (Scheme 4). To this end, sultone **14** was efficiently generated with complete diastereoselectivity from 2-bromo-4-methylfuran (**12**)[12] via intramolecular Diels–Alder reaction of the vinylsulfonate derived from alcohol **13**. The configuration of **14** was unambiguously established by X-ray diffraction analysis.[13] Upon subjecting **14** to a tandem elimination/alkoxide-directed 1,6-hydride addition,[14] the bicyclic compounds **15a**–**c** with the required *trans* relationship of the hydroxyl and the methyl substituent were isolated in good yield. Application of the reaction sequence tandem ozonolysis/cyclization, Lewis acid-catalyzed hydroxyl/phenylthio exchange, and tandem reductive elimination/hydrogenation already used for the synthesis of **6** finally led to **18** ($[\alpha]^{25}_D$=+29.5 (*c* 1.23, $CHCl_3$)), the methyl ester of the smaller fragment **4** with high diastereoselectivity (**18**:6-*epi*-**18**=17:1) for the final step. Further elaboration of ester **6** to the larger fragment **3** of pamamycin-607 (**2**) via hydroxyalkylfuran **5** is currently being investigated and will be reported in due course.

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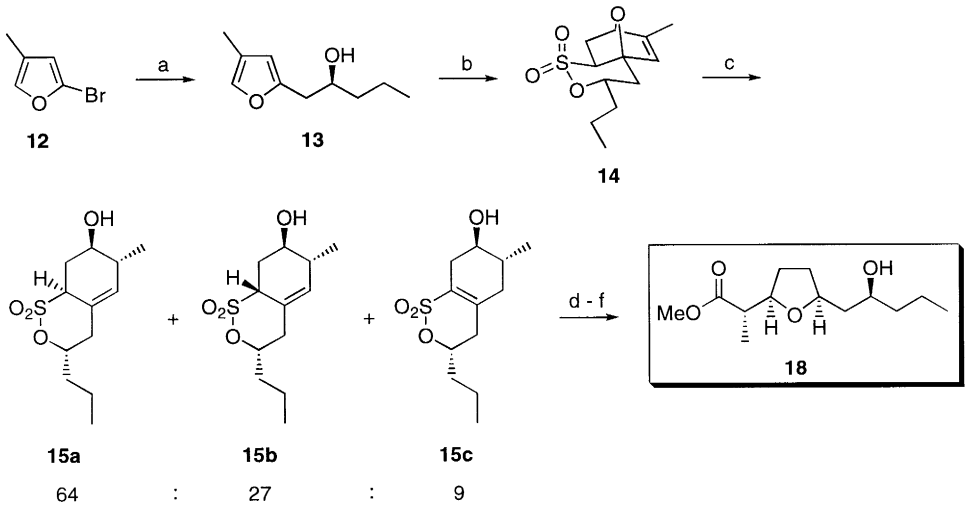

Scheme 4. (i) *t*-BuLi, THF, −78°C to −15°C, (ii) (*S*)-1,2-epoxypentane, −15°C to 25°C; 92%; (b) $CH_2{=}CHSO_2Cl$, NEt_3, THF, 0°C to 25°C, 94%; (c) (i) Red-Al®, toluene, 25°C; (ii) NH_4Cl, H_2O, 25°C, 59%; (d) (i) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78°C; (ii) Ac_2O, pyridine, CH_2Cl_2, 25°C, 57%; (e) PhSH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 25°C, 84%; (f) Raney Ni (W2), 50 bar H_2, EtOH, 25°C, 51%

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