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A shortcut to the smaller fragment of pamamycin-607†

Heiko Bernsmann,[a] Margit Gruner,[a] Roland Fröhlich[b] and Peter Metz[a,*]

[a]*Institut für Organische Chemie, Technische Universität Dresden, Mommsenstraße 13, D-01062 Dresden, Germany*
[b]*Organisch-Chemisches Institut, Universität Münster, Corrensstraße 40, D-48149 Münster, Germany*

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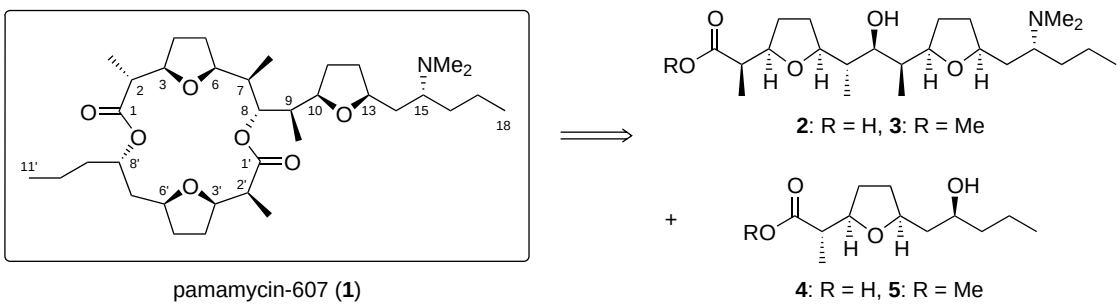
Abstract—Starting from a key intermediate for the synthesis of the larger hydroxy acid constituent of pamamycin-607 (**1**), an efficient three-step route to the methyl ester of the smaller fragment of **1** involving a Yamaguchi lactonization with concomitant C(2) epimerization was developed. Alternatively, the methyl ester of the smaller hydroxy acid portion of **1** was prepared by direct C(2) epimerization. © 2001 Elsevier Science Ltd. All rights reserved.

In the course of our studies[1] toward the enantioselective total synthesis of the macrodiolide antibiotic pamamycin-607 (**1**)[2–4] (Scheme 1), we have recently communicated a straightforward access to the methyl ester **3**[1a] of the larger hydroxy acid constituent **2** from furan via sultone methodology.[5] Using a similar strategy, we also developed a six-step route to the methyl ester **5** of the smaller fragment **4** from 2-bromo-4-methylfuran.[1c,d] Here we report two alternative syntheses of methyl ester **5** from an intermediate of our sequence to **3**, both of which provide a considerable shortcut to the smaller fragment of pamamycin-607 (**1**).

Due to our general interest in the chemistry of actic acids,[6] we investigated the Yamaguchi lactonization[7] of the enantiopure hydroxy acid **7a**, itself readily available by saponification[8] of the corresponding methyl ester **6a** that we used as a key precursor of **3**[1a] (Scheme 2). Cyclization under high dilution conditions[7,9] proceeded smoothly to give a mixture of two diastereomeric lactones **8a** and **9a**. While the formation of medium-sized lactones[10,11] is often hampered by competing diolide or oligomer production, the conformational constraint imposed by the 2,5-*cis* disubstituted tetrahydrofuran moiety is probably responsible for the high combined yield of lactones obtained in this case. To our surprise, the major lactone **8a** had undergone epimerization at C(2), which was clearly revealed by a 2D NOESY investigation of both lactone diastereomers **8a** and **9a**.[12] A similar observation was made for the Yamaguchi lactonization of racemic nonactic acid (*rac*-**7b**) prepared from racemic methyl nonactate (*rac*-**6b**).[6b,c] Again, the major resulting lactone (*rac*-**8b**) turned out to be epimerized at C(2),[12] which was unambiguously proven by X-ray diffraction (Fig. 1).[13,14]

While partial epimerization during Yamaguchi lactonizations had been reported earlier,[11b,15] the high degree of inversion observed here is unprecedented to the best of our knowledge. Nevertheless, this unex-



Scheme 1.

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* Corresponding author. Tel.: +49-351-463-7006; fax: +49-351-463-3162; e-mail: metz@coch01.chm.tu-dresden.de
† Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday.

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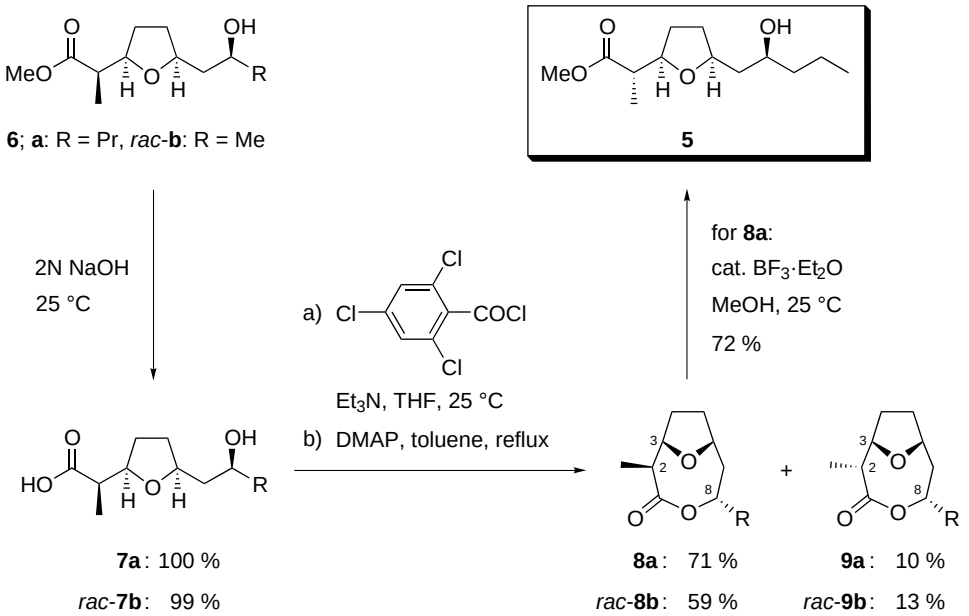


Scheme 2.

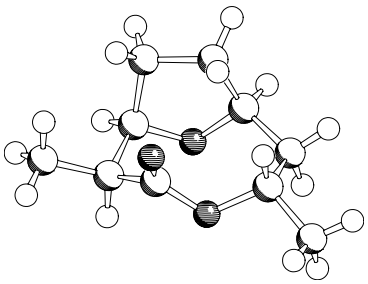


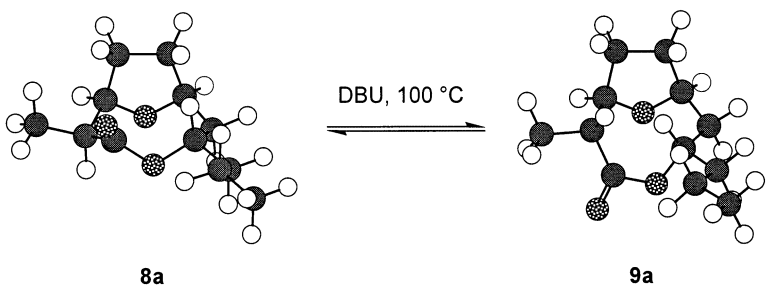
Figure 1. Crystal structure of lactone *rac*-**8b**; arbitrarily chosen enantiomer.[13,14]

pected result could be nicely exploited for our synthetic purposes. Subjecting the major lactone **8a**, easily separated from **9a** by flash chromatography,[16] to a Lewis acid catalyzed ring opening methanolysis[17] directly provided the isomerically pure methyl ester **5** of the smaller fragment. Since we prepare **6a** as a precursor for the larger fragment of **1** anyway,[1a] only *three extra steps* are necessary this way to additionally secure **5**.

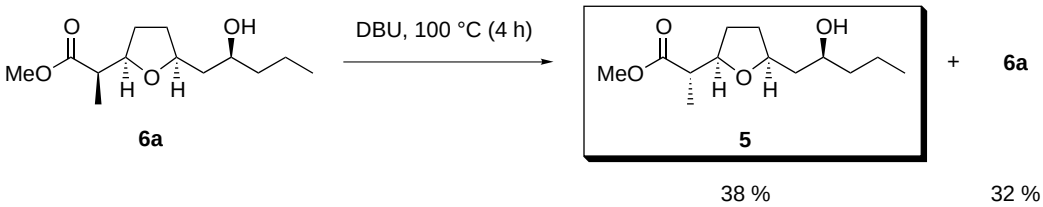
We first suspected this stereochemical result was due to a basic equilibration of the lactones subsequent to the cyclization. However, semi-empirical calculations using PM3[18] (Scheme 3) of both epimers **8a** (–146.31 kcal/mol) and **9a** (–149.39 kcal/mol) pointed to a contrathermodynamic formation of these compounds. Indeed, these calculations were experimentally verified by exposing the major epimer **8a** to a thermodynamically controlled base catalyzed equilibration in DBU at 100°C (Scheme 3, Table 1). After 24 h, a 19:81 mixture of lactones favoring the thermodynamically more stable epimer **9a** was isolated in 74% combined yield.

Thus, the Yamaguchi cyclization of **7a** to give a 71:10 mixture of **8a** and **9a** proceeds under kinetic control. The configurational inversion at C(2) is either due to an equilibration at the stage of the mixed anhydride coupled with a faster cyclization of the (2*S*) compound or to the intermediate formation of a ketene, as has been observed for Mukaiyama lactonizations,[19] coupled with a stereoselective protonation of the enol resulting from a hydroxy ketene cyclization.[20] Interestingly, no epimerization at all was observed for the Yamaguchi lactonization of the smaller fragment **4**[21] under the conditions listed in Scheme 2, and **8a** was obtained as the only cyclized product in 82% yield.

Encouraged by the efficient epimerization of **8a** to **9a**, we investigated if a direct epimerization of methyl ester **6a** to **5** was possible as well. To our delight, using conditions similar to those reported to be successful for



Scheme 3. Equilibration of lactone **8a**.[18]



Scheme 4.

Table 1. Equilibration of lactone **8a**[a]

Time (h)	Ratio **8a**:**9a**[b]
0	100:0
3	91:9
5	84:16
11	62:38
14	47:53
24[c]	19:81

[a] **8a** (1.34 mmol), DBU (3.75 mmol), 100°C.
[b] Isomeric ratio determined by GC.
[c] Work-up after 24 h yielded 60% **9a** and 14% **8a**.

methyl nonactate,[8c,22] a 1.2:1 mixture of the two C(2) epimers was obtained rather cleanly after a short reaction time, from which the desired isomer **5** could be isolated in 38% yield via careful flash chromatography[23] (Scheme 4).

Obviously, there is hardly any ring opening of the tetrahydrofuran by β-elimination and subsequent stereorandom recyclization.[24] Though the three-step sequence depicted in Scheme 2 affords a higher total yield of **5** from **6a**, only *one extra step* is required for the synthesis of the smaller fragment's methyl ester **5** via the DBU mediated isomerization depicted in Scheme 4.

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