

**STEREOSELECTIVE SYNTHESSES OF 2,5-DISUBSTITUTED  
HYDROXYFURAN DERIVATIVES AS SYNTHON OF POLYETHER  
ANTIBIOTICS<sup>†</sup>**

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**Abstract-** Stereoselective syntheses of optically active 2,5-dialkyltetrahydrofurans (**8**), (**11**) and (**12**), which correspond to a central moiety of pamamycin 607, have been achieved on the basis of lactone-ring transformation *via* a phenonium ion, intramolecular Friedel-Crafts reaction, oxidative decomposition of an aromatic ring and differentiation of two ester groups by a chemical or chemo-enzymatic method.

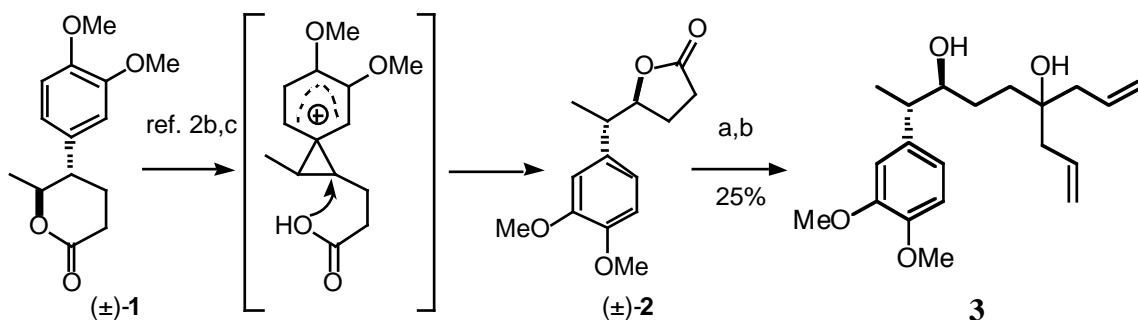
Nature abounds with compounds containing 2,5-disubstituted tetrahydrofurans as polyether antibiotics. Since these compounds are important in many biological processes, there is much interest in stereoselective preparation of such a moiety.<sup>1</sup> Recently, we developed a lactone-ring transformation of  $\alpha$ -lactone ( $\pm$ )-**1** into  $\beta$ -lactone ( $\pm$ )-**2** *via* a phenonium ion proposed by Cram (Scheme 1).<sup>2,3</sup> It is noteworthy that the benzylic asymmetric center on the ring can be stereospecifically transferred to a side chain in this ring transformation. The successful conversion stimulated us to carry out stereoselective installation of the second alkyl side chain with a view to developing a new route for synthesis of polyether antibiotics. Our initial attempt to install the second alkyl chain into the 5-membered ring was carried out using Kishi's method,<sup>4</sup> which was applied to the preparation of *cis*-2,6-disubstituted tetrahydropyran. Alkylation of ( $\pm$ )-**2** with allyl Grignard reagent followed by reduction with  $\text{Et}_3\text{SiH}/\text{BF}_3 \cdot \text{Et}_2\text{O}$  afforded diol (**3**) in low yield.

Faced with this problem, we decided to use an alternative method for installation of the second side chain. We report here the stereoselective syntheses of optically active hydrofurans (**8**), (**11**) and (**12**), which correspond to a central moiety of pamamycin 607 isolated from *S. alboniger* IFO 12738,<sup>6,7</sup> *via* lactone-ring transformation, intramolecular Friedel-Crafts reaction and decomposition of an aromatic ring.

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<sup>†</sup> This paper is dedicated to Prof. Yuichi Kanaoka in memory of his 75th birthday.

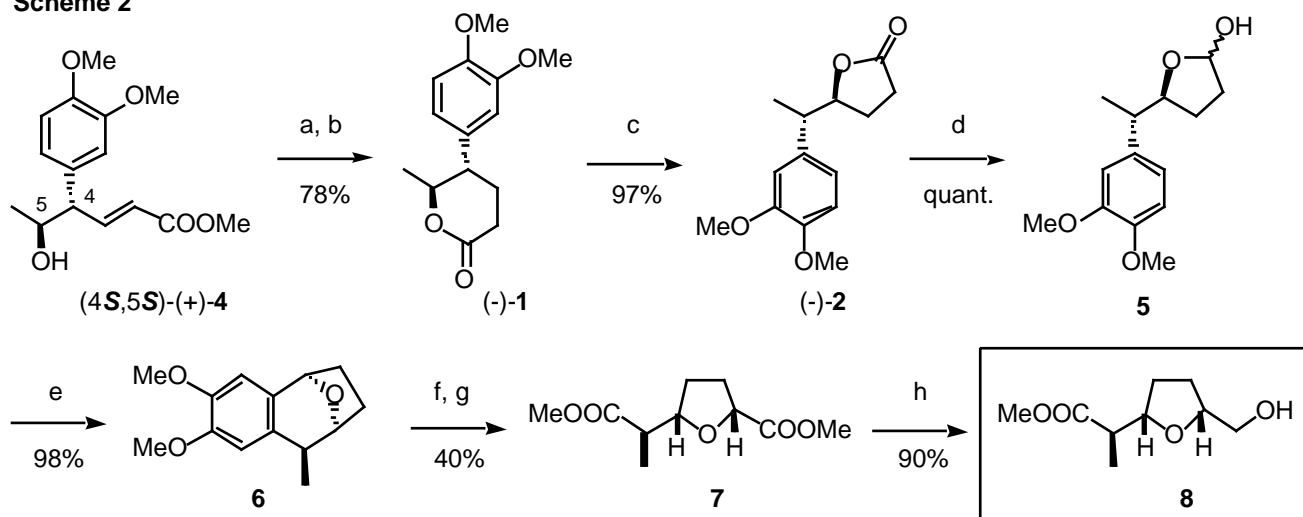
**Scheme 1**



Reagents: (a)  $\text{CH}_2=\text{CHCH}_2\text{MgBr}$ ,  $-78^\circ\text{C}$  (b)  $\text{Et}_3\text{SiH}$ ,  $\text{BF}_3\cdot\text{Et}_2\text{O}$

At first, we prepared optically active  $\alpha$ -lactone  $(-)$ -**1**<sup>5</sup> by hydrogenation of  $(4S,5S)$ -**4**<sup>8</sup> and subsequent acidic lactonization. Treatment of  $(-)$ -**1** with  $\text{TsOH}\cdot\text{H}_2\text{O}$  in  $\text{MeNO}_2$  at  $70^\circ\text{C}$  gave  $(-)$ -**2**<sup>5</sup> in 97% yield. After reduction of  $(-)$ -**2** with DIBALH, treatment of the resulting lactol (**5**)<sup>5</sup> with  $\text{BF}_3\cdot\text{Et}_2\text{O}$  resulted in an intramolecular Friedel-Crafts reaction,<sup>9</sup> giving a bridgehead tricyclic compound (**6**)<sup>5</sup> in 98% yield. The structure of **6** was determined by  $^1\text{H}$  and  $^{13}\text{C}$  NMR and other spectral data. The  $^1\text{H}$  NMR spectrum exhibited only two aromatic singlet resonances ( $\delta$  6.72, 6.48) and benzyl methine proton resonance ( $\delta$  4.95,  $J = 5.9$  Hz). A newly generated asymmetric center could be completely controlled by use of the nature of the bridgehead ring. Next, we attempted the oxidative decomposition of the aromatic ring using Sharpless's method.<sup>10</sup> Treatment of **6** with a catalytic amount of  $\text{RuCl}_3$  in the presence of  $\text{NaIO}_4$  in  $\text{MeCN}$ ,  $\text{CCl}_4$  and  $\text{H}_2\text{O}$  followed by methylation with  $\text{CH}_2\text{N}_2$  produced *cis*-diester (**7**)<sup>5</sup> in 40% yield (2 steps).

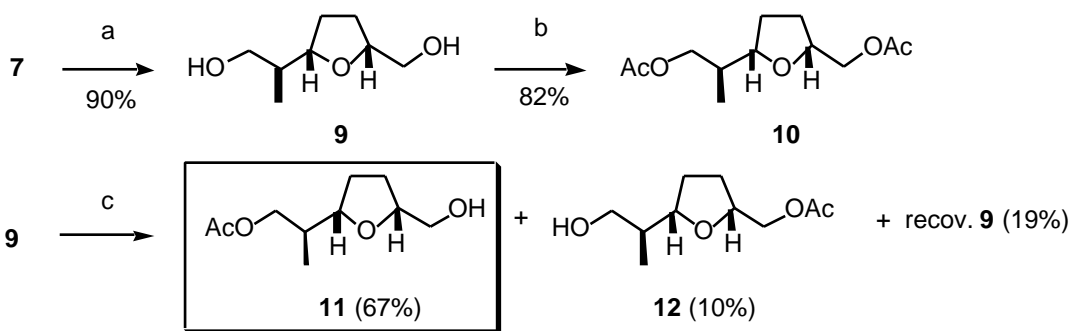
**Scheme 2**



Reagents: (a) 20%  $\text{Pd}(\text{OH})_2\text{-C}$ ,  $\text{H}_2$  (b) 2N  $\text{HCl}$  (c)  $p\text{-TsOH}\cdot\text{H}_2\text{O}$ ,  $\text{MeNO}_2$ ,  $70^\circ\text{C}$  (d) DIBALH,  $-78^\circ\text{C}$  (e)  $\text{BF}_3\cdot\text{Et}_2\text{O}$ ,  $\text{MeCN}$ ,  $0^\circ\text{C}$  (f)  $\text{RuCl}_3\cdot n\text{H}_2\text{O}$ ,  $\text{NaIO}_4$ ,  $\text{MeCN}$ ,  $\text{CCl}_4$ ,  $\text{H}_2\text{O}$ ,  $0^\circ\text{C}$  (g)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$  (h)  $\text{NaBH}_4$ ,  $\text{MeOH}$ ,  $0^\circ\text{C}$

The final step toward our goal was differentiation of the two ester groups of **7**. We used two methods. One of them was a chemical method. When **7** was treated with NaBH<sub>4</sub> in MeOH at 0 °C, reduction proceeded regioselectively to give **8**<sup>5</sup> in 90% yield.<sup>11</sup> As an alternative effort, we confirmed the regioselective enzymatic hydrolysis<sup>12,13</sup> of diacetate (**10**). Dimethyl ester (**7**) was converted into **10**<sup>5</sup> by LAH reduction of **7** followed by conventional acetylation. When **10** was treated with lipase Amamo PS (*Pseudomonas* sp.) in phosphate buffer at 33 °C for 4 h, hydrolysis proceeded with fairly good regioselectivity to give monoacetate (**11**)<sup>5</sup> in 67% yield along with **12**<sup>5</sup> (10%). Fortunately, these compounds could be separated by column chromatography with silica gel. Compounds (**8**), (**11**) and (**12**) can be used in the synthetic studies of pamamycin 607.

**Scheme 3**



Reagents: (a) LiAlH<sub>4</sub>, THF, 0 °C (b) Ac<sub>2</sub>O, DMAP, Py, 0 °C (c) lipase Amamo PS, 0.1 M phosphate buffer, 33 °C, 4 h

In conclusion, we synthesized **8**, **11** and **12** based on lactone-ring transformation *via* a phenonium ion, intramolecular Friedel-Crafts reaction, oxidative decomposition of an aromatic ring and differentiation of diester by a chemical or chemo-enzymatic method. Further attempts to convert of the compounds into pamamycin 607 are in progress.

## ACKNOWLEDGEMENTS

We are grateful to the Akiyama Foundation (to S. N.) for its support to a part of this project. We also thank Dr. Yoshihiko Hirose (Amano Pharmaceutical Co., Ltd.) for generous gift of Amamo PS.

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<sup>13</sup>C-NMR (68 MHz, CDCl<sub>3</sub>) 171.12 (s), 80.97 (d), 78.98 (d), 66.78 (t), 65.20 (t), 37.18 (d), 28.79 (t), 27.12 (t), 20.94 (q), 13.01 (q). **12** (colorless oil): [α]<sub>D</sub><sup>20</sup> -11.4° (c = 1.03, CHCl<sub>3</sub>); IR (neat) 3430, 1744 cm<sup>-1</sup>; EI-MS *m/z* 143 (M<sup>+</sup> - CH(CH<sub>3</sub>)CH<sub>2</sub>OH), 129; HR-MS *m/z* 143.0709 (Calcd for C<sub>7</sub>H<sub>11</sub>O<sub>3</sub> (M<sup>+</sup> - CH(CH<sub>3</sub>)CH<sub>2</sub>OH): 143.0708); <sup>1</sup>H-NMR (270 MHz, CDCl<sub>3</sub>) 4.17 (1H, dd, *J* = 10.6, 3.0 Hz), 4.15-3.99 (2H, m), 4.02 (1H, dd, *J* = 10.6, 5.6 Hz), 3.69 (1H, dd, *J* = 10.9, 7.3 Hz), 3.56 (1H, dd, *J* = 10.9, 4.3 Hz), 2.54 (1H, br), 2.13-1.60 (5H, m), 2.08 (3H, s), 0.91 (3H, d, *J* = 7.3 Hz); <sup>13</sup>C-NMR (68 MHz, CDCl<sub>3</sub>) 170.99 (s), 83.36 (d), 76.45 (d), 66.13 (t), 65.86 (t), 37.97 (d), 27.68 (t), 26.68 (t), 20.84 (q), 12.09 (q).

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