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STEREOSELECTIVE SYNTHESES OF 2,5-DISUBSTITUTED HYDROXYFURAN DERIVATIVES AS SYNTHON OF POLYETHER ANTIBIOTICS†

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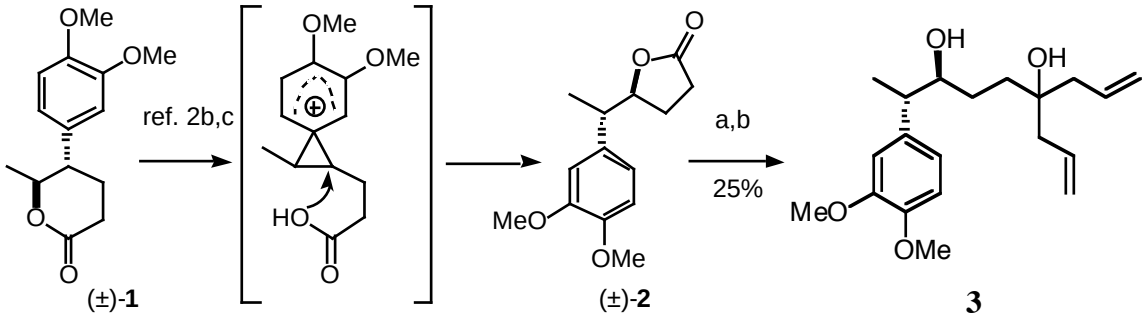
Abstract- Stereoselective syntheses of optically active 2,5-dialkyltetrahydrofurans (**8**), (**11**) and (**12**), which correspond to a central moiety of pamamycin 607, have been achieved on the basis of lactone-ring transformation *via* a phenonium ion, intramolecular Friedel-Crafts reaction, oxidative 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.[1] Recently, we developed a lactone-ring transformation of δ-lactone (±)-(**1**) into γ-lactone (±)-(**2**) *via* a phenonium ion proposed by Cram (Scheme 1).[2,3] 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,[4] which was applied to the preparation of *cis*-2,6-disubstituted tetrahydropyran. Alkylation of (±)-**2** with allyl Grignard reagent followed by reduction with $Et_3SiH/BF_3 \cdot Et_2O$ 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,[6,7] *via* lactone-ring transformation, intramolecular Friedel-Crafts reaction and decomposition of an aromatic ring.

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

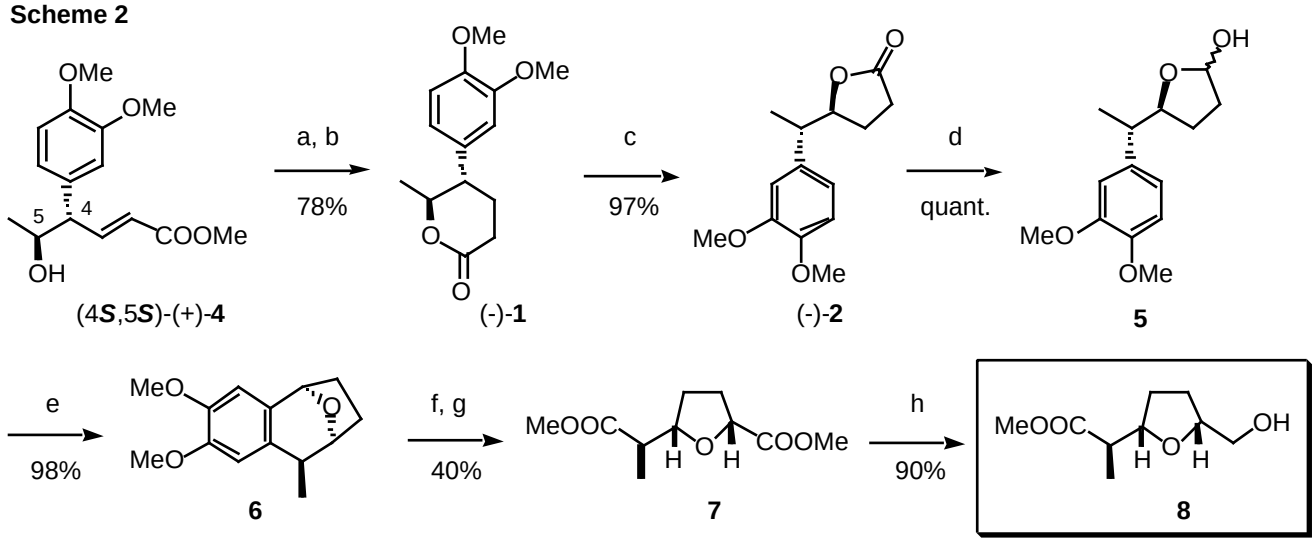
Scheme 1



Reagents: (a) CH_2=$CHCH_2MgBr$, -78˚C (b) Et_3SiH, BF_3•Et_2O

At first, we prepared optically active δ-lactone (-)-(**1**)[5] by hydrogenation of (4*S*,5*S*)-**4**[8] and subsequent acidic lactonization. Treatment of (-)-**1** with TsOH•H_2O in $MeNO_2$ at 70˚C gave (-)-**2**[5] in 97% yield. After reduction of (-)-**2** with DIBALH, treatment of the resulting lactol (**5**)[5] with BF_3•Et_2O resulted in an intramolecular Friedel-Crafts reaction,[9] giving a bridgehead tricyclic compound (**6**)[5] in 98% yield. The structure of **6** was determined by ^{1}H and ^{13}C NMR and other spectral data. The ^{1}H NMR spectrum exhibited only two aromatic singlet resonances (δ 6.72, 6.48) and benzyl methine proton resonance (δ 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.[10] Treatment of **6** with a catalytic amount of $RuCl_3$ in the presence of $NaIO_4$ in MeCN, CCl_4 and H_2O followed by methylation with CH_2N_2 produced *cis*-diester (**7**)[5] in 40% yield (2 steps).

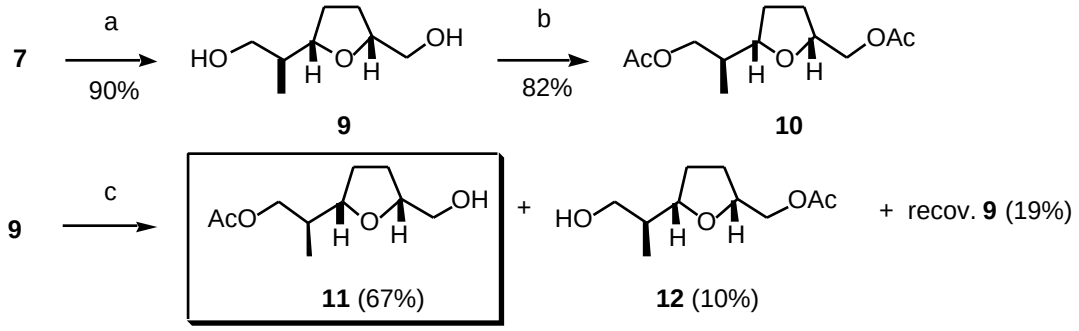
Scheme 2



Reagents: (a) 20%$Pd(OH)_2$-C, H_2 (b) 2N HCl (c) *p*-TsOH•H_2O, $MeNO_2$, 70˚C (d) DIBALH, -78˚C (e) BF_3•Et_2O, MeCN, 0˚C (f) $RuCl_3$•nH_2O, $NaIO_4$, MeCN, CCl_4, H_2O, 0˚C (g) CH_2N_2, Et_2O, 0˚C (h) $NaBH_4$, MeOH, 0˚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 $NaBH_4$ in MeOH at 0˚C, reduction proceeded regioselectively to give **8**[5] in 90% yield.[11] As an alternative effort, we confirmed the regioselective enzymatic hydrolysis[12,13] of diacetate (**10**). Dimethyl ester (**7**) was converted into **10**[5] 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**)[5] in 67% yield along with **12**[5] (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) $LiAlH_4$, THF, 0˚C (b) Ac_2O, DMAP, Py, 0˚C (c) lipase Amano 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.

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5 All new compounds were identified by spectroscopic data. For representative compounds, **6** (white needle): mp 89-91˚C (AcOEt-hexane); $[\alpha]_D^{20}$ –13.4˚ (c = 1.03, $CHCl_3$); EI-MS *m/z* 234 (M^+), 205; HR-MS *m/z* 234.1284 (Calcd for $C_{14}H_{18}O_3$: 234.1255); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 6.72 (1H, s), 6.48 (1H, s), 4.95 (1H, d, *J* = 5.9 Hz), 4.51-4.43 (1H, m), 3.85 (3H, s), 3.84 (3H, s), 3.45-3.32 (1H, m), 2.20-2.03 (1H, m), 1.94-1.83 (3H, m), 1.20 (3H, d, *J* = 7.3 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 148.07 (s), 147.00 (s), 132.23 (s), 128.92 (s), 110.12 (d), 107.24 (d), 79.09 (d), 77.15 (d), 55.97 (q), 55.92 (q), 36.74 (d), 35.69 (t), 22.34 (t), 14.78 (q). **7** (colorless oil): $[\alpha]_D^{20}$ –25.1˚ (c = 1.01, $CHCl_3$); IR (neat) 1738 cm^{-1}; EI-MS *m/z* 185 (M^+- OCH_3), 157; HR-MS *m/z* 185.0807 (Calcd for $C_9H_{13}O_4$ (M^+- OCH_3): 185.0813); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.47 (1H, dd, *J* = 8.2, 4.6 Hz), 4.11 (1H, dt, *J* = 8.2, 6.3 Hz), 3.73 (3H, s), 3.69 (3H, s), 2.72 (1H, quintet, *J* = 7.0 Hz), 2.32-2.15 (1H, m), 2.14-1.97 (2H, m), 1.83-1.66 (1H, m), 1.32 (1H, d, *J* = 7.0 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 174.40 (s), 172.96 (s), 81.83 (d), 76.58 (d), 51.46 (q), 51.13 (q), 44.28 (d), 29.79 (t), 28.56 (t), 13.98 (q). **8** (colorless oil): $[\alpha]_D^{20}$ –36.5˚ (c = 1.00, $CHCl_3$); IR (neat) 3454, 1738 cm^{-1}; EI-MS *m/z* 157 (M^+- CH_2OH), 125; HR-MS *m/z* 157.0860 (Calcd for $C_8H_{13}O_3$ (M^+- CH_2OH): 157.0864); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 4.10-3.98 (2H, m), 3.79-3.67 (1H, m), 3.69 (3H, s), 3.45 (1H, dd, *J* = 11.5, 5.5 Hz), 2.65 (1H, quintet, *J* = 6.9 Hz), 2.25-1.65 (5H, m), 1.23 (3H, d, *J* = 6.9 Hz); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 174.92 (s), 80.69 (d), 79.59 (d), 64.91 (t), 51.63 (q), 44.12 (d), 28.74 (t), 26.82 (t), 13.65 (q). **11** (colorless oil): $[\alpha]_D^{20}$ –4.9˚ (c = 1.27, $CHCl_3$); IR (neat) 3470, 1734 cm^{-1}; EI-MS *m/z* 171 (M^+- CH_2OH), 149; HR-MS *m/z* 171.1028 (Calcd for $C_9H_{15}O_3$ (M^+- CH_2OH): 171.1020); 1H-NMR (270 MHz, $CDCl_3$) δ 4.07 (1H, dd, *J* = 11.2, 6.3 Hz), 3.98 (1H, dd, *J* = 11.2, 6.6 Hz), 4.05-3.94 (1H, m), 3.88-3.78 (1H, m), 3.70 (1H, br d, *J* = 11.2 Hz), 3.48 (1H, dd, *J* = 11.2, 5.9 Hz), 2.06 (3H, s), 2.05-1.87 (3H, m), 1.77-1.56 (3H, m), 1.01 (3H, d, *J* = 6.9 Hz).

^{13}C-NMR (68 MHz, $CDCl_3$) δ 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): $[\alpha]_D^{20}$ –11.4° (c = 1.03, $CHCl_3$); IR (neat) 3430, 1744 cm^{-1}; EI-MS *m/z* 143 (M^+- $CH(CH_3)CH_2OH$), 129; HR-MS *m/z* 143.0709 (Calcd for $C_7H_{11}O_3$ (M^+- $CH(CH_3)CH_2OH$): 143.0708); ^{1}H-NMR (270 MHz, $CDCl_3$) δ 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); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 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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