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TOTAL SYNTHESIS OF D-(+)-SHOWDOMYCIN FROM *SYN*-2,5-DISUBSTITUTED TETRAHYDROFURAN

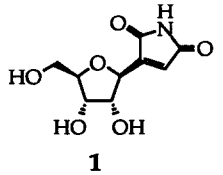
Sung Ho Kang* and Sung Bae Lee

Department of Chemistry, Korea Advanced Institute of Science and Technology,
Taejon 305-701, Korea

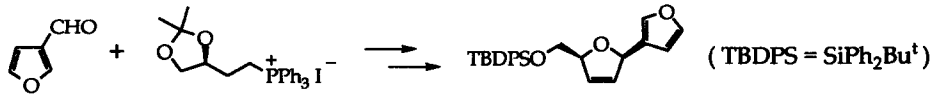
Abstract : D-(+)-Showdomycin, first isolated from *Streptomyces showdoensis*, has been synthesized starting from *syn*-2,5-disubstituted dihydrofuran **3**. The key conversion was the functionalization of 2-thiophenylfuranyl group in **13** into maleic acid moiety in **12**.

Iodoetherification of *trans*-4-(3'-furanyl)-3-butenols in this laboratory has established stereoselective synthetic routes to *syn*- and *anti*-2,5-disubstituted tetrahydrofurans.[1] Elimination reaction of the 3-iodotetrahydrofurans provides 2,5-dihydrofurans regioselectively. Since the dihydrofurans have two endocyclic stereogenic centers, in principle four chiral centers can be introduced to them. Therefore our developed tetrahydrofurans are considered to be of general synthetic utility for tetrahydrofuran-containing natural products.

C-Ribosides have become an increasingly interesting area in organic and medicinal chemistry on account of their potential utility as therapeutic agents such as antiviral, anticancer and anti-HIV drugs.[2] Structurally C-ribosides have more stable glycosidic bond by the isosteric substitution of nitrogen by carbon and can be classified into tetrahydrofuranyl derivatives. In an effort to expand the synthetic applicability of the stereoselectively generated tetrahydrofurans to C-ribosides, D-(+)-showdomycin **1** was chosen as a model target, which was first isolated from *Streptomyces showdoensis* by Nishimura *et al.*, and displays antibiotic and antitumor activity.[3] In this paper we wish to describe total synthesis[4] of D-(+)-showdomycin **1** starting from the enantiomerically pure *syn*-2,5-disubstituted dihydrofuran **3**,[1b] $[\alpha]_D$ = -11.7 °($CHCl_3$, c=0.83), which was produced in seven steps and 67% overall yield from 3-furfural and phosphonium salt **2** derived from (S)-1,2,4-butanetriol.[5]

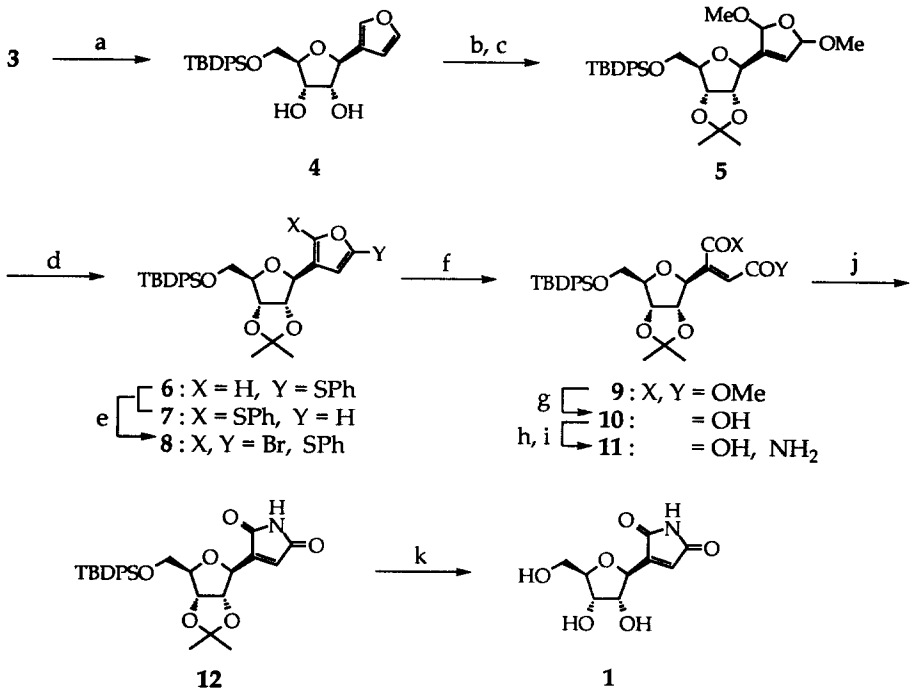


1



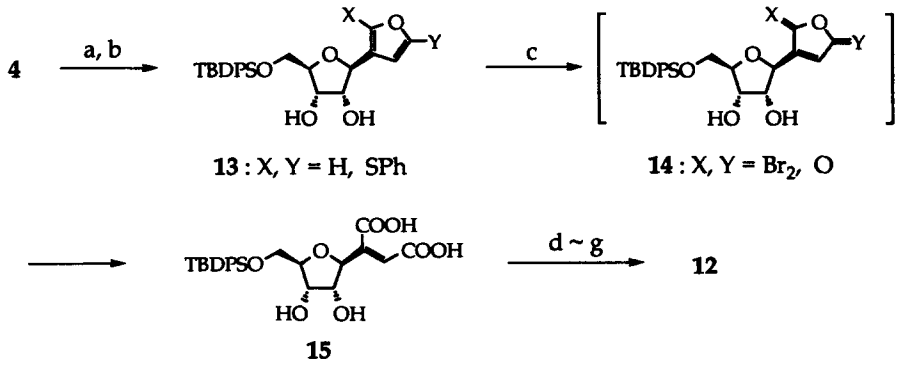
2 **3**

The synthesis began with dihydroxylation of **3** with a catalytic amount of osmium tetroxide in the presence of N-methylmorpholine N-oxide (NMO) at -20 °C to give the desired diol **4**, $[\alpha]_D$ =



Scheme 1 : *a*. OsO_4 (cat.)/NMO/aq. acetone/-20 °C (91%). *b*. p-TsOH (cat.)/acetone/rt (91%). *c*. Br_2 (2 eq.)/MeOH/0 °C (80%). *d*. PhSH (5 eq.)/p-TsOH (0.5 eq.)/CH_2Cl_2/rt ; $Me_2C(OMe)_2$/rt (96%). *e*. Br_2 (2 eq.)/THF/0 °C (93%). *f*. Br_2 (2 eq.)/MeOH/0 °C (86%). *g*. KOH/aq. dioxane/rt. *h*. CF_3COOH (2%)/Ac_2O/50 °C. *i*. NH_3/PhH/rt. *j*. AcCl (20 eq.)/DMF/rt (37% from **9**). *k*. CF_3COOH - H_2O (4 : 1)/rt (90%).

+5.9 °($CHCl_3$, c=0.73), in 91% yield along with 9% of the isomeric β-dihydroxylated product (Scheme 1). After protection of **4** as acetonide, it was subjected to bromine in methanol[6] to afford 2,5-dimethoxy-2,5-dihydrofurans **5** in 73% overall yield. Their sequential treatment with thiophenol in the presense of p-TsOH[7] and 2,2-dimethoxypropane produced a 2.3 : 1 mixture of thiophenylfurans **6** and **7** in 96% yield. Electrophilic substitution of the furanyl group in the mixture was carried out using bromine in THF to yield 93% of bromides **8**, which was transformed into dimethyl ester **9**, $[\alpha]_D$= -4.6 °($CHCl_3$, c=0.81), in 86% yield with bromine in methanol. After hydrolysis of **9** with potassium hydroxide in aqueous dioxane, the generated dicarboxylic acid was cyclized to anhydride[8] using acetic anhydride in the presence of trifluoroacetic acid and then its ammonolysis was conducted with ammonia in benzene to generate carboxylic acid amide **11**.[9] Cyclization of **11** with acetyl chloride in DMF[10] provided the protected showdomycin **12**, $[\alpha]_D$= +10.3 °($CHCl_3$, c=0.8), in 37% overall yield from **9**. Deprotection of **12** in aqueous trifluoroacetic acid completed our synthesis to furnish D-(+)-showdomycin **1**, m.p=150~151 °C, $[\alpha]_D$= 50.4 °(H_2O, c=0.5), in 90% yield, of which the spectroscopic data are identical to those reported in the literature.[11]



Scheme 2 : *a*. Br_2 (2 eq.)/K_2CO_3 (1 eq.)/MeOH/0 °C (94%). *b*. PhSH (5 eq.)/p-TsOH (0.5 eq.)/CH_2Cl_2/rt (95%). *c*. Br_2 (2 eq.)/THF/0 °C ; Br_2 (8 eq.)/THF - t-BuOH - H_2O(1 : 1 : 1)/rt. *d*. $Me_2C(OMe)_2$/acetone/p-TsOH (cat.)/rt ; 1 N aq. $NaHCO_3$ (pH=7). *e*. $(CF_3CO)_2O$/rt. *f*. NH_3/THF/0 °C. *g*. AcCl (15 eq.)/DMF/-20 ~ 0 °C (54% from **13**).

For the improvement of our synthetic pathway, a more facile transformation of furanyl group into maleic acid moiety was pursued.[12] After oxidation of diol **4** with bromine in the presence of potassium carbonate in methanol, the resulting 2,5-dimethoxy-2,5-dihydrofurans were rearomatized using thiophenol in the presence of p-TsOH to give a 1.6 : 1 mixture[13] of thiophenylfurans **13** in 89% overall yield (Scheme 2). The conversion of **13** into dicarboxylic acid **15** was performed in one-pot experiment by their treatment with bromine in THF followed by the sequential addition of aqueous t-butanol and bromine. This conversion is believed to proceed via dibromolactone **14**, which could be isolated in the course of the reaction.[14] After protection of **15** as acetonide,[15] the resulting dicarboxylic acid was subjected to trifluoroacetic anhydride[10] to afford the corresponding anhydride, which was transformed into the protected showdomycin **12** using the same reaction sequence as described in Scheme 1. The formation of **12** from **13** was attained in 54% overall yield and did not require any chromatographic purification in the course of the reaction sequence.

In conclusion our total synthesis of D-(+)-showdomycin was accomplished practically in 39% overall yield from *syn*-2,5-disubstituted 2,5-dihydrofuran **3** and showed the potential utility of **3** for the development of C-ribosides.

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5. (S)-1,2,4-Butanetriol was purchased from Aldrich Chemical Co.
6. a) Achmatowicz, Jr., O. ; Bukowski, P. ; Szechner, B. ; Zwierzchowska, Z. ; Zamojski, A. *Tetrahedron*, **1971**, *27*, 1973 - 1996. b) Jurczak, J. ; Pikul, S. *Tetrahedron Lett.*, **1985**, *26*, 3039 - 3040.
7. The acetonide group was partially hydrolyzed.
8. After protection of the hydroxyl groups in **4** as acetonide, the acetonide was treated with bromine in aqueous THF to give bislactols, which could be oxidized to monolactone but not to anhydride under various oxidation reaction conditions.
9. Kalvoda, L. ; Farkas, J. ; Sorm, F. *Tetrahedron Lett.*, **1970**, *11*, 2297 - 2300.
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11. Barrett, A. G. M. ; Broughton, H. B. *J. Org. Chem.*, **1986**, *51*, 495 - 503. ^{13}C NMR spectral data of showdomycin **1** (50 MHz, D_2O with 0.5% dioxane) : δ 62.11, 67.30 (dioxane as reference), 71.58, 75.20, 78.23, 84.01, 129.94, 147.83, 173.18, 173.79 ppm
12. The conversion of furanyl derivatives into pyrroles could not be realized using ethyl azidoformate : see Hafner, K. ; Kaiser, W. *Tetrahedron Lett.*, **1964**, *5*, 2185 - 2190.
13. The major isomer of **13** has the same furanyl structure as in **6**.
14. All new compounds showed satisfactory spectral data.
15. Although diol **15** could be converted into D-(+)-showdomycin **1**, the overall chemical yield of **1** was 15 ~ 25% from **4**.

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