A Stereocontrolled Synthesis of D-(+)-Showdomycin

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Total synthesis of D-(+)-showdomycin **1** is accomplished starting from the enantiomerically pure *syn*-2,5-disubstituted dihydrofuran **2**.

In recent years C-ribosides have received considerable attention, because of their metabolic stability, in the development of antiviral, anticancer or anti-AIDS drugs.[1] Classified as tetrahydrofuran derivatives, they may be synthesized efficiently by the preferential formation of a tetrahydrofuranyl ring, followed by the necessary functionalization. This synthetic approach, though rarely employed, can offer advantages owing to the relatively constrained steric environment of the ring system. With this consideration, we have developed the stereoselective synthesis of 2,5-disubstituted tetrahydrofurans.[2] We herein describe an enantioselective total synthesis[3] of an antitumour compound D-(+)-showdomycin **1**,[4] starting from the enantiomerically pure *syn*-2,5-disubstituted dihydrofuran **2**, $[\alpha]_D^{20}$ −11.7 ($CHCl_3$, *c* 0.83).[2b]

Osmylation of dihydrofuran **2** with a catalytic amount of osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO) at −20 °C produced a quantitative 10 : 1 mixture of the desired α-dihydroxylated product and the isomeric β-dihydroxylated compound (Scheme 1). The dihydroxy groups of the mixture were protected as acetonides, which were readily separated to afford the required acetonide **3**, $[\alpha]_D^{20}$ −2.2 ($CHCl_3$, *c* 0.82) in 82% yield. Acetonide **3** was oxidized using bromine[5] in the presence of potassium carbonate in aqueous THF at 0 °C, and the resulting lactols **4** were converted into the regio- and stereo-isomeric mixture of lactones **5** by the portionwise addition of chromium trioxide in Celite[6] in ethereal dichloromethane at 0 °C. Since the transformation of **4** or **5** into maleic anhydride was unsuccessful under various reaction conditions including Swern oxidation,[7] Dess–Martin periodinane,[8] Ley's tetrapropylammonium perruthenate[9] and so forth, compounds **5** were subjected to reaction with hydroxylamine in methanolic pyridine† followed by esterification with diazomethane to give methyl esters **7** *via* oxime carboxylic acids **6** in 86% overall yield from **3**. The oxime hydroxy groups were mesylated and subsequently eliminated using mesyl chloride in the presence of diisopropylethylamine† at −30 to 0 °C to furnish a 3 : 1 mixture of nitriles **8a** and **8b** in 88% combined yield.[10] For the construction of the required maleimide ring in showdomycin **1** from **8a** and **8b**, we attempted to hydrolyse their nitrile groups to amides. However, the desired hydrolysis could not be realized in our hands in spite of employing various reaction conditions such as manganese dioxide in silica,[11] basic hydrogen peroxide,[12] *tert*-butyl alcoholic potassium hydroxide,[13] *etc*. The major problem was the migration of the double bonds in **8a** and **8b** to the side of the tetrahydrofuranyl ring under basic reaction conditions. In order to avoid the use of basic media in the formation of maleimide, we decided to form the methoxymethyl esters instead of methyl esters. Accordingly, **6** was esterified using chloromethyl methyl ether (MOMCl) in the presence of diisopropylethylamine† at low temperature, and the resulting reaction mixture was treated *in situ* with mesyl chloride to provide a 3 : 1 mixture of nitriles **9a**, $[\alpha]_D^{20}$ −14.5 ($CHCl_3$, *c* 0.75) and **9b**, $[\alpha]_D^{20}$ +2.2 ($CHCl_3$, *c* 0.49) in 73% overall yield from **3**. Exposure of **9a** and **9b** to a mixture of trifluoroacetic acid and trifluoroacetic anhydride at 45 °C induced the cyclization of the conjugate nitrile ester functionality to maleimide,[3e,h] and the deprotection of the resulting products was completed by the addition of water to the same pot to produce the desired D-(+)-showdomycin **1**, mp. 150–151 °C, $[\alpha]_D^{20}$ 50.6 (H_2O, *c* 0.455) in 72% overall yield.

Total synthesis of D-(+)-showdomycin **1** has been accomplished in 43% overall yield starting from *syn*-2,5-disubstituted dihydrofuran **2**, in which the seven-step sequence of the conversion of the furanyl group into the maleimide moiety did not require any chromatographic purification.

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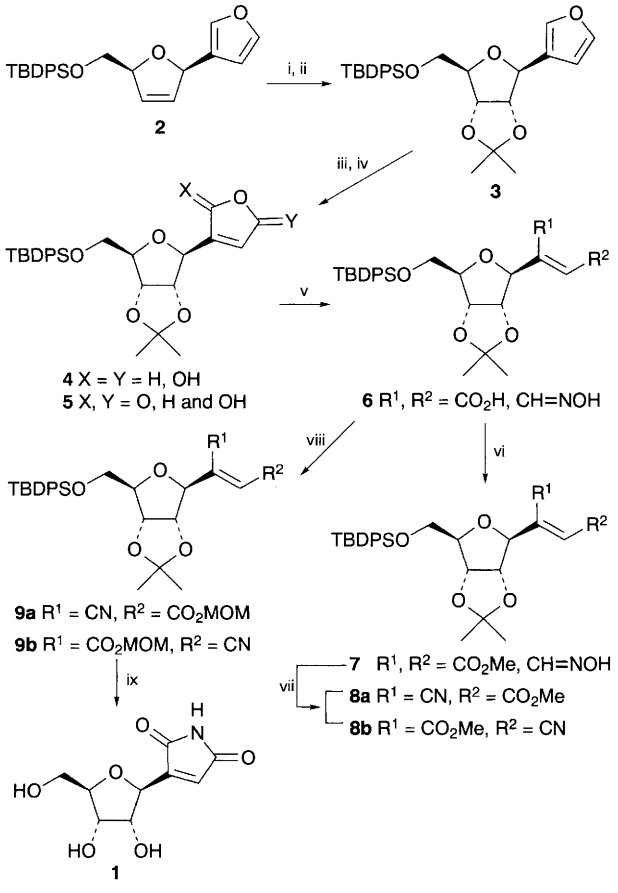

Scheme 1 *Reagents and conditions*: i, OsO_4 (cat.), NMO, aq. acetone, −20 °C; ii, *p*-TsOH (cat.), acetone, room temp.; iii, Br_2 (2 equiv.), K_2CO_3 (0.5 equiv.), THF–H_2O (5 : 1), 0 °C; iv, CrO_3 on Celite (3 equiv.), CH_2Cl_2–Et_2O (3 : 1), 0 °C; v, $HONH_2$·HCl, pyridine–MeOH (1 : 1), room temp.; vi, CH_2N_2, Et_2O, 0 °C; vii, $MeSO_2Cl$, Pr^i_2NEt, CH_2Cl_2, −20 to 0 °C; viii, MOMCl, Pr^i_2NEt, CH_2Cl_2, −30 to −20 °C, then $MeSO_2Cl$, −30 to 0 °C; ix, CF_3CO_2H, $(CF_3CO)_2O$, 45 °C, then H_2O, room temp.

Footnote

† The use of triethylamine induced the isomerization of the double bond to the side of the tetrahydrofuranyl ring.

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