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Total Synthesis of a Glyoxalase I Inhibitor and Its Precursor, (-)-KD16-U1

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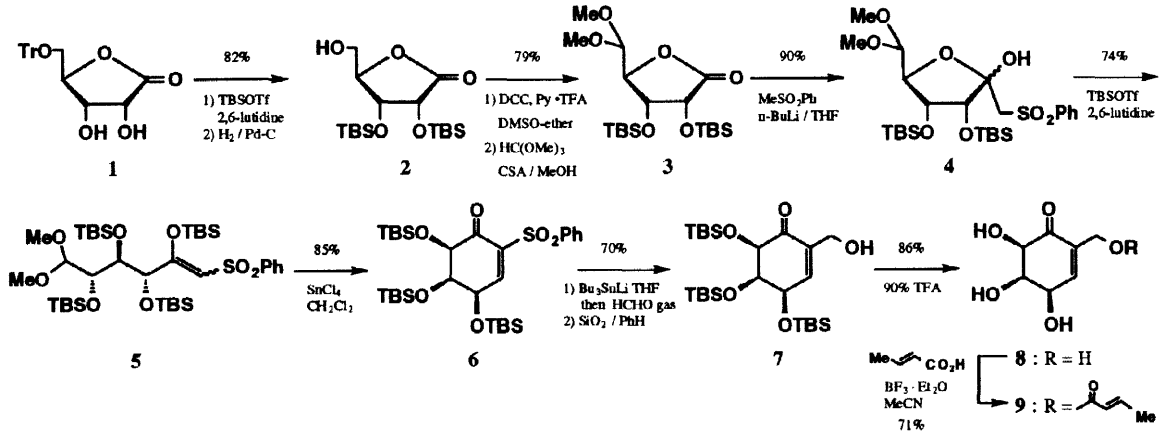
Abstract: A glyoxalase I inhibitor and (-)-KD16-U1 have been synthesized from D-ribonic acid γ-lactone through $SnCl_4$-promoted cyclization of a phenylsulfonyl enol silyl ether and regioselective introduction of a hydroxymethyl group. © 1997 Elsevier Science Ltd. All rights reserved.

A glyoxalase I inhibitor (**9**) was isolated in 1975 from the culture broth of *Streptomyces griseosporeus* by Umezawa and co-workers.[1] The absolute structure was determined by chemical studies and X-ray analysis.[2] Its precursor, (-)-KD16-U1 (**8**), had been already isolated in 1974 from the culture broth of *Streptomyces filipinensis* by a chemical screening method developed in our laboratories,[3] and converted to the aforementioned glyoxalase I inhibitor by treatment with crotonic acid and BF_3-Et_2O.[4] The glyoxalase system, which consists of glyoxalase I, glyoxalase II and reduced glutathione, catalyzes the conversion of α-keto aldehydes to α-hydroxy acids.[1] The glyoxalase I inhibitor (**9**) has also been reported to exhibit antitumor activities.[1] The structures and bioactivities of these compounds **8** and **9** have attracted our attention because of our program in developing novel methodology for the preparation of densely-functionalized carbocycles from carbohydrates.[5,6] The first synthesis was achieved by Vasella's group in which methyl α-D-glucopyranoside was effectively used as a starting material.[7] Recently, the $SnCl_4$-promoted aldol-like cyclization of phenylsulfonyl enol silyl ethers containing a dimethyl acetal has been explored extensively in our laboratories.[6] This transformation is ideally suited to the synthesis of carbocycle-containing natural products and carba-sugars, since the core skeleton arises after appropriate replacement of the phenylsulfonyl group. As an illustration of these strategies, we recently disclosed the total synthesis of (-)-PF1092s.[5] Herein, we describe the novel synthesis of (-)-glyoxalase I inhibitor (**9**) and its precursor, (-)-KD16-U1 (**8**).

In our retrosynthetic analysis, it was proposed that (-)-KD16-U1 (**8**) could be obtained from the



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corresponding α-phenylsulfonyl cyclohexenone **6** through the Michael type addition of tributylstannyl-lithium followed by trapping with formaldehyde and desulfonylation.[8] The cyclohexenone **6** would arise from the enol silyl ether containing the dimethyl acetal **5**, which originates from one-step opening of the phenylsulfonylmethyl furanose **4**. Thus, the starting material simplifies to commercially available D-ribonic acid γ-lactone.

In practice, the *O*-trityl derivative **1**[9] was silylated, followed by reductive de-*O*-tritylation to give the alcohol **2** (mp 116°C, $[\alpha]_D$ +46°)[10]. Pfitzner-Moffatt oxidation and acetal formation gave **3** (mp 93°C, $[\alpha]_D$ +14°). Reaction of **3** with lithiated methyl phenyl sulfone afforded the furanose **4** (mp 136°C, $[\alpha]_D$ +22°). This was silylated to produce, as expected,[5] the labile enol silyl ether **5** having a simultaneously silylated hydroxy group (mp 108°C, $[\alpha]_D$ +37°). The $SnCl_4$-promoted cyclization of **5** resulted in the formation of the cyclohexenone **6** (mp 197°C, $[\alpha]_D$ -120°). Addition of tributylstannyl-lithium[8] to **6** was followed by trapping of the intermediary β-tributylstannyl sulfone with formaldehyde. This reaction gave an adduct which, upon treatment with silica gel, was converted through β-elimination of the tributylstannyl group to the desired α-hydroxymethyl-cyclohexenone **7** (oil, $[\alpha]_D$ -72°). De-*O*-silylation with 90% TFA afforded **8** [mp 114°C, $[\alpha]_D$ -166°(H_2O)], which was identical with the natural (-)-KD16-U1 (**8**) in all respects.[3]

The synthetic (-)-KD16-U1 (**8**) was treated with crotonic acid and BF_3-Et_2O, as previously reported in our laboratories,[4] to give the selectively acylated product **9** [mp 181°C, $[\alpha]_D$ -111°(MeOH)] identical with the natural glyoxalase I inhibitor (**9**).[1]

Adaptation of this synthetic strategy for the construction of other cyclohexenones is under investigation.

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10. Optical rotations were measured in $CHCl_3$ using a 0.5 dm tube at 22°C, unless otherwise noted.

Significant ^{1}H-NMR spectral data (in $CDCl_3$; 270, 400 and 500 MHz, δ; TMS=0, unless otherwise noted) are the following. **2**: 1.90(1H, t, *J*=5.6Hz), 3.51(1H, ABq, *J*=3.0, 4.5, 5.6Hz), 3.96(1H, ABq, *J*=3.0, 4.0, 5.6Hz), 4.45(1H, dd, *J*=3.0, 4.5Hz), **3**: 3.47(3H, s), 3.50 (3H,s), 4.23(1H, d, *J*=3.0Hz), 4.37(1H, d, *J*=3.0Hz), **4**: 3.46(1H, d, *J*=15.4Hz), 4.26(1H, d, *J*=15.4Hz), 7.56(3H, m), 7.98(2H, m), **5**: 3.59(1H, d, *J*=9.0Hz), 3.79(1H, d, *J*=7.4Hz), 4.32(1H, d, *J*=9.0Hz), 4.45(1H, d, *J*=7.4Hz), 5.77(1H, s), **6**: 4.18(2H, m), 4.74(1H, dd, *J*=2.2, 2.0Hz), 7.70(1H, dd, *J*=2.2, 1.6Hz), **7**: 2.28(1H, br), 4.24(2H, m), 6.46(1H, m), **8** (D_2O): 4.25(1H, d, *J*=14Hz), 4.32(1H, d, *J*=14Hz), 4.47(2H, m), 4.82(1H, m), 6.78(1H, m), **9**(DMSO): δ 1.86(3H, dd, *J*=6.9, 1.8Hz), 4.17(2H, m), 4.55(1H, m), 4.63(1H, dt, *J*=13.5, 1.5Hz), 4.75(1H, dt, *J*=13.5, 1.5Hz), 5.07(1H, d, *J*=3.3Hz), 5.19(1H, d, *J*=5.5Hz), 5.37(1H, d, *J*=7.0Hz), 5.92(1H, dq, *J*=15.6, 1.8Hz), 6.62(1H, m), 6.93(1H, dq, *J*=15.6, 6.9Hz).