The polyoxygenated cyclohexanes, which have been isolated from the *Uvaria* genus, show anticancer, antiviral and antibiotic activities.1—3) *(1/11002)*-Zeylenone is one such example separated from *Uvaria grandiflora* and showed remarkable inhibition of nucleoside transport in Ehrlich carcinoma cells and interesting cytotoxicity to cultured cancer cells.4) Assessment of cytotoxicity of *(1/11002)*-zeylenone was performed on the following human tumor cell lines: HCT-8 (a human colonic tumor cell line), BGC-823 (a human gastric cancer cell line), and Bel-7402 (a human liver cancer cell line); and the IC$_{50}$ (nM) was 3.25, 5.26, and 4.69, accordingly.

We have built the total synthesis of *(1/11002)*-zeylenone in our former research work.5) As our continuous effort to study the structure-activity relationship of zeylenone, we improved the route and report herein a new approach of the enantioselective synthesis of *(1/11002)*-zeylenone from shikimic acid. The synthesis is starting from a selective protected shikimic acid, using Mitsunobu reaction, OsO$_4$ catalyzed oxidation, cyclic carbonates protection for the cis diol and a SeO$_2$ oxidation of olefin as the key steps (Chart 1).

We used shikimic acid as a starting compound, which could be easily found in a number of natural plants. After methylation of shikimic acid5) and regio-selective protection of trans vicinal diol 3,5) we performed a stereospecific conversion of the 3-OH of compound 4 with a Mitsunobu reaction.6,7) The alcohol 4 is treated with triphenylphosphine, diethyl azodicarboxylate (DEAD) and $p$-nitrobenzoic acid, followed by hydrolyzed with CH$_3$ONa, to give the alcohol 5 in 91% yield.5) As in our former work, before the reduction of methyl ester with diisobutylaluminum hydride (DIBAL-H), there should be an introduction of tert-butyldimethylsilyl (TBDMS) group to increase the stereoselectivity.9) Considering the target product 1 and the steric hindrance of the benzoyl group, the two hydroxyl groups of compound 6 were directly benzoylated with benzoyl chloride in 99% yield10) after the reduction of compound 5 with DIBAL-H in 90% yield.5) Fortunately, the olefin 7 was dihydroxylated with OsO$_4$ and $N$-methylmorpholine (NMO) in THF/H$_2$O (1 : 1) under Ar to give stereoselectively the sole diol isomer 8 in 92% yield (Chart 2).5) Therefore, the introduction and deprotection of TBDMS group were avoided and the total yield was raised.

The cis diol 8 had to be protected in the next steps. Though we had tried 2,2-dimethylpropane and chloromethyl methyl ether, we could not get the desired protected products (Chart 3). In view of the following deprotection of the trans...
violin diol with acid and the less sterile hindrance, we decided to choose the cyclic carbonate, which was steady under acidic conditions and smaller in stereo hindrance, as the protection for the cis vinyl diol. The compound 8 was treated with trichlorophenoxide and pyridine in CH₂Cl₂ at −78 °C under N₂ to give the cyclic carbonate 9 in 91% yield, followed by deprotection with TFA in CH₂Cl₂ to give the trans vinyl diol 10 in 87% yield. After that, compound 10 was treated with Ph₃P, imidazole and iodine in toluene at reflux to give the cylohexene 11 in 86% yield. 5) Afterwards the cylohexene 11 was oxidized by SeO₂ in dry THF at reflux for a day in 39% yield, and then the residue was deprotected with pyridine/H₂O at reflux for 20 min to give the target compound 1 in 90% yield. On account of the lower yield of the deprotection and obtained the higher total yield of 37% (Chart 4).

The melting point of the mixture of compound 1 and the natural product zeylenone was the same as that of zeylenone at 150—152 °C. The spectra data (including NMR, MS and IR) of compound 1 were identical with those of natural zeylenone. Moreover the value and sign of the optical rotation of the compound 1 \(\{[\alpha]_{D}^{20} = -25.0^\circ (c = 0.30, \text{CH}_3\text{OH}, [\alpha]_{D}^{20} = -119.5^\circ (c = 0.41, \text{CHCl}_3)\} \) for the natural product [lit.]\[\{[\alpha]_{D}^{20} = -26.0^\circ (c = 0.89, \text{CH}_3\text{OH}, [\alpha]_{D}^{20} = -126.5^\circ (c = 0.747, \text{CHCl}_3); \text{lit.}^{11} [\alpha]_{D}^{20} = -26.0^\circ (c = 0.26, \text{CH}_3\text{OH}, [\alpha]_{D}^{20} = -120^\circ (c = 0.60, \text{CHCl}_3)\} \). All the above proved that compound 1 and the natural zeylenone were the same products and the absolute configuration of the compound 1 was thus determined to be (1R,2S,3R).

In summary, we have described a new approach to the asymmetric total synthesis of (−)-zeylenone via a multi-step route starting from shikimic acid in 16% yield, which enables the synthesis of a wide variety of the analogues in relatively good yields. Further work on the synthesis of the analogues in progress.

Experimental

General Experimental Procedures Optical rotations were measured using a JASCO DIP-360 digital polarimeter. NMR spectra were recorded on a JEOL JNM-AL300 spectrometer. The FABMS were obtained on a Micro-Trap. NMR spectra were recorded on a JEOL JNM-AL300 spectrometer. The FABMS were obtained on a Micro-Trap digital polarimeter. NMR spectra were recorded on a JEOL JNM-AL300 spectrometer. The FABMS were obtained on a Micro-Trap digital polarimeter. NMR spectra were recorded on a JEOL JNM-AL300 spectrometer. The FABMS were obtained on a Micro-Trap digital polarimeter.
matography (acetone/petroleum ether 1:5) yielded I as white solids (183 mg, 37%). mp 150—152 °C; ¹H-NMR (CDCl₃) δ: 7.95—8.08, 7.56—7.62, 7.41—7.49 (4H, 2H, m, H of phenyl), 6.92 (1H, dd, J=2.4, 10.5 Hz, H-4), 6.31 (1H, dd, J=2.4, 10.5 Hz, H-5), 6.11 (1H, dd, J=2.4, 9.0 Hz, H-3), 4.75 (1H, d, J=11.4 Hz, H-7a), 4.67 (1H, d, J=11.4 Hz, H-7b), 4.35 (1H, d, J=9.0 Hz, H-2); ¹³C-NMR (CDCl₃) δ: 197.3, 166.0 (C=O), 146.4 (C-4), 133.7, 133.5, 129.9 (C×2), 129.7 (C×2), 129.2, 129.0, 128.6 (C×4), 128.0 (C-5), 79.3 (C-2), 77.4 (C-1), 61.8 (C-3), 64.3 (C-7). IR (KBr) cm⁻¹: 3408, 1712, 1701, 1258. FAB-MS m/z: 383.0 [M⁺]⁺. [α]D²⁰ = -25.0° (c=0.30, CH₂OH), [α]D²⁰ = -119.5° (c=0.41, CHCl₃).

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Reference