New Approach to the Total Synthesis of (−)-Zeylenone from Shikimic Acid

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The natural antitumor product (−)-zeylenone was prepared for the first time in a stereoselective synthesis from shikimic acid.

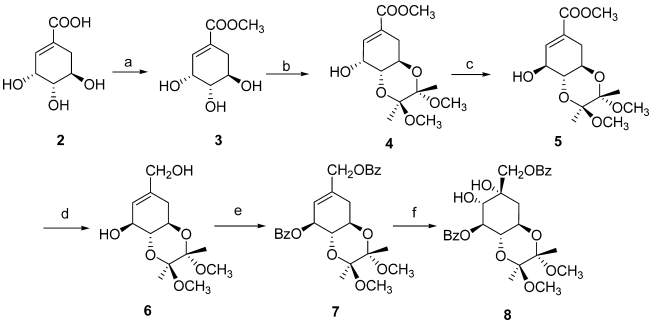
Key words zeylenone; shikimic acid; total synthesis

The polyoxygenated cyclohexanes, which have been isolated from the *Uvaria* genus, show anticancer, antiviral and antibiotic activities.[1—3] (−)-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 (−)-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 (+)-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 (−)-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 acid[5] 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_3ONa, to give the alcohol **5** in 91% yield.[8] 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% yield[10] after the reduction of compound **5** with DIBAL-H in 90% yield.[5] Fortunately, the olefin **7** was dihydroxylated with OsO_4 and *N*-methylmorphorline (NMO) in THF/H_2O (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*



(a) $SOCl_2$, CH_3OH, 10 °C, 93%; (b) $(CH_3CO)_2$, $CH(OCH_3)_3$, (±)CSA, CH_3OH, Ar, 48 h, 90 °C, 90%; (c) DEAD, Ph_3P, *p*-$O_2NC_6H_4COOH$, THF, Ar, 5 h, rt; CH_3ONa, CH_3OH, 2 h, rt, 91%; (d) DIBAL-H, toluene, −78 °C, 90%; (e) BzCl, DMAP, pyridine, rt, 99%; (f) OsO_4, NMO, THF/H_2O (1 : 1), Ar, 92%.

Chart 2. Reagents and Conditions

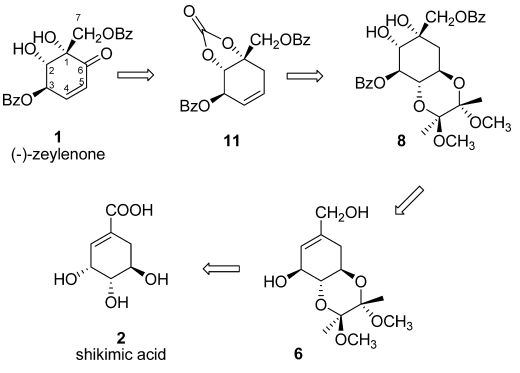
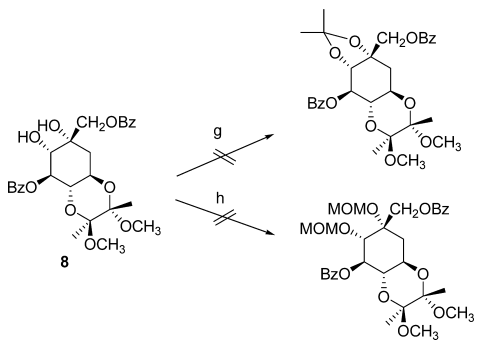


Chart 1. Retrosynthesic Analysis



(g) $(CH_3)_2C(OCH_3)_2$, TsOH, CH_2Cl_2, Ar, rt; (h) *i*-Pr_2NEt, MOMCl, CH_2Cl_2, Ar, rt.

Chart 3. Reagents and Conditions

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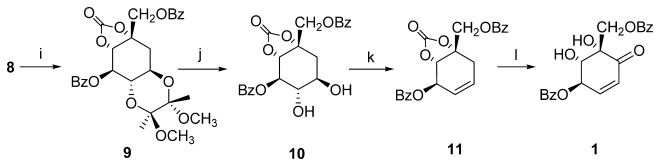

(i) triphosgene, pyridine, CH_2Cl_2, Ar, −78 °C, 91%; (j) TFA, CH_2Cl_2, rt, 87%; (k) Ph_3P, imidazole, I_2, reflux, 86%; (l) i SeO_2, THF, reflux; ii pyridine/H_2O (1 : 1), reflux, 0.5 h, 37%.

Chart 4. Reagents and Conditions

vicinal diol with acid and the less stereo 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* vicinal diol. The compound **8** was treated with triphosgene and pyridine in CH_2Cl_2 at −78 °C under N_2 to give the cyclic carbonate **9** in 91% yield, followed by deprotection with TFA in CH_2Cl_2 to give the *trans* vicinal diol **10** in 87% yield. After that, compound **10** was treated with Ph_3P, imidazole and iodine in toluene at reflux to give the cyclohexene **11** in 86% yield.[5] Afterwards the cyclohexene **11** was oxidized by SeO_2 in dry THF at reflux for a day in 39% yield, and then the residue was deprotected with pyridine/H_2O at reflux for 20 min to give the target compound **1** in 90% yield. On account of the lower yield of the oxidation, we decided to bring the oxidation together with 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** {$[\alpha]_D^{20}=-25.0°$ (c=0.30, CH_3OH), $[\alpha]_D^{20}=-119.5°$ (c=0.41, $CHCl_3$)} were almost the same as those of the natural product {lit.[4] $[\alpha]_D^{20}=-26.0°$ (c=0.89, CH_3OH), $[\alpha]_D^{20}=-126.5°$ (c=0.747, $CHCl_3$); lit.[11] $[\alpha]_D^{20}=-26.0°$ (c=0.26, CH_3OH), $[\alpha]_D^{20}=-120°$ (c=0.60, $CHCl_3$)}. 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 (1*S*,2*S*,3*R*).

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 is 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 Micromass ZabSpec mass spectrometer. Precoated Silica gel plates (Qingdao Haiyang Chem. Co.) were employed for TLC. For column chromatography, Silica gel (Qingdao Haiyang Chem. Co.) and Sephadex LH 20 (Pharmacia) were used.

(2*S*,3*S*,4*aR*,8*S*,8*aR*)-Methyl-8-hydroxy-2,3-dimethoxy-2,3-dimethyl-2,3,4*a*,5,8,8*a*-hexahydrobenzo[*b*][1,4]dioxine-6-carboxylate (5) Triphenylphosphine (12.6 g, 0.048 mol) and *p*-nitrobenzoic acid (8.1 g, 0.048 mol) was added to a solution of compound **4** (11.9 g, 0.039 mol) in dry THF (100 ml), and the whole mixture was stirred under Ar. After being cooled to 0 °C, a solution of diethyl azodicarboxylate (2.2 M, 20 ml) in toluene was added dropwise to the mixture. The reaction mixture was stirred for 5 h at room temperature and then the solvent was removed. The residue was solved in 150 ml MeOH and a new-made sodium methoxide was added dropwise to the solution. After being stirred for 2 h at room temperature, the mixture was treated with NH_4Cl and stirred for 10 min. And then the solvent was removed and the product was purified by column chromatography (acetone/petroleum ether 1 : 9), which yield **5** as white solids (10.8 g, 91%). mp 62—64 °C; ^{1}H-NMR ($CDCl_3$) δ: 6.70 (1H, m, H-2), 4.44 (1H, ddd, J=2.1, 4.2, 8.4 Hz, H-5), 3.81 (1H, dt, J=6.3, 10.5 Hz, H-3), 3.75 (3H, s, OCH_3), 3.62 (1H, dd, J=8.4, 10.8 Hz, H-4), 3.28 (3H, s, OCH_3), 3.25 (3H, s, OCH_3), 2.70 (1H, dd, J=4.2, 17.1 Hz, H-6a), 2.35 (1H, m, H-6b), 1.32 (3H, s, CH_3), 1.30 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 166.4, 138.2, 128.6, 99.3, 99.1, 74.0, 69.8, 65.3, 52.1, 48.0, 47.9, 29.6, 17.7 (C×2). $[\alpha]_D^{20}=+84°$ (c=0.064, $CHCl_3$).

((2*S*,3*S*,4*aR*,8*S*,8*aS*)-8-(Benzoyloxy)-2,3-dimethoxy-2,3-dimethyl-2,3,4*a*,5,8,8*a*-hexahydrobenzo[*b*][1,4]dioxin-6-yl)methyl benzoate (7) Benzoyl chloride (12.2 ml, 0.1 mol) was added dropwise to a solution of alcohol **6** (8.3 g, 30.3 mmol) and catalytic amount of DMAP (0.05 g, 0.4 mmol) in dry pyridine (250 ml) at room temperature during a period 20 min. Stirring was continued for another 4 h and then saturated aqueous $NaHCO_3$ (100 ml) was added to the reaction mixture to quench the reaction. The mixture was extracted with CH_2Cl_2 (3×100 ml), washed with brine (20 ml) and dried ($MgSO_4$). The solvent was removed in vacuum and purified by column chromatography (acetone/petroleum ether 1 : 10), which yielded benzoylated alcohol **7** as white solids (14.4 g, 99%). mp 102—104 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.00—8.11, 7.54—7.59, 7.39—7.48 (4H, 2H, 4H, m, H of phenyl), 5.75 (1H, br s, H-2), 5.73 (1H, m, H-3), 4.78 (1H, d, J=13.2 Hz, H-7a), 4.70 (1H, d, J=13.2 Hz, H-7b), 4.06 (1H, m, H-4), 4.02 (1H, m, H-5), 3.30 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 2.41 (2H, m, H-6), 1.31 (3H, s, CH_3), 1.27 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 166.1, 165.9, 134.3, 133.6, 133.2, 133.0, 130.1, 129.7 (C×4), 128.4 (C×4), 123.0, 99.3, 99.2, 72.5, 71.4, 66.8, 65.6, 48.1, 47.8, 30.9, 17.7, 17.6. $[\alpha]_D^{20}=+144°$ (c=0.066, $CHCl_3$).

((2*S*,3*S*,4*aR*,6*S*,7*S*,8*S*,8*aS*)-8-(Benzoyloxy)-6,7-dihydroxy-2-oxo-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[*b*][1,4]dioxin-6-yl)methyl benzoate (9) To a stirred solution of **8** (6.3 g, 12.2 mmol) in dried CH_2Cl_2, was added dropwise a solution of triphosgene (3.6 g, 12.1 mmol) in dried CH_2Cl_2 after dropping dried pyridine (10 ml, 12.5 mmol) under Ar at −78 °C. Once addition was completed, the reaction mixture was then allowed to warm to room temperature. The resultant homogeneous solution was quenched with 1 N HCl, then washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). The solvent was removed in vacuum and purified by column chromatography (acetone/petroleum ether 1 : 9) to yield **9** (6.0 g, 91%) as white solids. mp 97—99 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.97—8.06, 7.53—7.59, 7.40—7.45 (4H, 2H, 4H, m, H of phenyl), 5.42 (1H, dd, J=6.3, 10.5 Hz, H-3), 4.79 (1H, d, J=6.3 Hz, H-2), 4.52 (1H, d, J=11.7 Hz, H-7a), 4.38 (1H, d, J=11.7 Hz, H-7b), 4.01 (1H, m, H-5), 3.77 (1H, t, J=10.2 Hz, H-4), 3.27 (3H, s, OCH_3), 3.15 (3H, s, OCH_3), 2.49 (1H, dd, J=4.8, 15.0 Hz, H-6a), 1.92 (1H, dd, J=12.0, 15.0 Hz, H-6b), 1.28 (3H, s, CH_3), 1.20 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 165.7, 164.9, 152.7, 133.8, 133.4, 129.9 (C×2), 129.8 (C×2), 129.3 (C×2), 128.7 (C×2), 128.5 (C×2), 99.5, 99.4, 82.6 (C-2), 81.2 (C-1), 75.1 (C-3), 69.0 (C-4), 67.9 (C-7), 62.8 (C-5), 48.2, 47.9, 31.7 (C-6), 17.5, 17.4. $[\alpha]_D^{20}=+155°$ (c=0.082, $CHCl_3$).

((3*aS*,5*R*,6*S*,7*R*,7*aS*)-7-(Benzoyloxy)-5,6-dihydroxy-2-oxohexahydrobenzo[*d*][1,3]dioxol-3a-yl)methyl benzoate (10) To a vigorously stirred solution of **9** (3.7 g, 6.8 mmol) in CH_2Cl_2 (200 ml), TFA (7 ml) was added. After 6 h, 100 ml of 5% aqueous $NaHCO_3$ was added to the reaction mixture. Stirring for 5 min, the mixture was extracted with CH_2Cl_2 (3×100 ml), washed with brine (30 ml) and dried ($MgSO_4$). Removal of the solvent and purification of the residue by column chromatography (acetone/petroleum ether 1 : 4) gave diol **10** (2.5 g, 86%) as white solids. mp 124—125 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.94—7.98, 7.49—7.54, 7.19—7.40 (4H, 2H, 4H, m, H of phenyl), 5.17 (1H, t, J=7.5 Hz, H-3), 4.83 (1H, d, J=7.2 Hz, H-2), 4.62 (1H, d, J=12.0 Hz, H-7a), 4.35 (1H, d, J=12.0 Hz, H-7b), 4.00 (1H, m, H-5), 3.66 (1H, t, J=7.2 Hz, H-4), 2.50 (1H, dd, J=3.6, 15.0 Hz, H-6a), 1.95 (1H, dd, J=9.3, 15.0 Hz, H-6b); ^{13}C-NMR ($CDCl_3$) δ: 166.9, 165.8, 153.1, 133.9, 133.8, 130.0, 129.9 (C×2), 128.7 (C×3), 128.6 (C×3), 128.5, 82.7 (C-2), 79.0 (C-1), 77.8 (C-4), 74.9 (C-3), 68.1 (C-5), 67.9 (C-7), 32.8 (C-6). $[\alpha]_D^{20}=-46°$ (c=0.050, $CHCl_3$).

((1*S*,5*R*,6*S*)-5-(Benzoyloxy)-1,6-dihydroxy-2-oxocyclohex-3-enyl)methyl benzoate (1) A suspension of olefin **11** (0.5 g, 1.3 mmol) and SeO_2 (0.57 g, 5.2 mmol) in dried THF were stirred under reflux for 24 h. After cooling, the reaction mixture was poured into a flash chromatography and washed with EtOAc. After removing the solvent, the residue was dissolved in pyridine/H_2O (v/v, 1 : 1, 10 ml) and stirred under reflux for 20 min. Removal of the solvent and purification of the residue by column chro-

matography (acetone/petroleum ether 1 : 5) yielded **1** as white solids (183 mg, 37%). mp 150—152 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.95—8.08, 7.56—7.62, 7.41—7.49 (4H, 2H, 4H, 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); ^{13}C-NMR ($CDCl_3$) δ: 197.3, 166.0 (C×2), 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 $[M+1]^+$. $[\alpha]_D^{20}=-25.0°$ (c= 0.30, CH_3OH), $[\alpha]_D^{20}=-119.5°$ (c=0.41, $CHCl_3$).

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