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Enantioselective Total Synthesis of the (+) Antipode of Zeylenone

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Abstract: Starting from shikimic acid, the total synthesis of zeylenone was studied. The product was proved to be the (+)antipode of zeylenone through analysis and comparison of their respective spectra (including NMR, MS, IR and CD) and optical data. The absolute configuration of the natural product was thus determined to be (1S,2S,3R).

Keywords: Zeylenone, absolute configuration, shikimic acid, total synthesis, enantiomer.

A number of polyoxygenated cyclohexenes, which show anticancer, antiviral and antibiotic activities, have been isolated from the *Uvaria* genus[1]. As part of our project of searching for the anticancer constituents from the plant source, zeylenone **1** was isolated from *Uvaria grandiflora*, which showed remarkable inhibition of nucleoside transport in Ehrlich carcinoma cells and cytotoxicity to cultured cancer cells. The relative stereochemistry of zeylenone was assigned on the basis of the modern NMR techniques but the absolute configuration was not elucidated[2]. Kunio Ogasawara and co-workers reported the synthesis of (-)tonkinenin A which was an optical isomer of zeylenone[3]. As our continuous effort to confirm the structure and to study the structure-activity relationship of zeylenone, we report herein the total synthetic study of zeylenone from shikimic acid **2** [4].

Our retro-synthetic analysis is outlined in **Scheme 1**. Zeylenone could be obtained by oxidation of **3** with SeO_2. The olefin **3** could be synthesized from the *trans* diol **4**, which could be derived from olefin **5** by oxidation with OsO_4. The olefin **5** could be obtained from shikimic acid **2** by reduction and selective protection.

Thus, the protected *trans* vicinal diol **6** was prepared from shikimic acid **2** with $SOCl_2$ in MeOH, followed by regio-selective protection with 2,3-butanedione, (±) camphor- sulfonic acid (CSA, cat.) and trimethyl orthoformate in methanol at refulx[5]. After introduction of *tert*-butyldimethylsilyl (TBDMS) group[6], compound **7** was

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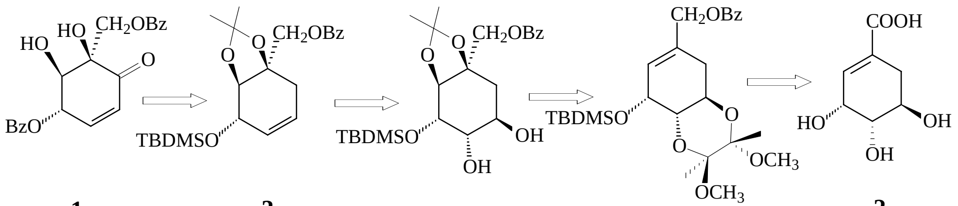
obtained in 97% yield from diol **6**. After reduction of **7** with diisobutylaluminum hydride (DIBAL- H)[7], benzoyl group was introduced to afford olefin **5** in 97%. The olefin **5** was dihydroxylated with OsO_4 and N-methylmorphorline-N-oxide (NMO) in THF/H_2O (1:1) under Ar to stereoselectively give the sole diol isomer **8** in 94% yield[8]. Protected with 2,2-dimethylpropane in 99% yield[9], followed by selective deprotecting with TFA/H_2O (1:1), the *trans* vicinal diol **4** was obtained from **8** in 79%[10].

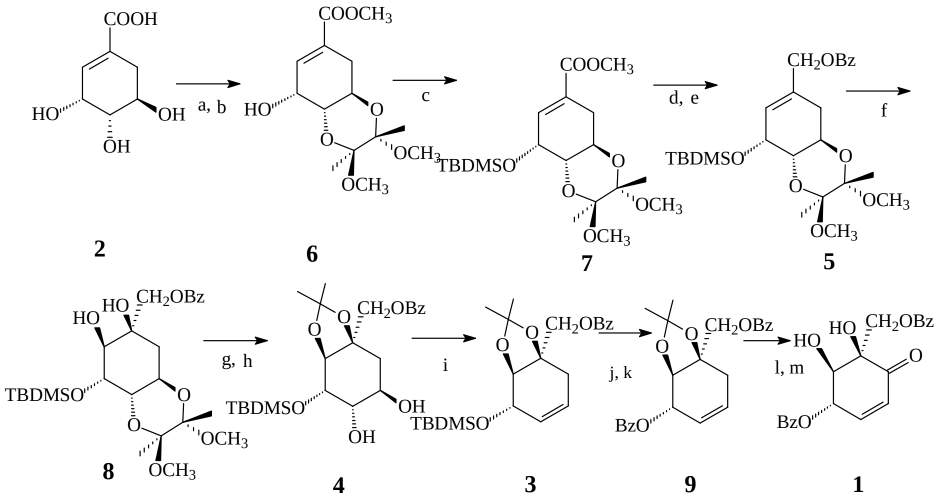
Treatment of *trans* vicinal diol **4** with Ph_3P, imidazole and iodine in toluene at reflux gave cyclohexene **3** in 87% yield[10]. The later was deprotected with tetrabutyl-ammonium fluoride (TBAF) in dry THF[11], and then protected by benzoyl group to give olefin **9**. Compound **1** was obtained from **9** by oxidation with SeO_2 in dry dioxane at reflux for 1 h in 30% yield, followed by deprotection with TFA/H_2O (6:1) in CH_2Cl_2 at room temperature in 76% yield (**Scheme 2**).

Scheme 1



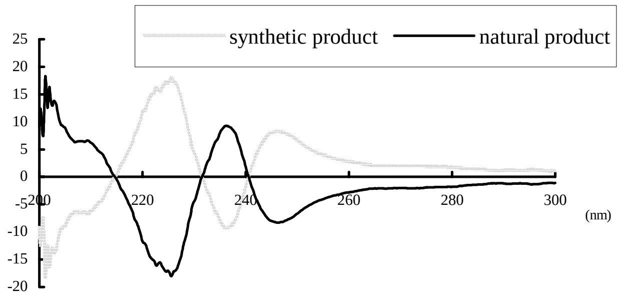
1 **3** **4** **5** **2**

Scheme 2



(a) $SOCl_2$, MeOH, 10 °C, 93%; (b) $(CH_3CO)_2$, $CH(OMe)_3$, (±) CSA, MeOH, Ar, 48h, 90°C, 87%; (c) TBDMSCl, imidazole, DMAP, CH_2Cl_2, r.t., 24h, 97%; (d) DIBAL-H, toluene, -78°C, 92%; (e) BzCl, DMAP, pyridine, r.t. 97%; (f) OsO_4, NMO, THF/H_2O (1:1), Ar, 94%; (g) $(CH_3)_2C(OCH_3)_2$, TsOH, CH_2Cl_2, Ar, r.t., 99%; (h) TFA/H_2O (1:1), CH_2Cl_2, 79%; (i) Ph_3P, imidazole, I_2, reflux, 87%; (j) TBAF, THF, r.t., 69%; (k) BzCl, DMAP, pyridine, r.t., 99%; (l) SeO_2, dioxane, reflux, 30%; (m) TFA/H_2O (6:1), CH_2Cl_2, 76%.

Figure 1 The CD sepectra of zeylenone



The spectral data[12] (including NMR, MS and IR) of compound **1** were identical with those of natural zeyleone, which indicated that the relative stereochemistry of **1** was the same as that of the natural product. The positive Cotton effect[13] of the synthetic product **1** suggested the absolute stereo-chemistry of **1** to be of (1R,2R,3S). But the value and sign of optical rotation of the compound **1** {$[\alpha]^{20}_{D}$ +118 (*c* 0.56, $CHCl_3$), $[\alpha]^{20}_{D}$ +26 (*c* 0.23, CH_3OH)} were opposite to those of the natural pruduct {Lit 2. $[\alpha]^{20}_{D}$ –126.5 (*c* 0.747, $CHCl_3$); lit 3. $[\alpha]^{27}_{D}$ –26.0 (*c* 0.89, MeOH); $[\alpha]^{20}_{D}$ –120 (*c* 0.60, $CHCl_3$), $[\alpha]^{20}_{D}$ -26 (*c* 0.26, CH_3OH)}. In addition, Cotton effects in CD spectrum of the two compounds were opposite too (**Figure 1**). All the data proved that compound **1** is the (+)antipode of the natural product. So the absolute configuration of the natural product was determined to be (1S, 2S, 3R), which also proved that zeylenone and (-)tonkinenin A were the same natural product.

In summary, we have achieved the asymmetric total synthesis of (+)antipode of zeylenone *via* a multi-step enantioselective route starting from shikimic acid. Through our study, the absolute configuration of the natural product zeylenone was proved to be (1S,2S,3R) and that zeylenone and (-)tonkinenin A were the same natural product. Further work on the synthesis of the natural product and its analogues is in progress.

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References and Notes

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8. Compound **8**: white powder, mp 136-138 °C; $[\alpha]_D^{10}$ = +73 ($CHCl_3$, *c* 0.21); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* in Hz): 4.85 (d, 1H, *J*= 12, H-7a), 4.45 (d, 1H, *J*= 12, H-7b), 4.16 (t, 1H, *J*= 3.3, H-3), 3.92 (m, 1H, H-5), 3.83 (dd, 1H, *J*= 10.5, 3.3, H-4), 3.81 (d, 1H, *J*= 3.3 H-2), 2.45-2.49 (m, 1H, H-6a), 1.87-1.92 (m, 1H, H-6b), 3.25 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 1.29 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.88 (s, 9H, $CH_3\times3$), 0.15 (s, 3H, CH_3), 0.08 (s, 3H, CH_3), benzoyl groups: δ 8.04 (d, 2H, J= 7.5), 7.59 (t, 1H, J= 7.5), 7.46 (d, 2H, J= 7.5); ^{13}C NMR (300 MHz, $CDCl_3$, *J* in Hz): δ 167.2, 133.4, 129.7 (2C), 128.5 (2C), 99.7, 99.0, 77.4, 77.0, 76.6, 74.2, 73.5, 71.9, 69.5, 62.4 (2C), 47.8, 47.6, 34.1, 25.7 (C×3), 18.2, 17.8, 17.6, -4.9, -5.3; HRTOFMS *m/z*: 549.2479 $[M+Na]^+$, EIMS *m/z*: 405, 315, 297, 237, 199, 197, 181, 169, 122, 105, 75.
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12. Compound **1**: white powder; 130 mg, mp 150-152 °C; $[\alpha]_D^{20}$ +118 (*c* 0.56, $CHCl_3$), $[\alpha]_D^{20}$ +26 (*c* 0.23, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm, *J* in Hz): 4.38 (dd, 1H, *J*= 3.3, 1.5, H-2), 4.59 (d, 1H, *J*= 11.4, H-7a), 4.86 (d, 1H, *J*= 11.4, H-7b), 5.95 (td, 1H, *J*= 4.2, 0.9, H-3), 6.35 (dd, 1H, *J*=10.2, 0.9, H-5), 6.96 (ddd, 1H, *J*= 10.2, 4.2, 0.9, H-4), two benzoyl groups: δ 8.00 (m, 4H), 7.52-7.58 (m, 2H), 7.40-7.47 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 65.5 (C-7), 69.1 (C-3), 71.6 (C-2), 77.2 (C-1), 128.6 (C-5), 142.6 (C-4), 196.2 (C-6), two benzoyl groups: δ 128.4, 128.5, 128.7 (2C), 129.7 (2C), 129.8 (2C), 133.4, 133.7, 165.3, 166.2; IR ν_{KBr} cm^{-1}: 3421, 1716, 1693, 1271, 1113, 714; EIMS *m/z*: 282, 260, 220, 136, 122, 105,94; HRMS(TOF): calcd. for $C_{21}H_{19}O_7$ (M+1) 383.1125, found 383.1126.
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