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Studies on Enantioselective Total Synthesis of Ascospiroketal B (I)†

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Ascospiroketal B (**1**) was isolated from the *Ascochyta slicorniae*, a marine-derived fungus known as rich sources of secondary metabolites, by OSMAC (One Strain-Many Compounds) approach.[1] Although the relative structure of ascospiroketal B (**1**) was elucidated by G. M. König in 2007 by use of ^{1}H NMR, ^{13}C NMR, IR, 2D HSQC, 2D NOESY and so on,[2] the relative configurations at C2', C3' and C15 still need to be determined, probably due to the flexibility of the side chain. Key structural features include a tricyclic spiro skeleton and eight stereogenic centers with one quaternary carbon center at C2 position. We report herein the first synthesis of C1-C10 fragment **20** of ascospiroketal B (**1**).

Retrosynthetic strategy is summarized in Figure 1. The C11-C12 bond would be introduced by Stille coupling of the vinyl tin **2** and C1-C11 fragmenet **3**. Fragment **3** should be derived from the intermediate **4** and the intermediate **4** could be synthesized from NHK reaction between vinyl iodide **5** and aldehyde **6**. We envisioned that installation of the quaternary chiral center at C2 of ascospiroketal B (**1**) would be accomplished by asymmetric alkylation protocol.

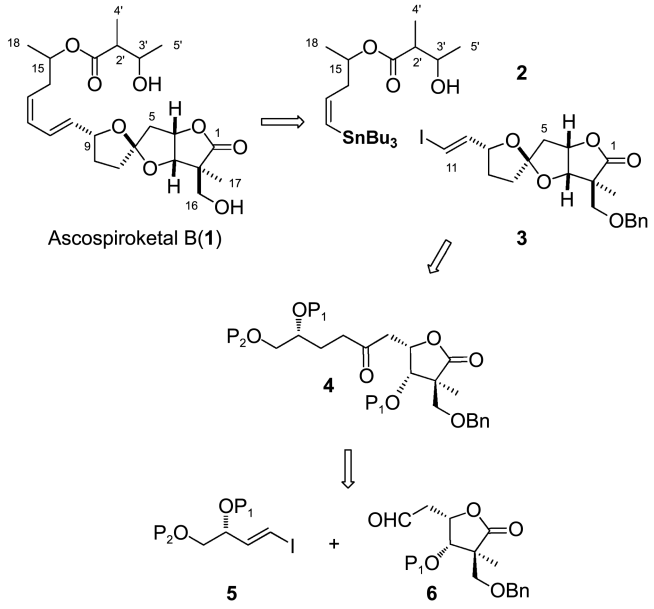
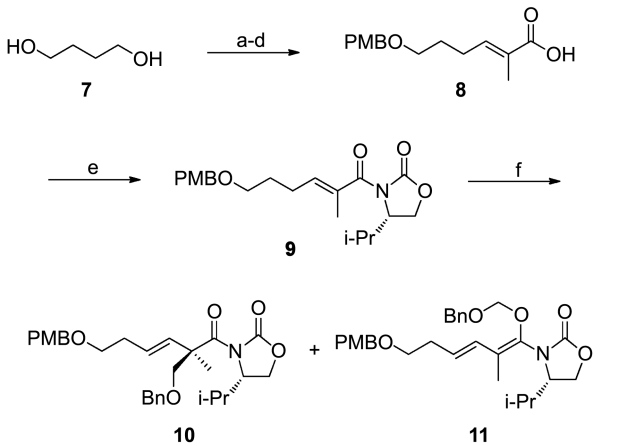


Figure 1. Retrosynthesis of Ascospiroketal B (**1**).

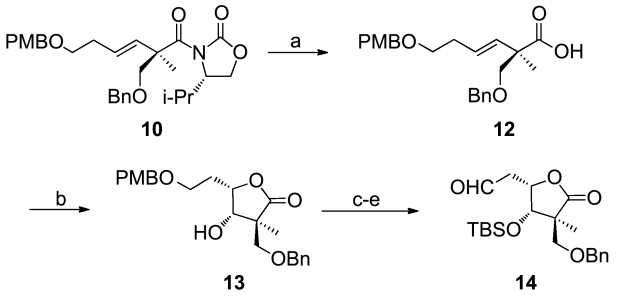
Key intermediate **10** was prepared from the commercially available 1,4-butanediol (**7**) (Scheme 1).[3] After mono-protection of the diol **7** using NaH, PMBCl, and TBAI in THF in 64% yield, the primary hydroxyl group was converted quantitatively to the aldehyde by Swern oxidation. Aldehyde was subsequently converted to α,β-unsaturated ester using stabilized Wittig reagent in benzene,[3] and hydrolysis using 2 N NaOH in MeOH provided the carboxylic acid **8** in 81% two-step yield. Pivaloylation of the acid moiety in **8** by pivaloyl chloride afforded the mixed anhydride, which was immediately treated with the lithium salt of (*S*)-4-isopropyloxazolidin-2-one to give the intermediate **9** in 73% yield. Quaternary center at C2 of the intermediate **9** was constructed with NaHMDS and BOMCl[4] to provide the desired *C*-alkylation product **10**(59%) along with the *O*-alkylated product **11**(11%). Use of HMPA as additive gave the *O*-alkylation product **11** only.

The chiral auxiliary in **10** was removed using LiOH and H_2O_2 in aqueous THF in 83% yield (Scheme 2). Although Sharpless asymmetric dihydroxylation of carboxylic acid **12** took 2 days using AD-mix-α and methanesulfonamide in *t*-BuOH and H_2O at 0 °C, the resulting 1,2-diol was cyclized

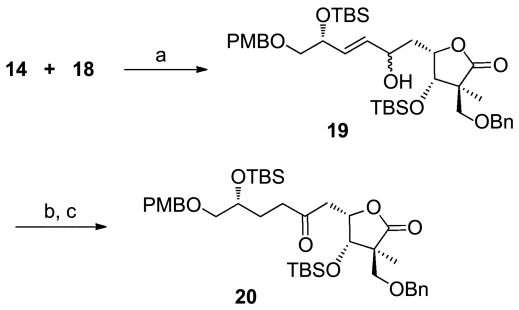


Scheme 1. Synthesis of intermediate 10. (a) PMBCl, TBAI, NaH, THF, 64% (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C, 100% (c) Ph_3P=C(Me)CO_2Et, benzene, 5 hr, reflux, 99% (d) 2N NaOH, MeOH, 60 °C, 2 hr, 82% (e) (i) PivCl, *N*-methylmorpholine (ii) (*S*)-4-isopropyloxazolidin-2-one, *n*-BuLi, 73% (f) NaHMDS, BOMCl, THF, 59%.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.



Scheme 2. Synthesis of aldyhyde 14. (a) LiOH, H_2O_2, THF, H_2O, 83% (b) AD-mix-α, methanesulfonamide, *t*-BuOH, H_2O, 0 °C, 2 days, 64% (c) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 95% (d) DDQ, CH_2Cl_2, H_2O, 2 hr, 81% (e) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C, 100%.



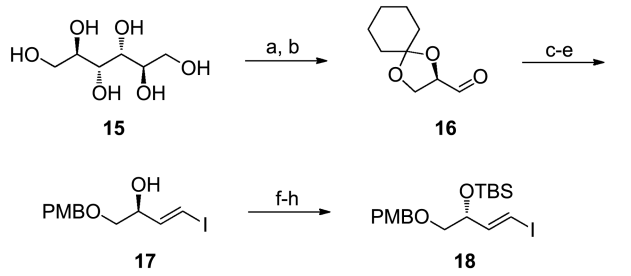
Scheme 4. Synthesis of intermediate 20. (a) $CrCl_2$, $NiCl_2$, DMSO, 64% (b) Dess-Martin periodinane, CH_2Cl_2, 83% (c) Pd/C, EtOH, 93%.

spontaneously by simple stirring in CH_2Cl_2 after normal work-up to afford the intermediate **13** in 64% overall yields. Butyrolactone **13** was further converted to the corresponding aldehyde **14** *via* TBS-protection, PMB-deprotection, and oxidation in 77% overall yields.

Synthesis of another key intermediate **18** was summarized in Scheme 3. Commercially available D-mannitol (**15**) was converted to aldehyde **16** by conversion of two 1,2-diol moieties to 1,3-dioxolane protecting groups and subsequent oxidative cleavage of the remaining 1,2-diol in 46% overall yields.[5] Takai protocol for the introduction of (*E*)-selective vinyl iodide,[6] TFA-mediated deprotection of the dioxolane protectiong group in MeOH,[7] and PMB-*mono*-protection of the resulting primary alcohol provided the secondary alcohol **17** in 51% three-step yields. Mitsunobu inversion of the secondary hydroxyl group in **17**,[8] methanolysis of the benzoate using K_2CO_3 in MeOH, and TBS-protection of the resulting alcohol provided the vinyl iodide **18** in 45% overall yields.

Finally, intermediate **19** was prepared by Nozaki-Hiyama-Kishi reaction between aldehyde **14** and vinyl iodide **18** in 64% yield (Scheme 4).[9] Without separation of two diastereomers, intermediate **19** was converted to α,β-unsaturated ketone by Dess-Martin periodinane in 83% yield, and selective reduction of double bond in the presence of carbonyl group was accomplished to provide the intermediate **20**, a C1-C10 precursor of ascospiroketal B (**1**),[10] by Pd/C in EtOH under H_2 atmosphere in 93% yield.

In summary, the C1-C10 fragment **20** (14 linear-steps, 4.5% overall yields from **7**) of ascospiroketal B (**1**) has been synthesized through asymmetric alkylation for the introduction of the quaternary chiral center and NHK-reaction as key steps.



Scheme 3. Synthesis of vinyl iodide 18. (a) Cyclohexanone, BF_3-OEt_2, $CH(OMe)_3$, DMSO, 24 hr (b) $NaIO_4$, Bu_4NBr(cat.), Et_2O, H_2O, 2 hr, 46% (over 2 steps) (c) $CrCl_2$, CHI_3, THF, 5 hr, 72% (d) TFA, MeOH, 72% (e) PMBOC(=NH)(CCl_3), *p*-TsOH(cat.), CH_2Cl_2, 98% (f) DEAD, PPh_3, BzOH, CH_2Cl_2, 0 °C, 2 hr, 76% (g) MeOH, K_2CO_3, 5 hr, 76% (h) TBSCl, imidazole, CH_2Cl_2, 78%.

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10. $[\alpha]_D$= +21.1 (c. 0.007, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.26 (m, 5H), 7.25 (d, *J*=8.5 Hz, 2H), 6.88 (d, *J*=8.5 Hz, 2H), 5.03 (m, 1H), 4.6-4.36 (m, 4H), 4.24 (d, *J*=5 Hz, 1H), 3.82 (m, 1H), 3,80 (s, 3H), 3.68 (d, *J*=4.5Hz, 1H), 3.52 (d, *J*=4.5 Hz, 1H), 3.36-3.27 (m, 2H), 2.97 (td, *J*=17.5, 7.5 Hz, 1H), 2.74 -2.62 (m, 1H), 2.46-2.37 (m, 1H), 1.86-1.81 (m, 1H), 1.71-1.64 (m, 1H), 1.31 (s, 3H), 0.91-0.86 (m, 18H), 0.07-0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.89, 178.23, 159.31, 137.94, 130.99, 130.53, 129.68, 129.64, 129.46, 129.41, 128.54, 128.00, 127.72, 127.60, 113.90, 78.66, 76.38, 76.29, 74.26, 73.61, 71.93, 70.44, 69.47, 65.55, 55.43, 49.77, 42.19, 42.09, 39.75, 39.29, 29.89, 28.31, 26.09, 26.08, 25.87, 18.96, 18.88, 18.32, 18.10 ppm; IR (neat) 2928, 2856, 1774, 1715, 1513, 1462, 1370, 1248, 1094, 833, 776 cm^{-1}; LC/MS: m/z calcd. for $C_{39}H_{62}O_8Si_2$ $[M+Na]^+$ 737.4, found: 737.7.