Model Study for the Biogenesis of Benzastatins

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Seven benzastatins were isolated from the culture broth of *Streptomyces nitrosporeus 30643*. These compounds have been found to possess inhibitory activity against glutamate toxicity and against lipid peroxidation in rat liver microsomes.[1] Benzastatin A and B contain a *p*-aminobenzamide unit and benzastatin C and D have a tetrahydroquinoline ring system[2] related to virantmycin.[3] On the other hand, benzastatin E, F, and G have an indoline skeleton rarely occurring in fungal metabolites.[4]

Considering the structures of benzastatin family, we are proposing a possible biogenesis for benzastatins as shown in Figure1. Benzastatin D and E could be derived from benzastatin A through the cyclization via some kind of an oxidized intermediate, such as the epoxide. Moreover, we suppose that benzastatin D and E can be interconvertable through the aziridine intermediate. In order to demonstrate the feasibility of our hypothesis, we carried out model study, and in this paper we would like to report our preliminary results from this effort.

Our first concern was whether the epoxide compound cyclizes to the tetrahydroquinoline or indoline ring system. The compound **8** was prepared as shown in Scheme 1. The Wittig reaction of the aldehyde **2**, easily prepared from 2-nitrophenylacetonitrile, with ethyl 2-(triphenylphosphoranylidene)propionate afforded (E)-olefin **3** as a major product (E : Z=13 : 1).[5] After the reduction of α,β-unsaturated ester **3** to the allylic alcohol **4**,[6] the allylic alcohol **4** was then methylated and oxidized with *m*-CPBA to give the desired epoxide compound **7**. Hydrogenation of the nitro group of **7** to the corresponding amine in the presence of 10% Pd/C in

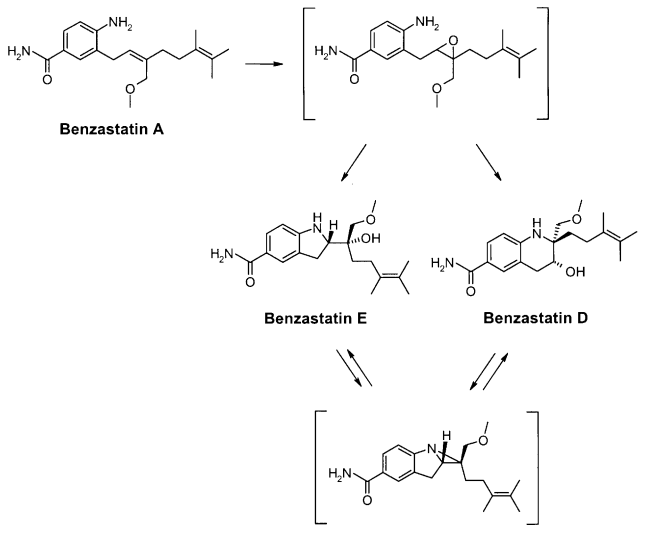
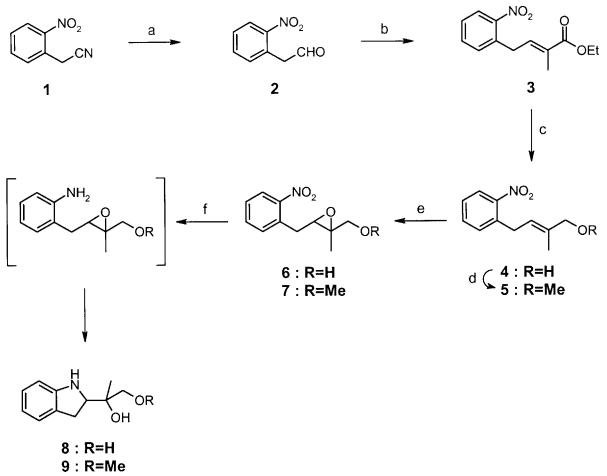


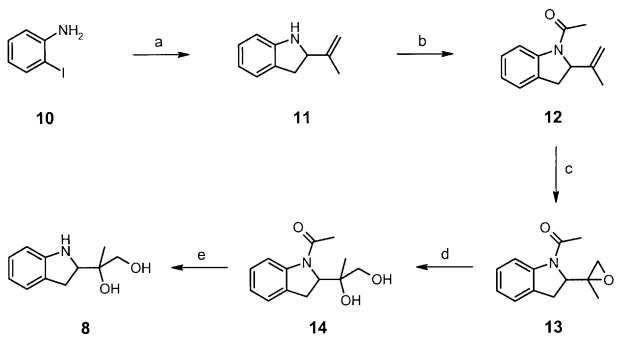
Figure 1



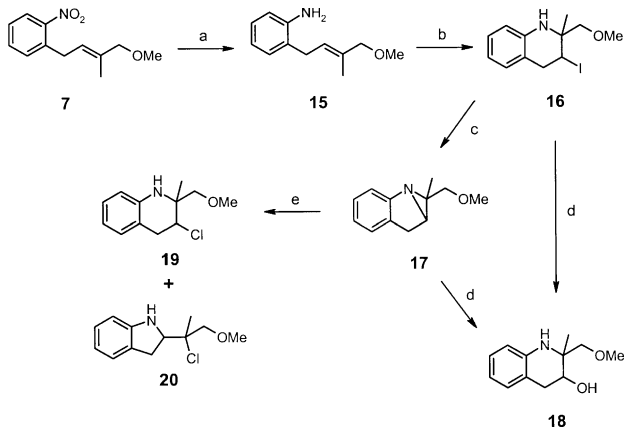
Scheme 1. *Reagents and conditions*: (a) Dibal-H, toluene, –78 °C, 1 hr. (b) 2-(triphenylphosphoranylidene)propionate, benzene, reflux, 24 hr, two steps 47%. (c) Dibal-H, toluene, –78 °C, 10 min, 86%. (d) MeI, NaH, DMF, rt, 30 min, 91%. (e) $VO(acac)_2$, TBHP, benzene, rt, 1 hr, 87%. (e) H_2. (g) 10% Pd/C, MeOH, rt, 3 hr, 82%.

methanol at room temperature gave the spontaneously cyclized product **9**. This indoline product was believed to be generated by the intramolecular epoxide opening following the Baldwin's rule.[7] The epoxy alcohol **6** cyclized to **8** under the same condition.

In order to confirm the structure **8** conclusively, we prepared the indoline **8** through an independent route as shown in Scheme 2. The palladium-catalyzed reaction of *o*-iodoaniline with isoprene in the presence of $Pd(OAc)_2$, triphenylphosphine and triethylamine afforded the indoline derivative **11**.[8] After the protection of the amino group with acetyl chloride, the epoxidation of **12** with *m*-CPBA gave



Scheme 2. *Reagents and conditions*: (a) isoprene, $Pd(OAc)_2$, Ph_3P, TEA, 130 °C, 39 hr, 72%. (b) AcCl, TEA, CH_2Cl_2, rt, 10 min, 89%. (c) *m*-CPBA, CH_2Cl_2, reflux, 24 hr, 61%. (d) 3% aq. $HClO_4$, DME, rt, 24 hr, 81%. (e) 3N NaOH, THF, rt, 24 hr, 56%.



Scheme 3. *Reagents and conditions*: (a) $NaBH_4$, $Cu(OAc)_2$, MeOH, rt, 10 min, 76%. (b) I_2, Na_2CO_3, CH_2Cl_2, rt, 1 hr, 44%. (c) DBU, toluene, 100 °C, 30 min, 67%. (d) $AgBF_4$, acetone/H_2O, rt, 15 min, 90%. (e) dry HCl, CH_2Cl_2, rt, 30 min, 62% (**19** : **20**=1 : 1).

13, which was hydrolyzed to the diol followed by the deprotection with 3N NaOH gave the compound **8**. The compound **8** obtained from two independent routes was found to be identical in all spectroscopic and chromatographic behaviors.[9]

Interestingly, when the compound **15**, prepared from **7**, was treated with I_2 in CH_2Cl_2, it underwent a different cyclization pathway to give the six-membered ring **16**. In order to test the possibility of interconversion of tetrahydroquinoline compound to indoline, **16** was treated with DBU in toluene at 100 °C to give the aziridine intermediate **17**. We then examined the solvolysis of the aziridine **17**. Treatment of aziridine **17** with $AgBF_4$ in aqueous acetone[10] or hydrochloric acid produced 3-hydroxytetrahydroquinoline **18** as the only reaction product. In addition, solvolysis of **16** under $AgBF_4$ condition gave **18**. However, the treatment of **17** with anhydrous hydrogen chloride gave a mixture of the chlorine derivatives of tetrahydroquinoline **19** and indoline **20**, indicating that the five-membered ring and the six-membered ring could be interconvertable.

In summary, we have demonstrated that the amino-olefin can be cyclized either to the six-membered ring product or to the five-membered ring product depending on the cyclization condition. Furthermore, we have demonstrated that the six-membered ring product could be converted to the five-membered ring system via the aziridine intermediate. In due course we will examine the reaction conditions for the conversion of indoline to aziridine.

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9. Spectral data for **8** : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 2.92 (dd, 1H, *J*=15.79, 10.89 Hz), 3.05 (dd, 1H, *J*=15.79, 9.27 Hz), 3.45 (d, 1H, *J*=11.54 Hz), 3.94 (d, 1H, *J*=11.54 Hz), 4.02 (dd, 1H, *J*=10.89, 9.27 Hz), 6.68 (d, 1H), 6.78 (dd, 1H), 7.11 (d, 1H), 7.65 (dd, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.41, 31.39, 67.09, 67.48, 72.98, 110.59, 119.99, 124.78, 127.41, 129.20, 149.69; MS (EI) m/z (%) 193 (M^+, 42), 162 (16), 144 (14), 130 (8), 118 (100), 106 (11), 91 (42).
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