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A stereoselective synthesis of the hexahydroazepine core of (−)-balanol☆

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Abstract—A stereoselective synthesis of the hexahydroazepine core of (−)-balanol is described. The key step of the route includes the bromosulfonamidation of an olefin using the intramolecular sulfilimine group as the nucleophile and the Pummerer ene reaction.

(−)-Balanol **1**, a fungal metabolite, was isolated independently by Kulanthaivel et al.[1] from *Verticillium balanoides* and by Ohshima et al.[2] from *Fusarium merismoides*. Balanol is a potent inhibitor of protein kinase C (PKC), a family of phospholipid dependent serine/threonine protein kinases, implicated in a number of diseases including AIDS, cancer, asthma, diabetes, cardio vascular disorders and central nervous system dysfunction. Investigations have revealed that the remarkable inhibitory activity of balanol is due to its binding to the ATP docking site of protein kinase.[3] The unique structure and the biological activity of balanol have attracted the attention of synthetic chemists and a number of reports have disclosed the total synthesis[4] or the synthesis of the fragments.[5] Balanol consists of the hexahydroazepine fragment and the benzophenone fragment (Fig. 1).

We recently described a methodology for the stereoselective elaboration of vicinal amino alcohol derivatives from allyl alcohols/ethers using an intramolecular sulfilimine as the nucleophile.[6] As a demonstration of the potential of the methodology, we describe herein a concise stereoselective synthesis of the hexahydroazepine subunit **2**, of balanol. By a retrosynthetic analysis (Scheme 1), the azidoaldehyde **3** was envisaged as the key intermediate, which could be derived from the alkene **4**. Compound **4** can be obtained from amino alcohol **5**, which in turn can be traced back to the allyl alcohol **7** via sulfilimine **6**.

The synthesis began with alcohol **7** (88% ee) obtained by Sharpless' kinetic resolution.[7] Treatment of **7** with thiophenol in the presence of DBU[8] yielded sulfide **8**.[9] Sulfide **8** on treatment with Chloramine-T afforded an

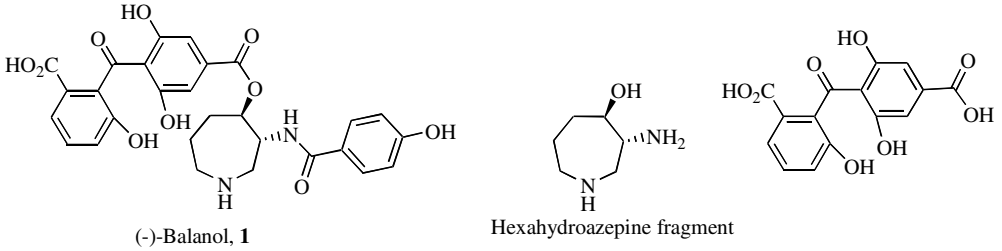

Figure 1.

Keywords: (−)-Balanol; Sulfilimine; Bromosulfonamidation; Pummerer ene reaction.
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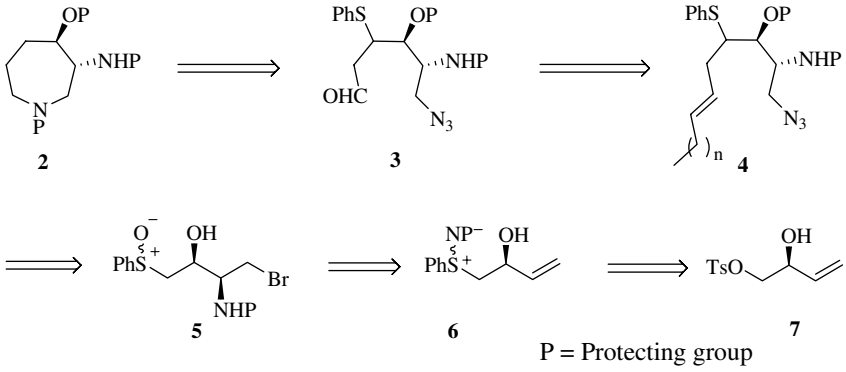
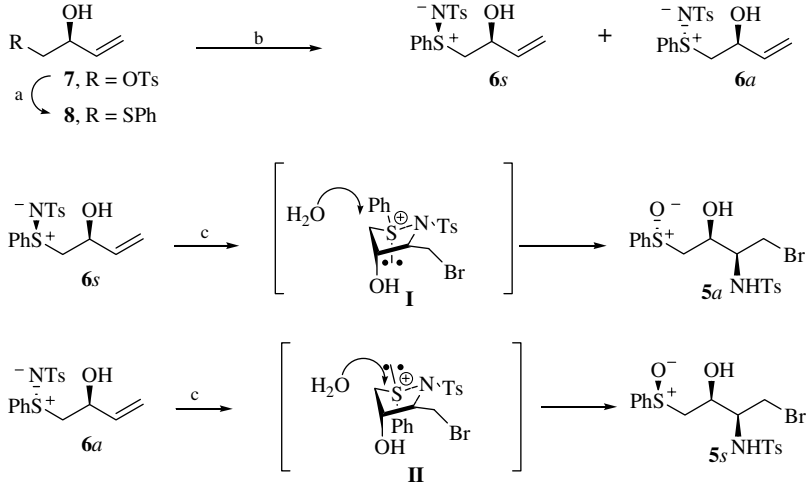


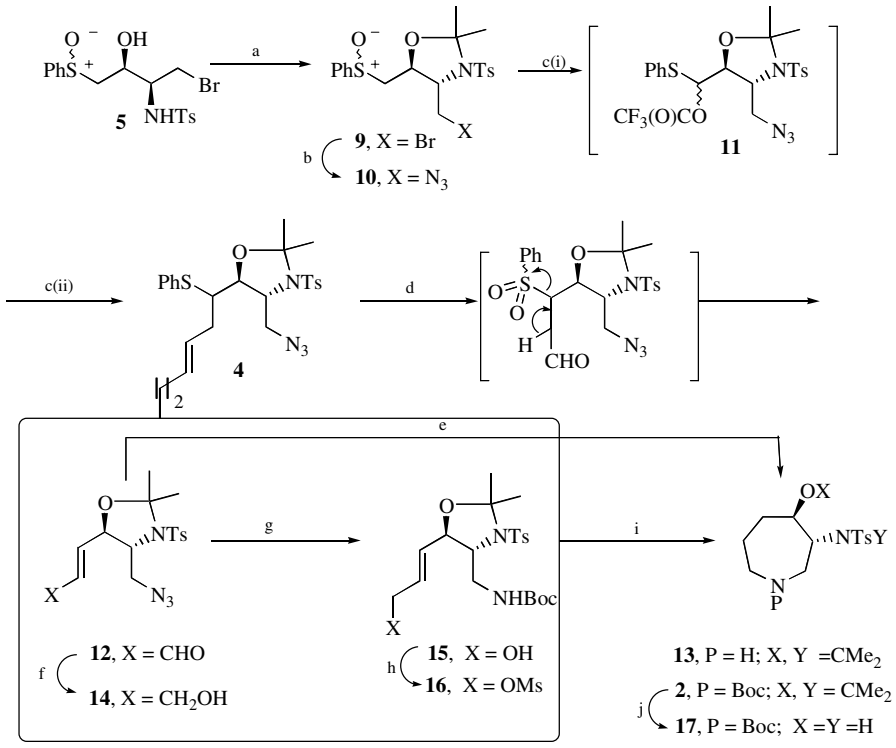
Scheme 1.

equimolar mixture of sulfilimines **6***s* and **6***a*. Compound **6** on reaction with *N*-bromosuccinimide yielded cleanly bromosulfonamides **5***a* and **5***s*.[6] The reaction proceeds via the intermediates **I** and **II**, formed by the 5-*exo* nucleophilic attack of the sulfilimine onto the olefin π-complexed to the bromonium ion. Hydrolysis by the attack of water on sulfur afforded the products (Scheme 2). Protection of **5** as an acetonide, followed by displacement of the bromide by azide gave **10** which on treatment with trifluoroacetic anhydride[10] yielded the Pummerer intermediate **11**. The intermediate without isolation was subjected to reaction with 1-hexene in the presence of $SnCl_4$ to afford the ene reaction product **4**.[11] The crude ^{1}H NMR spectrum of **4** revealed the presence of one compound only. The configuration at the newly created stereogenic center was not established since it was to be removed in the subsequent step. Elaboration of **4** to the hexahydroazepine core of balanol was planned by ozonolysis of the double bond followed by reductive cyclization of the resulting azidoaldehyde using Raney-Nickel with concurrent removal of the thiophenyl group. In the event, ozonolysis of **4** in dichloromethane did not yield **3** but **12** only. Under the reaction conditions, the sulfide is probably converted to the sulfone and the double bond into an ozonide. α,β-Unsaturated aldehyde **12** is presumably formed via β-elimination of phenylsulfinic acid (Scheme 3). Reductive amination of **12** would directly afford the hexahydroazepine moiety. Indeed, treatment of **12** with Pd/C in EtOH/EtOAc under an atmosphere of hydrogen afforded **13**. However, the reaction proved irreproducible; many spots were observed on TLC examination during scale up and the crude ^{1}H NMR spectrum revealed tosyl deprotection. Therefore, the hexahydroazepine fragment was elaborated in a stepwise manner. Aldehyde **12** was reduced using Luche's protocol[12] to afford allyl alcohol **14**. Hydrogenation of **14** with Pd/C in the presence of di-*tert*-butyl di carbonate in EtOAc afforded carbamate **15**. Mesylation of the alcohol cleanly yielded mesylate **16**, which without purification was treated with potassium *tert*-butoxide in anhydrous THF to cleanly afford **2**. During the work up, the acetonide group underwent deprotection to produce a small amount of alcohol **17**. Treatment of **2** with catalytic amount of PPTS in ethanol afforded **17**.[13]

In summary, we have disclosed a concise stereoselective synthesis of the hexahydroazepine core of balanol. The key steps of the synthesis include elaboration of bromosulfonamide **5** via intramolecular sulfilimine participation and Pummerer ene reaction. Efforts are in progress to synthesize other bioactive target molecules



Scheme 2. Reaction conditions: (a) PhSH, DBU, toluene, rt, 1 h, 80%; (b) NaNTsCl, CH_3CN, rt, 30 min, 90%; (c) NBS, toluene, rt, 1 h, 80%.



Scheme 3. Reaction conditions: (a) 2,2-dimethoxypropane, cat. CSA, acetone, 70 °C, 6 h, 70%; (b) NaN_3, DMSO, 80 °C, 6 h, 90%; (c) (i) TFAA, CH_2Cl_2, 0 °C, 30 min, (ii) 1-hexene, $SnCl_4$, 0 °C, 5 min, 70%; (d) O_3, CH_2Cl_2, −78 °C, 30 min, then Me_2S, −78 to 0 °C, 30 min, 75%; (e) H_2, Pd/C, EtOH/EtOAc, rt, 6 h; (f) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 30 min, 70%; (g) $(Boc)_2O$, Pd/C, H_2, rt, 6 h, 90%; (h) Ms-Cl, Et_3N, cat. DMAP, CH_2Cl_2, 0 °C, 30 min, 88%; (i) KO*t*Bu, THF, rt, 1 h, 70%; (j) PPTS, EtOH, 80 °C, 1 h, 83%.

possessing the vicinal amino alcohol unit using our methodology and the results from these investigations will be reported in the near future.

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