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An efficient approach for the synthesis of the hexahydroazepine segment of balanol†

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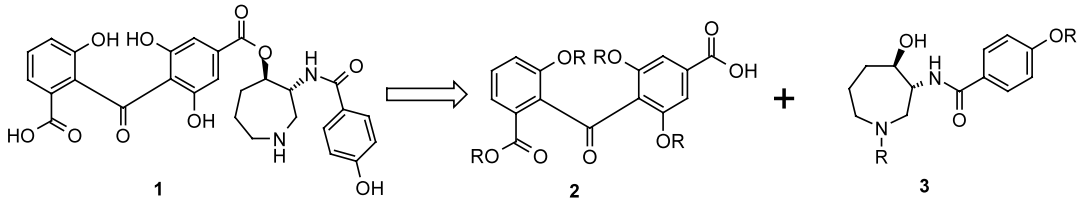
Abstract—An efficient approach for the synthesis of the hexahydroazepine segment of balanol is described in seven steps in a highly stereoselective manner starting from (*S*)-2,3-*O*-isopropylidine glyceraldehyde.

(−)-Balanol **1**, a structurally unusual metabolite isolated from the fungii *Verticillium balanoides*[1] and *Fusarium merismoides*,[2] represents an important new lead structure in the quest for selective inhibitors of protein kinase C (PKC). Protein kinase C (PKC) is a family of phospholipid-dependent serine/threonine specific protein kinases that mediate a wide range of signal transduction processes in cells. Human PKC enzyme consists of at least eight isoforms, which play important roles in cellular growth control, regulation and differentiation. Since activation of PKC enzymes has been implicated in a number of diseases such as cancer, cardiovascular disorders, central nervous system dysfunction, HIV infection, asthma, inflammatory diabetes, and so on, a selective inhibitor of PKC isozymes might have wide ranging therapeutic potential.[3]

(−)-Balanol **1** consists of two important fragments, the benzophenone carboxylic acid moiety **2** and the chiral hexahydroazepine domain **3** (Scheme 1). The first total synthesis of balanol was reported by Nicolaou et al. who prepared it in a highly stereoselective manner from D-serine.[4a] Several later approaches have been reported for the total synthesis of balanol[4] as well as for the construction of the chiral hexahydroazepine moiety.[5] The biological significance and novel fascinating structure of balanol prompted us to investigate the synthesis of balanol. In continuation of our interest towards the total synthesis of biologically interesting molecules such as sphingosine,[6] and camptothecin[7] etc., we herein describe a simple and efficient approach for the synthesis of the hexahydroazepine moiety of balanol using (*S*)-2,3-*O*-isopropylidene glyceraldehyde.

Accordingly, the aldehyde **4** was obtained from L-ascorbic acid by a known literature procedure.[8] Treatment of aldehyde **4** with allyl bromide in the presence of zinc and aq. NH_4Cl in THF at 0°C afforded the corresponding homoallyl alcohol **5** as a mixture of diastereoisomers (96:4 *anti*:*syn*). The free hydroxy functionality of the major isomer was protected as its benzyl ether using benzyl bromide in THF to give compound **6**, which was subjected to hydroboration using BH_3–DMS in THF to afford the alcohol **7**. The isopropylidene acetal in **7** was deprotected using TFA in THF:H_2O to furnish the key intermediate **8**.[9a] The two primary hydroxyls of compound **8** were selectively converted to their triflates using triflic anhydride and 2,6-



Scheme 1.

Keywords: balanol; kinetic resolution; triflic anhydride; azepine.

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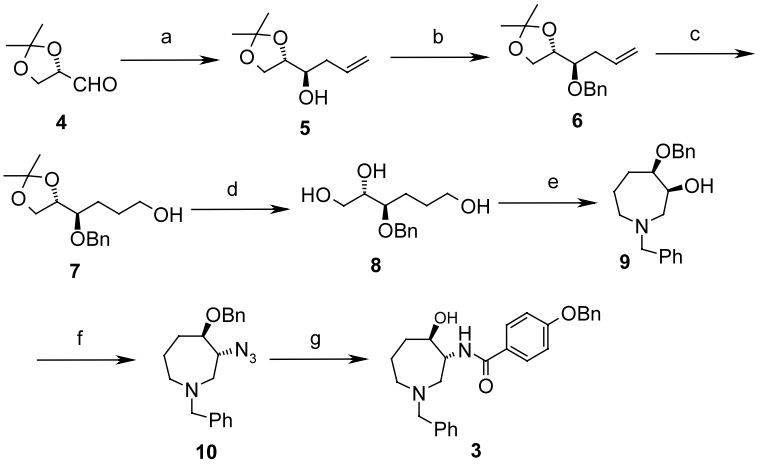
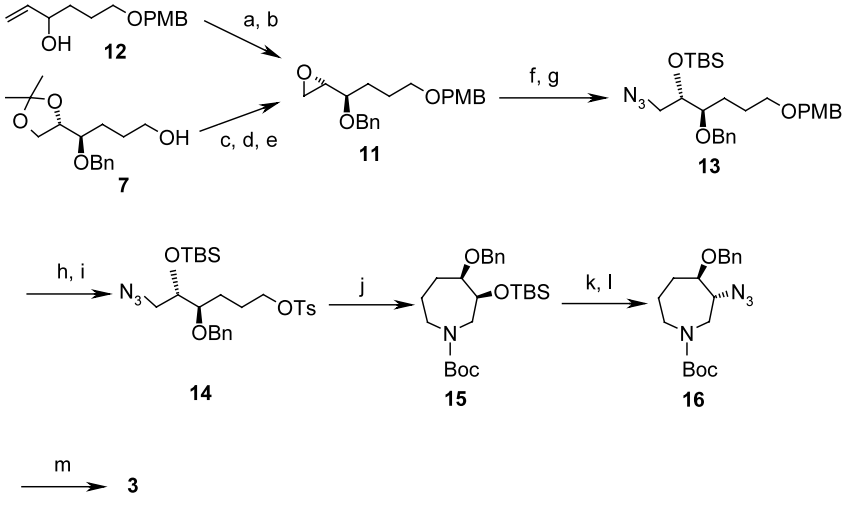
lutidine. The resultant product was cyclized with an excess of benzylamine to give azepine moiety **9**.[9b] Conversion of the hydroxyl group in **9** into an azido group using Mitsunobu conditions was unsuccessful, but treatment of **9** with triflic anhydride/2,6-lutidine in CH_2Cl_2, followed by displacement with NaN_3 in DMF afforded the desired compound **10** in excellent yield. The reduction of the azide to an amine and the simultaneous cleavage of the benzyl ether was achieved in ethyl acetate with PtO_2 under a H_2 atmosphere. The resultant crude aminol was coupled with *p*-benzyloxybenzoyl chloride using triethylamine in CH_2Cl_2 to afford the protected (3*R*,4*R*)-3-amino-4-hydroxyhexahydroazepine derivative **3** (overall yield 18.2%) with spectroscopic characteristics in full agreement with the published data (Scheme 2).[4d]

The azepine ring could also be synthesized from the intermediate **7** using a different approach (Scheme 3). Accordingly alcohol **7** was protected as its PMB ether, followed by cleavage of the acetonide to give the corresponding diol. The primary hydroxy functionality of the diol was tosylated followed by treatment with base to give the epoxide **11**.[9c] This epoxide could also be generated stereospecifically via kinetic resolution of **12** under Sharpless epoxidation conditions with *tert*-butylhydroperoxide (TBHP) and (–)-DIPT in $CHCl_2$ at –20°C.[10] The epoxide **11** was treated with NaN_3 to give the corresponding azido alcohol and the resultant secondary hydroxyl was protected as its TBDMS ether **13**. Cleavage of the PMB ether of **13** and tosylation of the free alcohol gave **14**. The azide **14** was treated with TPP in methanol under reflux followed by in situ treatment



Scheme 2. *Reagents and conditions*: (a) Allyl bromide, Zn, aq. NH_4Cl, THF, 0°C (93%); (b) BnBr, NaH, THF, rt (95%); (c) BH_3–DMS, H_2O_2, THF, 0°C (79%); (d) TFA, THF:H_2O, rt (97%); (e) Tf_2O, 2,6-lutidine, CH_2Cl_2, –78°C, then $BnNH_2$ (20 equiv.), –78°C to rt (52%); (f) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C, then NaN_3 in DMF, rt (91%); (g) PtO_2, H_2, EtOAc, rt, then *p*-benzyloxybenzoyl chloride, TEA, CH_2Cl_2, 0°C to rt (57%).



Scheme 3. *Reagents and conditions*: (a) TTIP, (–)-DIPT, TBHP, CH_2Cl_2, –20°C (40%); (b) BnBr, NaH, Bu_4NI, THF, rt (94%); (c) MPMBr, NaH, THF, rt (89%); (d) TFA, THF:H_2O, rt (93%); (e) TsCl (1 equiv.), TEA (1.1 equiv.), CH_2Cl_2, 0°C to rt, then K_2CO_3, MeOH, rt (87%); (f) NaN_3, NH_4Cl, DMF, 100°C (97%); (g) TBDMSCl, imidazole, DMAP (cat.), CH_2Cl_2, 0°C to rt (75%); (h) DDQ, CH_2Cl_2:H_2O, rt (95%); (i) TsCl, TEA, CH_2Cl_2, 0°C (91%); (j) TPP, MeOH, reflux, then $(BOC)_2O$, TEA, rt (67%); (k) TBAF, THF, 0°C to rt (89%); (l) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0°C, then NaN_3 in DMF, rt (90%); (m) Pd/C, H_2, MeOH, rt, then *p*-benzyloxybenzoyl chloride, TEA, CH_2Cl_2 0°C to rt (59%).

with $(BOC)_2O$ to give the cyclized product **15**. The 2° alcohol center of **15** was inverted after cleaving the TBDMS ether by converting the resultant hydroxyl, via its triflate, to the azide **16** with NaN_3. Reduction of the azide to the amine and simultaneous cleavage of the benzyl ether was achieved in methanol with Pd/C under a H_2 atmosphere. The resultant crude aminol was coupled with *p*-benzyloxybenzoyl chloride using triethylamine in CH_2Cl_2 to give the Boc-protected hexahydroazepine derivative **3**.

In summary, we have developed a simple, convenient and efficient approach for the synthesis of the hexahydroazepine moiety of balanol involving a sequence of reactions starting from (*S*)-2,3-*O*-isopropylidene glyceraldehyde. This approach offers high overall yield, useful stereoselectivity, readily available starting materials at low cost and simple experimental conditions which make it a useful and attractive process for the total synthesis of balanol. Further work is currently underway.

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9. Spectral data for selected compounds:
(a) Compound **8**: ^1H NMR (200 MHz, $CDCl_3$, *J* in Hz, TMS internal standard) 1.6–1.8 (m, 4H), 3.47–3.80 (m, 6H), 4.6 (m, 2H), 7.25 (m, 5H); *m*/*z* (FAB) 240 (M+); IR (neat/cm^{-1}): 698, 749, 1071, 1454, 2928, 3406; $[\alpha]_D = -1.95$ (*c* 1, $CHCl_3$).
(b) Compound **9**: ^1H NMR (200 MHz, $CDCl_3$, *J* in Hz, TMS internal standard) 1.70–1.97 (m, 4H), 2.62–2.75 (m, 2H), 2.8 (d, 2H, $J=5.9$), 3.47–3.57 (m, 1H), 3.75 (s, 2H), 3.82–3.97 (m, 1H), 4.57 (d, 1H, $J=11.9$), 4.62 (d, 1H, $J=11.9$), 7.25–7.42 (m, 10H); *m*/*z* (FAB) 312 (M+1); IR (neat/cm^{-1}): 699, 738, 1096, 1453, 2932, 3030, 3448; $[\alpha]_D = -7.09$ (*c* 0.7, $CHCl_3$).
(c) Compound **11**: ^1H NMR (300 MHz, $CDCl_3$, *J* in Hz, TMS internal standard) 1.6–1.85 (m, 4H), 2.65–2.75 (m, 2H), 2.85–2.9 (m, 1H), 3.22–3.3 (m, 1H), 3.35–3.45 (m, 2H), 3.8 (s, 3H), 4.4 (s, 2H), 4.45 (d, 1H, $J=12$), 4.62 (d, 1H, $J=12$), 6.82 (d, 2H, $J=10.8$), 7.2 (d, 2H, $J=10.8$), 7.27 (m, 5H); *m*/*z* (FAB) 342 (M+); IR (neat/cm^{-1}) 699, 740, 821, 1034, 1094, 1247, 1456, 1512, 1612, 2859, 2928. $[\alpha]_D = +7.61$ (*c* 1.5, $CHCl_3$).
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