A NOVEL AND CHIRAL SYNTHESIS OF BOTH ENANTIOMERS OF *TRANS*-3-AMINO-4-HYDROXYHEXAHYDROAZEPINE, A KEY INTERMEDIATE FOR THE SYNTHESIS OF BALANOL

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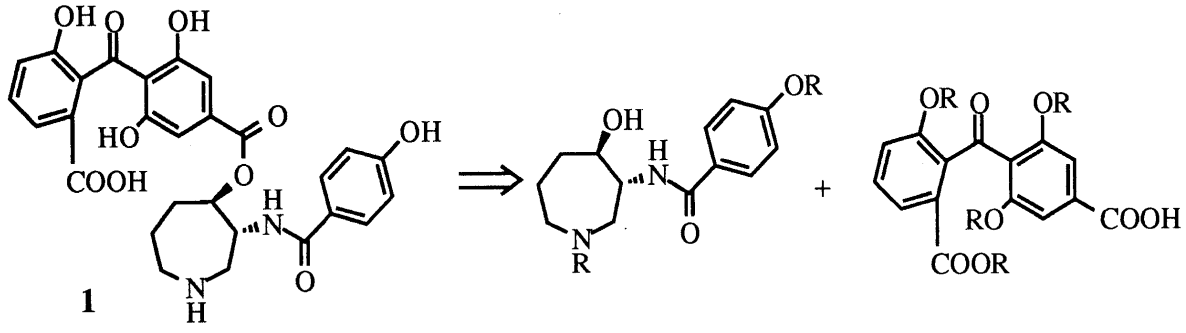
Both enantiomers of the hexahydroazepine (**7**), key intermediates for the synthesis of (-)-balanol (**1**) and its enantiomer, were effectively synthesized *via* the shortest route involving stannyl radical cyclization of the aldehyde (**4**) connected with oxime ether followed by the optical resolution of the resulting azepine (**7**).

KEY WORDS balanol; 3-amino-4-hydroxyhexahydroazepine; oxime ether; radical cyclization; chiral synthesis; PKC inhibitor

Three groups[1-3] of researchers have recently synthesized (-)-balanol (**1**), an unusual metabolite produced by the fungus *Verticillium balanoides*, which has been shown to be a potent inhibitor of protein kinase C enzymes.[4] The works could lead to the development of balanol analogs as potential new drugs against cancer and a wide range of other diseases associated with protein kinase C activation.[5] All synthetic methods reported involve the connection of two distinct structural domains, chiral hexahydroazepine-containing fragment[1-3, 6] and benzophenone fragment.[1-3]



In this communication, we wish to describe a novel and concise synthesis of both enantiomers of the chiral hexahydroazepine-containing fragment *via* the route involving the radical cyclization[7] of the aldehyde (**4**) connected with oxime ether followed by optical resolution of the racemic product.

4-Aminobutanol (**2**) was alkylated with α-chloroacetaldoxime benzyl ether,[8] readily prepared from the corresponding aldehyde and benzyloxyamine, to give the secondary amine which was acylated with di-*t*-butyl carbonate under the Schotten-Baumann condition to afford the hydroxy oxime ether (**3**)[9] in 67% yield from **2**. Mild oxidation of the alcohol (**3**) with chromium(VI) oxide-

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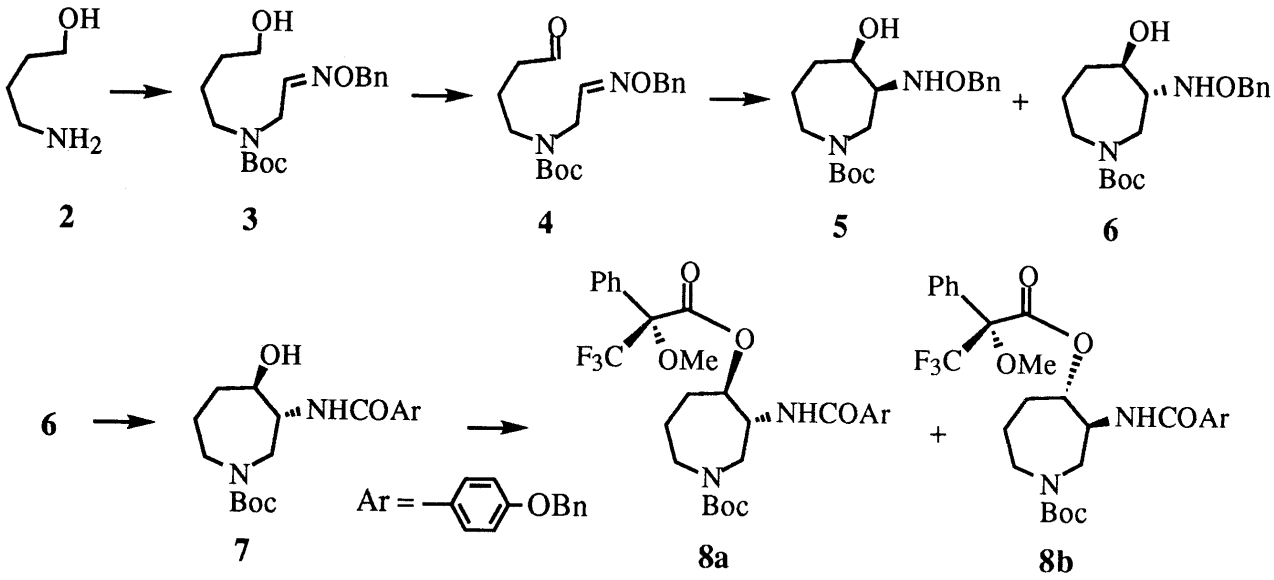
pyridine gave the unstable aldehyde (**4**)[9] in 77% yield. Stannyl radical cyclization[7] of the aldehyde (**4**) by treatment with tributyltin hydride (2 equiv.) in the presence of AIBN (1 equiv.) proceeded smoothly to give a 2:3 mixture of two cyclized products (**5**)[10] and (**6**)[10] in 58% combined yield which was readily separated by medium pressure column chromatography. Hydrogenolysis of the benzyloxy-amino group in *trans*-product (**6**) in the presence of platinum dioxide followed by *N*-acylation with *p*-(benzyloxy)benzoyl chloride afforded the desired azepine (**7**) in 58% yield from **6**. Thus, we have succeeded in the six-step synthesis of the racemic key intermediate (**7**)[1] for the synthesis of balanol.



Finally, in order to establish the biological activity residing in only one enantiomer, the racemic azepine (**7**) was subjected to optical resolution by forming the corresponding chiral esters *via* application of (-)-Mosher's acid, (-)-camphanic acid, and *N-Z-(L)*-alanine. (-)-Mosher's acid gave the readily separable diastereomeric esters (**8a**) and (**8b**) by a medium pressure column chromatography. Alkaline hydrolysis of two esters (**8a**) and (**8b**) gave the respective (3*R*,4*R*)-azepine (**7**)[11] and (3*S*,4*S*)-isomer[11] in 95% overall yield and in >99% ee. The enantiomeric purity was checked by chiral chromatography (Chiral Pack AD column) eluting with ethanol-heptane (15 : 85, v/v).[3] The (3*R*,4*R*)-azepine (**7**) was found to be identical with the authentic sample (-)-(**7**) upon comparisons of their spectral data including optical rotation.[12]

Our chiral synthesis of the key intermediate (**7**) and the enantiomer would open a novel asymmetric synthetic route for (-)- and (+)-balanols.

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9) The compounds (**3**) and (**4**) were the mixtures of *E* - and *Z* -isomers (3:2) in the geometry of the oxime ether group. **3**: IR ($CHCl_3$) cm^{-1}: 1686 (NCO_2). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.45-7.25 (28/5H, m, ArH and HC=N (*E*)), 6.70 (2/5H, br t, *J*=4 Hz, HC=N (*Z*)), 5.11 (4/5H, s, C*H*$_2$Ph (*Z*)), 5.07 (6/5H, s, C*H*$_2$Ph (*E*)), 4.15-4.00 (4/5H, m, C*H*$_2$CH=N (*Z*)), 4.00-3.80 (6/5H, m, C*H*$_2$CH=N (*E*)), 3.65-3.55 (2H, m, C*H*$_2$OH), 3.30-3.10 (2H, m, CH$_2$C*H*$_2$NBoc), 1.60-1.40 (4H, m, C*H*$_2$C*H*$_2$CH$_2$NBoc), 1.44 (9H, s, Me × 3). MS Calcd for $C_{18}H_{28}N_2O_4$ (M^+); 336.2047. Found: 336.2049. **4**: IR ($CHCl_3$) cm^{-1}: 1723 (CHO), 1688(NCO_2). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.74 (2/5H, t, *J*=1 Hz, CHO (*Z*)), 9.71 (3/5H, t,*J*=1 Hz, CHO (*E*)), 7.41-7.20 (5H, m, ArH), 7.40 (3/5H, br t, *J*=4 Hz, HC=N (*E*)), 6.69 (2/5H, br t, *J*=4 Hz, HC=N (*Z*)), 5.11 (4/5H, s, C*H*$_2$Ph (*Z*)), 5.06 (6/5H, s, C*H*$_2$Ph (*E*)), 4.15-4.00 (4/5H, m, C*H*$_2$CH=N (*Z*)), 3.98-3.82 (6/5H, m, C*H*$_2$CH=N (*E*)), 3.30-3.12 (2H, m, CH$_2$C*H*$_2$NBoc), 2.50-2.30 (2H, m, C*H*$_2$CHO), 1.90-1.70 (2H, m, C*H*$_2$CH$_2$NBoc), 1.44 (9H, s, Me × 3). MS *m/z*; 334 (M^+).
10) **5**: IR ($CHCl_3$) cm^{-1}: 1682 (NCO_2). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.42-7.28 (5H, m, ArH), 4.70 (2H, s, C*H*$_2$Ph), 4.05 (1H, m, 4-H), 3.66-3.07 (5H, m, 2-H$_2$, 3-H, 7-H$_2$), 2.08-1.55 (4H, m, 5-H$_2$, 6-H$_2$), 1.44 (9H, s, Me × 3). MS Calcd for $C_{18}H_{28}N_2O_4$ (M^+); 336.2047. Found: 336.2036. **6**: IR ($CHCl_3$) cm^{-1}: 1681 (NCO_2). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.42-7.25 (5H, m, ArH), 4.70 and 4.68 (2H, ABq, *J*=14 Hz, C*H*$_2$Ph), 3.71-2.83 (6H, m, 2-H$_2$, 3-H, 4-H, 7-H$_2$), 2.00-1.40 (4H, m, 5-H$_2$, 6-H$_2$), 1.44 (9H, s, Me × 3). MS Calcd for $C_{18}H_{28}N_2O_4$ (M^+); 336.2047. Found: 336.2032.
11) (3*R*,4*R*)-**7**: Colorless needles (MeOH), m.p. 136-138°C. $[\alpha]_D^{24}$ -2.9° (*c*=1.30, MeOH). (3*S*,4*S*)-**7**: Colorless needles (MeOH), m.p. 136-138°C. $[\alpha]_D^{23}$ +2.5° (*c*=1.26, MeOH).
12) Private communication from Dr. P. F. Hughes.

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