Diastereocontrolled Synthesis of Enantiopure *trans*- and *cis*-5-Allylprolinols via a Ring-Contraction Protocol

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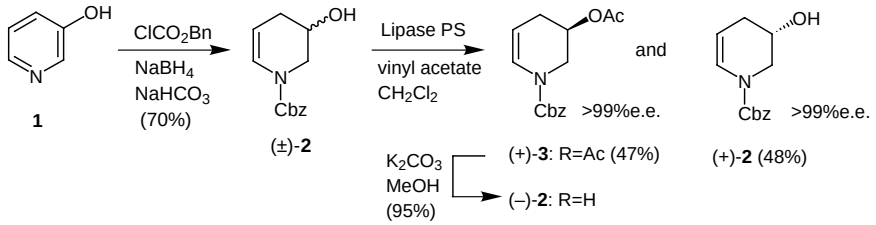
Abstract: A highly diastereocontrolled formation of *trans*- and *cis*-5-allyl-*N*-benzylprolinols from *trans*- and *cis*-2-allyl-*N*-benzyl-5-piperidinols has been achieved by employing a ring-contraction protocol.

Key words: chiral building block, ring contraction, 2-allyl-5-piperidinol, 5-allylprolinol, cesium acetate, Mitsunobu reaction

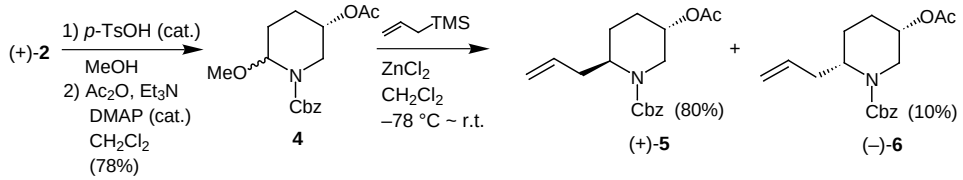
We have developed an efficient synthesis of *N*-carbobenzoxy-5,6-didehydro-5-piperidinol **2** in both enantiomeric forms from 3-hydroxypyridine **1** through an unprecedented reductive formation of the racemic didehydropiperidinol (±)-**2** followed by lipase-mediated kinetic resolution[1,2] (Scheme 1). Moreover, **2** was readily transformed into the 3-acetoxy-6-methoxypiperidine **4** which underwent diastereoselective allylation on exposure to allyltrimethylsilane in the presence of a Lewis acid to give 80% of *trans*-5-acetoxy-2-allyl-1-carbobenzoxypiperidine **5** and 10% of its *cis*-2,5-epimer **6** (Scheme 2).

Since there are a variety of physiologically active natural products carrying a 2,5-*cis*-substituted pyrrolidine core in their molecules,[3] we are interested in transformation of the above 2-allyl-5-piperidinol derivatives into the corresponding 2,5-disubstituted pyrrolidine derivatives by a ring-contraction pathway.[4] It was well established that piperidine derivatives carrying a leaving group at the 3 position undergo ring-contraction under appropriate nucleophilic conditions to give rise to 2-substituted pyrrolidines with 3-substituted piperidines through common aziridinium intermediates generated initially by intramolecular nucleophilic substitution. However, formation of piperidine derivatives prevails in most cases except some examples.[4,5] We explored conversion of the above isomeric enantiopure 2-allylpiperidines **5** and **6** into the 2,5-disubstituted pyrrolidines and found practically acceptable conditions for their diastereospecific conversion into 2,5-disubstituted pyrrolidine derivatives.

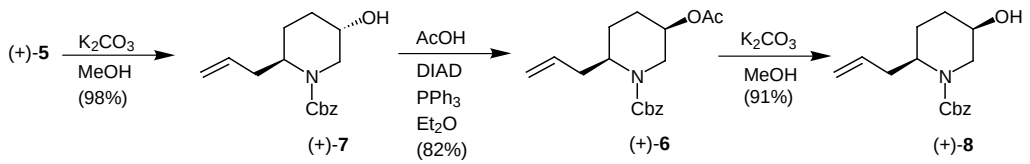
In order to secure the *cis*-acetate **6** which was generated as a minor component in the Lewis acid-mediated allylation of the methoxypiperidine **4**, conversion of the major *trans*-**5** into the minor *cis*-**6** was first examined by employing the Mitsunobu reaction.[6] Thus, (+)-**5**, $[\alpha]_D^{32}$+19.9 (c 0.9, $CHCl_3$), afforded the *trans*-alcohol (+)-**7**, $[\alpha]_D^{32}$+35.3 (*c* 0.9, $CHCl_3$), on alkaline methanolysis, which was treated with acetic acid in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) to furnish the *cis*-acetate (+)-**6**, $[\alpha]_D^{29}$+26.3 (*c* 1.0, $CHCl_3$). This gave the *cis*-alcohol (+)-**8**, $[\alpha]_D^{30}$+26.1 (c 0.8, $CHCl_3$), on alkaline methanolysis. Overall yield of (+)-**8** from (+)-**5** was 73% in three steps (Scheme 3).



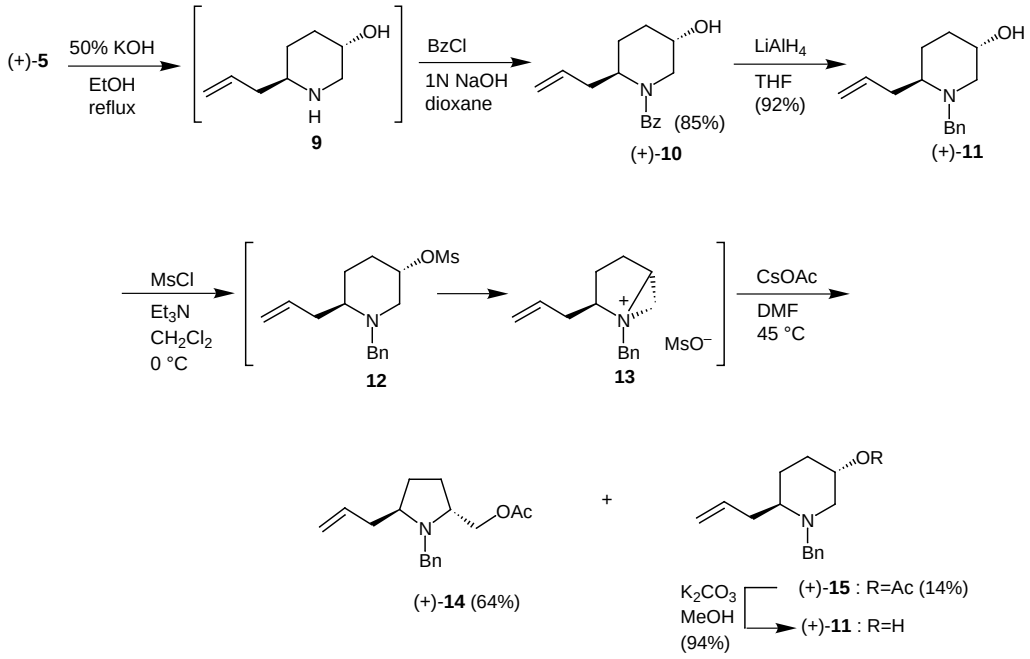
Scheme 1



Scheme 2



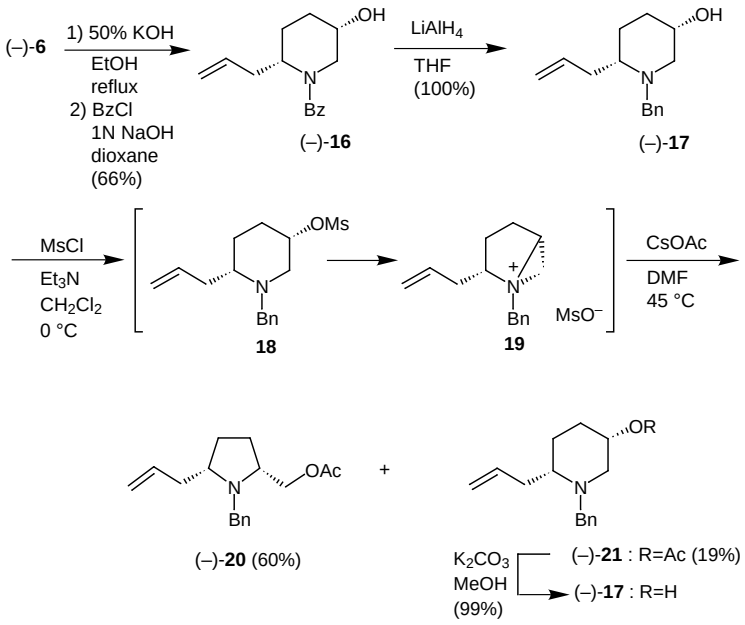
Scheme 3



Scheme 4

Having secured both diastereomeric acetates, the *trans*-acetate (+)-**5** was transformed into the *trans*-*N*-benzylaminoalcohol (+)-**11**, $[\alpha]_D^{29}$+37.2 (*c* 0.9, $CHCl_3$), in 78% overall yield by sequential alkaline hydrolysis, *N*-benzoylation, and hydride reduction via the aminoalcohol **9** and the *N*-benzamide (+)-**10**, mp 174-175 °C, $[\alpha]_D^{30}$+50.0 (*c* 1.0, $CHCl_3$). Mesylation of (+)-**11** in dichloromethane in the presence of triethylamine brought about spontaneous intramolecular reaction of the generated mesylate **12** to give the aziridinium salt **13**. Among the conditions examined, treatment of the salt **13** with cesium acetate[5,7] in DMF at 45 °C for 3 h furnished the ring-contracted product *trans*-5-allylprolinol acetate (+)-**14**, $[\alpha]_D^{31}$+88.2 (*c* 1.5, $CHCl_3$), in 64% yield accompanied with the readily separable *trans*-2-allyl-5-piperidinol acetate (+)-**15**, $[\alpha]_D^{29}$+40.6 (*c* 1.1, $CHCl_3$), in 14% yield. Optical rotation of the latter was virtually the same as that of the authentic acetate (+)-**15**, $[\alpha]_D^{31}$+40.1 (*c* 1.2, $CHCl_3$), obtained from the starting alcohol (+)-**11**, indicating the preservation of the original chiral integrity during the double inversion reaction. Although the ring-contraction did not proceed in a completely selective manner, the 2,5-disubstituted pyrrolidine (+)-**14** could be obtained in a practically acceptable yield and the piperidine byproduct (+)-**15** may be recycled after transformation into (+)-**11** by alkaline methanolysis (Scheme 4).

On the other hand, the *cis*-acetate (−)-**6** was transformed into the *cis*-*N*-benzylaminoalcohol (−)-**17**, $[\alpha]_D^{30}$ −89.6 (*c* 1.0, $CHCl_3$), in 66% overall yield by sequential alkaline hydrolysis, *N*-benzoylation, and hydride reduction via the benzamide (−)-**16**, $[\alpha]_D^{30}$ −30.5 (*c* 0.9, $CHCl_3$), as for the *trans*-counterpart (+)-**5**. Upon mesylation, (−)-**17** afforded the aziridinium salt **19**, through the mesylate **18**, which was treated with cesium acetate[5,7] to give diastereoselectively the *cis*-2,5-substituted pyrrolidine (−)-**20**, $[\alpha]_D^{29}$ −31.1 (*c* 1.6, $CHCl_3$), and the *cis*-2,5-substituted piperidine (−)-**21**, $[\alpha]_D^{29}$ −17.8 (*c* 1.0, $CHCl_3$), in yields of 60% and 19%, respectively, after separation by column chromatography. The latter was identical with the authentic (−)-**21**, $[\alpha]_D^{29}$ −18.6 (*c* 1.03, $CHCl_3$), obtained from (−)-**17**, which may be recycled after conversion into the alcohol (−)-**17**, $[\alpha]_D^{29}$ −91.6 (*c* 0.8, $CHCl_3$), by alkaline methanolysis. Yield of the ring-contraction product from the *cis*-substrate (−)-**17** was somewhat lower than that of the *trans*-counterpart (+)-**11**, but it is still acceptable for practical utilization (Scheme 5).



Scheme 5

In summary, we have achieved diastereoselective transformation of *trans*- and *cis*-2-allyl-5-hydroxy-1-benzylpiperidines into *trans*- and *cis*-5-allylprolinols in a practical manner by employing a ring-contraction protocol. Although the present procedure is accompanied with an unwanted piperidine byproduct, it may be recycled after deacetylation. Utilization of the 2,5-disubstituted pyrrolidines thus obtained for enantiocontrolled synthesis of pyrrolidine natural products is currently under investigation.

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References and Notes

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(7) Typical procedure: (a) for the *trans*-substrate (+)-**11**−To a stirred solution of (+)-**11** (860 mg, 3.72 mmol) in dichloromethane (15 mL) was added triethylamine (1.6 mL, 11.2 mmol) and methanesulfonyl chloride (0.43 mL, 5.6 mmol) at 0 °C and the stirring was continued for 30 min at the same temperature. After evaporation of the solvent under reduced pressure, the residue was dissolved in DMF (18 mL) and was stirred with cesium acetate (2.1 g, 11.2 mmol) at 45 °C for 3 h. The mixture was diluted in brine and extracted with ether. The extract was washed with 5% aqueous sodium hydrogen carbonate, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 30 g) to give the *trans*-prolinol acetate (+)-**14** (647 mg, 64%), $[\alpha]_D^{31}$+88.2 (*c* 1.5, $CHCl_3$), as a colorless oil from an EtOAc-hexane eluent (1: 12 v/v) and the *trans*-piperidinol acetate (+)-**15** (145 mg, 14%), $[\alpha]_D^{29}$+40.6 (*c* 1.1, $CHCl_3$), as a colorless oil from an EtOAc-hexane eluent (1:10 v/v). (+)-**14:** IR (film): ν = 1740, 1233 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 − 7.14 (5H, m), 5.81 − 5.61 (1H, m), 5.09 − 4.92 (2H, m), 4.11 − 3.89 (3H, m), 3.84 − 3.70 (1H, m), 3.26 −3.12 (1H, m), 3.12 − 2.99 (1H, m), 2.44 − 2.28 (1H, m), 2.09 − 1.08 (3H, m), 2.01 (3H, s), 1.69 − 1.54 (2H, m); ^{13}C NMR (125 Hz, $CDCl_3$): δ = 171.3, 140.3, 136.3, 128.3, 126.8, 116.5, 65.7, 60.2, 58.8, 51.8, 35.1, 27.7, 26.6, 21.0; MS: m/z = 272 (M^+ − 1), 91 (100%); HRMS: Calcd for $C_{14}H_{18}NO_2$ ($M^+ - C_3H_5$) = 232.1338, found = 232.1346. (+)-**15**: IR (film):ν = 1737, 1242 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 − 7.17 (5H, m), 5.97 − 5.77 (1H, m), 5.10 (1H, d, *J* = 4.1 Hz), 5.09 (1H, s), 4.82 − 4.68 (1H, m), 4.06 (1H, d, *J* = 13.5 Hz), 3.26 (1H, d, *J* = 13.5 Hz), 2.89 (1H, ddd, *J* = 11.3, 4.1, 1.8 Hz), 2.47 − 2.28 (2H, m), 2.02 (1H, dd, *J* = 10.8, 9.8 Hz), 1.97 (3H, s), 1.84 − 1.72 (1H, m), 1.57 (3H, m), 1.43 − 1.24 (1H, m); ^{13}C NMR (125 Hz, $CDCl_3$): δ = 170.5, 139.2, 135.4, 128.9, 128.4, 127.1, 116.9, 69.7, 59.6, 57.3, 55.1, 36.3, 29.3, 28.0, 21.2; MS : m/z = 272 (M^+ − 1), 91 (100%); HRMS : Calcd for $C_{14}H_{18}NO_2$ ($M^+ - C_3H_5$) = 232.1338, found = 232.1325. (b) for the *cis*-substrate (−)-**17**−As for (+)-**11**, (−)-**17** (87 mg, 0.38 mmol) was treated to give the *cis*-prolinol acetate (−)-**20** (61.9 mg, 60%), $[\alpha]_D^{29}$ −31.1 (*c* 1. 6, $CHCl_3$), as a colorless oil from an EtOAc-hexane eluent (1:12 v/v) and the *cis*-piperidinol acetate (−)-**21** (19.6 mg, 19%), $[\alpha]_D^{29}$ −17.8 (*c* 1.0, $CHCl_3$), as a colorless oil from an EtOAc-hexane eluent (1:10 v/v). (−)-**20**: IR (film):ν = 1738, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 − 7.17 (5H, m), 5.86 − 5.59 (1H, m), 5.17 − 4.93 (2 H, m), 3.88 (1H, d, *J* = 13.8 Hz), 3.78 (2H, d, *J* = 6.9 Hz), 3.75 (1H, d, *J* = 13.8 Hz), 3.09 − 2.96 (1H, m), 2.88 − 2.75 (1H, m), 2.32 − 2.19 (1H, m), 2.08 − 1.92 (1 H, m), 1.95

(3H, s), 1.90 − 1.72 (2H, M), 1.64 − 1.42 (2H, m); ^{13}C NMR (125 Hz, $CDCl_3$): δ = 171.2, 140.3, 136.1, 129.0, 128.3, 127.0, 116.3, 67.7, 65.1, 63.0, 58.3, 39.8, 29.3, 27.2, 20.9; MS: m/z = 272 (M^+ − 1), 91 (100%); HRMS : Calcd for $C_{14}H_{18}NO_2$ ($M^+ - C_3H_5$) = 232.1338, found = 232.1336.
(−)-**21**: IR (film):ν = 1735, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 − 7.17 (5H, m), 5.88 − 5.67 (1H, m), 5.16 − 4.98 (2H, m), 4.92 − 4.78 (1H, m), 3.82 (1H, d, *J* = 13.7 Hz), 3.57 (1H, d, *J* = 13.7 Hz), 2.72 − 2.56 (2H, m), 2.56 − 2.23 (3H, m), 2.02 (3H, s), 1.83 − 1.57 (4H, m); ^{13}C NMR (125 Hz, $CDCl_3$): δ = 170.8, 139.3, 136.4, 128.7, 128.4, 127.1, 116.6, 69.5, 58.0, 57.4, 51.7, 31.9, 26.2, 25.4, 21.3; MS: m/z = 272 (M^+ − 1), 91 (100%); HRMS: Calcd for $C_{14}H_{18}NO_2$ ($M^+ - C_3H_5$) = 232.1338, found = 232.1319.

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