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Enantio- and Diastereodivergent Synthesis of All Four Diastereomers of the 2,6-Disubstituted 3-Piperidinol Chiral Building Block

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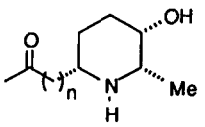
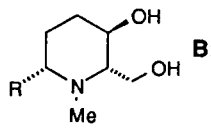
Abstract: Enantio- and diastereodivergent synthesis of all four diastereomers of 2,6-disubstituted 3-piperidinol has been achieved. The versatility of these compounds as the chiral building block for alkaloid synthesis has been demonstrated both by total synthesis of iso-6-cassine and by formal synthesis of prosopinine, cassine, and spectaline.

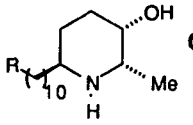
Naturally occurring 2,6(*cis* or *trans*)-disubstituted 3-piperidinols, such as *Prosopis* and *Cassia* alkaloids,[1] have received much attention owing to a variety of their biological activities. Consequently, much effort has been directed toward the stereoselective synthesis of these alkaloids to date.[2] Among the efforts are our recent



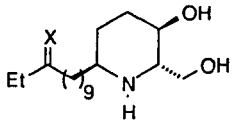
A: n = 10: cassine
n = 12: spectaline



B: R = Me(CH$_2$)$_3$(*E*-CH=CH)$_3$: micropine
R = EtC(O)(CH$_2$)$_9$: prosophylline



C: R = HO(CH$_2$)$_2$: julifloridine
R = MeC(O): iso-6-cassine

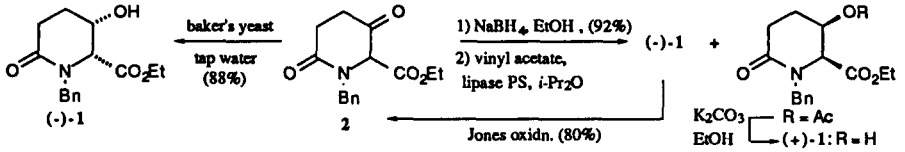


D: X = O: prosopinine
X = H, OH: prosopine

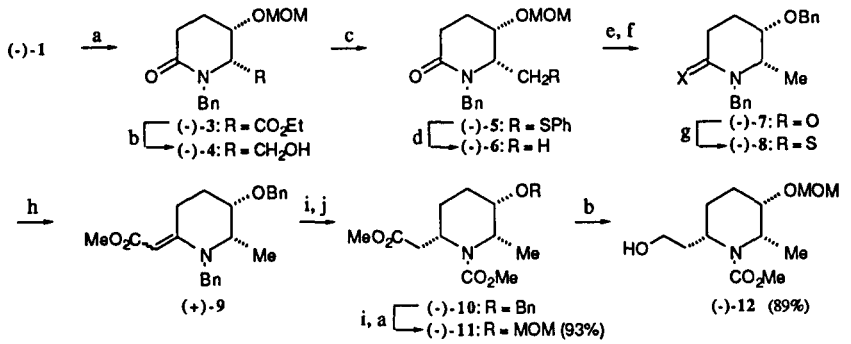
reports on the enantiodivergent synthesis of *cis, cis*-trisubstituted 3-piperidinol chiral building blocks[3] and their application to the synthesis of 3-piperidinol[4] and indolizidine alkaloids.[5]

In this communication, we wish to report an alternative design leading to the enantio- and diastereodivergent synthesis of these 3-piperidinol alkaloids from a single precursor.

First, we examined the enantiodivergent synthesis of the key piperidone **1**.[6] The lipase[7]-catalyzed transesterification of the hydroxy ester (±)-**1**, prepared from the $NaBH_4$ reduction of a β-keto ester (**2**),[8] afforded the acetate of (+)-**1**[9] in 47% yield (>99% ee)[10] along with (-)-**1** (52%, 91% ee). Hydrolysis of the acetate with K_2CO_3 gave (+)-**1** ($[\alpha]^{26}_D$ +64.3)[11] in 90% yield. The enantiomer (-)-**1**[12] was found to be derived more effectively from the baker's yeast reduction of **2** in high optical yield (98% ee).[10] Direct recrystallization of the crude reduction product resulted in obtaining the scalemic (-)-**1** ($[\alpha]^{26}_D$ -64.5) in 88% yield. In addition, the hydroxy ester **1** was found interconvertible with the starting β-keto ester (**2**) by the Jones oxidation in 80% yield.

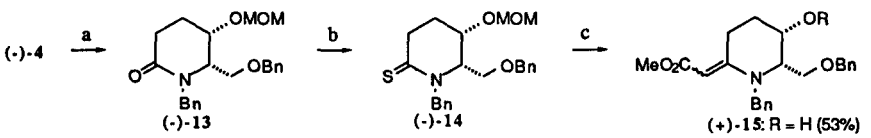


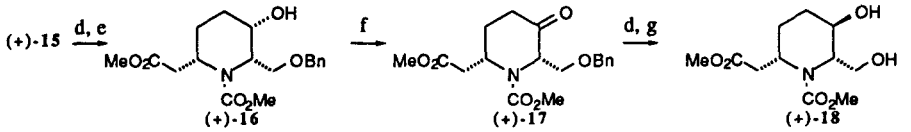
Next, we examined the diastereodivergent synthesis of all four diastereomers of 2,6-disubstituted 3-piperidinol starting with (-)-**1**. The 2,6(*cis*)-disubstituted 3-piperidinol chiral building block for the type A alkaloid was synthesized as follows. Protection of the hydroxyl in (-)-**1** and subsequent reduction of the resulting piperidone (-)-**3** ($[\alpha]^{26}_D$ -115.4) afforded the alcohol (-)-**4** ($[\alpha]^{26}_D$ -46.2), which was transformed into the piperidone (-)-**6** ($[\alpha]^{26}_D$ -69.4) *via* the phenylthio ether (-)-**5** ($[\alpha]^{26}_D$ -67.1). Conversion of (-)-**6** into the benzyl ether (-)-**7** ($[\alpha]^{26}_D$ -60.9) and subsequent homologation at the lactam carbonyl in (-)-**7** *via* the thiolactam (-)-**8** ($[\alpha]^{26}_D$ -158.6) by the Eschenmoser's sulfide-contraction protocol[13] afforded the vinylogous urethane (+)-**9**[14] ($[\alpha]^{26}_D$ +50.7). The catalytic hydrogenation of (+)-**9** followed by protection of the resulting amine provided the piperidine (-)-**10** ($[\alpha]^{26}_D$ -10.3) and small amounts of a 4:1 mixture of *cis*(2,6)- and *trans*(2,6)-*N*-benzylpiperidines. Hydrogenolysis of (-)-**10** and protection of the resulting alcohol provided the urethane (-)-**11** ($[\alpha]^{26}_D$ -1.3). Reduction of (-)-**11** furnished the alcohol (-)-**12** ($[\alpha]^{26}_D$ -29.9, lit.[4a] $[\alpha]^{26}_D$ -30.7). As the transformation of (-)-**12** or its enantiomer (+)-**12** into (+)-spectaline[4a] and (-)-methyl *N,O*-diacetylspicigerinate[4b] or into (-)-cassine[4a] had been furnished, the absolute stereochemistry of (-)-**1** was determined to be 2*R*, 3*S*.



a: MOMCl, Hünig base, $CHCl_3$, reflux (98%); b: Super-Hydride, 0 °C (96%); c: PhSSPh, *n*-Bu_3P, pyridine (95%); d: Raney Ni (W-4) (95%); e: c. HCl, MeOH, reflux; f: NaH, BnBr, 80 °C (84% in 2 steps); g: Lawesson's reagent (96%); h: $BrCH_2CO_2Me$ then Ph_3P, Et_3N (83%); i: H_2, $Pd(OH)_2$, MeOH; j: $ClCO_2Me$, K_2CO_3 (68% yield in 2 steps and the starting (+)-**9** in 20% recovery)

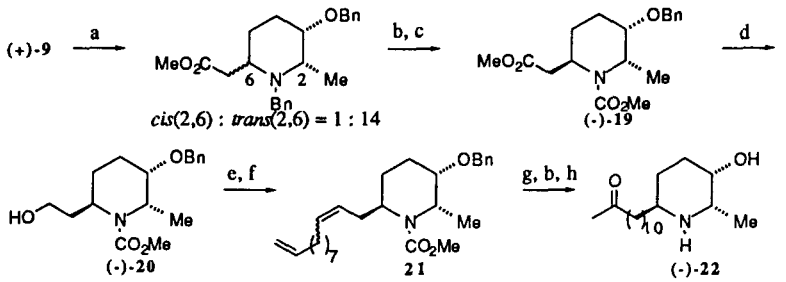
Another 2,6(*cis*)-disubstituted 3-piperidinol for the type B alkaloid was synthesized as follows. The alcohol (-)-**4** was transformed into the benzyl ether (-)-**13** ($[\alpha]^{26}_D$ -50.4), which was converted into the vinylogous urethane (+)-**15**[14] ($[\alpha]^{26}_D$ +10.5) *via* the thiolactam (-)-**14** ($[\alpha]^{26}_D$ -179.5). The catalytic hydrogenation of (+)-**15** and protection of the resulting amine afforded the urethane (+)-**16** ($[\alpha]^{26}_D$ +37.6). The PCC oxidation of (+)-**16** gave the ketone (+)-**17** ($[\alpha]^{26}_D$ +110.4), which was subjected, after hydrogenolysis, to the $NaB(OAc)_3H$ reduction to furnish the diol (+)-**18** ($[\alpha]^{26}_D$ +8.5) as a sole product.[15]





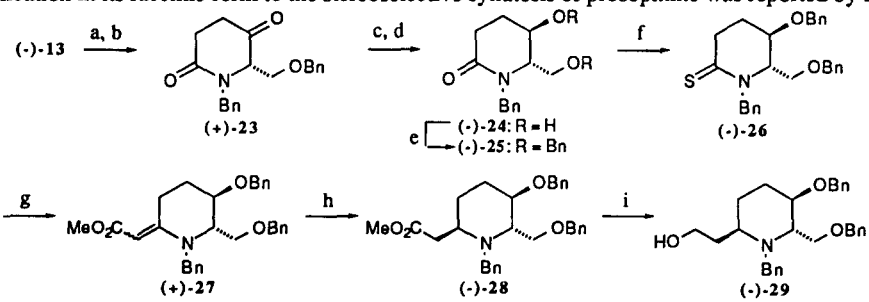
a: NaH, BnBr (96%); b: Lawesson's reagent (90%); c: $BrCH_2CO_2Me$ then Ph_3P, Et_3N {53% of (+)-15 and 31% of the MOM ether (R = MOM)}; d: H_2, $Pd(OH)_2$, MeOH; e: $ClCO_2Me$, K_2CO_3 {(+)-16 in 71% yield and the starting (+)-15 in 7% recovery}; f: PCC, AcONa (96%); g: $NaB(OAc)_3H$, AcOH (86% in 2 steps)

A 2,6(*trans*)-disubstituted 3-piperidinol for the type C alkaloid was synthesized as follows. Reduction of (+)-**9** with $NaBH_3CN$ in the presence of acid gave a 1:14 mixture of the *cis*(2,6)- and *trans*(2,6)-piperidines. Hydrogenolysis of the mixture over $Pd(OH)_2$ followed by treatment of the resulting amine with $ClCO_2Me$ provided *trans*-piperidine (-)-**19** ($[\alpha]^{26}_D$ -1.1) in 68% isolated yield. The first synthesis of (-)-iso-6-cassine (**22**)[16] ($[\alpha]^{26}_D$ -1.5[17], lit.[18] $[\alpha]^{25}_D$ +3.3) from (-)-**19** *via* the alcohol (-)-**20** ($[\alpha]^{26}_D$ -14.2) and the diene **21** was accomplished as depicted below.



a: $NaBH_3CN$, TFA, 0 °C (99% of combined yield); b: H_2, $Pd(OH)_2$, MeOH; c: K_2CO_3, $ClCO_2Me$ (68%); d: Super-Hydride (92%); e: Swern oxidn.; f: $CH_2{=}CH(CH_2)_8P^+Ph_3Br^-$, *n*-BuLi (80% in 2 steps); g: Wacker oxidn. (64%); h: TMSI, $CHCl_3$ (58% in 2 steps)

Finally, a 2,6(*trans*)-disubstituted 3-piperidinol for the type D alkaloid was synthesized as follows. Removal of the methoxymethyl in (-)-**13** and PCC oxidation of the resulting alcohol gave the scalemic ketone (+)-**23** ($[\alpha]^{26}_D$ +118.6) in 83% yield after recrystallization from *i*-Pr_2O. Hydrogenolysis of (+)-**23** and subsequent reduction with $NaB(OAc)_3H$ provided the *trans*-diol (-)-**24** ($[\alpha]^{26}_D$ -40.3) as a sole product.[19] Protection of (-)-**24** afforded the dibenzyl ether (-)-**25** ($[\alpha]^{26}_D$ -46.7), which was transformed into the vinylogous urethane (+)-**27**[14] ($[\alpha]^{26}_D$ +23.5) *via* the thiolactam (-)-**26** ($[\alpha]^{26}_D$ -105.9). Reduction of (+)-**27** with $NaBH_3CN$ in the presence of acid gave a 1:8 mixture of the 2,6-*cis*- and 2,6-*trans*-piperidine in 89% combined yield, and fractionation by repeated chromatography afforded the pure *trans*-piperidine (-)-**28** ($[\alpha]^{26}_D$ -23.2) in 53% isolated yield. Reduction of (-)-**28** with $LiAlH_4$ provided the alcohol (-)-**29** ($[\alpha]^{26}_D$ -37.9), whose application in its racemic form to the stereoselective synthesis of prosopinine was reported by Stille.[2a,b]



a: c. HCl, MeOH, reflux; b: PCC, AcONa (83% in 2 steps); c: H_2, $Pd(OH)_2$, MeOH; d: $NaB(OAc)_3H$, AcOH (97% in 2 steps); e: KOH, BnBr, MS 4A (79%); f: Lawesson's reagent (94%); g: $BrCH_2CO_2Me$ then Ph_3P, Et_3N (92%); h: $NaBH_3CN$, TFA, 0 °C; i: $LiAlH_4$, THF, reflux (84%)

Four diastereomers of 2,6(*cis* or *trans*)-disubstituted 3-piperidinol {(-)-**12**, (+)-**18**, (-)-**20**, and (-)-**29**} thus obtained and the counterenantiomer (+)-**1** would serve as promising chiral building blocks for the synthesis of other 3-piperidinol alkaloids, and additional studies on the synthetic utility of these heterocycles are in progress.

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2. Nonchiral synthesis: (a) Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669-1672. (b) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575-3584. (c) Natsume, M.; Ogawa, M. *Heterocycles* **1980**, *14*, 169-173. (d) Natsume, M.; Ogawa, M. *Heterocycles* **1980**, *14*, 615-618. (e) Natsume, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973-977. (f) Natsume, M.; Ogawa, M. *Heterocycles* **1983**, *20*, 601-605. (g) Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37-39. (h) Birkinshaw, T. N.; Holmes, A. B. *Tetrahedron Lett.* **1987**, *28*, 813-816. (i) Paterne, M.; Brown, E. *J. Chem. Res.* **1985**, 278-279. (j) Hasseberg, H.-A.; Gerlach, H. *Ann. Chem.* **1989**, 255-261. Chiral synthesis: (k) Hanessian, S.; Frenette, R. *Tetrahedron Lett.* **1979**, 3391-3394. (l) Saitoh, Y.; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980**, *21*, 75-78. (m) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488-492. (n) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473-3475. (o) Lu, Z.-H.; Zhou, W.-S. *Tetrahedron* **1993**, *49*, 4659-4664. (p) Tadano, K.; Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, I.; Maeda, K.; Ogawa, S. *SYNLETT* **1993**, 565-567. (q) Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681-5704.
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6. The piperidone of type **1** has been utilized as a key compound for stereoselective synthesis of alkaloids in racemic forms in the pioneering work by Stille.[2a,b] We planned the efficient and convenient, moreover, chiral construction of this heterocycle.
7. We are grateful to Amano Pharmaceutical Co., Ltd. for the generous gift of lipase PS.
8. Bonjoch, J.; Serret, I.; Bosch, J. *Tetrahedron* **1984**, *40*, 2505-2511.
9. Satisfactory analytical and spectral data were obtained for all new compounds.
10. The value of ee was determined by HPLC analysis using a column packed with CHIRALPAK AS (Daicel Chemical Co., Ltd., *i*-PrOH : *n*-hexane=1:3).
11. Optical rotations were taken in chloroform unless otherwise stated.
12. The relative stereochemistry of (-)-**1** was determined to be *cis* by the X-ray crystallographic analysis. Crystallographic data for (-)-**1**: monoclinic, space group $P2_1$, with a = 7.052(2) Å, b = 11.937(1) Å, c = 9.5217(9) Å, β = 106.54(1)°V = 768.4(2) Å^3, and Z = 2 (d_{calcd} = 1.199 g cm^{-3}), μ (MoKα) = 0.87 cm^{-1} absorption corrected by ω scans; 1856 unique reflections; 879 with $I > 3.00\sigma(I)$ were used in refinement; R = 5.4 %, R_W = 7.6 %. The authors have deposited atomic coordinate for (-)-**1** with the Cambridge Crystallographic Data Centre. The coordinate can be obtained , on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
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14. A single isomer was isolated, but the stereochemistry of the olefin moiety was not determined.
15. An authentic sample of the corresponding *cis* diol was prepared from the hydrogenolysis of (+)-**16** over $Pd(OH)_2$.
16. The synthetic (-)-**22** was identical in its ^{1}H and ^{13}C NMR data with the natural product.[17] Spectroscopic data for synthetic (-)-**22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (3H, d, J = 6.5 Hz), 1.17-1.38 (14H, br), 1.45-1.58 (4H, m), 1.59-1.73 (3H, m), 1.84 (1H, tt, J = 9.0, 4.3 Hz), 2.13 (3H, s), 2.41 (2H, t, J = 7.5 Hz), 2.81 (1H, quintet-like, J = 3.1 Hz), 3.10 (1H, qd, J = 6.5, 3.1 Hz), 3.66 (1H, quintet-like, J = 3.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 15.87, 23.84, 26.62, 27.71, 29.15, 29.36, 29.41, 29.50, 29.56, 29.67, 29.83, 33.01, 43.80, 49.67, 50.08, 69.22, 209.39.
17. The value of the optical rotation of the synthetic (-)-**22** was not changed after recrystallization of its hydrochloride (mp 118~120 °C, lit.[17] mp 123 °C) from EtOAc.
18. Christofidis, I.; Welter, A.; Jadot, J. *Tetrahedron* **1977**, *33*, 977-979.
19. An authentic sample of the corresponding *cis* diol was prepared from the hydrogenolysis of an alcohol which was obtained by the removal of the methoxymethyl of (-)-**13** with acid.

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