2-Piperidone Type of Chiral Building Block for 3-Piperidinol Alkaloid Synthesis

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An enantiomeric pair of a new 2-piperidone type of chiral building block (**1**) has been prepared by bakers' yeast reduction of *β*-keto ester (**2**) or lipase-mediated transesterification of hydroxy ester (±)-(**1**), derived from $NaBH_4$ reduction of **2**, in enantiopure form. The absolute stereochemistry of (−)-**1** was verified by its conversion to known piperidine (−)-**3**, an intermediate for the synthesis of (−)-spectaline. The 2-piperidone (−)-**1** was converted to all four diastereomers of 2,6-disubstituted 3-piperidinol chiral building blocks on the basis of homologation of (−)-**1** at the lactam carbonyl using the Eschenmoser method via corresponding thiolactams (−)-**9**, (−)-**20**, (−)-**25**, (−)-**27**, and (−)-**34**, followed by stereocontrolled reduction of the resulting vinylogous urethanes (+)-**10**, (+)-**15**, (+)-**23**, (+)-**28**, and (+)-**32**, respectively, and epimerization of the hydroxyls at the 3-position [(−)-**16** via (+)-**17** to (−)-**18** and (+)-**29** via (+)-**30** to (+)-**31**]. The versatility of these chiral buliding blocks has been demonstrated by the chiral synthesis of the 3-piperidinol alkaloids (+)-prosafrinine, (−)-iso-6-cassine, (−)-prosophylline, and (−)-prosopinine from (−)-**37**, (−)-**14**, (+)-**36**, and (−)-**26**, respectively.

Introduction

Functionalized piperidines are very important heterocycles because of their presence in numerous alkaloids, pharmaceuticals, and synthetic intermediates. As a result, a large number of synthetic designs for this ring system have been developed to date.[1] In particular, many α,α′-disubstituted 3-piperidinol alkaloids have been isolated, and many of them have shown important biological activities.[2]

Among the recent efforts in this area, we have exhibited a design for the chiral construction of both enantiomers of the *cis*-(2,3,6)-trisubstituted 3-piperidinol chiral building block[3a,4] and its utility for the chiral synthesis of the 3-piperidinol alkaloids (−)-cassine and (+)-spectaline[3b,4] and some 5,8-disubstituted indolizidine or 1,4-disubstituted quinolizidine types of *Dendrobates* alkaloids.[5]

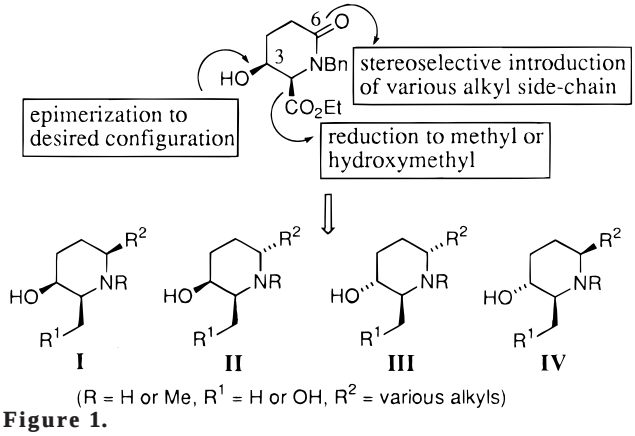

Figure 1.

In this paper, we describe a method for the construction of both enantiomers of a new 2-piperidone type of chiral building block (**1**)[6] leading to all four diastereomers (**I**−**IV**) needed for the synthesis of the above 3-piperidinol alkaloids in enantiomerically pure form.[7]

The basic strategy we used to prepare the building blocks (**I**−**IV**) from (−)-**1** is presented in Figure 1. The attachment of the C-6 side chain was installed by using the lactam functionality with stereochemical control.[8] In addition, the hydroxyl at the 3-position was readily epimerized to the desired configuration for the synthesis of corresponding alkaloids.

(1) For reviews, see: Wang, C.-L. J.; Wuorola, M. A. *Org. Prep. Proced. Int*. **1992**, *24*, 585−621. Takahata, H.; Momose, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 44, pp 189−256. Michael, J. P. *Nat. Prod. Rep*. **1995**, *12*, 535−552. Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493−3513. Daly, J. W. In *The Alkaloids*, Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 50, pp 141−169.

(2) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, pp 89−183. Aguinaldo, A. M.; Read, R. W. *Phytochemistry* **1990**, *29*, 2309−2313. Bolzani, V. da S.; Gunatilaka, A. A. L.; Kingston, D. G. I. *Tetrahedron* **1995**, *51*, 5929−5934. Astudillo, S. L.; Jürgens, S. K.; SchmedaHirschmann, G.; Griffith, G. A.; Holt, D. H.; Jenkins, P. R. *Planta Med*. **1999**, *65*, 161−162 and references therein. For recent synthesis of this type of alkaloids, see: Bayquen, A. V.; Read, R. W. *Tetrahedron* **1996**, *52*, 13467−13482. Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 3887−3893. Agami, C.; County, F.; Mathieu, H. *Tetrahedron Lett*. **1998**, *39*, 3505−3508. Agami, C.; County, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783−8796. Yang, C.-F.; Xu, Y.-M.; Liao, L.-X.; Zhou, W.-S. *Tetrahedron Lett*. **1998**, *39*, 9227−9228. Pahl, A.; Wartchow, R.; Meyer, H. H. *Tetrahedron Lett*. **1998**, *39*, 2095−2096. Kiguchi, T.; Shirakawa, M.; Honda, R.; Ninomiya, I.; Naito, T. *Tetrahedron* **1998**, *54*, 15589−15606 and references therein.

(3) (a) Momose, T.; Toyooka, N.; Jin, M. *Tetrahedron Lett*. **1992**, *33*, 5389−5390. (b) Momose, T.; Toyooka, N. *Tetrahedron Lett*. **1993**, *34*, 5785−5786.

(4) Momose, T.; Toyooka, N.; Jin, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2005−2013.

(5) Momose, T.; Toyooka, N. *J. Org. Chem*. **1994**, *59*, 943−945; Toyooka, N.; Tanaka, K.; Momose, T.; Daly, J. W.; Garraffo, H. M. *Tetrahedron* **1997**, *53*, 9553−9574.

(6) It was worthwhile noting Comins' work in the field of enantioselective synthesis of various alkaloids using chiral nonracemic 2,3-dihydro-4-pyridones (5,6-didehydro-4-piperidones); see: Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. J.; Concolino, T. E.; Rheingold, A. L. *J. Am. Chem. Soc*. **1999**, *121*, 2651−2652. Comins, D. L.; Zhang, Y.-M.; Zheng, X. *J. Chem. Soc., Chem. Commun*. **1998**, 2509−2510. Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem*. **1997**, *62*, 7435−7438. Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem*. **1997**, *62*, 8182−8187. Comins, D. L.; Joseph, S. P. In *Advances in Nitrogen Heterocycle*; JAI Press Inc., 1996; Vol. 2, pp 251−294 and references therein.

(7) For preliminary accounts, see: Toyooka, N.; Yoshida, Y.; Momose, T. *Tetrahedron Lett*. **1995**, *36*, 3715−3718.

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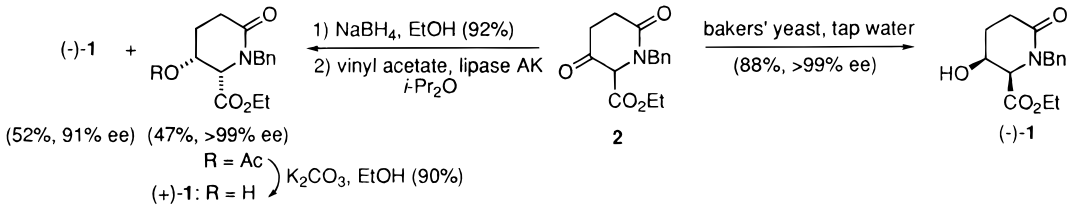
Scheme 1



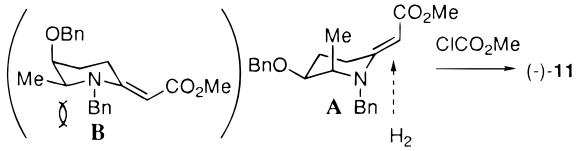
To verify the utility of the above 3-piperidinols as chiral building blocks for alkaloid synthesis, we planned the diastereodivergent synthesis of the 3-piperidinol alkaloids (+)-prosafrinine,[9] (−)-iso-6-cassine,[10] (−)-prosophylline,[11] and (−)-prosopinine.[12]

Herein, we wish to document the potential for a general use of **1** in alkaloid synthesis via the above 3-piperidinol building blocks (**I**−**IV**).

Results and Discussion

First, we examined the preparation of both enantiomers of 2-piperidone (**1**). To obtain **1** in an optically pure state, we investigated the lipase-mediated kinetic resolution of (±)-**1**, prepared from the $NaBH_4$ reduction of *β*-keto ester (**2**).[13] Kinetic resolution of (±)-**1** under the condition of treatment with lipase AK and vinyl acetate in *i*-Pr_2O proceeded nicely to afford the acetate of (+)-**1** in 47% yield (>99% ee) and alcohol (−)-**1** in 52% yield (91% ee), respectively. Hydrolysis of the acetate with K_2CO_3 gave enantiopure (+)-**1**. The enantiomer (−)-**1** was found to be prepared more effectively from bakers' yeast reduction of **2** under nonfermenting conditions[14] in high optical yield (98% ee), and direct recrystallization of the crude reduction product resulted in obtaining enantiopure (−)-**1** in 88% isolated yield (Scheme 1). Relative stereochemistry of (−)-**1** was verified with an X-ray analysis.

With the enantiomeric pair of scalemic **1** in hand, we next examined the determination of the absolute stereochemistry of (−)-**1** by its conversion to known piperidine (−)-**3**.[4] Protection of the hydroxyl in (−)-**1** with MOMCl afforded ether (−)-**4**, which was reduced with Super-Hydride[15] to yield alcohol (−)-**5**. Treatment of (−)-**5** with $(PhS)_2$ and Ph_3P in pyridine provided phenylthioether (−)-**6** which was desulfurized with Raney Ni (W-4) to give piperidone (−)-**7**. Conversion of (−)-**7** to benzyl ether (−)-**8**, which was subjected to homologation at the lactam carbonyl by Eschenmoser's sulfide−contraction reaction via thiolactam (−)-**9** to provide vinylogous urethane (+)-**10**. Catalytic hydrogenation of (+)-**10** over $Pd(OH)_2$ followed by protection of the resulting amine with $ClCO_2$-Me afforded the desired *cis*-(2,6)-piperidine (−)-**11**, which was converted to MOM ether (−)-**12** in the usual manner. This stereoselectivity may be attributed to the steric hindrance, by which the catalytic hydrogenation occurs from the less hindered site (α-face) of (+)-**10**. This will fix the conformation not in **B** but in as a result of **A** $A^{(1,2)}$ strain[16] between *N*-benzyl and α-methyl groups, to afford (−)-**11**.



Reduction of (−)-**12** with Super-Hydride gave alcohol (−)-**3**, an intermediate for the chiral synthesis of (+)-spectaline.[3b,4] Thus, the absolute stereochemistry of (−)-**1** was verified to be 2*R*,3*S*, and the preparation of a chiral building block of type **I** was completed (Scheme 2).

Next, we examined the transformation of (−)-**1** to the other three diastereomers (type **II**, **III**, and **IV**) to establish the process for the diastereodivergent synthesis of 2,6-disubstituted 3-piperidinol alkaloids. The *trans*-(2,6)-piperidines of types **II** and **III** were prepared by hydride reduction of iminium ions generated from the corresponding vinylogous urethanes in a highly stereoselective manner. Thus, reduction of (+)-**10** with $NaBH_3$-CN in the presence of trifluoroacetic acid (TFA) provided a 14:1 mixture of *trans*-(2,6)- and *cis*-(2,6)-piperidines. Because it was difficult to isolate the major, desired *trans*-(2,6)-piperidine in a pure state, the epimeric mix-

(8) Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669−1672; *J. Org. Chem.* **1994**, *59*, 3575−3584.

(9) Isolation: (a) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 443−458. Nonchiral synthesis: (b) Paterne, M.; Dhal, R.; Brown, E. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1321−1324.

(10) Isolation: Christofidis, I.; Welter, A.; Jadot, J. *Tetrahedron* **1977**, *33*, 977−979.

(11) Isolation: ref 7a. Nonchiral stereoselective synthesis: (a) Natume, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973. Chiral syntheses of desoxoprosophylline: (b) Saitoh, Y.; Moriyama, Y.; Takahashi, T.; Khuong-Huu, Q. *Tetrahedron Lett.* **1980**, 75. (c) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488. (d) Tadano, K.; Takao, K.; Nigawara, Y.; Nishio, E.; Takagi, I.; Maeda, K.; Ogawa, S. *Synlett* **1993**, 565−567; (e) *Tetrahedron* **1994**, *50*, 5681−5704. (f) Kadota, I.; Kawada, M.; Muramatsu, Y.; Yamamoto, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 3887−3893. (g) Yang, C.-F.; Xu, Y.-M.; Liao, L.-X.; Zhou, W.-S. *Tetrahedron Lett.* **1998**, *39*, 9227−9228. (h) Ojima, I.; Vidal, E. S. *J. Org. Chem.* **1998**, *63*, 7999−8003.

(12) Isolation: Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425−442. Chiral syntheses of prosopinine: Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776−777 and ref 9h. Chiral syntheses of desoxoprosopinine: Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473−3475 and refs 8d and 8e. Yuasa, Y.; Ando, J.; Shibuya, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1525−1526; *J. Chem. Soc., Perkin Trans. 1* **1996**, 793−802. Reference 9f. Agami, C.; County, F.; Mathieu, H. *Tetrahedron Lett.* **1998**, *39*, 3505−3508. Agami, C.; County, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783−8796. Nonchiral stereoselective synthesis of desoxoprosopinine: Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37−39. Cook, G. R.; Beholz, L. G.; Stille, J. R. *Tetrahedron Lett.* **1994**, *35*, 1669−1672. Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592−3596.

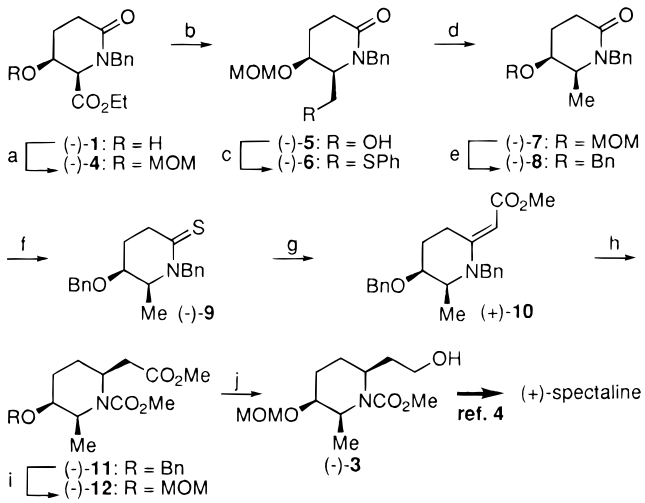
(13) Bonjoch, J.; Serret, I.; Bosch, J. *Tetrahedron* **1984**, *40*, 2505−2511.

(14) Seebach, D.; Roggo, S.; Maetzke, T.; Braunschweiger, H.; Cercus, J.; Krieger, M. *Helv. Chim. Acta* **1987**, *70*, 1605−1615.

(15) Use of Super-Hydride was extremely effective for reduction of this sterically hindered ester functional group. For example, no reduction proceeded with $LiAlH_4$ at room temperature for 14 h, and the starting material was recovered. Reduction with $LiBH_4$ (6 equiv) at room temperature for 23 h gave a 1:1 mixture of (−)-**4** and (−)-**5**. Reduction with DIBAL (2.2 equiv) at 0 °C for 1 h resulted in the formation of a complex mixture not including the desired alcohol (−)-**5**.

(16) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−413.

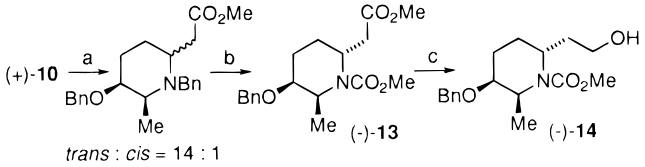
Scheme 2[a]



[a]a: MOMCl, Hünig base, $CHCl_3$, reflux (98%);
b: Super-Hydride, THF, 0 °C (96%);
c: PhSSPh, *n*-Bu_3P, pyridine (95%)
d: Raney Ni (W-4), EtOH, reflux (95%);
e: c. HCl, MeOH; NaH, BnBr, DMF-benzene=1:2, 80 °C (84%);
f: Lawesson's reagent, THF, reflux (96%);
g: $BrCH_2CO_2Me$ then Ph_3P, Et_3N, MeCN, reflux (83%);
h: H_2, $Pd(OH)_2$, MeOH; $ClCO_2Me$, K_2CO_3 (68%);
i: H_2, $Pd(OH)_2$, MeOH; MOMCl, Hünig base, $CHCl_3$, reflux (93%);
j: Super-Hydride, THF, 0 °C~rt (89%)

ture was used for subsequent transformation. Hydrogenation of the above mixture over $Pd(OH)_2$ followed by

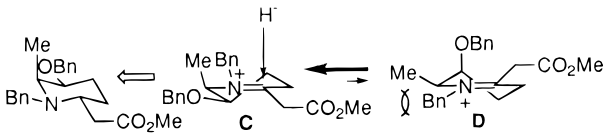
Scheme 3[a]



[a]a: $NaBH_3CN$, TFA, CH_2Cl_2, 0 °C (99% combined yield);
b: H_2, $Pd(OH)_2$, MeOH; K_2CO_3, $ClCO_2Me$, CH_2Cl_2-H_2O (68%);
c: Super-Hydride (92%);

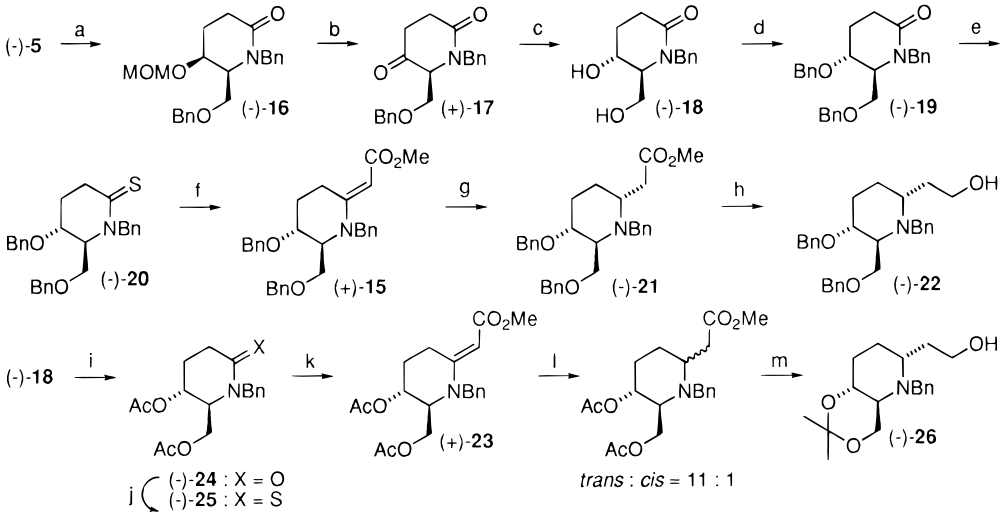
treatment of the resulting amine with $ClCO_2Me$ gave diastereopure *trans*-piperidine (−)-**13** in 68% isolated yield (Scheme 3). Reduction of (−)-**13** with Super-Hydride afforded alcohol (−)-**14** (type **II**) in 92% yield (Scheme 3).

The *trans*-selectivity observed in the above reduction is explained by the following factors. Conformer **C** for the iminium salt, generated from (+)-**10** under acidic conditions, is favored relative to **D** because of $A^{(1,2)}$ strain[16] between the *N*-benzyl and the methyl at the α-position, so the hydride reacts from the preferred *β*-axial site,[17] leading to a chairlike transition state to give *trans*-(2,6)-piperidine.



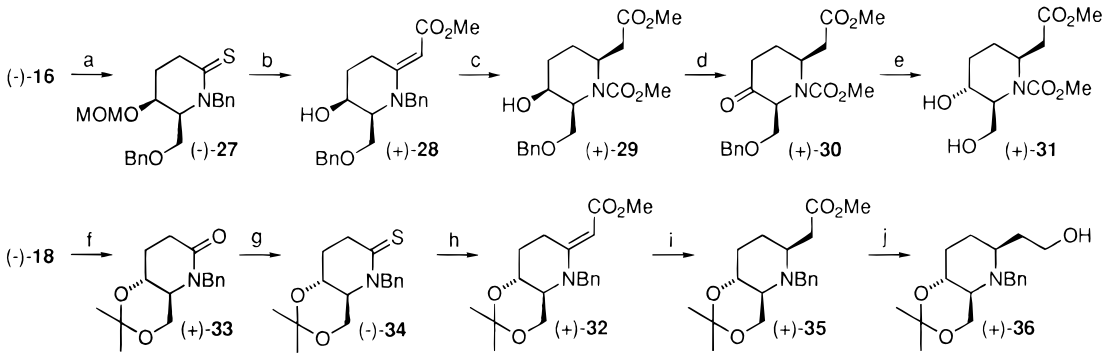
Another *trans*-(2,6)-piperidine of type **III** was synthesized in a similar iminium reduction of the corresponding vinylogous urethane of *trans*-(2,3)-congener (+)-**15**. Pro-

Scheme 4[a]



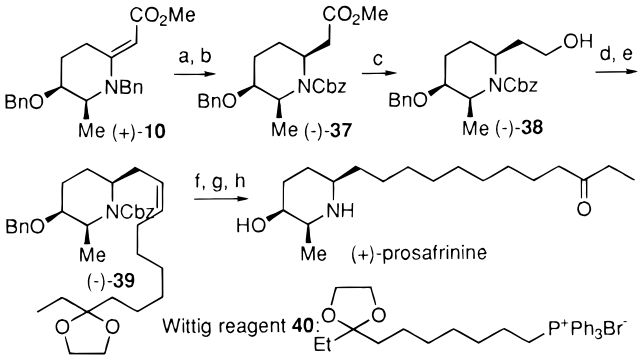
[a]a: NaH, BnBr, DMF-benzene=2:1 (96%);
b: c. HCl, MeOH, reflux; PCC, AcONa, CH_2Cl_2 (83%);
c: H_2, $Pd(OH)_2$, MeOH; $NaB(OAc)_3H$, AcOH (97%);
d: KOH, BnBr, THF, MS 4A (79%);
e: Lawesson's reagent, THF, reflux (94%);
f: $BrCH_2CO_2Me$ then Ph_3P, Et_3N, MeCN, reflux (92%);
g: $NaBH_3CN$, TFA, CH_2Cl_2, 0 °C (53%);
h: $LiAlH_4$, THF, reflux (84%);
i: Ac_2O, pyridine (88%);
j: Lawesson's reagent, THF, reflux (99%);
k: $BrCH_2CO_2Me$ then Ph_3P, Et_3N, MeCN, reflux (92%);
l: $NaBH_3CN$, TFA, CH_2Cl_2, 0 °C (84% combined yield);
m: $LiAlH_4$, THF, reflux (84%); 2,2-dimethoxypropane, *p*-TsOH, MS 5A, CH_2Cl_2, rt (75% in 2 steps)

Scheme 5[a]



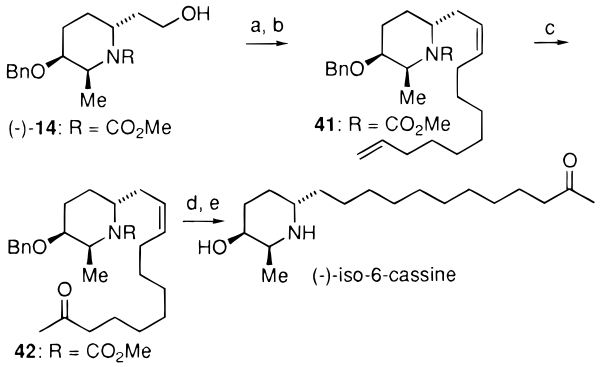
[a]a: Lawesson's reagent, THF, reflux (90%);
b: $BrCH_2CO_2Me$ then Ph_3P, Et_3N, MeCN, reflux {53%, 31% of the MOM ether of (+)-**28**};
c: H_2, $Pd(OH)_2$, MeOH; $ClCO_2Me$, K_2CO_3 (71%);
d: PCC, AcONa, CH_2Cl_2 (96%);
e: H_2, $Pd(OH)_2$, MeOH; $NaB(OAc)_3H$, AcOH, 0 °C~rt (86%);
f: 2,2-dimethoxypropane, *p*-TsOH, MS 5A, CH_2Cl_2, rt (91%);
g: Lawesson's reagent, THF, reflux (57%);
h: $BrCH_2CO_2Me$ then Ph_3P, Et_3N, MeCN, reflux (72%);
i: $NaBH_3CN$, TFA, 0 °C (59%);
j: $LiAlH_4$, THF, reflux (99%)

Scheme 6[a]



[a]a: H_2, $Pd(OH)_2$, MeOH;
b: CbzCl, K_2CO_3, CH_2Cl_2-H_2O (96% in 2 steps);
c: Super-Hydride, THF (90%);
d: Swern oxidn.;
e: Wittig reagent **40**, n-BuLi, THF (60% in 2 steps);
f: H_2, $Pd(OH)_2$, MeOH;
g: Na, liq. NH_3;
h: *p*-TsOH, acetone (50% in 3 steps)

Scheme 7[a]

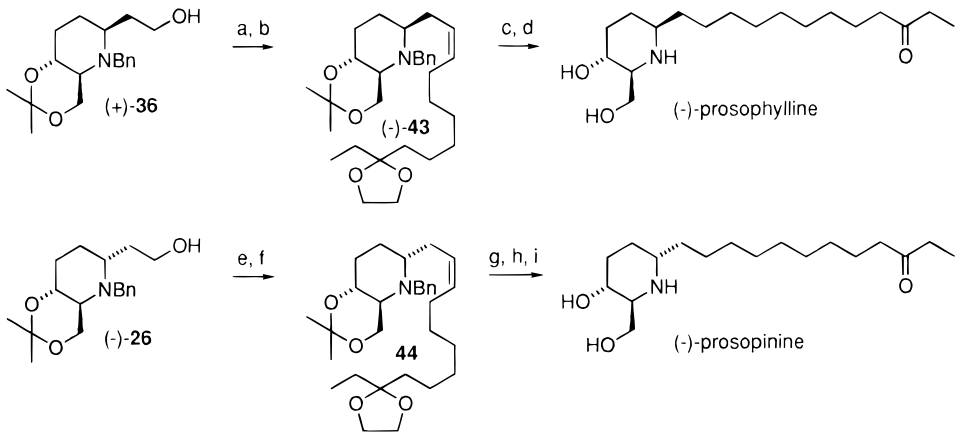


[a]a: Swern oxidn.;
b: CH_2=$CH(CH_2)_8P^+Ph_3Br^-$, *n*-BuLi, THF (80% in 2 steps);
c: O_2, CuCl, $PdCl_2$, DMF-H_2O (64%);
d: H_2, $Pd(OH)_2$, MeOH;
e: TMSI, $CHCl_3$, reflux (58% in 2steps)

tection of the hydroxyl in (−)-**5** with BnBr gave benzyl ether (−)-**16**, which was deprotected with concentrated HCl in MeOH. Oxidation with pyridinium chlorochromate (PCC) of the resulting alcohol in the presence of NaOAc afforded ketone (+)-**17** in 95% ee,[18] which was recrystallized from *i*-Pr_2O to give an enantiopure compound[18] in 83% isolated yield. When the oxidation was performed under Swern conditions, complete racemization occurred. Reduction of the keto alcohol obtained from hydrogenolysis of (+)-**17** with $NaB(OAc)_3H$ provided diol (−)-**18** with complete stereochemical control. Both hydroxyls in (−)-**18** were protected with BnBr to give dibenzyl ether (−)-**19**,[19] which was subjected to Eschenmoser's contraction−sulfide extrusion reaction, after conversion to thiolactam (−)-**20**, to provide vinylogous urethane (+)-**15**. Reduction of (+)-**15** with $NaBH_3CN$ afforded piperidine (*trans*:*cis* = 8:1, 89% combined yield), which was purified with fractionation by repeated chromatography to provide pure *trans*-piperidine (−)-**21** in 53% isolated yield. Reduction of (−)-**21** with $LiAlH_4$ furnished alcohol (−)-**22** (type **III**), whose application in its racemic form to the stereoselective synthesis of prosopinine was reported.[8] However, iminium reduction of vinylogous urethane (+)-**23**, prepared from (−)-**18** via diacetate (−)-**24** and thiolactam (−)-**25**, resulted in the formation of a 11:1 mixture of *trans*-(2,6)- and *cis*-(2,6)-piperidines in 84% combined yield. The mixture was reduced to the triol with $LiAlH_4$ in refluxing THF, and protection of the 1,3-glycol system in the resulting triol

(17) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−290.
(18) The enantiomeric excess was determined by HPLC analysis; see the Experimental Section in the Supporting Information.
(19) Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 4602−4616.

Scheme 8[a]



[a]a: Swern oxidn.;
b: Wittig reagent **40**, *n*-BuLi, THF (59% in 2 steps);
c: H_2, $Pd(OH)_2$, MeOH;
d: 10% HCl, EtOH (75% in 2 steps);
e: Swern oxidn.;
f: Wittig reagent **40**, *n*-BuLi, THF (60% in 2 steps);
g: H_2, $Pd(OH)_2$, MeOH;
h: 10% HCl, EtOH;
i: *p*-TsOH, acetone (72% in 3 steps)

with 2,2-dimethoxypropane afforded acetonide, which was purified with column chromatography to give diastereomerically pure *trans*-piperidine (−)-**26** (type **III**) in 75% isolated yield in two steps (Scheme 4).

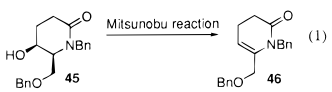
Finally, the type **IV** chiral building block was synthesized as follows. Benzyl ether (−)-**16** was subjected, after its conversion to thiolactam (−)-**27**, to the Eschenmoser method to give vinylogous urethane (+)-**28** along with the MOM ether of (+)-**28** (ca. 1.7:1). Catalytic hydrogenation of (+)-**28** over $Pd(OH)_2$ followed by protection of the resulting amine with $ClCO_2Me$ afforded urethane (+)-**29**. Finally, epimerization of the hydroxyl at the 3-position was achieved in a three-step sequence as follows.[20] PCC oxidation of alcohol (+)-**29** provided ketone (+)-**30**, which was hydrogenated over $Pd(OH)_2$, followed by reduction of the resulting keto alcohol with $NaB(OAc)_3H$ in AcOH to furnish a piperidine of type **IV** [(+)-**31**]. As an alternative route to the type **IV** chiral building block, we investigated the iminium reduction of vinylogous urethane (+)-**32**. Protection of the glycol in (−)-**18** with 2,2-dimethoxypropane afforded acetonide (−)-**33**, which was transformed to (+)-**32** via thiolactam (−)-**34**. Reduction of (+)-**32** with $NaBH_3CN$ in the presence of TFA provided *cis*-(2,6)-piperidine (+)-**35** exclusively, which was reduced to alcohol (+)-**36** with $LiAlH_4$ in 99% yield (Scheme 5). The absence of formation of *trans*-(2,6)-piperidine corresponding to (+)-**35** in the above reduction was proven by comparison of (+)-**36**, prepared from $LiAlH_4$ reduction of (+)-**35**, with (−)-**26** on the basis of ^1H NMR spectra.

Next, we examined the chiral synthesis of all-*cis*-trisubstituted alkaloid (+)-prosafrinine. Vinylogous urethane (+)-**10** was converted stereoselectively to piperidine (−)-**37** via catalytic hydrogenation followed by protection of the resulting amine with benzyl chloroformate (CbzCl). Reduction of (−)-**37** with Super-Hydride afforded alcohol (−)-**38** in 92% yield, which was transformed to olefin (−)-**39** via Swern oxidation followed by Wittig olefination using the Wittig reagent **40**. Finally, hydrogenation of (−)-**39** over $Pd(OH)_2$, cleavage of benzyl ether of resulting amine under the Birch condition and subsequent deprotection of the acetal moiety with acid provided (+)-prosafrinine in 60% overall yield (Scheme 6). ^1H and ^{13}C NMR spectra of our synthetic alkaloid were identical with those of the literature.[9]

In addition, we examined the chiral synthesis of the 2,3(*cis*)-2,6(*trans*)-trisubstituted 3-piperidinol iso-6-cassine. Swern oxidation of (−)-**14** and subsequent Wittig olefination of the resulting aldehyde gave diene **41** in 80% yield in two steps. Wacker oxidation of **41** afforded the methyl ketone **42** (Scheme 7), which was hydrogenated over $Pd(OH)_2$ in MeOH to provide the saturated ketone, whose methoxycarbonyl protecting group was cleaved by treatment with trimethylsilyl iodide (TMSI)[21] in refluxing $CHCl_3$ to furnish iso-6-cassine. ^1H and ^{13}C NMR spectra of the synthetic alkaloid were in agreement with the reported values.[10]

The alkaloids prosophylline and prosopinine were synthesized from the building blocks **III** and **IV**, respectively, in the same manner. Swern oxidation of (+)-**36** and subsequent Wittig reaction of the resulting aldehyde afforded olefin (−)-**43**, which was subjected to hydrogenation over $Pd(OH)_2$ followed by acid treatment to give (−)-prosophylline. ^1H and ^{13}C NMR spectra of synthetic alkaloid were identical with those of the literature.[9a] Similarly, the acetonide (−)-**26** was transformed to (−)-

(20) Direct inversion of the hydroxyl in **45** under the Mitsunobu reaction conditions afforded the enamine derivative **46** (eq 1).



(1)

This result was a contrast to the Mitsunobu inversion of the 2,3(*trans*)- to the 2,3(*cis*)-piperidinol derivative; see: Lu, Z.-H.; Zhou, W.-S. *Tetrahedron* **1993**, *49*, 4659−4664.

(21) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968−969.

prosopinine via the olefin **44** (Scheme 8). ^{1}H and ^{13}C NMR spectra of synthetic alkaloid were identical with those of the literature.[12]

Conclusion

We have established the diastereodivergent chiral synthesis of all four diastereomers of 2,6-disubstituted 3-piperidinols (types **I**−**IV**) via the 2-piperidone type of chiral building block (−)-(**1**), which was readily obtained by bakers' yeast reduction of **2** in an optically pure state. In addition, the enantiomer (+)-**1** has also been prepared by lipase-mediated kinetic resolution of (±)-**1**. This means that the stereoisomers of 2,6-disubstituted 3-piperidinol building blocks can be prepared arbitrarily in an optically pure state. Furthermore, we achieved the chiral synthesis of (+)-prosafrinine, (−)-iso-6-cassine, (−)-prosophylline, and (−)-prosopinine by the present methodology and also demonstrated that 3-piperidinols (types **I**−**IV**) prepared in this process were powerful chiral building blocks for the synthesis of the aforementioned alkaloids.

Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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