

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 ($\pm$)-(**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 building 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

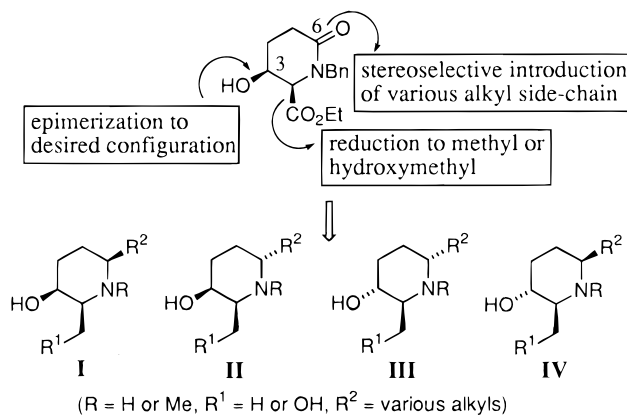


Figure 1.

In this paper, we describe a method for the construction of both enantiomers of a new 2-piperidone type of chiral building block (**1**) 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.

(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.; Kueth, 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.

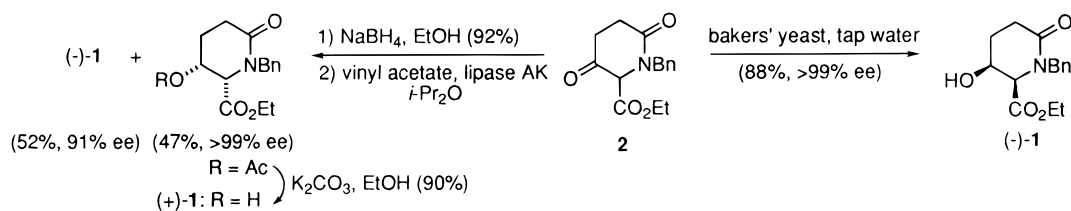
(1) For reviews, see: Wang, C.-L. J.; Wuorola, M. A. *Org. Prep. Proced. Int.* **1992**, 24, 585–621. Takahata, H.; Momose, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 44, pp 189–256. Michael, J. P. *Nat. Prod. Rep.* **1995**, 12, 535–552. Nadin, A. J. *Chem. Soc.,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

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 (-)-prosopphylline,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 ($\pm$)-**1**, prepared from the NaBH₄ reduction of β -keto ester (**2**).¹³ Kinetic resolution of ($\pm$)-**1** under the condition of treatment with lipase AK and vinyl acetate in *i*-Pr₂O 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 K₂CO₃ gave enantiopure (+)-**1**. The enantiomer (-)-**1** was found to be prepared more effectively from bakers' yeast reduction of **2** under nonfermenting conditions¹⁴ 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).

(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.

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(11) Isolation: ref 7a. Nonchiral stereoselective synthesis: (a) Natume, M.; Ogawa, M. *Heterocycles* **1981**, 16, 973. Chiral syntheses of desoxoprosopphylline: (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.

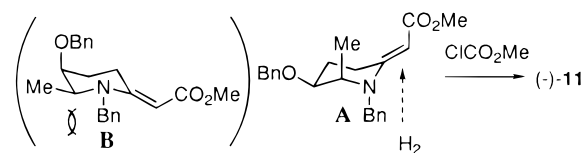
(12) Isolation: Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, 81, 425–442. Chiral syntheses of prosopinine: Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, 62, 776–777 and ref 9h. Chiral syntheses of desoxoprosopinine: 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.

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-Hydride¹⁵ to yield alcohol (-)-**5**. Treatment of (-)-**5** with (PhS)₂ and Ph₃P in pyridine provided phenylthioether (-)-**6** which was desulfurized with Raney Ni (W-4) to give piperidine (-)-**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 ClCO₂Me 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** (^{1,2} strain¹⁶ between *N*-benzyl and α -methyl groups, to afford (-)-**11**.

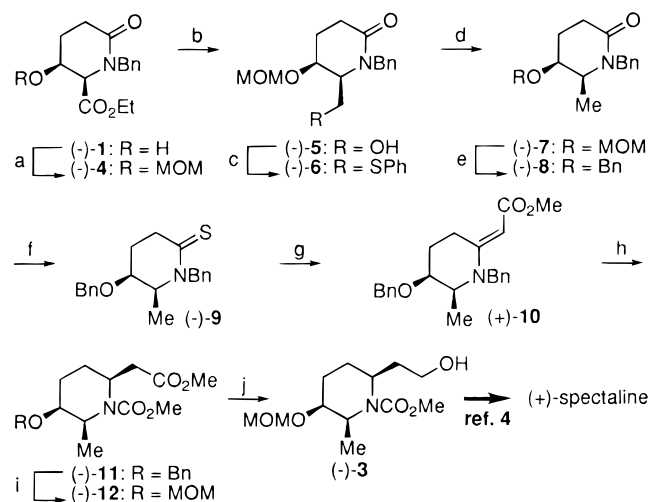


Reduction of (-)-**12** with Super-Hydride gave alcohol (-)-**3**, an intermediate for the chiral synthesis of (+)-spectaline.^{3b,4} Thus, the absolute stereochemistry of (-)-**1** was verified to be 2*R*,3*S*, and the preparation of a chiral building block of type **I** was completed (Scheme 2).

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 NaBH₃CN 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-

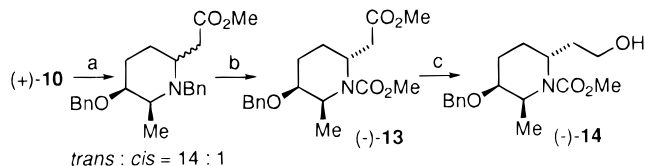
(15) Use of Super-Hydride was extremely effective for reduction of this sterically hindered ester functional group. For example, no reduction proceeded with LiAlH₄ at room temperature for 14 h, and the starting material was recovered. Reduction with LiBH₄ (6 equiv) at room temperature for 23 h gave a 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

- ^aa: MOMCl, Hünig base, CHCl₃, reflux (98%);
 b: Super-Hydride, THF, 0 °C (96%);
 c: PhSSPh, *n*-Bu₃P, 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: BrCH₂CO₂Me then Ph₃P, Et₃N, MeCN, reflux (83%);
 h: H₂, Pd(OH)₂, MeOH; ClCO₂Me, K₂CO₃ (68%);
 i: H₂, Pd(OH)₂, MeOH; MOMCl, Hünig base, CHCl₃, reflux (93%);
 j: Super-Hydride, THF, 0 °C~rt (89%)

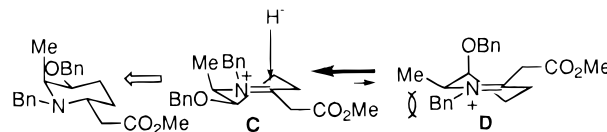
ture was used for subsequent transformation. Hydrogenation of the above mixture over Pd(OH)₂ followed by

Scheme 3^a

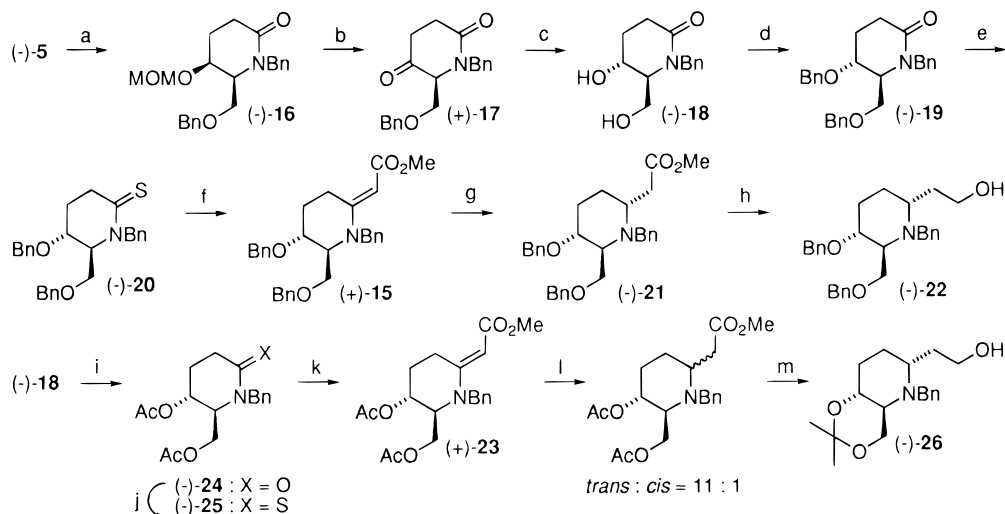
- ^aa: NaBH₃CN, TFA, CH₂Cl₂, 0 °C (99% combined yield);
 b: H₂, Pd(OH)₂, MeOH; K₂CO₃, ClCO₂Me, CH₂Cl₂-H₂O (68%);
 c: Super-Hydride (92%);

treatment of the resulting amine with ClCO₂Me 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).

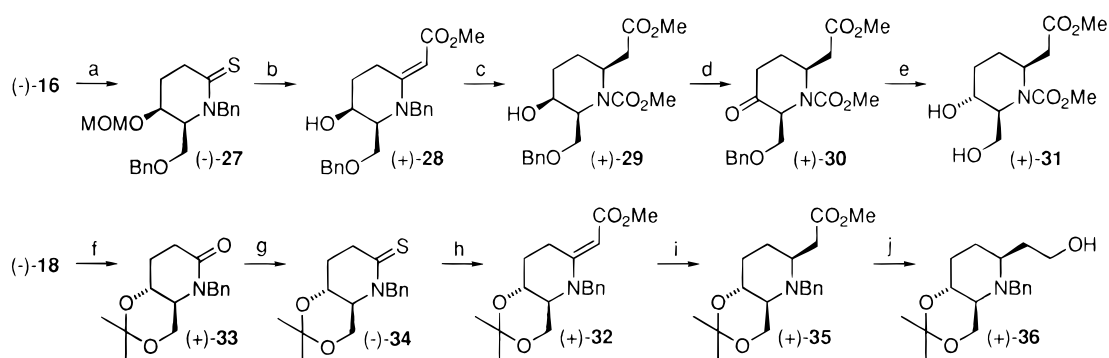
The *trans*-selectivity observed in the above reduction is explained by the following factors. Conformer **C** for the iminium salt, generated from (+)-10 under acidic conditions, is favored relative to **D** because of *A*^(1,2) strain¹⁶ between the *N*-benzyl and the methyl at the α -position, so the hydride reacts from the preferred β -axial site,¹⁷ leading to a chairlike transition state to give *trans*-(2,6)-piperidine.



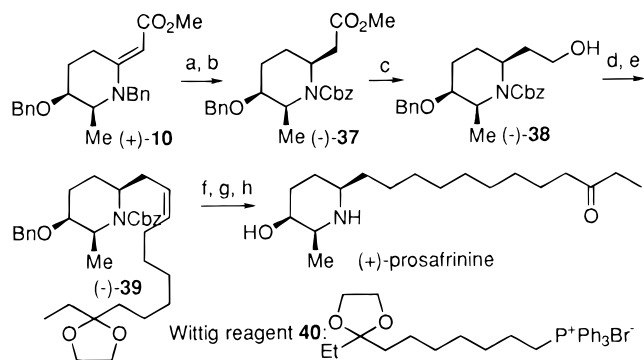
Another *trans*-(2,6)-piperidine of type III was synthesized in a similar iminium reduction of the corresponding vinylogous urethane of *trans*-(2,3)-congener (+)-15. Pro-

Scheme 4^a

- ^aa: NaH, BnBr, DMF-benzene=2:1 (96%);
 b: c. HCl, MeOH, reflux; PCC, AcONa, CH₂Cl₂ (83%);
 c: H₂, Pd(OH)₂, MeOH; NaB(OAc)₃H, AcOH (97%);
 d: KOH, BnBr, THF, MS 4A (79%);
 e: Lawesson's reagent, THF, reflux (94%);
 f: BrCH₂CO₂Me then Ph₃P, Et₃N, MeCN, reflux (92%);
 g: NaBH₃CN, TFA, CH₂Cl₂, 0 °C (53%);
 h: LiAlH₄, THF, reflux (84%);
 i: Ac₂O, pyridine (88%);
 j: Lawesson's reagent, THF, reflux (99%);
 k: BrCH₂CO₂Me then Ph₃P, Et₃N, MeCN, reflux (92%);
 l: NaBH₃CN, TFA, CH₂Cl₂, 0 °C (84% combined yield);
 m: LiAlH₄, THF, reflux (84%); 2,2-dimethoxypropane, *p*-TsOH, MS 5A, CH₂Cl₂, rt (75% in 2 steps)

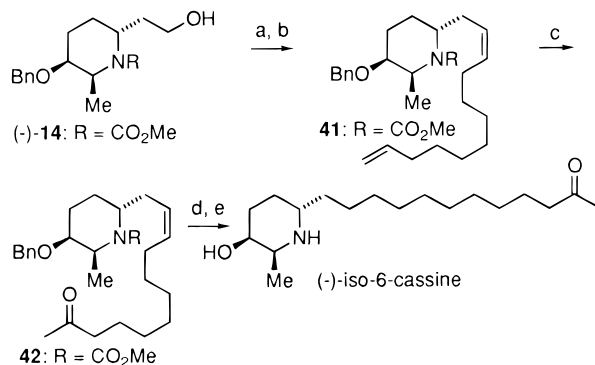
Scheme 5^a

- ^aa: Lawesson's reagent, THF, reflux (90%);
 b: BrCH₂CO₂Me then Ph₃P, Et₃N, MeCN, reflux {53%, 31% of the MOM ether of (+)-28};
 c: H₂, Pd(OH)₂, MeOH; ClCO₂Me, K₂CO₃ (71%);
 d: PCC, AcONa, CH₂Cl₂ (96%);
 e: H₂, Pd(OH)₂, MeOH; NaB(OAc)₃H, AcOH, 0 °C~rt (86%);
 f: 2,2-dimethoxypropane, *p*-TsOH, MS 5A, CH₂Cl₂, rt (91%);
 g: Lawesson's reagent, THF, reflux (57%);
 h: BrCH₂CO₂Me then Ph₃P, Et₃N, MeCN, reflux (72%);
 i: NaBH₃CN, TFA, 0 °C (59%);
 j: LiAlH₄, THF, reflux (99%)

Scheme 6^a

- ^aa: H₂, Pd(OH)₂, MeOH;
 b: CbzCl, K₂CO₃, CH₂Cl₂-H₂O (96% in 2 steps);
 c: Super-Hydride, THF (90%);
 d: Swern oxidn.;
 e: Wittig reagent **40**, *n*-BuLi, THF (60% in 2 steps);
 f: H₂, Pd(OH)₂, MeOH;
 g: Na, liq. NH₃;
 h: *p*-TsOH, acetone (50% in 3 steps)

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*-Pr₂O to give an enantiopure compound¹⁸ 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

Scheme 7^a

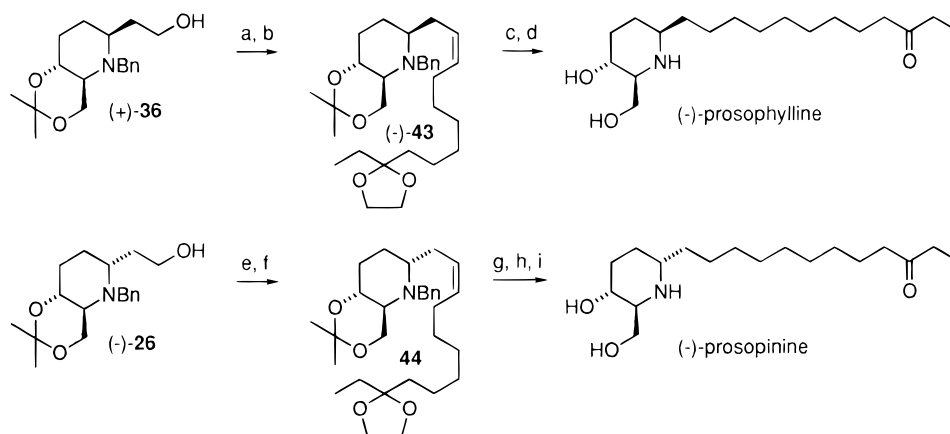
- ^aa: Swern oxidn.;
 b: CH₂=CH(CH₂)₈P⁺Ph₃Br[–], *n*-BuLi, THF (80% in 2 steps);
 c: O₂, CuCl, PdCl₂, DMF-H₂O (64%);
 d: H₂, Pd(OH)₂, MeOH;
 e: TMSI, CHCl₃, reflux (58% in 2 steps)

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 NaBH₃CN 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 LiAlH₄ 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 LiAlH₄ 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.

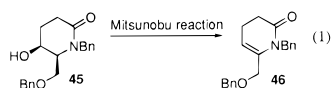
Scheme 8^a

- ^aa: Swern oxidn.;
 b: Wittig reagent **40**, *n*-BuLi, THF (59% in 2 steps);
 c: H₂, 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: H₂, 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 ClCO₂Me 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 NaBH₃CN in the presence of TFA provided *cis*-(2,6)-piperidine (+)-**35** exclusively, which was reduced to alcohol (+)-**36** with LiAlH₄ 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 LiAlH₄ reduction of (+)-**35**, with (–)-**26** on the basis of ¹H NMR spectra.

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

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 ¹³C 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 CHCl₃ to furnish iso-6-cassine. ¹H and ¹³C 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 ¹³C NMR spectra of synthetic alkaloid were identical with those of the literature.^{9a} Similarly, the acetonide (–)-**26** was transformed to (–)-

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

prosopinine via the olefin **44** (Scheme 8). ^1H 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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