Highly Enantiopure C_1-Symmetric *cis*-Piperidine-3,5-dimethanol Monoacetates by Enzymatic Asymmetrization[1]

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Ibogan type indole alkaloids possessing the *pseudo*-aspidosperma skeleton, e.g. (20*R*)-*pseudo*-aspidospermidine (**1**) and (20*R*)-dihydrocleavamine (**2**), and tacaman type indole alkaloids such as tacamonine (**3**) are characterized by a common nontryptaminic substructure in which a *cis*-3,5-disubstituted piperidine (**A**) can be recognized as depicted in Figure 1.[2] To obtain versatile chiral precursors for the enantiosynthesis of these alkaloids by a chemoenzymatic approach,[3] we became interested in the asymmetrization of meso cis 3,5-disubstituted piperidines. In a recent paper we demonstrated[4] that the biocatalytic hydrolysis of the C_s-symmetrical *N*-protected piperidine-3,5-dicarboxylates **4a** and **4b**, by means of lipase from *Candida cylindracea* (CCL), gave the corresponding C_1-symmetric hydrogen methyl (3*S*,5*R*)-piperidine-3,5-dicarboxylates **5a** and **5b** with moderate enantiomeric excess (78−80%), but with a fair degree of conversion (20−25% range yield, Scheme 1).

As a result of our efforts to obtain a more suitable chiral synthon with higher ee and chemical yield, we report here the enzymatic desymmetrization of *meso-cis*-piperidine-3,5-dimethanols **6a,b** and their diacetates **7a,b** and the determination of the absolute configuration of the corresponding asymmetrized compounds **8a,b** and **ent-8a,b**. Furthermore, to highlight the synthetic potential of these chiral building blocks, one of them was efficiently elaborated into advanced intermediates useful in the development of synthetic routes to the above-mentioned indole alkaloids.

Compounds **6a,b** and **7a,b** were prepared from **4a,b**[4,5] by following standard procedures (see Experimental Section). Initially, we have examined the irreversible acetylation of compounds **6a** and **6b** catalyzed by some commercially available lipases such as porcine pancreatic lipase (PPL), CCL, and *Pseudomonas fluorescens* lipase (PFL) in organic solvents using vinyl acetate as acyl donor. As can be seen from Table 1, PPL and PFL in neat vinyl acetate gave the best results and showed the same enantiomeric preference. In particular, PFL was the more promising enzyme for providing esters **8a** and **8b** with extremely high optical purities and in good

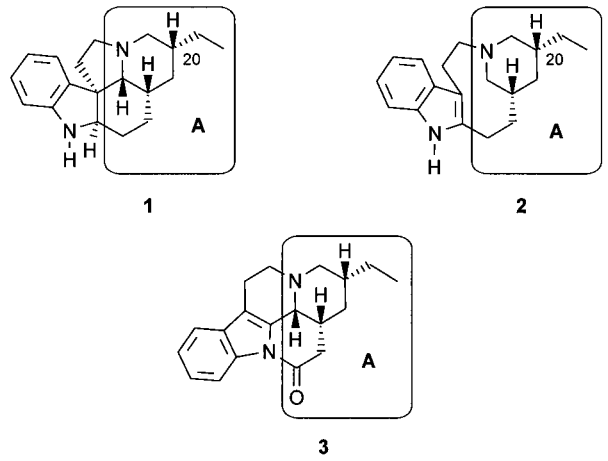

Figure 1.

Scheme 1

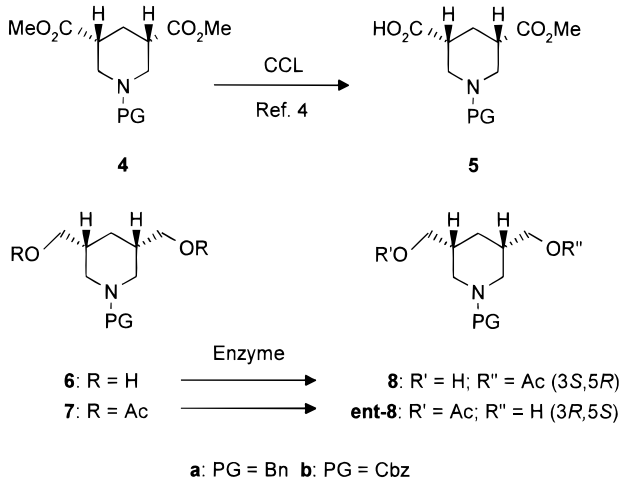

Table 1. Results of the Lipase Catalyzed Acetylation of 6a and 6b

entry	substrate	lipase[a]	method[b]	time (h)	product (% yield)[c]	% ee
1	**6a**	CCL	A	5	**ent-8a** (14)[d]	17
2		PPL	B	22	**8a** (12)	33
3		PPL	A	5	**8a** (23)	38
4		PFL	B	22	**8a** (61)	>98
5		PFL	A[e]	5	**8a** (74)	>98
6	**6b**	CCL	A	7	**ent-8b** (29)[d]	23
7		PPL	B	24	**8b** (31)[f]	74
8		PPL	A	7	**8b** (55)	68
9		PFL	B	22	**8b** (63)	>98
10		PFL	A[e]	6	**8b** (78)	>98

[a] CCL = *Candida cylindracea* lipase, PPL = Porcine pancreas lipase, PFL = *Pseudomonas fluorescens* lipase. [b] Method A: 1.0 mmol of substrate in vinyl acetate at 25 °C as described in the Experimental Section. Method B: 1.0 mmol of substrate in CH_3CN at 25 °C in the presence of vinyl acetate (2.0 equiv) as described in the Experimental Section. [c] Isolated yields. [d] The corresponding diacetate **7a** or **7b** was also isolated in the range of 33−38% yield. [e] This reaction was carried out starting with either 1.0 or 10.0 mmol of substrate as described in the Experimental Section. [f] The diacetate **7b** was also isolated in 15% yield.

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(1) Part of this work was presented at the 8th European Symposium of Organic Chemistry, 1993, Sitges, Barcellona, Spain.

(2) Danieli, B.; Palmisano, G. Alkaloids from *Tabernaemontana*. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 27, pp 1−130.

(3) Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. Chiral Synthons via Enzyme-Mediated Asymmetrization of Meso-Compounds. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; 1993; Vol. 1, pp 143-219.

(4) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Tetrahedron: Asymmetry* **1996**, *7*, 345−348.

(5) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Synth. Commun.* **1997**, *27*, 69−77.

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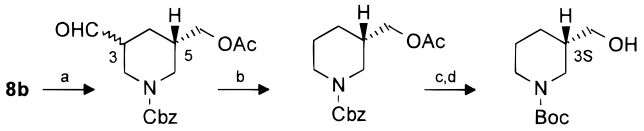
Table 2. Results of the Lipase Catalyzed Hydrolysis of 7a and 7b

entry	substrate	lipase[a]	method[b]	time (h)	product (% yield)[c]	% ee
1	**7a**	PPL	A	6	**ent-8a** (53)	55
2		PPL	B	6	**ent-8a** (51)	57
3		PFL	A	14	**ent-8a** (66)	>95
4		PFL	B[d]	20	**ent-8a** (73)	>98
5	**7b**	PPL	A	6	**ent-8b** (51)	28
6		PPL	B	6	**ent-8b** (44)	31
7		PFL	A	5	**ent-8b** (65)	>94
8		PFL	B[d]	5	**ent-8b** (77)	>98

[a] PPL = Porcine pancreas lipase, PFL = *Pseudomonas fluorescens* lipase. [b] Method A: 1.0 mmol of substrate in *t*-BuOMe/0.2 M phosphate buffer (pH 7.1) (1:3) at 25 °C as described in the Experimental Section. Method B: 1.0 mmol of substrate in 0.2 M phosphate buffer (pH 7.1) at 25 °C as described in the Experimental Section. [c] Isolated yields. [d] This reaction was carried out starting with either 1.0 or 10.0 mmol of substrate as described in the Experimental Section.

Scheme 2[a]



[a] (a) sulfur trioxide−pyridine complex, DMSO, Et_3N; (b) $(Ph_3)_3$-RhCl, toluene, reflux; (c) H_2, Pd/C (10%); (d) Boc_2O, NaOH, *t*-BuOH.

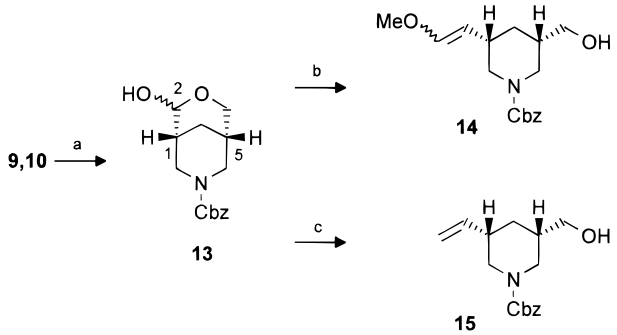
yields. On the other hand, the use of 2 equiv of vinyl acetate in organic solvent ranging from the very polar acetonitrile (see, for example, entries 2 and 7) to *n*-hexane dramatically reduced the rate and the enantioselectivity of the reaction.

The opposite enantioselectivity was observed with CCL; however, the poor yield and ee of monoacetates **ent-8a** and **ent-8b** and the competitive conversion to diacetates rendered these transformations of little value.

Since it is known that enzymatic alcoholysis is enantiocomplementary to enzymatic esterification,[3,6] we examined the hydrolysis of diacetates **7a** and **7b** in order to obtain a more convenient approach to the monoacetates **ent-8a** and **ent-8b**. The results of the hydrolysis of **7a** and **7b** are summarized in Table 2. Of the lipases employed for screening, PFL was the best choice again, and among the systems tested, the 0.2 M phosphate buffer (pH 7.1) system was the most effective for enhancing the enantioselectivity. The monoacetates **ent-8a** and **ent-8b**, with 3*R*,5*S* stereochemistry, were thus obtained in good yield, as optically pure compounds (ee > 98%). On the other hand, the reaction did not proceed with CCL nor with pig liver esterase (PLE). It is notable to observe that both the acetylation of **6a** and **6b** catalyzed by PFL (Table 1, entries 5, 10) and the hydrolysis of the diesters **7a** and **7b** catalyzed by the same lipase (Table 2, entries 4, 8) have been carried out conveniently on gram scales.

The absolute stereochemistry of the products **8a** and **8b** (and thus of **ent-8a,b**) was established by the conversion of **8b** into the known (3*S*)-*tert*-butyl 3-hydroxymethyl-1-piperidinecarboxylate **12**[7] (Scheme 2). The

Scheme 3[a]



[a] (a) NaOH, THF/H_2O, then 5% H_3PO_4 (aq); (b) $(MeOCH_2PPh_3)^+Cl^-$, *t*-BuOK, toluene, rt; (c) $(CH_3PPh_3)^+Br^-$, *t*-BuOK, toluene, rt.

Parikh[8] oxidation of **8b** provided a 2.3:1 inseparable mixture of the diasteromeric *cis*- and *trans*-aldehydes **9** and **10** in 72% yield.[9] The epimerization at C-3 in the aldehyde **9** (through enolate or enol formation) may be rationalized by taking into account that the presence of the amide sp^2 nitrogen in the hexacyclic ring removes one potentially unfavorable synaxial interaction in the trans isomer **10** with axial substituent at C-3 or C-5, leading to a drop of free energy difference between the two isomers.[10]

Removal of the formyl group of both **9** and **10**, with $(Ph_3P)_3RhCl$ in toluene at reflux,[11] afforded cleanly the nor-derivative **11** which was readily converted into **12**, in 65% overall yield, by alkaline hydrolysis and subsequent *N*-protecting group interchange. The optical rotation of **12** was found to be $[\alpha]_{365} = +60.5$ (*c* 1, EtOH) {lit.[7] $[\alpha]_{365} = +60.7$ (*c* 1, EtOH)}, thus establishing the absolute configuration as 3*S*. As a consequence, the absolute configuration of compound **8b** is 3*S*,5*R*. Since compound **8b** was converted into **8a** (see Experimental Section), the absolute configuration of the latter compound was established to be 3*S*,5*R*.

To develop versatile synthetic routes to *pseudo*-aspidosperma and tacamine alkaloids, **8a,b** or **ent-8a,b** required suitable homologations at both C-3 and C-5 appendages. To test this proposal, we considered the monoacetate **8b** and the thereof derived aldehyde **9**. The latter compound could be considered as an attractive intermediate if we were able to convert it into a configurationally stable equivalent form which prevents the epimerization at the C-3 carbon atom during the elaboration of the carbonyl group. This goal was reached by converting the epimeric 2.3:1 mixture of the aldehydes **9** and **10** into the stable *δ*-lactol-bridged piperidine **13**, as a 1.6:1 inseparable mixture of C-2 epimers, by means of alkaline hydrolysis followed by acidic workup in 95% yield[12] (Scheme 3). This transformation was the result

(6) Theil, F.; *Chem. Rev.* **1995**, *95*, 2203−2227.
(7) Wirz, B.; Walther, W. *Tetrahedron: Asymmetry* **1992**, *3*, 1049−1054.
(8) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.
(9) Similar diastereoisomeric ratios were obtained following different procedures of oxidation and when the mixture of **9** and **10** was subjected to thermodynamically equilibrated conditions.
(10) Inspection of the thermodynamic stability and conformational behavior of *cis*- and *trans*-aldehydes **9** and **10** by MM2 (HyperChem 5.0) revealed that **10**, with an axial formyl substituent at C-3, is less stable than **9** by only ca. 0.6 kcal/mol, which is consistent with experimental facts.
(11) Hono, M. *J. Am. Chem. Soc.* **1968**, *90*, 99.
(12) The same sequence of reactions was used to transform the enantiomeric aldehydes **ent-9** and **ent-10**, derived from **ent-8b** by a Parik oxidation, into the corresponding *δ*-lactol-bridged piperidine **ent-13**.

of the fast, entropy-favored, lactolization which occurs in a minor, less stable conformation of the *cis*-aldehyde **9,** in which the carbonyl and the hydroxymethyl group are juxtaposed in the synaxial disposition.[13] Close inspection of the ^{1}H and ^{13}C NMR (APT) spectra of **13** revealed that the both C-2 epimers exist in $CDCl_3$ solution as an equilibrium of two conformations about the CO−N bond, slowly interconverting on the NMR time scale (with respect to chemical shifts). Assignments of the ^{1}H and ^{13}C NMR signals of the four isomers were facilitated by HETCOR and COSY spectra. In particular, the latter experiment allowed the assignment of all the methine and methylene ^{1}H resonances, although most of them severely overlapped (see Supporting Information).

As an example of a highly stereocontrolled reaction on the lactol **13**, the Wittig olefination of **13** with [(methoxy)-methylene]triphenylphosphorane in THF led to the exclusive formation of the enol ether **14** as a 2.5:1 mixture of *E* and *Z* isomers in 88% yield. Compound **14** was confirmed to be the cis 3,5-disubstituted stereoisomer by the detailed examination of the ^{1}H NMR spectrum, which was essentially fully assigned. Interestingly, within the limits of detection by NMR, none of the trans 3,5-disubstituted diastereoisomers was present.

As a further demonstration, we also prepared the ethylidene derivative **15** by reacting the lactol **13** with methyltriphenylphosphorane; also in this case the cis 3,5-disubstituted diastereoisomer was exclusively formed.

In conclusion, our enzymatic procedure provided an efficient route for the preparation of both the heretofore unknown monoacetates **8a,b** and **ent-8a,b** (each >98% ee) on the gram scale. Moreover, the easily accessible homochiral *δ*-lactol-bridged piperidine **13**, featuring the cis 3,5-disubstituted piperidine substructure **A** (Figure 1), represents a valuable starting material for the preparation of advanced intermediates, such as **14** and **15**, useful for the future enantioselective synthesis of *pseudo*-aspidosperma and tacamine alkaloids.

Experimental Section[14]

Materials. Porcine pancreatic lipase (PPL, EC 3.1.1.3 of type II), *Candida cylindracea* lipase (CCL, EC 3.1.1.3. of type VIII), and pig liver esterase (PLE, EC 3.1.1.1 of type I) were obtained from Sigma Chemical Co., and *Pseudomonas fluorescens* lipase (PFL EC 3.1.1.3) was purchased from Fluka. All enzymes were used without further purification. Vinyl acetate and acetonitrile for enzymatic esterification (analytical grade) were used without further purification (apart from drying, by shaking with 3-Å molecular sieves (Merck)).

General Methods. Analytical liquid chromatography was carried out with a Kontron HPLC system equipped with a UV detector and a Chiralcel ODH HPLC column, using *n*-hexane/*i*-PrOH (9:1) as an eluant. Progress of the acetylations and hydrolysis was monitored by HPLC analysis, and the reactions were stopped when they come to a near standstill. All separations were carried out under flash chromatography (FC) conditions on silica gel 60 (230−400 mesh) using the indicated solvents. The organic extracts were dried over anhydrous Na_2SO_4 prior to solvent removal on a rotary evaporator.

General Procedure for Reduction of *N*-Protected Piperidine Diesters 4a and 4b. To an ice-cold stirred suspension of $LiBH_4$ (1.44 g, 66 mmol) in THF (150 mL) was added dropwise a solution of the diester **4a** or **4b**[4,5] (16.5 mmol) in THF (110 mL) over a period of 1 h. After additional stirring during 45 h at room temperature, the reaction mixture was poured into a stirred mixture of 400 mL of EtOAc and 100 mL of saturated acqueous $NaHCO_3$ (**caution: violent foaming**) and stirred vigorously for 5 min. After saturation of the aqueous phase with NaCl, the mixture was extracted four times with EtOAc, and the organic solvents were dried.

***N*-Benzyl-*cis*-3,5-bis(hydroxymethyl)piperidine (6a).** Flash chromatography (95:5 $CHCl_3$/MeOH as an eluent) of the crude diol mixture afforded **6a** in 80% yield as a white solid: R_f (95:5 $CHCl_3$/MeOH) 0.26; mp 127−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) *δ* 7.29 (m, 5 H), 3.54 (s, 2 H), 3.48 (dd, 1 H, J = 10.5, 6.0 Hz), 3.41 (dd, 1 H, J = 10.5, 6.5 Hz), 3.02 (br d, 2H, J = 11.7 Hz), 2.01 (m, 2 H), 1.89 (m, 2 H), 1.81 (br d, 1 H, J = 12.1 Hz), 1.68 (t, 2 H, J = 11.7 Hz), 0.69 (q, 1 H, J = 12.1 Hz); EIMS *m/z* (relative intensity) 235 (5, M^+), 144 (52), 91 (100). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71,55; H, 8.81; N, 6.04.

Benzyl *cis*-3,5-Bis(hydroxymethyl)-1-piperidinecarboxylate (6b). Flash chromatography of the crude diol with EtOAc afforded **6b** in 82% yield as a viscous oil: R_f (EtOAc) 0.24; IR ($CHCl_3$) 3630, 1685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) *δ* 7.38 (m, 5 H), 5.13 (s, 2 H), 4.29 (dd, 2 H, J = 12.1, 3.0 Hz), 3.53 (dd, 1 H, J = 11.5, 6.0 Hz), 3.47 (dd, 1 H, J = 11.5, 6.8 Hz), 2.45 (t, 2 H, J = 12.1 Hz), 1.88 (br d, 1 H, J = 12.1 Hz), 1.74 (m, 2 H), 0.92 (q, 1 H J = 12.1 Hz); EIMS *m/z* (relative intensity) 279 (2, M^+), 144 (35), 91 (100). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.72; H, 7.46; N, 5.19.

General Procedure for Acetylation of Diols 6a and 6b. A solution of **6a** or **6b** (30 mmol) in 10 equiv of anhydrous pyridine was acetylated by the addition of 0.05 equiv of DMAP as a catalyst and 4 equiv of Ac_2O. The solution was heated with stirring to about 100 °C and left to cool for 30 min. Solvents were evaporated to near dryness, and 200 mL of Et_2O and 50 mL of water was added. The ether portion was removed, and the aqueous phase was extracted two more times with ether. The combined organic fractions were dried and evaporated. In the case of diol **6b**, a minimum amount of 1 N HCl was used for the neutralization of the remaining pyridine, and the combined organic fractions were washed with saturated acqueous $NaHCO_3$ before drying and evaporating.

***N*-Benzyl-*cis*-3,5-bis(acetoxymethyl)piperidine (7a). 7a** was obtained in 79% yield as a colorless oil: R_f (9:1 $CHCl_3$/MeOH) 0.74; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) *δ* 7.30 (m, 5 H), 3.92 (dd, 1 H, J = 11.2, 6.0 Hz), 3.85 (dd, 1 H, J = 11.2, 6.5 Hz), 3.53 (s, 2 H), 2.92 (br dd, 2 H, J = 11.8, 4.2 Hz), 2.04 (m, 2 H), 2.02 (s, 6 H), 1.80 (br d, 1 H, J = 12.4 Hz), 1.65 (t, 2 H, J = 11.8 Hz), 0.73 (q, 1 H, J = 12.4 Hz); EIMS *m/z* (relative intensity) 319 (7, M^+), 228 (71), 91 (100). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.51; H, 7.76; N, 4.59.

Benzyl *cis*-3,5-Bis(acetoxymethyl)-1-piperidinecarboxylate (7b). 7b was obtained in 81% yield as a viscous oil: R_f (AcOEt) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) *δ* 7.34 (m, 5 H), 5.11 (s, 2 H), 4.29 (br d, 2 H, J = 12.3 Hz), 3.99 (dd, 1 H, J = 11.8, 4.5 Hz), 3.87 (dd, 1 H, J = 11.8, 6.7 Hz), 2.42 (br t, 2 H, J = 12.3 Hz), 2.03 (s, 6 H), 1.99−1.80 (m, 3 H), 0.94 (q, 1 H, J = 12.3 Hz); EIMS *m/z* (relative intensity) 363 (4, M^+), 228 (44), 91 (100). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 63.01; H, 7.06; N, 3.71.

General Procedure for Enzymatic Acetylation of *N*-Protected *cis*-3,5-Bis(hydroxymethyl)piperidines 6a and 6b. To a solution of **6a** or **6b** (1 mmol) in dry solvent (10 mL) was added an appropriate enzyme [(PPL, 45670 units/mmol substrate), (CCL, 200 units/mmol substrate), (PFL 236 units/mmol substrate)] and the mixture was shaken at room temperature. After the appropriate time, the enzyme was filtered off, the solvent was evaporated, and the reaction product purified by flash chromatography. The optical purity of the acetate **8a** was determined by chiral HPLC and also confirmed by ^{1}H NMR (300 MHz, $CDCl_3$,) spectroscopy in the presence of 0.4 mol equiv of Eu(hfc)$_3$.[15]

Since conditions for separating the signals of enantiomers of **8b** have not yet been found, neither by HPLC nor ^{1}H NMR, this

(13) Eliel, E. L. in *Stereochemistry of Organic Compounds;* J. Wiley & Son, Inc.: New York, 1994.

(14) For typical experimental protocols, see: Danieli, B.; Lesma, G.; Mauro, M.; Palmisano, G.; Passarella, D. *Tetrahedron* **1994**, *50*, 8837−8852.

(15) Under these conditions **8a** (3*S*,5*R*) and **ent-8a** (3*R*,5*S*) showed respectively at *δ* 3.70 and 3.65 for the methyl group of the acetate.

acetate was converted, in a straighforward two-step reaction sequence [H_2/Pd(C), EtOAc, then BnBr, K_2CO_3, dioxane, rt, (77%)], into its congener **8a** (vide infra) from which the ee could be determined as described above.

(3*S*,5*R*)-*N*-Benzyl-3-(acetoxymethyl)-5-(hydroxymethyl)-piperidine (8a) was obtained by reaction of **6a** with PFL in vinyl acetate after 5 h (Table 1, entry 5). Purification of the crude product by flash chromatography (9:1 $CHCl_3$/MeOH) gave 74% yield of **8a** (>98% ee) as an oil: R_f (9:1 $CHCl_3$/MeOH) 0.40; $[\alpha]_{365} = +5.3$ (*c* 1, MeOH); ^{1}H NMR(300 MHz, $CDCl_3$, 50 °C) δ 7.32 (m, 5 H), 3.93 (dd, 1 H, J = 11.7, 6.0 Hz), 3.86 (dd, 1 H, J = 11.7, 7.0 Hz), 3.58 and 3.50 (AB system, 2 H, J = 12.5 Hz), 3.48 (dd, 1 H, J = 10.5, 6.1 Hz), 3.42 (dd, 1 H, J = 10.5, 6.1 Hz), 2.99 (br d, 1 H, J = 11.8 Hz), 2.93 (br d, 1 H, J = 11.8 Hz), 2.04 (m, 1 H), 2.00 (s, 3 H), 1.90 (m, 1 H), 1.81 (br d, 1 H, J = 12.4 Hz), 1.69 (t, 1 H, J = 11.8 Hz), 1.65 (t, 1 H, J = 11.8 Hz), 1.45 (m, 1 H), 0.73 (q, 1 H, J = 12.4 Hz); HRMS calcd for $C_{16}H_{23}N_1O_3$ 277.1678, found 277.1688. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.11; H, 8.42; N, 5.01.

(3*S*,5*R*)-Benzyl 3-(acetoxymethyl)-5-(hydroxymethyl)-1-piperidinecarboxylate (8b) was obtained by reaction of **6b** with PFL in vinyl acetate after 6 h (Table 1, entry 10). Purification of the crude product by FC (EtOAc as an eluent) gave 78% yield of **8b** (>98% ee) as an oil: R_f (EtOAc) 0.33; $[\alpha]_{365} = +25.4$ (*c* 1, MeOH); IR (neat) 3635, 1725, 1690 cm^{-1}; ^{1}H NMR-(300 MHz, $CDCl_3$, 50 °C) δ 7.32 (m, 5 H), 5.12 (m, 2 H), 4.39−4.17 (m, 2 H), 3.99 (dd, 1 H, J = 10.5, 5.9 Hz), 3.86 (dd, 1 H, J = 10.5, 7.2 Hz), 3.51 (m, 2 H), 2.51−2.30 (m, 2 H), 2.03 (s, 3 H), 1.95−1.80 (m, 2 H), 1.80−1.55 (m, 2 H), 0.92 (q, 1 H, J = 11.6 Hz); HRMS calcd for $C_{17}H_{23}NO_5$ 321.1576, found 321.1569. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.31; H, 7.06; N, 4.41.

Conversion of 8b to 8a. A solution of **8b** (>98% ee; 0.8 g, 2.5 mmol) in EtOAc (9 mL) including 10% palladium on carbon (80 mg) was shaken under a hydrogen atmosphere for 12 h. The catalyst was filtered off, and the solution was concentrated to dryness. The residue was dissolved in 10 mL of dioxane, and K_2CO_3 (206 mg, 1.5 mmol) followed by BnBr (470 mg, 2.75 mmol) were added. After being stirred at room temperature for 15 h, the reaction mixture was concentrated in vacuo, the residue was poured into water and extracted with EtOAc, and the combined organic fractions were dried and evaporated. Flash chromatography of the residue gave **8a** (530 mg, 77% yield) which was found identical in all respects to that isolated from the PFL-catalyzed acetylation of **6a**.

General Procedure for Enzymatic Hydrolysis of *N*-Protected *cis*-3,5-Bis(acetoxymethyl)piperidines 7a and 7b. A suspension of substrate (1 mmol) and an appropriate enzyme [(PPL, 17040 units/mmol substrate), (CCL, 270 units/mmol substrate), (PFL, 315 units/mmol substrate), (PLE, 390 units/mmol substrate)] in an appropriate solvent system (10 mL) was shaken at room temperature, and the pH was kept at 7.0−7.2 by adding 0.1 M NaOH solution with an automatic pH starter. After an appropriate time, the reaction was stopped by addition of AcOEt. The aqueous solution was repeatedly extracted with AcOEt, and the collected organic layers were evaporated in vacuo affording a crude mixture which was purified by FC. The optical purity of the acetate **ent-8a** and **ent-8b** thus obtained was determined as described for the enantiomers **8a** and **8b**.

(3*R*,5*S*)- and (3*S*,5*S*)-Benzyl 3-(Formyl)-5-(acetoxymethyl)-1-piperidinecarboxylate (9 and 10) (Mixture of Diastereomers 2.3:1). To a magnetically stirred solution of **8b** (>98% ee; 2.50 g, 7.80 mmol) in dry DMSO (20 mL) under nitrogen was added triethylamine (2.40 g, 23.5 mmol) followed by dropwise addition of a solution of sulfur trioxide−pyridine complex (3.75 g, 23.5 mmol) in dry DMSO (16 mL). After 2 h, the reaction was quenched by addition of saturated $NaHCO_3$ (aqueous) and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated. FC (1:1 EtOAc/hexane) of the residue gave 1.80 g (72%) of an inseparable mixture of *cis*- and *trans*-aldehydes **9** and **10** (2.3:1 ratio from 300 MHz ^{1}H NMR): oil; R_f (1:1 EtOAc/hexane) 0.43; $[\alpha]_{365} = +34.5$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 1725, 1650 cm^{-1}; ^{1}H NMR(300 MHz, $CDCl_3$, 50 °C) δ 9.69 (br, s), 9.65 (br, s), 7.32 (m, 5 H), 5.14 (s), 5.17 and 5.11 (AB system, J = 11.8 Hz), 4.47 (br d, J = 12.2 Hz), 4.27 (br d, J = 12.2 Hz), 4.20 (dd, J = 13.0, 4.7 Hz), 4.02 (dd, 1 H, J = 11.0, 5.1 Hz), 3.92 (dd, 1H, J = 11.0, 7.2 Hz), 3.86 (br d, J = 13.0 Hz), 3.41 (dd, J = 13.0, 4.0 Hz), 2.93 (br dd, J = 13.0, 8.2 Hz), 2.73 (br t, J = 12.2 Hz), 2.51 (m), 2.49 (br t, J = 12.2 Hz), 2.20−2.05 (m), 2.03 (s), 2.01 (s), 1.92 (m), 1.54 (ddd, J = 13.2, 10.0, 5.2 Hz), 1.21 (q, J = 12.3 Hz); EIMS *m*/*z* (relative intensity) 319 (87, M^+), 291 (100), 274 (48), 216 (88). Anal. Calcd for $C_{17}H_{21}N_1O_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.79; H, 6.61; N, 4.28.

(3*S*)-Benzyl 3-(Acetoxymethyl)-1-piperidinecarboxylate (11). To a stirred solution of **9** and **10** (200 mg, 0.63 mmol) in dry toluene (6 mL) was added the complex $RhCl(PPh_3)_3$ (530 mg, 0.63 mmol). After heating at reflux for 24 h, the solvent was evaporated, Et_2O was added, and the solid was filtered off; after evaporation of Et_2O, the residue was purified by FC (2:1 hexane/AcOEt) to give **11** (147 mg, 80% yield), as an oil: R_f (2:1 hexane/AcOEt) 0.37; $[\alpha]_{365} = +47.6$ (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.36 (m, 5 H), 5.12 (s, 2 H), 4.05 (br d, 1 H, J = 12.6 Hz), 4.01−3.85 (m, 3 H), 2.90 (ddd, 1 H, J = 13.5, 10.7, 3.5 Hz), 2.72 (br t, 1 H, J = 12.6 Hz), 2.01 (s, 3 H), 1.92−1.74 (m, 2 H), 1.68 (m, 1 H), 1.47 (m, 1 H), 1.22 (m, 1 H); EIMS *m*/*z* (relative intensity) 291 (7, M^+), 246 (13), 140 (80), 91 (100). Anal. Calcd for $C_{16}H_{21}N_1O_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.11; H, 7.38; N, 4.99.

(3*S*)-*tert*-Butyl 3-(Hydroxymethyl)-1-piperidinecarboxylate (12). A solution of **11** (728 mg, 2.5 mmol) in EtOAc (10 mL) including 10% palladium on carbon (440 mg) was shaken under a hydrogen atmosphere for 12 h. The catalyst was filtered off, and the solution was concentrated to dryness to give a residue, which was subjected to the next reaction without purification.

To a stirred solution of the above product in *t*-BuOH (5 mL) and NaOH 1 N (10 mL) was added $(Boc)_2O$ (675 mg, 3 mmol). After 6 h at rt, the reaction mixture was poured into water and extracted with Et_2O; the organic phase was washed with brine, dried, and concentrated to give pure **12** (430 mg, 81% yield), as an oil: R_f (1:1 AcOEt/hexane) 0.23; $[\alpha]_{365} = +60.5$ (*c* 1, EtOH) {lit.[7] $[\alpha]_{365} = +60.7$ (*c* 1, EtOH)}. Compound **12** had IR, ^{1}H NMR, and MS spectra identical with those reported.[7]

(1*R*,5*S*)-7-Carbobenzyloxy-3-oxo-7-aza-bicyclo[3.3.1]-nonan-2-ol (13) (mixture 1.6:1 of C-2 epimers). To a room-temperature solution of the above-described mixture of aldehydes **9** and **10** (1.80 g, 5.64 mmol) in THF (40 mL) was added 0.25 *N* aqueous NaOH (45 mL), and the mixture was stirred at room temperature for 3 h. The reaction was then acidified with 5% aqueous H_3PO_4, and THF was evaporated. After partition between 50 mL of CH_2Cl_2 and 20 mL of brine, the aqueous phase was extracted three times with CH_2Cl_2, and the combined organic fractions were dried and evaporated. FC (EtOAc) of the residue afforded the lactol **13** (1.56 g, 95%) as an inseparable mixture of C-2 epimers (1.6:1 ratio from 300 MHz ^{1}H NMR): oil; R_f (EtOAc) 0.32; $[\alpha]_{365} = +77.9$ (*c* 1, $CHCl_3$); IR ($CHCl_3$) 3690, 3605, 3450, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.30 (m, 5 H), 5.20 (s), 5.12 (m, 2 H), 5.10 (s), 4.88 (br s), 4.85 (br s), 4.55 (br d, J = 13.5 Hz), 4.48 (br d, J = 13.5 Hz), 4.39 (br d, J = 13.5 Hz), 4.40−4.14 (m), 4.08 (br d, J = 10.5 Hz), 3.96 (br d, J = 10.5 Hz), 3.80 (m), 3.74 (br d, J = 10.5 Hz), 3.66 (br d, J = 10.5 Hz), 3.21−2.95 (m), 2.91 (br d, J = 13.5 Hz), 2.39 (br d, J = 12.8 Hz), 1.96 (br s), 1.91 (br s), 1.88−1.48 (m); EIMS *m*/*z* (relative intensity) 277 (17, M^+), 259 (27), 186 (24), 142 (100). Anal. Calcd for $C_{15}H_{19}N_1O_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.15; H, 6.97; N, 4.91.

(3*S*,5*S*)-Benzyl 3-(Hydroxymethyl)-5-(2-methoxyethenyl)-1-piperidinecarboxylate (14) (mixture 2.5:1 of *E* and *Z* isomers). To a stirred mixture of **13** (400 mg, 1.44 mmol) and $Ph_3P(CH_2OMe)(Cl)$ (738 mg, 2.15 mmol) in anhydrous toluene (15 mL) under N_2 was added *t*-BuOK (242 mg, 2.15 mmol) in four portions over a period of 1 h. After additional stirring during 2 h at room temperature, the reaction mixture was partitioned between 30 mL of EtOAc and 20 mL of water, and the aqueous phase was extracted twice with EtOAc. The organic fractions were dried and evaporated, and the residue was purified by FC (7:3 EtOAc/hexane) to give **14** (390 mg, 88%) as an inseparable mixture of *E* and *Z* isomers (2.5:1 ratio from 300 MHz ^{1}H NMR): colorless oil; R_f (EtOAc) 0.44; $[\alpha]_{365} = -69.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.35 (m, 5 H), 6.35 (d, J = 12.7 Hz), 5.87 (d, J = 6.5 Hz), 5.13 (m, 2 H), 4.56 (dd, J = 12.7, 7.5 Hz), 4.29 (br d, 1 H, J = 12.1 Hz), 4.13 (m, 1

H), 4.07 (dd, J = 7.5, 6.5 Hz), 3,55 (s), 3.53−3.42 (m, 2 H), 3,48 (s), 2.61 (m), 2.41 (t, 2 H, J = 12.1 Hz), 2.39 (t, 2 H, J = 12.1 Hz), 2.11 (m), 1.85 (br d, 1 H, J = 12.0 Hz), 1.74 (m, 1 H), 1.59 (m), 1.43 (m), 0.99 (q, 1 H, J = 12.0 Hz); EIMS m/z (relative intensity) 305 (38, M^+), 287 (96), 273 (100). Anal. Calcd for $C_{17}H_{23}N_1O_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.91; H, 7.74; N, 4.45.

(3*S*,5*S*)-Benzyl 3-(Hydroxymethyl)-5-(ethenyl)-1-piperidinecarboxylate (15). This compound was prepared according to the procedure for **14**, except $Ph_3P(Me)(Br)$ was used as the Wittig reagent. Thus, **13** (1 g, 3.8 mmol) was reacted to afford, after FC (7:3 AcOEt/hexane), 870 mg (85% yield) of **15** as a colorless oil: R_f (AcOEt) 0.47; $[\alpha]_{365} = -57.6$ (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 50 °C) δ 7.34 (m, 5 H), 5.68 (ddd, 1 H, J = 17.3, 10.3, 6.4 Hz), 5.12 (m, 2 H), 5.08 (br d, 1 H, J = 17.3 Hz), 5.01 (br d, 1 H, J = 10.3 Hz), 4.29 (m, 1 H), 4.21 (br m, 1 H), 3.49 (m, 2 H), 2.41 (m, 2 H), 2.19 (m, 2 H), 1.88 (br d, J = 12.4 Hz), 1.70 (m, 1 H), 1.00 (q, 1 H, J = 12.4 Hz); EIMS m/z (relative intensity) 275 (15, M^+), 257 (26), 140 (88), 91 (100). Anal. Calcd for $C_{16}H_{21}N_1O_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.97, H, 7.51; N, 5.14.

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Supporting Information Available: ^{1}H NMR spectra of compounds **6a,b**, **7a,b**, **8a,b**, **9-11**, and **13-15** and ^{13}C NMR spectrum of compound **13** accompained by subjective chemical shift assignments; 2D COSY and HETCOR spectra of compound **13** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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