Tetrahedron Letters, Vol. 33, No. 37, pp. 5389-5390, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

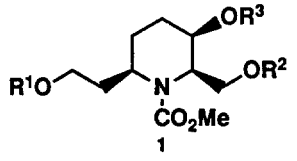
Asymmetric Twin-Ring Differentiation by Lipase-Catalyzed Enantiotoposelective Reaction of the Ring-Crossed *meso* Glycol: Asymmetric Synthesis of a Highly Functionalized Piperidine from the Conjoined Twin Piperidine System

Takefumi Momose,* Naoki Toyooka, and Makoto Jin

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama, 930-01, Japan

Abstract: Both enantiomers of the homochiral 3-oxygenated 2,6-*cis*-disubstituted piperidine **1** were synyhesized by starting with lipase-catalyzed transesterification or hydrolysis of the *meso* glycol or its diacetate in the conjoined twin piperidine system.

The enzyme-catalyzed asymmetric synthesis has become one of the practical methods for preparation of chiral building blocks for natural products.[1] In particular, the enzymatic dissymmetrization of *meso* compounds (so called "*meso* trick") is the most effective, and a number of reports have appeared with regard to the differential hydrolysis of the *meso* glycol diacetate located in an identical ring.[1] We now report the enantiotoposelective reaction of a glycol system bestridden over the bicyclo twin ring system, which leads to an efficient synthesis of both enantiomers of the alkaloid synthon 3-piperidinol (**1**),[2] one by starting with lipase-catalyzed transesterification of a *meso* diol (**2**)[3,4] and the other with ditto hydrolysis of a *meso* diacetate (**3**).[4] The transesterification of **2** is summarized in Table 1, and the enantiomerically pure (+)-ketone **5** ($[\alpha]_D^{26}$ +116.5°) was obtained in 74% overall yield from **2**.



1

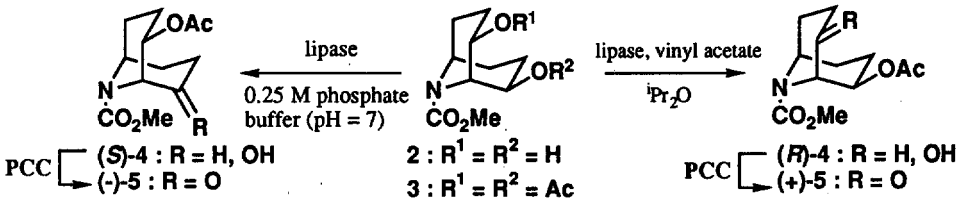


Table 1: Lipase-catalyzed transesterification of the *meso* diol **2**[a]

Lipase	Solvent[b]	Time (h)	Yield (%)[e]	Optical yield (% ee)[f]	Sign of rotation
CE[c]	$^iPr_2O$	109	85 (99)	90 (>99)	+
AY[c]	$^iPr_2O$	87	33 (99)	56	+
CCL[d]	$^iPr_2O$	91	15 (94)	54	+

a. All runs were conducted with the substrate (50 mg, 0.23 mmol), lipase (100 mg) and vinyl acetate (0.1 mL, 2 eqiv.) in $^iPr_2O$ (10 mL) at 32 ~35 °C. b. The use of hexane or benzene gave unsatisfactory results. c. Supplied by the Amano Pharmaceutical Co., Ltd. We are grateful to Amano Pharmaceutical Co., Ltd. for the generous gift of lipases. d. Purchased from the Sigma Chemical Co., Ltd. e. Yields in the isolated monoacetate **4**. Yields in parentheses are those based on the conversion rate. f. Determined for **5** by HPLC analyses using a column packed with CHIRALCEL AD (EtOH : *n*-hexane 1 : 9). The optical yield in parenthesis is the one after single recrystallization from $^iPr_2O$.

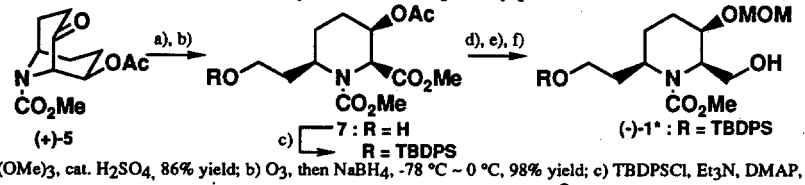
The lipase-catalyzed hydrolysis of **3** is summarized in Table 2, and the enantiomerically pure (-)-**5** ($[\alpha]_D^{26}$ -116.1°) was obtained in 65% overall yield from **3**.

Table 2: Lipase-catalyzed hydrolysis of the *meso* diacetate **3**[a]

Lipase	Solvent[d]	Time (h)	Yield (%)[e]	Optical yield (% ee)[f]	Sign of rotation
CE	B	23	84 (99)	80 (>99)	-
AY	B	35	42 (76)	78	-
CCL	B	66	23 (70)	58	-
PPL[b]	B+MeOH (5 : 1)	84	14 (45)	48	+
PLE-A[c]	B	48	39 (76)	75	-

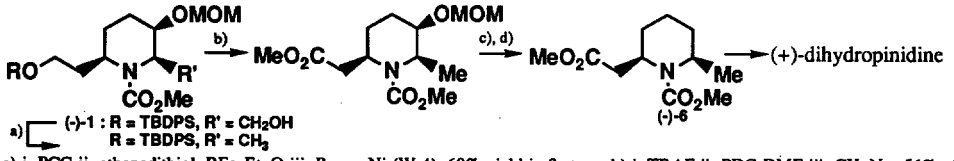
a. All runs were conducted with the substrate (50 mg, 0.17 mmol), lipase (100 mg) in the solvents (6 mL) at 32 ~ 35 °C. b. Purchased from the Sigma Chemical Co., Ltd. c. Supplied by the Amano Pharmaceutical Co., Ltd. d. Solvent B : 0.25 M phosphate buffer (pH = 7). e. Yields in the isolated **4**. Yields in parentheses are those based on the conversion rate. f. Determined for **5** as in the transesterification of **2**. The optical yield in parenthesis is the one after double recrystallization from $^{i}Pr_2O$.

Next, we examined the transformation of (+)-**5** into **1** (R^1 = TBDPS, R^2 = H, R^3 = MOM), and the desired piperidine (-)-**1** ($[\alpha]_D^{26}$ -7.2°) was synthesized in optically pure state as shown below.



a) $HC(OMe)_3$, cat. H_2SO_4, 86% yield; b) O_3, then $NaBH_4$, -78 °C ~ 0 °C, 98% yield; c) TBDPSCl, Et_3N, DMAP, 94% yield; d) K_2CO_3-MeOH; e) MOMCl, $Et(^{i}Pr)_2N$, 88% yield in 2 steps; f) Super-Hydride®, 87% yield; * (+)-**1** : $[\alpha]_D^{26}$ +7.1°.

The absolute configuration of (-)-**1** was established by its conversion into (+)-dihydropinidine *via* the piperidine (-)-**6**[5] ($[\alpha]_D^{26}$ -40.0°) as shown below.

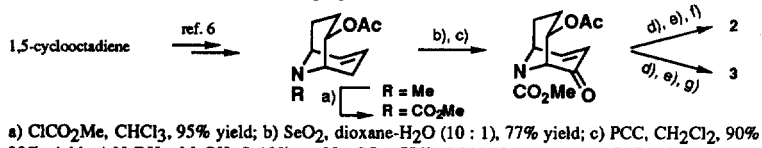


a) i. PCC ii. ethanedithiol, BF_3•Et_2O iii. Raney Ni (W-4), 60% yield in 3 steps; b) i. TBAF ii. PDC-DMF iii. CH_2N_2, 56% yield in 3 steps; c) i. c. HCl-MeOH ii. MsCl, Py iii. DBU-toluene, 48% yield in 3 steps; d) 5% Pd-C, H_2, 80% yield.

Thus, the group differentiation of the *meso* diol **2** or of its diacetate **3** resulted in ring differentiation in the twin piperidine system, and in obtaining both enantiomers of **1**. The piperidine **1** would serve as a promising chiral building block for the synthesis of piperidin-3-ol alkaloids such as cassine and spectaline.

REFERENCES AND NOTES

1. For recent reviews, see; Whitesides, G. M.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* 1985, **24**, 617; Chen, C.-S.; Sih, C. J. *ibid.* 1989, **28**, 695; Klibanov, A. M. *Acc. Chem. Res.* 1990, **23**, 114; Boland, W.; Frößl, C.; Lorenz, M. *Synthesis* **1991**, 1049 and references cited therein.
2. An elegant alternative synthesis of 2,6-disubstituted piperidin-3-ol derivatives has been reported; Natsume, M.; Ogawa, M. *Heterocycles* 1983, **20**, 601 and references cited therein.
3. Satisfactory analytical and spectral data were obtained for all new compounds. Optical rotations were taken in chloroform unless otherwise stated.
4. The *meso* diol **2** and diacetate **3** were prepared as follows.



a) $ClCO_2Me$, $CHCl_3$, 95% yield; b) SeO_2, dioxane-H_2O (10 : 1), 77% yield; c) PCC, CH_2Cl_2, 90% yield; d) H_2, 5%-Pd/C, MeOH, 98% yield; e) $NaBH_4$, MeOH; f) 10% aq. Na_2CO_3, 77% yield in 2 steps; g) Ac_2O, Py., 74% yield in 2 steps.
The stereochemistry of **2** was determined by X-ray crystallographic analysis after its conversion into the ditosylate and we are indebted to Dr. O. Muraoka, Kinki University, for the X-ray crystallographic data.

5. Momose, T.; Toyooka, N.; Hirai, Y. *Chem. Lett.* **1990**, 1319.
6. Portmann, R. E.; Ganter, C. *Helv. Chim. Acta* 1973, **56**, 1991.

(Received in Japan 20 May 1992)