Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 5, pp. 1085-1088, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00131-X

New Entry to C2 Symmetric *trans*-2,6-Bis(hydroxymethyl)-piperidine Derivatives *via* the Sharpless Asymmetric Dihydroxylation

Hiroki Takahata,* Shin-ichi Kouno, and Takefumi Momose*

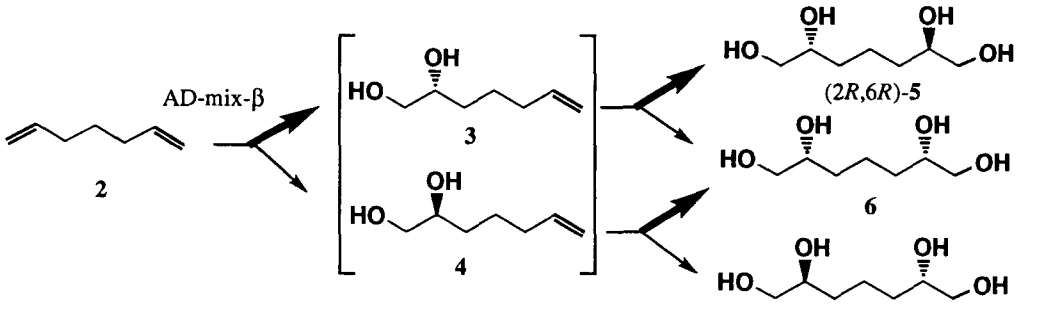
Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Abstract: A new synthesis of both enantiomers of C_2-symmetric *trans*-2,6-bis(hydroxymethyl)piperidine derivatives **1** by the use, as a key reaction, of the Sharpless asymmetric dihydroxylation of a symmetric diene **2** is presented.

Compounds with C_2 symmetry are emerging as valuable chiral auxiliaries in asymmetric synthesis since the reduction in number of competing, diastereomeric transition states often results in higher stereoselectivity.[1] Pioneering work by Katsuki et al has demonstrated that *O*-protected derivatives of *trans*-2,5-bis(hydroxymethyl)pyrrolidine are very useful as chiral auxiliaries.[2] The original report by Katsuki et al on the preparation of these auxiliaries[3] has been followed by more efficient approaches to these compounds.[4] However, the preparation of the 6-membered homologues *trans*-2,6-disubstituted piperidines[5] that serve as useful chiral auxiliaries in asymmetric induction for alkylation or intramolecular lactonization[6] has only been reported by Kurth et al. They achieved the enantiomeric excess in only 76% ee, and one of the enantiomers has been prepared from the chiral epoxide. Our interest in this field is directed towards the application of the Sharpless asymmetric dihydroxylation (AD) reaction[7] to the enantioselective construction of nitrogen heterocycles.[8] In this report, we describe a promising route to C_2 symmetric *trans*-2,6-bis(hydroxymethyl)piperidine derivatives **1** involving, as a crucial step, the application of the AD reaction of 1,6-heptadiene **2**.

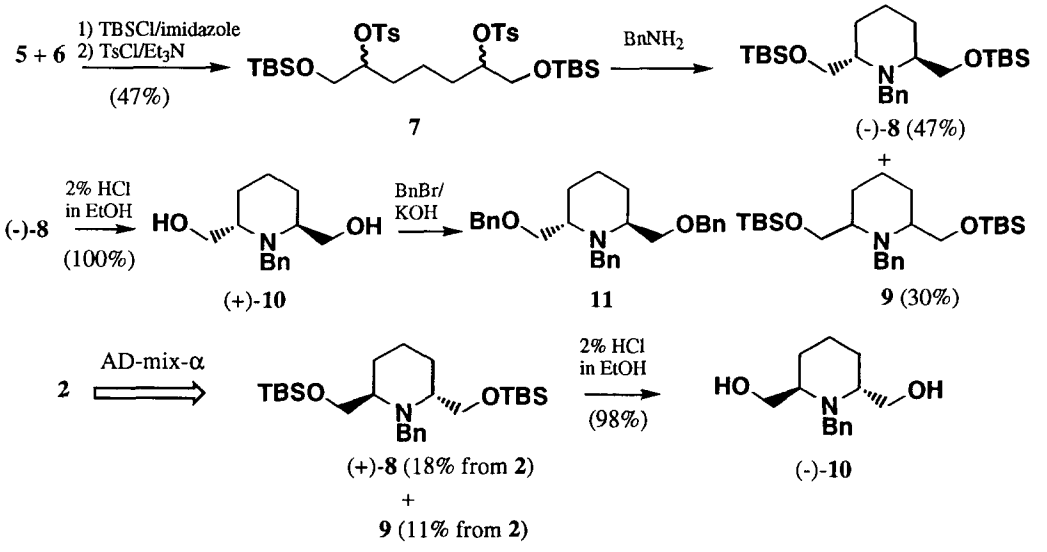
(2*S*,6*S*)-**1** R = TBS, Me, MOM (2*R*,6*R*)-**1**

Our synthetic approach to **1** began with the AD reaction of the diene **2**. The precedent established by the Sharpless group[9] suggested that enantiomeric excess in the case of terminal olefins might be modest (about 80% ee). In a symmetrical diene such as **2**, we anticipate that the stereoselectivity might be improved based on the following consideration: The first AD reaction (AD-mix-β) of **2** produces the major and minor enantiomers, **3** and **4**. Since each enantiomer undergoes the second AD reaction with essentially the same enantiofacial selectivity as in the first AD reaction, three tetraol products result; a C_2-symmetric compound (2*R*,6*R*)-**5**, a meso compound **6**, and (2*S*,6*S*)-**5** as shown in Scheme 1. The overall consequence is that most of the AD reaction resulting from the undesired enantiofacial attack leads to the meso compound **6**. Very little of the mirror image compound (2*S*,6*S*)-**5** is formed, and therefore the enantiomeric purity of the major product (2*R*,6*R*)-**5** will be high .



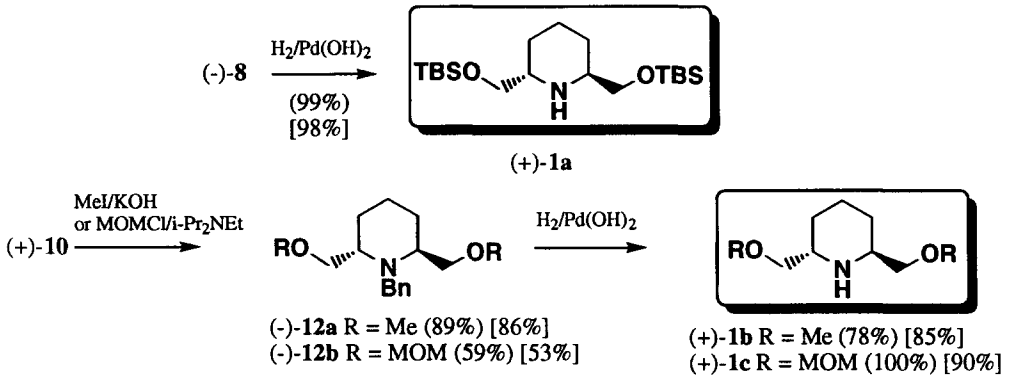
Scheme 1

Oxidation of **2** by the standard procedure (*t*-BuOH, water, 0 °C, 24 h) with commercially available AD-mix-β (0.2% osmium, 1% $(DHQD)_2$-PHAL ligand) provided an inseparable mixture of the tetraols **5** and **6** in 86% yield. Selective protection of the primary hydroxyls in **5** and **6** as *tert*-butyldimethylsilyl ethers followed by tosylation of the secondary hydroxyls gave a diastereomeric mixture of the ditosylates **7** in 47% yield. The mixture of the tosylates was stirred with an excess of benzylamine (30 eq.) at 70 °C for 15 h to effect cyclization, with inversion of the two stereogenic centers, into the desired C_2-symmetric piperidine (-)-**8** and the σ-symmetric piperidine **9** in 47% and 30% yields, respectively. Treatment of the piperidine (-)-**8** with 2% ethanolic HCl provided a bis(hydroxymethyl)piperidine ((+)-**10**)[10] in quantitative yield. At this stage, the enantioselectivity for (+)-**10** was determined by HPLC analysis with a chiral column (Daicel AS) to be 93% ee. Thus it was confirmed that the enantioselectivity was significantly enhanced as compared with that arising from a single AD reaction. The absolute configuration of (+)-**10**, though predicted by the Sharpless model, was unequivocally assigned to be 2*S*, 6*S* by conversion of (+)-**10** to the known compound **11**.[5,11] On the other hand, by using AD-mix-α [$(DHQ)_2$-PHAL ligand], we obtained (-)-**10** in 93% ee and an overall yield of 18% from **2**.



Scheme 2

With both enantiomers of the C_2 symmetry piperidines **8** and **10** in hand, our attention was centered on the transformation into the chiral auxiliaries: *trans*-2,6-bis(*O*-protected hydroxymethyl)piperidines (Scheme 3). At the outset, the AD-mix-β-derived piperidine (-)-**8** was converted by hydrogenolysis [H_2/Pd(OH)$_2$] to the 2,6-bis(*tert*-butyldimethylsilyloxymethyl)piperidine (+)-**1a**[10] in 99% yield. Next, *O*-alkylations (methylation and methoxymethylation) of (+)-**10** followed by hydrogenolysis gave (+)-**1b**[10] and (+)-**1c**[10] in 89% and 59% yields, respectively. In a similar manner, we obtained the enantiomers of **1a-c** by using the piperidines (+)-**8** and (-)-**10** from the AD-mix-α-induction, and the yields are shown in brackets.



(-)-**12a** R = Me (89%) [86%]
(-)-**12b** R = MOM (59%) [53%]

(+)-**1b** R = Me (78%) [85%]
(+)-**1c** R = MOM (100%) [90%]

Scheme 3

Since the recently introduced (DHQD)$_2$- or (DHQ)$_2$-PYR ligand generally gives better ees in the AD reaction of terminal olefins,[12] we obtained the (DHQD)$_2$-PYR ligand-derived C_2-symmetry piperidine (-)-**8** and σ-symmetry piperidine **9** in 21% and 7% yields, respectively, through a four-step procedure from **2**. Strikingly, (-)-**8** was converted to (+)-**10**, the version showing marked improvement of the ee as of >99%. In a similar manner, the (DHQ)$_2$-PYR ligand-used AD reaction of **2** gave (-)-**10** (>99% ee) in an overall yield of 16 % as expected. In summary, the promising synthesis of *O*-protected derivatives of C_2-symmetric *trans*-2,6-bis(hydroxymethyl)piperidine, potentially useful chiral auxiliaries, by means of the symmetry-assisted Sharpless AD reaction has been developed. We believe this protocol (especially PYR-ligand-used AD) should provide a general route to C_2-symmetric α,α'-bis(alkoxymethyl)azacycloalkanes and will report later on our efforts.

Acknowledgment. We thank Professor Barry Sharpless for a helpful advice, for a preprint of ref 7, and for samples of the PYR ligands. We also thank the Tamura Science Foundation for partial funding of this work and Mr. Seiki Takahashi for experimental work in an early stage.

References and Notes

1. For an excellent review, see: Whitesell, J. K. Chem. Rev. **1989**, *89*, 1581.
2. Katsuki, T.; Yamaguchi, M. *J. Syn. Org. Chem. Jpn.* **1986**, *44*, 532 and references cited therein.
3. Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857.

4. (a) Marzi, M.; Minetti, P.; Misti, D. *Tetrahedron* **1992**, *48*, 10127. (b) Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298. (c) Sibi, M. P.; Lu, J. *Tetrahedron Lett.* **1994**, *35*, 4915.
5. Najdi, S.; Kurth, M. J. *Tetrahedron Lett.* **1990**, *31*, 3279.
6. (a) Najdi, S.; Reichlin, D.; Kurth, M. J. *J. Org. Chem.* **1990**, *55*, 6241. (b) McKew, J. C.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 3389. (c) Moon, H.-S.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504.
7. For an excellent review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
8. (a) Takahata, H.; Inose, K.; Momose, T. *Heterocycles* **1994**, *38*, 269. (b) Takahata, H.; Inose, K.; Araya, N.; Momose, T. *Heterocycles* **1994**, *38*, 1961. (c) Takahata, H.; Bandoh, H.; Momose, T. *Heterocycles* in press.
9. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
10. All new compounds described herein gave satisfactory combustion or high resolution mass spectra and spectral data consistent with their structures. Selected spectral data: **1a** : ^{1}H-NMR ($CDCl_3$) δ 0.065 (12 H, s), 0.90 (18 H, s), 1.33-1.37 (2 H, m), 1.49-1.51 (2 H, m), 1.65-1.71 (2 H, m), 3.00-3.05 (2 H, m), 3.485 (2 H, dd, *J* = 9.70, 4.45 Hz), 3.65 (2 H, t, *J* = 9.70 Hz). ^{13}C-NMR ($CDCl_3$) δ -5.210, -5.151, 18.523, 19.922, 26.154, 26.168, 26.168, 26.725, 52.171, 65.030. **1b** ^{1}H-NMR ($CDCl_3$) δ 1.33-1.41 (2 H, m), 1.48-1.57 (2 H, m), 1.63-1.72 (2 H, m), 2.47-2.56 (1 H, br s), 3.14-3.20 (2 H, m), 3.30 (2 H, dd, *J* = 8.70, 4.3 Hz), 3.37 (6 H, s), 3.45 (2 H, t, *J* 8.70 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.915, 27.062, 50.062, 59.164, 74.578. **1c** ^{1}H-NMR ($CDCl_3$) δ 1.36-1.41 (1 H, m), 1.51-1.56 (1 H, m), 1.65-1.70 (1 H, m), 2.64 (1 H, br s), 3.14-3.19 (2 H, m), 3.36 (6 H, s), 3.43-3.36 (2 H, m), 3.59 (2 H, t, *J* = 9.4 Hz), 4.62-4.65 (4 H, m). ^{13}C-NMR δ 19.922, 27.208, 50.106, 55.444, 69.760, 96.722. **10** ^{1}H-NMR ($CDCl_3$) δ 1.31-1.35 (2 H, m), 1.61-1.70 (4 H, m), 3.05-3.10 (2 H, m), 3.44 (2 H, dd, *J* = 10.7, 5.6 Hz), 3.67, 3.95 (each 1 H, ABq, *J* = 13.8 Hz), 3.78 (2 H, t, *J* = 10.7 Hz), 7.25-7.36 (5 H, m). ^{13}C-NMR ($CDCl_3$) δ 20.807, 21.186, 49.914, 55.969, 61.630, 127.477, 128.631, 128.874, 139.982.
11. Specific rotation of the synthetic **11** showed $[\alpha]^{25}_{D}$ -31.6 (*c* 0.63, $CHCl_3$), lit.5 $[\alpha]_{D}$ -29.1 (*c* 1.12, $CHCl_3$).
12. Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785.

(*Received in Japan* 5 *April* 1995)