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New Entry to C_2 Symmetric *trans*-2,6-Bis(hydroxymethyl)-piperidine Derivatives *via* the Sharpless Asymmetric Dihydroxylation

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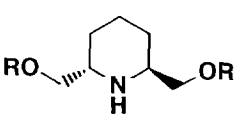
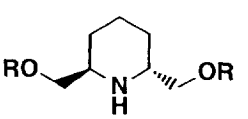
Abstract: A new synthesis of both enantiomers of C_2-symmetric *trans*-2,6-bis(hydroxymethyl)piperidine derivatives **1** by the use, as a key reaction, of the Sharpless asymmetric dihydroxylation of a symmetric diene **2** is presented.

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**.

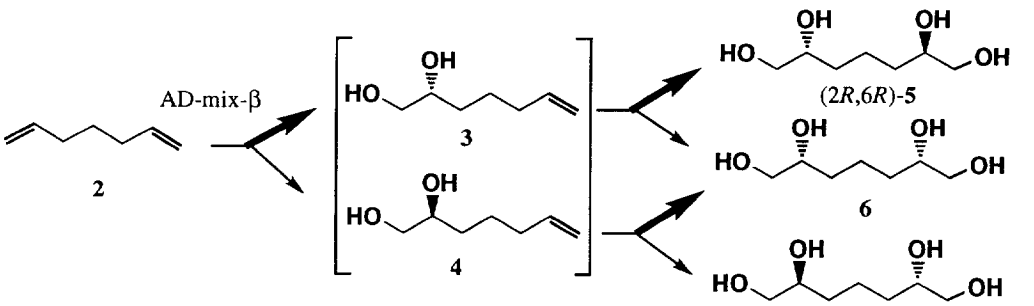


(2*S*,6*S*)-**1** R = TBS, Me, MOM



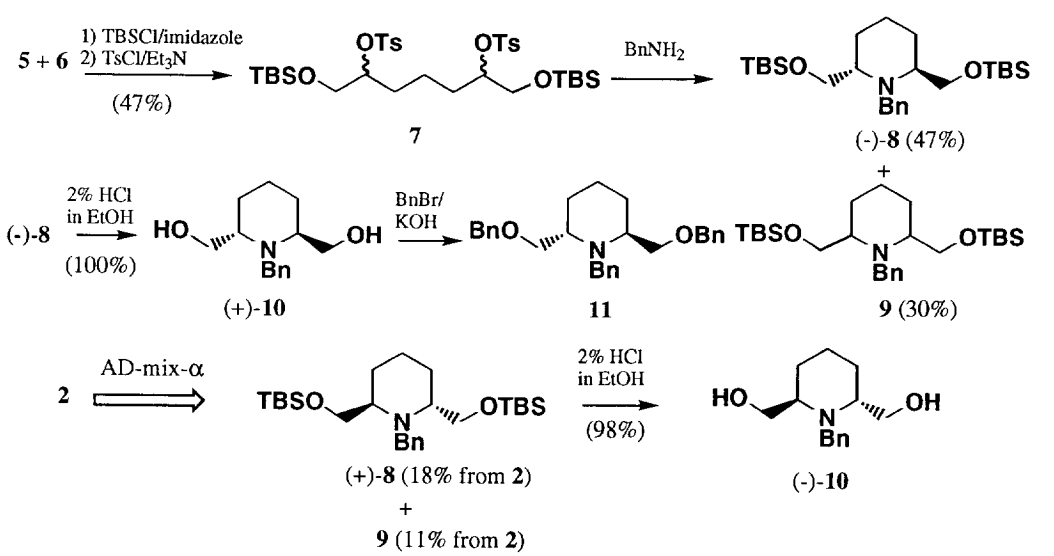
(2*R*,6*R*)-**1**

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 .



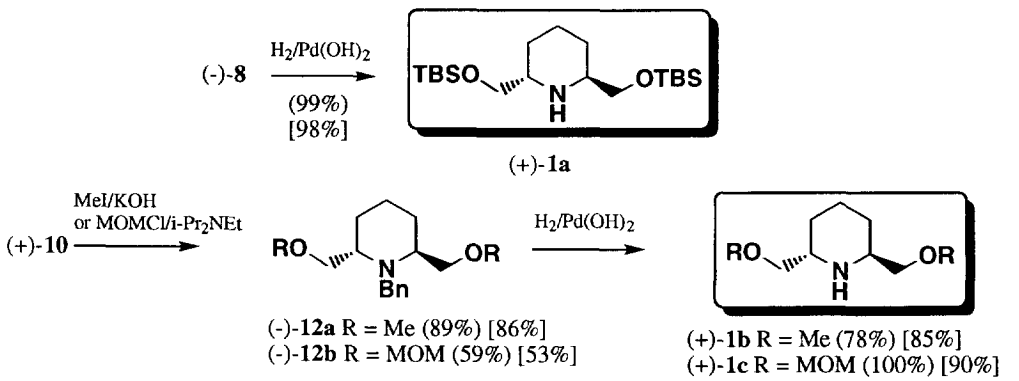
Scheme 1

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.



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.

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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, $CHCl_3$).
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