Pergamon

*Tetrahedron Letters*, Vol. 38, No. 19, pp. 3451-3454, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00643-6

# A General Entry to 2-(2-Hydroxyalkyl)piperidines *via* Iterative Asymmetric Dihydroxylation to Cause Enantiomeric Enhancement[1]

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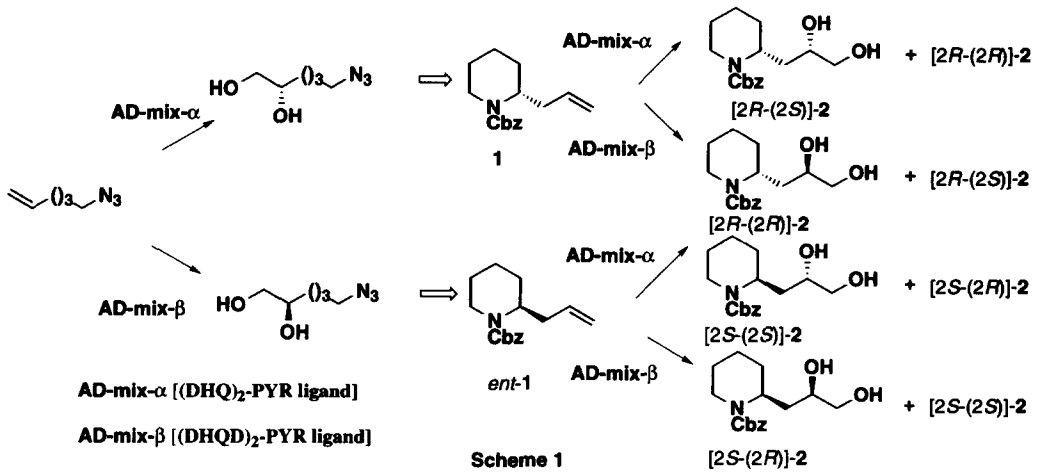
**Abstract**: Both enantiomers of 2-(2-propenyl)piperidine (**1**) (76-88% ee), prepared *via* the first AD of 5-hexenyl azide, underwent the second AD to provide all of the four stereoisomeric 2-(2-hydroxypropyl)-piperidines (**2**) with enantiomeric enhancement (>98% ee). An asymmetric synthesis, starting from **2**, of several 2-(2-hydroxyalkyl)piperidine alkaloids are demonstrated. © 1997 Elsevier Science Ltd.

Biologically active alkaloids of the substituted piperidine ring system have been the target of considerable synthetic efforts.[2] During our continuing studies on asymmetric synthesis of piperidine alkaloids,[3] we recently achieved a new asymmetric synthesis of both enantiomers of 2-(2-propenyl)piperidine (**1**) *via* the Sharpless asymmetric dihydroxylation (AD) of 5-hexenyl azide, the design leading to 2-substituted piperidine and related alkaloids.[4] However, the precedented AD established by the Sharpless group suggested that enantiomeric excess (ee) in the case of terminal olefins might be modest except for arylvinyls such as styrene.[5] In practice, the ee of **1** was of level of 76%-88%.[4] We now describe our findings that additional AD of **1** afforded all of the four isomers of 2-(2,3-dihydoxypropyl)piperidine (**2**) with enantiomeric enhancement, and demonstrate the synthetic utility of **2** by an expeditious asymmetric synthesis of the 2-(2-hydroxyalkyl)piperidine alkaloids (-)-halosaline, (+)-*N*-methylallosedridine, (+)-8-ethylnorlobelol, (+)-sedridine, (+)-allosedridine, (-)-allosedridine, and (+)-*N*-methylsedridine in short steps.

We anticipate that repeated AD for the terminal olefins might improve the stereoselectivity (ee) based on the following consideration: The first AD (AD-mix-α) reaction produces the major (*S*) and minor (*R*) enantiomers. After the introduction of the terminal olefin followed by the second AD (AD-mix-α), four products result; (*S,S*), (*S,R*), (*R,S*), and (*R,R*) isomers. The relationship between the desired (*S,S*)-isomer and the undesired (*S,R*)- and (*R,S*)-isomers is diastereomeric. Very little of the mirror image (*R,R*)-isomer is formed, and therefore the enantiomeric purity of the desired (*S,S*)-isomer will be high. On the other hand, the diastereomer of a mixture of (*S,R*)- and (*R,S*)-isomers could show low ee.[6]

An asymmetric synthesis of 2-(2-propenyl)piperidines **1** and *ent*-**1** *via* the first AD (PYR ligand) reaction of 5-hexenyl azide has been performed by us.[4] On the basis of the above principle, the second AD [$(DHQ)_2$-PYR ligand][7] reaction of the terminal olefin in **1** was carried out to afford a readily separable mixture of the major diastereomer [2*R*-(2*S*)]-**2** (> 98 % ee) and the minor diastereomer [2*R*-(2*R*)]-**2** (54 % ee). These results containing other three examples are shown in Table 1.[8] Since the enantioselectivities of all the four major diastereomers **2** were found to be more than 98% ee, the enantiomeric enhancement by repeated AD was exemplified.




Scheme 1

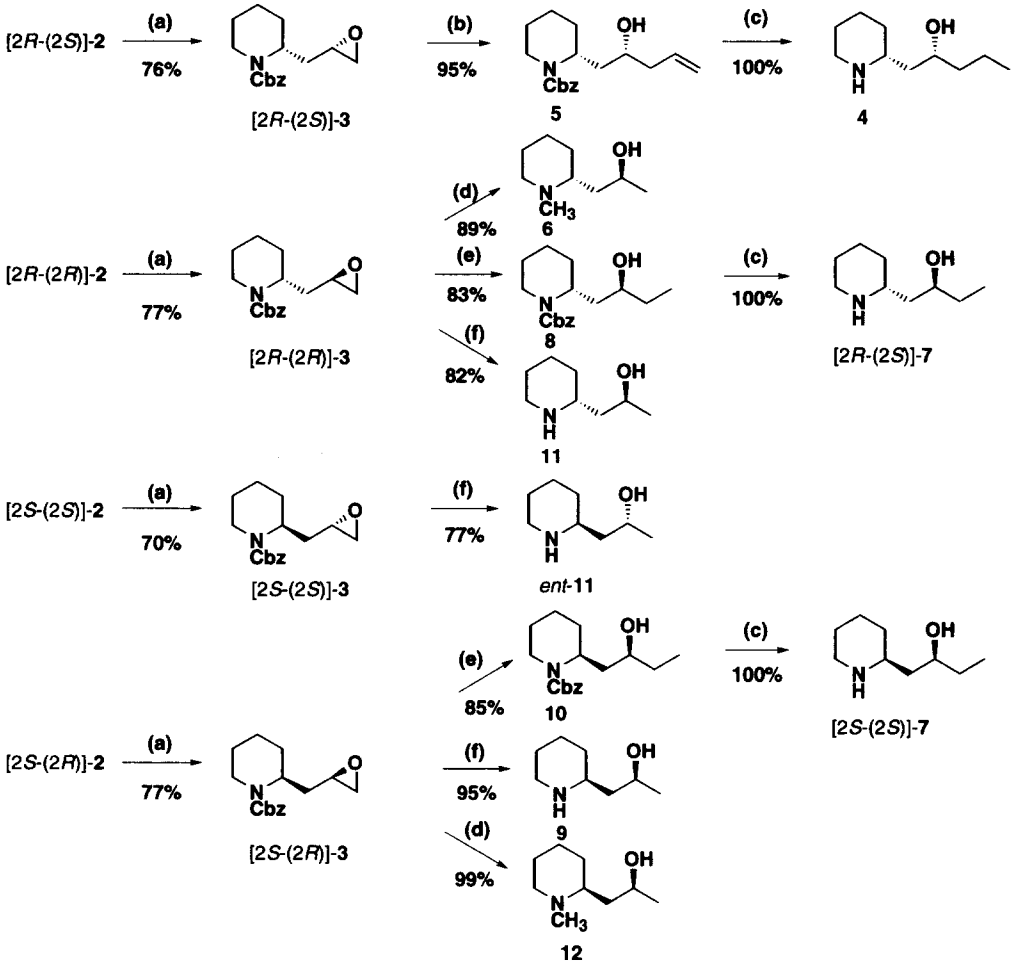
**Table 1 The AD reaction of both enantiomers of 1.**

| Substrate 1 | Ligand | major compd. 2 | Yield (ee) | minor compd. 2 | Yield (ee) |
|---|---|---|---|---|---|
| 1 | (DHQ)2-PYR | [2*R*-(2*S*)]-2 | 70% (>98%) | [2*R*-(2*R*)]-2 | 21% (54%) |
| 1 | (DHQD)2-PYR | [2*R*-(2*R*)]-2 | 69% (>98%) | [2*R*-(2*S*)]-2 | 22% (54%) |
| *ent*-1 | (DHQ)2-PYR | [2*S*-(2*S*)]-2 | 70% (>98%) | [2*S*-(2*R*)]-2 | 22% (72%) |
| *ent*-1 | (DHQD)2-PYR | [2*S*-(2*R*)]-2 | 74% (>98%) | [2*S*-(2*S*)]-2 | 14% (47%) |

With all the four homochiral 2-(2,3-dihydroxypropyl)piperidines **2** in hand, we focused our attention on their transformation into biologically active 2-(2-hydroxyalkyl)piperidine alkaloids. Our synthesis began with the epoxidation of **2**. The four diols **2** were converted into the four epoxides **3** by the Sharpless's one-pot procedure (1: $CH_3C(OCH_3)_3$/PPTS; 2: $CH_3COBr$; 3: $K_2CO_3$)[9] in good yields. Having obtained these results, the first asymmetric synthesis of (-)-halosarine (**4**),[10] isolated from *Haloxylon salicornicum,* was undertaken. The regioselective cleavage of the epoxide ring in [2*R*-(2*S*)]-**3** with vinymagnesium bromide in the combination with a cuprous bromide-dimethylsulfide complex was performed to yield the alcohol **5** in 95 % yield. Exposure of **5** to an atmosphere of hydrogen in the presence of $Pd(OH)_2$ as a catalyst in MeOH caused simultaneous reduction of its double bond and debenzyloxycarbonylation to give the desired (-)-**4**[11] {$[\alpha]_D$ -19.0° (EtOH), lit.[10b] -19.5° (EtOH)} in quantitative yield.

Two [2*R*-(2*S*)]-2-(2-hydroxyalkyl)piperidines, (+)-*N*-methylallosedridine (**6**),[12] isolated from *Sedum sarmentosum,* and (+)-8-ethylnorlobelol-I (**7**),[13] produced by *Loberia inflata,* are found. So far, an asymmetric synthesis of these alkaloids, to our knowledge, has not been reported. We began with the synthesis of **6**. Reduction of the epoxide [2*R*-(2*R*)]-**3** with $LiAlH_4$ gave **6** {$[\alpha]_D$ +78° (EtOH), lit.[12b] +67° (96% EtOH)} as a single product in 89 % yield. Its spectral data were identical with those reported.[14] Treatment of [2*R*-(2*R*)]-**3** with lithium dimethylcuprate underwent the cleavage of the epoxide ring to provide the alcohol **8**, which was converted into [2*R*-(2*S*)]-**7** {mp 53-4 °C; $[\alpha]_D$ +10.2° (EtOH)} by hydrogenolysis in 82 % overall yield. Surprisingly, both its melting point and specific rotation were obviously different from the reported values {mp 87 °C; $[\alpha]^{22}_D$ +22.3° (EtOH)}.[13] We considered the absolute configuration of natural (+)-8-ethylnorlobelol-I could be 2*S*-(2*S*) on the basis of the following speculation. Since halosarine (**4**) of [2*R*-

(2*R*)]-configuration appears levorotatory, both of [2*R*-(2*R*)]-**7** and [2*S*-(2*R*)]-**7** will be levorotatory. Accordingly, only [2*S*-(2*S*)] remains among three possible configurations. In fact, it is known that sedridine (**9**) of a [2*S*-2(*S*)]-configuration is dextrorotatory.[15] In practice, [2*S*-2(*S*)]-**7**[11] was synthesized from the epoxide [2S-2(R)]-**3** by the analogous procedure described for [2*R*-(2*S*)]-**7**. Both of the melting point (mp 88-89 °C) and the specific rotation {$[\alpha]_D$ +25.8° (EtOH)} are almost identical with those reported (vide supra).[13] It is thus concluded that the absolute configuration of natural (+)-8-ethylnorlobelol-I is 2*S*-(2*S*).[16]




**Scheme 2:** (a) 1) $(MeO)_3CMe$/PPTS; 2) MeCOBr; 3) $K_2CO_3$/MeOH; (b) vinylmagnesium bromide/$Me_2S$-CuBr; (c) $H_2$/$Pd(OH)_2$; (d) $LiAlH_4$; (e) $Me_2CuLi$; (f) 1) Super-Hydride®; 2) $H_2$/$Pd(OH)_2$

Next, an asymmetric synthesis of [2*S*-(2*S*)]-2-(2-hydroxypropyl)piperidine, (+)-sedridine (**9**),[15a] isolated from *Sedum acre*, was performed. Super-Hydride®-induced reduction of [2*S*-2(*R*)]-**3** resulted in only ring-cleavage to yield the alcohol, which was hydrogenated to give **9** {$[\alpha]_D$ +28.4° (EtOH), lit.[15b] +28.5° (EtOH)} in 95% yield. Its spectral data were in agreement with those reported.[15] In a similar fashion, the synthesis of both enantiomers (**11** and *ent*-**11**)[11] of allosedridine,[17,18] isolated from *Sedum nudum*, was achieved from [2*R*-(2*R*)]- and [2*S*-(2*S*)]-**3**, respectively, using a two-step sequence. Finally, *N*-

methylsedridine (**12**),[11,14,18] isolated from *Sedum polytrichoides*, was synthesized by reduction of [2*S*-2(*R*)]-**3** with $LiAlH_4$ in 99% yield. Its spectral data were consistent with those reported.[14]

In summary, we developed a general access to synthetically useful homochiral 2-(2,3-dihydroxypropyl)piperidines (**2**) starting from an achiral 5-hexenyl azide. The two stereogenic centers of **2** were constructed with highly enantiomeric enhancement in a sequence of two AD reactions. In practice, we demonstrated the synthetic utility of **2** as chiral synthons by the first asymmetric synthesis of several 2-(2-hydroxyalkyl)piperidine alkaloids except for **9**. Extension of this methodology (the enantiomeric enhancement *via* the twofold or more AD reactions) toward asymmetric synthesis of other biologically active compounds is under investigation.

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11. **4**; mp 83 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 0.91 (3 H, t, *J* = 6.9 Hz), 1.26-1.59 (12 H, m), 1.78-1.80 (1 H, m), 2.55 (1 H, td, *J* = 11.5, 2.75 Hz), 2.81-2.88 (1 H, m), 3.00-3.05 (1 H, m), 3.84-3.90 (1 H, m); $^{13}$C NMR (75 MHz, CDCl3) δ 14.32, 19.17, 24.87, 26.23, 31.67, 40.18, 42.21, 47.01, 54.84, 68.87; [2*S*-(2*S*)]-**7**; $^1$H NMR (300 MHz, $CDCl_3$) δ 0.91 (3 H, t, *J* = 7.4 Hz), 1.30-1.61 (9 H, m), 1.79-1.81 (1 H, m), 2.55 (1 H, td, *J* = 9.1, 2.8 Hz), 2.83-3.05 (4 H, m, 3.75-3.82 (1 H, m); $^{13}$C NMR (75 MHz, CDCl3) δ 10.38, 24.95, 26.30, 30.76, 31.58, 41.70, 47.14, 54.98, 70.69; **11**; mp 61 °C, lit.[17a] 62-3 °C; $[\alpha]_D$ +17.1° (c 1.55, MeOH), lit.[17a] $[\alpha]_D$ +16.2° (c 4.01, MeOH); $^1$H NMR (500 MHz, $CDCl_3$) δ 1.03-1.12 (1 H, m), 1.11 (3 H, d, *J* = 6.0 Hz), 1.21-1.31 (2 H, m), 1,41-1.52 (2 H, m), 1.56-1.62 (2 H, m), 1.77-1.80 (1 H, m), 2.56 (1 H, td, *J* = 13.9, 3.0 Hz), 2.69 (1 H, t, *J* = 10.7 Hz), 3.02 (1 H, d, *J* = 13.7 Hz), 3.50 (2 H, br s), 3.98 (1 H, dqd, *J* = 10.3, 6.2, 2.1 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 23.99, 24.56, 27.33, 34.33, 44.38, 46.09, 58.29, 69.16; *ent*-**11**; $[\alpha]_D$ -16.2° (c 1.55, MeOH); **12**; $[\alpha]_D$ -32.99° (c 0.675, EtOH), lit.[12b] $[\alpha]_D$ -31° (c 1.05, EtOH).
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(*Received in Japan* 13 *March* 1997; *revised* 2 *April* 1997; *accepted* 4 *April* 1997)