A NEW PROCEDURE FOR CONSTRUCTION OF 2,6-*TRANS*-DISUBSTITUTED PIPERIDINES USING OSMIUM-CATALYZED ASYMMETRIC DIHYDROXYLATION: APPLICATION TO THE SYNTHESIS OF (+)-EPIDIHYDROPINIDINE AND (+)-SOLENOPSIN A[1]

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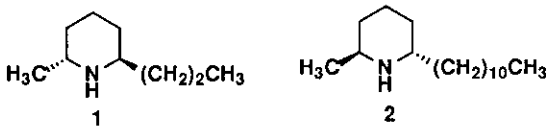
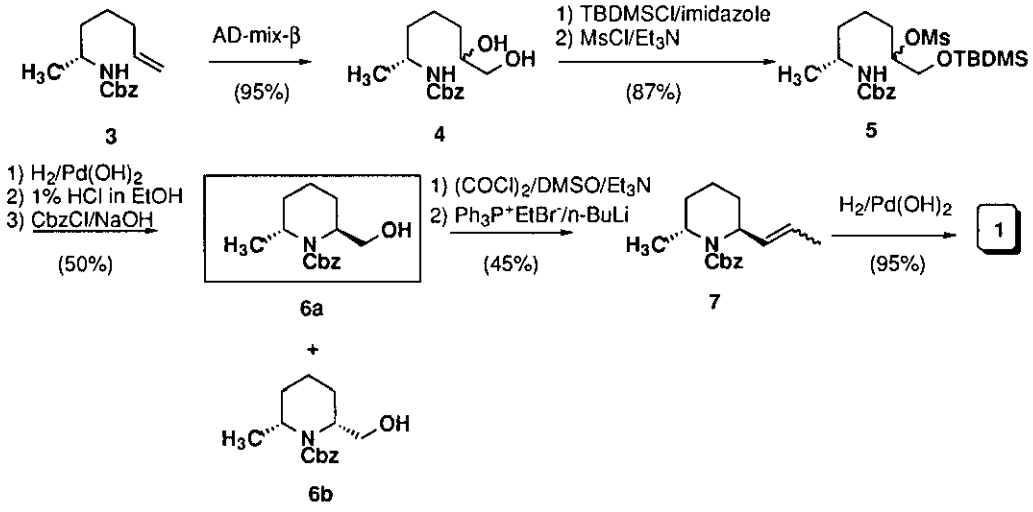
Abstract - An asymmetric synthesis of (+)-epidihydropinidine (**1**) and (+)-solenopsin A (**2**) has been achieved by starting with the Sharpless asymmetric dihydroxylation of the α-amino acid-derived *N*-alkenylurethanes (**3**) followed by subsequent aminocyclization.

Alkaloids containing a 2,6-disubstituted piperidine system are abundant in nature and many of them exhibit significant biological activity.[2] Accordingly, much attention is focused on their asymmetric synthesis, but the 2,6-*trans*-disubstituted piperidine is less available than the corresponding *cis* compeer. Our interest in this field is directed towards the synthetic utilization of the Sharpless asymmetric dihydroxylation (AD) reaction,[3] as employed for the enantioselective construction of oxygen[4] and nitrogen[5] heterocycles leading to natural products. In this communication, we describe a stereoselective synthesis, using AD reaction as a crucial step, of two 2,6-*trans*-disubstituted piperidine alkaloids: (+)-epidihydropinidine (**1**),[6] isolated from the extract of *Picea engelmannii*, and (+)-solenopsin A (**2**),[7] one of alkaloids present in the venom of the red fire ant (*Solenopsis invicta*).



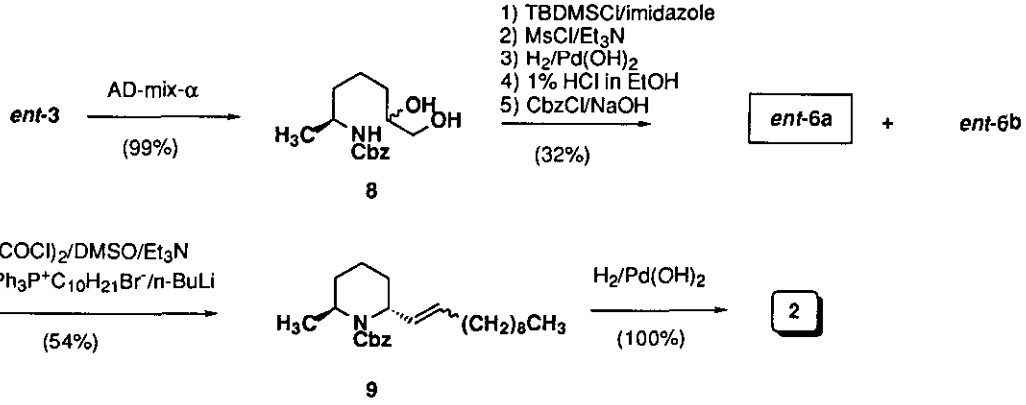
1 2

Although the absolute configuration of **1** was recently determined by X ray analysis,[8] its asymmetric synthesis has never been performed. Our synthesis of **1** began with the AD reaction of the *N*-alkenylurethane (**3**)[9] available from D-alanine. Treatment of **3** with AD-mix-β (Aldrich No. 39,276-6) at 0 °C in *tert*-butyl alcohol/water (1:1) for 24 h afforded a diastereomeric mixture of the diols **4** in 95% yield. Selective protection of the primary hydroxyl in **4** with *tert*-butyldimehylsilyl followed by mesylation of the secondary hydroxyl provided the mesylate **5** in 87% yield. Exposure of **5** to an atmosphere of hydrogen in the presence of $Pd(OH)_2$ as a catalyst in methanol caused concurrent debenzyloxycarbonylation and annulation to give the piperidine salt, which was converted by a two-step sequence (i, de-*tert*-butyldimethylsilylation; ii, *N*-bezyloxycarbonylation) to a separable 3:1 mixture of the 2,6-*trans*-disubstituted piperidine **6a** and its *cis* isomer **6b** in 50% overall yield from **5** . The Swern oxidation of **6a** was carried out to give the aldehyde, which on subsequent Wittig reaction using the corresponding triphenylphosphorane generated *in situ* from ethyltriphenylphosphonium bromide and butyllithium provided the olefin **7** in 45% overall yield from **6a**. Finally, **7** underwent simultaneous hydrogenation and hydrogenolysis over $Pd(OH)_2$ in an atmosphere of hydrogen to give the desired **1** in 95% yield. The synthetic (+)-epidihydropinidine possesses spectral data identical to those for the natural material and displays commensurate optical activity.[10] Thus, the first asymmetric synthesis of **1** was performed and its absolute configuration was confirmed chemically to be 2*R*,6*R*.



3 4 5 6a 7 6b

Keeping this achievement in mind, our attention was turned to the transformation of *ent*-**3** into (+)-solenopsin A (**2**).[11] The AD reaction of *ent*-**3**[12] using AD mix-α (Aldrich No. 39,275-8) gave **8** in 99% yield. According to the above method described for the synthesis of **6a,b**, the diol **8** was converted by a five-step sequence to *ent*-**6a** and *ent*-**6b** with a ratio (4:1) in 32% overall yield. The Wittig elongation of the aldehyde available from *ent*-**6a** using decylidenetriphenylphosphorane provided the piperidine **9** in 54% yield. Exposure of **9** to an atmosphere of hydrogen over catalyst gave the wanted **2** in quantitative yield. The spectral properties of our (+)-solenopsin A of the 2*S*,6*S* configuration[13] were in agreement with those reported.[14]



In conclusion, we have demonstrated the new construction of 2,6-*trans*-disubstituted piperidines based on osmium-catalyzed asymmetric dihydroxylation of α-amino acid-derived *N*-alkenylurethanes followed by reductive aminocyclization and its application to the asymmetric synthesis of (+)-epidihydropinidine (**1**) and (+)-solenopsin A (**2**). This protocol provides a new and promising entry to the stereoselective synthesis of the pyrrolidine and piperidine system, which could be led to the related biologically active compounds, and the results will be described in due course.

REFERENCES AND NOTES

1. This work was presented at the Seventh IUPAC Symposium on Organo-Metallic Chemistry directed towards Organic Synthesis, Kobe, September, 1993.

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10. The HCl salt of **1**; mp 175-6 °C, lit.[6] 164.5-165.5 °C; ^{1}H nmr (500 Mz, $CDCl_3$) δ 0.959 (3 H, t, J= 7.3 Hz), 1.38-1.50 (6 H, m), 1.62-1.75 (6 H, m), 1.91-2.02 (3 H, m), 3.30 (1 H, m), 3.55 (1 H, m); ^{13}C nmr ($CDCl_3$) δ 13.932, 17.013, 17.559, 19.229, 26.513, 29.078, 33.008, 48.123, 51.690; $[\alpha]_D^{25}$ +3.81° (*c* 0.77, EtOH), lit.[6] $[\alpha]_D^{29}$ +4.7° (*c* 3.8, EtOH).
11. For syntheses of the chiral solenopsin A, see: a) D. L. Comins and N. R. Benjelloun, *Tetrahedron Lett.*, 1994, **35**, 829; b) C. W. Jefford and J. B. Wang, *Tetrahedron Lett.*, 1993, **34**, 2911; c) Y. Ukaji, T. Watai, T. Sumi, and T. Fujisawa, *Chem. Lett.*, 1991, 1555; d) D. S. Grierson, J. Royer, L. Guerrier, and H.-P. Husson, *J. Org. Chem.*, 1986, **51**, 4475; for the chiral solenopsin B, e) H. Kotsuki, T. Kusumi, M. Inoue, Y. Ushio, and M. Ochi, *Tetrahedron Lett.*, 1991, **32**, 4159; f) D. F. Taber, P. B. Deker, H. M. Fales, T. H. Jones, and H. A. Lloyd, *J. Org. Chem.*, 1988, **53**, 2968.
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13. Its absolute configuration remains unknown due to the poor supply from natural sources.
14. **2**: ^{1}H Nmr (270 Mz, $CDCl_3$) δ 0.88 (3 H, t, J=6.5 Hz), 1.06-1.67 (26 H, m), 2.86-2.93 (1 H, m), 3.07-3.13 (1 H, m);^{13}C nmr ($CDCl_3$) δ 14.18, 19.36, 20.69, 22.76, 26.48, 29.44, 29.73, 29.82, 30.22, 32.00, 32.49, 33.70, 46.23, 51.07; $[\alpha]_D^{25}$ +1.6° (*c* 0.647, MeOH), lit.[11b] $[\alpha]_D^{20}$ -1.30° (*c* 1.3, MeOH) for *ent*-**2**.

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