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An efficient approach to 2-substituted *N*-tosylpiperdines: asymmetric synthesis of 2-(2-hydroxy substituted)-piperidine alkaloids

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Abstract—We have developed an efficient and a general approach to chiral 2-substituted *N*-tosylpiperidines starting from chiral α-substituted-*N*-tosylaziridines. Using this approach, we have synthesized (+)-coniine. The synthesis of chiral *N*-tosyl-2-piperidinyl-ethanol **15** and *ent*-**15**, was achieved from L- and D-aspartic acids, respectively in few steps. Piperidine **15** was converted into 2-(2-hydroxysubstituted)piperidines of type **2** in optically active form. By applying this strategy, asymmetric syntheses of halosaline (*R*,*R*)-**2a**, (+)- and (−)-sedamine **2b**, (+)- and (−)-allosedamine **2c**, (+)- and (−)-sedridine **2d**, (+)- and (−)-allosedridine **2e**, (+)-tetraponerine T-3 **3a**, T-4 **3c**, T-7 **3b**, and T-8 **3d** have been achieved in high yields. These stereoisomers can be interconverted via Mitsunobu inversion in excellent yields.

The asymmetric synthesis of 2-substituted piperidine alkaloids of type **1** (Fig. 1) is a field of intense research as these compounds display a broad range of biological activities.[1] As these alkaloids are usually available in only trace amounts from natural sources, there is a great need for diverse methods for their synthesis. Piperidine is a core unit for these alkaloids, which are widespread in Nature and occupy an important position both as bioactive targets and useful synthetic intermediates. (*S*)–2-Propylpiperdine **1a** (coniine), the simplest alkaloid in the family, is toxic to all classes of livestock and humans.[2] Among others, 2-(2-hydroxy substituted)piperidine-based alkaloids **2**, having 1,3-aminoalcohol connectivity where N is part of the heterocycle, are highly desirable and constitute a large family of compounds having a wide range of physiological activities.

Sedamine **2b** and sedridine **2d** are two alkaloids isolated from *Sedum acre*.[3] Later, these were obtained from other species also.[4] (−)-Allosedamine **2c** has been isolated from *Lobelia inflata* which is also known as Indian tobacco,[5] the crude extract of which has been used for treatment of respiratory illnesses such as asthma, bronchitis, and pneumonia.[6] Although several syntheses of sedamine have been reported as a single enantiomer,[7,8] there are not many reports in the literature for the synthesis of chiral allosedamine.[8d,9,10]

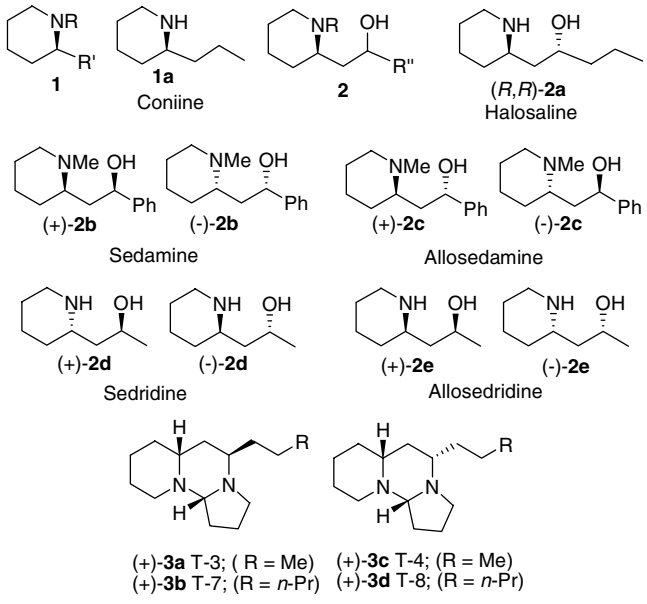

Figure 1. 2-Substituted piperidine alkaloids.

Both enantiomers of allosedridine **2e**,[11] which have memory-enhancing properties and may be effective for

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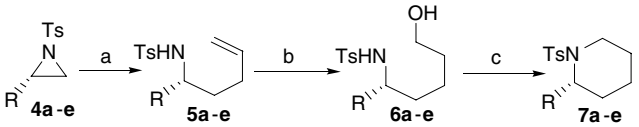
the treatment of Alzheimer's disease,[12] were isolated from *Sedum nudum*.[1] Halosaline **2a** is another important alkaloid which has received synthetic attention.[13] (+)-Tetraponerines **3** (Fig. 1) were isolated from the venom of a New Guinean ant *Tetraponera* sp.[14] These are toxic alkaloids which represent the major constituents of the contact poison. Since their isolation, several diastereoselective[15] and enantioselective[16] syntheses have been reported in the literature.

Initially, we were interested in developing a general flexible approach to chiral 2-substituted piperidines **1** from chiral α-substituted-*N*-tosylaziridines **4** (Scheme 1), which could be easily synthesized from naturally occurring L-α-amino acids.[17] The reason for using the tosylate protecting group was that it was quite stable under reaction conditions and could be removed easily. The regioselective cleavage of *N*-tosylaziridines **4** with allylmagnesium bromide was achieved in almost quantitative yields. Alkenes **5**, thus obtained, were subjected to hydroboration using BH_3·DMS followed by oxidative cleavage of the borane adduct to provide 1,5-*N*-tosyl aminoalcohols **6** in very good yields. Employing our established conditions,[18] *N*-tosyl-1,5 amino alcohols **6** were cyclized using triphenylphosphine and diisopropylazodicarboxylate (DIAD) via Mitsunobu condensation. Thus, several (*S*)-*N*-tosyl-2-alkyl piperidines **7** were synthesized in excellent yields (Scheme 1). Since cleavage of the *N*-tosyl bond in **7b** is already known in the literature,[19] a formal total synthesis of (*S*)-coniine **1a** was achieved in 70% overall yield.

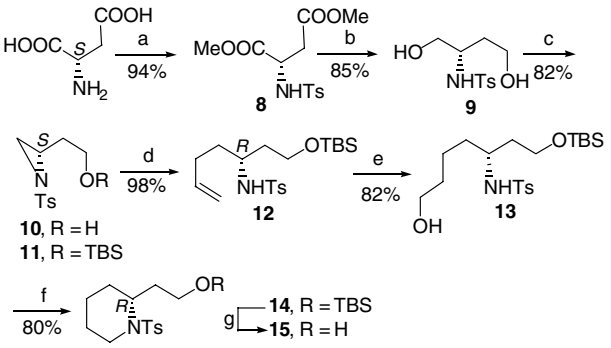
Having established an efficient route to 2-substituted-*N*-tosylpiperidine **7**, attention was turned toward chiral *N*-tosyl-2-piperidinylethanol **15** (Scheme 2), which can be used as a key intermediate for asymmetric syntheses of 2-(2-hydroxy substituted)piperidines of type **2** (Fig. 1). For this purpose, it was decided to investigate the Mitsunobu cyclization of an amino diol **9** in an attempt to produce an aziridine functionalized with a hydroxyl moiety. As outlined in Scheme 2, esterification of (*S*)-aspartic acid in the presence of $SOCl_2$ in MeOH, followed by protection of the amine as the tosylate furnished *N*-tosyldimethyl aspartate **8**, which was then reduced with $LiAlH_4$ at rt to afford amino diol **9** in high yield. Next, we decided to exploit the well-established preference for three-membered ring closure over four-membered ring closure.

It was heartening to note that the exposure of *N*-tosyl-aminodiol **9** to 1,1′-(azodicarbonyl)dipiperdine (ADDP)



a, R = Me; **b**, R = *n*-Pr; **c**, R = *i*-Pr; **d**, R = *s*-Bu; **e**, R = *i*-Bu

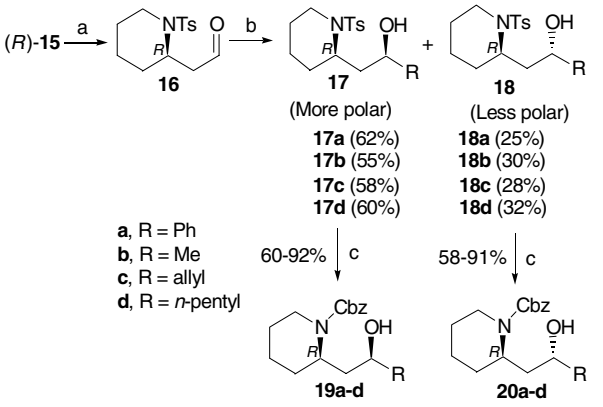
Scheme 1. An approach to 2-substituted piperidines. Reaction conditions: (a) Allylmagnesium bromide, THF–Et_2O (1:1), −78 °C–rt, 6 h (95–99% yield); (b) (i) BH_3·DMS, THF, −10 °C–rt, 8 h, (ii) H_2O_2, NaOH, 0 °C–rt, 2 h (77–85% yield); (c) DIAD, Ph_3P, THF, 0 °C–rt, 8 h (90–96% yield).



Scheme 2. Asymmetric synthesis of **15**. Reaction conditions: (a) $SOCl_2$, MeOH, 0 °C–rt, 12 h, then TsCl, Et_3N, 0 °C–rt, 12 h; (b) $LiAlH_4$, THF, 0 °C–rt, 12 h; (c) ADDP, *n*-Bu_3P, toluene, 0 °C–rt, 16 h, then TBSCl, Imidazole, THF, 0 °C–rt, 8 h; (d) Allylmagnesium bromide, THF–Et_2O (1:1), −78 °C–rt, 6 h; (e) BH_3·DMS, THF, −10 °C–rt, 8 h, then H_2O_2, NaOH, 0 °C–rt, 2 h; (f) DIAD, Ph_3P, THF, 0 °C–rt, 8 h; (g) TBAF, THF, rt, 6 h, 99%.

and *n*-Bu_3P under Mitsunobu condensation reaction conditions resulted in smooth and selective formation of aziridine **10**. Due to difficulties in removal of residual hydrazide during the purification step, the hydroxyl group was protected as TBS ether **11**. Regioselective ring opening of *N*-tosylaziridine **11** by an allyl Grignard reagent followed by construction of the piperidine ring using the protocol described in Scheme 1 gave (*R*)-**14**. Desilylation was efficiently carried out using tetrabutylammonium fluoride (TBAF) to afford enantiopure *N*-tosyl-2-piperidinylethanol (*R*)-**15** (Scheme 2).

N-Tosyl-2-piperdinylethanol **15** was oxidized under Swern conditions to aldehyde (*R*)-**16** (Scheme 3). Diastereoselective addition of phenyl or alkyl Grignards gave mixtures of *syn* alcohols **17** and *anti* alcohols **18**, where the former was the major isomer. These could easily be separated by silica gel column chromatography. The absolute stereochemistry was established at a later stage after converting some of them to natural products. The *N*–Ts bond of each compound was cleaved using Na and naphthalene and the resulting amine was Cbz protected in situ (Scheme 3).



Scheme 3. Asymmetric synthesis of **19** and **20**. Reaction conditions: (a) $(COCl)_2$, DMSO, Et_3N, −78 °C–rt, 8 h, 95%; (b) RMgX, THF–Et_2O (1:1), −78 °C–rt, 6 h, chromatographic separation; (c) Na, naphthalene, THF, 0 °C–rt, 2 h, then $NaHCO_3$, CbzCl, 2 h.

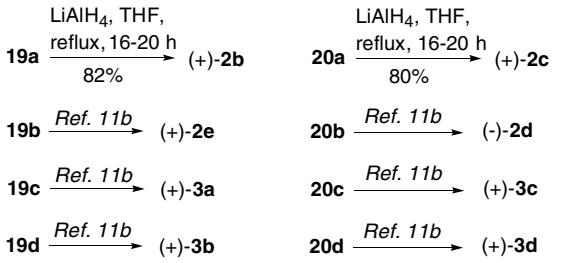
Piperdine **19a** was treated with $LiAlH_4$ to reduce the Cbz group to a methyl group to give (+)-sedamine **2b**. Similarly, (+)-allosedamine **2c** was synthesized from **20a** (Scheme 4). Since **19b–d** have already been converted into (+)-allosedridine **2e**, (+)-tetraponerine-3 (T-3) **3a**, and (+)-tetraponerine-7 (T-7) **3b**, we have completed formal syntheses of these alkaloids. Similarly, the conversions of **20b–d** to (−)-sedridine **2d**, (+)-tetraponerine-4 (T-4) **3c**, and (+)-tetraponerine-8 (T-8) **3d** are also known, we have completed formal total syntheses of these natural products (Scheme 4).

In order to synthesize the antipode of the above synthesized natural products, *ent*-**19a–b** and *ent*-**20a–b** were synthesized following the same sequence of reactions as in Schemes 2 and 3 using D-aspartic acid (Scheme 5). Treatment of *ent*-**19a** with $LiAlH_4$ gave (−)-sedamine **2b**. Similarly, (−)-allosedamine **2c** was synthesized from *ent*-**20a** in the same way. Since *ent*-**19b** and *ent*-**20b** have already been converted to (−)-allosedridine **2e** and (+)-sedridine **2d**, we have also completed the formal syntheses of these natural products.[20]

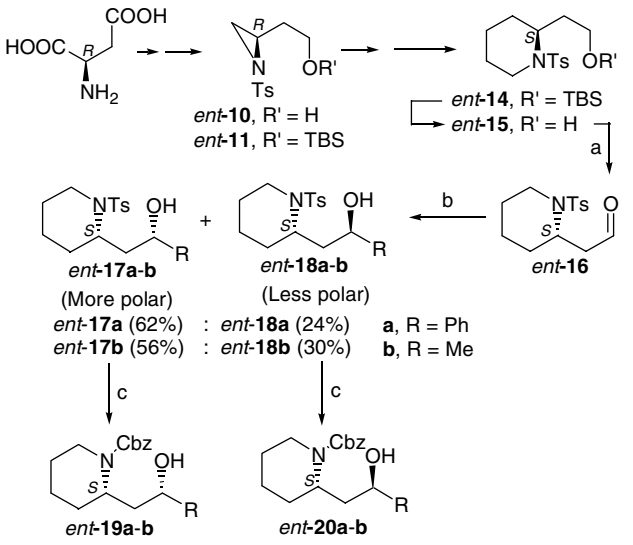
As we can see from Schemes 3 and 5, addition of the Grignard reagents to chiral aldehydes was *syn* selective. This can be explained by invoking the transition state model depicted in Figure 2. In the most stable conformation of the piperidine ring, the tosyl group attached to the '*N*' and carboxymethylene group attached to the C-2 position of the piperidine ring are equatorially oriented. Addition of the Grignard reagent to **16** or **ent-16** may generate a chelated six-membered transition static co-ordinating the Mg. In this orientation, the aromatic ring of the tosyl group blocks the *re* face of the aldehyde favoring the *si* face attack. In general, the selectivity was 70:30 in favor of the *syn* diastereomer. The low selectivity could be due to poor chelation as the nitrogen lone pair is not fully accessible.

In order to show versatility in our synthesis, all the stereoisomers of 2-(2-hydroxy substituted)piperidines **17**, **18**, and their antipodes were interconverted by Mitsunobu inversion (Scheme 6). In all cases, the yields were excellent.

In conclusion, we have developed an efficient and general approach to chiral 2-substituted *N*-tosylpiperidines and 2-(2-hydroxy substituted)piperidines of type **2** in optically active form. The approach is general in the sense that several of these compounds can be made from a single precursor. Using the Mitsunobu inversion method, it has been shown that the stereoisomer can be interconverted in excellent yields.



Scheme 4. Synthesis of 2-(2-hydroxy substituted)piperidine alkaloids.



Scheme 5. Asymmetric synthesis of *ent*-**19** and *ent*-**20**. Reaction conditions: (a) $(COCl)_2$, DMSO, Et_3N, −78 °C–rt, 8 h, 95%; (b) RMgX, THF–Et_2O (1:1), −78 °C–rt, 6 h, chromatographic separation; (c) Na, Napthalene, THF, 0 °C–rt, 2 h, then $NaHCO_3$, CbzCl, 2 h, 85–90%.

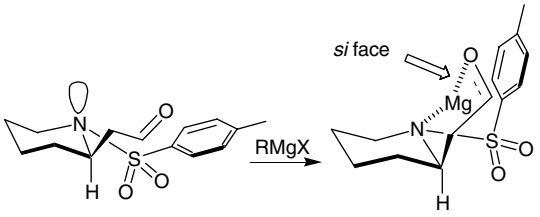
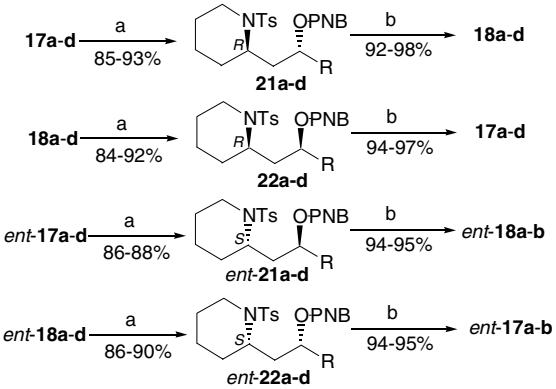


Figure 2. Diastereoselective Grignard addition.



Scheme 6. Interconversion of **17**, **18**, *ent*-**17**, and *ent*-**18** to their opposite diastereomers by Mitsunobu protocol. Reaction conditions: (a) *p*-$NO_2C_6H_4COOH$, DIAD, Ph_3P, THF, 0 °C–rt, 24 h, (b) K_2CO_3, MeOH, rt, 12 h.

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