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TETRAHEDRON: *ASYMMETRY*

# Asymmetric synthesis of functionalized piperidine derivatives: synthesis of (*S*)-anatabine[1]

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**Abstract**

A short and efficient chiral synthesis of 6-aryl-5-phenylsulfonyl-1,2,5,6-tetrahydropyridines was achieved in moderate yield and with good selectivity. The absolute configurations were assigned by extending the methodology to (*S*)-anatabine and as well with NMR experiments. 

Pyrrolidine and piperidine ring systems form the basic skeleton in many naturally occurring alkaloids and pharmaceutically important compounds.[2] Several simple piperidine derivatives exhibit important biological activities, to mention a few: 1-deoxynojirimycin is a glycosidase inhibitor,[3a] (−)-paroxetine·HCl is a serotonine uptake inhibitor,[3b] pipecolic acid derivatives are NMDA antagonists,[3c] and minor tobacco alkaloids are used for cognitive disorders.[3d] Hence, considerable attention has been focused in recent years on the synthesis of enantiopure piperidine building blocks for the construction of biologically active compounds.[4]

In connection with our studies towards chiral pyrrolidine and piperidine derivatives, we recently reported the synthesis of chiral non-racemic 2-arylpyrrolidines *via* a 3+2 cyclization.[5a] Furthermore, we have shown that lithiated sulfone carbanions can undergo stereoselective Michael additions to unsaturated esters.[5b] In this communication we wish to report a general synthesis of 6-aryl-5-phenylsulfonyl-1,2,5,6-tetrahydropyridines **6a**–**f** as single stereoisomers in three steps and moderate yields starting from readily accessible 4-phenylsulfonyl *cis*-but-2-en-1-ol **1** and chiral non-racemic aryl sulfinimines **2**.

The required chiral sulfinimines **2a**–**f** were prepared employing the method of Davis et al.[6] and allylsulfone **1** was obtained in two steps from commercially available *cis*-but-2-en-1,4-diol.[7]

Our initial attempts to prepare the piperidine derivatives in one step from 1-chloro-4-phenylsulfonyl *cis*-but-2-ene and chiral aryl sulfinimines **2** under the usual LDA conditions at low temperatures failed to give the expected products. However, when the dianion of **1** (2.4 equiv. LiHMDS, −78°C to −70°C, 0.5 h) was treated with chiral sulfinimine **2a** at −100°C, and allowed to warm to −60°C (1.5 h), quenching with saturated aqueous $NH_4Cl$ solution at −60°C followed by work up afforded the crude addition products in 80–85% yield.[8]

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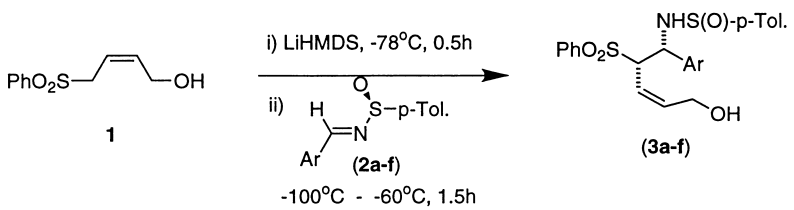
Table 1
Synthesis of **3a–f** and elaboration to piperidine derivatives **6a–f**[a]

| Entry | Ar | Yield | $[\alpha]^{25}_D$[b] | Yield | $[\alpha]^{25}_D$[c] | Yield[d] | $[\alpha]^{25}_D$[e] |
|---|---|---|---|---|---|---|---|
| | | **3** | | **5** | | **6** | |
| a | p-MePh | 48 | +64.9 (c 0.57) | 80 | +102(c 1) | 100(60) | +101(c 1) |
| b | Ph | 48 | +70(c 1) | 82 | +104.8(c 0.7) | 84 | +127.8(c 0.9) |
| c | p-MeOPh | 47 | +36(c 1) | 80 | +42(c 1) | 80(30) | +116.7(c 0.6) |
| d | p-ClPh | 45 | +18.2(c 0.55) | 78 | +40(c 1) | 84 | +126.8(c 0.56) |
| e | 2-Furyl | 50 | +39(c 1) | 72 | +85(c 1.2) | 54 | +148.3(c 0.6) |
| f | 3-Pyridyl | 57[f] | +49.6(c 1.1)[g] | 68 | h | - (70) | +45.5(c 1.1) |

a) All yields referred to isolated yield b) Solvent is chloroform unless otherwise mentioned c) Solvent is chloroform d) Numbers in paranthesis referred to yields obtained by Mitsunobu cyclization e) Solvent is methanol f) 82:18 mixture of diastereomers g)Solvent is methanol h) Optical rotation is not constant(fluxating)

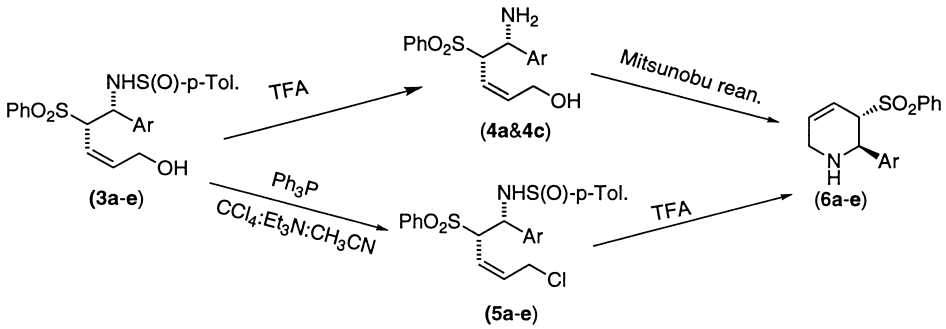
The $^1$H NMR spectrum of the crude product indicated the presence of four diastereomers, one being major (60–65%). Due to the overlapping of proton signals in the NMR, the ratio of diastereomers could not be assigned. Remarkably, purification by flash column chromatography (silica) followed by recrystallization ($CH_2Cl_2$/pet.ether) afforded the major diastereomer **3a** in 48% isolated yield[9] and in >95% diastereomeric purity based on $^1$H and $^{13}$C NMR. This reaction was found to be general with other aryl sulfinimines **2b–e** giving rise to the respective addition products **3b–e** in moderate yield and good diastereoselectivity[10] (Table 1, Scheme 1). The observed diastereoselectivity can be attributed to $Li^+$ chelation between the sulfonyl oxygen and the sulfinimine nitrogen forming a six-membered chair-like transition state which directs the aryl group to the equatorial position due to 1,3-diaxial Ar/Ph($SO_2$) repulsion.[11]




Scheme 1.

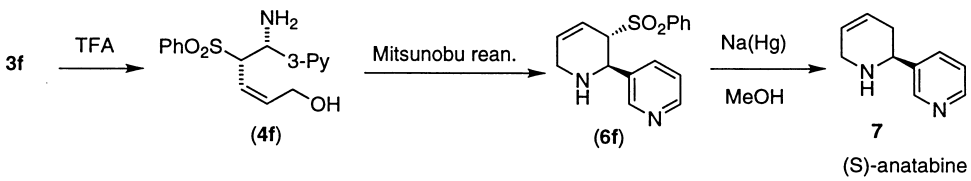
The attempted Mitsunobu cyclization of **3a** or **3b** to *N*-sulfinyl pyridines **6a** or **6b** respectively under a variety of conditions was unsuccessful. This might be due to poor nucleophilicity of the nitrogen which is attached to an aryl sulfoxide group. Hence the *N*-sulfoxide group in **3a** was removed by treatment with TFA to furnish **4a**. The Mitsunobu cyclization afforded the required piperidine **6a** in 60% yield.[12] However the yields were not satisfactory with other substrates under similar conditions. Hence an alternative general pathway to the target compounds was sought. Treatment of **3a** with $Ph_3P$ and a mixture of $CCl_4$:$Et_3N$:$CH_3CN$ at 0–25°C for 2–3 h under argon resulted in the corresponding chloro-derivative **5a** in 80% yield.[13] Interestingly, attempts to remove the *N*-sulfoxide group in **5a** by treatment with TFA furnished 6-(*p*-toluyl)-5-phenylsulfonyl-1,2,5,6-tetrahydropyridine **6a** directly in quantitative yield after passing through a prepacked silica gel column with ether:pet. ether (4:1) containing 1.5% $Et_3N$.[14] Similarly, other addition products **3b–e** were also successively transformed into the corresponding

hitherto unknown tetrahydropyridine derivatives **6b**–**e** in good yields[15] (Table 1, Scheme 2). The relative stereochemistry of aryl and phenylsulfonyl groups in **6a**–**e** was established as *trans* and as occupying pseudoaxial positions since the $H_5$ and $H_6$ protons are in a gauche relationship based on high resolution $^1$H NMR and NOSEY experiments.[16] We tentatively assigned the absolute configuration of **6a**–**e** as 5(*S*)-phenylsulfonyl-6(*R*)-aryl-1,2,5,6-tetrahydropyridine based on our subsequent synthesis of (*S*)-anatabine **7** from **3f** and our earlier studies with pyrrolines.[5a]




Scheme 2.

The synthesis of anatabine is outlined in Scheme 3. Compound **3f** was obtained as a 82:18 mixture of diastereomers (see Table 1) which could not be separated either by repeated column chromatography or by recrystallization. Though the chloro derivative **5f** was obtained in 68% yield, it failed to give **6f** under the conditions described in Scheme 2. Hence the *N*-sulfoxide group was removed from the addition product **3f** to get **4f** and after modification of the mode of addition in the Mitsunobu reaction[17], **6f** was obtained in a 70% yield (Scheme 3). The $^1$H and $^{13}$C NMR of **6f** showed only one set of signals, however the presence of an enantiomer cannot be ruled out. Treatment of **6f** with Na(Hg) in MeOH under buffered conditions[18] afforded anatabine **7**[19] in 60% isolated yield which showed $[\alpha]^{25}_{D}$ −128 [c 0.5, $CHCl_3$], lit.[19c] $[\alpha]_D$ −176. $^1$H and $^{13}$C NMR spectroscopic data of **7** were identical to those reported for (+)-anatabine.[19b,e] Based on the specific rotation, natural (*S*)-anatabine had been formed and the ee of **7** is 70%. By comparison with (*S*)-anatabine the absolute configuration of the precursor **6f** can be assigned as 5(*S*)-phenylsulfonyl-6(*R*)-3-pyridinyl-1,2,5,6-tetrahydropyridine and similarly the absolute configurations of **5a**–**e** can also be assigned as (5*S*)-phenylsulfonyl-6(*R*)-aryl-1,2,5,6-tetrahydropyridines.




Scheme 3.

In summary, we have accomplished a simple generalized route to functionalized chiral piperidine derivatives and also their absolute configurations were assigned based on a short synthesis to (*S*)-anatabine, a minor tobacco alkaloid. Further work is in progress to enhance selectivity and to find other routes to chiral pyrrolidine and piperidine derivatives.

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7. Refluxing (Z)-4-chloro-but-2-en-1-ol with sodium salt of sulfinic acid in MeOH for 8 h afforded **1** in 60% yield. (Z)-4-Chloro-but-2-en-1-ol was prepared from *cis*-but-2-en-1-ol following the procedure of Colonge, J.; Poilane, G. *Bull. Soc. Chim, Fr*., **1955**, 953–955.
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9. Studies were not done to improve the selectivity. However, 2.2 equiv. of LDA instead of LiHMDS under similar conditions afforded **3a** as a single diastereomer (95%) in 30% yield.
10. All compounds were characterized by $^{1}$H NMR, $^{13}$C NMR and mass spectroscopy. Data for compound **3a**: white solid, m.p. 106–107°C; $^{1}$H NMR ($CDCl_3$) (ppm), 2.29 (s, 3H), 2.32 (t, J=6 Hz, exchangeable with $D_2O$, 1H), 2.35 (s, 3H), 3.60 (m, 2H), 4.68 (ddd, J=11, 3.5, 1 Hz, 1H), 4.92 (dd J=8, 3.2 Hz, 1H), 5.64 (dt, J=11, 1 Hz, 1H), 5.69 (d, J=8 Hz, exchangeable with $D_2O$, 1H, –NH), 5.98 (dt, J=11, 7 Hz, 1H), 7.07 (AB quartet, J=8.5 Hz, 4H), 7.19 (d, J=8.5 Hz, 2H), 7.48 (d, J=9 Hz, 2H), 7.51 (tt, J=8, 1.2 Hz, 2H), 7.63 (tt, J=8, 1.2 Hz, 1H), 7.82 (dd J=8, 1.2 Hz, 2H); $^{13}$C NMR (ppm) 21.06 (q), 21.26 (q), 57.59 (t), 57.92 (d), 68.59 (d), 120.45 (d), 125.98 (d), 127.53 (d), 128.72 (d), 129.04 (d), 129.49 (d), 133.85 (d), 134.48 (s), 137.91 (s), 138.29 (s), 138.29 (s), 138.62 (d), 140.51 (s), 141.51 (s). HRMS observed mass=470.148291 (for $MH^+$, calculated value=470.14598).
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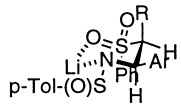


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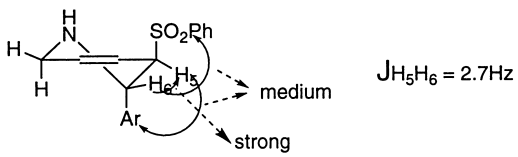
14. The crude product showed a mixture of an open chain amino compound and the cyclized desired compound, hence it is necessary to saturate the column with $Et_3N$ to obtain completely the cyclized compound after purification.
15. Spectral data of **6a**: viscous liquid, $^1H$ NMR ($CDCl_3$) (300 MHz) 2.27 (bs, 1H), 2.3 (s, 3H), 3.07 (dq, J=19, 2.7 Hz, 1H), 3.28 (m, 1H), 4.05 (m, 1H), 4.43 (d, J=2.7 Hz, 1H), 5.95 (m, 1H), 6.28 (m, 1H), 7.1 (AB quartet, J=9 Hz, 4H), 7.52 (m, 2H), 7.62 (m, 1H), 7.87 (m, 2H). $^{13}C$ NMR ($CDCl_3$) 20.96 (q), 41.02 (t), 53.66 (d), 62.04 (d), 116.81 (d), 127.24 (d), 128.83 (d), 129.03 (d), 129.10 (d), 133.63 (d), 136.41 (s), 136.7 (d), 137.38 (s), 137.88 (s). HRMS observed mass=314.12000 (for $MH^+$, calculated value=314.12148).
16. NOE details:




17. At −10°C, DIAD (1.4 equiv.) was added to $Ph_3P$ (1.4 equiv.) in THF under an argon atmosphere and after 15 min **4f** (1 equiv. in THF) was added at −10°C. The mixture was slowly warmed to RT and then stirred for 12 h. The solvent was removed under reduced pressure and the residue was chromatographed in a silica gel flash column using EtOAc and then 5% MeOH in EtOAc.
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