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Chiral Acetylenic Sulfoxide in Enantioselective Synthesis of Yohimbine Alkaloid

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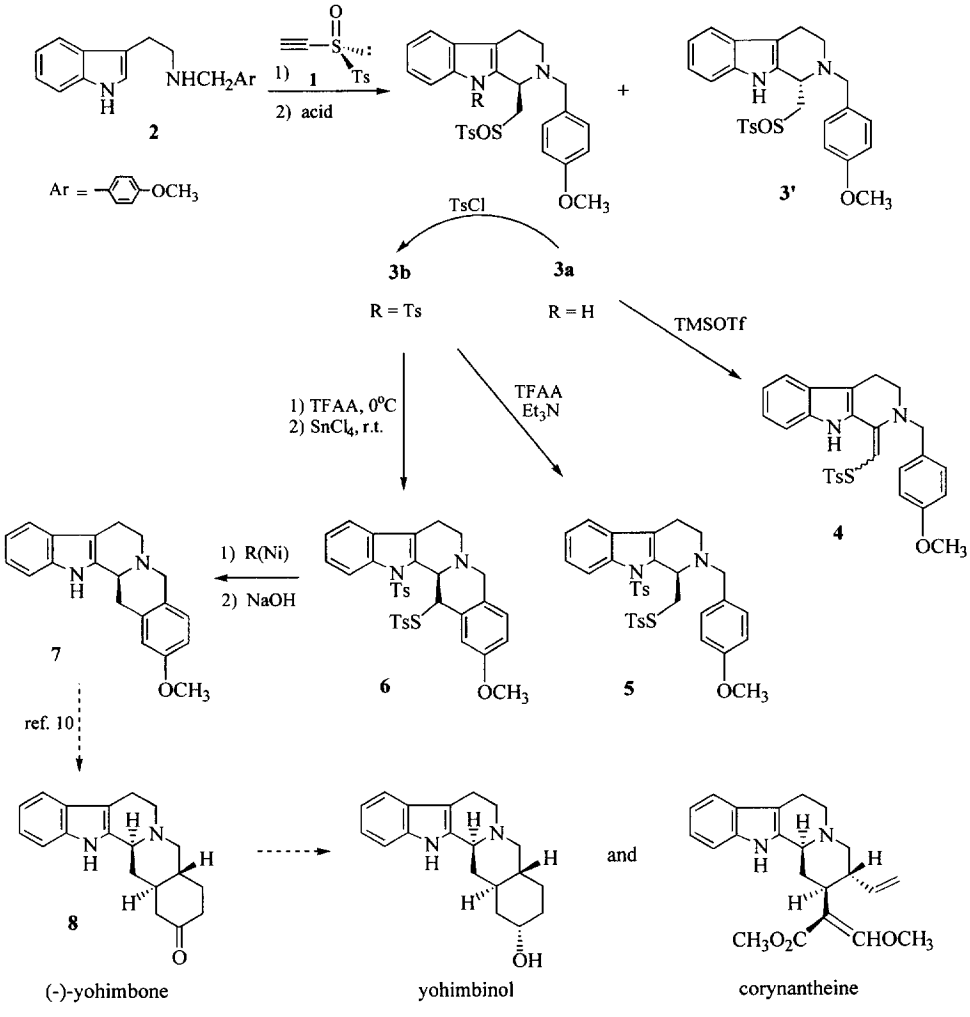
Abstract : Through Michael addition/acid induced cyclization of secondary amine to chiral acetylenic sulfoxide followed by Pummerer cyclization, an approach to the enantioselective syntheses of pentacyclic yohimbine alkaloids is presented. © 1997 Elsevier Science Ltd.

The Chiral sulfinyl group has been widely used as chiral inducer in numerous enantioselective transformations and syntheses of biologically active natural products.[1,2] For example, we reported the uses of chiral acetylenic sulfoxide (**1**) as a two-carbon synthon in the enantioselective synthesis of the tetrahydroisoquinoline[3,4] and β-carboline[5] alkaloid systems through a tandem Michael addition/acid induced cyclization reaction sequence. Members of the yohimbine alkaloid family possess a characteristic pentacyclic indole ring system. Many of these compounds exhibit a wide range of important pharmacological properties.[6] Many elegant synthetic approaches of these pentacyclic alkaloid systems included asymmetric syntheses were reported in literature. A good analysis of these various synthetic approaches has recently appeared.[7] We here reported the synthesis of homochiral intermediate **7** *via* the secondary amine cyclization approach.[4] Compound **7** is the known precursor of pentacyclic yohimbine alkaloids yohimbinol and corynantheine.[11]

Chiral acetylenic sulfoxide **1** prepared according to our published procedure[3] is a very good Michael acceptor for both primary and secondary amines. Michael addition of secondary amine **2** which was prepared from tryptamine through reductive amination with *p*-methoxybenzaldehyde took place readily in chloroform or methanol at room temperature (Scheme 1). Without isolation of any intermediate, acid induced cyclization afforded diastereomeric **3a** and **3'** in good yield. In the primary amine approach[5] using tryptamine as the nucleophile, **3'** was the major product. Starting with secondary amine **2**, in contrast, the diastereoselectivity bias is exactly the opposite with **3a** as the major product. Similar observation was found in the tetrahydroisoquinoline system.[4]


NHCH2Ar
1) 1 Ts
2) acid
2
Ar = OCH3
TsOS
OCH3
3'
TsCl
3b
R = Ts
3a
R = H
TMSOTf
4
1) TFAA, 0°C
2) SnCl4, r.t.
TFAA
Et3N
1) R(Ni)
2) NaOH
7
6
5
Ts
TsS
ref. 10
8
O
OH
(-)-yohimbone
yohimbinol
and
corynantheine
CH3O2C
CHOCH3

Scheme 1

To further explore the scope of this tandem Michael addition/acid induced cyclization reaction sequence, different protic and Lewis acids were used to effectuate the cyclization. As depicted in Table 1, *p*-toluenesulfonic acid afforded better diastereoselectivity than trifluoroacetic acid. Tin tetrachloride was also tried. Diastereoselectivity was good (9 : 1) but the chemical yield was poor. Lower the reaction temperature only marginally improved the yield.

Table 1 Tandem Michael Addition/Cyclization to Chiral Acetylenic Sulfoxide

solvent	**acid**	**temp.**	**ratio (3a : 3')**	**yield**	**time**
methanol	TsOH	0°C	70 : 30	89%	1 hr
		-35°C	75 : 25	85%	4 days
$CHCl_3$	TFA	-23°C	50 : 50	86%	2 hr
		-41°C	54 : 46	87%	3 hr
CH_2Cl_2	$SnCl_4$	r.t.	9 : 1	35%	0.5 hr

Compounds **3a** and **3'** can be readily separated by column chromatography. We envisioned that the sulfoxide group in **3a** can serve as a handle to trigger the final bond formation for the pentacyclic yohimbine system. Our plan was to activate the α-carbon of the sulfinyl group *via* Pummerer rearrangement condition and trapped the Pummerer intermediate by the *p*-methoxybenzene ring.[8] However, when **3a** was subjected to various Pummerer rearrangement conditions,[9] complex reaction mixtures were resulted with no sign of the formation of the desired ring closure product **7**. In one case, when TMSOTf was used, elimination product **4** was isolated. Although we do not know the exact geometry of the double bond of compound **4**, as shown by the ^{1}HNMR spectrum there was only one olefinic compound isolated.

We suspected that protection of the indolyl nitrogen may be crucial for the success of this cyclization. N-tosylated compound **3b** was prepared under phase transfer catalytic condition. When **3b** was treated with excess TFAA with or without triethyl amines at elevated temperature, deoxygenated compound **5** was the only identifiable product. Eventually, we found that treatment of **3b** with 1.1 eq. of TFAA at 0°C for 1 hr followed by 1.3 eq. of $SnCl_4$ at room temperature, pentacyclic product **6** was obtained in 61% isolated yield. Raney nickel desulfurization (51%) followed by deprotection with NaOH (65%) yielded optically pure **7**[10]. Compound **7** had been transformed to (-)-yohimbone (**8**) which is the precursor of corynantheine and yohimbinol.[11]

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10. Compound **7** : m.p. 105-106°C (lit. 103°C); $[\alpha]_D^{19}$ = -238, c = 1.2, CH_3OH (lit. $[\alpha]_D^{18}$ = -235°, c = 0.85, CH_3OH); IR, 3279 cm^{-1} (N–H); ^{1}HNMR ($CDCl_3$, 270 MHz): 2.71 (1H, dd, J = 4.05 and 4.10, CH$\underline{CH_2}$Ar); 2.76 (1H, m, $\underline{CH_2}CH_2N$); 3.03 (2H, m, $CH_2\underline{CH_2}N$); 3.12 (1H, dd, J = 4.03 and 3.95, CH$\underline{CH_2}$Ar); 3.29 (1H, m, $\underline{CH_2}CH_2N$); 3.67 (1H, m, indoly-$\underline{CH}$N); 3.72 (1H, d = 14.31, N$\underline{CH_2}$Ar); 3.78 (3H, s, ArO$\underline{CH_3}$); 4.05 (1H, d = 14.58, N$\underline{CH_2}$Ar); 6.73 (2H, m, ArH); 7.03 (1H, d, J = 8.37, ArH); 7.13 (2H, m, indoly-H); 7.33 (1H, d, J = 6.75, indoly-H); 7.53 (1H, d, J = 7.29, indoly-H); 7.91 (1H, s, NH); ^{13}CNMR: 21.89, 35.40, 52.83, 55.73, 56.68, 57.63, 109.17, 111.27, 112.73, 113.86, 118.69, 119.95, 122.05, 127.19, 127.58, 127.87, 134.74, 136.77, 158.45.
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