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CHIRAL ACETYLENIC SULFOXIDE IN ALKALOID SYNTHESIS. TOTAL SYNTHESIS OF (*R*)-(+)-CARNEGINE.

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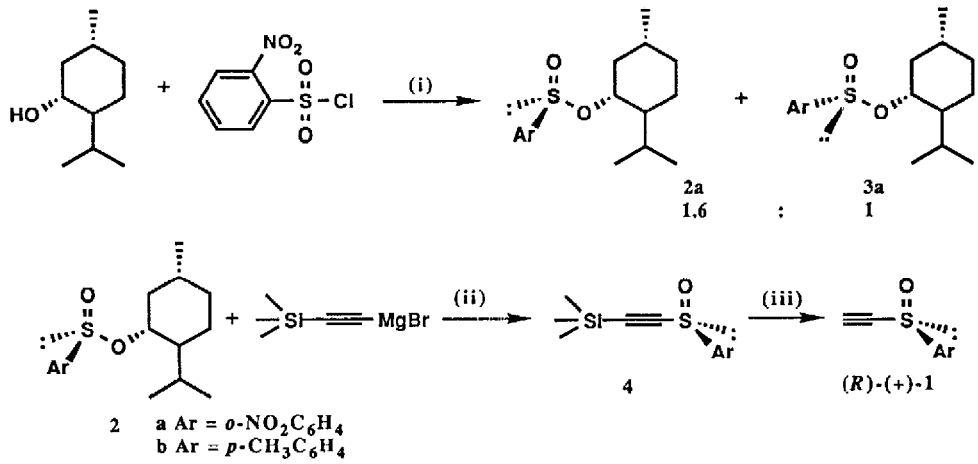
Abstract: Remarkable diastereoselectivity was observed in the cyclization of β-aminovinyl sulfoxide **5a** prepared from chiral acetylenic sulfoxide **1a** in acidic medium. The cyclized product **6a** was then converted to (*R*)-(+)-carnegine.

The use of sulfoxide functionality to control diastereoselectivity and enantioselectivity in organic synthesis has drawn attention of many research teams.[1] To follow studies on acetylenic sulfoxides in Diels-Alder reactions with moderate diastereoselectivity,[2,3] we now report the use of chiral acetylenic sulfoxide **1a** in the enantioselective synthesis of the tetrahydroisoquinoline alkaloid. The key step involved the cyclization of the vinyl sulfoxide **5a** in acidic medium. Remarkable diastereoselectivity was observed in this cyclization β to the sulfoxide moiety.

Among several known methods for the preparation of chiral sulfoxide, Andersen synthesis[4] still remains as a reliable synthetic route to give chiral sulfoxides with known absolute configurations. The starting material of the Andersen's method, in our case, (S_S)-(-)-menthyl *o*-nitrobenzenesulfinate (**2a**) was prepared according to the extremely efficient Sharpless' procedure[5] from commercial available *o*-nitrobenzenesulfonyl chloride (Scheme I). The diastereomeric mixture could be separated by chromatography on silca gel (ethyl acetate/ petr. ether, 1:49). The major diastereomer (S_S)-(-)-menthyl *o*-nitrobenzenesulfinate (**2a**), which absolute configuration was supported by literature precedent[5,6] based on the 250 MHz ^{1}HNMR data, was obtained as a yellow crystalline solid. [$[\alpha]^{26}_D$ = -449.1° (c 2.00, acetone); m.p. = 99-101°C]. Reaction of **2a** with trimethylsilylethynylmagnesium bromide[7] in toluene at -20°C afforded sulfoxide **4a** which was sequentially hydrolyzed during chromatography on silca gel to give (*R*)-(+)-ethynyl *o*-nitrophenyl sulfoxide (**1a**) as a pale yellow crystalline solid (Scheme I) [^{1}HNMR (60 MHz)($CDCl_3$): δ 8.53-7.57 (m, 4H), 3.50 (s, 1H); $[\alpha]^{26}_D$ = +363.9° (c 0.38, chloroform); m.p. = 116-118°C (decomp.)].

(*R*)-(+)-Ethynyl *o*-nitrophenyl sulfoxide (**1a**) is a very good Michael acceptor. Addition of 2-(3,4-dimethoxyphenyl)ethylamine to **1a** yielded β-aminovinyl sulfoxide **5a** when it was carried out at room temperature in chloroform (Scheme II). Without further purification, the reaction mixture was treated with eight equivalents of trifluoroacetic acid (TFA) at 0°C for 4 hours. After basified with 14% ammonium hydroxide and flash chromatography on silca gel (methanol/ethyl acetate, 1:9), tetrahydroisoquinoline **6a** was obtained as a yellow crystalline solid [^{1}HNMR (250 MHz)($CDCl_3$): δ 8.44 (dd, *J*= 1.29, 7.87 Hz, 1H), 8.31 (dd, *J*= 1.06, 8.11 Hz, 1H), 8.02-7.95 (m, 1H), 7.73-7.67 (m, 1H), 6.59 (s, 1H), 6.52 (s, 1H), 4.67

(dd, J= 3.18, 11.44 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.68 (dd, J= 11.62, 12.70 Hz, 1H), 3.34-3.25 (m, 2H), 2.93 (dd, J= 3.32, 12.83 Hz, 1H), 2.79-2.70 (m, 2H), 1.94 (br, 1H); ^{13}CNMR ($CDCl_3$): 148.5, 148.0, 144.9, 144.8, 135.5, 131.2, 128.1, 128.0, 127.0, 125.1, 112.9, 109.9, 63.2, 56.3, 56.1, 50.9, 39.4, 28.9; MS: 205.1096 (M^+ - o-$NO_2C_6H_4SOH$ found), 205.1103 (M^+ - o-$NO_2C_6H_4SOH$ calc.)[8]; $[\alpha]^{26}_D$ = +211.4° (c 0.18, chloroform); m.p. = 186-188°C (decomp.)]. The reactions can also be easily monitored by ^{1}HNMR if they are carried out in $CDCl_3$. The overall yield of this two-step reaction (**1a** to **6a**) was about 65%.

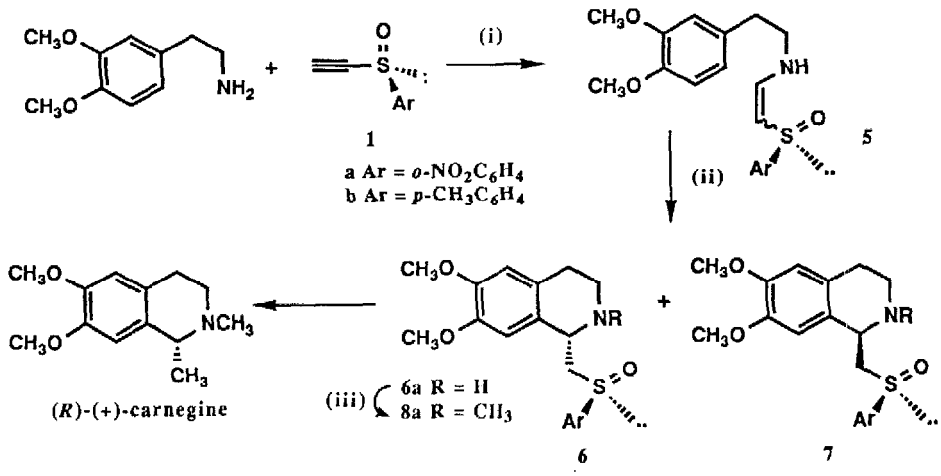


Reagents and conditions: (i) CH_2Cl_2, $(MeO)_3P$, Et_3N, reflux, 1 hr; (ii) toluene, -20°C, 1 hr; (iii) silica gel

Scheme I

Besides the sulfoxide chirality, a new chiral center was created at the C-1 position of the tetrahydroisoquinoline moiety (6). However, instead of two diastereomers (i.e. **6a** and **7a**), based on TLC and ^{1}HNMR (250 MHz) of the crude reaction product, the diastereomer **6a** was found to be the exclusive product in the cyclization of **5a** to **6a**. When the reaction was carried out at room temperature, similar high diastereoselectivity was observed although the yield was lowered. Besides using TFA, boron trifluoride etherate could also induce the cyclization with same diastereoselectivity but the reaction yield was much lowered. The result of the cyclization under different conditions was summarized in Table I.

Under the influence of excess TFA, it was no doubted that **10** (protonated **5**) and protonated imine **9** were in equilibrium with the latter as the predominant species (Scheme III). Close examination of the molecular model of **9** suggested that a hydrogen bonding might exist between the immonium hydrogen and the sulfoxide oxygen forming a six-member ring intermediate. We speculate this intramolecular hydrogen bonding may be responsible for the diastereoselectivity of the cyclization. Moreover, the ortho-substituted nitro group in the aryl substituent of the sulfoxide may also play a crucial role in the hydrogen bonding. To probe this, the reaction was repeated with (*R*)-(+)-ethynyl *p*-tolyl sulfoxide[7] (**1b**) prepared from commerical available sulfinate **2b** as the chiral starting material (Scheme I). The diastereoselectivity between **6b** and **7b**[9] was dropped to 2:1 (Table I). This clearly supported that the presence of the *o*-nitro substituent is very crucial to this remarkable diastereoselectivity.



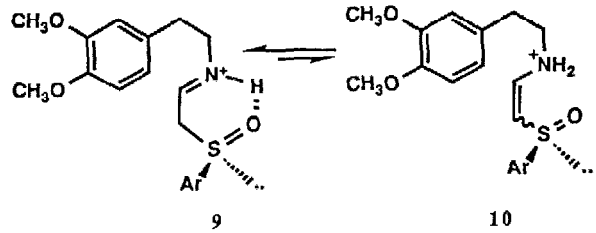
Reagents and conditions: (i) $CHCl_3$, r.t., 2 hr; (ii) TFA, 0°C, 4 hr; (iii) HCHO, $NaCNBH_3$, CH_3CN, 6 hr; (iv) Raney Nickel, 1 hr.

Scheme II

Table I. Cyclization of β-(arylethylamino)vinyl sulfoxide 5 in acidic medium

vinyl sulfoxide	acid	temp[a] (°C)	yield[b] (%)	diastereoselectivity (6:7)[c]
5a	TFA	-20	-[d]	-
5a	TFA	0	65	exclusively converted to 6a[e]
5a	TFA	r.t.	35	exclusively converted to 6a[e]
5a	BF_3.etherate	0	20	exlcusively converted to 6a[e]
5b	TFA	0	45	2:1

a. Reaction time: 4 hr, in chloroform; b. Overall isolated yield from 1; c. Determined by ^{1}HNMR (250 MHz) spectroscopy; d. The cyclization did not proceed; e. From ^{1}HNMR, no trace of 7a was observed



Scheme III

Finally, **6a** was transformed to (*R*)-(+)-carnegine with the following procedures (Scheme II): reductive methylation of **6a** with sodium cyanoborohydride and aqueous formaldehyde in acetonitrile[10] yielded **8a** [^{1}HNMR (250 MHz)($CDCl_3$): δ 8.42 (dd, *J*= 1.40, 7.89 Hz, 1H), 8.28 (dd, *J*= 1.14, 8.13 Hz, 1H), 8.00-7.94 (m, 1H), 7.71-7.64 (m, 1H), 6.59 (s, 1H), 6.53 (s, 1H), 4.23 (dd, *J*= 4.07, 11.91 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.62 (t, *J*= 12.39, 1H), 3.54-3.43 (m, 1H), 3.17-2.96 (m, 2H), 2.82 (dd, *J*= 4.12, 12.82, 1H), 2.66 (s, 3H), 2.47-2.39 (m, 1H); MS 219.1253 (M^+ - *o*-$NO_2C_6H_4SOH$ found), 219.1259 (M^+ - *o*-$NO_2C_6H_4SOH$ calc.)[8]; $[\alpha]^{26}_D$ = +256.7° (c 0.24, chloroform); m.p. = 174-176°C (decomp.)]. From NMR and TLC, once again there was no trace sign of the existence of the corresponding diastereomer. Desulfurization of **8a** with excess Raney Nickel in water saturated ether[11] yielded (*R*)-(+)-carnegine [$[\alpha]^{26}_D$ = +27.6° (c 0.15, ethanol); lit.[12c] $[\alpha]^{18}_D$ = +23.4° (c 0.15, ethanol)] as a viscous oil, which the spectroscopic data were identical with those reported in literatures.[12]

In summary, the chiral acetylenic sulfoxide **1a** had shown to be a versatile two-carbon synthon for the asymmetric synthesis of the tetrahydroisoquinoline alkaloid with high diastereoselectivity at the C-1 position. Further elaboration of the key intermediate **6a** to other tetrahydroisquinoline alkaloids and the use of *o*-nitrophenyl sulfinyl group in organic syntheses are in progress.

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