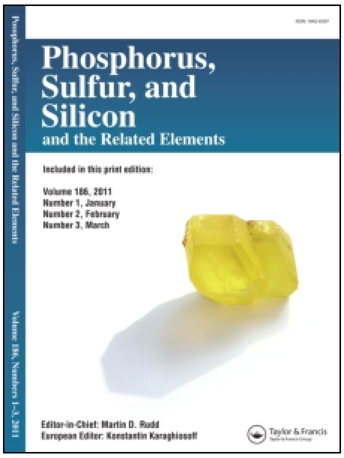

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PREPARATION OF R-(+)-3,4-DIMETHOXYBENZYL 2-METHOXY-1-NAPHTHYL SULFOXIDE AND DIASTEREOSELECTIVE ADDITION OF LITHIATED ANION OF THIS REAGENT TO CYCLIC NITRONE. ASYMMETRIC SYNTHESIS OF OPTICAL PURE ISOQUINOLINE ALKALOIDS

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The addition of the lithium carbanion of (R)-(+)-3,4-dimethoxybenzyl 2-methoxy-1-naphthyl sulfoxide **3** to cyclic nitrone **4**, under kinetically controlled conditions gave isoquinoline sulfoxide derivatives **5** and **6** in high diastereoselectivities, Under equilibrium controlled conditions poor diastereoselectivity results. The chiral (R)-(+)-3,4-dimethoxybenzyl 2-methoxy-1-naphthyl sulfoxide **3** was easily prepared by the reaction of 3,4-dimethoxybenzylmagnesium chloride **2** with (-)-(S) menthyl 2-methoxy-naphthalene sulfinate **1** in dry benzene. This methodology allows for the synthesis of the isoquinoline alkaloid (R)-(-)-norlaudanosine **8** in three efficient synthetic steps.

Keywords: Nitrone; Chiral sulfoxide; Alkaloid; Isoquinoline alkaloid; (-)-(*S*)-menthyl 2-methoxy-naphthalene sulfinate; (R)-(-)-norlaudanosine

INTRODUCTION

Sulfoxides are versatile compounds for organic synthesis and asymmetric synthesis.[1] The 1,2- and 1,4-additions of traditional lithiated alkyl and benzyl *p*-tolyl sulfoxides to carbonyl compounds and Michael acceptors,

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however is generally poorly diastereoselective.[1] A much improved diastereoselection can be achieved when sterically hindered versions of these sulfoxides are employed.[2] Unfortunately, the later sulfoxides are not readily prepared in high enantiomeric purity, and therefore their use in asymmetric synthesis has been limited.[3]

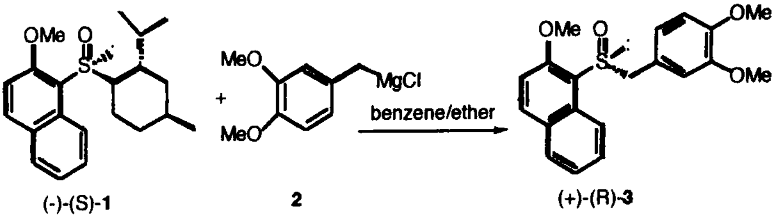
RESULTS AND DISCUSSION

As part of our continued effort to synthesise various biologically important alkaloids from the addition of non-racemic chiral sulfoxide to nitrone and oxaziridine,[4–7] our attention was focused on the development of efficient, highly sterically hindered, non-racemic chiral sulfoxide and reaction of these novel and highly steric reagents with cyclic imines. The chiral sulfoxide have been used for the synthesis of chiral alkaloids. However, the enantioselectivity is low, and catalyst used increased the expense of the method.[8,9]

In this paper, we report the synthesis of chiral (R)-(+)-3,4-dimethoxybenzyl 2-methoxy-1-naphthyl sulfoxide **3** from the reaction of 3,4-dimethoxybenzylmagnesium chloride **2** with (-)-(S) menthyl 2-methoxy-naphthalene sulfinate **1**[10] in dry benzene. Addition of chiral (R)-(+)-3,4-dimethoxybenzyl 2-methoxy-1-naphthyl sulfoxide **3** to cyclic nitrone **4**, under kinetic controlled afforded isoquinoline alkaloids **5** in high diastereoselectivity. Hydrogenolysis[4] and desulfurization[8] of **5** gave the chiral isoquinoline alkaloid (R)-(-)-norlaudanosine **8** in excellent yield.

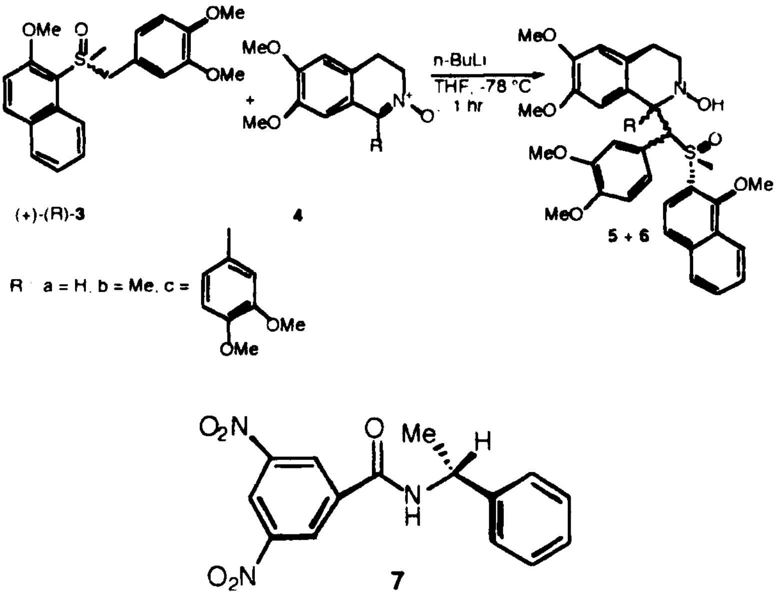
Our studies focused on the addition of the lithium carbanion of (R)-(+)-3,4-dimethoxybenzyl 2-methoxy-1-naphthyl sulfoxide **3** which can be synthesis by treatment of (-)-(S) menthyl 2-methoxy-naphthalene sulfinate **1**[10] with 3,4-dimethoxybenzylmagnesium chloride **2** in a mixture of ether/benzene at ambient temperature to give chiral (R)-(+)-3,4-dimethoxybenzyl 2-methoxy-1-naphthyl sulfoxide **3**. The enantiomeric purity of this compound was determined to be 99% from ^{1}H NMR shift studies using (-)-(R)-N-3,5-dinitrobenzoyl)-α-phenylethylamine **7** as chiral shift reagent.[11,12] To determine the enantiomeric purity of **3** we mixed it with one equivalent of chiral reagent **7** in a NMR tube.

The addition of the lithium carbanion of (R)-(+)-3,4-dimethoxybenzyl 2-methoxy-1-naphthyl sulfoxide **3** at –78°C to nitrone **4**[1] was highly dias-



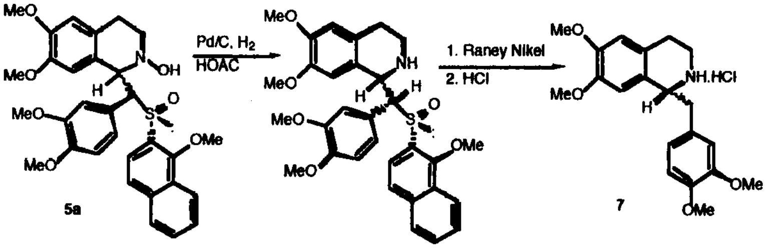
SCHEME 1

tereoselective (94:6 to 100:0) and gave the alkaloid **5** and **6** in good yields after purification by column chromatography.



SCHEME 2

After purification of diastereomer **5a**, by column chromatography, was converted to chiral (R)-(-)-norlaudanosine isoquinoline alkaloid **8** by hydrogenolysis[1] and reductive desulfurization[7] in excellent yield (Scheme 3).



SCHEME 3

The ^{1}H NMR spectrum of both diastereomers **5a** and **6a** are clearly evident via the presence of doublets at 5.54 (d, J = 3.2) and 5.34 (d, J = 3.2), respectively. Integration of these signal indicated that the diastereomeric ratio was 94:6. The product diastereoselection increased as the steric demands of the R substituent of the cyclic nitrones increased (Table I). The highest product diastereoselection was obtained with cyclic nitrone **4c** as shown in Table I.

The relative (*1S,1'S,SR*) stereochemistry in the major diastereomeric products **5** based on similarity of their ^{1}H NMR spectra to that of compound that was obtained from the addition of lithiated 2-methoxy-1-naphthyl sulfoxide to 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide.[13] The stereochemical outcome of these reactions can be rationalized as arising from the lithium chelated intermediate **9**. By analogy with the known solid state structure of lithiated sulfoxides,[14] the 3,4-dimethoxy-phenyl and 2-methoxy-1-naphthyl rings would be expected to have a trance disposition in lithiated **3** in order to minimized steric repulsion. The π-facial selectivity with respect to addition of the anion to the nitrone **4** would be expected as shown in **9** to minimize steric interactions between the sulfoxide ion and the ring system of the nitrone. The 2-methoxy group in lithiated **3**, by increasing the Lewis basicity of the sulfoxide oxygen, may also be responsible for the high diastereoselectivity in its reactions with **4**.[15]

In conclusion, we have developed an efficient method for the synthesis of sterically hindered sulfoxides in high enantiomeric purity. The addition of this sterically hindered sulfoxides to cyclic nitrones produced chiral isoquinoline alkaloid derivatives with high diastereoselectivity. The One chiral isoquinoline alkaloid derivative have been converted to the naturally occurring (R)-(-)-norlaudanosine isoquinoline alkaloid by hydrogenolysis and reductive desulfurization in excellent yield.

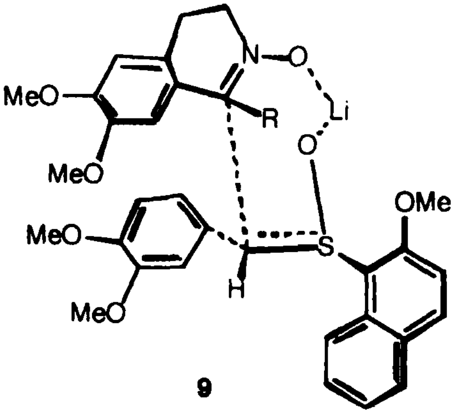


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TABLE I Addition of (+)-(R)-3 to Nitrone 4

Entry	*Nitrone 4*	*Diastereomeric Ratio of 5:6*[a]	*Yield% of 5+6*[b]
1	**4a**	94:6	72
2	**4b**	98:2	61
3	**4c**	100:0	69

a. From ^{1}H NMR (500 MHz) analysis of the crude reaction mixture.
b. After purification by column chromatography.

EXPERIMENTAL

General

The nitrone was prepared oxidation of corresponding amine with selenium dioxide.[16] All mps were taken on a Gallenkamp melting apparatus and were uncorrected. Elemental analysis was performed by the Research Institute of Petroleum Industry, Tehran, I. R. Iran. The ^{1}H NMR spectra were recorded on a Varian EM-390 NMR spectrometer operating at

90 MHz or on a Bruker Advance DRX 500 MHz NMR instrument operating at 500 MHz. The spectra were measured in $CDCl_3$, unless otherwise stated, relative to TMS (0.00 ppm). Optical rotation were recorded with a JASCO. Digital Polarimeter. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000px instrument.

Synthesis of (+)-(R)-3′,4′-Dimethoxybenzyl 2-methoxy-1-naphthyl sulfoxide 3

To a solution of (-)-(S)-menthyl 2-methoxy-1-naphthalene sulfinate (10.8 g, 30 mmol) in dry benzene (120 ml) at ambient temperature under nitrogen was added dropwise, via syringe over 30 min, a solution of 3,4-dimethoxybenzylmagnesium chloride, [prepared from magnesium (2 g) and 3,4-dimethoxybenzyl chloride (8 ml), in diethyl ether (70 ml)}. After addition was completed, the reaction mixture was stirred at ambient temperature for 2 hr and then it was quenched by the addition of saturated ammonium chloride solution (30 ml). The organic solvent was evaporated, and the aqueous layer was extracted with hexane (50 ml) to remove menthol and then with chloroform (4 × 50 ml). The combined chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, ethyl acetate). The second fraction was collected and evaporated to give 5.41 g (76% yield) of compound **3** as white needles. Mp 124–125°C, $[\alpha]_D^{25}$ +124.32 (C 0.1, $CHCl_3$). IR (nujol), ^1H NMR δ 9.05 (d, J = 8 Hz, 1 H), 7.90–6.80 (m, 8 H), 5.02 and 4.85 (AB quartet system, J = 13.2 Hz, 2 H), 3.98 (S, 3 H, OCH_3), 3.94 (S, 3 H, OCH_3), 3.83 (S, 3 H, OCH_3). Ms m/z 356 (100 %, M^+). Anal calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66; S, 8.99 %. Found: C, 67.30; H, 5.80; S, 8.70 %.

Reaction of (+)-(R)-3 to nitrone 4

General Method

(+)-(R)-3′,4′-Dimethoxybenzyl-2-methoxy-1-naphthyl sulfoxide (0.71 g, 2.0 mmol) in anhydrous THF (10 ml) was added dropwise to a cooled (-78 °C), stirred solution of LDA, prepared from diisopropylamine (0.58 ml, 4 mmol) and n-butyllithium (2.45 ml, 4 mmol of 1.6 M solution in hexane) in THF (5 ml). The mixture was allowed to reach −20 °C and then was quenched with saturated aqueous NH_4Cl (10 ml). The mixture was warmed to ambient temperature and then extracted with dichloromethane (3 × 15 ml). The combine extracts were washed with water, dried ($MgSO_4$), and then evaporated to dryness. The crude product was purified by column chromatography on silica gel using ethyl acetate/n-hexane (1:1) as eluent. The diastereoselection of these reactions was determined from ^1H NMR (500 MHz) analysis of the crude reaction product.

(1S,1′S,SR)-3,4-Dihydro-2-hydroxy-6,7-dimethoxy-1′(3′,4′-dimethoxy phenyl)-1′(2′-methoxynaphthylsulfinyl) isoquinoline 5a

MP 126–128 °C, $[\alpha]_D^{25}$ −28 (C 0.1, $CHCl_3$). IR (nujol) 3650–3150, 1115, 1032 cm^{-1}. ^1H NMR δ 9.10 (d, J=8 Hz, 1 H), 7.80–6.80 (m, 9 H), 6.40 (s, 1 H), 5.55 (d, J=3.2 Hz, 1 H), 5.34 (d, J=3.2 Hz, 1 H), 3.82 (S, 6 H, 2 × OCH_3), 3.76 (S, 6H, 2 × OCH_3), 3.73 (S, 3H, OCH_3), 3.56 (t, 2 H), 2.85 (t, 2 H). ^{13}C NMR δ 158.70, 148.70, 147.92, 145.50, 137.75, 135.70, 134.30, 132.60, 131.30, 129.30, 128.10, 127.50, 125.30, 125.10, 123.90, 121.30, 115.80, 114.50, 113.12, 112.80, 112.20, 109.80, 66.80, 64.20, 58.20, 56.70, 56.40, 56.20, 41.70. Ms m/z 563.70 (100 %, M^+). Anal calcd for $C_{31}H_{33}NO_7S$: C, 66.06; H, 5.90; N, 2.48; S, 5.69 %. Found: C, 65.80; H, 6.10; N, 2.40; S, 5.50 %.

(1R,1′R,SR)-3,4-Dihydro-2-hydroxy-6,7-dimethoxy-1′(3′,4′-dimethoxy phenyl)-1′(2′-methoxynaphthylsulfinyl) isoquinoline 6a

^1H NMR(in part) δ 9.02 (d, J = 8.12 Hz, 6.22 (s, 1 H), 5.15 (d, J=3.8 Hz, 1 H), 5.24 (d, J=3.8 Hz, 1 H).

(1S,1′S,SR)-3,4-Dihydro-1-methyl-2-hydroxy-6,7-dimethoxy-1′(3′,4′-dimethoxyphenyl)-1′(2′-methoxynaphthylsulfinyl) isoquinoline 5b

oil, $[\alpha]_D^{25}$ −32 (C 0.1, $CHCl_3$). IR (nujol) 3650–3150, 1115, 1035 cm^{-1}. ^1H NMR δ 9.00 (d, J=8 Hz, 1 H), 8.00–6.40 (m, 10 H), 5.10 (s, 1 H), 3.99 (S, 6 H, 2 × OCH_3), 3.88 (S, 3H, OCH_3), 3.78 (S, 6H, 2 × OCH_3), 3.56 (t, 2 H), 2.80 (t, 2 H), 1.45 (s, 3 H, Me). ^{13}C NMR δ 158.78, 148.74, 147.94, 147.50, 135.70, 134.10, 132.60, 132.20, 131.15, 129.10, 128.14, 127.70, 125.30, 125.10, 124.70, 121.10, 115.30, 113.80, 112.40, 111.80, 111.40, 110.60, 66.90, 64.20, 58.20, 56.60, 55.50, 55.28, 42.76, 28.20. Ms m/z 577.70 (100 %, M^+). Anal calcd for $C_{32}H_{35}NO_7S$: C, 66.53; H, 6.11; N, 2.42; S, 5.55 %. Found: C, 65.80; H, 6.10; N, 2.40; S, 5.40 %.

(1R,1′R,SR)-3,4-Dihydro-1-methyl-2-hydroxy-6,7-dimethoxy-1′(3′,4′-dimethoxyphenyl)-1′(2′-methoxynaphthylsulfinyl) isoquinoline 6b

^{1}H NMR(in part) δ 8.86 (d, J=8.10 Hz), 5.03 (s, 1 H).

(1S,1′S,SR)-3,4-Dihydro-1-(3,4-dimethoxyphenyl)-2-hydroxy-6,7-dimethoxy-1′(3′,4′-dimethoxyphenyl)-1′(2′-methoxynaphthylsulfinyl) isoquinoline 5c

oil, $[\alpha]_D{}^{25}$ –43 (C 0.1, $CHCl_3$). IR (nujol) 3650–3160, 1115, 1035 cm^{-1}. ^{1}H NMR δ 9.15 (d, J=8 Hz, 1 H), 7.8–6.90 (m, 12 H), 5.55 (s, 1 H), 3.91 (S, 6 H, 2 × OCH_3), 3.84 (S, 6H, 2 × OCH_3), 3.78 (S, 6H, 2 × OCH_3), 3.70 (s, 3 H, OMe), 2.76 (t, 4 H). ^{13}C NMR δ 158.60, 148.70 147.94, 147.50, 135.70, 134.60, 133.70, 131.60, 130.30, 129.60, 127.10, 126.50, 124.30, 123.20, 122.70, 120.10, 114.30, 113.20, 112.00, 111.90, 111.60, 108.60, 66.90, 64.20, 59.20, 56.70, 56.60, 56.20, 41.77,. Ms m/z 699.80 (100 %, M^+). Anal calcd for $C_{39}H_{41}NO_9S$: C, 66.94; H, 5.91; N, 2.00; S, 4.58 %. Found: C, 66.80; H, 6.10; N, 2.10; S, 4.40 %.

(-)-(R)-Norlaudanosine 7

To a solution of **5a** ((0.05 g, 0.9 mmol) in acetic acid (5 ml), was added 10% palladium on charcoal (0.237 g, 1.8 mmol). The reaction mixture was stirred vigorously under an atmospheric of hydrogen at ambient temperature for 60 hr. The catalyst was then separated by filtration through celite, and the filtrate was then evaporated under reduced pressure. The residue was dissolved in 1 M HCl (10 ml), and the solution was washed with ether (5 ml). The aqueous layer was made basic with 2 M NaOH, and the solution was extracted with dichloromethane (3 × 5 ml). The combined organic extracts were dried (Na_2SO_4), filtered, and then evaporated to dryness to give a pale yellow oil. The residual oil was treated with Raney nickel (W_2, ca, 1.2 g) in ethanol (10 ml), and the reaction mixture was stirred rapidly for 10 h. The mixture was then filtered through a pad of celite, and the ethanol was evaporated. The residue was then treated with 10% HCl and crystallized from MeOH-Et_2O to afford: (-)-(R)-Norlaudanosine 7. HCl (102 mg, 70%) as colourless prism. Mp 212–214 °C., $[\alpha]_D^{25}$ −37.89 (C 1, H_2O) [Lit.[17,18] mp 215°C $[\alpha]_D^{25}$ −37.0 (c 1.0, H_2O)]. ^1H NMR δ (D_2O), 7.90–6.70 (m, 4 H, ArH), 6.39 (s, 1 H, ArH), 5.47 (dd, 1 H, J=3.2, 6.0 Hz), 4.80 (dd, 1 H, J=3.6, 13.6), 4.68 (dd, 1 H, J=6.0, 13.6), 3.88 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 3.80 (s, 6 H, 2 × OMe), 2.85 (t, 4 H).

Acknowledgements

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