A FACILE ROUTE TO TETRAHYDROISOQUINOLINE ALKALOIDS *VIA* SULFOXIDE MEDIATED CYCLIZATION

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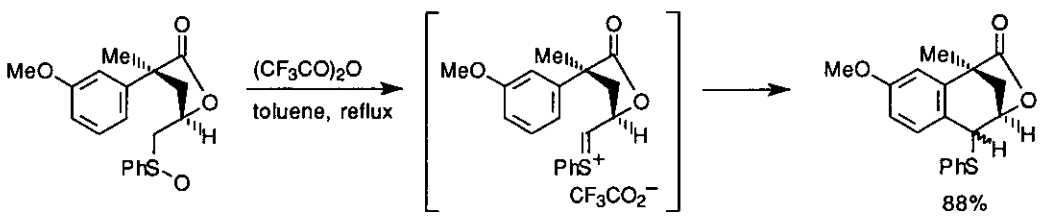
Abstract —— A facile route to 1,2,3,4-tetrahydroisoquinoline framework has been developed by employing the sulfoxide mediated cyclization reaction. Utilizing the reaction developed some naturally occurring isoquinoline alkaloids have been synthesized.

Although it has been well-recognized that activated sulfoxides such as β-keto sulfoxides can participate in cyclization reactions forming carbocycles and heterocycles under acidic conditions *via* generation of highly activated β-keto sulfenium intermediate,[1,2] only a small number of examples where simple sulfoxides involved in the cyclization reaction were so far reported.[3,4] In relation to the simple sulfoxide-mediated hydronaphthalene formation reaction which we developed recently (**Scheme 1**),[4] we now examined the construction of isoquinoline framework as an extension.



Scheme 1

We first prepared 2-aminoethyl phenyl sulfide[5] (**4**) from ethanolamine (**1**) in three steps. Thus, condensation of ethanolamine with phthalic anhydride followed by treating the resulting imide (**2**) with diphenyl disulfide

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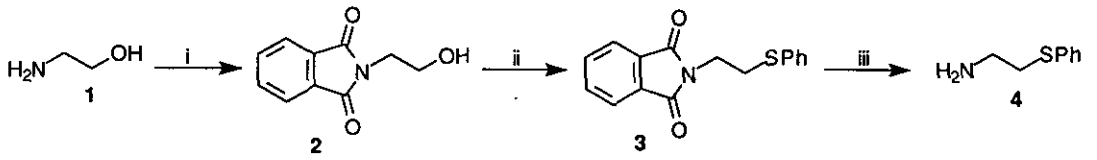
This paper is dedicated to Professor Edward C. Taylor on the occasion of his 70 th birthday.

in the presence of tri-*n*-butylphosphine[6] yielded the phenyl sulfide (**3**) which was exposed to hydrazine hydrate to give the amino sulfide (**4**) in 60% overall yield (**Scheme 2**).

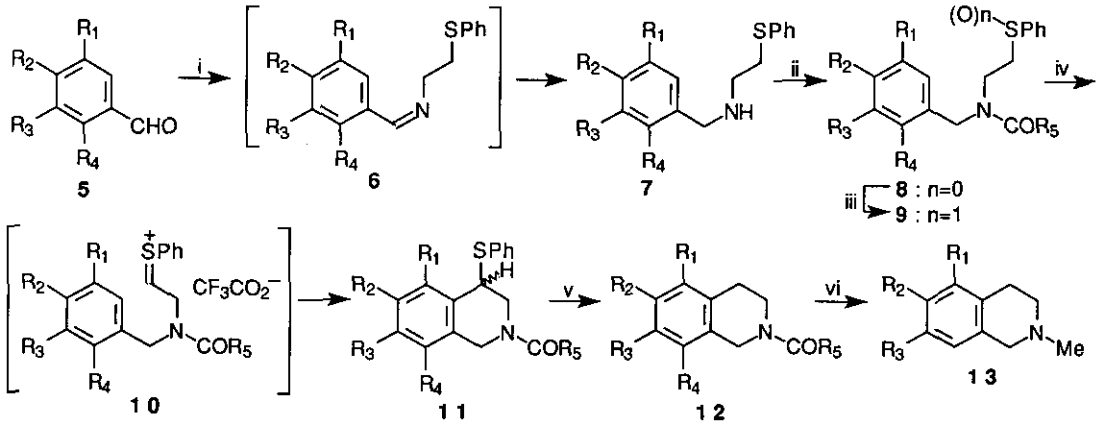


Scheme 2

Reagents and conditions: i) phthalic anhydride (1.0 equiv.), toluene, reflux, 3 h; ii) $(PhS)_2$ (1.5 equiv.), *n*-Bu_3P (1.5 equiv.), pyridine, 60 °C, 4 h; iii) $H_2NNH_2{\cdot}H_2O$ (3 equiv.), EtOH, reflux, 1 h.

Condensation of the amine (**4**) with aromatic aldehydes (**5a~f**), followed by reduction of the resulting Schiff bases (**6a~f**) with sodium borohydride afforded the secondary amines (**7a~f**) without difficulty in satisfactory overall yields. On sequential acylation and oxidation with *m*-chloroperbenzoic acid, the amines (**7a~f**) afforded the substrate sulfoxides (**9a~g**) in good overall yields *via* the sulfides (**8a~g**), respectively.

Upon exposure to 1,3 equiv. of trifluoroacetic anhydride in refluxing toluene,[4] the sulfoxides (**9a~g**) reacted within a minute to give the unstable cyclization products (**11a~g**) which were immediately treated with Raney



Scheme 3

Reagents and conditions: i) **4** (1.0 equiv.), *p*-TsOH (cat.), benzene, reflux, overnight, then $NaBH_4$ (4.0 equiv.), MeOH, room temperature, 2 h; ii) methyl chlorocarbonate (1.2 equiv.) for **a~f**, or acetyl chloride for **g**, pyridine (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h; iii) *m*-chloroperbenzoic acid (*m*-CPBA) (1.1 equiv.), $NaHCO_3$ (3.0 equiv.), CH_2Cl_2, –30 °C, 2.5 h; iv) trifluoroacetic anhydride (TFAA) (3.0 equiv.), toluene, reflux, 0.5 min; v) Raney Ni, EtOH, reflux, 3 h; vi) $LiAlH_4$ (9.0 equiv.), THF, reflux, 3 h.

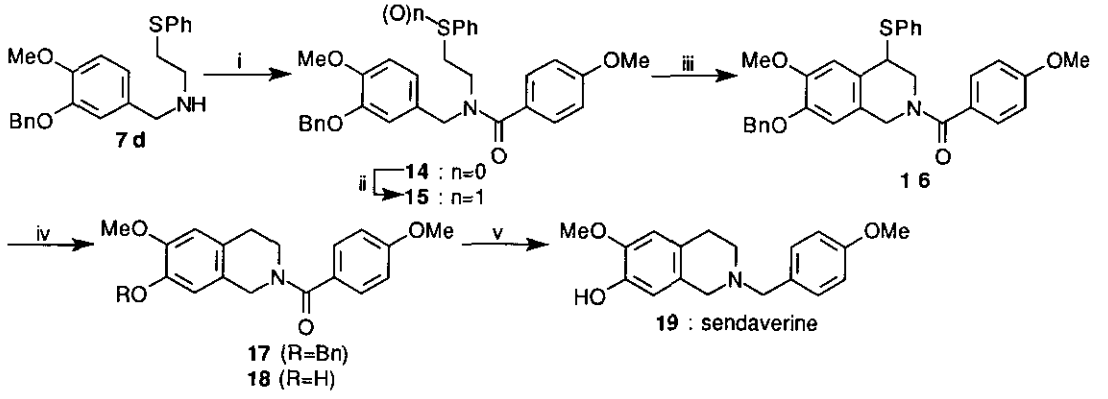
Table 1: Formation of the tetrahydroisoquinolines (**12**) from the Sulfoxides (**9**) *via* **11**

Sulfoxide (**9**)	R_1	R_2	R_3	R_4	R_5	Isoquinoline (**12**)	R_1	R_2	R_3	R_4	R_5	Yield (%)
(a)	H	$-OCH_2O-$		H	OMe	(a)	H	$-OCH_2O-$		H	OMe	38
(b)	H	MeO	MeO	H	OMe	(b)	H	MeO	MeO	H	OMe	36
(c)	MeO	MeO	MeO	H	OMe	(c)	MeO	MeO	MeO	H	OMe	44
(d)	H	MeO	BnO	H	OMe	(d)*	H	MeO	HO	H	OMe	62
(e)	H	H	MeO	MeO	OMe	(e)	H	H	MeO	MeO	OMe	30
(f)	H	H	MeO	BnO	OMe	(f)*	H	H	MeO	HO	OMe	46
(g)	H	MeO	MeO	H	Me	(g)	H	MeO	MeO	H	Me	53

* Concomitant debenzylation occurred under the desulfurization conditions.

nickel in ethanol to furnish the *N*-acyl-1,2,3,4-tetrahydroisoquinolines (**12a~g**) in moderate overall yields (**Table 1**). Among these products, reduction of the carbamates (**12a~d**) with lithium aluminum hydride in refluxing tetrahydrofuran furnished the naturally occurring alkaloids, hydrohydrastinine[7] (**13a**), methylcorypalline[8] (**13b**), tehaunine[9] (**13c**), and corypalline[10] (**13d**), respectively (**Scheme 3**).

On the other hand, the amine (**7d**) was transformed into the *p*-methoxybenzamide (**14**) which then was oxidized to the sulfoxide (**15**). Upon the same treatments above **15** furnished the *N*-*p*-methoxybenzoyltetrahydroisoquinoline (**18**) *via* **16** and **17** in 33% overall yield with spontaneous debenzylation. The resulting



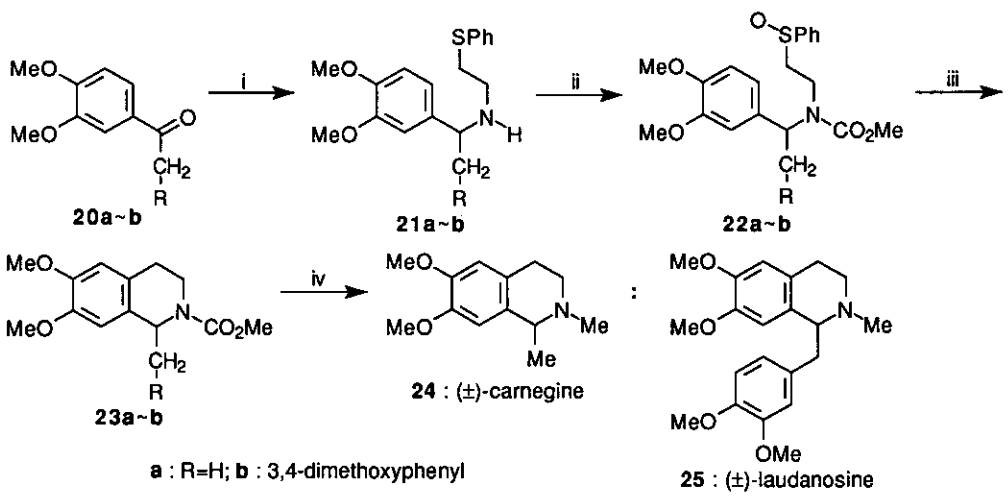
Scheme 4

Reagents and conditions: i) *p*-methoxybenzoyl chloride (1.2 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, room temperature, 1.5 h; ii) *m*-CPBA (1.2 equiv.), $NaHCO_3$ (3.0 equiv.), CH_2Cl_2, –30 °C, 2 h; iii) TFAA (3.0 equiv.), toluene, reflux, 0.5 min; iv) Raney Ni, EtOH, reflux, overnight; v) $LiAlH_4$ (9.0 equiv.), THF, reflux, 3 h.

amide (**18**) was reduced with lithium aluminum hydride to afford another naturally occurring alkaloid, sendaverine[11] (**19**), in 67% yield (**Scheme 4**).

To obtain 1-substituted isoquinoline alkaloids, we next carried out the reaction starting from the aryl ketones (**20a~b**). On reductive condensation with the sulfide amine (**4**), these gave the corresponding secondary amines (**21a~b**) which were sequentially carbamoylated and oxidized to furnish the corresponding sulfoxides (**22a~b**), respectively, in satisfactory yields *via* the sulfide (**21a~b**).

Upon exposure to 1.3 equivalent of trifluoroacetic anhydride in refluxing toluene followed by desulfurization with Raney nickel in refluxing ethanol as above, both of the sulfoxides (**22a~b**) afforded the corresponding 1-substituted tetrahydroisoquinolines (**23a~b**) in yields of 82 and 81%, respectively. The resulting carbamates (**23a~b**) were then reduced with lithium aluminum hydride to give (±)-carnegine[12] (**24**) and (±)-laudanosine[13] (**25**) in 79 and 80% yields, respectively (**Scheme 5**).



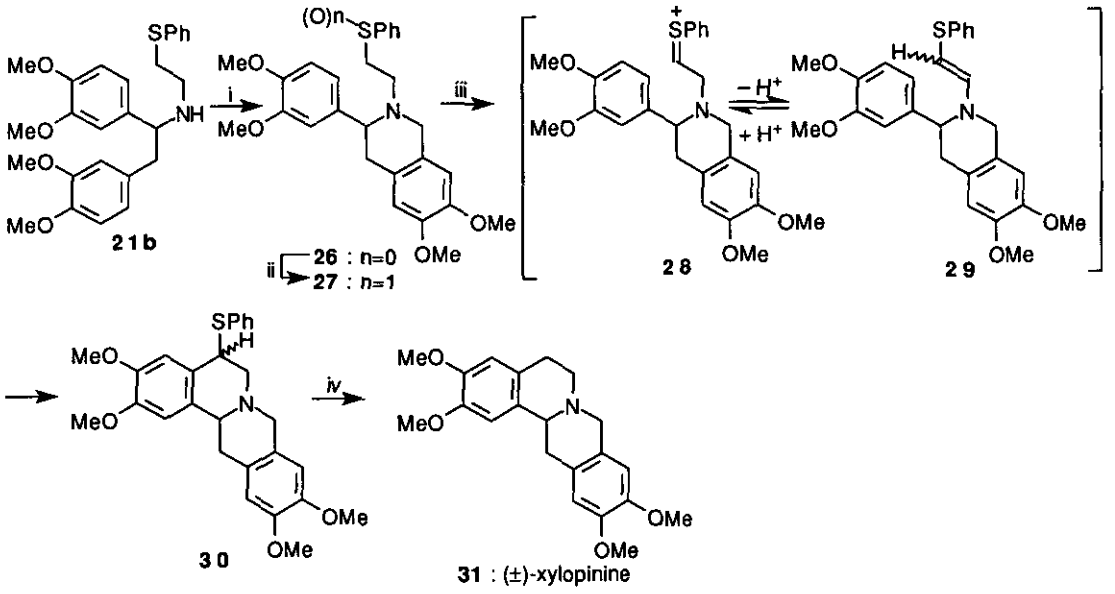
Scheme 5

Reagents and conditions: i) **4** (1.0 equiv.), *p*-TsOH (cat.), benzene, reflux, overnight, then $NaBH_4$ (4.0 equiv.), MeOH, room temperature, 5 h; ii) methyl chlorocarbonate (1.2 equiv.), pyridine (1.2 equiv.), CH_2Cl_2, 0 °C, 8 h, then *m*-CPBA (1.1 equiv.), $NaHCO_3$ (3.0 equiv.), CH_2Cl_2, –30 °C, 2 h; iii) TFAA (5.0 equiv.), toluene, reflux, 0.5 min then Raney Ni, EtOH, room temperature, overnight; iv) $LiAlH_4$ (9.0 equiv.), THF, room temperature, 3.5 h.

The secondary amine (**21b**), on the other hand, was treated with 30% formalin in refluxing methanol containing hydrochloric acid to give the 2,3-disubstituted tetrahydroisoquinoline (**26**) in 78% yield. Treatment of the resulting tertiary amine (**26**) with one equivalent of *m*-chloroperbenzoic acid in

dichloromethane at –30 °C in the presence of sodium hydrogen carbonate allowed chemoselective oxidation to give the sulfoxide (**27**) in 60% yield.

Upon the same cyclization conditions above, the sulfoxide (**27**) did not furnish the expected tetracyclic amine (**30**), but the unstable vinyl sulfide (**29**) as a stereoisomeric mixture which, presumably, was generated from the sulfenium intermediate (**28**) preceding to the cyclization. We, therefore, added trifluoroacetic acid to the reaction medium to maintain the sulfenium structure (**28**) with expectation to give rise to the cyclization product (**30**) rather than the vinyl sulfide (**29**). As expected when the sulfoxide (**27**) was treated with three equivalents of trifluoroacetic anhydride in refluxing toluene containing three equivalents of trifluoroacetic acid, the cyclization occurred to give the tetracyclic sulfide (**30**) as a mixture of diastereomers which afforded (±)-xylopinine[14] (**31**) in 42% overall yield on desulfurization with Raney nickel in refluxing ethanol (**Scheme 6**).



Scheme 6

Reagents and conditions: i) 30% formalin (1.2 equiv.), aq. HCl (cat.), MeOH, reflux, overnight; ii) *m*-CPBA (1.0 equiv.), $NaHCO_3$ (5 equiv.), CH_2Cl_2, –30 °C, 3.5 h; iii) trifluoroacetic anhydride (3.0 equiv.), trifluoroacetic acid (3.0 equiv.), toluene, reflux, 0.5 min; iv) Raney Ni, EtOH, reflux, overnight.

In conclusion the present method may be generally applicable for the construction of a variety of the isoquinoline alkaloids having 1,2,3,4-tetrahydroisoquinoline framework as a complement to the conventional Pomeranz-Fritch reaction[15] and the related isoquinoline formation reactions.

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