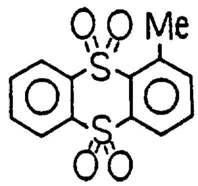

(10)

Figure 3.

Thermal isomerization from *trans*-(**3**) to *cis*-(**3**) has been reported to occur at 200 to 300 °C.[4] However, the corresponding isomerization of **9** did not occur at 160 °C to 180 °C at which temperature **9** sublimed.

When a large excess amount of hydrogen peroxide was used (**6**, 3.038 mmol, H_2O_2, 5 m*l*, 4h), 1-methylthianthrene 5, 5, 10, 10-tetroxide (**10**); mp 297-298 °C (CH_3CO_2H); ^1H NMR (DMSO-d_6, 100 MHz) δ 2.80 (s, 3H, Me), 7.82-7.97 (m, 4H, 2, 3, 7, 8 positions of Ar), 8.05-8.42 (m, 3H, 4, 6, 9 positions of Ar); IR (KBr) 1450, 1320-1150 (br) cm^{-1}; UV $\lambda_{max}^{CH_3OH}$ 294 (ϵ, 8,200), 284 (9,200) nm; MS *m/e* 294 (M^+). was obtained in 56% yield. It was unsuccessful to detect either sulfone or trioxide of **6**.

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Enantioselective Synthesis of Cryptostyline I, II and III *via* Asymmetric Reduction

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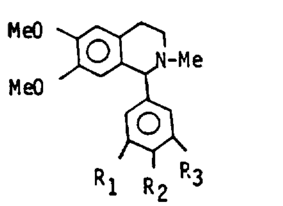
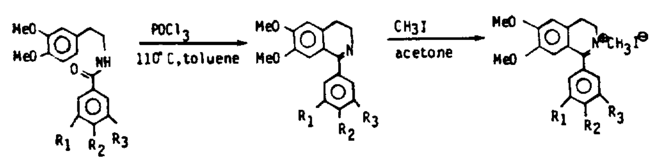
Since the first naturally occurring 1-substituted phenyl-2-methyl-1,2,3,4,-tetrahydroisoquinoline alkaloids, cryptostyline I, II and III, (**4a**, **4b** and **4c**, respectively) were isolated from *orchidaceae*, much efforts for the structural elucidation of **4** have been devoted.[1,2] However, no attempts of enantioselective synthesis of **4** have not been made.[3]

Recently a wide variety of high promising chiral reducing agents achieving excellent optical induction for prochiral ketones have been developed.[4] Among them, it was realized that chiral boron and aluminum hydrides, such as K glucoride[5] **5**, Itsuno's reagent[6] **6** and Mosher's reagent[7] **7** provide high optical inductions for asymmetric reduction of imine derivatives.[6,8] The compound **4** could be obtained by reduction of the corresponding iminium salts **3**[1b,9] Therefore, it appeared desirable to undertake the study of enantioselective



4

a: R_1= H, R_2 + R_3= -OCH$_2$O-
b: R_1= H, R_2 = R_3 = OMe
c: R_1= R_2= R_3 = OMe



1 **2** **3**

a: R_1= H, R_2+ R_3= -OCH$_2$O- b: R_1= H, R_2= R_3= OMe c: R_1= R_2= R_3= OMe

Scheme 1

synthesis of **4** by asymmetric reduction **3** using these hydrides. This paper describes the results. The requisite iminium salts **3** could be readily prepared by Bischler-Napieralski cyclization of amides **1** with phosphorus oxychloride[10], followed by quaternization with methyl iodide. (Scheme 1). The reaction conditons for reductions were initially chosen to mimic those found most successful for reduction of ketones with the reagents. Thus, the reaction with K glucoride **5** was carried out in THF at -78 °C. The reduction proceeded to completion within 6 h, giving cryptostylines **4** in the range of 80-86% yield. The asymmetric inductions afforded 37% *ee* for **3a**, 43% *ee* for **3c** and 25.2% *ee* for **3c**. Both **4a** and **4b** obtained are enriched with the *S* enantiomers, which are produced by *re face* attack of hyride. However, the opposite *R* enantiomer is given for **4c**. Itsuno's reagent **6** provides somewhat low optical inductions (13-21.1% *ee*) enriched with the opposite configurations in comparison to those produced by **5**. Mosher's reagent **7** gave

Table 1. Asymmetric Reduction of Iminium Salts 3 with Chiral Reducing Agents

Compound	Chiral reducing agent	Reaction Condition[a]	Products 4[c] Yield[b]	$[\alpha]_D^{23}$ obsd., deg.[d]	% *ee*	Abs. config.[2c]
	5	-78 ℃, 6h	84	20.64(c 2.75)	37.0[e]	S
3a	6	30 ℃, 15h	81	-9.22(c 2.82)	17.0[e]	R
	7	0 ℃, 20h	71	3.50(c 2.83)	6.3[e]	S
	5	-78 ℃, 3h	80	25.67(c 0.26)	43.0[f]	S
3b	6	30 ℃, 15h	71	-7.57(c 0.32)	13.0[f]	R
	7	0 ℃, 18h	74	-9.38(c 0.32)	16.0[f]	R
	5	-78 ℃, 3h	86	-19.62(c 0.18)	25.2[g]	R
3c	6	30 ℃, 15h	79	16.44(c, 0.16)	21.1[g]	S
	7	0 ℃, 18h	69	8.75(c 0.16)	11.2[g]	S

[a]Solvent: CH_2Cl_2-THF(1:1) for both **35** and **6**; CH_2Cl_2-Et_2O(1:1) for **7**. [b]Isolated products, purified by chromatography. [c]Spectral date in N.M.R., I.R. and U.V. for all products were identical with reported values.[1b] [d]In chloroform. [e]Based on $[\alpha]_D^{20}$ 56 (c 2.7, $CHCl_3$); ref. 2c. [f]Base on $[\alpha]_D$ 59 ($CHCL_3$); ref 2c. [g]Based on $[\alpha]_D$ 78.0 ($CHCl_3$); ref. 2c.

very low optical inductions. (6.3-16% *ee*). The results are summarized in Table 1. The following procedure is representive. Acylation of commercially available homoveratrylamine with 3,4-dimethoxyphenylacetylchloride afforded amide **1b** (87%), [m.p. 111-112 ℃ (lit.[1b] 113-114 ℃)], which was then cyclized with $POCl_3$ in toluene at 110 ℃ to cyclic imine **2b** (85%), [m.p. 166-168 ℃(lit.[2c] 171 ℃)]. Conversion of **2b** to iminium salt **3b** was achieved by treatment of excess methyl iodide in acetone. (98%), [m.p. 210-212 ℃(lit.[1b] 211-213 ℃)]. The solution of **3b** (3 mmol) in 9 m*l* of CH_2Cl_2 precooled to -78 ℃ was added to the solution of 5 (3.3 mmol) in 9 m*l* of THF at -78 ℃ via a double-ended needle. The reaction mixture was stirred at -78 ℃. After 3 h, unreacted hydride was quenched by injection anhydrous HCl in Et_2O precooled to -78 ℃. The reaction mixture was warmed to room temperature and treated with 3 m*l* of 6 N HCl for 1 h at 25 ℃. After evaporation of the volatiles under reduced pressure, the mixture was filtered. The filter cake was dessolved in water. The water layer separated was made alkaline with *c*-NH_4OH and extracted with CH_2Cl_2 (3 × 10 m*l*). The extract was dried over anhyrous K_2CO_3 and evaporated to obtain crude **4b**. Column chromatography on silica gel using AcOEt -Et_3N (9:1), followed by recrystrallization from Et_2O afforded **4b**. (yield. 80%), [m.p. 115-117 ℃ (lit.[1b] 117-118 ℃)], $[\alpha]_D^{23}$ 25.67(c 0.26, $CHCl_3$), which represents 43% *ee*, *R*, based on $[\alpha]_D$ 59.0($CHCl_3$).[2c] ^1H NMR ($CDCl_3$): 2.23(s, 3H, N-CH_3), 2.33-3.24(m, 4H, -(CH_2)$_2$) -), 3.60(s, 3H, OCH_3), 3.83(s, 3H, OCH_3), 3.86(s, 3H, OCH_3), 3.90(s, 3H, OCH_3), 4.11(s, 1H, CH-N), 6.63(s, 1H, ArH), 6.78-6.83(m, 3H, ArH).

This study provides the first example for enantioselective synthesis of 1-phenyl-2-methyl-1,2,3,4,-tetrahydroisoquinoline alkaloids. Further investigation for enantioselective synthesis of the other chiral tetrahydroisoquinoline alkaloids *via* asymmetric reduction are currently under way.

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