β-AMINO ALCOHOL-*N*-OXIDES AS PRECURSORS OF CHIRAL OXAZOLIDINES: SYNTHESIS OF (R)-(-)-CRYPTOSTYLINE I

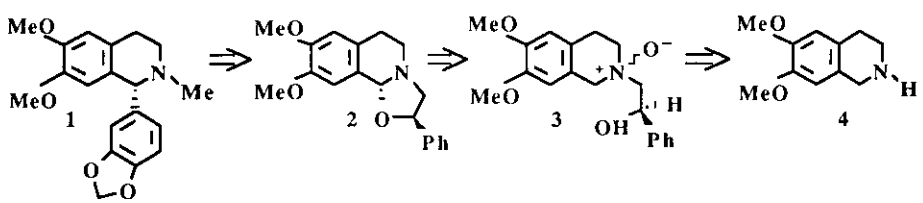
Anny-Claude Carbonnelle, Vincent Gott[a], and Georges Roussi*

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette, France

Abstract-The access to chiral oxazolotetrahydroquinoline by base deprotonation of 6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline-*N*-oxide, allowed the synthesis of (R)-(-)-cryptostyline I.

The efficient methodologies recently proposed for the stereoselective 1-alkylation of tetrahydroisoquinolines cannot be applied to the synthesis of 1-aryl derivatives.[1] These useful intermediates to the related alkaloids,[2] are classically obtained by arylation of immonium salts formed in building the heterocycle.[3] We report here a total synthesis of cryptostyline I (**1**), in which the key step is derived from our previous general method for the chain elongation of secondary amines,[4] involving the non-classical regiospecific formation of the oxazolidine (**2**) by base deprotonation of the β-amino alcohol *N*-oxide (**3**).

In the following retrosynthetic scheme, we postulated that C1 benzylic sites of *N*-oxide (**3**) should be regiospecifically deprotonated by *t*-BuOK as a base, leading to an oxazolidine (**2**) which can be treated with an appropriate aryl Grignard reagent .

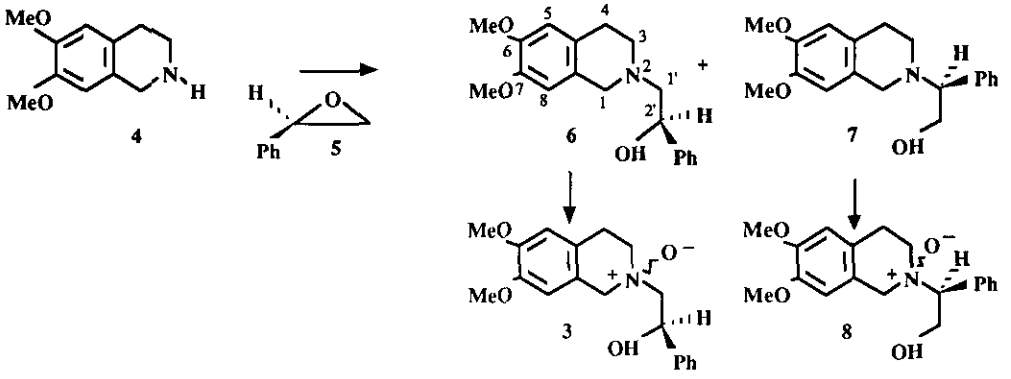


Results and Discussion

The ring opening of R(+)-styrene oxide (**5**) by commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4**), yielded 86% of a 70:30 mixture of the expected (2'R)-β-amino alcohol (**6**) along with its (1'S) isomer (**7**) resulting from addition of the amine to the most substituted carbon atom. The litterature reports that cata-

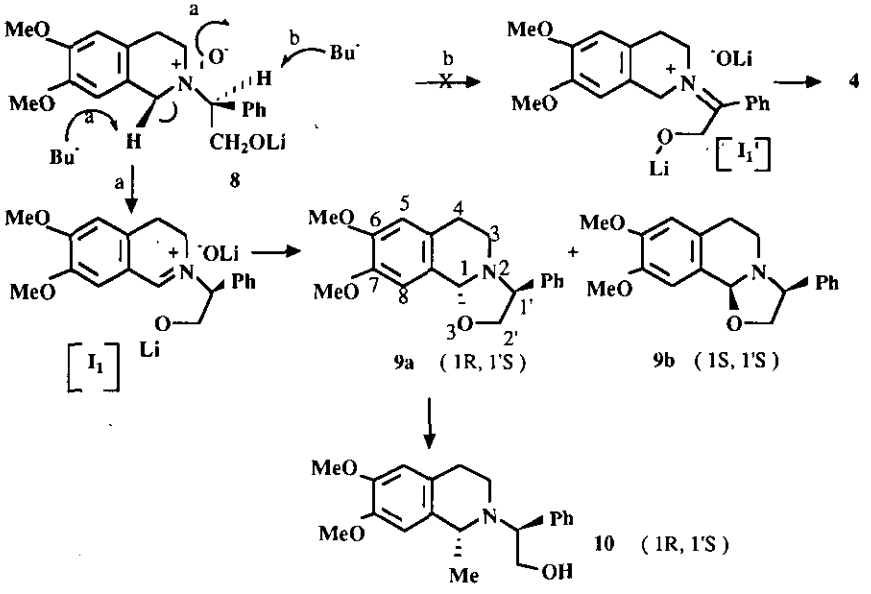
a) V. G. was a summer student in 1991.

lytic amounts of metal ion salts might improve the regioselectivity of the aminolysis,[5] but we made no attempt of that sort to favor the formation of **6**. The easy separation of each amino alcohol (**6**) and (**7**) by chromatography and their further oxidation gave quantitatively the corresponding *N*-oxides (**3**) and (**8**) as a mixture of cis and trans isomers.



Oxazolidine (9) from the *N*-oxide (8).

Prior to the synthesis of **1**, the amine oxide (**8**) was used as a model, to gain information on the deprotonation



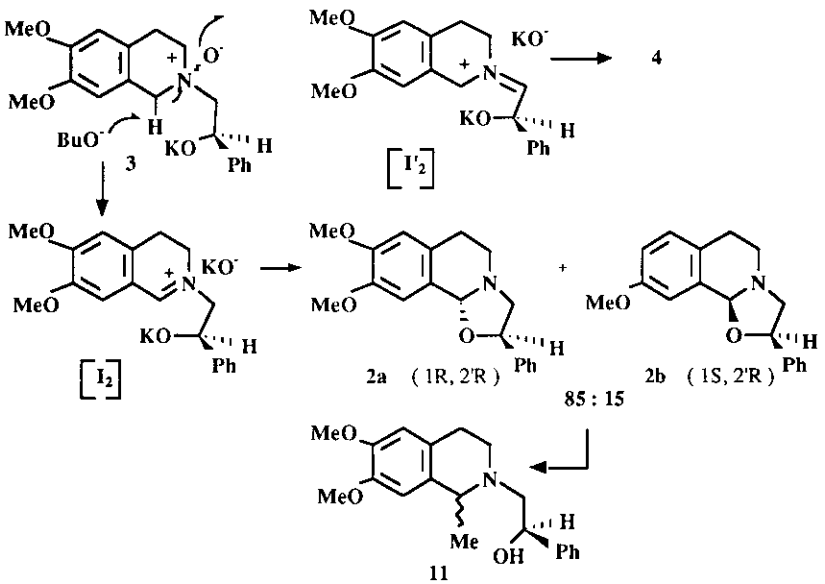
reaction to be carried out on **3** on the way to the target molecule cryptostyline I (**1**). The deprotonation occurred regiospecifically on C1 atom (path a), as proved by the fact that no 6, 7-dimethoxy-1, 2, 3, 4-tetrahydro-isoquinoline (**4**), resulting from the immonium salt [**I'1**] intermediate (path b), was recovered. Moreover, the substitution on C1' caused steric hindrance on carbon C1, as shown by the lack of reactivity of *t*-BuOK on the *N*-oxide (**8**), only deprotonated by the less crowdy BuLi. The oxazolidine (**9**) was formed as a mixture of diastereomers. An important observation was that the cyclisation was strongly dependent upon temperature. It

became stereospecific at 25°C.

The absolute configuration of the resulting oxazolidine (**9a**) was deduced to be (1R, 1'S) from Yamato's results who demonstrated that ring opening of the oxazolidine (**9**) with methylmagnesium iodide occurs with retention of configuration.[3a]

Access to (R)-(-)-cryptostyline I (1)

The above results gave support to our retrosynthetic scheme. As anticipated, the *N*-oxide (**3**) was regiospecifically deprotonated by simple heating at 60°C with *t*-BuOK. The phenyl group on C'2 carbon atom exerted no steric effect and the reaction led, *via* the potassium salt [**I2**] to a thermodynamic mixture of diasteromeric oxazolidines (**2**) in a 85:15 ratio, independent of the starting *N*-oxide (**3**) geometry. Such an im-

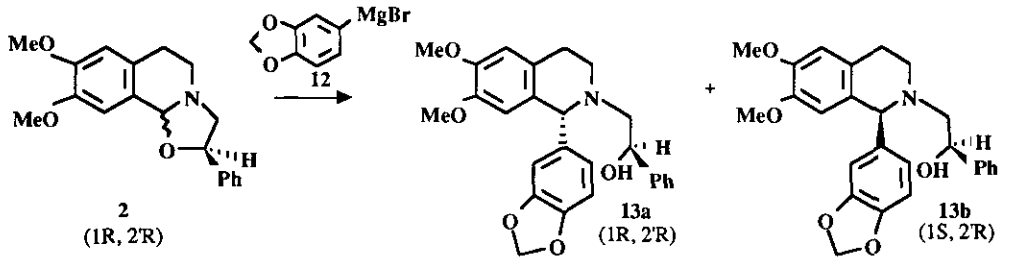


monium ion could conceivably be generated by treating the *N*-oxide (**3**) under modified Polonovski reaction (trifluoroacetic anhydride).[6] This reaction was not regioselective, the 6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline (**4**) resulting from **I'2** being formed along with the mixure of expected oxazolidines (**2**).

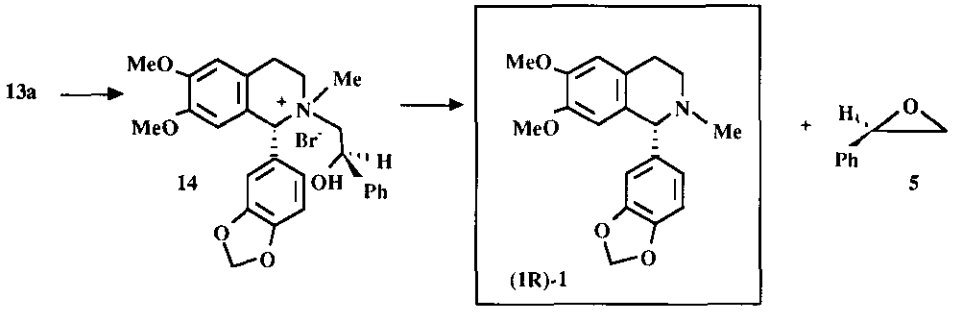
By analogy with the results obtained with compound (**8**) it was presumed that the major diastereomer (**2a**) is of (R) configuration at C1. The stereoselective ring opening of the mixture of 2' substituted oxazolidines (**2**) by methylmagnesium iodide was very poor as compared to that of **9** bearing a substituent on carbon C1', and the expected 1-methylated β-amino alcohol (**11**) was obtained, whatever the experimental conditions, as a mixture of unseparated diasteromers in a 60:40 ratio. The arylation was performed by treating the oxazolidine (**2**) with 1, 2-methylenedioxyphenylmagnesium bromide (**12**) as nucleophile. The arylated terahydroisoquinolines (**13**) were obtained in high yields as a 75:25 mixture of diastereomers, and it was assumed that the ring opening by Grignard reagents occurred with retention of configuration at C1 as in the case of **9a**. The resulting configuration of the major diastereomer (**13a**) is then (**1R, 2'R**). Pure **13a** and **13b** were obtained by column chromatography.

The cleavage of the phenylethanol chain and the methylation, achieved from **13a** in a "one pot" sequence *via*

the quaternary ammonium salt (**14**) according to our previously described method,[7] led to cryptostyline I (**1**)



and to the recovery of the chiral auxiliary styrene oxide (**5**). The sign and the value of the optical rotation were in accordance with the (1R) predicted configuration.[8]



An enriched mixture of the naturally occurring S-(+)-compound (**1**) was obtained when the reaction was run on the minor diastereomer (**13b**) contaminated with **13a**.

The proposed method for the enantioselective arylation of tetrahydroisoquinoline, illustrated by the synthesis of R-(-)- cryptostyline I (**1**), could be easily extended to other secondary amines.

EXPERIMENTAL SECTION

General. Low resolution mass spectra (ms) were obtained on a AEI-MS-50 spectrometer, chemical ionisation mass spectra (CIms) on a AEI-MS-9 spectrometer. ^{1}H Nmr and ^{13}C nmr spectra were recorded in $CDCl_3$ on a Bruker WP 200-54 (200 MHz). Chemical shifts from TMS are given in δ. Purifications were achieved by column chromatography or preparative thin layer chromatography (tlc, elution).

(2'R)-6,7-Dimethoxy-2-2'-hydroxy-2'-phenylethyl-1,2,3,4-tetrahydroisoquinoline (6) and (1'S)-6,7-dimethoxy-2-2'-hydroxy-1'-phenylethyl -1,2,3,4-tetrahydroisoquinoline (7).

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4**) (2.20 g, 11.4 mmol) in anhydrous methanol (30 ml) was treated at 100°C for 20 h in a pressure bottle in the presence of (R)-styrene oxide (**5**) (1.37 g, 11.4 mmol). Usual work up yielded a mixture of **6** and **7** (3.07 g, 86%) in 70:30 ratio. They were separated on column chromatography on alumina (heptane/AcOEt 80:20).

(**6**) ^{1}H Nmr δ 2.55-3.03 (m, 5H), 3.56-3.64 (d, J_{gem}= 13 Hz, 1H), 3.70-3.85 (d, J_{gem}= 13 Hz, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 4.70-4.84 (dd, J = 9, 5 Hz, 1H), 6.45 (s, 1H), 6.55 (s, 1H), 7.12-7.48 (m, 5H); ^{13}C nmr δ 28.68, 51.02, 55.45, 55.47, 56.03, 65.97, 69.17, 109.56, 111.58, 126.08, 126.23, 126.93, 127.57, 128.11, 142.22, 147.01; CIms MH^+ 314, 206, 107; mp 98°C (EtOH). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.81; H, 7.42;

N, 4.47. Found: C, 72.45; H, 7.18; N, 4.45.

(**7**) ^{1}H Nmr δ 2.78-2.83 (m, 2H), 2.45-2.60 (m, 1H), 2.88-3.05 (m, 1H), 3.50-3.59 (d, J_{gem} = 14 Hz, 1H), 3.65-3.73 (d, J_{gem} = 14 Hz, 1H), 3.70-3.87 (m, 2H), 3.76 (s, 3H), 3.81 (s, 3H), 4.01-4.09 (m, 1H), 6.50 (s, 1H), 6.57 (s, 1H), 7.26-7.37 (m, 5H); ^{13}C nmr δ 29.25, 47.00, 51.94, 55.44, 56.03, 60.88, 69.86, 109,71, 111.56, 126.20, 126.66, 128.93, 129.01, 129.30, 136.27, 147.40; CIms, MH^+ 314.

(2'R)-6,7-Dimethoxy-2-2'-hydroxy-2'-phenylethyl -1,2,3,4-tetrahydroisoquinoline *N*-oxides (3).

Compound (**6**) (700 mg, 2.24 mmol) in CH_2Cl_2 (30 ml) was treated at 0°C for 1 h with 80% *m*-chloroperbenzoic acid (600 mg, 2.80 mmol). Usual acidic and basic extraction with CH_2Cl_2 yielded the *N*-oxide (**3**) (720 mg, 98%), as a mixture of two isomers (**3a/3b** = 50:50) which were separated on a small scale by preparative thin layer chromatography on silica gel (CH_2Cl_2 /MeOH 90:10). For the preparation of oxazolidines (**2**), *N*-oxide (**3**) was used without separation of isomers.

(**3a**) ^{1}H Nmr δ 2.95-3.20 (m, 1H), 3.20-3.55 (m, 3H), 3.65-4.15 (m, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 4.26-4.42 (d, J_{gem} = 16 Hz, 1H), 4.43-4.59 (d, J_{gem} = 16 Hz, 1H) 5.25-5.40 (dd, J= 10, 2 Hz, 2H), 6.44 (s, 1H), 6.68 (s, 1H), 7.27-7.43 (m, 5H); ^{13}C nmr δ 26.52, 56.09, 61.30, 68.17, 70.10, 71.80, 109.42, 111.20, 120.71, 121.68, 126.27, 128.16, 128.66, 140.80, 149.22, 148.64; CIms, MH^+ 330, 314.

(**3b**) ^{1}H Nmr δ 2.85-3.05 (m, 1H), 3.25-3.53 (m, 3H), 3.53-3.70 (m, 2H), 3.89 (s, 3H), 3.92 (s, 3H), 4.72 (br s, 2H), 5.42-5.48 (dd, J = 10, 3 Hz, 2H), 6.64 (s, 1H), 6.69 (s, 1H), 7.28-7.43 (m, 5H); ^{13}C nmr δ 25.26, 56.17, 66.05, 66.33, 77.15, 77.47, 109.62, 111.36, 120.40, 122.53, 126.41, 128.24, 128.75, 140.90; FABms m/z 314, 296, 206.

(1'S)-6,7-Dimethoxy-2-2'-hydroxy-1'-phenylethyl-1,2,3,4-tetrahydroisoquinoline *N*-oxides (8).

Amino alcohol (**7**) (300 mg, 0.96 mmol) in CH_2Cl_2 (10 ml) was treated at 0°C for 1 h with 80% *m*-chloroperbenzoic acid (250 mg, 1.16 mmol). Usual acidic and basic extraction with CH_2Cl_2 yielded *N*-oxide (**8**) (302 mg, 95%), as a mixture of isomers (**8a/8b** = 70:30 as determined by ^{1}H nmr analysis) which could not be separated owing to their lability on preparative tlc.

(**8a**) (major compound) ^{1}H Nmr δ 2.60-2.85 (m, 1H), 3.10-3.40 (m, 1H), 3.45-3.90 (m, 6H), 3.80 (s, 3H), 3.82 (s, 3H), 4.09-4.9 (m, 5H), 6.48 (s, 1H), 6.65 (s, 1H), 7.32-7.49 (m, 5H); FABms m/z 329, 314, 282, 252, 206, 192, 165.

8b (minor compound) was evidenced by the presence of a singlet at 6.45 ppm.

(3S, 9bR)- and (3S, 9bS) -7,8-Dimethoxy-3-phenyl-3a*H*-2,3-dihydro-9b*H*-oxazolo [2,3-*a*] isoquinolines (9a and 9b). Freshly dried *N*-oxide (**8**) (200 mg, 0.61 mmol) in anhydrous THF (6 ml) was treated with BuLi in THF (2 mmol) at 0°C and the reaction allowed to reach to room temperature. After 5 h, hydrolysis and usual work up yielded quantitatively compound (**9a**) which was used without further purification.

(**9a**) ^{1}H Nmr δ 2.62-2.82 (m, 2H), 2.82-3.12 (m, 2H), 3.62-3.78 (m, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 4.25-4.35 (m, 1H), 4.42-4.55 (t, 1H), 5.41 (s, 1H), 6.63 (s, 1H), 6.87 (s, 1H), 7.22-7.45 (m, 5H); CIms MH^+ 312, 192, 121.

When the experiment was run at -78°C, a mixture of **9a/9b** = 0.8 was obtained while, at 0°C, the ratio was equal to 3.3.

The diastereomer (**9b**) was characterized by the presence of a singlet at 5.27 ppm in the ^{1}H nmr spectrum of the crude product.

(1R,1'S)-6,7-Dimethoxy-2-2'-hydroxy-1'-phenylethyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (10).
Oxazolidine (**9a**), (190 mg, 0.61 mmol) in anhydrous THF (15 ml) was added to methylmagnesium iodide in THF (3 mmol) at -78°C for 2 h. Usual work up and chromatography on alumina (hexane/AcOEt 30:60) yielded **10** as an oil (176 mg, 88%). ^{1}H Nmr δ 1.22-1.34 (d, J = 7 Hz, 3H), 2.25 (s, 1H), 2.40-3.30 (m, 4H), 3.60-4.32 (m, 4H), 3.80 (s, 3H), 3.85 (s, 3H), 6.42 (s, 1H), 6.56 (s, 1H), 7.20-7.49 (m, 5H); CIms MH$^+$ 328, 312, 242, 206.

(2R, 9bR)- and (2R,9bS)-7,8-Dimethoxy-2-phenyl-3a*H*-2,3-dihydro-9b*H*-oxazolo [2,3-*a*] isoquinolines (2a and 2b).
The isomeric mixture of *N*-oxides (**3**) (730 mg, 2.20 mmol) in *t*-BuOH (90 ml) were treated at 60°C for 3 h in the presence of freshly sublimated *t*-BuOK (1.60 g, 14 mmol). Usual work up yielded **2** (550 mg, 80%) as a mixture of isomers (**2a/2b** =84/16) as deduced by ^{1}H nmr.
(**2a**). ^{1}H Nmr δ 2.58-2.85 (m, 1H), 2.95-3.20 (m, 3H), 3.28-3.43 (m, 1H), 3.58-3.67 (m, 1H), 3.91 (s, 3H), 3.94 (s, 3H), 5.00-5.18 (dd, J = 6.6, 6.6 Hz, 2H), 5.65 (s, 1H), 6.70 (s, 1H), 6.95 (s, 1H), 7.34-7.58 (m, 5H); ^{13}C nmr δ 29.33, 46.06, 56.01, 56.10, 64.09, 74.92, 91.67, 110.83, 111.34, 124.29, 125.84, 126.70, 127.52, 128.66, 146.30; FABms m/z 312, 282, 190, 131.
(**2b**). It was evidenced in the mixture by the presence of a singlet at 5.41 ppm and signals in ^{13}C nmr spectrum: 29.32, 47.79, 62.43, 91.16.

6,7-Dimethoxy-2-2'-hydroxy-2'-phenylethyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (11).
Oxazolidine (**2**) (140 mg, 0.4 mmol) in anhydrous THF (10 ml) was added to methylmagnesium iodide (0.5 mmol) in THF (10 ml) at -78°C for 4 h. Usual work up and preparative tlc on silica gel (CH_2Cl_2/MeOH 90:10) yielded **11** as a mixture of diasteromers (**11a/11b** = 60:40), (103 mg, 78%).
(**11a**) ^{1}H Nmr δ 1.33-1.40 (d, J = 7 Hz, 3H), 2.45-3.01 (m, 5H), 3.05-3.30 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.85-4.01 (q, J = 7 Hz, 1H), 4.72-4.82 (t, J = 10 Hz, 2H), 6.50 (s, 1H), 6.58 (s, 1H), 7.30-7.37 (m, 5H).
11b was characterized in the spectrum of the mixture as a doublet (J = 8 Hz) between 1.40-1.48 ppm and a triplet (J = 10 Hz) between 4.70-4.78 ppm; ^{13}C nmr of the mixture δ 19.90-21.04, 26.75-26.86, 56.00-56.13, 56.57-57.22, 62.29, 69.05-69.35, 110.28, 110.47, 111.47-111.61, 125.92-128.42; CIms MH$^+$ 328, 220, 214.

(1R, 2'R)-6,7-Dimethoxy-2-2'-hydroxy-2'-phenylethyl-1-(1,2-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (13a) and (1S, 2'R)-6,7-dimethoxy-2-2'-hydroxy-2'-phenylethyl-1-(1,2-methylenedioxyphenyl)-1,2,3,4-tetrahydroisoquinoline (13b).
Oxazolidine (**2**), (130 mg, 0.42 mmol) in ahydrous THF (10 ml) was added to 1,2-methylenedioxyphenylmagnesium bromide (**12**) (3 mmol) in THF (5ml) at -78°C for 2 h. Usual work up yielded **13**, as a mixture of diastereoisomers in 75:25 ratio (140 mg; 0.32 mmol, 78%) which were separated by preparative tlc (heptane/CH_2Cl_2 98:12 saturated with NH_4OH).
(**13a**) ^{1}H Nmr δ 2.50-2.78 (m, 3H), 2.84-2.88 (m, 1H), 2.95-3.11 (m, 1H), 3.34-3.44 (m, 1H), 3.63 (s, 3H), 3.86 (s, 3H), 4.50 (s, 1H), 4.77-4.84 (dd, J =10, 4 Hz, 1H), 5.95-5.97 (br s, 2H), 6.18 (s, 1H), 6.61 (s, 1H), 6.68-6.77 (m, 3H), 7.19-7.33 (m, 5H); ^{13}C nmr δ 28.38, 46.99, 56.02, 61.96, 68.38, 69.14, 101.17, 107.80, 109.44, 111.02, 111.88, 123.16, 126.05, 126.69, 127.56, 128.39, 129.85, 137.66, 142.25, 147.15, 147.45, 147.88, 148.16; CIms MH$^+$ 434, 416, 326, $[\alpha]_D$=-66.5° (c, 0.23, EtOH).
(**13b**) ^{1}H Nmr δ 2.50-3.25 (m, 6H), 3.73 (s, 3H), 3.90 (s, 3H), 4.55-4.65 (dd, J = 10, 4 Hz, 1H), 4.80 (s, 1H),

5.95-5.99 (br s, 2H), 6.34 (s, 1H), 6.66 (s, 1H), 6.70-7.00 (m, 3H), 7.26-7.37 (m, 5H); CIms MH^+ 434, 416, 326, 107.

(R)-(-) Cryptostyline I (1).

13a, (40 mg, 0.09 mmol) in methanol (3 ml) reacted with $NaHCO_3$ (10 mg, 0.12 mmol) and methyl iodide (52 mg, 0.37 mmol) at room temperature for 16 h. After distillation of methanol, *t*-BuOK (100 mg, 0.89 mmol) was added in *t*-BuOH (3 ml) and the mixture was heated at 60°C for 4 h. Usual work up and preparative tlc on silica gel (CH_2Cl_2/MeOH 95:5) yielded **1** as white cristals (18 mg, 60%) and styrene oxide (**5**) (4 mg, 37%).

(**1**) ^1H Nmr δ 2.26 (s, 3H), 2.55-2.82 (m, 2H), 3.06-3.28 (m, 2H), 9.63 (s, 3H), 3.87 (s, 3H), 4.12 (s, 1H), 5.96 (s, 2H), 6.17 (s, 1H), 6.61 (s, 1H), 6.70-6.77 (m, 3H); CIms MH^+ 328, 204, 146, mp 99-100°C (ether), $[\alpha]_D$= -54° (c 0.23 in $CHCl_3$); lit.,[8] mp 101-102°C (ether); $[\alpha]_D$ = +56° (c 2.7 in $CHCl_3$).

REFERENCES

1. A. I. Meyers, J. S. Warmus, M. Gonzales, J. Guiles, and A. Akahane, , Tetrahedron Lett., **1991**, 32, 5509; R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, and H. Takaya, J. Amer. Chem. Soc., **1986**, 108, 7117; R. P. Polniazsek and J. A. Mckee, Tetrahedron Lett.,**1987**, 28, 4511; I. M. P. Huber and D. Seebach, Helv. Chim. Acta, **1987**, 70, 1944.
2. J. Lundstrôm, "The Alkaloids," Vol. 21, ed. by A. Brossi, Academic Press Inc., New York, **1983**, p. 255.
3. a) M. Yamato, K. Hashigaki, N. Qais, and S. Ishikawa, Tetrahedron, **1990**, 46, 5909; b) R. P. Polniazsek and L.W. Dillard, Tetrahedron Lett., **1990**, 31, 797.
4. G. Roussi and J. Zhang, Tetrahedron Lett., **1991**, 32, 1443.
5. M. Chini, P. Crotti, and F. Macchia, J. Org. Chem., **1991**, 56, 5939.
6. A. Ahond, A. Cavé, C. Kan-Fan, and P. Potier, Bull. Soc. Chim. Fr, **1970**, 2707.
7. G. Roussi and J. Zhang, Tetrahedron, **1991**, 47, 5161.
8. A. Brossi and S. Teitel, Helv. Chim. Acta, **1971**, 54, 1564.

Received, 6th January, 1993