

A FACILE SYNTHESIS OF 4-ARYL-1,2,3,4-TETRAHYDROISOQUINOLINES:
A TOTAL SYNTHESIS OF (±)-CHERYLLINE

Hiroshi Hara, Ryuichi Shirai, Osamu Hoshino, and Bunsuke
Umezawa*

Faculty of Pharmaceutical Sciences, Science University of Tokyo
Shinjuku-ku, Tokyo, 162, Japan

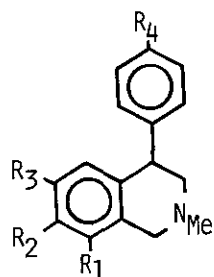
Abstract --- Reaction of benzylamines (3a-d) and styrene oxide at 140°C gave quantitatively β-hydroxyphenethylamine (2a-d), acid treatment of which afforded 4-aryl-1,2,3,4-tetrahydroisoquinolines (8a-d) in high yields. On the other hand, the styrene oxide (10 or 15) was treated with BF₃-Et₂O in MeOH yielding regioselectively a β-methoxyphenethyl alcohol (12 or 16), the mesylate of which reacted with the benzylamine (3e) in the presence of Hünig's base to give the N-benzyl-β-methoxyphenethylamine (2f or 2g). Acid treatment of 2f or 2g afforded (±)-cherylline (1) or (±)-4'-O-methylcherylline (14) in 85 or 67% overall yield from O-benzylisovanillin.

Synthetic studies on aryl-1,2,3,4-tetrahydroisoquinolines have attracted much attention owing to the potential biological activities.^{1,2)} Among others, the basic skeleton of a natural alkaloid, (-)-cherylline (1) being 4-aryl-1,2,3,4-tetrahydroisoquinoline, its synthesis has long been a fascinating target for many organic chemist.²⁾

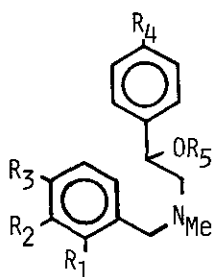
We considered that the key intermediate, N-benzyl-β-hydroxyphenethylamine derivatives (2), chosen by both Schwartz^{2c)} and Kametani^{2d)} was also suitable for our synthesis and decided to improve the preparation.

Here we wish to report a new methodology for the formation of 2 using a S_N2 reaction of amines (3)³⁾ with styrene oxides and an efficient synthesis of (±)-cherylline (1).

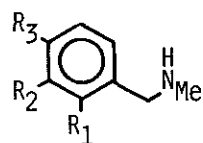
Heating the styrene oxide (4) and benzylmethylenamines (3a-d) at 140°C gave regioselective



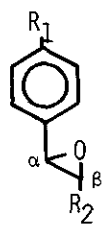
	R ₁	R ₂	R ₃	R ₄
<u>1</u>	H	OH	OMe	OH
<u>8a</u>	H	OH	OMe	H
<u>8b</u>	H	OCH ₂ O		H
<u>8c</u>	OH	OMe	H	H
<u>8d</u>	H	OMe	OH	H
<u>14</u>	H	OH	OMe	OMe



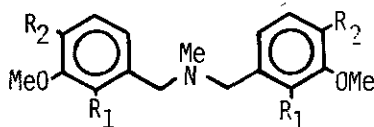
	R ₁	R ₂	R ₃	R ₄	R ₅
<u>2a</u>	H	OH	OMe	H	H
<u>2b</u>	H	OCH ₂ O		H	H
<u>2c</u>	OBz	OMe	H	H	H
<u>2d</u>	H	OMe	OBz	H	H
<u>2e</u>	H	OH	OMe	OBz	H
<u>2f</u>	H	OBz	OMe	OBz	Me
<u>2g</u>	H	OBz	OMe	OMe	Me



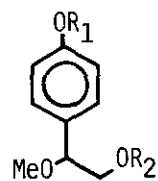
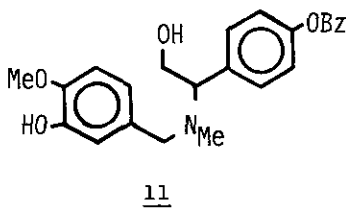
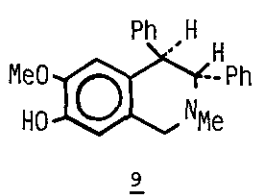
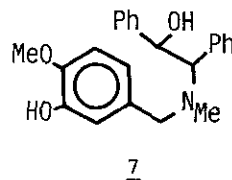
	R ₁	R ₂	R ₃
<u>3a</u>	H	OH	OMe
<u>3b</u>	H	OCH ₂ O	
<u>3c</u>	OBz	OMe	H
<u>3d</u>	H	OMe	OBz
<u>3e</u>	H	OBz	OMe
<u>3f</u>	OH	OMe	H
<u>3g</u>	H	OMe	OH



	R ₁	R ₂
<u>4</u>	H	H
<u>10</u>	OBz	H
<u>15</u>	OMe	H
<u>17</u>	H	Ph



	R ₁	R ₂
<u>5</u>	OH	H
<u>6</u>	H	OH



	R ₁	R ₂
<u>12</u>	OBz	H
<u>13</u>	OBz	Ms
<u>16</u>	OMe	H
<u>18</u>	OMe	Ms

BZ = CH₂Ph

ectively the desired N-benzyl-8-hydroxyphenethylamines (2a-d) in excellent yields, respectively (Table II). However, *o*-vanillyl-(3f) or vanillyl-methylamine (3g) was easily transformed to the dibenzylamine (5 or 6) at the reaction temperature, undoubtedly via *o*- or *p*-quinone methide. In such cases, the phenolic hydroxyl group was protected before use. Structures of products (2a-d) were determined on the basis of proton NMR spectra, i.e. double doublets of one proton around δ 4.73 were reasonably assigned to the phenyl carbinol methine proton (see Table II).⁴⁾ The reaction of 3a and stilbene oxide also afforded an amino alcohol (7), quantitatively. Without purification, 2a and 7 were cyclized into 4-phenyl-1,2,3,4-tetrahydroisoquinolines (8a and 9) by acid treatment, respectively. The cyclization proceeded smoothly at room temperature and 80% (w/w) sulfuric acid was the choice of acid. However, treatment of 2c or 2d with 80% H₂SO₄ gave rise to an intractable mixture of products probably as a result of the rearrangement of the benzyl group. In such cases, debenzylation procedure by refluxing for 1 h with conc. HCl-benzene was necessary prior to cyclization. Since the methylenedioxy group was sensitive to 80% H₂SO₄, reaction conditions were checked thoroughly as shown in Table III. Thus, 75% H₂SO₄ was found to be the best.

Structure of products (8a-d) was clearly determined by proton NMR spectra. Namely, in all compounds signals of two aromatic protons except phenyl protons and of C-4 proton (around δ 4.16) were appeared. The latter signal showed typical pattern of C-4 axial proton coupled with C-3 methylene protons. On the other hand, 3,4-diphenyl groups of 9 were *trans* oriented as shown by the coupling constant ($J=9$ Hz) between a pair of protons at C-3 and C-4 positions.

Next, we decided to apply the above method in order to synthesize (\pm)-cherylline (1). *p*-Benzyloxystyrene oxide (10) was quantitatively prepared from *p*-benzyloxybenzaldehyde by use of Kutsuma's method.⁵⁾ The reaction between 3a and 10 was attempted to give non-regioselectively a mixture of the *p*-benzyloxyphenethylamine (2e) and the dibenzylamine (11) in a ratio of 1:1. The fission between the α -carbon and the oxygen atoms was facilitated by an electron donating group at the *para* position.

To overcome the difficulty a by-pass was sought. Thus, treatment of the epoxide (10) with BF₃-Et₂O in MeOH at room temperature afforded solely the β -methoxyphenethyl alcohol (12) in an excellent yield.⁶⁾ Usual mesylation of 12 quantitatively gave the mesylate (13). The reaction of the benzylmethylamine (3e) with 13 proceeded nicely. Namely, heating of 3e and 13 together with Hünig's base in a seal-

Table I. Mp and Yield of Benzylmethylamines

	Mp(°C) and Recrystallizing solvent	Yield (%)
<u>3a</u>	142-144° (benzene), lit. ^{2e)} 142-143°	86
<u>3b</u>	191-193°* (iso-PrOH), lit. ⁸⁾ 194°	97
<u>3c</u>	145.5-146.5°* (iso-PrOH)	100
<u>3d</u>	172-173°* (iso-PrOH-ether)	94
<u>3e</u>	210-212°* (MeOH), lit. ⁹⁾ 209-211°	97
<u>3f</u>	92-94° (benzene-n-hexane)	97
<u>3g</u>	113-114° (benzene)	33

*Melting point of HCl salt.

Table II. Preparation of N-Benzyl- β -hydroxyphenethylamine derivatives

Starting material	Amine	Product	Yield (%)	NMR data of ArCH(OR)-	Reaction time (hr)
<u>4</u>	<u>3a</u>	<u>2a</u>	96	δ 4.69 (dd, J=5, 8 Hz)	1
<u>4</u>	<u>3b</u>	<u>2b</u>	94	δ 4.64 (dd, J=6, 8 Hz)	1
<u>4</u>	<u>3c</u>	<u>2c</u>	100	δ 4.58 (dd, J=6, 7 Hz)	1
<u>4</u>	<u>3d</u>	<u>2d</u>	100	δ 4.87 (dd, J=6, 7 Hz)	1
<u>17</u>	<u>3a</u>	<u>7</u>	100	δ 5.27 (d, J=6 Hz)	1
<u>13</u>	<u>3e</u>	<u>2f</u>	100	δ 4.18 (dd, J=6, 7 Hz)	24
<u>18</u>	<u>3e</u>	<u>2g</u>	100	δ 4.17 (dd, J=5, 7 Hz)	24

Table III. Preparation of 4-Aryl-1,2,3,4-tetrahydroisoquinolines

Starting material	Reaction condition*	Product	Mp(°C)	Yield (%)	NMR data of C-4 proton
<u>2a</u>	A	<u>8a</u>	161-162° (benzene)	89	δ 4.18 (dd, J=6, 8 Hz)
<u>7</u>	A	<u>9</u>	138-139° (iso-PrOH)	93	δ 3.33 [§] (d, J=9 Hz)
<u>2c</u>	B	<u>8c</u>	147-149° (iso-PrOH)	90	δ 4.19 (dd, J=6, 9 Hz)
<u>2d</u>	B	<u>8d</u>	183.5-184.5° (EtOH)	87	δ 4.13 (dd, J=6, 9 Hz)
<u>2b</u>	A	<u>8b</u>	237-239°	15	
<u>2b</u>	C	<u>8b</u>	(HCl salt)	13	δ 4.13 (dd, J=6, 8 Hz)
<u>2b</u>	D	<u>8b</u>	(iso-PrOH)	44	
<u>2b</u>	E	<u>8b</u>		61	
<u>2f</u>	F	<u>1</u>	208-211°	85	δ 4.01 [¶] (dd, J=6, 8 Hz)
<u>2g</u>	G	<u>14</u>	131-133°	67	δ 4.12 (dd, J=5, 7 Hz)

*A: 80% H₂SO₄, r.t., 1 h; B: i) conc.HCl-benzene, reflux, 1 h, ii) 80% H₂SO₄, r.t., 1 h; C: 70% H₂SO₄, r.t., 1 h; D: 75% H₂SO₄, r.t., 1 h; E: 75% H₂SO₄, r.t., 3 h; F: conc.HCl-benzene, reflux, 5 h; G: conc.HCl-benzene, reflux, 3 h.

[§]C-3 proton; [¶]In d₆-acetone

ed tube at 120°C for 24 h gave the expected β -methoxyphenethylamine (2f), mp 85-87°C (lit.^{2d}) 90-91°C), quantitatively. Finally, refluxing of 2f with conc. HCl-benzene for 5 h gave (\pm)-cherylline (1),⁷⁾ mp 208-211°C (lit.^{2e}) 209-211°C), in 85% yield. The overall yield from benzylisovanillin was 82%. Similarly, 4'-O-methylcherylline (14), mp 131-133°C (lit.^{2e}) 129-130°C), was prepared through the same route as above from p-methoxystyrene oxide (15) and the benzylmethylamine (3e) in a high yield.

Conclusively, we could establish a facile and general synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines by employment of styrene oxide as a crucial synthon.

ACKNOWLEDGEMENT The authors are indebted to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind supply of the starting material. Thanks are also due to Prof. H. Takayama of Teikyo University for NMR spectrum of (\pm)-cherylline, Mr. K. Satoh for his technical assistance, to Sankyo Co., Ltd. for elemental analyses, and to Miss N. Sawabe of this Faculty for NMR spectral measurements.

REFERENCES AND NOTES

1. a) Y. Ahmad and D. H. Hey, J. Chem. Soc., 1961, 3882; b) J. Sam, R. M. Shafik, and K. Aparajithan, J. Pharm. Sci., 1970, 59, 59; c) J. M. Bobbitt and S. Shibusya, J. Org. Chem., 1970, 35, 1181; d) D. L. Trepanier and S. Sunder, J. Med. Chem., 1973, 16, 342; e) M. Iorio, A. Brossi, and C. F. Chignell, Heterocycles, 1978, 9, 1; f) C. R. Ellefson, J. Org. Chem., 1979, 44, 1533; g) L. K. Dyll and C. J. Pullin, Aust. J. Chem., 1979, 32, 345; h) L. N. Pridgen, J. Heterocyclic Chem., 1980, 17, 1289; i) W. L. Mendelson, C. B. Spainhour, jr., S. S. Jones, B. L. Lam, and K. L. Wert, Tetrahedron Lett., 1980, 21, 1393; j) G. Bobowski and J. M. Gottlieb, J. Heterocyclic Chem., 1982, 19, 21; k) L. N. Pridgen, L. B. Killmer, and R. L. Webb, J. Org. Chem., 1982, 47, 1985; l) O. R. Andresen and E. B. Pedersen, Heterocycles, 1982, 19, 1467; m) H. Hara, O. Hoshino, and B. Umezawa, Chem. Pharm. Bull., 1983, 31, 730.
2. a) A. Brossi, G. Grethe, S. Teitel, W. C. Wildman, and D. T. Baily, J. Org. Chem., 1970, 35, 1100; b) A. Brossi and S. Teitel, J. Org. Chem., 1970, 35, 3559; c) M. A. Schwartz and S. W. Scott, J. Org. Chem., 1971, 36, 1827; d) T. Kame-tani, K. Takahashi, and C. V. Loc, Tetrahedron, 1975, 31, 235; e) D. J. Hart, P. A. Cain, and D. A. Evans, J. Amer. Chem. Soc., 1978, 100, 1548; f) H. Irie,

- A. Shiina, T. Fushimi, J. Katakawa, N. Fujii, and H. Yajima, Chem. Lett., 1980, 875; g) S. V. Kesser, P. Singh, R. Chawla, and P. Kumar, J. Chem. Soc. Chem. Comm., 1981, 1074; h) T. Kametani, K. Higashiyama, T. Honda, and H. Otomasu, J. Chem. Soc. Perkin I, 1982, 2935; i) T. Nomoto, N. Nasui, and H. Takayama, Heterocycles, 1983, 20, 133.
3. Benzylmethyamines (3a-g) were prepared from the corresponding aryl aldehydes in high yields, according to Evans's procedure^{2e)} (Table I).
 4. NMR spectra were taken with a JEOL model JNR-FX 100 or a Hitachi model R-24B in CDCl₃ by using Me₄Si as internal standard.
 5. T. Kutsuma, I. Nagayama, T. Okazaki, T. Sakamoto, and S. Akaboshi, Heterocycles, 1977, 8, 397.
 6. D. Swern, G. N. Biller, and H. B. Knight, J. Amer. Chem. Soc., 1949, 71, 1152.
 7. NMR spectrum of (\pm)-1 was superimposable on that of an authentic (\pm)-cherylline²ⁱ⁾ supplied by Prof. Takayama.
 8. A. Kaufmann and N. Dürst, Chem. Ber., 1917, 50, 1634.
 9. R. F. Borch, M. D. Bernstein, and H. D. Durst, J. Amer. Chem. Soc., 1971, 93, 2897.

Received, 21st June, 1983