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Studies on Tetrahydroisoquinolines. XXV.[1] A Synthesis of 4-Aryl-1,2,3,4-tetrahydroisoquinolines; Total Synthesis of (±)-Cherylline[2]

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Four 4-phenyl-1,2,3,4-tetrahydroisoquinolines (**8b**, **c**, **f**, **g**) were prepared from two simple synthons, styrene oxide and the benzylamines (**2b**—**e**), *via* the β-hydroxyphenethylamines (**3b**—**e**) in high yield. On the other hand, the β-methoxyphenethyl methanesulfonate (**16**), obtained from 4-benzyloxystyrene oxide (**11**), was coupled with the benzylamine (**2a**) to give the *N*-benzyl-β-methoxyphenethylamine (**17**). A facile total synthesis of (±)-cherylline (**1**) was accomplished by acid treatment of **17**. 4′-*O*-Methylcherylline (**18**) was also synthesized through the same pathway.

Keywords——4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinoline; (±)-cherylline; cyclization; styrene oxide; oxirane opening; regioselectivity

In spite of the increasing medicinal interest in 4-aryl-1,2,3,4-tetrahydroisoquinolines,[3] no facile method for their synthesis has been available. We now wish to report a facile synthesis of these compounds, as well as an efficient synthesis of (±)-cherylline (**1**),[4] an Amaryllidaceae alkaloid. The present method consists of two major operations, one being nucleophilic ring opening of styrene oxides with the benzylmethylamines (**2**) and the other being cyclization of the β-hydroxyphenethylamines (**3**) under the acidic conditions.

Since reductive amination of 3-benzyloxy-4-methoxybenzaldehyde (**4a**) with methylamine hydrochloride and sodium cyanoborohydride[5] partially gave the *N*,*N*-dibenzylmethylamine (**5**), Evans' method,[4] *i.e.*, sodium borohydride reduction of the Schiff's base (**6**), was employed for the synthesis of **2**. Yields and spectral data of **2** are listed in Tables I and II.

Heating of **2b**—**e**, with styrene oxide gave **3b**—**e** smoothly in high yields. Reaction of **2b** with *trans*-stilbene oxide analogously gave the expected β-hydroxyphenethylamine (**7**). Yields and proton nuclear magnetic resonance (^{1}H-NMR) data of the products are shown in Table III.

Ring closure of **3b** and **7** was best effected with 80% w/w sulfuric acid at room temperature to give the 1,2,3,4-tetrahydroisoquinolines **8b** and **9**, respectively. However, when a benzyloxy group was present in the molecule, such as in **3d**, **e**, an undesirable reaction, *i.e.* rearrangement of the benzyl group,[6] took place under the above conditions, giving intractable mixtures. In such cases, hydrolysis of the benzyloxy group with conc. hydrochloric acid in benzene prior to cyclization with 80% w/w sulfuric acid could overcome the difficulties, yielding the 1,2,3,4-tetrahydroisoquinolines **8f**, **g**.

Although the methylenedioxy group in **3c** was considerably damaged by 80% w/w sulfuric acid,[7] 75% w/w sulfuric acid could be used to give the 1,2,3,4-tetrahydroisoquinoline (**8c**) in fair yield. Yields and ^{1}H-NMR data of the 4-phenyl-1,2,3,4-tetrahydroisoquinolines **8b**, **c**, **f**, **g** and **9** are shown in Table IV.

TABLE I. Yields and Physical and Spectral Data for **2a**—**g**

	Yield (%)	mp (°C) (Lit.)	Recryst. solvent	NMR (δ)				
				NMe	$ArCH_2N$	OMe	$PhCH_2O$	OCH_2O
2a	97	210—212[a] (209—211)[5]	MeOH	2.36	3.59	3.81	5.08	—
2b	86	142—144 (142—143)[4]	Benzene	2.40	3.63	3.83	—	—
2c	97	191—193[a] (194)[16]	iso-PrOH	2.42	3.64	—	—	5.88
2d	100	144.5—146.5[a]	iso-PrOH	2.31	3.62	3.85	5.21	—
2e	94	172—173[a]	iso-PrOH–ether	2.17	3.63	3.85	5.07	—
2f	97	92—94	Benzene–*n*-hexane	2.41	3.88	3.80	—	—
2g	33	113—114	Benzene	2.23	3.43	3.57	—	—

a) Melting point of the HCl salt.

TABLE II. Analytical Data for **2d**—**g**

	Formula	Analysis (%)					
		Calcd			Found		
		C	H	N	C	H	N
2d	$C_{16}H_{19}NO_2 \cdot HCl$	65.41	6.86	4.77	65.50	6.87	4.76
2e	$C_{16}H_{19}NO_2 \cdot HCl$	65.41	6.86	4.77	65.40	6.84	4.76
2f	$C_9H_{13}NO_2$	64.65	7.84	8.38	64.61	7.85	8.36
2g	$C_9H_{13}NO_2$	64.65	7.84	8.38	64.65	7.75	8.28

TABLE III. Yields and NMR Spectral Data[a] for **3b**—**e** and **7**

	Yield (%)	NMR (δ)					
		NMe	$ArCH_2N$[b]		OMe	$PhCH_2O$	OCH_2O
3b	96	2.25	3.33	3.63	3.76	—	—
3c	94	2.24	3.31	3.61	—	—	5.80
3d	100	2.22	3.37	3.59	3.84	4.98	—
3e	100	2.27	3.36	3.66	3.83	5.06	—
7	100	2.20	3.14	3.53	3.73	—	—

a) These data are obtained for the oily product without purification in each case. *b*) Doublet ($J = 13$ Hz).

This cyclization seemed to occur readily when the leaving hydroxyl group was situated at the benzylic position.[8] In sharp contrast to the quinonoid intermediate reported by Kametani *et al.*,[9] the cyclization undoubtedly proceeded *via* the benzylic cation. Moreover an oxygen function situated *para* to the cyclization site seemed to be a necessary requirement.[10]

The reaction of **2f** with styrene oxide is noteworthy. Namely, the reaction gave a mixture, which was cyclized with 80% w/w sulfuric acid to give *N*,*N*-di(2-hydroxy-3-methoxybenzyl)methylamine (**10**) (31%) along with the expected cyclized product **8f** (21%). Since heating of **2f** gave mainly **10**, the intermediacy of an *o*-quinone methide was presumably re-

TABLE IV. Yields and Physical and Analytical Data for **8b, c, f, g** and **9**

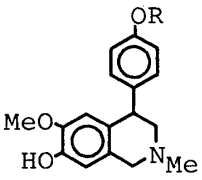
	Reaction time (h)[a]	Yield (%)	mp (°C)	Recryst. solvent	Formula	Analysis (%) Calcd (Found)		
						C	H	N
8b	1.5	89	161—162	Benzene–*n*-hexane	$C_{17}H_{19}NO_2$	75.81 (75.86	7.11 7.15	5.20 5.13)
8c	3	61	237—239[b]	iso-PrOH	$C_{17}H_{17}NO_2 \cdot HCl \cdot 1/4H_2O$	66.23 (66.60	6.04 6.09	4.54 4.55)
8f	3	90	147—149	iso-PrOH	$C_{17}H_{19}NO_2 \cdot 1/6C_3H_8O$	75.23 (75.06	7.34 7.29	5.01 5.02)
8g	6	87	183.5—184.5	MeOH	$C_{17}H_{19}NO_2$	75.81 (75.75	7.11 7.11	5.20 5.22)
9	3	93	138—139	iso-PrOH	$C_{23}H_{23}NO_2$	79.97 (79.99	6.71 6.68	4.05 4.07)

a) With 80 or 75% w/w sulfuric acid. *b*) Melting point of the HCl salt.

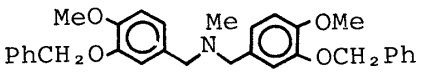
TABLE V. NMR Spectral Data (δ) for **8b, c, f, g** and **9**

	NMe	OMe	C_5-H	C_6-H	C_8-H	Others
8b	2.40	3.63	6.25	—	6.52	4.18 (dd, J=6, 8 Hz, C_4-H)
8c	2.39	—	6.26	—	6.48	4.13 (dd, J=6, 8 Hz, C_4-H), 5.81 (OCH_2O)
8f	2.45	3.82	6.30[a]	6.59[a]	—	4.19 (dd, J=6, 9 Hz, C_4-H)
8g	2.39	3.84	6.33	—	6.48	4.13 (dd, J=6, 9 Hz, C_4-H)
9	2.14	3.60	6.16	—	6.63	3.33 (d, J=9 Hz, C_3-H)

a) Doublet (J=8 Hz).



1 : R=H
18 : R=Me



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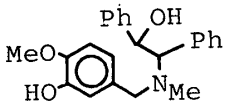

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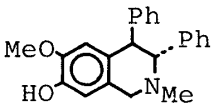

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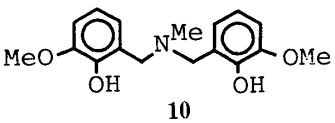

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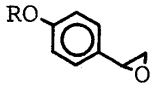
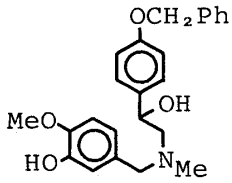


11 : R=CH_2Ph
19 : R=Me



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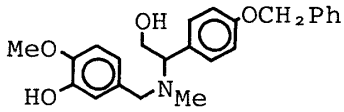

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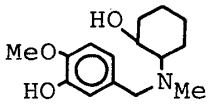

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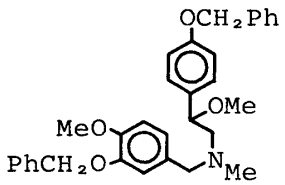

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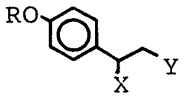
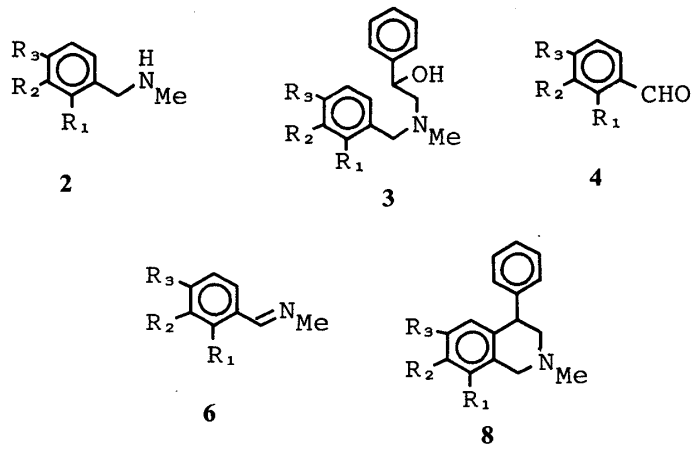


	R	X	Y
14:	CH_2Ph	OMe	Br
15:	CH_2Ph	OMe	OH
16:	CH_2Ph	OMe	OMs
20:	Me	OMe	OH
21:	Me	OMe	OMs

Fig. 1



	R_1	R_2	R_3
a:	H	OCH_2Ph	OMe
b:	H	OH	OMe
c:	H	OCH_2O	
d:	OCH_2Ph	OMe	H
e:	H	OMe	OCH_2Ph
f:	OH	OMe	H
g:	H	OMe	OH

Fig. 2

sponsible for the formation of **10**.

As an application of the present method, (±)-cherylline (**1**) was considered to be an interesting target for synthesis. For this purpose, 4-benzyloxystyrene oxide (**11**) was an indispensable synthon. Thus, **11** was prepared according to the known procedure[11] in good yield. Contrary to our expectation, heating of **2b** with **11** gave a 1 : 1 mixture of **12** and its isomer (**13**), indicating that the favorable regioselectivity of the reaction was lost completely.[12] To circumvent this difficulty, a synthon equivalent to Kametani's compound (**14**)[9] was required. Thus, **11** was first cleaved with methanol in the presence of boron trifluoride etherate to give β-(4-benzyloxyphenyl)-β-methoxyalcohol (**15**), mesylation of which gave β-(4-benzyloxyphenyl)-β-methoxyethyl methanesulfonate (**16**) in good yield. Heating of **2a** with **16** in the presence of Hünig's base gave the desired benzyl-β-methoxyphenethylamine (**17**), which was identical with Kametani's compound,[9] in a reasonable yield. Refluxing of **17** with conc. hydrochloric acid in benzene directly gave **1** (92%), mp 208—211 °C (lit.[4] 209—212 °C), the spectral data of which were identical with those reported by Evans and co-workers.[4] The overall yield from *O*-benzylisovanilline amounted to 82%. An analogous sequence of reactions starting from **2a** and **19** gave (±)-4′-*O*-methylcherylline (**18**), which has already been converted to **1**.[4]

Thus, the usefulness of the present method for the synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines was proved.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken with a JEOL JNX-FX-100 (100 MHz) or Hitachi R-24B instrument in $CDCl_3$ solution with Me_4Si as an internal standard, and infrared (IR) spectra were run on a Hitachi model 260 spectrometer in $CHCl_3$ solution, unless otherwise noted. Preparative thin-layer chromatography (TLC) was performed on precoated Silica gel 60 F_{254} plates (Merck) 2.0 mm thick.

Oxygenated Benzylmethylamines (2a—g)——These amines were prepared according to Evans' procedure.[4] Yields and physical and spectral data are shown in Table I. Analytical data are listed in Table II.

General Procedure for Reaction of 2b—e with Styrene Oxide——A mixture of one of **2b—e** and styrene oxide (1.2 eq) was heated in an oil bath (140 °C) for 1 h. After cooling, the whole was dissolved in 10% NaOH and washed with ether. The aqueous layer was made weakly alkaline by adding NH_4Cl and the product was extracted with $CHCl_3$. Usual work-up of the extract gave the corresponding oily oxygenated *N*-benzyl-*N*-methyl-β-hydroxyphenethylamine (**3b—e**). Reaction of **2b** with *trans*-stilbene oxide was carried out as above, giving *N*-(3-hydroxy-4-methoxybenzyl)-*N*-methyl-β-hydroxy-α-phenylphenethylamine (**7**). Yields and NMR data are shown in Table III.

Intramolecular Cyclization[13]——**3b** and **7**: A solution of the β-hydroxyphenethylmethylamine in 80% w/w H_2SO_4 (17- to 27-fold excess by weight) was stirred for 1.5 to 3 h. The reaction mixture was poured onto crushed ice

and made basic with conc. ammonia. The product was extracted with $CHCl_3$. Usual work-up of the extract gave the desired 4-phenyl-1,2,3,4-tetrahydroisoquinoline.

3c: The cyclization was carried out with 75% w/w H_2SO_4 (49-fold excess by weight, 3 h). To remove the unchanged starting material, the reaction mixture was purified by preparative TLC ($CHCl_3$: MeOH = 10 : 1) after acetylation.

3d and **3e**: Before being subjected to the above cyclization, these compounds were hydrolyzed by boiling with excess conc. HCl in benzene.

Reaction of 2f with Styrene Oxide and Subsequent Acid Treatment——Heating of a mixture of **2f** (1 g, 6 mmol) and styrene oxide (860 mg) in an oil bath (140 °C) for 1 h gave a reaction mixture, which was treated with 80% w/w H_2SO_4 as above. Usual work-up afforded an oily product, which was chromatographed on silica gel (20 g). Elution with $CHCl_3$–MeOH (20 : 1) gave **8f** (331 mg, 21%), mp 130–134 °C (dec.) (iso-PrOH) and *N*,*N*-di(2-hydroxy-3-methoxybenzyl)methylamine (**10**) (277 mg, 31%), mp 86—87 °C (iso-PrOH–H_2O). The latter was also obtainable in 80% yield on heating (bath temperature 140 °C, 1 h) of **2f**, in addition to unchanged **2f** (20%). Separation of **10** and **2f** was effected by silica gel chromatography ($CHCl_3$). An analytical sample of **10** had mp 88.5—89 °C (iso-PrOH–H_2O). *Anal.* Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.31; H, 6.89; N, 4.64. NMR δ: 2.18 (3H, s, NCH_3), 3.67 (4H, s, 2 × $ArCH_2N$), 3.80 (6H, s, 2 × OCH_3), 6.65 (6H, s, ArH), 7.80 (2H, br s, 2 × OH).

4-Benzyloxy (11)- and 4-Methoxy (19)-styrene Oxides——These compounds were prepared according to the procedure of Kametani *et al.*[11] **11**: 99%, mp 93—96 °C (benzene–*n*-hexane).[14] NMR δ: 2.72 (1H, dd, J=3, 6 Hz), 3.05 (1H, dd, J=4, 6 Hz), 3.73 (1H, dd, J=3, 4 Hz), 4.97 (2H, s, $PhCH_2O$), 6.80 (2H, d, J=8 Hz, C_3- and C_5-H), 7.07 (2H, d, J=8 Hz, C_2- and C_6-H), 7.23 (5H, s, PhH). IR: 1240 (epoxide) cm^{-1}. **19**: 86%, bp 97.5 °C/5 mmHg (lit.[11] 98—99 °C/3 mmHg). NMR δ: 2.75 (1H, dd, J=2, 5 Hz), 3.07 (1H, dd, J=4, 5 Hz), 3.77 (3H, s, OCH_3), 3.78 (1H, dd, J=2, 4 Hz), 6.80 (2H, d, J=8 Hz, C_3- and C_5-H), 7.13 (2H, d, J=8 Hz, C_2- and C_6-H). IR (neat liq.): 1240 (epoxide) cm^{-1}.

Reaction of 11 and 19 with MeOH–$BF_3 \cdot Et_2O$ Followed by Mesylation——$BF_3 \cdot Et_2O$ (0.2—0.5 ml) was added dropwise to a stirred solution of **11** or **19** (1 g) in a mixture of MeOH (5 ml) and benzene (10 ml)[15] under ice-cooling and the whole was strirred for 30 min at the same temperature. Neutralization with $NaHCO_3$ (solid) and extraction with benzene followed by usual work-up gave the β-methoxyethyl alcohol (**15** or **20**).

β-4-(Benzyloxyphenyl)-β-methoxyethylalcohol (**15**): 1.12 g (98%), colorless crystals, mp 49—53 °C. NMR δ: 2.60 (1H, br t, J=6 Hz), 3.25 (3H, s, OCH_3), 3.56 (1H, br t, J=6 Hz), 4.20 (1H, t, J=6 Hz), 5.00 (2H, s, $PhCH_2O$), 5.83 (2H, d, J=8 Hz, C_3- and C_5-H), 6.11 (2H, d, J=8 Hz, C_2- and C_6-H), 7.26 (5H, s, PhH). IR: 3200—3000 (OH) cm^{-1}.

β-Methoxy-β-(4-methoxyphenyl)ethylalcohol (**20**): 1.1 g (91%), oil. NMR δ: 2.43 (1H, t, J=6 Hz), 3.24 (3H, s, OCH_3), 3.53 (1H, t, J=6 Hz), 3.75 (3H, s, OCH_3), 4.19 (1H, t, J=6 Hz), 6.82 (2H, d, J=8 Hz, C_3- and C_5-H), 7.05 (2H, d, J=8 Hz, C_2- and C_6-H). IR: 3200—3000 (OH) cm^{-1}.

Mesylation (mesyl chloride/pyridine) gave the mesylate (**16** or **21**).

β-(4-Benzyloxyphenyl)-β-methoxyethyl Methanesulfonate (**16**): mp 91—93 °C (AcOEt–*n*-hexane). *Anal.* Calcd for $C_{17}H_{20}O_5S$: C, 60.70; H, 5.99. Found: C, 60.82; H, 5.92. NMR δ: 2.90 (3H, s, CH_3SO_3), 3.22 (3H, s, OCH_3), 4.00—4.45 (3H, m), 4.97 (2H, s, $PhCH_2O$), 6.80 (2H, d, J=9 Hz, C_3- and C_5-H), 7.10 (2H, d, J=9 Hz, C_2- and C_6-H), 7.22 (5H, s, PhH). IR: 1170, 1345 (sulfonate) cm^{-1}.

β-Methoxy-β-(4-methoxyphenyl)ethyl Methanesulfonate (**21**): mp 53—54 °C (*n*-hexane). *Anal* Calcd. for $C_{11}H_{16}O_5S$: C, 50.76; H, 6.20. Found: C, 50.81; H, 6.22. NMR δ: 2.97 (3H, s, CH_3SO_3), 3.26 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.03 (3H, m), 6.77 (2H, d, J=9 Hz, C_3- and C_5-H), 7.14 (2H, d, J=9 Hz, C_2- and C_6-H). IR: 1170, 1350 (sulfonate) cm^{-1}.

(±)-Cherylline (1)——A mixture of **2a** (100 mg, 0.389 mmol), **16** (157 mg, 1.2 eq), and Hünig's base (120 mg, 2.4 eq) was heated at 120 °C (bath temperature) in a sealed tube for 14 h. The reaction mixture was dissolved in benzene and the benzene layer was washed successively with conc. ammonia and brine. Usual work-up gave an oil (123 mg), purification of which by preparative TLC ($CHCl_3$: MeOH = 20 : 1) gave crystalline *N*-(4′-benzyloxy-β-methoxyphenethyl)-3-benzyloxy-4-methoxy-*N*-methylbenzylamine (**17**), 137 mg (71%), mp 85—87 °C (lit.[9] 90—91 °C). NMR δ: 2.22 (3H, s, NCH_3), 2.40 (1H, dd, J=6, 13 Hz), 2.73 (1H, dd, J=7, 13 Hz), 3.16 (3H, s, OCH_3), 3.44 (2H, br s, $ArCH_2N$), 3.80 (3H, s, OCH_3), 4.18 [1H, dd, J=6, 7 Hz, $ArC\underline{H}(OMe)$], 4.94, 5.01 (each 2H, s, $PhCH_2O$), 6.66 (2H, s, ArH), 6.76 (1H, s, ArH), 6.78, 7.03 (each 2H, d, J=8 Hz, ArH), 7.03—7.43 (10H, m, 2 × PhH). Conc. HCl (10 ml) was added to a solution of **17** (133 mg, 0.268 mmol) in benzene (20 ml) and the whole was refluxed for 2 h. The benzene layer was extracted with 10% HCl. After neutralization of the combined aqueous layer with saturated Na_2CO_3 solution, the product was extracted with AcOEt. Usual work-up gave (±)-cherylline (**1**), 70 mg (92%), mp 208—211 °C ($CHCl_3$–MeOH) (lit.[4] 209—211 °C). NMR (acetone-d_6) δ: 2.31 (3H, s, NCH_3), 2.43 (1H, dd, J=8, 11 Hz, C_3-$H_{ax.}$), 2.82 (1H, dd, J=6, 11 Hz, C_3-$H_{eq.}$), 3.46 (2H, s, $PhCH_2N$), 3.60 (3H, s, OCH_3), 4.01 (1H, dd, J=6, 8 Hz, C_4-H), 6.33 (1H, s, C_5-H), 6.52 (1H, s, C_8-H), 6.70 (2H, d, J=8 Hz, $C_{3'}$- and $C_{5'}$-H), 7.00 (2H, d, J=8 Hz, $C_{2'}$- and $C_{6'}$-H). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH).

(±)-4′-*O*-Methylcherylline (18)——A similar series of reactions starting from **2e** (500 mg) and **21** (555 mg) gave **18** (387 mg, 67%), mp 131—133 °C (lit.[4] 129—130 °C). NMR δ: 2.39 (3H, s, NCH_3), 2.44 (1H, dd, J=7, 11 Hz, C_3-

$H_{ax.}$), 2.96 (1H, dd, $J=5$, 11 Hz, C_3-$H_{eq.}$), 3.45 (1H, dd, $J=14$ Hz, C_1-H), 3.64, 3.78 (each 3H, s, OCH_3), 4.12 (1H, dd, $J=5$, 7 Hz, C_4-H), 6.27 (1H, s, C_5-H), 6.56 (1H, s, C_8-H), 6.78 (2H, d, $J=9$ Hz, $C_{3'}$- and $C_{5'}$-H), 7.05 (2H, d, $J=9$ Hz, $C_{2'}$- and $C_{6'}$-H).

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References and Notes

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7) Ring closure of **3c** with 80% w/w sulfuric acid at room temperature for 1 h gave **8c** in a yield of only 15%.
8) A preliminary experiment showed that usual secondary alcohols reacted poorly. Namely, *N*-(2-hydroxycyclohexyl)-*N*-(3-hydroxy-4-methoxybenzyl)methylamine (**22**), prepared from **2a** and cyclohexane oxide, gave no cyclized product. **22**: mp 110—111 °C (benzene–*n*-hexane). *Anal.* Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.92; H, 8.72; N, 5.34.
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12) Reaction of **2b** with 4-methoxystyrene oxide[11] also gave a 1 : 1 mixture. Thus, the presence of an electron-donating group at the *p*-position was unfavorable for the regioselectivity.
13) No reaction conditions except for the concentration of H_2SO_4 were optimized.
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15) Benzene was unnecessary in the reaction of **19**.
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