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Studies on the Alkaloids of *Thalictrum Thunbergii* DC. XVIII.[1] Total Synthesis of optically Active Natural O-Methylthalicberine[2]

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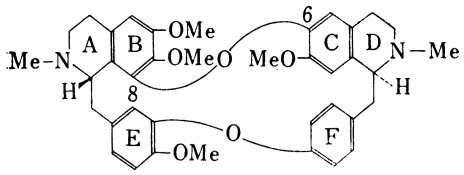
Optically active O-methylthalicberine, a major bisbenzylisoquinoline-type alkaloid of *Thalictrum Thunbergii* DC., was synthesized through a number of steps of reactions shown in Charts 4 to 7. A preliminary confirmation of its structure has also been described.

O-Methylthalicberine is the first bisbenzylisoquinoline alkaloid isolated from a Ranunculaceae plant, *Thalictrum Thunbergii* DC. (Japanese name "Akikaramatsu"), by Fujita and Tomimatsu.[4] Its structure[5] and absolute configuration[6] have been determined to be **1**.



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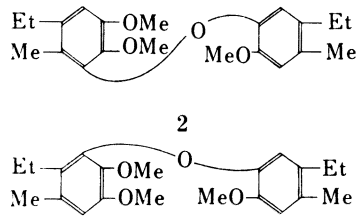
O-Methylthalicberine is also the first bisbenzylisoquinoline alkaloid having a diphenyl ether between C-8 and C-6 of two tetrahydroisoquinolines. Thereafter, the similar alkaloids, thalicberine,[4] thalmetine,[7a] O-methylthalmetine,[7a] thalfoetidine[7b] and O-methylisothalicberine[8] have been isolated from the various plants. Some of these were converted into O-methylthalicberine and the others were characterized by comparing their spectra with those of O-methylthalicberine.

In order to give their structures an exact chemical evidence, we attempted a total synthesis of O-methylthalicberine and have succeeded.

Prior to the synthesis, ether linkage between rings B and C was re-examined to clarify the following ambiguity. The location of the ether linkage had been determined[5] by identification of the infrared (IR) spectrum of O-methylthalicberine's degradation product **2** with that of the synthetic compound **2**. An alternative structure **3** for O-methylthalicberine, however, could not be completely excluded, because the difference between **2** and **4** which should be derived from **3** *via* **11** might be little upon the IR spectra.

First, the Hofmann degradation of O-methylthalicberine was re-investigated, and three reaction products were isolated. The first product which had the largest *Rf* value in the

1) Part XVII: S. Kubota, T. Masui, E. Fujita, and S.M. Kupchan, *J. Org. Chem.*, **31**, 516 (1966).
2) For preliminary communication, see *Chem. Pharm. Bull.* (Tokyo), **18**, 2591 (1970).
3) Location: *Uji, Kyoto.*
4) E. Fujita and T. Tomimatsu, *Yakugaku Zasshi*, **79**, 1256 (1959).
5) E. Fujita and T. Tomimatsu, *Yakugaku Zasshi*, **79**, 1260 (1959); T. Tomimatsu, *ibid.*, **79**, 1386 (1959); E. Fujita, T. Tomimatsu, and Y. Kano, *ibid.*, **80**, 1137 (1960); T. Tomimatsu and Y. Kano, *ibid.*, **83**, 153 (1963); E. Fujita, T. Tomimatsu, and Y. Kano, *ibid.*, **83**, 159 (1963); E. Fujita, K. Fuji, and T. Suzuki, *Bull. Inst. Chem. Res., Kyoto Univ.*, **43**, 449 (1965).
6) M. Tomita and J. Kunitomo, *Yakugaku Zasshi*, **82**, 741 (1962).
7) *a*) N.M. Mollov, H.B. Dutschewska, and H.G. Kirjakov, *Chem. Ind.* (London), **1965**, 1595.
b) N.M. Mollov and V. St. Georgiev, *Chem. Ind.* (London), **1966**, 1178.
8) M.R. Falco, J.X. de Vries, A.G. de Brovetto, Z. Maccio, S. Rebuffo, and I.R.C. Bick, *Tetrahedron Letters*, **1968**, 1953.



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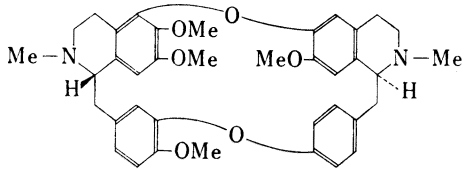
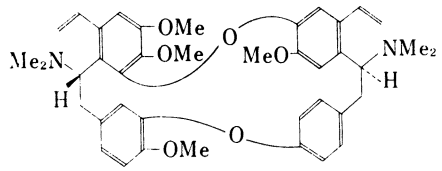


thin-layer chromatogram (TLC) was amorphous and its IR spectrum suggested the presence of vinyl group(s). The nuclear magnetic resonance (NMR) spectrum suggested the presence of two NMe_2 groups, four OMe groups, and two vinyl groups. On the basis of these observations, the structure **5** was assigned to this compound.



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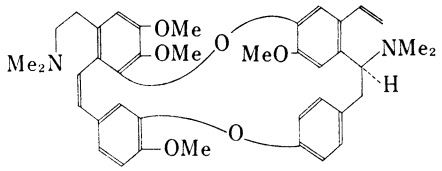

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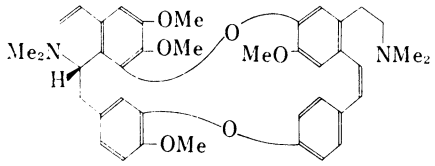

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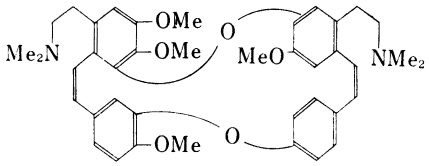

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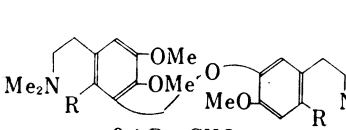
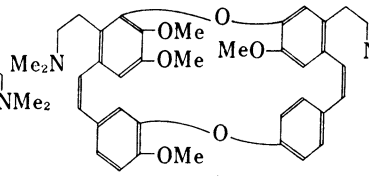
The second product, which had a middle *Rf* value, was viscous oil, and its IR spectrum showed a vinyl group band. The NMR spectrum suggested the presence of two NMe_2 groups, four OMe groups, and one vinyl group. These data led to presentation of formula **6** or **7** to this compound. The formula **6** seems preferrable, from our preliminary experiment[9] and the result of Hofmann degradation of isotetrandrine by Tomita, *et al.*[10]



9 : R=CHO
10 : R=CH_2OH



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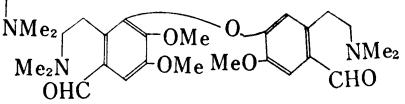

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The last product, which had the smallest *Rf* value, was also viscous oil. No vinyl group could be recognized, when its IR and NMR spectra were examined. From the NMR spectrum, however, the presence of two NMe_2 groups and four OMe groups was supported. So, the structure **8** was assigned to this compound. The ozonolysis of this compound yielded an oily basic dialdehyde, whose IR and NMR spectra allowed an assignment of structure **9**.

9) Cleavage with sodium in liquid ammonia, after being hydrogenated on two double bonds, of this compound gave two products, which corresponded to the products from **6**.
10) M. Tomita and T. Ibuka, *Yakugaku Zasshi*, **82**, 1659 (1962).

The reduction of compound **9** with $NaBH_4$ afforded a basic dialcohol **10** as an oily product. Its NMR spectrum showed the presence of two NMe_2 groups, three OMe groups, two C_6H_5-CH_2OH groups, and three aromatic protons. When the NMR spectrum of **10** was compared with that of **9**, a diamagnetic shift of a singlet signal of one proton from τ 2.52 to 3.06 was observed. It was, therefore, recognized that compound **9** has only one hydrogen at an *ortho*-position to one aldehyde substituent. Thus, an alternative formula **12** derived from **11** instead of **9** was denied. A further evidence was provided by the following synthesis.

(±)-8-Bromo-O-methylarmepavine(**18**) was synthesized by a procedure published by Tomita, *et al.*[11] from 3-bromo-4,5-dimethoxyphenethylamine (**13**)[12] and 4-methoxy-phenylacetic acid (**14**)[13] *via* amide **15**, 3,4-dihydroisoquinoline derivative **16**, and tetrahydroisoquinoline derivative **17**. The compound **18** was identical in all respects with an authentic sample[14] which had been yielded by methylation of 8-bromoarmepavine. The Hofmann degradation of the compound **18** gave 2-bromo-6-(N,N-dimethylaminoethyl)-3,4,4′-trimethoxystilbene (**19**), which was separated as a crystalline oxalate.

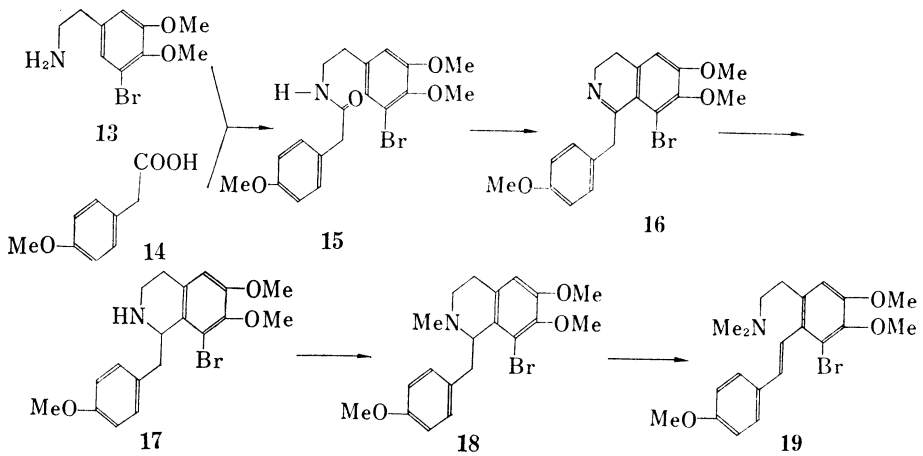


Chart 1

An analogous series of reactions afforded (±)-O-methylarmepavine ((±)-O,O,N-trimethylcoclaurine) (**24**). This compound has been synthesized by Marion, *et al.*[15] Tomita, *et al.*,[16] and Kapadia, *et al.*[17] These procedures are very similar, but a little different, when compared to ours. Condensation of 3,4-dimethoxyphenethylamine (**20**)[16] and 4-methoxyphenylacetic acid (**14**) gave amide **21**, whose Bischler-Napieralski cyclization afforded 3,4-dihydroisoquinoline derivative **22**. The $NaBH_4$ reduction followed by N-methylation yielded (±)-O-methylarmepavine (**24**), mp 89—91°. The compound **24** was converted into O,N-dimethylisococlaurine (**25**) by lithium in liquid ammonia.[18] Hofmann degradation of compund **25** gave 2-(N,N-dimethylaminoethyl)-4′,5-dimethoxy-4-hydroxystilbene (**26**) as crystals, mp 175—178°.

11) M. Tomita, Y. Masaki, K. Fujitani, and Y. Sakatani, *Chem. Pharm. Bull.* (Tokyo), **16**, 688 (1968).
12) K. Fujitani, T. Kishimoto, and S. Niimura, *Yakugaku Zasshi*, **83**, 412 (1963); M. Tomita, Y. Aoyagi, Y. Sakatani, and K. Fujitani, *Chem. Pharm. Bull.* (Tokyo), **15**, 1996 (1967).
13) U.V. Solmssem and E. Wenis, *J. Am. Chem. Soc.*, **70**, 4200 (1948).
14) M. Tomita, T. Shingu, K. Fujitani, and H. Furukawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 921 (1965).
15) L. Marion, L. Lemay, and V. Portelance, *J. Org. Chem.*, **15**, 216 (1950).
16) M. Tomita and H. Yamaguchi, *Chem. Pharm. Bull.* (Tokyo), **1**, 10 (1953).
17) G.J. Kapadia, N.J. Shah, and R.J. Highet, *J. Pharm. Sci.*, **53**, 1431 (1964).
18) M. Tomita and Y. Kondo, *Yakugaku Zasshi*, **77**, 1019 (1957).

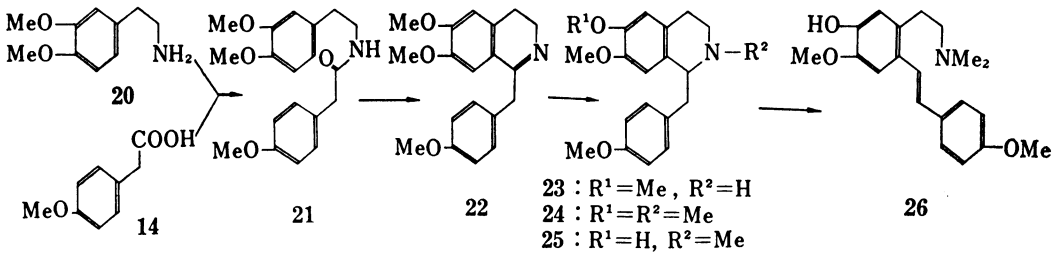


Chart 2

The Ullmann condensation of **19** with **26** afforded the compound **27** as an oily product in 26% yield. Its NMR spectrum exhibited protons signals due to two NMe_2 groups and five OMe groups. Ozonolysis of **27** followed by $NaBH_4$ reduction yielded a basic diol **10** *via* a dialdehyde **9**. The IR and NMR spectra of **9** and **10** were proved to be completely identical with those of the corresponding degradation products from O-methylthalicberine, respectively.

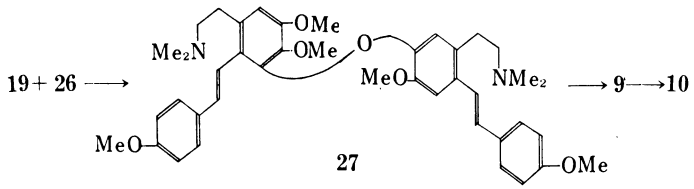


Chart 3

These preliminary investigations strongly supported structure **1** originally presented for O-methylthalicberine. Then, we tried the total synthesis of the natural product to give a final confirmative evidence.

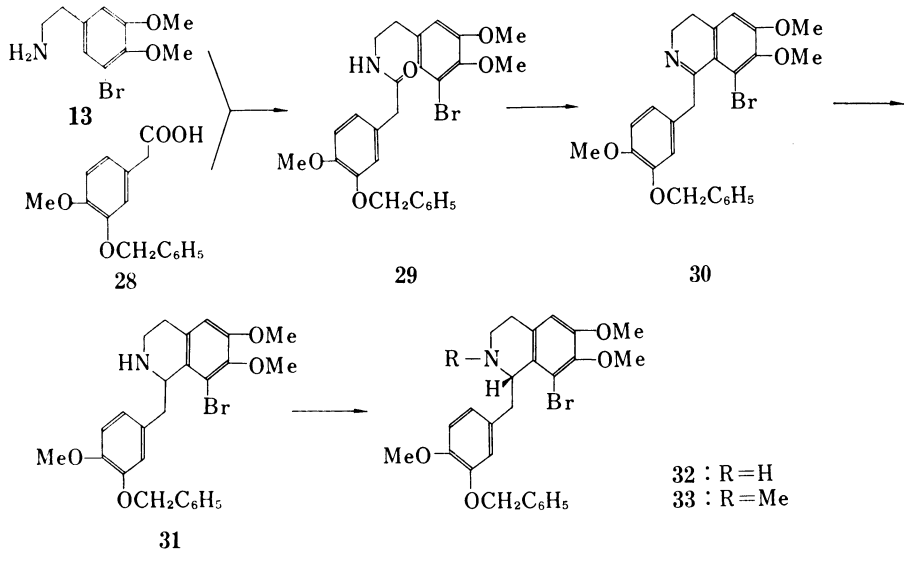


Chart 4

To synthesize O-methylthalicberine efficiently, we applied a route through which isotetrandrine, phaeanthine, and tetrandrine had been synthesized by Inubushi, *et al.*[19] An important intermediate, (*S*)-(+)-O-benzyl-8-bromolaudanidine (**33**) was synthesized *via* (+)-O-benzyl-8-bromo-N-norlaudanidine (**32**) from 3-bromo-4,5-dimethoxyphenethylamine (**13**)[12] and 3-benzyloxy-4-methoxyphenylacetic acid (**28**)[20] as shown in Chart 4.

According to Inubushi's procedure,[19] amide **29**, synthesized from **13** and **28**, on Bischler-Napieralski reaction gave a dihydroisoquinoline derivative **30**. Its successive treatment with $NaBH_4$ gave (±)-O-benzyl-8-bromo-N-norlaudanidine (**31**)[19] in 40% yield. Racemate **31** was resolved, *via* its salt with (−)-tartaric acid, to (+)-O-benzyl-8-bromo-N-norlaudanidine (**32**), whose N-methylation yielded (*S*)-(+)-O-benzyl-8-bromolaudanidine (**33**). The structure and optical purity of the compounds **32** and **33** were confirmed by the comparison with their enantiomers synthesized by Inubushi, *et al.*[19] as shown in Table I.

TABLE I

Compounds	mp (°C)	$[\alpha]_D^t$
32-(−)-tartarate	184—186.5	+22° (t=25, c=1, $CHCl_3$)
ent[a]-**32**-(+)-tartarate[19]	179	−29° (t=24, c=1, $CHCl_3$)
32	98—99	+38.7° (t=25, c=2, $CHCl_3$)
ent-**32**[19]	99—102	−38° (t=18, c=2, $CHCl_3$)
33	100—101	+21° (t=25, c=2, $CHCl_3$)
ent-**33**[19]	90	−27° (t=23, c=2, $CHCl_3$)

a) *enantio*

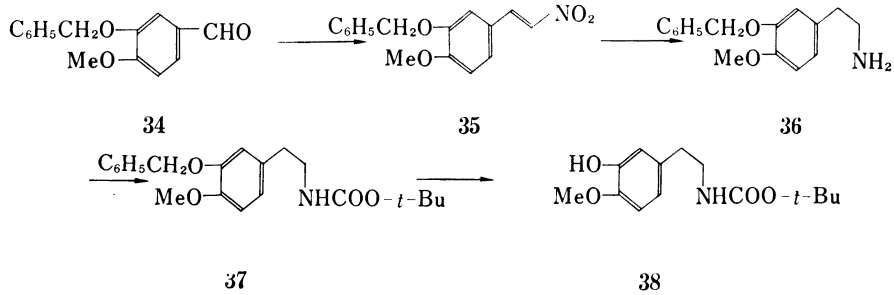


Chart 5

Another important intermediate, N-*t*-butoxycarbonyl-3-hydroxy-4-methoxyphenethylamine (**38**), was synthesized, by a route shown in Chart 5.

The reaction of *t*-butylazidoformate with 3-benzyloxy-4-methoxyphenethylamine (**36**)[21] which was synthesized from O-benzylisovanillin (**34**) *via* 3-benzyloxy-4-methoxy-β-nitrostyrene (**35**) gave N-*t*-butoxycarbonyl-3-benzyloxy-4-methoxyphenethylamine (**37**) in 84% yield, which, upon catalytic hydrogenolysis, afforded N-*t*-butoxycarbonyl-3-hydroxy-4-methoxyphenethylamine (**38**).

The Ullmann condensation of (+)-O-benzyl-8-bromolaudanidine (**33**) with N-*t*-butoxycarbonyl-3-hydroxy-4-methoxyphenethylamine (**38**) afforded an ether **39** as an oil in 39% yield. The IR spectrum exhibited an ester carbonyl absorption at 1700 cm^{-1} and the NMR

19) Y. Inubushi, Y. Masaki, S. Matsumoto, and F. Takami, *Tetrahedron Letters*, **1968**, 3399; *idem*, *J. Chem. Soc.* (*C*), **1969**, 1547.
20) *a*) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, **1931**, 3163; *b*) S.M. Kupchan and A. Yoshitake, *J. Org. Chem.*, **34**, 1062 (1969).
21) M. Tomita and H. Yamaguchi, *Yakugaku Zasshi*, **72**, 1219 (1952).

spectrum supported the presence of one *t*-butyl group, one NMe group, and four OMe groups. Hydrogenolysis of **39** yielded phenol **40** as an oily product in 55% yield. Its IR and NMR spectra supported the structure.

The second Ullmann condensation of phenol **40** with methyl *p*-bromophenylacetate (**41**) gave a bis diphenyl ether derivative **42** as a viscous oily product in 79% yield. Its IR spectrum showed ester carbonyl absorptions at 1730 and 1708 cm^{-1}, and the phenolic hydroxy group's absorption at 3570 cm^{-1} of the starting material **40** disappeared. The NMR spectrum also supported the structure. The methyl ester **42** was hydrolyzed with alkali to give the free acid **43**, which, without purification, was converted into *p*-nitrophenyl ester **44** with *p*-nitrophenol and dicyclohexylcarbodiimide. The *t*-butoxycarbonyl group was then removed with trifluoroacetic acid, to give the *p*-nitrophenyl ester-phenethylammonium trifuoroacetate (**45**), which was cyclized to a crystalline cycloamide in 75% yield by adding a solution of the former in anhydrous dimethylformamide to pyridine at 70°, under the high-dilution condition. Its IR absorption and NMR spectrum supported the structure **46**.

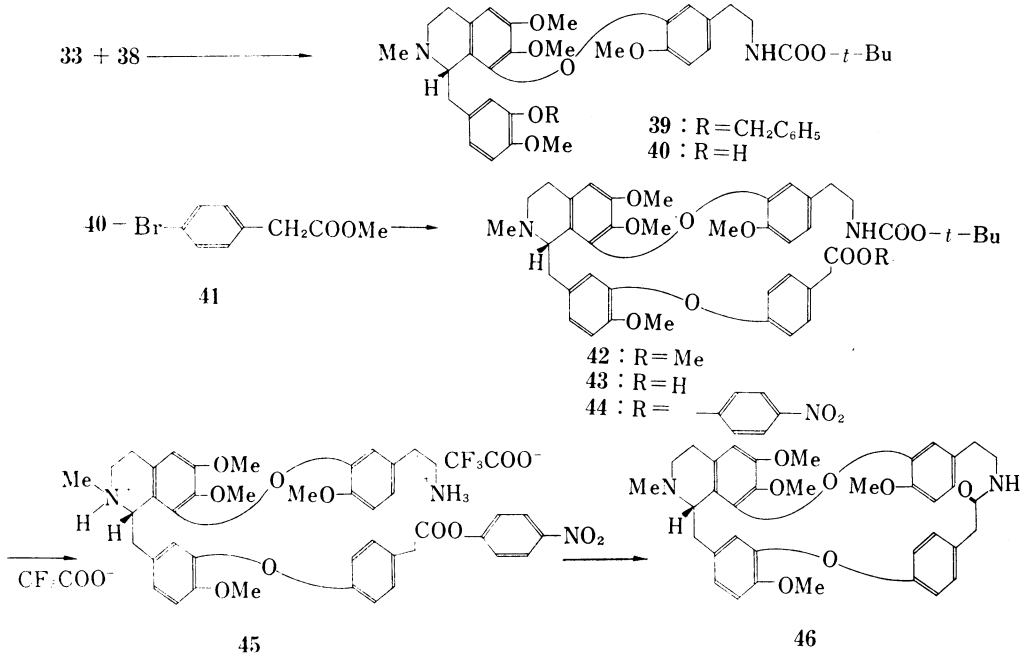
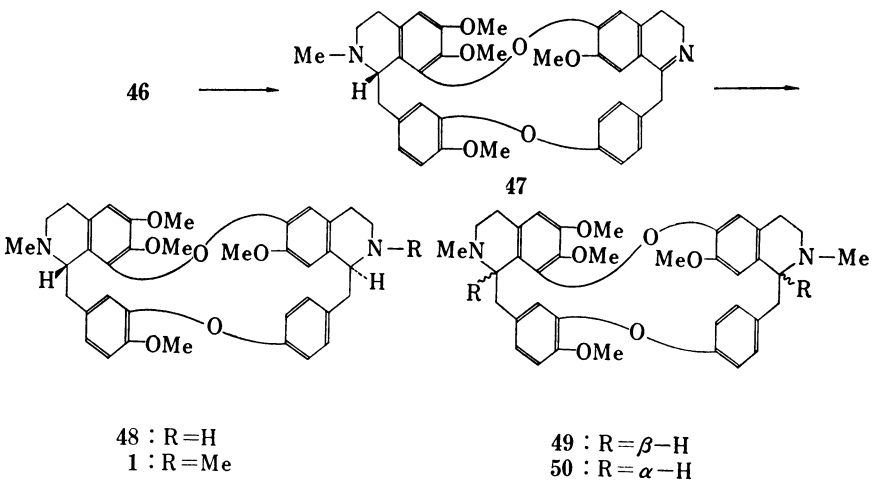


Chart 6

The Bischler–Napieralski reaction with **46** gave the 3,4-dihydroisoquinoline derivative **47** in 38% yield. The latter compound corresponds to O-methylthalmetine,[7a] but crystallization was unsuccessful because of high solubility in various organic solvents and easy coloring under treatment with solvents. The NMR spectrum of **47**, however, was completely identical with that of the authentic sample of O-methylthalmetine.

Reduction of compound **47** with $NaBH_4$ afforded only a product, mp 262—264°, $[\alpha]_D$ +245° ($CHCl_3$), stereoselectively in 70% yield. The NMR spectrum of this product in both crude and purified forms was identical with that of O-methylthalicberine except a singlet signal at τ 7.43 in the latter, and signal at τ 7.62, which was assigned to the left-hand N-methyl protons of O-methylisothalicberine (**50**)[10] and, therefore, is reasonably expected to be assignable to the left-hand N-methyl protons of the enantiomer (**49**) of O-methylisothalicberine, was never recognized. Hence, this reduction product must be N-nor-O-methylthalicberine



48 : R=H
1 : R=Me

49 : R=β-H
50 : R=α-H

Chart 7

(**48**) and the conformation of N-nor-compound **48** and O-methylthalicberine was shown to be the same. This stereoselectivity in the $NaBH_4$ reduction of **47** was unexpected and the reason remains unclarified because of the unknown conformation of the macro ring structure **47**.

The N-methylation of N-nor-O-methylthalicberine (**48**) with formalin and $NaBH_4$ yielded the final product, mp 184°, $[\alpha]_D^{25}$ +243°, which was proved to be identical with the natural alkaloid, O-methylthalicberine (**1**) in all respects.

Thus, a total synthesis of the alkaloid was accomplished, which established the structure and stereochemistry **1**.

Experimental

Melting points were determined on a Yanagimoto micro mp apparatus and uncorrected. The UV spectra were taken on a Hitachi model EPS-3 recording Spectrophotometer, IR spectra on a Hitachi model EPI-S2 Spectrophotometer, NMR spectra on a Varian A-60 Spectrometer, using TMS as internal standard, and mass spectra on a Hitachi RMU-6D Mass Spectrometer. Specific rotations were measured by Jasco DIP-SL-type Automatic Polarimeter. Woelm Alumina Akt. I (neu) was used for column chromatography, and Woelm Alumina neu. DC. for thin-layer chromatography.

Hofmann Degradation of O-Methylthalicberine (1)——A mixture of O-methylthalicberine (**1**) (780 mg) and MeI (4 g) in methanol (15 ml) was refluxed for 2 hr. After evaporation of the excess of MeI and solvent, the residue was dissolved in methanol (20 ml), to which AgCl (500 mg) was added. The deposited AgI was filtered off, and a solution of NaOH (15 g) in H_2O (20 ml) was added to the filtrate. The mixture was refluxed for 2 hr, and, after cooling, acidified with acetic acid, then made alkaline with aq. NH_4OH. Extraction with ether, and the ethereal extract was treated as usual to give a crude products mixture, which was chromatographed on neutral alumina by elution with $CHCl_3$ to separate 3 components (A,B, and C).

Compound-A (**5**): Amorphous powder (0.11 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1000, 905 (-CH=CH_2). NMR ($CHCl_3$) τ: 7.92 (6H, s, NMe_2), 7.63 (6H, s, NMe_2), 6.74 (3H, s, OMe), 6.53 (3H, s, OMe), 6.17 (3H, s, OMe), 6.13 (3H, s, OMe), 4.85 (1H, dd, J=2,11), 4.78 (1H, dd, J=2,11), 4.53 (1H, dd, J=2,18), 4.49 (1H, dd, J=2,18), 2.11 (1H, dd, J=11,18), 2.00 (1H, dd, J=11,18 Hz).

Compound-B (**6**): Viscous oil (0.37 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 995, 905 (-CH=CH_2). NMR ($CHCl_3$) τ: 7.72 (12H, s, 2 NMe_2), 6.44 (3H, s, OMe), 6.24 (3H, s, OMe), 6.12 (3H, s, OMe), 6.09 (3H, s, OMe), 4.98 (1H, dd, J=2,10), 4.92 (1H, dd, J=2,18), 2.22 (1H, dd, J=10,18 Hz).

Compound-C (**8**): Viscous oil (0.07 g). NMR ($CHCl_3$) τ: 7.76 (6H, s, NMe_2), 7.70 (6H, s, NMe_2), 6.38 (3H, s, OMe), 6.16 (3H, s, OMe), 6.08 (3H, s, OMe), 6.06 (3H, s, OMe).

Ozonolysis of Compound 8——Compound **8** (170 mg) was dissolved in 2% aq. AcOH (10 ml). A little excess of 1% ozone in oxygen was passed through the ice-cooled solution for 30 min at 0—3°. The resultant colorless solution was stirred under addition of 5% Pd-C (50 mg) in an atmosphere of H_2. After the catalyst was filtered off, the filtrate was washed with ether. The aq. layer was made alkaline with aq. NH_4OH

and extracted with $CHCl_3$. The extract was treated as usual to afford an oily basic dialdehyde **9** (85 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2730, 1675 (-CHO). NMR ($CDCl_3$) τ: 7.76 (6H, s, NMe_2), 7.63 (6H, s, NMe_2), 6.28 (3H, s, OMe), 6.02 (6H, s, 2 OMe), 3.54 (1H, s, arom. H), 3.23 (1H, s, arom. H), 2.52 (1H, s, arom. H), −0.16 (1H, s, -CHO), −0.22 (1H, s, -CHO).

Reduction of the Basic Dialdehyde 9——Sodium borohydride (20 mg) was added in portions to a stirred solution of the basic dialdehyde **9** (108 mg) in MeOH (2 ml) at room temperature. Stirring was then continued for 2 hr. A few drops of AcOH and H_2O (2 ml) were added and MeOH was removed under reduced pressure. The residual solution was made alkaline with aq. NH_4OH, and extracted with $CHCl_3$. After drying with K_2CO_3, the solvent was evaporated to give the basic diol **10** (94 mg) as an oily product. NMR ($CDCl_3$) τ: 7.82 (6H, s, NMe_2), 7.74 (6H, s, NMe_2), 6.29 (3H, s, OMe), 6.12 (3H, s, OMe), 6.06 (3H, s, OMe), 5.54 (2H, s, C_6H_5-CH_2-OH), 5.52 (2H, s, C_6H_5-CH_2-OH), 3.63 (1H, s, arom. H), 3.35 (1H, s, arom. H), 3.06 (1H, s, arom. H).

N-(3-Bromo-4,5-dimethoxyphenethyl)-4-methoxyphenylacetamide (15)——A mixture of 3-bromo-4,5-dimethoxyphenethylamine (**13**)[12] (14.2 g) and 4-methoxyphenylacetic acid (**14**)[13] (10 g) in decalin (150 ml) was heated under reflux for 1 hr. The solution was cooled and the deposited crystals were filtered. The crystals were dissolved in $CHCl_3$, and washed with dilute alkali, dilute acid, and H_2O successively. After drying with $MgSO_4$, the solvent was removed to give a crystalline residue, which was recrystallized from MeOH to yield pure amide **15** (16.5 g: 73% yield), mp 110—113°. *Anal.* Calcd. for $C_{19}H_{22}O_4NBr$: C, 55.89; H, 5.43; N, 3.43; Br, 19.57. Found: C, 56.09; H, 5.51; N, 3.15; Br, 19.62. IR ν_{max}^{KBr} cm^{-1}: 3270 (N-H), 1640 (C=O). NMR ($CDCl_3$) τ: 6.51 (2H, s, C_6H_5-CH_2-CO), 6.19 (6H, s, 2 OMe), 6.16 (3H, s, OMe), 3.40 (1H, d, J=2, arom. H), 3.15 (1H, d, J=2, arom. H), 3.14, 2.90 (each 2H, A′$_2$B′$_2$, q, J=8.5 Hz).

(±)8-Bromo-6,7-dimethoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline ((±)-8-Bromo-O,O,N-trimethylcoclaurine) (18)——To a solution of amide **15** (10 g) in anhydrous toluene (100 ml), $POCl_3$ (20 g) was added. After the mixture was heated under reflux for 2.5 hr, the solvent and $POCl_3$ were removed. The residue was dissolved in $CHCl_3$, washed with H_2O, and dried with $MgSO_4$. Removal of the solvent left the crude hydrochloride of dihydroisoquinoline **16**. This salt was dissolved in MeOH (150 ml), and $NaBH_4$ (4 g) was added in portions to this solution. Then, the mixture was refluxed for 1 hr. The solvent was removed by evaporation to give a residue, which was extracted with $CHCl_3$. The $CHCl_3$ solution was treated as usual to afford a crude product of tetrahydroisoquinoline derivative **17** (9.5 g), to whose solution in MeOH (150 ml) 37% formaldehyde (9 g) was added under stirring. After stirring for 30 min, $NaBH_4$ (2.5 g) was portionwise added. After further stirring for 30 min, the solvent was removed, and the residue was extracted with $CHCl_3$. The extract was treated as usual and then purified by chromatography on neutral alumina column by elution with benzene to give (±)-8-bromo-O,O,N-trimethylcoclaurine (**18**) (4.6 g: 46%), mp 92° (from MeOH). *Anal.* Calcd. for $C_{20}H_{24}O_3NBr$: C, 59.11; H, 5.95; N, 3.45; Br, 19.55. Found: C, 59.32; H, 6.20; N, 3.17; Br, 19.55. NMR ($CDCl_3$) τ: 7.68 (3H, s, NMe), 6.22 (3H, s, OMe), 6.16 (6H, s, 2 OMe), 3.40 (1H, s, arom. H), 3.18, 2.78 (each 2H, A′$_2$B′$_2$, q, J=9 Hz).

2-Bromo-6-(N,N-dimethylaminoethyl)-3,4,4′-trimethoxystilbene (19)——A solution of 8-bromo-O,O,N-trimethylcoclaurine (**18**) (1.6 g) and MeI (2 ml) in MeOH (40 ml) was refluxed for 1 hr. The solvent and excess MeI were distilled off to leave a residue, which was dissolved in MeOH (50 ml). To this solution, AgCl (1 g) was added, and AgI formed was filtered off. A solution of NaOH (15 g) in H_2O (5 ml) was added to the filtrate, and the mixture was refluxed for 2 hr. Methanol was distilled off and the residual solution was acidified with dilute HCl, then made alkaline with aq. NH_4OH. Extraction with ether and usual work up gave a crude mixture which was shown by thin-layer chromatography to consist of two components. The mixture was dissolved in acetone, to which a saturated solution of oxalic acid in EtOH was added to isolate 2-bromo-6-(N,N-dimethylaminoethyl)-3,4,4′-trimethoxystilbene (**19**) as the crystalline oxalate (0.94 g: 47%), mp 184—187° (from EtOH). *Anal.* Clacd. for $C_{21}H_{26}O_3NBr \cdot C_2H_2O_4$: C, 54.13; H, 5.52; N, 2.74. Found: C, 53.91; H, 5.66; N, 2.77. Free base **19**: an oil. UV λ_{max}^{EtOH} nm: 285 (ε 18800). NMR ($CDCl_3$) τ: 7.46 (6H, s, NMe_2), 6.14 (6H, s, 2 OMe), 6.09 (3H, s, OMe), 3.43 (1H, d, J=17, olefinic H), 3.13 (1H, d, J=17, olefinic H), 3.12 (1H, s, arom. H), 3.08, 2.55 (each 2H, A′$_2$B′$_2$, q, J=9 Hz, arom. H).

N-(3,4-Dimethoxyphenethyl)-4-methoxyphenylacetamide (21)——A mixture of 3,4-dimethoxyphenethylamine (**20**)[16] (19 g) and 4-methoxyphenylacetic acid (**14**) (14 g) in decalin (150 ml) was heated under reflux for 2 hr. The solution was cooled and the deposited crystals were collected. They were dissolved in $CHCl_3$ and the solution was worked up as usual to give amide (**21**) (9.1 g: 26%), mp 124—127° (lit.[22] mp 123.5°) (from MeOH). *Anal.* Calcd. for $C_{19}H_{23}O_4N$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.02; H, 7.10; N, 4.44. IR ν_{max}^{KBr} cm^{-1}: 3300 (N-H), 1645 (C=O). NMR ($CDCl_3$) τ: 6.21 (3H, s, OMe), 6.18 (3H, s, OMe), 6.14 (3H, s, OMe), 7.33 (2H, t, J=7 Hz, C_6H_5-CH_2-CH_2-), 6.51 (2H, s, C_6H_5-CH_2-CO-).

6,7-Dimethoxy-1-(4-methoxybenzyl)-3,4-dihydroisoquinoline (22)——To a solution of amide **21** (9.1 g) in anhydrous toluene (60 ml), $POCl_3$ (11 ml) was added, and the mixture was heated under reflux for 4 hr. A usual work up of the reaction mixture gave a 3,4-dihydroisoquinoline derivative (**22**) as the hydrochloride (9 g: 93%), mp 178—180° (from MeOH–acetone 1: 1) (lit.[22] mp 190—191°).

22) H. Kondo and T. Kondo, *Yakugaku Zasshi*, **48**, 324 (1928).

(±)6,7-Dimethoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline ((±)-O-Methylarmepavine) (24)——The crude hydrochloride (5.6 g) of compound **22** was dissolved in MeOH (100 ml) and reduced with $NaBH_4$ (2 g) at room temperature with stirring. The mixture was worked up as usual and the crude product was extracted with $CHCl_3$. The dried (K_2CO_3) extract was evaporated and the residue gave the crude (±)-O,O-dimethylcoclaurine (**23**) as a viscous oil (6.5 g). A solution of crude **23** (6.5 g) in MeOH (100 ml) was treated with 37% formalin (8 g) and $NaBH_4$ (2 g) at room temperature. The mixture was worked up as usual and a non-phenolic base was extracted with $CHCl_3$. The dried (K_2CO_3) extract was evaporated and the residue gave (±)-O-methylarmepavine (**24**) as needles (2.6 g: 50%), mp 89—91° (from ether–petroleum benzin) (lit.[15] mp 92°). *Anal.* Calcd. for $C_{20}H_{25}O_3N$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.40; H, 7.79; N, 4.18. NMR ($CDCl_3$) τ: 7.48 (3H, s, NMe), 6.43 (3H, s, OMe), 6.23 (3H, s, OMe), 6.16 (3H, s, OMe), 3.94 (1H, s, arom. H), 3.44 (1H, s, arom. H), 3.19, 2.98 (each 2H, $A'_2B'_2$, q, J=9 Hz).

(±)-6-Hydroxy-7-methoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline ((±)-O,N-Dimethylisococlaurine) (25)——To the liquid ammonia (400 ml) in which lithium had been added in portions until the blue color remained after complete mixing, a solution of (±)-O-methylarmepavine (**24**) (3 g) in anhydrous tetrahydrofuran (60 ml) and lithium were alternately added in portions at −35——40° in the nitrogen atomosphere. After stirring for further 2 hr the reaction mixture was allowed to stand at room temperature to evaporate ammonia. The residual tetrahydrofuran solution was worked up as usual to afford a phenolic amine, (±)-O,N-dimethylisococlaurine (**25**) (1.2 g: 42%) as crystals, mp 139—141° (from ether–petroleum benzin) (lit.[18] mp 145°). *Anal.* Calcd. for $C_{19}H_{23}O_3N$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.64; H, 7.45; N, 4.43. NMR ($CDCl_3$) τ: 7.48 (3H, s, NMe), 6.44 (3H, s, OMe), 6.23 (3H, s, OMe), 4.03 (1H, s, arom. H), 3.39 (1H, s, arom. H), 3.20, 3.00 (each 2H, $A'_2B'_2$, q, J=9 Hz).

2-(N,N-Dimethylaminoethyl)-4',5-dimethoxy-4-hydroxystilbene (26)——A mixture of O,N-dimethylisococlaurine (**25**) (1.5 g) and MeI (2 ml) in MeOH (30 ml) was refluxed for 1 hr. Evaporation of the solvent and the excess of MeI left a residue, to whose solution in MeOH (80 ml) AgCl (1 g) was added. To the filtrate from the deposited AgI, a solution of NaOH (20 g) in H_2O (20 ml) was added, and the mixture was refluxed for 2 hr. A usual work up and a phenolic base was extracted with ether. The dried (Na_2SO_4) extract was evaporated and the residue gave a mixture which was shown to contain two components by thin-layer chromatography. Fractional crystallization of the mixture afforded 2-(N,N-dimethylaminoethyl)-4',5-dimethoxy-4-hydroxystilbene (**26**) (0.3 g: 20%), mp 175—178° (from MeOH). *Anal.* Calcd. for $C_{20}H_{25}O_3N$: C, 73.37; H, 7.70; N, 4.28. Found: C 73.16; H, 7.86; N, 4.56. UV λ_{max}^{EtOH} nm (ε): 298 (17200), 308 (17000), 332 (20000). UV $\lambda_{max}^{EtOH+NaOH}$ nm (ε): 257 (9700), 320 (11700), 362 (22000). IR ν_{max}^{KBr} cm^{-1}: 960 (*trans* -CH=CH-). NMR ($CDCl_3$) τ: 7.65 (6H, s, NMe_2), 6.18 (3H, s, OMe), 6.08 (3H, s, OMe), 3.26 (1H, s, arom. H), 3.08 (1H, s, arom. H), 2.92 (2H, s, olefinic H), 3.12, 2.58 (each 2H, $A'_2B'_2$, q, J=8.5 Hz).

2,3-Dimethoxy-5-(N,N-dimethylaminoethyl)-6-(4-methoxystyryl)-phenyl-5-(N,N-dimethylaminoethyl)-2-methoxy-4-(4-methoxystyryl)-phenyl Ether (27)——A mixture of compounds **19** (850 mg), **26** (500 mg), and anhydrous K_2CO_3 (150 mg) in anhydrous pyridine (3 ml) was heated under a stream of dry nitrogen to 150°, and a fine cupric oxide powder (50 mg) was added, then the mixture was heated at 150° for 4 hr. After cooling, cupric oxide was filtered off. The filtrate was evaporated to remove pyridine. The residue was dissolved in benzne, washed with water, and extracted with 10% aq. HCl. The acidic layer was made alkaline with aq. NH_4OH and extracted with $CHCl_3$. Usual treatment of the extract, and chromatography of the crude product on neutral alumina column by elution with benzne yielded a pure product **27** as an oil (400 mg: 26%). NMR ($CDCl_3$) τ: 7.75 (6H, s, NMe_2), 7.68 (6H, s, NMe_2), 6.23 (3H, s, OMe), 6.21 (3H, s, OMe), 6.17 (3H, s, OMe), 6.07 (6H, s, 2 OMe).

2,3-Dimethoxy-5-(N,N-dimethylaminoethyl)-6-formylphenyl-5-(N,N-dimethylaminoethyl)-4-formyl-2-methoxyphenyl Ether (9)——The diphenyl ether derivative **27** (230 mg) was dissolved in 2% aq. HOAc (10 ml). A little excess of 1% ozone in oxygen was passed through this solution for 30 min at 0——3°. The resultant colorless solution was stirred with 5% Pd-C in an atmosphere of hydrogen at room temperature. After the catalyst was filtered off, the filtrate was washed with ether. The aq. layer was made alkaline with aq. NH_4OH and extracted with $CHCl_3$. A usual treatment of the extract afforded dialdehyde **9** as an oil (85 mg: 54%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2730, 1675 (-CHO). NMR ($CDCl_3$) τ: 7.76 (6H, s, NMe_2), 7.58 (6H, s, NMe_2), 6.32 (3H, s, OMe), 6.05 (6H, s, 2 OMe), 3.56 (1H, s, arom. H), 3.23 (1H, s, arom. H), 2.56 (1H, s, arom. H), −0.07 (1H, s, -CHO), −0.10 (1H, s, -CHO). These spectroscopic data are identical with those of the degradation product **9** from O-methylthalicberine.

2,3-Dimethoxy-5-(N,N-dimethylaminoethyl)-6-hydroxymethylphenyl-5-(N,N-dimethylaminoethyl)-4-hydroxymethyl-2-methoxyphenyl Ether (10)——Sodium borohydride (20 g) was added in portions to the stirred solution of the preceding synthesized dialdehyde **9** (50 mg) in MeOH (2 ml) at room temperature. Stirring was continued for further 2 hr. Subsequently, a few drops of HOAc were added to decompose the excess of $NaBH_4$, and the mixture was extracted with $CHCl_3$. A usual work up gave diol **10** as an oily product (41 mg: 82%). NMR ($CDCl_3$)τ: 7.83 (6H, s, NMe_2), 7.75 (6H, s, NMe_2), 6.29 (3H, s, OMe), 6.11 (3H, s, OMe), 6.05 (3H, s, OMe), 5.55 (2H, s, C_6H_5-CH_2-OH), 5.53 (2H, s, C_6H_5-CH_2-OH), 3.63 (1H, s, arom. H), 3.35 (1H, s, arom. H), 3.05 (1H, s, arom. H). The NMR and IR ($CHCl_3$) spectra of this synthesized compound **10** are identical with those of a degradation product **10** from the natural alkaloid, respectively.

3-Benzyloxy-N-(3-bromo-4,5-dimethoxyphenethyl)-4-methoxy-phenylacetamide (**29**)——A mixture of 3-bromo-4,5-dimethoxyphenethylamine (**13**) (60 g), O-benzylisohomovanillic acid (**28**) (55 g), and decalin (600 ml) was heated under reflux for 2 hr, according to Inubushi's procedure.[19] A usual work up gave amide **29** (75 g: 73%), mp 133—134° (from MeOH). (lit.[19] mp 126—127°). *Anal.* Calcd. for $C_{26}H_{28}O_5NBr$: C, 60.70; H, 5.49; N, 2.72; Br, 15.54. Found: C, 60.86; H, 5.56; N, 2.72; Br, 15.81. IR ν_{max}^{KBr} cm^{-1}: 3250 (N-H), 1637 (C=O). NMR ($CDCl_3$) τ: 6.58 (2H, s, $C_6H_5CH_2CO$-), 6.21 (3H, s, OMe), 6.18 (3H, s, OMe), 6.13 (3H, s, OMe), 4.89 (2H, s, $C_6H_5CH_2O$-).

(±)-1-(3-Benzyloxy-4-methoxybenzyl)-8-bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline((±)-O-Benzyl-8-bromo-N-norlaudanidine) (**31**)——To a solution of the amide **29** (35 g) in anhydrous benzene (300 ml) was added $POCl_3$ (50 g). The mixture was heated under reflux for 3 hr. A usual work up[19] gave the crude 1-(3-benzyloxy-4-mehtoxybenzyl)-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline (**30**) hydrochloride (33 g), which was dissolved in MeOH (300 ml) and reduced with $NaBH_4$ (21 g) at room temperature. The mixture was worked up as usual to give a crude tetrahydroisoquinoline derivative (**31**), which was purified *via* oxalate, mp 186—188° (from MeOH). The purified free base was yielded as prisms (9 g: 40%), mp 119—121° (from MeOH) (lit.[19] mp 115—116°). NMR ($CDCl_3$) τ: 6.15 (6H, s, 2 OMe), 6.11 (3H, s, OMe), 4.80 (2H, s, $C_6H_5CH_2O$-), 3.38 (1H, s, arom. H).

Resolution of (±)-O-Benzyl-8-bromo-N-norlaudanidine (**31**)——To a solution of racemate **31** in MeOH was added a soution of D-(−)-tartaric acid in etahnol. The mixture was allowed to stand for 24 hr at room temperature and the deposited tartarate was repeatedly recrystallized from MeOH. (*S*)-(+)-O-Benzyl-8-bromo-N-norlaudanidine (**32**) D-(−)-tartarate: mp 184—186.5°, $[\alpha]_D^{25}$+22° (*c*=1, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{28}O_4NBr \cdot 1/2C_4H_6O_6$: C, 58.64; H, 5.45; N, 2.44; Br, 13.94. Found: C, 58.70; H, 5.48; N, 2.31; Br, 14.18. (*S*)-(+)-O-Benzyl-8-bromo-N-norlaudanidine (**32**): mp 98—99° (from MeOH), $[\alpha]_D^{25}$+38.7° (*c*=2, $CHCl_3$). *Anal.* Calcd. for $C_{26}H_{28}O_4NBr$: C, 62.65; H, 5.66; N, 2.81. Found: C, 62.70; H, 5.61; N, 2.78.

(*S*)-(+)-O-Benzyl-8-bromolaudanidine (**33**)——A solution of (*S*)-(+)-O-benzyl-8-bromo-N-norlaudanidine (**32**) (9.2 g) in MeOH (100 ml) was treated with 37% formalin (1.65 g) and $NaBH_4$ (1 g) at room temperature and the mixture was worked up as usual. The non-phenolic base was extracted with benzene and the dried (K_2CO_3) extract was evaporated. The residue gave (*S*)-(+)-O-benzyl-8-bromolaudanidine (**33**) (9.3 g: 99%), mp 100—101° (from MeOH), $[\alpha]_D^{25}$+21° (*c*=2, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{30}O_4NBr$: C, 63.28; H, 5.90; N, 2.56; Br, 15.60. Found: C, 63.30; H, 5.98; N, 2.56; Br, 15.69. NMR ($CDCl_3$) τ: 7.73 (3H, s, NMe), 6.16 (6H, s, 2 OMe), 6.13 (3H, s, OMe), 4.83 (2H, s, $C_6H_5CH_2O$-), 3.39 (1H, s, arom. H).

3-Benzyloxy-4-methoxy-β-nitrostyrene (**35**)——A mixture of O-benzylisovanillin (**34**) (60 g), ammonium acetate (18 g), nitromethane (90 ml), and HOAc (180 ml) was heated under reflux for 1.5 hr. After cooling, it was poured into ice-water, and the deposited crystals were collected and recrystallized from CH_2Cl_2–EtOH to yeild 3-benzyloxy-4-methoxy-β-nitrostyrene **35** (52 g), mp 132—135° (lit.[23] mp 129—130°).

3-Benzyloxy-4-methoxyphenethylamine (**36**)——To a solution of $LiAlH_4$ (20 g) in anhydrous tetrahydrofuran (80 ml), a solution of β-nitrostyrene **35** (40 g) in tetrahydrofuran (270 ml) was dropwise added under ice-cooling and stirring. Further, the mixture was stirred at 5—10° for 1 hr. Addition of MeOH (200 ml) to decompose an excess of $LiAlH_4$, evaporation of the solvent, extraction with ether after addition of H_2O, and evaporation of the dried (K_2CO_3) extract afforded a crude oily base **36** (39.3 g), to whose solution in MeOH was added a saturated solution of oxalic acid in EtOH. The deposited crystals were recrystallized from MeOH to yield oxalate (35.8 g) of **36**, mp 204—206° (lit[21] mp 158—160°), from which the free base **36** (27.6 g) was recovered.

N-*t*-Butoxycarbonyl-3-benzyloxy-4-methoxyphenethylamine (**37**)——To a solution of the phenethylamine **36** (18.6 g) and triethylamine (9 g) in ethyl acetate (120 ml), *t*-butylazidoformate (10.5 g) was added dropwise with stirring at room temperature, and the mixture was stirred for 2 hr at 55°. The solvent was evaporated and the residue was extracted with benzene, and the extract was successively washed with 5% aq. citric acid, a dilute sodium hydrogen carbonate solution, and H_2O. Evaporation of the dried (Na_2SO_4) organic phase and recrystallization of the residue from acetone gave N-*t*-butoxycarbonyl-3-benzyloxy-4-methoxyphenethylamine (**37**) (21.8 g: 84%), mp 99—102°. *Anal.* Calcd. for $C_{21}H_{27}O_4N$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.59; H, 7.73; N, 3.91. IR ν_{max}^{KBr} cm^{-1}: 3360 (N-H), 1686 (C=O). NMR ($CDCl_3$) τ: 8.54 (9H, s, $OCMe_3$), 7.32 (2H, t, *J*=8, C_6H_5-CH_2-CH_2-NH-), 6.64 (2H, t=8 Hz, C_6H_5-CH_2-CH_2-NH-), 6.13 (3H, s, OMe), 4.86 (2H, s, C_6H_5-CH_2-O-).

N-*t*-Butoxycarbonyl-3-hydroxy-4-methoxyphenethylamine (**38**)——A solution of N-*t*-butoxycarbonyl-3-benzyloxy-4-methoxyphenethylamine (**37**) (19.7 g) in MeOH (700 ml) was hydrogenolyzed over 5% Pd-C (2 g)at atmospheric pressure and room temperature. After the catalyst was filtered off, the solvent was evaporated to dryness under reduced pressure. The residue was dissolved in 5% aq. NaOH and washed with ether. The aq. layer was acidified with citric acid and extracted with ether. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue gave crystals of *N-t*-butoxycarbonyl-3-hydroxy-4-methoxyphenethylamine (**38**) (13 g: 90%), mp 101—102° (from acetone). *Anal.* Calcd. for $C_{14}H_{21}O_4N$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.06; H, 8.04; N, 5.14. IR ν_{max}^{KBr} cm^{-1}: 3470 (O–H), 3320 (N-H), 1677

23) E. Späth and M. Pailer, *Chem. Ber.*, **67**, 1214 (1934).

(C=O). NMR ($CDCl_3$)τ: 8.55 (9H, s, $OCMe_3$), 7.29 (2H, t, J=7, C_6H_5-CH_2CH_2-NH-), 6.58 (2H, t, J=7 Hz, C_6H_5-CH_2-CH_2-NH-), 6.11 (3H, s, OMe).

(*S*)-(+)-1-(3-Benzyloxy-4-methoxybenzyl)-8-(5-*t*-butoxycarbonylaminoethyl-2-methoxyphenoxy)-2-methyl-6,7-dimethoxy-1,2,3,4-tertrahydroisoquinoline (39)——A mixture of (*S*)-(+)-O-benzyl-8-bromolaudanidine (**33**) (2.9 g), N-*t*-butoxycarbonyl-3-hydroxy-4-methoxyphenethylamine (**38**) (2 g) and anhydrous K_2CO_3 (2 g) in dry pyridine (20 ml) was heated under nitrogen to 130°, then cupric oxide powders (1 g) was added. Heating under stirring was continued at 150° for 5 hr. After cooling, the mixture was diluted with CH_2Cl_2 (20 ml), and filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was extracted with benzene; the extract was washed successively with 2% aq. NaOH, 5% aq. citric acid, and H_2O. The dried (K_2CO_3) extract was evaporated and the residue gave an oily mixture (4.2 g), which was chromatographed on a neutral alumina column by elution with benzene. The eluate was separated into two fractions.

The first fraction contained the starting material **33** (1.7 g). The second fraction gave an oily substance **39** (1.6 g: 39%), $[\alpha]_D^{25}$+8° (c=2.5, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (N-H), 1700 (C=O). NMR ($CDCl_3$) τ: 8.61 (9H, s, $OCMe_3$), 7.81 (3H, s, NMe), 6.32 (3H, s, OMe), 6.18 (3H, s, OMe), 6.16 (3H, s, OMe), 6.12 (3H, s, OMe), 5.01 (2H, s, C_6H_5-CH_2-O-), 3.60 (1H, d, J=1.5 Hz, arom. H), 3.46 (1H, s, arom. H).

(*S*)-(+)-8-(5-*t*-Butoxycarbonylaminoethyl-2-methoxyphenoxy)-1-(3-hydroxy-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (40)——The benzyloxy-base **39** (2.5 g), dissolved in EtOH (200 ml), was hydrogenolyzed over 5% Pd-C (0.5 g) at room temperature and atmospheric pressure. After filtration, the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with benzene and the extract was shaken with 5% aq. citric acid. The aq. layer was basified with aq. NH_4OH and extracted with benzene. The extract was dried (Na_2SO_4) after washing with H_2O, and evaporated to leave an oily phenolic base **40** (1.2 g: 55%), $[\alpha]_D^{25}$+16° (c=2, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540 (O-H), 3440 (N-H), 1710 (C=O). NMR ($CDCl_3$) τ: 8.61 (9H, s, $OCMe_3$), 7.77 (3H, s, NMe), 6.31 (3H, s, OMe), 6.22 (3H, s, OMe), 6.14 (3H, s, OMe), 6.06 (3H, s, OMe).

(*S*)-(—)-8-(5-*t*-Butoxycarbonylaminoethyl-2-methoxyphenoxy)-6,7-dimethoxy-1-[4-methoxy-3-(4-methoxycarbonylmethylphenoxy)-benzyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline (42)——A mixture of the phenolic base **40** (0.5 g), methyl 4-bromophenylacetate (**41**) (0.3 g), and anhydrous K_2CO_3 (0.25 g) in dry pyridine (15 ml) was heated under nitrogen with stirring to 130°, and then fine cupric oxide powders (0.15 g) was added. Heating was continued at 150° for 4 hr. The mixture, after cooling, was diluted with CH_2Cl_2 (15 ml) and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was extracted with benzene and the extract was washed with 5% aq. citric acid and dried (K_2CO_3). Evaporation left a crude substance, which was dissolved in MeOH and was treated with activated charcoal under reflux. After filtration of charcoal, the solvent was evaporated and the residue was chromatographed on neutral alumina in benzene to give a viscous oil **42** (0.49 g: 79%), $[\alpha]_D^{25}$—8.1° (c=2.35, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (N-H), 1730 (C=O), 1708 (C=O). NMR ($CDCl_3$) τ: 8.59 (9H, s, $OCMe_3$), 7.75 (3H, s, NMe), 6.42 (2H, s, C_6H_5-CH_2-CO-), 6.33 (3H, s, OMe), 6.31 (3H, s, OMe), 6.24 (3H, s, OMe), 6.22 (3H, s, OMe), 6.14 (3H, s, OMe), 3.65 (1H, br s, arom. H), 3.47 (1H, br s, arom. H).

Cycloamide 46——The ester **42** (0.89 g) was dissolved in a mixture of 5% aq. NaOH (5 ml) and MeOH (15 ml) and stirred overnight. After removal of MeOH, the residual solution was acidified with oxalic acid and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to dryness. The residue **43** was dissolved in EtOAc (15 ml). After addition of *p*-nitrophenol (0.21 g), the mixture was cooled to 0—5°. Then, a solution of dicyclohexylcarbodiimide (0.37 g) in ether (5 ml) was dropwise added with stirring at 0—5° and the mixture was stirred for a further 30 min under cooling, then for 1 hr at room temperature. Dicyclohexylurea was filtered off. The filtrate was evaporated to dryness under reduced pressure. The residue was washed with *n*-hexane to remove excess of dicyclohexylcarbodiimide, dissolved in trifluoroacetic acid (10 ml) and allowed to stand at room temperature for 1 hr. Excess of trifluoroacetic acid was removed under reduced pressure and the residue, the crude phenethylamine trifluoroacetate **45**, was dissolved in anhydrous dimethylformamide. The solution was dropwise added to dry pyridine (200 ml) at 80° with stirring during 3 hr. Stirring was continued at same temperature for 1 hr. The solvent was removed to give a residual oil, which was dissolved in CH_2Cl_2 and then washed with 2% aq. NaOH. The organic phase was dried (Na_2SO_4) and evaporation of the solvent left a viscous oil, which was crystallized from MeOH to give the cycloamide **46** (0.55 g: 75%), mp 281—284° (from MeOH), $[\alpha]_D^{25}$+112° (c=1, $CHCl_3$). *Anal.* Calcd. for $C_{37}H_{40}O_7N_2 \cdot 1/2CH_3OH$: C, 70.29; H, 6.61; N, 4.37. Found: C, 70.28; H, 6.74; N, 4.27. IR ν_{max}^{KBr} cm^{-1}: 3380 (N-H), 1665 (C=O). NMR ($CDCl_3$) τ: 8.07 (3H, s, NMe), 6.47 (2H, s, C_6H_5-CH_2-CO-), 6.24 (6H, s, 2 OMe), 6.14 (3H, s, OMe), 6.12 (3H, s, OMe), 4.18 (1H, d, J=2 Hz, arom. H), 3.77 (1H, s, arom. H). Mass Spectrum *m/e*: 624 (M^+), 609 (M^+-CH_3), 326, 211.

O-Methylthalmetine (47)——A mixture of the cycloamide **46** (397 mg) and $POCl_3$ (1.2 g) in anhydrous $CHCl_3$ (20 ml) was heated under reflux for 1 hr. Evaporation of $CHCl_3$ and $POCl_3$ under reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was treated with dil. NH_4OH and washed with H_2O. After drying, the solvent was evaporated off to give a crude base (0.38 g), which was purified by chromatography on alumina column to yield **47** as the amorphous powders (0.15 g: 38%), $[\alpha]_D^{25}$+175° (c=

2.5, $CHCl_3$). NMR ($CDCl_3$) τ: 8.06 (3H, s, NMe), 6.29 (3H, s, OMe), 6.16 (3H, s, OMe), 6.12 (3H, s, OMe), 6.10 (3H, s, OMe), 5.78 (2H, br s, C_6H_5-CH_2-Ċ=N-).

N-Nor-O-methylthalicberine (48)——To a solution of 3,4-dihydroisoquinoline derivative **47** (146 mg) in MeOH (15 ml) was added $NaBH_4$ (100 mg) in small portions at room temperature with stirring. Stirring was then continued for 30 min. The mixture was worked up as usual and N-nor-O-methylthalicberine (**48**) was obtained as crystals (105 mg: 70%), mp 262—264° (from $MeOH \cdot H_2O$), $[\alpha]_D^{25}$ +245° (c=1, $CHCl_3$). *Anal.* Calcd. for $C_{37}H_{40}O_6N_2 \cdot H_2O$: C, 70.90; H, 6.76; N, 4.47. Found: C, 71.17; H, 6.81; N, 4.48. NMR ($CDCl_3$) τ: 7.91 (3H, s, NMe), 6.35 (3H, s, OMe), 6.22 (3H, s, OMe), 6.13 (3H, s, OMe), 6.10 (3H, s, OMe), 3.88 (1H, s, arom. H). Mass Spectrum m/e: 608 (M^+), 381 (M^+-$C_{15}H_{15}O_2$), 149. Its NMR spectrum was identical with that of O-methylthalicberine (**1**) except a singlet signal at τ 7.43 in **1**.

O-Methylthalicberine (1)——To a stirred solution of N-nor-O-methylthalicberine (**48**) (15 mg) in MeOH (5 ml) was dropwise added formalin at room temperature. After stirring for 1 hr, $NaBH_4$ (300 mg) was added in small portions and the mixture was stirred for further 30 min. A usual work up yielded O-methylthalicberine (**1**) (15 mg), mp 184° (from EtOH), $[\alpha]_D^{25}$ +243° (c=0.21, $CHCl_3$). NMR ($CDCl_3$) τ: 7.91 (3H, s, NMe), 7.43 (3H, s, NMe), 6.34 (3H, s, OMe), 6.22 (3H, s, OMe), 6.13 (3H, s, OMe), 6.10 (3H, s, OMe). Mass Spectrum m/e: 622 (M^+), 395, 381, 204, 198, 174. The IR, NMR, and mass spectra were completely identical with those of natural O-methylthalicberine, respectively. The mixture melting point was not depressed. The behaviors on TLC were also completely the same.

O-Methylthalicberine Picrate——a) Synthetic: mp 184—194° (decomp.) (from EtOH), $[\alpha]_D^{25}$ +138° (c=0.3, $CHCl_3$); b) from natural alkaloid: mp 188—199° (decomp.) (from EtOH), $[\alpha]_D^{25}$ +140° (c=0.3, $CHCl_3$).

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