A. Indeed, nigakihemiacetal C gave nigakilactone A,¹⁾ I (R=O, R'=H), on oxidation with Ag₂O. Thus, nigakihemiacetal C should be represented by I (R=OH, H; R'=H). The presence of hydrogen bond between carbonyl at C₁ and hydroxyl group at C₁₁ leads to structure I (R=OAc, H; R'=Ac) for the diacetate.

Spectral data of nigakilactone I, mp 255—256°, C₂₁H₂₈O₆ (M⁺ at *m/e* 376), suggest that this bitter substance would be identical with picrasin B.²⁾ This was confirmed by direct comparison with the authentic specimen.²⁾

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Total Synthesis of Optically Active Natural O-Methylthalicberine

O-Methylthalicberine is the first bisbenzylisoquinoline alkaloid isolated from a Ranunculaceae plant, that is, *Thalictrum Thunbergii* DC (Japanese name "Akikaramatsu") by Fujita and Tomimatsu.¹⁾ Its structure²⁾ and absolute configuration^{2,3)} has been clarified and its unique 19-membered macro-ring system was the first example⁴⁾ in the bisbenzylisoquinoline alkaloids. We describe here the total synthesis of optically active natural O-methylthalicberine, which confirms its structure and absolute configuration **1b**.

An important intermediate, (S)-(+)-O-benzyl-8-bromo-N-nor-laudanidine (**2a**), mp 98—99°, [α]_D +38.7° (CHCl₃), was yielded by the optical resolution of the synthetic racemate of **2a** via its (—)-tartaric acid salt. N-Methylation of the resolved base **2a** gave (+)-O-benzyl-8-bromolaudanidine (**2b**). The structure and optical purity of the compounds **2a** and **2b** was assured by the comparison of the melting point and the specific rotation with those of their enantiomers which have been synthesized by Inubushi, *et al.*,⁵⁾ respectively.

The Ullmann condensation of the base **2b** with N-*t*-butoxycarbonyl-3-hydroxy-4-methoxyphenethyl amine (**3**), mp 101—102°, C₁₄H₂₁O₄N, synthesized from O-benzylisovanillin via a usual pathway afforded the compound **4a** as an oily product⁶⁾ in 39% yield. Hydrogenolysis

1) E. Fujita and T. Tomimatsu, *Yakugaku Zasshi*, **79**, 1256 (1959).

2) 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).

3) M. Tomita and J. Kunitomo, *Yakugaku Zasshi*, **82**, 741 (1962).

4) For the similar system found later, see a) N.M. Mollov, H.B. Dutschewska, and H.G. Kirjakov, *Chem. Ind. (London)*, **1965**, 1595; b) M.R. Falco, J.X. de Vries, A.G. de Brovotto, Z. Macció, S. Rebuffo, and I.R.C. Bick, *Tetrahedron Letters*, **1968**, 1953.

5) Y. Inubushi, Y. Masaki, S. Matsumoto, and F. Takami, *Tetrahedron Letters*, **1968**, 3399; *idem*, *J. Chem. Soc. (C)*, **1969**, 1547.

6) The infrared (IR) and nuclear magnetic resonance (NMR) spectra of the amorphous or oily substance marked with this symbol showed reasonable patterns for the corresponding structure to each compound and homogeneity was also verified by thin-layer chromatography and NMR spectrum measurements.

of the compound **4a**, followed by the Ullmann condensation with methyl *p*-bromophenylacetate gave a bis diphenyl ether derivative **5a** as a viscous oily product⁶⁾ in 79% yield. The methyl ester **5a** was converted into *p*-nitrophenyl ester **5b** via the free acid, and **5b**, after removal of the protecting *t*-butoxycarbonyl group by trifluoroacetic acid, was transformed into the cycloamide **6**, mp 281–284°, $[\alpha]_D^{25} +112^\circ$ (CHCl₃), C₃₇H₄₀O₇N₂·½CH₃OH, in 75% yield.

The Bischler–Napieralski reaction with **6** gave the 3,4-dihydroisoquinoline derivative **7** in 38% yield. The latter compound corresponds to O-methylthalmetine,^{4a)} but the crystallisation was unsuccessful because of high solubility in various organic solvents and easy colouring under treatment with solvents. The nuclear magnetic resonance (NMR) spectrum of **7**, however, was completely identical with that of the authentic sample of O-methylthalmetine.⁷⁾

Reduction of **7** with NaBH₄ afforded a product, mp 262–264°, $[\alpha]_D^{25} +245^\circ$ (CHCl₃), C₃₇H₄₀O₆N₂·H₂O, stereoselectively in 70% yield. The NMR spectrum of this product was identical with that of O-methylthalicberine except a singlet signal at τ 7.43 in the latter, hence the product must be N-nor-O-methylthalicberine (**1a**) and the conformation of both compounds was shown to be the same. The N-methylation of **1a** yielded the final product, mp 184°,

7) The authentic sample was kindly supplied by Dr. N. Mollov, Bulgarian Academy of Science.

$[\alpha]_D +243^\circ$, $C_{38}H_{42}O_6N_2$, which was proved to be identical with the natural alkaloid, O-methyl-thalicberine (**1b**) (mp, mixed mp, IR, and NMR spectra).

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