

A NOVEL SYNTHESIS OF 5- OR 13-OXYGENATED  
TETRAHYDROPROTOBERBERINES<sup>§</sup>

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In order to introduce O-functional groups at the 5- or 13-position in tetrahydroprotoberberine, we tried lead tetraacetate oxidation of (±)-2-hydroxy-3,10,11-trimethoxy (3)- or (±)-10-hydroxy-2,3,11-trimethoxy (12)-tetrahydroprotoberberine, a moiety of which was 1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-isoquinoline convertible to the corresponding 4,7-diacetate via p-quinol acetate.

(±)-2-Phenol (3) yielded a p-quinol acetate (4), which was transformed to several 5-oxygenated tetrahydroprotoberberines (6,7,8,9,10, and 11). Similarly, some 13-oxygenated derivatives (14,15, and 16) were prepared from (±)-10-phenol (12).

Protoberberine alkaloids carrying a hydroxyl group at the

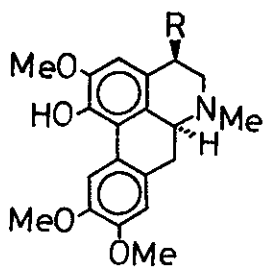
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<sup>§</sup> Dedicated to Emeritus Professor S. Sugasawa of University of Tokyo on the occasion of his eightieth birthday.

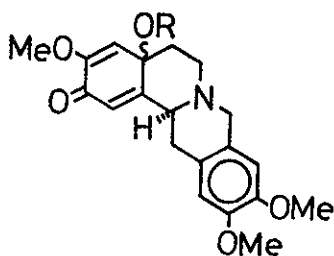
5-<sup>1)</sup> or 13-<sup>2)</sup> position have been known and their syntheses have also been achieved by several methods such as Pomeranz-Fritsch type cyclization leading to 5-hydroxy compounds<sup>3)</sup>, hydroboration-oxidation to a 5-<sup>4)</sup> or 13<sup>5)</sup>-hydroxy compound, and conversion of phthalide isoquinolines<sup>6)</sup>, Mannich reaction of  $\alpha$ -hydroxybenzylisoquinolines<sup>7)</sup> or hydride reduction of the oxidation products of berberine-acetone<sup>8a)</sup>, berberine<sup>8b)</sup>, and dihydroberberine<sup>2b,8c)</sup> to 13-hydroxy compounds.

Our success that ( $\pm$ )-thaliporphine (1) has on oxidation with lead tetraacetate [Pb(OAc)<sub>4</sub>] been stereospecifically transformed in one step to ( $\pm$ )-4 $\beta$ -acetoxythaliporphine (2)<sup>9)</sup> encouraged us to carry out similar reactions on 2- or 10-phenolic tetrahydroprotoberberine in an anticipation to introduce oxygen functions at the 5- or 13-position. This communication deals with a novel synthesis of the title compounds in a stereoselective manner by use of Pb(OAc)<sub>4</sub>.

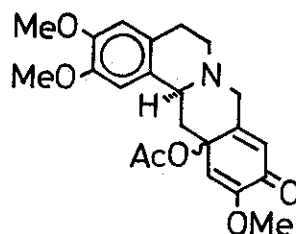
To a solution of ( $\pm$ )-2-hydroxy-3,10,11-trimethoxy-tetrahydroprotoberberine (3)<sup>10)</sup> (400 mg) in acetic acid (4 ml) was added Pb(OAc)<sub>4</sub> (624 mg, 1.1 eq.) in one portion and the whole was stirred for 30 min at room temperature. Contrary to the anticipation, usual work-up<sup>12)</sup> gave a p-quinol acetate (4) [mp 159-161°; IR<sup>13)</sup>: 1740 (OCOCH<sub>3</sub>), 1670, 1645, 1630 cm<sup>-1</sup> (dienone)] (455 mg, quantitative). The p-quinol acetate was by no means a mixture of diastereoisomers because it displayed a sole spot on TLC and a simple pattern consisting of all singlet peaks [NMR<sup>13)</sup>  $\delta$ : 2.02 (3H, s, NCH<sub>3</sub>), 3.66, 3.78, 3.80 (each 3H, s, 3xOCH<sub>3</sub>), 5.88, 6.28 (each 1H, s, 2 x olefinic H), 6.50, 6.61 (each 1H, s, 2 x aromatic H)] ascribable to a diastereoisomer. However, attempted hydrolysis of 4 failed to give a p-quinol



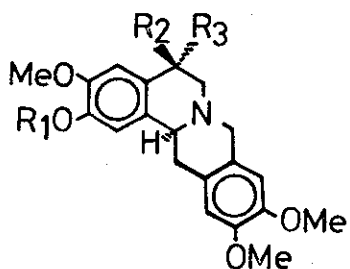
R  
1 : H  
2 : OAc



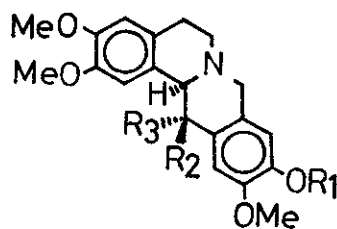
R  
4 : Ac  
5 : H



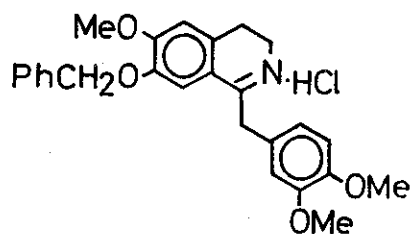
13



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
<u>3</u> :	H	H	H
<u>6</u> :	Ac	OAc	H
<u>7</u> :	H	OH	H
<u>8</u> :	Me	OH	H
<u>9</u> :	Me	OAc	H
<u>10</u> :	H	H	OMe
<u>11</u> :	H	OMe	H



	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
<u>12</u> :	H	H	H
<u>14</u> :	Ac	OAc	H
<u>15</u> :	Ac	H	OAc
<u>16</u> :	H	H	OMe



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(5) leaving stereochemistry of 4 unsolved.

Accordingly, a usual rearrangement technique in this region<sup>12)</sup> was next tried. Namely, to a stirred suspension of the unpurified 4 (455 mg) in acetic anhydride (4 ml) under ice-cooling, was added conc. sulfuric acid (0.8 ml) drop by drop during 30 sec. The whole was stirred for 1 hr at room temperature and work-up as usual gave stereospecifically ( $\pm$ )-2, 5 $\beta$ -diacetate (6) [IR: 1760, 1725  $\text{cm}^{-1}$ ; NMR  $\delta$ : 6.00 (1H, t,  $J=2.5\text{Hz}$ )] (468 mg, 91%). Purification on a silica gel short column and repeated recrystallization from acetone-pet. ether yielded colorless fine needles, mp 150-151°. Hydrolysis with conc. hydrochloric acid of 6 gave ( $\pm$ )-2, 5 $\beta$ -diol (7) [mp 165-170°; IR: 3540  $\text{cm}^{-1}$  (OH); NMR (in  $\text{d}_5$ -pyridine)  $\delta$ : 4.84 (1H, t,  $J=2.5\text{Hz}$ )], re-acetylation of which with acetic anhydride and pyridine led back to 6. For further confirmation of their structures, two derivatives of the diol (7) were prepared by conventional methods; ( $\pm$ )-5 $\beta$ -hydroxy-2,3,10,11-tetramethoxytetrahydroprotoberberine (8)<sup>14)</sup> [mp 189-190° (lit.<sup>3a)</sup> mp 194-195°] and ( $\pm$ )-5 $\beta$ -acetate (9)<sup>14)</sup> [mp 184-186° (lit.<sup>3a)</sup> mp 188-189°].

Treatment<sup>12)</sup> of a suspension of 6 in MeOH with 5% KOH and purification on preparative TLC<sup>15)</sup> ( $\text{CHCl}_3$ : MeOH=30:1) gave rise to ( $\pm$ )-5 $\alpha$ -methoxy (10)-[mp 179-181° (dec.); IR: 3540  $\text{cm}^{-1}$ ; NMR  $\delta$ : 4.58 (1H, dd,  $J=5, 10\text{Hz}$ )] and ( $\pm$ )-5 $\beta$ -methoxy (11)-[mp 137.5-138°; IR: 3540  $\text{cm}^{-1}$ ; NMR  $\delta$ : 4.20 (1H, t,  $J=2.5\text{Hz}$ )] 2-hydroxy-3,10,11-trimethoxytetrahydroprotoberberines in 29% and 35% yield, respectively.

Similarly,  $\text{Pb}(\text{OAc})_4$  oxidation of ( $\pm$ )-10-hydroxy-2,3,11-trimethoxytetrahydroprotoberberine (12)<sup>16)</sup> gave quantitatively an oily p-quinol acetate (13) [IR: 1740, 1675, 1645, 1630  $\text{cm}^{-1}$ ,

NMR  $\delta$ : 2.12 ( $\text{OCOCH}_3$ ), 3.67, 3.83, 3.86 (each 3H, s,  $3 \times \text{OCH}_3$ ), 5.87, 6.24 (each 1H, s, 2 x olefinic H), 6.58, 6.59 (each 1H, s, 2 x aromatic H)], stereochemistry of which was unknown though homogeneous. Similar acid treatment with acetic anhydride and conc. sulfuric acid followed by purification on a silica gel column<sup>15)</sup> gave ( $\pm$ )-10, 13 $\beta$ -diacetate (14)<sup>17)</sup> [mp 166-167°; IR: 1765, 1730  $\text{cm}^{-1}$ ; NMR  $\delta$ : 6.54 (1H, d,  $J=2.5\text{Hz}$ )] and ( $\pm$ )-10, 13 $\alpha$ -diacetate (15)<sup>17)</sup> [mp 168.5-169°; IR: 1760, 1730  $\text{cm}^{-1}$ ; NMR  $\delta$ : 6.14 (1H, d,  $J=7.5\text{Hz}$ )] in a ratio of 3:1. This result was consistent with a suggestion on relative steric effect between 13 $\alpha$ - and 13 $\beta$ -hydroxytetrahydroprotoberberines<sup>5)</sup>.

Although attempted hydrolysis of 14 and 15 to their respective diols was futile, reaction with 5% KOH in MeOH of 14 and 15 took place to give solely ( $\pm$ )-10-hydroxy-13 $\alpha$ -methoxy-2,3,11-trimethoxytetrahydroprotoberberine (16) [mp 146-148°; IR: 3530  $\text{cm}^{-1}$ ; NMR  $\delta$ : 4.64 (1H, d,  $J=9\text{Hz}$ )] in 28% and 27% yield, respectively. However, the reason why the reaction lacked stereoselectivity as observed in the case of the rearrangement of 13 remained unexplained in spite of the common belief that these reactions proceeded through a p-quinone methide<sup>12)</sup>.

Thus, 5- and 13-oxygenated tetrahydroprotoberberines were synthesized stereoselectively (partly stereospecifically) starting from 2- and 10-phenolic congeners according to an entirely different method from hitherto known ones. In particular, synthesis of the 13-acetoxytetrahydroprotoberberines in the manner described above could be referred as biomimetic<sup>18)</sup>. One step synthesis of 5- or 13-acetoxytetrahydroprotoberberine on  $\text{Pb}(\text{OAc})_4$  oxidation of 3- or 11-phenolic congener is currently investigated.

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10. Compound (3) was prepared from 3,4-dihydroisoquinoline hydrochloride (17)<sup>11)</sup> with NaBH<sub>4</sub> reduction, cyclization (98% HCOOH/37% HCHO) and debenzylation (H<sub>2</sub>/Pd-C, MeOH, H<sup>+</sup>). All new compounds gave satisfactory analytical data.
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13. NMR spectra were taken with a Japan Electron Optics Labs. Model JNR-4H-100 spectrometer in CDCl<sub>3</sub> solution by using (CH<sub>3</sub>)<sub>4</sub>Si as an internal standard, unless otherwise noted. IR spectra were run on a Hitachi 225 spectrometer in CHCl<sub>3</sub>.
14. NMR and IR spectroscopic data of 8 and 9 were consistent with those given in the literature<sup>3a)</sup>.
15. Preparative TLC was run on silica gel HF<sub>254</sub> (Merck). Column chromatography was performed on silica gel (Kanto Chemical), eluant: CHCl<sub>3</sub>.
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17. Configuration of the 13-acetoxyl group was determined by values of the coupling constant of the 13-hydrogen and these were well accordant with those of other models<sup>2b,6b,8b</sup>.
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