



A total synthesis of dendrobine
by Cheol Hae Lee

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in
Chemistry

Montana State University

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Abstract:

The total synthesis of (dl)-dendrobine is described.

Dendrobine, the major alkaloid isolated from the Chinese drug "Chin-Chai-Shi-Hu", could be synthesized in eight linear steps from 2-methylcyclopent-2-enone 26 and acylchloride 8. Acylchloride 8 was prepared from 2-isopropylfumaric acid 15 by regioselective esterification. The key step of the synthesis was acylnitrilium ion cyclization of isonitrile 7, which generated acylpyrroline 6 as a single stereo isomer.

Acylpyrroline 6 was converted into the N-methylpyrrolidine 5 by stereoselective reduction of N-methyltriflate 34. Sml₂-mediated cyclization of N-methylpyrrolidine 5B-S produced tricyclic β -hydroxyester 52, which was transformed into (dl)-dendrobine(1) in four steps.

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**MONTANA STATE UNIVERSITY
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April 1991

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APPROVAL

of a thesis submitted by

Cheol Hae Lee

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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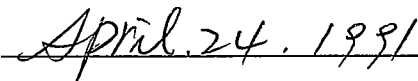
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To My Wife, Kyung Hie

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ABSTRACT

The total synthesis of (dl)-dendrobine is described.

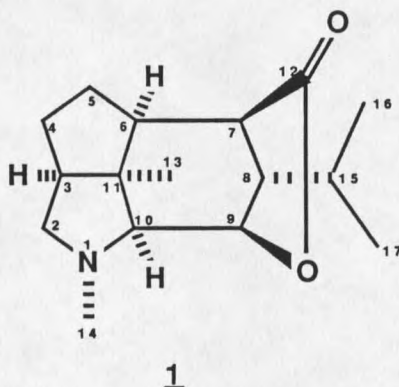
Dendrobine, the major alkaloid isolated from the chinese drug "Chin-Chai-Shi-Hu", could be synthesized in eight linear steps from 2-methylcyclopent-2-enone 26 and acylchloride 8. Acylchloride 8 was prepared from 2-isopropylfumaric acid 15 by regioselective esterification. The key step of the synthesis was acylnitrilium ion cyclization of isonitrile 7, which generated acylpyrroline 6 as a single stereo isomer.

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INTRODUCTION

Nature of Dendrobine

Dendrobine (1) is an archetypical member of a class of sesquiterpenoid alkaloids having a bridging lactone and the hydrindane ring system as shown.

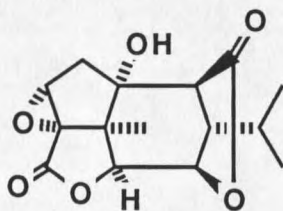


Dendrobium nobile Lindl. (Orchidaceae), known in China as "Chin-Chai-Shi-Hu," is used as a tonic in traditional medicine. The stems of the plant are prescribed to improve appetite, stimulate salivary secretion, and promote general health¹. The herb is frequently taken by opera singers to improve their voices.

Dendrobine was the first alkaloid to be isolated from *Dendrobium nobile* Lindl. by H. Suzuki in 1932. Reports of chemical investigations of dendrobine disappeared from the chemical literature until 1963-64

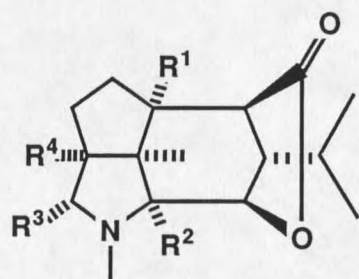
when three groups independently proposed structure of 1 for dendrobine on the basis of degradative studies³. Subsequent investigation has revealed that, in addition to 1, the alkaloids dendramine⁴ (2), dendroxine⁵ (6), 6-hydroxydendroxine^{4c} (7), nobilonine^{3a,6} (13), and five minor quaternary salts⁷ are produced by *Dendrobium nobile* Lindl. The occurrence of these alkaloids is not restricted to *D. nobile* L. as dendrobine has been detected in three additional *Dendrobium* species, *D. linawianum* Rchb.f.⁸, *D. hildebrandii* Rolfe⁹, and *D. findayanum* Par et. Rchb. f.¹⁰ In addition, the three latter species have yielded 10-hydroxydendrobine¹⁰ (3), 3-hydroxy-2-oxodendrobine¹¹ (5), and 6-hydroxynobilonine⁹ (14) respectively, bringing the total of known *Dendrobium* alkaloids to fourteen (Figure 1).

The absolute configuration of dendrobine has been determined by concordant ORD studies of various degradation products¹² and confirmed by the comparison of the circular dichroism curves of nobilonine (13) and picrotoxinin¹³ (15).

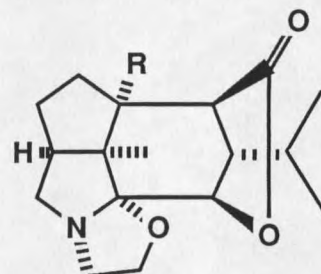


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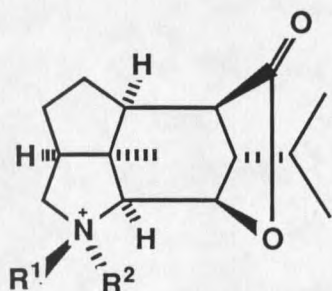
Figure 1. Naturally Occurring Dendrobine-type Alkaloids



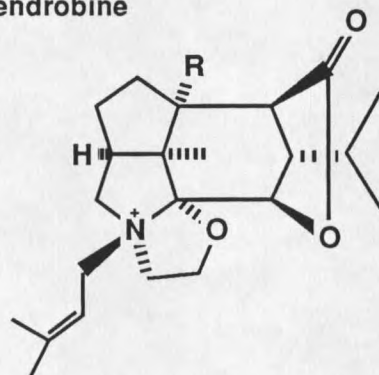
1. $R^1=R^2=R^3=R^4=H$, Dendrobine
2. $R^2=R^3=R^4=H$, $R^1=OH$, Dendramine
3. $R^1=R^3=R^4=H$, $R^2=OH$, 10-Hydroxydendrobine
4. $R^1=R^2=R^4=H$, $R^3=CH_2CO_2CH_3$, Dendrine
5. $R^1=R^2=H$, $R^3=O$, $R^4=OH$, 3-Hydroxy-2-oxodendrobine



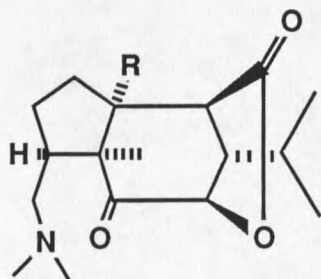
6. $R=H$, Dendroxine
7. $R=OH$, 6-Hydroxydendroxine



8. $R^1=R^2=CH_3$, N-Methyldendrobine
9. $R^1=CH_3$, $R^2=CH_2CH=C(CH_3)_2$, N-Isopentyldendrobine
10. $R^1=O^-$, $R^2=CH_3$, Dendrobine N-oxide



11. $R=H$, N-Isopentyldendroxine
12. $R=OH$, N-Isopentyl 6-Hydroxyldendroxine

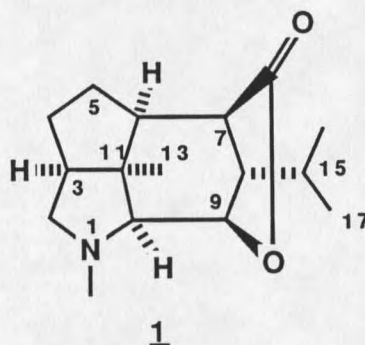


13. $R=H$, Nobilonine
14. $R=OH$, 6-Hydroxynobilonine

All structures of racemic substances included in this thesis are written in the configuration for natural dendrobine (1).

The observed physical and spectral properties of dendrobine (1) are listed in Table 1.

Table 1. Physical and Spectral Properties of Dendrobine.

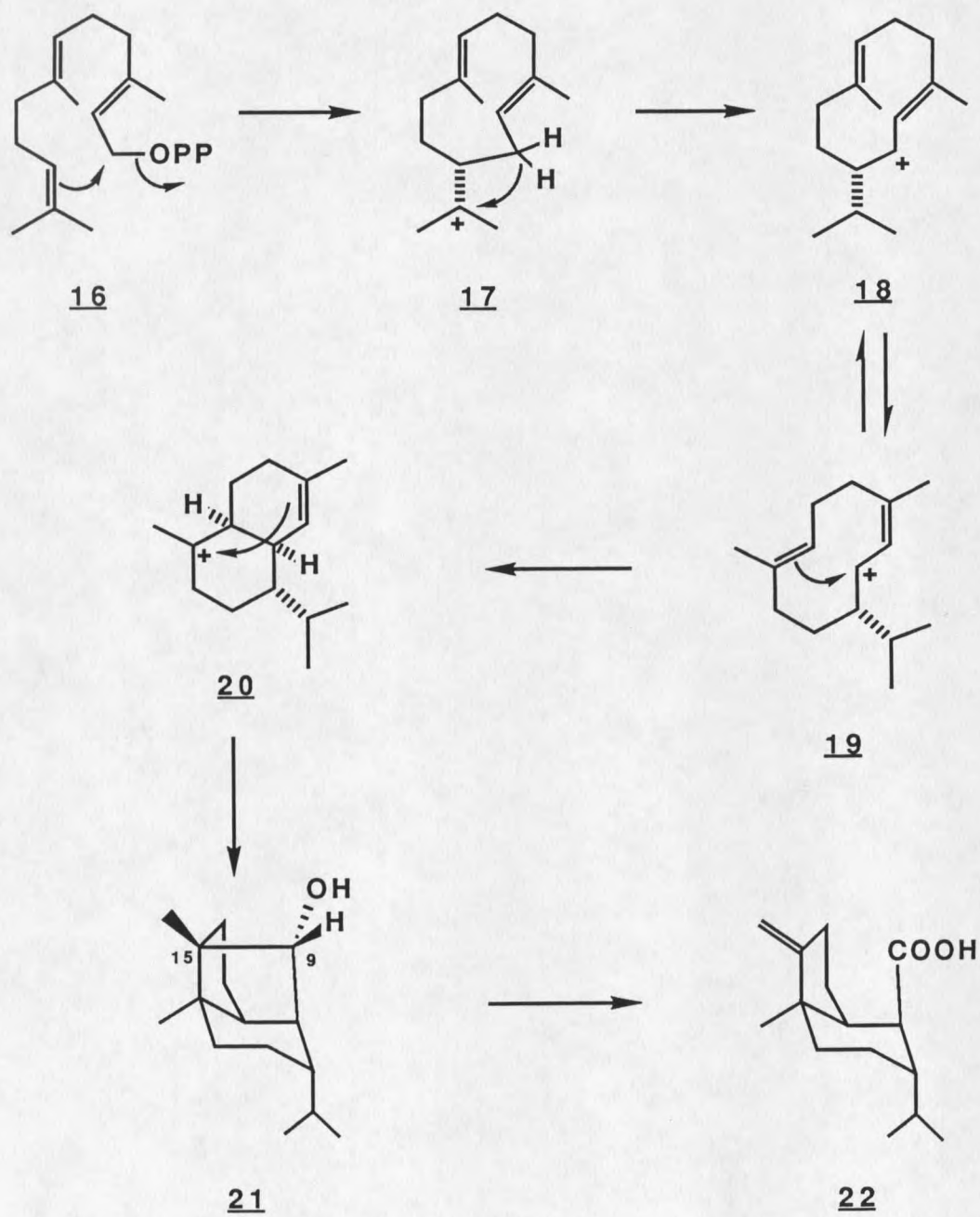


M.P.	135 ⁰ -136 ⁰ °C	
[α] _D	-46.8 ⁰ (EtOH)	
M.W.	263.19	
M.F.	C ₁₆ H ₂₅ O ₂ N	
IR(<i>V</i> _{max} , KBr)	1765 cm ⁻¹ (lactone)	
¹ H NMR(δ , TMS)	4.80(q, J=3,6 Hz)	CH-9
	2.49(s)	CH ₃ -14
	1.33(s)	CH ₃ -13
MASS	263(M ⁺), 206, 192, 178, 164, 136, 109, 108, 81, 58, 41, 28	

The biosynthesis of dendrobine most probably proceeds by the path outlined in Figure 2. Trans, trans farnesyl pyrophosphate(16), a known biosynthetic precursor of 1, cyclizes to the germacradiene cation 17, which undergoes a 1,3-hydride shift to cation 18. This cation must equilibrate between its two geometrical isomers so that the isomer 19 can cyclize to the copaborneol¹⁶ (21) via the cation 20. Subsequent oxidative fission of C₉-C₁₅ bond of 21 gives the picrotoxane (22) which is a likely precursor of dendrobine¹⁷.

In addition to the antipyretic activity of "Chin-Chai-Shi-Hu," these compounds exhibit weak analeptic and analgesic activities. In small dosages, 1 lowers blood pressure, retards cardiac activity, supresses respiration and produces moderate hyperglycemia. The alkaloid can be used as an antidote for barbituate overdoses, but this treatment is not prescribed since dendrobine produces convulsions and death in large doses. The scope of the biological activities of 1 is similar to that of picrotoxinin (15), but they are generally five to seven times weaker in action¹⁸.

Figure 2. Biosynthesis of Dendrobine



Previous Total Syntheses of Dendrobine

Interest in the synthesis of Orchidaceae alkaloids stems from the biological activity, its central position in a moderately large class of natural products and its challenging structure which incorporates a total of seven stereogenic centers distributed among 17 skeletal atoms arranged in four rings. Given its intricate architecture, it is thus not surprising that dendrobine has been selected as a target by a number of investigators, and these efforts have culminated in 5 total syntheses of dendrobine¹⁹. Interestingly, dendramine (2) and dendroxine (6) have never been synthesized since their isolation.

In the first dendrobine synthesis by Inubushi and coworkers^{19a,c}, which is outlined in Figure 3, the cis-perhydroindane nucleus was established by a selective catalytic hydrogenation of ketonitrile 6. This intermediate was prepared from the ketol 3. The stereocenter at C₁ in Intermediates 5, 6, and 7 was opposite to that required for pyrrolidone formation, but this was rectified by an acid catalyzed epimerization reaction during the hydrolysis of 7 under conditions whereby the unsaturated acid 8 underwent an intramolecular Michael reaction, leading to 9. Compound 9 was heated with aqueous CH₃NH₂

