



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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in

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**MONTANA STATE UNIVERSITY
Bozeman, Montana**

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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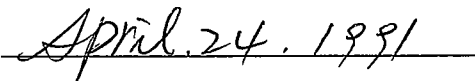
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To My Wife, Kyung Hie

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ABSTRACT

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

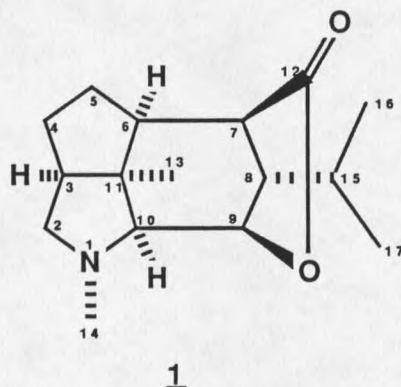
Dendrobine, the major alkaloid isolated from the chinese drug "Chin-Chai-Shi-Hu", could be synthesized in eight linear steps from 2-methylcyclopent-2-enone 26 and acylchloride 8. Acylchloride 8 was prepared from 2-isopropylfumaric acid 15 by regioselective esterification. The key step of the synthesis 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.

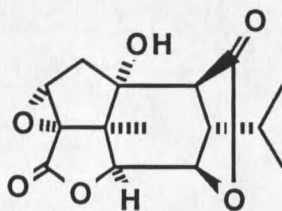


Dendrobium nobile Lindl. (Orchidaceae), known in China as "Chin-Chai-Shi-Hu," is used as a tonic in traditional medicine. The stems of the plant are prescribed to improve appetite, stimulate salivary secretion, and promote general health¹. The herb is frequently taken by opera singers to improve their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

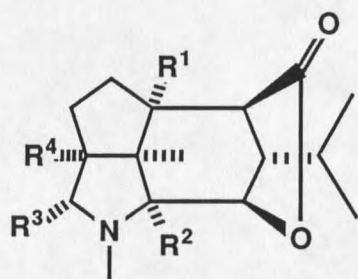
when three groups independently proposed structure of 1 for dendrobine on the basis of degradative studies³. Subsequent investigation has revealed that, in addition to 1, the alkaloids dendramine⁴ (2), dendroxine⁵ (6), 6-hydroxydendroxine^{4c} (7), nobilonine^{3a,6} (13), and five minor quaternary salts⁷ 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).

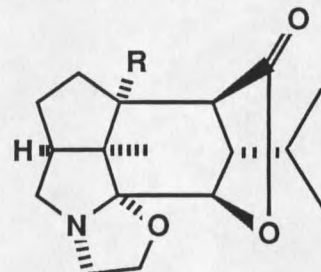


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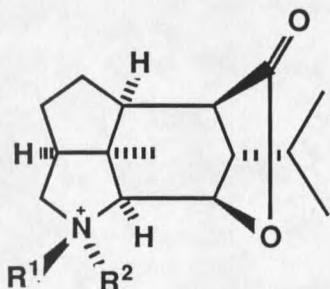
Figure 1. Naturally Occurring Dendrobine-type Alkaloids



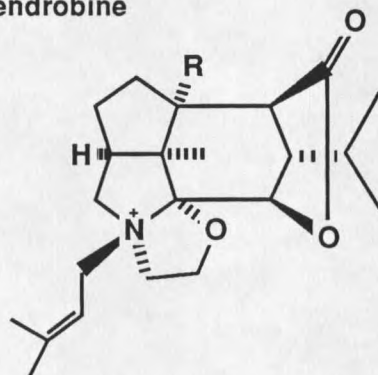
1. $R^1=R^2=R^3=R^4=H$, Dendrobine
2. $R^2=R^3=R^4=H$, $R^1=OH$, Dendramine
3. $R^1=R^3=R^4=H$, $R^2=OH$, 10-Hydroxydendrobine
4. $R^1=R^2=R^4=H$, $R^3=CH_2CO_2CH_3$, Dendrine
5. $R^1=R^2=H$, $R^3=O$, $R^4=OH$, 3-Hydroxy-2-oxodendrobine



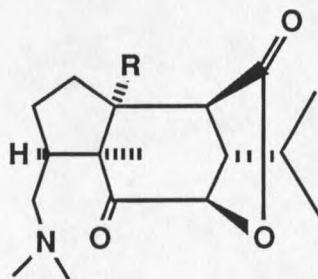
6. $R=H$, Dendroxine
7. $R=OH$, 6-Hydroxydendroxine



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



11. $R=H$, N-Isopentenylidendroxine
12. $R=OH$, N-Isopentenyl 6-Hydroxydendroxine

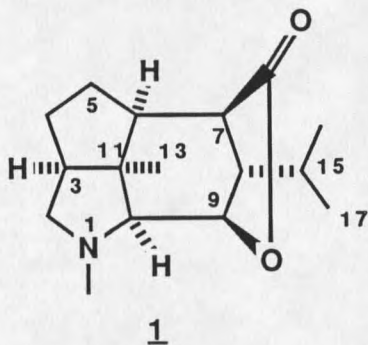


13. $R=H$, Nobilonine
14. $R=OH$, 6-Hydroxynobilonine

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.

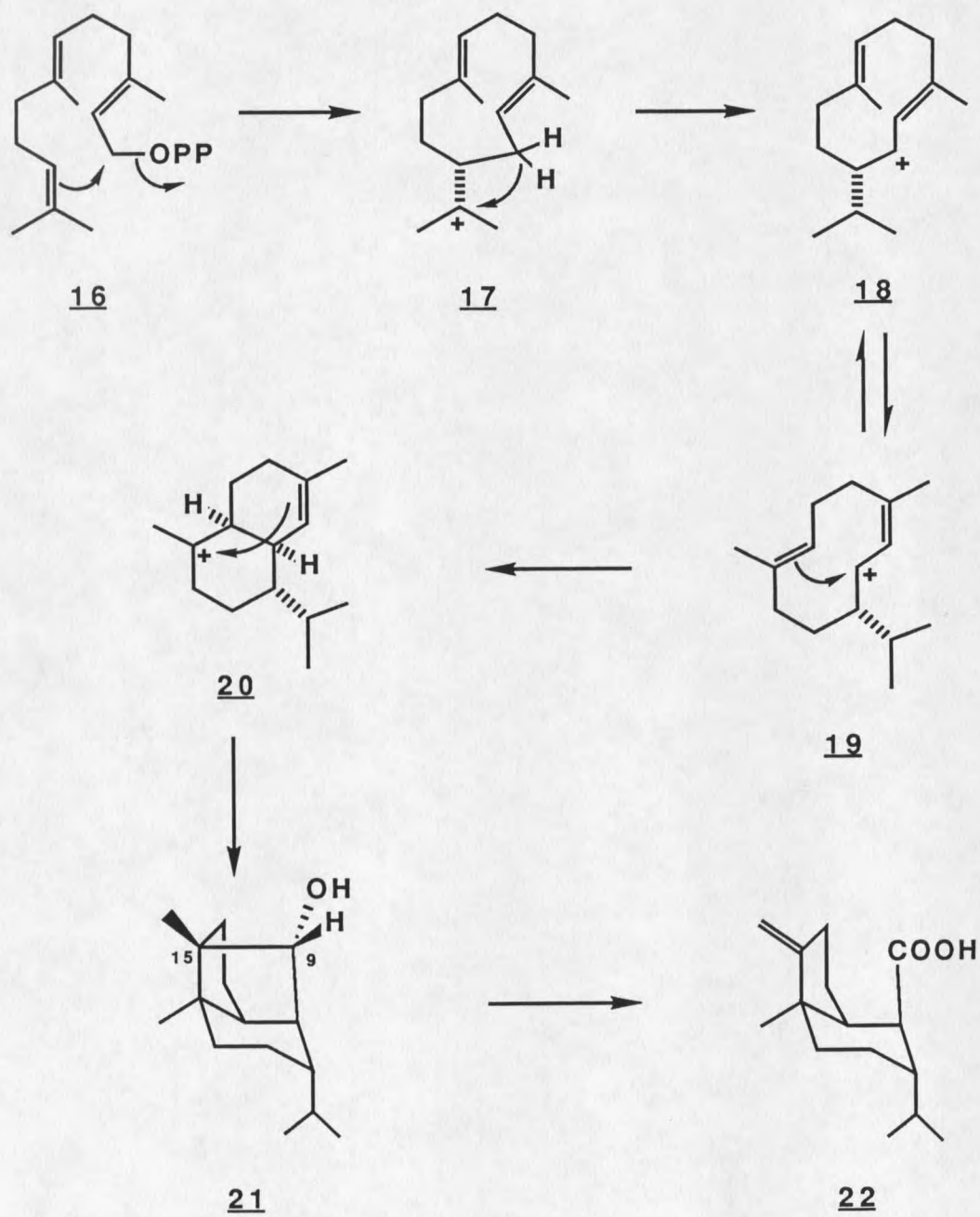


M.P.	135 ⁰ -136 ⁰ C	
[α] _D	-46.8 ⁰ (EtOH)	
M.W.	263.19	
M.F.	C ₁₆ H ₂₅ O ₂ N	
IR(<i>V</i> _{max} , KBr)	1765 cm ⁻¹ (lactone)	
¹ H NMR(δ , TMS)	4.80(q, J=3,6 Hz)	CH-9
	2.49(s)	CH ₃ -14
	1.33(s)	CH ₃ -13
MASS	263(M ⁺), 206, 192, 178, 164, 136, 109, 108, 81, 58, 41, 28	

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

Figure 3. Inubushi's Synthesis of Dendrobine

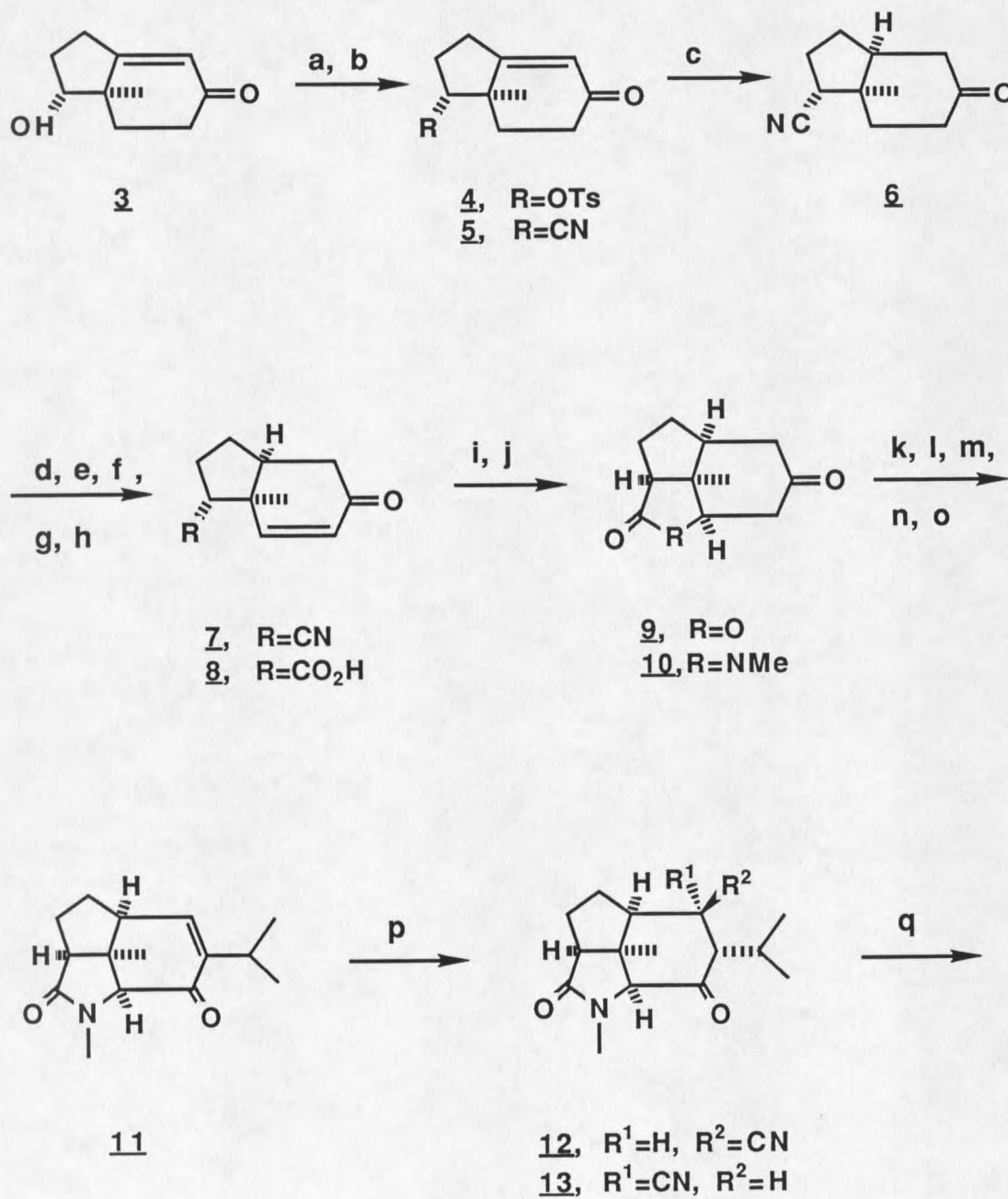
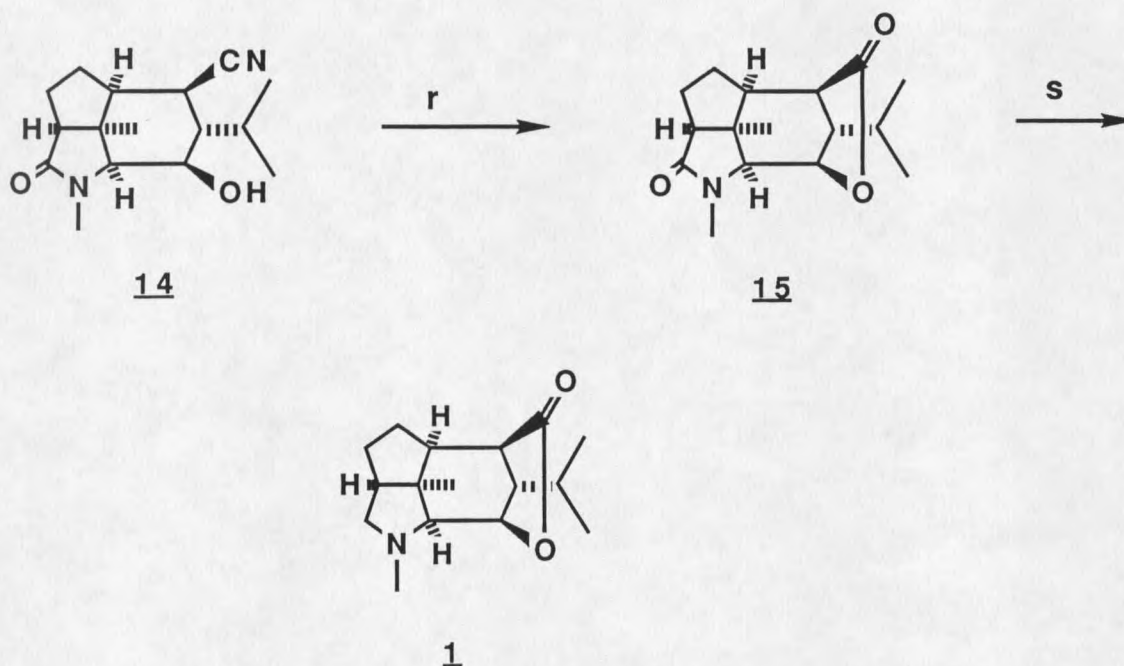


Figure 3 - Continued



a, TsCl ; b, NaCN; c, 5% Pd-SrCO₃; d, Br₂; e, Dehydrobromination; f, Acetalisation; g, aq. KOH-HOCH₂CH₂OH, reflux; h, dil HCl; i, 25% H₂SO₄; j, MeNH₂, HCl; k, i-PrMgBr; l, KHSO₄; m, I₂-AcOAg-AcOH-H₂O; n, H₂O-KOH-MeOH; o, CrO₃-pyridine; p, Et₂AlCN; q, NaBH₄; r, aq. KOH, dil HCl; s, Triethyloxonium fluoroborate

in the presence of HCl to give the lactam 10, which was then converted into the enone 11 through several steps. Hydrocyanation of 11 with Et₂AlCN gave a mixture of cyanoketones 12 and 13. Reduction of 13 with NaBH₄, followed by hydrolysis with aqueous KOH and acidification with dilute HCl, yielded (dl)-oxodendrobine (15), which was reduced to give (dl)-dendrobine (1) in 19 overall steps.

Yamada has synthesized dendrobine in 24 steps from dihydronaphthalenone 16 via an intramolecular Michael reaction^{19c} (Figure 4). Compound 16 was converted into the enol acetate 17. Ozonolysis of 17 followed by hydrolysis of the anhydride afforded the acid 18. The Wittig reaction of 18 followed by treatment with aqueous oxalic acid gave the keto acid 19, which was transformed to the diketo acid 21 in several steps. The cis-perhydroindane 22 was generated by the same Michael reaction as in the case of 21. An interesting aspect of this cyclization is that the stereocenter at C₁ of 22 was controlled by the intramolecular aldol condensation of an intermediate diketone. Aldol 24 was converted into enol acetate 25, which was ozonized to give keto acid 26. Heating of 26 and N,N'-carbonyldiimidazole followed by treatment with methylamine afforded the lactam 28, which was then converted into the bromo derivative 29. Treatment of 29 with NaH followed by acidification yielded the pyrrolidone 30, which was transformed into a mixture of 31 and 32. Compound 31 was treated with n-butyl mercaptan and 10-camphorsulfonic acid giving 33, which on treatment with lithium dimethylcuprate gave 34. Isomerization of 34 followed by reduction and acidification gave (dl)-oxodendrobine (15).

Treatment of 15 with triethyloxonium fluoroborate followed by reduction with NaBH_4 yielded (dl)-dendrobine (1).

Figure 4. Yamada's Synthesis of Dendrobine

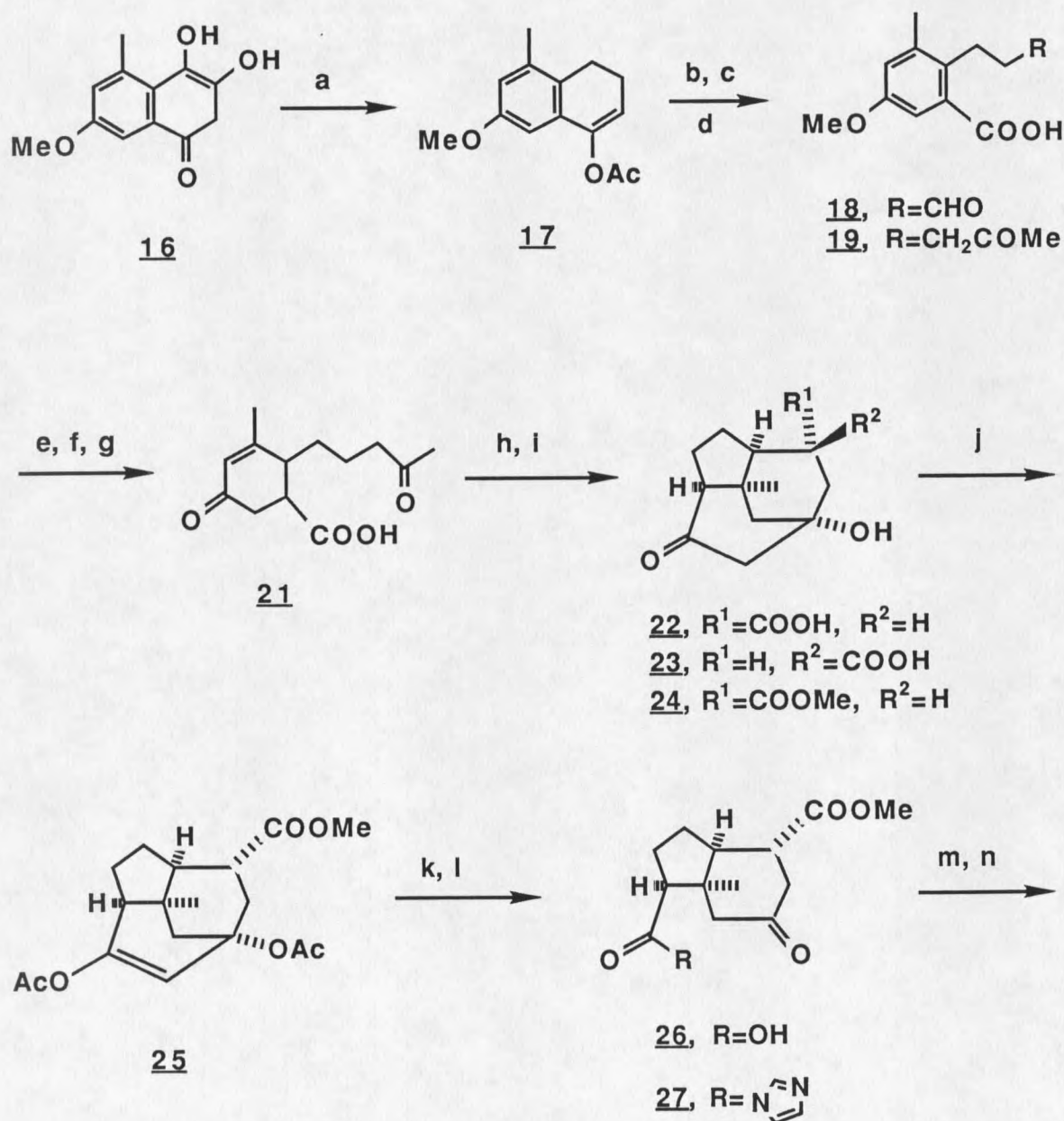
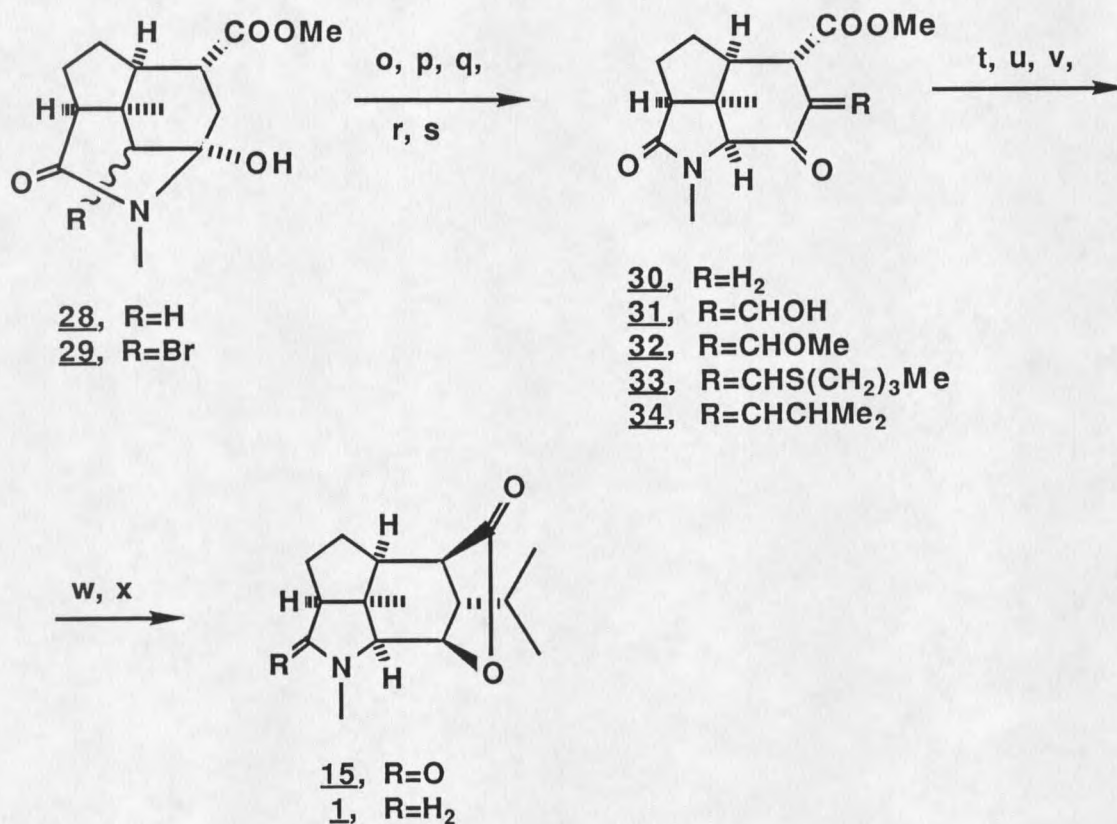


Figure 4 - Continued



a, Ac₂O, TsOH, reflux; b, O₃; c, Wittig reaction; d, HOCH₂CH₂OH, H⁺; e, Li / NH₃(liq.); f, aq. (CO₂H)₂; g, H₃O⁺, reflux; h, t-BuOK; i, CH₂N₂; j, Ac₂O; k, O₃; l, CDI; m, aq. MeNH₂; n, pyridiniumbromide perbromide; o, NaH; p, HCO₂Me/NaOMe; q, CH₂N₂; r, HSCH₂CH₂OH, H⁺; s, Me₂CuLi; t, NaH; u, NaBH₄; v, H₃O⁺; w, triethyloxonium fluoroborate; x, NaBH₄.

Kende has also prepared dendrobine in 14 steps from triacetate 35 via a Diels-Alder reaction and an intramolecular aldol condensation followed by a reductive amination^{19d}(Figure 5). Saponification and FeCl₃ oxidation of 35 gave the quinone 36, which with butadiene in EtOH

yielded the Diels-Alder adduct 37. Its methyl ester 38 was selectively hydroxylated at the isolated double bond and then treated with periodic acid followed by an aldol condensation to give aldehyde 40. Reductive amination of 40 afforded keto pyrrolidine 41. In this step, the stereochemistry at C₈ was generated by kinetic protonation of an intermediate enamine. Michael reaction on 42 gave ketone 43, which was elaborated into ketoester 44 by oxidation and epimerization¹². Sodium borohydride reduced 44 to the corresponding alcohol which spontaneously cyclized to yield dendrobine.

Roush has contributed greatly to the chemistry of this field through his synthesis of dendrobine^{19e} (Figure 6). The perhydroindenone 48 was prepared from 4-pentynoyl chloride 45 via the Wittig and the intramolecular Diels-Alder reactions. Compound 48 was transformed into nitrile 49 and 50. Hydrolysis of 49 by treatment with H₂O₂ afforded amide, which was oxidized with NBS to give bromo lactone 51. Sequential reduction processes provided primary alcohol 52, which was converted into the mixture of epoxides 53. The minor epoxide 53 α was transformed into dendrobine (1) via methyl ketodendrobinate (44).

Figure 5. Kende's Synthesis of Dendrobline

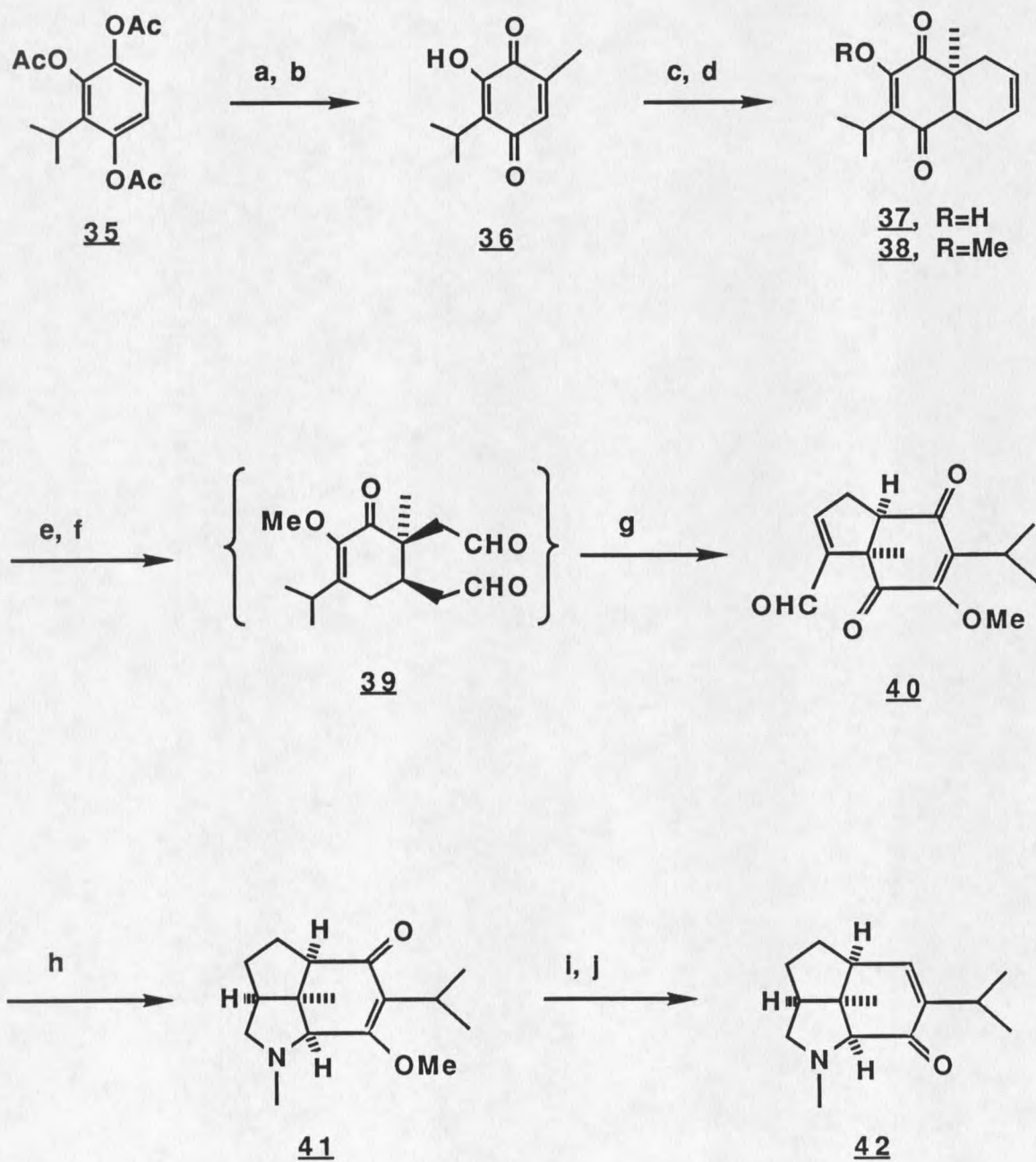
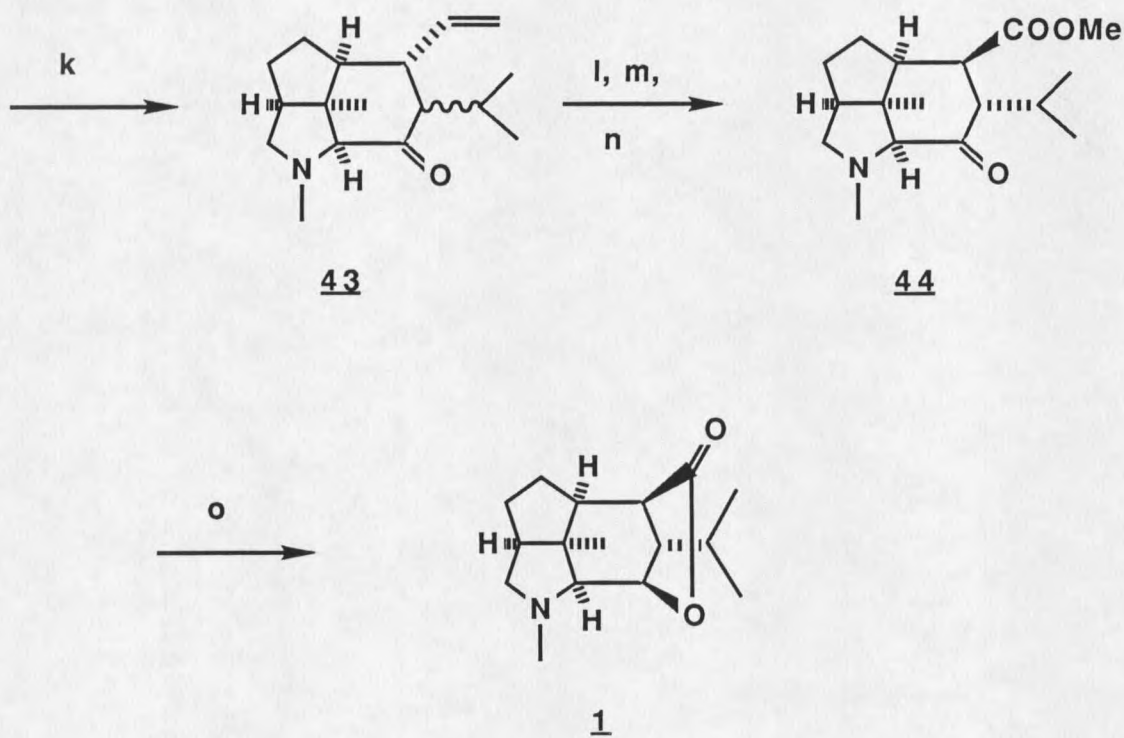


Figure 5 - Continued



a, OH^- ; b, FeCl_3 ; c, butadiene ; d, MeI ; e, OsO_4 ;
 f, IO_4^- ; g, Pyrrolidine acetate ; h, $\text{MeNH}_2 \cdot \text{HCl}$, NaBH_3CN ;
 i, LiAlH_4 ; j, H_3O^+ ; k, Lithium divinylcuprate ; l, RuO_4 ;
 m, CH_2N_2 ; n, NaOMe ; o, NaBH_4

Figure 6. Roush's Synthesis of Dendrobline

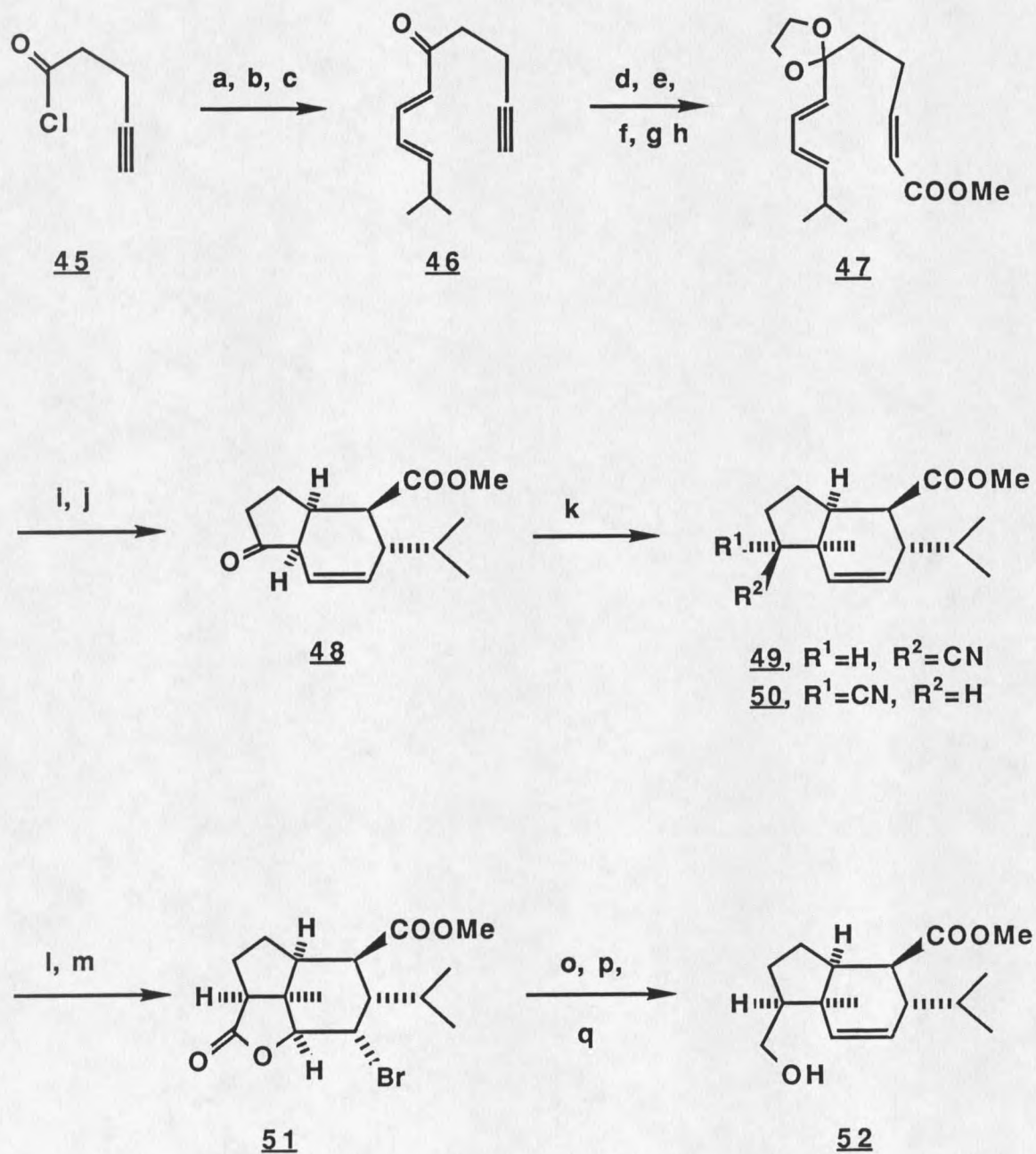
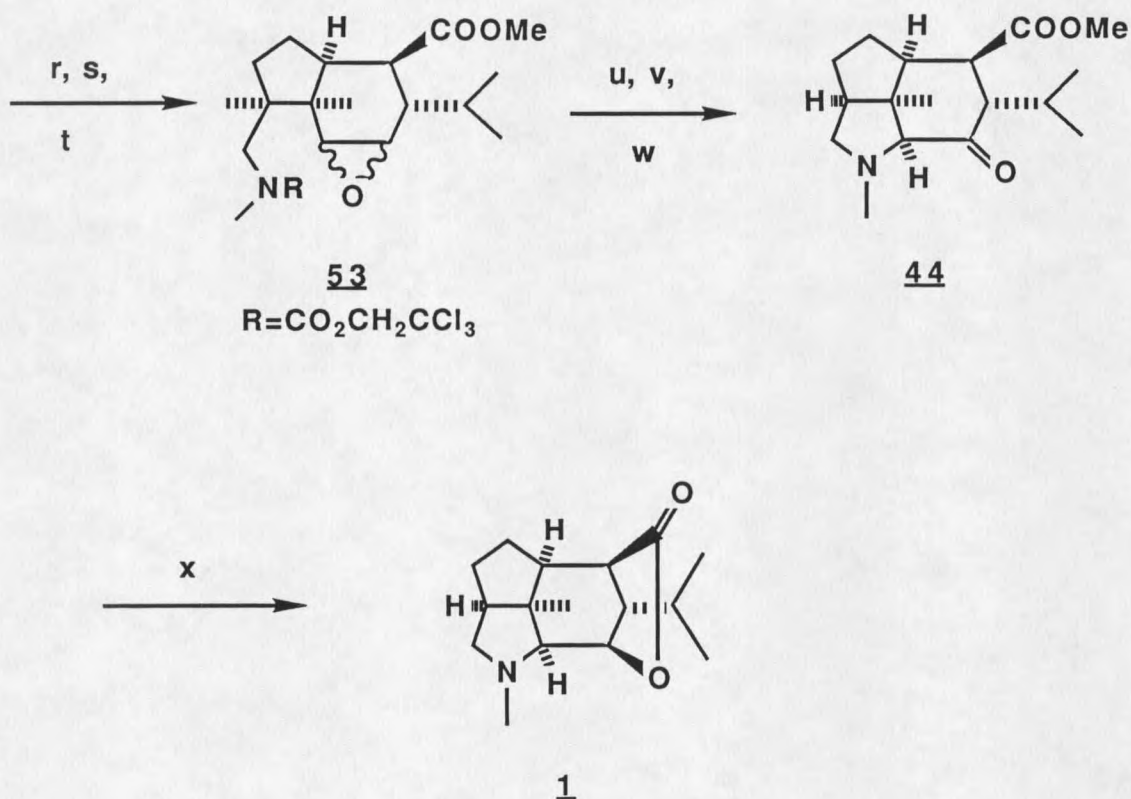


Figure 6 - Continued



a, imidazole; b, $\text{CH}_2=\text{PPh}_3$; c, $\text{Me}_2\text{CHCH}=\text{CHCHO}$; d, H^+ , $\text{HOCH}_2\text{CH}_2\text{OH}$; e, $n\text{-BuLi}$; f, ClCO_2Me ; g, H_2 , $\text{Pd} / \text{CaCO}_3 \cdot \text{P}$; h, 180°C ; i, OH^- ; j, 1N HCl ; k, TsCH_2NC ; l, H_2O_2 , NaOH ; m, NBS ; n, Zn , AcOH ; o, $(\text{COCl})_2$; p, $\text{LiAlH}(\text{O}-t\text{-Bu})_3$; q, MsCl ; r, MeNH_2 ; s, $\text{ClCO}_2\text{CH}_2\text{CCl}_3$; t, $m\text{CPBA}$; u, Zn , DME-MeOH ; v, 2N HCl ; w, Jones ; x, NaBH_4 .

Martin has recently published a short synthesis of tricyclic enone **11**, a key intermediate in Inubushi's synthesis^{19a}, via an intramolecular Diels-Alder reaction^{19g} (Figure 7). Triene amide **57** was prepared by

the condensation of aldehyde 54 with methyl amine followed by N-acylation of the intermediate imine 55 with the acid chloride 56.

Thermolysis of 57 furnished a mixture of two cycloadducts 58 and 59.

Compound 58 was then converted into the allylic alcohol 60 by rearrangement of the corresponding epoxide. Oxidation of 60 with PDC afforded tricyclic enone 11, which could be converted in several steps into dendrobine according to Inubushi's procedure^{19a}.

Figure 7. Martin's Synthesis of Tricyclic enone 11

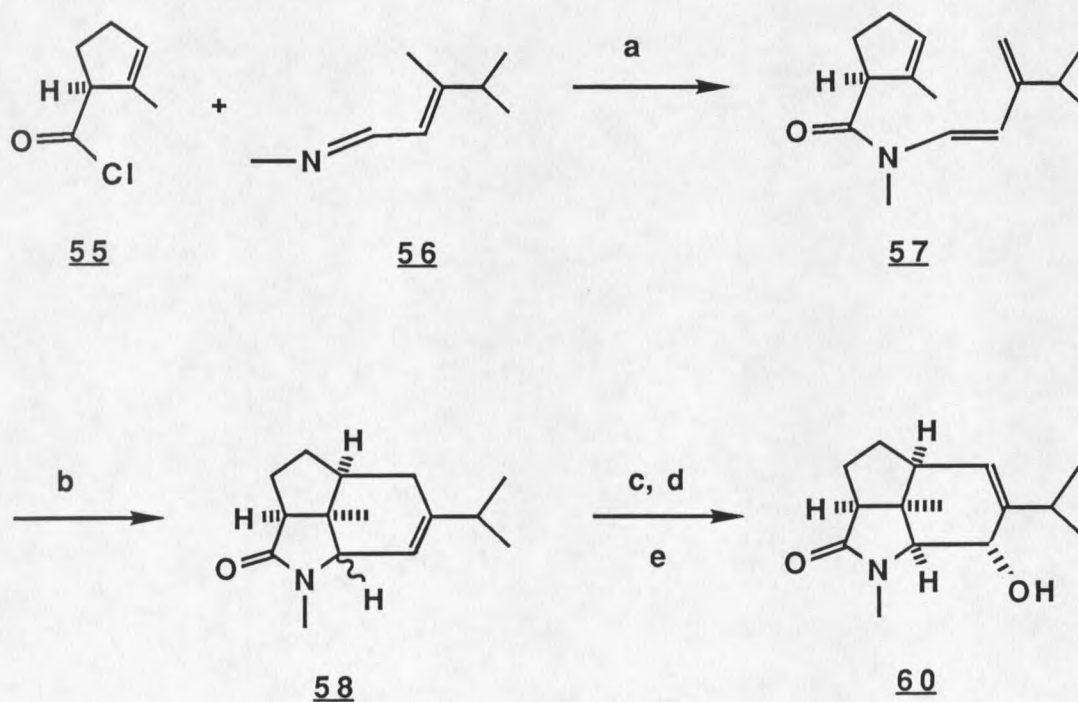
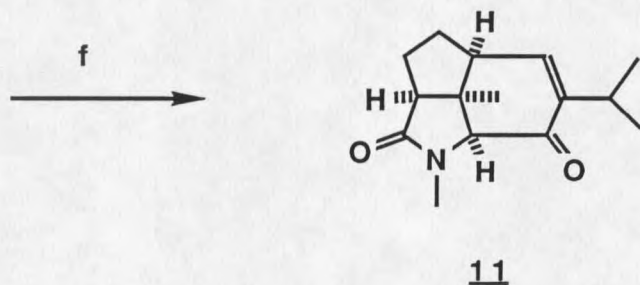
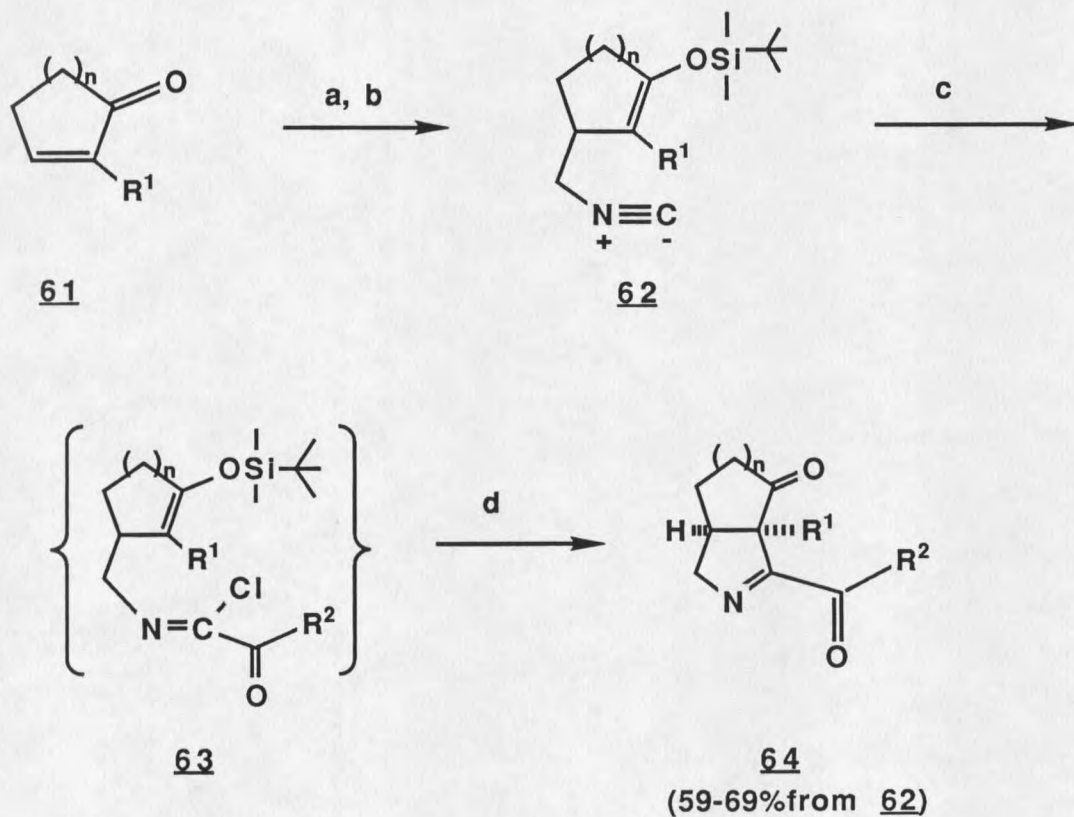


Figure 7 - Continued

a, PhNEt_2 ; b, 180°C , Xylene ; c, mCPBA ; d, TMSOTf ; e, PDC.

Recently, Livinghouse and Westling²⁰ have developed a convergent method for the preparation of 2-acylpyrrolines 64 via the intramolecular acylation of isonitriles 62 with α -ketoimidoyl chlorides 63 (Figure 8). The isonitriles 62 were prepared as previously described²¹ by the exposure of the corresponding enones 61 to lithio-methyl isocyanide²² followed by silylation. The acylation of isonitriles 62 was conveniently achieved by their exposure to acylchlorides to give α -ketoimidoyl chlorides 63, which was cyclized by treatment with AgBF_4 to afford 2-acylpyrrolines 64.

Studies which are currently underway are intended to apply this method to the synthesis of the Orchideceae alkaloids, and this thesis concerns a total synthesis of dendrobine (1).

Figure 8. Livinghouse's Synthesis of 2-Acylpyrrolines 64

$n=1, 2, 3$ $R^1=H, \text{ Me}$

$R^2=i\text{-Pr}, t\text{-Bu}, \text{MeO}_2\text{CCH}_2\text{CH}_2, \text{MeO}_2\text{CCH}=\text{CHMe}$

a, LiCH_2NC ; b, $\text{ClSi}(\text{CH}_3)_3$; c, $\text{R}^2\text{COCl}, \text{CH}_2\text{Cl}_2$; d, AgBF_4

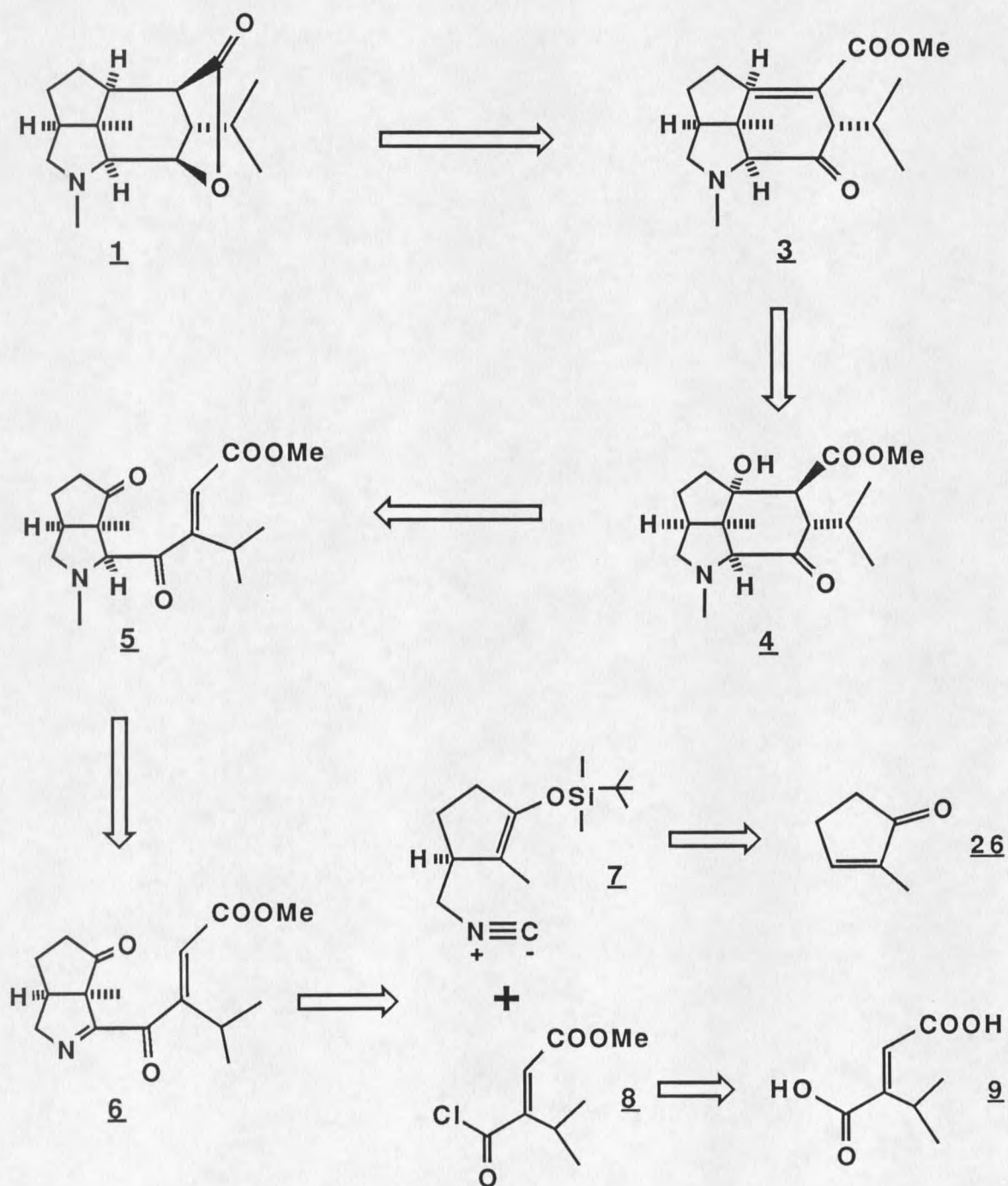
RESULTS AND DISCUSSION

Synthetic Strategy

Orchidaceae alkaloids have been a challenging synthetic target owing to their potent biological activity and unique polycyclic structures. Figure 9 contains an outline of our analysis of the synthetic strategy. It was anticipated that the α, β -unsaturated ester 3 could be formed by the dehydration of β -hydroxy ester 4. Compound 4, a key intermediate to the synthesis of dendrobine (1) would be prepared by a reductive cyclization of pyrrolidinone 5. Generation of a cis-fused perhydroindane ring system was anticipated on the basis of the steric effect of cis-fused bicyclic reactant 5.

Bicyclic pyrrolidine 5 could be prepared from the corresponding 2-acylpyrroline 6 through N-methylation followed by stereoselective reduction of iminium intermediate 34. As indicated in the introduction, an efficient entry into the 2-acylpyrroline ring system has been developed by Livinghouse and Westling²⁰ (Figure 8).

Figure 9. Retrosynthetic Strategy



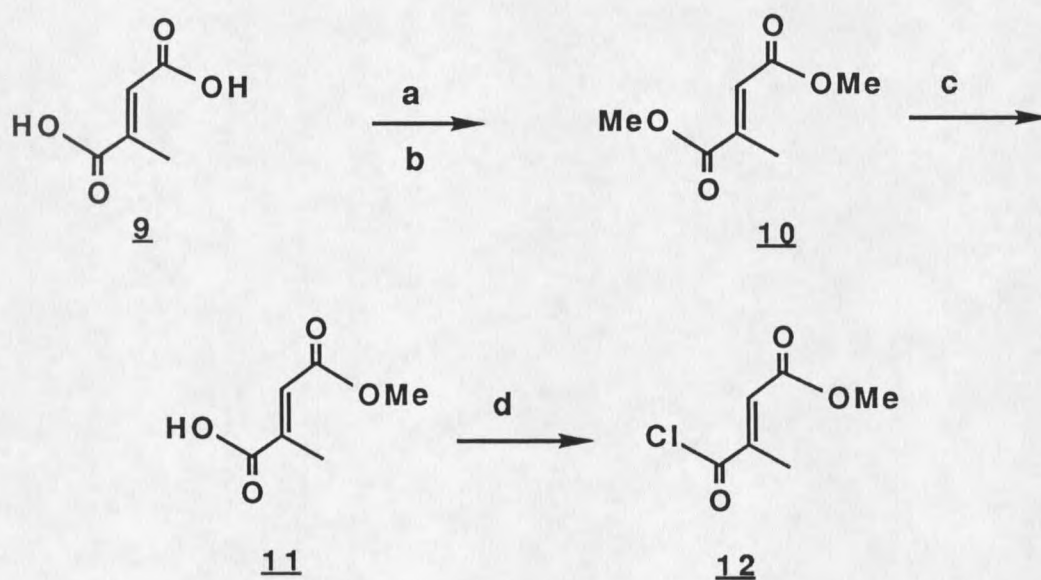
2-Acylpyrroline 6 could be constructed from the isonitrile 7 via the acylnitrilium ion initiated cyclization.

We have completed a total synthesis of dendrobine according to above synthetic strategy. This thesis provides a full account of this work.

Synthesis of Acylchlorides

In an effort to gauge the feasibility of the proposed synthetic strategy, a model study was initially pursued which used (E)-2-methyl-3-carbomethoxypropenoyl chloride(12) instead of the isopropyl analog 8 required for the natural products. This acylchloride was readily prepared in multigram quantities by a modification of Drugman's synthesis²³ of 2-methyl-3-carbomethoxypropenoic acid (Figure 10).

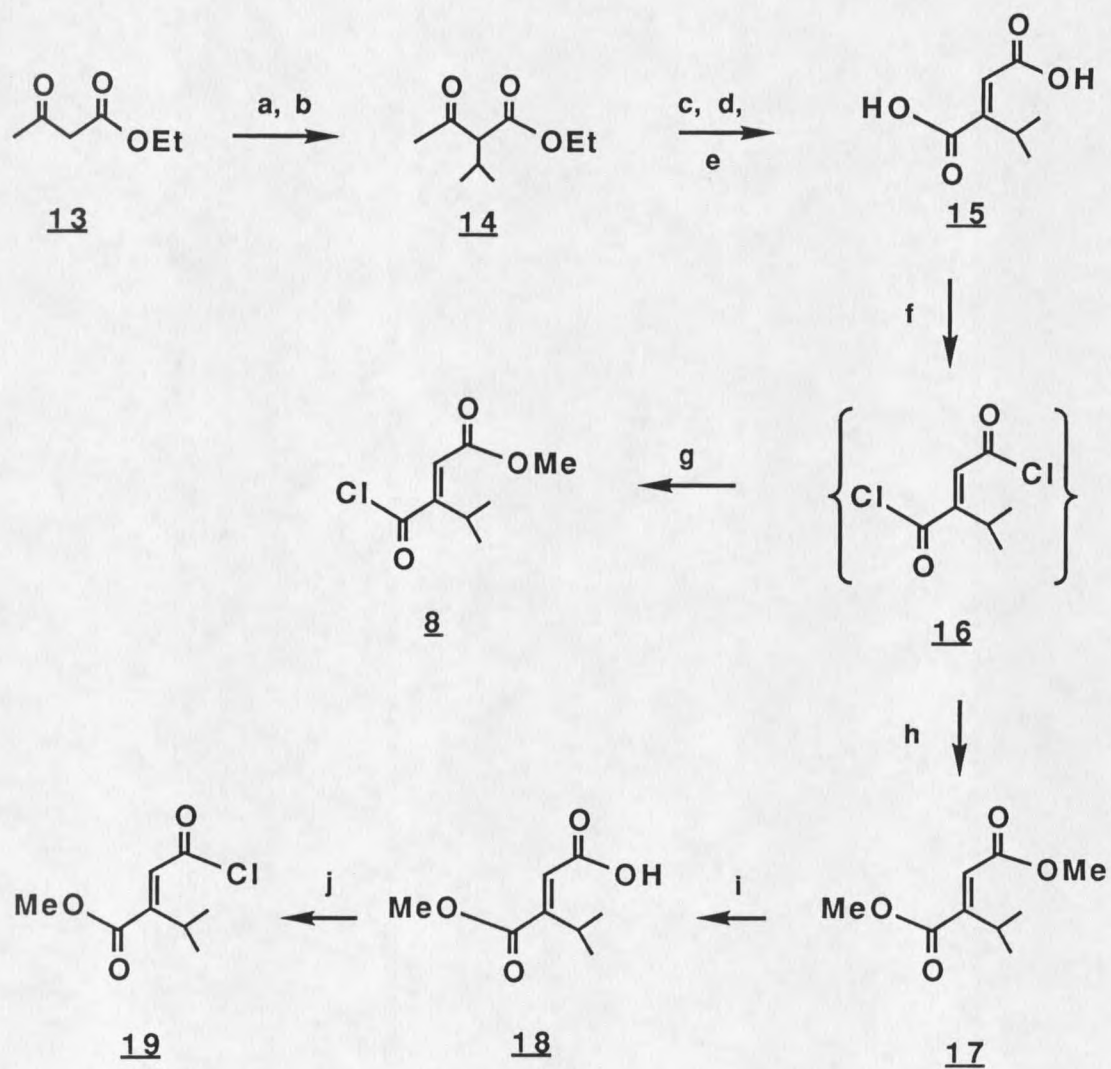
Sequential treatment of mesaconic acid (9) with thionyl chloride followed by anhydrous methanol afforded methyl (3-carbomethoxy-2-methyl)propenoate (10) in 94.2% yield. The ester 10 was selectively saponified with KOH (MeOH, 0 °C) to provide (E)-3-carbomethoxy-2-methylpropenoic acid (11) in 92% yield. The acid was then converted

Figure 10. Preparation of Acylchloride 12

a, SOCl_2 , CCl_4 , rt ; b, excess MeOH, rt ; c, 1 eq. KOH,
MeOH, 0 °C- rt ; d, i) LiH, ether, ii) $(\text{COCl})_2$

into the lithium salt and treated with oxalyl chloride to give (E)-3-carbomethoxy-2-methylpropenoyl chloride (12) in 74.6% yield.

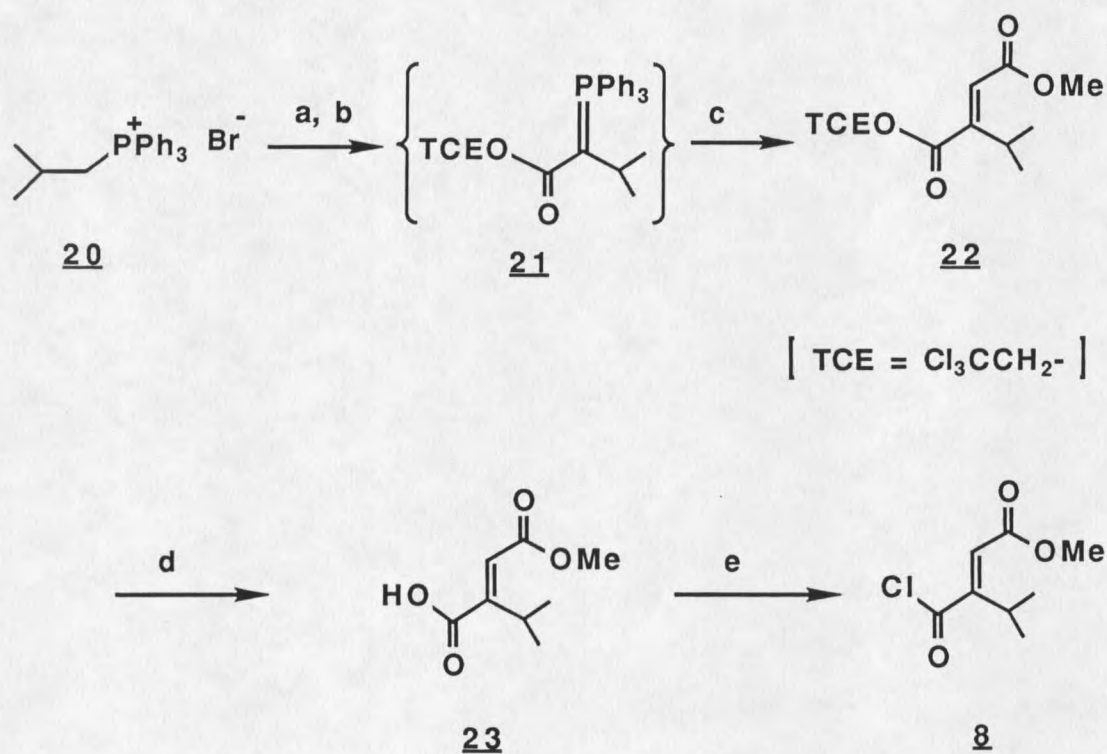
To prepare the isopropyl analog 8, we made isopropyl fumaric acid (15) from ethyl acetoacetate via alkylation followed by treatment of the product 14 with bromine and then KOH in ethanol to effect a Favorskii rearrangement^{24,25} in 44.7% overall yield (Figure 11).

Figure 11. Preparation of Acylchlorides 8 and 19

a, NaOEt; b, i-PrBr; c, Br₂; d, KOH, EtOH, reflux;
 e, 6N HCl; f, 3 equiv. SOCl₂, CH₂Cl₂, reflux; g, 4 equiv.
 MeOH, 0 °C-r t; h, MeOH (excess), r t; i, 1 equiv. KOH,
 MeOH, r t; j, i) LiH, Et₂O, ii) (COCl)₂, r t.

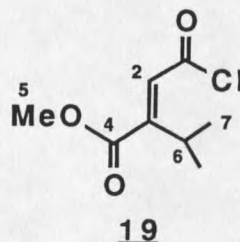
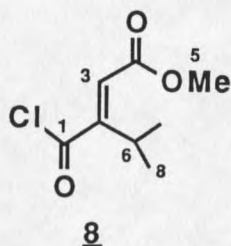
With diacid 15 in hand, we attempted to prepare acylchloride 17, by using the same procedure which had been used for the methyl analog 12. But hydrolysis of diester 17 with 1 equiv. of KOH gave the undesired half acid 18, which was then converted to the corresponding acylchloride 19 by treatment of 18 with lithium hydride and oxalyl chloride in 78.1% purified yield.

This result indicates that the steric hindrance of the isopropyl group inhibits the hydrolysis of adjacent ester and favors hydrolysis of the alternative ester which was unincumbered by the isopropyl group. We applied this propensity to examine the regioselective esterification of diacylchloride 16 with 1-5 equiv. of methanol. Thus, treatment of isopropyl fumaric acid (15) with 3 equiv. of SOCl_2 in the presence of catalytic amounts of DMF (CH_2Cl_2 , reflux) gave diacylchloride 16 in quantitative yield. Regioselective esterification of unpurified 16 was conveniently achieved by its exposure to 4 equiv. of methanol (CH_2Cl_2 , 0°C - r. t.). After distillation, the desired acylchloride 8 was obtained as a colorless liquid in 79.5% yield (Figure 11). 300 MHz NMR spectrum of 8 was identical with the authentic sample of 8 which was prepared from half acid 23 as shown in Figure 12.

Figure 12. Alternative Preparation of Acylchloride 8

a, n-BuLi; b, $\text{ClCO}_2\text{CH}_2\text{CCl}_3$; c, MeO_2CCHO ; d, Zn, KH_2PO_4 ;
 e, i) LiH, ii) (COCl_2) .

Comparisons of NMR spectra of acylchloride 8 and 19 are shown in Table 1.

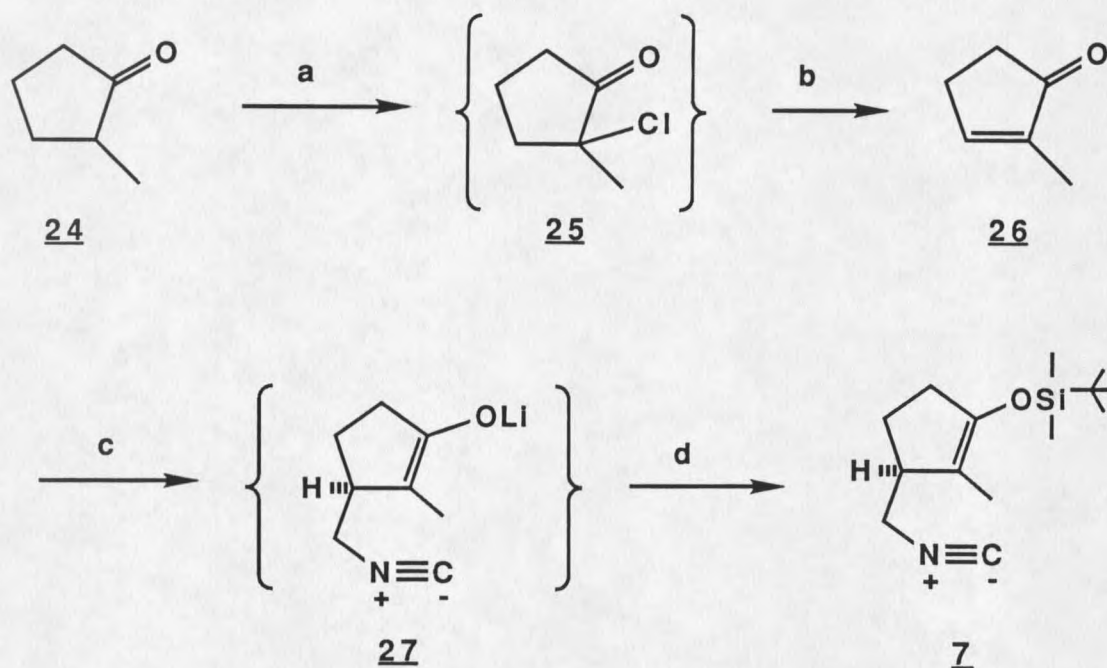
Table 2. NMR Data of Acylchloride 8 and 19

¹ H NMR			¹³ C NMR		
Proton	<u>8</u>	<u>19</u>	Carbon	<u>8</u>	<u>19</u>
H--3	6.81(s)	6.65(s)	C--1	165.13	164.37
CH ₃ --5	3.79(s)	3.80(s)	C--2	130.22	128.69
H--6	3.75(m)	3.48(m)	C--3	156.12	156.67
CH ₃ --7	1.19 (d)	1.18(d)	C--4	167.31	166.01
CH ₃ --8	(J=7.0Hz)	(J=7.0Hz)	C--5	52.09	52.38
			C--6	29.33	29.11
			C--7	20.28	20.36
			C--8		

Acynitrilium Ion Cyclization

The synthesis of 2-acylpyrroline 6, a key intermediate for dendrobine (1), began with the preparation of isonitrile 7. 2-Methylcyclopent-2-en-1-one (26) was readily obtained from 2-methylcyclopentanone (24) by treatment with sulfuryl chloride (CCl₄, 20 °C) followed by dehydrochlorination (100 °C) as shown in Figure 13.

The isonitrile 7, substrate for the acynitrilium ion initiated cyclization, was prepared by a modification of Livinghouse's method²¹.

Figure 13. Preparation of Isonitrile 7

a, SO_2Cl_2 , CCl_4 , 10°C - rt ; b, 100°C ; c, i) CH_3NC , $n\text{-BuLi}$, THF, -78°C , ii) HMPA, iii) 26, -78°C ; d, TBSCl, $-78^\circ \sim 0^\circ\text{C}$.

Lithiation of methyl isocyanide ($n\text{-BuLi}$, THF, -78°C) furnished a suspension of isocyanomethyl lithium. Sequential treatment of this mixture with 2-methylcyclopent-2-en-1-one in the presence of HMPA at -78°C , followed by t-butyldimethylsilyl chloride afforded the desired isonitrile 7 in 71% purified yield. The sterically hindered 1,2-adduct was not trapped at an appreciable rate by t-butyldimethylsilyl chloride.

Now the stage was set for the acylnitrilium ion initiated cyclization of 7. This method was to rely on the use of silylenol ether of 7 as nucleophilic addend in an intramolecular cyclization. The required cation 30 was expected to be accessible via the silver cation mediated ionization of α - ketoimidoyl chloride 29. This intermediate, in turn, was to be prepared by the reaction of 7 with an acylchloride.

Organic isonitriles have been known to react with electrophilic species for many years²⁶. However, despite the apparent nucleophilicity of the isonitrile moiety, the utilization of this functional group in carbon-carbon bond forming operations has remained quite limited.

In 1961, Ugi demonstrated that acylchlorides would insert into isonitriles in refluxing benzene to afford α - ketoimidoyl chlorides in fair yield²⁷. But, these conditions were far more vigorous than necessary. Recently, Livinghouse and Westling²⁰ reported the facile conversion of the isonitriles into the α - ketoimidoyl chlorides at room temperature.

Treatment of isonitrile 7 with acylchloride 12 in CH_2Cl_2 at room temperature afforded the anticipated α - ketoimidoyl chloride 28 in quantitative yield (Figure 14). It was noteworthy that there was no

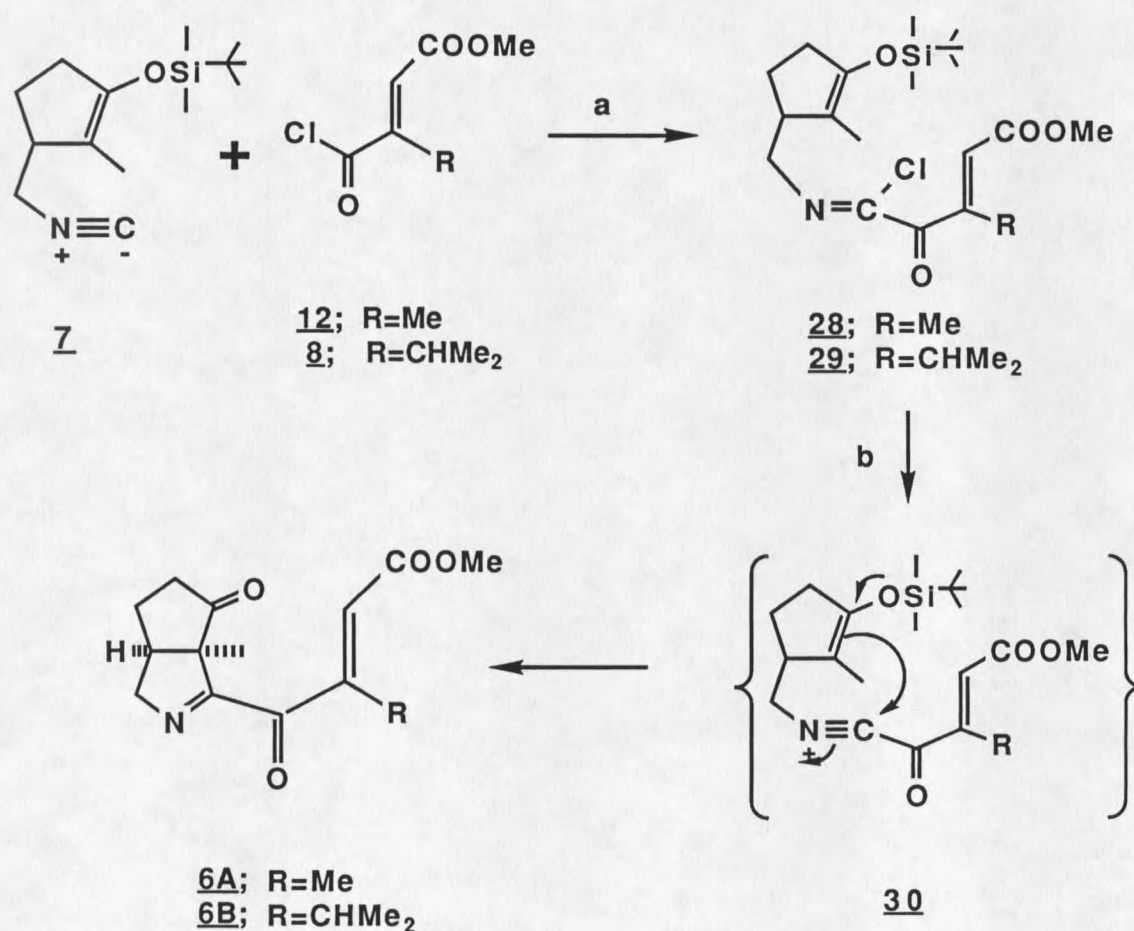
observable isomerization of the thermodynamically favored tetra substituted silylenol ether. The crude imidoyl chloride 28 was then treated directly with 1.10 equiv. of AgBF_4 (CH_2Cl_2 - $\text{ClCH}_2\text{CH}_2\text{Cl}$, -78°C) to afford the desired 2-acylpyrroline 6A. Owing to the acid sensitivity, the crude product was filtered through Florisil to give the product 6A in 99.8% yield from 7. This product was used in the following reaction without further purification.

The formation of 2-acylpyrroline 6A under the ionizing set of reaction conditions involving AgBF_4 can be rationalized by invoking acylnitrilium cation 30 as shown in Figure 14.

Having established that an acylnitrilium ion initiated cyclization could be exploited for construction of bicyclic pyrroline subunit of 1, We directed our studies to the more sterically hindered isopropyl analog of acylchloride 8. Reaction of 8 with 7 was very sluggish at room temperature and required warming to $40-43^\circ\text{C}$. Optimization of the insertion reaction for isopropyl analog 8 was accomplished by monitoring the reaction via NMR. Acylation of a 2.3 molar solution of 7 in CH_2Cl_2 was accomplished with acylchloride 8 (1.2 equiv., reflux) in the presence of powdered 4A^0 -molecular sieves.

The insertion reaction was completed in 3 h (CH_2Cl_2 , reflux). The resulting α - ketoimidoyl chloride 29 was then subjected to acylnitrilium ion initiated cyclization to furnish the desired 2-acylpyrroline 6B in 87.7% isolated yield.

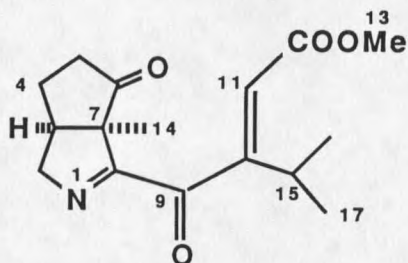
Figure 14. Preparation of 2-Acylpyrrolines 6A and 6B via Acylnitrilium Ion Initiated Cyclization



a, CH_2Cl_2 ; b, AgBF_4 , CH_2Cl_2 - $\text{ClCH}_2\text{CH}_2\text{Cl}$, -78°C

Assignment of ^1H NMR and ^{13}C NMR data for 2-acylpyrroline 6B

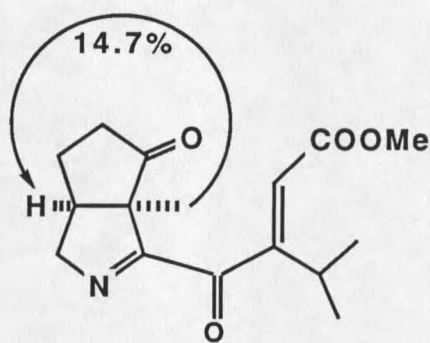
is presented in Table 3.

Table 3. NMR Data of 2-Acylpyrroline 6B

^1H NMR		^{13}C NMR	
Proton	ppm	Carbon	ppm
H--2a	4.31 (dd, J=17.9, 7.1Hz)	C--2	67.3
H--2b	4.03 (dd, J=17.9, 2.6Hz)	C--3	47.5
H--3	2.69 (t t, J=7.6, 7.1Hz)	C--4	25.1
H--4a	2.19 (q, J=7.6Hz)	C--5	36.7
H--4b	1.59 (m)	C--6	212.9
CH ₂ --5	2.34 (dt, J=7.6, 5.6Hz)	C--7	68.5
H--11	6.06 (s)	C--8	158.9
CH ₃ --13	3.72 (s)	C--9	193.5
CH ₃ --14	1.37 (s)	C--10	165.5
H--15	3.73 (hept, J=7.0Hz)	C--11	126.1
CH ₃ --16	1.17 (d, J=7.0Hz)	C--12	170.7
CH ₃ --17		C--13	51.5
		C--14	18.8
		C--15	28.6
		C--16	20.5
		C--17	20.5

It is of particular interest that the cyclization of α - ketoimidoyl chlorides 28 and 29 gave only the cis-fused pyrrolines 6A and 6B. None of the alternative trans isomers were detectable by high field ^{13}C NMR.

Support for the existence of the cis-fused ring junction of 6B was provided by nuclear Overhauser enhancement difference (NOED) spectroscopy and proton decoupling experiments. A significant positive NOE (14.7%) between H-3 and angular methyl proton of C-14 was observed.



NOE of 6B

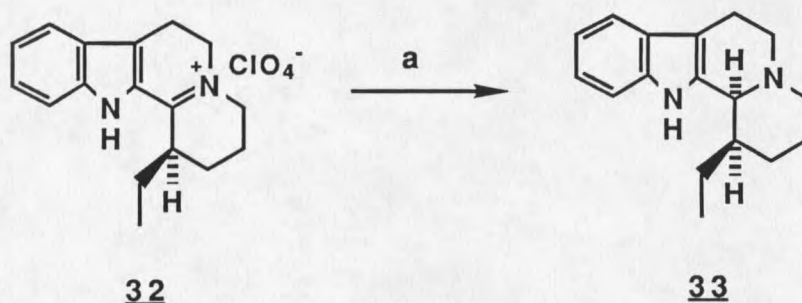
Stereoselective Synthesis of the Tricyclic β -Hydroxyester (52)

The next stage of the synthesis involved N-methylation of 2-acyl pyrrolines 6 and reduction of the resultant iminium salt to provide N-methyl pyrrolidines 5. N-methylation was conveniently accomplished by treating 2-acylpyrrolidines 6 with 1.2 eq. of methyl trifluoromethanesulfonate (CH_2Cl_2 , 0°C - r. t.) in quantitative yield (Figure 15).

With iminium salt 34 in hand, we have examined a variety of reduction systems to prepare the corresponding N-methylpyrrolidines 5 in a stereospecific manner.

For the synthesis of natural product 1, a hydrogen atom must be introduced from the back-side of the intermediate 34 at the C-8 position. Selective metal hydride reduction of the iminium salt 34, using NaBH_3CN , $\text{K}(\text{t-BuO})_3\text{AlH}$, K-selectride or $(\text{Ph}_3\text{P})_2\text{CuBH}_4$, was not achievable in the presence of the carbonyl and α,β -unsaturated ester moieties of 34.

Tollari and coworkers²⁸ demonstrated that the tri-n-butyl tin hydride (TBTH) reduction of the cyclic iminium salt 32 resulted in the corresponding tertiary amine 33 by hydride delivery from the less hindered axial direction.

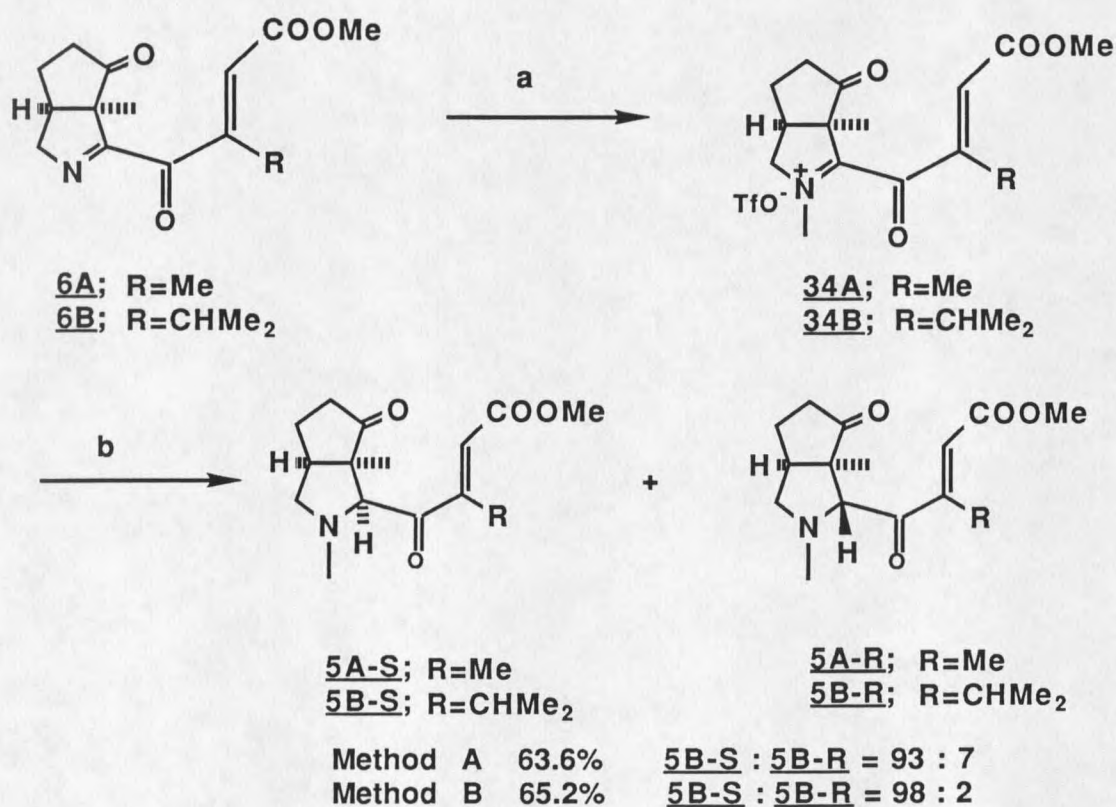


a, 2.5 equiv. $(\text{n-Bu})_3\text{SnH}$, MeOH , $25\text{ }^\circ\text{C}$; 95%

Treatment of 34B with 2.5 equiv. of TBTH in dimethoxyethane ($0\text{ }^\circ\text{C}$ -r.t., 3 h) produced a mixture of N-methylpyrrolidines 5B-S and 5B-R in a ratio of 83:17 (NMR).

The stereoselectivity of reduction was found to be coupled to both solvent polarity and concentration. Reaction of 0.05 molar solution of 34B in methanol with 2.5 equiv. of TBTH (r. t., 2.5 h) furnished the best ratio (93:7) of 5B-S and 5B-R in 63.6% purified yield from 6B.

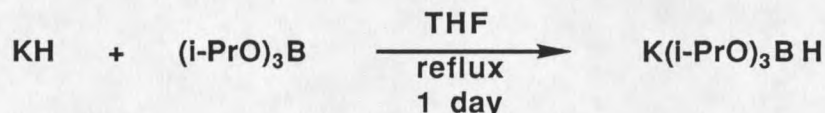
Figure 15. Preparation of N-Methylpyrrolidines 5A and 5B



a, MeOTf, CH₂Cl₂, 0--r.t., 3 h; b, Method A : (n-Bu)₃SnH, MeOH, r.t., 2.5 h; Method B : KBH(O-tBu)₃, THF, -78 °C, 5 min.

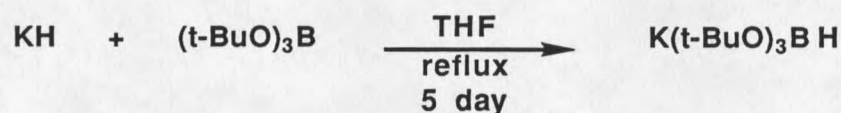
Unfortunately, this TBTH method must be carried out under high dilution to get good stereoselectivity. This limitation prompted us to explore alternative methods for stereoselective reduction.

According to Brown and coworkers²⁹, potassium tri-isopropoxy borohydride (KIPBH) reduces 2-methylcyclohexanone to the less stable isomer, cis-2-methylcyclohexanol with high selectivity (91% cis-isomer). But the reduction was very slow at -25 °C and required 3 days for completion. We examined the selective reduction of our iminium triflate 34 with KIPBH, which was prepared from tri-isopropoxyborane and KH by refluxing in THF²⁹.



Reduction of 34B with 1 equiv. of KIPBH in THF at -78 °C afforded N-methylpyrrolidines, 5B-S and 5B-R in a ratio of 86:14. The ratio was further improved by reacting at -90 °C in toluene-liquid nitrogen bath (5B-S:5B-R = 92:8). On the other hand, reaction in CH₂Cl₂ at -78 °C furnished 5B-S and 5B-R in lower ratio of 64:36. To compare the steric effect of hydride, we then examined potassium tri-t-butoxyboro-

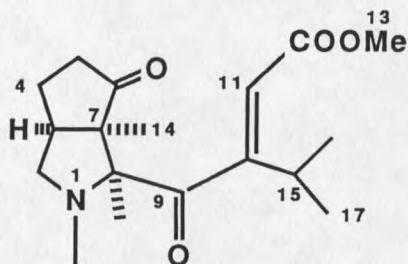
hydride (KTBH). KTBH was also prepared as described²⁹ by the reaction of KH and tri-*t*-butoxyborane.



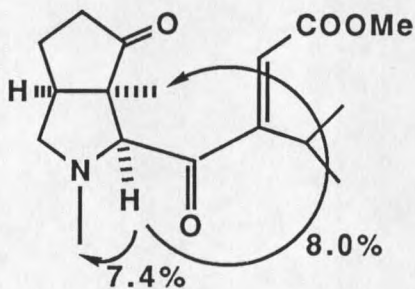
When the iminium triflate 34B was reacted with 1 equiv. of KTBH (THF, -78 °C, 5 min), the diastereoselectivity was further improved to 98 : 2 (5B-S:5B-R) and the desired diastereomer 5B-S was isolated in 65.2% purified yield. It is therefore considered that these hydrides attack from the less hindered side due to their bulky tri-isopropyl and tri-*t*-butyl substituents.

The stereochemistry of 5B-S was assigned by ¹H NMR and NOE experiments. Positive NOE (8.0%) effects were observed between the H-8 and angular methyl proton of C-14. Furthermore, NOE between N-methyl proton and H-8 was also positive (7.4%). These facts indicate that N-methyl group is in close proximity to angular methyl and H-8 proton at the same direction.

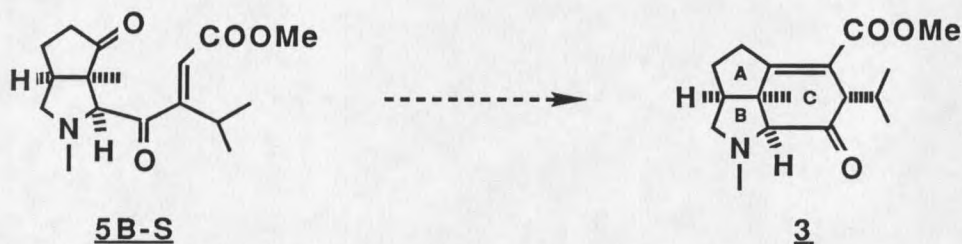
Assignment of ¹H NMR and ¹³C NMR data for N-methylpyrrolidine 5B-S is presented in Table 4.

Table 4. NMR Data of N-Methylpyrrolidine 5B-S

^1H NMR		^{13}C NMR	
Proton	ppm	Carbon	ppm
$\text{CH}_3\text{--N}$	2.20 (s)	N--CH_3	40.9
H--2a	3.02 (dd, $J=9.5, 1.3$ Hz)	C--2	62.6
H--2b	2.65 (dd, $J=9.5, 7.4$ Hz)	C--3	47.6
H--3	2.51 (pent. $J=9.5$ Hz)	C--4	25.9
H--4a	2.02 (m)	C--5	38.7
H--4b	1.91 (m)	C--6	219.7
H--5a	2.45 (m)	C--7	59.9
H--5b	2.24 (m)	C--8	82.2
H--8	3.29 (s)	C--9	201.2
H--11	6.50 (s)	C--10	160.9
$\text{CH}_3\text{--13}$	3.75 (s)	C--11	124.5
$\text{CH}_3\text{--14}$	1.26 (s)	C--12	166.4
H--15	3.52 (hept. $J=7.1$ Hz)	C--13	51.6
$\text{CH}_3\text{--16}$	1.22 (d, $J=7.1$ Hz)	C--14	22.6
$\text{CH}_3\text{--17}$	1.18 (d, $J=7.1$ Hz)	C--15	29.1
		C--16	21.2
		C--17	20.6

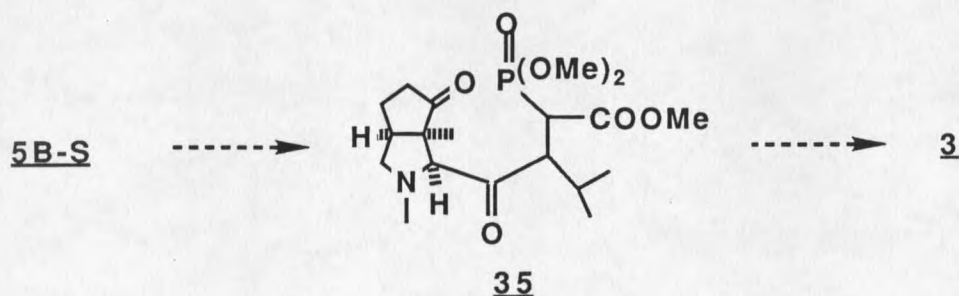
NOE of 5B-S

The next phase of our plan called for the construction of the C-ring from the N-methylpyrrolidine 5B-S.



It was initially anticipated that tricyclic compound 3 could be prepared directly from 5B-S by a Horner-Wadsworth-Emmons (HWE) reaction. Unfortunately, compound 3 was not obtained when 5B-S was sequentially treated with dimethyl phosphite and lithium chloride in CD_3CN in the presence of DBU or diisopropylethylamine³⁰.

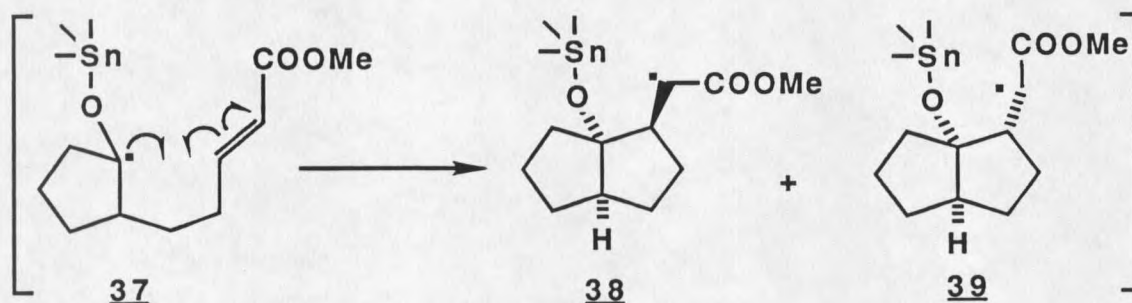
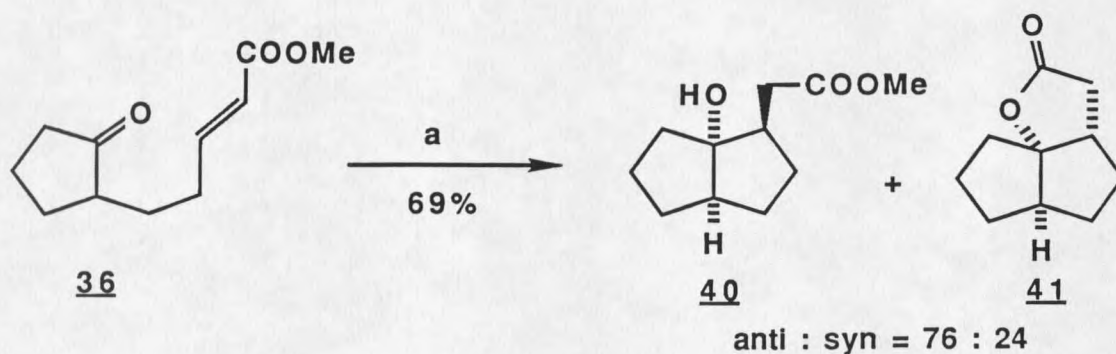
Attempts to prepare the phosphonate 35 from the reaction of 5B-S with dimethyl phosphite in the presence of trimethyl aluminum³¹ were also unsuccessful.



a, $(\text{MeO})_2\text{POH}$, LiCl , DBU, CD_3CN , r.t., or $(\text{MeO})_2\text{POH}$, AlMe_3 , CH_2Cl_2 , r.t.

The failure of the Wittig-type cyclization prompted us to explore the reductive coupling reactions. In recent years a number of groups have examined radical cyclizations to make 5-membered ring systems. While a variety of methods are available to generate ketyls that are subsequently trapped by olefins³⁵, we envisioned that new methods such as O-stannyl and O-samarium ketyls might suit our purposes.

O-stannyl ketyls³², produced by the reaction of a carbonyl functional group with a trialkyltin radical, can provide a carbon-centered radical for these cyclization reactions. Enholm³³ has published that aldehydes or ketones connected by a tether to an olefin cyclize in a free radical reaction mediated by tributyltin hydride (Figure 16). The reaction was probably mediated by a homolytic chain mechanism and proceeded by the addition of a tributyltin radical to the ketone carbonyl in 36 to produce O-stannyl ketyl intermediate³⁴ 37. A subsequent free radical cyclization by addition to the olefin produced the carbon-centered free radical intermediates 38 and 39. The two diastereomeric products arose from the syn- and anti-dispositions of the alcohol and substituted appendage and reflected the formation of two new sp^3 centers from the two sp^2 centers of the ketone and olefin.

Figure 16. Butyltin hydride-mediated Radical Cyclizations³³

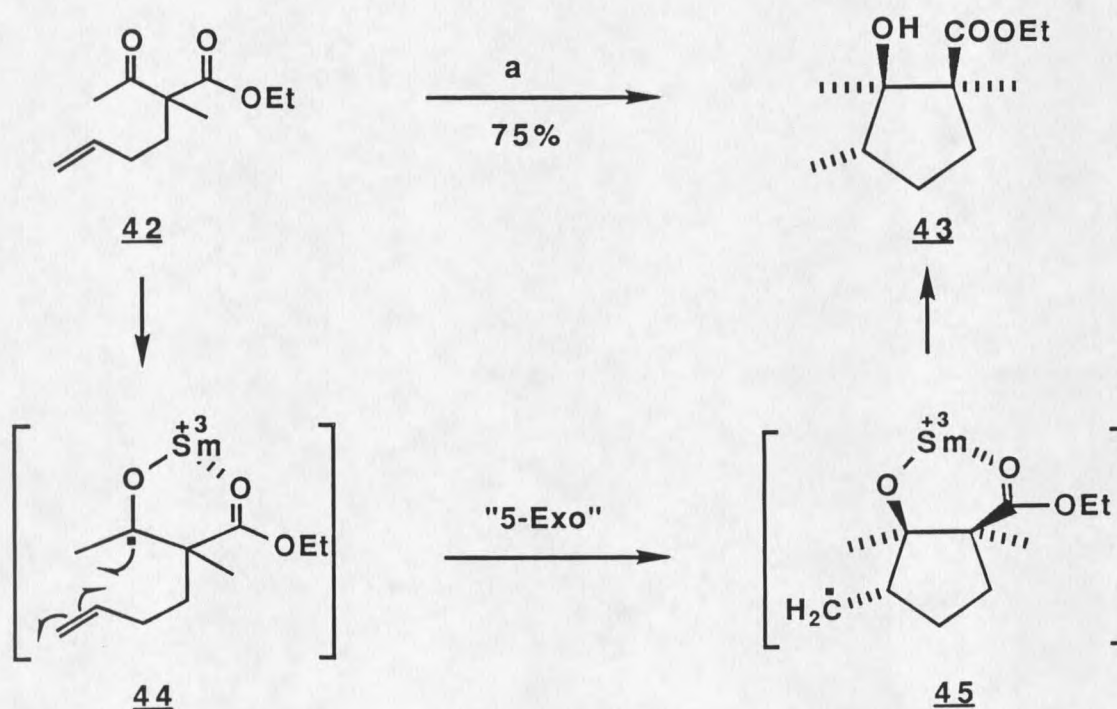
a, $n\text{-Bu}_3\text{SnH}$, AIBN, CH_3CN , PhH , 80°C .

Recently, Molander and Kenny^{35a} have reported some related radical cyclizations of alkenyl β -keto ester **42** using 2 equiv. of samarium iodide in THF in the presence of an added proton source (Figure 17).

In this radical cyclization reaction, the major product was derived from the thermodynamically less favored radical intermediate. The ketyl

generated from samarium iodide underwent 5-exo cyclization to afford the primary radical 45, rather than 6-endo cyclization to generate a more stable secondary radical.

Figure 17. SmI_2 -mediated Radical Cyclization^{35a}



a, 2 eq. SmI_2 , 2 eq. $t\text{-BuOH}$, THF, $-78^\circ \sim 0^\circ\text{C}$.

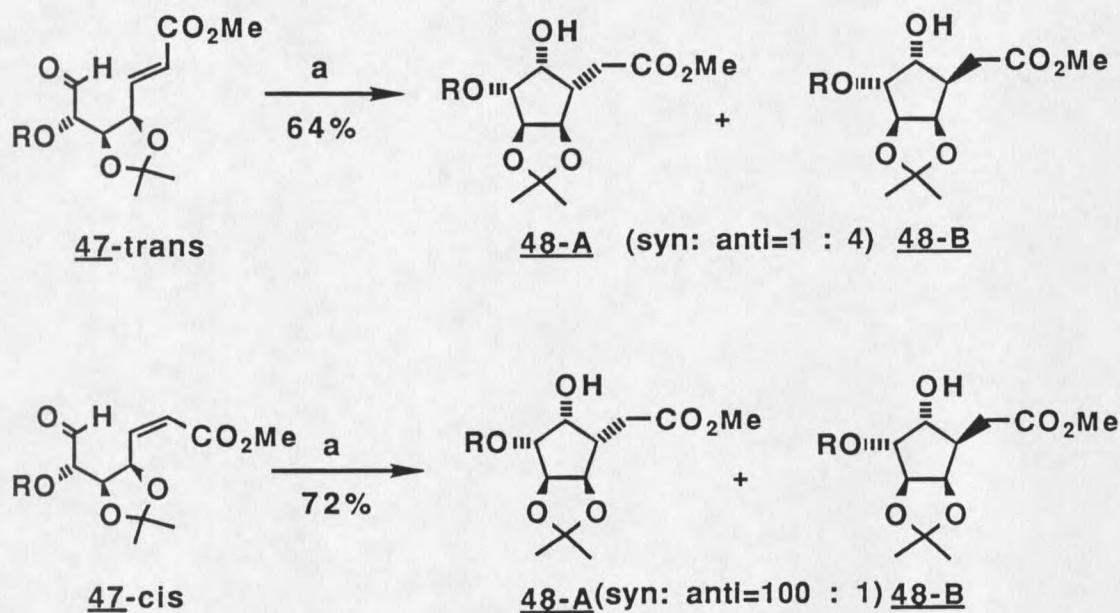
According to Beckwith³⁶, alkyl radicals preferentially attack π -systems through an unsymmetrical transition state to maximize orbital overlap between the semioccupied orbital (SOMO) and the empty π^* -

orbital (LUMO) of the olefin.

In addition to regiochemical control, Enholm and Trivellas³⁷ have also demonstrated a reversal in the diastereoselectivity in the products depending on whether the olefin geometry of the reactant is *cis* or *trans*. When 47-*trans* was treated with samarium iodide, two products were observed in a 1 : 4 ratio (*syn* : *anti*). In contrast, when 47-*cis* was treated under identical conditions, *syn* isomer of 48 was obtained as an almost exclusive product (Figure 18).

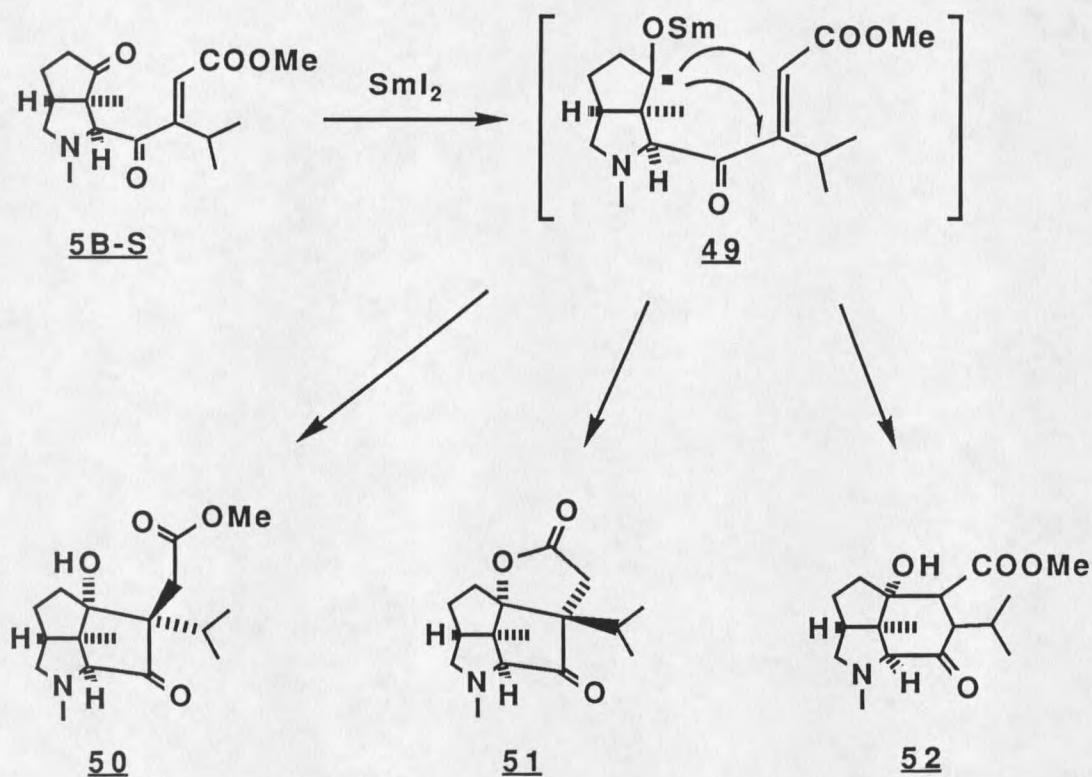
We postulated that we could take advantage of the inherent stereochemical control exhibited in intramolecular coupling reactions and extend stereochemical control to a third center through chelation utilizing tri-*n*-butyl tinhydride or samarium iodide as the reducing agents.

The butyl tinhydride-mediated cyclization was unsuccessful. But, when the *N*-methylpyrrolidine 5B-S was treated with 3 equiv. of SmI_2 and 4 equiv. of *t*-butanol as a proton source (THF, $-78^\circ\text{C} \sim \text{r. t.}$, 1 h), the major observed product was the tetracyclic lactone 51 (Figure 19).

Figure 18. Correlation of Olefin Geometry³⁷

a, SmI_2 , THF, -78°C .

Treatment of 5B-S with samarium iodide in THF-HMPA (10 : 1) at -78°C resulted the same product 51, which was derived from the 5-exo cyclization. However the reaction of 5B-S without any proton source or coadditive at -78°C gave the reduced product 57 as a major product. Since the desired product is the tricyclic β -hydroxy ester 52, we need to find some other factors to control the regioselectivity in the cyclization reaction.

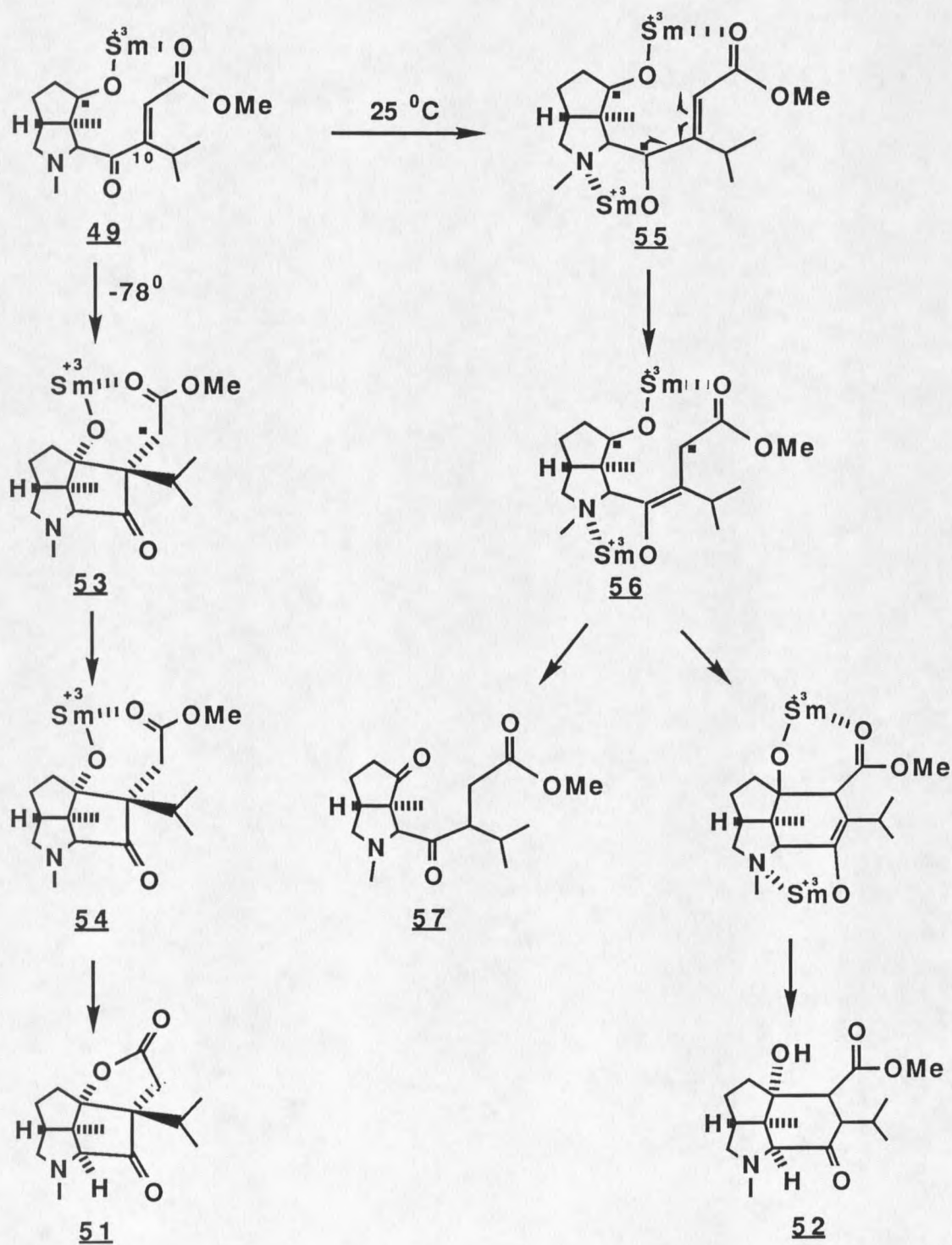
Figure 19. Possible Products from SmI_2 -mediated Cyclization.

We assumed that the proper choice of a Lewis acid might conspire to provide an enolate intermediate, which could lead to the formation of 6-membered ring. After examinations of several Lewis acids, we have found that the treatment of **5B-S** with samarium iodide (3 equiv.) in the presence of trimethylaluminum (3 equiv.) in THF ($0^\circ\text{C} \sim \text{r.t.}$) gave the desired tricyclic β -hydroxy ester **52** in 35 ~ 43% yield. However, we

discovered later that the reaction temperature plays a major role in the partitioning of 5B-S between 5-exo and 6-endo modes of cyclization. Reaction of 5B-S with samarium iodide (4 equiv.) in THF at -78°C gave lactone 51 without any desired product 52. On the other hand, exposure of 5B-S to samarium iodide (4 equiv.) in THF at $23 \sim 25^{\circ}\text{C}$ afforded a moderate yield (53%) of desired 6-membered hydroxy ester 52 and only a small amount (5%) of reduced product 57 (Figure 20).

From these results, we can suggest a possible mechanism for the cyclization. Single electron reduction of the ketone moiety by SmI_2 first generates a ketyl intermediate. Chelation of the Lewis acid, Sm(III) , then produces an eight membered ring ketyl intermediate 49. At lower temperature (-78°C), ketyl intermediate 49 adds to C-10 of the olefin (5-exo cyclization). The second equivalent of SmI_2 reduces the cyclic radical intermediate to a transient carbanion, which is immediately protonated and lactonized to afford tetracyclic lactone 51.

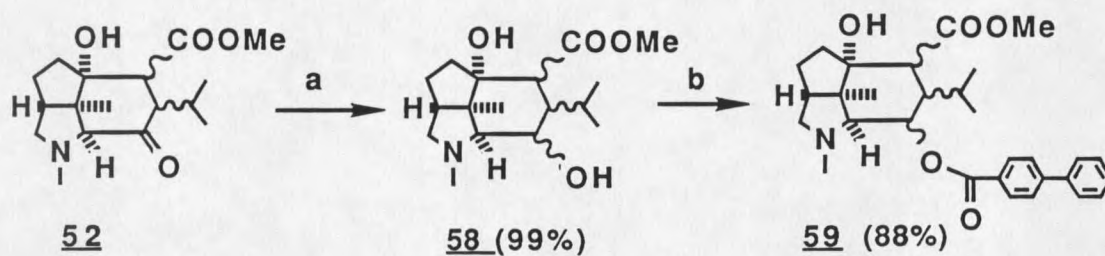
On the other hand, at higher temperature (25°C), the second equivalent of SmI_2 reduces unsaturated ketone to generate di-ketyl intermediate 55, which can be migrated into another di-radical intermediate 56 leading to the formation of 52 or reduced product 57.

Figure 20. A Possible Mechanism of SmI_2 -mediated Cyclization.

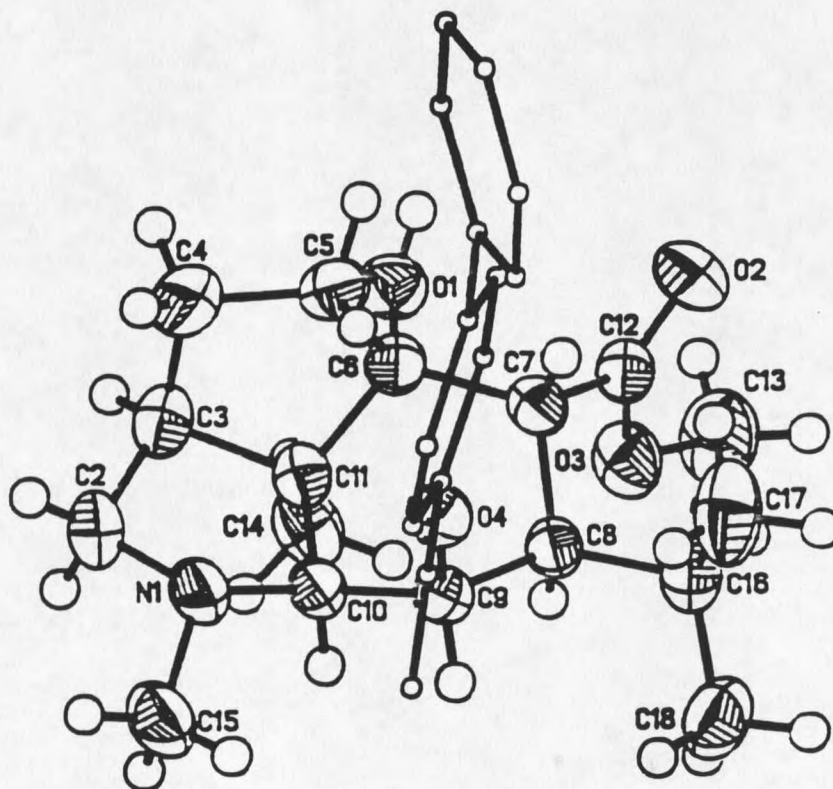
To our knowledge, the formation of 6-membered ring from SmI_2 -mediated cyclization between ketone and olefin has never been reported in the literature. Furthermore, cyclization at 25°C provided tricyclic β -hydroxyester 52 as a single stereoisomer. The stereochemistry of the carbomethoxy group was assumed to be trans with respect to the isopropyl moiety on the basis of the coupling constant ($J=12.1\text{ Hz}$). But it was difficult to determine the stereochemistry of the hydroxy group with respect to the carbomethoxy group without X-ray analysis.

In order to determine the absolute configuration of 52 by X-ray analysis, transformation of 52 into a crystalline derivative was investigated. Thus 52 was reduced by the Luche method ($\text{NaBH}_4\text{-CeCl}_3$) to the diol 58, which was then treated with biphenylcarbonyl chloride (DMAP, CH_3CN , r.t.) to give the biphenyl ester 59 (Figure 21).

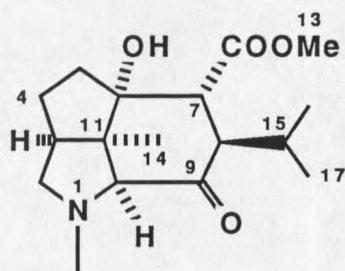
Recrystallization of 59 in ether-hexane mixture gave a crystalline compound, mp $136\sim 137^\circ\text{C}$. The crystal structure of 59, determined by X-ray analysis, is shown in Figure 22. This result made clear the absolute stereochemistry of 59 and eventually the absolute configuration of tricyclic β -hydroxyester 52.

Figure 21. Preparation of Biphenyl Ester 59.

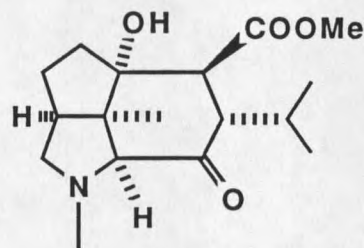
a, NaBH₄-CeCl₃·7H₂O, MeOH, r.t. , 2 h. b, biphenylcarbonyl chloride, DMAP, CH₃CN, r.t. , 4 h.

Figure 22. Molecular Structure of Biphenyl Ester 59.

The absolute configuration of 52 has now been determined as syn-anti compound 52, which is opposite to the desired anti-anti isomer 4.



52 (syn-anti)



4 (anti-anti)

Assignment of ^1H NMR and ^{13}C NMR data for 52 is shown in Table 5.

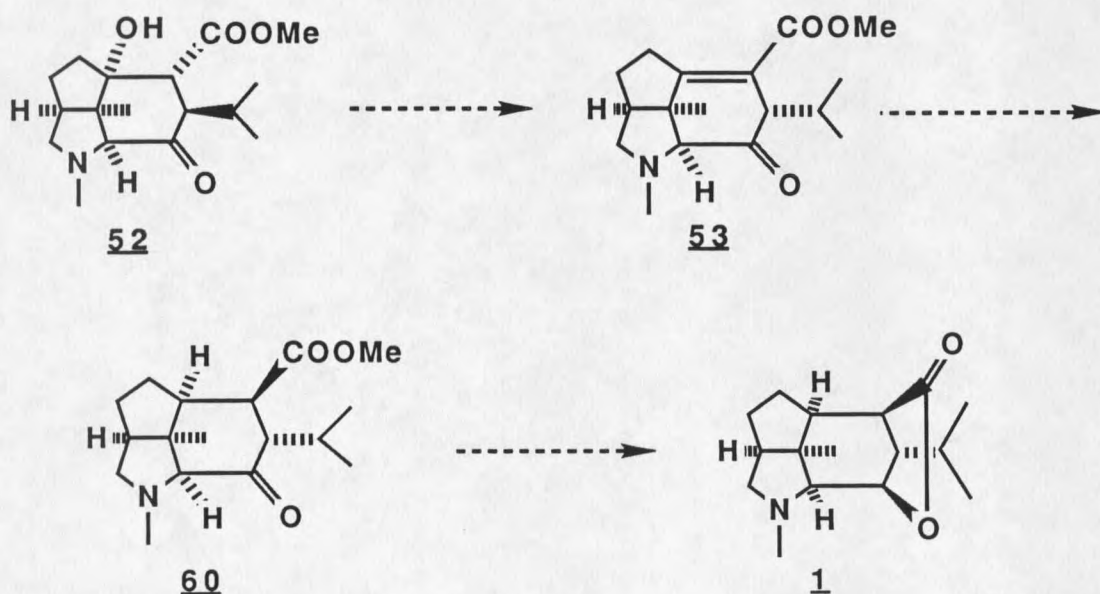
Table 5. NMR Data of Tricyclic β -Hydroxyester 52

^1H NMR		^{13}C NMR	
Proton	ppm	Carbon	ppm
$\text{CH}_3\text{--N}$	2.08 (s)	N--CH_3	41.5
H--2a	2.79 (d, $J=8.5$ Hz)	C--2	62.7
H--2b	2.73 (d, $J=8.5$ Hz)	C--3	51.5
H--3	2.21 (pent. $J=8.5$ Hz)	C--4	29.1
H--4a	1.78 (m)	C--5	39.0
H--4b	1.57 (m)	C--6	79.8
H--5	1.94 (m)	C--7	46.4
HO--6	3.60 (s)	C--8	51.1
H--7	3.97 (d, $J=12.1$ Hz)	C--9	202.0
H--8	2.58 (dd, $J=12.1, 4.4$ Hz)	C--10	82.5
H--10	2.07 (s)	C--11	57.6
$\text{CH}_3\text{--13}$	3.97 (s)	C--12	176.5
$\text{CH}_3\text{--14}$	1.04 (s)	C--13	51.9
H--15	1.47 (m)	C--14	23.6
$\text{CH}_3\text{--16}$	0.99 (d, $J=6.9$ Hz)	C--15	51.1
$\text{CH}_3\text{--17}$	0.87 (d, $J=6.9$ Hz)	C--16	20.4
		C--17	20.1

Total Synthesis of (dl)-Dendrobine (1).

Since the absolute configuration of the Sml_2 -mediated cyclization product has now been determined as syn-anti isomer 52, dehydration and epimerization were initially considered for the conversion of 52 into dendrobine (Figure 23).

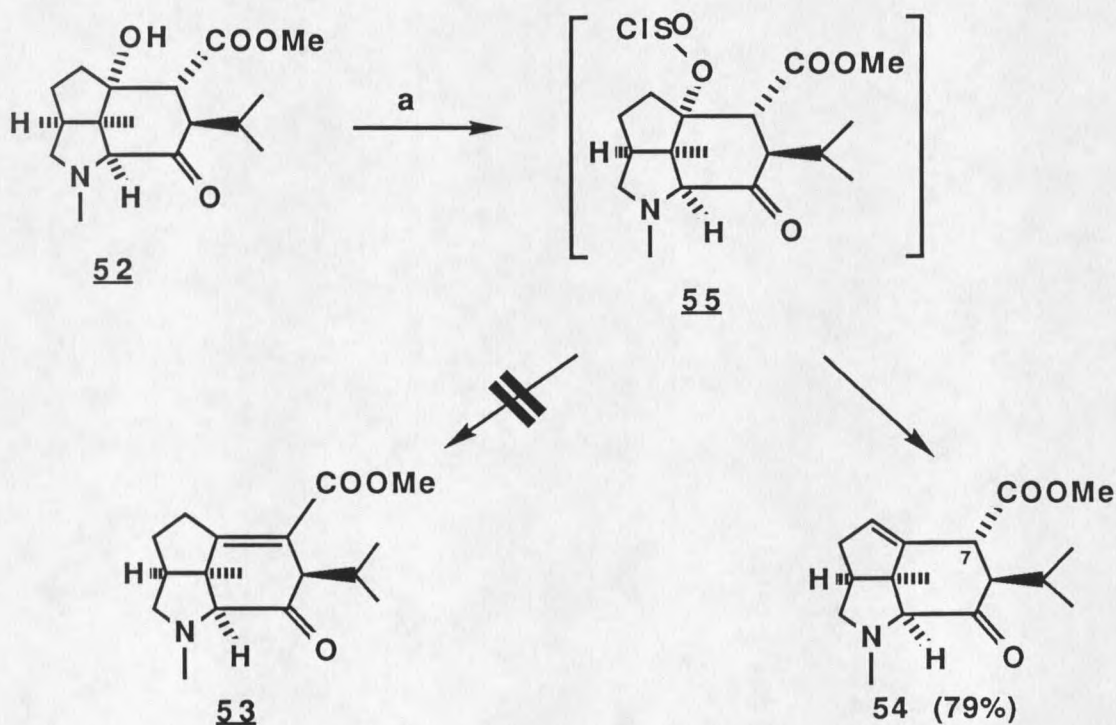
Figure 23. Synthetic Route to Dendrobine (1).



We examined dehydration of β -hydroxy group of 52 under a variety of reaction conditions only to recover the reactant. After considerable experimentation, we discovered that dehydration could be realized by treatment of 52 with thionyl chloride (3 equiv.) and triethylamine

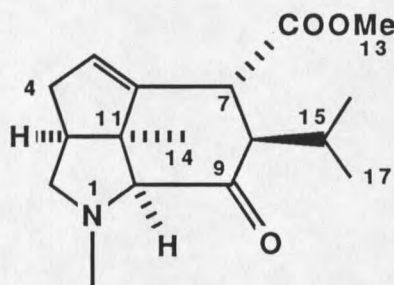
(30 equiv.) in ethyl acetate ($0^{\circ}\text{C} \sim \text{r.t.}$). Under these conditions, the product was not the expected α,β -unsaturated ester 53 but the β,γ -unsaturated ester 54 in 79% yield (Figure 24). Presumably, steric effects control the formation of the β,γ -unsaturated ester 54.

Figure 24. Dehydration of Tricyclic β -Hydroxyester 52.



a, 3 equiv. SOCl_2 , 30 equiv. Et_3N , EtOAc , $0^{\circ}\text{C} \sim \text{r.t.}$, 6 h.

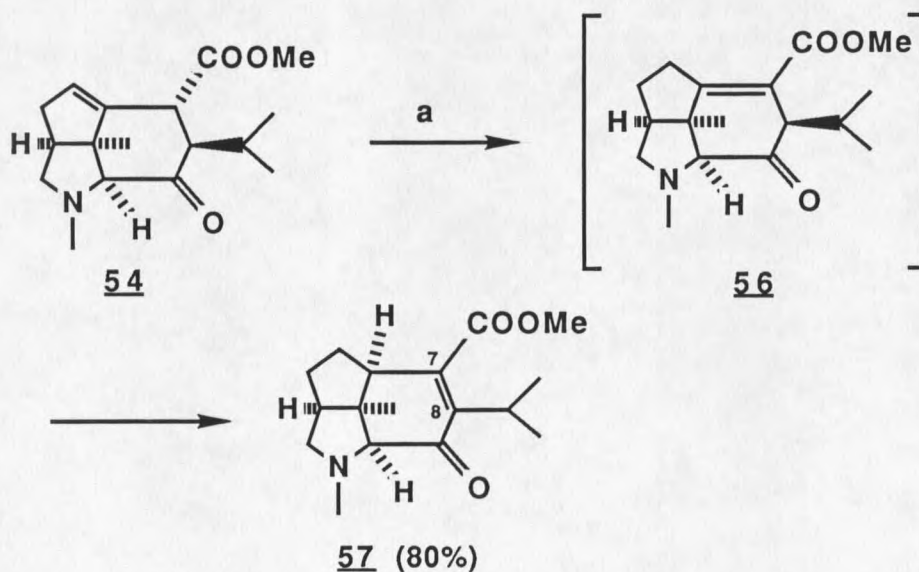
The ^1H NMR spectrum of dehydrated product 54 contained a olefinic signal at δ 5.64.

Assignment of ^1H NMR and ^{13}C NMR data for β,γ -unsaturated ester54 is shown in Table 6.Table 6. NMR Data of β,γ -Unsaturated Ester 54

^1H NMR		^{13}C NMR	
Proton	ppm	Carbon	ppm
$\text{CH}_3\text{--N}$	2.33 (s)	N--CH_3	42.0
H--2a	2.71 (t, $J=8.4$ Hz)	C--2	64.8
H--2b	2.31 (t, $J=8.4$ Hz)	C--3	55.3
H--3	2.17 (m)	C--4	38.8
H--4a	2.77 (dd, $J=9.5, 2.4$ Hz)	C--5	129.8
H--4b	2.53 (dd, $J=9.5, 7.8$ Hz)	C--6	138.3
H--5	5.64 (t, $J=2.4$ Hz)	C--7	46.1
H--7	3.61 (d, $J=5.7$ Hz)	C--8	49.2
H--8	2.84 (dd, $J=9.0, 5.7$ Hz)	C--9	210.3
H--10	2.46 (s)	C--10	82.3
$\text{CH}_3\text{--13}$	3.66 (s)	C--11	61.8
$\text{CH}_3\text{--14}$	1.29 (s)	C--12	173.3
H--15	1.16 (m)	C--13	52.2
$\text{CH}_3\text{--16}$	0.87 (d, $J= 7.0$ Hz)	C--14	24.9
$\text{CH}_3\text{--17}$	0.84 (d, $J= 7.0$ Hz)	C--15	27.8
		C--16	21.2
		C--17	19.8

With β,γ -unsaturated ester 54 in hand, we then examined the isomerization of double bond to the α,β -unsaturated esters 56 or 57. Thus, treatment of 54 with DBU (4 equiv.) in refluxing dioxane afforded 57 as a major product in 80% isolated yield. The position of double bond of 57 was assigned by ^1H NMR, ^{13}C NMR and DEPT experiments. There was no olefinic signal in ^1H NMR but two di-substituted olefinic carbons (δ 145.1 and 138.0) were shown in ^{13}C NMR. DEPT experiments indicated that the double bond was located in between C-7 and C-8 of compound 57 (Figure 25).

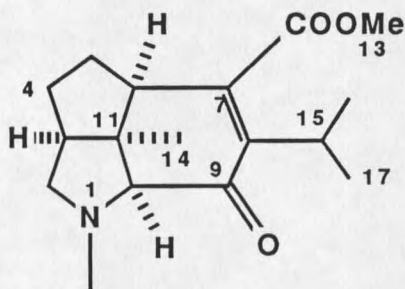
Figure 25. Isomerization of β,γ -Unsaturated Ester 54 to α,β -Unsaturated Ester 57.



a, 4 equiv. DBU, dioxane, reflux, 1 day.

Assignment of ^1H NMR and ^{13}C NMR data for α,β -unsaturated ester 57 is shown in Table 7.

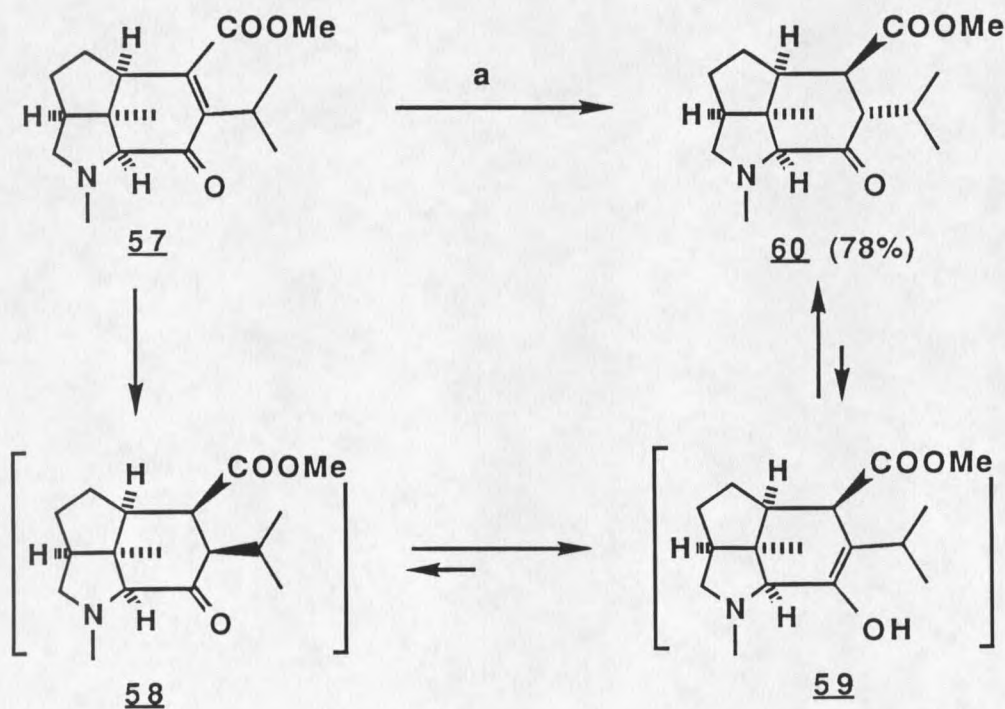
Table 7. NMR Data of α,β -Unsaturated Ester 57



^1H NMR		^{13}C NMR	
Proton	ppm	Carbon	ppm
$\text{CH}_3\text{--N}$	2.10 (s)	N--CH_3	41.1
H--2a	2.71 (t, $J=8.4$ Hz)	C--2	64.4
H--2b	2.45 (t, $J=8.4$ Hz)	C--3	50.0
H--3	2.17 (m)	C--4	33.4
H--4a	1.83 (t, $J=5.7$ Hz)	C--5	33.5
H--4b	1.69 (t, $J=5.7$ Hz)	C--6	49.0
H--5	1.86 and 1.77 (m)	C--7	138.0
H--6	2.43 (dd, $J=7.5$ Hz)	C--8	145.1
H--10	2.23 (s)	C--9	200.4
$\text{CH}_3\text{--13}$	3.77 (s)	C--10	80.1
$\text{CH}_3\text{--14}$	1.17 (s)	C--11	53.5
H--15	2.70 (seventet, $J=7.0$ Hz)	C--12	169.6
$\text{CH}_3\text{--16}$	1.17 (d, $J=7.0$ Hz)	C--13	51.7
$\text{CH}_3\text{--17}$	1.10 (d, $J=7.0$ Hz)	C--14	25.9
		C--15	30.1
		C--16	21.7
		C--17	19.8

Completion of the synthesis of (dl)-dendrobine required hydrogenation and reduction followed by lactonization. We planned to pursue this transformation through 3 steps: catalytic hydrogenation, epimerization, and metal hydride reduction. Previous syntheses of dendrobine^{19d,e} showed that reduction of methyl ketodendrobinate 60 with sodium borohydride led directly to 1. Therefore we focused on hydrogenation and epimerization steps to prepare 60.

Figure 26. Hydrogenation of α,β -Unsaturated Ester 57.



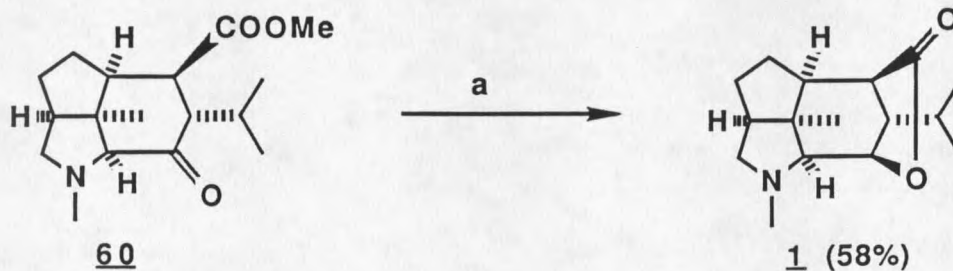
a, H₂, PtO₂, AcOH, 40 psi, r.t., 20 h.

After examination of a variety of hydrogenation conditions, we fortunately discovered that hydrogenation of 57 with platinum(IV)oxide in acetic acid (40 psi) furnished directly the desired 60 in 78% yield. Presumably, acetic acid plays an important role to transform the initial cis product 58 to trans product 60 through intermediate 59.

The spectroscopic properties of compound 60 were in excellent agreement with those reported by Roush^{19c}. Assignment of ¹H NMR and ¹³C NMR data for methyl ketodendrobinatate 60 is shown in Table 8.

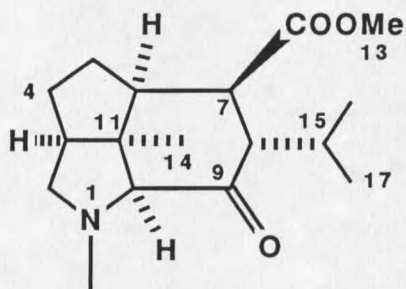
Finally, reduction of 60 with sodium borohydride (2-propanol, 20^o, 3 day) gave (dl)-dendrobine (1) in 58% purified yield. Careful recrystallization of 1 in ether furnished a crystalline dendrobine (1). mp, 129 ~ 131 ^oC (lit.^{19e} mp, 130 ~ 132 ^oC).

Figure 27. Synthesis of (dl)-Dendrobine (1).



a, NaBH₄ , 2-propanol, 20 ^oC, 3 days.

Table 8. NMR Data of Methyl Keto Dendrobinate (60)



^1H NMR		^{13}C NMR	
Proton	ppm	Carbon	ppm
$\text{CH}_3\text{--N}$	2.20 (s)	N--CH_3	41.3
H--2a	2.79 (dd, $J=9.3, 1.4$ Hz)	C--2	64.5
H--2b	2.54 (t, $J=9.3$ Hz)	C--3	50.8
H--3	1.99 (pentet, $J=9.3$ Hz)	C--4	28.3
H--4	1.60 and 1.44 (m)	C--5	31.9
H--5	1.97 and 1.70 (m)	C--6	46.8
H--6	2.14 (m)	C--7	48.1
H--7	3.17 (dd, $J=11.4, 4.1$ Hz)	C--8	48.7
H--8	2.99 (dd, $J=11.4, 4.1$ Hz)	C--9	213.8
H--10	2.23 (s)	C--10	82.4
$\text{CH}_3\text{--13}$	3.67 (s)	C--11	57.5
$\text{CH}_3\text{--14}$	1.24 (s)	C--12	173.5
H--15	1.87 (m)	C--13	51.7
$\text{CH}_3\text{--16}$	0.98 (d, $J= 6.9$ Hz)	C--14	26.3
$\text{CH}_3\text{--17}$	0.93 (d, $J= 6.9$ Hz)	C--15	29.4
		C--16	20.5
		C--17	18.0

The absolute stereochemistry of synthetic (dl)-dendrobine (1) was determined by X-ray analysis (Figure 28). The 300 MHz ^1H NMR, 75 MHz ^{13}C NMR, MS, and IR spectra of synthetic and natural³⁸ 1 were identical (Figure 29, 30 and 31). Natural and synthetic 1 were also indistinguishable chromatographically. Assignment of ^1H and ^{13}C NMR data for synthetic (dl)-dendrobine (1) is shown in Table 9.

Figure 28. Molecular Structure of Synthetic (dl)-Dendrobine (1).

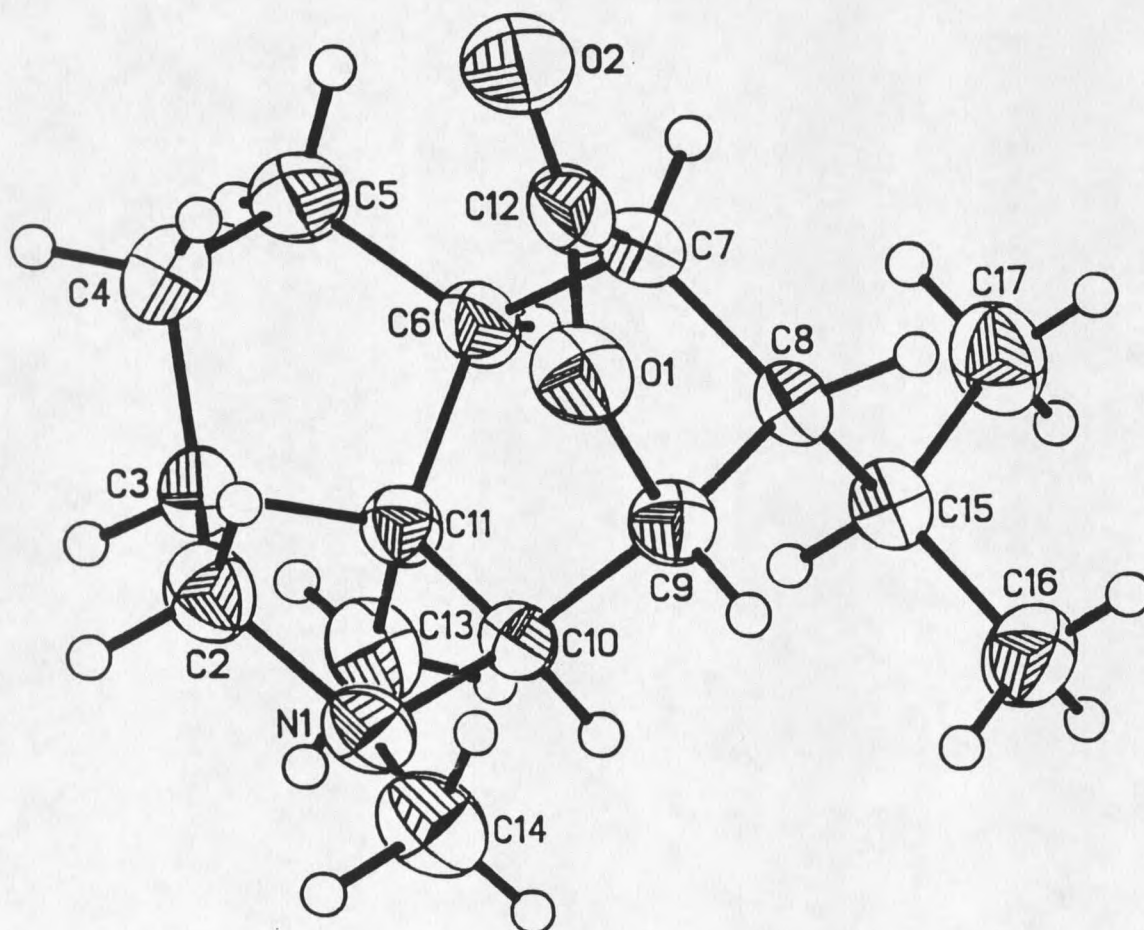
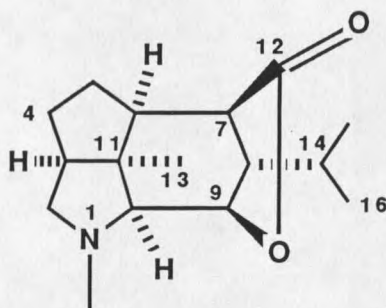


Table 9. NMR Data of Synthetic (dl)-Dendrobine (1).



¹ H NMR		¹³ C NMR	
Proton	ppm	Carbon	ppm
CH ₃ --N	2.50 (s)	N--CH ₃	36.6
H--2a	3.15 (t, J=8.7 Hz)	C--2	62.0
H--2b	2.69 (t, J=8.7 Hz)	C--3	51.6
H--3	2.36 (pentet, J=8.7 Hz)	C--4	32.9
H--4	1.85 and 1.55 (m)	C--5	30.8
H--5	2.12 and 2.05 (m)	C--6	44.0
H--6	2.02 (m)	C--7	53.9
H--7	2.45 (dd, J=9.5, 4.0 Hz)	C--8	43.1
H--8	2.12 (m)	C--9	79.3
H--9	4.84 (dd, J=5.5, 3.0 Hz)	C--10	67.1
H--10	2.66 (d, J=3.0 Hz)	C--11	52.5
CH ₃ --13	1.38 (s)	C--12	179.0
H--14	1.76 (heptet, J=6.5 Hz)	C--13	32.8
CH ₃ --15	0.97 (d, J= 6.5 Hz)	C--14	24.5
CH ₃ --16	0.96 (d, J= 6.5 Hz)	C--15	21.1
		C--16	20.4

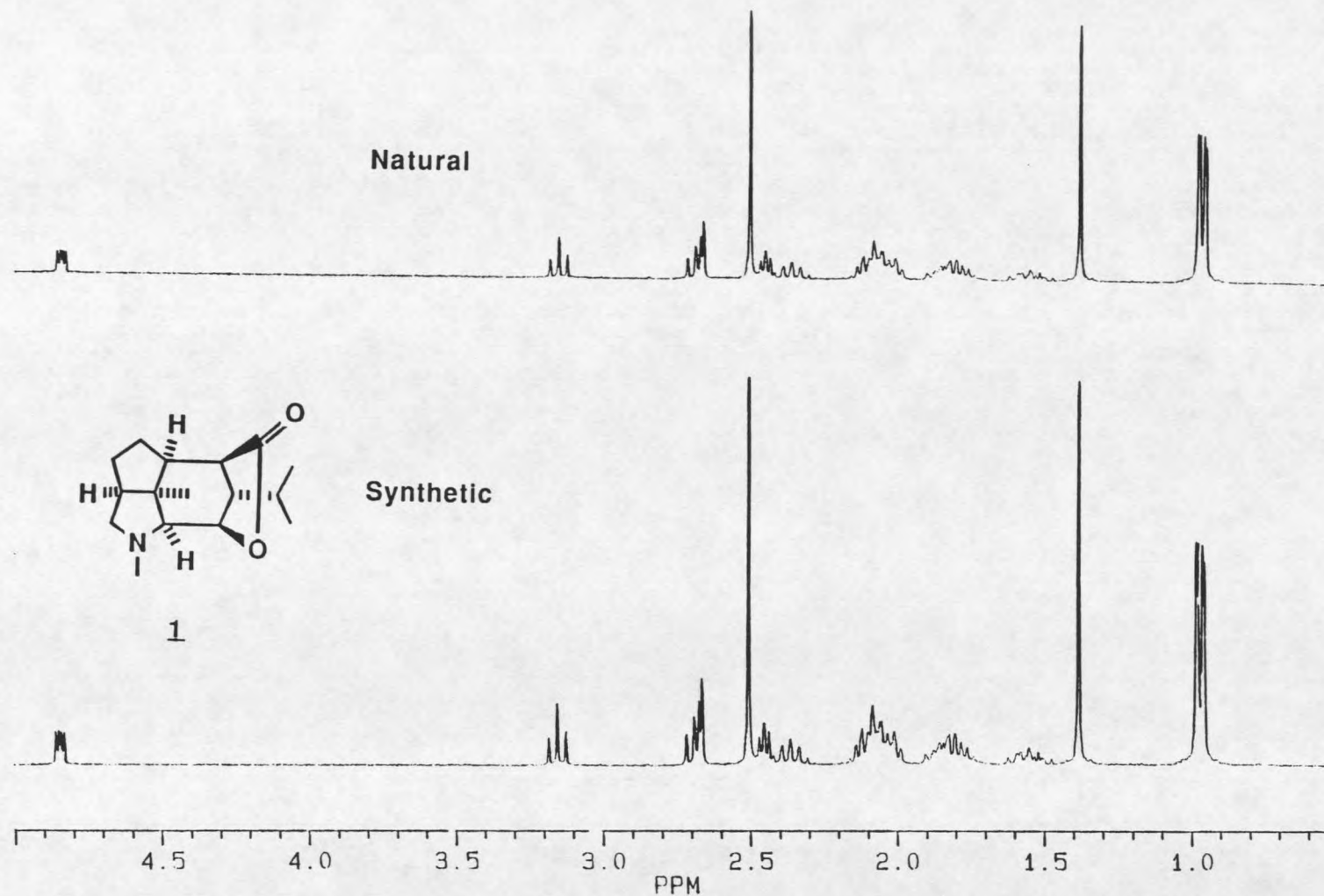


Figure 29. Comparison ^1H Spectra of Naturally Derived vs Synthetic (dl)-Dendrobine (1)

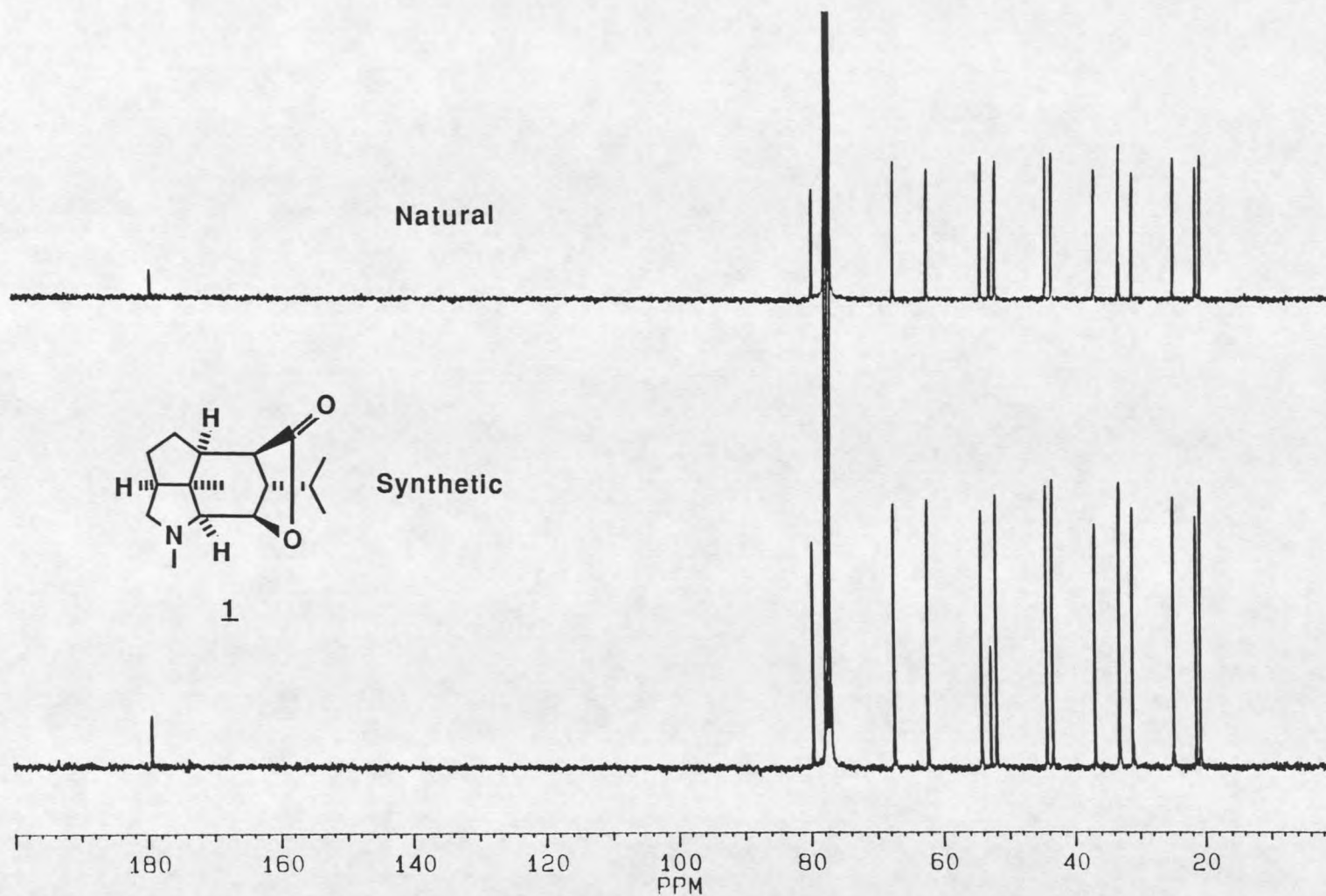


Figure 30. Comparison ^{13}C Spectra of Naturally Derived vs Synthetic (dl)-Dendrobine (1)

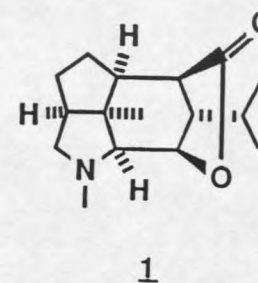
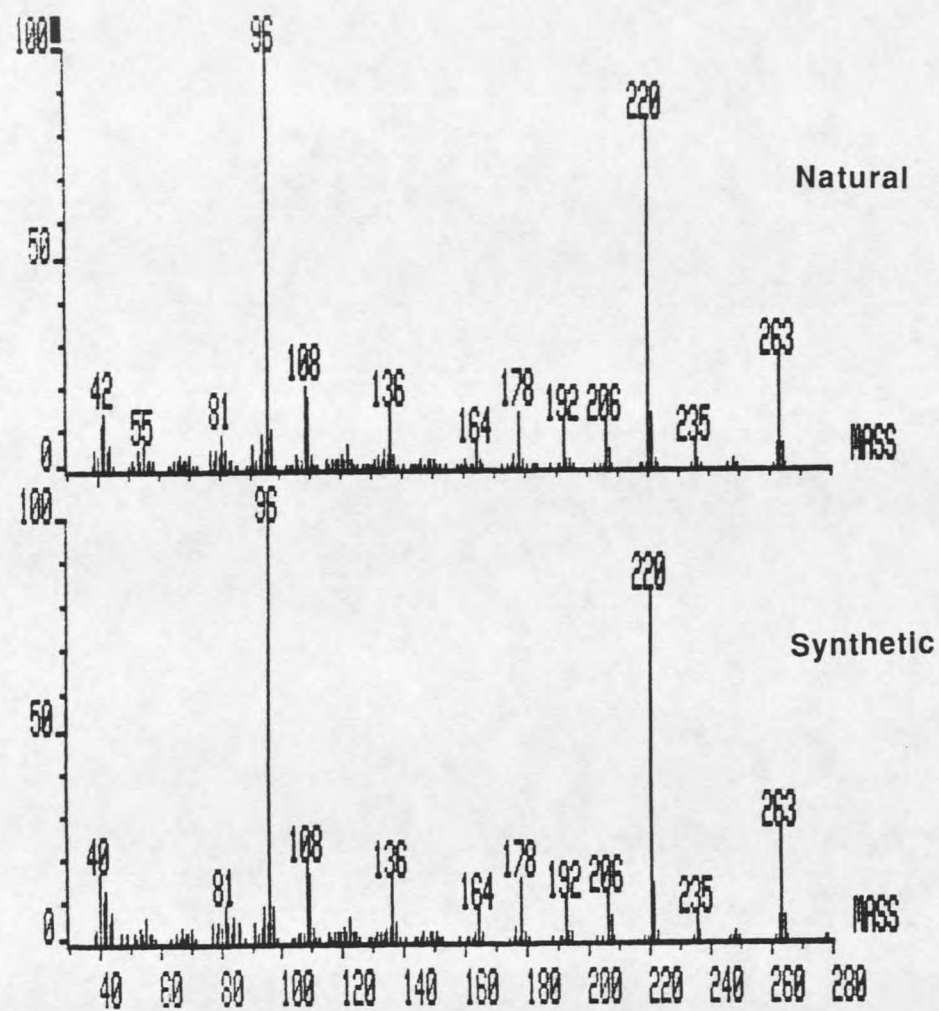


Figure 31. Comparison Mass (EI) Spectra of Naturally Derived vs Synthetic (dl)-Dendrobine (1)

The synthetic approach to (dl)-dendrobine (1) described in this thesis involved eight linear steps in 6.2% overall yield.

The above successful, experimentally verified route demonstrates the power of the acylnitrilium ion initiated cyclization and SmI_2 -mediated cyclization for establishing stereochemistry for use in natural product synthesis. This synthesis is noteworthy for its highly convergent nature which should show promise for the synthesis of other analogs and which provides rapid entry to the acylpyrroline skeletons in high yield.

SUMMARY

The goal of my thesis research has been to apply the study of the acylnitrilium ion initiated cyclization and Sml_2 -mediated cyclization to natural product synthesis. Dendrobine (1) is the major alkaloidal component isolated from the ornamental orchid "Chin-Chai-Shi-Hu", which has been employed in traditional medicine in China as a tonic for the promotion of general health.

Exposure of 2-methylcyclopent-2-en-1-one (26) to lithiomethyl isocyanide followed by silylation afforded isonitrile 7.

Treatment of isopropylfumaric acid with thionyl chloride gave diacylchloride 16, which was selectively esterified with methanol to furnish the desired acylchloride 8.

The acylation of 7 was conveniently achieved by its exposure to 8 to afford α - ketoimidoyl chloride 29, which was then subjected to AgBF_4 -mediated cyclization to provide 2-acylpyrroline 6.

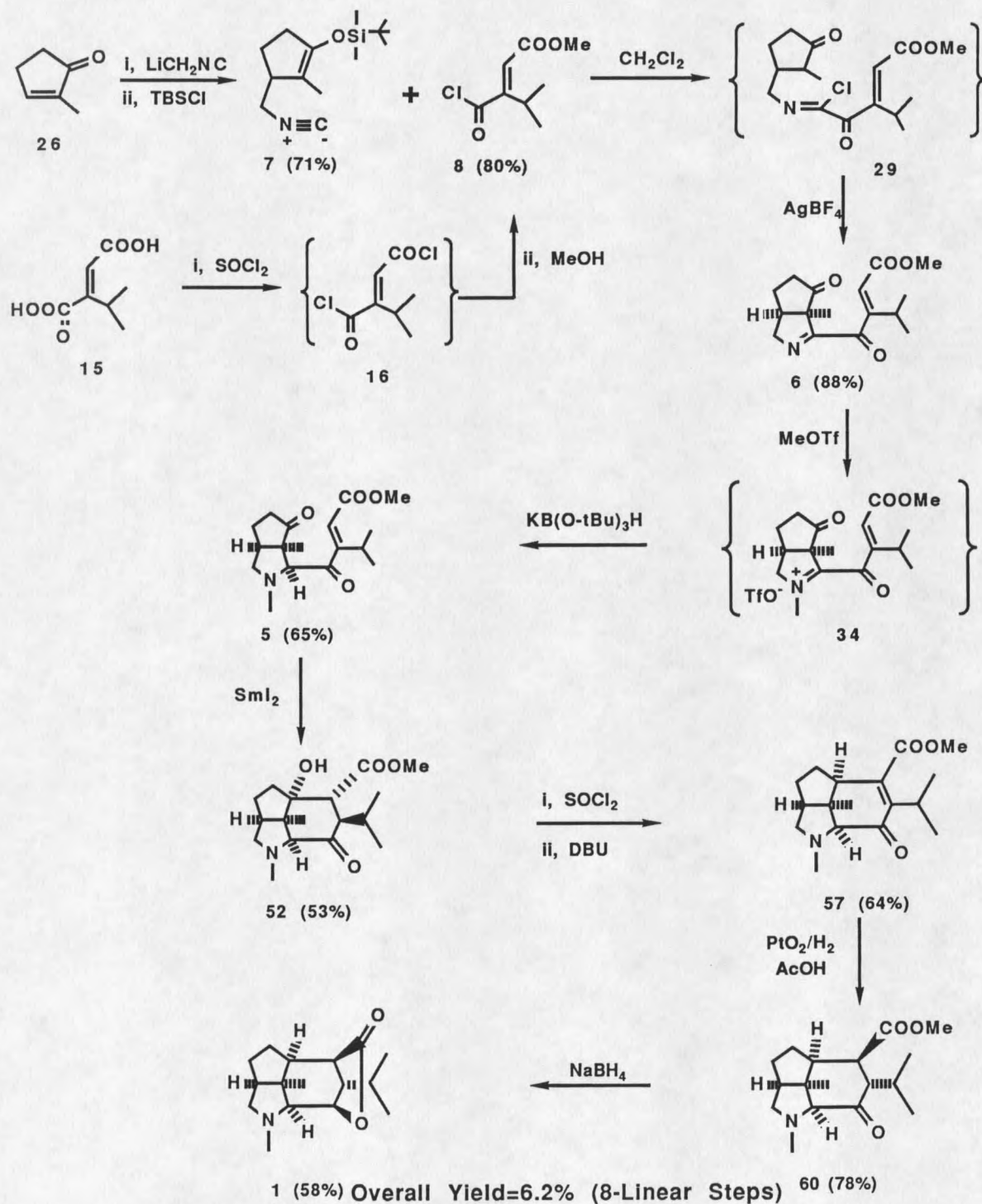
N-Methylation was accomplished by treating 6 with MeOTf . The resultant iminium triflate 34 was selectively reduced with $(n\text{-Bu})_3\text{SnH}$

or $\text{KHB}(\text{O}-t\text{-Bu})_3$ to give N-methylpyrrolidine 5.

Reduction of 5 with SnI_2 produced tricyclic β -hydroxyester 52, which was treated with thionyl chloride followed by isomerization with DBU to give α,β -unsaturated ester 57.

Hydrogenation of 57 with PtO_2 in acetic acid gave methyl keto dendrobinatate (60). Finally, reduction of 60 with NaBH_4 led directly to (dl)-dendrobine (1). Its spectroscopic properties were in excellent agreement with authentic natural dendrobine and its structure was determined for the first time by X-ray analysis.

Figure 32. Summary of a Total Synthesis of Dendrobine (1)



EXPERIMENTAL

General Procedures

All reactions were performed in flame-dried apparatus under a positive pressure of nitrogen. Reaction mixture was stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred by syringe or cannular and introduced to reaction vessels through rubber septum caps. Reaction product solutions were concentrated using a Buchi rotary evaporator at aspirator pressure.

Materials

Commercial grade reagents and solvents were used without further purification unless otherwise indicated. Materials designated as "distilled" in experimental procedures were purified as follows:

Distilled under nitrogen or vacuum: 1,5-diazabicyclo [5.4.0] undec-5-ene (DBU), oxalyl chloride,

Distilled under nitrogen or vacuum from calcium hydride: acetonitrile, benzene, 1,2-dichloroethane, diisopropylethyl amine, N,N-dimethylformamide, hexamethylphosphoramide (HMPA), hexane, methylene chloride, pentane, triethylamine.

Distilled under nitrogen from sodium benzophenone ketyl:

1,2-dimethoxyethane, diethylether, tetrahydrofuran (THF).

Distilled under nitrogen from magnesium: methanol, ethanol.

Distilled under nitrogen from phosphorous pentoxide: chloroform,
carbon tetrachloride, ethyl acetate.

Distilled under nitrogen from triphenyl phosphite: thionyl chloride.

Distilled under nitrogen from acetic anhydride: acetic acid.

Borane solutions [$\text{K}(\text{i-PrO})_3\text{BH}$ and $\text{K}(\text{t-BuO})_3\text{BH}$] were titrated according to the procedure of Brown²⁹.

Chromatography

Analytical thin layer chromatography was performed on silica gel K42-G plates (Alltech Associates, Inc. Germany). Visualizaton of spots was affected by one or more of the following techniques: (a) ultraviolet illumination (254 nm); (b) exposure to iodine vapor; (c) immersion of the plate in a 1% aqueous solution of potassium permanganate containing 2% sodium bicarbonate; (d) immersion of the plate in a 3% solution of vanillin in ethanol containing 0.5% concentrated sulfuric acid, followed by heating to dry the plate, and reimmersion and then heating to ca. 200 °C.

Column chromatography was performed using 100-200 mesh

florisil (U.S. Silica Company) and silica gel 60 (EM Science). The following chromatography solvents were distilled prior to use ; ethyl acetate, hexane, methanol, methylene chloride.

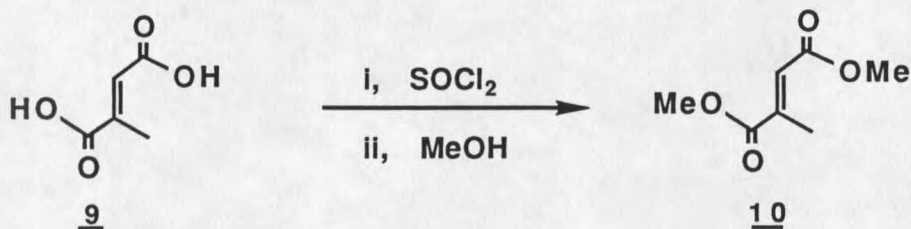
Physical Data

Melting points (mp) were determined with a Buchi melting point apparatus and are uncorrected. Boiling points (bp) are uncorrected.

Infrared (IR) spectra were measured on Bio-Rad FTS-Qualimatic Infrared spectrophotometer and are reported in wave numbers (cm^{-1}).

Nuclear magnetic resonance (NMR) spectra were measured at 300 MHz on a Bruker WM-300 instrument. Chemical shifts are reported in parts per million (ppm) downfield from internal tetramethyl silane (δ). Multiplicity is indicated using the following abbreviations : s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), etc. Coupling constants are reported in Hz.

Mass spectra (EI and High resolution) were measured on a VG 70E-HF double-beam focusing mass spectrometer. Principal molecular fragments are reported.

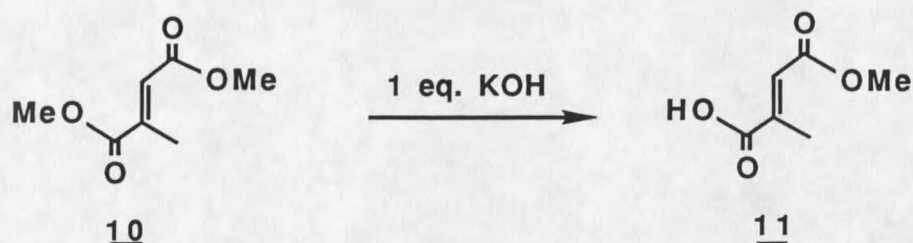
Methyl-(E)-2-methylbut-2-ene-1,4-dioate (10)

An oven-dried flask fitted with a nitrogen bubbler, addition funnel and magnetic stirring bar was charged with 26.0 g (0.2 mol) of mesaconic acid (9), 4 drops of DMF, and 400 mL of CH₂Cl₂. To this solution was added 44.0 mL (0.6 mol) of SOCl₂ dropwise at room temperature. The mixture was then stirred for 20 h. The reaction mixture was then treated with 150 mL (3.7 mol) of MeOH and stirred for an additional 16 h at room temperature. The volatile components were removed *in vacuo* and the residue was dissolved in 150 mL of CH₂Cl₂, washed with 10% KHCO₃, brine, and dried over anhydrous Na₂SO₄. After removing the solvent under reduced pressure, the residue was distilled (62 °C at 0.15 torr) to give 29.8 g (94.2%) of the diester 10.

¹H NMR : 2.25 (3H, d, J=1.60 Hz, CH₃), 3.76 (3H, s, CH₃O), 3.79 (3H, s, CH₃O), 6.74 (1H, q, J=1.55 Hz).

¹³C NMR : 167.49 (s), 166.23 (s), 126.59 (s), 52.60 (q), 51.70 (q), 14.31 (q).

IR(CDCl₃) : 3010-2840, 1730, 1725, 1630 .

(E)-3-Carbomethoxy-2-methylpropenoic acid (11)

An oven-dried flask fitted with an addition funnel, bubbler and stirring bar was charged with 20.0 g (126.0 mmol) of 10 in 40 mL of MeOH and cooled to 0 °C. With stirring a solution of 7.1 g (126.0 mmol) of KOH in 50 mL of MeOH was added dropwise. The reaction mixture was stirred for 1 h at 0 °C, then allowed to warm to room temperature and stirred for 48 h. The solvent was then removed *in vacuo*, and the residue was dissolved in 50 mL of water. This solution was evaporated *in vacuo* again. The residue was redissolved in 50 mL of water, cooled to 0 °C, covered with 50 mL of ether and acidified with 6N HCl to pH 1.0. The ether layer was separated, the aqueous layer was saturated with NaCl and extracted with 3 x 50 mL of ether. The combined ether fractions were dried over anh. MgSO₄ and the solvent was removed *in vacuo*. The crude product was subjected to chromatography on silica gel (20% ethyl acetate - hexane for elution) to give

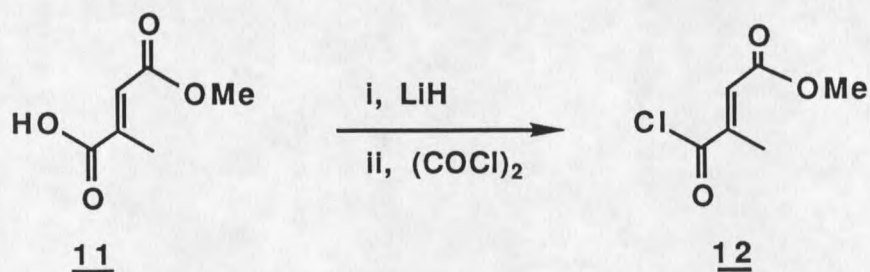
19.0 g (92.0%) of the pure half acid 11.

^1H NMR : 6.87 (1H, q, $J=1.53$ Hz, vinyl CH), 3.77 (3H, s, CH_3O), 2.27 (3H, d, $J=1.53$ Hz, CH_3).

^{13}C NMR : 172.46 (s), 166.03 (s), 142.77 (s), 128.82 (d), 51.88 (q), 13.92 (q).

IR (KBr) : 3520-2860, 1730, 1705, 1650 .

(E)-3-Carbomethoxy-2-methylpropenoyl chloride (12)



An oven-dried flask fitted with an addition funnel, a nitrogen bubbler and a magnetic stirring bar was charged with 0.3 g (37.0 mmol) of lithium hydride suspended in 10 mL of ether. With stirring, a solution of 5.3 g (37.0 mmol) of half acid 11 in 10 mL of ether was added dropwise over 30 min. The suspension was stirred for 2 h and then 3.5 mL (41.0 mmol) of oxalyl chloride in 10 mL of ether was added dropwise.

The reaction mixture was then stirred for an additional 2 h, filtered through celite, and the solvent was removed under reduced pressure. The residue was then distilled from calcium hydride. The fraction distilling between 105 - 108 °C at 42 torr was collected to yield 4.5 g (74.6%) of the acyl chloride 12 as a colorless liquid.

¹H NMR : 6.99 (1H, q, J=1.41 Hz, vinyl CH), 3.78 (3H, s, CH₃), 2.29 (3H, d, J=1.46 Hz).

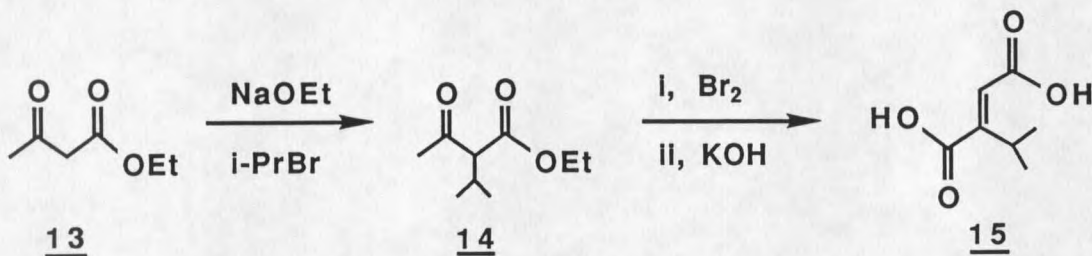
¹³C NMR : 169.47 (s), 165.05 (s), 146.48 (s), 132.39 (d), 52.18 (q), 14.99 (q).

IR (CDCl₃) : 2995, 2960, 1765, 1740, 1635, 1220.

Mass (EI) : 163 (M+H)⁺, 131, 127, 103, 99, 68, 59.

Exact Mass :	Calcd. for	C ₆ H ₇ ClO ₃	163.0162 (M+H) ⁺
	Found		163.0160 (M+H) ⁺

Isofumaric acid (15)



To a solution of sodium ethoxide prepared by dissolving 19.2 g (84.0 mmol) of sodium in 300 mL of anhydrous ethanol was added 96 mL (74.0 mmol) of ethyl acetoacetate dropwise over 20 min. The solution

was stirred for an additional 10 min. and 92 mL (980 mmol) of isopropyl bromide was added slowly. Following the addition, the reaction mixture was heated at reflux for 12 h and was then allowed to cool. The solution was poured into 200 mL of water and then extracted with 3 x 300 mL of ethyl acetate. The organic extracts were washed with water and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure to give a pale yellow oil which was purified through distillation at 16 torr to give 97.1 g (76.2%) of 2-isopropylacetoacetate ethylester (14) as a colorless oil.

^1H NMR : 4.14 (2H, q, $J=14.3$ Hz, CH_2), 3.13 (1H, d, $J=9.5$ Hz, CH), 2.38 (1H, m, CH), 2.18 (3H, s, CH_3), 1.23 (3H, t, $J=7.2$ Hz, CH_3), 0.91 (6H, dd, $J=6.7$ Hz, 2 x CH_3)

^{13}C NMR : 203.11 (s), 169.23 (s), 67.71 (d), 61.10 (t), 29.08 (d), 28.62 (q), 20.49 (q), 20.39 (q), 14.11 (q).

To a vigorously stirred solution of 26 g (150 mmol) of the ester 14 in 200 mL of dry diethyl ether was slowly added 48 g (300 mmol) of Br_2 and the solution then refluxed for 3 h. The solvent and HBr were removed under reduced pressure to give the dibromide, which was added slowly to a solution of 160 mL of EtOH containing 48 g (860 mmol) of powdered KOH with rapid stirring. The mixture was refluxed for 0.5 h

and was then steam distilled until 700 mL of distillate had been collected. The acidified solution with 6N HCl was extracted with 3 x 200 mL of ethyl acetate and the extracts were washed with brine and dried over anhydrous Na_2SO_4 . After filtration, the filtrate was decolorized with active charcoal and reduced in volume under reduced pressure to give an amorphous off-white solid. The product was recrystallized from ethyl acetate-hexane to give 14.0 g (58.6%) of isopropylfumaric acid (15) as white crystals. mp 180 ~ 182 °C (lit.²⁵ mp 183 ~ 184 °C)

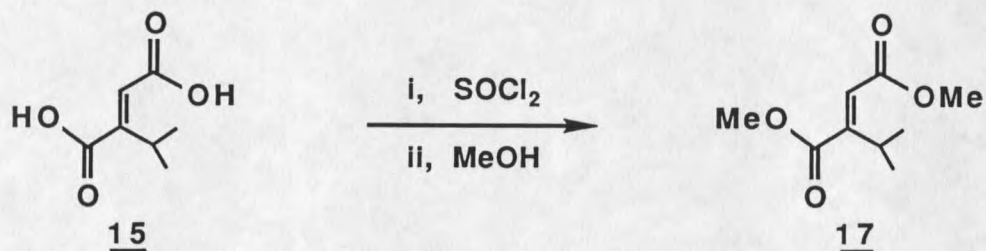
^1H NMR (D_2O - NaHCO_3 , HOD at 4.6 ppm) : 6.16 (1H, s, CH), 2.24 (2H, t, $J=7.5$ Hz, CH_2), 1.19 (2H, m, $J=7.5$ Hz, CH_2), 0.67 (3H, t, $J=7.5$ Hz, CH_3).

^{13}C NMR (D_2O - NaHCO_3) : 176.12 (s), 174.62 (s), 149.02 (s), 121.02 (d), 28.29 (d), 19.05 (2 x q).

IR (Nujol) : 1700, 1640 .

Mass (EI) : 140, 120.

Methyl-(E)-2-(1'-methyl)ethylbut-2-ene-1,4-dioate (17).

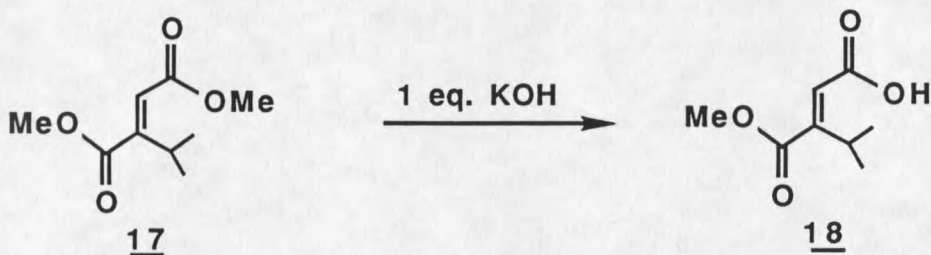


An oven-dried flask fitted with a bubbler, addition funnel and magnetic stirring bar was charged with 10.3 g (65.0 mmol) of isopropyl fumaric acid (15), 3 drops DMF, and 150 mL of CH₂Cl₂. To this solution was added 14.3 mL (195.0 mmol) of thionyl chloride dropwise at room temperature. After refluxing 12 h, the mixture was cooled to 0 °C, treated with 50 mL of methanol, and stirred for an additional 18 h at room temperature. The volatile components were removed under reduced pressure and the residue was dissolved in 100 mL of CH₂Cl₂, washed with 10% aqueous KHCO₃, brine and dried over anh. Na₂SO₄. The solvent was removed under reduced pressure to give crude product. This was purified by flash chromatography with 5% ethyl acetate-hexane for elution to provide 9.1 g (81.0%) of the pure diester 17 as a colorless liquid.

^1H NMR : 6.44 (1H, s, CH), 3.75 (3H, s, CH_3), 3.74 (1H, m, CH)
3.73 (3H, s, CH_3), 1.17 (6H, d, $J=7.1$ Hz, 2 x CH_3).

^{13}C NMR : 167.22 (s), 166.03 (s), 153.67 (s), 124.23 (d), 51.87 (q), 51.60 (q), 28.04 (d), 20.53 (2 x q).

(E)-1-Carbomethoxy-2-(1'-methyl)ethylpropenoic acid (18).

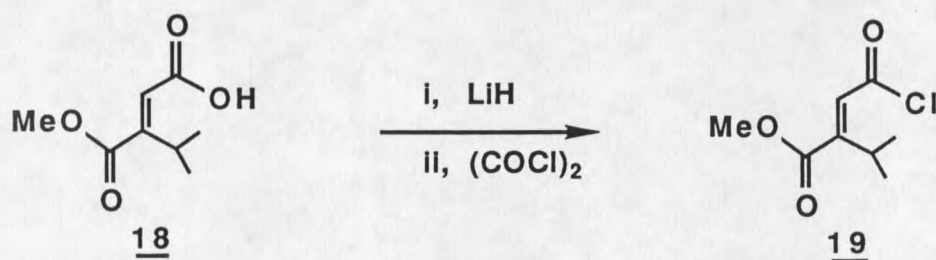


An oven-dried flask was charged with 9.1 g (48.8 mmol) of diester 17 in 15 mL of methanol and cooled to 0 $^{\circ}\text{C}$. With stirring a solution of 2.8 g (48.8 mmol) of KOH in 20 mL of methanol was added dropwise. The reaction mixture was stirred for 1 h at 0 $^{\circ}\text{C}$, then allowed to warm to room temperature and stirred for 60 h. Solvent was then removed under reduced pressure and the residue was dissolved in 20 mL of water. This solution was evaporated under reduced pressure. The residue was redissolved in 25 mL of water,

cooled to 0⁰ C, covered with 30 mL of ethyl ether and acidified to pH 1. The organic layer was separated, the aqueous layer was saturated with NaCl and extracted with 3 x 30 mL of ethyl ether. The combined extracts were dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure to give 6.0 g (71.4%) of half acid 18.

¹H NMR : 6.43 (1H, s, CH), 3.78 (3H, s, CH₃), 3.76 (1H, m, CH), 1.19 (6H, d, J=7.1 Hz, 2 x CH₃)

(E)-1-Carbomethoxy-2-(1'-methyl)ethylpropenoyl chloride (19).



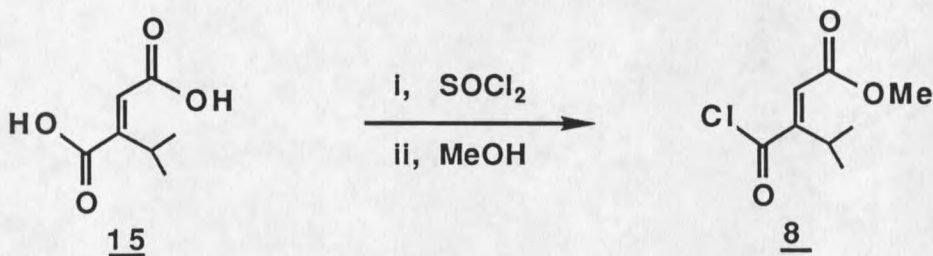
An oven-dried flask was charged with 272.0 mg (34.0 mmol) of lithium hydride suspended in 10 mL of ether. With stirring, a solution 5.9 g (34.0 mmol) of half acid 18 in 10 mL of ether was added dropwise over 30 min. The reaction mixture was stirred for an additional 2h, filtered through celite, and the solvent was removed under reduced

pressure. The residue was then distilled (74 ~ 76 °C at 1 torr) to give 5.1 g (78.1%) of the acyl chloride 19 as a colorless liquid.

¹H NMR : 6.65 (1H, s, CH), 3.80 (3H, s, CH₃), 3.48 (1H, m, CH) 1.18 (6H, d, J=7.1 Hz, 2 x CH₃).

¹³C NMR : 166.01 (s), 164.37 (s), 156.67 (s), 128.69 (d), 52.38 (q), 29.11 (d), 20.36 (2 x q).

(E)-3-Carbomethoxy-2-(1'-methyl)ethylprop-2-enoyl chloride (8).



An oven-dried flask was charged with 6.4 g (40.0 mmol) of isopropyl fumaric acid, 3 drops DMF, and 64 mL of CH₂Cl₂. To this solution was added 8.9 mL (120.0 mmol) of thionyl chloride dropwise at room temperature. After refluxing for 6 h, the reaction mixture was cooled to 0 °C and then treated with 6.5 mL (160.0 mmol) of methanol. The mixture was stirred for 30 min. at ice-bath temperature and stirred

for an additional 3 h at room temperature. After removing the volatile components under reduced pressure, the residue was distilled (58 ~ 60 °C at 1 torr) to give 6.1 g (79.7%) of the acyl chloride 8 as a colorless oil.

¹H NMR : 6.83 (1H, s, CH), 3.79 (3H, s, CH₃), 3.75 (1h, m, CH), 1.19 (6H, d, J=7.0 Hz, 2 x CH₃)

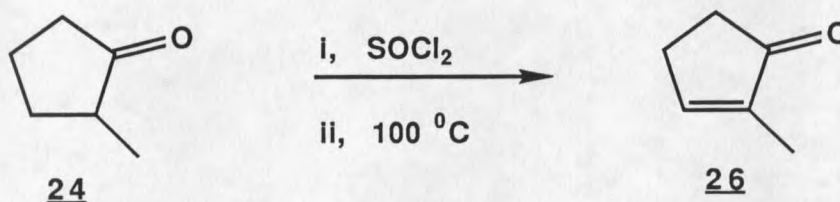
¹³C NMR : 167.31 (s), 165.13 (s), 156.12 (s), 130.22 (d), 52.09 (q), 29.33 (d), 20.28 (2 x q).

IR (CDCl₃) : 2970, 2880, 1730, 1765, 1640, 1235, 1175, 795.

Mass (EI) : 191, 159, 154, 131, 126, 111, 95, 81, 67, 59, 53, 50.

Exact Mass :	Calcd. for	C ₈ H ₁₁ ClO ₃	191.0475
	Found		191.0463

2-Methylcyclopent-2-en-1-one (26)



An oven-dried 3-necked flask fitted with a thermometer, addition funnel, N₂ inlet adaptor, rubber septum, and a magnetic stirring bar,

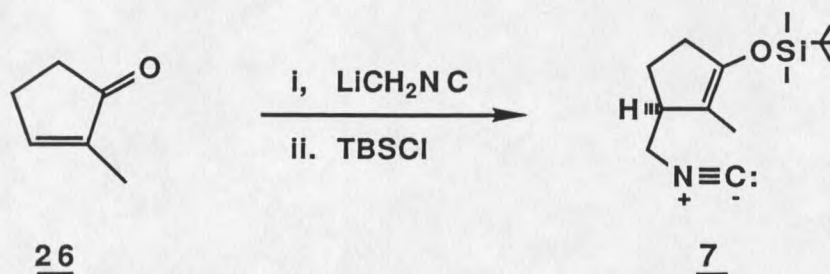
was charged with 42.8 mL (400.0 mmol) of 2-methylcyclopentanone (24), 200 mL of CCl_4 and cooled to 10°C . To this solution was added 35.4 mL (440.0 mmol) of sulfuryl chloride in 60 mL of CCl_4 for 30 min. at 12°C . After stirring at room temperature for 3 h, the reaction mixture was washed with water, saturated NaHCO_3 , water, brine, and dried over anhyd. MgSO_4 . The solvent was removed under reduced pressure. The residue was heated to 100°C for 15 min. to remove HCl gas and distilled ($56 \sim 58^\circ\text{C}$ at 16 torr) to give 52.1 g (86.3%) of product 28 as a colorless oil.

^1H NMR : 7.11 (1H, m, CH), 2.31 (2H, m, CH_2), 2.11 (2H, m, CH_2), 1.51 (3H, q, $J=3.5$ and 1.9 Hz, CH_3).

^{13}C NMR : 209.18 (s), 157.44 (s), 141.35 (s), 33.93 (t), 25.88 (t), 9.47 (q).

Mass (EI) : 96, 67, 53.

Exact Mass :	Calcd for	$\text{C}_6\text{H}_8\text{O}$	96.0575
	Found		96.0571

1-t-Butyldimethylsilyloxy-3-(isocyanomethyl)-2-methylcyclopentene (7)

An oven-dried flask fitted with a thermometer, addition funnel, N₂ adaptor, rubber septum and a magnetic stirring bar was charged with 4.5 mL (45.0 mmol) of n-BuLi (10 M in hexane), 120 mL of THF and cooled to -78 °C. To this solution was added 2.2 mL (42.0 mmol) of methyl isocyanide in 20 mL of THF at such a rate, so as not to exceed -60 °C. The resultant white suspension was stirred at -78 °C for 20 min, 20 mL of HMPA in 20 mL of THF was added dropwise, and then 3.5 mL (36.0 mmol) of 2-methylcyclopent-2-en-1-one in 20 mL of THF maintaining at -78 °C. The reaction mixture was stirred at -78 °C for 2 h and then was added 6.2 g (42.0 mmol) of t-butyldimethylchlorosilane in 50 mL of pentane. The reaction mixture was stirred 30 min. at -78 °C and then allowed to warm to 0 °C for 30 min. The reaction mixture was poured into saturated NH₄Cl. The organic layer was separated, washed with brine and dried over anh. MgSO₄. After filtration through Florisil,

the solvent was removed under reduced pressure to give the crude isonitrile 7 as an oil, which was subjected to chromatography on silica gel with 2% ethyl acetate-hexane for elution to afford 6.4 g (71.0%) of the pure isonitrile 7 as a pale yellow oil.

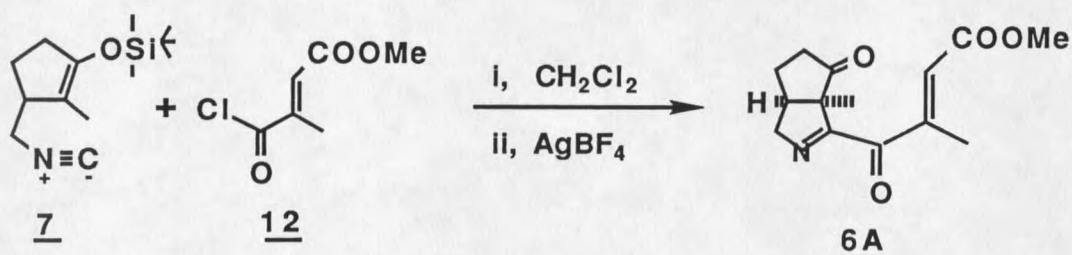
¹H NMR : 3.45 (1H, ddt, J=14.67,5.74,1.73 Hz, CH₂), 3.30 (1H, ddt, J=14.67, 6.42, 1.73 Hz, CH₂), 2.73 (1H, br s, CH), 2.43 (1H, m, CH₂), 2.34 (1H, m, CH₂), 2.20 (1H, m, CH₂), 1.70 (1H, m, CH₂), 1.52 (3H, t, J=1.02 Hz, CH₃), 0.94 (9H, s, 3 x CH₃), 0.13 (3H, s, CH₃), 0.12 (3H, s, CH₃).

¹³C NMR : 156.45 (s), 149.89 (s), 111.03 (s), 45.15 (t), 44.8 (d), 32.24 (t), 25.62 (q), 24.10 (t), 18.02 (s), 9.87 (q), 4.10 (q), 4.04 (q).

IR (CDCl₃) : 2995, 2930, 2860, 2150, 1690, 1260, 845.

Mass (EI) : 251, 211, 194, 167, 73, 59.

Exact Mass :	Calcd. for	C ₁₄ H ₂₅ NOSi	251.1702
	Found		251.1705

2-Acylpyrroline (6A)

An oven-dried flask was charged with 5.3 g (21.0 mmol) of isonitrile **7**, 14 mL of CH_2Cl_2 , and 3.2 mL (25.0 mmol) of acyl chloride **12**. After stirring 3 h at room temperature, the mixture was diluted with 25 mL of CH_2Cl_2 and 40 mL of 1,2-dichloroethane, cooled to -78°C , and this was added dropwise, *via* cannular, to a solution of 50 mL (25.5 mmol) of AgBF_4 (0.51 M in 1,2-dichloroethane) and 55 mL of CH_2Cl_2 maintaining at -78°C . The reaction mixture was stirred for 1.5 h at -78°C and kept at -20°C for 16 h. The mixture was poured into 200 mL of 10% aqueous KHCO_3 , and the organic layer was separated. The aqueous layer was extracted with 50 mL of 10% ethyl acetate - hexane. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure to give 5.5 g (99.8%) of crude product **6A**. This was purified by flash chromatography with 40% ethyl acetate-hexane for elution to afford 3.71

g (67.1%) of the pure 2-acylpyrroline 6A.

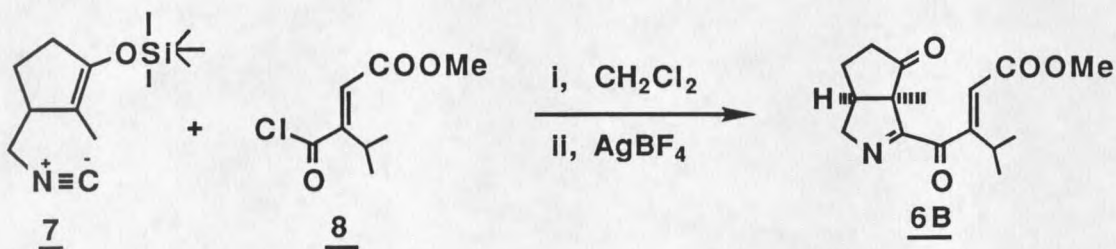
^1H NMR : 6.48 (1H, q, $J=1.42$ Hz, CH), 4.30 (1H, dd, $J=17.54$, 6.99 Hz, CH_2), 4.05 (1H, dd, $J=17.54$, 2.43 Hz), 3.74 (3H, s, CH_3), 2.70 (1H, m, CH), 2.29 (2H, m, CH_2), 2.23 (3H, d, $J=1.42$ Hz, CH_3), 1.60 (2H, m, CH_2), 1.34 (3H, s, CH_3),

^{13}C NMR : 213.48 (s), 193.02 (s), 170.11 (s), 166.00 (s), 149.17 (s), 130.34 (d), 69.29 (s), 67.39 (t), 51.86 (q), 47.25 (d), 36.90 (t), 25.49 (t), 18.91 (q), 12.93 (q).

IR (CDCl_3) : 3050-2850, 1740, 1730, 1670, 1635, 1620 .

Exact Mass :	Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_4$	263.2901
	Found	263.2907

2-Acylpyrroline (6B)



An oven-dried flask was charged with 0.22 g (0.88 mmol) of isonitrile 7, 2 mL of CH_2Cl_2 , 0.11 g of 4 Å-molecular sieve and 0.17 mL

(1.03 mmol) of acyl chloride 8. After refluxing for 3.5 h at the mixture was allowed to cool to room temperature and diluted with 2 mL of CH_2Cl_2 and 4 mL of 1,2-dichloroethane, cooled to -78°C , and this was added dropwise, via cannular, to a solution of 2.5 mL (1.28 mmol) of AgBF_4 (0.51 M in 1,2-dichloroethane) and 2.5 mL of CH_2Cl_2 maintaining at -78°C . The reaction mixture was stirred for 1.5 h at -78°C and kept at -20°C for 16 h. The mixture was poured into 20 mL of 10% aq. KHCO_3 , and the organic layer was separated. The aqueous layer was extracted with 15 mL of 10% ethyl acetate - hexane. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure to provide 224 mg (87.7%) of crude 6B (92.4% purity by NMR). This crude product was used in the next step without further purification. For the analytical sample, the crude 6B was purified by flash column chromatography with 35% ethyl acetate-hexane for elution to afford the pure 6B.

^1H NMR : 6.06 (1H, s, CH), 4.31 (1H, dd, $J=17.9, 7.1$ Hz, CH_2), 4.03 (1H, dd, $J=17.9, 2.64$ Hz, CH_2), 3.72 (3H, s, CH_3), 3.73 (1H, heptet, $J=7.0$ Hz, CH), 2.69 (1H, tt, $J=7.6, 7.1$ Hz, CH_2), 2.34 (2H, dt, $J=7.6, 5.6$ Hz, CH_2), 2.19 (1H, q, $J=7.6$ Hz, CH_2), 1.59 (1H, m, CH_2), 1.37 (3H, s, CH_3), 1.17 (6H, d, $J=6.97$ Hz, 2 x CH_3).

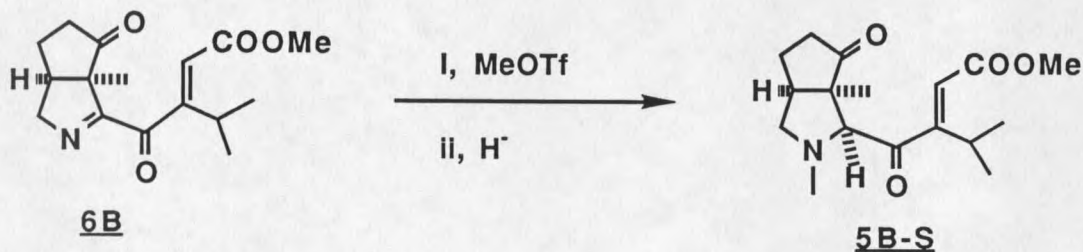
^{13}C NMR : 212.85 (s), 193.45 (s), 170.67 (s), 165.53 (s), 158.91 (s), 126.09 (d), 68.47 (s), 67.25 (t), 51.53 (q), 47.48 (d), 36.68 (t), 28.57 (d), 25.12 (t), 20.46 (2xq), 18.76 (q).

IR (CDCl_3) : 2990, 2880, 1735, 1680, 1635, 1460, 1215, 1045, 920.

Mass (EI) : 291, 276, 259, 244, 232, 216, 204, 188, 176, 155, 137, 127, 108, 95, 81, 67, 59, 53, 41.

Exact Mass :	Calcd for	$\text{C}_{16}\text{H}_{21}\text{NO}_4$	291.1471
	Found		291.1464

N-Methylpyrrolidine (5B-S)



An oven-dried flask fitted with N_2 inlet adaptor, rubber septum, and a magnetic stirring bar was charged with 240 mg (0.8 mmol), of pyrroline 6B in 5 mL of CH_2Cl_2 . The solution was cooled to 0°C and 120 mg (0.1 mmol) of methyl trifluoromethane sulfonate was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for an additional 4 h. The volatile components

were removed *in vacuo* to give iminium triflate 34B in a quantitative yield as a yellow foam.

¹H NMR : 6.76 (1H, s, CH), 5.01 (1H, dd, J=15.3, 9.1 Hz, CH₂), 4.50 (1H, dd, J=15.3, 4.7 Hz, CH₂), 3.80 (3H, s, CH₃), 3.62 (3H, s, CH₃), 3.48 (1H, m, CH), 3.32 (1H, m, CH), 2.81 (1H, m, J=9.1 Hz, CH₂), 2.53 (1H, m, CH₂), 2.29 (1H, m, CH₂), 2.14 (1H, m, CH₂), 1.53 (3H, s, CH₃), 1.24 (6H, d, J=7.1 Hz, 2 x CH₃).

¹³C NMR : 207.74 (s), 187.33 (s), 164.63 (s), 159.00 (s), 151.82 (s), 140.27 (d), 68.05 (t), 52.51 (q), 43.70 (d), 40.42 (s), 36.67 (t), 28.42 (d), 23.93 (t), 20.94 (q), 20.71 (q), 19.90 (q), 19.78 (q).

Method A [(n-Bu)₃SnH] ; To a solution of 91 mg (0.2 mmol) of 34B in 10 mL of methanol was added 0.14 mL (0.5 mmol) of tri-n-butyltin hydride at 0 °C. The reaction mixture was warm to room temperature and stirred for 2.5 h. The solvent was removed on a rotary evaporator and the residue was dissolved in 10 mL of CH₂Cl₂ and washed with saturated NaHCO₃, water, and brine. After drying over anh. Na₂SO₄, the solvent was removed under reduced pressure and the residue was purified by chromatography on a silica gel with 40% ethyl acetate - hexane for elution to afford 39 mg (63.6%) of the mixture of 5B-S and 5B-R in a ratio of 93:7 (5B-S:5B-R).

Method B [K(t-BuO)₃BH] : To a vigorously stirring solution of 374 mg (0.8 mmol) of 34B in 6 mL of THF was added 0.85 mL (0.8 mmol) of potassium tri-t-butoxyborohydride (0.97 M in THF) maintained at -78 °C. After 5 min. at -78 °C, the reaction mixture was quenched with 1 mL of methanol and allowed to warm to 0 °C. The mixture was poured into cold water and extracted with 3 x 15 mL of ethyl acetate. The combined extracts were washed with brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give 218 mg (94.9%) of crude products, which were purified by chromatography on silica gel with 40% ethyl acetate - hexane for elution to give 150 mg (65.2%) of the mixture of 5B-S and 5B-R in a ratio of 98:2 (5B-S:5B-R).

N-Methylpyrrolidine (5B-S)

¹H NMR : 6.50 (1H, s, CH), 3.75 (3H, s, OCH₃), 3.52 (1H, heptet, J=7.1 Hz, CH), 3.29 (1H, s, CH), 3.02 (1H, dd, J=9.5, 1.3 Hz, CH₂), 2.65 (1H, dd, J=9.5, 7.4 Hz, CH₂), 2.51 (1H, pentet, 9.5 Hz, CH), 2.45 and 2.24 (2H, m, CH₂), 2.20 (3H, s, NCH₃), 2.02 and 1.91 (2H, m, CH₂), 1.26 (3H, s, CH₃), 1.22 (3H, d, J=7.1 Hz, CH₃), 1.18 (3H, d, J=7.1 Hz).

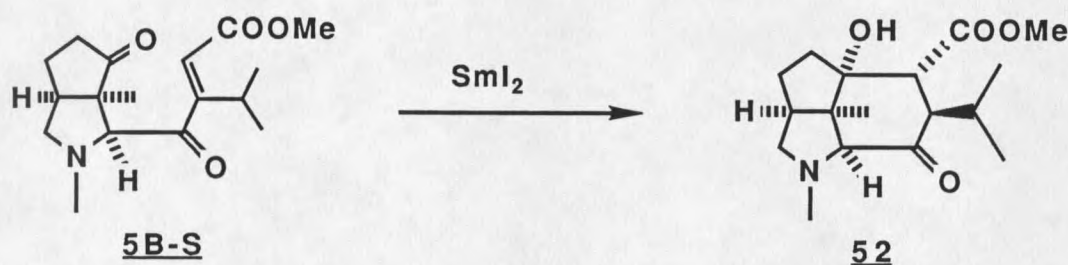
¹³C NMR : 219.70 (s), 201.23 (s), 166.40 (s), 160.85 (s), 124.49 (d), 82.15 (d), 62.61 (t), 59.88 (s), 51.63 (q), 47.58 (d), 40.87 (q), 38.70 (t), 29.11 (d), 25.92 (t), 22.56 (q), 21.17 (q), 20.60 (q).

IR (CDCl₃) : 2960, 2880, 1740, 1680, 1445, 1215, 1115, 745.

Mass (EI) : 293, 262, 218, 165, 152, 137, 108, 97, 81, 69, 53.

Exact Mass :	Calcd for	C ₁₇ H ₂₅ NO ₄	308.1862
	Found		308.1863

Tricyclic β -Hydroxyester (52)



An oven-dried flask fitted with a thermometer, addition funnel, N₂ inlet adaptor, rubber septum and a magnetic stirring bar, was charged with 3.6 g (24 mmol) of samarium metal powder and 120 mL of THF. To this slurry was added 3.4 g (12 mmol) of 1,2-diodoethane at room temperature. The mixture was stirred for 1 h in which time the reaction color was changed from olive-green to deep blue. To the resulting samarium (II) iodide solution was added 0.9 g (4 mmol) of N-methyl pyrrolidine (5B-S) in 30 mL of THF at 22 ~ 25 °C for 15 min. After

stirring for 1 h, the mixture was poured into 100 mL of saturated aqueous K_2CO_3 and separated the organic layer. The aqueous layer was extracted with 3x30 mL of ethyl acetate. The combined organic layers were washed with water, brine and dried over anhy. Na_2SO_4 . Evaporation of solvent and filter through florisil with 50% ethyl acetate-hexane gave 1.1 g (88.9%) of crude product, which was purified by flash chromatography with 15% ethyl acetate - hexane for elution to afford 660 mg (53.3%) of pure tricyclic β -hydroxy ester 52.

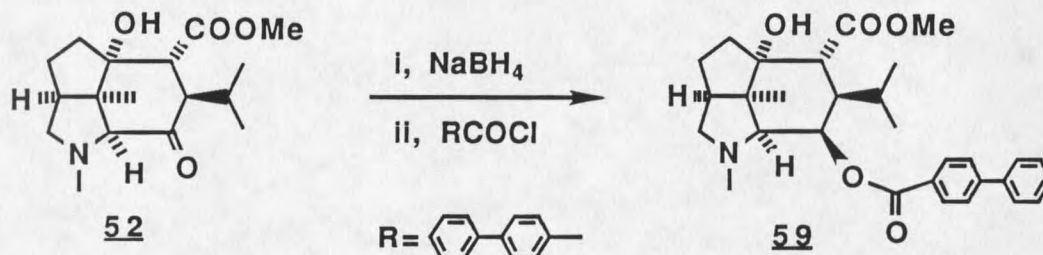
^1H NMR : 3.97 (1H, d, $J=12.1$ Hz, CH), 3.72 (3H, s, OCH_3), 3.60 (1H, s, OH), 2.79 and 2.23 (2H, d each, $J=8.5$ Hz, CH_2), 2.58 (1H, dd, $J=12.1, 4.4$ Hz, CH), 2.22 (1H, pentet, $J=8.5$ Hz, CH), 2.08 (3H, s, NCH_3), 2.07 (1H, s, CH), 1.94 (2H, m, CH_2), 1.78 and 1.57 (2H, q each, $J=8.5$ Hz, CH_2), 1.47 (1H, m, CH), 1.04 (3H, s, CH_3), 0.99 (3H, d, $J=6.9$ Hz, CH_3), 0.87 (3H, d, $J=6.9$ Hz, CH_3).

^{13}C NMR : 201.98 (s), 176.49 (s), 82.50 (d), 79.75 (s), 62.68 (t), 57.62 (s), 51.85 (q), 51.45 (d), 51.12 (d), 46.41 (d), 41.52 (q), 38.96 (t), 30.44 (d), 29.14 (t), 23.62 (q), 20.44 (q), 20.12 (q).

IR ($CDCl_3$) : 3500, 2960, 2790, 1710, 1455, 1255, 1205, 1170, 1045, 895.

Mass (EI) : 310, 281, 238, 205, 190, 153, 138, 125, 108, 96, 57.

Exact Mass :	Calcd for $C_{17}H_{27}NO_4$	309.1940
	Found	309.1949

Biphenyl ester (59)

An oven-dried flask fitted with N₂ inlet adaptor, rubber septum and magnetic stirring bar, was charged with 100 mg (32×10^{-2} mmol) of tricyclic β -hydroxyester (52) in 5 mL of methanol. The solution was cooled to 0 °C and 240 mg (64×10^{-2} mmol) of cerium (III) chloride heptahydrate followed by 30 mg (80 mmol) of sodium borohydride. After stirring for 30 min. at 0 °C and 2 h at room temperature, the reaction mixture was poured into saturated sodium bicarbonate and extracted with 3x30 mL of methylene chloride. The combined extracts were dried over anh. sodium sulfate. The solvent was removed under reduced pressure to give 100 mg (99.0%) of dihydroxy ester.

¹H NMR : 4.04 (1H, d, J=6.2 Hz, CH), 3.68 (3H, s, OCH₃), 3.62 (1H, s, OH), 3.14 (1H, d, J=11.4 Hz, CH), 2.88 and 2.06 (2H, d each, J=9.1 Hz, CH₂), 2.59 (1H, dd, J=6.2 Hz, CH), 2.48 (1H, m, CH), 2.32 (1H, s, OH), 2.30 (3H, s, NCH₃), 2.13 (1H, m, CH), 1.89 and 1.84 (2H, m, CH₂), 1.72 (2H, m, CH₂), 1.30 (1H, m, CH), 1.20 (3H, s, CH₃), 0.99 (3H, d, J=6.7 Hz, CH₃), 0.95 (3H, d, J=6.7 Hz, CH₃).

¹³C NMR : 175.69 (s), 82.36 (s), 76.87 (d), 62.97 (t), 62.82 (d), 54.80 (s), 51.43 (q), 50.65 (d), 50.25 (d), 45.73 (d), 43.81 (t), 41.05 (q), 30.59 (t), 30.28 (d), 24.48 (q), 21.30 (q), 19.55 (q).

To a stirred solution of 76 mg (24×10^{-2} mmol) of dihydroxy ester in 4 mL of acetonitrile was added 37 mg (31×10^{-2} mmol) of DMAP and 66 mg (31×10^{-2} mmol) of biphenylcarbonyl chloride at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 4 h. The reaction mixture was poured into ice and extracted with ethyl acetate. The combined extracts were washed with water, brine and dried over anh. sodium sulfate. The solvent was evaporated under reduced pressure to give 106 mg (88.4%) of biphenyl ester 59, which was recrystallized from ethylether-hexane mixture giving the pure crystal for x-ray analysis. mp 136 ~ 137 °C.

¹H NMR : 7.68 - 7.35 (9H, m, ArH), 5.80 (1H, dd, J=7.8 and 3.6 Hz, CH), 3.73 (3H, s, OCH₃), 3.69 (1H, d, J=11.8 Hz, CH), 3.25 (1H, s, OH), 2.76 (1H, d, J=9.4 Hz, CH), 2.36 (3H, s, NCH₃), 1.21 (3H, s, CH₃), 1.06 (3H, d, J=7.0 Hz, CH₃), 0.91 (3H, d, J=7.0 Hz, CH₃).

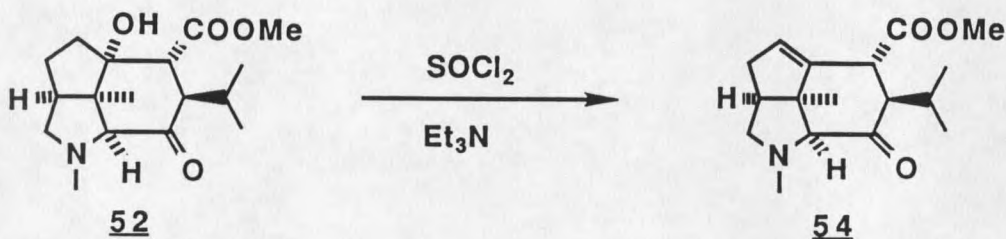
¹³C NMR : 177.04 (s), 165.83 (s), 145.72 (s), 140.03 (s), 130.12 (d), 129.30 (d), 128.92 (d), 128.13 (d), 127.25 (d), 127.20 (d), 80.92 (s), 75.42 (d), 70.87 (d), 63.15 (t), 55.46 (s), 51.67 (q), 49.13 (d), 46.62 (d), 43.00 (q), 41.98 (d), 39.83 (t), 29.50 (t), 27.31 (d), 23.41 (q), 21.85 (q), 19.27 (q).

IR (CDCl₃) : 3505, 2950, 2795, 1715, 1605, 1275, 1105, 750, 700.

Mass (EI) : 491, 460, 448, 394, 293, 250, 193, 181, 152, 100, 96.

Exact Mass :	Calcd for	C ₃₀ H ₃₇ NO ₅	491.2672
	Found		491.2676

β,γ-Unsaturated Ketoester (54)



An oven-dried flask fitted with N₂ inlet adaptor, rubber septum and a magnetic stirring bar, was charged with 0.27 g (0.87 mmol) of tricyclic β-hydroxyester 52 in 15 mL of ethyl acetate. The solution was cooled to 0 °C and 3.65 mL (26.2 mmol) of triethylamine was added. To this solution was added 0.19 mL (2.6 mmol) of thionyl chloride for 30 min. at 0 °C. After 30 min. at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 6 h. The

resulting mixture was poured into ice water and extracted with 3x20mL of methylene chloride. The combined extracts were washed with saturated sodium bicarbonate, and dried over anh. sodium sulfate.

The solvent was removed under reduced pressure to give crude 54, which was purified by chromatography on silica gel with 40% ethyl acetate-hexane for elution to afford 200 mg (79.4%) of pure β,γ -unsaturated ketoester (54) as a red oil.

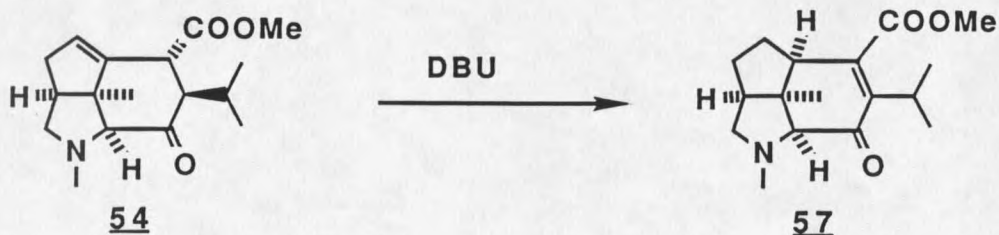
$^1\text{H NMR}$: 5.64 (1H, t, $J=2.4$ Hz, CH), 3.66 (3H, s, OCH_3), 3.61 (1H, d, $J=5.7$ Hz, CH), 2.84 (1H, dd, $J=9.0, 5.7$ Hz, CH), 2.77 (1H, dd, $J=9.5, 2.4$ Hz, CH_2), 2.71 and 2.31 (2H, t each, $J=8.4$ Hz, CH_2), 2.53 (1H, dd, $J=9.5, 7.8$ Hz, CH_2), 2.46 (1H, s, CH), 2.33 (3H, s, NCH_3), 2.17 (1H, m, CH), 1.29 (3H, s, CH_3), 1.16 (1H, m, CH), 0.87 (3H, d, $J=7.0$ Hz, CH_3), 0.84 (3H, d, $J=7.0$ Hz, CH_3).

$^{13}\text{C NMR}$: 201.26 (s), 173.33 (s), 138.33 (s), 129.78 (d), 82.30 (d), 64.75 (t), 61.77 (s), 55.25 (d), 52.18 (q), 49.18 (d), 46.08 (d), 41.96 (q), 38.77 (t), 27.83 (d), 24.92 (q), 21.23 (q), 19.80 (q).

IR (CDCl_3) : 2950, 2795, 1740, 1645, 1460, 1245, 1210, 1170, 805, 735.

Mass (EI) : 292 ($\text{M}+1$)⁺, 263, 248, 220, 204, 96.

Exact Mass :	Calcd for	$\text{C}_{17}\text{H}_{25}\text{NO}_3$	291.1834
	Found		291.1828

α,β -Unsaturated Ketoester (57)

An oven-dried flask fitted with a reflux condenser, N₂ inlet adaptor, rubber septum and a magnetic stirring bar, was charged with 125 mg (0.4 mmol) of β,γ -unsaturated ketoester (54) in 4 ml of dioxane.

To this solution was added 0.3 mL (1.8 mmol) of DBU. After refluxing 24 h, the reaction mixture was allowed to cool to 20 °C, diluted with 10 mL of methylene chloride, and poured into saturated sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with 2x5 mL of methylene chloride. The combined organic layers were washed with water, brine, and dried over anh. sodium sulfate. The solvent was removed under reduced pressure to give 125 mg (100%) of crude product, which was purified by chromatography on florisil with 15% ethyl acetate-hexane for elution to afford 101 mg (80.8%) of α,β -unsaturated ketoester (57).

^1H NMR : 3.77 (3H, s, OCH_3), 2.71 (1H, t, $J=8.4$ Hz, CH_2), 2.70 (1H, septet, $J=7.0$ Hz, CH), 2.45 (1H, t, $J=9.1$ Hz, CH_2), 2.43 (1H, dd, $J=7.5$ Hz, CH), 2.23 (1H, s, CH), 2.17 (1H, m, CH), 1.86 and 1.77 (2H, m, CH_2), 1.83 and 1.69 (2H, t each, $J=5.7$ Hz, CH_2), 1.17 (3H, s, CH_3), 1.17 and 1.10 (6H, d each, $J=7.0$ Hz, $2\times\text{CH}_3$).

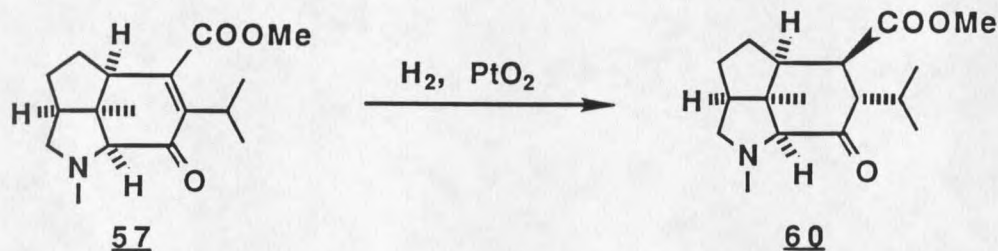
^{13}C NMR : 200.35 (s), 169.56 (s), 145.14 (s), 138.00 (s), 80.12 (d), 64.42 (t), 53.55 (s), 51.74 (q), 50.02 (d), 48.98 (d), 41.14 (q), 33.48 (t), 33.36 (t), 30.10 (d), 25.87 (q), 21.66 (q), 19.77 (q).

IR (CDCl_3) : 2960, 2790, 1730, 1675, 1660, 1455, 1245, 795.

Mass (EI) : 291, 276, 248, 220, 204, 122, 109, 108, 96, 81, 40.

Exact Mass :	Calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_3$	291.18344
	Found	291.18338

Methy Ketodendrobinate (60)



To a solution of 50 mg (0.17 mmol) of α,β -unsaturated ketoester (57) in 2 mL of anh. acetic acid was added 10 mg of platinum(IV)oxide. This reaction mixture was hydrogenated at a hydrogen pressure of 50 psi.

After shaking for 20 h at room temperature, the mixture was filtered through celite and washed with methylene chloride. The solvent was evaporated under reduced pressure and the residue was dissolved in 10 mL of methylene chloride. This solution was poured into 25 ml of saturated sodium bicarbonate and extracted with 3x15 mL of methylene chloride. The combined extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*, giving 39 mg (77.5%) of methyl ketodendrobinate (60) as a pale yellow crystalline.

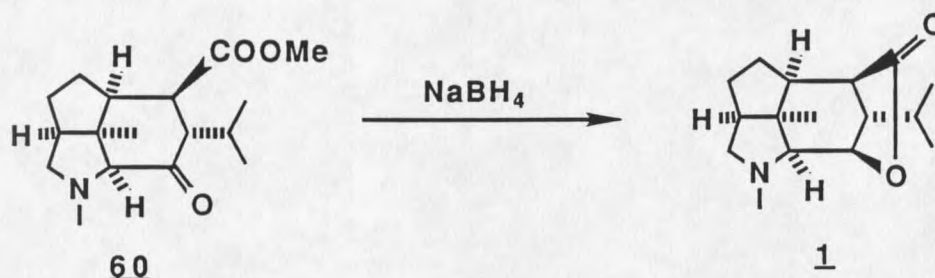
¹H NMR : 3.67 (3H, s, CH₃), 3.17 (1H, dd, J=4.9, 11.4 Hz, CH), 2.99 (2H, dd, J=4.1, 11.4 Hz, CH), 2.79 (1H, dd, J=1.4, 9.3 Hz, CH₂), 2.54 (1H, t, J=9.3 Hz, CH₂), 2.23 (1H, s, CH), 2.20 (3H, s, NCH₃), 2.14 (1H, m, CH), 1.99 (1H, pentet, J=9.3 Hz, CH), 1.97 and 1.70 (2H, m, CH₂), 1.87 (1H, d septet, 4.1, 6.9 Hz, CH), 1.60 and 1.44 (2H, m, CH₂), 1.24 (3H, s, CH₃), 0.98 and 0.93 (6H, d each, J=6.9 Hz, 2xCH₃).

¹³C NMR : 213.83 (s), 173.52 (s), 82.44 (d), 64.46 (t), 57.49 (s), 51.70 (q), 50.82 (d), 48.71 (d), 48.07 (d), 46.80 (d), 41.30 (q), 31.94 (t), 29.43 (d), 28.34 (t), 26.32 (q), 20.49 (q), 18.04 (q).

IR (CDCl₃) : 2960, 2890, 1740, 1680, 1460, 1375, 1260, 1170, 920, 810, 740.

Mass (EI) : 293, 265, 250, 222, 206, 137, 122, 109, 96, 81, 44.

Exact Mass :	Calcd for	C ₁₇ H ₂₇ NO ₃	293.1991
	Found		293.1974

(dl)-Dendrobine (1)

An oven-dried flask fitted with N₂ inlet adaptor, rubber septum, and a magnetic stirring bar, was charged with 25 mg (85×10^{-3} mmol) of methyl ketodendrobinate (60) in 2 mL of 2-propanol. To this solution was added 12 mg (0.32 mmol) of sodium borohydride and stirred for 3 days at 20 °C. The reaction mixture was cooled to 0 °C and quenched by addition of 2.5 mL of 1N hydrochloric acid. After 30 min. at room temperature, the mixture was poured into 25 mL of saturated sodium bicarbonate and extracted with 3x10 mL of methylene chloride. The combined extracts were dried over anh. sodium sulfate and concentrated under reduced pressure to give 20 mg (89%) of crude synthetic (dl)-dendrobine (1), which was purified by recrystallization with ethyl ether to afford 13 mg (58%) of pure crystalline (dl)-dendrobine (1). mp: 129 ~ 131 °C (lit.^{19e} mp 130 ~ 132 °C).

¹H NMR : 4.84 (1H, dd, J=5.5, 3.0 Hz, CH), 3.15 and 2.69 (2H, t each, J=8.7 Hz, CH₂), 2.66 (1H, d, J=3.0 Hz, CH), 2.50 (3H, s, NCH₃), 2.45 (1H, dd, J=9.5, 4.0 Hz, CH), 2.36 (1H, pentet, J=8.7 Hz, CH), 2.12 and 2.05 (2H, m each, CH₂), 2.02 (1H, m, CH), 1.85 and 1.55 (2H, m, CH₂), 1.76 (1H, heptet, J=6.5 Hz, CH), 1.38 (3H, s, CH₃), 0.97 and 0.96 (6H, d each, J=6.5 Hz, 2xCH₃).

¹³C NMR : 178.99 (s), 79.31 (d), 67.05 (d), 61.95 (t), 53.88 (d), 52.49 (s), 51.64 (d), 44.03 (d), 43.11 (d), 36.60 (q), 32.85 (t), 32.78 (q), 30.75 (t), 24.52 (d), 21.10 (q), 20.42 (q).

IR (CDCl₃) : 2970, 2920, 2860, 1765, 1435, 1420, 1365, 1125, 975.

Mass (EI) : 263, 220, 206, 178, 136, 108, 40.

Exact Mass :	Calcd for	C ₁₆ H ₂₅ NO ₂	263.1885
	Found		263.1887

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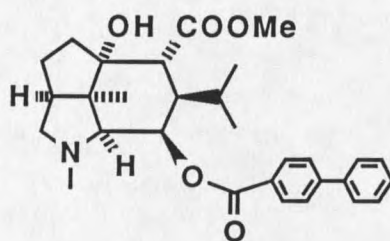
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38. The author is grateful to Professor K. Yamama for providing a generous sample of natural dendrobine used for comparative purposes.

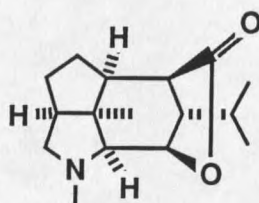
APPENDIX
X-RAY DATA

59Table 10. Bond Lengths ($\text{\AA}$).

N(1)-C(2)	1.461(3)	N(1)-C(10)	1.461(3)
N(1)-C(15)	1.458(3)	C(2)-C(3)	1.511(4)
C(3)-C(4)	1.528(4)	C(3)-C(11)	1.555(3)
C(4)-C(5)	1.530(4)	C(5)-C(6)	1.534(3)
C(6)-O(1)	1.442(3)	C(6)-C(7)	1.565(3)
C(6)-C(11)	1.542(3)	O(1)-Ho	0.860(13)
C(7)-C(8)	1.541(3)	C(7)-C(12)	1.511(3)
C(8)-C(9)	1.525(3)	C(8)-C(16)	1.547(3)
C(9)-C(10)	1.544(3)	C(9)-O(4)	1.457(3)
C(10)-C(11)	1.557(3)	C(11)-C(14)	1.529(4)
C(12)-O(2)	1.200(3)	C(12)-O(3)	1.335(3)
O(3)-C(13)	1.444(3)	C(16)-C(17)	1.520(4)
C(16)-C(18)	1.514(3)	O(4)-C(19)	1.342(3)
C(19)-O(5)	1.203(3)	C(19)-C(20)	1.488(3)
C(20)-C(21)	1.385(3)	C(20)-C(25)	1.391(3)
C(21)-C(22)	1.384(4)	C(22)-C(23)	1.392(3)
C(23)-C(24)	1.395(4)	C(23)-C(26)	1.491(4)
C(24)-C(25)	1.371(4)	C(26)-C(27)	1.381(4)
C(26)-C(31)	1.395(4)	C(27)-C(28)	1.383(5)
C(28)-C(29)	1.369(5)	C(29)-C(30)	1.352(4)
C(30)-C(31)	1.395(4)		

Table 11. Bond Angles (°).

C(2)-N(1)-C(10)	106.2(2)	C(2)-N(1)-C(15)	111.6(2)
C(10)-N(1)-C(15)	113.1(2)	N(1)-C(2)-C(3)	104.5(2)
C(2)-C(3)-C(4)	115.2(2)	C(2)-C(3)-C(11)	104.0(2)
C(4)-C(3)-C(11)	106.6(2)	C(3)-C(4)-C(5)	107.2(2)
C(4)-C(5)-C(6)	105.0(2)	C(5)-C(6)-O(1)	109.1(2)
C(5)-C(6)-C(7)	113.1(2)	O(1)-C(6)-C(11)	109.7(2)
C(5)-C(6)-C(11)	104.2(2)	O(1)-C(6)-C(11)	105.7(2)
C(7)-C(6)-C(11)	114.7(2)	C(6)-O(1)-Ho	106.4(16)
C(6)-C(7)-C(8)	114.9(2)	C(6)-C(7)-C(12)	111.2(2)
C(8)-C(9)-C(12)	110.5(2)	C(7)-C(8)-C(9)	111.5(2)
C(7)-C(8)-C(16)	112.1(2)	C(9)-C(8)-C(16)	116.1(2)
C(8)-C(9)-C(10)	109.4(2)	C(8)-C(9)-O(4)	107.9(2)
C(10)-C(9)-O(4)	112.4(2)	N(1)-C(10)-C(9)	113.4(2)
N(1)-C(10)-C(11)	107.4(2)	C(9)-C(10)-C(11)	117.1(2)
C(3)-C(11)-C(6)	104.9(2)	C(3)-C(11)-C(10)	103.1(2)
C(6)-C(11)-C(10)	113.5(2)	C(3)-C(11)-C(14)	111.7(2)
C(6)-C(11)-C(14)	113.2(2)	C(10)-C(11)-C(14)	109.8(2)
C(7)-C(12)-O(2)	124.3(2)	C(7)-C(12)-O(3)	113.2(2)
O(2)-C(12)-O(3)	122.4(2)	C(12)-O(3)-C(13)	116.6(2)
C(8)-C(16)-C(17)	115.7(2)	C(8)-C(16)-C(18)	111.4(2)
C(17)-C(16)-C(18)	110.1(2)	C(9)-O(4)-C(19)	118.1(2)
O(4)-C(19)-O(5)	124.6(2)	O(4)-C(19)-C(20)	111.6(2)
O(5)-C(19)-C(20)	123.8(2)	C(19)-C(20)-C(21)	123.6(2)
C(19)-C(20)-C(25)	118.1(2)	C(21)-C(20)-C(25)	118.3(2)
C(20)-C(21)-C(22)	120.6(2)	C(21)-C(22)-C(23)	121.3(2)
C(22)-C(23)-C(24)	117.6(2)	C(22)-C(23)-C(26)	121.2(2)
C(24)-C(23)-C(26)	121.2(2)	C(23)-C(24)-C(25)	121.1(2)
C(20)-C(25)-C(24)	121.1(2)	C(23)-C(26)-C(27)	120.8(2)
C(23)-C(26)-C(31)	121.2(2)	C(27)-C(26)-C(31)	118.0(3)
C(26)-C(27)-C(28)	121.6(3)	C(27)-C(28)-C(29)	119.6(3)
C(28)-C(29)-C(30)	120.1(3)	C(29)-C(30)-C(31)	121.1(3)
C(26)-C(31)-C(30)	119.6(3)		



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Table 12. Bond Lengths (Å)

N(1)-C(2)	1.453(4)	N(1)-C(10)	1.462(3)
N(1)-C(14)	1.459(3)	C(2)-C(3)	1.532(4)
C(3)-C(4)	1.526(4)	C(3)-C(11)	1.553(4)
C(4)-C(5)	1.509(4)	C(5)-C(6)	1.527(4)
C(6)-C(7)	1.553(4)	C(6)-C(11)	1.557(4)
C(7)-C(8)	1.524(4)	C(7)-C(12)	1.503(4)
C(8)-C(9)	1.524(3)	C(8)-C(15)	1.535(3)
C(9)-C(10)	1.535(4)	C(9)-O(1)	1.473(3)
C(10)-C(11)	1.546(3)	C(11)-C(13)	1.539(3)
C(12)-O(1)	1.357(3)	C(12)-O(2)	1.198(4)
C(15)-C(16)	1.515(4)	C(15)-C(17)	1.525(4)

Table 13. Bond Angles (deg).

C(2)-N(1)-C(10)	108.5(2)	C(2)-N(1)-C(14)	115.2(2)
C(10)-N(1)-C(14)	116.6(2)	N(1)-C(2)-C(3)	103.6(2)
C(2)-C(3)-C(4)	117.6(2)	C(2)-C(3)-C(11)	105.4(2)
C(4)-C(3)-C(11)	106.7(2)	C(3)-C(4)-C(5)	105.2(2)
C(4)-C(5)-C(6)	105.9(2)	C(5)-C(6)-C(7)	113.8(2)
C(5)-C(6)-C(11)	104.0(2)	C(7)-C(6)-C(11)	114.6(2)
C(6)-C(7)-C(8)	111.3(2)	C(6)-C(7)-C(12)	111.8(2)
C(8)-C(7)-C(12)	100.0(2)	C(7)-C(8)-C(9)	97.9(2)
C(7)-C(8)-C(15)	118.8(2)	C(9)-C(8)-C(15)	118.4(2)
C(8)-C(9)-C(10)	111.4(2)	C(8)-C(9)-O(1)	102.6(2)
C(10)-C(9)-O(1)	110.9(2)	N(1)-C(10)-C(9)	117.3(2)
N(1)-C(10)-C(11)	102.4(2)	C(9)-C(10)-C(11)	114.5(2)
C(3)-C(11)-C(6)	106.1(2)	C(3)-C(11)-C(10)	105.2(2)
C(6)-C(11)-C(10)	116.9(2)	C(3)-C(11)-C(13)	109.3(2)
C(6)-C(11)-C(13)	110.2(2)	C(10)-C(11)-C(13)	108.9(2)
C(7)-C(12)-O(1)	108.6(2)	C(7)-C(12)-O(2)	130.3(3)
O(1)-C(12)-O(2)	121.1(2)	C(9)-O(1)-C(12)	108.2(2)
C(8)-C(15)-C(16)	110.6(2)	C(8)-C(15)-C(17)	110.2(2)
C(16)-C(15)-C(17)	110.6(2)		

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