



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. SmI₂-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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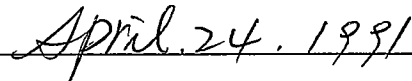
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To My Wife, Kyung Hie

TABLE OF CONTENTS

	Page
APPROVAL.....	ii
TABLE OF CONTENTS.....	vi
LIST OF TABLES.....	ii
LIST OF FIGURES.....	viii
ABSTRACT.....	x
INTRODUCTION.....	1
Nature of Dendrobine.....	1
Previous Total Syntheses of Dendrobine.....	7
RESULTS AND DISCUSSION.....	21
Synthetic Strategy.....	21
Synthesis of Acylchlorides.....	23
Acynitrilium Ion Cyclization.....	28
Stereoselective Synthesis of Tricyclic Hydroxyester.....	34
Total Synthesis of (dl)-Dendrobine.....	52
SUMMARY.....	66
EXPERIMENTAL.....	69
REFERENCES.....	103
APPENDIX.....	107
X-Ray Data.....	107

LIST OF TABLES

Table	Page
1. Properties of Dendrobine <u>1</u>	4
2. NMR Data of Acylchloride <u>8</u> and <u>19</u>	28
3. NMR Data of 2-Acylpyrroline <u>6B</u>	33
4. NMR Data of N-Methylpyrrolidine <u>5B-S</u>	39
5. NMR Data of Tricyclic β -Hydroxy Ester <u>52</u>	51
6. NMR Data of β,γ -Unsaturated Ester <u>54</u>	54
7. NMR Data of α,β -Unsaturated Ester <u>57</u>	56
8. NMR Data of Methyl Keto Dendrobinate <u>60</u>	59
9. NMR Data of Synthetic (dl)-Dendrobine <u>1</u>	61
10. Bond Lengths of Biphenyl Ester <u>59</u>	108
11. Bond Angles of Biphenyl Ester <u>59</u>	109
12. Bond Lengths of (dl)-Dendrobine <u>1</u>	110
13. Bond Angles of (dl)-Dendrobine <u>1</u>	110

LIST OF FIGURES

Figure	Page
1. Naturally Occurring Dendrobine-type Alkaloids.....	3
2. Biosynthesis of Dendrobine.....	6
3. Inubushi's Synthesis of Dendrobine.....	8
4. Yamada's Synthesis of Dendrobine.....	11
5. Kende's Synthesis of Dendrobine.....	14
6. Roush's Synthesis of Dendrobine.....	16
7. Martin's Synthesis of Dendrobine.....	18
8. Livinghouse's Synthesis of 2-Acylpyrrolines.....	20
9. Retrosynthetic Strategy.....	22
10. Preparation of Acylchloride <u>12</u>	24
11. Preparation of Acylchloride <u>8</u> and <u>19</u>	25
12. Alternative Preparation of Acylchloride <u>8</u>	27
13. Preparation of Isonitrile <u>Z</u>	29
14. Preparation of 2-Acylpyrrolines.....	32
15. Preparation of N-Methylpyrrolidines.....	36
16. Butyltinhydride-mediated Radical Cyclization.....	42
17. Sml ₂ -mediated Radical Cyclization.....	43
18. Correlation of Olefin Geometry.....	45
19. Possible Products from Sml ₂ -mediated Cyclization.....	46

LIST OF FIGURES - Continued

Figure	Page
20. A Possible Mechanism of SmI_2 -mediated Cyclization.....	48
21. Preparation of Biphenyl Ester <u>59</u>	50
22. Molecular Structure of Biphenyl Ester <u>59</u>	50
23. Synthetic Route to Dendrobine <u>1</u>	52
24. Dehydration of Tricyclic β -Hydroxy Ester <u>52</u>	53
25. Isomerization of β,γ -Unsaturated Ester <u>54</u> to α,β -Unsaturated Ester <u>57</u>	55
26. Hydrogenation of α,β -Unsaturated Ester <u>57</u>	57
27. Synthesis of (dl)-Dendrobine <u>1</u>	58
28. Molecular Structure of Synthetic (dl)-Dendrobine <u>1</u>	60
29. Comparison ^1H Spectra of Naturally Derived vs. Synthetic Dendrobine <u>1</u>	62
30. Comparison ^{13}C Spectra of Naturally Derived vs. Synthetic Dendrobine <u>1</u>	63
31. Comparison Mass Spectra of Naturally Derived vs. Synthetic Dendrobine <u>1</u>	64
32. Summary of a Total Synthesis of Dendrobine <u>1</u>	68

ABSTRACT

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

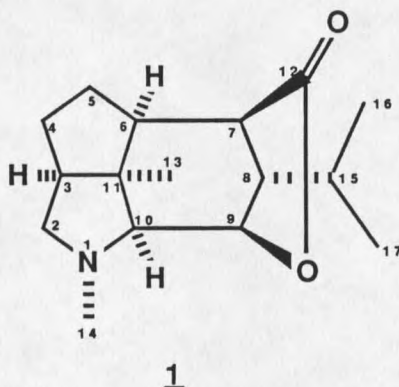
Dendrobine, the major alkaloid isolated from the chinese drug "Chin-Chai-Shi-Hu", could be synthesized in eight linear steps from 2-methylcyclopent-2-enone 26 and acylchloride 8. Acylchloride 8 was prepared from 2-isopropylfumaric acid 15 by regioselective esterification. The key step of the synthesis 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. SmI_2 -mediated cyclization of N-methylpyrrolidine 5B-S produced tricyclic β -hydroxyester 52, which was transformed into (dl)-dendrobine(1) in four steps.

INTRODUCTION

Nature of Dendrobine

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

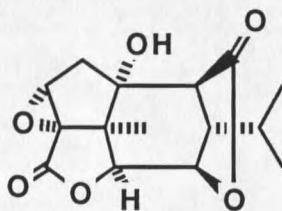


Dendrobium nobile Lindl. (Orchidaceae), known in China as "Chin-Chai-Shi-Hu," is used as a tonic in traditional medicine. The stems of the plant are prescribed to improve appetite, stimulate salivary secretion, and promote general health¹. The herb is frequently taken by opera singers to improve their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

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

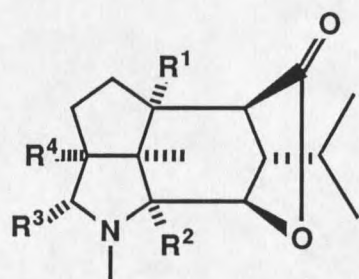
when three groups independently proposed structure of 1 for dendrobine on the basis of degradative studies³. Subsequent investigation has revealed that, in addition to 1, the alkaloids dendramine⁴ (2), dendroxine⁵ (6), 6-hydroxydendroxine^{4c} (7), nobilonine^{3a,6} (13), and five minor quaternary salts⁷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

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

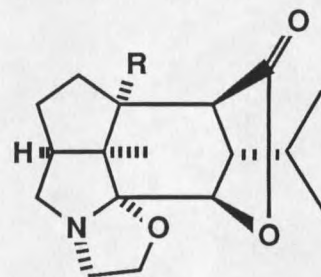


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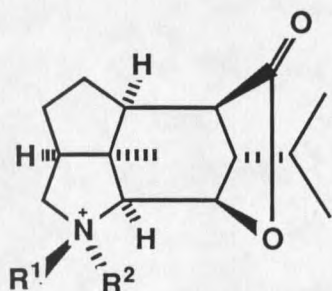
Figure 1. Naturally Occurring Dendrobine-type Alkaloids



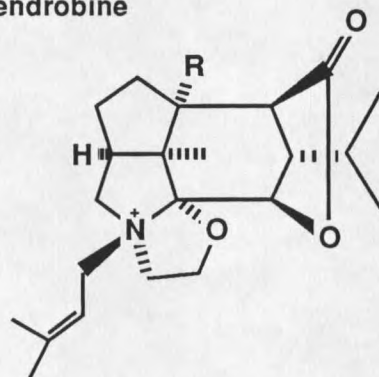
1. $R^1=R^2=R^3=R^4=H$, Dendrobine
2. $R^2=R^3=R^4=H$, $R^1=OH$, Dendramine
3. $R^1=R^3=R^4=H$, $R^2=OH$, 10-Hydroxydendrobine
4. $R^1=R^2=R^4=H$, $R^3=CH_2CO_2CH_3$, Dendrine
5. $R^1=R^2=H$, $R^3=O$, $R^4=OH$, 3-Hydroxy-2-oxodendrobine



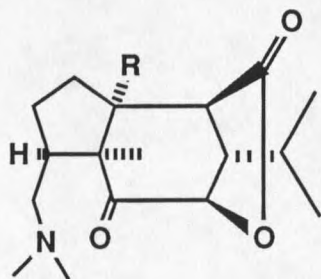
6. $R=H$, Dendroxine
7. $R=OH$, 6-Hydroxydendroxine



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



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

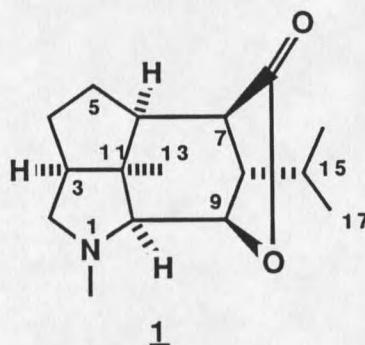


13. $R=H$, Nobilonine
14. $R=OH$, 6-Hydroxynobilonine

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

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

Table 1. Physical and Spectral Properties of Dendrobine.

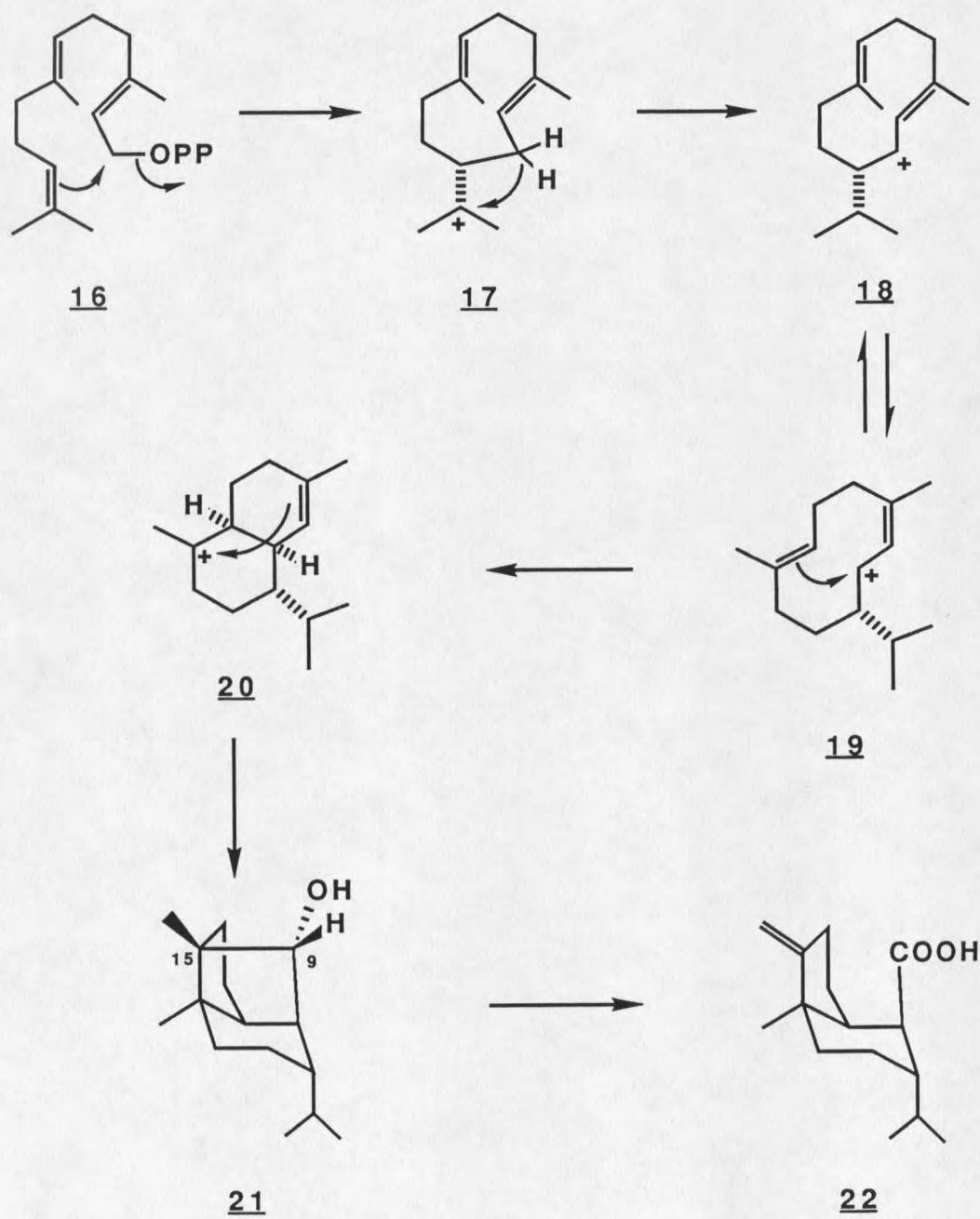


M.P.	135 ⁰ -136 ⁰ C	
[α] _D	-46.8 ⁰ (EtOH)	
M.W.	263.19	
M.F.	C ₁₆ H ₂₅ O ₂ N	
IR(<i>V</i> _{max} , KBr)	1765 cm ⁻¹ (lactone)	
¹ H NMR(δ , TMS)	4.80(q, J=3,6 Hz)	CH-9
	2.49(s)	CH ₃ -14
	1.33(s)	CH ₃ -13
MASS	263(M ⁺), 206, 192, 178, 164, 136, 109, 108, 81, 58, 41, 28	

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

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

Figure 2. Biosynthesis of Dendrobine



Previous Total Syntheses of Dendrobine

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

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

Figure 3. Inubushi's Synthesis of Dendrobine

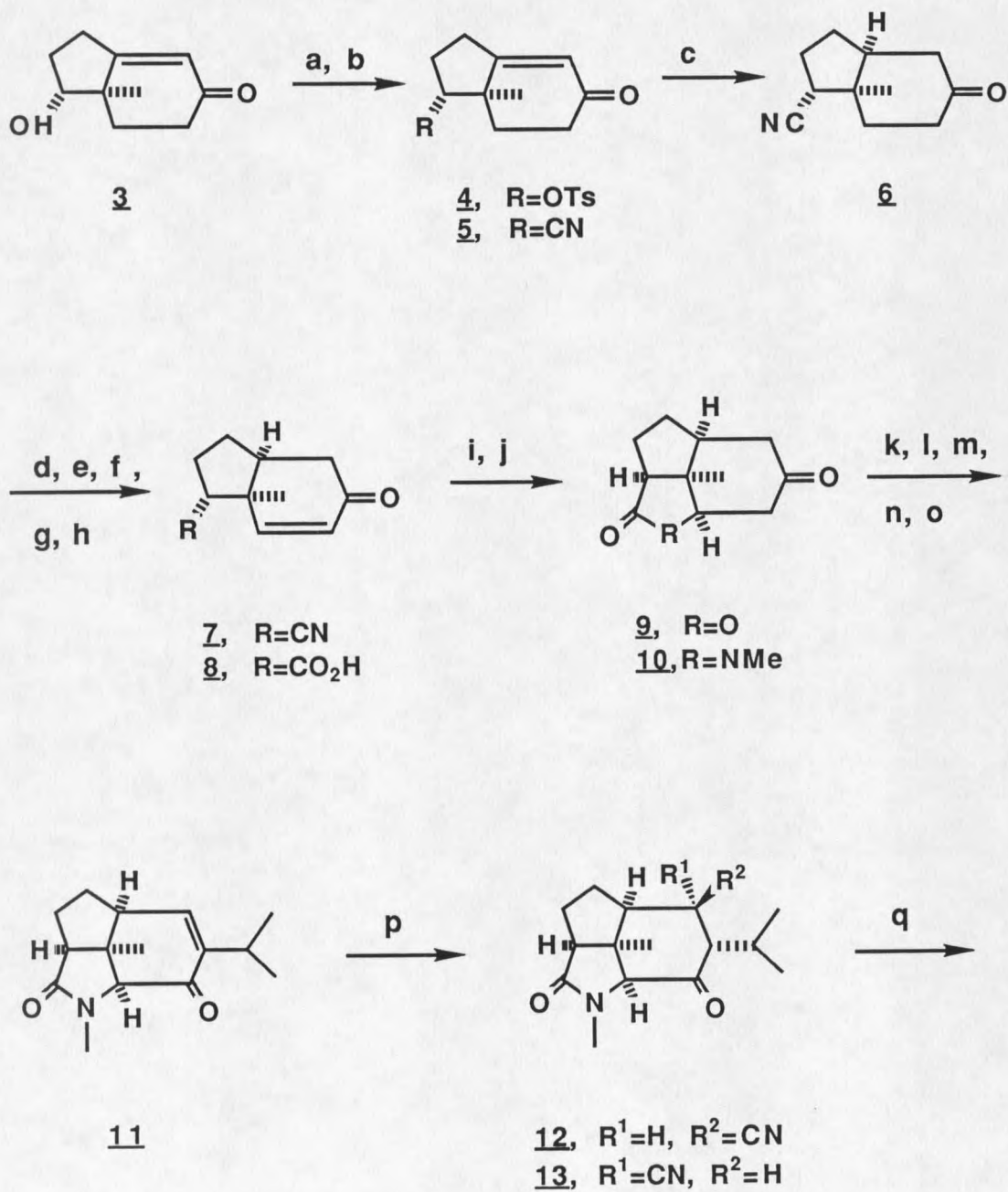
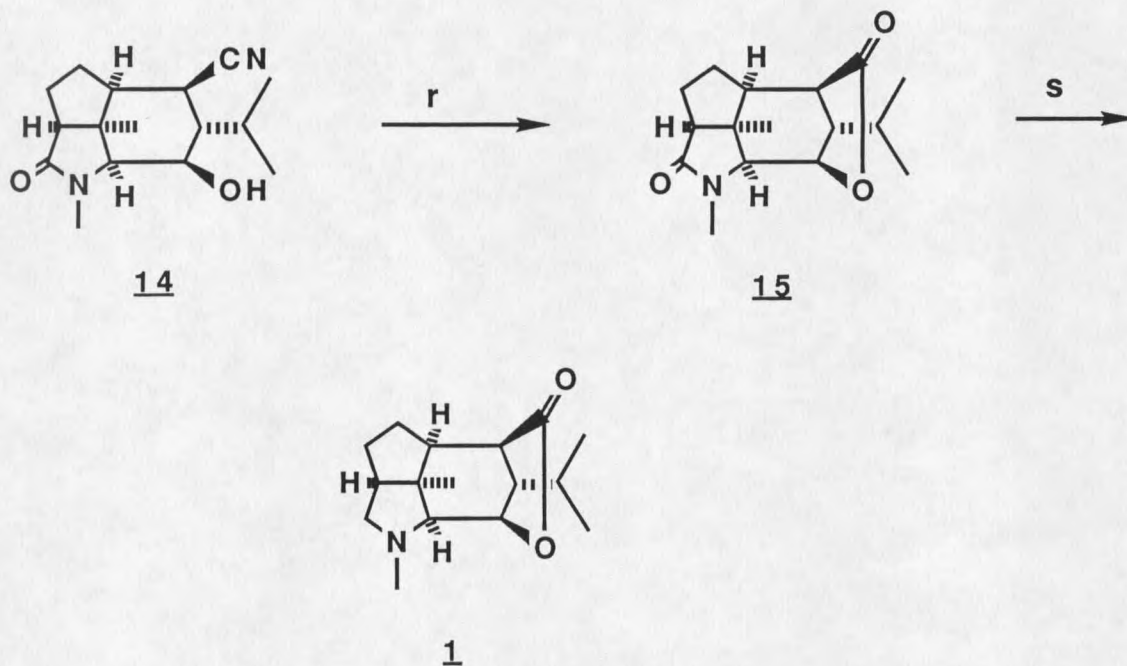


Figure 3 - Continued

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

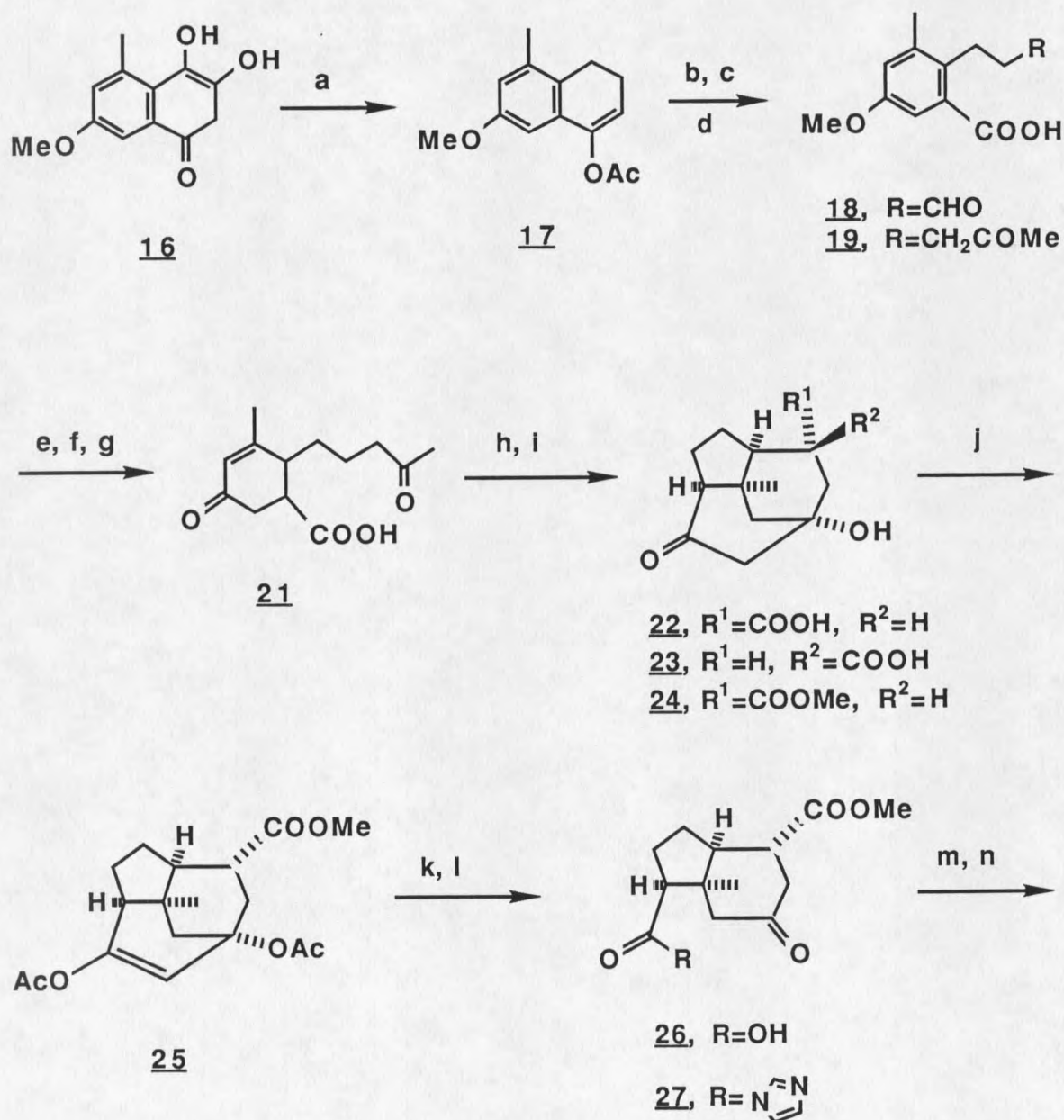
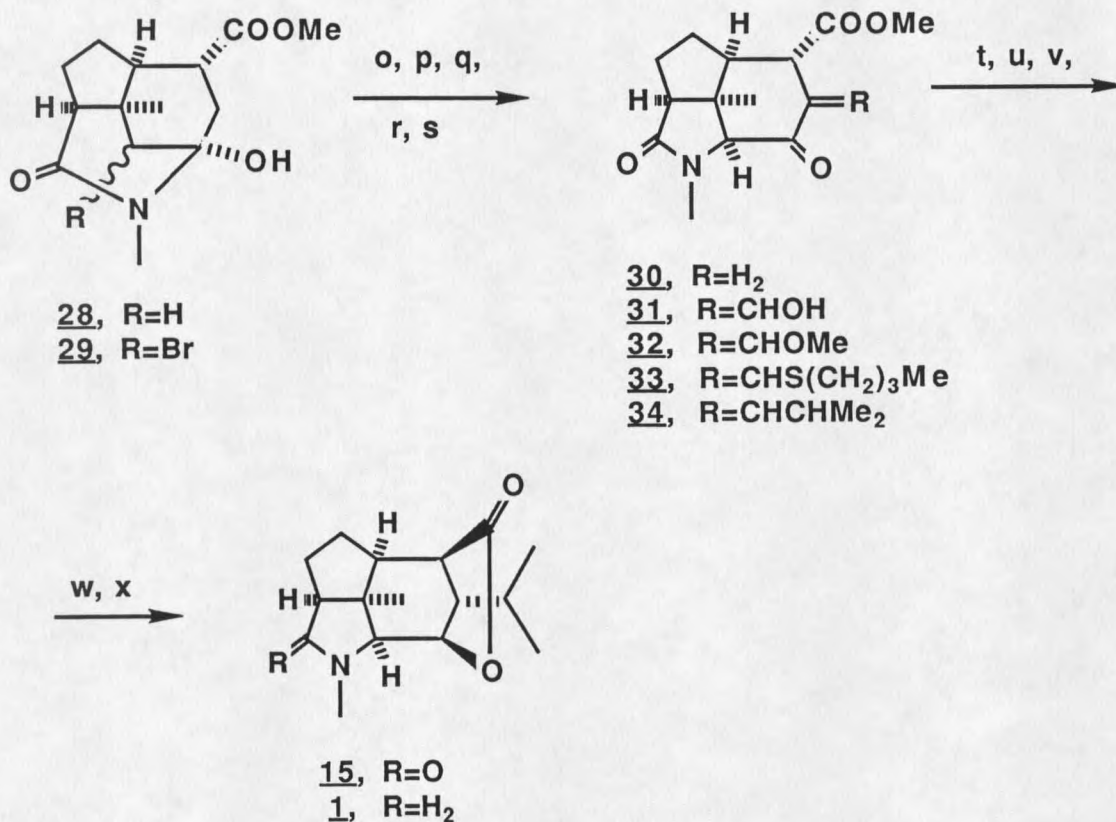


Figure 4 - Continued



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 Dendrobine

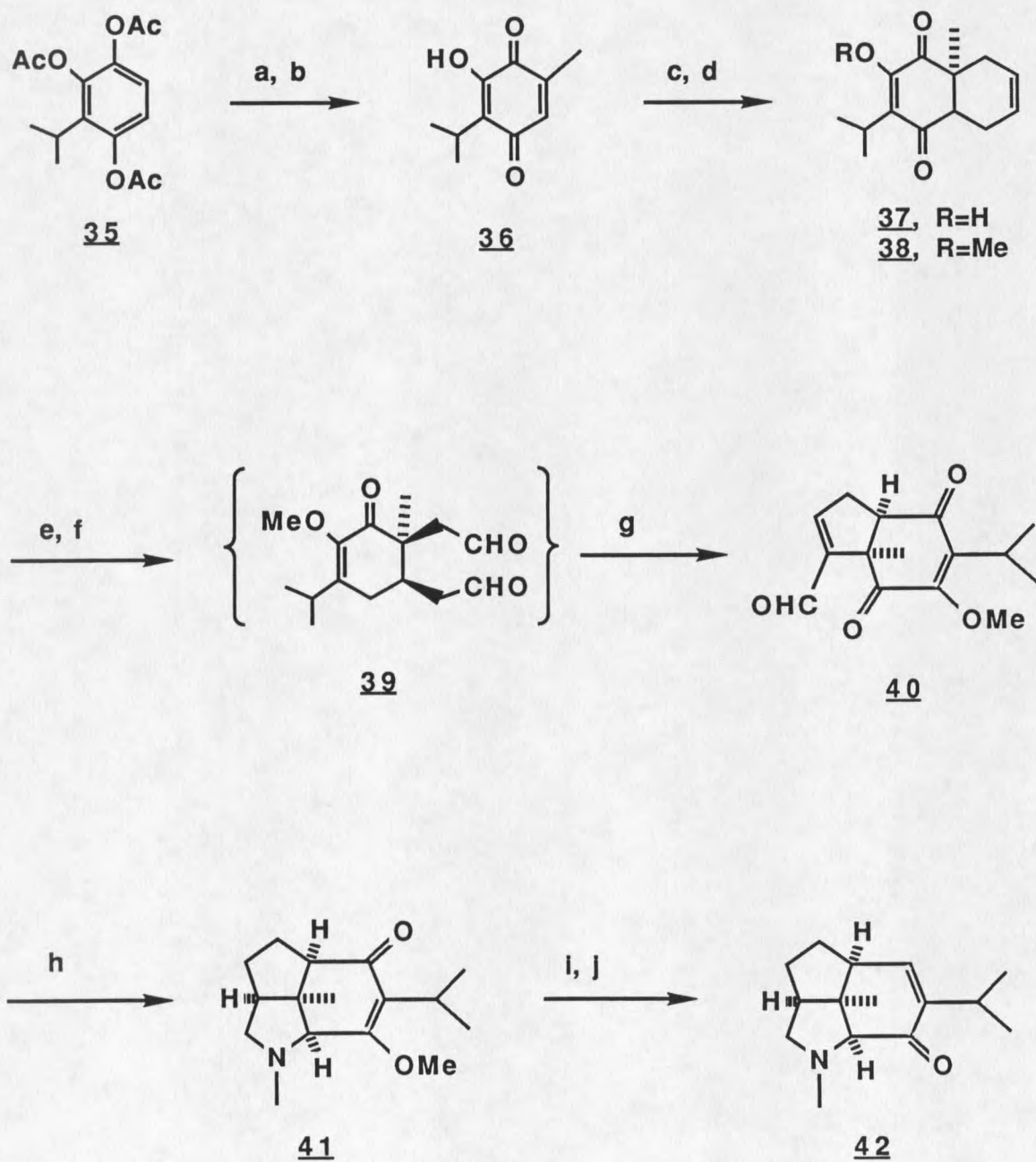
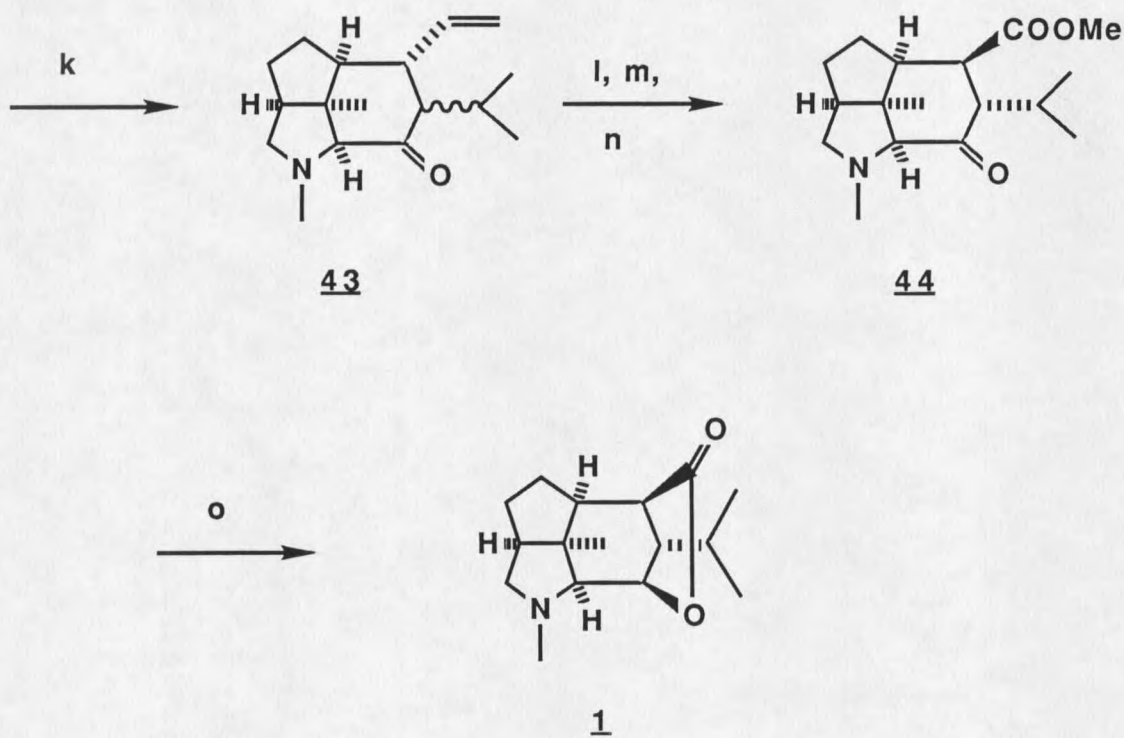
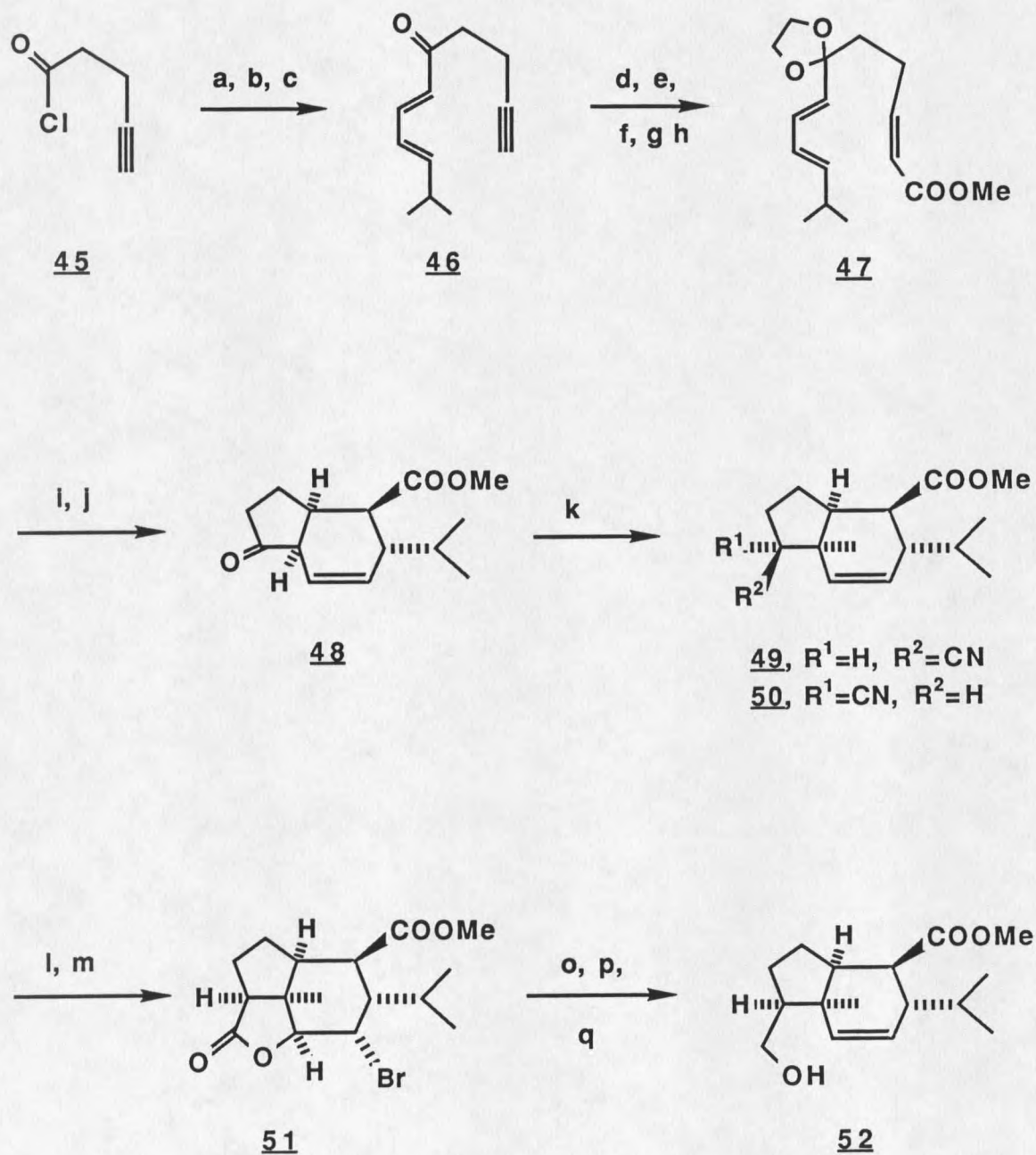


Figure 5 - Continued

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 Dendrobine



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

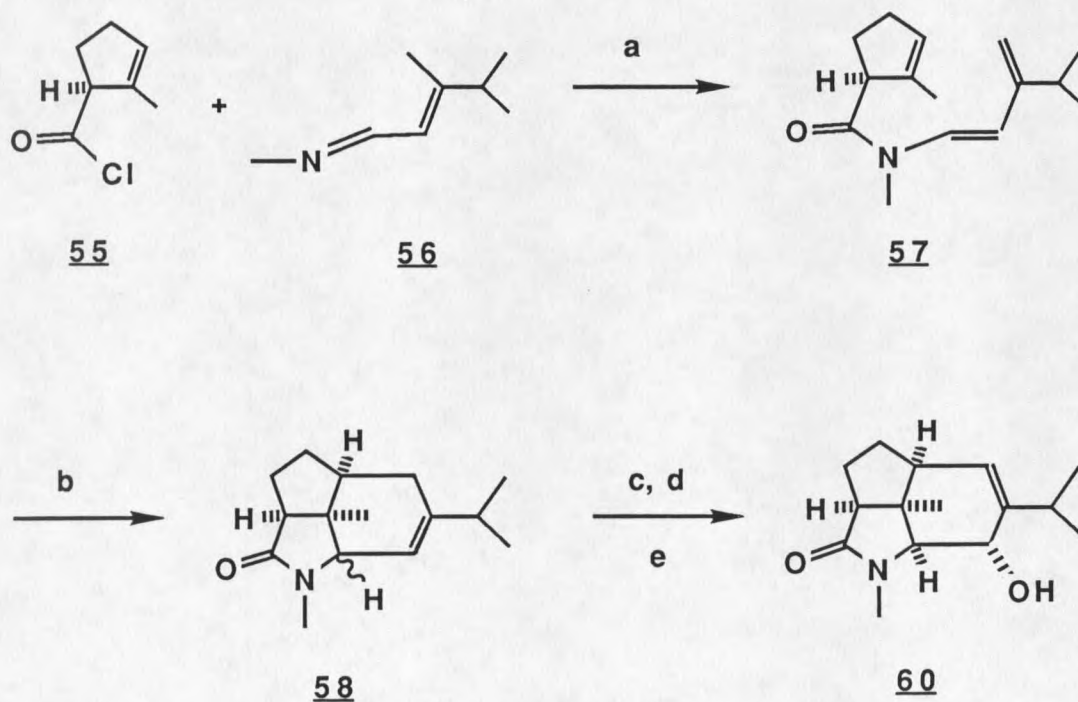
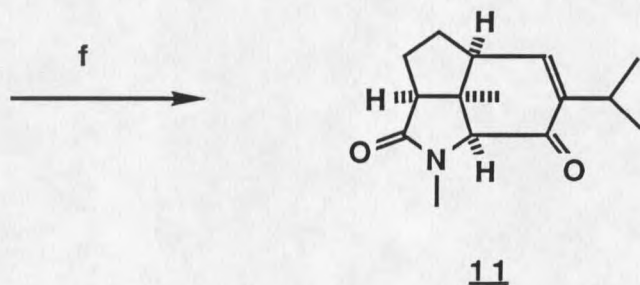
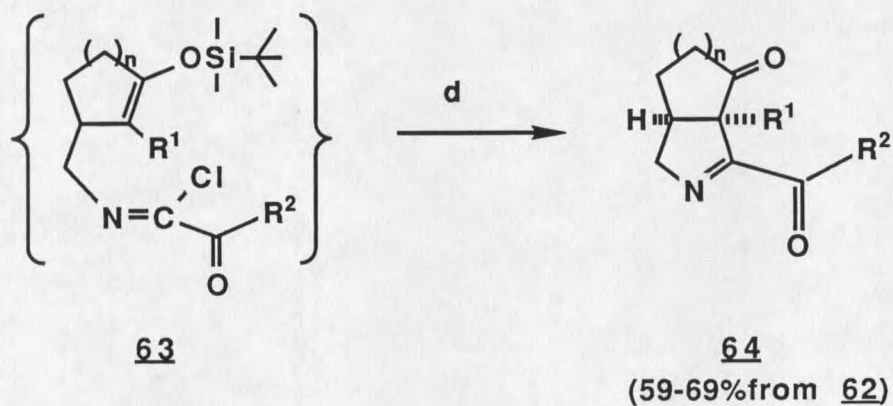
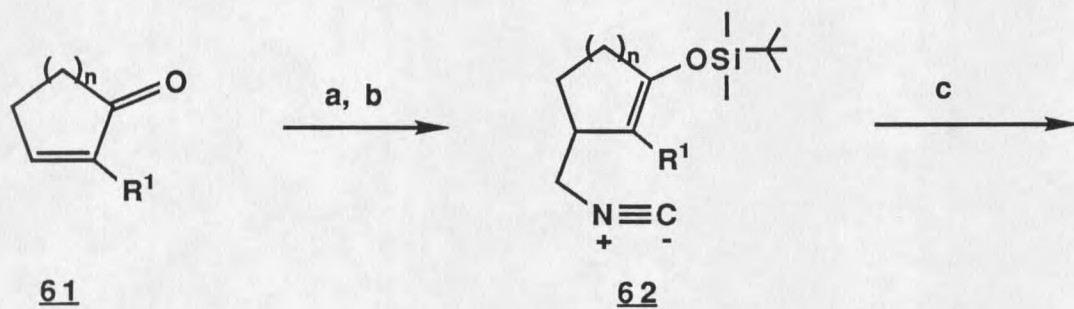


Figure 7 - Continued

a, PhNEt₂ ; 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 AgBF₄ 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

$n=1, 2, 3$ $R^1=H, Me$

$R^2=i-Pr, t-Bu, MeO_2CCH_2CH_2, MeO_2CCH=CHMe$

a, $LiCH_2NC$; b, $ClSi(CH_3)_3$; c, R^2COCl, CH_2Cl_2 ; d, $AgBF_4$

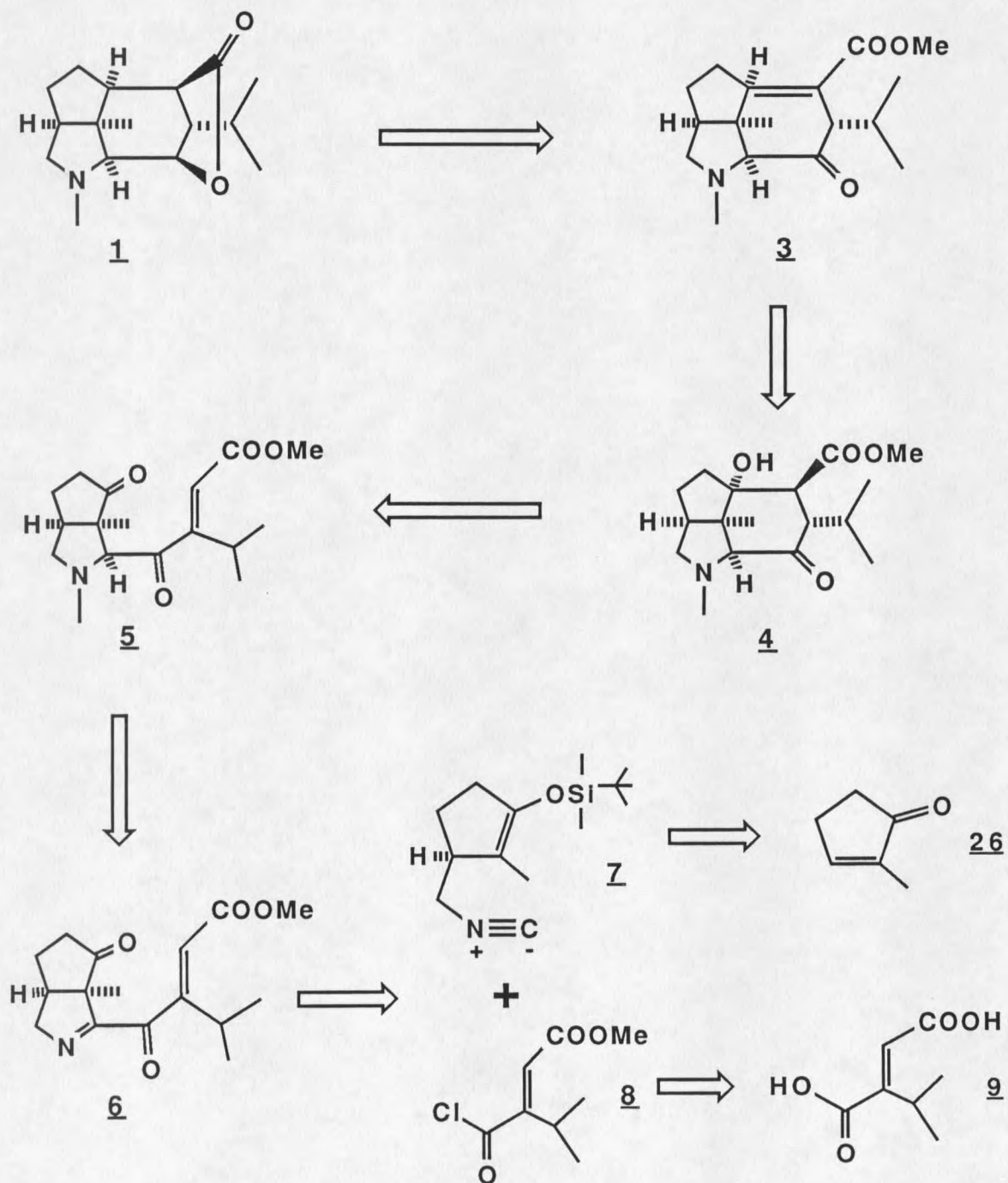
RESULTS AND DISCUSSION

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



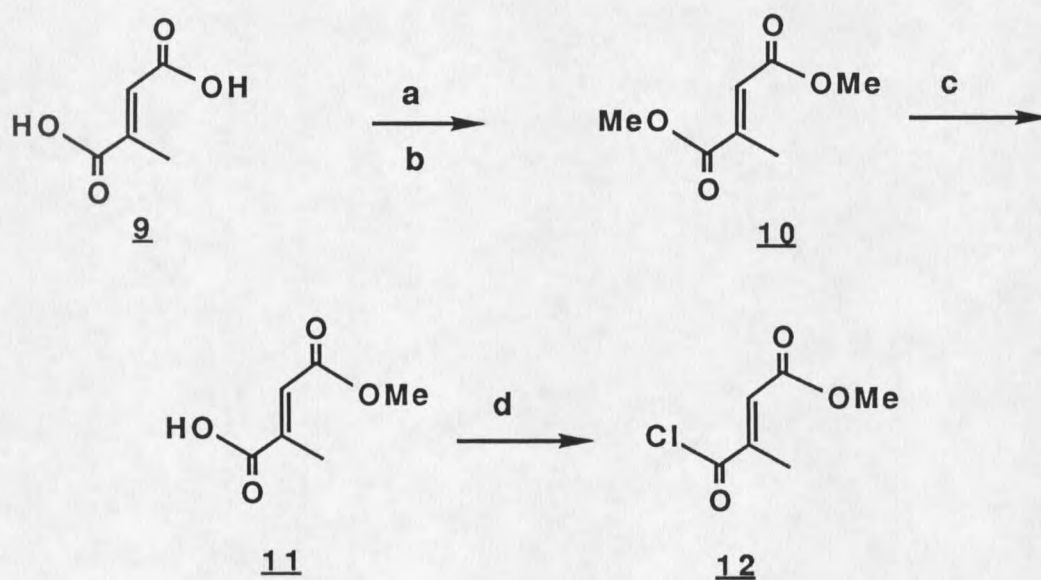
2-Acylpyrroline 6 could be constructed from the isonitrile 7 via the acylnitrilium ion initiated cyclization.

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).

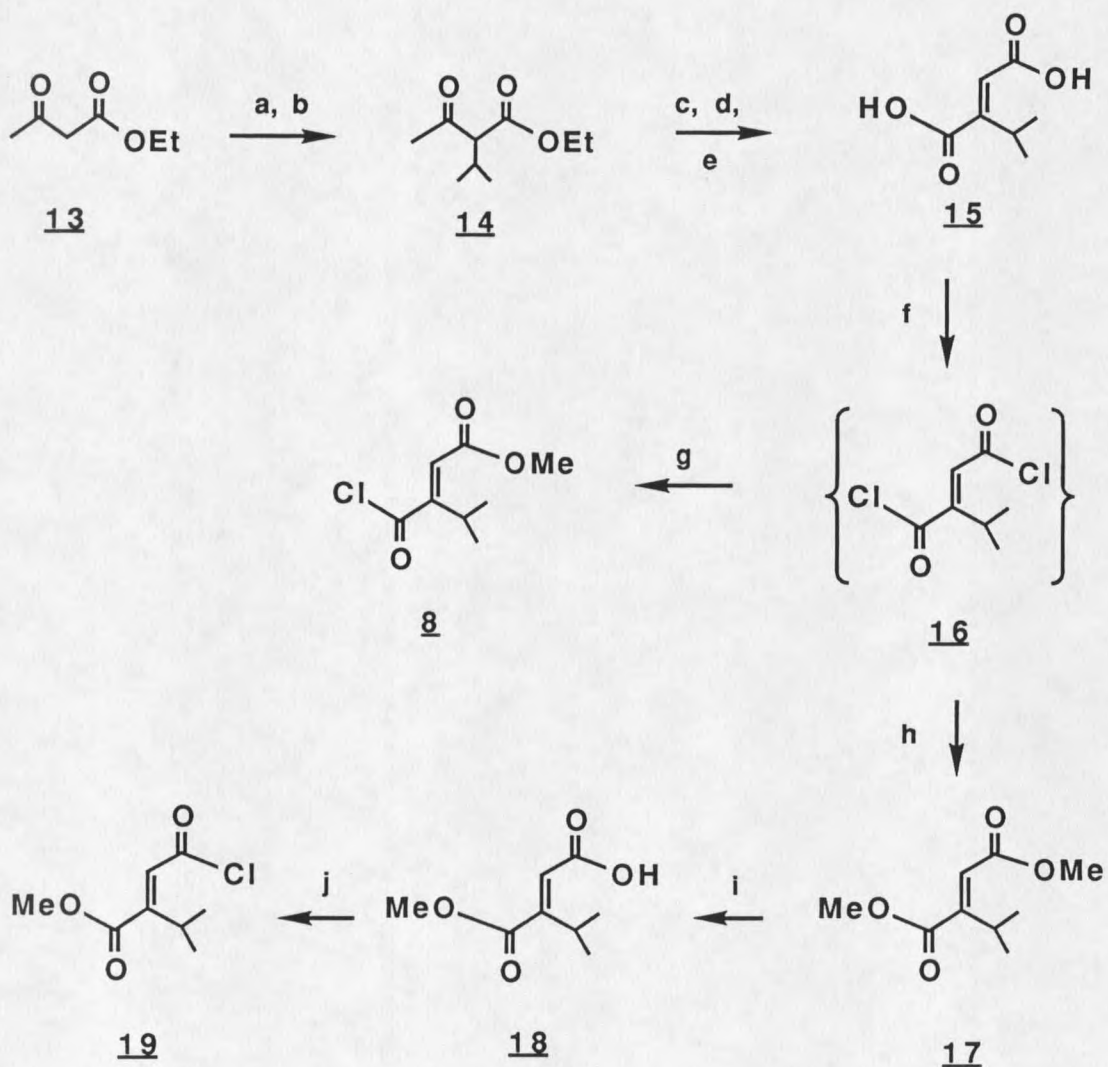
Sequential treatment of mesaconic acid (9) with thionyl chloride followed by anhydrous methanol afforded methyl (3-carbomethoxy-2-methyl)propenoate (10) in 94.2% yield. The ester 10 was selectively saponified with KOH (MeOH, 0 °C) to provide (E)-3-carbomethoxy-2-methylpropenoic acid (11) in 92% yield.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

Figure 10. Preparation of Acylchloride 12

a, SOCl₂, CCl₄, rt ; b, excess MeOH, rt ; c, 1 eq. KOH,
 MeOH, 0 °C- rt ; d, i) LiH, ether, ii) (COCl)₂

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

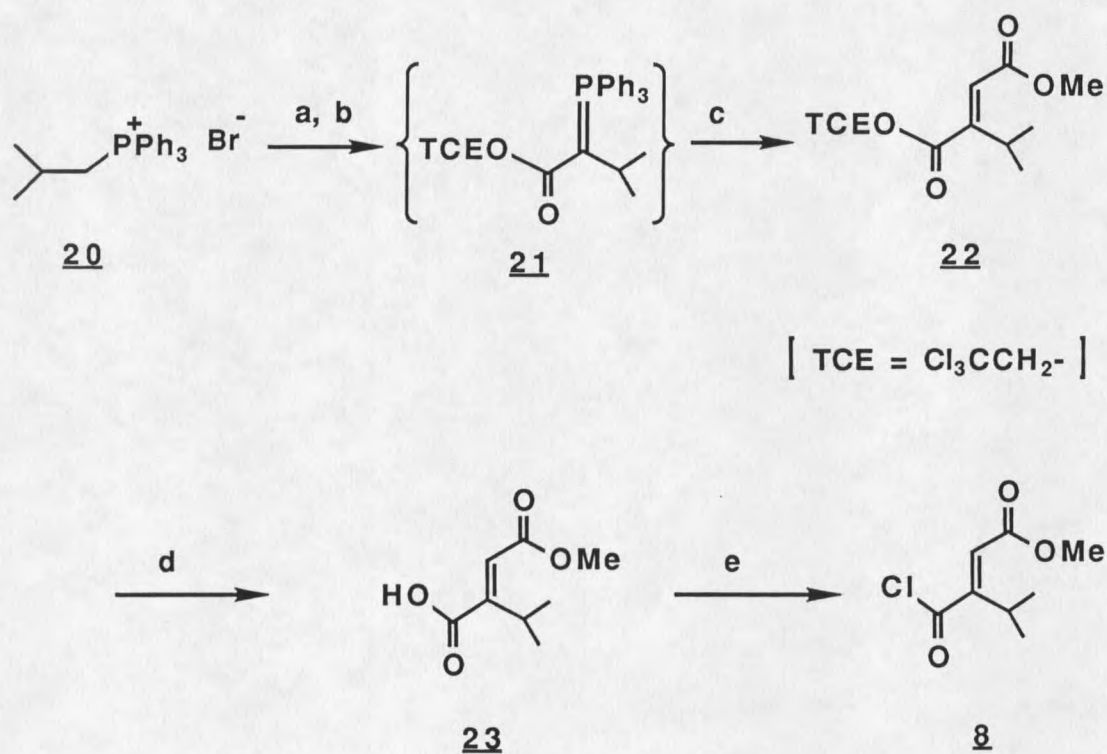
To prepare the isopropyl analog 8, we made isopropyl fumaric acid (15) from ethyl acetoacrylate via alkylation followed by treatment of the product 14 with bromine and then KOH in ethanol to effect a Favorskii rearrangement^{24,25} in 44.7% overall yield (Figure 11).

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.

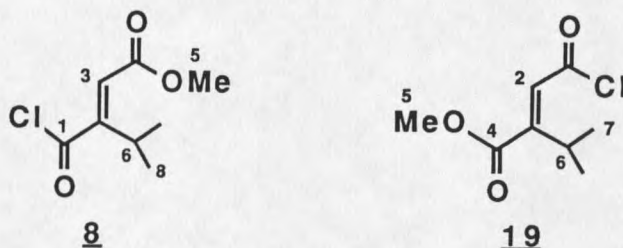
With diacid 15 in hand, we attempted to prepare acylchloride 17, by using the same procedure which had been used for the methyl analog 12. But hydrolysis of diester 17 with 1 equiv. of KOH gave the undesired half acid 18, which was then converted to the corresponding acylchloride 19 by treatment of 18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

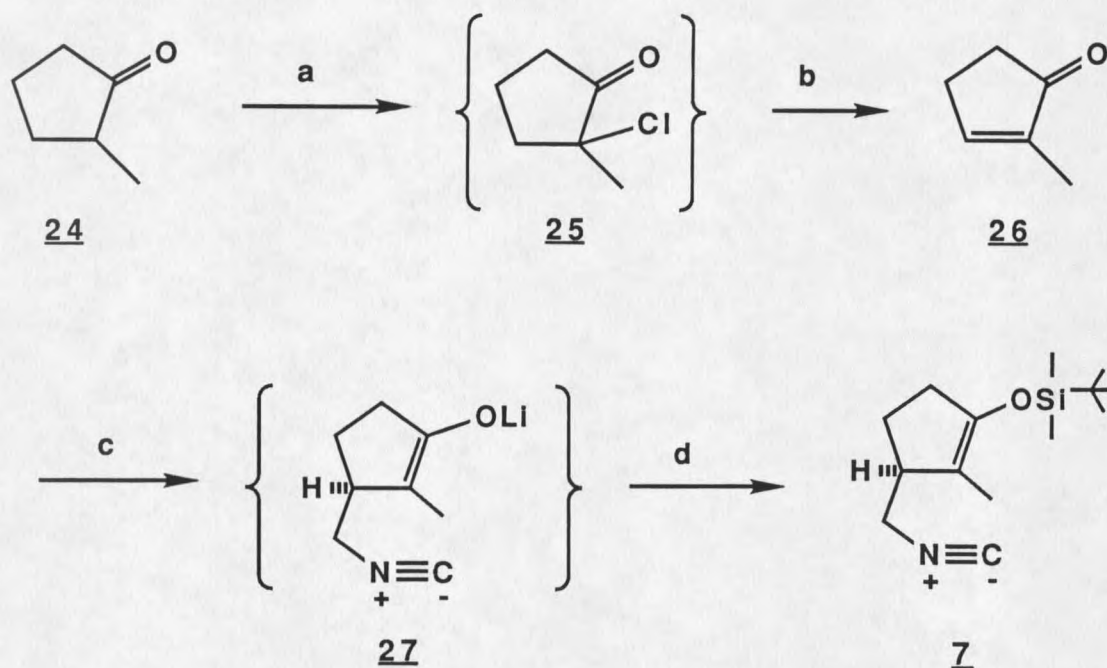
Table 2. NMR Data of Acylchloride 8 and 19

Proton	¹ H NMR		Carbon	¹³ C NMR	
	<u>8</u>	<u>19</u>		<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-BuLi, THF, -78°C , ii) HMPA, iii) 26, -78°C ; d, TBSCl, $-78^\circ \sim 0^\circ\text{C}$.

Lithiation of methyl isocyanide (n-BuLi, THF, -78°C) furnished a suspension of isocyanomethylithium. 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 acylitrilium 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

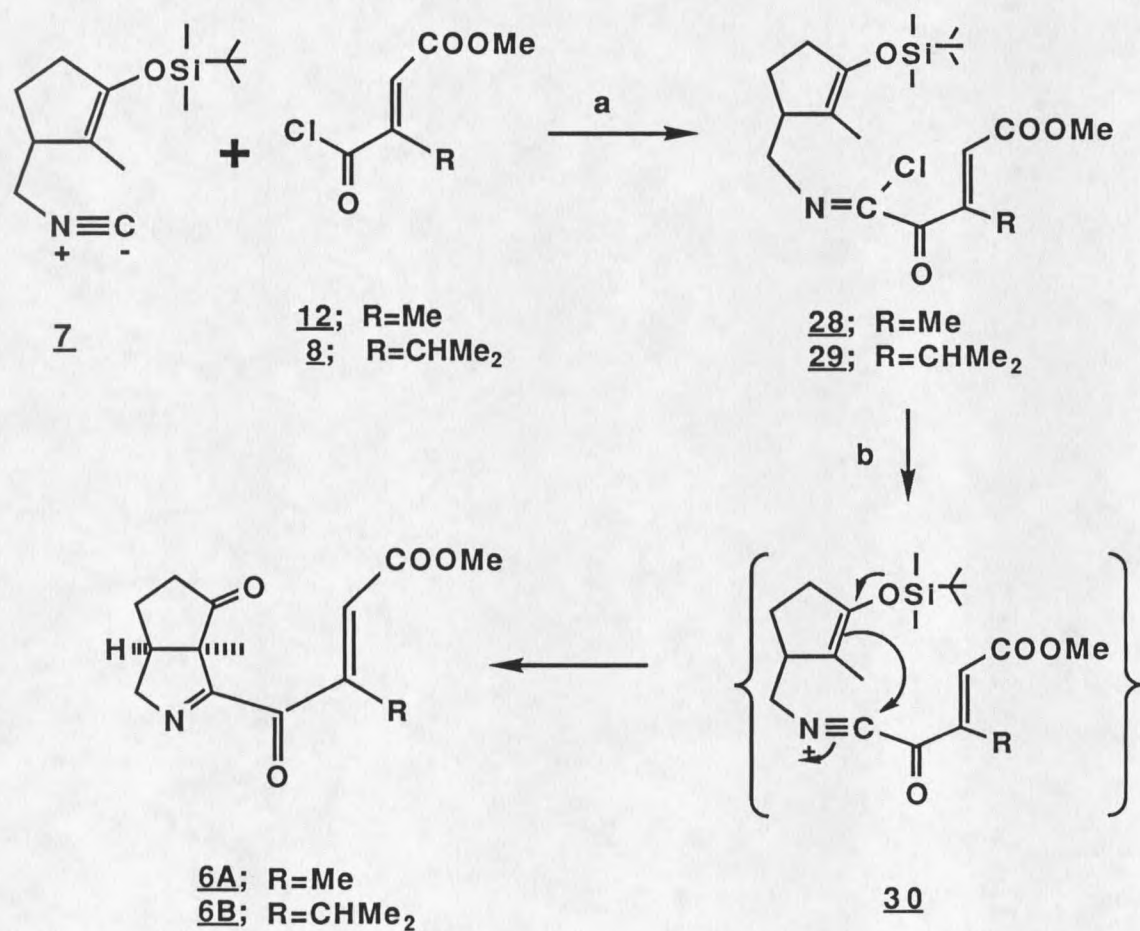
observable isomerization of the thermodynamically favored tetra substituted silylenol ether. The crude imidoyl chloride 28 was then treated directly with 1.10 equiv. of AgBF_4 (CH_2Cl_2 - $\text{ClCH}_2\text{CH}_2\text{Cl}$, -78°C) to afford the desired 2-acylpyrroline 6A. Owing to the acid sensitivity, 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 $40\text{-}43^\circ\text{C}$. 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

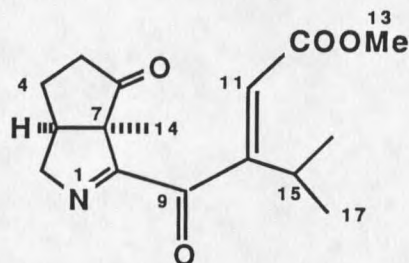


a, CH_2Cl_2 ; b, AgBF_4 , CH_2Cl_2 - $\text{ClCH}_2\text{CH}_2\text{Cl}$, -78°C

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

is presented in Table 3.

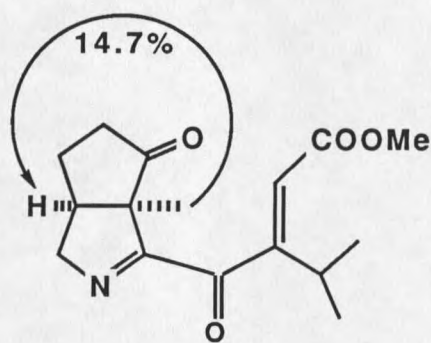
Table 3. NMR Data of 2-Acylpyrroline 6B



^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

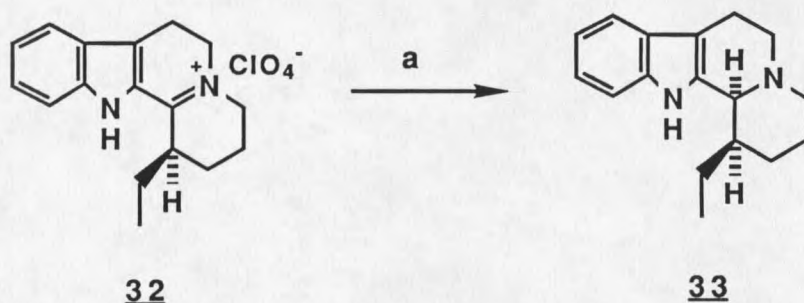
Stereoselective Synthesis of the Tricyclic β -Hydroxyester (52)

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.

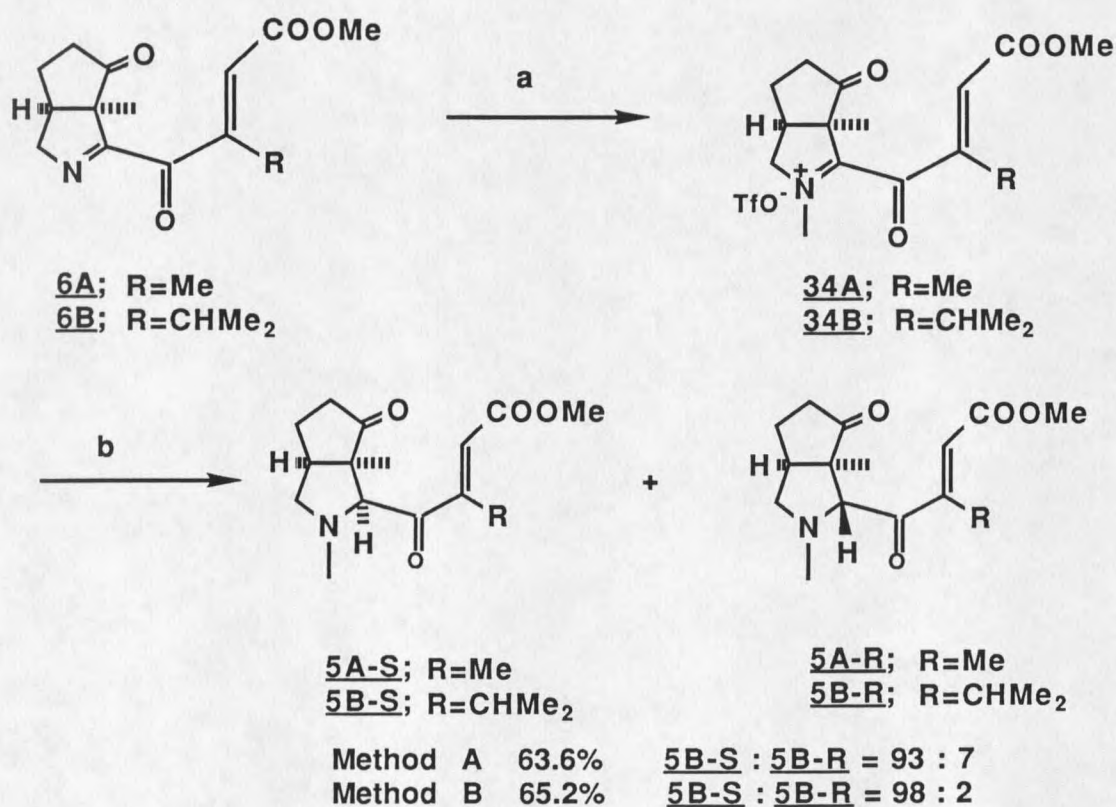


a, 2.5 equiv. $(\text{n-Bu})_3\text{SnH}$, MeOH , $25\text{ }^\circ\text{C}$; 95%

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**.

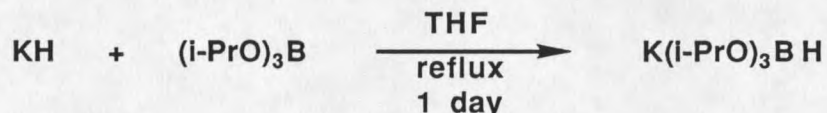
Figure 15. Preparation of N-Methylpyrrolidines **5A** and **5B**



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.

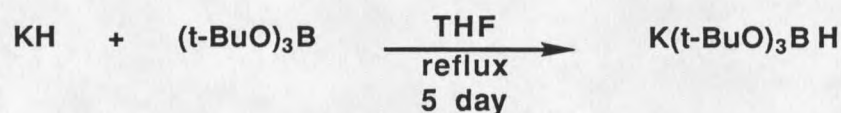
Unfortunately, this TBTH method must be carried out under high dilution to get good stereoselectivity. This limitation prompted us to explore alternative methods for stereoselective reduction.

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-

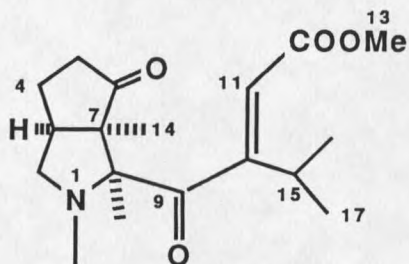
hydride (KTBH). KTBH was also prepared as described²⁹ by the reaction of KH and tri-*t*-butoxyborane.



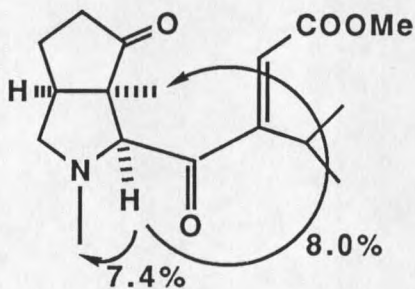
When the iminium triflate 34B was reacted with 1 equiv. of KTBH (THF, -78 °C, 5 min), the diastereoselectivity was further improved to 98 : 2 (5B-S:5B-R) and the desired diastereomer 5B-S was isolated in 65.2% purified yield. It is therefore considered that these hydrides attack from the less hindered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

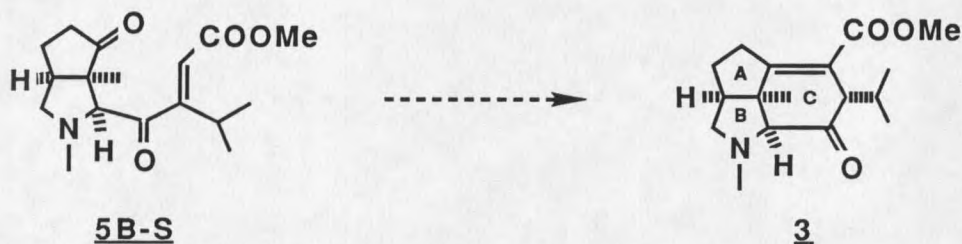
Assignment of ¹H NMR and ¹³C NMR data for N-methylpyrrolidine 5B-S is presented in Table 4.

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

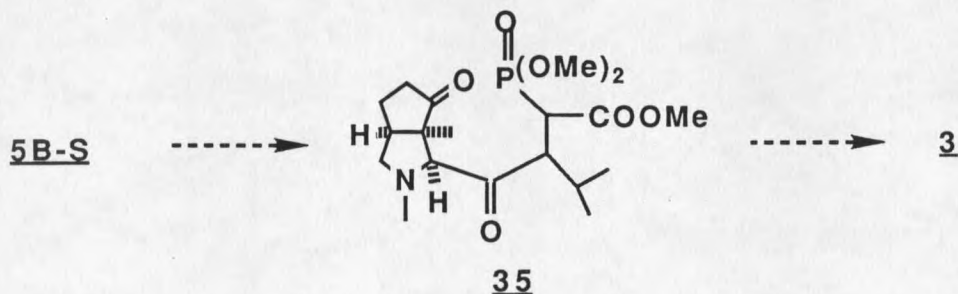
NOE of 5B-S

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.

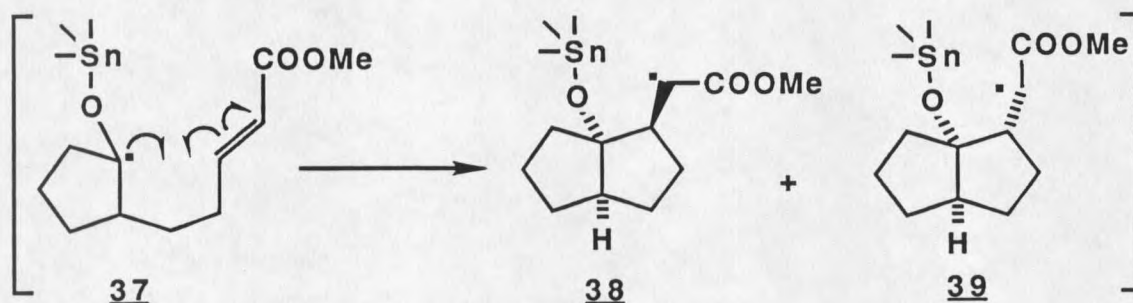
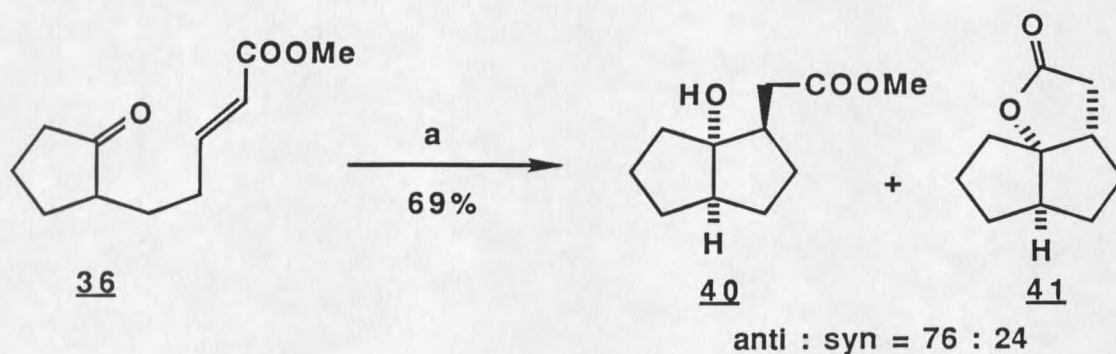
Attempts to prepare the phosphonate 35 from the reaction of 5B-S with dimethyl phosphite in the presence of trimethyl aluminum³¹ were also unsuccessful.



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

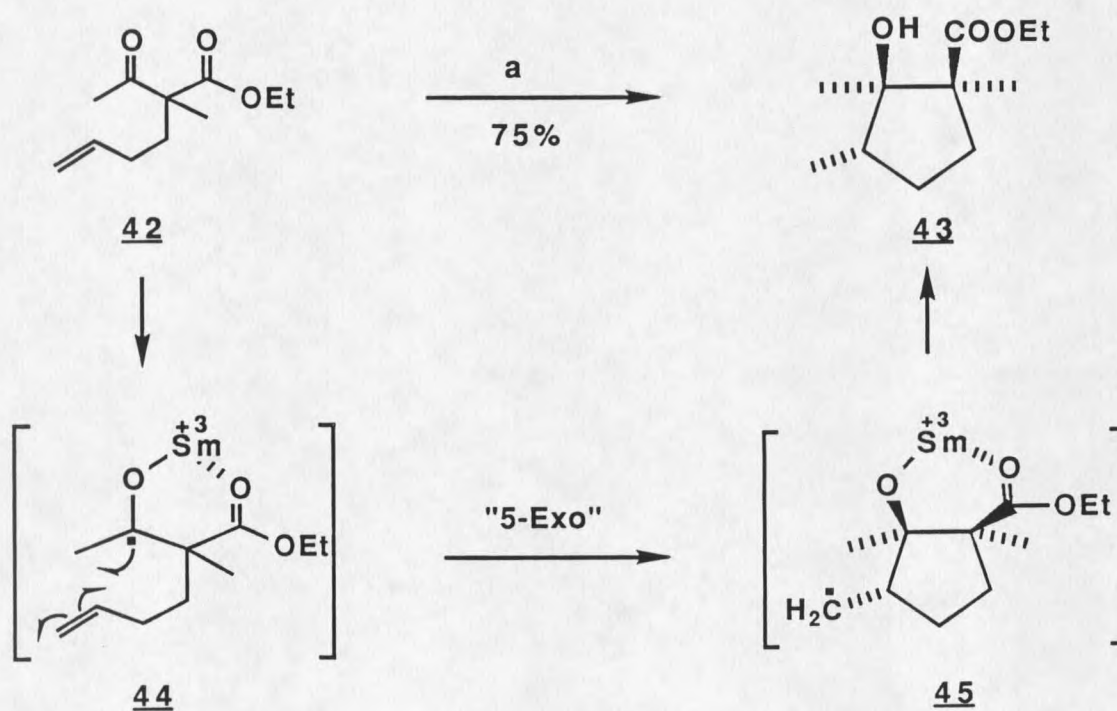
a, $n\text{-Bu}_3\text{SnH}$, AIBN, CH_3CN , PhH, 80°C .

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, $-78^\circ \sim 0^\circ\text{C}$.

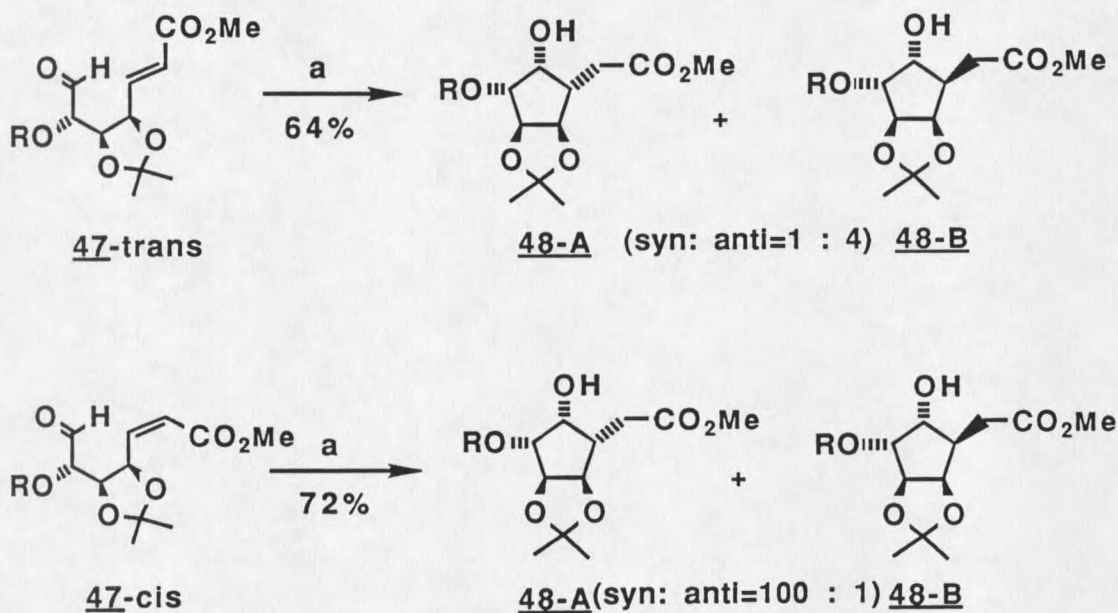
According to Beckwith³⁶, alkyl radicals preferentially attack pi-systems through an unsymmetrical transition state to maximize orbital overlap between the semioccupied orbital (SOMO) and the empty pi^* -

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.

