STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF HISTRIONICOTOXIN

Thesis by

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To My Mom and Dad

and

To My Wife, Robin

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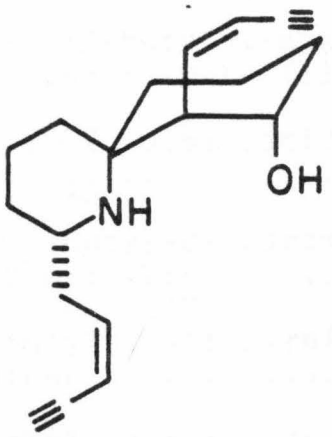
ABSTRACT

Histrionicotoxin (HTX) is a unique alkaloid secreted from the skin glands of the arrow poison frog, Dendrobates histrionicus. This base has been found to be a highly active venom as well as a mucosal tissue irritant toward both mammals and reptiles. Syntheses of perhydrohistrionicotoxin (H_{12}-HTX), which exhibits all of the biological activities that histrionicotoxin does, and a photoaffinity labeled derivative of H_{12}-HTX are described.

An approach to the synthesis of the cis-enyne moieties in HTX is presented. This method utilizes the stereoselective synthesis of β-hydroxy acid derivatives obtained via the boron enolates of 3-acyl-oxazolidine-2-ones.



Histrionicotoxin

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CHAPTER I

A Stereoselective Synthesis of (±) H_{12}-Histrionicotoxin and Related Photoaffinity Labeled Congeners

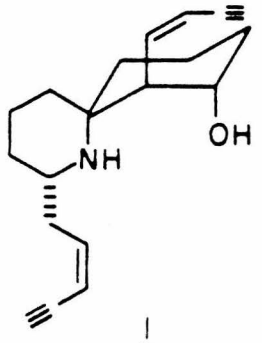
Abstract. A practical six-step stereoselective total synthesis of (±)-perhydrohistrionicotoxin (4a) (H_{12}-HTX) is reported. The desired 6,6-azaspiro[5.5]undecane ring system found in these alkaloid toxins has been constructed via the formic acid-induced cyclization of either dihydropyridone 6 or carbinolamide 9. The photoaffinity labeled toxin analog 4c has also been prepared which binds to Torpedo californica electroplax membrane fragments with comparable binding affinities to (±) H_{12}-HTX (4a).

Introduction

In recent years the tropical "arrow poison frogs," belonging to the genera Dendrobates have been found to yield a host of new structurally unique alkaloids.[2,3] These bases, which are localized in the frog's defensive skin secretions, have been found to be highly active venoms as well as mucosal tissue irritants towards both mammals and reptiles. The meticulous investigations of Daly, Witkop, Karle and co-workers have been instrumental in revealing the structures of many of these physiologically active alkaloids which have attracted widespread interest as targets for total synthesis.[3] Three representative alkaloids which have been isolated by the NIH group are shown below to illustrate several common substructural relationships.

The C_{19}-alkaloids histrionicotoxin (HTX)[2a-d] (1) and gephyrotoxin (2)[4] (Dendrobates histrionicus) share common cis-enyne sidechains while pumiliotoxin-C (3)[4] (Dendrobates pumilio) and gephyrotoxin (2) are both elaborated cis-decahydroquinolines. Other pumiliotoxin-C class alkaloids of the C_{19} type possessing the cis-enyne moiety have recently been tentatively identified.[4]

Both histrionicotoxin (1) and perhydrohistrionicotoxin



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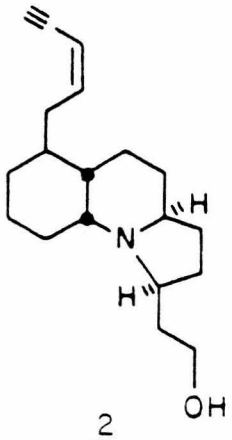

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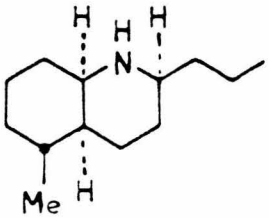

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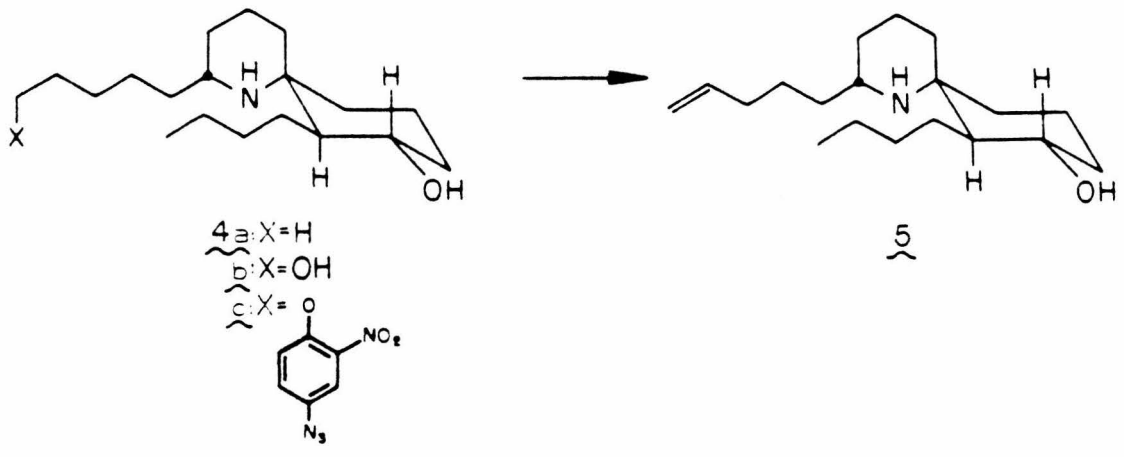
(H_{12}-HTX) (4a) have attracted considerable interest from the standpoint of total synthesis, and while a total synthesis of HTX is yet to be accomplished, several different approaches to the construction of H_{12}-HTX have been reported.[5,6] The attention given to these objectives stems from their unique properties as neurotoxins in conjunction with the scarcity of HTX (ca 200 μg per frog). It has been shown that both 1 and 4a selectively bind to the acetylcholine receptor and interupt transsynaptic transmission of neuromuscular impulses.[7] Both 1 and 4a also block postsynaptic

membrane depolarization while not interferring with acetylcholine binding. It has been postulated that these toxins prevent membrane depolarization by reversible binding to the receptor ion channel or "ion conductance modulator."[7]

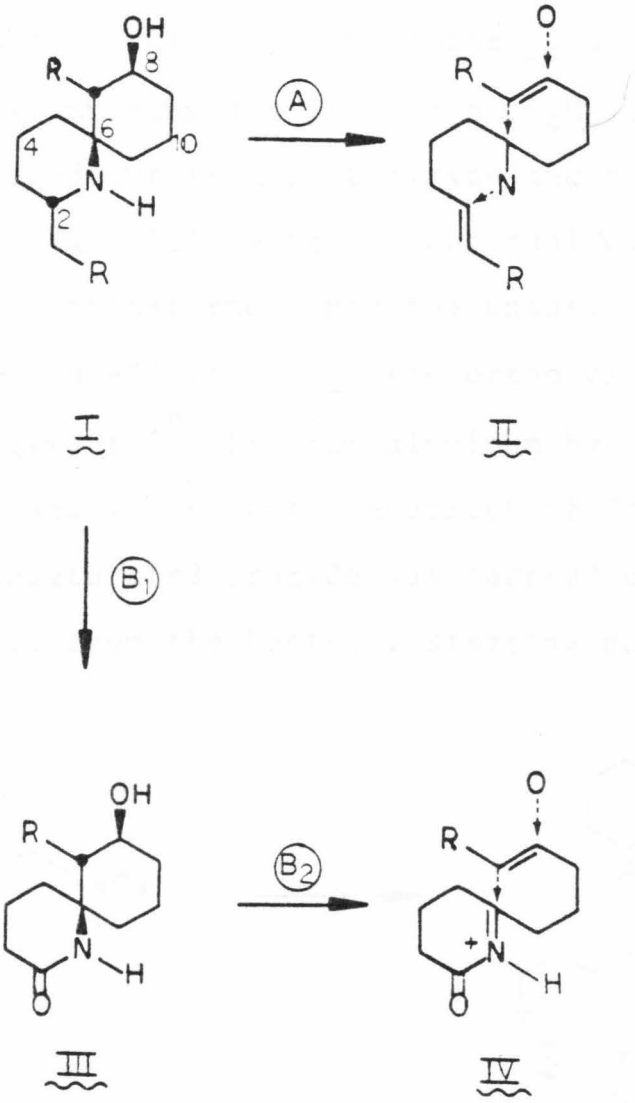
The objectives of the current study have been to develop a highly practical laboratory synthesis of (±)-perhydrohistrionicotoxin (4a) as well as a suitably functionalized photoaffinity labeled congener, e.g., 4c, that might be employed to label that (those) polypeptide(s) which is the structural component(s) of the acetylcholine receptor ion channel.[8] The rationale for selecting the



C_5-sidechain terminus for photoaffinity labeling was predicated upon choosing a site distal to both the amine and C_8-hydroxyl functions which are probably critical to toxin receptor binding. Accordingly, the functionalized HTX derivative 5 was chosen as the penultimate objective for the present study.

The two basic approaches to the synthesis of histrionicotoxin (1), perhydrohistrionicotoxin (4a) and related congeners under investigation in these laboratories is illustrated in Scheme I. Both 1 and 4a (R = $\overset{H}{\underset{}{C}}=\overset{H}{\underset{}{C}}-C\equiv CH$ or -n-C_4H_9), as depicted in I, possess a latent skeletal symmetry element which is revealed when the N-C_1, C_6-C_7, and C_8-OH bonds are disconnected as in transform A. In principle, the requisite stereocenters at C_6, C_7, and C_8 can be constructed in a single step via electrophilic olefin addition. In the present study the less symmetric toxin congeners 4 were derived by a variant on this approach from spirolactam III (R = n-C_4H_9) which had been prepared earlier by Kishi[5a,b] and Corey[5c] in a successful synthesis of 4a. The choice of this latter route becomes compelling in the face of the uncertainties surrounding the construction of photoaffinity labeled toxin analogs which might retain high receptor binding affinities. The following discussion describes the

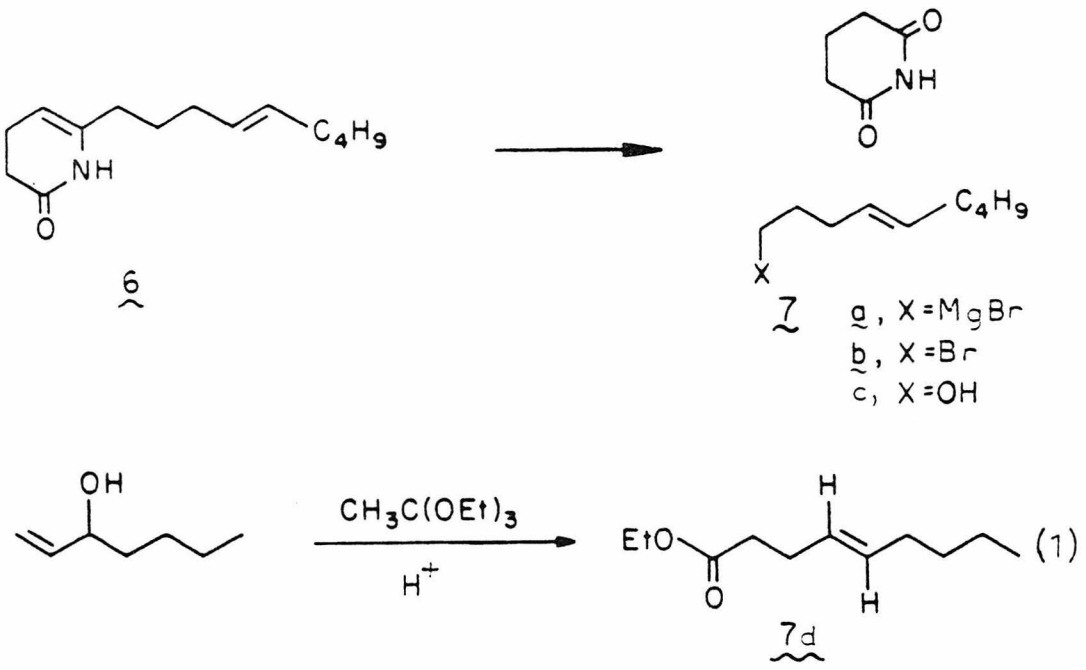
Scheme I



viability of employing the acylimmonium ion approach, IV → III, in a practical synthesis of histrionicotoxin congeners 4 and 5.[9]

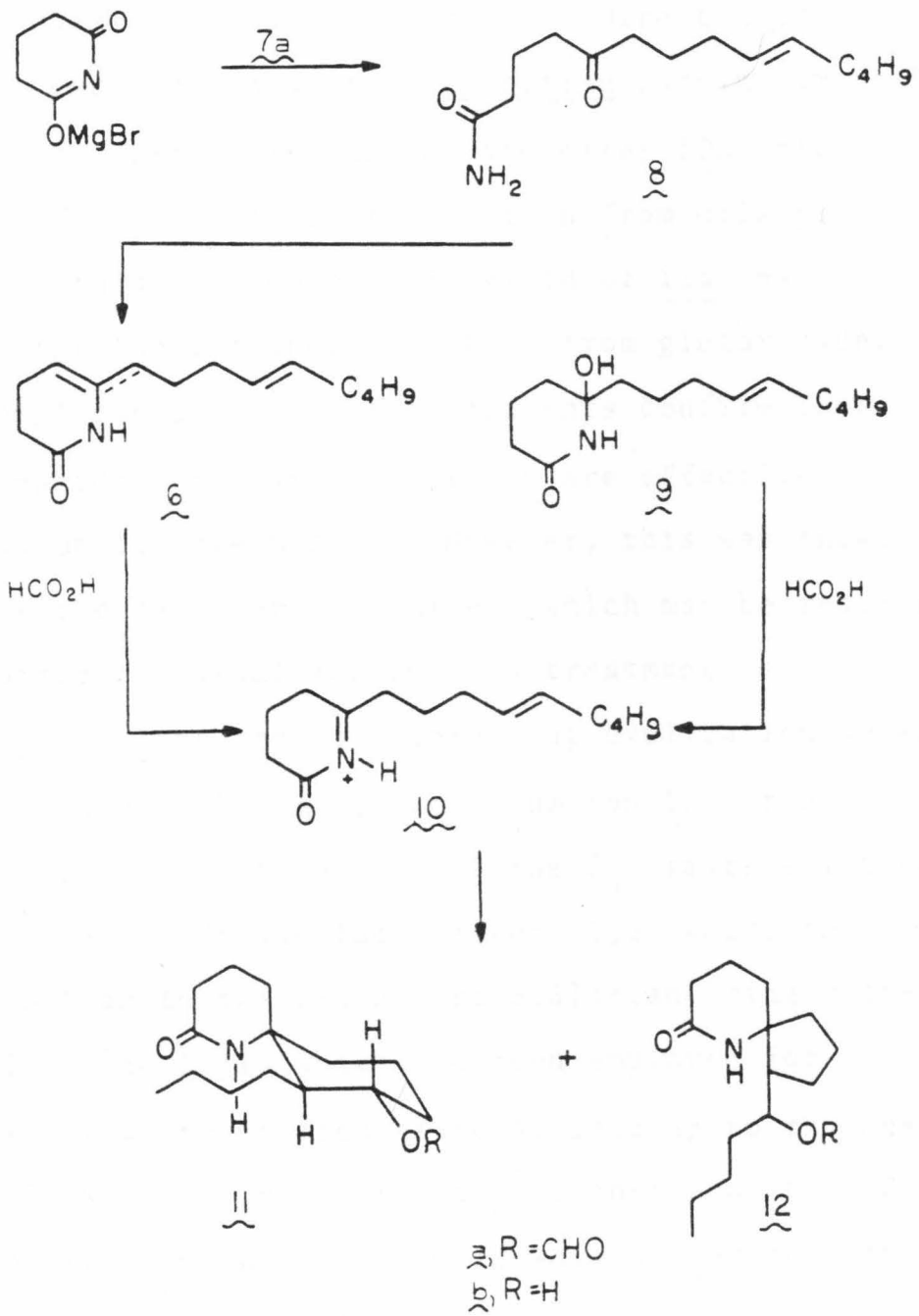
Results and Discussion

The synthesis of the dihydropyridone 6, a suitable precursor to acylimmonium ion IV (R = n- C_4H_9), was efficiently carried out from glutarimide and the Grignard reagent 7a. Following conventional lines, 1-hepten-3-ol was transformed into the unsaturated ester 7d (eq. 1) in 95% yield via the ortho ester Claisen rearrangement.[10] Lithium aluminum hydride reduction of 7d and subsequent conversion of 7c to the corresponding unsaturated bromide was carried out in a 66% overall yield from the heptenol starting material.



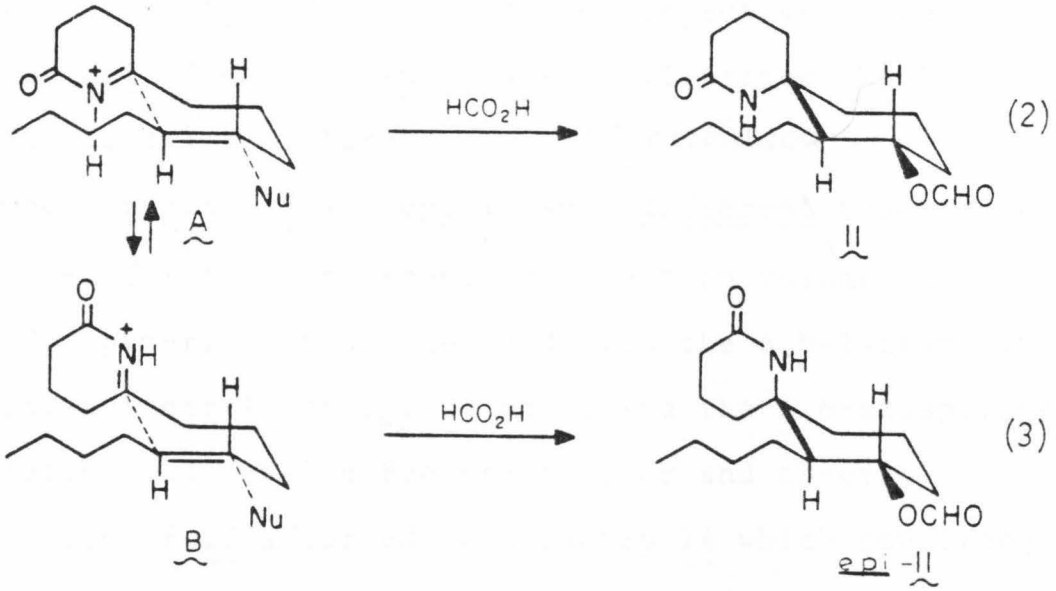
Following established precedent,[11] the addition of Grignard reagent 7a to the bromomagnesium salt of glutarimide in diethyl ether afforded a 62% yield of both ketoamide 8 and carbinolamide 9 as a 1:1-mixture (Scheme II). Although 8 and 9 could not be effectively separated, the mixture could efficiently be transformed to the dihydropyridone 6 accompanied by minor amounts of its exocyclic olefinic isomer (K_{eq} endo $\rightleftarrows$ exo = 9) in 75% yield by acid catalysis with azeotropic removal of water. In exploring conditions to improve the overall efficiency of the Grignard addition step, it was found that if a solution of the glutarimide salt was prepared in dichloromethane the addition of Grignard reagent 7a proceeded in nearly quantitative yield to afford the carbinolamide 9 uncontaminated by ketoamide 8. After exploring a range of acid catalyzed cyclization conditions it was found that 0.1 molar solutions of 6 in anhydrous formic acid (25°C, 32 h) afforded a mixture of lactam cyclization products from which the nicely crystalline lactam 11a was isolated in 40% yield after chromatography. Hydrolysis of the formate ester (MeOH, MeONa) afforded hydroxylactam 11b, mp 133-136°C, which was found to be identical in all respects to a independently prepared sample provided by Professor Kishi.[5a] An experimentally simplified

Scheme II



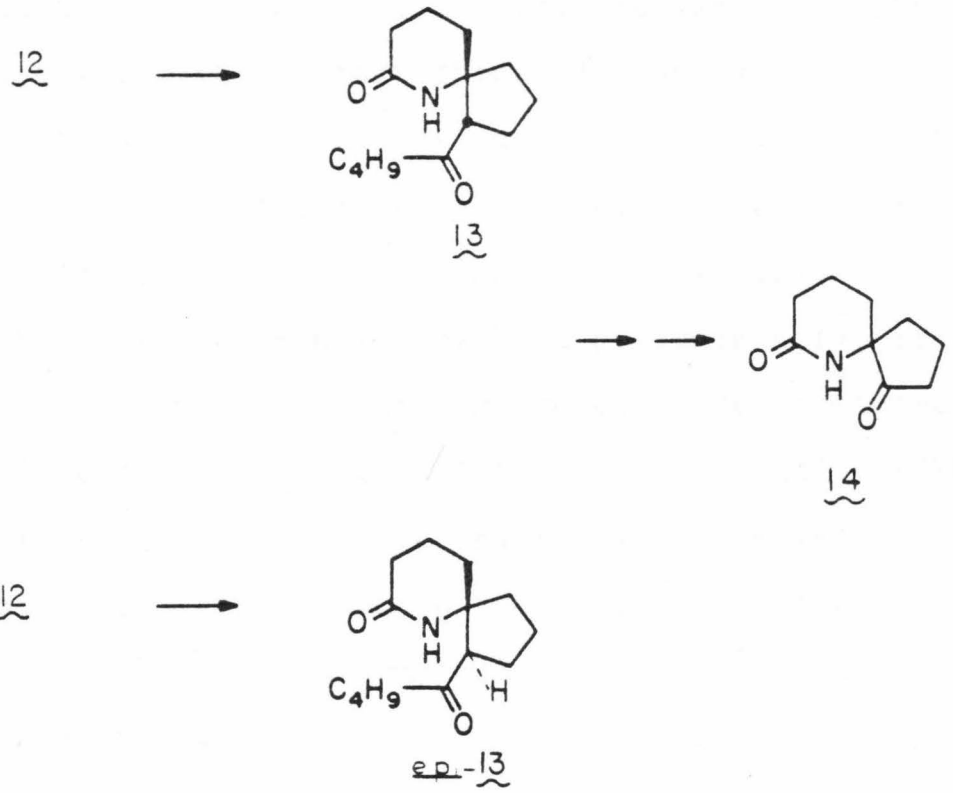
procedure for the synthesis of the desired lactam 11a was developed once the technical details for the synthesis of carbinolamide 9 had been refined. Direct acid catalyzed cyclization of the unpurified carbinolamide 9 afforded the desired lactam formate ester 11a which could be purified by direct crystallization from diisopropyl ether. By this procedure a 33% yield of 11a was realized for the combined two steps from glutarimide. These complementary sets of experiments confirm that either enamide 6 or carbinolamide 9 are effective acylimmonium ion precursors. However, this was shown not to be the case for ketoamide 8 which may be recovered intact after the usual formic acid treatment.

A priori there are four competing cyclization modes which are accessible to acylimmonium ion 10; two of these result in the formation of the C_6-diastereoisomeric 1-azaspiro[5.5]undecane lactams (eq. 2,3) while the other two lead to the 1-azaspiro[5.5]decane ring system (c.f. 12). The logic which had been employed for predicting that transition state A, leading to the desired lactam 11, would be preferred over transition state B rested on two tenuous points: It was assumed that the C_4H_9-sidechain would prefer to eclipse trigonal rather than tetrahedral atoms ($\Delta H_A^{\ddagger} < \Delta H_B^{\ddagger}$); and transition



state NH-solvent hydrogen bonding reorganization would be greater for B than A ($\Delta S_B^{\ddagger} < \Delta S_A^{\ddagger}$). In order to provide information pertaining to the relative energetics of the competing cyclization modes accessible to acyl-immonium ion 10, a careful analysis of all reaction products was undertaken by high pressure liquid chromatography. The isolated products were found to be: 10% recovered enamide 6, 10% of the enamide dimer,[12] 40% of the desired lactam 11a, 20% of the 6,5-spirolactam 12a and 10% of a diastereoisomeric 6,5-spirolactam epi-12a. The structures of both 12a and epi-12a were

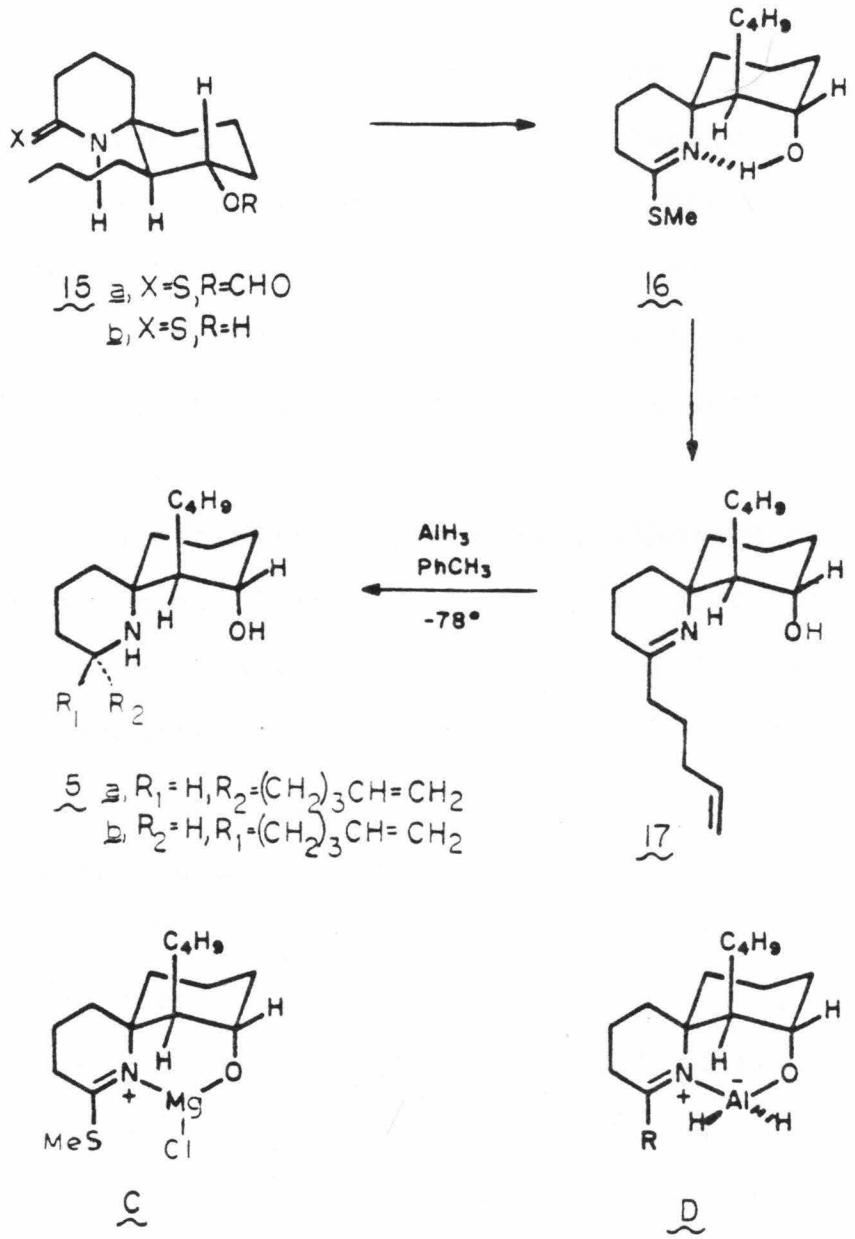
determined in the following manner. Jones oxidation of both 12b and epi-12b afforded the respective ketones 13 and epi-13 each of which was equilibrated (MeOH, MeONa) to a 1:1-mixture. The HPLC retention volumes of both 13 and epi-13 were different than those observed for the corresponding retention volumes of the two C_7-epimeric ketones derived from the 6,6-lactam 11b. Hence, neither 12 or epi-12 possessed the 6,6-azaspirane skeleton. Successive Baeyer-Villiger and chromate oxidation of 13 afforded keto lactam 14 which confirmed the presence of the 6,5-azaspirane skeleton in both 12 and epi-12. Within the error limits of ca. 5% it is



concluded that: (a) 6,6-spirocyclization is preferred over 5,5-spirocyclization by a ratio of 4:3; and (b) the observed diastereoselection in the 6,6-spirocyclization manifold to produce the desired Kishi lactam 11 (eq. 2 vs 3) is very large. During the course of this study Speckamp and co-workers disclosed a similar synthesis of 11a (23%) via the same strategy.[13a] It is noteworthy that these workers did not observe any of the alternate cyclization mode (e.g., 10 → 12) in their investigation, but this path becomes dominant in closely related analogs.[13b]

The elaboration of lactam 11a to the HTX skeleton is illustrated in Scheme III. Transformation of 11a to the crystalline hydroxy thioamide 15b was accomplished in 91% yield by successive treatment with phosphorus pentasulfide and sodium hydroxide. Subsequent methylation (MeI) afforded a quantitative yield of methylthioimidate 16 which existed predominantly, if not exclusively, in the depicted hydrogen bonded conformation as evidenced by both high dilution infrared and ^{1}H-NMR studies. Both of the above reactions were based upon analogous reactions executed by Kishi on 15 (X = O, R = $C(O)CH_3$).[5a,b] Pretreatment of hydroxy thioimidate 16 with anhydrous magnesium chloride (CH_2Cl_2) to form

Scheme III



15 a, X=S, R=CHO
b, X=S, R=H

16

5 a, R_1 = H, R_2 = $(CH_2)_3CH=CH_2$
b, R_2 = H, R_1 = $(CH_2)_3CH=CH_2$

17

C

D

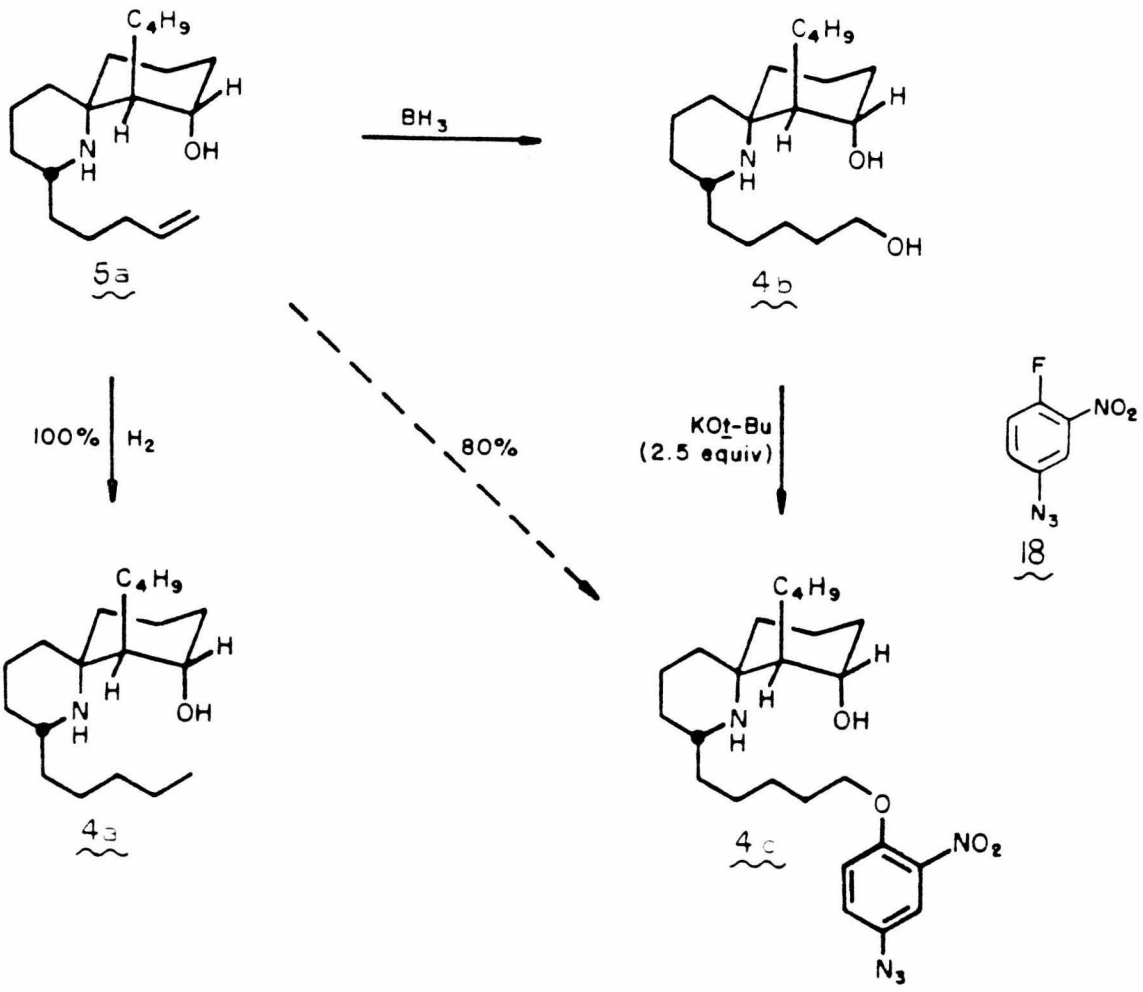
the presumed chelate C[14] followed by the addition of 4-pentenylmagnesium chloride afforded a 67% yield of the imine 17.[15] The success of this reaction was found to be critically dependent upon the preformation of the magnesium-imine complex in methylene chloride; direct treatment of 16 with an excess of the desired Grignard reagent lead only to apparent enolization. In our hands, the reported diisobutylaluminium hydride-promoted organolithium addition reactions were only marginally successful.[5a]

Based upon established precedent, aluminum hydride reduction of imine 17 in toluene (-70°C) proceeded stereoselectively to the desired HTX congener 5a along with minor amounts of the C_2-epimer 5b (5a:5b = 93:7).[5a,16] The structure of H_{10}-HTX (5a) was confirmed by catalytic hydrogenation (Pd-C, THF) to H_{12}-HTX (4a) in quantitative yield (Scheme IV). H_{12}-HTX prepared via this route proved to be identical in all respects [^{1}H-NMR, IR, mixed mp (HCl salt), HPLC, biological activity] to an authentic sample of (±) H_{12}-HTX provided to us by Professor Y. Kishi.[5a,b]

The elaboration of H_{10}-HTX (5a) to the photoaffinity labeled toxin congener 4c is illustrated in Scheme IV. Hydroboration ($BH_3 \cdot SMe_2$, CH_2Cl_2) of 5a with excess

reagent followed by basic peroxide treatment afforded the amino diol 4b. Treatment of 4b (THF) with 2.5 equiv of potassium tert-butoxide followed by one equiv of 4-fluoro-3-nitrophenylazide (18)[18] selectively formed the toxin-labeled phenoxy azide 4c in 80% yield (based upon H_{12}-HTX (5a) after purification by chromatography). It is presumed that this reaction proceeded via the bis-potassium alkoxide derived from 4b. The origin of the demonstrated greater reactivity of the primary alkoxide in this reaction was anticipated since the C_8-alkoxide could be stabilized via nitrogen chelation. In earlier abortive experiments designed to derivatize diol 4b with acid chloride-derived photoaffinity labels, it was found that acylation (PhC(O)Cl,2,6-lutidine) proceeded selectively at the C_8-hydroxyl function from which acyl transfer to the secondary amine was observed. This result is compatible with the normally observed nucleophilic enhancement of alcohols proximal to amine functions. The binding affinity of the photoaffinity-labeled toxin 4c, carried out on Torpedo californica electroplax membrane fragments by a competition assay, revealed that the presence of the phenoxyazide moiety on the C_5-terminus in 4c does not significantly alter toxin binding properties (for 5a, $K_I = 1 \cdot 10^{-6}$ M; for

Scheme IV



4c, $K_I = 5 \cdot 10^{-6}$ M).[17] Receptor polypeptide labeling studies will be reported in due course.

Grignard reagents were prepared from one equivalent of alkyl halide and one equivalent of magnesium in diethyl ether, decanted, and titrated.[19] All temperatures refer to the reaction itself.

(E)-Ethyl-4-nonenoate (7d). A solution of 1-hepten-3-ol (45.6 g, 0.4 mol), triethyl orthoacetate (453.6 g, 2.8 mol) and propionic acid (1.7 g, 24 mmol) was heated between 120-150°C for 1 h, until ethanol ceased to distill from the mixture. After removal of the remaining solvent by distillation under 1 atm, the crude product was distilled to afford 69.7 g (95%) of 7d as a colorless liquid, bp 83-86°C/2 mm Hg (lit.[20] 60°C/0.3 mm Hg). The distilled product was homogeneous by gas chromatography [5% FFAP (9 feet)/120°C]. ^{1}H-NMR ($CDCl_3$) δ 5.39 (m, 2H, =C-H), 4.10 (q, 2H, J = 6.1 Hz, -O-CH_2), 1.62-2.11 (m, 2H), 1.10-1.45 (m, 7H), 0.88 (t, 3H, J = 5.5 Hz, -CH_3); IR (neat) 2950, 2920, 1728, 1362, 1157, 962 cm^{-1}.

(E)-4-Nonen-1-ol (7c). Ester 7d (60.9 g, 0.33 mol) and lithium aluminum hydride (12.5 g, 0.33 mol) in diethyl ether (1.0 ℓ) were stirred for 14 h at 25°C under nitrogen. The reaction mixture was quenched by the slow addition of water (12.5 mL), sodium hydroxide (12.5 mL, 15% aqueous) and then water (37.5 mL). The white precipitate was removed by filtration, and the organic phase dried (Na_2SO_4). Filtration, removal of

the solvent *in vacuo*, and distillation afforded 42.0 g (90%) of 7c, bp 55°C/0.4 mm Hg (lit.[20] 83°C/0.3 mm Hg). ^{1}H-NMR ($CDCl_3$) δ 5.37 (m, 2H, =CH), 3.55 (t, 2H, J = 6.0 Hz, O-CH_2), 1.78-2.50 (m, 5H), 1.42-1.78 (m, 2H), 1.03-1.42 (m, 4H), 0.88 (t, 3H, J = 5.5 Hz, CH_3); IR (neat) 3360, 2950, 2920, 1045, 962 cm^{-1}.

(E)-1-Bromo-4-nonene (7b). Methanesulfonyl chloride (34.4 g, 0.3 mol) was added over 10 min to a magnetically stirred solution of alcohol 7c (39.0 g, 0.27 mol), triethylamine (40.4 g, 0.4 mol) and dichloromethane (1 ℓ) cooled to 0°C under nitrogen. The reaction mixture was stirred at 0°C for 45 min. The organic phase was washed with water (500 mL), saturated aqueous sodium bicarbonate (250 mL), saturated aqueous sodium chloride (250 mL), dried (Na_2SO_4), and filtered. Removal of the solvent *in vacuo* afforded the crude mesylate. ^{1}H-NMR ($CDCl_3$) δ 5.43 (m, 2H, =CH), 4.23 (t, 2H, -CH_2O), 3.00 (s, 3H, CH_3SO_2-), 0.87-2.00 (m, 13H, alkyl). IR (neat) 2920, 1460, 1350, 1171, 970, 928, 830, 733 cm^{-1}. The crude mesylate and lithium bromide (94.0 g, 1.08 mol) in acetone (500 mL) were stirred at 25°C for 14 h under nitrogen. The reaction was filtered, concentrated, and diluted with ether (500 mL). The ether layer was extracted with water (2 x 100 mL), dried (Na_2SO_4), and the solvent removed *in vacuo*. Distillation afforded 45.7 g (82%) as

a colorless oil, bp 93-95°C/10 mm Hg (lit.[20] 50°C/0.2 mm Hg). ^{1}H-NMR ($CDCl_3$) δ 5.08-5.65 (m, 2H, =C-H), 3.34 (t, 2H, J = 6.0 Hz, Br-CH_2), 1.65-2.21 (m, 6H), 1.02-1.45 (m, 4H), 0.70-0.95 (m, 3H).

Grignard addition of 7a to glutarimide in diethyl ether. Grignard reagent 7a was formed from 7b (11.52 g, 72 mmol) and magnesium turnings (1.92 g, 0.08 g-atom) in diethyl ether (100 mL) under nitrogen. In a separate flask glutarimide (6.78 g, 60 mmol) and methylmagnesium iodide (27.2 mL, 60 mmol) were heated at reflux in diethyl ether (100 mL) for 0.5 h. Grignard reagent 7a was added to the iodomagnesium salt of glutarimide and the entire mixture was heated at reflux for 0.5 h; the reaction mixture was cooled to 0°C, and quenched with saturated aqueous ammonium chloride (100 mL). The resultant suspension was filtered; the organic and aqueous layer separated; and the aqueous layer was extracted with chloroform (5 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvents removed in vacuo to give a mixture of 8 and 9 (1:1 by NMR). Chromatography (Waters Prep 500 chromatograph, Silica Gel, ethyl acetate, retention volumes: [9 (13.88 mL), 8 (15.06 mL)] afforded 8.95 g (62%) of a mixture of endocyclic and exocyclic enamides 6, ketoamide

8, and carbinolamide 9.

Ketoamide 8. Mp 90-91°C, ^{1}H-NMR ($CDCl_3$) δ 5.65 (bs, 2H, $-NH_2$), 5.24-5.30 (m, 2H, =CH), 1.40-2.56 (m, 14H, alkyl), 1.12-1.40 (m, 4H), 0.76-0.96 (m, 3H, $-CH_3$); IR (nujol) 3382, 3190, 2920, 1700, 1655, 1640, 960 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 210.6 (C_5), 174.7 (C_1), 131.5, 128.9 (C_9, C_{10}), 42.1, 41.4, 34.7, 32.2, 32.0, 31.7, 23.6, 19.6, 19.5, 14.0.

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53. Found: C, 69.94; H, 10.11.

Carbinolamide 9, ^{1}H-NMR ($CDCl_3$) δ 8.04 (bs, 1H, -NH), 5.10-5.57 (m, 2H, =CN), 2.83-0.69 (m, 22H); IR (neat) 3320, 3240, 3180, 2930, 1670, 1640, 1465, 970 cm^{-1}.

Endocyclic and exocyclic enamide 6. A mixture of ketoamide 8 and carbinolamide 9 (2.0 g, 8.4 mmol), toluene (50 mL), dimethylformamide (1 mL) and p-toluensulfonic acid (5 mg) were heated at reflux for 48 h under nitrogen. The mixture was concentrated, diluted with diethyl ether (50 mL), and extracted with saturated aqueous sodium bicarbonate (1 x 100 mL). The organic portion was dried ($MgSO_4$), evaporated in vacuo, and chromatographed (Silica Gel, 50% hexane/50% ethyl acetate) to yield enamide 6 (9:1 ratio by ^{1}H-NMR of endocyclic:exocyclic, 75%). Endocyclic enamide 6, ^{1}H-NMR ($CDCl_3$) δ 5.28-5.42 (m, 2H,

=CH), 4.68-4.86 (m, 1H, N-C=CH), 1.00-2.52 (m, 16H, alkyl), 0.78-1.00 (m, 3H, $-CH_3$); IR (neat) 3220, 3140, 3100, 2930, 1687, 1665, 1378, 1167, 966 cm^{-1}.

Anal. Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.90; H, 10.35; N, 6.30.

Exocyclic enamide 6. ^{1}H-NMR ($CDCl_3$) δ 7.48 (bs, 1H, -NH), 5.21-5.41 (m, 2H, =CH), 4.32 (t, 1H, J = 6.0 Hz, N-C=CH), 2.16-2.50 (m, 3H), 1.52-2.16 (m, 6H), 1.00-1.52 (m, 7H), 0.74-1.00 (m, 3H, $-CH_3$). IR (neat) 3220, 2960, 2930, 1682, 1665, 1380, 1182, 965 cm^{-1}.

Rel-(6S,7S,8S)-8-(7-butyl-1-azaspiro[5.5]undecane-2-one)formate (11a). i. From enamide 6. Enamide 6 (1.29 g, 5.8 mmol) was dissolved in anhydrous formic acid (60 mL) and stirred at 25°C for 32 h. The solvent was removed in vacuo, and the residue dissolved in toluene. Removal of the solvent in vacuo followed by chromatography [Waters Prep 500 chromatograph (Silica Gel, ethyl acetate)] afforded 0.70 g (40%) of 11a as a white crystalline solid, mp 148-149°C. ^{1}H-NMR ($CDCl_3$) δ 8.06 (s, 1H, O-CH), 6.89 (s, 1H, NH), 4.78-5.16 (m, 1H, -CHO-), 2.10-2.44 (m, 2H), 0.72-2.10 (m, 20H, alkyl); IR ($CHCl_3$) 3400, 2900, 1716, 1650, 1185 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 171.9 (C_2), 160.1 (formate), 73.9 (C_8), 58.5 (C_6), 50.7 (C_7), 36.1 (C_3), 32.2, 31.4, 29.5, 27.8, 26.7, 23.0, 18.5, 16.9, 13.9.

Anal. Calcd. for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43; N, 5.24. Found: C, 67.48; H, 9.16; N, 5.25.

ii. From glutarimide. Methylmagnesium bromide (26 mL, 2.9 M in ether) was added to a magnetically stirred solution of glutarimide (9.31 g, 82.3 mmol) in dichloromethane (1400 mL) under argon. A white precipitate formed and the reaction was heated to reflux for 30 min. The reaction mixture was cooled to 25°C, and the Z-4-nonenylmagnesium bromide 7a (90 mL, 1.2 M ether) was added. The reaction mixture was heated to reflux for 18 h, cooled to 0°C, and quenched with saturated aqueous ammonium chloride (520 mL). The resultant suspension was filtered, and the organic and aqueous layers separated. The aqueous phase was extracted with dichloromethane (4 x 250 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents removed in vacuo to give the carbinolamide 9 which was carried on without purification. Cyclization of 9 was carried out in anhydrous formic acid (850 mL) at 25°C for 48 h. The solvent was removed in vacuo, and the residue dissolved in toluene (500 mL). Removal of the solvent in vacuo and recrystallization (isopropyl ether) afforded 7.3 g (33%) of 11a as a white crystalline solid, mp 148-150°C.

Product analysis of formic acid cyclization of 6 or 9.

Chromatographic separation (Waters Prep 500 chromatograph, Silica Gel, ethyl acetate) of the formic acid cyclization products from enamide 6 or carbinolamide 9 afforded 11a (40%), 12a (20%), and epi-12a (10%). Observed retention volumes: [analytical HPLC, μ-Poracil (30 cm), ethyl acetate, 6 mL/min] 11a (14.3 mL), 12a (11.2 mL), epi-12a (13.1 mL). Compound 12a was isolated as a white crystalline solid, mp 118-120°C. IR ($CHCl_3$) 3190, 3040, 2958, 1708, 1650, 1180 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.05 (s, 1H, O=CH), 7.45 (s, 1H, NH), 5.13 (dd, 1H, J_1 = 5.4 Hz, J_2 = 10.8 Hz, -OCH-), 2.10-2.42 (m, 2H), 1.0-2.10 (m, 17H, alkyl), 0.70-1.00 (m, 3H, $-CH_3$); ^{13}C-NMR ($CDCl_3$) δ 172.0 (C_7), 160.3 (formate), 72.8 (C_{11}), 64.2 (C_5), 52.2 (C_1), 40.0 (C_8), 33.5, 31.3, 27.4, 26.7, 24.5, 22.4, 19.9, 17.8, 13.9.

Anal. Calcd. for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.43. Found: C, 67.27; H, 9.31.

Compound epi-12a was isolated as an oil. IR (neat) 3200, 3064, 2940, 1715, 1650, 1180 cm^{-1}.

Rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]-undecane-2-one (11b). Formate 11a (1.0 g, 3.75 mmol) was added to a magnetically stirred solution of sodium methoxide (270 mg, 5 mmol) and methanol (150 mL) under nitrogen. The solution was stirred at 25°C for 0.5 h.

The solvent was removed in vacuo and the residue was diluted with dichloromethane (250 mL). The organic portion was extracted with water (25 mL), dried (Na_2SO_4), filtered, and concentrated to give crude 11b as a white solid. Recrystallization (diethyl ether/ethyl acetate) gave 855 mg (95%) as a white, crystalline solid, mp 133-136°C (lit.[5a] 133-134°C). ^{1}H-NMR ($CDCl_3$) δ 8.60 (s, 1H, NH), 5.50-5.68 (m, 1H, OH), 4.00 (bs, 1H, O-CH), 2.03-2.32 (m, 2H, O=C-CH_2), 0.68-2.03 (m, 20H, alkyl); IR ($CHCl_3$) 3360, 2951, 1623, 1462, 970, 828, 658 cm^{-1}; ^{13}C-NMR ($CHCl_3$) δ 171.4 (C_2), 69.7 (C_8), 57.4 (C_6), 49.3 (C_7), 33.1 (C_3), 32.5, 31.1, 30.4, 28.4, 27.3, 22.9, 16.5, 16.0, 14.0.

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.35; H, 10.67; N, 5.57.

Rel-(6S,7S)-7-butyl-1-azaspiro[5.5]undecane-2,8-dione

A solution of 11b (70 mg, 0.29 mmol) and acetone (5 mL) was cooled to 0°C and Jone's reagent was added dropwise until the red color persisted. The reaction was quenched with 2-propanol, filtered, concentrated, diluted with dichloromethane (20 mL), extracted with saturated aqueous sodium bicarbonate (2 x 2 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a ketone (70 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ 7.19 (s, 1H, NH), 1.00-2.48 (m,

19H), 0.72-1.00 (m, 3H); IR (neat) 3200, 2950, 1720, 1650, 1400, 1038, 730 cm^{-1}; Anal. HPLC (μ-Poracil, 97% ethyl acetate/3% methanol, 6 mL/min); Retention volume 10.7 mL.

1-(1-Hydroxypentyl)-6-azaspiro[4.5]decane-7-one (12b). In a manner similar to the methanolysis of 11b, 12a (400 mg, 1.5 mmol) was converted to 12b (370 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ 6.45 (s, 1H, NH), 3.74 (bs, 1H, O-CH), 1.04-2.65 (m, 20H), 0.76-1.04 (m, 3H, $-CH_3$); IR (neat) 3360, 2950, 1640, 1460, 1400, 905, 730 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 172.2 (C_7), 69.6 (C_{11}), 64.7 (C_5), 54.6 (C_1), 40.1 (C_8), 37.2, 31.5, 28.2, 27.4, 22.7, 22.4, 20.3, 18.1. 14.0.

Epi-12b. In a manner similar to the methanoloysis of 11b, epi-12a (70 mg, 0.27 mmol) was converted to epi-12b (61 mg, 92%). IR (neat) 3200, 2940, 1650, 1450, 1400 cm^{-1}.

1-(1-Oxopentyl)-6-azaspiro[4.5]decane-7-one (13). Preformed Collins' reagent [CrO_3 (1.0 g, 10 mmol); pyridine (1.6 g, 20 mmol); CH_2Cl_2 (25 mL)] was employed to oxidize 12b (239 mg, 1.0 mmol) in dichloromethane (20 mL) for 15 min. The ketone was isolated by decantation of the reaction mixture, concentration, and dilution with ether (100 mL). This solution was filtered through

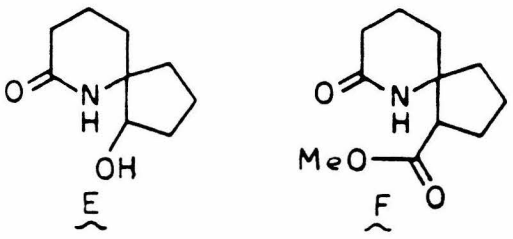
Florisil and the solvent removed *in vacuo* to yield 170 mg (72%) of ketone 13. ^{1}H-NMR ($CDCl_3$) δ 7.80 (s, 1H, NH), 2.98 (t, 1H, J = 8.1 Hz, O=C-CH), 2.03-2.54 [m, 4H, O=C-CH_2, O=C(N)-CH_2], 1.06-2.01 (m, 16H), 0.74-1.00 (m, 3H, -CH_3); IR (neat) 3200, 2945, 1697, 1650, 1400 cm^{-1}; Anal. HPLC (97% ethyl acetate/3% methanol, 6 mL/min); Retention volume 8.4 mL. After equilibration with base, two compounds were present in a 1:1 ratio with retention volumes of 8.4 mL and 8.6 mL.

Epi-13. In a similar manner to the oxidation of 11b, *epi*-12b (61 mg, 0.25 mmol) was oxidized to *epi*-13 (50 mg, 82%). IR (neat) 3320, 1700, 1650 cm^{-1}; Anal. HPLC (97% ethyl acetate/3% methanol, 6 mL/min); Retention volume 8.6 mL.

6-Azaspiro[4.5]decane-1.7-dione (14). i: Baeyer-Villager oxidation of 13 was done with trifluoroperacetic acid formed from hydrogen peroxide (0.8 mL, 90% aqueous) and trifluoroacetic anhydride (0.5 mL, 3.6 mmol) in dichloromethane (0.5 mL). The peracid was added to a magnetically stirred solution of the preceeding ketoamide (40 mg, 0.18 mol) and Na_2HPO_4 (300 mg) in dichloromethane (1.5 mL). The reaction mixture was stirred at 25°C for 2 h followed by refluxing for 2 h. The mixture was filtered, and the solid salts were washed with dichloro-

methane (20 mL). The organic portion was extracted with saturated aqueous sodium bicarbonate (1 x 3 mL), dried (Na_2SO_4), filtered, and concentrated. Chromatography (Silica Gel, diethyl ether) afforded 14 mg (31%) of a mixture of two esters. ^{1}H-NMR ($CDCl_3$) δ 6.48 (s, 1H, NH), 6.22 (s, 1H, NH), 4.98 (m, 1H, O-CH), 4.08 (t, 2H, J = 6.1 Hz, O-CH_2); IR (neat) 1726, 1732, 1652 cm^{-1}.

ii: In a manner similar to the methanolysis of 11a, the preceeding mixture of esters (14 mg, 0.055 mmol) were converted to alcohols. Recrystallization (pentane) afforded 4.9 mg of E as a semi-solid. IR ($CHCl_3$) 3260, 2958, 1646, cm^{-1}. 6.9 mg of F were recovered by concentration of



the pentane fraction. IR (neat) 3240, 1720, 1650, 1400, 800 cm^{-1}.

iii: Compound E (4 mg, 0.023 mmol) was heated to reflux with chromic acid on a polymer (100 mg, 0.25 mmol) in dichloromethane (2 mL) for 4 h. The reaction

mixture was filtered, and the solvent removed in vacuo to afford 3 mg (75%) of 14. IR ($CHCl_3$) 3380, 1718, 1650 cm^{-1}.

Exact mass calcd. for $C_9H_{13}NO_3$: 167.093. Found: 167.095.

Rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]-undecane-2-thione (15b).[5b] A magnetically stirred solution of amide 11a (1.0 g, 3.74 mmol) and phosphorous pentasulfide (0.69 g, 3.11 mmol) in benzene (95 mL) was heated at reflux for 1.5 h under argon. The reaction mixture was dissolved in dichloromethane (200 mL), extracted with saturated sodium bicarbonate (3 x 75 mL), dried ($MgSO_4$) and the solvent removed in vacuo to give 0.95 g of 15a as a yellow-orange oil. The oil was dissolved in methanol (95 mL), and sodium hydroxide (4.86 mmol, 1 N in water) was added. The solution was stirred at 25°C for 3 h. Acetic acid (1.6 mL) was added to the reaction mixture and the solvent removed in vacuo. The residue was dissolved in dichloromethane (200 mL) and extracted with saturated sodium bicarbonate (1 x 75 mL) and saturated sodium chloride (1 x 75 mL). The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo to give 15b as a yellow-orange solid. Recrystallization (toluene) gave 0.87 g (91%) of 15b as a white crystalline

solid, mp 157-159°C (lit.[5b] 166-168°C), ^{1}H-NMR ($CDCl_3$) δ 10.6 (br s, 1H, -NH-), 4.03 (br s, 1H, -CHO-), 3.73 (br s, 1H, -OH), 3.16-0.80 (m, 22H, alkyl); IR ($CHCl_3$) 3600, 3440-3100, 2960, 2880, 2860, 1540, 1520, 1460, 1160, 1090 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 199.7 (C_2), 69.9 (C_8), 60.7 (C_6), 49.2 (C_7), 38.5 (C_3), 32.9, 31.0, 30.8, 28.6, 27.1, 22.7, 16.7, 16.0, 13.7.

Anal. calcd. for $C_{14}H_{25}NO_5$: C, 65.83; H, 9.87; N, 5.48. Found: C, 65.45; H, 9.93; N, 5.32.

Rel-(6S,7S,8S)-7-butyl-8-hydroxy-1-azaspiro[5.5]-undecane-2-methylthioimidate (16). Methyl iodide (1.8 mL, 28.4 mmol) was added to a magnetically stirred solution of 15b (0.73 g, 2.84 mmol) in dichloromethane (23.0 mL) under argon. The solution was stirred at room temperature for 18 h, and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (200 mL) and extracted with saturated sodium bicarbonate (1 x 100 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed in vacuo to give 0.77 g (100%) of 16 as a light-yellow oil. ^{1}H-NMR ($CDCl_3$) δ 6.71 (d, 1H, J = 9.0 Hz, -OH), 3.97 (dm, 1H, J = 9.0 Hz, -CHO-), 2.27 (s, 3H, $-SCH_3$), 2.33-0.78 (m, 22H, alkyl); IR (neat) 3560-3060, 2940, 2860, 1625, 1450, 1420, 1130, 1070, 1020 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 164.3 (C_2), 70.3 (C_8), 61.7 (C_6), 49.6 (C_7), 39.1 (C_3), 33.3, 32.6, 30.7, 28.2,

27.2, 22.6, 16.0, 15.8, 13.6, 12.0.

Exact mass calcd. for $C_{15}H_{27}NO_5$: 269.1814. Found: 269.1835.

Rel-(6S,7S,8S)-7-butyl-8-hydroxy-2-(4-pentenyl)-1-azaspiro[5.5]undecane (17). 4-Pentenylmagnesium chloride (2.0 mL, 1.9 M in ether) was added to a magnetically stirred solution of thioimidate (16) (67.8 mg, 0.25 mmol) and anhydrous magnesium chloride (210.4 mg, 2.21 mmol) in dichloromethane (10 mL). The light-red solution was heated at reflux for 24 h under argon, cooled to 0°C, and saturated ammonium chloride (1 mL) was added. The slurry was filtered through Celite and the residue was washed with dichloromethane (50 mL). The organic phase was extracted with saturated sodium bicarbonate (1 x 25 mL). The aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and the solvent removed in vacuo to give a yellow oil. Flash chromatography[21] (Silica Gel, 97% toluene/2.8% 2-propanol/0.2% saturated aqueous ammonium hydroxide) gave 48.9 mg (67%) of 17 as a light yellow oil. ^{1}H-NMR ($CDCl_3$) δ 6.00-5.33 (m, 1H, -CH=C-), 5.10-4.82 (m, 2H, -C=CH_2), 3.93 (br s, 1H, -CHO-). 2.30-0.77 (m, 29H, alkyl); IR (neat) 3560-3060, 2960, 2860, 1660, 1630, 1450, 1260, 1020, 800 cm^{-1}.

Exact mass calcd. for $C_{19}H_{33}NO$: 291.2562. Found: 291.2594.

Rel-(2R,6S,7S,8S)-7-butyl-8-hydroxy-2-(4-pentenyl)-1-azaspiro[5.5]undecane (5a). A magnetically stirred solution of imine 17 (50.0 mg. 0.17 mmol) and toluene (8 mL) was cooled to -72°C under argon. Aluminum hydride[22] (5.4 mL, 0.16 M suspension in toluene) was added over 10 min, and the suspension was stirred for an additional 5 h at -72°C. The reaction was warmed slowly to 25°C and stirred for 14 h. The mixture was cooled to 0°C and quenched with saturated ammonium chloride (1.0 mL) over 15 min. The toluene was evaporated in vacuo and the residue diluted with ether (50 mL). The organic phase was washed with aqueous 1 N sodium hydroxide (25 mL), saturated sodium bicarbonate (25 mL), saturated sodium chloride (25 mL), dried (Na_2SO_4), and filtered. Removal of the solvent in vacuo afforded a 93:7 mixture of 5a:5b as analyzed by HPLC [Alumina (4 feet) column, $CHCl_3$, 1 mL/min]. Chromatography (Silica Gel, 90% chloroform/9.3% 2-propanol/0.7% saturated aqueous ammonium hydroxide) or recrystallization of the hydrochloride salt (diethyl ether/isopropanol) gave 35.8 mg (71%) of 5a as a colorless oil, mp (hydrochloride salt) 168-169.5°C. ^{1}H-NMR ($CDCl_3$) δ 6.03-5.53 (m, 1H, -CH=C-), 5.08-4.82 (m, 2H, -C=CH_2), 3.87 (bs, 1H, -CHO-), 3.07-2.73 (m, 1H, -CHN), 2.30-0.80 (m, 30H, alkyl);

IR (neat) 3560-3100, 3080, 2930, 2860, 1640, 1445, 1130, 910 cm^{-1}.

Exact mass calcd. for $C_{19}H_{35}NO$: 293.2718. Found: 293.2717.

Rel-(2R,6S,7S,8S)-7-butyl-8-hydroxy-2-pentyl-1-azaspiro-[5.5]undecane (4a). Olefin 5a (33.0 mg, 0.11 mmol) was dissolved in tetrahydrofuran (8.3 mL) containing 5% Pd/C (82.5 mg) and was reduced with hydrogen at atmospheric pressure for 4 h. The slurry was filtered through Celite and the residue washed with ether (20 mL). Removal of the solvents in vacuo gave 33.0 mg (100%) of 4a as a colorless oil, mp (hydrochloride salt) 158-160°C (lit.[5a] 159-161°C). ^{1}H-NMR ($CDCl_3$) δ 3.89 (br s, 1H, -CHO-), 2.89-2.52 (m, 1H, -CHN-), 2.33-0.70 (m, 35H, alkyl); IR ($CHCl_3$) 2930, 2860, 1460, 1450 cm^{-1}; mixed mp 158-160°C.

Exact mass calcd. for $C_{19}H_{37}NO$: 295.2875. Found: 295.2878.

Anal. (hydrochloride salt) Calcd. for $C_{19}H_{38}ClON$: C, 68.74; H, 11.54; N, 4.22. Found: C, 68.54; H, 11.31; N, 3.90.

Rel-(2R,6S,7S,8S)-7-butyl-8-hydroxy-2-(5-hydroxy-pentyl)-1-azaspiro[5.5]undecane (4b). Borane methyl sulfide (0.35 mmol, 9.3 M) was added to a magnetically stirred solution of 5a (20.7 mg, 0.071 mmol) and dichloromethane (2.0 mL) under

argon. The solution was stirred at room temperature for 5 h. Sulfuric acid (0.25 mL, 10% in water) was added slowly and the reaction mixture was stirred at room temperature for 1 h. Sodium hydroxide (0.75 mL, 15% in water) was added followed by hydrogen peroxide (0.50 mL, 30% in water). The solution was stirred for 13 h at room temperature and was diluted with ether (40 mL). The organic phase was extracted with sodium tartrate (3 x 20 mL, 10% in water) and saturated sodium chloride (1 x 20 mL). The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo to give 4a as a colorless oil homogeneous by TLC (Silica Gel, 90% chloroform/9.3% 2-propanol/0.7% saturated aqueous ammonium hydroxide). Streaking normally accompanied chromatography under these conditions which resulted in loss of material. Normally the crude 4b was carried directly on to the next experiment. ^{1}H-NMR ($CDCl_3$) δ 3.88 (br s, 1H, -CHO-), 3.60 (br t, 2H, $-CH_2O-$), 3.13-2.58 (m, 1H, -CHN-), 2.32-0.77 (m, 33H, alkyl); IR ($CHCl_3$) 3620, 3500-3010, 2930, 2860, 1445 cm^{-1}.

Exact mass Calcd. for $C_{19}H_{37}NO_2$: 311.2824. Found: 311.2805.

Rel-(2R,6S,7S,8S)-7-butyl-8-hydroxy-2-[5-(2-nitro-4-azidophenoxy)pentyl]-1-azaspiro[5.5]undecane (4c). Potassium-t-butoxide (12.6 mg, 0.112 mmol) was added to a magnetically stirred solution of 4b (14.0 mg, 0.045 mmol) and

tetrahydrofuran (2.0 mL) in a flask wrapped in aluminum foil under nitrogen. The solution turned yellow as the potassium alkoxides formed. 4-Fluoro-3-nitro phenylazide (8.2 mg, 0.045 mmol) was added, and the solution was stirred at room temperature for 14 h. A reddish-brown precipitate formed. The reaction was diluted with ether (35 mL) and extracted with water (2 x 20 mL) and saturated sodium chloride (1 x 20 mL). The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo to give a yellow oil. Chromatography (Silica Gel, chloroform followed by 90% chloroform/9.3% 2-propanol/0.7% saturated aqueous ammonium hydroxide) gave 17.0 mg of 4c (80%) based on olefin 5a. ^{1}H-NMR ($CDCl_3$) δ 7.48-6.97 (m, 3H, aromatic), 4.05 (t, 2H, J = 6.5 Hz, $-CH_2O-$) 3.87 (br s, 1H, -CHO-), 3.07-2.67 (m, 1H, -CHN-), 2.37-0.73 (m, 32H, alkyl); IR ($CHCl_3$) 2940, 2860, 2120, 1525, 1490, 1406, 1350 cm^{-1}.

Exact mass Calcd. for $C_{25}H_{39}N_5O_4$: 473.3001. Found: 473.2983.

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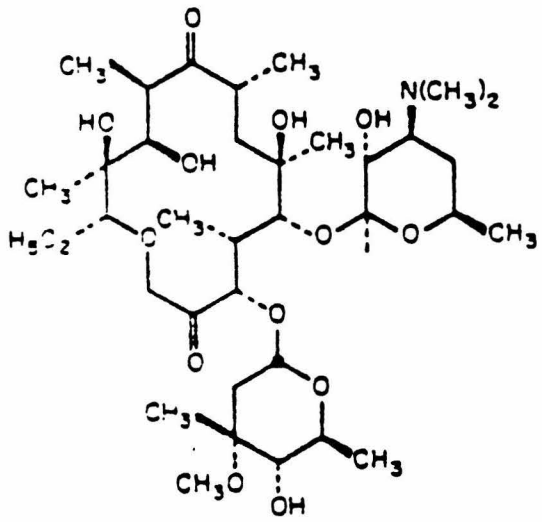
22. A solution of aluminum hydride in ether was prepared by method 2 of E. C. Ashby, J. R. Sanders, P. Claudy, and R. Schwartz, J. Am. Chem. Soc., 95, 6485 (1973). To prepare a suspension in toluene the ether was removed in vacuo and the resultant white solid (caution-pyrophoric) placed under high vacuum for 15 h. Toluene was then added with stirring under argon.

CHAPTER II

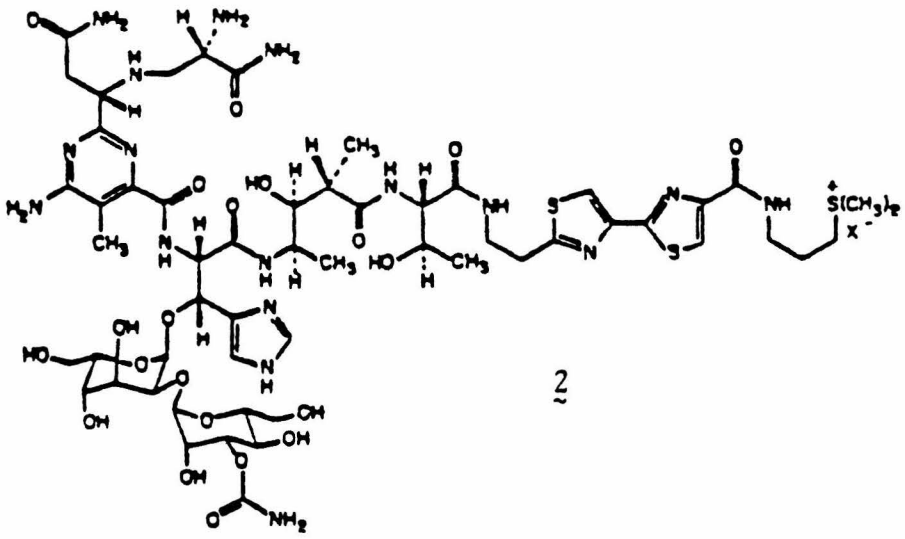
Erythro-Aldol Products *Via* 3-Acyl-oxazolidine-2-ones

Introduction

The aldol condensation is a reaction of fundamental importance in biosynthesis. For example this reaction is employed in an iterative sequence in both erythromycin-A (1) and bleomycin (2) biosynthesis. In the aldol bond



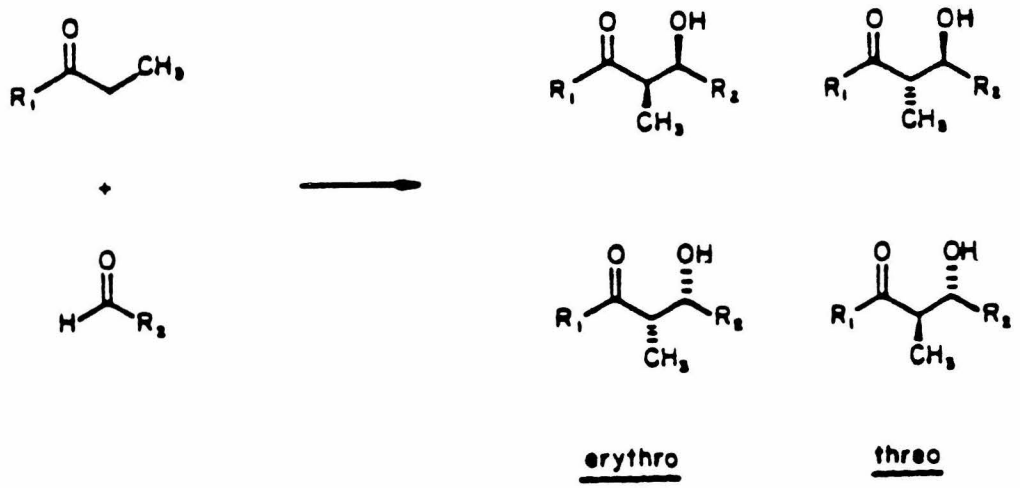
1



2

construction two new centers of asymmetry are created; hence four stereoisomeric products are possible (Scheme I), two erythro and two threo diastereomers. The first problem in controlling the stereochemical outcome of this reaction focusses on the formation of either an erythro

Scheme I



or threo diastereomer preferentially. The second problem focuses on preparation of either diasteromer in an optically active form.

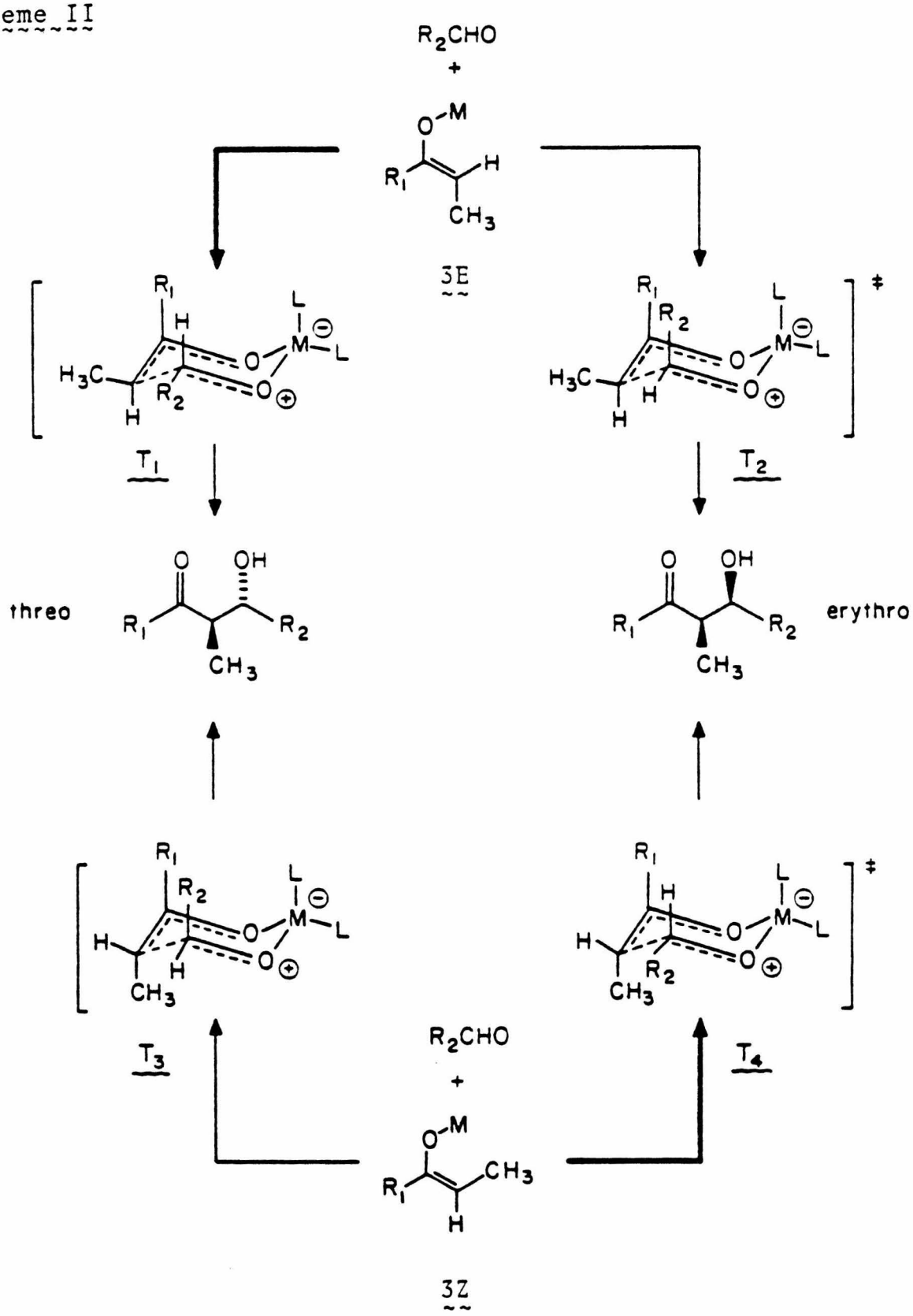
It is now well appreciated that kinetic aldol stereoselection is, in part, defined by enolate geometry for

those condensations wherein two new stereocenters are created in the condensation step (Scheme II).[1,2] Given the reasonable postulate that the reaction proceeds *via* a pericyclic process,[1a,2a] the influence of variable steric parameters can be analyzed to determine their effects upon the relative heats of formation of diastereomeric transition states from an enolate of defined geometry. For example, for a ($\underset{\sim}{3}$E)-enolate the transition state T_2 can be destabilized relative to T_1 by maximizing both $R_2 \leftrightarrow R_1$ and $R_2 \leftrightarrow L$ steric parameters. When these parameters are maximized, ($\underset{\sim}{3}$E)-enolates will lead to *threo* aldol products and ($\underset{\sim}{3}$Z)-enolates will lead to *erythro* aldol products.[3]

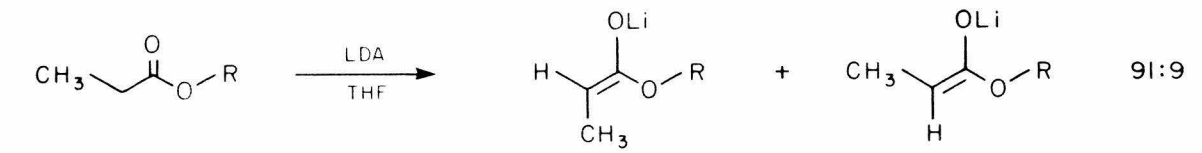
Enolate geometries for representative carboxylic acid derivatives are shown in Scheme III. Enolates derived from esters,[4] oxazolidines,[5] and thioesters[3a] could lead to *threo* aldol products whereas enolates derived from amides[6] and thioesters[7] could lead to *erythro* aldol products. It should be pointed out that lithium enolates of discrete geometry do not necessarily translate to good aldol product stereoselection, whereas boron enolate geometry translates directly to *erythro* and *threo* aldol product ratios.[3]

One potential use of the derived β-hydroxy acid derivatives is for the stereoselective synthesis of the

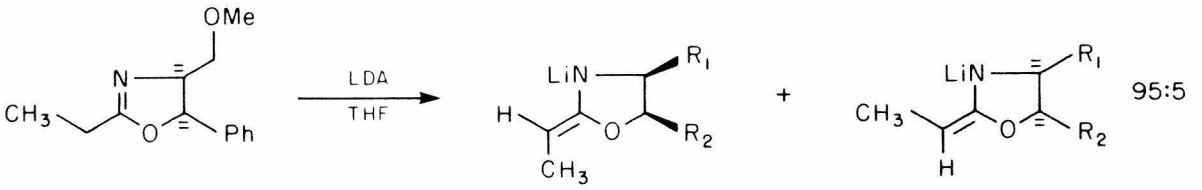
Scheme II



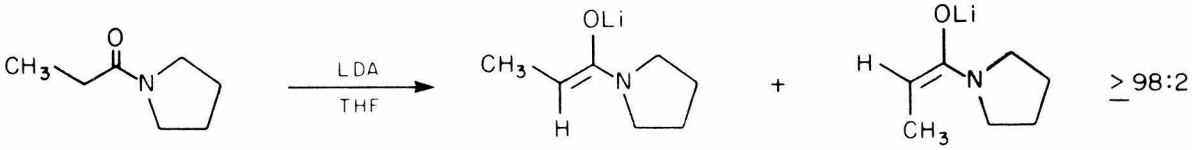
Scheme III



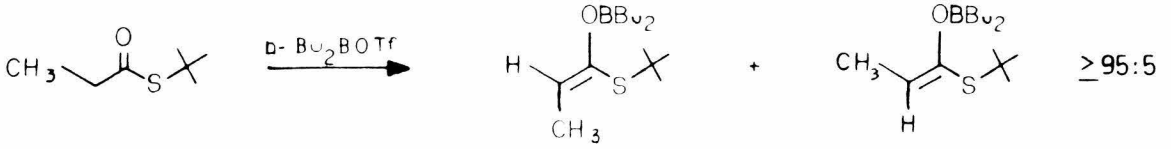
Ireland[4]



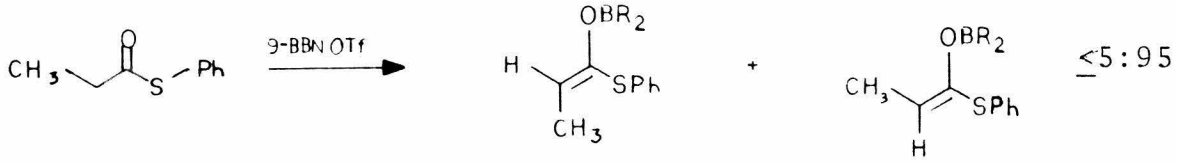
Meyers, Newcomb[5]



Evans[6]



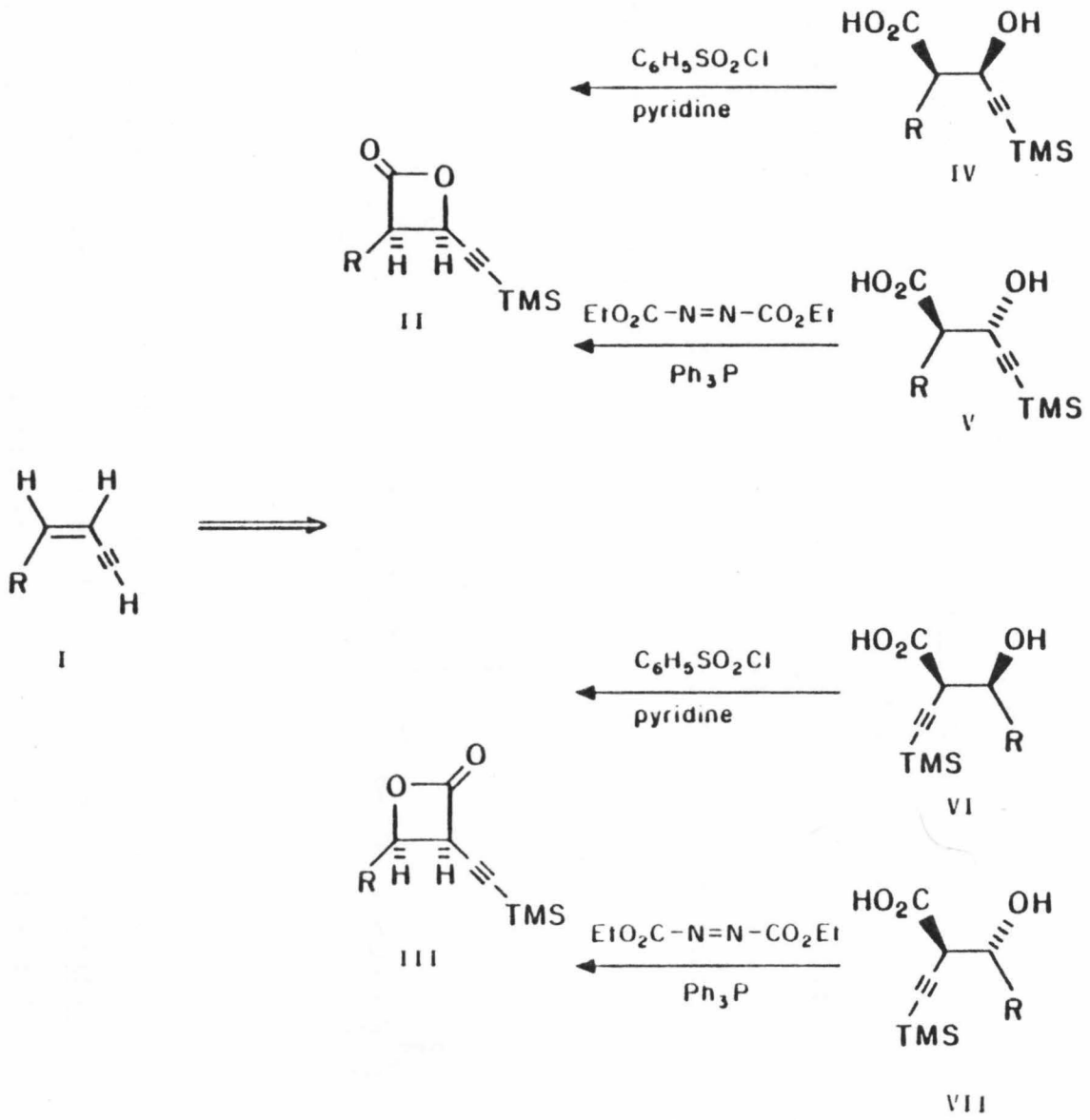
Evans[3a]



Masamune[7]

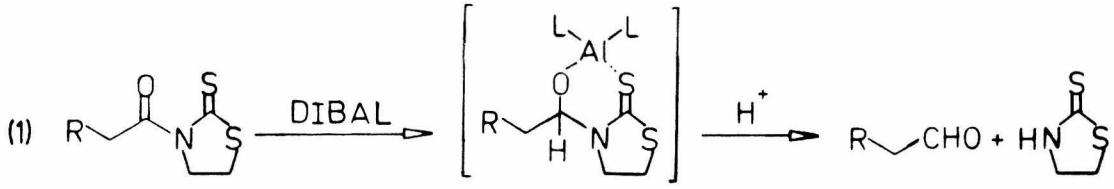
cis-enyne functionality found in histrionicotoxin (Scheme IV). Adam has demonstrated the utility of β-lactones as precursors for stereoselective olefin synthesis.[8] In principle there are two β-lactone regioisomers II and III, which could suffice for the preparation of the enyne I. Either threo or erythro β-hydroxy acids can serve as precursors of the desired β-lactone II. Treatment of the erythro β-hydroxy acid IV with benzenesulfonyl chloride and pyridine should lead to II. The conversion of the threo acid V to the β-lactone II requires an inversion at the alcohol center. This inversion can be accomplished by use of triphenylphosphine and diethyldiazodicarboxylate.[9] Therefore, the stereoselective synthesis of either an erythro or threo -hydroxy acid should provide for the synthesis of I. We decided to concentrate our efforts on the stereoselective synthesis of either IV or V because of the anticipated lability of VI or VII. We reasoned that compounds VI and VII might readily eliminate the elements of water due to the acidic nature of the proton alpha to the carboxyl group.

Scheme IV


HO2C
OH
C6H5SO2Cl
pyridine
R
TMS
IV
O
O
R
H
H
TMS
II
EtO2C-N=N-CO2Et
Ph3P
V
H
H
R
H
I
HO2C
OH
C6H5SO2Cl
pyridine
TMS
R
VI
O
O
R
H
H
TMS
III
EtO2C-N=N-CO2Et
Ph3P
VII

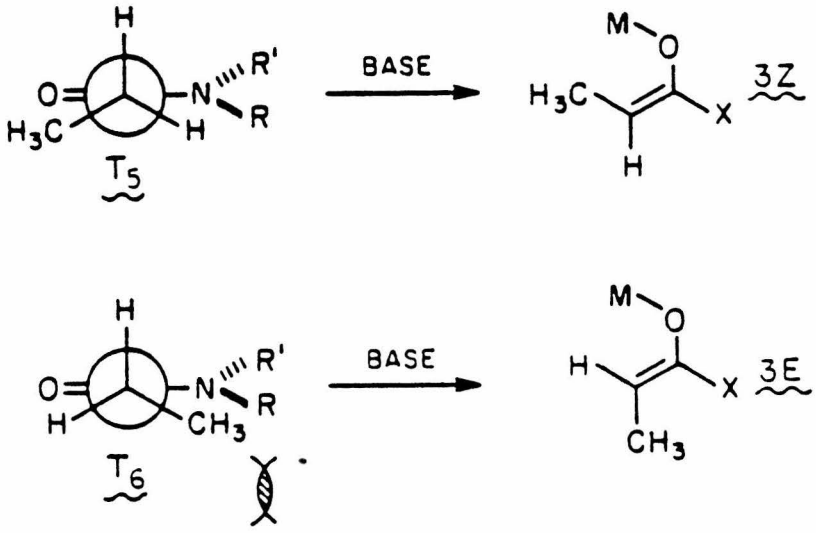
Results and Discussion

3-Acyl-thiazolidine-2-ones have been shown to react readily with nucleophiles to form acid derivatives.[10] Mukaiyama has shown that 3-acyl-thiazolidine-2-ones may also serve as aldehyde precursors through reduction with diisobutylaluminum hydride.[11] Chelation serves to stabilize the tetrahedral intermediate to prevent further reduction (equation 1).



Imide derivatives may also serve for the stereoselective synthesis of (3Z)-enolates, leading to erythro-aldol adducts. The transition state leading to the (3E)-enolate (Scheme V), T_6, would be destabilized relative to the transition state leading to the (3Z)-enolate, T_5, due to A-strain.[12] This is exemplified by the deprotonation of pyrrolidino propionamide to afford a $\geq$98:2 ratio of 3Z:3E enolates as mentioned previously. Therefore, imide derivatives should serve as precursors for

Scheme V



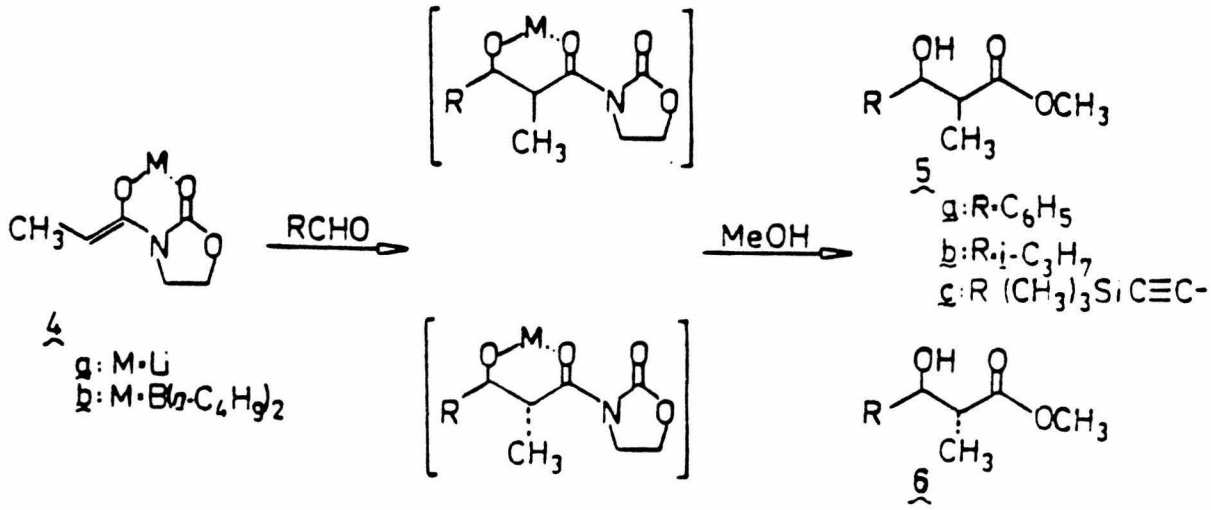
erythro-β-hydroxy acids as well as serving for the synthesis of erythro-β-hydroxy aldehydes, ketones, and other carboxylic acid derivatives.

Attempted deprotonation of 3-propionyl-thiazolidine-2-one leads to the elimination of 2-thiazolidone, and formation of products derived from a ketene intermediate. However, deprotonation of 3-propionyl-oxazolidine-2-one with lithium diisopropylamide (tetrahydrofuran, -78°C)

afforded a stable lithium enolate. Reaction of the lithium enolate 4a with benzaldehyde (tetrahydrofuran, -78°C, 15 sec) followed by quenching of the reaction mixture with methanol afforded β-hydroxy esters directly. Analysis of the reaction mixture by ^{1}H-NMR, erythro: δ 5.02 (d, 1H, J = 4.5 Hz, -CHO-); threo : δ 4.72 (d, 1H, J = 8.5 Hz, -CHO-)[13] indicated that a 45:55 mixture of erythro (5a)- and threo (6a)-β-hydroxy esters had been formed (Scheme VI).

The boron enolate 4b is formed upon treatment of a dichloromethane solution of 3-propionyl-oxoazolidine-2-one with di-n-butylboron triflate[14] and diisopropylethylamine at -78°C. The aldehyde is added and the mixture is allowed to stir at -78°C for 0.5 h and is then warmed to 25°C over 1 h. Under these conditions the aldol product should be the result of complete kinetic stereoselection.[3] Methanolysis of the aldol product readily occurs in the heterogeneous medium of sodium methoxide and dichloromethane. We attribute the ease of methanolysis to activation of the propionyl carbonyl by complexation. No attack of methoxide at the oxazolidine carbonyl is observed. The resultant boron chelate is oxidized with hydrogen peroxide to provide the erythro-β-hydroxy ester 5. It should be noted that the reaction

Scheme VI



sequence is performed in one pot, and that all the by-products are removed by an extractive work-up. The only product isolated, as determined by ^{1}H-NMR is a β-hydroxy ester.

Reaction of 4b with benzaldehyde affords, after methanolysis, the erythro-β-hydroxy ester 5a as determined

by ^{1}H-NMR,[13] δ 5.06 (d, 1H, J = 4.0 Hz, -CHO-). Replacing benzaldehyde as the electrophilic partner with isobutyraldehyde or trimethylsilylpropynal[15] affords only erythro-β-hydroxy esters (vide infra) in 57% and 61% yields respectively (Table I).

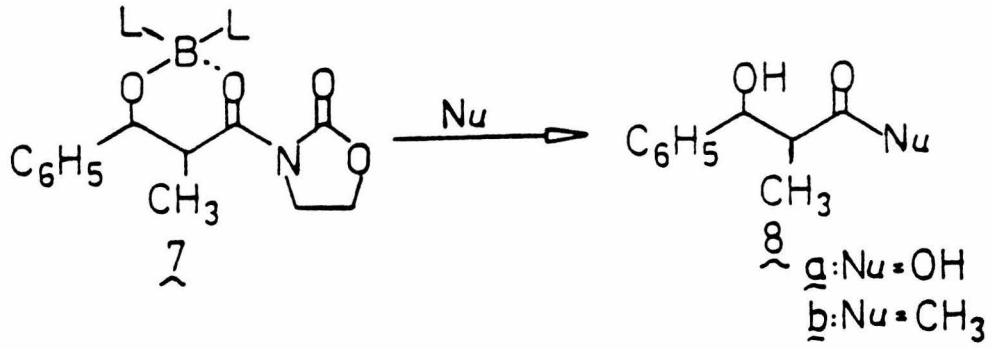
Table I. Aldol condensation which leads to β-hydroxy esters.

Aldehyde	Metal, M	Ratio Erythro-Threo	Yield, %
C_6H_5CHO	Li	45:55	72
	$B(n\text{-}C_4H_9)_2$	>95:<5	58
$i\text{-}C_3H_7CHO$	$B(n\text{-}C_4H_9)_2$	>95:<5	57
$(CH_3)Si\text{-}C\equiv C\text{-}CHO$	$B(n\text{-}C_4H_9)_2$	>95:<5	61

The intermediate boron aldol alkoxide 7 may also be converted smoothly, with aqueous sodium hydroxide, to an erythro-β-hydroxy acid (Scheme VII). This approach eliminates the need for oxidative removal of the boron residue, $(n\text{-}C_4H_9)_2BOH$, for it is easily extracted from the water soluble carboxylate salt.

The intermediate boron alkoxide 7 may also be transformed into ketones as demonstrated by the reaction of 7 with methylmagnesium bromide. This reaction affords

Scheme VII



the erythro-β-hydroxy ketone 8b in 65% yield. In this example the ketone formed (8b) is obtained from a kinetic enolate and aldol condensation, but the product is that expected from thermodynamic enolization. This is the first example of such an erythro aldol product. The utility of the aldol condensation with 3-propionyl-oxazolidine-2-one is summarized in Table II utilizing benzyaldehyde as the electrophilic component.

Attempted deprotonation of 3-acyl-oxazolidine-2-ones, where the alkyl group in the acyl portion becomes large, results in elimination of 2-oxazolidone, and formation

Table II. Reactions of 6 with various nucleophiles.

Nucleophile	Ratio Erythro:Threo	Yield, %
$NaOCH_3$	>95:<5	58
NaOH	>95:<5	78
CH_3MgBr	>95:<5	65

of products derived from a ketene intermediate. Investigation of other imide derivatives which will not eliminate as readily is being actively pursued.

Conclusions

The boron enolate derived from 3-propionyl-oxazolidine-2-one undergoes the aldol condensation with a variety of aldehydes to give erythro-aldol products. These aldol products can be converted to either β-hydroxy acids, esters or ketones. Investigation of the asymmetric induction obtained from the aldol condensation and alkylation of imides derived from chiral 2-oxazolidines which can be prepared from chiral amino alcohols is currently being pursued.

Experimental Section

Infrared spectra were recorded on a Beckman 4210 spectrophotometer. ^{1}H magnetic resonance spectra were recorded on Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), integration, coupling constant (Hz), and interpretation. ^{13}C magnetic resonance spectra were recorded on a JEOL FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. Mass spectra were recorded on a Kratos MS-9 spectrometer. Data are reported as follows: mass, elemental composition, and percent intensity. Mass spectral analyses were performed by University of California, Los Angeles, Mass Spectrometry Laboratory. Combustion analyses were performed by California Institute of Technology Microanalytical Laoboratory.

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran was distilled from benzophenone ketyl. Methanol was distilled from magnesium. Dichloromethane was dried by passing through a column of activity I aluminum oxide. Diisopropylethylamine and diisopropyl-

amine were distilled from calcium hydride. n-Butyllithium was titrated by the procedure of Watson and Eastham.[16] All reaction temperatures refer to the reaction itself.

3-Propionyl-oxazolidine-2-one. A magnetically stirred solution of 2-oxazolidone (3.48 g, 0.044 mol) and dry tetrahydrofuran (150 mL) was cooled to 0°C under nitrogen. n-Butyllithium (0.044 mol, 1.6 M in hexane) was added dropwise as a white precipitate formed. After stirring at 0°C for 30 min propionic anhydride (5.64 mL, 0.044 mol) in tetrahydrofuran (50 mL) was added dropwise over 20 min. The mixture was stirred at 25°C for 1 h and diluted with dichloromethane (500 mL). The solution was washed with water (3 x 250 mL), saturated sodium chloride (1 x 250 mL) and dried (Na_2SO_4). After filtration, removal of the solvent and recrystallization from hexane/ether there was obtained 5.4 g (94%) of 3-propionyl-oxazolidine-2-one as white needles, mp 80-82°C. IR ($CHCl_3$) 3020, 2980, 2920, 1780, 1700, 1480, 1385, 1260, 1230, 1210 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.48-3.87 (m, 4H, $-NCH_2CH_2O-$), 2.89 (q, 2H, J = 7 Hz, $-CH_2CO-$), 1.16 (t, 3H, J = 7 Hz, CH_3-).

Anal. calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.50; H, 6.26; N, 9.82.

Aldol condensation of 4a. To a solution of 1.1 mmol of lithium diisopropylamide in 3 mL of anhydrous THF,

prepared by the addition of 0.746 mL of 1.50 N n-BuLi to a solution of 0.111 g (1.1 mmol) of diisopropylamine in 3 mL of THF, cooled at dry ice temperatures under argon was added 0.143 g (1 mmol) of 3-propionyl-oxazolidine-2-one in 2 mL of THF over a period of 5 min. The resulting pale yellow suspension was allowed to stir for 15 min at -72°C and 0.106 g (1 mmol) of benzaldehyde was then added in one portion. The suspension immediately gave way to a yellow solution which was quenched by the addition of 0.2 mL of dry methanol after 15 sec. The cooling bath was removed and the solution was warmed to room temperature. The mixture was cast into CH_2Cl_2 (50 mL), washed with water (50 mL), and dried (Na_2SO_4). Concentration in vacuo provided 0.179 g (72%) of a mixture of erythro and threo β-hydroxy esters 5 and 6 (45:55) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) erythro δ 7.33 (s, 5H, phenyl), 5.02 (d, 1H, J = 4.5 Hz, -CHO-), 3.62 (s, 3H, $-OCH_3$), 3.2-2.6 (m, 1H, $-CHCO_2CH_3$), 1.13 (d, 3H, J = 7.2 Hz, $-CHCH_3$); threo δ 7.33 (s, 5H, phenyl), 4.72 (d, 1H, J = 8.5 Hz, -CHO), 3.70 (s, 3H, $-OCH_3$), 3.2-2.6 (m, 1H, $-CHCO_2CH_3$), 1.02 (d, 3H, J = 7.2 Hz, $-CHCH_3$).

General procedure for the synthesis of 5. A magnetically stirred solution of 3-propionyl-oxazolidine-2-one (0.143 g, 1.0 mmol) and dichloromethane (3.0 mL) was cooled to -72°C under nitrogen. Di-n-butylboron triflate (0.37 mL, 1.1 mmol)[14] was added via syringe followed

by diisopropylethylamine (0.21 mL, 1.2 mmol). The solution was stirred at -72°C for 2 h and the aldehyde (1.0-1.2 mmol) was added in dichloromethane (1.0 mL) *via* syringe in one portion. The solution was stirred at -72°C for 0.5 h and at 25°C for 1 h. Methanol (0.41 mL, 10.0 mmol) was added followed by sodium methoxide (0.189 g, 3.5 mmol), and the mixture was stirred at 25°C for 1 h. The mixture was cooled to 0°C. Methanol (3 mL) and pH 7 buffer (1 mL) was added followed by hydrogen peroxide (1 mL, 30% aqueous). The solution was stirred for 15 min at 0°C followed by removal of the methanol *in vacuo*. The residue was dissolved in ether (60 mL) and washed with sodium hydroxide (3 x 30 mL, 1 N aqueous) and saturated sodium chloride (1 x 30 mL). The organic phase was dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to afford pure 5.

Erythro-methyl-2-methyl-3-hydroxy-phenyl propionate (5a). The title compound was prepared in accordance with the prescribed procedure from 1.0 mmol of 3-propionyl-oxazolidine-2-one and 1.0 mmol of benzaldehyde. The desired *erythro*-β-hydroxy ester 5a, 0.125 g (58%), was obtained as a light yellow oil homogeneous by ^{1}H-NMR. IR ($CHCl_3$) 3600, 3520-3440, 3010, 1715, 1450, 1435, 1190, 1055, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.32 (bs, 5H, phenyl),

5.06 (d, 1H, J = 4.0 Hz, -OCH-), 3.63 (s, 3H, $-OCH_3$), 3.06 (bs, 1H, -OH), 2.87-2.63 (dq, 1H, J = 4.0 Hz, J = 7.5 Hz, $-CHCO_2CH_3$), 1.12 (d, 3H, J = 7.5 Hz, $-CHCH_3$); mass spectrum (70 eV) m/e: 194.0955 (M^+, calcd. 194.0943, 2), 106.0412 ($M^+ - C_4H_8O_2$, 90), 105.0335 ($M^+ - C_4H_9O_2$, 96), 77.0303 ($M^+ - C_5H_9O_3$, 100).

Erythro-methyl-2,4-dimethyl-3-hydroxy-pentanoate (5b). The title compound was prepared in accordance with the prescribed procedure from 1.0 mmol of 3-propionyl-oxazolidine-2-one and 1.2 mmol of isobutyraldehyde. The desired erythro-β-hydroxy ester 5b, 0.091 g (57%), was obtained as a light yellow oil homogeneous by ^{1}H-NMR. IR ($CHCl_3$) 3640-3440, 2960, 2880, 1715, 1455, 1435, 1195, 1045, 975 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.68 (s, 3H, $-OCH_3$), 3.53 (dd, 1H, J = 4.0 Hz, J = 6.5 Hz, -OCH-), 2.85-2.49 (m, 2H, -OH, $-CHCO_2CH_3$), 1.83-1.40 [m, 1H, $-CH(CH_3)_2$], 1.16 (d, 3H, J = 7.0 Hz), 0.99 (d, 3H, J = 6.5 Hz); mass spectrum (70 eV) m/e: 145.0881 ($M^+ - CH_3$, calcd. 145.0865, 3), 117.0547 ($M^+ - C_3H_7$, 42), 88.0529 ($M^+ - C_3H_8O$, 100), 85.0298 ($M^+ - C_4H_{11}O$, 65).

Erythro-methyl-2-methyl-3-hydroxy-5-trimethylsilyl-4-pentynoate (5c). The title compound was prepared in accordance with the prescribed procedure from 1.0 mmol of 3-propionyl-oxazolidine-2-one and 1.1 mmol of tri-

methylsilylpropynal.[15] The desired erythro-β-hydroxy ester 5c, 0.130 g (61%), was obtained as a light yellow oil homogeneous by ^{1}H-NMR. IR ($CHCl_3$) 3620-3280, 2960, 2180, 1725, 1505, 1450, 1430, 1250, 1025, 845 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.60 (d, 1H, J = 5.0 Hz, -OCH-), 3.70 (s, 3H, $-OCH_3$), 2.91-2.57 (dq, 1H, J = 5.0 Hz, J = 8.0 Hz, $-CHCO_2CH_3$), 1.29 (d, 3H, J = 8.0 Hz, $-CHCH_3$), 0.17 [s, 9H, $-Si(CH_3)_3$]; mass spectrum (70 eV) m/e: 199.0799 ($M^+ - CH_3$, calcd. 199.0791, 6), 111.0268 ($M^+ - C_5H_{11}O_2$, 48), 88.0525 ($M^+ - C_6H_{10}OSi$, 100), 83.0307 ($M^+ - C_6H_{11}O_3$, 42), 77.0223 ($M^+ - C_8H_{13}Si$, 76).

Erythro-3-methyl-3-hydroxy-phenylpropionic acid (8a). A magnetically stirred solution of 3-propionyl-oxazolidine-2-one (0.143 g, 1.0 mmol) and dichloromethane (3.0 mL) was cooled to 0°C under nitrogen. Di-n-butylboron triflate (0.27 mL, 1.1 mmol)[14] was added via syringe followed by diisopropylethylamine (0.21 mL, 1.2 mmol). The solution was stirred at 0°C for 15 min followed by 2 h at 25°C. The solution was cooled to 0°C and benzaldehyde (0.10 mL, 1.0 mmol) in dichloromethane (1.0 mL) was added via syringe in one portion. The solution was stirred at 0°C for 0.5 h followed by 1 h at 25°C. Sodium hydroxide (4.0 mmol, 1.0 N in water) was added, and the reaction mixture stirred at 25°C for 1 h. The mixture was diluted with

saturated sodium bicarbonate (25 mL) and extracted with ether (3 x 15 mL). The aqueous layer was cooled to 0°C and carefully acidified to pH 2.5 with concentrated hydrochloric acid. The aqueous layer was then saturated with sodium chloride and extracted with ethyl acetate (4 x 15 mL). The combined ethyl acetate extracts were washed with saturated sodium chloride (1 x 30 mL) and dried (Na_2SO_4). After filtration removal of the solvent *in vacuo* gave 0.140 g (78%) of **8a** as a light yellow oil. IR ($CHCl_3$) 3600-2800, 1710, 1205, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.27 (bs, 5H, phenyl), 7.03 (bs, 2H, -OH), 5.12 (d, 1H, J = 3.0 Hz, -CHO-), 2.93-2.63 (dq, 1H, J = 3.0 Hz, J = 6.5 Hz, $-CHCO_2-$), 1.07 (d, 3H, J = 6.5 Hz, $-CH_3$); mass spectrum (70 eV) *m/e*: 180.0791 (M^+, calcd. 180.0786, 4), 107.0503 ($M^+ - C_3H_5O_2$, 100), 79.0532 ($M^+ - C_4H_5O_3$, 66), 77.0383 ($M^+ - C_4H_7O_3$ 49).

Erythro-3-methyl-4-hydroxy-phenylbutan-2-one (8b). A magnetically stirred solution of 3-propionyl-oxazolidine-2-one (0.143 g, 1.0 mmol) and dichloromethane (3.0 mL) was cooled to -72°C under nitrogen. Di-*n*-butylboron triflate (0.27 mL, 1.1 mmol)[14] was added *via* syringe followed by diisopropylethylamine (0.21 mL, 1.2 mmol). The solution was stirred at -72°C for 2 h, and benzaldehyde (0.10 mL, 1.0 mmol) was added in dichloromethane (1.0 mL) *via* syringe

in one portion. The solution was stirred at -72°C for 0.5 h and at 25°C for 1 h. The reaction was cooled to -72°C and methylmagnesium bromide (3.5 mmol, 2.8 min ether) was added dropwise over 10 min. The solution was stirred at -72°C for 0.5 h followed by 0°C for 0.5 h. Methanol (3 mL) and pH 7 buffer (1 mL) were added followed by hydrogen peroxide (1 mL, 30% aqueous). The solution was stirred for 15 min at 0°C followed by removal of the methanol in vacuo. The residue was dissolved in ether (60 mL) and washed with ethylenediaminetetraacetic acid, tetrasodium salt (2 x 30 mL, 1 min water) followed by sodium hydroxide (2 x 30 mL, 1 N in water) and saturated sodium chloride (1 x 30 mL). The organic phase was dried (Na_2SO_4), filtered, and the solvent removed in vacuo to give 0.115 g (65%) of 8b as a light yellow oil. IR ($CHCl_3$) 3600-3300, 3010, 1700, 1600, 1450, 1355, 1210, 1170, 695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.30 (bs, 5H, phenyl), 5.06 (d, 1H, J = 4.5 Hz, -CHO-), 3.11 (bs, 1H, -OH), 2.94-2.66 (dq, 1H, J = 4.5 Hz, J = 7.0 Hz, -CHCO), 2.07 (s, 3H, CH_3CO-), 1.04 (d, 3H, J = 7.0 Hz, -$CHCH_3$); mass spectrum (70 eV) m/e: 178.1002 (M^+, calcd. 178.0993, 1), 106.0414 (M^+ - C_4H_8O, 88), 105.0340 (M^+ - C_4H_9O, 86), 77.0383 (M^+ - $C_5H_9O_2$, 100).

References and Notes

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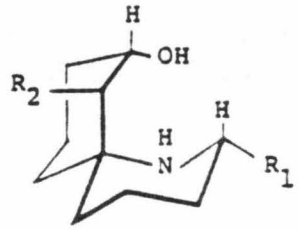
APPENDIX I

Naturally Occurring Histrionicotoxins

The following table is a compilation of the naturally occurring side chains (R_1 and R_2) found in the histrionicotoxins.[1]



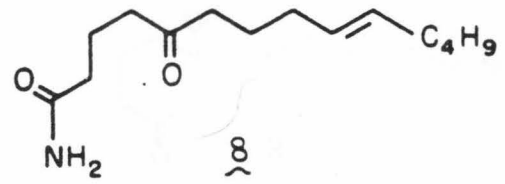
R_1	R_2
$-CH_2-C(H)=C(H)-C\equiv CH$	$-C(H)=C(H)-C\equiv CH$
$-CH_2-CH(CH_2-C(H)=C=CH_2)-$	$-C(H)=C(H)-C\equiv CH$
$-CH_2-C(H)=C(H)-C\equiv CH$	$-CH(CH=CH_2)-CH=CH-$
$-CH_2-C(H)=C(H)-C(H)=CH_2$	$-C(H)=C(H)-C(H)=CH_2$
$-CH_2-CH(CH_2-C(H)=C=CH_2)-$	$-CH(CH=CH_2)-CH=CH-$
$-CH_2-CH(CH_2-CH=CH_2)-$	$-CH_2-CH(CH=CH_2)-$
$-CH_2-CH(CH_2-C\equiv CH)-$	$-C(H)=C(H)-C\equiv CH$
$-CH_2-CH(CH_2-C\equiv CH)-$	$-C(H)=C(H)-C(H)=CH_2$

1. (a) Y. Inubishi and T. Ibuka, Heterocycles, 8, 633 (1977); (b) J. W. Daly, A. B. Brown, M. Mensah-Dwumah and C. W. Meyers, Toxicon, 16, 163 (1978).

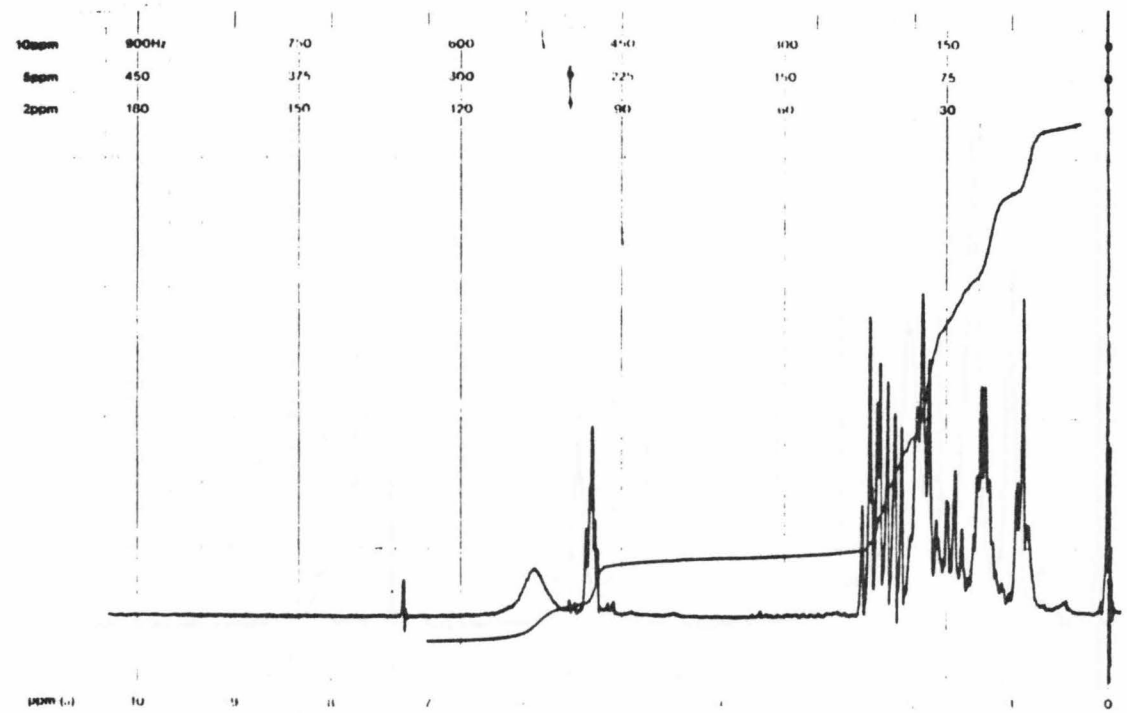
APPENDIX II

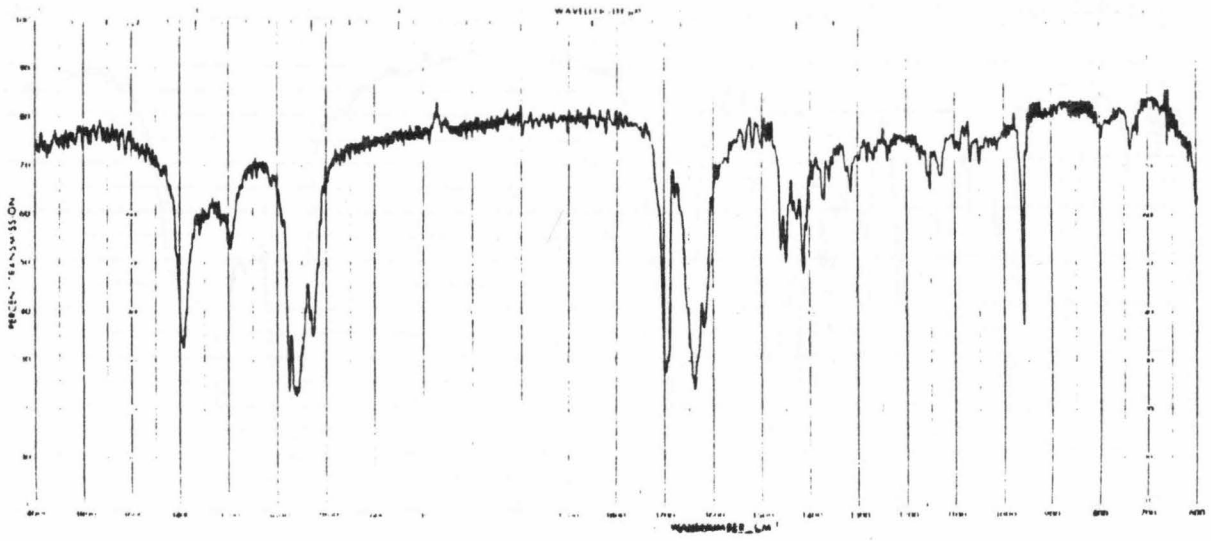
IR and 'H-NMR Spectral Catalog for Chapter I

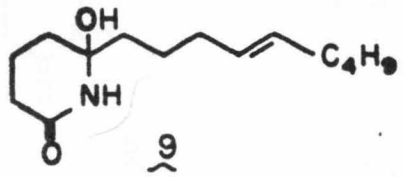
IR and ^{1}H-NMR spectra were run under the conditions defined in the experimental section for Chapter I.


O
O
C_4H_9
NH_2

8


10ppm
900Hz
750
600
450
300
150
5ppm
450
375
300
225
150
75
2ppm
180
150
120
90
60
30
ppm (δ)
10
9
8
7
1
0





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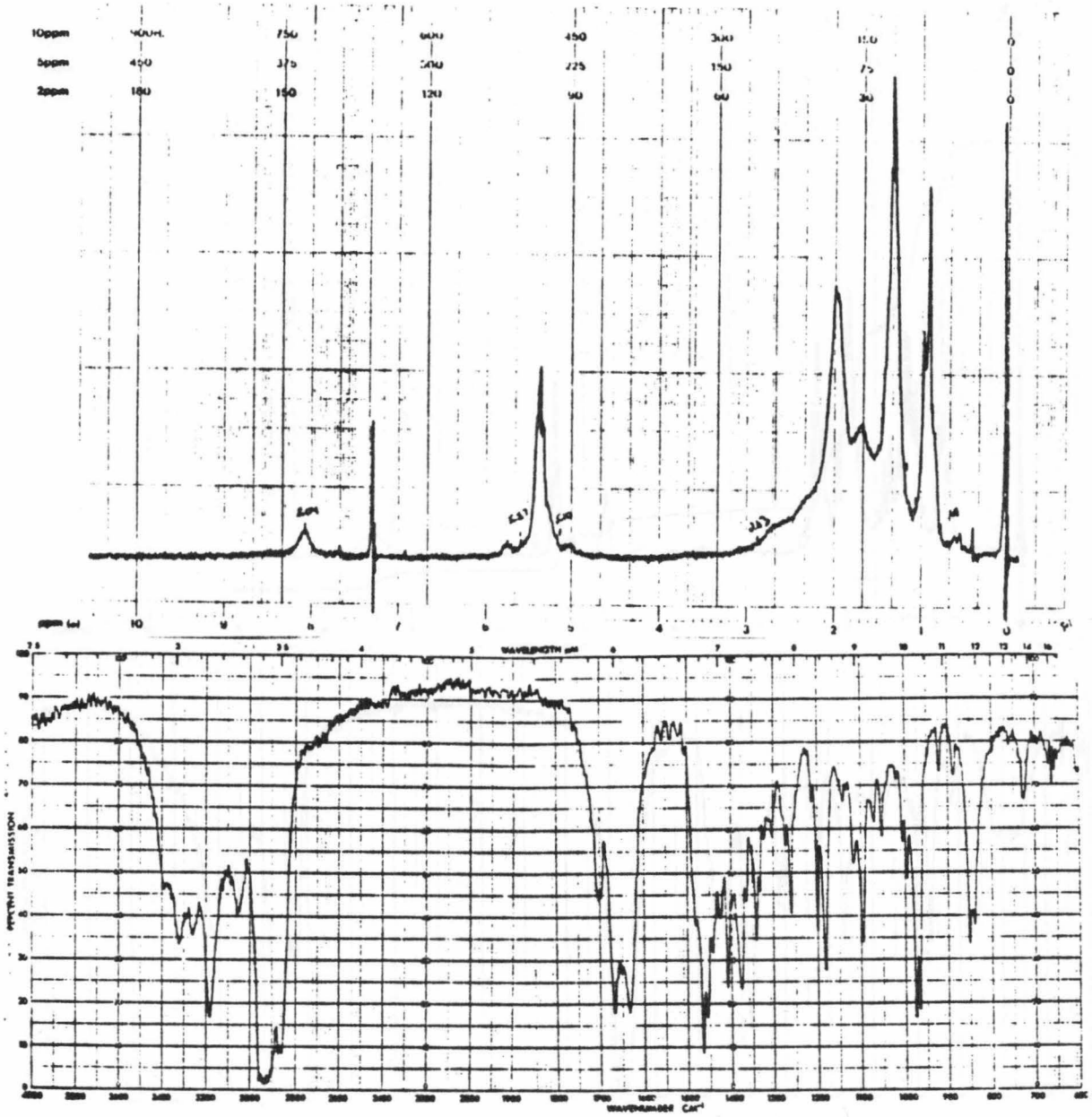
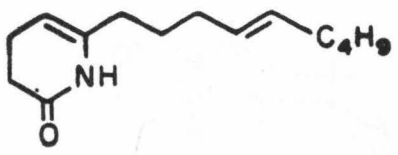
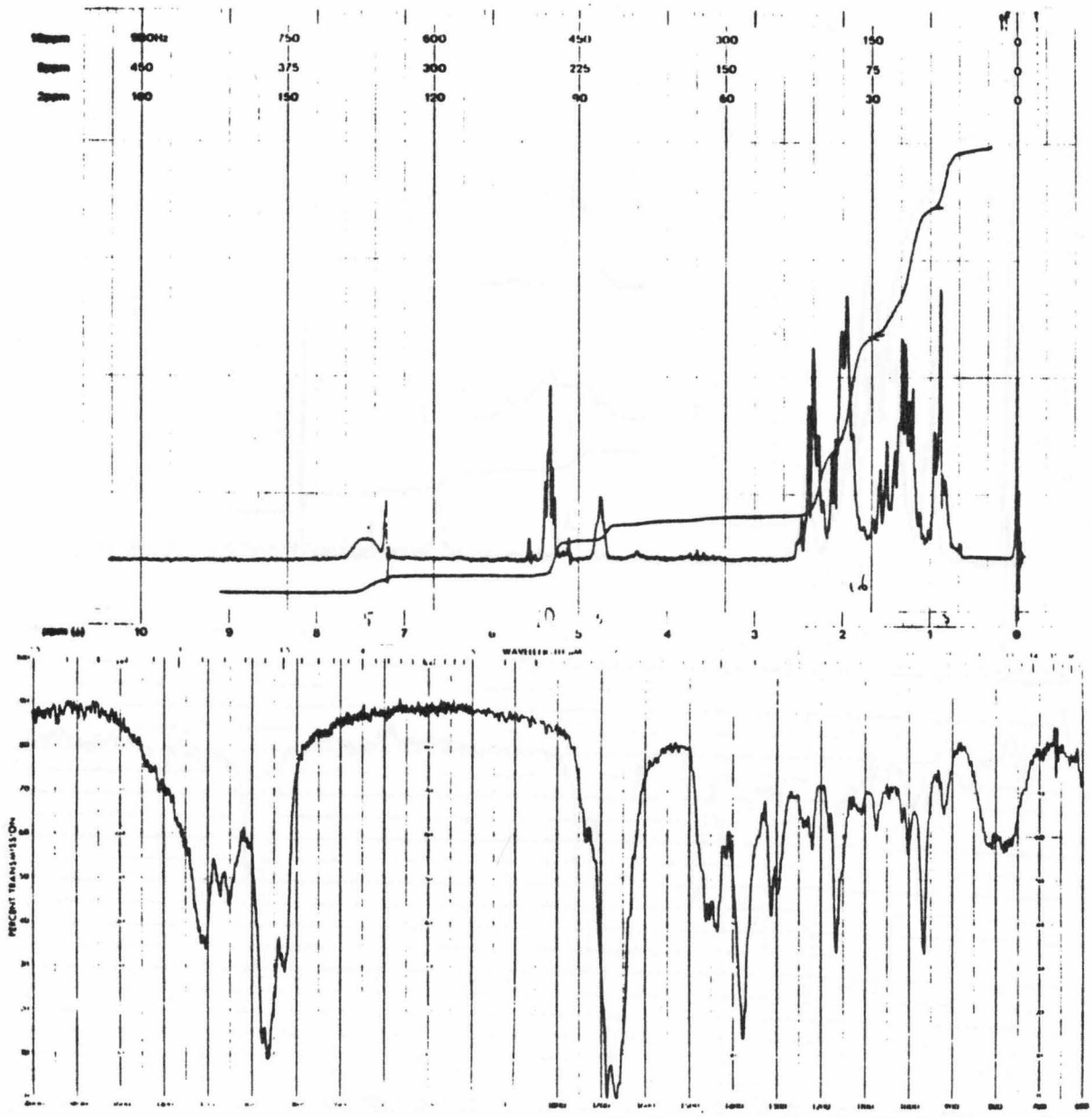
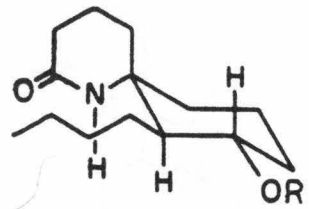


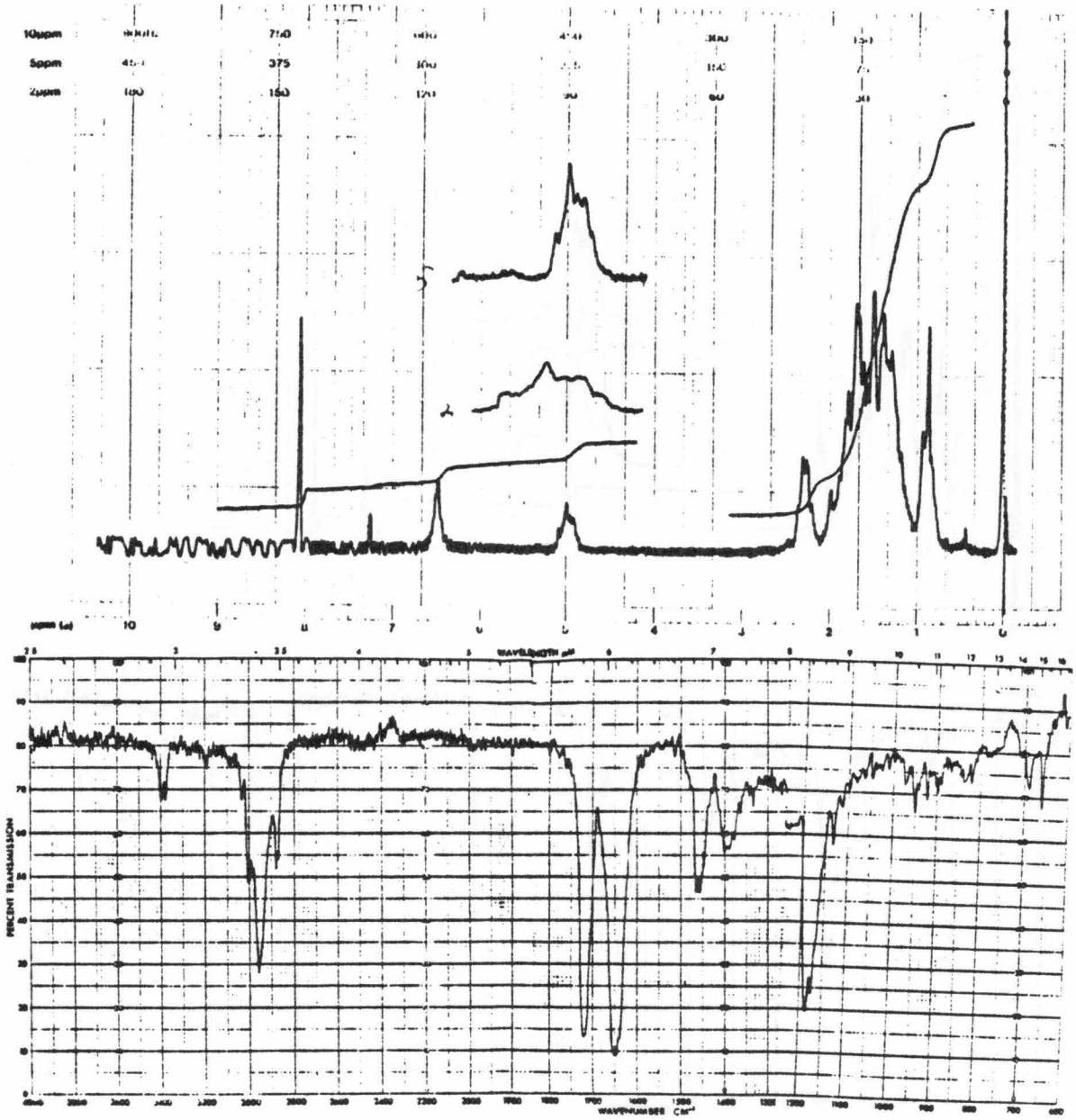


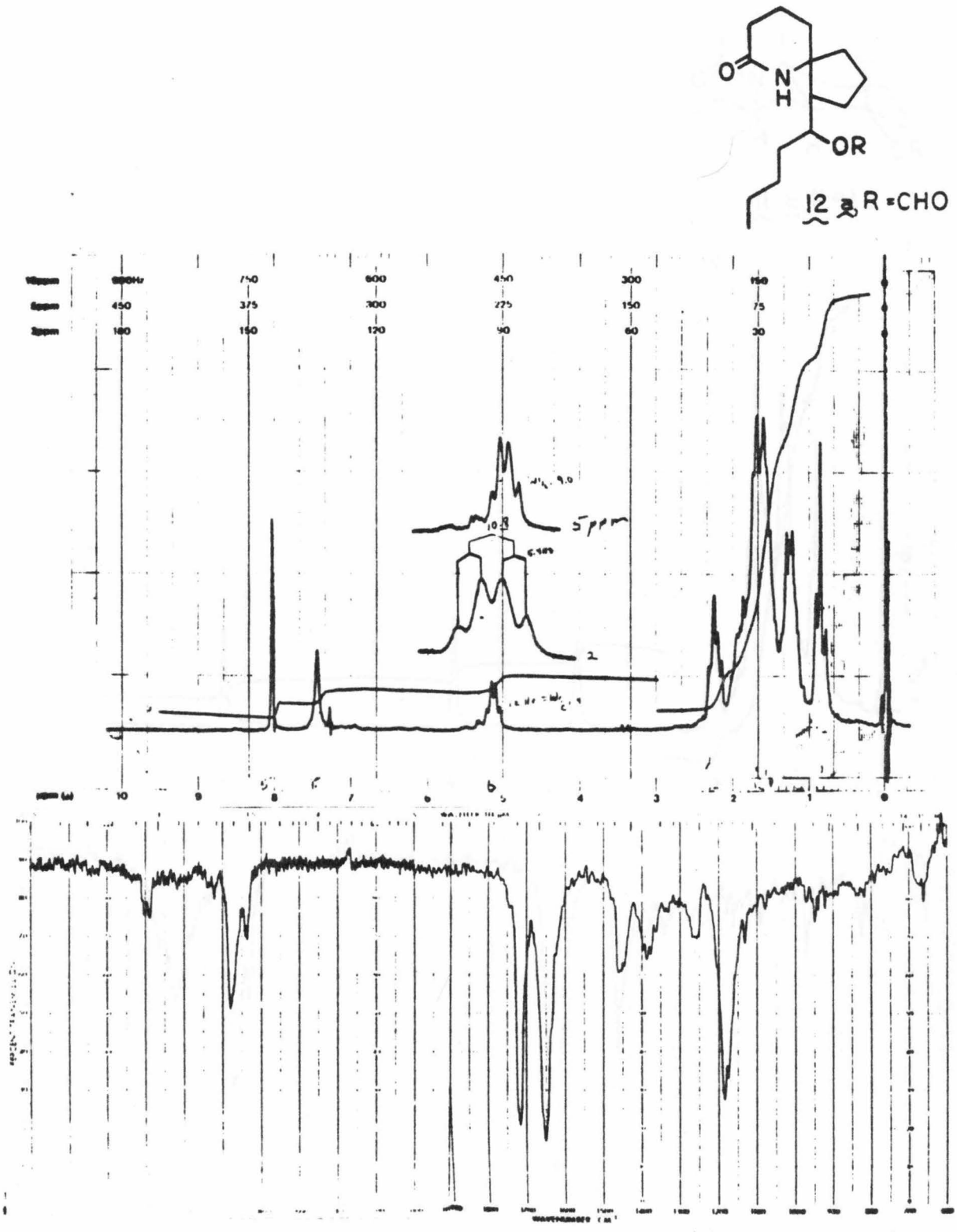
6

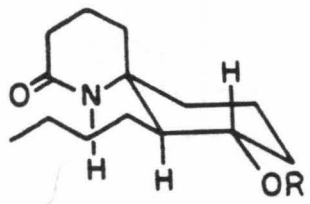



O
N
H
H
H
OR

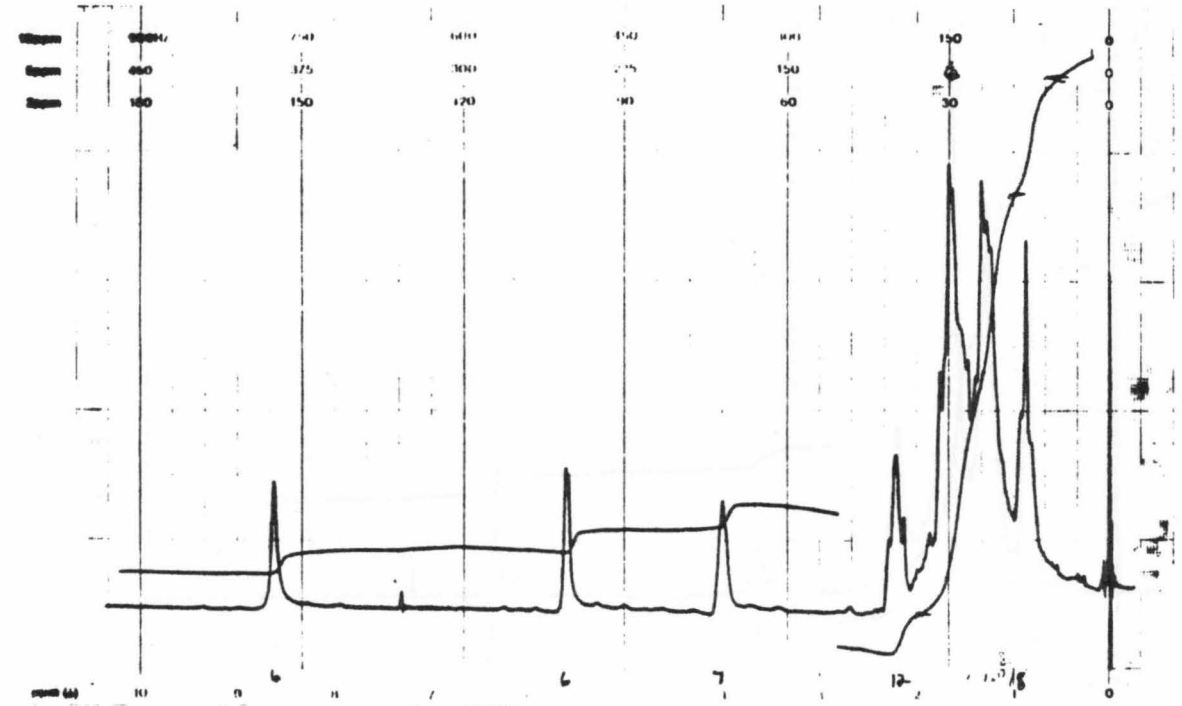
II a R=CHO

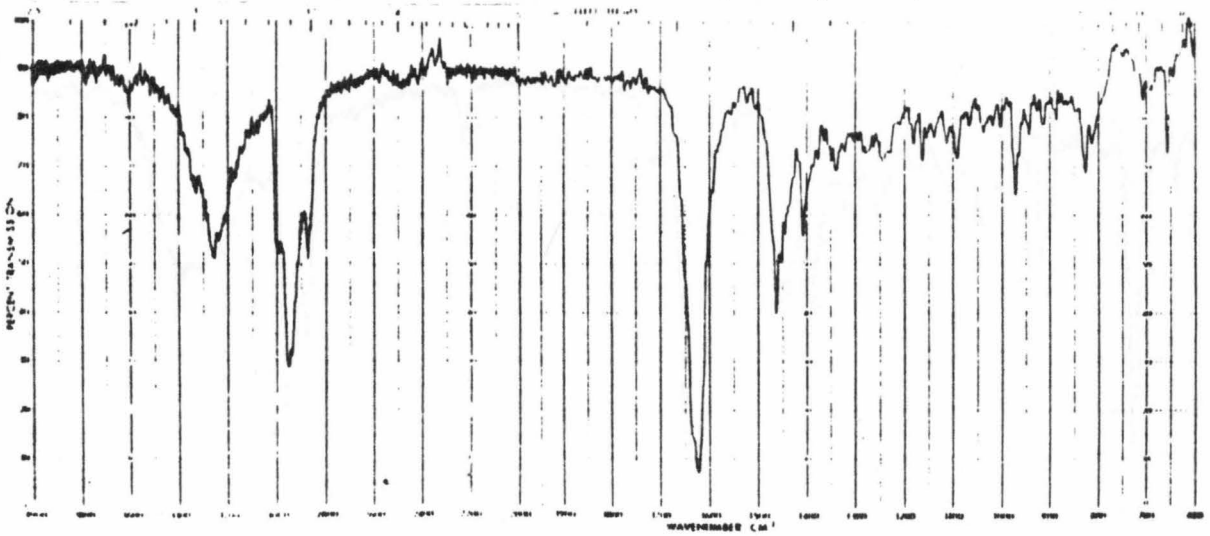

PERCENT TRANSMISSION
WAVELENGTH μM
WAVENUMBER CM⁻¹

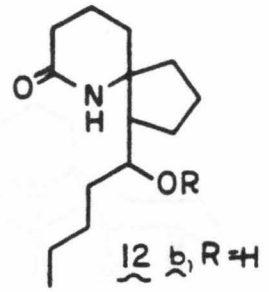

O
N
H
OR
12 & R=CHO



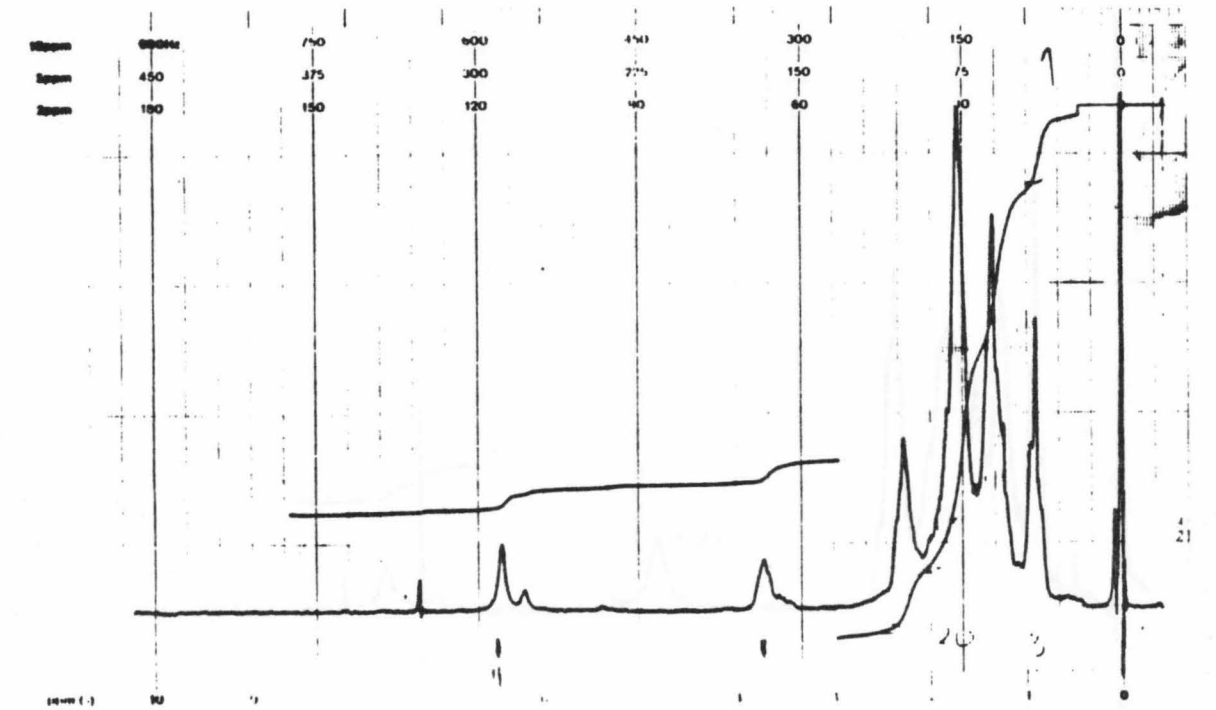
II b, R=H

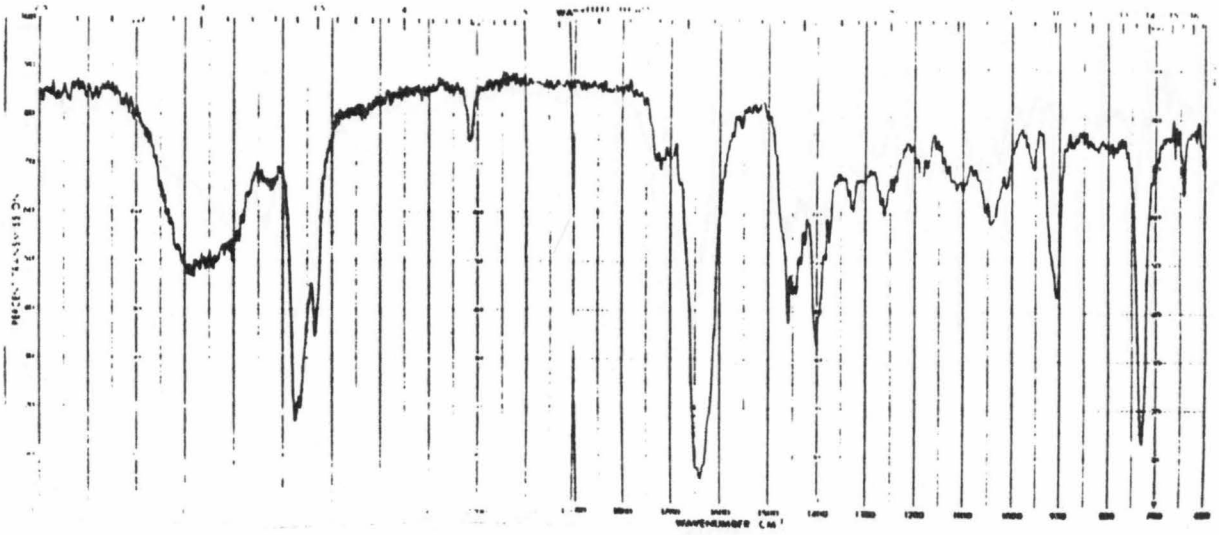


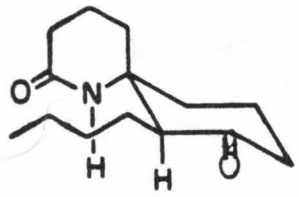


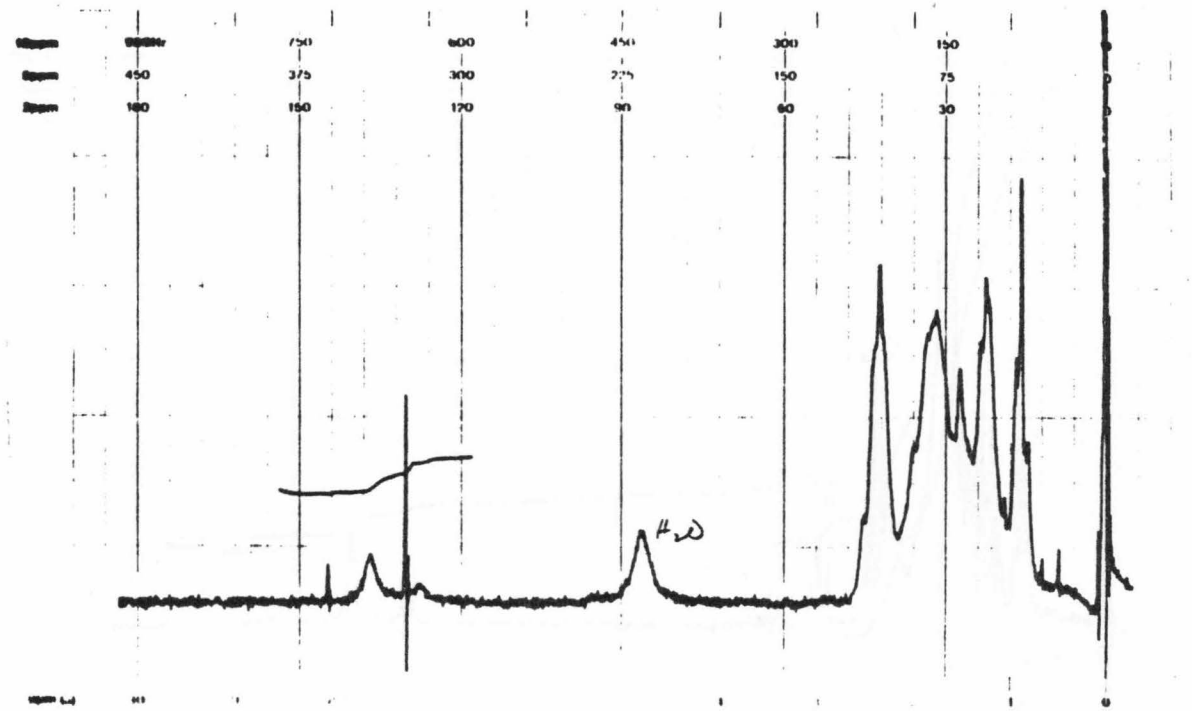


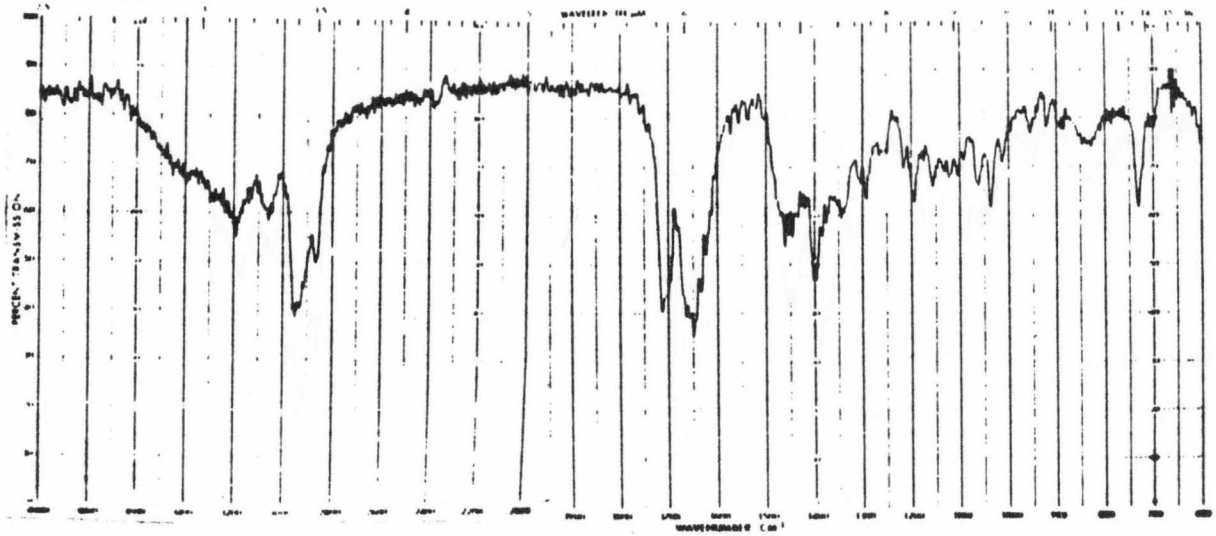
12 b, R = H

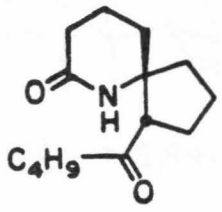




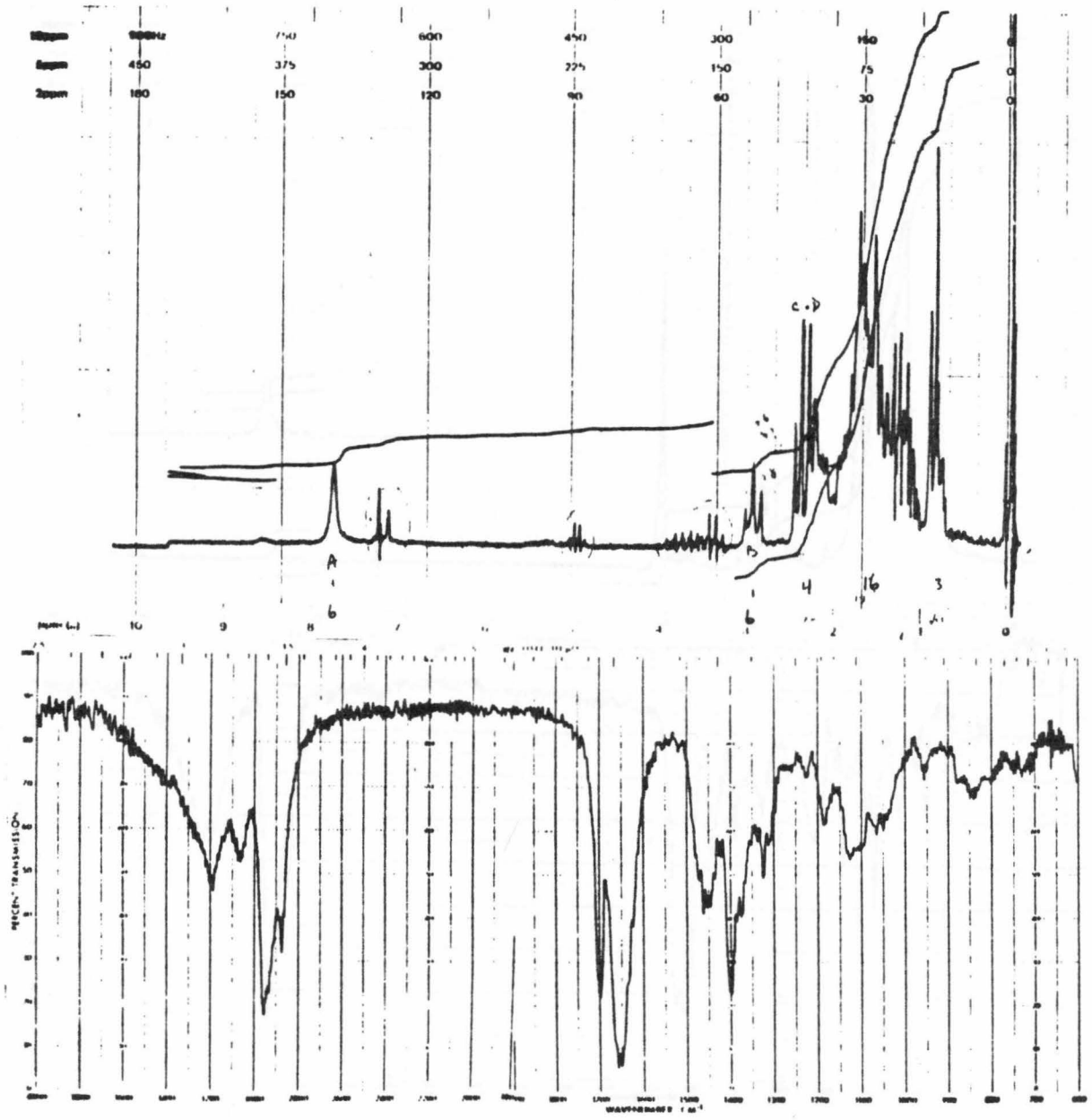

O
N
H
H
O

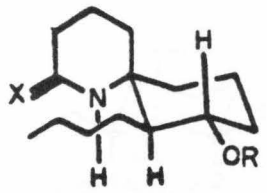

750
600
450
300
150
450
375
300
225
150
75
180
150
120
90
60
30



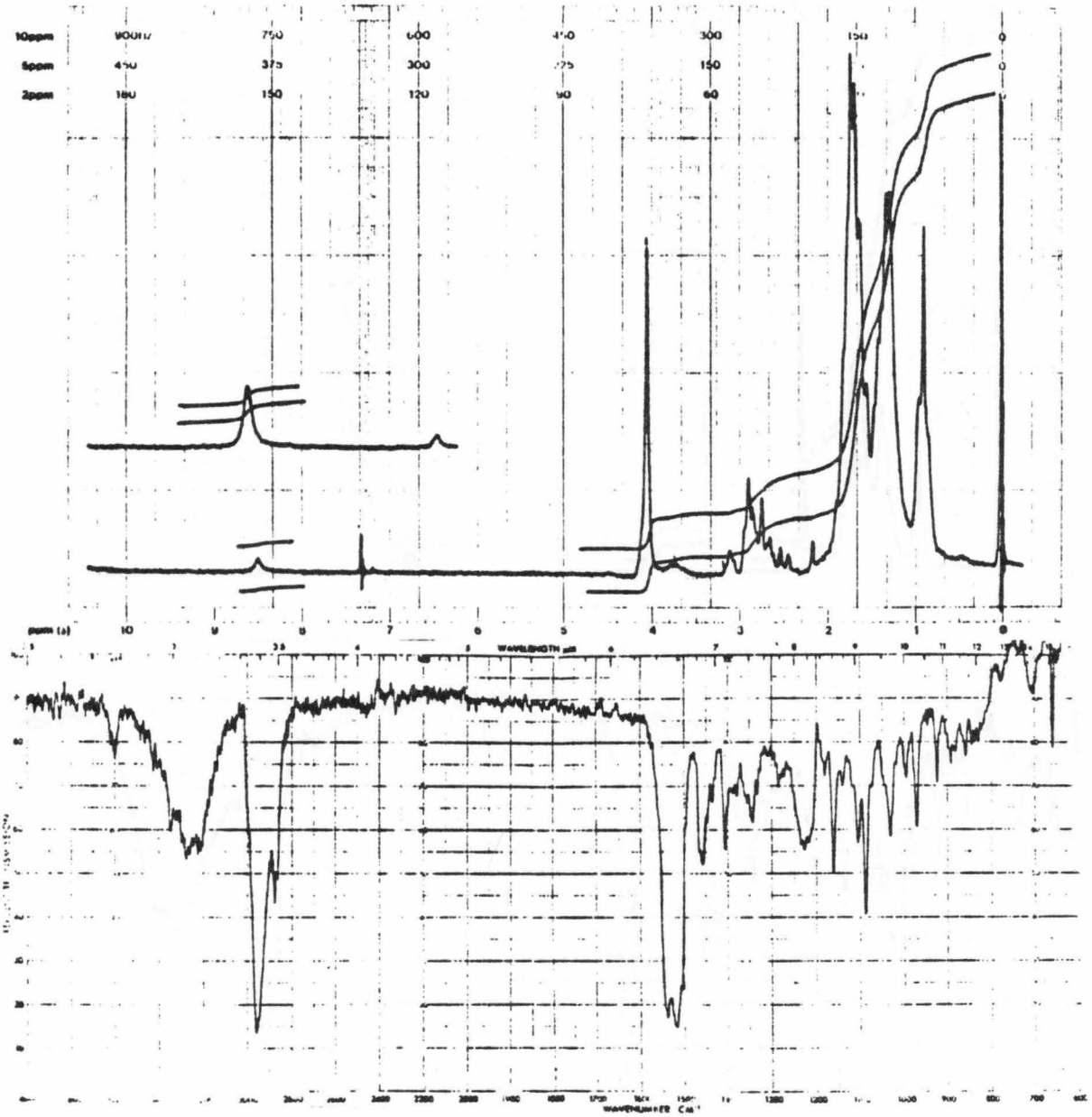


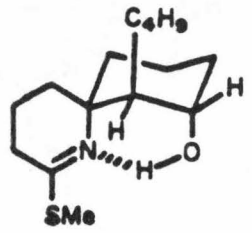
13



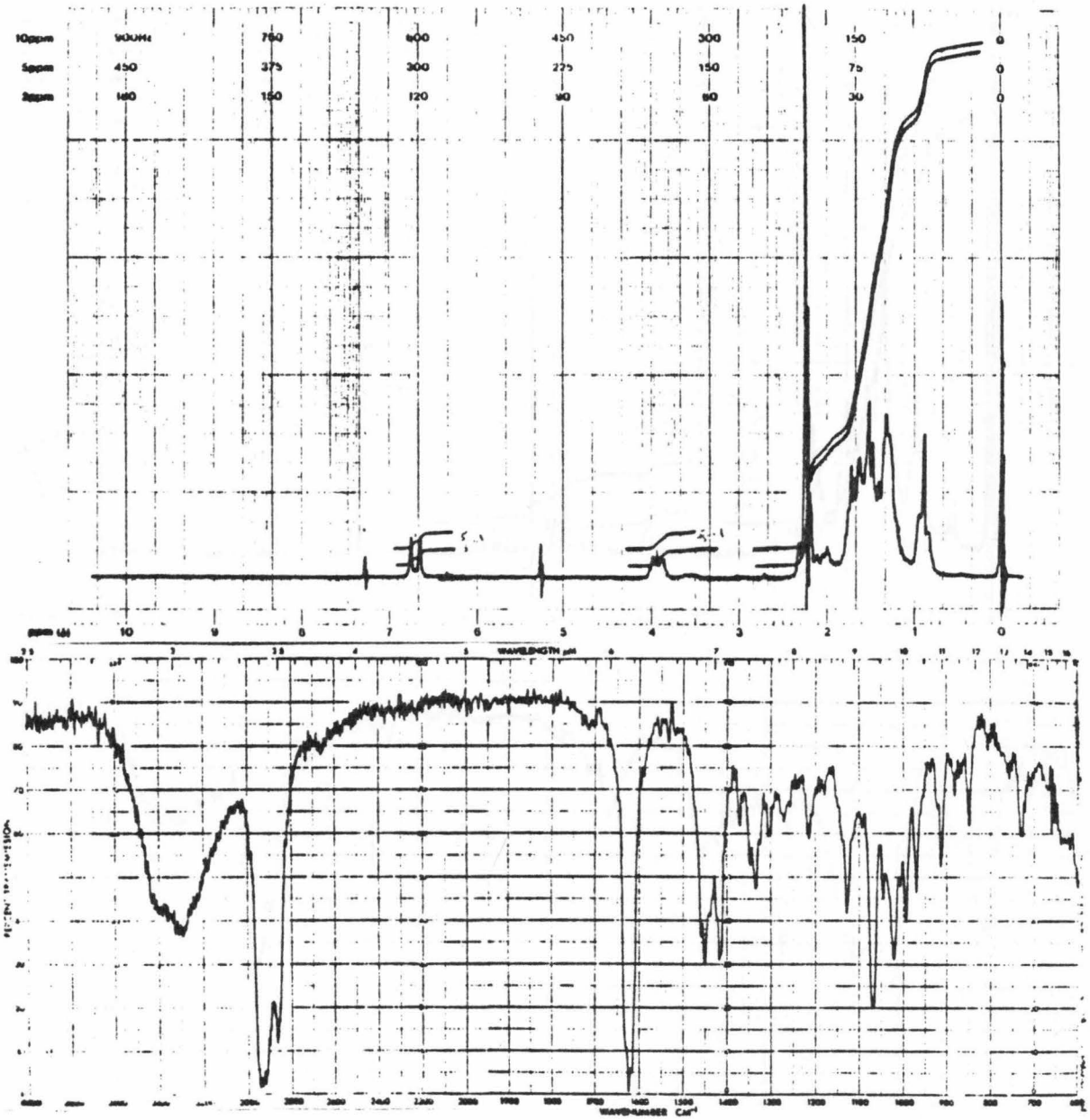


15 b, X=S, R=H




C4H9
H
H
N
H
O
SMe

16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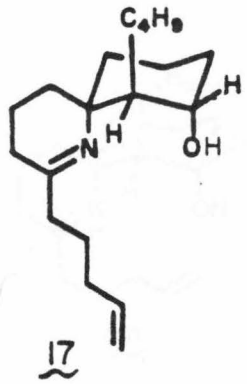
5ppm
2ppm
WAVELENGTH μm
WAVENUMBER Cm⁻¹



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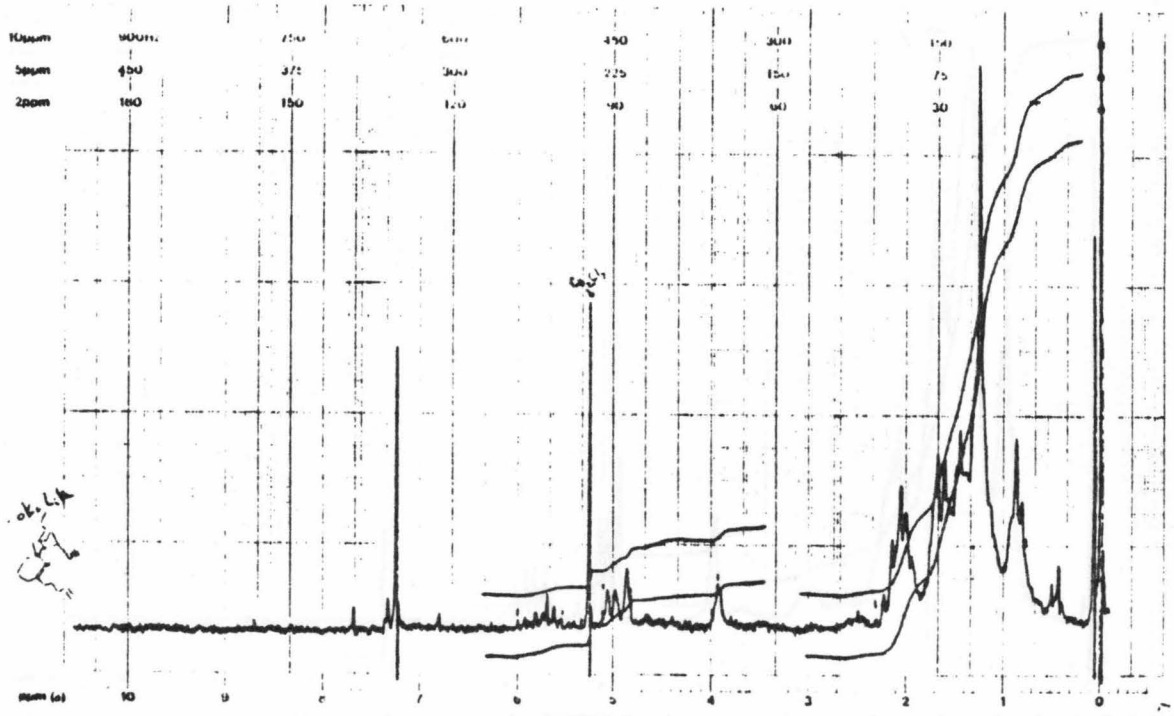
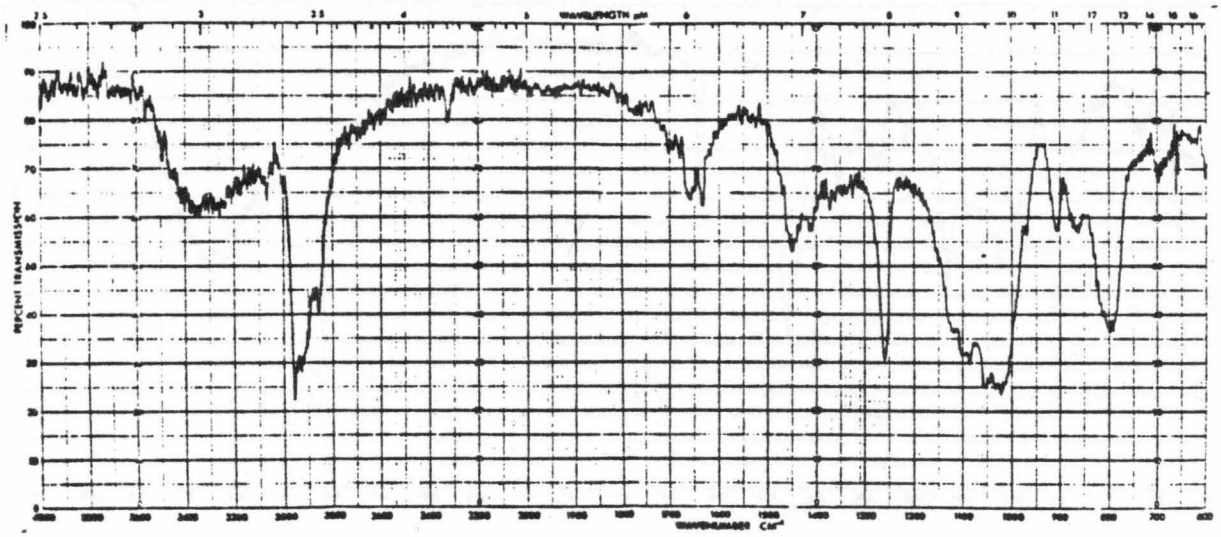
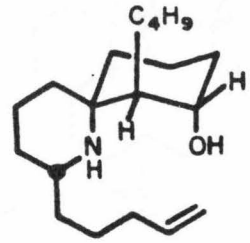
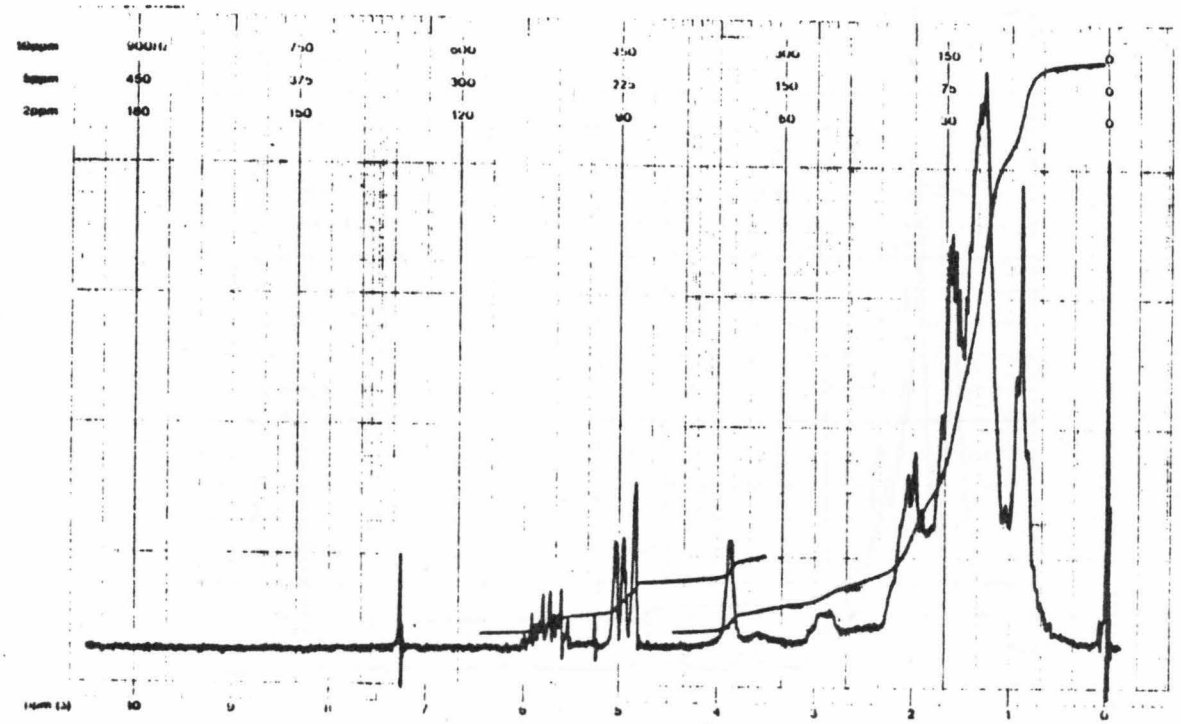
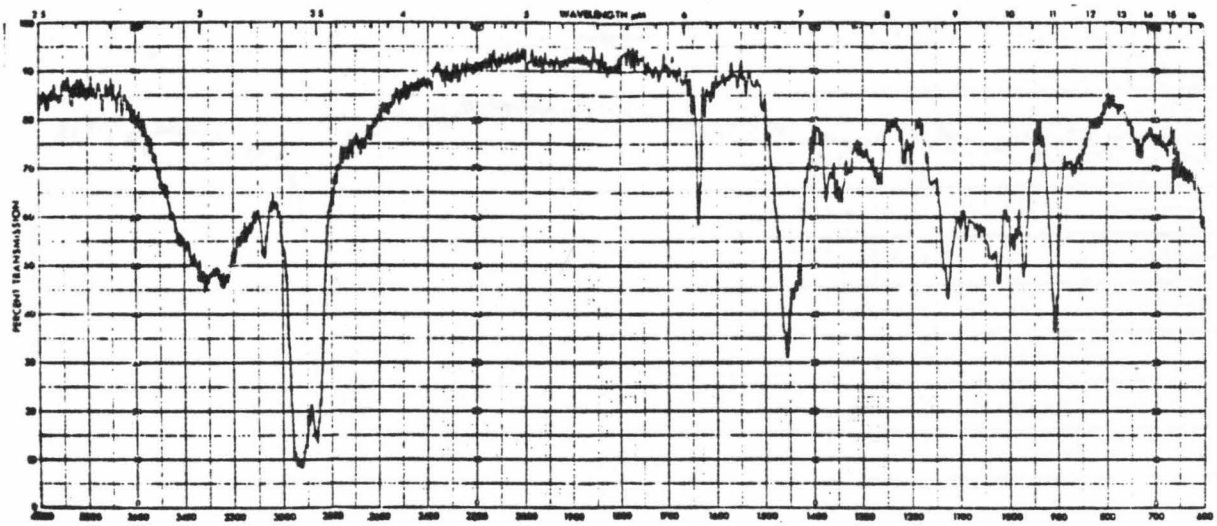


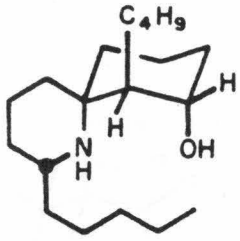




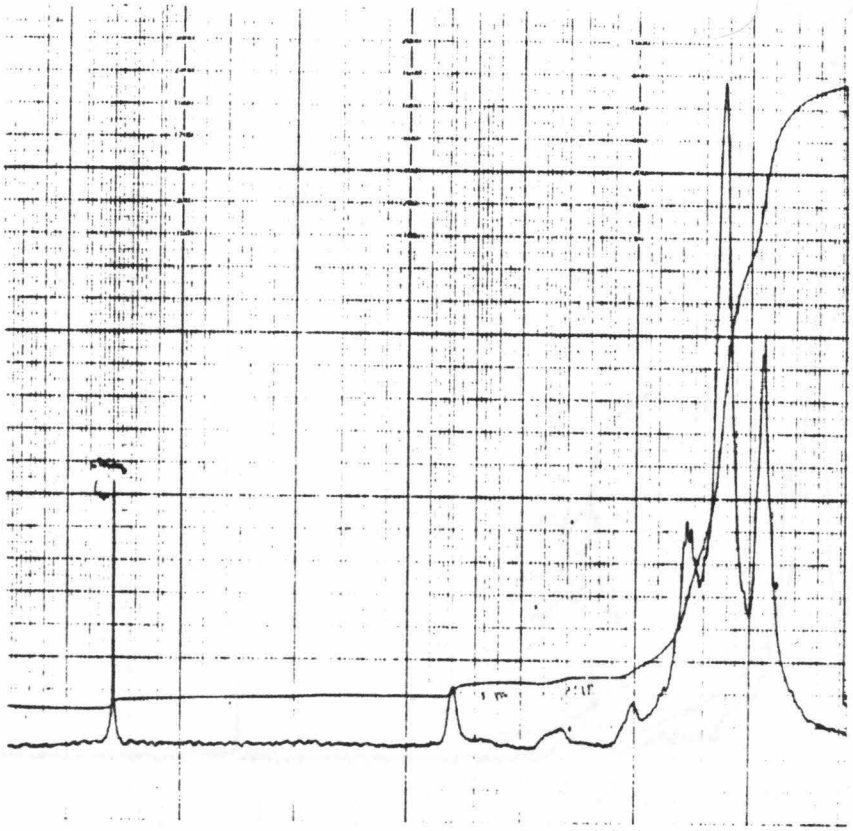
5a

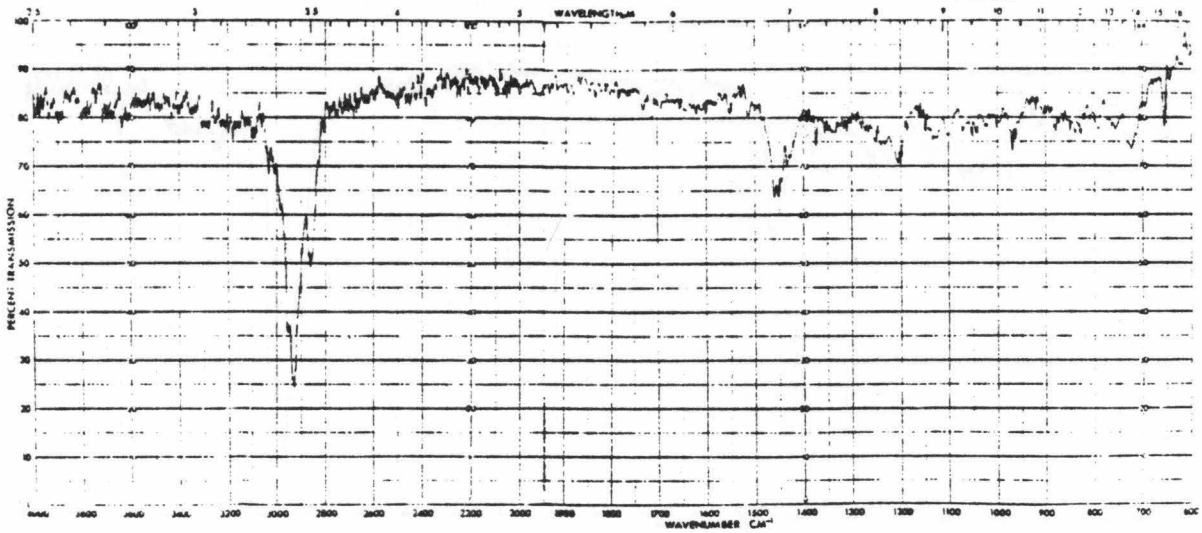


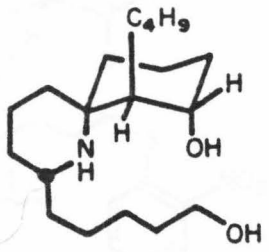



C4H9
H
H
OH
N
H

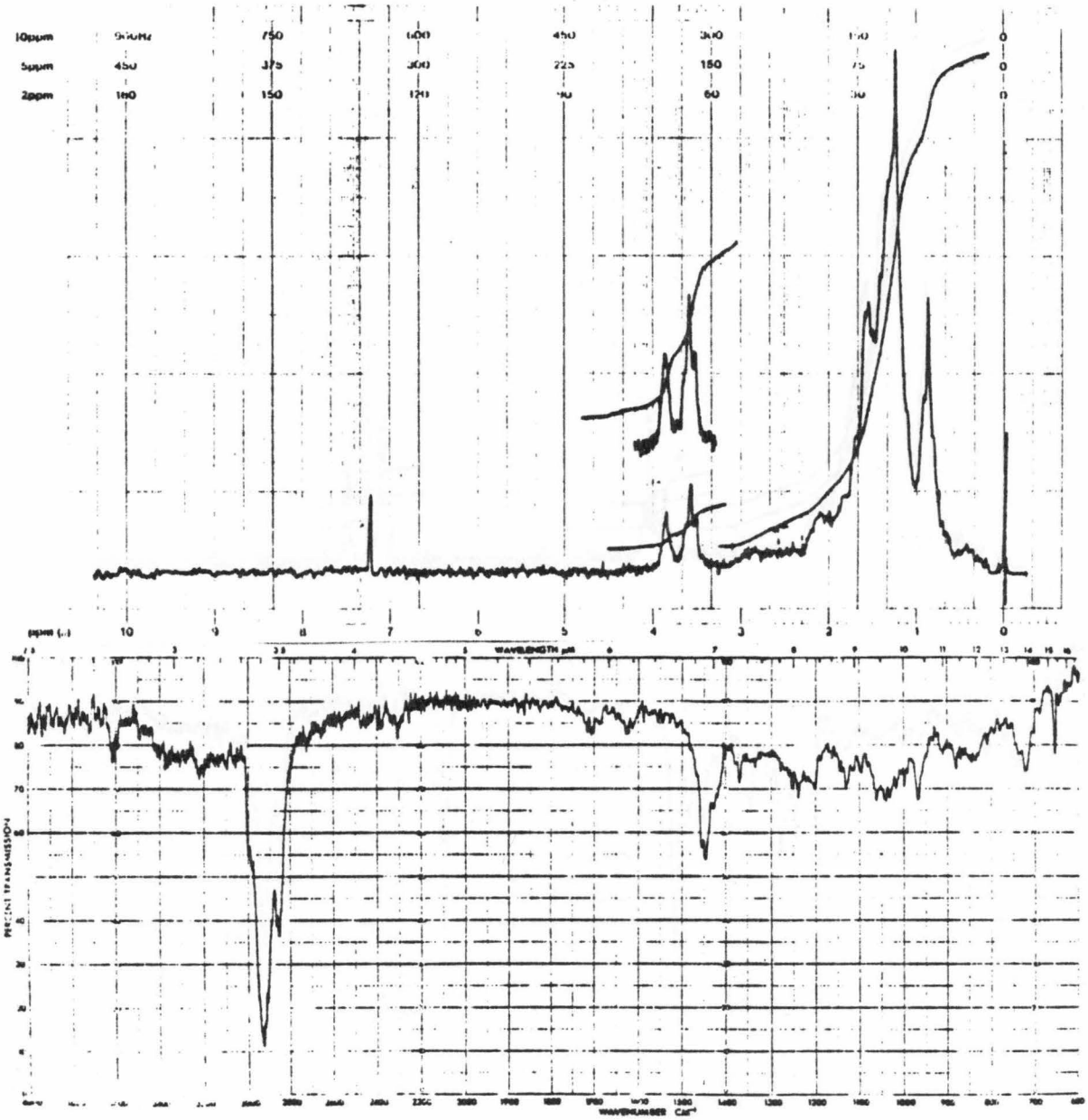
4a

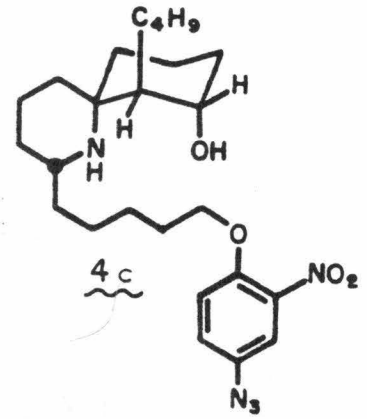


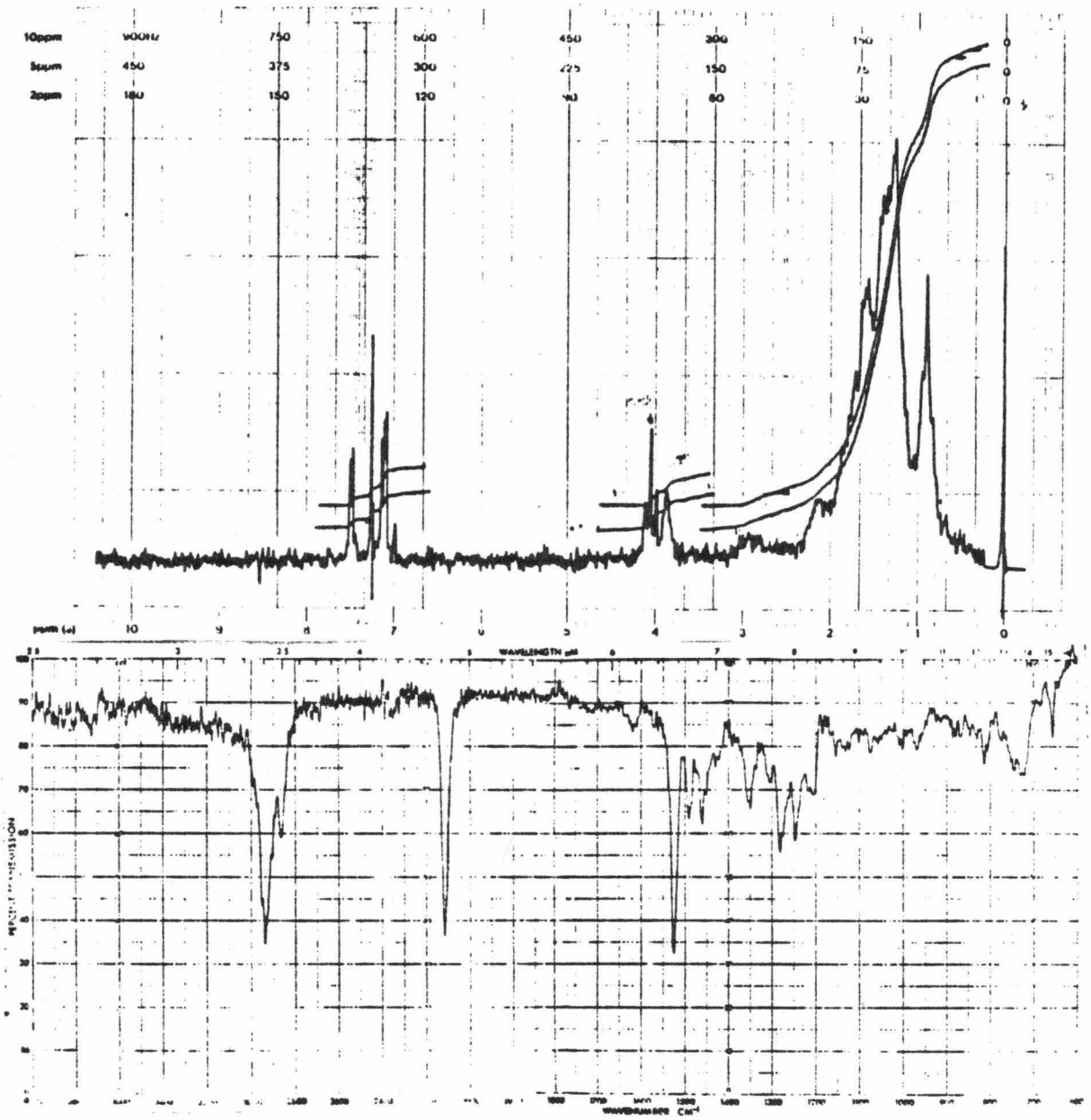

WAVELENGTH μm
PERCENT TRANSMISSION
WAVENUMBER CM⁻¹



4b



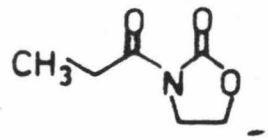

C4H9
H
H
N
H
OH
O
4c
NO2
N3

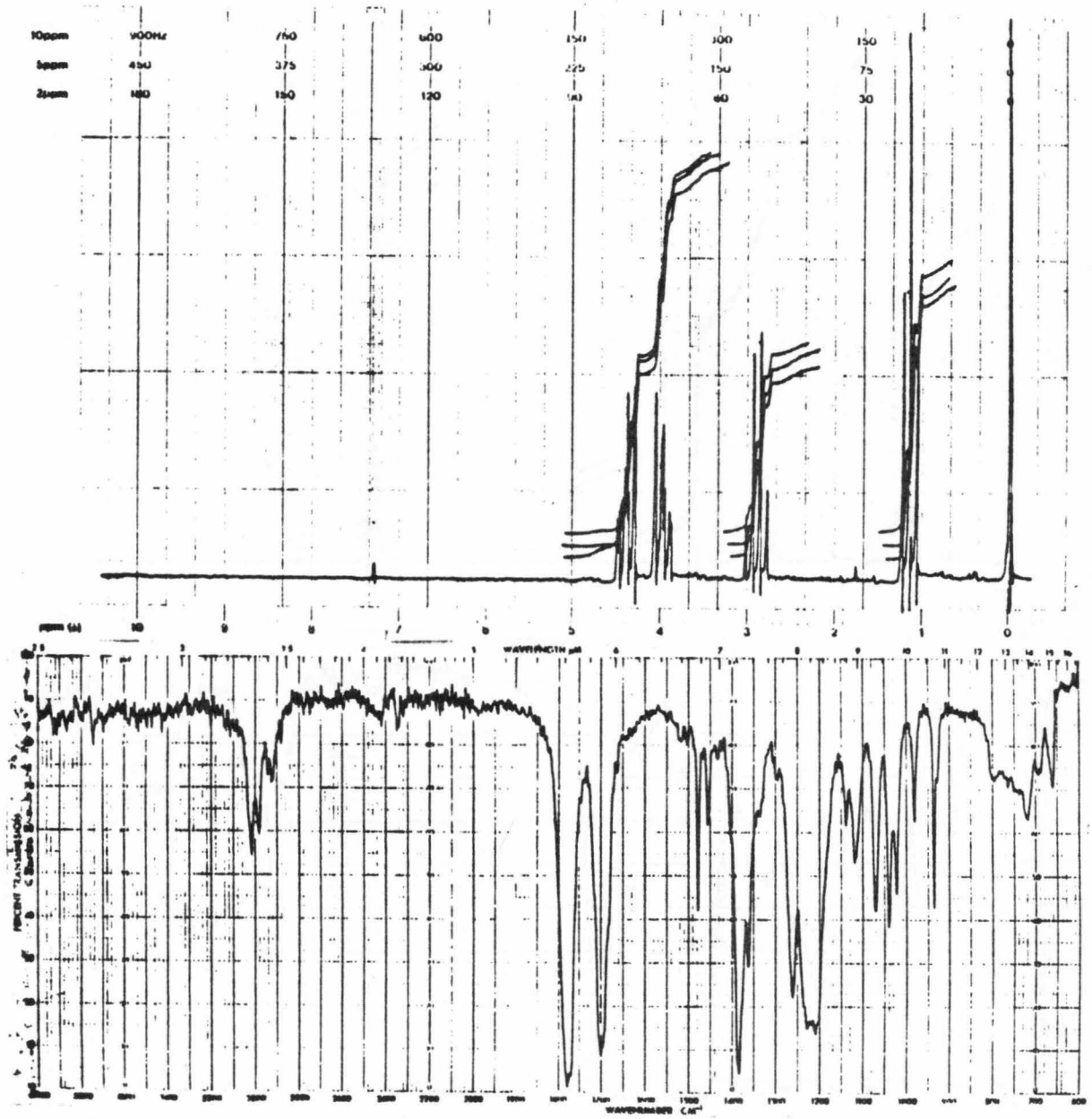


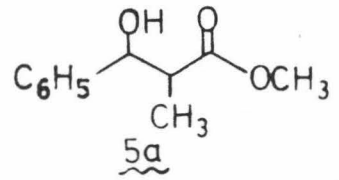
APPENDIX III

IR and 'H-NMR Spectral Catalog for Chapter II

IR and ^{1}H-NMR spectra were run under the conditions defined in the experimental section for Chapter II.



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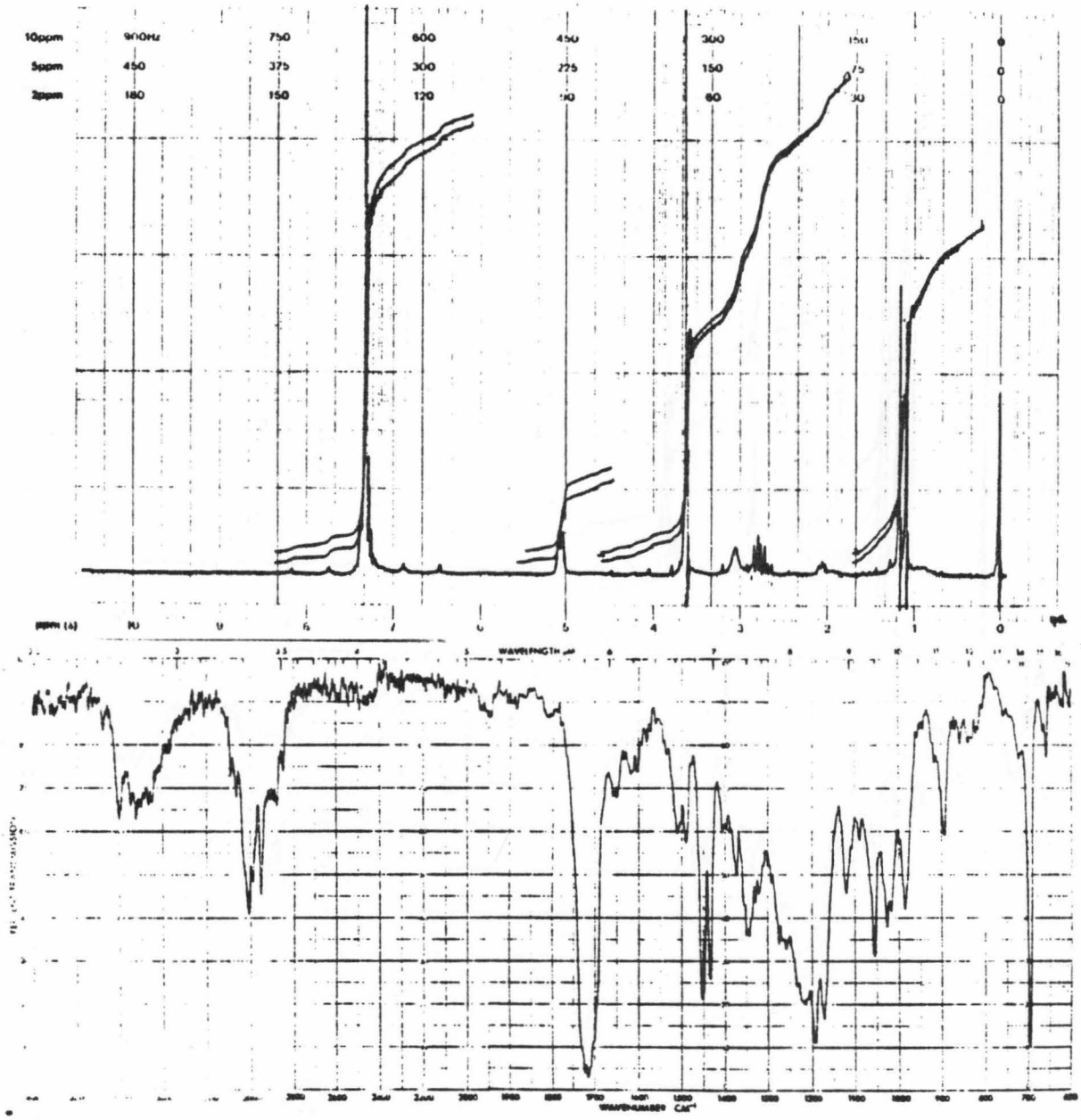
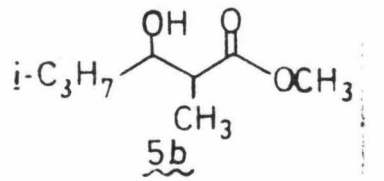
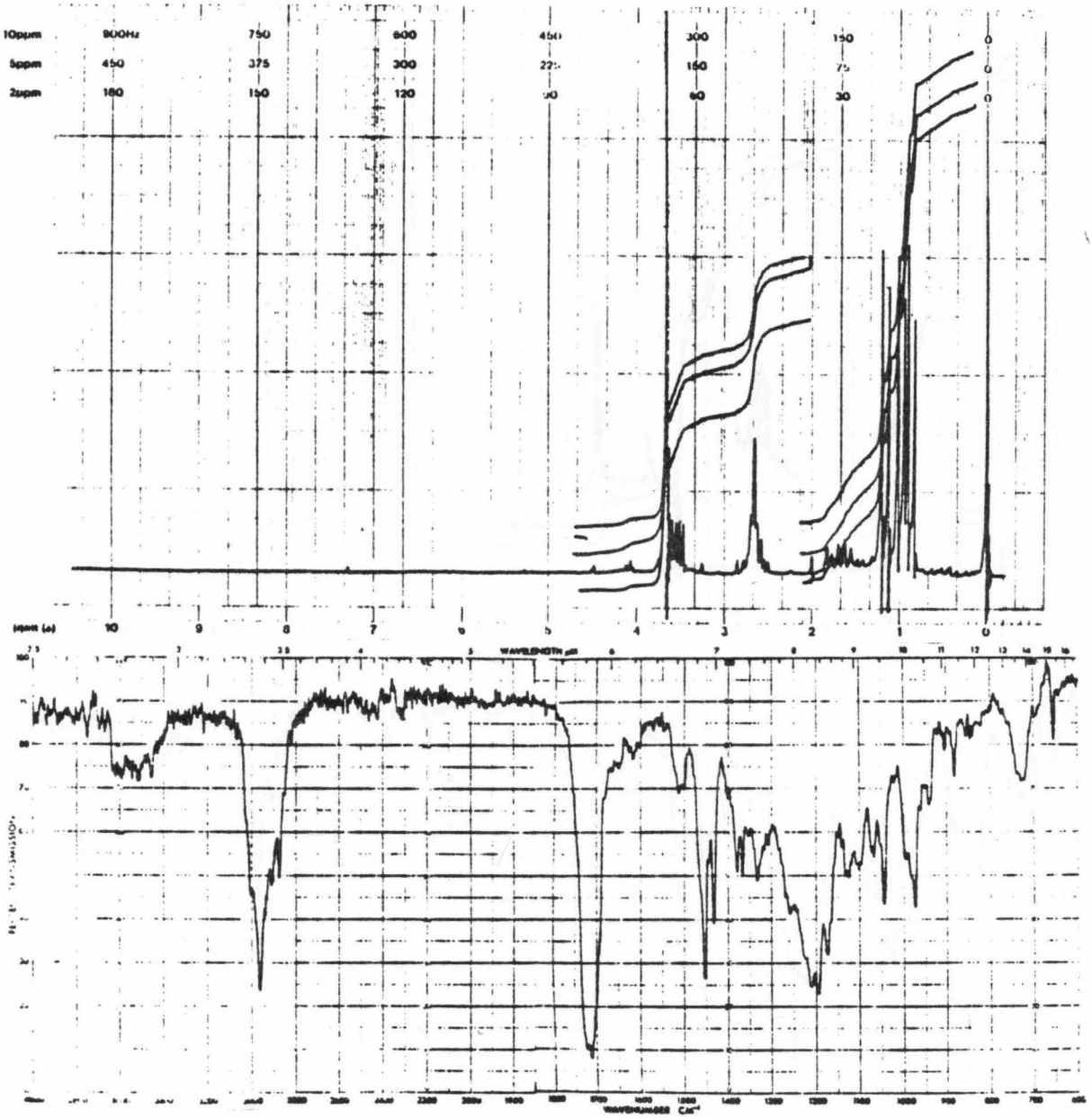
O
C_6H_5
OCH_3
CH_3

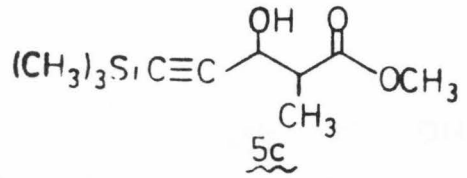
5a


10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
450
225
300
150
60
150
75
30
0
0



5b





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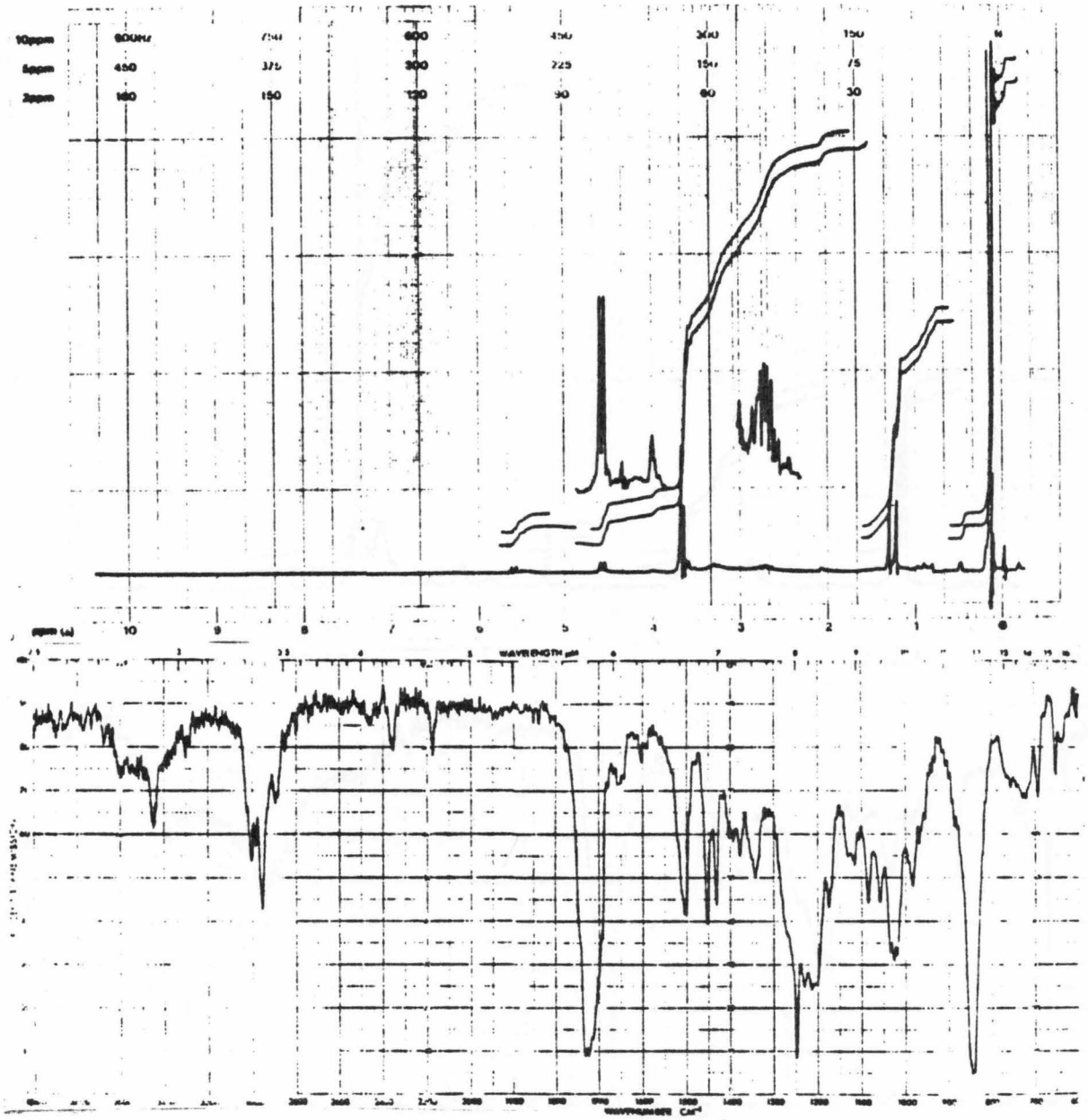
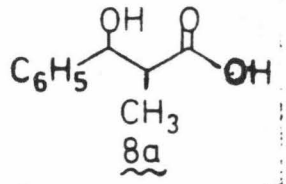
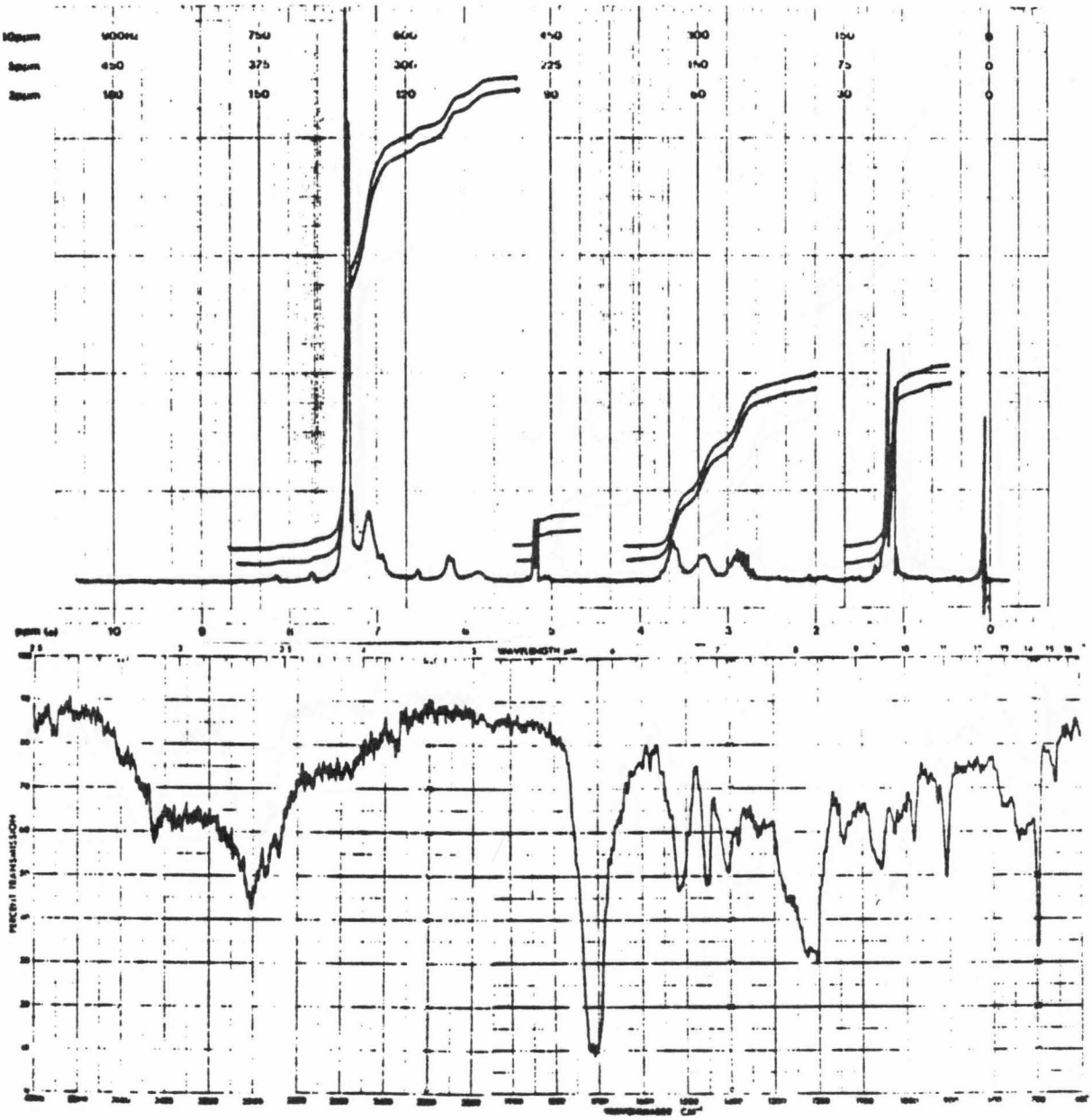
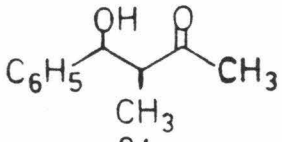


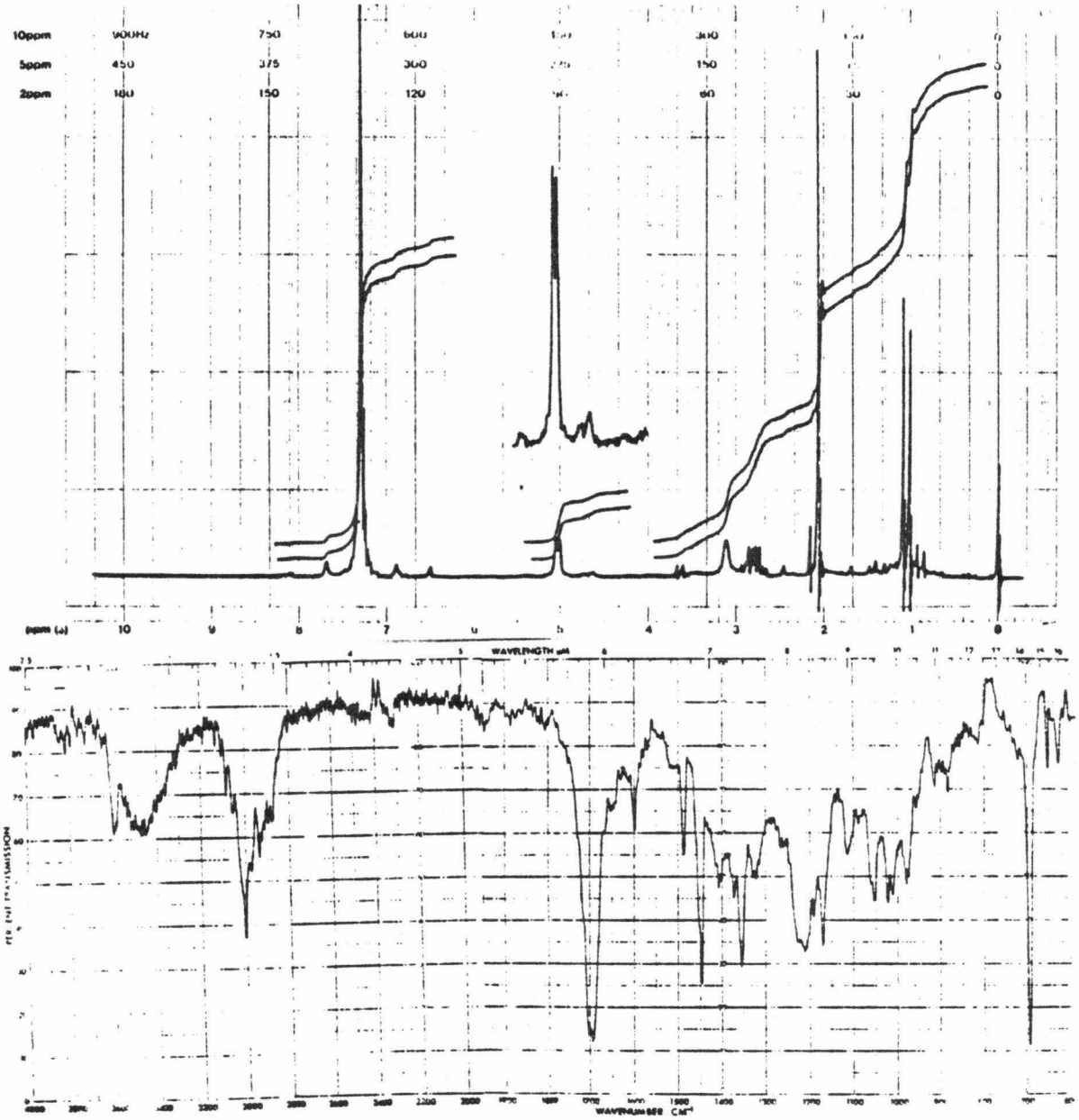


8a




OH
O
C6H5
CH3
CH3

8b


10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
600
300
120
300
150
60
WAVELENGTH μM
WAVENUMBER CM⁻¹

PROPOSITIONS

ABSTRACTS

PROPOSITION I: A synthesis of the antitumor compound shikodonin is proposed *via* the novel formation of a vinyl anion formally derived from an allylic alcohol.

PROPOSITION II: A general synthetic route to the ergoline nucleus is proposed, and the total synthesis of the ergot alkaloids festuclavine, dihydrolysergol, and their derivatives D-6-methyl-8-cyanomethyl-ergoline, Uterdina, and MCE are outlined.

PROPOSITION III: A mechanism for the mode of action of the insect antifeedant warburganal is proposed. The use of warburganal in studying the molecular basis of taste reception in human beings and insects is proposed.

PROPOSITION IV: Two three-carbon ring expansion reactions are proposed and are utilized in a synthesis of d,l-muscone.

PROPOSITION V: An endocyclic enamine synthesis utilizing an alkytin mediated cyclization is proposed.

PROPOSITION I

A synthesis of the antitumor compound shikodonin (1) is proposed *via* the novel formation of a vinyl anion formally derived from an allylic alcohol.

* * * * * * * *

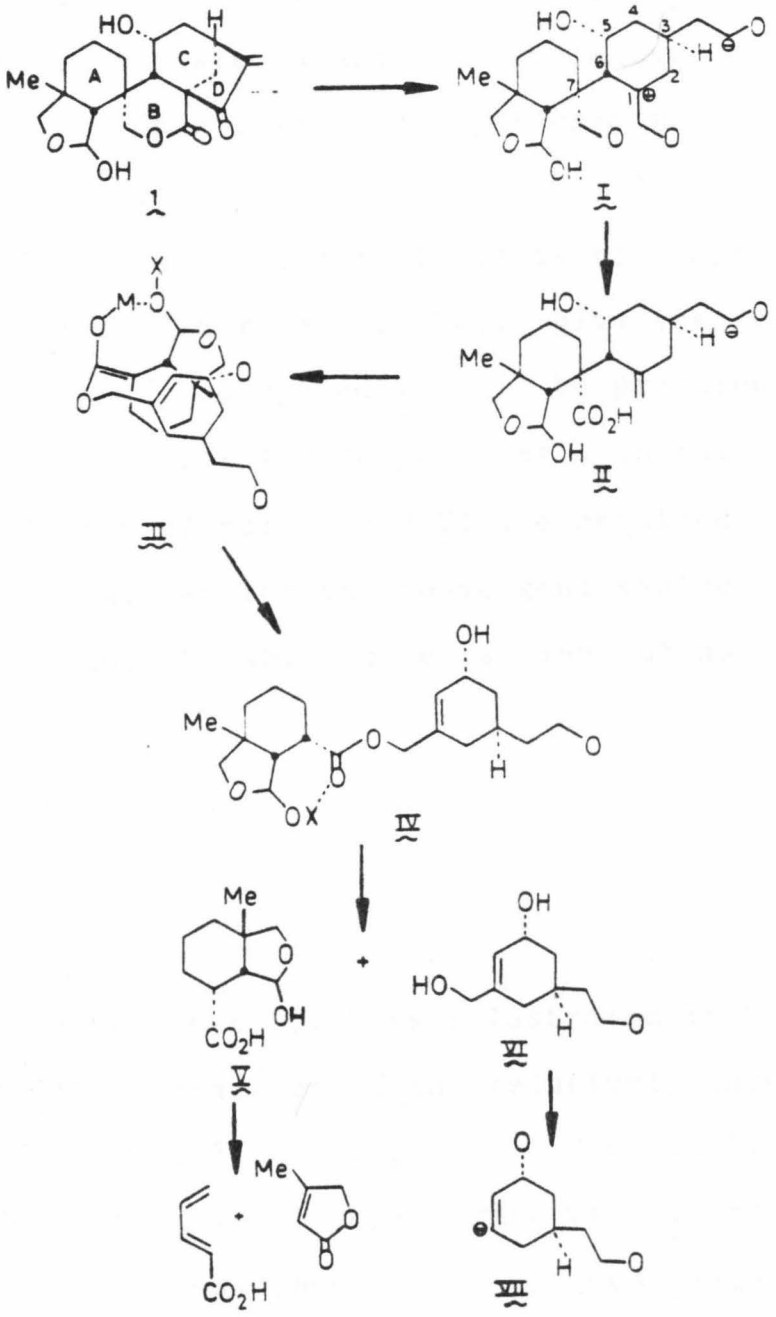
Introduction

Shikodonin (1), which possesses cytotoxic and antitumor activity, has recently been isolated in 0.00005% yield from the leaves of *Isodon shikokianus*.[1] Shikodonin (1) also exhibits insect growth inhibitory activity specifically against Lepidoptera larvae.[1] The detailed structure and relative stereochemistry of 1 were established by X-ray diffraction methods and were shown to contain a unique spirosecokaurene skeleton.[1] The scarcity of material form natural sources, high biological activity, and unique carbon skeleton make shikodonin (1) an enticing synthetic target. A chiral synthesis of 1 would confirm the absolute stereochemistry as determined by circular dichroism.[1]

Strategy

The proposed carbon-carbon bond formations are illustrated in a retrosynthetic format in Scheme I. The D-ring will be formed late in the synthesis due to the susceptibility of the 1,3-dione moiety to cleavage. Establishing the correct relative stereochemistry at C-3 will serve to introduce the correct relative stereochemistry at C-1 (I, II). This might result from a connection of the hypothetical equivalents illustrated in I and II with an olefin precursor as the source of the tertiary carbonium ion. The formation of the critical carbon-carbon bond between rings A and C will be accomplished *via* an ester-enolate Claisen rearrangement.[2] The correct relative stereochemistry will be formed if: (1) pieces V and VI are chiral; (2) the correct enolate geometry is obtained; (3) the Claisen rearrangement proceeds from the convex side of rings A and B; and (4) the Claisen rearrangement occurs through a chair transition state. Esters substituted with heteroatoms at the α and β positions have been shown to afford the enolate in which the heteroatom is syn to the enolate alkoxide;[3] therefore, the required enolate should be formed upon deprotonation of IV with lithium diisopropylamide or lithium diisopropylamide-

Scheme I


HO
H
Me
A
B
C
D
O
OH
1
HO
5
4
3
H
O
Me
6
7
2
1
O
O
OH
I
HO
H
O
Me
CO2H
O
OH
II
X
M
O
O
O
O
O
III
OH
Me
O
O
H
O
O
X
IV
Me
O
OH
CO2H
V
OH
HO
H
O
VI
Me
O
O
CO2H
O
H
O
VII

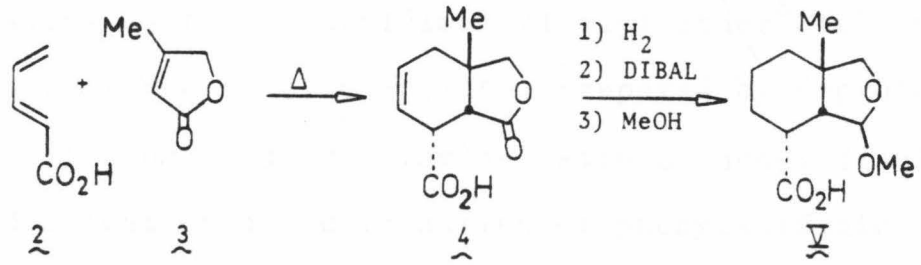
magnesium chloride.[3] An examination of molecular models of III reveals that attack upon the double bond should occur from the convex side of rings A and B, and that the chair transition state should be favored over the boat.[2,3a] Prior to undertaking the synthesis model studies are proposed.

Cleavage of the ester bond in IV leads to compounds V and VI. The Diels-Alder reaction will give the requisite stereochemistry for V. Compound VI will be prepared from the vinyl anion VII. For the purposes of a chiral synthesis resolution of both V and VI are required. This proposed strategy allows for the convergent synthesis of shikodonin and should be able to be carried out as follows.

Synthesis of V

The proposed synthesis of V is illustrated in Scheme II. The Diels-Alder reaction of the relatively unreactive diene 2 and dienophile 3 should give 4. Previously Diels-Alder cycloadditions have been performed with 2 and acrylic acid.[4] This reaction was shown to go in good yield, and the only product observed resulted from exclusive ortho

Scheme II



2 3 4 V

and endo addition.[4] It is proposed that the carboxylic acid 4 will be resolved via a chiral amine salt. The reduction of the olefin with hydrogen followed by treatment with diisobutylaluminum hydride and quenching with methanol should give acetal V. As has been observed the reduction of the lactone to the lactol should occur in preference to reduction of the carboxylic acid.[5]

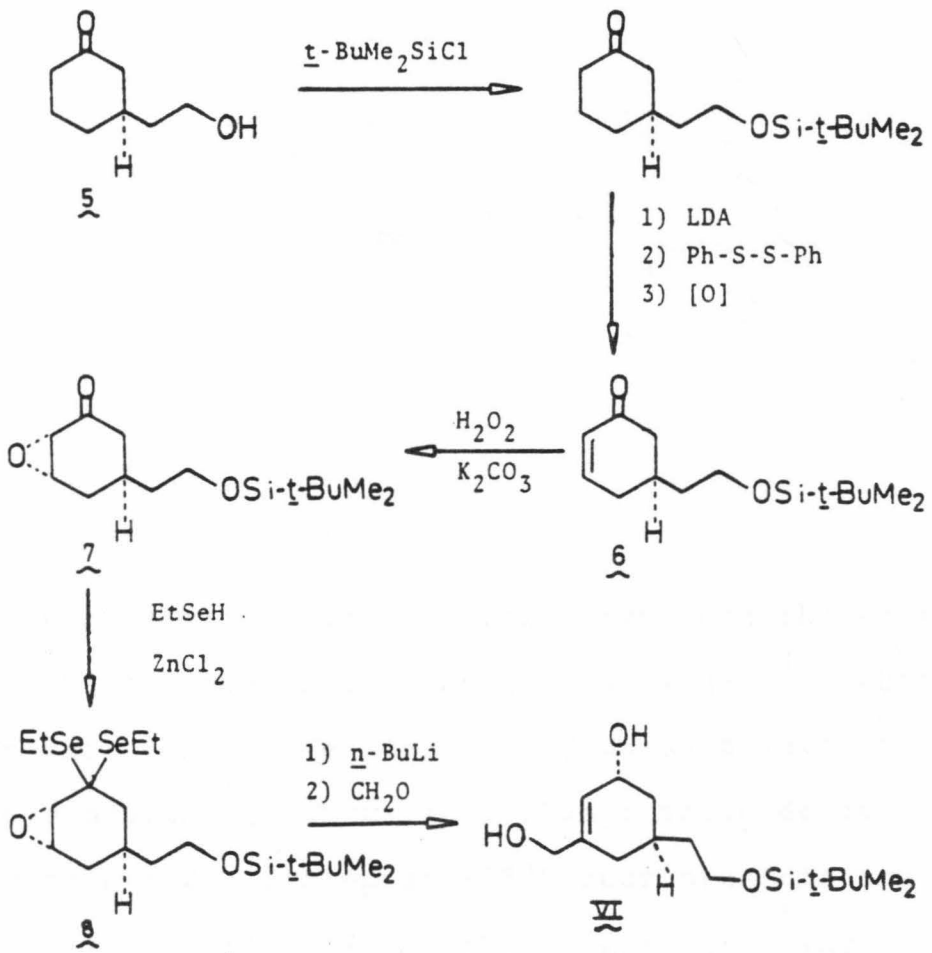
Synthesis of VI

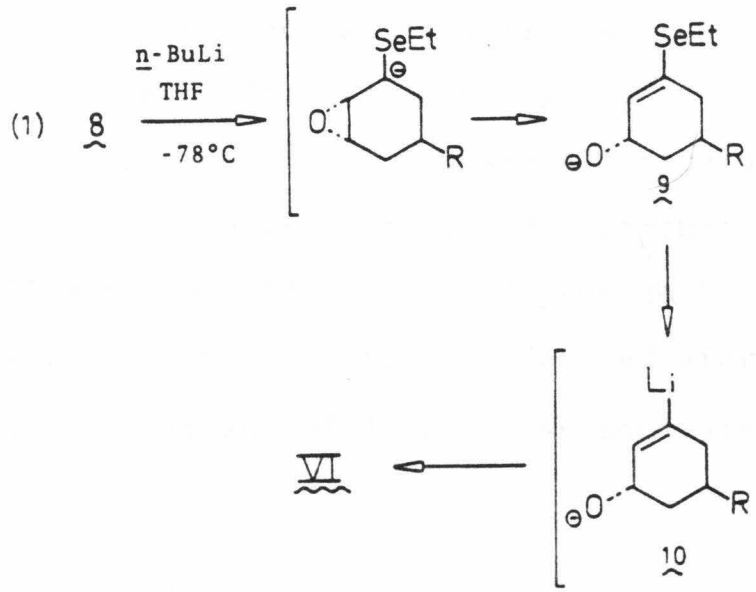
The proposed synthesis of VI is outlined in Scheme III. The readily available compound 5[6] may be resolved through an optically active carbamate.[7] Protection of the alcohol functionality as the t-butyldimethylsilyl ether[8] followed by trapping of the kinetic enolate (prepared by deprotonation with lithium diisopropylamide) with diphenyl disulphide and oxidation and elimination of phenylsulfenic acid should give enone 6.[9]

The question of the stereochemistry of the secondary alcohol will be approached via an epoxide cleavage. Basic hydrogen peroxide has been shown to produce an epoxide of the desired stereochemistry when the side chain is a methyl group.[10] Application of this technology to enone 6 should provide epoxy ketone 7 which would then be treated with ethyl selenol and zinc chloride.[11] Under these conditions the selenoacetal should form without any complications.[12]

Treatment of selenoacetal 8 with two equivalents of n-butyllithium should result in the transformation depicted in equation 1. Selenoacetals are readily transmetallated with n-butyllithium at -78°C.[13] This should result in formation of vinyl selenide 9 via epoxide

Scheme III

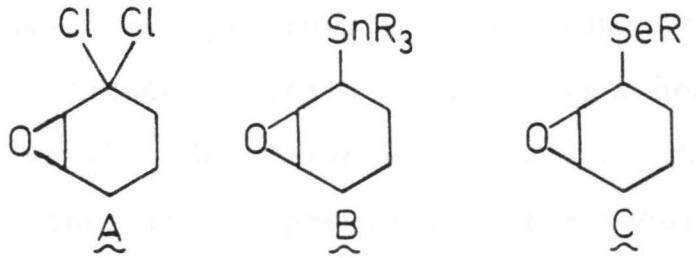

t-BuMe2SiCl
OH
OSi-t-BuMe2
5
1) LDA
2) Ph-S-S-Ph
3) [O]
H2O2
K2CO3
7
6
EtSeH
ZnCl2
EtSe SeEt
1) n-BuLi
2) CH2O
HO
8
VI



opening. Direct attack of n-butyllithium upon the epoxide should not be observed under these conditions.[14] Raucher has shown that vinyl selenides will transmetallate at -78°C in tetrahydrofuran.[15] When vinyl phenyl selenide is treated with n-butyllithium at -78°C four products are obtained: (1) addition of butyllithium to the vinyl selenide (5%); (2) abstraction of the vinyl proton (15%); and (3) transmetallation to form a mixture of phenyllithium and vinyllithium (80%).[15] In the system depicted in equation 1, vinyl proton abstraction will not be a

problem, nor will formation of ethyllithium be due to the large pK_a difference between ethylene and ethane. Abstraction of a proton from the ethyl group on selenium also should pose no problem.[16] Transmetallation of 9 should occur to give the vinyl anion 10. Capture of the vinyl anion 10 with formaldehyde would provide VI.

Other possible precursors for the desired vinyl anion 10 are A → C. Treatment of A with two equivalents of



A B C

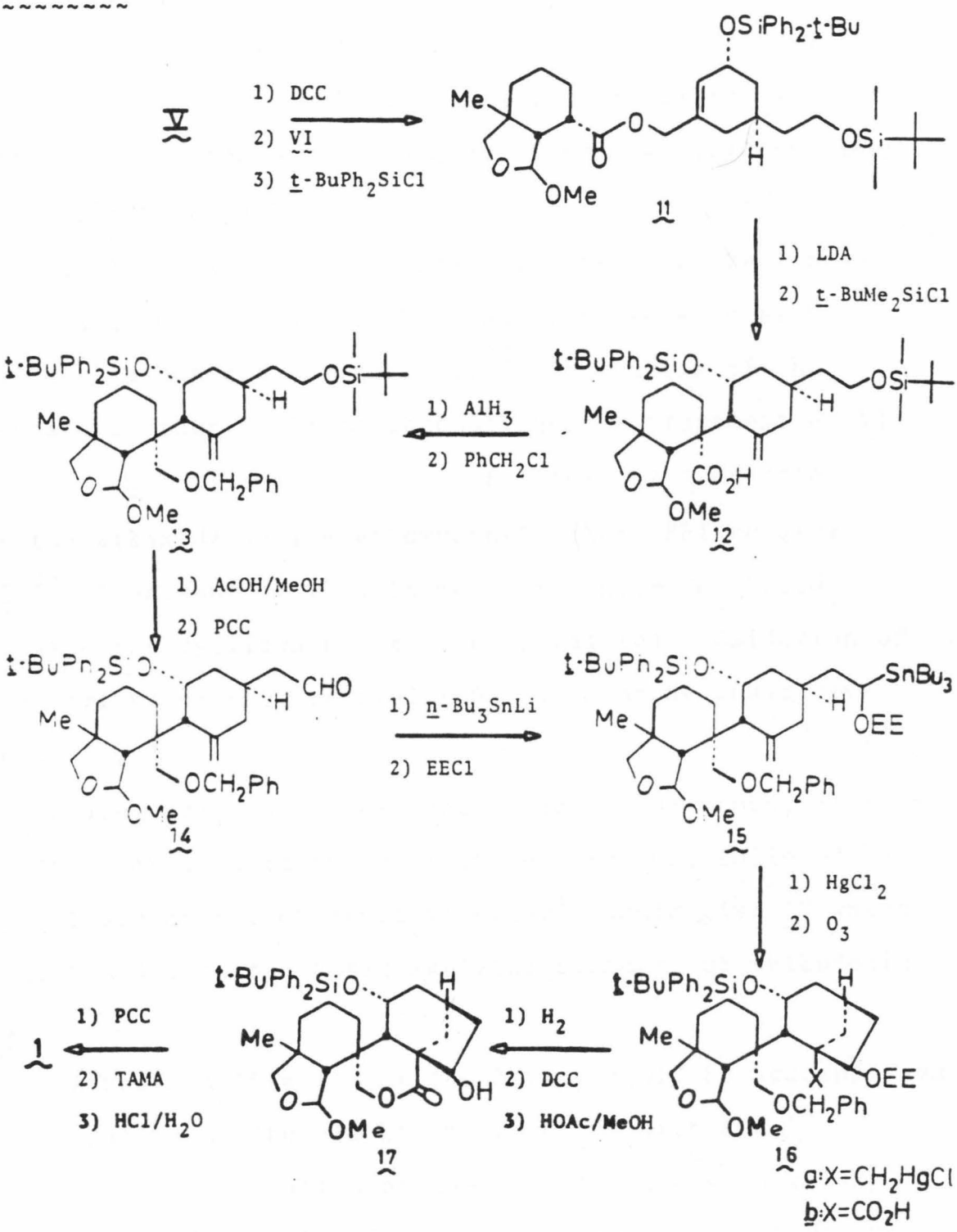
n-butyllithium should lead to 10. Compounds B and C may also be converted to 10 by treatment with lithium diisopropylamide, isolation of the vinyl selenide or stannane and treatment with n-butyllithium. Vinyl stannanes have been shown to readily transmetallate.[17] This novel formation of a vinyl anion of an allylic alcohol from an α,β-unsaturated ketone,[18] as depicted above, should allow for the synthesis of 10.

Synthesis of 1

The completion of the synthesis of shikodonin (1) is outlined in Scheme IV. Ester formation from acid V and alcohol VI with dicyclohexylcarbodiimde (DCC) followed by protection of the secondary alcohol with t-butyldiphenylsilyl chloride[19] would provide 11. Ester formation is expected to occur with the primary hydroxyl of VI rather than at the more sterically hindered secondary hydroxyl. The ester enolate Claisen rearrangement of 11 should afford 12 as described previously. The reduction of acid 12 with alane followed by its protection as a benzyl ether would give 13. Selective hydrolysis of the t-butyldimethylsilyl ether in the presence of the t-butyldiphenylsilyl ether as has been described would provide an intermediate primary alcohol.[19] Oxidation of the primary alcohol to aldehyde 14 could be accomplished under nearly neutral conditions with pyridinium chlorochromate (PCC), thus, preserving the acid labile functional groups.[20]

The formation of the D-ring might be accomplished by utilizing an α-stannyl ether as an equivalent for the anionic center in I. An olefin may serve as the source of the cationic center in this bond disconnection. Peterson and others have shown that homoallyl stannanes react with

Scheme IV


V
1) DCC
2) VI
3) t-BuPh2SiCl
OSiPh2-t-Bu
Me
O
H
OSi
OMe
11
1) LDA
2) t-BuMe2SiCl
t-BuPh2SiO
OSi
H
Me
CO2H
OMe
12
1) AlH3
2) PhCH2Cl
OCH2Ph
13
1) AcOH/MeOH
2) PCC
CHO
14
1) n-Bu3SnLi
2) EECl
SnBu3
OEE
15
1) HgCl2
2) O3
X
16
a: X=CH2HgCl
b: X=CO2H
1) H2
2) DCC
3) HOAc/MeOH
OH
17
1) PCC
2) TAMA
3) HCl/H2O
1

a wide variety of electrophiles, including mercuric chloride to form cyclopropanes.[21] Recently, Macdonald has applied an intramolecular alkyltin mediated cyclization for the formation of 6,6- and 6,5-fused carbocycles along with 6,5-spiranes.[22]

Still has shown that α-stannyl ethers may be trans-metallated with n-butyllithium and reacted with alkyl halides, aldehydes, or ketones.[23] Generation of the α-stannyl ether would be accomplished by treatment of 14 with tri-n-butylstannyllithium followed by protection of the alkoxide as the ethoxyethyl ether (EE) to give 15.[23] Treatment of 15 with mercuric chloride should provide the cyclized primary mercurial 16a. Oxidation of the derived organomercurial (16a) with ozone would give acid 16b.[24]

Hydrogenolysis of the benzyl protecting group, closure of the hydroxy acid to the lactone with DCC, followed by hydrolysis of the ethoxyethyl ether[19] would give 17 which contains all of the basic skeletal elements of shikodonin (1).

Refunctionalization of the D-ring could be accomplished by oxidation of the alcohol to a ketone with PCC,[20] followed by elaboration of the exomethylene with trioxymethylene and methylanilinium trifluoroacetate (TAMA) under

extremely mild conditions.[25] Hydrolysis of the t-butyldiphenylsilyl protecting group would yield optically active shikodonin (1).

Conclusion

A synthesis of the antitumor compound shikodonin (1) is proposed. The key carbon-carbon bond forming reactions are: (1) an ester enolate Claisen rearrangement; (2) an olefin cyclization performed via an α-stannyl ether to construct the D-ring; and (3) hydroxymethylation of a vinyl anion formally derived from an allylic alcohol.

The vinyl anion will be derived from an α,β-unsaturated ketone in a novel sequence which should be of general utility. The proposed synthesis of shikodonin (1) should provide compound 1 and synthetic intermediates in optically pure form for medical and biomedical testing in addition to serving to verify the assigned absolute configuration of 1.

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18. For example, see D. A. Evans and G. C. Andrews, Acc. Chem. Res., 7, 147 (1974).
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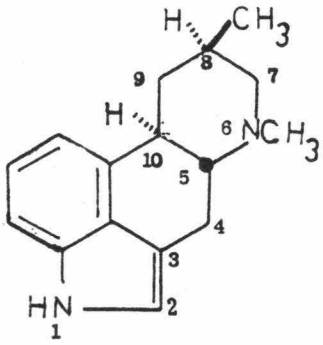
Proposition II

A general synthetic route to the ergoline nucleus is proposed, and the total synthesis of the ergot alkaloids festuclavine (1), dihydrolysergol (2) and their derivatives D-6-methyl-8-cyanomethylergoline (3), Uterdina (4), and MCE (5) are outlined.

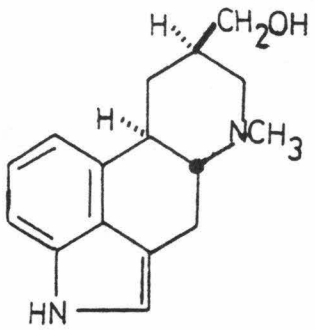
* * * * *

The ergot alkaloids exhibit useful and interesting biological properties and have become the target of frequent syntheses.[1] Festuclavine (1) and dihydrolysergol (2) are naturally occuring ergot alkaloids of the clavine series. D-6-Methyl-8-cyanomethylergoline (3), which has been claimed to exhibit antifertility effects,[2] and the amides of 6-methyl-8-β-aminomethyl-10-α-ergoline are ergot derivatives which exhibit significant biological activity.[1a, 3] 6-Methyl-8-β-acetylaminomethyl ergoline (Uterdina, 4) exhibits specific oxytocic activity with minimal side effects, and 1, 6-dimethyl-8-β- (benzyloxycarbonyl)-aminomethyl ergoline (MCE, 5) exhibits long lasting action against serotonin.

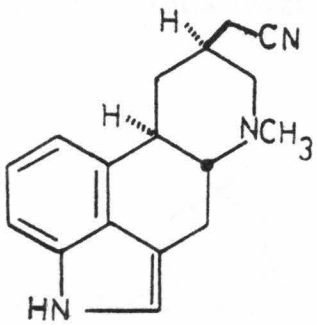
The purpose of this proposal is to propose a synthesis for these useful alkaloids through the common intermediate 6. This intermediate will be made through a hydroboration reaction which will introduce all


H
CH3
8
9
7
H
6
NCH3
10
5
4
3
HN
1
2

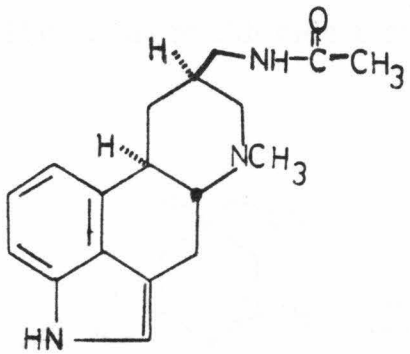
1


H
CH2OH
H
NCH3
HN

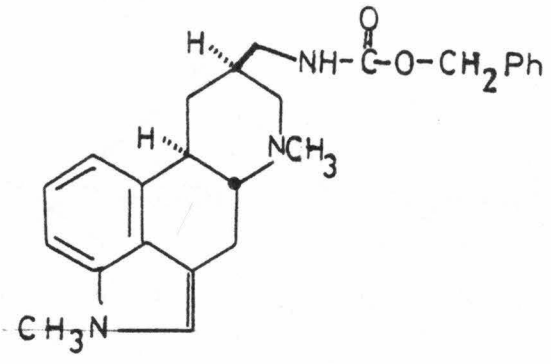
2


H
CN
H
NCH3
HN

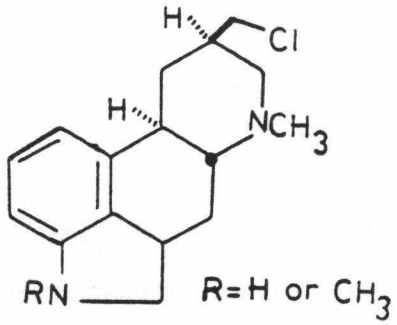
3


H
NH
C
O
CH3
H
NCH3
HN

4


H
NH
C
O
O
CH2Ph
H
NCH3
CH3N

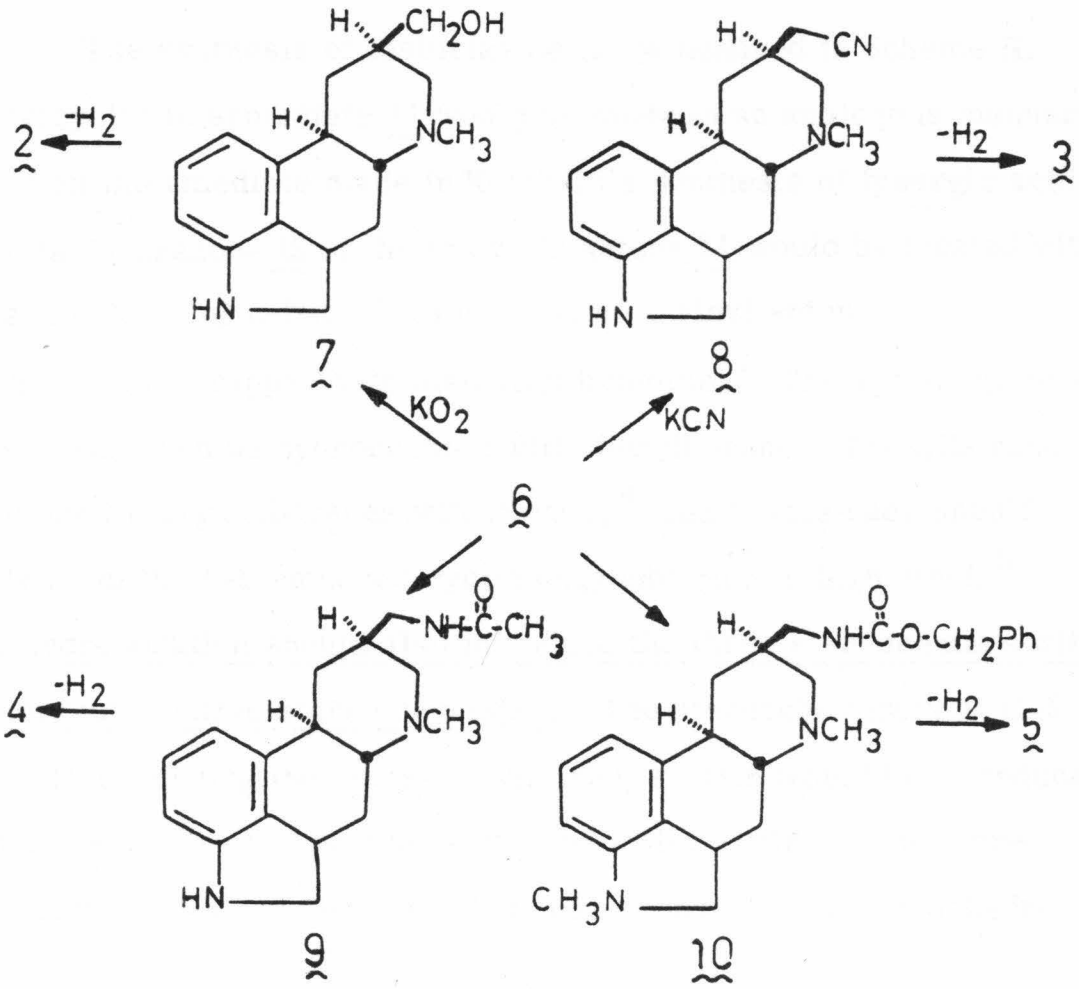
5



6

three stereocenters in one step. Scheme I shows how one could attain the various ergot alkaloids from 6. The primary chloride 6 could be

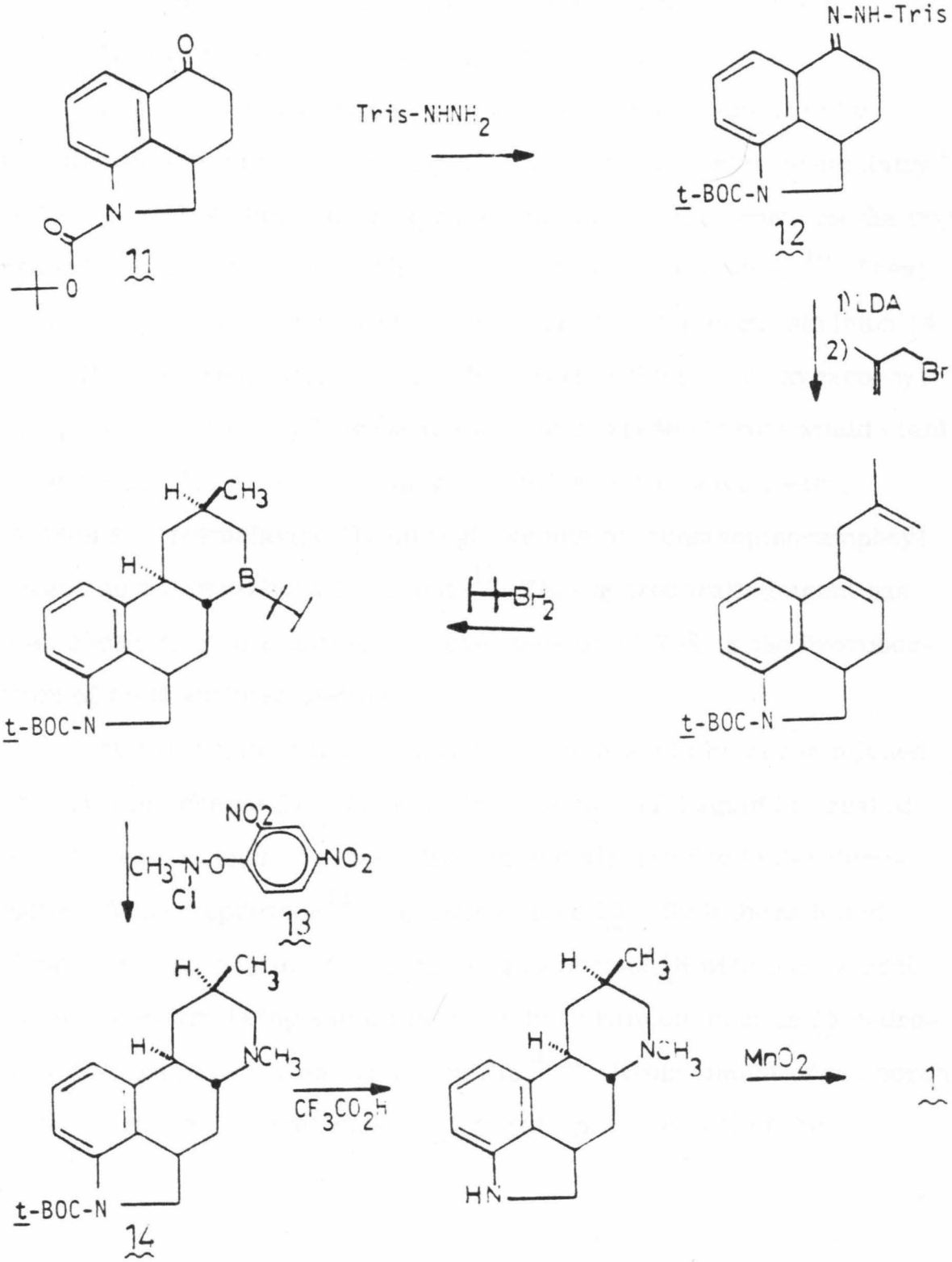
SCHEME I



reacted with potassium superoxide in DMF/DMSO containing 18-crown-6 to produce the primary alcohol 7.[4] The nitrile 8 would be obtained from the primary chloride 6 by reaction with potassium cyanide in DMSO, and amides 9 and 10 would be produced from the primary chloride 6 by reaction with the appropriate amide anion. Manganese dioxide, along with other dehydrogenating reagents, dehydrogenates similar indolines to indoles.[5] Dehydrogenation of 7, 8, 9, and 10 would lead to dihydrolysergol (2), D-6-methyl-8-cyanomethylergoline (3), Uterdina (4), and MCE (5), respectively. Thus, from one common intermediate, various ergot alkaloids and their derivatives may be made.

The synthesis of festuclavine (1) is outlined in Scheme II. The tricyclic intermediate 11 would be made in an analogous manner to that of an intermediate made in Kornfeld's synthesis of lysergic acid.[6] The trisylhydrazone 12 of the tricyclic ketone 11 would be treated with two equivalents of n-butyl lithium to yield a vinyl anion which would be trapped with methallyl bromide.[7] The 1,4-diene produced would then be hydroborated with thexylborane. Thexylborane forms cyclic organoboranes with dienes,[8] and in this case should easily form the 6-membered cyclic organoborane in high yield.[9] This hydroboration should also introduce the three stereocenters with the correct relative stereochemistry. The stereochemistry at C-5 and C-10 producing the trans-decalin ring system would be introduced via the cis-addition of borane to the endocylic olefin.[8] The stereochemistry at C-8 can be controlled under conditions where dehydro-

SCHEME II


Tris-NHNH2
N-NH-Tris
t-BOC-N
11
12
1) LDA
2)
Br
H
CH3
B
BH2
13
NO2
CH3
N
O
Cl
NCH3
CF3CO2H
MnO2
HN
14
1

boration-rehydroboration can occur. This should lead to the more stable epimer at C-8 where the methyl group is equatorial. The α-methyl epimer would have a bad 1, 3-diaxial interaction with the hydrogen at C-10 in the rigid trans-decalin ring system.

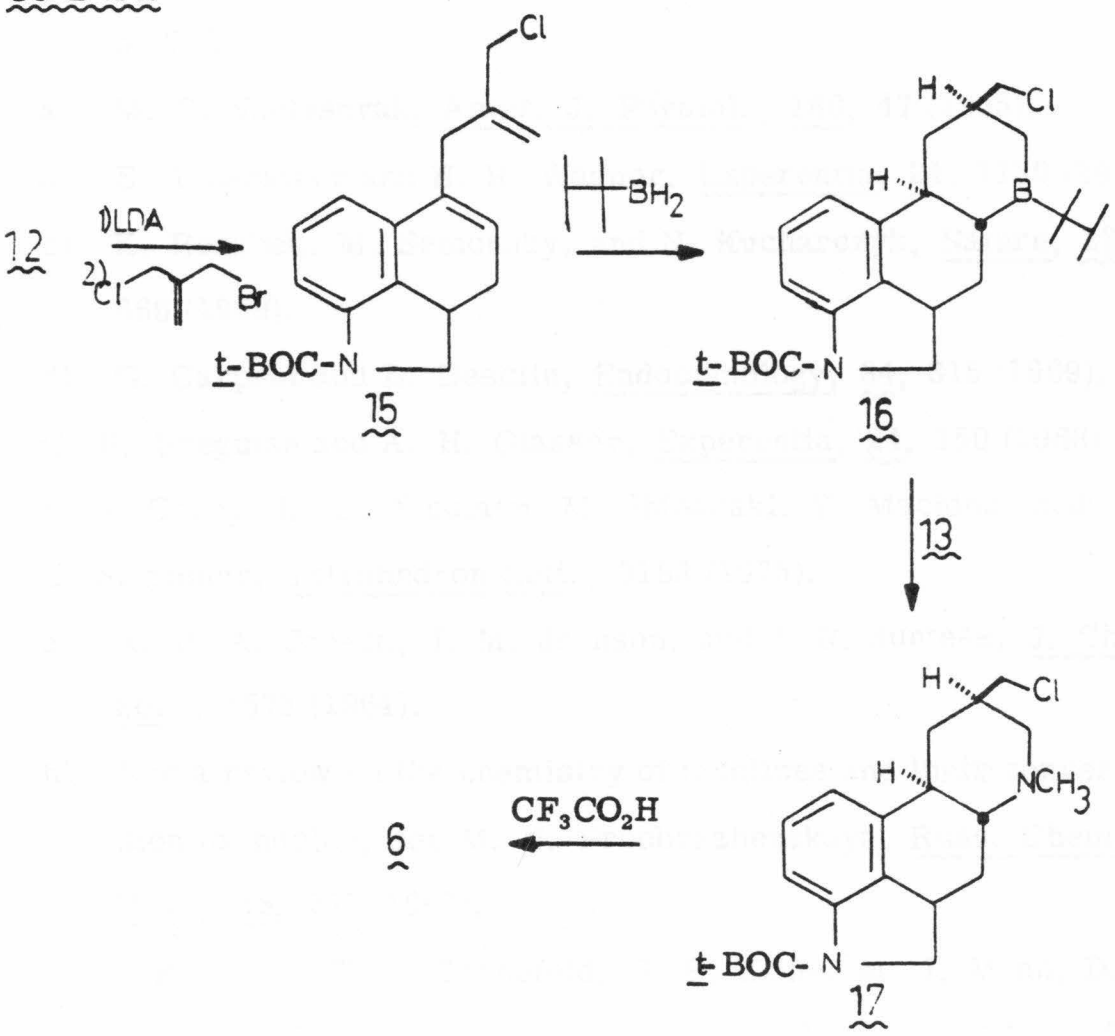
Recently, Mueller has shown that two alkyl groups may be transferred from boron to nitrogen with retention of stereochemistry.[10] N-Methyl-N-2, 4-dinitrophenoxychloramine (13) which contains the two needed leaving groups would be made by Mueller's method.[10] Treatment of the organoborane with 13 would produce the ergot skeleton 14 with all the stereocenters intact. Removal of the t-butyloxycarbonyl group followed by dehydrogenation with manganese dioxide would yield festuclavine (1). This route may also allow for an asymmetric synthesis of festuclavine (1) through the use of monoisopinocampheyl borane as the hydroborating agent.[11] This hydroborating agent has been shown to give enantiomeric excesses of 53-73% in the hydroboration of trisubstituted olefins.

The synthesis of the key intermediate 6 would be accomplished as shown in Scheme III. Trisylhydrazone 12 would again be treated with two equivalents of n-butyl lithium and alkylated with 2-chloromethyl-3-bromopropene[12] to produce diene 15. Hydroboration of diene 15 should produce the cyclic organoborane 16 with the correct stereochemistry being established. Allylic halides such as 15 hydroborate at the primary end of the olefin.[8, 13] Replacement of the boron with nitrogen as before leads to 17 which upon removal of the

t-butyloxycarbonyl group would the key intermediate 6 (R = H). In the synthesis of MCE (5) the t-butyloxycarbonyl group would be replaced by an N-methyl group in indoline 11.

Intermediate 6, which is made via a hydroboration reaction that introduces all the relative stereochemistry in one step, could then be converted to any of the desired alkaloids mentioned previously.

SCHEME III



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PROPOSITION III

A mechanism for the mode of action of the insect antifeedant warburganal is proposed. The use of warburganal in studying the molecular basis of taste reception in human beings and insects is proposed.

* * * * * * * * *

Introduction

Relatively little is understood on the molecular level about the mechanism of taste. This lack of understanding of how a taste stimulus binds to a taste receptor and triggers it to respond has been hampered by the inherently weak binding of taste stimuli to taste receptors.[1] The insect antifeedant compound warburganal (1) has been shown to bind irreversibly to the taste sensilla of the African armyworm Spodoptera exempta.[2c] A mechanism is proposed for the mode of action of the insect antifeedant warburganal (1). An understanding of the mechanism of action of insect antifeedants could help lead in the design of non-polluting insect control agents. It is also proposed to use warburganal (1) as a tool in helping understand

the biochemical action of taste reception in insects by the isolation of an insect taste receptor site. In addition the binding of 1 to human taste receptors may allow an investigation of taste perception in humans. It should be pointed out that no convincing demonstration of the isolation of a taste receptor molecule has yet appeared.[3]

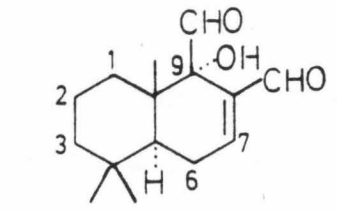
Methods of Discussion

I. Mechanism of Action

Figure 1 illustrates some structure-activity relationships amongst warburganal derivatives.[2] These tests indicate that the enal-aldehyde functionality plays an essential role in the antifeedant activity. Epimerization of the 9β-aldehyde of polygodial (4) to the 9α-aldehyde (6) results in loss of activity. Oxidation or reduction of either of the aldehyde functions of polygodial to produce 7 → 11 also results in loss of activity.[2] Nakanishi and Kubo have shown that the addition of an equimolar equivalent of cysteine to warburganal (1) blocks its activity. They have suggested that the enal unit acts as a nucleophile acceptor (SH), and that the 9β-aldehyde acts as a

Antifeeding Activity

Active



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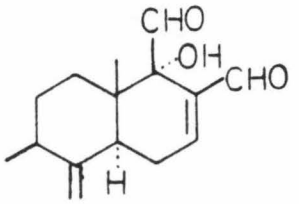

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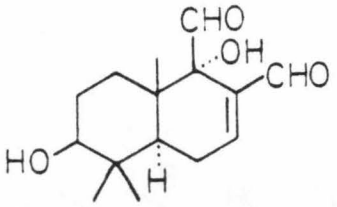

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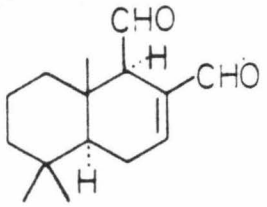

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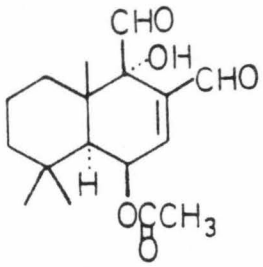

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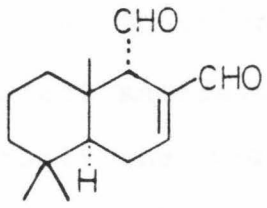
Inactive



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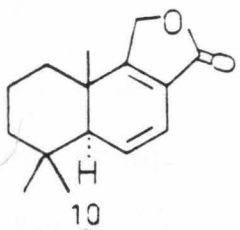

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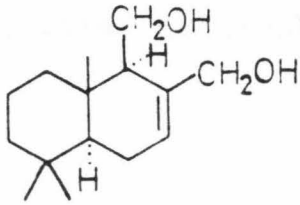

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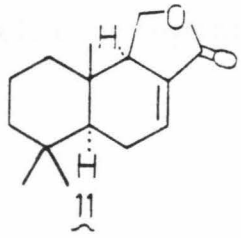

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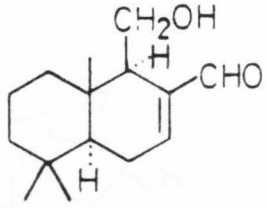

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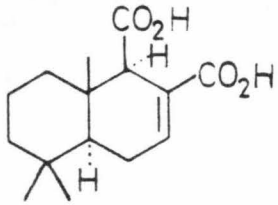

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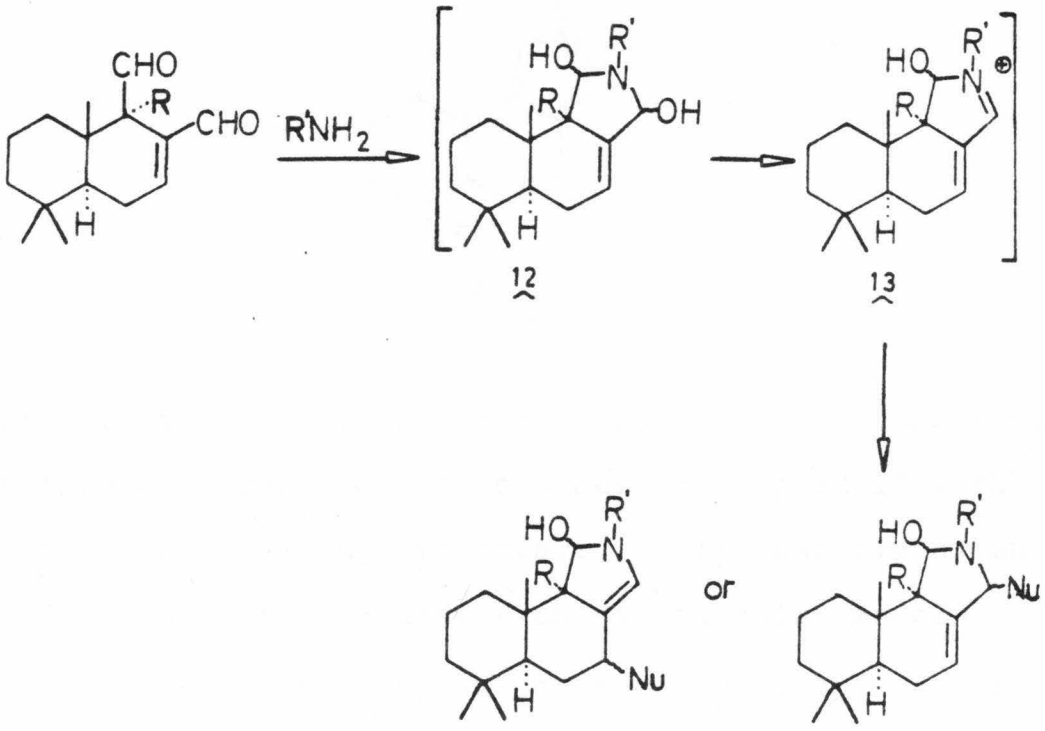
Figure I

hydrogen bond or nucleophile acceptor which is located at a critical distance from the enal function.[2e]

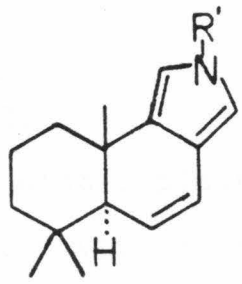
It is proposed that these insect antifeedants react first with a primary amine, probably the ε-amino group of lysine to form the activated nucleophile acceptor 13 (Scheme I). The need for an activated nucleophile acceptor

Scheme I



may be demonstrated by the inactivity of 7 → 11.

Polygodial (4) has less antifeedant activity than warburganal (1).[2] The proposed mechanism of action offers an explanation for this phenomena. The activated nucleophile acceptor (13, R = H) formed from 4 can lead to a less active nucleophile acceptor by formation of pyrrole 14. The formation of 14 is not likely from the warburganal intermediate 13 (R = OH) because there is not an acidic proton at C-9.



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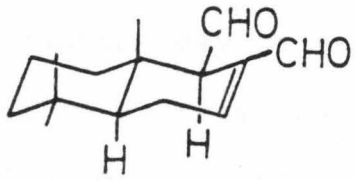
Epi-polygodial (6), with a 9α-axial aldehyde function, cannot form the proposed active acceptor complex 13 with the lysine ε-amino group; therefore, it is inactive as an antifeedant compound. Examination of molecular models of 4 and 6 reveals that the 9β-equatorial aldehyde (4) is in close proximity to the enal and may be able to form the pyrrollidine ring in 12; whereas, the 9α-axial aldehyde (6) is stubstantially farther from the dienal and should



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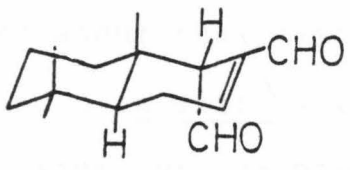

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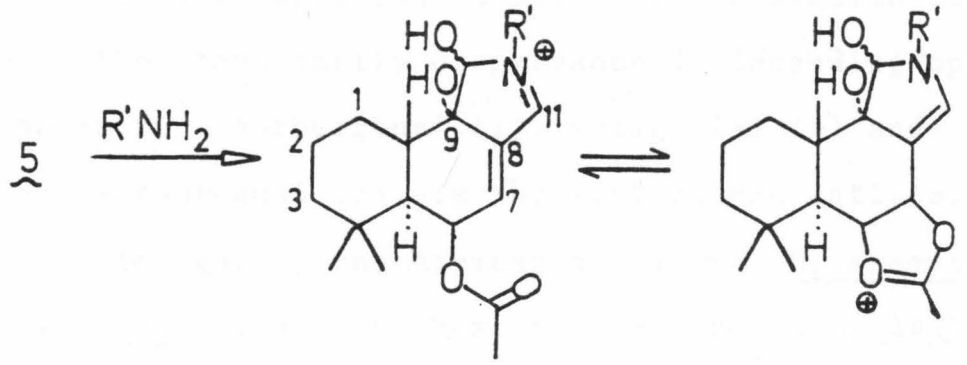
not form intermediate 12.

This hypothesis may also explain why cinnamodial (5) shows less antifeedant activity than 4. The 6-β-o-acetate unit of 5 could serve as an internal nucleophile and may



capture the developing ene-imonium ion. If this were to occur the electrophilicity of carbons C-7 and C-11 may change and disrupt the interception of a biological nucleophile.

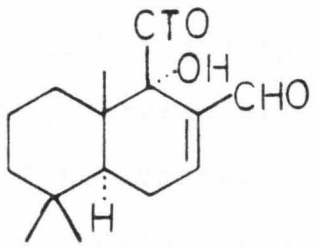
Some information may be gained about the feasibility of this mechanism by treating 4 and 6 *in vitro* with one molar equivalent of lysine and looking for the proposed intermediates spectroscopically. The ultimate proof would lie in the isolation of the irreversibly inhibited taste sensilla of the African armyworm, *S. exempta*, followed by degradation and identification of the resulting fragments.

II. Use of Warburganal in Isolating Insect Taste Receptors

Insect antifeedants can result in the cessation of feeding either temporarily or permanently depending upon their potency.[4] Warburganal (1), muzigidial (3) and 3-hydroxy warburganal (3) are the most potent antifeedants known to date against the African armyworms *S. exempta* and *S. littoralis*, and the Mexican bean beetle *Epilachna varivestis*.[2] Three successive applications of warburganal (1) to the taste sensilla of the African armyworm results

in its taste sense being irreversibly blocked, resulting in the death of the insect by starvation.[2c]

Warburganal has been the target of much synthetic effort.[5] The published syntheses would easily allow for the introduction of a tritium label via a reduction of an ester function with ^{3}H-lithium aluminum hydride[6] to produce 15. Application of 15 to the taste sensilla



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of S. exempta, followed by separation of the molecules that it is comprised of by centrifugation or chromatographic means, and identification of the radioactive fragments should provide information about the structure of the receptor molecules.

The receptor molecules might also be isolated by attachment of 3-hydroxy warburganal (3) to an affinity column.[7] Binding of 3 to an affinity column through the hydroxyl at C-3 and passage of digested taste receptor proteins through such a column may afford the insect receptor

fragment after cleavage of 3 from the column. In such a manner the first taste receptor molecule might be isolated.

III. Use of Warburganal in Studying Human Taste Receptors

Active warburganal-type insect antifeedants have been noted to exhibit a lasting hot and spicy taste (approximately 15-30 minutes) to humans, whereas all inactive derivatives (Figure 1) are devoid of hot taste. This may indicate that warburganal (1) binds with a high affinity to human taste receptor sites. Binding studies on human taste tissue have been done by Cagan and Morris with tritiated monellin, a sweet tasting polypetide.[3] A similar experiment with radiolabelled 15 would give information concerning the reversibility of the binding of warburganal (1) to human taste receptors. Human taste receptor molecules may then be isolated as discussed above for the insect taste receptors. Highly purified, defined receptor molecules would thus enable more definitive studies on the binding interactions of various taste stimuli.

Summary

A mechanism is proposed for the mode of action of warburganal (1). An understanding of the mechanism of action of insect antifeedants could help lead in the design of non-polluting insect control agents. It is proposed to use warburganal (1) to study the biochemical action of taste reception in human beings and insects. Warburganal may allow for the first isolation of a taste receptor molecule.

References and Notes

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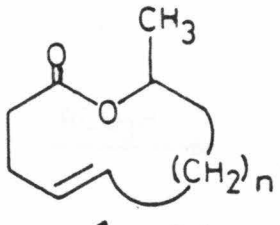
Proposition IV

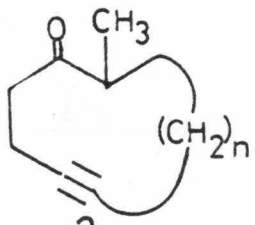
Two three-carbon ring expansion reactions are proposed and are utilized in a synthesis of d,l-muscone (10).

* * * * *

There has been much interest generated recently in the synthesis of macrocycles. These macrocycles have exhibited some interesting biological activities and have played an important role in the perfume industry. One way to approach the synthesis of these molecules is through the use of ring expansion reactions.[1-3] There are an increasing number of macrocycles containing the functionality as shown in 1.[4] One could use as a precursor to 1 the structure shown in 2, which could be attained via a three-carbon ring expansion reac-



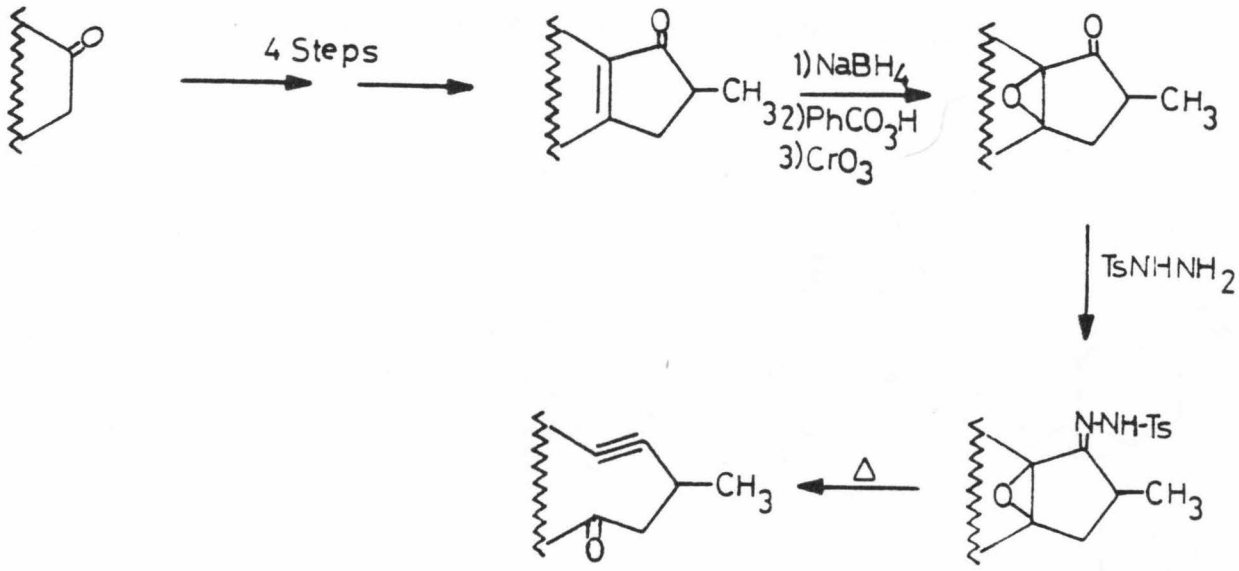
1 n= 2,4



2

tion. Eschenmoser has made alkynones such as 2 via fragmentation of epoxy hydrazones to produce three-carbon ring expanded products[5] as shown in Scheme I. However, this method suffers because it is quite lengthy, and epoxidation of α,β-unsaturated ketones

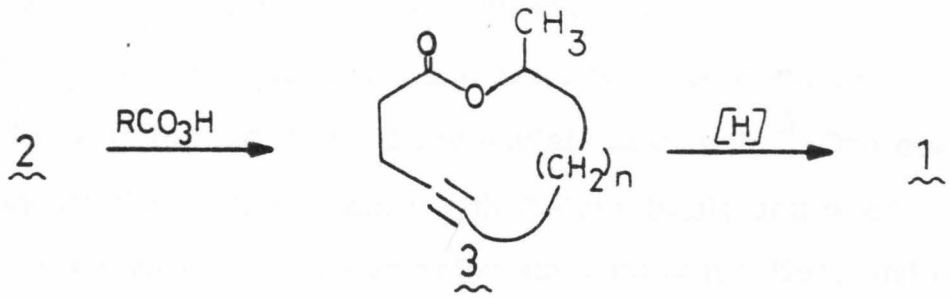
SCHEME I



may be difficult at times.

Scheme II shows how one could attain 1 from 2. Baeyer-Villager

SCHEME II

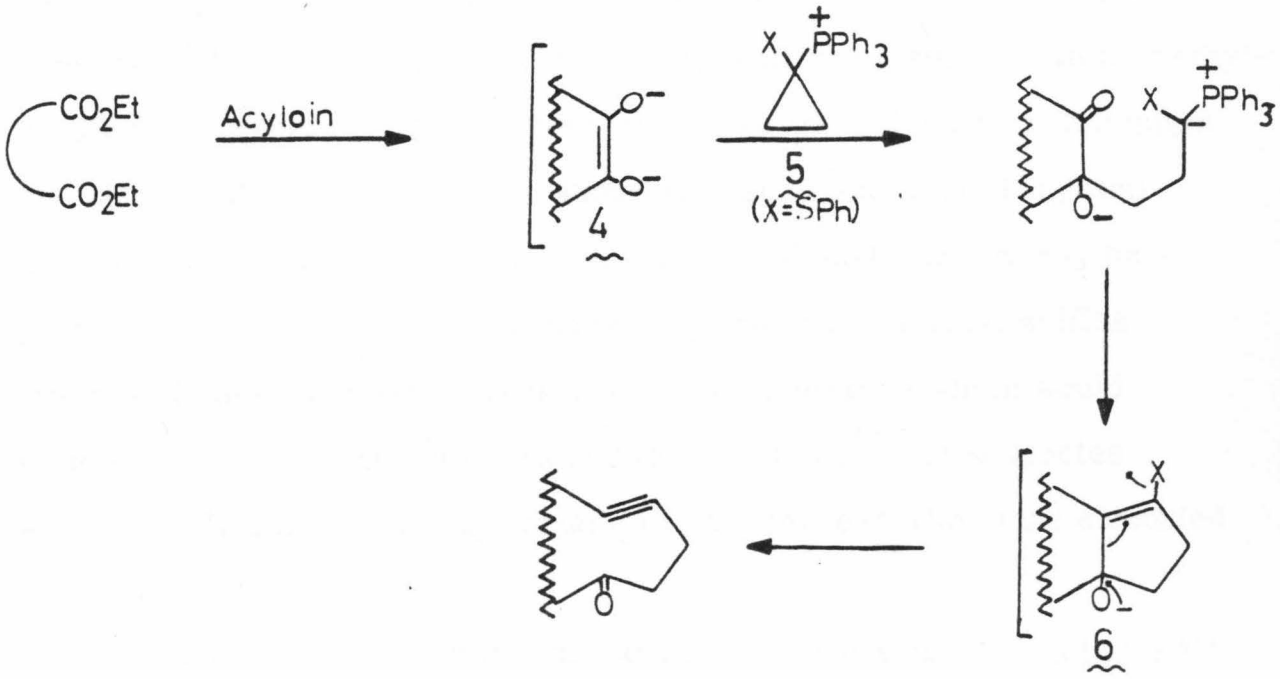


oxidation of 2 should proceed smoothly to give 3 as acetylenes are one thousand times less reactive towards peracids than are olefins,[6] and it has been shown that Baeyer-Villager oxidation of ketones may occur in systems containing olefins of low reactivity.[7] Reduction of the

acetylene would then yield either a cis or trans olefin depending on the conditions employed.

The first of the three-carbon ring expansion reactions proposed is shown in Scheme III. Acyloin products from the

SCHEME III

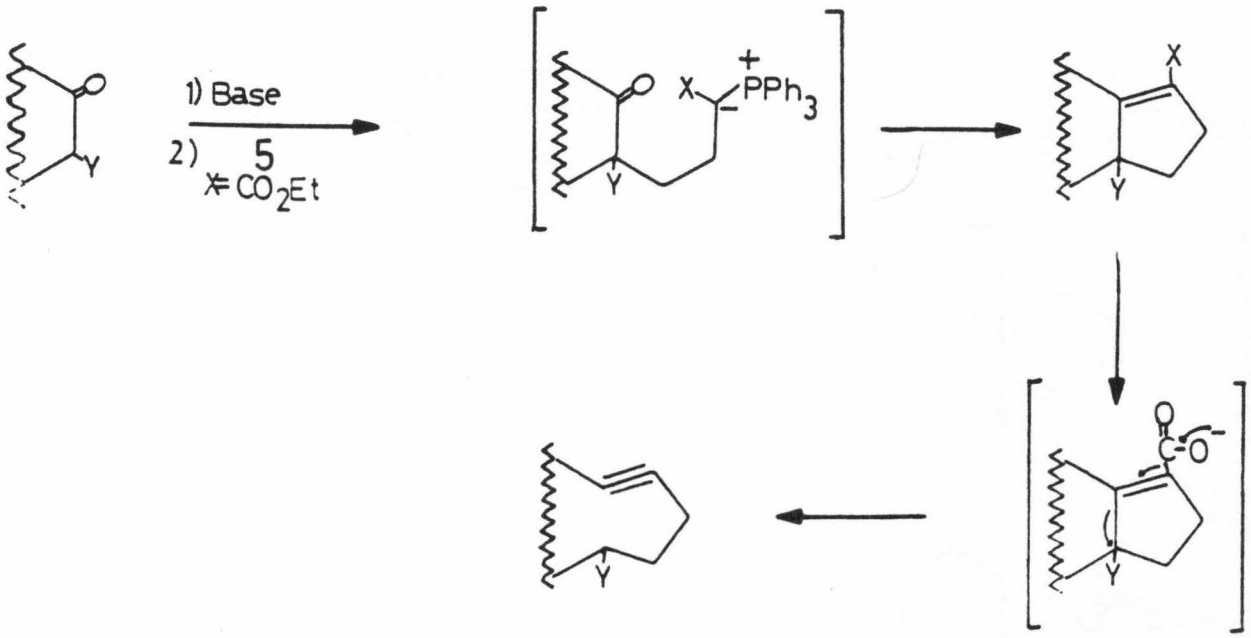


condensation of diesters have been shown to undergo alkylations, Michael additions, and aldol condensations on carbon through the thermodynamic enolate dianion 4.[9] One could then alkylate the enolate dianion with the geminally activated cyclopropane 5 where X would be an anion stabilizing function, and could also serve as a leaving group. One such possibility would be X = SPh. Marino has shown that this cyclopropanone can be opened by enolates, and then after the alkylation an intramolecular Wittig reaction occurs to form a vinyl sulfide.[10]

A fragmentation similar to that of intermediate 6 occurs in the case where X = Cl.[11] The thiophenoxy group of intermediate 6 could serve as a leaving group, or it could be converted to a sulfonium salt which would serve as still a better leaving group. The trans antiperiplanar arrangement of the fragmenting species should greatly facilitate the fragmentation.[12] The conversion of the thiophenoxy group into a sulfonium salt could be accomplished by alkylating the hydroxy vinyl sulfide on sulfur with trimethyloxonium tetrafluoroborate followed by making the alkoxide. α-Sulfonium alkoxides of this type have been shown to displace methyl phenyl sulfide to form epoxides,[13] although in this case demethylation may be a problem. Still a better way of converting the hydroxy vinyl sulfide into a sulfonium salt would be to react it with benzyne which would yield the diphenyl sulfonium salt and the alkoxide.[14] This species should easily undergo a fragmentation to the three-carbon ring expanded acetylenic ketone.

Another three-carbon ring expansion is illustrated in Scheme IV. In this case, Y would also need to be a group that could stabilize a carbanion. The thiophenoxy group could again be used, but there are also other possibilities that exist. α-Thiophenoxy ketones, which are readily obtained from ketones,[15] have been shown to alkylate on the carbon bearing the thiophenoxy group, and the acidity of the proton on the carbon bearing the thiophenoxy group is enhanced by at least three pK_A units.[16] It has been shown that the desired geminally activated cyclopropane 5 (X = CO_2Et) can be opened by enolates, and readily undergoes an intramolecular Wittig reaction to form the five-

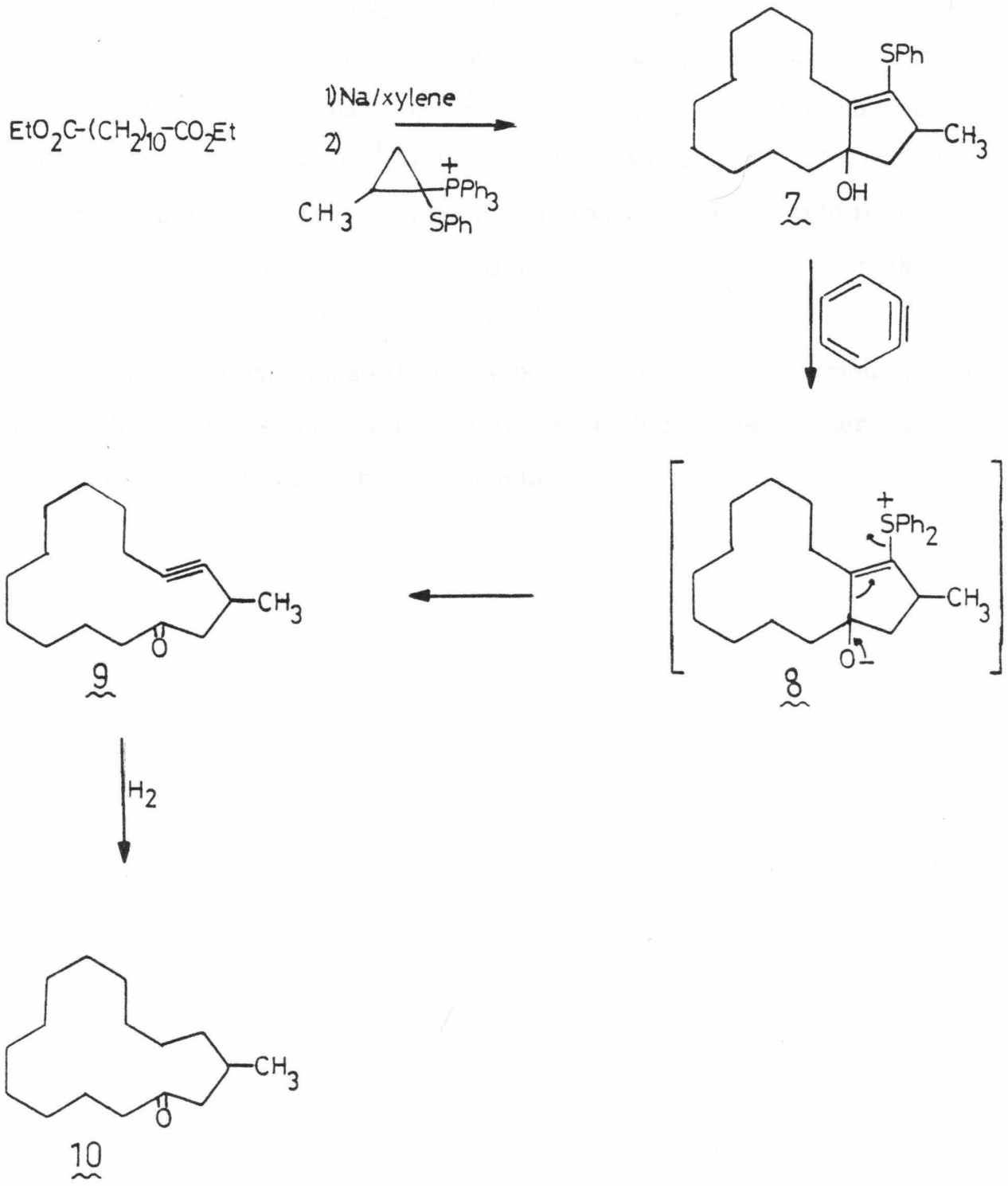
SCHEME IV



membered ring annelated product.[17] The ester would then be hydrolyzed to the carboxylic acid salt which should undergo decarboxylative fragmentation. Carbon-carbon bond cleavages similar to this type have been reported.[18] Again, the trans antiperiplanar arrangement of the fragmenting species should greatly facilitate the fragmentation.[12] If the thiophenoxy group is not a good enough carbanion stabilizing group for the fragmentation to proceed smoothly, a sulfonium salt could be used which would be made by the methods discussed previously. The sulfonium salt would then lead to the more stable sulfur ylid. A protic solvent may also serve to facilitate the fragmentation. The three-carbon ring expanded acetylene also has, in this case, further functionality to elaborate the ring.

Scheme V shows the application of this synthetic method to the

SCHEME V


EtO2C-(CH2)10-CO2Et
1) Na/xylene
2)
CH3
PPh3
SPh
SPh
CH3
OH
7
SPh2
CH3
8
CH3
9
H2
CH3
10

synthesis of d,l-muscone (10), a macrocyclic ketone used in the perfume industry.[19] The desired acyloin adduct has been prepared in a yield of 64-89%.[8] Alkylation with the needed cyclopropane, which could be prepared by the method of Marino,[10, 20] would occur at the least substituted carbon in aprotic solvents[21] to yield the hydroxy sulfide 7. Treatment with benzyne would yield the sulfonium alkoxide 8 which should fragment to acetylenic ketone 9. Reduction of the acetylene has been shown to give d,l-muscone (10) in high yield.[5a]

In conclusion, these three-carbon ring expansion reactions could lead to larger rings containing acetylenes which could be further elaborated to macrocyclic natural products.

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PROPOSITION V

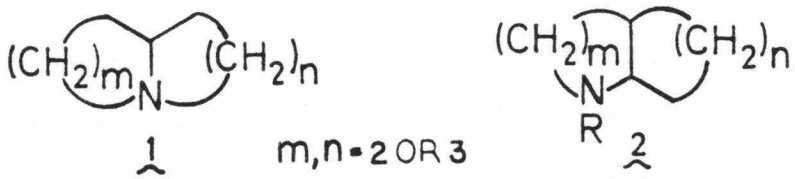
An endocyclic enamine synthesis utilizing an alkyltin mediated cyclization is proposed.

* * * * * * *

Introduction

The synthesis of alkaloids, which exhibit a wide range of biological activity, has provided a substantial challenge to synthetic organic chemists due to the structural diversity and complexity of this family of compounds. Recently attention has been focused on general methods for the synthesis of alkaloid skeleta which can be elaborated into the natural products.[1-5] Inspection of numerous classes of alkaloids reveals the occurrence of the fused nitrogen containing ring systems 1 or 2. The development of general synthetic methodology which would be amenable to the facile preparation of both 1 and 2 would therefore be of significant chemical, biochemical, and medicinal interest. This proposal focuses on the development of a general methodology, incorporating functionalized organostannanes for the

synthesis of compounds 1 and 2. Through this study more insight may also be gained to the limits of using organostannanes as terminators for cyclization reactions.



1 2

Methods and Discussion

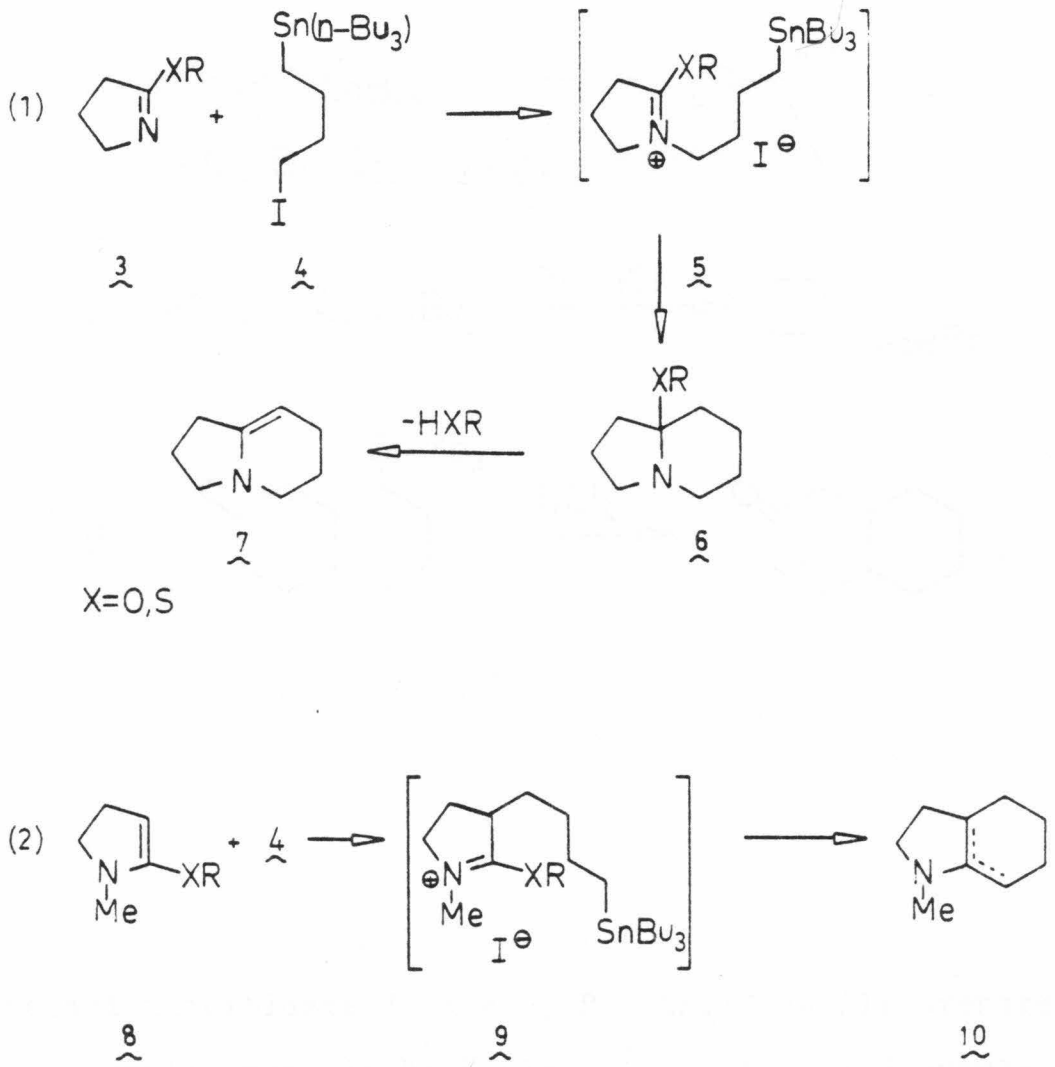
The elegant work of Stevens[1] and Wenkert[2] have shown endocyclic enamines to be particularly useful as basic alkaloid building blocks. However, their means of endocyclic enamine synthesis do not allow for the construction of compounds of type 1 and 2 with any combination of both five and six fused rings. This problem has been solved by Evans through the bis-alkylation of imines, but this method requires the sometimes difficult regiospecific

alkylation of imines.[6]

The proposed endocyclic enamine synthesis is illustrated in Scheme I. Organostannanes have been shown to be latent nucleophiles in cyclization reactions (Scheme II). Peterson and others have shown that homoallyl stannanes react with a wide variety of electrophiles to form cyclopropanes (equation 3).[7] Nicolaou has shown that cyclobutanes may also be formed via stannyl terminated cyclizations (equation 4).[8] Recently, Macdonald has applied an intramolecular alkyltin mediated cyclization for the formation of carbocycles (equation 5).[9] All of the reactions listed above allow for the formation of both electrophilic and nucleophilic centers concurrently. Thus, formation of an alkyltin intermediate with the required reactive electrophilic center[7] such as 5 should cyclize to form 6.

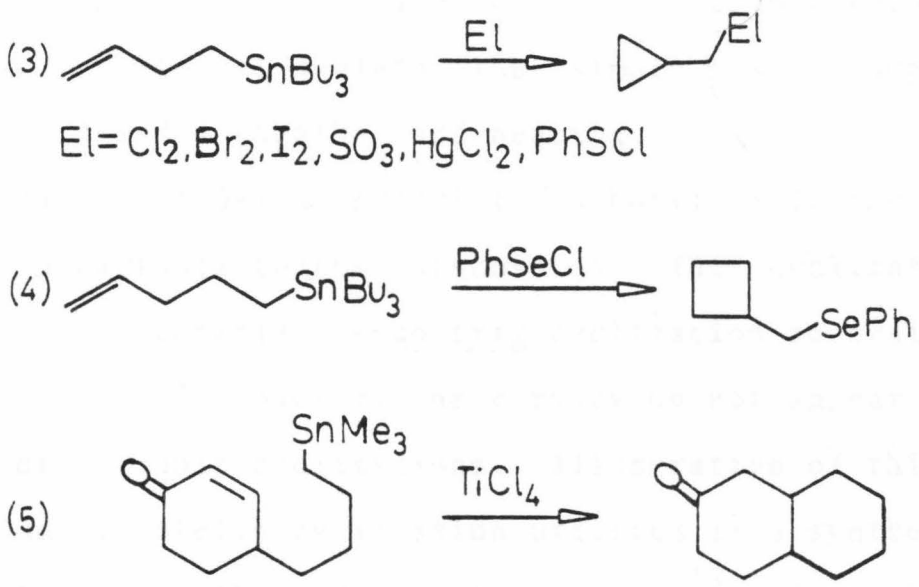
Reaction of alkyl halides with imidates (3, X = O) results in formation of alkoxymethylenimonium salts if R is secondary alkyl or aryl.[10] If R is primary alkyl the alkoxymethyleneimonium salt is dealkylated to form an amide.[10] Reaction of alkyl halides with the more nucleophilic thioimidates (3, X = S) leads to formation of mercaptomethyleneimonium salts.[11] This reaction is independent of the nature of R.[11] Thus, treatment of

Scheme I



3 4 5 6 7 8 9 10

Scheme II



the methyl thioimidate 3 (X = S, R = CH_3), easily prepared from 2-pyrrolidinone in high yield,[11b] with 4-iodobutyl-tri-n-butyltin 4[12] would afford the methylmercaptomethylene-imonium salt 5 (X = S, R = CH_3). Alkyltin mediated cyclization of 5 followed by loss of methanethiol would yield endocyclic enamine 7. Reduction of 7 has been reported to give

the indolizidine alkaloid δ-coniceine.[13] Iodotin compounds such as 4 have been prepared in varying carbon chain lengths and are compatible with a variety of functional groups.[12] This method thus allows for a general entry into alkaloids which have the general skeleton 1 by simply mixing compounds of the type 3 and 4 together and heating.

Utilization of 3-iodo propyl-tri-n-butyltin in the cyclization warrants further discussion. This cyclization is formally an unfavorable 5-endo-trig cyclization according to Baldwin's rules.[14] However, these rules do not appear to be general for cationic cyclizations. Illustrative of this is the imonium ion-olefin cyclization utilized in a synthesis of the pyrrolizidine alkaloid isoretronecanol,[15] and the 5-endo-trig imonium ion-olefin cyclization utilized in the synthesis of the mitosenes.[16] Furthermore, the rotational barrier about the C-N bond in an alkylmercaptomethyleneimonium salt is lower than in an amide[17] indicating that the cyclization may not in actuality be an unfavorable 5-endo-trig cyclization, but a favorable 5-exo-trig cyclization.[14b]

Ketene N,O-acetals (8, X = O) have been shown to react with alkyl halides exclusively on carbon with greater reactivity than enamines.[11b,18] Ketene N,S-acetals (8, X = S) also react with a variety of electrophiles on carbon.[11b,19] Reaction of ketene N,S-acetal 8 [X = S, R = CH_3, prepared

from thiomidate 3 (X = S, R = CH_3) in high yield via alkylation with methyl iodide followed by deprotonation of the methylmercaptomethyleneimonium salt with potassium-t-butoxide[20] with 4 would lead to the methylmercaptomethylimonium salt 9 (X = S, R = CH_3). Alkyltin mediated cyclization of 9 followed by loss of methanethiol would afford endocyclic enamine 10. This method allows for a general entry into alkaloids which have the general skeleton 2 by simply mixing compounds of type 8 and 4 together and heating.

Summary

A general method of endocyclic enamine synthesis is proposed which could allow for the synthesis of numerous classes of alkaloids. This method, which utilizes an alkyltin mediated cyclization, should be compatible with a wide variety of functional groups due to the mild reaction conditions.

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