STEREOCHEMISTRY AND STRUCTURE PROOF
OF (7*S*)-*CIS*,*CIS*-NEPETALACTONE
AND RELATED COMPOUNDS

By

REBECCA LYNN IRVIN

Bachelor of Science

Southwestern State College

Weatherford, Oklahoma

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Thesis Approved:

E J Eisenbraun
Thesis Adviser

Eldon C. Nelson

I. Dwaine Eubanks

Ernest M. Hodnett

N N Durham
Dean of the Graduate College

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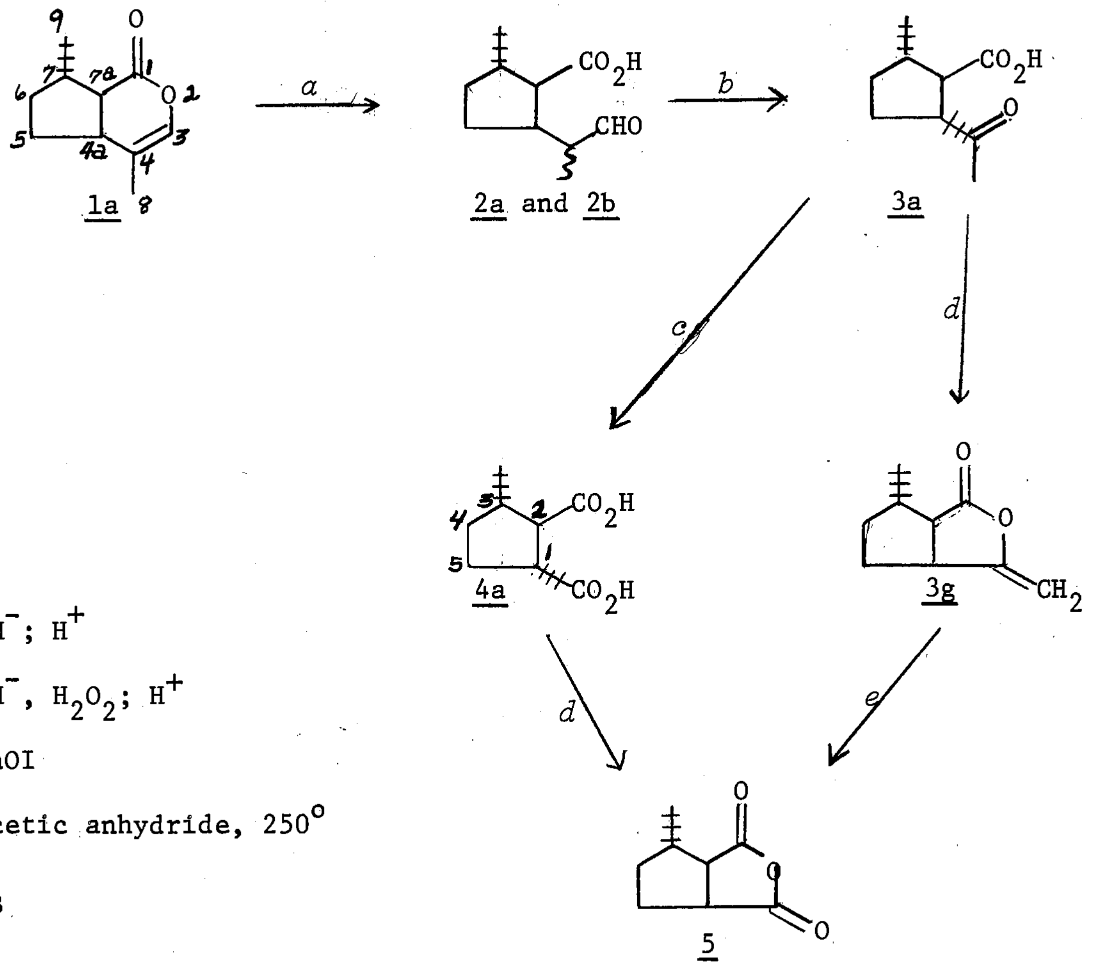
CHAPTER I

INTRODUCTION AND HISTORICAL

The major volatile constituent of the oil of the common catnip plant, *Nepeta cataria*, is (7*S*)-*cis*,*trans*-nepetalactone (1a).[1c] This enol-lactone has been investigated in great detail, and its chemistry has been well documented.[1a,1b] Its property as a feline attractant which elicits a characteristic behavior pattern in cats is well known.[2a,2b]

The structure of 1a was determined by McElvain, Eisenbraun and others in the following manner.[3,4,5,6] *Cis*,*trans*-nepetalactone (1a) was hydrolyzed to the epimeric nepetalic acids 2a and 2b (Figure 1). These nepetalic acids were then treated with alkaline hydrogen peroxide to give nepetonic acid 3a. Oxidation of 3a with sodium hypoiodite afforded the nepetic acid 4a, which was cyclized to the *cis* anhydride 5 by heating 4a at 250° with acetic anhydride. The nepetic anhydride 5 was also prepared by ozonolysis of nepetonolactone 3g, obtained from nepetonic acid 3a. The formation of the anhydride 5 was evidence that the carboxyl and -CH(CH_3)CHO substituents occupy adjacent positions on the cyclopentane ring in the nepetalic acids 2a and 2b and thus, in nepetalactone 1a.

The methyl substituent on the cyclopentane ring of 2a and 2b was shown to be adjacent to the carboxyl substituent by a series of reactions, shown in Figure 2, beginning with lead dioxide oxidative decarboxylation of nepetonic acid 3a. This gave (-)-3-methyl-1-cyclopentenyl



$^{a}\mathrm{OH}^-$; H^+

$^{b}\mathrm{OH}^-$, H_2O_2; H^+

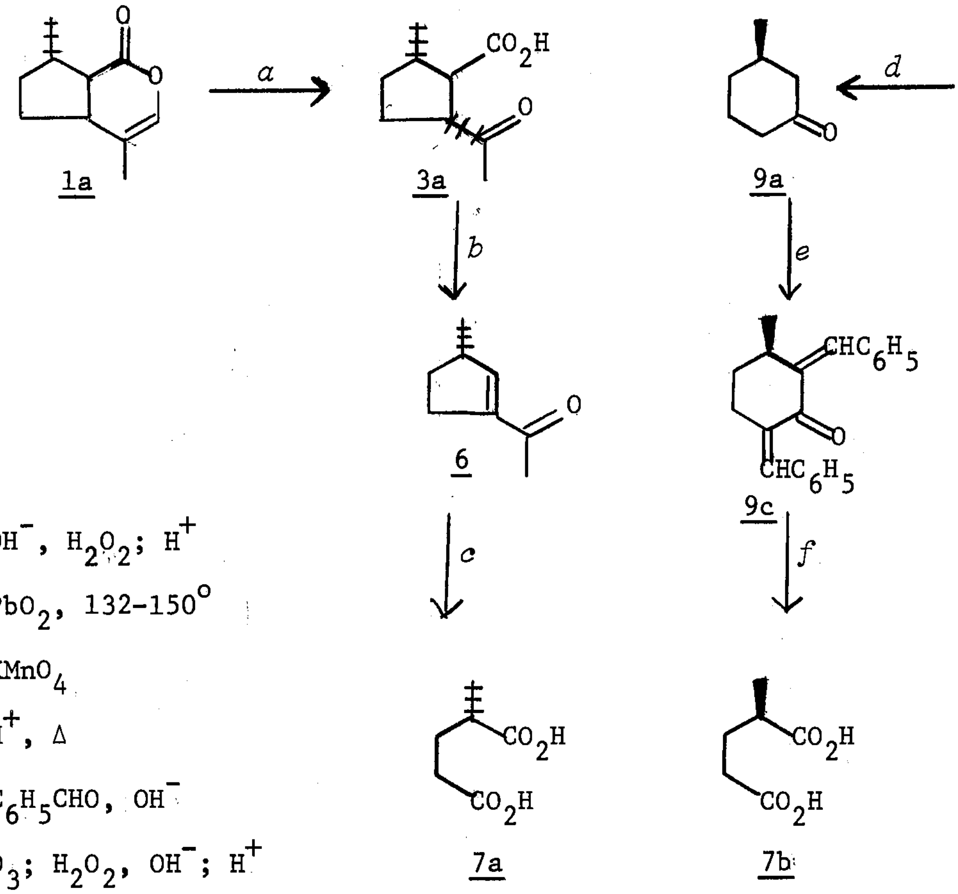
^{c}NaOI

^{d}Acetic anhydride, 250°

$^{e}O_3$

Figure 1. Degradation of *cis,trans*-Nepetalactone (<u>1a</u>)

methyl ketone (<u>6</u>), which was subsequently oxidized with potassium permanganate to (+)-α-methylglutaric acid (<u>7a</u>).[4,5] This procedure also establishes the absolute configuration at C-7 in *cis, trans*-nepetalactone (<u>1a</u>), and shows that <u>1a</u> is in the stereochemical series opposite to that of (+)-pulegone (<u>8</u>). The latter gives (−)-α-methylglutaric acid (<u>7b</u>) *via* ozonolysis of the dibenzylidine derivative <u>9c</u> of (+)-3-methylcyclohexanone (<u>9a</u>).



^{a}OH^{-}, H_2O_2; H^+

^{b}PbO$_2$, 132-150°

^{c}KMnO$_4$

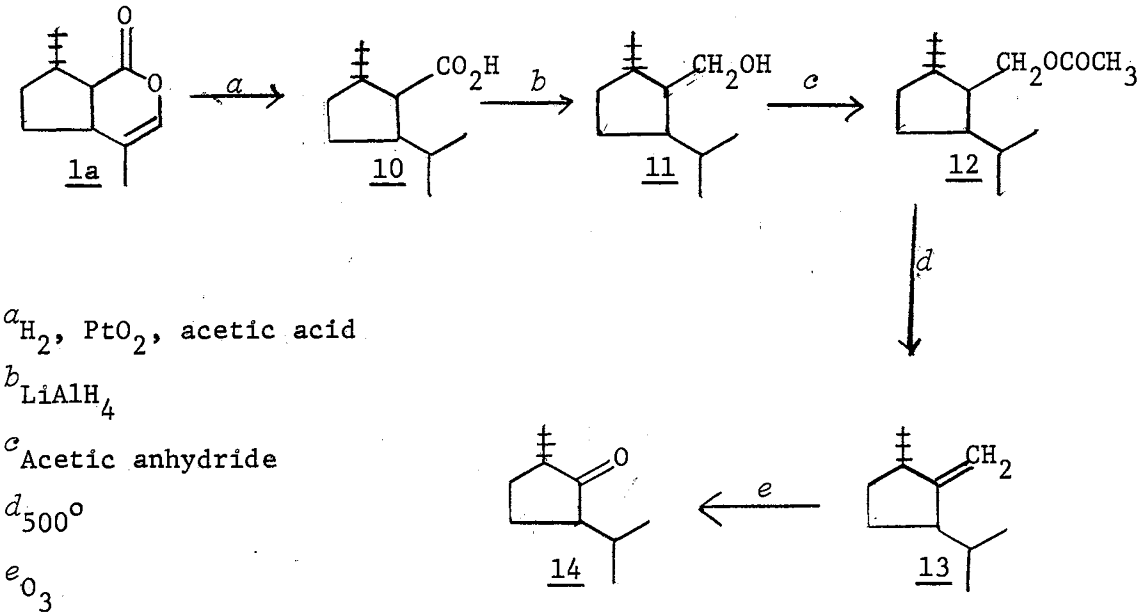
^{d}H$^+$, Δ

^{e}C$_6$H$_5$CHO, OH^{-}

^{f}O$_3$; H_2O_2, OH^{-}; H$^+$

Figure 2. Determination of the Absolute Configuration at C-7 in *cis,trans*-Nepetalactone (1a)

Another structure determination of 1a has been made by Meinwald, in which *cis,trans*-nepetalactone (1a) was converted to 2-methyl-5-isopropylcyclopentane carboxylic acid (10) by hydrogenolysis, followed by the lithium aluminum hydride reduction of 10 to the alcohol 11, which in turn, was converted to the acetate 12 (Figure 3).[6] Pyrolysis of 12 gave 13, which was ozonized to 2-methyl-5-isopropylcyclopentanone (14).



${}^{a}H_2$, PtO_2, acetic acid

${}^{b}LiAlH_4$

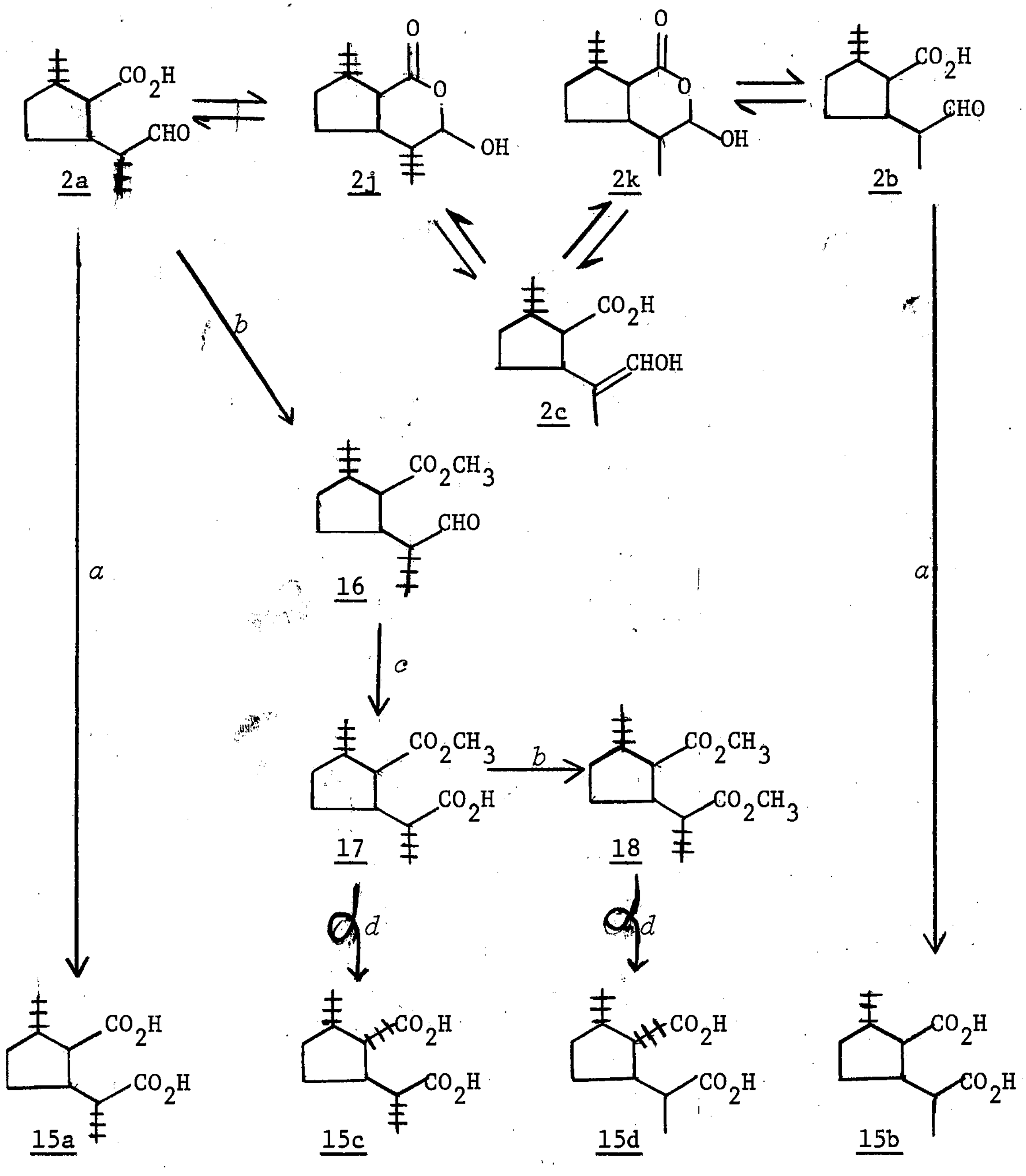
^{c}Acetic anhydride

${}^{d}500^{\circ}$

${}^{e}O_3$

Figure 3. Conversion of Nepetalactone 1a to 2-Methyl-5-isopropylcyclopentanone (14)

The *trans* relationship of the C-7 and C-4a substituents of 1a was established through a study of the nepetalinic acids (15a, 15b, 15c, and 15d), as shown in Figure 4.[4,7] The nepetalic acids 2a and 2b exhibit aldehydo-lactol tautomerism.[3] Nepetalic acid 2a was oxidized with chromic acid to the nepetalinic acid 15a, melting point 85°. Nepetalic acid 2b was likewise oxidized to give the nepetalinic acid 15b, melting point 117°. Separation of 15a and 15b was facilitated by the water insolubility of the barium salt of 15a. Treatment of nepetalic acid 2a with diazomethane gave the methyl ester 16 which was readily oxidized to the half-ester 17. Epimerization of 17 with sodium methoxide and methanol, followed by saponification, gave the nepetalinic acid 15c,



*a*Chromic acid

bCH_2N_2

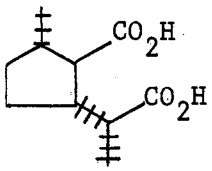
*c*Autoxidation

*d*Sodium methoxide, methanol; saponification

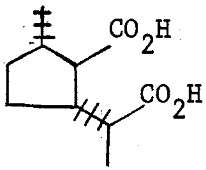
Figure 4. Nepetalinic Acids from the Degradation of *cis, trans*-Nepetalactone (1a)

melting point 115°. The half-ester 17 was converted to the dimethyl nepetalinate 18, and this diester was epimerized with sodium methoxide and methanol, followed by saponification, to the nepetalinic acid 15d, melting point 111°.

If the C-7 and C-4a substituents are in a *trans* arrangement, then the four nepetalinic acids 15a, 15b, 15c, and 15d are the only such acids which could result from a degradation of *cis,trans*-nepetalactone (1a) in which the asymmetric centers at C-7 and C-4a remain unchanged. Conversely, the possibility of a *cis* arrangement between the C-7 and C-4a substituents is disproved, since a *cis* arrangement would be expected to yield only two nepetalinic acids, 15e and 15f. This is because formation of any acids other than 15e and 15f would require epimerization to a less stable *cis* arrangement of the substituents in the nepetalinic acids. The nepetalinic acids 15e and 15f were later isolated (from degradation of iridodial) and shown to be different from the nepetalinic acids obtained from degradation of 1a.[8a,8b]



15e



15f

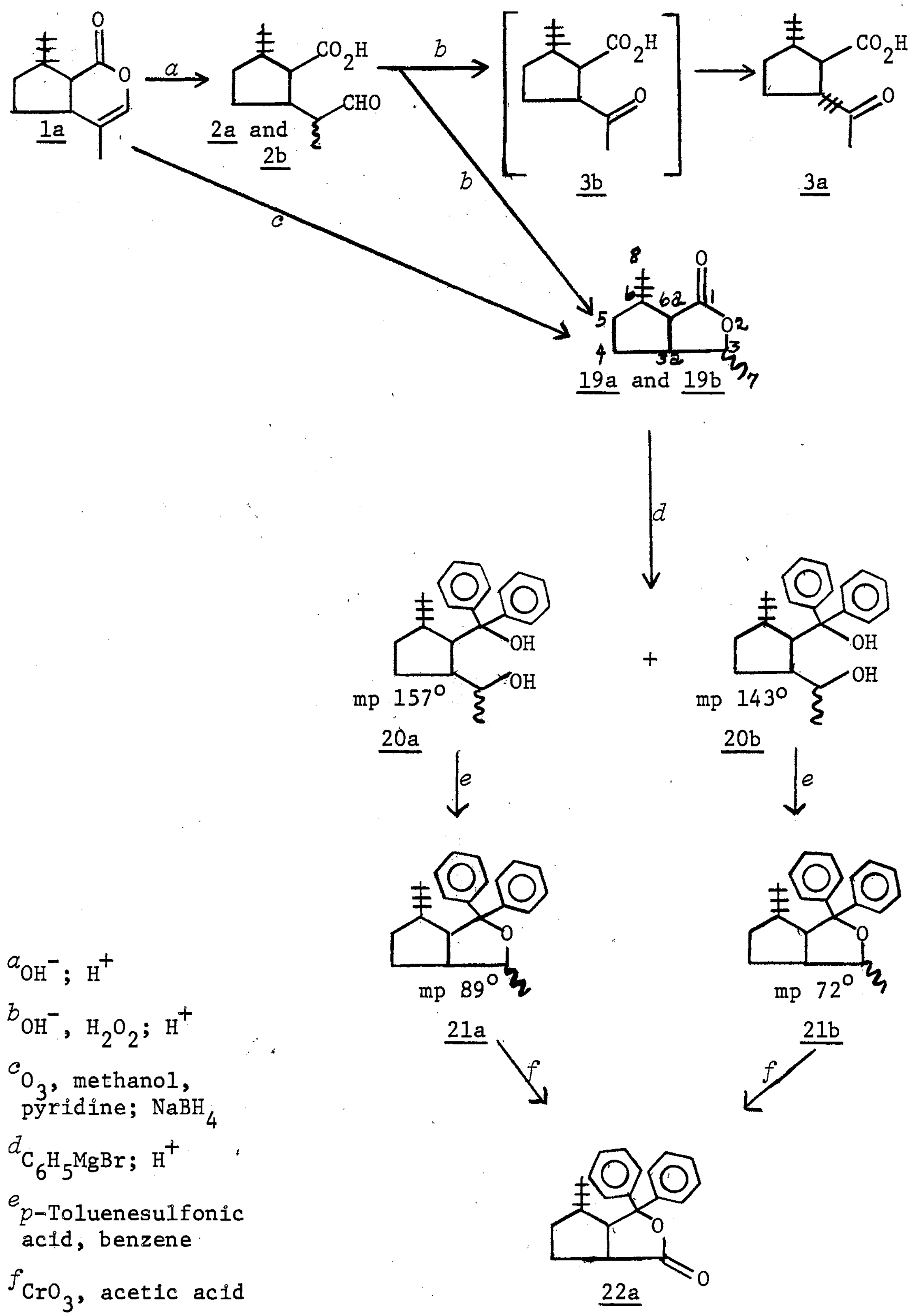
Eisenbraun, McElvain, and others have shown that the ring junction in 1a is *cis* (Figure 5).[4,7] The nepetalic acids 2a and 2b, when treated with alkaline hydrogen peroxide, followed by acidification, gave the nepetonic acid 3a, by epimerization of nepetonic acid 3b. This reaction also gave the *cis,trans*-nepetolactones (19a and 19b). The ring fusion in these γ-lactones must be *cis*, for a *trans* ring fusion of two five-membered rings would be thermodynamically unstable. Further evidence that the ring fusion in 1a is *cis* was obtained from the reaction of *cis,trans*-nepetalactone (1a) with ozone, followed by decomposition of the ozonide with sodium borohydride. This procedure also gave the nepetolactones 19a and 19b.

The lactones 19a and 19b have been shown by McElvain and Eisenbraun to be epimers at C-3 (Figure 5).[4] This was accomplished by converting 19a and 19b to a pair of diols, 20a and 20b, through reaction with phenylmagnesium bromide. These diols were separated and then cyclized by treatment with *p*-toluenesulfonic acid to the two cyclic ethers, 21a and 21b. Each of these ethers was oxidized to the same γ-lactone, 22a. Thus, in the oxidation the epimeric center was destroyed.

The structure and stereochemical assignments of *cis,trans*-nepetalactone (1a) have been verified through independent syntheses of 1a and its isomers. These studies follow.

Sakan and coworkers have verified the structure of 1a by synthesizing racemic *cis,trans*-nepetalactone as outlined in Figure 6. Sakan was able to show through infrared studies that his synthetic material "accorded in all respects with the natural lactone in their ir charts except only a slight difference of the absorption intensities near 11.4 and 12.2μ."

Achmad and Cavill prepared (7*R*)-*cis,trans*-nepetalactone (1e) stereospecifically, starting from (+)-pulegone (8), as shown in Figure 7.[13] They report that the glc retention time of their synthetic nepetalactone



^{a} OH^-; H^+

^{b} OH^-, H_2O_2; H^+

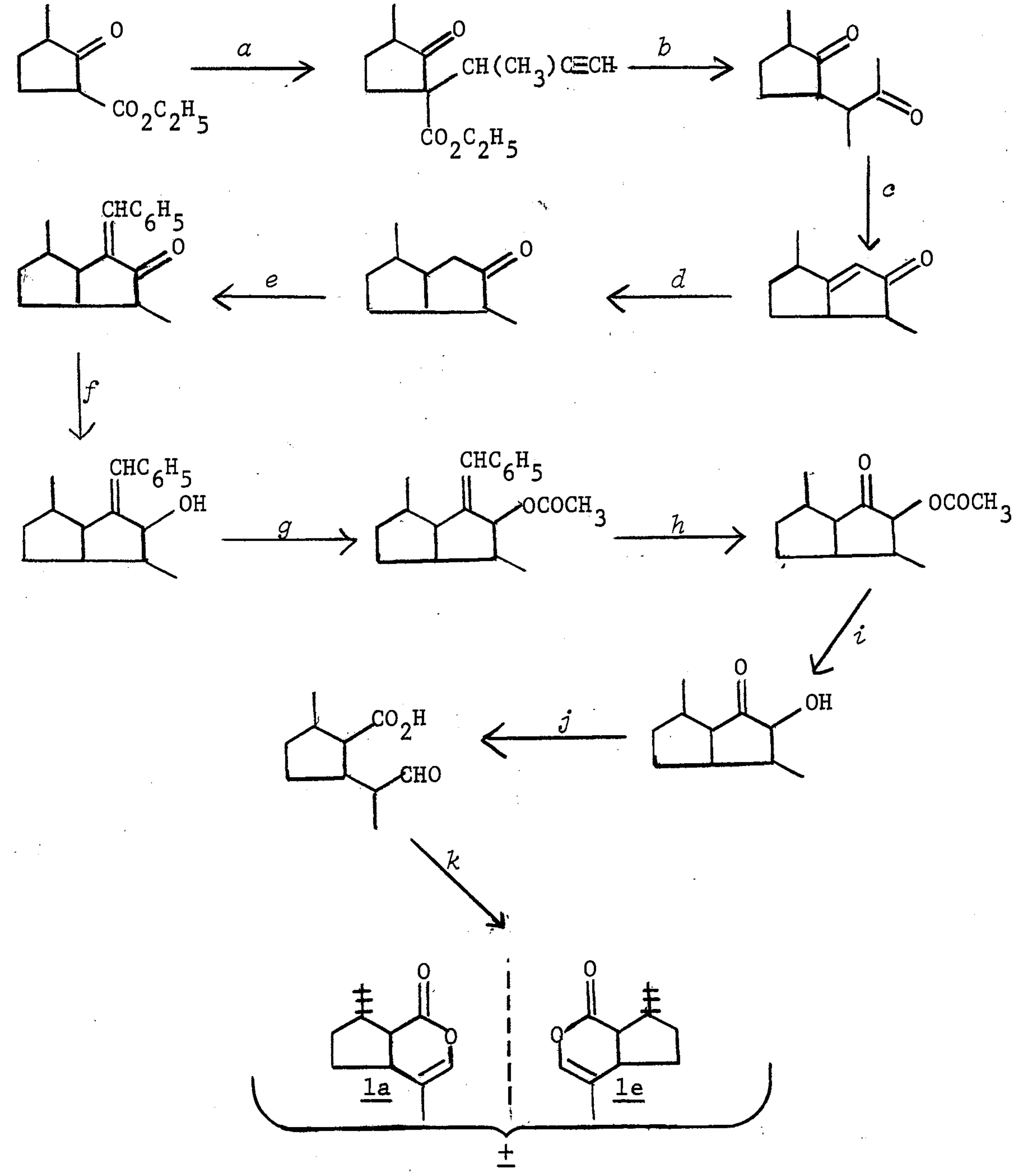
^{c} O_3, methanol, pyridine; $NaBH_4$

^{d} C_6H_5MgBr; H^+

^{e} *p*-Toluenesulfonic acid, benzene

^{f} CrO_3, acetic acid

Figure 5. Evidence for a *cis* Ring Junction in Nepetalactone 1a



[a] 3-Bromobutyne

[b] Hydration; hydrolysis

[c] Condensation

[d] Catalytic hydrogenation

[e] C_6H_5CHO, OH^-

[f] $NaBH_4$

[g] Acetic anhydride

[h] O_3

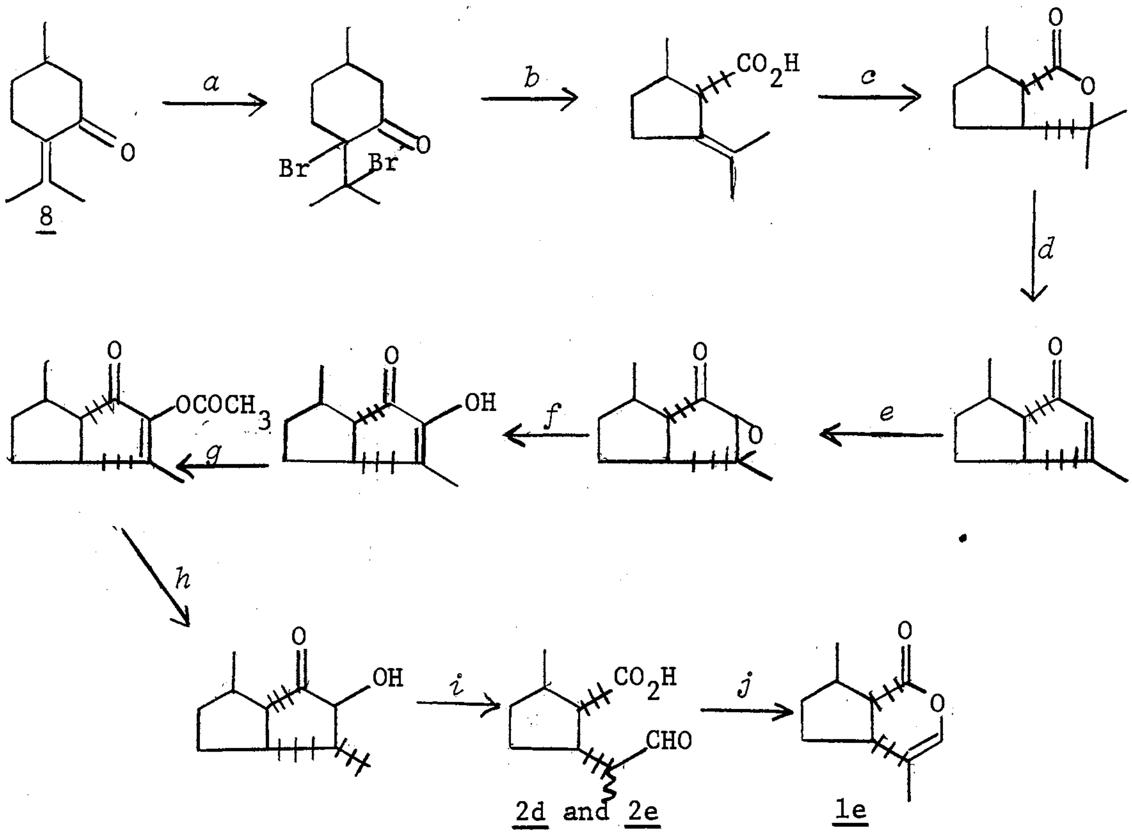
[i] Saponification

[j] Periodate

[k] Pyrolysis

Figure 6. Synthesis of Racemic *cis,trans*-Nepetalactone

1e matches exactly that of naturally occurring nepetalactone 1a. The ir spectrum of their enantiomeric nepetalactone also "corresponds closely" with that of 1a. However, Achmad and Cavill did not report whether the enantiomer (1e) of 1a was physiologically active toward cats.



[a] Br_2

[b] Sodium methoxide, methanol

[c] Methanol, H^+

[d] Phosphorous pentoxide, phosphoric acid

[e] Alkaline H_2O_2

[f] H_2SO_4, acetic acid

[g] Acetylation

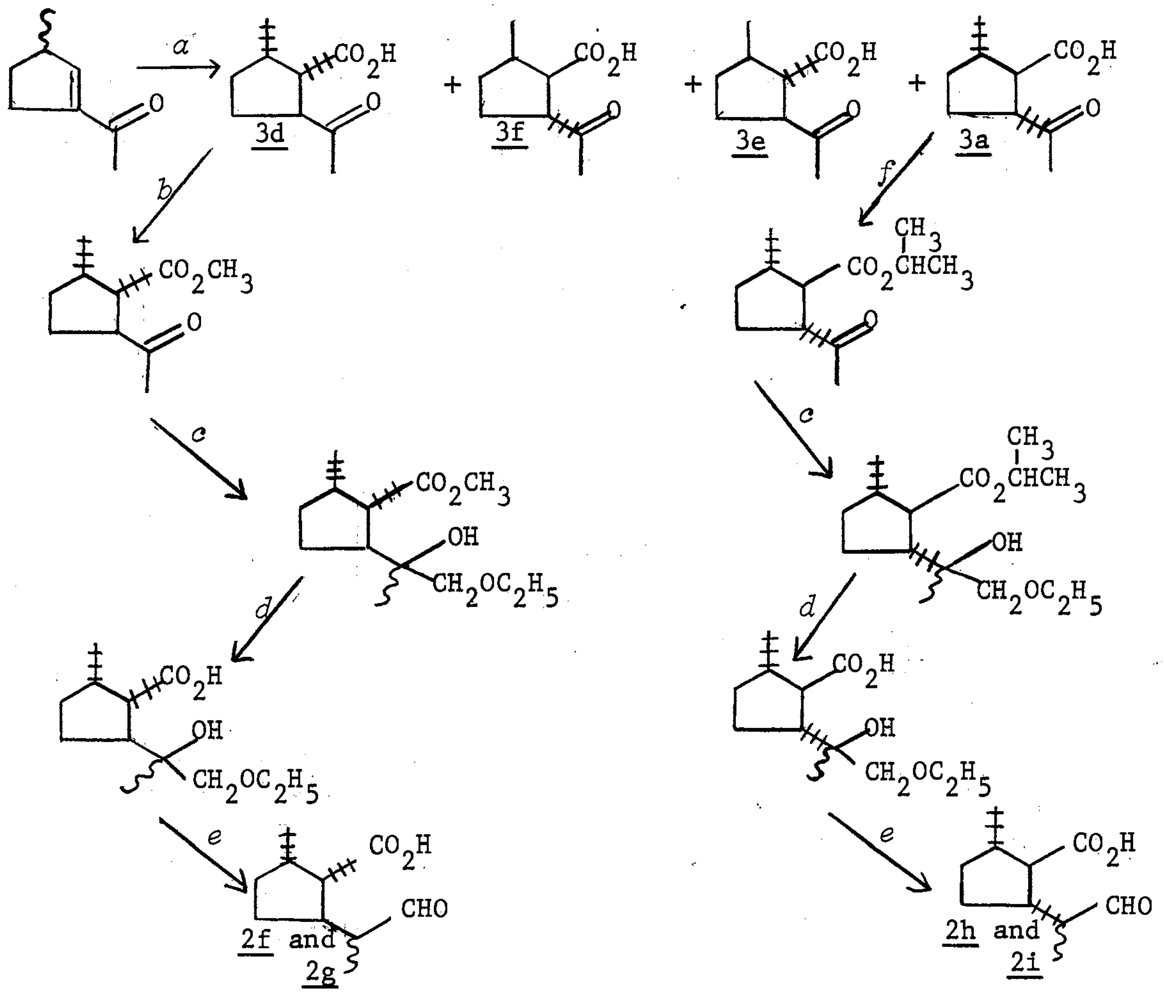
[h] H_2, PtO_2; saponification

[i] Lead tetraacetate, acetic acid

[j] Pyrolysis

Figure 7. Synthesis of (7*R*)-*cis,trans*-Nepetalactone (1e)

Trave, Marchesini, and Garanti have synthesized a number of compounds related to those derived from catnip.[14,15,16,17,18,19,20] The four stereoisomers of (7*S*)-nepetalactone, <u>1a</u>, <u>1b</u>, <u>1c</u>, and <u>1d</u>, were prepared (Figures 8 and 9).[14] The first stage of the synthesis was the preparation of the nepetalic acids <u>2f</u>, <u>2g</u>, <u>2h</u>, and <u>2i</u> as shown in Figure 8.



[a] HCN; hydrolysis

[b] CH_2N_2

[c] $ClCH_2OC_2H_5$, Mg

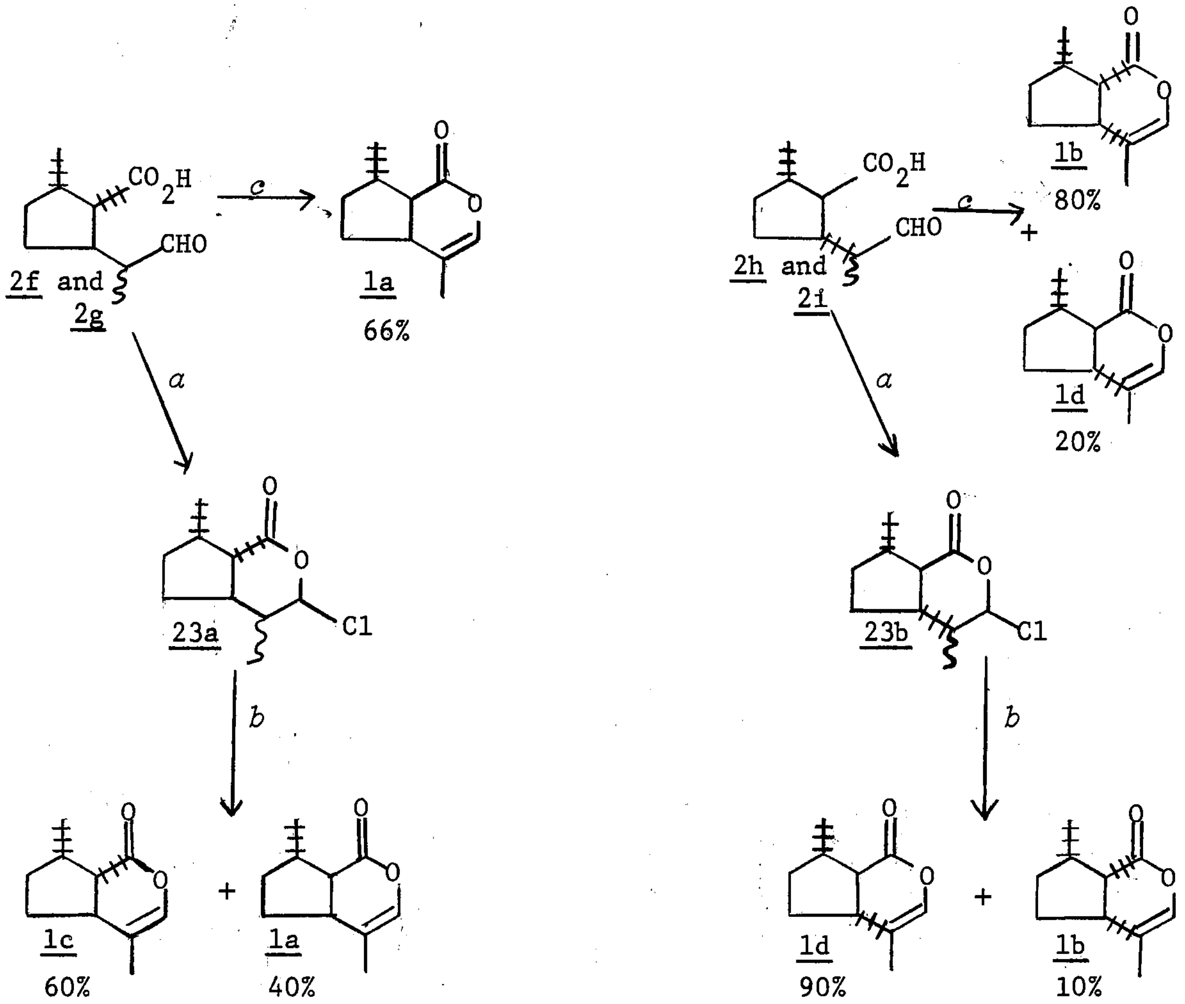
[d] Saponification

[e] HCO_2H, Δ

[f] 2-Propanol, H^+

Figure 8. Synthesis of Nepetalic Acids <u>2f</u>, <u>2g</u>, <u>2h</u>, and <u>2i</u>

These nepetalic acids were then converted to the (7*S*)-nepetalactones 1a, 1b, 1c, and 1d as shown in Figure 9. Pyrolysis of a mixture of nepetalic acids 2f and 2g afforded *cis,trans*-nepetalactone (1a) in 66% yield, while pyrolysis of nepetalic acids 2h and 2i gave *cis,cis*-nepetalactone (1b) and *trans,cis*-nepetalactone (1d) in a glc ratio of 80:20. When the nepetalic acids 2f and 2g were converted to the chlorolactone 23a, followed by dehydrohalogenation on a glc column, a ratio of 60%



^{a}CH_3COCl

^{b}Dehydrohalogenation on a glc column

^{c}Pyrolysis

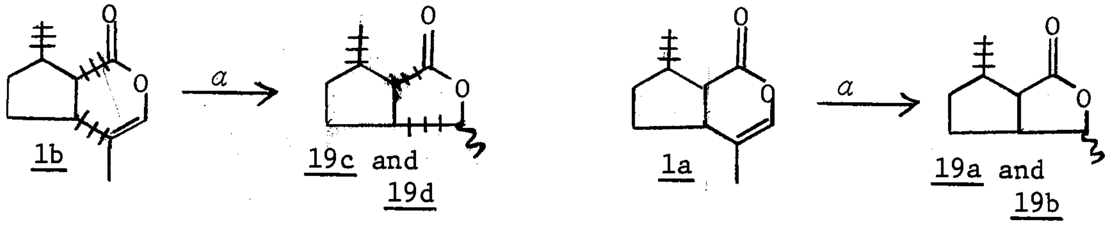
Figure 9. Synthesis of the (7*S*)-Nepetalactones (1a, 1b, 1c, and 1d)

trans,trans-nepetalactone (1c) and 40% *cis,trans*-nepetalactone (1a) was produced. A corresponding procedure applied to nepetalic acids 2h and 2i gave a glc ratio of 90% *trans,cis*-nepetalactone (1d) and 10% cis,cis-nepetalactone (1b).

The physical properties (optical rotation, refractive index, etc.) and spectra (nmr and ir) of synthetic 1a and 1a isolated from *N. cataria* agreed. In addition, synthetic 1a was ozonized, followed by ozonide decomposition with sodium borohydride, to the nepetolactones 19a and 19b. Synthetic 1a was also converted to nepetonic acid 3a by ozonolysis, with catalytic ozonide decomposition to give nepetonic acid 3b, which was then epimerized to 3a.

Studies of the volatile oil of another catnip species, *N. mussini*, have shown that the major constituent of the oil of this plant is an isomer of *cis,trans*-nepetalactone (1a). It is also thought to have a pronounced effect on the behavior of cats.[21] Regnier has stated that the nepetalactone present in *N. mussini* is *cis,trans*-nepetalactone (1a), which was said to comprise nearly 100% of the volatile oil of the plant.[22] However, he later states that the structure of the *N. mussini* nepetalactone isomer is that shown for nepetalactone 1c, which has a *trans* ring junction.[23a,23b] Nepetalactone 1c is also known to be a constituent of the oil of the *N. cataria* species (as much as 25% 1c with 75% 1a).[23a,23b] However, it must be noted that Regnier's conclusions concerning the stereochemistry of the nepetalactone from *N. mussini* were based on gas chromatography and mass spectral studies only.

McGurk investigated the oil of the *N. mussini* species, and suggested that the structure of the nepetalactone isomer from this plant is that shown by structure 1b.[24] His conclusion was based on the following evidence. Nepetalactone from *N. mussini* was ozonized, and the ozonide was decomposed with sodium borohydride (Figure 10). This procedure gave a pair of nepetolactones, 19c and 19d, which were shown to differ from the nepetolactones 19a and 19b obtained from *cis,trans*-nepetalactone



$^{a}O_3$, methanol, pyridine; $NaBH_4$

Figure 10. Synthesis of Nepetolactones 19a, 19b, 19c, and 19d

(1a). Structure 1c for the nepetalactone isomer in *N. mussini* is ruled out here, since the formation of the γ-lactones 19c and 19d requires that the ring junction in nepetalactone be *cis*.

It was planned in this work to further investigate the lactone obtained from *N. mussini*, and to verify the structure 1b for this compound.

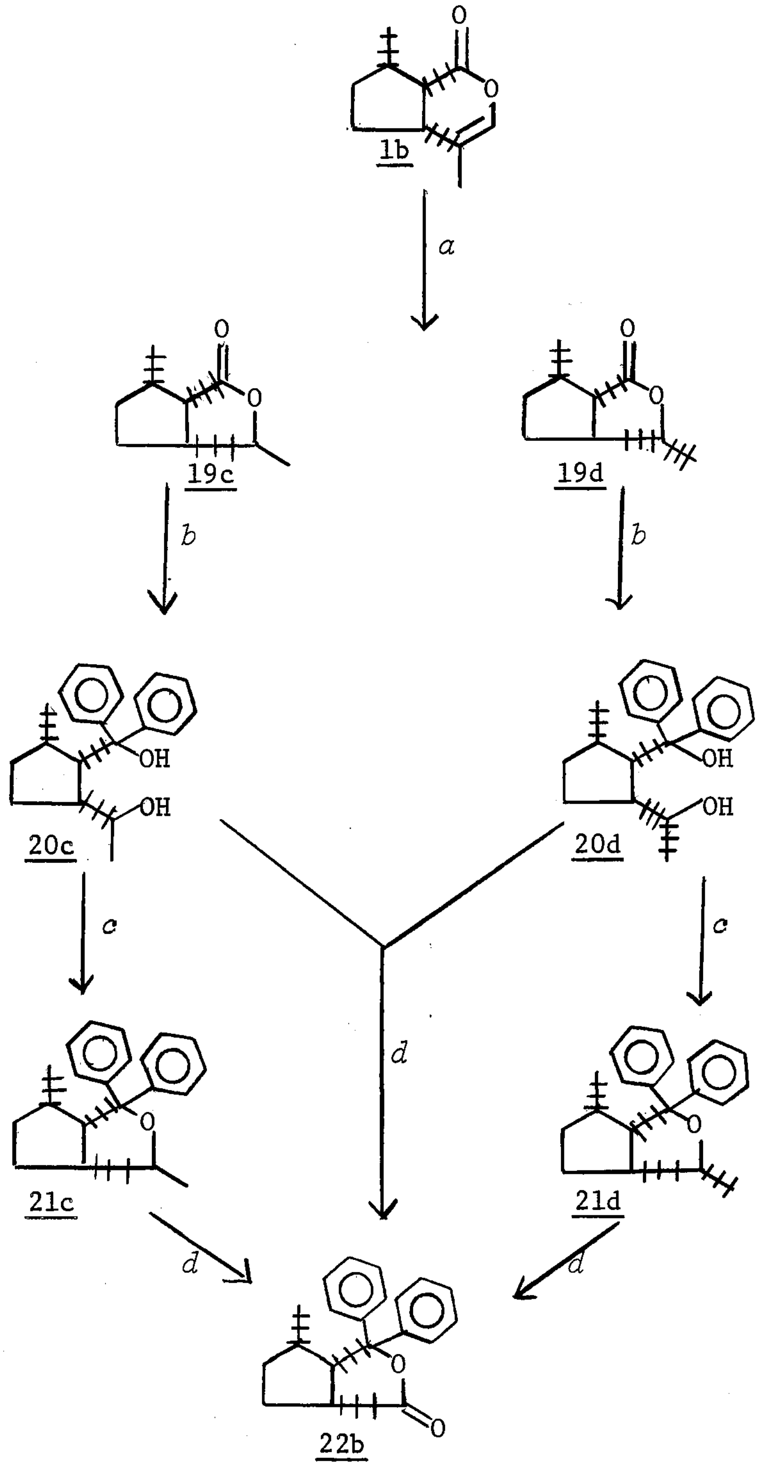
CHAPTER II

CHEMICAL DEGRADATION AND STRUCTURE PROOF OF *CIS,CIS*-NEPETALACTONE

The *N. mussini* plant produces nepetalactone <u>1b</u> which is isolated by steam distillation of the leaves and stems of the plant. Gas chromatography[27d] of the steam volatile material shows that <u>1b</u> constitutes more than 95% of *N. mussini* oil. The plants were steamed immediately after harvesting to minimize any enzymatic degradation of <u>1b</u>. Two alternative procedures were employed in harvesting the plants. In the first procedure, the plants were severed at ground level and then directly steam distilled. This procedure gave 0.4% yield of oil. A more efficient isolation of oil resulted from shredding the plant material in a Waring Blendor before steam distillation. This latter procedure provided a 0.5% yield of *N. mussini* oil.

Since the chemistry of (7*S*)-*cis,trans*-nepetalactone (<u>1a</u>) has been so extensively studied, the method chosen for the structure proof of the nepetalactone isomer found in *N. mussini* was to correlate its chemistry with that of <u>1a</u>. The nmr,[27a] ir,[27b] and mass spectra[27c] for nepetalactones <u>1a</u> and <u>1b</u> are shown in Figures 15, 16, 29, and 30 and in Table I at the end of this chapter.

The reaction scheme outlined for *cis,trans*-nepetalactone (<u>1a</u>) in Figure 6 has been applied to *cis,cis*-nepetalactone (<u>1b</u>) (Figure 11). McGurk reported that the ozonolysis of <u>1b</u> in methanol containing pyridine,



[a] O_3, methanol, pyridine; $NaBH_4$, H_2O; H^+

[b] Phenylmagnesium bromide; H^+

[c] *p*-Toluenesulfonic acid, benzene

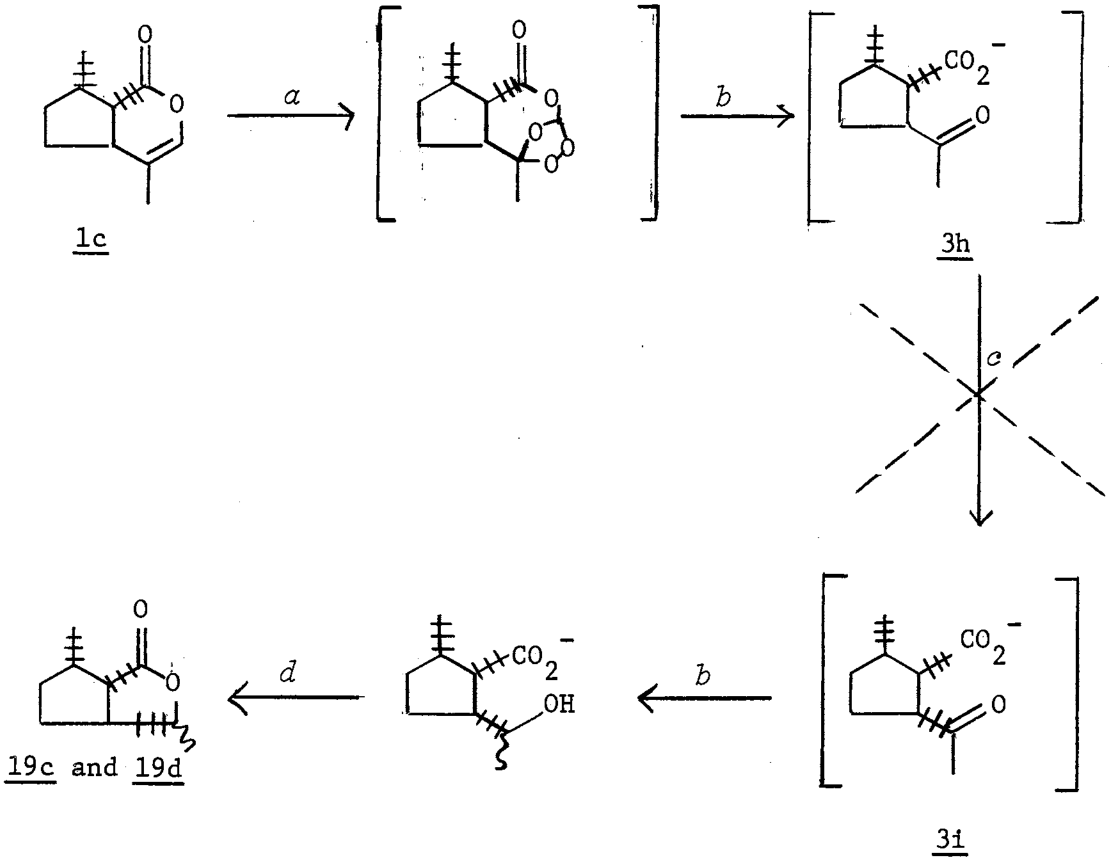
[d] CrO_3, acetic acid, 50-60°

Figure 11. Structure Determination of *cis,cis*-Nepetalactone (1b)

followed by ozonide reduction with sodium borohydride gave a pair of epimeric nepetolactones 19c and 19d.[24] A similar pair of epimeric lactones, 19a and 19b, was obtained from the ozonolysis of *cis*,*trans*-nepetalactone (1a), as shown in Figure 5. The separation of these lactones (19a from 19b and 19c from 19d) was accomplished by McGurk through preparative gas chromatography and by the author through column chromatography on silicic acid with an ethyl ether and petroleum ether eluant. The nmr spectra,[27b] shown in Figures 17, 18, 19, and 20, were obtained from each lactone by placing a sealed capillary tube filled to a depth of 1 cm or less with lactone inside a thick walled nmr tube, containing CCl_4 and tetramethylsilane. In this way, although only milligram quantities of the lactones were available, it was possible to obtain nmr spectra on the neat compounds, and thus to eliminate any possibility of solvent effects. The nmr spectra of the nepetolactones 19a, 19b, 19c, and 19d are discussed in detail in Chapter IV.

The formation of the nepetolactones 19c and 19d requires that the ring fusion in these lactones be *cis*, and therefore that the fusion of the methylcyclopentane ring and the lactone ring in nepetalactone 1b also must be *cis*. A *trans* relationship of the two rings in the nepetalactone from *N. mussini* would be very unlikely, because to produce the *cis*-fused γ-lactones by ozonolysis would require an epimerization of nepetonate 3h to a less stable *cis* configuration 3i as shown in Figure 12.

The *cis*,*cis*-nepetolactones 19c and 19d were converted to the diols 20c and 20d with phenylmagnesium bromide (Figure 11). When the reaction was carried out on a mixture containing approximately 90% 19c and 10% 19d, diol 20c was obtained in a 68% yield. When the Grignard reaction



^{a}O$_3$, methanol

^{b}NaBH$_4$, H$_2$O

^{c}OH$^-$

^{d}H$^+$

Figure 12. Proposed Ozonolysis of Nepetalactone 1c

was conducted with a mixture of lactones 19c and 19d in the ratio 1.6:1, the diols 20c and 20d were produced in the same ratio, as determined from comparison of glc peak areas. A similar Grignard reaction using pure nepetolactone 19c gave a single diol, 20c (mp 133°). The nmr,[27a] ir,[27b] and mass spectra[27c] for the diols 20a, 20b, and 20c are shown in Figures 21, 22, 23, 31, 32, and 33 and in Table I at the end of this chapter.

The diol 20c (Figure 11) was treated with *p*-toluenesulfonic acid in refluxing benzene which gave the cyclic ether 21c in 100% yield. Gas chromatography[27d] of a mixture of diol 20c and ether 21c showed no separation of the two compounds. Injections of a mixture of the *cis,trans* diols and ethers (20a with 21a and 20b with 21b) also showed no separation of the corresponding diols and ethers. Therefore, it is concluded that under the gas chromatography conditions employed, dehydration of the diols occurred to give the corresponding cyclic ethers. Nmr,[27a] ir,[27b] and mass spectra[27c] of the ethers 21a, 21b, and 21c are shown in Figures 24, 25, 26, 34, 35, and 36 and in Table I.

The ether 21c was oxidized with chromium trioxide and acetic acid to give the lactone 22b in 92% yield, melting point 202-203°. Glc analysis[27d] of lactone 22b and lactone 22a, melting point 213°, showed two distinct peaks, thus eliminating any possibility that 22a and 22b are the same compound. The nmr,[27a] ir,[27b] and mass spectra[27c] for 22a and 22b are shown in Figures 27, 28, 37, and 38 and in Table I. The infrared spectra of both 22a and 22b show the characteristic carbonyl absorption of γ-lactones at 5.7μ.

It was also shown that lactone 22b could be obtained (21% yield) by direct oxidation of diol 20c with chromium trioxide and acetic acid. Likewise, a milligram-scale oxidation of the *cis,trans* diol 20a gave the corresponding lactone 22a, determined by glc analysis.[27d] The proposed mechanism for these reactions is shown for the all *cis* compounds in Figure 13.[25]

A mixture consisting of 62% diol 20c and 38% diol 20d was oxidized with CrO_3 and acetic acid. Gas chromatography[27d] showed that both were

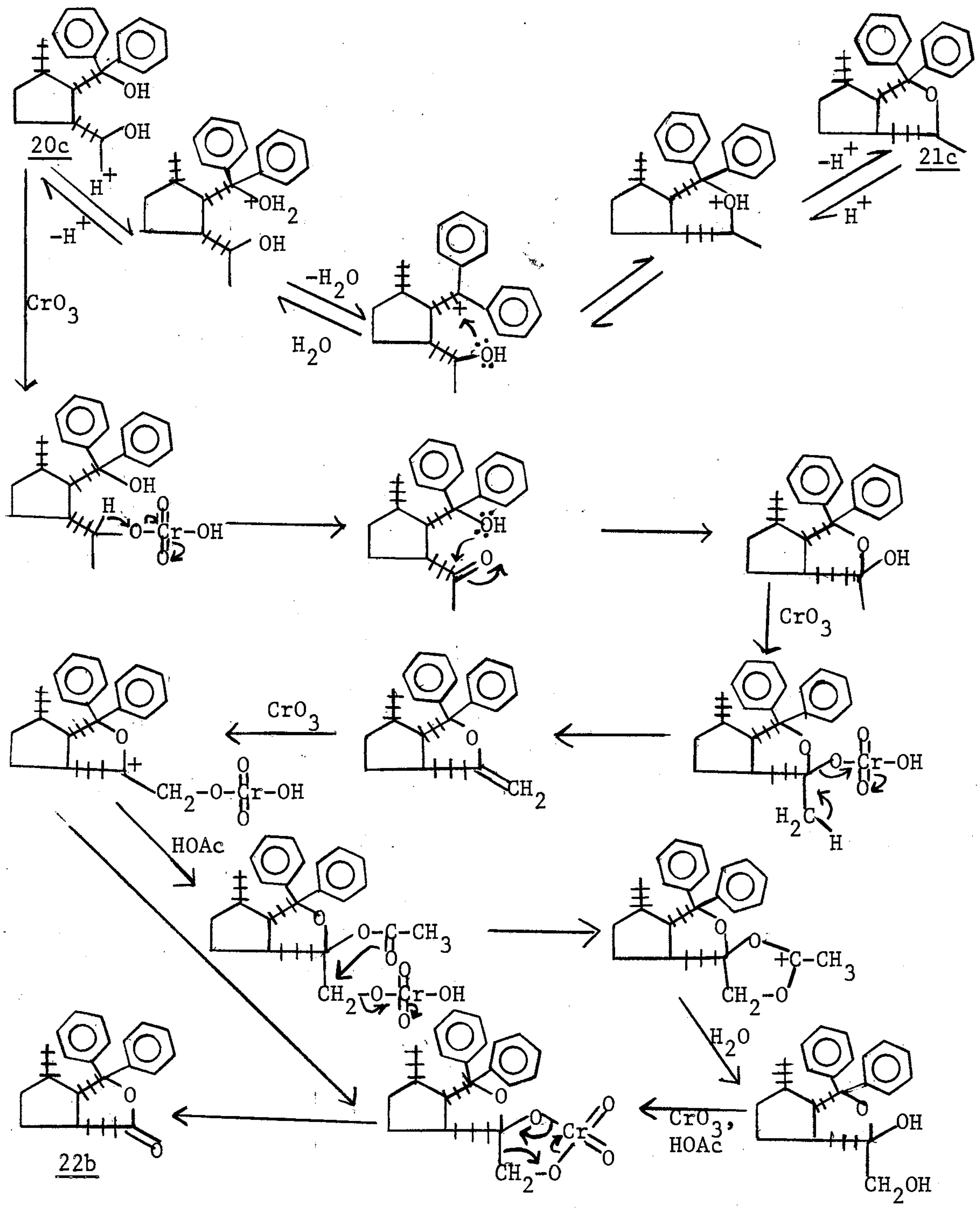


Figure 13. Proposed Mechanism for Conversion of Diol 20c to Lactone 22b with Chromium Trioxide and Acetic Acid

converted to the same lactone, 22b.

In the oxidation of the diols 20c and 20d, the loss of a methyl group destroyed a center of asymmetry. Thus, the epimeric *cis,cis*-nepetolactones (19c and 19d) were converted through several steps to the same lactone 22b.

Eisenbraun and McElvain showed the *cis,trans*-nepetolactones (19a and 19b) to be epimers at C-3 as shown in Figure 5.[4,7] However, they did not separate 19a and 19b, but instead separated the isomeric diols 20a and 20b which resulted from the reaction of phenylmagnesium bromide with a mixture of 19a and 19b.

The nepetolactones 19a and 19b have now been separated, and their individual properties have been studied. The absolute configuration

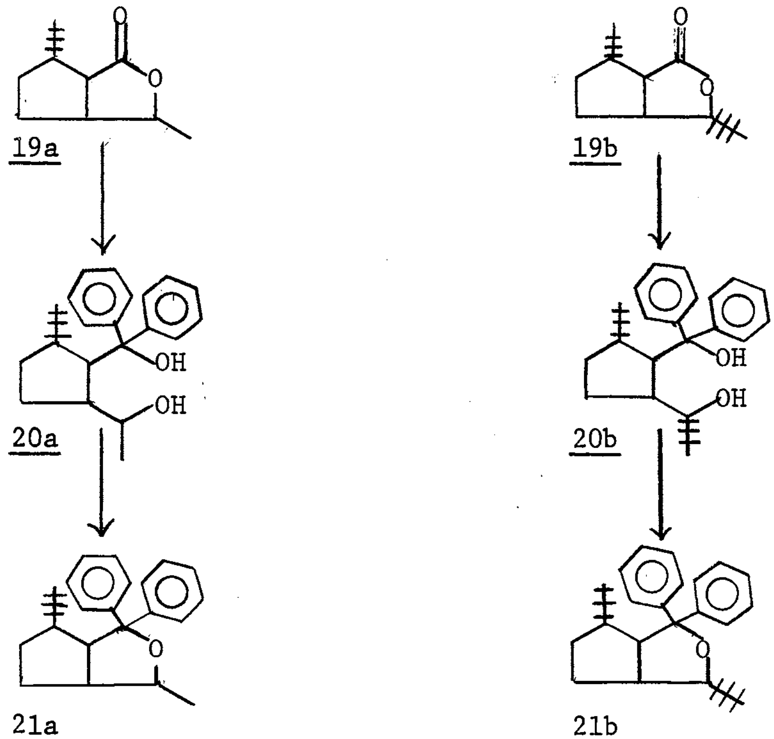


Figure 14. Absolute Configuration at the Epimeric Center of Diols 20a and 20b and Ethers 21a and 21b

assignments at C-3 in the *cis,trans*-nepetolactones (19a and 19b) (and in the nepetolactones 19c and 19d, as shown in Figure 11) have been made from their nuclear magnetic resonance spectra, which are discussed in Chapter IV. On the basis of these stereochemistry assignments, the absolute configurations at the epimeric center in the diols 20a and 20b and the ethers 21a and 21b can now be made. A sample of 98% nepetolactone 19a was reacted with phenylmagnesium bromide to give diol 20a, melting point 157°. Therefore the absolute configuration of the diols 20a and 20b and the ethers 21a and 21b are as shown in Figure 14.

TABLE I

MASS SPECTRA (RELATIVE INTENSITY)

m/e	Lactone <u>1a</u>	Lactone <u>1b</u>	Diol <u>20a</u>	Diol <u>20b</u>	Diol <u>20c</u>	Ether <u>21a</u>	Ether <u>21b</u>	Ether <u>21c</u>	Lactone <u>22a</u>	Lactone <u>22b</u>
39	21	4	6		9	12		38		11
40		20	4	8		7	21	6		
41	44	14	8		13	23	5	25		15
42	7	34	5	8		9	71	7		
43	43	10	12		12	14	5	55		
44		40	3	10			26			
45		5	10		40	7		4		
46		3								
47										
48										
49										
50			10	9	4	14		13		5
51	7	8	9		14	19	4	12		20
52		21	8	5		10	29	12		3
53	18	9	11		5	12	4	24		4
54	4	50	6	8		10	16	8		4
55	11	18	10		11	26	6	43		4
56	9	57	5			23	27	10		
57	6	8	6			4		8		
58	33	9								
59										
60										
61										
62						4				
63			5			4	6	15		4

TABLE I (Continued)

m/e	Lactone 1a	Lactone 1b	Diol 20a	Diol 20b	Diol 20c	Ether 21a	Ether 21b	Ether 21c	Lactone 22a	Lactone 22b
64		5				3		4		
65	7		7		4	19	5	18	7	4
66	3	17	3			8	4	4		
67	35	7	45	13	18	21	38	52		22
68	11	64	30	6	5	21	7	45		
69	51	15		4	3	44	5	72		
70		100				3		3		
71	4	4	4			3		5		
72										
73										
74						6		8		
75			3		3	10	4	9	12	
76			8	4	6	21	9	21		4
77	12		78	100	26	47	100	92		64
78		25	22	12	12	35	20	36		13
79	11	5	3	7	6	35	12	37		4
80	33	25	4			13		10		
81	39	39	67	39	31	47	54	100		5
82	18	100	38	5	5	43	7	25		10
83	11	17	3			5		5		5
84	11	17								
85	15	17								
86		21						3		
87	5					4	3	5		
88						5		5		
89						15		18	8	3
90										

TABLE I (Continued)

m/e	Lactone 1a	Lactone 1b	Diol 20a	Diol 20b	Diol 20c	Ether 21a	Ether 21b	Ether 21c	Lactone 22a	Lactone 22b
91	9		5	16	17	22	29	24		10
92		16				7	5	8		
93	10	3				9	5	8		
94	14	12				4		3		
95	100	16	8	23	21	13	4	35		
96	16	60	3			16	4	10		
97	5	21						5		3
98		8								
99										
100										
101						10		12		
102						13	7	17		
103			4	3	4	13	4	3	13	
104								4	6	
105	12		31	49	79	73	17	84		28
106		12	18	14	21	47		20		8
107	9				4	8		23		
108		15						4		
109	38		23	20	19	29		20		
110	12	30	19	21	6	42		50		
111	6	8				11		5		
112		16								
113						4		4	4	
114						3		4		
115			8	8	14	11	3	17		10
116					3	89		11		
117			3		3	7		11		
118						63		4		

TABLE I (Continued)

m/e	Lactone 1a	Lactone 1b	Diol 20a	Diol 20b	Diol 20c	Ether 21a	Ether 21b	Ether 21c	Lactone 22a	Lactone 22b
119										
120	6									
121	14	7								
122	3	12								
123	88	5								
124	9	98								
125		9						3		
126						7		10	3	
127				4	4	17		22	5	7
128			5	6	9	33		52		9
129			5	6	8	23	3	36		6
130						4		4		
131	3					5		7		
132										
133	3							7		
134										
135										
136										
137	12									
138	28	12								
139	3	14				10		16		
140										
141						9		15		3
142						4		6		
143						3		6		
144								38		
145										

TABLE I (Continued)

m/e	Lactone 1a	Lactone 1b	Diol 20a	Diol 20b	Diol 20c	Ether 21a	Ether 21b	Ether 21c	Lactone 22a	Lactone 22b
146										
147				4	3			3		
148										
149	4							4		
150		3						3	4	
151	10					6		11		4
152	4	8	5	8	10	26	6	42	3	9
153	5		34	4	7	12		26		5
154			10	11	26	26		31		10
155			4	6	14	10		25		4
156	4		4		7			4		
157										
158										
159						6		22		
160								4		
161										
162										
163						7		11	12	
164						5		7	5	
165	3		10	14	18	73	16	29	5	15
166	33	55		4	5	21	6	32		5
167	18	8	8	12	4	31	6	57		5
168						5		8		
169								3		
170										
171								3		
172										

TABLE I (Continued)

m/e	Lactone 1a	Lactone 1b	Diol 20a	Diol 20b	Diol 20c	Ether 21a	Ether 21b	Ether 21c	Lactone 22a	Lactone 22b
173										
174										
175										
176						4		7	4	
177								4		
178				3	5	14	7	28		6
179						6		11	5	
180										
181			5	10	14	9		32		6
182			5	13	18	21	3	18	10	5
183			100	39	100	100	64	55	100	100
184			7	12	21	33	9	15	48	45
185				4	6			6	5	4
186										
187									4	
188										
189						10	4	20	7	3
190								7		
191					4	13	4	28		5
192							3	14		4
193					4	3	3	14		
194-200										
201									3	
202						9	4	18		3
203					3	7	4	16	4	5
204						5		11		
205				3	7	8	5	18		5
206				3	4		9			
207										

TABLE I (Continued).

m/e	Lactone <u>1a</u>	Lactone <u>1b</u>	Diol <u>20a</u>	Diol <u>20b</u>	Diol <u>20c</u>	Ether <u>21a</u>	Ether <u>21b</u>	Ether <u>21c</u>	Lactone <u>22a</u>	Lactone <u>22b</u>
208										
209								3		
210								3		
211										
212										
213										
214								9		
215			6	8	31	69	34	91	22	29
216					6	27	7	43	4	5
217								14		
218										
219					5			7		
220										
221										
222								6		
223-232										
233				3	16			4		
234-247										
248				6	8			13		
249								3		
250-290										
291								14		
292			0.3	11	10	13	59	69	59	38
293				3	3	2	6	5	11	9
294-309										
310			1.3	2.2	15					
311			0.3	0.7	5					

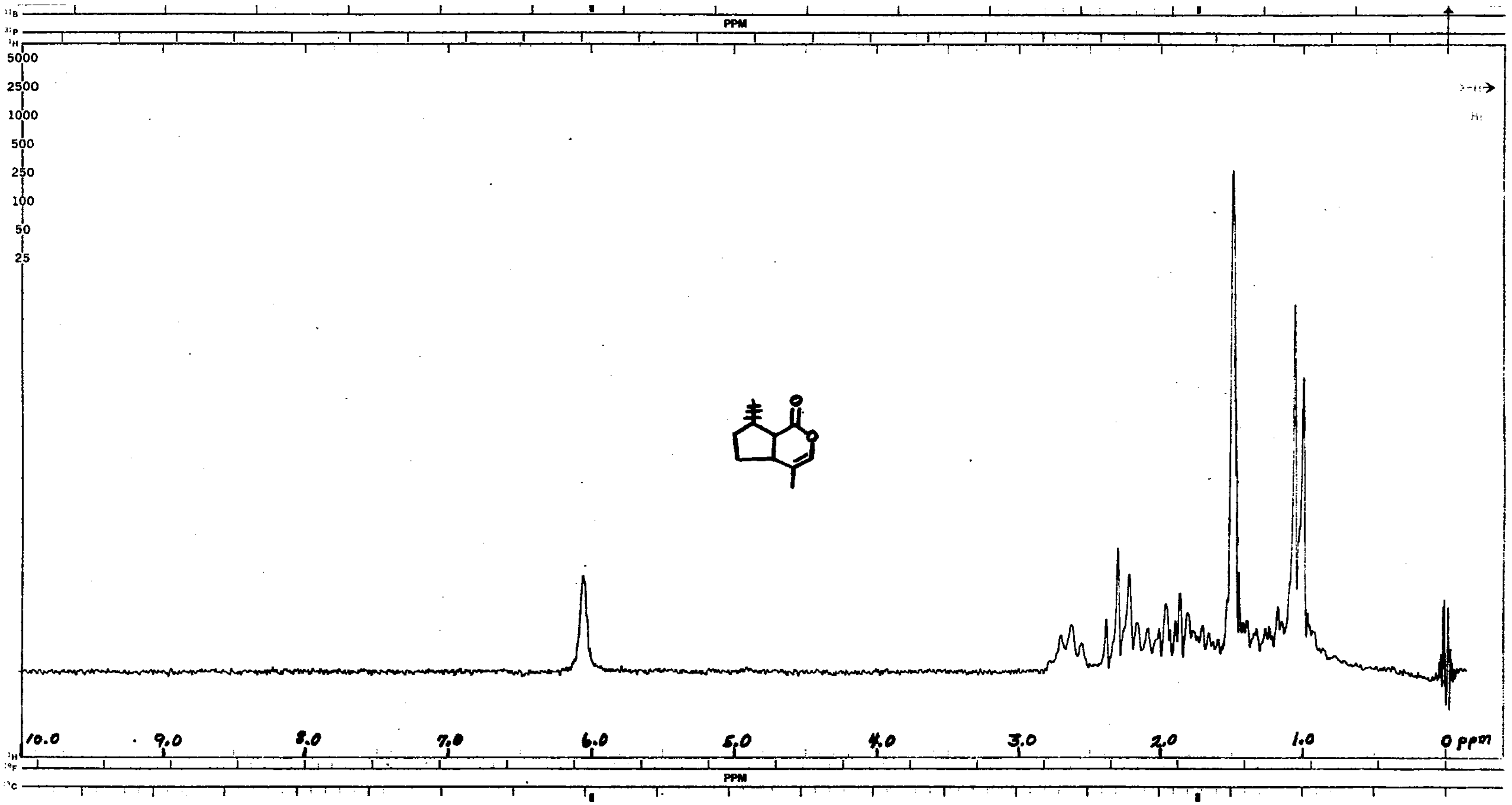


Figure 15. Nmr Spectrum of (7*S*)-*cis*,*trans*-Nepetalactone (1a)

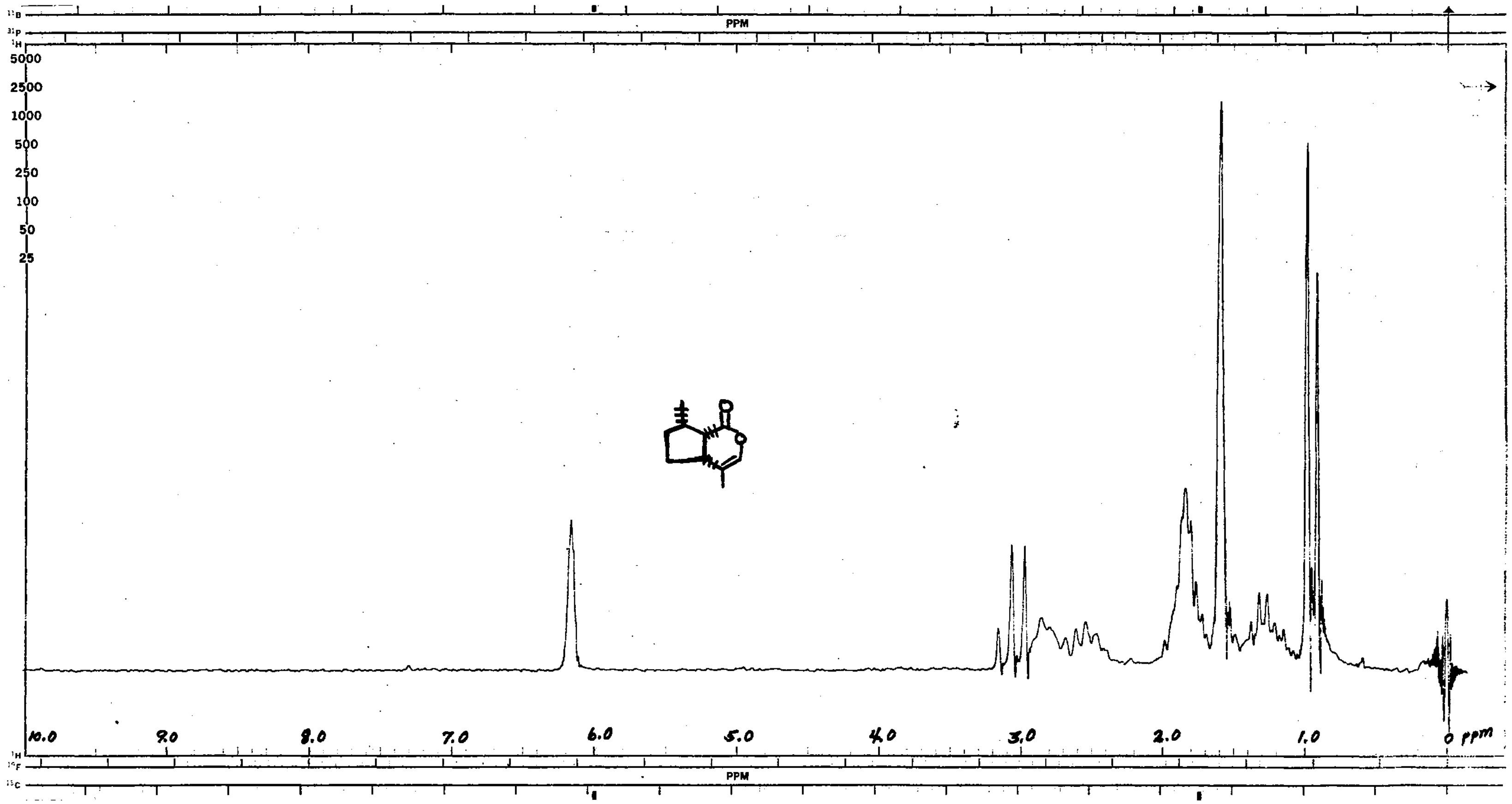


Figure 16. Nmr Spectrum of (7*S*)-*cis,cis*-Nepetalactone (1b)

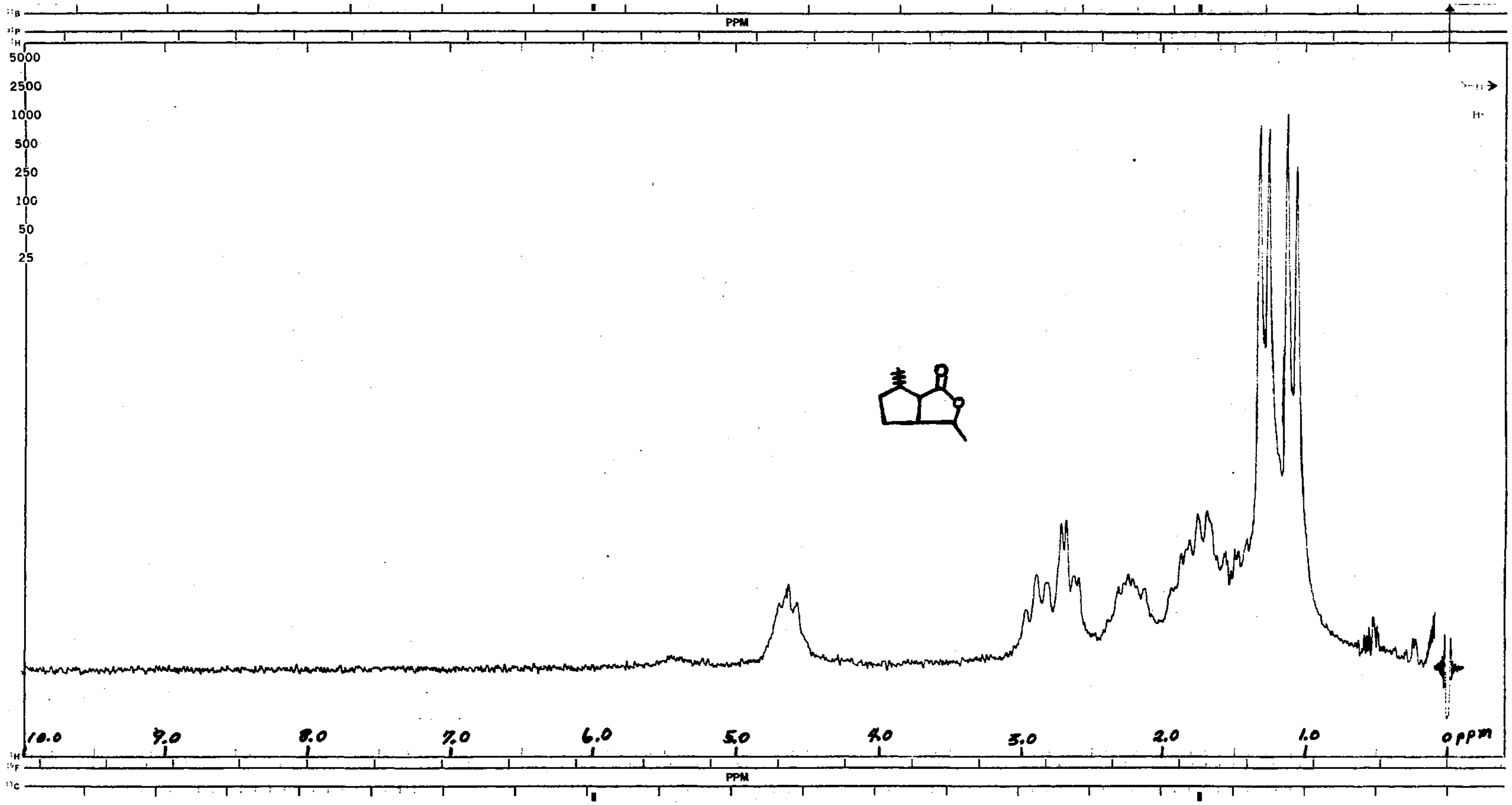


Figure 17. Nmr Spectrum of (3*S*,6*S*)-*cis*,*trans*-Nepetolactone (19a)

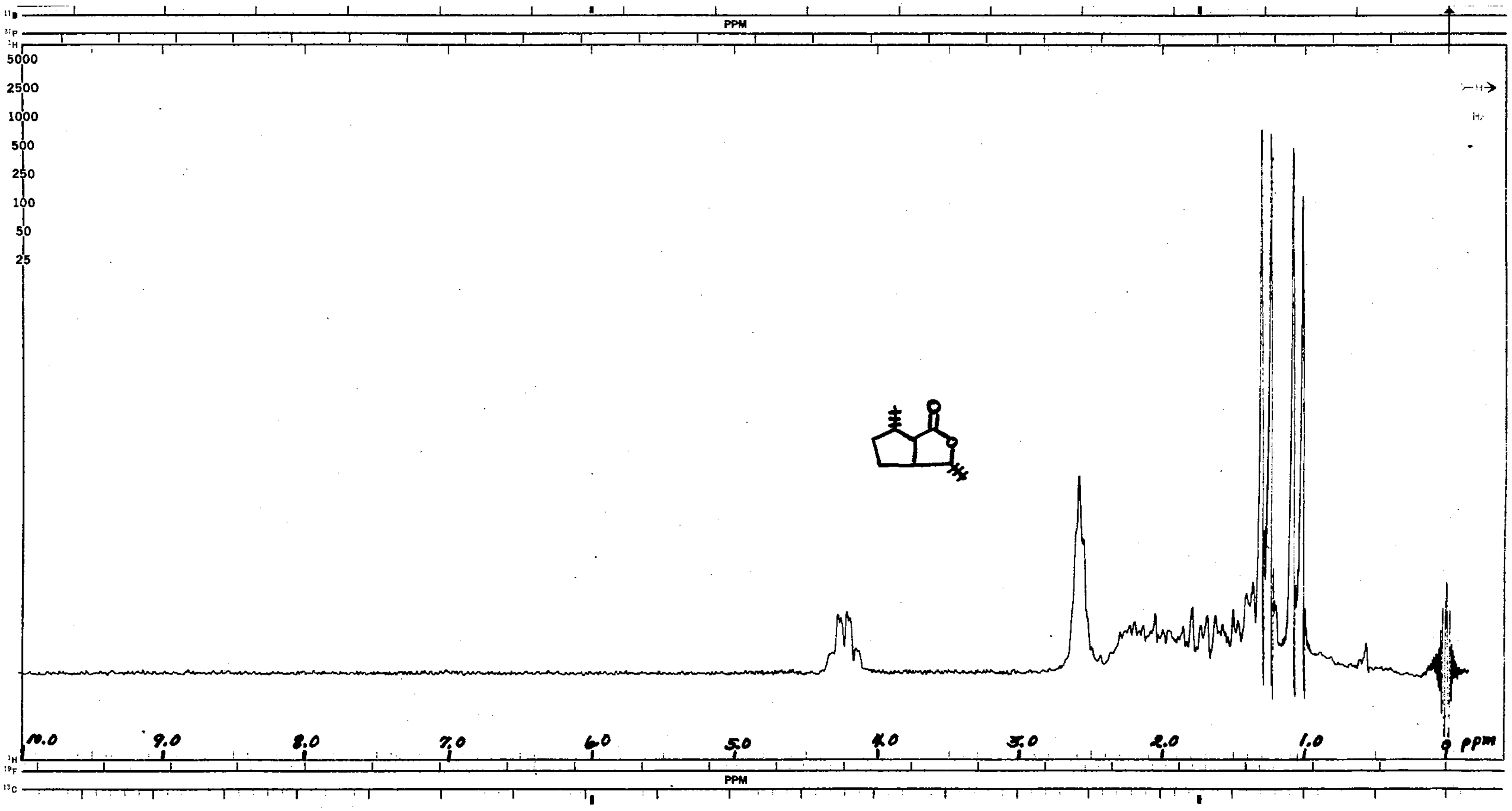


Figure 18. Nmr Spectrum of (3*R*,6*S*)-*cis*,*trans*-Nepetolactone (19b)

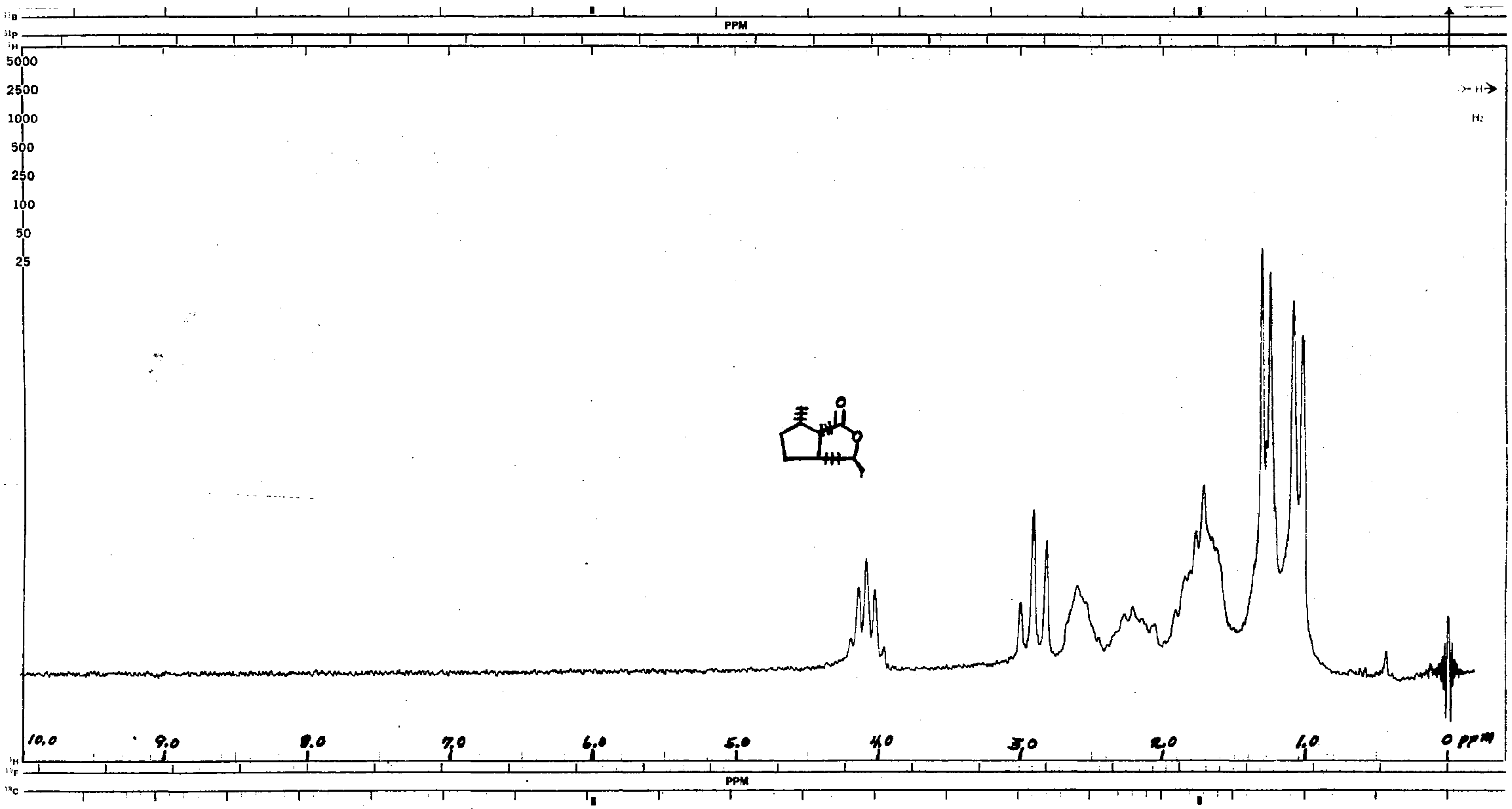


Figure 19. Nmr Spectrum of (3*S*,6*S*)-*cis*,*cis*-Nepetolactone (19c)

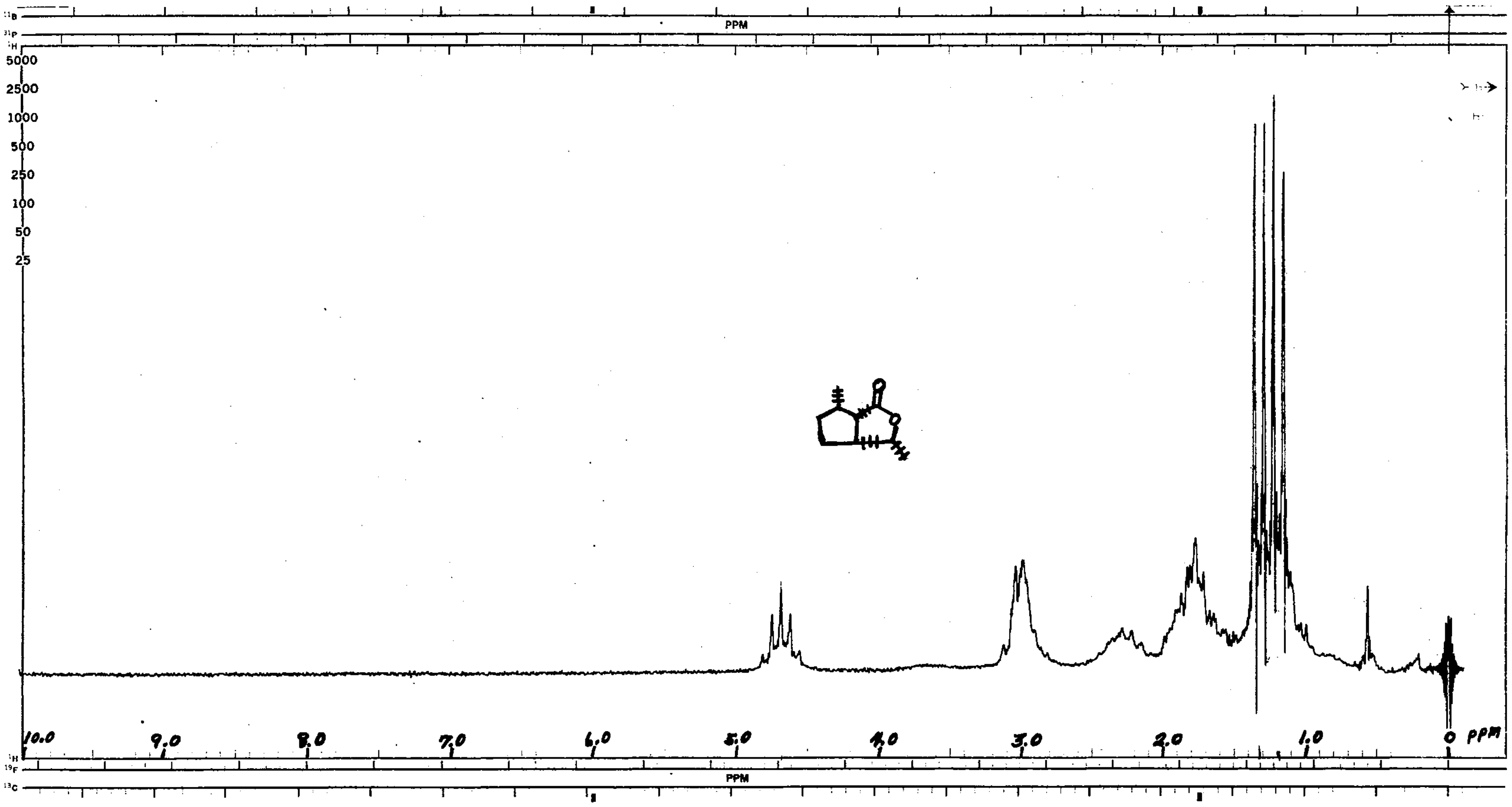


Figure 20. Nmr Spectrum of (3*R*,6*S*)-*cis*,*cis*-Nepetolactone (19d)

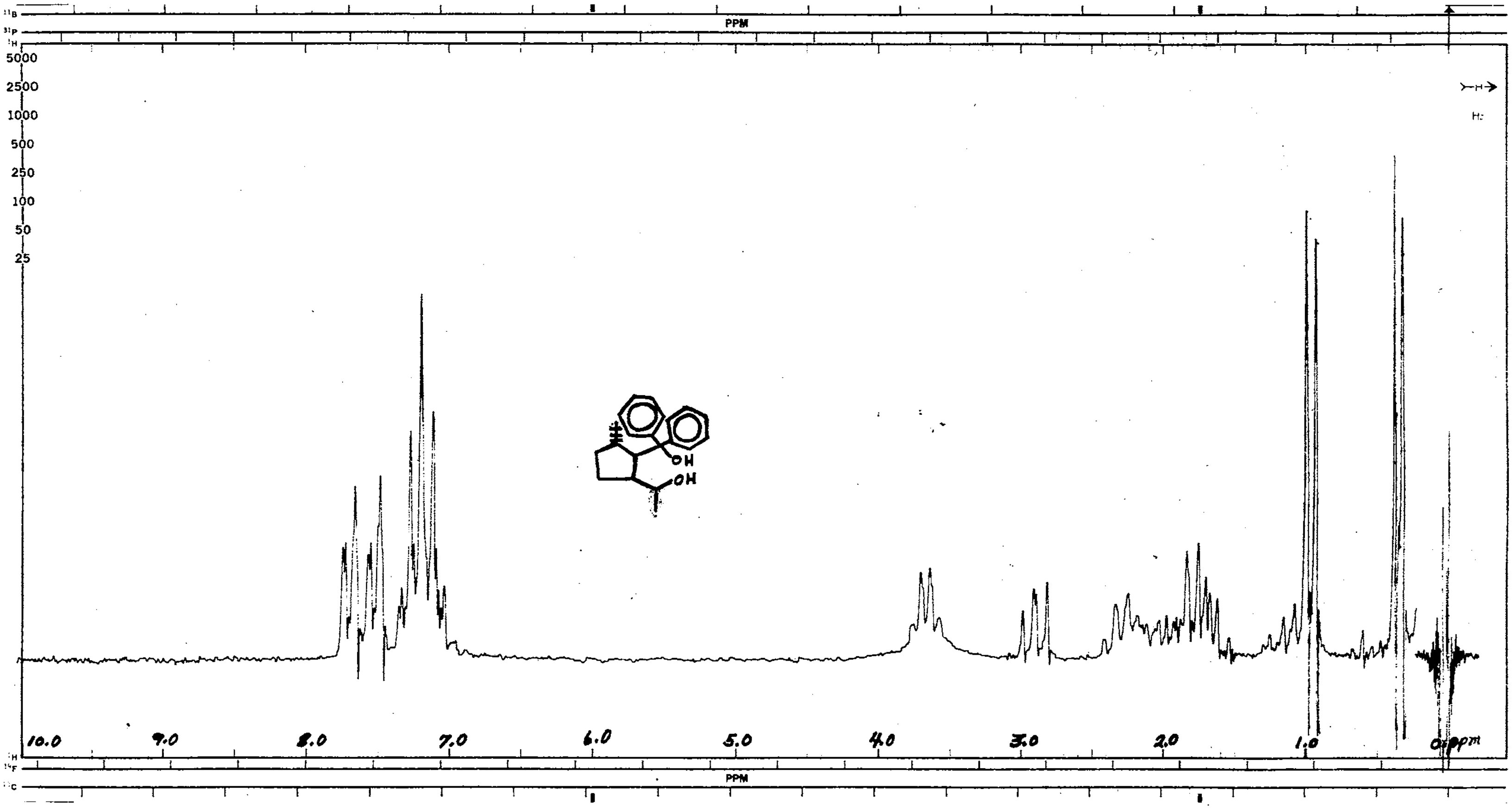


Figure 21. Nmr Spectrum of *cis,trans*-Diol 20a (mp 157°)

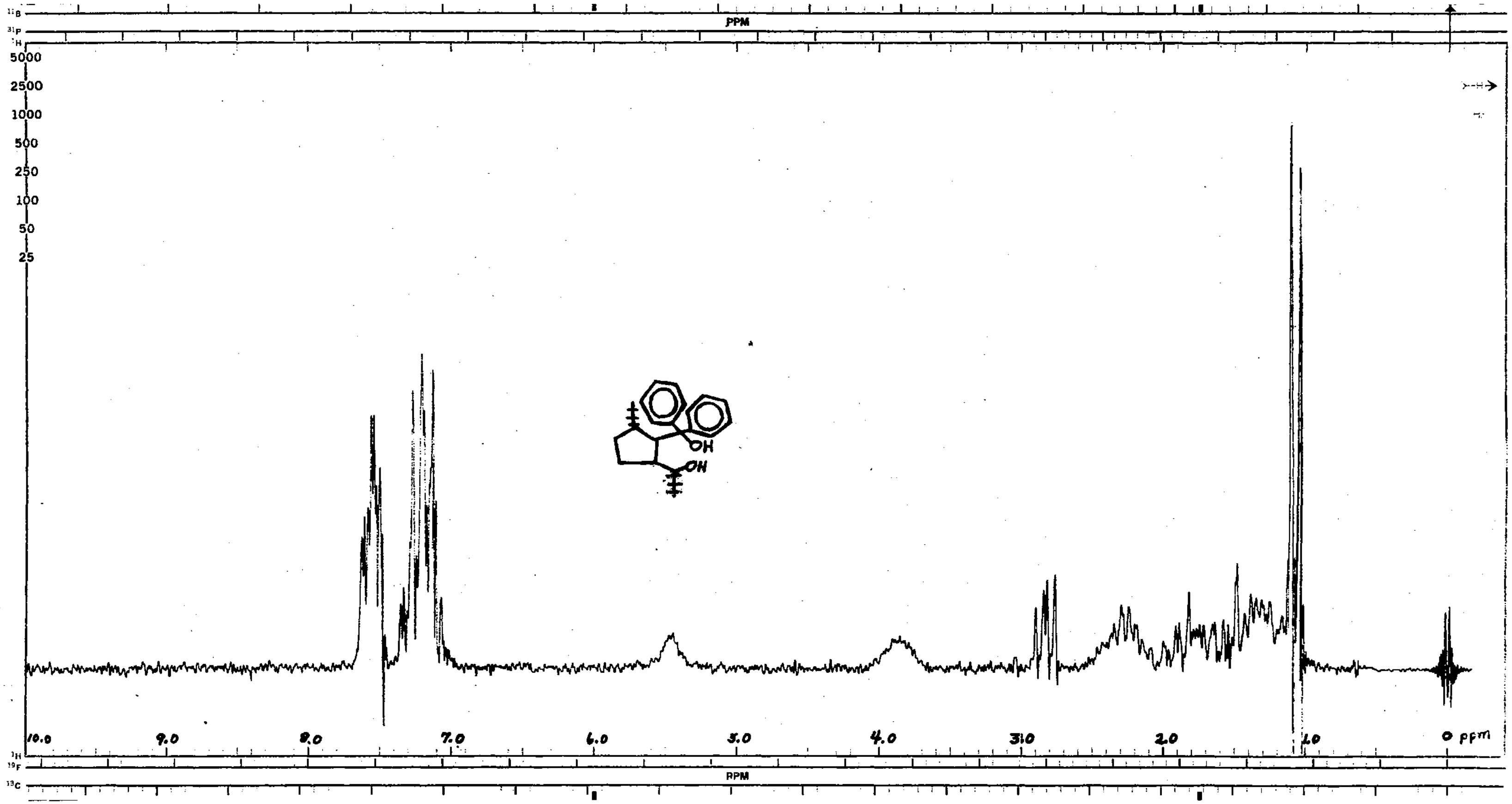


Figure 22. Nmr Spectrum of *cis*,*trans*-Diol 20b (mp 143°)

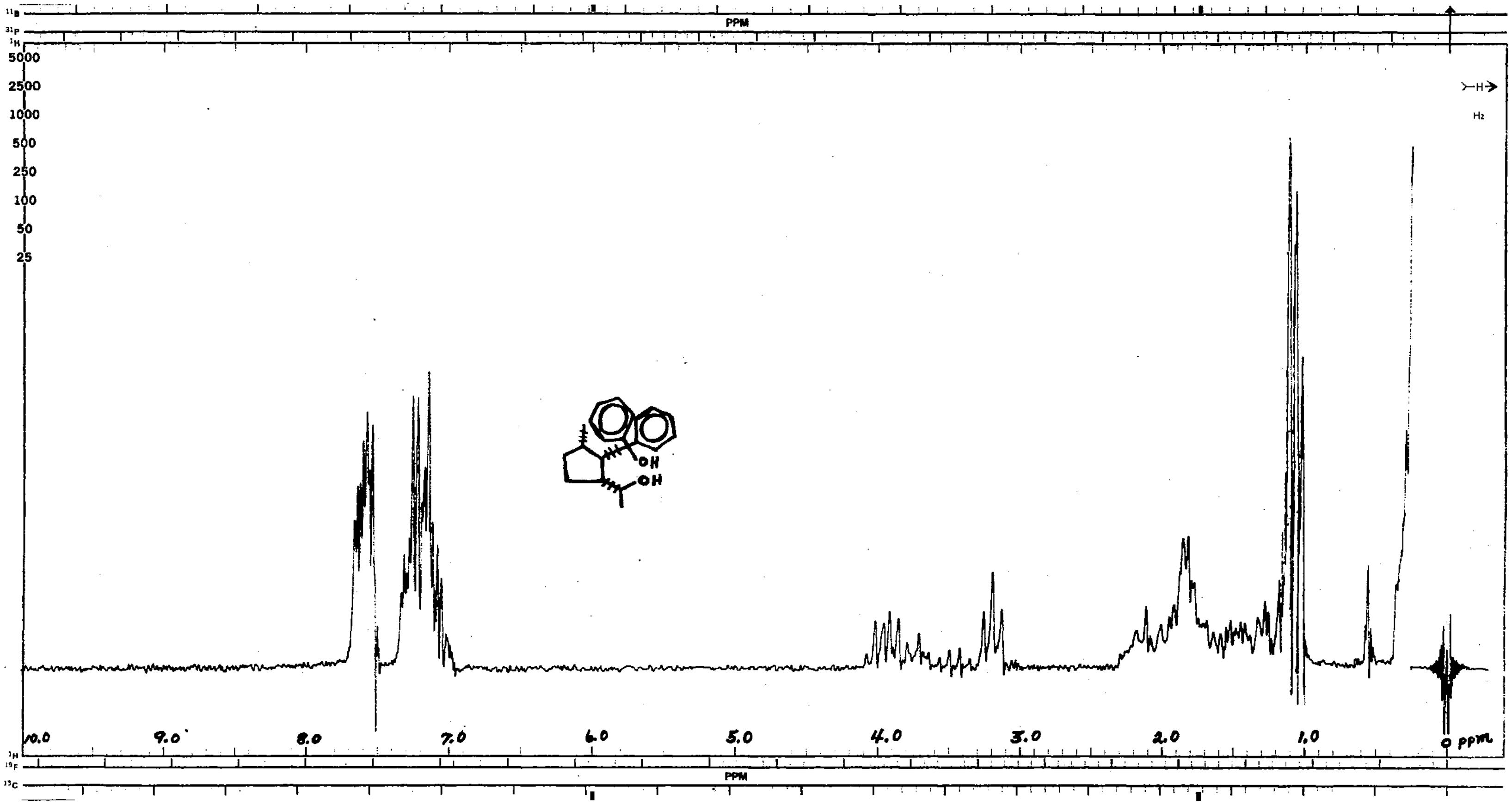


Figure 23. Nmr Spectrum of *cis,cis*-Diol 20c (mp 133°)

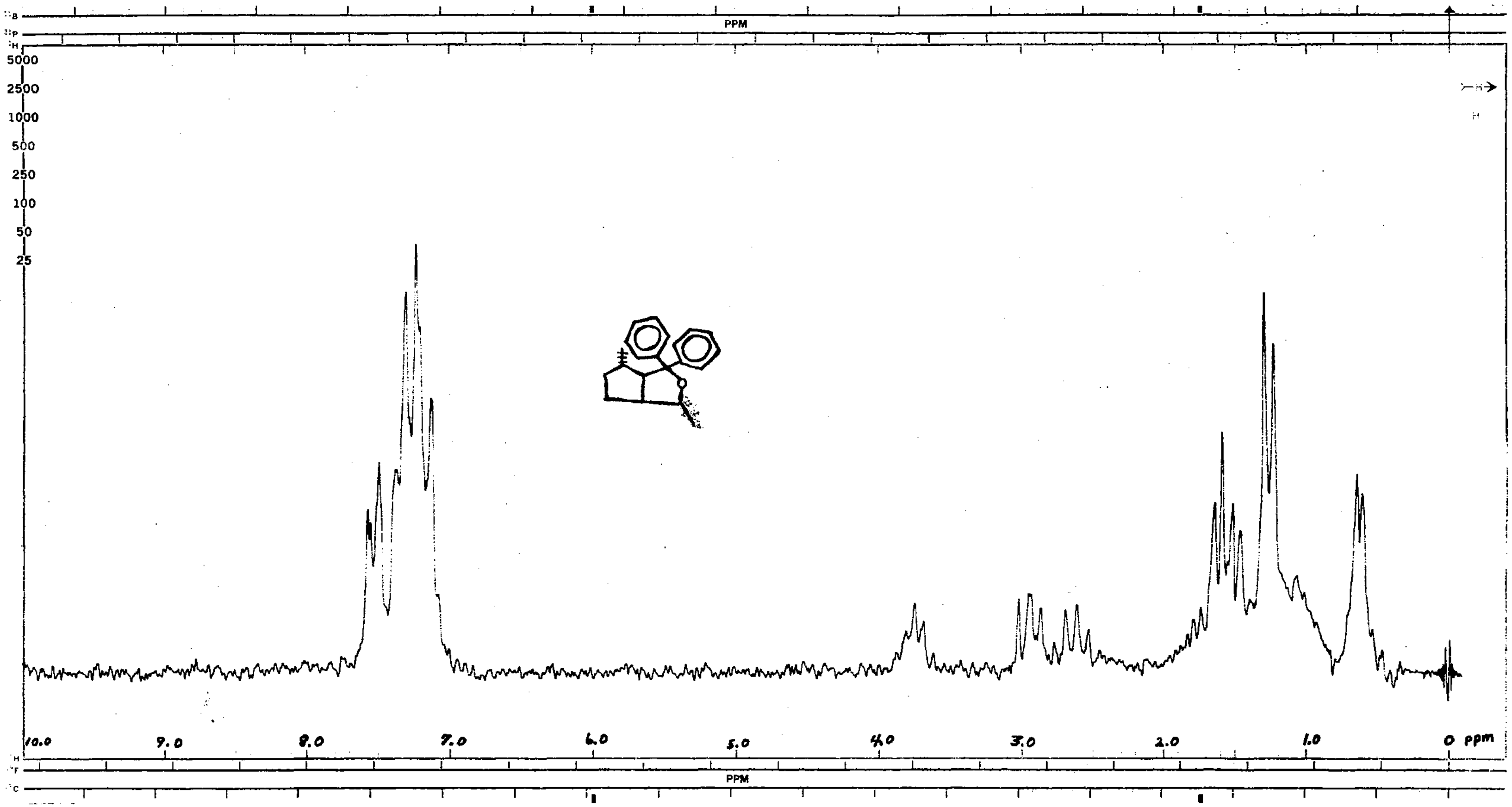


Figure 24. Nmr Spectrum of *cis,trans*-Ether 21a (mp 89°)

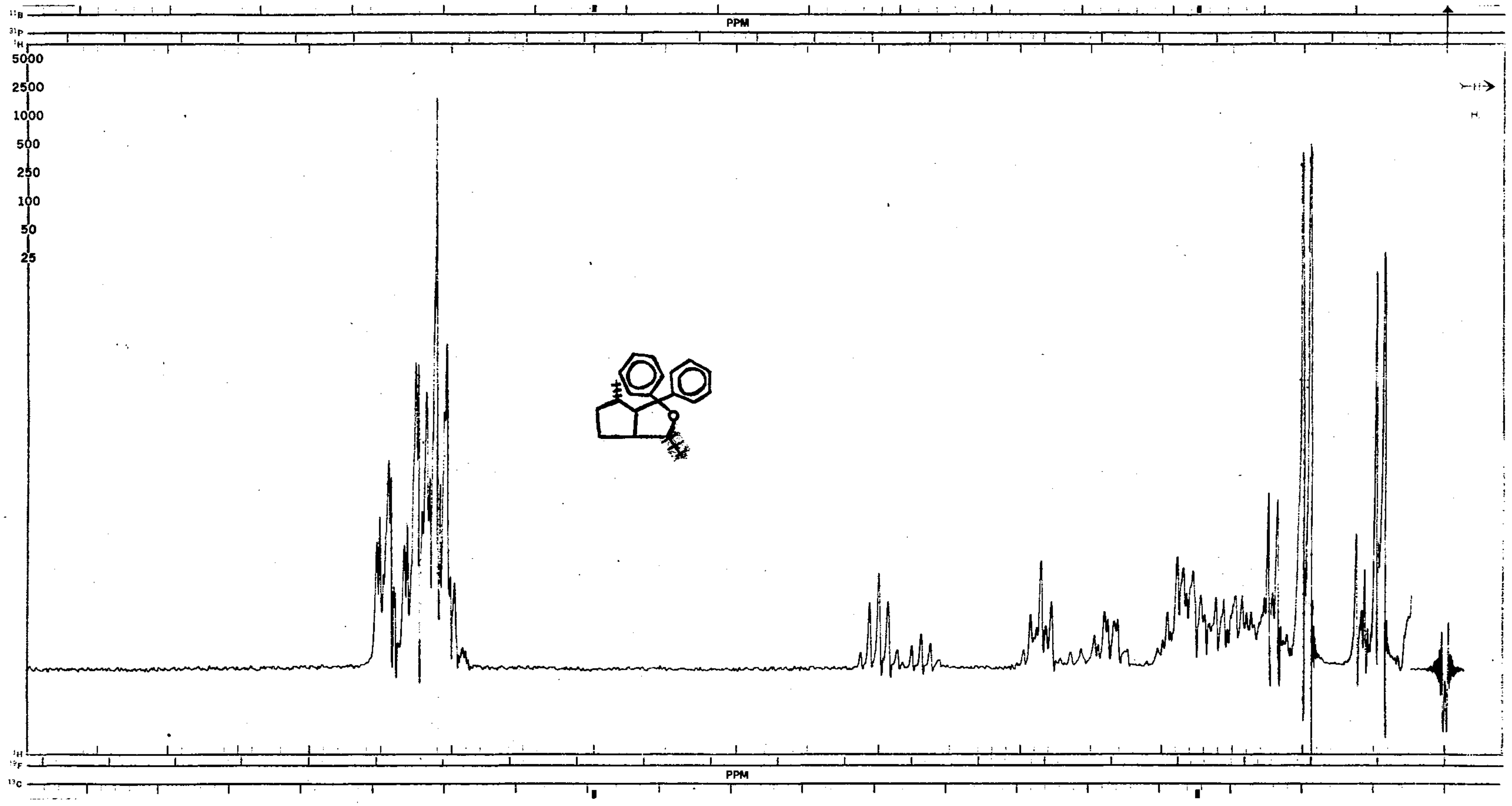


Figure 25. Nmr Spectrum of *cis,trans*-Ether 21b (mp 72°)

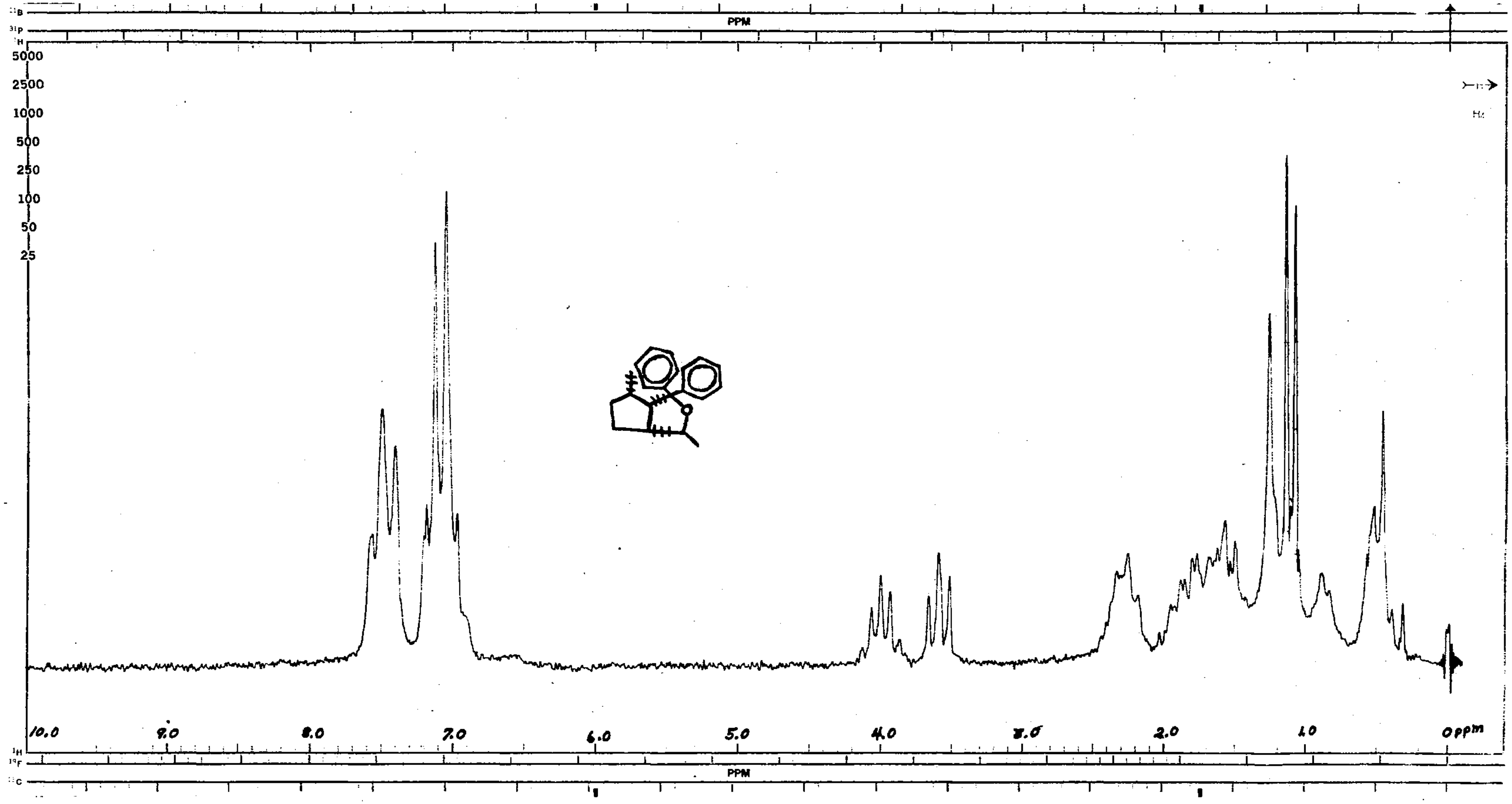


Figure 26. Nmr Spectrum of *cis*,*cis*-Ether 21c (mp 118°)

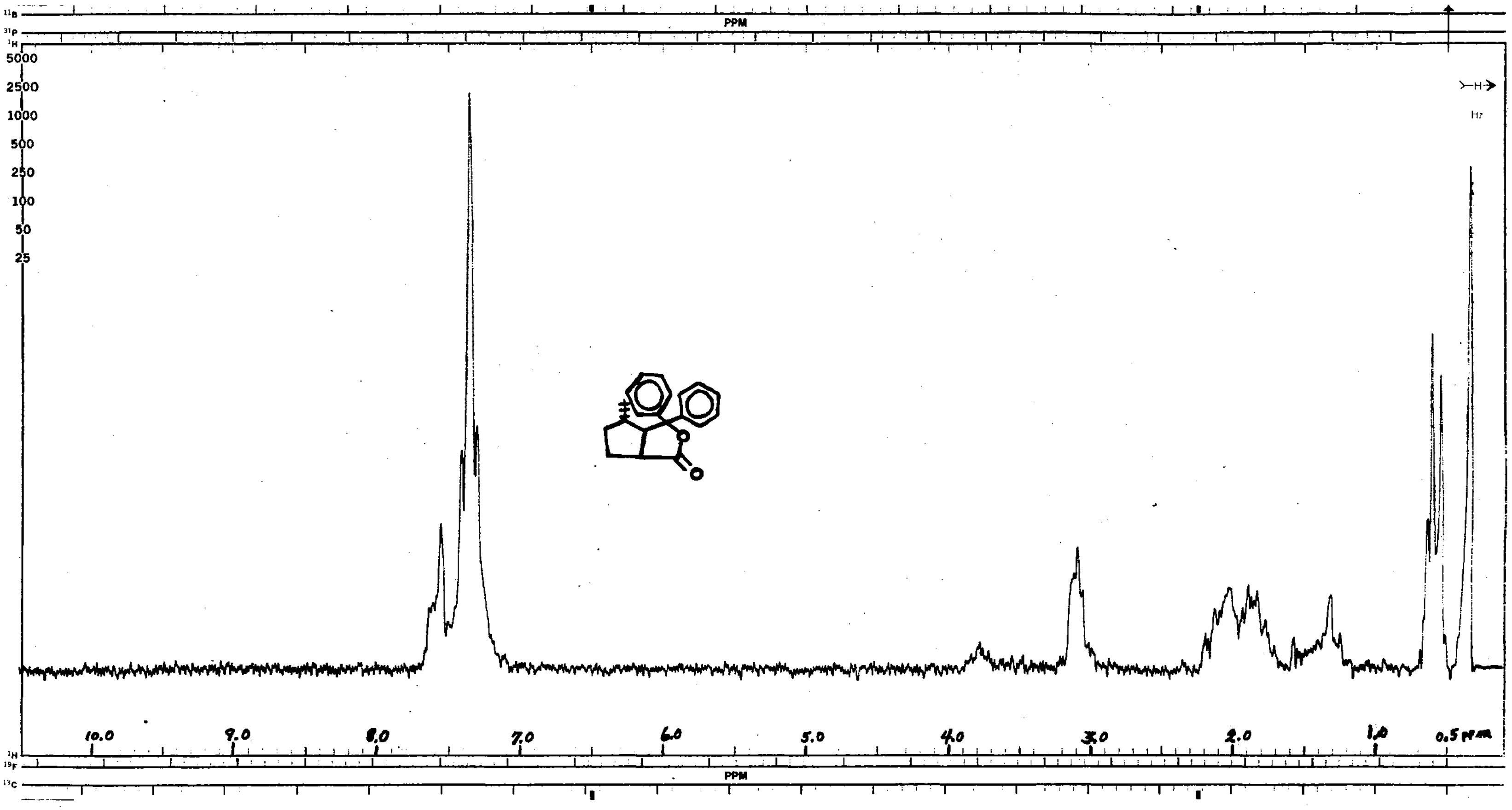


Figure 27. Nmr Spectrum of *cis,trans*-Lactone 22a (mp 213°)

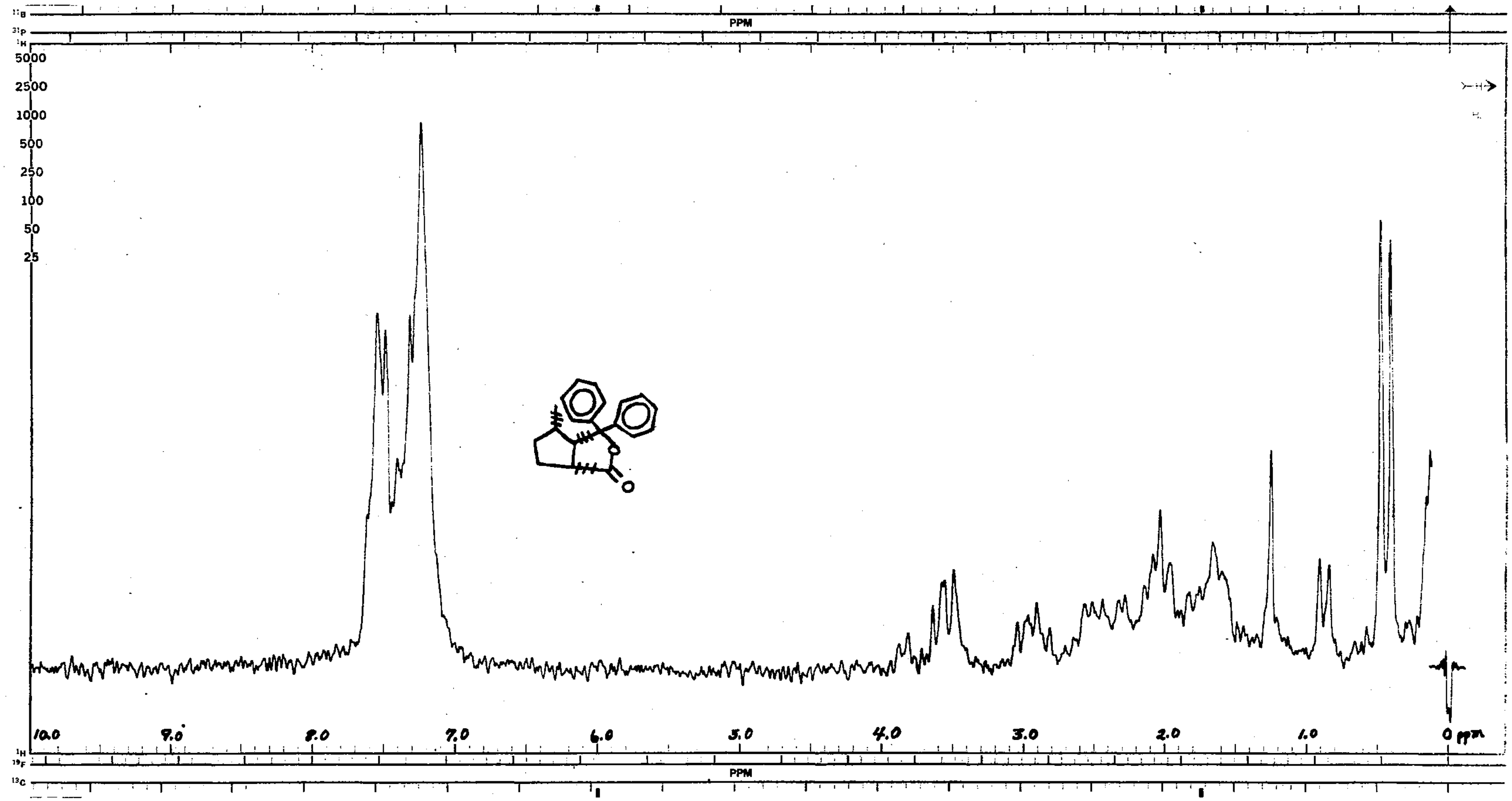


Figure 28. Nmr Spectrum of *cis,cis*-Lactone 22b (mp 203°)

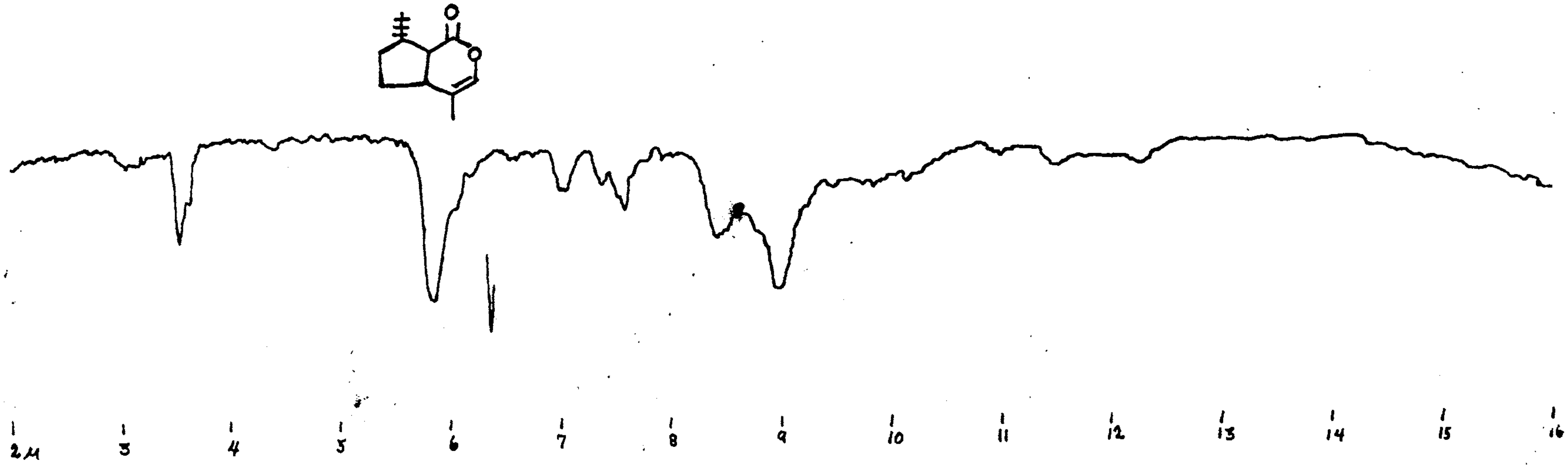


Figure 29. Ir Spectrum of (7*S*)-*cis,trans*-Nepetalactone (<u>1a</u>)

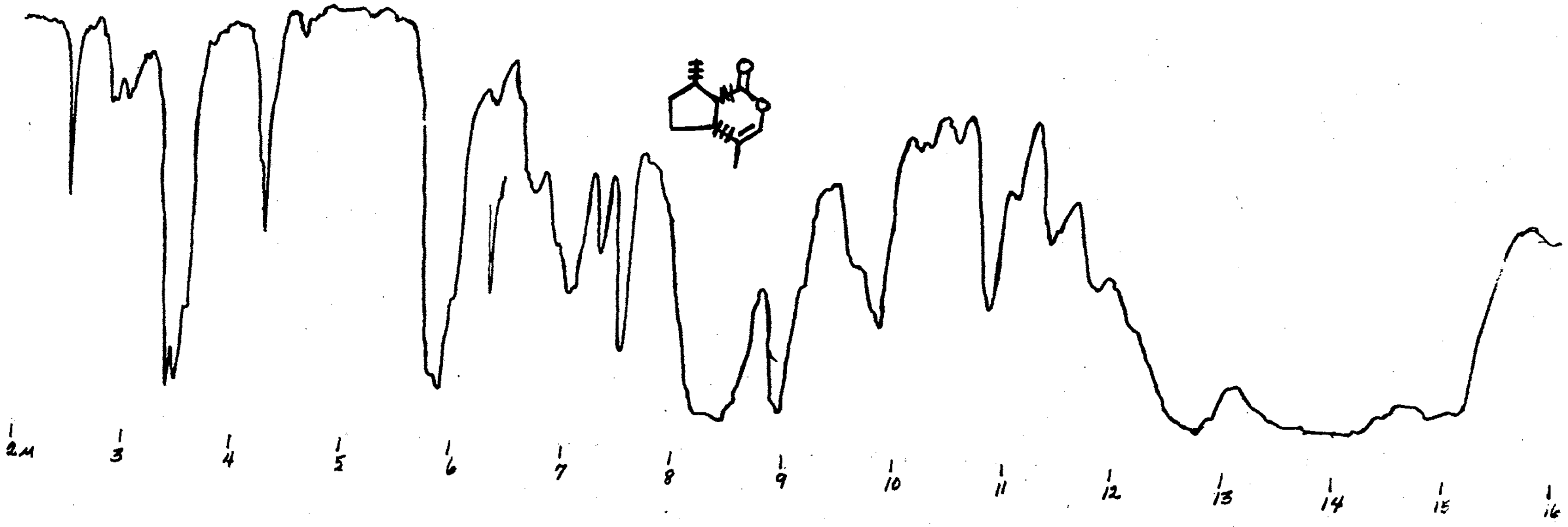


Figure 30. Ir Spectrum of (7*S*)-*cis*,*cis*-Nepetalactone (1b)

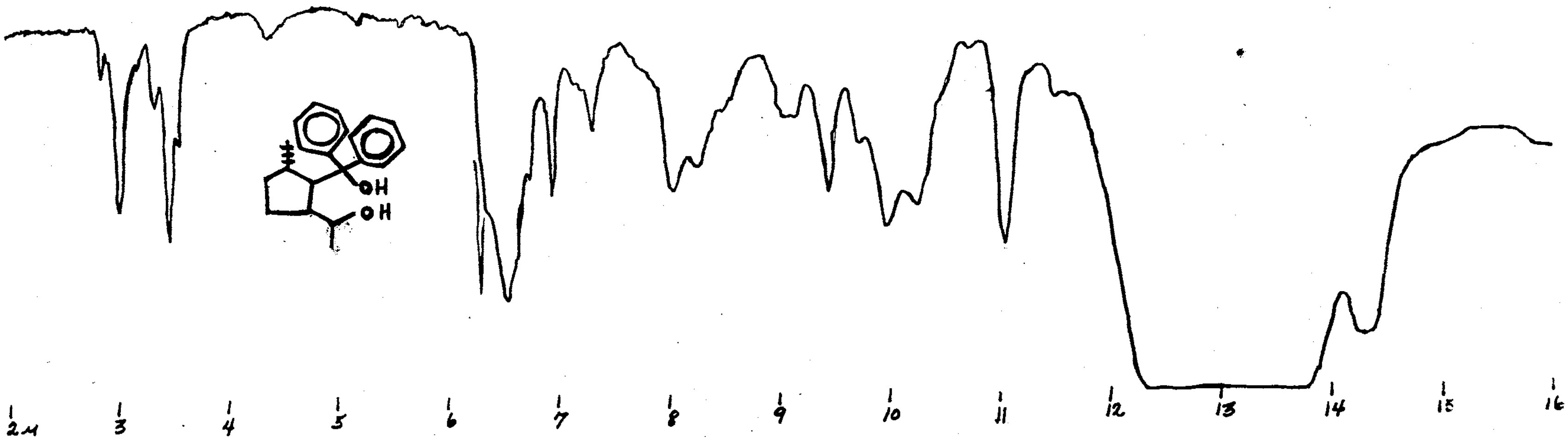


Figure 31. Ir Spectrum of *cis,trans*-Diol 20a (mp 157°)

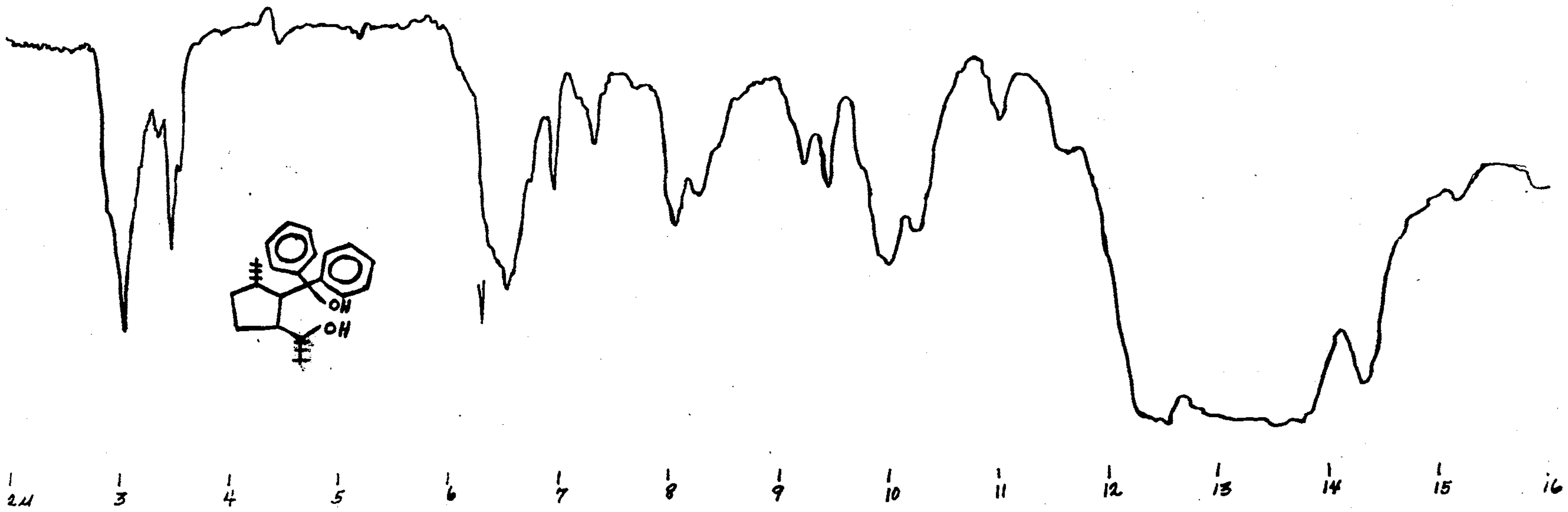


Figure 32. Ir Spectrum of *cis,trans*-Diol 20b (mp 143°)

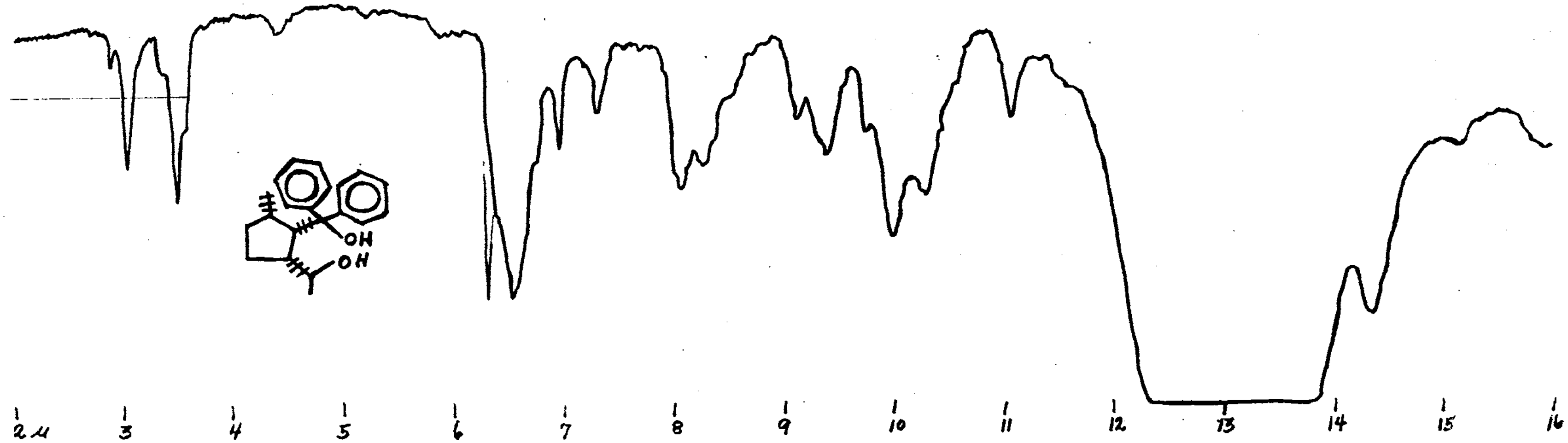


Figure 33. Ir Spectrum of *cis,cis*-Diol 20c (mp 133°)

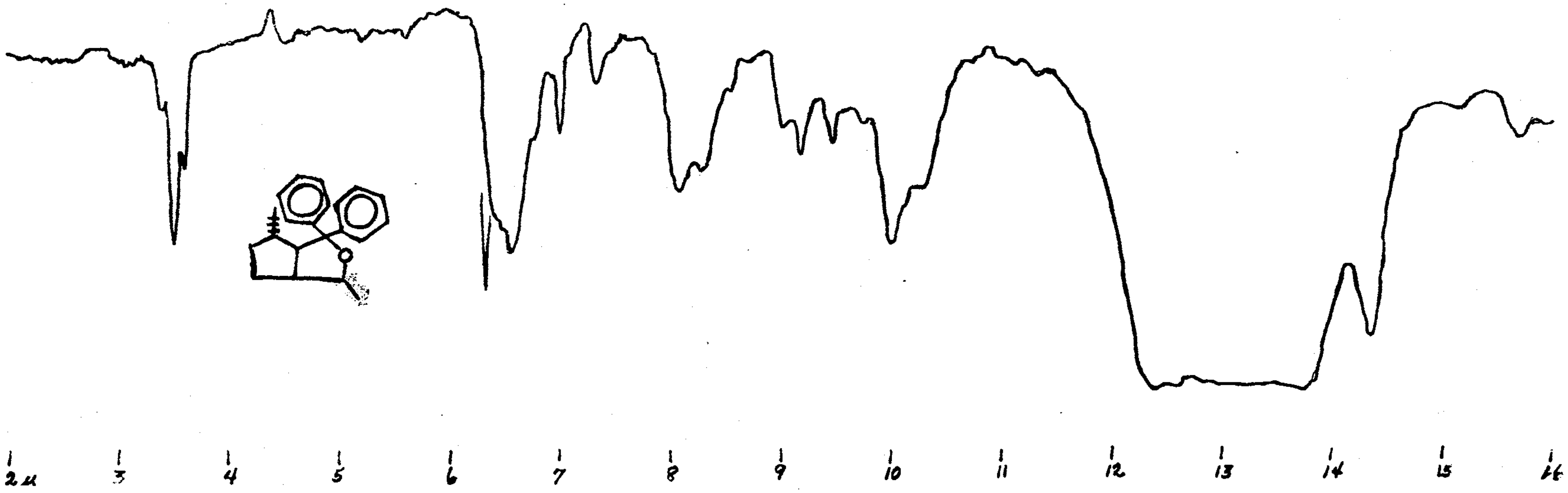


Figure 34. Ir Spectrum of *cis,trans*-Ether 21a (mp 89°)

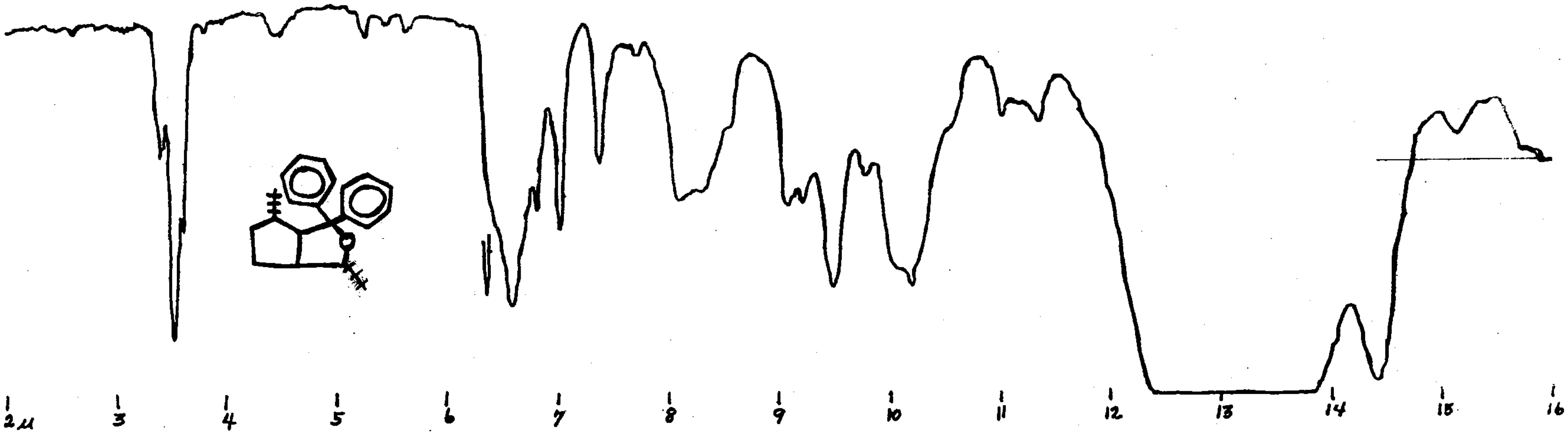


Figure 35. Ir Spectrum of *cis,trans*-Ether 21b (mp 72°)

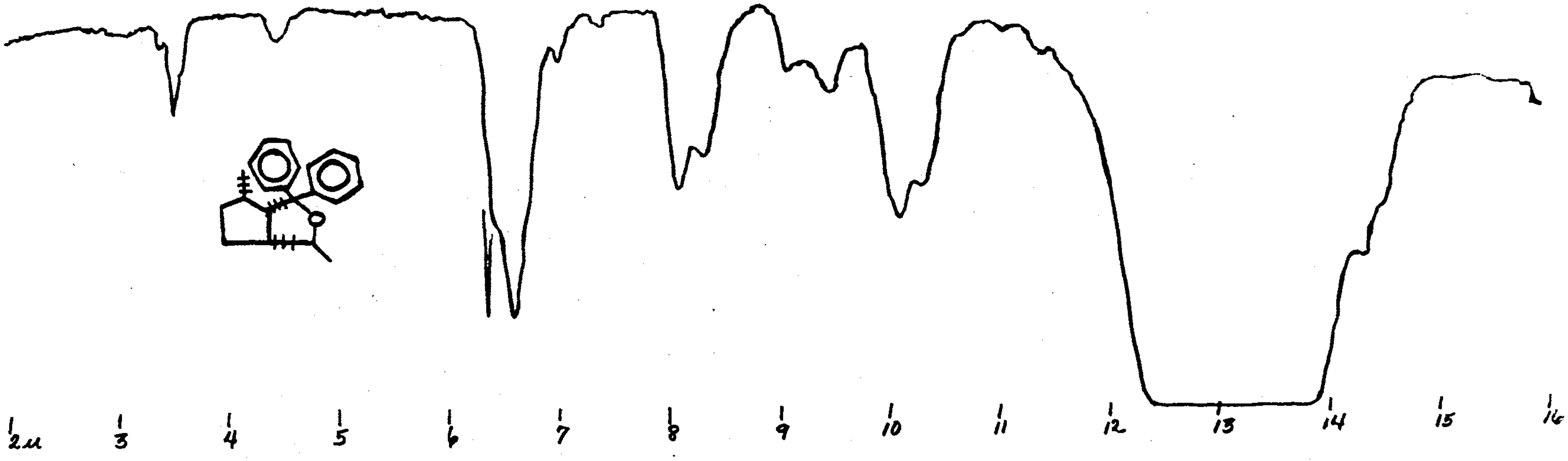


Figure 36. Ir Spectrum of *cis,cis*-Ether <u>21c</u> (mp 118°)

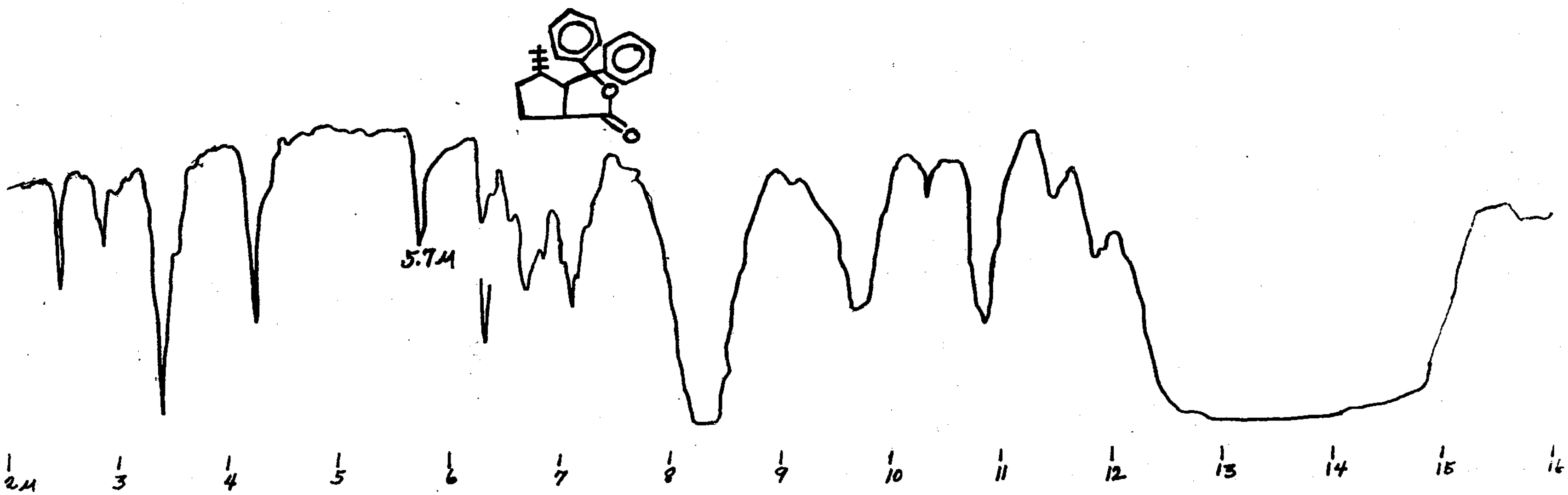


Figure 37. Ir Spectrum of *cis,trans*-Lactone 22a (mp 213°)

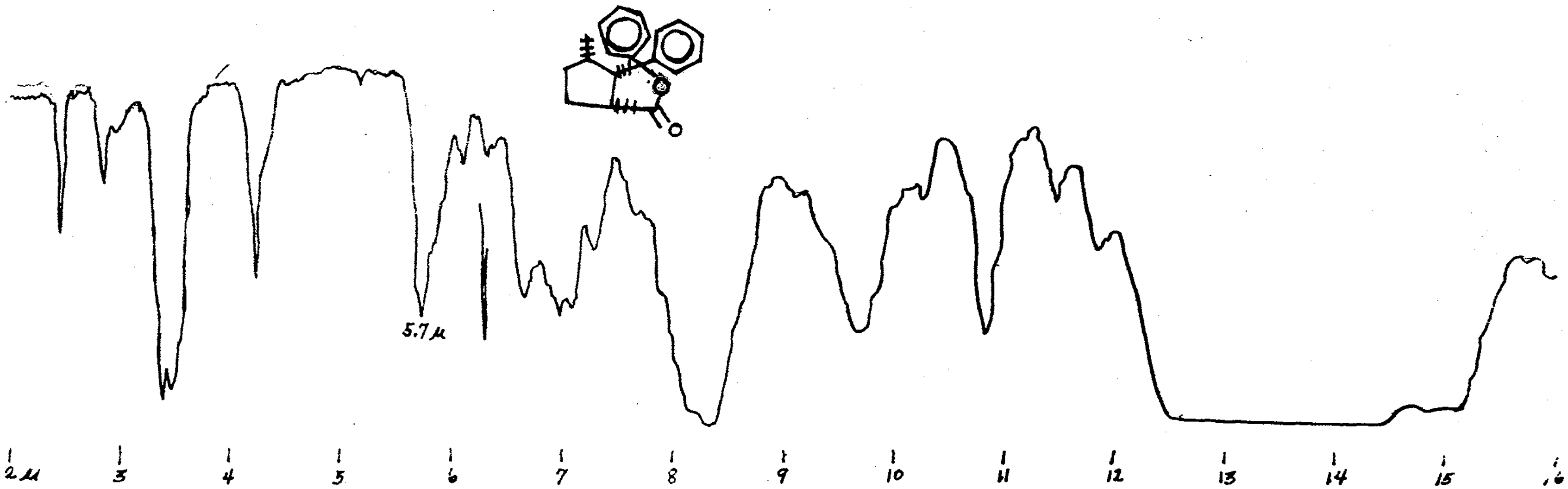
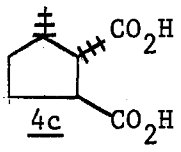


Figure 38. Ir Spectrum of *cis,cis*-Lactone <u>22b</u> (mp 203°)

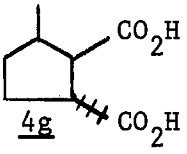
CHAPTER III

THE ABSOLUTE CONFIGURATION OF *CIS*, *CIS*-NEPETALACTONE FROM *N. MUSSINI*

The absolute configuration of the *cis*,*cis*-nepetalactone (1b) from *N. mussini* was obtained by determining the absolute configuration at C-7. This was accomplished by degrading 1b to nepetic acid 4c of known absolute configuration.

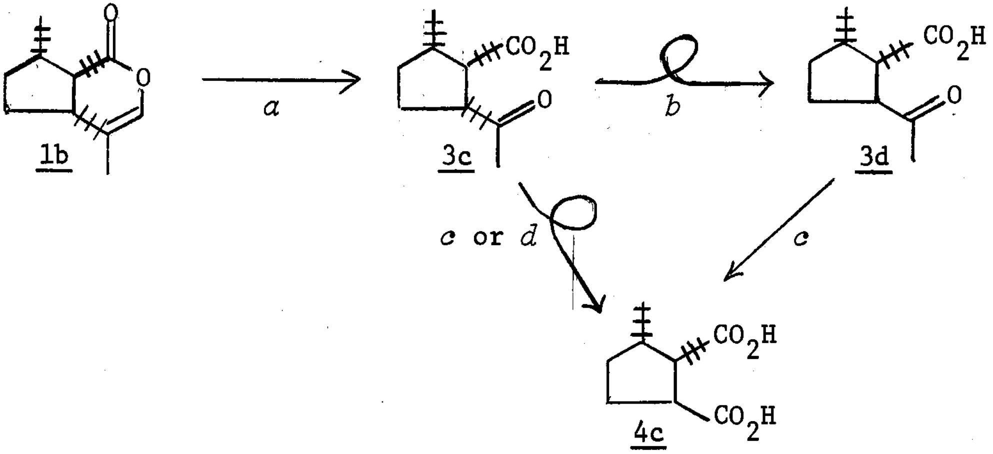


4c



4g

The reaction sequence used in this degradation is shown in Figure 39. *Cis*,*cis*-nepetalactone (1b) was ozonized, followed by ozonide decomposition with dimethyl sulfide to give a 76% yield of a mixture of 95% nepetonic acid 3c (2,4-dinitrophenylhydrazone of methyl ester, melting point 122-123.5°) and 5% nepetonic acid 3d (2,4-dinitrophenylhydrazone of methyl ester, melting point 73-74°). The *cis*,*cis*-nepetonic acid 3c was epimerized to the more stable nepetonic acid 3d. Treatment of 3d with hypoiodite readily precipitated iodoform, and acidification of the reaction mixture afforded a *trans*-nepetic acid. The two possibilities for the absolute configuration of this nepetic acid obtained *via* degradation of <u>1b</u> are either (+)-*t*-(3*S*)-methyl-*r*-1,*t*-2-cyclopentanedicarboxylic acid (<u>4c</u>) or (-)-*t*-(3*R*)-methyl-*r*-1,*t*-2-cyclopentanedicarboxylic acid (<u>4g</u>) (Figure 41).[1d] Both <u>4c</u> and <u>4g</u> have been independently synthesized, and were available for comparison with the nepetic acid obtained by degradation of <u>1b</u>.[9,10]



[a] O_3, methanol, pyridine; dimethyl sulfide

[b] OH^-; H^+

[c] OH^-, Br_2; H^+

[d] OH^-, I_2, KI; H^+

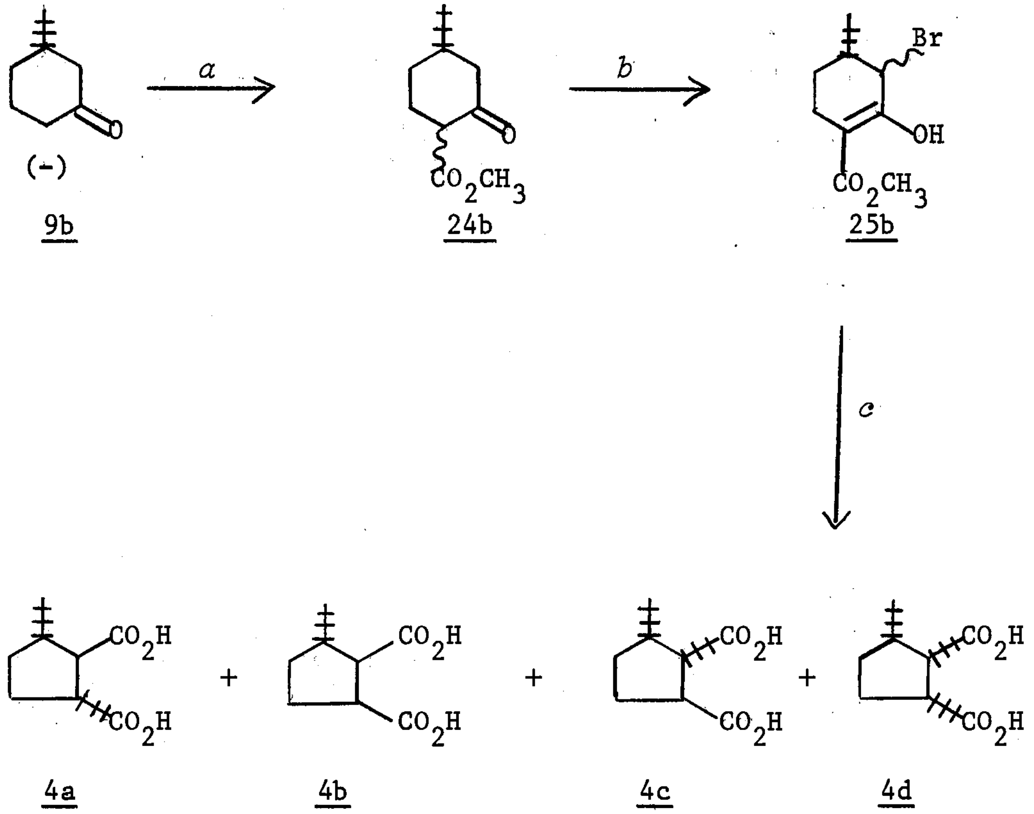
Figure 39. Determination of the Absolute Configuration of (7*S*)-*cis*,*cis*-Nepetalactone (<u>1b</u>) from *N. mussini*

Eisenbraun, Adolphen, and others have prepared nepetic acid 4c *via* the pathway shown in Figure 40.[9,10] (-)-3-Methylcyclohexanone (9b) was treated with dimethyl carbonate and sodium hydride to give 24b, which was brominated to yield the enol 25b. Favorskii rearrangement of 25b afforded the (3*S*)-methylcyclopentane-1,2-dicarboxylic acids 4a, 4b, 4c, and 4d.

Eisenbraun, Hanel, *et al.* synthesized the (3*R*)-methylcyclopentane-1,2-dicarboxylic acids by an analogous series of reactions beginning with (+)-pulegone (8), which was converted to (+)-3-methylcyclohexanone (9a) (Figure 41).[10] Reaction of 9a with dimethyl carbonate and sodium hydride gave the keto-ester 24a, which was brominated to 25a. Favorskii rearrangement of 25a produced the nepetic acids 4e, 4f, 4g, and 4h.

Glc analysis of a mixture of the nepetic acid obtained *via* degradation of *cis,cis*-nepetalactone (1b) with *trans,trans*-nepetic acids 4c and 4g showed only one peak. The melting point of an equal mixture of the nepetic acid (melting point 105-110°) from degradation of 1b and nepetic acid 4c (melting point 109-112°, literature value 115°), crystallized together, showed no depression (melting point of mixture 107-111°). Conversely, an equal mixture of the nepetic acid from degradation of 1b and nepetic acid 4g (melting point 105-110°, literature value 115°), crystallized together, had a melting point range of 125-130°. The melting point for racemic *trans,trans*-nepetic acid is reported to be 135-136°.[11] Thus it is concluded that the nepetic acid obtained from degradation of *cis,cis*-nepetalactone (1b) from *N. mussini* has the 7*S* absolute configuration.

Further confirmation of this absolute configurational assignment to 1b from *N. mussini* was obtained from comparison of the specific rotation

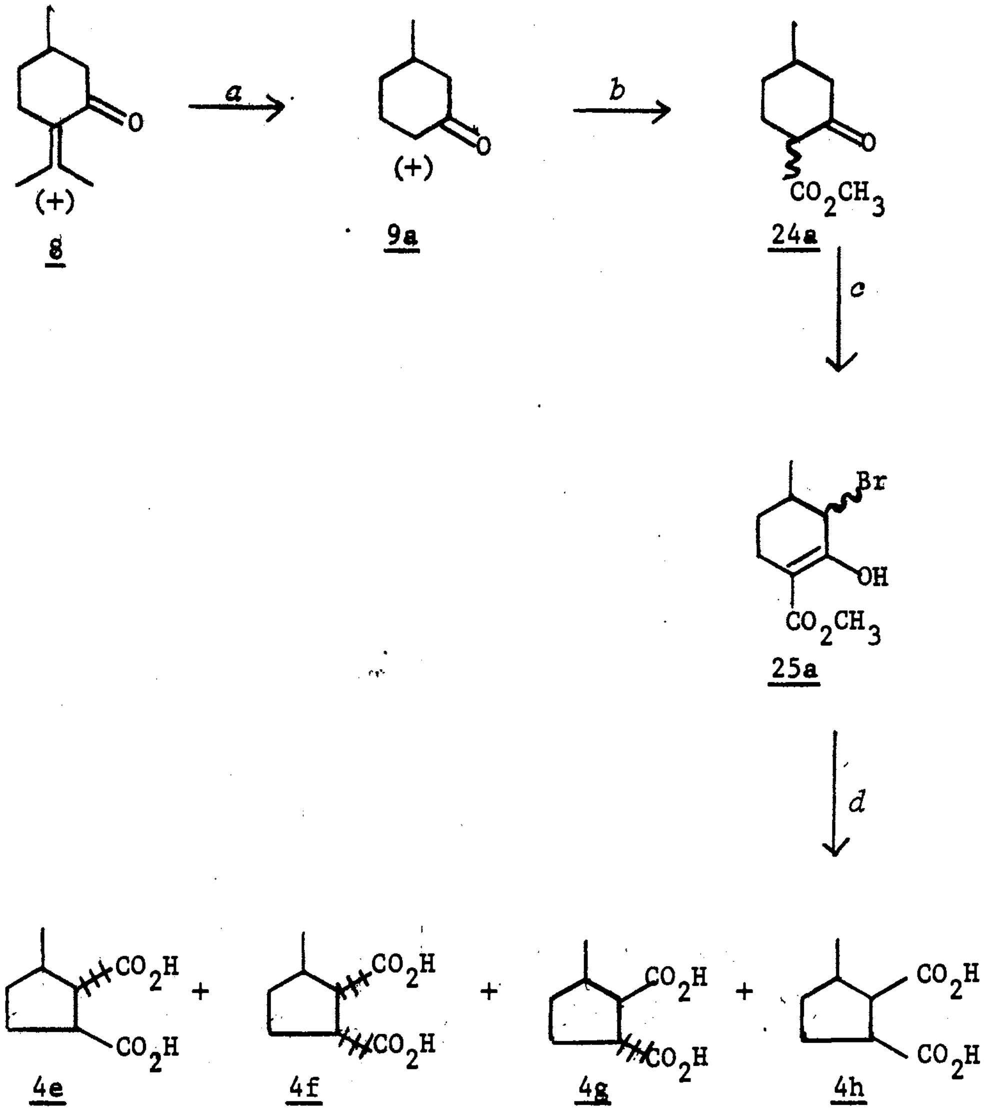


[a] Dimethyl carbonate, NaH, dioxane

[b] Br_2, Et_2O

[c] OH^-; H^+

Figure 40. Synthesis of the (3*S*)-Methylcyclopentane-1,2-dicarboxylic Acids (4a, 4b, 4c, and 4d)



${}^{a}H^{+}$, Δ

^{b}Dimethyl carbonate, NaH, dioxane

${}^{c}Br_2$, Et_2O

${}^{d}OH^{-}$; H^{+}

Figure 41. Synthesis of the (3*R*)-Methylcyclopentane-1,2-dicarboxylic Acids (4e, 4f, 4g, and 4h)

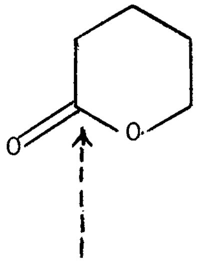
of *cis*,*cis*-nepetalactone from *N. mussini* with that of synthetically prepared (7*S*)-*cis*,*cis*-nepetalactone (<u>1b</u>).[14] Nepetalactone freshly distilled from *N. mussini* oil had a specific rotation of +80.7°. The specific rotation reported by Trave, *et al.* for synthetic (7*S*)-*cis*,*cis*-nepetalactone is +82.4°.

CHAPTER IV

COMPARISON OF NUCLEAR MAGNETIC RESONANCE AND CIRCULAR DICHROISM OF THE *CIS,CIS*- AND *CIS,TRANS*-NEPETOLACTONES

The circular dichroism of the nepetolactones 19a, 19b, 19c, and 19d has been measured by Klyne and Scopes, who have correlated the observed Cotton effects for these compounds with predictions of their absolute configurations at C-3. The nepetolactones should be acceptable for application of the lactone sector rule, because the *cis*-fusion of two five-membered rings imparts rigidity to the lactone ring.[26a,26b]

In applying the lactone sector rule the lactone ring is considered to be planar, and the molecule is viewed in the plane of the lactone group along the bisectrix of the O-C-O angle, that is, the line of the carboxyl carbon and its attached carbon atom.



The space around the lactone group is divided into sectors by planes meeting at the carboxyl carbon, and the contribution to the Cotton effect of lactone ring substituents lying in these sectors is as shown in Figure 42.

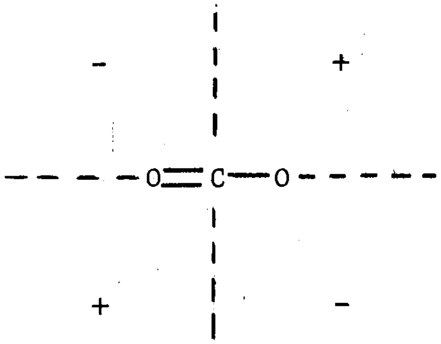


Figure 42. Lactone Sector Rule: Viewing Molecule Along the Bisectrix of the O-C-O Angle

The lactones must also be considered in a second projection in order to predict the sign of the Cotton effect. In this projection, the molecule is viewed from above, as shown in Figure 43. Both carbon-oxygen bonds are considered to have some double bond character, and the molecule is treated in terms of the ketone octant rule.[26b] Each carbon-oxygen bond is considered as a double bond in turn, and the two diagrams then are superimposed to give the third diagram. Thus, the signs of contributions of atoms in sectors A, C, D, and F cancel, in the back upper right sector E a positive contribution is reinforced, and in the back upper left sector B a negative contribution is reinforced.

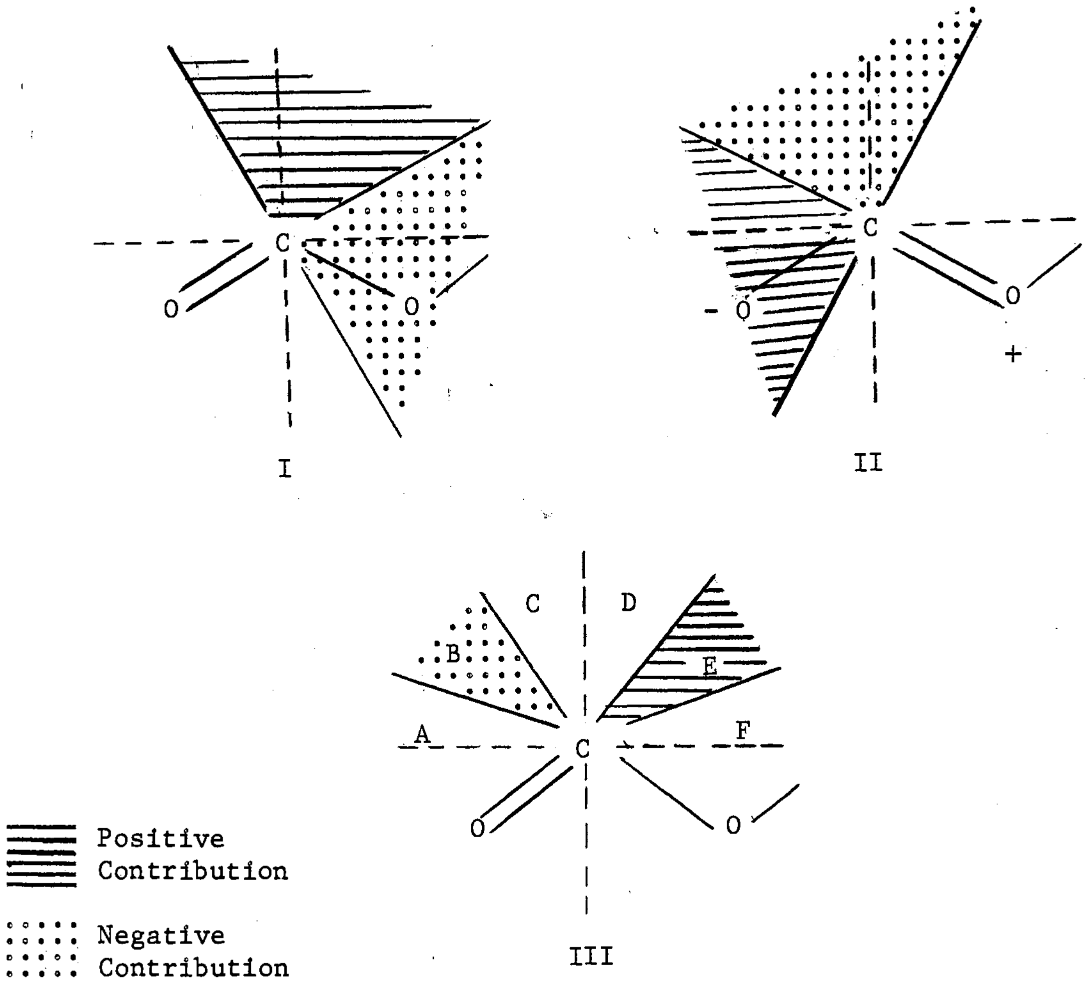


Figure 43. Lactone Sector Rule: Viewing Molecule From Above

The lactone sector rule has been used to predict the sign of the Cotton effects of the nepetolactones 19a, 19b, 19c, and 19d.[25] The projections of these molecules are shown in Figures 44 and 45.

For the *cis,trans*-nepetolactones (19a and 19b), shown in Figure 44, the only difference is in the stereochemistry at C-3. For structure A the C-7 methyl group lies in a positive contributing region. In structure B the C-7 methyl lies in a negative contributing region. Thus for these

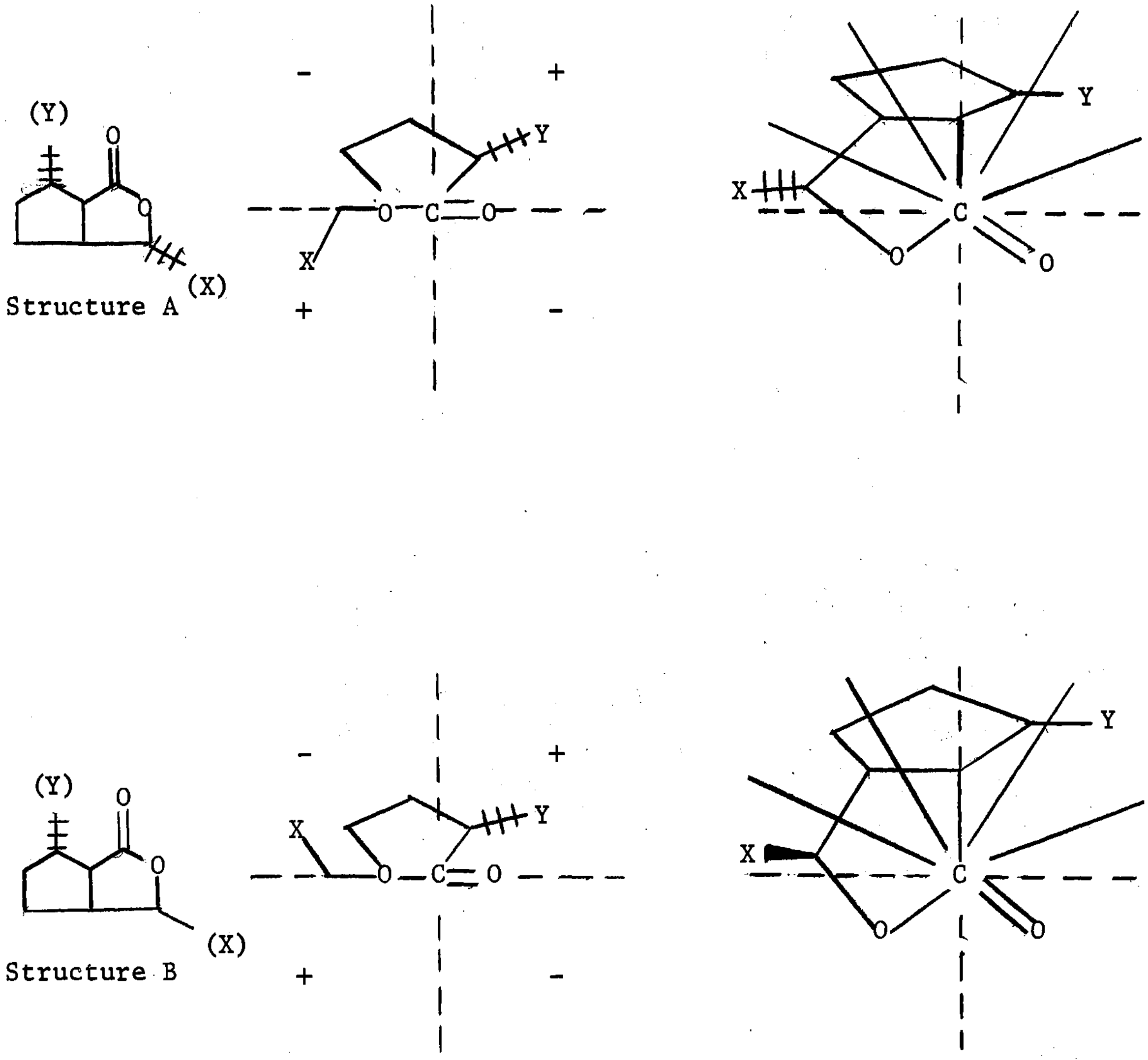


Figure 44. Lactone Sector Rule Projections for the (6*S*)-*cis,trans*-Nepetolactones

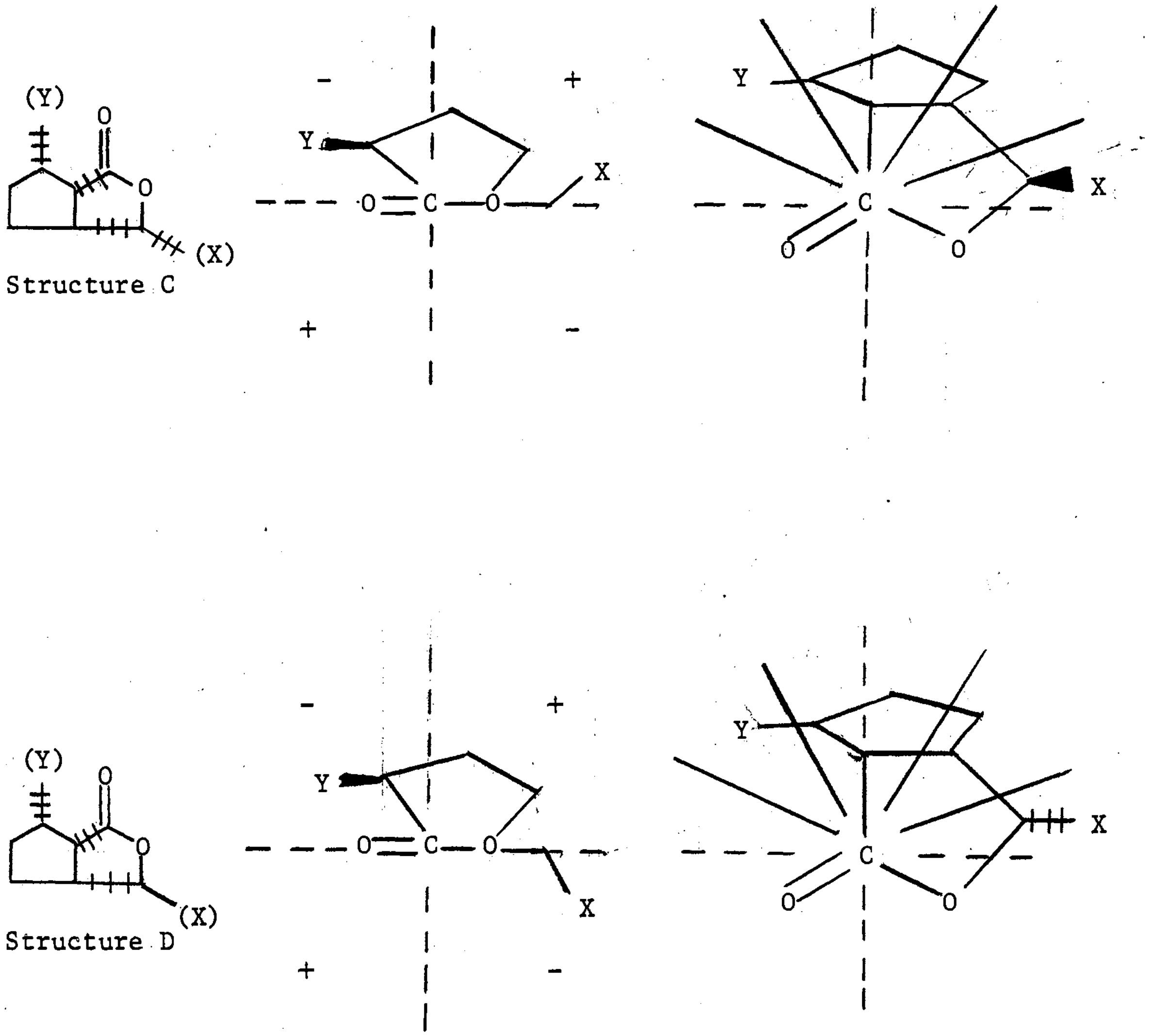
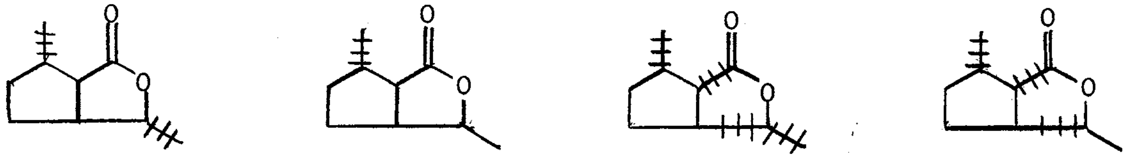


Figure 45. Lactone Sector Rule Projections for the (6*S*)-*cis*,*cis*-Nepetolactones

two structures, structure A should exhibit the more positive Cotton effect.

Likewise, for the *cis,cis*-nepetolactones (<u>19c</u> and <u>19d</u>), the C-7 methyl group lies in a positive contributing region in structure C and in a negative contributing region in structure D. Therefore, lactone C would be expected to exhibit the more positive Cotton effect for these two compounds.

The experimental circular dichroism data are shown in Figure 46, which also shows the structures predicted for the four nepetolactones from the lactone sector rule.



Structure A
$\Delta\varepsilon = -0.57$

Structure B
$\Delta\varepsilon = -1.66$

Structure C
$\Delta\varepsilon = +0.85$

Structure D
$\Delta\varepsilon = -0.24$

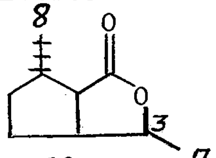
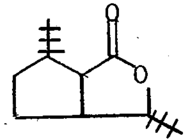
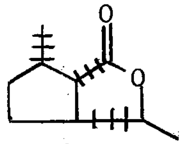
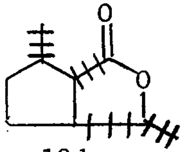
Figure 46. Absolute Configurations of the (6*S*)-Nepetolactones Predicted from the Lactone Sector Rule

The nmr chemical shifts for the four nepetolactones are given in Table II, along with the structure assignments given the four lactones on the basis of their nmr spectra (Figures 17, 18, 19, and 20 in Chapter 2). The circular dichroism data are also listed. The assignments made on the basis of the nmr data of lactones 19a, 19b, 19c, and 19d are opposite to those predicted from the lactone sector rule (Figure 46). The stereochemical assignments for the nepetolactones were based on the following reasoning.[24] For the lactone pair 19a and 19b, the C-3 proton in 19b is inside the envelope of the fused five-membered rings and is therefore shielded and absorbs at a higher field (4.24 ppm) than the C-3 proton in 19a (4.64 ppm). Correspondingly, for the lactone pair 19c and 19d, the C-3 proton in 19c is shielded, and absorbs at a higher field (4.08 ppm) than the C-3 proton in nepetolactone 19d (4.68 ppm).

McGurk arrived at the same assignments by comparison of the mass spectra of the nepetolactones 19a, 19b, 19c, and 19d. The mass spectra of 19b and 19c, which have the more exposed C-7 methyl groups, show a much larger M-15 peak than do the spectra of 19a and 19d (19b:19a; 9.4:1.0 and 19c:19d; 4.2:1.0).

TABLE II

INSTRUMENTAL DATA AND STEREOCHEMICAL ASSIGNMENTS AT C-3 OF THE (6*S*)-NEPETOLACTONES

Nepetolactone	Proton Magnetic Resonance (ppm)			Circular Dichroism	
	C-8 Methyl	C-7 Methyl	C-3 Proton	Δε	λ (nm)
 19a	1.09	1.28	4.64	-0.57	215
 19b	1.06	1.27	4.24	-1.66	213
 19c	1.04	1.27	4.08	+0.85	212
 19d	1.18	1.32	4.68	-0.24	227

CHAPTER V

EXPERIMENTAL[26a,27]

Cis,cis-Nepetalactone (1b).—*Nepeta mussini* plants (674 g) were harvested by severing the plants at ground level and immediately shredding them in a Waring Blendor with 1 l. of water. The plant material was then steam distilled, and the steam distillate was saturated with NaCl and extracted with ether. Concentration of the ether extract afforded 4 g (0.6% yield) of *N. mussini* oil, which was shown by gas chromatography to be approximately 95% *cis,cis*-nepetalactone (1b). A similar procedure using 780 g of *N. mussini* plants, harvested as stated, but excluding the blending step, gave 3 g (0.4% yield) of oil. Pure 1b was obtained by column chromatography on silicic acid using a mixture of petroleum ether (bp 60-68°) and ether as eluant: bp 75° (0.1 mm); $[\alpha]_D^{23}$ +80.7° ($CHCl_3$ 0.0382 g/ml); ir (CCl_4) 1730 (C=O) cm^{-1}; nmr (CCl_4) ppm 0.97 (d, 3, C-9 CH_3), 1.60 (s, 3, C-8 CH_3) and 6.12 (s, 1, C-3 H); mass spectrum (70 eV) *m/e* (rel intensity) 167 (8), 166 (55), 124 (98), 96 (60), 82 (100), 70 (100), 68 (64), 56 (57), 54 (50), 44 (40); circular dichroism (methanol) $\Delta\varepsilon$ +3.9 m (λ 233 nm).

Cis,cis-Nepetolactones (19c and 19d).—A solution of 1.5 g (9 mmol) of 1b in 75 ml of methanol and 1.5 ml of pyridine was cooled to -70°. Ozone was bubbled through the mixture for 1 hr. The excess ozone was flushed from the reaction mixture (as evidenced by disappearance of the blue color), and the mixture was transferred to an ice bath. Aliquots of 1.5 g $NaBH_4$ in 15 ml of water were added to the stirred mixture immediately and at intervals of 0.5, 1, 2, and 4 hr. The mixture was acidified with 10% HCl and extracted with ether. The ether extract was washed with $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated to yield 500 mg (36% yield) of a mixture of 19c and 19d. The lactones 19c and 19d were separated by chromatography on silicic acid using a mixture of petroleum ether (bp 60-68°) and ether eluants. The lactone 19c had bp 60-65° (0.05 mm); nmr (neat) ppm 1.04 (d, 3, C-8 CH_3), 1.27 (d, 3, C-7 CH_3) and 4.08 (m, 1, C-3 H); circular dichroism (methanol) $\Delta\varepsilon$ +0.85 m (λ 212 nm).

The lactone 19d had bp 60-65° (0.05 mm); nmr (neat) ppm 1.18 (d, 3, C-8 CH_3), 1.32 (d, 3, C-7 CH_3) and 4.68 (m, 1, C-3 H); circular dichroism (methanol) $\Delta\varepsilon$ -0.24 m (λ 227 nm).

Reaction of *cis,cis*-Nepetolactones (19c and 19d) with Phenylmagnesium Bromide.—A 1.20 g (8 mmol) sample of a mixture of 68% 19c and 32% 19d in 10 ml of ether was added dropwise to 45 mmol of phenylmagnesium bromide in 20 ml of ether. The mixture was heated at reflux for 3 hr. Excess phenylmagnesium bromide was destroyed by the addition of 10% HCl to the cooled reaction mixture. The ether and aqueous layers were separated, and the ether fraction was concentrated and steam distilled to remove biphenyl. Extraction of the non-steam volatile material gave 1.75 g (70% yield) of a mixture of 83% 20c and 17% 20d, from which 20c was crystallized: mp 133-133.5°; ir (CCl_4) 3220 (OH) cm^{-1}; nmr ($CDCl_3$) ppm 1.00-1.16 (overlapping m, 6, CH_3 and CH_3), 3.19 (t, 1, $CH_3C\underline{H}OH$), 3.64-4.10 (overlapping m, 2, OH and OH) and 6.96-7.72 (m, 10, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 311 (5), 310 (15), 292 (10), 215 (31), 183 (100), 154 (26), 105 (79), 95 (21), 81 (31), 77 (26), 45 (40).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.48, H, 8.65.

A similar experiment using 25 mg of a mixture of 62% 19c and 38% 19d with 5 ml 3M phenylmagnesium bromide in ether was carried out as stated. The excess Grignard reagent was destroyed with 10% HCl, the ether and aqueous layers were separated, and a glc of the ether fraction showed 62% 20c and 38% 20d had been formed. The reaction was also conducted with 140 mg of pure 19c in 10 ml ether with 5 ml 3M phenylmagnesium bromide in the manner stated. The reaction time was 1.5 hr. Steam distillation of the product, followed by ether extraction of the non-steam volatile material gave a 40% yield of diol 20c, mp 133°.

Reaction of *cis,trans*-Nepetolactone 19a with Phenylmagnesium Bromide.—A 10 mg sample of *cis,trans*-nepetolactone 19a in 10 ml ether was added dropwise to 7 ml of 3M phenylmagnesium bromide in ether. An additional 10 ml of ether was added, and the mixture was heated at the reflux temperature for 1 hr. The excess Grignard reagent was destroyed with 10% HCl, and the ether and aqueous layers were separated. The ether fraction was concentrated and steam distilled to remove biphenyl. Extraction of the non-steam volatile material afforded 16 mg (80% yield) of diol 20a, mp 155-157°.

Reaction of Diol 20c with *p*-Toluenesulfonic Acid.—A solution of 110 mg of the diol 20c in 50 ml of benzene containing 40 mg of *p*-toluenesulfonic acid was heated at the reflux temperature for 1.5 hr. When cool, the reaction mixture was washed with $NaHCO_3$ solution and water. After drying (Na_2SO_4) and concentrating the benzene solution, 104 mg (100% yield) of the ether 21c was obtained: mp 116-118°; ir (CCl_4) 2850, 1520, 1235, 1195, 990 cm^{-1}; nmr (CCl_4) ppm 2.1-2.5 (m, 2), 3.5-4.1

(overlapping m, 2), 7.1 (m, 6, ArH), 7.5 (m, 4, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 293 (5), 292 (69), 215 (91), 183 (55), 167 (57), 105 (84), 81 (100), 77 (92), 69 (72), 43 (55).

Anal. Calcd for $C_{21}H_{24}O$: C, 86.25; H, 8.27. Found: C, 86.01; H, 8.49.

Conversion of Diol 20c to Lactone 22b.—A solution of 500 mg of diol 20c in 50 ml of glacial acetic acid containing 500 mg of CrO_3 was heated for 4 hr at 50-60°. The acetic acid was removed by rotary evaporation, and 50 ml of water was added to the residue, which was then extracted with ether. The ether extract was concentrated to give 220 mg of a mixture of benzophenone and lactone 22b. The mixture was steam distilled, and the non-steam volatile material was extracted with ether, from which 100 mg (21% yield) of lactone 22b was obtained: mp 202-203°, sublimed at 140° (1.4 mm); ir ($CHCl_3$) 1748 cm^{-1} (C=O); nmr ($CDCl_3$) ppm 0.42 (d, 3, CH_3) and 7.1-7.7 (overlapping m, 10, ArH); mass spectrum (70 eV) *m/e* (rel intensity) 293 (9), 292 (38), 215 (29), 184 (45), 183 (100), 165 (15), 105 (28), 77 (64), 67 (22), 51 (20).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 81.97; H, 6.92.

The reaction was repeated with 10 mg of a mixture of 62% 20c and 38% 20d with 10 mg CrO_3 in 10 ml glacial acetic acid. The reaction mixture was heated at 50-60° for 1 hr, followed by removal of the acetic acid by rotary evaporation, and extraction of the residue with ether. Gas chromatography of the ether extract showed a new peak corresponding in retention time with 22b.

Conversion of Diol 20a to Lactone 22a.—A solution of 100 mg of diol 20a in 50 ml of glacial acetic acid with 100 mg of CrO_3 was heated at 50-60° for 8 hours. The acetic acid was removed by rotary evaporation. The residue was taken up in 25 ml of water and extracted with ether. The ether extract was concentrated, and the residue was steam distilled. Ether extraction of the non-steam volatile material afforded 50 mg (53% yield) of lactone 22a.

Conversion of Ether 21c to Lactone 22b.—A solution of 26 mg of ether 21c in 10 ml of glacial acetic acid containing 50 mg of CrO_3 was heated at 50-60° for 1.5 hr. After removal of the acetic acid by rotary evaporation, 10 ml of water was added to the residue, which was then extracted with ether. The ether extract was concentrated and steam distilled. Ether extraction of the non-steam volatile material afforded 24 mg (92% yield) of lactone 22b, mp 199-202°. A gas chromatogram of this lactone mixed with 22b obtained by direct oxidation of diol 20c with CrO_3 and acetic acid showed only one peak. No depression in melting point was observed when the two lactone samples were mixed.

Ozonolysis of *cis,cis*-Nepetalactone (1b) with Dimethyl Sulfide Ozonide Decomposition.—A solution of 0.4 g of freshly distilled 1b in 75 ml methanol containing 1 ml pyridine was cooled to -70°. Ozone was bubbled through the mixture for 1 hr. Excess ozone was flushed from the reaction mixture, and the solution was transferred to a chilled (0°) flask. A 5 ml portion of dimethyl sulfide was added, and the mixture was stirred for 1 hr while it warmed to room temperature. The solvent was removed by rotary evaporation, and the residue was dissolved in $NaHCO_3$ solution and was ether extracted. The $NaHCO_3$ solution was acidified with 10% HCl and ether extracted to give, on concentration, 0.33 g (76% yield) of nepetonic acid 3b. The 2,4-DNP of the methyl ester of 3b had mp 122-123.5°. A solution of 0.1 g of 3b in 10 ml of 10% NaOH was stirred under N_2 for 2 hr. Acidification of the basic solution, followed by ether extraction gave 0.1 g of 3a. The 2,4-DNP of the methyl ester of 3a had mp 73-74°.

Conversion of Nepetonic Acid 3a to Nepetic Acid 4c.—A solution of 0.28 g of nepetonic acid 3a was dissolved in 10 ml of 10% NaOH. A 3 ml portion of KI-I_2 reagent (KI:I_2; 2:1) was added. Iodoform immediately precipitated. The solution was warmed to 60° for 4 hr. After cooling the solution, the CHI_3 was filtered out and 20 ml of a 10% Na_2SO_3 solution was added, and the solution was acidified with 10% HCl. The solution was repeatedly extracted with ether. After concentration of the ether solution 50 mg of nepetic acid 4c was obtained, mp 100-105° (lit. 115°). The melting point of an equal mixture of this nepetic acid with (+)-*t*-(3*S*)-methyl-*r*-1,*t*-2-cyclopentanedicarboxylic acid (4c) (mp 109-112°, lit. 115°), crystallized together, showed no depression. A melting point of an equal mixture of the nepetic acid obtained from degradation of 1b with (-)-*t*-(3*R*)-methyl-*r*-1,*t*-2-cyclopentanedicarboxylic acid (4g) (mp 105-110°, lit. 115°), crystallized together, had a range of 125-130°.

Conversion of Nepetonic Acid 3b to Nepetic Acid 4c.—A solution of 10 ml of sodium hypobromite (prepared by adding 1 ml of bromine to 10 ml of water and 4 g of NaOH at -5°) was added to a solution of 50 mg of nepetonic acid 3b in 5 ml of ether at 0°. The solution was kept at 0° for 0.5 hr, followed by removal of excess hypobromite with 5 ml of 10% Na_2SO_3 solution. The mixture was then acidified with 10% HCl and extracted with ether. Diazomethane was added to the ether solution, and a glc of the ether solution showed the major product (approx. 90%) to be the methyl ester of nepetic acid 4c. The reaction was also done using NaOH and KI-I_2 reagent, as described above, followed by esterification with diazomethane of the product, and again glc showed the major product to be the methyl ester of nepetic acid <u>4c</u>.

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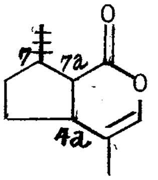
(c) To eliminate ambiguity in naming nepetalactone isomers, the stereochemistry of the cyclopentane ring substituents is referenced to the orientation of the substituent at C-4a. The C-7a group is considered first. Thus in *cis,trans*-nepetalactone (1a), the C-7a substituent is *cis* to the C-4a substituent, and the C-7 methyl is *trans* to the C-4a substituent.



A similar system is used in assigning the stereochemistry of the nepetalinic acids, nepetolactones, nepetic acids, and derivatives of the nepetolactones.

(d) In naming the nepetic acids, the symbol "*r*" designates the reference atom.

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27. (a) The nmr spectra were obtained with a Varian XL100 Spectrometer, using tetramethylsilane as a standard (ppm = 0).

(b) The ir spectra were obtained with a Beckman IR-5A instrument.

(c) The mass spectra were obtained with a CIC Model 21-110B mass spectrometer.

(d) Glc analyses were obtained with a Hewlett-Packard Model 5750 gas chromatograph fitted with a hydrogen flame detector using helium as the carrier gas and using a 0.25 in. x 11.5 ft 6% UC W-98 (silicone rubber) column. The nepetalactones **1a** and **1b**, nepetolactones **19a**, **19b**, **19c**, and **19d**, the methyl esters of the nepetonic acids **3c** and **3d**, and the dimethyl esters of the nepetic acids **4c** and **4g** were chromatographed at 150° or 160°. The diols **20a**, **20b**, **20c**, and **20d**, the esters **21a**, **21b**, **21c**, and **21d**, and the lactones **22a** and **22b** were chromatographed at 230° or 250°.

(e) The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

(f) Ozone was generated with a Wellsbach T-23 ozonator.

VITA

Rebecca Lynn Irvin

Candidate for the Degree of

Doctor of Philosophy

Thesis: STEREOCHEMISTRY AND STRUCTURE PROOF OF (7*S*)-*CIS*,*CIS*-NEPETALACTONE AND RELATED COMPOUNDS

Major Field: Chemistry

Biographical:

Personal Data: Born in Ft. Baker, California, December 15, 1947, the daughter of John W. and Edna G. Irvin.

Education: Graduated from Hinton High School, Hinton, Oklahoma, in 1966; received the Bachelor of Science degree from Southwestern State College, Weatherford, Oklahoma, in June, 1970, with a major in Chemistry and a minor in Mathematics; completed requirements for the Doctor of Philosophy degree at Oklahoma State University in July, 1974.

Professional Experience: Teaching assistant and research assistant at Oklahoma State University from 1970 to 1974; Gulf Oil Corporation Fellow, summer, 1973; Phillips Petroleum Company Fellow, summer, 1974; American Petroleum Institute Research Assistant, 1971 to 1974.

Professional and Honorary Societies: Who's Who in American Colleges and Universities, 1970; American Chemical Society.