SYNTHESIS AND NUCLEAR MAGNETIC RESONANCE SPECTROSCOPIC INVESTIGATION OF CROWDED ANISOLES

By

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SYNTHESIS AND NUCLEAR MAGNETIC RESONANCE
SPECTROSCOPIC INVESTIGATION OF
CROWDED ANISOLES

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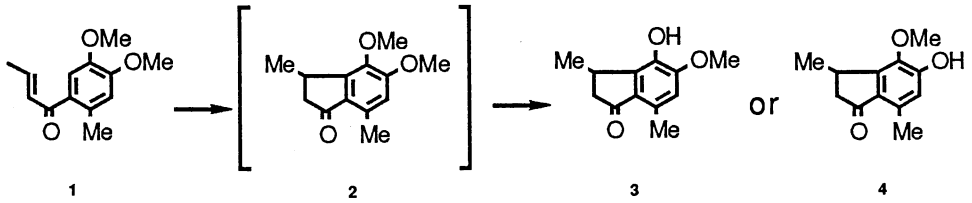
SYMBOLS AND ABBREVIATIONS

°C	degree Centigrade
cm	centimeter
d	doublet
FT	Fourier transform
g	gram
GC	gas chromatography
h	hour
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infrared
L	liter
LDA	lithium diisopropylamide
M	molar
m	multiplet
mCPBA	*m*-chloroperoxybenzoic acid
mL	milliliter
mm	millimeter
mmol	millimole
MMPP	magnesium monoperoxyphthalate
mol	mole
mp	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
ppm	parts per million
psi	pounds per square inch
q	quartet
RT	room temperature
s	singlet
t	triplet
THF	tetrahydrofuran
TMS	tetramethylsilane
W	Watt

CHAPTER I

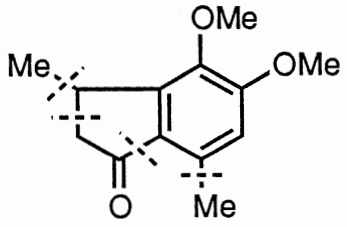
INTRODUCTION AND HISTORICAL

Interest in anisoles, aromatic compounds substituted with methoxy groups, has been stimulated by their occurrence in many natural products, notably musks,[1] alkaloids,[2] aromatic ethers occurring in plant extracts, and phenols (potential methoxy groups) found in these extracts. The latter is a broad topic having several journals devoted to its study.[3] Aromatic compounds substituted with crowded methoxy groups (anisoles having 2,6-disubstitution) show unusual chemical properties,[4,5,6] spectroscopic properties[7,8], and computational results.[7,9,10,11] Of historical importance to the current study,is the early observation that the regiospecific[12] demethylation of the more crowded aromatic methoxy group in 3-alkyl-1,2-dimethoxybenzenes with Lewis acids such as boron tribromide and iodotrimethylsilane.[6] This initially became apparent in a cyclization-demethylation reaction shown below in which 4',5'-dimethoxy-2-methylcrotonophenone (**1**) was found to cyclize and to demethylate a specific methoxy group.[4,5]



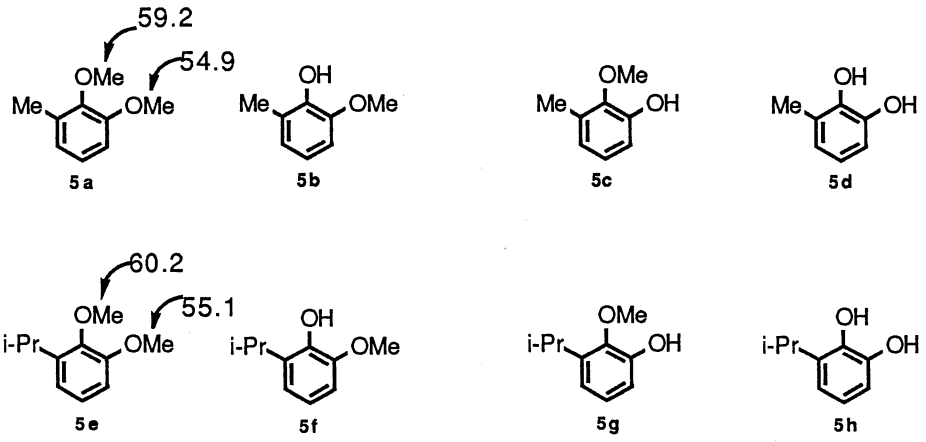
1 2 3 4

At the time it was unknown whether the cyclization-demethylation product was 3,7-dimethyl-4-hydroxy-5-methoxy-1-indanone (**3**) or 3,7-dimethyl-5-hydroxy-4-methoxy-1-indanone (**4**) and whether demethylation preceded cyclization or cyclization preceded demethylation. The latter question was resolved by subsequent preparation of 3,7-dimethyl-4,5-dimethoxy-1-indanone (**2**) and showing that it specifically demethylated to the same product obtained through acid-catalyzed cyclization-demethylation. Subsequently **2** was found as a minor reaction product of the cyclization suggesting that, under the acidic cyclization conditions, **2** is cleaved too rapidly to survive as a major product. Significantly **2** showed a pronounced downfield ^{13}C NMR chemical shift of the signal from one methoxy methyl group and it was this methoxy methyl group which failed to survive the cyclization-demethylation.[5] To clarify this ^{13}C NMR observation, a series of substituted anisoles were selected as model structures simulating a portion of **2** as shown below.[6,7]



2

These structures with the pertinent ^{13}C NMR signals are listed below.[7]



This study showed that regiospecific cleavage of 2,3-dimethoxytoluene (**5a**) to 2-methoxy-6-methylphenol (**5b**) took place with no detectable formation of 2-methoxy-3-methylphenol (**5c**). In the presence of excess reagent , 3-methylcatechol (**5d**) resulted. The monophenols **5b** and **5c** are readily separated and distinguished by their solubility in aqueous sodium hydroxide. The latter is soluble in 2% sodium hydroxide solution whereas the former requires a 10% sodium hydroxide solution to effect solubility. This work is summarized in Table I which gives the product distribution obtained on treatment of **5a** and **5e** with iodotrimethylsilane and boron tribromide. Treatment of 3-alkyl-1,2-dimethoxybenzenes (**5a-5e**) with iodotrimethylsilane resulted in the regiospecific demethylation of the crowded methoxy group to give methoxyphenols (**5b, 5f**) in excellent yield (94-96%); starting material (**5a, 5e**) and completely demethylated products (**5d, 5h**) were found in trace amounts.[6] Boron tribromide was found to be less selective resulting in a larger recovery of starting material (**5a, 5e**) and fully demethylated products (**5d, 5h**). It is to be emphasized that the monodemethylation product,

corresponding to the cleavage of the least hindered methoxy group (**5c, 5g**), was not observed.

TABLE I

PRODUCT DISTRIBUTION IN THE DEMETHYLATION OF CATECHOL METHYL ETHERS

Starting Material	Equiv. Me_3SiI	Equiv. BBr_3	....Product Ratios[a]....			
			5a	**5b**	**5c**	**5d**
5a	1.1		6	94	0	0
5a		1.1	40	43	0	18
5a	3.3		0	30	0	70
5a		3.3	0	0	0	100
			5e	**5f**	**5g**	**5h**
5e	1.1		0	96	0	4
5e		1.1	30	24	0	46
5e	3.3		0	47	0	53
5e		3.3	0	0	0	100

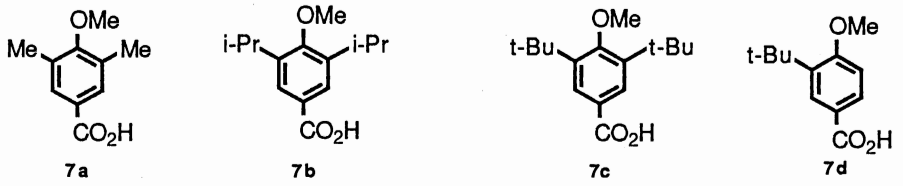
[a]Determined by HPLC.

The observed pattern of regioselective cleavage of the most hindered methoxy group is not intuitively expected on initial consideration of steric interactions and further investigation into this problem was merited. The

Halgren-Lipscomb partial retention of diatomic differential overlap (PRDDO) program[7] was used to determine the atomic charges for various nuclei at different dihedral angles and the total energy of each molecule. The results of these studies indicated that the crowded methoxy substituent is forcibly rotated out of the plane of the benzene ring. As a result, the oxygen of the methoxy group acquires a higher electron density due to reduced electron donation to the aromatic ring by the methoxy oxygen.[13] The rotation of the methoxy group out of the plane of the aromatic ring causes the C_{ar}-O bond to lose it's resonance stabilized double bond character.[14]

This observation was confirmed for analogous molecules using CNDO/2 computations.[15] Consideration of the calculated rotational energy barriers indicated that the methoxy group of 2,6-disubstituted anisoles was essentially blocked from lying in the plane of the benzene ring as shown for **6a**, **6b**, and **6c** in Figure 1.

This result has been confirmed by X-ray crystallographic studies of dialkylanisic acids[9] (compounds **7a-7c**).



In anisoles without two ortho substituents, the methoxy substituent was found to lie in the plane of the aromatic ring[7,9] (compounds **6a** and **6b**[7] and **7d**[9]). Coplanarity of the methoxy group and the aromatic ring for anisoles without two ortho substituents, as in the case of **7d** and earlier examples,[7] is the most favorable arrangement for orbital overlap between oxygen's *p*-type orbitals and the π system of the aromatic ring. This result has also been

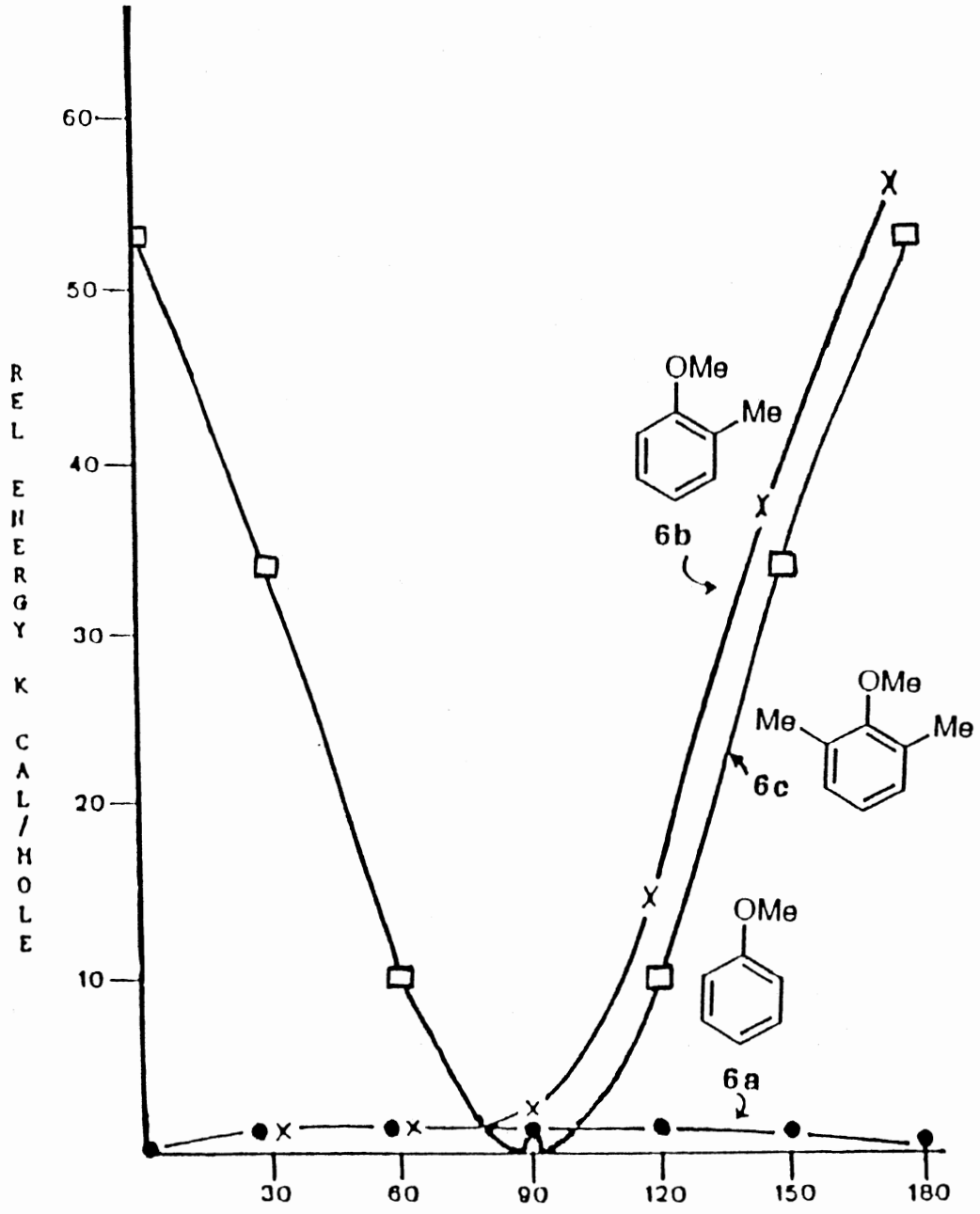


Figure 1. Rotational Energy Barrier for **6a**, **6b**, and **6c**.

supported by NMR T_1 measurements, since the major mechanism of relaxation for carbon bound to protons is through the ^{13}C-H dipole-dipole mechanism. The T_1 values for crowded methoxy groups were $\geq$ 6.6 s in every case whereas those methoxy groups which are not crowded showed T_1 values of $\leq$ 5.1 s in every case.[7]

The suggestion, from these calculations, that the oxygen of a crowded methoxy group has an excess of electron density has been studied through use of natural abundance ^{17}O NMR[8] and is being continued in this laboratory.[8,16] The NMR signal of an oxygen atom with excessive electron density (oxygen of a crowded methoxy group), should show an upfield shift relative to the NMR signal of an oxygen atom having a normal electron charge. This expected ^{17}O NMR shift for the oxygen signal of a crowded methoxy group has been confirmed. It has also been shown that an uncrowded methoxy group fails to show this upfield chemical shift in the ^{17}O NMR signal.[8]

The reason for regiospecific demethylation of the crowded anisoles discussed earlier (pp. 3-4) now becomes clear. The Lewis acids, as electrophilic reagents, interact with the oxygen bearing the higher electron density and, thus, are preferentially complexed. In addition, the orbitals of the unhindered methoxy oxygen are sterically "shielded" by the adjacent methoxy group. Since the nonbonding oxygen orbitals of hindered methoxy groups project away from the aromatic ring, they preferentially are available for attack.[7] These results also explain the significant downfield chemical shift of the methyl signal observed in the ^{13}C NMR spectra and the upfield ^{17}O NMR chemical shift of the methoxy oxygen signal of sterically crowded methoxy groups.[8]

CHAPTER II

RESULTS AND DISCUSSION

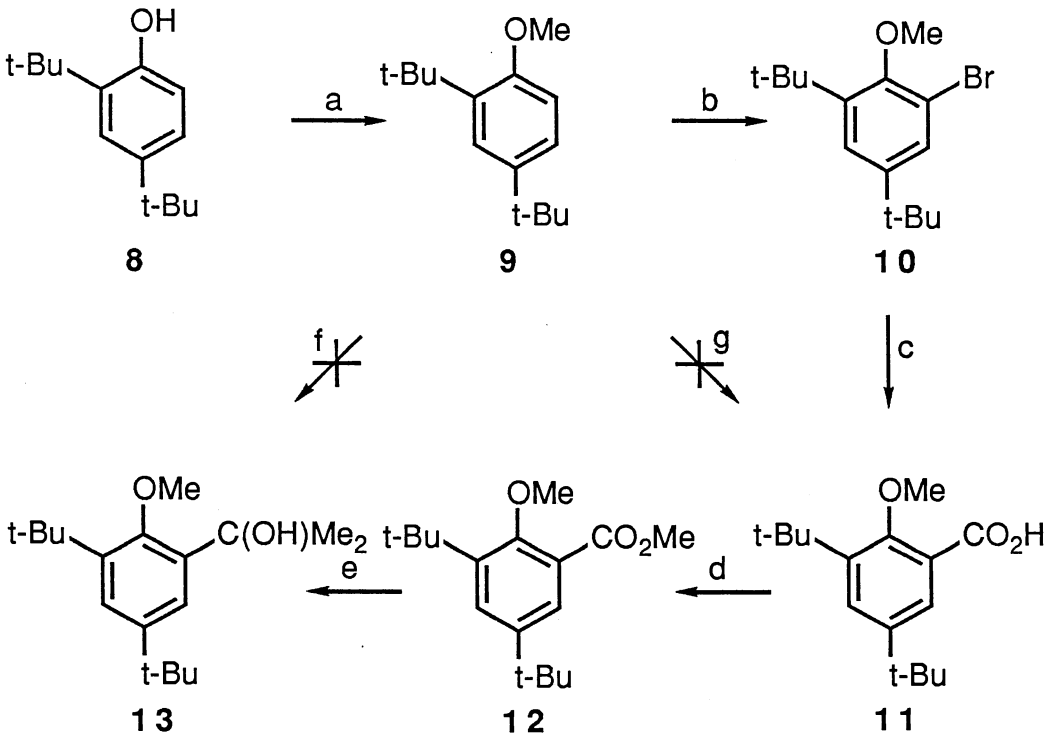
Synthesis Problems and Studies

The effects of steric hindrance on the chemical and (^{17}O and ^{13}C NMR) spectral properties of crowded anisoles where one of the crowding substituents is a methoxy group has been documented.[7,8,9,13]

As a follow up and extension of this earlier work, a series of substituent groups having varied steric requirements was needed to study their effect on the hindered methoxy group. As different groups were to be placed ortho to the methoxy group, this was to be followed by ^{13}C NMR studies to learn which changes in steric bulk would influence the downfield shift of ^{13}C NMR methoxy signals.

For this study, a series of related compounds was chosen in which one of the substituents ortho to the crowded methoxy group would be a tertiary butyl group. The *t*-butyl group was selected due to its availability and because, as an alkyl group, it provided the maximum available steric bulk. The remaining ortho position, to the methoxy group, would be a series of substituents varying in steric bulk from hydrogen to a fully substituted carbon.

The reaction sequence shown in Figures 2 and 3 was chosen because the starting material was available and each of the reaction intermediates would also be of interest in the study.

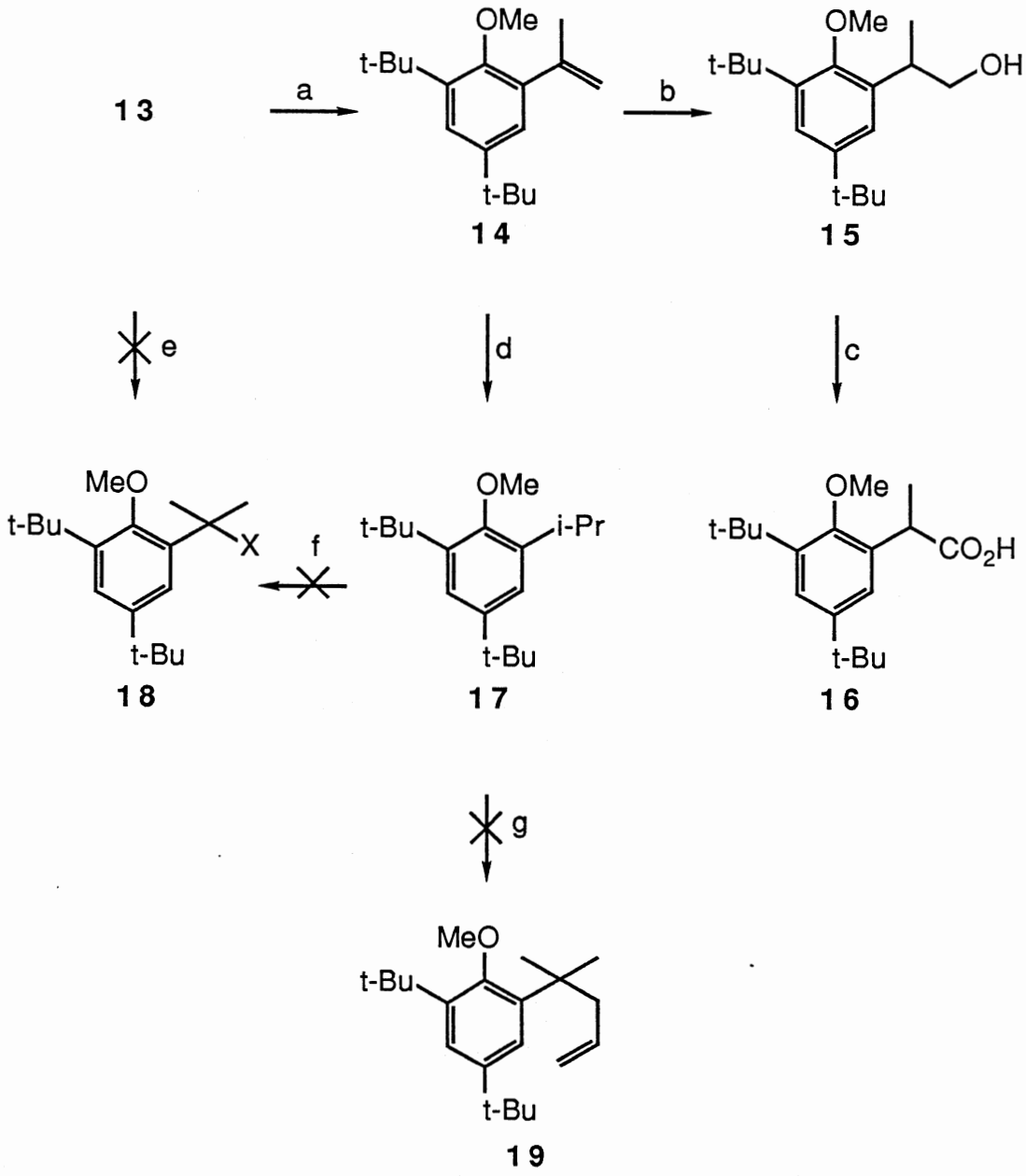


[a](CH3O)2SO2, NaOH, CH2Cl2. [b]Br2, CCl4, or Br2, KBr, H2O. [c]Mg, ether; CO2. [d]CH2N2, ether. [e]CH3MgBr, ether. [f]CH3(CH2)3Li, CH3COCH3; [g]CH3(CH2)3Li, CO2.

Figure 2. Synthesis of 2-(3,5-Di-t-butyl-2-methoxy)phenyl-2-propanol (**13**).

The methylation of 2,4-di-*t*-butylphenol (**8**) proceeded smoothly at room temperature in excellent yields using Vibromixer agitation, of a mixture of **8**, sodium hydroxide, dimethyl sulfate, tetra-*n*-butylammonium bromide, water, and dichloromethane. This procedure was a modification of an earlier procedure[17].

Two methods were used for the bromination of 2,4-di-*t*-butylanisole (**9**). For small-medium scale reactions (≤100 g),.a buffered aqueous bromination was used (anisole:Br_2:KBr ratio was 1:2:4). This procedure has the



[a]$CuSO_4$, distill or toluene, I_2, reflux. [b]BH_3-THF, THF, NaOH, H_2O_2. [c]CrO_3, H_2SO_4, CH_3COCH_3. [d]Pd/C, AcOH, H_2. [e]HCl or $HBr_{(g)}$. [f]NBS, CCl_4, hυ or $BrCCl_3$, MMPP or hυ, Br_2. [g]$(CH_3)_3CLi$, $CH_2=CHCH_2Br$.

Figure 3. Synthesis of **17** and Attempted Synthesis of **18** and **19.**

advantage that , on a small scale, the reaction mixture is easily purified by extraction with petroleum ether, filtering through acidic and basic alumina, and on distillation (Kugelrohr) a white crystalline solid is obtained. This procedure also tends to give 7-10% higher yields. To increase the scale beyond 100 g, copious amounts of water are needed and the reaction mixtures become difficult to handle. A more convenient procedure for larger-scale reactions consistes of bromination in carbon tetrachloride which decreases the volumes of solvents and minimized the effort required in work up. This procedure involves the production of hydrogen bromide as a side product with some cleavage of the t-butyl group at the C-6 position as indicated by loss of the crowded methoxy group signal in the ^{13}C NMR spectrum of the product and the splitting pattern of aromatic protons in the ^{1}H NMR spectrum.

The conversion of 2-bromo-4,6-di-*t*-butylanisole (**10**) to the carboxylic acid **11** was accomplished by first converting **10** to the Grignard reagent, then by treating with dry carbon dioxide. The resulting acid **11** was soluble in ether but attempts to remove any neutral material by extracting **11** from the ether solution with alkali failed because of the formation of an emulsion and the extreme insolubility of the sodium salt. The sodium salt could not be easily isolated by either extraction with ether or through filtration since it clogged the filtering medium (Dicalite and paper). Later experiments revealed that the ammonium salt of **11** is appreciably soluble in water allowing **11** to easily be purified by extraction from ether with ammonium hydroxide, acidification, and recrystallization from either ethanol (powder or rosettes), or diethyl ether (plates or broad needles).

Attempts to prepare methyl 2-methoxy-3,5-di-*t*-butylbenzoate (**12**) from **11** by esterification with methanol and acid (Amberlyst-15) was not satisfactory and gave mostly starting material. Stronger acids were avoided

because of concern about the loss of t-butyl groups. Satisfactory esterification was accomplished by adding a solution of diazomethane in diethyl ether until the yellow color of diazomethane persisted and the evolution of nitrogen was no longer evident.

The reaction of methylmagnesium bromide with **12** to form 2-(2-methoxy-3,5-di-*t*-butylphenyl)-2-propanol (**13**) proceeded smoothly and in 90% yield. To prevent the acid-catalyzed dehydration of the tertiary alcohol **13**, this reaction mixture was quenched with a saturated solution of ammonium chloride rather than 10% hydrochloric acid.

For the dehydration of **13**, two methods were used depending on the amount of material needed. For samples weighing less than 10 g, dehydration was most effectively done by distilling a mixture of **13** from anhydrous copper sulfate using a Kugelrohr apparatus. This method was not satisfactory for larger samples as the mixture formed a solid mass which overheated the compound and resulted in decomposition. For samples larger than 10 g, dehydration was effectively accomplished by refluxing a toluene solution of **13** with a catalytic amount of iodine. A Dean-Stark trap was used to remove the water and the reaction was followed by measuring the amount of water collected in the Dean-Stark trap. The product was then concentrated to an oil by rotary evaporation, distilled under vacuum (Kugelrohr apparatus), and filtered through acidic and basic alumina with petroleum ether to achieve purification, with iodine being the most persistent impurity.

Hydroboration of **14** to **15** and oxidation of the latter was selected for the synthesis of **16** since this reaction could be expected to give high selectivity. However, impurities accompanied **15** which prevented its purification. Accordingly, **15** was not rigorously purified, but was oxidized with the Jones reagent[18] to the acid **16**. This acid, in contrast to **11**, formed an

insoluble sodium salt which was easy to filter out allowing the removal of neutral impurities.

The alkene side chain of **14** was catalytically hydrogenated to **17** for comparison by ^{13}C NMR with other crowded anisoles. This hydrogenation was carried out in the presence of 5% Pd/C in acetic acid, using a Paar hydrogenation apparatus.

Attempts to make 2-(2-methoxy-3,4-di-*t*-butylphenyl)-2-halopropane (**18**) were unsuccessful. When this conversion was attempted by treating the tertiary alcohol **13** with concentrated hydrochloric acid, only starting material **13** and the dehydration product **14** was recovered. A second attempt at functional group interconversion using acidic conditions was to treat a chloroform solution of either the alcohol **13** or the alkene **14** with dry gaseous hydrogen bromide. For **13**, the results were the same as those obtained with concentrated hydrochloric acid. In the case of the alkene **14**, only starting material was recovered. The failure of acidic conditions was considered to be due to instability of **18** leading to elimination. To avoid the generation of acid during the reaction, benzylic bromination of **17** was tried using a variety of bromine radical donors. The methods attempted were treating **17** with *N*-bromosuccinimide (NBS) in carbon tetrachloride irradiated with a 100W IR lamp, NBS in carbon tetrachloride with *m*-chloroperoxybenzoic acid (mCPBA) or magnesium monoperoxyphthalate (MMPP) as radical initiator, bromotrichloromethane irradiated with a 100W IR lamp,[19] or bromotrichloromethane with MMPP. All of these methods failed to provide a satisfactory yield of **18**. Later it was found that attempts to prepare 2-bromo-2-phenylpropane from cumene through benzylic bromination resulted in multiple products through elimination and rebromination.[20] Further efforts to

make **18** were not attempted since the presence of the ortho methoxy group probably would add difficulties to this problem.

An attempt to make 4-(2-methoxy-3,5-di-*t*-butylphenyl)-4-methyl-1-pentene (**19**) from **17** by treating **17** with *t*-butyllithium followed by allyl bromide was unsuccesful. The major material recovered from this reaction mixture corresponded to **17**.

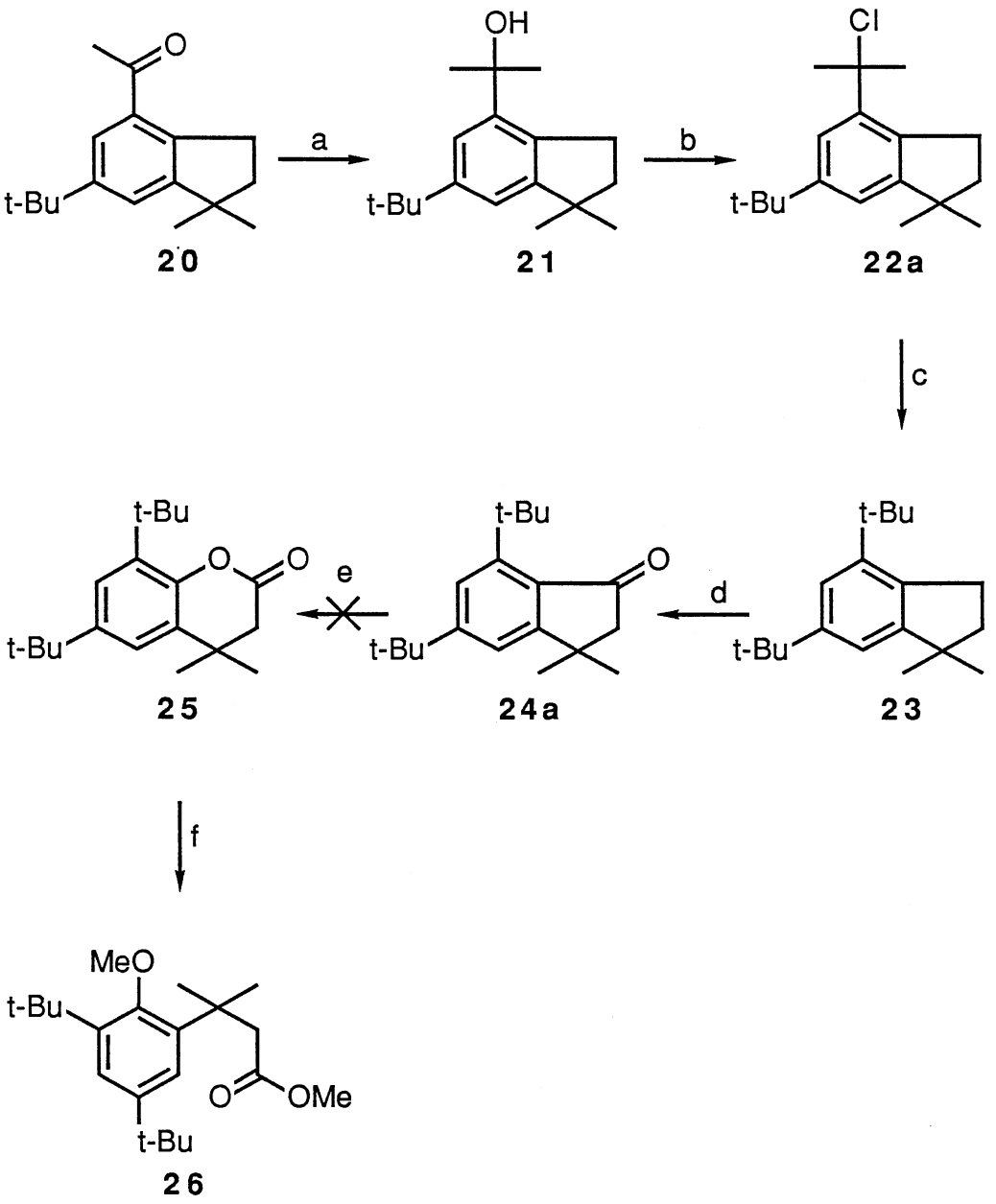
Both attempts to shorten the reaction sequence for the formation of **13**, shown in Figure 2, were unsuccessful due to failure in forming the lithium derivative of **9.** This was tested by treating **9** with *n*-butyllithium followed by treatment with D_2O. A ^1H NMR spectrum of the product showed there was no protium-deuterium exchange as had been observed for related compounds[21].

The failure to form **19** from **17** prompted several attempts to make a similar product by a different and shorter reaction sequence. The first is shown in Figure 4 following the procedure of similar work previously done in this laboratory (corresponding to steps a, b, and c).[22,23] Celestolide (**20**) was treated with methylmagnesium bromide in ether and worked up with a saturated solution of ammonium chloride to give 6-*t*-butyl-1,1,α,α-tetra-methyl-4-indanmethanol (**21**).

To form 6-*t*-Butyl-1,1-dimethyl-4-(α-chloro-α,α-dimethylmethyl)indan (**22a**), **21** was shaken with concentrated hydrochloric acid for 30 min. The chloride **22a** was extracted from the concentrated hydrochloric acid with petroleum ether and concentrated to a white solid by rotary evaporation. It was immediately treated with an excess of methyl magnesium bromide to form 4,6-di-*t*-butyl-1,1-dimethylindan (**23**). The reaction solution was treated with 10% hydrochloric acid to dissolve the magnesium salts. Hydrocarbon **23** was extracted from this solution with ether and was filtered through acidic and basic alumina using petroleum ether.

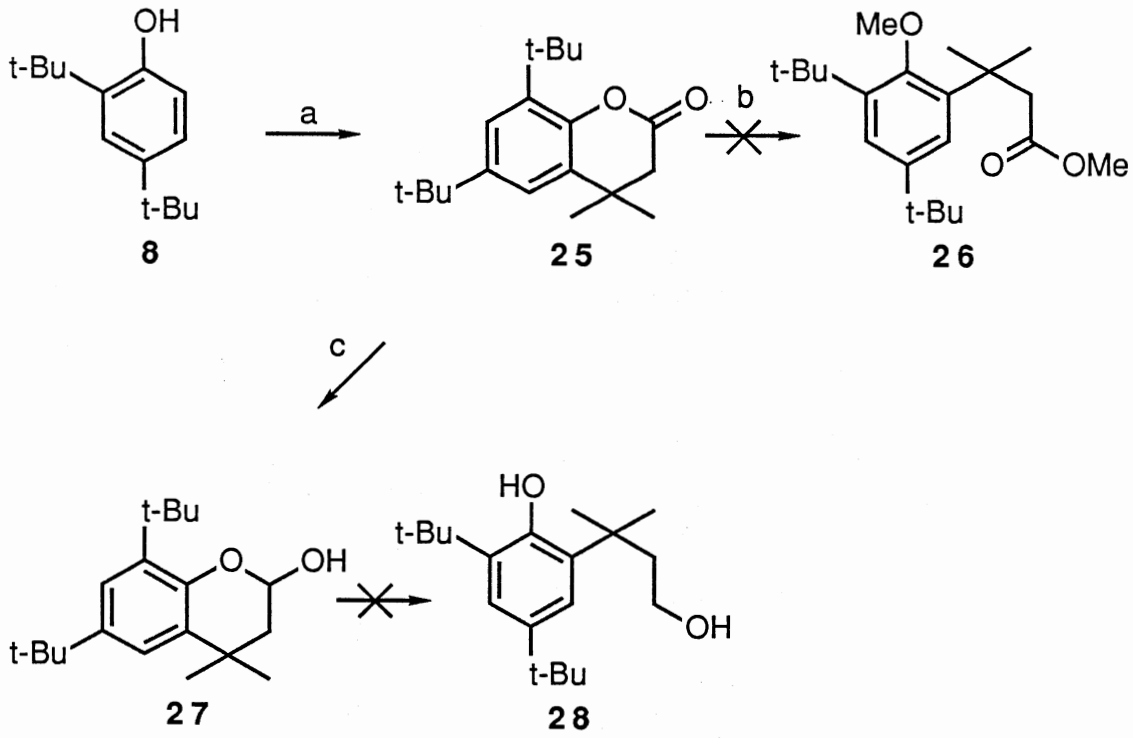
The hydrocarbon **23** was then oxidized to 5,7-di-*t*-butyl-3,3-dimethyl-1-indanone (**24a**) by chromic acid oxidation[23] to give a good yield of **24a**. The Baeyer-Villiger oxidation of **24a** to **25** was initially expected to proceed in good yield. Although several different sets of reaction conditions were attempted, this reaction failed and the desired lactone **25** was not obtained. These included mCPBA in dichloromethane, MMPP in methanol, MMPP in dichloromethane, and peroxytrifluoroacetic acid in dichloromethane. A less substituted indanone (3,3,4,5,7-pentamethyl-1-indanone (**24b**)) treated under similar conditions gave a 15%-50% yield of lactone depending on reaction conditions. Thus, the reaction appears to be sensitive to steric effects.

The final step in Figure 4 involving the opening of the lactone **25** to a phenolic-acid followed by methylation was also expected to be a reaction which would go in good yields. Therefore, a different synthesis of **25** was investigated. The successful method consisted of briefly treating phenol **8** with ethyl 3,3-dimethylacrylate in methanesulfonic acid[24] as shown in Figure 5. This reaction mixture was immediately quenched by pouring it into an alkaline solution. The solution was allowed to cool to room temperature and the lactone was extracted with petroleum ether. The mixture obtained from the petroleum extracts corresponds to the desired lactone **25** and products corresponding to lactones resulting from loss of t-butyl groups from **25**. To separate these lactones, differences in their rates of hydrolysis were utilized. Aqueous sodium hydroxide (0.5 eq) was added and this mixture was stirred at reflux for 3 days. This left **25** unreacted and it was extracted from the reaction mixture with petroleum ether. For further purification, recrystallization from ethanol was effective.



[a]CH_3MgBr, ether. [b]HCl. [c]CH_3MgBr. [d]AcOH, CrO_3. [e]mCPBA. [f]NaOH, $(CH_3O)_2SO_2$, CH_2Cl_2..

Figure 4. Synthesis of **24a** and Attempted Conversion of **24a** to **25** and **26**.

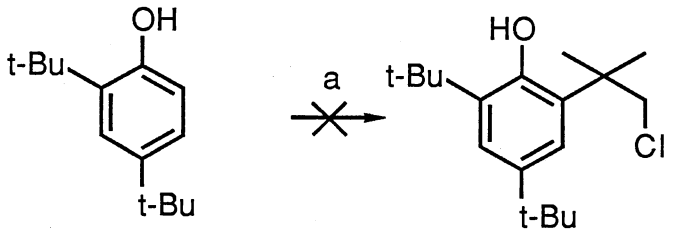


[a]CH_3SO_3H, $(CH_3)_2C{=}CHCO_2Et$ [b]NaOH, $(CH_3O)_2SO_2$, CH_2Cl_2. [c]$LiAlH_4$.

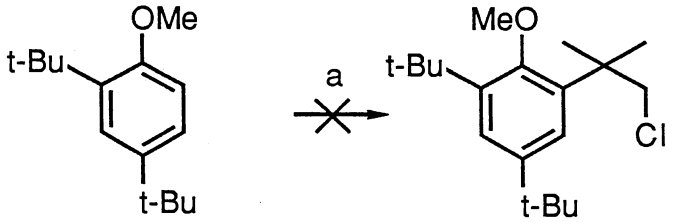
Figure 5. Synthesis of **25** and **27** and Attempted Conversion of **25** to **26** and **27** to **28**.

The resistance of **25** to hydrolysis was beneficial for its purification, but this resistance proved to be detrimental in the attempted conversion to **26**. Though various bases and conditions were used in the attempt to hydrolyze and methylate **25**, the desired product corresponding to **26** was not obtained. To get around this problem, it was thought that conversion of **25** to **28** by reduction of the lactone would be successful. This was tried by treating **25** with an excess of lithium aluminum hydride, but the only material which was recovered corresponded to **27**.

Another attempt to make a product similar to **19** was through the use of the reaction sequences shown in Figure 6. However, due to the ease of cleavage of the tertiary butyl groups under acidic conditions, neither of these reactions was successful and the products recovered corresponded to a replacement or loss of the t-butyl groups.



8 **29**



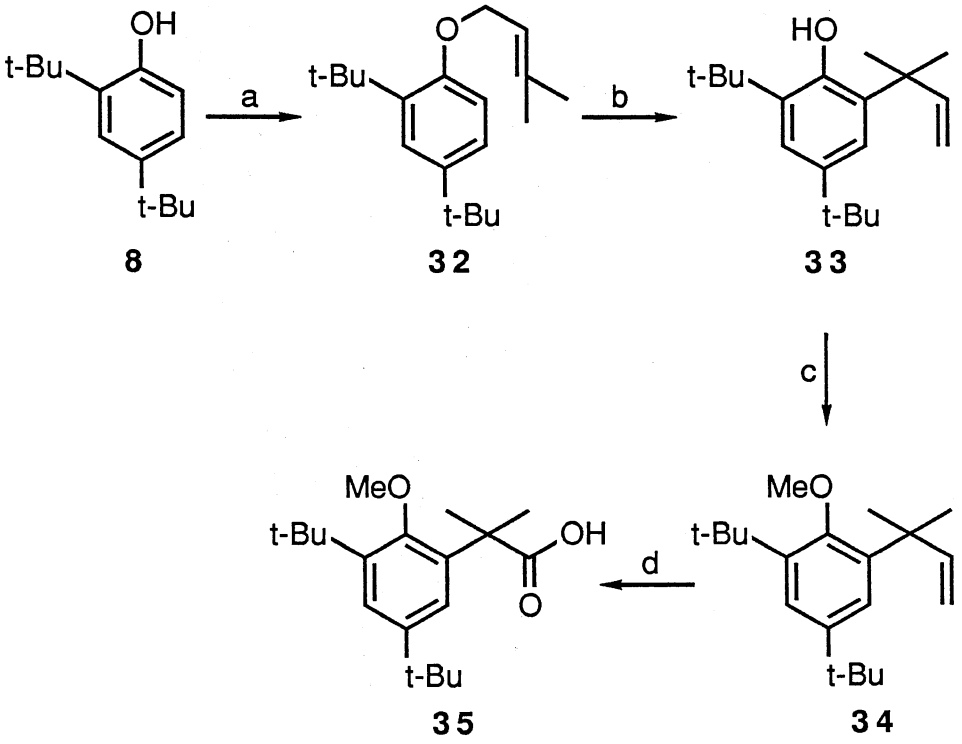
9 **30**

[a]C_6H_6, $CH_2=C(CH_3)CH_2Cl$, H_2SO_4 or Amberlyst 15 and HCl.

Figure 6. Attempted conversion of **8** to **29** and **9** to **30**.

Another approach that was considered to make additional compounds that could be used in this study is shown in Figure 7. A few preliminary runs with model compounds was attempted but after the Claisen rearrangement step, a complex mixture of products was obtained which could not be

separated. Further investigation of the literature revealed that under the conditions of the Claisen rearrangement, the desired product could form, but this product would be expected to undergo rearrangement to an unwanted product.[25] Due to the difficulties encountered in the preliminary work and this additional information, this method was not pursued further. A recently published method using polar solvents at lower temperature and, thus, milder conditions has been reported[26]. This has not been tried on our system and



[a]NaH, benzene; $ClCH_2CHC(CH_3)_2$. [b]diethylaniline, Δ. [c]NaOH, $(CH_3O)_2SO_2$,CH_2Cl_2. [d]O_3; Jones reagent.

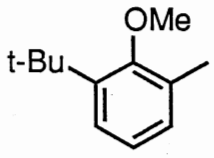
Figure 7. Proposed Synthesis of **35** Using Claisen Rearrangement.

might give the desired products. If the desired rearrangement could be effected, this product would then require methylation to give the methyl ether **34**. Ozonolysis with an oxidative work-up should then provide **35**.

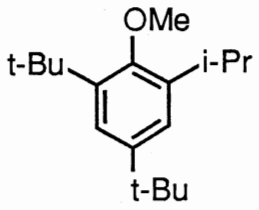
^{13}C NMR Spectra

The ^{13}C NMR spectra of the anisoles prepared in this study were expected to show that all crowded methoxy signals would be shifted to greater than 59 ppm.[7,9] This is supported by the ^{13}C NMR chemical shifts in Tables II and III which show the range to be 60-64.6 ppm. In the earlier studies[7,9] the majority of ortho substituents crowding the methoxy group were alkyl or halogen.[7,9] The current study sought to introduce different ortho functionalities (**10**, Br; **11**, CO_2H; **12**, CO_2CH_3; **13**, *t*-OH; **14**, vinyl) and functionalities at more remote location (**15**, β-hydroxyl; **16**, CH_2CO_2H), which could serve to alter the steric and electronic environment of the methoxy group.

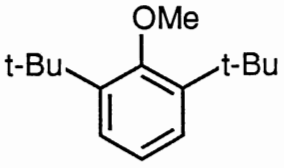
The most obvious comparison, which confirms predictions from earlier work[7,9] is to consider the series **31**,[9] **17**, and **6f**[9] shown below.



31



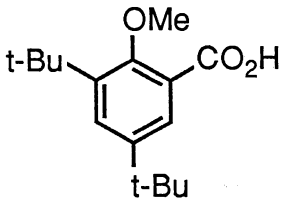
17



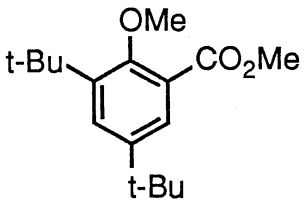
6f

In compound **17** the *p*-*t*-butyl group is immaterial since it is known that substituting an alkyl group for hydrogen at the para position of an anisole does not significantly alter the position of the crowded aromatic methoxy groups ^{13}C NMR signal.[27]

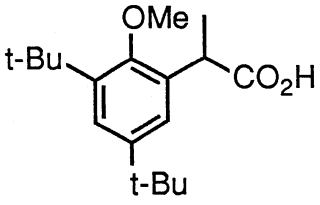
Another interesting comparison is to consider the series **11**, **12**, and **16** where the bulkier methoxycarbonyl group of **12** fails to produce more downfield shift than the carboxyl group of **11**. This difference obviously results from the hydrogen bonding in **11**. Unfortunately the methyl ester of **16** is not currently available for comparison.



11

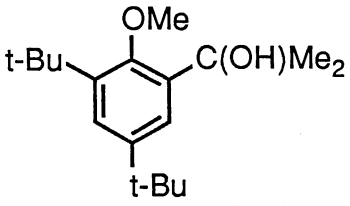


12

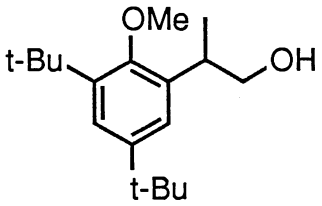


16

Comparison of the alcohols **13** and **15** is less clear and the greater downfield shift of **13** may be due to hydrogen bonding as well as steric bulk.

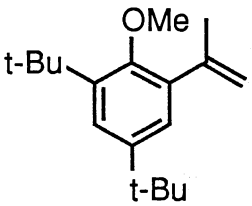


13

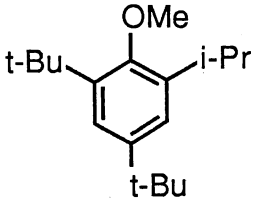


15

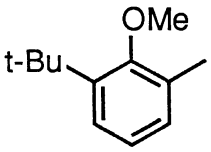
The remaining comparison of **14** with **17** suggests that the electron field of the vinyl group of **14** is shielding the methoxy methyl group, as shown



14



17



31

by the signal at 60.0 ppm, since **31** (ortho methyl substituent) shows the methoxy methyl signal at 60.8 ppm.

This clearly indicates that while there are factors which affect the chemical shift of the crowded methoxy group other than steric interactions, none of these are capable of shifting the ^{13}C NMR methoxy methyl signal to the 55-56 ppm range of a noncrowded anisole. Thus ^{13}C NMR spectroscopic measurements can be used as a valuable diagnostic tool since it can clearly distinguish crowded and noncrowded anisoles.

TABLE II

^{13}C NMR Chemical Shifts in Numerical Sequence

Compound	^{13}C NMR Chemical Shift
9	54.9
14	60.0
31	60.8
10	61.3
12	62.0
17	62.4
15	62.6
16	62.8
11	63.8
6f	64.1
13	64.6

TABLE III

^{13}C NMR Chemical Shifts by Compound

Compound	^{13}C NMR Chemical Shift
6f	64.1
9	54.9
10	61.3
11	63.8
12	62.0
13	64.6
14	60.0
15	62.6
16	62.8
17	62.4
31	60.8

The study of crowded methoxy groups is still a relatively unexplored field and there are areas which were not within the scope of this study and have not been completely investigated. One of these is to follow up the study of building up sufficient bulk at the C-2 and C-6 position of the hindered anisoles such that free rotation of the methoxy group would be sufficiently restricted to permit resolution into enantiomers. To accomplish this goal, the molecule needs a functional group to permit the use of a chiral resolving agent. Initial investigation into this area was done on 3-(2,3-

dimethoxyphenyl)propionic acid using (+) 2-amino-1-phenylpropane or the (-) isomer as the chiral resolving agent to isolate the R or S isomer having a hindered methoxy group by selective crystalization[5]. This acid was separated into its respective enantiomers as indicated by X-ray diffraction analysis; however, the barrier to the rotation was not high enough to allow the study of the enantiomers in solution since they appeared to quickly racemize in solution. The compounds made in this study such as **11** and **16** could be used to investigate this observation. Other parameters that are not known is the degree of optical activity that a hindered methoxy group imparts on these molecules and the actual energy barrier of rotation which could be determined by measuring the rate of racemization for these enantiomers.

CHAPTER III

EXPERIMENTAL

General Information. NMR spectral data were recorded on a Varian XL-300 spectrometer with ^{1}H and ^{13}C data being taken at 299.99 Hz and 75.4 Hz with reference to TMS in δ values or ppm respectively; J values are reported in Hz. Melting points were determined with a Thomas-Hoover Unimelt apparatus and were uncorrected. The exact masses of certain compounds were obtained from the mass spectral laboratory with a VG-analytical ZAB 2-SE-high resolution, reversed-geometry mass spectrometer. Gas chromatographic analyses were performed on a Micro Tek 220 instrument using a 6' X 1/4", U-shaped, glass column packed with 1% OV-17 on Chromosorb B 60 / 80 mesh.

2,4-Di-*t*-butylanisole (9). A 12-L round-bottomed flask equipped with a Vibromixer was charged with **8** (412.6 g, 2.0 mol), NaOH (160.00 g, 4.0 mol), tetra-*n*-butylammonium bromide (19.00 g, 58.9 mmol), H_2O (2 L), CH_2Cl_2 (4 L), and dimethyl sulfate (454.0 g, 340.6 mL, 3.44 mol). This mixture was stirred for 24 h and the CH_2Cl_2 was distilled off and collected. The excess dimethyl sulfate was destroyed by the addition of NH_4OH (2 L). The remaining reaction mixture was extracted with petroleum ether (2 X 500 mL), washed with H_2O (1 L), washed with a saturated NaCl solution (500 mL), dried ($MgSO_4$, 20 g), and concentrated to a yellow solid by rotary evaporation. The solid was filtered through acidic alumina (200 g) and basic alumina (200

g) with petroleum ether. The petroleum ether was removed by rotary evaporation and the remaining material was distilled using a Kugelrohr apparatus (116 °C, 0.5 mmHg) to give **9** as a white solid (386 g; 88% yield) mp 35.0-37.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.32 (d, J = 2.4, 1H), 7.18 (dd, J_1 = 2.4, J_2 = 8.4, 1H), 6.80 (d, J = 8.4, 1H), 3.80 (s, 3H), 1.38 (s, 9H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 156.2, 142.4, 137.3, 123.8, 123.3, 110.8, 54.9, 35.0, 34.2, 31.6, 29.8.

2-Bromo-4,6-di-*t*-butylanisole (10), Method 1. A mixture of water (2 L), KBr (250 g, 2.10 mol), bromine (175 g, 1.10 mol), and **9** (100 g, 0.45 mol) was heated at reflux for 24 h and extracted with petroleum ether (4 X 500 mL). The combined petroleum ether extracts were washed with 20% NaOH (2 X 500 mL), H_2O (2 X 500 mL), saturated NaCl solution (500 mL) and filtered through basic alumina (300 g) and acidic alumina (400 g). The petroleum ether was removed by rotary evaporation giving a clear oil. The oil was distilled using a Kugelrohr apparatus (125 °C, 0.5 mm Hg) and after standing for 5 days it formed a white solid (115 g, 84% yield) mp 36.1-37.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 2.4, 1H), 7.28 (d, J = 2.4, 1H), 3.90 (s, 3H), 1.39 (s, 9H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.1, 147.2, 144.0, 128.8, 123.5, 117.6, 61.3, 35.7, 34.5, 31.4, 30.9.

2-Bromo-4,6-di-*t*-butylanisole (10), Method 2. A 1-L Erlenmeyer flask equipped with a Teflon-coated stirring bar and reflux condenser was charged with **9** (110.2 g, 500 mmol.), CCl_4 (500 mL), and Br_2 (83.9 g, 525 mmol). This reaction mixture was irradiated with a 375W clear IR lamp placed at a distance of 10 cm for 8 h, concentrated to a yellow solid by rotary evaporation, distilled using a Kugelrohr apparatus (130 °C, 0.5 mmHg), and filtered through basic alumina (150 g) and acidic alumina (150 g) with petroleum ether. The petroleum ether extract was concentrated by rotary

evaporation and the resulting solid was recrystallized from methanol giving **10**. (109.5 g, 77%). The spectral data corresponded to that obtained for the product using Method 1.

2-Methoxy-3,5-di-*t*-butylbenzoic acid (11). A 500-mL, 3-necked, round-bottomed flask with a Teflon-coated stirring bar, gas inlet / outlet, septum, and reflux condenser was charged with magnesium (6.37 g, 262 mmol), iodine (1 crystal), diethyl ether (300 mL), and **10** (78.3 g, 261.2 mmol). This reaction mixture was heated at reflux for 24 h. While reflux was maintained, CO_2 was bubbled through this solution for 5 h. This solution was poured onto ice and the magnesium salts were dissolved by adding a 10% solution of HCl. The acid **11** was extracted from the aqueous layer with diethyl ether (300 mL) and the ether layer was washed with H_2O (2 X 1 L). To separate **11** away from neutral materials, the ether layer was extracted with a 50% NH_4OH solution (2 X 1 L). The NH_4OH layer was acidified to pH = 3 with HCl and extracted with diethyl ether (2 X 500 mL). The ether was washed with saturated NaCl (500 mL), dried over $MgSO_4$ (10 g), concentrated to a yellow-white solid by rotary evaporation, and recrystallized from diethyl ether to give **11** as a white solid (49.8 g, 72% yield), mp 164.1-165.3 °C; ^1H NMR ($CDCl_3$) δ 7.86 (d, J = 2.6, 1H), 7.59 (d, J = 2.6, 1H), 3.88 (s, 3H), 1.43 (s, 9H), 1.33 (s, 9H), the acidic proton was not found due to deuterium exchange; ^{13}C NMR ($CDCl_3$) δ 169.1, 157.7, 146.4, 142.8, 129.8, 127.6, 122.6, 63.8, 35.5, 34.7, 31.3, 31.0; exact mass calc. 264.1725, found 264.1725.

Methyl 3,5-di-*t*-butyl-2-methoxybenzoate (12). An ether solution of **11** was made by dissolving 17.59 g (66.5 mmol) in 250 mL of diethyl ether. Diazomethane in ether was added with a Pasteur pipette until the yellow color of diazomethane remained and nitrogen did not evolve. This solution was allowed to stand for 1h. The reaction was quenched with formic

acid (5 mL), concentrated, and distilled using a Kugelrohr apparatus (104 °C, 0.5 mmHg) to give **12** as a colorless oil which later crystallized to a white solid (16.3 g, 88% yield). mp 39.5-40.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, J = 2.6, 1H), 7.49 (d, J = 2.6, 1H), 3.94 (s, 3H), 3.78 (s, 3H), 1.40 (s, 9H), 1.31 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.5, 157.4, 144.9, 142.5, 127.9, 126.1, 123.8, 62.0, 52.3, 35.4, 34.5, 31.4, 30.7; exact mass calc. 278.1882, found 278.1882.

2-(3,5-Di-*t*-butyl-2-methoxyphenyl)-2-propanol (13). A 250-mL, 3-necked round-bottomed flask equipped with a Teflon-coated stirring bar, septum, nitrogen inlet / outlet, and reflux condenser was charged with **12** (9.74 g, 35 mmol), and diethyl ether (100 mL). Methylmagnesium bromide (3 M in ether, 38 mL, 114 mmol) was added over a period of 15 min. The reaction mixture was heated at reflux for 3.5 h, cooled to room temperature (RT), poured onto crushed ice, and the magnesium salts were dissolved by the addition of a saturated NH_4Cl solution. This mixture was extracted with diethyl ether (100 mL), washed with saturated NaCl (100 mL), dried ($MgSO_4$,1 g), and concentrated to a solid. The solid was recrystallized from ether giving **13** as a white solid (8.75 g, 90% yield), mp 65.0- 70.1 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (d, J = 2.5, 1H), 7.14 (d, J = 2.5, 1H), 5.39 (s, 1H), 3.86 (s, 3H), 1.65 (s, 6H), 1.43 (s, 9H), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.7, 145.8, 142.5, 140.1, 124.2, 122.6, 74.4, 64.6, 35.8, 34.6, 33. 0, 31.9, 31.5.

2-(3,5-Di-*t*-butyl-2-methoxyphenyl)propene (14). Method 1. The alkene **14** was distilled (90-95 °C, 0.5 mm Hg) from a mixture of **13** (5.90 g, 21.1 mmol), and anhydrous $CuSO_4$ (5.9 g) using a Kugelrohr apparatus. The distillate was dissolved in petroleum ether, dried ($MgSO_4$, 0.5 g), filtered, and concentrated to give **14** as a white solid (5.20 g, 95% yield), mp 50.9-52.8 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 2.3, 1H), 7.03 (d, J = 2.3, 1H), 5.10-5.15 (3-line m, 2H, vinylic H), 3.72 (s, 3H), 2.15 (s, 3H), 1.40 (s, 9H), 1.30 (s,

9H); ^{13}C NMR ($CDCl_3$) δ 154.7, 146.0, 144.9, 141.5, 136.3, 125.2, 123.0, 114.9, 60.0, 35.2, 34.4, 31.6, 30.9, 22.7.

2-(3,5-Di-*t*-butyl-2-methoxyphenyl)propene (14). Method 2. A 500 mL round-bottomed flask equipped with a Teflon-coated stirring bar, and a Dean-Stark trap with condenser was charged with **13** (52.3 g, 188 mmol), toluene (300 mL), and iodine (1 crystal). This mixture was heated at refluxed for 6 h with 3.3 mL of water collecting in the Dean-Stark trap. The solution was allowed to cool to RT, dried ($MgSO_4$, 5.0 g), concentrated by rotary evaporation, filtered through acidic alumina (100 g), and basic alumina (50 g) with petroleum ether. The ether was removed by rotary evaporation to give **14** as a white solid (46.7 g, 95% yield). The spectral data matched the material isolated from Method 1.

2-(3,5-Di-*t*-butyl-2-methoxyphenyl)-1-propanol (15). A 250-mL, 3-necked round-bottomed flask equipped with a thermometer, Teflon-coated stirring bar, nitrogen inlet / outlet, and dropping funnel was charged with **14** (5.00 g, 19.2 mmol), and THF (10.0 mL). The temperature of this solution was adjusted to 0 °C using a NaCl-ice bath and borane in THF (1.0 M, 20 mL, 20 mmol) was added dropwise over a period of 15 min. This solution was heated to 30 °C for 4 h and the excess borane was destroyed by the dropwise addition of H_2O (5.0 mL). The resulting borane was worked up by the dropwise addition of NaOH (3M, 2.1 mL) and H_2O_2 (15%, 1 mL) to the reaction mixture held at 50 °C for 1 h. This mixture was poured into a separatory funnel containing water (500 mL) and this was extracted with ether (3 X 250 mL). The combined ether extracts were washed with a saturated NaCl solution (100 mL), dried ($MgSO_4$, 5 g), and concentrated by rotary evaporation to give **15** as a white solid (5.1 g; 97% yield). ^1H NMR ($CDCl_3$) δ 7.23 (d, 1H), 7.09 (d, 1H), 3.75 (s, 3H), 3.70 (d, 3H), 3.43 (m, 1H), 1.85 (s, 1H),

1.40 (s, 9H), 1.30 (s, 9H), 1.25 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 155.8, 146.0, 141.9, 136.3, 122.7, 121.8, 66.7, 62.6, 35.4, 34.8, 31.6, 31.3, 25.6, 18.3.

2-(3,5-Di-*t*-butyl-2-methoxyphenyl)propionic acid (16). A solution of **15** was made by dissolving 5.14 g (18 mmol) in 500 mL of acetone. Jones reagent (see below) (2.50 M, 10.0 mL, 25.0 mmol) was added and stirred for 15 min. Petroleum ether (500 mL) was added and the chromium salts were removed by vacuum filtration through Dicalite. The filtrate was washed with H_2O (4 X 500 mL), and added to a 10% NaOH solution (80 mL). The resulting white precipitate was vacuum filtered and washed with petroleum ether. The crystalline solid was transferred to a separatory funnel, acidified to pH = 3 with 10% HCl, and extracted with diethyl ether (500 mL). The ether extract was washed with a saturated NaCl solution, dried ($MgSO_4$, 5 g), and concentrated by rotary evaporation to give **16** as a white solid (3.40 g, 63% yield). ^1H NMR ($CDCl_3$) δ 7.27 (d, J = 2.5, 1H), 7.21 (d, J = 2.5, 1H), 4.17 (q, J = 7.1, 1H), 3.82 (s, 3H), 1.48 (d, J = 7.1, 3H), 1.40 (s, 9H), 1.28 (s, 9H) the acidic proton was not found due to deuterium exchange; ^{13}C NMR ($CDCl_3$) δ 180.8, 154.8, 146.1, 141.9, 133.2, 123.6, 123.1, 62.8, 38.2, 35.4, 34.6, 31.5, 31.3, 19.1.

Jones Reagent- Chromium (VI) Oxide (50.0 g, 0.5 mol) was dissolved in a minimum amount of water, H_2SO_4 (43.4 mL) was added, and this mixture was diluted to 200 mL with distilled water.[18]

2,4-Di-*t*-butyl-6-isopropenylanisole (17). A stainless steel flask (1 L) equipped with an H_2 inlet, was charged with **14** (5.20 g, 20.1 mmol), acetic acid (100 mL), and 5% Pd/C (0.25 g). The flask was place in a Paar-apparatus, evacuated, pressured up to 30 psi with H_2, evacuated, pressured up to 30 psi with H_2 and the Paar apparatus was started. The reaction was continued until no H_2 was taken up (5 h). This reaction mixture was filtered

through Dicalite, concentrated to 10 mL by rotary evaporation, diluted with H_2O (1 L), and extracted with hexane (2 X 500 mL). The combined hexane extracts were washed with a saturated $NaHCO_3$ solution, dried ($MgSO_4$, 5 g), filtered, concentrated by rotary evaporation, and distilled to give 4.88 g (93%) **17** as a white solid , mp = 87.5-88.1 °C. ^1H NMR ($CDCl_3$) δ 7.17 (d, J = 2.5, 1H), 7.14 (d, J = 2.5, 1H), 3.77 (s, 3H), 3.34 (septet, J = 6.9, 1H), 1.40 (s, 9H), 1.31 (s, 9H), 1.25 (d, J = 6.9, 6H); ^{13}C NMR ($CDCl_3$) δ 154.5, 147.2, 145.5, 141.4, 121.8, 121.6, 62.4, 35.4, 34.6, 31.6, 31.3, 26.5, 24.5.

6-*t*-Butyl-1,1,α,α-tetra-methyl-4-indanmethanol (21). A slurry of celestolide (**20**) (424 g; 1.74 mol) in ether (200 mL) was added to CH_3MgBr (1.9 mol in a mixture of THF / toluene / ether). This reaction mixture was heated at reflux for 4 h, cooled overnight, and acidified with a 10% HCl solution (1 L). The ether extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated to a solid. The solid was recrystallized from petroleum ether to give 336 g (74% yield) of **21**, mp 98-99 °C.

6-*t*-Butyl-1,1-dimethyl-4-(α-chloro-α,α-dimethyl)indan (22a). A mixture of **21** (50.0 g, 0.192 mol), which had been ground to a fine powder with a mortar and pestle, and concentrated HCl (800 mL) was shaken in a 2 L separatory funnel for 30 min. Petroleum ether (100 mL) was added and the mixture was shaken until all solid material was dissolved. The solution was allowed to stand for 3 h, and the concentrated HCl was extracted with petroleum ether (3 X 200 mL). The petroleum ether was removed by rotary evaporation to give a white solid. The remaining HCl was removed by passing dry air through the white solid to give **22a** (53.54 g, quantitative yield): ^1H NMR ($CDCl_3$) δ 7.31 (s, 1H), 7.12 (s, 1H), 3.21 (t, 2H), 2.04 (s, 6H), 1.92 (t, 2H), 1.34 (s, 9H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.1, 149.3, 140.5, 138.1, 119.8, 118.8, 70.6, 43.1, 41.6, 34.9, 33.6, 31.6, 30.9, 28.5.

6-*t*-Butyl-1,1-dimethyl-4-(2-propenyl)indan (22b) from 21. The alcohol **21** (10 g, 38 mmol) was distilled in the presence of anhydrous $CuSO_4$ (10 g, 63 mmol) by using a Kugelrohr apparatus. The distillate was dissolved in petroleum ether (20 mL), dried over $MgSO_4$ (1 g), filtered through basic alumina (10 g), and concentrated by rotary evaporation to give **22b** as a clear oil (6.3 g, 68% yield). ^1H NMR ($CDCl_3$) δ 7.13 (s, 1H), 7.11 (s, 1H), 5.19 (s, 1H), 5.03 (s, 1H), 2.90 (t, 2H), 2.13 (s, 3H), 1.90 (t, 2H), 1.35 (s, 9H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 152.8, 149.5, 145.0, 138.9, 136.9, 122.2, 117.9, 114.5, 43.9, 41.6, 34.7, 31.6, 29.7, 28.6, 23.5.

6-*t*-Butyl-1,1-dimethyl-4-(2-propenyl)indan (22b) from 22a. A solution of **22a** was made by dissolving 1.00 g (3.59 mmol) in 10 mL of petroleum ether. This solution was filtered through basic alumina (10 g), and concentrated by rotary evaporation to give **22b** as a clear oil (0.87 g, quantitative yield). The spectral data were the same as those obtained by the dehydration of **21**.

4,6 Di-*t*-butyl-1,1-dimethylindan (23). A 1-L 3-necked round-bottomed flask equipped with a reflux condenser, a thermocouple, an addition funnel, a nitrogen inlet / outlet, a septum, and a Teflon-coated stirring bar was charged with CH_3MgBr (3M, 40 mL, 120 mmol). A solution of **22a** (12.85 g, 46.1 mmol) in ether (700 mL)was added dropwise to the Grignard reagent over a period of 1.5 h. The reaction mixture was stirred at RT for 3 h. The excess CH_3MgBr was destroyed with a 10% HCl solution (250 mL). The ether layer was set aside and the water layer was extracted with ether (2 X 100 mL). The combined ether extracts were washed with H_2O (250 mL), a saturated NaCl solution (100 mL), dried over $MgSO_4$ (1 g), filtered, and concentrated to a solid. The solid was dissolved in petroleum ether (250 mL), and filtered through basic alumina (10 g), and acidic alumina (10 g). The petroleum ether

was removed *in vacuo* to give11.8 g (99.2%) of **23** as a white solid, mp 114 °C. The spectral data were: ^{1}H NMR ($CDCl_3$) δ 7.25 (d, 1H), 7.05 (d, 1H), 3.05 (t, 2H), 1.90 (t, 2H), 1.38 (s, 9H), 1.34 (s, 9H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 153.3, 149.2, 145.5, 137.2, 120.8, 116.7, 42.8, 41.7, 35.8, 34.8, 31.7, 31.4, 30.5, 28.6.

5,7-Di-*t*-butyl-3,3-dimethyl-1-indanone (24a). In a 4 L Erlenmeyer flask equipped with a Teflon-coated stirring bar, **23** (4.00 g, 15.5 mmol) was dissolved in acetic acid (1 L). Chromium(VI) oxide (7.5 g; 69 mmol), dissolved in H_2O (75 mL), was added and the solution was stirred for 24 h. This solution was concentrated by rotary evaporation to 200 mL. Water (3 L) was added and the mixture was extracted with ether (2 X 250 mL). The ether extracts were washed with H_2O (500 mL), a saturated $NaHCO_3$ solution (400 mL), and a saturated NaCl solution (200 mL), dried ($MgSO_4$, 5 g), filtered, and concentrated to light pink crystals. Filtration through acidic alumina (10 g), and basic alumina (10 g) with petroleum ether, and concentration by rotary evaporation gave **24a** (4.03 g, 96% yield) as colorless crystals, mp 135-137 °C. The spectral data were: ^{1}H NMR ($CDCl_3$) δ 7.43 (d, 1H), 7.32 (d, 1H), 2.57 (s, 2H), 1.46 (s, 9H), 1.39 (s, 6H), 1.35 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 205.0, 167.3, 158.0, 150.9, 130.5, 122.4, 117.7, 54.3, 37.2, 36.0, 35.6, 31.2, 30.4, 29.8.

5,7-Di-*t*-butyl-3,3-dimethyldihydrocoumarin (25). A 1-L pear-shaped flask equipped with a Teflon-coated stirring bar, and reflux condenser was charged with **8** (67.50 g, 327.2 mmol) and ethyl 3,3-dimethylacrylate (50.00 g, 390.1 mmol). This reaction mixture was heated to 67 °C (oil bath), CH_3SO_3H (500.0 mL) was added, and stirring was maintained for 1.5 h thereafter. This reaction mixture was added to a NaOH solution (280 g NaOH, 3L H_2O) in a 6 L separatory funnel (pH = 3 after addition), and extracted with

ether (1 L). The ether extract was washed with a saturated $NaHCO_3$ solution (2 X 500 mL), a saturated NaCl solution (500 mL), dried ($MgSO_4$, 10 g), and concentrated to a yellow slush (92.2 g crude). This mixture was transfered to a 2 L flask equipped with a reflux condenser, and magnetic stirring bar. Sodium hydroxide (10.4 g, 0.26 mol) dissolved in H_2O (40 mL), and methanol (400 mL) was added and this reaction mixture was heated at reflux for 3 days. Water (200 mL) was added and the methanol was distilled off. The remaining material was extracted with ether (1 L). The ether extract was washed with 5M NaOH (2 X 400 mL), 10% HCl (400 mL), saturated $NaHCO_3$ (200 mL), saturated NaCl (200 mL), dried ($MgSO_4$, 5 g), filtered, and concentrated to an off-white solid. The solid material was recrystallized in ethanol to give **25** (41.5 g, 44% yield) as a white solid . ^1H NMR ($CDCl_3$) δ 7.30 (d, J = 2.3, 1H), 7.19 (d, J = 2.3, 1H), 2.60 (s, 2H), 1.44 (s, 9H), 1.36 (s, 6H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.3, 147.1, 146.6, 137.2, 131.6, 122.9, 118.8, 43.5, 35.1, 34.8, 33.4, 31.5, 30.2, 27.8; exact mass calc 288.2089, found 288.2084

Attempt to make 3-(3,5-Di-*t*-butyl-2-hydroxyphenyl)-3-butanoic acid (28). A 200-mL, 2-neck round-bottom flask equipped with a Teflon-coated stirring bar, dropping funnel, a nitrogen inlet / outlet, and reflux condenser was charged with $LiAlH_4$ (1.00 g, 26.35 mmol) and diethyl ether (60 mL). An ether solution of **25** (5.00 g, 17.34 mmol) was added dropwise and the resulting mixture was heated at reflux for 2 h and then allowed to cool to RT. The following were sequentially added dropwise to this reaction mixture; H_2O (1 mL), 15% NaOH (1 mL), and H_2O (3 mL). The mixture was filtered through Dicalite, washed with 20% HCl (100 mL), saturated $NaHCO_3$ (200 mL), saturated NaCl (200 mL), dried ($MgSO_4$, 1.0 g), and concentrated to a white solid. This solid was chromatographed on silica gel with 3% ether and 97% petroleum ether to give **27** as a white solid. Upon methylation using

NaOH and $(CH_3O)_2SO_2$, the spectra obtained were; ^1H NMR δ 7.20 (d, J = 2.4, 1H), 7.15 (d, J = 2.4, 1H), 5.03 (4 line m, 1 H), 3.62 (s, 3H), 1.88 (m, 2H), 1.42 (s, 9H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (s, 9H);.^{13}C NMR ($CDCl_3$) δ 148.1, 142.1, 136.7, 130.5, 122.1, 120.8, 99.1, 56.9, 42.6, 35.2, 34.4, 32.7, 32.4, 31.6, 31.2, 30.0

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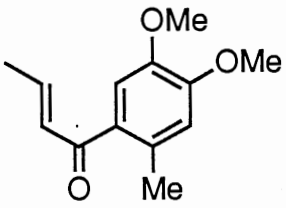
APPENDIX A

GLOSSARY OF STRUCTURES



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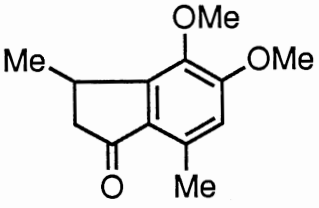

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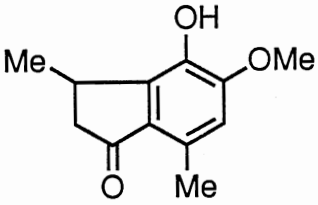

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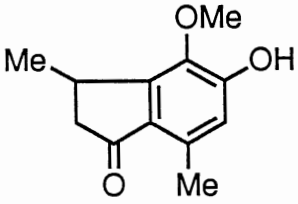

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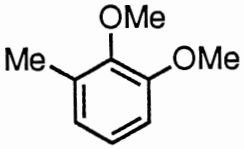

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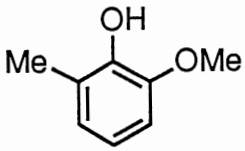

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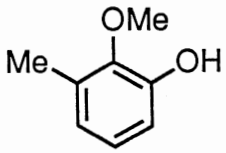

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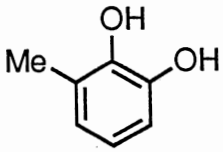

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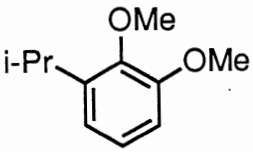

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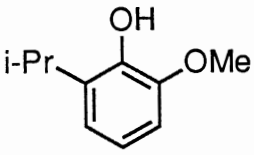

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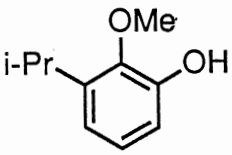

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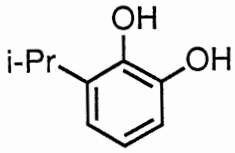

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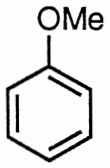

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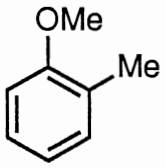

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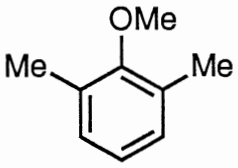

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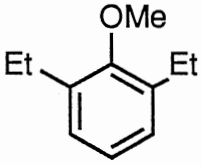

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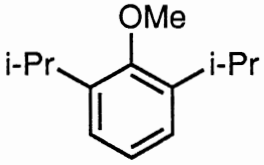

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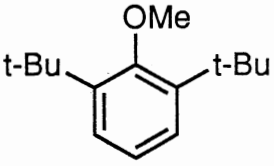

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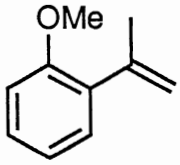

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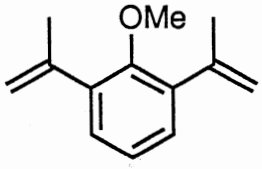

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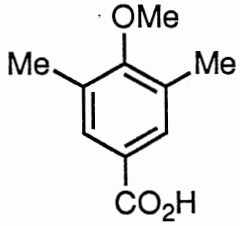

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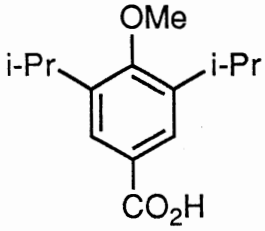

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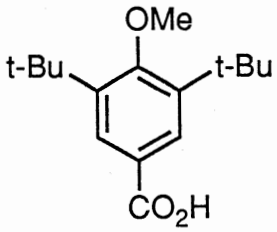

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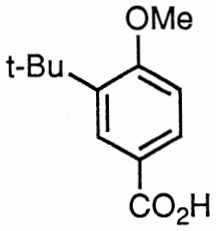

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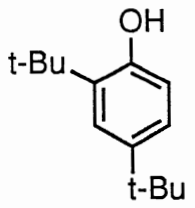

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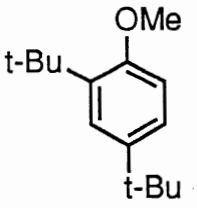

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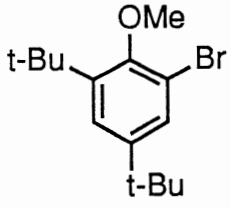

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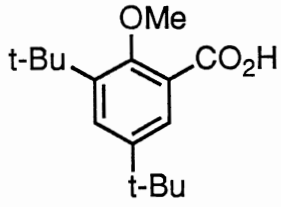

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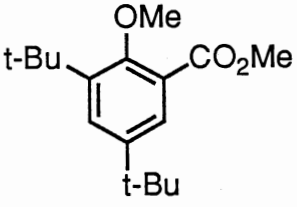

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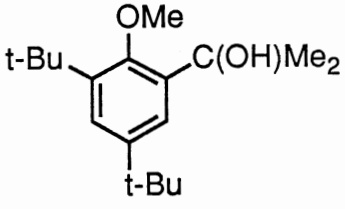

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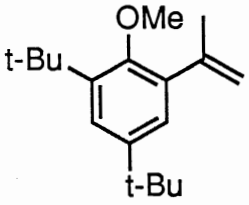

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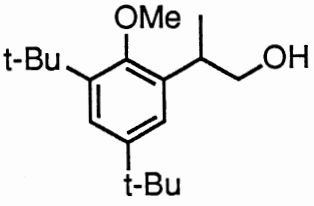

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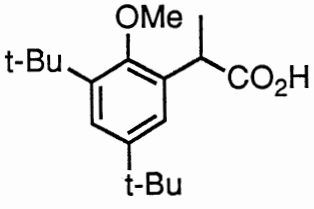

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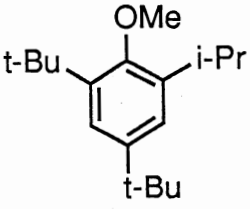

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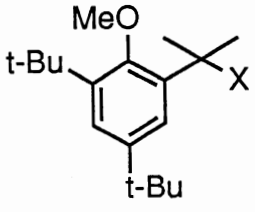

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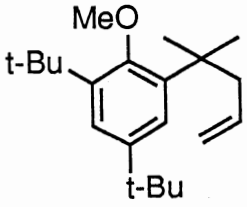

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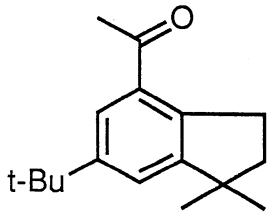

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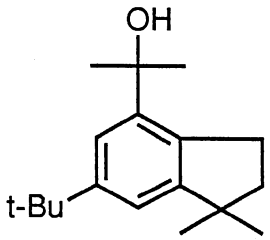

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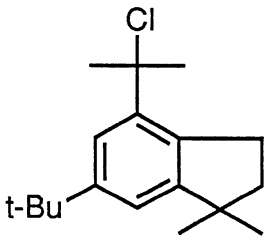

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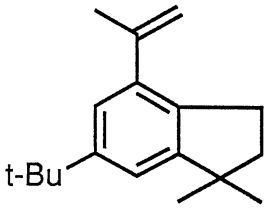

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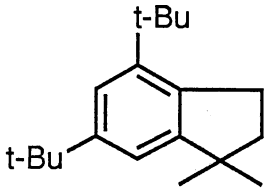

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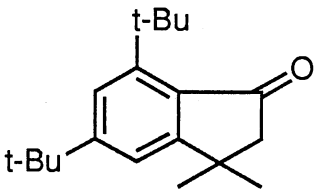

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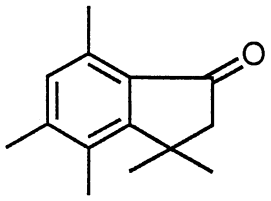

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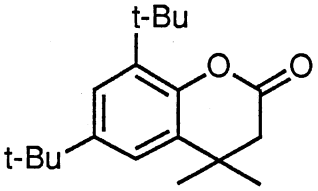

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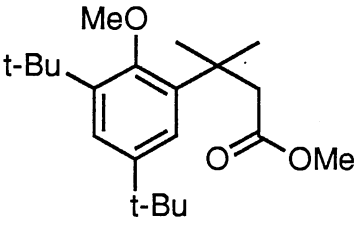

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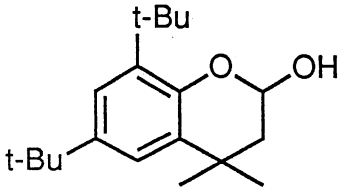

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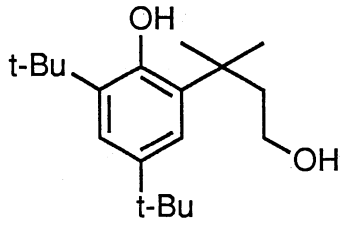

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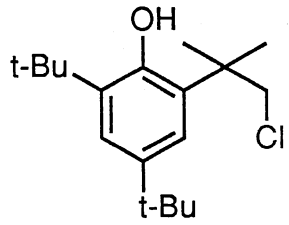

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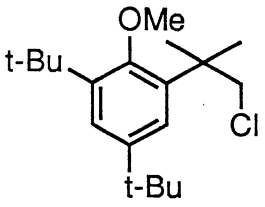

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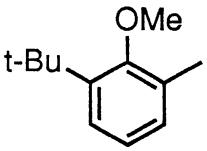

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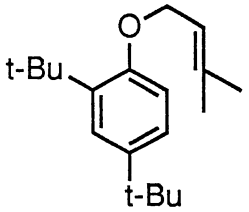

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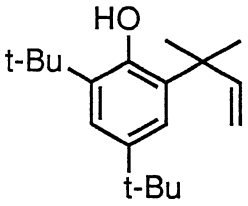

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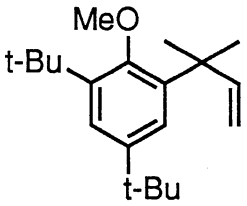

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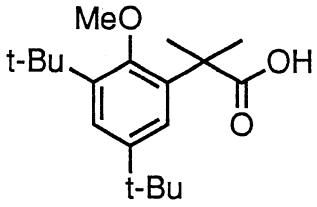

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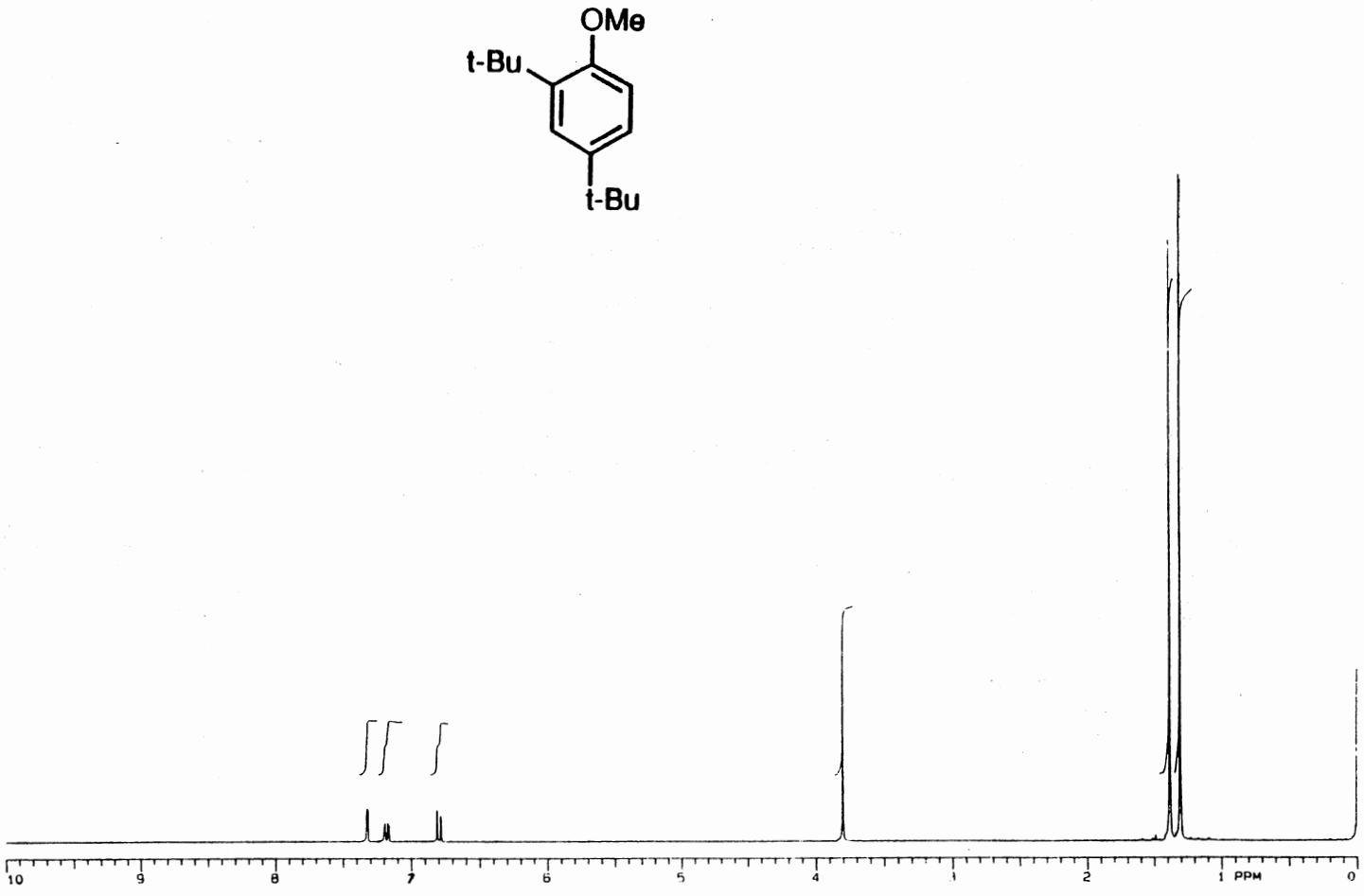
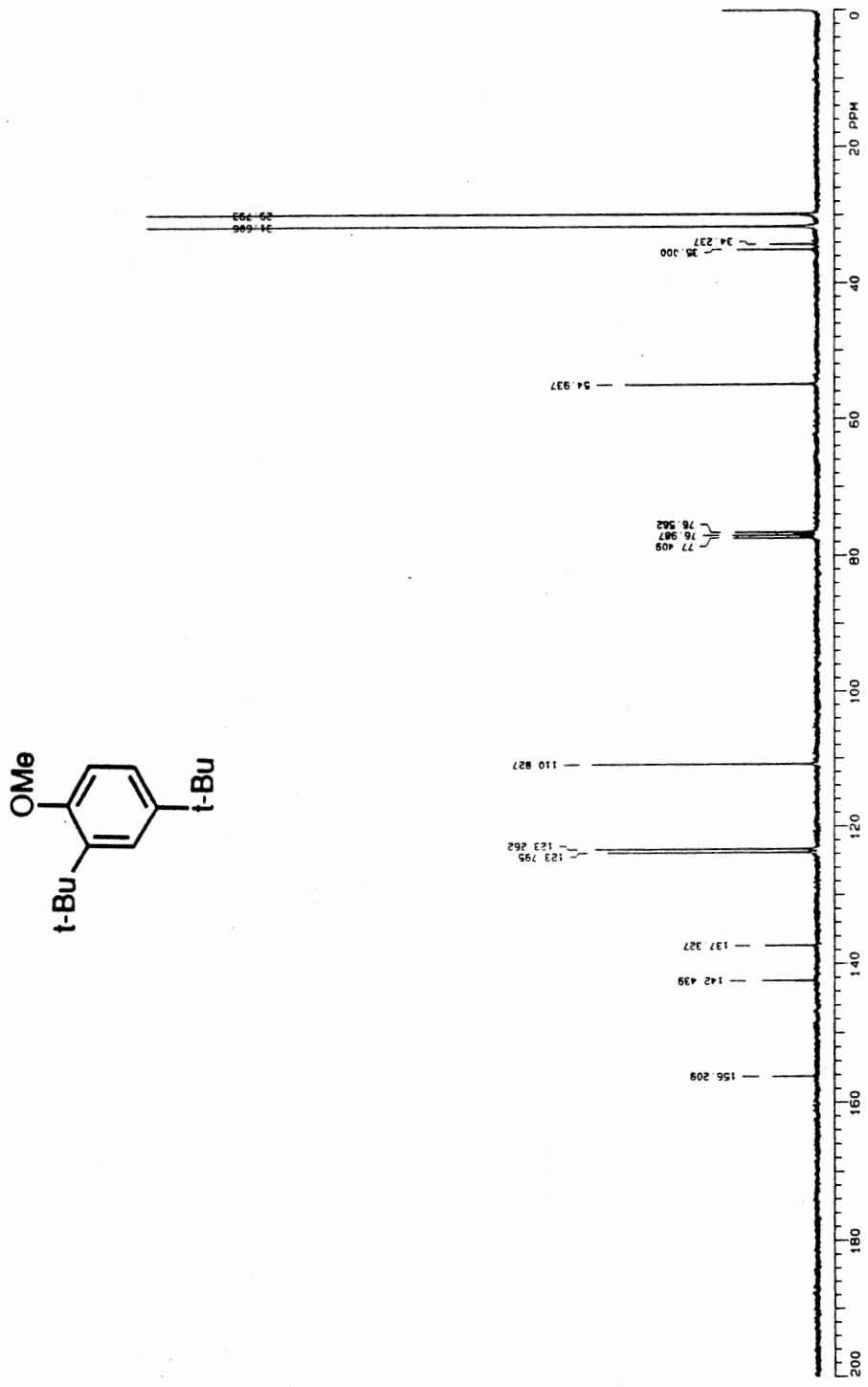
APPENDIX B

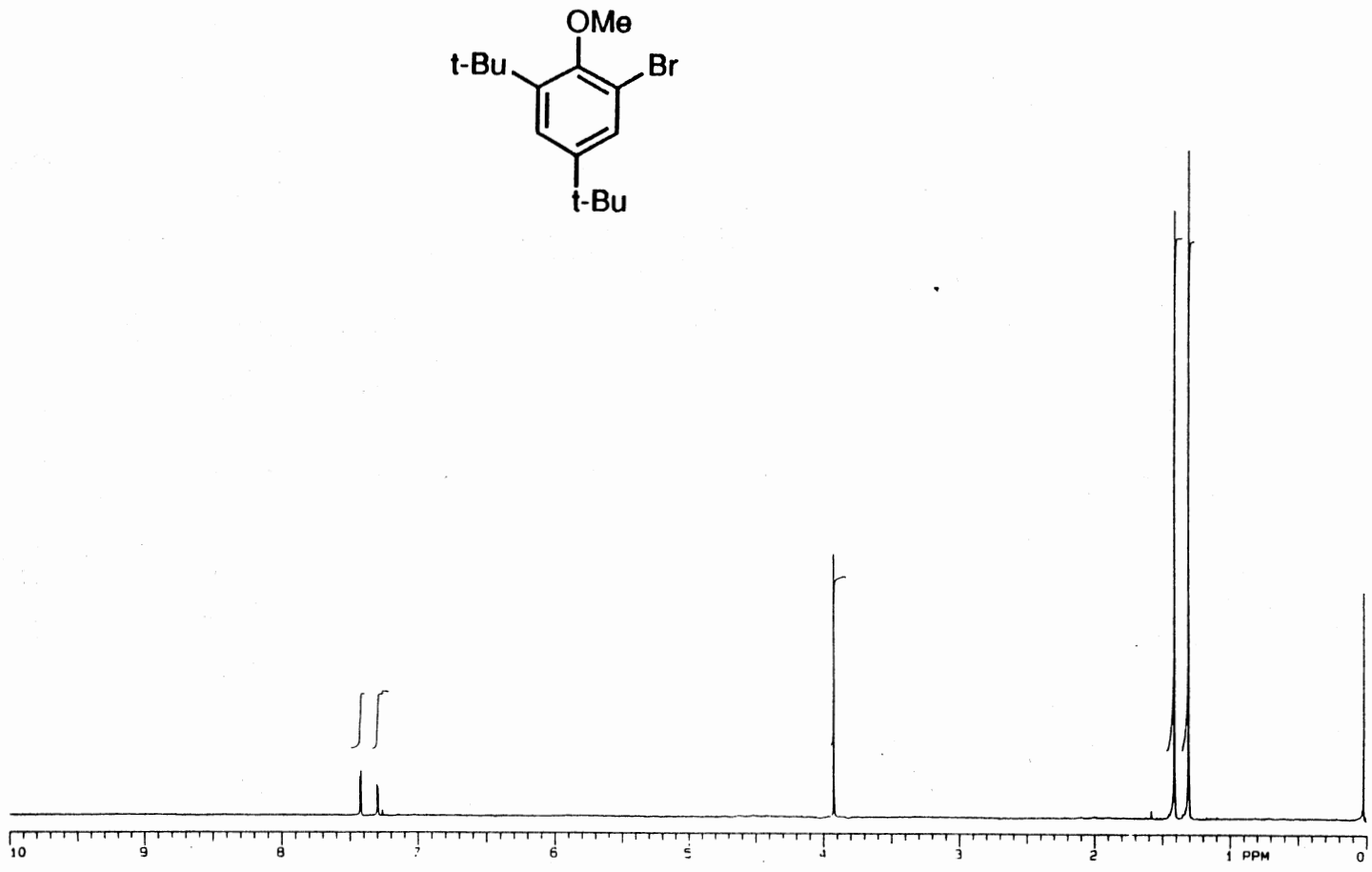
SELECTED ^{1}H AND ^{13}C NMR SPECTRA



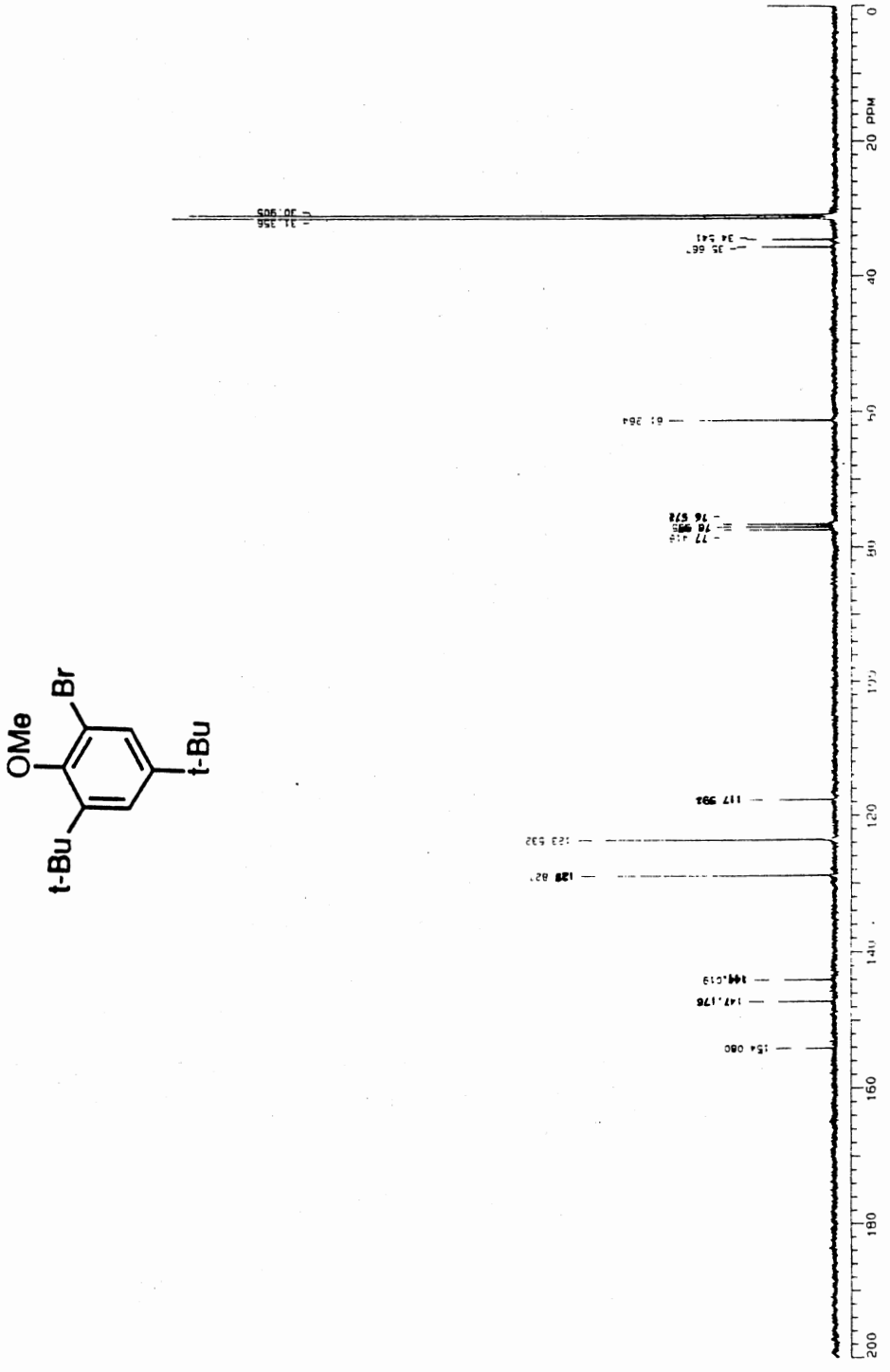
Spectrum 1a. ^{1}H NMR of 2,4-Di-t-butylanisole (**9**).



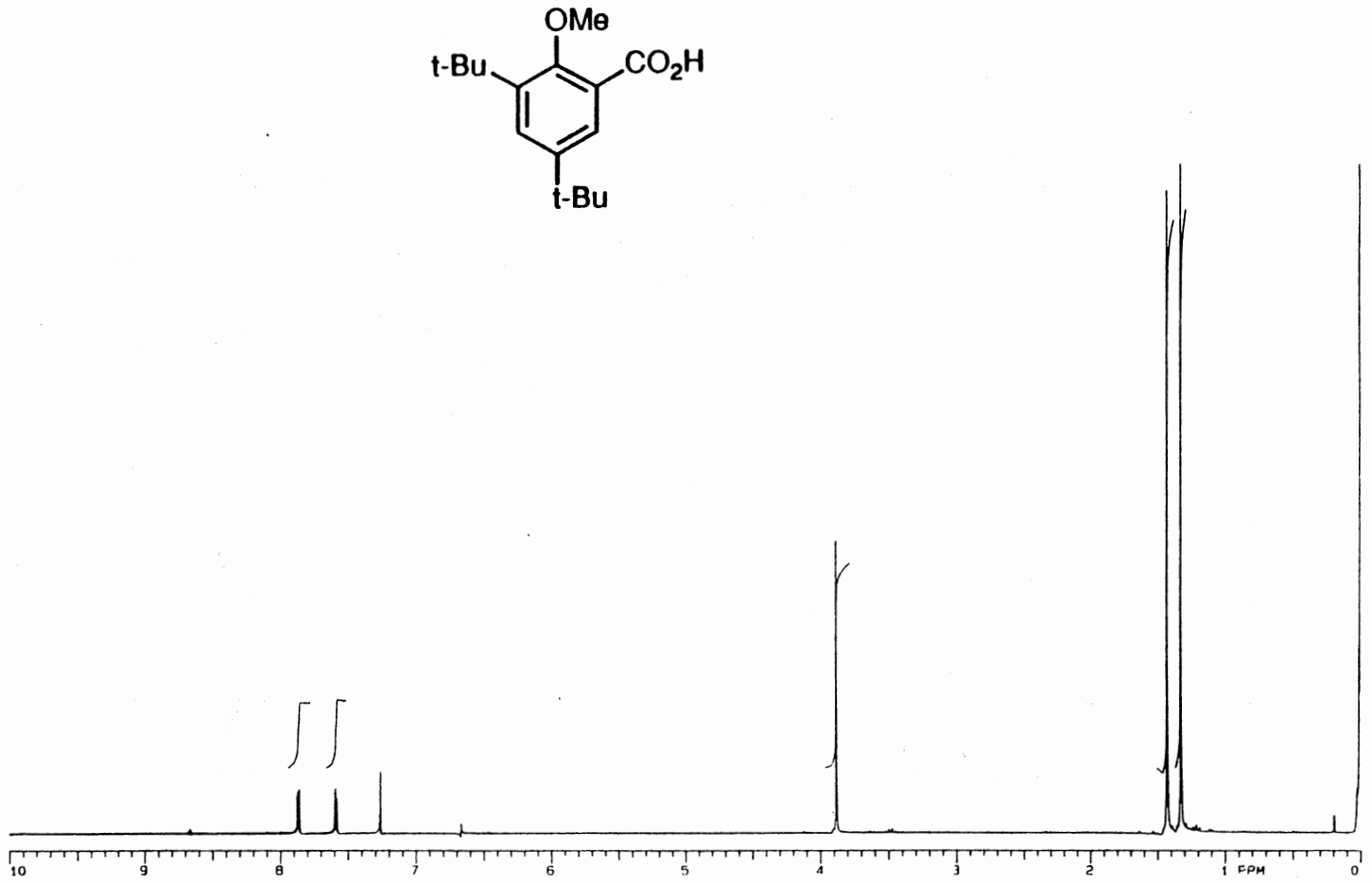
Spectrum 1b. ^{13}C NMR of 2,4-Di-t-butylanisole (**9**).



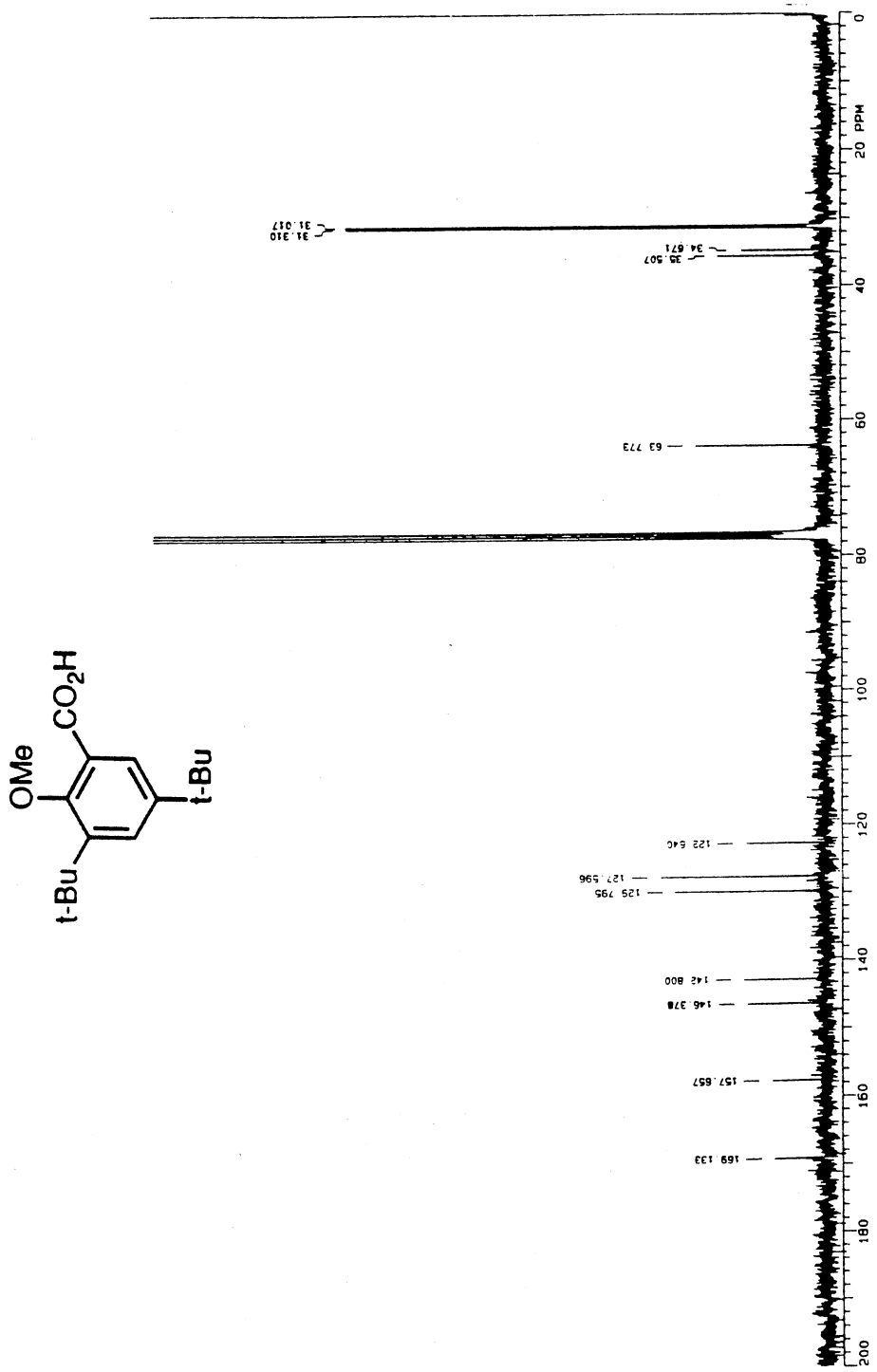
Spectrum 2a. ^{1}H NMR of 2-Bromo-4,6-di-t-butylanisole (**10**).



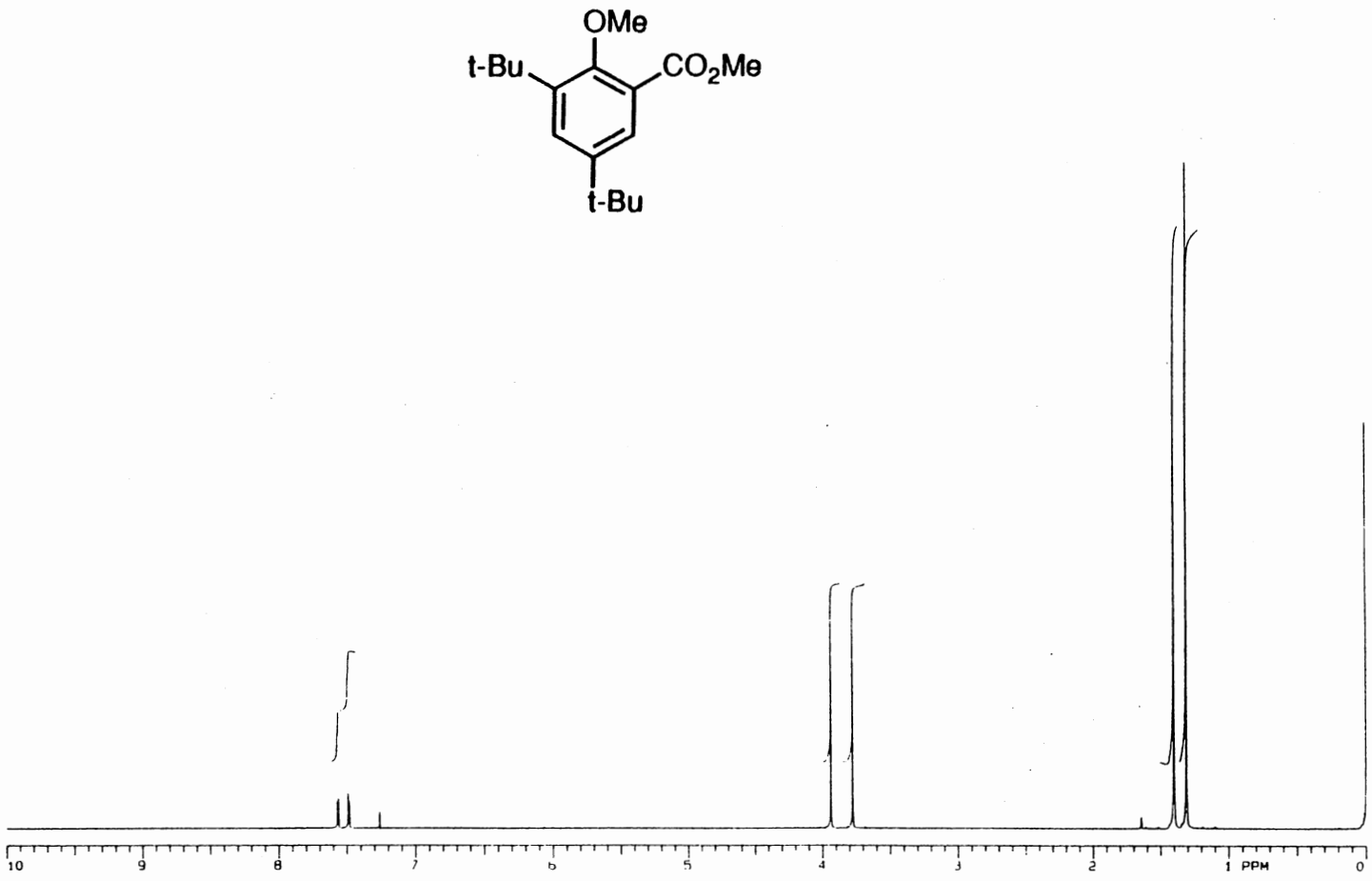
Spectrum 2b. ^{13}C NMR of 2-Bromo-4,6-di-t-butylanisole (**10**).



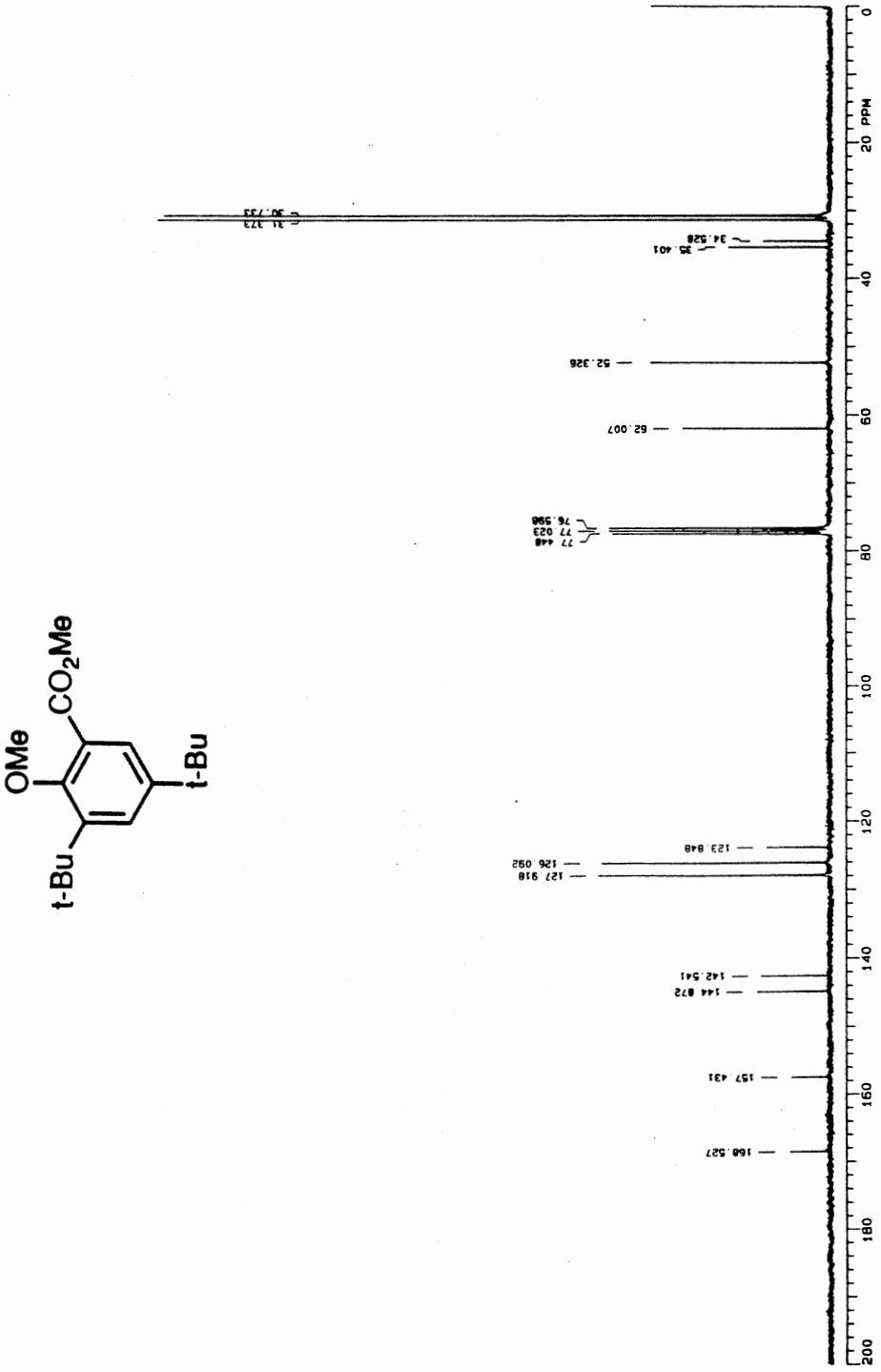
Spectrum 3a. ^1H NMR of 3,5-Di-t-butyl-2-methoxybenzoic acid (**11**).



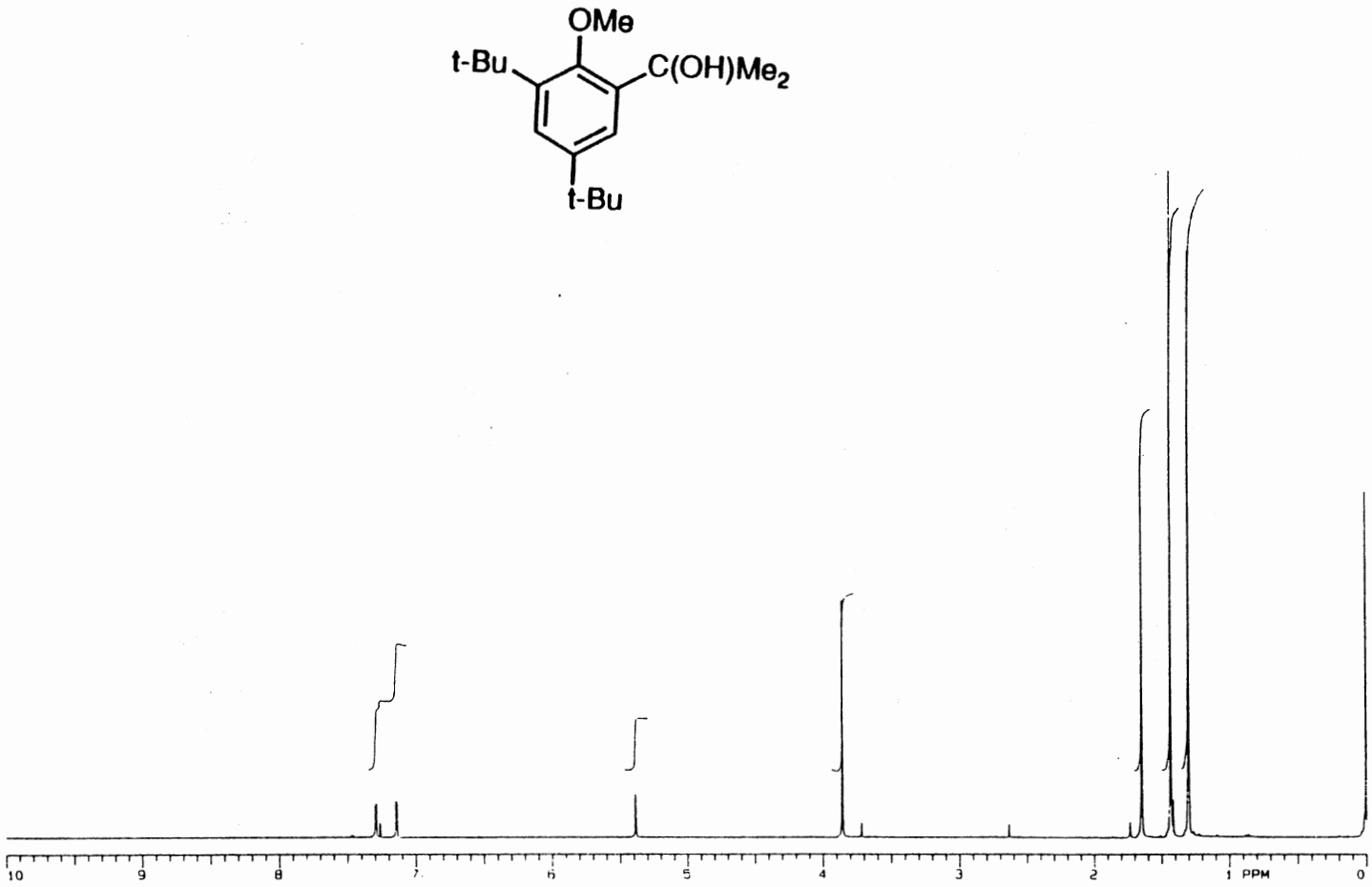
Spectrum 3b. ^{13}C NMR of 3,5-Di-t-butyl-2-methoxybenzoic acid (11).



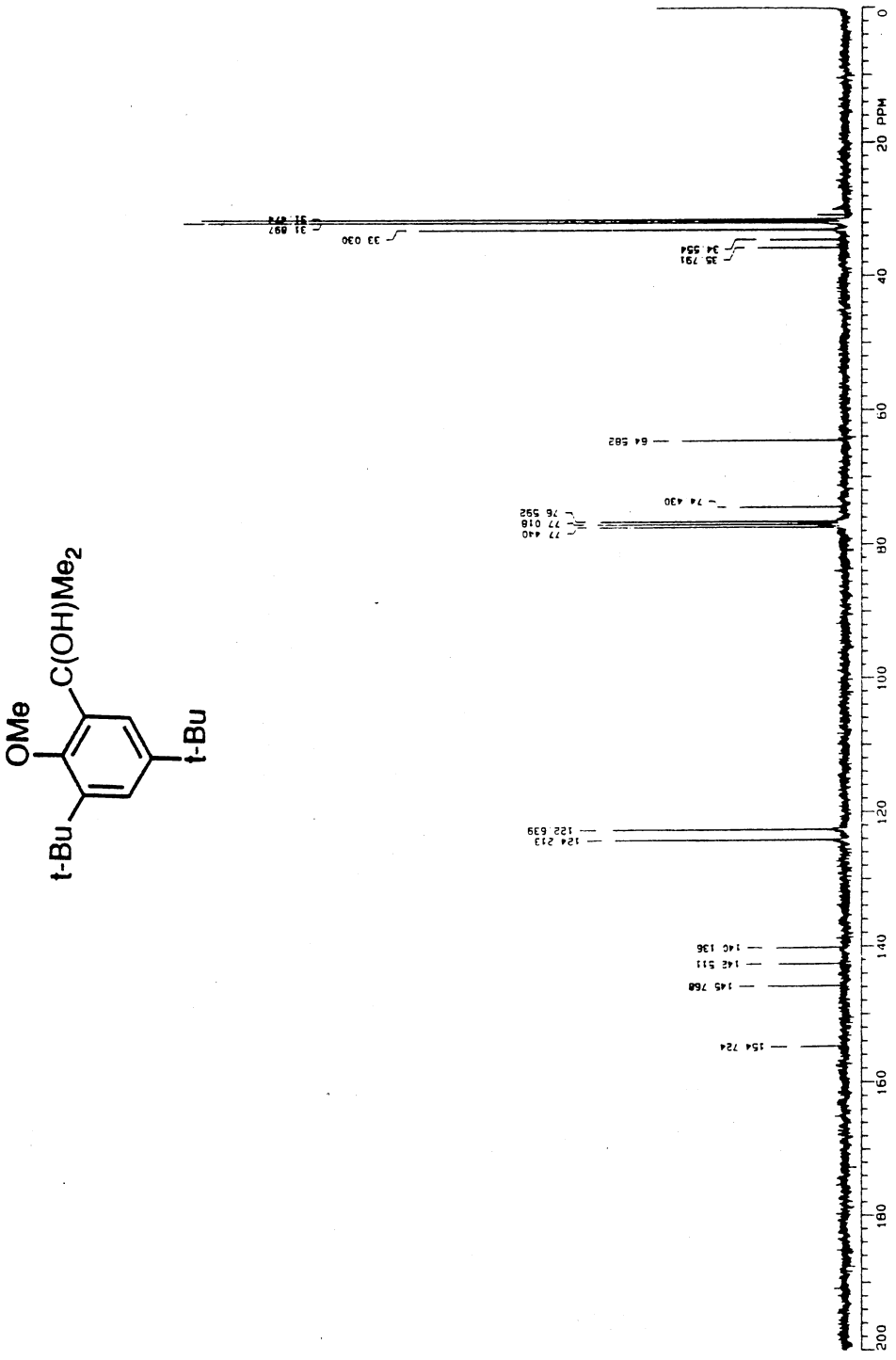
Spectrum 4a. ^{1}H NMR of Methyl 3,5-di-t-butyl-2-methoxybenzoate (**12**).



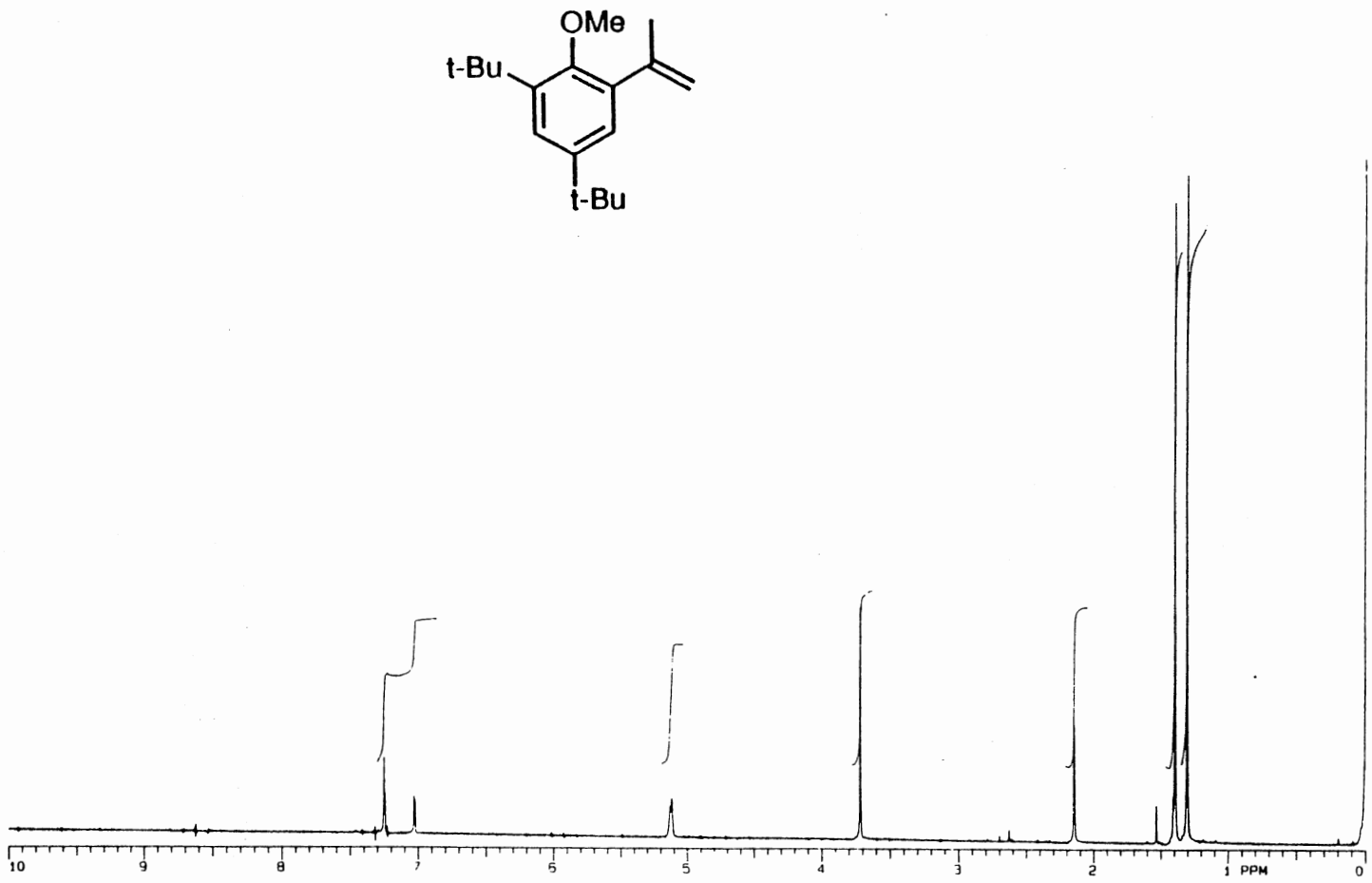
Spectrum 4b. ^{13}C NMR of Methyl 3,5-di-t-butyl-2-methoxybenzoate (12).



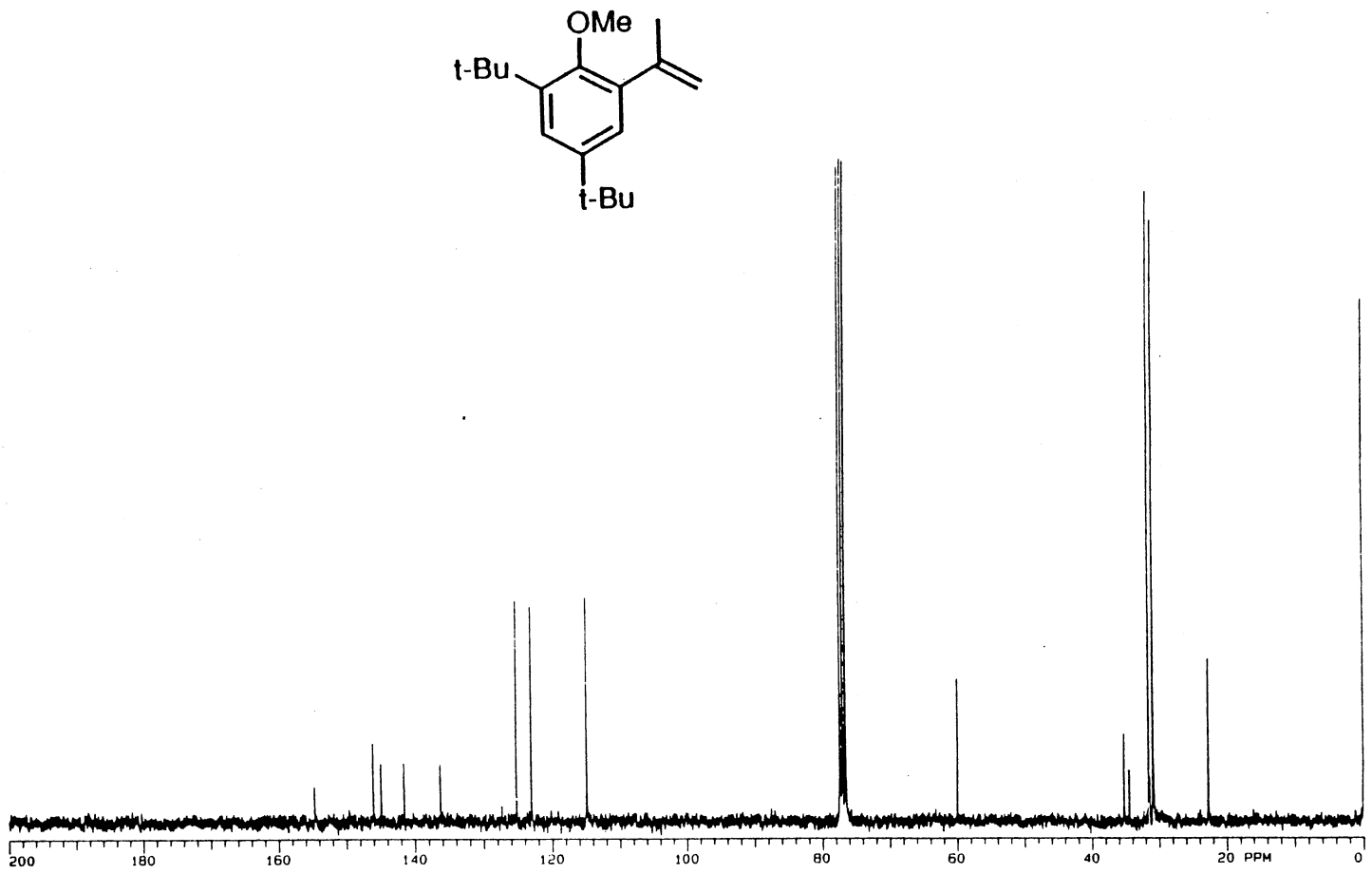
Spectrum 5a. ^{1}H NMR of 2-(3,5-Di-t-butyl-2-methoxyphenyl)-2-propanol (**13**).



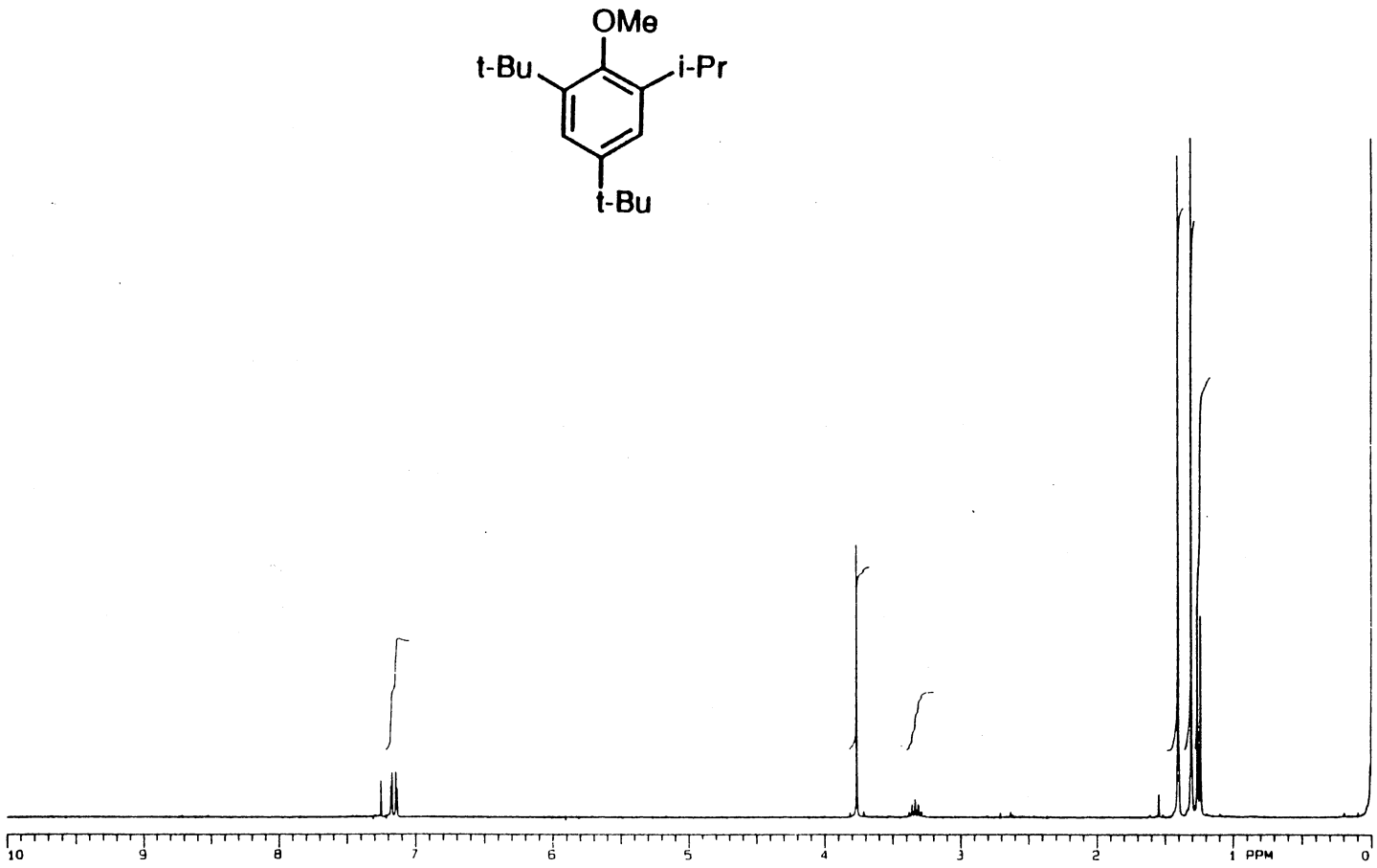
Spectrum 5b. ^{13}C NMR of 2-(3,5-Di-t-butyl-2-methoxyphenyl)-2-propanol (**13**).



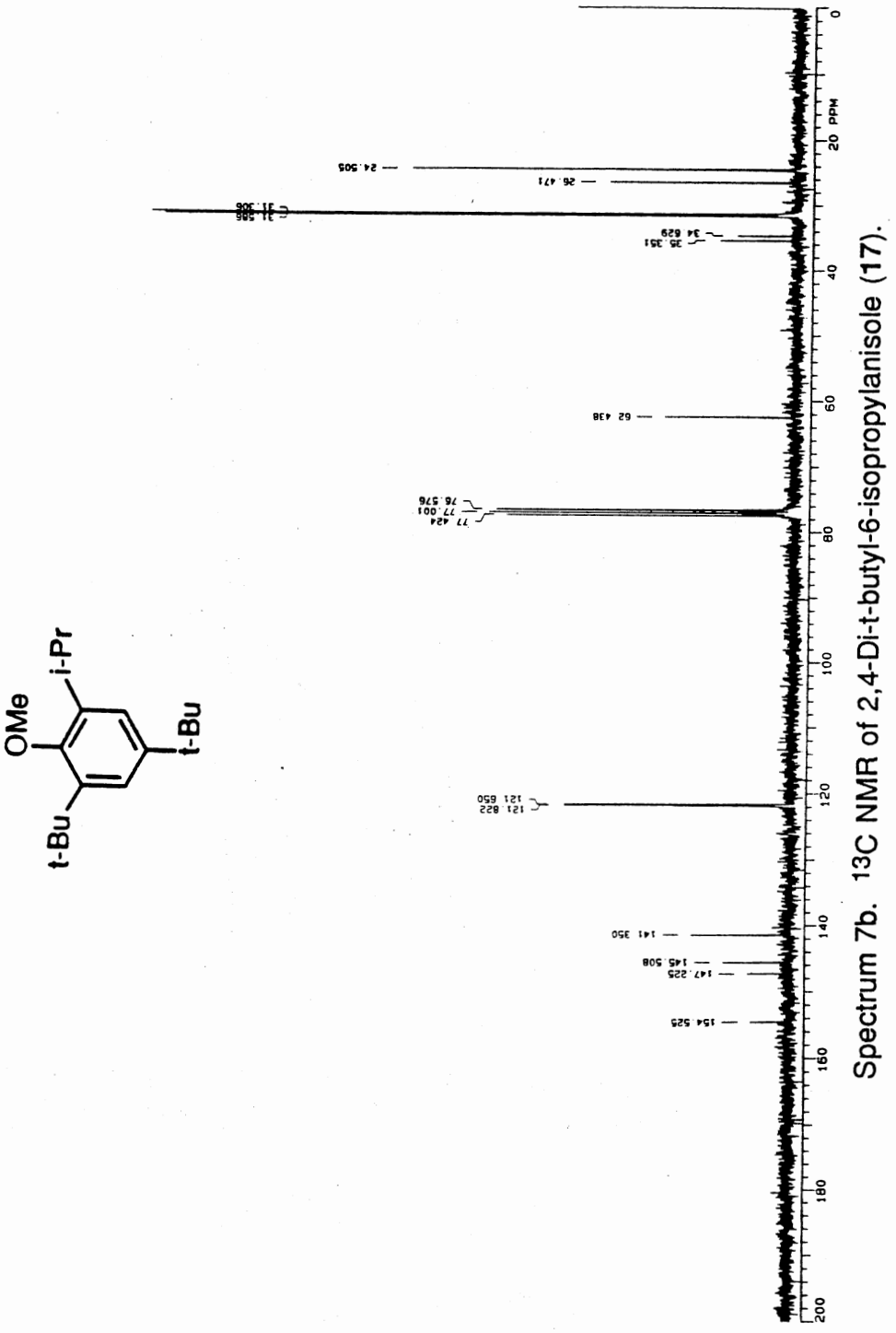
Spectrum 6a. ^{1}H NMR of 2-(3,5-Di-t-butyl-2-methoxyphenyl)propene (**14**).



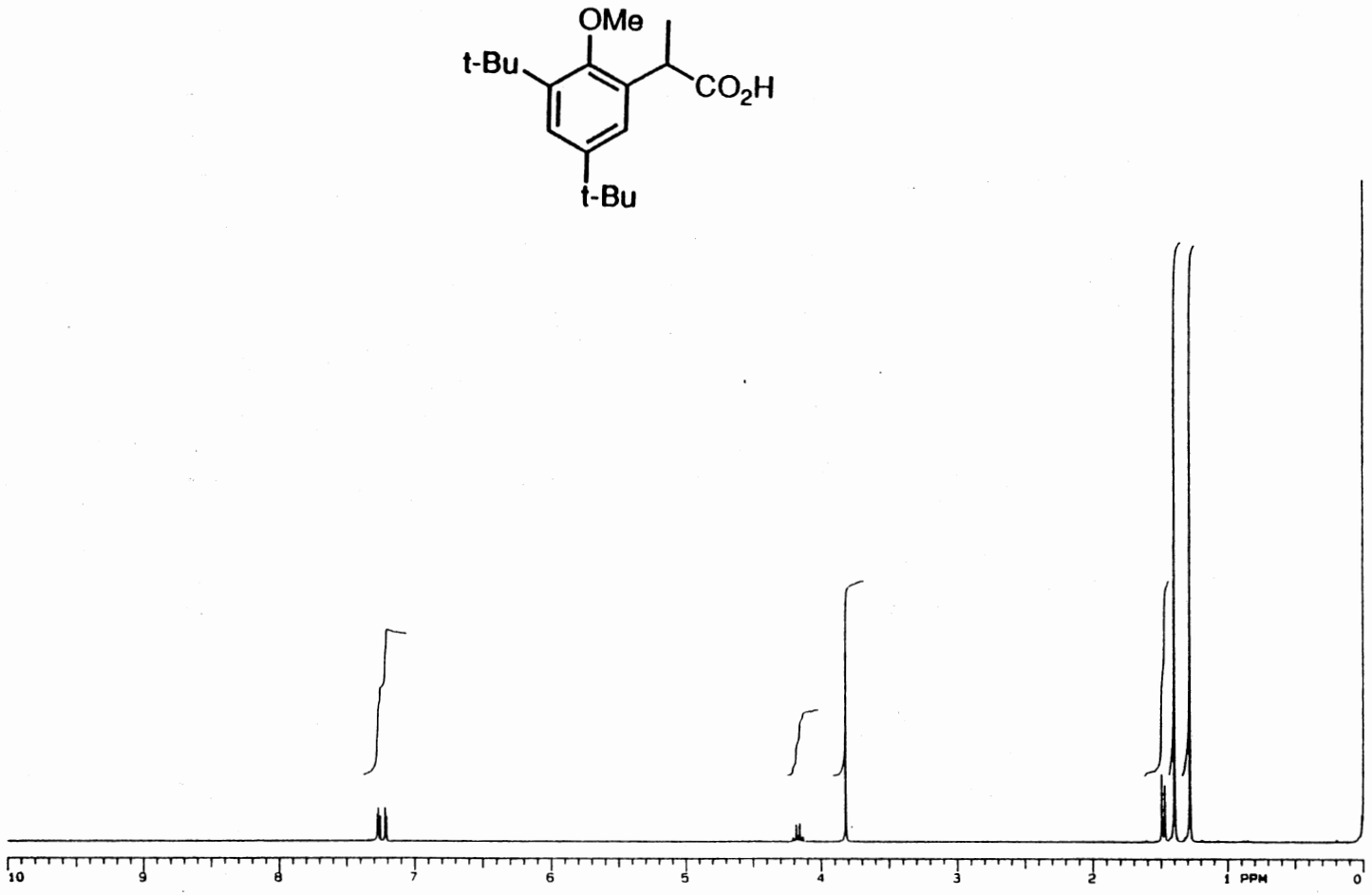
Spectrum 6b. ^{13}C NMR of 2-(3,5-Di-t-butyl-2-methoxyphenyl)propene (**14**).



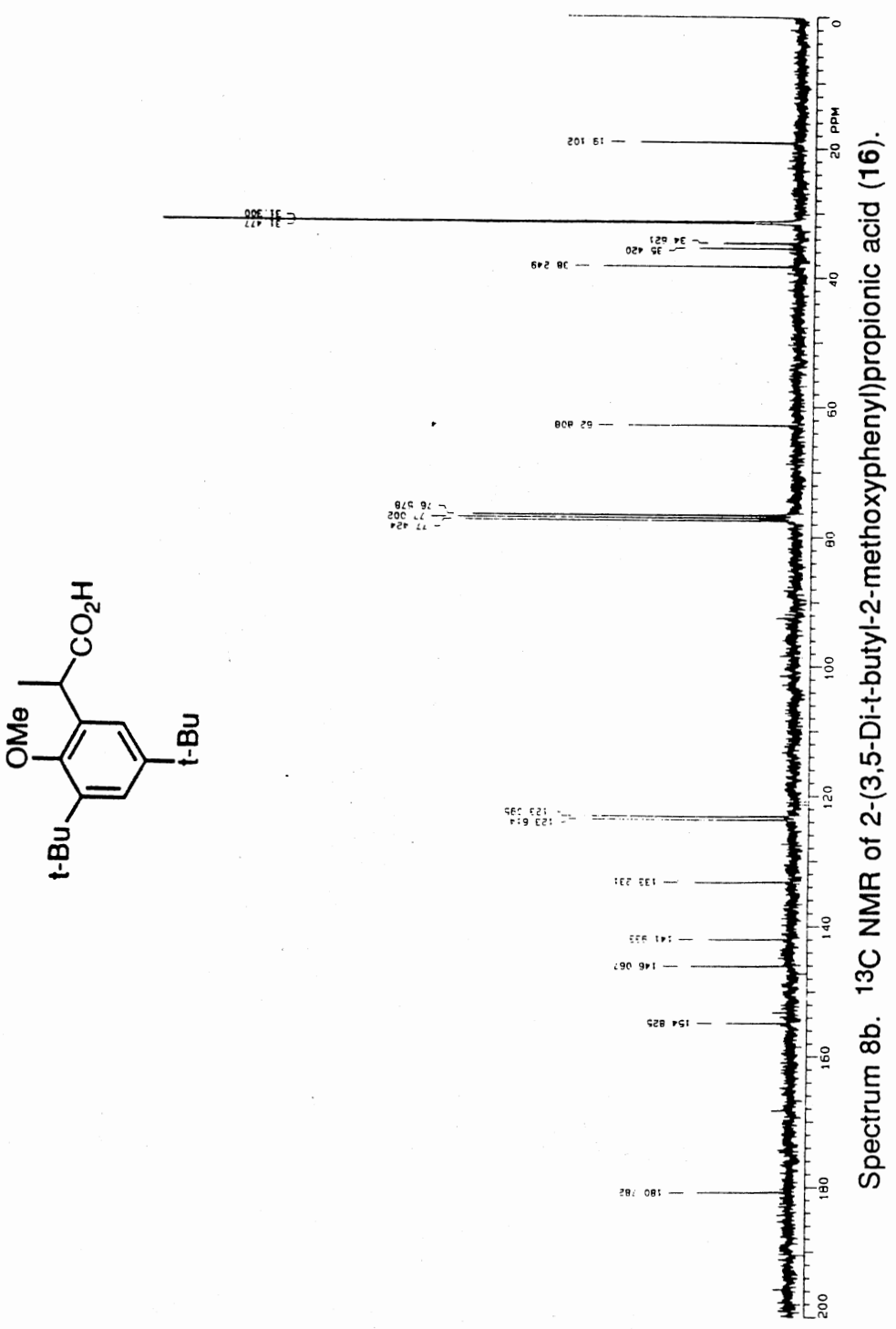
Spectrum 7a. ^{1}H NMR of 2,4-Di-t-butyl-6-isopropylanisole (**17**).



Spectrum 7b. ^{13}C NMR of 2,4-Di-t-butyl-6-isopropylanisole (17).



Spectrum 8a. ^1H NMR of 2-(3,5-Di-t-butyl-2-methoxyphenyl)propionic acid (**16**).



Spectrum 8b. ^{13}C NMR of 2-(3,5-Di-t-butyl-2-methoxyphenyl)propionic acid (**16**).

VITA

Mike Douglas Cagle

Candidate for the Degree of

Master of Science

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