OXIDATIVE SPIROANNULATION OF PHENOLIC SUBSTRATES

A Thesis

Submitted to the Faculty of Graduate Studies

in Partial Fulfilment of the Requirements for the Degree

of Master of Science

by

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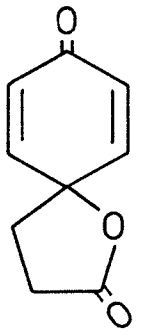
ABSTRACT

The oxidative cyclizations of the following arylalkanoic acids and arylalkanols are described: 3-(3-methoxy-4-hydroxyphenyl)propionic acid, 3-(4-hydroxyphenyl)propionic acid, 3-(3-methoxy-4-hydroxyphenyl)-propanol, 3-(4-hydroxyphenyl)propanol and 2-(3-methoxy-4-hydroxyphenyl)ethanoic acid. The best results are obtained when lead tetraacetate (LTA) and thallium (III) trifluoroacetate (TTFA) are used as the oxidant.

Characterization of the spiroadducts is discussed and the following structures are assigned to the products obtained:



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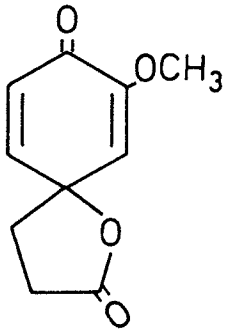

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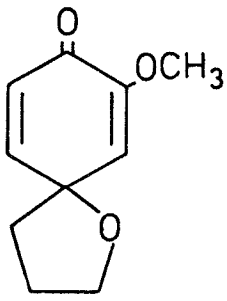

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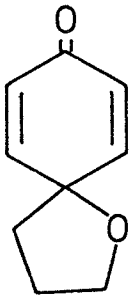

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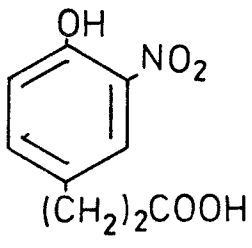

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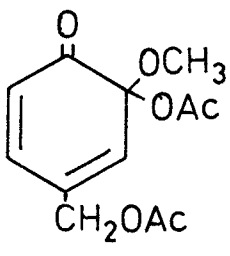

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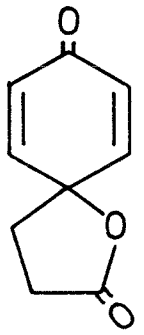
1. INTRODUCTION

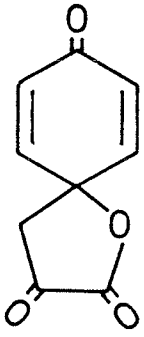
1.0 INTRODUCTION

In the past twenty years, a lot of work involving spiro-compounds has been reported. However, it seems that the formation of simple spirodienone lactones has not been a major field of interest. Most of the time, these compounds were reported in articles involving, the study of other compounds (for example; the conversion of tyrosine into homogentisic acid), the study of other reactions or were synthesized to help elucidate mechanisms, as shown in the following review.

In a related study, Davies and coworkers [1] wanted to study the rearrangement of spirolactone 1 expecting that it would be similar to the rearrangement of spirolactone 2, which was thought to be involved in the conversion of tyrosine into homogentisic acid.

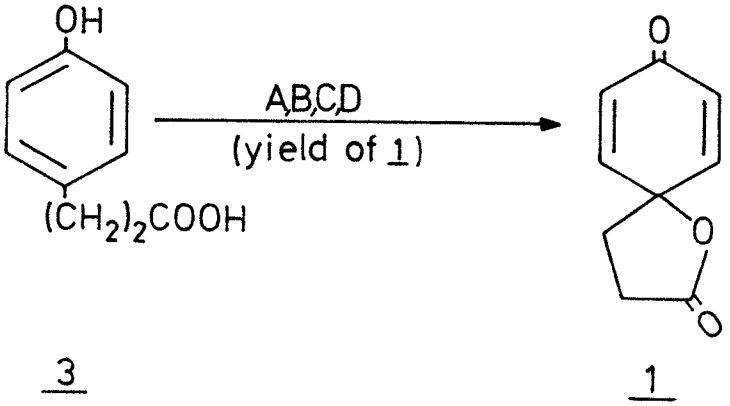


1



2

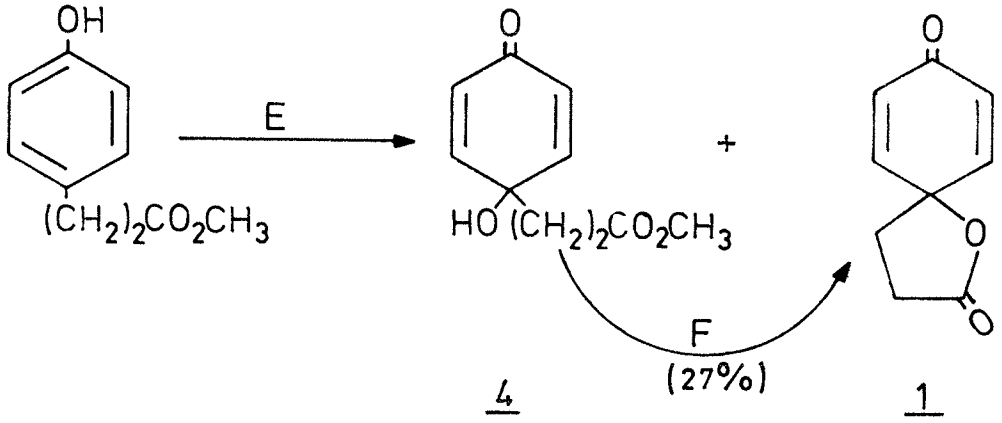
They prepared 1 from phloretic acid (3) using four different methods, but none of them gave very good results.



3 1

A) peracetic acid (2%); B) electrolytic oxidation (13%)
C) AcOH, 30% H_2O_2 (12%); $Pb(OAc)_4$, methanol (7%)

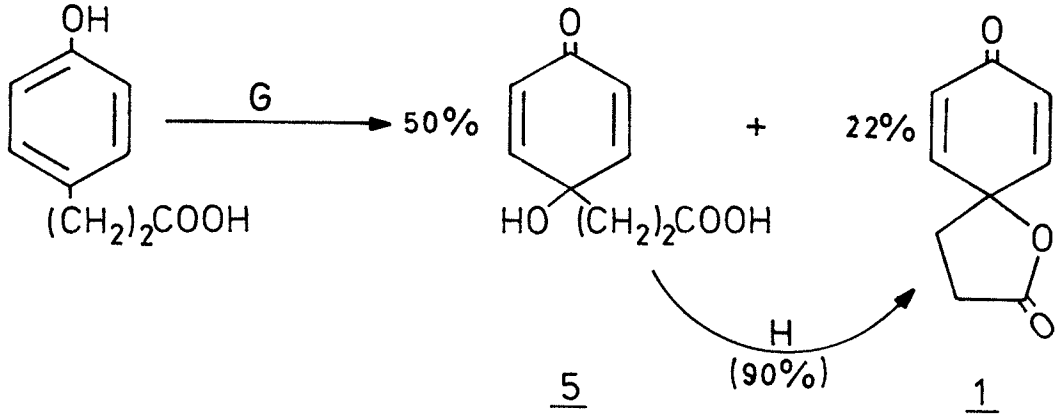
Other studies related to homogentisic acid have also involved the production of lactone 1. Schweizer and coworkers [2], in an attempt to synthesize a proposed intermediate in the metabolic transformation of p-hydroxyphenylpyruvic acid into homogentisic acid, obtained the spirolactone 1 and the p-quinol 4, which was further transformed into 1 when treated with acid.



4 1

E) Pb(IV) phosphate, H_2O/isopropanol; F) heat, AcOH/HCl

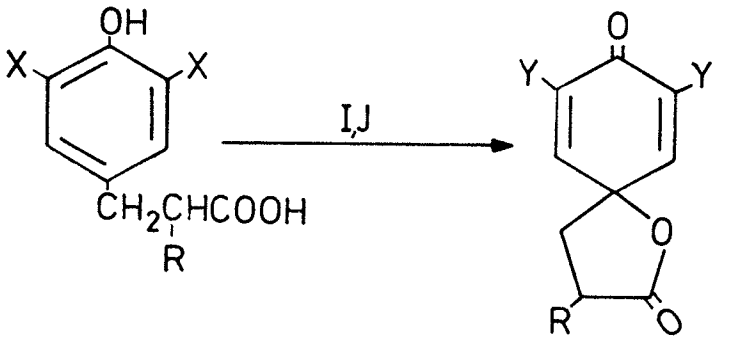
In a similar study, Saito and coworkers [3,4] oxidized a variety of phenols, in the hope that this might be of help in the elucidation of the mechanism of the enzymatic reaction mentioned above, and obtained the spirolactone 1 and the p-quinol 5.



G) Photooxidation using 500-W tungsten bromine lamp (Ushio JPD-C) and Rose Bengal as sensitizer
H) DDC (N,N'-dicyclohexylcarbodiimide)

Such spirodienone lactones have also been found in studies involving the oxidative cleavage of tyrosyl-peptide bonds. Schmir et al. [5] studied the action of N-Bromo-succinimide (NBS) on derivatives of tyrosine and simpler phenols and obtained the spirodienone lactones 6.

Similar results were obtained by Cohen et al. [6], when they oxidized 3,5-diiodophloretic acid (7a) and its derivatives, using a weaker oxidant, N-Chlorosuccinimide (NCS).



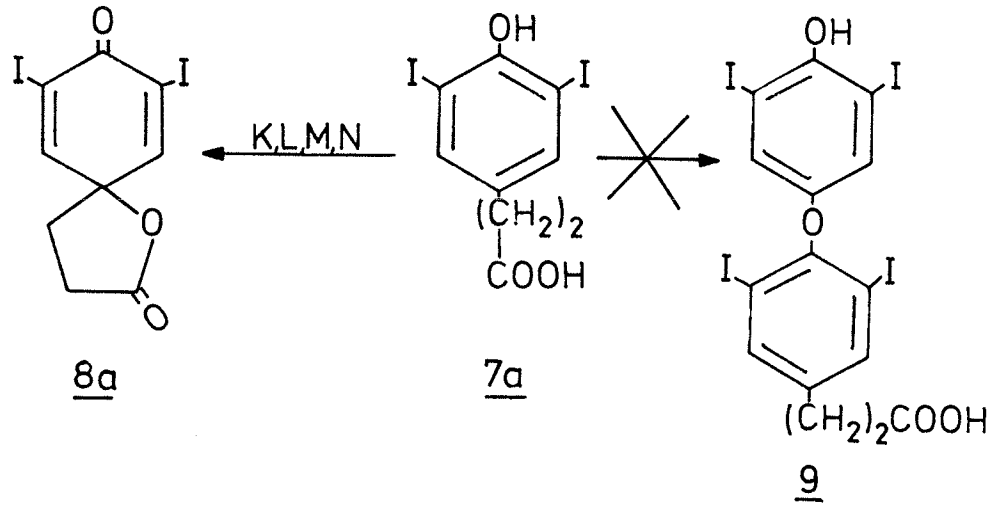
7* (X=H)
7 (X=I)

6 (Y=Br)
8 (Y=I)

a; R=H b; R=NHCOC$_6$H$_5$ c; R=NHCOOC$_6$H$_5$

I) NBS, CH$_3$CN, (pH=4.6); J) NCS, CH$_3$CN, (pH=4.5)

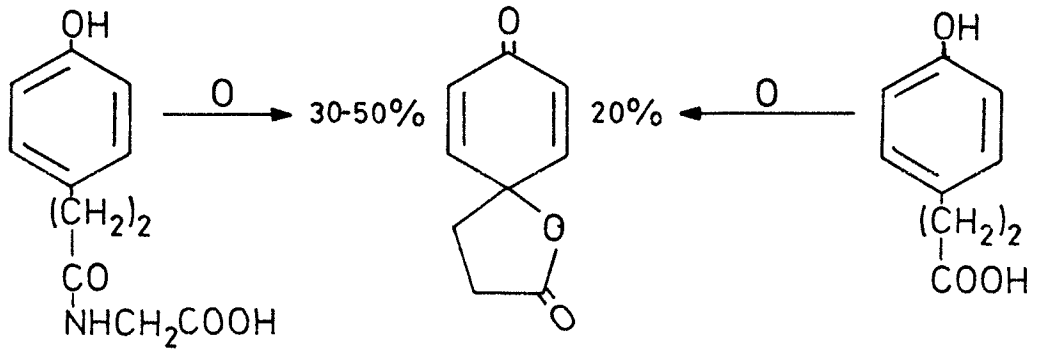
Matsuura et al. [7] also reported the formation of 8a. They wanted to elucidate the mechanism by which 3,5-diiodophloretic acid (7a) is autoxidized to 3,5,3',5'-tetraiodothyropropionic acid (9). Unfortunately for them, they obtained the diiodospirolactone 8a instead of the desired product 9.



8a 7a 9

K) Ammonium persulfate L) NBS M) Sodium hypochlorate-30% H_2O_2 N) Erythrosin-phosphate buffer (pH=7.6), 500W tungsten lamp, O_2

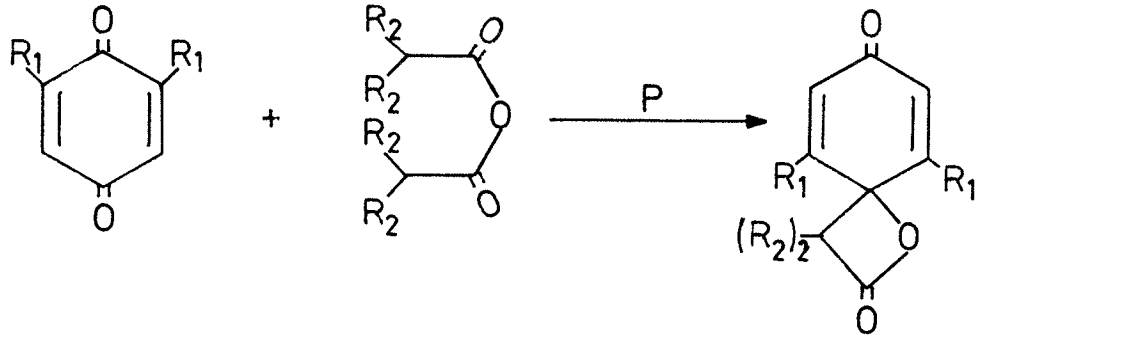
In other studies [8,9] related to the tyrosyl-peptide bond cleavage, the spirocompound 1 was obtained by electrolytic oxidation of phloretic acid (3) or phloretylglycine (10), with production of glycine in the latter case.



10 1 3

O) Electrolysis performed at 25°C. Current flow of 1-2 ma. per square cm. at a potential of 50 volts

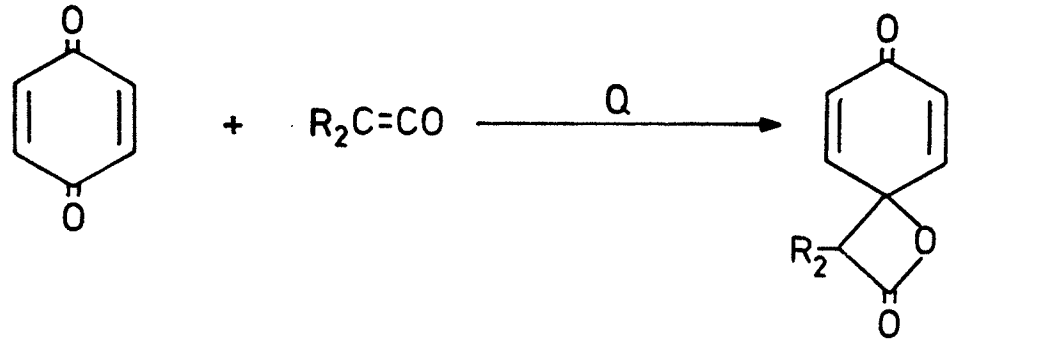
Only two examples of the formation of spirolactones, having a 4-membered lactone ring, are reported in the literature, but they do not involve oxidative processes. In the first example, Lounasmaa [10,11] synthesized the lactone 11, thinking that this compound could be an intermediate in the Perkin reaction with quinones.



11 (R_1=OCH_3; R_2=CH_3)

P) propionic anhydride, sodium propionate, 95°C, 2h.

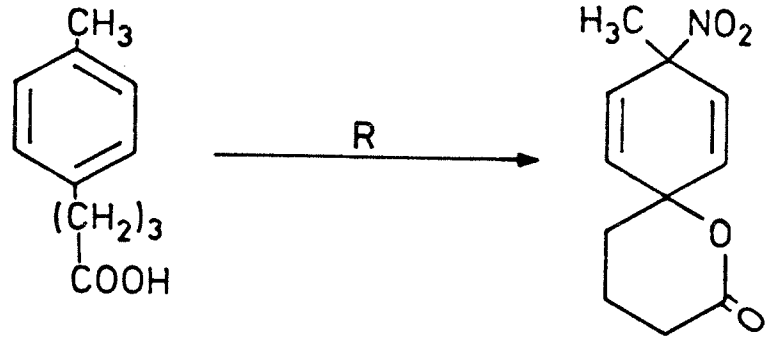
Chitwood et al. [12] also synthesized this type of spiro-compound from p-benzoquinone and diphenyl- or dimethyl-ketene. They obtained spirolactones 12 and 13.



12 ($R=CH_3$)
13 ($R=C_6H_5$)

Q) THF, 0°C, N_2

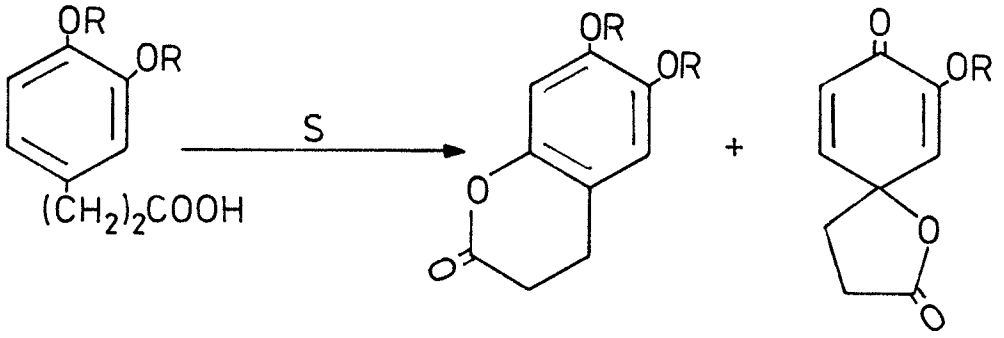
One example of a spirolactone, having a 6-membered lactone ring, is reported by Fischer and coworkers [13]. They synthesized the spirolactone 14 on nitration of 4-(p-tolyl)butyric acid.



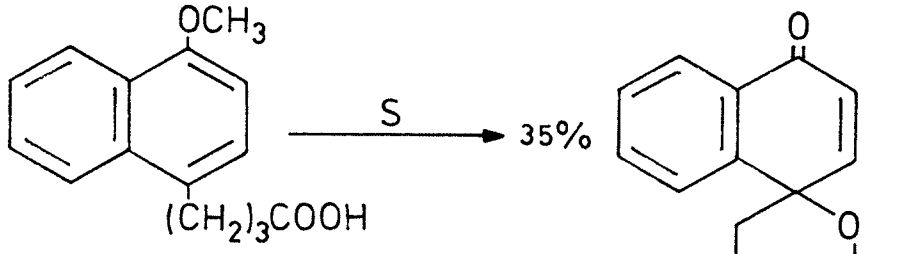
14

R) HNO_3, acetic anhydride, -78°C

The most extensive work done on the formation of these spirolactones has been reported by Taylor et al. [14,15]. They studied the oxidation of arylalkanoic acids and arylalkanols by thallium (III) trifluoroacetate (TTFA), and proposed a mechanism for these transformations.



15 (R=CH_3) 16 (R=CH_3)
17 (R=C_2H_5) 18 (R=C_2H_5)



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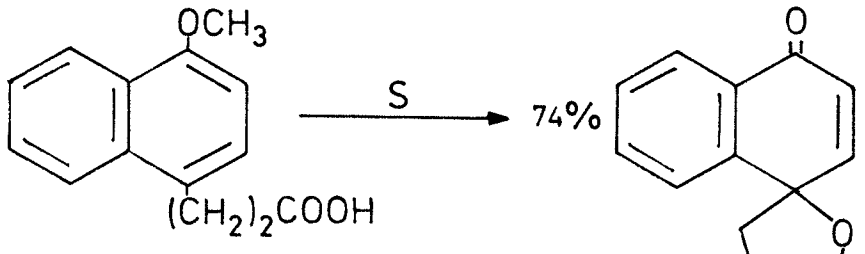
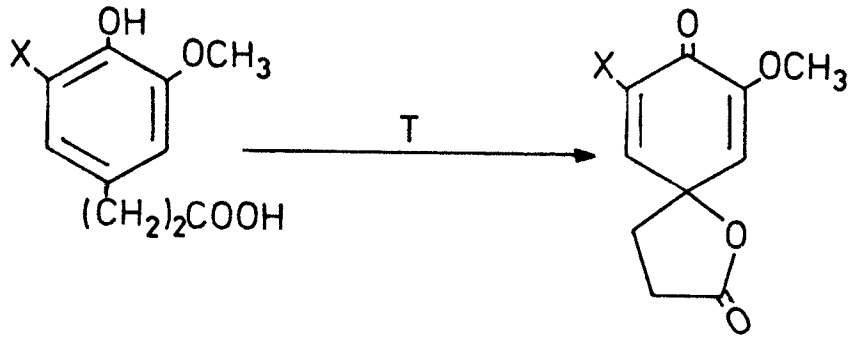


20

S) TTFA, trifluoroacetic acid, CH_2Cl_2, BF_3/Et_2O, $-20^{\circ}C$, N_2

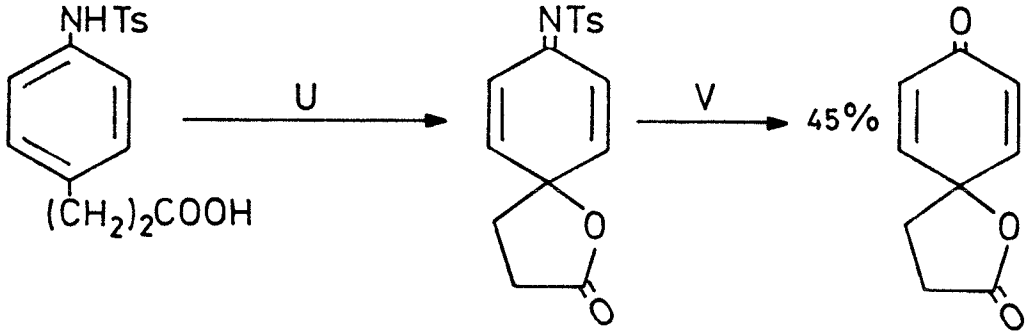
More recently, Nishiyama et al. [16] reported the formation of spirolactones 16 and 17, which were obtained in good yield by the anodic oxidation of phenolic substrates.



16 (X=H)
17 (X=OCH_3)

T) MeOH, $LiClO_4$, (+800 mV vs SCE; 56-20 mA)

Finally, Coutts and coworkers [17], who wanted to use spirolactone 1 in another investigation*, reported a new method for its preparation, and obtained 1 in good yield.



1

U) Electrochemical oxidation; 1.4v vs SCE, CH_3CN (65%)
V) neutral alumina (45% overall yield)
*Note: Unfortunately, it seems that the results of this other investigation have not been published yet.

As can be seen from this brief review, the formation of these spirodienone lactones has not been the major factor in these studies. Even in the study done by Taylor [14,15], the major interest was not to synthesize the spirolactones, but rather to see the oxidative effect of TTFA on the substrates used. In terms of yield, the most successful work reported are from Nishiyama [16] and Coutts [17], who synthesized the spirolactones 16 and 1 in 51% and 45% yield respectively.

It then becomes obvious that there is a lack of good methods for the synthesis of simple spirolactones such as 1 and 16. Having this in mind, our goals were, firstly, to find a simple way of making these compounds, so one could study their reactivity as dienophiles in Diels-Alder studies and possibly, one could use them as starting material to prepare larger molecules. Secondly, we wanted to use the methods developed to synthesize spiroethers, analog to the spirolactones, and also to synthesize spirolactones having only a 4-membered lactone ring.

In order to investigate the scope of the spirolactonization reaction, the three 4-hydroxyphenyl alkanoic acids 21, 3 and 27 were treated with the oxidizing agents shown in table 1 (see appendix 2).

The 4-hydroxyphenyl alkanols 23 and 24 were treated with the same oxidizing agents to determine if a reaction, analogous to the spirolactonization, would lead to spiroethers.

2. DISCUSSION

2. DISCUSSION

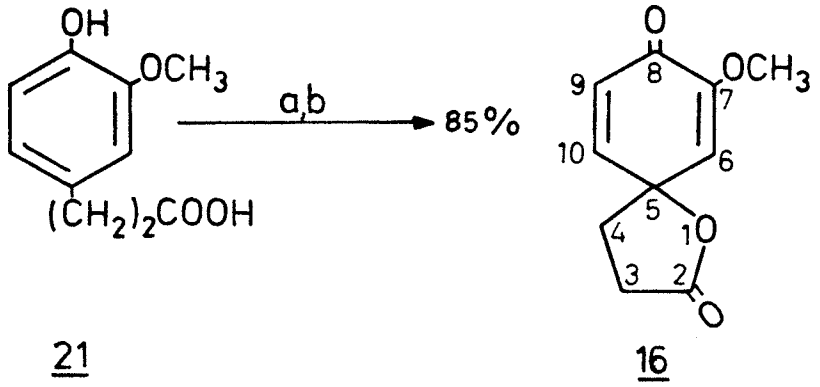
2.1 Methoxyspirolactone 16:

Many oxidizing agents were used for the preparation of 16, but only lead tetraacetate (LTA) and thallium (III) trifluoroacetate (TTFA) gave good results (Table 1).

In the first place, a solution of the arylalkanoic acid 21 (obtained by hydrogenation of 4-hydroxy-3-methoxy-cinnamic acid, as described in the experimental section) in methylene chloride was treated with LTA and afforded 16 in 85% yield. The same percentage yield was obtained when the arylalkanoic acid was treated with TTFA in acetonitrile. Both reactions were performed at room temperature and were followed by tlc. The reactions were stopped when the tlc showed complete disappearance of the starting material. If necessary (appearance on the plate of the starting material spot), more oxidant (LTA or TTFA) was added. It must be noted that only 1.1 equivalents of TTFA was required, for the preparation of 16 or 23 (see 2.3), when the source of TTFA was a fresly opened bottle. However, more TTFA was required (up to 2.5 equivalents) when a previously opened bottle of TTFA was used. This is probably due to the decomposition of TTFA, which could occur when the compound is not well protected from water and/or light [18,19].

The workup procedure afforded the spirodienone lactone 16, which was recrystallized from benzene. Establishment of the structure was done by analysis of ^{1}H-NMR, ^{13}C-NMR,

IR and mass spectra.



21 16

a) LTA, CH_2Cl_2, 25°C; b) TTFA, CH_3CN, 25°C

2.1.1 ^{1}H-NMR

The ^{1}H-NMR spectroscopy was the most useful tool for determination of the structure of our products. The ^{1}H-NMR spectrum (spectrum 1) of 16 exhibits absorbances in four different regions of the spectrum indicating the presence of four different types of protons in the molecule.

In the downfield region there were three signals, a doublet of doublets at 6.85 ppm and two doublets at 6.27 and 5.71 ppm. Each of them integrates for one proton. Hence, according to the integrations and the chemical shifts [18a], they are the three protons on the dienone ring. The first proton, at 6.85 ppm, is coupled to two other protons, which are non-equivalent, since it is represented by a doublet of doublets.

In an aromatic ring, the coupling effect that a proton can have is not limited to the hydrogen on the adjacent

carbon atom. It can often affect a proton meta or para to itself. The coupling constants observed are usually characteristic of the position of each proton relative to the others [19a].

If one assumes that the protons of the dienone ring of 16 are similar to aromatic protons, then the coupling constants should also be characteristic of the position of each proton relative to the others. Therefore, the large coupling in this pattern (J=10 Hz) is characteristic of the coupling of two protons ortho to each other. The small coupling (J=2.8 Hz), represents the coupling of two protons meta to each other. From this, it is obvious that the proton represented by the doublet of doublets has to be H_{10}, since it is the only one which can be coupled with protons ortho and meta from its position. Thus, the large doublet (J=10 Hz) at 6.27 ppm represents H_9 and the small doublet (J=2.8 Hz) at 5.71 ppm represents H_6.

The second signal, at 3.71 ppm, is simply a singlet. It integrates for the three protons of the methoxy group on C_7 of the dienone ring.

The last two signals, at 2.79 and 2.41 ppm, are two triplets in which each peak is split again into a doublet. The signal at 2.79 ppm represents the protons on C_3, which are downfield from those on C_4 (2.41 ppm), because of the adjacent lactone carbonyl.

It seems that the methoxy group, which makes the molecule unsymmetrical, causes the two protons on C_3 as well as

those on C_4 to be chemically different. However, this effect is probably not very important since the geminal coupling, which would be large [22a], is not observed. Therefore, since the protons are different, this system cannot be an A_2X_2 system, but is most likely and AA'XX' system. This phenomenon of obtaining apparent triplets for an AA'XX' system has been reported before [22b, 23]. In this system (Figure 1), A is coupled to X and also to X', and A' is coupled to X' and also to X.

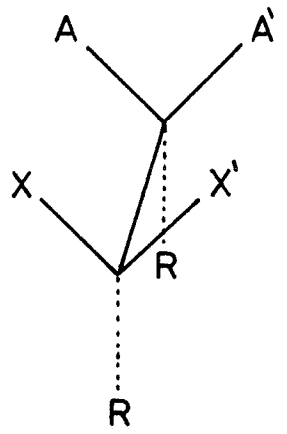


Figure 1.

Here, the coupling constants will depend on the angle (ϕ) betweem the protons and can be estimated by the Karplus correlation [22c]. Hence, J_{AX} and $J_{A'X'}$ will be large (J≈6-8 Hz) since the angle (ϕ) is small, while $J_{AX'}$ and $J_{A'X}$ will be smaller since the angle (ϕ) is larger (Figure 2).

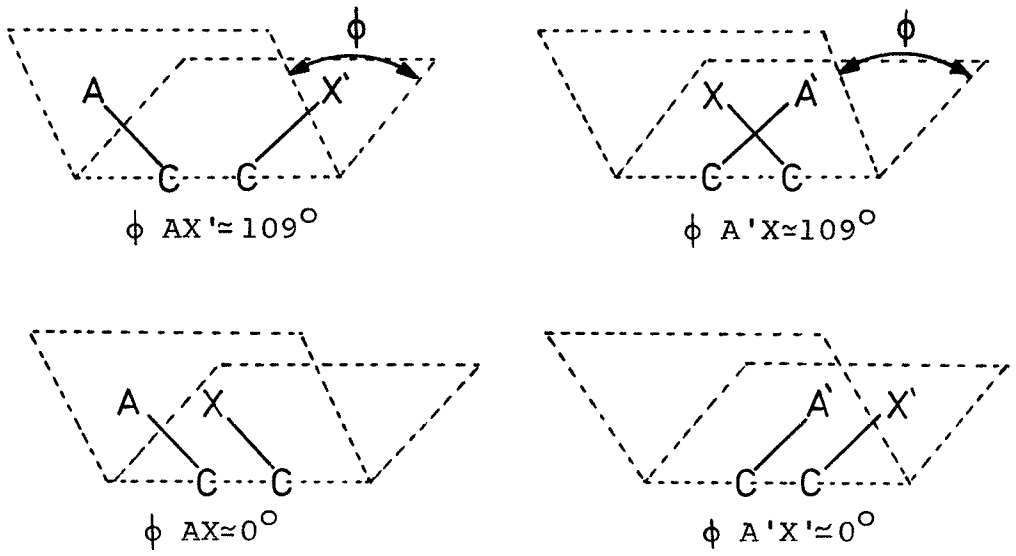


Figure 2.

This is indeed what was observed, a large coupling (J≃7 Hz) and a small one (J≃1 Hz). The fact that triplets are observed can be rationalized as follows. The cis protons are coupled to each other to give two pairs of large doublets, close enough that they might be overlapping and are observed as triplets. The trans protons are coupled to each other and show small doublets for each peak of the triplets (Figure 3).

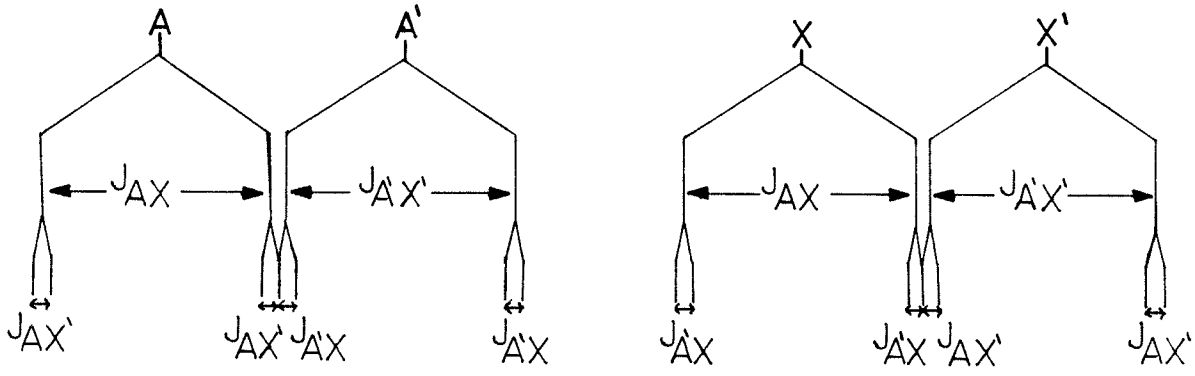


Figure 3.

However, the AA'XX' system is usually very complex. Therefore, this should not be considered as an extensive analysis but rather a possible explanation. Here, it must be mentioned that the data obtained from the ^{1}H-NMR spectrum, coupling constants and chemical shifts, are all in agreement with those reported by Taylor et al. [14] in 1981 and by Nishiyama [16] in 1983.

The extra peaks observed in the ^{1}H-NMR spectrum of 16 are due to impurities in the sample. The first one at 7.36 ppm is probably due to trace of benzene, which was used for recrystallization, while the second one at 7.25 ppm is due to trace of chloroform present in $CDCl_3$ used to prepare the sample. The small peak at 3.66 ppm probably represents the protons of a methoxy group, which will be part of another molecule present as an impurity. The last one at 1.60 ppm is due to water [24].

2.1.2 ^{13}C-NMR

Carbon-13 NMR is also a very useful tool to elucidate the structures of our products. It is usually very straightforward to distinguish between carbonyl carbons and other carbons, because of their chemical shifts. Carbonyls show peaks in the region of 160 to 220 ppm, while other types of carbon show peaks up to about 150 ppm, in the case of alkene carbons for example [20b]. The intensity of carbonyl peaks is also very characteristic. They are smaller, because they have no attached hydrogens [20c]. Therefore, in the case of

16, the values at 179.6 and 175.2 ppm obviously represent the carbonyl groups in the molecule. Since any functional group that introduces more electron density on the carbonyl carbon will tend to cause an upfield shift [20d], it was then assumed that C_2, which is bound to an oxygen atom in the lactone ring, would be upfield from C_8, the latter being bound to two alkene carbons. Hence, the values mentioned earlier represent C_8 and C_2 respectively.

The alkane carbons of the molecule are also very easy to assign. They are usually found in the region of 0-50 ppm [20b]. There are two alkane carbons in the lactone ring of 16 (C_3 and C_4), which have chemical shift values of 33.3 and 28.3 ppm. Because C_3 is adjacent to a carbonyl group, the electron density on C_3 is decreased [20b], therefore it is shifted downfield from C_4. It has the greater chemical shift value (33.3 ppm) of these two carbons. The methoxy carbon is at 55.2 ppm, downfield from C_3 and C_4. This due to the electron withdrawing effect of the oxygen, causing the electron density around the methoxy carbon to be less. As a result, a downfield shift is observed.

The last alkane carbon in this molecule is C_5. It is a quaternary carbon, therefore, it will be found downfield from other alkane carbons and also its peak will be less intense, since it has no attached hydrogens. C_5 is thus at 80.9 ppm.

This leaves us with the alkene carbons of the dienone ring (C_6, C_7, C_9 and C_{10}). Of these four, the

easiest one to assign is C_7. The intensity of the peak will be small, for the same reason as mentioned in the case of C_5. Also because it has an attached oxygen atom, it is shifted downfield to 151.0 ppm.

The other three carbons on the dienone ring are influenced by the carbonyl group. Let's first consider C_9 and C_{10}. Because of the carbonyl C-O bond polarization, there is a delocalization of the electrons of the double bond causing the electron density to be less on C_{10} than on C_9 [20d]. As a result, there will be an upfield shift for C_9 and a downfield shift for C_{10}. This is also true for C_6. Therefore, C_6 should be shifted downfield. However, the presence of the methoxy group has to be taken into consideration. Here, the methoxy group is attached to an alkene carbon (C_7), giving to the molecule the resonance structures A and B (Figure 4).

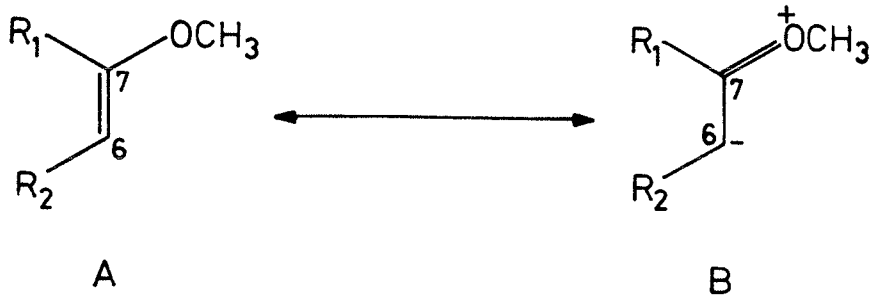


Figure 4.

As can be seen, for one of these structures (B) the electron density on C_6 is increased which will result in an upfield shift. From this, it is very difficult to say which one of C_6 or C_9 is at higher field. Since C_{10} is affected by the carbonyl, shifting it downfield, it was expected to find it downfield from C_9 and C_6. Hence, C_{10} is at 145.9 ppm.

In order to assign a chemical shift value to C_9 and C_6, a model was required to compare the chemical shifts. Such a model was found in the work reported by Polonsky and Baskevith [25], where they assigned chemical shifts for several quassinoid terpenic substances (Table 2). From that comparison, the chemical shift value of 128.2 ppm was assigned to C_9 and 112.9 ppm to C_6.

2.1.3 IR spectrum

The IR spectrum of 16 also helps to elucidate the structure of the product obtained by confirming the presence of the carbonyl groups. The OH absorption at 3500 cm^{-1}, which was observed in the IR spectrum of the starting material, has completely disappeared, as well as the broad absorption of the carboxylic acid carbonyl at 1700 cm^{-1}. Instead, the presence of the expected broad C=O absorption of the lactone is observed at higher frequencies (1766 cm^{-1}) [21b]. In addition, the presence of the new conjugated ketone is confirmed from its sharp absorptions at lower frequencies (1676 and 1650 cm^{-1}). Thus, these data,

which were also reported by two other authors [14,16], confirm the presence of two carbonyl groups.

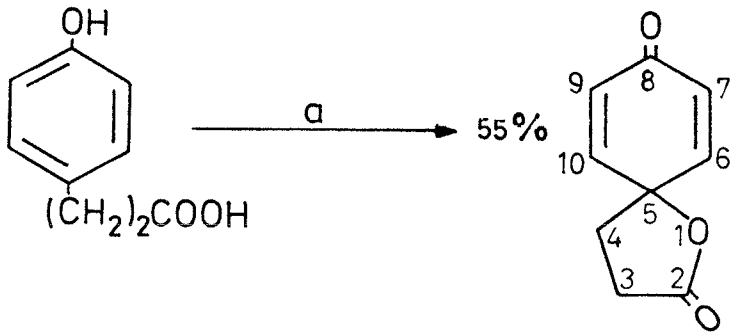
2.1.4 Mass spectrum

The mass spectrum and the elemental analysis of this compound (16) are also in agreement with the structure proposed. In the mass spectrum, the peak which appears at m/e 194 was assigned to the parent ion peak (M^+), since it corresponds to the molecular weight of the molecule. The peak at m/e 166 is due to M^+-28, corresponding to the loss of C_2H_4. This species could then lose a methyl radical to give the peak m/e 151. Loss of CO and C_2H_2 from M^+ gives the peak at m/e 140, while the loss of CH_2CO, also from M^+, gives the peak at m/e 152. This radical ion (m/e 152) could then lose $CH_3O^\bullet$ to give m/e 121.

2.2 Spirolactone 1

As in the case of 16, many oxidizing agents were used for the preparation of 1. Lead tetraacetate and thallium (III) trifluoroacetate, which gave good results in the preparation of 16, were expected to give similar results for 1. It turned out that TTFA was the only oxidant that gave reasonable results in the preparation of 1 (Table 1).

The arylalkanoic acid 3 (obtained from Aldrich), dissolved in acetonitrile, was treated with TTFA and afforded 1 in 55% yield. The reaction was performed at room temperature and was followed by tlc. The workup procedure yielded the desired spirolactone (1), which was sublimed under reduced pressure and the structure established by ^{1}H-NMR, ^{13}C-NMR, IR and mass spectroscopy.



3 1

a) TTFA, acetonitrile, 25°C

As indicated previously (2.1), more oxidant was required when old TTFA was used. However, in the preparation of 1 or 25 (see 2.4), the amount of TTFA required was always raised by a factor of three, compared with the amounts used in the preparation of 16 (see 2.1) or 23 (see 2.3), no matter if the TTFA used was old or fresh.

Thus, it was assumed that part of the TTFA used reacted with the phenol (3 or 24) to give the desired spirocompound (1 or 25), while the rest reacted in a different way with the phenols to give other products. This could also explain the fact that the yields are lower in the preparation of 1 and 25, compared with the results obtained in the preparation of 16 and 23. This second reaction, presumably required more than one equivalent of TTFA. This supposition is supported by the work reported by Taylor [26,27], who needed two equivalents of TTFA to oxidize phenols into quinones.

However, no other product(s) than the spirocompounds (1,25) have been observed by tlc (except in the case of 25 where two extra weak spots were observed on the tlc plate before purification), and no other products than the spirocompounds have been isolated.

2.2.1 ^{1}H-NMR

The first signals of the ^{1}H-NMR spectrum (spectrum 2) show two distorted doublets (J=10.1 Hz) at 6.86 and 6.29 ppm. However, when extended, the spectrum shows a

definite pattern easily identifiable as an AA'BB' system [22b]. Both distorted doublets integrate for two protons and because of their chemical shifts, characteristic of alkene protons [21c], represent the protons of the dienone ring. The first doublet at 6.86 ppm represents H_{10} and H_6, while the second at 6.29 ppm represents H_9 and H_7. The difference in chemical shift is due to the fact that the electron density on C_{10} and C_6 is decreased because of the presence of the carbonyl (see 2.1.1).

The other two signals in the spectrum are at 2.80 and 2.38 ppm. They are triplets and both integrate for two protons. However, if carefully observed, it could be seen that some peaks of these triplets are split into doublets. This indicates that the pattern observed is probably an AA'XX' system, as encountered in the case of 16, but with a smaller coupling constant for the trans coupling ($J \simeq 0.5$ Hz) and a larger coupling constant for the cis coupling ($J = 8.3$ HZ), indicating that this system is closer to an A_2X_2 system than that one encountered in the case of 16 (see 2.1.1). Because of the adjacent carbonyl, the protons on C_3 are shifted downfield from those on C_4. Therefore, the H_3 protons are at 2.80 ppm and the H_4 protons at 2.38 ppm. Once again, peaks due to impurities are observed at 7.25 ($CHCl_3$) and at 1.60 ppm (water).

2.2.2 ^{13}C-NMR

As expected, the ^{13}C-NMR spectrum of 1 shows only seven peaks. This is due to the symmetry of the molecule making C_9 and C_7, as well as C_{10} and C_6, identical. Therefore, only one peak is expected for each pair of carbons.

There are three very small peaks in the spectrum, suggesting that the carbons represented by those peaks have no attached hydrogens. These peaks are located at 184.1, 175.1 and 78.4 ppm. The first two represent the carbonyls, C_8 and C_2, for the same reasons as mentioned in the case of 16 (see 2.1.2). The third one represents C_5, since it is the only quaternary carbon left in the molecule. The peaks at 32.3 and 28.0 ppm represent C_3 and C_4 respectively, C_3 being downfield from C_4 because of the adjacent carbonyl.

The last two peaks of the spectrum represent the four alkene carbons of the dienone ring. As indicated above, because of the symmetry in the molecule, only two peaks are observed for these four carbons. The peak at 145.5 ppm represents C_{10} and C_6, which is downfield from C_9 and C_7 (129.3 ppm), because the electron density on C_{10} and C_6 is decreased.

2.2.3 IR and mass spectra

The carbonyls observed in the ^{13}C-NMR are also present in the IR spectrum. The broad C=O absorption of the lactone

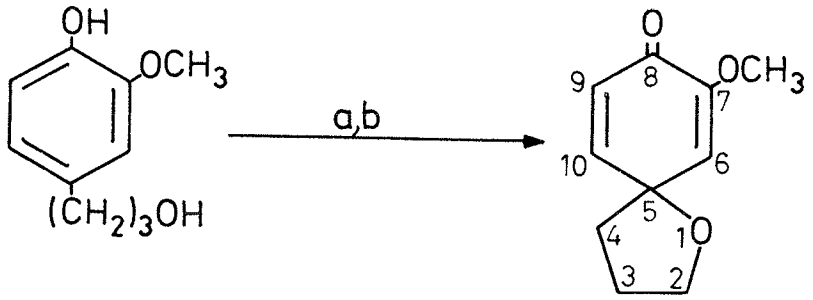
is observed at high frequencies (1768 cm^{-1}) and the appearance of the conjugated ketone is also observed (1672, 1632 cm^{-1}), these data being in agreement with those reported by different authors [1,2,9].

Once again, the mass spectrum and the elemental analysis of 1 are in agreement with the structure proposed. The peak at m/e 164 is assigned to the parent ion peak (M^+). The peak m/e 136 is due to M^+- 28 corresponding to the loss of C_2H_4. Loss of CH_2CO from M^+ afforded the peak at m/e 122, and the combined loss of CO and C_2H_2 from M^+ gives m/e 110. Rearrangement of M^+ gives the cation at m/e 55, the base peak.

2.3 Methoxyspiroether 23

Because of the similarity of the arylalkanoic acid (21) used in the preparation of 16 and the arylalkanol (22) used to prepare 23, only LTA and TTFA were expected to give good results in the preparation of the new spiroether (23), since only these oxidizing agents afforded good results in the preparation of 16 (Table 1).

Therefore, a solution of the arylalkanol (22) (obtained by treatment of 21 with borane as described in the experimental section) and the appropriate solvent was treated with LTA and TTFA, and afforded 23 in 82% and 85% yield respectively. The reactions were performed at room temperature and were followed by tlc. The workup procedure afforded the new spiroether 23, which was distilled under reduced pressure and the structure was established by the methods used before.



22 23

a) LTA, CH_2Cl_2, 25°C (82%)
b) TTFA, CH_3CN, 25°C (85%)

2.3.1 ^{1}H-NMR

The first pattern observed in the ^{1}H-NMR spectrum (spectrum 3) of 23 is identical to that observed in the case of 16 (spectrum 1). It consists of a doublet of doublets, and two doublets, each integrating for one proton. Since this pattern is the same, the doublet of doublets (J=10.0 Hz) at 6.82 ppm is easily assigned to H_{10}, the doublet (J=10.0 Hz) at 6.14 ppm represents H_9 and the second doublet (J=2.7 Hz) at 5.71 ppm represents H_6 (see 2.1.1).

The rest of the spectrum is also very easy to assign. The strong singlet at 3.68 ppm represents the methoxy protons, while the multiplet at 4.08 ppm represents the protons on C_2, which are downfield from those on C_3 and C_4 because of the C_2 oxygen bond. The last signal of this spectrum is a multiplet centered at 2.15 ppm which integrates for four protons. It represents the protons on C_3 and C_4.

As mentioned previously (2.1.1), the methoxy group creates dissymmetry in the molecule. As a result, protons on the same carbon atom (C_2, C_3 and C_4) are different and are coupled to each other in different ways. In addition, there are trans and cis couplings between protons on adjacent carbon atoms, making the signals observed even more complex. A long range coupling between C_2 and C_4 [22e] is probably not present, since it is not observed in the similar molecule (25) (see 2.4.1) for the protons on

C_2. The peak due to water is, once more, observed in this spectrum at 1.60 ppm.

2.3.2 ^{13}C-NMR

The ^{13}C-NMR spectrum of 23 is also very similar to that of 16. Thus, it can be analysed by comparison with that spectrum. As expected, one carbonyl peak is observed. It is small and the further downfield. Hence, the peak at 180.9 ppm represents C_8. The other small peaks in the spectrum represent the alkene carbon C_7 (149.7 ppm) and the quaternary carbon C_5 (79.4 ppm), as explained before (see 2.1.2).

The peaks in the alkane region are easily assigned by comparison of chemical shifts. The peak at 54.8 ppm represents the methoxy carbon, while the peaks at 37.7 and 26.8 ppm represent C_4 and C_3 respectively. Here, C_3 is assigned upfield from C_4 because of the following reasons. In the case of 16, the effect of the carbonyl on C_3 was greater than the effect on C_4. Therefore, C_3 was assigned downfield from C_4. However, in the case of 23, the carbonyl has disappeared and C_3 is affected only by the oxygen of the spiroether ring, while C_4 is affected by that same oxygen and also by the dienone ring. Because of that double effect on C_4, it is assigned downfield from C_3.

The last carbon in the alkane region is C_2 (68.9 ppm), downfield from C_3 and C_4 because of the bonding to an

oxygen atom. The three carbons left are in the alkene region. As mentioned in the case of 16 (2.1.2), C_{10} is downfield from C_9 and C_6. Hence, C_{10} is at 150.2 ppm, C_9 at 126.2 ppm and C_6 at 116.7 ppm.

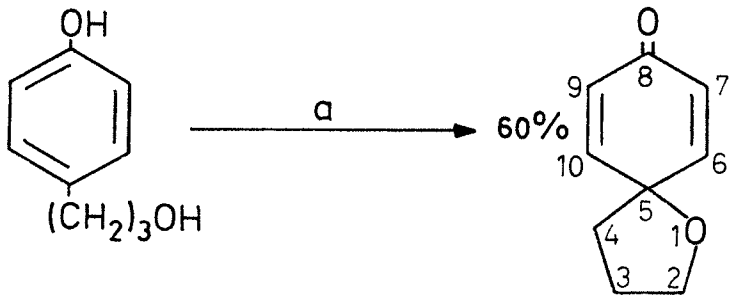
2.3.3 IR and mass spectra

Once again, the IR spectrum confirms the presence of the functional group in the molecule. As expected, the double absorption of the conjugated ketone is observed at 1680 and 1645 cm^{-1}, confirming the presence of only one carbonyl.

The mass spectrum, as well as the elemental analysis, are also in agreement with the structure proposed (23). Since the molecular weight of the molecule is 180, the peak at m/e 180 is the parent ion peak (M^+). The loss of C_2H_4 from M^+ gives the peak at m/e 152 and the loss of CO from that species gives m/e 124. The cation at m/e 137 is formed by the loss of $CH_2{}^{\bullet}CH{=}O$ from M^+. The species, resulting of the loss of $CH_2{=}CH{-}{}^{\bullet}CH_2$ from M^+, looses CH_2O to give m/e 109.

2.4 Spiroether 25

According to the results obtained for 1 (Table 1), TTFA was the only oxidant which was expected to give good results in the preparation of 25. The arylalkanol 24 (obtained by treatment of 3 with borane as described in the experimental section) was treated with TTFA in acetonitrile and afforded the new spiroether 25 in 60% yield. The reaction was performed at room temperature and was followed by tlc. The workup procedure yielded the desired spirocompound (25) which was distilled under reduced pressure and the structure established by the usual spectroscopic methods.



24 25

a) TTFA, acetonitrile, 25°C

2.4.1 ^{1}H-NMR

The ^{1}H-NMR spectrum (spectrum 4) of 25 shows characteristic peaks for the structure proposed. The AA'BB' system, which was observed in the spectrum (spectrum 2) of 1, was also expected to be observed in this case, since both

molecules have similar structures. This system was indeed observed. Two distorted doublets (J=10.1 Hz), both integrating for two protons, are observed at 6.81 and 6.14 ppm. The first one represents H_{10} and H_6, while H_9 and H_7 are represented by the second doublet. Once again, the decrease in electron density on C_{10} and C_6 causes the distorted doublet, representing the corresponding protons, to be downfield from the other one.

The triplet at 4.09 ppm, which integrates for two protons, represents the protons on C_2, which are coupled to those on C_3. They are downfield from those on C_3 and C_4, represented by the multiplet at 2.12 ppm, because of the bond that C_2 has with the oxygen atom. The peak at 7.3 ppm is due to $CHCl_3$ in the $CDCl_3$ used as solvent,

2.4.2 ^{13}C-NMR

The peaks observed in the ^{13}C-NMR spectrum were also expected and can be compared to those obtained in the spectrum of 1. Two small peaks are observed at 185.7 and 77.4 ppm. They represent the carbonyl carbon C_8 and the quaternary carbon C_5 respectively. Three peaks are observed in the alkane region. One of them is easily assigned to C_2 because of its chemical shifts, 69.3 ppm. The other two peaks represent C_4 at 37.0 ppm and C_3 at 26.9 ppm, C_4 being downfield from C_3 for the same reasons mentioned before (see 2.3.2). The strong peaks in the alkene region are assigned to C_{10} and C_6 for one,

and to C_9 and C_7 for the second peak. For the same reasons mentioned earlier (see 2.2.2), the peak representing C_{10} and C_6 is downfield (149.9 ppm) from that one representing C_9 and C_7 (127.6 ppm).

2.4.3 IR and mass spectra

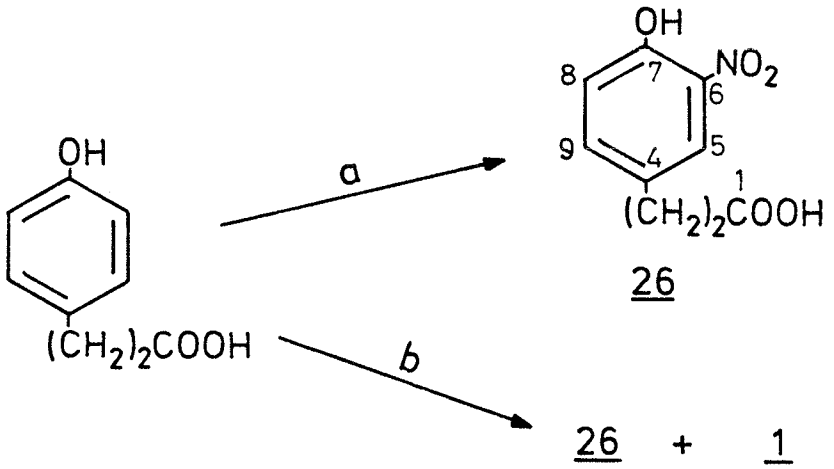
The elemental analysis, the mass spectrum and the IR spectrum of 25 are all in agreement with the structure proposed. In the IR spectrum, the carbonyl group of the dienone ring can be observed at 1672 and 1630 cm^{-1}. The mass spectrum shows a strong peak at m/e 150 corresponding to the parent ion peak (M^+). Another strong peak at m/e 122 corresponds to the loss of CO or C_2H_4 from M^+. A loss of the radical $CH_2{=}CH{-}^{\bullet}CH_2$ from M^+ gives the peak at m/e 109, while $M^+ - CH_2{-}^{\bullet}CH{=}O$ gives the peak at m/e 107. The peak at m/e 94 is the result of two losses of 28 (CO and C_2H_4) from $M^{+\bullet}$

2.5 Miscellaneous

Other compounds have been isolated when trying to form the desired spirocompounds. This is the case for the dibromospirolactone 6a (see part 1.) which was easily identified according to the data previously reported [5].

2.5.1 Nitrophenylpropionic acid 26

This is also the case for the acid 26. This nitro compound was obtained from the reaction of 3 with $(NH_4)_2Ce(NO_3)_6$ or TTN, with accompanying production of the spirocompound (1) in the latter case. The reactions were performed at room temperature and were followed by tlc. The workup procedure afforded the known [28] nitro compound 26 and 1 in a 1:1 molar ratio, in the case of TTN, and 26 in 35% yield in the case of $(NH_4)_2Ce(NO_3)_6$ (nitrations using this reagent have been reported before [29]).



a) $(NH_4)_2Ce(NO_3)_6$, acetonitrile, 25°C (35%)
b) TTFA, acetonitrile, 25°C (1:1 molar ratio)

Since the melting point (88-89°C) of 26 was in agreement with the value found in the literature (89-90.5°C), only the IR and ^{1}H-NMR spectra of that compound were obtained to confirm the structure of the product.

The ^{1}H-NMR spectrum (spectrum 5) of 26 shows two triplets, each integrating for two protons, at 2.95 and 2.68 ppm, a broad singlet at 10.5 ppm representing the acidic proton and the characteristic pattern [21a] for the aromatic protons consisting of a doublet at 7.95 ppm, a doublet of doublets at 7.45 and a doublet at 7.10 ppm.

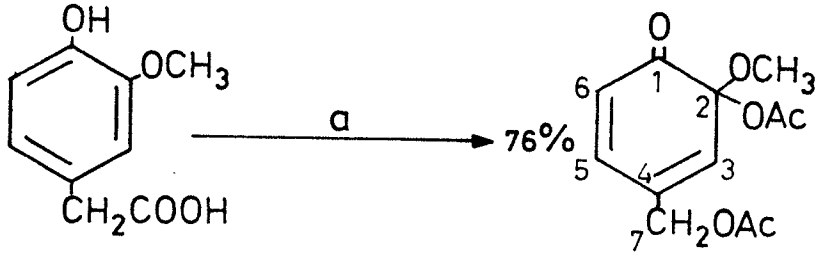
The IR spectrum also confirms the structure proposed. The C=O absorption of the acid group is observed at 1720 cm^{-1}, the NO stretch of the nitro group is at 1546 cm^{-1} and the OH absorption at 3200 cm^{-1}.

The corresponding methyl ester was also obtained when the reaction was performed in methanol instead of CH_3CN.

2.5.2 Diacetoxy dienone 28

An unexpected compound was also obtained when the preparation of a four-membered spirolactone was tried. The treatment of homovanillic acid (27) (obtained from Aldrich or from the synthesis described by Hibbert [33]) by LTA afforded the diacetoxy compound 28. The reaction was performed at room temperature and was followed by tlc. The workup procedure yielded 28, in 76% yield, which was pure by tlc. The structure of the product obtained was established

without further purification, since the product showed sensitivity to any purification techniques.



27 28

a) LTA, CH_2Cl_2, 25°C

Because of the similarity of homovanillic acid (27) with 21 and 22, which were used in the preparation of 16 and 23, the ^{1}H-NMR spectrum of the anticipated spirolactone was expected to be similar to those of 16 and 23. The fact that the spectrum of the product obtained (spectrum 6) does not show the same characteristic pattern in the alkene region, suggests that the reaction did not proceed as expected and 28 was obtained rather than the anticipated lactone.

In addition, the ^{13}C-NMR spectrum (spectrum 7a) of that product shows twelve peaks, confirming the presence of an unexpected product. The presence of three carbonyl groups was indicated in the lowfield region of the spectrum. Of these three carbonyls, two seem to be very similar, since their chemical shifts are almost the same (170.4 and 169.6 ppm).

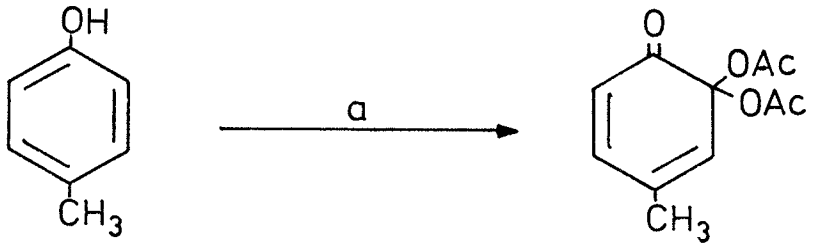
The spectrum also shows four alkene peaks, one of them being a quaternary carbon, since it is less intense than the others. Another quaternary carbon is observed around 100 ppm, while the last four peaks in that spectrum are located in the alkane region. Once again, two of them seem to be similar, their chemical shifts being almost the same (20.8 and 20.5 ppm).

The INEPT technique, applied to the ^{13}C-NMR spectrum, turned out to be the most useful tool in the characterization of 28. That spectrum (spectrum 7b) confirmed that our product contained the three carbonyls mentioned before (191.2, 170.4 and 169.6 ppm) as well as two other quaternary carbons at 133.5 and 97.7 ppm, three CH's (139.1, 131.6 and 126.6 ppm), one CH_2 (64.4 ppm) and three CH_3's (51.4, 20.8 and 20.5 ppm).

According to those data and the fact that the reaction of a variety of arylethanoic acids with lead tetraacetate is known [30] to give the corresponding acetate, the structure 28 was suggested for the product obtained in that reaction. That structure is also in agreement with the ^{1}H-NMR spectrum (spectrum 6) mentioned earlier. The large peak at 2.11 ppm, integrating for six protons, represents the methyls of the acetoxy groups, while the other large peak at 3.46 ppm, which integrates for three protons, represents the methoxy protons. The peak at 4.71 ppm represents the methylene protons H_7, downfield because they are on a carbon attached to an oxygen atom.

The last pattern observed in that spectrum shows a doublet of doublets (J=10.1 Hz, 2.1 Hz) at 6.85 ppm, which probably represents the protons on C_5 coupled with those on C_6 and C_3, a broad singlet at 6.20 ppm and another small singlet at 6.19 ppm. The integration of the broad singlet is equivalent to about 1.5 protons, while the other singlet integrates for about 0.5 proton. This suggests that the pattern observed is probably a singlet and a doublet, which are overlapping, and are observed as two singlets.

To confirm that fact, a model having a dienone ring similar to that one of 28 was required. This model (29) was prepared according to the procedure used by Goodwin and Witkop [31].



29

a) AcOH, LTA

The ^{1}H-NMR spectrum (spectrum 8) of 29 shows the same doublet of doublets (J=10.0 Hz, 2.1 Hz) (6.76 ppm) observed in the spectrum of 28. It also shows a doublet (J=10.0 Hz) at 6.29 ppm and a broad singlet at 5.71 ppm, confirming the possibility that the last two might be overlapping, in the case of 28, and are observed as two singlets. The

^{13}C-NMR spectrum (spectrum 9) of 29 is also in agreement with that one of 28, the peaks observed having similar chemical shifts.

The IR spectrum of 28 confirms the presence of the carbonyls, by showing a peak at 1746 cm^{-1} for the acetoxy groups and 1696 cm^{-1} for the ketone. This is, once again, in agreement with the model prepared (1742 and 1700 cm^{-1}).

However, with the mass spectrum of 28, it is not possible to be absolutely sure that the structure proposed is the right one. Assuming that this structure is correct, then the parent ion could lose an acetoxy radical (M^+-59) to give the peak at m/e 195. A loss of 42 (CH_2=C=O) from M^+ could give the peak at m/e 212. This species could then lose acetic acid to give m/e 152.

However, as was mentioned, these are only suppositions since the parent ion, which should be at m/e 254, is not observed in this spectrum. However, according to the data obtained from all these spectroscopic techniques, the structure 28 is assigned to the product obtained.
Note: All the data (^{1}H-NMR, IR and mass spectra) presented in this section (discussion), as well as the experimental conditions, are summarized in Table 3.

3. CONCLUSION

3. CONCLUSION

Good results were obtained for the formation of the spirolactones 1 and 16, as well as for the new spiroethers 23 and 25, when LTA and TTFA were used as the oxidant.

However, TTFA was found to be the most versatile of these two oxidants. It gives the same results as LTA for the formation of 16 (85%) and 23 (85%), but it is the only oxidant tried that gave reasonable results for the preparation of 1 (55%) and 25 (60%).

On the other hand, the preparation of a four-membered spirolactone (4 attempts) or spiroether (2 attempts) failed with any of the oxidant used. For instance, when homovanillic acid was treated with LTA, the unexpected diacetoxy dienone 28 was obtained.

Therefore, the use of LTA and TTFA, as oxidant in these transformations, provides a good method to easily synthezise spirolactones and spiroethers such as 1, 16, 23 and 25, thus, making these compounds readily available for other investigations.

4. EXPERIMENTAL

4. EXPERIMENTAL

Melting points were determined with a FISHER-JOHNS melting point apparatus and were uncorrected. Infrared spectra were recorded on a UNICAM SP 1000 IR spectrophotometer. Mass spectra were recorded on a FINNIGAN 1015 mass spectrometer under electron-impact at 70 eV ionizing voltage. Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Bruker AM 300 (at 300.13 MHz) spectrometer or on a Varian Anaspect EM 360 NMR spectrometer (at 60 MHz). Spectra were measured in deuterochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard. Carbon-13 magnetic resonance (^{13}C-NMR) spectra were recorded on a Bruker AM 300 (75.4 MHz) spectrometer or on a Bruker WH-90 (22.63 Hz) spectrometer equipped with NIC 1180 computer, 293 A' pulse programmer, home built phase shifter and NTC FT software. ^{13}C-NMR spectra were measured in $CDCl_3$ with $CDCl_3$ as internal standard whose chemical shift was taken as being about 77.2 ppm relative to TMS. Analyses were performed by the Guelph Chemical Laboratories Ltd.

Analytical thin layer chromatography (tlc) were performed on precoated silica gel sheets, 60 F_{254} (EM Reagents) 0.2 mm thickness. Ethyl acetate was used as the developing solvent. Spots were detected under ultraviolet light or visualized in an iodine chamber. Flash chromatography [32] was performed in a column (40 cm x 2.5 cm) packed with silica gel (6 cm high) Kieselgel 60 (230-400 mesh ASTM)

using ethyl acetate as the eluent. Distillations under reduced pressure were performed in an Aldrich Kugelrohr distillation apparatus, connected to a Sargent-Welch DIRECTORR vacuum pump. All solvent evaporations were carried out in a Büchi HB-140 rotary evaporator. All solvents were used as received without further purification, except for benzene, tetrahydrofuran (THF) and acetonitrile which were distilled prior to their use. All chemicals (starting materials and oxidizing agents) were used as received from Aldrich Company and were not further purified, except for N-Bromosuccinimide (NBS) which was recrystallized from water prior its use.

4-Hydroxy-3-methoxycinnamic acid [34]:

To a mixture of vanillin (30.0g, 0.2 mole) and malonic acid (45.36g, 0.44 mole), pyridine (24 mL) and aniline (0.6 mL) were added. The mixture was kept at 55°C for 14 hours and the solid formed was put in 50% HCl (400 mL), stirred for 15 minutes, filtered and washed with 10% HCl. A pale yellow solid (24.65g, 76%; mp: 174-175°C; pure by tlc) was obtained after drying. Further purification was not attempted.

3-(4-Hydroxy-3-methoxyphenyl)propionic acid (21):

To an aqueous solution (250 mL) of sodium hydroxide (5.0g, 0.13 mole) was added, 4-hydroxy-3-methoxycinnamic acid (19.4g, 0.1 mole) and the mixture was stirred at room

temperature until complete dissolution of the cinnamic acid. After, 10% Palladium on charcoal (2g) was added, the apparatus was flushed several times with hydrogen and addition of hydrogen (2.5 L) was done over a period of 8 hours. The basic aqueous solution was acidified to pH=2 and the acidic solution extracted with methylene chloride (5 x 100 mL) and dried over $MgSO_4$. Evaporation of the solvent yielded a white solid (17.1g, 87%; mp: 85-86°C; pure by tlc). Further purification was not attempted.

3-(4-Hydroxy-3-methoxyphenyl)propanol (22) [35]:

To a solution of 3-(4-hydroxy-3-methoxyphenyl)propionic acid (21) (15.0g, 90.4 mmoles) dissolved in tetrahydrofuran (THF) (230 mL) was slowly added, under nitrogen at 0°C, BH_3 (210 mL) from a 1M solution of BH_3 in THF. The solution was stirred at 0°C for 30 minutes and at room temperature until completion of the reaction (tlc). Excess BH_3 was destroyed by adding water (100 mL). A 3N solution of sodium hydroxide (130 mL) was added and the mixture stirred vigorously for 20 minutes. The organic layer was evaporated and the residue added to the aqueous layer which was acidified to pH=2 and extracted continuously overnight with methylene chloride (150 mL). The methylene chloride layer was dried over $MgSO_4$ and evaporation of the solvent yielded a yellow oil (12.9g, 90%). Distillation (115°C, 0.05 mm Hg) afforded a colorless oil which solidified on standing at 0°C for one hour to give a white solid (11.3g,

69%; mp: 63-65°C).

3-(4-Hydroxyphenyl)propanol (24) [35]:

To a solution of 3-(4-hydroxyphenyl)propionic acid (10.0g, 60 mmoles) dissolved in THF (170 mL) was slowly added, under nitrogen at 0°C, BH_3 (150 mL) from a 1M solution of BH_3 in THF. The solution was stirred at 0°C for 30 minutes and at room temperature until completion of the reaction (tlc). Excess BH_3 was destroyed by adding water (25 mL). A 3N solution of sodium hydroxide (100 mL) was added and the mixture stirred vigorously for 20 minutes. The organic layer was evaporated and the residue was added to the aqueous layer which was acidified to pH=2, extracted with ether (4 x 50 mL), and activated charcoal was added to the solution. After filtration, the ether solution was dried over $MgSO_4$ and evaporated. The residue obtained was dissolved in methylene chloride (350 mL) and dried over $MgSO_4$. Evaporation of the solvent yielded a pale yellow solid (8.4g, 92%; mp: 47-50°C). Distillation (112-115°C, 0.01 mm Hg) afforded a white solid (7.0g; mp: 50-51°C).

Homovanillic acid [3-(4-Hydroxy-3-methoxyphenyl)acetic acid] (27):

The acid was prepared according to the procedure used by Fisher and Hibbert [33], starting with 40.0g (0.26 mole) of vanillin and 35.0g (0.26 mole) of rhodanine. Homovanillic

acid (7.56g; mp: 141-143°C; reported 142-143°C) was obtained after purification.

2-(4-Hydroxy-3-methoxyphenyl)ethanol [35]:

To a solution of homovanillic acid (2.0g, 11 mmoles) dissolved in THF (50 mL) was added, under nitrogen at 0°C, BH_3 from a 1M solution of BH_3 in THF. The solution was stirred at room temperature until completion of the reaction (tlc) and excess BH_3 was destroyed by adding water (10 mL). A 3N solution of NaOH (20 mL) was added and the mixture stirred vigorously for 20 minutes. The organic layer was evaporated and the residue added to the aqueous layer which was acidified to pH=2, extracted with methylene chloride (4 x 50 mL) and dried over $MgSO_4$. Evaporation of the solvent yielded a pale yellow oil (1.7g, 91%). Distillation (110-115°C, 0.3 mm Hg) afforded a colorless oil (1.4g).

General Procedure A: Oxidative cyclizations with Lead tetraacetate (LTA) used as the oxidant.

To a solution of the appropriate substrate (2.75 to 22 mmoles of arylalkanoic acid or arylalkanol), dissolved in methylene chloride, was added in one portion LTA (2.5 to 4.0 equivalents) and the resulting solution was stirred at room temperature until completion of the reaction (tlc). The precipitate formed was filtered and the excess lead tetraacetate was destroyed by adding ethylene glycol to the

filtrate and by stirring the solution for 5 minutes. The methylene chloride layer was washed with 5% $NaHCO_3$ (3 x 100 mL) and water (3 x 100 mL), stirred with activated charcoal, dried over $MgSO_4$ and the solvent evaporated.

General Procedure B: Oxidative cyclizations with Thallium (III) trifluoroacetate (TTFA) used as the oxidant.

To a solution of the appropriate substrate (2.6 to 4.5 mmoles of arylalkanoic acid or arylalkanol), dissolved in acetonitrile (50 to 75 mL), was added in one portion TTFA (1.5 to 6 equivalents) and the solution was stirred at room temperature or 0°C until completion of the reaction (tlc). After evaporation of the solvent, methylene chloride (100 mL) and 5% $NaHCO_3$ (100 mL) were added to the thick brown residual liquid. The dark brown precipitate, which appeared upon addition of sodium bicarbonate, was filtered and the organic layer washed with 5% $NaHCO_3$ (3 x 50 mL) and water (3 x 50 mL), stirred with activated charcoal, dried over $MgSO_4$ and the solvent evaporated.

General Procedure C: Oxidative cyclizations when neither LTA nor TTFA were used as the oxidant.

To a solution of the appropriate substrate (2.6 to 6.1 mmoles of arylalkanoic acid or arylalkanol), dissolved in methylene chloride (50 mL) or acetonitrile (50 mL), the oxidizing agent (1.0 to 1.9 equivalents) was added in one portion. The resulting mixture was stirred at room

temperature until completion of the reaction (tlc) and the organic layer was washed with 5% $NaHCO_3$ (3 x 50 mL) and water (3 x 50 mL). When acetonitrile was used as the solvent, it was evaporated and methylene chloride (100 mL) was added to the residue before washing. The methylene chloride solution was stirred with activated charcoal, dried over $MgSO_4$ and the solvent evaporated.

7-Methoxy-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione (16):

a) LTA oxidation:

The reaction of 3-(4-hydroxy-3-methoxyphenyl)propionic acid (21) (2.00g, 10.2 mmoles), dissolved in methylene chloride (200 mL), with LTA (8.72g, 25.5 mmoles) according to procedure A (ethylene glycol used: 100 mL) afforded a pale yellow solid (1.69g, 85%*; mp: 94-96°C). Recrystallization from benzene yielded white plates (1.29g; mp: 95-96°C; pure by tlc).

IR (Nujol), cm^{-1}: 1766 [C=O stretch of lactone], 1676,1650 [C=O stretch of conjugated ketone], 1620 [C=C stretch].

^{1}H-NMR (300 MHz) in $CDCl_3$, ppm: dd at 6.85 (1H,H_{10}) [$^3J(10,9)$=10.0 Hz, $^4J(10,6)$=2.8 Hz], d at 6.27 (1H,H_9) [$^3J(9,10)$=10.0 Hz], d at 5.71 (1H,H_6) [$^4J(6,10)$=2.8 Hz], s at 3.71 (3Hs,H_{11}), t at 2.79 (2Hs,H_{3a},H_{3b}), t at 2.41 (2Hs,H_{4a},H_{4b}).

^{13}C-NMR (22.6 Hz) in $CDCl_3$, ppm: 179.6 (C_8), 175.2 (C_2), 151.0 (C_7), 145.9 (C_{10}), 128.2 (C_9), 112.9 (C_6), 80.9 (C_5), 55.2 (methoxy carbon), 33.3 (C_3), 28.3 (C_4).

ms, m/z: 194 (21) [M^+], 166 (17) [M - C_2H_4], 152 (8) [M - CH_2CO], 151 (8) [166 - CH_3], 140 (50) [M - (CO + C_2H_2)], 121 (29) [152 - CH_3O], 55 (100) [CH_2=CH-CO]$^+$

Anal. calculated for $C_{10}H_{10}O_4$: C, 61.84; H, 5.19.

Found: C, 61.65; H, 5.45.

*Average yield over 4 reactions was 82% (from 80 to 85%). The purity of the product obtained was estimated, from ^{1}H-NMR and tlc, to be 95+%.

b) TTFA oxidation:

The reaction of (21) (0.50g, 2.6 mmoles), dissolved in acetonitrile (50 mL), with TTFA (2.21g, 4 mmoles) at 0°C according to procedure B afforded a pale yellow solid (0.42g, 85%*; mp: 93-95°C). Recrystallization from benzene yielded white plates (0.32g, 65%; mp: 95-96°C). Results from ^{1}H-NMR (60 MHz), mass spectrum and tlc were identical to those obtained with LTA.

*Average yield over 4 reactions was 77% (from 62 to 85%).

Note: When fresly received TTFA was used, 1.1 equivalents were required for the reaction.

c) Ammonium Cerium (IV) nitrate oxidation:

The reaction of (21) (0.50g, 2.6 mmoles), dissolved in acetonitrile (50 mL), with Ammonium Cerium (IV) nitrate (2.74g, 5 mmoles) according to procedure C (prior to acetonitrile evaporation, nitric acid that had been formed was neutralized with 5% $NaHCO_3$) afforded a yellow solid (0.34g, 69%; mp: 87-93°C). Recrystallization was not attempted. Results from ^{1}H-NMR (60 MHz) and tlc were

identical to those obtained with LTA.

d) Thallium (III) nitrate trihydrate (TTN) oxidation:

The reaction of (21) (0.50g, 2.6 mmoles), dissolved in acetonitrile (60 mL), with TTN (1.11g, 2.5 mmoles) according to procedure C (the precipitate formed was filtered before evaporation of the solvent) afforded a pale yellow oil (0.22g, 45%) which crystallized on standing at room temperature overnight. Recrystallization was not attempted. ^{1}H-NMR (60 MHz), mass spectrum and tlc were identical to results previously obtained.

e) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation:

The reaction of (21) (0.50g, 2.6 mmoles), dissolved in acetonitrile (50 mL), with DDQ (0.75g, 3.3 mmoles) according to procedure C afforded a yellow oil (0.1g, 20%). Further purification was not attempted. ^{1}H-NMR (60 MHz) and tlc were identical to results previously obtained. Acidification and extraction of the aqueous layer with methylene chloride (2 x 50 mL) did not yield any unreacted arylpropionic acid or any compounds other than the black tar.

f) Sodium periodate oxidation:

The reaction of (21) (0.50g, 2.6 mmoles) with sodium periodate (1.06g, 5 mmoles), in a two-phase system of methylene chloride (50 mL) and water (25 mL), according to procedure C yielded a yellow oil (0.09g, 18%). Further purification was not attempted. ^{1}H-NMR (60 MHz) was identical to results previously obtained.

Acidification and extraction of the aqueous layer with methylene chloride (2 x 50 mL) did not yield any unreacted arylpropionic acid or any other compounds.

g) N-Bromosuccinimide (NBS) oxidation:

To a solution of (21) (1.20g, 6.1 mmoles), dissolved in methylene chloride (50 mL), was added an aqueous solution (50 mL) of sodium acetate (5.21g, 64 mmoles). The mixture was stirred vigorously and NBS (2.0g, 11 mmoles) was added in one portion. After completion of the reaction (tlc), the organic layer was washed with $NaHCO_3$ (3 x 20 mL), water (3 x 20 mL) and dried over $MgSO_4$. Evaporation of the solvent yielded a pale yellow liquid (1.04g) which showed more than one product by thin layer chromatography. Flash chromatography of the mixture afforded the desired spirolactone (16) (0.05g; pure by tlc). ^{1}H-NMR (60 MHz) was identical to results previously obtained.

h) Other oxidizing agents:

Negative results were obtained for the reaction of (21) with any of the following oxidizing agents; Mercury (II) oxide, Potassium ferricyanide, 4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD), Barium manganate, Ceric trihydroxy hydroperoxide (CTH), N-Chlorosuccinimide/dimethyl sulfide complex and Ferric chloride. In most cases, the starting material (21) was recovered after acidification and extraction of the aqueous layer with methylene chloride.

7-Methoxy-1-oxaspiro[4.5]deca-6,9-diene-8-one (23):

a) LTA oxidation:

The reaction of 3-(4-hydroxy-3-methoxyphenyl)propanol (22) (4.00g, 22 mmoles), dissolved in methylene chloride (400 mL), with LTA (29.84g, 87.3 mmoles) according to procedure A (ethylene glycol used: 300 mL) afforded a dark orange oil (3.26g, 82%*). Distillation (88-90°C, 0.05 mm Hg) of the product obtained yielded a yellow oil (2.19g, 55%; pure by tlc).

IR (Neat), cm^{-1}: 1680,1645 [C=O stretch of conjugated ketone], 1615 [C=C stretch].

^{1}H-NMR (300 MHz) in $CDCl_3$, ppm: dd at 6.82 (1H,H_{10}) [$^{3}J(10,9)$=10.0 Hz, $^{4}J(10,6)$=2.7 Hz], d at 6.14 (1H,H_9) [$^{3}J(9,10)$=10.0 Hz], d at 5.71 (1H,H_6) [$^{4}J(6,10)$=2.7 Hz], m centered at 4.08 (2Hs,H_{2a},H_{2b}), s at 3.68 (3Hs, methoxy protons), m centered at 2.15 (4Hs,H_{4a},H_{4b},H_{3a},H_{3b}).

^{13}C-NMR (22.6 Hz) in $CDCl_3$, ppm: 180.9 (C_8), 150.2 (C_{10}), 149.7 (C_7), 126.2 (C_9), 116.7 (C_6), 79.4 (C_5), 68.9 (C_2), 54.8 (C_{11}), 37.7 (C_4), 26.8 (C_3).

ms, m/z: 180 (64) [M^+], 152 (40) [M - C_2H_4], 137 (100) [M - CH_2-$^{\bullet}$CH=O], 124 (48) [M - (CO + C_2H_4)], 109 (76) [M - (CH_2=CH-$^{\bullet}CH_2$ + CH_2O)].

Anal. calculated for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72.
Found: C, 66.47; H, 6.97.

*Average yield over 4 reactions was 77% (from 72 to 82%). The purity of the product obtained was estimated, from the tlc and ^{1}H-NMR (300 MHz), to be 95+%.

b) TTFA oxidation:

The reaction of (22) (0.53g, 2.9 mmoles), dissolved in acetonitrile (50 mL), with TTFA (2.53g, 4.7 mmoles) according to procedure B yielded a yellow oil (0.44g, 85%*). Distillation (88-90°C, 0.05 mm Hg) afforded a pale yellow oil (0.32g, 62%; pure by tlc).

^{1}H-NMR (60 MHz), tlc and mass spectra were identical to those obtained with LTA.

*Average yield over 5 reactions was 75% (from 61 to 86%).

Note: When freshly received TTFA was used, 1.1 equivalents was required for the reaction.

1-Oxaspiro[4.5]deca-6,9-diene-2,8-dione (1):

a)TTFA oxidation:

The reaction of 3-(4-hydroxyphenyl)propionic acid (3) (0.75g, 4.5 mmoles), dissolved in acetonitrile (75 mL), with TTFA (14.75g, 27.1 mmoles) according to procedure B at room temperature afforded a yellow solid (0.41g, 55%*; mp: 101-104°C). Sublimation under reduced pressure (90-95°C, 0.05 mm Hg) yielded white plates (0.14g; mp: 107-108°C; pure by tlc).

IR (Nujol), cm^{-1}: 1768 [C=O stretch of lactone], 1672,1632 [C=O stretch of conjugated ketone], 1614 [C=C stretch].

^{1}H-NMR (300 MHz) in $CDCl_3$, ppm: distorted d at 6.86 (2Hs,H_{10},H_6) and distorted d at 6.29 (2Hs,H_9,H_7) [AA' BB' spin system] [$^3J(10,9)$=10.1 Hz], t at 2.80 (2Hs,H_3) [$^3J(3,4)$=8.4 Hz], t at 2.38 (2Hs,H_4) [$^3J(4,3)$=8.4 Hz].

^{13}C-NMR (75.4 MHz) in $CDCl_3$, ppm: 184.1 (C_8), 175.1 (C_2), 145.5 (C_{10},C_6), 129.3 (C_9,C_7), 78.4 (C_5), 32.3 (C_3), 28.0 (C_4).

ms, m/z: 164 (58) [M^+], 136 (21) [M - C_2H_4], 122 (44) [M - CH_2CO], 110 (19) [M - (CO + C_2H_2)], 55 (100) [CH_2=CH-CO]$^+$.

Anal. calculated for $C_9H_8O_3$: C, 65.83; H, 4.91.

Found: C, 66.15; H, 5.18.

*Average yield over 5 reactions was 55% (from 47 to 63%). The purity of the product obtained was estimated, from tlc and ^{1}H-NMR (300 MHz), to be 95+%.

When freshly received TTFA was used, 3.1 equivalents were required for the reaction.

b) LTA oxidation:

The reaction of (3) (0.50g, 3.0 mmoles), dissolved in methylene chloride (50 mL), with LTA (2.57g, 7.5 mmoles) according to procedure A (ethylene glycol used: 30 mL, 5% $NaHCO_3$: 3 x 50 mL, water: 3 x 50 mL) afforded a pale yellow liquid (0.07g, 14%). Further purification was not attempted.

^{1}H-NMR (60 MHz) and tlc were similar to results previously obtained.

c) Thallium (III) nitrate trihydrate (TTN) oxidation:

The reaction of (3) (0.50g, 3.0 mmoles), dissolved in acetonitrile (50 mL), with TTN (1.33g, 3.0 mmoles) according to procedure C (the precipitate formed was filtered before acetonitrile evaporation) afforded a pale yellow solid

(0.23g; mp: 74-82°C). Recrystallization from water afforded yellow needles (mp: 87-88°C) which were identified, from tlc and ^{1}H-NMR (60 MHz) (see below), as being 3-(4-hydroxy-3-nitrophenyl)propionic acid (reported mp: 90.5°C [28]).

d) Other oxidizing agents:

Negative results were obtained for the reaction of (3) with lead oxide (PbO_2) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In both cases, neither unreacted arylpropionic acid nor any other compound was recovered.

1-Oxaspiro[4.5]deca-6,9-diene-8-one (25):

a)TTFA oxidation:

The reaction of 3-(4-hydroxyphenyl)propanol (24) (0.56g, 3.1 mmoles), dissolved in acetonitrile (50 mL), with TTFA (8.03g, 14.8 mmoles) according to procedure B afforded a yellow oil (0.33g, 60%*). Distillation (85-90°C, 0.05 mm Hg) of the product obtained yielded a yellow liquid (0.19g). A second distillation (65-70°C, 0.05 mm Hg) afforded a pale yellow liquid (0.14g; pure by tlc).
IR (Neat), cm^{-1}: 1672,1630 [C=O stretch of conjugated ketone], 1604 [C=C stretch].
^{1}H-NMR (300 MHz) in $CDCl_3$, ppm: distorted d at 6.81 (2Hs,H_{10},H_6) and distorted d at 6.14 (2Hs,H_9,H_7) [AA' BB' spin system] [$^3J(10,9)$=10.1 Hz], t at 4.09 (2Hs,H_2) [$^3J(2,3)$=6.6 Hz], m centered at 2.12 (4Hs,H_4,H_3).

^{13}C-NMR (75.4 MHz) in $CDCl_3$, ppm: 185.7 (C_8), 149.9 (C_{10}, C_6), 127.6 (C_9,C_7), 77.4 (C_5), 69.3 (C_2), 37.0 (C_4), 26.9 (C_3).

ms, m/z: 150 (93) [M^+], 122 (88) [M - CO] or [M - C_2H_4], 109 (39) [M - CH_2=CH-$^{\bullet}CH_2$], 107 (37) [M - CH_2-$^{\bullet}$CH=O], 94 (100) [M - (CO + C_2H_4)].

Anal. calculated for $C_9H_{10}O_2$: C, 71.96; H, 6.72.

Found: C, 71.83; H, 7.12.

*Average yield over 4 reactions was 62% (from 57 to 67%). The purity of the product obtained was estimated, from tlc and ^{1}H-NMR (300 MHz), to be 95+%.

Note: When freshly received TTFA was used, 3.1 equivalents were required for the reaction.

b) LTA oxidation:

The reaction of (24) (0.50g, 2.75 mmoles), dissolved in methylene chloride (50 mL), with LTA (6.08g, 13.7 mmoles) according to procedure A (ethylene glycol used: 30 mL, 5% $NaHCO_3$: 3 x 50 mL, water: 3 x 50 mL) afforded a yellow oil (0.3g).

^{1}H-NMR (60 MHz) did not show any peaks of the expected spiroether. Thin layer chromatography confirmed the absence of the expected product (showed 5 spots, none of them being identified as the spiroether). Further purification was not attempted.

c) Ferric chloride oxidation:

Negative result was obtained for the reaction of (24) with ferric chloride. The starting material (24) was

recovered after acidification and extraction of the aqueous layer with methylene chloride.

7,9-Dibromo-1-oxaspiro[4.5]deca-6,9-diene-2,8-dione (6a):

To a solution of 3-(4-hydroxyphenyl)propionic acid (3) (0.50g, 3.0 mmoles), dissolved in methylene chloride (25 mL), was added an aqueous solution (25 mL) of sodium acetate (2.47g, 30.1 mmoles). The mixture was stirred vigorously and N-Bromosuccinimide (NBS) (25.0g, 12.6 mmoles) was added in one portion. After the completion of the reaction (tlc), the methylene chloride layer was washed with 5% $NaHCO_3$ (3 x 25 mL), water (3 x 25 mL) and dried over $MgSO_4$. Evaporation of the solvent yielded a yellow solid (0.83g, 86%; mp: 163-172°C). Recrystallization from carbon tetrachloride afforded colorless needles (mp: 173-175°C; reported 174-176°C [5]).

IR (Nujol), cm^{-1}: 1790 [C=O stretch of lactone], 1682 [C=O stretch of conjugated ketone], 1614 [C=C stretch].

^{1}H-NMR (60 MHz) in $CDCl_3$, ppm: s at 7.37 (2Hs,H_6, H_{10}), m centered at 2.66 (4Hs,H_3,H_4).

^{13}C-NMR (22.6 Hz) in $CDCl_3$, ppm: 209.7 (C_8), 174.0 (C_2), 146.2 (C_6,C_{10}), 123.6 (C_7,C_9), 81.4 (C_5), 31.9 (C_3), 27.7 (C_4).

Anal. calculated for $C_9H_6Br_2O_3$: C, 33.58; H, 1.88; Br, 49.65
Found: C, 33.60; H, 1.86; Br, 49.93.

3-(4-Hydroxy-3-nitrophenyl)propionic acid (26):

The reaction of 3-(4-hydroxyphenyl)propionic acid (3) (0.50g, 3.0 mmoles), dissolved in acetonitrile (100 mL), with Ammonium Cerium (IV) nitrate (1.42g, 6.0 mmoles) according to procedure C afforded a yellow solid (0.22g, 35%; mp: 78-80°C). Recrystallization from water yielded yellow needles (mp: 88-89°C; reported 90.5°C [28]). IR (Nujol), cm^{-1}: 1720 [C=O stretch of acid], 1626 [C=C stretch], 1546 [NO stretch], 3200 [OH stretch]. ^{1}H-NMR (300 MHz) in $CDCl_3$, ppm: broad s at 10.5 (1H, acidic proton), d at 7.95 (1H,H_5) [$^4J(5,9)$=2.2 Hz], dd at 7.45 (1H,H_9) [$^3J(9,8)$=8.6 Hz, $^4J(9,5)$=2.2 Hz], d at 7.10 (1H,H_8) [$^3J(8,9)$=8.6 Hz], t at 2.95 (2Hs,H_2) [$^3J(2,3)$=7.4 Hz], t at 2.68 (2Hs,H_3) [$^3J(3,2)$=7.4 Hz].

Methyl-3-(4-hydroxy-3-nitrophenyl)propionate:

To a solution of 3-(4-hydroxyphenyl)propionic acid (3) (0.50g, 3.0 mmoles), dissolved in methanol (40 mL), was added in one portion thallium (III) nitrate trihydrate (TTN) (1.33g, 3.0 mmoles) and the solution was stirred at room temperature until completion of the reaction (tlc). The solvent was evaporated, methylene chloride (50 mL) and 5% $NaHCO_3$ (50 mL) were added to the red-brown residue. The organic layer was washed with 5% $NaHCO_3$ (2 x 25 mL), water (2 x 25 mL) and dried over $MgSO_4$. Evaporation of the solvent yielded a dark yellow oil (0.47g, 69%) which solidified on standing at room temperature overnight.

Recrystallization from hexane afforded yellow needles (mp: 60-61°C; reported 64°C [28]; pure by tlc).
^{1}H-NMR (60 MHz) in $CDCl_3$, ppm: d at 7.99 (1H,H_5) [$^4J(5,9)$=1.8 Hz], dd at 7.51 (1H,H_9) [$^3J(9,8)$=8.7 Hz, $^4J(9,5)$=1.8 Hz], d at 7.11 (1H,H_8) [$^3J(8,9)$=8.7 Hz], s at 3.71 (3Hs,methyl group of ester), m centered at 2.82 (4Hs,H_2,H_3).

2-Acetoxy-2-methoxy-4-acetoxymethyl-3,5-cyclohexadiene-1-one (28):

To a solution of homovanillic acid (0.50g, 2.7 mmoles), dissolved in methylene chloride (60 mL), was added in one portion LTA (2.35g, 5.3 mmoles) and the mixture was stirred at room temperature until completion of the reaction (tlc). Ethylene glycol (30 mL) was added and the solution stirred for 5 minutes. The methylene chloride layer was washed with 5% $NaHCO_3$ (2 x 50 mL) and water (2 x 50 mL), stirred with activated charcoal and dried over $MgSO_4$. Evaporation of the solvent yielded an orange oil (0.53g, 76%; pure by tlc).
IR (Neat), cm^{-1}: 1746 [C=O stretch of acetoxy groups], 1696 [C=O stretch of conjugated ketone].
^{1}H-NMR (300 MHz) in $CDCl_3$, ppm: dd at 6.85 (1H,H_5) [$^3J(5,6)$=10.1 Hz, $^4J(5,3)$=2.1 Hz], d at 6.19 (1H,H_6) and broad s at 6.20 (1H,H_3) overlapping, s at 4.71 (2Hs, H_7), s at 3.46 (3Hs,methoxy protons), s at 2.11 (6Hs, methyls of acetoxy groups).
^{13}C-NMR (75.4 MHz) in $CDCl_3$, INEPT, ppm: 191.2 (C=O,C_1),

170.4 and 169.6 (carbonyls of acetoxy groups), 139.1 (CH, C_5), 133.5 (quaternary C, C_4), 131.6 (CH, C_3), 126.6 (CH, C_6), 92.7 (quaternary C, C_2), 64.4 (CH_2, C_7), 51.4 (CH_3, methoxy group), 20.8 and 20.5 (2 CH_3, methyls of acetoxy groups).

ms, m/z: M^+ not observed, 212 [M - CH_2=C=O], 195 [M - $CH_3COO^{\cdot}$], 152 [212 - CH_3COOH].

Anal. calculated for $C_{12}H_{14}O_6$: C, 56.67; H, 5.55.

Found: C, 55.81; H, 5.41.

Note: Attempted purification by distillation (110-120°C, 0.2 mm Hg), flash chromatography, preparative tlc and recrystallization, afforded only decomposed materials.

4-Methyl-2,2-diacetoxy-3,5-cyclohexadiene-1-one (29):

To a solution of p-cresol (1.03g, 9.5 mmoles), dissolved in acetic acid (AcOH) (100 mL), was added lead tetraacetate (LTA) (3.8g, 8.6 mmoles), previously moistened with AcOH, and the solution was stirred at room temperature until completion of the reaction (tlc). Acetic acid was evaporated and water (200 mL) was added to the residue. The PbO_2 formed was filtered and the liquor extracted with ether (3 x 50 mL). The ether extract was washed with 5% $NaHCO_3$ (3 x 50 mL), water (3 x 50 mL) and dried over $MgSO_4$. Evaporation of the solvent yielded an orange oil (1.12g, 52%) which solidified (mp: 135-141°C) on cooling. Sublimation (75°C, 0.05 mm Hg) of the product yielded white plates (mp: 141-143°C; reported 141-142°C [31]).

IR (Nujol), cm^{-1}: 1742 [C=O stretch of acetoxy groups], 1700 [C=O stretch of conjugated ketone].

^{1}H-NMR (300 MHz) in $CDCl_3$, ppm: dd at 6.76 (1H,H_5) [$^{3}J(5,6)$=10 Hz, $^{4}J(5,3)$=2.1 Hz], d at 6.29 (1H,H_6) [$^{3}J(6,5)$=10 Hz], broad s at 5.97 (1H,H_3), s at 2.09 (3Hs,H_7), s at 2.001 and s at 1.995 (6Hs, methyls of acetoxy groups).

^{13}C-NMR (75.4 MHz) in $CDCl_3$, ppm: 190.2 (C_1), 167.9 (C=O of acetoxy groups), 141.5 (C_2), 137.4 (C_5), 127.1 (C_3), 125.6 (C_6), 92.2 (C_4), 21.5 (CH_3 of acetoxy groups), 20.5 (C_7).

6-Methoxy-1-oxaspiro[3.4]nona-5,8-diene-2,7-dione:

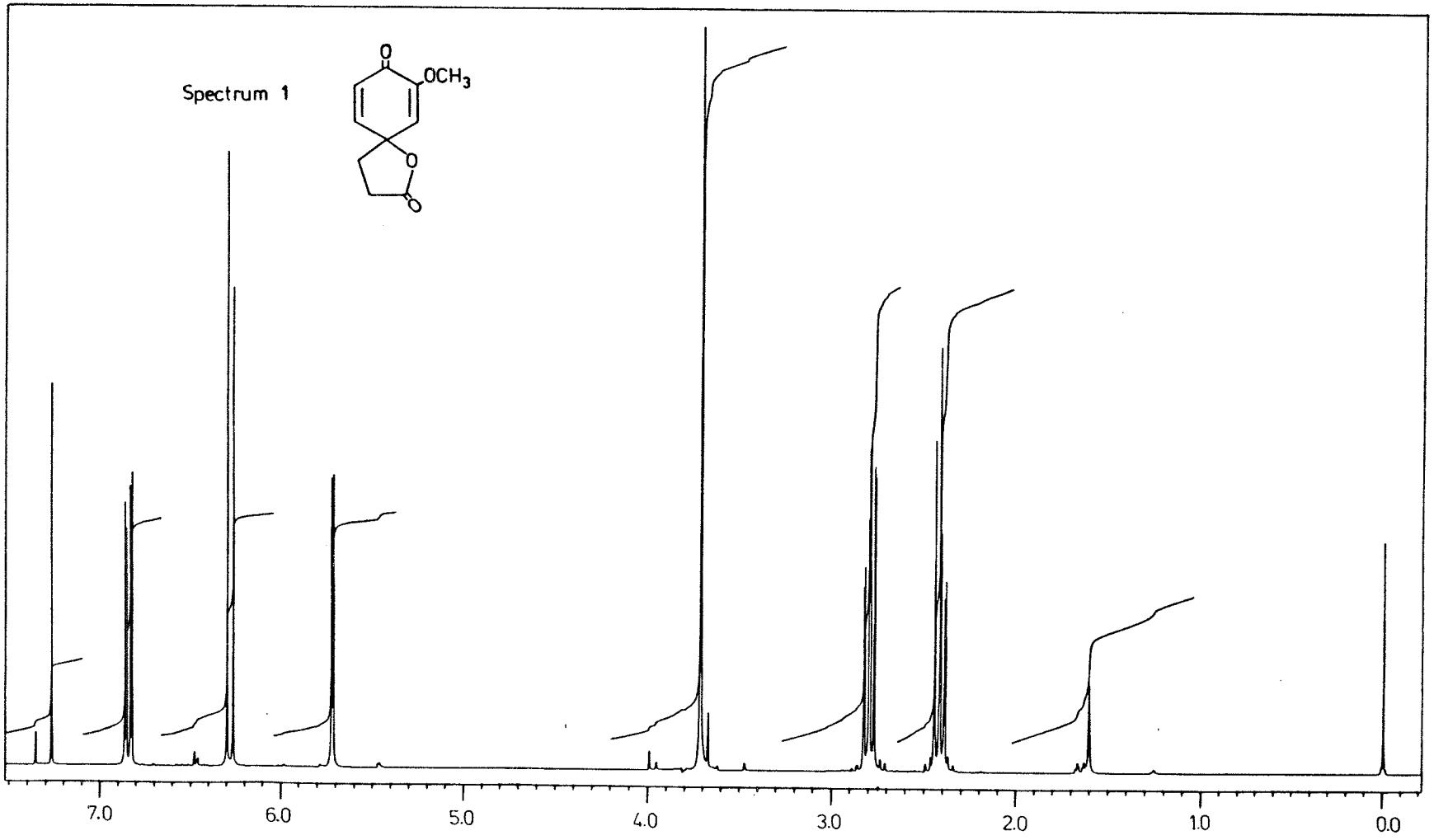
Negative result was obtained for the reaction of homovanillic acid and TTFA. Approximately 20% of the homovanillic acid used was recovered by acidifying the aqueous layer and extracting it with methylene chloride. No product was obtained.

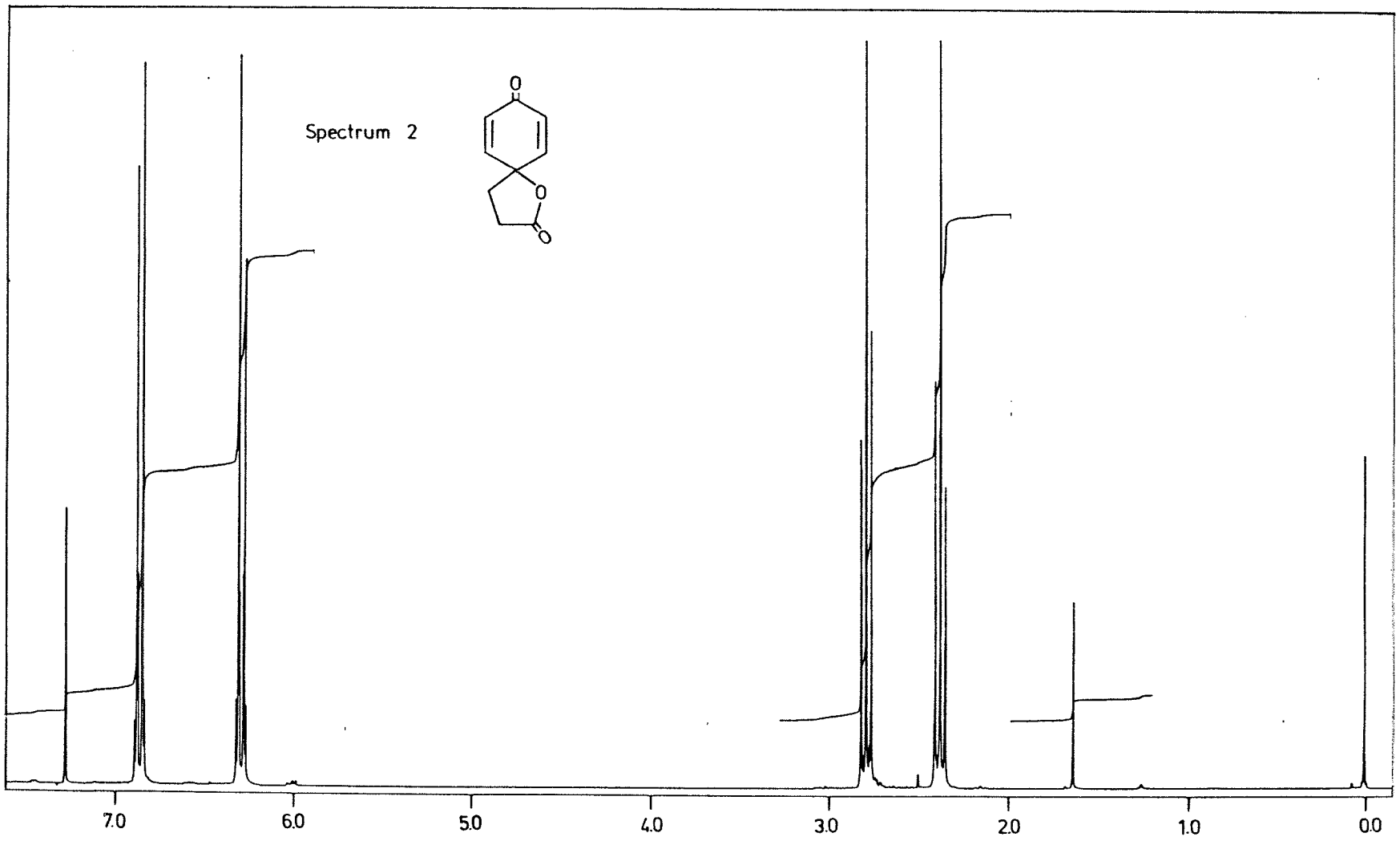
6-Methoxy-1-oxaspiro[3.4]nona-5,8-diene-7-one:

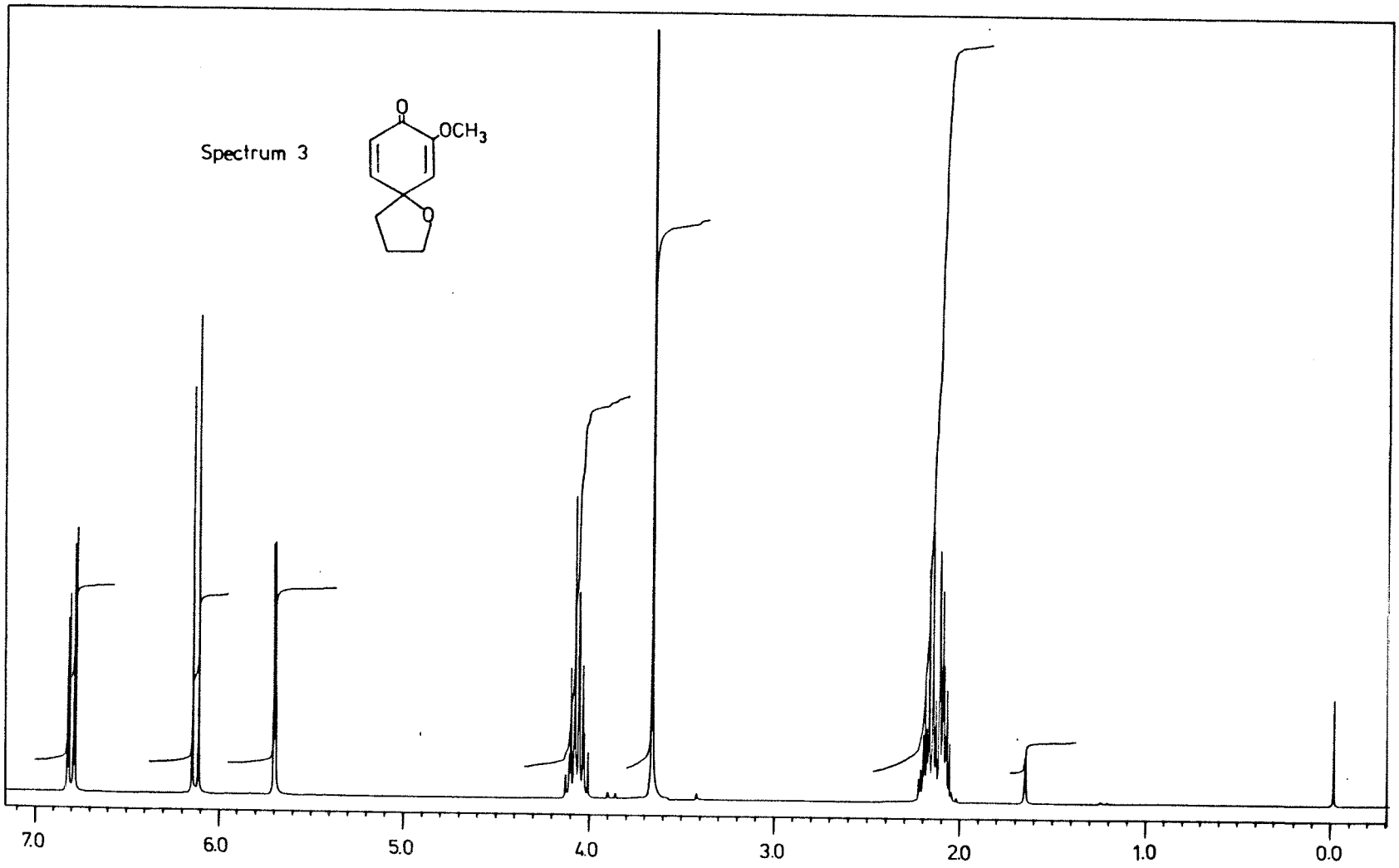
The reaction of 2-(4-hydroxy-3-methoxyphenyl)ethanol with lead tetraacetate or thallium (III) trifluoroacetate did not give positive results. None of the starting alcohol was recovered and no identifiable product was obtained.

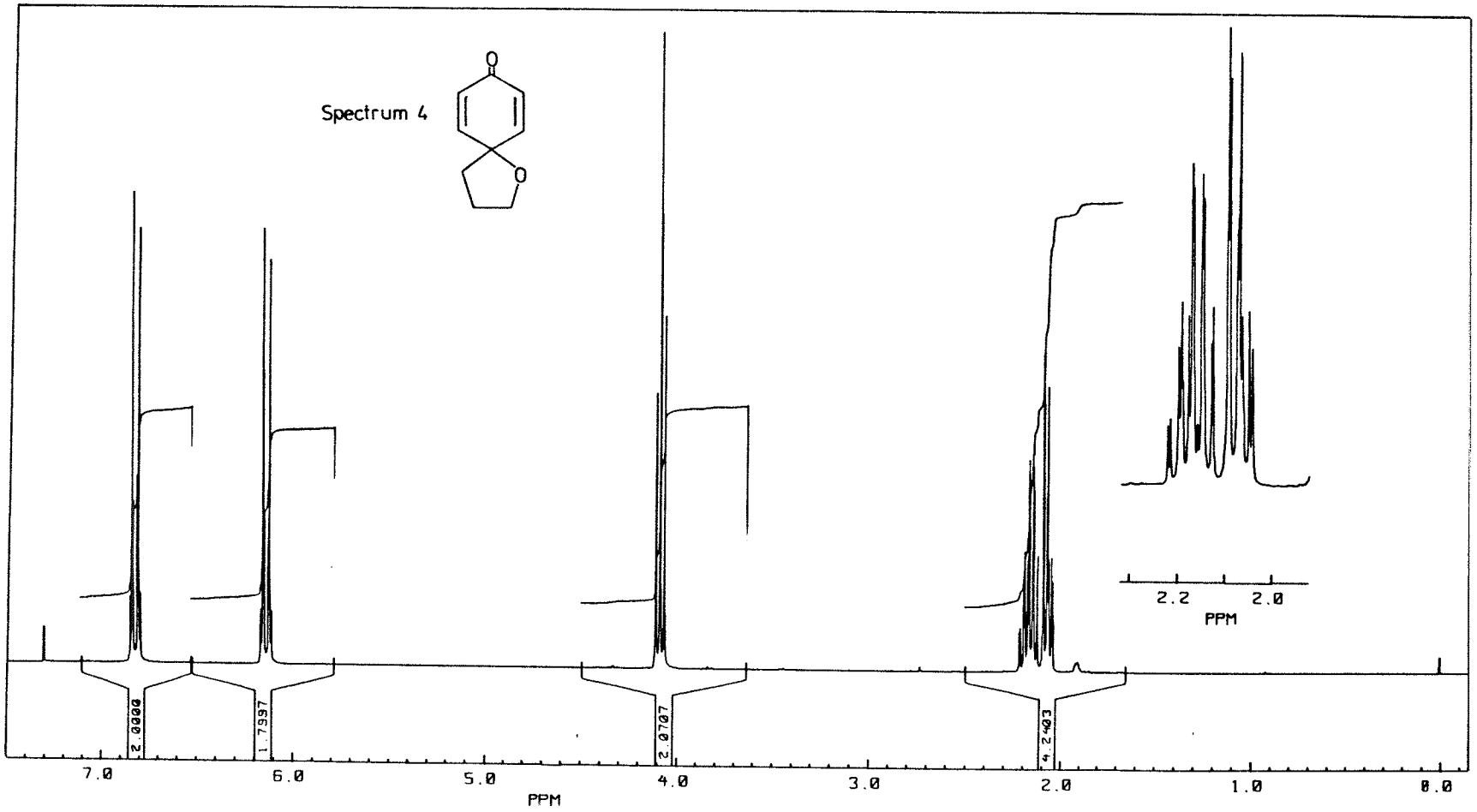
5.1 APPENDIX 1

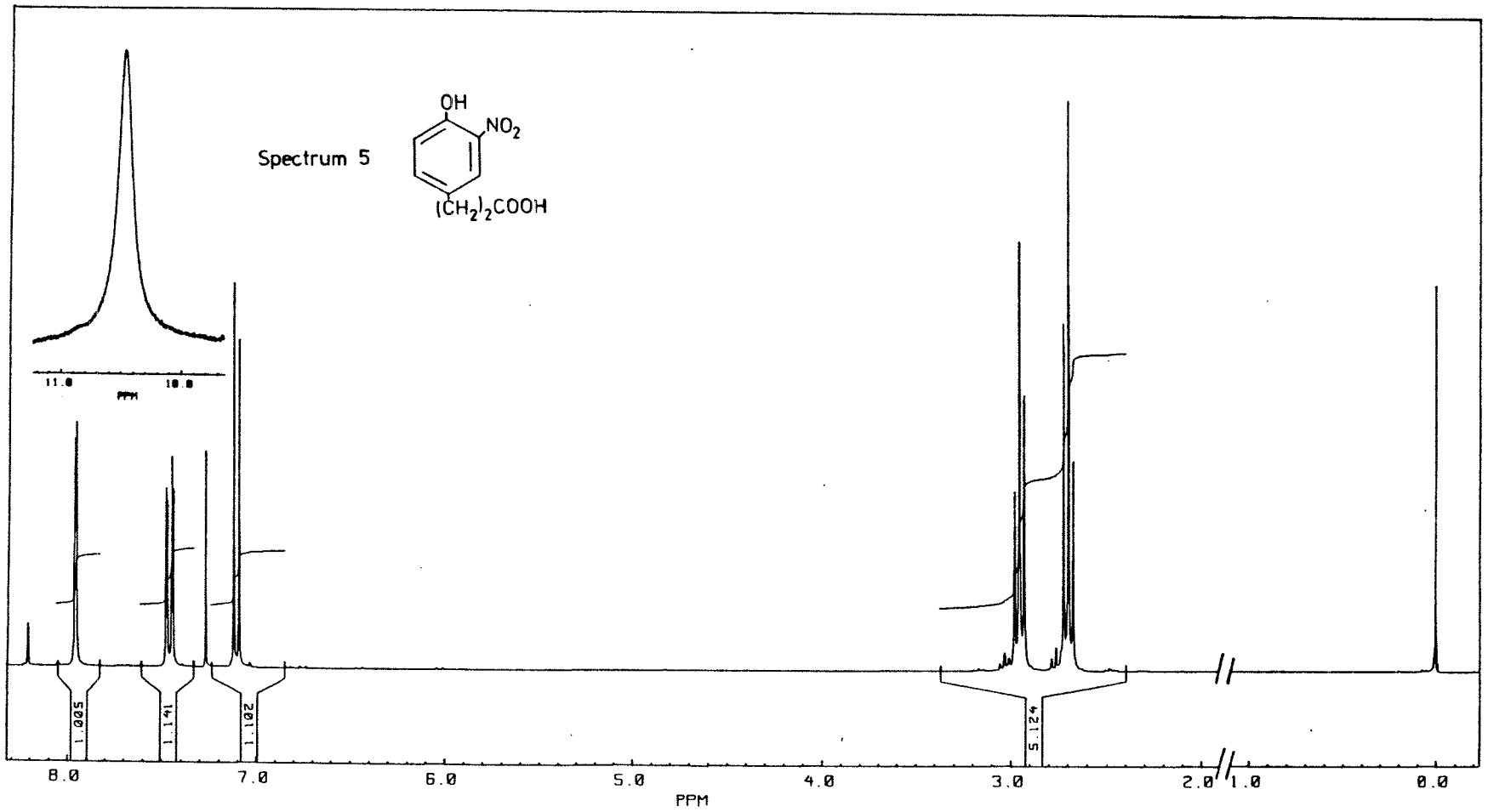
^{1}H-NMR and ^{13}C-NMR SPECTRA

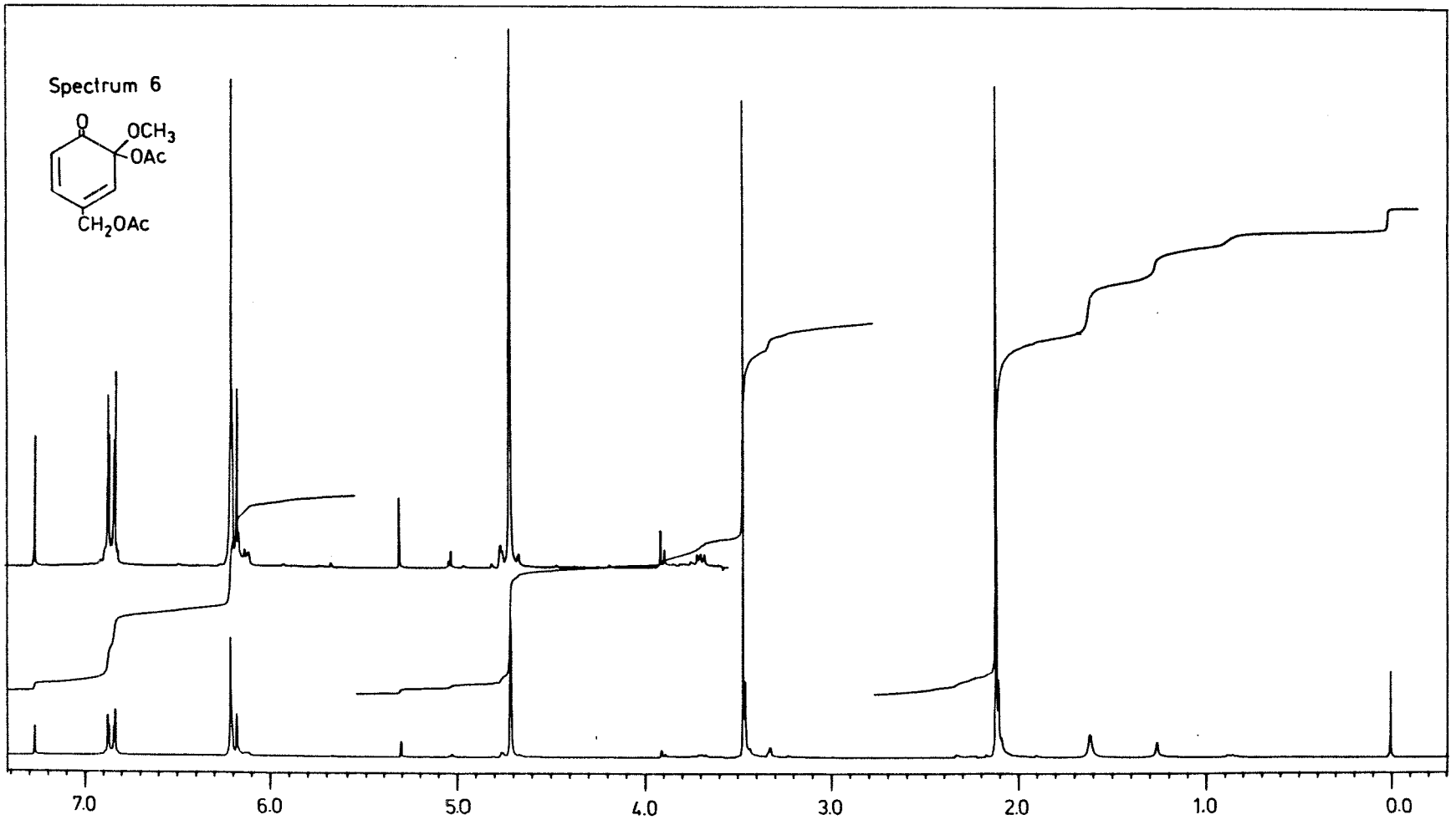

Spectrum 1
O
OCH3
O
O
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

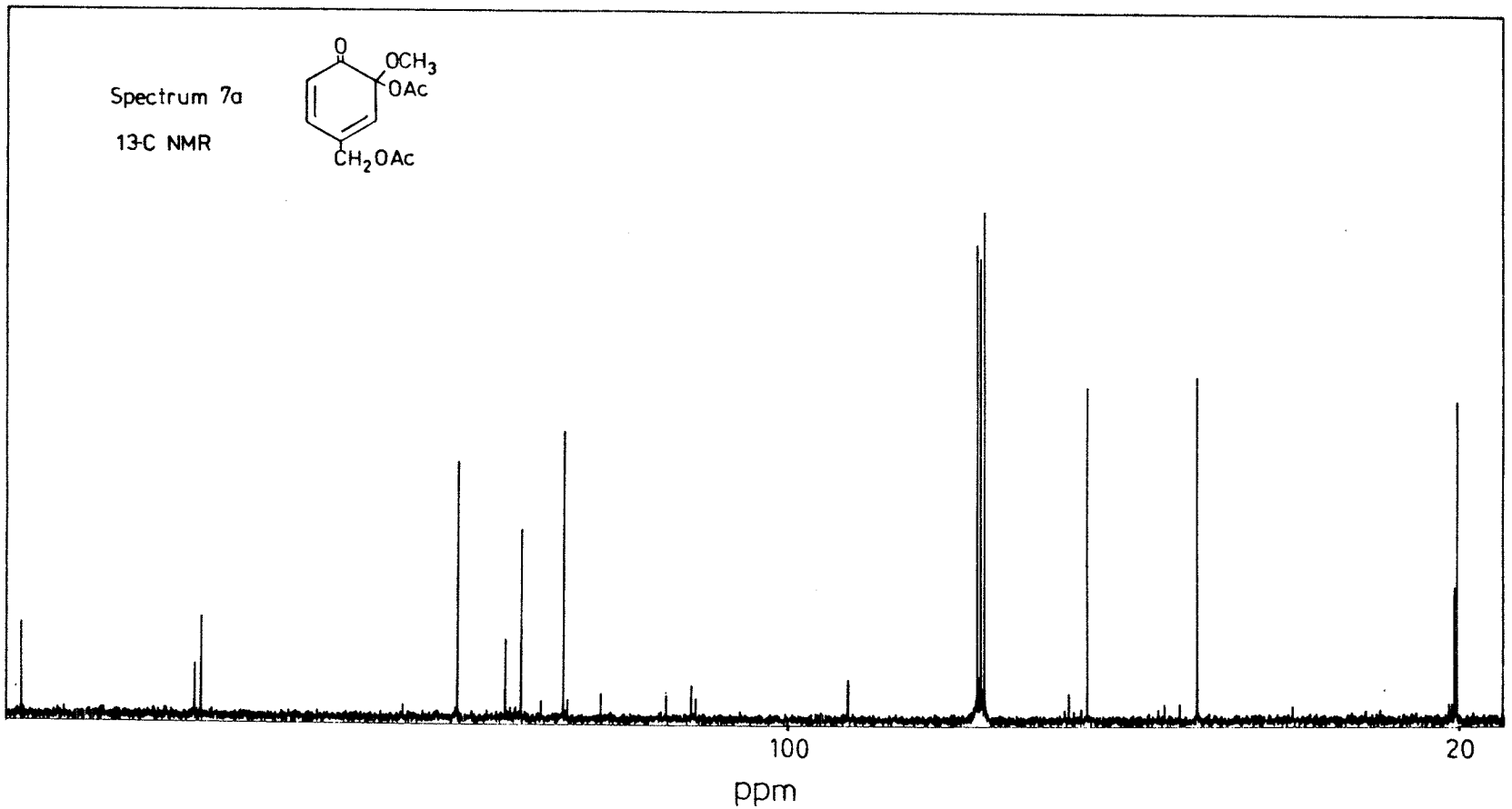

Spectrum 2
O
O
O
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

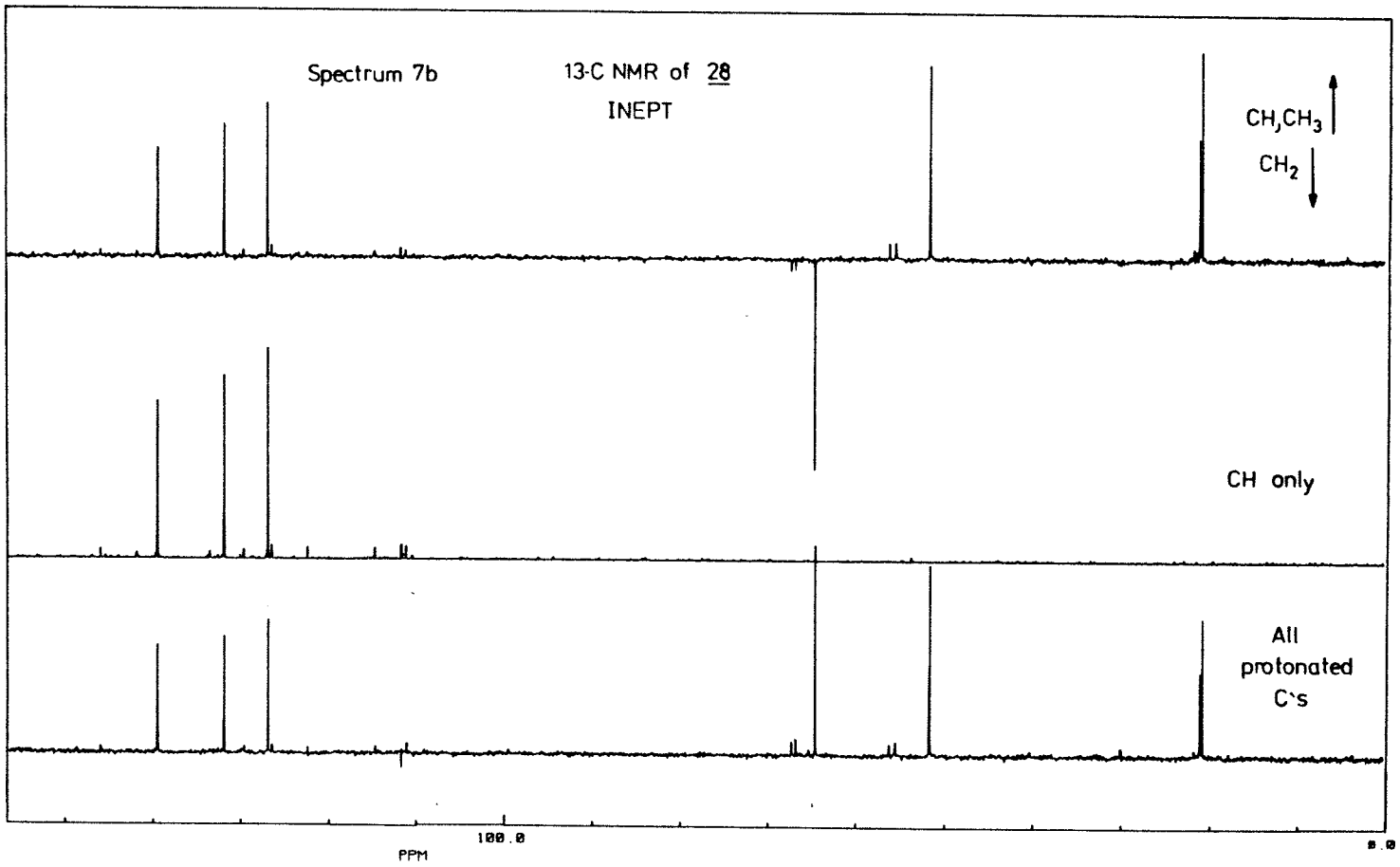

Spectrum 3
O
OCH3
O
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

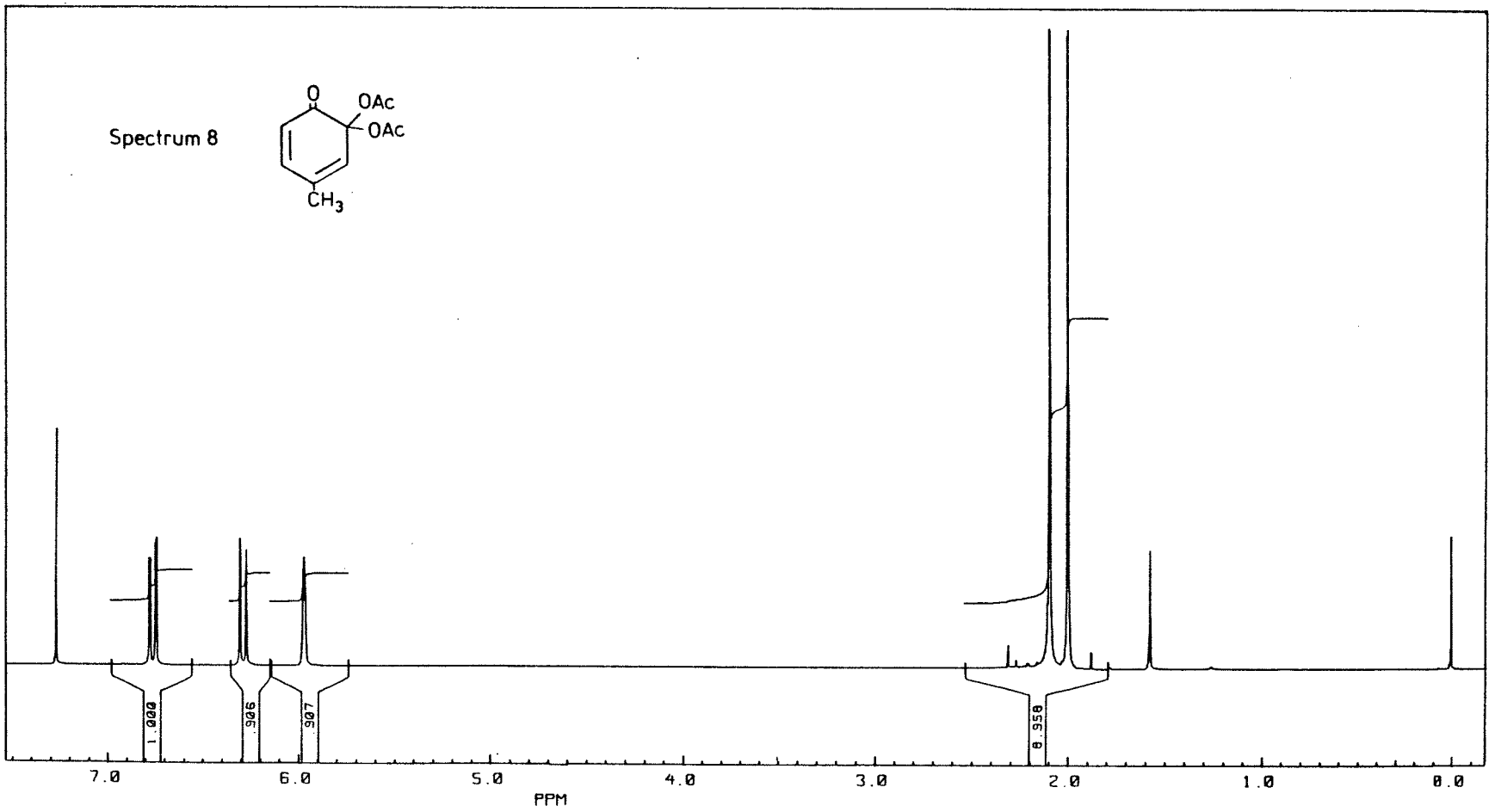

Spectrum 4
O
O
2.0000
1.7937
2.0707
4.2403
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
2.2
2.0
PPM

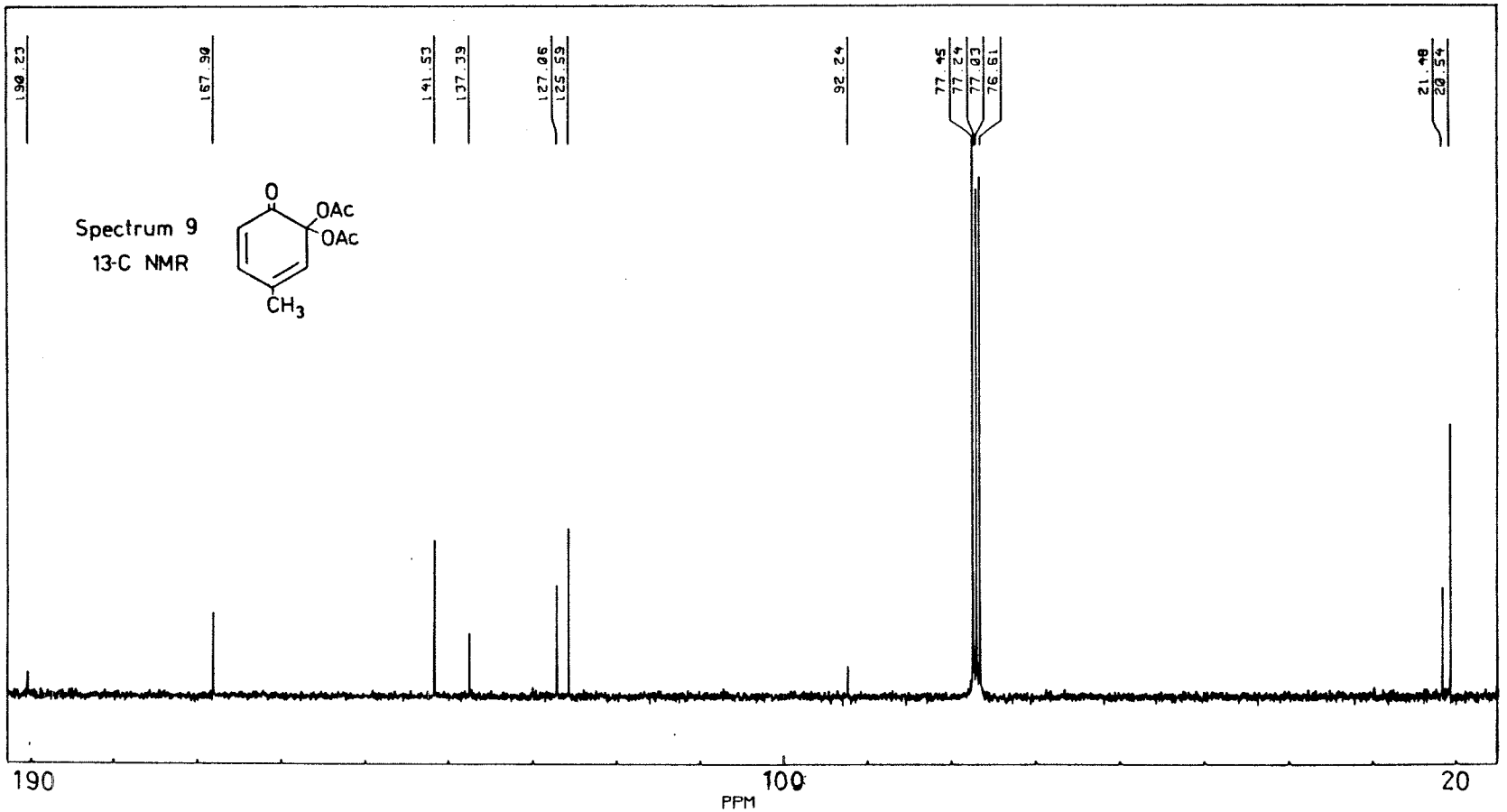

Spectrum 5
OH
NO2
(CH2)2COOH
11.0
10.0
PPM
1.005
1.141
1.102
5.124
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


Spectrum 6
O
OCH3
OAc
CH2OAc
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0


Spectrum 7a
13-C NMR
O
OCH3
OAc
CH2OAc
100
20
ppm


Spectrum 7b
13-C NMR of 28
INEPT
CH,CH3
CH2
CH only
All
protonated
C's
100.0
PPM
0.0

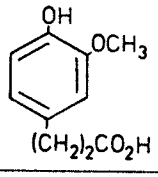
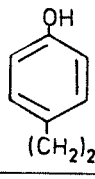
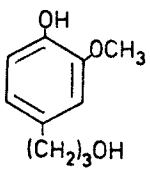
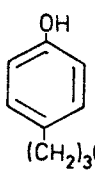
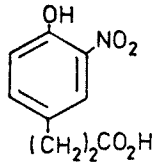
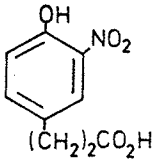
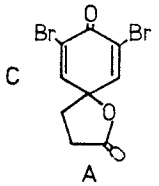

Spectrum 8
O
OAc
OAc
CH3
1.000
.906
.907
8.959
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


190.23
167.90
141.53
137.39
127.06
125.59
92.24
77.45
77.24
77.03
76.61
21.48
20.54
Spectrum 9
13-C NMR
O
OAc
OAc
CH3
190
100
20
PPM

5.2 APPENDIX 2

TABLES

Table 1. Oxidants used for oxidations

Oxidants \ Substrates				
LTA	C (85)	C (14)	C (82)	D
TTFA	C (85)	C (55)	C (85)	C (60)
$(NH_4)_2Ce(NO_3)_6$	C (69)	C 	A	A
TTN	C (45)	C (40) + 	A	A
DDQ	C (20)	B	A	A
$NaIO_4$	C (18)	A	A	A
NBS	C (4)	C 	A	A
HgO	B	A	A	A
$K_3[Fe(CN)_6]$	B	A	A	A
PTAD	B	A	A	A
$BaMnO_4$	B	A	A	A
$Ce(OH)_3OOH$	B	A	A	A
$NCS/(CH_3)_2S$	B	A	A	A
$FeCl_3$	B	A	A	B
PbO_2	A	B	A	A

A: oxidant not used; B: no reaction with oxidant; C: oxidant used (yield of spirocompound); D: reaction with oxidant, but did not obtain spirocompound.

Table 2. Chemical shifts of quassinoid terpenic substances

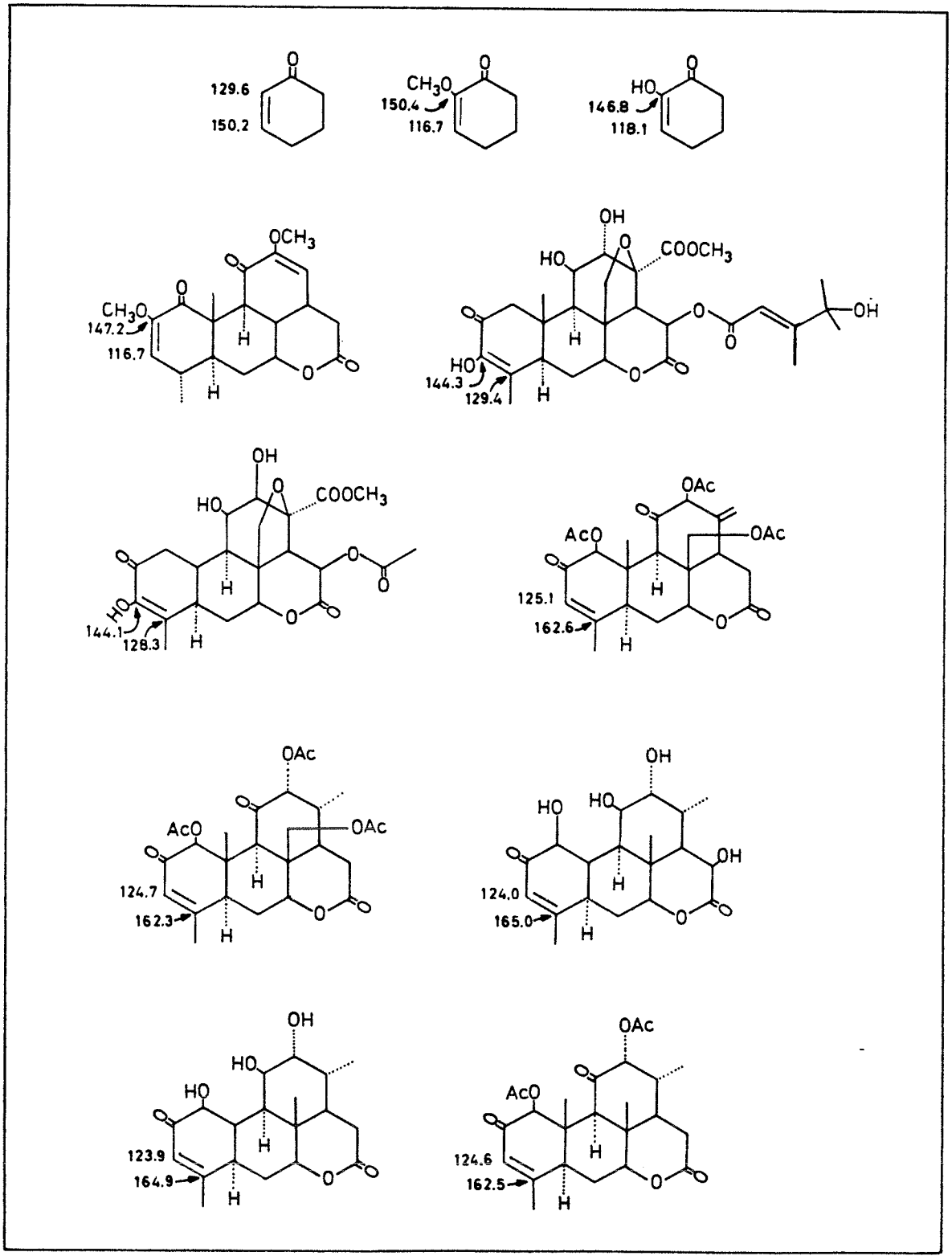


Table 3. Spectroscopic data obtained from spirocompounds (Part 1)

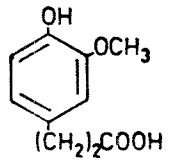
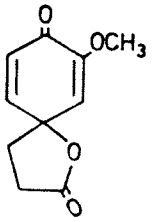
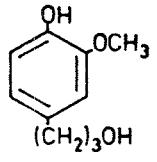
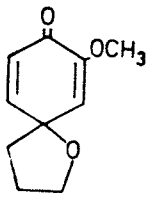
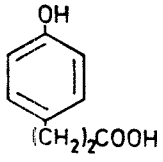
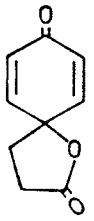
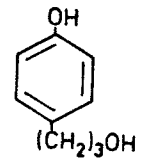
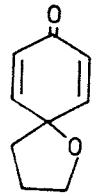
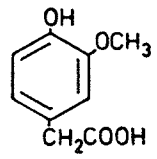
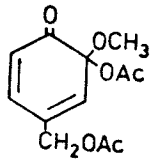
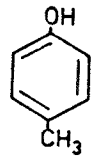
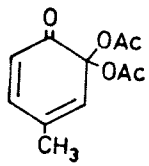
Substrate	Reaction conditions	Product obtained (% yield)	^{1}H-NMR (ppm)	IR (cm^{-1})	Mass (m/e)
	a) LTA (2.5eq.), CH_2Cl_2, r.t., 20 min. (85) b) TTFA (1.6eq.)*, CH_3CN, 0^oC, 60 min. (85)		6.85 dd 1H 6.27 d 1H 5.71 d 1H 3.71 s 3H's 2.79 t 2H's 2.41 t 2H's	1766 C=O 1676,1650 C=O 1620 C=C	194(M^+), 166, 152, 151, 140, 121, 55
	a) LTA (2.5eq.), CH_2Cl_2, r.t., 15 min. (82) b) TTFA (1.6eq.)*, CH_3CN r.t., 30 min. (85)		6.82 dd 1H 6.14 d 1H 5.71 d 1H 4.08 m 2H's 3.68 s 3H's 2.15 m 4H's	1680 C=O 1615 C=C	180(M^+), 152, 137, 124, 109
	TTFA (6eq.)*, CH_3CN, r.t., 20 min. (55)		6.86 d 2H's 6.29 d 2H's 2.80 t 2H's 2.38 t 2H's	1768 C=O 1672,1632 C=O 1614 C=C	164(M^+), 136, 122, 110, 55

Table 3. Spectroscopic data obtained from spirocompounds (Part 2)

Substrate	Reaction conditions	Product obtained (% yield)	^{1}H-NMR (ppm)	IR (cm^{-1})	Mass (m/e)
	TTFA (3.1eq.)**, CH_3CN, r.t., 45 min.	 (60)	6.81 d 2H's 6.14 d 2H's 4.09 t 2H's 2.12 m 4H's	1672,1630 C=O 1604 C=C	150(M^+), 122, 109, 107, 94
	LTA (2.5eq.), CH_2Cl_2, r.t., 30 min.	 (76)	6.85 dd 1H 6.19(d), 6.20(s) overlapping 2H's 4.71 s 2H's 3.46 s 3H's 2.11 s 6H's	1746 C=O 1696 C=O	M^+: not observed 212, 195, 152
	LTA, AcOH, r.t.	 (52)	6.76 dd 1H 6.29 d 1H 5.97 s 1H 2.09 s 3H's 2.00 s 6H's	1742 C=O 1700 C=O	***

*old TTFA was used **new TTFA was used ***spectrum not taken

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6. REFERENCES

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