STUDIES DIRECTED AT THE STEREOSELECTIVE SYNTHESIS OF FLAVONOIDS THROUGH THE HYDROGENATION OF PROCHIRAL PRECURSORS

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by

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Johannes H. van Tonder

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CHAPTER 1

INTRODUCTION

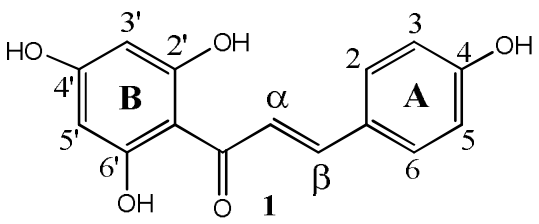
Flavonoids are an extensive group of polyphenolic compounds that occur commonly in plants. They are prominent secondary plant metabolites that are present in dietary components, including fruits, vegetables, olive oil, tea and red wine. As a group, flavonoids contain more than 8000 known compounds and this number is constantly growing due to the great structural diversity arising from the various hydroxylation, methoxylation, glycosylation and acylation patterns.

Many flavonoids are known to show biological activities such as anti-inflammatory,[1,2,3] antiallergic,[4,5,6,7] antithrombotic,[8,9,10,11,12] antibacterial,[13] antifungal[14] and antitumoral[15,16,17,18,19] properties. They are also active as anti-oxidants although the *in vivo* anti-oxidant activity is very limited due to weak absorption (around 5%) in the small intestine, together with rapid metabolizing and excretion. Physiological activities will be discussed in subsequent paragraphs (*cf*. paragraph 1.2).

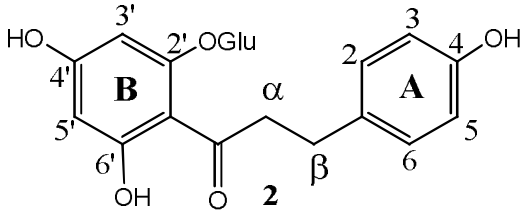
1.1 Structural diversity

While all monomeric flavonoids exhibit the basic C_6-C_3-C_6 skeleton, some may occur as compounds with a heterocyclic ring, while others are acyclic with regard to the C_3 portion of the molecule. 'Acyclic' flavonoids include compounds like chalcones (**1**), dihydrochalcones (**2**) and *retro*-chalcones (**3**); all of which may or may not contain oxygenated substitution at either the α- or β-positions (**4**), (**5**). The term *retro*-chalcone is used to indicate that the typical substitution pattern of the A- and B-rings of the chalcone has been inverted, i.e. the

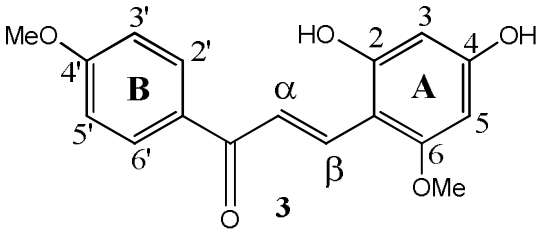
usual substitution displayed by the A-ring is now present on the B-ring (next to the carbonyl group) and *vice versa*.



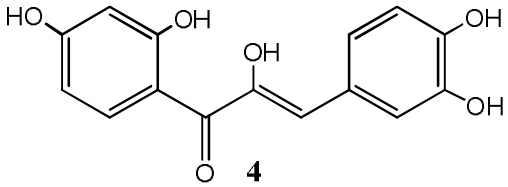
Nonaringenin



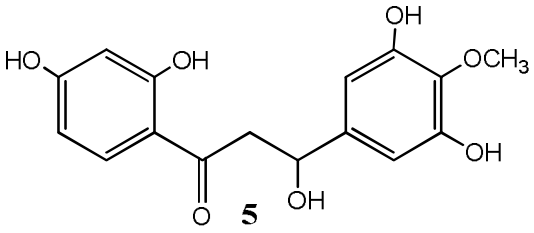
Phloridzin



2,4-dihydroxy-4',6-dimethoxychalcone



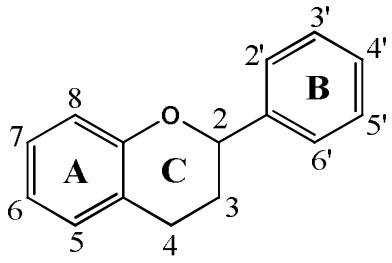
α-hydroxy butein



β,2',3,4',5-pentahydroxy-4-methoxy dihydrochalcone

Depending on the position of the phenyl substituent, the 'cyclic' flavonoids are divided into three major groups; i.e. flavonoids with a 2-phenylchromane skeleton, (**6**), isoflavonoids with a 3-phenylchromane skeleton, (**7**)**,** and the 4-phenylchromane compounds known as the neoflavonoids, (**8**). The 2-phenylchromenylium or flavylium cation (**9**) forms the skeleton for anthocyanidins and anthocyanins*.

* In the 'cyclic' flavonoids the ring next to the heterocyclic ring now becomes the A-ring.



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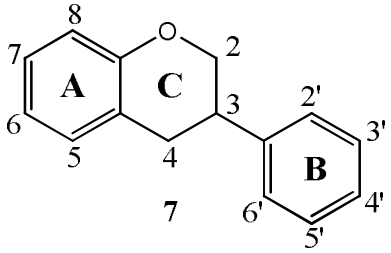

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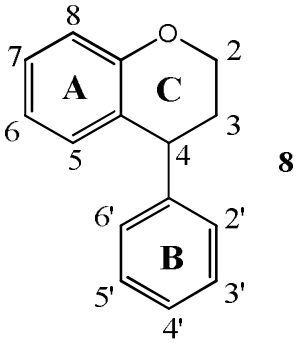

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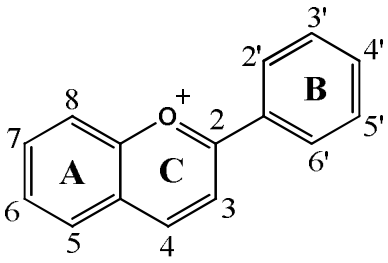
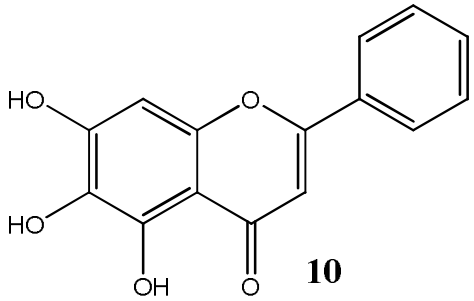


9

The ring oxygenation patterns of flavonoids vary considerably. While most compounds show either phloroglucinol (e.g. **1**) or resorcinol (e.g. **4**) type A-rings ('cyclic' nomenclature), representative examples with a pyrogallol A-ring substitution pattern (eg. Baicalein, **10**) are also known and even analogues with fully oxygenated A-rings (eg. Konakugin, **11**) have been isolated. With regards to B-ring oxygenation, flavonoids may exhibit oxygen functionality at the 4-, 2,4-, 3,4-, or 3,4,5-positions and very rarely at the 2,4,5-positions. The diverse oxygenation patterns represented amongst the flavonoids may also be accompanied by C- or O-methylation, alkylation, acylation and/or glycosylation. Cyclization of these alkyl or acyl groups onto other ring positions (eg. Flemichin-D, **12**) or the C_3 moiety (eg. Medicarpin, **13**) of the compounds lead to a further degree of complexity in the structure of flavonoids.



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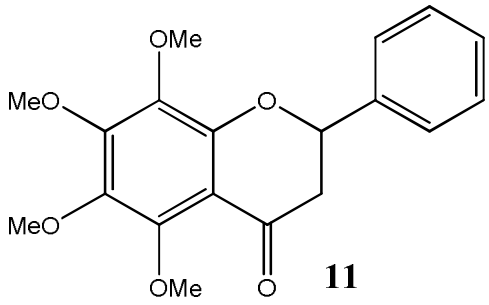

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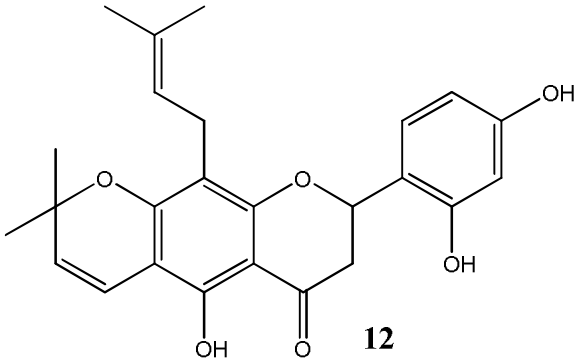

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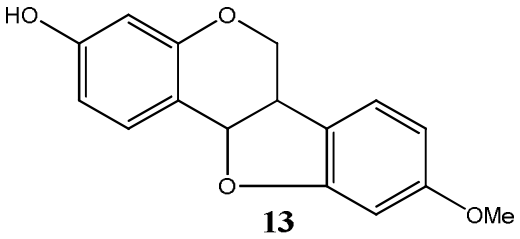
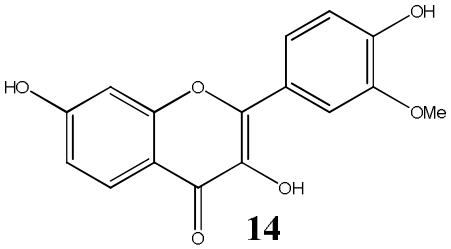
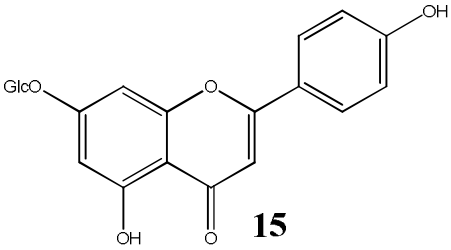
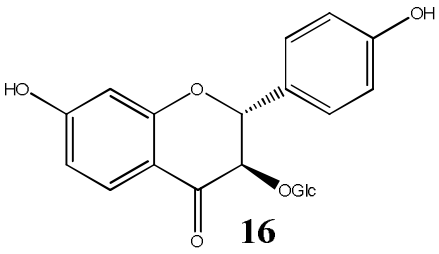
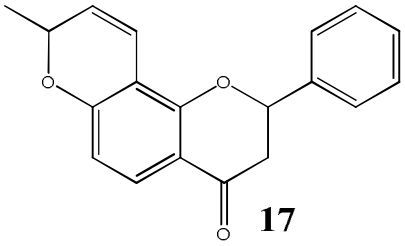
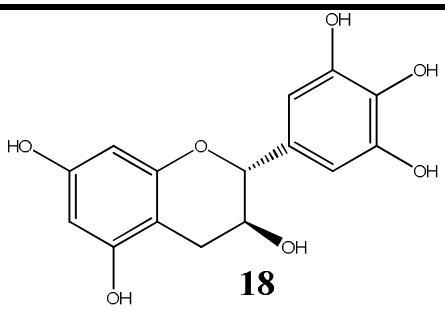
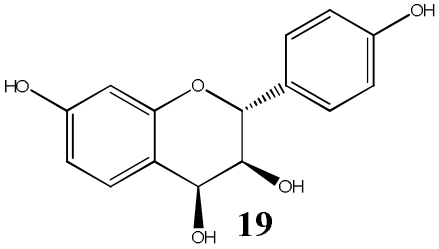
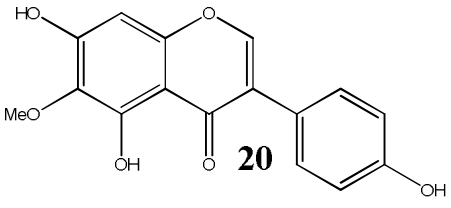


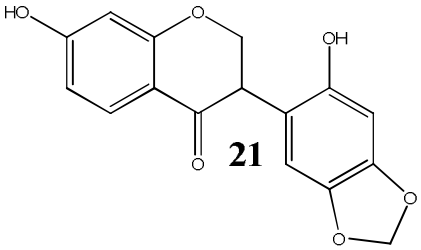
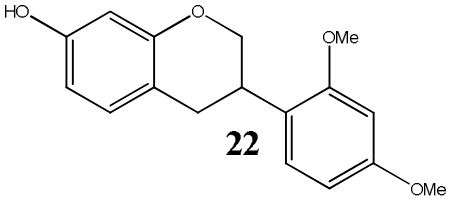
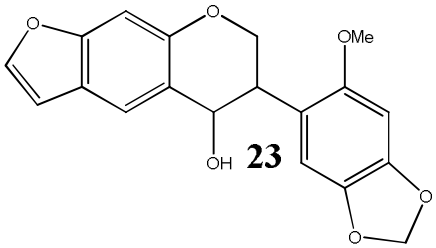
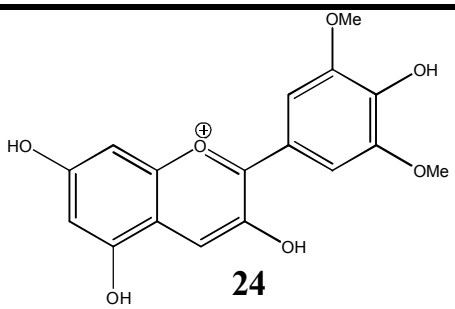
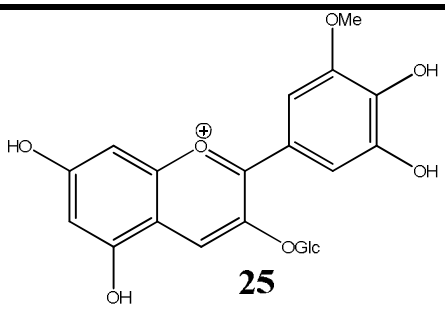
13

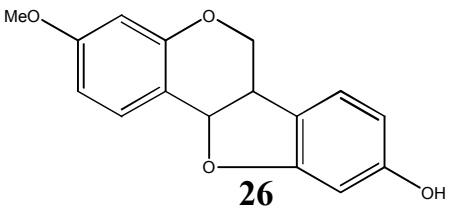
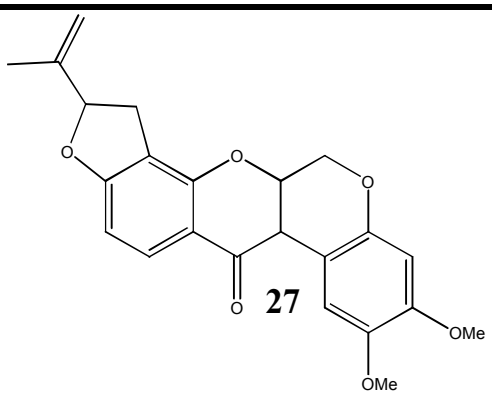
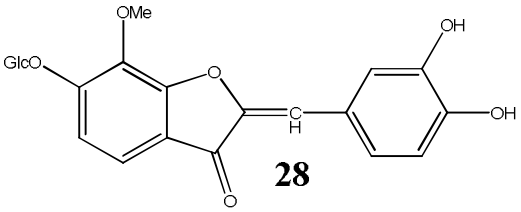
The oxidation state and oxygenation pattern of the heterocyclic C ring of the 'cyclic' flavonoids provide further grounds for differentiation. These categories include flavonols, flavones, dihydroflavonols, flavanones, flavanols, flavandiol, isoflavones, isoflavanones, isoflavans, isoflavanol, pterocarpans, rotenoids, aurones, anthocyanidins and glycosides of the latter, anthocyanins (Table 1-1). Of all types of flavonoids, flavones and flavonols are the most abundant compounds in natural sources.

Table 1-1: Examples from different flavonoid categories

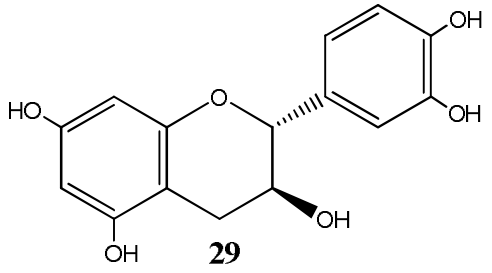
Category	Structure	Trivial name
Flavonol	 **14**	Geraldol
Flavone	 **15**	Cosmosiin

Category	Structure	Trivial name
Dihydroflavonol	 **16**	Lecontin
Flavanone	 **17**	Isolonchocarpin
Flavanol	 **18**	(+)-Gallocatechin
Flavandiol	 **19**	(+)-Guibourtacacidin
Isoflavone	 **20**	Tectorigenin

Category	Structure	Trivial name
Isoflavanone	 **21**	Sophorol
Isoflavan	 **22**	Sativan
Isoflavanol	 **23**	Ambanol
Anthocyanidin	 **24**	Malvidin
Anthocyanin	 **25**	3-Glucoside petunidin

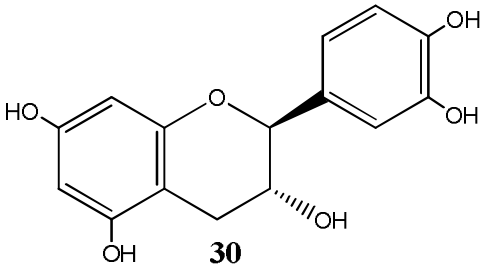
Category	Structure	Trivial name
Pterocarpan	 **26**	Isomedicarpin
Rotenoid	 **27**	Rotenone
Aurone	 **28**	Leptosin

Another area of structural diversity in the flavonoids is to be found in the absolute- and relative stereochemistry of the C_3 moiety. Flavanols, flavanones, dihydroflavonols, isoflavanones and isoflavans all contain one or more chiral centres. The absolute configuration of substituents at these chiral centres is often included in the trivial names of these compounds. The flavan-3-ol, catechin (**29** and **30**), for example, contains two chiral centres, which results in four stereoisomers. If the *trans*-configuration is observed, the compound is known as catechin, whereas, the *cis*-configuration is designated by the prefix epi. Epicatechin (**31** and **32**) will therefore be the 3,4-*cis* version of catechin. The definition of absolute configuration is completed by the sign of the optical rotation [(+) or (-)] associated with the specific compound. In agreement with the rule that all flavan-3-ols with a 2*S* absolute configuration are denoted the prefix *ent*, (-)-catechin and (-)-epicatechin may also be designated by addition of the prefix *ent* to the basic name.[20]



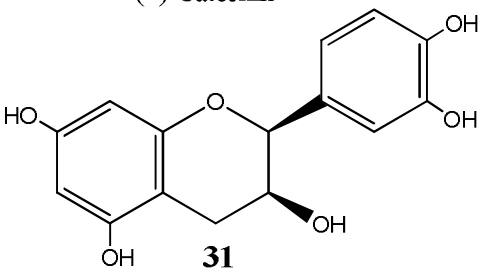
29

(+)-Catechin



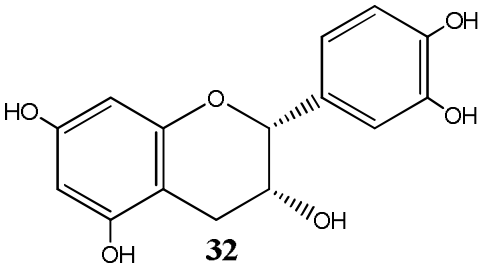
30

(-)-Catechin or *Ent*-catechin



31

(+)-Epicatechin



32

(-)-Epicatechin or *Ent*-epicatechin

For naturally occurring flavanones (eg. Isolonchocarpin, **17**) and dihydroflavonols (eg. Lecontin, **16**) the optical activity is usually levorotatory implying one configuration predominating in nature.[21] The dihydroflavonols (eg. Lecontin, **16**) generally exhibit *trans* configuration with absolute stereochemistry being mainly 2*R*:3*R* in correspondence with the 2*S* flavanone isomer.

The absolute stereochemistry at the C-2 chiral centre of flavanones can also be determined with circular dichroism (CD). Two transition bands, i.e. *ca*. 285 – 290 nm and 330 – 340 nm correlating respectively to the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of the carbonyl group, are important in the assignment of the absolute configuration of flavonoids. In a non-empirical study, Giorgio *et al*.[22] and Gaffield *et al*.[23] were able to correlate the 2*S*-configuration of the natural flavanone, naringenin (4',5,7-trihydroxyflavanone), with a negative Cotton Effect (CE) at *ca*. 290 nm. When the flavanone is drawn with the basic C_6-C_3-C_6 skeleton horizontally, A-ring to the left, B-ring to the right and the heterocyclic oxygen to the top, this would mean that the 2-aryl ring would occupy an equatorial α-orientation. A positive CE at 290 nm would then indicate an axial or β-orientated B-ring corresponding in most instances to a 2*R* configuration. It must be pointed out that care should be taken in assigning *R* and *S* absolute configuration to flavanones as it is dependent on the priorities of the substituents

attached to the chiral centre, which is in turn influenced by the oxygenation pattern on the heterocyclic C- as well as aromatic B-ring.

1.2 Physiological activity

Flavonoids are the pigments responsible for the shades of yellow, orange and red in flowering plants.[24,25] They also play a pivotal role in plant development, growth and defence.[25,26,27] Many of these molecules are biologically active exhibiting anti-inflammatory,[1,2,3] antiallergic,[4,5,6,7] antithrombotic,[8,9,10,11,12] antibacterial,[13] antifungal[14] and antitumoral activities.[15,16,17,18,19] Some flavonoids are also believed to inhibit certain enzymes in biological systems, such as lipoxygenase, cyclo-oxygenase, mono-oxygenase, xanthine oxidase, mitochondrial succinoxidase, reduced nicotinamide-adenine dinucleotide (NADH) oxidase, phospholipase A_2, topoisomerases and protein kinase.[21,25]

In total the pharmacological effects of flavonoids are mainly ascribed to their antioxidant activities[28,29,30,31] as radical scavengers, reductants and metal chelators,[32] but their nonantioxidant functions are also believed to make a contribution. The latter include interactions with different enzymes, inhibition of calcium ion reflux into cells and regulation of cell signalling and gene expression.[16] As a reductant, the flavonoids are oxidized in order to reduce other biological molecules. Acting as a metal chelating agent they reduce the capacity of a metal to produce free radicals. These effects can, however, not be assigned exclusively to the flavonoids since other biological components may directly contribute or enhance them. Several flavonoid-based herbal medicines are known which rely on these activities (Table 1-2).[16]

Table 1-2: Herbal medicines

Herb	Herbal species	Uses
Bilberry fruit extract	*Vaccinium myrtillus*	Capillary weakness Venous insufficiency Diarrhoea
Elder flower	*Sambucus nigra*	Feverish conditions Common cold

Herb	Herbal species	Uses
St. John's wort	*Hypericum perforatum*	Mild to moderate depression
Witch hazel leaf/bark	*Hamamelis virginiana*	Skin injuries Varicose veins Hemorrhoids
Linden flowers	*Tilia cordata*	Cold relief Nervous tension

The phenolic compounds of fruits and vegetables have proven to be powerful free radical scavengers both *in vitro* (neutralizing synthetic free radicals) and *in vivo* (neutralizing physiologically relevant peroxyl radicals, hydroxyl radicals and superoxides).[33] Catechin (**29** and **30**) for instance was shown to scavenge radicals *via* electron transfer or by acting as a hydrogen donor.

Berries, green leafy vegetables and citrus fruits all have high potential of antioxidant activities but these potentials differ vastly even within the same variety. Different cultivation sites, climates, stages of maturity and sample preparation and extraction procedures are believed to contribute to this observation.[34]

Consumption of flavonoid-containing foods was found to be inversely related to coronary heart disease[35] and genotoxic activity[36]. Atherosclerosis is caused by cholesterol-loaded macrophages, which originates from the internal oxidation of low-density lipoproteins (LDL). Dietary consumption of flavonoids causes an increase in antioxidant capacity in cells which result in an inhibition of oxidation of LDL thus preventing atherosclerosis to a certain extent. *Glycyrrhiza glabra*, the licorice plant, generally used as sweetening or flavouring agent, is one example which reduces LDL oxidation. This corresponds with the well-known French paradox in which the population of southern France suffers a low cardiovascular mortality in spite of having a diet which is high in saturated fats but is accompanied with moderate daily consumption of red wine.[35]

1.3 Known dietary sources of flavonoids

A Chinese emperor accidentally discovered one of the major dietary sources of flavonoids; tea (*Camellia sinensis*). Depending on the preparation, tea can be categorised as green-, oolong-, black- or pu'er tea. Pu'er tea is almost exclusive to Asia and is fermented by anaerobic bacteria rather than enzymes.[37] Due to the differences in preparation these teas have different compositions giving each some special properties.[38]

Fresh leaves and buds are used to produce green tea.[38] The leaves and buds are pan-fried, rolled and dried. Green tea contains catechins, bioflavonoids and high levels of fluoride. The high amount of fluoride may reduce teeth decay and help strengthen teeth and bones.[39]

Oolong tea is obtained by slightly bruising wilted leaves and partially fermenting them.[40] Decreasing of cholesterol levels, blood pressure and blood clotting tendencies are some of the properties ascribed to oolong tea.[38] These properties may thus reduce the possibility of arterial diseases. This tea has also exhibited an inhibitory effect on dental caries in rats.[40]

A higher degree of fermentation of the slightly wilted leaves, yields black tea. Black tea is rich in tannins and can be used to relieve certain types of headaches and for the treating of diarrhoea.[38] Damp black tea bags can also be used to reduce itching and redness of tired eyes and insect bites.[38]

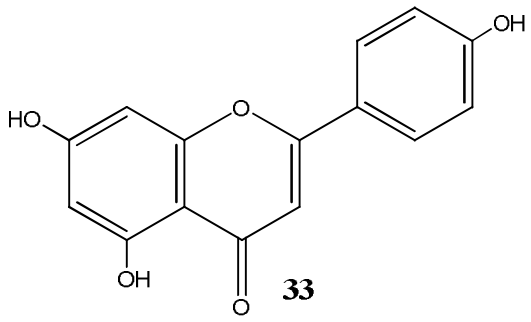
Generally the teas contain relatively large amounts of flavan-3-ols. The fermentation processes cause polymerization of the monomeric units (catechins) to yield dimers (theaflavins) and other oligomers (tannins). Flavonols and flavones are also present but in lesser amounts.

Red wine is another good source of flavonoids. Flavonols, flavan-3-ols, anthocyanins and proanthocyanidins are all present. The composition is, however, greatly influenced by the cultivar and maturity of the grapes used as well as environmental factors and the wine-making techniques employed. Ethanol quantity is also believed to influence the biological activity of the wines.[41]

Citrus fruits and cranberries also contain flavonoids in noticeable amounts. Citrus fruits contain mainly monomers[42] whereas cranberries contain large amounts of proanthocyanidins. The A-type proanthocyanidins are believed to have urinary bacterial anti-adhesion activities which help in maintaining a healthy urinary tract.[43,44]

Improvements in memory performance and cognitive functions as well as an inhibitory effect on the progression of Alzheimer's disease have been observed with the consumption of *Ginkgo biloba*.[45] Flavonoids also play a role in preventing neurodegeneration[46] and neuroregeneration[47]. This together with the ability to protect cells from oxidative stress might contribute to the observed neural effects.

Daily antioxidant intake can also be increased with herbs. Ethanol extracts of ginseng (*Panax ginseng*) may contain up to 2333 mg of phenolics and 1199 mg of flavonoids from 100 g of fresh herb.[48] Other herbs like parsley (*Petroselinum crispum*) and dill (*Anethum graveolens*) may contain up to 630 mg apigenin (**33**) and 110 mg quercetin (**34**), respectively, per 100 g of fresh herb.[49]



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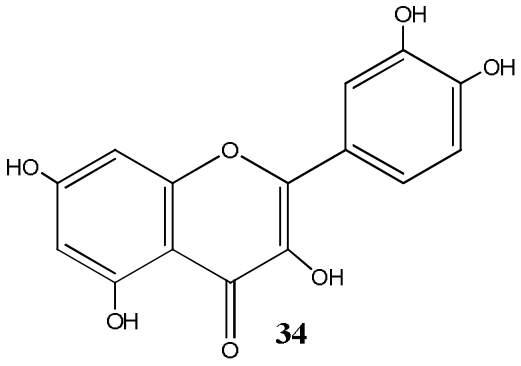

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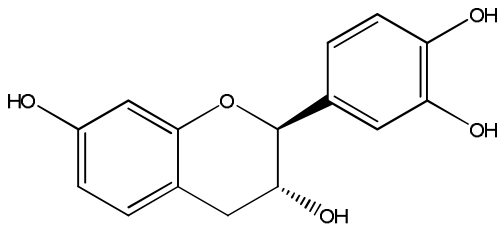
CHAPTER 2

STEREOSELECTIVE SYNTHESIS OF FLAVONOIDS

2.1 Introduction

It is clear that the physiological activities of flavonoids are not well understood and no definitive mechanisms for any of their health promoting effects are available. This emphasises the need for *in vitro* studies of these compounds in order to explain how they are metabolized. Although progress has been made, further investigations are hampered by the inaccessibility of the enantiomeric pure monomeric starting materials, e.g. (+)- and (-)-fisetinidol (**35** and **36**). Physiological activity and other investigations into the properties of proanthocyanidins are therefore confined to the substitution patterns exhibited by those monomeric natural compounds, like (+)-catechin (**29**) and (-)-epicatechin (**31**), that are available in quantities sufficient for preparative purposes.



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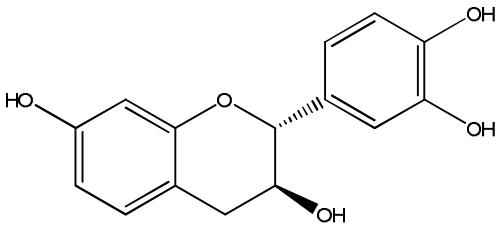

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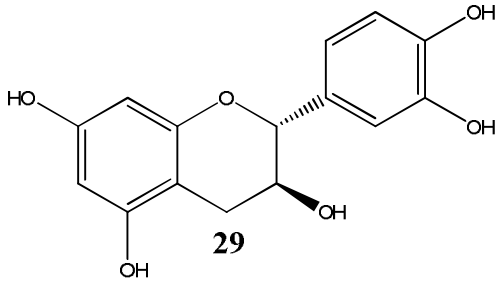

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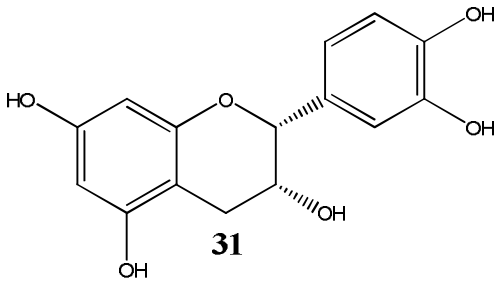
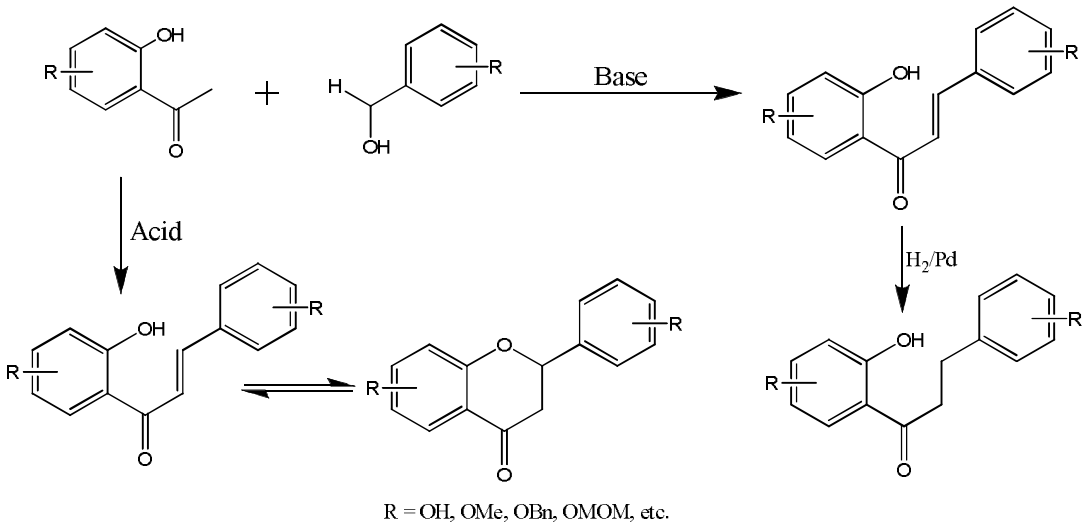
(+)-Catechin



31

(-)-Epicatechin

Chalcones, considered to be the most important intermediate C_6-C_3-C_6-precursor to other flavonoids, are readily accessible by means of two well established routes, i.e. the base - or acid catalysed aldol condensation of 2'-hydroxyacetophenones with benzaldehydes (Scheme 2-1).[1] Since the acid catalysed protocol is prone to subsequent cyclization, to the corresponding racemic flavanones, the base catalyzed route represents the better methodology for synthesising chalcones. The conventional base catalyzed aldol condensation usually employs NaOH or KOH, but other bases like NaH have also been utilized to produce chalcones in up to 89 % yield.[2] These compounds can also be obtained in high yields (75 - 96 %) by Lewis acid catalysis, e.g. borontrifluoride-etherate.[3]



Scheme 2-1: Acid- and base-catalyzed synthesis of chalcones, racemic flavanones and dihydrochalcones

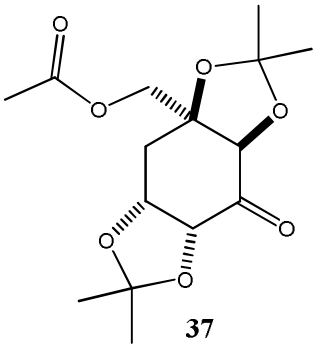
2.2 Epoxidation of α,β-unsaturated carbonyl compounds

2.2.1 Ketone- and alkaloid based catalysts

Metal catalyzed epoxidation of chalcones has been investigated by numerous workers in the field of oxidation chemistry. Elston *et al*.[4] developed chiral lithium and magnesium catalysts utilizing (+)- and (-)-diethyl tartrate as the chiral inducing agent and *t*-BuOOH as oxidant. High e.e.s were obtained (*ca.* 81 – 94 %) but chemical yields were moderate to low (*ca.* 36 – 54 %).

A catalyst system which utilises molecular oxygen as oxidant for the epoxidation of α,β-unsaturated ketones was developed by Enders and co-workers.[5,6] This complex comprising diethylzinc and (*R,R*)-*N*-methylpseudoephedrine gave high yields (94 %) but moderate e.e.s of 61 %. Diethylzinc together with chiral polybinaphthyl zinc complexes were used by Yu *et al*.[7] in the epoxidation of a number of chalcone substrates (*ca*. 67 – 98 % yield, up to 81 % e.e.). Successful application of the free lanthanoid complexes, BINOL-lanthanum and –gadolinium, led to various chalcone epoxides being produced in 78 – 93 % yield and 83 % e.e.[8] Suspensions of these catalysts were later synthesised and showed increased efficacy.[9] A series of chalcone substrates were epoxidized in high yields (*ca*. 81 – 95 %) and high e.e.s (*ca.* 73 – 95 %) utilising this catalyst system. Despite considerable success towards the epoxidation of variously substituted chalcones mentioned above, oxygen substitution on all of the chalcones never exceeded a 2'-methoxymethyl group and none of the substrates came close to the oxygenation patterns exhibited by typical natural products.

In an effort to apply the well known dioxirane epoxidation technology to the asymmetric epoxidation of olefins, Wang *et al*.[10,11,12] utilised chiral ketones[13] in the epoxidation reaction. The initial catalyst constituted a fructose-derived ketone (**39**)[10] and a wide range of *trans*-disubstituted olefinic substrates, including *trans*-chalcone, were tested resulting in moderate to high yields (*ca*. 41 – 99 %) and high enantiomeric excess (e.e.) (*ca*. 81 – 98 %). Application of the same technology with (-)-quinic acid derived ketones (**37** and **38**) yielded the (+)-(2*S*,3*R*)-chalcone epoxide in 80 % and 85 % yield (94 % and 96 % e.e) respectively.[12] In a similar reaction, Klein *et al.* [14] could only obtain 24 % conversion and 67 % e.e. for *trans*-chalcone when utilising chiral ketone (fructose derivative **39**).



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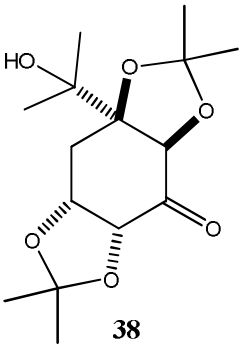

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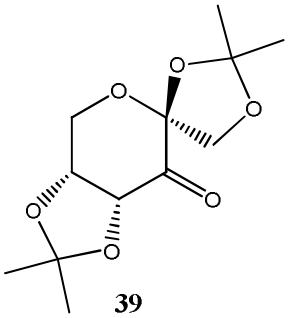
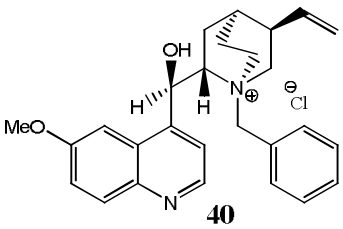
(-)-Quinic acid derivatives



39

Fructose derivative

Utilization of quaternary ammonium salts as chiral inducing agents under phase transfer conditions allowed Wynberg *et al.*[15,16] to produce optically active unsubstituted as well as 2'-methoxy- and 4-methoxychalcone epoxides. The quinine- and quinidine salts (**40**) and (**41**) were employed in a biphasic system consisting of an organic solvent and water together with alkaline hydrogen peroxide (H_2O_2) to give excellent chemical yields (*ca.* 92 – 99 %) but disappointingly poor e.e.s (10 – 54 %). When H_2O_2 was replaced with *tert*-butyl hydroperoxide (*t*-BuOOH) as oxidising agent, however, the (+)-chalcone epoxide was obtained in contrast to the (-)-chalcone epoxide in the case of H_2O_2. Through the employment of another quinidine based chiral phase transfer catalyst (**42**), Arai *et al.*[17] were able to produce a variety of non-oxygenated chalcone epoxides in high yields (*ca*. 95 – 100 %) and e.e.s (*ca*. 87 – 92 %).



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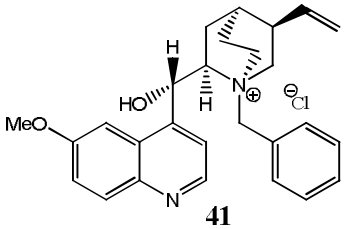
Quinine salt



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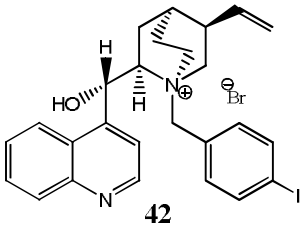
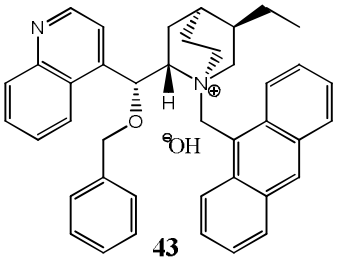


42

Quinidine salt

Inspired by Wynberg's work, Lygo *et al.*[18,19,20] utilised catalysts (**43**) and (**44**) derived from *Cinchona* alkaloids in the synthesis of chalcone epoxides and were able to obtain both (-)- and (+)-*trans*-chalcone epoxide in 90 % yield and > 81 % e.e. Both enantiomers of 4-methoxychalcone epoxide, 3,4-methylenedioxychalcone epoxide and 3',4'-methylenedioxychalcone epoxide were also produced in 86 - 97 % yield and 81 - 89 % e.e. when toluene was used as solvent. When the solvent was switched to DCM the choice of

oxidant had a profound influence on the stereochemical outcome of the reaction. Thus (-)-*trans*-chalcone epoxide (71 % yield, 23 % e.e.) was obtained with 11 % NaOCl, while the (+)-enantiomer (75 % yield, 11 % e.e.) was isolated when 30 % H_2O_2 was used as oxidant.



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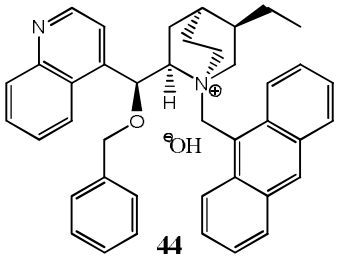
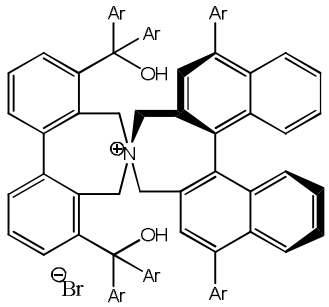
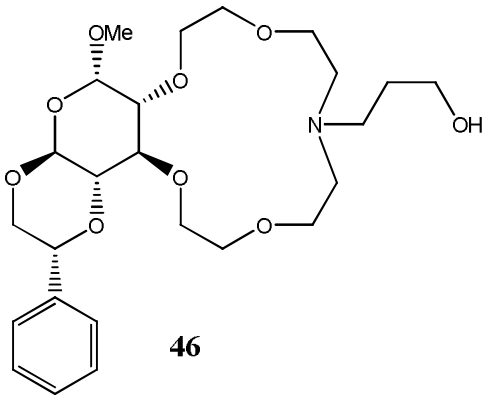


44

Cinchona alkaloid derivatives



45 Ar = 3,5-Ph_2-C_6H_3



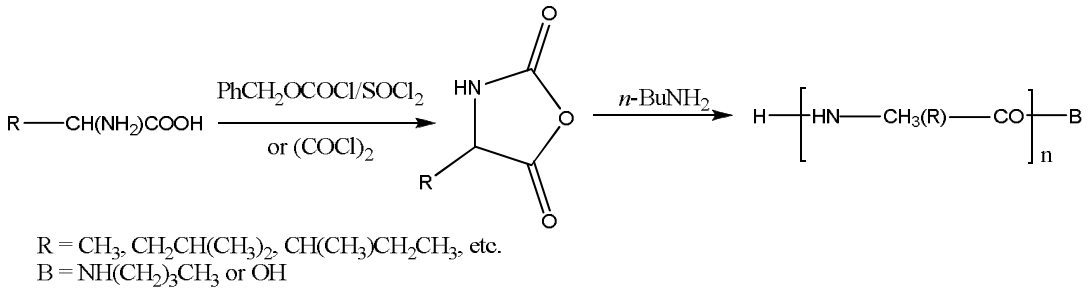
46

Methyl-4,6-*O*-benzylidene-α-D-glucopyranoside derivative

Another asymmetric epoxidation system based on phase transfer catalysis (**45**) was developed by Ooi *et al.*[21] This system gave the epoxides from a wide range of α,β-unsaturated substrates, including *trans*-chalcone (99 %, 96 % e.e.) and 4-methoxychalcone (83 % yield and 96 % e.e.). Chiral crown ethers derived from *D*-glucose, *D*-galactose and *D*-mannitol have also been utilised in this regard.[22,23] These catalysts were applied in the epoxidation of a wide variety of chalcone substrates and giving yields of 28 – 82 % and e.e.s of 8 – 92 %. The best of these catalysts (**46**) gave 82 % yield and 92 % e.e. for the reaction with *trans*-chalcone, while only 53 % yield was obtained in the reaction of 4'-methoxychalcone, the highest oxygenated substrate investigated.

2.2.2 Poly amino acid systems

In the quest to synthesise optically active chalcone epoxides, Juliá *et al.*[24] developed an epoxidation catalyst system that was based on bovine serum albumin.[25] This triphasic system, consisting of toluene, H_2O and the poly amino acid catalyst (prepared according to Scheme 2-2), was believed to be closely related to stereospecific enzymatic reaction systems.



Scheme 2-2

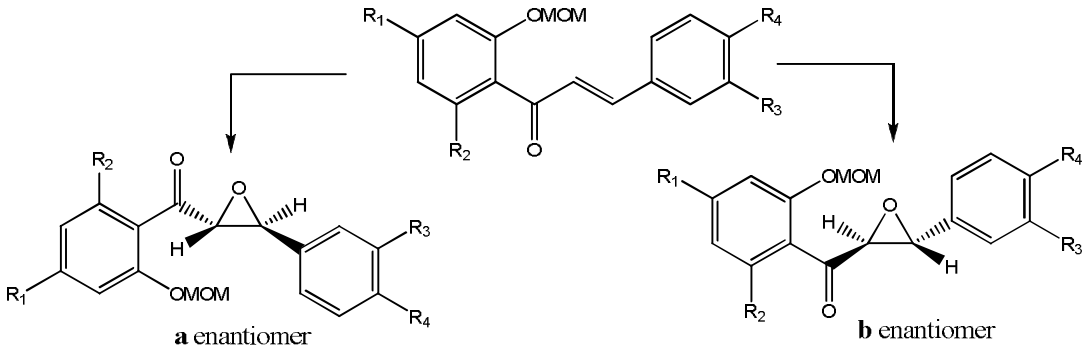
Different initiators and varying degrees of polymerization (*n*) yielded a range of polymeric catalysts. The best e.e. (96 %) was obtained from poly-(*L*)-alanine with *n* = 30, while poly-(L)-leucine (*n* = 30) and copolymers synthesized from (L)-alanine and (L)-leucine also led to acceptable reactions (e.e.s > 85 % and 95 % respectively). An evaluation of oxidizing agents indicated NaOH/H_2O_2 to be the best, while 80 % *t*-BuOOH proved to be completely inactive. Replacing NaOH with K_2CO_3 yielded only racemic chalcone epoxide, while the absence of the polymer either gave very poor yields or no reaction at all. Poly-(*D*)-alanine (*n* = 10) yielded a product with 90 % e.e., but of reversed optical rotation when compared to the product obtained from the poly-(*L*)-alanine reaction.[26] Although some uncertainty about the actual origin of the stereochemical induction from the amino acid to the chalcone epoxide still exists, it is believed that hydrogen bonding between the peptide group and the carbonyl functionality of the chalcone as well as the α-helical structure of the amino acid plays a pivitol role in this regard. This theory was supported by the fact that reactions performed in MeOH (believed to result in no hydrogen bonding between the peptide's amidic hydrogens and the CO of the chalcone) with amino acid polymers, like valine and phenylalanine, which form β-sheets, and poly-*L*-proline (lacking amidic hydrogens) showed very low e.e.s and even no reaction for the latter.[27]

Poly(styrene-co-divinylbenzene)-supported poly(*L*)-leucine was later developed and although the polymer had a lower degree of polymerization (*n* = 10) it was found to be very active with yields and e.e.s > 90 %.[28] Together with its high performance the polymer based catalyst could also be recycled up to 12 times with no loss in reaction capacity.

In an improvement on the original Juliá-Colonna procedure, Roberts *et al.*[29] replaced the three phase system with a non-aqueous two phase system employing urea hydrogen peroxide as oxidant and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[30,31] as base. The new two phase

system also eliminated the necessity for the polymer to be activated prior to use. The poly amino acid-on-silica catalyst (PaaSiCat) was then developed by immobilizing the original polymer on silica.[32,33] The result was a more robust and even more reactive epoxidation catalyst. Only 23 % of the catalyst normally employed was required and generally higher yields were obtained than for the unmodified catalyst even in the biphasic system. No loss of activity was experienced and even after six runs, high e.e.s (≥ 93 %) were still obtained. This catalyst was, however, not tested on highly oxygenated chalcone substrates.

Although a variety of possible epoxidation routes are available very little is known about the epoxidation of poly-oxygenated chalcones. Juliá-Colonna's triphasic system[34,35,36] and the biphasic system[37,38] developed by Roberts are two that have successfully been used on these substrates (Scheme 2-3, Table 2-1).[1]



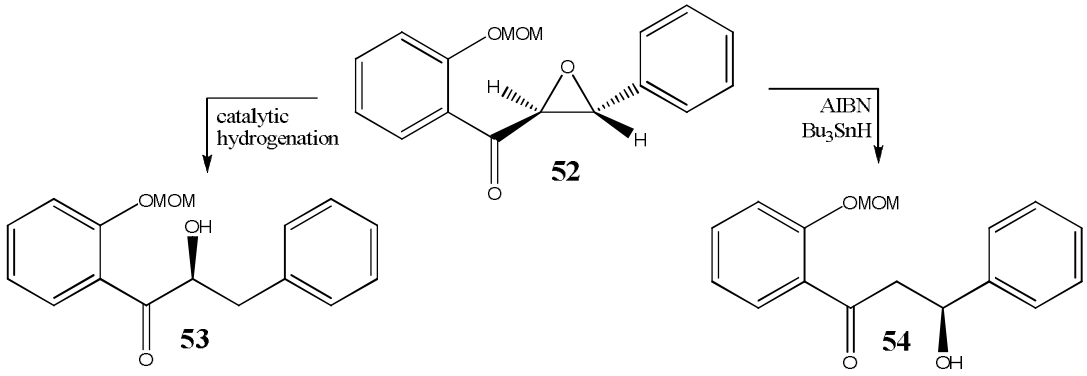
Scheme 2-3: ***See Table 2-1***

Table 2-1: ***Results from Scheme 2-3: See***

		Biphasic System		Triphasic System	
		% Yield	% e.e.	% Yield	% e.e.
47a	$R_1 = R_2 = R_3 = H$, $R_4 = OMe$	71	85	99	84
47b	$R_1 = R_2 = R_3 = H$, $R_4 = OMe$	69	81	98	69
48a	$R_2 = R_3 = H$, $R_1 = R_4 = OMe$	80	95	98	86
48b	$R_2 = R_3 = H$, $R_1 = R_4 = OMe$	76	90	98	74
49a	$R_2 = H$, $R_1 = R_3 = R_4 = OMe$	64	88	99	67
49b	$R_2 = H$, $R_1 = R_3 = R_4 = OMe$	61	87	98	58
50a	$R_3 = H$, $R_1 = R_2 = R_4 = OMe$	36	60	97	70
50b	$R_3 = H$, $R_1 = R_2 = R_4 = OMe$	33	61	97	53
51a	$R_1 = R_2 = R_3 = R_4 = OMe$	21	53	79	49
51b	$R_1 = R_2 = R_3 = R_4 = OMe$	19	50	76	49

2.3 α- and β-Hydroxydihydrochalcone

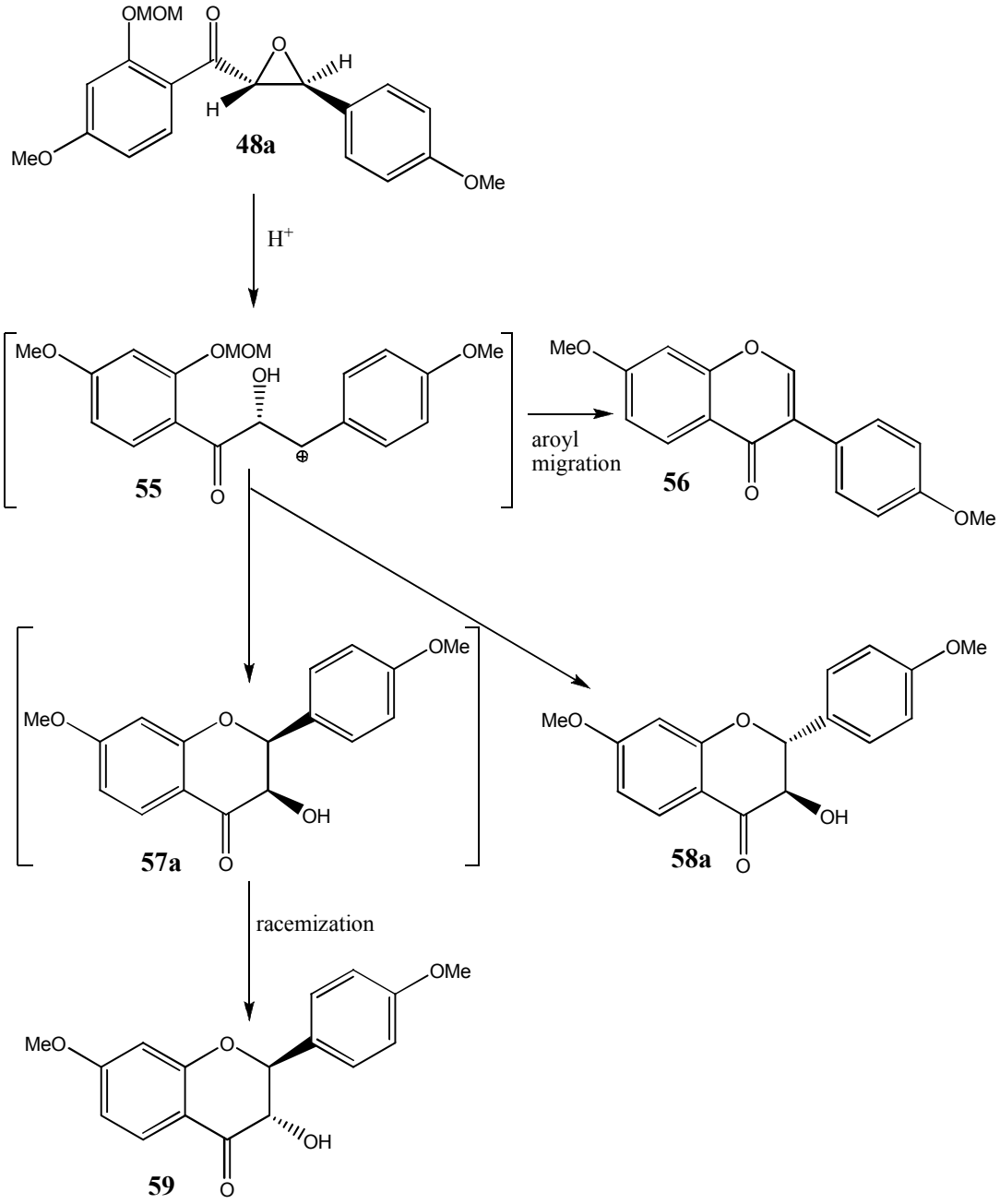
Chiral chalcone epoxides can be used as intermediates in the synthesis of optically active α- and β-hydroxydihydrochalcones. The α-hydroxydihydrochalcones are readily obtained in quantitative yield and with no loss in stereochemistry by Pd catalysed [Pd on $BaSO_4$ or Pd on C (5 or 10 %)] hydrogenation (Scheme 2-4).[1,36,37,38] A radical reduction process on the other hand [azoisobutyronitrile (AIBN) and tributyltinhydride $(Bu)_3SnH$], leads to the β-hydroxydihydrochalcones[1,36,37,38,39,40,41] in > 80 % e.e. and > 70 % yield (Scheme 2-4). Benzeneselenolate has also been reported to afford ring opening of α,β-epoxy ketones to yield β-hydroxy ketones (95 % e.e. – no recorded yield).[42]



Scheme 2-4

2.4 Dihydroflavonol

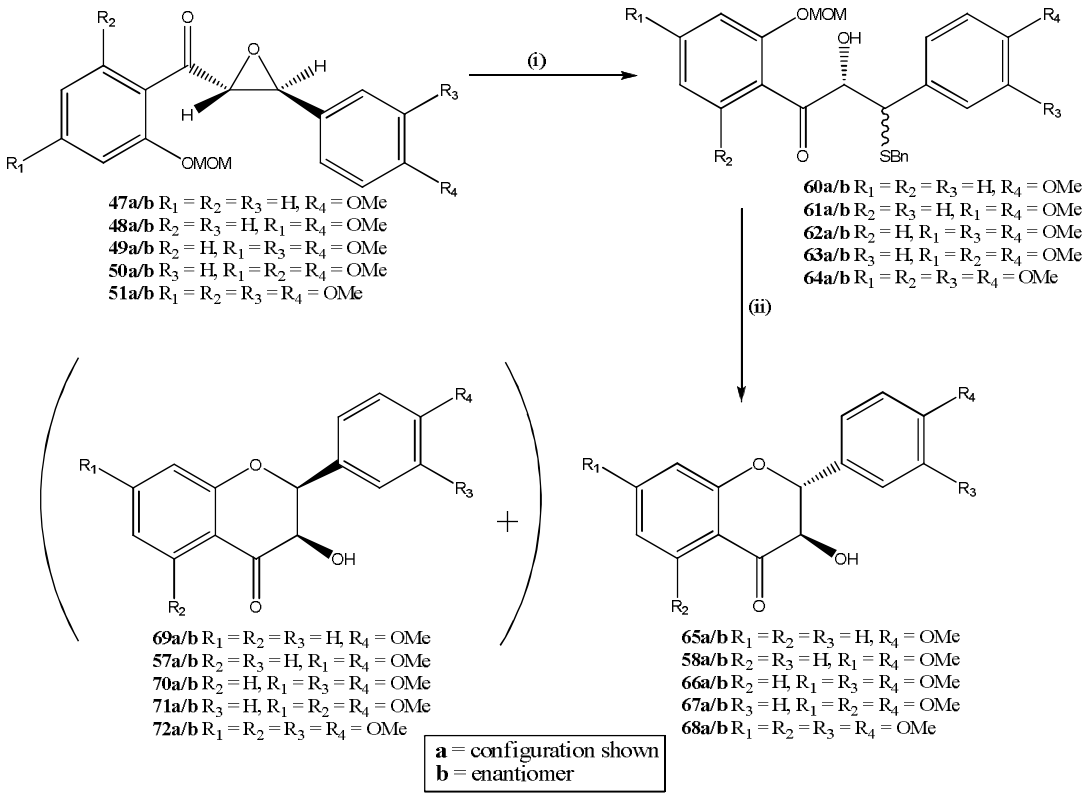
Since cyclization of chalcone epoxides will introduce the stereoselectivity at both C2 and C3 of dihydroflavonols, the first attempts at synthesis of enantiomerically enriched dihydroflavonols, centred around efforts to achieve this cyclization without loss in optical purity. Direct acid catalysed cyclization (HCl/MeOH),[35] however, led to low yields (51 %) of the desired dihydroflavonol, which was accompanied by considerable amounts of unwanted isoflavone, formed through aroyl migration (Scheme 2-5). Subsequent deprotection and cyclization with Lewis acids like $MgBr_2$-Et_2O and BF_3-Et_2O were also attempted but although almost no loss in e.e.s (*ca.* 78 %) were observed, chemical yields remained low (*ca.* 20 %).[43]



Scheme 2-5

In an attempt to limit the aroyl migration process, which was believed to originate from the inability of the substrates to undergo cyclization while the 2'-OH was still protected, Van Rensburg *et al.*[44] decided to selectively cleave the C_β-O with tin tetrachloride ($SnCl_4$) and benzylmercaptan (BnSH) leading to the dihydrochalcone intermediate (**60** - **64**). This compound could then be deprotected prior to cyclization with a suitable thiophilic Lewis acid

like silver tetrafluoroborate ($AgBF_4$). Application of this methodology gave both the *trans*-(**58**, **65** - **68**) and *cis*-dihydroflavonol (**57**, **69** - **72**) in up to 86% total yield and up to 84% e.e., albeit with low *trans* to *cis* ratio (*ca*. 4:1) (Scheme 2-6, Table 2-2).[1] Circular dichroism (CD) confirmed that the optical integrity of the epoxide was preserved throughout the transformation.[44]



Reagents and conditions: (i) BnSH (4 eq.), $SnCl_4$ (0.2 eq.), -20 °C to 0 °C; (ii) $AgBF_4$ (5 eq.), DCM, 0 °C

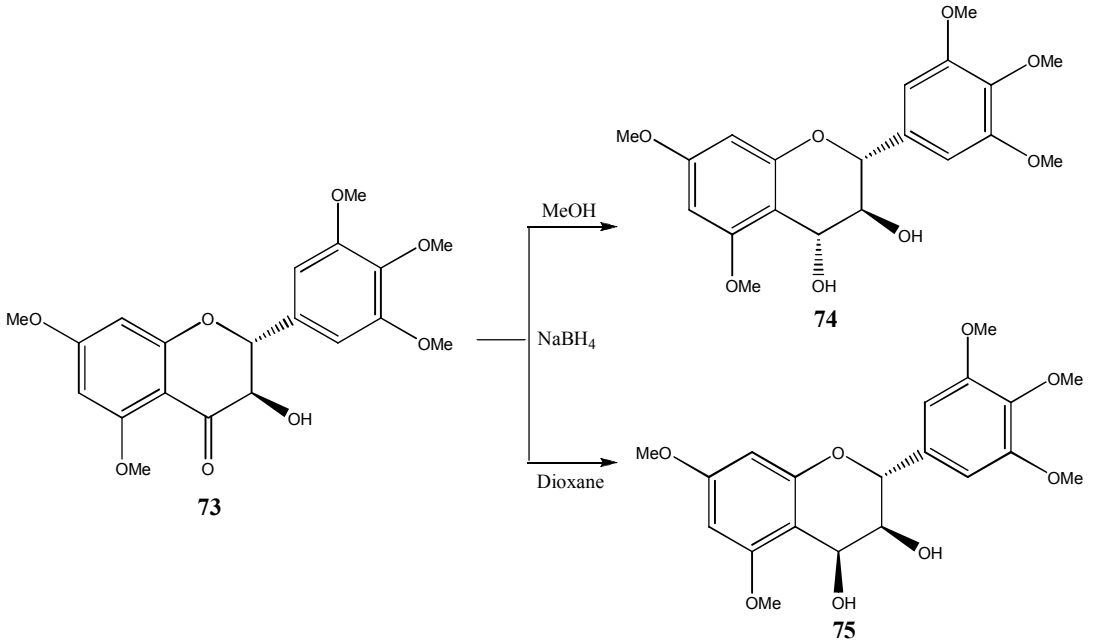
Scheme 2-6: ***See Table 2-2***

Table 2-2: ***Results from Scheme 2-6***

	Dihydrochalcone	Yield		Dihydroflavonol	Yield	e.e.	*trans:cis*
60a	$R_1 = R_2 = R_3 = H$, $R_4 = OMe$	86	**65a**	$R_1 = R_2 = R_3 = H$, $R_4 = OMe$	86	83	93:7
60b	$R_1 = R_2 = R_3 = H$, $R_4 = OMe$	90	**65b**	$R_1 = R_2 = R_3 = H$, $R_4 = OMe$	83	69	94:6
61a	$R_2 = R_3 = H$, $R_1 = R_4 = OMe$	93	**58a**	$R_2 = R_3 = H$, $R_1 = R_4 = OMe$	71	84	79:21
61b	$R_2 = R_3 = H$, $R_1 = R_4 = OMe$	90	**58b**	$R_2 = R_3 = H$, $R_1 = R_4 = OMe$	72	75	83:17
62a	$R_2 = H$, $R_1 = R_3 = R_4 = OMe$	89	**66a**	$R_2 = H$, $R_1 = R_3 = R_4 = OMe$	81	68	85:15
62b	$R_2 = H$, $R_1 = R_3 = R_4 = OMe$	91	**66b**	$R_2 = H$, $R_1 = R_3 = R_4 = OMe$	79	58	86:14
63a	$R_3 = H$, $R_1 = R_2 = R_4 = OMe$	89	**67a**	$R_3 = H$, $R_1 = R_2 = R_4 = OMe$	65	69	78:22
63b	$R_3 = H$, $R_1 = R_2 = R_4 = OMe$	89	**67b**	$R_3 = H$, $R_1 = R_2 = R_4 = OMe$	64	53	84:16
64a	$R_1 = R_2 = R_3 = R_4 = OMe$	91	**68a**	$R_1 = R_2 = R_3 = R_4 = OMe$	61	47	82:18
64b	$R_1 = R_2 = R_3 = R_4 = OMe$	88	**68b**	$R_1 = R_2 = R_3 = R_4 = OMe$	63	44	80:20

2.5 Flavan-3,4-diol

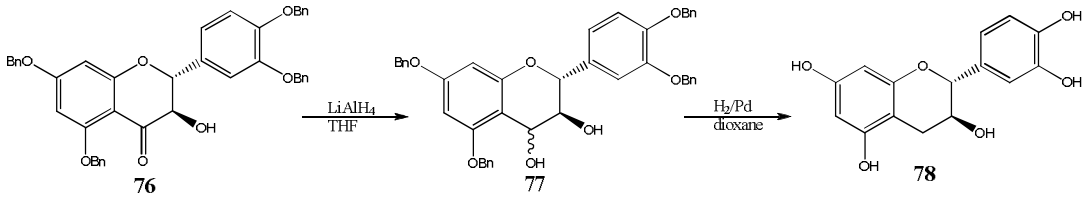
Enantiomerically enriched flavan-3,4-diols were obtained through the obvious reduction ($NaBH_4$) of the corresponding dihydroflavonols. With MeOH as solvent the 2,3-*trans*-3,4-*trans* isomers were obtained, while reactions in 1,4-dioxane gave the 2,3-*trans*-3,4-*cis* isomers.[1,36] The reversal in hydride attack was explained in terms of hydrogen bonding between the aprotic solvent, 1,4-dioxane, and the 3-OH (Scheme 2-7).



Scheme 2-7

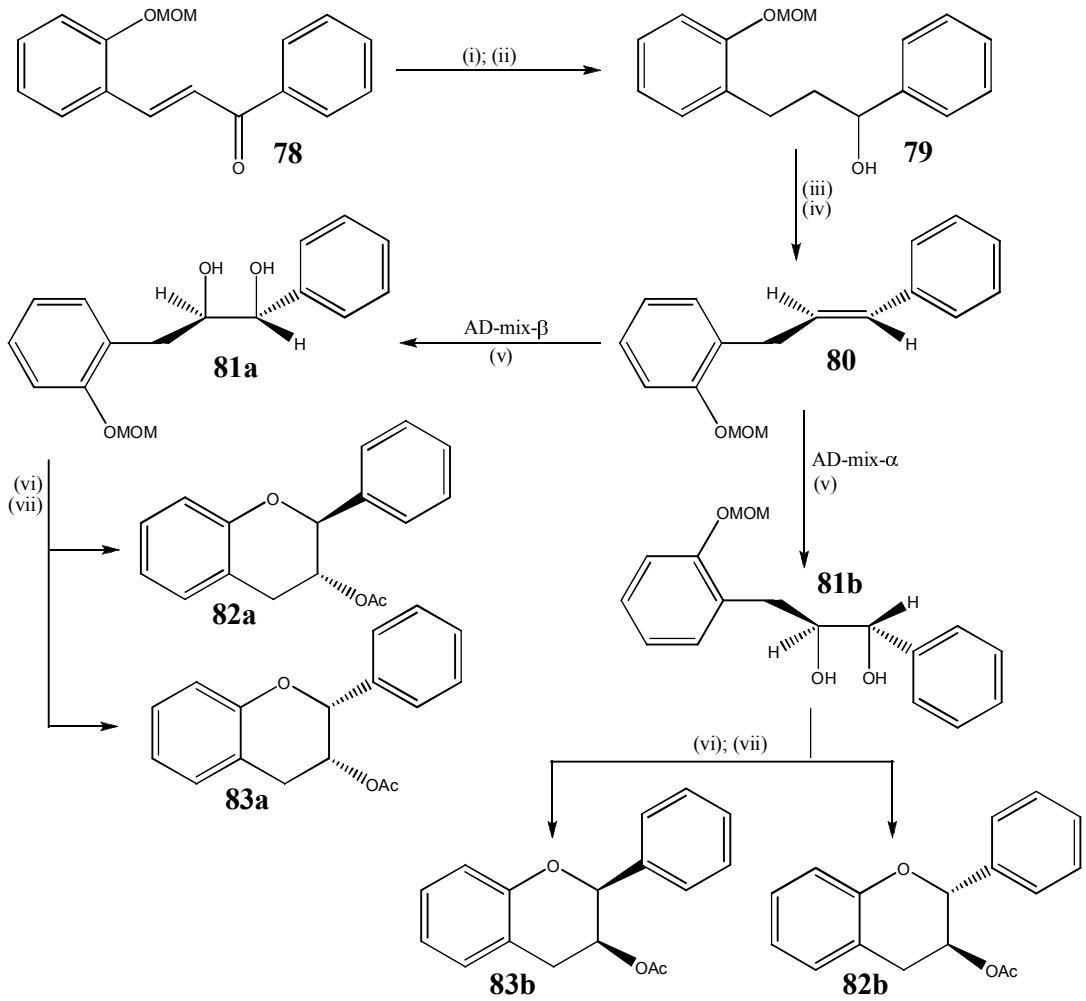
2.6 Flavan-3-ol

One of the most important groups in flavonoids, the flavan-3-ols or catechins, are readily available in high yields (*ca*. 93 %) from the flavan-3,4-diol analogues through reductive deoxygenation with $NaBH_3CN$.[2] These compounds can also be prepared from the corresponding dihydroflavonol by consecutive reduction with $LiAlH_4$ and hydrogenation over Pd/C (Scheme 2-8).[1]



Scheme 2-8

In a completely different approach, Van Rensburg *et al.*[45,46] utilized the *retro*-chalcone (**78**) as primary starting material for synthesising scalemic flavan-3-ols. During the application of this methodology, the *retro*-chalcone is transformed into the diarylpropanol (**79**) by reduction (Scheme 2-9). Subsequent dehydration ($SOCl_2$ then DBU) and asymmetric Sharpless dihydroxylation (AD-mix)[47,48,49] afforded the corresponding propandiol (**81a/b**) (83 – 85 %, e.e. > 99 %) (Scheme 2-9). Acid catalyzed cyclization yield a *trans:cis* (*ca*. 3:1) mixture (60 – 65 %) of the flavan-3-ol derivatives (**82a/b** and **83a/b**) (e.e. > 99 %).



Reagents and conditions: (i) Pd/H_2/EtOH; (ii) $NaBH_4$/EtOH; (iii) $SOCl_2$/DCM; (iv) DBU/DCM/reflux; (v) AD-mix, *t*-BuOH:H_2O (1:1, v/v), $MeSO_2HNH_2$/0 °C; (vi) 3M HCl/MeOH:H_2O (3:2, v/v); (vii) Ac_2O/pyridine

Scheme 2-9

2.7 References

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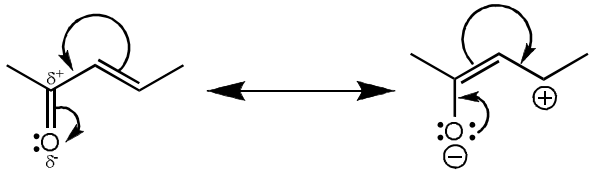
CHAPTER 3

REDUCTION OF DOUBLE BONDS

3.1 The α,β-unsaturated carbonyl functionality

Although several reagents are known for the individual reduction of either an olefin or aldehyde/ketone, combining the two functional groups leads to a conjugated system with properties very different from that of the individual functionalities, thus introducing the issue of regioselectivity into this reduction reaction.

All olefins are nucleophilic in nature whether or not they are substituted with electron-withdrawing groups (EWG) or electron-donating groups (EDG).[1] Conjugation with a carbonyl, however, creates a functional group with hard and soft reaction centres, which can undergo nucleophilic attack at either the carbonyl carbon (hard) or the β-carbon (soft position). This phenomenon is due to the π bonds reacting as a conjugated system rather than individual double bonds. The partial positive charge on the carbonyl carbon is delocalized through the double bond and shared by the β-carbon, resulting in the β-carbon being slightly electrophilic.[1] The true electron distribution therefore lies between the two extreme polarized structures shown in Scheme 3-1.



Scheme 3-1

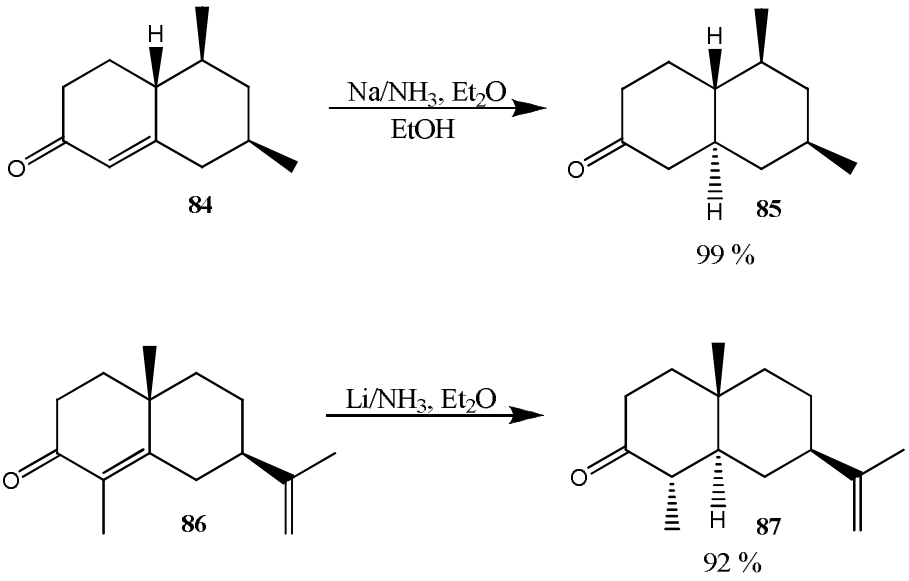
By employing the 'hard' and 'soft' acid and base concept, distinction can be made between the two reactive sites.[2] In the conjugated system the carbonyl carbon can be classified as the hard electrophile due to the partial positive charge created by the oxygen (hard nucleophile). The β-carbon on the other hand represents the soft electrophile with delocalized electron density toward the carbonyl. Reaction of conjugated carbonyl compounds with hard nucleophiles usually results in direct addition reactions, whereas soft nucleophiles generally lead to conjugate addition. Proper selection of the reducing agent could therefore, in principle, result in regioselective reduction in the desired position.

3.2 Regioselective reduction of α,β-unsaturated ketones/aldehydes

Since the first identification of this combination of functional groups in Organic Chemistry, regioselectivity in the reduction of α,β-unsaturated aldehydes and ketones have posed a challenge to the scientific community. Over the years several methods like dissolved metals in liquid ammonia, hydrogen transfer hydrogenation, hydride reducing reagents, and catalytic hydrogenation, have been investigated as a way for achieving either allylic alcohols or saturated aldehydes/ketones from α,β-unsaturated analogues.

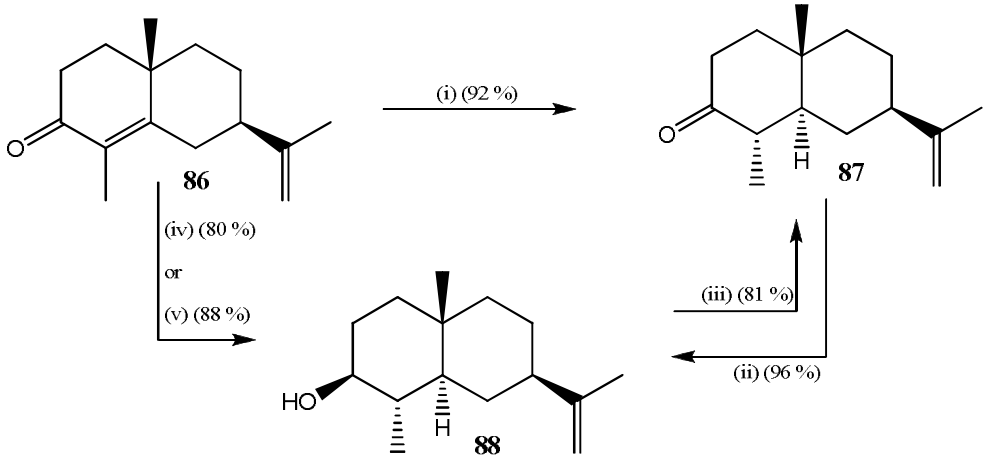
3.2.1 Alkali or alkaline earth metals in liquid ammonia

As one of the earliest reduction methods in organic chemistry, dissolving metal reductions or internal electrolytic reduction is not widely employed today but is still in use due to its advantageous regioselectivity in some substrate systems. For cyclic substrates this reduction proceeds regioselectively in a conjugated fashion leading to products with *axially* orientated hydrogens.[3,4] The reaction is believed to proceed *via* a radical intermediate[5] making isolated olefins stable towards these conditions (Scheme 3-2)[6].



Scheme 3-2

Selective reduction in the presence of an aromatic system is also possible, but requires a proton donor (Birch reduction). Proton donors are usually added to increase reaction rate but they can also play an important role in the regioselectivity of the reduction. For example, lithium, with methanol or ethanol as proton donor, produce saturated alcohols, whereas ammonium chloride or *t*-butanol as proton donor, will retain the carbonyl functionality (Scheme 3-3).[7,8]



Reagents and conditions: (i) Li, liq. NH_3, NH_4Cl; (ii) $LiAl(OBu^t)_3H$; (iii) CrO_3-pyridine; (iv) Li, liq. NH_3, EtOH; (v) Na, *i*-PrOH

Scheme 3-3

3.2.2 Hydrogen transfer hydrogenation

Hydrogen transfer hydrogenation is a process in which an organic hydrogen donor is catalytically oxidized to produce the reduction product of an α,β-unsaturated carbonyl substrate. Reactions of α,β-unsaturated aldehydes are, however, hampered by self-condensation leading to lower yields than those observed for their ketone counterparts.[5]

While many types of reducible compounds, like formats,[9] formic acid,[10] silicon- and tin hydrides[11] can be used as hydrogen donors, primary[12] or secondary alcohols[13,14] are the most commonly used for reactions involving conjugated enones. Even sugars containing free anomeric hydoxy groups (e.g. 2,3,5,6-di-*O*-isopropylidene-*D*-mannofuranose (**89**))[15] and poly(methylhydrosiloxane)[16] have been utilised as hydrogen source in the 1,4-reduction of *trans*-chalcones (**90**) (Scheme 3-4)[15]. Many organometallic compounds containing a variety of metals and ligands, i.e. $RuCl_2(PPh_3)_3$,[17] $RuH_2(PPh_3)_4$,[15] $RuHCl(PPh_3)_3$,[18] Ir(3,4,7,8-Me_4-phen)COD]Cl,[13,*] and $[Ru(PPh_3)_2(CH_3CN)_3Cl][BPh_4]$[10] have been employed for the required transfer of hydrogen from the host to guest molecule, while acidic co-catalysts (like anhydrous $ZnCl_2$)[19] are reported for enhancing reaction rates. Other catalyst systems described in literature, include copper carbene complexes[16] as well as powdered zinc in the presence of Cp_2TiCl[12,*] (generated *in situ* from Cp_2TiCl_2) and heterogeneous palladium-based mesoporous silicate molecular sieve catalysts (PdMCM-41)[9].

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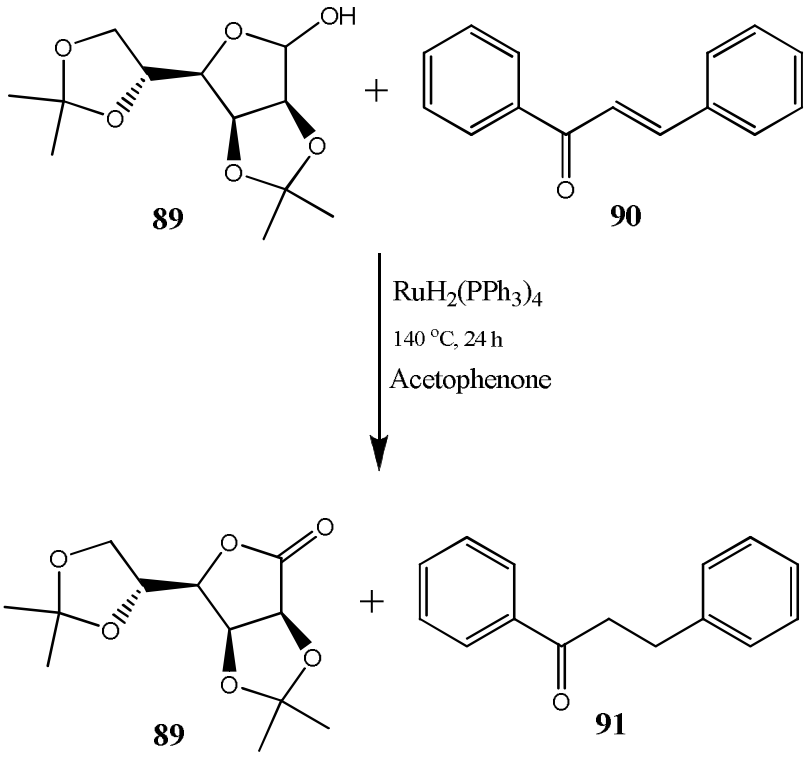
[*] COD = Cycloocta-1,5-diene

[*] Cp = Cyclopentadienyl (π-C_5H_5)

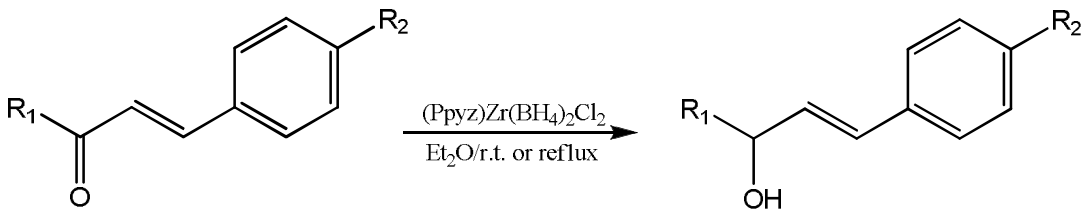


Scheme 3-4

3.2.3 Hydride reducing agents

While hydride reducing reagents are capable of reducing conjugated double bonds in either a 1,2- or 1,4-fashion, selectivity in these reactions is explicable in terms of the hard/soft acid/base theory. Borohydride reagents are in general softer than their aluminium counterparts. Both types of reagents can, however, be hardened by the incorporation of alkoxy groups on the metal centre, while the smaller lithium counter ion also brings more hardness to the reagent when compared to the sodium equivalent. Indium hydride, produced from sodium borohydride ($NaBH_4$) and indium(III)chloride, also exhibit selectivity towards conjugate reduction,[20,21] while addition of pyridine or triethylamine (Et_3N) is believed to produce a soft borine species, $Et_3N{\cdot}BH_3$,[5] which also yields the saturated ketone/aldehyde exclusively. Regioselectivity of the hard lithium aluminiuhydride ($LiAlH_4$) is manipulated to favour conjugate addition by incorporation of lanthanoid salts (e.g. $CeCl_3$),[22] crown ethers[23] and cryptands.[24] Coordination of the lithium with these additives, rather than the carbonyl, decrease the 1,2-reduction rate favouring conjugate hydride addition. $CoH(CO)_4$ is speculated as the reactive species in a fairly novel system employing $Co_2(CO)_8$ and water to produce saturated carbonyls with high selectivity.[25]

If the 1,2-reduction product or allylic alcohol is the desired product, it can be achieved by slow addition of sodium borohydride ($NaBH_4$) to a methanol solution of the substrate which, through *in situ* alkoxy formation (e.g. $NaBH(OMe)_3$, will promote direct addition.[5,26] Lanthanide salts (e.g. $CeCl_3$) have a reverse effect with $NaBH_4$ than with $LiAlH_4$. Coordination of the lanthanide with the carbonyl group activates this functionality which promotes 1,2-reduction when $NaBH_4$ is employed.[27,28,29,30] Direct reductive amination with $NaBH_4$ and guanidine hydrochloride[31] or 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$)[32] also produce allylic alcohols. The zirconium borohydride piperazine complex ($(Ppyz)Zr(BH_4)_2Cl_2$)* is another selective reducing agent that yields unsaturated alcohols from chalcone type structures in high yields (Scheme 3-5).[33]



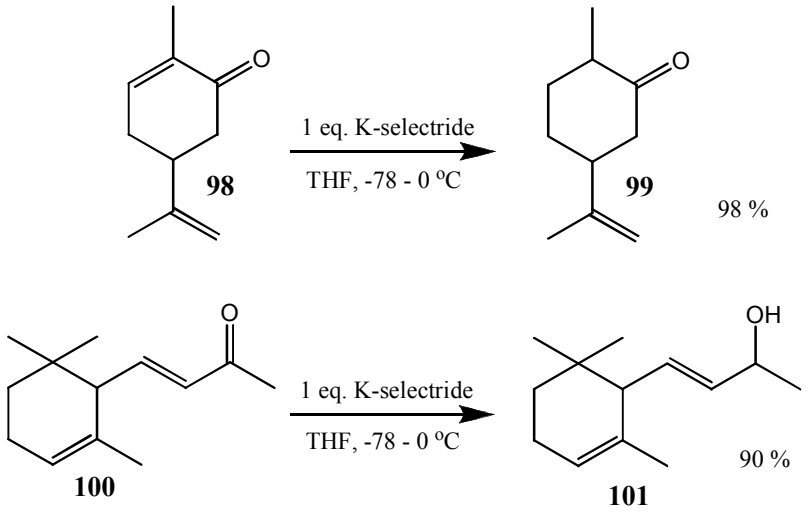
(**92**) $R_1 = R_2 = H$
(**93**) $R_1 = p$-Cl-Ph; $R_2 = CH_3$
(**94**) $R_1 = CH_3$; $R_2 = H$

(**95**) $R_1 = R_2 = H$ (93 %)
(**96**) $R_1 = p$-Cl-Ph; $R_2 = CH_3$ (85 %)
(**97**) $R_1 = CH_3$; $R_2 = H$ (86 %)

Scheme 3-5

Although regioselectivity in hydride reduction reactions are largely determined by the reagent, examples of substrate structure playing an overriding role in the outcome of the reaction have been reported. Lithium- or potassium tri-*sec*-butylborohydrides (L- and K-selectride) usually produce 1,4-reduced products in cyclic substrates, but the allylic alcohols are obtained when linear substrates are subjected to the same reaction (Scheme 3-6).[7] In general, increased steric hindrance at the β-carbon of the substrate or bulky reagents like 9-BBN (9-bora-bicyclo[3.3.1]nonane) can inhibit conjugate addition.[34,35]

* Ppyz = Piperazine



Scheme 3-6

Other metals like tin, copper, iron and silicon (in particular hydrosilylation),[36] can also produce hydrides which can be used for the reduction of α,β-unsaturated systems.[5,14] Together with the large number of derivatives which can be produced from sodium, lithium and aluminium species the reagent list is endless.

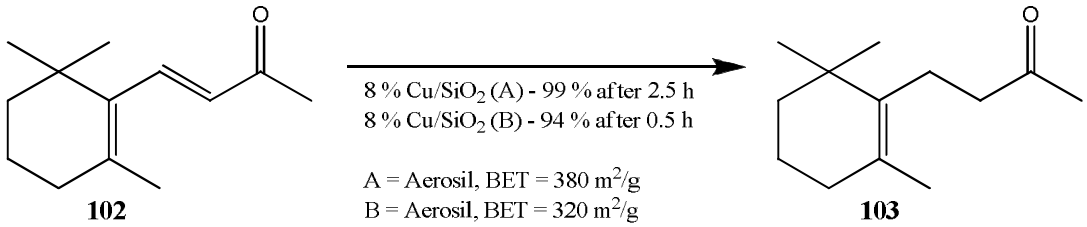
3.2.4 Catalytic hydrogenation

Regioselectivity, in the hydrogenation of α,β-unsaturated systems, can either be selective towards the double bond or the carbonyl. This is dependent on the catalyst, since some catalysts (metals) are more selective toward specific functionalities. Since carbonyl hydrogenation is slower than the reduction of conjugated olefins, saturated aldehydes/ketones can generally be obtained by stopping the reaction after the uptake of 1 mol of hydrogen. For heterogeneous hydrogenation, the course of the reaction is also influenced by the nature of the solvent and the acidity or basicity of the reaction mixture.[5]

Conjugated hydrogenation

Hydrogenation of the conjugated double bond can be achieved through a number of standard heterogeneous catalysts. Adam's catalyst (PtO_2), platinum on carbon (Pt/C), palladium on carbon (Pd/C), rhodium on carbon (Rh/C), nickel-aluminium alloy in 10 % NaOH, and zinc-reduced nickel in an aqueous medium are all known examples. Selectivity is usually increased through modification, e.g. Pt/SiO_2 (Degussa silica support), PtSn-OM (organobimetallic catalyst) and PtSn-BM (bimetallic catalyst) are modified platinum catalysts

that exhibit increased selectivity toward conjugate reduction.[37] The latter two modified species of Pt/SiO_2 are available through application of controlled modification techniques with tin like the "surface organometallic chemistry on metals" technique.[37] The organobimetallic (OM) species still contain organic ligands, whereas the bimetallic (BM) catalyst underwent further modification to remove all organic ligands. The latter is thus an activated form of the former. 8 % Cu/SiO_2 is another example of a heterogeneous catalyst with high selectivity and activity towards conjugate addition. The hydrogenation of β-ionone (**102**) yielded the saturated ketone in 99 % yield after 2.5 h (full conversion). Utilisation of a less porous SiO_2 resulted in an increase in reaction rate (full conversion after 0.5 h), but a slight decrease in yield (94 %) was noted (Scheme 3-7).[38]



102 **103**

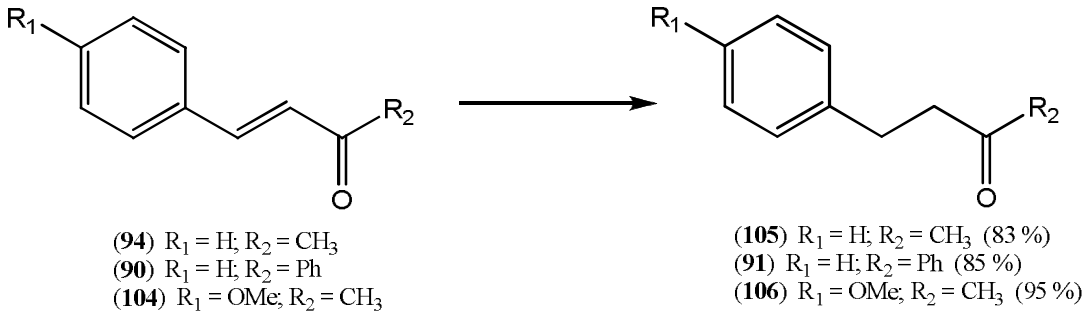
Scheme 3-7

Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) is a well known homogeneous catalysts but supporting this catalyst on alumina (γ-Al_2O_3) yielded a heterogeneous complex which is more robust toward sulphur poisoning and has increased activity compared to the homogeneous analogue.[39]

Some homogeneous catalysts like $K_3(Co(CN)_5H)$[40], under phase transfer conditions, and $[RhHCl_2(PCy_3)_2]$[*] are an attractive alternative to Wilkinson's catalyst, since the active species of these complexes are isoelectronic[41] to Wilkinson's catalyst. Palladium(II)chloride/triethylsilane is also selective toward olefin hydrogenation in a number of compounds, including ordinary *trans*-chalcone (**90**), to yield the saturated dihydrochalcone (**91**) in high yield (87 %).[42]

[*] Cy = Cyclohexyl

Ionic hydrogenation can also be used to reduce enones to saturated ketones. This process, which usually requires superacidity, can be conducted with cyclohexane and H-form zeolites (Scheme 3-8).[43]



(**94**) $R_1 = H; R_2 = CH_3$
(**90**) $R_1 = H; R_2 = Ph$
(**104**) $R_1 = OMe; R_2 = CH_3$

(**105**) $R_1 = H; R_2 = CH_3$ (83 %)
(**91**) $R_1 = H; R_2 = Ph$ (85 %)
(**106**) $R_1 = OMe; R_2 = CH_3$ (95 %)

Scheme 3-8

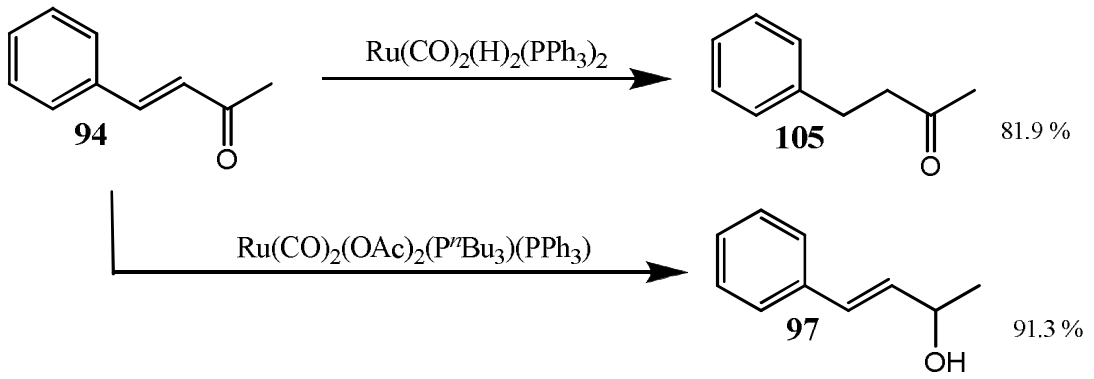
Carbonyl hydrogenation

Reports on the catalytic hydrogenation of the carbonyl group in α,β-unsaturated systems are rare, since hydride reductions are more convenient. Gold supported on an iron goethite (Au/FeOOH) show high activity and selectivity in hydrogenating benzalacetone (**94**) and cinnamaldehyde (**92**) to the corresponding unsaturated alcohol.[44] Similarly, Au^0 nanocolloids show regioselectivity towards producing crotyl alcohol (73 % at 98 % conversion) from crotonaldehyde.[45] Heterogeneous osmium represents another catalyst that normally exhibits preference for carbonyl hydrogenation in α,β-unsaturated systems.

Addition of ionic metal promoters to some of the previously mentioned heterogeneous catalysts (*cf.* olefinic hydrogenation) enhance selectivity towards hydrogenation of the carbonyl *via* coordination and polarization of the C=O bond. In this regard iron (from $FeCl_3$) will donate electron density to a heterogeneous platinum catalyst (e.g. Pt/C) producing electron deficient iron, which coordinates with the C=O, and electron rich platinum, which is less likely to accept olefinic π-electrons.[46] Effectiveness of the promoter depends on the charge and the amount of promoter absorbed on the catalyst.[46] Rhenium black,[47] cationic rhodium catalyst $[RhH_2P_2S_2]ClO_4$ (S = solvent; P = phosphine ligand e.g. PPh_2Me, $PPhMe_2$, PMe_3),[48] and hydridoiridium phosphine ($[Ir(PEt_2Ph)_4]_4$)[49] are all homogeneous catalysts which produce allylic alcohols during hydrogenation.

Shift in regioselectivity through small changes in catalyst composition and reaction conditions

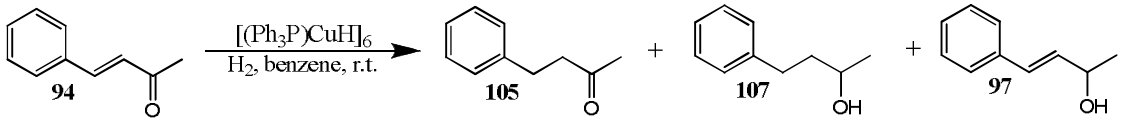
While some catalysts display a preference for direct hydrogenation of the carbonyl group *vs.* reduction of the double bond in conjugated systems, it is possible through small changes in the catalyst composition to alter the preferred selectivity from the one to the other. Thus hydrogenation with the very similar homogeneous ruthenium catalysts, $Ru(CO)_2(H)_2(PPh_3)_2$ and $Ru(CO)_2(OAc)_2(P^nBu_3)(PPh_3)$ produced 4-phenylbutan-2-one (**105**) and *trans*-4-phenyl-3-buten-2-ol (**97**) respectively from *trans*-benzalacetone (**94**) (Scheme 3-9) (selectivity: 81.9 % and 91.3 %; and conversion: 4.4 % and 26 % respectively) under the same reaction conditions.[50] When these reagents were utilised in the reduction of cyclohexen-2-one (at 25 bar H_2 pressure and 25 ^oC) the same selectivity for direct *vs.* conjugate addition was observed and cyclohex-2-enol (90 % selectivity; 33 % conversion) and cyclohexanone (96 % selectivity; 2.7 % conversion) were obtained, respectively.[51]



Reagents and conditions: 1.50 mmol substrate, 15.0 μmol catalyst, toluene (4 ml), H_2 (50 bar at 20 °C), 60 °C/3 h

Scheme 3-9

A change in selectivity from olefin to carbonyl hydrogenation has also been reported for the copper(I) hydride, $([(Ph_3P)CuH]_6)$,[52] with and without added triphenylphosphine (Scheme 3-10).[52]



(1) No added phosphine, 10 h 2.7 mol % catalyst, 10 bar H_2	91	:	9	:	0	89 % yield
(2) Ph_3P (12 eq./Cu), 24 h 2.7 mol % catalyst, 17 bar H_2	0	:	92	:	8	95 % yield
(3) Me_2PPh (6 eq./Cu), 18 h 0.83 mol % catalyst, 5 bar H_2	0	:	8	:	92	91 % yield

Scheme 3-10

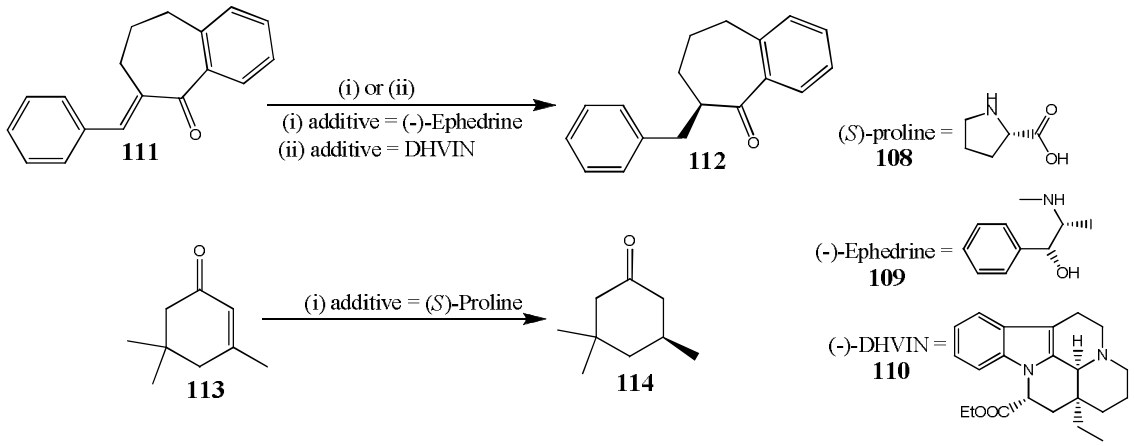
3.3 Stereoselective reduction of conjugated C=O and C=C double bonds

Although several stereoselective reducing agents are available especially for the hydrogenation of double bonds, reports describing the regio- and stereoselective reduction of α,β-unsaturated aldehyde/ketone systems are almost non-existent. During stereoselective reactions chiral induction is either brought about by the reagent (or catalyst) or an element of asymmetry already present in the substrate. Since the element causing stereoselectivity in subsequent reactions already exists in the molecule in the latter case, the reagent does not directly influence the stereochemical outcome of the reaction. Chirality is therefore not primarily introduced into the substrate molecule through the action of the reagent (or catalyst) in this case and it will therefore not be discussed in this paragraph.

3.3.1 Stereoselective hydrogenation

Double bond hydrogenation in α,β-unsaturated systems can be conducted with either heterogeneous or homogeneous catalysts. Examples of stereoselective heterogeneous catalysts are: 10 % Pd/C with (*S*)-proline (**108**)[53] or (-)-ephedrine (**109**)[54] as chiral inducing agent, and palladium black together with (-)-dihydroapovincaminic acid ethyl ester (DHVIN; **110**).[55] All three examples contain the chiral modifiers in less than stoichiometric amounts and are 100 % selective for the olefinic double bond in α,β-unsaturated systems. The first and second catalysts (Pd/C with proline and ephedrine) yield (*R*)-2-benzyl-1-benzosuberone (**112**) in 20 % and 36 % e.e. respectively when used for reduction of the exocyclic substrate, (*E*)-2-benzylidene-1-benzosuberone (**111**) (Scheme 3-11). In another report the reduction of

isophorone (**113**) to (*S*)-3,3,5-trimethylcylcohexanone (**114**) with the DHVIN and the (*S*)-proline systems is described (40 % and 80 % e.e. respectively) (Scheme 3-11).[56]

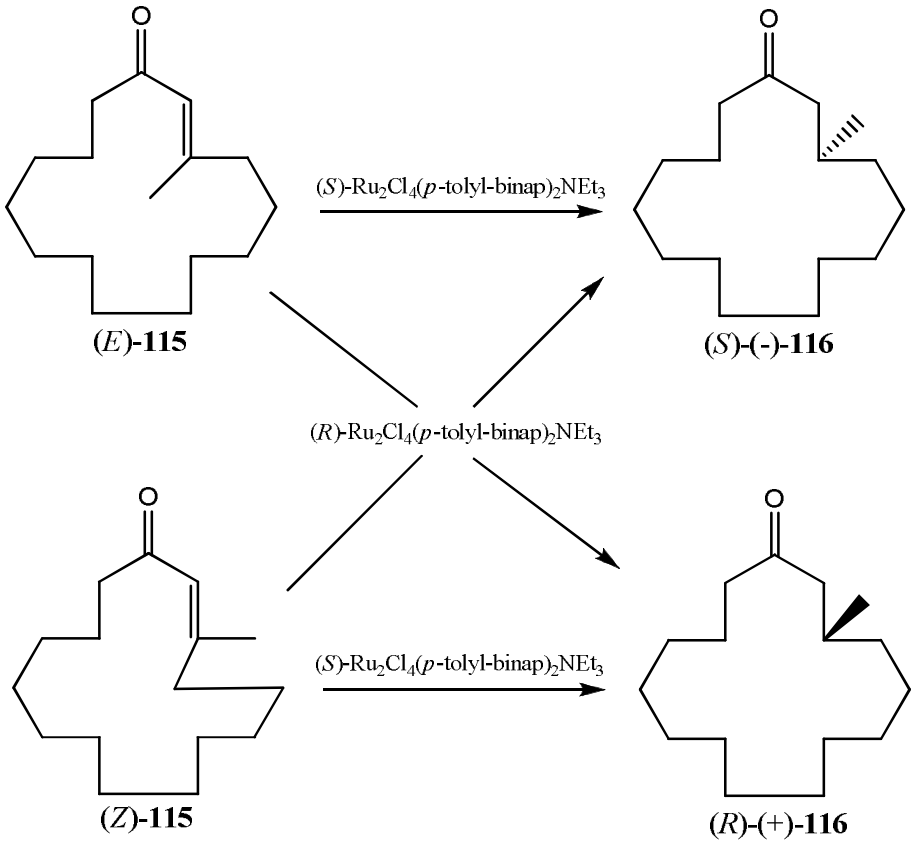


Reagents and conditions: (i) 10 % Pd/C (0.02-0.03 eq.), additive (0.5 eq.), acetonitrile, H_2 (balloon); (ii) Substrate (0.5 g), Pd black (0.05 g), toluene (20 ml), additive (0.0025 g), 2 h , H_2 (50 bar), 25 °C

Scheme 3-11

On the homogeneous catalysis side the binap based catalyst system, Ru_2Cl_4(*p*-tolyl-binap)$_2$NEt$_3$ (both (*R*)- and (*S*)-*p*-tolyl-binap)* has been described for olefinic hydrogenation in α,β-unsaturated systems. This catalyst was used to successfully hydrogenate (*E*)- and (*Z*)-3-methyl-2-cyclopentadecen-1-one (**115**) to the corresponding saturated ketones ((*R*)- and (*S*)-**116**) (100 % conversion; > 98 % e.e.).[57] The inverted product isomer is obtained if the (*R*)-*p*-tolyl-binap catalyst is employed as apposed to the (*S*)-*p*-tolyl-binap catalyst (Scheme 3-12).[57]

* *p*-tolyl-binap = 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl

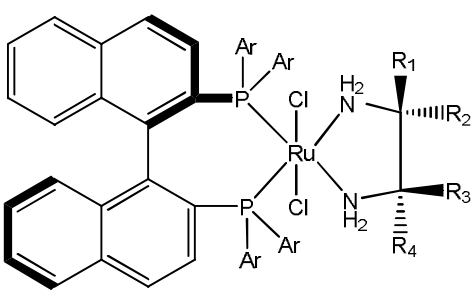


Reagents and conditions: Substrate (1 mmol), catalyst (0.001 mmol), MeOH (10 ml), 25 °C, H_2 (70 atm)

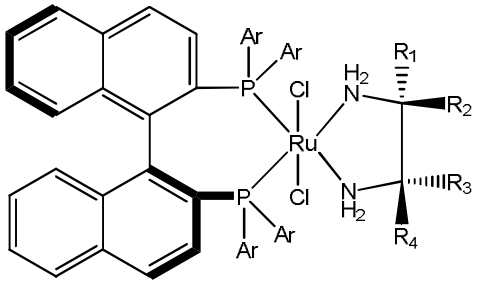
Scheme 3-12*

$RuCl_2$(phosphine)$_2$(1,2-diamine) (**117** and **118**)[58] represents the only catalyst to have been reported for the stereoselective hydrogenation of the carbonyl group in α,β-unsaturated systems. The phosphine ligand, which is binap based, is stable in air and is tolerant of heterocyclic rings.[59] As for the previous example (Scheme 3-12), an inversion in catalyst configuration yields the opposite absolute configuration in the product. Two applied examples of this catalyst are illustrated in Scheme 3-13.

* (*R*) and (*S*) product configuration is indicated incorrectly in reference

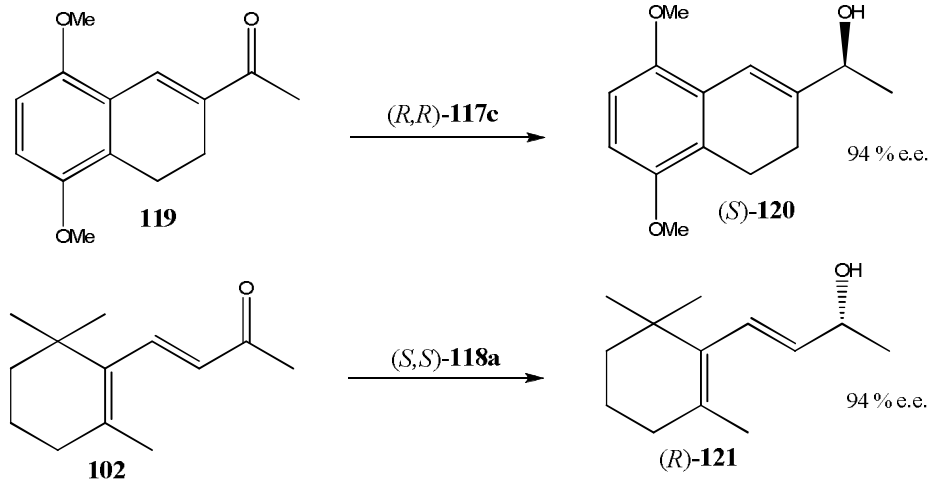


(*R*,*R*)- or (*R*,*S*)-**117a/b/c/d**



(*S*,*S*)- or (*S*,*R*)-**118a/b/c/d**

a = Ar = 3,5-$(CH_3)_2C_6H_3$; $R_1 = R_2$ = 4-$CH_3OC_6H_4$; $R_3 = (CH_3)_2CH$; R_4 = H
b = Ar = 4-$CH_3C_6H_4$; $R_1 = R_4 = C_6H_5$; $R_2 = R_3$ = H
c = Ar = C_6H_5; $R_1 = R_2$ = 4-$CH_3OC_6H_4$; $R_3 = (CH_3)_2CH$; R_4 = H
d = Ar = C_6H_5; $R_1 = R_4$ = H; $R_2 = R_3 = C_6H_5$



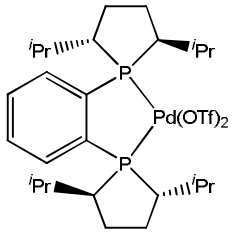
Reagents and conditions: Catalyst, room temperature, H_2 (1 - 8 atm), 2-propanol, alkaline base (eg. KOH (Ru:base < 1:2))

Scheme 3-13

3.3.2 Stereoselective hydrogen transfer hydrogenation

Three catalyst systems, i.e. Pd-^{i}Pr-duphos (**122**), $[Ir(COT)_2Cl]_2$,* and $[RuCl_2(p\text{-cymene})]_2$ modified with *N*-[(1*R*,2*R*)-2-amino-1,2-diphenylethyl]-4-methylbenzene-sulfonamide (**123**), have been described for stereoselective hydrogen transfer hydrogenation of α,β-unsaturated aldehydes/ketones. The first (Pd-^{i}Pr-duphos) utilizes 4Å molecular sieves together with ethanol as hydrogen source and gave the saturated ketone with (*S*) absolute configuration (**135**) in 98 % yield with 70 % e.e. when applied to the reduction of β-isopropyl-benzalacetone (**128**) (Scheme 3-14, Table 3-1).[59]

* COT = cycloocta-1,3,5-triene



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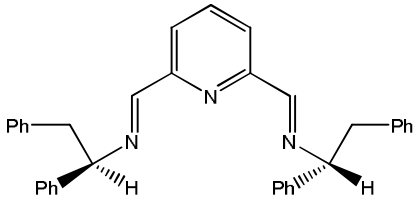

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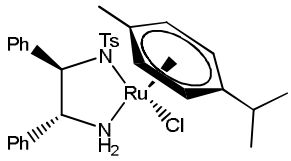

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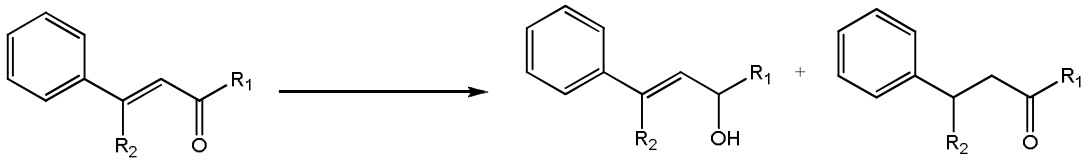
$[Ir(COT)_2Cl]_2$, *in situ* modified with the chiral ligand (*R,R*)-2,6-pyridine-1,2-diphenyl-ethyldiimine (PDPBI) (**124**), on the other hand, produces allylic alcohols with isopropanol as hydrogen source and KOH as co-catalyst.[60] Benzalacetone (**94**) is reduced to (*S*)-(-)-4-phenylbut-3-en-2-ol (*S*)-(**97**) in 93 % yield but only 67 % e.e. with (*R,R*)-PDPBI, while the enantiomer of the catalyst, as expected, also produces the enantiomer of the product. The e.e. can be increased to 82 % if the reaction is terminated after ~ 50 % conversion (Scheme 3-14, Table 3-1). The ruthenium catalyst (**123**), with *N*-[(1*R*,2*R*)-2-amino-1,2-diphenylethyl]-4-methylbenzenesulfonamide[61] as chiral inducer, has also been utilized for the 1,2-reduction of benzalacetone. When ordinary *trans*-chalcone (**90**) is subjected to the reaction, however, the saturated ketone (**91**) is obtained as product.[61] It was further determined that the stereochemical bulk of the substituent attached to the benzalacetone plays a decisive role in the regiochemical outcome of the reaction with *t*-Bu* leading to 71 % of the saturated ketone being produced. Although the worst yield of allylic alcohol (13 %) is obtained with the *t*-Bu substituent (**131**), this example exhibited the highest e.e. (57 %) (Scheme 3-14, Table 3-1).



Scheme 3-14: ***See Table 3-1***

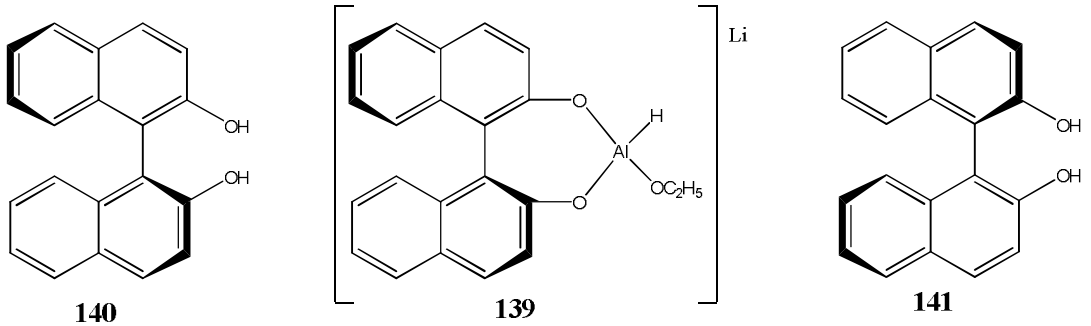
* *t*-Bu = *tert*-Butyl

Table 3-1: ***Results for Scheme 3-14***

Compound		Catalyst	% conv. Alcohol	% conv. Ketone	% e.e.	Confign.	Ref.
(**125**)	$R_1 = R_2 = CH_3$	Pd catalyst ( )	-	96	16	(*S*)-(**132**)	59
(**126**)	R_1 = Ph; $R_2 = CH_3$	"	-	96	26	(*S*)-(**133**)	59
(**127**)	$R_1 = CH_3$; $R_2 = CH_2CH_3$	"	-	84	32	(*S*)-(**134**)	59
(**128**)	$R_1 = CH_3$; $R_2 = CH(CH_3)_2$	"	-	98	70	(*S*)-(**135**)	59
(**94**)	$R_1 = CH_3$; R_2 = H	$Ir(COT)_2Cl_2$ + (*R,R*)-PDPBI	43	-	82	(*S*)-(-)-(**97**)	60
(**94**)	$R_1 = CH_3$; R_2 = H	"	93	-	67	(S)-(-)-(**97**)	60
(**94**)	$R_1 = CH_3$; R_2 = H	$Ir(COT)_2Cl_2$ + (*S,S*)-PDPBI	43	-	82	(*R*)-(+)-(**97**)	60
(**94**)	$R_1 = CH_3$; R_2 = H	"	90	-	67	(R)-(+)-(**97**)	60
(**94**)	$R_1 = CH_3$; R_2 = H	Ru catalyst ( )	75	0	30	(*R*)-(**97**)	61
(**129**)	$R_1 = CH_2CH_3$; R_2 = H	"	90	4	6	(*R*)-(**136**)	61
(**130**)	$R_1 = CH(CH_3)_2$; R_2 = H	"	48	30	28	(*R*)-(**137**)	61
(**131**)	$R_1 = C(CH_3)_3$; R_2 = H	"	13	71	57	(*R*)-(**138**)	61

3.3.3 Stereoselective hydride reduction

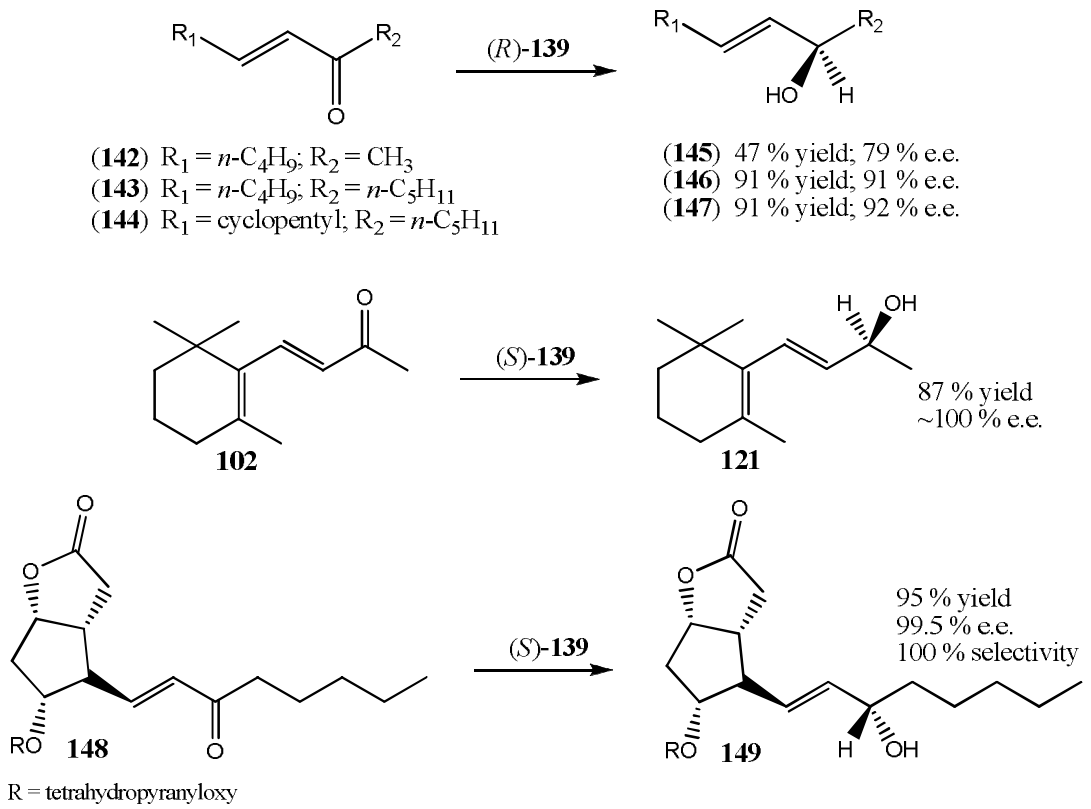
Only one hydride reducing reagent, developed by Noyori *et al.*,[62,63,64] has proven itself over a vast variety of substrates as worth a while in the stereoselctive reduction of the carbonyl group in α,β-unsaturated ketones. Thus $LiAlH_4$ modified *in situ* with optically active 2,2'-dihydroxy-1,1'-binaphthyl (binap) (**139**) and EtOH reduce carbonyls to allylic alcohols of the same optical orientation as the binap employed, i.e. (*S*)-binap (**140**) yield (*S*)-alcohols and (*R*)-binap (**141**) yield (*R*)-alcohols (Scheme 3-15).



140 **139** **141**

It has to be noted that in the reduction of β-ionone (**102**), the lithium aluminium hydride reagent gives slightly better e.e.s than the homogeneous ruthenium-binap hydrogenation catalyst (**117** and **118**) (*cf.* Scheme 3-13). The ruthenium compound, however, is air stable and acts as a catalyst, while the aluminium analogue has to be used stoichiometrically

although up to 90 % of the binap can be recovered after completion of the reaction (Scheme 3-15).[62]

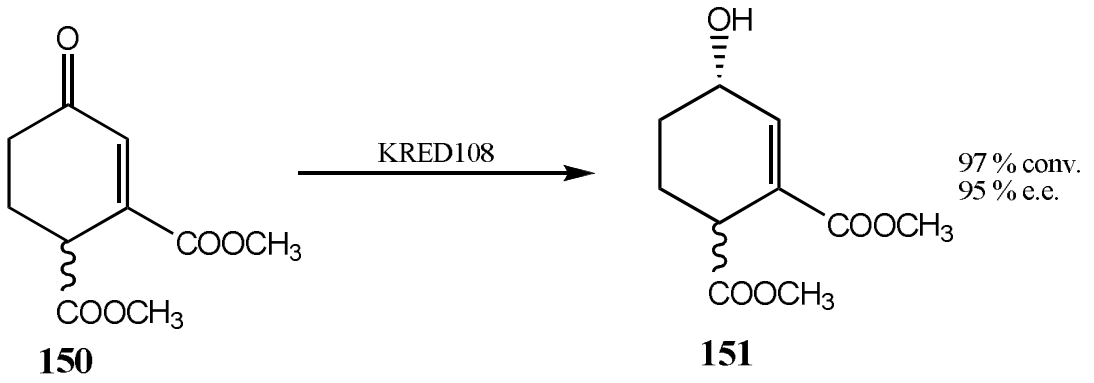


Scheme 3-15

3.3.4 Bio-catalytic reduction

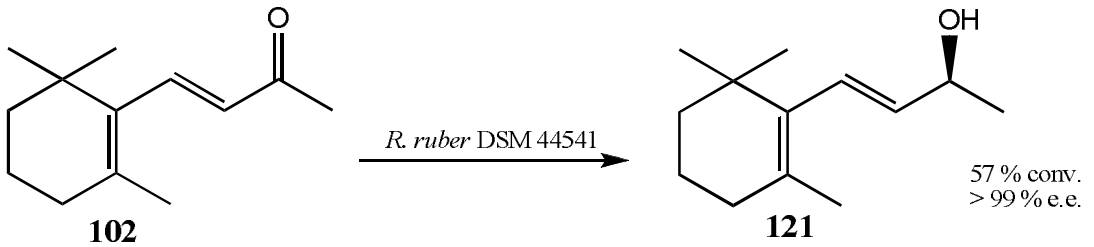
Although chemists tend to prefer chemical methodology, reduction of α,β-unsaturated aldehydes/ketones can also be achieved by utilising biological systems. While all bio-catalytic reductions employ the reduced form of the coenzyme nicotinamide adenine diphosphate (or its phosphate) [NAD(P)H], the correct choice of enzyme or micro-organism is crucial since high selectivity toward specific functional groups is displayed by certain systems.[65] These biological reductions are generally conducted in dilute systems at ambient temperatures and neutral pH, which are favoured conditions for acid and base labile moieties. Immobilized enzymes and utilization of organic solvents are some of the modifications that can be applied to this general method to accommodate a specific reaction.

A number of ketoreductase enzymes invesitgated by Kosjek *et al.*[66] showed high diastereo- and enantioselectivity to produce allylic alcohols from α,β-unsaturated ketones of which KRED108 showed the greatest potential (Scheme 3-16). *Rhodococcus ruber* DSM 44541[67] can also be used for this purpose (Scheme 3-17).



150 **151**

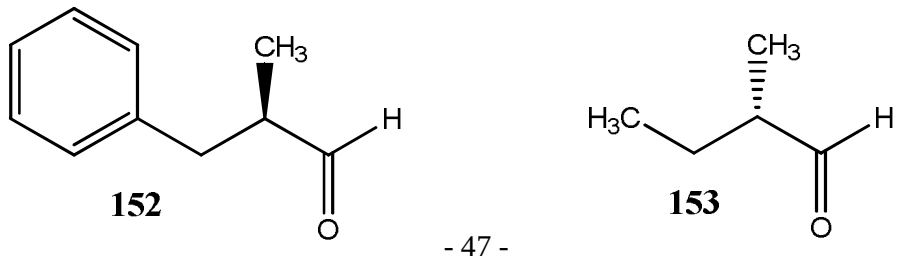
Scheme 3-16



102 **121**

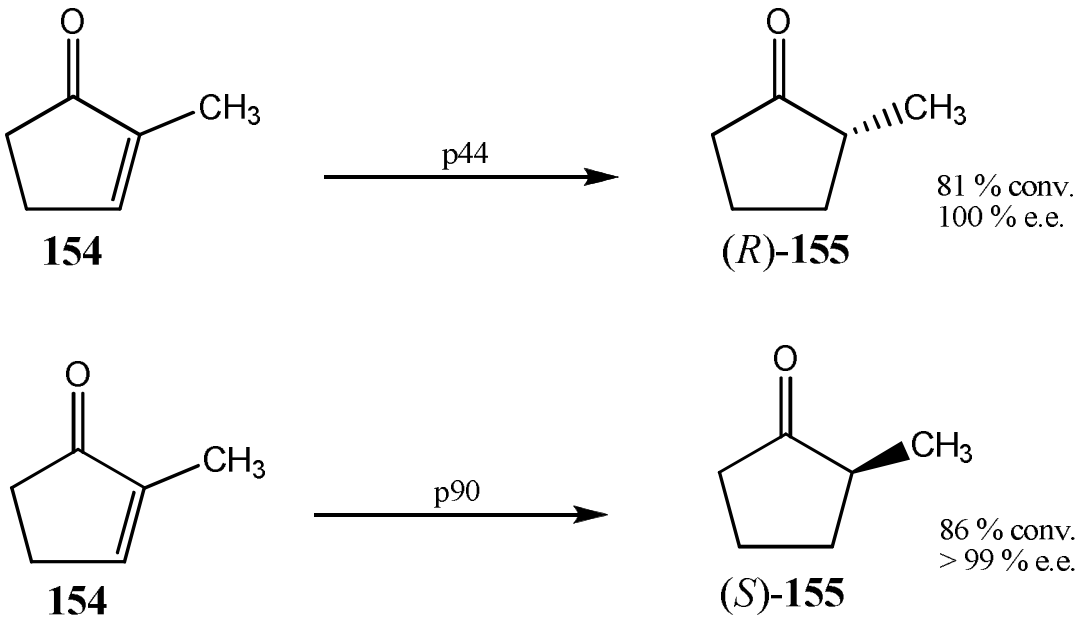
Scheme 3-17

A number of reductases produce saturated ketones from their α,β-unsaturated counterparts. Old Yellow Enzymes (OYE) 1, 2 and 3 and a novel reductase, NCS from *Zymomonas mobilis*, investigated by Müller *et al.*[68] yielded (*R*)-3-phenyl-2-methylpropanal (**152**; *ca*. 50 - 75 % e.e.) and (*S*)-2-methylpentanal (**153**; *ca*. 70 - 100 % e.e.) from their corresponding unsaturated precursors. Since the only difference between the two mentioned substrates is 3-phenyl *vs.* 3-methyl it is clear that the substrate has a significant influence on the absolute configuration of the product.



152 **153**

p44 Reductases and p90 reductases from *Nicotiana tabacum*,[69] also produce (*R*) and (*S*) α-alkylated saturated ketones respectively from the α,β-unsaturated compounds (Scheme 3-18).



Scheme 3-18

Saccharomyces cerevisiae (bakers' yeast)[70,71] and *Beauvaria sulfurescens* (ATCC 7159)[72,73] are examples of micro-organisms known to produce saturated ketones from α,β-unsaturated ketones.

3.4 References

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RESULTS AND DISCUSSION

CHAPTER 4

HYDROGENATION

4.1 Introduction

As mentioned earlier (*cf.* Paragraph 2.1), metabolic studies of flavonoids are greatly hampered by inaccessibility to a wide range of different optically active monomeric units. Although nearly all monomeric flavonoids are synthetically obtainable, preparative methods differ greatly from one skeleton to the next and especially with regards to stereoselective synthesis consists of tedious routes. The majority of these pathways also produce the desired compounds in low yield and enantiomeric excess making them even less favourable.

Since most α,β-unsaturated flavonoids, like flavones, isoflavones and flavonols (Figure 4-1) are easily obtainable in high yields from readily available starting materials, it was decided to investigate the utilisation of these compounds as staring materials in the stereoselective synthesis of chiral flavonoids. The approach of the current study therefore was to utilise the hydrogenation reaction in converting these prochiral flavonoids into their corresponding optically active saturated counterparts in one step. Since many of the target compounds still contain a C-4 carbonyl together with chirality at C-2 and C-3, the hydrogenation needed to be regioselective towards the double bond in addition to being stereoselective.

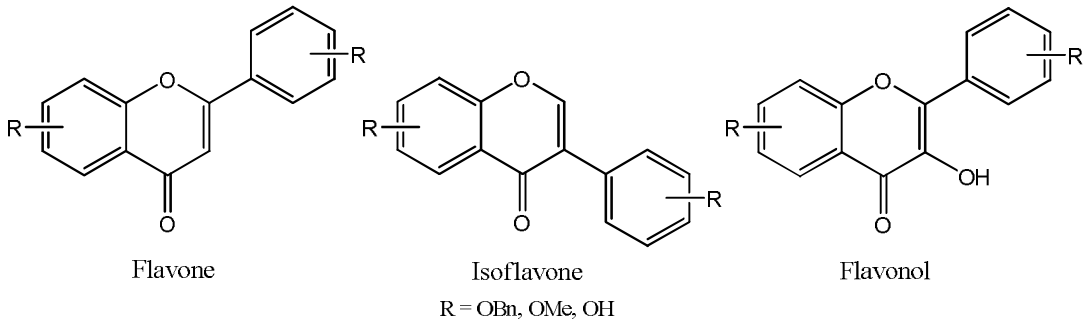
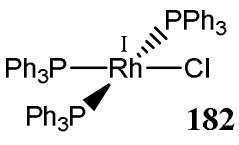


Figure 4-1

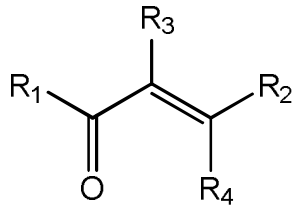
Although the chiral induction should be the more difficult of the two issues, it was felt that once the right metal catalyst for introducing the regioselectivity was found, this catalyst could be modified with one of the host of chiral ligands known in literature[1,2,3,4] for introducing the required stereoselectivity. The first focus of the current investigation therefore was to find the right catalyst for regioselective 1,4-reduction of the α,β-unsaturated flavonoids mentioned above. While many heterogeneous catalysts (*cf.* Paragraph 3.2.4) and hydride reducing agents (*cf.* Paragraph 3.2.3) have been described in literature for the 1,4-reduction of α,β-unsaturated carbonyl compounds, not many systems have the potential to be modified with chiral ligands. In order to have a catalytic system available it was furthermore decided to look beyond hydride reducing agents and focus on homogeneous metal catalysts applied to the hydrogenation of olefins. In this regard many rhodium and ruthenium systems have been reported for the reduction of isolated olefinic double bonds,[5,6,7,8,9,10,11,12] but very little is known about the 1,4-reduction of α,β-unsaturated aldehydes and ketones. Since Wilkinson's catalyst has a high selectivity towards olefinic double bonds and numerous modifications to rhodium catalysts have been done in order to obtain stereoselectivity during hydrogenation reactions.[2,3] Wilkinson's catalyst (**182**) was selected as the first candidate in the development of technology for the selective reduction of the 2,3-double bond in flavonoid precursors.



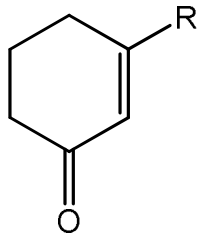
182

Like almost all transition metal catalysts, Wilkinson's catalyst (**182**) is sensitive towards steric bulk around the olefinic double bond. Since all of the flavonoid substrates targeted for this investigation contain a trisubstituted double bond, the effect of steric bulk on the catalyst's ability to perform hydrogenation reactions on these substrates was envisaged as one of the first factors to be investigated. Furthermore, it was also evident from literature that the hydrogenation of α,β-unsaturated systems by means of Wilkinson's catalyst (**182**) represents an unexplored

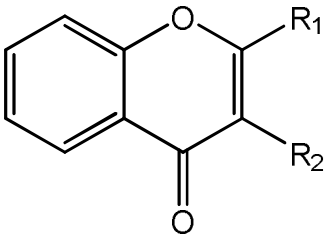
area of research. Due to these factors, it was decided to initiate the study on substrates (**156** - **162**) less complex than the target flavonoids with the flavonoid substrates (**90**, **163** - **166**) to follow once conditions and effect of substituents on the reaction have been established. While substrates (**90**), (**156**) – (**164**) and (**166**) were commercially available, the isoflavonoid compound to be subjected to the hydrogenation investigation, had to be synthesised.



(**156**) $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$
(**157**) $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$
(**158**) $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
(**159**) $R_1 = R_2 = R_4 = CH_3$; $R_3 = H$
(**160**) $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$
(**90**) $R_1 = R_2 = Ph$; $R_3 = R_4 = H$



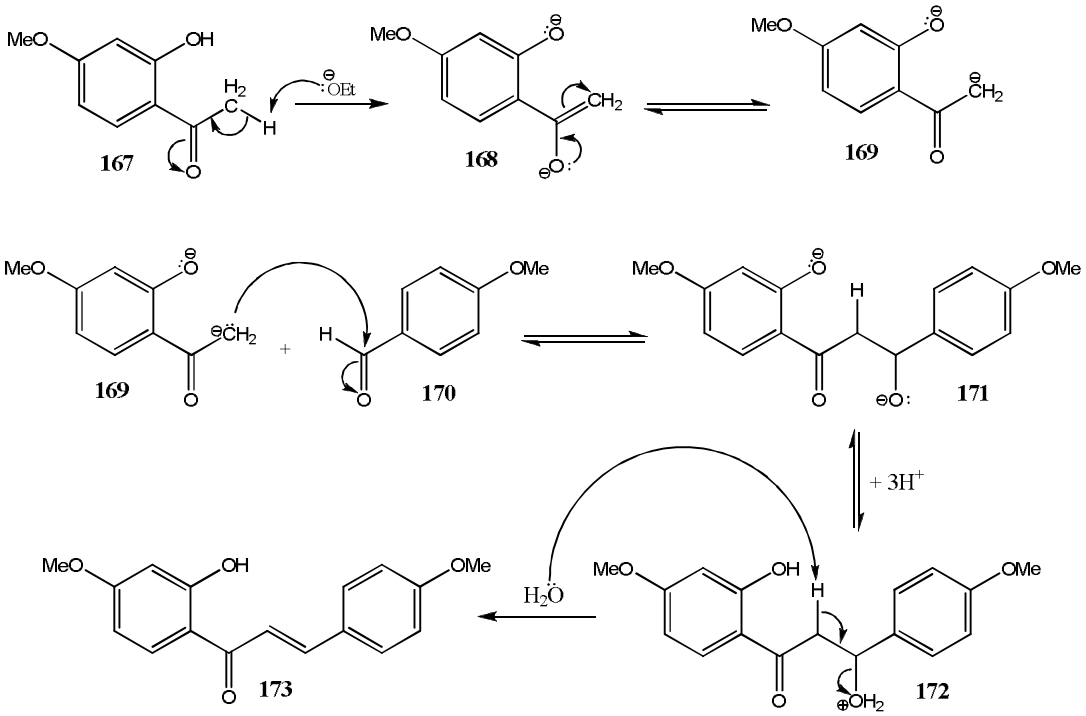
(**161**) R = H
(**162**) $R = CH_3$



(**163**) $R_1 = R_2 = H$
(**164**) $R_1 = Ph$; $R_2 = H$
(**165**) $R_1 = H$; $R_2 = Ph$
(**166**) $R_1 = Ph$; $R_2 = OH$

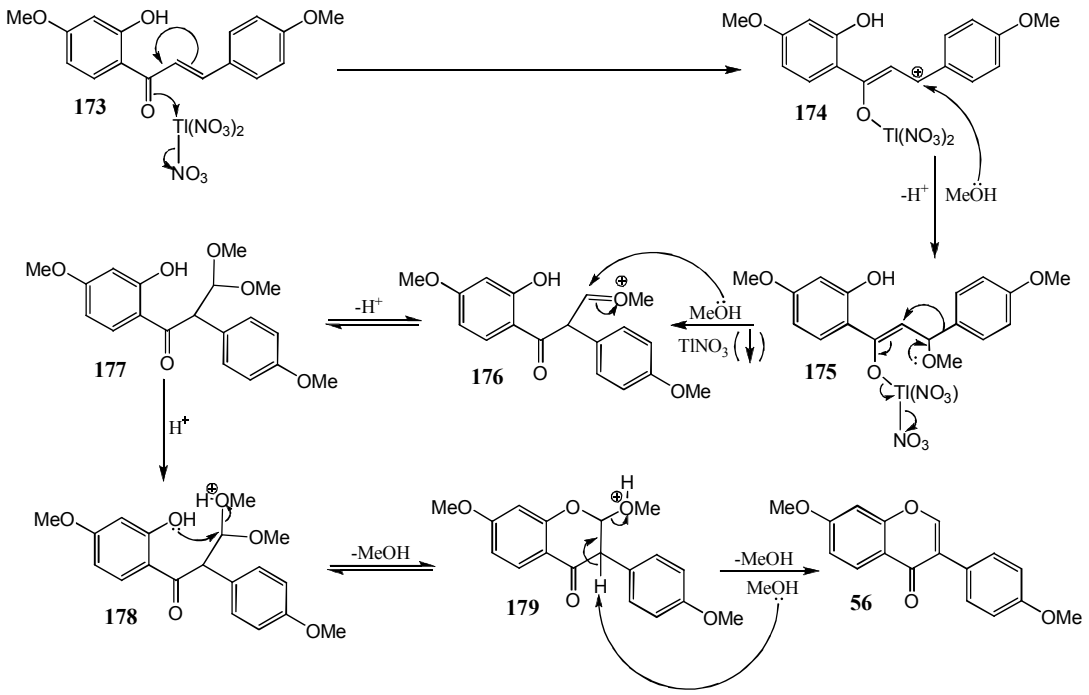
4.2 Preparation of isoflavone

Since isoflavones are easily accessible *via* rearrangement of the corresponding chalcone, the synthesis of 4',7-dimethoxyisoflavone (**56**) was started by forming the required chalcone. Thus 2'-hydroxy-4,4'-dimethoxychalcone (**173**) [^{1}H NMR (300 MHz, $CDCl_3$) (plate 1) δ ppm 7.86 (1H, d, *J* = 15.54 Hz, H-β), 7.82 (1H, m, H-6'), 7.61 (2H, d, *J* = 8.88 Hz, H-2 and H-6), 7.45 (1H, d, *J* = 15.54 Hz, H-α), 6.94 (2H, d, *J* = 8.88 Hz, H-3 and H-5), 6.48 (2H, m, H-3' and H-5'), 3.86 (3H, s, -OC$\underline{H_3}$), 3.85 (3H, s, -OC$\underline{H_3}$)] was obtained as yellow crystals[13] (69.1 %) through Claisen-Schmidt condensation[14] of 2'-hydroxy-4'-methoxyacetophenone (**167**) and *p*-anisaldehyde (**170**) (Scheme 4-1). The ^{1}H-NMR spectrum of this chalcone (plate 1) showed the α- and β-proton resonances as doublets with 15.54 Hz coupling constants at δ 7.45 ppm and δ 7.86 ppm respectively, thus proving the product to be the *trans*-chalcone.



Scheme 4-1

Thallium(III) nitrate (TTN) induced rearrangement[15] of 2'-hydroxy-4,4'-dimethoxychalcone (**173**) followed by cyclization and methanol elimination from the intermediate acetal (**177**) yielded 7,4'-dimethoxyisoflavone (**56**, 64.0 %) (Scheme 4-2). The ^{1}H NMR spectrum (plate 2) of the product displayed a singulet at 7.90 ppm characteristic of an isoflavone H-2 together with the expected aromatic protons and methoxy groups, thus confirming the product to be the desired isoflavone.

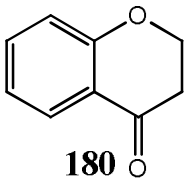


Scheme 4-2

4.3 Hydrogenation results

With all the starting materials in hand, attention was subsequently turned to finding the optimal reaction conditions for conjugate hydrogenation over Wilkinson's catalyst (**182**). Since solubility of hydrogen and thus hydrogen concentration in the solvent, would play a pivotal role in the rate of reaction, this was the first aspect to receive attention.

In order to evaluate a system as close to the flavonoid substrates as possible, chromone (**163**) was subjected to hydrogenation over Wilkinson's catalyst in different solvents. It was decided to utilize NMR spectroscopy for analysis of reaction mixtures. NMR spectroscopy would not only confirm hydrogenation but would also quantify product formation. The H-2 (δ 6.33 ppm) and H-3 (δ 7.85 ppm) doublets of chromone (**163**) [^{1}H NMR (300 MHz, $CDCl_3$) (plate 3) δ ppm 8.20 (1H, dd, *J* = 1.62, 7.87 Hz, H-5), 7.85 (1H, d, *J* = 6.06 Hz, H-3), 7.66 (1H, ddd, *J* = 1.62, 7.06, 8.48 Hz, H-7), 7.45 (1H, dd, *J* = 1.01, 8.48 Hz, H-8), 7.40 (1H, ddd, *J* = 1.01, 7.06, 7.87 Hz, H-6), 6.33 (1H, d, *J* = 6.06 Hz, H-2)] would be replaced by two triplets at δ 4.52 ppm and δ 2.79 ppm representing the α- and β-protons of chromanone (**180**)



180

[^{1}H NMR (300 MHz, $CDCl_3$) (plate 4) δ ppm 7.88 (1H, dd, *J* = 1.82, 7.87 Hz, H-5), 7.45 (1H, ddd, *J* = 1.82, 7.27, 8.28 Hz, H-7), 6.99 (1H, ddd, *J* = 0.81, 7.27, 7.87 Hz, H-6), 6.95 (1H, dd, *J* = 0.81, 8.28 Hz, H-8), 4.52 (2H, t, *J* = 6.46 Hz, H-2), 2.79 (2H, t, *J* = 6.46 Hz, H-3)].

Acetone, THF (tetrahydrofuran) and DCM (dichloromethane) yielded 7.8%, 14.3% and 46.2% chromanone (**180**) respectively over a 24 hour period under the same reaction conditions. This pointed to DCM being the solvent of choice for this reaction and it was therefore used in all subsequent reactions during the current investigation. The same conclusion was reached in a simultaneous independent study on 1-octane by Robb and Cole-Hamilton.[16] During this study it was noticed that ambient temperature did not suffice for a decent reaction rate due to very slow product formation. Increases in hydrogen pressure and temperature showed a direct correlation to reaction rate. The profound effect of temperature and pressure found during the Robb study clearly indicated that a close investigation of the influence of these parameters on the reaction rate of the hydrogenation of α,β-unsaturated systems with Wilkinson's catalyst (**182**) is required.

4.3.1 Investigations at St. Andrews University

Since all the equipment needed for a proper investigation into the kinetics of the hydrogenation of the selected α,β-unsaturated carbonyl substrates was not available at the University of the Free State, it was decided to involve Prof. Cole-Hamilton in the investigation and start the study during a visit to St. Andrews University in Scotland.

Experimental set-up

The reactor set-up at the St. Andrews facility is depicted in Diagram 4-1 and consisted of a reaction vessel, ballast vessel, two pressure gauges, and two valves with a pressure regulator in between. For all of the reactions 1 ml of substrate was injected into 9 ml of preheated catalyst solution (1 mg of catalyst per 1 ml DCM) under a set pressure inside the reactor vessel. In contrast to the other liquid substrates, the chalcone (**90**), being a solid at room temperature, was added to the reactor as a DCM solution (*ca*. 1.0 g in 1 ml DCM). Before starting the reaction, the ballast vessel was pressurised to a value of *ca*. 70 bar and the regulator set to maintain the pressure inside the reactor at the required constant level by feeding hydrogen from the ballast vessel into the reactor. Gas consumption (by the reaction)

was therefore reflected by a pressure drop in the ballast vessel, which was digitally recorded as a function of time.

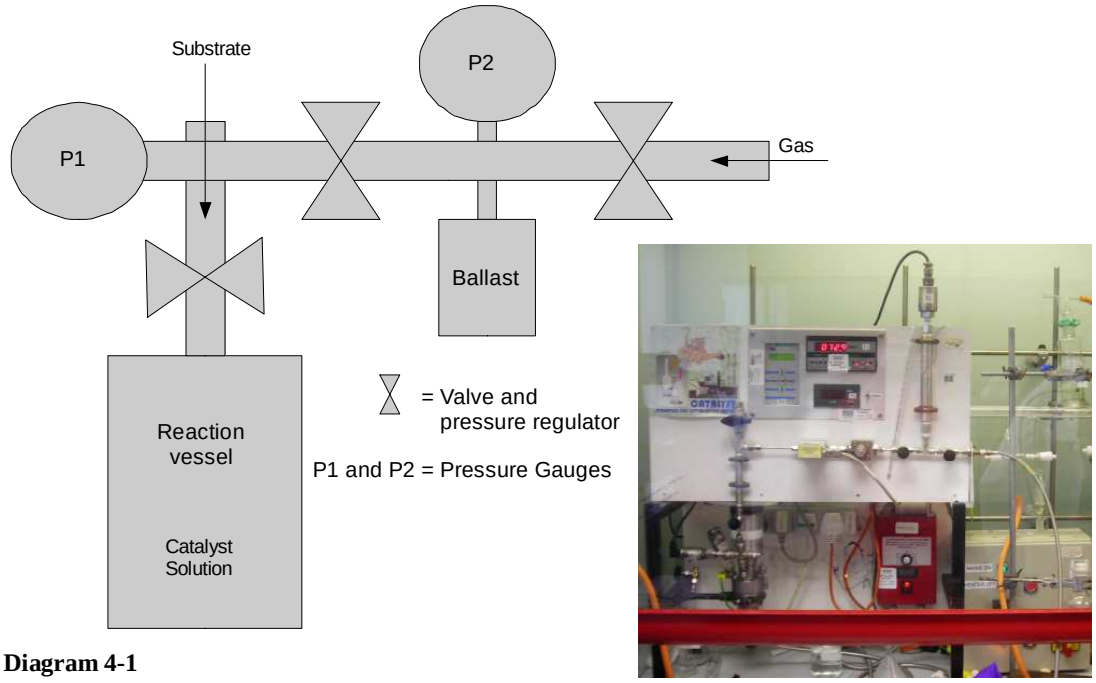


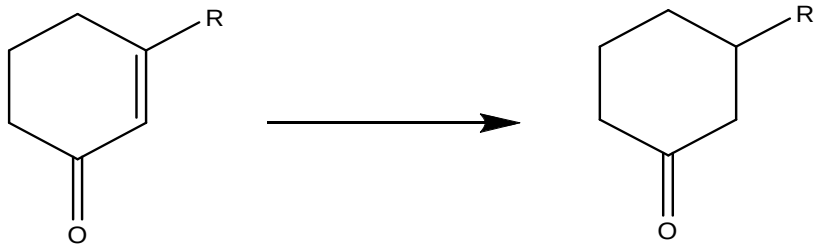
Diagram 4-1

Results

In order to see if Wilkinson's catalyst (**182**) is capable of reducing α,β-unsaturated ketones in the way it was anticipated and since *cis* substitution generally favours reactions over organometallic catalysts, the study was initiated by exposing cyclohex-2-enone (**161**) to the reducing conditions of 80 ^{o}C and 10 bar H_2 pressure (Table 4-1, entry 1). Through GC/MS analysis, it was established that the desired product was indeed formed, but the reaction was rather slow with a reaction rate of only 0.0002540 s^{-1}. In order to evaluate the effect of pressure, the reaction was repeated at 20, 30, and 40 bar (Table 4-1; entries 2, 3 and 4) with the expected significant increase in reaction rate (from 0.0002600 s^{-1} to 0.003964 s^{-1}) for the 20 and 30 bar reactions. The reaction at 40 bar (Table 4-1; entry 4), however, gave no detectable product with considerable quantities of rhodium black being observed when the reactor was opened up. Several repetitions of the reaction at 40 bar gave similar results, so it could be concluded that 30 bar was the optimum working pressure for the hydrogenation of cyclohex-2-enone (**161**) with Wilkinson's catalyst (**182**). With the optimum pressure determined, attention was turned towards identifying the ideal temperature and reaction

temperatures were increased by 10 °C at a time to 90 °C, 100 °C and 110 °C (Table 4-1; entries 5 - 8), while the pressure was kept at 30 bar.

Table 4-1

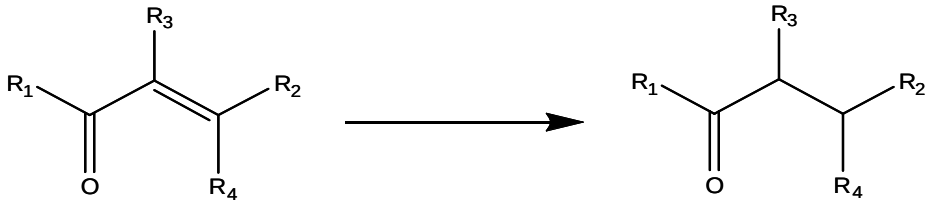


Entry		T (°C)	P (bar)	k_{obs} (s^{-1})
1	(**161**) R = H	80	10	0.0002540250
2		80	20	0.0025995160
3		80	30	0.0039638810
4		80	40	Rh fall-out
5		90	30	0.0112725380
6		100	30	0.0144199360
7		100	30	0.0186246500
8		110	30	Rh fall-out
9	(**162**) R = CH_3	80	20	0.0001746440

Temperature increases to 90 °C and 100 °C led to the expected increases in k_{obs} of 0.01127 s^{-1} and 0.01442 s^{-1} respectively (Table 4-1, entries 5 and 6), but the reaction at 110 °C again led to only Rh fall–out to be observed (Table 4-1; entry 8). In order to ensure reproducibility, the reaction at 100 °C was repeated once (Table 4-1, entry 7) and that at 110 °C several times, but while the 100 °C reaction led to an even better reaction rate (k_{obs} = 0.01862 s^{-1}) no indication of any product formation could be detected from all of the 110 °C reactions. It was therefore concluded that the optimum reaction conditions for the hydrogenation of cyclohex-2-enone (**161**) over Wilkinson's catalyst (**182**) was 100 °C at 30 bar hydrogen pressure. Finally, the effect of increased substitution around the double bond was investigated and 3-methylcyclohex-2-enone (**162**) subjected to the starting reaction conditions of 20 bar and 80 °C. While product was indeed formed, as indicated by GC/MS analysis, the reaction proved to be more than an order of magnitude slower with a reaction rate of only 0.0001746 s^{-1} (Table 4-1, entry 9).

Subsequently, attention was turned towards evaluating acyclic substrates in the hydrogenation reaction and assessing the effect of increased substitution around the double bond of these compounds on conjugate reduction. Hydrogenation [80 ^{o}C, 10 bar H_2 pressure (Table 4-2, entry 1)] of 3-buten-2-one (methyl vinyl ketone, MVK) (**156**) gave the desired reduction product (identified by GC/MS) at a higher reaction rate (k_{obs} = 0.01011 s^{-1}) when compared to cyclohex-2-enone (**161**) (Table 4-1, entry 1), but some rhodium black was observed when the reactor was opened. The reaction was therefore repeated under the same conditions and a 150 % increase in k_{obs} (0.02457 s^{-1}) was found (Table 4-2, entry 2). It has to be pointed out at this stage that reproducibility of results proved to be rather difficult to achieve, since Rh fall-out was observed from time to time and could not be prevented entirely. Increased pressure to 15 and 20 bar respectively showed the same increase in reaction rate as observed before (Table 4-2, entries 3 and 4), so it was concluded that the effects of pressure and temperature found for cyclohex-2-enone (**161**) (Table 4-1) would prevail for the acyclic ketones.

Table 4-2



Entry		T (^{o}C)	P (bar)	k_{obs} (s^{-1})
1	(**156**) $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$	80	10	0.0101129000
2		80	10	0.0245703000
3		80	15	0.0112676000
4		80	20	0.2621590000
5	(**158**) $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$	80	10	0.0002268520
6	(**159**) $R_1 = R_2 = R_4 = CH_3$; $R_3 = H$	80	10	No reaction
7	(**160**) $R_1 = R_2 = R_3 = CH_3$; $R_4 = H$	80	10	No reaction
8	(**90**) $R_1 = R_2 = Ph$; $R_3 = R_4 = H$	80	10	0.000143572
9	(**181**) $R_1 = R_3 = R_4 = H$; $R_2 = CH_3$	80	10	No reaction

With the effect of factors like temperature and pressure being determined, it was decided to keep these variables constant and continue the investigation by looking at the influence of substitution around the olefinic double bond on the reaction. Similar to cyclohex-2-enone (**161**) (Table 4-1), the addition of a substituent to the β-carbon led to a dramatic effect with

the reaction rate being lowered by two orders of magnitude (from 0.01011 s^{-1} to 0.0002269 s^{-1}) when compared to the reaction of MVK (**156**) under the same conditions (Table 4-2, entries 1 and 5 respectively). Addition of another substituent to the double bond, either in the α- or β-position, yielded no reaction at all (Table 4-2, entries 6 and 7 respectively). From these results it was clear that the acyclic trisubstituted substrates were sterically inaccessible for the catalyst to perform any hydrogenation. Furthermore when compared to the cyclic substrates of the same order of substitution, i.e. cyclohex-2-enone (**161**) (Table 4-1, entry 1) *vs*. 3-penten-2-one (**158**) (Table 4-2, entry 5) and 3-methylcyclohex-2-enone (**162**) (Table 4-1, entry 9) *vs*. mesityl oxide (**159**) (Table 4-2, entry 6), it is clear that on the disubstituted level cyclization has virtually no effect on the accessibility of the double bond towards Wilkinson's catalyst (k_{obs} = 0.0002540 s^{-1} *vs*. k_{obs} = 0.0002269 s^{-1}), but at the trisubstituted level a large effect is observed with the acyclic double bond being completely inaccessible at 80 ^{o}C.

Since the ultimate aim of the study was the utilization of Wilkinson's catalyst (**182**) in the hydrogenation of phenolic substrates, chalcone (**90**) was subsequently subjected to the hydrogenation procedure. The phenyl rings might have increased steric bulk when compared to the methyl substituents in 3-penten-2-one (**158**) and have diverse electronic effects since the α,β-unsaturated functionality is now conjugated with the aromatic systems. A further *ca*. 50 % decrease in reaction rate when compared to 3-penten-2-one (**158**) (Table 4-2, entries 5 and 8) was unfortunately observed for the chalcone substrate.

For the sake of completeness hydrogenation was also performed on crotonaldehyde (**181**) (Table 4-2; entry 9), but no reaction was observed even after several attempts. This indicates that the α,β-unsaturated aldehydes must react differently with the catalyst than the α,β-unsaturated ketones. Further studies would, however, be required to comment on this phenomenon.

4.3.2 Studies at the University of the Free State

With the influence of external parameters established and good working conditions obtained, direct kinetic evaluations were no longer required. This part of the investigation was therefore aimed at determining the scope and limitations of conjugate hydrogenation with Wilkinson's catalyst (**182**) towards flavonoid substrates. Since reproducibility during the

investigations at St. Andrews might have been compromised by oxidative addition of the Rh catalyst to the DCM solvent while the reactor was being brought to temperature, it was decided to change the order of addition of reagents during the remaining experimentation. In the reactor set-up as indicated in Diagram 4-2, the substrate solution (25 ml) was therefore heated to the desired temperature in the reactor before the reaction was initiated by injection of the catalyst (20 mg in 5 ml of DCM) from the sample cylinder into the substrate solution. As with the solvent study, analysis of the reaction mixtures were performed by NMR spectroscopy where the disappearance of the chalcone's β-proton (δ 7.83 ppm; plate 5) and appearance of the dihydrochalcone's α- and β-protons (δ 3.08 ppm and 3.31 ppm; plate 6) were used as probes for the concentration of the starting material and product in solution. Samples were taken at fixed time intervals and relative comparisons between reaction rates were thus still possible.

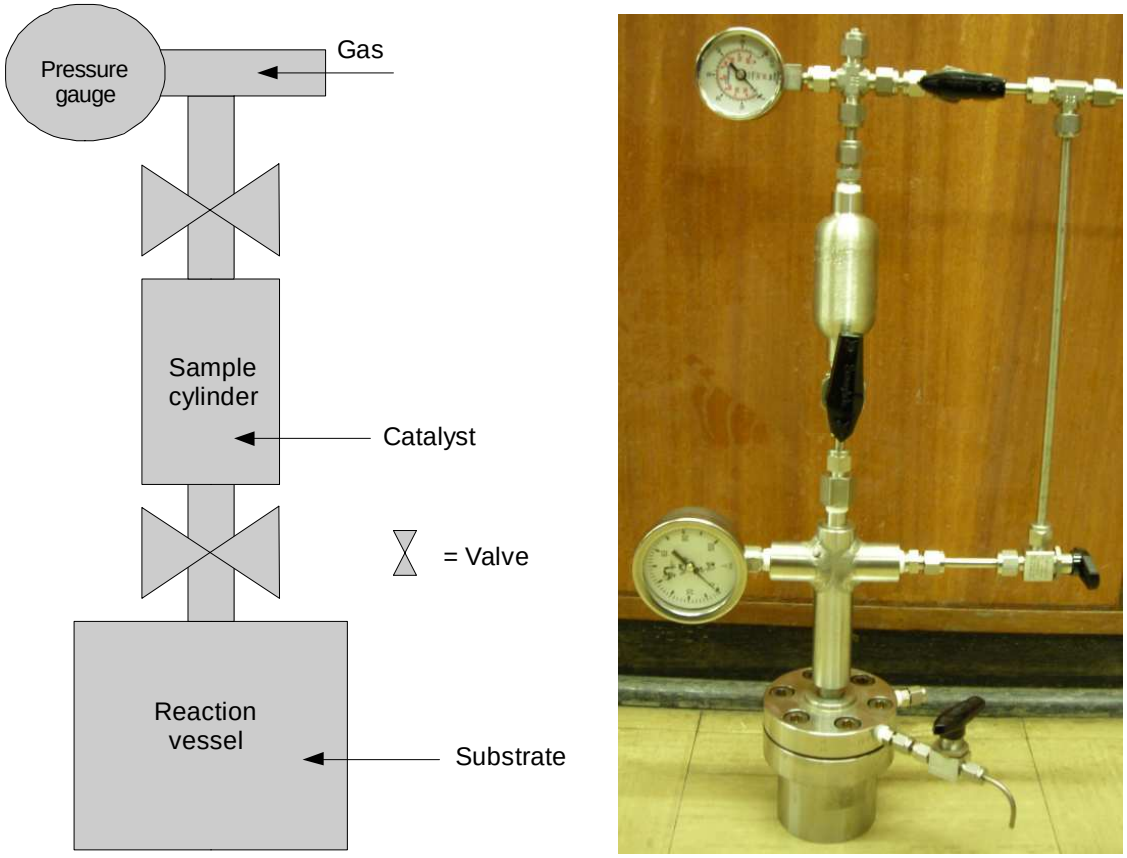
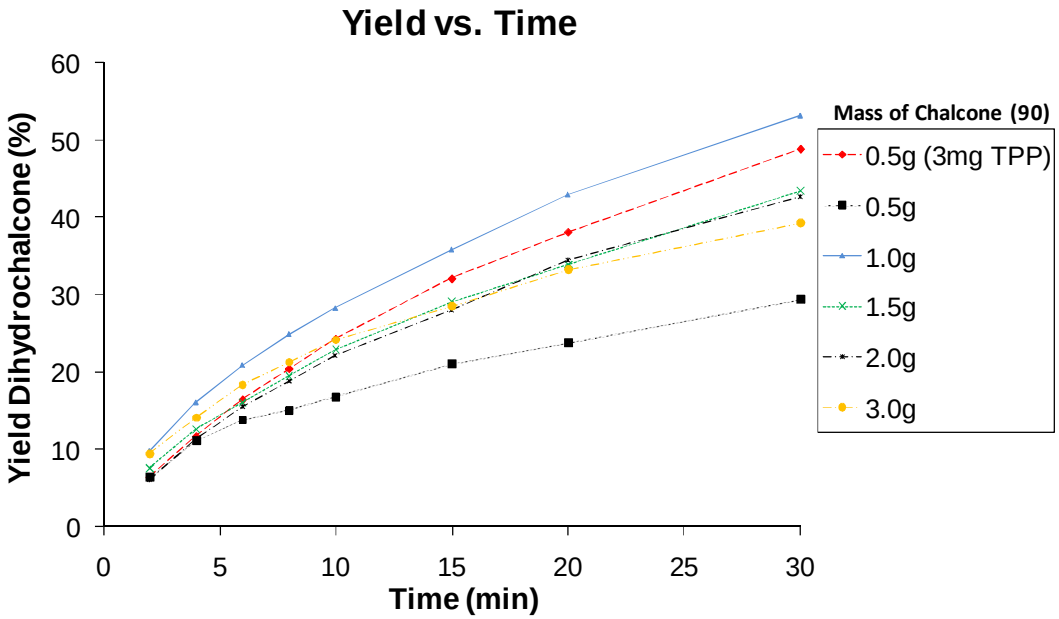


Diagram 4-2

Since chalcone (**90**) represents an electronic and steric environment similar to the cyclic flavonoids that were the ultimate aim of the project and it was successfully hydrogenated at

St. Andrews University the investigation was continued on this substrate with the aim of reproducing or improving on the results obtained at St. Andrews. Due to the size of the available reactor (50 ml) and the cost of Wilkinson's catalyst (**182**), the quantities of reagents used during the St. Andrews investigation could not be repeated and the concentration of chalcone and catalyst in the DCM was lowered to 1.0 g and 20 mg in 30 ml of solvent respectively. This reaction at conditions of 80 ^{o}C and 20 bar hydrogen pressure (Graph 4-1) proved to be considerably faster (27 min *vs*. 80 min for *ca*. 50% conversion) than the one performed at St. Andrews University. While the effect of the increased pressure could not be excluded, the last result indicated substrate concentration to have a profound influence on the reaction rate, so it was decided to investigate the effect of substrate concentration on the rate of reaction. The total reaction volume (30 ml), catalyst volume and concentration (20 mg in 5 ml DCM), temperature (80 ^{o}C) and pressure (20 bar) were all kept constant, while the concentration of chalcone (**90**) was varied between 0.5 g and 3 g in 25 ml of DCM solvent.

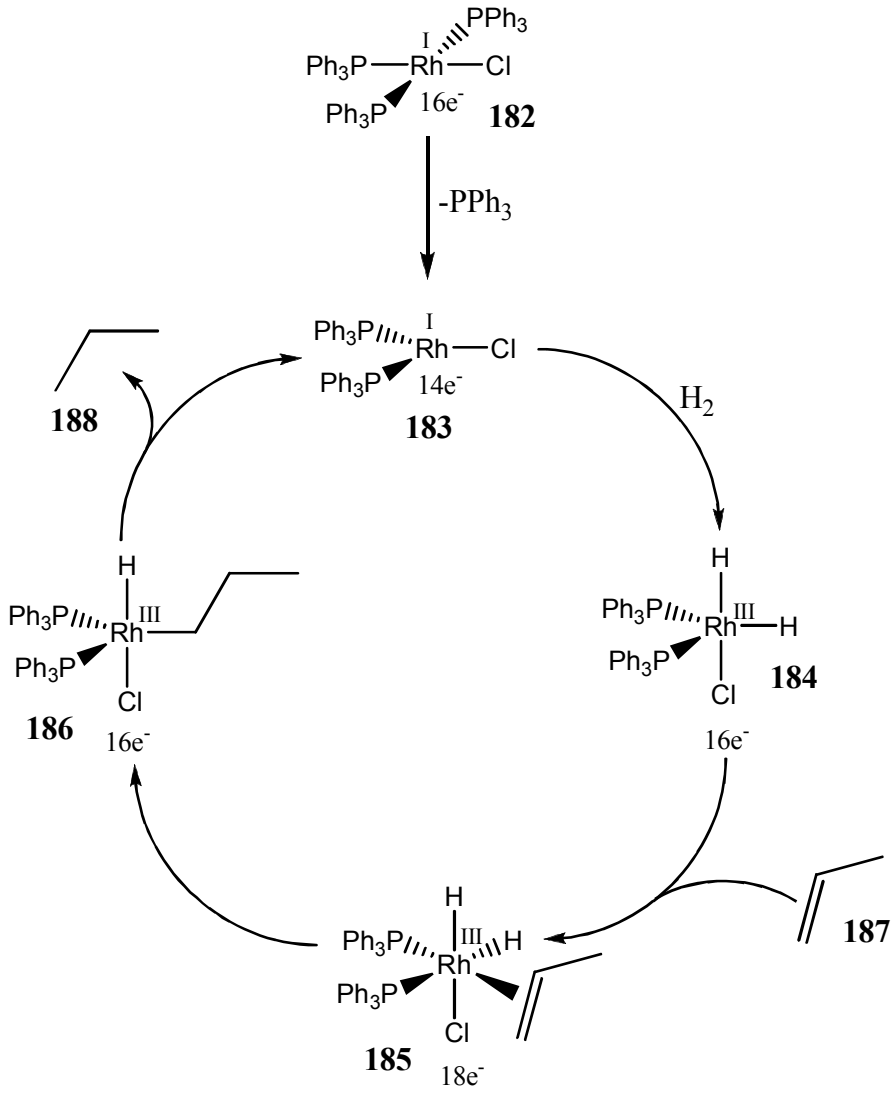
While it is expected for bimolecular reactions that an increase in concentration of one or both of the reactants should lead to an increase in the reaction rate, the inverse was found in this instance and apart from the 0.5 g reaction, an increase in chalcone (**90**) concentration in fact led to a decrease in rate (Graph 4-1). Although not perfectly similar, this result was in agreement with that found at the St. Andrews laboratory and can probably be explained in terms of reduced solubility of hydrogen in the solutions having a higher chalcone (**90**) concentration. The fact that the St. Andrews reaction at *ca*. 1 g in 10 ml being considerably slower than the current reaction of the same concentration (3 g in *ca*. 30 ml) could probably be explained in terms of the surface of the solution being exposed to hydrogen being smaller in the St. Andrews case (*ca*. 30 mm *vs*. *ca*. 50 mm) or an increased stirring rate or more efficient stirring during the current investigation leading to an increased H_2 concentration in the solution. The result from the 0.5 g reaction clearly needs some comment: While it cannot be excluded that this result represents an outlier (especially if the repeat of this concentration during the evaluation of the effect of added triphenylphosphine is taken into account, *vide infra*), it may also indicate that at this chalcone concentration the effect of chalcone on the absorption of hydrogen into the solution is not a factor anymore and the 'normal' effect of concentration is being observed.



Graph 4-1

While the mechanism for hydrogenation of alkenes with Wilkinson's catalyst (**182**) (Scheme 4-3)[17] clearly indicates that one of the triphenylphosphine (TPP) ligands needs to leave the metal complex for opening up coordination sites for hydrogen and the alkene to bind to the metal and it is a well known fact that some commercial samples of Wilkinson's catalyst (**182**) do contain some free TPP,[18] it was thought that the difference in quality of Wilkinson's catalyst (**182**) used at St. Andrews University and the Free State could be the cause of the observed difference in reaction rate of chalcone (**90**) hydrogenation. Since the reaction rate of the chalcone reaction executed at St. Andrews was lower than that found at the University of the Free State it was envisaged that some free TPP in the catalyst used at St. Andrews might have inhibited dissociation of the TPP from the metal complex and consequently led to a slower reaction. It was therefore decided to look into the effect of added TPP (3 mg) to the reaction rate of the 0.5 g chalcone (**90**) in 30 ml DCM reaction (Graph 4-1). Surprisingly the addition of free TPP to the catalyst solution led to an increase in reaction rate when compared to the reaction where no extra TPP was added (Graph 4-1). While this result is inexplicable in terms of the dissociation of TPP from the metal complex in order for the alkene to be able to bind, it does make sense from the point of view of stabilising Wilkinson's catalyst (**182**) in solution by preventing rhodium black formation during the reaction. Since repeatability posed a problem throughout all of the investigations, stabilising the catalyst complex towards

decomposition *vs.* inhibition of the reaction by some added TPP might hold the key towards improved reactions conditions and has to be investigated in a subsequent study.

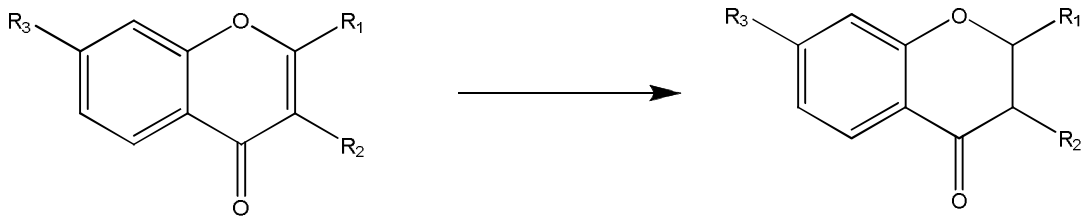


Scheme 4-3

With conditions around the hydrogenation of phenyl disubstituted α,β-unsaturated carbonyl systems sorted out, attention was shifted towards evaluating the possible effect of the unsaturated system being part of a heterocyclic ring, so chromone (**163**) was subjected to the optimised reaction conditions of 1 g of substrate in 30 ml of solvent and 80 ^{o}C and 20 bar hydrogen pressure. Although the olefinic double bond in this instance had a *cis* orientation and the substrate contained no additional substituents, chromanone (**180**) [characterised by a triplet at δ 4.52 ($J_{H\text{-}2,H\text{-}3}$ = 6.46 Hz) ppm in the ^{1}H NMR (plate 4)] formation proved to be

more than an order of magnitude slower than the corresponding dihydrochalcone production (*ca*. 66 % conversion after 72 h *vs*. *ca*. 50 % after 30 min.). Since the reaction rate difference between 3-penten-2-one (**158**) and cyclohex-2-enone (**161**) proved to be negligible (Table 4-2, entry 5 and Table 4-1 entry 1), the tremendous drop in reaction rate of the chromone (**163**) reaction when compared to chalcone (**90**) can probably be ascribed to the influence of the heteroatom present in the C-ring. Although this result was not too promising towards extending the investigation to the envisaged real flavonoid substrates, this was never the less embarked upon and flavone (**164**) and isoflavone (**165**) subjected to the optimised reaction conditions (1 g in 30 ml of solvent, 80 ^{o}C, and 20 bar) from the chalcone (**90**) hydrogenation

Exposure of 4',7-dimethoxyisoflavone (**56**) as well as flavone (**164**) to the hydrogenation conditions, however, led to no reduction products being found (Scheme 4-4), so it was concluded that the electronic effect of the heterocyclic oxygen together with the sterically very demanding trisubstituted double bond rendered these substrates unsuitable for hydrogenation over Wilkinson's catalyst (**182**). Since the tetra-substituted flavonol (**166**) would be sterically even more demanding, this substrate was not even subjected to this hydrogenation reaction.



(**163**) $R^1 = R^2 = R^3 = H$
(**164**) $R^1 = Ph$; $R^2 = R^3 = H$ (no reaction)
(**56**) $R^1 = H$; $R^2 =$ p-methoxyphenyl; $R^3 = OMe$ (no reaction)

Scheme 4-4

4.4 Conclusions

Although the envisaged conjugate hydrogenation of flavonoid substrates like flavones and isoflavones could not be accomplished during the current study, it was shown that Wilkinson's catalyst (**182**) is indeed capable of selectively reducing α,β-unsaturated ketones to the corresponding saturated ketones and no 1,2-reduction or over-reduction to the

secondary alcohols could be detected. Furthermore it was established that increased substitution around the double bond of the α,β-unsaturated system has a profound negative effect on the reaction rate. In contrast to cyclic substrates where some hydrogenation still occurred, trisubstitution around the double bond of acyclic compounds rendered them completely inaccessible to the organometallic catalyst and thus hydrogenation over Wilkinson's catalyst (**182**). Interestingly indications were also found that Wilkinson's catalyst (**182**) shows some effect towards electronic influences exerted by heteroatoms as well as conjugated systems like aromatic rings. This preliminary conclusion from the current study stands to be confirmed by a more complete and systematic investigation that will form part of the candidate's Ph.D. studies.

4.5 References

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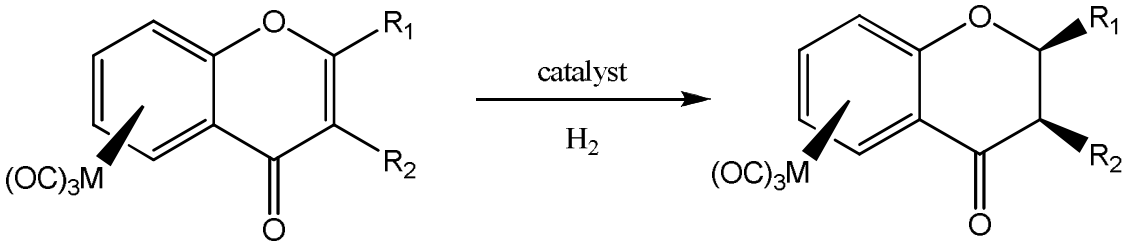
CHAPTER 5

CHROMIUM COMPLEXES

5.1 Introduction

Although stereoselective hydrogenation was by no means exhaustively investigated, it was, at this stage, not looking too promising so it was decided to look at the introduction of chirality into a planar flavonoid molecule by means of an arene metal complex. If a bulky metal tricarbonyl centre could be directed to one face of the A-ring of a flavonoid unit, that face of the heterocyclic C-ring would be inaccessible to a hydrogenating reagent.[1] This would result in hydrogenation only occurring from the other face of the molecule, which will lead to stereoselective product formation (Scheme 5-1).



(163) $R_1 = R_2 = H$
(164) $R_1 = Ph$; $R_2 = H$
(165) $R_1 = H$; $R_2 = Ph$
(166) $R_1 = Ph$; $R_2 = OH$
M = Fe/Cr/Mn

(180) $R_1 = R_2 = H$
(195) $R_1 = Ph$; $R_2 = H$
(201) $R_1 = H$; $R_2 = Ph$
(202) $R_1 = Ph$; $R_2 = OH$

Scheme 5-1

If an arene-metal complex is to be synthesised from a flavonoid molecule, complexation may occur onto either the A- or the B-ring, so selectivity becomes an issue. Since the chromium and manganese, or other metal in the $M(CO)_3$ moiety, would be electrophilic in nature,[2,3,4] it is sensible to think that if two reaction sites are present in a substrate, complex formation preferentially occur at the ring with higher nucleophilicity. Due to the B-ring being able to rotate freely in the flavonoid molecule, chiral induction would, furthermore, be impossible if the metal should show preference for this aromatic ring. It is therefore clear that for this approach to be successful the critical issue to be solved would be A-ring specific complexation of the flavonoids to the metal tricarbonyl reagent. The aim of this part of the dissertation, therefore, was to investigate the orientation of the metal tricarbonyl complex formation onto flavonoid substrates.

5.2 Selection of complexing reagent

While tricarbonyl complexes of mangenese, chromium and iron are all well documented only arene tricarbonyliron complexes have been reported for flavonoid substrates and these compounds were prepared by coupling the preformed arene tricarbonyliron to the flavonoid unit.[5,6] In contrast to the other two metal carbonyls, tricarbonyliron(0) exhibit some electron donating properties, thus enhancing the nucleophilicity of the aromatic ring attached to it.[7] Tricarbonylmanganese(0) and –chromium(0) arene complexes, on the other hand, display increased acidity (~7 pK_a values for chromium)[4] of the aromatic protons, which indicate an increase in the electrophilicity of the aromatic ring attached to the metal complex in this instance.[8] The total effect of tricarbonylchromium(0) and –manganese(0) complexes on the properties of aromatic systems is summarised in Figure 5-1.[9]

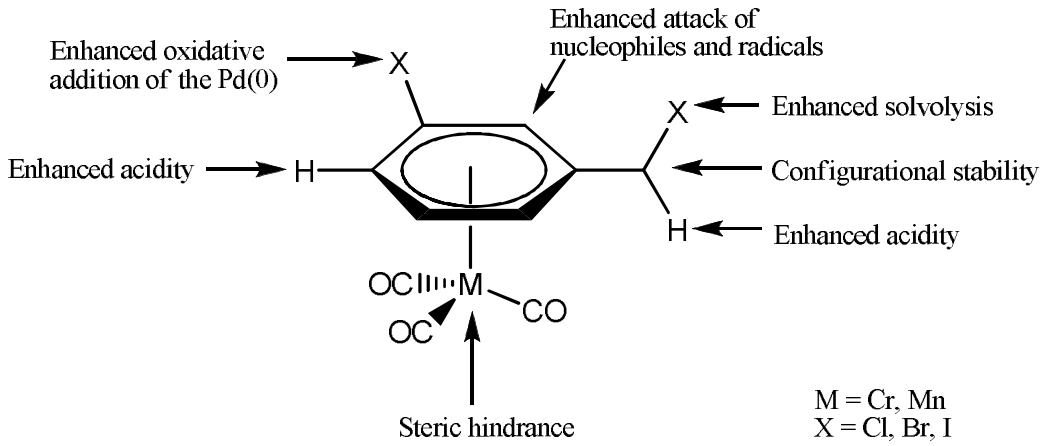


Figure 5-1

Since it was also envisaged that alterations to the flavonoid substitution- or oxygenation pattern, after attachment of the tricarbonyl complex, could be of value during subsequent studies,[10,11,12,13] it was decided to utilize a metal tricarbonyl that would display stability towards a wide variety of reagents and reactions especially hydrogenation/reduction conditions. The known stability of the tricarbonylchromium(0) arene complexes at low and high pH levels[1,14] as well as the fact that these complexes are virtually inert toward strong bases (e.g. organo lithium salts[4] and NaH[14]), hydride reducing reagents (e.g. $LiAlH_4$,[15] $LiBH_4$,[16] etc.), radicals,[17,18] a variety of Pd catalyzed reactions,[19,20,21,22] Grignard-[23] and Wittig[24] reagents, hydroformylation reactions[25] and, more importantly, hydrogenation conditions[26] made these compounds the ideal candidates for application during the current investigation. The synthesis of tricarbonylchromium(0) complexes of flavonoid substrates was therefore to be investigated during the study.

5.3 Synthesis and properties of η^6-arene chromium complexes

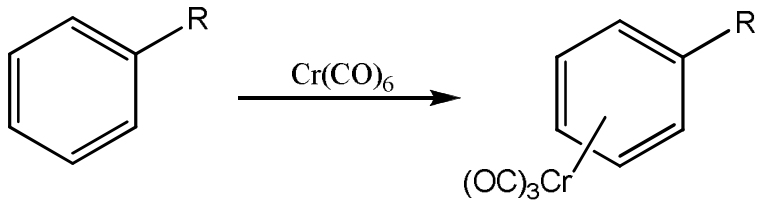
Since the properties of arene tricarbonylchromium(0) complexes have been studied extensively, several procedures for the preparation of these compounds were described. Although arene exchange between the desired substrate and another arene tricarbonylchromium(0) compound, like $Cr(CO)_3(\eta^6$-naphthalene)[27] or $Cr(CO)_3(\eta^5$-1-methylpyrrole),[28] have been reported, the preferred method for the synthesis of arene

tricarbonylchromiums still remains thermolysis of hexacarbonylchromium(0) ($Cr(CO)_6$) and the target arene under an inert atmosphere. This procedure is, however, hampered by sublimation of the $Cr(CO)_6$ which leads to all of the hexacarbonylchromium(0) reagent being collected against the walls of the reflux condenser. In order to prevent complete removal of the reagent from the refluxing solution containing the substrate, and still have a high enough boiling point to facilitate reaction with the arene compound, several solvent systems have been reported for this reaction. The solvent system most frequently used comprises a 9:1 mixture of dibutyl ether (Bu_2O) and tetrahydrofuran (THF).[29] In order to lower the energy required for complex formation and thus making it possible to utilise low boiling solvents for the reaction, several carbonyl complexes containing three 'dummy' ligands like pyridine or acetonitrile [$Cr(CO)_3(CH_3CN)_3$ or $Cr(CO)_3Py_3$] have been reported. Utilisation of a combination of such a system, $Cr(CO)_3(NH_3)_3$, and a Lewis acid (BF_3-etherate) led to complex formation being possible even at room temperature.[30] It has also been found that increased chemo- and diastereoselectivity could be achieved through the application of these, much milder, reaction conditions.

Once formed, the generally crystalline tricarbonylchromium(0) complexes can be stored in the solid state for prolonged periods of time provided they are kept in the dark. Due to the ease of oxidation of Cr(0) to Cr(III) (or higher oxidation state), the stability of these chromium compounds are compromised by exposing them to light, or high temperature and oxygen.[31] One of the challenges when working with these compounds, therefore, is removal of the high boiling solvent without the chromium being oxidised during the work-up process.

5.4 Model substrates

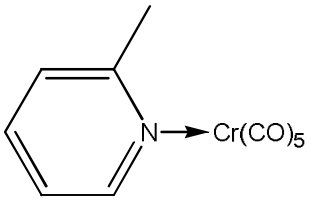
While the main aim of the current study was set as the investigation of the regioselectivity of complexation of chromium carbonyls to flavonoids, being able to form these complexes would be a prerequisite to this objective, so an investigation into the best method for attaching the tricarbonylchromium(0) species to an aromatic ring and testing the methodology on simple aromatic systems like benzene (**189**), chlorobenzene (**190**), toluene (**191**), anisole (**192**) and acetophenone (**193**) was first attempted (Scheme 5-2).



(**189**) R = H
(**190**) R = Cl
(**191**) R = CH_3
(**192**) R = OMe
(**193**) R = $COCH_3$

(**189a**) R = H
(**190a**) R = Cl
(**191a**) R = CH_3
(**192a**) R = OMe
(**193a**) R = $COCH_3$

Scheme 5-2



194

In order to find the best method for attaching a tricarbonylchromium(0) unit to an aromatic system and optimize reaction conditions, benzene (**189**) was subjected to complexation onto the chromium species. Since it was believed that the known sublimation of the $Cr(CO)_6$ in the condenser would be circumvented with this system and the 2-picoline would activated the chromium towards complexation at lower temperatures, the first reaction explored was based on 2-picoline as a stoichiometric catalyst/activator.[32] It is presumed that a (2-picoline)pentacarbonylchromium (**194**) or a related species is generated *in situ*[32] which then reacts with the arene compound producing the tricarbonyl(η^6-arene)chromium(0) complex at reflux temperatures. Although Schlenk conditions were employed, exclusion of oxygen proved to be a major challenge during the first number of reactions with the reaction mixtures turning green over the course of a 7 hour reaction period thus indicating oxidation of the tricarbonylchromium(0) moiety to have occurred. Despite rigorous exclusion of oxygen, this result implied that oxygen was somehow entering the reaction setup. Since all solvents were thoroughly degassed and positive argon pressure was sustained throughout the reaction process, the only plausible explanation for this observation was oxygen impurity in the argon used during the reactions.

Through personal communication with Dr. A.E. McConnell of Sasol Technology, a catalyst for removing trace amounts of oxygen and water from inert gasses was identified, prepared and used to scrub all oxygen from the argon used during the entire process.[33,34] This chromium based catalyst is readily oxidized causing a colour change from blue to black, while any moisture present in the gas is also removed leading to the catalyst turning orange.

With the problems around trace quantities of oxygen in the argon, used for creating a completely inert atmosphere, solved, formation of the tricarbonyl(η^6-benzene)chromium(0) (**189a**) complex was repeated with the 2-picoline system and the product obtained as yellow needles (upon cooling) in 87.0 % yield. The ^{1}H NMR spectrum (plate 8a) of the product revealed an up-field shift of the benzene singulet from δ 7.38 (plate 7a) to 5.32 ppm (plate 8a), while a significant shift in the ^{13}C NMR signal from δ 128.48 (plate 7b) to 92.89 ppm (plate 8b) was also noticed. The structure was further corroborated by an additional peak at δ 232.95 ppm in the ^{13}C NMR spectrum, which, in agreement with literature values,[35] was assigned to the carbonyl groups attached to the tricarbonylchromium(0) unit. Assignment of the resonance at δ 232.95 ppm in the ^{13}C NMR to the CO's of the tricarbonyl system was confirmed by an HMQC (Heteronuclear Multiple Quantum Coherence – direct C – H bond correlation) (plate 8c) experiment which indicated no correlation between this signal and any proton in the ^{1}H NMR spectrum. Final proof of structure (**189a**) for the product came from the MS spectrum (MS Scheme 1) where the molecular ion [*m/z* 214 (56.0 %)] was clearly visible. Despite the fact that this complexation could be executed successfully, removal of the 2-picoline from the crystals proved to be rather difficult so evaluation of other solvent systems were continued.

Since Woodgate *et al.*,[36] reported the utilization of 1,4-dioxane as sole solvent, this was attempted next as replacement for the high boiling Bu_2O system. Although this solvent was lower boiling than Bu_2O, the boiling point is still high enough to provide sufficient energy for thermolysis to occur. Reactions with hexacarbonylchromium(0) in dioxane, however, were hampered by low yields (< 60 %) which could be attributed to large amounts of $Cr(CO)_6$ subliming onto the condenser. Despite the drawback of the high boiling point of dibutyl ether, the traditional Bu_2O-THF solvent system was evaluated next.[27,,37] *In vacuo* evaporation of the solvent at *ca*. 40 ^oC under conditions where oxygen could not be excluded, however, led to only slight oxidation of the chromium and the tricarbonyl(η^6-benzene)chromium(0) complex (**189a**)[38] could be isolated in 97 % yield. The Bu_2O-THF combination was, therefore, identified as the solvent of choice for the reaction of aromatic compounds with hexacarbonylchromium(0) and used in all subsequent reactions.

With the best reactions conditions and work-up procedure determined, attention was shifted toward looking at the influence of substrate properties on the reaction. In order to compare

the effect of electron donating- and deactivating substituents on the reaction, toluene (**191**) and anisole (**192**) as well as chlorobenzene (**190**) and acetophenone (**193**) were to be subjected to the reaction conditions. The presence of the carbonyl on the acetophenone molecule would also present the first step towards mimicking the flavonoid skeleton.

Refluxing toluene (**191**) and anisole (**192**) (*ca.* 10 g each) with hexacarbonylchromium(0) (0.04 eq.) in Bu_2O-THF (9:1, 100 ml) for 72 hours led to the products, tricarbonyl(η^6-toluene)chromium(0) (**191a**)[39] and tricarbonyl(η^6-anisole)chromium(0) (**192a**),[40] being obtained as yellow needles and -cubes in 97.1 % and 85.0 % yield respectively. The structures of the products (**191a** and **192a**) were confirmed by the aromatic protons resonating at δ 5.41 – 5.12 and 5.55 – 4.86 ppm respectively in the ^{1}H NMR spectra (plates 10a and 12a) *vs.* δ 7.29 – 7.17 and 7.35 – 6.93 ppm (plates 9a and 11a) for the respective starting materials. Although smaller in magnitude, an up-field shift was also observed for the methyl substituent of toluene (from δ 2.36 to 2.19 ppm) and the methoxy group (from δ 3.83 to 3.71 ppm) of anisole. The same trends were observed in the ^{13}C NMR spectra (plates 10b and 12b) of the two products where the aromatic carbons shifted from *ca*. δ 137.99 – 125.45 ppm (plate 9b) to *ca.* δ 110.07 – 76.95 ppm and from *ca.* δ 159.67 – 113.99 ppm (plate 11b) to *ca*. δ 143.44 – 78.41 ppm for tricarbonyl(η^6-toluene)chromium(0) (**191a**) and tricarbonyl(η^6-anisole)chromium(0) (**192a**), respectively. The HMQC spectra (plates 10c and 12c) of both metal complexes also displayed two pairs of hydrogen uncorrelated carbon signals at δ 110.07 and 233.45 ppm and δ 143.44 and 233.34 ppm respectively. While the resonances at δ 110.07 and 143.44 ppm could be assigned to the *ipso* carbons the chemical shifts values of the metalcarbonyl signals (at δ 233.45 and 233.34 ppm respectively) were in agreement with literature values for these carbons. Final confirmation of the assigned structures (**191a**) and (**192a**) for the two products came from the MS spectra (MS Scheme 1) where M^+ ions at *m/z* 228 (39.5 %) and *m/z* 244 (35.0 %) were clearly visible.

Following the successful reaction of toluene (**191**) and anisole (**192**) with hexacarbonylchromium(0), the investigation was subsequently extended to the electron deficient substrates chlorobenzene (**190**) and acetophenone (**193**) and the expected products (**190a**)[41] and (**193a**)[42] obtained in 98 and 40 % yields respectively. Again the ^{1}H NMR spectra (plates 14a and 16a) of the products revealed a significant *ca*. 2 ppm up-field shift of the aromatic protons when compared to their respective starting materials (plates 13a and 15a

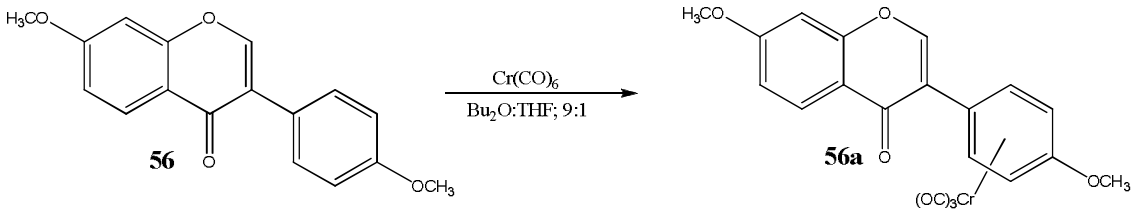
respectively), while the ^{13}C NMR spectra (plates 14b and 16b) also displayed the expected *ca*. 35 ppm shift of the aromatic carbons to higher field which was observed for the other complexes. Apart from the carbons with hydrogens attached to them, the spectra of these compounds also displayed two (for the chlorobenzene derivative) and three resonances each that could not be correlated to any hydrogens in the HMQC spectra (plates 14c and 16c). Since one of these resonances in each spectrum appeared in the δ 230 ppm region those could be allocated to the metal carbonyls, while the remaining signals at δ 113.03 and 95.81 ppm were assigned to the chlorine– and acyl bearing carbons of tricarbonyl(η^6-chlorobenzene)chromium(0) (**190a**) and tricarbonyl(η^6-acetophenone)chromium(0) (**193a**) respectively. The acyl carbonyl group in the spectrum of the acetophenone derivative also displayed a slight up-field shift in the chromium complex from δ 198.09 to 195.02 ppm. Molecular ions at *m/z* 248 (49.8 %) and *m/z* 258 (27.6 %) in the MS spectra (MS Scheme 1) of the products supplied further credence to the proposed structures.

After successful complexation of the benzene type substrates, the effect of having a heterocycle attached to the basic aromatic skeleton was investigated and chroman-4-one (**180**) subjected to the standard reaction conditions. In this instance the tricarbonylchromium(0) derivative (**180a**)[42] could, however, not be isolated from the reaction mixture by mere crystallization but was obtained as a deep orange coloured solid (28.1 % yield) after flash column chromatography (FCC) (R_f 0.25; H:A; 8:2). The ^1H NMR, ^{13}C NMR, and HMQC spectra (plates 17a, 17b and 17c) of the product (**180a**) again showed the characteristic up-field shift of the aromatic protons (δ 6.18 – 5.02 ppm) and carbons (δ 144.44 – 79.49 ppm), while the presence of the metal carbonyls were confirmed by a resonance at δ 230.68 ppm in the carbon spectrum. The structure of the product was further corroborated by the MS data (MS Scheme 2), which, clearly displayed the molecular ion at *m/z* 284 (97.9 %).

Since all of the above reactions were run for a fixed period of time (72 h) the low product yields (49.8 and 27.6 % respectively *vs*. 85.0 to 97.1 %), corresponding to low conversions, obtained for the carbonyl containing substrates, acetophenone (**193**) and chroman-4-one (**180**), clearly indicated that complex formation is less facile in the case of substrates containing deactivating substituents.

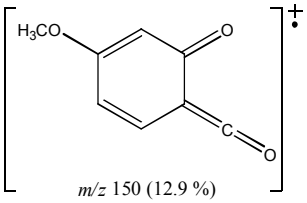
5.5 Flavonoid substrates

With the confidence of having successfully reacted substrates with a single aromatic ring, at hand, attention was subsequently turned towards the substrates of real interest, i.e. the flavonoids, where selectivity between the two aromatic rings available for reaction with the chromium complex was of paramount importance for the envisaged methodology for stereoselective synthesis of flavonoids. Due to it having very distinct substitution patterns associated with the A- and B-rings respectively (an ABX spin system for the A-ring and an AA'BB' system associated with the B-ring) and it being available from the previous hydrogenation study (*cf.* Chapter 4), this part of the investigation was started with 4',7-dimethoxyisoflavone (**56**) as substrate. Thus the isoflavone (**56**) (1.28 g) was reacted with hexacarbonylchromium(0) (1.0 eq) in Bu_2O-THF (9:1, 100 ml) under argon atmosphere for 72 hours and the product (R_f 0.18) obtained as a yellow solid (0.48 g, 25.0 %) after FCC (H:A; 8:2) (Scheme 5-3). Since the ^1H NMR spectrum (plate 18a) of the product indicated an up-field shift for the B-ring protons [from δ 7.49 and 6.87 ppm (plate 2a) to δ 5.85 and 5.21 ppm (each d, each 2H, J = 6.78 Hz)], it was clear that reaction between the isoflavone and the chromium complex occurred at the B-ring of the isoflavone. The presence of the metal carbonyl moiety in the molecule was further confirmed by the typical CO resonance at δ 232.89 ppm in the ^{13}C NMR spectrum (plate 18b) of the tricarbonyl(B-η^6-4',7-dimethoxyisoflavone)chromium(0) product (**56a**).

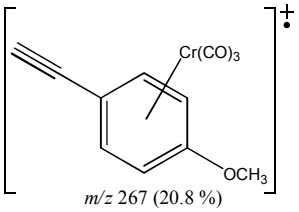


Scheme 5-3

The presence and position of the chromium complex attached to the flavonoid moiety was further corroborated by MS data (MS Scheme 3) where, apart from the M^+-2CO fragment at *m/z* 362 (0.5 %), A- and B-ring fragments from RDA (*retro*-Diels-Alder) fragmentation of the chromium containing isoflavone unit [*m/z* 150 (12.9 %) and *m/z* 267 (20.8 %)] could be identified. The fact that no product with the chromium attached to the A-ring could be isolated, together with the previous observation that hexacarbonylchromium(0) shows preference for reaction with electron rich rings, led to the conclusion that A-ring complexation was inhibited by the deactivating carbonyl group. It was therefore decided to subsequently investigate a substrate where the deactivating properties of the carbonyl group would be carried through by conjugation to the B-ring and see if the preference for B-ring reaction would still prevail.

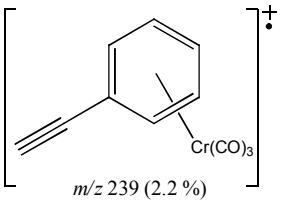


m/z 150 (12.9 %)

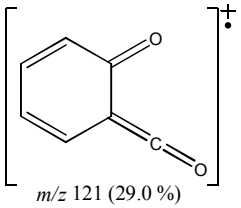


m/z 267 (20.8 %)

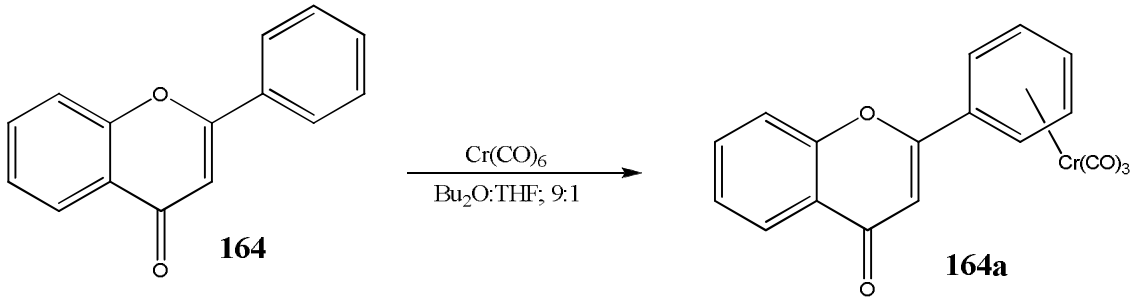
Flavone (**164**, 1.01 g) was therefore treated with hexacarbonylchromium(0) (1.0 eq.) in refluxing dibutyl ether-THF (9:1; 100 ml) under argon and the product (**164a**, R_f 0.11) isolated as orange crystals from DCM (0.70 g, 42.9 %) after FCC (H:A:DCM; 7:1:2) (Scheme 5-4). The shift of five aromatic protons to δ 6.01 – 5.40 ppm in the ^{1}H NMR (plate 20a), compared to the four protons still resonating in the aromatic region (δ 8.24 - 7.42 ppm), indicated that complexation occurred at the B-ring. The low-field doublet observed at δ 8.22 ppm, which is diagnostic to H-5 of a flavone/isoflavone/flavanone/isoflavanone moiety, further confirmed that the A-ring did not react. From the ^{13}C NMR- and HMQC spectra (plates 20b and 20c respectively) where an uncorrelated carbon peak (δ 231.08 ppm) could clearly be identified it was confirmed that the molecule indeed contained a tricarbonyl metal moiety. The structure of the product was further corroborated by the mass spectrum (MS Scheme 4) where, apart from the M^+ ion at *m/z* 358 (4.4 %), RDA fragments at *m/z* 239 (2.2 %) and 121 (29.0 %) could clearly be identified.



m/z 239 (2.2 %)



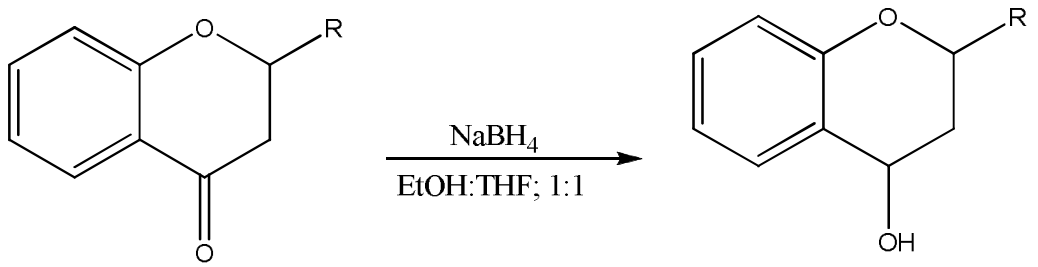
m/z 121 (29.0 %)



164 **164a**

Scheme 5-4

From the results obtained it is clear that despite conjugation with the B-ring, the deactivating effect of the 4-carbonyl functionality renders the A-ring less nucleophilic than the B-ring and therefore results in the B-ring being the preferred reaction site during complexation with the chromium reagent. In order to remove the influence of the carbonyl group and since it is known that benzylic alcohols are capable of directing chromium complexes to the adjacent aromatic ring,[43,44] it was decided to subject the 4-hydroxylated version of the flavone, flavan-4-ol (**197**), to the complexation reaction. Since the flavan-4-ol (**197**) was not readily available and had to be prepared, it was decided to test this reaction on a model substrate first before proceeding to the flavan-4-ol derivative.



(180) R = H
(195) R = Ph

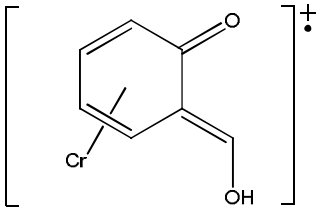
(196) R = H
(197) R = Ph

Scheme 5-5

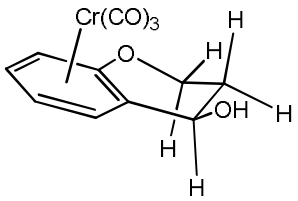
$NaBH_4$ reduction of chroman-4-one (**180**) and flavan-4-one (**195**) yielded the chroman-4-ol (**196**) and flavan-4-ol (**197**) as a colourless oil and white powder in 97.2 and 99.7 % yield, respectively (Scheme 5-5). The ^{1}H NMR spectrum (plate 21a) of the chroman-4-ol (**196**) showed the presence of an extra proton at δ 4.72 ppm (t, J = 4.04 Hz, H-4) when compared to that of the chroman-4-one (**180**; plate 4a), thus confirming that reduction in fact occurred, while the spectrum of the flavan-4-ol (**197**; plate 23a) displayed two resonances [δ 5.20 ppm

(dd, J = 1.92 and 11.55 Hz) and δ 5.12 ppm (ddd, J = 6.22, 8.67 and 10.68 Hz)] in the heterocyclic region of the spectrum. Since addition of D_2O to the NMR solution led to disappearance of the signal at δ 1.73 ppm (J = 8.67 Hz) and collapse of the ddd resonance at δ 5.12 ppm to a doublet-of-doublets, the resonances at δ 1.73, 5.12 and 5.20 could be allocated to the 4-OH, H-4, and H-2 respectively.

Following the successful reduction of chroman-4-one (**180**), the model substrate, chroman-4-ol (**196**), was subsequently subjected to complexation with $Cr(CO)_6$ and an inseparable mixture of two isomeric products (**196a**) and (**196b**) (R_f 0.14) in a ratio of *ca*. 0.28:1.00 obtained as a yellow solid (13.8 %) after FCC (H:A; 8:2). While clearly showing the presence of more than one compound, the ^{13}C NMR spectrum (plate 22b) of the product mixture also displayed the resonance typical of metal carbonyl groups at δ 233.15 ppm, while the presence of the chromium moiety in the molecule was further confirmed by the MS spectrum (MS scheme 5) where peaks for the M^+ ion [*m/z* 286 (75.2 %)] as well as fragments M^+-OH [*m/z* 269 (6.8 %)], M^+-3CO [*m/z* 202 (90.0 %)] and RDA splitting of the heterocyclic ring [*m/z* 174 (92.3 %)] were visible. The ^1H NMR spectrum (plate 22a) of the product mixture also clearly displayed duplication of all resonances in the aromatic region, while several 'extra' signals were visible in the heterocyclic and aliphatic regions of the spectrum. Since all the aromatic signals were shifted up-field from δ 7.28 – 6.83 ppm in the spectrum of the starting material (plate 21a) to δ 5.82 – 4.81 ppm in the spectrum of the product mixture, it could be concluded that both products contained a chromium moiety. Since the starting material contained only one aromatic ring and both products had chromium attached to it, the only possibility for the existence of two isomers would be the diastereomers (**196a**) and (**196b**) where the relative orientation of the OH-group and the chromium moiety could be either *cis* or *trans*.

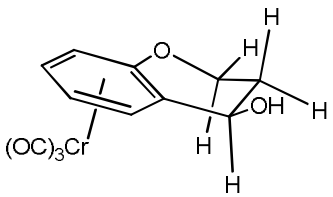


m/z 174 (92.3 %)



cis-tricarbonyl(η^6-chroman-4-ol)chromium(0)

196a



trans-tricarbonyl(η^6-chroman-4-ol)chromium(0)

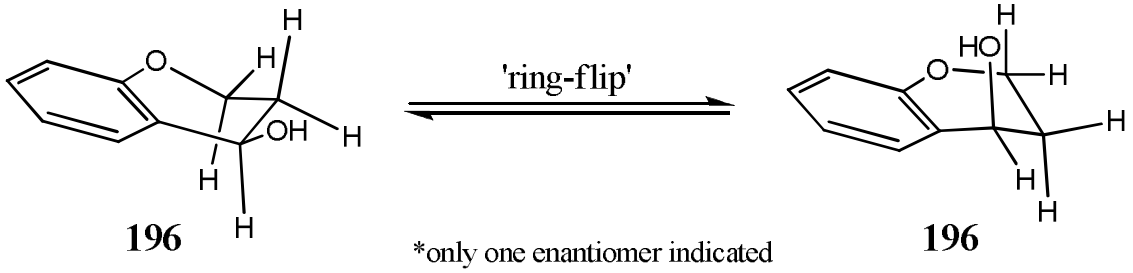
196b

*only one enantiomer indicated

In order to be able to assign structures to the different diastereomers, a closer look at the ^{1}H NMR (plate 22a) spectrum revealed that for one isomer H-2(axial) and H-2(equatorial) (δ 4.32 – 4.28 and 4.17 – 4.13 ppm respectively) are non-equivalent, while the protons of the 3-CH_2-group appears as a single multiplet (δ 2.20 – 2.14 ppm). For the other isomer, on the other hand, the inverse, *i.e.* the 2-CH_2 appearing as a one multiplet (δ 4.26 – 4.24 ppm) and H-3(a) and H-3(e) as two separate multiplets (δ 2.37 – 2.32 and 1.98 – 1.94 ppm respectively), is observed. When the geometry of *trans*-tricarbonyl(η^6-chroman-4-ol)chromium (**196b**) is examined, it is clear that H-2(a) and H-4 should experience the same effect from the tricarbonylchromium(0) as these protons are attached to the same face of the molecule, while H-2(e), being equatorial, should be influenced differently, thus leading to different chemical shift values for the two C-2 protons. For the 3-CH_2 group the axial proton is pointing away from the chromium moiety, thus leading to diminished influence from the metal on the chemical shift of this proton, therefore, leading to the chemical shifts of the 3-axial and equatorial protons being almost the same. In the case of the *cis*-isomer (**196a**), however, H-3(a) is pointing in the direction of the nearby chromium moiety thus leading to different chemical shift values for the axial and equatorial protons at C-3, while the protons at C-2 being equatorial and α-axial should not be influenced differently thus appearing as a single multiplet. Since the first argument fits the spectrum of the minor isomer and the second is observed in the spectrum as the major isomer, the main product from the reaction was determined as the *cis* diastereomeric isomer (**196a**).

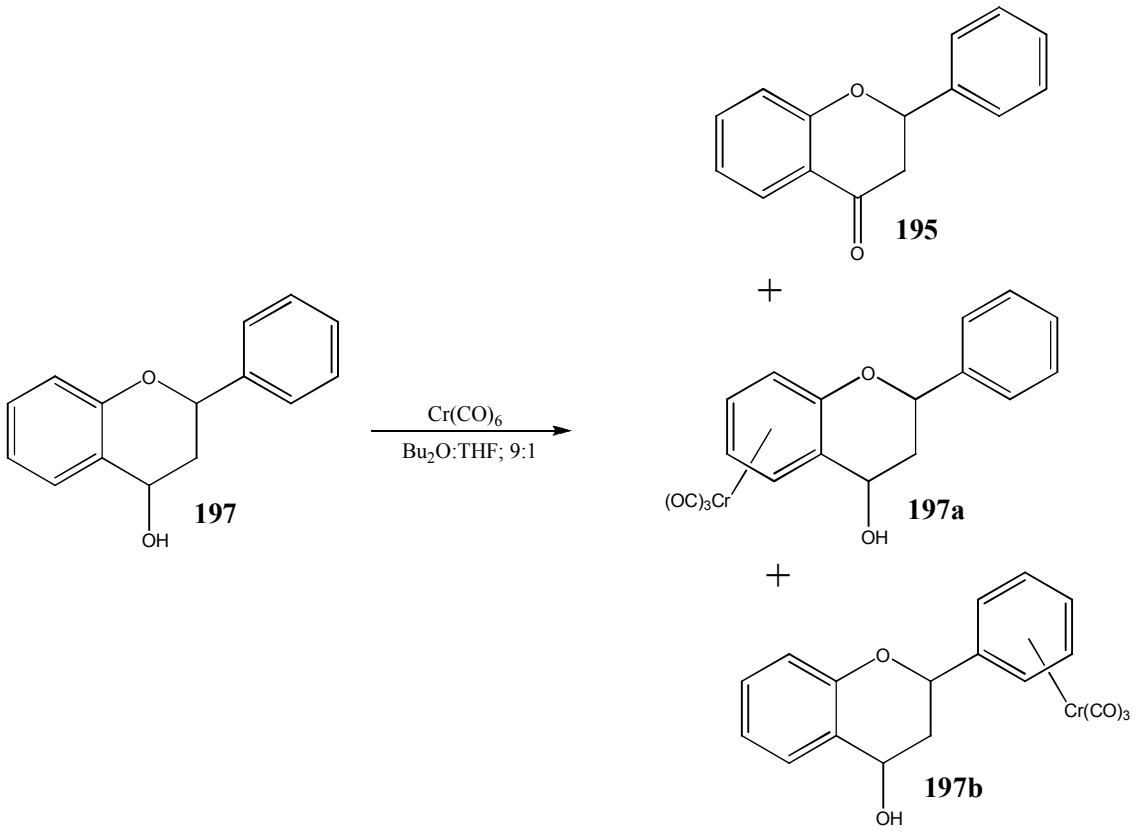
Since it is known from literature that a benzylic hydroxyl group is capable of directing complexation of chromium onto the face of an adjacent aromatic ring in a *cis* fashion,[43,44] formation of the *trans*-tricarbonyl(η^6-chroman-4-ol)chromium(0) (**196b**) product during the current study, needs some comment and is probably explicable in terms of the conformation of the heterocyclic ring. The preferred half-chair conformation of this ring would probably be the one with the 4-OH group in a quasi-equatorial orientation, while the other half-chair conformer will have the hydroxyl group in the quasi-axial position (Scheme 5-6). While it is clear that the directing influence of the axial OH, if present, would lead to the *cis*–product being formed, the preferred conformation with a quasi-equatorial hydroxy-group would have very limited directing influence as the hydroxyl function is almost co-planar with regard to the aromatic ring. In this instance it can be expected that some of the *trans*-product might

also be formed. It is, however, also possible that the OH group is only facilitating binding of the chromium to the aromatic ring and that complex formation may occur from the α-face without any assistance of the OH as directing group. The observed lack of selectivity towards a particular ring for the flavonoid substrates might also be the result of thermodynamic- rather than kinetic control, since the reactions were performed at relative high temperatures (refluxing dibutyl ether). The directing abilities of the OH-group may also be influenced/eliminated by the nature of the solvent.



Scheme 5-6

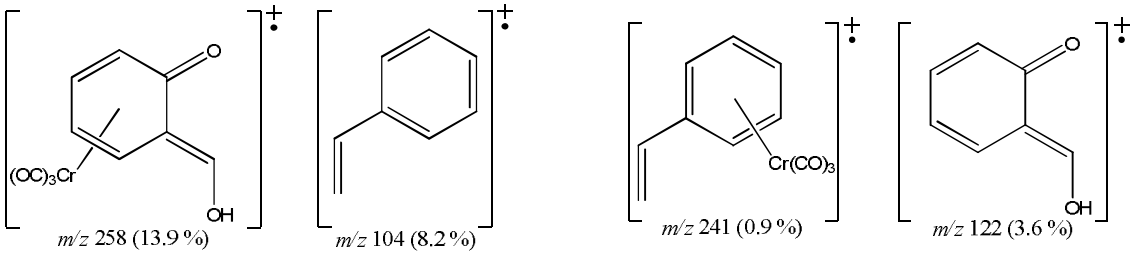
With the experience of the model reaction at hand, attention was subsequently shifted back to the real flavonoid substrates. Flavan-4-ol (**197**) (0.94 g) was therefore subjected to the reaction with hexacarbonylchromium(0) (Scheme 5-7) and three main products (R_f 0.64, 0.14 and 0.10) isolated after FCC (H:A; 8:2). The first product (R_f 0.64) obtained as a white solid (0.05 g, 5.6 %) was identified as the flavan-4-one (**195**) with ^{1}H NMR– and ^{13}C NMR spectra (plates 24a and 24b respectively) being identical to that of the commercial flavan-4-one. While formation of the oxidation product was rather surprising and difficult to explain, its formation can only be attributed to formation of some chromium(II) or chromium(III) species which could then be responsible for oxidation of the 4-hydroxy group and regeneration of chromium(0).



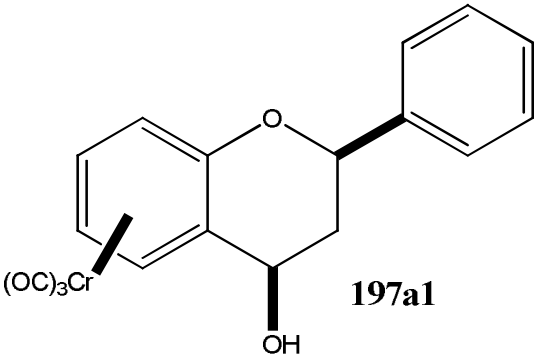
Scheme 5-7

The ^{13}C NMR spectra (plates 25b and 26b) of the second and third products (R_f 0.14 and 0.10 respectively), obtained as orange and yellow solids respectively (0.03 g, 1.7 % and 0.04 g, 2.8 %), both displayed the presence of a metal carbonyl moiety (δ 233.60 and 232.53 ppm respectively), whereas the ^{1}H NMR spectra (plates 25a and 26a) each indicated one set of aromatic protons being shifted up-field to *ca*. δ 5.50 ppm, while the other set remained at *ca*. δ 7.30 ppm. It was therefore clear that the products were either *cis*- and *trans*-isomers of an A-ring tricarbonylchromium complex or isomers with the chromium moiety attached to the A- and B-rings respectively. Since both the A- and B-rings of the flavonoid unit contained no additional substitution, identifying the protons that were shifted up-field by coupling pattern proved to be rather difficult, so the integral values were used as probe for deciding what happened during the reaction. In this way it was determined that in the case of the third product (R_f 0.10; plate 26a) five aromatic protons experienced dearomatization, thus indicating this product to have a B-ring chromium complex, so structure (**197b**) could be assigned to it. The ^{1}H NMR spectrum of the other product (R_f 0.14; plate 25a) clearly showed four protons in the δ 5.96 to 5.65 ppm region with five proton resonances remaining

in the usual aromatic area, thus indicating this compound to be tricarbonyl(A-η^6-flavan-4-ol)chromium(0) (**197a**). The position of the chromium moieties on the A- and B-rings respectively of the two products were further confirmed by MS data (MS schemes 6 and 7) where the spectrum of (**197a**) displayed RDA fragments at *m/z* 258 (13.9 %) and *m/z* 104 (8.2 %), while the spectrum of the B-ring derivative (**197b**) contained RDA fragments at *m/z* 122 (3.6 %) and *m/z* 241 (0.9 %).



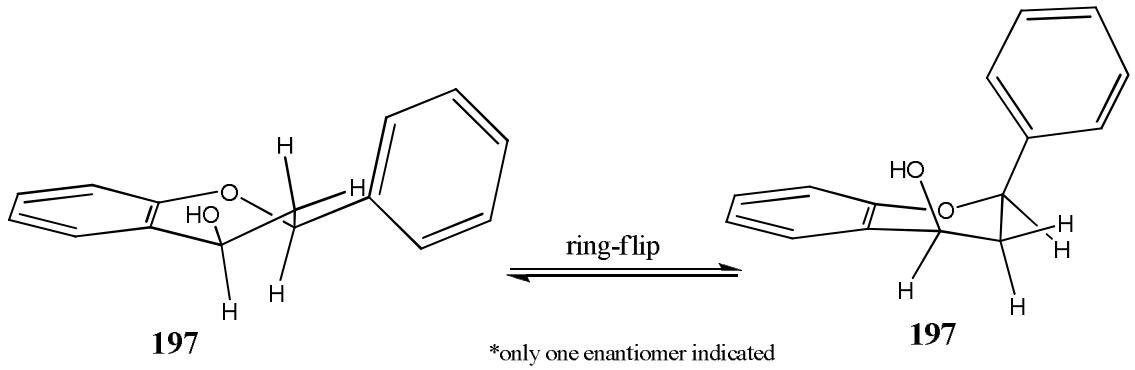
Since both the *cis* - and *trans*-isomers of the product were found during the chroman-4-ol reaction (*vide supra*), the last aspect of the structure of the second product that had to be determined was the relative orientation of the OH group and the chromium moiety. The aliphatic region of the ^{1}H NMR spectrum of this flavan-4-ol product (**197a**; plate 25a) clearly indicated the chemical shift of H-3(e) [δ 2.48 (ddd, *J* = 0.97, 5.65 and 13.55 Hz) to be different from that of H-3(a) [δ 2.28 – 2.22 (m)]. This region of the spectrum, therefore, resembles that of the *cis*-tricarbonyl(η^6-chroman-4-ol)chromium(0) derivative (**196a**), so a *cis* orientation between the 4-OH and the chromium moiety and thus structure (**197a1**), could be assigned to the second product from the reaction.



197a1

While both the *cis*- (**196a**) and *trans*-(**196b**) products were found during the chroman-4-ol reaction, the fact that only 4,A-*cis*-tricarbonyl(A-η^6-flavan-4-ol)chromium (**197a1**) was obtained during the current reaction needs some comment. Since the flavan-4-ol starting material was formed through reduction of the flavanone (**195**) it can be assumed that delivery of the hydrogen to C-4 took place from the face of the carbonyl group opposite to the B-ring, thus leading to the 2,4-*cis* product being formed. This 2,4-*cis* relative configuration is confirmed by large coupling constants between H-2 and H-3(a) (*J* = 11.55 Hz) as well as

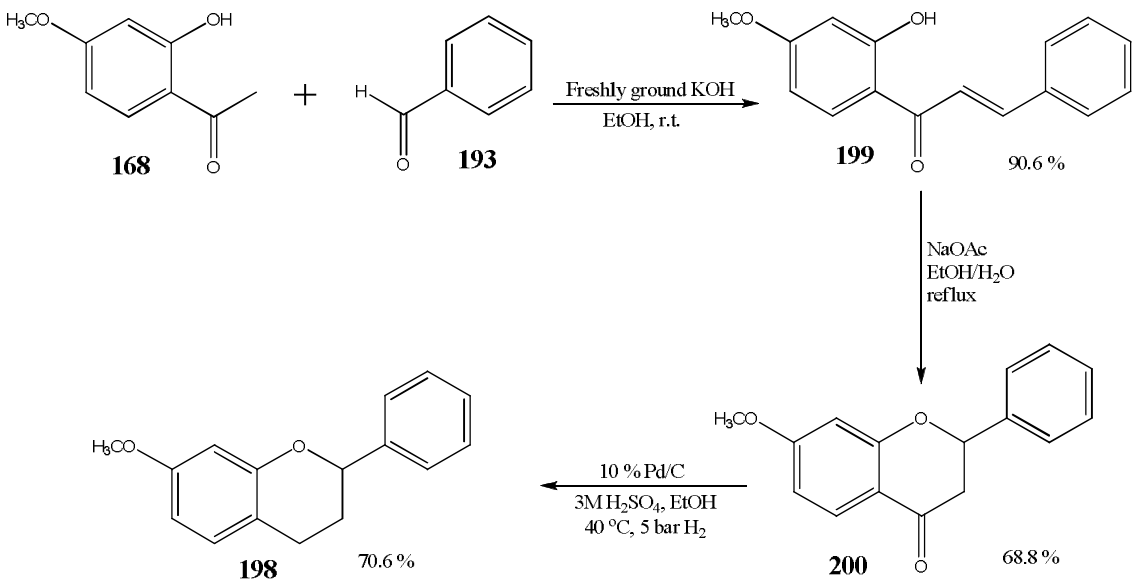
between H-3(a) and H-4 (J = 10.68 Hz) in the ^{1}H NMR spectrum of the flavan-4-ol (plate 23a), implying *ca*. 180^o dihedral angles between these protons. A 2,4-*cis* relative configuration between the B-ring and the 4-OH further means that both groups are either quasi-axial or, in the preferred conformation, in the quasi-equatorial position (Scheme 5-8). If the 4-OH occupies the quasi-equatorial position it should, like in the case of chroman-4-ol, have limited influence in directing the incoming chromium reagent towards a certain face of the aromatic A-ring as was found with the chroman-4-ol reaction. The fact that no 4,A-*trans*-tricarbonyl(A-η^6-flavan-4-ol)chromium(0) product was found can either be explained by assuming that this product was indeed formed, but was, due to the low conversion, overlooked during the isolation process, or a special mechanism that would allow additional directing effects should be prevailing. Since it is known from literature that a metal moiety may undergo ring migration,[3,45] the preferred complexation of the chromium to the B-ring (which is not present in the chroman-4-ol) might lead to some of the chromium migrating from an axial B-ring conformation to the β-face of the A-ring, thus explaining the exclusive formation of the 4,A-*cis*-tricarbonyl(A-η^6-flavan-4-ol)chromium(0) (**197a1**).



Scheme 5-8

From the results of the flavan-4-ol reaction it became evident that despite the alleged directing effect of the 4-hydroxyl group, complexation could still not be shifted to favour the A-ring exclusively. In an attempt to also remove the possible negative inductive effect of the benzylic 4-hydroxyl group, it was decided to investigate substrates that only have oxygen substitution on the aromatic rings. Flavan (**6**) and 7-methoxyflavan (**198**), with higher electron density on the A-ring and thus a bigger difference between the two aromatic ring, were therefore prepared for reaction with the chromium complex.

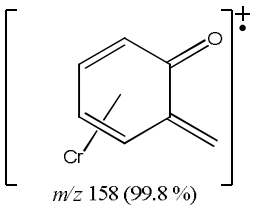
Full hydrogenation of the commercially available flavan-4-one (**195**), however, proved to be more difficult than expected and could only be achieved by utilising the relatively harsh conditions of 10 % Pd/C in EtOH containing 3M H_2SO_4 at 40 ^oC under 5 bar hydrogen pressure. After 2 days the catalyst was filtered off and the flavan (**6**) [R_f 0.77 (H:A; 8:2), ^1H NMR ($CDCl_3$, 300 MHz) (plate 27a) δ 7.38 (5H, m, Ar-H), 7.15 (2H, m, Ar-H), 6.90 (2H, m, Ar-H), 5.08 (1H, dd, J = 2.45, 9.98 Hz, H-2), 3.02 (1H, ddd, J = 6.03, 11.02, 16.46 Hz, H-4(a)), 2.81 (1H, ddd, J = 3.58, 4.71, 16.46 Hz, H-4(e)), 2.15 (2H, m, H-3)] isolated as a colourless oil (0.94 g; 49.9 %) after FCC (H:A, 8:2). The 7-methoxyflavan (**198**) [R_f 0.65 (H:DCM:EtOAc; 50:50:1), ^1H NMR ($CDCl_3$, 300 MHz) (plate 32a) δ ppm 7.44 – 7.41 (2H, m, Ar-H), 7.40 – 7.37 (2H, m, Ar-H), 7.34 – 7.31 (1H, m, Ar-H), 6.99 – 6.97 (1H, m, Ar-H), 6.50 – 6.47 (2H, m, Ar-H), 5.05 (1H, dd, *J* = 2.37, 10.19 Hz, H-2), 3.77 (3H, s, -OCH$_3$), 2.95 – 2.90 (1H, ddd, *J* = 6.02, 10.92, 16.08 Hz, H-4(a)), 2.77 – 2.72 (1H, ddd, *J* = 3.40, 5.12, 16.08 Hz, H-4(e)), 2.22 – 2.18 (1H, m, H-3), 2.11 – 2.04 (1H, m, H-3)] was prepared according to Scheme 5-9 and obtained as a colourless oil (0.67 g) in 46.3 % overall yield.



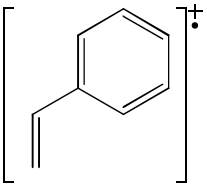
Scheme 5-9

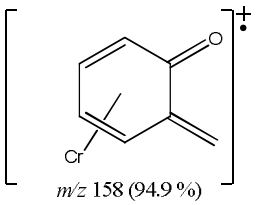
Reaction of the flavan (**6**) (0.51 g) with hexacarbonylchromium(0) (0.9 eq.) under the standard conditions for 72 hours yielded two products (R_f 0.29 and 0.23) after FCC (H:A; 8:2) (Scheme 5-10). Due to the fact that five protons in the ^1H NMR spectrum (plate 28a) of the second product (R_f 0.23) retained their aromatic properties, as was evident from the chemical shift values (*ca*. δ 7.47 – 7.35 ppm), and four protons were shifted up-field to *ca*. δ

5.56 – 4.88 ppm, this product, isolated as a yellow solid (0.08 g, 9.2 %), was identified as tricarbonyl(A-η^6-flavan)chromium(0) (**6a1** or **6a2**). The ^{13}C NMR spectrum of this compound (plate 28b) confirmed the presence of the metal carbonyls with a resonance at δ 234.06 ppm, while the full structure and thus the position of the metal moiety was confirmed by the MS data (MS Scheme 8), which yielded a molecular ion [M^+ *m/z* 346 (39.0 %)] as well as RDA fragments at *m/z* 158 (99.8 %) and *m/z* 104 (7.8%). The ^{1}H NMR spectrum (plate 29) of the R_f 0.29 fraction from the reaction indicated it to be a 0.8:1.0 mixture of two compounds. Since all efforts to separate the two compounds and get data for the pure products failed, it was attempted to identify the compounds from the spectrum of the mixture and at least get an idea of what else was formed during the reaction. A close look at the spectrum of the mixture revealed resonances from both A- and B-ring protons in the traditional aromatic region of the spectrum (δ 7.50 to 6.80 ppm), while the heterocyclic region of the spectrum, apart from H-2, also contained several resonances typical of a chromium containing ring or rings. When compared to the spectrum of tricarbonyl(A-η^6-flavan)chromium(0) (**6a1** or **6a2**) (plate 28a) where the A-ring hydrogens are moved up-field, it is evident that the A-ring protons of the flavan (without complexation) appear as two multiplets at δ 7.14 – 7.07 and 6.93 – 6.6.88, while the B-ring is reflected by resonances at δ 7.50 - 7.20 ppm. Since the aromatic region of the mixture clearly showed peaks from both A- and B-ring protons (in a 4:5 ratio) and the other product from the reaction has already been identified as tricarbonyl(A-η^6-flavan)chromium(0) (**6a1** or **6a2**) the only possible structures for the two compounds in the mixture would be the tricarbonyl(B-η^6-flavan)chromium(0) (**6b**) complex and the other stereoisomer of the tricarbonyl(A-η^6-flavan)chromium(0) (**6a1** or **6a2**) as indicated in Scheme 5-10. The idea of the R_f 0.29 product being a mixture of A- and B-ring chromium containing isomers was further enhanced by the presence of both A- and B-ring RDA (-3 x CO) fragments, [*m/z* 158 (94.9 %) and *m/z* 156 (7.0 %)] with chromium attached in the MS spectrum.

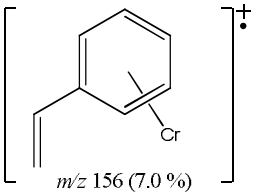


m/z 158 (99.8 %)

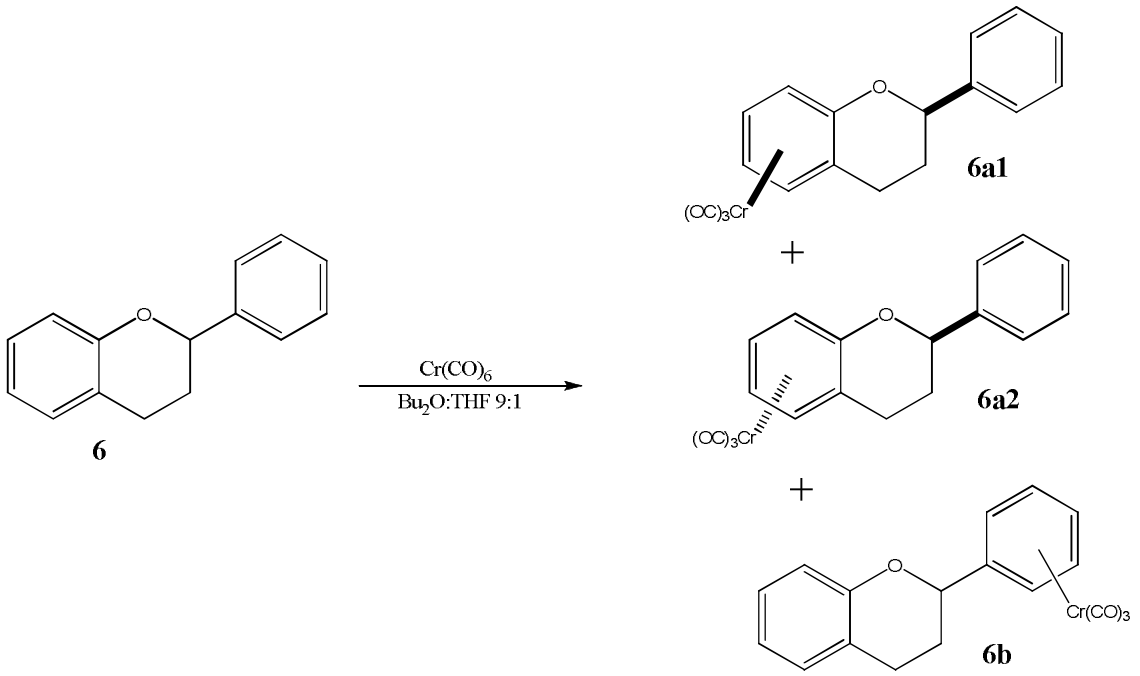

m/z 104 (7.8 %)



m/z 158 (94.9 %)



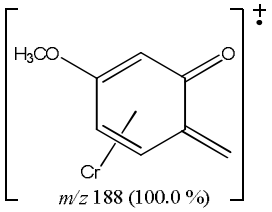
m/z 156 (7.0 %)

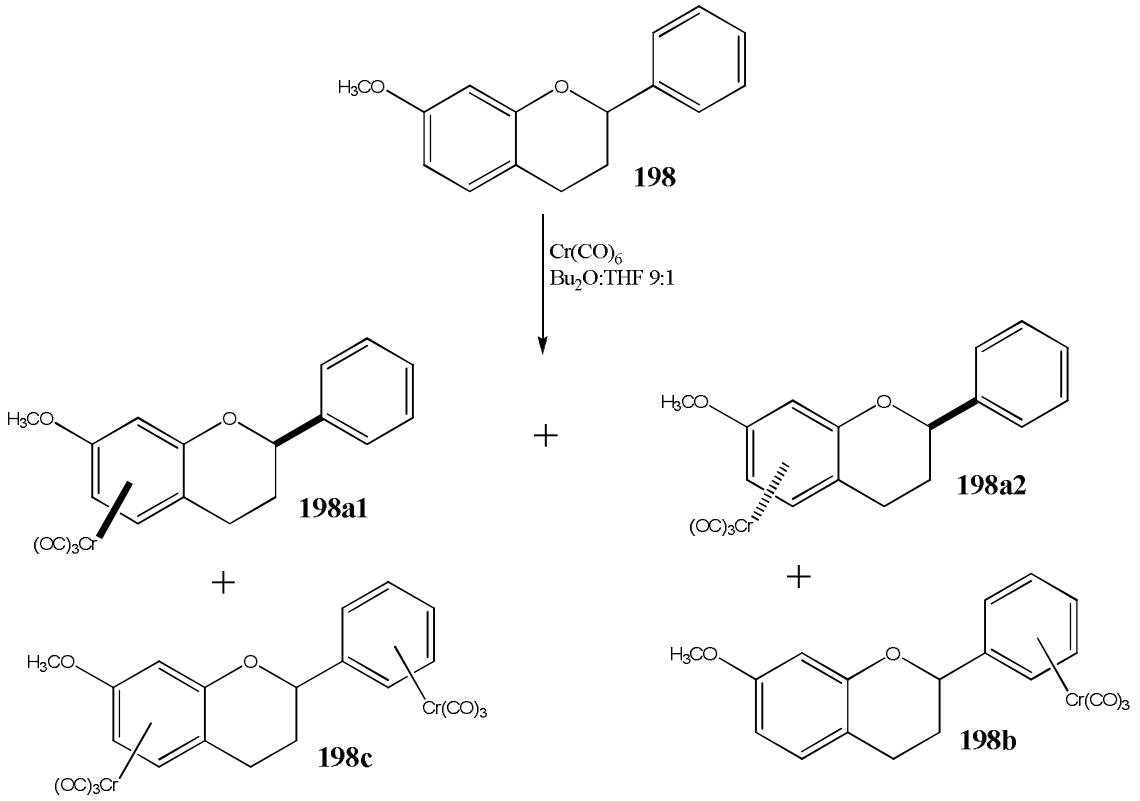


Scheme 5-10

Since exclusive A-ring complexation could still not be achieved, it was decided to subject 7-methoxyflavan (**198**) to the chromium complex forming reaction as a final attempt. Treatment of this flavan (**198**) with hexacarbonylchromium(0), as described earlier, led to the isolation of three major products (R_f 0.26, 0.23, and 0.11) after FCC (H:A; 8:2) (Scheme 5-11). The presence of five aromatic protons at δ 7.48 (2H, d, J = 7.15 Hz), δ 7.40 (2H, dd, J = 7.15, 8.66 Hz) and δ 7.37 ppm (1H, m) in the ^{1}H NMR spectrum (plate 33a) of the second product (R_f 0.23) indicated this compound (isolated as a yellow solid, 0.07 g, 16.6 %) to be tricarbonyl(A-η^6-7-methoxyflavan)chromium(0) (**198a1** or **198a2**). Strong nOe associations between the methoxy group [δ 3.72 (s)] and the two adjacent aromatic protons, H-8 and H-6, indicated these protons to be resonating at δ 5.15 (s) and δ 4.90 – 4.86 (m, 2H) ppm respectively. It should be noted that due to the aromaticity of the A-ring being diminished (removed), *m*-coupling is removed from the spectrum and H-8, therefore, appears as a singlet. Since the HMQC spectrum (plate 32c) of the 7-methoxyflavan starting material indicated C-2 to resonate at δ 77.98 ppm and the chemical shift of a carbon as distant to the chromium moiety as C-2 should not be influenced much by the presence of the metal, one of the peaks δ 74.42 ppm or δ 80.56 ppm in the ^{13}C NMR spectrum of the R_f 0.23 product (plate 33b) could be assigned to C-2 of the chromium complex. Since both these carbon peaks correlate to the resonance at δ 4.90 – 4.86 (m, 2H) in the proton spectrum and H-6 was already assigned to

this resonance, it can be concluded that H-2 is the other proton at this chemical shift. The doublet at δ 5.64 ppm in the spectrum of tricarbonyl(A-η^6-7-methoxyflavan)chromium(0) (**198a1** or **198a2**) can therefore be assigned to H-5. The ^{13}C NMR spectrum (plate 33b) of this compound displayed a metal carbonyl peak at δ 234.44 ppm confirming the presence of the chromium moiety. The proposed structure was further confirmed by MS data (MS Scheme 9) which revealed the molecular ion [M^+ *m/z* 376 (13 %)] and RDA-3CO fragment at *m/z* 188 (100.0 %).

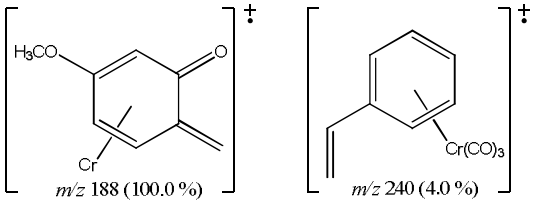




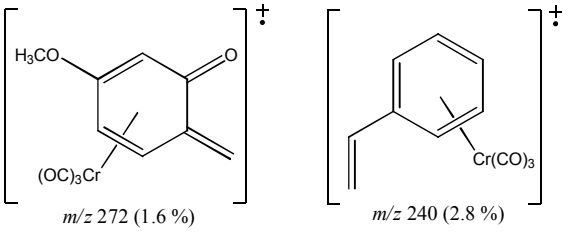
Scheme 5-11

^{1}H NMR (plate 34) investigation of the first fraction (R_f 0.26) from the reaction indicated the co-elution of two compounds that could not be separated by additional chromatographic efforts. Since the spectrum again contained resonances typical of both A- and B-ring chromium containing compounds as well as two methoxy signals and it was found in the previous case (flavan chromium derivative) that one of the A-ring stereoisomers and the B-ring complexed product are inseparable, it was concluded that this mixture probably also consists of a tricarbonyl(A-η^6-7-methoxyflavan)chromium(0) diastereoisomer (**198a1** or

198a2) and the tricarbonyl(B-η^6-7-methoxy-flavan)chromium(0) (**198b**). This conclusion was again supported by the MS data, where RDA fragments containing chromium from both rings [*m/z* 188 (100 %) and *m/z* 240 (4.0 %)] were found.



The ^{1}H NMR spectrum (plate 35) of the third product (R_f 0.11) from the reaction revealed no proton resonances in the aromatic region of the spectrum, but displayed resonances adding up to 9 protons in the heterocyclic area instead. This, taken in conjunction with the fact that complexation to the metal results in an up-field shift of the aromatic proton signals, indicated this product to be the bimetallic complex (**198c**). The fact that several peaks integrating for *ca*. half a proton as well as signals having double that value being identifiable in the heterocyclic region of the spectrum, is probably explicable in terms of this product also being a mixture of diastereoisomers. This idea is enhanced by two methoxy resonances, one of which integrates for less than three protons, being visible in the spectrum. The bimetallic nature of the R_f 0.11 product was corroborated by MS (MS Scheme 10) where a M^+-4CO [*m/z* 400 (0.2 %)] as well as RDA fragments containing a tricarbonylchromium species at *m/z* 272 (1.6 %) and *m/z* 240 (2.8 %) were observed.



5.6 Conclusions

While the chromium complexes of electron rich mononuclear aromatic compounds could be formed in high yields, the study indicated that complex formation is hampered by the presence of a deactivating substituent on the aromatic ring. Although it was shown that the chromium complexes of flavonoid substrates could indeed be formed, these reactions were rather slow and conversions low. The deactivating effect of a 4-carbonyl group in these substrates led to only the B-ring chromium derivates being formed, while even for compounds with no substituent in the 4-position and a relatively activated A-ring, preference towards the B-ring for complex formation still prevails. While the claimed directing effect of a benzylic hydroxy-group towards the aromatic ring next to it was, to some extent, observed, it was by no means exclusive and it seemed as if some complex formation without any assistance from the hydroxyl group also happened. The observed lack of selectivity towards a particular ring for the flavonoid substrates might also be the result of thermodynamic- rather than kinetic control, since all of the reactions were performed at relative high temperatures (refluxing dibutyl ether). Identification of a reagent system that would allow complex formation at lower temperatures and thus favouring kinetic control during the reaction, will be part of a subsequent Ph.D. study.

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EXPERIMENTAL

CHAPTER 6

EXPERIMENTAL

6.1 Chromatography

6.1.1 Thin layer chromatography

Qualitative thin layer chromatography (TLC) was conducted on "Merck TLC-aluminium plates: Silica Gel F_{254}" (0.2 mm layer) divided into strips of *ca.* 2.5 x 5 cm. R_f values are those observed in these qualitative TLC assessments.

6.1.2 Flash column chromatography (FCC)

A glass column was charged with 200 g of Merck Kieselgel 60 (230-400 mesh) for column chromatography for every 1 g of crude product. Air was disposed of by elution with the appropriate solvent under N_2-pressure (*ca.* 50 kPa). The crude product was adsorbed onto a minimum amount of the silica and loaded on top of the column. The purified products were recovered by elution under N_2-pressure with the appropriate solvent system and collected in fractions. Clean fractions were combined and evaporated under reduced pressure at 40 ^{o}C.

6.1.3 Development of chromatograms with ferrichloride-perchloric acid

The spraying reagent was prepared by mixing 35 % (v/v) *aq.* perchloric acid (100 ml) and 0.5 M ferrichloride (5 ml). Thin layer chromatograms were gently sprayed with the ferrichloride-perchloric acid solution and developed with heat.

A dipping reagent was prepared by diluting the ferrichloride-perchloric acid spraying solution (10 ml) with methanol (90 ml). Thin layer chromatograms were dipped in the solution and developed with heat.

6.2 Abbreviations

6.2.1 Solvent abbreviations

The following abbreviations for solvents are used throughout the experimental section:

A	=	acetone	Et_2O	=	diethyl ether
T	=	toluene	Bu_2O	=	dibutyl ether
B	=	benzene	MeOH	=	methanol
THF	=	tetrahydrofuran	EtOH	=	ethanol
H	=	hexane	EtOAc	=	ethyl acetate
DCM	=	dichloromethane			

6.2.2 Chemical abbreviations

The following abbreviations for chemicals are used throughout the experimental section:

NaOAc = sodium acetate

KOH = potassium hydroxide

Pd/C = palladium on carbon

HCl (c) = concentrated hydrochloric acid

$Rh(PPh_3)_3Cl$ = Wilkinson's catalyst

H_2SO_4 = sulphuric acid

Na_2SO_4 = anhydrous sodium sulphate

$NaHCO_3$ = sodium bicarbonate

H_2 = hydrogen gas

$NaBH_4$ = sodium borohydride

Ar = argon gas

$Cr(CO)_6$ = hexacarbonylchromium

NaH = sodium hydride*

* Prior to use, a suspension of NaH in mineral oil was washed with dry hexane or -benzene and stored overnight in a vacuum dessicator.

6.3 Spectroscopical and spectrometrical methods

6.3.1 Nuclear magnetic resonance spectroscopy (NMR)

NMR-spectroscopy was performed on a Bruker AM 300 or a Bruker AM 600 FT-spectrometer at 296 K with, unless specified to the contrary, deuterochloroform ($CDCl_3$) as solvent. Chemical shifts are reported in parts per million (ppm) with the solvent residual peak at 7.26 ppm for proton spectra and 77.16 ppm for carbon spectra on the δ-scale, whereas coupling constants are given in Hz. Chemical impurity in proton spectra resonating as a singulet at 1.56 ppm is identified as moisture in accordance to Gottlieb *et al.*[1]

6.3.2 Mass spectrometry (MS)

Mass spectrometry of the chromium complexes were performed by means of electron impact (EI) ionization through direct injection onto the mass spectrometer of a Shimadzu GC-MS QP-2010 gas chromatograph-mass spectrometer.

6.4 Melting points

Melting points were determined with a Barloworld Scientific Stuart Melting Point (SMP3) apparatus and are uncorrected.

6.5 Standard work-up procedure

Unless specified otherwise, water was added to the reaction mixture and the *aqueous* phase extracted with EtOAc or Et_2O. The organic extract was washed with water, dried over Na_2SO_4 and the solvent removed *in vacuo* at *ca*. 40 ^oC. Subsequent purification *via* FCC or crystallization afforded the product.

6.6 Hydrogenation reactions

6.6.1 2'-Hydroxy-4,4'-dimethoxychalcone (167)[2]

60 % aqueous KOH (33 ml; 357.1 mmol; 39.7 eq.) was added to a solution of 2'-hydroxy-4'-methoxyacetophenone (**168**) (1.50 g; 9.0 mmol) in EtOH (25 ml). The solution was stirred at room temperature for 30 min. before addition of 4-methoxybenzaldehyde (**169**) (1.80 g; 13.2 mmol; 1.4 eq.). Stirring was continued till the reaction was completed (TLC; H:A; 8:2). Crushed ice (200 g) was added prior to acidification with HCl (c) (litmus). The reaction mixture was then extracted into EtOAc (3 x 100 ml). The organic layers were combined, washed with water (2 x 50 ml), saturated $NaHCO_3$ solution (litmus), dried (Na_2SO_4) and evaporated under reduced pressure. Crystallization of the crude product from EtOH yielded the target compound (**167**) (1.78 g; 69.1 %) as yellow crystals. R_f 0.39 (H:A; 8:2); Mp 108.3 ^oC; ^1H NMR (300 MHz, $CDCl_3$) (plate 1) δ ppm 7.86 (1H, d, *J* = 15.39 Hz, H-β), 7.83 – 7.81 (1H, m, H-6'), 7.61 (2H, d, *J* = 8.77 Hz, H-2 and H-6), 7.45 (1H, d, *J* = 15.39 Hz, H-α), 6.94 (2H, d, *J* = 8.77 Hz, H-3 and H-5), 6.50 – 6.46 (2H, m, H-3' and H-5'), 3.86 (3H, s, -OC$\underline{H_3}$), 3.85 (3H, s, -OC$\underline{H_3}$).

6.6.2 4',7-Dimethoxyisoflavone (56)[3]

A solution of 2'-hydroxy-4,4'-dimethoxychalcone (**167**) (2.51 g; 8.8 mmol) and $Tl(NO_3)_3$ (4.02 g; 10.3 mmol; 1.2 eq) in dry MeOH:dry dioxane (1:1; 200 ml) was stirred at room temperature for 5 days. 3 M HCl (30 ml) was added and the reaction mixture refluxed for 2 h. The precipitate was filtered off and the solvent evaporated *in vacuo*. The remaining aqueous phase was extracted into EtOAc (3 x 100 ml) and neutralized with *aq*. $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent evaporated. Recrystallization from EtOH yielded isoflavone (**56**) (1.58 g; 63.8 %) as light yellow needles. R_f 0.43 (H:A, 8:2);

Mp 161.5 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) (plate 2a) δ ppm 8.20 (1H, d, *J* = 8.93 Hz, H-5), 7.90 (1H, s, H-2), 7.49 (2H, d, *J* = 8.88 Hz, H-2' and H-6'), 6.98 (1H, dd, *J* = 2.42, 8.93 Hz, H-6), 6.96 (2H, d, *J* = 8.88 Hz, H-3' and H-5'), 6.83 (1H, d, *J* = 2.42 Hz, H-8), 3.90 (3H, s, -O$\underline{CH_3}$), 3.83 (3H, s, -O$\underline{CH_3}$); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 2b) δ ppm 55.42, 55.91, 100.21, 114.06, 114.41, 114.61, 118.55, 124.37, 124.96, 127.88, 130.23, 152.16, 158.06, 159.70, 164.08, 175.93.

6.6.3 Hydrogenation procedure as executed in St. Andrews equipment

Substrate (0.5 ml; 4.4 mmol – 6.0 mmol depending on substrate) was injected, under the desired pressure, to a heated (desired temperature), stirring solution of $Rh(PPh_3)_3Cl$ (**182**) (9 mg) in DCM (9 ml). Gas consumption, electronically recorded over time, revealed completion of the reaction after which the product was identified by means of GC-MS (HP 6890 fitted with HP 5973 mass selective detector (MSD); National Institute of Standards and Technology (NIST) 98 library) without purification.

For summarized results see Paragraph 4.2.

6.6.3.1 Dihydrochalcone (91)

A solution of chalcone (**90**) (1.10 g; 5.3 mmol) in DCM (1 ml) was injected under pressure (desired pressure) into a heated (desired temperature) solution of catalyst.

6.6.4 Hydrogenation procedure as executed at University of the Free State[4]

A degassed solution of $Rh(PPh_3)_3Cl$ (**182**) (20 mg; 0.02 mmol) in dry DCM (5 ml) was injected, under 20 bar pressure, to a degassed, heated (80 ^{o}C) and stirred substrate solution in dry DCM (30 ml).[*]

For kinetic studies seven samples were taken at 20 min. intervals. ^{1}H NMR spectroscopy of these reaction mixtures was employed to calculate the yield at the respective time intervals.

[*] Degassing of solution were accomplished with Ar (x3) using standard Schlenk techniques. The catalyst solution was also degassed with H_2 (x3) prior to injection.

For summarized results see Paragraph 4.3.

6.6.4.1 Dihydrochalcone (91) in the presence of triphenylphosphine (TPP)

A solution of $Rh(PPh_3)_3Cl$ (20 mg; 0.02 mmol) and TPP (3 mg; 0.01 mmol) in DCM (5 ml) was injected to a solution of *trans*-chalcone (**90**) (0.50 g; 2.4 mmol) in DCM (30 ml). ^1H NMR (600 MHz, $CDCl_3$) (plate 6) δ ppm 7.97 – 7.96 (2H, m, H-2' and H-6'), 7.57 – 7.55 (1H, m, Ar-H), 7.47 – 7.44 (2H, m, Ar-H), 7.32 – 7.29 (2H, m, Ar-H), 7.27 – 7.26 (2H, m, Ar-H), 7.22 – 7.20 (1H, m, Ar-H), 3.31 (2H, t, *J* = 7.74 Hz, H-α), 3.08 (2H, t, *J* = 7.74 Hz, H-β).

6.6.4.2 Dihydrochalcone (91)

trans-chalcone (**90**) (0.50 g; 1.00 g; 1.50 g; 2.00 g; 3.00 g respectively). ^1H NMR (600 MHz, $CDCl_3$) (plate 6) δ ppm 7.97 – 7.96 (2H, m, H-2' and H-6'), 7.57 – 7.55 (1H, m, Ar-H), 7.47 – 7.44 (2H, m, Ar-H), 7.32 – 7.29 (2H, m, Ar-H), 7.27 – 7.26 (2H, m, Ar-H), 7.22 – 7.20 (1H, m, Ar-H), 3.31 (2H, t, *J* = 7.74 Hz, H-β), 3.08 (2H, t, *J* = 7.74 Hz, H-α).

6.6.4.3 Chroman-4-one (180)

Chromone (**163**) (1.00 g; 6.8 mmol). ^1H NMR (300 MHz, $CDCl_3$) (plate 4a) δ ppm 7.88 (1H, dd, *J* = 1.82, 7.87 Hz, H-5), 7.45 (1H, ddd, *J* = 1.82, 7.27, 8.28 Hz, H-7), 6.99 (1H, ddd, *J* = 0.81, 7.27, 7.87 Hz, H-6), 6.95 (1H, dd, *J* = 0.81, 8.28 Hz, H-8), 4.52 (2H, t, *J* = 6.46 Hz, H-2), 2.79 (2H, t, *J* = 6.46 Hz, H-3); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 4b) δ ppm 37.88, 67.10, 117.97, 121.45, 127.22, 136.04, 161.96, 191.85.

6.7 Chromium reactions

6.7.1 Chromium on silica for obtaining oxygen-free Argon:

6.7.1.1 Preparation of catalyst bed

Argon used during all chromium reactions were passed through a catalyst bed obtained from Sigma-Aldrich Chromium(VI)oxide 99.9% and Merck Silica Gel 40 (0.2 - 0.5 mm) as described below:

Aqueous CrO_3 (50 g in 1.5 L H_2O) was added to silica gel (1 kg). The contents were mixed thoroughly, before the water was decanted off and the silica dried overnight at 120 ^oC.

6.7.1.2 Activation and regeneration of catalyst bed

Activation and regeneration of the catalyst was achieved by using a "CTF 12/65/550 Wire Wound Tube Furnace" as described below:

The column was heated to 500 ^oC while vented with O_2. O_2 was replaced with Ultra High Purity (UHP) N_2 (nitrogen gas) (10 min), before switching to UHP CO (carbon monoxide gas). The column was vented with UHP CO until a colour change from orange to blue was observed. The column was then cooled to room temperature while being vented with UHP N_2.

6.7.2 Standard $NaBH_4$ reduction procedure[5,6]

Freshly ground $NaBH_4$ (1 eq) was added to a solution of substrate, in EtOH:THF (1:1; 5ml/100mg substrate). The reaction mixture was then stirred overnight at room temperature. Acetone (1 ml per 200 mg substrate) was added and the reaction mixture stirred for another 30 min. The mixture was evaporated to dryness and the crude product extracted into Et_2O (3 x 10 ml per 100 mg substrate). The extract was washed with water (2 x 50 ml per 300 ml Et_2O), dried (Na_2SO_4) and the Et_2O evaporated *in vacuo*. The crude product was purified by means of FCC.

6.7.2.1 Chroman-4-ol (196)

Chromanone (**180**) (0.51 g, 3.4 mmol), $NaBH_4$ (0.13 g, 3.4 mmol; 1 eq.), THF:EtOH (1:1; 30 ml). Purification by means of FCC yielded chroman-4-ol (**196**) (0.50 g; 97.2 %) as a colourless oil. Mass 0.50 g; 97.2 % yield; R_f 0.33 (H:B:A; 5:4:1); ^{1}H NMR (300 MHz, $CDCl_3$) (plate 21a) δ ppm 7.28 (1H, dd, *J* = 1.41, 7.27 Hz, H-5), 7.19 (1H, ddd, *J* = 1.41, 7.27, 8.07 Hz, H-7), 6.90 (1H, ddd, *J* = 0.81, 7.27, 7.27 H-6), 6.83 (1H, dd, *J* = 0.81, 8.07 Hz, H-8), 4.72 (1H, t, *J* = 4.04 Hz, H-4), 4.24 – 4.20 (2H, m, 2 x H-2), 2.13 – 1.92 (2H, m, 2 x H-3); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 21b) δ ppm 30.88, 62.00, 63.16, 117.05, 120.59. 124.38, 129.68, 129.79, 154.59.

6.7.2.2 Flavan-4-ol (197)

Flavanone (**195**) (0.50 g, 2.2 mmol), $NaBH_4$ (0.10 g, 2.6 mmol, 1.2 eq.), THF:EtOH (1:1; 30 ml). Purificatin by means of FCC yielded flavan-4-ol (**197**) (0.50 g; 99.7 %) as a white solid. Mass 0.50 g; 99.7 % yield; R_f 0.33 (H:B:A; 5:4:1); Mp 141.3 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) (plate 23a) δ ppm 7.53 (1H, d, *J* = 7.67 Hz, H5), 7.46 – 7.45 (2H, m, H-2' and H-6'), 7.42 – 7.40 (2H, m, H-3' and H-5'), 7.36 – 7.34 (1H, m, H-6), 7.22, (1H, ddd, *J* = 0.99, 7.43, 8.20 Hz, H-7), 7.00 (1H, dt, *J* = 0.78, 7.68, 7.68 Hz, H-4'), 6.91 (1H, dd, *J* = 0.55, 8.20 Hz, H-8), 5.20 (1H, dd, *J* = 1.92, 11.55 Hz, H-2), 5.12 (1H, ddd, *J* = 6.22, 8.67, 10.68 Hz, H-4), 2.54 (1H, ddd, *J* = 1.92, 6.22, 13.14 Hz, H-3(e)), 2.16 (1H, ddd, *J* = 10.68, 11.55, 13.14 Hz, H-3(a)), 1.73 (1H, d, *J* = 8.67 Hz, -O<u>H</u>); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 23b) δ ppm 40.16, 65.94, 116.88, 121.11, 125.87, 126.23, 127.11, 128.36, 128.80, 129.31, 140.64.

6.7.3 <u>2'-Hydroxy-4'-methoxychalcone (199)</u>

Freshly ground KOH (4.05 g; 4.8 eq.) was added to a cold (ice bath) stirred solution of 2'-hydroxy-4'-methoxyacetophenone (**168**) (2.53 g; 15.2 mmol) and benzaldehyde (1.80 g; 17.0 mmol; 1.1 eq.) in EtOH (100 ml). The reaction mixture was heated to room temperature and stirred for 4 days. Ice was added to the reaction mixture before acidification with conc. HCl (litmus). Extraction was done with EtOAc (3 x 200 ml). The organic phase was neutralized with a saturated solution of $NaHCO_3$ (litmus), washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Crystallization from DCM and toluene (8:2) yielded (**199**) (3.47 g; 90.6 %) as yellow needles. R_f 0.38 (H:A; 8:2); Mp 107.5 ^{o}C; ^{1}H NMR ($CDCl_3$, 600 MHz) (plate 30) δ ppm 7.89 (1H, d, *J* = 15.47 Hz, H-β), 7.84 (1H, d, *J* = 8.77 Hz, H-6'),

7.67 – 7.65 (2H, m, Ar-H), 7.59 (1H, d, *J* = 15.47 Hz, H-α), 7.45 – 7.41 (3H, m, Ar-H), 6.50 (1H, dd, *J* = 2.55 Hz and 8.77 Hz, H- 5'), 6.48 (1H, d, *J* = 2.55 Hz, H-3'), 3.87 (3H, s, -OCH$_3$).

6.7.4 7-Methoxyflavan-4-one (200)[7]

A mixture of 2'-hydroxy-4'-methoxychalcone (**199**) (1.53 g; 6.0 mmol) in EtOH (150 ml) and NaOAc (1.00 g; 12.2 mmol; 2 eq.) in H_2O (15 ml) was heated to reflux for 24 h. The reaction mixture was cooled and evaporated *in vacuo*. The remaining *aqueous* solution was extracted with Et_2O (3 x 100 ml). The organic layers were combined, washed with H_2O (2 x 50 ml), dried (Na_2SO_4) and evaporated *in vacuo* at 40 ^oC. Purification of the crude product with FCC yielded the flavan-4-one (**200**) (1.05 g; 68.8 %) as a white solid. R_f 0.18 (H:DCM:EtOAc; 50:50:1); Mp 86.3 ^oC; ^1H NMR ($CDCl_3$, 600 MHz) (plate 31) δ ppm 7.88 (1H, d, *J* = 8.80 Hz, H-5), 7.49 – 7.48 (2H, m, H-2' and H-6' or H-3' and H-5'), 7.45 – 7.43 (2H, m, H-2' and H-6' or H-3' and H-5'), 7.40 – 7.37 (1H, m, H-4'), 6.62 (1H, dd, *J* = 2.38 Hz and 8.80 Hz, H-6), 6.51 (1H, d, *J* = 2.38 Hz, H-8), 5.48 (1H, dd, *J* = 2.90 Hz and 13.30 Hz, H-2), 3.84 (3H, s, -OCH$_3$), 3.04 (1H, dd, *J* = 13.30 Hz and 16.86 Hz, H-3(a)), 2.84 (1H, dd, *J* = 2.90 Hz and 16.86 Hz, H-3(e).

6.7.5 Standard ketone hydrogenation procedure

3 M H_2SO_4 (*aq*.) was added to a solution of the substrate and 10 % Pd/C (10 mass % of substrate mass) in EtOH. The reaction mixture was heated to 40 ^oC while being stirred under H_2 pressure (5 bar) till completion. The reaction mixture was cooled, depressurized and the solvent evaporated under reduced pressure. Purification was achieved by means of FCC.

6.7.5.1 Flavan (6)

Flavan-4-one (**195**) (2.00 g; 8.9 mmol), 10 % Pd/C (0.20 g), 3 M H_2SO_4 (*aq*.) (1 ml), EtOH (50 ml). Purification by means of FCC yielded flavan (**6**) (0.94 g; 49.9 %) as a colourless oil. R_f 0.77 (H:A; 8:2); ^1H NMR ($CDCl_3$, 600 MHz) (plate 27a) δ ppm 7.46 – 7.30 (5H, m, Ar-H), 7.21 – 7.10 (2H, m, Ar-H), 6.94 – 6.86 (2H, m, Ar-H), 5.08 (1H, dd, *J* = 2.45, 9.98 Hz, H-2), 3.02 (1H, ddd, *J* = 6.03, 11.02, 16.46 Hz, H-4(a)), 2.81 (1H, ddd, *J* = 3.58, 4.71, 16.46 Hz, H-4(e)), 2.27 – 2.04 (2H, m, 2 x H-3); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 27b) δ ppm

25.18, 30.06, 77.82, 117.04, 120.43, 121.93, 126.10, 127.45, 127.91, 128.61, 129.63, 141.87, 155.25.

6.7.5.2 7-Methoxyflavan (198)

7-Methoxyflavan-4-one (**200**) (1.00 g; 3.9 mmol), 10 % Pd/C (0.10 g), 3 M H_2SO_4 (aq.) (1 ml), EtOH (30 ml). Purification by means of FCC yielded 7-methoxyflavan (**198**) (0.67 g; 70.6 %) as a colourless oil. R_f 0.65 (H:DCM:EtOAc; 50:50:1); ^{1}H NMR (600 MHz, $CDCl_3$) (plate 32a) δ ppm 7.44 – 7.41 (2H, m, H-2' and H-6'), 7.40 – 7.37 (2H, m, H-3' and H-5'), 7.34 – 7.31 (1H, m, H-4'), 6.99 – 6.97 (1H, m, H-5), 6.50 – 6.47 (2H, m, H-6 and H-8), 5.05 (1H, dd, *J* = 2.37, 10.19 Hz, H-2), 3.77 (3H, s, -OC<u>H</u>$_3$), 2.92 (1H, ddd, *J* = 6.02, 10.92, 16.08 Hz, H-4(a)), 2.74 (1H, ddd, *J* = 3.40, 5.12, 16.08 Hz, H-4(e)), 2.22 – 2.18 (1H, m, H-3), 2.11 – 2.04 (1H, m, H-3); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 32b) δ ppm 24.47 (C-4), 30.19 (C-3), 55.38 (-O<u>C</u>H$_3$), 77.98 (C-2), 101.71 (C-6/8), 107.54 (C-6/8), 114.01, 126.11, 127.93, 128.61, 130.05, 141.79, 155.91, 155.91, 159.23.

6.7.6 Standard chromium complexation procedure[8,9,10]

A solution of the substrate and $Cr(CO)_6$ in Bu_2O:THF (9:1; 10 ml per 100 mg $CrCO_6$) was degassed with Ar (x 3), using standard Schlenk techniques, and refluxed (24 h) under an oxygen free atmosphere. The reaction mixture was cooled to room temperature and the solvent evaporated *in vacuo*. The purified product was obtained through crystallization or FCC.

6.7.6.1 Tricarbonyl(η^6-benzene)chromium(0) (189a)[11]

Benzene (**189**) (10 ml, 112.8 mmol, 24.5 eq.), $Cr(CO)_6$ (1.00 g, 4.6 mmol). Tricarbonyl(η^6-benzene)chromium(0) (**189a**) (0.95 g; 97.2 %) was obtained as yellow cubes upon cooling of the reaction mixture. Mp 162.4 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) (plate 8a) δ ppm 5.32 ppm (6H, s, Ar-<u>H</u>); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 8b) δ ppm 92.89 (Ar-<u>C</u>), 232.95 (Cr-<u>C</u>O); MS (MS Scheme 1) *m/z* 214 (M^+, 56.0 %), 186 (M^+-CO, 4.0), 158 (M^+-2CO, 9.0), 130 (M^+-3CO, 98.0), 78 (M^+-$Cr(CO)_3$, 100.0).

6.7.6.2 Tricarbonyl(η^6-toluene)chromium(0) (191a)[12]

Toluene (**191**) (10 ml, 94.6 mmol, 20.6 eq.), $Cr(CO)_6$ (1.00 g, 4.6 mmol). Tricarbonyl(η^6-toluene)chromium(0) (**191a**) (1.00 g; 97.1 %) was obtained as yellow cubes upon cooling of the reaction mixture. Mp 80.8 ^oC; ^1H NMR (600 MHz, $CDCl_3$) (plate 10a) δ ppm 5.40 (2H, dd, *J* = 6.40, 6.40 Hz, H-3 and H-5), 5.15 (2H, d, *J* = 6.40 Hz, H-2 and H-6), 5.14 (1H, dd, *J* = 6.40, 6.40 Hz, H-4), 2.19 (3H, s, -C$\underline{H}_3$); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 10b) δ ppm 20.65 (-$\underline{C}H_3$), 89.98, 93.16 (C-2, C-4 and C-6), 94.12 (C-3 and C-5), 110.07 (C(*i*)), 233.45 (Cr-$\underline{C}O$); MS (MS Scheme 1) *m/z* 228 (M^+, 39.5 %), 200 (M^+-CO, 43.4), 172 (M^+-2CO, 7.9), 144 (M^+-3CO, 100.0), 92 (M^+-$Cr(CO)_3$, 6.0), 77 (M^+-$Cr(CO)_3$, -CH_3, 6.7).

6.7.6.3 Tricarbonyl(η^6-anisole)chromium(0) (192a)[13]

Anisole (**192**) (10 ml, 92.6 mmol, 20.1 eq.), $Cr(CO)_6$ (1.01 g, 4.6 mmol). Tricarbonyl(η^6-anisole)chromium(0) (**192a**) (0.95 g; 85.0 %) was obtained as yellow cubes upon cooling of the reaction mixture. Mp 80.8 ^oC; ^1H NMR (600 MHz, $CDCl_3$) (plate 12a) δ ppm 5.54 (2H, dd, *J* = 5.87, 6.60 Hz, H-3 and H-5), 5.12 (2H, d, *J* = 6.60 Hz, H-2 and H-6), 4.87 (1H, dd, *J* = 5.87, 6.60 Hz, H-4), 3.71 (3H, s, -OC$\underline{H}_3$); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 12b) δ ppm 55.60 (-O$\underline{C}H_3$), 78.41 (C-2 and C-6), 85.66 (C-4), 95.35 (C-3 and C-5), 143.44 (C(*i*)), 233.34 (Cr-$\underline{C}O$); MS (MS Scheme 1) *m/z* 244 (M^+, 35.0 %), 216 (M^+-CO, 5.7), 188 (M^+-2CO, 20.2), 160 (M^+-3CO, 100.0), 145 (M^+-3CO, -CH_3, 5.8), 108 (M^+-$Cr(CO)_3$, 6.0), 93 (M^+-$Cr(CO)_3$, -CH_3, 3.1), 77 (M^+-$Cr(CO)_3$, -OCH_3, 7.2).

6.7.6.4 Tricarbonyl(η^6-chlorobenzene)chromium(0) (190a)[14]

Chlorobenzene (**190**) (10 ml, 99.1 mmol, 21.5 eq.), $Cr(CO)_6$ (1.01 g, 4.6 mmol). Tricarbonyl(η^6-chlorobenzene)chromium(0) (**190a**) (1.12 g; 98.0 %) was obtained as yellow cubes upon cooling of the reaction mixture. Mp 101.7 ^oC; ^1H NMR (600 MHz, $CDCl_3$) (plate 14a) δ ppm 5.44 – 5.42 (4H, m, H-2, H-3, H-5 and H-6), 5.04 – 5.00 (1H, m, H-4); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 14b) δ ppm 88.23 (C-4), 91.28, 93.28 (C-2, C-3, C-5 and C-6), 113.03 (C(*i*)), 231.67 (Cr-$\underline{C}O$); MS (MS Scheme 1) *m/z* 248 (M^+, 49.8 %), 220 (M^+-CO, 5.3), 192 (M^+-2CO, 11.5), 164 (M^+-3CO, 100.0), 129 (M^+-3CO, -Cl, 7.4), 112 (M^+-$Cr(CO)_3$, 9.1), 87 (35.2), 77 (M^+-$Cr(CO)_3$, -Cl 41.6).

6.7.6.5 Tricarbonyl(η^6-acetophenone)chromium(0) (193a)[15]

Acetophenone (**193**) (0.6 ml, 0.29 g, 2.4 mmol), $Cr(CO)_6$ (0.82 g, 3.7 mmol, 1.6 eq.). Separation of the crude product with FCC yielded tricarbonyl(η^6-acetophenone)chromium(0) (**193a**) (0.22 g; 35.7 %) as an orange solid. R_f (H:A; 8:2); Mp 71.8 ^oC; ^1H NMR (600 MHz, $CDCl_3$) (plate 16a) δ ppm 6.05 (2H, d, *J* = 6.24 Hz, H-2 and H-6), 5.63 (1H, t, *J* = 6.24, 6.24 Hz, H-4), 5.27 (2H, t, *J* = 6.24 Hz, H-3 and H-5), 2.45 (3H, s, -COC$\underline{H}_3$); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 16b) 25.23 (-CO$\underline{C}H_3$), 89.55 (C-3 and C-5), 94.37 (C-2 and C-6), 95.38 (C-4), 95.81 (C(*i*)), 195.02 (-$\underline{C}OCH_3$), 230.71 (Cr-$\underline{C}O$); MS (MS Scheme 1) *m/z* 258 (M^+, 27.6 %), 228 (M^+-CO, 8.0), 200 (M^+-2CO, 27.9), 172 (M^+-3CO, 100.0), 157 (M^+-3CO, -CH_3, 0.1), 129 (M^+-3CO, -$COCH_3$, 8.1), 120 (M^+-$Cr(CO)_3$, 0.2), 105 (M^+-$Cr(CO)_3$, -CH_3, 8.0), 77 (M^+-$Cr(CO)_3$, -$COCH_3$, 20.8).

6.7.6.6 Tricarbonyl(η^6-chroman-4-one)chromium(0) (180a)[15]

Chromanone (**180**) (0.50 g, 3.4 mmol), $Cr(CO)_6$ (0.83 g, 3.8 mmol, 1.1 eq.). Purification by means of FCC yielded a diastereomeric mixture of tricarbonyl(η^6-chromanone)chromium(0) (**180a**) (0.27 g; 28.1 %) as an orange solid. R_f 0.25 (H:A; 8:2); Mp 107.1 ^oC; ^1H NMR (600 MHz, $CDCl_3$) (plate 17a) δ ppm 6.18 (1H, d, *J* = 6.24 Hz, H-5), 5.74 (1H, dd, *J* = 6.60, 6.97 Hz, H-7), 5.21 (1H, d, *J* = 6.60 Hz, H-8), 5.02 (1H, dd, *J* = 6.24, 6.97 Hz, H-6), 4.55 – 4.51 (1H, m, H-2), 4.46 – 4.24 (1H, m, H-2), 2.88 (1H, ddd, *J* = 4.45, 6.29, 17.28, H-3(e)), 2.75 (1H, ddd, *J* = 5.05, 9.31, 17.28, H-3(a)); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 17b) δ ppm 36.77 (C-3), 67.08 (C-2), 79.49 (C-8), 82.25 ($\underline{C}$(*i*)-CO), 85.35 (C-6), 90.26 (C-5), 95.56 (C-7), 144.44 (C(*i*)-O), 189.59 (C-4), 230.68 (Cr-$\underline{C}O$); MS (MS Scheme 2) *m/z* 284 (M^+, 97.9 %), 256 (3.6), 228 (16.0), 200 (100.0), 172 (0.9), 144 (9.1), 120 (24.3).

6.7.6.7 Tricarbonyl(B-η^6-4',7-dimethoxyisoflavone)chromium(0) (56a)

4',7-Dimethoxyisoflavone (**56**) (1.28 g; 4.5 mmol), $Cr(CO)_6$ (1.00 g; 4.6 mmol; 1 eq.). Purification through FCC yielded *tricarbonyl(B-η^6-4',7-dimethoxyisoflavone)-chromium(0)* (**56a**) (0.48 g; 25.0 %) as a yellow solid. R_f 0.18 (H:A; 8:2); Mp 127.0 ^oC (dec.); ^1H NMR (600 MHz, $CDCl_3$) (plate 18a) δ ppm 8.15 (1H, d, *J* = 9.04 Hz, H-5), 8.09 (1H, s, H-2), 7.01 (1H, dd, *J* = 1.88, 9.04 Hz, H-6), 6.86 (1H, d, *J* = 1.88 Hz, H-8), 5.85 (2H, d, *J* = 6.78 Hz, H-2' and H-6'), 5.21 (2H, d, *J* = 6.78 Hz, H-3' and H-5'), 3.92 (3H, s, -OC$\underline{H}_3$), 3.75 (3H, s, -

OC<u>H</u>$_3$); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 18b) δ ppm 55.88 (-O<u>C</u>H$_3$), 56.06 (-O<u>C</u>H$_3$), 77.37 (C-3' and C-5'), 94.71 (), 97.63 (C-2' and C-6'), 100.45 (C-8), 115.32 (C-6), 117.67, 121.16, 127.71 (C-5), 143.39 (<u>C</u>(*i*)-OCH$_3$ B-ring), 154.78 (C-2), 158.07, 164.60, 175.26 (C-4), 232.89 (Cr-<u>C</u>O); MS (MS Scheme 3) *m/z* 362 (M^+-2CO, 0.5 %), 343 (2.1), 282 (100.0), 267 (20.8), 252 (3.0), 239 (10.9), 224 (3.7), 211 (3.8), 196 (3.5), 183 (1.2), 168 (2.9), 150 (12.9), 141 (6.1), 131 (69.5), 122 (10.7), 107 (7.9), 103 (2.4).

6.7.6.8 Tricarbonyl(B-η^6-flavone)chromium(0) (164a)

Flavone (**164**) (1.01 g; 4.5 mmol), $Cr(CO)_6$ (1.0 g; 4.6 mmol; 1 eq.). Purification of the crude product was performed with FCC yielding *tricarbonyl(B-η^6-flavone)chromium(0)* (**164a**) (0.70 g; 42.9 %) as an orange solid. R_f 0.11 (H:A:DCM; 7:1:2); Mp 160.6 ^{o}C (dec.); ^{1}H NMR (600 MHz, $CDCl_3$) (plate 19a) δ ppm 8.21 (1H, d, *J* = 7.91 Hz, H-5), 7.72 (1H, dd, *J* = 7.53, 7.91 Hz, H-6), 7.54 (1H, d, *J* = 8.28 Hz, H-8), 7.44 (1H, dd, *J* = 7.53, 8.28 Hz, H-8), 6.61 (1H, s, H-3), 6.00 (2H, d, *J* = 6.38 Hz, H-2' and H-6'), 5.57 (1H, t, *J* = 6.14 Hz, H-4'), 5.41 (2H, dd, *J* = 6.14, 6.38 Hz, H-3' and H-5'); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 19b) δ ppm 89.91 (C-3' and C-5'), 91.04 (C-2' and C-6'), 93.77 (C-4'), 94.98, 107.38 (C-3), 118.08 (C-8), 124.0, 125.79 (C-5 or C-7), 125.92 (C-5 or C-7), 134.33 (C-6), 156.13, 161.02, 177.56, 231.08(-Cr(<u>C</u>O)$_3$); MS (MS Scheme 4) *m/z* 358 (M^+, 4.4), 330 (0.9), 302 (2.1), 274 (11.3), 239 (2.2), 223 (100.0), 210 (0.6), 183 (2.6), 155 (3.5), 121 (29.0), 103 (4.7).

6.7.6.9 Tricarbonyl(η^6-chroman-4-ol)chromium(0) (196a and 196b)

Racemic chroman-4-ol (**196**) (0.52 g; 3.5 mmol), $CrCO_6$ (0.82 g; 3.7 mmol; 1.1 eq.). Purification by means of FCC yielded a *cis-trans* diastereomeric mixture of *tricarbonyl(η^6-chroman-4-ol)chromium(0)* (**196a** and **196b**) (0.13 g; 13.8 %) as a yellow solid. Mass 0.13 g; 13.8 % yield; R_f 0.14 (H:A; 8:2); Mp 54.2 ^{o}C; ^{1}H NMR (600 MHz, $CDCl_3$) (plate 22a) δ ppm 5.82 (d, *J* = 6.22 Hz, H-5*), 5.72 (d, *J* = 6.13 Hz, H-5), 5.62 (dd, *J* = 6.60, 7.34 Hz, H-7*), 5.52 (dd, *J* = 6.24, 7.34 Hz, H-7), 5.13 (d, *J* = 6.80 Hz, H-8), 5.03 (d, *J* = 6.75 Hz, H-8*), 4.87 (dd, *J* = 6.24, 7.34 Hz, H-6), 4.81 (dd, *J* = 5.87, 6.60 Hz, H-6*), 4.68 – 4.64 (m, H-4), 4.60 – 4.56 (m, H-4*), 4.32 – 4.28 (m, H-2(a)*), 4.26 – 4.24 (m, H-2(a) and H-2(e)), 4.17 – 4.13 (m, H-2(e)*), 2.37 – 2.32 (m, H-3(a)), 2.20 – 2.14 (m, H-3(a)* and H-3(e)*), 2.11 (d, *J* = 4.04 Hz, -O<u>H</u>), 1.98 – 1.94 (m, H-3(e)), 1.62 (d, *J* = 8.80 Hz, -O<u>H</u>*) (where * = *trans*-isomer); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 22b) δ ppm 1.11, 14.21, 19.31, 22.78, 29.44,

29.74, 29.78, 30.02, 30.14, 30.97, 31.31, 32.01, 61.62, 62.03, 62.80, 62.97, 63.42, 64.36, 78.21, 79.39, 83.70, 85.42, 93.96, 94.81, 95.69, 95.73, 96.79, 99.24, 117.19, 120.76, 129.81, 129.89, 140.40, 142.00, 233.15; MS (MS Scheme 5) *m/z* 286 (M^+, 75.2 %), 269 (6.8), 258 (3.0), 241 (2.0), 230 (23.4), 213 (3.5), 202 (90.0), 184 (100.0), 174 (92.3), 156 (23.0), 149 (11.5), 133 (47.8), 121 (13.0), 117 (34.1), 105 (54.3).

6.7.6.10 Chromium complexation onto flavan-4-ol (197)

Flavan-4-ol (**197**) (0.94 g; 4.2 mmol), $Cr(CO)_6$ (1.10 g; 5.0 mmol; 1.2 eq.). Seperation of the crude product on FCC (H:A; 8:2) yielded three products of interest with R_f values of 0.64, 0.14 and 0.10 respectively.

a) Flavan-4-one (195)

The R_f 0.64 yielded flavan-4-one (195) as a white powder from the eluent. Mass 0.05 g; 5.6 % yield; Mp 74.5 ^oC; ^1H NMR (600 MHz, $CDCl_3$) (plate 24a) δ ppm 7.94 (1H, dd, J = 1.76, 8.03 Hz, H-5), 7.53 – 7.50 (3H, m, Ar-H), 7.46 – 7.43 (2H, m, Ar-H), 7.41 – 7.38 (1H, m, Ar-H), 7.08 – 7.05 (2H, m, Ar-H), 5.50 (1H, dd, *J* = 2.85, 13.45 Hz, H-2), 3.10 (1H, dd, *J* = 13.45, 16.87 Hz, H-3(a)), 2.91 (1H, dd, J = 2.85, 16.87 Hz, H-3(e)); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 24b) δ ppm 44.79, 79.72, 118.25, 121.08, 121.74, 126.27, 127.18, 128.89, 128.97, 136.30, 138.88, 161.68, 192.04.

b) Tricarbonyl(A-η^6-flavan-4-ol)chromium(0) (197a)

The R_f 0.14 fraction yielded *tricarbonyl(A-η^6-flavan-4-ol)chromium(0)* (**197a**) as an orange solid from the eluent. Mass 0.03 g; 1.7 % yield; ^1H NMR (600 MHz, $CDCl_3$) (plate 25a) δ ppm 7.46 – 7.36 (5H, m, H-2', H-3', H-4', H-5', H-6'), 5.96 (1H, d, *J* = 6.40 Hz, H-5/8), 5.66 (1H, ddd, *J* = 0.65, 6.40, 7.15 Hz, H-6/7), 5.08 – 5.06 (2H, m, H-5/8 and H-2), 4.92 (1H, ddd, *J* = 5.65, 10.91, 11.30 Hz, H-4), 4.84 (1H, dd, *J* = 6.16, 7.15 Hz, H-6/7), 2.48 (1H, ddd, *J* = 0.97, 5.65, 13.55 Hz, H-3(e)), 2.28 – 2.22 (1H, m, H-3(a)), 1.59 (1H, d, *J* = 11.30 Hz, -O<u>H</u>); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 25b) δ ppm 39.69 (C-3), 64.13 (C-4), 77.28, 79.41, 83.99 (C-6/7), 92.71 (C-5/8), 96.40 (C-6/7), 99.82, 126.52, 129.04, 129.15, 138.51, 142.22 (C(*i*)-O-), 233.60 (-Cr(<u>C</u>O)$_3$); MS (MS Scheme 6) *m/z* 362 (M^+, 25.7 %), 306 (5.2), 278 (78.9), 260

(22.0), 258 (13.9), 250 (65.1), 241 (1.4), 230 (1.2), 226 (0.5), 184 (1.1), 174 (100.0), 156 (9.0), 144 (5.8), 122 (4.0), 115 (13.8), 105 (2.2), 104 (8.2).

c) Tricarbonyl(B-η^6-flavan-4-ol)chromium(0) (197b)

The R_f 0.10 fraction yielded *tricarbonyl(B-η^6-flavan-4-ol)chromium(0)* (**197b**) as a yellow solid from the eluent. Mass 0.04 g; 2.8 % yield; ^{1}H NMR (600 MHz, $CDCl_3$) (plate 26a) δ ppm 7.49 (1H, d, *J* = 7.35 Hz, H-5/8), 7.22 (1H, dd, *J* = 8.28, 9.04 Hz, H-6/7), 7.01 (1H, dd, *J* = 7.35, 9.04 Hz, H-6/7), 6.92 (1H, d, *J* = 8.28 Hz, H-5/8), 5.59 (1H, d, *J* = 4.89 Hz, H-2'/6'), 5.43 (1H, d, *J* = 4.89 Hz, H-2'/6'), 5.37 – 5.33 (3H, m, H-3', H-4' and H-6'), 5.12 – 5.08 (1H, m, H-4), 4.82 (1H, d, *J* = 11.48 Hz, H-2), 2.59 – 2.56 (1H, m, H-3), 2.10 – 2.05 (1H, m, H-3), 1.82 (1H, d, *J* = 7.86, -O<u>H</u>); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 26b) δ ppm 29.83, 39.64 (C-3), 65.51 (C-4), 74.47 (C-2), 90.879, 91.37, 91.50, 91.68, 92.58, 110.25, 116.87, 121.68 (C-6/7), 125.42 (C-5/8), 126.23, 127.01, 128.82, 129.57, 153.86, 232.53 (-Cr(<u>C</u>O)$_3$); MS (MS Scheme 7) *m/z* 362 (M^+, 3.8 %), 334 (2.2), 306 (21.8), 278 (100.0), 260 (19.2), 250 (30.3), 241 (0.9), 226 (1.2), 213 (1.0), 209 (5.1), 185 (0.8), 174 (25.0), 164 (23.9), 156 (11.1), 122 (3.6), 104 (10.4).

6.7.6.11 Tricarbonyl(A-η^6-flavan)chromium(0) (6a)

Flavan (**6**) (0.51 g; 2.4 mmol; 1.1 eq.), $CrCO_6$ (0.53 g; 2.4 mmol). Purification by means of FCC yielded *tricarbonyl(A-η^6-flavan)chromium(0)* (**6a**) as a yellow solid. Mass 0.08 g; 9.2 % yield; R_f 0.23 (H:A; 8:2); Mp 170.4 ^{o}C (dec.); ^{1}H NMR (600 MHz, $CDCl_3$) (plate 28a) δ ppm 7.46 (2H, d, J = 7.30 Hz, H-2' and H-6'), 7.40 (2H, dd, *J* = 7.24, 7.30 Hz, H-3' and H-5'), 7.37 – 7.35 (1H, m, H-4'), 5.56 (1H, d, *J* = 6.03 Hz, H-5), 5.48 (1H, dd, *J* = 6.02, 6.69 Hz, H-7), 5.20 (1H, d, *J* = 6.69 Hz, H-8), 4.90 – 4.88 (2H, m, H-2 and H-6), 3.00 (1H, ddd, *J* = 5.27, 12.42, 15.95 Hz, H-4(a)), 2.64 (1H, dd, *J* = 4.14, 15.95 Hz, H-4(e)), 2.31 (1H, ddd, *J* = 4.14, 12.42, 13.93 Hz, H-3(a)), 2.17 (1H, dd, *J* = 5.27, 13.93 Hz, H-3(e)); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 28b) δ ppm 25.94 (C-4), 29.67 (C-3), 80.00 (C-2/6/8), 80.29 (C-2/6/8), 85.87 (C-2/6/8), 94.50 (C-5/7), 95.60 (C-5/7), 126.49 (C-2' and C-6'), 128.80, 128.89, 139.71, 234.06 (-Cr(<u>C</u>O)$_3$); MS (MS Scheme 8) *m/z* 346 (M^+, 39.0), 290 (2.7), 263 (22.1), 222 (56.9), 193 (12.0), 167 (100.0), 158 (99.8), 149 (68.9),129 (1.9), 127 (13.0), 121 (27.0), 106 (31.3), 104 (4.8), 103 (7.8).

6.7.6.12 Chromium complexation onto 7-methoxyflavan (198)

7-Methoxyflavan (**198**) (0.27 g; 1.1 mmol; 1.1 eq.), $CrCO_6$ (0.25 g; 1.1 mmol). Purification by means of FCC (H:A; 8:2) yielded two products of interest with R_f values of 0.23 and 0.11 respectively.

a) Tricarbonyl(A-η^6-7-methoxyflavan)chromium(0) (198a)

The R_f 0.23 fraction yielded *tricarbonyl(A-η^6-7-methoxyflavan)chromium(0)* (**198a**) as a yellow solid from the eluent. Mass 0.07 g; 16.6 % yield; Mp 148.4 ^oC; ^1H NMR (600 MHz, $CDCl_3$) (plate 33a) δ ppm 7.49 (2H, d, *J* = 7.15 Hz, H-2' and H-6'), 7.41 (2H, dd, *J* = 7.15, 8.66 Hz, H-3' and H-5'), 7.39 – 7.35 (1H, m, H-4'), 5.65 (1H, d, *J* = 6.61 Hz, H-5), 5.15 (1H, s, H-8), 4.90 – 4.86 (2H, m, H-2 and H-6), 3.72 (3H, s, -OCH3), 2.93 (1H, ddd, *J* = 4.89, 12.43, 15.65 Hz, H-4(a)), 2.54 (1H, dd, *J* = 4.14, 15.65 Hz, H-4(e)), 2.31 (1H, ddd, *J* = 4.14, 12.43, 13.68 Hz, H-3(a)), 2.13 (1H, dd, *J* = 4.89, 13.68 Hz, H-3(e)); ^{13}C NMR (600 MHz, $CDCl_3$) (plate 33b) δ ppm 25.52 (C-4), 29.52 (C-3), 55.86 (-O<u>C</u>H$_3$), 68.31 (C-8), 74.42 (C-2/6), 80.56 (C-2/6), 89.11, 94.55 (C-5), 126.61, 128.83, 128.89, 139.62, 140.30, 143.33, 234.44 (-Cr(<u>C</u>O)$_3$); MS (MS Scheme 9) *m/z* 376 (M^+, 13.0), 344 (0.2), 320 (0.1), 292 (70.7), 277 (0.2), 256 (0.1), 240 (5.8), 225 (0.5), 209 (0.3), 188 (100.0), 173 (0.4), 146 (10.0), 137 (2.1), 121 (2.0), 104 (5.1).

b) Tricarbonyl(A,B-η^6-7-methoxyflavan)chromium(0) (198c)

The R_f 0.11 fraction yielded *tricarbonyl(A,B-η^6-7-methoxyflavan)chromium(0)* (**198c**) from the eluent. Mass 0.07 g; 12.4 % yield; Mp 192.8 ^oC (dec.); ^1H NMR (600 MHz, $CDCl_3$) (plate 35) δ ppm 5.71 (1.00H, d, *J* = 6.39 Hz), 5.63 (1.03H, d, *J* = 6.75 Hz), 5.57 (0.56 H, d, *J* = 6.80 Hz), 5.50 (0.50H, d, *J* = 6.25 Hz), 5.44 (0.51H, d, *J* = 6.52 Hz), 5.39 (1.53H, dd, *J* = 6.02, 7.15 Hz), 5.37 – 5.28 (4.53H, m), 5.26 (0.45H, d, *J* = 1.83 Hz), 5.19 (0.96H, d, *J* = 1.88 Hz), 4.95 (0.45H, dd, *J* = 1.92, 6.96 Hz), 4.88 (1.00H, dd, *J* = 1.92, 6.71 Hz), 4.82 (0.45H, dd, *J* = 1.75, 10.23 Hz), 5.51 – 4.47 (1.00H, m), 3.74 (3.00H, s), 3.71 (1.47H, s), 2.90 (1.27H, ddd, *J* = 8.35, 9.70, 16.19 Hz), 2.81 – 2.68 (1.19H, m), 2.53 (1.14H, ddd, *J* = 3.01, 4.52, 15.81 Hz), 2.30 – 2.26 (0.69H, m), 2.24 – 2.19 (2.30H, m), 2.07 – 1.91 (0.68H, m); MS (MS Scheme 10) *m/z*

400 (M^+-4CO, 0.2 %), 376 (11.9), 344 (2.2), 292 (69.5), 277 (0.6), 272 (1.6), 256 (0.3), 240 (2.8), 229 (0.2), 225 (0.8), 217 (0.2), 211 (0.4), 201 (0.3), 188 (100.0), 183 (0.3), 173 (1.5), 156 (0.9), 149 (15.0), 136 (3.7), 129 (2.2), 121 (2.3), 104 (4.7).

6.7.7 Tricarbonyl(η^6-anisole)chromium(0) (192a) *via* nucleophilic substitution[16,17]

A solution of NaH (0.08 g; 3.2 mmol; 1.6 eq.) in dry MeOH (2 ml) was added to a solution of tricarbonyl(η^6-chlorobenzene)chromium(0) (**190a**) (0.47 g; 2.0 mmol) in dry MeOH. The reaction mixture was degassed employing standard Schlenk techniques and refluxed overnight in an oxygen free environment. The reaction mixture was cooled to room temperature and the solvent evaporated *in vacuo*. Evaluation of the crude product *via* ^{1}H NMR indicated a 31.6 % yield of anisoletricarbonylchromium(0) (**192a**).

6.8 References

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APPENDIX A

REPRESENTATIVE NMR SPECTRA

Plate 1; ^{1}H NMR [$CDCl_3$]: 2'-Hydroxy-4,4'-dimethoxychalcone (**167**)

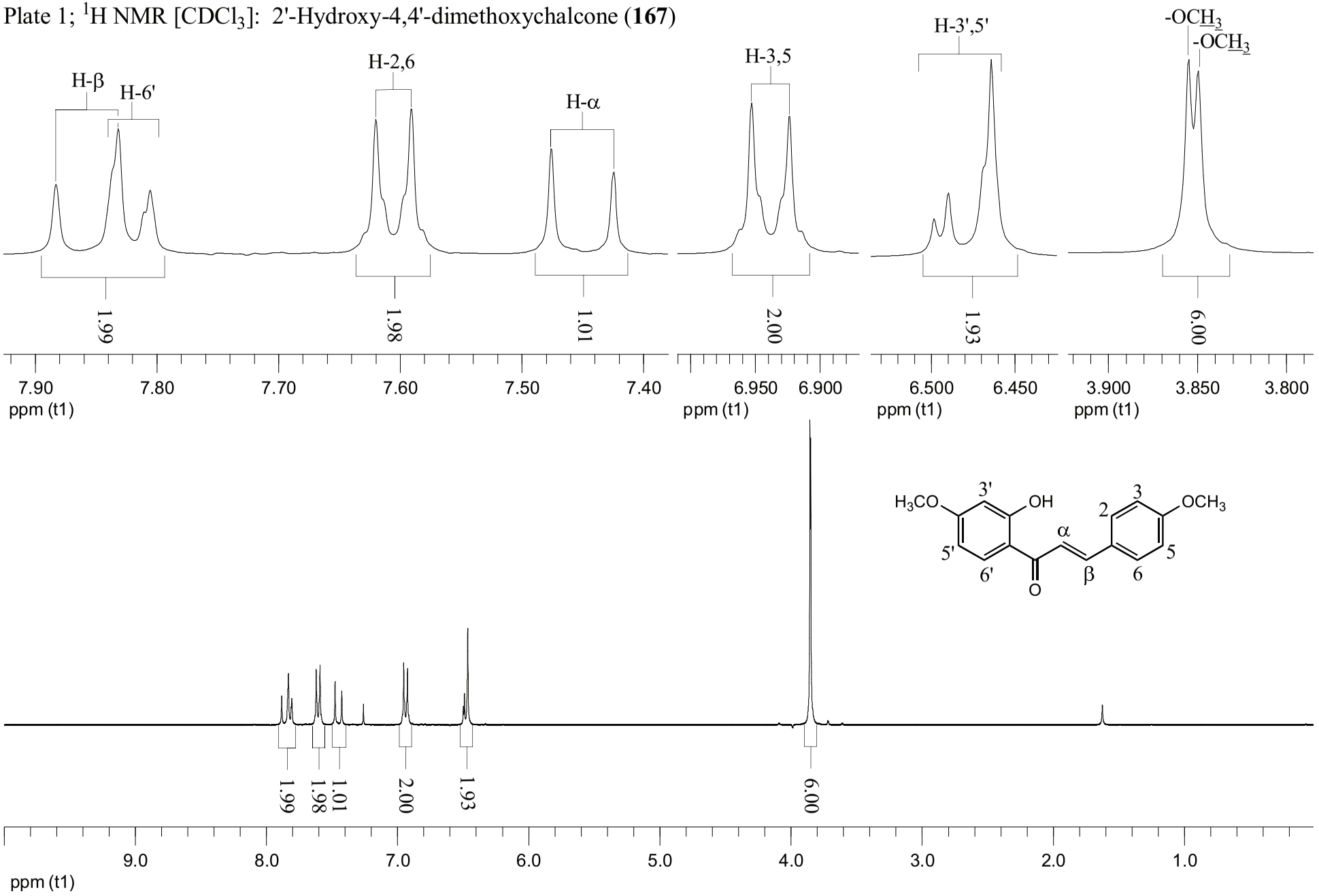
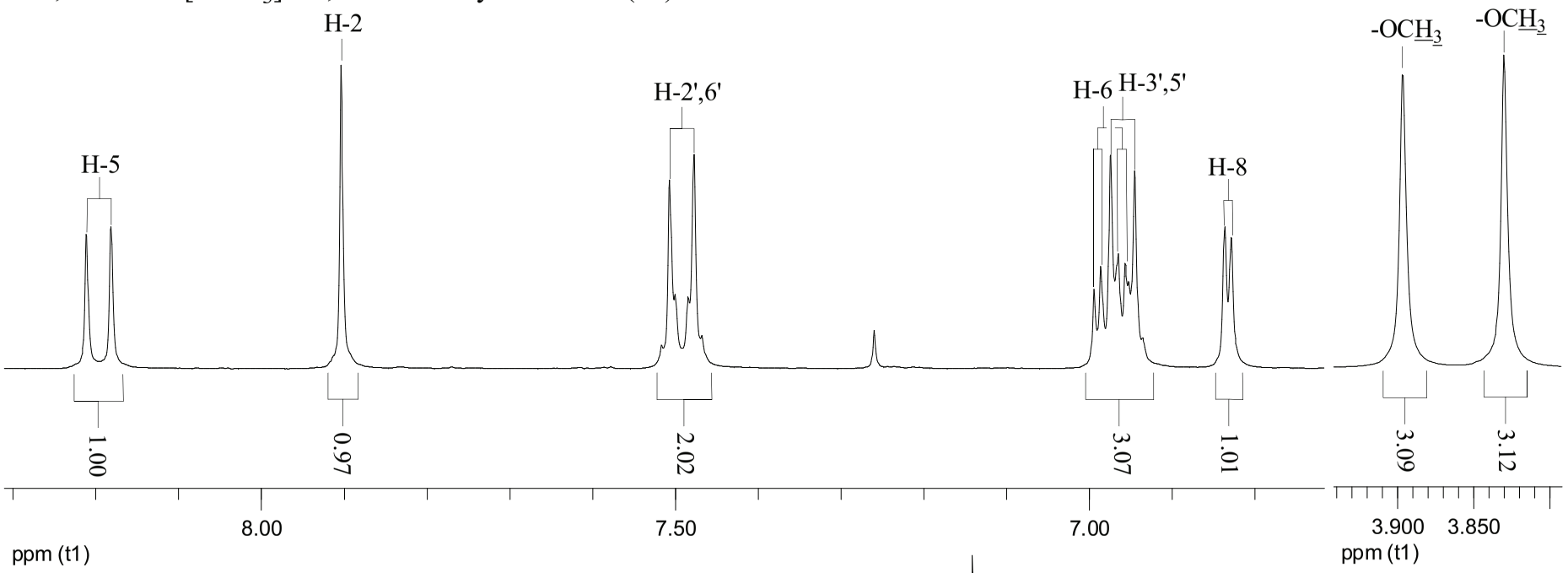


Plate 2a; ^{1}H NMR [$CDCl_3$]: 4',7-Dimethoxyisoflavone (**56**)



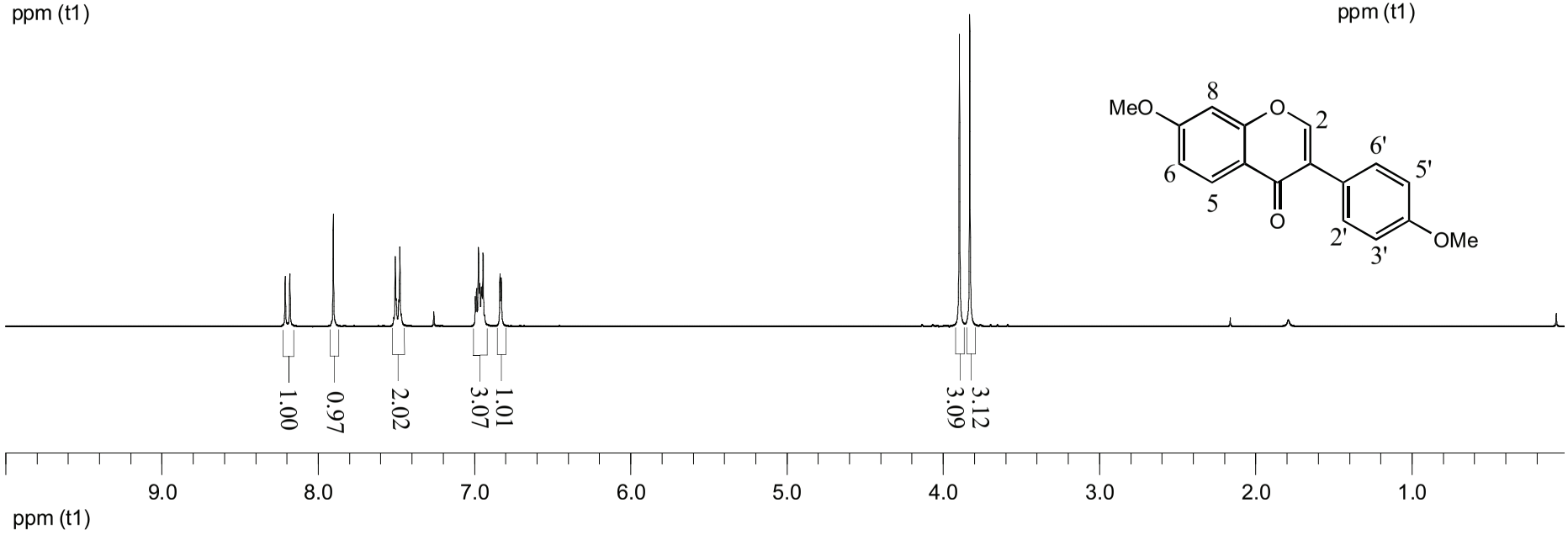


Plate 2b; ^{13}C NMR [$CDCl_3$]: 4',7-Dimethoxyisoflavone (**56**)

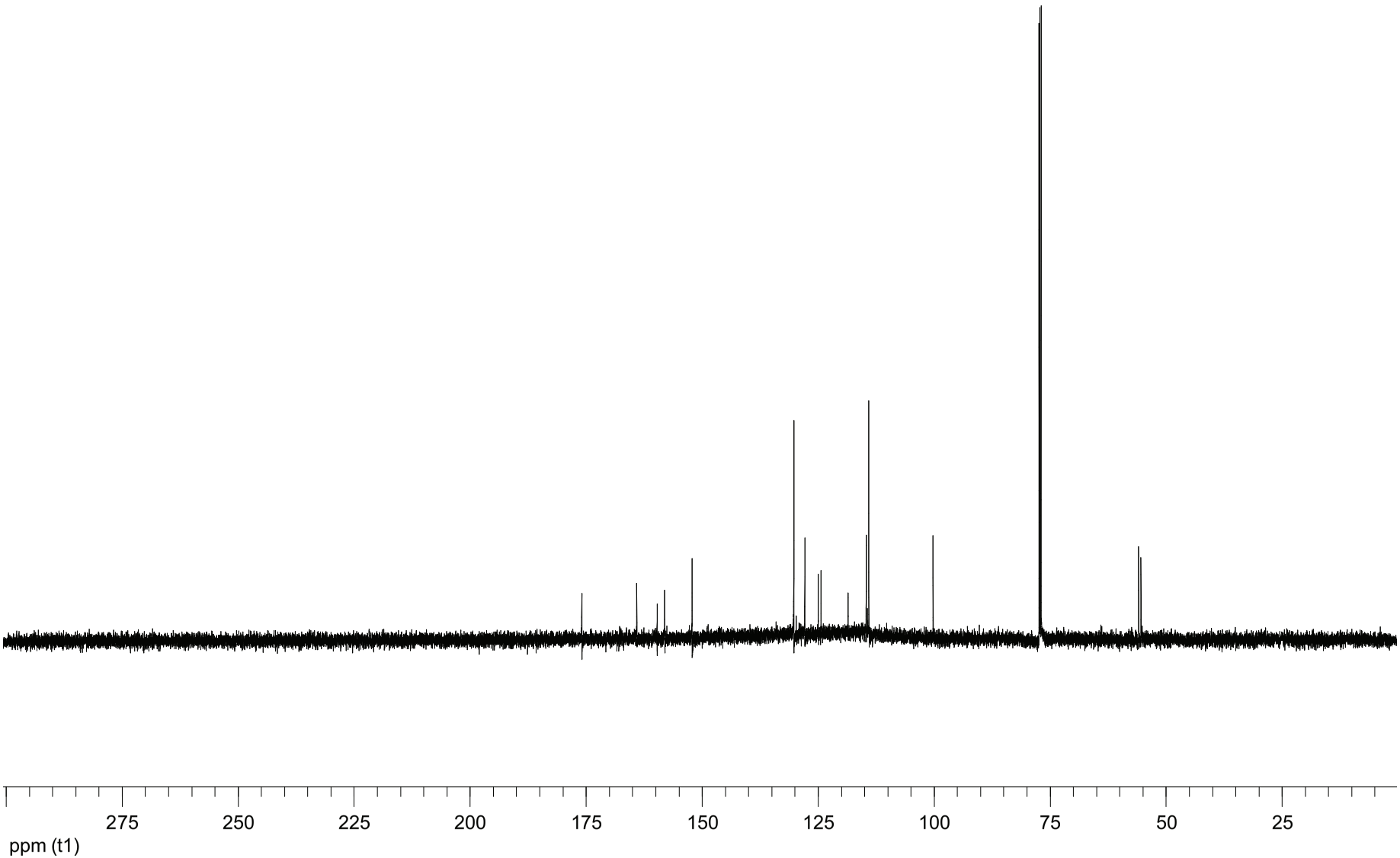
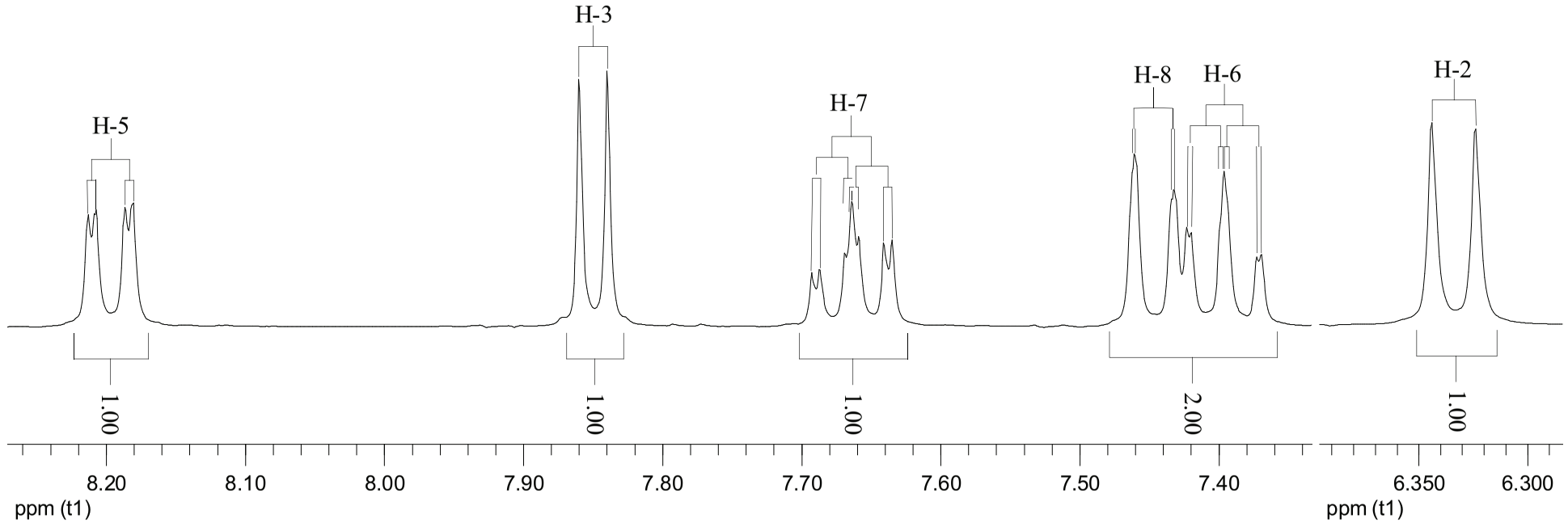


Plate 3; ^{1}H NMR [$CDCl_3$]: Chromone (**163**)



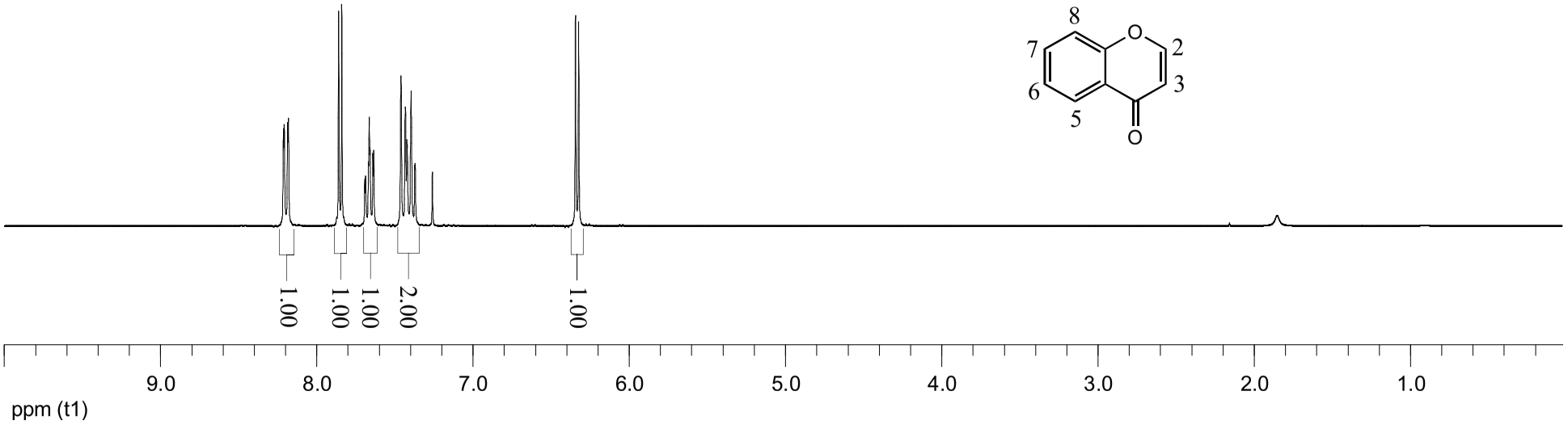


Plate 4a; ^{1}H NMR [$CDCl_3$]: Chroman-4-one (**180**)

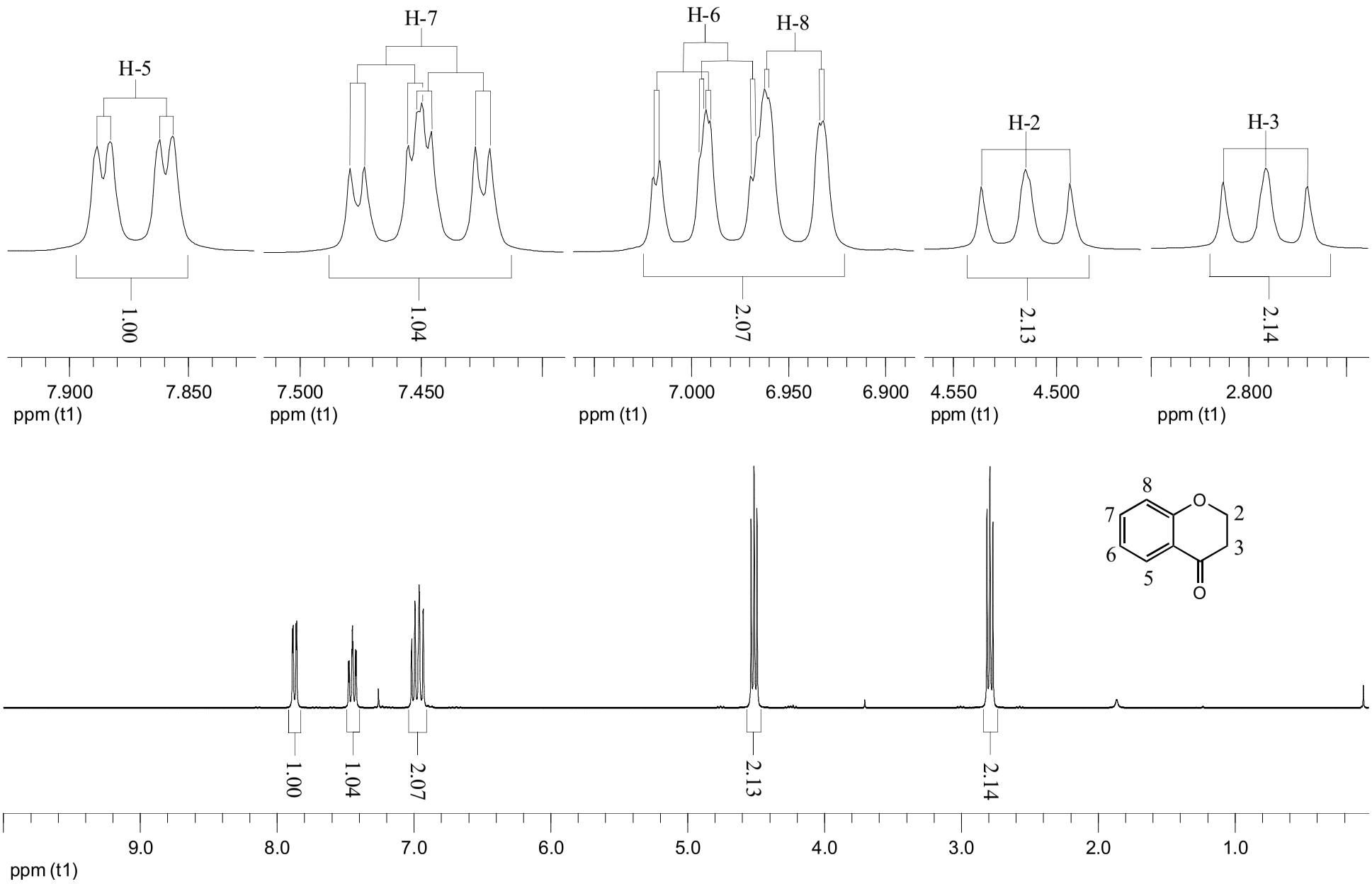


Plate 4b; ^{13}C NMR [$CDCl_3$]: Chroman-4-one (**180**)

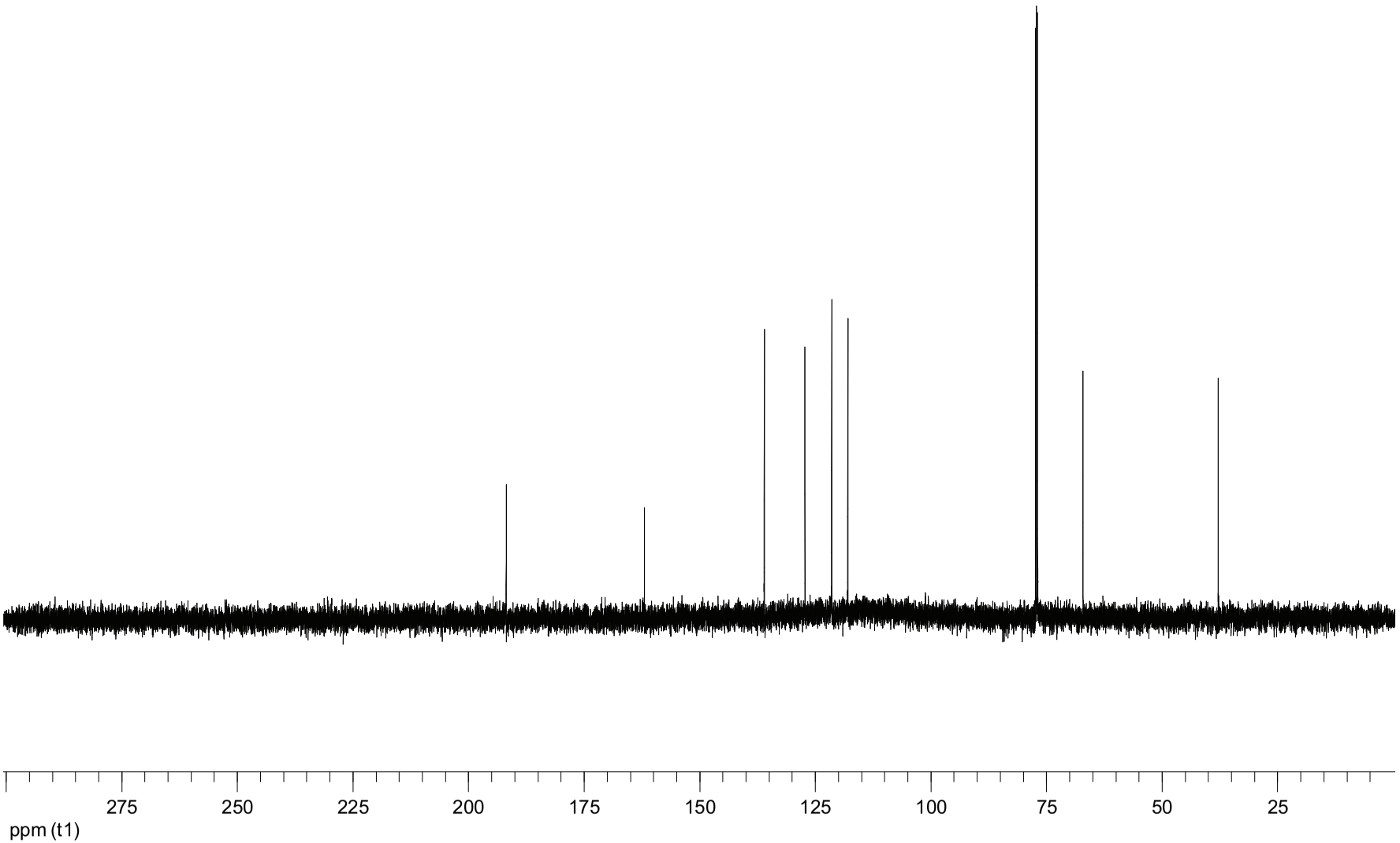
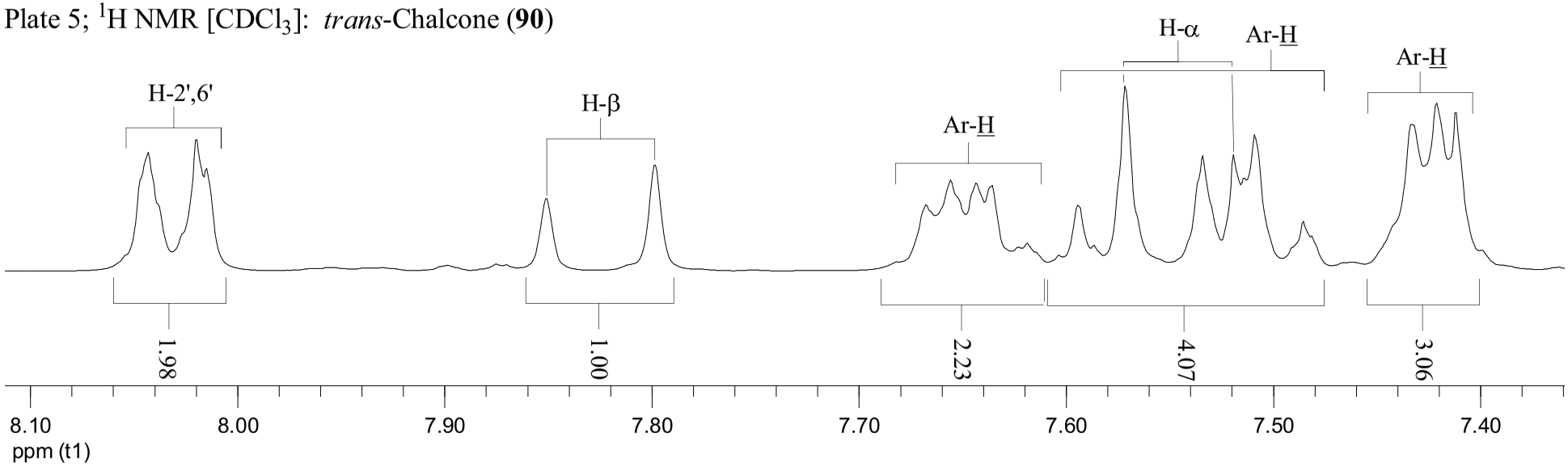


Plate 5; ^{1}H NMR [$CDCl_3$]: *trans*-Chalcone (**90**)



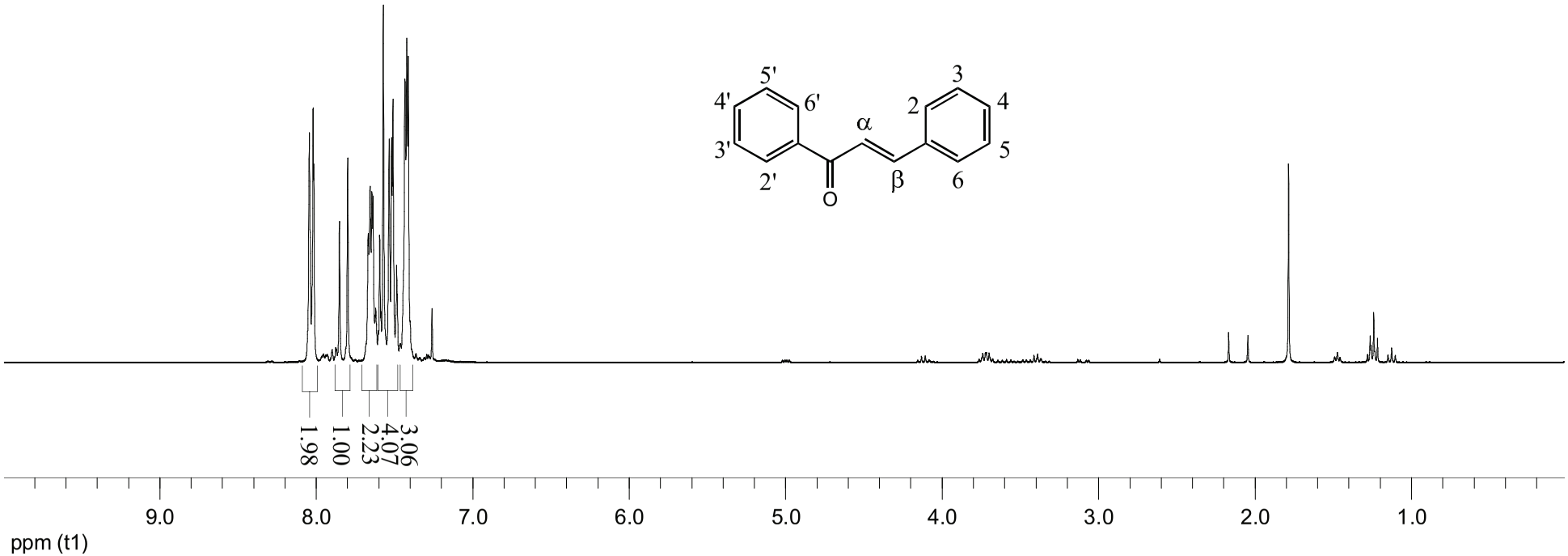


Plate 6; ^{1}H NMR [$CDCl_3$]: Dihydrochalcone (**91**)

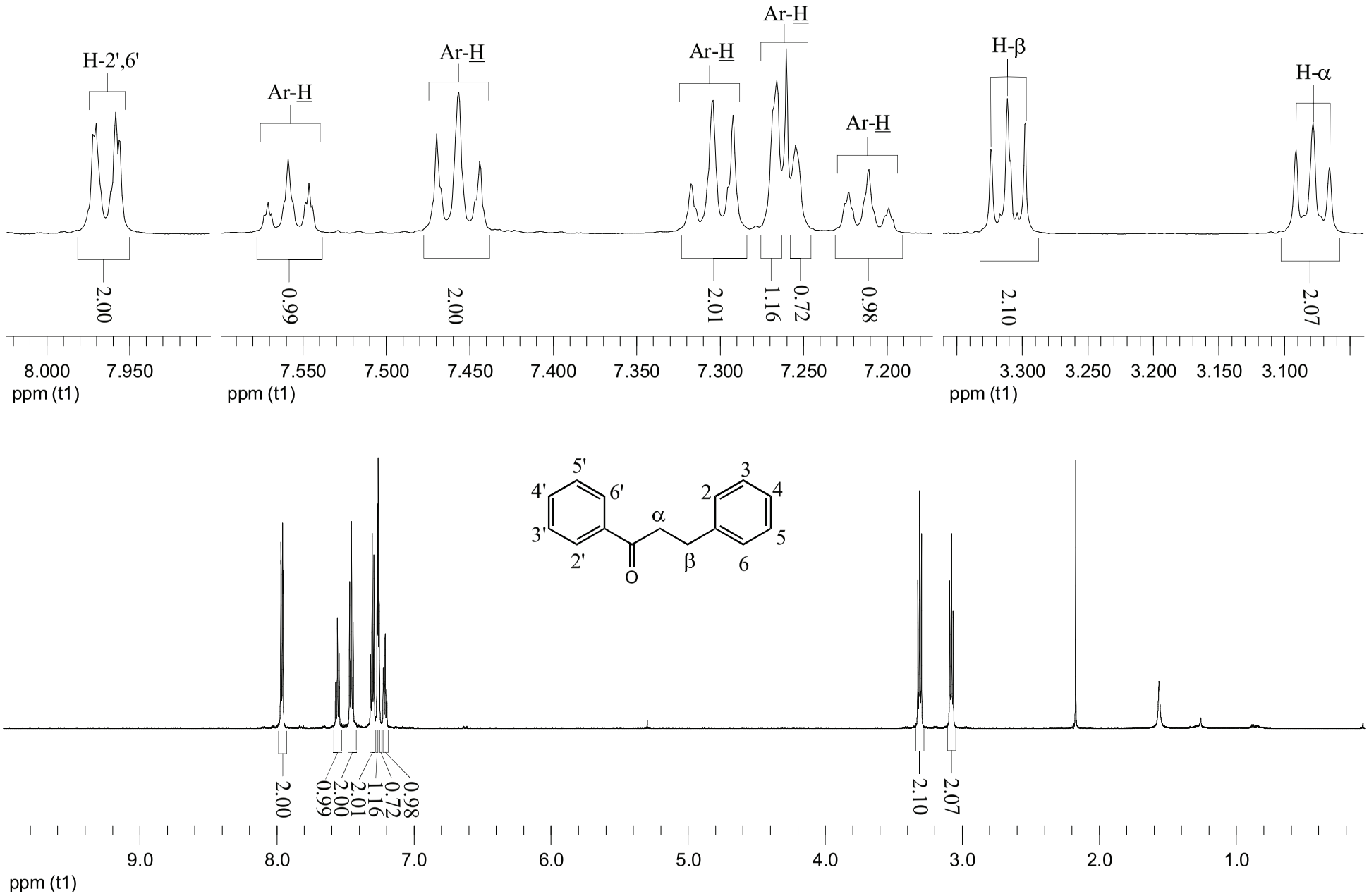


Plate 7a; ^{1}H NMR [$CDCl_3$]: Benzene (**189**)

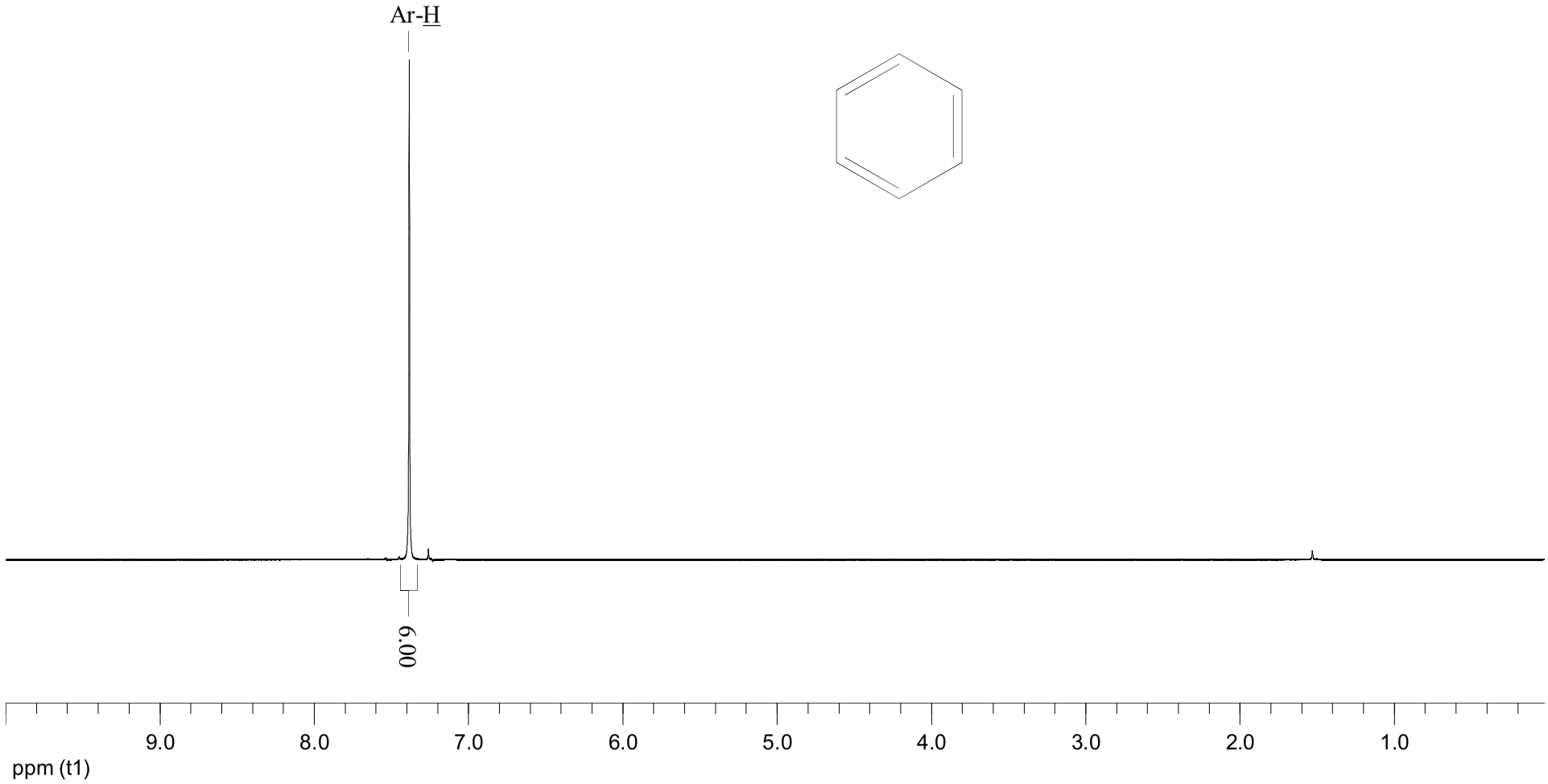


Plate 7b; ^{1}H NMR [$CDCl_3$]: Benzene (**189**)

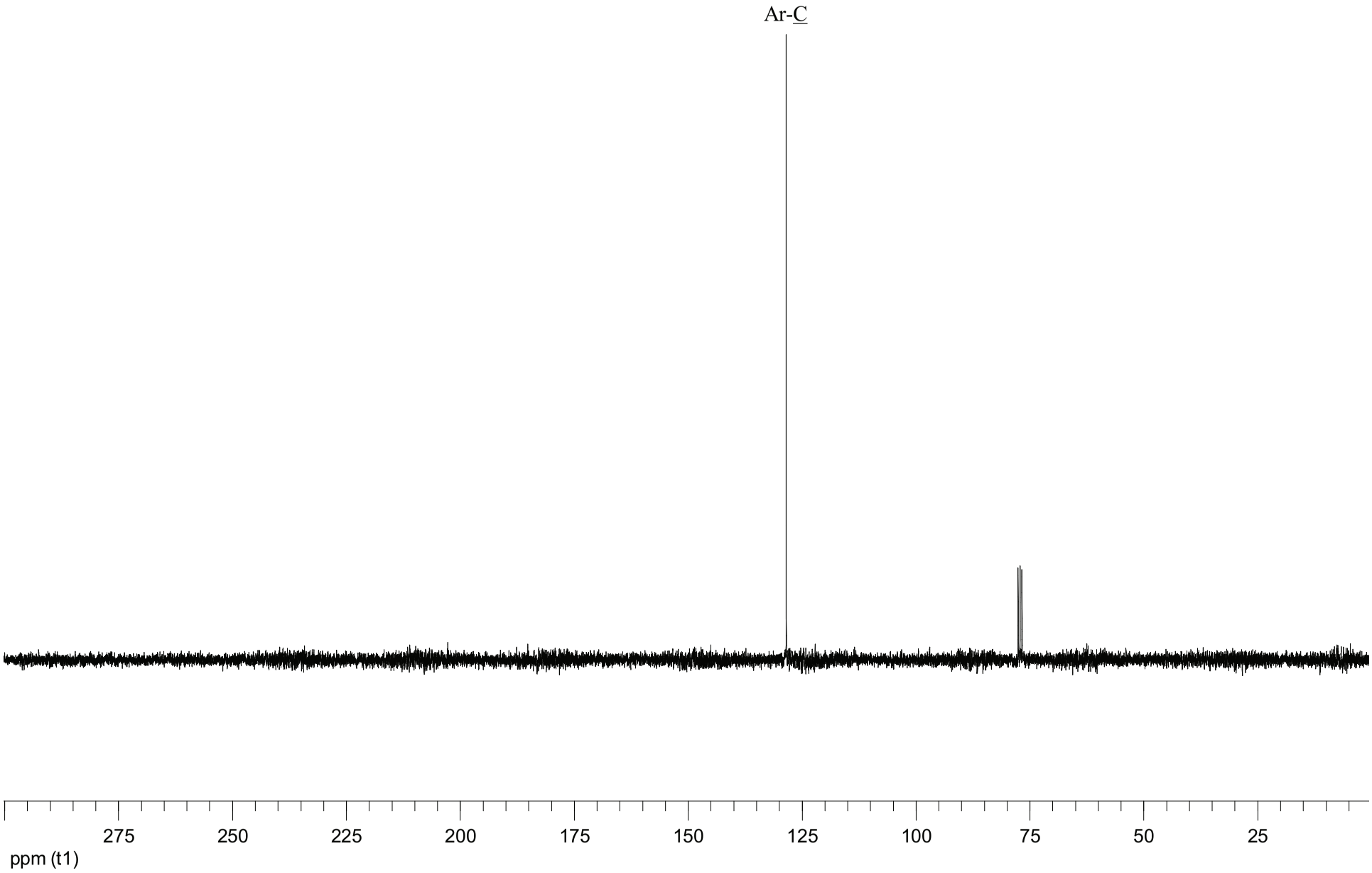


Plate 8a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(η^6-benzene)chromium(0) (**189a**)

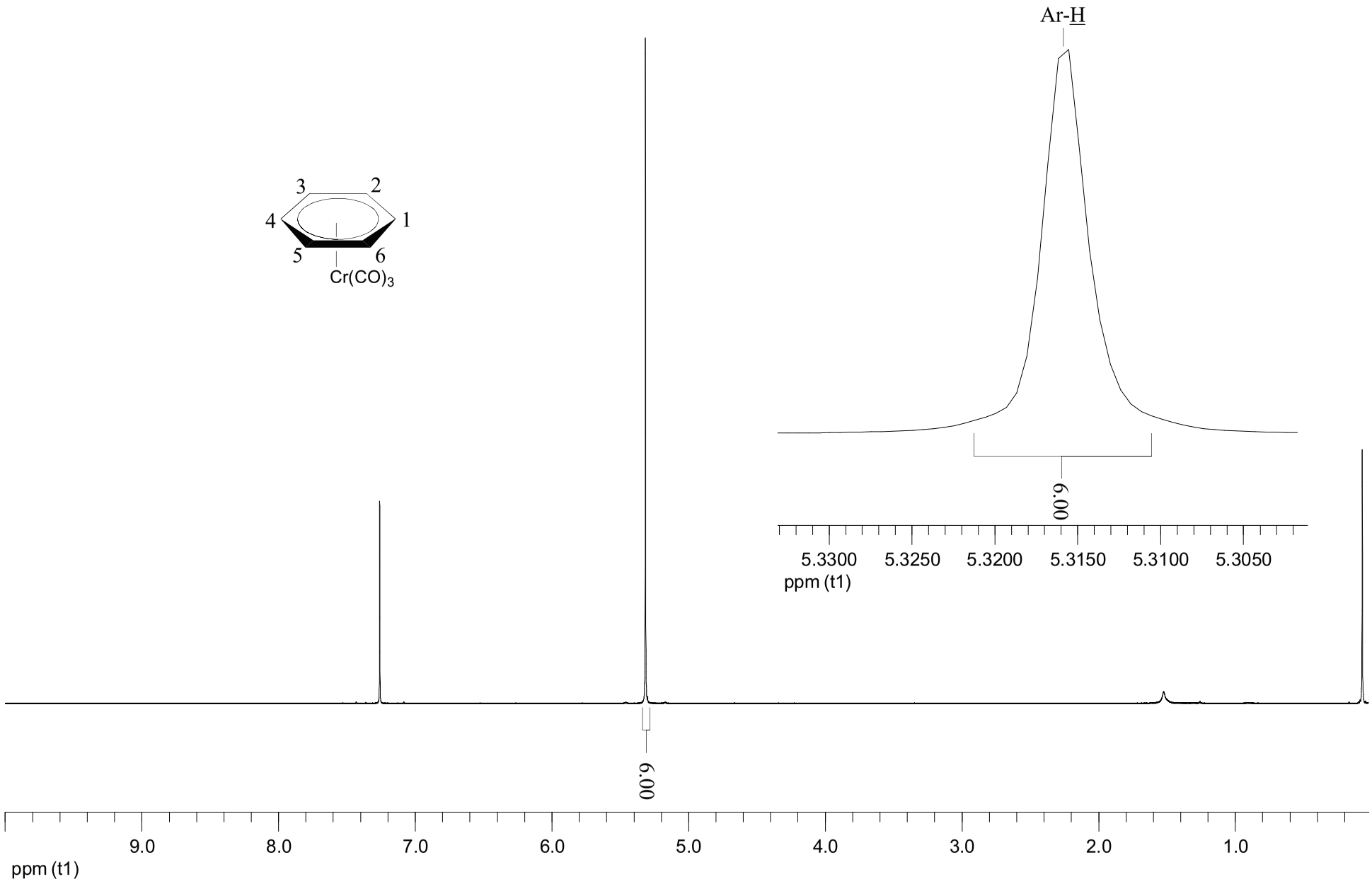


Plate 8b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(η^6-benzene)chromium(0) (**189a**)

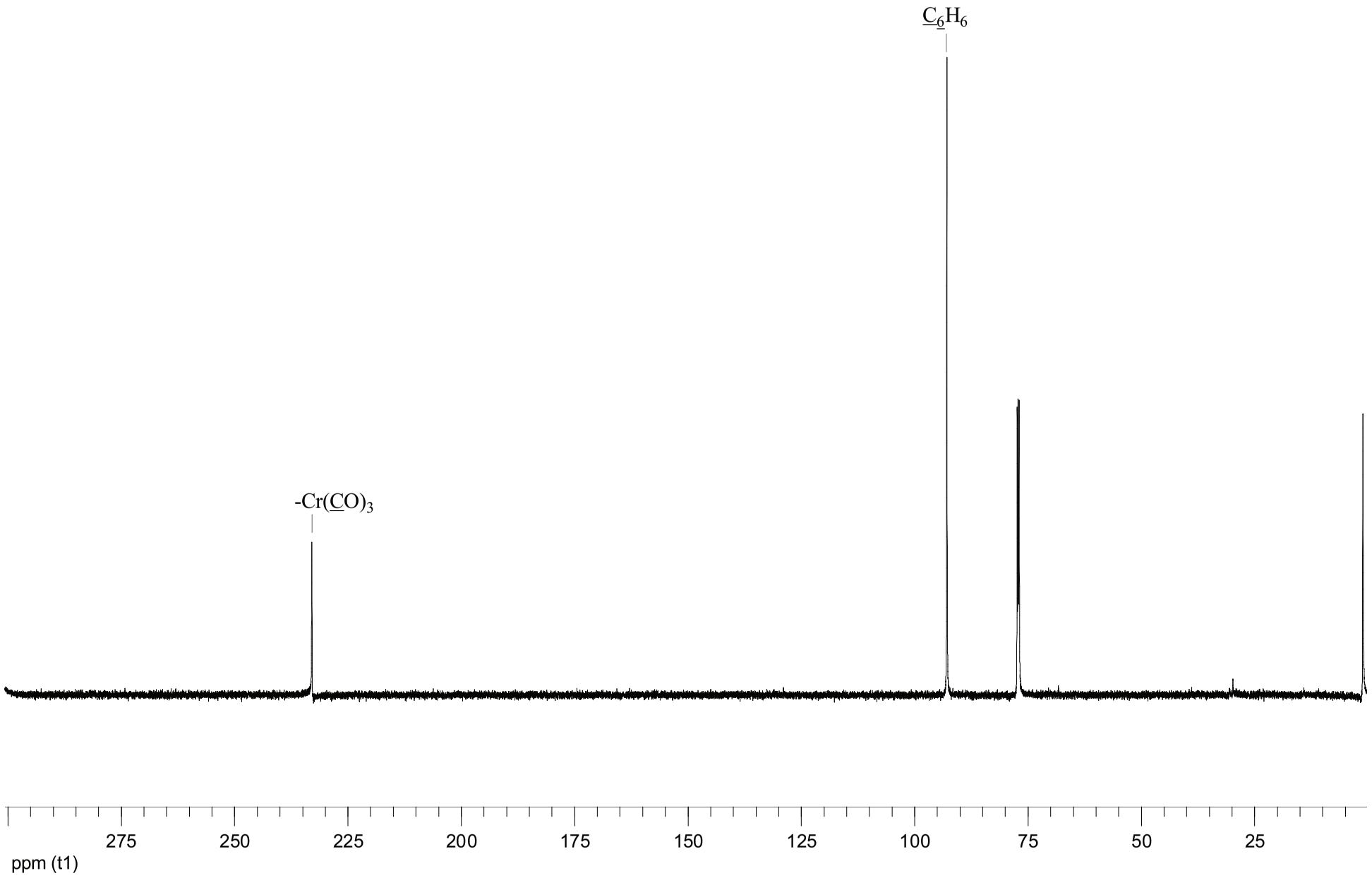


Plate 8c; HMQC NMR [$CDCl_3$]: Tricarbonyl(η^6-benzene)chromium(0) (**189a**)

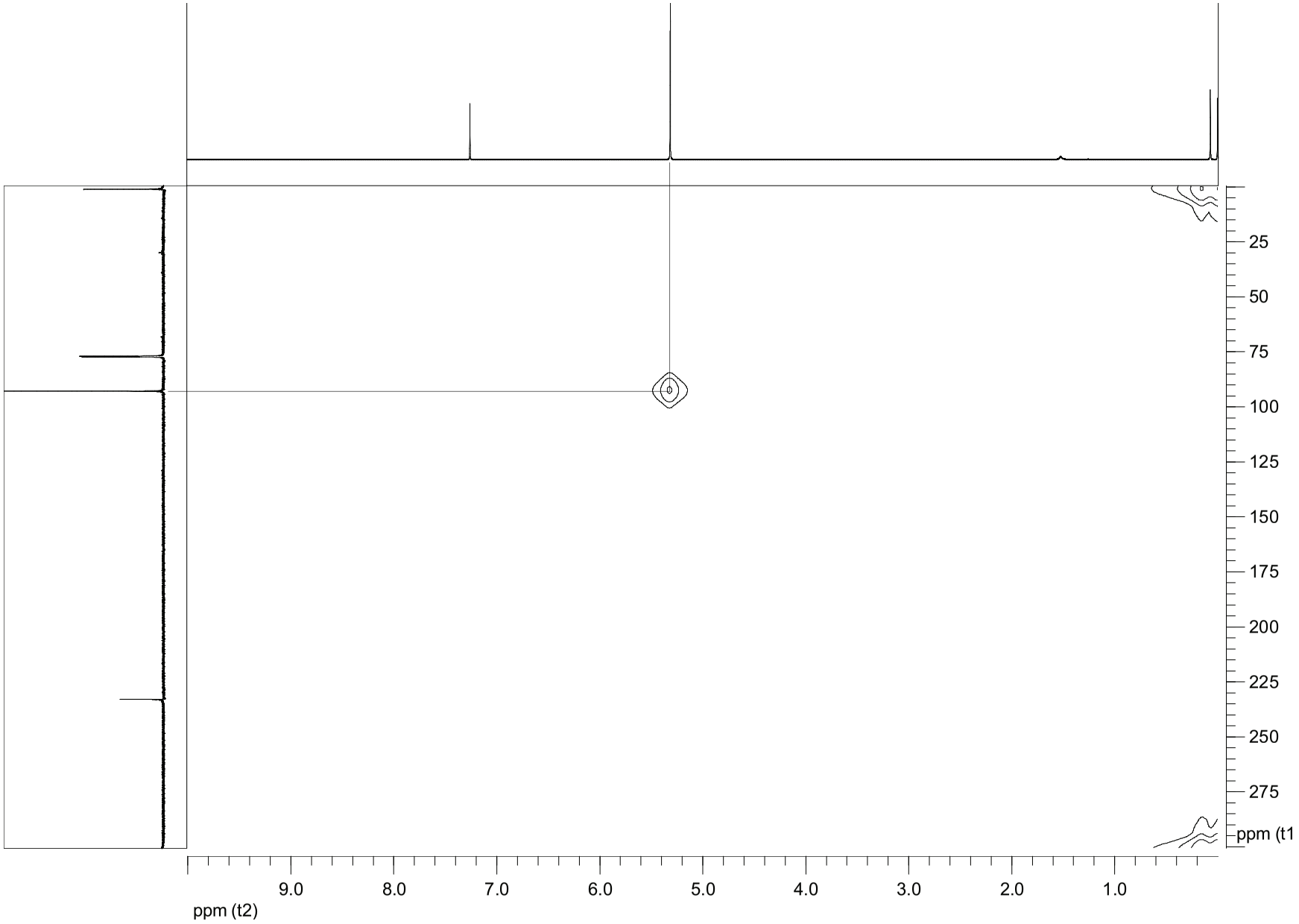


Plate 9a; ^{1}H NMR [$CDCl_3$]: Toluene (**191**)

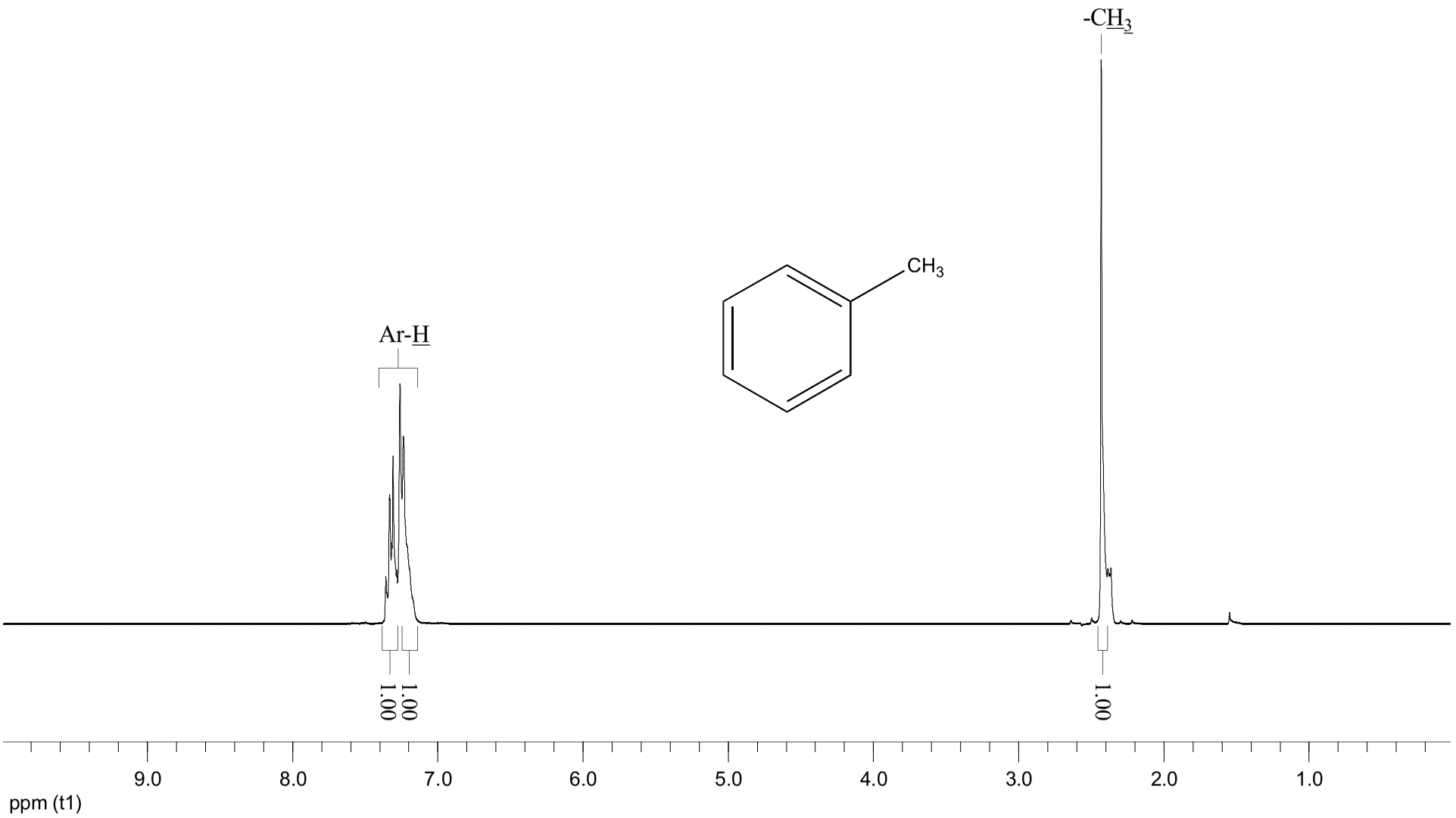


Plate 9b; ^{13}C NMR [$CDCl_3$]: Toluene (**191**)

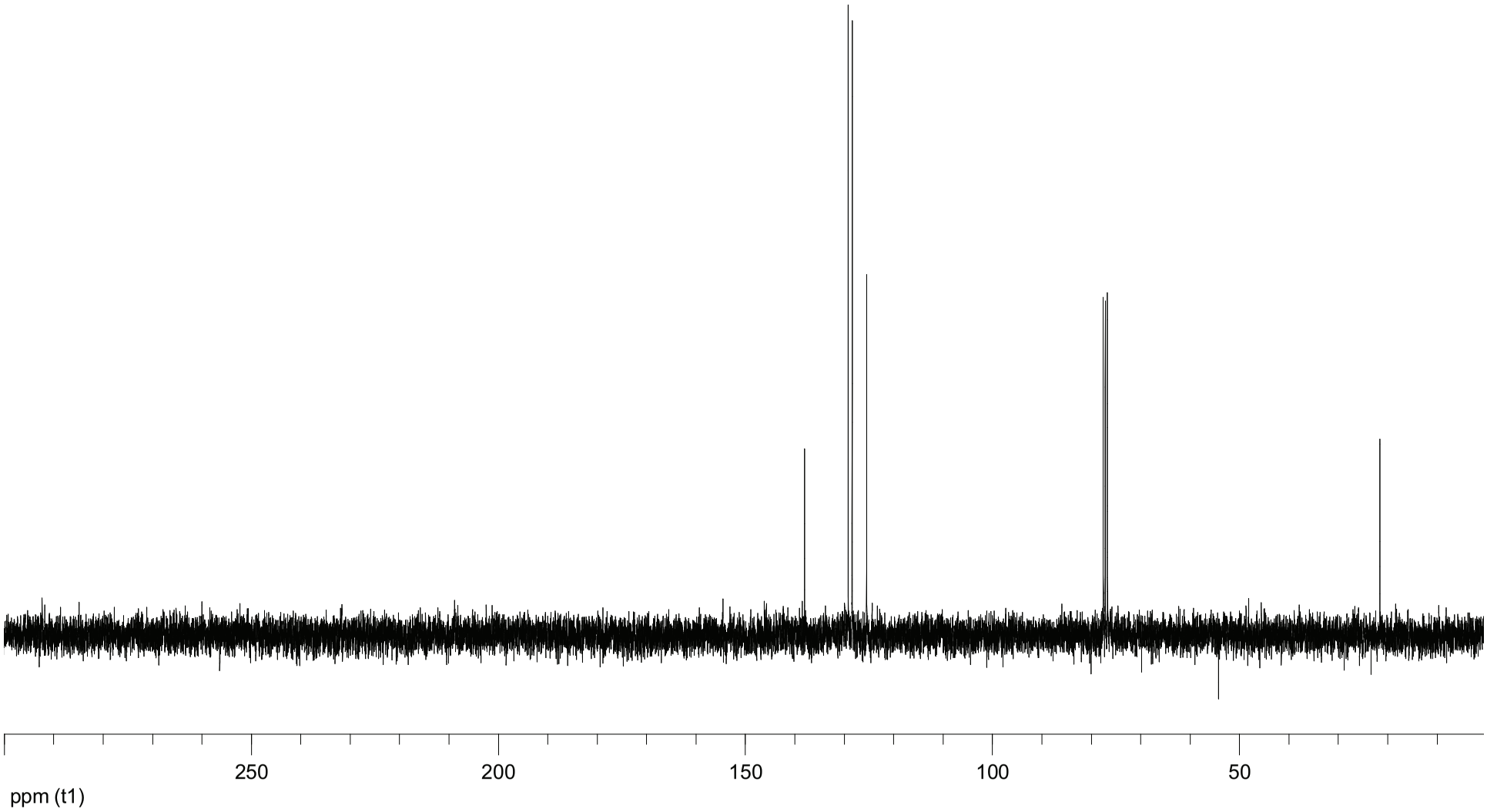


Plate 10a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(η^6-toluene)chromium(0) (**191a**)

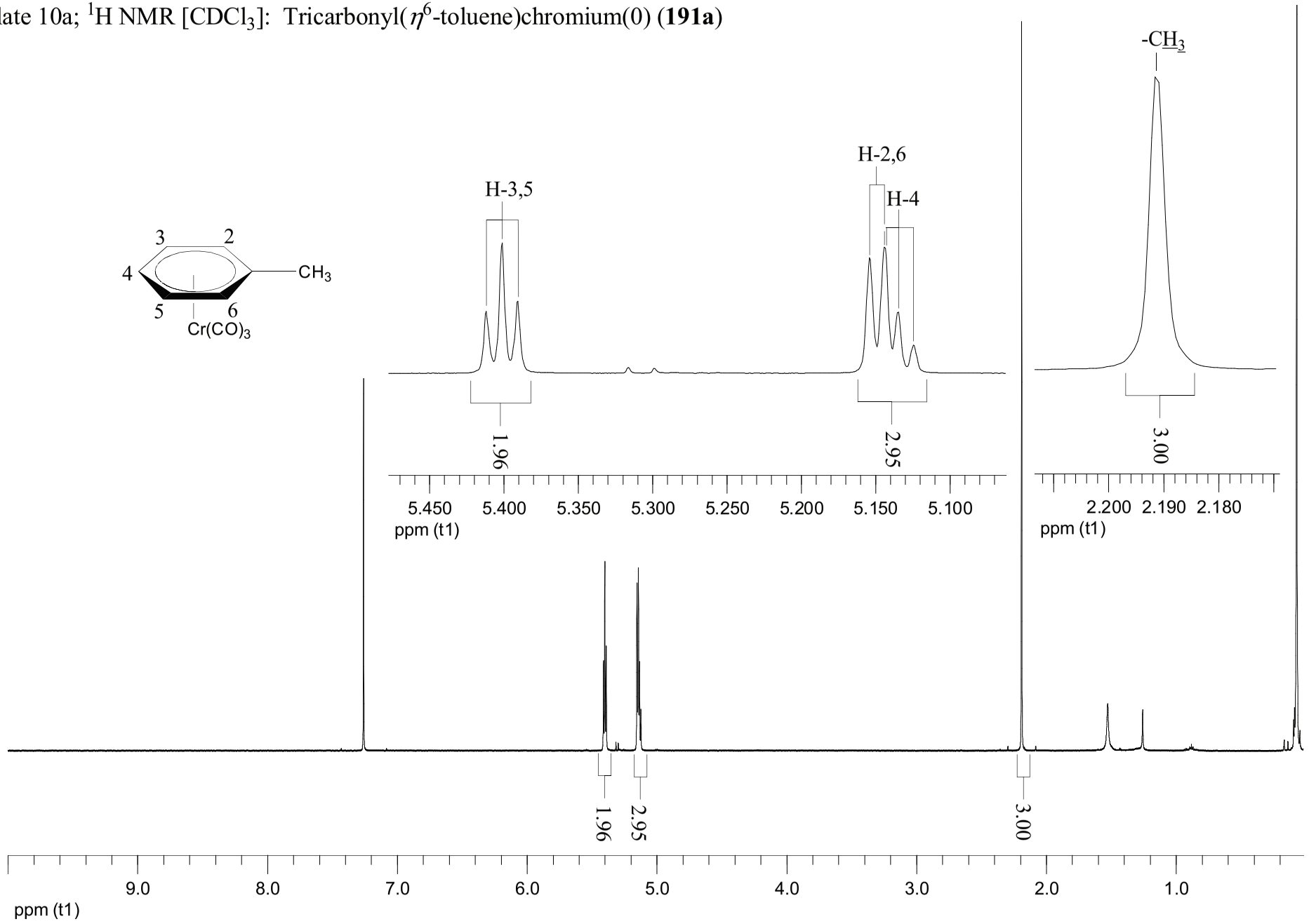


Plate 10b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(η^6-toluene)chromium(0) (**191a**)

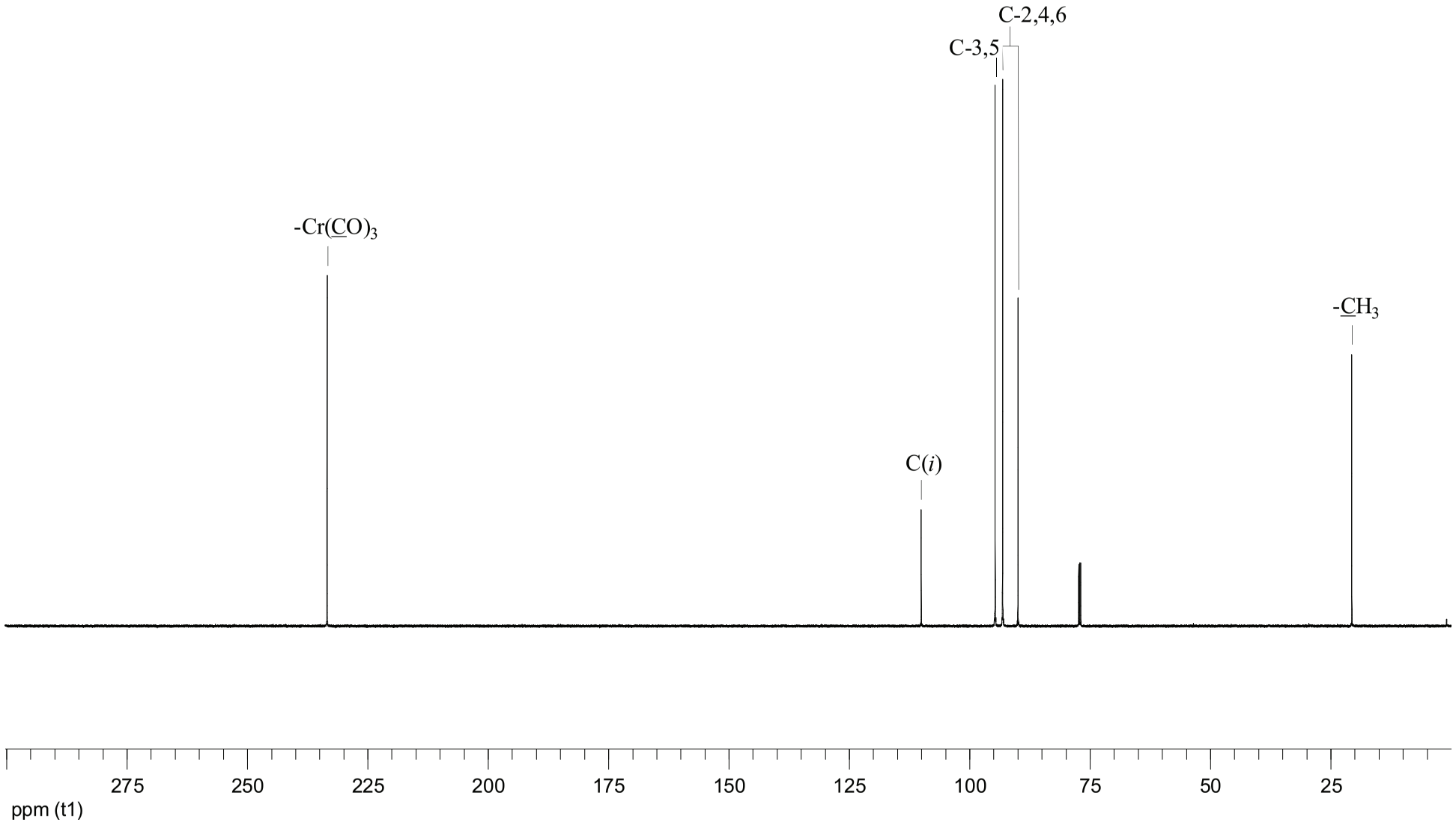


Plate 10c; HMQC NMR [$CDCl_3$]: Tricarbonyl(η^6-toluene)chromium(0) (**191a**)

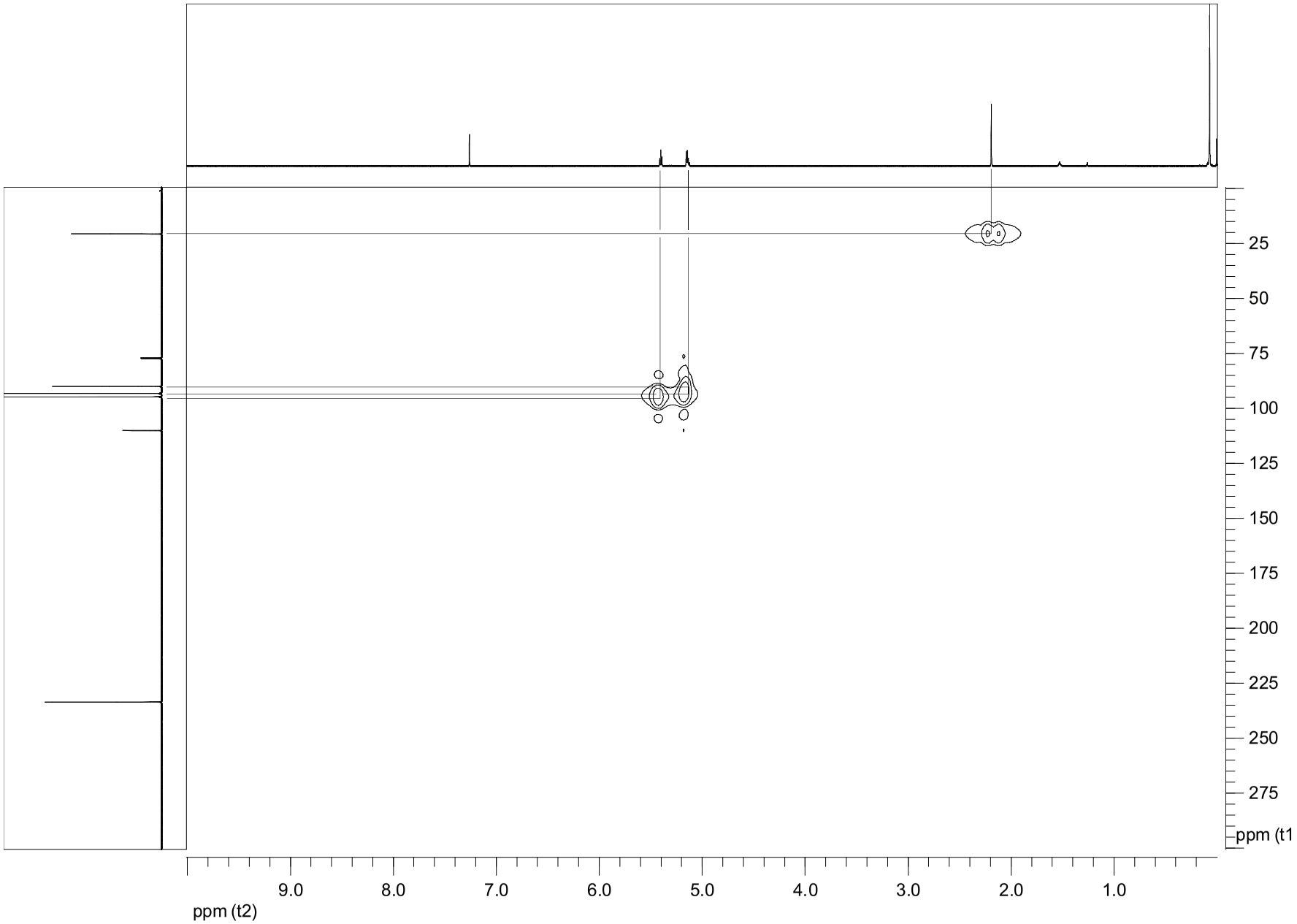


Plate 11a; ^{1}H NMR [$CDCl_3$]: Anisole (**192**)

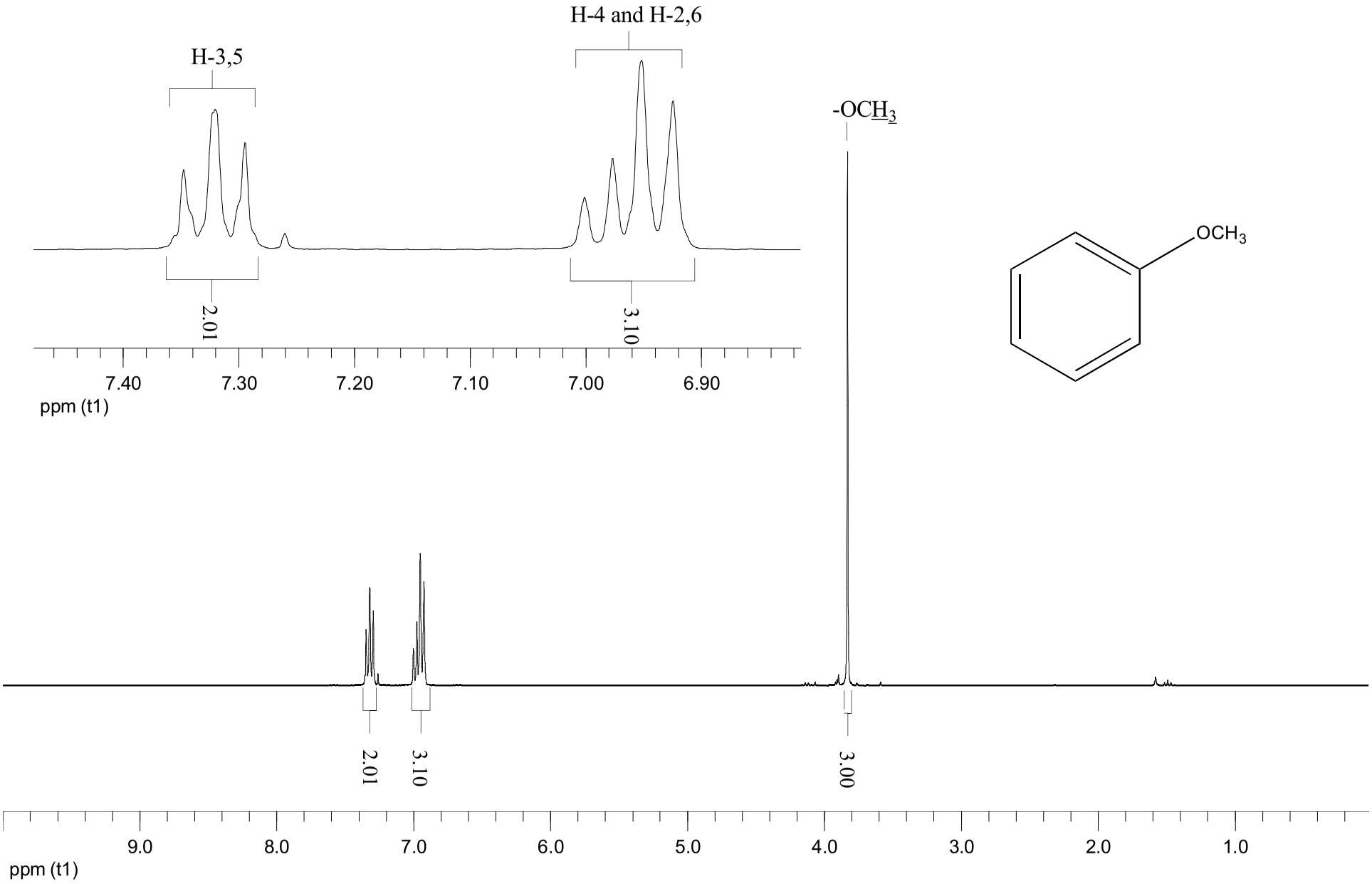


Plate 11b; ^{13}C NMR [$CDCl_3$]: Anisole (**192**)

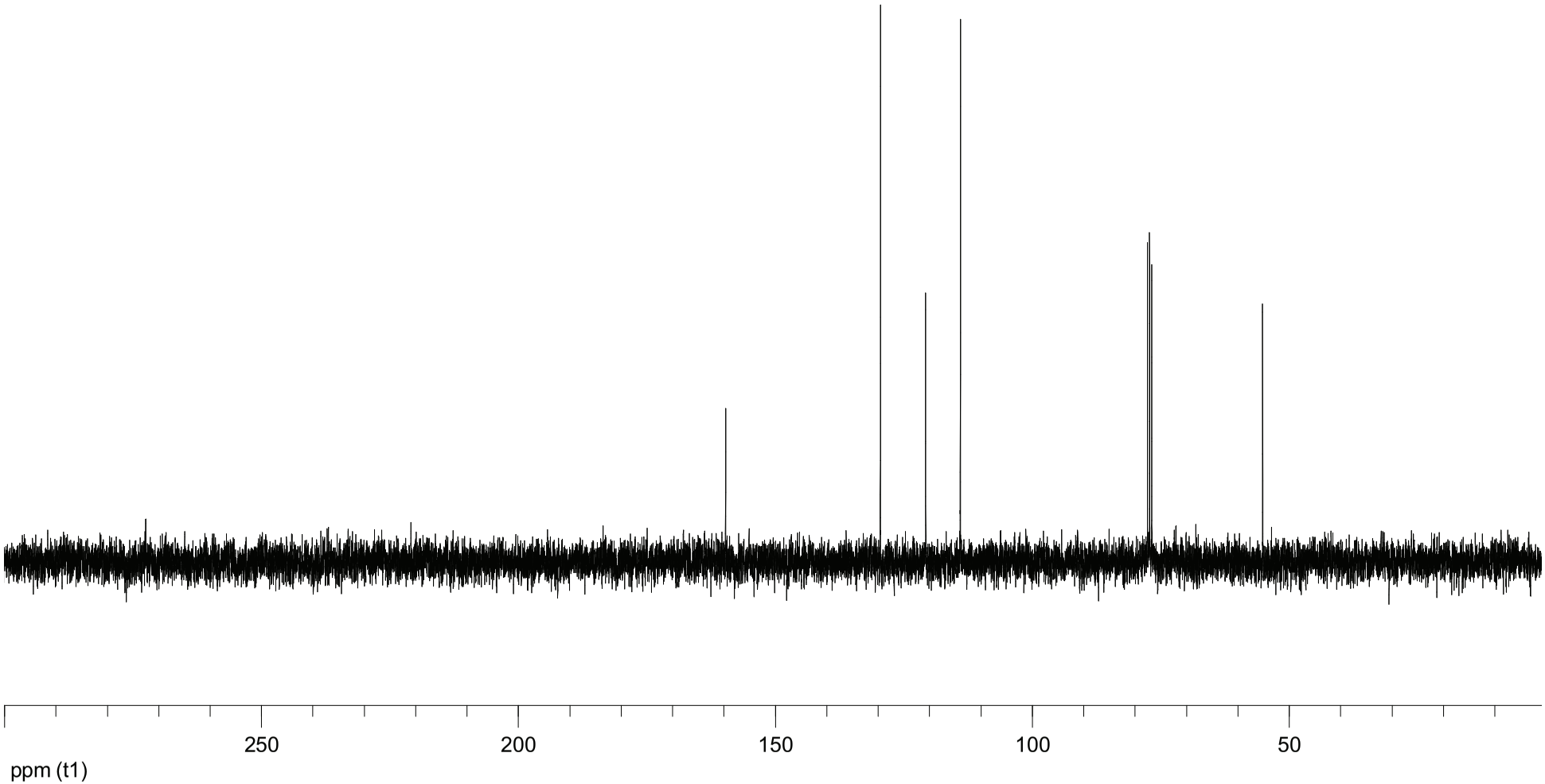


Plate 12a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(η^6-anisole)chromium(0) (**192a**)

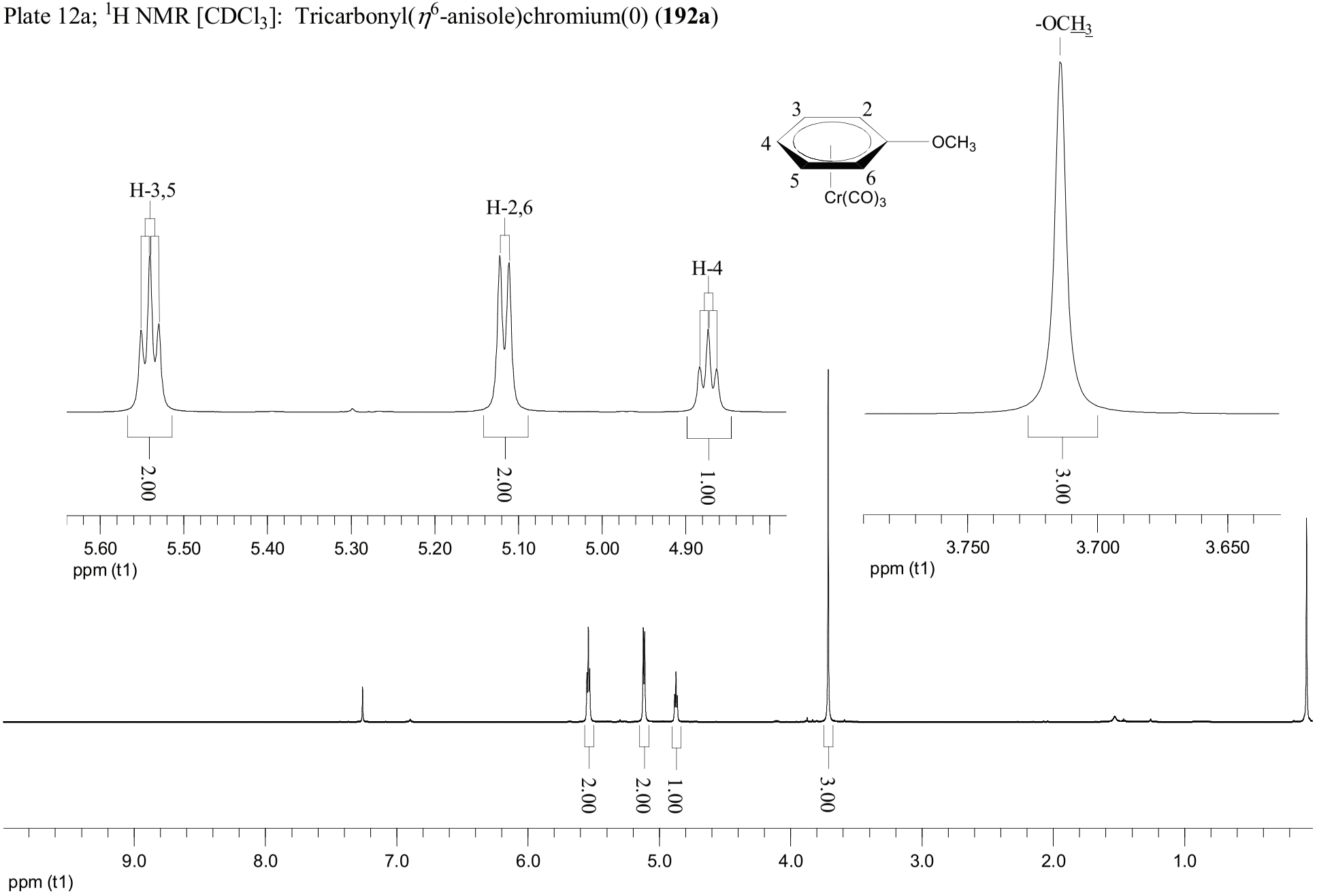


Plate 12b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(η^6-anisole)chromium(0) (**192a**)

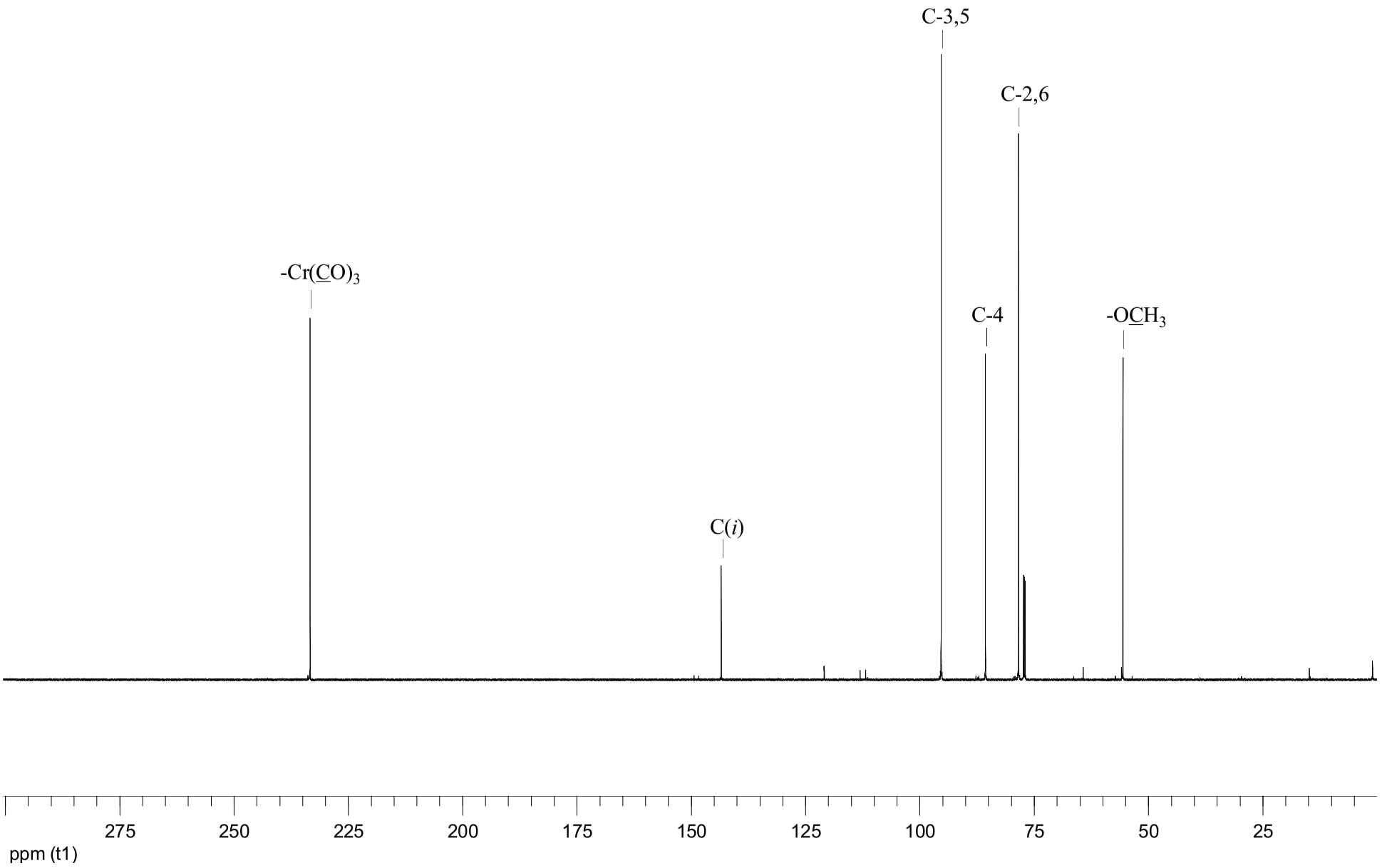


Plate 12c; HMQC NMR [$CDCl_3$]: Tricarbonyl(η^6-anisole)chromium(0) (**192a**)

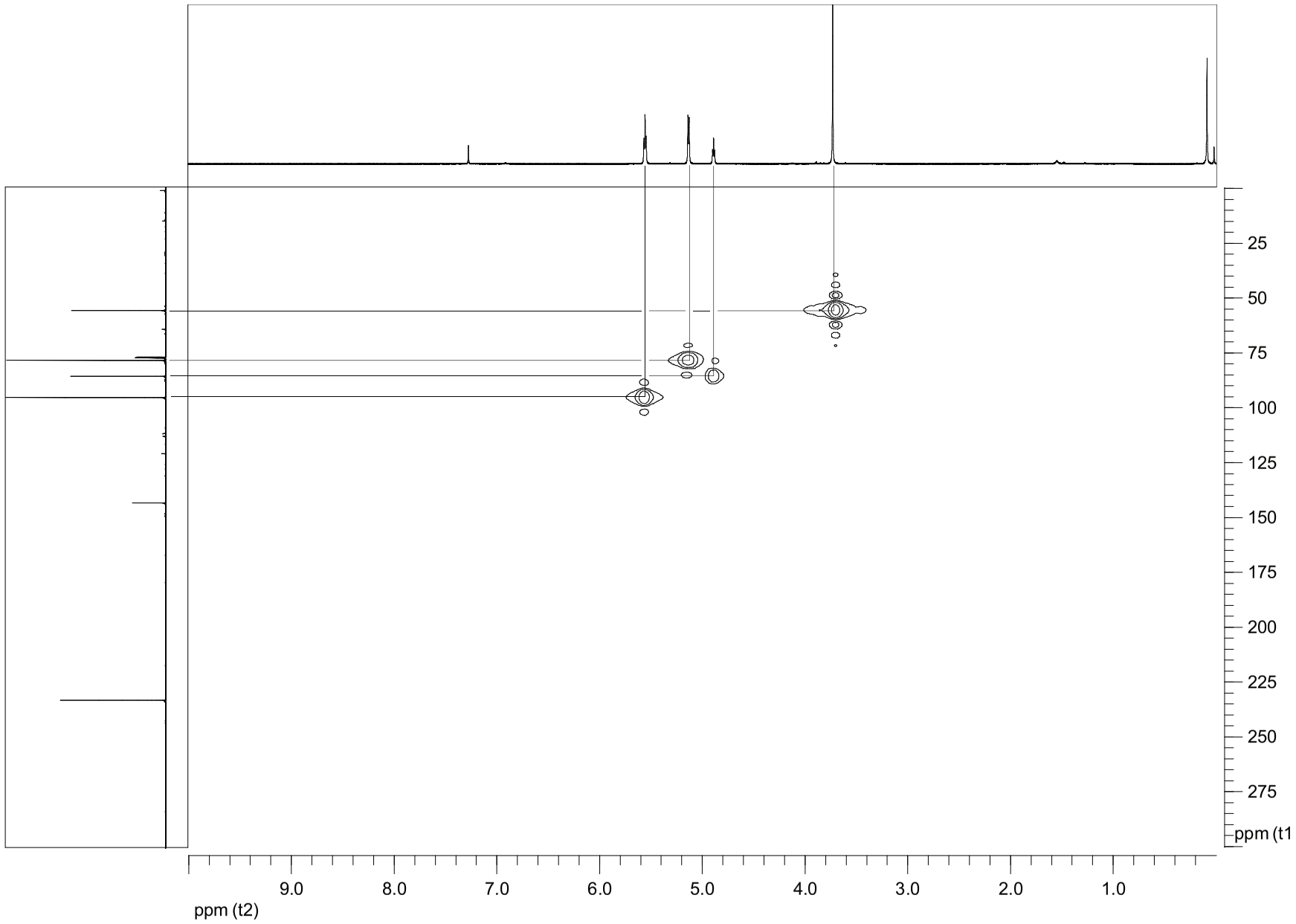


Plate 13a; ^{1}H NMR [$CDCl_3$]: Chlorobenzene (**190**)

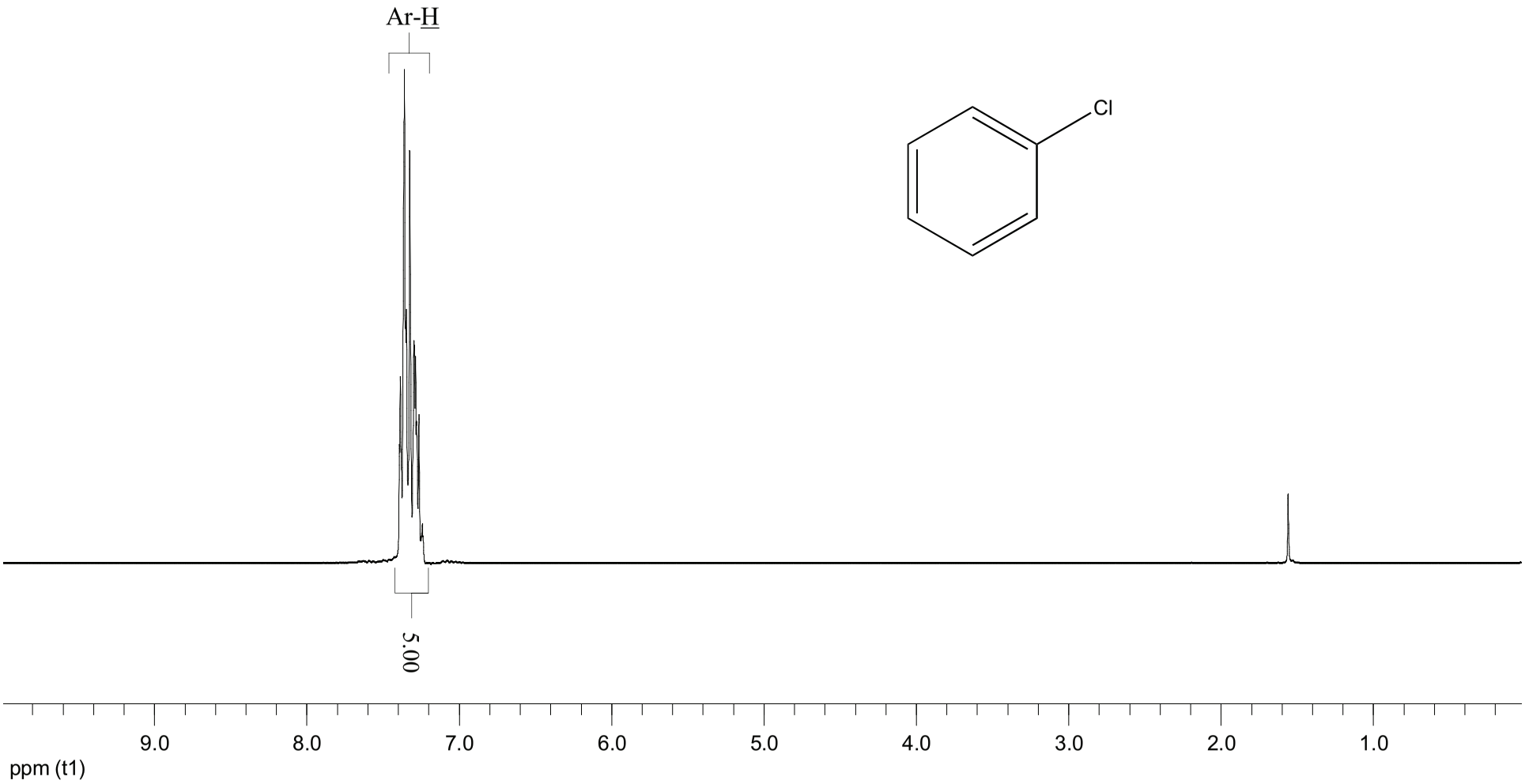


Plate 13b; ^{13}C NMR [$CDCl_3$]: Chlorobenzene (**190**)

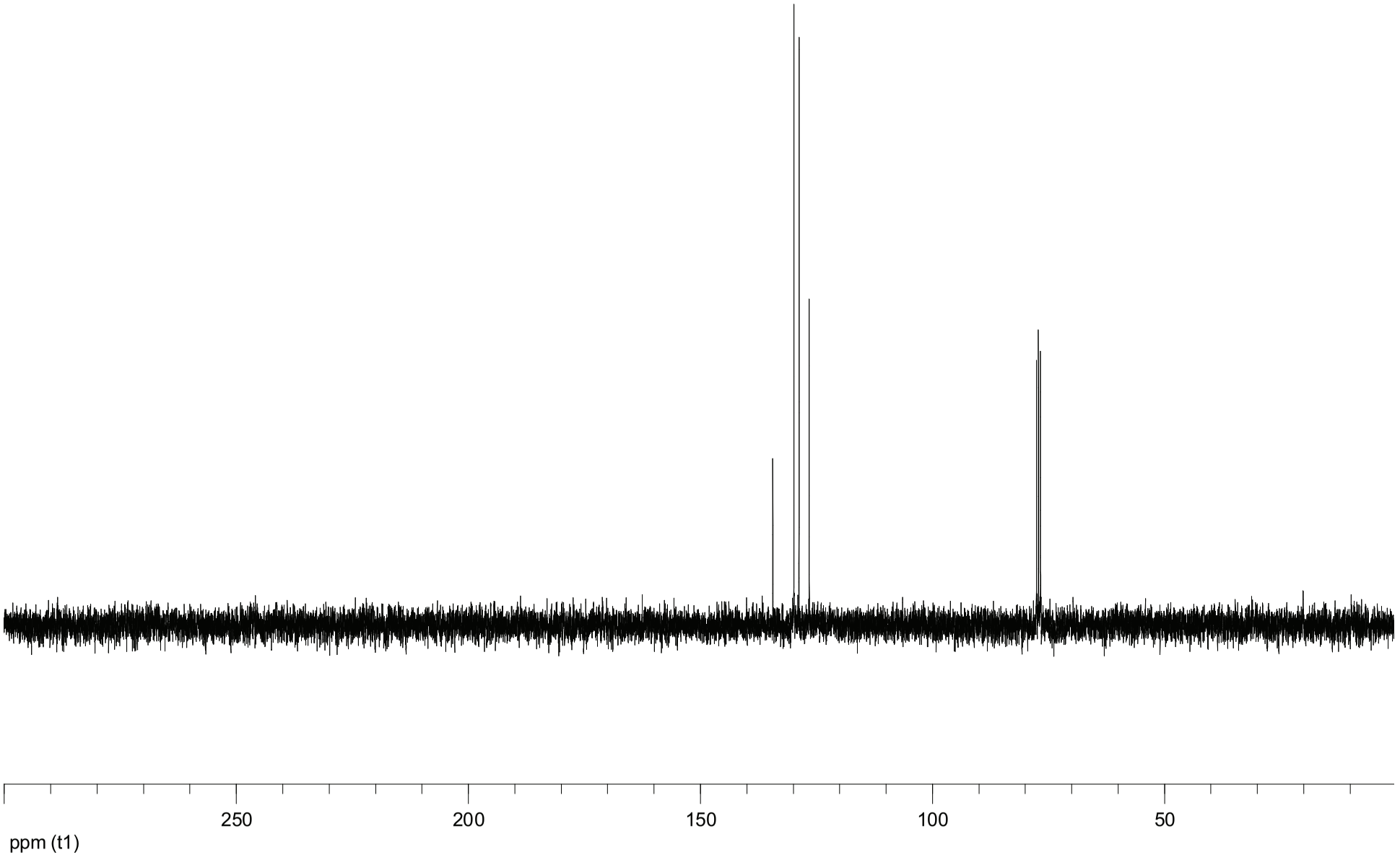


Plate 14a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(η^6-chlorobenzene)chromium(0) (**190a**)

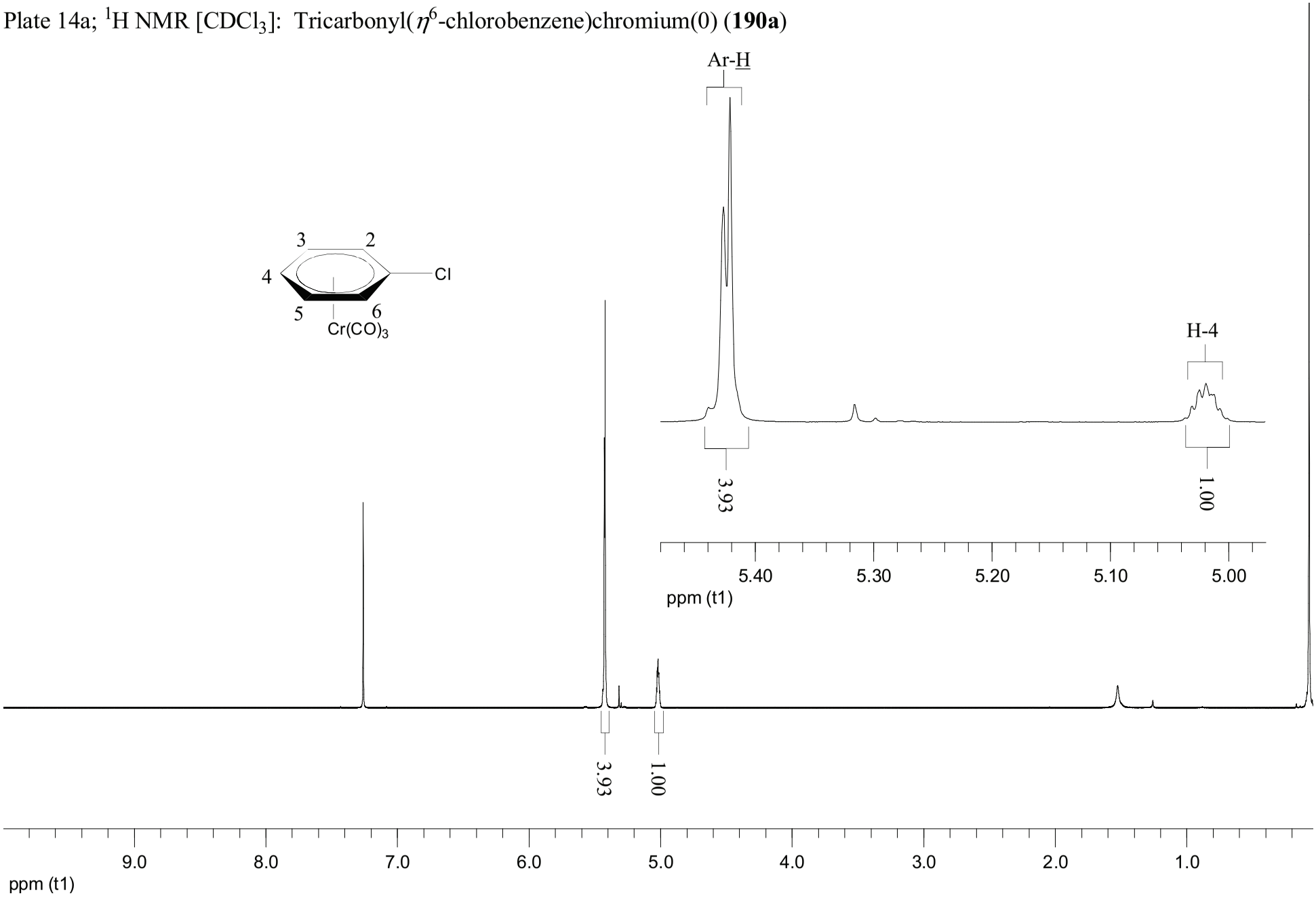


Plate 14b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(η^6-chlorobenzene)chromium(0) (**190a**)

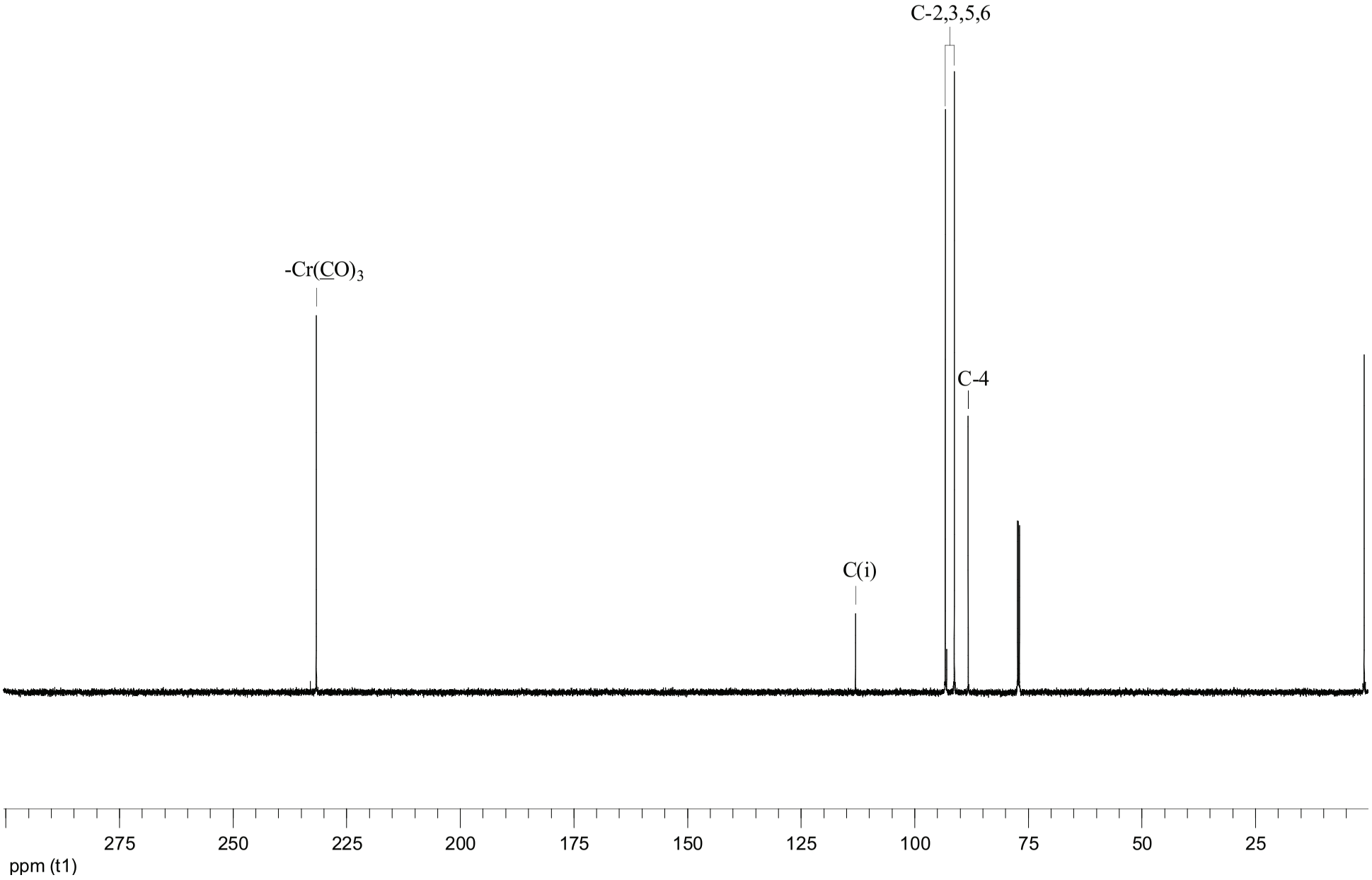


Plate 14c; HMQC NMR [$CDCl_3$]: Tricarbonyl(η^6-chlorobenzene)chromium(0) (**190a**)

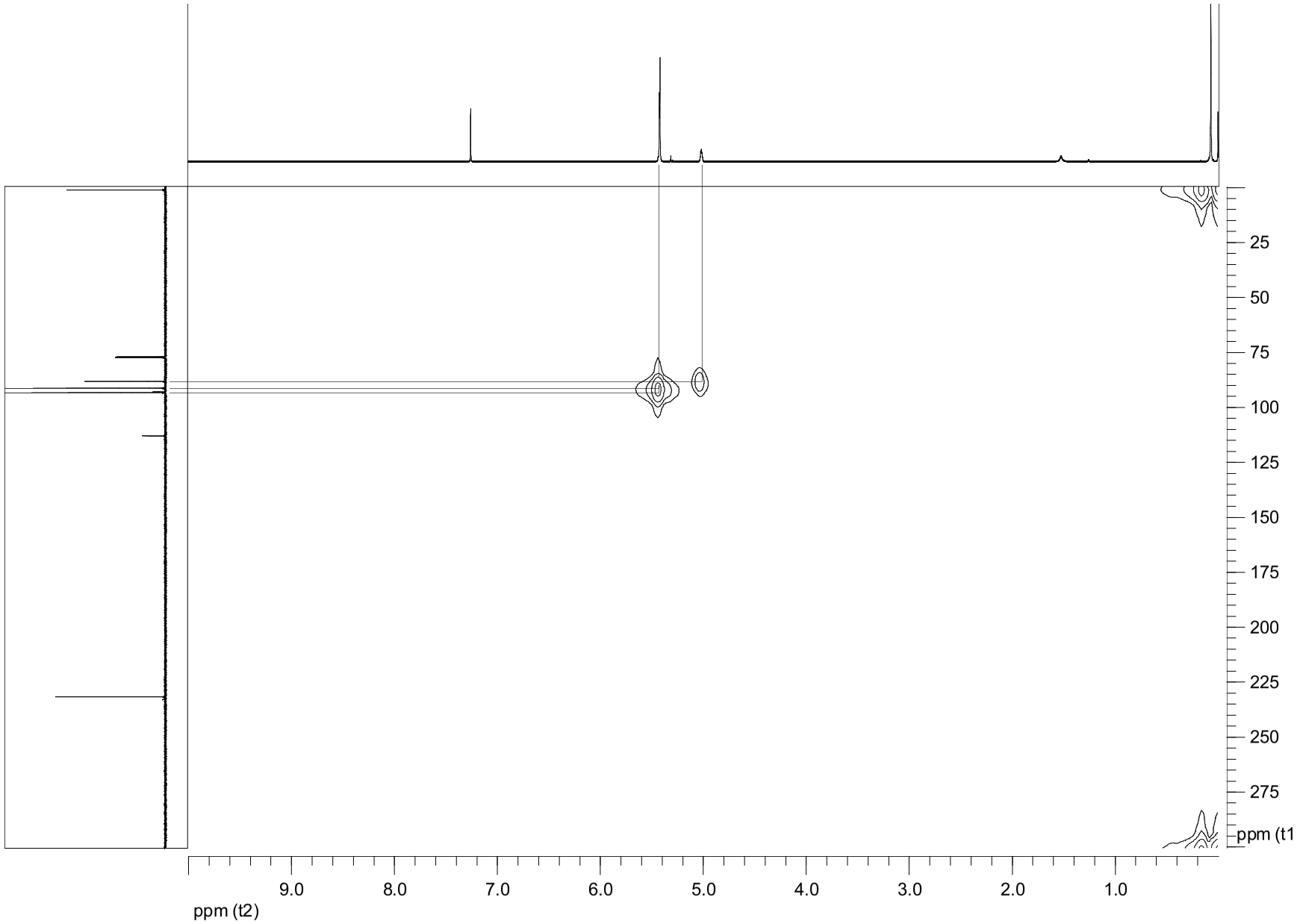


Plate 15a; ^{1}H NMR [$CDCl_3$]: Acetophenone (**193**)

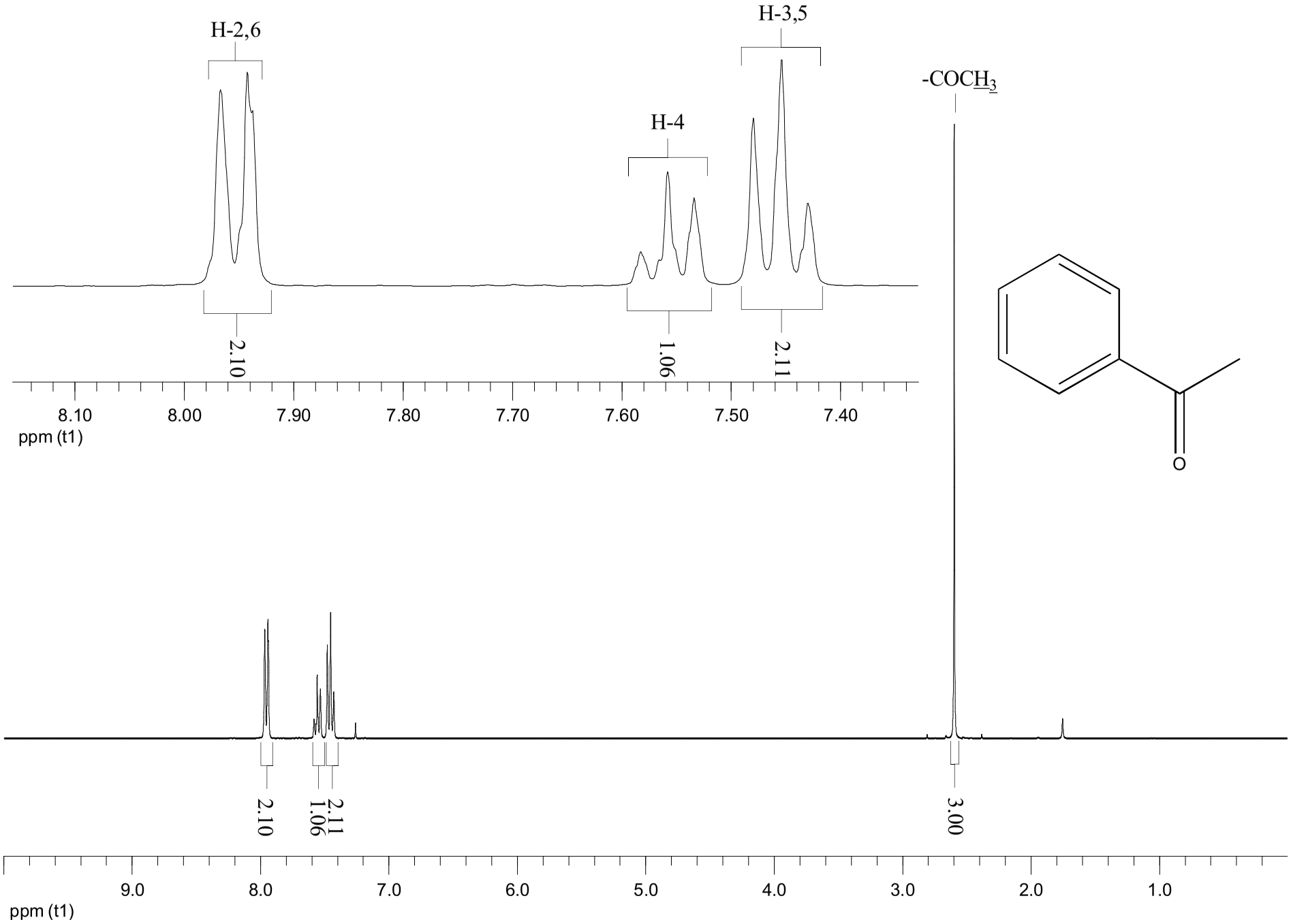


Plate 15b; ^{13}C NMR [$CDCl_3$]: Acetophenone (**193**)

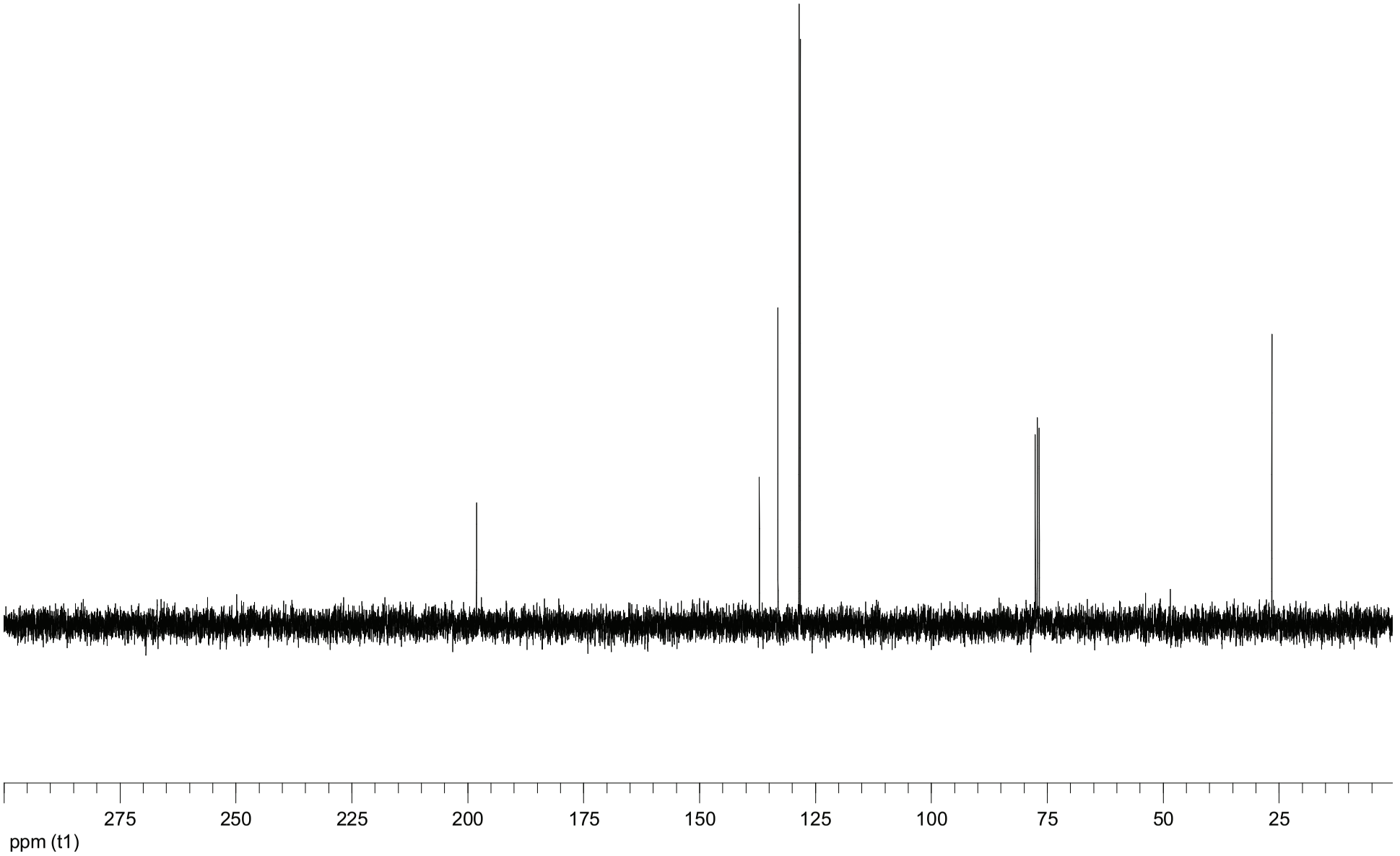


Plate 16a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(η^6-acetophenone)chromium(0) (**193a**)

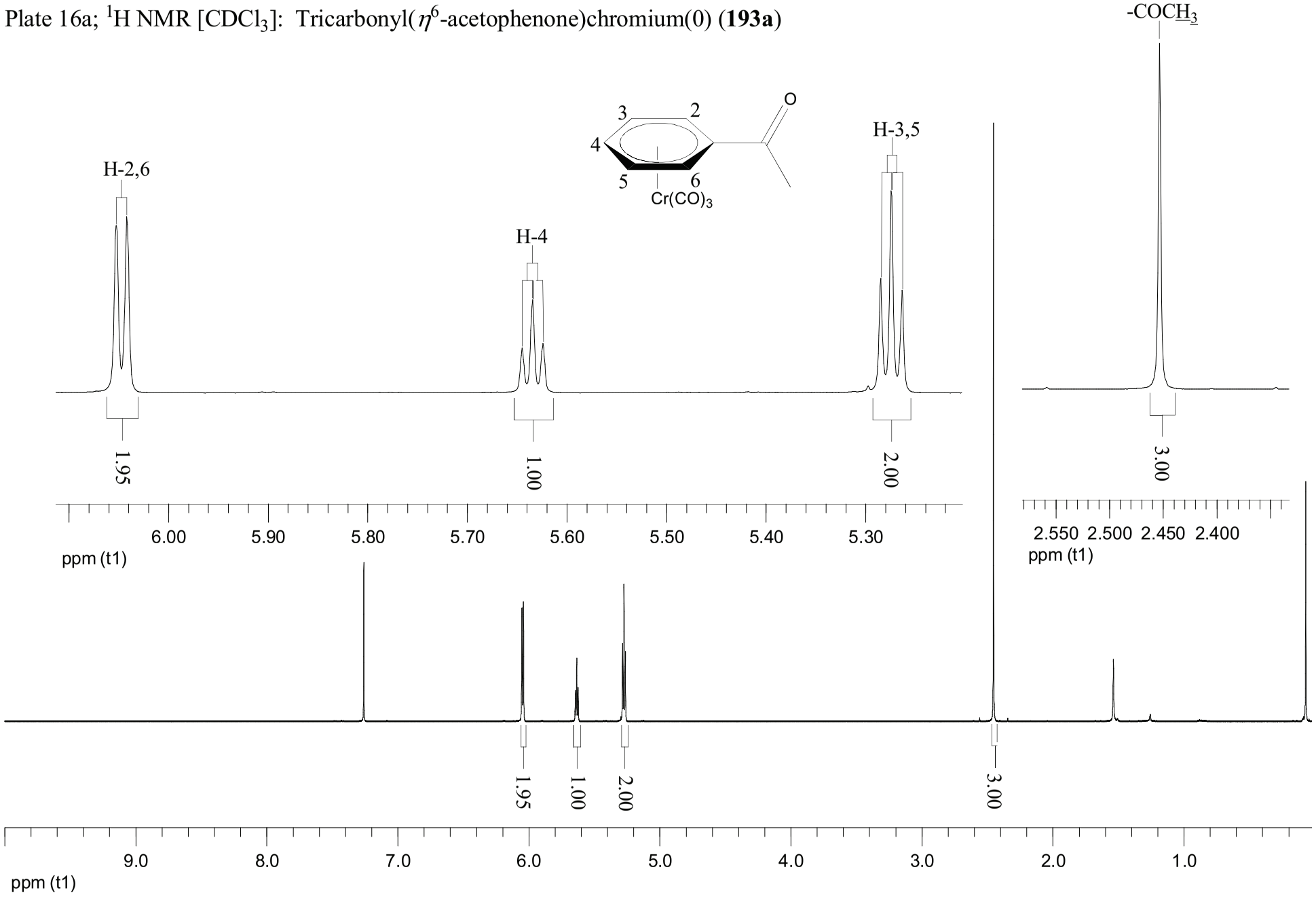


Plate 16b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(η^6-acetophenone)chromium(0) (**193a**)

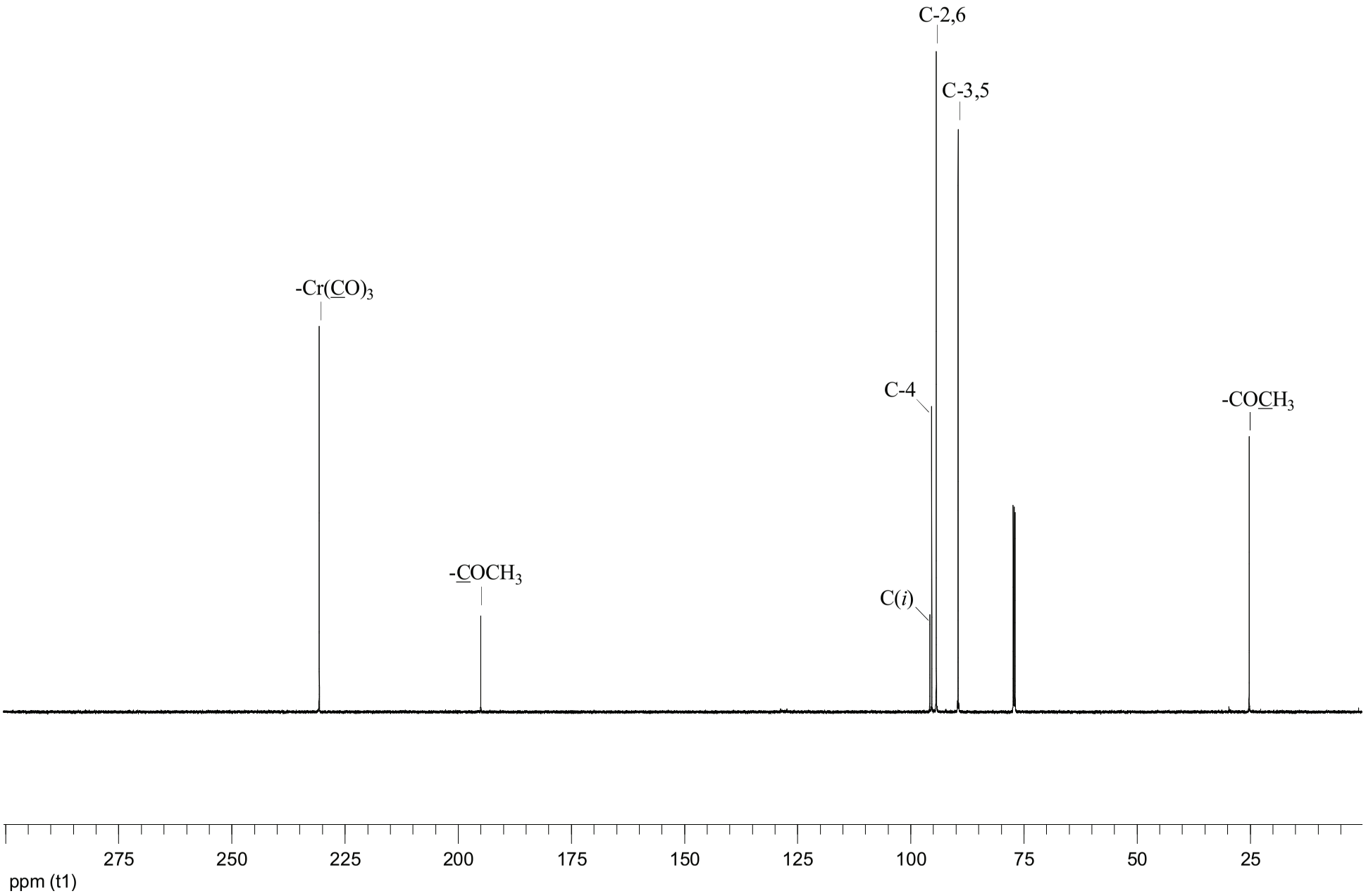


Plate 16c; HMQC NMR [$CDCl_3$]: Tricarbonyl(η^6-acetophenone)chromium(0) (**193a**)

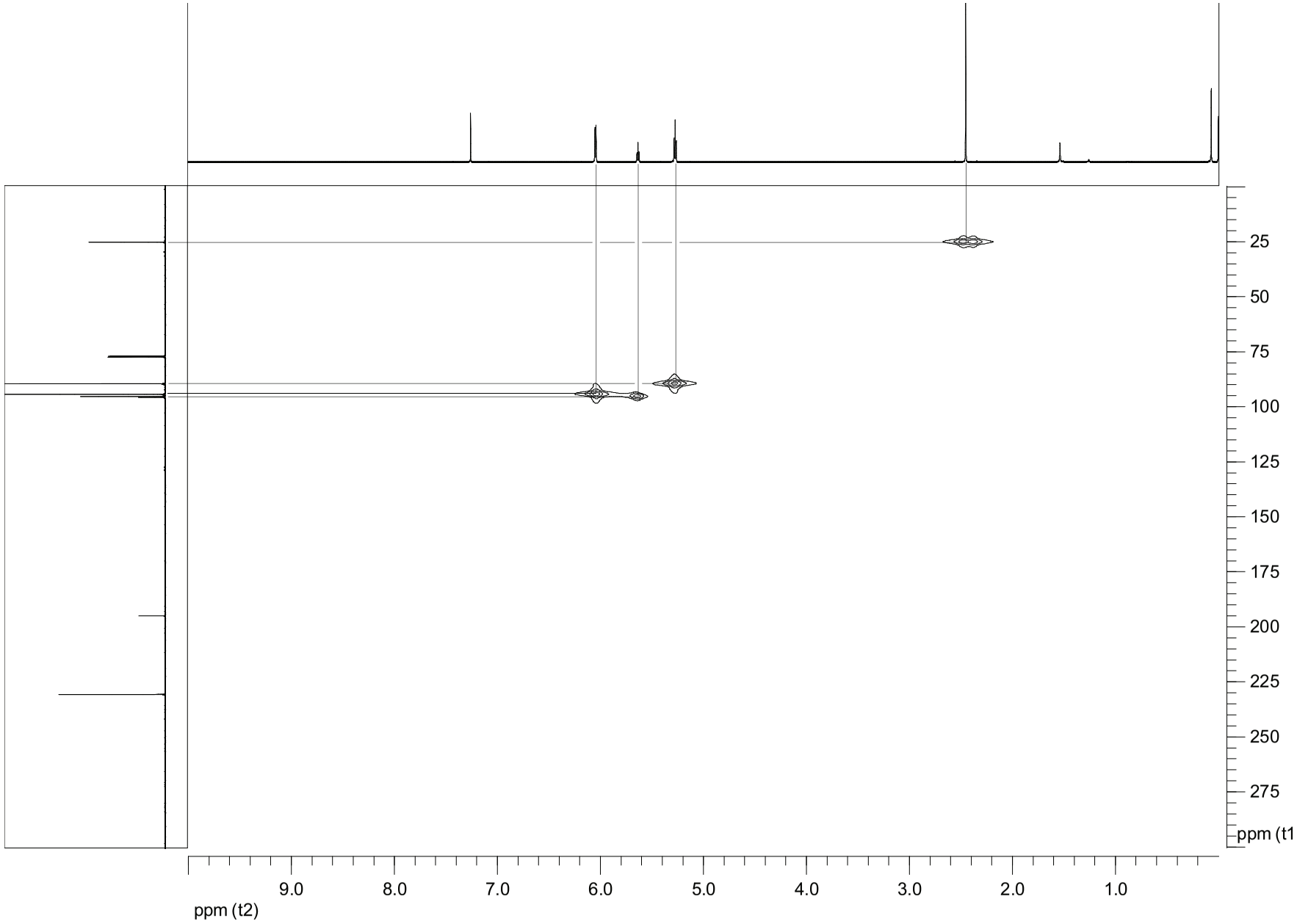


Plate 17a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(η^6-chroman-4-one)chromium(0) (**180a**)

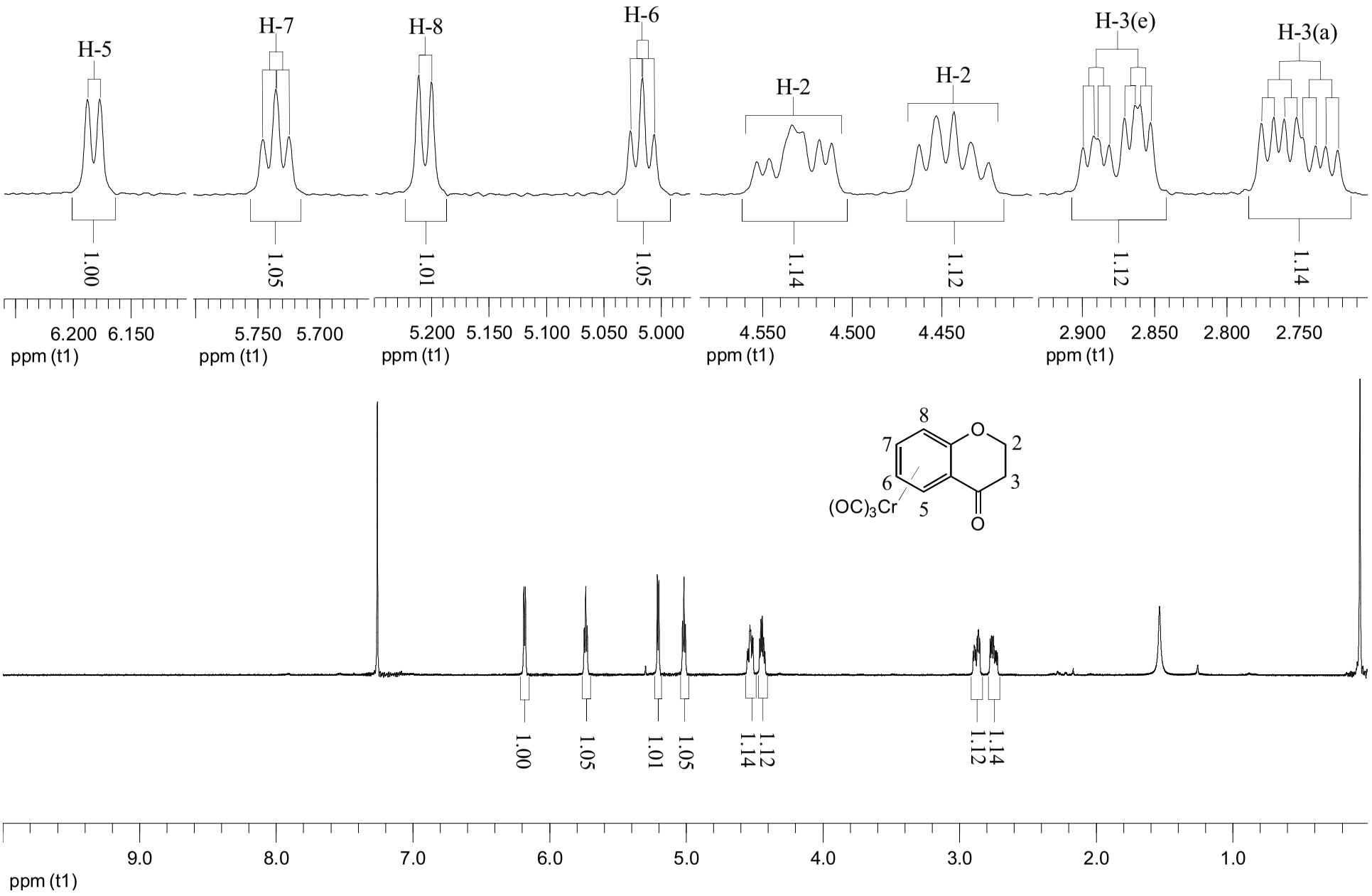


Plate 17b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(η^6-chroman-4-one)chromium(0) (**180a**)

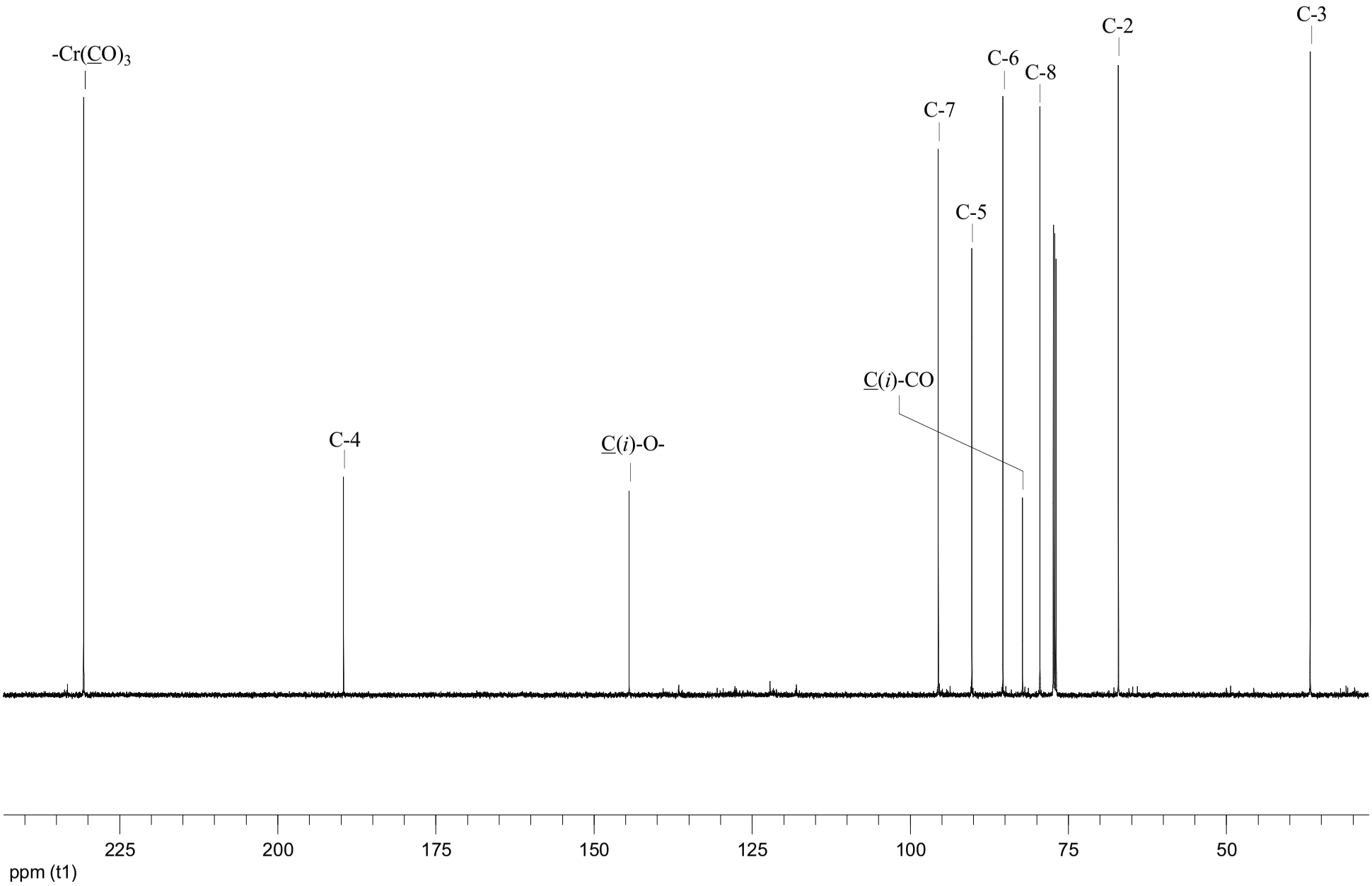


Plate 17c; HMQC NMR [$CDCl_3$]: Tricarbonyl(η^6-chroman-4-one)chromium(0) (**180a**)

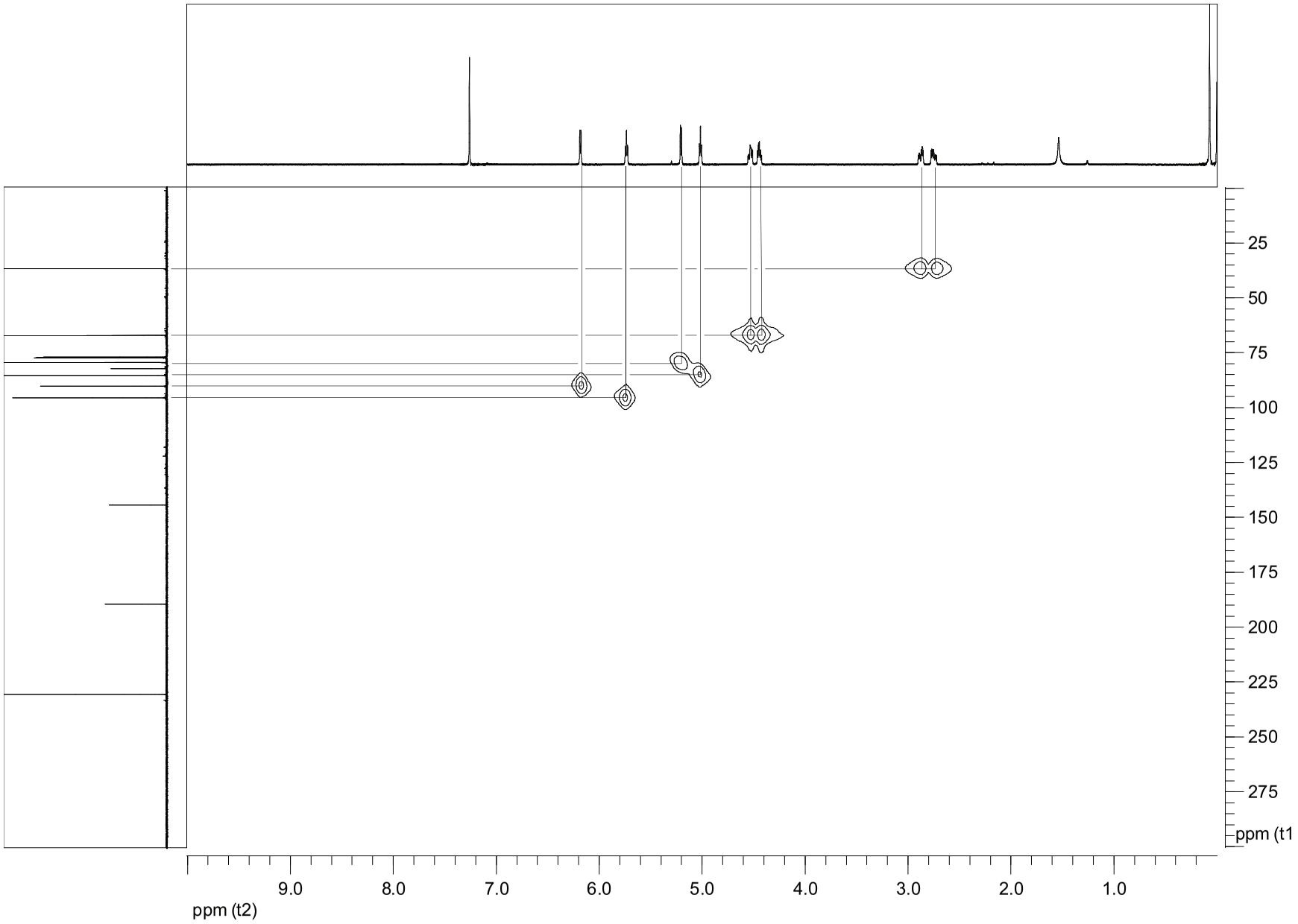


Plate 18a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(B-η^6-4',7-dimethoxyisoflavone)chromium(0) (**56a**)

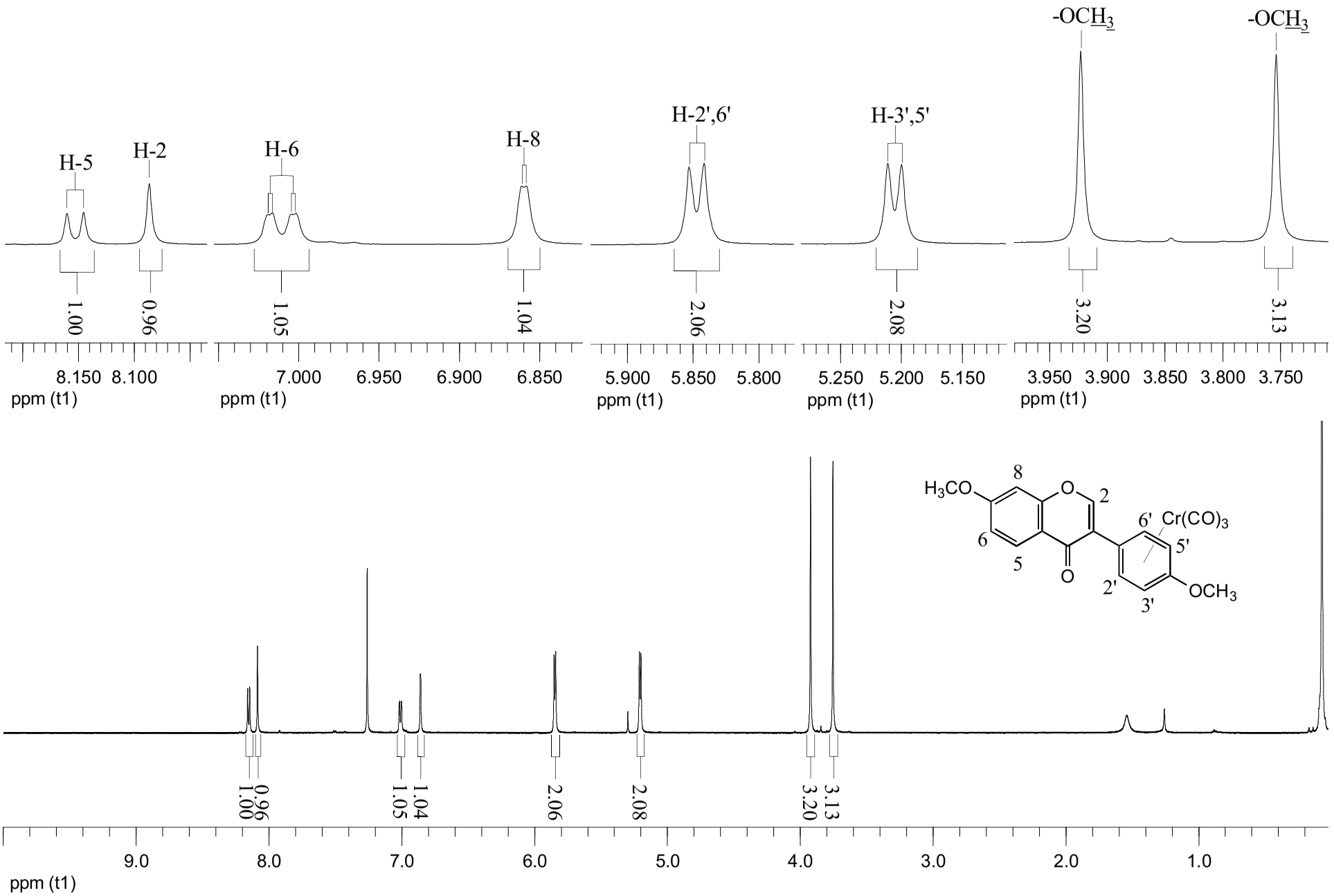


Plate 18b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(B-η^6-4',7-dimethoxyisoflavone)chromium(0) (**56a**)

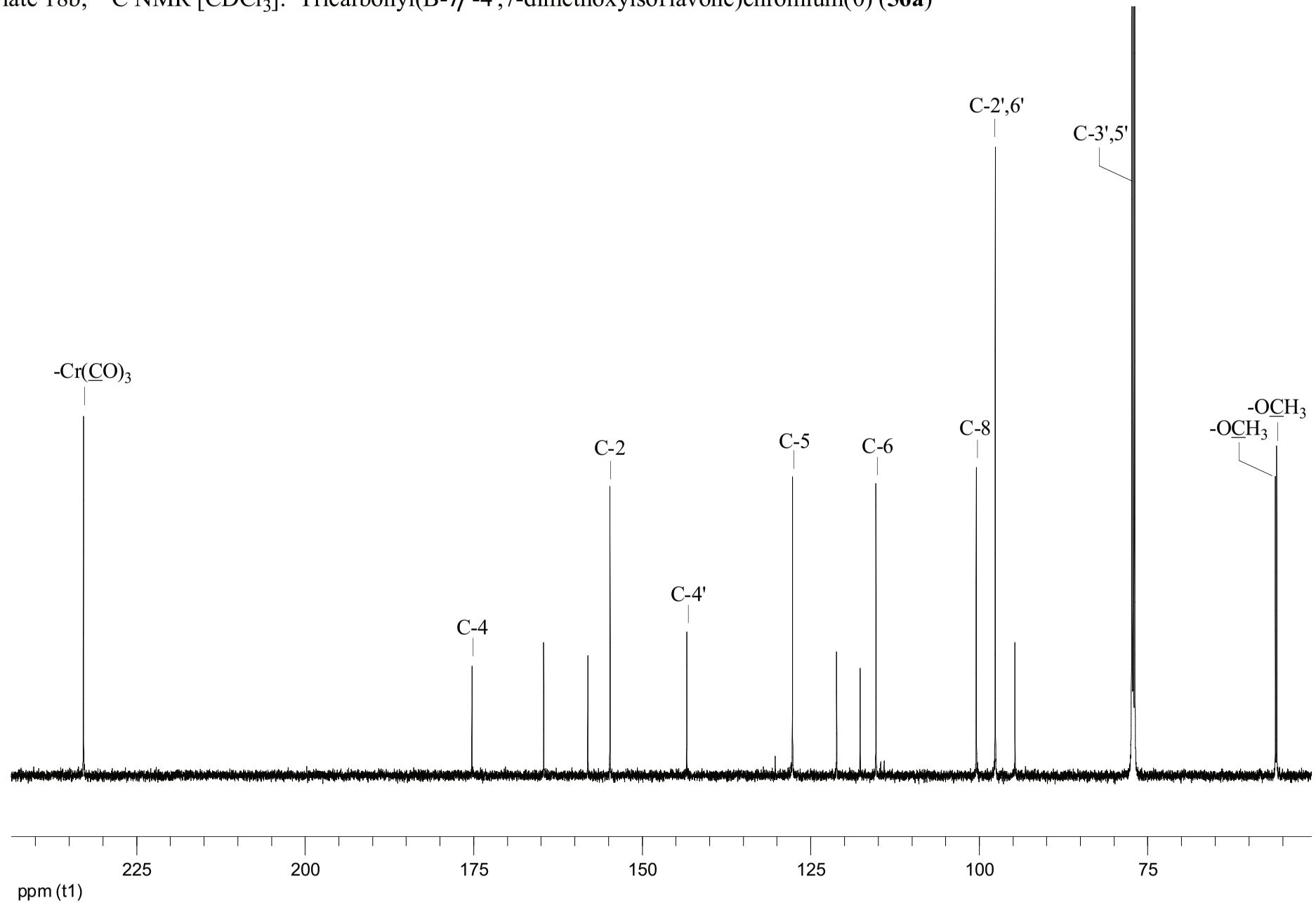


Plate 18c; HMQC NMR [$CDCl_3$]: Tricarbonyl(B-η^6-4',7-dimethoxyisoflavone)chromium(0) (**56a**)

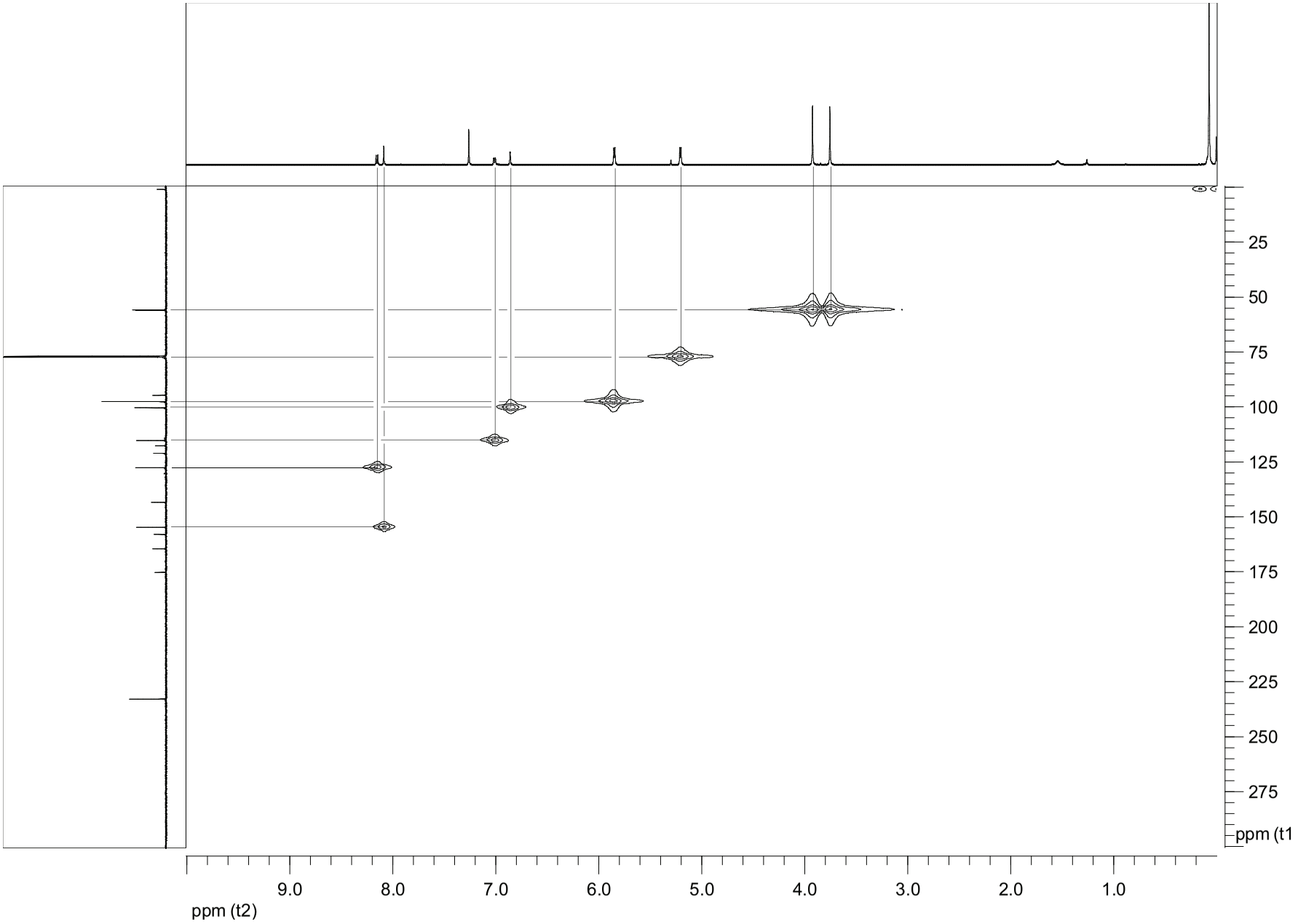
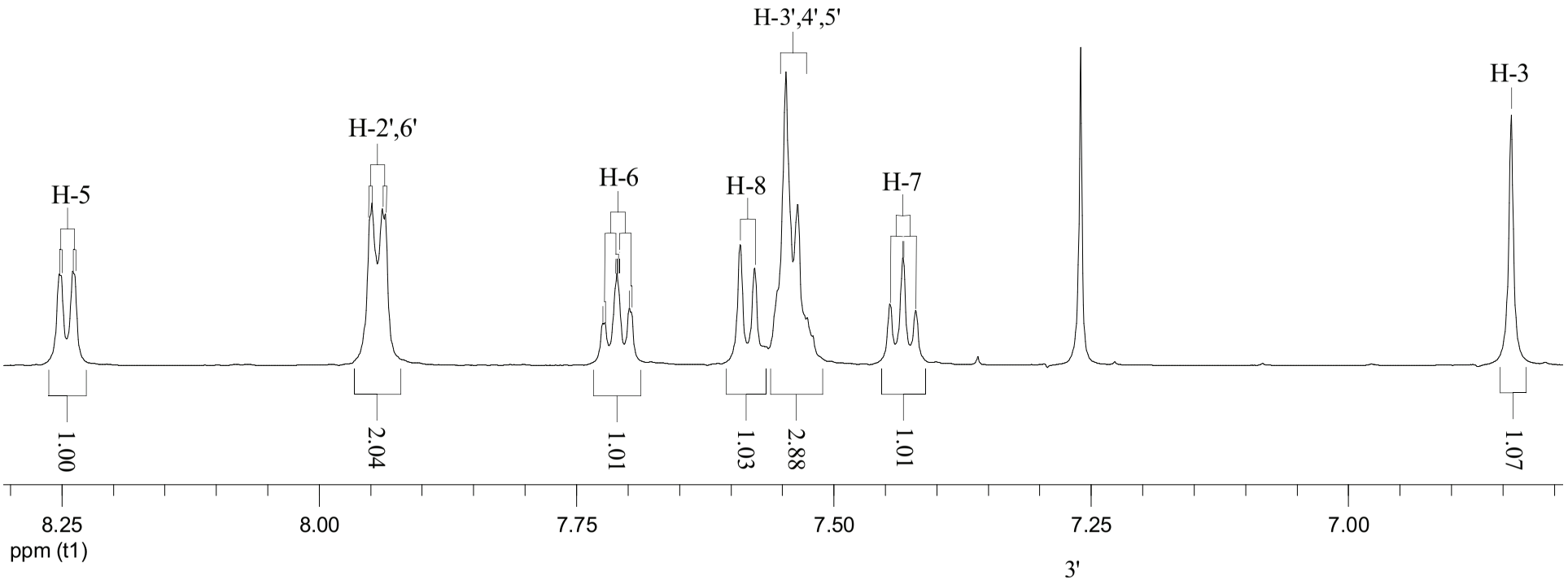
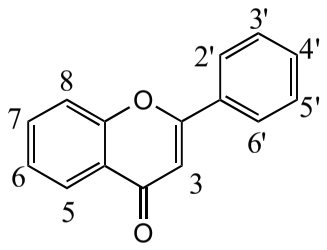


Plate 19a; ^{1}H NMR [$CDCl_3$]: Flavone (**164**)





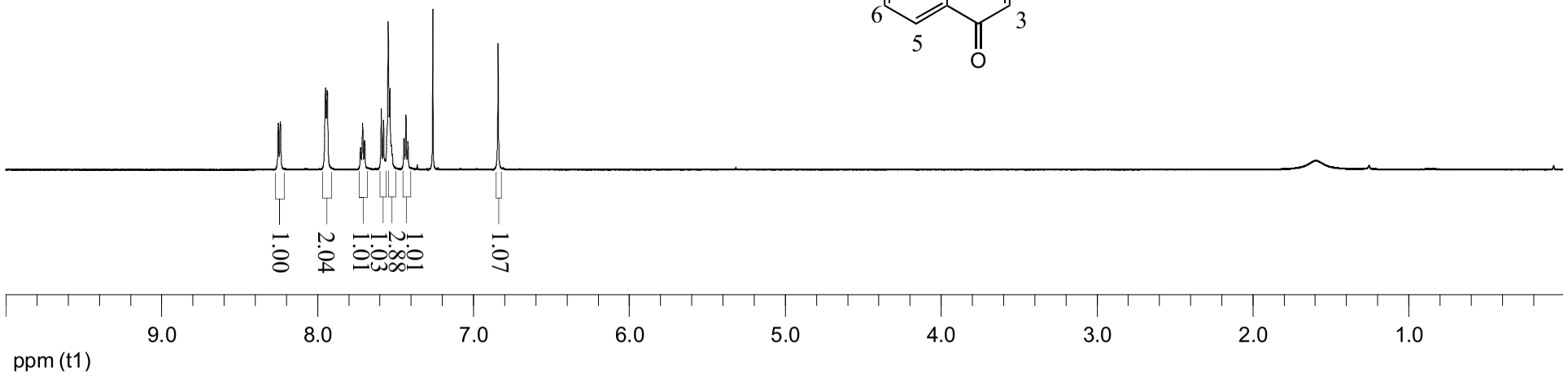


Plate 19b; ^{13}C NMR [$CDCl_3$]: Flavone (**164**)

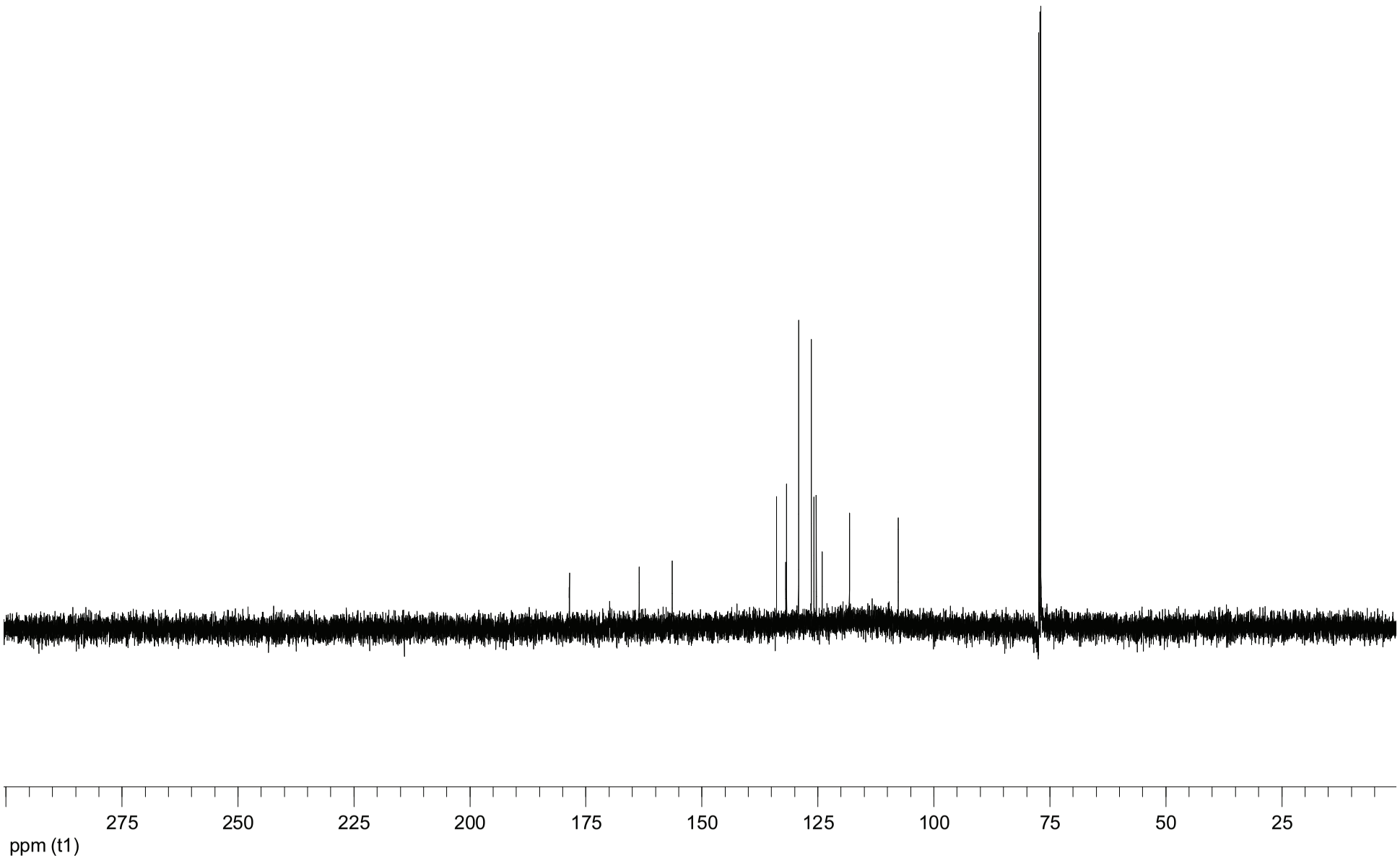
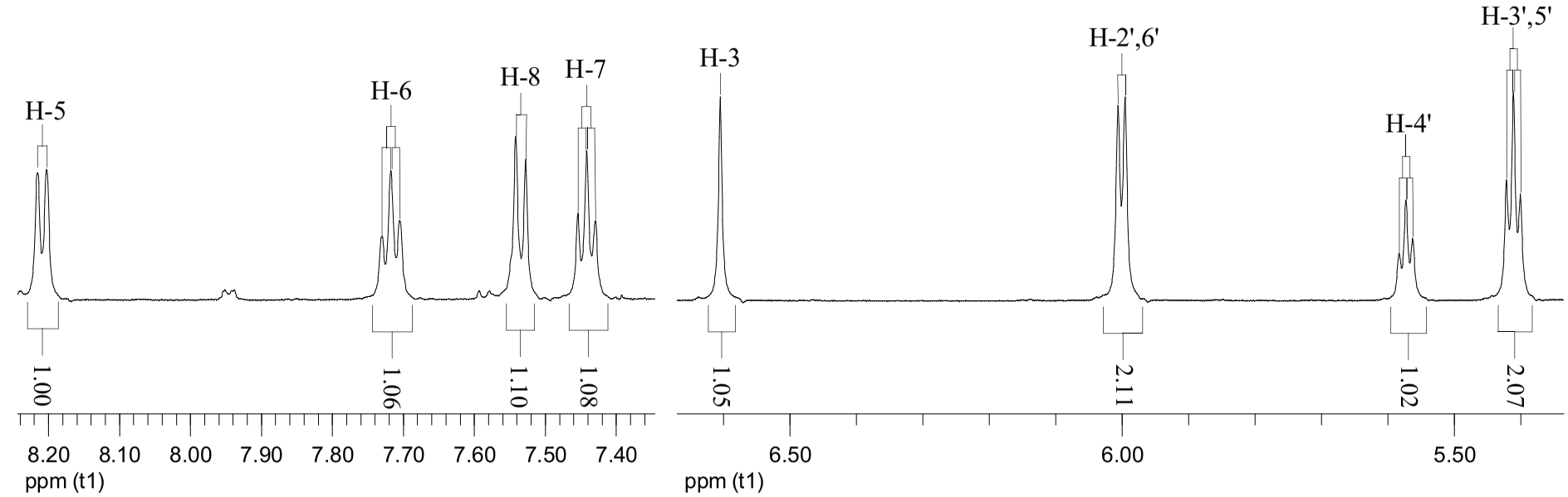


Plate 20a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(B-η^6-flavone)chromium(0) (**164a**)



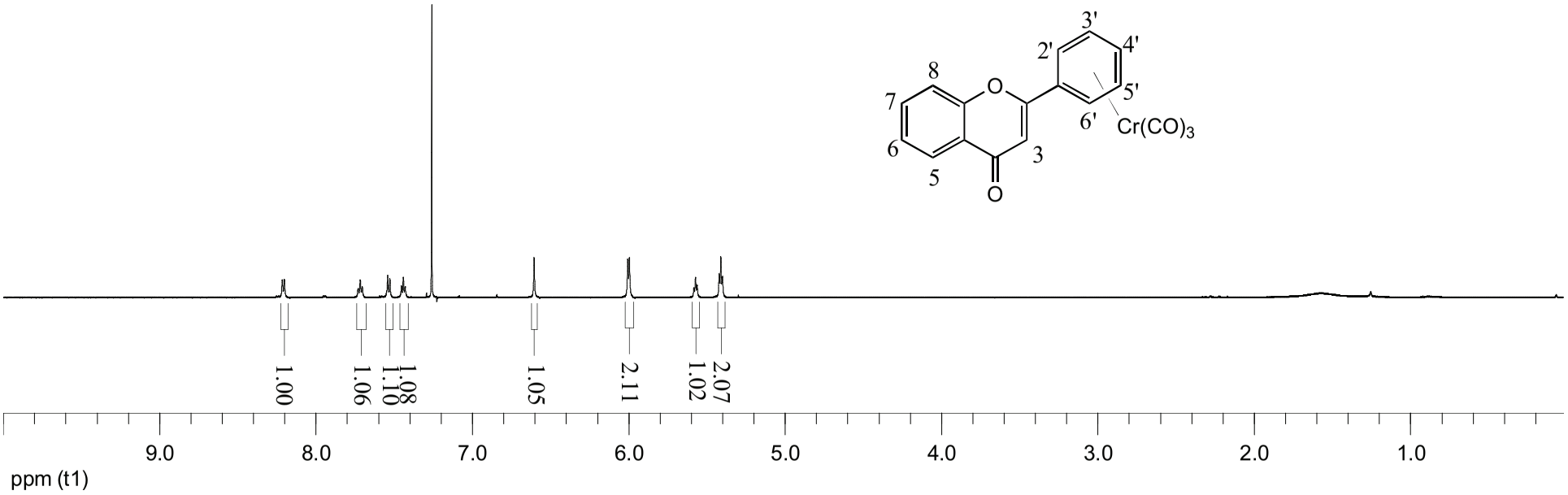


Plate 20b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(B-η^6-flavone)chromium(0) (**164a**)

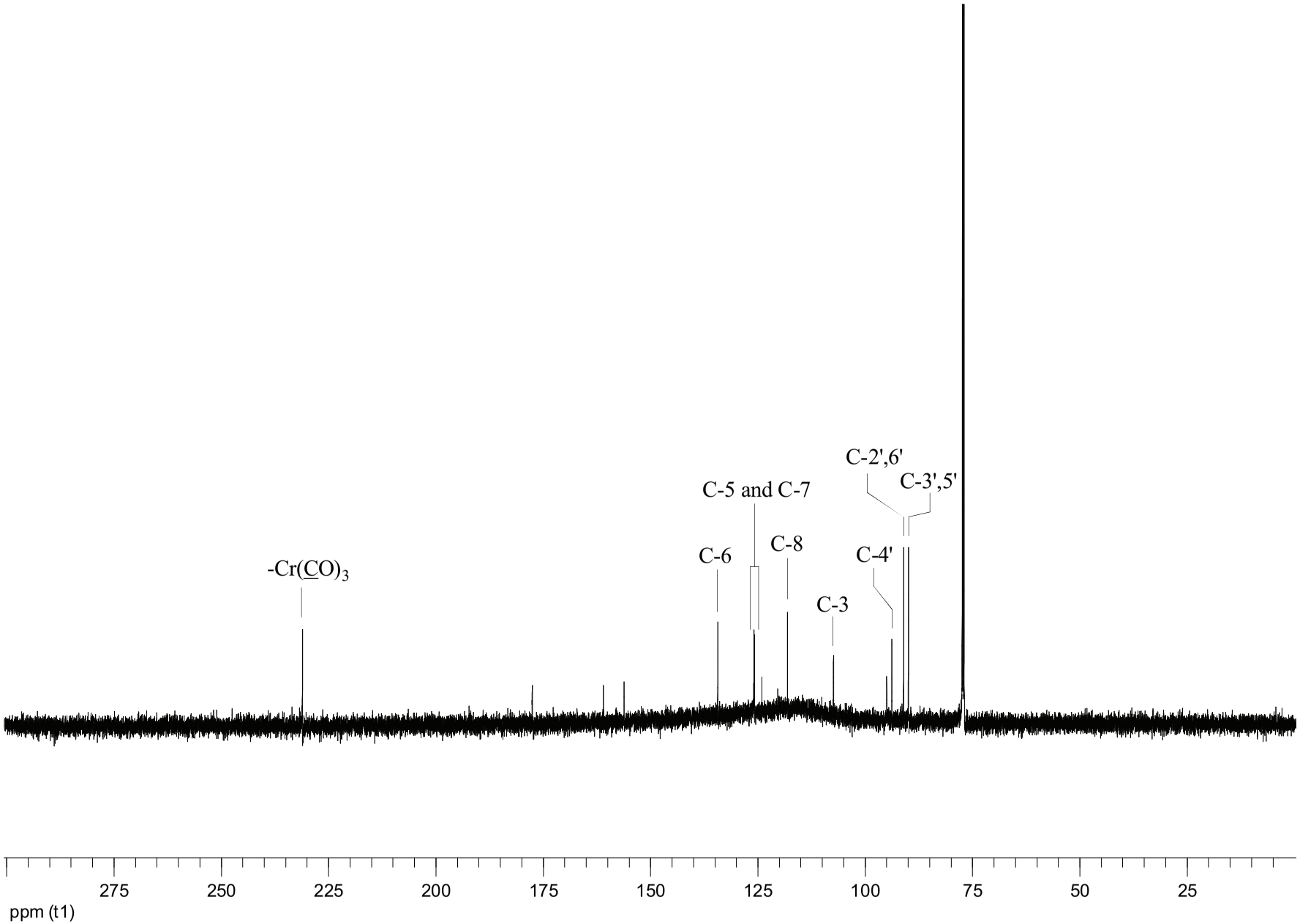


Plate 20c; HMQC NMR [$CDCl_3$]: Tricarbonyl(B-η^6-flavone)chromium(0) (**164a**)

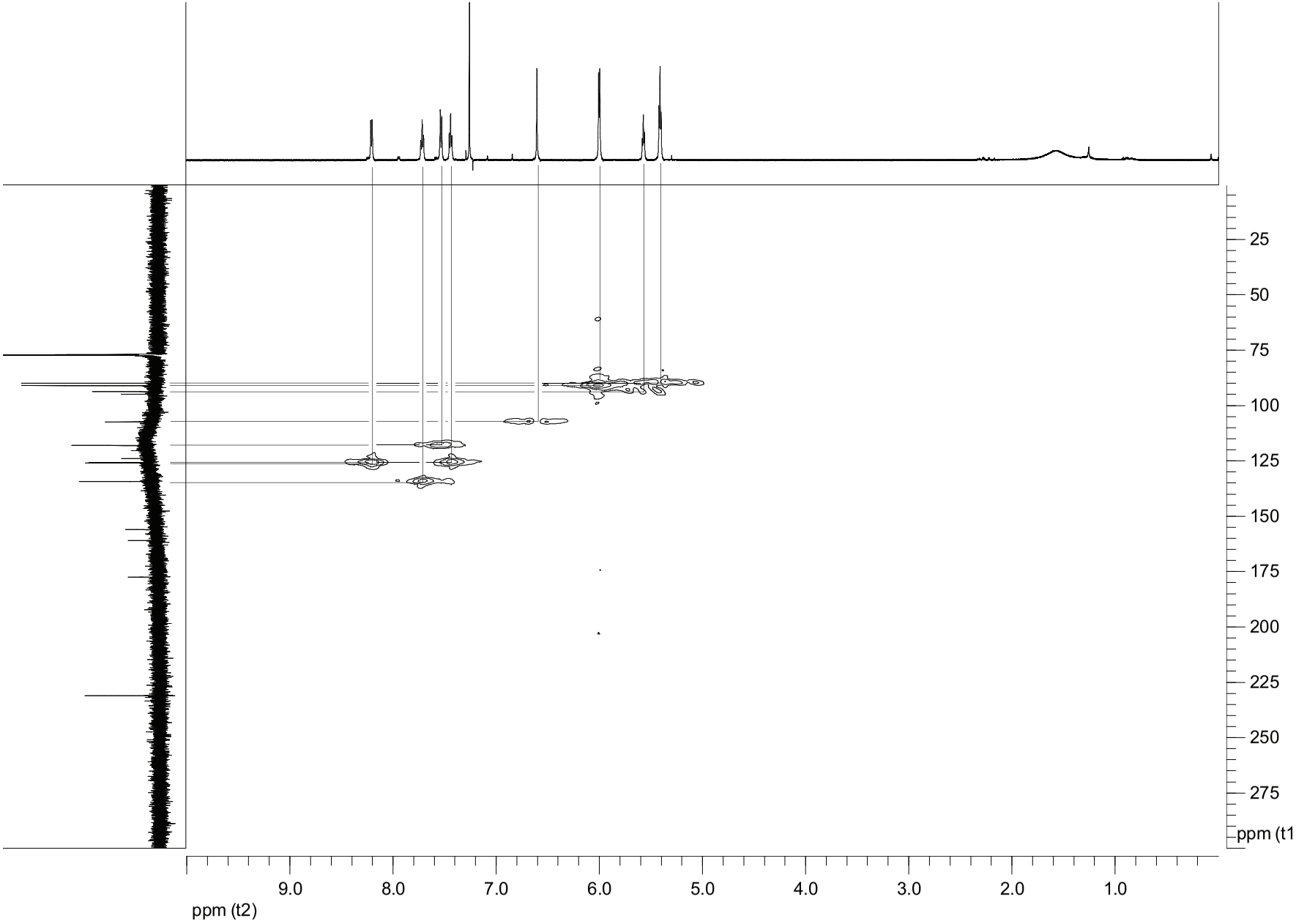


Plate 21a; ^{1}H NMR [$CDCl_3$]: Chroman-4-ol (**196**)

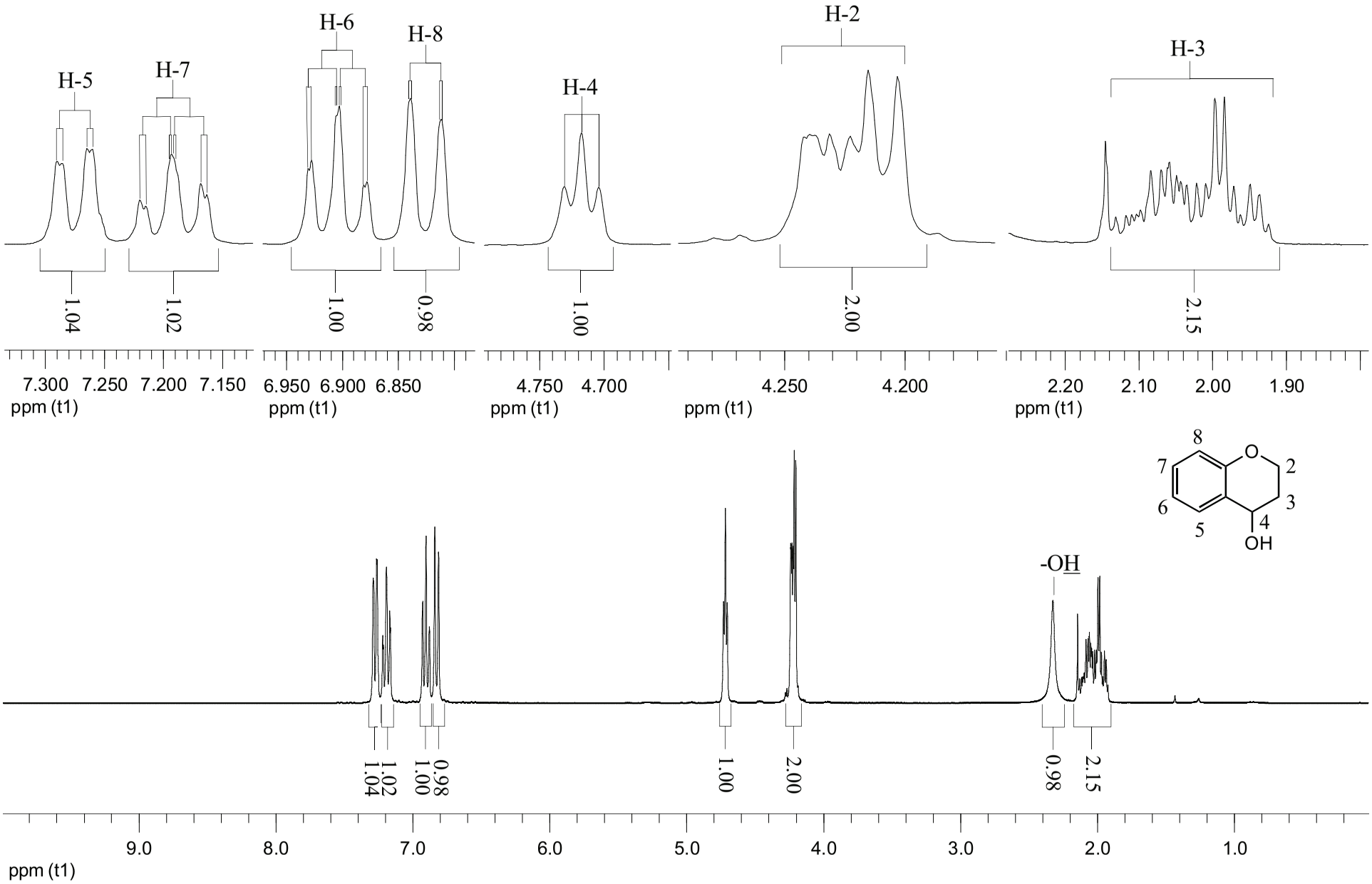


Plate 21b; ^{13}C NMR [$CDCl_3$]: Chroman-4-ol (**196**)

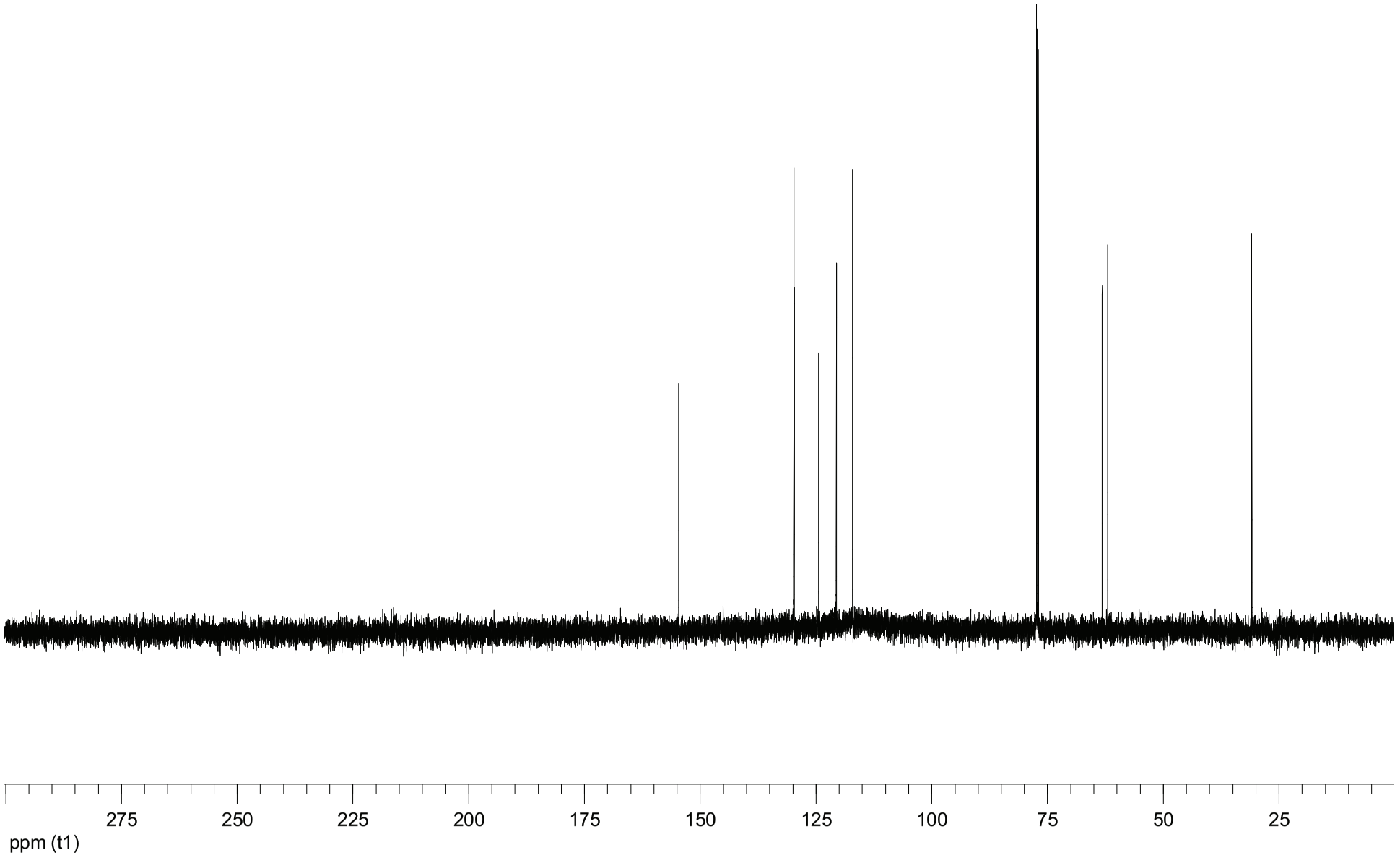


Plate 22a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(η^6-chroman-4-ol)chromium(0) (**196a**)

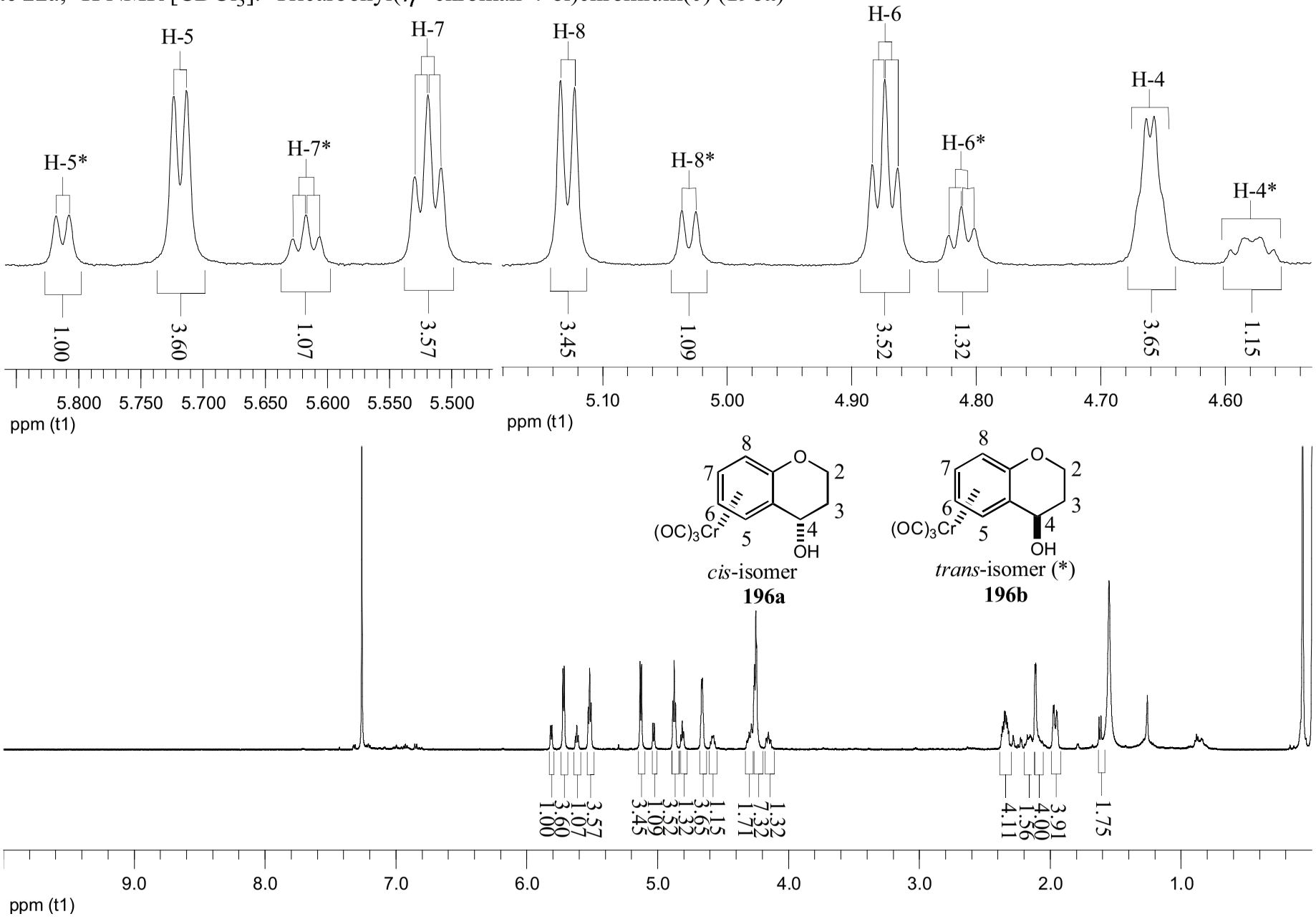


Plate 22a cont.; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(η^6-chroman-4-ol)chromium(0) (**196a** and **196b**)

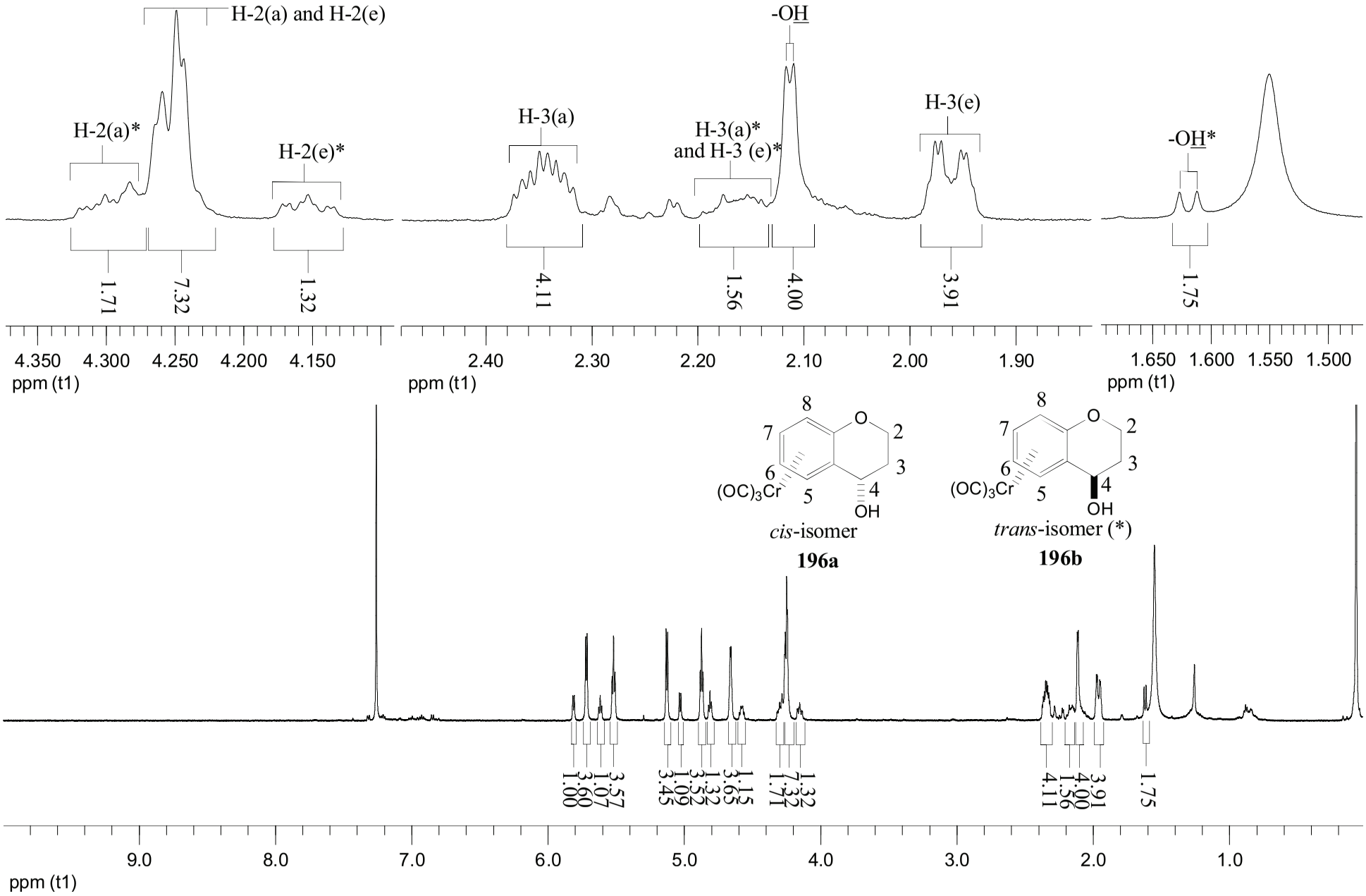


Plate 22b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(η^6-chroman-4-ol)chromium(0) (**196a** and **196b**)

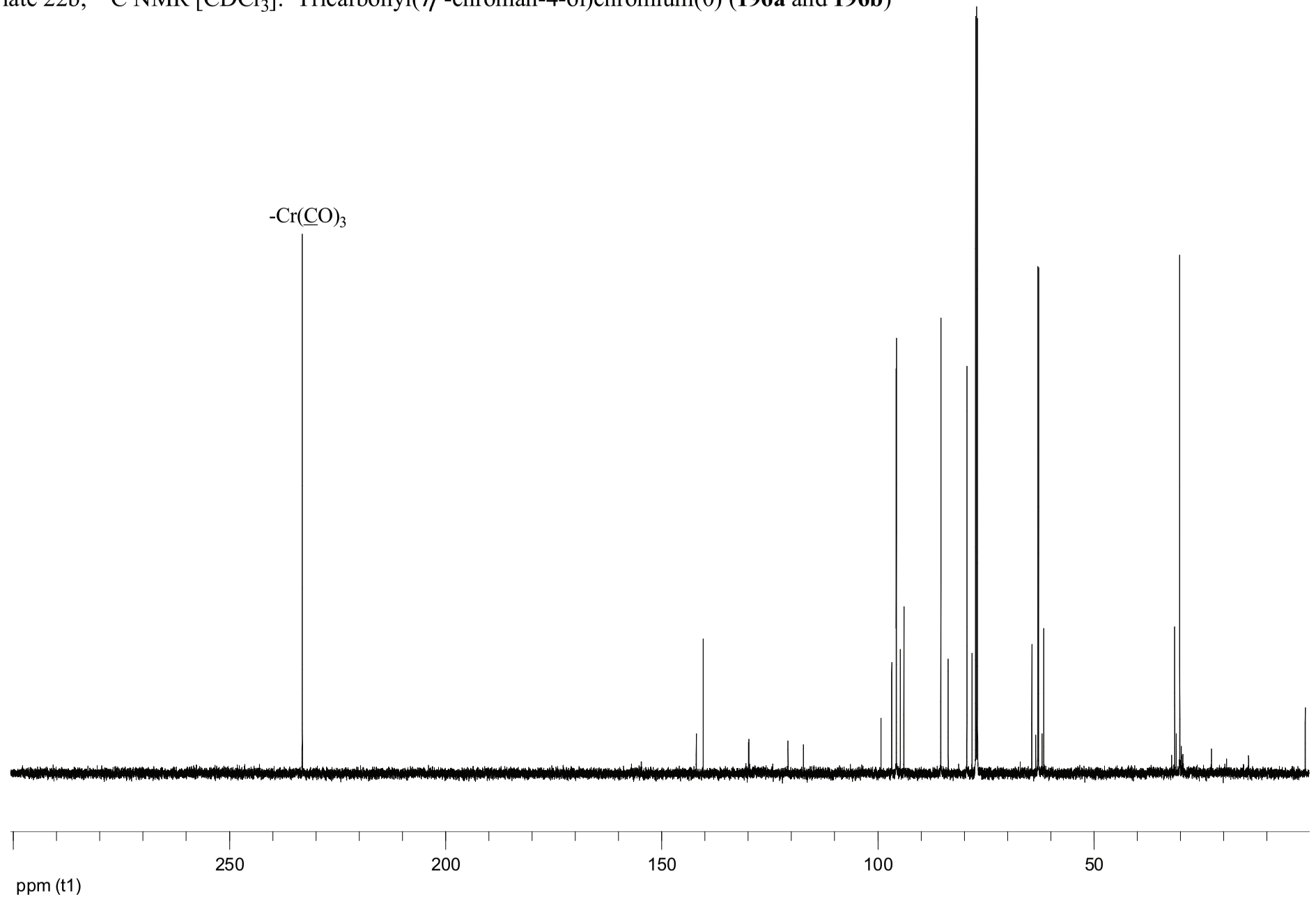


Plate 22c; HMQC NMR [$CDCl_3$]: Tricarbonyl(η^6-chroman-4-ol)chromium(0) (**196a** and **196b**)

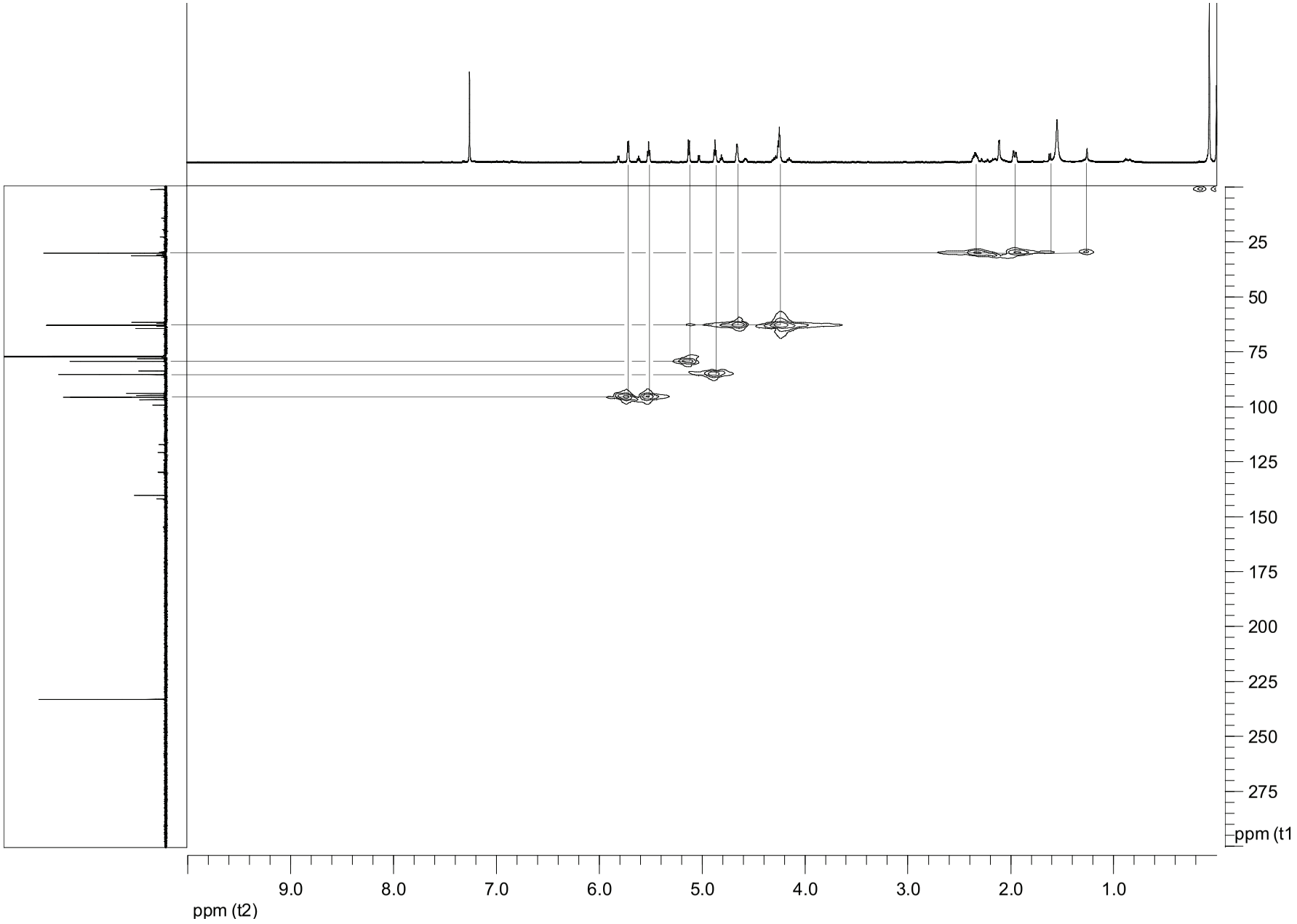


Plate 23a; ^{1}H NMR [$CDCl_3$]: Flavan-4-ol (**197**)

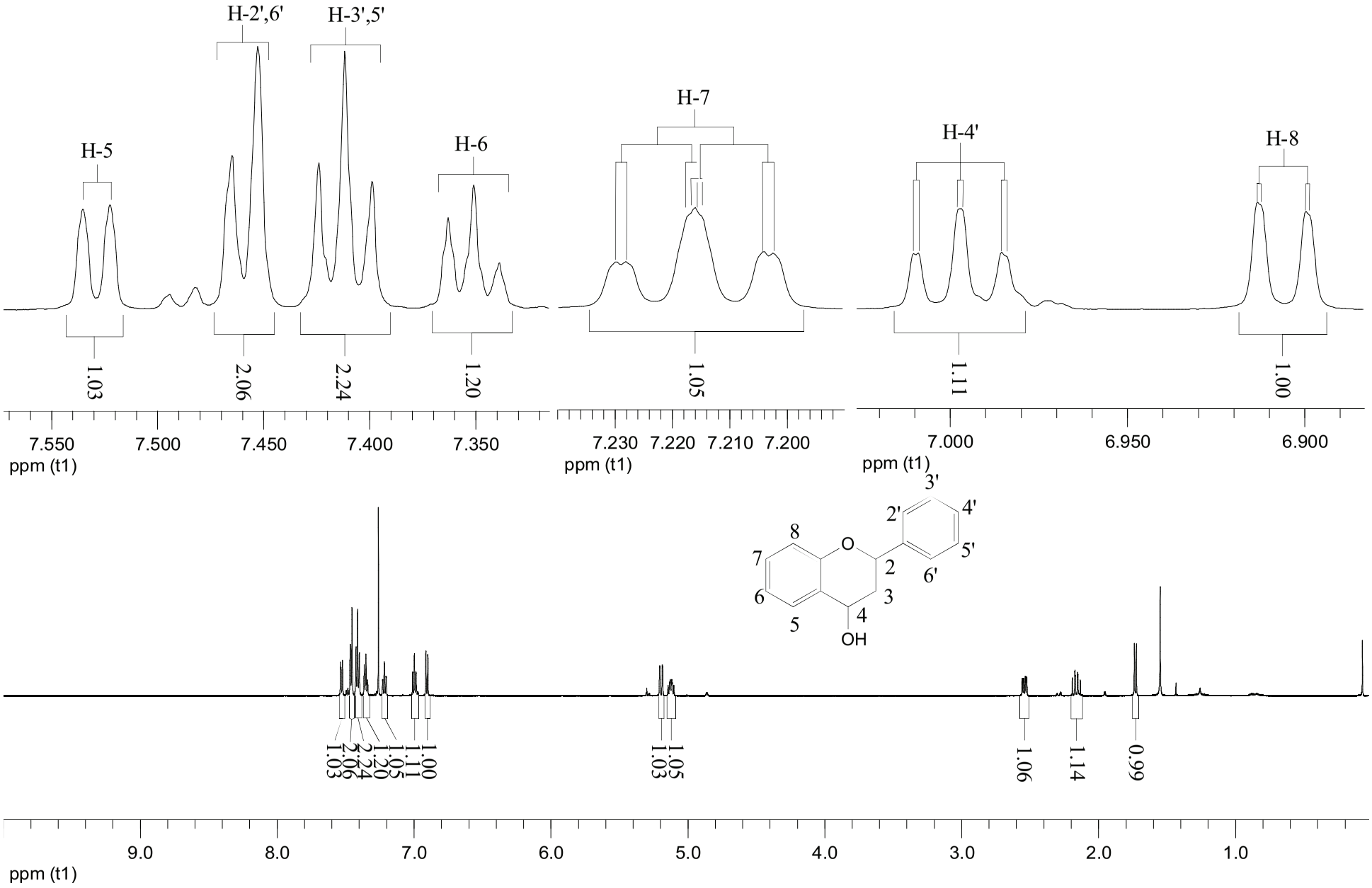


Plate 23a cont.; ^{1}H NMR [$CDCl_3$]: Flavan-4-ol (**197**)

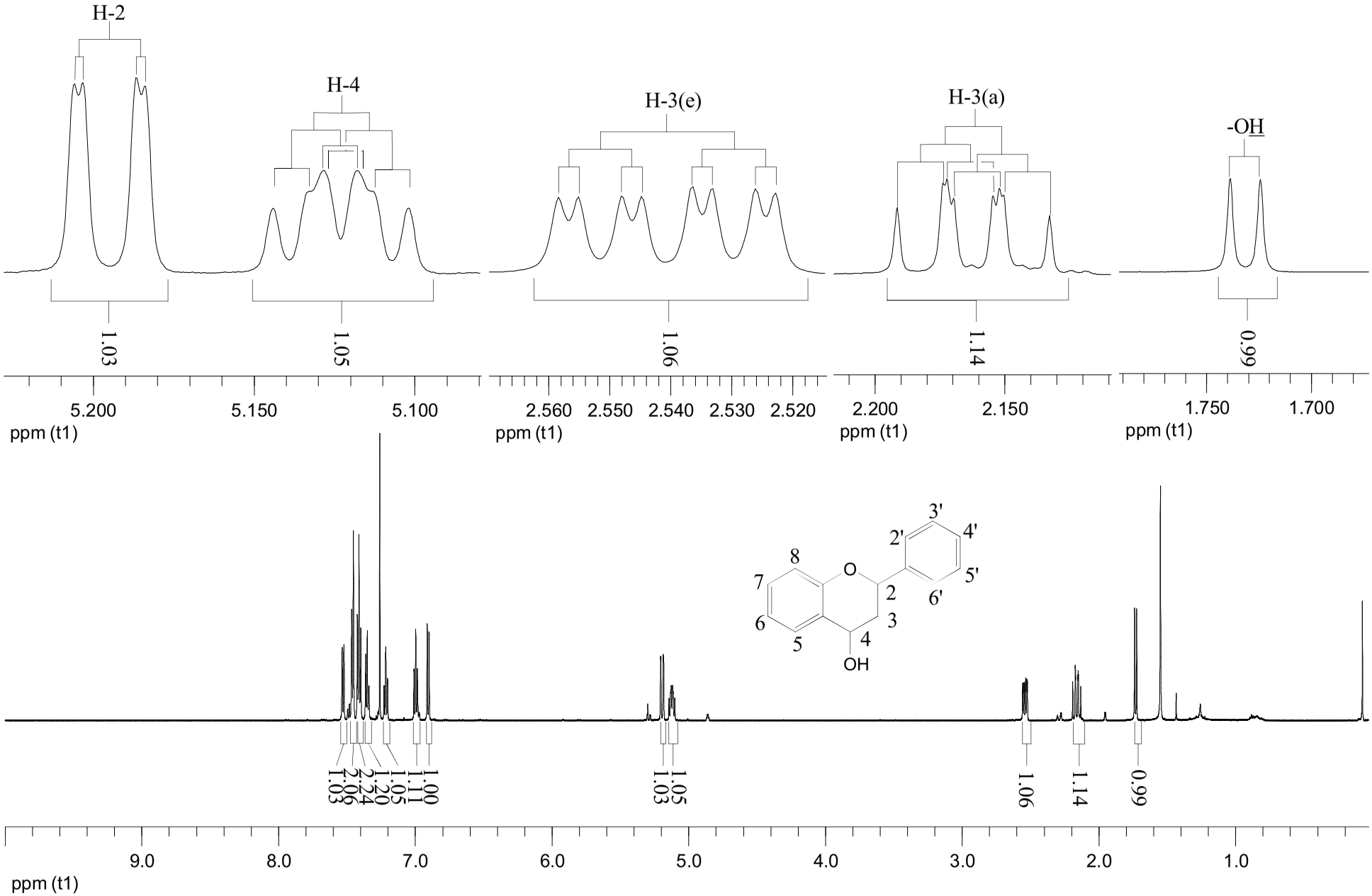


Plate 23b; ^{13}C NMR [$CDCl_3$]: Flavan-4-ol (**197**)

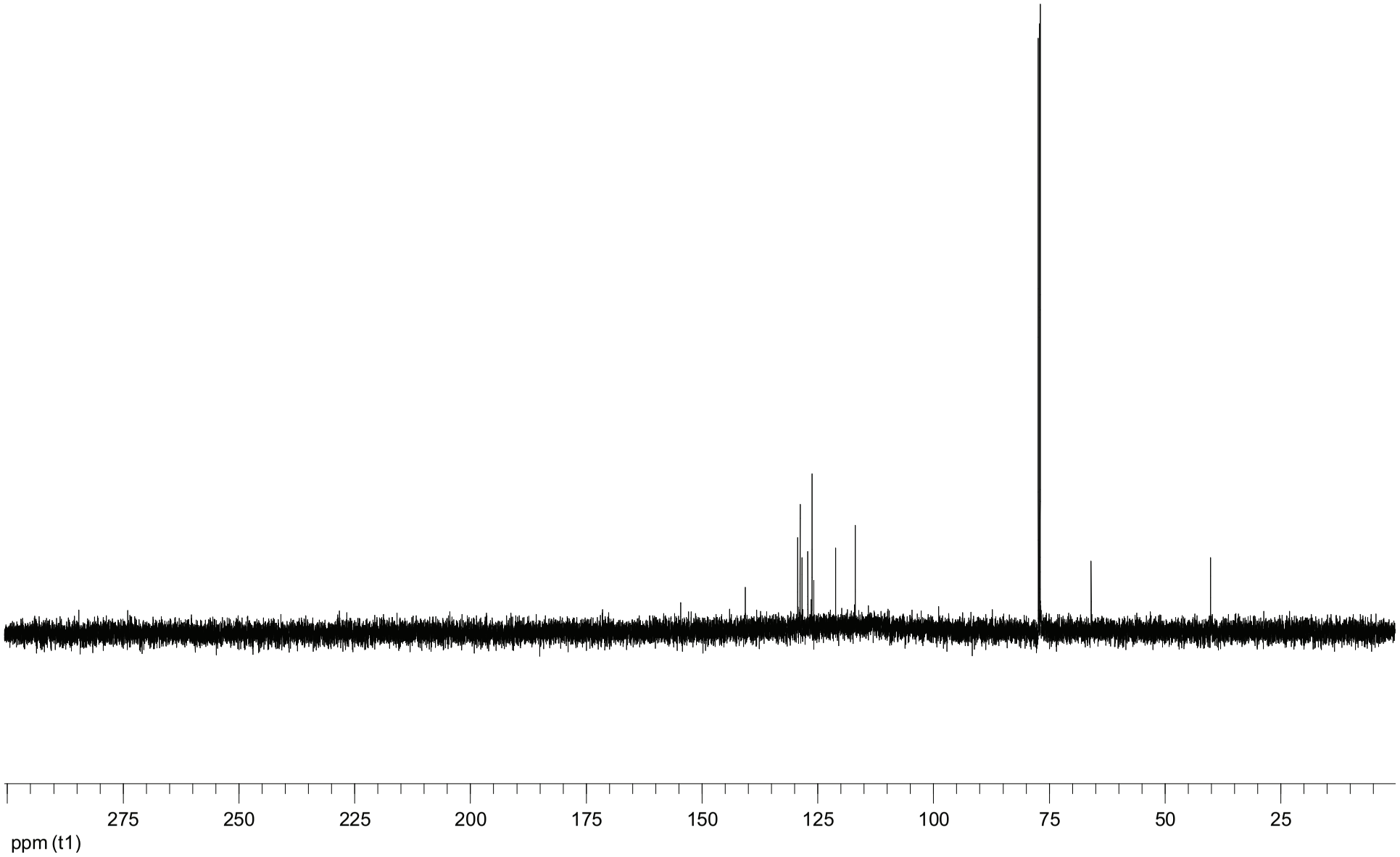


Plate 24a; ^{1}H NMR [$CDCl_3$]: Flavan-4-one (**195**)

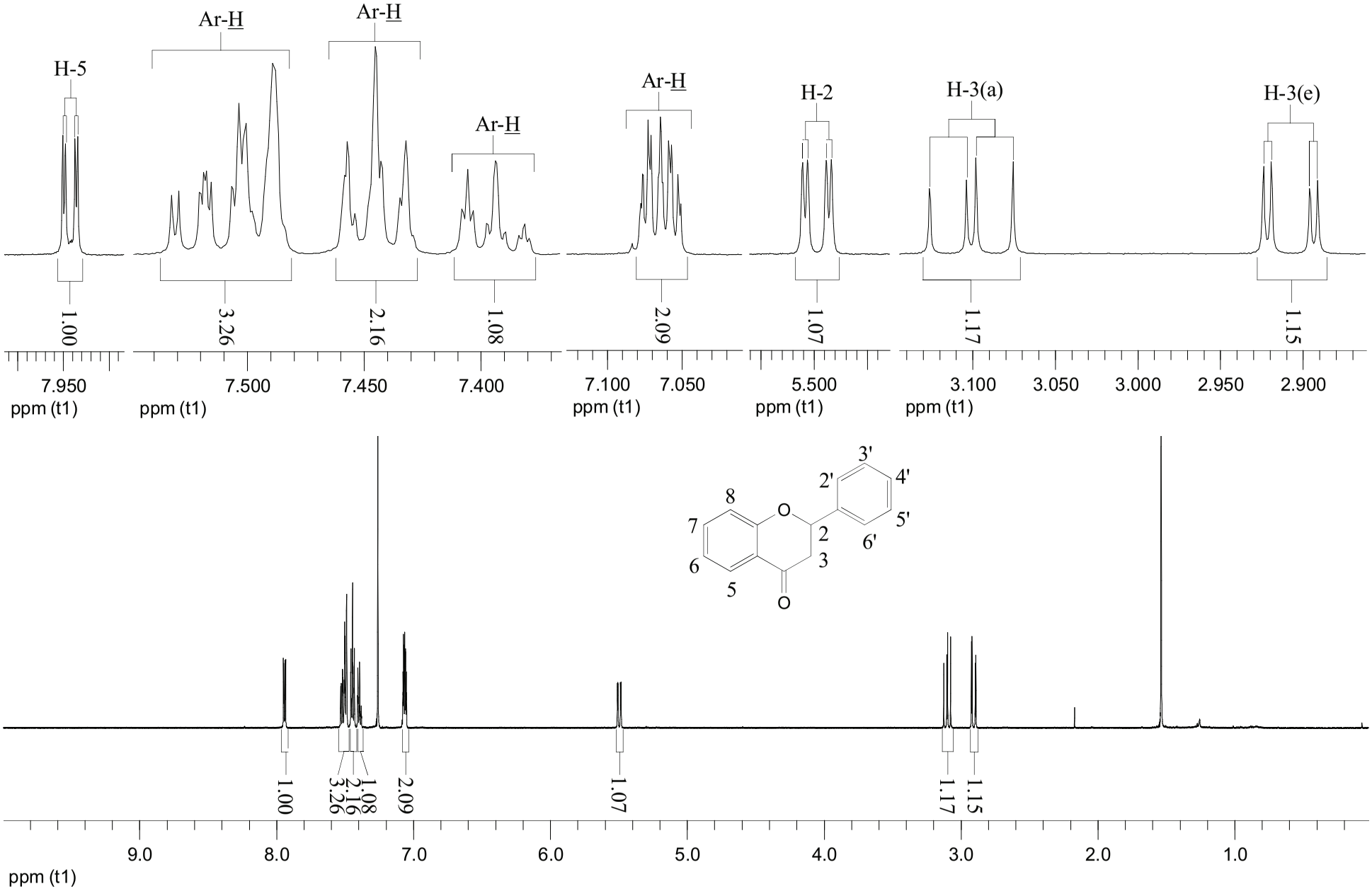


Plate 24b; ^{13}C NMR [$CDCl_3$]: Flavan-4-one (**195**)

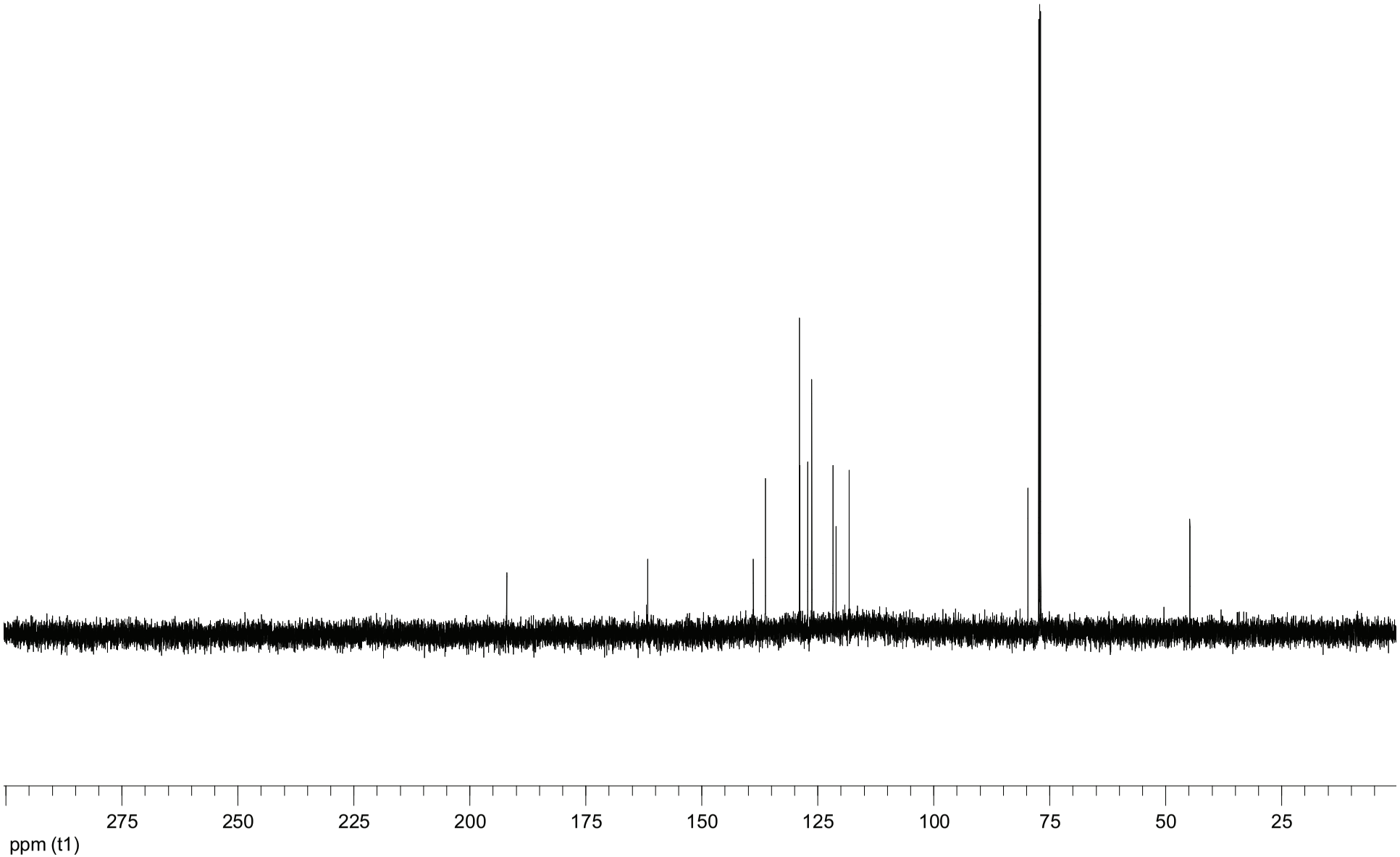


Plate 25a; ^{1}H NMR [$CDCl_3$]: 4,A-*cis*-Tricarbonyl(A-η^6-flavan-4-ol)chromium(0) (**197a1**)

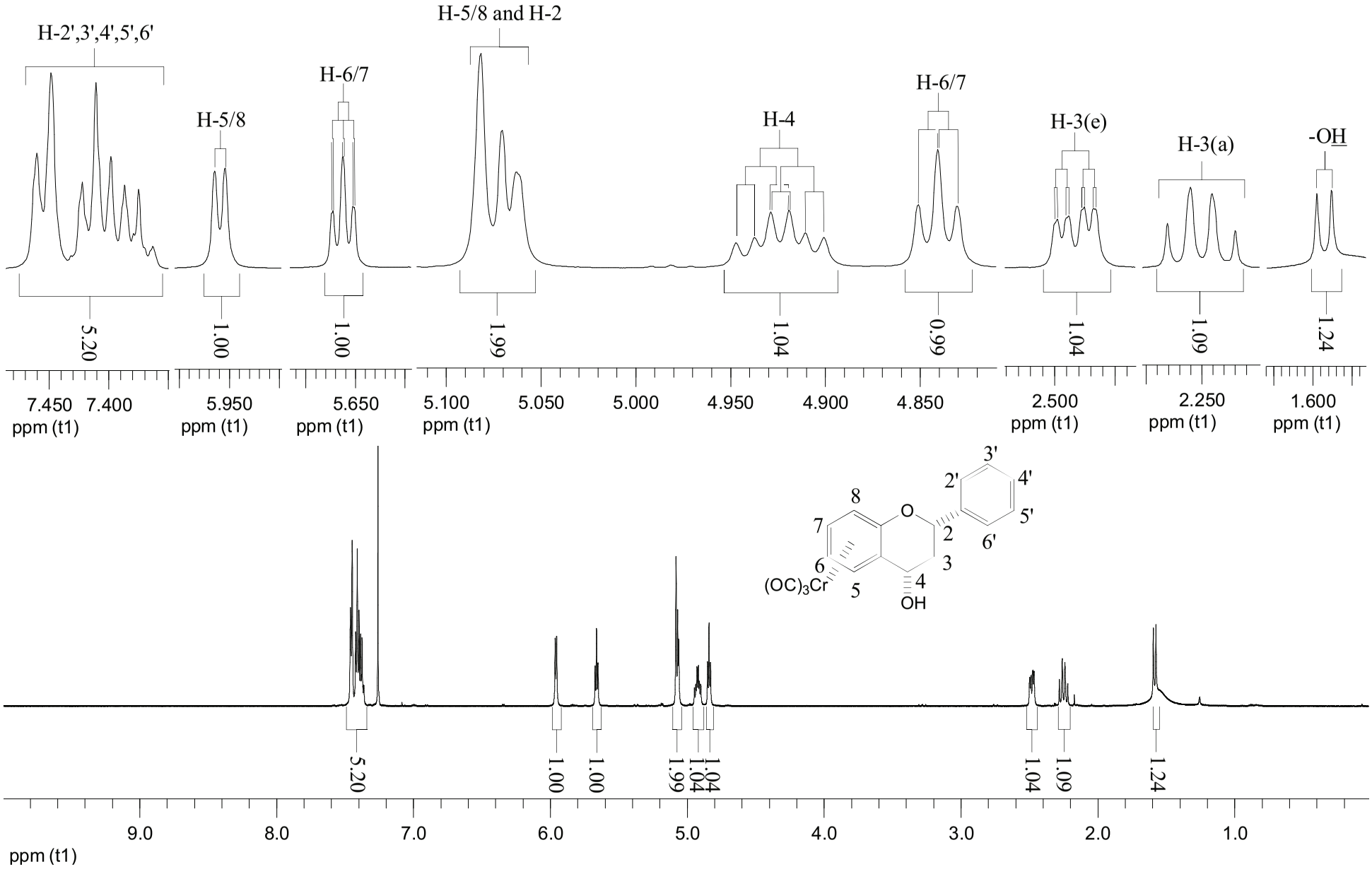


Plate 25b; ^{13}C NMR [$CDCl_3$]: 4,A-*cis*-Tricarbonyl(A-η^6-flavan-4-ol)chromium(0) (**197a1**)

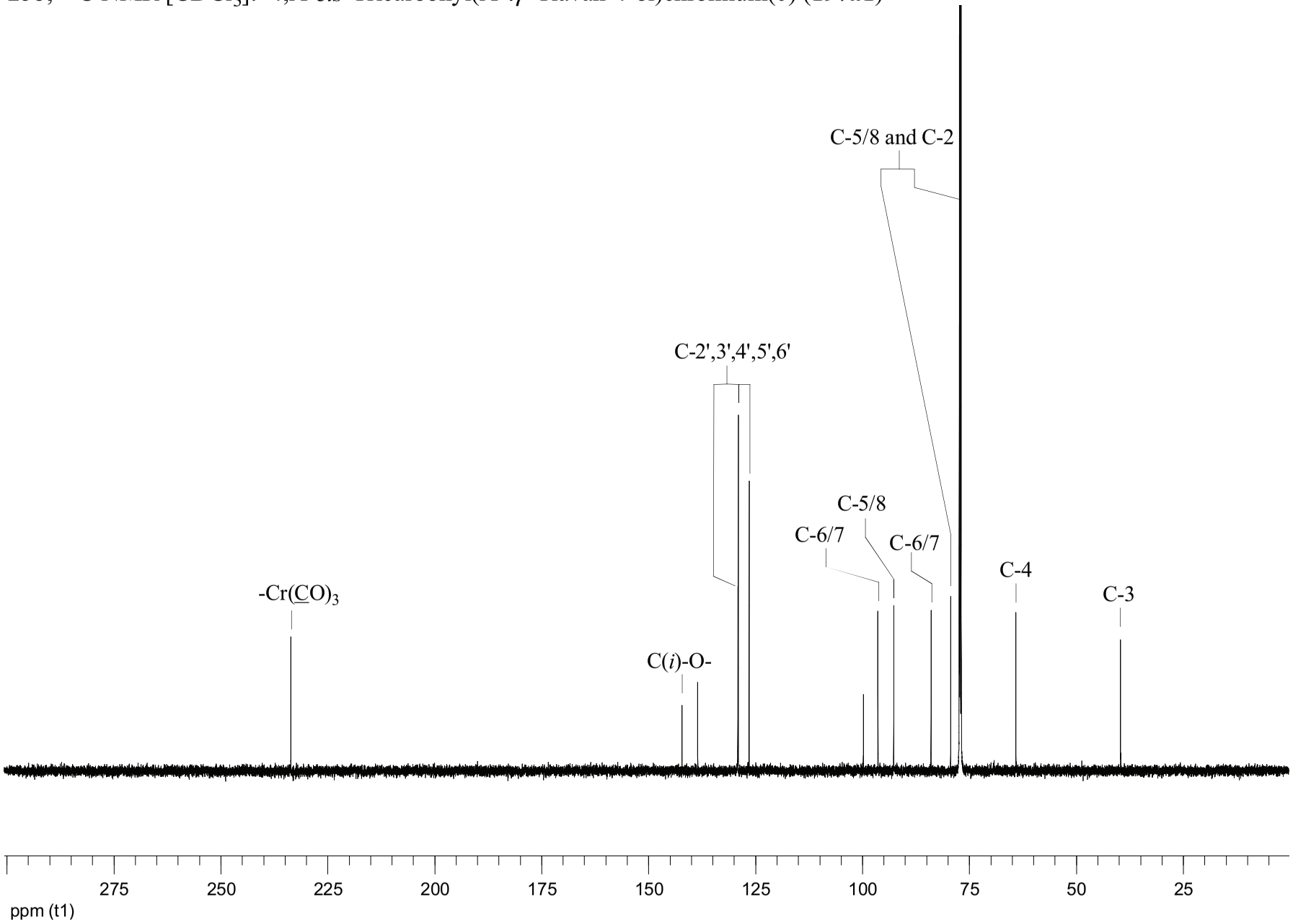


Plate 25c; HMQC NMR [$CDCl_3$]: 4,A-*cis*-Tricarbonyl(A-η^6-flavan-4-ol)chromium(0) (**197a1**)

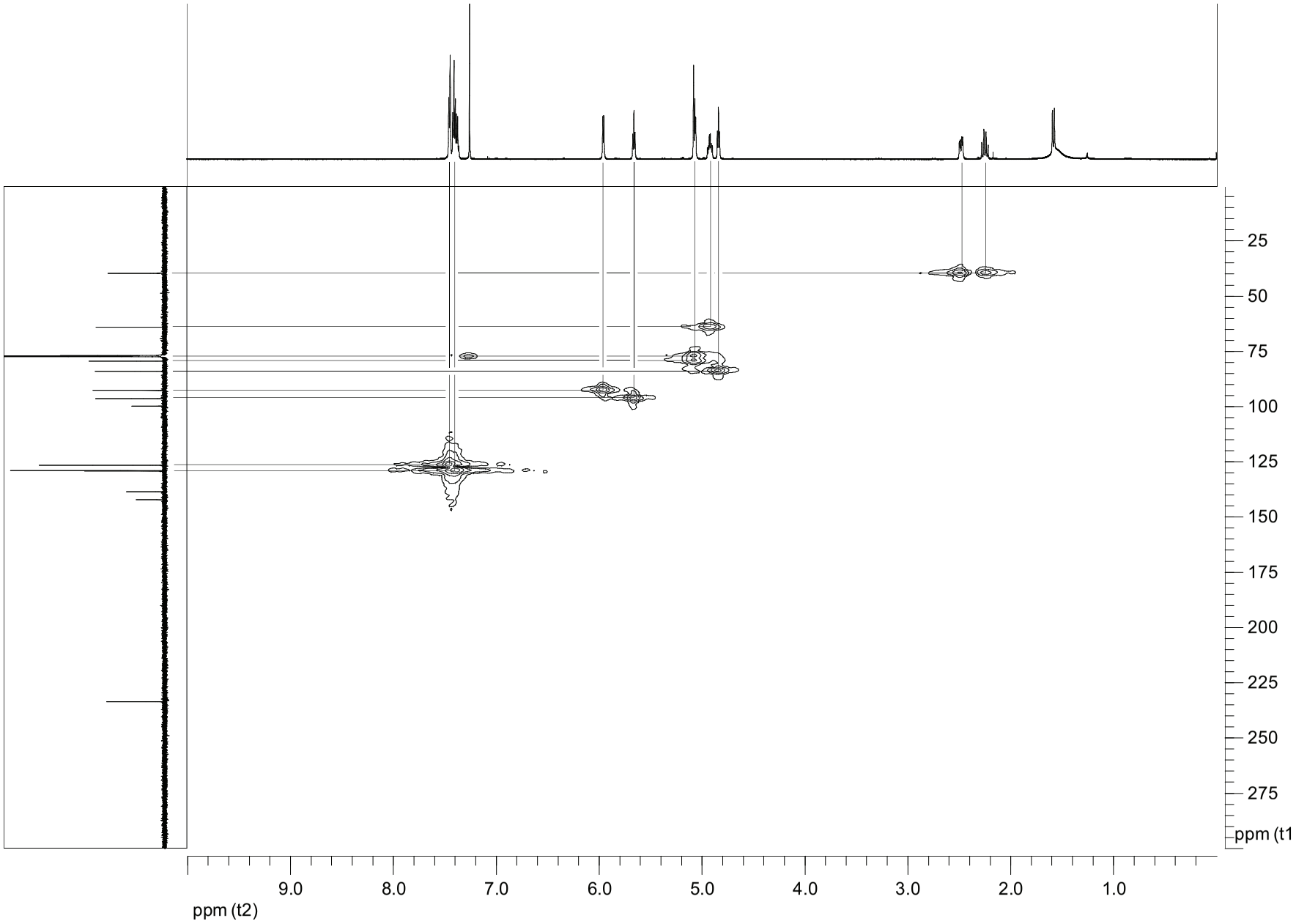


Plate 26a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(B-η^6-flavan-4-ol)chromium(0) (**197b**)

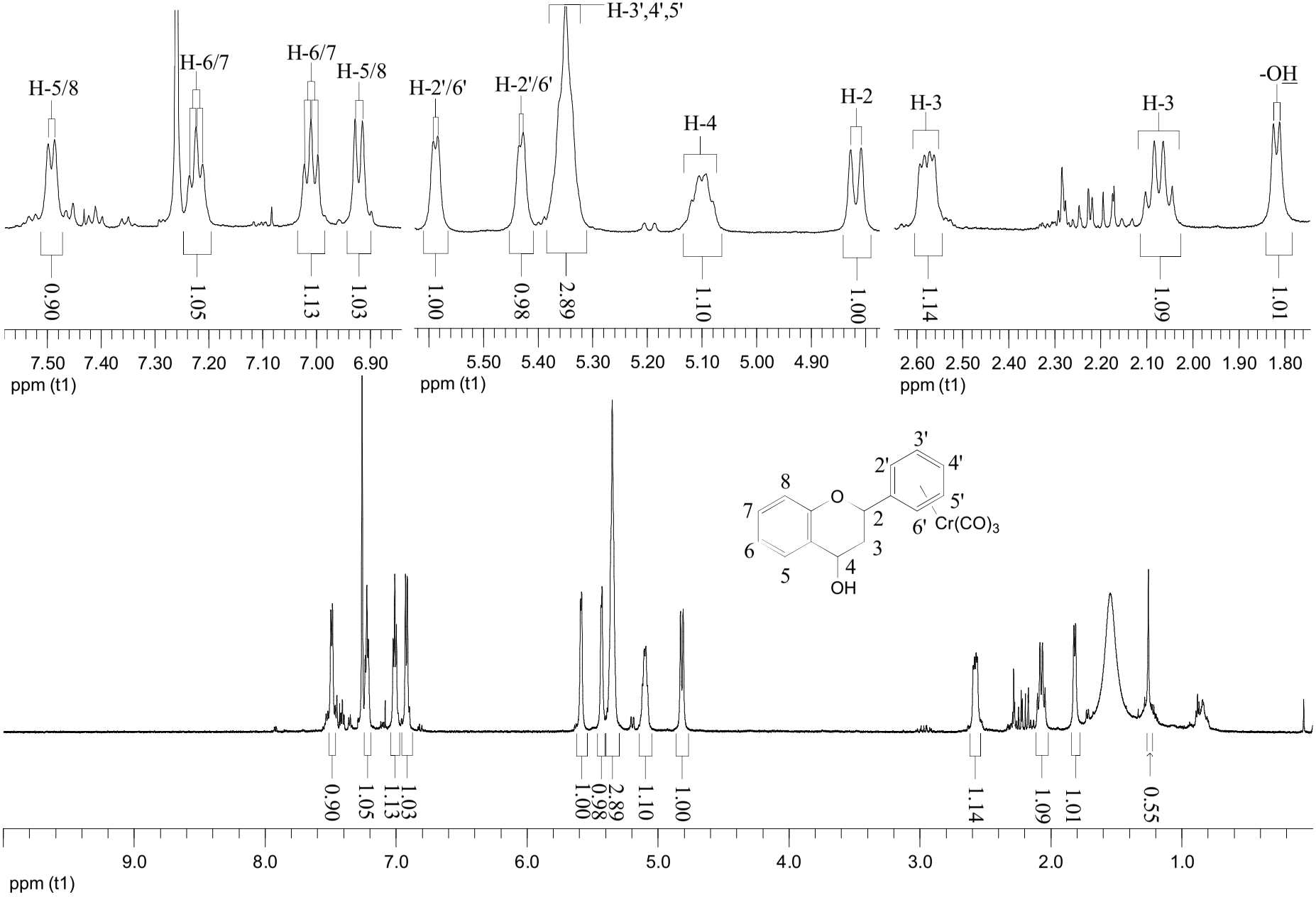


Plate 26b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(B-η^6-flavan-4-ol)chromium(0) (**197b**)

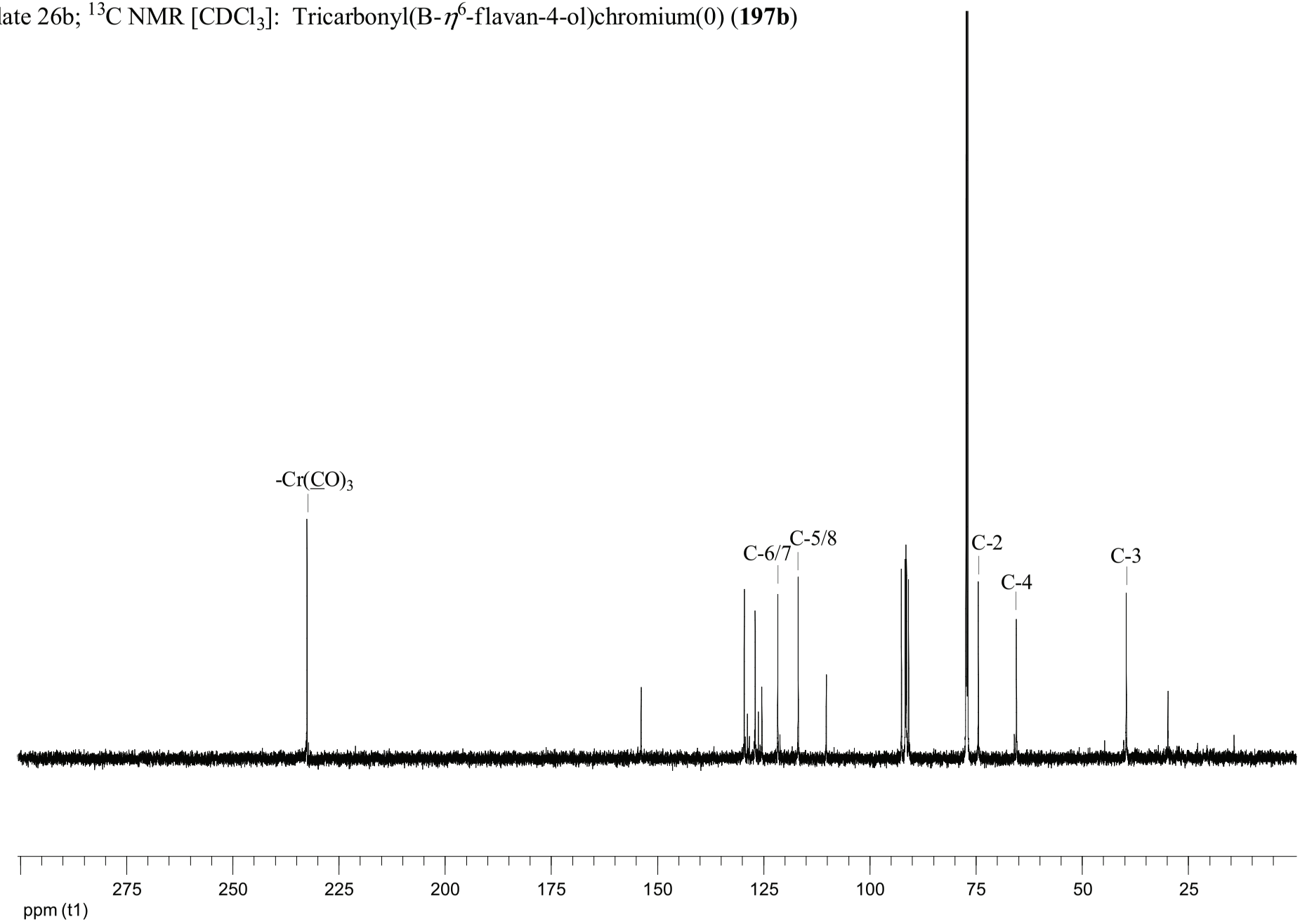


Plate 26c; HMQC NMR [$CDCl_3$]: Tricarbonyl(B-η^6-flavan-4-ol)chromium(0) (**197b**)

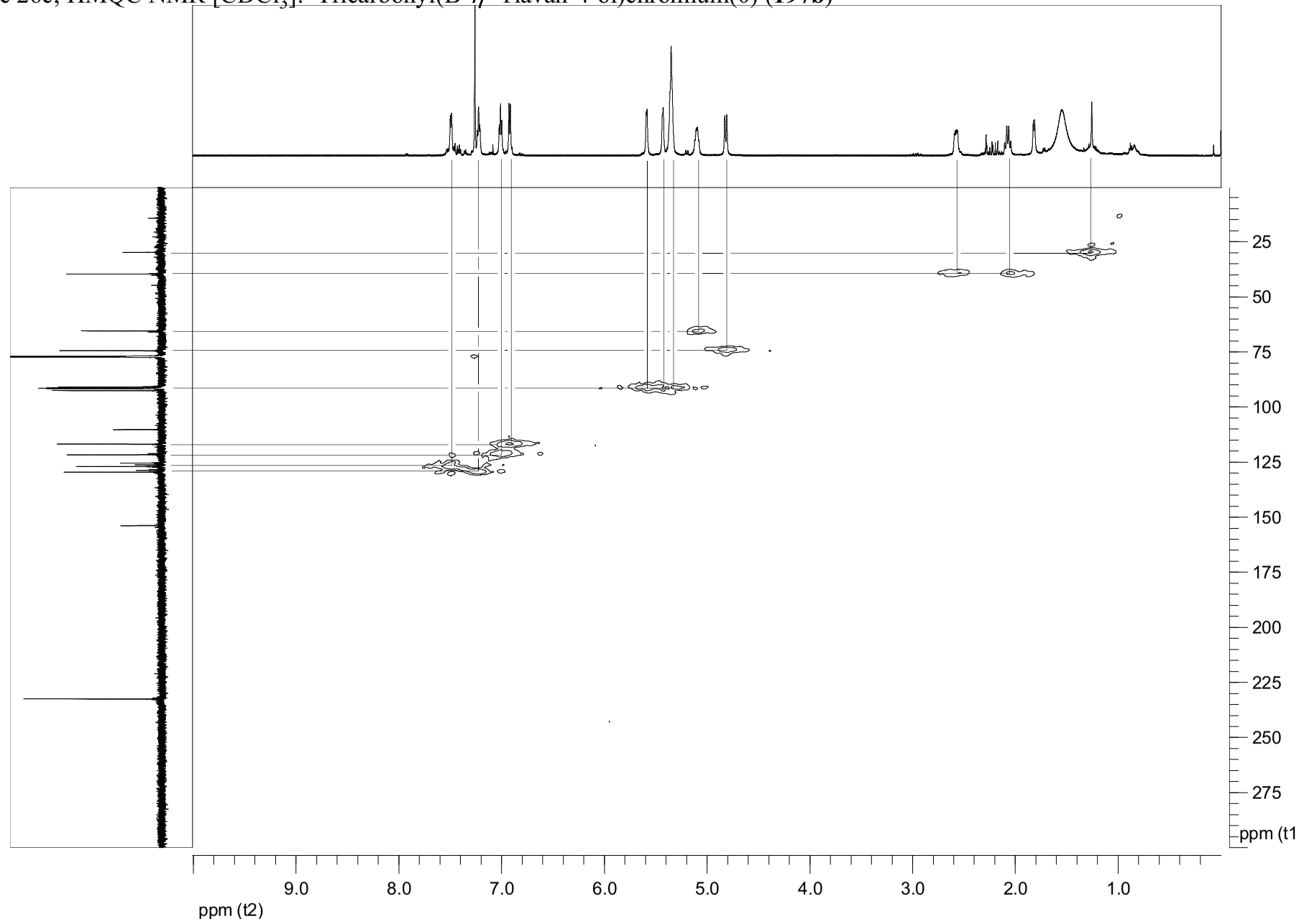


Plate 27a; ^{1}H NMR [$CDCl_3$]: Flavane (**6**)

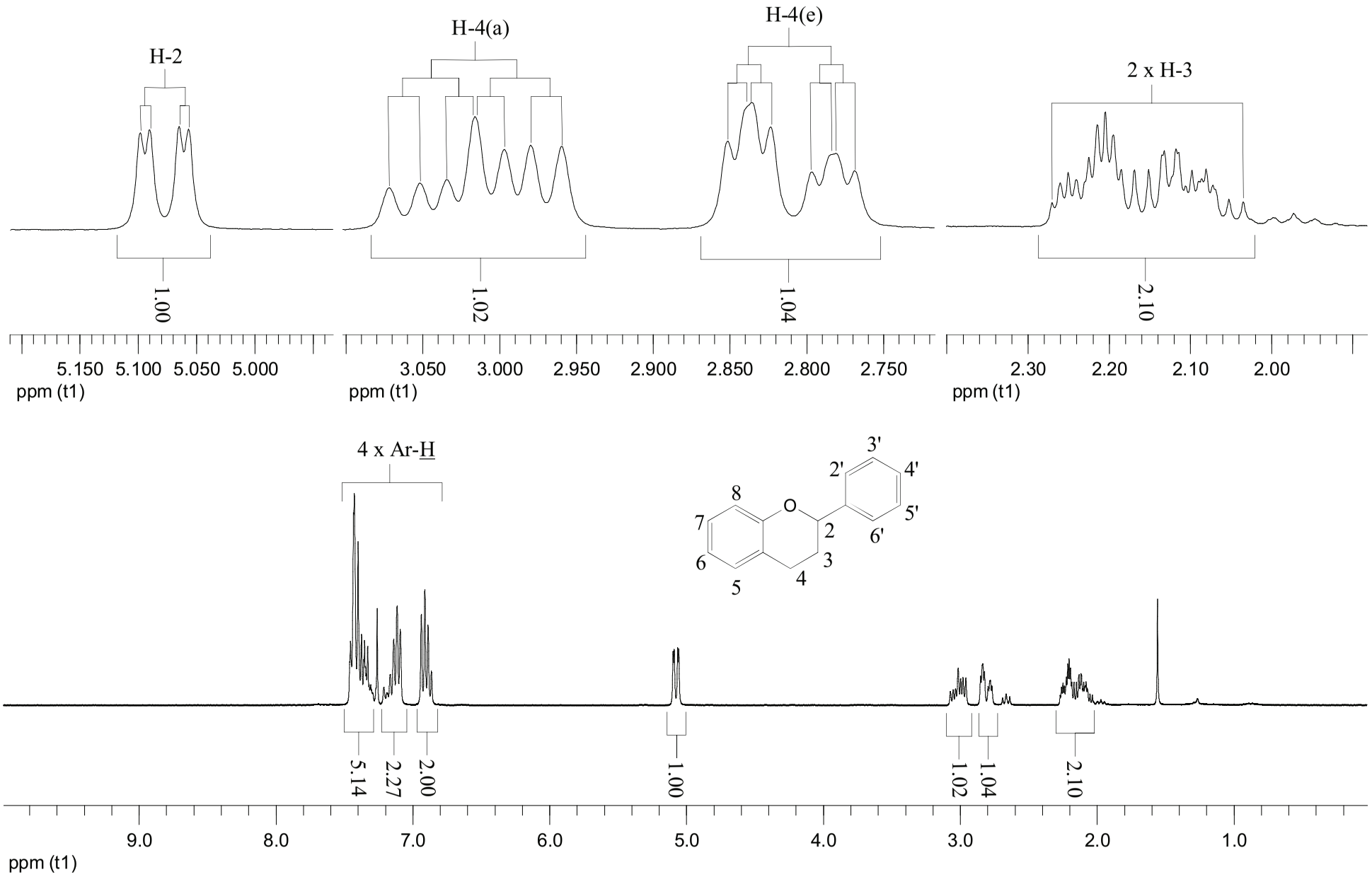


Plate 27b; ^{13}C NMR [$CDCl_3$]: Flavan (**6**)

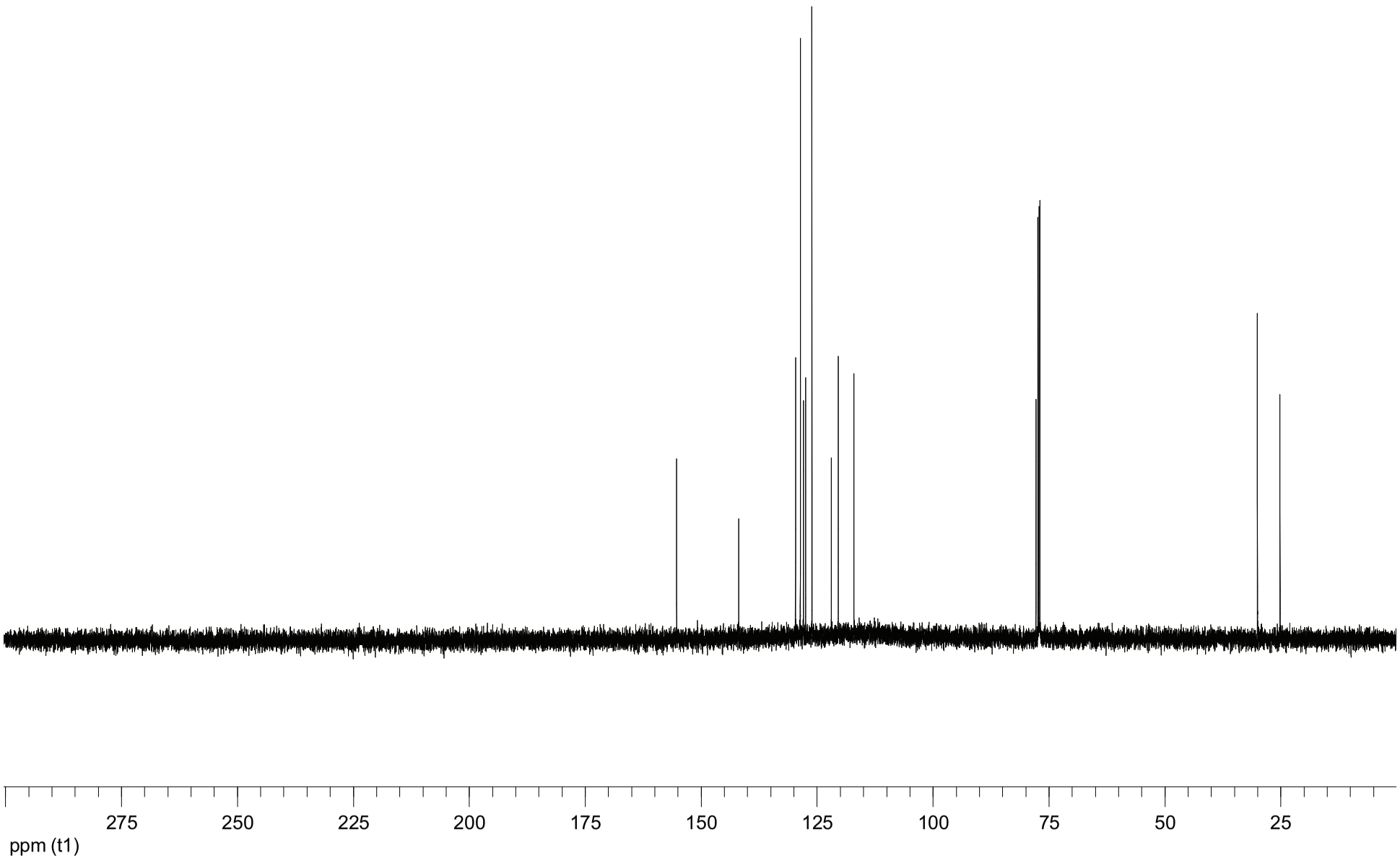


Plate 28a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(A-η^6-flavane)chromium(0) (**6a**)

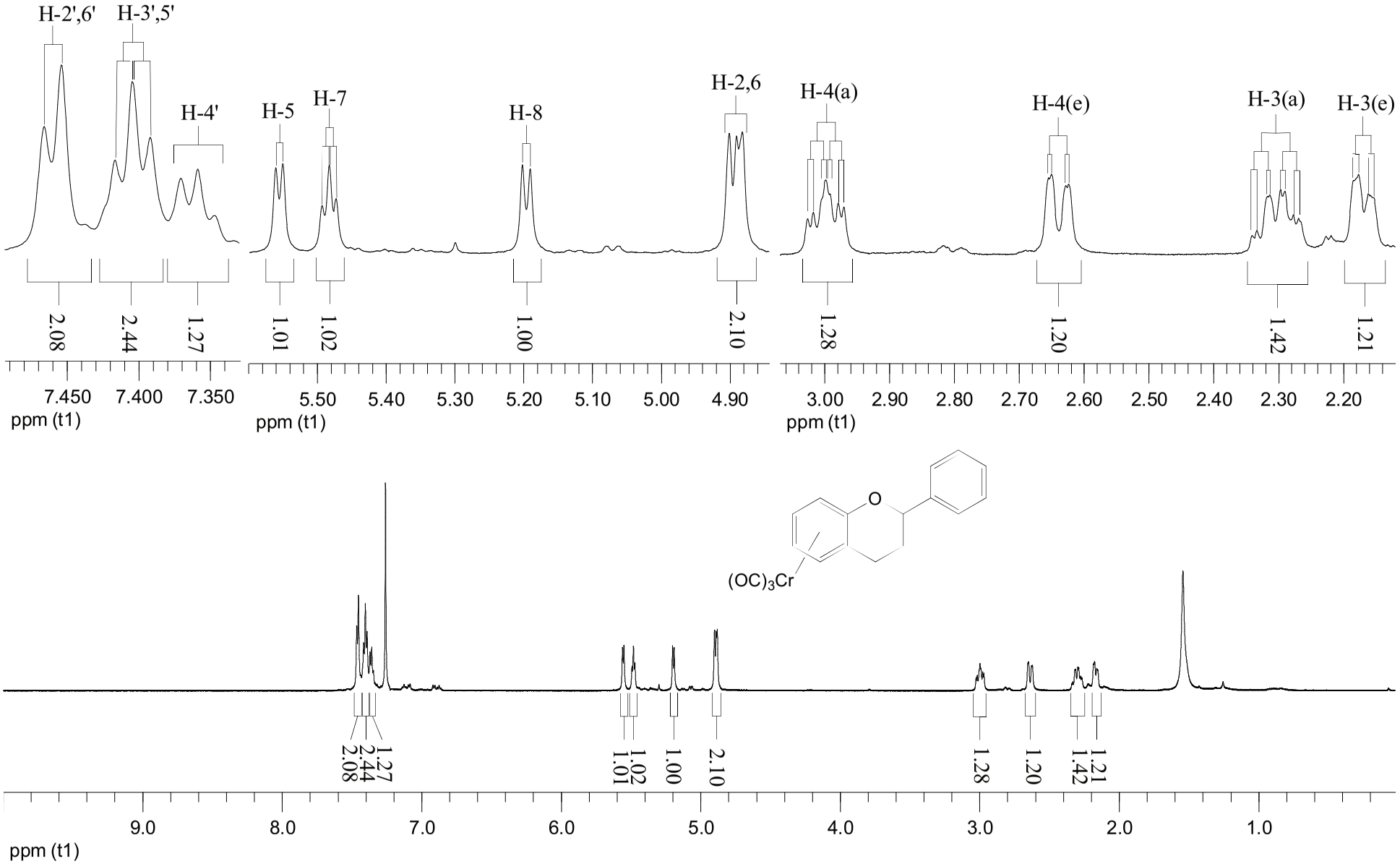


Plate 28b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(A-η^6-flavane)chromium(0) (**6a**)

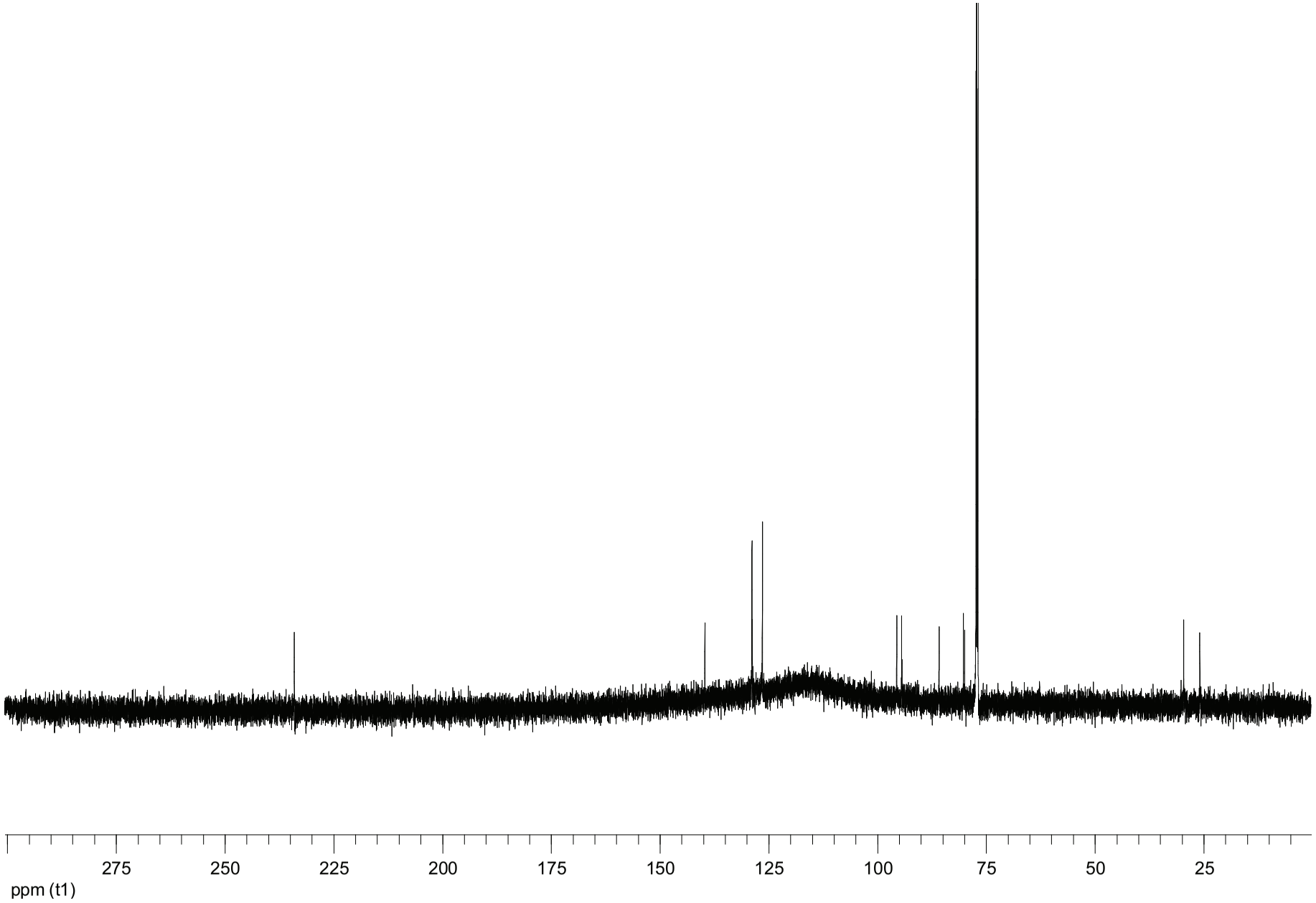


Plate 28c; HMQC NMR [$CDCl_3$]: Tricarbonyl(A-η^6-flavane)chromium(0) (**6a**)

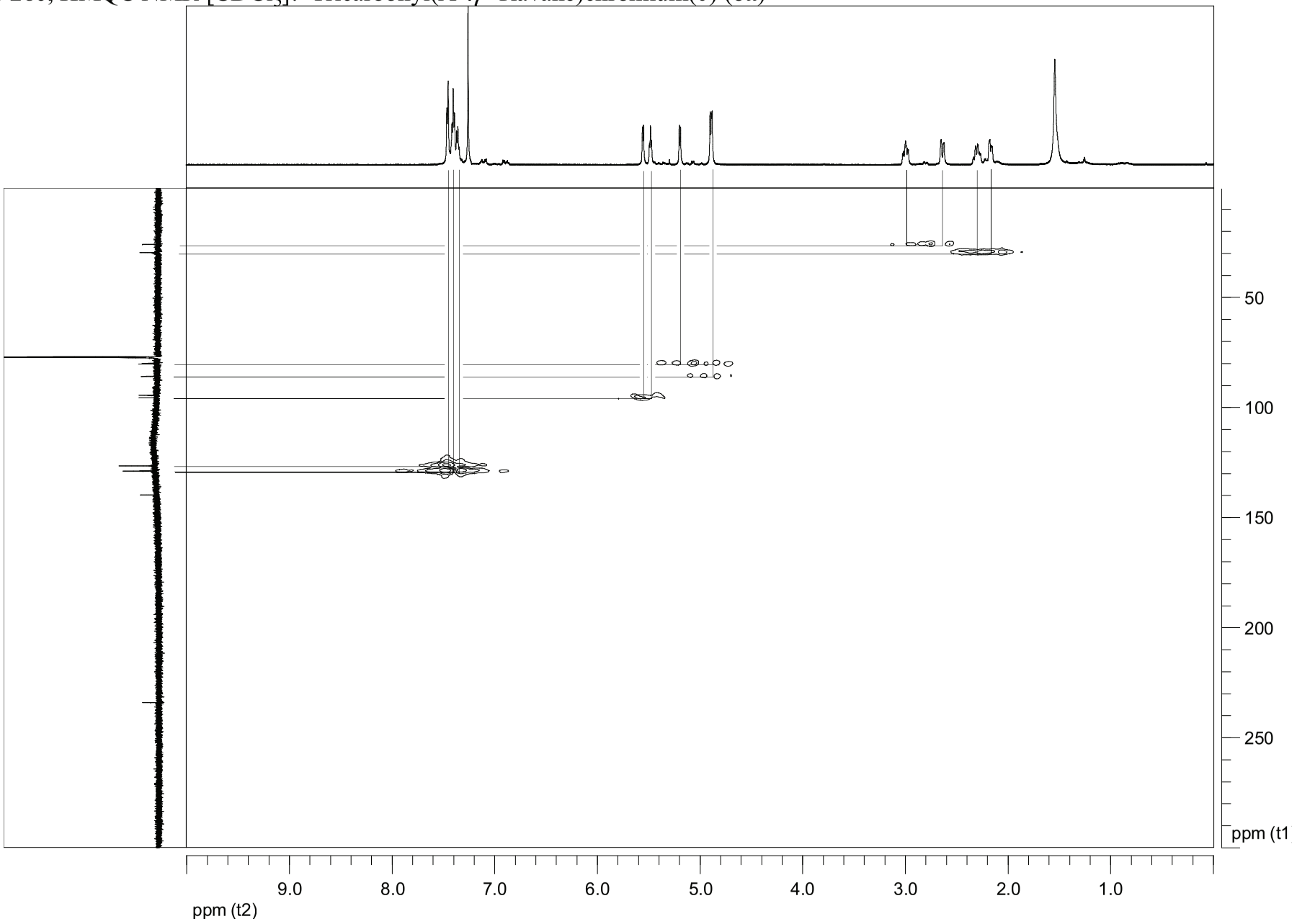


Plate 29; ^{1}H NMR [$CDCl_3$]: R_f 0.29 from flavan (**6**) complexation

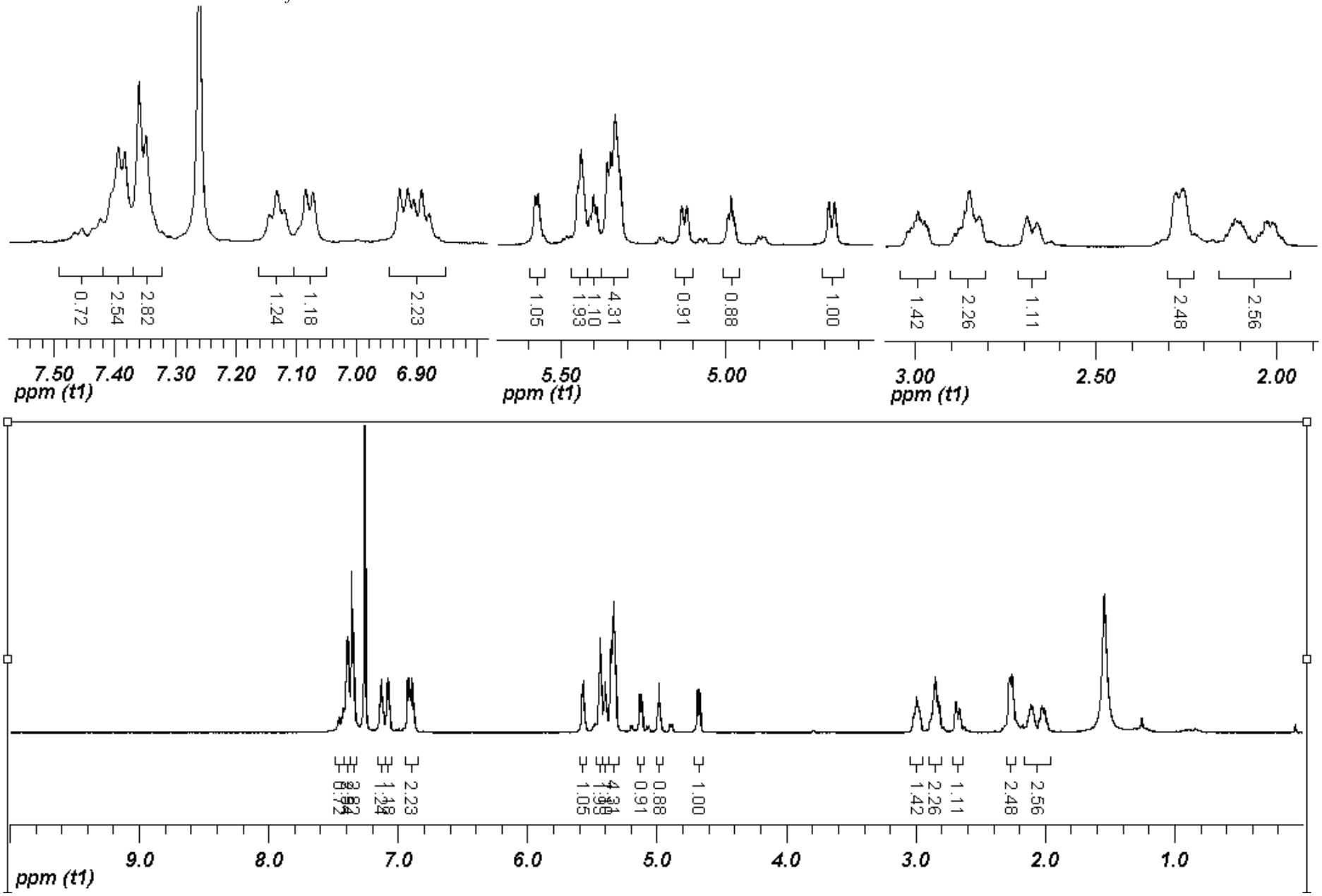


Plate 30; ^{1}H NMR [$CDCl_3$]: 2'-Hydroxy-4'-methoxychalcone (**199**)

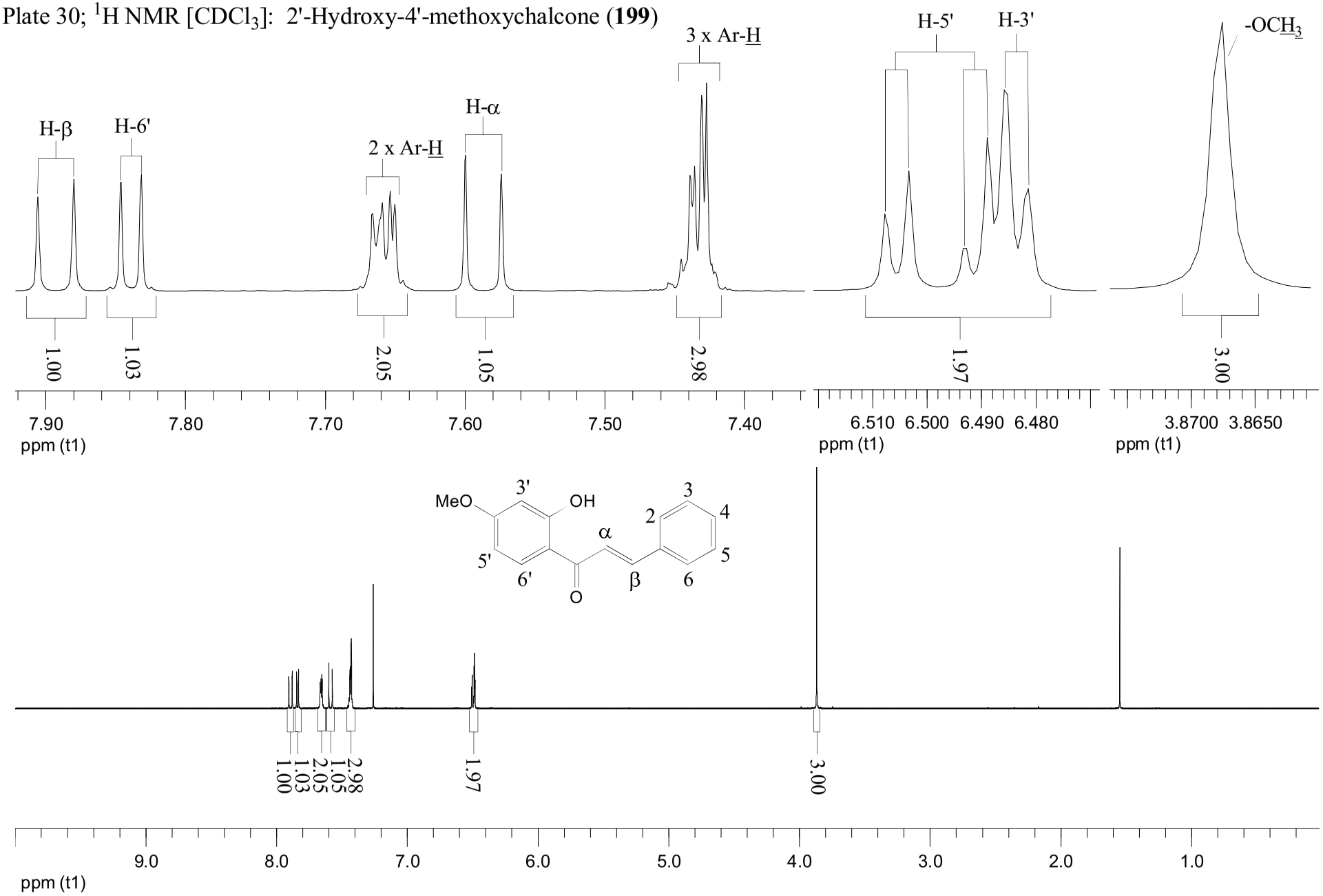


Plate 31; ^{1}H NMR [$CDCl_3$]: 7-Methoxyflavanone (**200**)

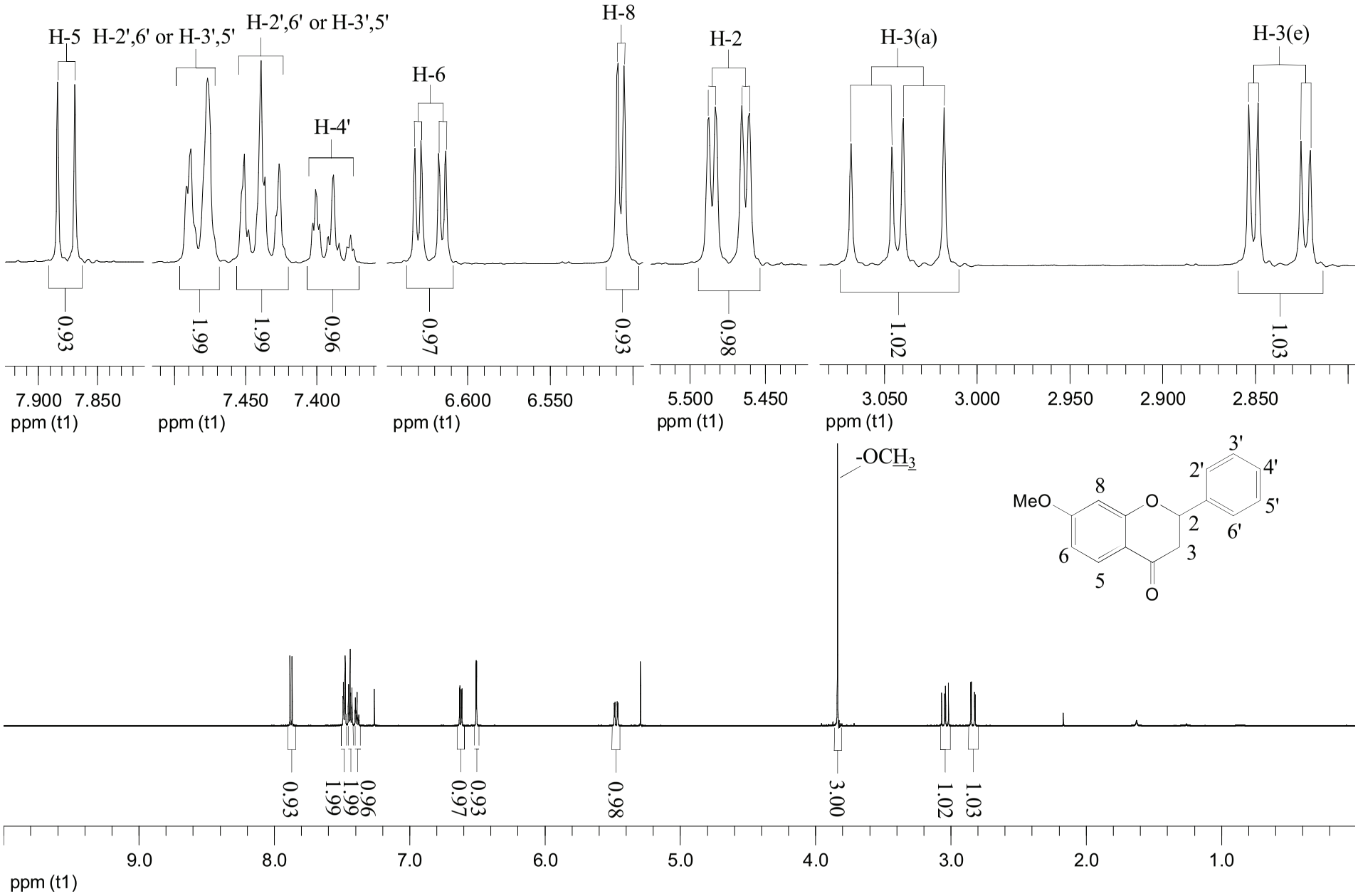


Plate 32a; ^{1}H NMR [$CDCl_3$]: 7-Methoxyflavan (**198**)

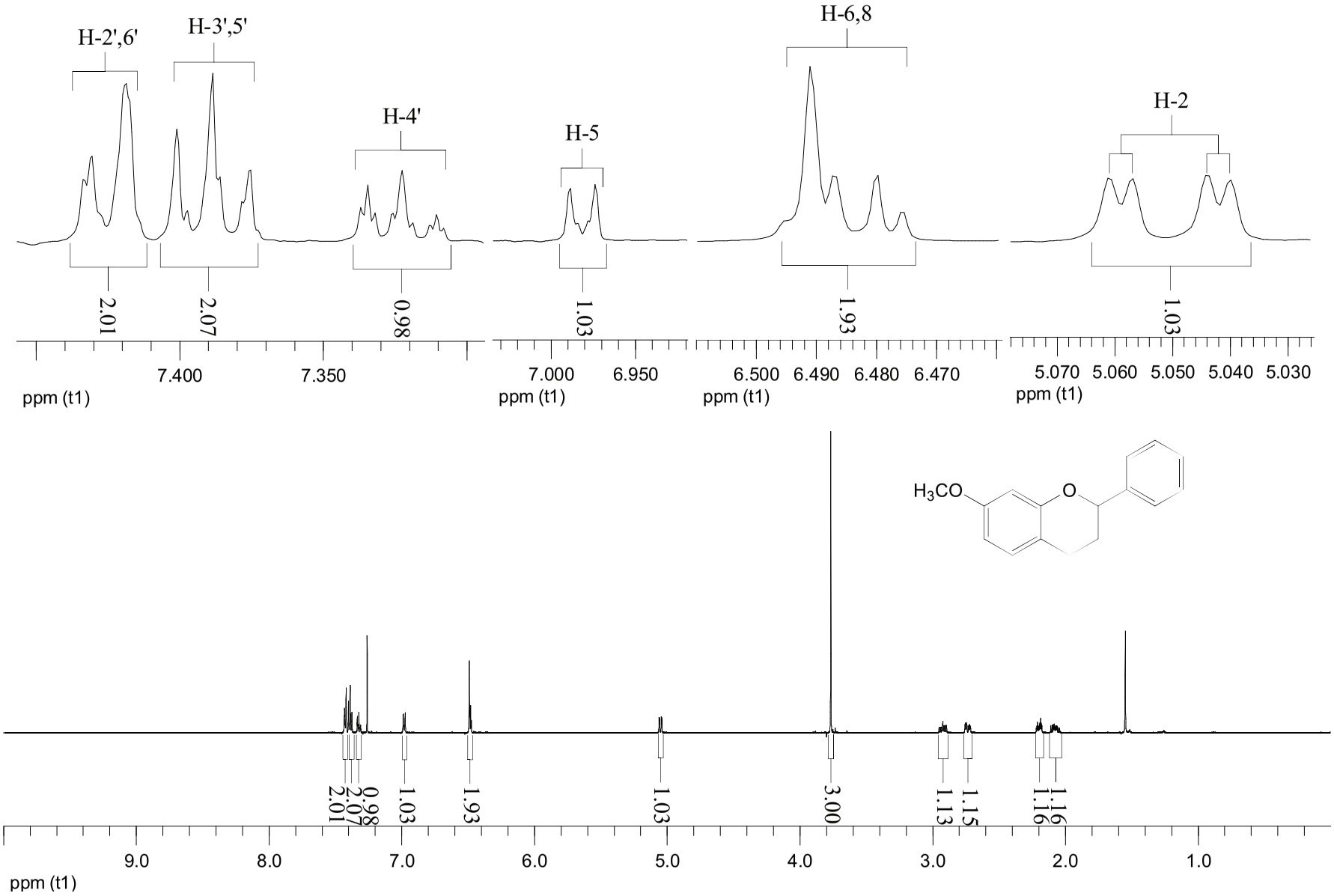


Plate 32a cont.; ^{1}H NMR [$CDCl_3$]: 7-Methoxyflavan (**198**)

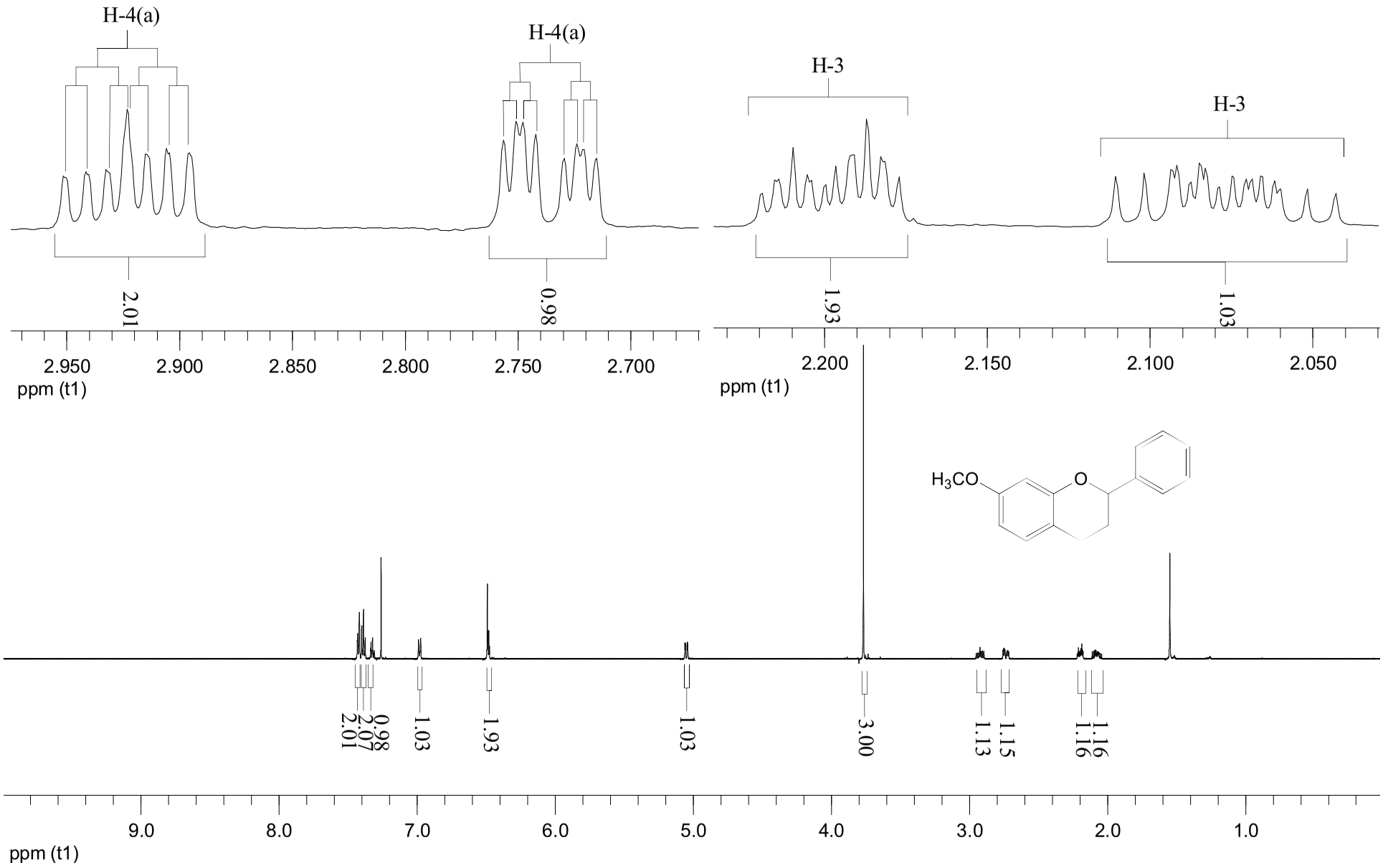


Plate 32b; ^{13}C NMR [$CDCl_3$]: 7-Methoxyflavan (**198**)

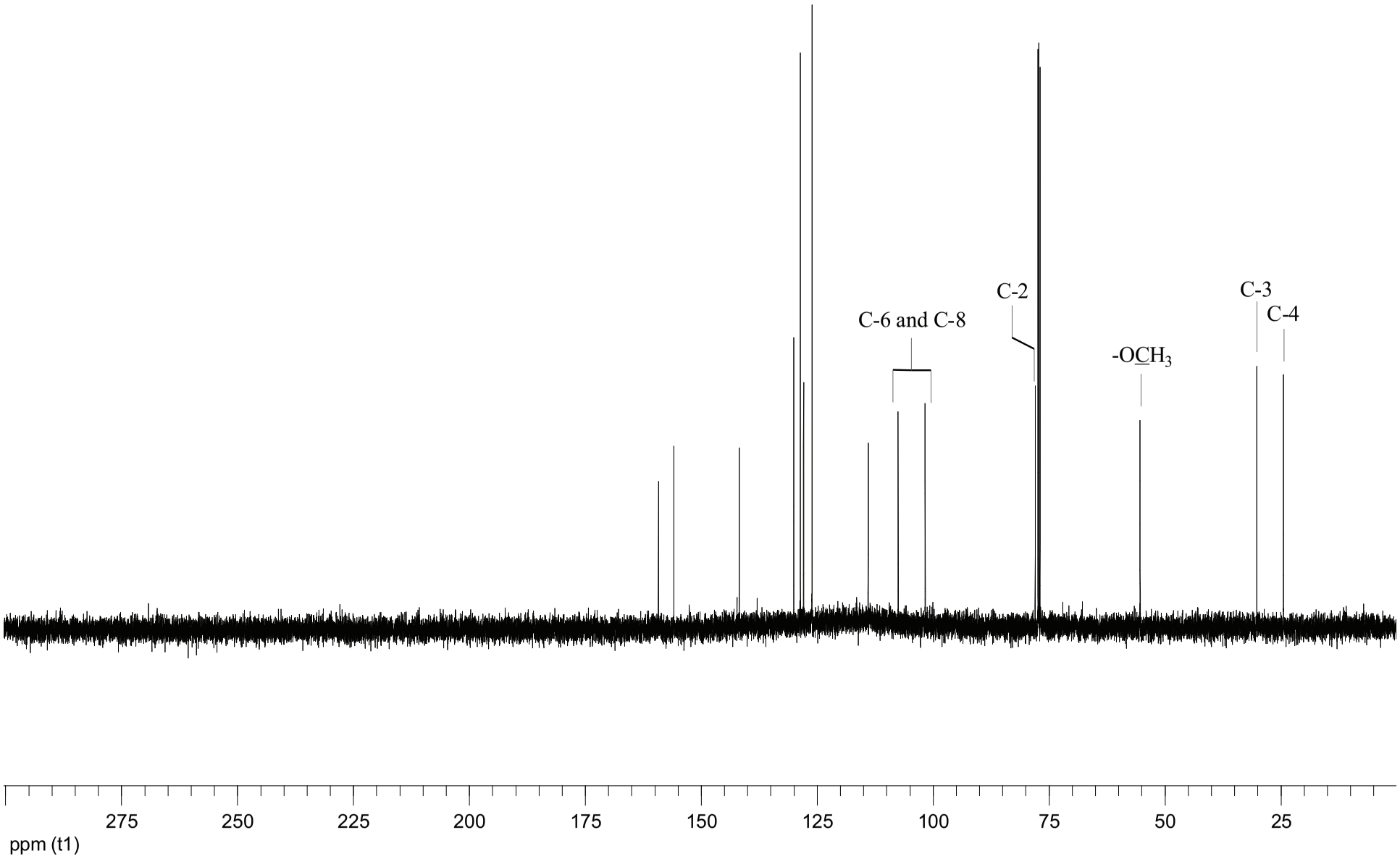


Plate 32c; HMQC NMR [$CDCl_3$]: 7-Methoxyflavane (**198**)

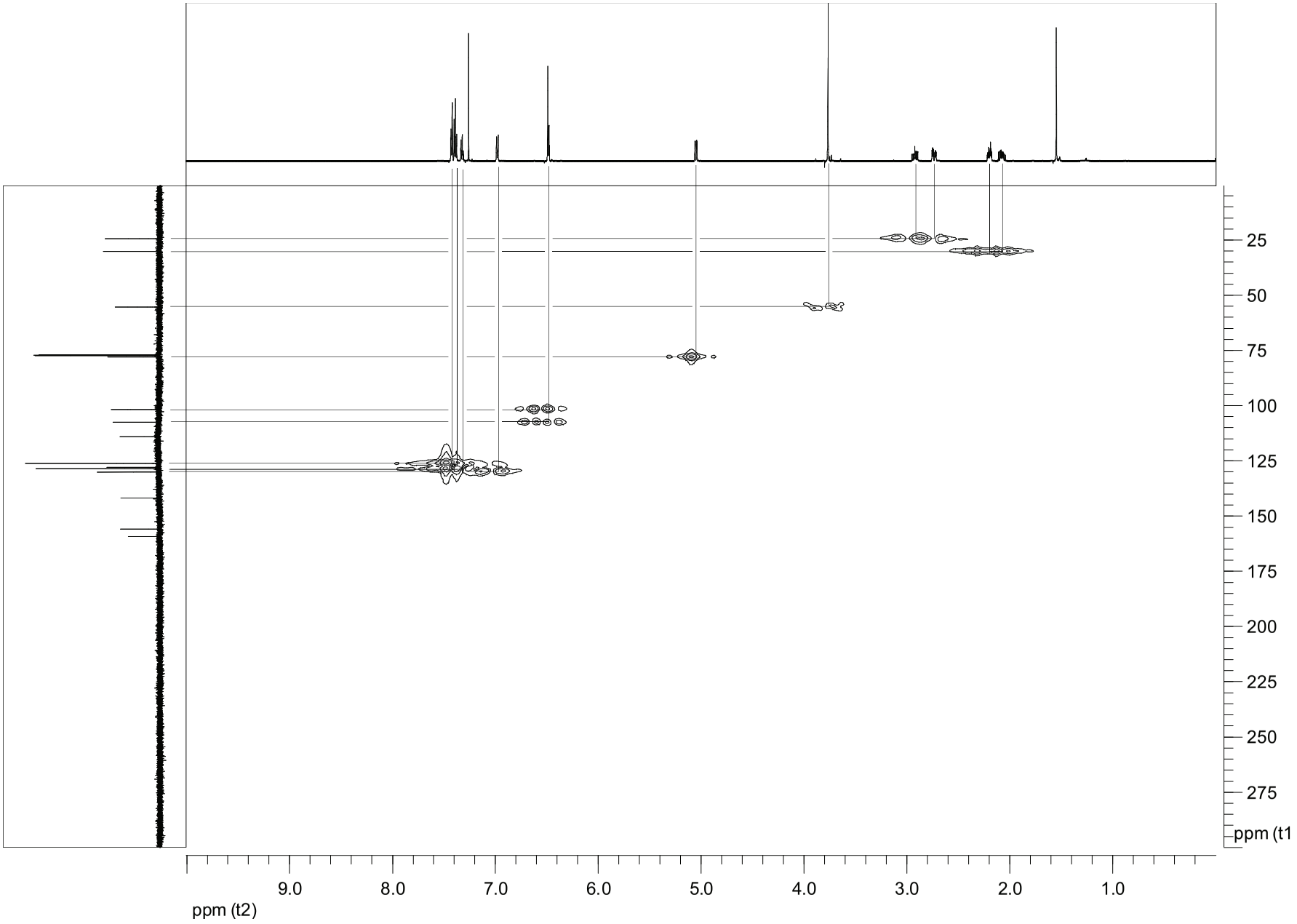


Plate 33a; ^{1}H NMR [$CDCl_3$]: Tricarbonyl(A-η^6-7-methoxyflavane)chromium(0) (**198a**)

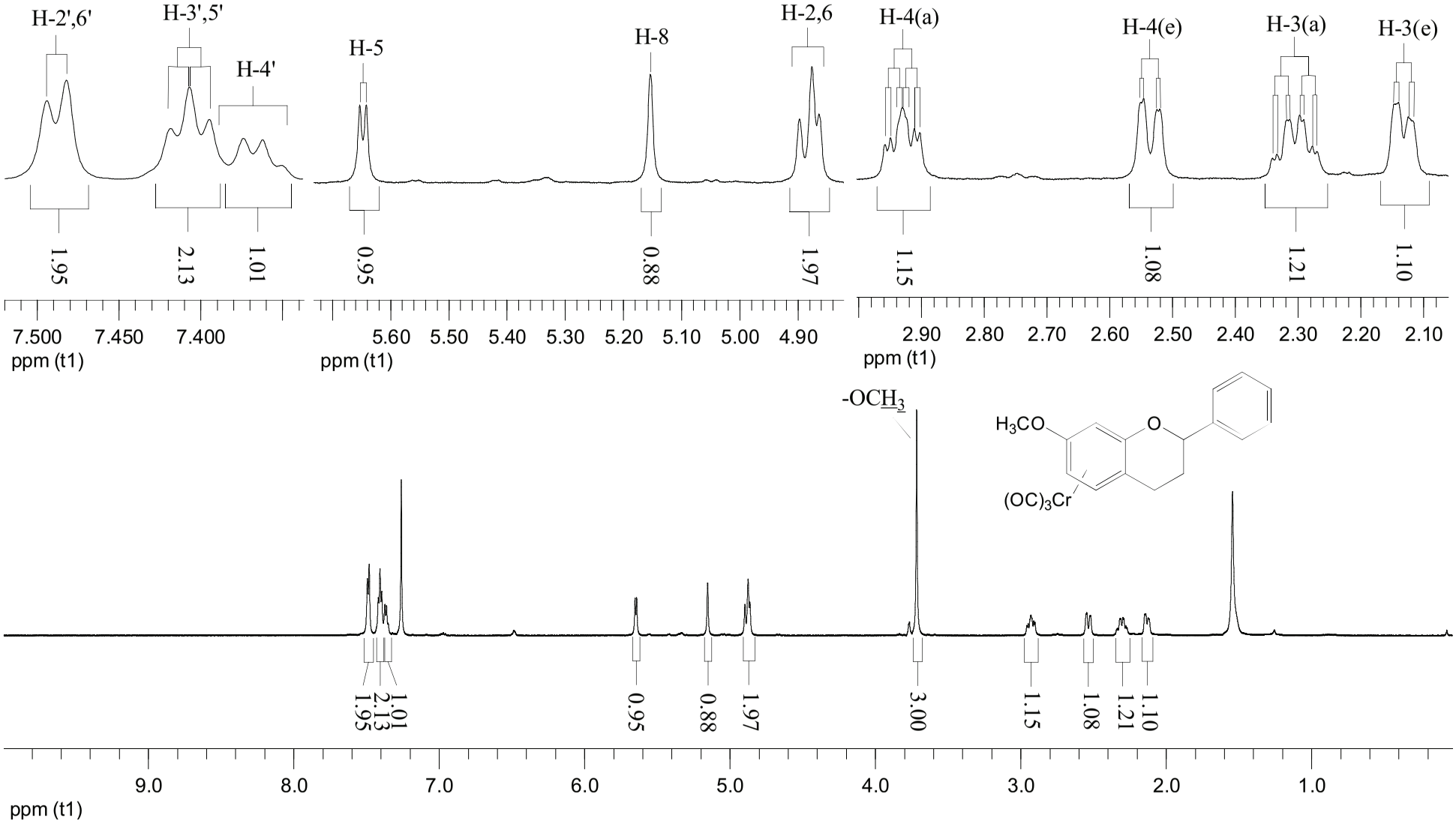


Plate 33b; ^{13}C NMR [$CDCl_3$]: Tricarbonyl(A-η^6-7-methoxyflavane)chromium(0) (**198a**)

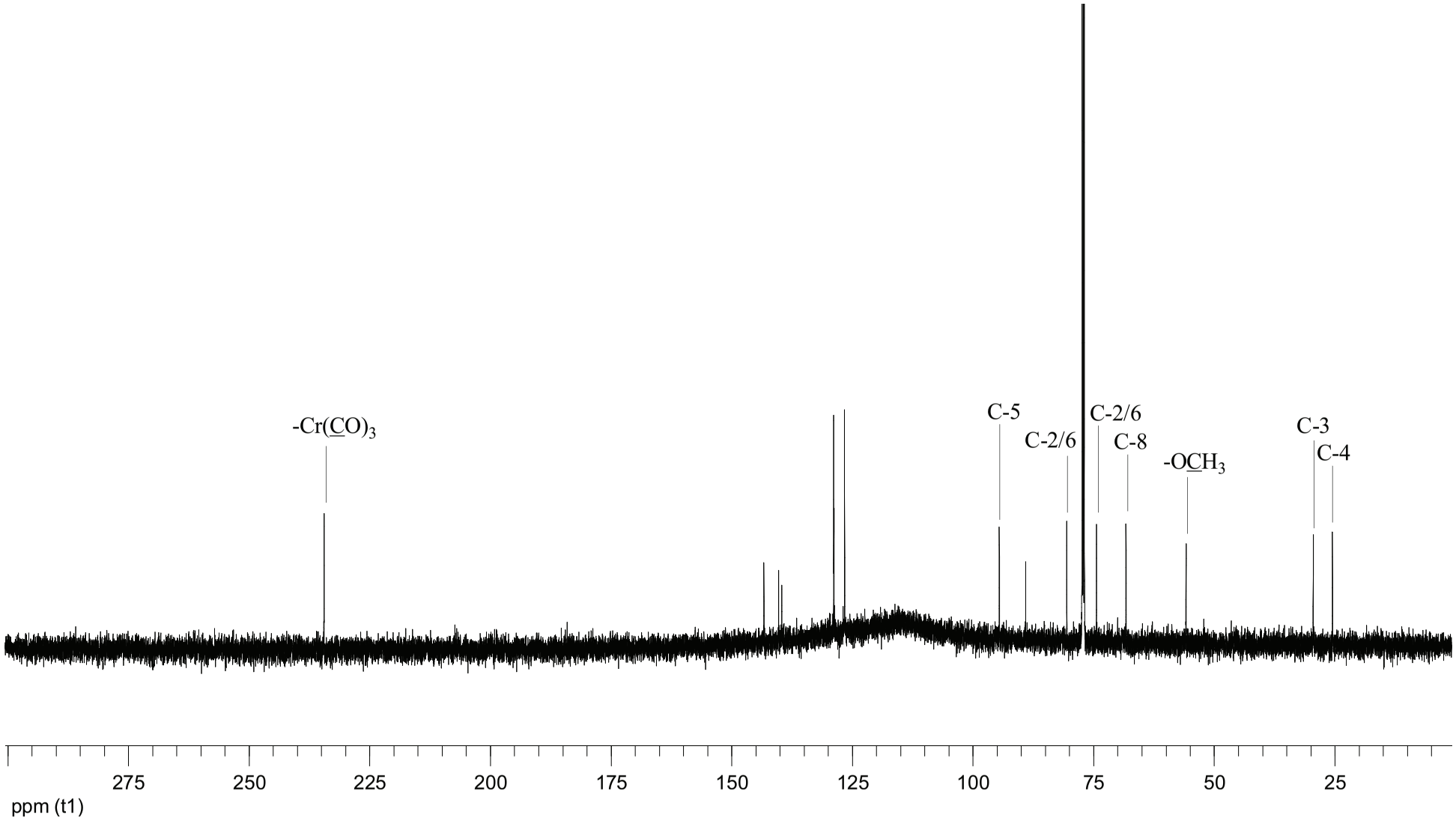


Plate 33c; HMQC NMR [$CDCl_3$]: Tricarbonyl(A-η^6-7-methoxyflavane)chromium(0) (**198a**)

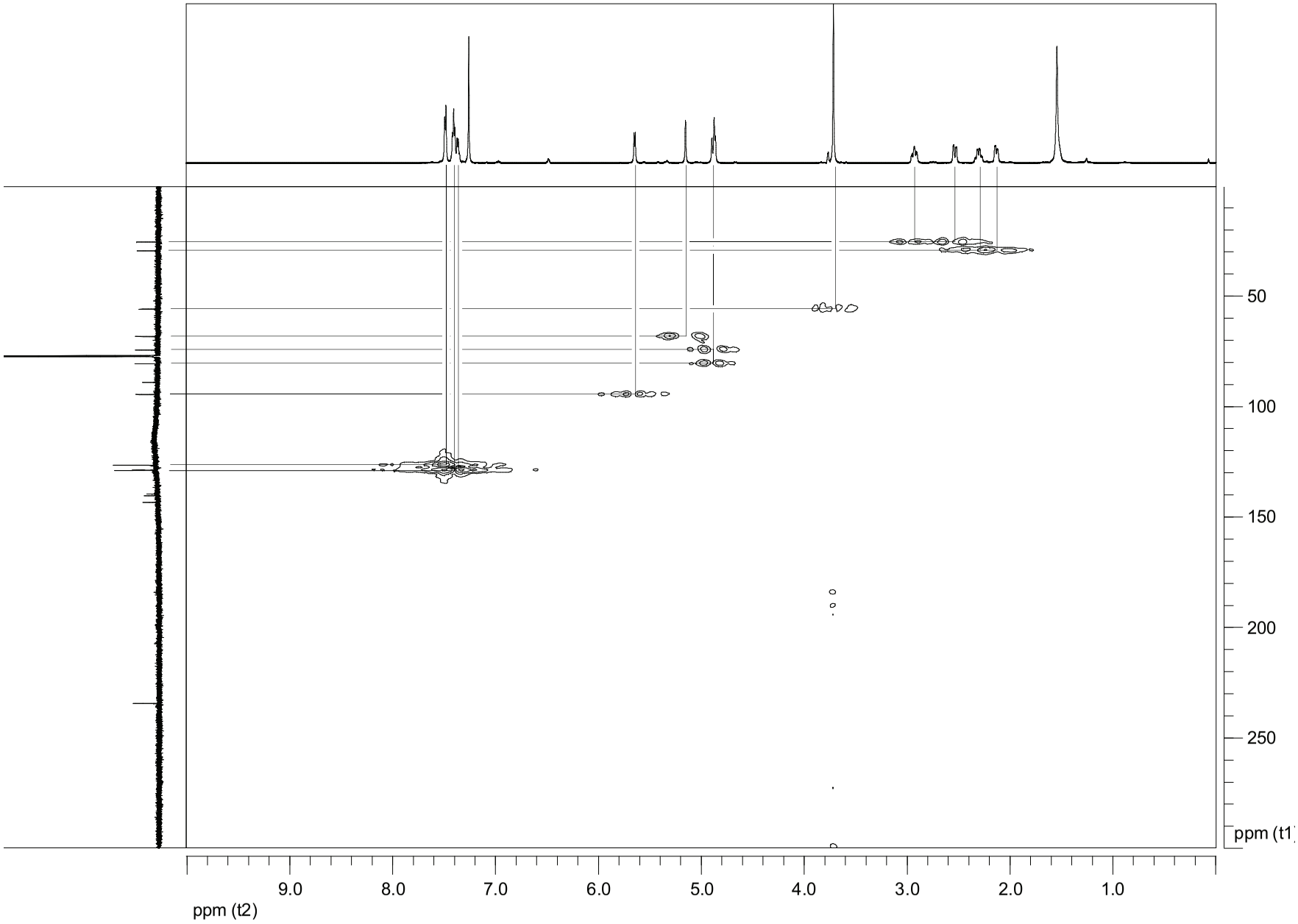
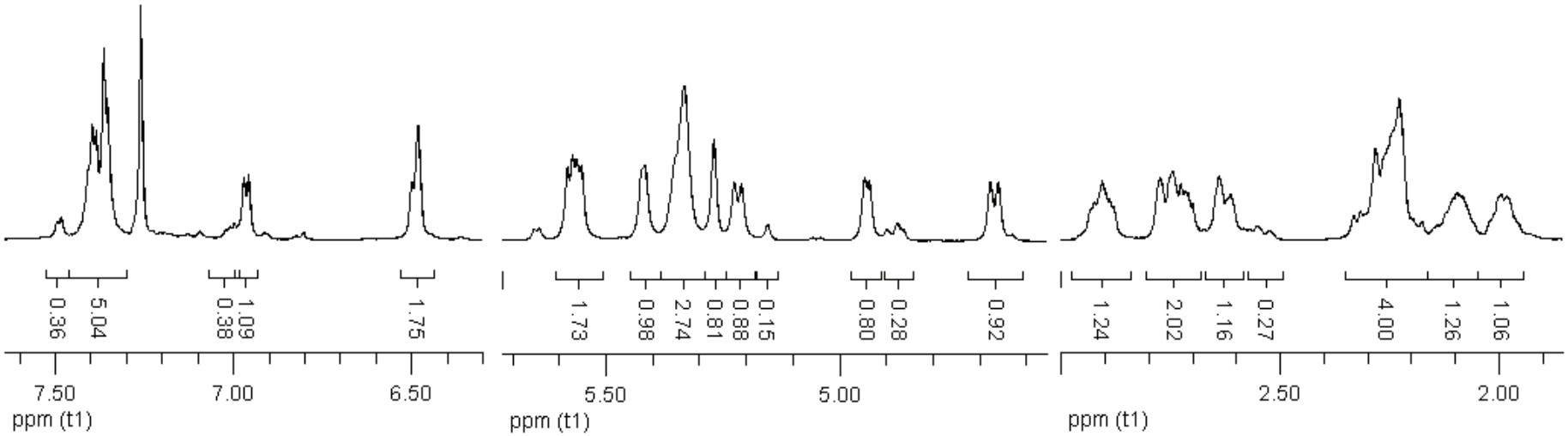


Plate 34; ^{1}H NMR [$CDCl_3$]: R_f 0.26 from 7-methoxyflavan (**198**) complexation



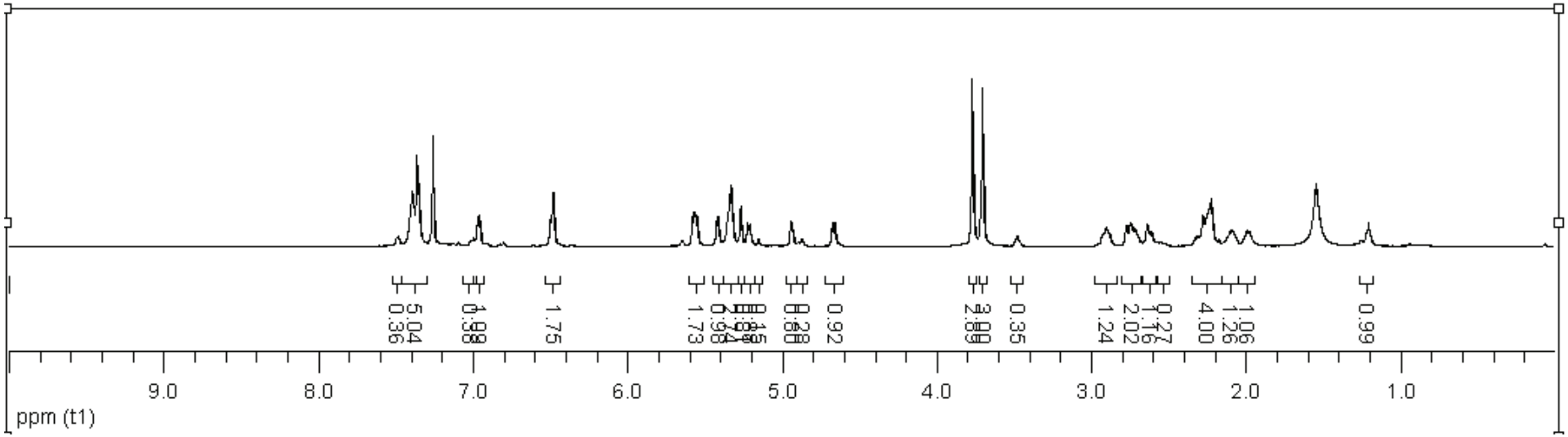
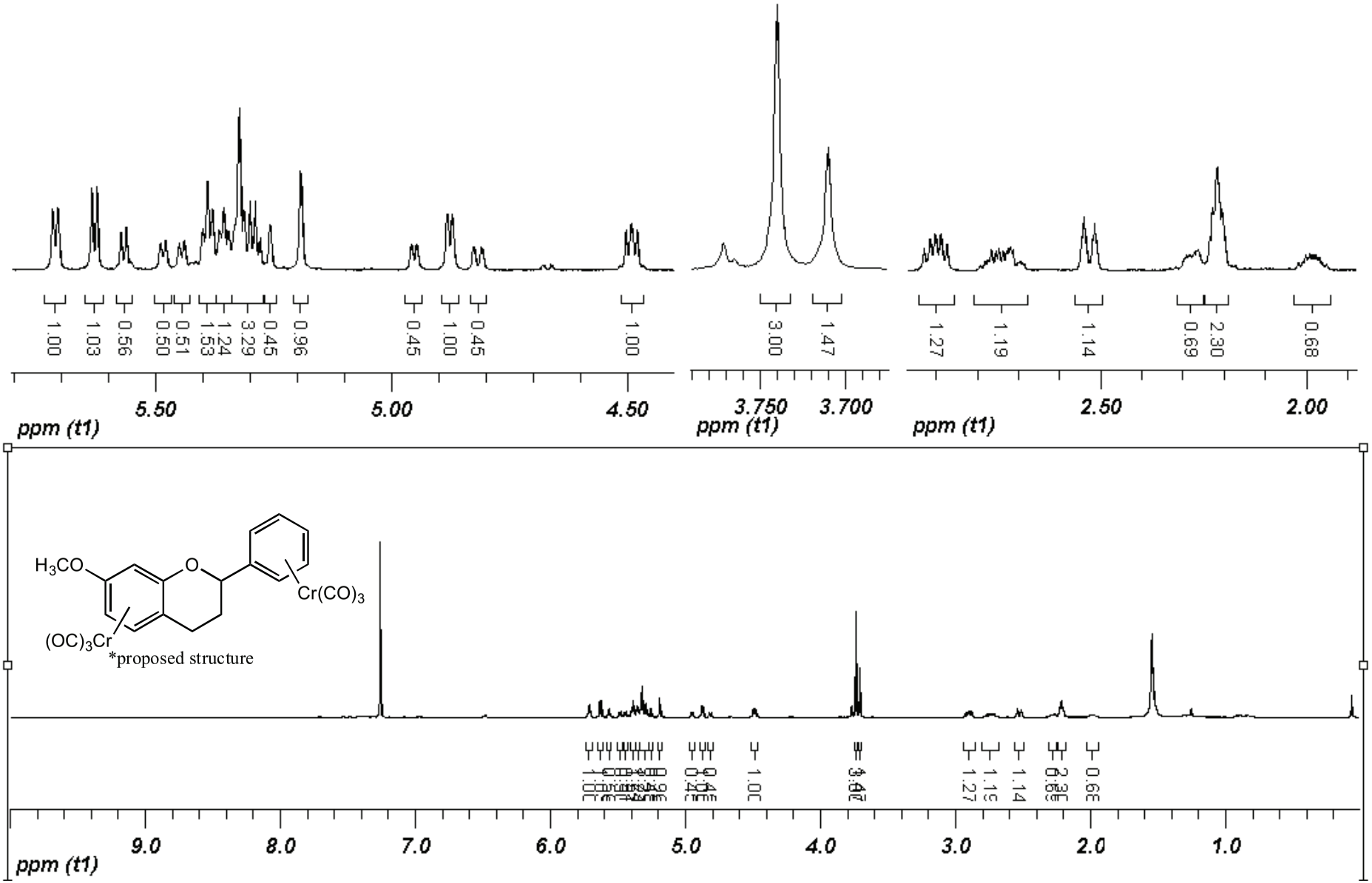


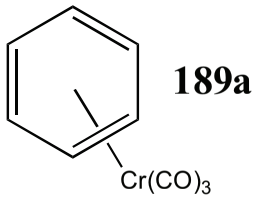
Plate 35; ^{1}H NMR [$CDCl_3$]: R_f 0.11 from 7-methoxyflavan (**198**) complexation



APPENDIX B

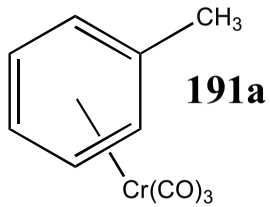
REPRESENTATIVE MS SCHEMES

MS Scheme 1; Tricarbonyl(η^6-arene)chromium(0) complexes



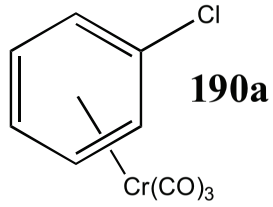
189a

214 (M^+, 56.0 %)
-CO = 186 (4.0)
-2CO = 158 (9.0)
-3CO = 130 (98.0)
-$Cr(CO)_3$ = 78 (100.0)



191a

228 (M^+, 39.5 %)
-CO = 200 (43.4)
-2CO = 172 (7.9)
-3CO = 144 (100.0)
-$Cr(CO)_3$ = 92 (6.0)
-$Cr(CO)_3$, -CH_3 = 77 (6.7)

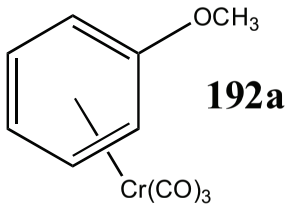


190a

248 (M^+, 49.8 %)
-CO = 220 (5.3)
-2CO = 192 (11.5)
-3CO = 164 (100.0)
-3CO, -Cl = 129 (7.4)

OR

248 (M^+, 49.8 %)
-$Cr(CO)_3$ =112 (9.1)
-$Cr(CO)_3$, -Cl = 77 (41.6)

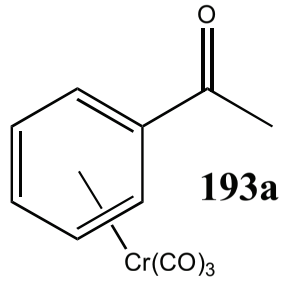


192a

244 (M^+, 35.0 %)
-CO = 216 (5.7)
-2CO = 188 (20.2)
-3CO = 160 (100.0)
-3CO, -CH_3 = 145 (5.8)

OR

244 (M^+, 35.0 %)
-$Cr(CO)_3$ = 108 (6.0)
-$Cr(CO)_3$, -CH_3 = 93 (3.1)
-$Cr(CO)_3$, -OCH_3 = 77 (7.2)



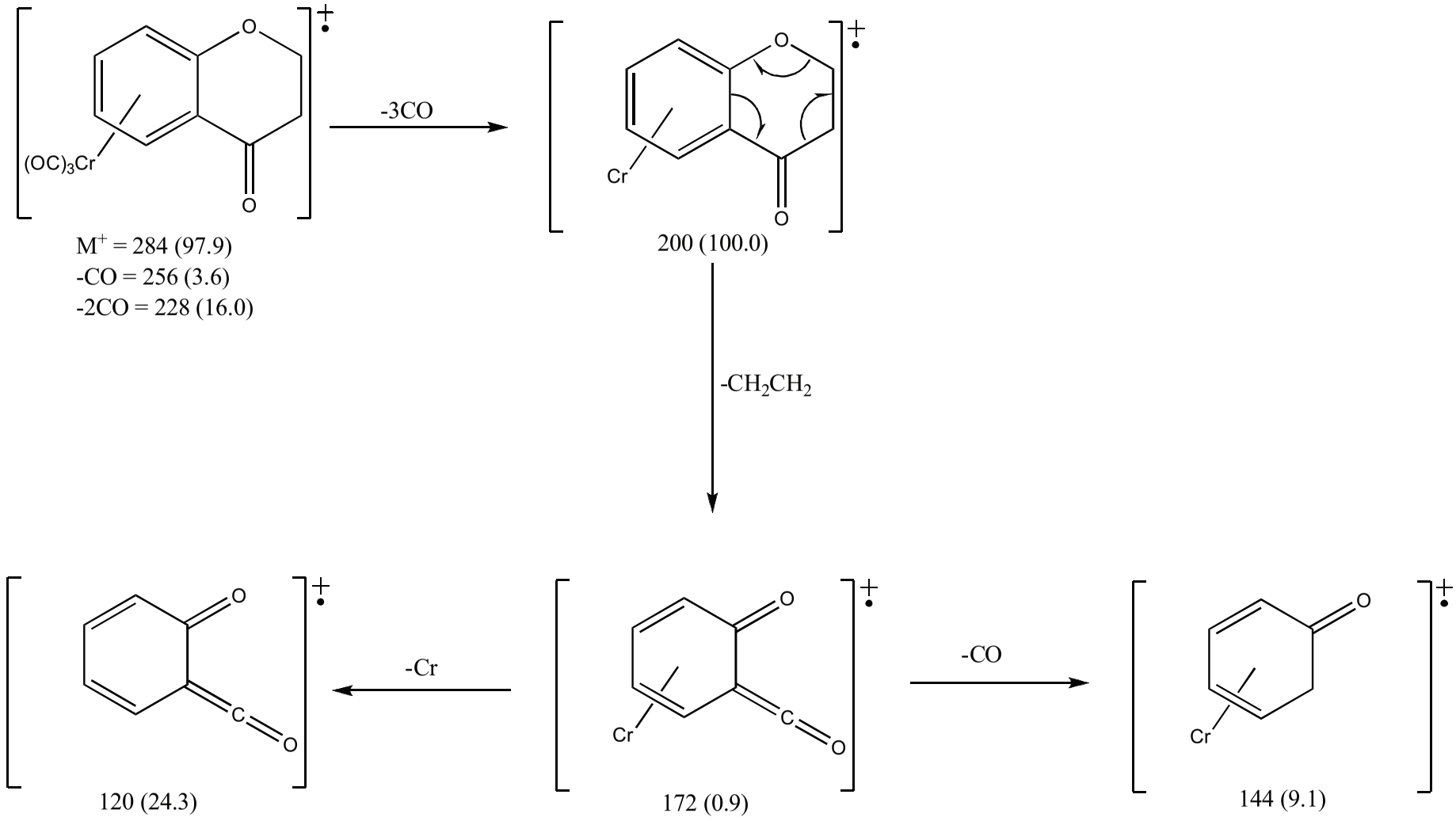
193a

258 (M+, 27.6 %)
-CO = 228 (8.0)
-2CO = 200 (27.9)
-3CO = 172 (100.0)
-3CO, -CH3 =157 (0.1)
-3CO, - COCH3 = 129 (8.1)

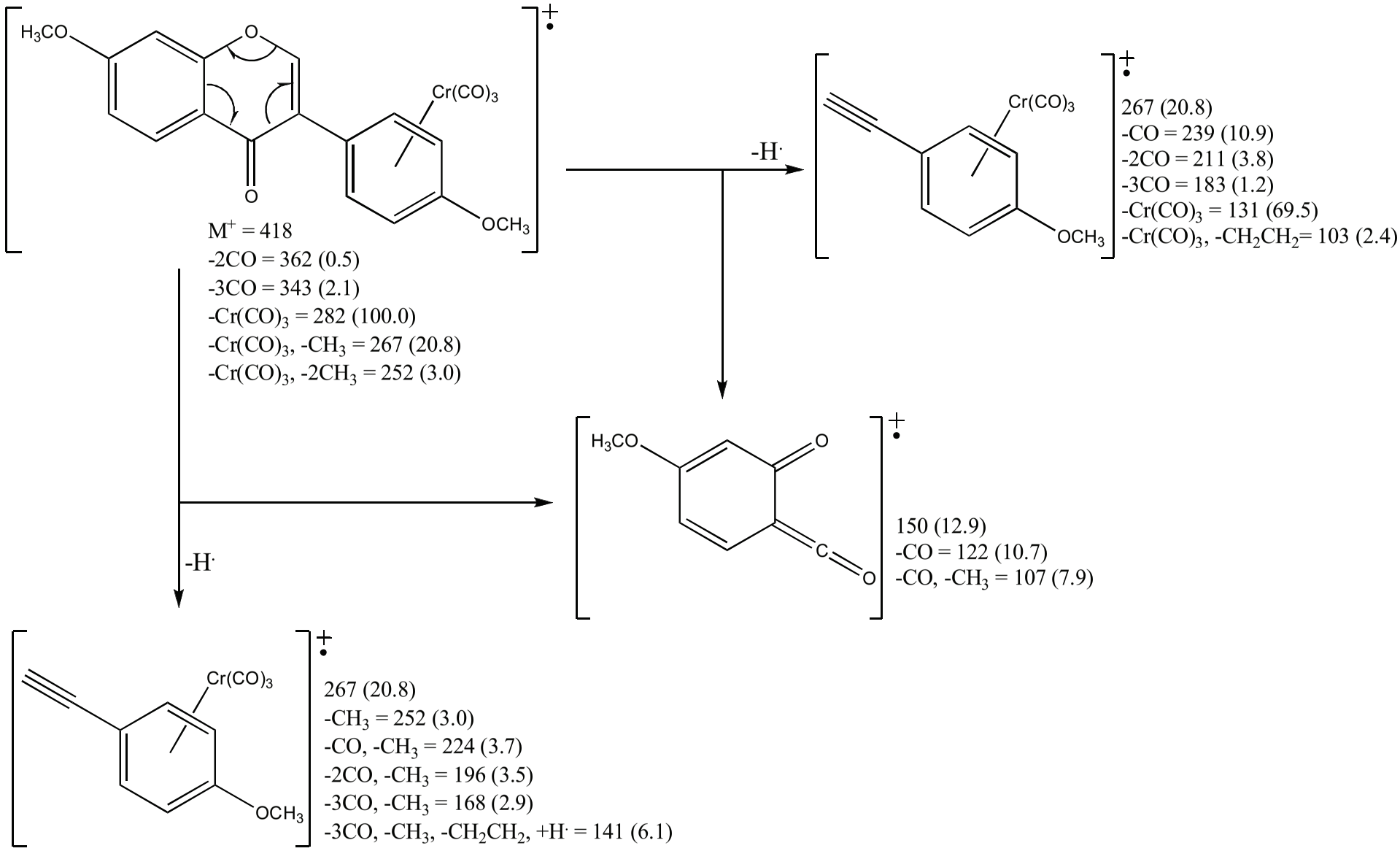
OR

258 (M^+, 27.6 %)
-$Cr(CO)_3$ = 120 (0.2)
-$Cr(CO)_3$, -CH_3 = 105 (8.0)
-$Cr(CO)_3$, -$COCH_3$ = 77 (20.8)

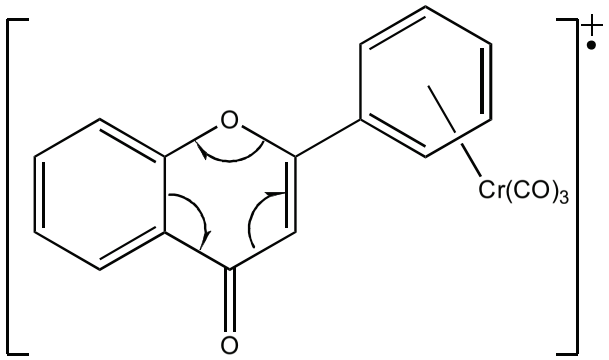
MS Scheme 2; Tricarbonyl(η^6-chroman-4-one)chromium(0) (**180a**)



MS Scheme 3; Tricarbonyl(B-η^6-4',7-dimethoxyisoflavone)chromium(0) (**56a**)

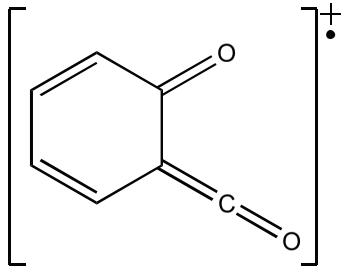


MS Scheme 4; Tricarbonyl(B-η^6-flavone)chromium(0) (**164a**)



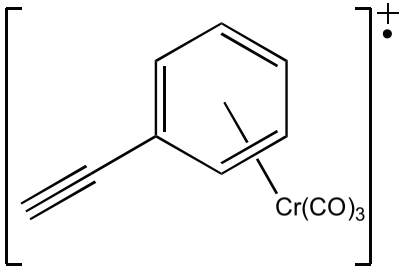
M^+ = 358 (4.4)
-CO = 330 (0.9)
-2CO = 302 (2.1)
-3CO = 274 (11.3)
-$Cr(CO)_3$, +H· = 223 (100.0)

+H·



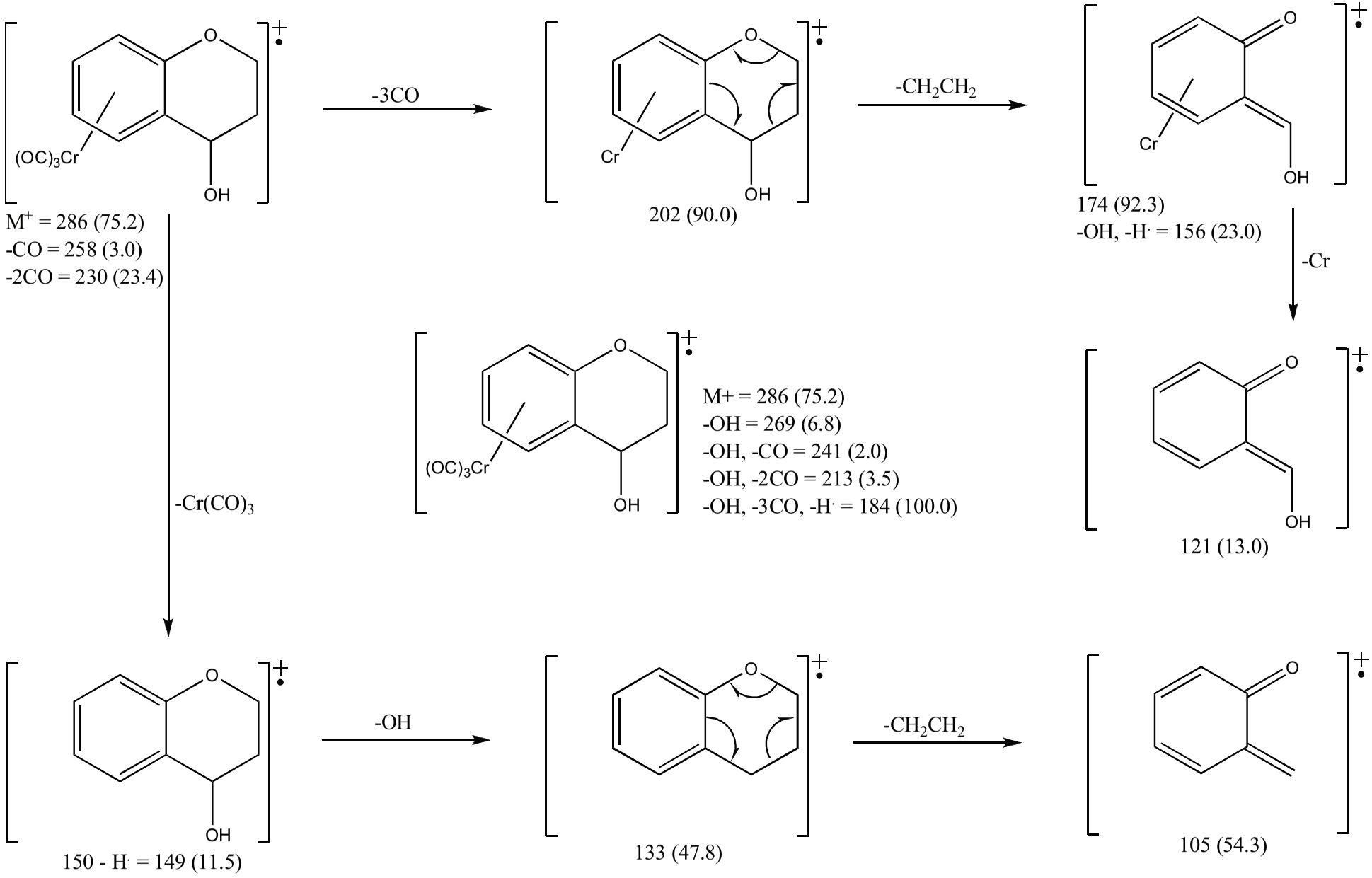
121 (29.0)

+H·

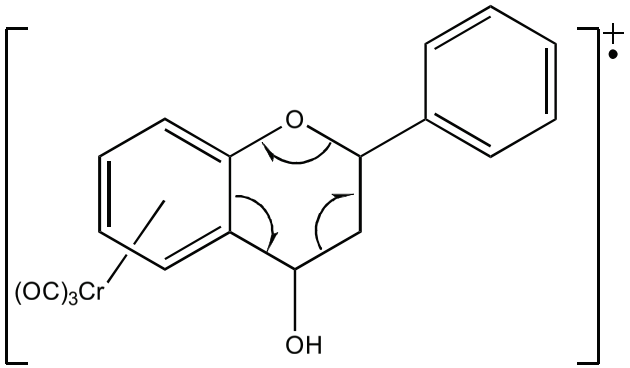


239 (2.2)
-CO = 210 (0.6)
-2CO, +H· = 183 (2.6)
-3CO, +H· = 155 (3.5)
-$Cr(CO)_3$, +H· = 103 (4.7)

MS Scheme 5; Tricarbonyl(η^6-chroman-4-ol)chromium(0) (**196a** and **196b**)



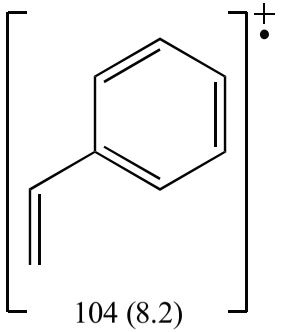
MS Scheme 6; Tricarbonyl(A-η^6-flavan-4-ol)chromium(0) (**197a**)



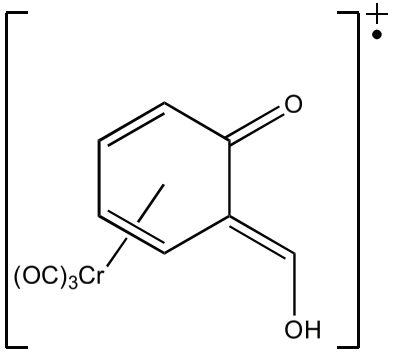
M^+ = 362 (25.7)
-2CO = 306 (5.2)
-3CO = 278 (78.9)
-$Cr(CO)_3$ = 226 (0.5)

OR

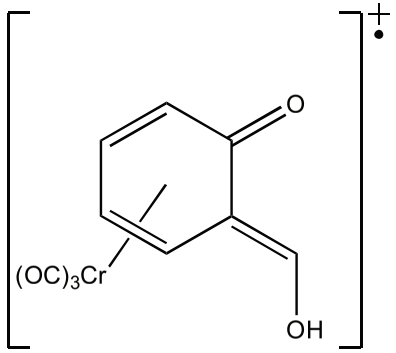
M^+ = 362 (25.7)
-OH, -3CO, -H· = 260 (22.0)



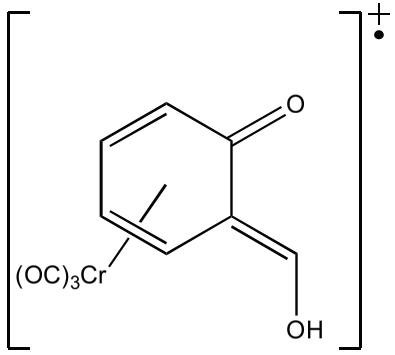
104 (8.2)



258 (13.9)
-OH = 241 (1.4)
-OH, -2CO, -H· = 184 (1.1)
-OH, -3CO, -H· = 156 (9.0)
-OH, -$Cr(CO)_3$ = 105 (2.2)

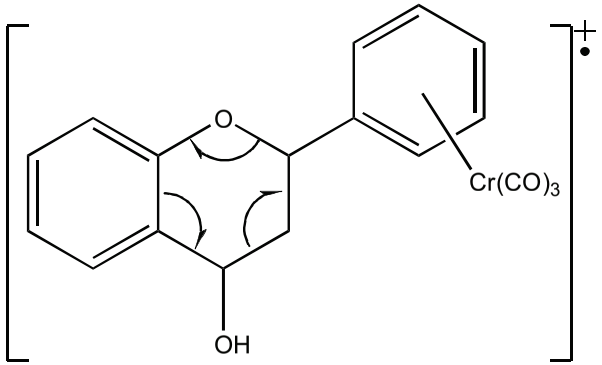


258 (13.9)
-CO = 230 (1.2)
-3CO = 174 (100.0)
-3CO, -CHOH = 144 (5.8)



258 (13.9)
-$Cr(CO)_3$ = 122 (4.0)
-$Cr(CO)_3$, -OH = 105 (2.2)

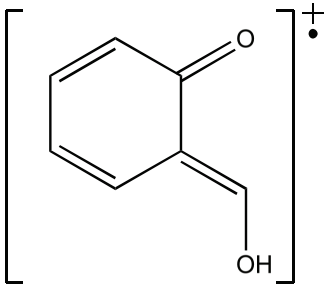
MS Scheme 7; Tricarbonyl(B-η^6-flavan-4-ol)chromium(0) (**197b**)



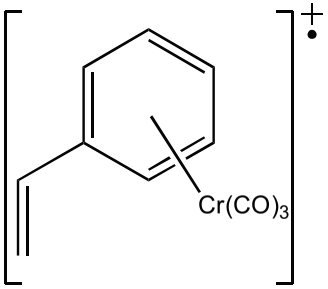
M^+ = 362 (3.8)
-CO = 334 (2.2)
-2CO = 306 (21.8)
-3CO = 278 (100.0)
-$Cr(CO)_3$ = 226 (1.2)

OR

M^+ = 362 (3.8)
-3CO, -OH, -H. = 260 (19.2)
-$Cr(CO)_3$, -OH = 209 (5.1)

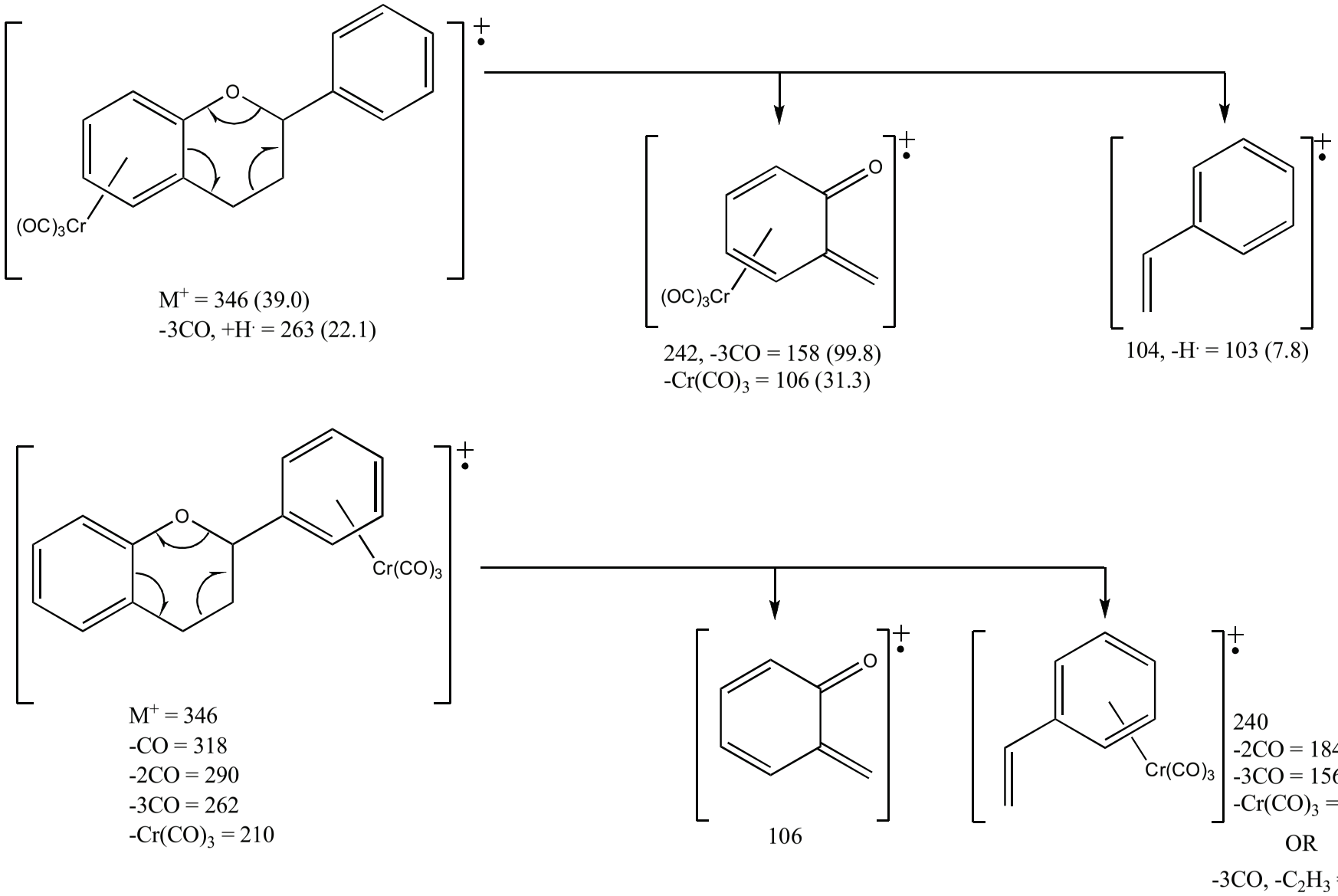


122 (3.6)
-OH, -$H^{\cdot}$ = 104 (10.4)

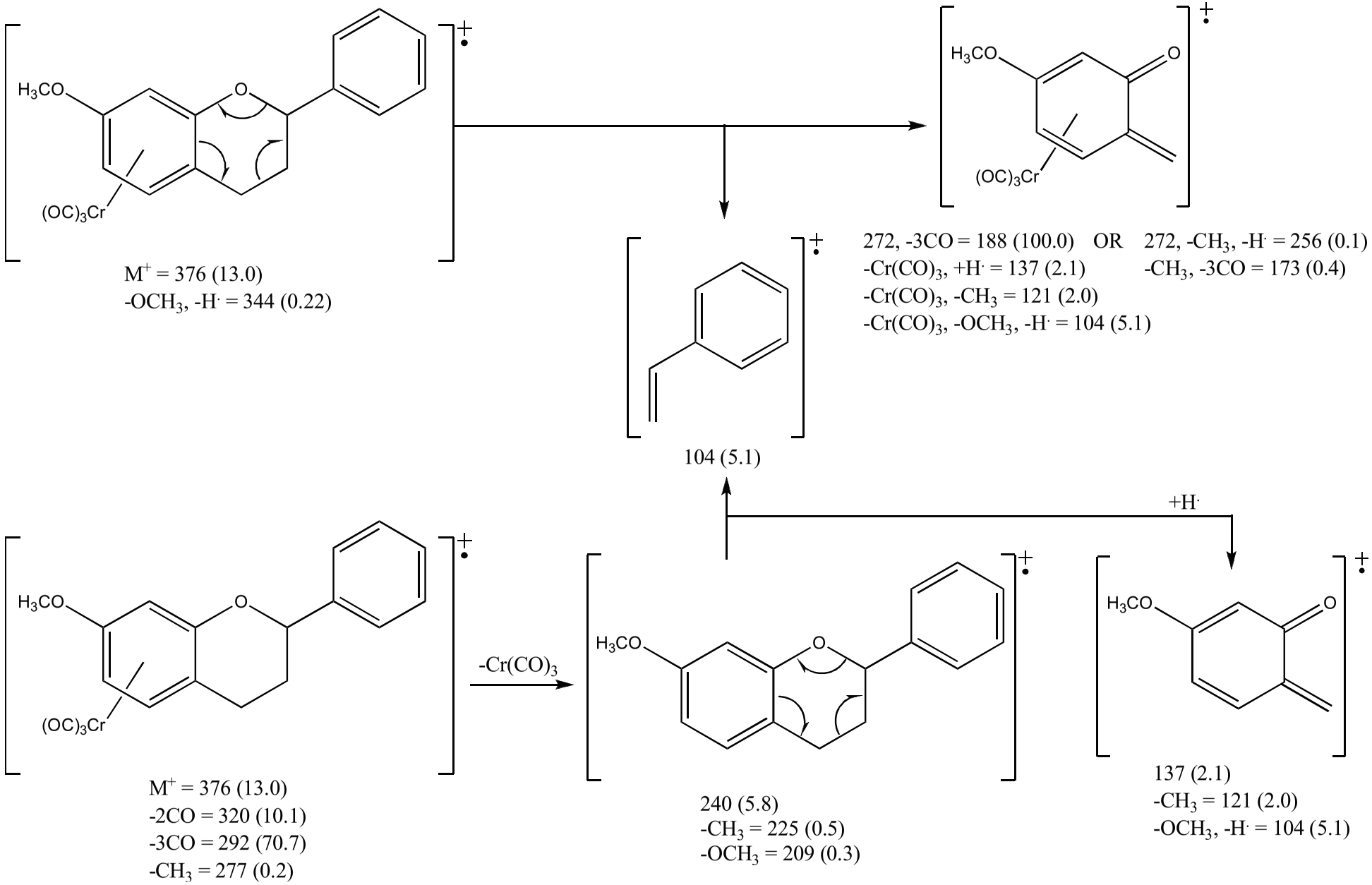


241 (0.9)
-CO = 213 (1.0)
-2CO = 185 (0.8)
-3CO, -$H^{\cdot}$ = 156 (11.1)
-$Cr(CO)_3$ = 104 (10.4)

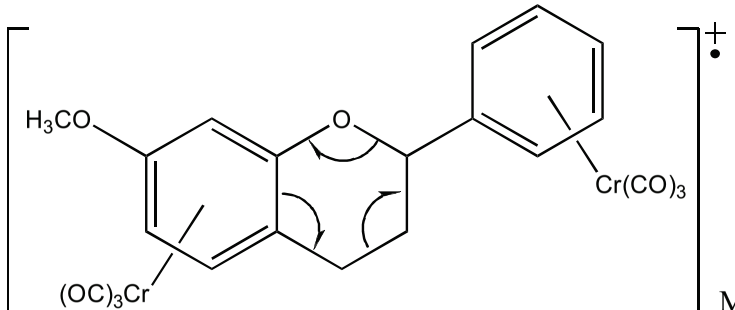
MS Scheme 8; Tricarbonyl(A-η^6-flavan)chromium(0) (**6a**) and tricarbonyl(B-η^6-flavan)chromium(0) (**6b**)



MS Scheme 9; Tricarbonyl(A-η^6-7-methoxyflavan)chromium(0) (**198a**)



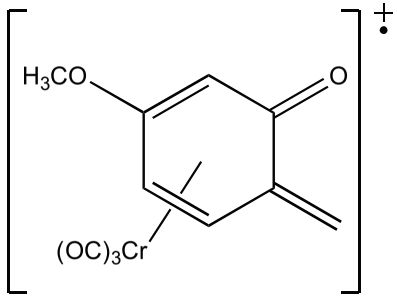
MS Scheme 10; Tricarbonyl(A,B-η^6-7-methoxyflavan)chromium(0) (**198c**)



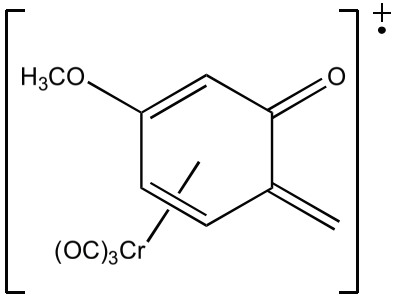
M^+, -3CO, -$Cr(CO)_3$, -CH_3 = 277 (0.6)
-2$Cr(CO)_3$, -CH_3 = 225 (0.8)

OR

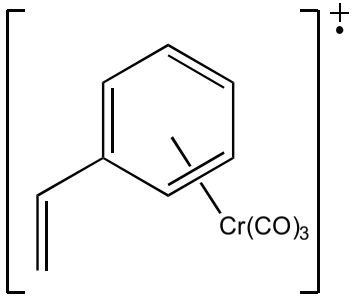
M^+, -4CO = 400 (0.2)
-6CO = 344 (2.2)
-3CO, -$Cr(CO)_3$ = 292 (69.5)
-2$Cr(CO)_3$ = 240 (2.8)



272 (1.6)
-CH_3, -$H^{\cdot}$ = 256 (0.3)
-CH_3, -CO = 229 (0.2)
-CH_3, -2CO = 201 (0.3)
-CH_3, -3CO = 173 (1.5)
-CH_3, -$Cr(CO)_3$ = 121 (2.3)



272 (1.6)
-2CO, +$H^{\cdot}$ = 217 (0.2)
-3CO = 188 (100.0)
-$Cr(CO)_3$ = 136 (3.7)
-$Cr(CO)_3$, -CH_3 = 121 (2.3)



240 (2.8)
-CO, -$H^{\cdot}$ = 211 (0.4)
-2CO, -$H^{\cdot}$ = 183 (0.3)
-3CO = 156 (0.9)
-C_2H_3 = 129 (2.2)

OR

240 (2.8)
-$Cr(CO)_3$ = 104 (4.7)

SUMMARY

Summary

The *in vitro* studies of biologically active flavonoids are hampered by the inaccessibility of all monomeric units in enantiomerically pure form. Although a number of these scalemic flavonoids can be obtained synthetically, current methodologies are tedious and often result it low yields and e.e.s being obtained. Stereoselective conjugated hydrogenation of the more readily available prochiral α,β-unsaturated carbonyl flavonoid motifs, i.e. flavones, isoflavones and flavonols, provide a plausible solution to this problem and was therefore investigated during the first part of this dissertation.

Since the stereoselective 1,4-reduction of an α,β-unsaturated system also contains an element of regioselectivity, a regioselective hydrogenation study was conducted first before the reaction would be extended to include stereoselective aspects. Because Wilkinson's catalyst is commercially available, has the potential to be modified with chiral ligands and is a well known hydrogenation catalyst, it was chosen as catalyst for the initial evaluation of the idea. While Wilkinson's catalyst is well known for hydrogenation of ordinary alkenes, no literature on it being used for the reduction of α,β-unsaturated carbonyl compounds could be found, so the effectiveness of this catalyst in the hydrogenation of differently substituted non-flavonoid substrates were first investigated. In this regard a solvent study on chromone, evaluating acetone, tetrahydrofurane and dichloromethane (DCM), showed DCM to be the solvent of choice for this reaction and led to the formation of 4-chromanone in 7.8 %, 14.3 % and 46.2 % respectively. By using 2-cyclohexenone as substrate, optimum hydrogenation conditions were determined to be *ca*. 30 bar and 100 ^{o}C, because reactions at higher temperatures (110 ^{o}C) and pressures (40 bar) were inhibited by rhodium fall-out. In order to evaluate the effect of different levels of substitution around the olefinic double bond on the reaction rate for cyclic- as well as acyclic olefins, 2-cyclohexenone, 3-methyl-2-cyclohexenone, 3-buten-2-one, 3-penten-2-one, 4-methyl-3-penten-2-one, 3-methyl-3-penten-2-one, crotonaldehyde, and chalcone were subjected to the hydrogenation reaction.

While no hydrogenation could be achieved for the trisubstituted acyclic ketones, *i.e.* 4-methyl-3-penten-2-one and 3-methyl-3-penten-2-one, as well as crotonaldehyde, the trisubstituted cyclic equivalent, 3-methyl-2-cyclohexenone, indeed gave the saturated ketone albeit with a very low reaction rate [k_{obs} = 0.000174644 s^{-1} (80 ^{o}C and 20 bar)]. The

hydrogenation rates of the remaining acyclic substrates, 3-buten-2-one and 3-penten-2-one (k_{obs} = 0.0245703 and 0.000226852 s^{-1} respectively at 80 ^{o}C and 10 bar), followed the expected order of monosubstituted > disubstituted, while the effect of a cyclic structure proved to be rather insignificant (k_{obs} = 0.000254025 s^{-1} for 2-cyclohexenone). Aromatic disubstitution, however, reduced the reaction rate by *ca*. 50 % (k_{obs} = 0.000143572 s^{-1} for chalcone).

While the reaction rate (k_{obs}) for the volatile substrates could easily be determined by GC and GC/MS analysis, the reactor set-up and analytical methodology were changed for the flavonoid like solid substrates. For these solids, reactions were followed by NMR and $t_{½}$ (time to achieve 50 % conversion) used as indication of the reaction rate. In order to be able to compare $t_{½}$ with the previously measured reaction rate, the hydrogenation of chalcone was repeated and it was found that the concentration of the reactant has a major influence on the rate of the reaction. In a study where the concentration of chalcone was varied between 0.083 M and 0.50 M the optimum concentration was determined as 0.166 M ($t_{½}$ = 27 min.) for reactions at 80 ^{o}C, 20 bar hydrogen pressure and a catalyst concentration of 0.72 mM. Extension of the reaction to chromone indicated the heterocyclic ring to have a profound influence on the reaction rate ($t_{½}$ = 72 h *vs.* 27 min. for chalcone), while the flavonoid substrates, flavone and 4',7-dimethoxyisoflavone, having trisubstituted double bonds could not be hydrogenated at all using Wilkinson's catalyst.

In a completely different approach, the introduction of chirality into a planar flavonoid molecule (flavone or isoflavone type compound) by means of an arene metal complex was investigated. If a bulky tricarbonylmetal centre could be directed to one face of the A-ring of a flavonoid unit, that face of the adjacent unsaturated heterocyclic C-ring would become inaccessible to a hydrogenating reagent. In order to investigate the feasibility of such an approach, the tricarbonylchromium(0) complexes of several mononuclear and flavonoid type substrates were to be synthesised. Compounds like benzene, toluene, anisole, chlorobenzene, acetophenone, and chromanone were therefore subjected to thermolysis (72 h) with hexacarbonylchromium(0) in refluxing dibutyl ether-THF and it was found that while the activated substrates showed excellent reactions (85 - 98 % conversion), conversions for the compounds containing deactivating substituents [acetophenone (40 %) and chromanone (28 %)] were rather low.

With the knowledge of the mononuclear substrates in hand, the study was extended to the flavonoids where selectivity between the two aromatic rings would be a major issue in the success of the envisaged methodology. Although successful from a reaction point of view (products obtained in 33 and 43 % yield respectively), reaction of the carbonyl containing substrates 4',7-dimethoxyisoflavone and flavone, with hexacarbonylchromium(0), however, yielded only the 'unwanted products', tricarbonyl(B-η^6-4',7-dimethoxyisoflavone)-chromium(0) and tricarbonyl(B-η^6-flavone)chromium(0). In an effort to move complex formation to the A-ring of the flavonoid moiety, substrates with increasing levels of reduced heterocyclic rings like chroman-4-ol, flavan-4-ol, flavan, and 7-methoxyflavan, were subjected to the reaction with hexacarbonylchromium(0). Although the first two compounds still contained a 4-subsitutent with a negative inductive effect, it is known that a benzylic OH group is capable of directing complexation towards the adjacent aromatic ring and it was hoped that this influence would facilitate reaction onto the A-ring. Formation of *cis*- and *trans*-tricarbonyl(η^6-chroman-4-ol)chromium(0) in an *ca*. 3:1 ratio (14 % yield) from the reaction of chroman-4-ol with the chromium reagent, confirmed the benzylic–OH to be capable of directing the attacking chromium moiety to the anticipated face of the adjacent aromatic ring. Reaction of the flavan-4-ol substrate, however, indicated the A-ring still not to be the preferred binding site, since tricarbonyl(B-η^6-flavan-4-ol)chromium(0) and tricarbonyl(A-η^6-flavan-4-ol)chromium(0) were formed in 2.8 and 1.7 % yields, respectively. Finally, reaction of both flavan and 7-methoxyflavan, the latter with an activated dihydroxylated A-ring, yielded products originating from complexation onto both the A- and B-rings, *i.e*. tricarbonyl(A-η^6-flavan)chromium(0), tricarbonyl(B-η^6-flavan)chromium(0), tricarbonyl(A-η^6-7-methoxyflavan)chromium(0), and tricarbonyl(B-η^6-7-methoxyflavan)-chromium(0) as well as the bimetallic complex from the 7-methoxyflavan.

Keywords:

flavonoids, synthesis, catalytic hydrogenation, α,β-unsaturated ketone, Wilkinson's catalyst, kinetics, arene-tricarbonylchromium(0), anaerobic complexation.

SAMEVATTING

Samevatting

Die *in vitro* bestudering van die biologiese aktiwiteit van flavonoïede word ernstig in die wiele gery deur die ontoeganklikheid tot monomeriese verbindings wat in enantiomeries suiwer vorm beskikbaar is. Hoewel verskeie metodes waarvolgens monomeriese flavonoïede in opties suiwer vorm gesintetiseer kan word, wel bekend is, is baie van hierdie metodes omslagtig en is die opbrengste en ee's nie altyd aanvaarbaar hoog nie. Stereoselektiewe 1,4-hidrogenering van die meer algemeen beskikbare prochirale α,β-onversadigde karboniel bevattende flavonoïede soos flavone, isoflavone en flavonole bied 'n voor die hand liggende oplossing vir hierdie probleem en is dus tydens die huidige studie ondersoek.

Weens die feit dat regio- en stereoselektiwiteit tydens die 1,4-reduksie van α,β-onversadigde karbonyl verbindings hand aan hand gaan, is besluit dat laasgenoemde aandag sal kry sodra bevestig is dat die regioselektiewe aspek van die reaksie suksesvol bemeester is. Aangesien Wilkinson se katalisator kommersiëel beskikbaar is en maklik m.b.v. modifisering met chirale ligande in 'n stereoselektiewe katalisator omgeskakel kan word, is op hierdie katalisator vir die aanvanklike evaluering van die idee besluit. Hoewel Wilkinson se katalisator bekend is vir die hidrogenering van eenvoudige alkene, kon geen benutting daarvan vir die reduksie van α,β-onversadigde karboniel verbindings in die literatuur gevind word nie, en is besluit om die effek van verskillende grade van substitusie om die dubbelbinding te ondersoek voordat die werklike flavonoïed substrate aangepak sou word. Ten einde die beste oplosmiddel vir die reaksie te bepaal is die hidrogenering van chromoon in asetoon, tetrahidrofuraan (THF) en dichlorometaan (DCM) uitgevoer en is die chromanoon produk in 7.8, 14.3 en 46.2 % opbrengs onderskeidelik verkry. Vervolgens is optimisering van die kondisies van druk en temperatuur m.b.v. die hidrogenering van 2-sikloheksenoon uitgevoer en is gevind dat die beste omskakeling by 30 bar en 100 ^{o}C bereik word, aangesien hoër temperature (110 ^{o}C) en drukke (40 bar) tot die vorming van rhodiumswart aanleiding gegee het. Ten einde die invloed van verskillende vlakke van substitusie om die dubbelbinding op die reaksie te bepaal, is die reaksiesnelheid van sikliese- sowel as asikliese substrate, soos 2-sikloheksenoon, 3-metiel-2-sikloheksenoon, 3-buten-2-oon, 3-penten-2-oon, 4-metiel-3-penten-2-oon, 3-metiel-3-penten-2-oon en chalkoon, bepaal.

Hoewel tri-gesubstutieerde liniêre substrate soos 4-metiel-3-penten-2-oon, 3-metiel-3-penten-2-oon, asook krotonaldehied geen reaksie getoon het nie, het die ooreenstemmende sikliese ekwivalent, 3-metiel-2-sikloheksenoon, wel die versadigde ketoon gelewer. Die reaksietempo [k_{obs} = 000174644 s^{-1} (80 ^{o}C en 20 bar)] in hierdie geval was egter aansienlik laer as by die ongesubstitueerde 2-sikloheksenoon. Hidrogenering van die oorblywende asikliese substrate, 3-buten-2-oon en 3-penten-2-oon (k_{obs} = 0.0245703 en 0.000226852 s^{-1} onderskeidelik by 80 ^{o}C en 10 bar), het die verwagte tempo van mono-gesubstitueerd > di-gesubstitueerd gevolg, terwyl die invloed van ‘n siklise struktuur weglaatbaar geblyk te gewees het (k_{obs} = 0.000254025 s^{-1} vir 2-siklohexenoon). Die waargenome reaksietempo het in die geval van ‘n aromatiese digesubstitueerde verbinding (chalkoon) egter met *ca*. 50 % gedaal (k_{obs} = 0.000143572 s^{-1}).

Waar GC en GC/MS metings met vrug gebruik kon word om die reaksietempo (k_{obs}) vir die vlugtige substrate te bepaal, moes die reaksieopstelling sowel as die analitiese metodologie aangepas word vir die vastestof flavonoïed substrate. In laasgenoemde geval is KMR benut om $t_{½}$ (tyd om 50 % omskakeling te bereik), wat as aanduiding van reaksietempo gebruik is, te bepaal. Ten einde die $t_{½}$ waardes met die vorige reaksietempos te kan vergelyk, is die hidrogenering van chalkoon herhaal en is gevind dat die substraat konsentrasie ‘n beduidende invloed op die snelheid van die reaksie uit oefen. Tydens ‘n studie waar die konsentrasie van chalkoon tussen 0.083 M en 0.50 M gewissel is, is vasgestel dat 0.166 M ($t_{½}$ = 27 min) die optimum konsentrasie verteenwoordig indien die reaksie by 80 ^{o}C, 20 bar waterstof druk en 0.72 mM katalis konsentrasie uitgevoer word. Uitbreiding van hierdie ondersoek na chromoon het aangedui dat die heterosiklise ring ‘n nadelige invloed op die reaksietempo het ($t_{½}$ = 72 h *vs*. 27 min vir chalkoon), terwyl die flavonoïed substrate, flavoon en 4’,7-dimetoksie-isoflavoon, wat tri-gesubstitueerde dubbelbindings vertoon, geen reaksie met Wilkinson se katalisator getoon het nie.

Aangesien dit geblyk het dat flavonoïed substrate nie m.b.v. die genoemde hidrogeneringskatalisatore in opties aktiewe vorm berei sou kon word nie, is die moontlikheid van die benutting van areen-metaal kompleks vir chirale induksie vervolgens ondersoek. Indien kompleksering van ‘n lywige trikarbonielmetaal eenheid aan een aansig van die A-ring van ‘n flavonoïedeenheid bewerkstellig kan word, sou hierdie vlak van die aangrensende onversadigde heterosikliese C-ring ontoegangklik wees vir ‘n hidrogeneringsreagens. Ten einde die uitvoerbaarheid van hierdie benadering te bepaal is ‘n

reeks trikarbonielchroom(0) komplekse van monosikliese en flavonoïed substrate gesintetiseer. Verbindings soos benseen, tolueen, anisool, chlorobenseen, asetofenoon en chromanoon is met heksakarbonielchroom(0) in dibutieleter-THF onder terugvloei verhit (72 h) en dit is gevind dat die geaktiveerde substrate uitstekende opbrengste lewer (85 – 98 % omskakeling), terwyl met substrate met deaktiverende substituente (asetofenoon en chromanoon) slegs 40 en 28 % omskakeling respektiewelik bereik kon word.

Die ondersoek is voorts uitgebrei na flavonoïedsubstrate waar selektiwiteit tussen die twee aromatiese ringe van kardinale belang vir die sukses van hierdie benadering sou wees. Alhoewel kompleksering tussen heksakarbonielchroom(0) en 4',7-dimetoksie-isoflavoon en flavoon onderskeidelik wel waargeneem is, is slegs die 'ongewensde B-ring produkte', trikarboniel(B-η^6-4',7-dimetoksie-isoflavoon)chroom(0) en trikarboniel(B-η^6-flavoon)-chroom(0) in 33 en 43 % opbrengs onderskeidelik, verkry. In 'n poging om metaal kompleksering na die A-ring te verskuif, is substrate met toenemende vlakke van versadigdheid in die C-ring, soos chroman-4-ol, flavan-4-ol, flavaan en 7-metoksieflavaan, aan die reaksie met heksakarbonielchroom(0) blootgestel. Hoewel die eerste twee substrate steeds oor 'n 4-substituent wat 'n negatiewe induktiewe effek uitoeffen beskik het, is dit ook bekend dat 'n bensiliese OH groep kompleksering na die aangrensende aromatiese ring kan rig en is gehoop dat hierdie eienskap daartoe sal bydra dat reaksie by voorkeur met die A-ring sal plaasvind. Isolasie van die *cis*- en *trans*-trikarboniel(η^6-chroman-4-ol)chroom(0) produkte in 'n *ca*. 3:1 verhouding (14 % opbrengs) uit die reaksie tussen chroman-4-ol en die chroom reagens, het die rigtende effek van die bensiliese OH bevestig. Tydens reaksie van flavan-4-ol met die chroom reagens is egter vasgestel dat die A-ring in hierdie geval steeds nie die verkose ring vir kompleksering is nie en is trikarboniel(B-η^6-flavan-4-ol)chroom(0) en trikarboniel(A-η^6-flavan-4-ol)chroom(0) in onderskeidelik 2.8 en 1.7 % opbrengs verkry. Ten einde enige moontlike deaktiverende effekte op die A-ring te verwyder en dit selfs met een en twee aktiverende groepe te vervang, is flavaan en 7-metoksieflavaan laastens aan die reaksie onderwerp. Beide A- en B-ring gekomplekseerde produkte, nl. trikarboniel(A-η^6-flavaan)chroom(0), trikarboniel(B-η^6-flavaan)chroom(0), trikarboniel(A-η^6-7- metoksie-flavaan)chroom(0) en trikarboniel(B-η^6-7-metoksieflavaan)chroom(0) asook die bimetaliese kompleks van 7-metoksieflavaan, is egter vanaf beide substrate verkry.