CHIRAL ALDEHYDES IN THE SYNTHESIS OF TETRAHYDROFURANS

by

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DECLARATION

I hereby certify that this research is the result of my own investigation which has not been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed:.....

O.L. NJAMELA

I hereby certify that this statement is correct.

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ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
Ar	aryl
AZT	3´azido-3´deoxythymidine
BINAP	bis(diphenyphosphino)-1,1-binaphthyl
BMS	Borane-methyl sulphide
b.p.	boiling point
Bn	benzyl
Boc	^{t}butyloxycarbonyl
br	broad
Bu	butyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
de	diastereomeric excess
DIBAL	diisobutyl aluminium hydride
ee	enantiomeric excess
EI	electron impact
Et	ethyl
Eu(hfc)$_3$	tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium
HIV	human immunodeficiency virus
LDA	lithium diisopropylamide
LMPT	lithium 2,2,6,6-tetramethylpiperidine
m	multiplet
MA	methyl acrylate
Me	methyl
MOM	methoxymethyl
m.p.	melting point
Ms	methanesulfonyl
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
OTFA	Trifluoroacetate
Oxdn	Oxidation
PAMP	(R,R)-1,2-bis-[2-methoxyphenyl)phenyl phosphino]ethane
PCC	pyridinium chlorochromate

PDC	pyridinium dichromate
Ph	phenyl
Pr	propyl
QDL	3-quinuclidinol
s	singlet
t	triplet
TAI	trichloroacetylisocyanate
TBCO	2,4,6-tetrabromo-2,5-cyclohexadienone
TBDMS	1-^{t}butyldimethylsilyl
THP	tetrahydropyranyl
tlc	thin layer chromatography
TMS	tetramethylsilane
p-TsOH	*p*-toluenesulphonic acid

SUMMARY

Iodine-induced cyclisation of γ-benzyloxy-α-alkylacrylates to form tetrahydrofurans has been investigated. The γ-benzyloxy-α-alkylacrylates were prepared by the Baylis-Hillman reaction of β-benzyloxy aldehydes with methyl acrylate.

Initially, salicylaldehyde was used as a model system to study various ways in which β-hydroxy aldehydes can be used in the Baylis-Hillman reaction.
From a study of the *intramolecular* Baylis-Hillman reaction utilising the acrylate of salicylaldehyde **(i)**, the quarternary coumarin salt **(ii)** was isolated. The events that lead to the formation of the salt **(ii)** prove for the first time that the elusive Michael adduct, postulated by all researchers in this area, but hitherto not isolated, does exist.
An alternative use of β-hydroxy aldehydes involves protection of the hydroxyl group. Thus, benzyl protected salicylaldehyde **(iii)** reacted with methyl acrylate to form **(iv)** in good yield. Addition of primary amines in a Michael type fashion, followed by debenzylation, led to the formation of variously substituted coumarin derivatives **(v)** and provides a general entry into this class of compounds.

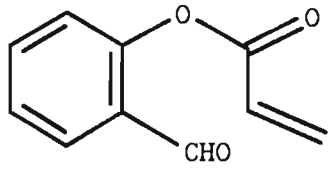
In the second phase of this study, β-chiral β-benzyloxy aldehydes **(vi)** and **(vii)** were prepared in a number of transformations starting from baker's yeast and asymmetric hydrogenation of ethyl acetoacetate respectively. The β-benzyloxy-α-methylaldehydes **(viii)** and **(ix)** were prepared by similar procedures starting from the corresponding commercially available esters. *(3S,4)*-O-Isopropylidene butyraldehyde **(x)** was accessible from *(S)*-malic acid. *(2R)*-Dibenzyloxyglyceraldehyde **(xi)** was prepared from *(S,S)*-tartaric acid in a series of known transformations but an overall new synthetic route. This synthetic route was

adapted for ascorbic acid to produce isopropylidene aldehydes **(xii)** and **(xiii)** and *(2S)*-dibenzyloxy-glyceraldehyde **(xiv)**.

The Baylis-Hillman reaction of the aldehydes **(vi)** - **(xiv)** has been studied. In general the reactions of chiral aldehydes with methyl acrylate show little or reasonable diastereoselective formation of acrylates **(xv)**.
α-Unsubstituted β-chiral aldehydes **(vi)** and **(vii)** reacted stereorandomly while α-chiral aldehydes **(viii)** and **(ix)** gave reasonable stereoselectivity (65:35). Isopropylidene butyraldehyde **(x)** and glyceraldehyde **(xiii)** showed high diastereofacial selection with the former showing exceptionally high (75:25) diastereoselectivity. α-Unsubstituted aldehydes **(vi)** and **(vii)** and α-methyl aldehydes **(vii)** and **(ix)** were *syn*-selective while α-alkoxy aldehydes **(xi)** - **(xiv)** were *anti*-selective. In contrast, isopropylidene aldehyde **(x)** showed high preference for *anti* selectivity. The relative configurations were established by derivatisation using TAI and by cyclisation to tetra-hydofurans. The results obtained in this study have been formulated into a mechanistic rationale involving open transition states as postulated by Felkin and Anh.

Intramolecular iodoetherification of the substituted alkyl acrylates was strictly 5-*exo*-*trig* and proceeded with high stereochemical control.
The isopropylidene acrylates, produced from the reaction of **(x)**, **(xii)** and **(xiii)**, did not undergo cyclisation. On the other hand, γ-benzyloxyacrylates represented by general structure **(xvi)** showed a marked difference in reactivity. The reactivity was found to be strongly influenced by the relative configuration of the allylic hydroxyl group to the homoallylic substituent R_1 or in the absence of the latter, on the benzyloxy group. In the former, only the 1,2-*anti* substrates cyclised while 1,3-*syn* substrates cyclised in the latter case. In general, the iodocyclisation provided

cis-2-iodomethyl-3-hydroxy tetrahydrofurans **(xvii)** in high yield. The stereochemistry was assigned by NOE for all the tetrahydrofurans and in the case of **(xvii)** where R_1 = CH_3 and R_2 = H corroborated by X-ray analysis. A mechanistic pathway to rationalise these results is proposed.



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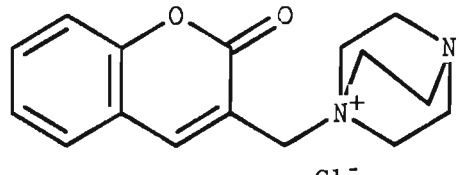

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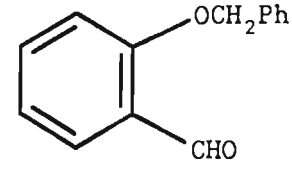

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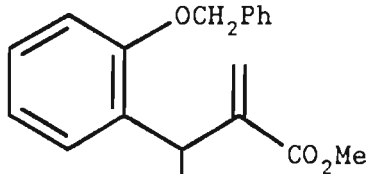

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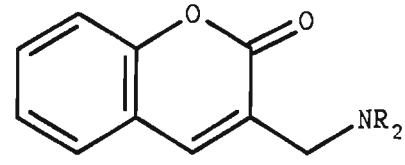

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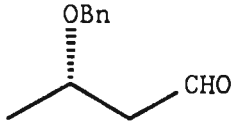

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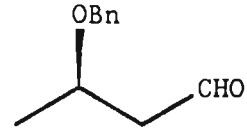

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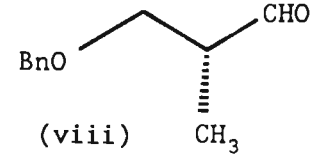

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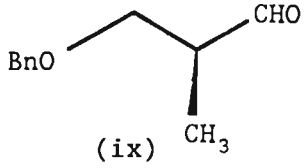

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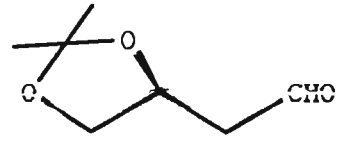

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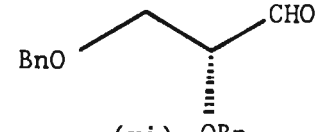

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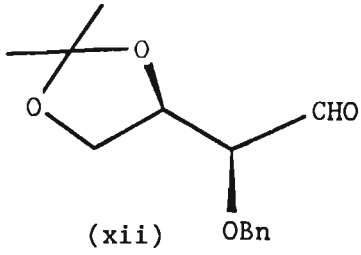

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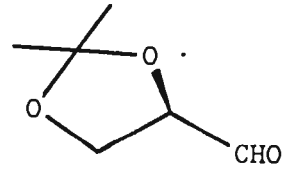

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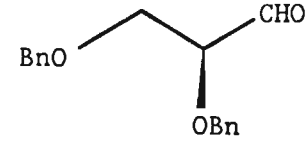

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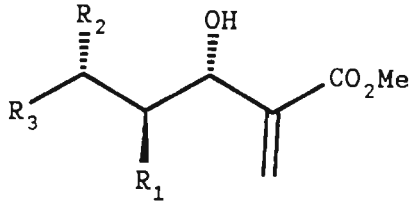

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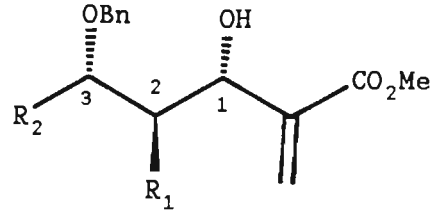

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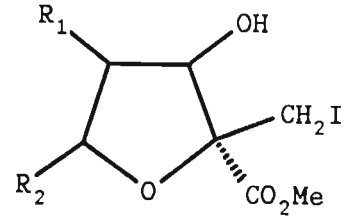

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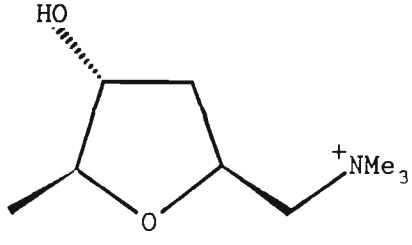
1. INTRODUCTION

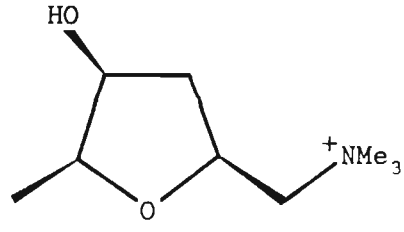
The synthesis of structurally and substitutionary complex molecules continues to be an important area of research. In particular, the diastereoselective process has become a powerful tool and a contributory factor in the synthesis and understanding of interactions of a variety of optically active compounds.[1,2,3]

Many of the optically active compounds possess biological activity, the specific activity being assigned only to one stereoisomer, the other being either less effective, ineffective or, at worst, detrimental.[4]

For example muscarine **(1)** - an alkaloid isolated from the red fly agaric mushroom *Amanita muscaria* - is known for its ability to reproduce faithfully some of the responses to



Muscarin (1)



Epimuscarin (2)

stimulation of the autonomous nervous sytem.[5] When the hydroxyl group is *cis* to either or both the methyl and the trimethylaminomethyl groups *e.g.* **2**, there is an enormous decrease in muscarinic activity.[6] Epimuscarine, **2**, is then described as a partial agonist since it does not provoke a full response.[3]

In the past, it was acceptable to leave isolation of the correct isomer (enantiomer or disastereomer) to the last step. However, in recent years, the challenge has been to produce the desired stereochemistry at the earliest possible

step in the sequence and then use the stereochemistry of that centre to control the stereochemistry of subsequent reactions. This constitutes asymmetric synthesis, a term that has been in use for over eighty years.
Morrison and Mosher[7] have defined asymmetric synthesis as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereomeric products (enantiomeric or diastereomeric) are produced in unequal amounts."

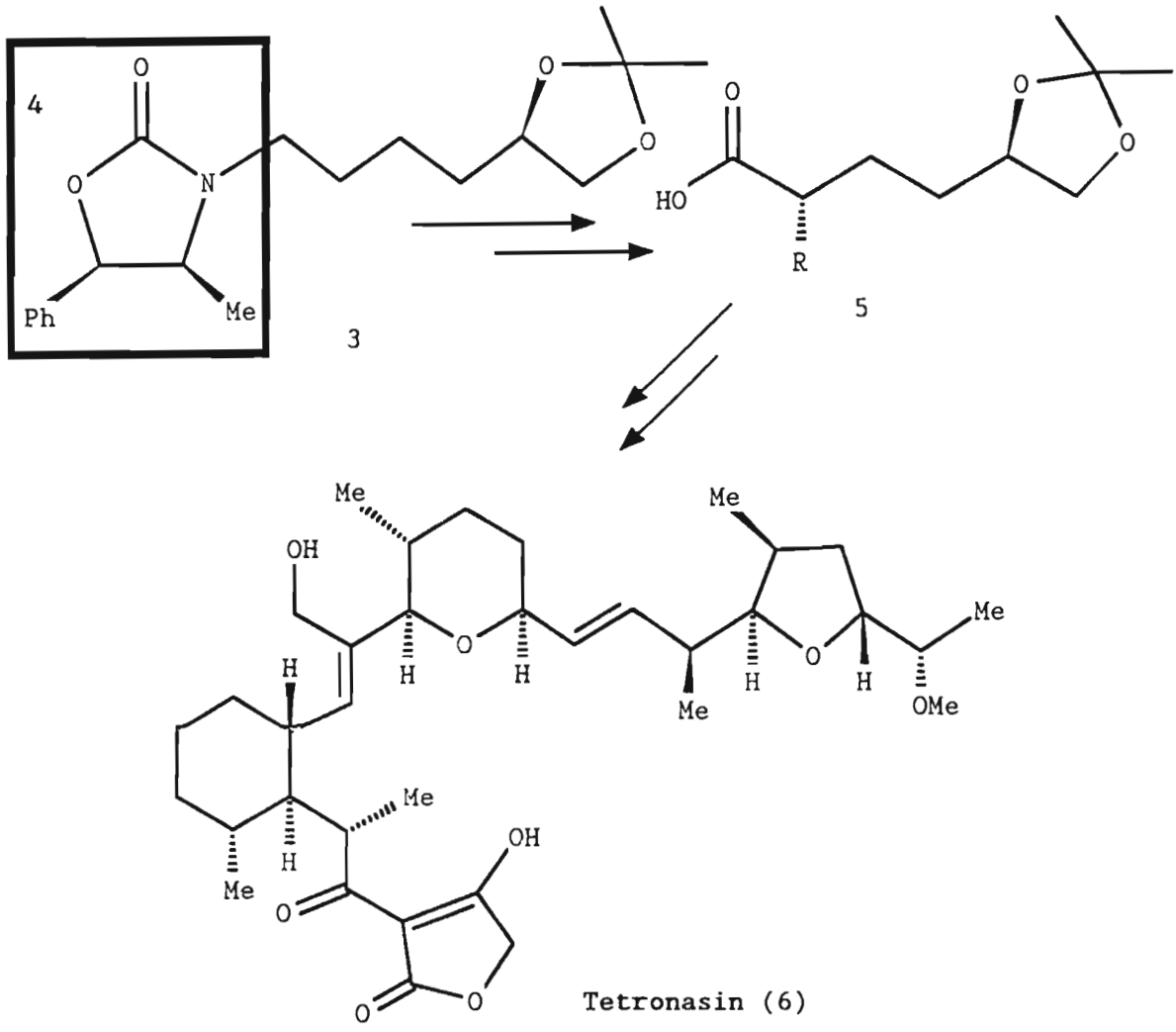
An ideal asymmetric synthesis can be characterised by the following features:[8,9]

a) in addition to high chemical yield, the desired isomer is produced in high stereomeric yield.
b) the chiral auxiliary is readily available, inexpensive and recoverable in good yield and undiminished purity.
c) the chiral product is easily seperated from the chiral auxiliary.
d) it is possible to synthesise both enantiomers or diastereomers selectively.

With these features as guidelines, two principal synthetic strategies can be used. Firstly, homochirality in the synthesis of a target molecule can be introduced by the use of an external chiral auxiliary reagent. Secondly, a chiral fragment of known absolute configuration can be used. In both respects, nature's "chiral pool"[10,11] and the use of enzymes[12-14] play an important role.

Introduction of homochirality using external chiral auxiliary has been employed with great success by Meyers,[15] Enders,[16] Evans,[17] Oppolzer,[18] and Schöllkopf.[19]
For example, Evans' chiral auxiliary **4** plays an important role for the preparation of the key intermediate **5** in the

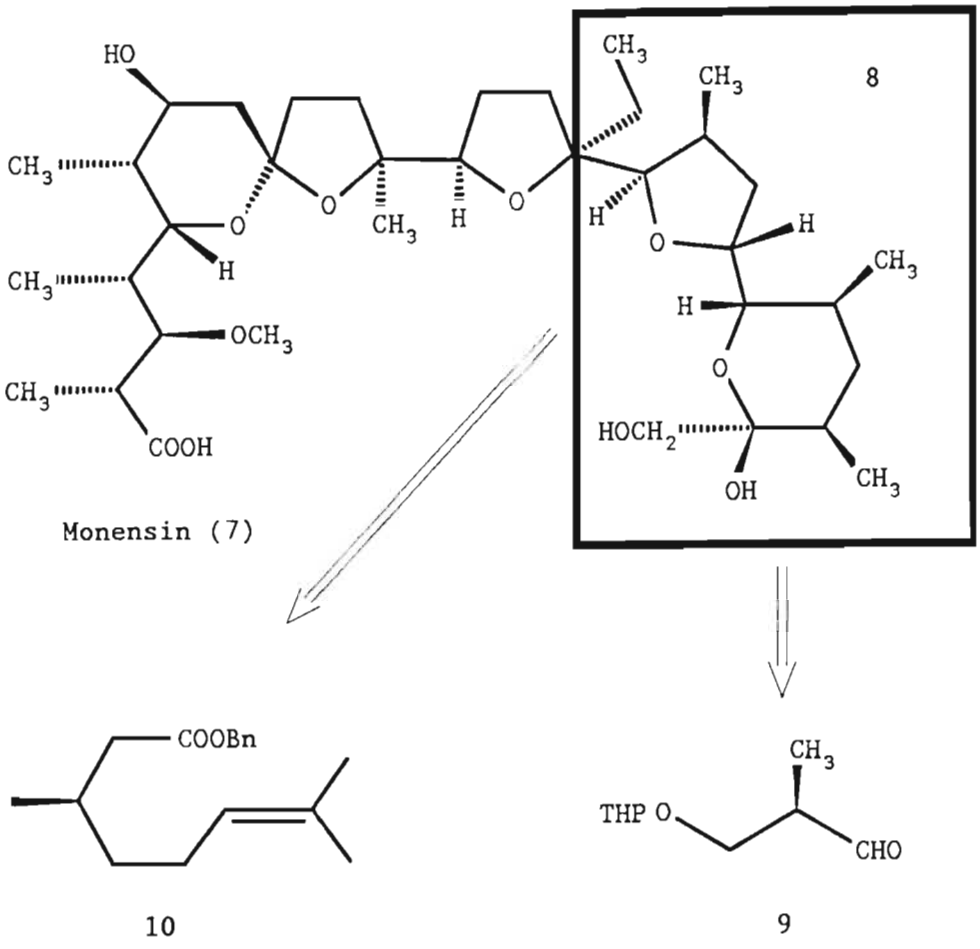
synthesis of tetronasin, **6** - an acetotronic acid ionophore antibiotic (Scheme 1).[20] The intermediate **5** is prepared by alkylation of **3** and the chiral auxiliary is prepared from norephedrine.[21]



Scheme 1.

The second approach, *i.e.*, incorporation of chiral fragments of known configuration is exemplified by the total synthesis of monensin **(7)** - a naturally occurring ionophore antibiotic (Scheme 2).[22]

The key fragment **8** is prepared from the two structural building blocks **9** and **10** (Scheme 2), whose absolute configuration is known. The former, **9**, is obtainable from enzymatic reduction[23] and the latter from naturally occurring citronellol.



Scheme 2.

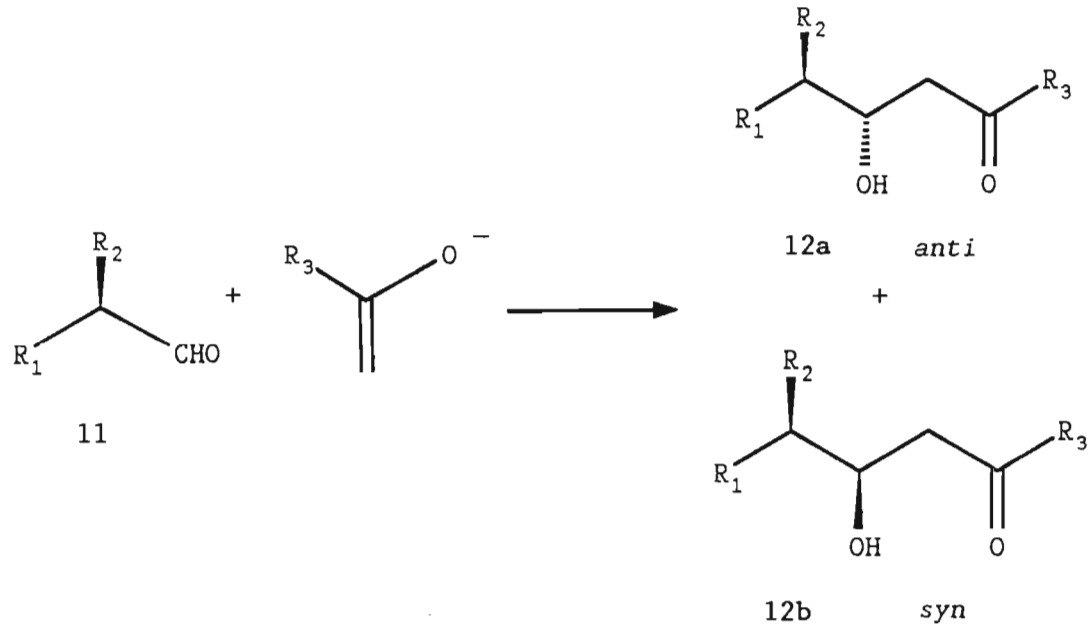
The two approaches can be applied simultaneously as will be seen in the following sections.

Asymmetric synthesis using these strategies remains the major contributor in the synthesis of homochiral natural products. In particular, asymmetric C-C bond formation is a crucial tool in all syntheses. In a large number of the syntheses, aldehydes have been used as electrophilic counterparts. In recent years, there has been a growing interest in the use of chiral non-racemic aldehydes because of the development of effective methods for controlling stereochemistry of several basic reactions. This chapter will focus on the reactions of chiral aldehydes. Because chiral aldehydes are widely used in organic synthesis, this introduction presents selected examples to highlight certain

facts and is not exhaustive.

1.1. THE TERMINOLOGY OF ASYMMETRIC SYNTHESIS

The two carbonyl faces on a chiral aldehyde are diastereotopic; addition of C-nucleophiles such as Grignard reagents or enolates creates a new chiral centre and is therefore diastereogenic (an example is illustrated in Scheme 3).



Scheme 3.

In reactions such as the one depicted in Scheme 3, the approaching nucleophile will in principle, exhibit varying degrees of preference from one face to the other. The degree of preference, as reflected on the products, is defined as diastereofacial selectivity.[24] In reactions in which differentiation of faces is influenced by simultaneous action of chiral aldehydes and chiral nucleophiles, the addition process is termed double stereodifferentiation.[25,26]

In such circumstances, the two reactants may reinforce one

another (consonant double stereodifferentiation) or oppose one another (dissonant double diastereoselection).[27,28]

In regard to the addition products, several groups have addressed their stereo-nomenclature.[29]

Research groups concerned with aldol additions, notably the group of Heathcock, predominantly use the terms *threo* for **12a** and *erythro* for **12b**.[30]

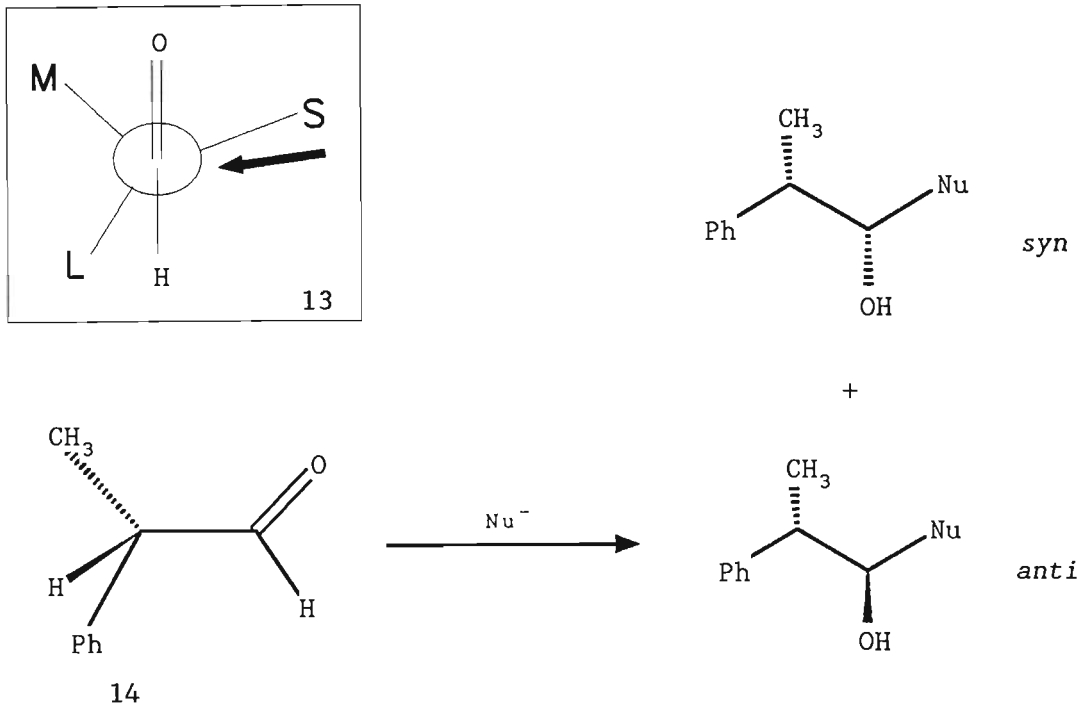
The terms *syn* and *anti* first proposed by Masamune[31] have been adopted by several authors including Heathcock, Evans, Mukaiyama, Hoffmann, Reetz and Braun. Consequently this stereostructural notation will be used here. Thus, **12a** would be *anti* and **12b** *syn* correspondingly as depicted in Scheme 3.

1.2. STEREOCHEMICAL MODELS

In addition reactions such as the one described above (Scheme 3), the electronic and steric factors of the chiral aldehyde and the attacking nucleophile play an important role to determine the stereochemical outcome (*anti/syn*) of the reaction. Several authors[32-33] have formulated models on empirical basis to predict the qualitative diastereofacial preference of chiral aldehydes. In the interests of relevance to this work, only Cram's model,[32] Cram's cyclic model[33] and Felkin's model[34] will be considered in brief.

In **Cram's model**[32] **13**, an α-chiral aldehyde such as **14** is assumed to adopt a conformation in which the largest of the three α-substituents is antiperiplanar to the carbonyl function, nucleophilic attack then occurs from the sterically less hindered side to give about 66:34 (*anti:syn*)

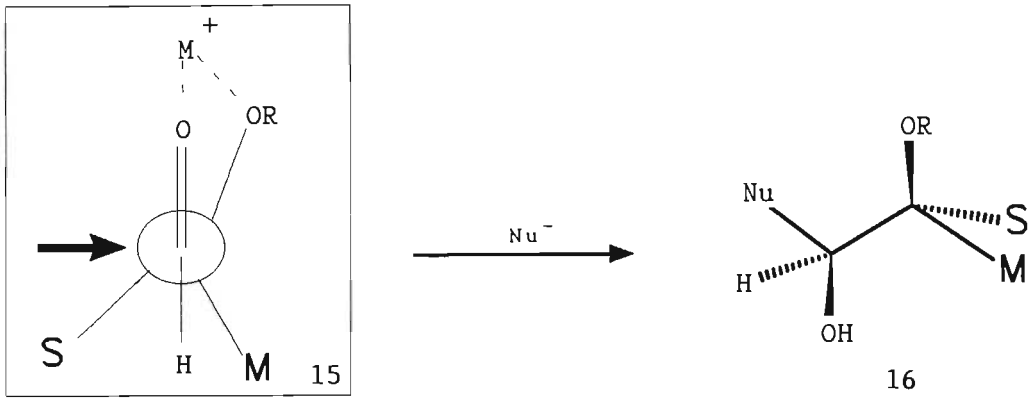
mixture of products depending on the nucleophile and the α-substituent (Figure 1).



L = large M = medium S = small group

Figure 1.

Cram's "cyclic" model[33] **15** was proposed for carbonyl compounds which contain an α-substituent (OR, NR_2) that is capable of co-ordinating the cationic counterpart of the nucleophile. Due to co-ordination, the α-substituent is then eclipsed with the double bond. The result, attack of the nucleophile at the less encumbered side, leads to preferential formation of *syn* products **16** (Figure 2).



M = metal

Figure 2.

In **Felkin's model**,[34] **17a** (Figure 3), co-ordination is neglected and intermediates are assumed to be more reactant-like rather than product-like. In this context, conformations in which the bond to the largest substituent (*e.g.* OR, NR_2 etc.) is perpendicular to the carbonyl bond are suggested for the transition state. This model has been refined by Anh **17b**, who postulated nonperpendicular attack (Bürgi-Dunitz trajectory as shown in Figure 3) on the basis of molecular orbital considerations.[37] An in-depth discussion on the Felkin-Anh model will be covered in the DISCUSSION.

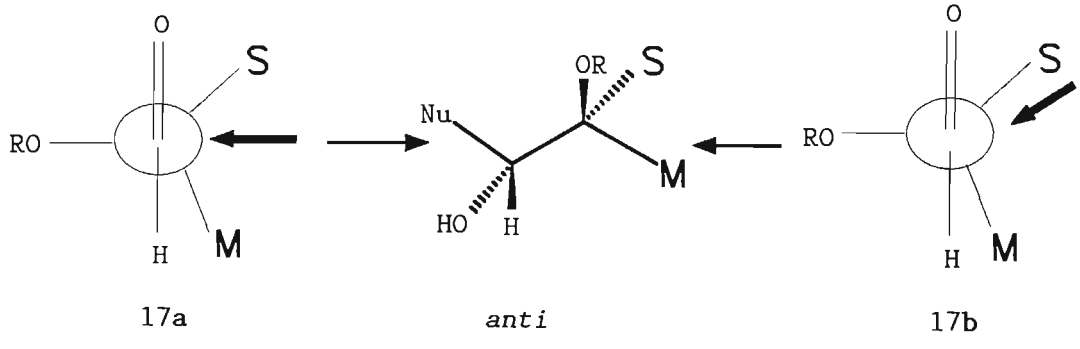


Figure 3.

1.3. NUCLEOPHILIC ADDITION REACTIONS OF CHIRAL ALDEHYDES

1.3.1. METALLO-ORGANIC ADDITION REACTIONS

Addition reactions of organometallic compounds to chiral aldehydes are of considerable interest in the context of understanding acyclic stereocontrol and of significant importance in stereoselective synthesis of natural products, *e.g.*, ionophores, pheromones and carbohydrates.[38-40]

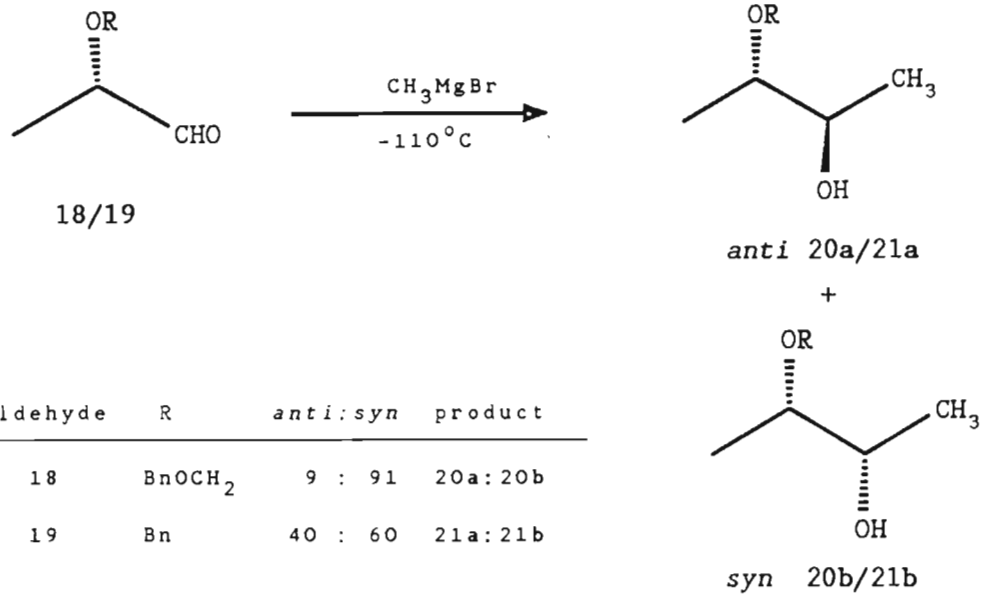
The stereochemical outcome of organometallic addition to chiral α, β-*N* or *O*-substituted aldehydes can be controlled by (i) use of Lewis acidic reagents which form intermediate chelates resulting in nucleophilic attack on the sterically less hindered side **(Chelation control)** or (ii) use of reagents incapable of chelation in which the electronic and steric factors of the aldehyde and nucleophile are the sole determinants of the stereoselectivity **(Non-chelation)**.[41] The two methods are generally complementary, *i.e.*, they lead to opposite sense of diastereoselectivity.

1.3.1.1 CHELATION CONTROL

In the pioneering work, Cram *et al.*[32,33] and Stocker[42] studied the addition of Grignard and RLi to alkoxy (or hydroxy) compounds and asymmetric induction was rationalised on the basis of Cram's rule. The stereochemical outcome ranged between stereorandom (55:45) and high (96:4).
Ever since this treatise by Cram, organometallic additions have received growing attention as evidenced by reports and excellent reviews covering this subject.[41-45]

Reetz[46] reported that the choice of reaction conditions, type of protecting group and Grignard reagent strongly

influence the extent (and in some cases, the sense) of diastereoselectivity.

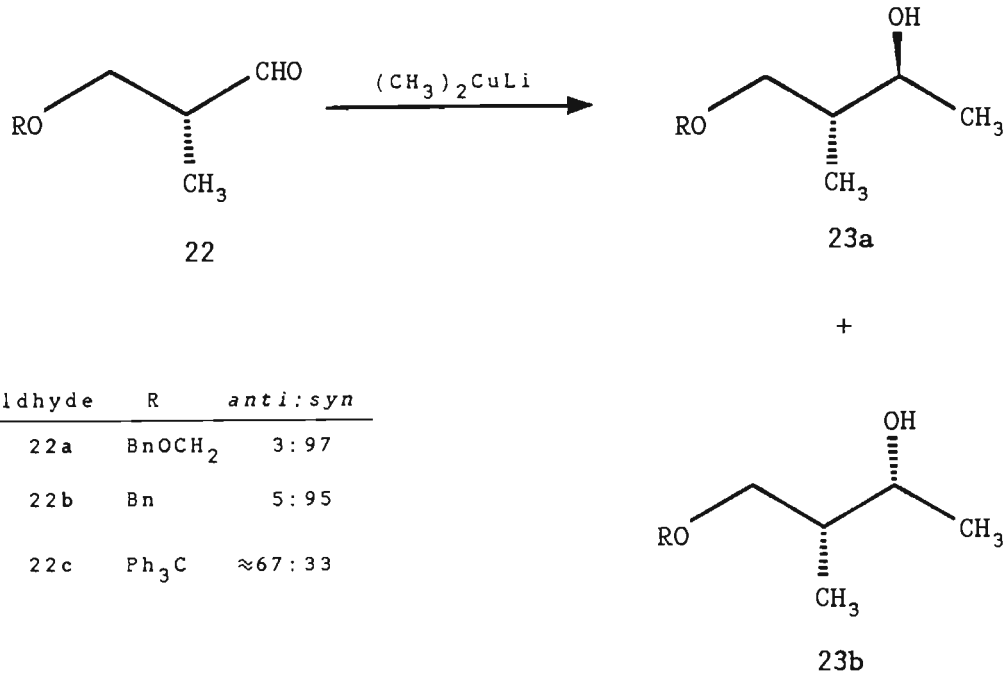


aldehyde	R	*anti*:*syn*	product
18	$BnOCH_2$	9 : 91	20a:20b
19	Bn	40 : 60	21a:21b

Scheme 4.

The benzyloxymethyl protected aldehyde **18** for example, reacted with CH_3MgBr to give a diastereomeric ratio of 9:91 (*anti*/*syn*) products **20** - whereas the benzyl protected analogue **19** reacts with the same reagent fairly unselectively to produce **21** (*anti*:*syn* = 40:60) (Scheme 4). The results were explained on the basis of five-membered chelate in accordance with Cram 's cyclic model.

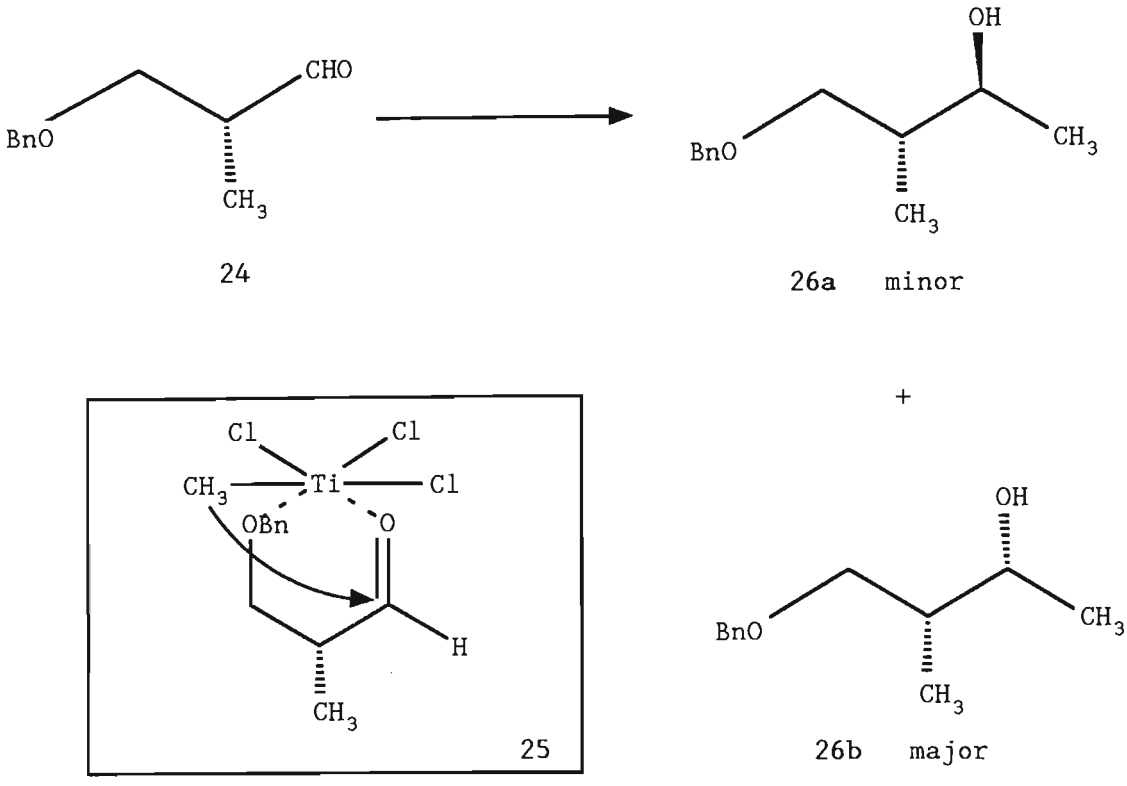
Generally, nucleophilic additions with organolithium and organomagnesium reagents give low diastereoselectivities. In contrast, use of lithium cuprates dramatically improves the diastereoselectivity.[47,48] For instance, the



Aldhyde	R	*anti:syn*
22a	$BnOCH_2$	3:97
22b	Bn	5:95
22c	Ph_3C	≈67:33

Scheme 5.

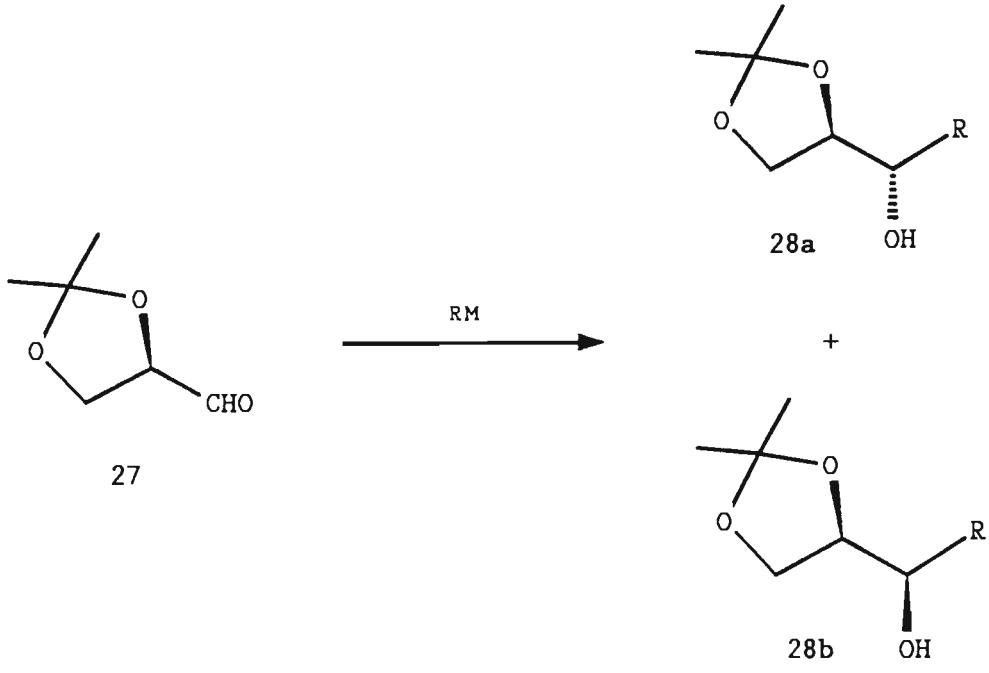
α-substituted aldehydes **22a** - **22c** react with CH_3MgX or RLi to produce a nearly equal mixture of diastereomers **23a/b** while diastereoselectivity ratios of up to 97:3 were obtained with $(CH_3)_2CuLi$ (Scheme 5). The benzyloxy protected aldehyde **22b** again reacted less selectively. Furthermore, diastereoselection was not observed for the bulky protecting group in **22c**. It is unclear why cuprates but not RMgX and RLi lead to efficient β-chelation.
Use of reagents with pronounced Lewis acidity and chelating ability *e.g.*, $TiCl_4$, $SnCl_4$ and $MgBr_2$ dramatically improved the selectivity. This was observed when CH_3TiCl_3 was used to methylate **24**.



Scheme 6.

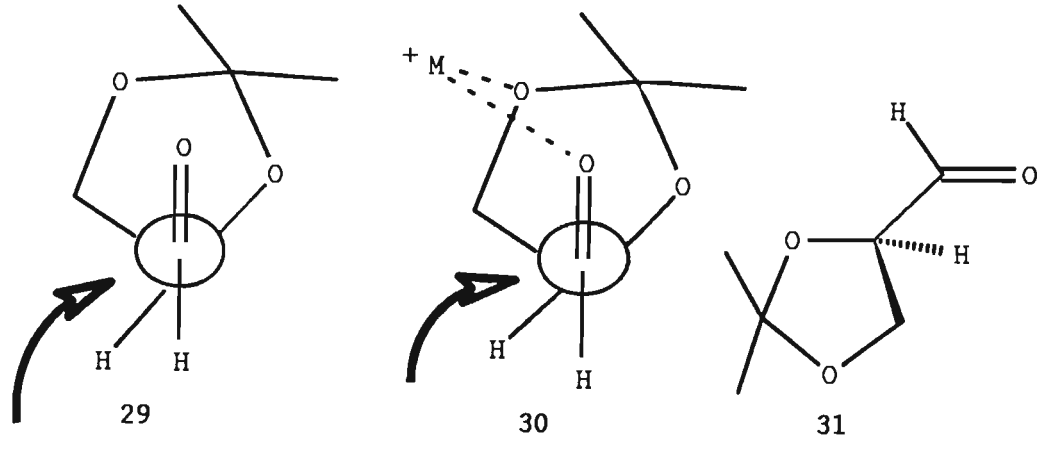
The mixture of diastereomer **26a/b** was produced *via* the intermediate chelate **25** in high diastereoselectivity 8:92 (*anti:syn*). Complexation of **24** with $TiCl_4$ prior the addition of soft nucleophiles such as $(CH_3)_2Zn$ also gave the same result.[46]

Addition of metallo-organic compounds to polyoxygenated aldehyde functions that occur in carbohydrates has been studied by several groups.[41-43,49-51]
The isopropylidene glyceraldehyde **27** or its enantiomer and related aldehydes have been allowed to react with a large number of organometallic compounds. For example, Mulzer and Angermann[52] reported on the structure of the nucleophile and the stereoselectivity of addition to the aldehydes **27** (Scheme 7).

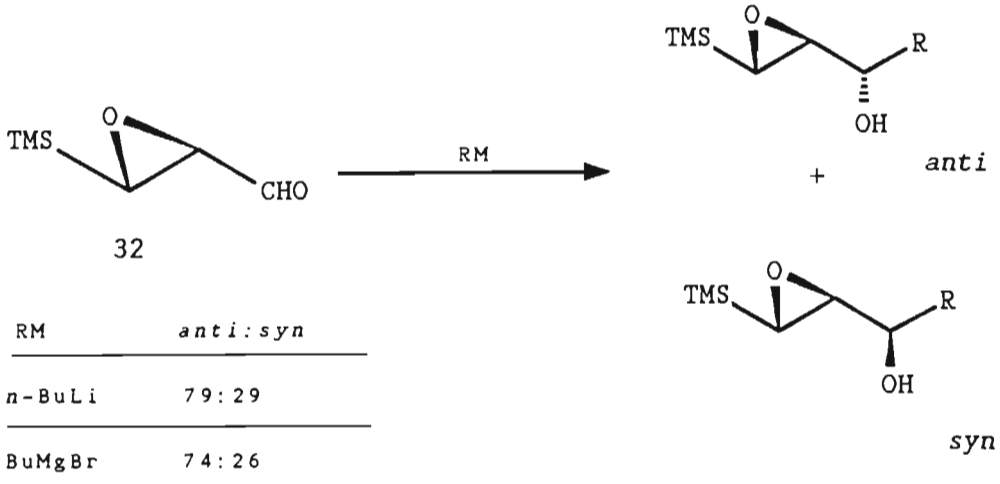


Scheme 7.

All reagents generally favoured formation of the *anti* isomer **28a** over the *syn* isomer except phenyltriisopropoxytitanium which afforded the *syn* isomer **28b** with high selectivity. The high preference for *anti* selectivity has been explained by the Felkin model **29** in which there is no complexation to the α- or β-oxygen. β-Chelation as in **30** has also been postulated and leads to reinforcement of *anti* selectivity. The data can also be explained by adopting Conforth model **31**.[34]



Reverse selectivity in chelation controlled addition of orgonometallic compounds to aldehydes has also been reported by Sato and coworkers.[53] Moderate to good diastereoselectivity ratios were observed in nucleophilic additions to the epoxy trimethylsilyl aldehyde **32** (Scheme 8)

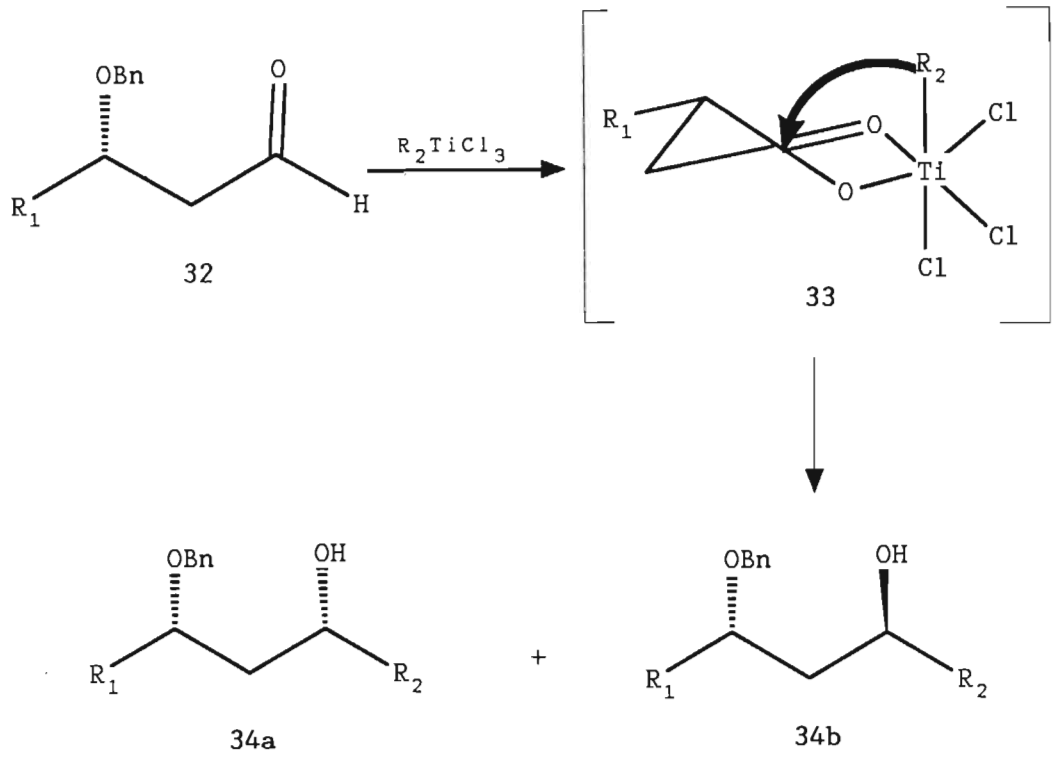


32

RM	*anti:syn*
n-BuLi	79:29
BuMgBr	74:26

Scheme 8.

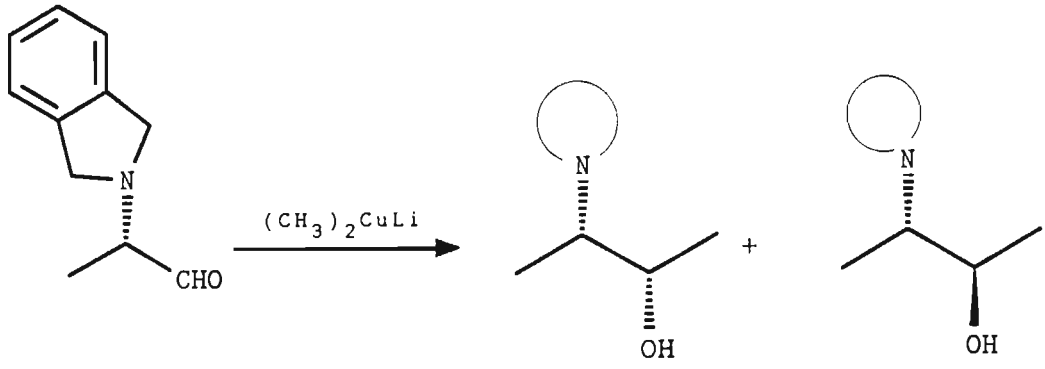
Stereocontrol in the addition of metalloorganic reagents to β-alkoxy aldehydes is not possible using ordinary organometallic compounds such as RMgX, RLi or R_2CuLi.[48] Reetz,[54] was able to achieve high levels of stereoselectivity by employing Lewis acids that have high affinity for complexation.[55] In this context, addition of $TiCl_4$ or $SnCl_4$ followed by the nucleophile or direct addition of organotitanium reagents to aldehydes led to unprecedented levels of asymmetric induction. For example, **32** is converted *via* **33** to **34a** with high diastereofacial selectivity (Scheme 9).



Scheme 9.

Stereocontrolled addition of Grignard reagents to chiral α-amino aldehydes under chelation control has been reported by several research groups[56-58] to give poor to good diastereoselectivity. Addition of $SnCl_4$ and $TiCl_4$ improves the level of diastereoselection to greater than 8:92 in favour of *syn* product.[59,60] The effect of the two Lewis acids was reported to be diminished as a result of weak *N*-Ti and *N*-Sn coordination resulting in formation of noncyclic chelates.

Available data also show that use of less sterically demanding protecting groups results in efficient chelation control. For example, a change from the dibenzyl protecting group - which gives 1:1 ratio of *anti:syn* - to protecting groups such as in **35**, results in chelation controlled reaction even with $(CH_3)_2CuLi$ leading to preferential formation of *syn* **35a** (Scheme 10).



35 36a 90:10 36b

Scheme 10.

1.3.1.2. NON-CHELATION CONTROL

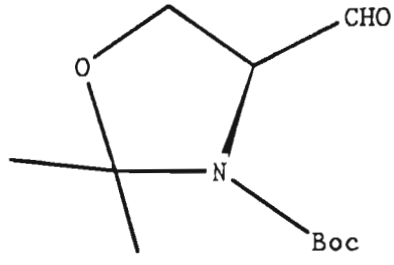
Stereochemical controlled addition of Grignard reagents and a variety of other organometallic compounds can also be directed solely by the electronic and steric nature of the aldehyde and the reagent. In this regard, Cram's acyclic model[32] or one of Conforth[34] or Felkin-Anh[36] model may be used to explain the diastereoselection.

Non-chelation control is generally difficult to accomplish because there is no general way to reduce the number of degrees of freedom of non-complexed molecules.[41] However, the groups of Reetz,[46] Kishi[61] and Mulzer[62] have been able to effect non-chelation controlled additions to chiral aldehydes.

Reetz *et al.*[46] demonstrated that chelation and non-chelation control can be made complementary processes to give either *anti* or *syn* depending on the ligands on titanium. For example, addition of CH_3TiCl_3 to **24** gave 8:92 ratio of *anti*:*syn* products **26** (**a** and **b**) (Scheme 6 *vide supra*). On the other hand, non-chelation controlled addition using $CH_3Ti(OCHMe_2)_3$ afforded the *anti* isomer **26a**

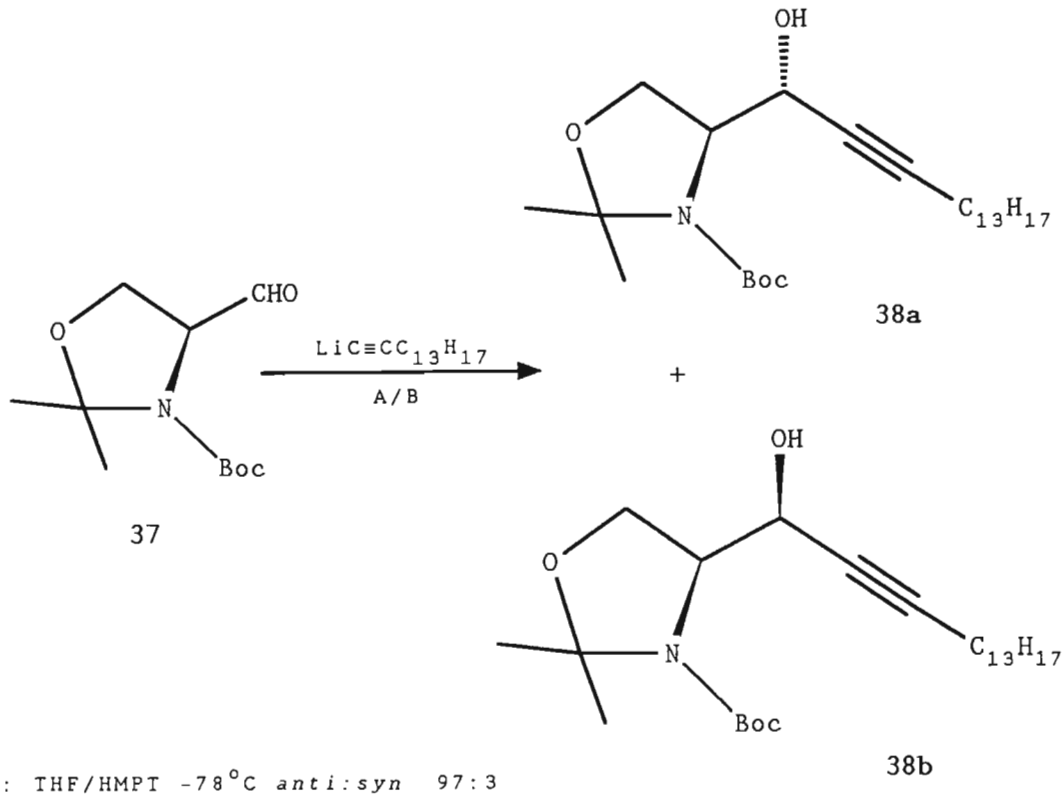
as the major product (*anti/syn* 92:8). Herold[63] and Procter and coworkers[64] have also studied the complementary nature of these process.

Herold[63] reported additions, under different conditions, to Garner's aldehyde **37**.[64,65] Numerous addition reactions of various organometallic reagents to the aldehyde **37** have been well documented but many of them report selective formation of *anti* adducts only.[66-73]



37

In studies directed towards the synthesis of sphingosine derivatives, Herold[63] demonstrated that silylalkyne metals add to **37** to give either *anti* **38a** or *syn* **38b** depending on the reaction conditions. Thus, the *anti* isomer **38a** was formed (ratio 97:3) by addition of lithium pentadacyn in THF/HMPT whereas the corresponding *syn* isomer **38b** was produced (ratio 3:97 *syn*) in the presence of $ZnBr_2$ in Et_20.



A: THF/HMPT -78°C *anti:syn* 97:3

B: $ZnBr_2/Et_2O$ *anti:syn* 3:97

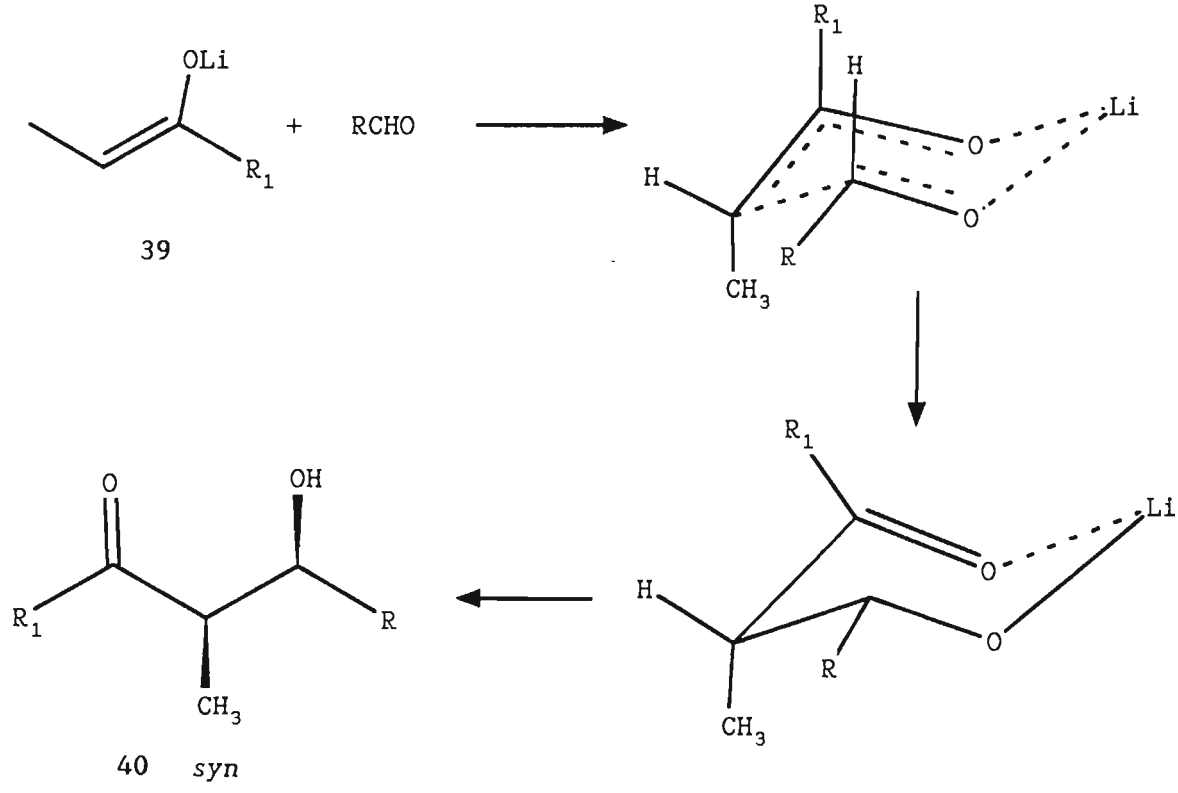
Scheme 11.

1.3.2. THE ADDITION OF METAL ENOLATES TO CHIRAL ALDEHYDES - THE ALDOL REACTION

In the last two decades, the aldol reaction has been revolutionalised by the ability to study stereoselectivity by modern methods, advances in Lewis acid catalysts and advances in calculations. The impetus for this revival is the discovery that its stereochemistry can be controlled through the use of preformed enolates.[30a,74] This aspect of the aldol reaction has since been extensively studied by Heathcock,[29,30a] Evans,[17,74] Masamune,[75] Mukaiyama[76,77] and others.

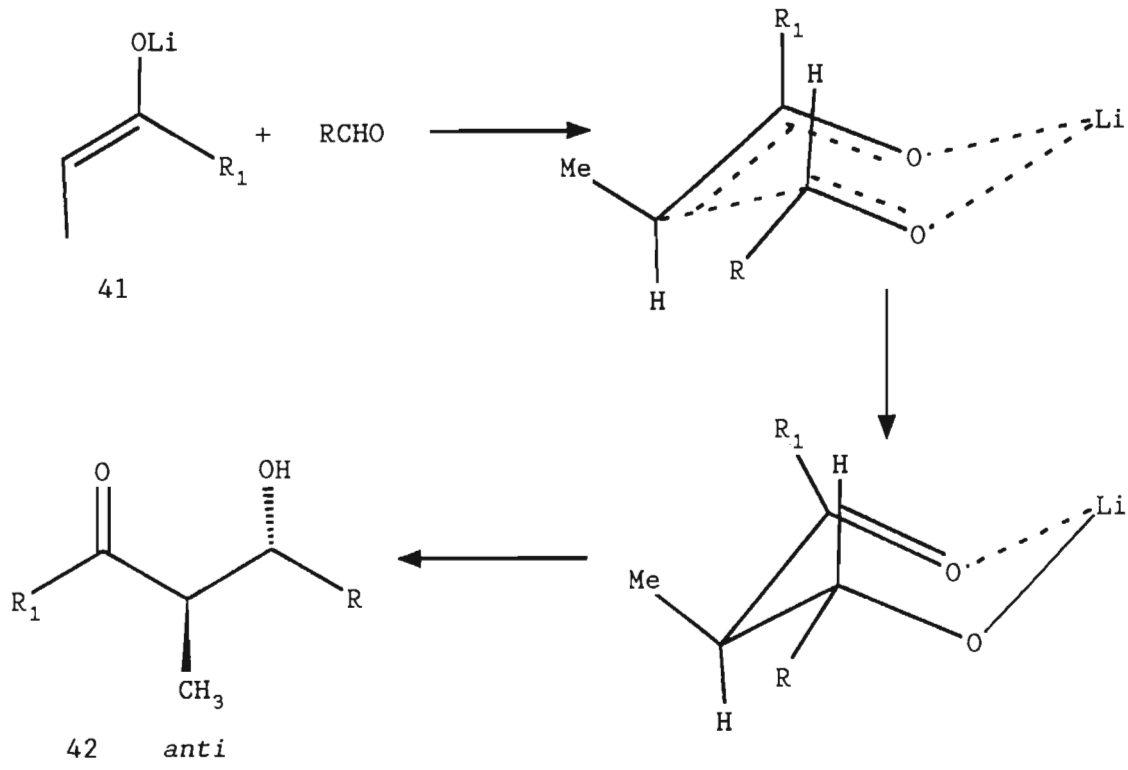
In the aldol reaction of achiral aldehydes with enolates, Heathcock *et al.*[78] found that there is a correlation between

the enolate geometry and the stereochemistry of the resultant aldol. Generally, *Z*-enolates give *syn* aldols and *E*-enolates give *anti* aldols provided the group attached to the oxygen-bearing carbon of the enolate is bulky. Since either the *Z*- or *E*-enolate can be selectively formed under kinetic conditions, stereochemical control can be manipulated to give either isomer.



Scheme 12.

Hence, under kinetic conditions, the *Z*-enolate proceeds as depicted in Scheme 12 to give the *syn* aldol **40**. On the other hand, formation of the *anti* isomer **42** is favoured when the starting enolate has the *E*-configuration **41**.

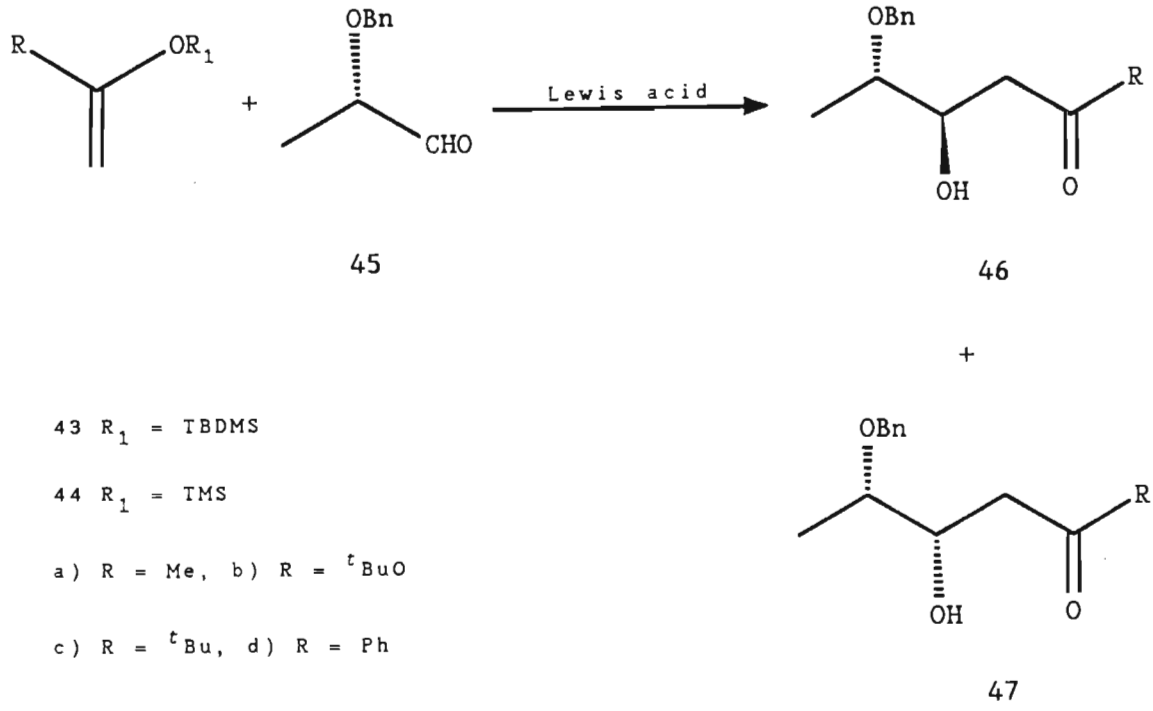


Scheme 13.

Under thermodynamic conditions (*i.e.*, equilibrium conditions), the *anti* isomer becomes the major product since the more stable chairlike conformer of the intermediate chelate has the maximum number of equatorial substituents and hence thermodynamicaly stable.

Use of chiral aldehydes gives a different perspective to the stereochemical pathway of the aldol reaction because the faces of the carbonyl group are diastereotopic. For addition of lithium enolates to chiral aldehydes in which the stereogenic centre is adjacent to the carbonyl group, the intrinsic diastereofacial preference is usually low.[79,80]

High diastereoface selectivity has been reported by Heathcock and coworkers[80] to be accessible by addition of Lewis acids. For example, the aldol reaction of the enol silanes **43** and **44** and *O*-benzyllactaldehyde **(45)** proceeds



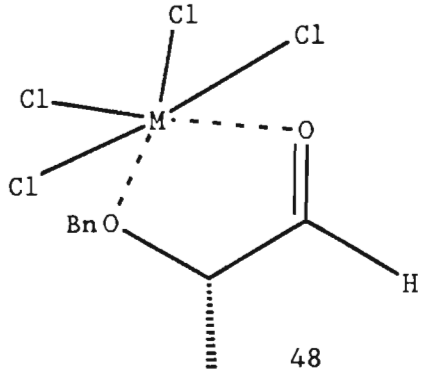
Scheme 14.

TABLE 1. Diastereomer ratios in the reactions of chiral enol silanes with aldehydes 45 given as *anti:syn* (Scheme 14).

Entry	Enol silane	Lewis acid	Isomer Ratio
1	43a	$BF_3 \cdot OEt_2$	40:60
2	43b	$SnCl_4$	35:65
3	44c	$SnCl_4$	1:99
4	44d	$SnCl_4$	1:99
5	44d	$TiCl_4$	1:99

with high diastereoselection to give *syn* aldols **46 and 47** (Scheme 14, Table 1). For achiral ketene acetal **43a** and **43b**, low diactereoselectivity ratios were observed (entries 1 and 2). Enol silanes **44c** and **44d** gave virtually *syn* aldols as the sole products with $SnCl_4$ and $TiCl_4$. The authors invoked formation of a five-membered metal chelate **48** by

$SnCl_4$ and $TiCl_4$. This results in nucleophilic addition to the less encumbered face *i.e.*, Cram's cyclic model. This is unlikely to form in the case of BF_3 since it cannot expand its ligancy beyond four.



48 M = Sn, Ti

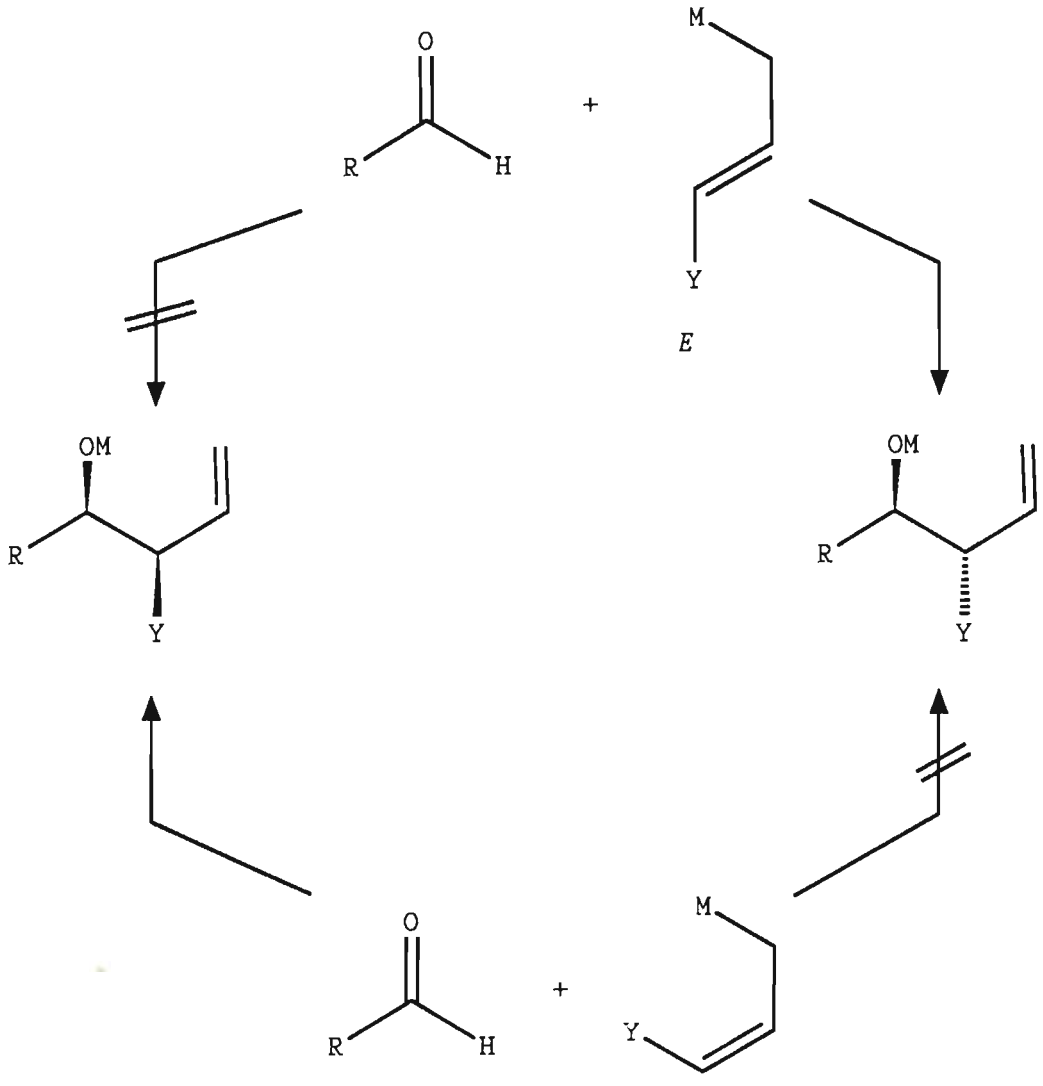
Several other incidences of chelation controlled aldol reactions have been reported recently by Reetz[81,82] and Kita and coworkers[83] using $LiClO_4$[84] and Casiraghi *et al.*[85] using conventional Lewis acids.

The phenomenon of double stereodifferentiation has been widely used in aldol condensations and is becoming more successful as demonstrated by Evans in the synthesis of rutamycins.[86,87]

1.3.3. ADDITION OF CROTYLMETAL COMPOUNDS TO CHIRAL ALDEHYDES

The Lewis acid mediated condensation reaction of allyl- or crotylmetal reagents is a widely recognised method for the stereoselective synthesis of homoallylic compounds.[88-90]

The addition of crotylmetal reagents to aldehydes is structurally and, probably also, mechanistically analogous to the aldol addition.

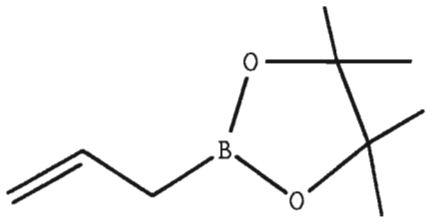


Scheme 15.

Clearly, the configuration of the double bond (*E* or *Z*) which depends on the reaction conditions, plays an important role in stereochemical control of the reaction (Scheme 15).[91] Stereocontrolled addition of crotylmetals to chiral aldehydes has been studied by several groups notably those of Hoffmann,[92] Roush,[93] and Reetz[94] to name a few.

Hoffmann *et al.*[91a] reported that the chirality of an aldehyde is not the sole determinant in stereocontrolled addition reactions; the configuration of the double bond plays a crucial role. In this respect, addition of *E*-crotyl

boronates **49 -51** to α-substituted β-alkoxy aldehydes **52a, b** and **53** resulted in predominant formation of *syn* adducts (Table 2, entry 1 and 2). On addition of *Z*-crotylboronates to the same aldehyde, the *anti* products are preferentially formed (Table 2, column 3).



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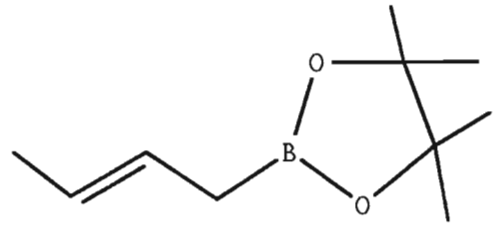

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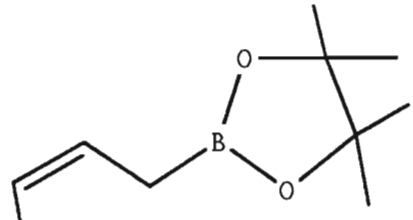
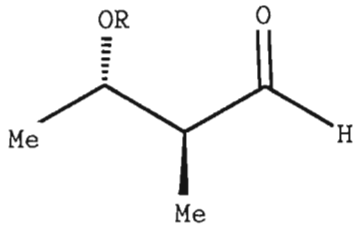


51

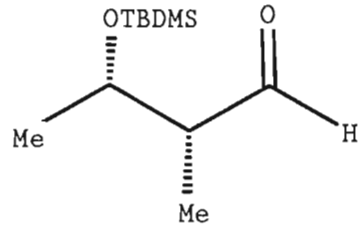
Table 2. Diastereoselectivity on addition of allylboronates to α-chiral aldehydes: given as *syn:anti*].

Entry	Allyl	*E*-Crotyl	*Z*-Crotyl
1	49:50	95:5	9:91
2	61:39	89:11	22:78
3	79:21	98:2	40:60



52a R = TBDMS

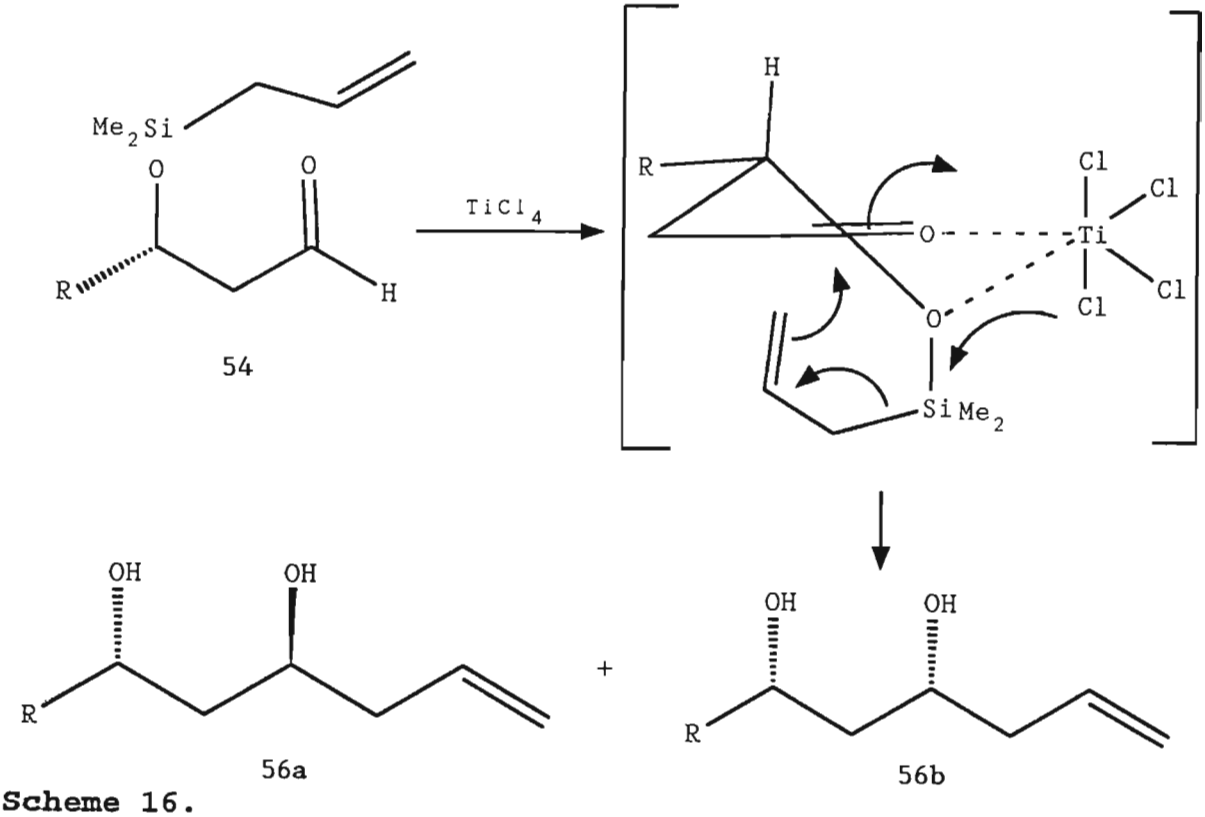
b R = MOM



53

It is also discernible from the table that change in the protecting group in the aldehyde (entry 1, 2) has a minor effect on the diastereoselectivity. Moreover, the relative configuration on the β-alkoxy group in the aldehyde does not have a major influence. Furthermore, use of the allylboronate **49** results, generally in *syn* selectivity. Use of the *E*-crotylboronate **50** reinforces *syn* selectivity.

Syn selectivity was also reported by Reetz *et al.*[46] and others[95,96] to be accessible by chelation controlled addition of crotylstannanes using $TiCl_4$ as a Lewis acid. Addition of the mono-coordinating $BF_3.OEt_2$ results in preferential formation of *anti* adduct. The reagent control for stereoselection using chelation or non-chelation procedure can be applied using various other crotylmetal reagents.[97,98] The intramolecular allylstannane additions to chiral silyloxy aldehydes **54** in the presence of $TiCl_4$ (Scheme 16) provides yet another approach to these adducts **56**.[99,100]



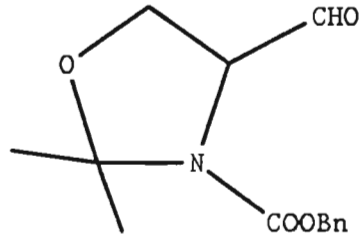
54

56a

56b

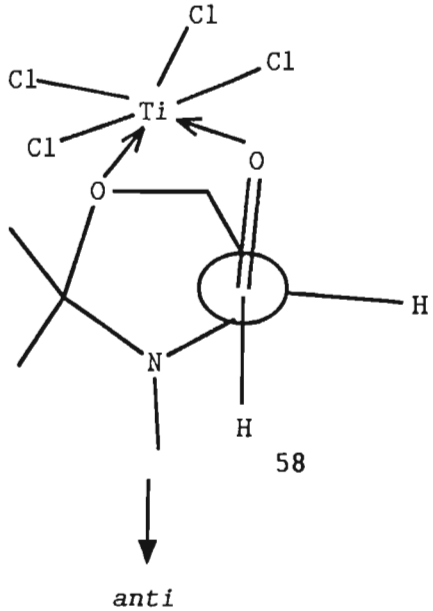
Scheme 16.

Recently, Kiyooka *et al.*[101] reported that the diastereoselectivity of chelation controlled addition of allylsilane to α-*N*-carbobenzyloxyamino aldehyde **57** is strongly influenced by the quantity of $TiCl_4$ in the



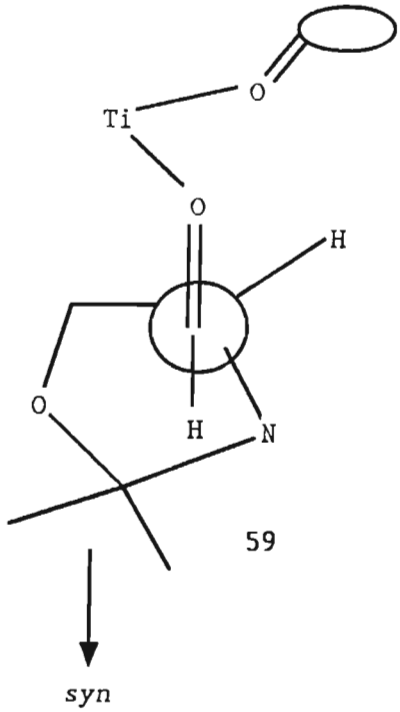
57

reaction. For example, high *anti* stereoselectivity (20:1) was observed when one equivalent of $TiCl_4$ was used whereas the use of 0.5 equiv. of $TiCl_4$ produced a good *syn* selectively (8:1).[102] The *anti* selectivity rapidly decreases as the quantity of $TiCl_4$ is increased over 1 equiv. This trend is interpreted in terms of two differently derived species: aldehyde-$TiCl_4$ 1:1 **58** and 2:1 complexes **59** which can proceed to their respective transition states.



58

anti

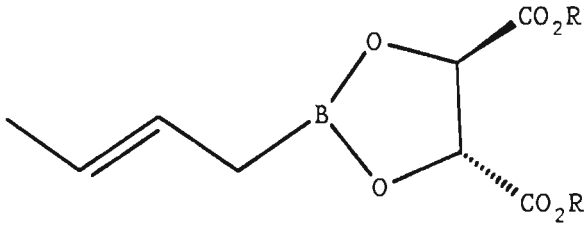


59

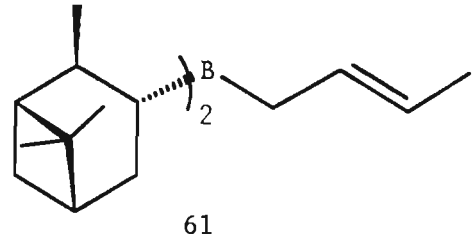
syn

In crotylmetal additions, as in the aldol reaction, double

asymmetric synthesis using chiral reagents is often necessary to achieve synthetically useful levels of aldehyde stereoselectivity. Several chiral allylboron reagents **60** - **63** have been developed by the groups of Roush - **60**,[103] Hoffmann - **61**,[104] Brown - **62**,[105] and Corey - **63**.[106] These reagents have, in several cases, enhanced the diastereoselectivity of crotylmetal additions to aldehydes.



60 R = ^{i}Pr, Et



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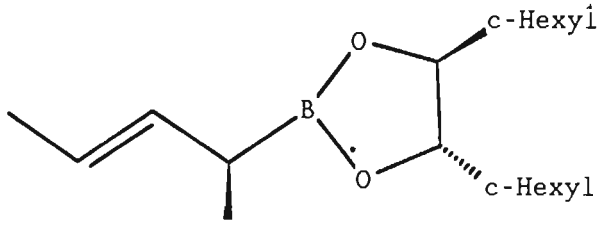

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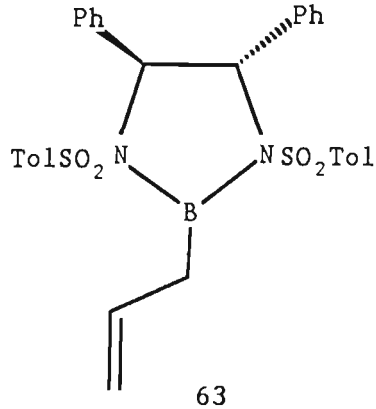
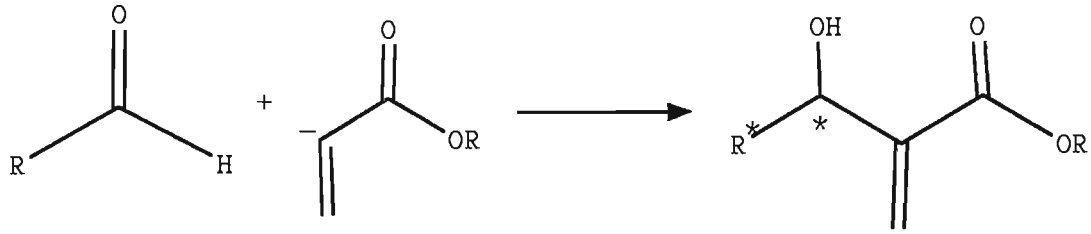


63

1.3.4. THE BAYLIS-HILLMAN REACTION

Which of the methods described above is suitable for effective direct addition of acrylate unit **64a** to chiral aldehydes?

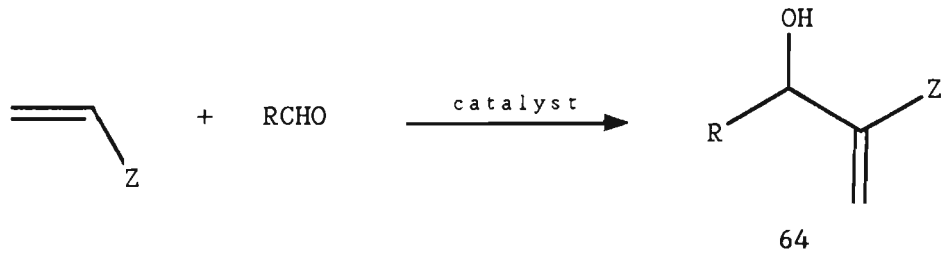


64a 64

The aldol reaction? The direct coupling of electrophiles with carbanions requires proficient choice of reagents and extremely mild conditions. For example, Feit *et al.*[107] demonstrated that direct generation of vinyl carbanions from α-unsubstituted acrylate using bases such as LDA or LTMP suffers from severe limitation due to facile anionic polymerisation.

Organometallic addition? By adeptly choosing lithium vinyl cuprates as addition reagent, Marino *et al.*[108] were able to successfully couple aldehydes with vinyl cuprates to form the desired α-hydroxyalkylacrylates. However, the cuprate reagent required very low temperatures for very long periods (-78°C for 16-18 h) and gave moderate yields.

The difficulties associated with the introduction of carbanion character can be solved by using the Baylis-Hillman reaction.[109]
The Baylis-Hillman reaction is the nucleophilic addition of an acrylic system to an aldehyde (or ketone) in the presence of a tertiary amine catalyst to form an α-(hydroxyalkyl)acrylic product (Scheme 18).



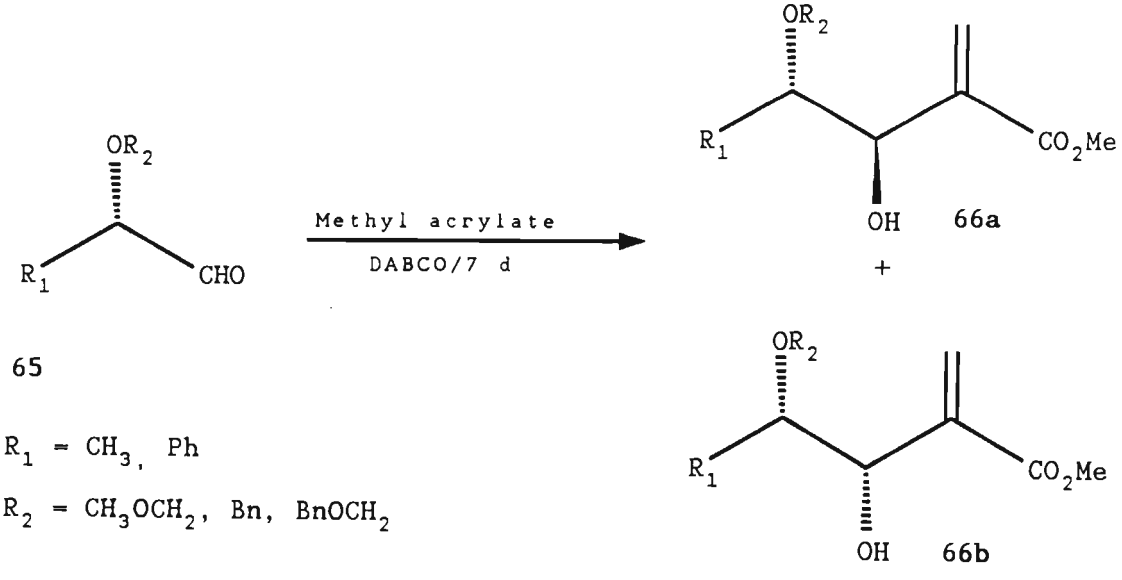
Z = CO_2R, COR, CN, SO_2R,

Catalyst = tertiary amine *e.g.*, DABCO, QDL

Scheme 18.

There has been growing interest in asymmetric synthesis using the Baylis-Hillman reaction[110-114] and coupling with chiral aldehydes has been investigated by the groups of Drewes and Roos.

Drewes, Roos *et al.*[115] studied the reactivity and stereochemical control in the Baylis-Hillman reaction of chiral aldehydes with a variety of acrylate systems. The α-alkoxy aldehydes **65** (Scheme 19) were found to be fairly reactive giving chemical yields and diastereoselectivities that are in the synthetically useful range.



65

R_1 = CH_3, Ph

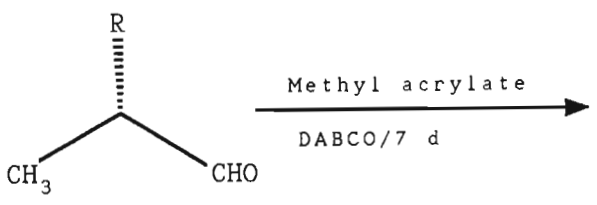
R_2 = CH_3OCH_2, Bn, $BnOCH_2$

Scheme 19.

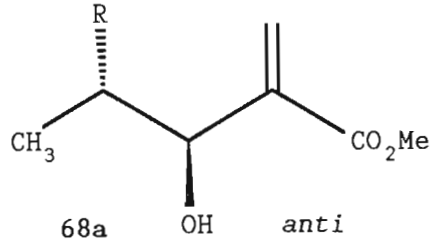
In all cases studied, formation of the *anti* isomer **66a** was

favoured over the *syn* isomer **66b** (Scheme 19). The methoxymethyl protecting group was found to exhibit higher levels of diastereoselectivity than the benzyl and the benzyloxymethyl protecting groups. The nature of the catalyst had a minor effect on the stereochemical outcome of the reaction.[116] The results were rationalised on the basis of Felkin's model.

In a projected extension of this approach, Manickum and Roos[117] investigated the reactivity and stereocontrol of variously α-protected α-*N*-amino aldehydes.



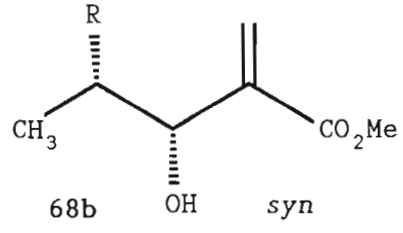
67



68a *anti*

Entry	R	*Anti:Syn*
1	NBn_2	72:28
2	NBn_2	67:33 subst. CH_3 for Ph
3	HN^tBoc	29:71
4	NPht	46:54
5	HNTs	44:56

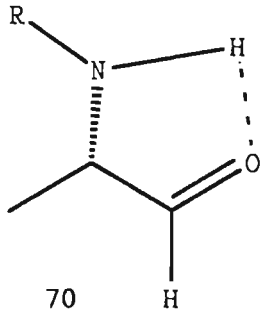
\+



68b *syn*

Scheme 20.

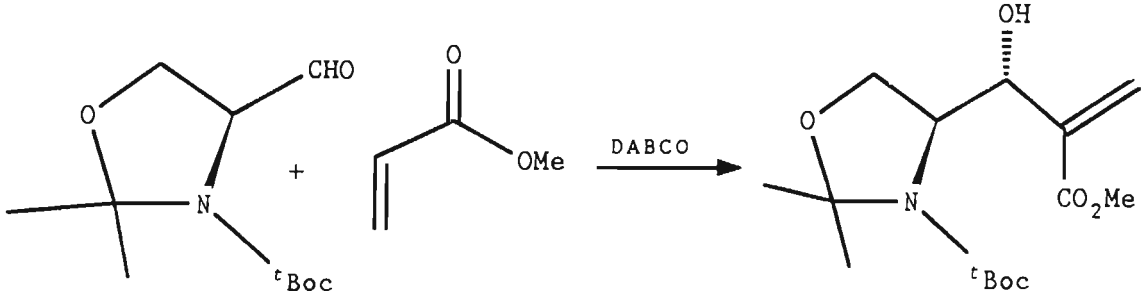
In this series of aldehydes the stereochemical outcome was found to be dependent on the type of protecting group. For doubly protected amino aldehydes (entries 1, 2 and ref 116 for other examples) *anti* selectivity was favoured whereas amines bearing a hydrogen atom proceeded with *syn* stereofacial selectivity. For the latter the authors invoked Cram 's cyclic model to rationalise their results.



70

R = Ts, ^{t}Boc

A variation of this method involves use of α-cyclic amino aldehydes and has been explored by Drewes *et al.*.[118] In studies directed towards the synthesis of sphingosine analogues,[119] Garner's aldehyde **37** was coupled with methyl acrylate to produce the *anti* isomer **71** as the major product (*anti:syn* = 75:25).



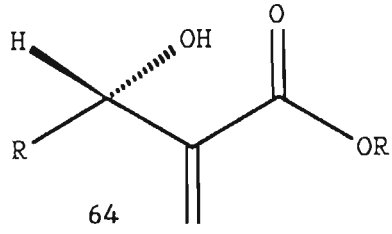
37 71

Scheme 21.

This result and others represent admirable asymmetric induction achieved *via* the Baylis-Hillman reaction.

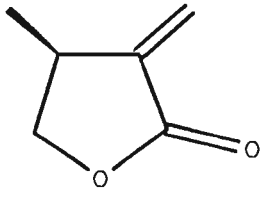
2. DISCUSSION

Aldehydes play a significant role in organic synthesis because of their reactivity towards a variety of reagents. Of special interest is the versatility of this class of compounds in C-C bond-forming reactions, in particular, towards the synthesis of α-hydroxyalkylacrylates **64.**

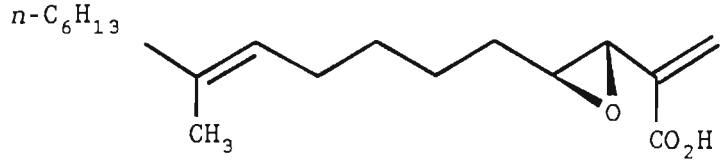


64

Apart from the fact that the acrylate unit occurs in many naturally occurring compounds of biological interest *e.g.*, tulipalin **(72)** and conocandin **(73)** - a fungistatic antibiotic - it contains versatile functional groups and consequently it is a valuable intermediate for further elaboration.



Tulipalin (72)



Conocandin (73)

Several methods have been used for the synthesis of systems such as **64** including α-methylenation of esters,[120] condensation of masked acrylates[121,122] or vinyl cuprates[108] with aldehydes. These methods however, suffer from lack of generality and drastic conditions under which some of the reagents are used.

The Baylis-Hillman reaction is clearly the most general and useful coupling reaction that leads to the multifunctional

α-hydroxyalkylacrylates in a single step. Other important features of the Baylis-Hillman reaction are ease of implementation, mild conditions and obviated need for masking which avoid the anxieties of low temperature metal-enolates.

Various aldehydes have been used in the Baylis-Hillman reaction specially, aromatic aldehydes. They have featured in several studies including kinetic,[123] mechanistic[124] and stereoselective studies.[125-128]

Surprisingly, the commercially available aromatic aldehyde, salicylaldehyde has rarely been used in the Baylis-Hillman reaction despite the fact that it offers three options in which it may be used, *viz.*,

i) it may be used directly without modification (this method has been carried out *vide infra*)

ii) the hydroxyl group may be used to make an acrylic ester of salicylaldehyde which may be used to gain insight into the feasibility of intramolecular Baylis-Hillman reaction and possibly to cast more light on its mechanism alternatively,

iii) protection of the hydroxyl group and use of the resulting alkoxy aldehyde in the Baylis-Hillman reaction.

It is interesting to note that salicylaldehyde is a β-hydroxy aldehyde. Consequently it can be used as a model to study various ways in which chiral β-hydroxy aldehydes may be used in the Baylis-Hillman reaction.

α-Chiral aldehydes have played a significant role in stereochemical control particularly, in understanding 1,2-asymmetric induction in the Baylis-Hillman reaction. A logical extension of this approach is to study the 1,3-asymmetric induction that results from use of chiral β-alkoxy aldehydes.

α-Hydroxyalkylacrylates, prepared by the Baylis-Hillman reaction, have repeatedly served as synthetic intermediates towards the synthesis of more complex molecules.[129-132] Among other transformations, the Baylis-Hillman reaction has gained entry in the synthesis of α-methylene lactones,[133] indolizines[134] and pyrazolidinones.[135] However, despite the conciseness and the elegance of these transformations in exploitation of the versatile functional groups provided by the α-hydroxyakylacrylates **64**, use of functionalised chiral aldehydes followed by further elaboration has not been explored.

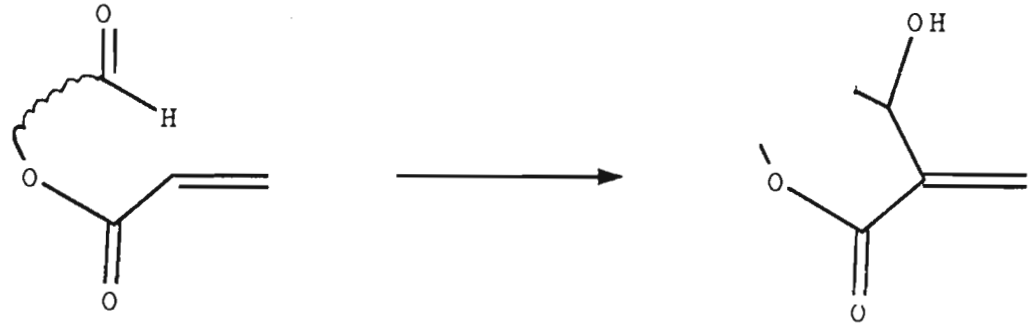
Use of chiral β-alkoxy aldehydes in particular, would produce γ,δ-unsaturated alkyl/benzyl ethers - substrates that are suitably substituted for electrophile-induced cyclofunctionalisation to multifunctionalised tetrahydrofurans.

With this background information, the initial aims of this investigation were set out as follows:

a) To study the use of various derivatives of salicylaldehyde in the Baylis-Hillman reaction as a model for β-hydroxy aldehydes.
b) To prepare functionalised chiral β-alkoxy aldehydes and investigate their reactivity and stereochemical control in the Baylis-Hillman reaction and
c) To investigate stereocontrol in iodocyclisation of the resultant α-hydroxy-(δ′-alkoxy)alkylacrylates to substituted tetrahydrofurans.

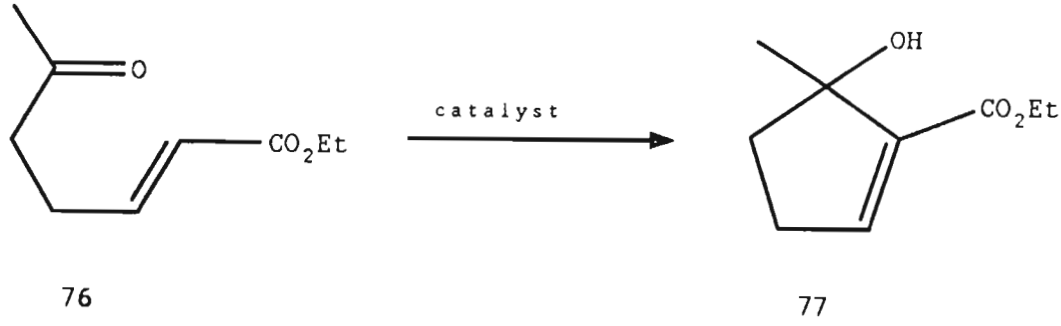
2.1. USE OF SALICYLALDEHYDE IN THE BAYLIS-HILLMAN REACTION

In order to expand the scope of the Baylis-Hillman reaction, a system that accommodates an intramolecular Baylis-Hillman reaction was designed. Such a system requires an electrophile-bearing α-unsubstituted acrylate **74**. This would allow expedient preparation of derivatives of the type **75** directly from acrylate systems **74**.



74 75

An intramolecular variant of the Baylis-Hillman has been reported only once previously by Fráter and coworkers.[136] Their substrate, an α,β-unsaturated-ε-keto ester **76**, was treated with various (tertiary amine and tertiary phosphine) catalysts to effect cyclisation (Scheme 22).



76 77

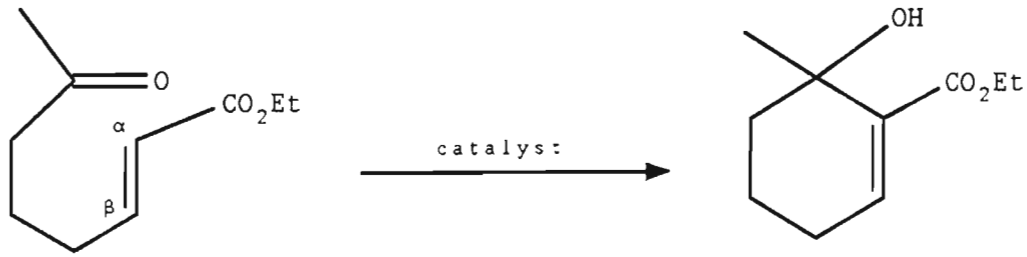
Catalyst: DABCO, (-)-PAMP, (-)-CAMP

Scheme 22.

Unlike tertiary amines - which were completely ineffective - tertiary phosphines such as (-)-PAMP and (-)-CAMP effected the condensation, giving the cyclic product **77** in 30-70%

yields.

Application of this methodology to α,β-unsaturated-ζ-keto ester **78**, with a view to make six-membered adduct **79**, gave mediocre results (Scheme 23).



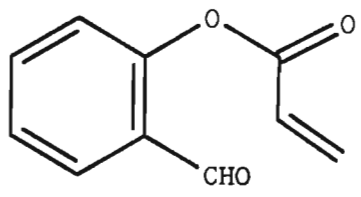
78 79

Catalyst: DABCO, (-)-PAMP, (-)-CAMP

Scheme 23.

Use of acrylate systems **76** and **78** in the Baylis-Hillman reaction has two drawbacks. Firstly, it involves the rather less reactive ketone group (relative to an aldehyde) as an internal electrophile. Secondly, assuming initial nucleophilic attack of the acrylate by the catalyst as the first step in the mechanism (*vide infra*), β-substitution of the acrylate as in **76** and **78** obviously diminishes the reactivity of the acrylate. This could be due to steric and electronic effects.

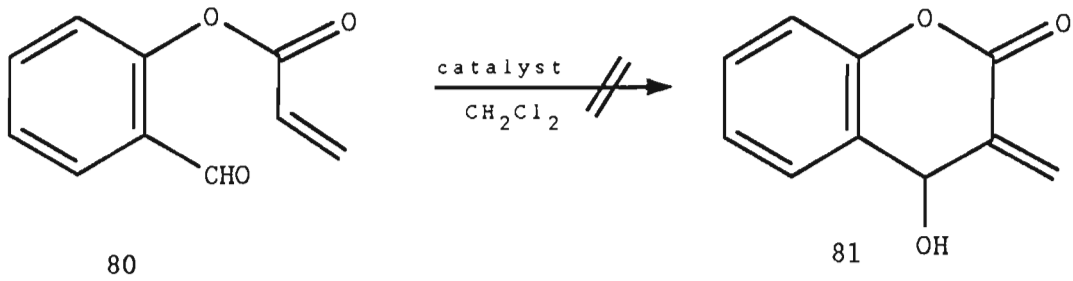
In this investigation, the acrylate ester of salicylaldehyde **80** was chosen as a model to study the intricacies of an intramolecular Baylis-Hillman reaction.



80

The acrylate **80** is easily accessible from base-catalysed esterification[137] of salicylaldehyde with acryloyl chloride.

When the acrylate **80** was treated with DABCO in CH_2Cl_2 at 0°C (exothermic reaction!), a bright yellow precipitate which was expected to be 4-hydroxy-3-methylenebenzopyranone, **81**, formed immediately (Scheme 24).



80 81

Catalyst: DABCO, QDL

Scheme 24.

Formation of the precipitate was solvent dependent; precipitation occurred in CH_2Cl_2 and $CHCl_3$ only. The precipitate was unreactive to alkoxy and phenoxy anions and several carbanions. The yellow powder was soluble in polar solvents such as water, methanol and dimethyl sulfoxide, suggesting that it was ionic in nature. Also, it was clear from MS and spectral data that the product was not the benzopyranone **81**.

Examination of the GC-MS showed two peaks: m/z = 112 and 194. This information, which suggests presence of a DABCO (M^+ 112) fragment, was at first bewildering. Further elucidation by NMR confirmed the presence of *N*-substituted DABCO. The DABCO methylene groups which usually resonate as a singlet appeared as two beautifully split multiplets (Figure 4).

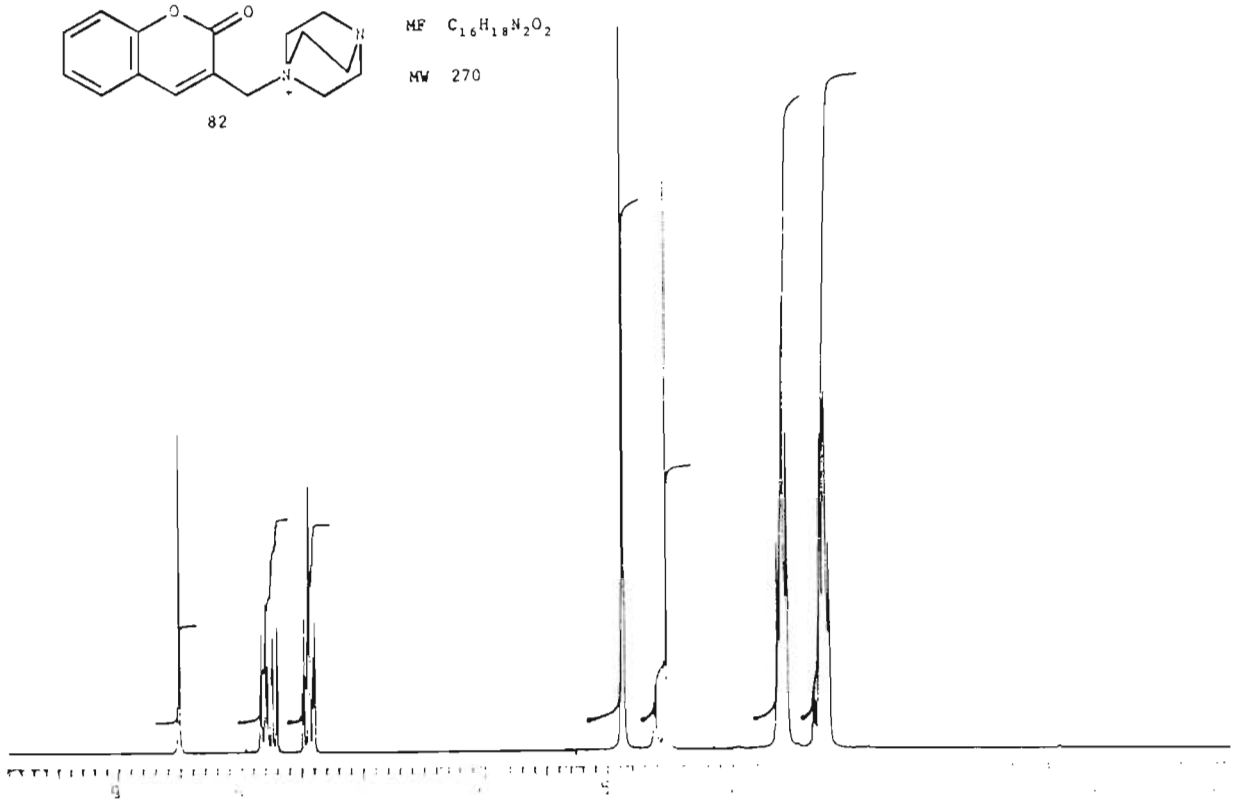
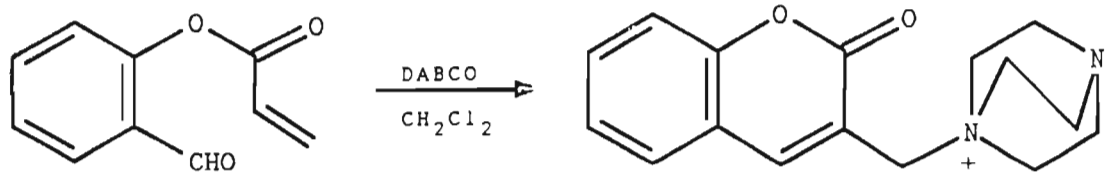


Figure 4.

With all this information, evidence pointed towards the coumarin ammonium cation **82** (Scheme 25).



80 82

Scheme 25.

The final task was to establish the identity of the counter ion. Perusal of the MS and high resolution MS indicated the four isotopes of chlorine with their respective natural abundance. Furthermore, counter anion exchange with $AgPF_6$ in methanol gave a white precipitate which tested positive for AgCl. Finally, the structure was confirmed by X-ray analysis (Figure 5), which confirmed that the counter ion was indeed Cl^-.

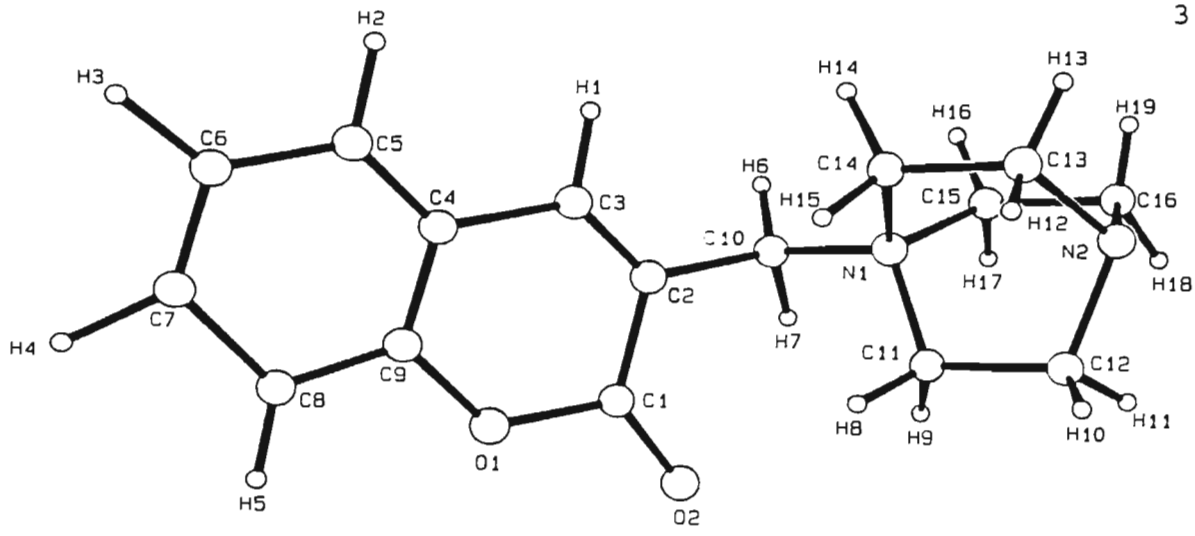
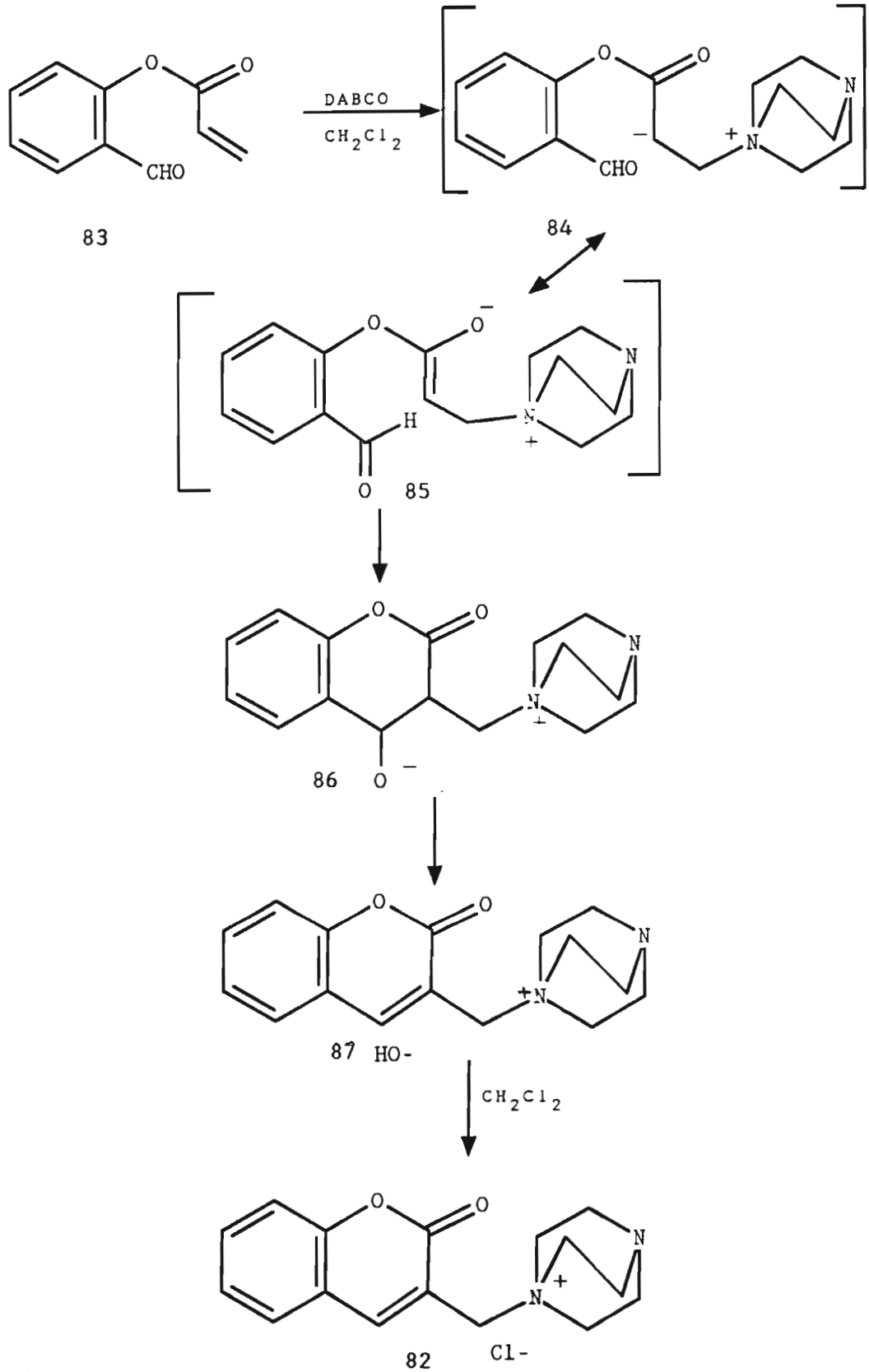


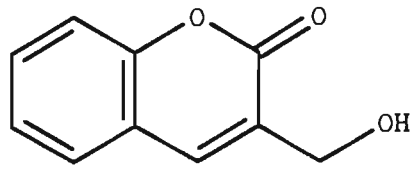
Figure 5.

A mechanistic pathway for the formation of the novel coumarin salt **82** is proposed in Scheme 26.
The reaction is initiated by nucleophilic attack of DABCO on the acrylate to form resonance stabilised intermediate **84**. This is followed by intramolecular nucleophilic addition to the aldehyde group to form **86**. With DABCO still intact, proton migration and hydroxide elimination to form the conjugated system **87** ensues. Finally, interaction between the hydroxide **87** and the solvent (CH_2Cl_2 or $CHCl_3$) produces the chloride ion.

An intriguing inference can be drawn from this finding; it proves, for the first time, that the elusive Michael adduct postulated by all researchers in this area but hitherto not isolated does exist. The trapping of the intermediate rather than the usual elimination which ensues after reaction with aldehyde, is positively influenced by the stability of the product.
Under these reaction conditions, some elimination occurred but this was a minor pathway and afforded the coumarin **88** *via* allylic rearrangement of **81**.

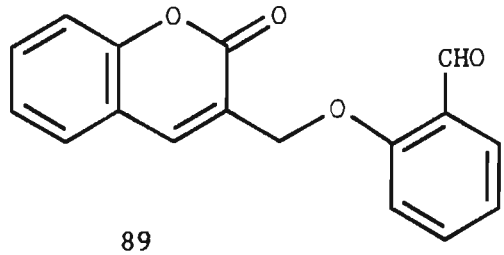


Scheme 26.



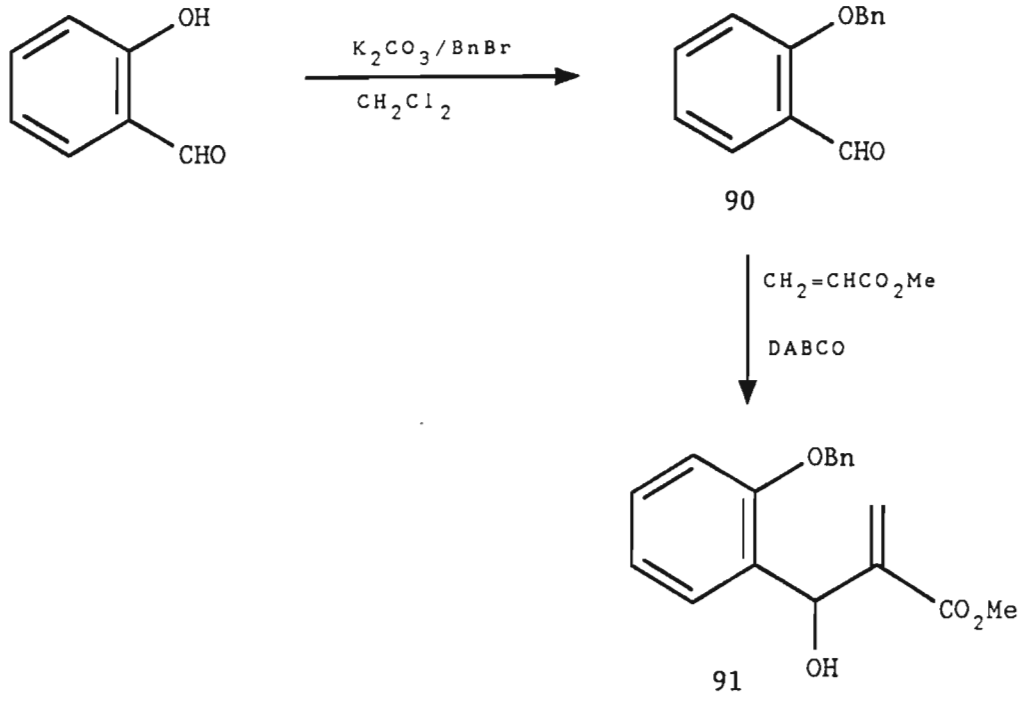
88

Previously, Bode and Kaye[139] attempted to use unmodified salicylaldehyde in the Baylis-Hillman reaction but were only able to isolate **89** in 9.7% yield.



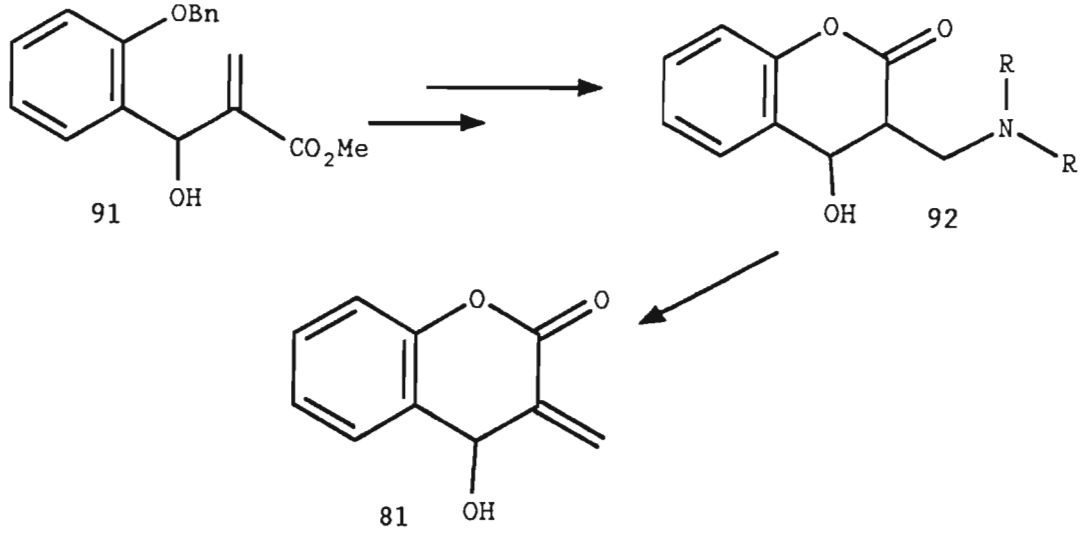
89

Alternative use of salicylaldehyde involves protection of the hydroxyl group and use of the resulting aldehyde in the Baylis-Hillman reaction. Thus, the benzyl ether of salicylaldehyde **90**, prepared by a base-catalysed reaction[140] of salicylaldehyde with benzyl bromide, was subjected to the usual coupling conditions to afford the acrylate **91** (Scheme 27).



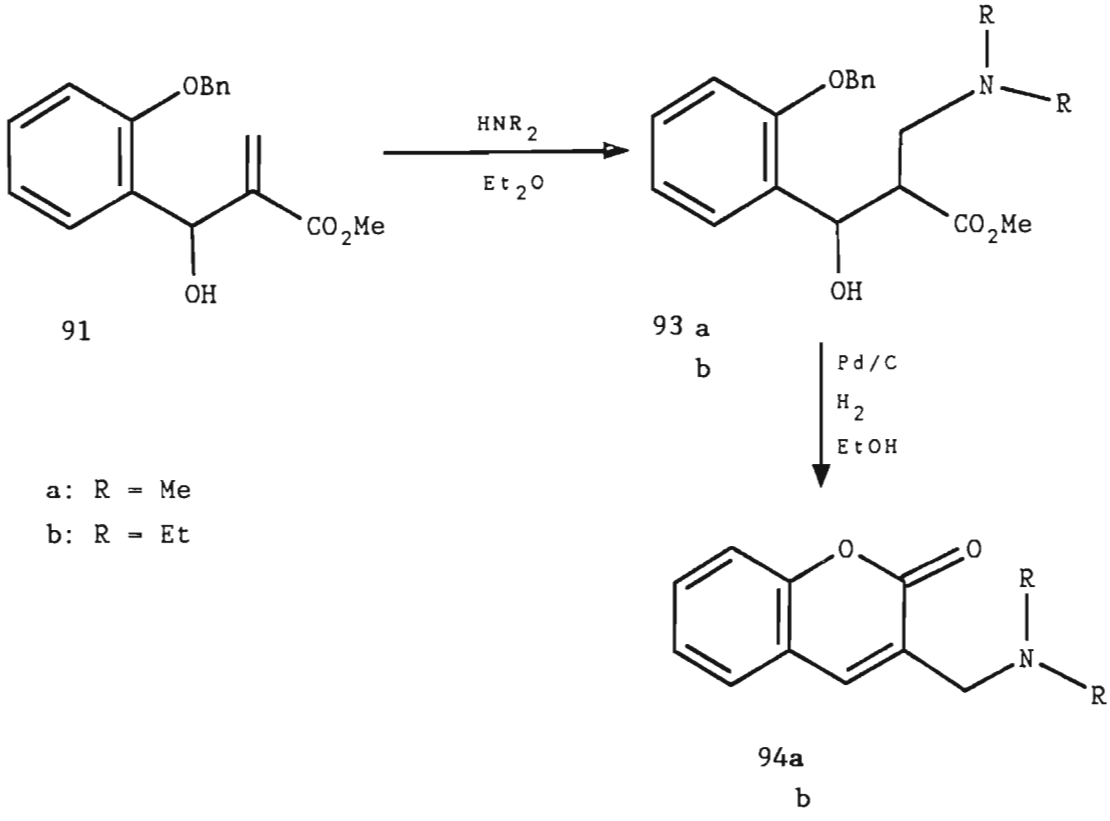
Scheme 27.

In an attempt to exploit the synthetic utility of this reaction, it was envisaged that masking the acrylate followed by deprotection-transesterification would afford the benzopyranone **92** which on unmasking would afford 3-methylene benzopyranone **81** (Scheme 28).



Scheme 28.

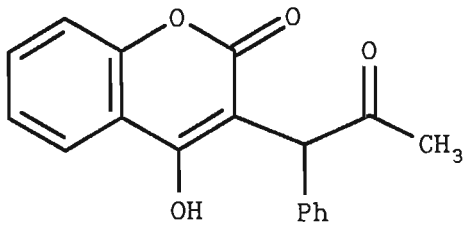
In the event, the acrylate **91** was masked[122] giving **93** without incident, but debenzylation[141] afforded the 3-substituted coumarin **94** in 86% overall yield (Scheme 29).



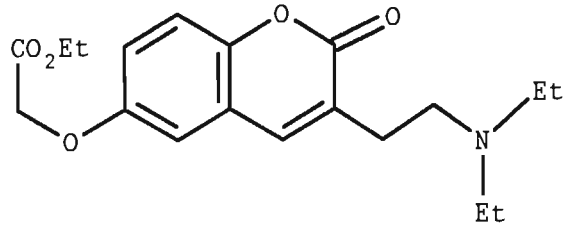
Scheme 29.

The use of salicylaldehyde in the Baylis-Hillman reaction has introduced a new entry; synthesis of coumarins. Coumarins are well known for their anthelmintic, hypnotic, insecticidal and antifungal properties as well as their anticoagulant effect on blood.[142]

Compounds such as **94a**, **94b** and further analogues, which are currently receiving attention in these laboratories, are of particular interest because of their similarity to warfarin **(95)** and chromonar, **96**. Warfarin is an approved anticoagulant and a widely used rodenticide[143] while chromonar finds use as a coronary vasodilator.[144]



Warfarin (95)



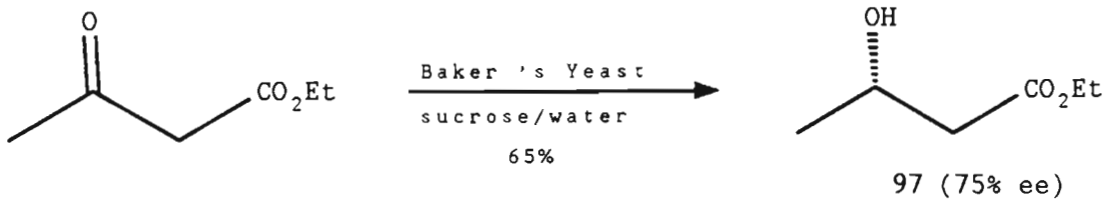
Cromonar (96)

2.2. SYNTHESIS OF CHIRAL ALDEHYDES

Optically active β-hydroxy esters are attractive starting materials for the synthesis of β-hydroxy or β-alkoxy aldehydes.

β-Hydroxy esters and acids were prepared by enzymatic reduction, asymmetric hydrogenation and some from naturally occurring acids - "chiral pool". The crucial operation in these syntheses was introduction of chirality in the first step.

Initial studies involved reduction of β-keto esters. The reduction of β-keto esters by baker's yeast is probably the most extensively studied microbial transformation that leads to the β-hydroxy esters.[145,146] Baker's yeast has been widely used for this transformation because it is inexpensive, its growth does not require the assistance of a microbiologist and most significantly the reduction is highly enantioselective. Consequently, baker's yeast was employed for enantioselective reduction of ethyl acetoacetate.[147]



Scheme 29.

Indeed, compound **97** was obtained with high optical purity and reasonable chemical yield (Scheme 29). The enantiomeric excess was determined using chiral shift reagent ($Eu(fod)_3$) and by comparison with authentic samples. The optical yields were not reproducible and the reaction workup was physically demanding, tedious and resulted in low recovery of product. Nevertheless the result was sufficient for initial studies.

Inspired by this result, the synthesis of the enantiomer of **97** was considered.

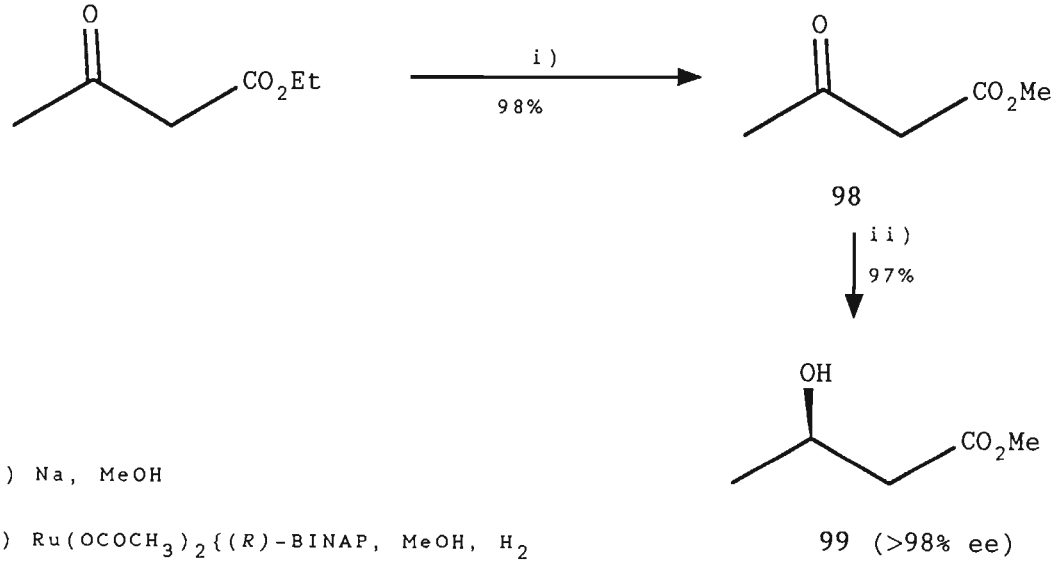
Immobilisation of baker's yeast with magnesium alginate and other inorganic salts has been reported to reverse the selectivity of the reduction of some substrates. Unfortunately, application of this method on ethyl acetoacetate leads to an increase in enantioselectivity.[148]

Seebach and Züger[149] have prepared the enantiomer of **97** by depolymerisation of naturally occurring polyhydroxybutyrate.

Noyori and coworkers[150,151] have demonstrated that β-hydroxy esters are accessible by asymmetric hydrogenation of β-keto esters catalysed by Ru-BINAP complexes (BINAP = (*R*)- or (*S*)-bis(diphenylphosphino)-1,1-binaphthyl). Either isomer can be synthesised selectively and in high enantioselectivity by the judicious choice of BINAP configuration. Thus (*S*)-BINAP converts acetoacetic esters to β-hydroxy esters that

have the (*S*) configuration while (*R*)-3-hydroxy esters are available using (*R*)-BINAP.[150,151]

The latter method was adopted for the synthesis of the enantiomer of **97**. The hydrogenation of ethyl acetoacetate in ethanol gave the desired ester in a low yield even after prolonged periods. When the hydrogenation was performed in methanol, complete hydrogenation of the keto group occurred but unfortunately the ethyl ester was accompanied by a transesterification product. Ultimately, the desired hydroxy compound **99** was synthesised by hydrogenation of methyl acetoacetate (**98**) which was prepared by transesterification of ethyl acetoacetate using a catalytic amount of *in situ* prepared NaOMe (Scheme 30).

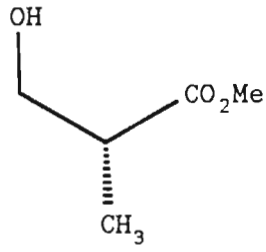


Scheme 30.

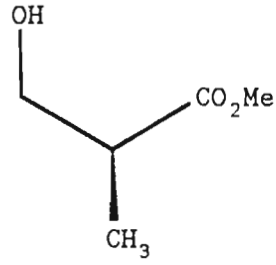
Compound **99** was produced in high enantioselectivity and nearly quantitative yield. The preparation of the catalyst was time consuming and the whole method is potentially unsafe.

The second pair of enantiomeric β-hydroxy esters **100** and **101** are commercially available and were used without

purification in the next step.



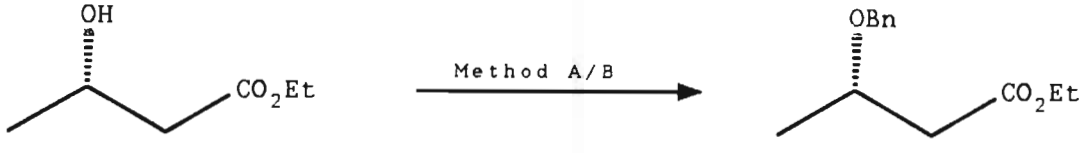
100



101

The next step was to convert the hydroxy esters **97**, **99**, **100** and **101** to the required aldehydes. Preliminary studies[152] had shown that the hydroxy group required protection prior to conversion of these substrates to aldehydes. In the same study, the methoxymethyl protecting group and the benzyl protecting group were found to be the most convenient protecting groups. In this study only the latter will be used.

Incorporation of the benzyl protecting group, bearing in mind that the optical integrity of the substrate must remain unaltered, is not a simple task. This operation was carried out in nonionic conditions using freshly prepared silver oxide and benzyl bromide (Scheme 31, method A). However,



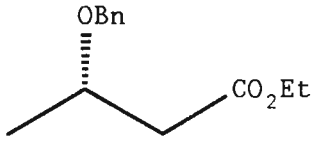
Method A: Ag_2O, BnBr, Et_2O

Method B: $BnOC(NH)CCl_3$

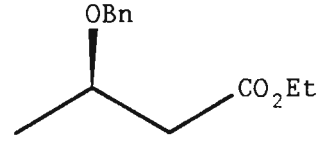
Scheme 31.

the yields were low and the unreacted starting material racemised during seperation. Attempts to improve the chemical yields by using sonication[153] resulted in a slight improvement.

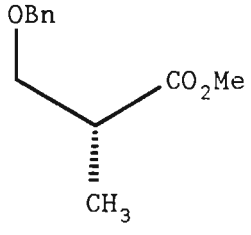
An alternative mild method for the incorporation of the benzyl group involved the use of benzyl chloroacetimidate[154,155] (Scheme 31, method B). This method uses a large excess of the benzylating reagent and yields again were low in the order of 40 - 50%. In the absence of a quantitative benzylating method, both methods (Scheme 31), albeit with low yields, were used to prepare β-benzyloxy esters **102 - 105**.



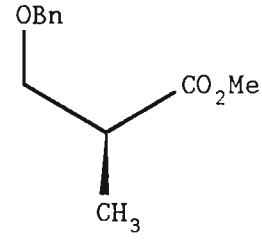
102



103

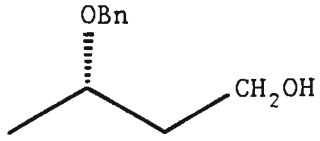


104

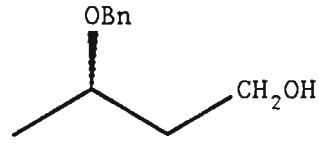


105

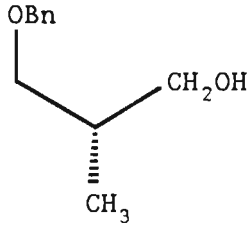
The next step was to convert the esters to aldehydes. DIBAL reduces esters at low temperature directly to the aldehydes. However, the aldehyde is often accompanied by the overreduction product *i.e.*, the alcohol.[156]
An alternative approach is to reduce the esters to the corresponding alcohols followed by oxidation to aldehydes.
The first step posed no problems and was readily accomplished by lithium aluminium hydride reduction.[157] The following alcohols were thus obtained in 90% average yield.



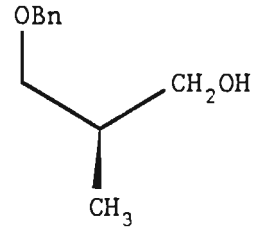
106



107

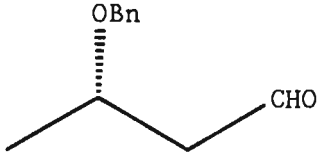


108

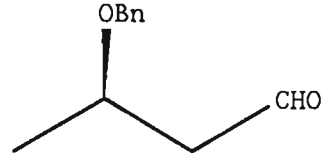


109

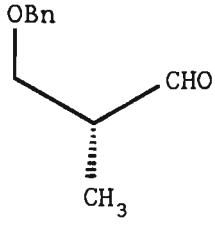
Finally, to execute the last transformation, there were several oxidising methods[158] to choose from. These include the Jones oxidation, Collins, Dess-Martin, PDC, PCC and Swern oxidation. The Swern oxidation[159] was the most convenient and consequently was used for the preparation of the following aldehydes.



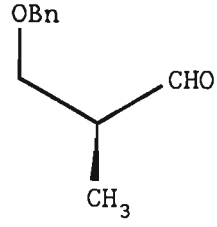
110



111



112



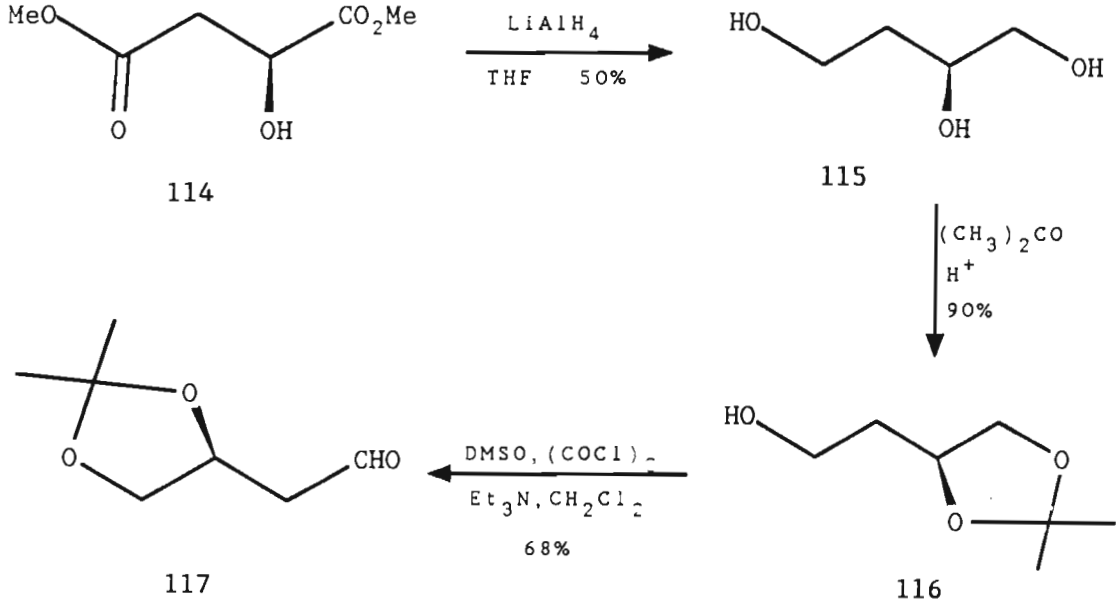
113

The aldehydes **110** to **113** were produced with an average yield of 70% based on the alcohol and an overall yield of a low 35%.

The chiral pool also provides a reliable source of

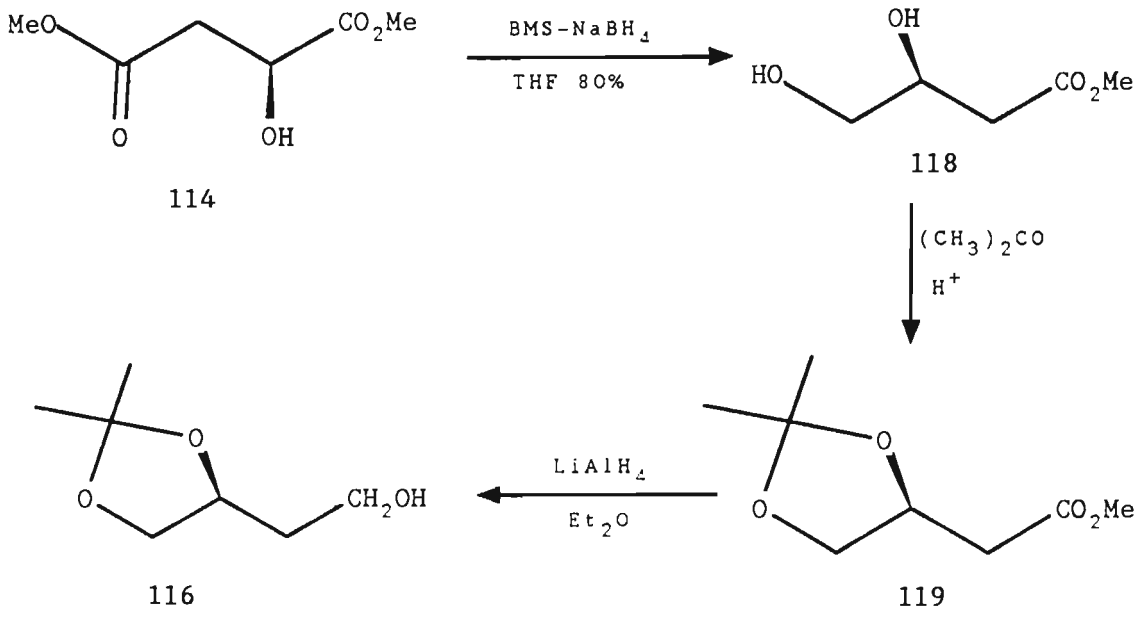
chiral β-hydroxy acids that can be transformed to aldehydes. The second series of aldehydes were prepared from malic acid, tartaric acid and ascorbic acid.

(*S*)-Malic acid was esterified to the known dimethyl ester **114**[160] to facilitate reduction with lithium aluminium hydride. The triol **115** thus obtained upon reduction (50% yield) was converted to its acetonide (90% yield) which according to NMR consisted only of the five-membered species **116**. Swern oxidation of the alcohol **116** afforded the aldehyde[160] in good yield.



Scheme 32.

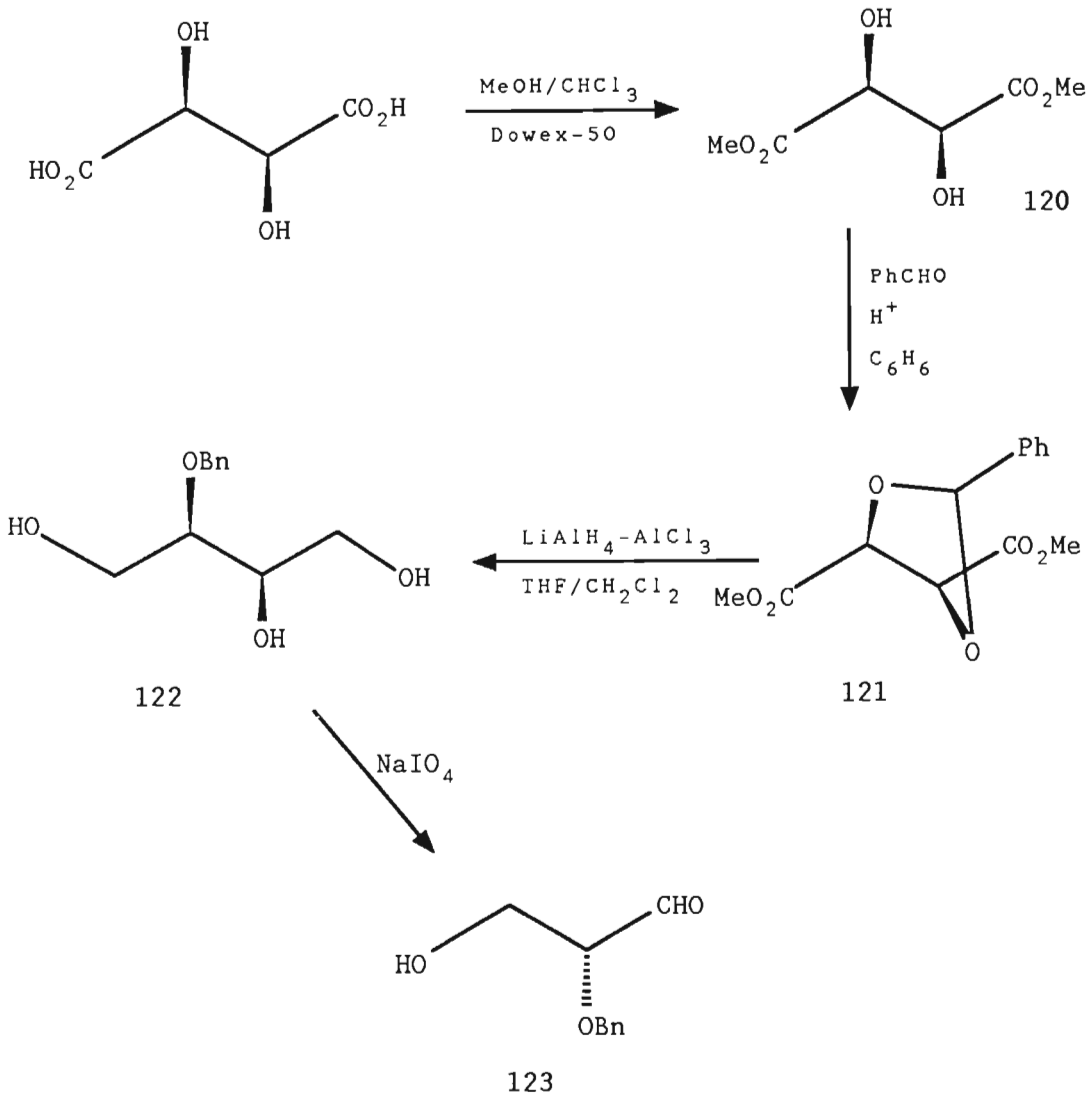
Unfortunately, the use of the above approach is impeded by difficulties in the recovery of the triol. An alternative procedure would be to selectively reduce the ester group adjacent to the hydroxyl group followed by protection. In fact, regioselective reduction of the ester **114** was carried out using BMS complex and $NaBH_4$ afforded the 1,2-diol in 80% yield.[162] The diol **118** was protected as the acetonide **119** (Scheme 33) which was ready for reduction to the acetonide alcohol **116**. The overall yield of the aldehyde **117** *via* this approach was improved by 17%.



114 118 119 116

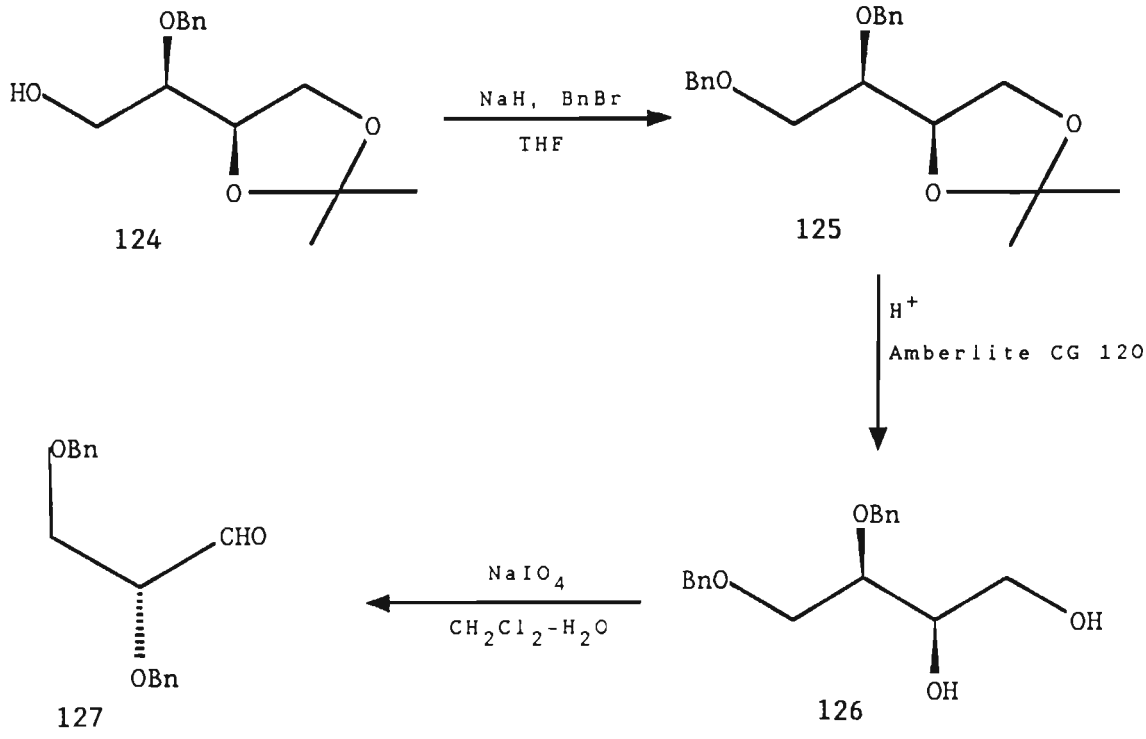
Scheme 33.

Another source of aldehydes was the isomer of naturally occurring tartaric acid.[163] The methyl ester of tartaric acid **120** was protected as the benzylidene acetal **121** and reductively cleaved to form the tetrol **122** according to Seebach's procedure.[164] Oxidative cleavage of the 3,4-diol fragment with sodium periodate[165] produced benzyl glyceraldehyde **123** (Scheme 34).



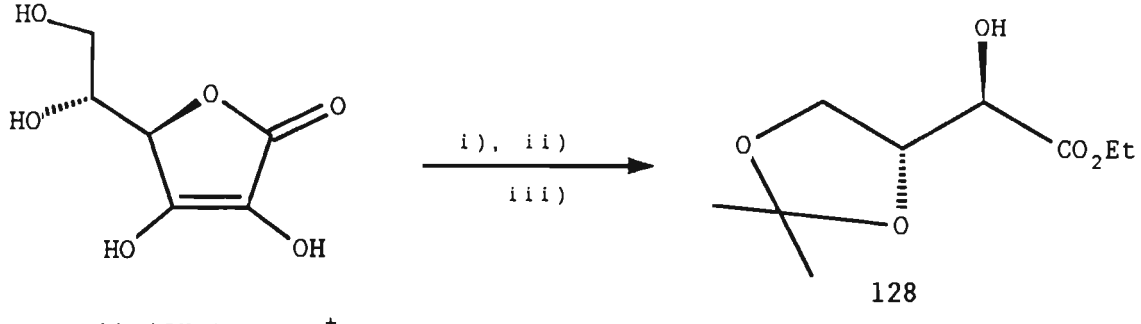
Scheme 34.

To further exploit tartaric acid as a source of chiral aldehydes, a system that produces dibenzyloxyglyceraldehyde was designed. Thus benzyl tetrol **122** was protected as the acetonide **124** in order to effect the protection of the terminal hydroxyl group in **124**. Incorporation of the benzyl group was effected by sodium hydride and benzyl bromide giving **125** in high yield. The acetonide group was removed to give dibenzyl tetrol **125** which was cleaved oxidatively to afford dibenzyloxyglyceraldehyde **127** (Scheme 35).



Scheme 35.

Finally, the last series of aldehydes were produced from ascorbic acid by adaptation of chemical transformations as published by Abushanab *et al.*.[166] Ascorbic acid was first converted to the protected trihydroxy ester **128** in three steps (Scheme 36).

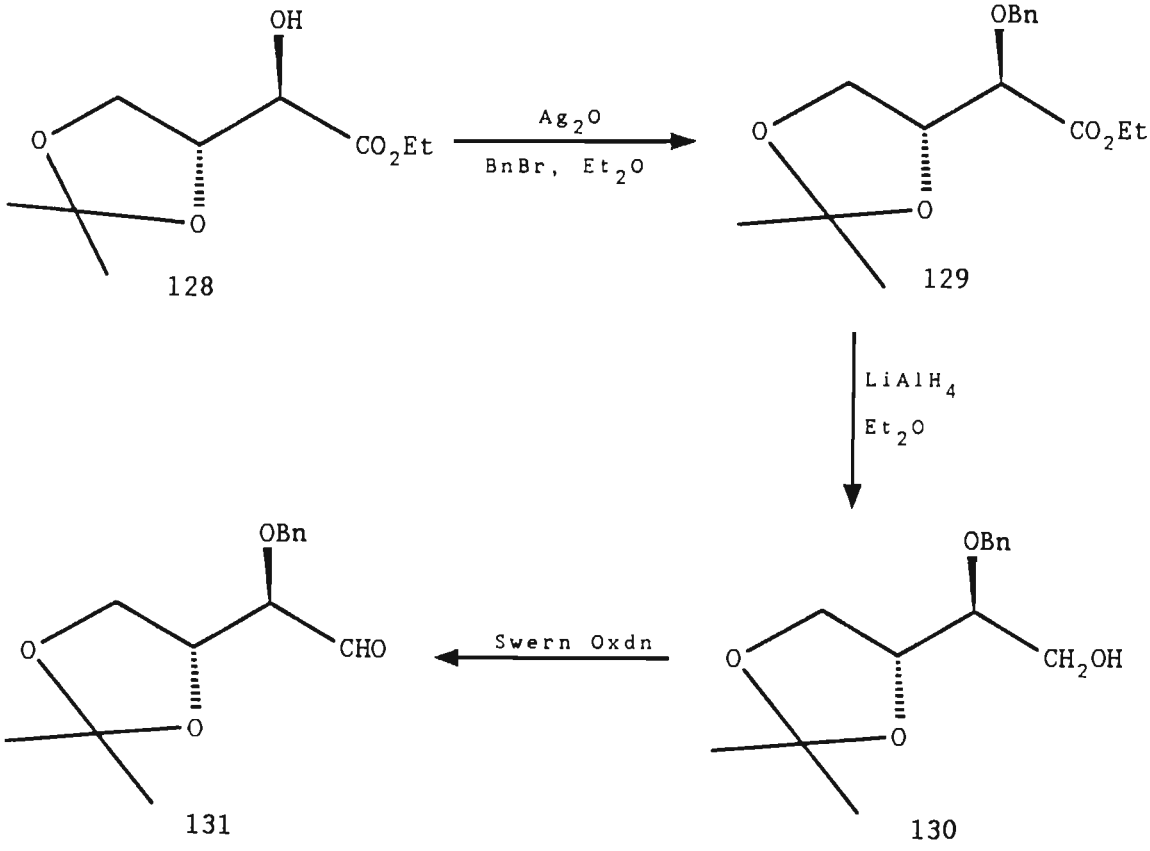


i) $(CH_3)_2CO$, H^+
ii) K_2CO_3, H_2O_2, H_2O
iii) EtI, CH_3CN

Scheme 36.

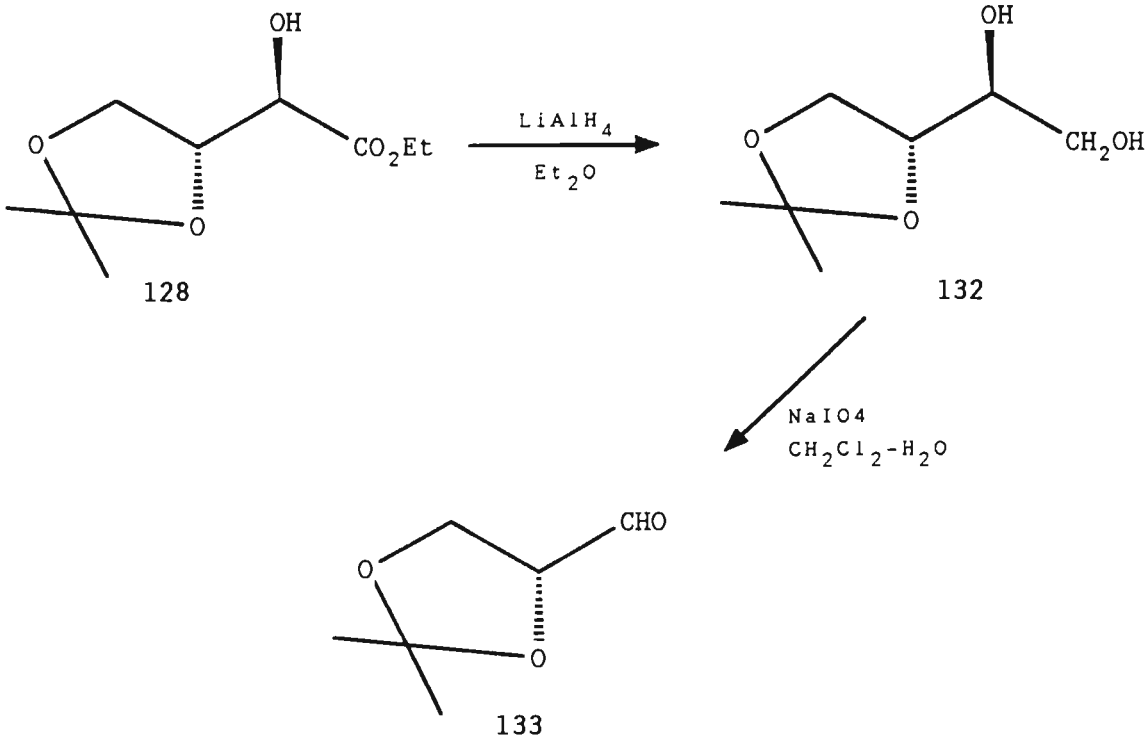
Synthesis of the first aldehyde commenced by hydroxyl

protection of the ester **128**. This was achieved by treatment of **128** with freshly prepared silver oxide[167] and benzyl bromide to give **129** in high yield. Reduction of the ester with lithium aluminium hydride produced **130** in quantitative yield. Oxidation of the alcohol **130** using Swern oxidation afforded the aldehyde **131** (Scheme 37).



Scheme 37.

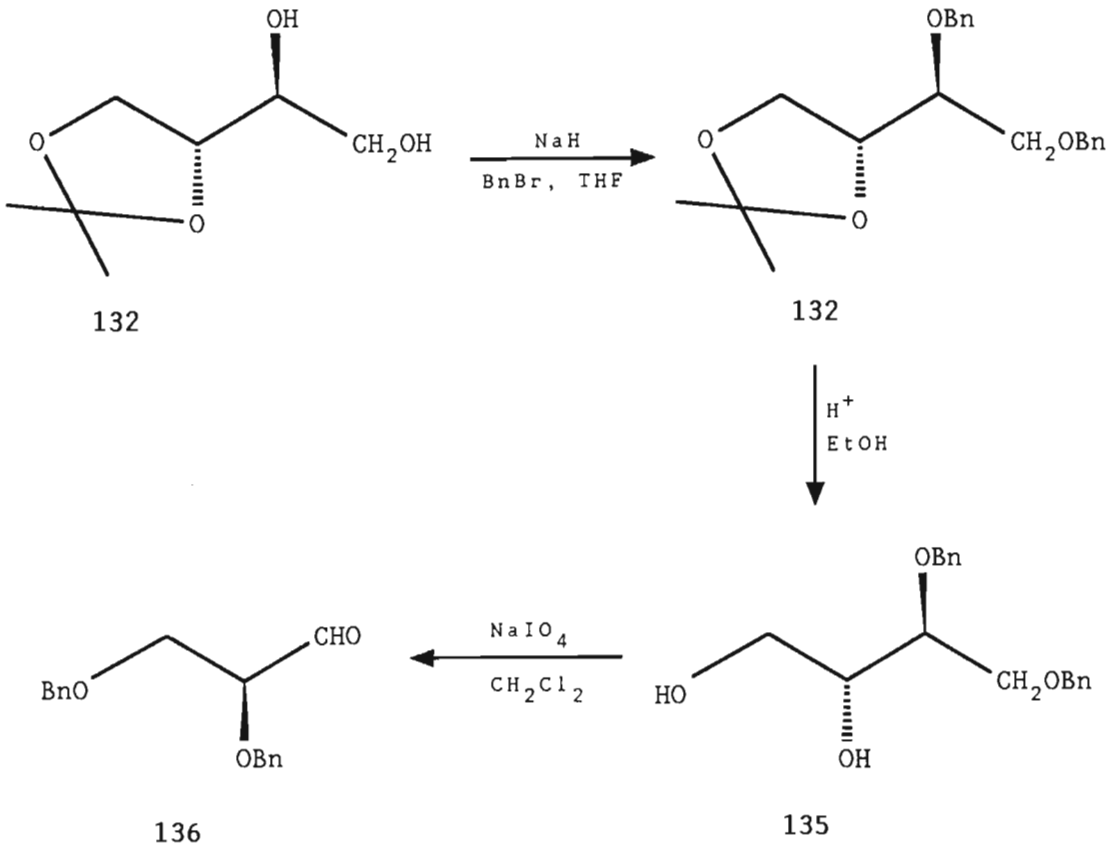
In another procedure, the ester **128** was reduced with lithium aluminium hydride, without protecting the free hydroxyl group, to produce **132**. Oxidative cleavage of the tetrol **132** produced isopropylideneglyceraldehyde **133** in good yield (Scheme 38).



Scheme 38.

Several methods for the preparation of isopropylidene-glyceraldehydes (*R* and *S*) have been reported in the literature.[43] Only once previously has the aldehyde **133** been prepared from ascorbic acid and the method is tedious.[43]

The last aldehyde was prepared using **132** as the substrate. Treatment of **132** with 2 equivalents of benzyl bromide in the presence of sodium hydride furnished the dibenzyl derivative **134**. Acid hydrolysis of the isopropylidene function on **134** led to the tetrol **135** which was converted to the aldehyde **136** *via* Swern oxidation (Scheme 39).



Scheme 39.

Previously,[43] the dibenzyloxyglyceraldehydes **127** and **136** have been prepared from D-mannitol in six steps $[\alpha]_D$ (for **127**) = +52° (*c* 2.0 benzene). The optical rotation obtained in this investigation ($[\alpha]_D$= + 20° (*c* 2.173 $CHCl_3$) was relatively low probably due to racemisation by silica gel.

2.3. THE BAYLIS-HILLMAN REACTION

According to the salicylaldehyde model study

i) A β-hydroxy aldehyde can be protected as an acrylic ester and converted *via* intramolecular Baylis-Hillman reaction to cyclic adducts, or

ii) It can be protected as a benzyl ether and coupled with

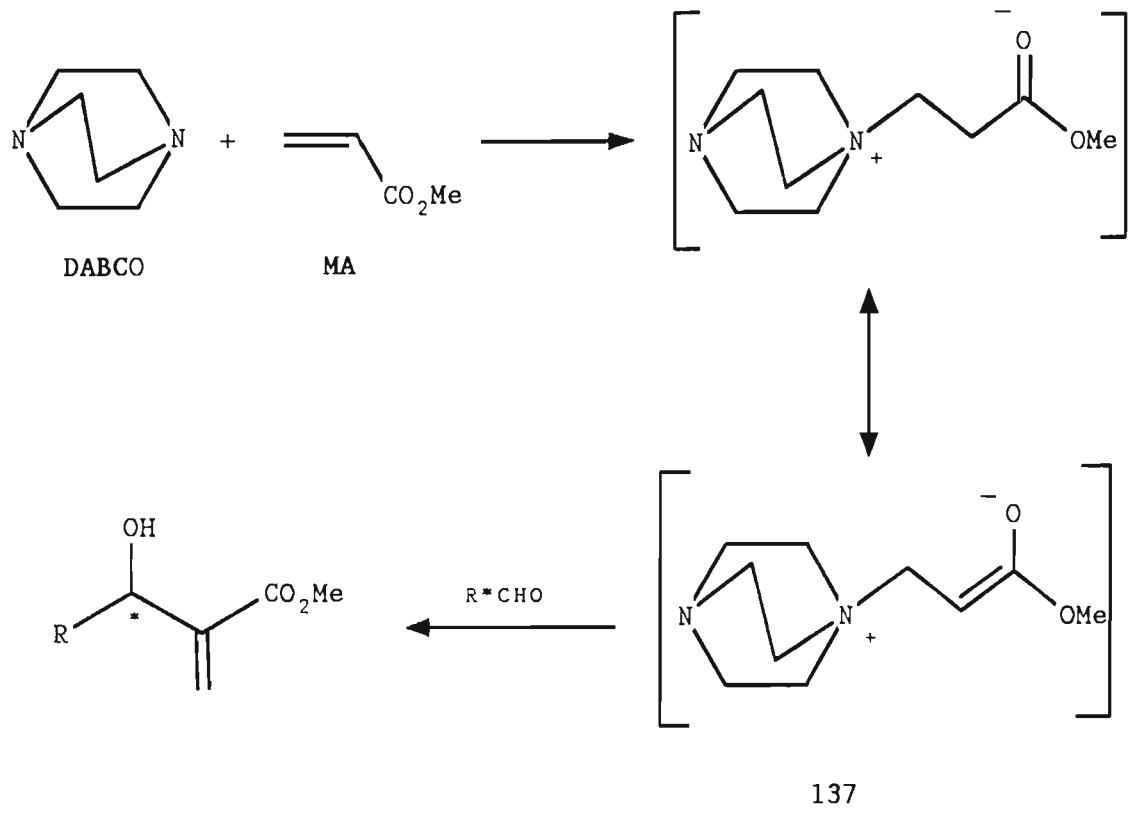
carbanions.

The first approach cannot be applied to aldehydes **110**, **111**, **112**, **113**, **117**, **127**, **131**, **133** and **136**, since it would require deprotection which has been found resulting in decomposition of the aldehydes.[152] Also, the hydroxyl groups of aldehyde **123** could not be protected as the acrylic ester since it forms acetals within minutes of its isolation and therefore this route was abandoned.

Since the aldehydes contain a β-alkoxy group with lone pairs of electrons, some organometallic compounds can in principle form intermediate chelates (see introduction) result in attack of the electrophilic carbon from the less encumbered face to afford a chelation-controlled product - generally, *syn*.

In the absence of chelation, free rotation around the C-C bond pertains and brings about a different scenario. In such circumstances prediction of the stereochemical outcome is generally difficult. One possibility is the application of the Felkin-Anh model which predicts formation of non-chelation controlled adducts which may have the *syn* or the *anti* relationship. The Baylis-Hillman reaction falls in this category *i.e.*, abscence of chelating metal.

In the Baylis-Hillman reaction, the vinyl carbanion **137** generated by the Michael-type addition of a tertiary amine base to the acrylate (see section 2.1), adds to chiral aldehydes (Scheme 40). Usually a catalytic amount of base is used. The acrylate plays a dual role; that of a reagent as well as the solvent. The reaction is generally slow (*c.a.* 7 days) and the reaction profile is monitored by the disappearance of the aldehyde peak and change of the vinyl region in the NMR spectrum of the reaction mixture.



137

Scheme 40.

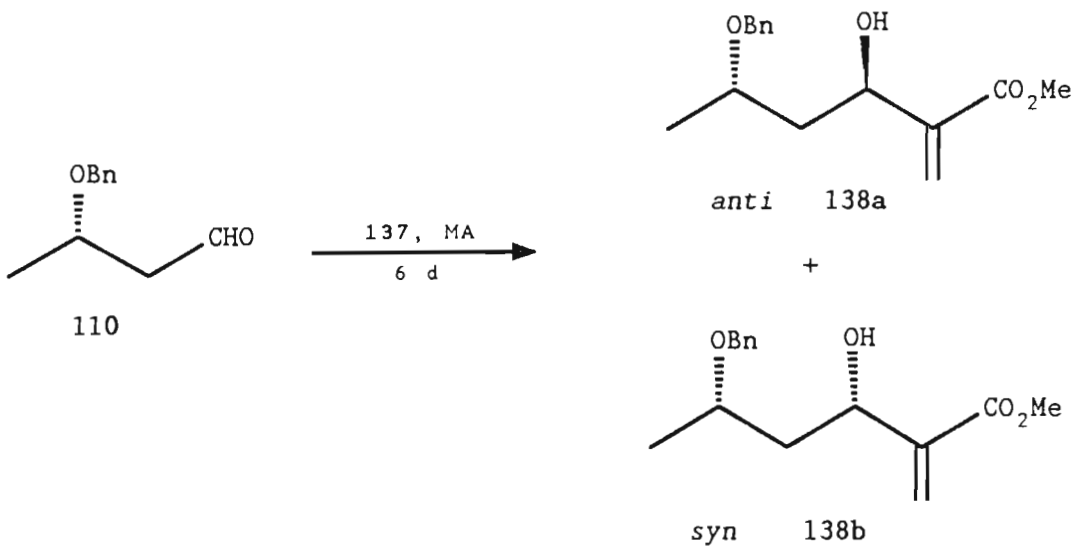
Several tertiary amine bases have been used as catalysts.[110] Especially, DABCO and QDL have been widely used because they are structurally simple and consequently it is easier to monitor the reaction profile. Although QDL has been found to enhance the reaction rate, DABCO enjoys frequent use because of its simplicity (single resonance peak in the NMR spectrum), clean reaction and ease of removal for the isolation of the product. Catalytic amounts of DABCO were used even though it is fairly obvious that an increase in catalyst concentration would enhance the reaction rate.[111,117] The reason for this will be discussed in detail later.

Concerning the acrylate; a variety of acrylic systems[110,171,172] have been used and the choice of acrylate, among other factors, has a profound effect on reaction rate.[110,124,173,174] In this study methyl acrylate

was used.

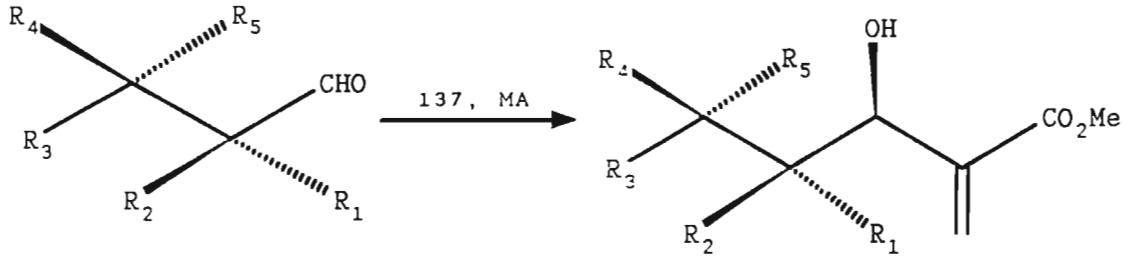
2.3.1. THE BAYLIS-HILLMAN REACTION OF METHYL ACRYLATE WITH CHIRAL ALDEHYDES

The first experiment involved the reaction of the aldehyde **110** with the DABCO-generated zwitterionic intermediate **137** (Scheme 41).



Scheme 41.

A mixture of diastereomers **138a/b** was obtained. In order to fully assess the reactivity and stereocontrol of chiral aldehydes in the Baylis-Hillman reaction, this system was extended to the enantiomer **111** and the α-substituted aldehydes **112**, **113**, **117**, **127**, **131**, **133** and **136** (Scheme 42). The results are shown in Table 3.



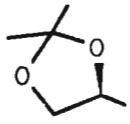
anti and *syn* products

110 R_1 R_2 R_4 = H, R_3 = CH_3, R_5 = OBn [138]

111 R_1 R_2 R_5 = H, R_3 = CH_3, R_4 = OBn [139]

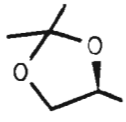
112 R_1 = CH_3, R_2 R_3 R_4 = H, R_5 = OBn [140]

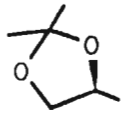
113 R_2 = CH_3, R_1 R_3 R_4 = H, R_5 = OBn [141]

117 R_1 R_2 R_5 = H, R_3 R_4 =  [142]

123 R_1 = OBn, R_2 R_3 R_4 = H, R_5 = OH [143]

127 R_1 = OBn, R_2 R_3 R_4 = H, R_5 = OBn [144]

131 R_2 = OBn, R_1 R_4 = H, R_3 R_5 =  [145]

133 R_2 R_3 =  , R_1 R_4 R_5 = H [146]

136 R_2 = OBn, R_1 R_2 R_4 = H, R_5 = OBn [147]

Scheme 42.

TABLE 2.: Diastereomer ratios in the Baylis-Hillman reaction of chiral aldehydes with MA (Scheme 42).

Entry	Aldehyde	Reaction Time /d	Products *anti:syn*	Yield /%	Isomer Ratio *anti:syn*
1	110	5	138a:138b	68	49:51
2	111	5	139a:139b	69	49:51
3	112	6	140a:140b	65	33:67
4	113	6	141a:141b	66	34:66
5	117	12	142a:142b	60	75:25
6	123	8	143	60	-
7	127	7	144a:144b	65	66:34
8	131	12	145a:145b	48	66:34
9	133	15	146a:146b	60	69:31
10	136	7	147a:147b	65	66:34

An important practical aspect of the reactions summarised in Scheme 42 is relevant at this point. This concerns the order of addition of reagents. In a typical reaction, DABCO is added to a four-fold excess of methyl acrylate (MA) (*i.e.*, with respect to the aldehyde) and allowed to stir at room temperature for 20 min. The aldehyde is then added in one portion. If the reagents are added in any sequence other than the one described, a yellow deposit forms at the bottom of the flask and little or no conversion occurs. The formation of the precipitate is partially eliminated by dissolving DABCO prior to the addition of the aldehyde.

2.3.1.1. DETERMINATION OF DIASTEREOSELECTIVITY RATIOS

The reaction of chiral aldehydes with the zwitterionic intermediate **137** resulted in a mixture of diastereomers.

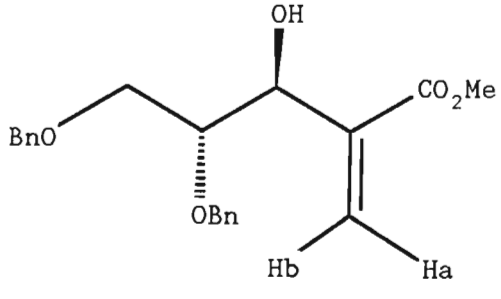
The determination of the extent of such intrinsic diastereofacial selectivity has been addressed by a number of authors. Unlike determination of enantiomeric ratio, which requires derivatisation with a chiral substance,[175] the diastereomeric ratio can be determined directly by GC-MS, HPLC or NMR spectroscopy on the mixture. The diastereomeric ratio can also be determined by use of these techniques on achiral derivatives such as silyl ether, acetyl, benzoyl or trifluoroacetyl (^{19}FNMR) derivatives of the diastereomers.[175]

Recently, Roos and Watson[176] have reported on a rapid *in situ* determination of diastereomeric ratios of alcohols by ^{1}HNMR spectroscopy. The method involves derivatisation of the alcohol with trichloroacytylisocyanate (TAI) resulting in the appearance of the carbamate *NH* singlets in the usual uncluttered 8.5 - 100 ppm region of the spectrum.

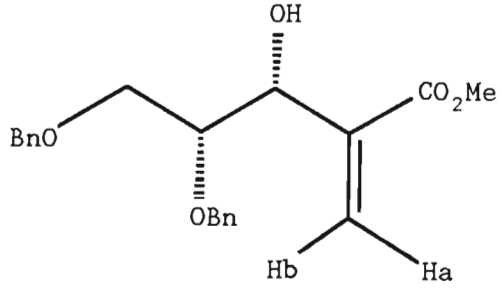
In this investigation the de ratios were determined by GC-MS, ^{1}HNMR on unpurified mixture of isomers and by ^{1}HNMR of TAI derivaties of the same mixture. Results are shown in Table 3. To illustrate this point, selected examples are discussed below.

Case 1: Use of ^{1}HNMR.

Figure 6 shows the resonance signals of the vinyl protons of compounds **144a** and **144b** (mixture of diastercomers).



144a



144b

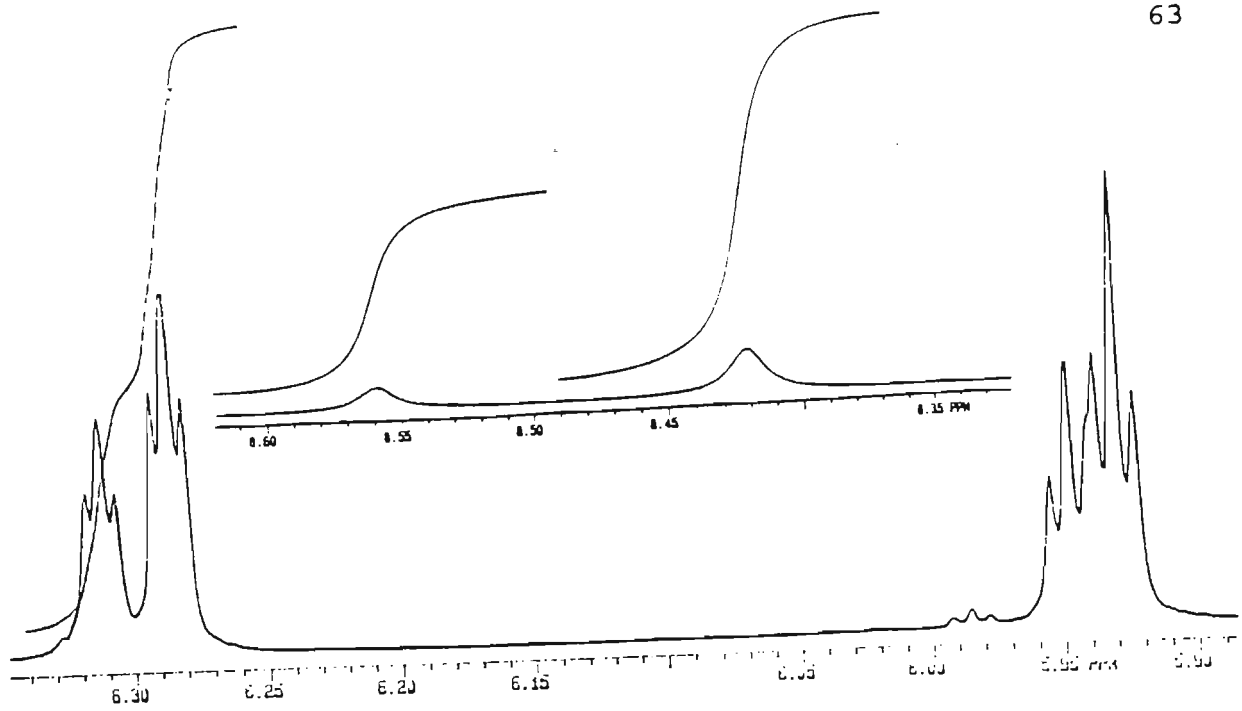


Figure 6.

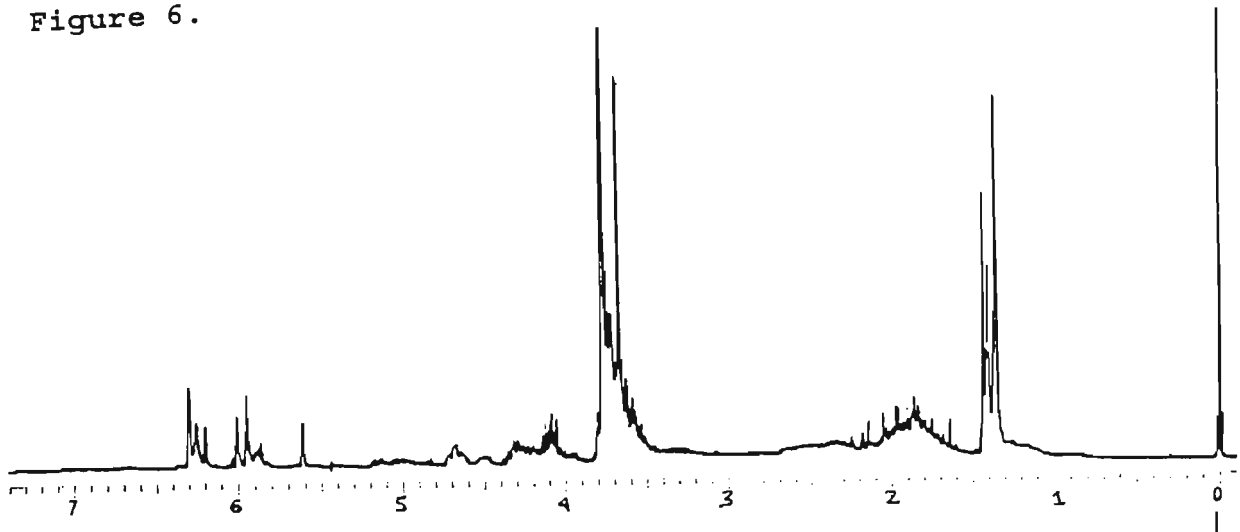


Figure 7.

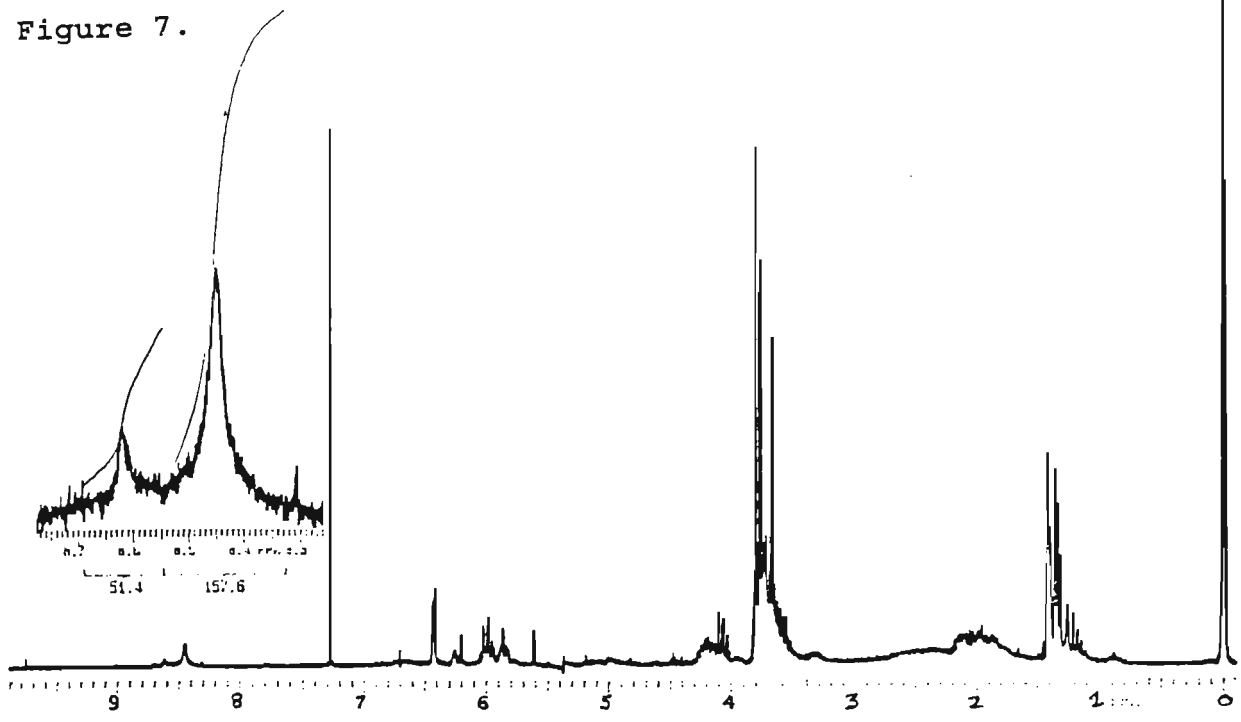
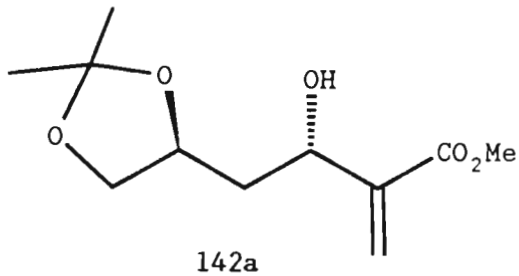


Figure 8.

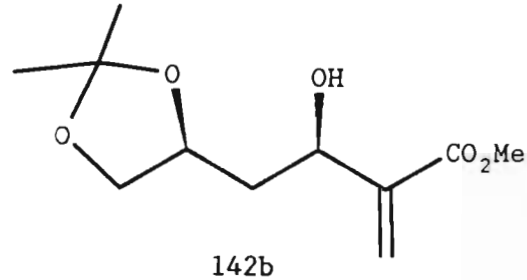
The two pseudo triplets around 6.30 ppm are due to one of these protons, (say H_b), of both isomers. The relative concentration of **144a** : **144b** in the mixture can thus be derived from integration of these peaks. This gives a ratio of [*anti:syn*] 66:34. The major peak is due to the *anti* isomer (See Stereostructural Assignment page 65).

Case II: Use of TAI.

Figure 7 shows the NMR spectrum of the mixture of diastereomers **142a** and **142b**.

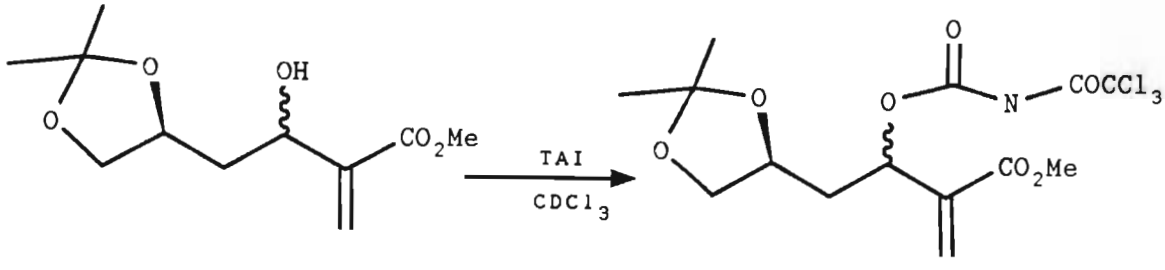


142a



142b

The derivatisation of the mixture with TAI in an NMR tube forms the carbamates **148a/b** (Scheme 43) whose spectrum is shown in Figure 8. This figure shows clearly the ratio of the isomers, as derived from the integration of the carbamate NH peaks.



148a/b (*anti:syn*)

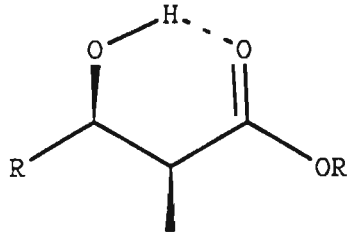
Scheme 43.

Interestingly, the two methods were corroborative *e.g.*, determination of the de of **144a/b** by the TAI protocol (insert in Figure 6) gave virtually the same de ratio. The

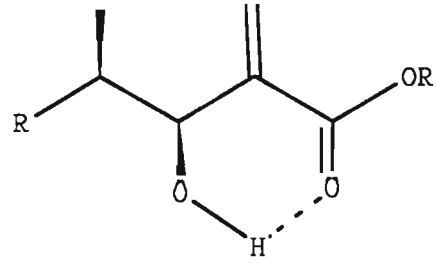
results also compared reasonably with GC-MS data. Application of these techniques on other mixtures gave the results as shown in Table 3.

2.3.1.2 STEREOSTRUCTURAL ASSIGNMENT

The relative configuration (*anti/syn*) of aldol-type products is generally determined by ^{1}HNMR and ^{13}CNMR. This task is generally easy for aldols in which the α- and β-carbons bear a hydrogen atom as in **149**, since the coupling constant J_{AB} has proven to be a reliable diagnostic tool in this regard.[177]



cf



149 150

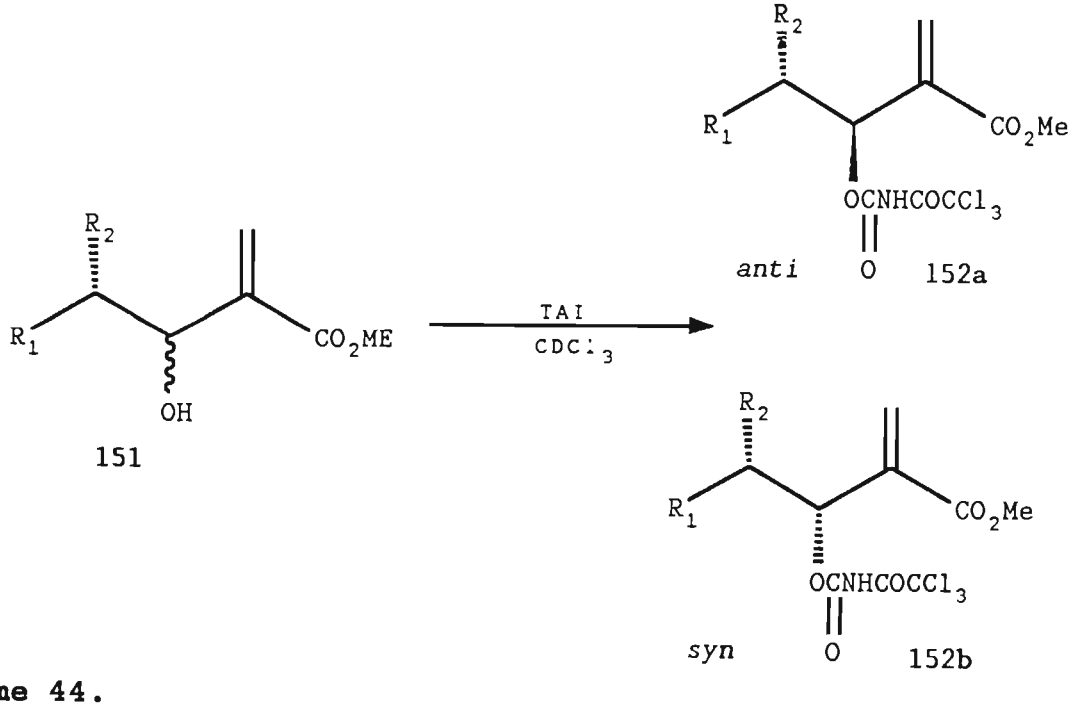
In system such as **149**, J_{AB} is usually in the range 2 - 6 Hz for the *syn* isomer (as a result of gauche relationship) and J_{AB} = 7 - 10Hz for the *anti* isomer. Intramolecular hydrogen bonding was shown to have a profound effect on these coupling constants.[29]

Clearly, the two systems **149** and **150** are structurally different and therefore this method of assignment cannot be used as a reliable precedent in this study.

Apart from the difference in structure - which has been reported to give non uniform J_{AB} values[29] - the relevant resonance signals were in most cases not clearly resolved or were masked by other signals.
Poor resolution of the protons in question in the ^{1}HNMR

spectra is not uncommon. To circumvent this problem, Heathcock[178] reported a versatile technique that employs ^{13}CNMR spectroscopy as a diagnostic tool for stereostructural assignment. However, this method could not be applied without some uncertainty in the present study due to fundamental structural differences between compounds **149** and the system **150**.

At this stage the only stereostructural diagnostic tool that was available for the compounds **138** - **147** was the use of TAI. Roos and co-workers[179] had reported that the TAI protocol for de determination could be extended to include assignment of relative configuration. They assigned the relative configurations on empirical basis as *anti/syn* by observing δ_{NH} differences in the NMR spectrum of compounds **152** which were derived from **151** by simply adding TAI (Scheme 44).



Scheme 44.

The operative relationship was $\delta_{NH}(syn) > \delta_{NH}(anti)$ in all cases studied.

This technique appeared fairly simple and consequently was applied for stereostructural assignments (Figure 6 and 8 inserts). The results are shown in Table 3.

Relative configurations have also been solved in the past by conversion of the aldol products or related systems to cyclic compounds.[80,180] The relative configuration is then determined by comparison with authentic samples or alternatively derived by using the notion of vicinal coupling constants as well as ^{13}CNMR chemical shifts.

In this investigation, coupling products were converted to tetrahydrofuran derivatives (covered in detail in Section 2.4) and this proved to be a useful diagnostic tool for stereostructural assignments.

Consider compounds **139a/b** (page 60). When this compound is subjected to iodocyclisation conditions, only one isomer undergoes cyclisation. Figure 9 shows the ^{1}HNMR spectrum of the mixture of products **139a/b** before cyclisation and Figure 10 is the spectrum of the unreactive substrate - isolated from the reaction mixture when the cyclisation had attained >90% completion. Clearly, it is discernible from the two figures that the minor isomer has cyclised.

In the cyclic product, whose stereochemistry was deduced by NOE, coupling constants and unambiguously by X-ray analysis, the relative configuration of the hydroxyl group to the methyl group is *cis*. Since there is no inversion of configuration at any stage during the cyclisation, this product can only arise from **139a** which has the *anti* relative configuration.

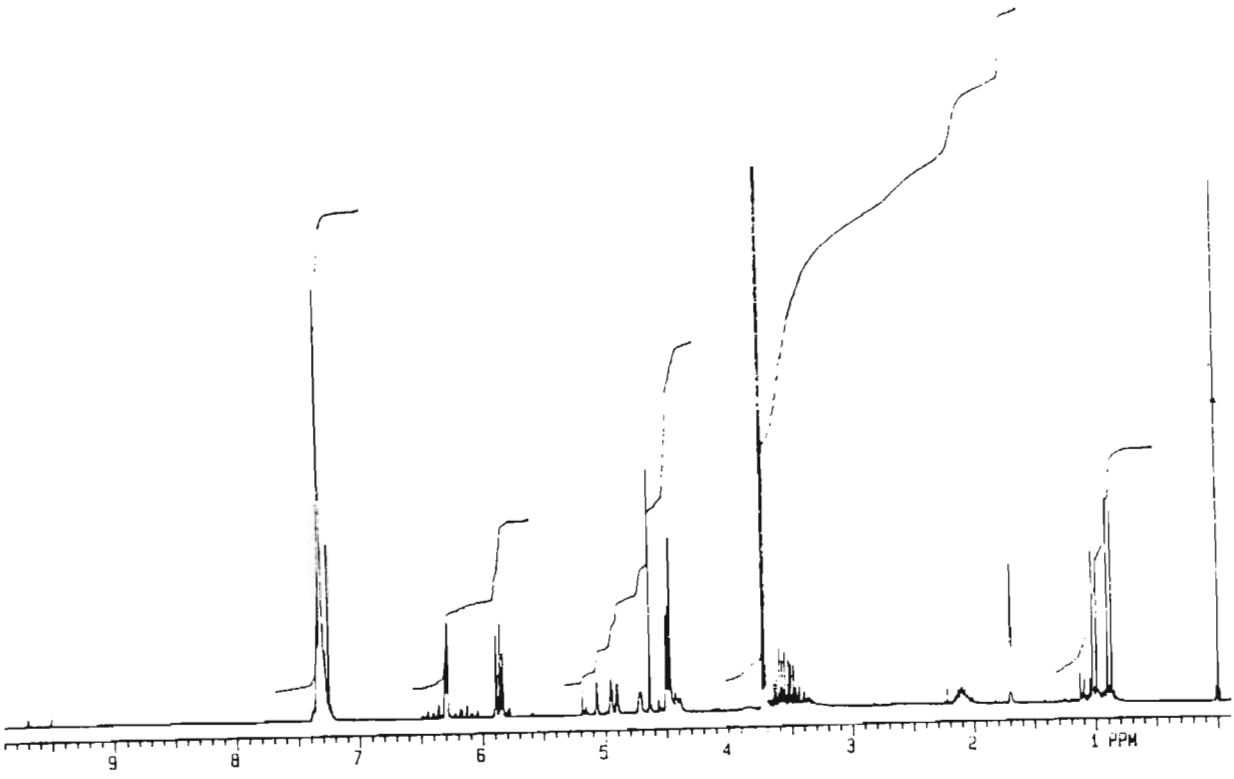


Figure 9.

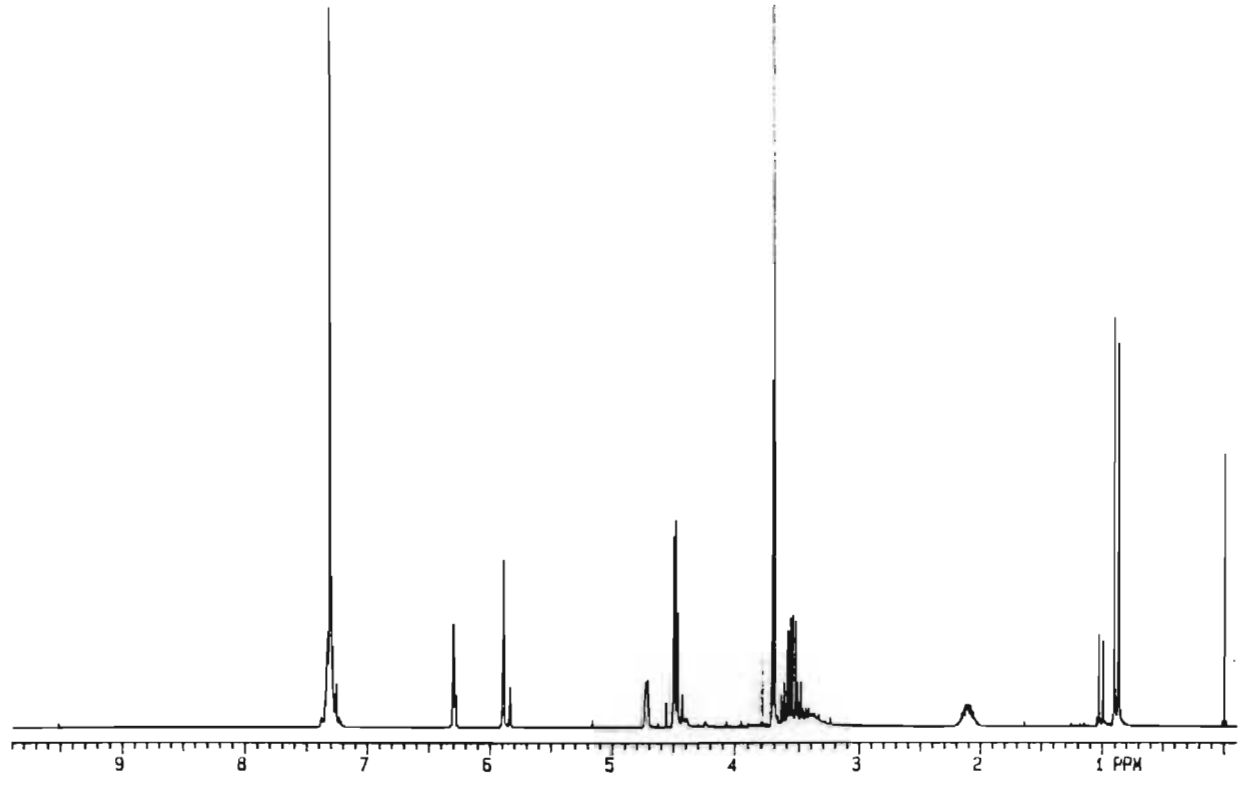


Figure 10.

These results obtained from the cyclic products fully corroborated the earlier assignments based on the TAI protocol. Similar deductions were made for other compounds and some assignments were deduced by analogy

2.3.1.3. THE REACTIVITY OF ALDEHYDES

The Baylis-Hillman reaction of aldehydes with methyl acrylate is generally slow. Data from Table 3 show the difference in reactivity of chiral aldehydes. α-Unsubstituted aldehydes **110** and **111** reacted relatively faster than the α-methyl aldehydes **112** - **113** and the α-O-benzyl aldehydes **127**, **131** and **136** reacted even more sluggishly.

This observation is however, not unexpected and can readily be rationalised by assuming that both steric and inductive effects operate.

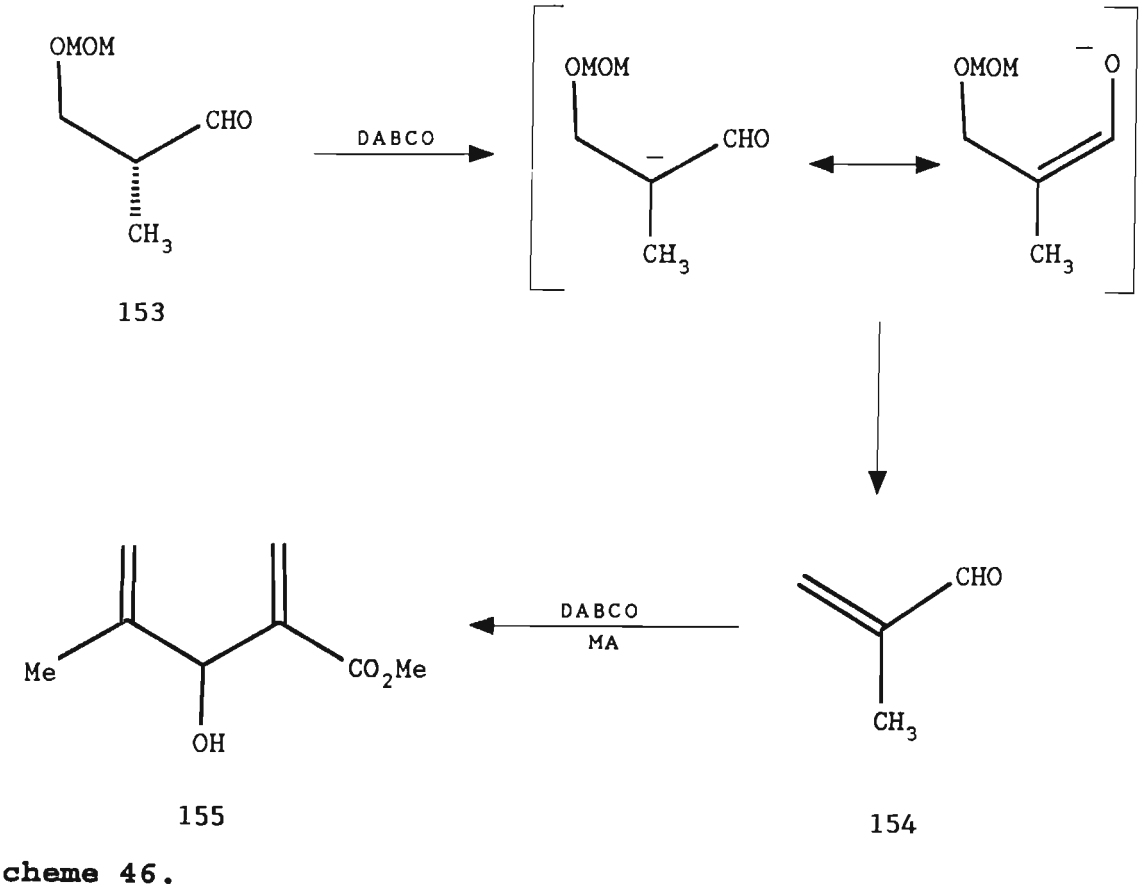
For the α-unsubstituted aldehydes **110** and **111** the aldehyde function is relatively less hindered and inductive effect is minimal.

In the case of the α-methyl substituted aldehydes **112/113** the methyl group brings about steric hindrance thereby inhibiting nucleophilic attack by the approaching nucleophile. This results in a lowered rate of the reaction. Furthermore, since the methyl group is electron donating, inductive effects cannot be ignored.

For the α-O-benzyl series **127**, **131** and **137**, it is assumed that the strong electron donor capability of this group in addition to some steric effect has a profound effect on the reactivity of these aldehydes.

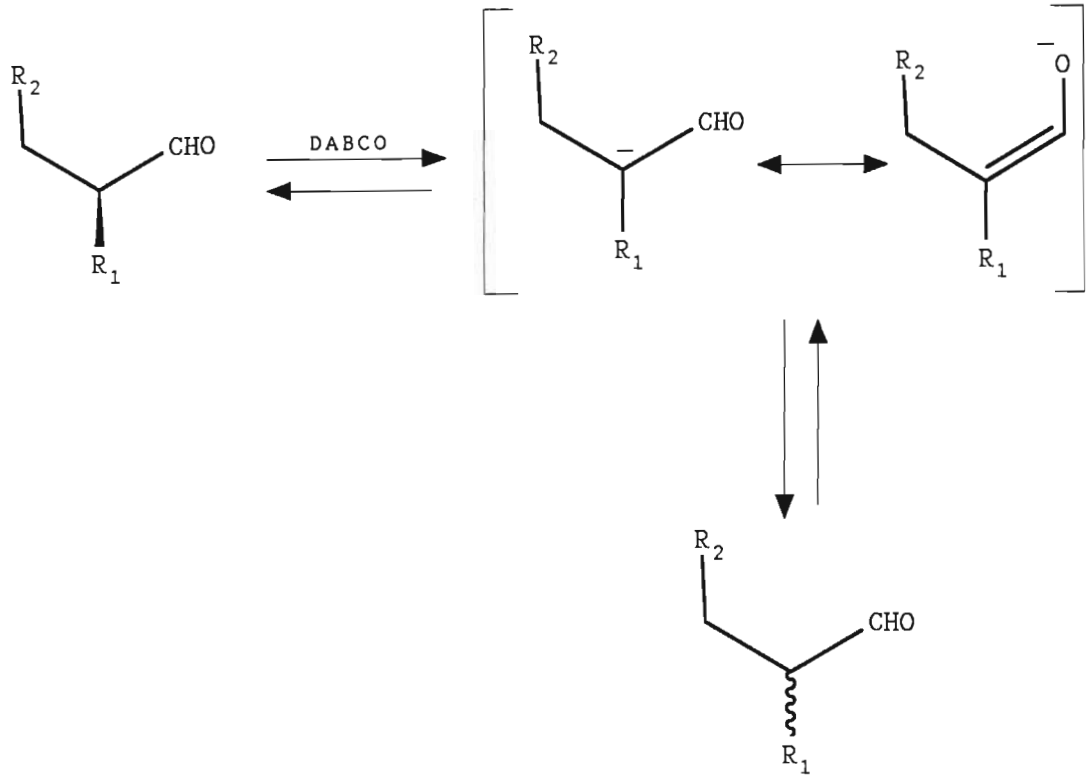
The yields of the reactions of **110** - **113**, **127** **131** and **137** were in the synthetically useful range.

Anomalies were observed in the reaction of the acetonide aldehydes **117**, **131** and **133**. These aldehydes reacted sluggishly, giving low yields and generally resulted in a mixture of products. Cleavage of the isopropylidene group cannot be ruled out especially in view of earlier finding[152] that protecting groups with good leaving group ability are eliminated *via* proton abstration by DABCO. For example, when the aldehyde **153** is reacted with DABCO, evidence shows production of methacrolein **154** *in situ* which then reacts with methyl acrylate to form the diene **155** (Scheme 46). The proposed mechanism for the formation of **154** involves abstraction of the α-proton of the aldehyde followed by elimination of the hydroxyl protecting group.



Scheme 46.

In view of this, it is also not surprising that all the α-substituted aldehydes gave virtually racemic aldol-type products. DABCO presumably abstracts the α-proton of the aldehyde - yellow precipitate during mixing - in an equilibrium reaction that results in racemisation (Scheme 47).



Scheme 47.

Therefore it was essential to use a minimum amount of DABCO (catalytic) so as to minimise racemisation of the aldehyde. Unfortunately, this was met with little success in the case of α-substituted aldehydes.

The Baylis-Hillman reaction of aldehyde **123** gave a host of unidentifiable products which were of no relevance to the present study.

2.3.1.4. RATIONALISATION OF THE STEREOCHEMICAL OUTCOME OF THE BAYLIS-HILLMAN REACTION

Since the Baylis-Hillman reaction involves nucleophilic addition to aldehydes in the absence of a chelating metal reagent, stereofacial selectivity is governed solely by steric and electronic factors *i.e.*, non-chelation control. Under these circumstances, a logical prediction would be overall *anti* selectivity as predicted by Cram's model. However, examination of the results in Table 3 shows:

a) *Syn* selectivity for α-unsubstituted aldehydes **110** and **111** (entries 1 and 2). As might be expected, the intrinsic 1,3-asymmetric induction is virtually stereorandom. This is in agreement with addition of organometallic reagents,[48] enolates[41] and crotylmetal reagents,[41,88] to β-chiral α-unsubstituted aldehydes (see INTRODUCTION).

b) *Syn* selectivity for α-methyl substituted aldehydes **112** and **113** (entries 3 and 4). The diastereofacial selectivity is relatively enhanced by the α-methyl substituent compared to the α-unsubstituted aldehydes **110** and **111** (entries 1 and 2). This suggests that steric effects do indeed contribute in this addition reaction. A similar trend was observed by Reetz 's group in both chelation and non-chelation controlled additions.[41]

c) That the diastereoselectivity in the case of α-O-benzyl aldehydes **127**, **131** and **136** (entries 7, 8 and 10) is principally of the same degree as in (b) above but reversed, *i.e.*, *anti* selectivity is preferred in the case of α-O-benzyl aldehydes (entries 7, 8 and 10). This appears to imply that not only steric factors operate in

both cases but electronic factors play a crucial role.

d) That the isopropylidene aldehydes **117** and **133** give higher levels of diastereofacial selectivity (entries 5 and 9) with the former giving exceptionally high results. In comparison, the similar system **131** (entry 8) gives standard results suggesting that the α-substituent has a major directing effect. The preferred diastereoselectivity in the addition reaction to the acetonide **133** (entry 9) is *anti* and is in line with the other α-alkoxy substituted aldehydes (entries 7, 8 and 10). The increase in stereoselectivity (entry 9) could be due to the steric bulk provided by the acetonide group as well as the rigidity of this group. Also electronic effects cannot be ruled out.

The observed *anti* selectivity in the case of aldehyde **117** (entry 5) is opposite that of α-unsubstituted aldehydes and is exceptionally high. This was initially surprising and indeed confusing. However, consideration of the chain length and rationalisation of the stereochemical outcome by employing stereochemical models (*vide infra*) shed some light on this problem.

To rationalise the stereochemical outcome of the Baylis-Hillman reaction of methyl acrylate with chiral aldehydes, Felkin's model later modified by Anh and Einstein operates (Figure 3 page 8).

To recapitulate, the model by Felkin and his co-workers[36] was initially designed for symmetrical ketones (such as cyclohexanone). These workers proposed that, unlike in Cram or Karabatsos models, the dominant interaction is that between incoming nucleophile and the largest group attached to the stereogenic centre; that is that the nucleophile

attacks antiperiplanar to the large group (Figure 3 page 8).

Anh and Einstein evaluated the Cram, Karabatsos and Felkin models by *ab initio* calculation of hypothetical transition state structures.[181] The Felkin conformers were found to be significantly lower in energy than either the Cram or Karabatsos conformers. In addition the authors postulated that if the two carbonyl ligands are the same (as in symmetrical ketones or formaldehyde) then the attacking nucleophile will approach along the Burgi-Dunitz trajectory in the plane that bisects the compound. This is essentially the normal plane as was earlier pointed out by Felkin (Figure 3 page 8). However, if the two carbonyl ligands are not the same, the nucleophile will follow a trajectory that keeps it further away from the larger of the two carbonyl ligands as shown below.

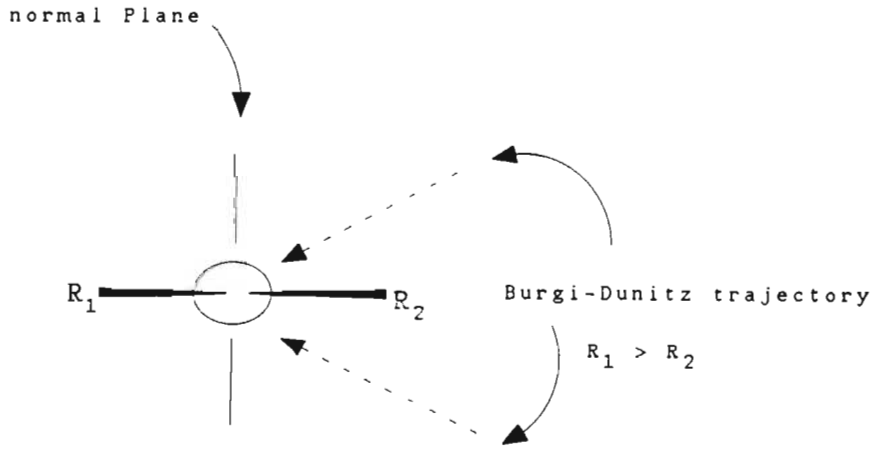
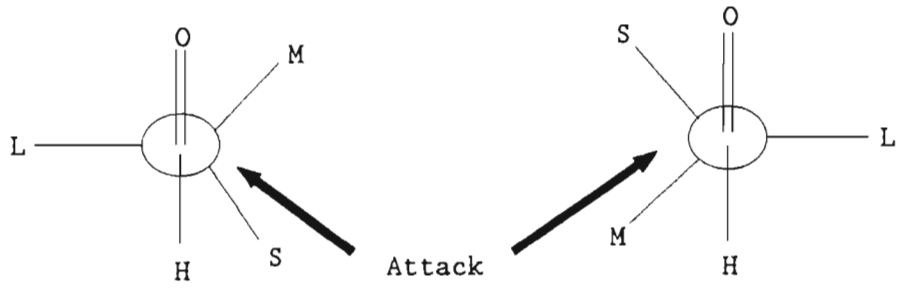


Figure 11.

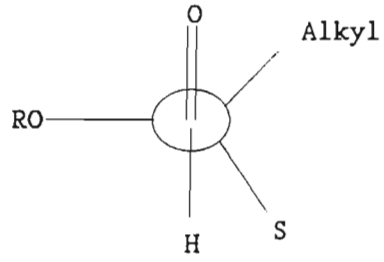
The amount of distortion away from the normal plane will be related to the difference in steric bulk on the two sides of the normal plane.

Incorporation of the Burgi-Dunitz trajectory to the energetically favoured Felkin model as shown in **156** and **157** simplifies the problem of rationalisation of stereochemical outcome.



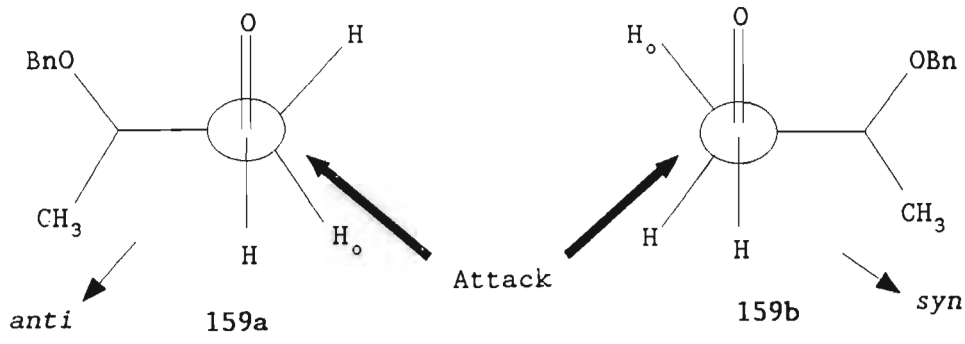
156 157

Here, the assumptions relating to the magnitudes of O⟷M and M⟷H interactions are completely irrelevant. That is, it is implicitly assumed that conformations **156** and **157** are of comparable intrinsic energy and that stereodifferentiation arises from differential interactions of the attacking nucleophile with the small and medium ligands. Furthermore it was proposed on the basis of frontier molecular orbital arguments that the ligand with the lowest lying orbital, rather than the sterically most demanding group is perpendicular to the carbonyl plane and *anti* to the attacking nucleophile. What this means is that in the case of alkyl and O-alkyl groups, the latter will assume perpendicular arrangement to the carbonyl group in all cases as in **158**.



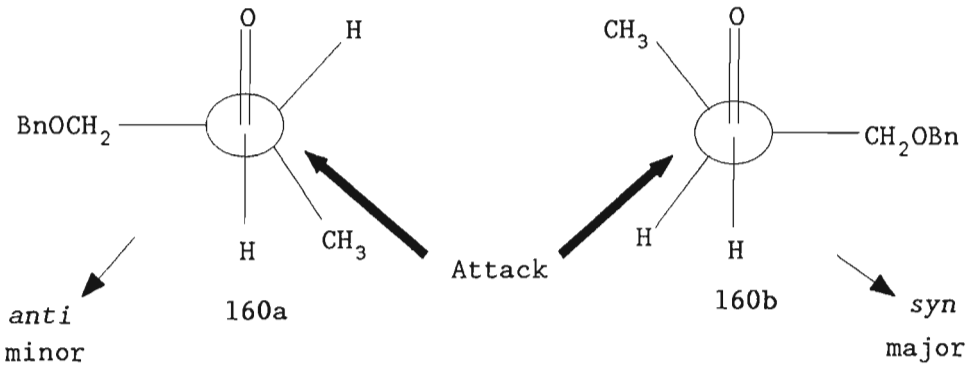
158

To explain the stereochemical outcome in addition reaction to aldehydes **110** and **111**, consider the Newman projections **159**. The view in **159** is along C_1-C_2 and all ligands at quarternary centres are assumed to be staggered.

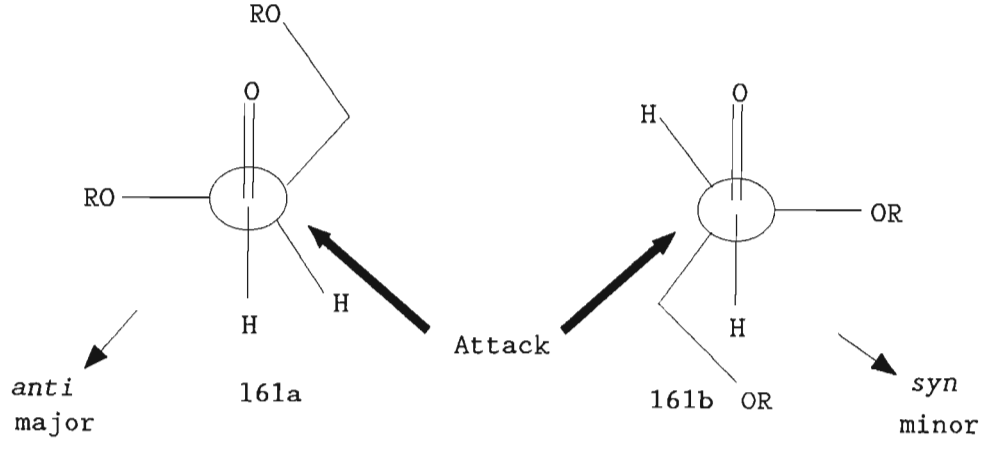


Since there are two groups of equal size (both small), addition to the aldehydes **110** and **111** would be expected to be stereorandom. Indeed, it is (Table 3). The slight discrepancy (51:49) is assumed to be due to electronic repulsion between the incoming carbanion and the oxygen of the protecting group (OBn, H_o is *syn* to this group) thereby favouring attack as illustrated in **159b**. This results in a slight preference for the *syn* isomer **138b** and **139b** (Table 3, entries 1 and 2).

In view of this, it would not be surprising to see an increase in intrinsic diastereofacial selectivity when one of the hydrogen atoms is replaced by an alkyl group (medium group). In fact, this is the case with aldehydes **112** and **113** (Table 3, entries 2 and 3). Of the two Felkin-Anh conformers **160a** and **160b** preferential attack of the latter predominates at the expense of the former. In **160a**, interaction between the methyl group and the incoming nucleophile pushes the attacking species further away until an arrangement as in **160b** is achieved. This results in preferential formation of the *syn* isomer. Electronic repulsions as mentioned above might also play a role.

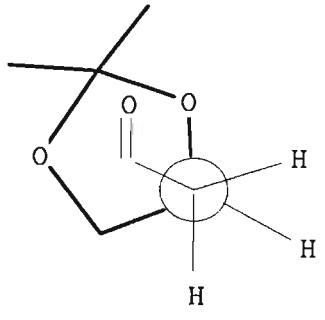


Application of the Felkin-Anh theory also explains the stereochemical outcome of the α-alkoxy aldehydes. Consider the Newman projections **161** of aldehydes **127**, **131**, **133** and **136** (Table 3, entries 7 - 10). The operating Felkin/Anh conformers for these aldehydes are shown below. The alkoxy group OBn assumes perpendicular allignment to the carbonyl double bond as required by Anh-Einstein hypothesis. Attack

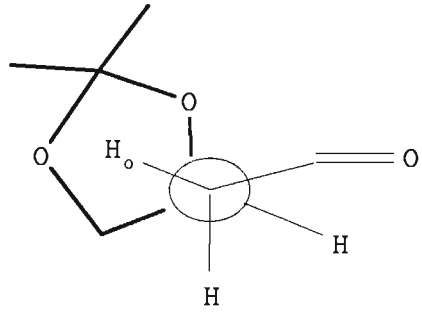


of conformer **161a** is favoured because the incoming species experiences less steric interaction as well as electronic repulsion. Consequently the *anti* isomer predominates (Table 3, entries 7 - 10). These results are in accordance with recent observations by Roos and Manickum[117] and Drewes *et al.*.[115,118] The preferred *syn* selectivity by α-unsubstituted aldehydes **110**, **111**, **112** and **113** (Table 3, entries 1 - 4) and the predominance of *anti* products with aldehydes **127**, **131**, **133**, **136** (entries 7 - 10) can also be explained by invoking Karabatsos model.

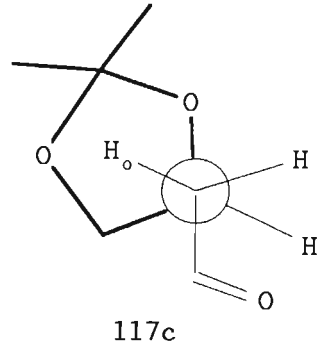
A surprisingly high degree of diastereoface selection and *anti* selectivity was observed in the addition reaction of aldehyde **117** (entry 5). The reasons for this bewildering anomaly are not fully understood but the stereochemical outcome can be partially reconciled by considering Newman projections **117a**, **117b** and **117c** in which the molecule is viewed along C_2-C_3 axis with all ligands in staggered fashion. The first of these representations **117a** can be ruled out on the basis of electronic repulsions between the carbonyl group and the oxygen atoms of the isopropylidene group.



117a



117b



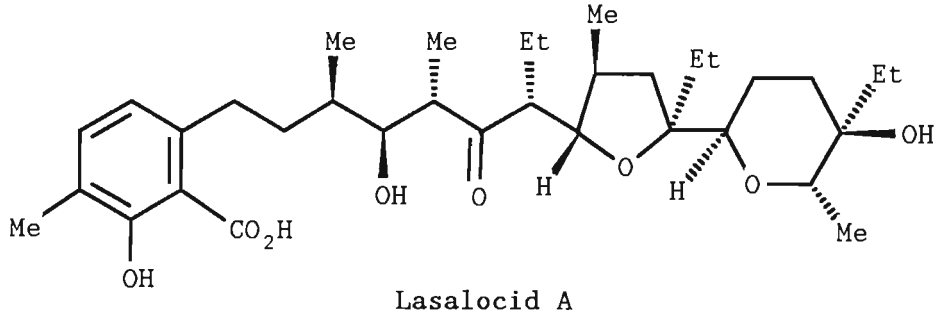
117c

The Felkin-Anh conformers of **117b** and **117c** (not shown) suggest that attack of the carbonyl along H_o (which leads to *syn* products) is disfavoured on the basis of electronic repulsion between the in-coming nucleophile and the oxygen atoms of the isopropylidene group. The steric bulk of the protecting group enforces the electronic effect by effectively shielding one face of the aldehyde.

2.4. SUBSTITUTED TETRAHYDROFURANS

The tetrahydrofuran unit features in a large number of naturally occurring polyfunctionalised molecules such as polyether[182] and macrolide[183] antibiotics.

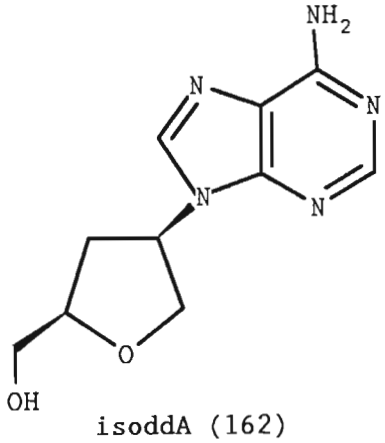
Polyether antibiotics are a large group of naturally occurring monocarboxylic acid ionophores. Their ability to transport metal ions across lipid bilayers,[182] act as antimicrobial agents,[184] cause growth promotion in ruminants[184] or produce cardiovascular responses[185] has made them challenging synthetic targets. An examples of a polyether antibiotic, Lasalocid A is given below.



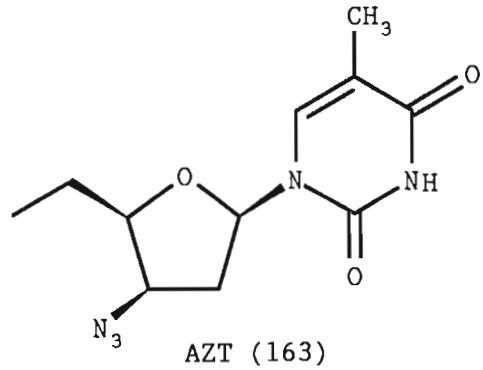
Lasalocid A

The tetrahydrofuran unit, other than carbohydrate derivatives, also features in a new class of nucleoside analogues that show potent anti-HIV activity.[186] For example isoddA **(162)** possesses good anti-HIV activity that can make it a reliable substitute for the rather toxic AZT

(163). The latter is one of the major drugs approved for the treatment of AIDS.



isoddA (162)

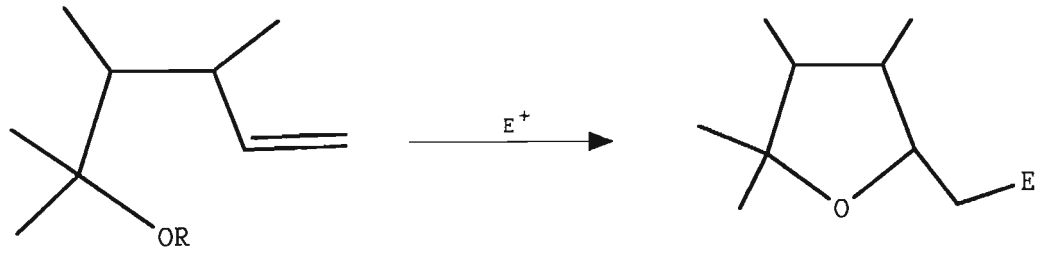


AZT (163)

Polyether antibiotics contain a plethora of asymmetric centres and functional groups dominated by substituted tetrahydrofurons. In this regard, regio- and stereochemical control in simultaneous creation of contiguous stereogenic centres have become particularly important in the construction of these ring systems. Several approaches towards achievement of this goal have received growing interest evidenced by the number of reports and excellent reviews written on this subject.[188-190]

2.4.1. ELECTROPHILE-INDUCED CYCLISATIONS

The functionalisation of the double bond, promoted by an electrophile is a common reaction in the construction of five-membered O-heterocycles. In principle, construction of tetrahydrofuran ring systems by electrophile-induced cyclisation involves addition of an electrophile to an alkene containing a suitably situated internal necleophile, followed by intramolecular ring closure in which a carbon of the double bond becomes attached to a group specifically chosen to allow further modification. This is summarised in Equation 1.



Equation 1.

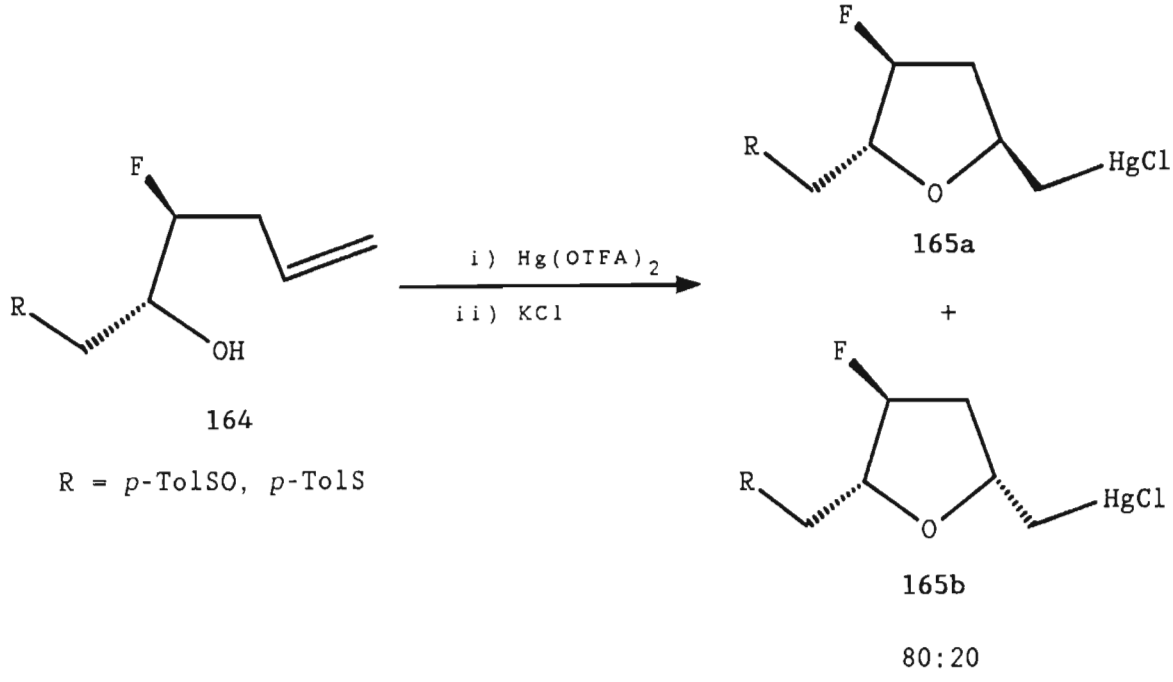
A large number of intramolecular ring closure reactions conform to this general principle termed cyclofunctionalisation.[191]

Although rings of all sizes are present in naturally occurring compounds, of special interest are the more common tetrahydrofurans. The chemoselectivity and the regiospecificity of ring-forming processes is governed by the size of the carbon skeleton of the substrate and electronic properties of the internal nucleophile. Baldwin[192] has formulated some rules on an empirical bases to predict the relative facility of ring-forming reactions. The rules are based on the trajectory of the reagent that attacks the electrophile-activated carbon centre leading to the ring closure reaction.

A number of electrophilic reagents have been employed in order to effect ring closure and the nature of the electrophile plays an important role in regio- and stereochemical control.

Mercuric acetates such as $Hg(OAc)_2$ and $Hg(OTFA)_2$ are generally employed to promote mercurycyclisation.[193-195] These reagents effect the cyclisation of γ,δ-unsaturated alcohols to give *trans*-2,5-disubstituted tetrahydrofurans as major products. For example, cyclisation of β-fluoro-γ-hydroxy alkenes **164** , carried out by using $Hg(OTFA)_2$ has been reported by Bravo *et al.*[195] to give

preferential formation of *trans*-2,5-disubstituted tetrahydrofurans **165** (Scheme 48).



164

R = *p*-TolSO, *p*-TolS

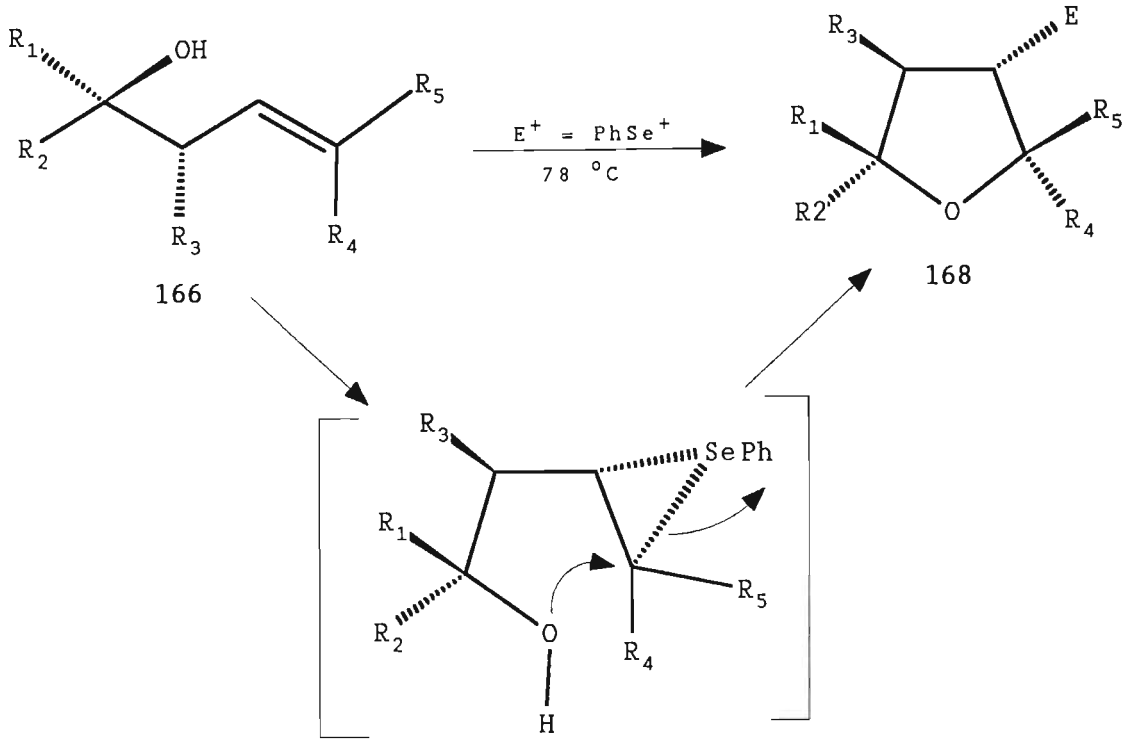
165a

165b

80:20

Scheme 48.

Cyclisation of suitably substituted alkenes has also been effected by selenium-based electrophiles such as phenylselenium chloride, N-phenylselenophthalimide (NPSP) and phenylselenium triflate.[196-198] Phenylselenoetherification (Scheme 49) is endocyclic and occurs at low temperature (-78°C) to give tetrahydrofurans in which the stereochemisty of the phenylseleno group is always *trans* to that of oxygen.[196] The mechanism that rationalises this stereochemical outcome is outlined in Scheme 49.

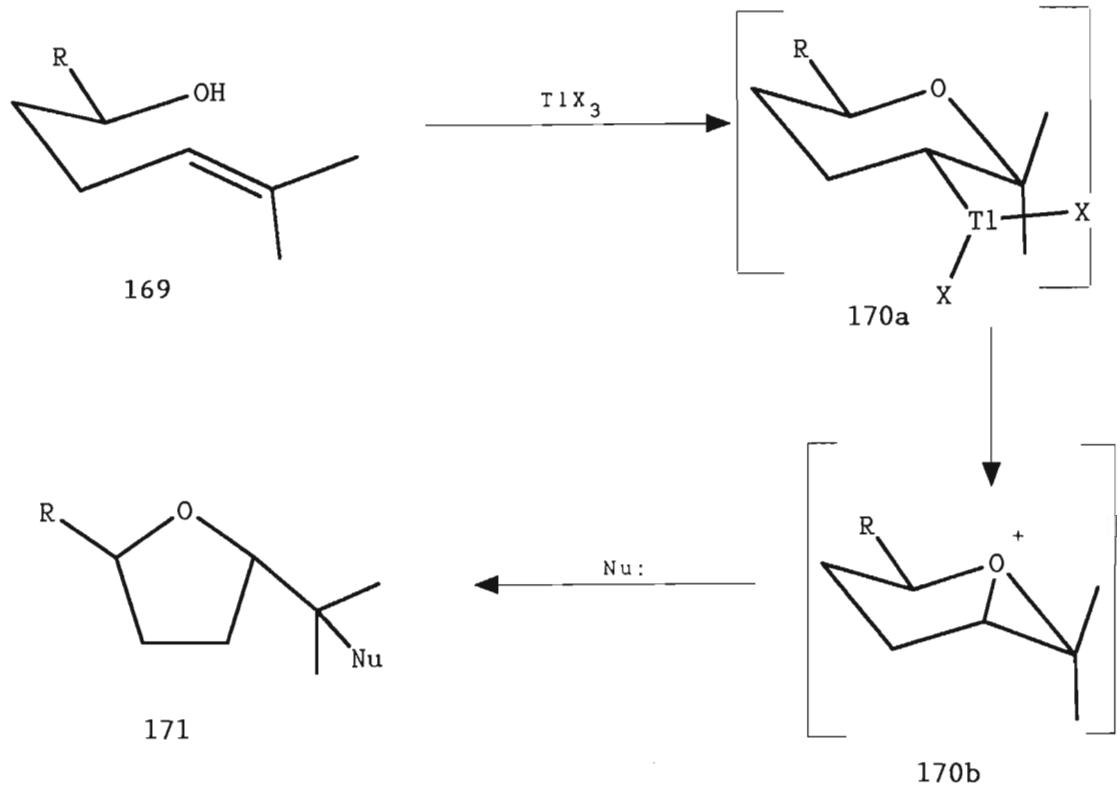


Scheme 49.

It involves activation of the double bond of the homoallylic alcohol substrate **166** by phenylselenium cation to form intermediate **167**. Subsequent intramolecular nucleophilic attack produces the tetrahydrofuran **168**. Recent findings by Mihelich and Hite[199] show that the overall stereochemical outcome of the reactions is influenced by the relative stereochemistry (*anti/syn*) of the allylic and homoallylic substituents and also by the configuration of the double bond.

Substitution pattern across the double bond also plays a role in the synthesis of tetrahydrofurans *via* ring contraction of tetrahydropyrans. The most commonly used electrophiles for this process are 2,4,4,6-tetra-bromo-2,5-cyclohexadienone (TBCO)[200] and thallium salts.[201,202] Michael *et al.*[201,203] reported that 2,5-*trans*-disubstituted tetrahydrofurans **171** are conveniently prepared by Tl^{+}-induced cyclisation *via* ring

contraction of organothallium intermidiates **170**. They found that regio- and stereocontrol was high in the case of terminally disubstituted olefinic substrates **169**. (Scheme 50).



Scheme 50.

The authors proposed a mechanistic pathway that involves formation (*in situ*) of the organothallium cyclic ether **170a**. The organothallium intermediate **170a** then undergoes spontantaneous decomposition *via* bridged oxonium ion **170b** assisted by nucleophilic attack, resulting in the formation of β-alkoxy tetrahydrofurans **171** (Nu = OR Scheme 50).

Halogens constitute the most widely used class of electrophiles by far. Since this method was used for cyclisations, it will be dealt with in greater detail.

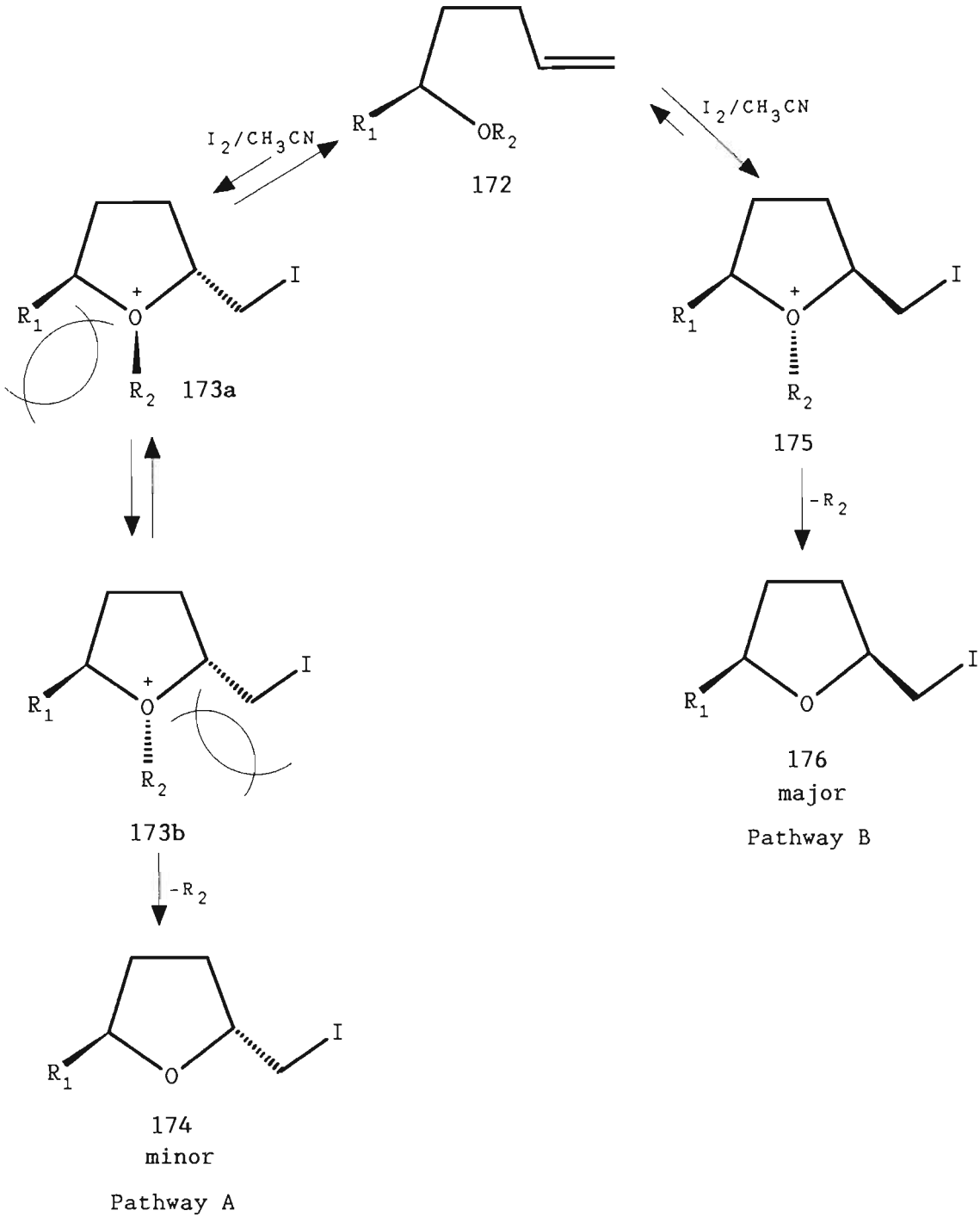
2.4.2. HALOCYCLISATION REACTIONS

Halogen-induced cyclisation of γ,δ-unsaturated alcohols and corresponding ethers provides an interesting route to the synthesis of substituted tetrahydrofuran derivatives.[188-190] Application of this elegant method, first developed by Bartlett,[204] can be manipulated to give either *cis* or *trans* substituted tetrahydrofurans. In fact, cyclisation of γ,δ-unsaturated alcohols under kinetic conditions preferentially gives *cis*-2,5-disubstituted tetrahydrofurans while the corresponding *trans*-2,5-disubstituted products predominate under thermodynamic conditions.

2.4.2.1. THERMODYNAMICALLY CONTROLLED CYCLISATION

Thermodynamically controlled cyclisation is carried out by allowing the olefinic substrate, a γ,δ-unsaturated benzyl or alkyl ether such as **172**, to stir in a solvent (CH_3CN) in the presence of an electrophile (I_2). Due to the nature of the substrate - which is usually an alkyl ether, the cyclisation attains equilibrium and is forced to the right because of the stability of products **174** and **176** (Scheme 51).

The stereochemical outcome of thermodynamically controlled cyclisation is rationalised on the basis of the mechanistic pathway outlined in Scheme 51.

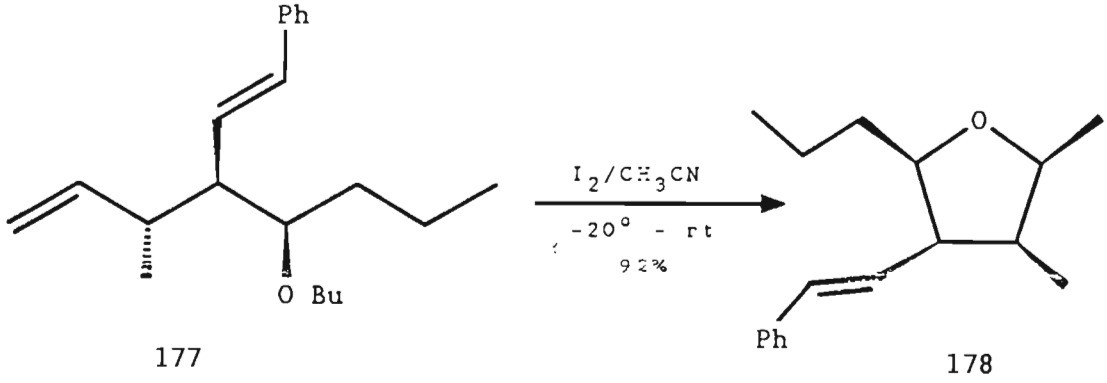


Scheme 51.

According to pathway A, intermediates **173a** and **173b** are in equilibrium with the starting substrate **172**. In each of the two intermediates there exists strain due to steric hindrance of the ethereal group R. Intermediate **173a** suffers from 1,5-strain while intermediate **173b** suffers

from 1,2-strain. Consequently little conversion of the starting material to the *trans* substituted product is observed. On the other hand, both steric strains are easily avoided in pathway B (Scheme 51). This results in preferential formation of the *cis* isomer **176**.

In accordance with this mechanism, it may be assumed that the bulkier the ether R_2 group the better the diastereoselection. Indeed, as has been reported by Marek *et al.*,[205] use of the bulky butyl group in the cyclisation of **177** dramatically increased the stereoselectivity to give **178** as the sole product (Scheme 52).



177 178

Scheme 52.

Electrofugal capability of the hydroxyl protecting group (R_2 in **172**) also influences the stereoselectivity of the cyclisation. For example, 2,6-dichlorobenzyl ether provides higher yields of *cis* products compared to benzyl ether since it has the most steric and electronic properties.

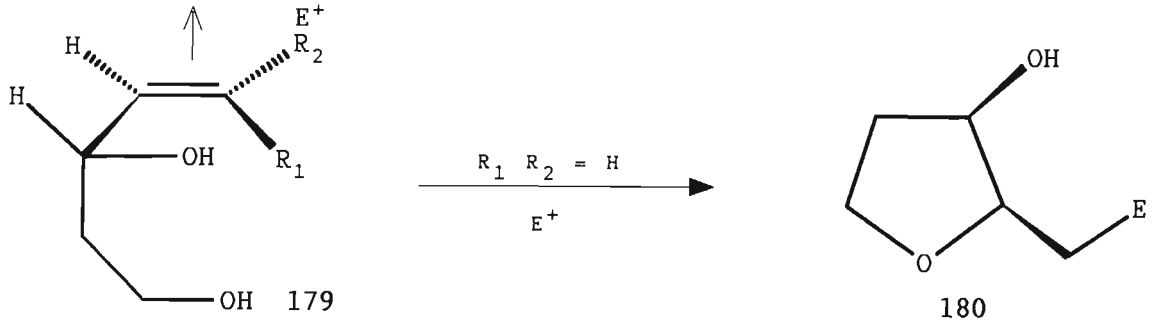
2.4.2.2. KINETICALLY CONTROLLED CYCLISATION

The cyclisation of free hydroxy γ,δ-unsaturated alcohols promoted by an electrophile usually in the presence of base

in aqueous medium is considered to be kinetic controlled conditions.[207] Several electrophiles including $I_2/NaHCO_3/THF$, $I_2/CHCl_3$, $NIS/CHCI_3$, $I_2/THF/py$, are all considered kinetic conditions and have been used with great success.[188-190]

Regio- and stereochemical outcome of halocyclisation under kinetic conditions appear to be directed by a number of factors notably, allylic hydroxyl group of the substrate,[208-210] relative stereochemistry of the nucleophilic carbinol group to allylic substituent,[212,212] and the configuration (*E* or *Z*) of the double bond.

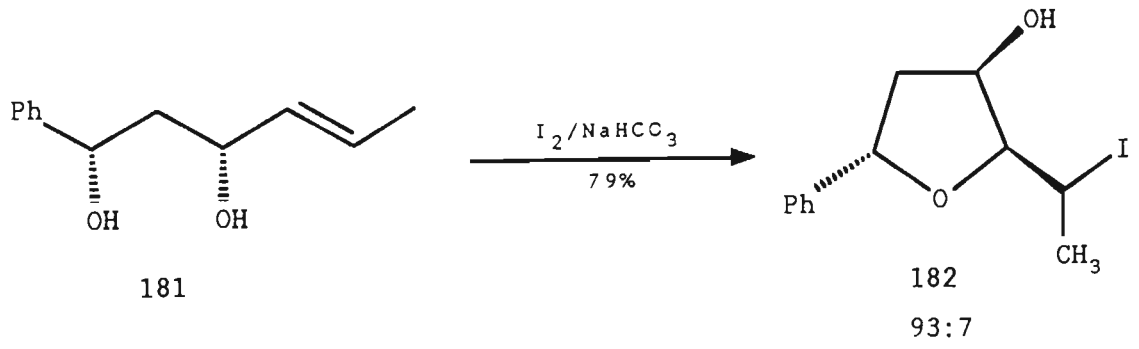
Chamberlin *et al.*[213] have developed a model for the attack under kinetic control of an electrophile to an olefin containing an internal nucleophile, based on the relative affinity of the diastereotopic faces of the double bond towards a proton. The proposed mechanism involves intramolecular attack on a complex. In the presence of an allylic hydroxyl group, preferential attack of an electrophile on the OH-in-plane conformer **179** occurs from the face of the double bond *syn* to the allylic hydrogen (Equation 2).



Equation 2.

When $R_1 = R_2 = H$ the *cis* diastereomer **180** is formed as the major product. This stereochemical outcome is also observed with substrates that have the *trans* configuration across the double bond. For example Iodocyclisation of the diol **181**

affords the 1,2-*cis* tetrahydrofuran **182** (Scheme 53).[211]

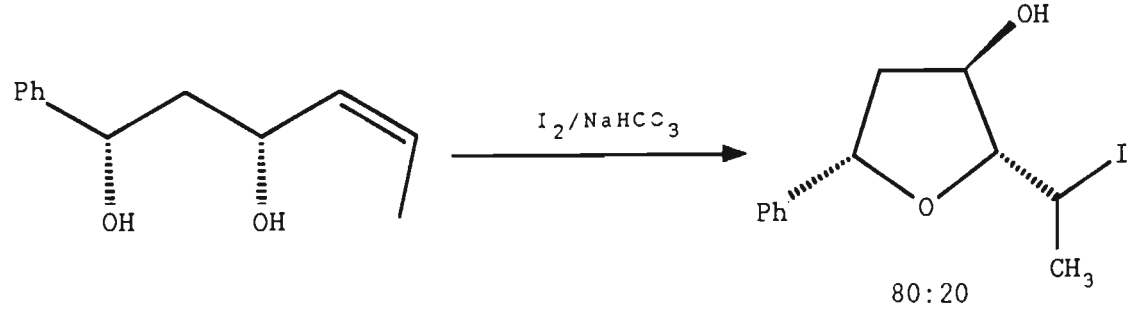


181 182

93:7

Scheme 53.

On the other hand, substrates with *cis* substituents on the double bond (relative to the stereogenic allylic centre), which destabilise the OH-in-plane conformer, react on the opposite face (Scheme 54).



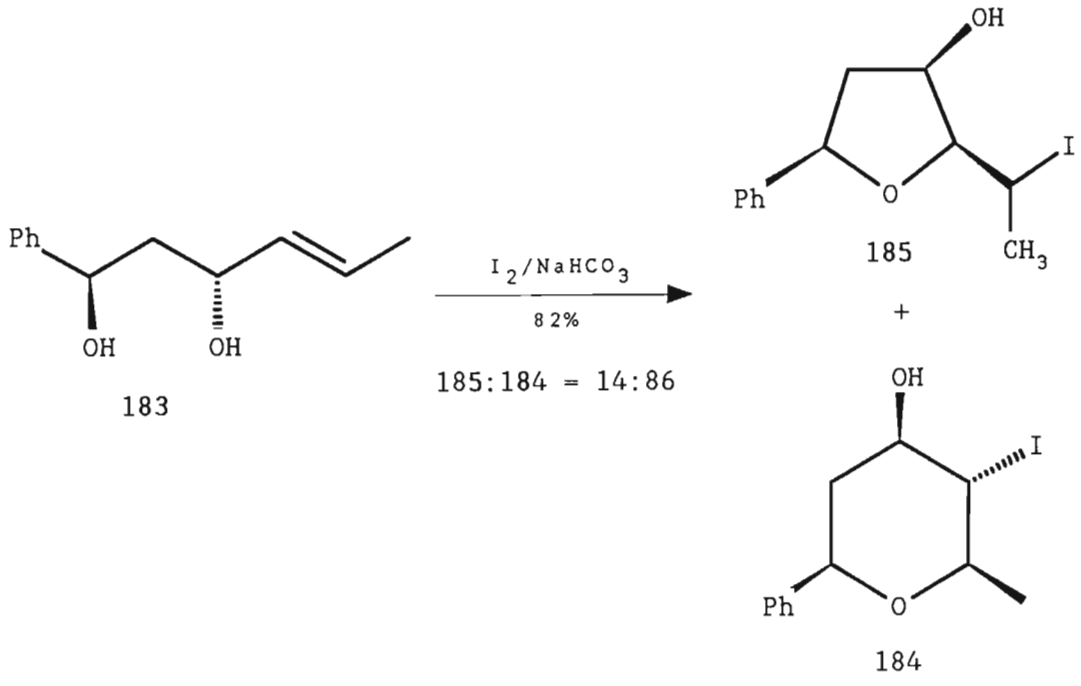
80:20

Scheme 54.

The reversal of stereochemistry (Scheme 53 *vs* 54) has been rationalised on the basis of destabilisation of the OH-in-plane conformer with the H-in-plane conformer energetically more accessible in the latter (Scheme 54).

The regio- and stereochemical outcome of kinetically controlled iodosyclisation reactions is also strongly influenced by the relative configuration (*syn:anti*) of the allylic substituents to the nucleophilic carbinol.[213-215] For example, iodocyclisation of 1,3-*syn* dihydroxy olefin **181** proceeds with exclusive 5-*exo*-*trig*[192] ring closure to form 1,2-cis tetrahydrofuran **182** as the major product (Scheme 53 above). On the other hand, 6-*endo*-*trig*[192] ring closure

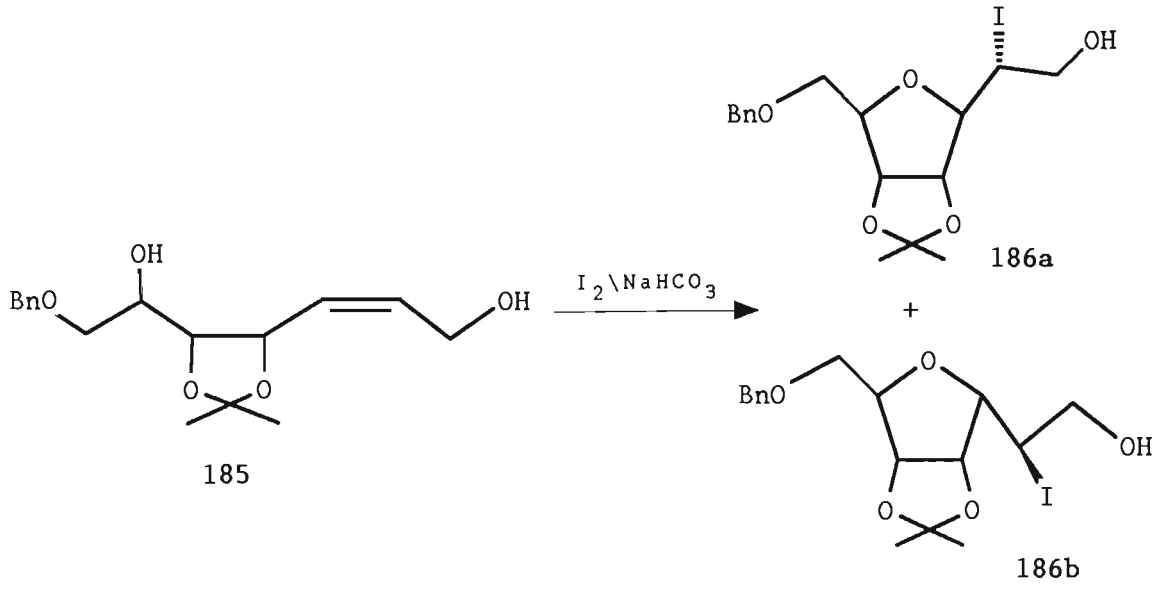
leading to formation of tetrahydropyran **184** is predominantly favoured by the 1,3-*anti* substrate **183** (Scheme 55).



Scheme 55.

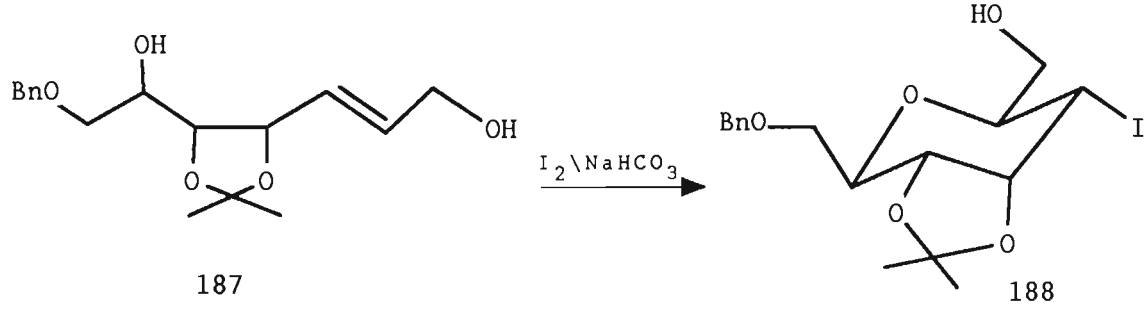
The tetrahydropyran **184** is accompanied by a small percentage of 5-*exo-trig* product **185**.

Geometric arrangement and substitutionary pattern across the double bond have been found to have similar effects on the regio- and stereochemical outcome of the reaction.[209,216,217] For example, iodocyclisation of *Z*-olefinic substrate **185** gives 5-*exo-trig* ring closure with a diastereoselectivity ratio of 60:40 (2,5-*cis* **186a**:2,5 *trans* **186b**) (Scheme 56).[209]



Scheme 57.

On the other hand cyclisation of the corresponding *E*- isomer **187** gives **188** as the sole product. Clearly, **188** is formed *via 6-endo-trig* ring closure (Scheme 57).



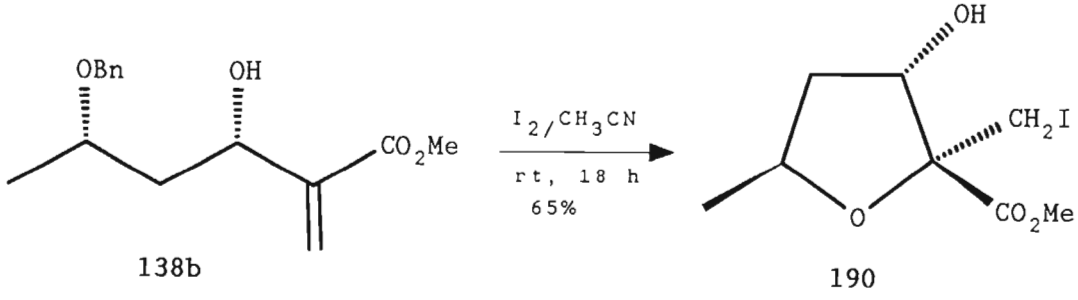
Scheme 57.

The above examples highlight advances in kinetically controlled iodocyclisation reactions. From these examples, it is clear that regio- and stereochemical control in kinetically controlled iodocyclisation has been extensively studies. In contrast, apart from the influence of ethereal groups, little is known of the factors that affect regio- and stereochemical control in thermodycamically controlled iodocyclisation.

2.4.3. THE IODOCYCLISATION OF γ-ALKOXY-α-HYDROXYACRYLATES

A series of γ-alkoxy-α-hydroxy acrylates **138** - **147** were prepared by the Baylis-Hillman reaction. Separation of the mixture of the diastereomers was very difficult by chromatography and in some of the cases the diastereomers were inseparable. Nevertheless small quantities of diastereomers **138a** and **138b** were obtained in pure form by careful collection of the first and the last fraction.

The first iodocyclisation experiment was performed on pure **138a** and **138b** separately. The substrate **138a** or **138b** was allowed to stir with a two fold excess of iodine in dry acetonitrile overnight. The diastereomer **138a** was unreactive even for prolonged periods. On the other hand **138b** reacted cleanly to produce tetrahydrofuran **190** within 18 hours (Scheme 58). Interestingly, no other diastereomer of 190 was detected by GC and NMR.



138b 190

Scheme 58.

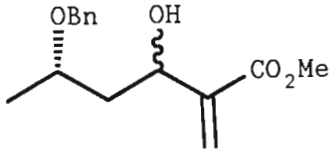
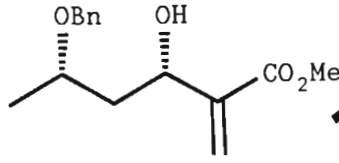
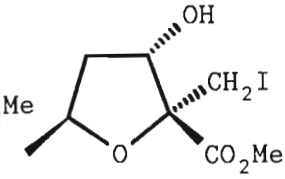
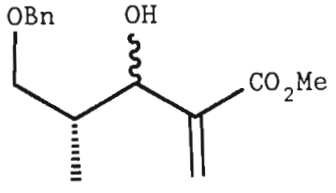
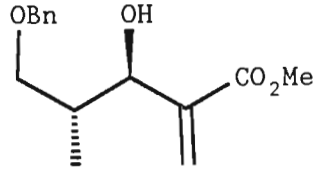
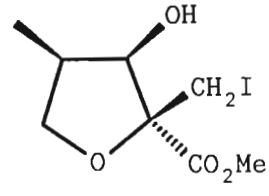
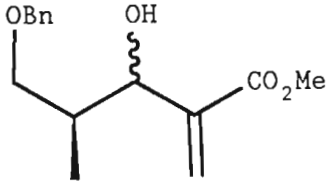
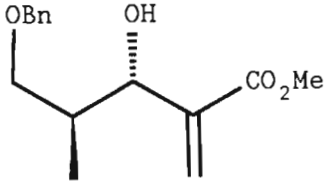
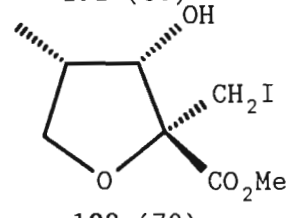
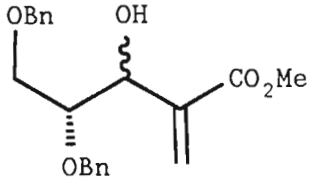
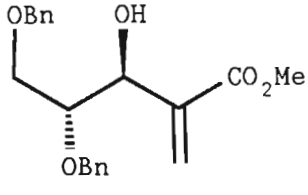
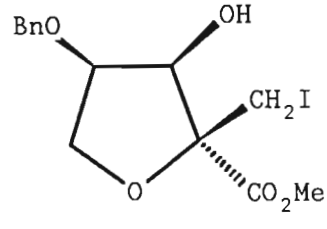
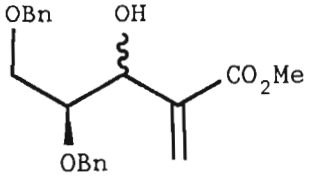
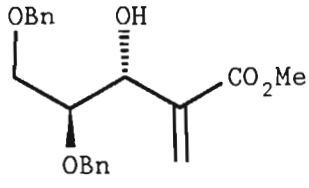
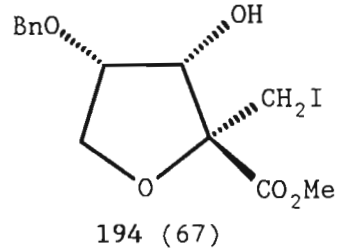
At this point, two tentative inferences were made; that only one diastereomer undergoes iodocyclisation at room temperature and the reaction proceeds with high diastereofacial selectivity.

Subsequently, the mixtures of diastereomers **138**, **140** - **142** and **144** - **147** (entries 1, 3-5, and 7-10 Table 3) were subjected to the iodocyclisation conditions without prior

separation. The cyclisation product from **139** (Table 3, entry 2) was only detected by GC-MS and not isolated. Hence, it will not be discussed. The isopropylidene acrylates **131**, **133** and **142** did not undergo cyclisation. In all the other cases, the reaction was generally clean and three spots ascribable to benzyl iodide (by-product), the tetrahydrofuran and the ureacted substrate were observed on tlc. The results are summarised in Table 4.

The yields refer to the product isolated by means of flash column chromatography and in all cases complete conversion of the reactive isomer occurred within 18 hours.

TABLE 4.: Iodocyclisation of γ-bezyloxy-α-hydroxyalkyl-acrylates.

Substrate[a]	Reactive Subtrate[b]	Product[c]	de Ratio
		 190 (68)	100:0
		 191 (68)	100:0
		 192 (70)	100:0
		 193 (65)	>95:5
		 194 (67)	>95:5

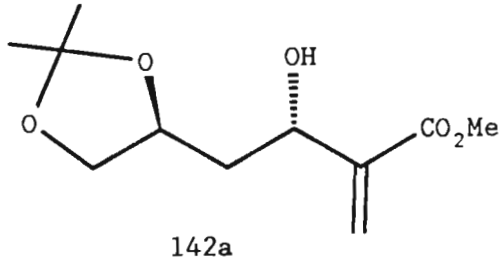
[a] Refers to a mixture of diastereomers. [b] The unreacted isomer was quantitatively recovered. [c] Percentage yield given in brackets. Refers to yield isolated by chromatography based on the reactive isomer.

The diastereomeric excess was determined by ^{1}HNMR, and GC-MS. It is interesting to note that

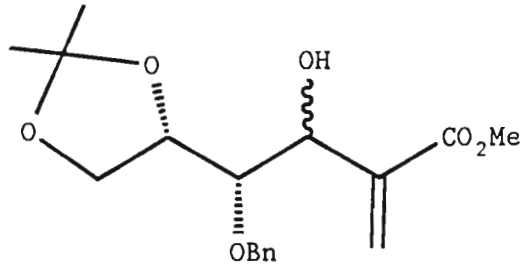
γ-benzyloxy-α-hydroxyalkylacrylates (Table 4, first - third entry) gave single diastereomers of the tetrahydrofurans. The analogous α-benzyloxy substituted substrates (fourth and fifth entries) were also highly selective (>95:5). As is apparent from Table 4 concerning iodocyclisation substrates, irrespective of the substitution pattern, the reaction gave 1,2-*cis* selectivity *i.e.*, the configuration of the hydroxyl group relative to the iodomethyl group is *cis*.

2.4.3.1. REACTIVITY OF ISOPROPYLIDENE ACRYLATES

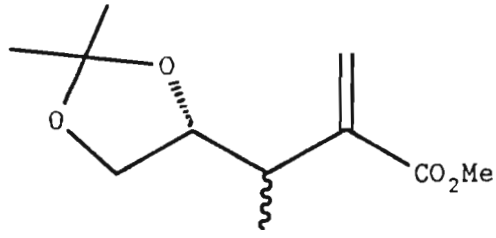
Regarding the reactivity, isopropylidene acrylates **142**, **145** and **146** did not undergo cyclisation under the present conditions.



142a



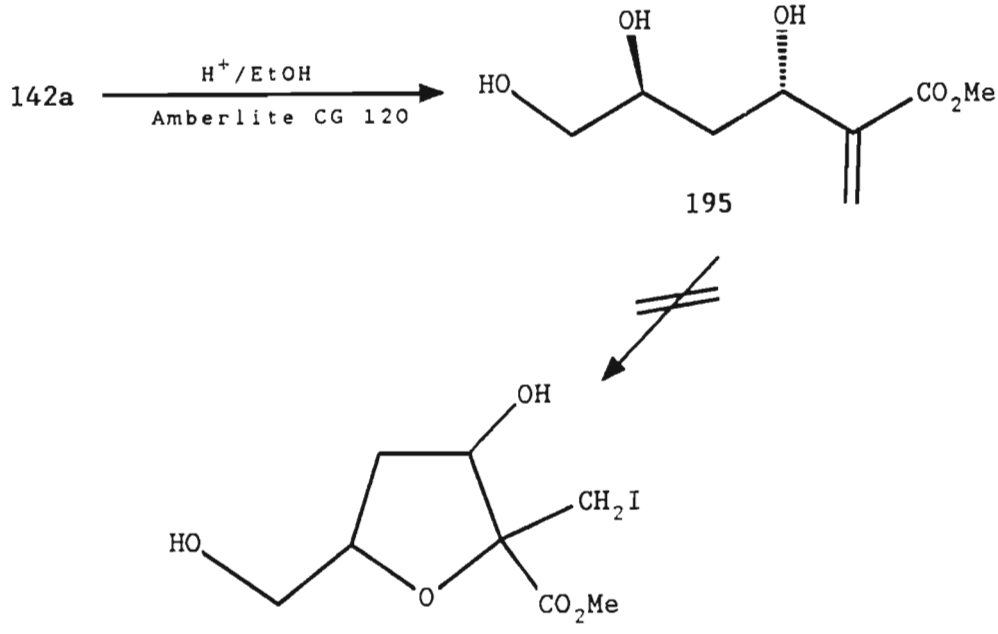
145



146 OH

Attempts were made to cyclise **142a** at elevated temperatures but a tarry mixture with no identifiable product was obtained. A further attempt involved deprotection of the isopropylidene protecting group followed by iodocyclisation. This was achieved by treatment of **142** to form the triol **195** (Scheme 59). The triol was subjected to iodocyclisation under kinetic control ($I_2/NaHCO_3$ Et_2O-H_2O, Scheme 59). This procedure also gave a complex mixture of unrecognisable products. A considerable amount of the triol **195** was

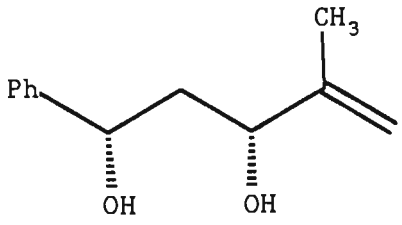
recovered unchanged.



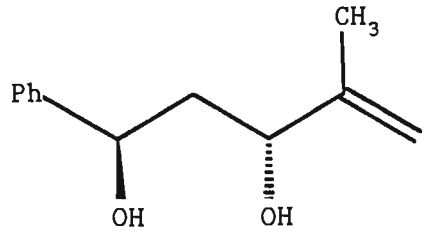
Scheme 59.

The reason for the lack of reactivity in the isopropylidene series **131**, **133** and **134**, is not entirely understood but the nature of the isopropylidene group probably contributes. The isopropylidene group apparently does not have the requisite electrofugal properties consequently it does not cleave or the cleavage is slow. Similar reactivity was observed for methyl ethers.[204] Bartlett and Rychnovsky[204] reported that due to poor electrofugal property of the methyl group, cleavage of the <u>other</u> C-O bond ensues and only 15% conversion to tetrahydrofuran occurs.

The lack of reactivity of the triol **195** under kinetically controlled conditions might be due to the relative configuration (*i.e.*, *anti:syn* relationship) of the allylic hydroxyl group to the γ-hydroxyl group (γ, relative to acrylate). This anomaly is not uncommon and has been observed by Yoshida and co-workers.[211] They reported that under similar conditions, the *syn* diol **196** is selectively consumed to form a tetrahydrofuran while the *anti* isomer **197** is recovered unchanged.

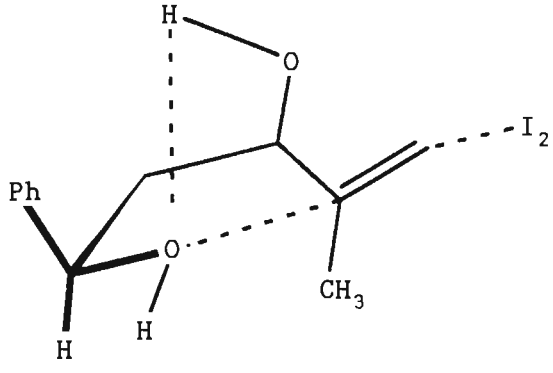


196

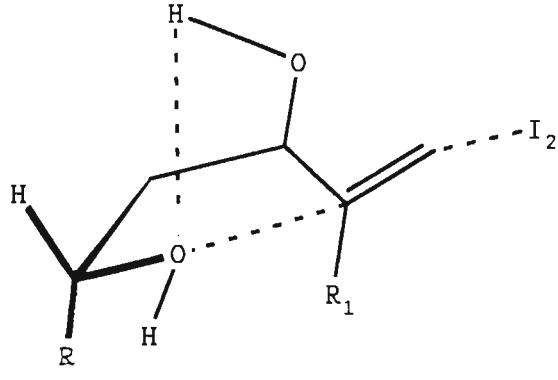


197

The authors[211] proposed formation of transition state **198b** to explain the lack of reactivity of **197**. This transition state is characterised by (i) an intramolecular hydrogen bonding, forming a six-membered ring, (ii) a nearly eclipsed conformation of the C_3 hydroxyl group in the C_4-C_5 double bond plane and (iii) a more or less concerted iodocyclisation, which proceeds in a *trans* fashion.



198a



198b R = Ph, R_1 = CH_3

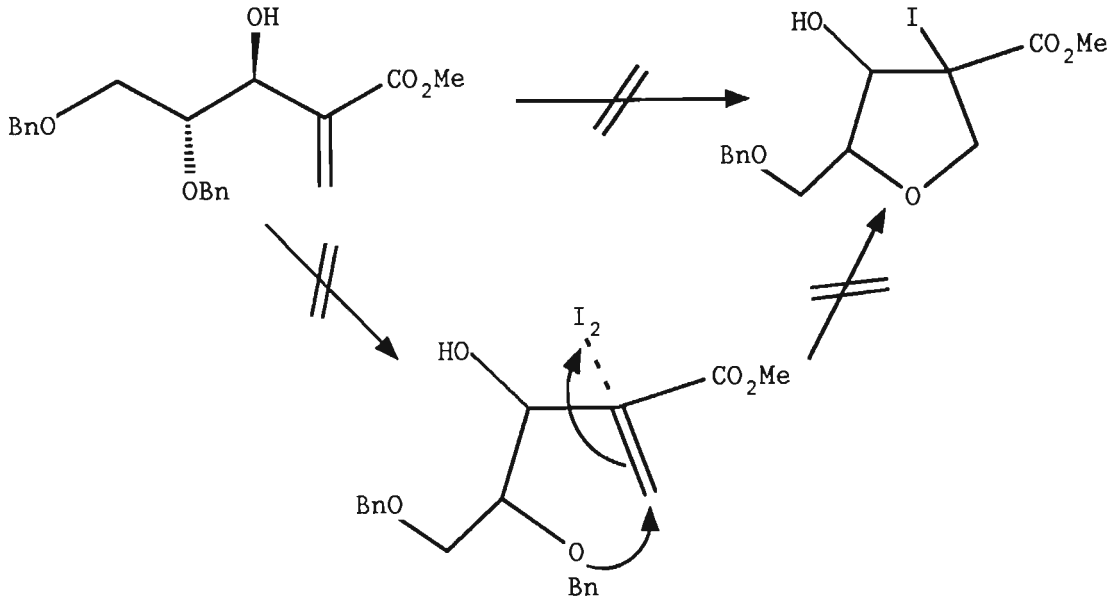
198c R = CH_2OH R_1 = CO_2Me

The *syn* substrate **196** easily forms the proposed transition state **198a**. However, the *anti* derivative **197** is energetically most unfavourable to form a bicyclic structure in an analogous transition state **198b** owing to an increase of nonbonding interactions and hence the low reactivity. Similarly, steric interaction between the axial groups (CH_2OH and CO_2Me) in the *anti* triol **195** disallow formation of the proposed intermediate state **198a** hence show the observed lack of reactivity.

2.4.3.2. REACTIVITY OF γ-ALKOXY-α-HYDROXYACRYLATES

As for the reactivity of γ-alkoxy-α-hydroxyalkylacrylates, data from Table 4 show a fascinating difference in the reactivity of *syn/anti* diastereomers. The *syn* isomer **138b** reacted at room temperature within 18 h to form the tetrahydrofuran **190** while the *anti* isomer **138a** was completely unreactive under the same conditions. A similar reactivity pattern was observed in the iodocyclisation of γ-benzyloxy-β-methyl-α-hydroxyalkylacrylates **140** and **141** (Table 4, second and third entry). Interestingly, it was the *anti* isomer that cyclised in this series to give exclusive formation of tetrahydrofurans **191** and **192**. In comparison, the β-benzyloxyacrylates **144** and **147** gave relatively less diastereoselection (>95:5) in the formation of tetrahydrofurans **193** and **194**. Nevertheless, the observed diastereoselectivity is synthetically valuable.

In all these cases, the cyclisation occurred with firm regioselective control *i.e.*, no formation of six-membered ethers was observed. The cyclisation proceeded according to Baldwin's rules[192] *i.e.*, only the favoured 5-*exo-trig* ring closure occurred. Also, the possible but disfavoured 5-*endo-trig* ring closure in the dibenzyloxy series (entries 1 and 2) did not occur (Scheme 60).



Scheme 60.

2.4.3.3. ASSIGNMENT OF THE STEREOCHEMISTRY

Stereochemical assignments of tetrahydrofurans containing an iodomethyl group is usually determined by comparison of the iodomethyl carbons.[218] The iodomethyl carbon of the *cis* isomer resonates at higher field (by *ca.* 5 ppm) relative to the *trans* isomer due to shielding in the ^{13}CNMR. Also the iodomethyl protons in the *cis* isomers resonate far down field compared with those of corresponding *trans* isomers.

Clearly, for the two diagnostic features to operate, a mixture of diastereomers is necessary. Consequently, this method is not applicable in the reactions in which single isomers of tetrahydrofurans were obtained (entries 1 - 3). For tetrahydrofuran **193** and **194**, the minor isomer did not appear on ^{13}CNMR but the iodomethyl protons were clearly visible in the ^{1}HNMR spectrum, without use of chiral shift reagent, at a relatively high field shift compared with the 1,2-*cis* isomer. Consequently it was concluded that the relative configuration of the hydroxyl group to the

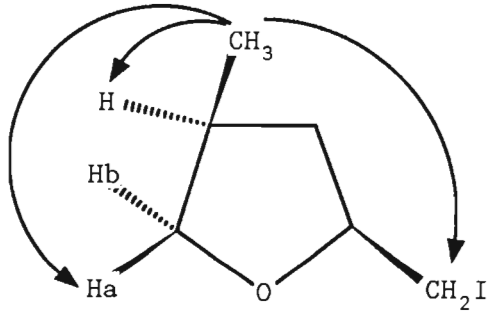
iodomethyl group of the tetrahydrofurans **193** and **194** is *cis*.

In order to confirm the above conclusion and to further establish the stereochemistry at other centres in the molecule, NOE experiments[219] were performed on all compounds. To illustrate this, NOE studies on tetrahydrofuran **191** will be discussed.

Figure 11 shows spectra for NOE experiments on **191**.

(a) is the control spectrum obtained without irradiation.

(b) irradiation of the high field methyl group enhances the C_4-H proton as might be expected. This experiment also leads to enhancement of C_5-H_a and the CH_2I and gives a negative effect on C_5-H_b, a proton which is a geminal partner of C_5-H_a. This experiment clearly assigns the relative configuration at the three centres as



The configuration at C_3 is known from starting material. other functional group are not shown.

Irradiation of methyl group.

irradiation of the C_5-H_a proton (not shown) gives enhancement to its geminal partner and also of the methyl group and CH_2I.

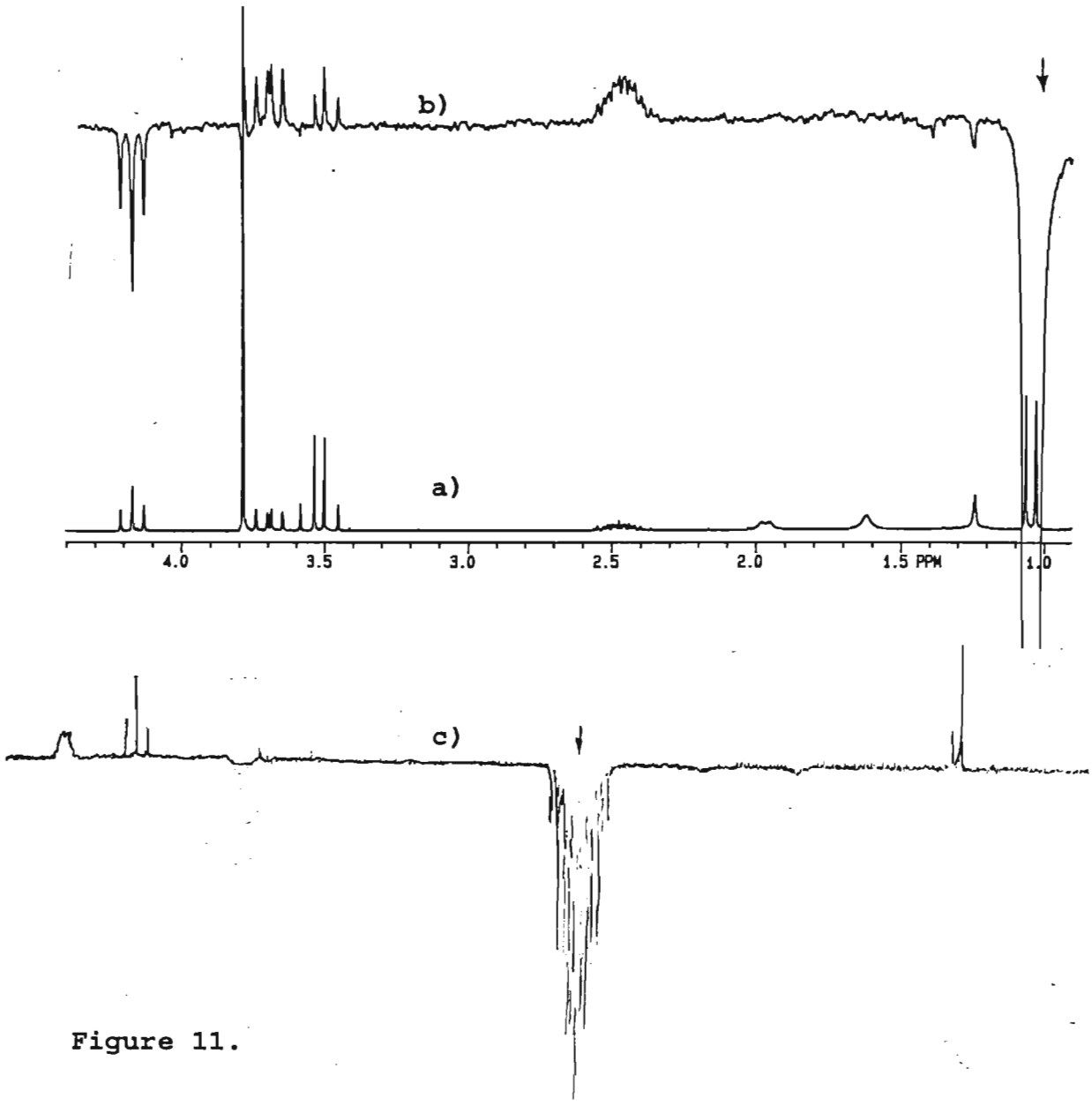


Figure 11.

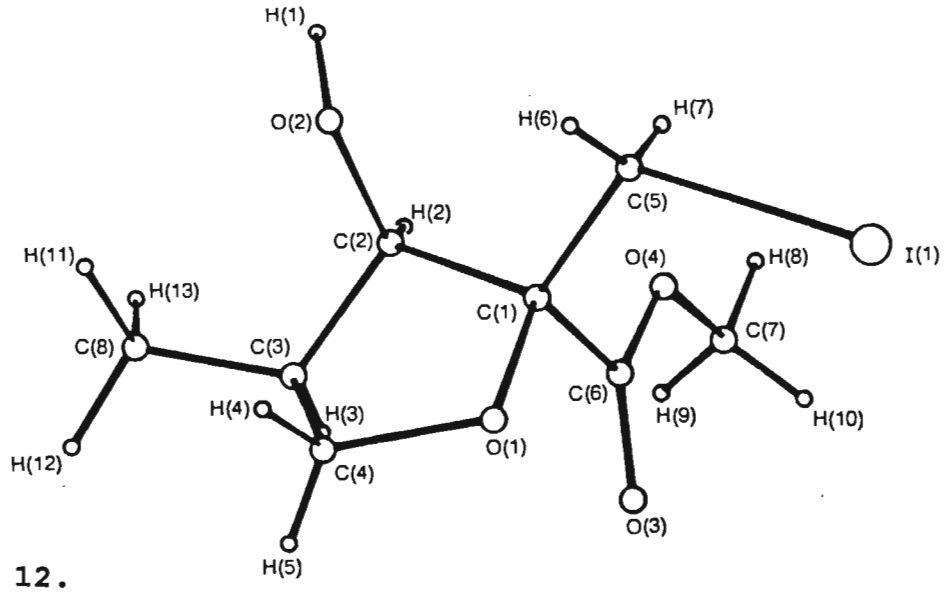
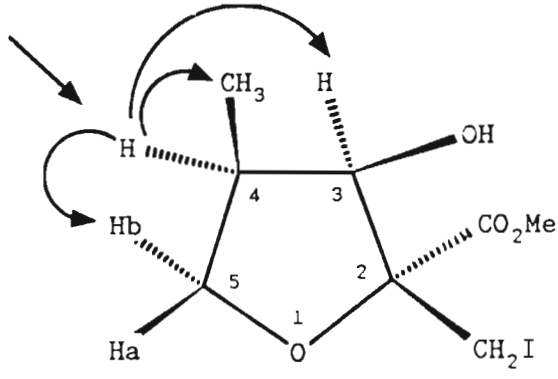


Figure 12.

(c) Irradiation of C_4-H gives some enhancement to the methyl group (expected) and significant enhancement to H_b and also C_3-H. From this experiment the relative configuration at the three centres is as follows:

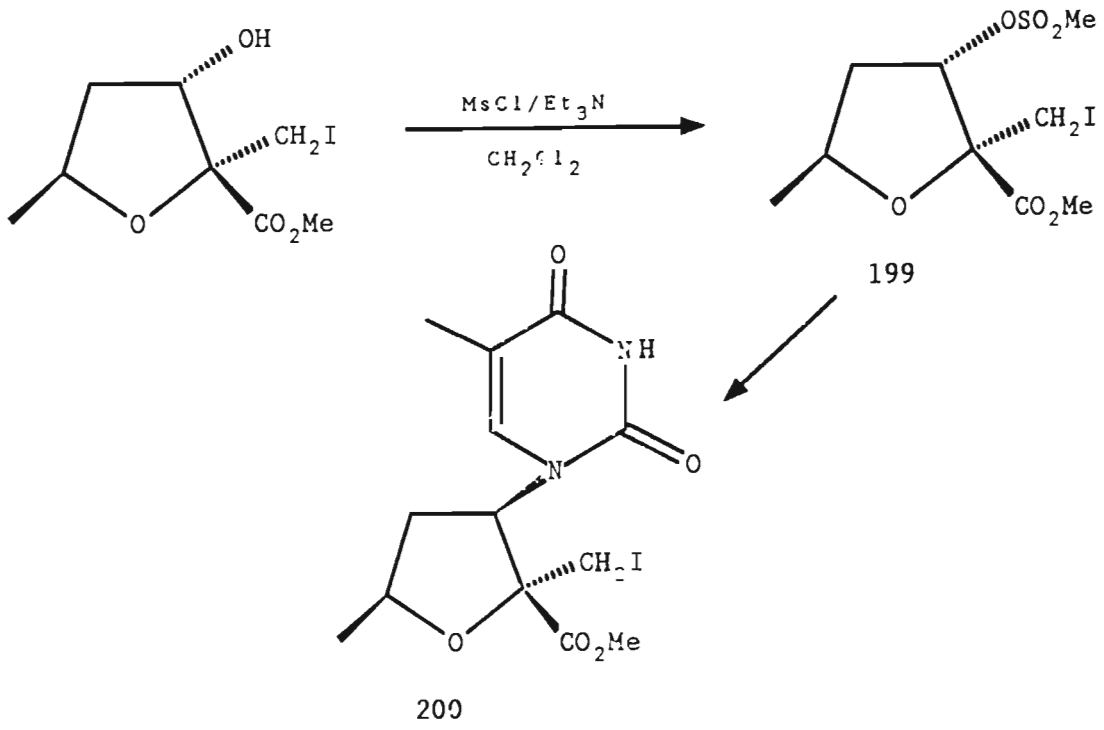


Irradiation of C_4-H

Further irradiation at other centres also supported these assignments and no further information could be extracted from them. Nevertheless, the two experiments sufficed and the structure was assigned as shown in Table 4.

This structural assignment was confirmed by a single structure X-ray analysis as shown in Figure 12.

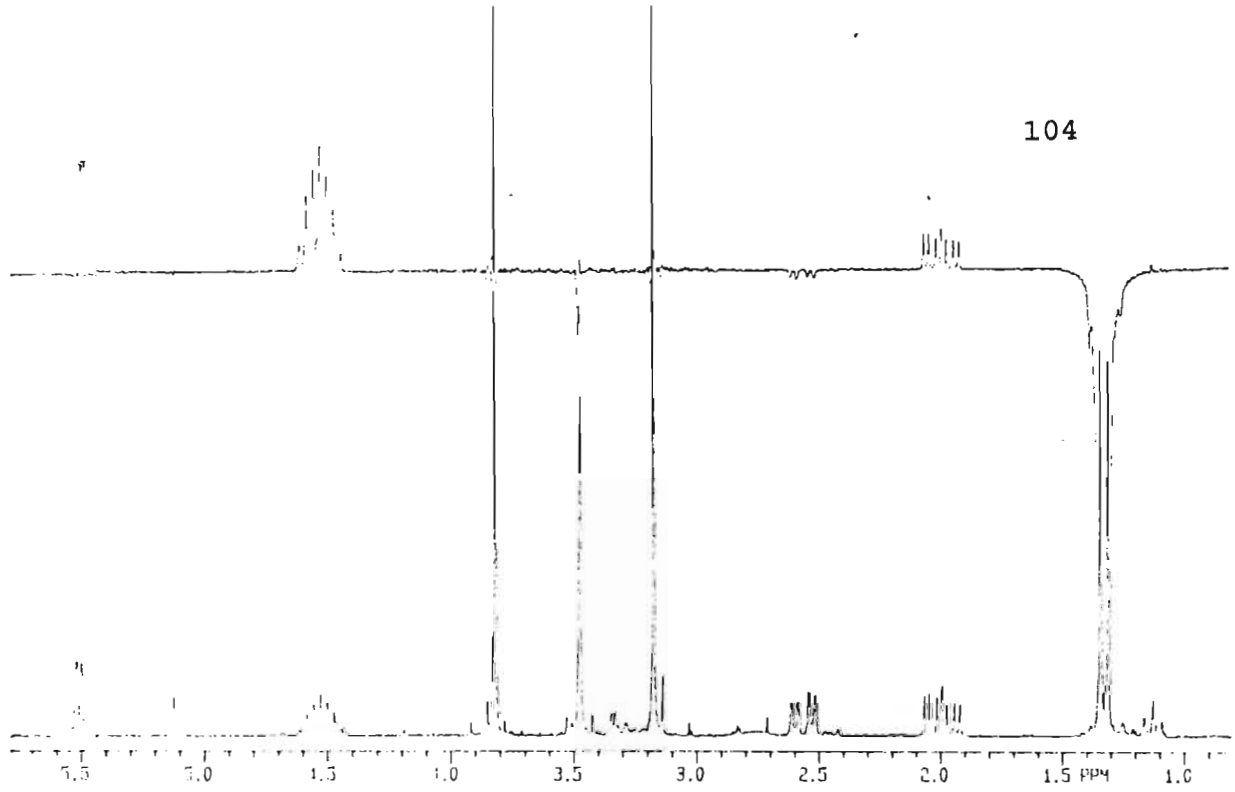
NOE experiments were also performed on tetrahydrofurans **192** - **194** and the results are shown in Table 4.
Unfortunately, the absolute configuration of tetrahydrofuran **190** could not be determined directly by NOE without some uncertainty. During studies directed towards the synthesis of the nucleoside analogue **200** (comprehensive studies will be done in the future), the services of a good leaving group at C_3 were required and the mesylate group was chosen for



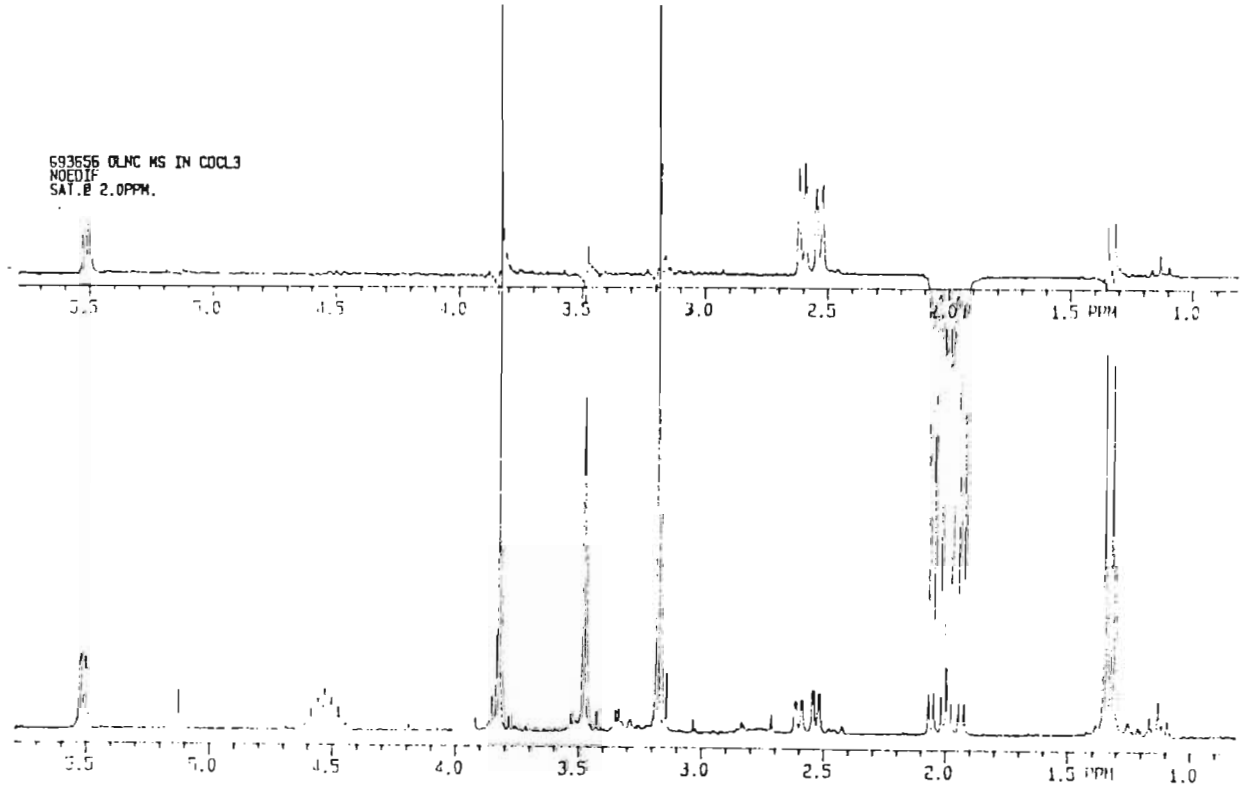
Scheme 61.

this purpose. Incorporation of the mesyl group (Scheme 61) gave **199** (78% yield) and all the signals in the NMR spectrum of this compound were clearly resolved. The NOE experiments on **199** shown in Figure 13 confirmed the assigned configuration. The first experiment, (a), identifies the C_4 proton (C_4-H^a) that is *cis* to CH_3. This is achieved by irradiation of the high field methyl group. Irradiation on this signal *i.e.*, C_4H^a signal, shown in (b), gives enhancement of its geminal partner (expected) and importantly, enhancement of the C_3-H signal. The reverse experiment shown in (c) gives some enhancement on CH_3 resonance signals and a huge enhancement of C_4-H^a. From these experiments, it was concluded that the CH_3 group is on the same side as C_3-H *i.e.*, *trans* to OMs. The last experiments *e.g.*, (d) and others that are not shown, confirmed this assignment. Consequently, the absolute configuration of tetrahydrofuran **190** was concluded to be *(2S, 3R, 5S)*, since the configuration at C_5 was known from the starting material.

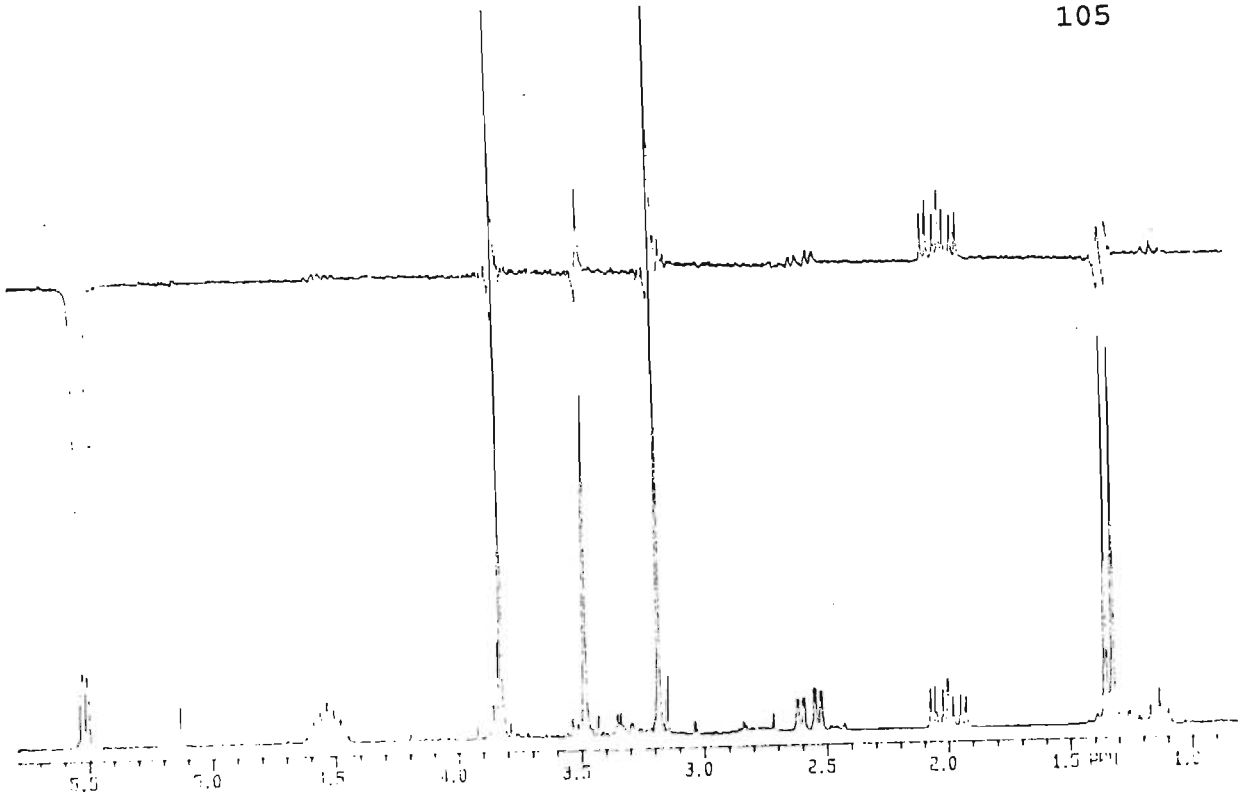
a)


3.5
3.0
1.5
1.0
3.5
3.0
2.5
2.0
1.5 PPM
1.0

b)


693656 OLNC MS IN COCL3
NOEDIF
SAT.@ 2.0PPM.
3.5
3.0
2.5
1.5 PPM
1.0

c)



d)

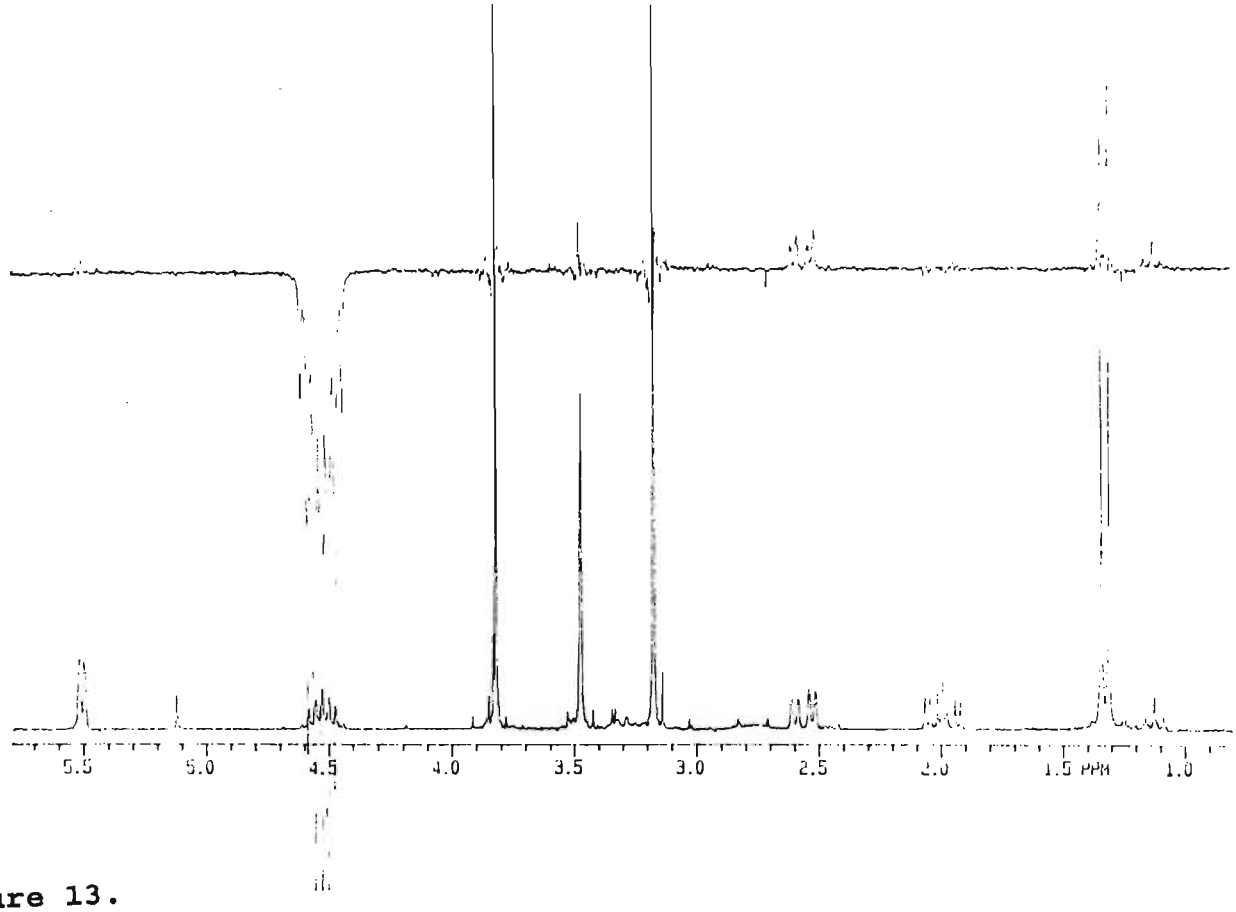
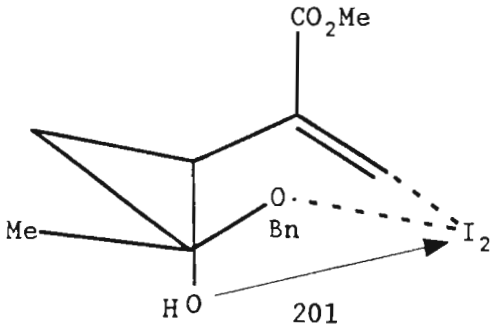


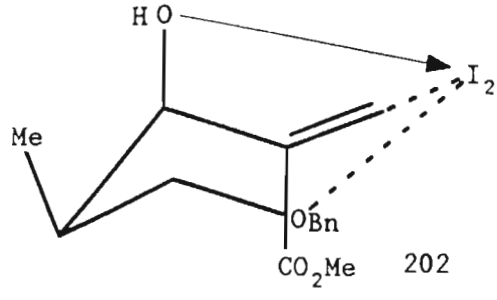
Figure 13.

2.4.3.4. RATIONALISATION OF STEREOCHEMICAL OUTCOME

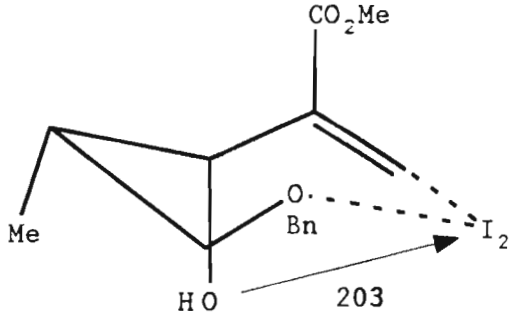
The reasons for the observed stereochemical outcome are not entirely understood but the observations seem to conform to a pattern that can be rationalised by assuming conformers **201** - **203** operate for substrates **138b** **140a** and **141a** respectively.



201



202



203

The conformers **202** and **203** also apply to compounds **144a** and **136a.** These conformers are characterised by the following features.

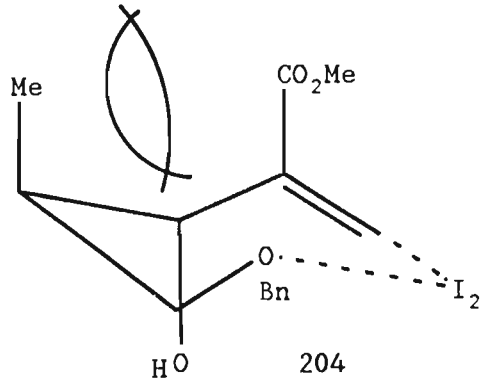
(i) A chair conformation in which the double bond is an integral part of the framework.

(ii) The hydroxyl group is always eclipsed with the double bond *i.e.*, OH-in-plane conformer.

(iii) Absence of 1,3-diaxial nonbonding interaction, particularly between the ester functional group and the methyl or benzyl substituents. In all the conformers the methyl or benzyl substituents assume an equatorial position. In this manner, 1,3-diaxial

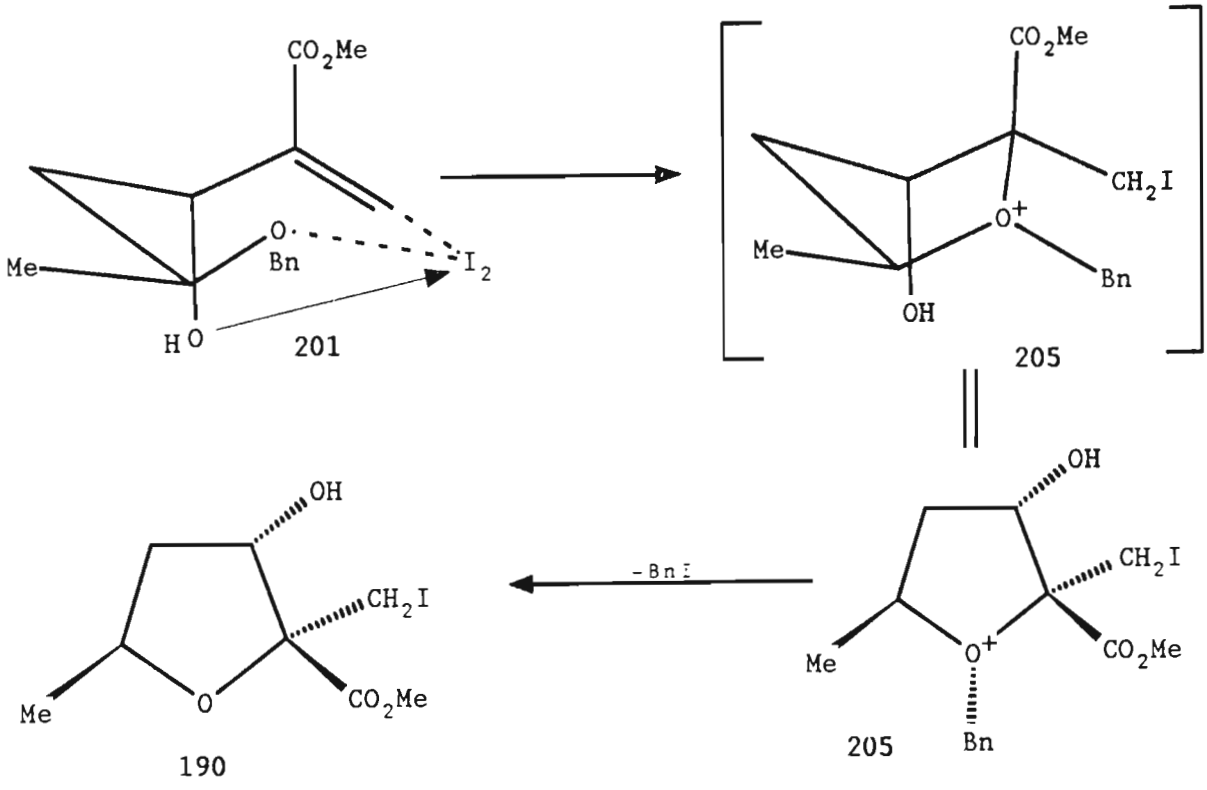
interactions are avoided.

The latter is invoked to explain the lack of reactivity of the opposite isomers of these substrates. For example, **203** represents the reactive conformer for *anti* isomer of **141a**. The corresponding *syn* isomer cannot assume a similar conformation since it is energetically unfavourable due to increased 1,3-diaxial strain *e.g.*, **204**.



204

Characteristic features (i) and (ii) are invoked to explain the common 1,2-*syn* relative configuration between CH_2I and the OH group. In all three conformers **201** - **203**, conformational preference to position the hydroxyl group *syn* to the halogen presumably arises because of stabilising interactions between the developing charge and the oxygen lone pairs as shown. This is in accord with the observation of Chamberlin *et al.*[213] and the results by Yoshida's group.[211] It is believed that the most stable conformation sets up the stage for thermodynamically controlled cyclisation. In accord with thermodynamic control, the relative stereochemical outcome at C_2 and C_5 is such that the more bulky groups are on the same side of the ring as in the oxonium intermediate **205** (Scheme 62).



Scheme 62.

The term 2,5-*cis* used in the earlier literature[204] will be inappropriate in this case since the priorities at C_2 are in fact in reversed order relative to C_5. Moreover, this notation was used as a relative term to compare bulky groups in which the other functional group was always H.

As it is apparent from the data in Table 4, the substituents at C_2 and C_4 appear to influence the degree of diastereofacial selection (cf. entries 2 and 3 with 4 and 5).

It is not clear whether this influence is a result of steric or electronic effects.

In summary, the results show that the stereochemical outcome is directed by the energeticaly favourable conformation as well as steric interactions in an intermedite cyclic oxonium ion. The results are in agreement with recent findings by Reitz *et al.*[208] In their systems the stereochemical outcome

is directed by an allylic benzyloxy group. A similar directing influence by an allylic hydroxy group has also been reported by Williams *et al.*[210]

2.4.3.5. CONCLUSIONS

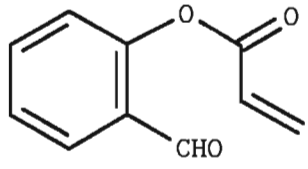
This study has shown that the Baylis-Hillman reaction does indeed involve a Michael-type addition. The resulting Michael adduct adds to α and β-chiral β-benzyloxy aldehydes with reasonable diastereofacial selection and the results are in agreement with Felkin-Anh model. Iodocyclisation of the resulting δ-benzyloxyalkylacrylates proceeds with strict regiochemical control and high diastereoselection to form 1,2-*cis*-tetrahydrofurans. The mechanism of asymmetric transfer is explained by an OH-in-plane conformer.
The 1,2-*cis* relative configuration and the multifunctional nature of the tetrahydrofurans will be useful in synthesis of polyether antibiotics.

3. EXPERIMENTAL

3.1 INSTRUMENTATION AND CHEMICALS

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were determined using Perkin-Elmer 240B and 2400 elemental analysers. NMR spectra (^{1}H 200 MHz and ^{13}C 50 MHz) were recorded on a Gemini 200 instrument, and unless specified to the contrary, $CDCl_3$ was used as a solvent and TMS as internal standard. Mass spectra were recorded on a Hewlett-Packard gas chromatographic-mass spectrometer (HP5988A) and a Varian high resolution spectrometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Infra-red were recorded on a Perkin-Elmer 1420 spectrophotometer. Kieselgel 60 F_{254} Merck plastic sheets were used for thin layer chromatography. Preparative column chromatography was performed using the technique of Still *et al.*[220] on Merck silica gel 60 (230-400 mesh). Solvents were dried using standard techniques and were distilled before use . Low temperatures were maintained using CO_2-solvent baths according to the procedure of Phipps and Hume.[221] Diastereomeric excesses were determined either by NMR spectroscopy or gas chromatographic-mass spectrometry while enantiomeric excesses were determined by ^{1}H NMR using $Eu(hfc)_3$ shift reagent. Chemical shifts for NMR spectroscopy denote those of the major diastereomers. Where applicable, shifts of the minor diastereoisomer are denoted in square brackets.

2-Formylphenyl acrylate **(80)**



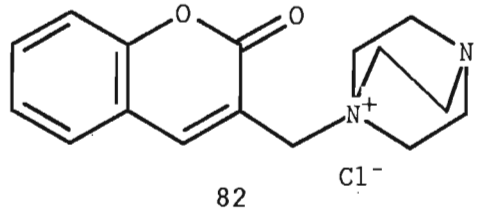
MF $C_{10}H_8O_3$

MW 176

80

To a mixture of salicylaldehyde (10 g, 0.082 mol) and potassium carbonate (22 g, 0.160 mol) at 0°C was added acryloyl chloride (7.5 g, 0.083 mol) dropwise. The mixture was allowed to stir at 0°C for 1 h. The suspended potassium salts were filtered and the filtrate washed with brine. Evaporation of the solvent afforded the acrylate **80** (13.5 g, 92%). This product polymerised on standing. Consequently, it was used without isolation from the mother liquor, δ_H 6.03 - 6.71 ppm (3H, m, CH_2=CHCO), 7.19 - 7.90 (4H, m, Ar *H*'s) and 10.12 (1H, s, CHO); δ_C 123.7, 126.8, 127.4, 130.7 and 135.7 ppm (5d, Ar *C*'s and vinyl CH), 134.1 (t, CH_2) and 189.0 (d, CHO); *m/z (EI)* (%) 176 (M^+, 3), 121 (100), 104 (6), 93(18),

3-N(1,4-diazabicyclo-2,2,2-octyl)methyl coumarin chloride **(82)**



MF $C_{16}H_{19}N_2O_2Cl$

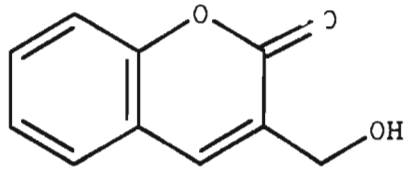
MW 306

82

A solution of *o*-formylphenyl acrylate **(80)**, (8.8 g, 0.05 mol) in anhydrous dichloromethane (100 ml) was treated with DABCO (5.6 g, 0.05 mol) at -10°C. After 2.5 h, a yellow precipitate had formed. The precipitate was filtered off, washed with dichloromethane and recrystallised from methanol/dichloromethane to afford **82** as colourless needles (11.9 g, 78%), [Found: M^+-HCl, 270.1349. $C_{16}H_{18}N_2O_2$ requires

270.1368]; m.p. 250°C (decomp); δ_H (CD_3OD) 3.22 - 3.35 ppm (6H, m, $(CH_2)_3N^+$), 3.56 - 3.64 (6H, m, $(CH_2)_3N$, 4.54 (2H, s, $-CH_2N^+$), 7.40 - 7.50 and 7.71 - 7.85 (4H, 2m, Ar *H's*) and 8.52 (1H, s, 4-*H*); δ_C (CD_3OD) 46.5 (t, $NCH_2CH_2N^+$), 54.1 (t, $^+NCH_2CH_2N$), 64.1 (t, CCH_2N), 117.9, 126.6, 131.0, 135.4, 153.07 (d, Ar *CH's* and 4-*C*), 116.8, 120.3 (s, 2 x Ar *C* and 3-*C*) 163.3 (s, *C*=O); *m/z (EI)*(%) 270 (M^+-HCl, 40), 194(50) and 159 (100).

3-Methanolcoumarin **88**



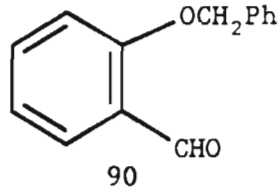
88

MF $C_{10}H_8O_3$

MW 176

The filtrate from the above experiment was washed successively with dilute HCl, dilute $NaHCO_3$ and brine. Evaporation of solvent under reduced pressure afforded **88** (0.88 g, 10%); (Found C 68.16, H 4.49. $C_{10}H_8O_3$ requires C 68.18, H 4.58); m.p. 285°C; δ_H (CD_3COCD_3) 4.96 ppm (2H, s, CH_2O), 6.83 - 7.32 (4H, m, Ar *H's*) and 7.5 (1H, s, CH=C); δ_C 65.1 ppm (t, CH_2), 116.7 (d, CH=), 122.6, 129.9, 132.7, and 133.8 (d, Ar *CH's*), 121.9 (s, *C*=CH), 123.9 and 156.0 (s, Ar *C's*), 165.8 (s, C=O); *m/z (EI)* (%) 176 (M^+, 28), 131 (100), 103 (14), 77 (25) 51 (16).

o-Benzyloxybenzaldehyde **(90)**



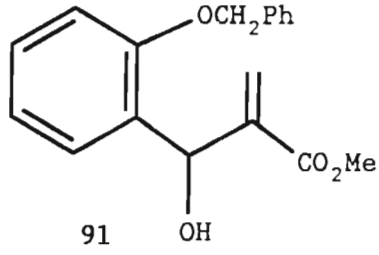
90

MF $C_{14}H_{12}O_2$

MW 212

A mixture of salicylaldehyde (5 g, 0.041 mol), benzyl bromide (7 g, 0.041 mol) and 2 equivalents of potassium carbonate were stirred at room temperature for 1 h. The mixture was filtered and washed with dilute HCl and brine. Evaporation of the solvent followed by chromatography afforded **90** as white powder (7.9, 90%); m.p. 36°C; δ_H 5.14 ppm (2H, s, CH_2Ph), 6.95 - 7.86 (9H, m, Ar *H*'s) and 10.54 (1H, s, *CHO*); δ_C 70.55 ppm (t, CH_2Ph), 113.3, 121.3, 127.6, 128.6, 128.7, 129.1 and 136.3 (d, Ar *CH*'s) and 190.2 (d, *CHO*); *m/z(EI)* (%) 212 (M^+, 4), 183 (6), 121 (12%) and 91 (100).

Methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **(91)**



91

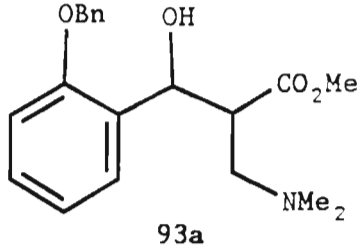
MF $C_{18}H_{18}O_4$

MW 298

Ortho-benzyloxybenzaldehyde **(90)** (2.0 g, 9.43 mmol) was added to a solution of DABCO (0.75 g, 6.7 mmol) in methyl acrylate (0.69 g, 8.0 mmol). After 12 days the mixture was diluted with CH_2Cl_2 and washed successively with dilute HCl and aqueous $NaHCO_3$. Removal of the solvent afforded **91** (1.89 g) 90%, as a yellow oil. It was further purified on silica gel using ethyl acetate/hexane (1:9); δ_H 3.66 ppm (1H, br s , OH), 3.67 (3H, s, OCH_3), 5.04 (2H, s, OCH_2Ph), 5.68 and

6.26 (2H, m, $=CH_2$), 5.93 (1H, s, *CH*OH), 6.88 - 6.99, 7.18 - 7.41 (10H, m, Ar *H's*); δ_C 52.0 ppm (t, OCH_3), 68.4 (d, *CH*OH), 70.3 (t, OCH_2Ph), 126.2 (t, $=CH_2$), 111.8, 120.9, 127.3, 127.7, 128.1, 128.4, 129, and 129.2(d, Ar *CH's*), 136.7, 141.4, 155.7(d, Ar *H's*), 167.0 (s, C=O); *m/z (EI)* (%) 298 (M^+, 0.5), 175 (30), 131 (20) and 91 (100).

Methyl 3-(2-Benzyloxyphenyl)-3-hydroxy-2-N,N-dimethyl-aminomethylbutanoate **(93a)**



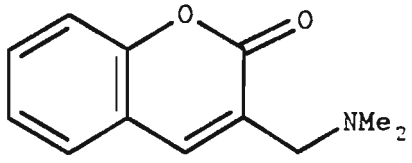
93a

MF $C_{20}H_{25}NO_4$

MW 343

A solution of methyl 3-(2-benzyloxyphenyl)-3-hydroxy-2-methylenepropanoate **(91)** (1.5 g, 5.0 mmol) in ether (10 ml) was added to a cooled (0°C) solution of an excess dimethylamine (40%) in water, 6 mmol). After 12 h at room temperature the aqueous layer was separated, the organic layer dried and chromatographed (9:1 hexane:ethyl acetate) to give an oil (1.65 g) 96%; Found C, 69.8; H 7.6; N 4.0; $C_{20}H_{25}NO_4$ requires C, 69.9; H, 7.3; N, 4.1); δ_H 2.23 ppm (6H, s, 2 x CH_3), 2.66 (1Ha, dd, CH_2NMe_2), 2.91 (1H, dd, CH_2NMe_2), 3.19 (1H, dt, *J* 8.0 Hz, $CHCH_2NMe$), 3.42 (3H, s, OCH_3), 5.07 (2H, pseudo d, OCH_2Ph), 5.30 (1H, br s, OH), 5.35 (1H, d, *J* 7.69 Hz, *CH*OH) and 6.88 - 7.49 (9H, m, Ar H's); δ_C 45.6 ppm (q, $N(CH_3)_2$), 48.5 (d, $CHCH_2NMe_2$), 51.6 (q, CH_3), 60.4 (t, CH_2N), 70.4 (t, OCH_2Ph), 73.0 (d, CHOH), 111.9, 121.3 127.7, 128.2, 128.7, 128.8 and 129.1 (d, Ar CH's), 130.3, 137.0 and 155.8 (s, Ar C's), 172.8 (s, C=O).

3-N,N-dimethylaminomethyl coumarin **(94a)**



94a

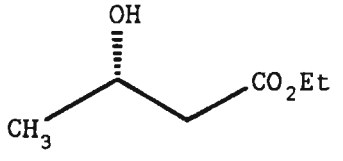
MF $C_{12}H_{13}O_2$

MW 203

A mixture of methyl 3-(*o*-benzyloxyphenyl)-3-hydroxy-2-N,N-dimethylbetanoate **(93a)** (2,5 g, 7.3 mmol) and a catalytic amount of pre-equilibrited palladium (19% on charcoal) in 95% ethanol (40 ml) was hydrogenated at room temperature and atmospheric pressure. Hydrogen absorption ceased after the uptake of 1 equivalent of hydrogen. The mixture was filtered and the filtrate evaporated at reduced pressure to afford **94a** as a yellow oil (1.46 g, 99%); (Found: M^+ 203.0946. $C_{12}H_{13}NO_2$ requires 203.0932); δ_H 2.4 ppm (6H, s, $N(CH_3)_2$), 3.5 (2H, d, *J* 1.3 Hz, CH_2N), 7.3 - 7.6 (4H, m, Ar H's), 7.8 (1H, s, CH=C); δ_C 45.5 (q, $N(CH_3)_2$), 57.7 (t, CH_2N), 116.4, 124.4, 127.7 and 131.1 (d, Ar CH's), 140.7 (d, *CH*=C), 119.3 (s, =CCO), 125.9, 153.1 (s, Ar C's) 161.4 (s, C=O); *m/z(EI)* (%) 203 (M^+, 13), 188 (M^+-15, 100), 159 (33), 131 (32), 115 (1), 77 (30).

Yeast Reduction of Ethyl Acetoacetate

(S)-(+)-Ethyl 3-hydroxybutyrate **(97)**



97

MF $C_6H_{12}O_3$

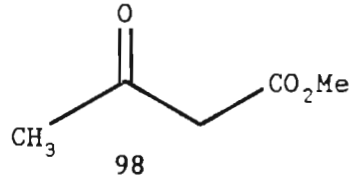
MW 132

To a solution of sugar (300 g) in 1600 ml tap water, baker's yeast (200 g) was added and the solution was left to stir at 30°C. After 1 h had elapsed, ethyl acetoacetate (20 g, 154 mmol) was added and stirring was continued for 24 h. A warm solution of sugar (200 g in 1000 ml tap water) was added.

After 1 h had elapsed a second portion of ethyl acetoacetate (20 g, 154 mmol) was added. The mixture was allowed to stir for seven days. The mixture was filtered under vacuum using celite. The filtrate was saturated with sodium chloride and extracted with ether. The ether extracts were dried with magnesium sulfate. The ether was removed by evaporation. Fractional distillation of the residue to afford the β-hydroxy ester **97** (30 g, 70%) as a colourless oil, b.p. 77 -78°C/15-20 mm Hg (lit.,[147] 71 - 73/12 mm Hg); $[\alpha]_D^{25}$ 30.6° (*c* 1.003 $CHCl_3$); δ_H 1.15 ppm (3H, d, $CHCH_3$), 1.28 (3H, t, $CHCH_3$), 2.35 (2H, d, $CHCH_2CO$), 3.15 (1H, s, *OH*); 4.05 (2H, q, OCH_2CH_3) and 4.15 (1H, m, $CHCH_3$); δ_C 14.23 ppm (q, OCH_2CH_3), 22.63 (q, $CHCH_3$), 43.20 (t, $CHCH_2CO$), 60.86 (t, OCH_2CH_3), 64.52 (d, $CHCH_3$) and 173.36 (s, *C=O*); *m/z(EI)* (%) 131 (M^+-H, 3), 117 (76), 88 (100),71 (69) and 45 (39).

Transesterification of Ethyl Acetoacetate

Methyl Acetoacetate **(98)**



98

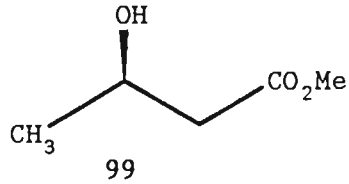
MF $C_5H_8O_3$

MW 116

Sodium hydride (0.74 g, 0.031 mol) was dissolved in dry methanol (200 ml) under nitrogen atmosphere at room temperature. The solution was cooled to 0°C and ethyl acetoacetate (40 g, 0.308 mol) was added dropwise and the solution refluxed for 1 h. It was then cooled to room temperature and treated with water (1 ml). The solvent was removed under vacuum and the residue taken up in ether. The ether solution was washed with dilute HCl, 5% $NaHCO_3$ and brine. Removal of the solvent afforded **98** (34.5 g, 96%); δ_H 2.28 ppm (3H, s, CH_3CO), 3.49 (2H, s, CH_2C) and 3.74 (3H, s, OCH_3); δ_C 30.2 (q, CH_3CO), 49.8 (t, CH_2), 52.33 (q, OCH_3), 167.7 (s, $COOCH_3$) and 200.7 (s, CH_3CO).

Hydrogenation of Methyl Acetoacetate

(R)-(-)-Methyl 3-hydroxybutyrate **(99)**



99

MF $C_5H_{10}O_3$

MW 118

To a reddish solution of $Ru(OCOCH_3)_2$[(*R*)-binap] {prepared by treatment of $[Ru(cod)Cl_2]_n$ with BINAP and triethylamine and the silver acetate} (201 mg, 0.239 mmol) in degassed CH_2Cl_2 (10 ml) was added 1.42N HCl in 90% methanol (0.35 ml, 0.5 mmol). After the resulting dark red solution was stirred at 23°C for 1 h, the solvent was removed under reduced pressure to give $RuCl_2$[(*R*)-binap] (160 mg) as a reddish brown catalyst.

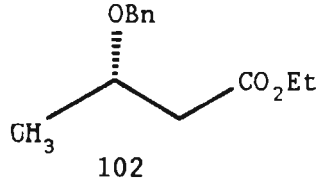
A solution of **98** (20 g, 0.172 mol) in degassed anhydrous methanol (30 ml) was degassed by 3-freeze-thaw cycles and placed in a stainless steel autoclave containing a solution of the RU-BINAP catalyst (80 mg) in degassed methanol (30 ml). Hydrogen was pressurised to 70 atm and the solution was stirred at 30 - 50°C for 36 h. The solvent was removed under reduced pressure and the residue distilled to give **99** (19.5 g, 96%); b.p. 40°C (2 mmHg) $[\alpha]_D$-21.65° (neat) {lit.,[150] $[\alpha]_D$-23° (neat)}; δ_H 1.23 ppm (3H, d, *J* 6.3 Hz, CH_3CH), 2.45 - 2.49 (2H, m, CH_2CO), 3.38 (1H, s, OH), 3.71 (3H, s, OCH_3) and 4.16 - 4.26 (1H, m, CH_3CH)); δ_C 22.6 ppm (q, CH_3CH), 42.9 (t, CH_2CO), 51.7 (q, OCH_3), 64.3 (d, CHOH) and 173.2 (s, C=O). *m/z(EI)* (%) 118 (M^+, 0.3), 117 (40), 88 (49), 71 (50), 59 (48) and 43 (100).

General Procedure 1.

Benzyl protection of β-hydroxy esters

To a solution of the β-hydroxy ester (112 mmol) and benzyl bromide (20.9 9, 122 mmol) in anhydrous ether (100 ml), portions of freshly prepared silver oxide (34.0 g, 0.147 mol) were added so as to maintain gentle reflux. When the addition was complete, the mixture was refluxed for a further 30 min. The solid material was removed by filtration and washed with ether. The ether was evaporated and the residue purified by chromatography (hexane:EtOAc, 9:1) to give the benzyl ethers.

Ethyl (S)-3-benzyloxybutyrate **(102)**



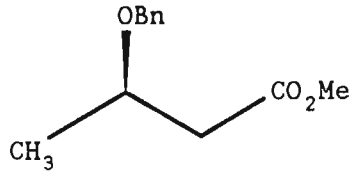
102

MF $C_{13}H_{18}O_3$

MW 222

Yield (13.4 g, 54%); δ_H 1.19 ppm (3H, t, *J* 7.1 Hz, OCH_2CH_3); 1.85 (3H, d, *J* 7.1 Hz, $CHCH_3$), 3.68 (2H, s, CH_2Ph), 4.12 (3H and 1H, q and m, *J* 7.1 Hz for q, OCH_2CH_3 and $CHCH_3$ overlap) and 7.2 (5H, m, Ar *H*'s). According to the ^1H NMR spectra, the product was contaminated with 5 - 7% dibenzyl ether. Nevertheless the product was used without further purification in the next step.

Methyl (R)-benzyloxybutyrate **(103)**



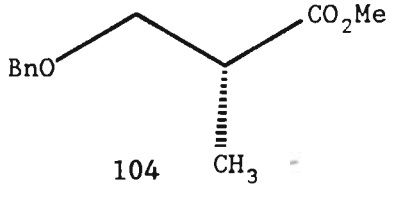
103

MF $C_{12}H_{16}O_3$

MW 208

Yield 11.6 g (56%); $[\alpha]_D$-63.69° (*c* 1.127 $CDCl_3$); δ_H 1.25 ppm (3H, d, *J* 6.2 Hz, CH_3CH), 2.42 (1H, dd, J 5.7 and 16 Hz, CH^aCO), 2.65 (1H, dd, *J* 7.2 and 16 Hz, CH^bCO), 3.66 (3H, s, OCH_3), 3.95 - 4.05 (1H, m, $CHCH_3$), 4.52 (2H, 2 x pseudo d, OCH_2PH) and 7.24 - 7.43 (5H, m, Ar *H's*); δ_H 19.8 ppm (q, CH_3CH), 41.8 (t, CH_2CO), 51.6 (q, OCH_3), 70.8 (t, OCH_2Ph), 71.9 (d, $CHCH_3$), 127.6, 127.6, and 128.30 (3 x d, Ar *H's*), 138.43 (s, Ar quarternary *C*) and 171.9 (s, C=O). *m/z (EI)* (%) 208 (M^+, 3), 177 (37), 149 (65), 91 (100) and 59 (39); No satisfactory analysis was obtained.

Methyl (R)-2-benzyloxy-3-methylpropionate **(104)**



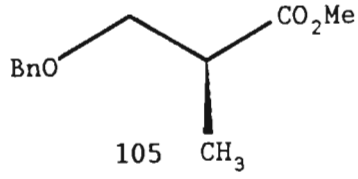
104

MF $C_{12}H_{16}O_3$

MW 208

Yield 18.6 g (80%); b.p. 110°C/0.5 mm Hg; $[\alpha]_D$-15° (*c* 1.36 $CHCl_3$) δ_H 1.17 ppm (3H, d, *J* 7.1 Hz, $CHCH_3$), 2.73 - 2.83 (1H, m, $CHCH_3$), 3.48 (1H, dd, *J* 5.7/9.1 Hz, CH^aOCH_2Ph), 3.65 (1H, dd, *J* 7.3 and 9.1 Hz, CH^bOCH_2PH), 3.67 (3H, s, OCH_3), 4.55 (2H, s, OCH_2Ph) and 7.25 - 7.37 (5H, m, Ar *H's*); δ_C 14.00 ppm (q, $CHCH_3$), 40.27 (d, $CHCH_3$), 51.83 (q, OCH_3), 72.13 (t, OCH_2Ph), 72.26 (t, CH_2OCH_2Ph), 127.91, 128.12 and 128.70 (d, Ar *CH's*), 138.66 (s, Ar quarternary C); *m/z (EI)* (%) 208 (0.6), 177 (16), 149 (23), 117 (33), 91 (100), 59 (30) and 44 (55). No satisfactory elemental analysis was obtained.

Methyl (S)-3-benzyloxy-2-methylpropionate **(105)**



MF $C_{12}H_{16}O_3$

MW 208

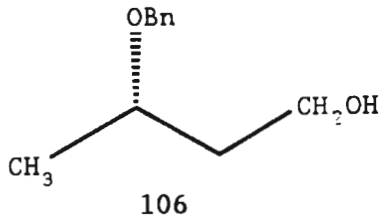
Yield 20.0 g (86%) (pure by ^1H NMR and GC/MS); $[\alpha]_D^{25}$ +11.3° (*c* 1.54 $CHCl_3$); δ_H 1.17 ppm (3H, d, *J* 7 Hz, $CHCH_3$), 2.73 - 2.83 (1H, m, $CHCH_3$), 3.48 (1H, dd, *J* 5.8/9.0 Hz, CH^aOCH_2Ph), 3.64 (1H, dd, *J* 7.4/9.1 Hz, CH^bOCH_2Ph), 3.67 (3H, s, OCH_3), 4.51 (2H, s, OCH_2Ph) and 7.25 - 7.34 (5H, m, Ar *H*'s); δ_C 13.96 ppm (q, $CHCH_3$), 40.16 (d, $CHCH_3$), 51.68 (q, OCH_3), 71.93 (t, CH_2OBn), 73.06 (t, $PhCH_2C$), 127.55, 127.58 and 128.33 (d, Ar *CH*'s), 138.15 (s, Ar quarternary C) and 175.25 (s, CO_2Me); *m/z (EI)* (%) 208 (0.6), 177 (16), (23), 117 (33), 91 (100), 59 (30) and 44 (55). No satisfactory elemental analysis was obtained.

General Procedure 2.

Reduction of β-benzyloxy esters

To a stirred suspension of $LiAlH_4$ (1.2 g, 32.4mmol) in anhydrous ether (40 ml), a concentrated ethereal solution of the ester was added dropwise to maintain gentle reflux. When the addition was complete, the mixture was refluxed for 45 min. Water (1.2 ml), 12% NaOH (1.2 ml) and water (1.3 ml) were added successively at 0°C. The reaction mixture turned white. The lithium salts were filtered, dried and dissolved in a minimum volume of 2N H_2SO_4. The solution was extracted with ether and washed with brine. The ether extract was dried ($MgSO_4$) and evaporated to dryness. The alcohols were purified by distillation or chromatography.

(S)-3-Benzyloxybutanol **(106)**



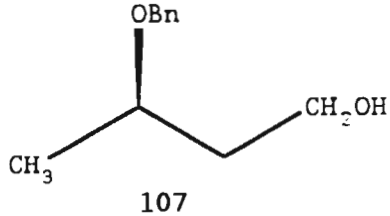
106

MF $C_{11}H_{16}O_2$

MW 180

Prepared as described in GP 2 to give (4.5 g, 90%); b.p. 99 - 101°C/0.3 mm Hg; $[\alpha]_D^{25}$+57.5° (*c* 1.304 $CHCl_3$); δ_H 1.25 ppm (3H, d, $CHCH_3$), 1.71 - 1.81 (2H, dd, $CHCH_2CH_2$), 2.83 (1H, s, *OH*), 3.70 - 3.82 (1H and 2H, m and t, $CHCH_3$ and CH_2OH overlap), 4.52 (2H, 2 x pseudo d, CH_2Ph), and 7.28 - 7.36 (5H, m, Ar *H's*); δ_C 19.44 ppm (q, $CHCH_3$), 38.94 (t, $CHCH_2CH_2$), 60.54 (d, $CHCH_3$), 70.62 (t, CH_2OH), 74.61 (t, CH_2Ph), 128.02, 128.08 and 128.82 (3 x d, Ar *CH's*) and 138.82 (s, Ar quarternary C); *m/z(EI)* (%) 180 (M^+, 4), 162 (13), 107 (56) and 91 (100).

(R)-3-Benzyloxybutanol **(107)**



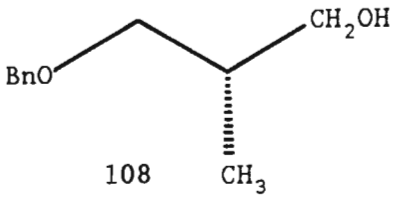
107

MF $C_{11}H_{16}O_2$

MW 180

Prepared as described in GP 2. Yield 94% (purified by chromatography to obtain a colourless oil); [α]-63° (*c* 1.24 $CHCl_3$) δ_H 1.24 ppm (3H, d, *J* 6.1 Hz, CH_3CH), 1.71 - 1.81 (2H, m, $CHCH_2CH_2$), 2.74 (1H, br s, OH), 3.70 - 3.82 (2H, m, CH_2OH), 4.52 (2H, 2 x pseudo d, OCH_2Ph) and 7.28 - 7.36 (5H, m, Ar *H's*); δ_H 19.4 ppm (q, CH_3CH), 38.8 (t, $CHCH_2CH_2$), 60.7 (t, CH_2OH), 70.4 (t, OCH_2Ph), 74.5 (d, *CH*OBn), 127.7, 127.7 and 128.5 (3 x d, Ar *H's*) and 138.4 (s, Ar quarternary C). *m/z(EI)* (%) 180 (M^+, 1), 118 (1), 107 (39), 91 (100), 79 (12), 65 (15) and 43 (9).

(S)-3-Benzyloxy-2-methylpropanol **(108)**



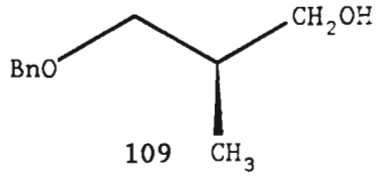
108

MF $C_{11}H_{16}O_2$

MW 180

Prepared as described in GP 2. Yield 92% (as colourless oil); $[\alpha]_D$ -17.06°(*c* 3.247) δ_H 0.87 ppm (3H, d, *J* 6.8 Hz, $CHCH_3$), 2.00 (1H, m, $CHCH_3$), 3.00 (1H, br. s, *OH*), 3.36 - 3.52 (2H, m, OCH_2CH), 3.55 (2H, d, *J* 6.0 Hz, $CHCH_2OH$), 4.48 (2H, s, $PhCH_2O$) and 7.22 - 7.34 (5H, m, Ar *H's*); δ_C 13.55 ppm (q, $CHCH_3$), 67.10 (t, CH_2OH), 73.25 (t, OCH_2CH), 74.86 (t, CH_2Ph), 127.54 and 127.63 (3 x d, Ar *CH's*) and 138.09 (s, Ar quarternary C); *m/z(EI)* (%) 180 (M^+,0.01), 118 (2), 107 (39), 91 (100), 79 (12), 65 (15) and 43 (9).

(R)-3-Benzyloxy-2-methylpropanol **(109)**



109

MF $C_{11}H_{16}O_2$

MW 180

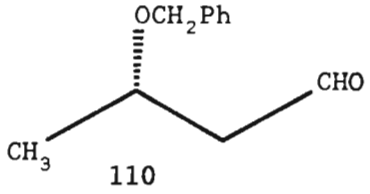
Following GP 2, the title compound was obtained as a colourless oil. Yield 95%; $[\alpha]_D^{25}$ +11.06° (*c* 1.54 $CHCl_3$); δ_H 0.88 ppm (3H, d, *J* 7.0 Hz, $CHCH_3$), 1.99 - 2.08 (1H, m, $CHCH_3$), 2.93 (1H, br. s, *OH*), 3.36 - 3.49 (2H, m, CH_2OBn), 3.49 - 3.59 (2H, m, CH_2OH), 4.49 (2H, s, CH_2Ph) and 7.23 - 7.35 (5H, m, Ar *CH's*); δ_C 13.59 (q, $CHCH_3$), 35.75 (d, $CHCH_3$), 67.41 (d, *CHOH*), 73.49 (t, CH_2Ph), 75.17 (t, CH_2OBn), 127.94, 128.02 and 128.78 (3 x d, Ar *CH's*) and 138.50 (s, Ar quarternary C); *m/z(EI)* (%) 180 (M^+, 5), 161 (4), 120 (4), 107 (67), 91 (100), 77 (20) and 65 (31). No satisfactory elemental analysis was obtained.

General Procedure 3

Oxidation of alcohols

Oxidation of alcohols was effected by the method of Swern.[159] Thus a solution of oxalyl chloride (2.37 g, 18.7 mmol, 1.1 equiv) in CH_2Cl_2 (30 ml) was stirred mechanically and cooled to -62°C in a dry ice-acetone bath. Dimethyl sulfoxide (2.92 g, 37.4 mmol, 2.2 equiv) in CH_2Cl_2 (6 ml) was added dropwise. After 4 minutes, the solution of the alcohol (16.7 mmol) in CH_2Cl_2 (10 ml) was added dropwise. After 40 minutes triethylamine (7.91 9, 78.7 mmol, 4.6 equiv) was added dropwise. The solution was allowed to warm to room temperature and diluted with distilled water (30 ml). The organic layer was washed with 5% aqueous HCl (50 ml) and saturated $NaHCO_3$ (50 ml), dried and filtered. Evaporation of the solvent gave the crude aldehyde as a residual oil. No satisfactory elemental analyses were obtained for all the aldehydes.

(S)-3-benzyloxybutyraldehyde **(110)**



110

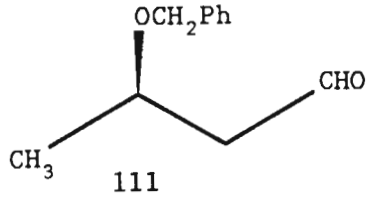
MF $C_{11}H_{14}O_2$

MW 178

Oxidation of **106** (3.01 g, 16.7 mmol) as described in GP 3 afforded **110** (2.68 g, 90%), $[\alpha]_D^{25}$ +33.5° (*c* 1.643 $CHCl_3$); δ_C 1.27 ppm (3H, d, $CHCH_3$), 2.57 (2H, dd, *J* 1.8/14.6 Hz, CH_2CHO), 4.04 (1H, m, $CHCH_3$), 4.52 (2H, 2 pseudo d, OCH_2), 7.35 (5H, m, Ar *CH*'s) and 9.70 (1H, t, *J* 1.8 Hz, *CHO*); δ_C 19.81 (q, $CHCH_3$), 50.59 (t, CH_2CO), 70.41 (d, $CHCH_3$), 70.75 (t, CH_2Ph), 128.02 and 128.76 (3 x d, Ar *CH*'s), 138.63 (s,

Ar quarternary C) and 201.97 (d, *CHO*); *m/z(EI)* (%) 178 (M^+, 3), 107 (74), 91 (100) and 79 (26).

(R)-Benzyloxybutyraldehyde **(111)**



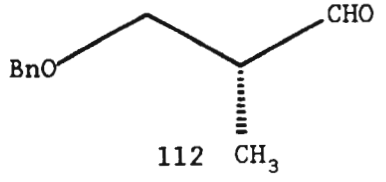
111

MF $C_{11}H_{14}O_2$

MW 178

Prepared as described in GP 3. The alcohol **107** (3.01 g, 16.7 mmol) afforded 2.4 g of **111** (80%) as a light yellow oil, $[\alpha]_D^{25}$ -18.8°(*c* 2.987 $CHCl_3$); δ_H 1.30 ppm (3H, d, *J* 6.2 Hz, CH_3CH), 2.43 - 2.77 (2H, m, CH_2CHO), 4.04 - 4.13 (1H, m, $CHCH_3$), 4.54 (2h, 2 x d pseudo d, CCH_2Ph), 7.26 - 7.36 (5H, m, Ar *H's*), 9.79 (1H, t, *J* 2.5 Hz, CHO); δ_C 19.8 (q, CH_3), 50.5 (t, CH_2CHO), 70.2 (d, $CHCH_3$), 70.6 (t, OCH_2Ph), 127.7, 128.4 (2 x d, Ar *CH's*) and 201.5 (d, CHO). *m/z (EI)* (%) 178 (M^+, 0.1), 108 (14), 91 (100) and 79 (36).

(R)-Benzyloxy-2-methylproprionaldehyde **(112)**



112

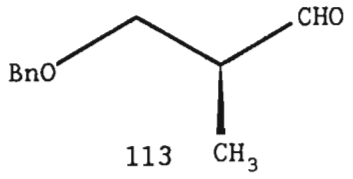
MF $C_{11}H_{14}O_2$

MW 178

Prepared as described in GP 3. Thus **108** (3.01 g, 16.7 mmol), afforded **112** 2.02 g (68%) as a colcurless oil, $[\alpha]_D^{25}$ -21.1° (*c* 1.888 $CHCl_3$); δ_H 1.11 ppm (3H, d, *J* 7.1 Hz, $CHCH_3$), 2.59 -2.69 (1H, m, $CHCH_3$), 3.57 - 3.68 (2H, m, CH_2OBn), 4.51 (2H, s, OCH_2Ph), 7.24 - 7.38 (5H, m, Ar *CH's*) and 9.71 (1H, d, *J* 1.6 Hz, *CHO*); δ_C 10.69 (q, $CHCH_3$), 46.88 (d, $CHCH_3$), 70.24 (t, OCH_2Ph), 73.44 (t, CH_2OBn), 127.94, 128.07 and 128.77 (3 x d, Ar *CH's*) and 204.43 (d, *CHO*); *m/z(EI)* (%) 178 (M^+,

0.1), 107 (50), 91 (100), 87 (22).

(S)-Benzyloxy-2-methylproprionaldehyde **(113)**



MF $C_{11}H_{14}O_2$

MW 178

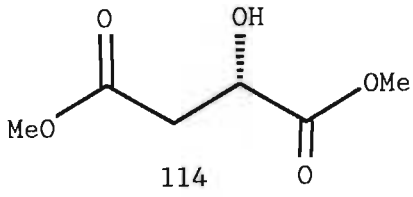
Prepared as described in GP 3. Thus **109** (3.01 g, 16.7 mmol) gave 2.08 g (70%) of **113** as a colourless oil, $[\alpha]_D^{25}$ +23.9° (*c* 3.61 $CHCl_3$); δ_H 1.10 ppm (3H, d, *J* 7.0 Hz, $CHCH_3$), 2.58 - 2.69 (1H, m, $CHCH_3$), 3.64 (2H, dd, *J* 1.2/5.9 Hz, OCH_2CH), 4.50 (2H, s, CH_2Ph), 7.24 - 7.37 (5H, m, Ar *CH*'s) and 9.70 (1H, d, *J* 1.6 Hz, *CHO*); δ_C 10.66 (q, $CHCH_3$), 46.75 (d, $CHCH_3$), 70.04 (t, CH_2OBn), 73.21 (t, CH_2Ph), 127.55, 127.68 and 128.38 (3 x d, Ar *CH*'s), 137.90 (s, Ar quarternary C) and 206.01 (d, *CHO*); *m/z(EI)* (%) 178 (M^+, 0.1), 107 (50), 91 (100), 87 (22).

General Procedure 4

Esterification of acids

A mixture of acid (0.746 mol) and Dowex 50 W-X8 H^+-ion exchange resin (7 g) in MeOH (110 ml) and $CHCl_3$ (160 ml) was heated under reflux through a Soxhlet thimble containing $MgSO_4$ (80 g). The drying agent was replaced twice during the reflux period of 14 h. The solution was filtered, the solvents were removed and the residue was distilled to give a colourless oily liquid.

Dimethyl (S)-malate **(114)**



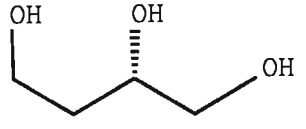
114

MW $C_6H_{10}O_5$

MW 162

Prepared as in GP 4. Thus, malic acid (50 g, 0.37 mol) was converted to **114** in 90% yield (54 g), $[\alpha]_D^{25}$ -26° (neat) (Lit.,[160] -29° (neat)); δ_H 2.81 - 2.86 ppm (2H, m, CH_2CO_2Me), 3.58 (1H, s, OH), 3.72 (3H, s, OCH_3), 3.81 (3H, s OCH_3) and 4.54 (1H, m, *CH*OH); δ_C 38.7 ppm (t, CH_2CO), 52.2 (q, OCH_3), 52.9 (q, OCH_3), 67.5 (d, *CH*OH), 171.7 and 174.3 (2 x s, 2 x OCH_3); *m/z (EI)* 162 (M^+, 0.03), 159 (52), 101 (22), 99 (100) and 85 (38).

S)-1,2,4-Butanetriol **(115)**



115

MF $C_4H_{10}O_3$

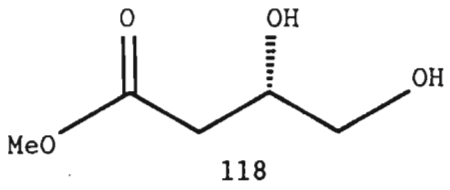
MW 106

(*S*)-(-)-Dimethyl malate (25.9 g, 0.154 mol), dissolved in dry THF (30 ml), was added dropwise to a suspension of $LiAlH_4$ (21.0 g, 0.55 mol) in dry THF (1000 ml) and refluxed overnight. Addition of water (160 ml) gave a white precipitate, which was filtered and washed with four 130 ml portions of dry EtOH. The combined solution was evaporated to near dryness *in vacuo*. The inorganic material contained in the residual oil was removed by short column chromatography over 50 g of silica gel [elution with 560 ml (3:1 v/v) and 670 ml (2:1 v/v) of $CHCl_3$-EtOH]. Removal of solvent gave about 12 g (74%) of a yellow oil, indicated to be slightly impure by ^{1}HNMR. This oil was submitted to fractional distillation to give a colourless oil (7.8 g, 48%

- 50%); (lit.,[161] b.p. 145 -148 °C (1.4 mm Hg); $\delta_H(C_5D_5N)$ 0.66 - 0.85 ppm (2H, m, CH_2CH_2OH)), 2.60 (2H, d, *J* 5.5, $OHCH_2CH$), 2.74 - 2.83 (2H, m, CH_2CH_2OH), 2.96 - 3.08 (1H, m, *CH*OH) and 4.87 (3H, s, 3 x OH); $\delta_C(C_5D_5N)$ 37.9 (t, CH_2CH_2OH), 60.1 (t, CH_2CH_2OH), 67.9 (t, $CHCH_2OH$) and 71.1 (d, CH_2CHCH_2). *m/z(EI)* (%) 88 (M^+-18, 1), 76 (5), 75 (100), 61 (5), 57 (29) and (9).

Regioselective reduction of (S)-malic acid

Methyl (S)-3,4-dihydroxybutyrate **(118)**



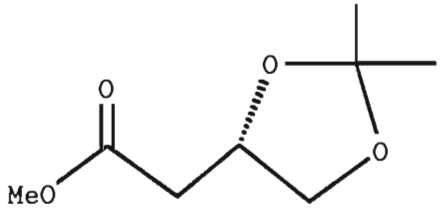
118

MF $C_5H_{10}O_4$

MW 134

To a solution of (*S*)-(-)-dimethyl malate (**114**) (19.4 g, .12 mol) in dry THF (250 ml) was added BMS (12.2 ml, 0.122 mol) and the mixture was stirred at 20°C for 0.5 h. Then, $NaBH_4$ (0.2 g, 6.0 mmol) was thrown into the mixture and the resulting mixture was stirred for an additional 0.5 h, followed by the addition of dry MeOH (77 ml), stirring being continued for 0.5 h. The solvent was removed by using rotary evaporator to give a colourless oil which was purified by means of column chromatography on silica gel (EtOAc), affording **118** in 88% yield (14.1 g), b.p. 105°C (0.3 mmHg) $[\alpha]_D^{25}$-22.6°(*c* 3.025 $CHCl_3$); δ_H 2.53 ppm (2H, d, *J* 5.6 Hz, CH_2CO), 3.50 - 4.18 (5H, m, CH_2OH, 2 x OH, *CH*OH) and 3.70 (3H, s, OH); δ_C 37.9 ppm (t, CH_2CO), 51.9 (q, OCH_3), 65.7 (t, CH_2OH), 68.7 (d, *CH*OH) and 172.7 (s, C=O); *m/z(EI)* (%) 134 (M^+, 0.07%), 131 (100), 101 (12) 85 (12), 71 (74) and 43 (34).

Methyl (S)-1,2-O-Isopropylidenebutyrate **(119)**



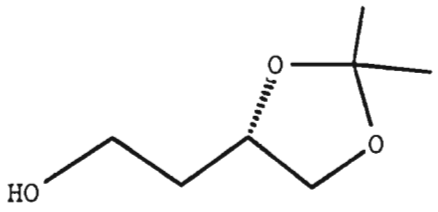
MF $C_8H_{14}O_4$

MW 174

119

A mixture of methyl 3,4-dihydroxybutyrate (10.0 g, 74.6 mmol) and dimethoxypropane (8.3 g, 80.0 mmol) in acetone (100 ml) was stirred with *p*-toluenesulphonic acid at room temparature for 1.5 h, $NaHCO_3$ was suspended in the solution, and the stirring was continued for an additional 10 min. The acetone was evaporated to dryness; the residue was taken up in EtOAc and washed with aqueous solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. After removal of the solvent, distillation of the residue gave 12.0 g (92%) of a colourless oil; b.p. 43 - 45°C (0.4 mm Hg); $[\alpha]_D$ +17.4° (*c* 1.68 $CHCl_3$); δ_H 1.36 and 1.42 ppm (6H, 2 x s, $C(CH_3)_2$), 2.53 (1H, dd, *J* 7 and 14 Hz, CH^aCO), 2.73 (1H, dd, *J* 6 and 16 Hz, CH^bCO), 3.66 (1H, dd, *J* 6.3 and 10 Hz, $CHCH^aOCC$), 3.70 (3H, s, OCH_3), 4.16 (1H, dd, *J* 8.3 and 6 Hz, $CHCH^bOCC$) and 4.14 - 4.54 (1H, m, CH_2CHCH_2); δ_C 25.5 and 26.9 ppm (2 x q, $C(CH_3)_2$), 38.8 (t, CH_2COO), 52.0 (q, OCH_3), 69.3 (t, $CHCH_2O$), 72.3 (d, CH_2CHO) 171.1 (s, quarternary C). *m/z(EI)* (%) 131 (100), 101 (14), 85 (14), 71 (78), 59 (18) and 43 (41)

(S)-1,2-O-Isopropylidenebutane-1,2,4-triol **(116)**



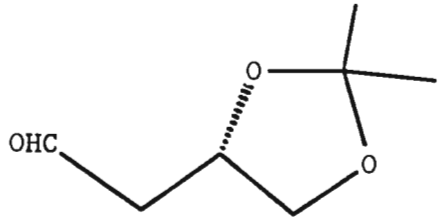
MF $C_7H_{14}O_3$

MW 146

116

(*S*)-1,2,4-Butanetriol (9 g, 0.085 mol) was stirred in acetone (500 ml) with *p*-toluenesulphonic acid at room temparature for 1.5 h, $NaHCO_3$ was suspended in the solution, and the stirring was continued for an additional 10 min. The acetone was evaporated to dryness; the residue was taken up in EtOAc and washed with aqueous solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. After removal of the solvent , distillation of the residue gave 11.6 g (93%) of a colourless oil; b.p. 50°C (5 mm Hg) [lit.,[161] b.p. 87 °C (22 mm Hg)]; $[\alpha]_D^{24}$+10.87° (*c* 1.39 $CHCl_3$); δ_H 1.37 and 1.43 ppm (6H, 2 x s, $C(CH_3)_2$), 1.78 - 1.87 (2H, m, CH_2CH_2OH), 2.68 (1H, br s, OH), 3.59 (1H, dd, *J* 7.3 and 8 Hz, $CHCH^aO$), 3.78 (2H, m, CH_2OH), 4.10 (1H, dd, *J* 8 and 6 Hz, $CHCH^bO$) and 4.13 - 4.31 (1H, m, CH_2CHCH_2); δ_C 25.7 and 26.9 ppm (2 x q, $C(CH_3)_2$), 35.7 (t, CH_2CH_2OH), 60.3 (t, CH_2OH), 69.5 (t, $CHCH_2O$), 74.9 (d, CH_2CHCH_2) and 109.0 (s, CCH_3).

(S)-O-Isopropylidenebutane-3,4-diol-1-al **(117)**



MF $C_7H_{12}O_3$

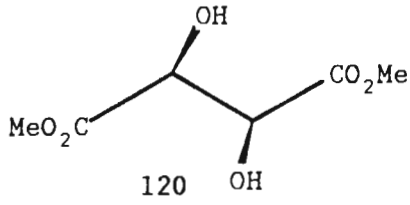
MW 146

117

Swern oxidation of **116** (3 g, 0.021 mol), as described in GP 3, afforded **117** (1.87 g, 61%); b.p. 27°C (0.4 mm Hg); $[\alpha]_D$+15.0° (*c* 2.226 $CHCl_3$); δ_H 1.36 and 1.42 ppm (6H, 2 x s,

C(CH_3)$_2$), 2.62 -2.91 (2H, 2 x d, all spectral lines are doubled, CH_2CHO), 3.59 (1H, dd, *J* 6.7 and 8 Hz, CHCH^aO), 4.18 (1H, dd, *J* 8.3 and 6.8 Hz, CHCH^bO), 4.47 - 4.60 (1H, m, CH_2CHCH_2) and 9.80 (1H, t, *J* 1.6 Hz, CHO); δ_C 25.5 and 26.8 ppm (2 x q, C(CH_3)$_2$), 47.8 (t, CH_2CHO), 69.1 (t, CHCH_2O), 70.7 (d, CH_2CHCH_2), 109.2 (s, C(CH_3)$_2$) and 200.0 (CHO); *m/z (EI)* (%) 129 (70), 101 (7), 85 (12), 72(13) and 69 (100).

(S,S)-Dimethyl tartrate **(120)**



120

MF $C_6H_{10}O_6$

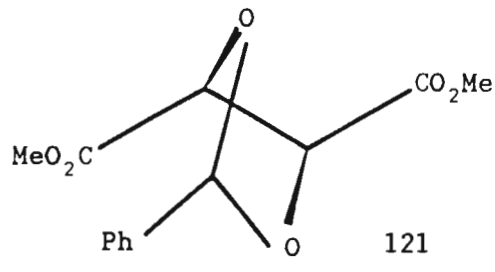
MW 178

Prepared as outlined in GP 4. Thus, esterification of tartaric acid (100 g, 0.562 mol) afforded dimethyl tartrate **(120)** (118.0 g, 100%), δ_H 3.83 ppm (2H, br. s, exchanges with D_2O, 2 x OH), 3.83 (6H, s, 2 x OCH_3) and 4.59 (2H, s, 2 x *CH*OH); δ_C 53.06 (q, OCH_3), 72.27 (d, CHOH) and 172.05 (s, CO_2Me); *m/z(EI)* (%) 179 (M^++1, 2), 147 (1), 119 (29) and 90 (100)

Dimethyl (2S,3S)-O-benzylidenebutyrate **(121)**

MF $C_{13}H_{14}O_6$

MW 266

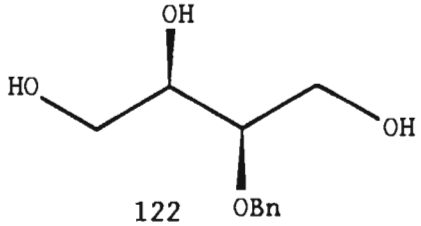


121

A mixture of dimethyl tartrate (111.17 g, 0.62 mol), benzaldehyde (52.8 g, 0.50 mol) and a catalytic amount of *p*-TsOH in C_6H_6 was refluxed overnight with the removal of

water (Dean and Stark). $[\alpha]_D^{24}$+26.8°(*c* 1.786); m.p. 65 -66 δ_H 3.72 ppm (3H, s, CO_2CH_3), 3.75 (3H, s, $COCH_3$), 4.84 (1H, d, *J* 3.9 Hz, CHOC), 4.97 (1H, d, *J* 3.9 Hz, CHOC), 6.12 (1H, s, *CH*Ph) and 7.34 - 7.59 (5H, m, Ar *CH*'s); δ_C 52.74 (q, OCH_3), 77.09 and 77.44 (2 x d, 2 x *CH*CO_2Me), 106.64 (d, *CH*Ph), 127.27, 128.36 and 129.98 (3 x d, Ar *CH*'s), 169.58 and 170.02 (2 x s, 2 x CO_2CH_3); *m/z(EI)* (%) 265 (M^+-1, 1), 207 (13), 145 (9), 105 (100), 91 (56) and 77 (26).

(2S,3S)-2-Benzyloxy-1,3,4-butane-triol **(122)**



122

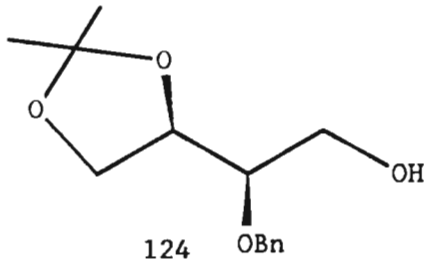
MF $C_{11}H_{16}O_4$

MW 212

$LiAlH_4$ (30.4 g, 800 mmol) was suspended in dry ether (600 ml) at -40°C under nitrogen. To the stirred mixture was added dropwise a solution of $AlCl_3$ (106.7 g, 800 mmol) in ether (360 ml) at -5 to -10°C. After the addition of CH_2Cl_2(100 ml), a solution of dimethyl 2,3-benzylidenebutyrate (53.2 g, 0.2 mol) in CH_2Cl_2 (600 ml) was added dropwise during 45 min. to the ice cooled reaction mixture. After stirring for 1 h at room temperature the reaction mixture was refluxed for 3 h. The reaction mixture was quenched cautiously with H_2O (57.5 ml) and a solution of KOH (134 g) in water (224 ml) at -20°C. The acetone-dry ice bath was removed and the reaction mixture was stirred for a further period of 2 h at 30°C, until the colour of the reaction mixture is white. After filtration over celite, the filter cake was suspended in CH_2Cl_2 (500 ml), refluxed for 45 min. and filtered again. The combined filtrates were concentrated *in vacuo* to give **122** (27 g, 64%) as white crystals. The yield was improved to about 90% by washing the

filter cake with CH_2Cl_2(200 ml) in a Soxhlet over 3 days . Recrystallisation from CH_2Cl_2 give an analytically pure sample , m.p. 74 - 75 °C (lit.,[164] 75.5 -76.5 °C); $[\alpha]_D$ -13.5° (*c* 1.147 EtOH); (Found C, 61.70, H, 7.98. $C_{11}H_{16}O_4$ requires C, 61.89, H, 8.09); δ_H (CD_3COCD_3) 3.57 ppm (9H, m, 2 x *CH*$_2$OH, *CH*OH, *CH*OBn and 3 x OH), 4.69 (2H, 2 x pseudo d, *CH*$_2$Ph), and 7.26 - 7.43 (5H, m, Ar *CH*'s); δ_C 62.1 ppm (t, CH_2OH), 64.1 (t, CH_2OH), 73.4 (t, O*CH*$_2$Ph), 73.4 (d, *CH*OBn), 81.57 (d, CHOH), 128.6, 128.9 and 129.5 (d, Ar *CH*'s) and 140.1 (s, Ar quarternary C); *m/z(EI)* (%) 212 (M^+, 4%), 181 (4), 91 (100) and 65 (9).

3-O-Benzyl-1,2-O-isopropylidenebutane-1,2,3,4-tetrol **(124)**



124

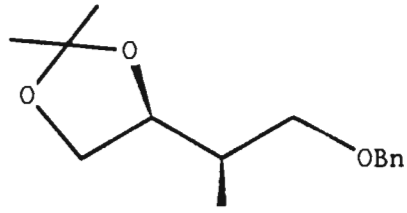
MF $C_{14}H_{20}O_4$

MW 252

A mixture of 2-benzyloxy-1,2,4-butane-triol (3.0 g, 0.014 mol) and dimethoxy propane (3.68 g, 0.035 mol) in acetone (100 ml) was stirred with *p*-toluenesulphonic acid at room temparature for 1.5 h, $NaHCO_3$ was suspended in the solution, and the stirring was continued for an additional 10 min. The acetone was evaporated to dryness; the residue was taken up in EtOAc and washed with aqueous solutions of $NaHCO_3$ and NaCl and dried over $MgSO_4$. After removal of the solvent, **124** 3.5 g (98%) was obtained as a colourless oil; [Found C, 66.69, H, 7.47. $C_{14}H_{20}O_4$ requires C, 66.65, H, 7.99]; $[\alpha]_D^{21}$ +15.5° (*c* 1.713 $CHCl_3$); δ_H 1.34 ppm (3H, s, C*CH*$_3$), 1.41 (3H, s, C*CH*$_3$), 2.89 (1H, br s, *OH*), 3.44 - 3.67 (3H, m, *CH*$_2$OH and *CH*OBn), 3.73 (1H, dd, *J* 8.0 and 7.2 Hz, *CH*^{a}OCCH$_3$), 3.95 (1H, dd, *J* 8.0 and 6.6 Hz, *CH*^{b}OCCH$_3$), 4.21 - 4.30 (1H, m, *CH*OCCH$_3$), 4.69 (2H, 2 x pseudo d, *J* 11.9 Hz, O*CH*$_2$Ph) and 7.22 - 7.36 (5H, m, Ar *CH*'s); δ_C 25.3 and 26.4 ppm (2 x q, 2

x CH_3), 61.8 (t, CH_2OH), 65.8 (t, CH_2OCCH_3), 72.9 (t, CH_2OBn), 76.8 (d, $CHOBn$), 79.7 (d, $CHOCCH_3$), 109.2 (s, $C(CH_3)_2$), 127.7, 127.8 and 128.3 (d, Ar CH's) and 138.3 (s, Ar quaternary C); *m/z*(EI) (%) 253 (M^+-1, 0.4%), 227 (3), 194 (12), 163 (3), 101 (69) and 91 (100).

3,4-Di-O-benzyl-1,2 O-isopropylidenebutane-1,2,3,4-diol **(125)**



125

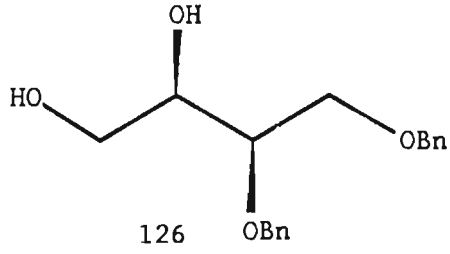
MF $C_{21}H_{26}O_4$

MW 342

To a mechanically stirred suspension of NaH (1.1 g, 0.048 mol; previously washed three times with THF) in dry DMF (50 ml) was added dropwise a solution of **124** (4.93 g, 0.019 mol) in DMF (15 ml). The reaction was stirred for 10 min. and then BnBr (3.34 g, 0.019 mol) was added dropwise. Excess NaH was decomposed by addition of water. The product was extracted with $CHCl_3$ and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 6.1 g (91%) of a light yellow oil (pure by NMR). An analytical sample of **125** was obtained by chromatography eluting with hexane-EtOAc (9:1): [Found C, 73.48, H, 7.55. $C_{21}H_{26}O_4$ requires C, 73.66, H, 7.65]; $[\alpha]_D^{20.8}$ +2.4° (*c* 1.796 EtOH); δ_H 1.35 ppm (3H, s, $OCCH_3$), 1.39 (3H, s, $OCCH_3$), 3.56 - 3.63 (3H, m, CH_2OBn and $CHOBn$), 3.74 (1H, dd, *J* 7.4/8 Hz, CH^aOCCH_3), 3.97 (1H, dd, *J* 6.5/10 Hz, CH^bOCCH_3), 4.24 -4.27 (1H, m, $CHOCCH_3$), 4.49 (2H, 2 x pseudo d, CH_2OCH_2Ph), 4.74 (2H, 2 x pseudo d, $CHOCH_2Ph$) and 1.23 - 7.37 (10H, m, Ar CH's); δ_C 25.4 and 26.4 ppm (2 x q, 2 x CH_3), 65.8 (t, CH_2OCCH_3), 70.2 (t, CH_2OBn), 72.8 (t, OCH_2Ph), 73.4 (t, OCH_2Ph-terminal), 76.8 (d, $CHOBn$), 78.2 (d, $CHOCCH_3$), 109.0 (s, $C(CH_3)_2$), 127.5, 127.6, 127.7, 127.8, 128.2 and 128.3 (10 x d, Ar CH's), 137.96 and 138.5

(2 x s, Ar quarternary C's); *m/z(EI)* (%) 344 (M^+, 2), 284 (2), 251 (13), 193 (38) and 91 (100).

1,2-Di-O-benzylbutane-1,2,3,4-tetrol **126**



126

MF $C_{18}H_{22}O_4$

MW 302

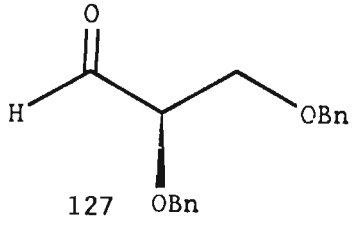
Compound **125** (7 g, 0.02 mol) was dissolved in 95% EtOH (40 ml) to which water (5 ml), concentrated HCl (0.2 ml) and acid activated Amberlite CG-120 resin (6 g) were added. The reaction was stirred at room temperature and was monitored by tlc until the disappearance of **125**. After filtration of the resin, the remaining acid was neutralised with a saturated solution of $NaHCO_3$. The reaction mixture was concentrated, the product was extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 6.14 g (87%) of **126**. Analytically pure **126** was obtained by silica gel column chromatography using hexane-EtOAc (9:1) and then absolute EtOH as eluant. The product was isolated in the EtOH fraction: [Found C, 71.48, H, 7.40. $C_{18}H_{22}O_4$ requires C, 71.51, H, 7.33]; $[\alpha]_D^{22.8}$-31.3° (*c* 1.977 $CHCl_3$) δ_H 2.80 ppm (1H, br s, *OH*), 3.08 (1H, br. s, *OH*), 3.60 - 3.70 (5H, m, *CH*$_2$OH, *CH*$_2$OBn and *CH*OBn), 3.76 - 3.77 (1H, m, *CH*OH), 4.52 (2H, 2 x pseudo d, O*CH*$_2$Ph terminal), 4.62 (2H, 2 x pseudo d, O*CH*$_2$Ph) and 7.22 - 7.35 (10H, m, Ar *CH*'s); δ_C 63.5 ppm (t, *CH*$_2$OH), 69.4 (t, *CH*$_2$OPh), 72.0 (d, *CH*OH), 72.7 (t, O*CH*$_2$Ph), 73.5 (t, O*CH*$_2$Ph terminal), 78.2 (d, *CH*OBn), 127.7, 127.8, 127.9, 128.0 and 128.4 (10 x d, Ar *CH*'s), 137.7 and 137.9 (2 x s, Ar quarternary C's); *m/z(EI)* (%) 267 (1), 212 (6), 181 (5),107 (56), 91 (100) and 65 (20).

General Procedure 5

Oxidative Cleavage of 1,2-diols

1,2-Di-O-benzylbutane-1,2,3,4-tetrol (2.77 g, 9.17 mmol) was dissolved in CH_2Cl_2 (25 ml) and the flask was placed in a water bath at 25°C. $NaIO_4$ (3.83 g, 18.3 mmol)was added with vigorous mechanical stirring, followed by distilled water (1 ml). The reaction temperature gradually rose to about 30°C and the stirring was continued until the reaction was judged to be complete by tlc. Powdered anhydrous $MgSO_4$ (3 g) was added and stirring contintued for 15 min. The reaction mixture was filtered and the cake washed with CH_2Cl_2 (2 x 10 ml). Evaporation of the solvent gave the corresponding aldehyde.

(R)-1,2-Di-O-benzylglyceraldehyde **(127)**



127

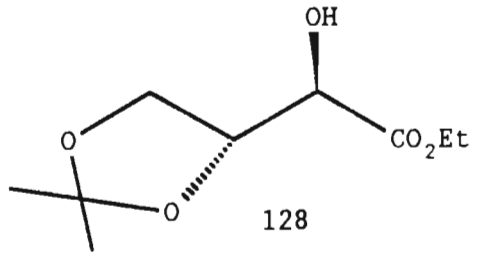
MF $C_{17}H_{18}O_3$

MW 270

Prepared as in GP 5. Thus evaporation of the solvent gave 1.84 g (75%) of **127**: [Found C, 75.61, H, 6.74. $C_{17}H_{18}O_3$ requires C, 75.51, H, 6.71]; $[\alpha]_D$ +20° (*c* 2.173 $CHCl_3$) (lit.,[169] +52° (*c* 2.0 C_6H_6); δ_H 3.74 - 3.77 ppm (2H, m, CH_2OBn), 3.94 - 3.99 (1H, m, *CH*OBn), 4.53 (2H, 2 x pseudo d, OCH_2Ph terminal), 4.69 (2H, 2 x pseudo d, OCH_2Ph), 7.21 - 7.36 (10H, m, Ar *CH*'s) and 9.70 (1H, d, *J* 1.2 Hz, *CH*O); δ_C 69.1 ppm (t, CH_2OBn), 72.7 (t, OCH_2Ph), 73.4 (t, OCH_2Ph terminal), 82.6 (d, *CH*OCH_2Ph), 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.5 and 128.6 (10 x d, Ar *CH*'s), 137.1 and 137.5 (2 x s, Ar quarternary C's) and 202.1 (d,

CHO); *m/z(EI)* (%) 242 (M^+-28, 1), 181 (4), 179 (5), 164 (2), 146 (20), 107 (1), 91 (100) and 65 (17).

Ethyl (2R,3R)-3,4-o-isopropylidene-2,3,4-trihydroxybutanoate **(128)**



128

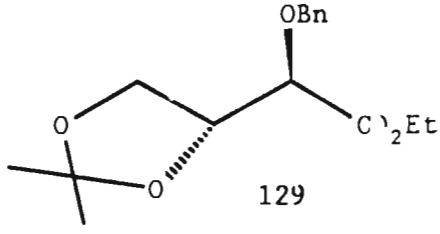
MF $C_9H_{16}O_5$

MW 204

A mechanically stirred solution of D-isoascorbic acid (200 g, 1.14 mol) in acetone (4.5 L) was treated with anhydrous $CuSO_4$ (300 g). After the reaction was stirred at room temperature for 24 h, a second portion of $CuSO_4$ (300) was added, and stirring was continued for an additional 24 h. The reaction was then filtered and concentrated, giving a near-quantitative yield of 3,4-*O*-isopropylidene-D-isoascorbic acid. The isopropylidene derivative was then dissolved in water (1.2 L) containing K_2CO_3 (312 g). This solution was chilled in an ice bath and stirred while 30% H_2O_2 (249 ml) was slowly added. During the addition the temperature was maintained below 20°C. The solution was stirred over night and then concentrated *in vacuo*. The moist solute was extracted with boiling absolute ethanol (6 x 500 ml). After filtration and evaporation, the salt was dried under vacuum to provide 230 g of material. Treatment of a mechanically stirred suspension of the salt with EtI (241 g) in CH_3CN (1.5 l) at reflux for 24 h gave, after concentration and removal of the inorganic salt, 200 g of the crude ester. Distillation under reduced pressure gave pure **128**: Yield 184.7 g (79%); $[\alpha]_D$ +18.3°C (*c* 1.597 MeOH); δ_H 1.32 ppm (3H, t, *J* 7.2 Hz, CH_3CH_2), 1.36 and 1.43 (6H, 2 x s, $C(CH_3)_2$), 3.31 (1H, d, *J* 7.8 Hz, OH), 3.97 - 4.44 (6H, m, CH_2CH_3, CHOH, CH_2CHCH, $CHCH_2O$); δ_C 13.9 ppm (q, CH_3CH_2), 25.1, 25.9 (2 x q, $C(CH_3)_2$), 61.8 (t, CH_3CH_2), 65.5(t, $CHCH_2O$), 70.3 (d, CHOH), 76.4 (d, $CHOCCH_3$), 109.9 (s,

$C(CH_3)_2$) and 172.4 (s, C=O).

Ethyl (2R,3R)-2-O-benzyl-3-4-isopropylidenebutyrate **(129)**



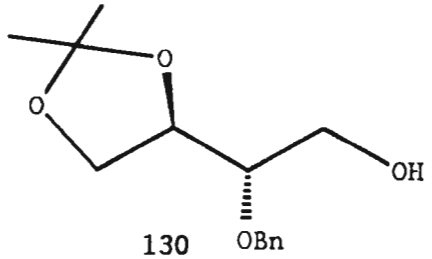
129

MF $C_{16}H_{22}O_5$

MW 294

Prepared as in GP1. Thus **129** was produced in 80% (26 g) yield. (**128** is the only substrate that gave nearly complete conversion to the benzyl ether). $[\alpha]_D^{25}$+51.7 (*c* 1.460); δ_H 1.28 ppm (3H, t, *J* 7 Hz, CH_3CH_2), 1.34 and 1.39 (6H, 2 x s, $C(CH_3)_2$), 3.91 - 4.04 (3H, m, CH_2CHCH, CH_2CHCH), 4.21 (2H, q, *J* 7 Hz, CH_2CH_3), 4.35 - 4.44 (1H, m, *CH*OBn), 4.64 (2H, 2 x pseudo d, OCH_2Ph) and 7.23 - 7.39 (5H, m, AR *H's*); δ_C 14.3 (q, CH_3CH_2), 25.4 and 26.3 (2 x q, $C(CH_3)_2$), 61.3 (t, CH_3CH_2O), 65.6 (t, $CHCH_2O$), 72.9 (t, OCH_2Ph), 76.1 (d, *CH*$OCCH_3$), 78.7 (d, *CH*OBn), 110 (s, CCH_3), 128.3, 128.5 and 128.8 (d, Ar *CH's*), 137 (s, Ar quarternary C) and 170.5 (s, C=O).

3-O-Benzyl-1,2-O-isopropylidenebutane-1,2,3,4-tetrol **(130)**



130

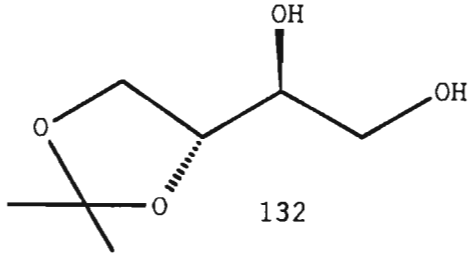
MF $C_{14}H_{20}O_4$

MW 252

Prepared in 92% yield from $LiAlH_4$ reduction of **129** following general procedure 2; δ_H 1.35 ppm (3H, s, CCH_3), 1.42 (3H, s, CCH_3), 2.77 (1H, br s, *OH*), 3.47 - 3.72 (3H, m, CH_2OH and *CH*OBn), 3.73 (1H, dd, *J* 8.0 and 7.2 Hz, CH^aOCCH_3), 3.95 (1H,

dd, *J* 8.0 and 6.6 Hz, CH^bOCCH_3), 4.21 - 4.30 (1H, m, $CHOCCH_3$), 4.69 (2H, 2 x pseudo d, *J* 11.9 Hz, OCH_2Ph) and 7.24 - 7.38 (5H, m, Ar *CH*'s); δ_C 25.4 and 26.4 ppm (2 x q, 2 x CH_3), 61.8 (t, CH_2OH), 65.8 (t, CH_2OCCH_3), 72.9 (t, CH_2OBn), 76.8 (d, *CH*OBn), 79.6 (d, $CHOCCH_3$), 109.7 (s, $C(CH_3)_2$), 128.2, 128.3 and 128.8 (d, Ar *CH*'s) and 138.6 (s, Ar quarternary C); *m/z*(EI) (%) 253 (M^+-1, 0.4%), 227 (3), 194 (12), 163 (3), 101 (69) and 91 (100).

(2R,3S)-1,2-O-isopropylidenebutane-1,2,3,4-tetrol **(132)**



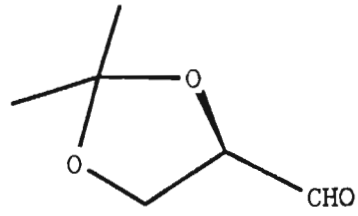
132

MF $C_7H_{14}O_4$

MW 162

Prepared by $LiAlH_4$ reduction (GP1) in 94% yield. Purified by chromatography (EtOAc:Hex 2:8); $[\alpha]_D^{25}$+3.89° (*c* 4.81 EtOH) [Lit.,[166] +7.82° (*c* 4.18 EtOH)]; δ_H 1.37 and 1.44 ppm (6H, 2 x s, $C(CH_3)_2$), 3.61 - 3.69 (3H, m, CH_2OC and OH, exchanges with D_2O), 3.75 - 3.79 (3H, m, CH_2OH and OH), 4.01 - 4.08 (1H, m, *CH*OC) and 4.11 - 4.20 (1H, m, CHOH); δ_C 25.3 and 26.4 (2 x q, $C(CH_3)_2$), 63.8 (t, CH_2OC), 65.7 (t, CH_2OH), 72.3 (d, *CH*OC), 76.5 (d, CHOH) and 109.5 (s, $C(CH_3)_2$; *m/z(EI)* (%) 147 (47), 132 (M^+-31, 0.6), 101 (100), 87 (27) and 60 (25).

(S)-2,3-O-Isopropylideneglyceraldehyde **(133)**



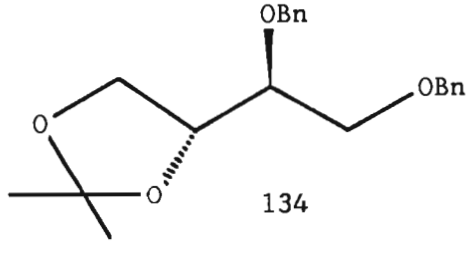
MF $C_6H_{10}O_3$

MW 130

133

Prepared according to GP5. Thus, **132** (1.36 g, 10.3 mmol) was oxidised to give **133** ; b.p. 55 - 58°C/20 mm Hg (Lit.,[43] 60 - 62°C/20 mm Hg); $[\alpha]_D^{25}$+36° (*c* 1.734 C_6H_6) [Lit.,[168] $[\alpha]_D$+64.9° (*c* 8.28 C_6H_6); δ_H 1.40 and 1.47 (6H, 2 x s, $C(CH_3)_2$), 3.93 4.23 (2H, m, $CHCH_2$), 4.33 (1H, m, CH_2CH), 9.57 (1H, d, CHO), δ_C 25.2 and 26.3 (2 x q, $C(CH_3)_2$), 65.5 (t, CH_2CH), 79.9 (d, $CHCH_2$), 111.2 (s, $OCCH_3$) and 201.7 (d, CHO); *m/z (EI)* (%) 130 (M^+, 0.2), 115 (85), 101 (100), 86 (2), 85 (35).

(2R,3S)-3,4-Di-O-isopropylidenebutane-1,2,3,4-tetrol **(134)**



MF $C_{21}H_{26}O_4$

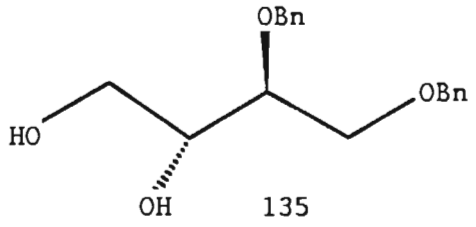
MW 342

134

Prepared following the same procedure as for **127**. Thus, **132** (2 g, 0.012 mol) gave **134** (3.77, 92%) as a light yellow oil after chromatography. $[\alpha]_D^{25}$-1.89° (*c* 1.76 EtOH); δ_H 1.34 and 1.38 ppm (6H, 2 x s, $C(CH_3)_2$), 3.54 - 3.64 (3H, m, CH_2OBn overlaps with *CH*OBn), 3.73 (1H, dd, *J* 7.3 and 8 Hz, CH^aOC), 3.93 (1H, dd, *J* 6.5 and 8 Hz, CH^bOC), 4.19 - 4.29 (1H, m, CHOC), 4.47 (2H, 2 x pseudo d, CH_2OCH_2Ph), 4.72 (2H, 2 x pseudo d, $CHOCH_2Ph$) and 7.17 - 7.37 (10H, m, Ar *H's*); δ_C 25.5 and 26.4 ppm (2 x q, $C(CH_3)_2$), 65.8 (t, CH_2CO), 72.8 (t, $CHOCH_2Ph$), 73.4 (t, CH_2OCH_2Ph), 76.8 (d, *CH*OBn), 78.2

(d, *CH*CO), 109.0 (s, $C(CH_3)_2$, 127.5, 127.6, 127.8, 128.2 and 128.3 (5 x d, Ar *CH*'s), 138.5 and 137.9 (5 x s, Ar quarternary C); *m/z(EI)* (%) 342 (0.06), 327 (0.2), 251 (4), 160 (6), 115 (3), 107 (19), 101 (52) and 91 (100).

(2S,3R)-1,2-O-Dibenzylbutane-1,2,3,4-triol **(135)**



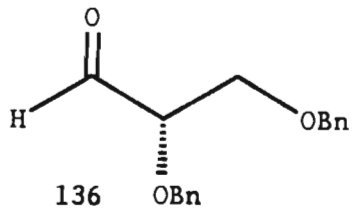
135

MF $C_{18}H_{22}O_4$

MW 302

Removal of the isopropylidene group was carried out using HCl and Amberlite CG 120 as describe in the preparation of **126** to afford **135** (85%); δ_H 1.26 ppm (1H, br s, D_2O exchangeable OH), 3.09 (1H, br s, D_2O exchangeable OH), 3.53 - 3.58 (5H, m, CH_2OH and CH_2OBn overlap with *CH*OBn), 3.61 - 3.73 (1H, m, *CH*OH), 4.45 (2H, s, CH_2OCH_2Ph), 4.56 (2H, 2 x pseudo d, $CHOCH_2Ph$) and 7.16 - 7.29 (10H, m, Ar *CH*'s); δ_C 62.9 and 68.9(2 x t, CH_2OH and CH_2CBn), 72.2 and 73.0 (2 x t, CH_2OCH_2Ph and $CHOCH_2Ph$), 71.5 and 77.6 (2 x d, *CH*OH and *CH*OBn), 127.3 127.4, 127.5, 127.6 and 128.1 (5 x d, Ar *CH*'s) and 137.7 and 137.9 (2 x s, Ar quarternary C's); *m/z(EI)* (%) 267 (0.08), 211 (5), 105 (6), 91 (100), 77 (4), 65 (11).

(S)-1,2-Di-O-benzylglyceraldehyde **(136)**



136

MF $C_{17}H_{18}O_3$

MW 270

Prepared by oxidative cleavage of **135** (1 g, 3.31 mmol) following GP5 to give 0.58 g of **136** (65%). Chromatography

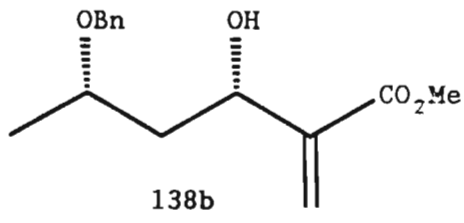
using hexane:ethyl acetate as eluant (9:1) gave pure **136** (61%). [Found C, 75.52, H, 6.71. $C_{17}H_{18}O_3$ requires C, 75.54, H, 6.71]; $[\alpha]_D^{26}$-9.8° (*c* 2.0 $CHCl_3$); δ_H 3.71 ppm (2H, d, *J* 1.3 Hz, $CHCH_2$), 3.90 - 3.95 (1H, m, $CHOCH_2$), 4.49 (2H, s, CH_2OCH_2Ph), 4.66 (2H, 2 pseudo d, $CHOCH_2Ph$), 7.23 - 7.35 (10H, m, Ar *CH* 's) and 9.66 (1H, d, *J* 1.1, CHO), δ_C 69.0 (t, $CHCH_2$), 72.6 (t, CH_2OCH_2Ph), 73.5 (t, $CHOCH_2Ph$), 82.6 (d, $CHOCH_2$), 127.6, 127.7, 127.8, 127.9 and 128.0 (5 x d, Ar *CH*'s), 137.2 and 137.5 (2 x s, Ar quarternary C's) and 202.0 (d, CHO); *m/z(EI)* (%) 242 (0.04), 193 (2), 179 (9), 107 (6), 91 (100), 77 (15), 65 (33).

General Procedure 6

The coupling of aldehydes with methyl acrylate

The aldehyde (1 equivalent) was added to a solution of DABCO (0.1 equivalent) in an excess of methyl acrylate. The mixture was allowed to stir until ^{1}H NMR indicated complete consumption of the aldehyde. The mixture was taken up in CH_2Cl_2, washed successively with dilute HCl, 5% $NaHCO_3$ and brine. The CH_2Cl_2 solution was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a mixture of diastereomers.

Methyl 5-benzyloxy-3-hydroxy-2-methylenehexanoate **(138b)**



138b

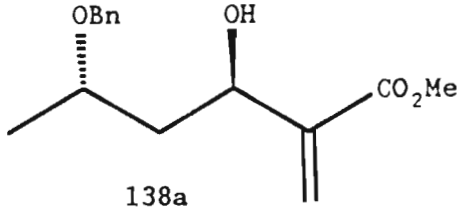
MF $C_{15}H_{20}O_4$

MW 264

(Prepared as in GP6). Yield of the diastereomeric mixture 68%; $[\alpha]_D$ +22.87° (*c* 1.29 $CHCl_3$).

The mixture was separated partially by chromatography to give the major diastereomer of **138b** ; $[\alpha]_D$ = +35,10 (c 1.56 $CHCl_3$); (Found: C, 68.1; H 7.6. $C_{15}H_{20}O_4$ requires C, 68.2, H 7.6); δ_H 1.22 ppm (3H, d, *J* 6 Hz, $CHCH_3$), 1.63 - 1.92 (2H, m, $CHCH_2CH$), 3.69 (3H, s, OCH_3), 3.81 -3.95 (1H, m, $CHCH_3$), 3.94 (1H, s, *OH*), 4.39 and 4.61 (2H, 2 pseudo d, OCH_2Ph), 4.68 (1H, t, *J* 1.3, CH_2CHOH), 5.94 and 6.23 (2H, 2 x m, CH_2=C) and 7.24 - 7.33 (5H, m, Ar *H*'s); δ_C 19.56 ppm ($CHCH_3$), 43.91 ($OCHCH_2CH$), 51.78 (OCH_3), 70.08 ($CHCH_3$), 70.56 (CH_2Ph), 75.75 (CH_2CHOH), 125.01 (C=CH_2), 128.13, 128.20, 128.86 (Ar *CH*'s), 138.4 (Ar quarternary C's), 142.88 (*C*=CH_2) and 167.03 (C=O); *m/z(EI)* (%) 205 (2) (M^+-CO_2Me), 140 (17), 125 (22), and 91 (100).

The minor diastereomer **138a** was characterised after



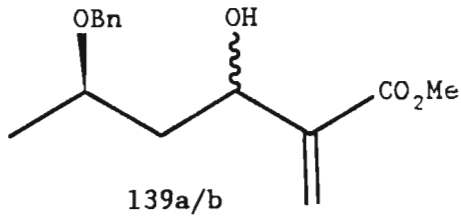
138a

MF $C_{15}H_{20}O_4$

MW 264

cyclisation of the major isomer $[\alpha]_D$+36° (*c* 1.56 $CHCl_3$) ; (Found: 246.1229. $C_{15}H_{18}O_3$ (M^+-18) requires 246.1256); δ_H 1.26 ppm (3H, d, *J* 6.2, $CHCH_3$), 1.83 - 1.90 (2H, m, $CHCH_2CH$), 3.37 (1H, br. s, *OH*), 3.73 (3H, s, OCH_3), 3.71 - 3.88 (1H, m, $CHCH_3$), 4.39 - 4.61 (2H, 2 pseudo d, OCH_2Ph), 4.72 - 4.78 (1H, m, CH_2CHOH), 5.87 and 6.26 (2H, 2 x m, CH_2=C) and 7.23 -7.34 (5H, m, Ar *H*'s); δ_C 19.1 ppm ($CHCH_3$), 41.8 ($CHCH_2CH$), 51.7 (OCH_3), 68.3 (CH_2CHOBn), 70.5 (OCH_2Ph), 72.9 (*CCHOH*), 125.0(C=CH_2), 127.7, 127.8 (Ar *CH*'s), 138.2 (Ar quarternary C), 142.6 (*C*=CH_2) and 166.8 (C=O); *m/z(EI)* (%) 233 (M^+-31), 205 (1), 143 (3), 115 (11), 91 (100) and 83 (17).

Methyl 5-benzyloxy-3-hydroxy-2-methylenehexanoate **(139)**



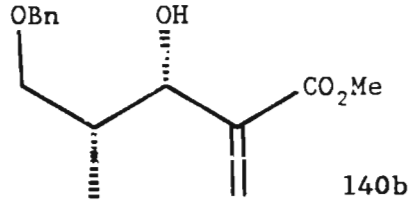
139a/b

MF $C_{15}H_{20}O_4$

MW 264

(Prepared as in GP6). Yield of the diastereomeric mixture 68%; $[\alpha]_D$-31.3° (*c* 1.09 $CHCl_3$). Spectral data were similar to those of **138**. The mixture was not separated.

Methyl (3,4)-syn-5-benzyloxy-3-hydroxy-4-methyl-2-methylene-pentanoate **(140b)**



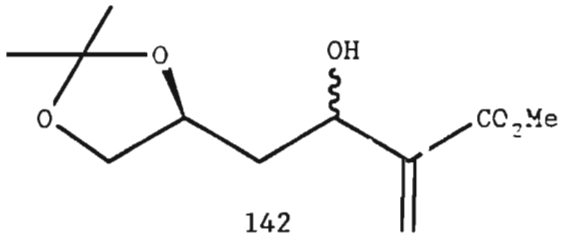
140b

MF $C_{15}H_{20}O_4$

MW 264

(Prepared as in GP6). Yield of diastereomeric mixture 65%; **140b** was characterised after cyclisation; (Found: 264.1364. $C_{15}H_{20}O_4$ requires 264.1362); δ_H 0.90 ppm (3H, d, J 7.2 Hz, $CHCH_3$), 2.17 - 2,37 (1H, m, $CHCH_3$), 3.52 - 3.69 (2H, m, CH_2OBn), 3.73 (3H, s, OCH_3), 4.51 (2H, s, OCH_2Ph), 4.69 - 4.74 (1H, m, *CH*OH), 5.90 and 6.32 (2H, 2 x m, CH_2=C) and 7.26 - 7.38 (5H, m, Ar *H*'s); δ_C 11.6[11.3] ppm ($CHCH_3$), 36.3[36.6] ($CHCH_3$), 52.1[52.0] (OCH_3), 71.4 (CH_2OBn), 71.8 (OCH_2Ph), 72.0 (*CH*OH), 126.0 (CH_2=C), 127.9, 128.0 and 128.1 (Ar *CH*'s), 138.3 (Ar quarternary C) and 162.0 (C=O); *m/z(EI)* (%) 246 (M^+-18, 0.4), 233 (0.1), 205 (3), 187 (1), 155 (1), 125 (13), 115 (18), 91 (100) and 55 (12).
Acrylate **141b** had similar analytical and NMR data.

Methyl 3-hydroxy-5,6-isopropyledene-2-methylenehexanoate **(142)**



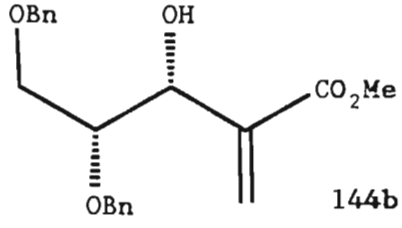
142

MF $C_{11}H_{18}O_5$

MW 230

(Prepared as described in GP6). Yield 65%; (Found 212.1049. $C_{11}H_{16}O_4$(M^+-18) requires 212.1049); $[\alpha]_D^{21}$+11.1° (*c* 1.367 $CHCl_3$); δ_H 1.37 ppm and 1.43 (6H, 2 x s, $C(CH_3)_2$), 1.60 - 1.97 (2H, m, $CHCH_2CH$), 3.77 (3H, s, OCH_3), 3.59 - 3.77 (1H, dd, $CH^aOC(CH_3)_2$ overlaps with OCH_3), 4.11 (1H, dd, *J* 3.7 Hz and 9, $CH^bOC(CH_3)_2$), 4.24 - 4.38 (1H, m, CH_2CHCH_2), 4.67 (1H, m, *CH*OH), 5.94 and 6.30 (2H, AB system, CH_2=C); δ_C 25.8 ppm (CCH_3), 27.0 (CCH_3), 39.2[40.3] ($CHCH_2CH$), 52.0 ($COCH_3$), 68.4 ($CHOC(CH_3)_2$), 69.5 ($CH_2OC(CH_3)_2$), 73.8 (*CH*OH), 108.9[109.4] (s, CCH_3), 125.2[125.5] (CH_2=C), 142.3[1.41.8] (*C*=CH_2) and 166.6 (C=O); *m/z(EI)* (%) 215 (M^+-15, 37), 155 (17), 141 (54), 123 (100), 95 (40), 83 (62) and 59 (29).

Methyl (3,4)-syn-4,5-dibenzyloxy-3-hydroxy-2-methylene-pentenoate **(144b)**



144b

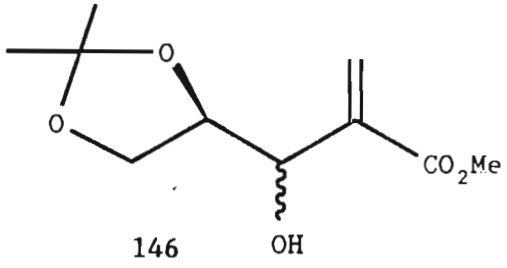
MF $C_{21}H_{24}O_5$

MW 356

(Prepared as described in GP6). Yield 65%; **144b** isolated after cyclisation of the mixture; (Found: M^+ 356.1618. $C_{21}H_{24}O_5$ requires 356.1625); δ_H 3.67 ppm (3H, s, OCH_3), 3.66- 3.78 (1H, m, *CH*OBn), 4.49 and 4.68 (2H, 2

pseudo d, $CHOCH_2Ph$), 4.67 (2H, s, CH_2OCH_2Ph), 4.74 - 4.77 (1H, m, *CH*OH), 5.95 and 6.32 (2H, 2 x m, C=CH_2) and 7.24 - 7.37 (10H, m, Ar *H's*); δ_C 51.9 ppm (OCH_3), 69.7 (CH_2OBn), 71.6 ($CHOCH_2Ph$), 72.3 (OCH_2Ph), 73.6 (OCH_2Ph), 79.4 (*CH*OH), 127.0 (CH_2=C), 128.0, 128.1, 128.2, 128.3, 128.4 and 128.7 (AR *CH's*), 137.9 and 138.1 (Ar quarternary C's), 139.9 (*C*=CH_2) and 166.6 (C=O); *m/z(EI)* (%) 338 (M^+-18, 0.3), 247 (0.9), 217 (4), 181 (16), 159 (5), 115 (2) and 91 (100).

Methyl 3-hydroxy-4,5-isopropylidenedioxy-2-methylenepentanoate **(146)**



146

MF $C_{10}H_{16}O_5$

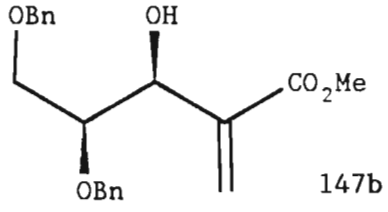
MW 216

Prepared as described in GP6 to give **146** (54%) as a mixture of diastereomers which were separated by chromatography using hexane-ethyl acetate (70:30) as eluant. The major isomer was found to be *anti* **(146a)**: [Found C 55.54, H 7.59. Calculated for $C_{10}H_{16}O_5$ (216.24) C 55.55, H 7.46)], δ_H 1.35 and 1.44 ppm (6H, 2 x s, $C(CH_3)_2$), 3.12 (1H, d, *J* 4.9, OH), 3.79 (3H, s, OCH_3), 3.93 (2H, d, *J* 6.3, $OCHCH_2O$), 4.35 (1H, m, CH_2CHO), 4.55 (1H, m, *CH*OH), 6.01 (1H, t, *J* 1.3, CH^a=C), 6.37 (1H, t, *J* 1.0, CH^b=C); δ_C 25.1 and 26.1 ppm (2 x q, $C(CH_3)_2$), 52.2 (q, OCH_3), 65.3 (t, OCH_2CHO,), 71.2 (d, CHOH), 76.8 (d, OCH_2CHO), 110.1 (s, $C(CH_3)_2$), 127.9 (t, CH_2=C), 138.5 (s, *C*=CH_2), 167.1 (s, C=O).

For the minor isomer **146b**: δ_H 1.36 and 1.46 ppm (2 x s, $C(CH_3)_2$), 2.96 (1H, d, *J* 7.0, OH), 3.79 (3H, s, OCH_3), 3.89 (2H, d, *J* 6.50, OCH_2CHO), 4.01 (1H, m, $OCHCH_2$), 4.50 (1H, m, *CH*OH), 6.00 (1H, t, *J* 1.2, CH^a=C), 6.39 (1H, t, CH^b=C); δ_C 25.2 and 26,5 ppm (2 x s, $C(CH_3)_2$), 52.4 (q, OCH_3), 66.4 (t, OCH_2CHO), 70.9 (d, CHOH), 77.8 (d, $OCHCH_2O$), 110.1 (s,

$C(CH_3)_2$), 127.6 (t, CH_2=C), 139.9 (s, C=CH_2) and 167.0 (s, C=O); *m/z(EI)* (%) 201 M^+-15, 11), 141 (5), 127 (7), 115 (3), 101 (100), 85 (8).

Methyl 4,5-dibenzyloxy-3-hydroxy-2-methylenepentanoate **(147b)**



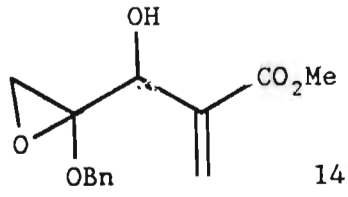
147b

MF $C_{21}H_{24}O_5$

MW 356

(Prepared as described in GP6). Yield 65%; **147b** was characterised after cyclisation. (Found: 338.1504. $C_{21}H_{22}O_4$(M^+-18) requires 338.1508); δ_H 3.20 ppm (1H, br. s, *OH*), 3.62 (3H, s, OCH_3), 6.62 - 3.80 (2H, m, CH_2OPh overlaps with OCH_3), 3.81 - 3.87 (1H, m, *CH*OBn), 4.45 and 4.64 (2H, 2 pseudo d, CHOCH_2Ph), 4.67 (2H, s, OCH_2Ph), 4.73 - 4.76 (1H, m, *CH*OH), 5.93 and 6.29 (2H, 2 x m, CH_2=C) and 7.20 - 7.34 (10H, m, Ar *H*'s); δ_C 51.9 ppm (OCH_3), 69.7 (CH_2OBn), 71.4 (*CH*OBn), 72.3 and 73.6 (2 x OCH_2Ph), 79.3 (*CH*OH), 126.9 (CH_2=*C*), 128.0, 128.1, 128.3 and 128.7 (Ar *CH*'s), 137.9 and 139.3 (Ar quaternary C's), 140.0 (C=CH_2) and 166.6 (C=O); *m/z(EI)* (%) 247 (0.3), 217 (1), 181 (1), 159 (3), 127 (1), 115 (18), 91 (100), 83 (9) and 65 (7).

Methyl 3-benzyloxy-4,5-epoxy-3-hydroxy-2-methylenepentanoate **(143)**



143

MF $C_{14}H_{16}O_5$

MW 264

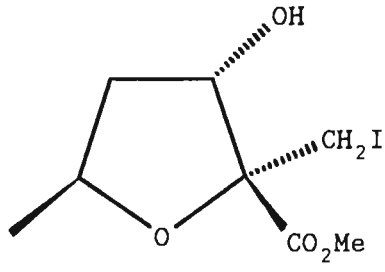
(Prepared as described in GP6). Yield 60%; (found C, 63.4%; H, 6.3. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1); δ_H 3.29 ppm (1H, d, *J* 7.2 Hz, *OH*), 3.73 (3H, s, OCH_3), 4.20 and 4.39 (2H, 2 pseudo d, CH_2O), 4.77 (2H, s, OCH_2Ph), 4.99 (1H, d, *J* 7.1 Hz, *CHOH*), 5.92 and 6.31 (2H, AB system, CH_2=C), and 7.25 -7.35 (5H, m, Ar H's); δ_C 51.9 ppm (OCH_3), 69.6 (OCH_2Ph), 71.7 (*CHOH*), 73.9 (CH_2O) 126.6 (CH_2=C), 128.2, 128.8, 128.9 (Ar *CH*'s), 137.6 Ar quarternary C), 139.7 ($C=CH_2$), 161.1 (*COBn*) and 166.6 (C=O); *m/z(EI)* 189 (0.2%), 143 (4), 133 (1), 115 (11), 91 (100) and 83 (9).

General Procedure 7

Iodoetherification of α-(δ'-benzyloxyalkyl)acrylates

To a solution of the α-methylene-β-hydroxy-δ-benzyloxy esters in anhydrous acetonitrile was added a solution of iodine (2 equiv) in anhydrous acetonitrile. The mixture was stirred at room temperature away from light for *ca.* 12 h. A saturated solution was added and the mixture turned pale yellow. The mixture was extracted with ether (3 times). The combined ether extracts were dried ($MgSO_4$) and concentrated to give a viscous material. The mixture was purified by chromatography to give the tetrahydrofuran derivatives **190 - 194** (Table 4).

Methyl cis,trans-3-hydroxy-2-iodmethyl-5-methyltetrahydrofuran-2-carboxylate **(190)**



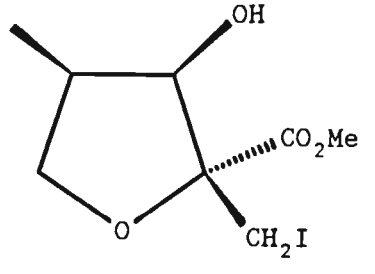
190

MF $C_8H_{13}IO_4$

MW 300

The white powder was recrystallised from CH_2Cl_2/petroleum ether to give colourless needles. Yield 68%; m.p. 91 - 92°C; (Found C, 32.04, H, 4.16. $C_8H_{13}IO_4$ requires C, 32.02; H, 4.37); $[\alpha]_D$+46.18° (*c* 0.94 $CHCl_3$); υ 1149.5 cm^{-1} (C-O-C) and 1746.5 (C=O); δ_H 1.30 ppm (3H, d, *J* 6 Hz, $CHCH_3$), 1.89 (1H, ddd, *J* 5.2, 10.0, and 13.3 Hz, C_4H^aCHMe), 2.18 (1H, ddd, *J* 2.0, 5.4 and 13.2 Hz, C_4H^bCHMe), 2.49 (1H, d, *J* 4.2 Hz, OH), 3.51 (2H, dd, *J* 9.8 and 12.8 Hz, CH_2I), 3.80 (3H, s, OCH_3) and 4.51 (1H, poorly resolved t, CH_2CHOH); δ_C 5.33 ppm (CH_2I), 21.14 ($CHCH_3$), 42.39 (CH_2CHOH), 59.99 (OCH_3), 76.63 ($CHCH_3$), 76.45 (CH_2CHOH), 89.08 ($OCCH_2I$), and 172.64 (C=O); *m/z(EI)* (%) 241 (M^+-CO_2CH_3, 100), 169 (35), 141 (13), and 114 (52),

Methyl cis,cis-3-hydroxy-2-iodomethyl-4-methyltetrahydrofuran-2-carboxylate **(191)**



191

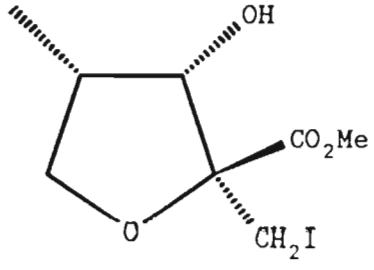
MF $C_8H_{13}IO_4$

MW 300

(For preparation see GP7). Yield 68%; m.p. 114 - 115°

(recrystallised from EtOAc/petroleum ether); (Found C, 32.2; H, 4.5. $C_8H_{13}IO_4$ requires C, 32.0; H, 4.4); υ 1157 cm^{-1}, (C-O-C) and 1738 (C=O); δ_H 1.06 ppm (3H, d, *J* 6.8 Hz, $CHCH_3$),2.02 (1H, br. s, *OH*), 2.45 - 2.53 (1H, m, $CHCH_3$), 3.50 and 3.58 (2H, 2 pseudo d, CH_2I), 3.71 (1H, dd, *J* 7.9 Hz and 12, $COCH^aCHMe$), 3.80 (3H, s, OCH_3), 4.19 (1H, dd, *J* 8.0 Hz and 8.0, $COCH^bCHMe$), and 4.45 (1H, d, *J* 4.5 Hz, *CHOH*), δ_C 5.8 ppm (CH_2I), 10.05 ($CHCH_3$), 38.80 ($CHCH_3$), 53.03 (OCH_3), 74.03 (CH_2OC), 76.7 (*CHOH*), 90.16 ($OCCH_2I$), and 172.59 (C=O); *m/z(EI)* (%) 300 (M^+, 1), 241 (100), 199 (3), 169 (25) and 114 (13).

Methyl cis,cis-3-hydroxy-2-iodomethyl-4-methyltetrahydrofuran-2-carboxylate **(192)**



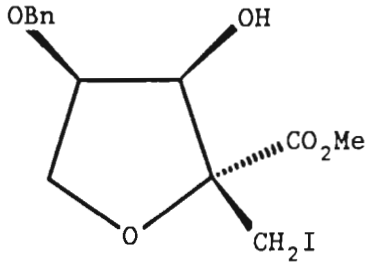
192

MF $C_8H_{13}IO_4$

MW 300

(For preparation see GP7). Yield 70%; m.p. 114-115°C (recrystallised from EtOAc/petroleum ether); (Found C, 32.1; H, 4.4. $C_8H_{13}IO_4$ requires C, 32.0; H, 4.4); υ 1157 cm^{-1} (C-O-C), and 1739 (C=O); δ_H 1.06 ppm ((3H, d, *J* 7 Hz, $CHCH_3$), 2.05 (1H, d, *J* 5.8 Hz, *OH*), 2.43 - 2.54 (1H, m, $CHCH_3$), 3.50 and 3.58 (2H, 2 pseudo d, CH_2I), 3.72 (1H, dd, *J* 8.0 Hz and 10.6, OCH^aCHMe), 3.80 (3H, s, OCH_3), 4.19 (1H, dd, *J* 8.1 and 8.2 Hz, OCH^bCHMe), and 4.45 ((1H, d, *J* 5.8 Hz, *CHOH*); δ_C 5.53 ppm (CH_2I), 10.29 ($CHCH_3$), 38.95 ($CHCH_3$), 53.15 (OCH_3), 74.08 ($CHCH_2O$), 76.47 (*CHOH*),90.16 ($OCCH_2I$) and 172.34 (CO_2CH_3); *m/z(EI)* (%) 199 (6), 169 (52), 141 (18), 114 (69), 103 (95), 71 (100) and 55 (32).

Methyl cis,cis-4-benzyloxy-3-hydroxy-2-iodomethytetrahydrofuran-2-carboxylate **(193)**



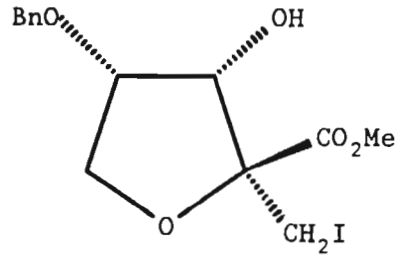
193

MF $C_{14}H_{17}IO_5$

MW 392

For preparation see GP7). Yield 65%; (Found 392.0151. $C_{14}H_{17}IO_5$ requires 392 .0123); υ 3382 cm^{-1}, 1751 (C=O) and 1154 (C-O-C); δ_H 3.10 ppm (1H, br. S, *OH*), 3.46 and 3.65 (2H, pseudo d, *CH*$_2$I), 3.78 (3H, s, O*CH*$_3$), 3.99 (1H, dd, *J* 4.6 and 10 Hz, *CH*^{a}OC), 4.02 - 4.20 (1H, m, *CH*OBn), 4.25 (1H, dd, *J* 4.0 and 5.0 Hz, *CH*^{b}OC), 4.38 - 4.44 (1H, d, *J* 5 Hz, *CH*OH), 4.56 and 4.62 (2H, 2 pseudo d, O*CH*$_2$Ph), and 7.27 - 7.39 (5H, m, Ar *H*'s); δ_C 5.62 ppm (*CH*$_2$I), 53.04 (O*CH*$_3$), 70.08 (CH$_3$CH*CH*$_2$OC), 72.80 (O*CH*$_2$Ph), 74.05 (*CH*OH), 78.49 (*CH*OBn), 87.55 (CH_2OCCH_2I), 128.28, 128.71 and 129.03 (Ar C*H*'s), 136.58 (Ar quarternary C) and 171.73 (C=O); *m/z(EI)* (%) 392 (*M*$^+$, 0.1), 333(1), 265 (0.1), 241 (0.6), 205 (5), 175 (6), 115 (5), 91 (100), 83 (6) and 65 (10).

Methyl cis,cis-4-benzyloxy-3-hydroxy-2-iodomethyltetrahydrofuran-2-carboxylate **(194)**



194

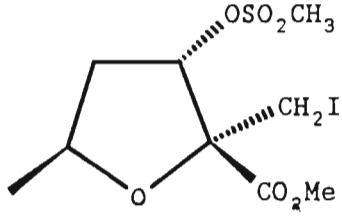
MF $C_{14}H_{17}IO_5$

MW 392

(For preparation see GP7). Yield 67%; m.p. 107-109°C; (Found 392.0145. $C_{14}H_{17}IO_5$ requires 392.0123); υ 3382 cm^{-1},

1751 (C=O), 1279, 1194, and 1154 (C-O-C); δ_H 4.14 ppm (1H, d, *J* 6.4 Hz, *OH*), 3.46 and 3.65 (2H, 2 pseudo d, CH_2I), 3.78 (3H, s, OCH_3), 3.99 (1H, dd, *J* 4.5 and 10.7 Hz, CH^aOC), 4.06 - 4.20 (1H, m, CH_2CHOBn), 4.26 (1H, dd, *J* 4.5 and 6.0 Hz, CH^bOC), 4.38 - 4.44 (1H, dd, *J* 5.2 and 6.0 Hz, *CHOH*), 4.55 and 4.63 (2H, 2 pseudo d, OCH_2PH) and 7.27 and 7.39 (5H, m, Ar *CH's*); δ_C 5.53 ppm (CH_2I), 52.88 (OCH_3), 69.89 (CH_3CHCH_2OC), 72.63 (OCH_2Ph), 73.79 (*CHOH*), 78.27 (*CHOBn*), 87.6 (CH_2OCCH_2I), 127.7, 127.9 and 128.3 (Ar *CH's*), 136.6 (Ar quarternary C) and 171.7 (C=O); *m/z(EI)* (%) 392 (M^+, 0.5), 334(1), 240 (3), 208 (12) and 91 (100).

cis,trans-2-Iodomethyl-2-methoxycarbonyl-5-methylterahydrofu-ranyl methanesulfonate **(199)**



199

MF $C_9H_{15}IO_6S$

MW 378

To a solution of **190** (0.06 g, 0.2 mmol) and triethylamine (0.024 g, 0.24 mmol) in CH_2Cl_2 (10 ml) at 0°C was added mesyl chloride (0.024 g, 0.21 mmol) with continuous stirring. After 30 min had elapsed, water was added and the aqueous phase extracted twice with diethyl ether. The organic extracts were dried with $MgSO_4$ and the ether was evaporated. The residue was subjected to column chromatography (hexane:ethyl acetate 8:2) to afford **199** (0.059 g, 78%) as a colourles oil; [Found 378.1509 required for $C_9H_{15}IO_6S$ 378.1511]; $[\alpha]_D^{23}$+65.6° (*c* 0.564 $CHCl_3$); δ 1.33 ppm (3H, d, *J* 6.1 Hz, CH_3CH), 2.00 (1H, ddd, *J* 4.5, 12 Hz, C_4H^a), 2.55 (1H, m, C_4H^b), 3.18 (3H, s, CH_3SO_2), 3.48 (2H, 2 pseudo d, CH_2I), 3.83 (3H, s, OCH_3), 4.53 (1H, m, $CHCH_3$), 5.52 (1H, d, *J* 3.6 Hz, CHOS); δ_C 3.15 ppm (t, CH_2I),

20.8 (q, *C*H_3CH), 38.9 (q, SCH_3), 41.4 (t, CH*C*H_2CH), 53.4 (q, OCH_3), 76.7 and 83.1 (2 x d, *C*HCH_3 and *C*HCH), and 170.0 (s, *C*OCH); *m/z (EI)* (%) 378 (0.6), 319 (38), 223 (100), 169 (67), 141 (25), 96 (72), and 79 (68).

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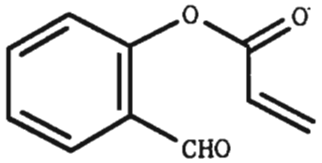
APPENDIX

Selected ^{1}H and ^{13}C nuclear magnetic resonance spectra



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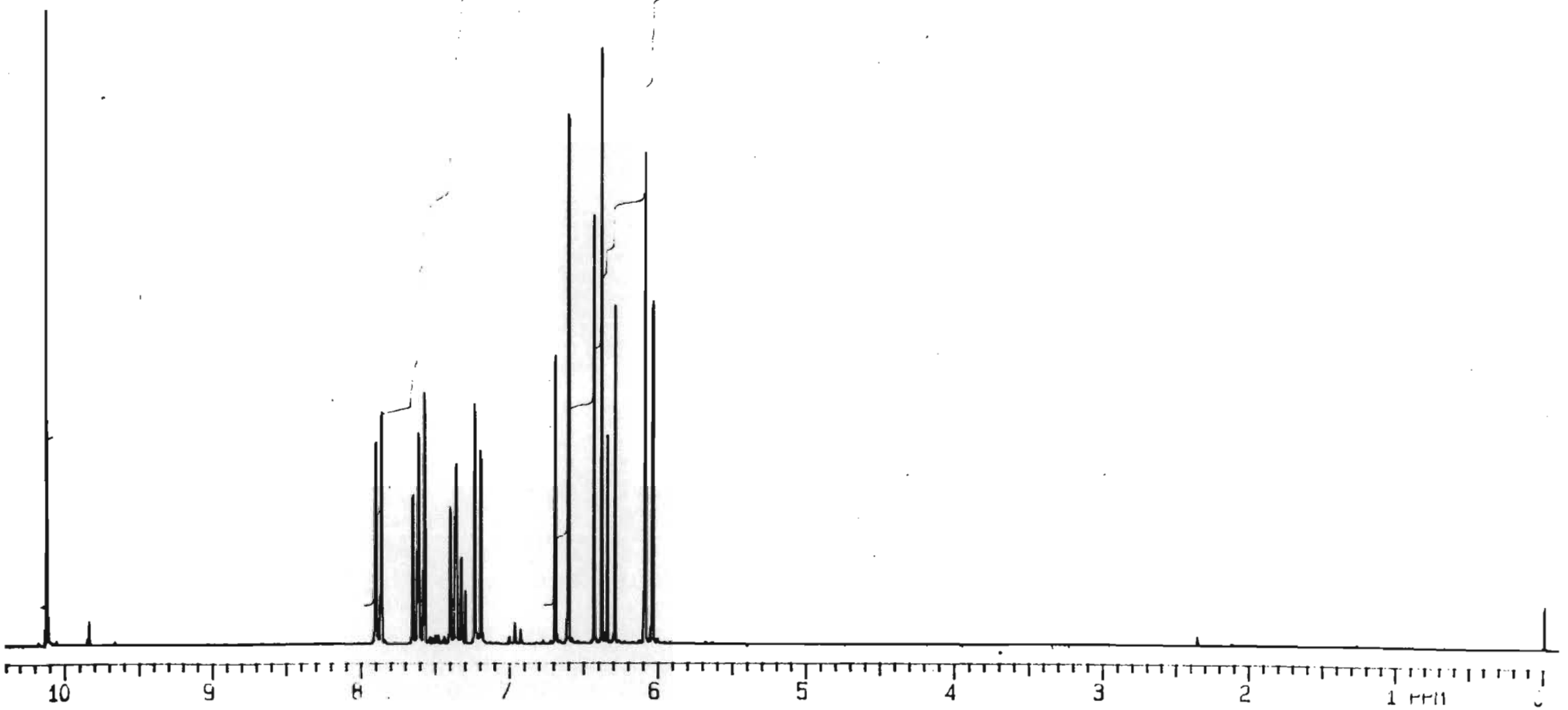
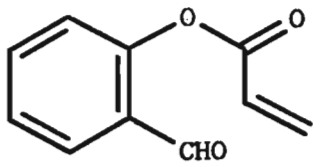
MF $C_{10}H_8O_3$

MW 176





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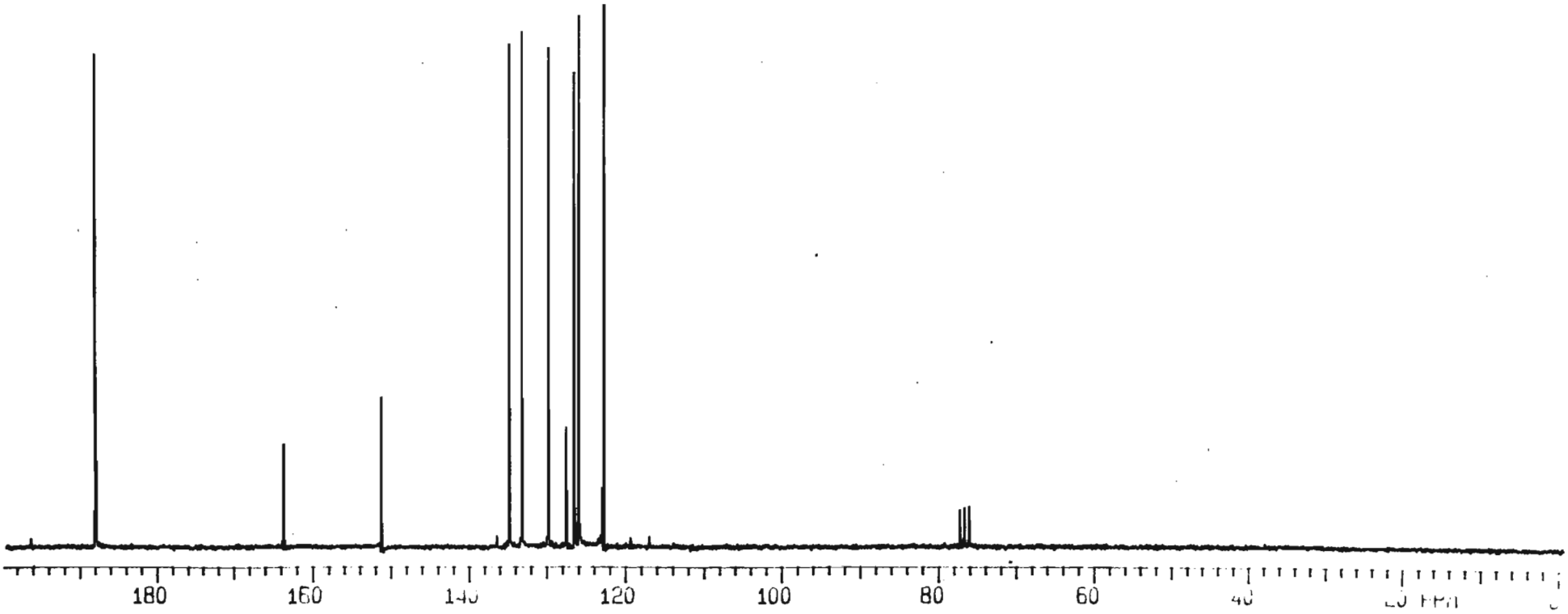

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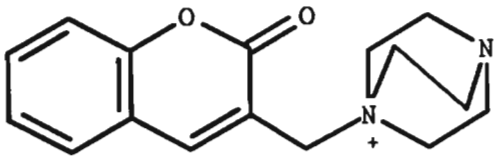

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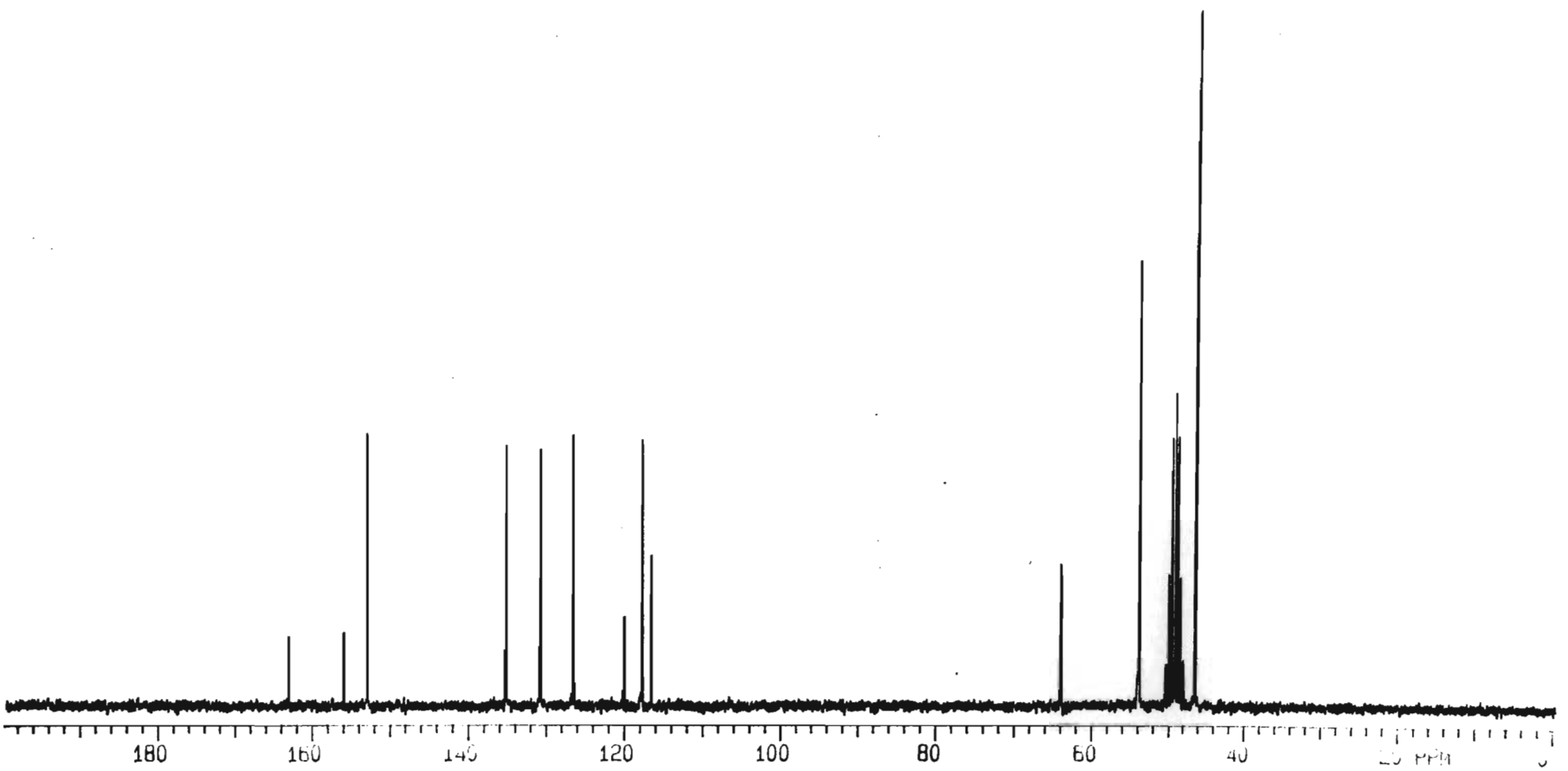

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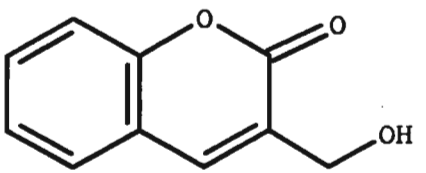

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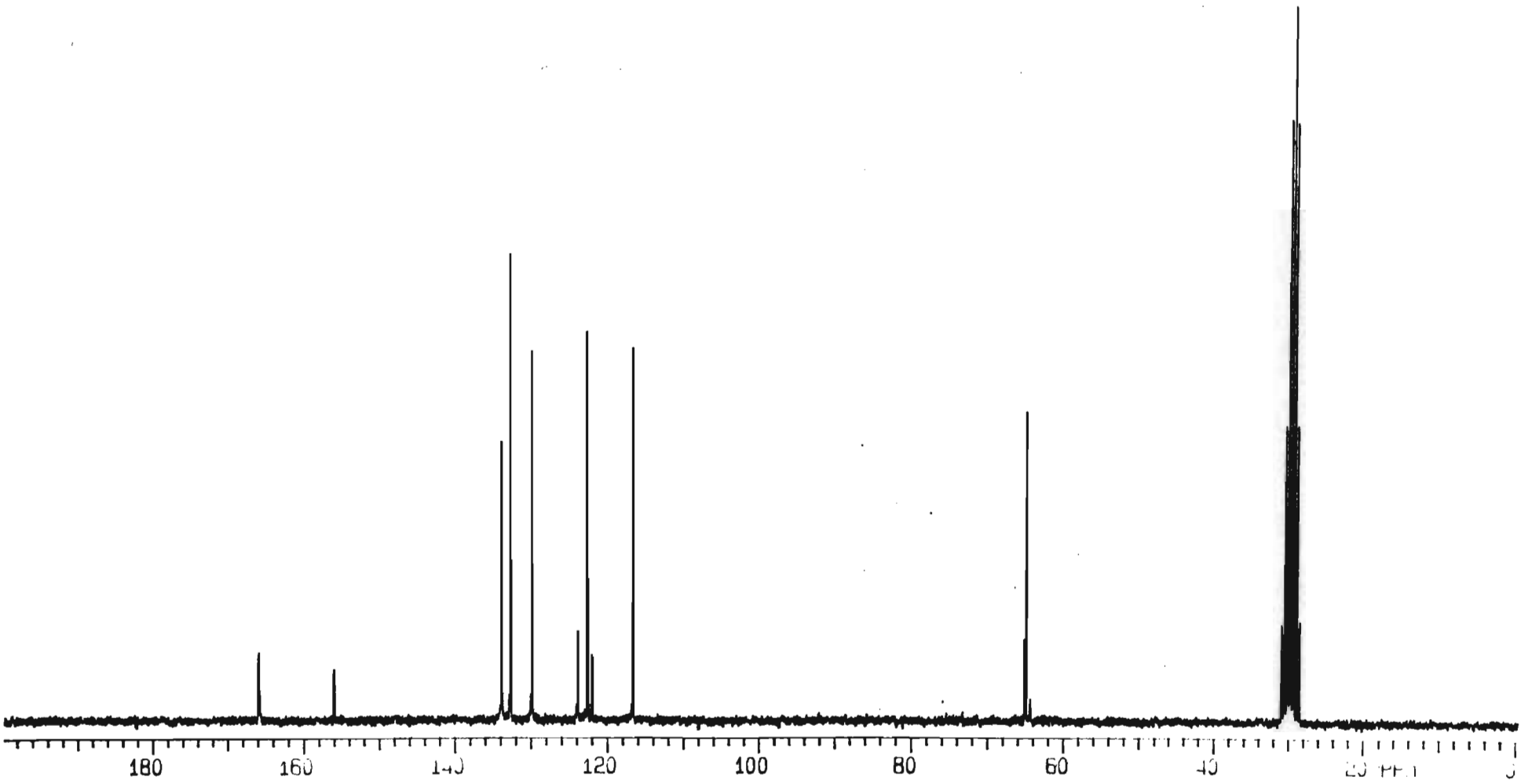
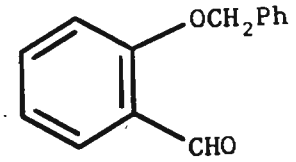
MW 176





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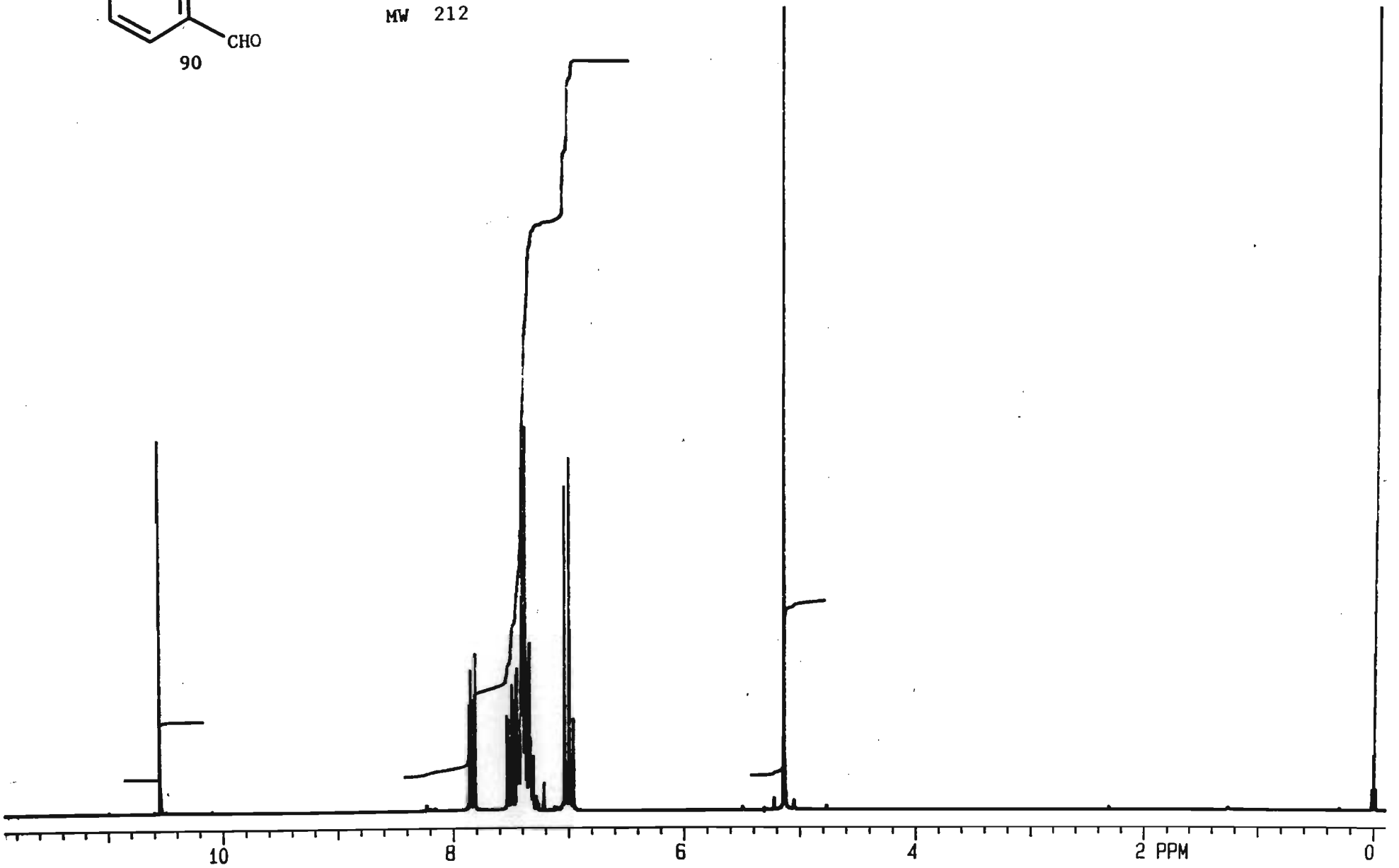

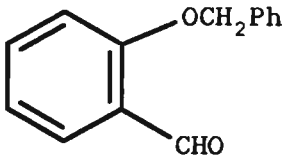

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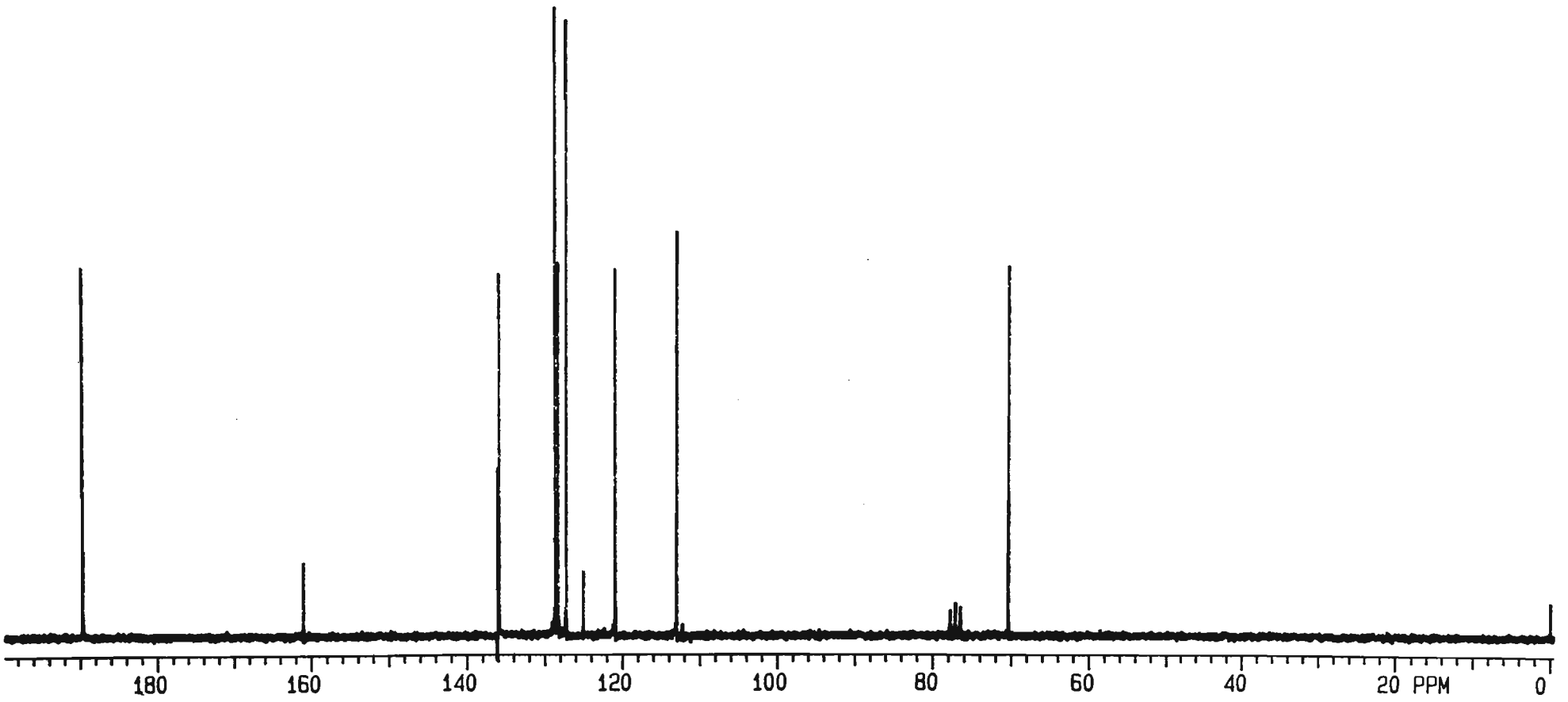
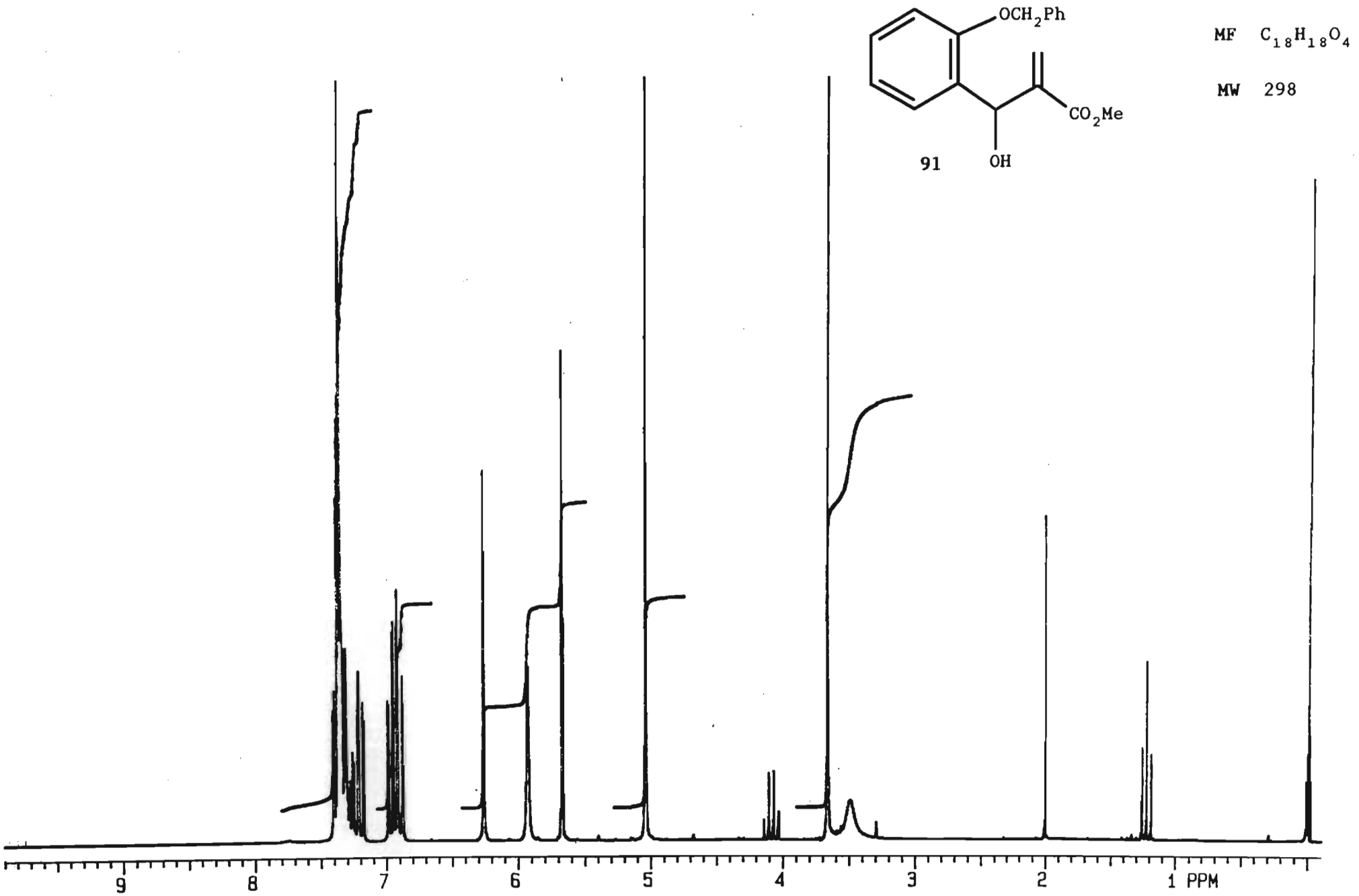
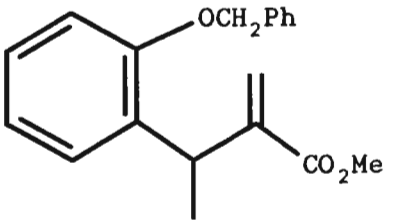
MW 212



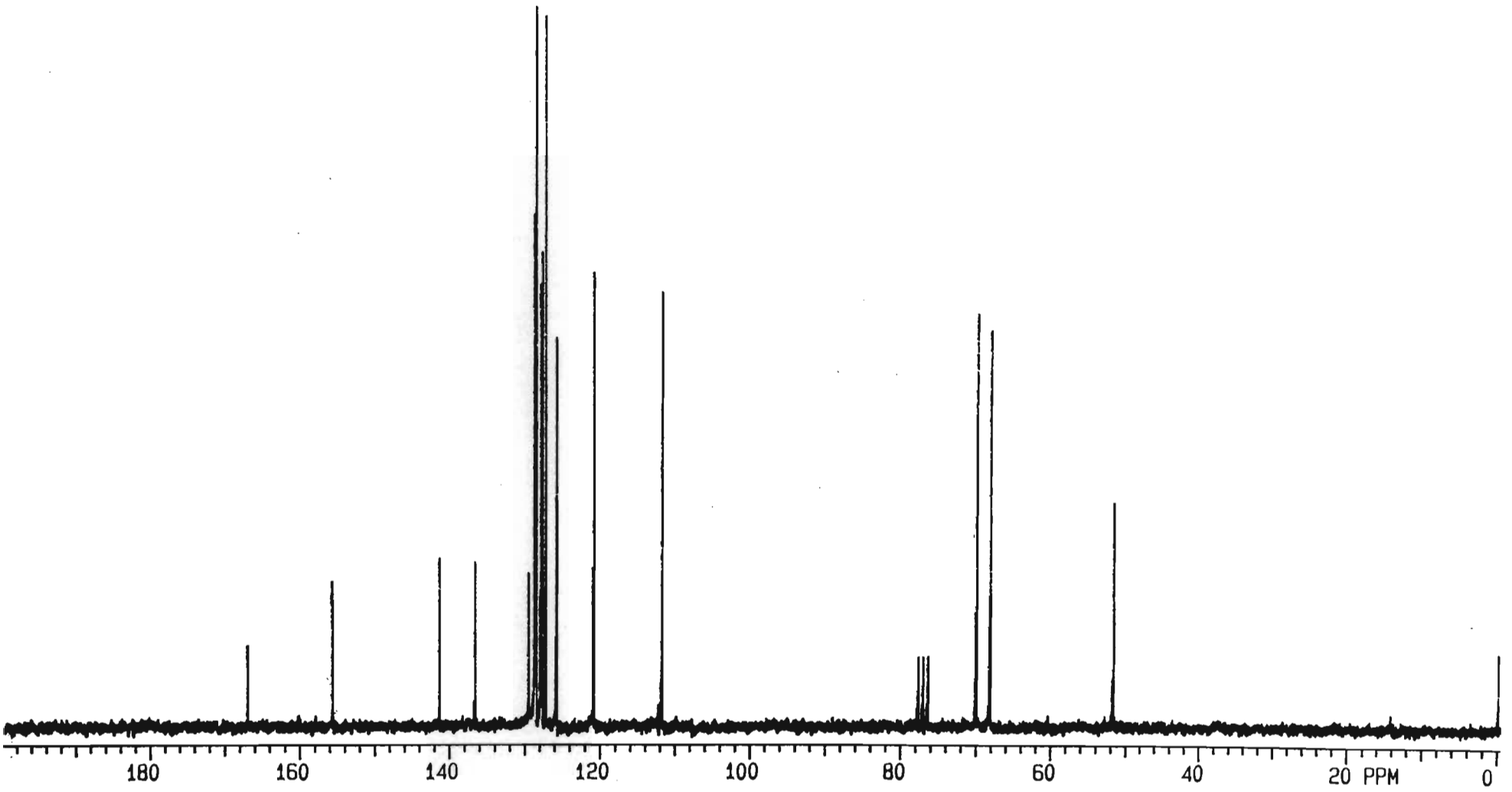

OCH2Ph
CO2Me
OH
91
MF C18H18O4
MW 298
9
8
7
6
5
4
3
2
1 PPM

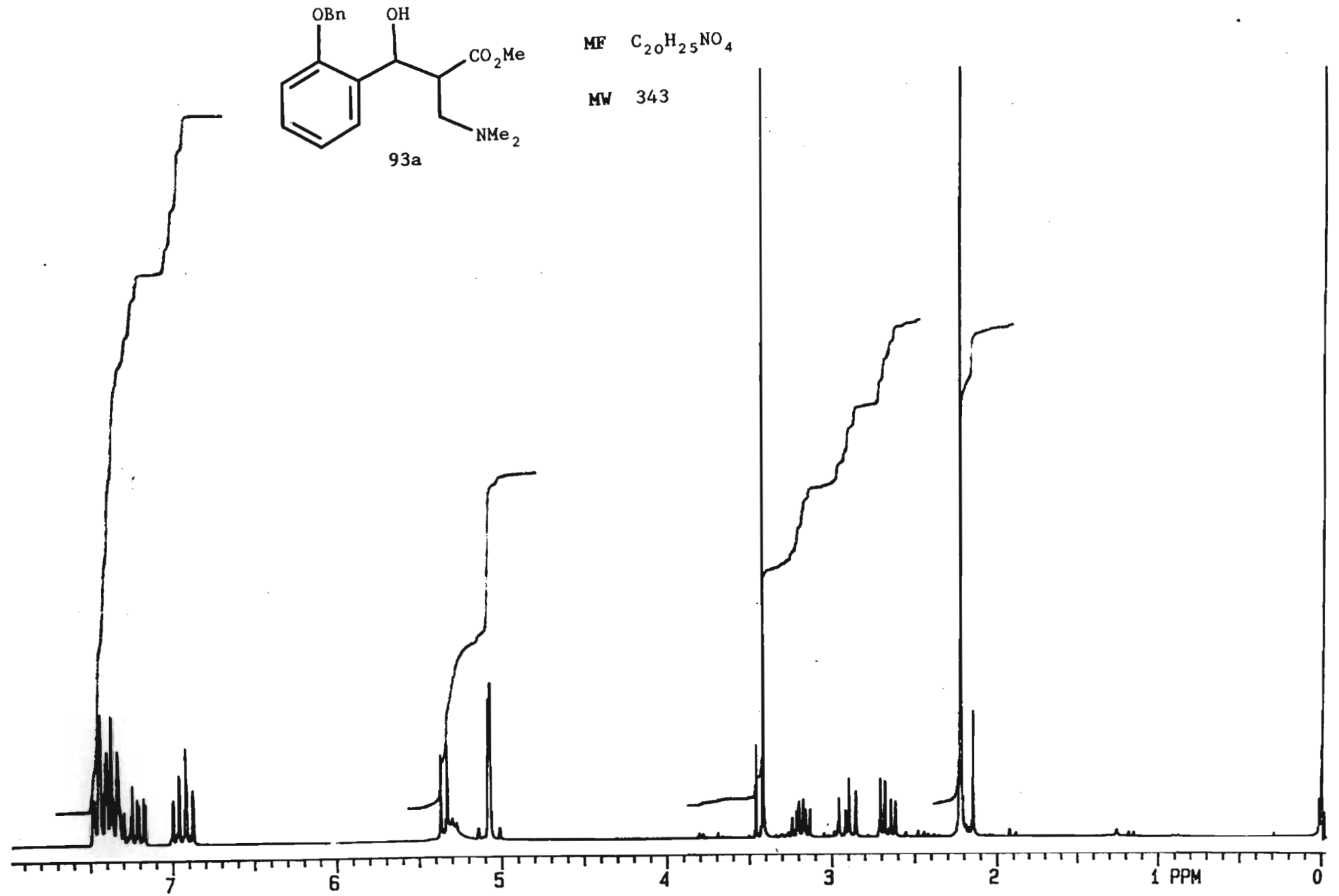


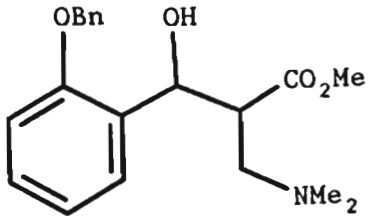
91

MF $C_{18}H_{18}O_4$

MW 298



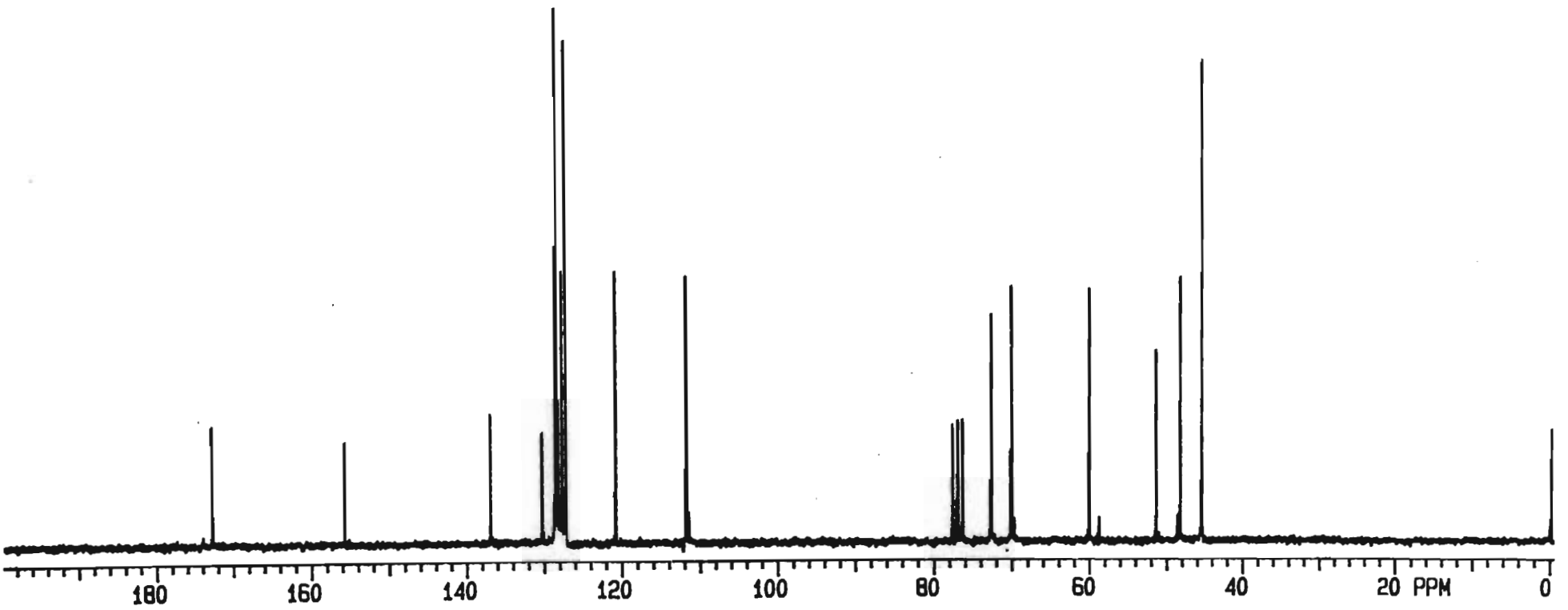

OBn
OH
CO2Me
NMe2
93a
MF C20H25NO4
MW 343
7
6
5
4
3
2
1 PPM
0

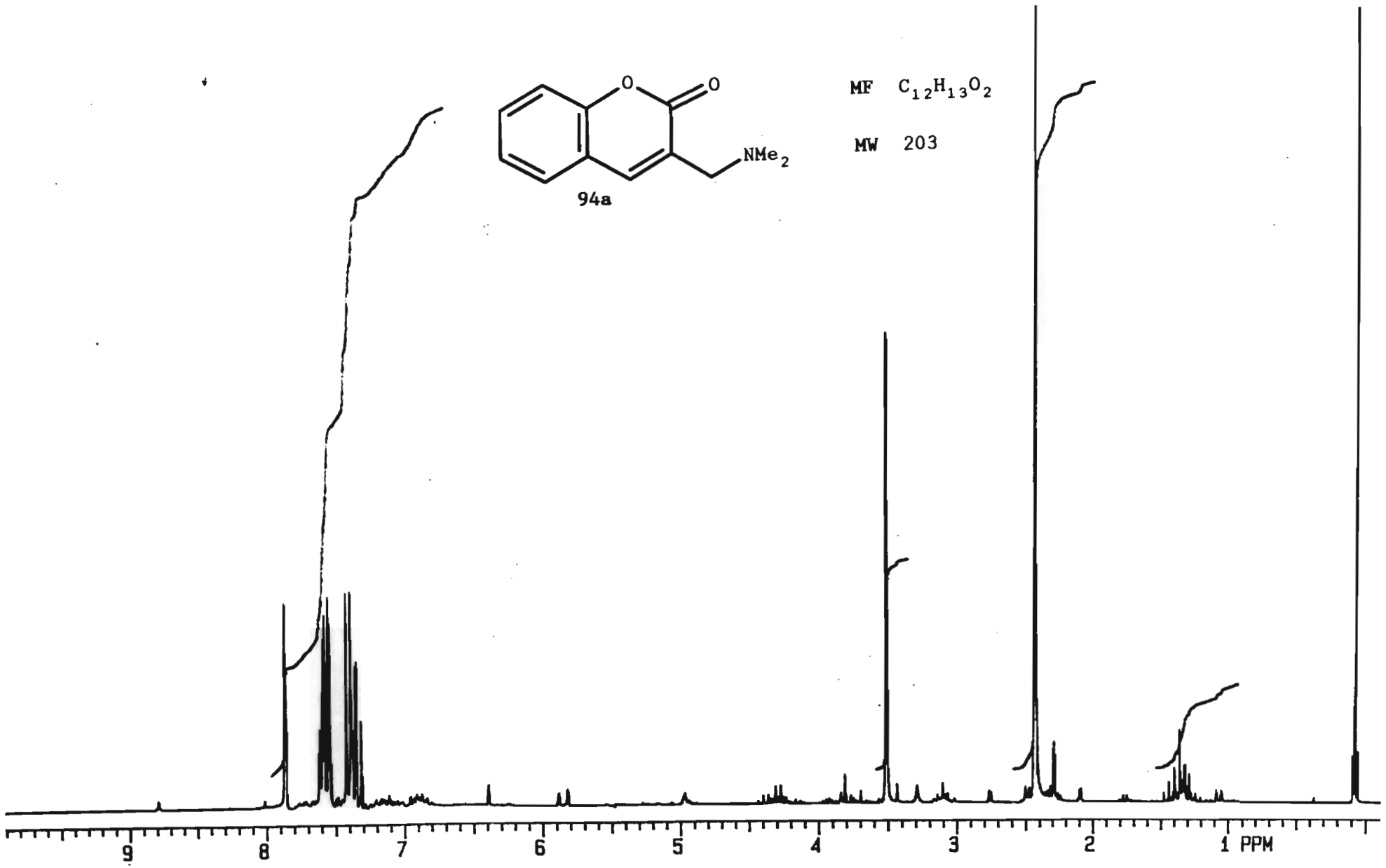


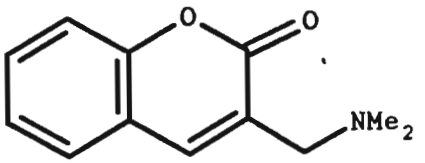
93a

MF $C_{20}H_{25}NO_4$

MW 343



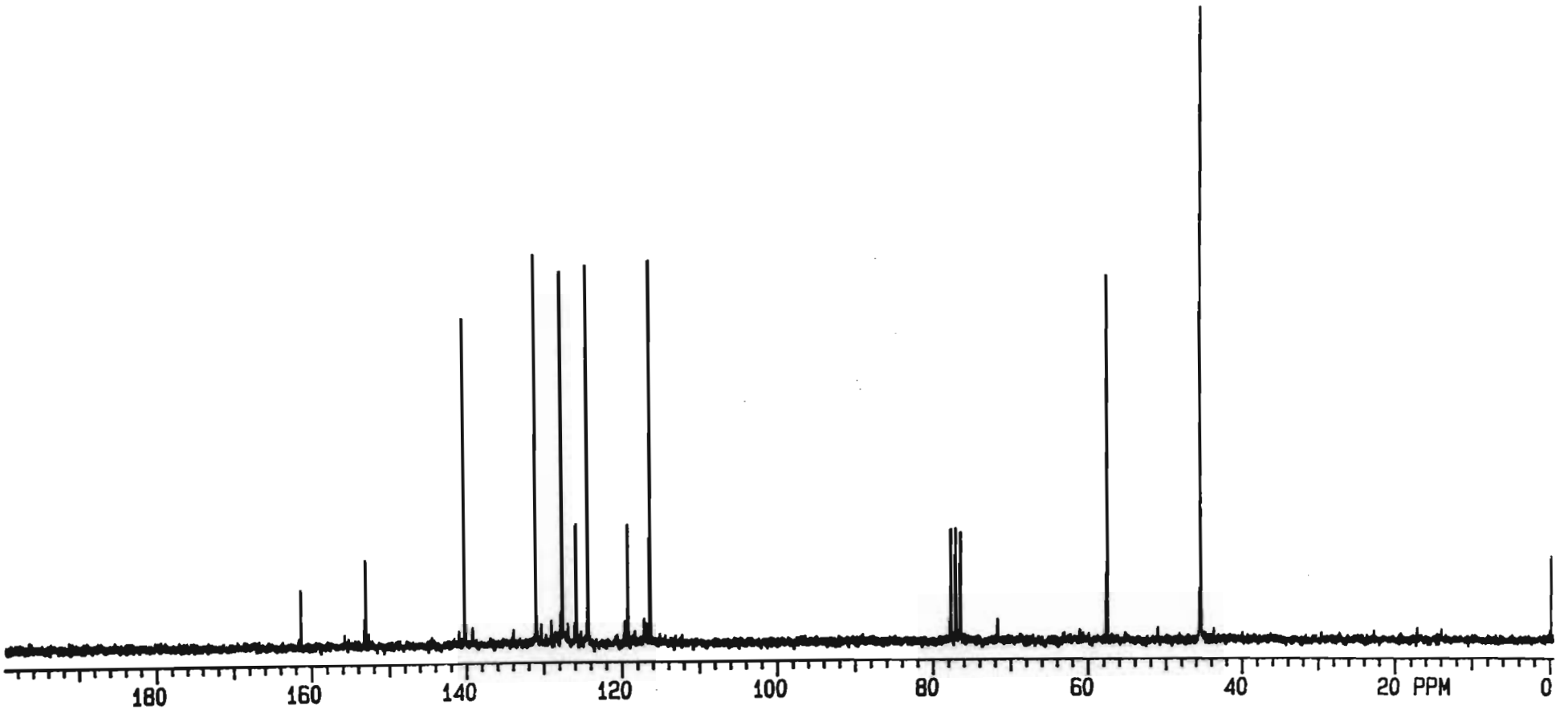

O
O
NMe2
94a
MF C12H13O2
MW 203
9
8
7
6
5
4
3
2
1 PPM

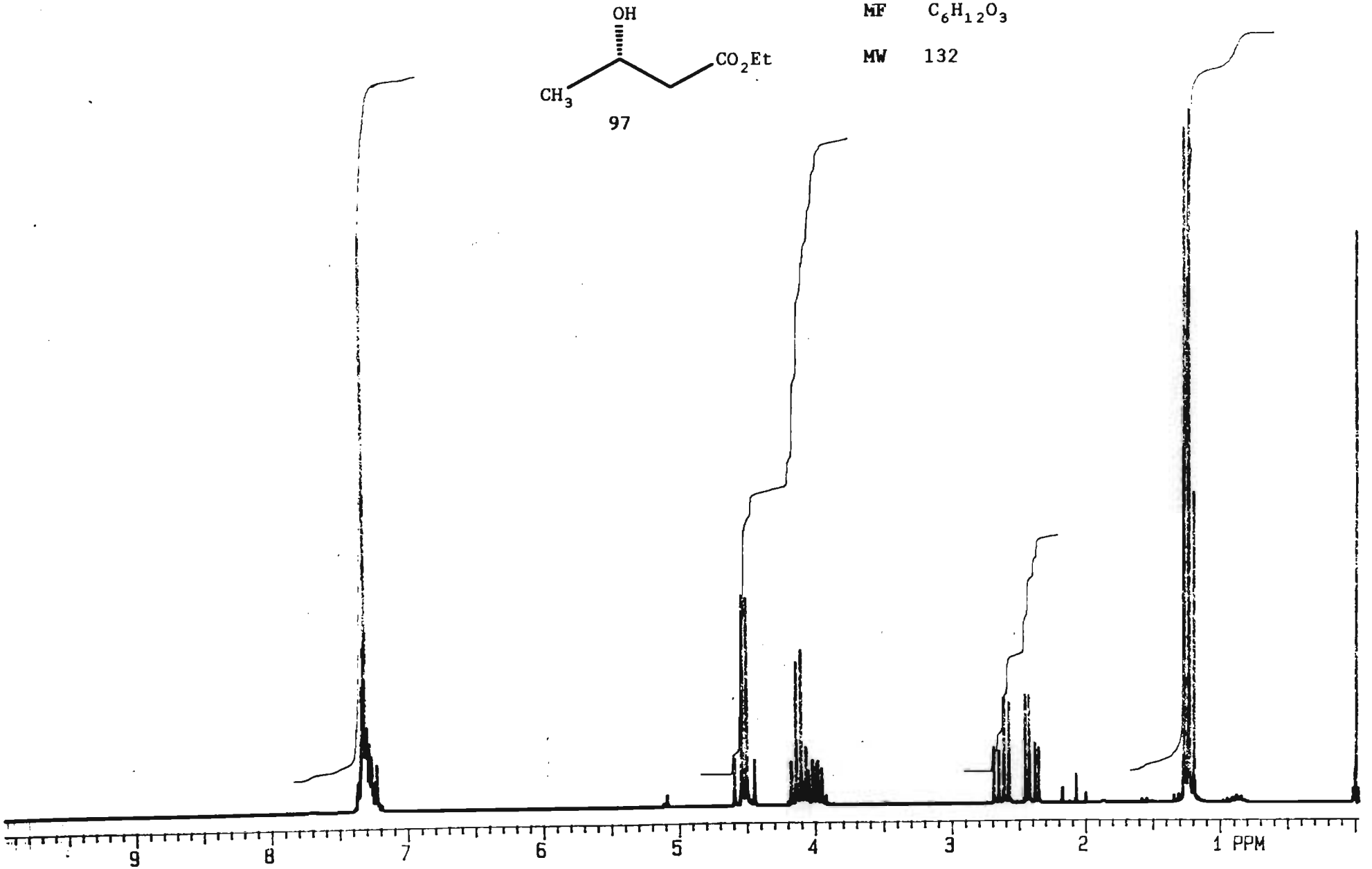


94a

MF $C_{12}H_{13}O_2$

MW 203

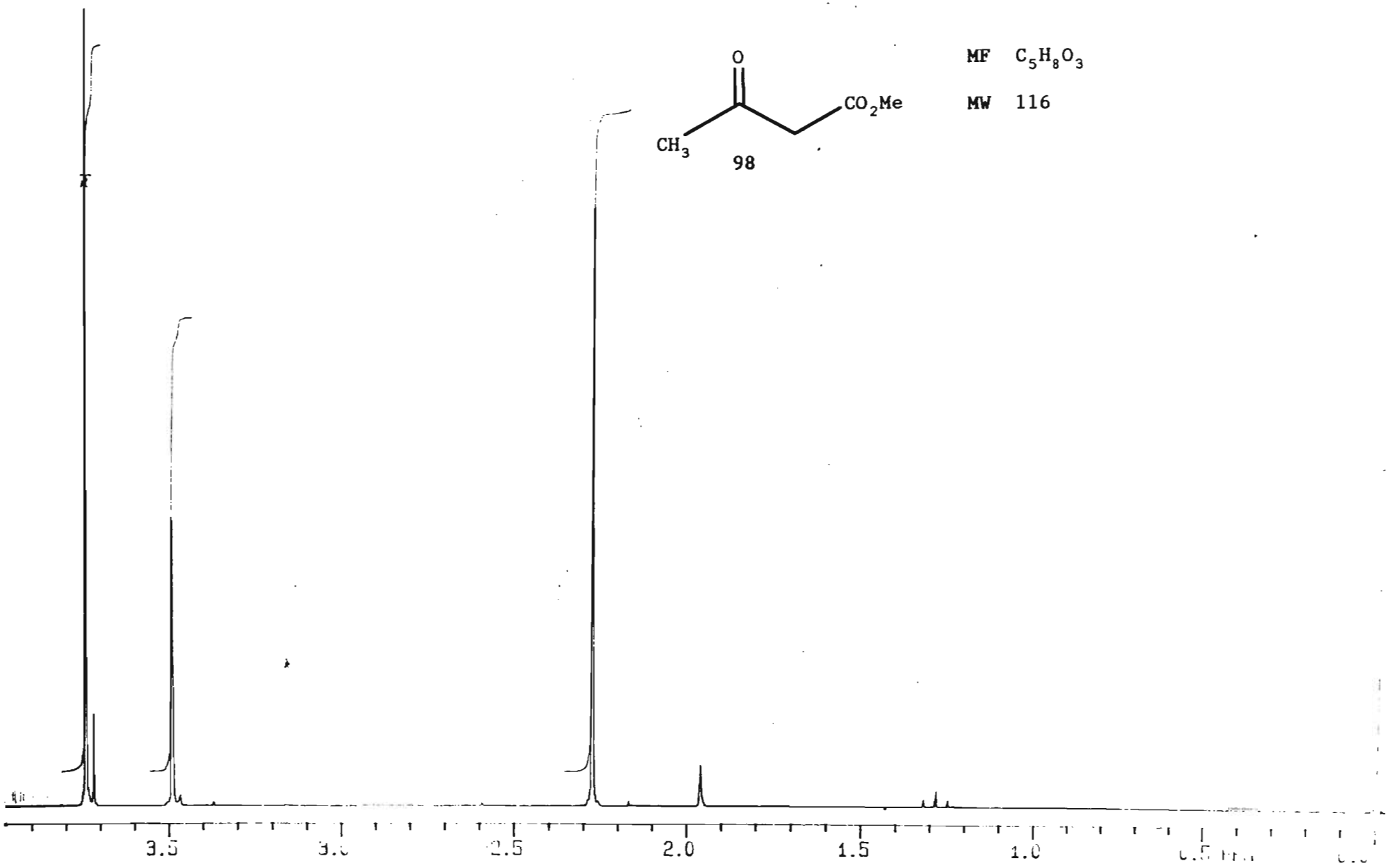


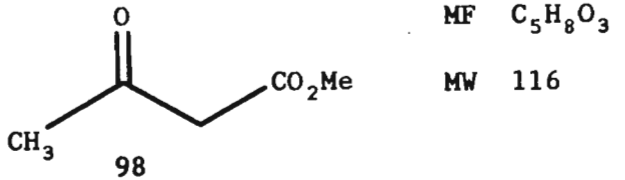

OH
CO2Et
CH3
97
MF C6H12O3
MW 132
9
8
7
6
5
4
3
2
1 PPM

97

MF $C_6H_{12}O_3$

MW 132

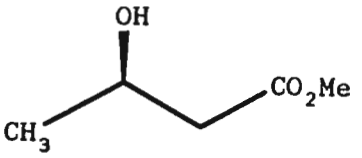

O
CO2Me
CH3
98
MF C5H8O3
MW 116
3.5
2.0
1.5
1.0



98

MF $C_5H_8O_3$

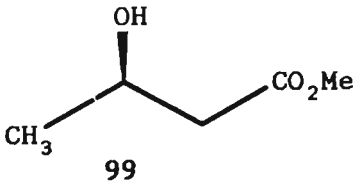
MW 116



99

MF $C_5H_{10}O_3$

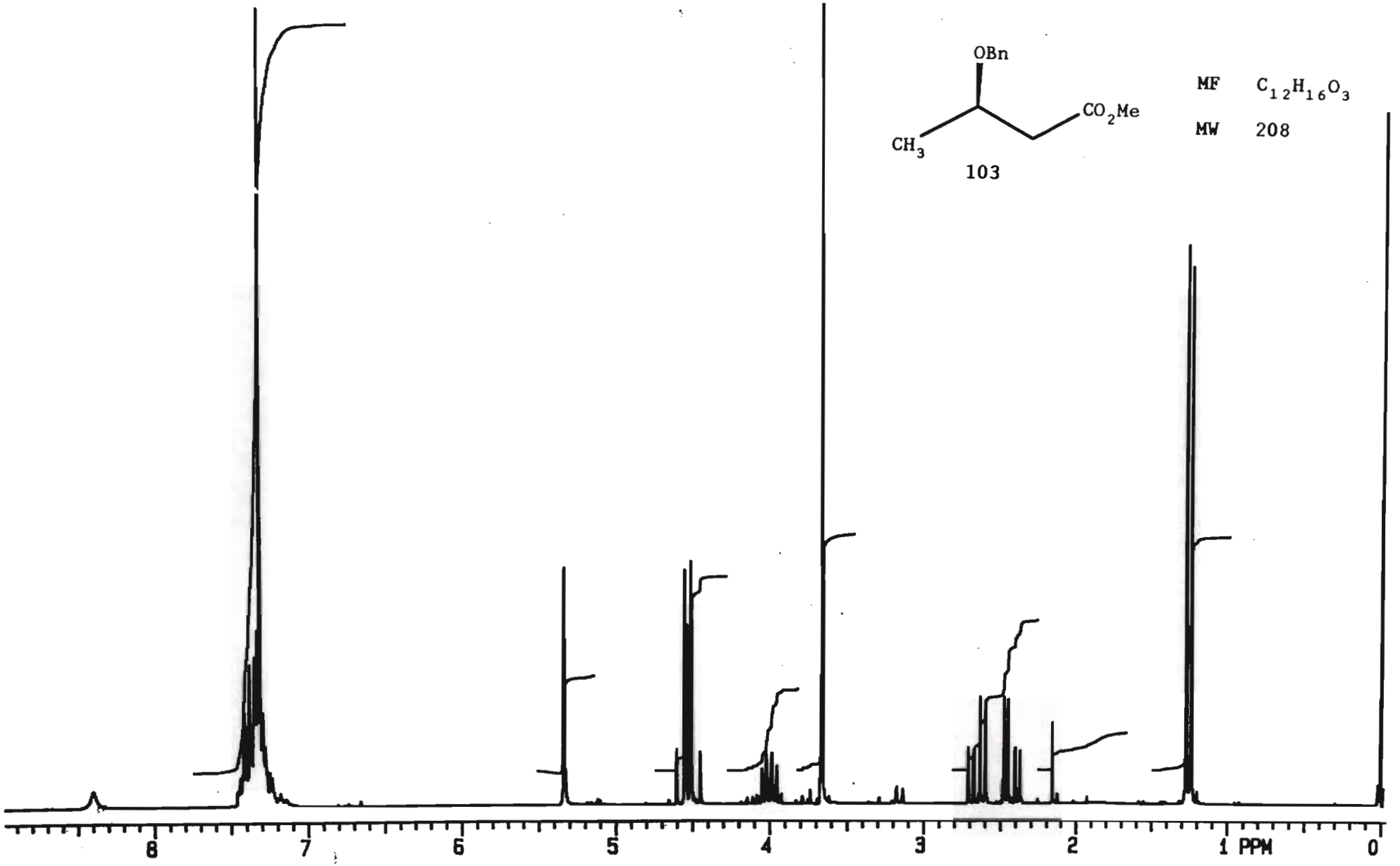
MW 118

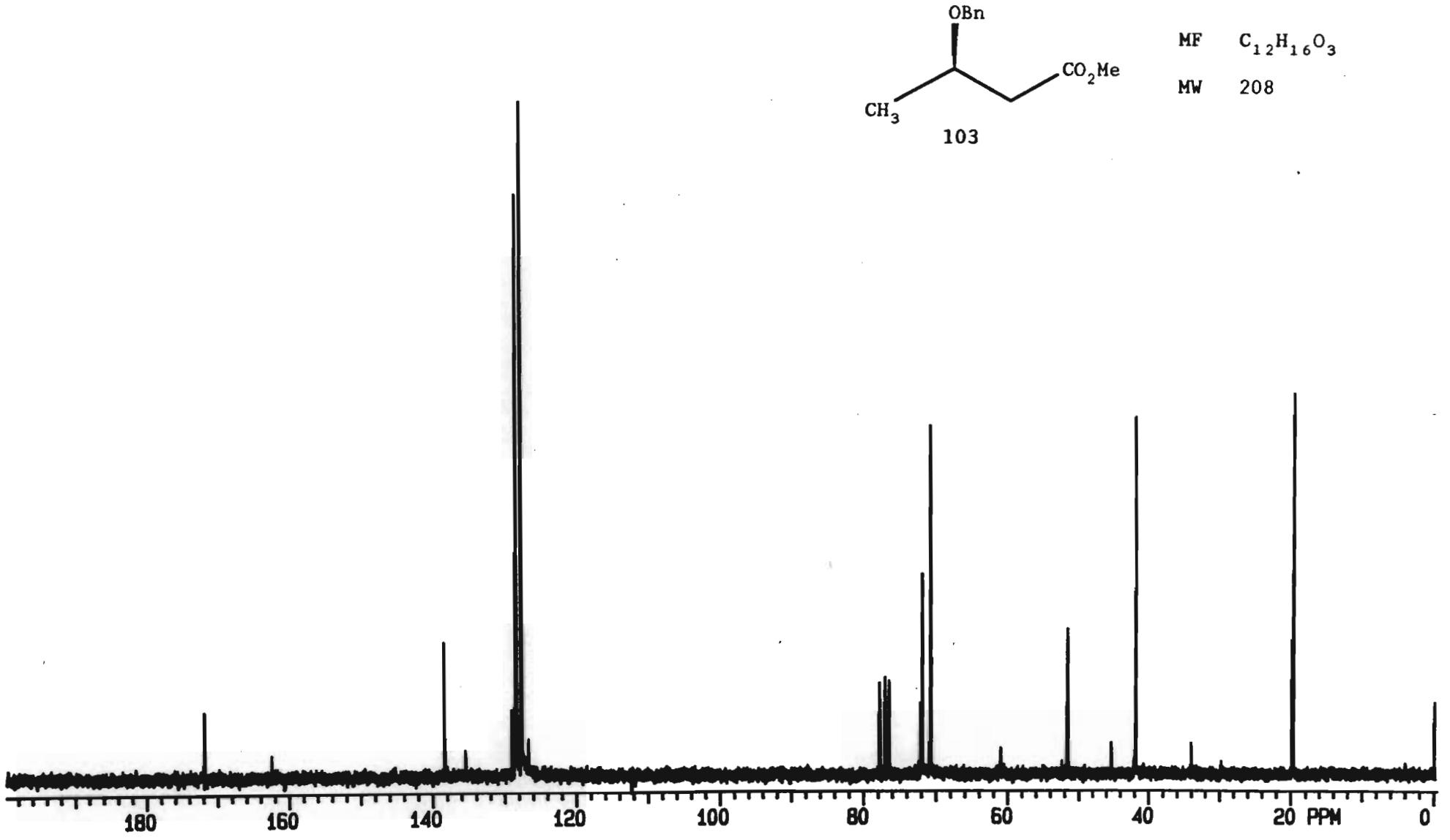


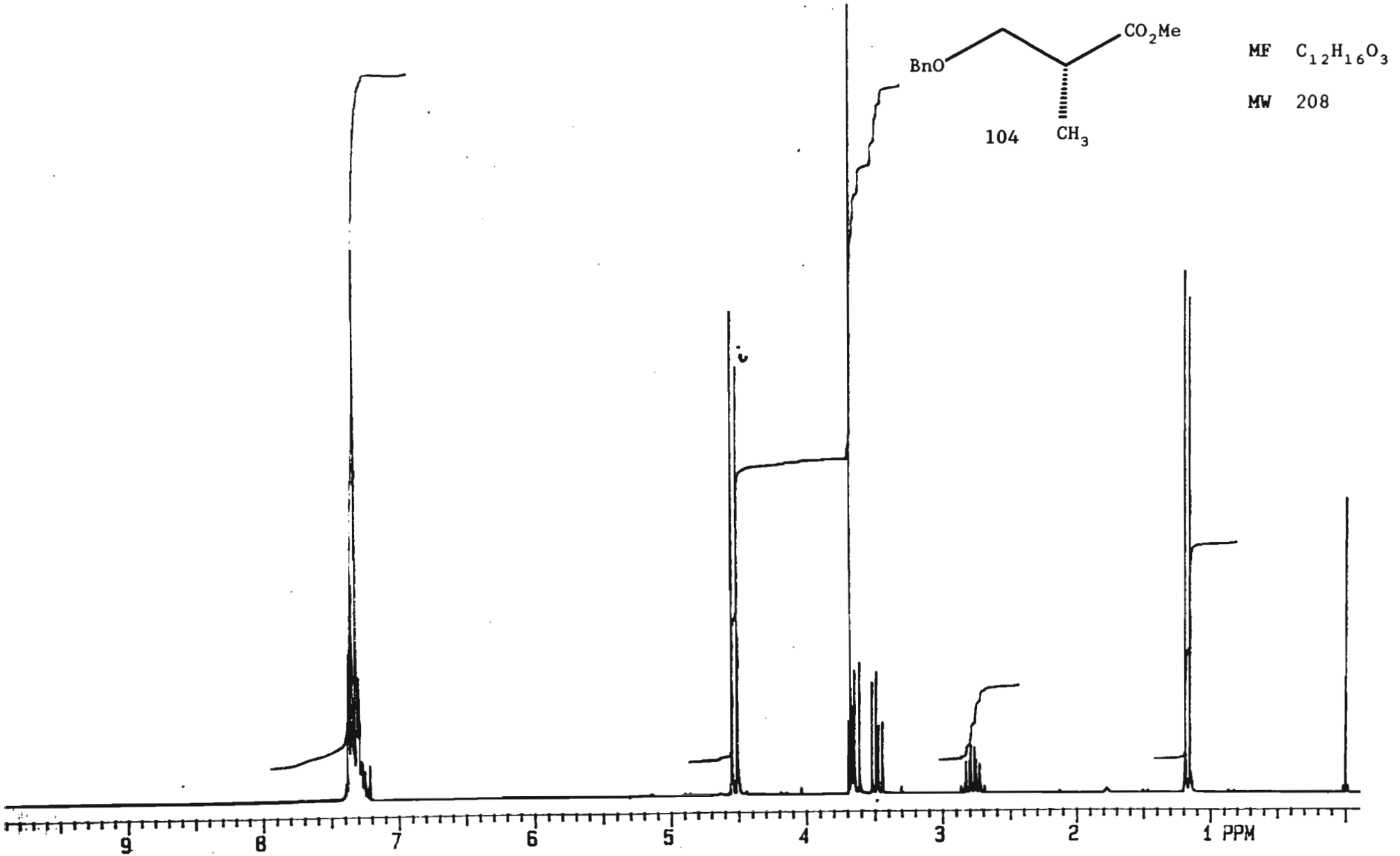
99

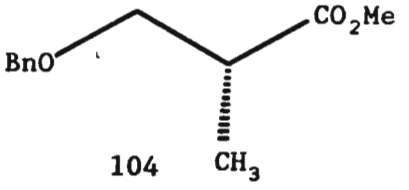
MF $C_5H_{10}O_3$

MW 118


OBn
CO2Me
CH3
103
MF C12H16O3
MW 208
8
7
6
5
4
3
2
1 PPM
0


OBn
CO2Me
CH3
103
MF C12H16O3
MW 208
180
160
140
120
100
80
60
40
20 PPM
0

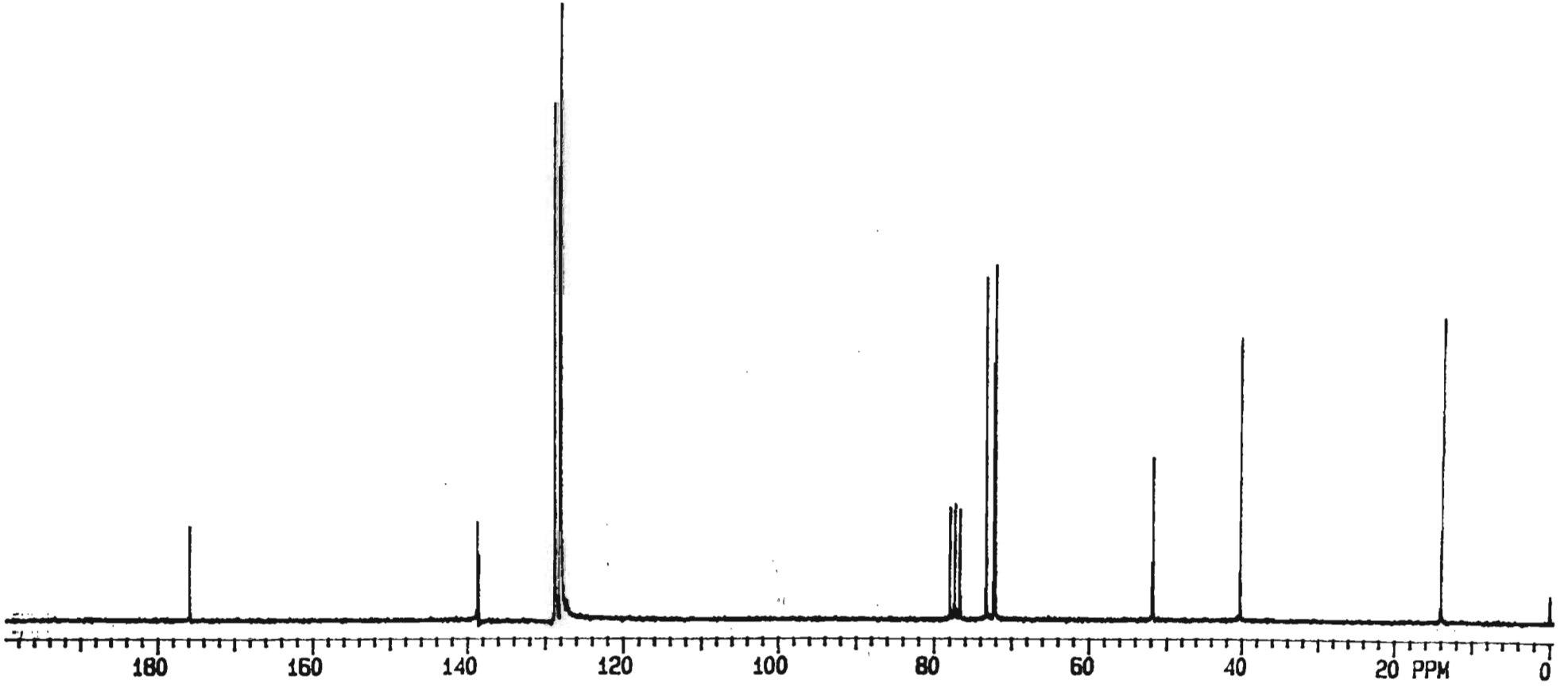

BnO
CO2Me
CH3
104
MF C12H16O3
MW 208
9
8
7
6
5
4
3
2
1 PPM

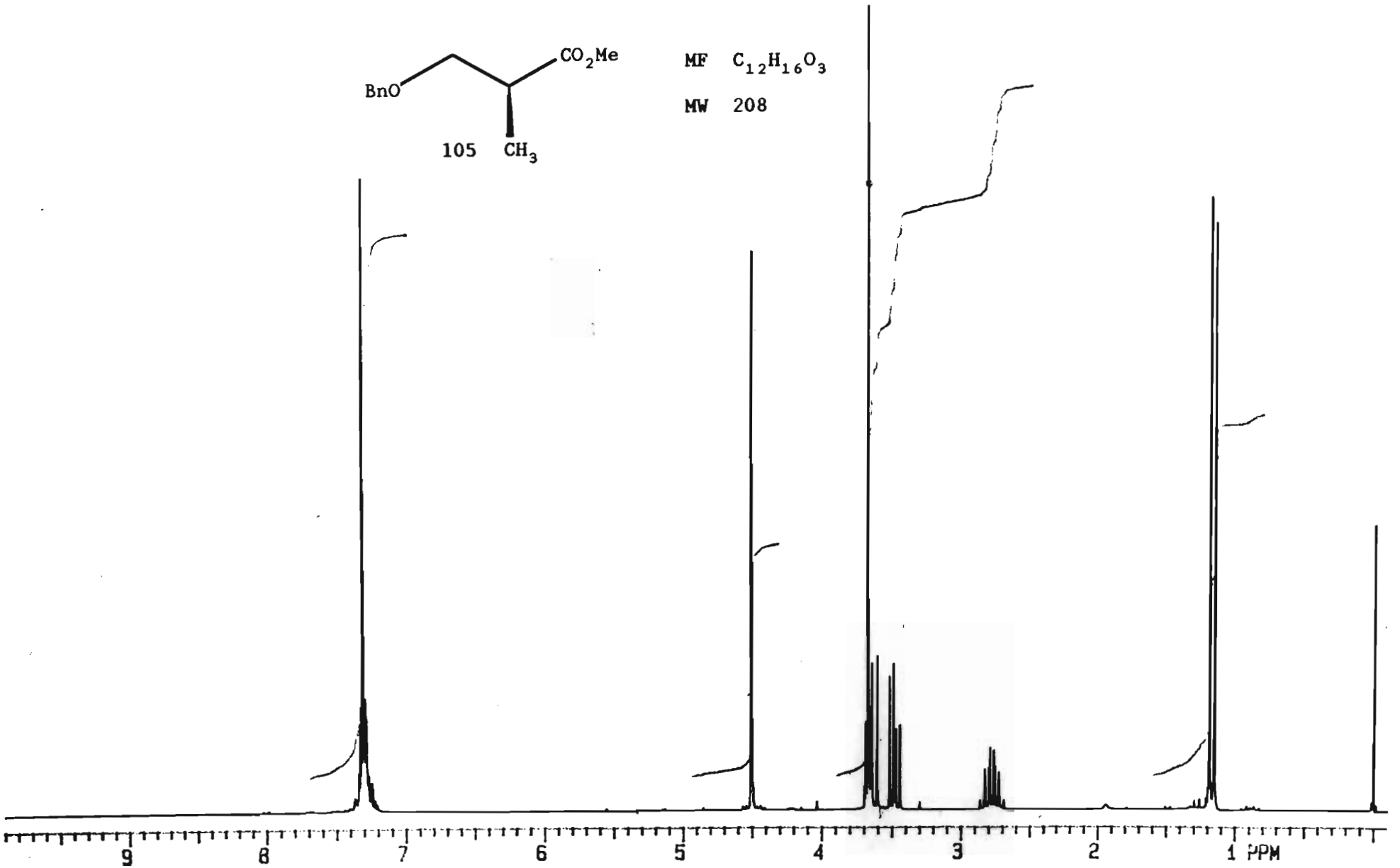


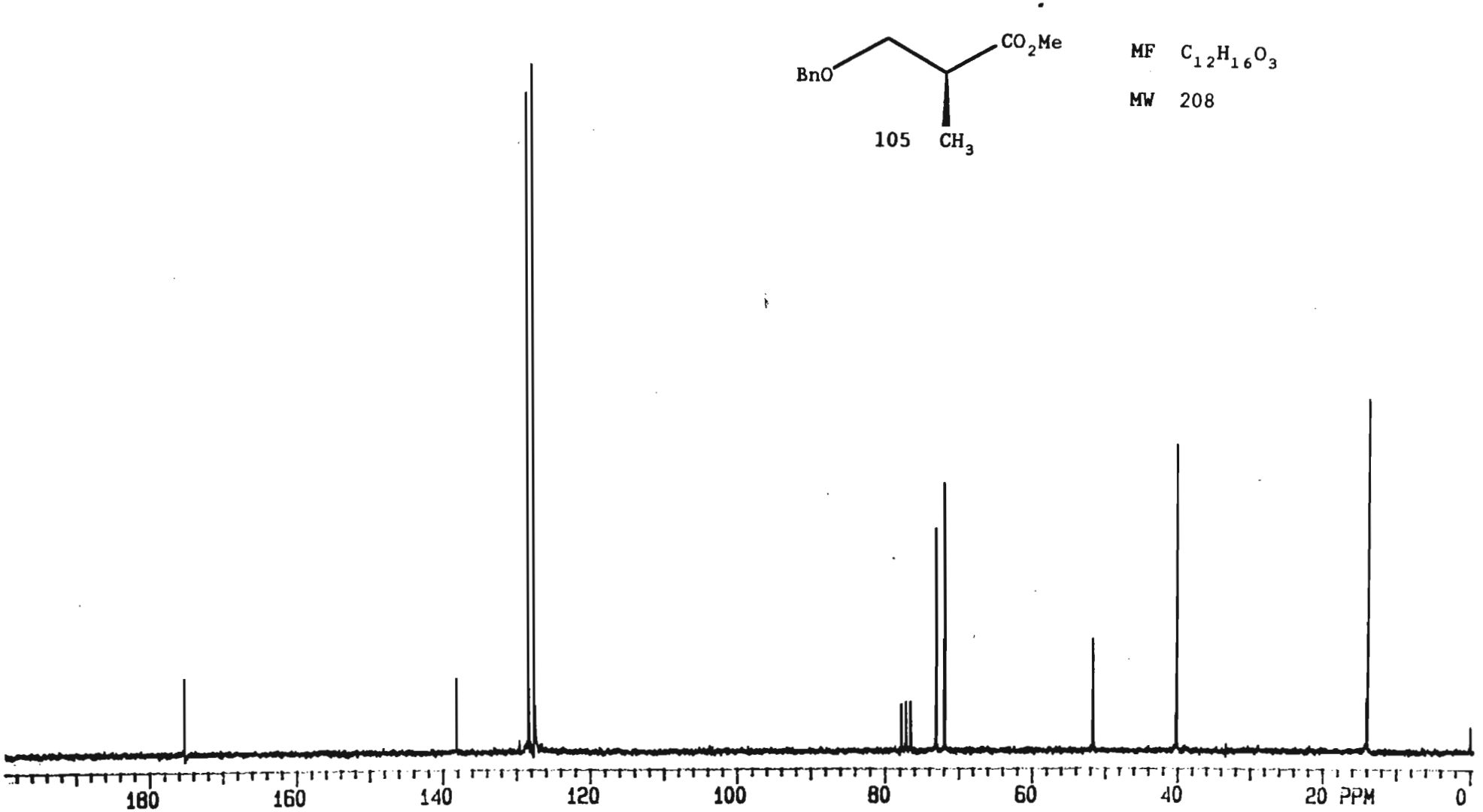
104

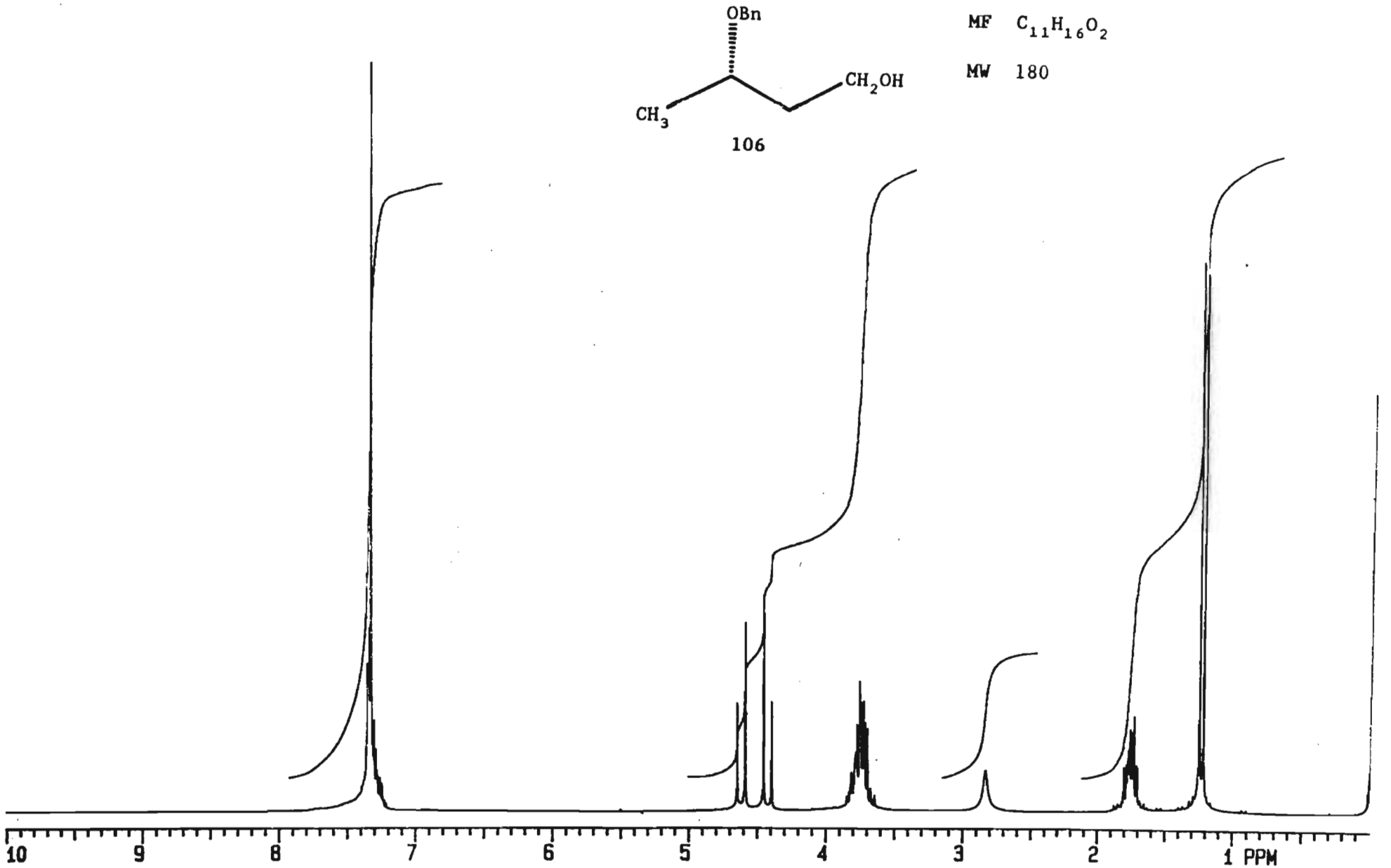
MF $C_{12}H_{16}O_3$

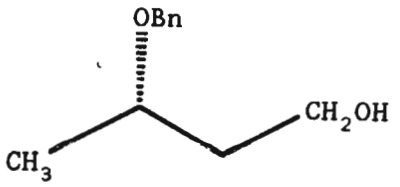
MW 208




BnO
CO2Me
105
CH3
MF C12H16O3
MW 208
9
8
7
6
5
4
3
2
1 PPM


BnO
CO2Me
105
CH3
MF C12H16O3
MW 208
180
160
140
120
100
80
60
40
20
PPM
0

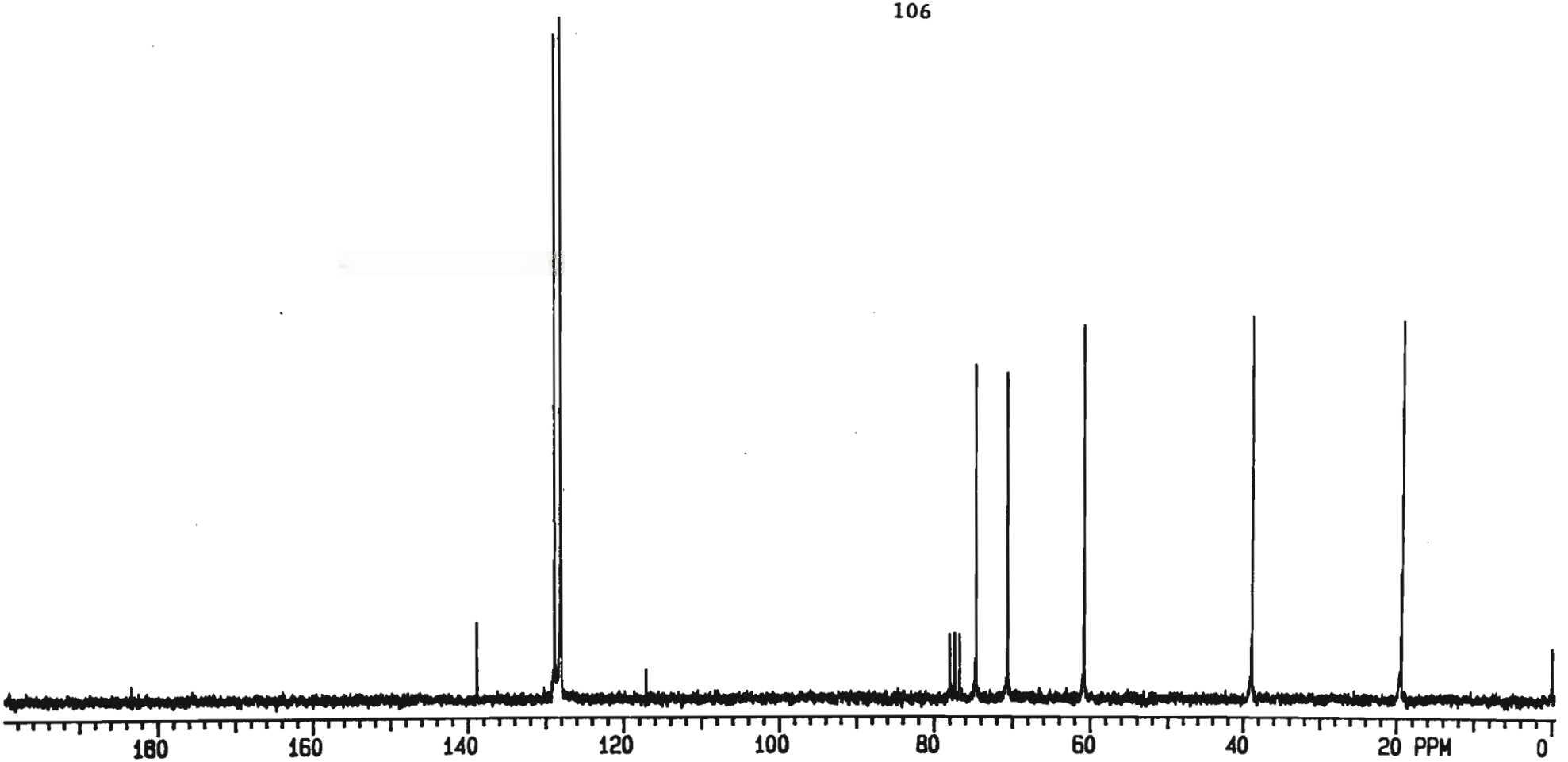

OBn
CH2OH
CH3
MF C11H16O2
MW 180
106
10
9
8
7
6
5
4
3
2
1 PPM



106

MF $C_{11}H_{16}O_2$

MW 180



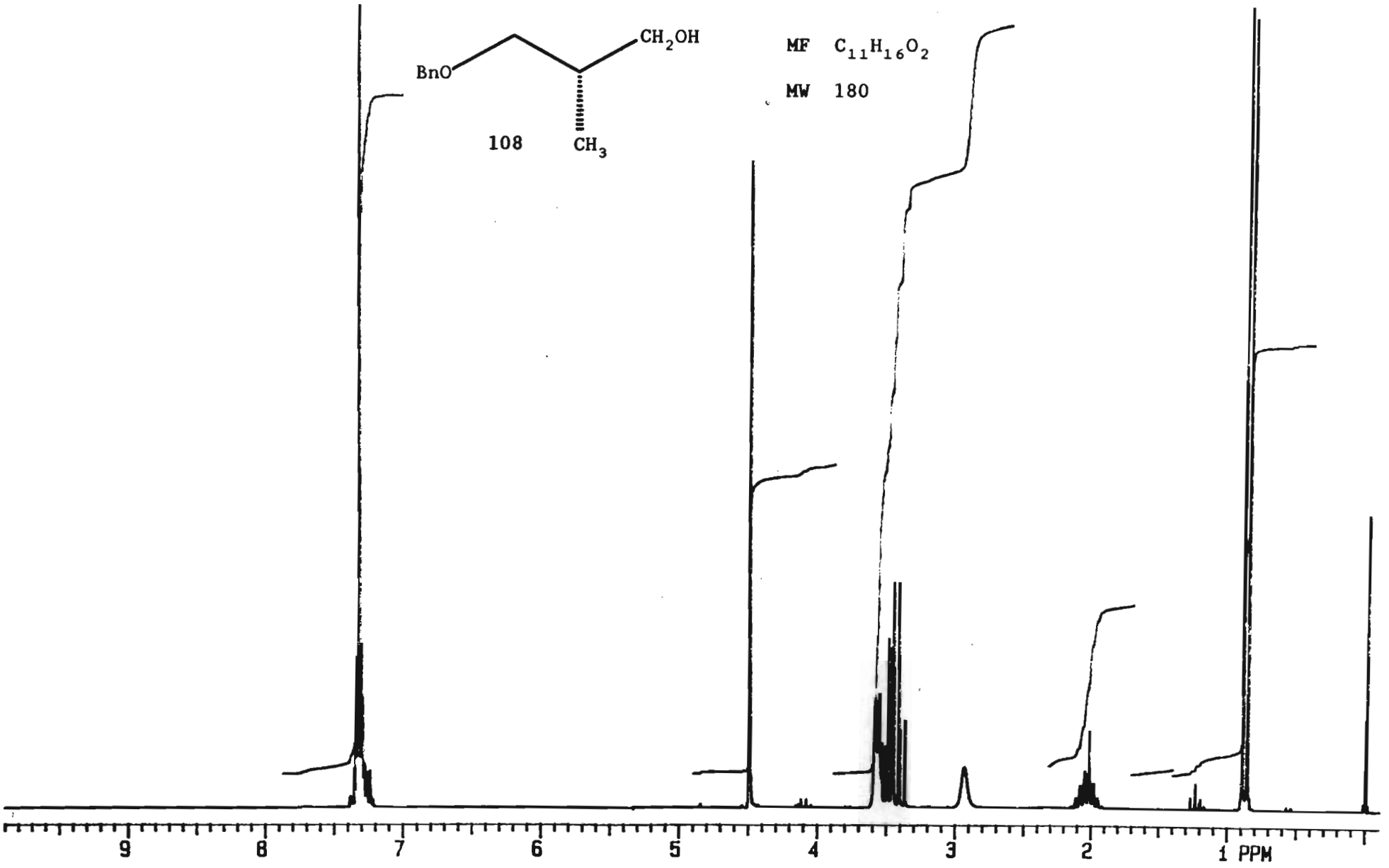
107

MF $C_{11}H_{16}O_2$

MW 180

MF $C_{11}H_{16}O_2$

MW 180


BnO
CH2OH
CH3
108
MF C11H16O2
MW 180
9
8
7
6
5
4
3
2
1 PPM

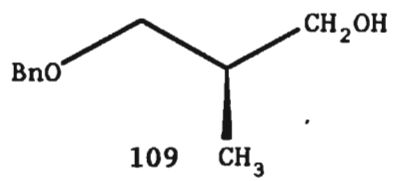
108

MF $C_{11}H_{16}O_2$

MW 180

1 PPM
2
3
4
5
6
7
8
9
BnO
109
CH3
CH2OH

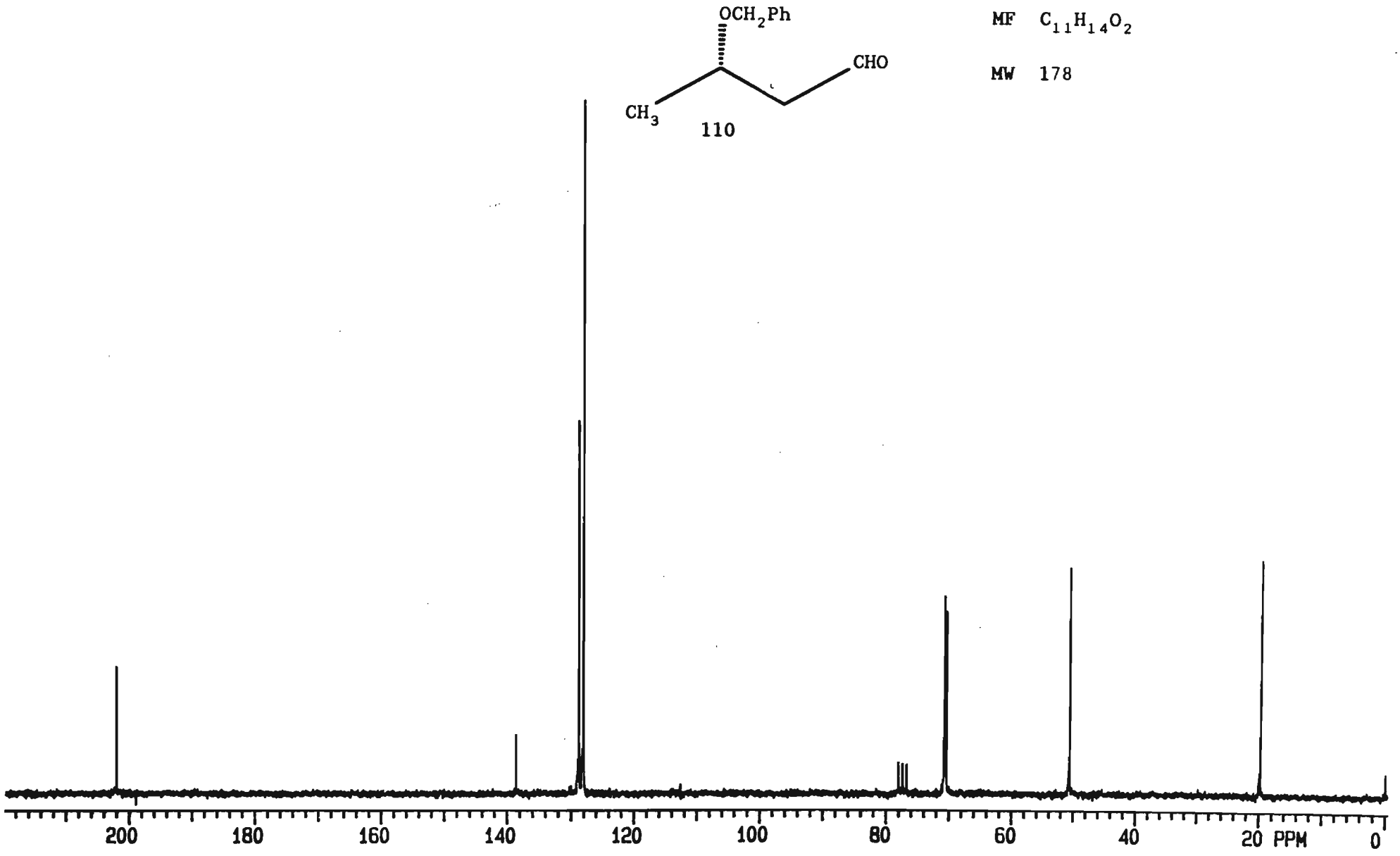
6032/91 QLCOM 2.2 IN CDCL3

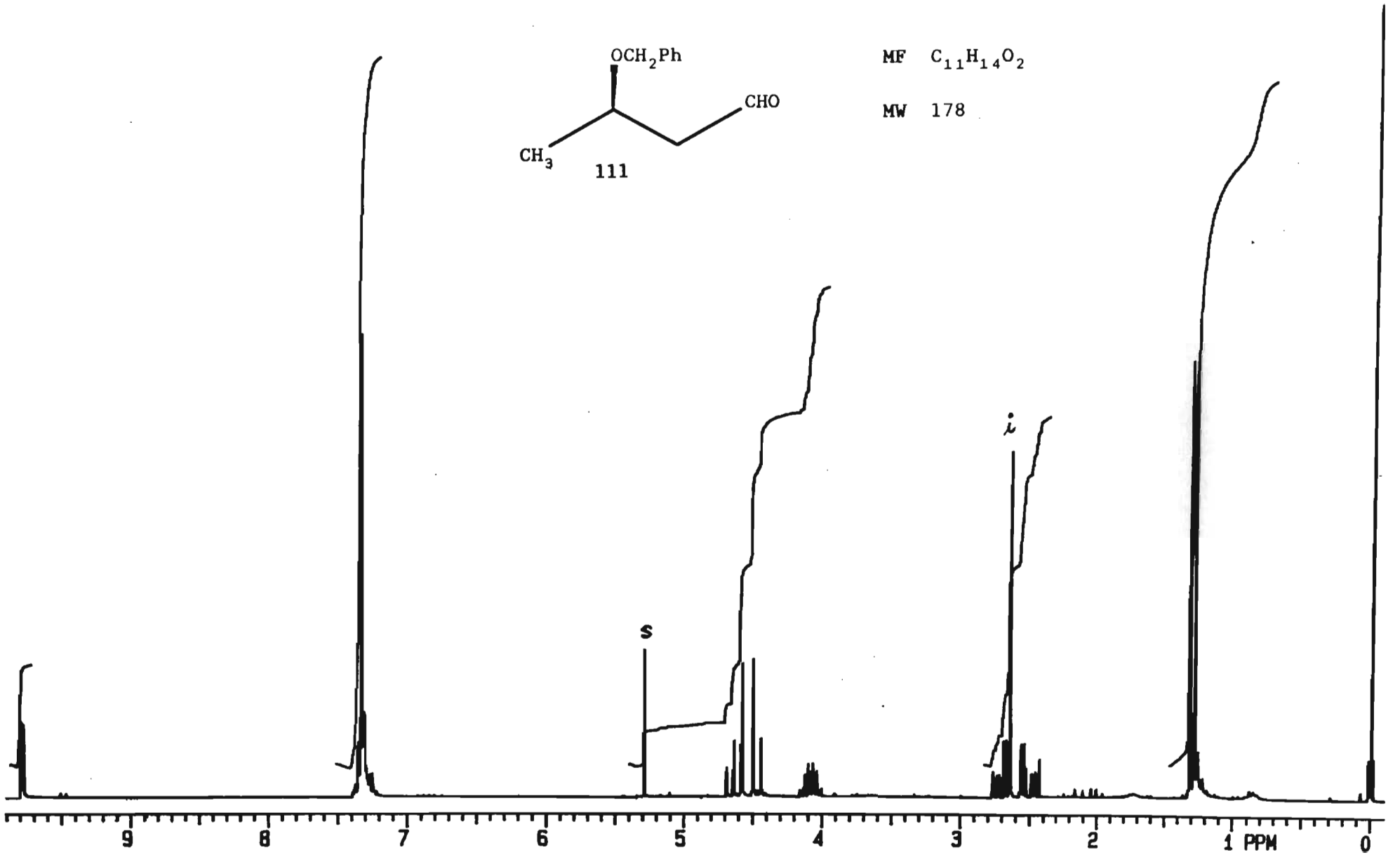


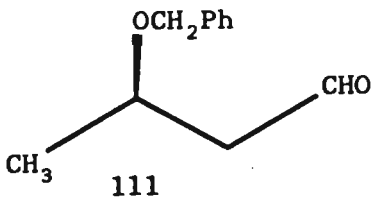
MF $C_{11}H_{16}O_2$

MW 180

10
9
8
7
6
5
4
3
2
1 PPM
CH3
110
OCH2Ph
CHO


OCH2Ph
CHO
CH3
110
MF C11H14O2
MW 178
200
180
160
140
120
100
80
60
40
20 PPM
0

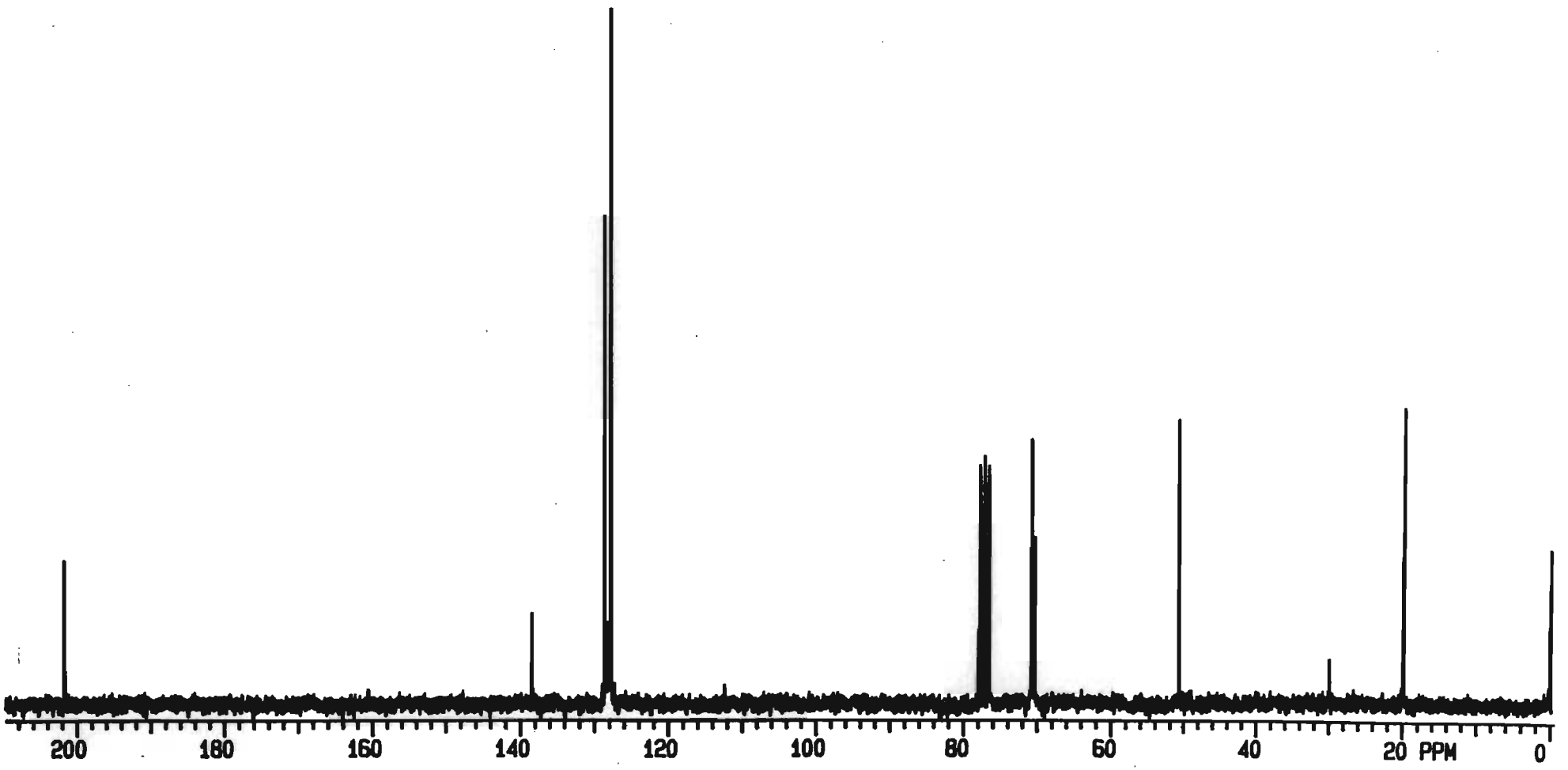

OCH2Ph
CHO
CH3
111
MF C11H14O2
MW 178
s
i
9
8
7
6
5
4
3
2
1 PPM
0



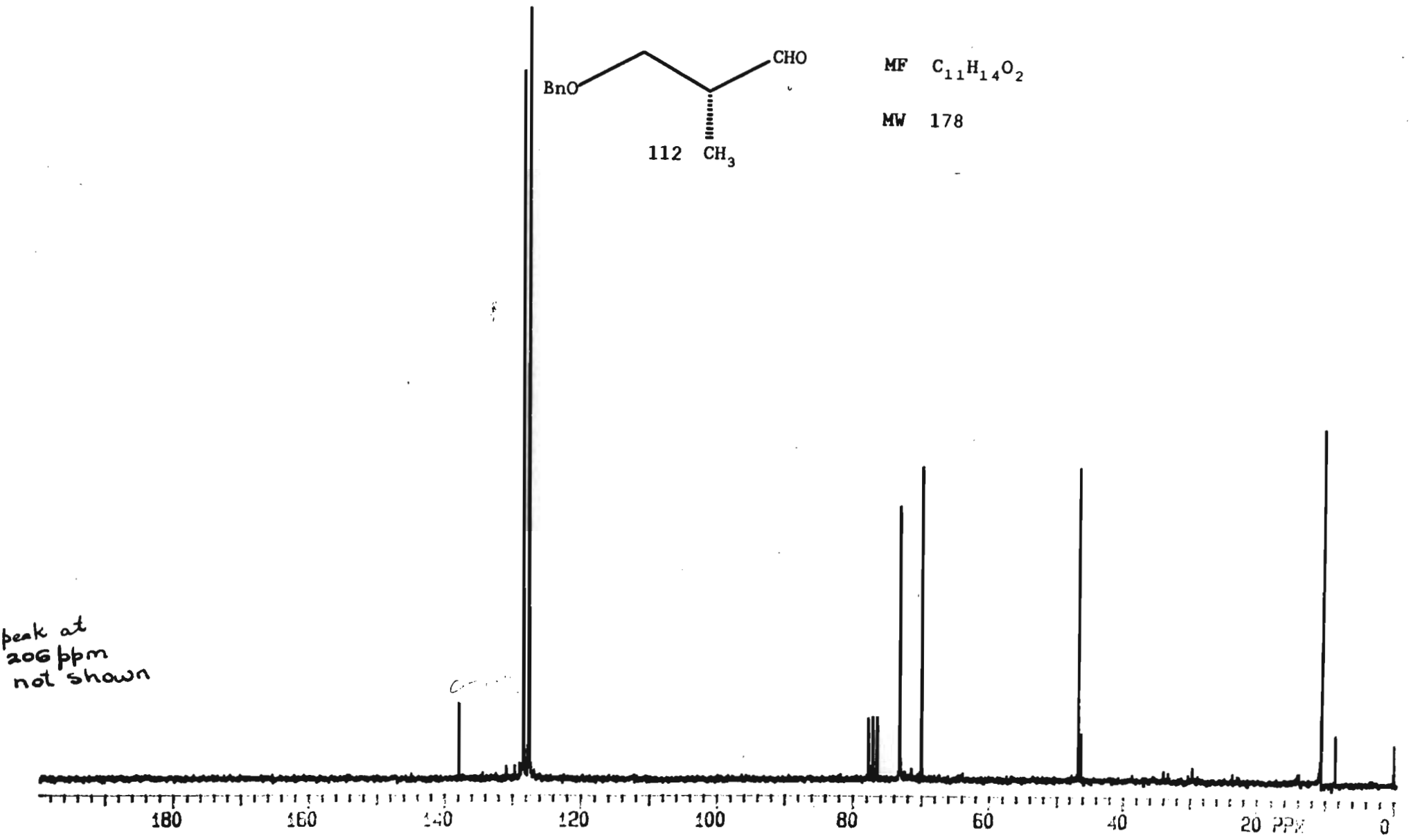
111

MF $C_{11}H_{14}O_2$

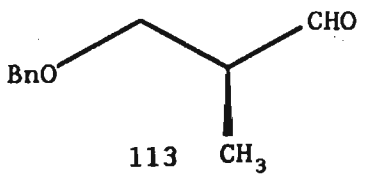
MW 178



BnO
112
CH3
CHO
10
9
8
7
6
5
4
3
2
0

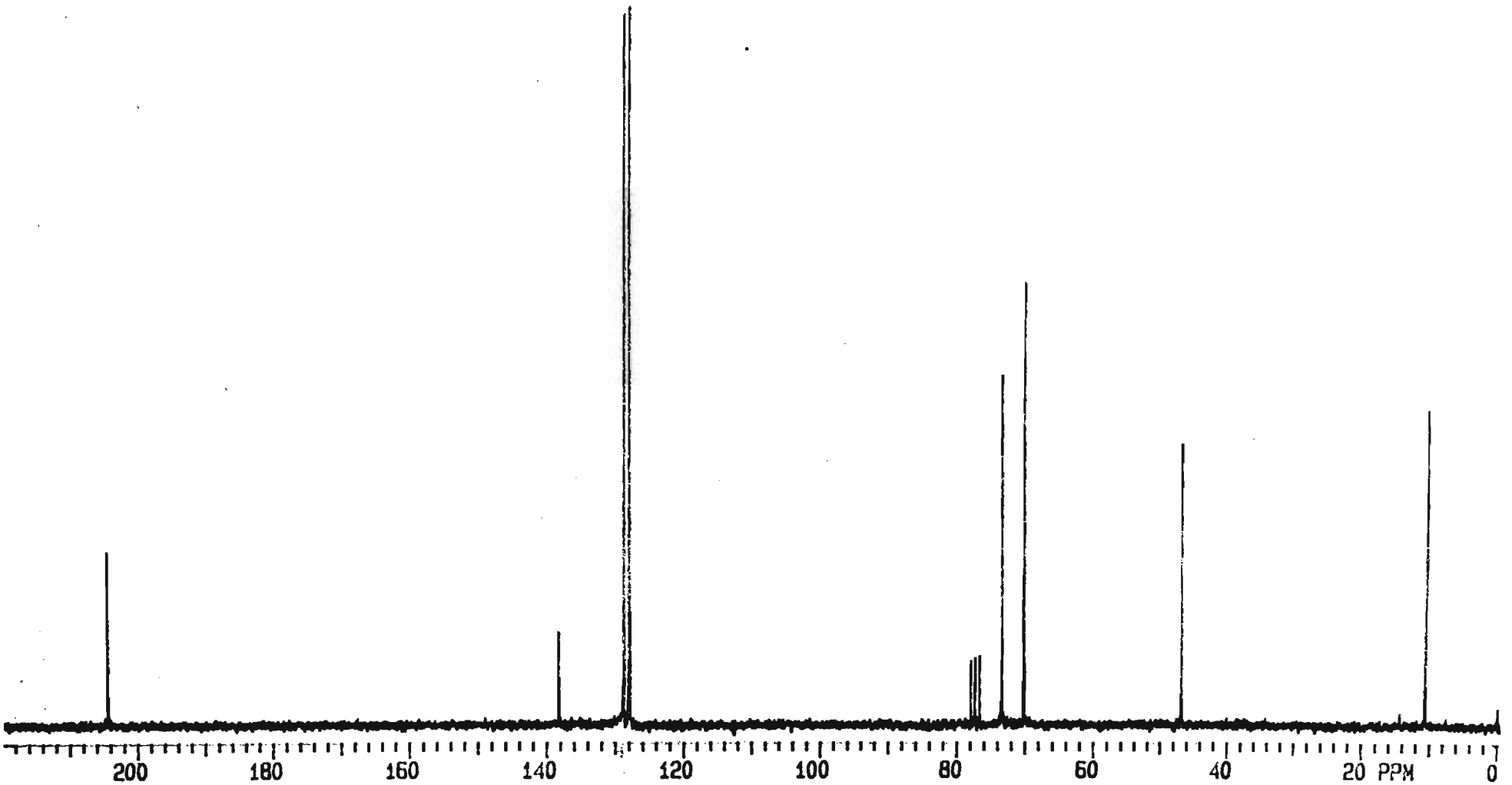

BnO
CHO
112
CH_3
MF $C_{11}H_{14}O_2$
MW 178
peak at
206 ppm
not shown
180
160
140
120
100
80
60
40
20 PPM
0

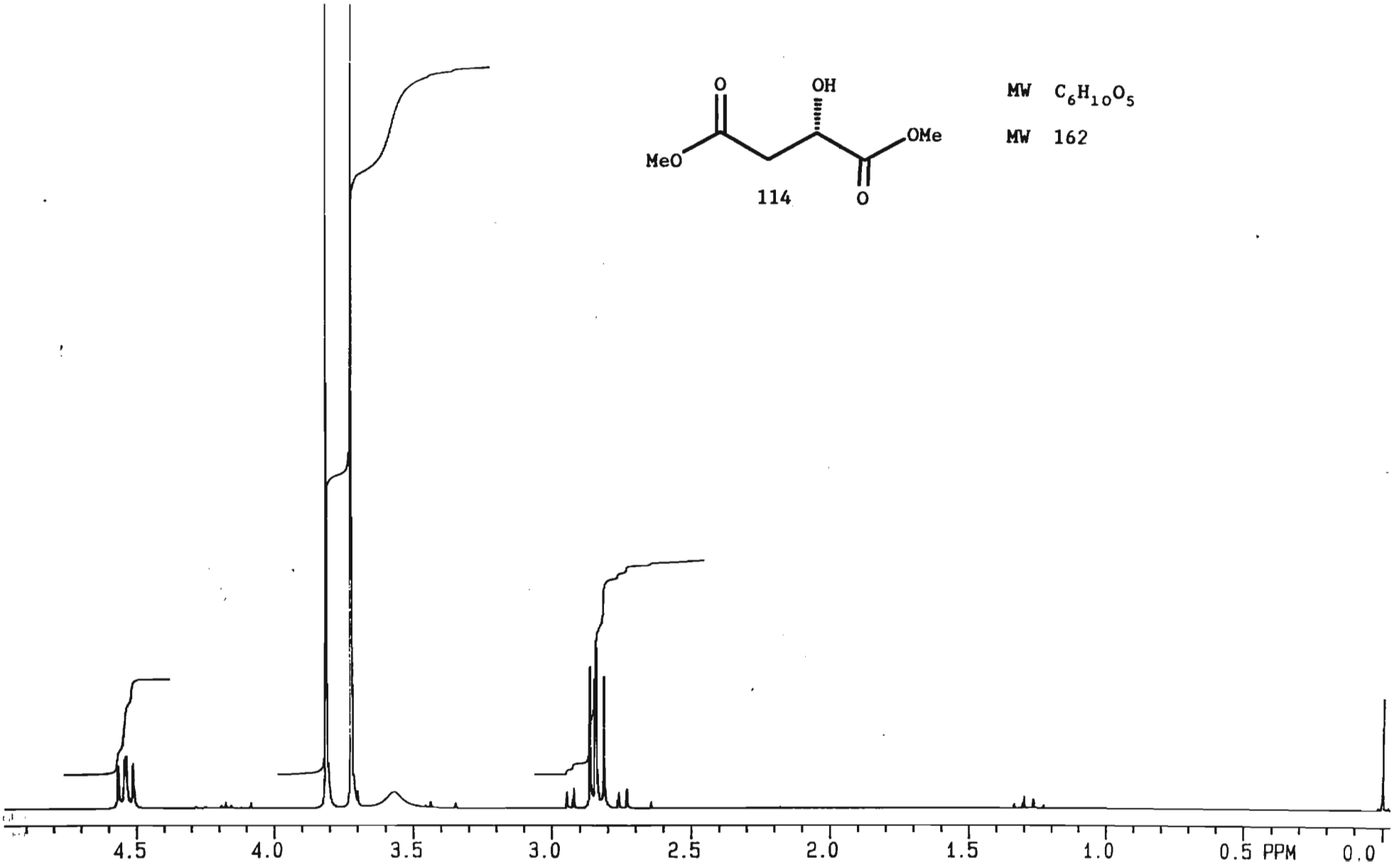
BnO
113
CH3
CHO
PPM
1
2
3
4
5
6
7
8
9



MF $C_{11}H_{14}O_2$

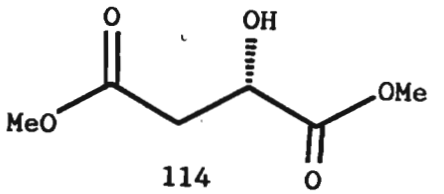
MW 178





MW $C_6H_{10}O_5$

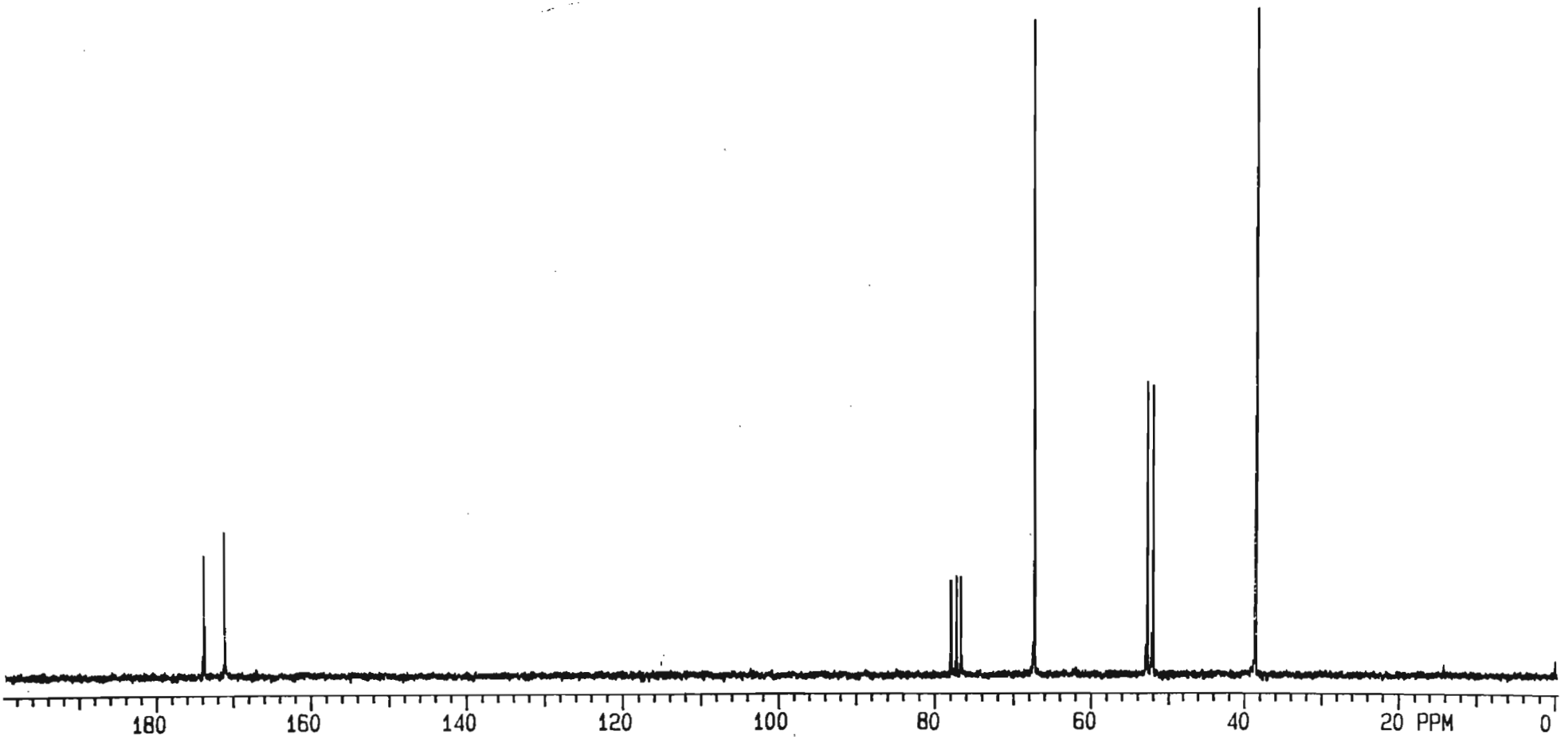
MW 162

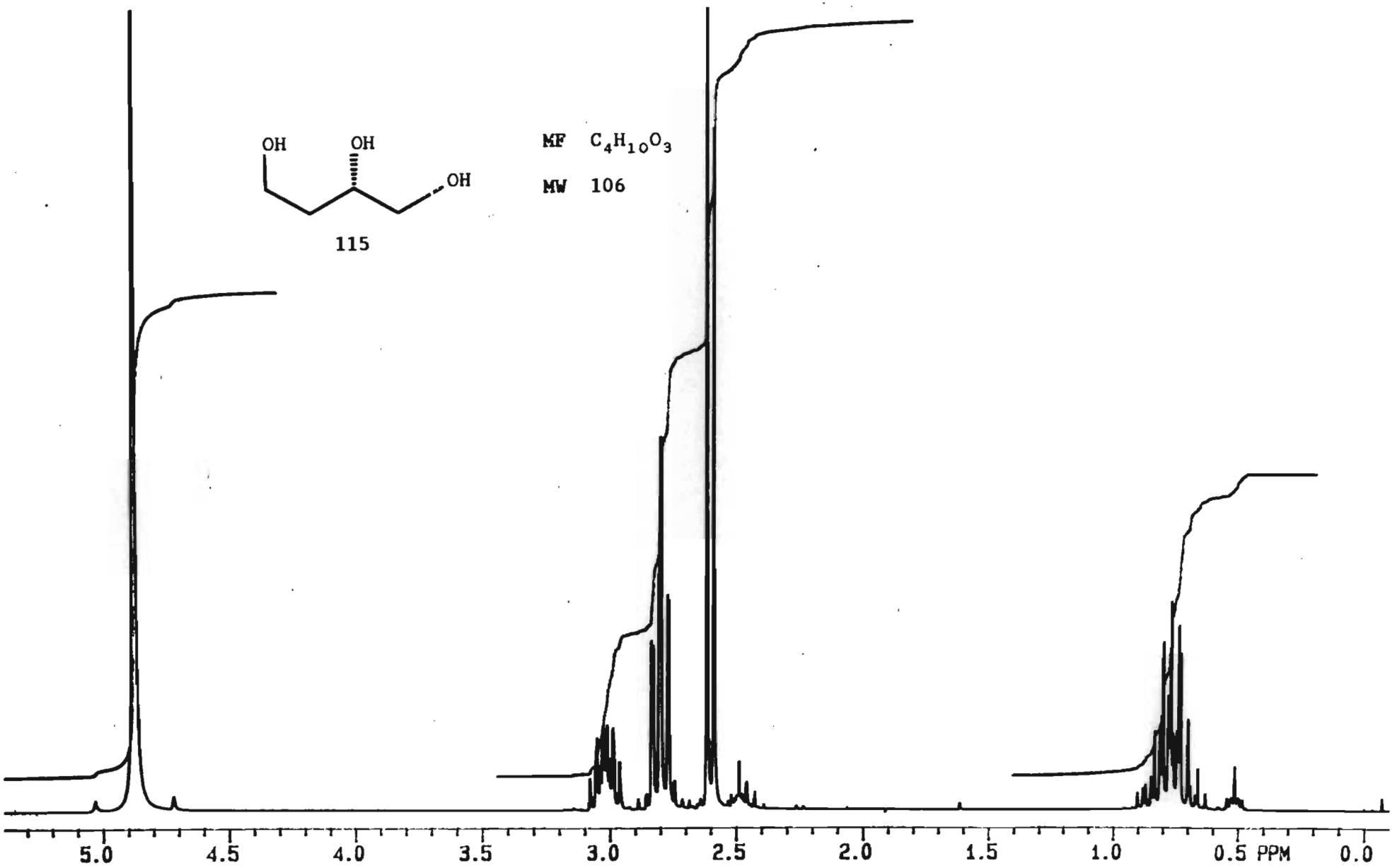


114

MW $C_6H_{10}O_5$

MW 162



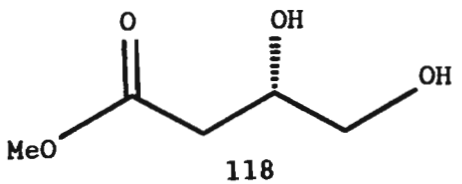

OH
OH
OH
115
MF $C_4H_{10}O_3$
MW 106
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 PPM
0.0

115

MF $C_4H_{10}O_3$

MW 106

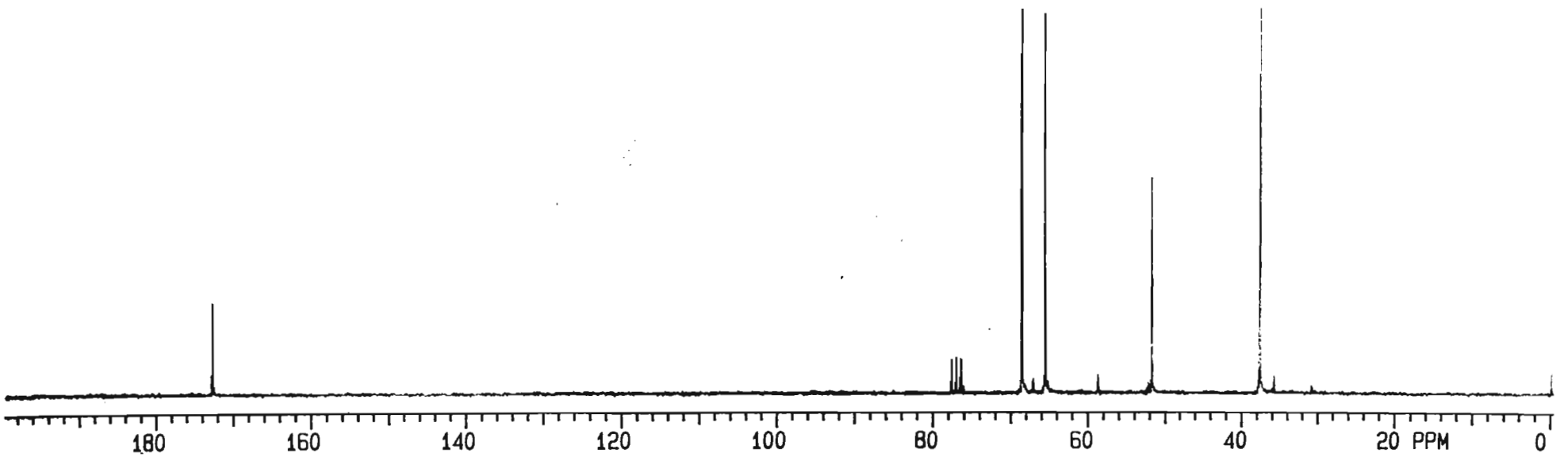
MeO
O
OH
OH
118
MF C5H10O4
MW 134
0
1 PPM
2
3
4
5
6
7
8
9



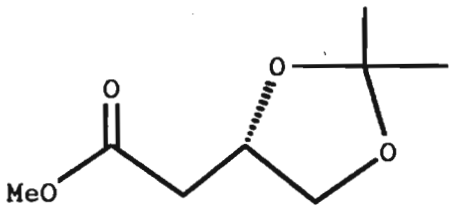
118

MF $C_5H_{10}O_4$

MW 134



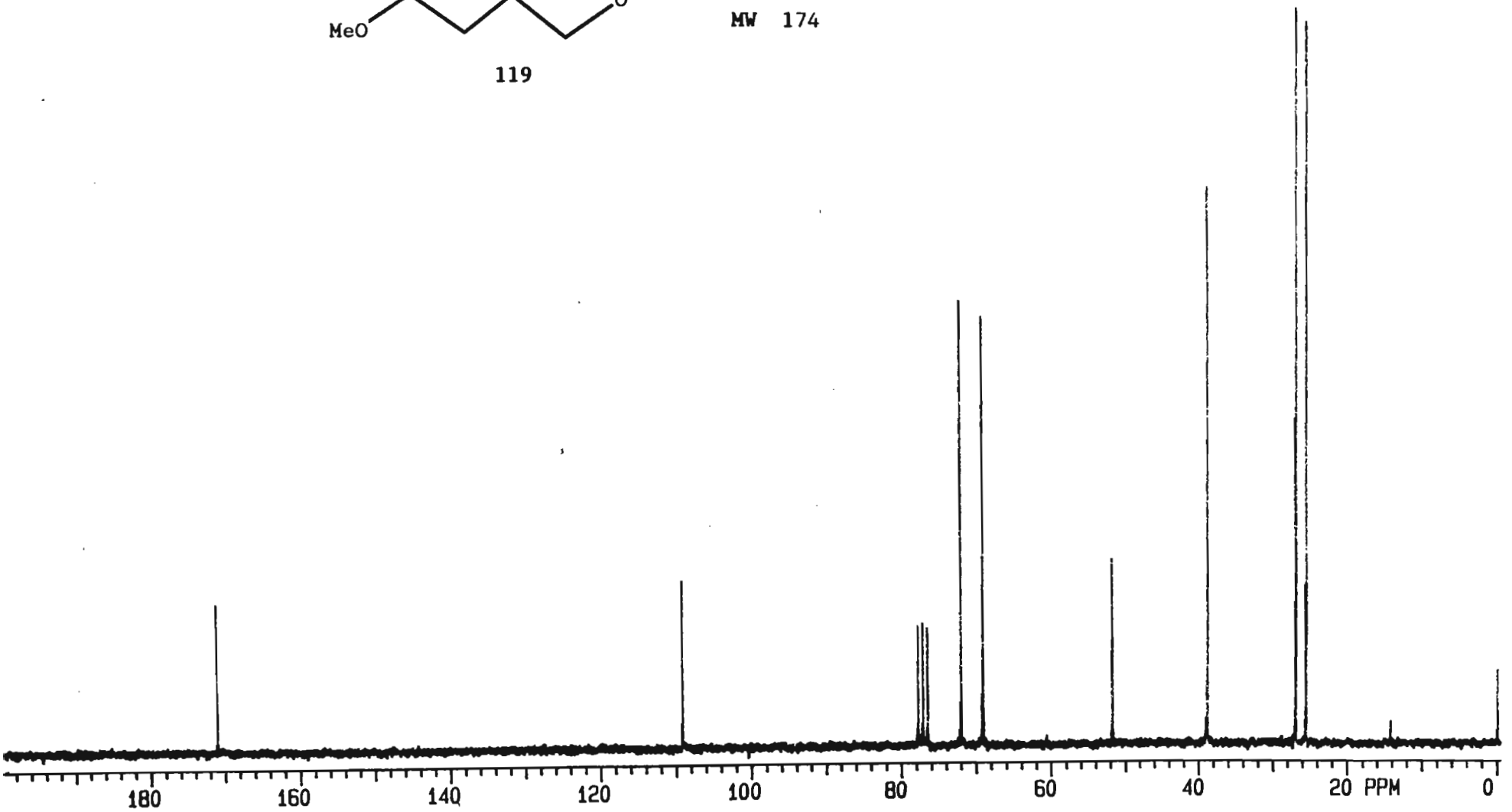
MeO
O
O
O
119
MF C8H14O4
MW 174
1 PPM
2
3
4
5
6
7
8
9

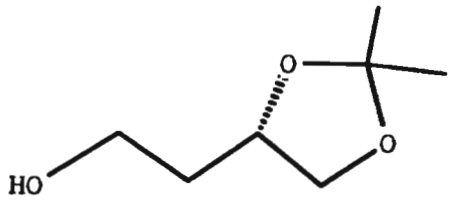


119

MF $C_8H_{14}O_4$

MW 174





116

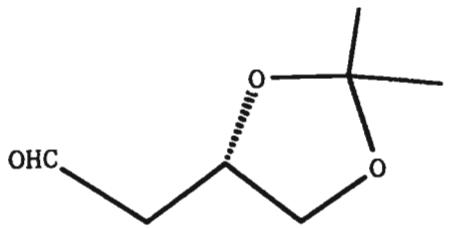
MF $C_7H_{14}O_3$

MW 146

116

MF $C_7H_{14}O_3$

MW. 146



117

MF $C_7H_{12}O_3$

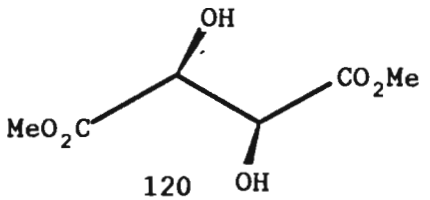
MW 146

117

ME $C_7H_{12}O_3$

MW 146

MeO2C
OH
120
OH
CO2Me
MF C6H10O6
MW 178
1 PPM
2
3
4
5
6
7
8
9

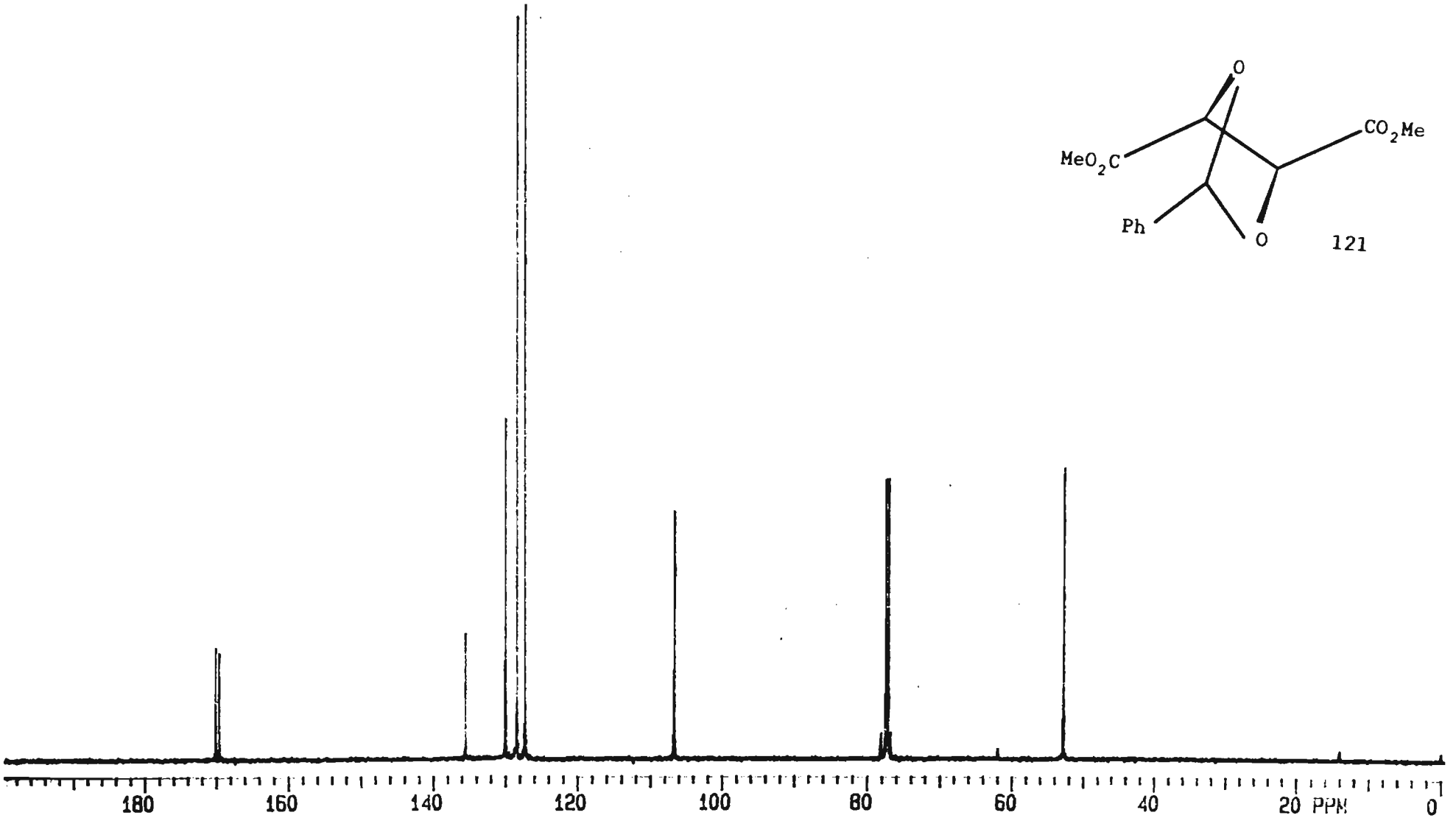


120

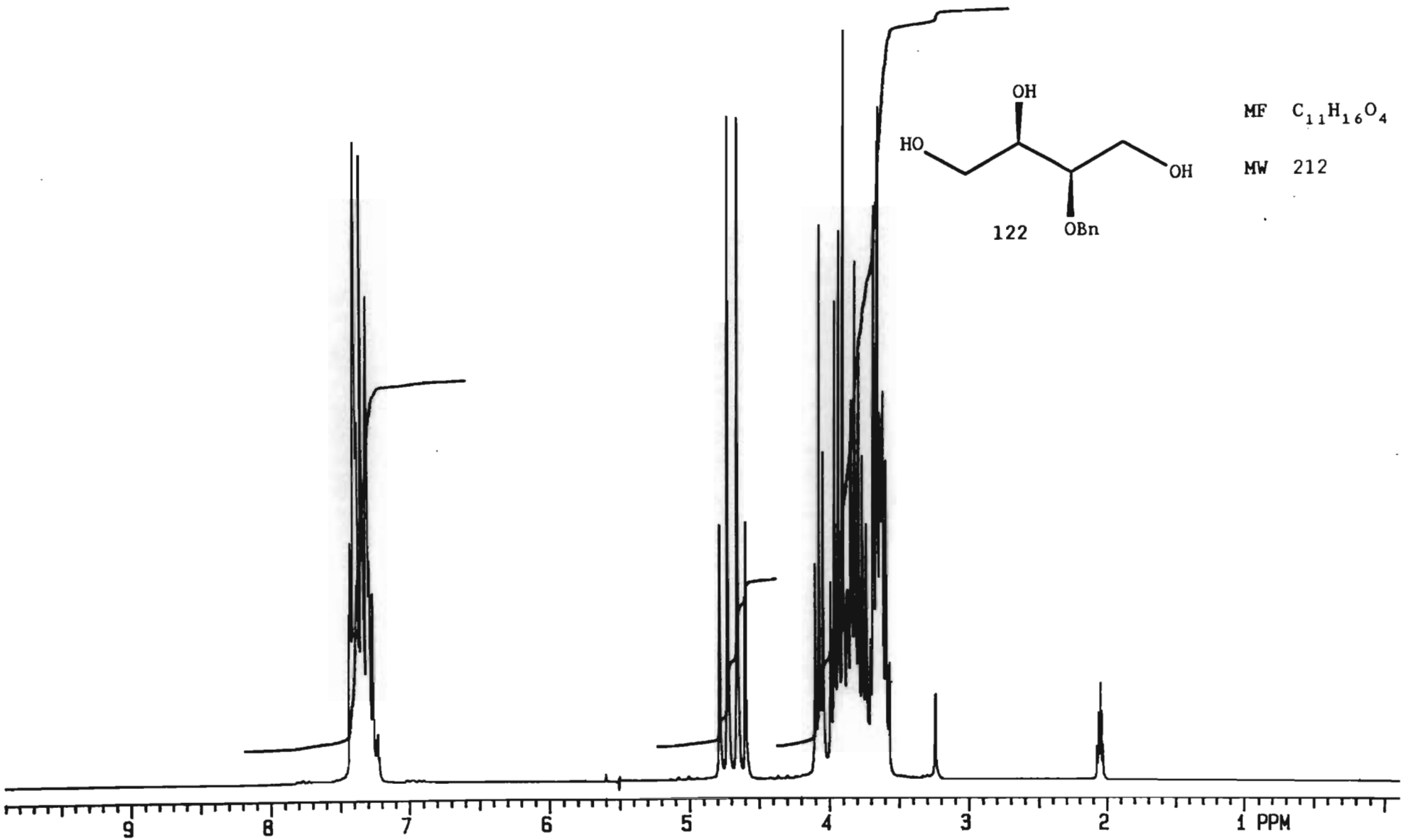
MF $C_6H_{10}O_6$

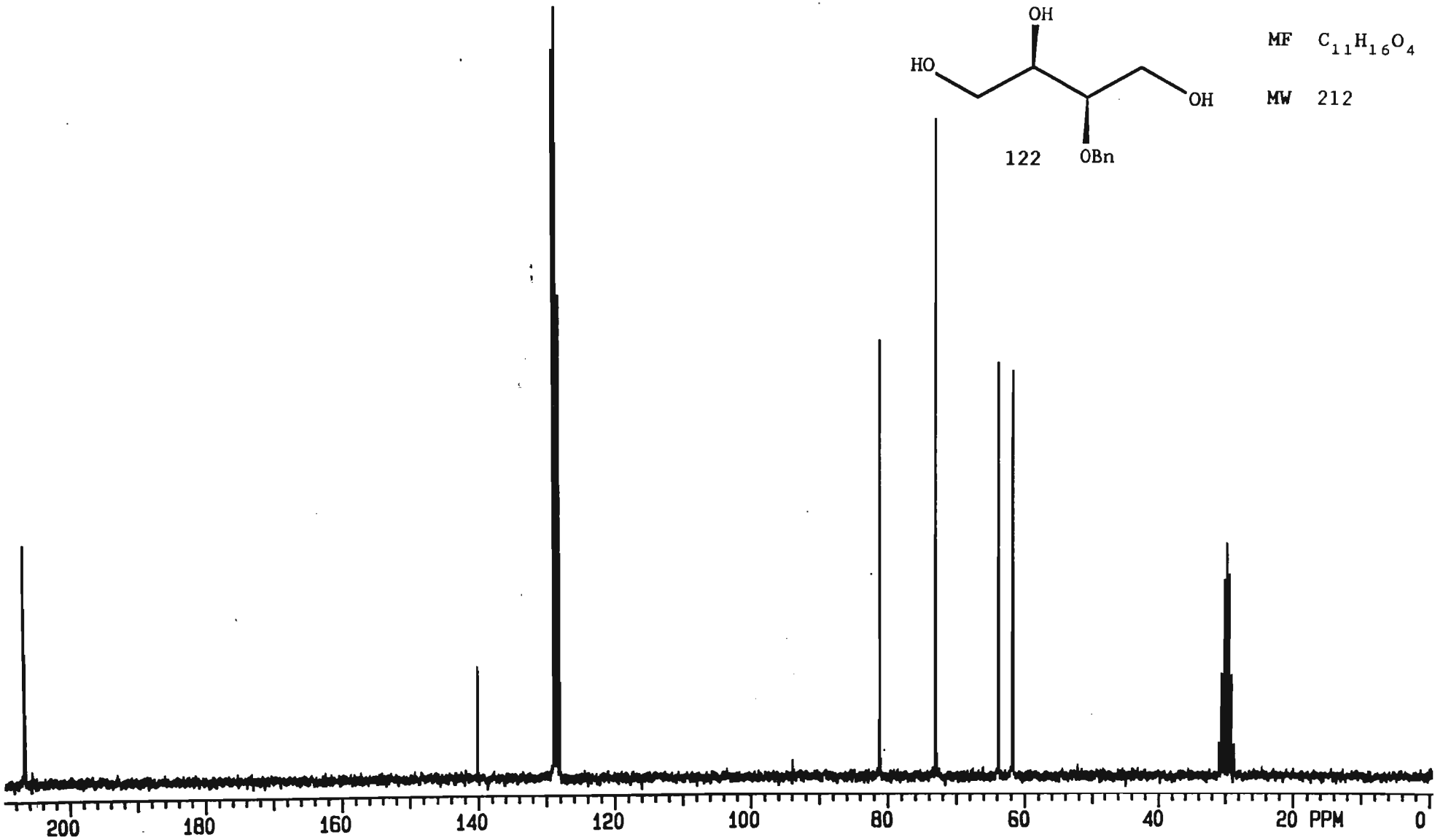
MW 178

121



121


OH
HO
OH
OBn
122
MF C11H16O4
MW 212
9
8
7
6
5
4
3
2
1 PPM

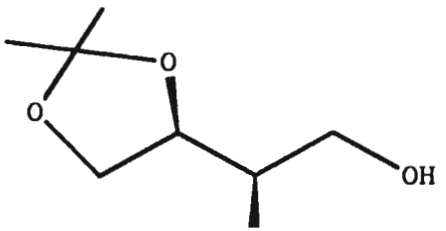


122

MF $C_{11}H_{16}O_4$

MW 212

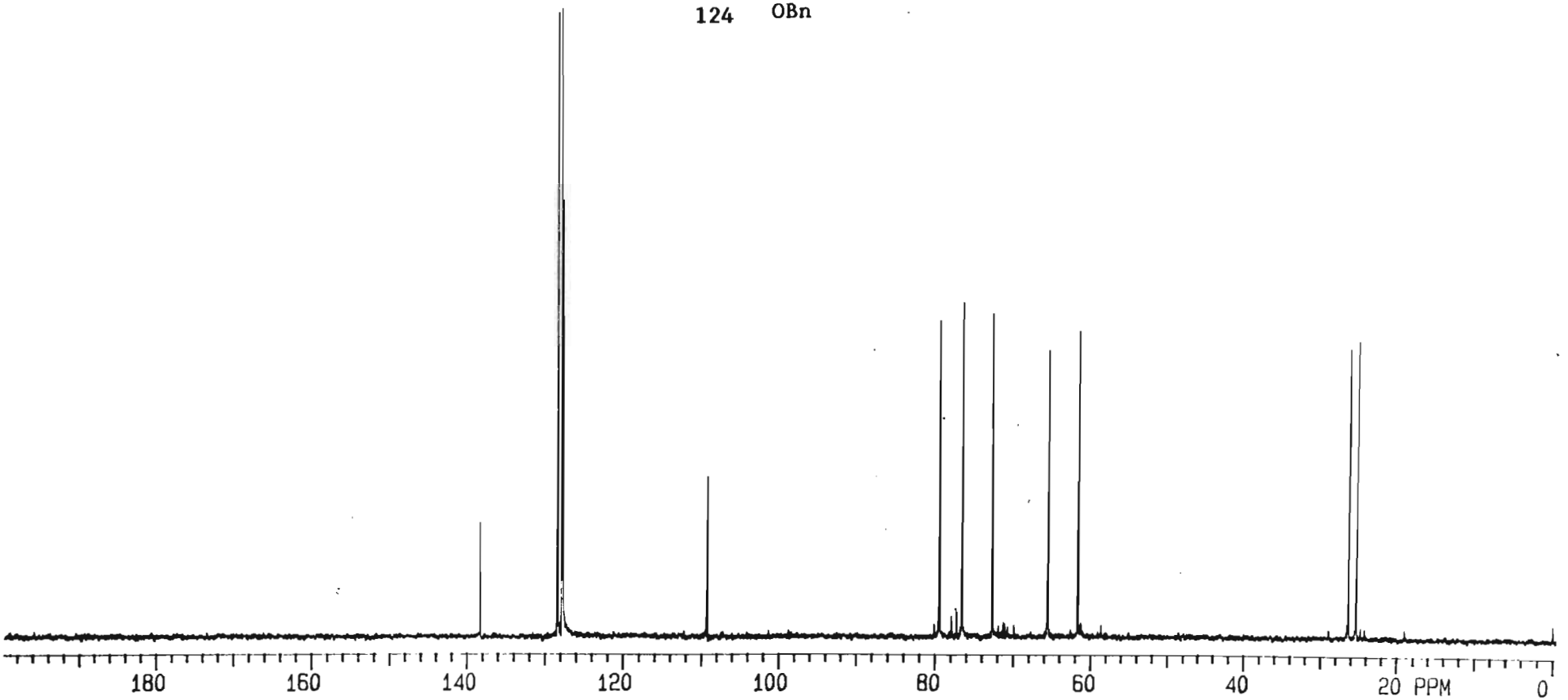
124
OBn
OH
O
O
PPM
1
2
3
4
5
6
7
8
9

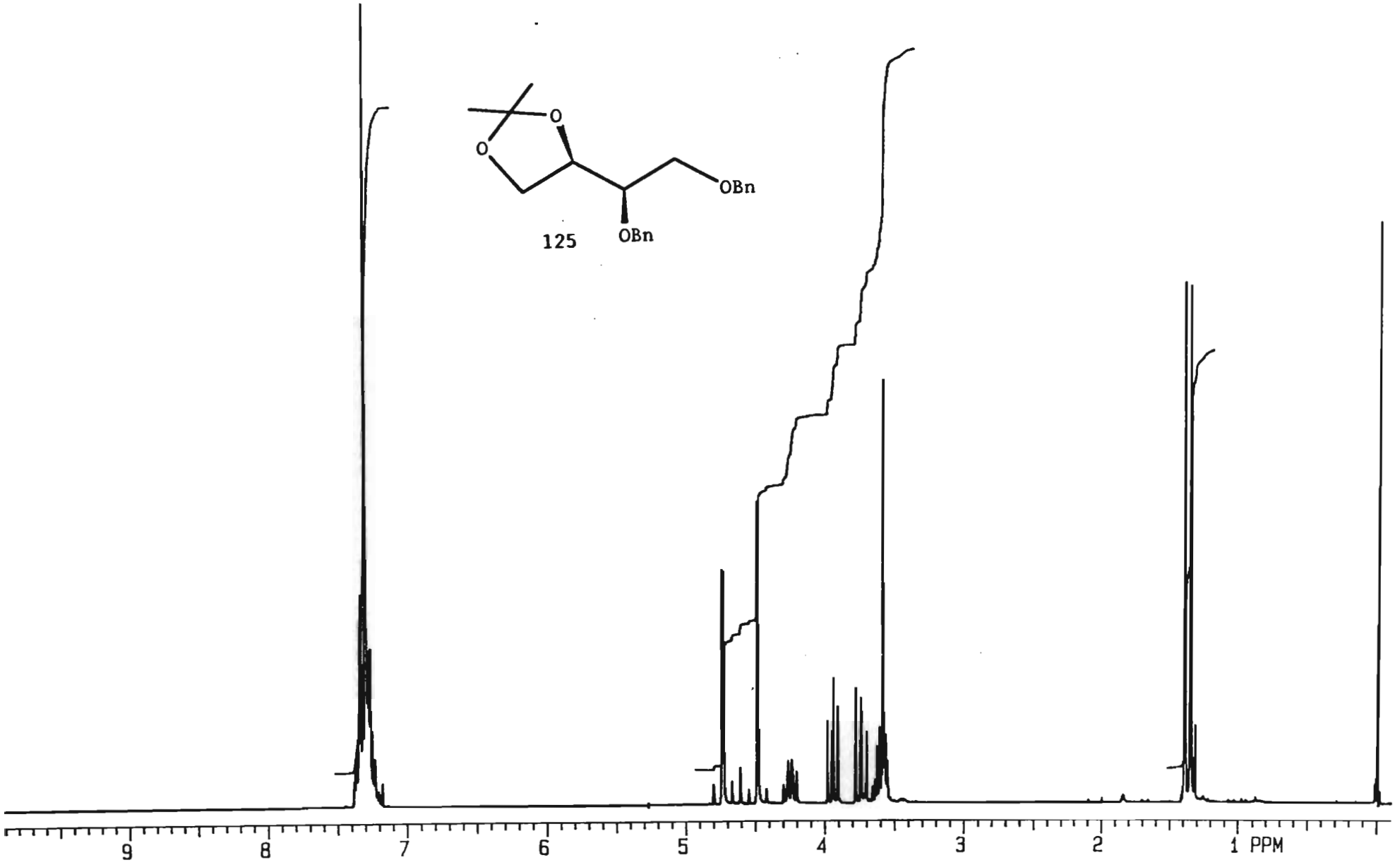


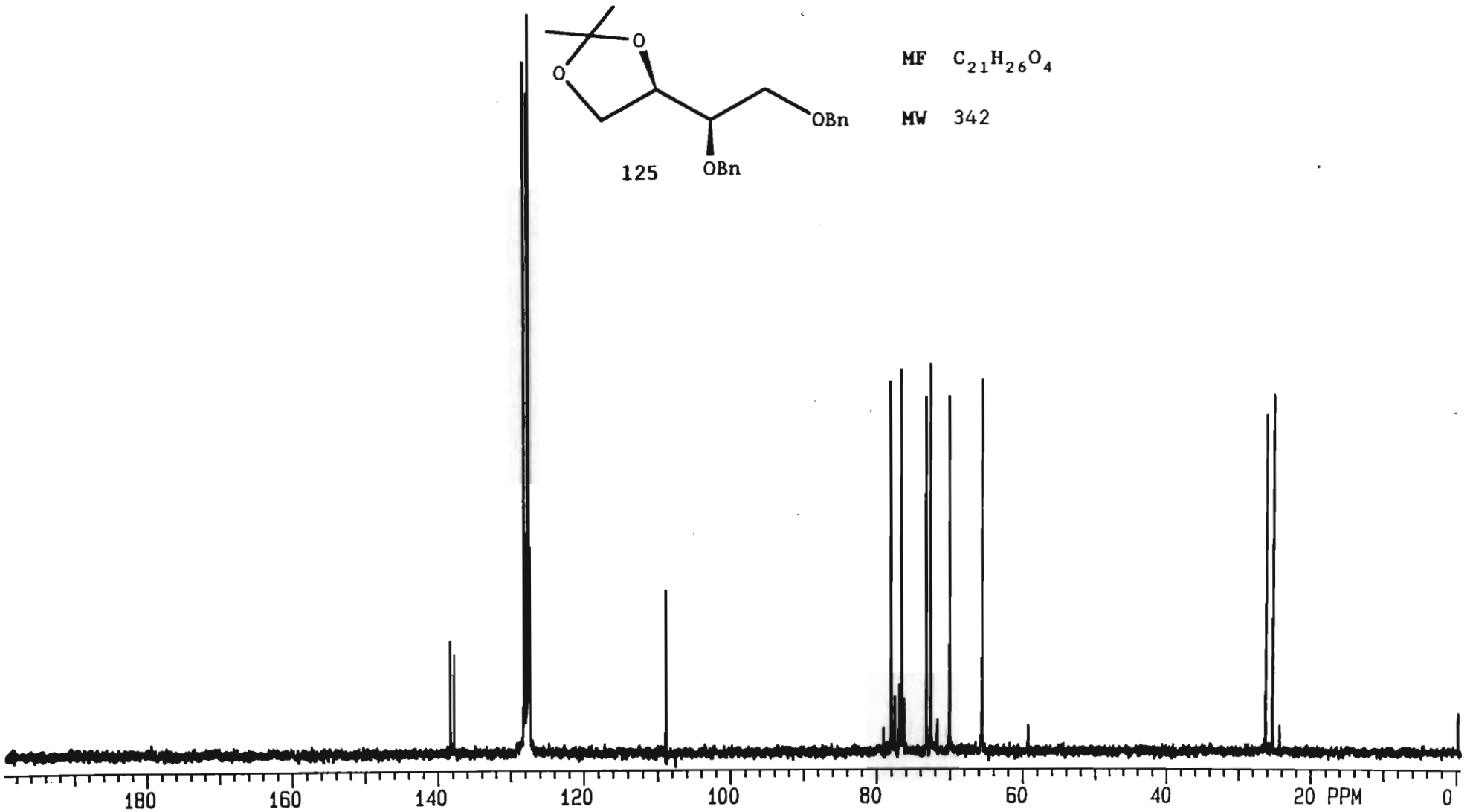
124

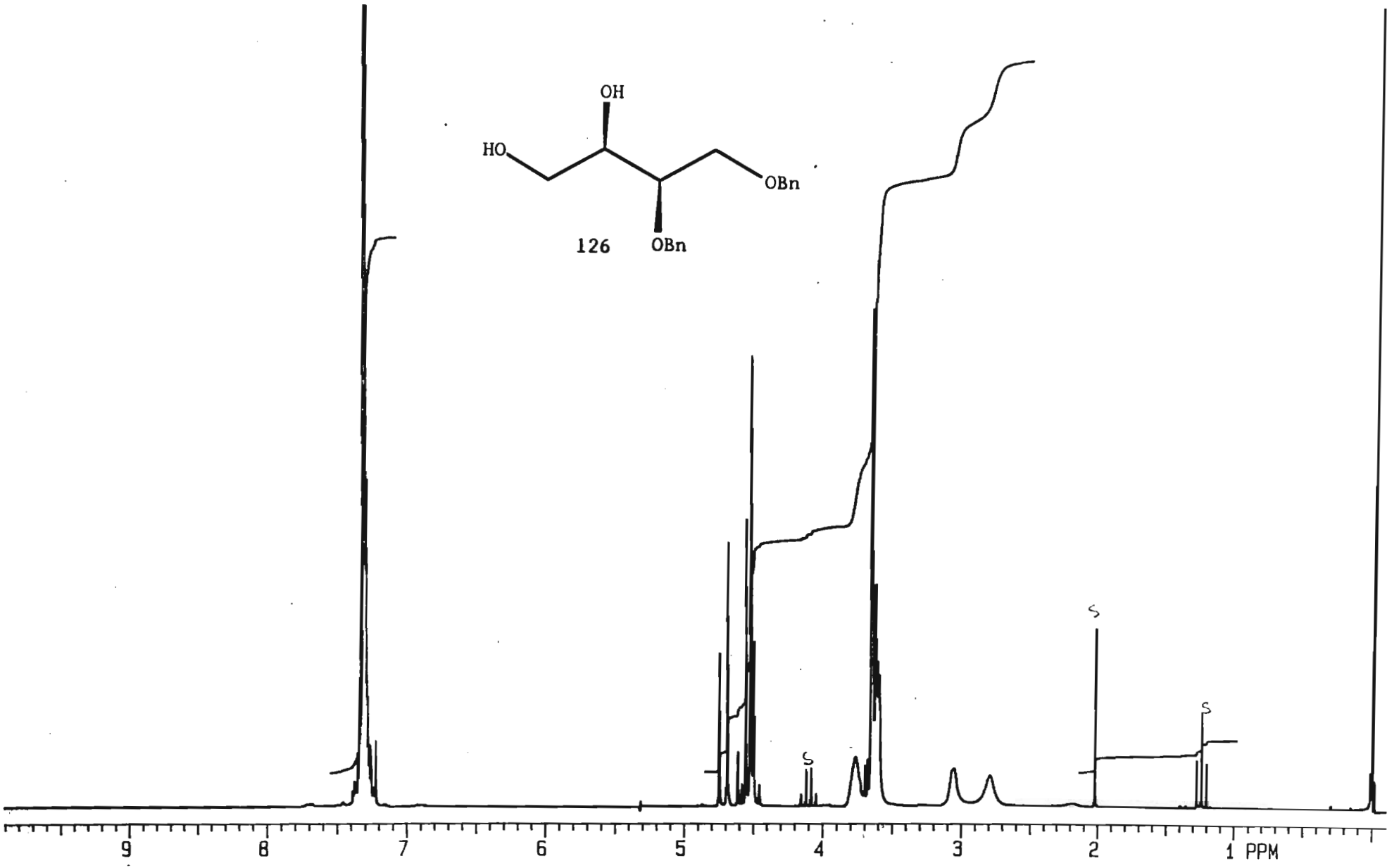
MF $C_{14}H_{20}O_4$

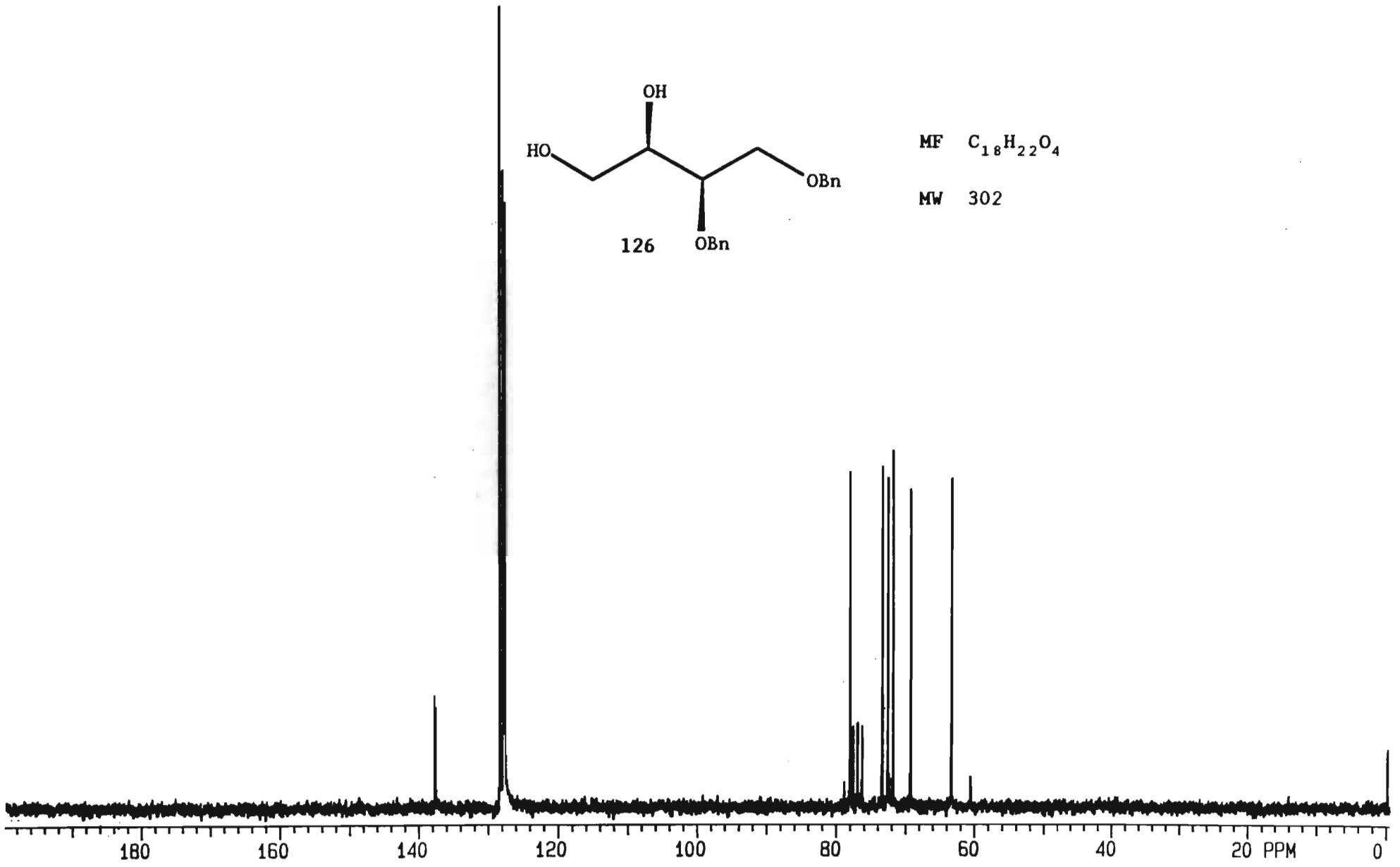
MW 252

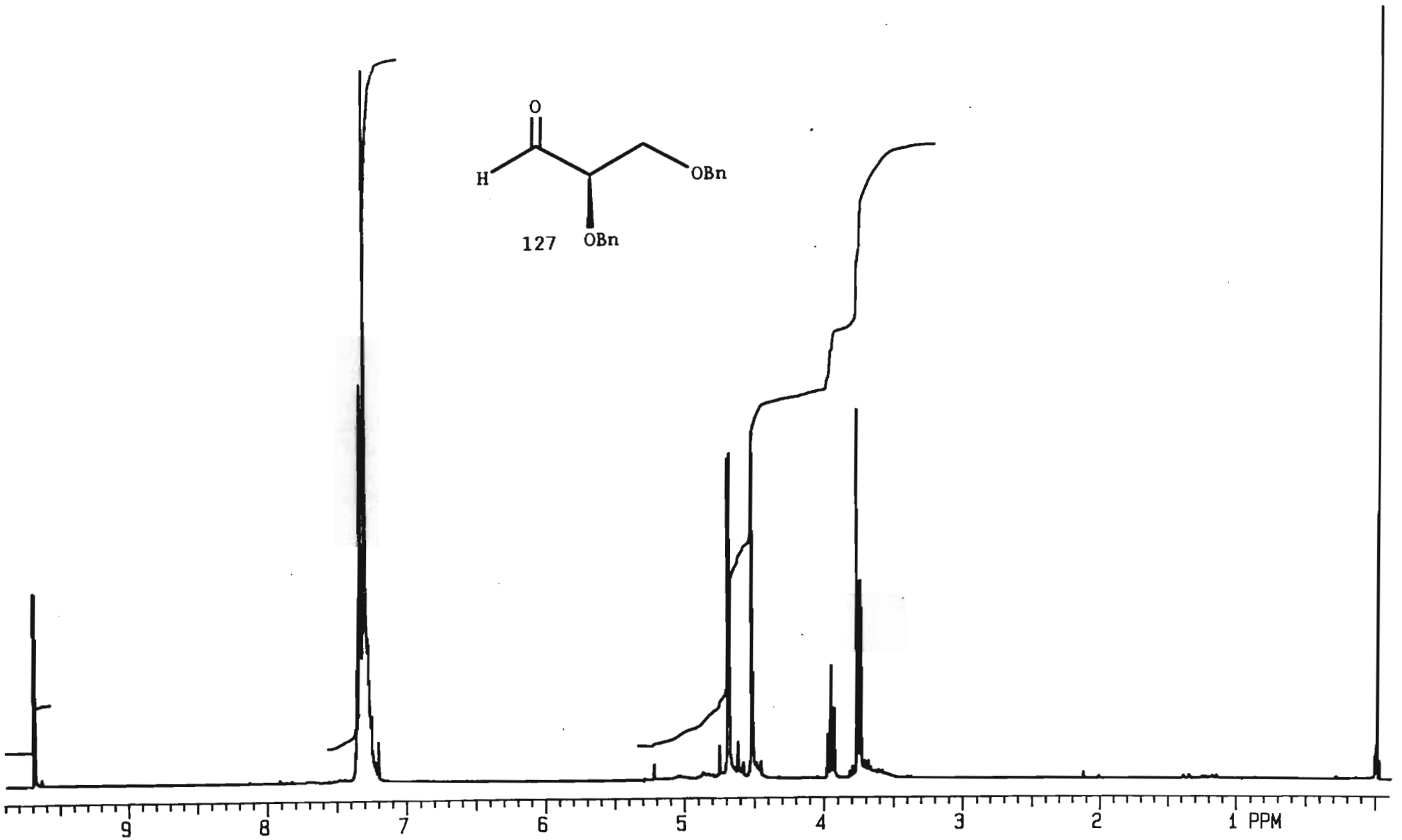


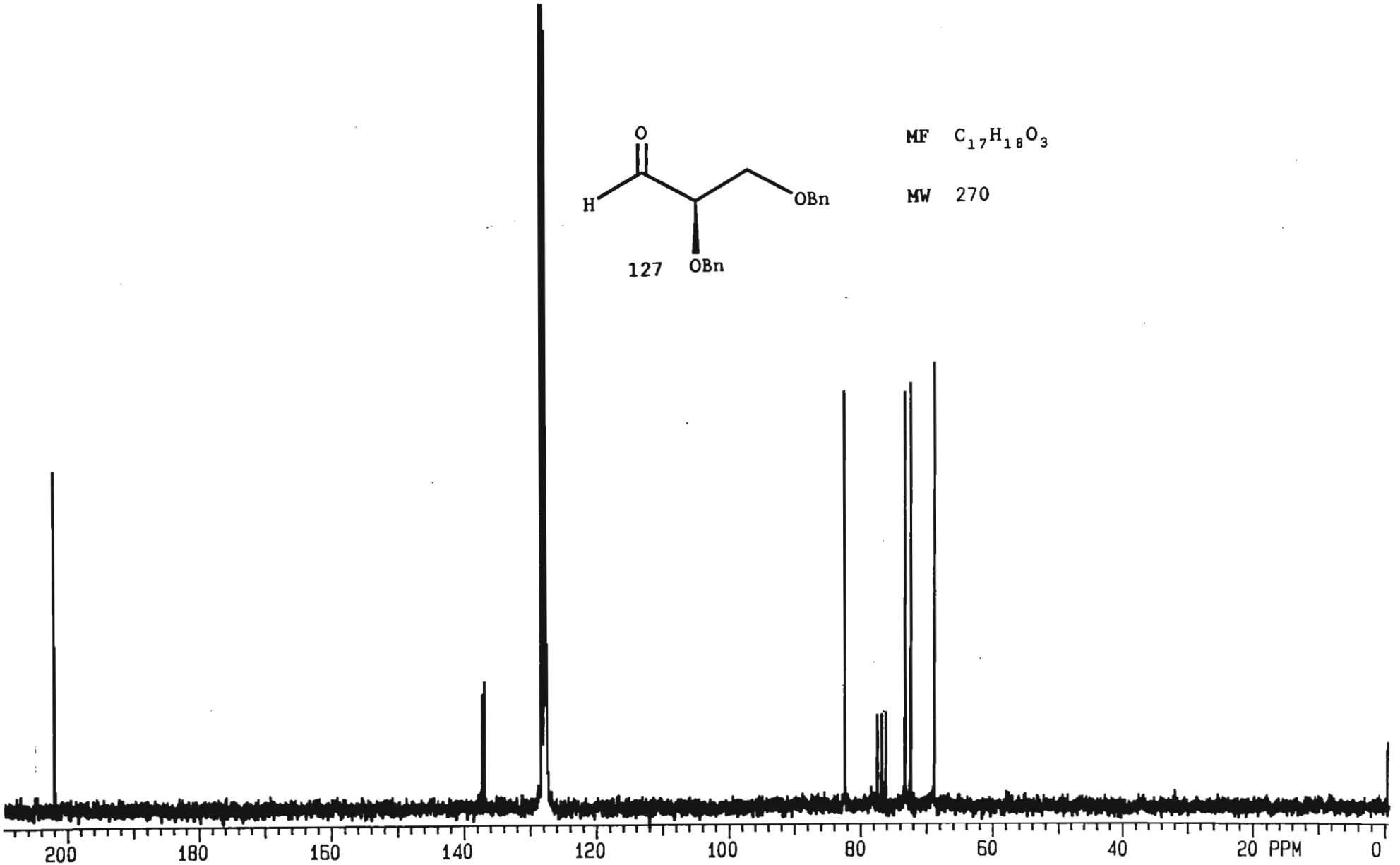

O
O
OBn
OBn
125
9
8
7
6
5
4
3
2
1 PPM

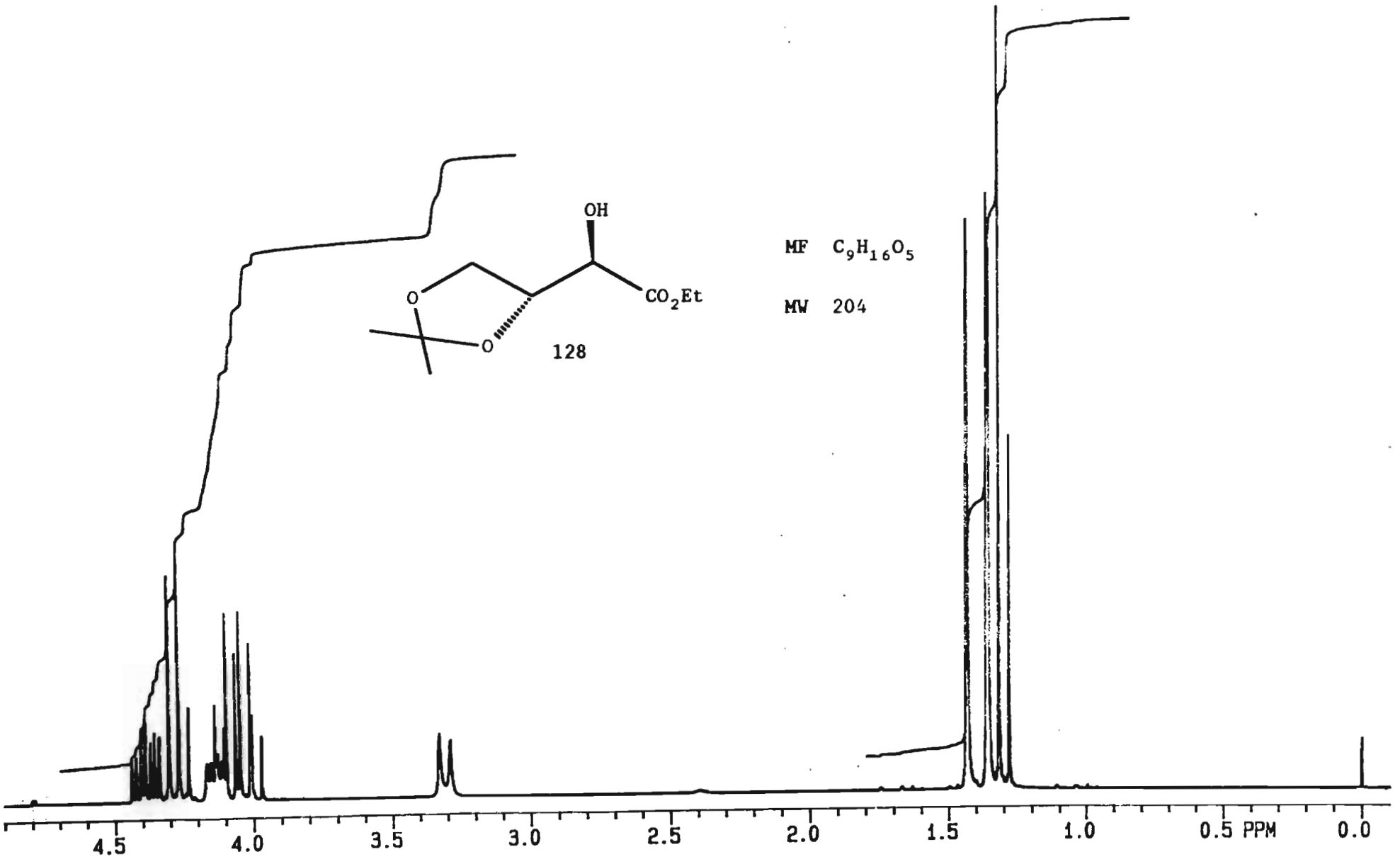

O
O
OBn
OBn
125
MF $C_{21}H_{26}O_4$
MW 342
180
160
140
120
100
80
60
40
20 PPM
0


OH
HO
OBn
126
OBn
9
8
7
6
5
4
3
2
1 PPM


OH
HO
OBn
OBn
126
MF C18H22O4
MW 302
180
160
140
120
100
80
60
40
20 PPM
0

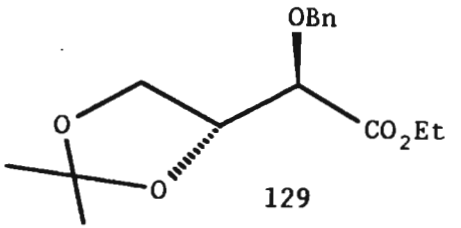

O
H
OBn
127
OBn
9
8
7
6
5
4
3
2
1 PPM


O
H
OBn
127
OBn
MF C17H18O3
MW 270
200
180
160
140
120
100
80
60
40
20
PPM
0


OH
CO2Et
O
O
128
MF C9H16O5
MW 204
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 PPM
0.0

180
160
140
120
100
80
60
40
20
0
PPM
128
MF C9H16O5
MW 204

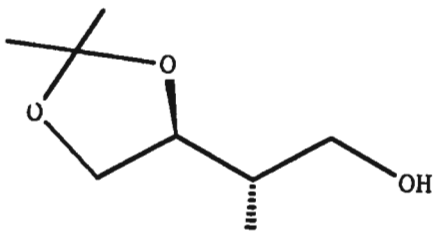
129



129

MF $C_{16}H_{22}O_5$

MW 294

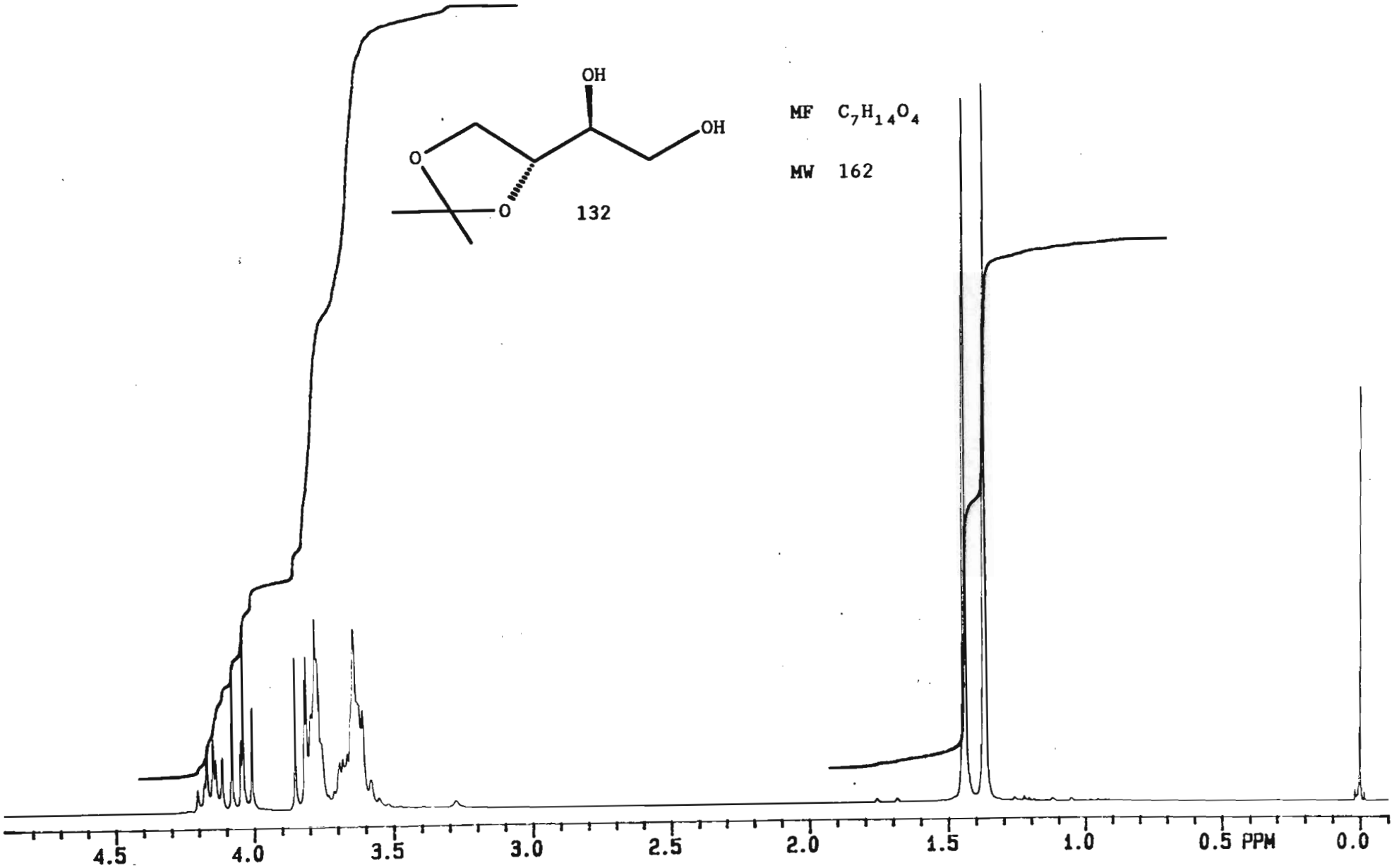


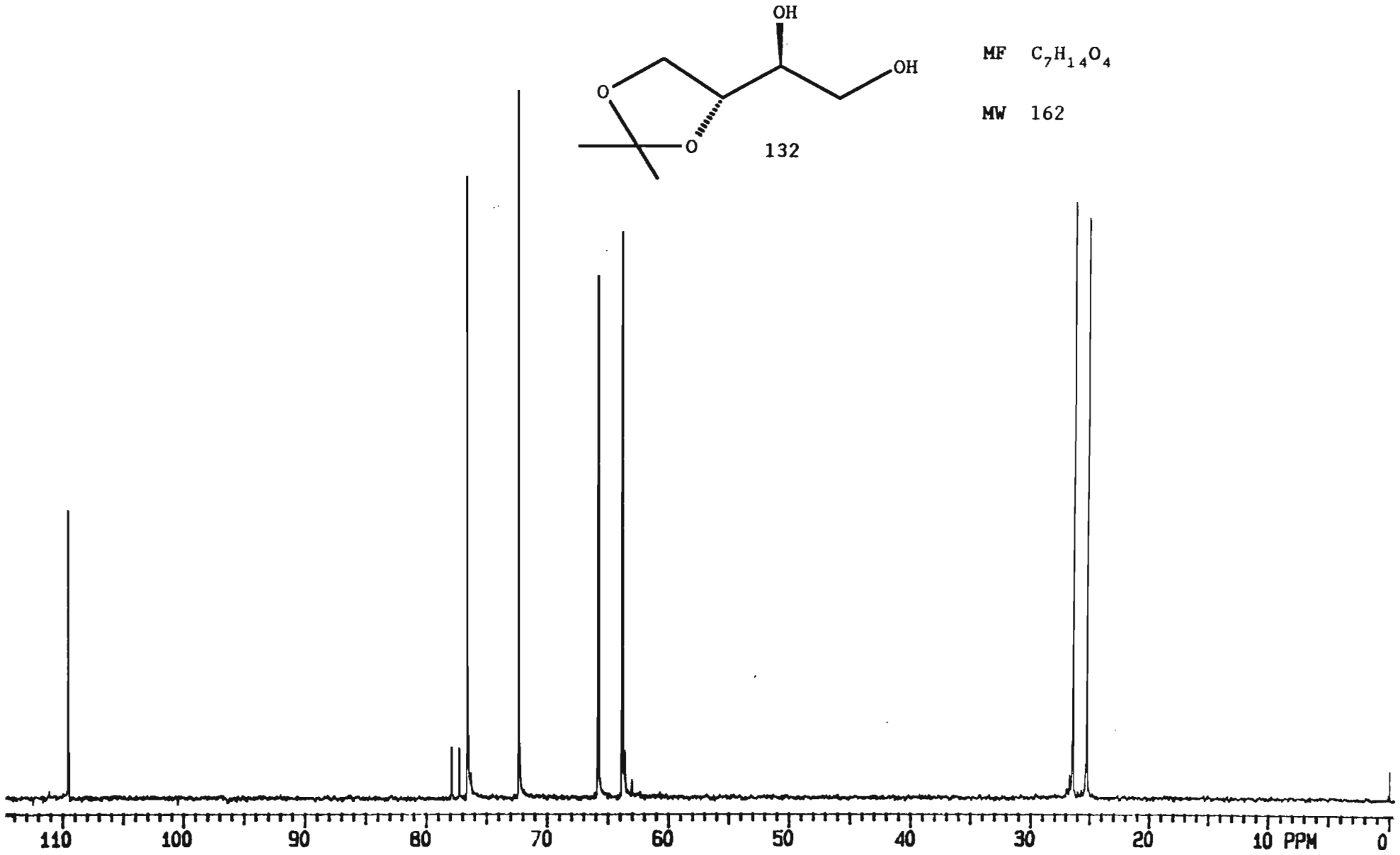
130

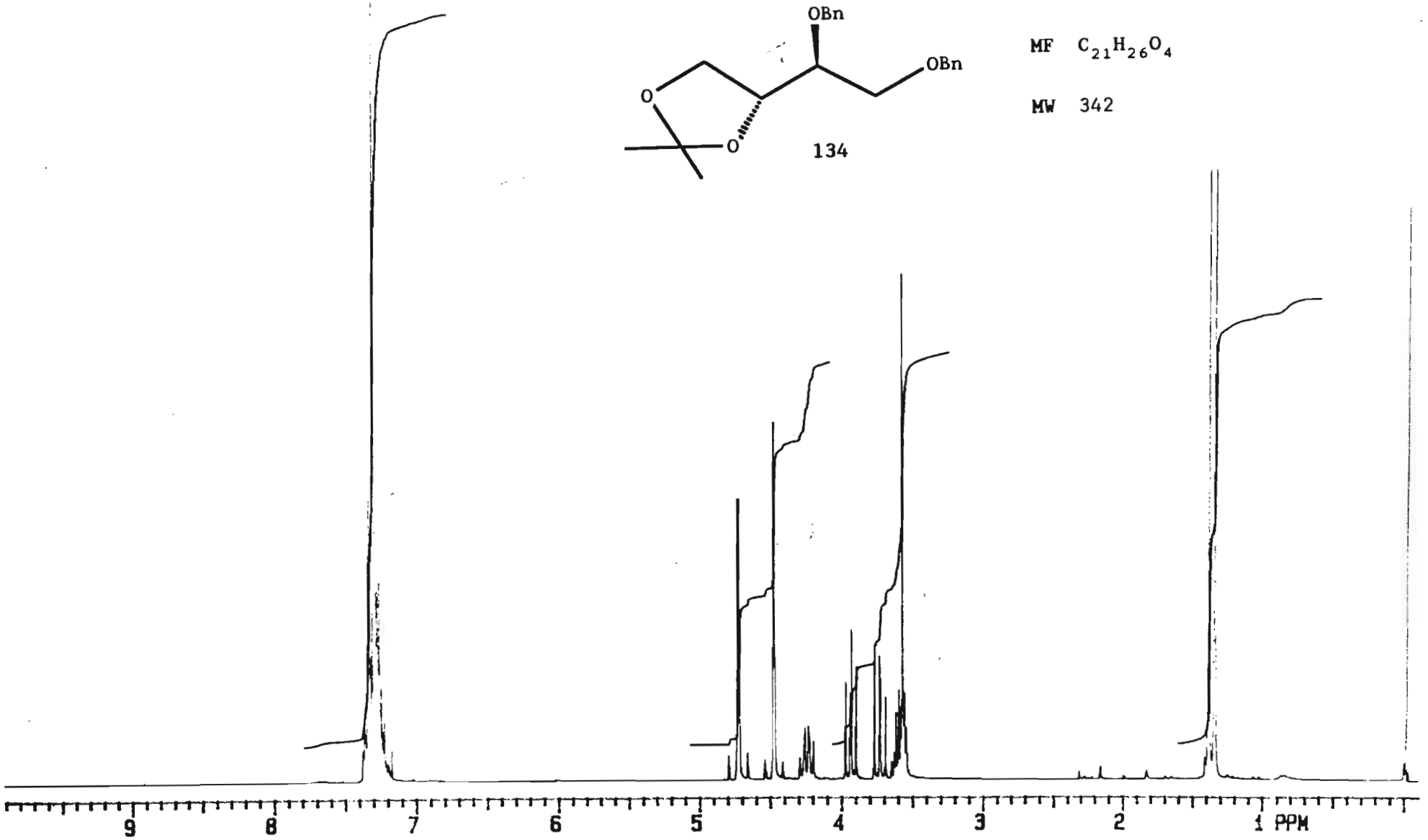
MF $C_{14}H_{20}O_4$

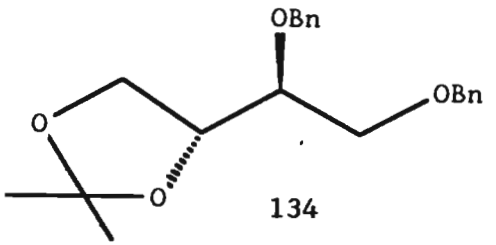
MW 252

180
160
140
120
100
80
60
40
20
PPM
0
130
OBn
OH
O
O


OH
OH
O
O
132
MF C7H14O4
MW 162
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 PPM
0.0


OH
OH
O
O
132
MF C7H14O4
MW 162
110
100
90
80
70
60
50
40
30
20
10 PPM
0

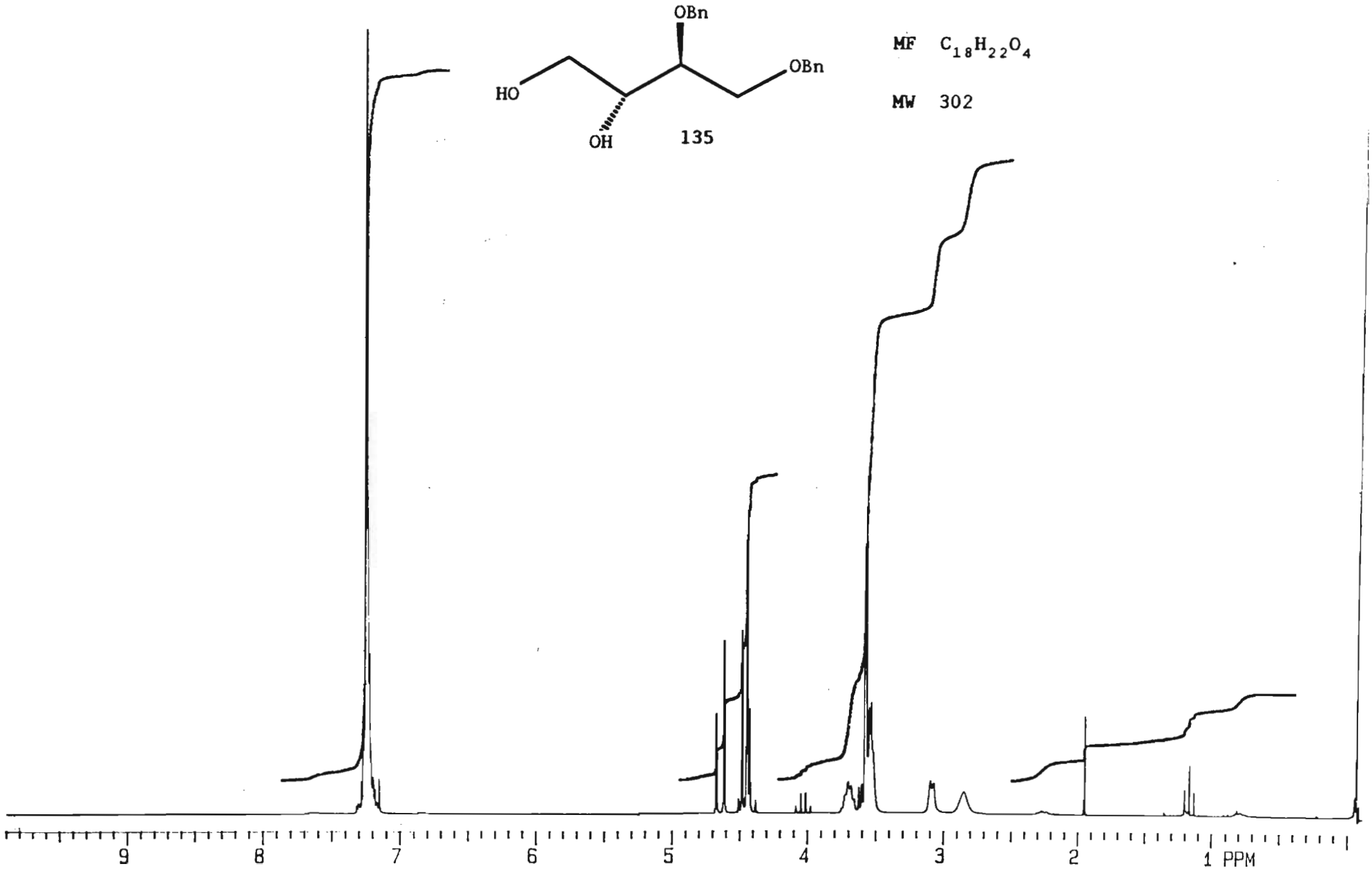

OBn
OBn
O
O
134
MF C21H26O4
MW 342
9
8
7
6
5
4
3
2
1 PPM

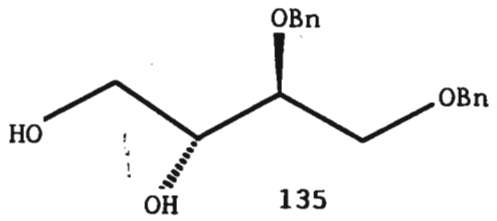


134

MF $C_{21}H_{26}O_4$

MW 342

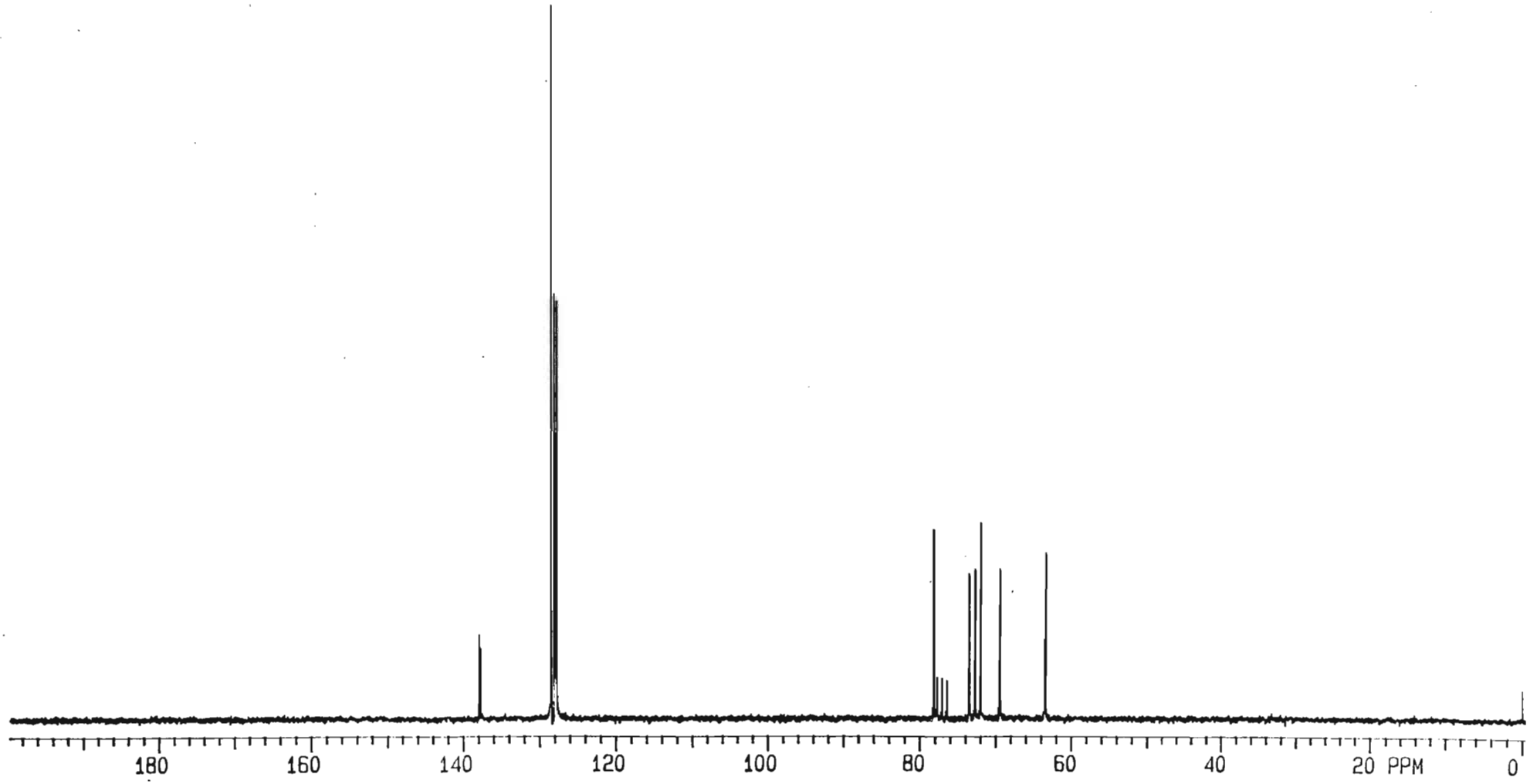

OBn
HO
OBn
OH
135
MF C18H22O4
MW 302
9
8
7
6
5
4
3
2
1 PPM

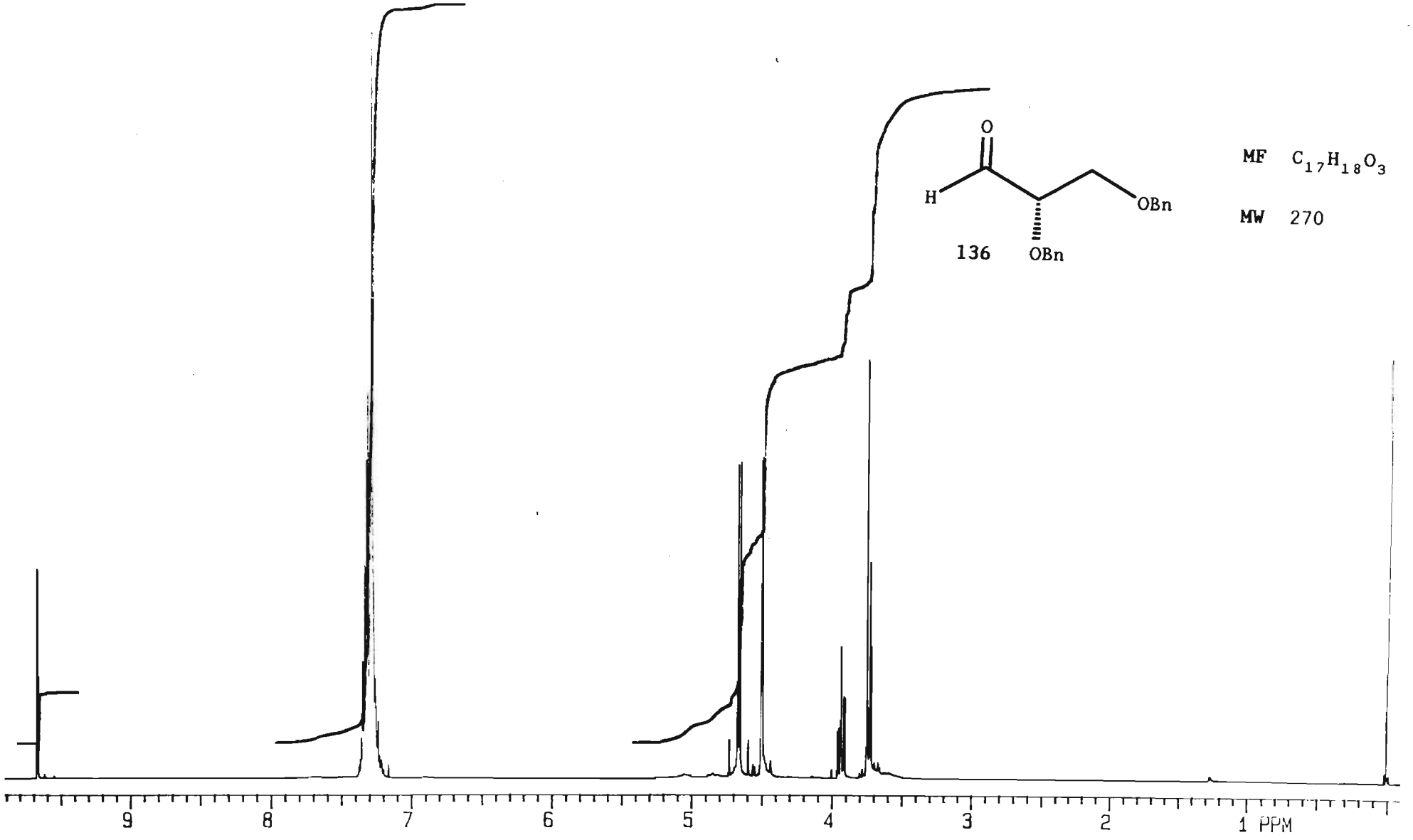


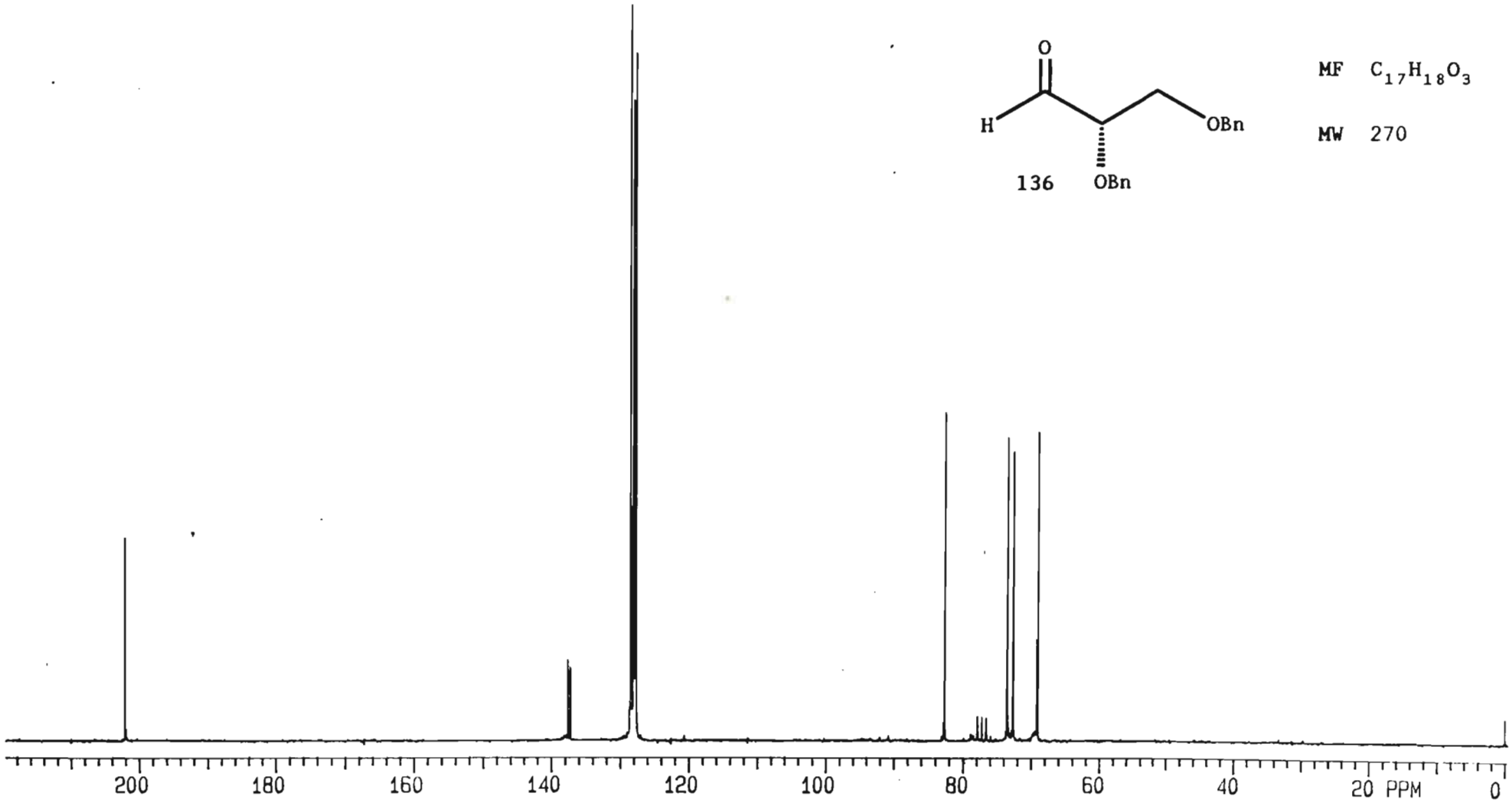
135

MF $C_{18}H_{22}O_4$

MW 302



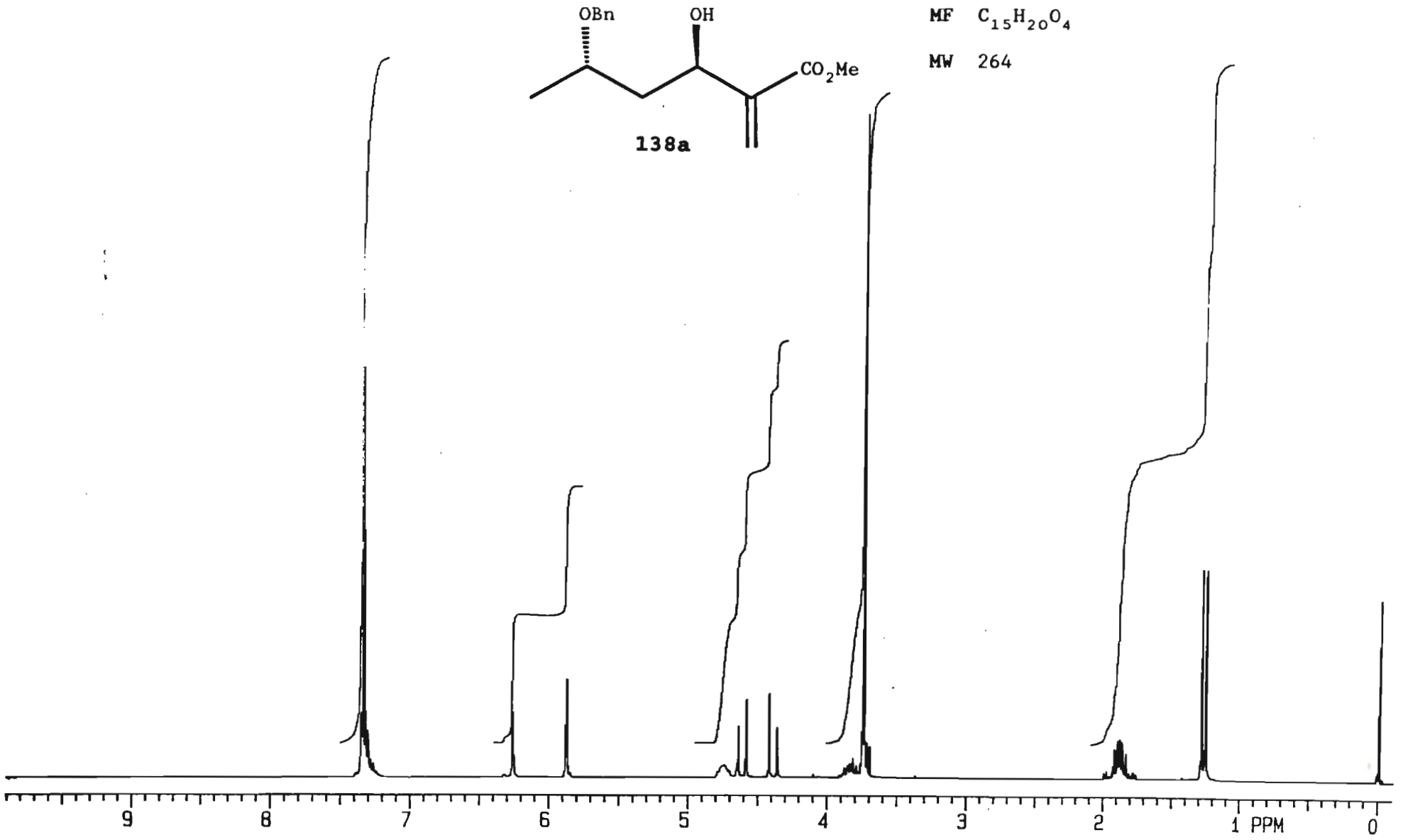

O
H
OBn
OBn
136
MF C17H18O3
MW 270
9
8
7
6
5
4
3
2
1 PPM



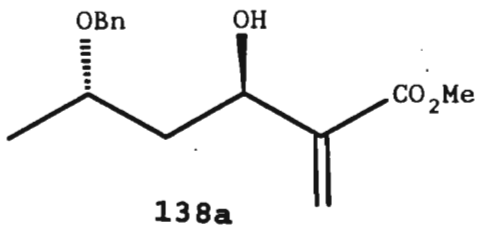
136

MF $C_{17}H_{18}O_3$

MW 270



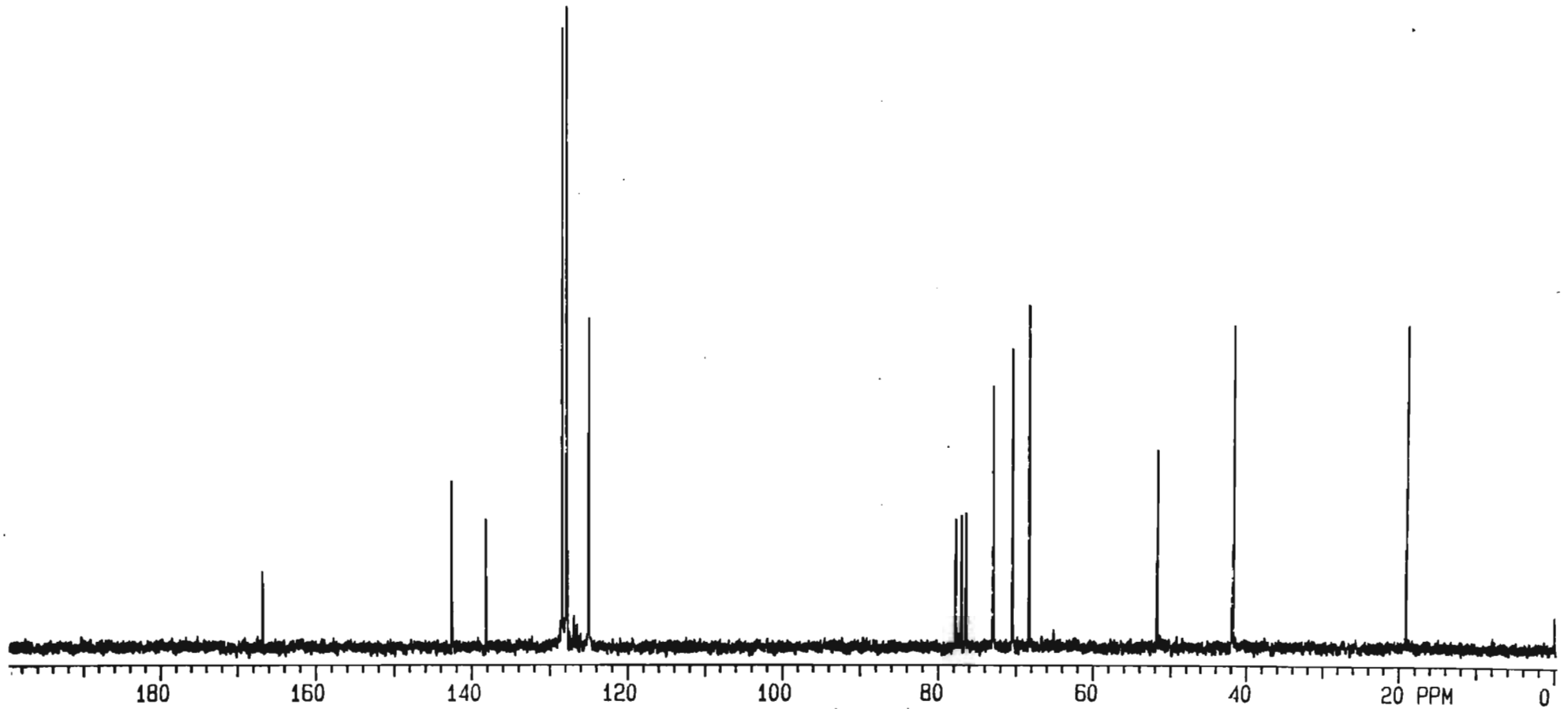
138a

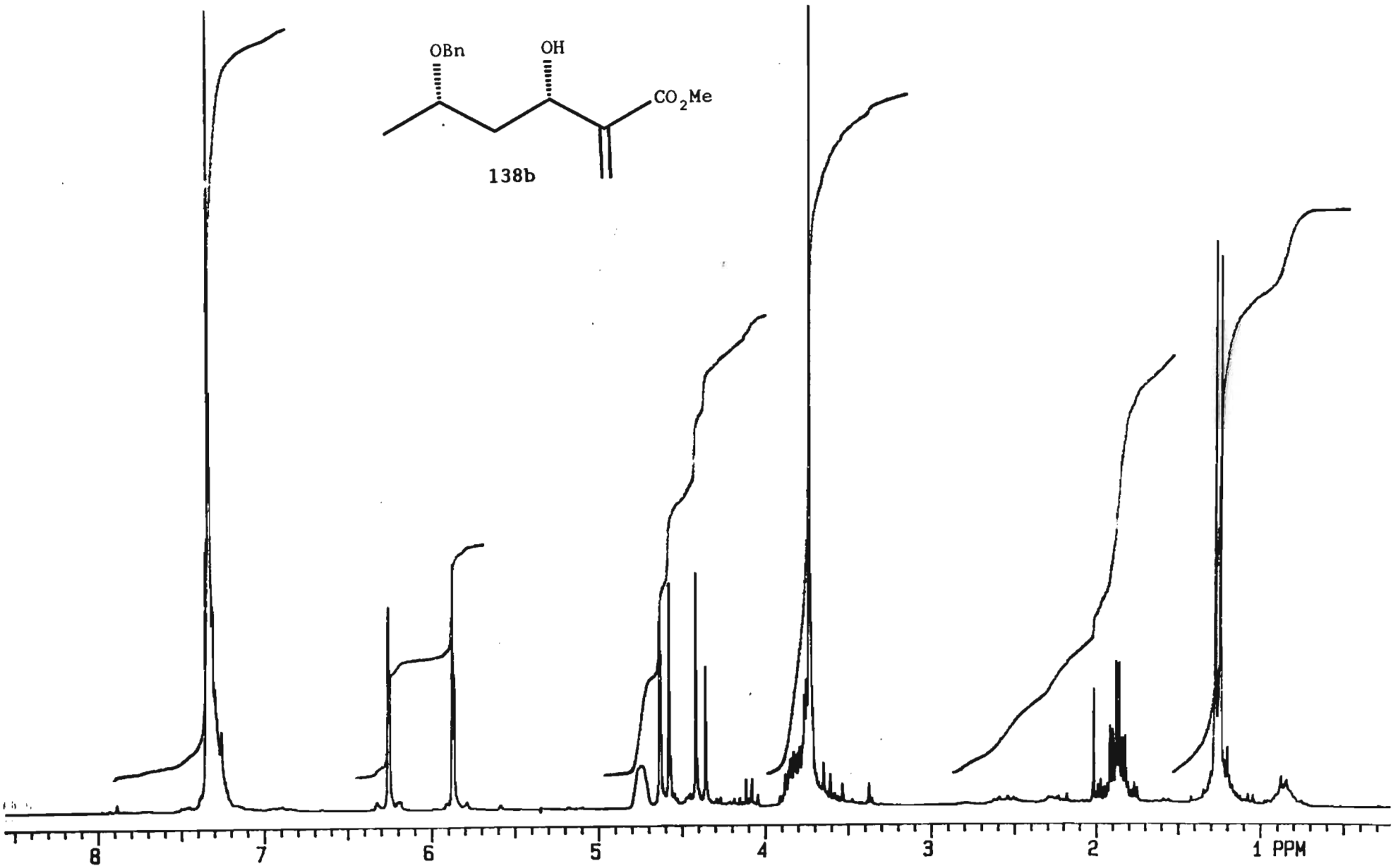


138a

MF $C_{15}H_{20}O_4$

MW 264

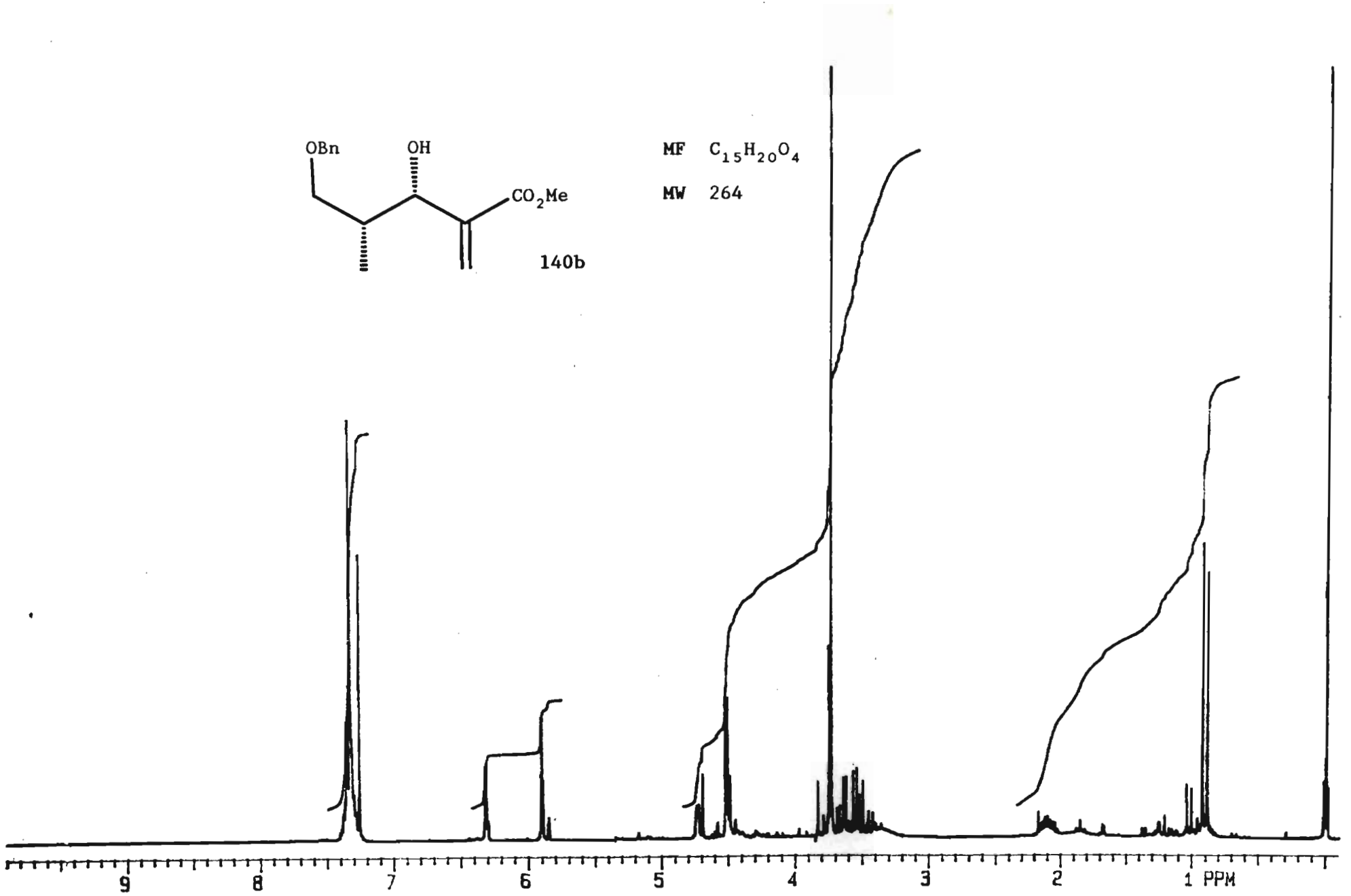


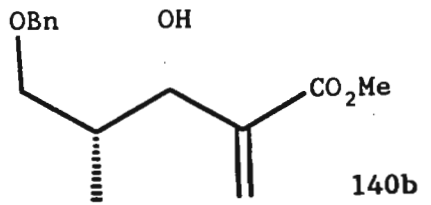

OBn
OH
CO2Me
138b
8
7
6
5
4
3
2
1 PPM

138b

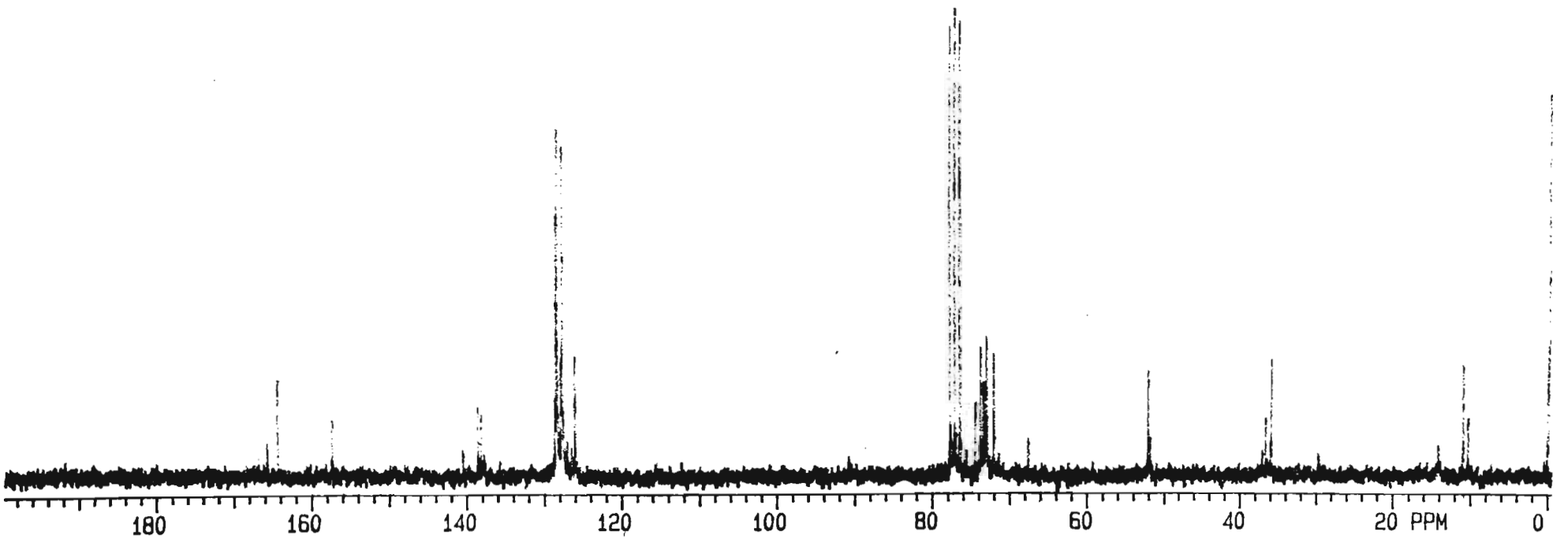
MF $C_{15}H_{20}O_4$

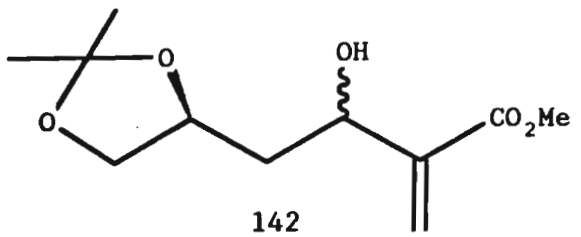
MW 264


OBn
OH
CO2Me
MF C15H20O4
MW 264
140b
9
8
7
6
5
4
3
2
1 PPM



140b

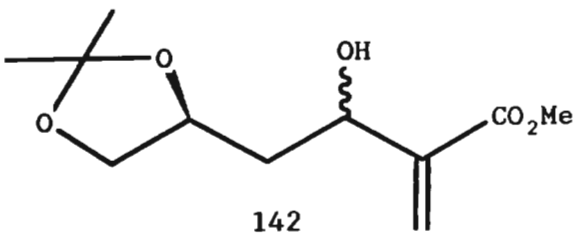




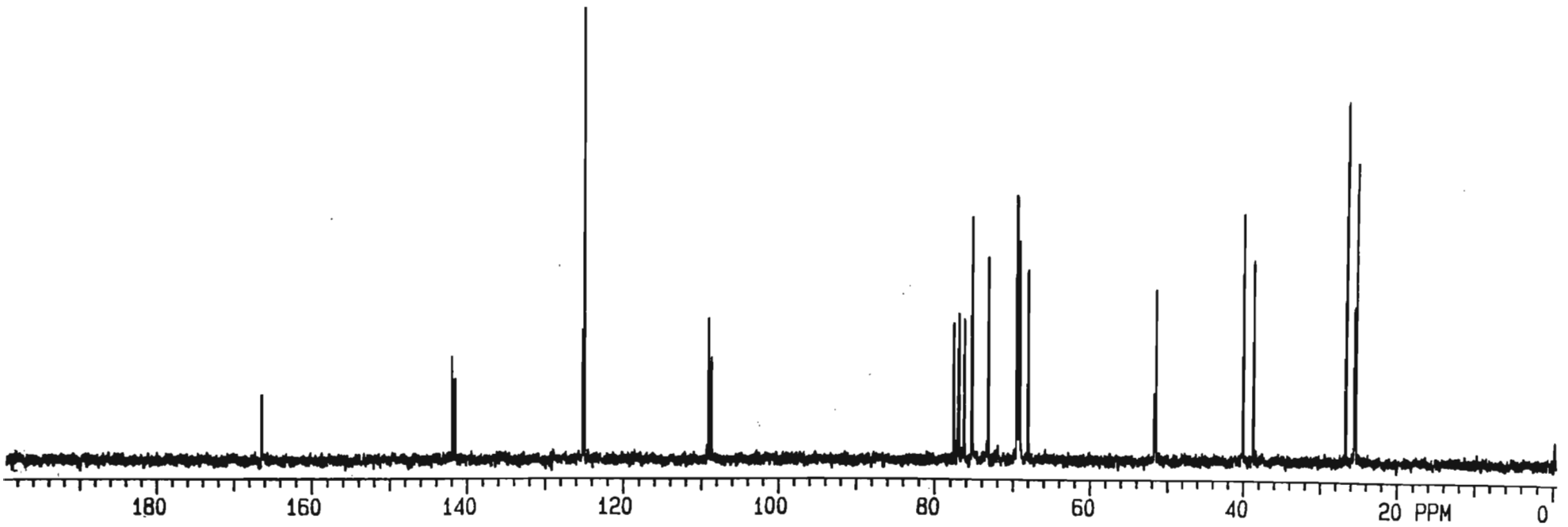
142

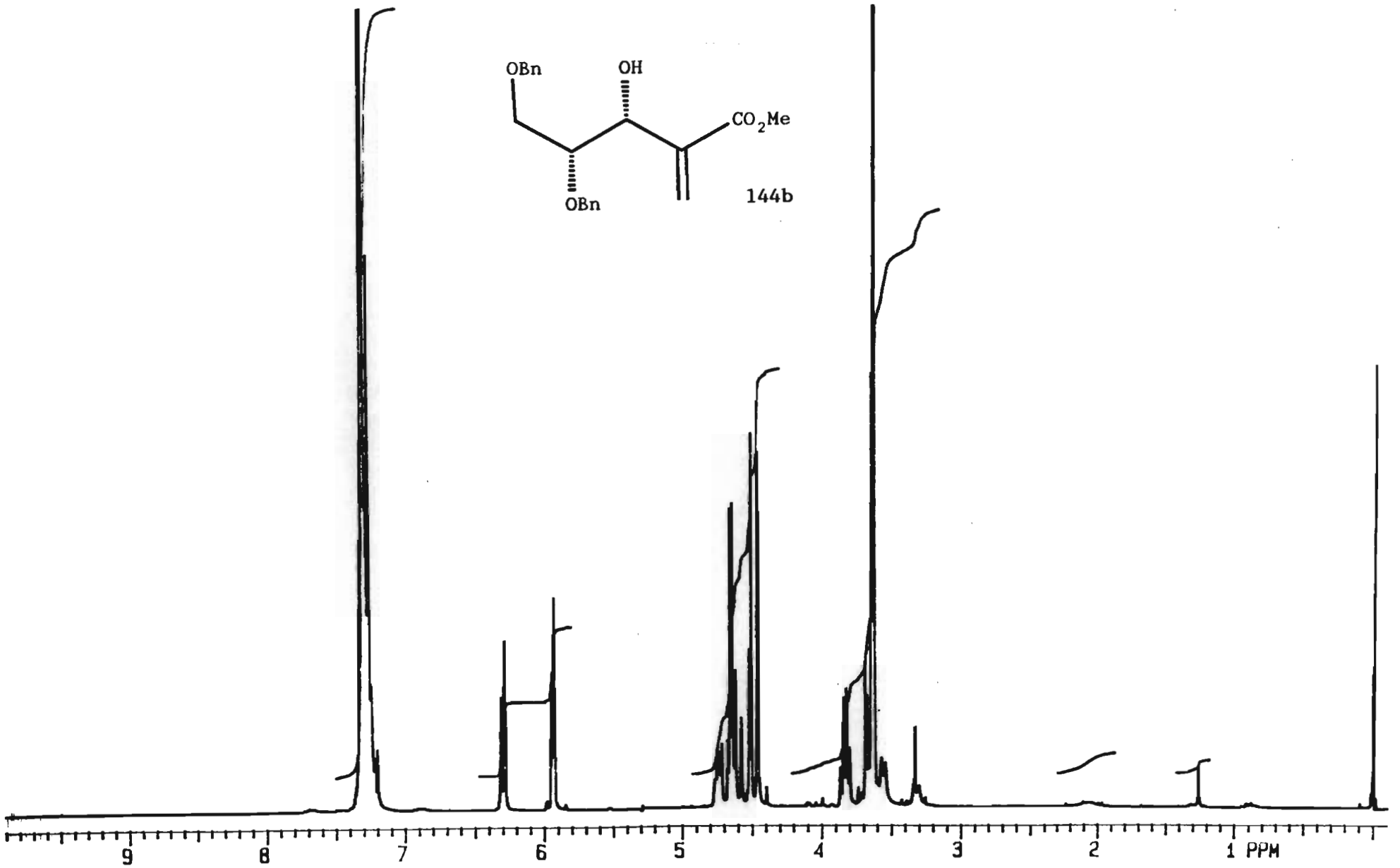
MF $C_{11}H_{18}O_5$

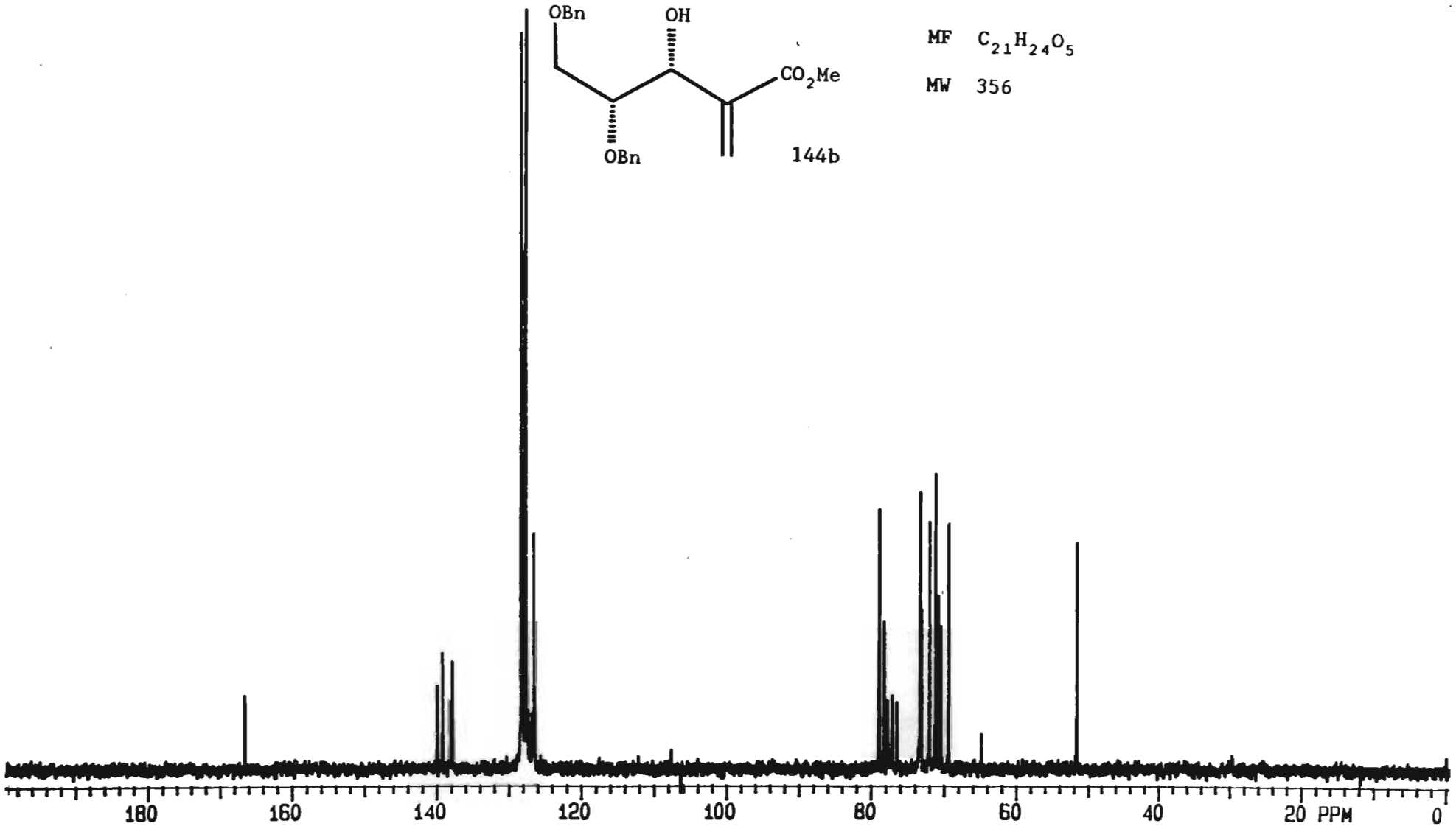
MW 230



142

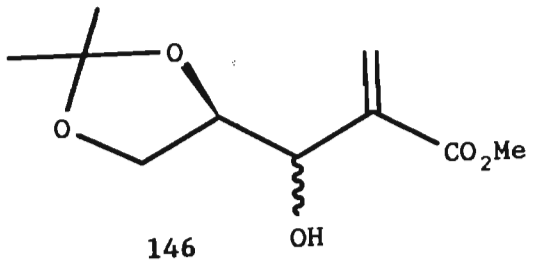



OBn
OH
CO2Me
OBn
144b
9
8
7
6
5
4
3
2
1 PPM


OBn
OH
CO2Me
OBn
144b
MF C21H24O5
MW 356
180
160
140
120
100
80
60
40
20 PPM
0

MF $C_{10}H_{16}O_5$

MW 216

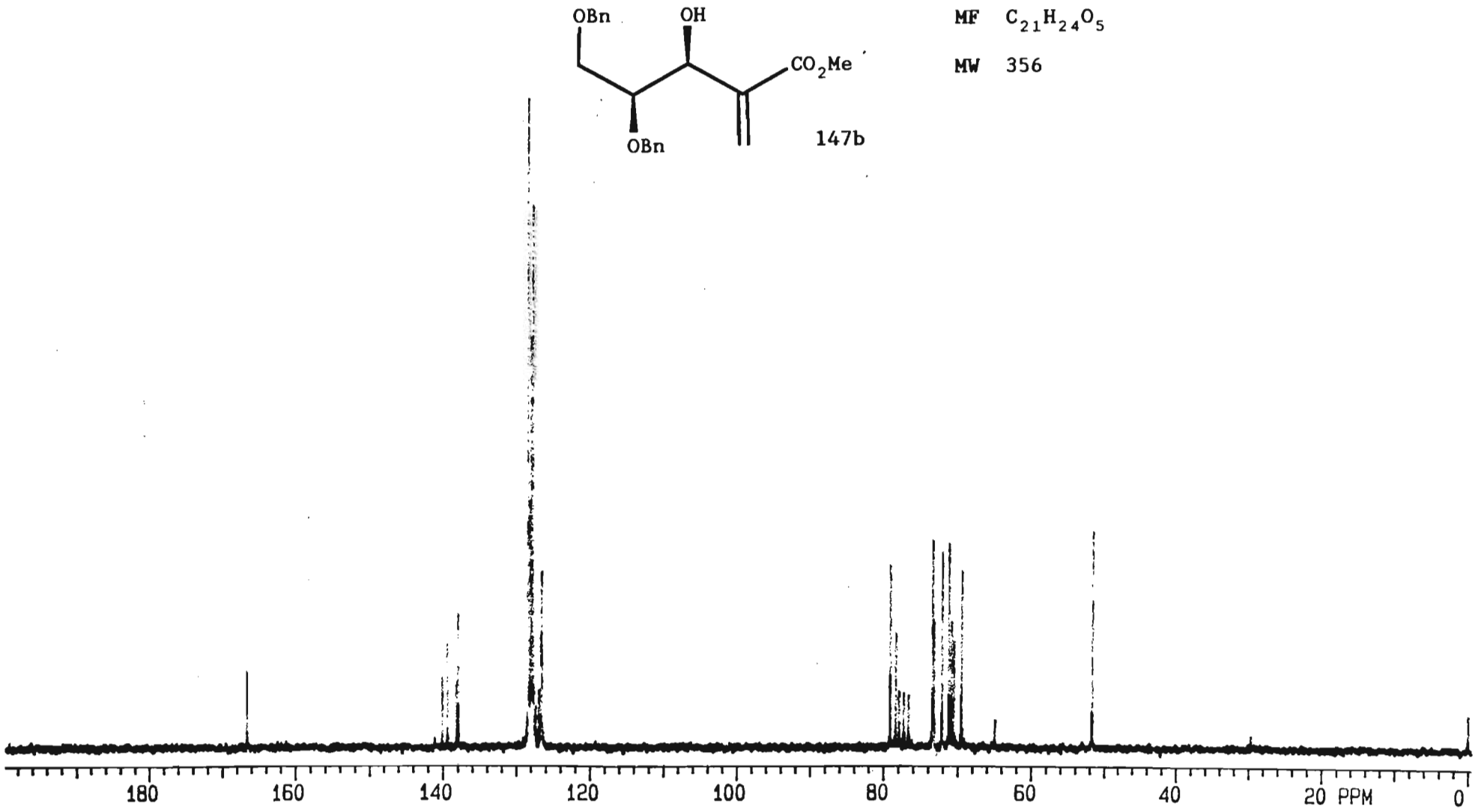


146

MF $C_{10}H_{16}O_5$

MW 216

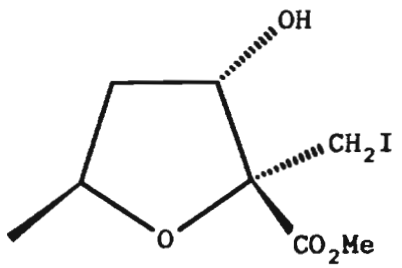
OBn
OH
OBn
CO2Me
147
9
8
7
6
5
4
3
2
1 PPM



147b

MF $C_{21}H_{24}O_5$

MW 356



190

MF $C_8H_{13}IO_4$

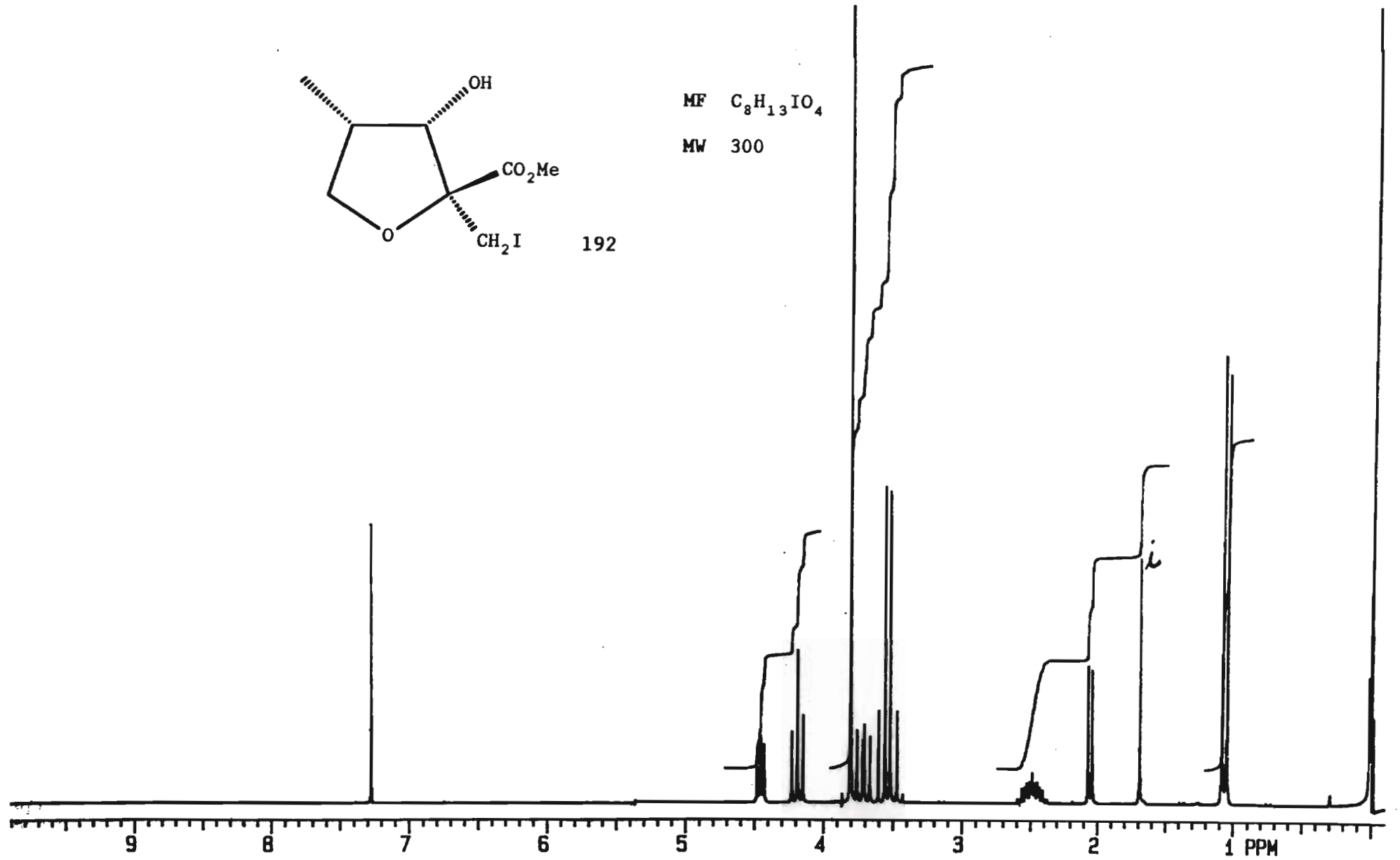
MW 300

190

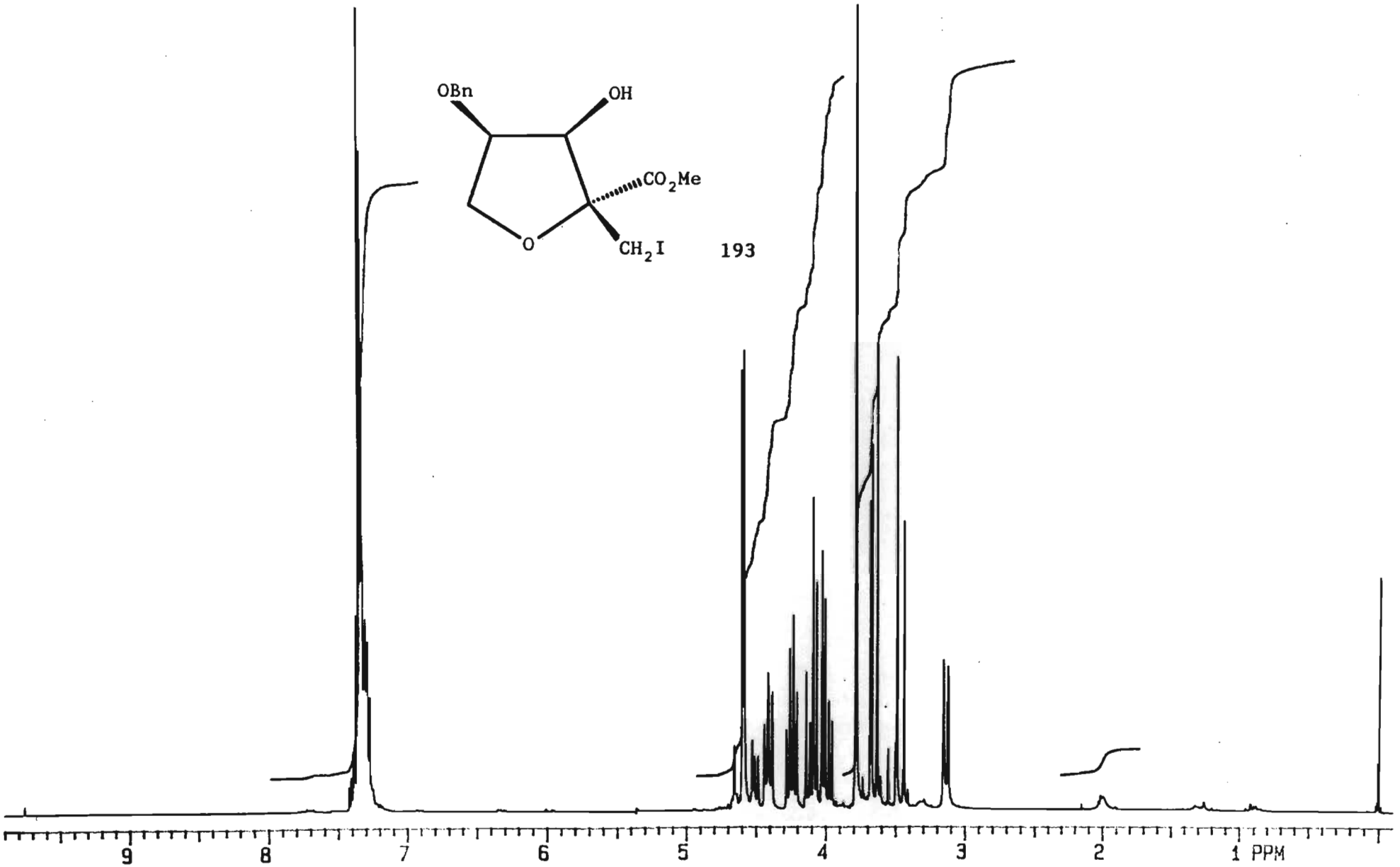
1 PPM
2
3
4
5
6
7
8
9
O
OH
CO2Me
CH2I
191
MF C8H13IO4
MW 300

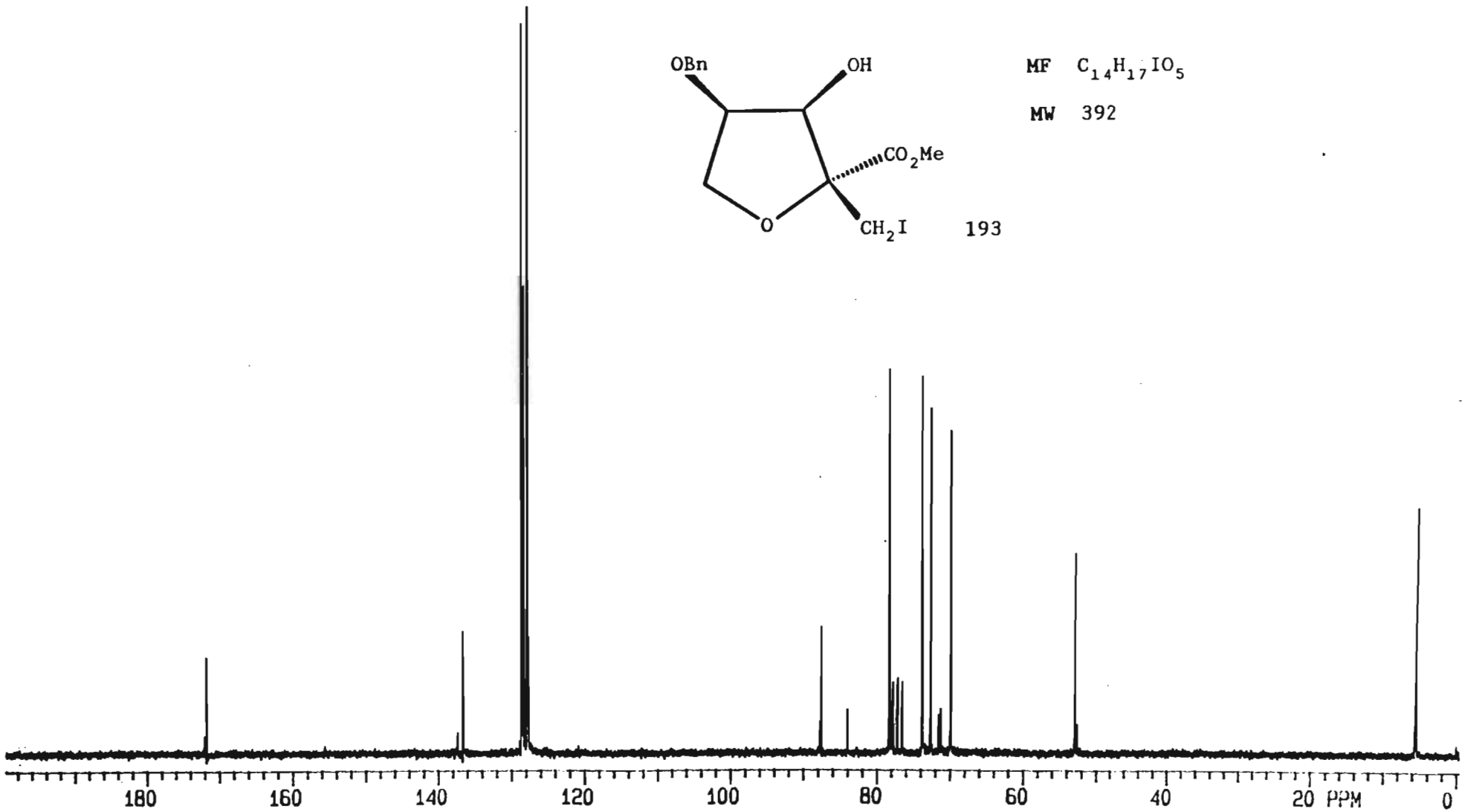
180
160
140
120
100
80
60
40
20
0
PPM
79.5 79.0 78.5 78.0 77.5 77.0 76.5 76.0 PPM
O
OH
CO2Me
CH2I

191

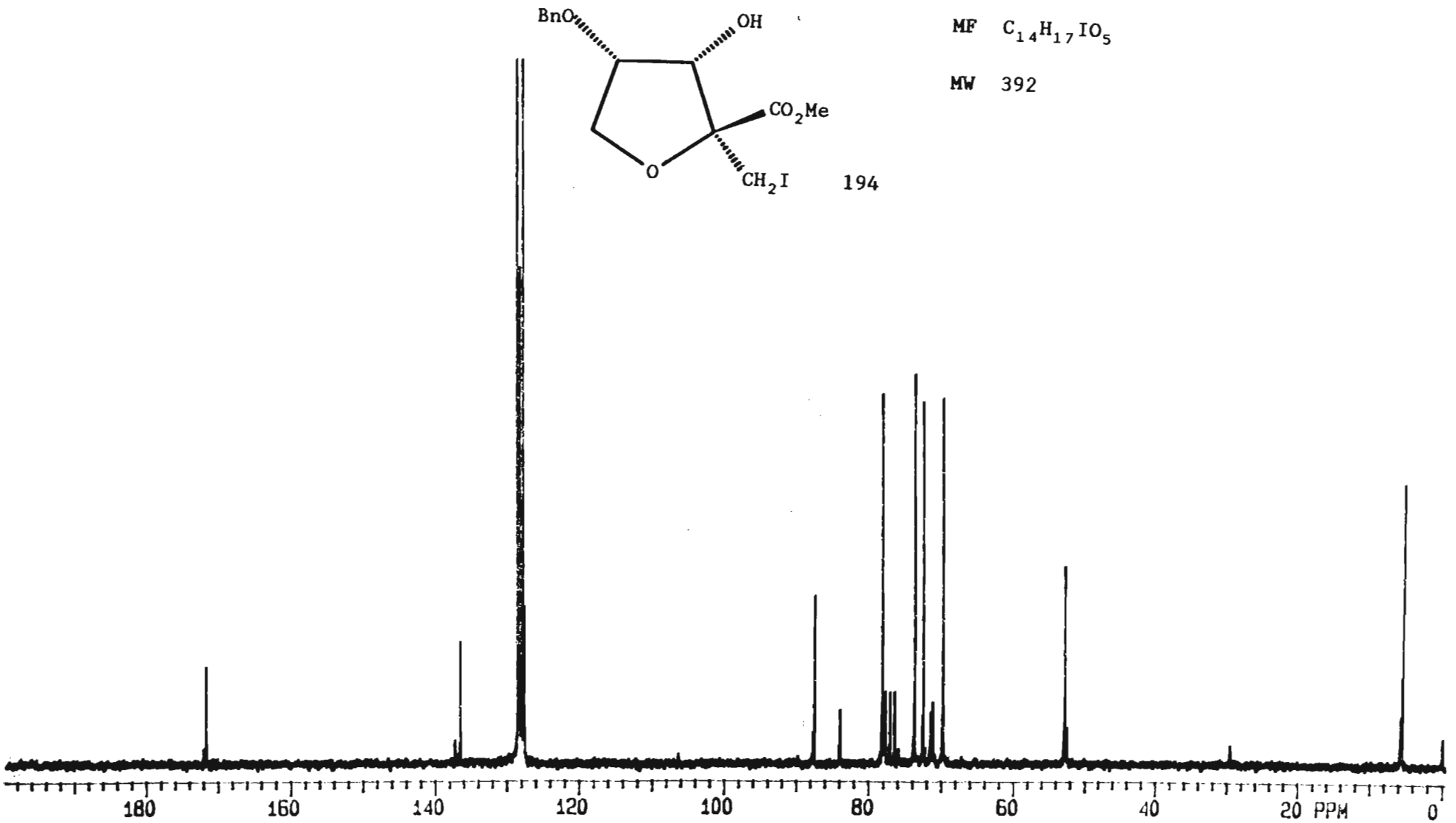

OH
CO2Me
O
CH2I
192
MF C8H13IO4
MW 300
i
9
8
7
6
5
4
3
2
1 PPM

192


OBn
OH
CO_2Me
O
CH_2I
193
9
8
7
6
5
4
3
2
1 PPM


OBn
OH
CO2Me
O
CH2I
MF C14H17IO5
MW 392
193
180
160
140
120
100
80
60
40
20 PPM
0

BnO
O
OH
CH2I
CO2Me
194
9
8
7
6
5
4
3
2
1 PPM


BnO
OH
CO2Me
O
CH2I
194
MF C14H17IO5
MW 392
180
160
140
120
100
80
60
40
20 PPM
0

199
MF C9H15IO6S
MW 378
OSO2CH3
CH2I
CO2Me
O
PPM

MF $C_9H_{15}IO_6S$

MW 378