CHAPTER - V

SYNTHESIS OF (R) & (S)-N-PHTHALOYL PROTECTED 2-AMINO BUTANALS AND THEIR WITTIG REACTIONS

5.1 INTRODUCTION

The synthesis of optically active organic compounds is one of the most important problems of contemporary chemistry. Pure enantiomers attain increasing commercial interest, especially in the field of pharmaceutical products. During recent years, asymmetric synthesis has greatly contributed to progress in highly controlled formation of new chiral centers.[1] These processes still remain the basic problems in the total synthesis of natural products. Preparation of the latter in an optically pure form by application of chiral starting materials is very advantageous, enabling precise programming and efficient realization of synthetic pathways. Many monosaccharides and their readily available derivatives are versatile substrates for the synthesis of optically active target molecules.[2] α-Amino acids are the second important natural source of chiral substrates, useful in stereocontrolled organic synthesis.[2,3]

Naturally occurring amino acids constitute an attractive source of chiral, non-racemic starting materials for asymmetric synthesis. This is due in part to the commercial availability of these substances, which in many cases involve the unnatural antipode as well. Active esters of amino acid derivatives represent one of the most important classes of activation for peptide coupling.

In recent years there has been a growing interest in chiral nonracemic aldehydes because of the development of new and effective methods for controlling stereochemistry of several basic organic reactions, such as metalloorganic addition to the carbonyl group,[4] aldol condensation,[5] [4 + 2] cycloaddition with carbonyl heterodienophiles.[6] Protected α-hydroxy aldehydes 1 and α-amino aldehydes 2 (**Figure V.1**) are of special interest, owing to their ready availability in both enantiomeric forms from natural sources and to pronounced versatility due to the presence of both the formyl group and suitably protected hydroxy or amino functionality in the molecule.

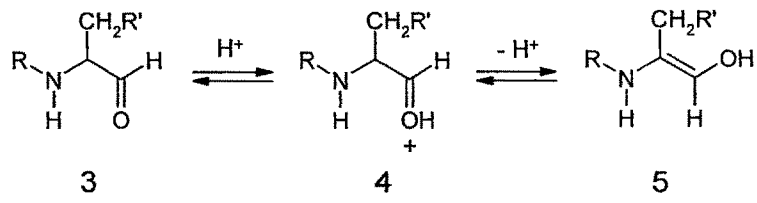
1 2

Figure V.1

α-Amino aldehydes are versatile building blocks, frequently used in the synthesis of natural products.[7-15] Adducts of α-amino aldehydes and acetylenic compounds are easily transformable to a variety of chiral natural products containing many contiguous stereogenic carbon atoms. Among these products are glycosidic antibiotics,[13] cytostatics,[9] as well as antiviral[15] and anthelmintic[14] compounds.

5.1.1 Properties of N-protected α-amino aldehydes

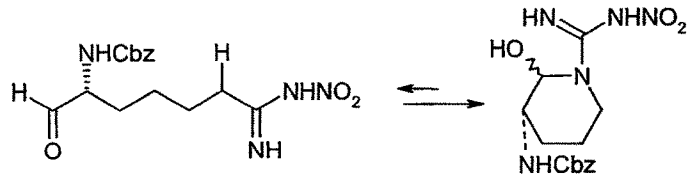
N-Protected α-amino aldehydes are relatively unstable both chemically and configurational -ly, particularly in solution. For this reason their elemental analysis and optical rotation measurements should be considered as only approximate. Therefore, it is recommended to use these compounds immediately after preparation; however, if purification is necessary, two methods are available: flash chromatography on silica gel[16] or formation of much more stable semicarbazone[17] followed by simple chromatography and subsequent decomposition to return the pure aldehyde. The optical stability of some N-protected α-amino aldehydes during chromatography on silica gel was first studied by Ito *et al.*[18] **(Scheme V.1).**



3 4 5

Scheme V.1

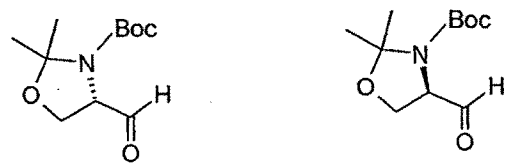
racemization of Cbz-L-α-amino aldehydes on silica gel was as follows: Cbz-S-Bzl-L-cysteinal >> Cbz-L-phenylalaninal > Cbz-L-leucinal >> Cbz-NG-nitro-L-argininal. The authors[18] proposed a racemization mechanism for compounds 3 involving the protonated form 4 and enol 5 (**Scheme V.1**). Aldehydes with an enol-stabilizing R' group, e.g., Cbz-



6 7

Scheme V.2

S-Bzl-cysteinal, racemize extremely quickly during contact with silica gel. Limited racemization of Cbz-N^G-nitro-*L*-argininal (6) seems to be related to its cyclic carbinolamine structure 7 (**Scheme V.2**), which probably prevents the nitroargininal derivative 6 from racemization due to keto-enol tautomerism. Evans *et al.*[19] observed that Boc-L-phenylalaninal appeared to be much less stable than Boc-L-luecinal. Recently, two important reports on configurational stability of N-protected α-amino aldehydes have appeared. The first one by Lubell and Rapoport[20] describes the synthesis of N-(9-(9-phenylfluorenyl))-*L*-alaninal. Exposure to silica gel or to a non-nucleophilic base caused no detectable racemization. The PhFI N-protecting group also maintains the configurational integrity of *L*-alaninal during C-C bond-forming reactions, affording enantiomerically pure products from Wittig reactions, aldol condensations, and Grignard additions.[20] The second report by Garner and Park[21] describes the synthesis of N,O-diprotected *L*-serinal 8 and *L*-threoninal 9 (**Figure V.2**).



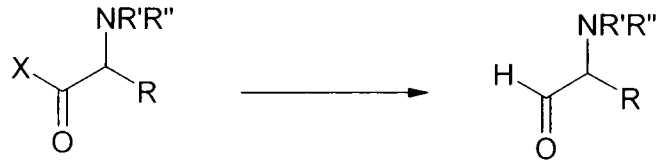
8 9

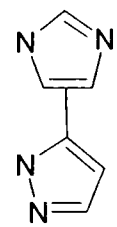
Figure V.2

These differentially protected β-hydroxy-α-amino aldehydes were shown to be produced in a 93-95 % enantiomeric excess. The configurational stability of compounds 8 and 9 during their purification either by vacuum distillation or by flash chromatography was also demonstrated.[21]

5.1.2 Preparative Methods of N-protected α-Amino Aldehydes

α-Amino aldehydes are mainly obtained from amino acids. Usually the synthetic route proceeds via esters or active amides of α-amino acids, which are finally reduced. A second approach is based on α-amino alcohols from α-amino acids, which are oxidized to afford the desired α-amino aldehydes. The reducing agents generally used are DIBAL or $LiAlH_4$. Procedures based on reduction of esters and/ or active amides of N-protected α-amino acids are listed in the table V.1:



X	Y	Temp °C	Time	R'	R''	Yield	Ref.
OMe, OEt	DIBAL	-50	50min	H	Cbz	33-68	18
	DIBAL	-78	6 min	H	Boc	85-97	22, 23
	DIBAL	-65	45 min	H	Boc	80	24
	$LiAlH_4$	-20	45min	H	Cbz	50	25
	DIBAL	-40	30min	H	Cbz,	52-83	26
	$LiAlH_4$	-20	2 h	H	Boc	85-95	27
					Cbz, Boc		

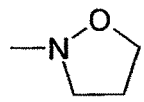
-N(OMe)Me 	$LiAlH_4$ $LiAlH_4$	0 0	20min 20min	H	Boc PhFI	86-96 90	28, 29 20
-O(O)CoAlk	H_2/Pd-C	5	4-11h	H	Ac	12-81	30
-Cl	H_2/Pd-C	100	3 h	H	Pht	60	31

Table V.1: Preprative methods of α-amino aldehydes from amino acids, amino Esters or amides of amino acids

Procedures based on the oxidation of N-protected α-amino alcohols are listed in the table:

(O)	Temp,°C	Time	R'	R''	Yield, %	Ref.
CrO_3	-10	30 min	H	Boc	56-67	19, 32
DMSO/SO_3-Py	20	10 min	H	Boc	35	33,34
DMSO/$(COCl)_2$	-63	30 min	H	Boc	90	33,35

PCC	25	4h	Bzl	Ts	75	36
PDC	20	24h	H	Boc	75-95	19,37,38

Table V.2: Preparative methods of N-protected α-amino aldehydes from N-protected amino alcohols

The N-protected α-amino aldehydes are best obtained by borane-tetrahyrofuran reduction of N-protected α-amino acids or by sodium borohydride-lithium chloride or sodium borohydride-calcium chloride reduction of the corresponding methyl ester. Collins reagent was the first oxidizing reagent providing an efficient racemization-free procedure for Boc-L-luecinal synthesis. Various activated dimethyl sulfoxide oxidations are also generally used for synthesis of α-amino aldehydes. Pyridinium dichromate(PDC) oxidation is suspected to cause racemization to various extents, depending upon the the type of α-amino aldehyde whereas pyridinium chlorochromate (PCC) was found to be convenient for the oxidation of N-benzyl-N-tosyl α-amino alcohols without racemization.

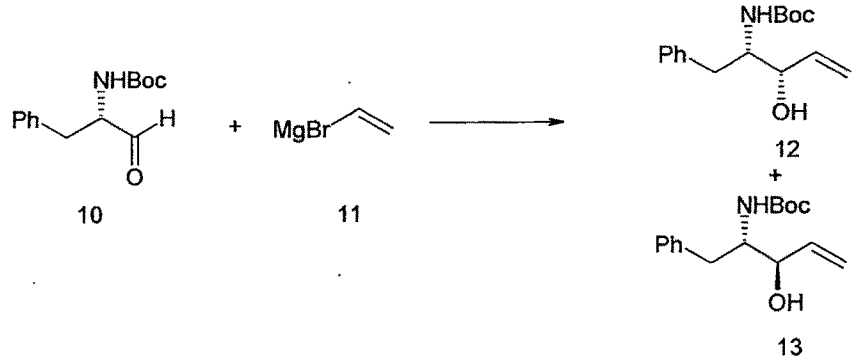
α-Amino alcohols with non polar side chains, such as L-luecinol, L-phenylalaninol and L-valinol, were found to be good substrates for alcohol dehydrogenase from horse liver, affording the respective α-aminoaldehydes.

5.1.3 Reactions of N-protected α-amino aldehydes

Reactions of metalloorganic reagents with chiral aldehydes are of considerable interest in the context of acyclic stereoselective synthesis. This type of reaction in N-protected α-amino aldehydes is often used in the synthesis of peptide isosteres.

Simple addition of vinylmagnesium bromide to Boc-phenylalaninal (10) carried out at -78°C in tetrahydrofuran afforded a 56:44 mixture of syn (threo) and anti (erythro) allylic alcohols respectively. The diastereoselectivity was improved in favor of the chelation

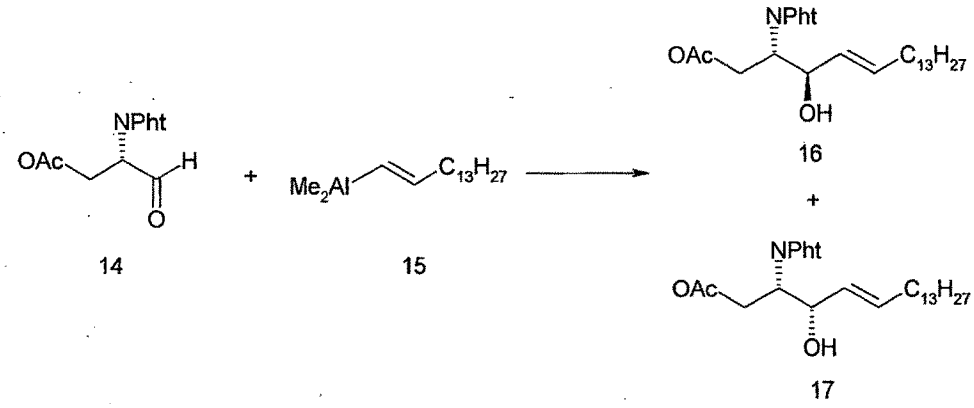
controlled Cram-product by carrying out the addition reaction at 25°C, which gave a 70:30 mixture of the corresponding alcohols 12 and 13 (**Scheme V.3**).[39]



10 11 12 + 13

Scheme V.3

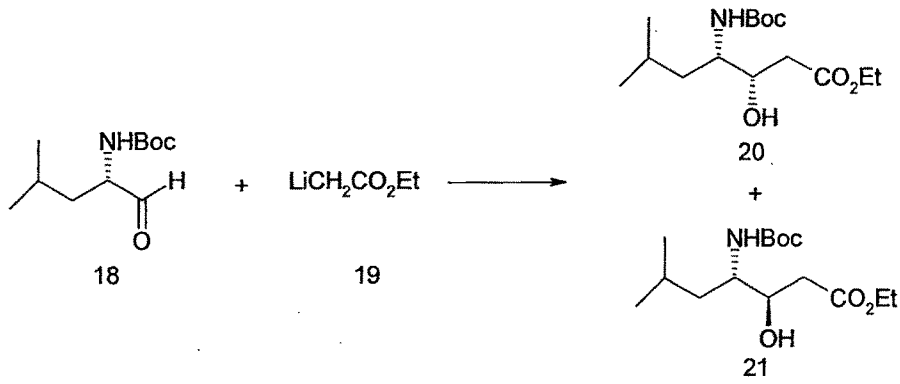
Addition of vinylalane 15 to O-Ac-N-Pht-L-serinal 14 carried out in a 2:1 mixture of benzene and ether at 5-10°C, afforded the desired alcohols anti and syn 16 and 17 respectively in a 4:1 ratio (**Scheme V.4**).[40]



14 15 16 + 17

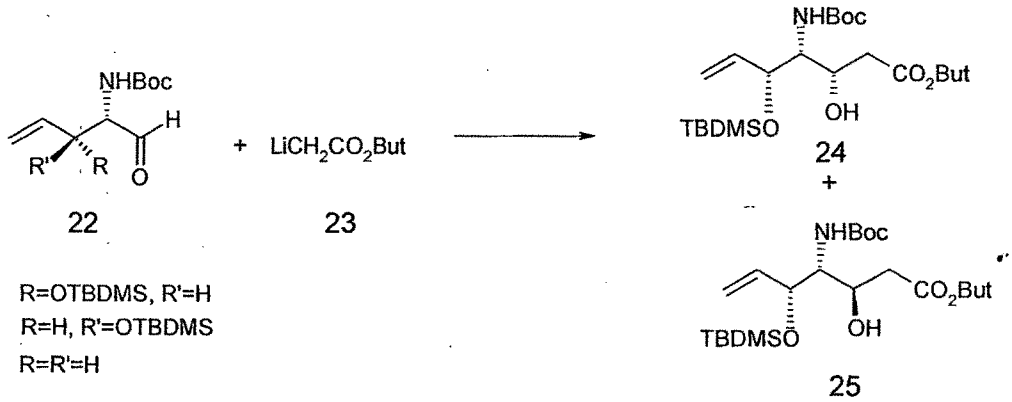
Scheme V.4

A number of syntheses of natural products, starting from N-protected α-amino aldehydes involve aldol condensation as the key step. Unfortunately, aldol condensation with N-protected α-amino aldehydes is characterized as in the case of metalloorganic addition by a rather low diastereoselectivity. Simple condensation of the lithiated acetic ester 19 with Boc-L-leucinal 18 provided a 1:1 mixture of diastereomeric alcohols (**Scheme V.5**).[19]



Scheme V.5

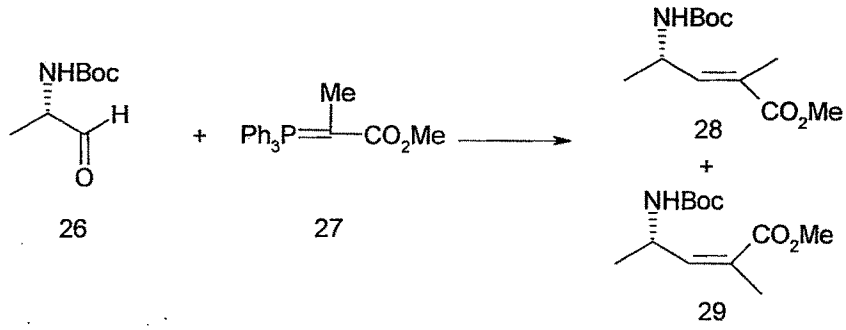
Significant diastereoselctivity was observed for β-substituted N-protected α-amino aldehydes. Condensation of aldehydes with lithiated tert-butyl acetate afforded a 6.5:1 mixture of diastereomeric alcohols syn and anti in 96% yield. The selectivity of this reaction is dependent on the configuration of the β-substituent and decreased to a 3:1 ratio of the respective alcohols when the anti aldehyde was employed under the same reaction conditions. The condensation of the aldehyde 22 with lithiated tert-butyl acetate 23 afforded a equimolar mixture of diastereomers 24 and 25 (**Scheme V.6**).[38]



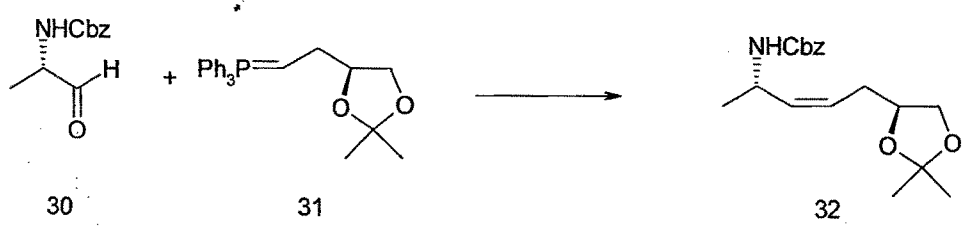
Scheme V.6

In N-protected α-amino aldehydes, the carbonyl group not only participates in reactions leading to the formation of a new chiral centre but also may be transformed into other

functionalities. N-protected α-amino aldehydes undergo Wittig reactions which enables introduction of a C=C bond to replace the formyl group of N-protected α-amino aldehydes. The chiral centre in the N-protected α-amino aldehydes plays no part in the stereochemical outcome of the reaction. The E/Z ratio mainly depends upon the nature of the ylide and on the reaction conditions. The reaction of Boc-alaninal 26 with 2-(triphenylphosphoranylidene) propionate (27) afforded the E-olefin 28 as the predominant product.(**Scheme V.7**)[41] In case of reaction of Cbz-L-alaninal with the chiral ylide Z-olefin 32 was the exclusive product (**Scheme V.8**).[42]



Scheme V.7



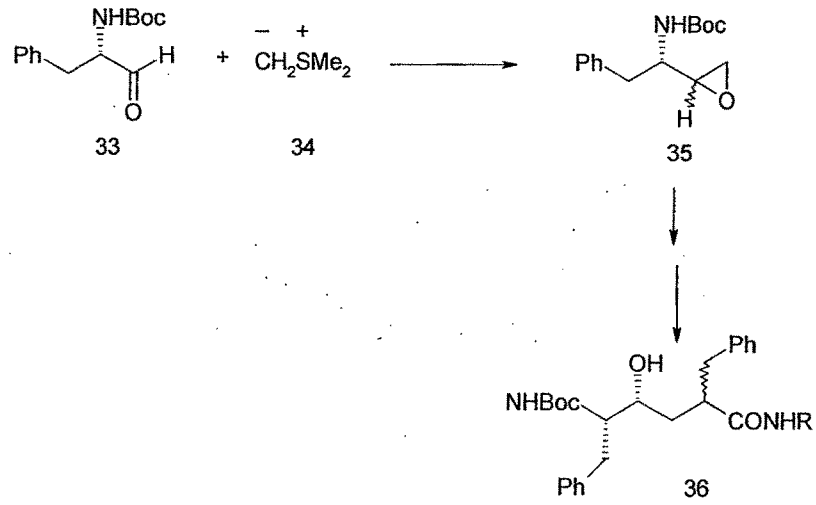
Scheme V.8

Scholz *et al.*[43] have studied the Wittig reaction of α-amino aldehydes with a number of α-substitued alkoxycarbonyl phosphoranes . The reaction was found to proceed smoothly to yield the corresponding α, β-unsaturated -γ-amino esters which are the precursors to α, β –unsaturated-γ-amino acids.

Another recent study of the Wittig reaction of N-protected amino aldehydes with stabilized phosphorous ylides, with a special emphasis on the influence of the solvent on

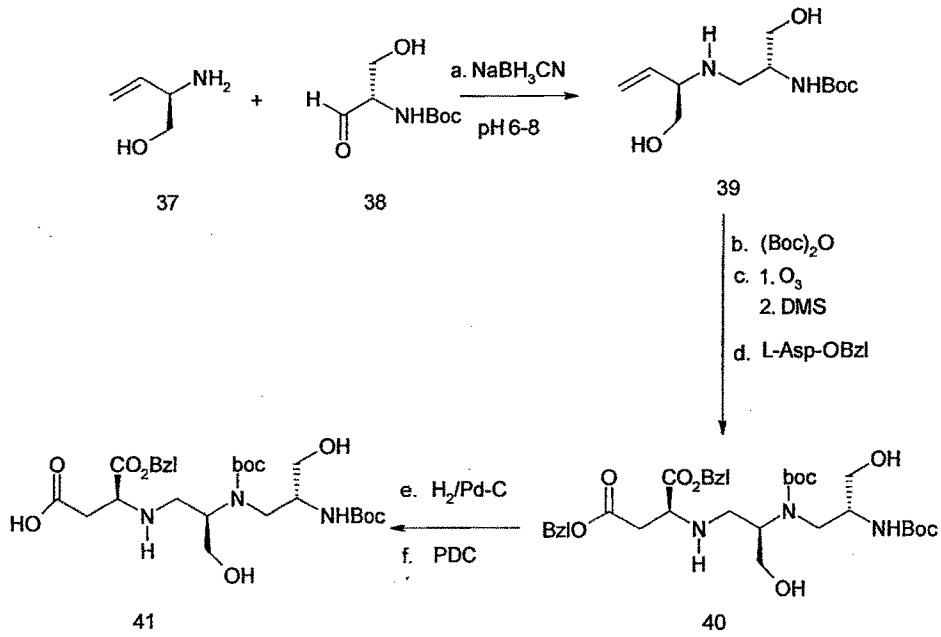
the stereochemical outcome was carried out by Bernardo *et al.*[44] The reactions in aprotic solvents were highly E-stereoselective, independent of the structure of the aldehyde, wher -eas the use of methanol as a solvent in combination with a suitable protecting group afforded the Z-alkene as the major isomer.

N-protected α-amino aldehydes are very suitable starting materials for modified peptide synthesis. Evans *et al.* [45] described the stereocontrolled synthesis of the isosteric hydroxy methylene dipeptide. The method is based on the reaction between ylide and Boc-L-phenylalaninal (33) leading to a mixture of epoxides which was used for the synthesis of several dipeptide analogues (**Scheme V.9**).



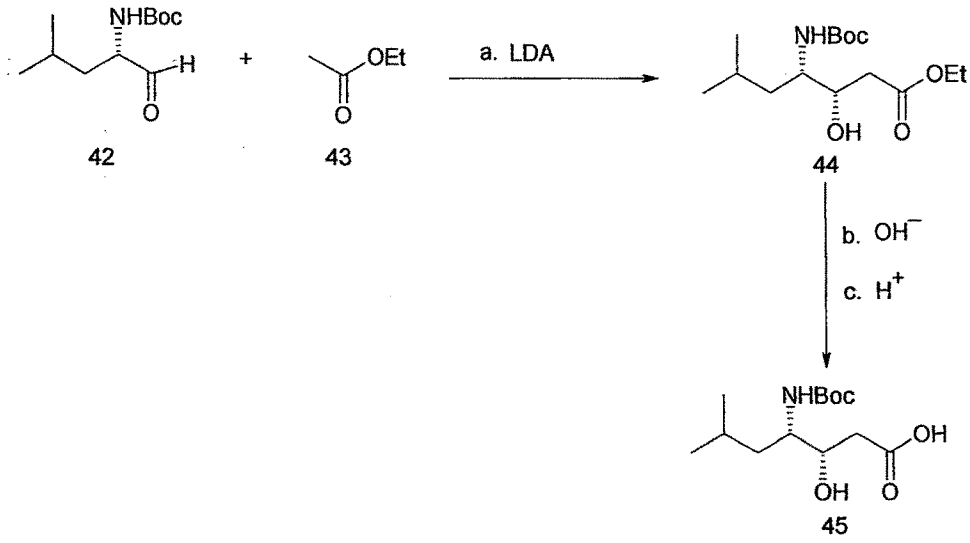
Scheme V.9

Poly(amino acids) in which the amino acid moieties are linked by the N-alkyl bond attracted considerable attention since they possess interesting biological activities. Synthesis of a typical representative of this class of compounds-aspergillomarasmine A acid from N-α-amino aldehydes is as shown in (**Scheme V.10**).[46]



Scheme V.10

The synthesis of unusual amino acids is of growing interest. L-Statine is one of the most important members of this class of compounds because of its presence in a number of recently discovered protease inhibitors. A simple and efficient methodology for synthesis of L-Statine (45) from N-protected α-amino-aldehydes is as shown in **Scheme V.11**[47]

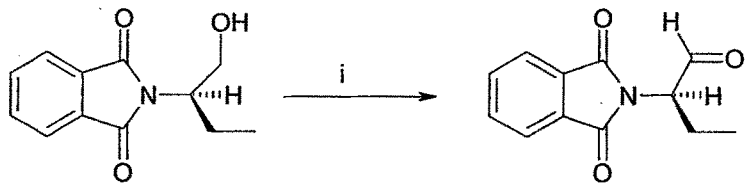


Scheme V.11

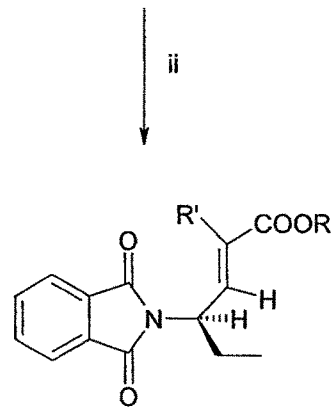
Thus N-protected amino aldehydes are versatile chirons, widely recognized, inexpensive and easily availaible from natural sources.

5.2 RESULTS AND DISCUSSION

(*R*) or (*S*)-2-(1-hydroxymethylpropyl) isoindol-1, 3-dione (46) or (49) on reaction with pyridi -nium dichromate synthesized from a mixture of chromium trioxide and pyridine at 0°C in dry dichloromethane and overnight stirring resulted in the formation of (*R*) or (*S*)-(1,3-Dioxo-1,3-dihydro isoindol-2-yl)butyraldehydes (47) or (50) in 38-40% yields. Subsequent reaction of the aldehydes with the wittig reagents(carboethoxy triphenyl phosphorane, carbomethoxy triphenyl phoshorane, α-allyl methyledene triphenyl phosphorane) in dry benzene furnished the corresponding alkenes 48a-48c or 51a-51c in 80-90% yields.

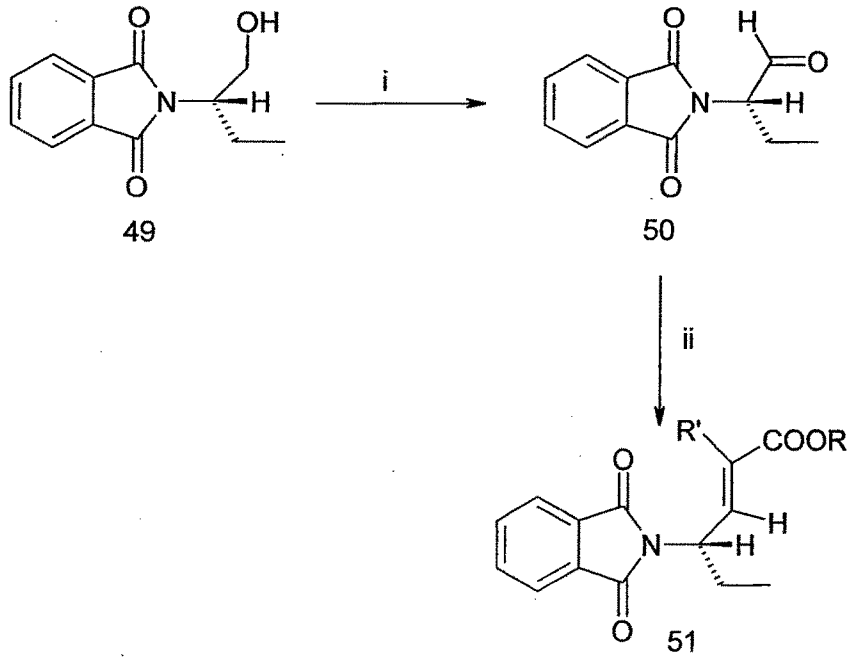


46 47



48

48a. R= -$COOCH_2CH_3$, R'= -H; 48b. R= -$COOCH_2CH_3$, R'= -Allyl; 48c. R= -$COOCH_3$, R'= -H



51a. R= -$COOCH_2CH_3$, R'= -H; 51b. R= -$COOCH_2CH_3$, R'= -Allyl; 51c. R= -$COOCH_3$, R'= -H

SchemeV.15: i. PDC, DCM, 0°C to RT, Overnight;

ii. Ph_3P=CH (R') COOR, R=-CH_2CH_3, R'=H, Allyl; R=-CH_3; R'=H.

The 1H NMR of 47 and 50 showed a triplet at δ 0.9 corresponding to the methyl group, a multiplet at δ2.0-2.5 is assigned to the methylene group. Another multiplet at δ4.7 can be assigned to the –CH group. A multiplet at δ7.3-8.0 shows the presence of four protons in the aromatic region. (**Figure V.3**) A typical singlet for –CH of the aldehyde is obtained at δ9.75. ^{13}C shows a peak at δ196.75 for the carbonyl of aldehyde, a peak at δ168.10 for the carbonyl of the imide, peaks at δ60.57 for –CH, at δ20.90 for $-CH_2$ and δ10.83 for $-CH_3$.(**Figure V.4**) I.R. of the aldehyde shows a υC-O band for aldehyde at 1730cm^{-1} and bands for imide carbonyl at 1719 and 1703 cm^{-1}.(**Figure V.5**) 1H nmr of 4-((*R*)-(E)-1,3-Dioxo-1,3-dihydro-isoindol-2-yl)hex-2-enoic acid ethyl ester (48a) showed a triplet at δ0.92 corresponding to the $-CH_3$ group, another triplet at δ1.26 for three protons of methyl group of ester group. The multiplet at δ2.0 can be assigned to one of the protons of the methylene group and another multiplet at δ2.18 for the other proton of the methylene group. A quintet at δ4.8 corresponds

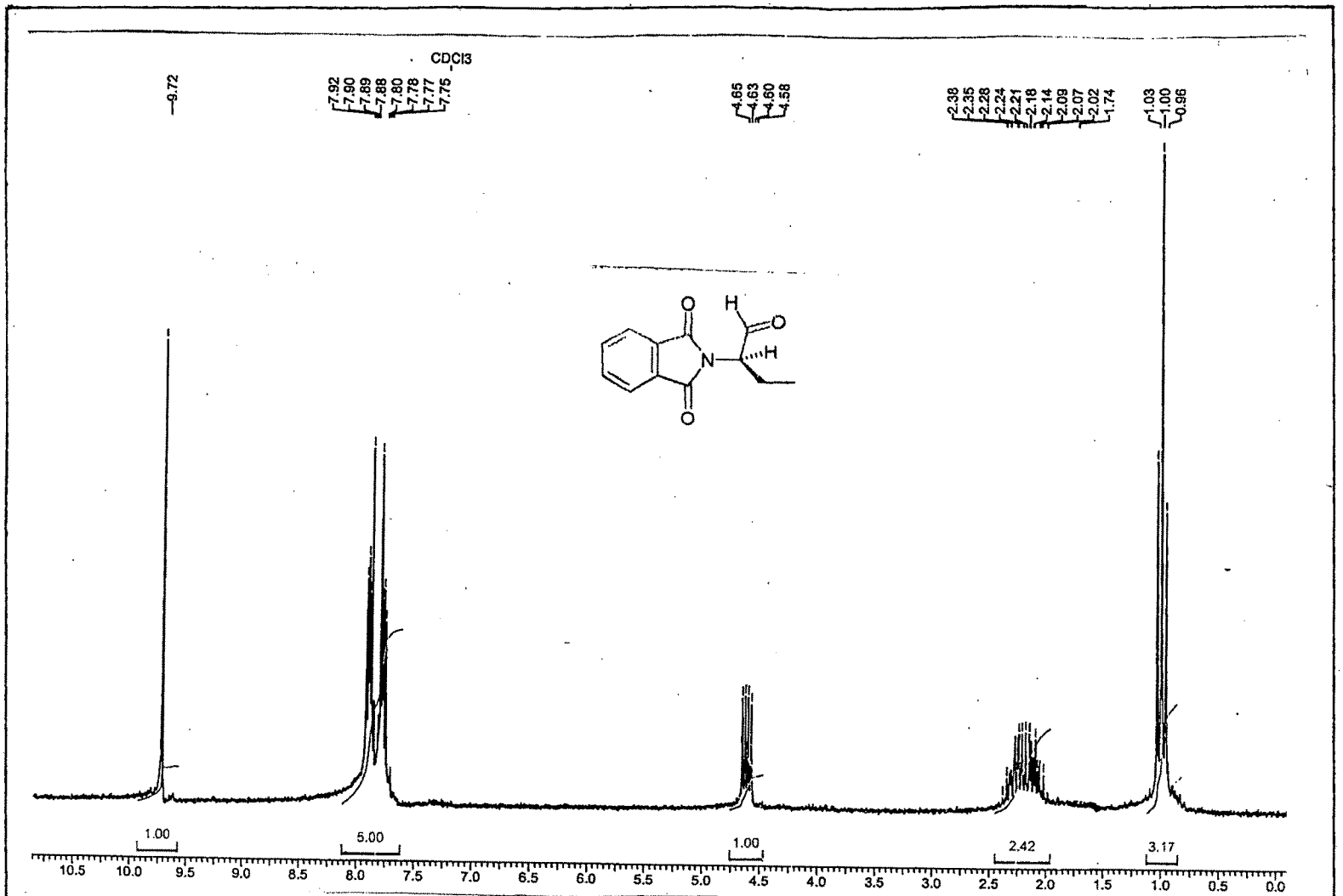


Figure V.3 1H NMR($CDCl_3$) spectrum of (*R*) -2-(1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl) butyraldehyde (47)

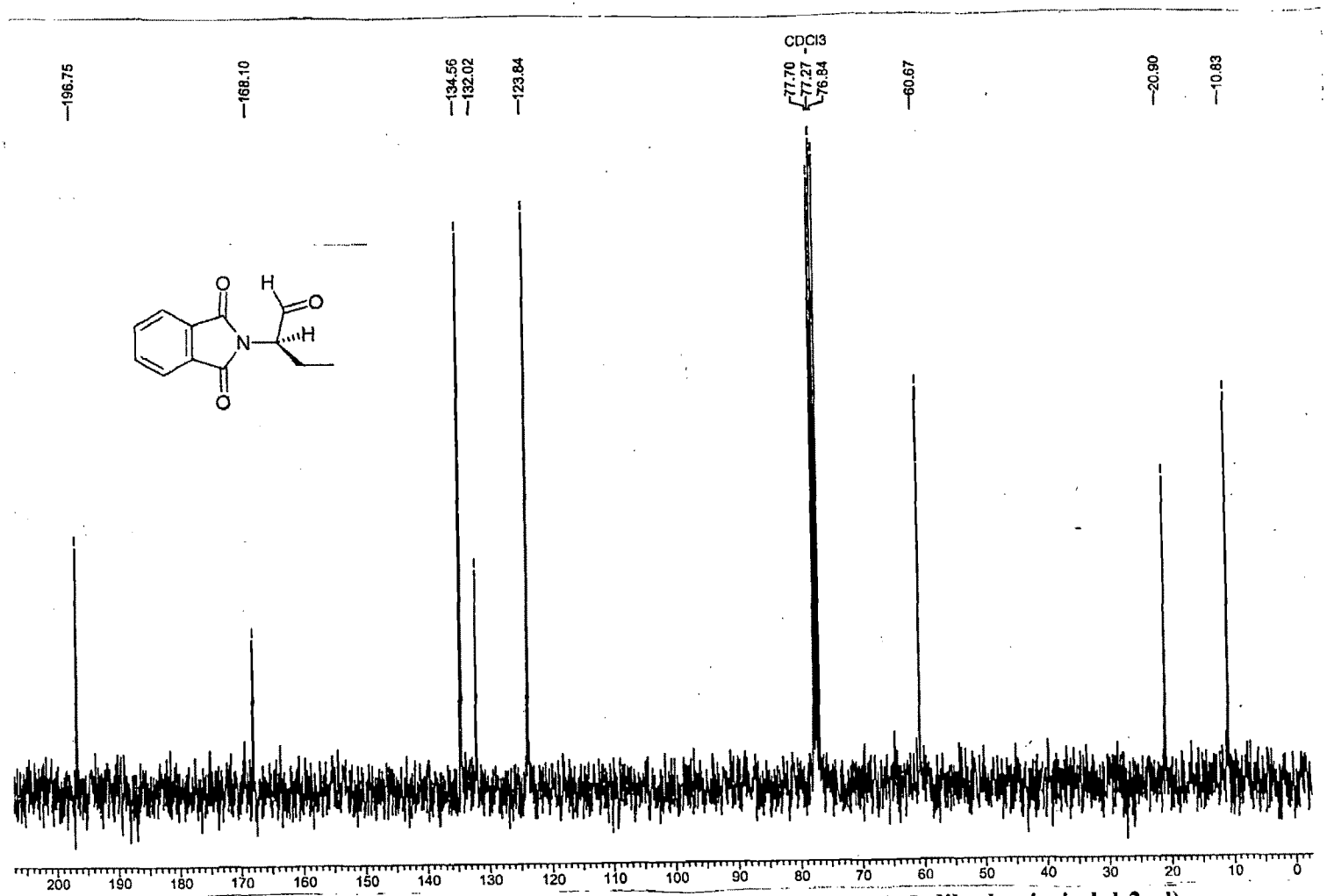


Figure V.4 ^{13}C NMR($CDCl_3$) spectrum of (*R*) -2-(1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl) butyraldehyde (47)

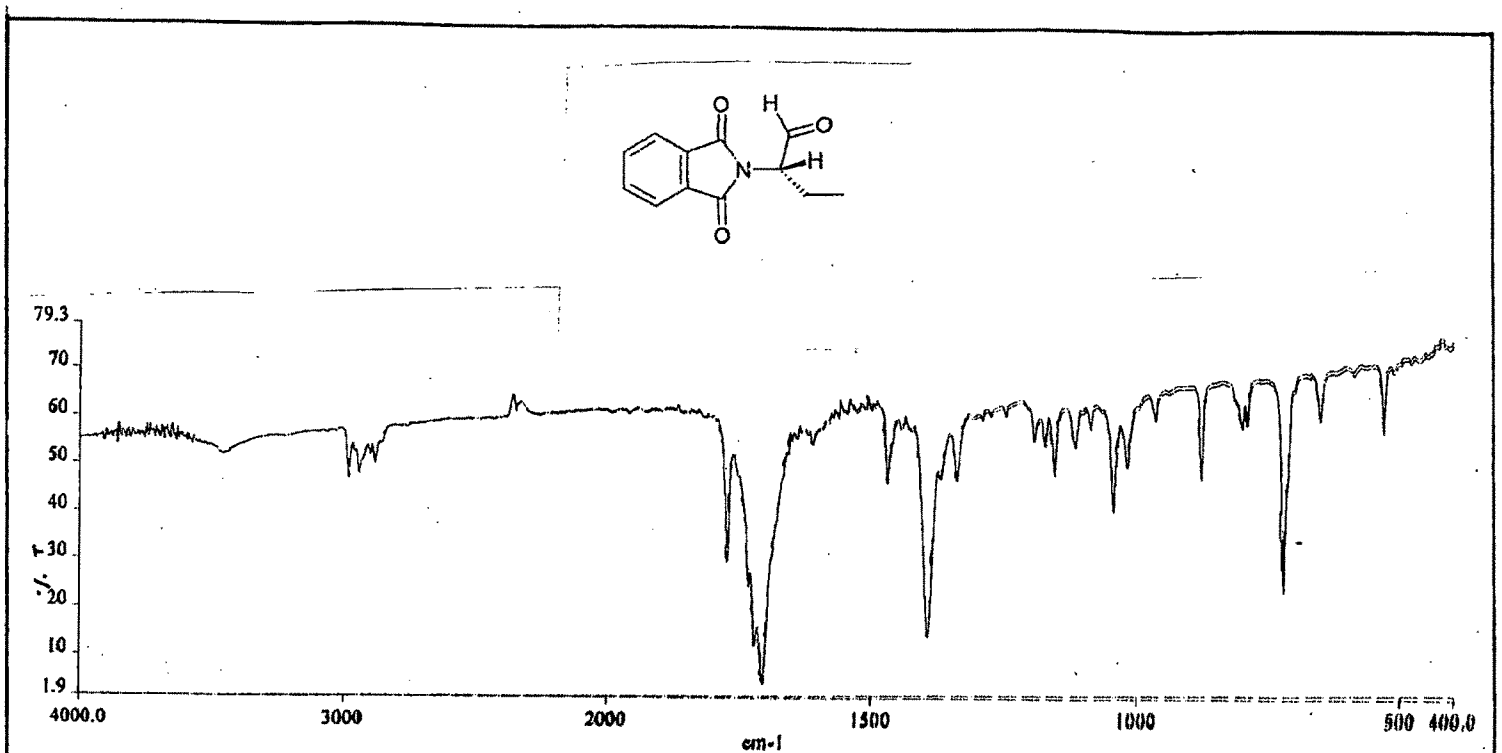


Figure V.5 IR(KBr) spectrum of (*R*) -2-(1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl) butyraldehyde (47)

to the –CH proton. A doublet at δ5.93 indicates the presence of the double bonded CH near the electron withdrawing ester group. A double doublet observed at δ7.17 can be attributed to the other doubly bonded CH proton. The coupling constant for the CH=CH protons is found from proton nmr to be 15Hz. This shows a trans relationship in between the two protons. This fact can again be gauged from the fact that =CH next to =CH directly bonded to the ester group is deshielded to a greater extent showing a greater level of conjugation with the ester group which is only possible if the CH=CH are in a trans relationship. Thus the configuration at the CH=CH can be assigned as E. **(Figure V.6)** A similar observation can be made for its enantiomer 51a. **(Figure V.7)**. The 13C spectra for 48a and 51a showed the required peaks**(Figure V.8)**.The infrared spectra of (48a) showed a band at 1772cm^{-1} for the carbonyl of the ester group, a band at 1711cm^{-1} for the carbonyl of the imide and a band at 1659cm^{-1} for the carbon-carbon double bond. **(Figure V.9)**. 4-((*R*)-(E)-1,3-Dioxo-1,3-dihydro-isoindol-2-yl)hex-2-enoic acid methyl ester (48c) showed a triplet at δ0.92 for $-CH_2CH_3$, a multiplet at δ 2.0 and δ2.2 for methylene protons. A singlet at δ 3.62 can be attributed to the $-CH_3$ of the ester group ($-COOCH_3$). A quintet at δ4.8 can be assigned to the —CH group. A singlet at δ3.62 can be attributed to the $-CH_3$ of the ester ($-COOCH_3$) group. A quintet at δ4.8 can be assigned to the –CH group. A doublet at δ5.9 can be attributed to the =CH group lying next to the =CH-COOCH3 group. The aromatic region shows the required multiplet at δ7.5-8.0 for the four protons.**(Figure V.10)** .The J value for CH=CH is found to be 15.8Hz which again indicates the presence of a trans relationship in between the doubly bonded CH protons. Again the configuration of the CH=CH can be assigned as the E configuration. The allyl substituted derivatives (48b or 51b) **(Figure V.11** or **Figure V.12)** shows in addition to the required peaks a multiplet at δ 4.8-5.0 for $=CH_2$ and =CH group and a singlet at δ3.2 for the $-CH_2$ group. Again based on the previous two observations it can be predicted that a trans relationship must exist in between the allyl group and the hydrogen of the double bonded carbons.

The oxidation of N-Phthaloyl-2-amino-1-butanol using pyridinium dichromate gives the corresponding aldehydes in low yields. Although the N-protected amino aldehydes were found to be unstable, N-phthaloyl substituted amino aldehydes were found to be very stable chemically and its rotation values also remained unchanged for a long time. The reaction with

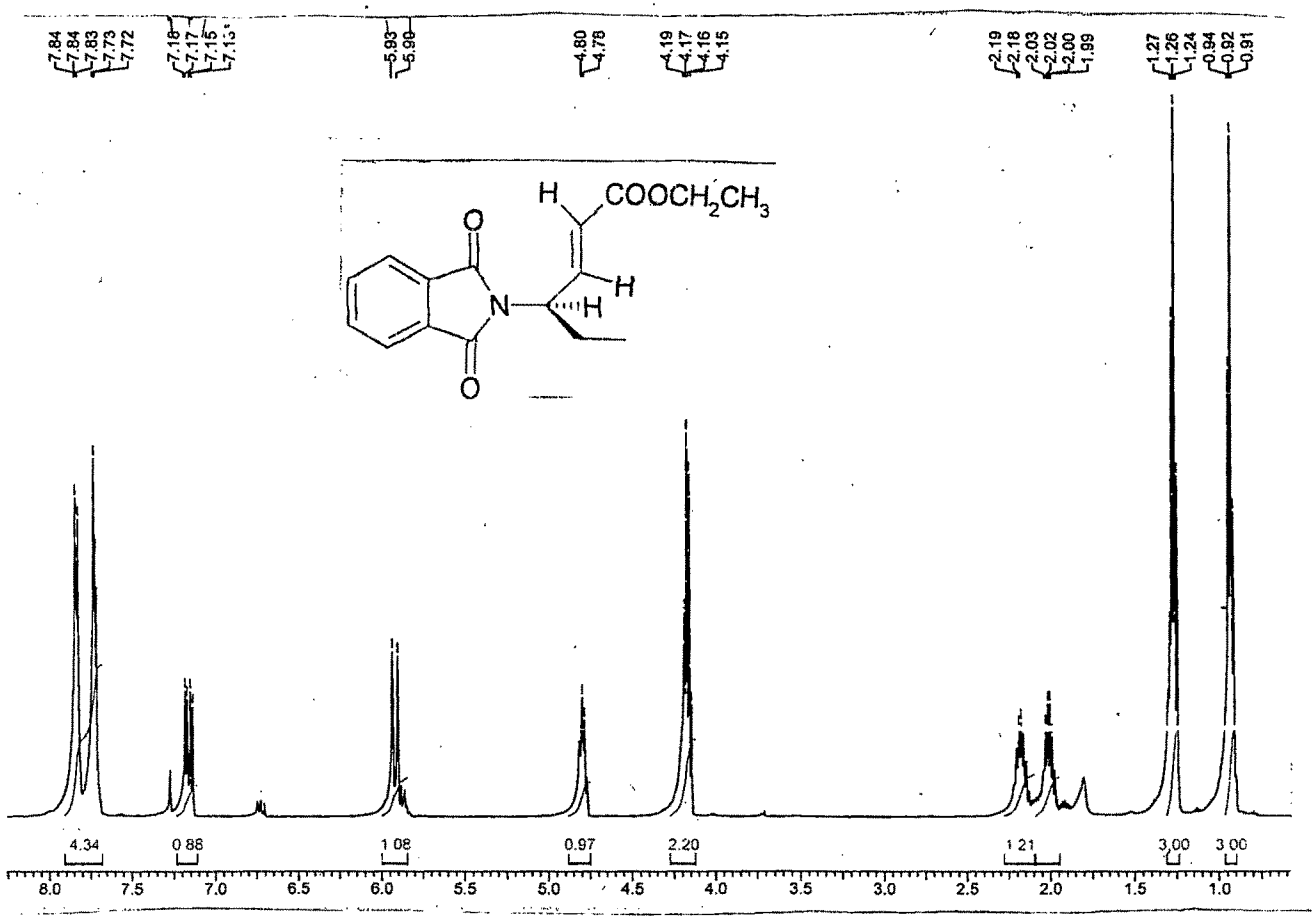


Figure V.6 1HNMR($CDCl_3$) spectrum of 4-((E)-(R)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid ethyl ester (48a)

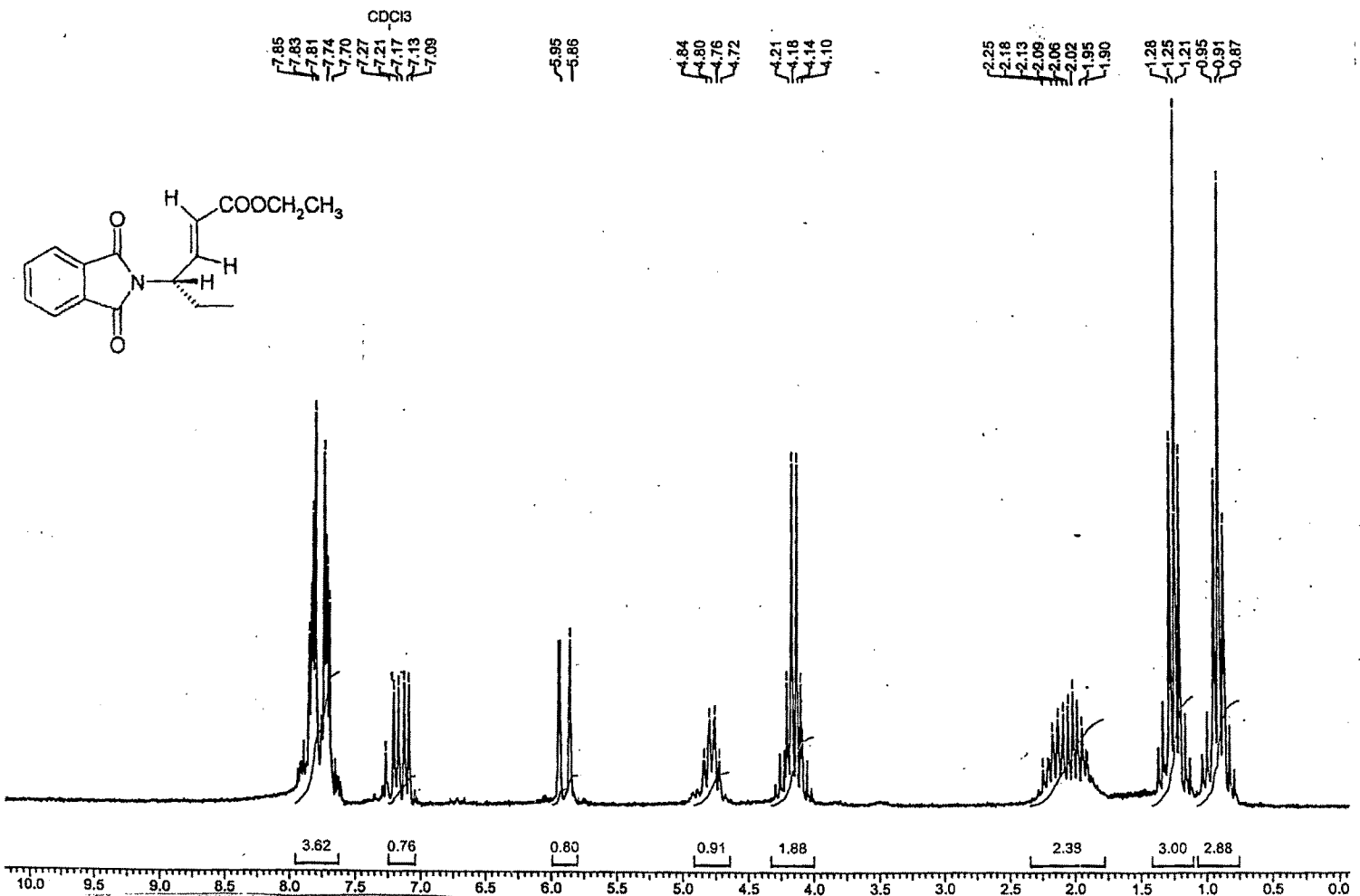


Figure V.7 1HNMR($CDCl_3$) spectrum of 4-((E)-(S)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid ethyl ester

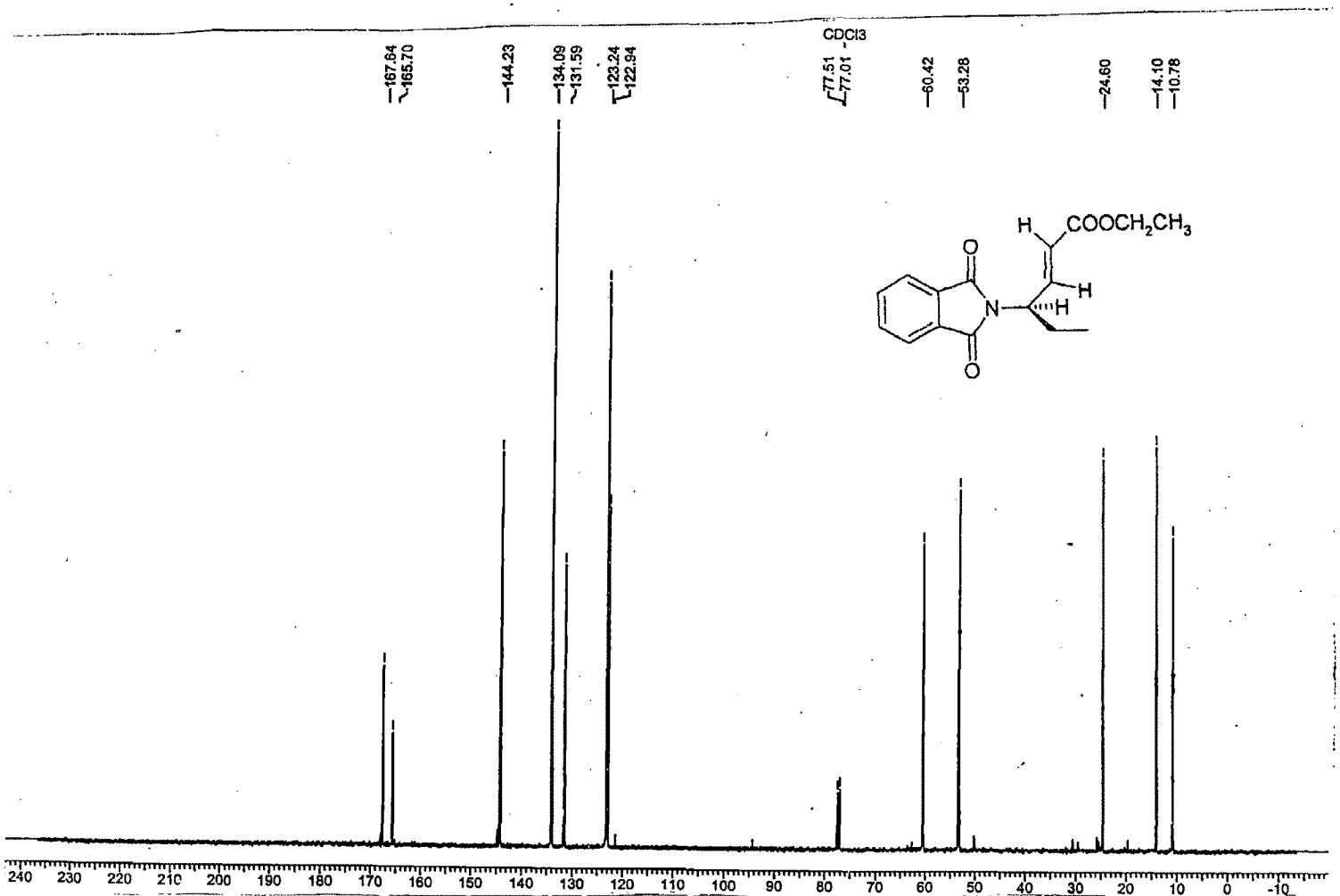
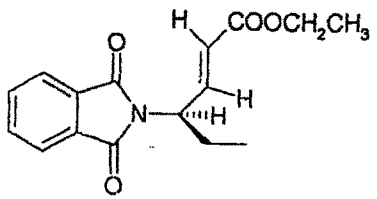


Figure V.8 ^{13}C NMR($CDCl_3$) spectrum of 4-((E)-(R)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid ethyl ester (48a)



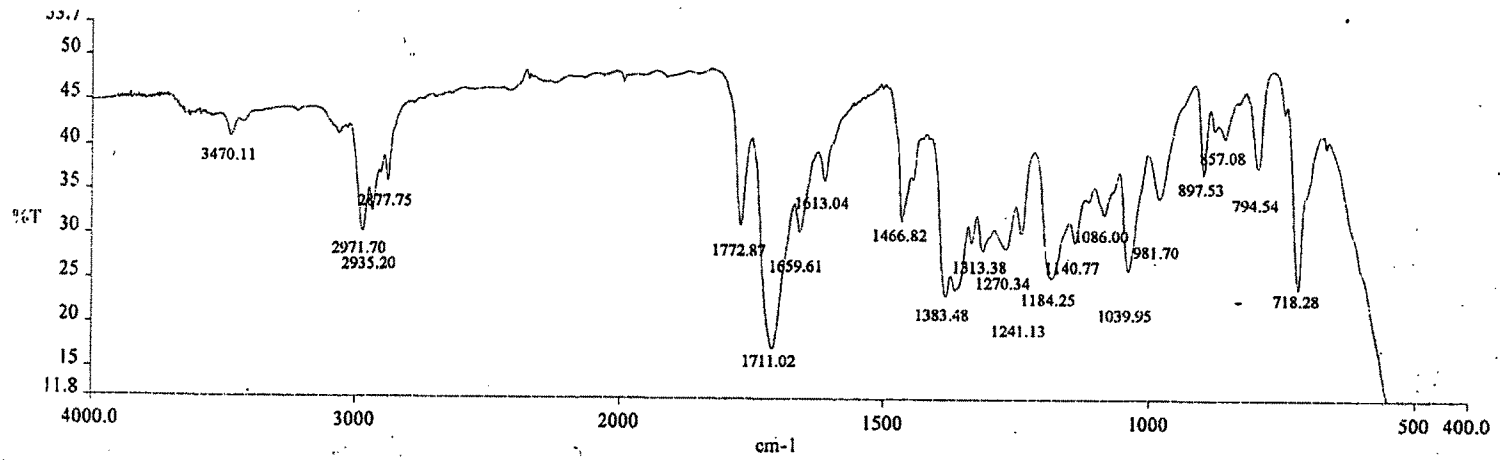


Figure V.9 IR(KBr) spectrum of 4-((E)-(R)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid ethyl ester (48a)

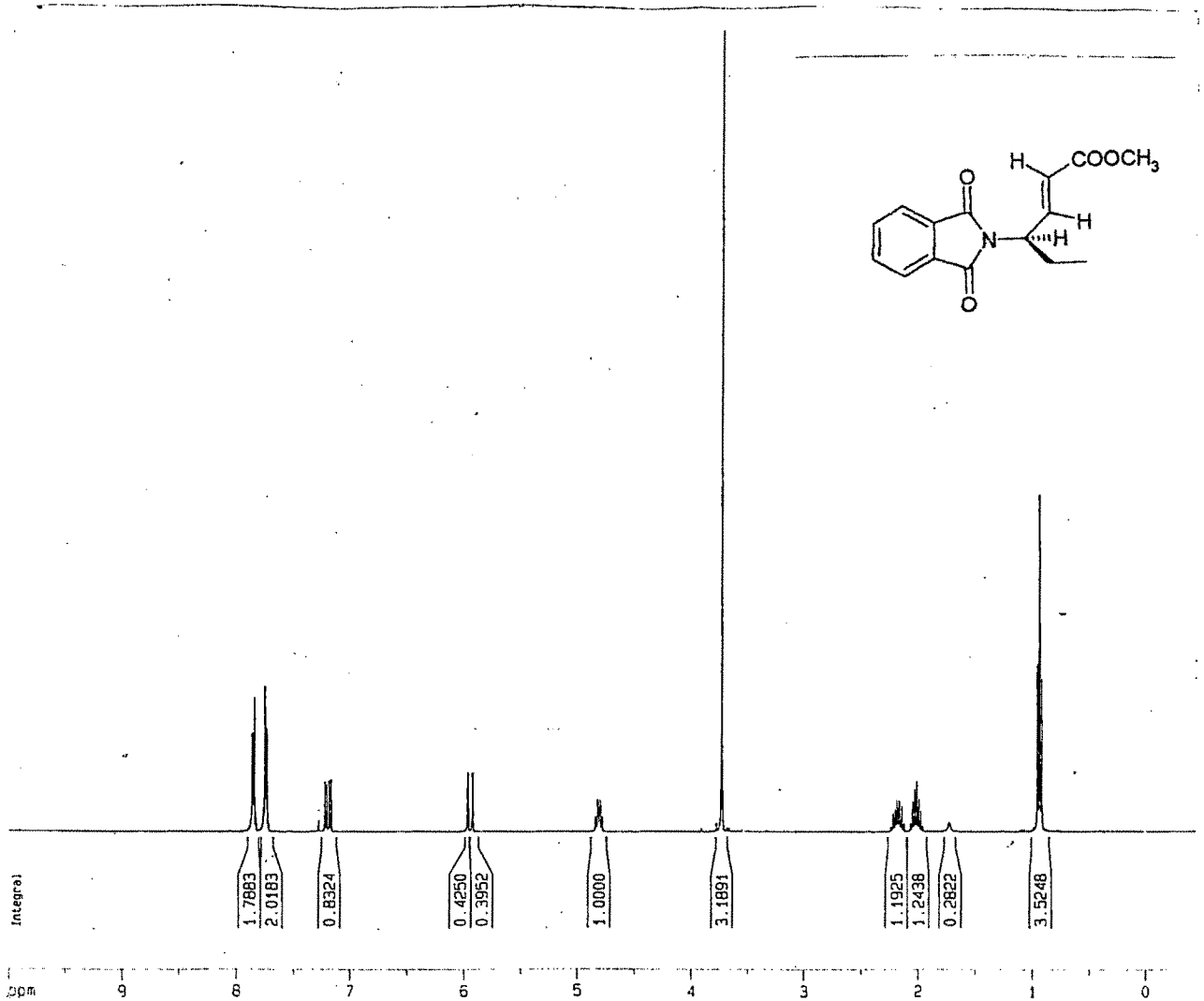


Figure V.10 1H NMR($CDCl_3$) spectrum of 4-((E)-(R)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid methyl ester (48c)

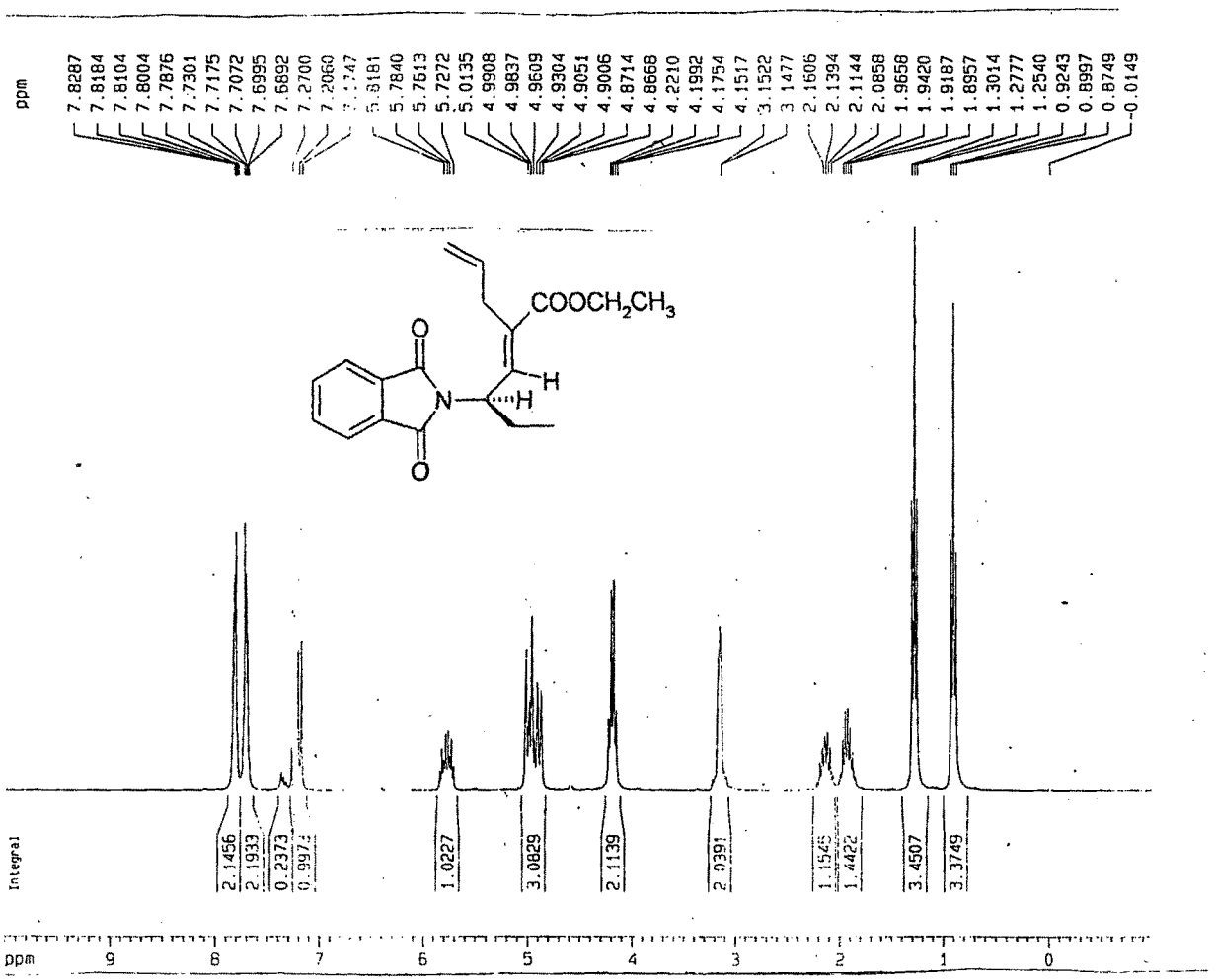


Figure V.11 1H NMR($CDCl_3$) spectrum of 4-((E)-(R)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-2-allyl-hex-2-enoic acid ethyl ester(48b)

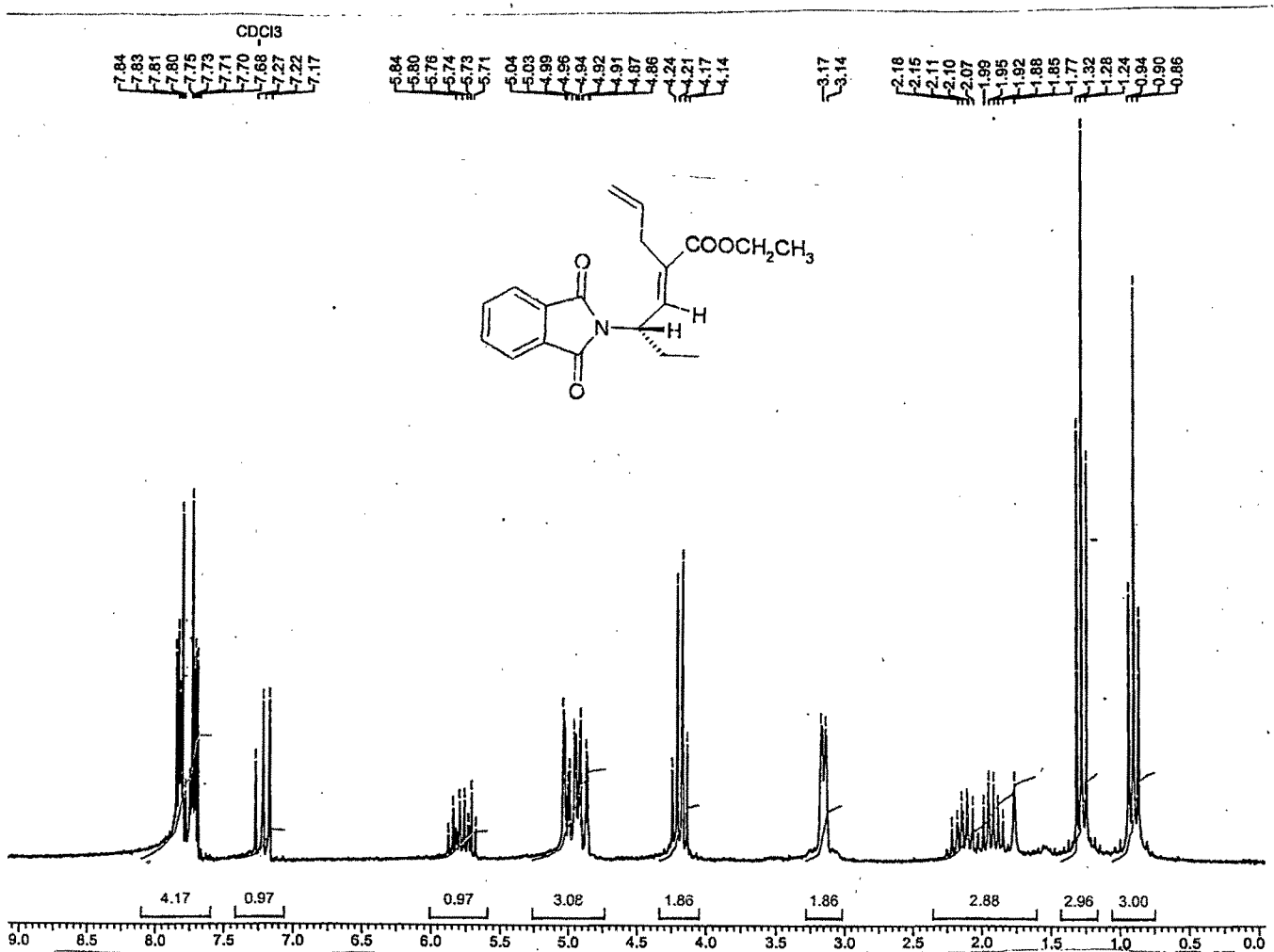


Figure V.12 1H NMR($CDCl_3$) spectrum of 4-((E)-(S)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-2-allyl-hex-2-enoic acid ethyl ester (51b)

the stabilized Wittig reagents proceeds with good yields. The stereo chemical outcome of the Wittig reaction is as expected. The stabilized Wittig reagents as well as a non polar solvent favor the formation of the trans isomer. Again the reaction proceeds with the formation of only the E isomer in excess since no formation of the Z isomer is observed during the reaction as is evident from the pmr as well as the ^{13}C spectra of the products. Also there is no effect of the adjacent chiral centre on the final outcome of the reaction since the enantiomers show similar spectral characteristics and a similar stereo chemical outcome.

5.3 EXPERIMENTAL

Reagent chemicals were purchased from Lancaster synthesis ltd and Aldrich chemical co. ltd. and were purified when necessary before use. Solvents were distilled and dried before use. Dichloromethane (MDC) was dried, distilled and stored over 4A° molecular sieves before use. Benzene was dried and distilled over sodium wire. Column chromatography was carried out using silica gel (60-120 mesh). Thin layer chromatography (TLC) was carried out using silica gel (75μ). Yields are quoted for isolated, purified and dried products. Infrared spectra for the solids were recorded in the range 4000-600cm^{-1} using Perkin-Elmer FT-IR16PC spectrometer using the KBr pellet technique or neat in case of liquids. Proton NMR was recorded using Bruker 400 & 500 MHz spectrometer. Elemental analysis was carried out on a Perkin-Elmer C, H, and N elemental analyzer. Specific rotations were measured using JOSCO P-1030 polarimeter.

5.3.1 Synthesis of (*R*) or (*S*)-2-(1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl) butyraldehyde (47) or (50)

Finely powdered chromium trioxide (22.82g, 229mmoles) is added portionwise to a solution of dry pyridine (36.11g, 459mmoles) in dichloromethane (500mL) at 0-5°C. (R) or (S)-2-(1-hydroxybutyl) isoindol-1, 3-dione (46) or (49) (5g, 22.8mmoles) in dry dichloromethane (25mL) was added in 5-10 minutes to the solution. The reaction mixture was stirred at 0°C for 30 minutes and was further stirred overnight at room temperature. Removal of the solvent gave a residue which was extracted with 100mL portions of

diethyl ether. Filtration through celite and removal of the solvent furnished the product as a viscous liquid which was chromatographed over silica gel using petroleum ether (60-80°C)-ethyl acetate (80:20) to give 1.99g (38%) of the aldehyde 47 or 50.

5.3.2 Synthesis of Carboethoxy or Carbomethoxy triphenyl phosphorane [48]

Triphenyl phosphine (15.7g, 60mmole) in dry benzene(30mL) was added to a solution of ethyl bromoacetate (11.7g,70mmole) or methyl bromoacetate (10.7, 70mmole)in dry benzene (10mL) at room temperature resulting in the elevation of temperature to about 70°C followed by precipitation of the salt. After allowing the mixture to cool, the flask was vigorously shaken and left overnight. The separated solid was filtered and washed with dry benzene and dried. The stirred solution of the above salt in water(150mL) and benzene (100mL) was neutralized by aqueous NaOH to a phenopthalein end point. The benzene layer was separated, dried (anhydrous Na_2SO_4) and concentrated to about one-third volume. Addition of petroleum ether(60-80°C) resulted in the separation of the crystalline product which was filtered and dried to afford 13.5gms of triphenyl ethoxy or methoxy carbrthoxy methylene phosphorane.

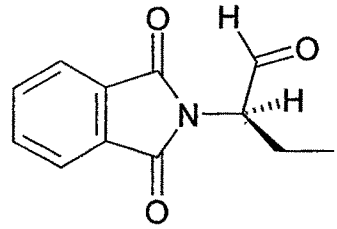
5.3.3 Synthesis of α-Allyl methyledene triphenyl phosphorane [49, 50]

A solution of allyl bromide(3.47g, 2.87mmol) in dry $CHCl_3$ (5mL) was added to a solution of carbethoxy methylene triphenyl phosphorane (10g, 2.87mmol) in $CHCl_3$ (20mL). The reaction mixture was refluxed for 11hours and then excess of solvent was removed to give the corresponding salt, the above salt was then dissolved in water (125mL), benzene (100mL) and a few drops of phenopthalein were added to the above solution.. A solution of 1N NaOH was then added to it with stirring till the pink colour persisited. The benzene layer was saperated and the aqueous layer extracted with benzene (50mL). Combined benzene layer is dried over anhydrous Na_2SO_4 and the excess solvent is removed under vacuum to obtain the α-allyl methyledene triphenyl phosphorane.

5.3.4 Wittig reactions of (*R*) & (S)-2-(1, 3-Dioxo-1, 3-dihydro-isoindol-yl) butyraldehyde (General Methodology)

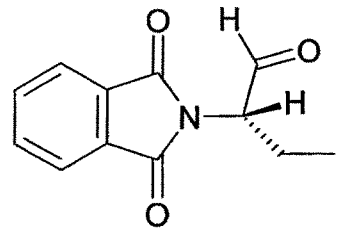
(*R*) or (*S*)-2-(1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl) butyraldehyde (2.53mmol) (47) or (50) and the corresponding Wittig reagent (carboethoxy methylene triphenyl phosphorane, carbomethoxy methylene triphenyl phosphorane or carboethoxy α-allyl methyledene triphenyl phosphorane) (2.58mmol) were dissolved in 50mL dry benzene. The mixture was refluxed for 12 hours with stirring. Benzene was distilled off under vacuum and the resulting residue was loaded on the silica gel column and the products 48a-48c or 51a-51c were eluted by petroleum ether (60-80°C)-ethyl acetate (90:10) as a viscous liquid.

(*R*) -2-(1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl) butyraldehyde (47)



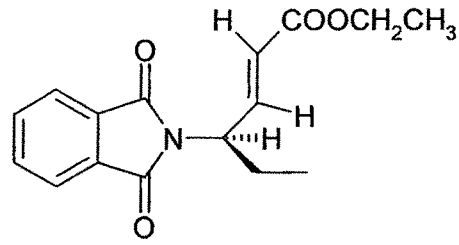
State	White crystalline solid
Molecular formula	$C_{12}H_{11}NO_3$
Yield	38%
Melting point	110-112°C
$[\alpha]_D^{20}$	+1.56° [*c* 0.72 ,MeOH]
CHN	C-66.19(66.35), H-4.67(5.069),
found(calculated)	N-6.93(6.45)
ν_{max} (KBR)/ cm^{-1}	2941,2881,1730,1719,1703
δ_H (200MHz, $CDCl_3$)	0.9(3H,t,-CH_3), 2.0-2.5(2H,m,CH_2), 4.7(1H,m,-CH), 7.3-8.0(4H,m,Ar-H), 9.75(1H,s,-CH(aldehyde))
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	196.75(C), 168.10(C) {134.56, 132.02, 123.84}(Ar-C), 60.57(CH), 20.90(CH_2), 10.83(CH_3).

(S) -2-(1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl) butyraldehyde (50)



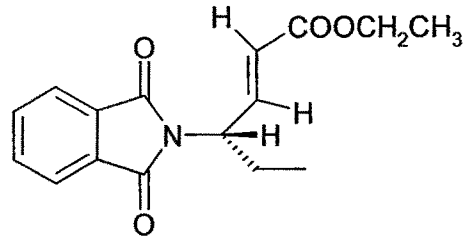
State	White crystalline solid
Molecular formula	$C_{12}H_{11}NO_3$
Yield	40%
Melting point	102-104°C
$[\alpha]_D^{20}$	-1.58°[*c* 0.72 MeOH]
CHN	C-66.29(66.35), H-4.80(5.069),
found(calculated)	N-6.53(6.45)
ν_{max} (KBR)/ cm^{-1}	2941,2881,1730,1719,1703
δ_H (200MHz, $CDCl_3$)	0.9(3H,t,-CH_3), 2.0-2.5(2H,m,CH_2), 4.8(1H,m,-CH), 7.3-8.0(4H,m,Ar-H), 9.70(1H,s,-CH(aldehyde))
^{13}C NMR	196.05(C), 168.20(C) {134.56, 132.02, 123.84}
δ_C ($CDCl_3$,50.33MHz)	(Ar-C), 60.07(CH), 20.98(CH_2), 10.13(CH_3).

4-((E)-(R)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid ethyl ester (48a)



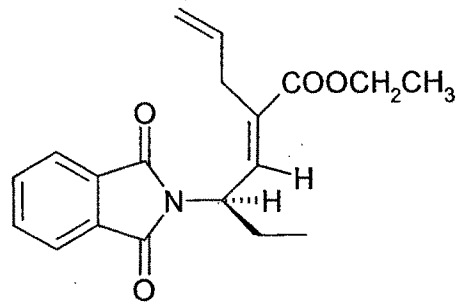
State	Liquid
Molecular formula	$C_{16}H_{17}NO_4$
Yield	80%
CHN	C-67.23(66.89), H-6.01(5.923),
found(calculated)	N-5.07(4.87)
ν_{max} (KBR)/ cm^{-1}	1750, 1719,1620
δ_H (500MHz, $CDCl_3$)	0.92(3H,t,-CH_3), 1.26(3H,t,-CH_3), 2.0(1H,m, -CHaCHb), 2.18(1H, m,-CHaHb), 4.8(1H,q,-CH), 5.93 1H,d,=CH,J=15Hz), 7.17(1H,dd,=CH,J=15Hz), 7.5-8.0(4H,m,Ar-H)
^{13}C NMR	168.02(C), 166.10(C), {145, 134.35, 132.02}(Ar-C),
δ_C ($CDCl_3$,50.33MHz)	123.6(=CH), 123.41(=CH), 60.79(-CH_2), 53.7(-CH), 24.98(-CH_2), 14.42(-CH_3), 11.09(-CH_3)

4-((E)-(S)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid ethyl ester (51a)



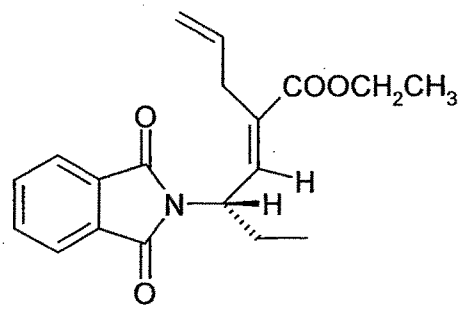
State	Liquid
Molecular formula	$C_{16}H_{17}NO_4$
Yield	85%
CHN	C-67.03(66.89), H-6.01(5.923),
found(calculated)	N-4.97(4.87)
ν_{max} (KBR)/ cm^{-1}	1750, 1719,1620
δ_H (500MHz, $CDCl_3$)	0.90(3H,t,-CH_3), 1.26(3H,t,-CH_3), 2.0(2H,m, -CHaCHb), 2.18(2H, m,-CHaHb), 4.8(1H,q,-CH), 5.92(1H,d,=CH,J=15Hz), 7.17(1H,dd,=CH, J=15Hz), 7.5-8.0(4H,m,Ar-H)
^{13}C NMR	169.0(C), 167.0(C), {145.0, 134.35, 132.02}(Ar-C),
δ_C ($CDCl_3$,50.33MHz)	123.8(=CH), 123.41(=CH), 60.79(-CH_2), 53.7(-CH), 24.98(-CH_2), 14.45(-CH_3), 11.01(-CH_3)

4-((E)-(R)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-2-allyl-hex-2-enoic acid ethyl ester(48c)



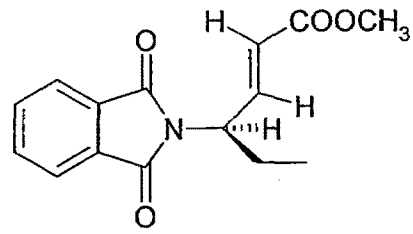
State	Liquid
Molecular formula	$C_{19}H_{20}NO_4$
Yield	90%
CHN	C-69.93(70.13), H-6.13(6.49),
found(calculated)	N-3.96(4.29)
ν_{max} (KBR)/ cm^{-1}	1750, 1720, 1620
δ_H (200MHz, $CDCl_3$)	0.90(3H,t,CH_3), 1.2(3H,t,CH_3), 1.9(2H,m, -CHaCHb), 2.2(2H, m,-CHaHb), 3.2(2H,s, CH_2), 4.2(2H, q, CH_2), 4.8-5.0(3H,m,=CH_2,=CH), 5.7(1H,m,-CH), 7.2(1H,d.=CH), 7.5-8.0(4H,m,Ar-H)
^{13}C NMR	167.93(C), 167.11(C), {138.77, 135.0, 134.35}
δ_C ($CDCl_3$,50.33MHz)	(Ar-C),133.18(=CH), 131.87(=CH) 123.5(=CH), 115.64(=CH_2), 61.0(-CH_2), 50.04(-CH), 31.25(-CH_2), 25.70(CH2) 14.29(-CH_3), 10.91(-CH_3)

4-((E)-(S)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-2-allyl-hex-2-enoic acid ethyl ester (51c)



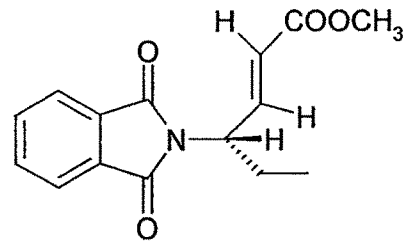
State	Liquid
Molecular formula	$C_{19}H_{20}NO_4$
Yield	92%
CHN	C-70.03 (70.13), H-6.23(6.49),
found(calculated)	N-4.06(4.29)
ν_{max} (KBR)/ cm^{-1}	1750, 1720, 1620
δ_H (200MHz, $CDCl_3$)	0.90(3H,t,CH_3), 1.2(3H,t,CH_3), 1.9(2H,m, -CHaCHb), 2.2(2H, m,-CHaHb), 3.2(2H,s, CH_2), 4.2(2H, q, CH_2), 4.8-5.0(3H,m,=CH_2,=CH), 5.7(1H,m,-CH), 7.2(1H,d.=CH), 7.5-8.0(4H,m,Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	167.93(C), 167.11(C), {138.77, 135.0, 134.35} (Ar-C),133.18(=CH), 131.87(=CH) 123.5(=CH), 115.64(=CH_2), 61.0(-CH_2), 50.04(-CH), 31.25(-CH_2), 25.70(CH2) 14.29(-CH_3), 10.91(-CH_3)

4-((E)-(R)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid methyl ester (48b)



State	Liquid
Molecular formula	$C_{18}H_{18}NO_4$
Melting point	68°C
Yield	90%
CHN	C-69.03 (69.23), H-5.70(5.76),
found(calculated)	N-4.26(4.48)
ν_{max} (KBR)/ cm^{-1}	1750, 1720, 1620
δ_H (400MHz, $CDCl_3$)	0.90(3H,t,CH_3), 2.0 (2H,m, -CHaCHb), 2.2(2H, m,-CHaHb),3.6(3H,s,CH_3),4.8(1H,q,CH), 5.9(1H,d,=CH, J=15.8Hz),7.20(1H,dd,=CH,J=15.8Hz), 7.5-8.0(4H,m, Ar-H)
^{13}C NMR	167.93(C), 167.11(C), {138.77, 135.0, 134.35}(Ar-C),
δ_C ($CDCl_3$,50.33MHz)	123.5(=CH),123.20(=CH),50.04(-CH),31.25(-CH_2), 25.70(CH2), 14.29(-CH_3), 10.91(-CH_3).

4-((E)-(S)-1, 3-Dioxo-1, 3-dihydro-isoindol-2-yl)-hex-2-enoic acid methyl ester (51b)



State	Solid
Molecular formula	$C_{18}H_{18}NO_4$
Yield	92%
Melting point	69°C
CHN	C-69.13 (69.23), H-5.60(5.76),
found(calculated)	N-4.33(4.48)
ν_{max} (KBR)/ cm^{-1}	1750, 1720, 1620
δ_H (400MHz,$CDCl_3$)	0.92(3H,t,CH_3), 2.0 (2H,m, -CHaCHb), 2.2(2H, m,-CHaHb), 3.62(3H,s, CH_3), 4.8(1H, q, CH),5.9(1H,d, =CH,J=15.8Hz),7.20(1H,dd,.=CH,J=15.8Hz),7.5-8.0 (4H,m,Ar-H)
^{13}C NMR	167.93(C), 167.10(C), {138.70, 135.0, 134.35}(Ar-C),
δ_C($CDCl_3$,50.33MHz)	123.5(=CH),123.20(=CH),50.10(-CH),31.25(CH_2),25.7 (CH_2), 14.29(-CH_3), 10.90(-CH_3).

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SHORT PAPER

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Synthesis of phenyl and substituted phenyl 3-ethyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-ones†

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Addition of various aryl magnesium bromides to (*R*) or (*S*)-2-(1-hydroxybutyl)phthalimide results in the formation of substituted (*R*) or (*S*)-3-hydroxy-2(1-hydroxybutyl)isoindol-1-ones which are subsequently cyclised under highly acidic conditions to give the title compounds in moderate yields.

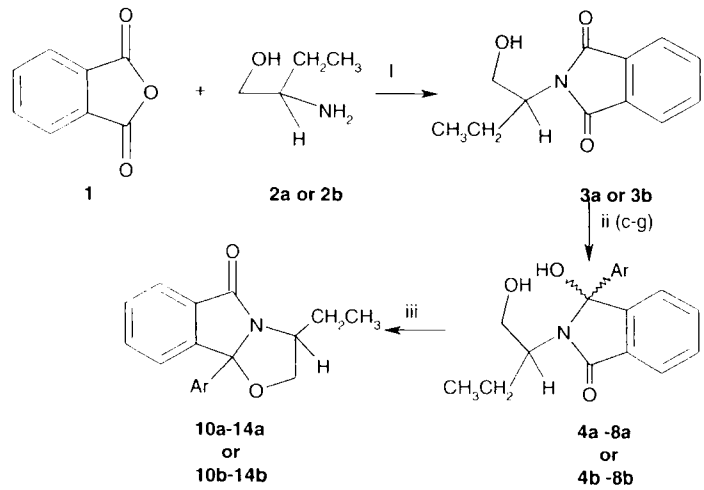
Keywords: amino butanol, chiral synthon, isoindolinones

Oxazolo[2,3-a]isoindol-5-one derivatives exhibit anti-convulsant and anti inflammatory activities.[1] The chemistry and reactivity of isoindolinone ring system is an area of interest because of its biological activity.[2] Recently Allin and coworkers[3] have reported a new synthesis of non-racemic isoindolinone targets through application of oxazolo-[2,3-a]isoindolinones as N-acyl iminium ion precursors in reactions with carbon and hydride nucleophiles. We had earlier reported the formation of a novel 10 membered chiral ring system[4] while attempting to synthesise oxazolo-[2,3-a]isoindol-5(9bH)-one using (*R*) or (*S*)-2-amino-1-butanol via Meyers methodology[5] involving reduction of the imide and cyclisation using trifluoro acetic acid. The phenyl group was introduced by the addition of phenyl magnesium bromide (**c**) to (*R*) or (*S*)-2-(1-hydroxy)phthalimides **3a** or **3b**. These were derived from phthalic anhydride **1** and (*R*)-(-)-2-amino-1-butanol **2a** or (*S*)-(+)-2-amino-1-butanol **2b**. The resulting dihydroxy compounds **4a** or **4b** were not isolated, but were directly subjected to acid-catalysed cyclisation to furnish the 9b-phenyl substituted oxazolo[2,3a] isoindolinones **10a** or **10b** in 40-50% yields. In a similar fashion the addition of *p*-fluoro(**d**), *p*-chloro(**e**), *p*-methoxy(**f**) and *p*-methyl(**g**) substituted phenyl magnesium bromides furnished the corresponding 9b-substituted-phenyl substituted oxazolo[2,3a] isoindolinones **11a–14a** or **11b–14b** respectively (Scheme 1).

Table 1 Preparation of tricyclic lactams through addition of different Grignard reagents and subsequent cyclisation

Substrate	Grignard reagent	Ar	Product
3a	c	Ph	**10a**
3b	c	Ph	**10b**
3a	d	4-FPh	**11a**
3b	d	4-FPh	**11b**
3a	e	4-ClPh	**12a**
3b	e	4-ClPh	**12b**
3a	f	4-OCH_3	**13a**
3b	f	4-OCH_3	**13b**
3a	g	4-CH_3	**14a**
3b	g	4-CH_3	**14b**

Compound **10b** was subjected to a single crystal X-ray diffraction analysis[6] and its structure was solved and refined by SHELX 97 program[7] (Fig. 1). The absolute configuration of the phenyl substituted oxazolo[2,3-a]isoindolin-5-one was found to be (3*S*, 9b*R*).



Scheme 1 Reagents and conditions (i) Neat, 140°C (ii) **c**- C_6H_5MgBr, **d**- *p*-FC_6H_4MgBr, **e**-*p*-ClC_6H_4MgBr, **f**- *p*-$OCH_3C_6H_4MgBr$, **g**-*p*-$CH_3C_6H_4MgBr$, 3 hours, N_2 atmos., R.T. (iii) CF_3COOH, CH_2Cl_2, 2–3 hours.

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† This is a Short Paper, there is therefore no corresponding material in *J. Chem. Research (M)*.

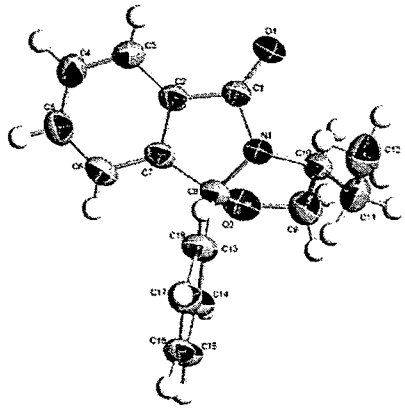
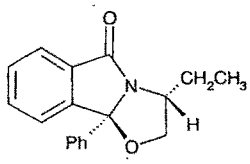
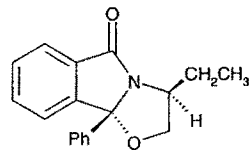


Fig. 1 ORTEP plot of compound **10b**. Ellipsoids drawn at 50% probability.

The structures of **10a** and **10b** can be given as follows:



10a



10b

Cyclisation takes place via the usual N-acyl iminium ion species. The N-acyl iminium ion being planar, attack of the hydroxyl group can take place from either of the two possible sides, but in this case attack takes place on one of the sides. This can be attributed to the fact that the folded shape of the fused 5.5-bicyclic system requires both the 3-ethyl and 9b-phenyl substituents to be *cis* on the *exo* face. The Grignard reactions proceeded with low yields. However, they may provide a valuable tool for introducing a number of substituted phenyl groups into the tricyclic lactams.

Experimental

Reagent chemicals were purchased from Lancaster Synthesis Ltd and Aldrich Chemical Co. Ltd. and were purified when necessary before use. Solvents were distilled and dried before use. Tetrahydrofuran (THF) for Grignard reactions was distilled over sodium wire and stored over sodium wire. Dichloromethane (MDC) was dried, distilled and stored over 4A° molecular sieves before use. Column chromatography was carried out using silica gel (60–120 mesh). Thin layer chromatography (TLC) was carried out using silica gel (75μm). Yields are quoted for isolated, purified and dried products. Infrared spectra for the solids were recorded in the range 4000–600cm^{-1} using Perkin-Elmer FT-IR16PC spectrometer with KBr pellet. Proton NMR was recorded using Bruker 200 MHz spectrometer. Elemental analysis was carried out on a Perkin-Elmer C, H, and N elemental analyzer. Specific rotations were measured using JASCO P-1030 polarimeter.

Synthesis of phenyl and substituted phenyl oxazolo[2,3-a] isoindolinones (general method): Grignard reagents were prepared by the usual procedure using the corresponding aryl bromides and magnesium in THF under nitrogen atmosphere.

(*R*) or (*S*)- 2-(1-Hydroxybutyl)phthalimide **3a** or **3b** (2.0g, 9.13 mmol) dissolved in dry THF is taken in two neck round bottom flask flushed with nitrogen. Grignard reagent **c–g** (3 equivalents) was added within 4–5 minutes. Then the solution was stirred for 3 hours at room temperature. A saturated solution of ammonium chloride was added and the solution extracted with dichloromethane. Removal of the solvent gave the crude product, which was dissolved in dry dichloromethane and added in portions to a stirred solution of trifluoroacetic acid (10 equivalents) in dry dichloromethane. The solution was stirred at room temperature for 2–3 hours. A saturated solution of sodium bicarbonate was added. The dichloromethane extract was washed with brine and dried over sodium sulfate. Dichloromethane was then distilled off to obtain a crude product which was purified using column chromatography with petroleum ether:ethylacetate (80:20) to obtain the corresponding cyclic products **10a–14a** or **10b–14b** in pure form.

10a: (45%), $[\alpha]_D^{20}$ 261.97° (c 1.0, methanol); [Found: C, 77.53; H, 6.12; N, 4.93. $C_{18}H_{17}O_2N$ requires C, 77.41; H, 6.093; N, 5.017%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-CH_3$), 1.4 (2H, m, $-CH-CH_2-CH_3$), 3.8 (1H, t, *J* 8.0, $-CH-CH_2-O$), 4.2 (1H, q, *J* 8.0, $-CH_2-CH-CH_2-$), 4.6 (1H, t, *J* 8.0, $-CH-CH_2-O$); 7.1–7.8 (9H, m, Ar–H); ^{13}C NMR δ_C ($CDCl_3$, 50.33MHz) 175.27(C), {147.77, 139.59, 133.80, 131.82, 130.69, 129.37, 129.26, 126.32, 124.98, 124.06}(Ar–C), 101.36(C), 76.74(CH), 58.13(CH_2), 28.11(CH_2), 11.86(CH_3); ν_{max}/cm^{-1}(KBr pellet) 1716, 1610, 1450, 1320, 1240, 750. **10b**: (47%), $[\alpha]_D^{20}$ –263.72° (c 1.0, methanol); [Found: C, 77.55; H, 6.09; N, 4.92. $C_{18}H_{17}O_2N$ requires C, 77.41; H, 6.093; N, 5.017 %]; δ_H (200MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-CH_3$), 1.4 (2H, m, $-CH_2-CH_2-CH_3$), 3.8 (1H, t, *J* 8.0, $-CH-CH_2-O$), 4.2 (1H, q, *J* 8.0, $CH_2-CH-CH_2$), 4.6 (1H, t, *J* 8.0 Hz, $-CH-CH_2-O$), 7.1–7.8 (9H, m, Ar–H); ^{13}C NMR δ_C ($CDCl_3$, 50.33MHz) 175.27(C), {147.77, 139.59, 133.80, 131.82, 130.69, 129.37, 126.32, 124.98, 124.06}(Ar–C), 101.36(C), 76.74(CH), 58.13(CH_2), 28.11(CH_2), 11.86(CH_3); ν_{max}\cm^{-1}(KBr pellet) 1716, 1610, 1450, 1320, 1240, 750. **11a**: (40%), $[\alpha]_D^{20}$ 264.8° (c 1.0, $CHCl_3$); [Found: C, 72.51; H, 5.40; N, 4.69. $C_{18}H_{16}O_2NF$ requires C, 72.72; H, 5.38; N, 4.71%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-CH_3$), 1.4 (2H, m, $-CH-CH_2-CH_3$), 3.8 (1H, t, *J* 7.0–8.0, $-CH-CH_2-O$), 4.2 (1H, q, *J* 8.0, $-CH_2-CH-CH_2-$), 4.6 (1H, t, *J* 7.0–8.0, $-CH-CH_2-O$), 7.1–7.8 (8H, m, Ar–H); ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.16(C), {161.09, 147.59, 135.50, 134.27, 133.58, 131.63, 130.58, 128.28, 125.017, 123.91}(Ar–C), 100.98(C), 76.69(CH), 58.14(CH_2), 28.08(CH_2), 11.78(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1737, 1600, 1463, 1377, 722 .**11b**: (41%), $[\alpha]_D^{20}$ –242.19° (c 1.0, $CHCl_3$); [Found: C, 72.65; H, 5.30; N, 4.70. $C_{18}H_{16}O_2NF$ requires C, 72.72; H, 5.38; N, 4.71%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-CH_3$), 1.4 (2H, m, $-CH-CH_2-CH_3$), 3.8 (1H, t, *J* 7.0–8.0, $-CH-CH_2-O$), 4.6 (1H, t, *J* 7.0–8.0, $-CH-CH_2-O$), 4.2 (1H, q, *J* 8.0, $-CH_2-CH-CH_2-$), 7.1–7.8 (8H, m, Ar–H) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.16(C), {161.09, 147.59, 135.50, 134.27, 133.58, 131.63, 130.58, 128.28, 125.017, 123.91}(Ar–C), 100.98(C), 76.69(CH), 58.14(CH_2), 28.08(CH_2), 11.78(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1737, 1600, 1463, 1377, 722. **12a**: (43%), $[\alpha]_D^{20}$ 266.64° (c 1.0, $CHCl_3$); [Found: C, 68.90; H, 5.03; N, 4.41. $C_{18}H_{16}O_2NCl$ requires C, 68.89; H, 5.10; N, 4.46%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-CH_3$), 1.4 (2H, m, $-CH-CH_2-CH_3$), 3.8 (1H, t, *J* 7.0–8.0, – $CH-CH_2-O$), 4.2 (1H, q, *J* 8.0, $-CH_2-CH-CH_2-$), 4.6 (1H, t, *J*7.0–8.0, $-CH-CH_2-O$), 7.1–7.8 (8H, m, Ar–H) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.10(C), {150.11, 147.35, 135.24, 133.9, 131.66, 130.86, 129.61, 127.81, 125.06, 123.93}(Ar–C), 100.90(C), 76.72(CH), 58.15(CH_2), 28.10(CH_2), 11.79(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1736, 1599, 1462, 1376, 722.**12b**: (41%), $[\alpha]_D^{20}$ –250.22° (c 1.0, $CHCl_3$); [Found: C, 68.70; H, 5.05; N, 4.42. $C_{18}H_{16}O_2NCl$ requires C, 68.89; H, 5.10; N, 4.46%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-CH_3$), 1.4 (2H, m, $-CH-CH_2-CH_3$), 3.8 (1H, t, *J*7.0–8.0, $-CH-CH_2-O$), 4.2 (1H, q, *J* 8.0, $-CH_2-CH-CH_2-$), 4.6 (1H, t, *J*7.0–8.0, $-CH-CH_2-O$), 7.1–7.8 (8H, m, Ar–H); ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.10(C), {150.11, 147.35, 135.24, 133.9, 131.66, 130.86, 129.61, 127.81, 125.06, 123.93}(Ar–C), 100.90(C), 76.72(CH), 58.15(CH_2), 28.10(CH_2), 11.79(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1736, 1599, 1462, 1376, 722 .**13a**: (52%). $[\alpha]_D^{20}$ 207.14° (c 1.0, $CHCl_3$); [Found: C, 73.85; H, 6.04; N, 4.48. $C_{19}H_{19}O_3N$ requires C, 73.78; H, 6.14; N, 4.53%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-CH_3$), 1.4 (2H, m, $-CH-CH_2-CH_3$), 3.8 (1H, t, *J* 7.0–8.0, $-CH-CH_2-O$), 3.81(3H, s, $-OCH_3$) 4.2 (1H, q, *J* 8.0, $-CH_2-CH-CH_2-$), 4.6 (1H, t, *J* 7.0–8.0, $-CH-CH_2-O$), 7.1–7.8 (8H, m, Ar–H) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.15(C), {160.43, 147.89, 133.67, 131.62, 131.29, 130.47, 127.52, 124.79, 123.85, 114.63}(Ar–C), 101.18(C), 76.58(CH), 57.99(CH_2), 55.81(CH_3), 28.01(CH_2), 11.79(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1732.47, 1611, 1510, 1459, 1377, 722. **13b**: (55%), $[\alpha]_D^{20}$ –212.99° (c 1.0, $CHCl_3$); [Found: C, 73.71; H, 6.10; N, 4.52. $C_{19}H_{19}O_3N$ requires C, 73.78; H, 6.14; N, 4.53%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-CH_3$), 1.4 (2H, m, $-CH-CH_2-CH_3$), 3.8 (1H, t, *J* 7.0–8.0, $-CH-CH_2-O$), 3.81(3H, s, $-OCH_3$) 4.2 (1H, q, *J* 8.0, $-CH_2-CH-CH_2-$), 4.6 (1H, t, *J* 7.0–8.0, $-CH-CH_2-O$), 7.1–7.8 (8H, m, Ar–H) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.15(C), {160.43, 147.89, 133.67, 131.62, 131.29, 130.47, 127.52, 124.79, 123.85, 114.63}(Ar–C), 101.18(C), 76.58(CH), 57.99(CH_2), 55.81(CH_3), 28.01(CH_2), 11.79(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1732.47, 1611, 1510, 1459, 1377, 722. **14a**: (48%). $[\alpha]_D^{20}$ 221.49°

(c 1.0, $CHCl_3$): [Found: C, 77.76; H, 6.16; N, 4.69. $C_{19}H_{19}O_2N$ requires C, 77.81; H, 6.48; N, 4.78%]: δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-C\underline{H}_3$), 1.4 (2H, m, $-CH-C\underline{H}_2-CH_3$), 2.3(3H, s, $-CH_3$), 3.8 (1H, t, *J* 7.0–8.0, $-CH-C\underline{H}_2-O$), 4.2 (1H, q, *J* 8.0, $-CH_2-C\underline{H}-CH_2-$), 4.6 (1H, t, *J* 7.0–8.0, $-CH-C\underline{H}_2-O$), 7.1–7.8 (8H, m, Ar–H); ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.10(C), {147.76, 138.90, 136.39, 133.61, 131.65, 130.44, 129.94, 126.09, 124.74, 123.86}(Ar–C), 101.23(C), 76.54(CH), 57.94(CH_2), 27.97(CH_2), 21.67(CH_3), 11.75(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1732.65. **14b**: (45%), $[\alpha]_D^{20}$ –215.69° (c 1.0, $CHCl_3$): [Found: C, 77.73; H, 6.39; N, 4.65. $C_{19}H_{19}O_2N$ requires C, 77.81; H, 6.48; N, 4.78%]: δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, $-CH_2-C\underline{H}_3$), 1.4 (2H, m, $-CH-C\underline{H}_2-CH_3$), 2.3(3H, s, $-CH_3$), 3.8 (1H, t, *J* 7.0–8.0, $-CH-C\underline{H}_2-O$), 4.2 (1H, q, *J* 8.0, $-CH_2-C\underline{H}-CH_2-$), 4.6 (1H, t, *J* 7.0–8.0, $-CH-C\underline{H}_2-O$), 7.1–7.8 (8H, m, Ar–H) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.10(C), {147.76, 138.90, 136.39, 133.61, 131.65, 130.44, 129.94, 126.09, 124.74, 123.86}(Ar–C), 101.23(C), 76.54(CH), 57.94(CH_2), 27.97(CH_2), 21.67(CH_3), 11.75(CH_3); ν_{max}/cm^{-1}(Nujol mull)1732, 1462, 1377, 722 .

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6 Single crystals of compound **10b** were grown by slow evaporation of the solution in ethyl acetate / petroleum ether solvent mixture. Transparent crystal of approximate size 0.237 x 0.461 x 0.556 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. 2θ range = 4.04 to 57.7 °, completeness to 2θ of 57.7 ° is 90.7%. SADABS correction applied. $2 \times (C_{18}H_{17}NO_2)$, *M* = 558.65. Crystals belong to monoclinic, space group P 2_1, *a* = 8.338 (2), *b* = 20121 (4), *c* = 9.416 (2) Å, β = 109.440 (3) °, *V* = 1489.7(5) $Å^3$, *Z* = 2, D_c = 1.245 mg m^{-3}, μ (Mo–K_α) = 0.081 mm^{-1}, *T* = 293(2) K, 8976 reflections measured, 5894 unique [I>2σ(I)], R value 0.0448, wR_2 = 0.1163 (all data R = 0.0528, wR_2 = 0.1208). All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2.

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