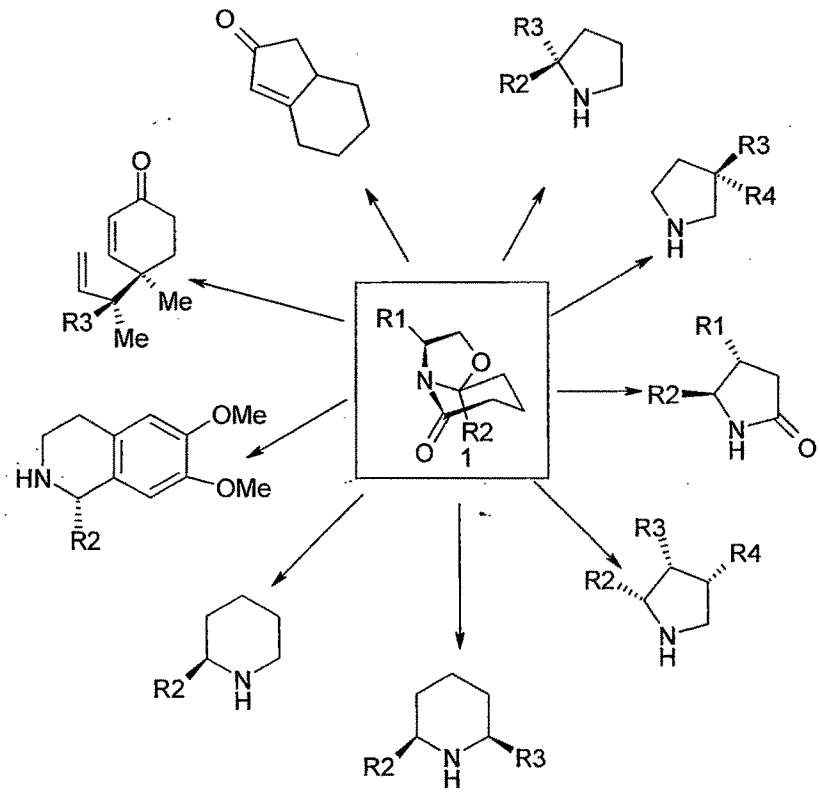
CHAPTER - II

SYNTHESIS OF OXAZOLO [2,3-A] ISOINDOL-5-ONES

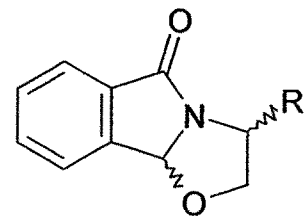
2.1 INTRODUCTION

As reviewed recently by Meyers *et al.*[1], the bicyclic N,O-acetal product, commonly known as bicyclic lactam, has proven to be an exceptional chiral building block for the asymmetric construction of a wide variety of natural and unnatural carbocyclic and heterocyclic compounds containing one or more stereogenic centers **(Scheme II.1).**[2]



Scheme II.1

However structurally related aromatic tricyclic lactams of general structure 2 are little explored in literature, a fact that is reflected in the few reports of synthetic applications of nitrogen heterocycles[3-11]. As a consequence of the greater potential of these tricyclic lactams, notable advances concerning the synthesis and reactivity of these species continued to be made.



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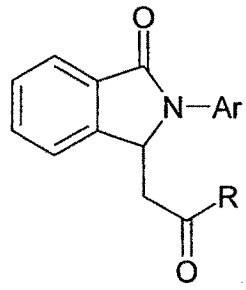
2.1.1 Importance Of Isoindolinone Ring System

The chemistry and reactivity of the isoindolinone ring system is currently an area of interest for many research groups due to its biological activity. It has been recognized that 3-substituted isoindolinones of general structure 3[12] possess anxiolytic activity and are of interest as sedatives, hypnotics and muscle relaxants[13] including the anxiolytic pazinaclone (4)[14] and the anxiolytic/ anticonvulsant zopiclone (5).[15] Other bioactive 3-substituted isoindolinone derivatives include the 5-HT antagonist 6[16] and the non-nucleosidic HIV-reverse transcriptase inhibitor 7 **(Figure II.1).**[17]



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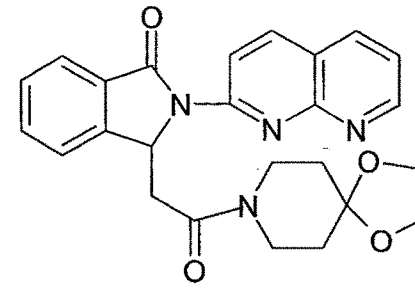

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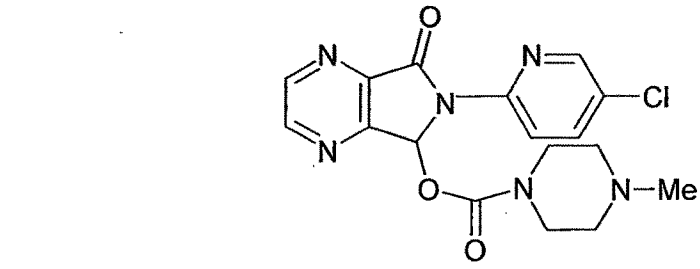

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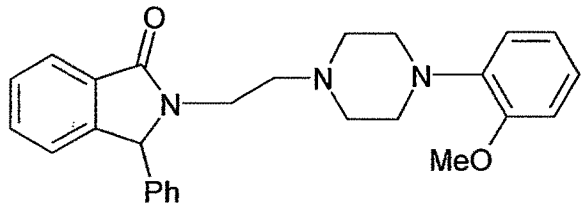

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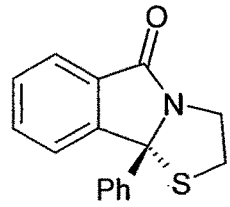

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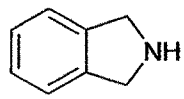
Figure II.1

Isoindoline (2, 3-dihydro-1H-isoindole) and isoidolin-1-one (phtalimidine) 9, moieties are an integral part of some naturally occurring products. For example, chilenine 10, lennoxamine (11) and other isoindol benzazepines, nuevamine (12), an isoindolo isoquinoline and magallanesine (13) have been isolated by Shamma and co-workers[18] from various Berberis species. Similarly, staursporine (14), an alkaloid containing the isoindolinone moiety, isolated from a saccharothrise species has antimicrobial, hypotensive and cytotoxic activities[19]. Also cytochalasin (15) containing a perhydro isoindolone ring fused to 11 to 14 membered macrocyclic rings have been isolated from varieties of molds and organisms[20]. Naturally occurring and synthetic isoindolin-1-ones have a range of biological activites[21], including antihypertensive[22], antipsychotic[23], anti-inflammatory[24], anesthetic[25], antiulcer[26], vasodilatory[27], antiviral[28], and antiluekemic[29] properties. A number of isoindolin-1-ones have been found to be potent herbicides[29]. Isoindolin-1-ones have also been extensively used for the synthesis of various drugs[30] and naturally occurring compounds **(Figure II.2).**[31]



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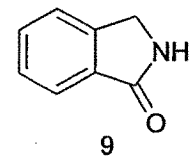
Isoindoline



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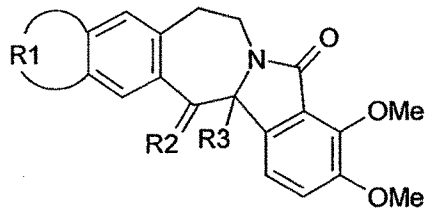
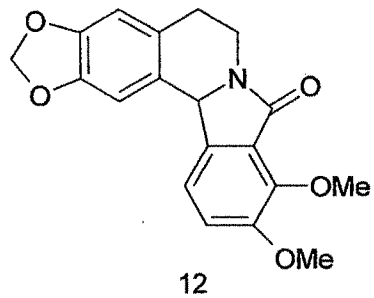
Isoindolin-1-one



Chilenine 10, R1= -O-CH_2-O- , R_2=O , R_3=OH

Lennoxamine 11 R_1=H , R_2=H,H R_3=H



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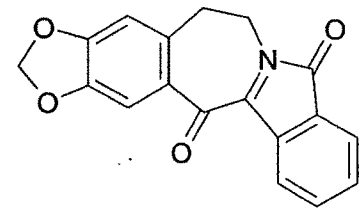
Nuevamine



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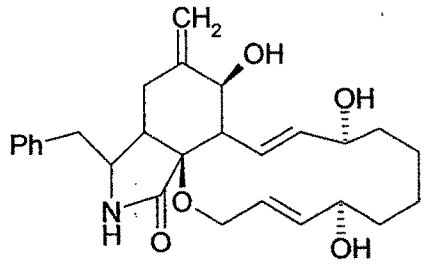
Magallanesine



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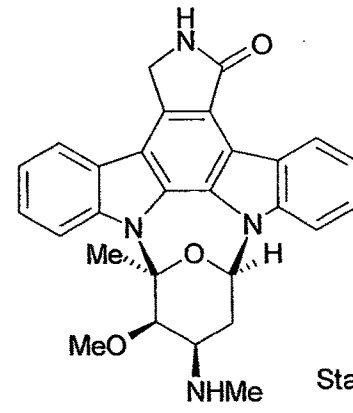
Cytochalasin B



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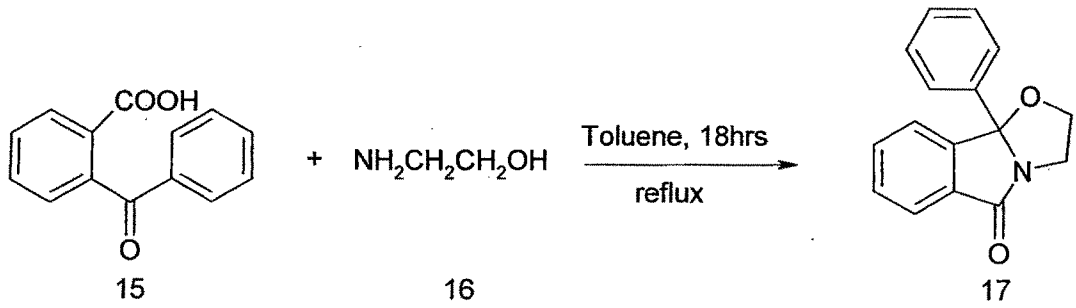
Staursporine

Figure II.2

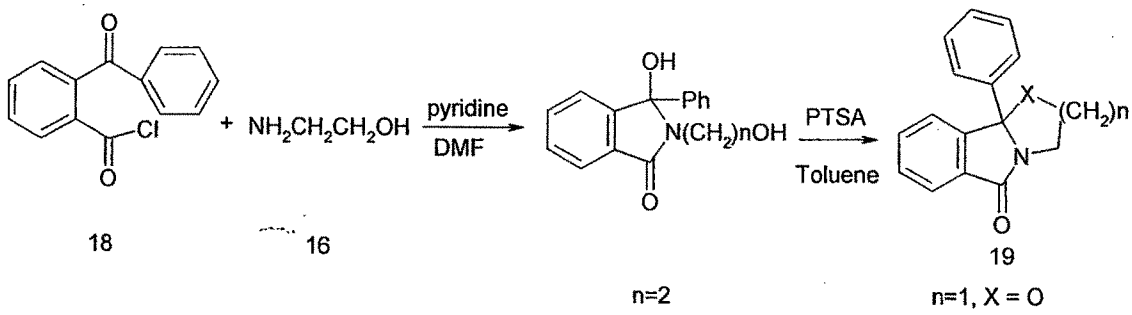
2.1.2 Methods for synthesis of oxazolo [2, 3-a] isoindol-5-ones

The synthesis of 2,3-dihydro-9b-phenyl oxazolo[2,3-a]isoindol-5(9bH)ones (17) were first reported by the reaction of oxobenzoic acid 15 and alkanol amine 16 in an inert solvent at 30-100 °C for 1-24 hours by Braun *et al.* **(Scheme II.2).**[32]



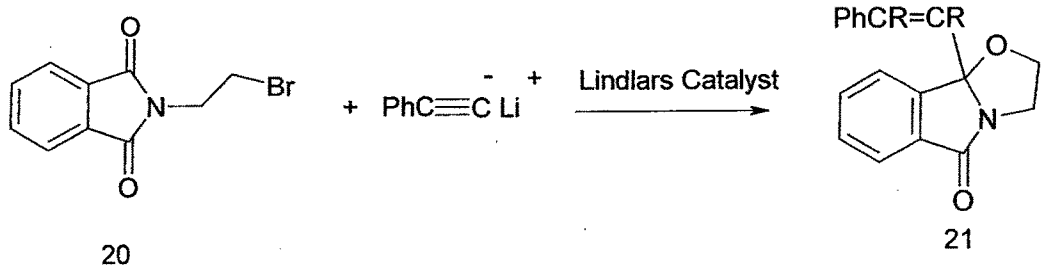
Scheme II.2

In another method of synthesis the cyclic compound 19 was synthesized by reaction of ethanol amine (16), o-benzoyl benzoyl chloride (18) and pyridine in DMF at 60 °C and treatment of the resulting compound with catalytic amount of PTSA in toluene **(Scheme II.3).**[33]



Scheme II.3

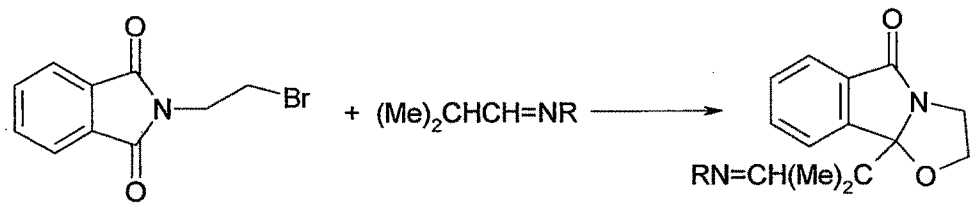
The reaction of PhC:CLi with *N*-(2-bromoethyl)phthalimide (20), followed by partial reduction over Lindlar's catalyst, gave 2,3-dihydro-9b-phenylethenyloxazolo[2,3-*a*]isoindol-5(9b*H*)-one (21) **(Scheme II.4).**[34]



20 21

Scheme II.4

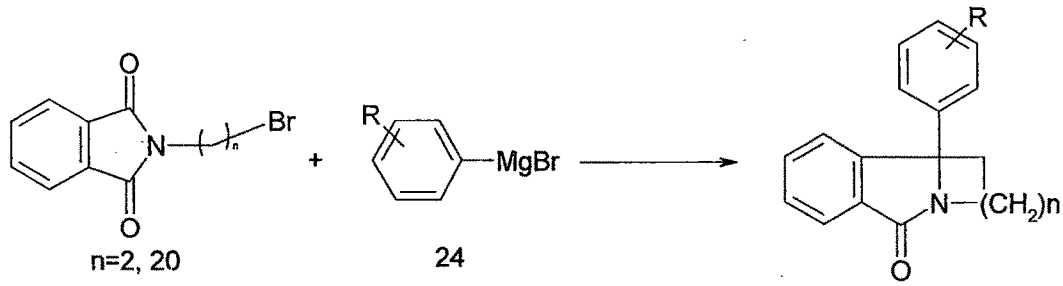
Oxazoloisoindolinones 22 were prepared by the condensation of *N*-(2-bromoethyl) phthalimide (20) with azaallylic carbanions of $Me_2CHCH{:}NR$ **(Scheme II.5).**[35]



20 22

Scheme II.5

The reaction of *N*-(bromoalkyl)phthalimides 20, 23 with RC_6H_4MgBr 24 (R = H, 3-Cl, 4-F, 3-, 4-Me, 4-Ph) yielded oxazoloisoindoles 19 and oxazinoisoindoles 25. Triarylated oxazoloisoindoles were also obtained in several cases depending on the reaction conditions **(Scheme II.6).**[36]



n=2, 20
n=3, 23

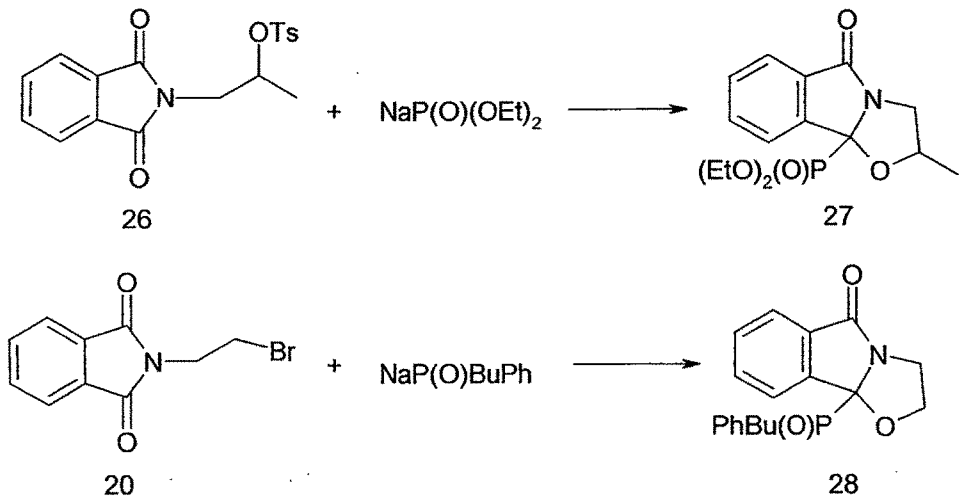
24

n=2, 19
n=3, 25

(R = H, 3-Cl, 4-F, 3-, 4-Me, 4-Ph)

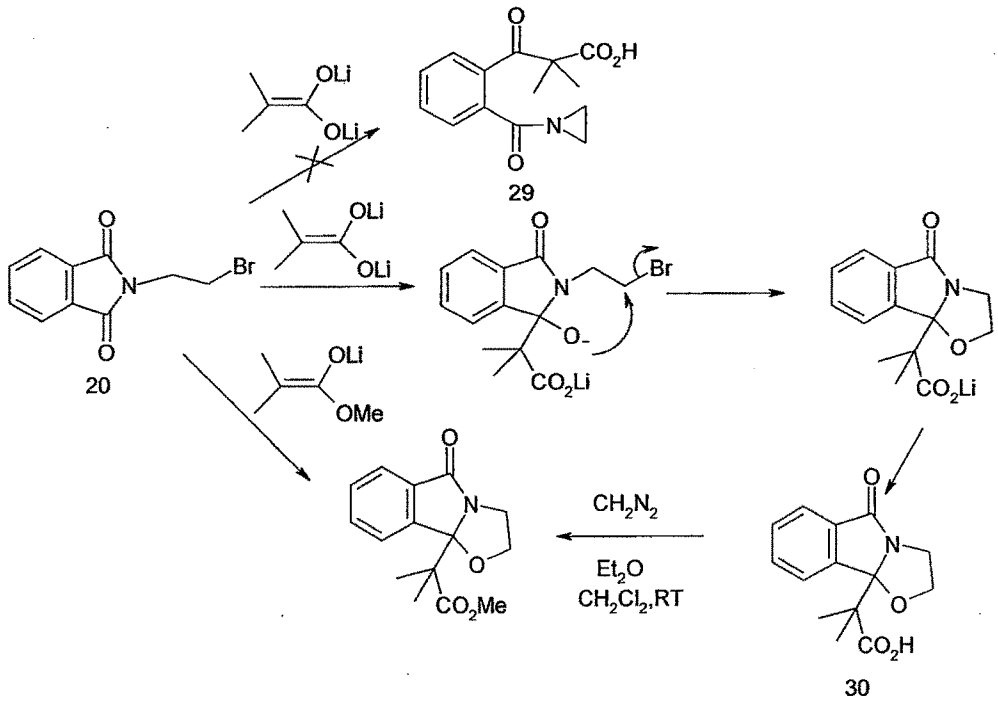
Scheme II.6

Di-Et sodiophosphonate and the tosylate of (2-hydroxypropyl)phthalimide (26) as starting materials, leads to (oxazolo[2,3-a]isoindolyl)phosphonates (27). Similarly N-(2-bromoethyl)phthalimide 20 reacted with butyl(benzene)sodiophosphinate to give (oxazolo[2,3-a]isoindolyl)(phenyl)phosphinates (28) **(Scheme II.7).**[37]



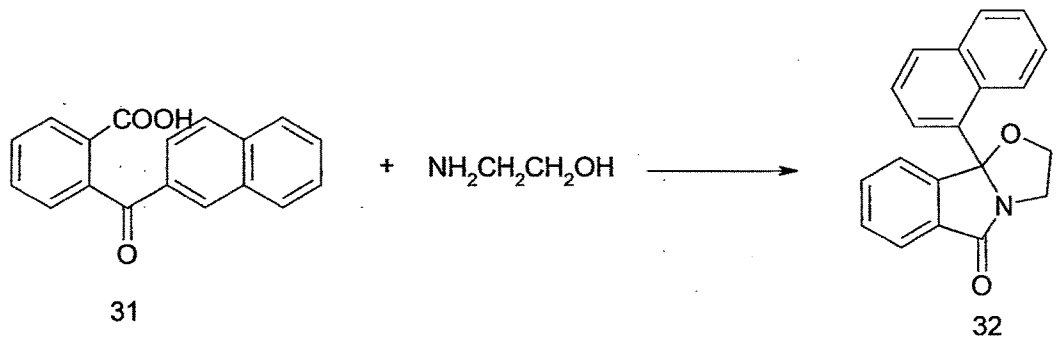
Scheme II.7

When the condensation of N-(2-bromoethyl)phthalimide (20) with the dianion of isobutyric acid was carried out, the reaction surprisingly leads to the formation of dimethyloxazolo[2,3-a]isoindole-9b(5H)-acetic acid (30) instead of the expected 3{2-[(1-aziridinyl)carbonyl]phenyl}-2,2-dimethyl-3-oxopropanoic acid (29) **(Scheme II.8).**[38]



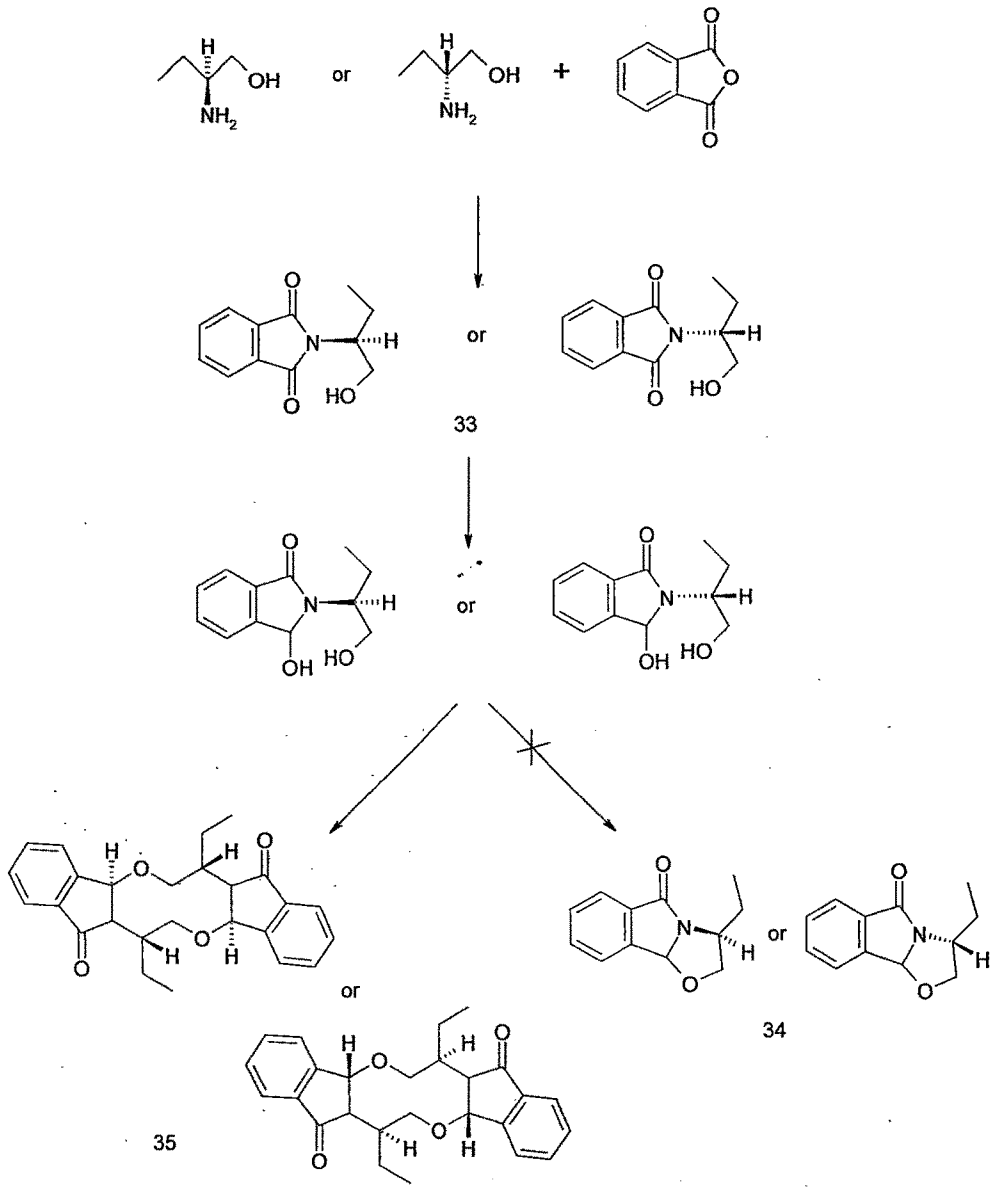
Scheme II.8

Refluxing 2-(1-naphthoyl)benzoic acid (31) with ethanolamine resulted in the formation of 9b-(1-naphthyl)-2,3-dihydrooxazolo[2,3-*a*]isoindole-5(9b*H*)-one (32) **(Scheme II.9).**[39]



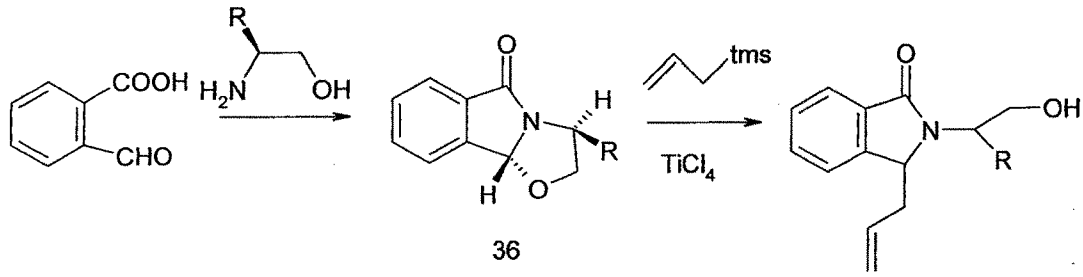
Scheme II.9

An earlier attempt by Bijukumar *et al* [40] to synthesise oxazolo[2,3-a]isoindol-5(9bH)one (34) using (*R*) or (*S*)-2-amino-1-butanol via Meyers methodology involving reduction of the imide 33 and cyclisation using trifluoroacetic acid resulted in the foremation of a novel ten membered ring system 35 **(Scheme II.10).**



Scheme II.10

Allin and coworkers[41] have recently reported a new synthesis of non-racemic isoindolinone targets through application of oxazolo [2, 3-a] isoindolinones (36) as N-acyl imminium precursors **(Scheme II.11).**



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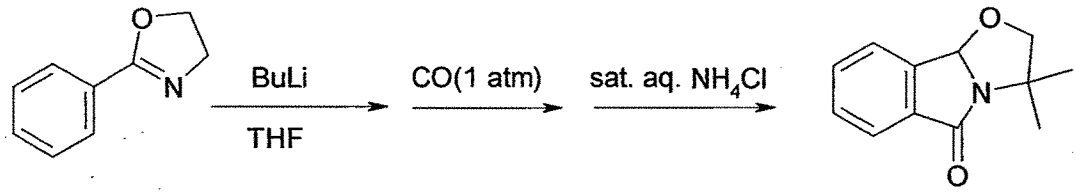
Scheme II.11

The carbonylation of a phenyllithium containing an oxazoline group at the ortho position, followed by quenching with water, afforded a tricyclic compd., 3,3-dimethyl-2,3-dihydrooxazolo[2,3-a]isoindol-5(9bH)one(37) **(Scheme II.12).**[42]



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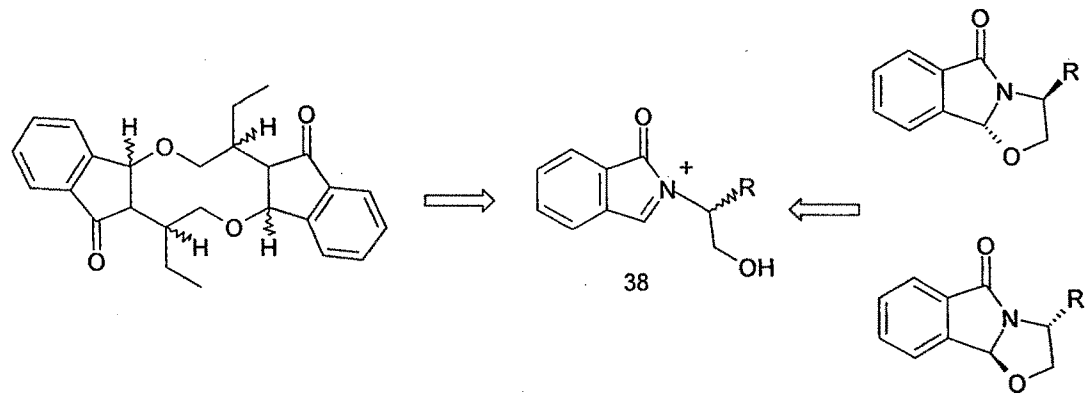
Scheme II.12

Substituted oxazolo, oxazino-, and oxazepinoisoindolinones are obtained in three steps according to an acidic α-oxoamidoalkylation reaction from ready available phthalic anhydride by successive imidation, sodium borohydride reduction, and intramolecular cationic cyclization involving N-acyliminium species (38) **(Scheme II.13).**[43]



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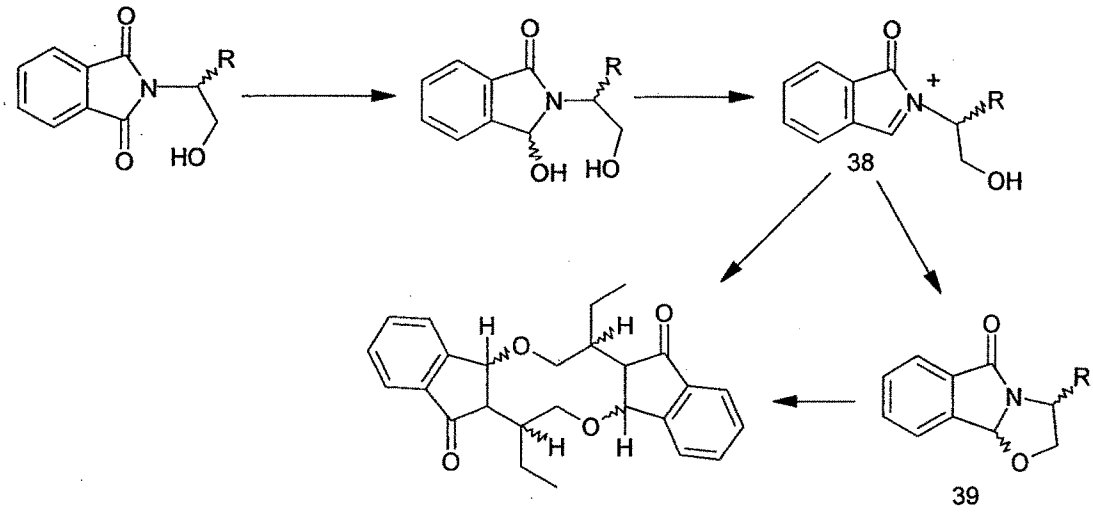
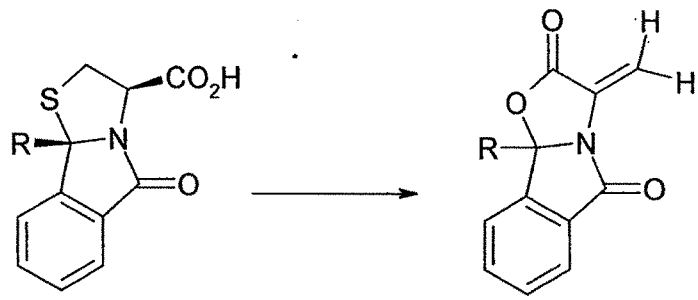
Scheme II.13

Oxazolo[2,3-a]isoindol-5(9bH)one(39) have been prepared from suitable β-amino-alcohols and phthalic anhydride in a three-step sequence in moderate to good yields . High levels of the chemoselectivity is observed during the intermolecular or intramolecular cyclization **(Scheme II.14).**[44]



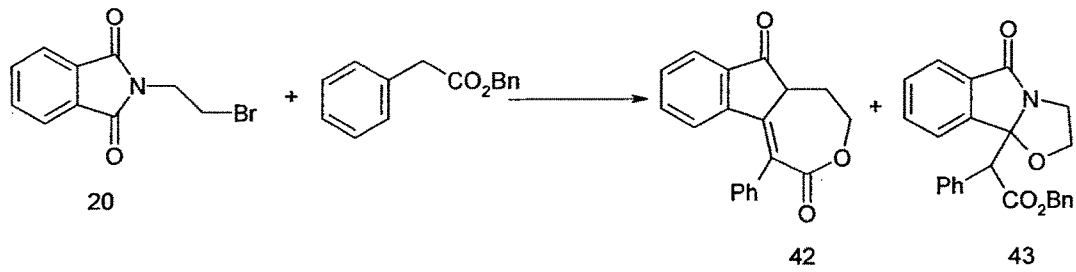
Scheme II.14

3-Methylene-2,5-dioxo-3H,9bH-oxazolo[2,3-a]isoindoles 41 were prepared by the thermolysis of (3R,9bS)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-a]isoindole-3-carboxylic acids 40 in acetic anhydride **(Scheme II.15).**[45]



Scheme II.15

The cyclocondensation of N-(2-bromoethyl)phthalimide 20 with the enolate of benzyl Phenyl acetate afforded two possible products 42 and 43 depending on the experimental conditions used **(Scheme II.16)**.[46]

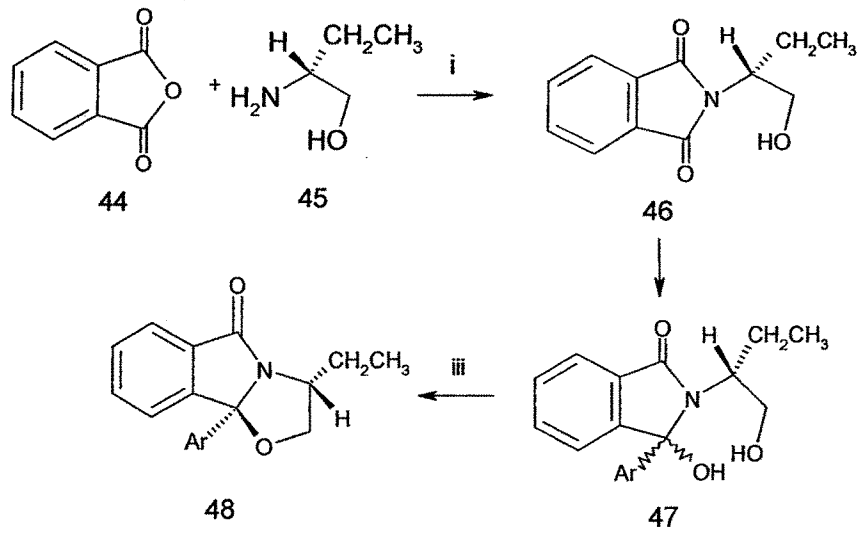


Scheme II.16

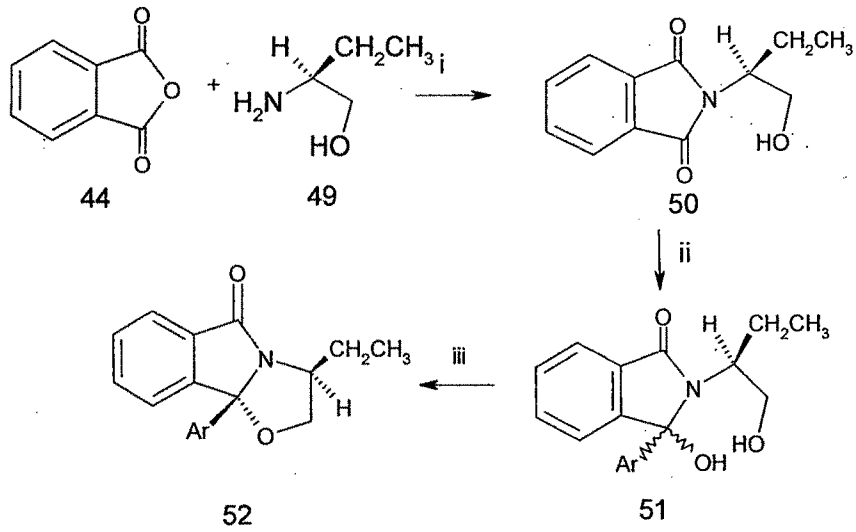
Owing to the importance of oxazolo[2,3-a] isoindolinones in terms of its activity and its use as an intermediate in the synthesis of 3-substituted isoindole derivatives and a lack of methods for its stereo selective synthesis, development of methodologies for synthesis of these molecules is an attractive target.

2.2 RESULTS AND DISCUSSION

(*R*) or (*S*) - 2-Amino-1-butanol (45) or (49) were reacted with phthalic anhydride (44) to furnish (*R*) or (*S*)-2-(1-hydroxy) phthalimides 46 or 50. The phenyl group was introduced by addition of phenyl magnesium bromide (**a**) to (*R*) or (*S*)-2-(1-hydroxy) phthalimides (46) or (50). The resulting dihydroxy compounds 47 or 51 were not isolated, but were directly subjected to acid catalysed cyclisation to furnish the 9b-phenyl substituted oxazolo[2,3a] isoindolinones (48a) or (52a) in 40-50% yields. In a similar fashion the addition of p-fluoro, p-chloro, p-methoxy and p-methyl substituted phenyl magnesium bromides furnished the corresponding 9b-substituted oxazolo [2, 3-a] isoindolinones 48b-48e or 52b-52e **(Scheme II.17)**.[47]



Ar = -C_6H_5 (48a), p-FC_6H_4 (48b), p-ClC_6H_4MgBr (48c), p-$OCH_3C_6H_4$ (48d) p-CH3C6H4MgBr (48e)



Ar = -C_6H_5 (52a), p- FC_6H_4 (52b), p-ClC_6H_4MgBr (52c), p-$OCH_3C_6H_4$ (52d), p-$CH_3C_6H_4MgBr$ (52e)

Scheme II.17 Reagents and conditions(i) Neat, 140°C (ii) **a**- C_6H_5MgBr, **b**- p-FC_6H_4MgBr, **c**-p-ClC_6H_4MgBr, **d**- p-$OCH_3C_6H_4MgBr$, **e**-p-$CH_3C_6H_4MgBr$, 3 hours, N_2 atmosphere., R.T. (iii) CF_3COOH, CH_2Cl_2, 2-3 hours

The ^{1}H NMR of (9b*S*)-9-Phenyl-(3*R*)-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one(48a) (**Figure II.3**) showed a triplet at ∂1.0 is assigned to methyl group. A multiplet at ∂1.4 is assigned to the methylene group next to the methyl group. In a high resolution spectra it was observed that this methylene group splitted into two multiplets indicating the non equivalence of the two protons of the methylene group. The triplet corresponding to ∂ 3.8 was observed for one of the protons of the methylene group (-CH-CH_ACH_B) while the other proton shows another triplet at ∂ 4.6. A quintet at ∂ 4.2 can be attributed to the tertiary carbon atom –CH. The nine aromatic protons were observed as a multiplet in the region ∂ 7.1-7.8. The proton decoupled ^{13}C spectra (**Figure II.4**) showed a singlet at ∂ 11.86 for the CH_3 group, a singlet at ∂ 28.11 for $-CH_2-CH_3$ group. Another singlet at ∂ 58.13 was observed for $-CH-CH_2-O$ group. A singlet at ∂ 76.74 was observed for the tertiary carbon atom –CH while the typical singlet for the quarternary carbon atom was observed at ∂ 101.36. Nine singlets for the nine aromatic carbon atoms were shown in the region ∂ 124.06-147.7. A singlet at a high field ∂ 175.27 indicated the presence of a carbonyl carbon. The I.R spectra showed a band at 1716 cm^{-1} indicating ν c-o stretching for the carbonyl group, bands at 1600, 1450 cm^{-1} due to aromatic groups, for cyclic ethers, a band at 758cm^{-1} indicating disubstituted aromatic ring(**Figure II.5**).

(9b*R*)-9-Phenyl–(3*S*)-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (52a) (**Figure II.6**) also showed similar spectral characteristics as that of (48.a). (48a) and (52a) showed equal and opposite specific rotation values indicating that they are enantiomers. The 1H NMR of (9b*S*)-9-(4-methylphenyl)-(3*R*) -3-ethyl-2, 3, 5,9btetrahydro [1, 3] oxazolo[2,3-a] isoindol-5-one (48e) and (9b*R*)-9-(4-methylphenyl)-(3*S*)-3-ethyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (52e) showed the required peaks and an additional singlet at ∂ 2.3 for the aromatic methyl group(**Figure II.7**) . The proton decoupled ^{13} C NMR (**Figure II.8**) also showed an additional peak at ∂ 21.67 for the aromatic methyl group. (9b*S*)- (4-Flouorophenyl)-(3*R*)-3-ethyl -2, 3, 5, 9b tetrahydro [1, 3]

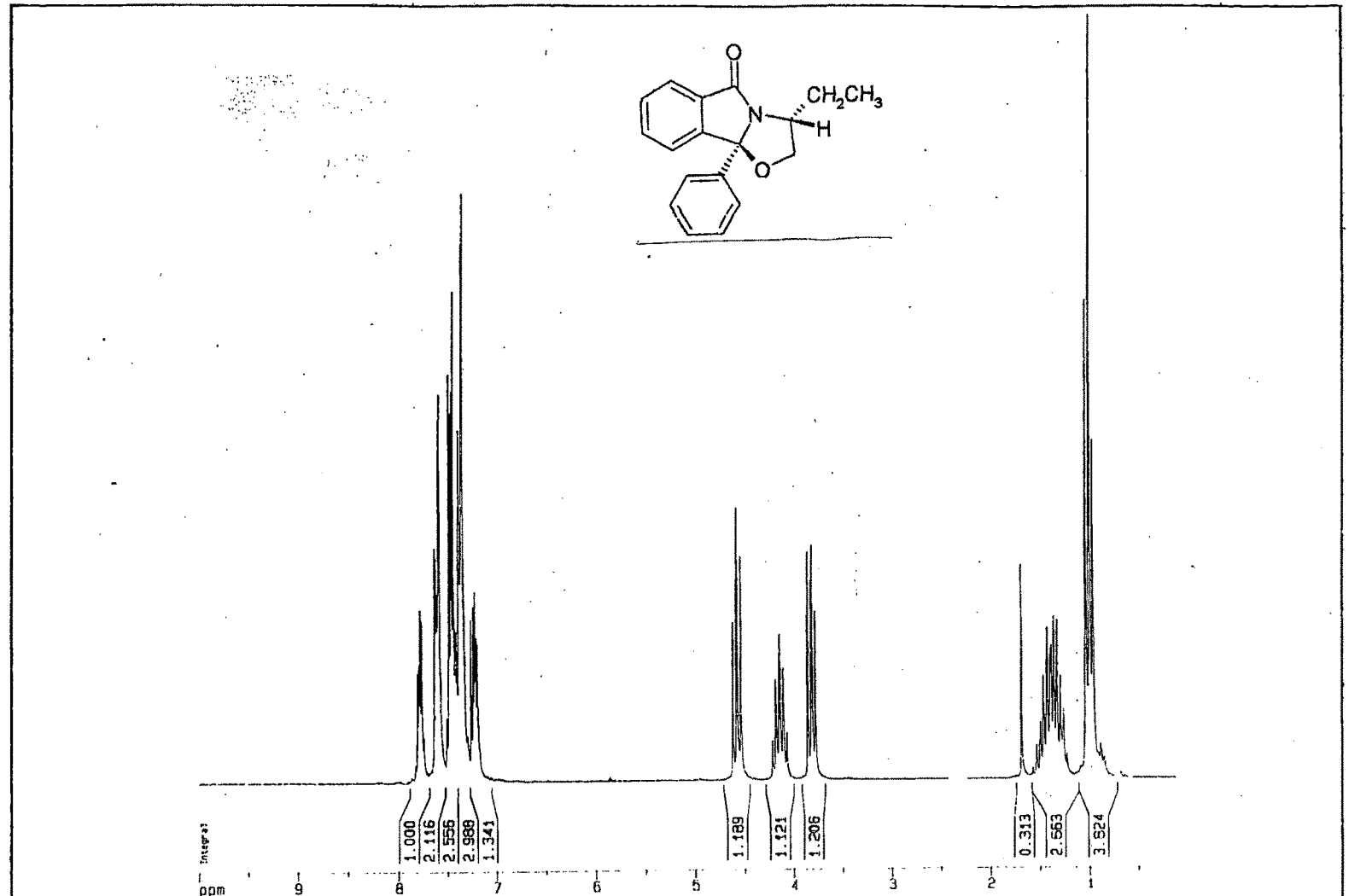
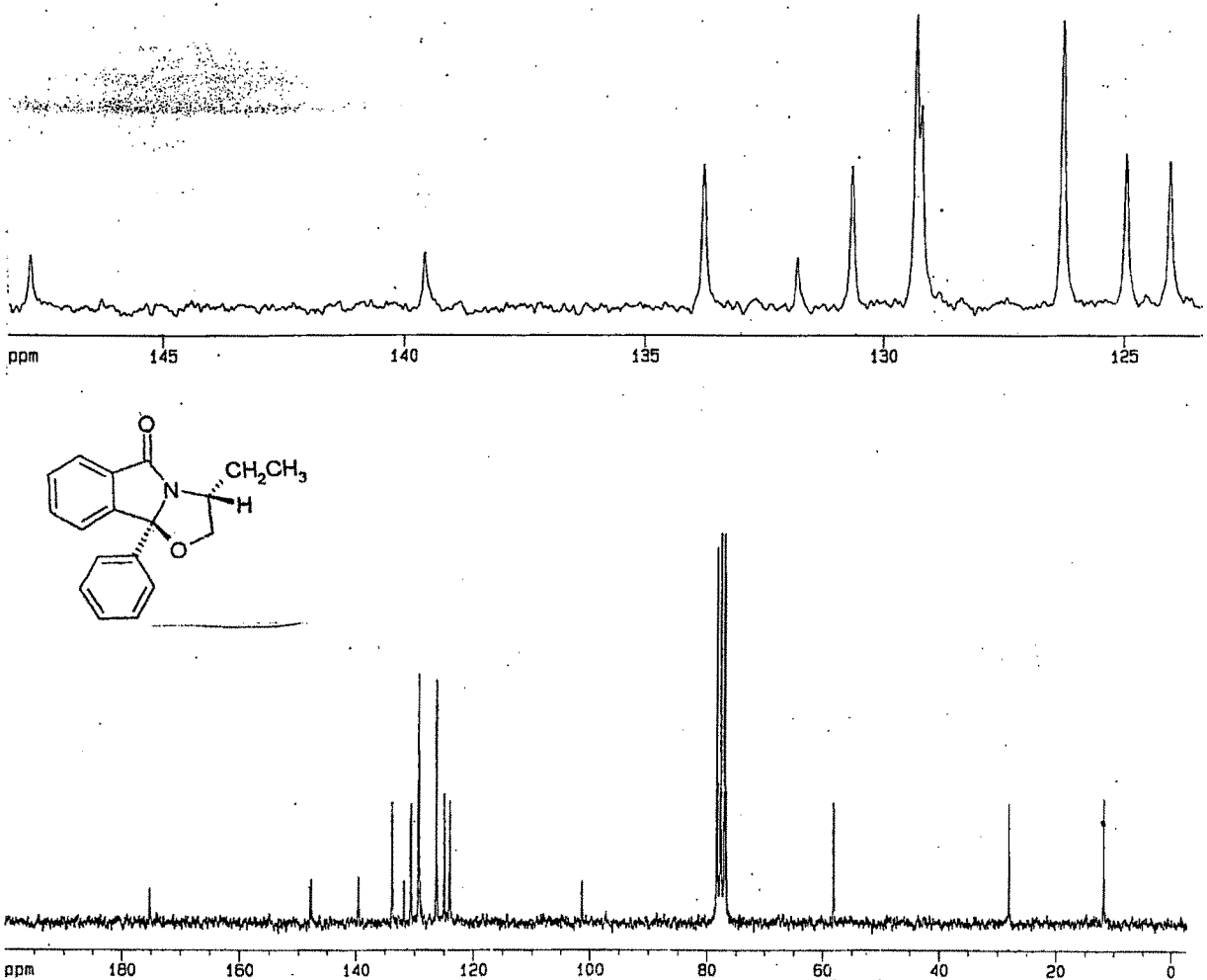


Figure II.3 1H NMR($CDCl_3$) spectrum of (9b*S*)-9-Phenyl-(3*R*)-3-ethyl-2,3,5,9btetrahydro [1,3]oxazolo[2,3-a]isoindol-5-one(48a)



FigureII.4 ^{13}C NMR($CDCl_3$) spectrum of (9b*S*)-9-Phenyl-(3*R*)-3-ethyl-2,3,5,9btetrahydro [1,3]oxazolo[2,3-a]isoindol-5-one(48a)

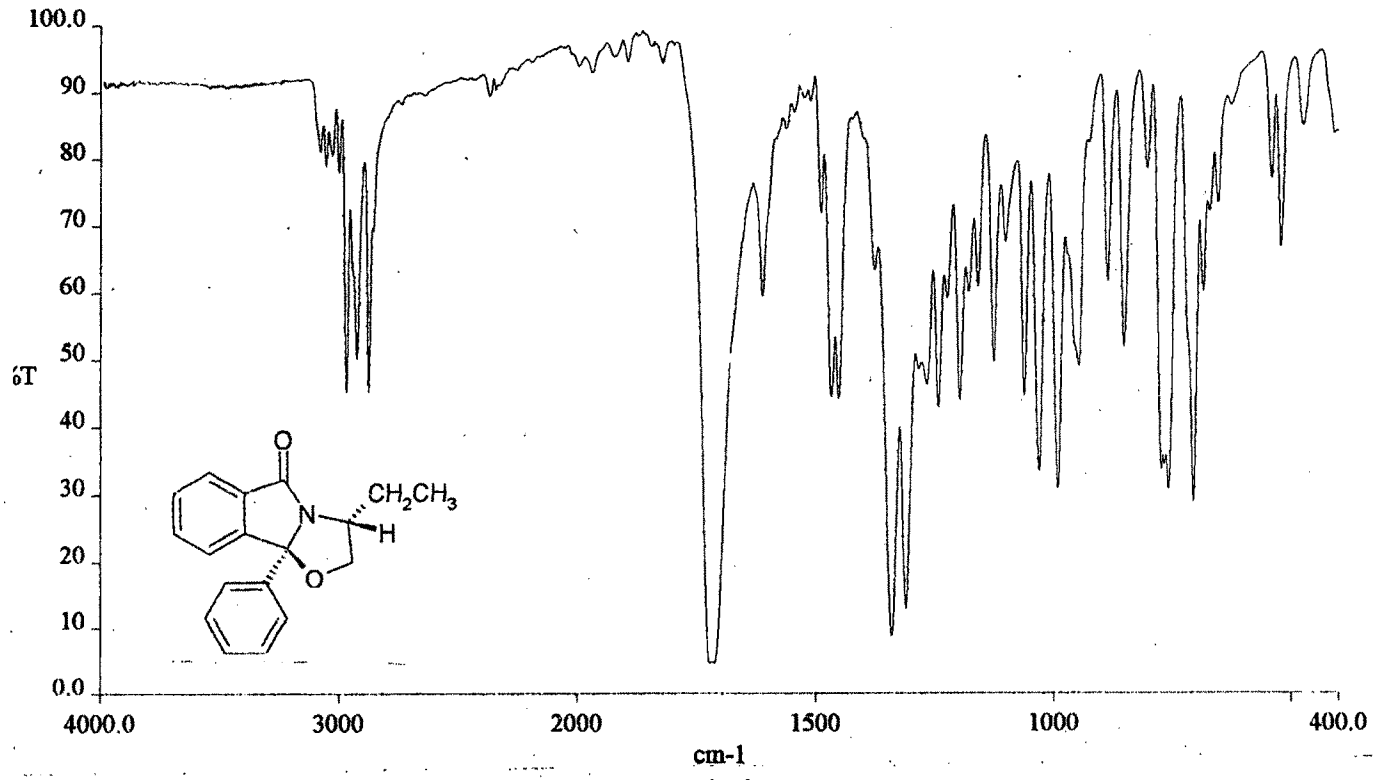


Figure II.5 IR(KBr) spectrum of (9b*S*)-9-Phenyl-(3*R*)-3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one(48a)

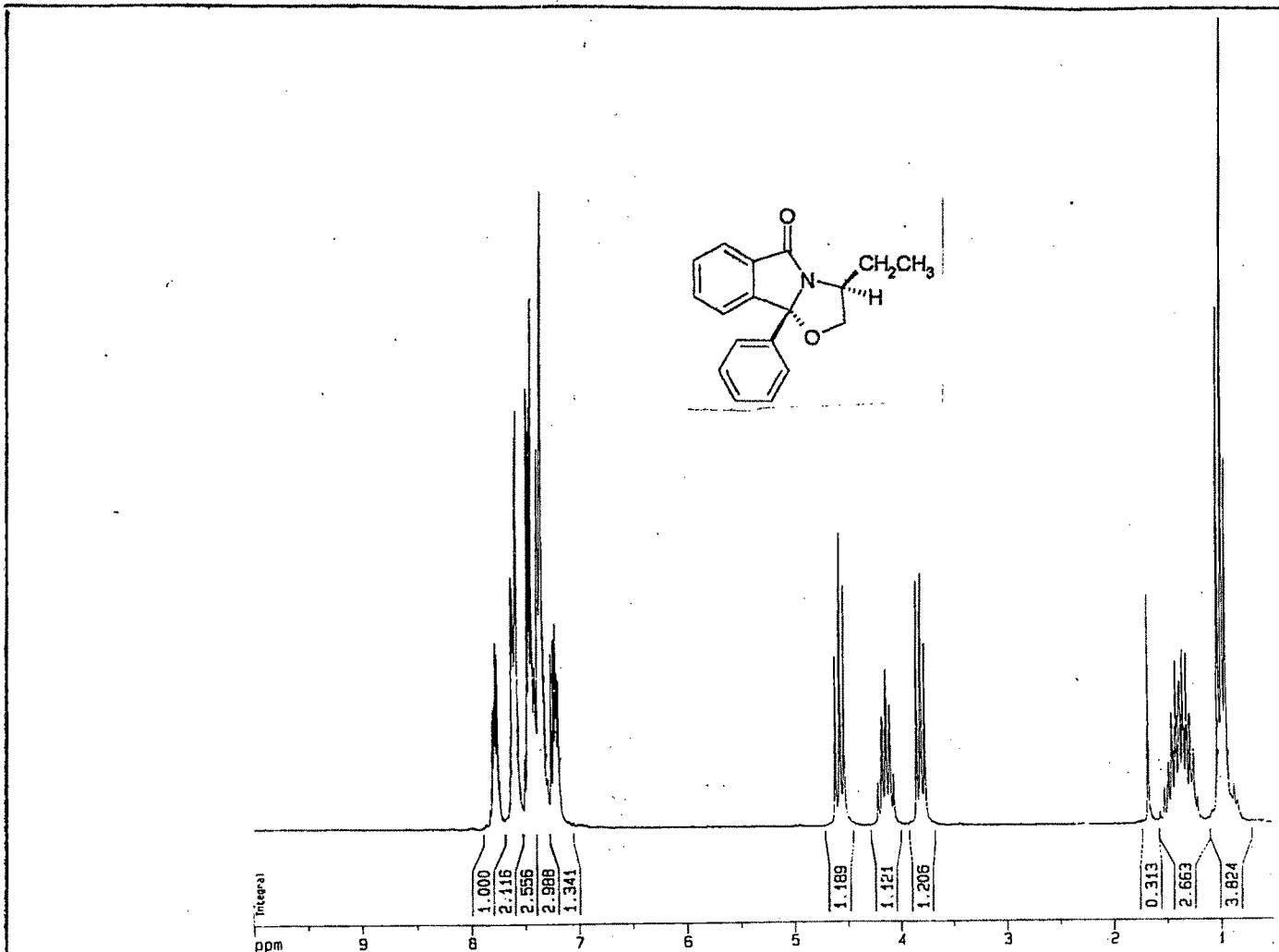


Figure II.6 1H NMR($CDCl_3$) spectrum of (9b*R*)-9-Phenyl–(3*S*)-3-ethyl-2,3,5,9b tetrahydro [1,3]oxazolo[2,3-a]isoindol-5-one(52a)

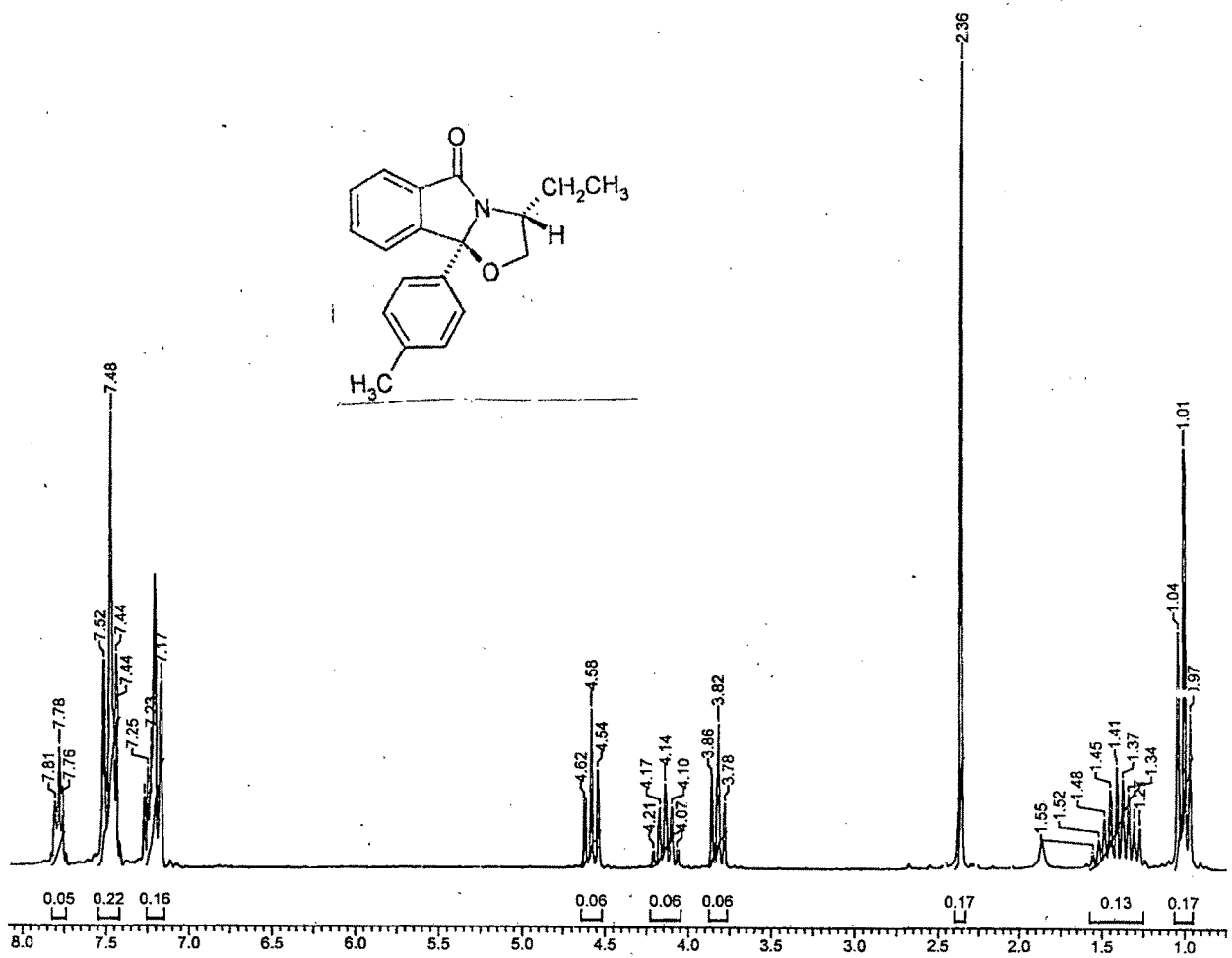


Figure II.7 1H NMR($CDCl_3$) spectrum of (9b*R*)-9-(4-methylphenyl)-(3*S*)-3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (48e)

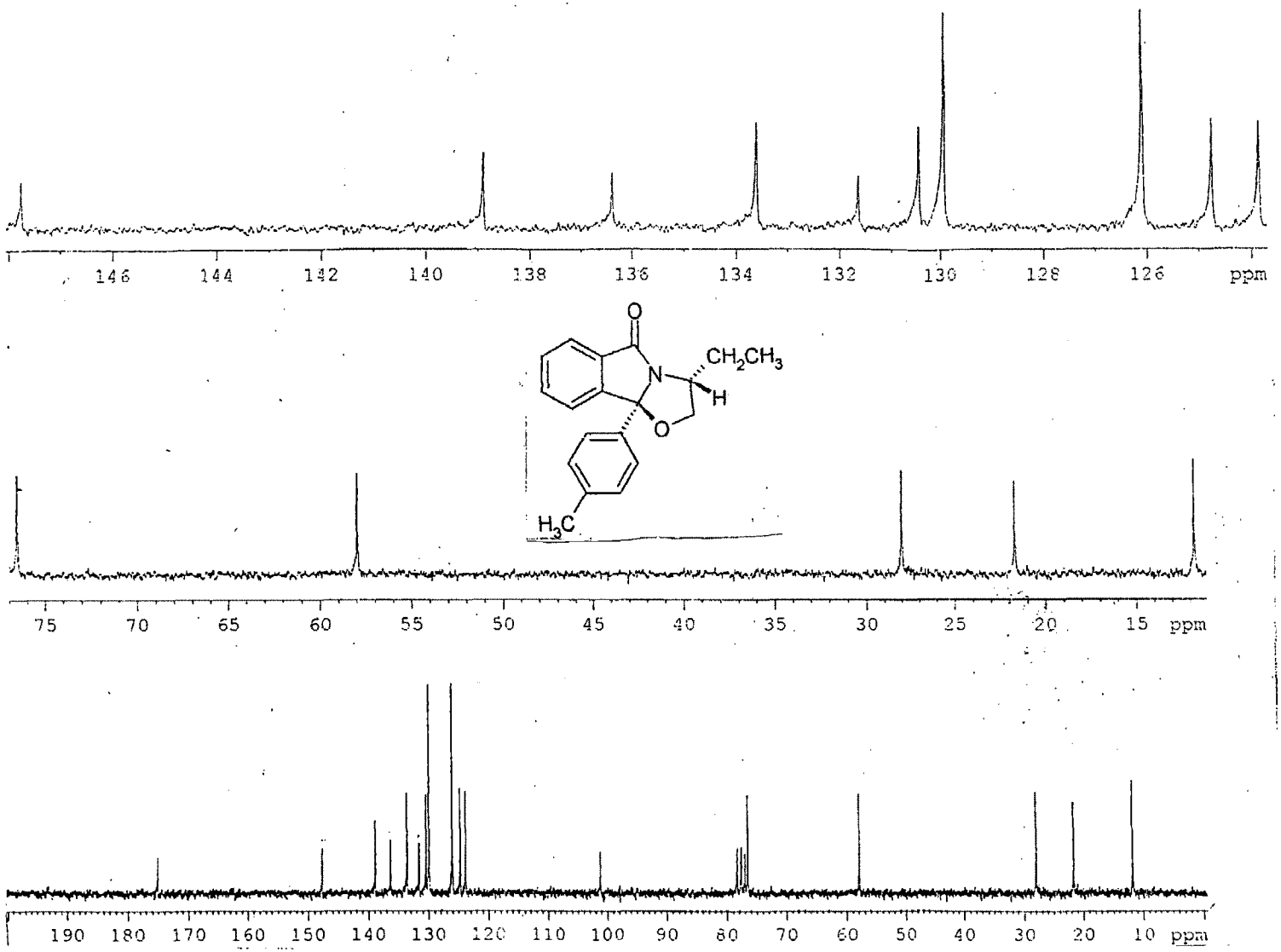
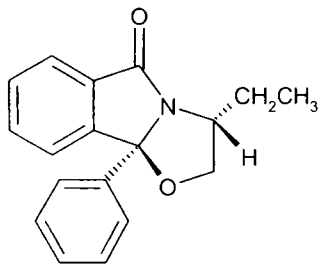


Figure II.8 ^{13}C NMR($CDCl_3$) spectrum of (9b*R*)-9-(4-methylphenyl)-(3*S*)-3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (48e)

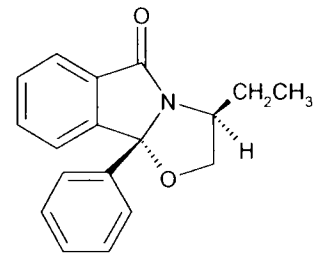
oxazolo[2,3-a]isoindol-5-ones (48b) and (9b*R*)-9-(4-Flouorophenyl)-(3*S*)-3-ethyl - 2,3,5,9b tetrahydro [1,3]oxazolo [2,3-a] isoindol-5-ones (52b) show the required ^{1}H NMR(**Figure II.9**), ^{13} C NMR and I.R spectral characteristics. Similarly (9b*S*)-9-(4-Chlorophenyl)-(3*R*)–3-ethyl-2,3,5,9b tetrahydro [1,3] oxazolo [2,3-a] isoindol-5-one (48e) and (9b*R*)-9-(4-Chlorophenyl) –(3*S*)-3- ethyl 2,3,5,9b tetrahydro [1,3] oxazolo [2,3-a] isoindol-5-one(52e) show the required spectral characteristics.

The compound 52a was subjected to a single crystal X-ray diffraction analysis and its structure was confirmed by SHELX 97 program[48]. The absolute configuration of the phenyl substituted oxazolo [2, 3-a] isoindol-5-one (52a) was found to be (3*S*, 9bR). The ORTEP plot of 52a is shown in the **Figure II.10**. The single crystal x-ray packing is as shown in **Figure II.11.**

From the pmr data and the single crystal data the structures of 48a and 52a are as follows:



48a



52a

The products obtained from (*R*) or (*S*)-2-Amino-1-butanols are enantiomeric and the stereo specificity of the final products occurs during the final cyclisation step. In the second step of the reaction, addition of the Grignard reagent to one of the carbonyl groups of the phthalimide, may lead to the formation of two diastereomers as the aryl group of the Grignard reagent can approach the carbonyl group from either of the two sides. However, one of the diastereomers may be formed in excess, because magnesium probably gets locked in between the oxygen of carbonyl of the imide and oxygen of the

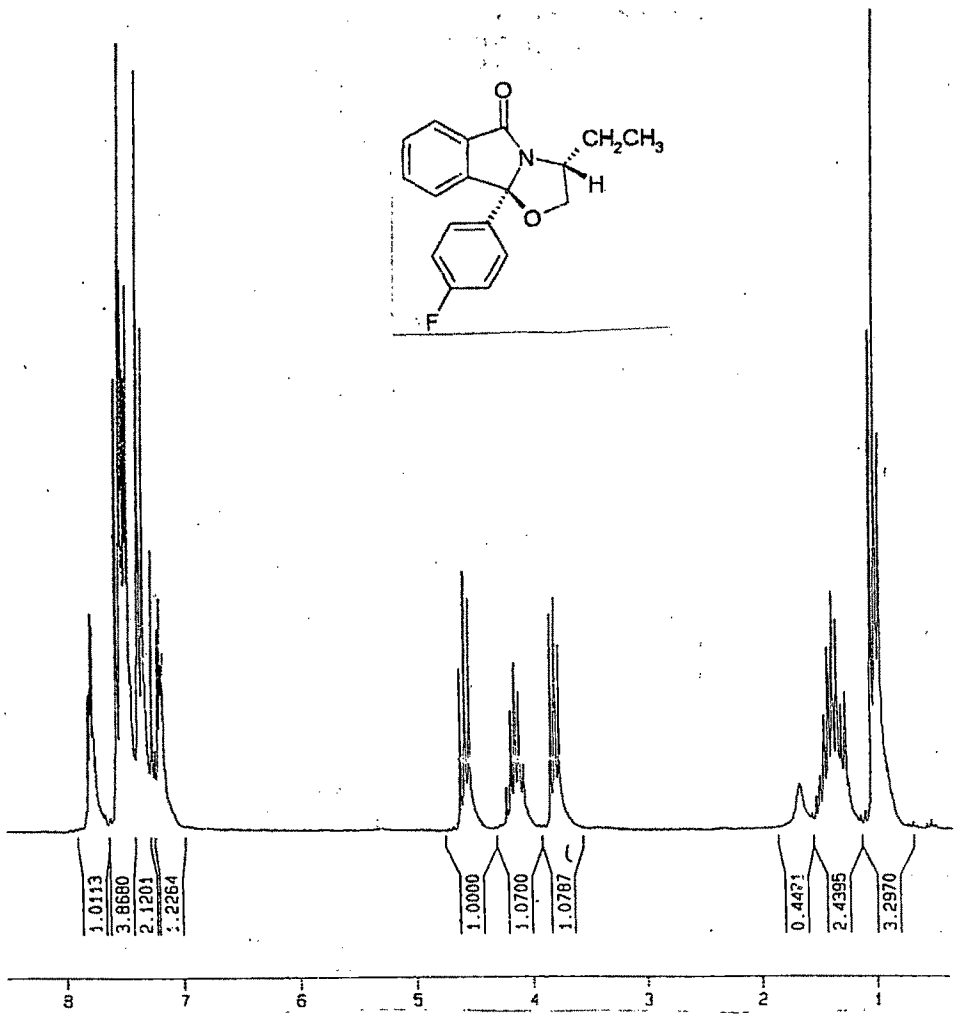


Figure II.9 1H NMR($CDCl_3$) spectrum of (9b*S*)-(4-Flouorophenyl)-(3*R*)-3-ethyl-2,3,5,9b tetrahydro [1,3] oxazolo [2,3-a] isoindol-5-ones (48b)

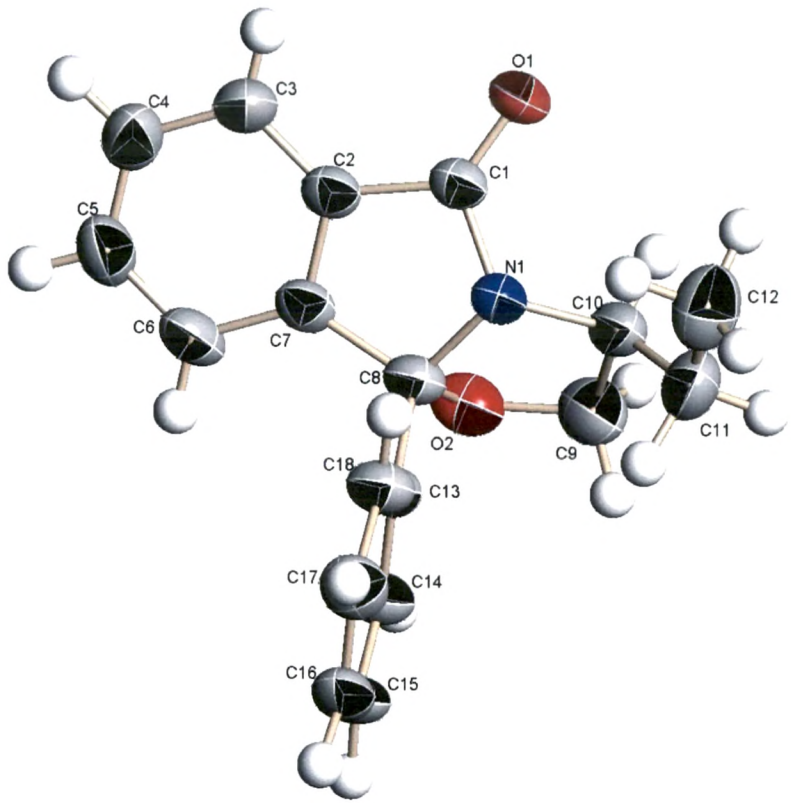


FIG. II.10 ORTEP PLOT OF (9bR)-9-PHENYL-(3S)-3-ETHYL-2,3,5,9b-TETRAHYDRO[1,3]OXAZOLO[2,3-a]ISOINDOL-5-ONE(52a)

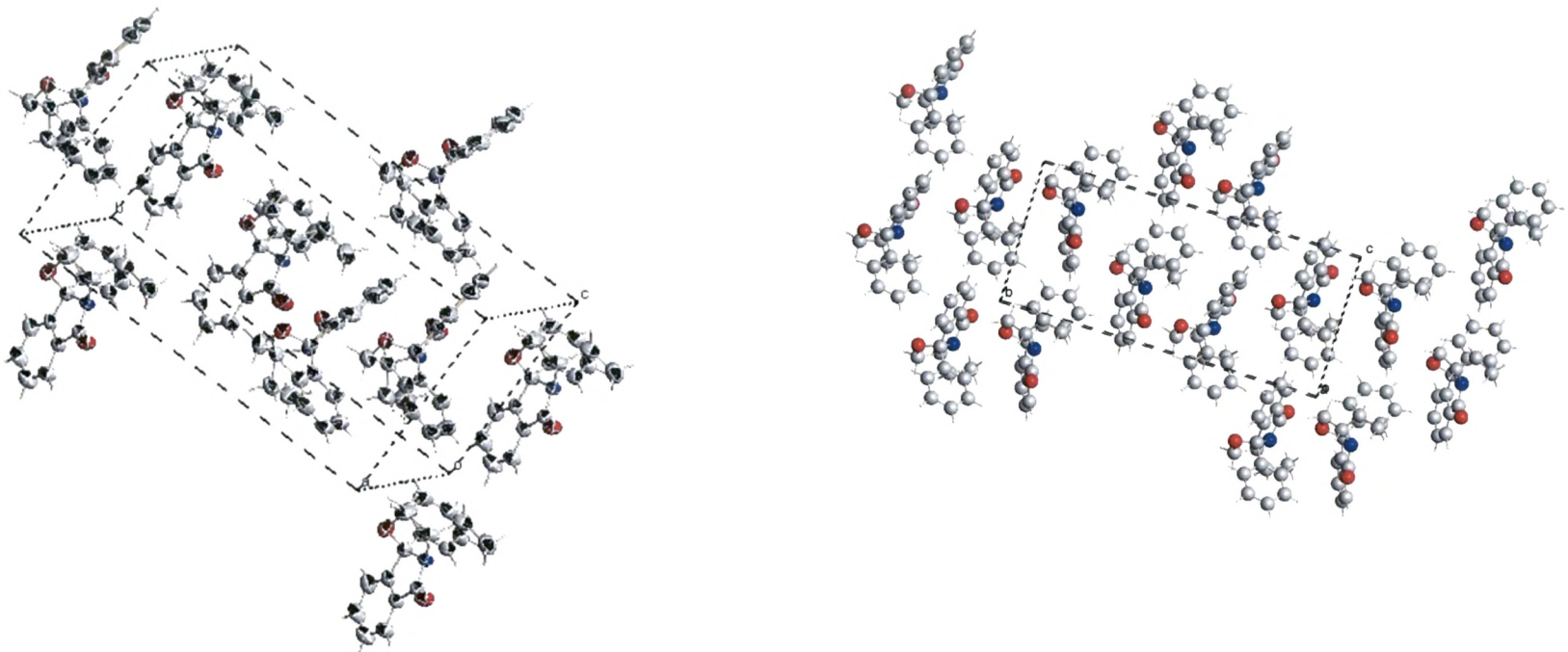
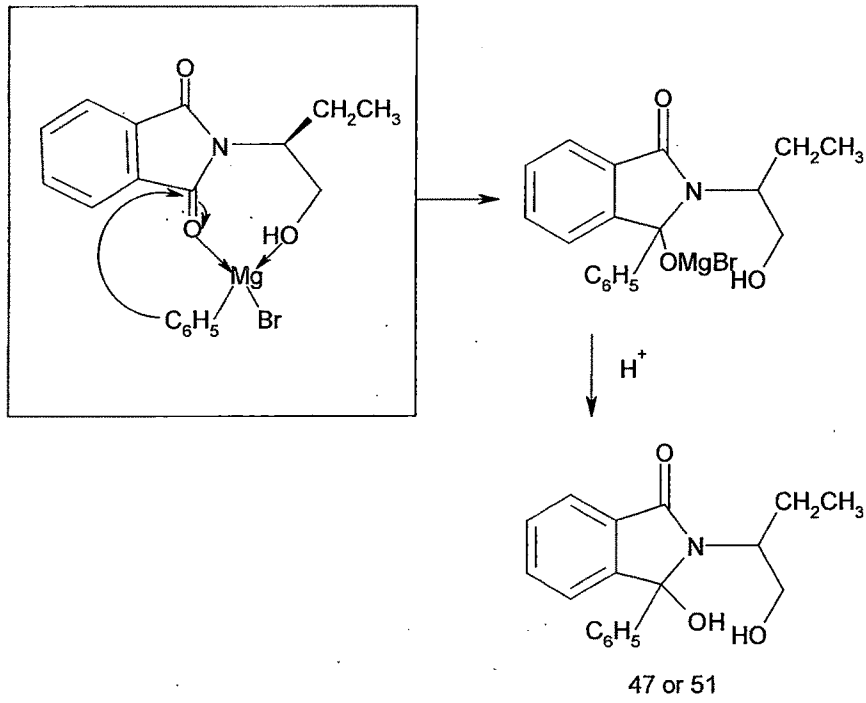


FIG. II.11 UNIT CELL PACKING STRUCTURE OF (9bR)-9-PHENYL-(3S)-3-ETHYL-2,3,5,9b-TETRAHYDRO[1,3]OXAZOLO[2,3-a]ISOINDOL-5-ONE(52a)

hydroxyl group, then addition of the phenyl group takes place from one of the sides of the carbonyl group **(Scheme II.18).**

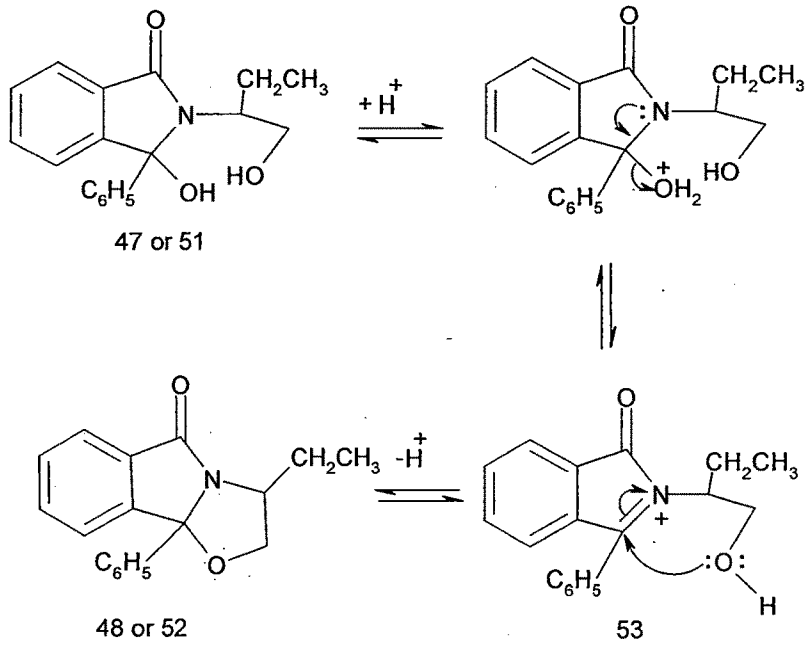


Scheme II.18

In the next step, however when the dihydoxy compound 47 or 51 is treated with trifluoroacetic acid the quarternary hydroxyl group gets protonated and is pushed out by electron pair donation by adjacent nitrogen, leading to the formation of the N-acyl imminium ion species, which being planar at the carbon bearing the phenyl group, the stereospecificity of the grignard addition will be lost at this stage both diastereomers will give rise to the same N-acyl imminium ion 53. In the N-acyl imminium ion, the positive charge will be on the nitrogen, which will be adjacent to the carbonyl group due to which as soon as it is formed, it tries to look for a source of electrons, which in our case comes from the oxygen of the hydroxyl group which leads to the subsequent instant cyclisation. The stereospecificity of the final product comes from the fact that the folded shape of the 5, 5-bicycic system requires both 3-ethyl and 9b-phenyl substituent to be cis on the exo face. Thus depending upon which plane the ethyl group is present in (*R*) or (*S*)-2-(1-hydroxybutyl)phthalimide, the final product will be formed, thus leading to the

enantiomeric cyclic products. This has been confirmed by X-ray crystallographic studies as well as by simple chemical models.

A plausible mechanism for the cyclisation is presented in **Scheme II.19**:



Scheme II.19

Cyclodehydration of o-Benzoylbenzoic acid (54) with (*R*)-2-Amino-1-butanol (45) and (*S*)-2-Amino-1-butanol (49) yielded the cyclic products (9b*S*)- Phenyl –(3*R*)- 3-ethyl 2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one(57) and (9b*R*)- Phenyl –(3*S*) 3-ethyl 2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one(60). The products obtained from the Grignard addition and subsequent acidic cyclisation and those obtained by the cyclodehydration process were found to be the same as they have similar specific rotation values (which indicate same configuration), infrared spectra, splitting pattern of protons in pmr spectra (**Figure II.12**), melting points and mass spectra. **(Scheme II.20)**

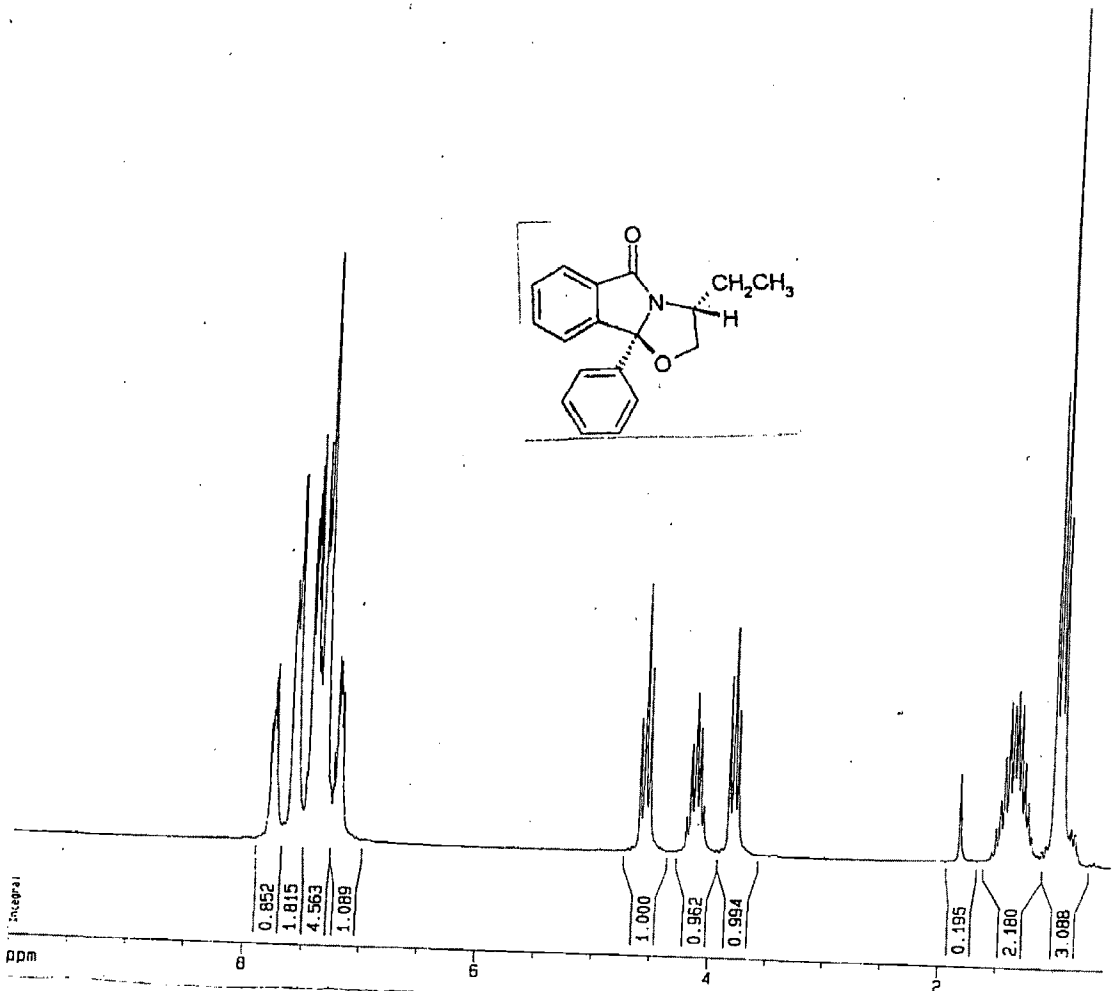
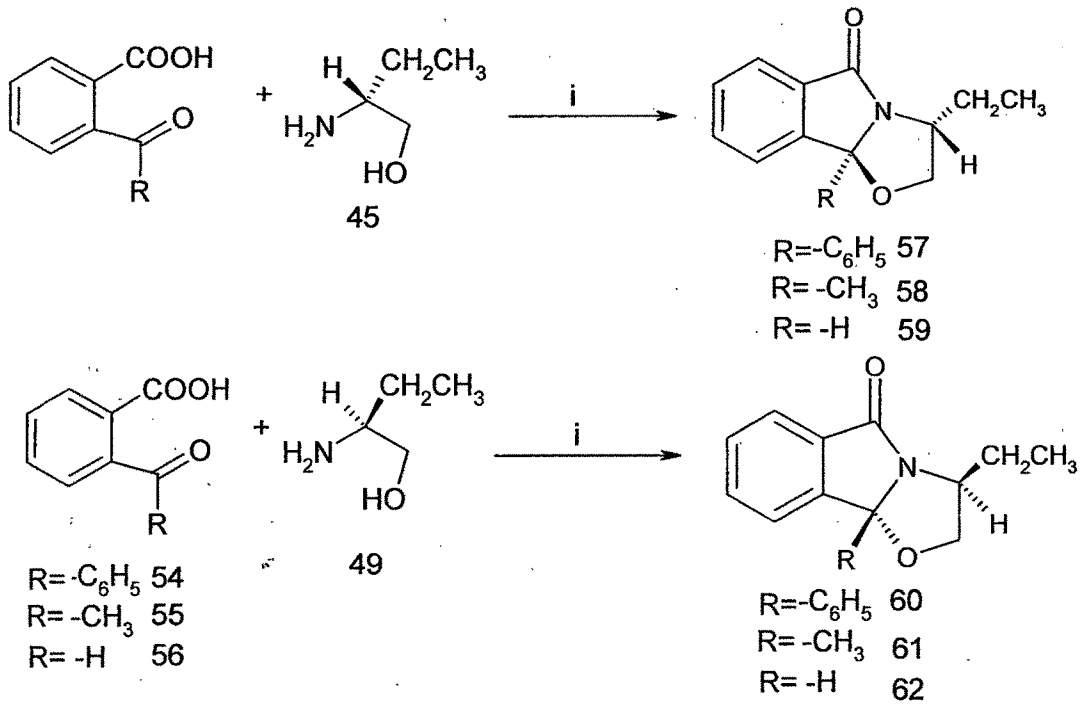


Figure II.12 1H NMR ($CDCl_3$) spectrum of (9b*S*)-Phenyl –(3*R*)- 3-ethyl -2,3,5,9b tetrahydro [1,3]oxazolo[2,3-a]isoindol-5-one(57)



Scheme II.20 Reagents and conditions Toluene, dean-stark, reflux, 12 hours

Similarly cyclodehydration of O-Acetyl benzoic acid (55) with (*R*)-2-Amino-1-butanol (45) and (*S*)-2-Amino-1-butanol (49) yielded (9b*S*)-9-Methyl–(3*R*)-3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (58) and (9b*R*)-9-Methyl–(3*S*)-3-ethyl 2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (61). The 1H NMR of 58 (**Figure II.13**) showed a triplet at ∂ 1.3 for methyl group, a singlet at ∂ 1.7 for methyl at 9b position, a multiplet at ∂ 1.6 for $-CH_2$ group, a multiplet at ∂ 3.8-4.5 for $-CH-CH_2-O$ group and a multiplet at ∂7.5-8.0 for four aromatic protons. The ^{13}C NMR(**Figure II.14**) of 58 showed a peak at ∂22.83 for the methyl group at 9b position other than the required peaks.(9b*R*)-9-Methyl-3*S*-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (61) showed similar spectral characteristics. Equal and opposite specific rotation values show that 58 and 61 are enantiomers.

Cyclodehydration of O-Carboxybenzaldehyde (56) with (*R*)-2-Amino-1-butanol (45) and (*S*)-2-Amino-1-butanol (49) yielded (9b*S,3R*)-9-Dihydro-3- ethyl-2,3,5,9b

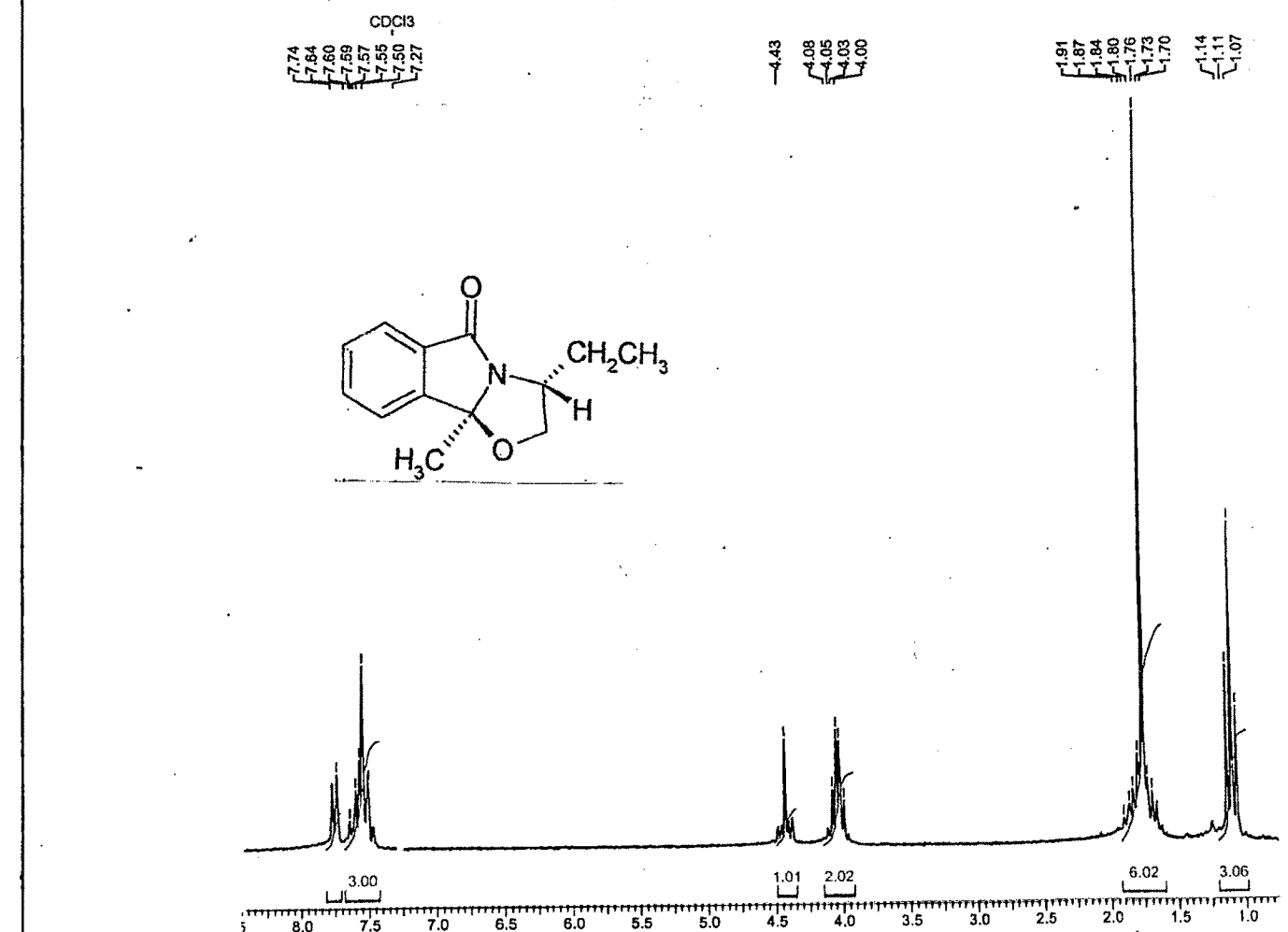


Figure 11.13 1H NMR($CDCl_3$) spectrum of (9b*S*)-9-Methyl–(3*R*)-3-ethyl-2,3,5,9b tetrahydro [1,3]oxazolo[2,3-a]isoindol-5-one (58)

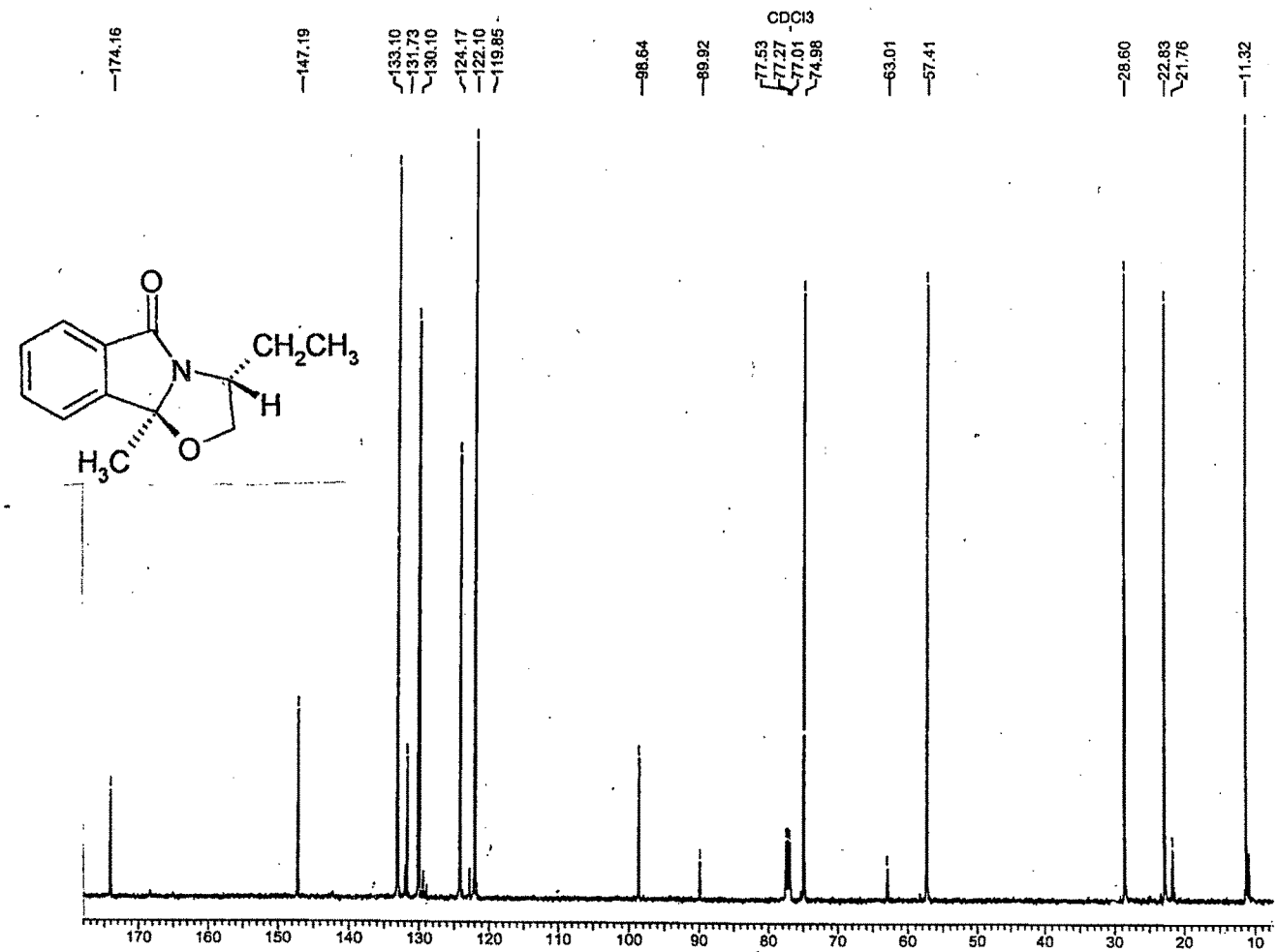


Figure II.14 ^{13}C NMR($CDCl_3$) spectrum of (9b*S*)-9-Methyl-(3*R*)-3-ethyl-2,3,5,9b tetrahydro [1,3]oxazolo[2,3-a]isoindol-5-one(58)

tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (59) and (9b*R*,3*S*)-9-Dihydro-3-ethyl 2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (62). The 1H NMR spectra (**Figure II.15**) for 59 showed a triplet at ∂ 0.94 for $-CH_3$ group, a multiplet at ∂1.5 for $-CH_2$ group, a triplet at ∂ 3.6 for H_A of CH_AH_B, another triplet for H_B of CH_AH_B at ∂ 4.4, a quartet for 1H of –CH group, a singlet at ∂ 5.7 for 1H at 9b position, a multiplet for four aromatic protons at ∂ 7.3-7.8. The ^{13}C spectra (**Figure II.16**) showed the required peaks. 9b*R*,3*S*-Dihydro-3-ethyl-2,3,5,9tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (62) showed similar spectral characteristics as 59. Equal and opposite specific rotation values indicate that (59) and (62) are enantiomers.

The prediction that the products 57-62 formed have the respective configurations is based upon the fact that Stevens *et al*[6] have also condensed (*R*) and (*S*) - phenyl glycinol with O-benzoyl benzoic acid and the most stable products formed were the ones in which the phenyl at the 3rd position and the phenyl at the position 9 are cis to each other on the exo face. Stevens *et al* have established the configuration of the products formed on the basis of single crystal x-ray data of the products. They have also proposed a mechanism explaining the stereochemical outcome of the reaction. It involves initial formation of a hydroxylamine/oxazolidine intermediate. Reversible cyclisation of hydroxyimine 63 could produce both the cis oxazolidine(64) and trans oxazolidine (65). Ring closure of 64 with concomitant loss of water yields the observed tricyclic lactam product 66. In the case of 65 however, cyclisation appears from simple molecular models to be highly disfavoured due to the remote orientation of the reactive functional groups. The tricyclic lactam 66 appears to be the thermodynamically more favorable product isomer. **(Scheme II.21)**

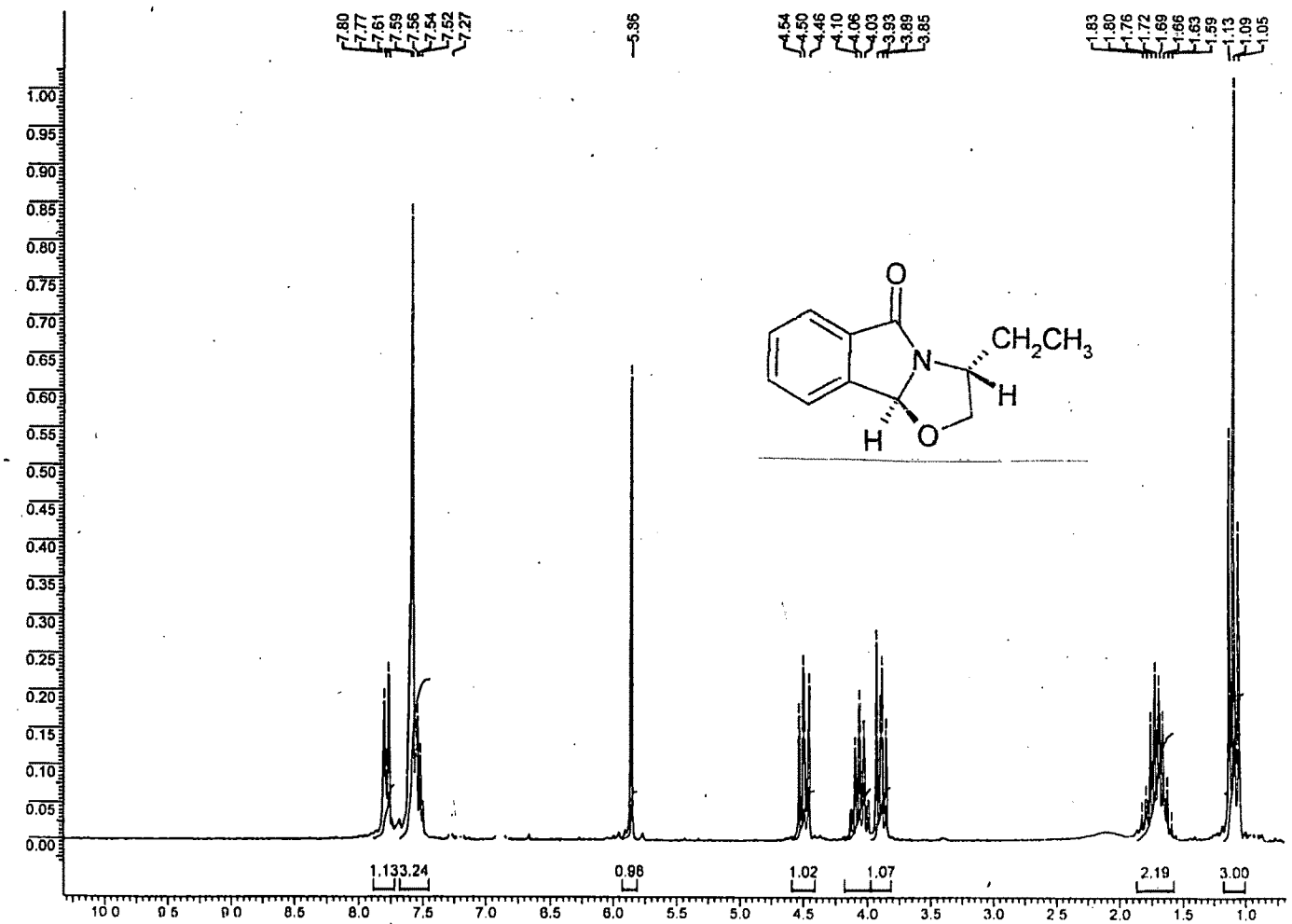


Figure II.15 1H NMR($CDCl_3$) spectrum of (9b*S, 3R*)-9-Dihydro-3- ethyl 2,3,5,9b tetrahydro [1,3]oxazolo[2,3-a]isoindol-5-one (59)

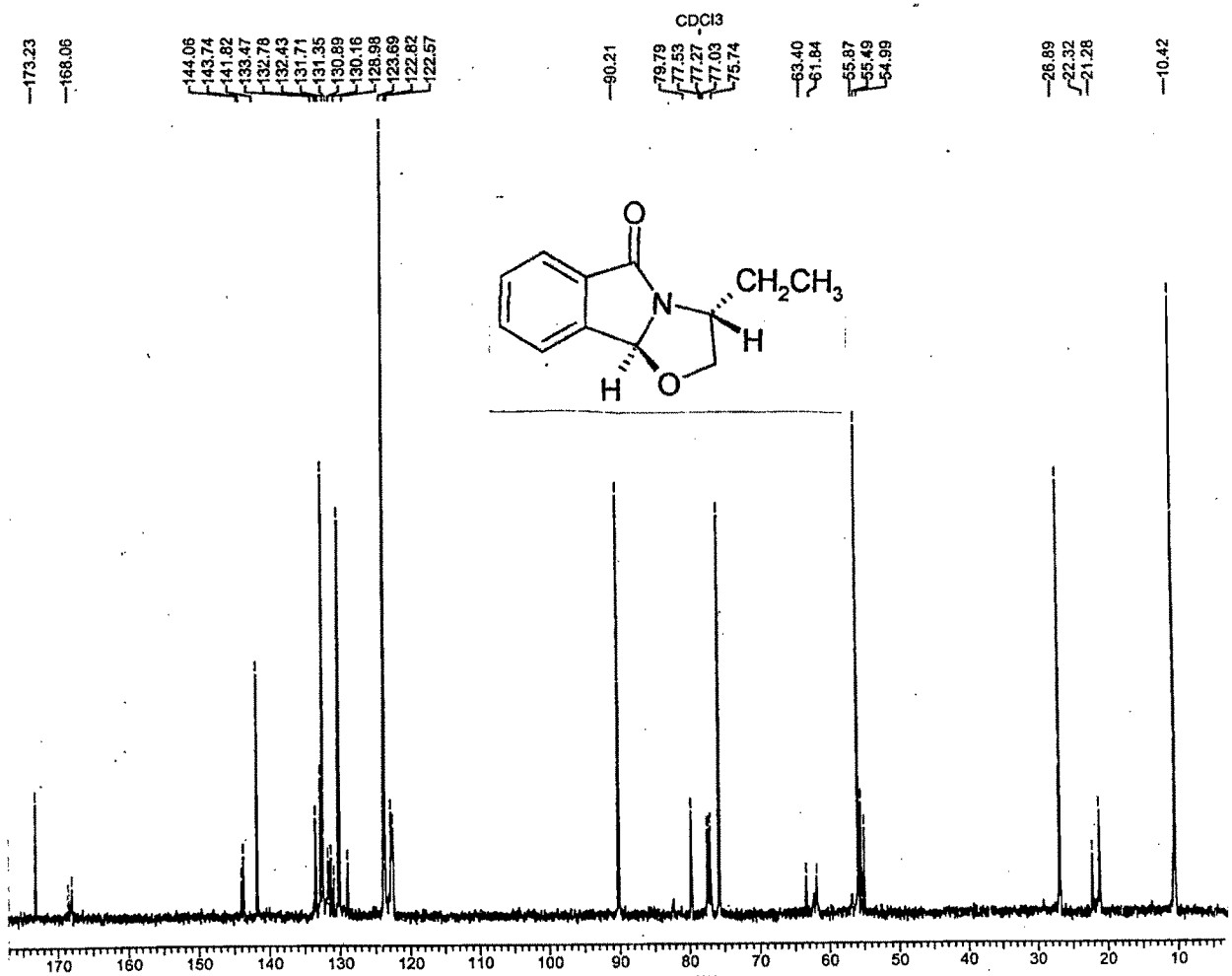
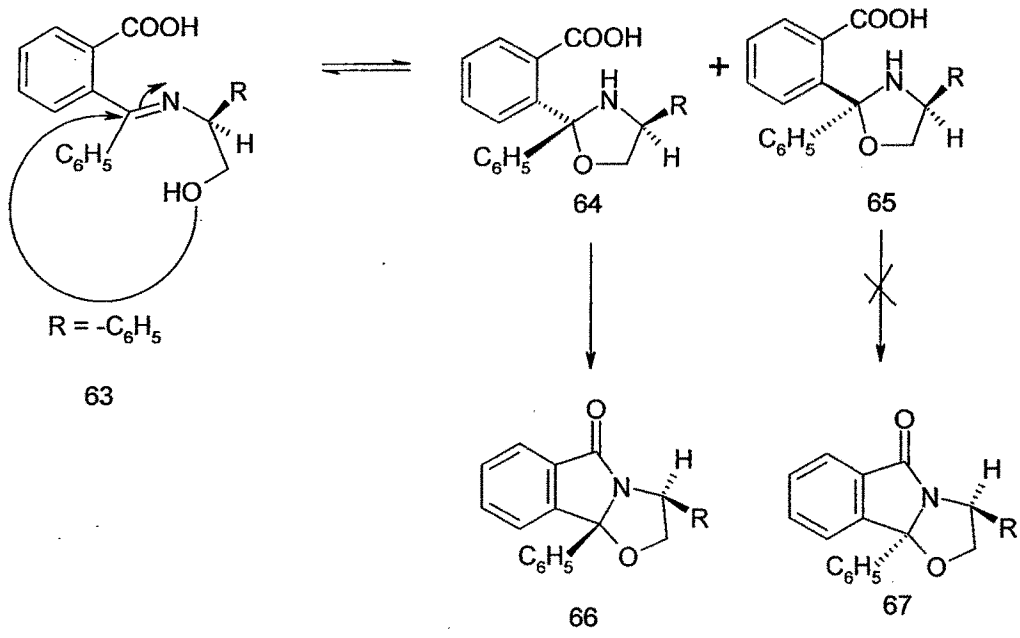
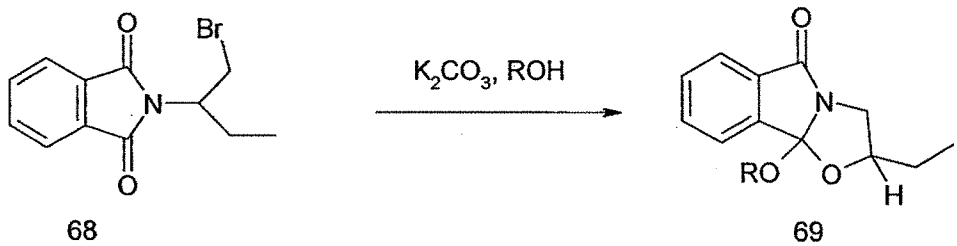


Figure II.16 ^{13}C NMR($CDCl_3$) spectrum of (9b*S*, *3R*)-9-Dihydro-3-ethyl 2,3,5,9b tetrahydro [1,3]oxazolo[2,3-a]isoindol-5-one (59)



Scheme II.21

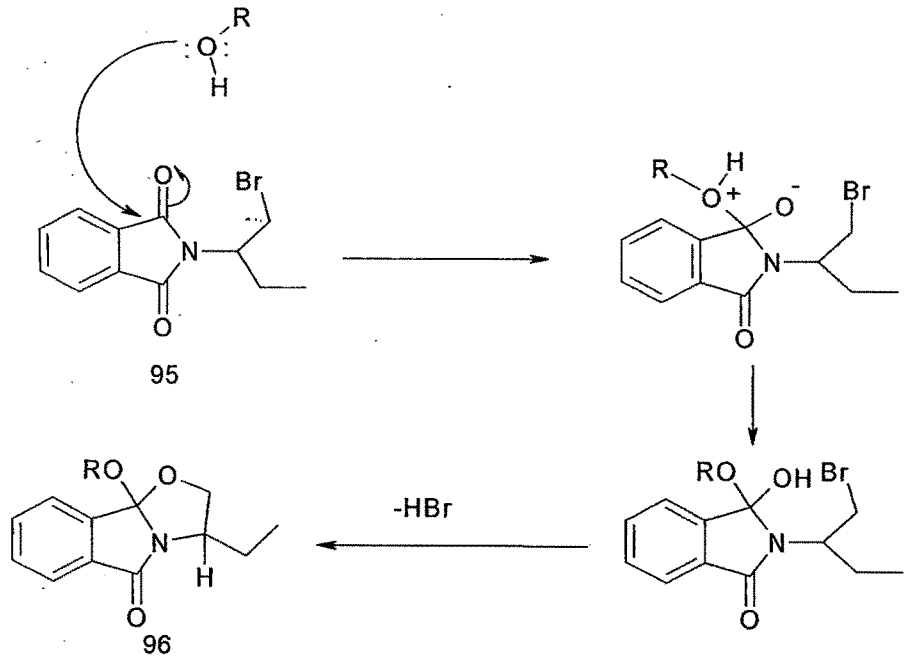
2-(1-Bromomethylpropyl)isoindol-1,3-dione (68) on treatement with anhydrous K_2CO_3 furnished a product which was identified as 9b-Ethoxy-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one (69b). Similar reaction of2-(1-Bromomethylpropyl) isoindol-1, 3-dione (68) with methanol, n-propanol, n-butanol and n-pentanol furnished the corresponding alkoxy substituted isoindol-5-one derivatives 69a, 69c-e **(Scheme II.22).**



R = $-CH_3$ (69a), $-CH_2CH_3$ (69b), $-CH_2CH_2CH_3$ (69c), $-CH_2$ $(CH_2)_2CH_3$ (69d), $-CH_2(CH_2)_3CH_3$ (69e)

Scheme II.22 Reagent and conditions ROH, anhydrous K_2CO_3, 8-10 hours

The 1HNMR of 9b-methoxy-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 69a (**Figure II.17**) shows a triplet at δ1.01 for $-CH_3$, a multiplet for two protons at δ1.65 for $-CH_2CH_3$, a singlet for three protons for $-OCH_3$, a multiplet at δ4.04 for one proton of CH_2-O, another multiplet at δ4.22 for one proton of –CH, a multiplet at δ4.47 for one proton of CH_2-O, a multiplet at 7.25-7.75 for Ar-H. The ^{13}C spectra (**Figure II.18**) of 69a also shows typical peaks at δ10.0 for-CH_3, δ 29.0 for-CH_2 at δ 53.0 for -OCH_3 at δ 68.0 for-CH_2,at δ 73.0 for CH ,peaks at δ 128.0-133.0 for six aromatic carbons at 163.0 & 168.0 for carbonyl carbon and quaternary carbon atom. Other alkoxy substituted isoindole-5-one derivatives also show the corresponding spectral characteristics. The probable mechanism for the formation of the 9b-Alkoxy-3-ethyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one derivatives may involve attack of the alcohol at the carbonyl carbon followed by intramolecular attack and elimination of hydrogen bromide to give the corresponding cyclic compound **(Scheme II.23)**



Scheme II.23

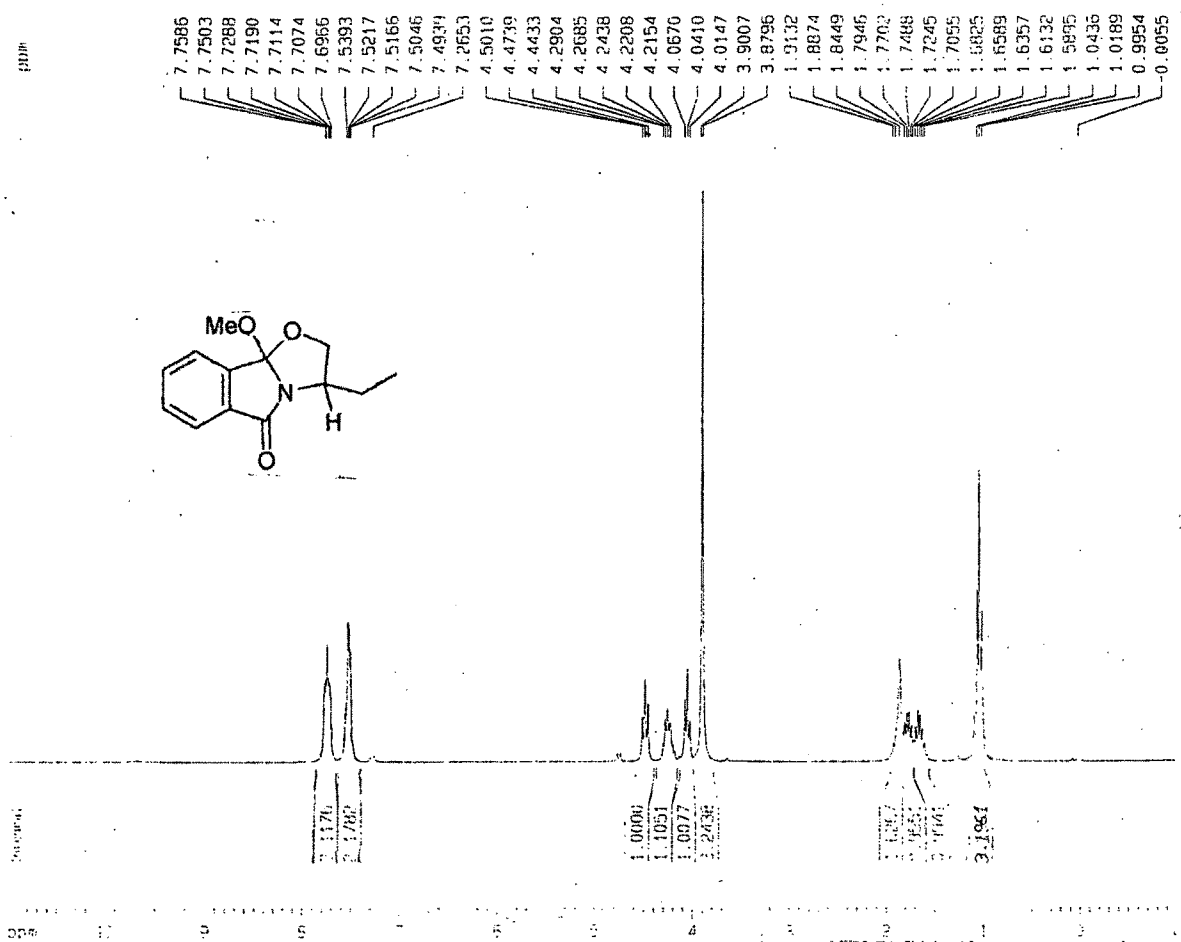


Figure II.17 1H NMR($CDCl_3$) spectrum of 9b-Methoxy-3-ethyl-2,3,5,9btetrahydro[1,3] oxazolo[2,3-a]isoindol-5-one 69a

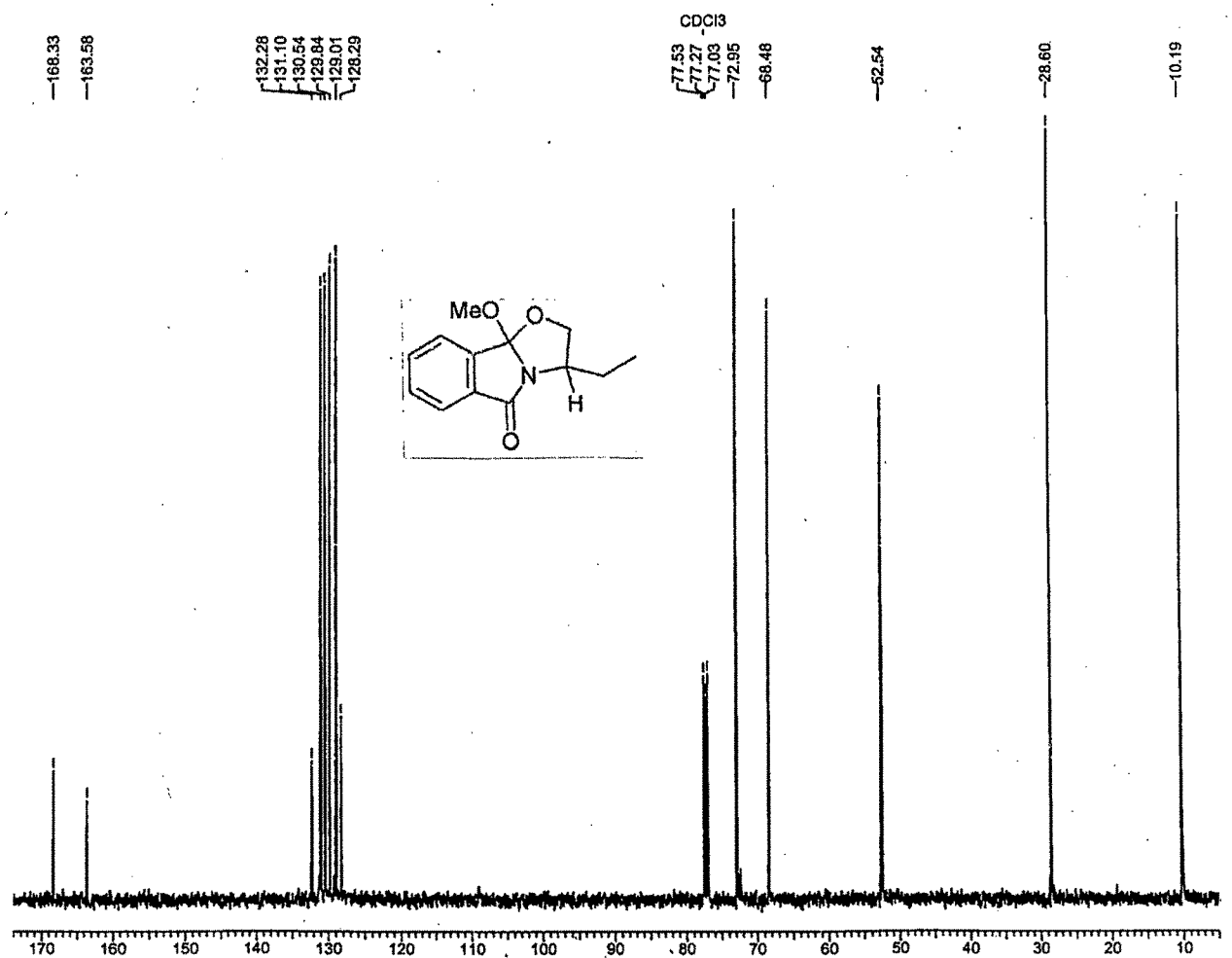


Figure II.18 ^{13}C NMR($CDCl_3$) spectrum of 9b-methoxy-3-ethyl-2,3,5,9btetrahydro[1,3] oxazolo[2,3-a]isoindol-5-one 69a

Thus we have synthesized phenyl and substituted phenyl 3-ethyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-ones by addition of various aryl magnesium bromides to (*R*) or (*S*)-2(1-hydroxybutyl)phthalimides followed by cyclisation using trifluoro acetic acid in moderate yields. The absolute configuration of the phenyl substituted oxazolo [2, 3-a] isoindol-5-one obtained from (*S*)-2-Amino-1-butanol was determined by single crystal x-ray diffraction as (3*S*, 9bR).Thus this methodology provides a highly diastereoselective method towards synthesis of these compounds. A different methodology involving cyclocondensation of 2-Acyl benzoic acids and (*R*) and (*S*)-2-Amino-1-butanols was also carried out to obtain the corresponding substituted oxazolo [2, 3-a] isoindolinones. Refluxing 2-(1-bromobutyl) phthalimide in different alcohols in alkaline conditions unexpectedly resulted in the formation of alkoxy substituted oxazolo [2, 3-a] isoindolinones in good yields

2.3 EXPERIMENTAL

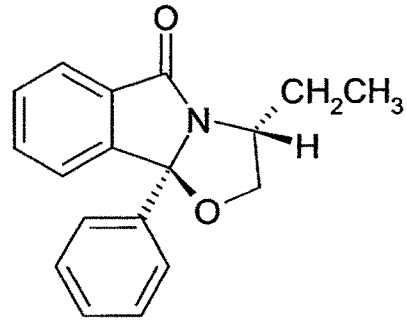
Reagent chemicals were purchased from Lancaster synthesis ltd and Aldrich chemical co. ltd. and were purified when necessary before use. Solvents were distilled and dried before use. Tetrahydrofuran (THF) for Grignard reactions was distilled over sodium wire and stored over sodium wire. Dichloromethane (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 (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. 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 JOSCO P-1030 polarimeter.

2.3.1 Synthesis of phenyl and substituted phenyl oxazolo [2, 3-a] isoindolinones by Grignard reaction (general method)

Grignard reagents were prepared by the usual procedure using the corresponding aryl bromides and magnesium in THF under nitrogen atmosphere.

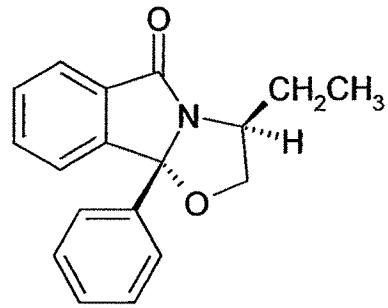
(*R*) or (*S*) - 2-(1-Hydroxybutyl) phthalimide 46 or 50 (2.0g, 9.13 mmol) dissolved in dry THF is taken in two neck round bottom flask flushed with nitrogen. Grignard reagent c-g (3 equivalents) is added to it within 4-5 minutes. Then the solution was stirred for 3 hours at room temperature. A saturated solution of ammonium chloride is added to it and extracted two to three times with dichloromethane. Removal of the solvent gave the crude product, which was dissolved in dry dichloromethane and added portion wise to a stirring solution of triflouroacetic acid (10 equivalents) in dry dichloromethane. Stirring is continued at room temperature for 2-3 hours. A saturated solution of sodium bicarbonate is added to it. Dichloromethane extract is washed with brine and dried with sodium sulphate. Dichloromethane is then distilled off to obtain a crude product which is purified using column chromatography with petether: ethylacetate (80:20) to obtain the corresponding cyclic products **48a-48e** or **52a-52e** in pure form.

(9b*S*,3*R*) 9-Phenyl-3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 48a



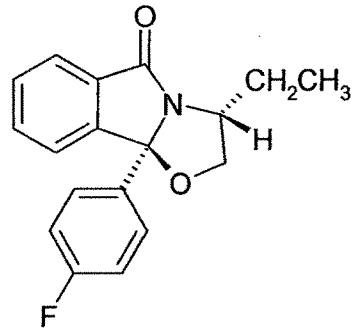
State	White crystals
Molecular formula	$C_{18}H_{17}NO_2$
m.p.	104 °C
Yield	45 %
$[\alpha]_D^{20}$	+261.97° (*c* 1.0, MeOH)
CHN	C-77.53 (77.41); H-6.12 (6.093);
found (calculated)	N-4.93 (5.017)
ν_{max} (KBR)/ cm^{-1}	1716, 1610, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	1.0(3Ht,-CH_2-$C\underline{H}_3$),1.4(2H,m,CH-$C\underline{H}_2$-CH_3), 3.8(1H,t ,*J* 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* 8.0, -CH-$C\underline{H}_2$-O) ,7.1-7.8 (9H, M, Ar-$\underline{H}$)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	175.27(C), {147.77, 139.59, 133.80, 31.82,130.69, 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)

(9b*R*,3*S*)9-Phenyl–3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 52a



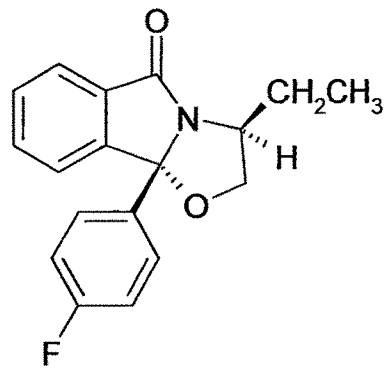
State	White crystals
Molecular formula	$C_{18}H_{17}NO_2$
m.p.	103 °C
Yield	47 %
$[\alpha]_D^{20}$	-263.72 °(*c* 1.0,MeOH)
CHN	C- 77.55 (77.41); H- 6.09(6.093);
found (calculated)	N- 4.92(5.017)
ν_{max} (KBR)/ cm^{-1}	1716, 1610, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	1.0(3Ht,-CH_2-C<u>H</u>$_3$),1.4(2H,m,CH-C<u>H</u>$_2$-CH_3), 3.8(1H,t ,*J* 8.0, -CH-C<u>H</u>$_2$-O), 4.2 (1H,q, *J*8.0,CH_2-C<u>H</u>-CH_2-),4.6(1H,t,*J* 8.0, -CH-C<u>H</u>$_2$-O) ,7.1-7.8 (9H, m, Ar-<u>H</u>)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	175.27(C), {147.77, 139.59, 133.80, 31.82,130.69, 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)

(9b*S*,3*R*)9-(4-Flouorophenyl)–3-ethyl -2,3,5,9b tetrahydro [1,3] oxazolo [2,3-a] isoin -dol-5-one 48b



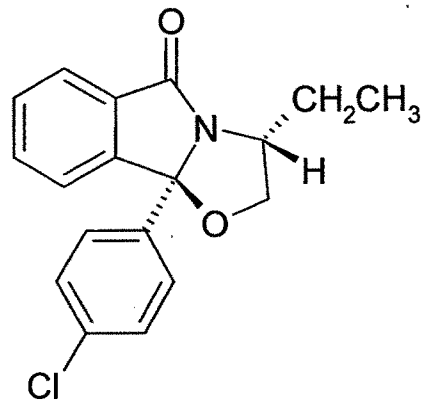
State	Thick colourless liquid
Molecular formula	$C_{18}H_{16}O_2NF$
Yield	40 %
$[\alpha]_D^{20}$	+264.8° (*c* 1.0, MeOH)
CHN found(calculated)	C- 72.51 (72.72); H- 5.40(5.38); N- 4.69(4.71)
ν_{max} (KBR)/ cm^{-1}	1737, 1600, 1463, 1377, 722.
δ_H (200MHz, $CDCl_3$)	1.0(3H,t,-CH_2-$C\underline{H}_3$),1.4(2H,m,-CH-$C\underline{H}_2$-CH_3),3.8 (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-$\underline{H}$)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	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)

(9b*R*,3*S*) 9-(4-Flouorophenyl)-3-ethyl 2,3,5,9b tetrahydro [1,3] oxazolo [2,3-a] isoin -dol-5-one 52b



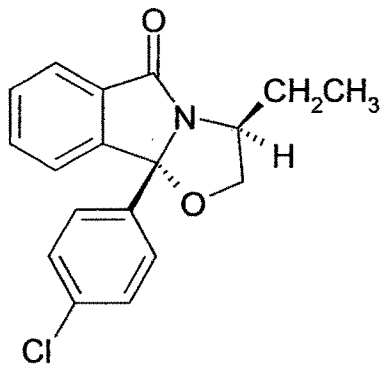
State	Thick colorless liquid
Molecular formula	$C_{18}H_{16}O_2NF$
Yield	41 %
$[\alpha]_D^{20}$	-242.19° (*c* 1.0, MeOH)
CHN found(calculated)	C- 72.65 (72.72); H- 5.30(5.38); N- 4.70(4.71)
ν_{max} (KBR)/ cm^{-1}	1737, 1600, 1463, 1377, 722.
δ_H (200MHz, $CDCl_3$)	1.0(3H,t,-CH_2-$C\underline{H}_3$),1.4(2H,m,-CH-$C\underline{H}_2$-CH_3), 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-$\underline{H}$)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	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)

(9b*S*,3*R*) 9- (4-Chlorophenyl)-3- ethyl-2,3,5,9b tetrahydro [1,3] oxazolo [2,3-a] isoin -dol-5-one 48c



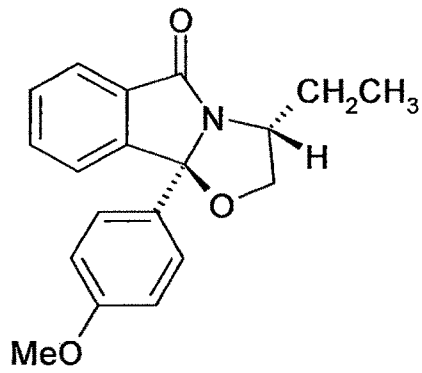
State	Thick colourless liquid
Molecular formula	$C_{18}H_{16}O_2NCl$
Yield	43 %
$[\alpha]_D^{20}$	+266.64° (*c* 1.0,MeOH)
CHN found (calculated)	C- 68.90(68.89); H- 5.03(5.10); N- 4.41(4.46)
ν_{max} (KBR)/ cm^{-1}	1736, 1599, 1462, 1376, 722
δ_H (200MHz, $CDCl_3$)	1.0 (3H, t, $-CH_2-C\underline{H}_3$), 1.4 (2H, m, $-CH-C\underline{H}_2-CH_3$), 3.8 (1H,t ,*J* 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* 8.0, $-CH-C\underline{H}_2-O$) , 7.1-7.8 (8H, m, Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	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)

(9b*R*,3*S*) 9-(4-Chlorophenyl)-3-ethyl-2,3,5,9btetrahydro[1,3] oxazolo [2,3-a] isoindol 5-one 52c



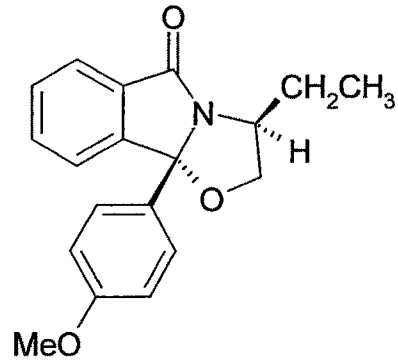
State	Thick colorless liquid
Molecular formula	$C_{18}H_{16}O_2NCl$
Yield	41%
$[\alpha]_D^{20}$	–250.22° (*c* 1.0,MeOH)
CHN found (calculated)	C- 68.70(68.89); H- 5.05(5.10); N- 4.42(4.46)
ν_{max} (KBR)/ cm^{-1}	1736, 1599, 1462, 1376, 722
δ_H (200MHz, $CDCl_3$)	1.0 (3H, t, -CH_2-C<u>H</u>$_3$), 1.4 (2H, m, -CH-C<u>H</u>$_2$-CH_3), 3.8 (1H,t ,*J* 8.0, -CH-C<u>H</u>$_2$-O), 4.2 (1H, q, *J* 8.0, -CH_2- C<u>H</u>-CH_2-), 4.6 (1H, t, *J* 8.0, -CH-C<u>H</u>$_2$-O) , 7.1-7.8 (8H, m, Ar-<u>H</u>)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	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)

(9b*S*, 3*R*) 9-(4-methoxyphenyl)-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3a]isoindol-5-one 48d



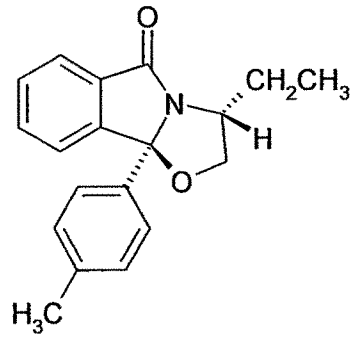
State	Thick colorless liquid
Molecular formula	$C_{19}H_{19}O_3N$
Yield	52 %
$[\alpha]_D^{20}$	+ 207.14° (c 1.0, MeOH)
CHN	C- 73.85 (73.78); H- 6.04(6.14);
found (calculated)	N- 4.48(4.53)
ν_{max} (KBR)/ cm^{-1}	1732, 1611,1510, 1459, 1377, 1240, 722
δ_H (200MHz, $CDCl_3$)	1.0 (3H, t, -CH_2-C<u>H_3</u>), 1.4 (2H, m, -CH-C<u>H_2</u>-CH_3), 3.8 (1H,t ,*J* 8.0, -CH-C<u>H_2</u>-O), 3.81(3H, s, -OCH_3) 4.2 (1H, q, *J* 8.0, -CH_2-C<u>H</u>-CH_2-), 4.6 (1H, t, *J* 8.0, -CH-C<u>H_2</u>-O) ,7.1-7.8 (8H, m, Ar-<u>H</u>)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	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)

(9b*R*,3*S*)-9-(4-methoxyphenyl)-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3a]isoindol-5-one 52d



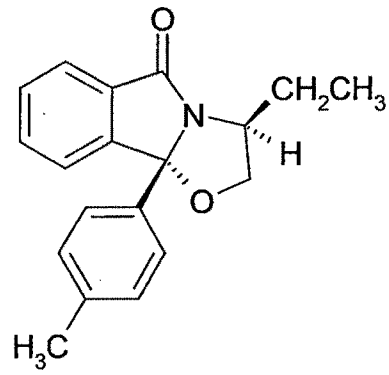
State	Thick colorless liquid
Molecular formula	$C_{19}H_{19}O_3N$
Yield	55 %
$[\alpha]_D^{20}$	- 212.99° (*c* 1.0, $CHCl_3$)
CHN	C- 73.71 (73.78); H- 6.10(6.14);
found (calculated)	N- 4.52(4.53)
ν_{max} (KBR)/ cm^{-1}	1732, 1611,1510, 1459, 1377, 1240, 722
δ_H (200MHz, $CDCl_3$)	1.0 (3H, t, -CH_2-C<u>H</u>$_3$), 1.4 (2H, m, -CH-C<u>H</u>$_2$-CH_3), 3.8 (1H,t ,*J* 8.0, -CH-C<u>H</u>$_2$-O), 3.81(3H, s, -OCH_3) 4.2 (1H, q, *J* 8.0, -CH_2-C<u>H</u>-CH_2-), 4.6 (1H, t, *J* 8.0, -CH-C<u>H</u>$_2$-O) ,7.1-7.8 (8H, m, Ar-<u>H</u>)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	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)

(9b*S*,3*R*)-9-(4-methylphenyl)-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 48e



State	Thick colorless liquid
Molecular formula	$C_{19}H_{19}O_2N$
Yield	48 %
$[\alpha]_D^{20}$	+221.49° (*c* 1.0, $CHCl_3$)
CHN	C- 77.76 (77.81); H- 6.16(6.48);
found (calculated)	N- 4.69(4.78)
ν_{max} (KBR)/ cm^{-1}	1732, 1610, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	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* 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* 8.0, $-CH-C\underline{H}_2-O$), 7.1-7.8 (8H, m, Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	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)

(9b*R*,3*S*)-9-(4-methylphenyl)-3-ethyl 2, 3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 52e



State	Thick colorless liquid
Molecular formula	$C_{19}H_{19}O_2N$
Yield	45 %
$[\alpha]_D^{20}$	-215.69 °(*c* 1.0, $CHCl_3$)
CHN	C-77.73 (77.81); H- 6.39(6.48);
found (calculated)	N- 4.65 (4.78)
ν_{max} (KBR)/ cm^{-1}	1732, 1610, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	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* 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* 8.0, $-CH-C\underline{H}_2-O$), 7.1-7.8 (8H, m, Ar-<u>H</u>
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	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)

Crystal Data And Structure Refinement

Crystal data of 52a: Single crystals of the complex 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. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, Hemisphere data acquisition. Total scans = 3, total frames = 1271, Oscillation / frame - 0.3°, exposure / frame = 20.0 sec / frame, maximum detector swing angle = –30.0°, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, 2θ range = 4.04 to 57.7 °, completeness to 2θ of 57.7 ° is 90.7%. SADABS correction applied. 2 x (C18H17NO2), 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, wR2 = 0.1163 (all data R = 0.0528, wR2 = 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. Data collection and refinement parameters are listed (**Table II.3.1**)

Empirical formula	$2x(C_{18}H_{17}NO_2)$
Formula weight	558.65
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P21
Unit cell dimensions	a = 8.338 (2) A b = 20.121(4) A c = 9.416 (2) A beta = 109.440(3)
Volume	1489.7(5) A^3
Z, Calculated density	2, 1.245 Mg/m^3
Absorption coefficient	0.081 mm^{-1}
F(000)	592

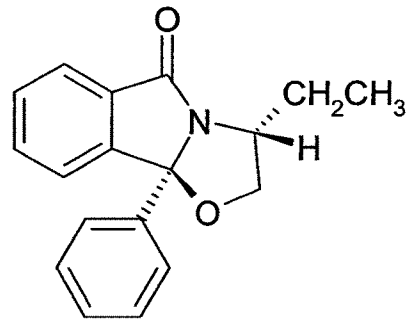
Crystal size	0.237 x 0.461 x 0.556 mm
Theta range for data collection	2.02 to 28.35 deg
Limiting indices	-11<=h<=9, -26<=k<=25, -12<=l<=12
Reflections collected / unique	8976 / 5894 [R(int) = 0.0254]
Completeness to theta	28.35 90.7 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5894 / 1 / 515
Goodness-of-fit on F^2	0.968
Final R indices [I>2sigma(I)]	R1 = 0.0448, wR2 = 0.1163
R indices (all data)	R1 = 0.0528, wR2 = 0.1208
Absolute structure parameter	2.0(10)
Largest diff. peak and hole	0.179 and -0.167 e. A^{-3}

Table II.3.1

2.3.2 Synthesis of oxazolo[2,3-a] isoindolinones using cyclodehydration method (general method)

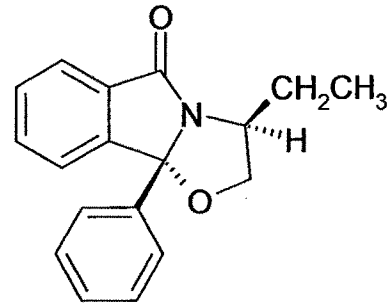
The corresponding 2- substituted ketoacid (54-56) (13.32 mmoles) is dissolved in 50mL of dry toluene. (*R*) or (*S*) - 2- Amino-1-butanol 45 or 49 (13.32 mmoles) is added drop wise to it with continuous stirring when the solution becomes hazy and slightly warm. The reaction mixture is refluxed under dean stark conditions for 12 hours. Toluene is distilled off under vacuum. The remaining residue is taken up for column chromatography and the required compounds 57-62 are isolated using petroleum ether-ethyl acetate as the eluent.

(9b*R*, 3S)-9-Phenyl -3-ethyl- 2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 57



State	White crystals
Molecular formula	$C_{18}H_{17}NO_2$
m.p.	104 °C
Yield	45 %
$[\alpha]_D^{20}$	+261.97° (*c* 1.0, MeOH)
CHN	C - 77.53 (77.41); H - 6.12 (6.093);
found (calculated)	N- 4.93 (5.017)
ν_{max} (KBR)/ cm^{-1}	1716, 1610, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	1.0(3Ht,-CH_2-$C\underline{H}_3$),1.4(2H,m,CH-$C\underline{H}_2$-CH_3), 3.8(1H,t „*J* 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* 8.0, -CH-$C\underline{H}_2$-O) ,7.1-7.8 (9H, m, Ar-$\underline{H}$)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	175.27(C), {147.77, 139.59, 133.80, 31.82,130.69, 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)

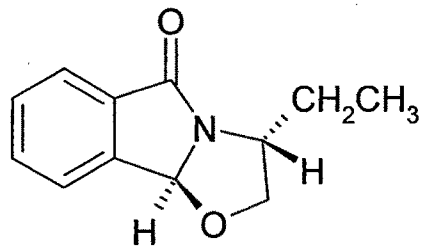
(9b*S*,3*R*)-9-Phenyl –3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 60



State	White crystals
Molecular formula	$C_{18}H_{17}NO_2$
m.p.	102 °C
Yield	47 %
$[\alpha]_D^{20}$	-263.72° (*c* 1.0, MeOH)
CHN	C- 77.55 (77.41); H- 6.09(6.093);
found (calculated)	N- 4.92(5.017)
ν_{max} (KBR)/ cm^{-1}	1716, 1610, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	1.0(3Ht,-CH_2-$C\underline{H}_3$),1.4(2H,m,CH-$C\underline{H}_2$-CH_3), 3.8(1H,t ,*J* 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* 8.0, -CH-$C\underline{H}_2$-O) ,7.1-7.8 (9H, m, Ar-$\underline{H}$)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	175.27(C), {147.77, 139.59, 133.80, 31.82,130.69, 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)

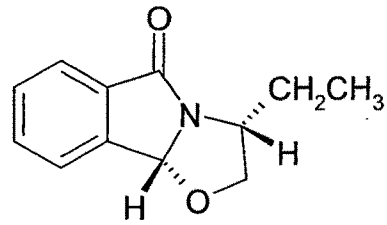
(9b*R*,3*S*)9 – Dihydro- 3 -ethyl 2,3,5,9b tetrahydro [1,3] oxazolo [2,3-a] isoindol-5-one

59



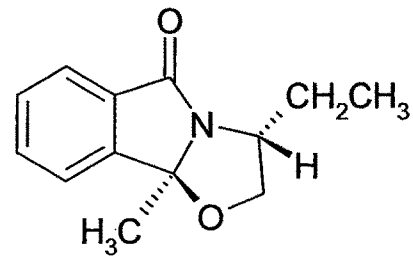
State	Thick colourless liquid
Molecular formula	$C_{12}H_{13}NO_2$
Yield	85 %
$[\alpha]_D^{20}$	+72.59 (*c* 1.0, $CHCl_3$)
CHN found (calculated)	C- 70.59 (70.93); H- 6.54(6.4); N- 6.86(6.89)
ν_{max} (KBR)/ cm^{-1}	1710, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	0.94 (3H, t, -CH_2-C<u>H</u>$_3$), 1.5 (2H, m, -CH-C<u>H</u>$_2$-CH_3), 3.6 (1H,t ,*J* 8.0, -CH-C<u>H</u>$_2$-O), 3.8 (1H, q, *J* 8.0, -CH_2-C<u>H</u>-CH_2-), 4.4 (1H, t, *J* 8.0, -CH-C<u>H</u>$_2$-O),5.7 (1H, s, C<u>H</u>) ,7.3-7.8 (4H, m, Ar-<u>H</u>)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	173.23(C), {144.06, 141.82, 131.71, 130.89, 128.98, 123.69}(Ar-C), 90.21(CH), 75.74(CH), 55.49(CH_2), 10.42(CH_3)

(9b*S*,3*R*)9– Dihydro- 3 –ethyl- 2,3,5,9b tetrahydro [1,3] oxazolo [2,3-a] isoindol -5-one 62



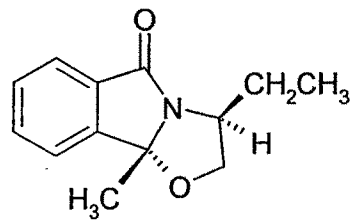
State	Thick colourless liquid
Molecular formula	$C_{12}H_{13}NO_2$
Yield	87 %
$[\alpha]_D^{20}$	-73.85° (*c* 1.0, $CHCl_3$)
CHN found (calculated)	C- 70.45 (70.93); H- 6.35(6.4); N- 6.8(6.89)
ν_{max} (KBR)/ cm^{-1}	1710, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	0.94 (3H, t, -CH_2-C<u>H</u>$_3$), 1.5 (2H, m, -CH-C<u>H</u>$_2$-CH_3), 3.6 (1H,t ,*J* 8.0, -CH-C<u>H</u>$_2$-O), 3.8 (1H, q, *J* 8.0, -CH_2-C<u>H</u>-CH_2-), 4.4 (1H, t, *J* 8.0, -CH-C<u>H</u>$_2$-O), 5.7(1H, s, C<u>H</u>), 7.3-7.8 (4H, m, Ar-<u>H</u>)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	173.13(C), {144.0, 141.82, 131.71, 130.89, 128.98, 123.69}(Ar-C), 90.20(CH), 75.04(CH), 55.19(CH_2), 10.22(CH_3)

(9b*R*,3*S*)-9-Methyl -3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 58



State	Colorless crystals
Molecular formula	$C_{13}H_{15}NO_2$
Yield	90 %
$[\alpha]_D^{20}$	+19.08° (*c* 1.24, $CHCl_3$)
CHN found (calculated)	C- 70.55 (71.88); H- 6.90(6.91); N- 6.5 (6.45)
ν_{max} (KBR)/ cm^{-1}	1705, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	1.2 (3H, t, -CH_2-CH_3), 1.6 (2H, m, -CH-CH_2-CH_3), 1.7 (3H, s, -CH_3),3.8 (1H,t ,*J* 8.0, -CH-CH_2-O), 4.2 (1H, q,8.0,-CH_2-CH-CH_2-), 4.6 (1H, t, *J* 8.0, -CH-CH_2-O), 7.5-7.8 (4H, m, Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33MHz)	174.16(C), {147.19, 133.10, 130.10, 124.17, 122.10, 119.85}, 98.64(CH), 74.98(CH), 57.41(CH_2), 28.60(CH_2), 22.83(CH_3), 11.32(CH_3)

(9b*S*, 3*R*)-9- Methyl –3-ethyl-2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 61



State	Colorless crystals
Molecular formula	$C_{13}H_{15}NO_2$
Yield	92%
$[\alpha]_D^{20}$	-19.24° (*c* 1.24, $CHCl_3$)
CHN	C- 70.55 (71.88); H- 6.90(6.91);
found (calculated)	N- 6.5 (6.45)
ν_{max} (KBR)/ cm^{-1}	1705, 1450, 1320, 1240, 750
δ_H (200MHz, $CDCl_3$)	1.2 (3H, t, $-CH_2-\underline{CH_3}$), 1.6 (2H, m, $-CH-\underline{CH_2}-CH_3$), 1.7 (3H, s, $-CH_3$),3.8 (1H,t ,*J* 8.0, $-CH-\underline{CH_2}-O$), 4.2 (1H, q,8.0,$-CH_2-\underline{CH}-CH_2-$), 4.6 (1H, t, *J* 8.0, $-CH-\underline{CH_2}-O$), 7.5-7.8 (4H, m, Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33)	174.10(C), {147.11, 133.10, 130.10, 124.27, 122.10, 119.05}, 98.14(CH), 74.08(CH), 57.0(CH_2), 28.60(CH_2),22.83(CH_3), 11.32(CH_3)

2.3.3 Synthesis of 9-Alkoxy-3-ethyl 2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one

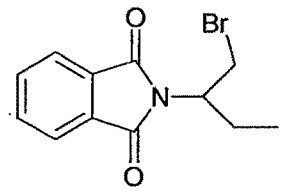
2.3.3a Synthesis of 2-(1-Bromomethylpropyl)isoindol-1,3-dione 68 :-

Freshly distilled PBr_3 is added to 2-(1-hydroxybutyl) phthalimide slowly with stirring. The reaction flask is then placed on a steam bath and heated under reflux with occasional shaking for 7-8 hours. The hot liquid is then poured into ice water and stirred for 1-2 hours and subsequent extraction with DCM is carried out two to three times. The DCM layer is then washed with 10%$NaHCO_3$, brine solution and then water. The DCM layer is separated, dried over anhyd.Na_2SO_4 and is distilled off under vacuum. The resulting residue is then loaded onto a silica gel column and the product 68 was isolated as white crystalline solid using 90:10 petroleum ether and ethyl acetate as the solvent system.

2.3.3b Synthesis of 9-Alkoxy-3-ethyl 2,3,5,9b tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 69a-69e (General Method)

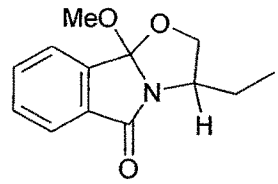
2-(1-Bromomethylpropyl) isoindol-1, 3-dione 68 and anhydrous K_2CO_3 are refluxed with the corresponding alcohol for 8-10 hours. The alcohol is distilled off under vacuum and the residue is washed with water and extracted with DCM. The DCM layer is dried over anhydrous Na_2SO_4 and the DCM layer is distilled off under vacuum. The residue is loaded onto a silica gel column and the products 69a-69e is isolated as a liquid using 80:20 petroleum ether and ethyl acetate as the solvent system.

2-(1-Bromomethylpropyl)isoindol-1,3-dione 68



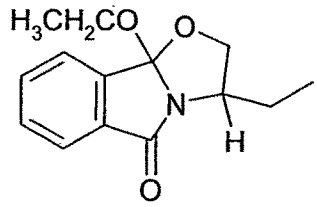
State	Colorless crystals
Molecular formula	$C_{12}H_{12}NO_2Br$
M.P.	68°C
Yield	70%
CHN found (calculated)	C- 51.72 (51.06); H- 3.74(4.25); N-4.79 (4.96)
δ_H (200MHz, $CDCl_3$)	0.92 (3H, t,-CH_2),1.91 (1H,m,-CH_2), 2.07(1H,m,-CH_2), 3.66(1H, t,CH_2),4.05(1H,t,-CH_2), 4.40(1H, m, -CH),7.71-7.86(4H,m,Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33)	11.10(-CH_3),24.47(-CH_2),32.28(-CH_2), 54.90(CH),123,131.59,134.07 3xArC),168.0(C)

9b-Methoxy-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 69a



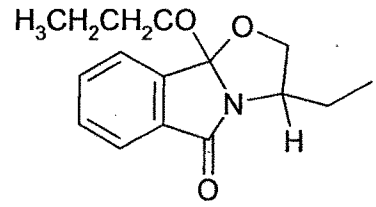
State	Colorless liquid
Molecular formula	$C_{13}H_{13}NO_3$
Yield	65%
CHN found (calculated)	C- 67.35 (66.95); H- 6.41(6.43); N-5.90 (6.0)
δ_H (200MHz, $CDCl_3$)	1.01(3H,t,-CH_3),1.65(2H,m,-CH_2), 1.74(2H,m,-CH_2),3.9(3H,t,OCH_3),4.04(2H,m,CH_2), 4.22(1H,m,-CH), 4.47(1H,m,CH_2), 7.25-7.75 (4H,m,Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33)	10.0(-CH_3), 29.0(-CH_2), 53.0(-OCH_3), 68.0(-CH_2),73.0(CH),128.0-133.0(Ar-C), 163.0(C),168.0(C)

9b-Ethoxy-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 69b



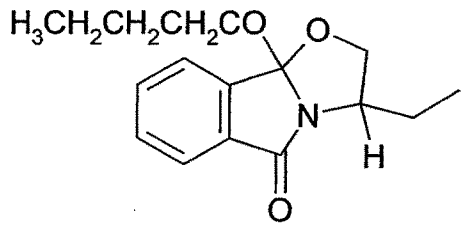
State	Colorless liquid
Molecular formula	$C_{14}H_{15}NO_3$
Yield	68%
CHN found (calculated)	C- 66.49 (68.75); H- 7.11(6.122); N-5.71 (6.16)
δ_H (200MHz, $CDCl_3$)	0.82(3H,t,-CH_3), 1.16(3H,t,-CH_3),1.50(2H,m, -CH_2), 3.79-4.31(5H,m,-OCH_2,-OCH_2,-CH), 7.27-7.58 (4H,m,Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33)	10.0(-CH_3),14.0(-CH_3),29.0(-CH_2),61.0 (-OCH_3),69.0(CH_2),74.0(CH),128.15-132.72(Ar-C),163.40(C),167.74(C)

9b-Propyloxy-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 69c :-



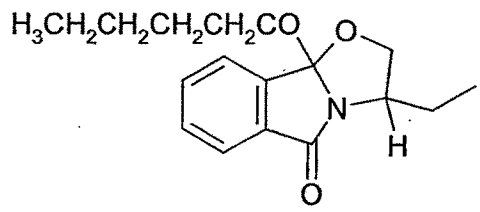
State	Colorless liquid
Molecular formula	$C_{15}H_{19}NO_3$
Yield	62%
CHN found (calculated)	C- 66.28 (68.96); H- 7.25(7.27); N-5.06 (5.36)
δ_H (200MHz, $CDCl_3$)	0.97(6H, m, 2 CH_3), 1.70(4H, m, $2CH_2$), 3.99-4.47(5H,m, $-OCH_2$,$-CH_2$,$-OCH_2$), 7.43-7.73 (4H,m,Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33)	10.19($-CH_3$),10.49($-CH_3$),22.09(-CH2),28.56($-CH_2$),67.11($-OCH_3$),68.54(CH_2),72.91(CH),128.33-130.83(Ar-C),163.64(C),167.79

9b-Butyloxy-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 69d :-



State	Colorless liquid
Molecular formula	$C_{16}H_{21}NO_3$
Yield	65%
CHN found (calculated)	C- 68.28 (69.81); H- 7.70(7.63); N-5.89 (5.09)
δ_H (200MHz, $CDCl_3$)	0.93(6H,m,2x-CH_3),1.37-1.73(6H,m,3xCH_2), 3.99-4.45(5H,m,-OCH_2,-CH,-OCH_2), 7.43-7.73(4H,m,Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33)	10.10(-CH_3),13.67(-CH_3),19.19(-CH_2),28.47(-CH_2), 30.70(-CH2) 65.67(-OCH_2),68.48(-OCH_2), 72.78(-CH),128.33-132.75(ArC),163.52(C),167.73(C)

9b-Pentyloxy-3-ethyl-2,3,5,9btetrahydro[1,3]oxazolo[2,3-a]isoindol-5-one 69e :-



State	Colorless liquid
Molecular formula	$C_{17}H_{23}NO_3$
Yield	60%
CHN found (calculated)	C- 69.59 (70.58); H- 7.65(7.95); N-4.85 (4.84)
δ_H (200MHz, $CDCl_3$)	0.94,1.01(6H,m,2xCH_3),1.36(4H,m,-CH_2), 1.69(4H,m,-CH_2),4.02(1H,t,CH_2),4.24(3H,m,-CH_2, -CH), 4.46(1H,t,-CH_2),7.47-7.74(4H,m,Ar-H)
^{13}C NMR δ_C ($CDCl_3$,50.33)	10.10(-CH_3),13.67(-CH_3),19.19(-CH_2),28.47(- CH_2),30.70(-CH2) 65.67(-OCH_2),68.48(-OCH_2), 72.78(-CH),128.33-132.75(Ar-C),163.52(C),167.73(C)

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