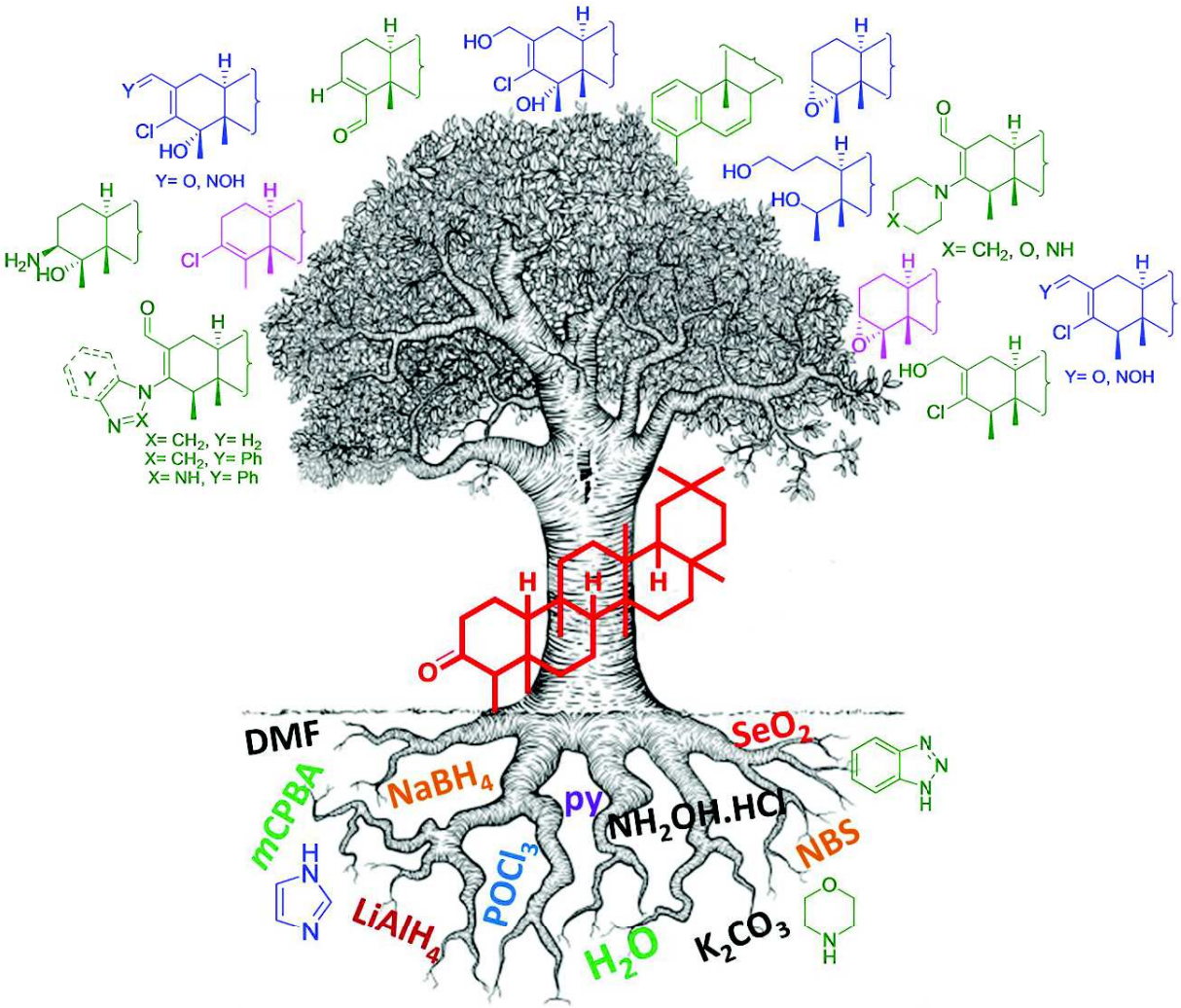
Syntheses of new friedelane triterpenoids: A-ring modifications including 2-*homo*derivatives



Abstract

First, the A-ring modified friedelane triterpenoids are reviewed in brief, which forms indeed the present day basis of the different type of A-ring modifications of this particular PT either of natural occurrence or due to various transformative reactions.

And, the practical work associated with the chapter constitutes the syntheses of a library of A-ring modified friedelane triterpenoids. The modifications also include the all new 2-*homo*derivatives. The syntheses of the novel 2-*homo*friedelanes are based on the transformative reactions of the designed triterpenoid 3-chloro-2-formylfriedel-2-ene (**402**) which was isolated as the major product from the reaction of friedelin (**000**) with the novel Vilsmeyer-Haack reagent. Some new derivatives of the friedelane series were also prepared from cerin (**0000**, a naturally occurring PT; structurally 2α-hydroxy friedelin) as well as using one of the new derivative **401**, structurally 3-chlorofriedel-2-ene, isolated as a side product from the key reaction. Moreover, considering the beauty of 3-chloro-2-en-al moiety, associated with the A-ring of the triterpenoid, a number of heterocycle-linked- (bonded to C3) 2-*homo*friedelane triterpenoids were synthesized.

IV.A Introduction: A brief review on the A-ring modified friedelane triterpenoids

A pentacyclic triterpenoid was extracted from the bark of *Querques Suber* as far back as 1807 by Chevreul[1,2] and was named friedelin (**115**) in honour of Friedel who was probably the first one to disclose the presence of a ketone group in the triterpenoid.[3] That one of the compound extracted contained a ketone functional group was again confirmed by Istrati and Ostrogovich.[4] Later, Drake et al. established the molecular formula of friedelin and prepared the oxime, enol esters and carbonyl derivatives, and it was converted to the saturated parent hydrocarbon friedelane. The oxime was transformed into the oxime acetate (by refluxing with acetic anhydride), Beckmann rearrangement product (with PCl_5) and was reconverted to friedelin on hydrolysis with H_3PO_4 in *n*-amyl alcohol.[5-9] But it was the success of Corey and Ursprung, and Dutler, Jeger and Ruzicka, separately, in 1956 to provide the complete structures of friedelin (**115**) and cerin (**116**) and then Brownnlie and his collaborators produce the stereochemistry of these triterpenoids (**Figure 4.1**).[10-12]

Thus, friedelin and associated triterpenoids which are generally named as friedelane triterpenoids are a group of triterpenoids bearing a [6-6-6-6-6]-fused pentacyclic skeleton with eight methyl groups at C(4), C(5), C(9), C(13), C(14), C(17), and C(20) (geminal-dimethyl), respectively (**Figure 4.1**). The final structural knowledge indeed made available a broad scope of study of the transformative reactions on friedelin and associated friedelane triterpenoids.

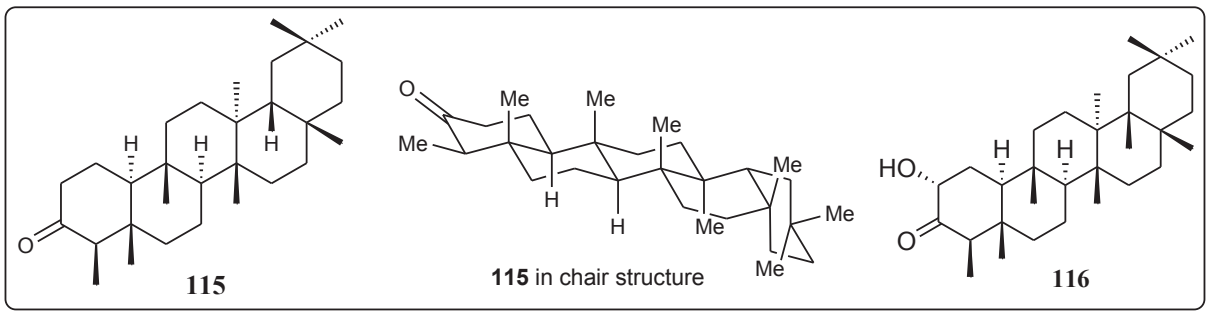


Figure 4.1 Friedelin (**115**), its chair form and cerin (**116**).

IV.A.1 Naturally occuring A-ring modified friedelane triterpenoids

More than 400 natural friedelane triterpenoids are isolated till date. The friedelane triterpenoids are found to be distributed more commonly in the families such as *Celastraceae*, *Hippocrateaceae*, *Euphorbiaceae*, *Flacourtiaceae*, and *Guttiferae* and among them the first two

are the richest sources of it. Based on the structural aspects, the FTs can be classified into five major classess such as i) normal friedelanes (**Type A**); ii) secofriedelanes (**Type B**); iii) norfriedelanes (**Type C**); iv) dimeric friedelanes (**Type D**) and v) rearranged friedelanes (**Type E**) (**Figure 4.2**). Leaf and twig parts provide mainly the first two classess of FTs whereas the classess (iii) and (iv) are isolated mainly from the root parts. Interestingly, friedelanes are also found to be present in some fungi.[13-14] Surprisingly, though there are reports of other triterpenoids which are found in nature as saponins, friedelanes are not being found as glycosides in nature.[15-17] Zhan et al. have summarized the natural sources of friedelane triterpenoids recently in their beautiful review.[18] Again, some selective interesting naturally occuring FTs where the A-ring got modified are described herein in short.

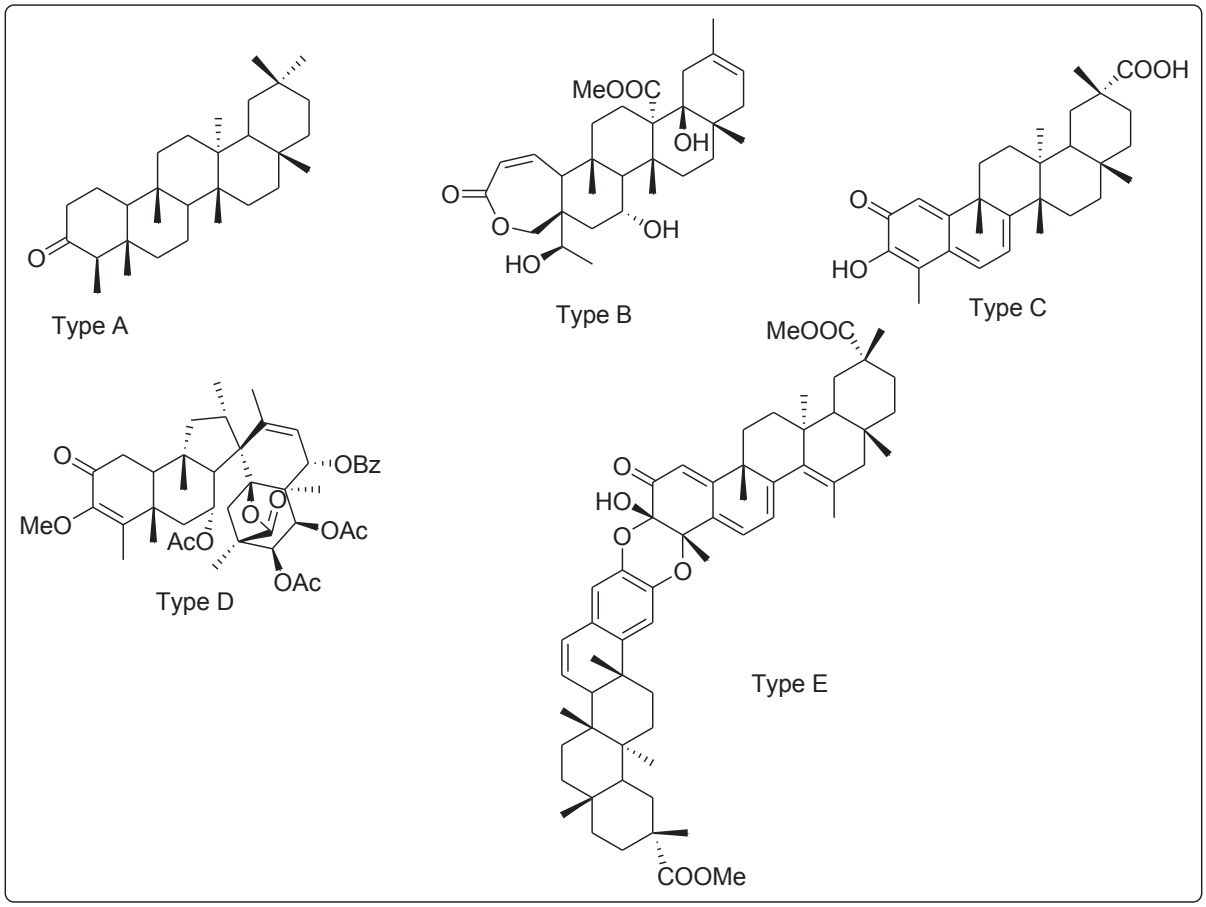


Figure 4.2 Diferent types of friedelanes (**Type A-E**).

Friedelin (**115**) and friedelane-l,3-dione (**1208**) (**Figure 4.3**),[19] along with some other friedelane triterpenoids were isolated from the stem and bark extract of *Peritassa compta*.

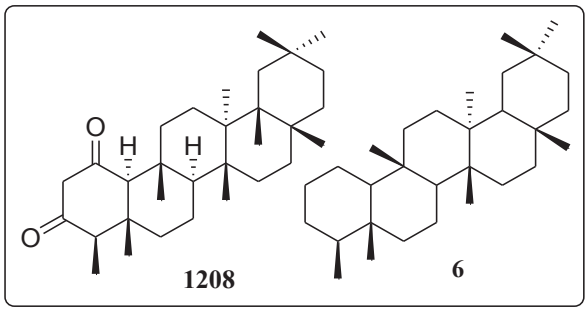


Figure 4.3 Friedelane-l,3-dione (**1208**) and friedelane (**6**).

Friedelin was also found to be a major constituent of *Grapefruit epicuticular* Wax,[20] *A. indica*[21] and also the stem bark exudates of *Maytenus macrocarpa,* which produced friedelane (**6**) also (**Figure 4.3**).

The biocidal activities of **6** were studied and found to be inactive to the antitumor activity against P-388 lymphoid neoplasm, A-549 human lung carcinoma, HT-29 human colon carcinoma, or MEL-28 human melanoma cell lines, but showed weak activity against aldose reductase.[22]

4-*Epi*friedelin (**1209**) along with twelve other known terpenoids (**Figure 4.4**) were found in the leaves of *Syzygium formosanum.*[23]

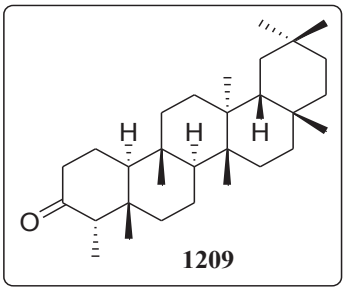


Figure 4.**4** 4-*epi*friedelin (**1209**).

Friedelin (**115**) and 3β-hydroxy friedelane (**1210**) (**Figure 4.5**) were isolated from *Artocarpus altilis*[24] and friedelin (**115**) along with 4-*epi*friedelin (**1209**) were isolated from the leaves of *Salacia chinensis.*[25]

Friedelin (**115**) and 3β-hydroxy friedelane (**1210**) were again isolated from *Celastrus vulcanicola* and the photosynthetic inhibitory activity of these compounds revealed **1210** to be an "energy transfer inhibitor, interacting and enhancing the light activated Mg^{2+}-ATPase"[26].

The foliar epicuticular waxes of the leaves of *A. Esperanzae* were found to contain 4-*epi*friedelin (**1209**). [27,28]

Baskar et al. isolated friedelin (**115**) from the leaves of *Azima tetracantha* and found friedelin to result 75.28% antifeedant, 66% larvicidal and 66.66% pupicidal activities against *H. armigera* and *S. Litura* respectively.[29]

During the phytochemical investigation of *Maytenus truncata* Reiss, both the epimers of 3-hydroxy friedelane (β: **1210** and α: **1211**) were isolated (**Figure 4.5**).[30]

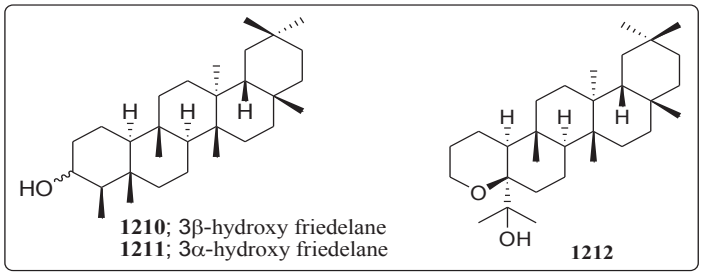


Figure 4.5 3β-Hydroxy- and 3α-hydroxy friedelane (**1210** and **1211**, respectively) and terminaline A (**1212**).

The plant extracts of *Maytenus aquifolium* and *M. ilicifolium* show anti-ulcer activity and these are indeed used medicinally in Brazil under the name "espinheirasanta". Lancas et al., showed that friedelin (**115**) and 3β-hydroxy friedelane (**1210**) are the markers of these plants.[31-32] The leaves and root barks of *M. aquifolium* and *S. campretris* were found to accumulate friedelin and quinonemethide respectively. From the enzymatic extracts of the leaves it was found that cyclase converted the substrate oxidosqualene to the triterpenes, 3β-hydroxy friedelane (**1210**) and friedelin (**115**). Moreover, when mevalonolactone was administrated to the leaves of *M. aquifolium* seedlings, radio labelled friedelin was found to be produced in the leaves, twigs and stems, while labelled maytenin and pristimerin were found in the root bark. From these important observations it was concluded that triterpenes once biosynthesized in the leaves were translocated to the root bark and further transformed into the antitumoral quinonemethide triterpenoids.[32-33]

Investigation of the leaves and barks of the Indian *L. racemosa* collected from Sundarban and Kakinada[33] and the stems of the same collected from the Indian Bhiravapalem Island[34]

revealed the presence of friedelin. *Terminalia glaucescens* was also found to contain an A-ring modified secotriterpene terminaline A (**1212**, **Figure 4.5**) and friedelin.[35]

Faure et al. isolated 3,4-secofriedelane-3,28-dioic acid (**1213**) and two other new friedelane-type triterpenoids from the leaves of *Calophyllum inophyllum* (Clusiaceae) found in French Polynesia (**Figure 4.6**).[36]

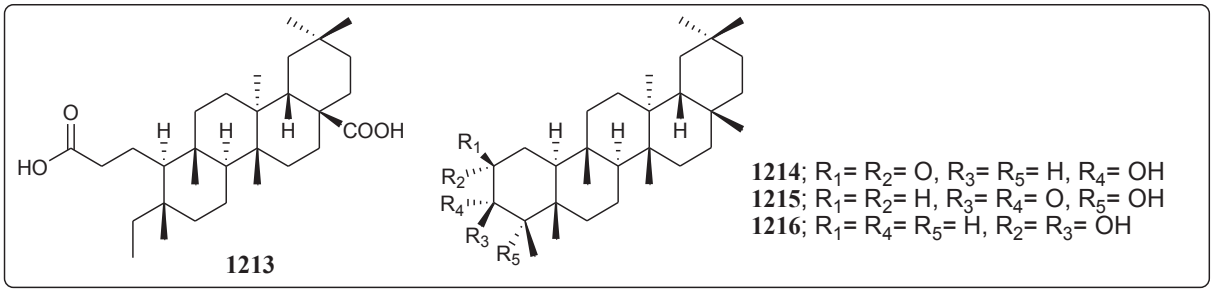


Figure 4.6 3,4-Secofriedelane-3,28-dioic acid (**1213**) and (**1214-1216**).

The stem and bark of the Mangrove plant *Hibiscus tiliaceus* was found to contain a number of A-ring modified friedelane triterpenoids (**115**, **1210**, **1214-1216**) (**Figure 4.6**).[37]

Lobatanhydride (**1217**) is the first example of a triterpenoid anhydride which contains a seven-membered A-ring. It was isolated, along with friedelin (**115**), 3α,25-dihydroxyfriedelan-2-one (**1218**) and 1β,25-dihydroxyfriedelan-3-one (**1219**), 2α-hydroxy-3-oxofriedelan-30-oic acid (**1220**), 28-hydroxyfriedelane-1,3-dione (**1221**), and 29-hydroxyfriedelane-1,3-dione (**1222**) (**Figure 4.7**) from *Crossopetalum lobatum* Lundell.[38]

1,2-Dehydro-2,3-secofriedelan-3-oic acid (**1223**), 1β-hydroxyfriedelin (**1224**), and 3β-hydroxyfriedelan-23-oic acid (**1225**) and friedelin-3,4-lactone (**1226**) were isolated from the leaves of *Garcia pariflora* (**Figure 8**).[39] A number of derivatives (**1208**, **1227-1234**) of **1224** were then prepared using various oxidation, reduction and esterification strategy (**Scheme 4.1**). Cytotoxicity of the synthetic as well as the natural compounds was also tested against human cancer cell lines U251, PC-3, K562, HCT-15, MCF-7 and SKLU-1.

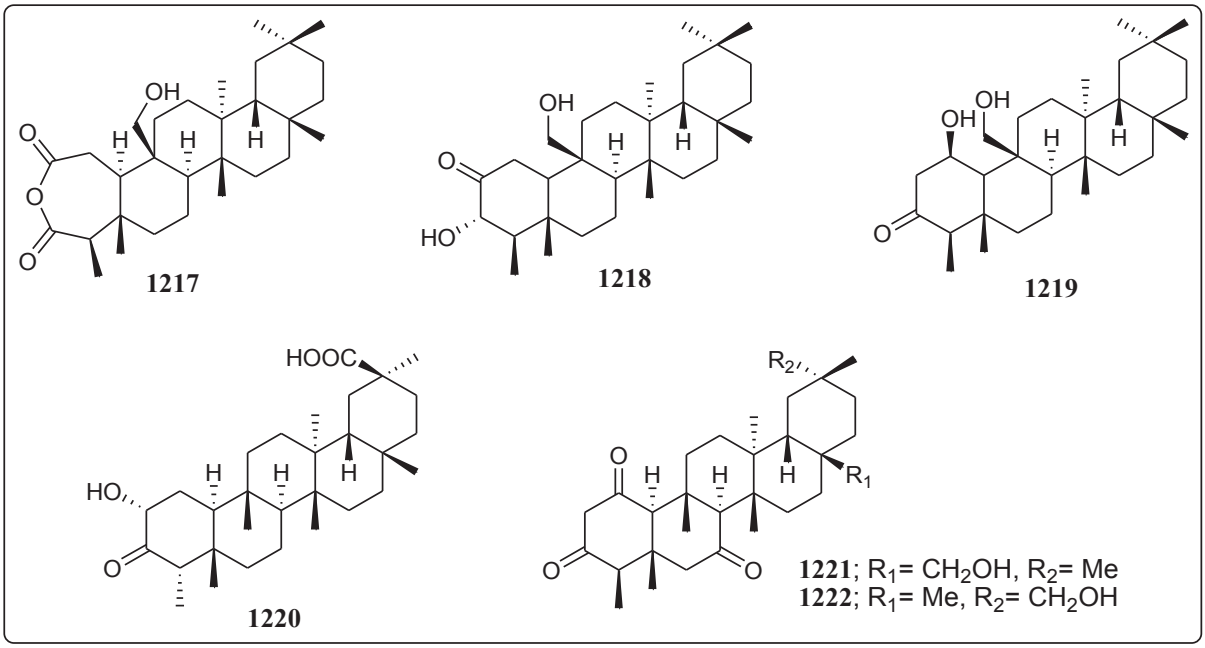
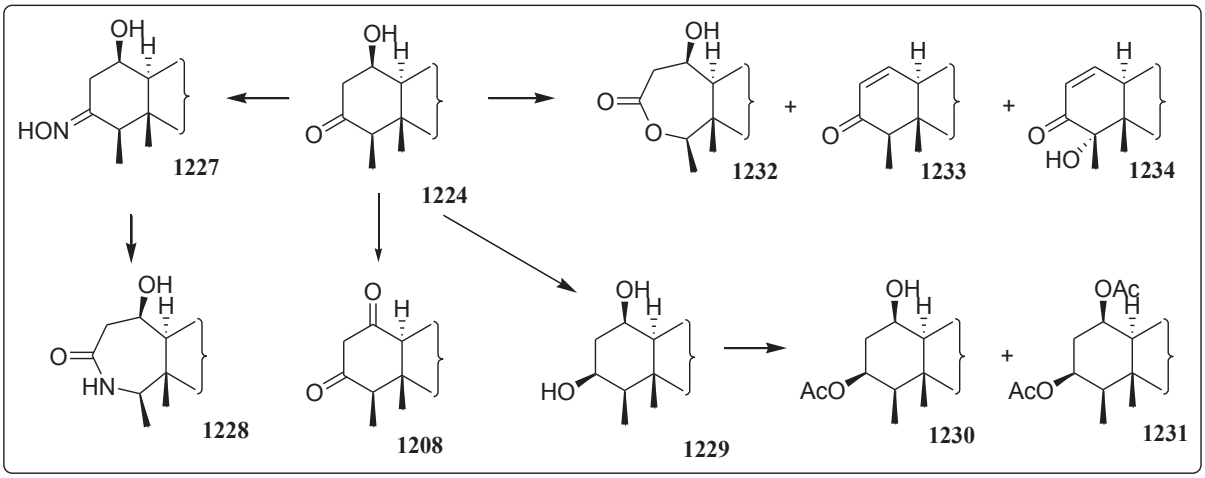


Figure 4.7 Lobatanhydride (**1217**), 3α,25-dihydroxyfriedelan-2-one (**1218**), 1β,25-dihydroxyfriedelan-3-one (**1219**), 2α-hydroxy-3-oxofriedelan-30-oic acid (**1220**), 28-hydroxyfriedelane-1,3-dione (**1221**) and 29-hydroxyfriedelane-1,3-dione (**1222**).



Scheme 4.1 Derivatives of **1224** [1]

[1] Details of scheme, ref. 39.

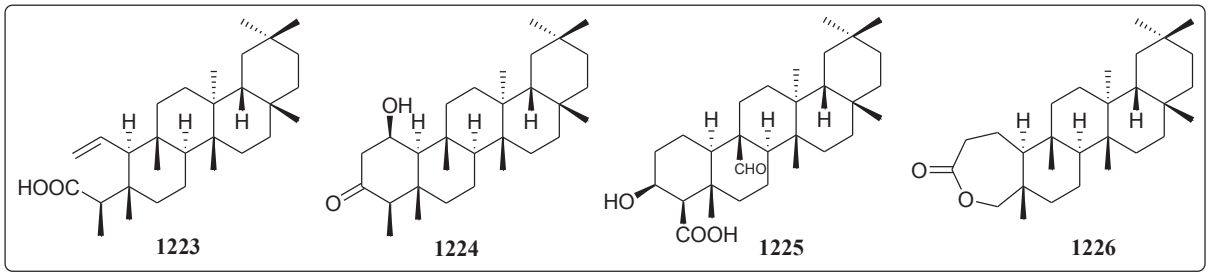


Figure 4.8 1,2-Dehydro-2,3-secofriedelan-3-oic acid (**1223**), 1β-hydroxyfriedelin (**1224**), 3β-hydroxyfriedelan-23-oic acid (**1225**), friedelin-3,4-lactone (**1226**).

Very recently, Liu and his group isolated three novel norfriedelanes (**1235-1237**) (**Figure 4.9**) from the branches and roots of *Malpighia emarginata*. Among them norfriedelanes **1235** and **1237** were found to show acetylcholine esterase inhibitory effects having IC_{50} values of 10.3 and 28.7 μM, respectively.[40]

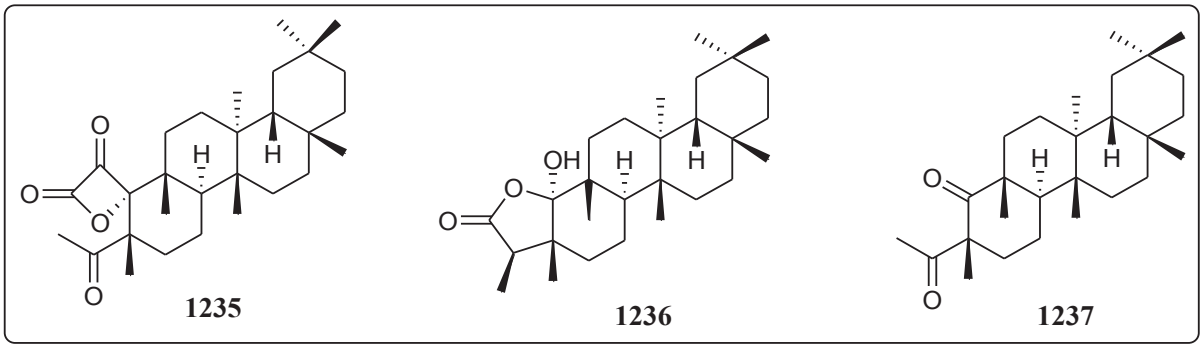


Figure 4.9 Structures of norfriedelanes **1235-1237**.

Friedelin (**115**), 29-hydroxymethyl friedelin (**1238**) and 3,4-seco-friedelan-3-oic acid (**1239) (Figure 4.10**) were isolated from the bark extract of Chinese *Heritiera littoralis*.[41]

Luis and his group isolated a friedo-olean triterpenoid, from the root extract of *Schaefferia cuneifolia,* which was proved structurally to be 2-oxofriedoolean-3-en-29-oic acid (**1240**).[42] The corresponding methyl ester derivative (**1241**) was also prepared (**Figure 4.10**).

The choloroform extract of *Tripterygium wilfordii* was found to contain salaspermic acid (**1242**, **Figure 4.10**), a friedelane triterpene acid. The compound resulted the inhibition of HIV

replication in H9 lymphocytes with an IC_{50} value of 5 μg/mL (10 μM), and the inhibition of uninfected H9 cell growth had an IC_{50} value of 53 μM.[43]

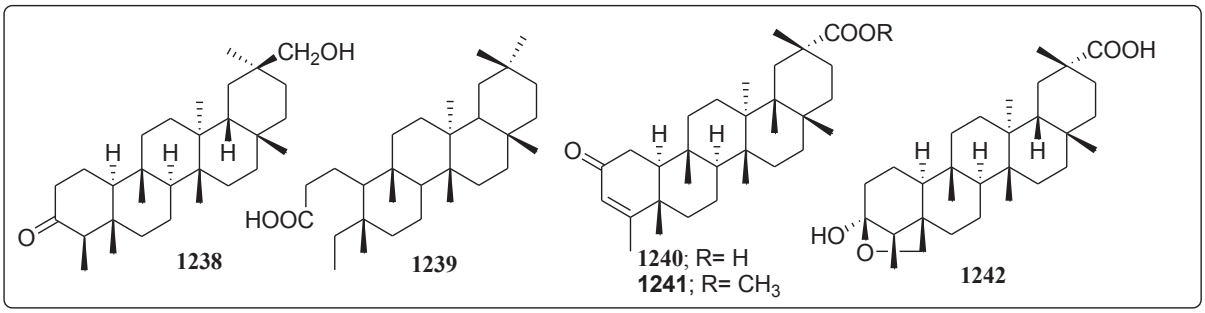


Figure 4.10 29-Hydroxymethyl friedelin (**1238**), 3,4-Seco-friedelan-3-oic acid (**1239**), 2-oxofriedoolean-3-en-29-oic acid (**1240**), its methyl ester derivative (**1241**) and salaspermic acid (**1242**).

In addition, among the large number of natural A-ring modified friedelane triterpenoids, 2α,3β-dihydroxyfriedelan-28-oic acid (**1243**) from the leaves of *Marila pluricostata*,[44] 2β-hydroxy-3-oxofriedelan-30-oic acid (**1244**) from *Dichapetalum barteri*,[45] Dzununcanone (**1245**), a 3,24-dinor-2,3-seco-friedelane derivative from *Hippocrate excels,*[46] **1246** from *Passiflora wilsonit*[47] were isolated. Other norfriedelane derivatives such as trifloralactone **1247** and triptocalline B **1248** were isolated from *Microtropis triflora,*[48] and milicifolines A–D (**1249-1252)** from *Maytenus ilicifolia.*[49] Milicifolines B (**1250)** and -C (**1251)** related to the cheiloclines were also reported by the same group in 2005. (**Figure 4.11)**

Besides the wide distribution of friedelane triterpenoid in the plant origin, the fermented broth of the fungus *Leptosphaeria maculanns* was found to contain euphorcinol (**1253**) and this was actually the first report of the occurrence of a friedelane triterpenoid in fungi (**Figure 4.11**).[13] Compound **1254** (**Figure 4**.**12**) was also found in marine endophytic fungus.[14]

IV.A.2 Synthetic A-ring modified friedelane triterpenoids

Chemical transformation is a very important useful tool in organic chemistry towards a number of diverse attempts including structural elucidation, structural modification, target-based structure-synthesis (semisynthesis and total synthesis), evaluation of the scope and limitations of a reaction/ reagent, etc. And it is very much obvious that these all imply enriching chemistrty to lead humans and their sourroundings toward a better existence from all the directions starting from food to technology and health to healthy imagination!

Besides the natural friedelane triterpenoids, a number of synthestic derivatives have so far been reported which include numerous transformative protocols. Though many transformations include different strategies (viz., oxidation, reduction etc.) simultaneously, herein an attempt is made to arrange the main transformative reactions under some different suitable titles.

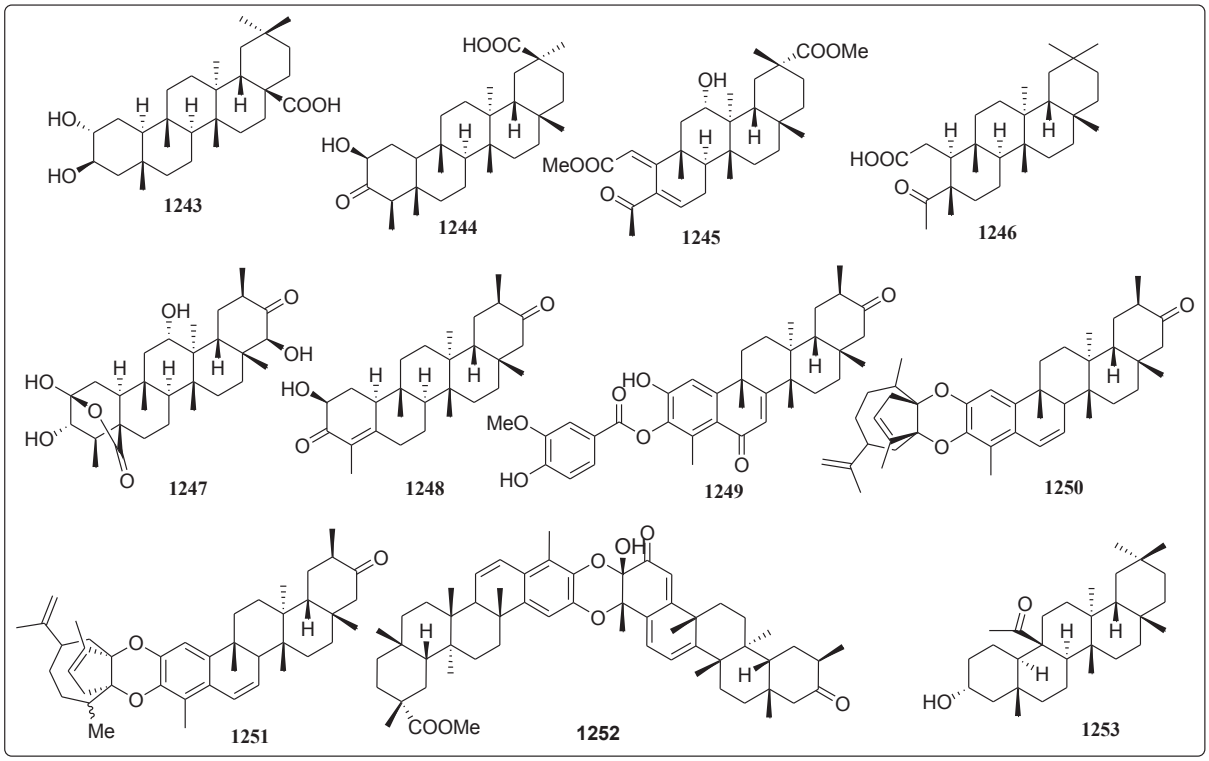


Figure 4.11 2α,3β-Dihydroxyfriedelan-28-oic acid (**1243**), 2β-hydroxy-3-oxofriedelan-30-oic acid (**1244**), dzununcanone (**1245**), trifloralactone **1246**, triptocalline B **1247,** triptocalline B **1248,** milicifolines A–D (**1249-1252)** and euphorcinol (**1253**).

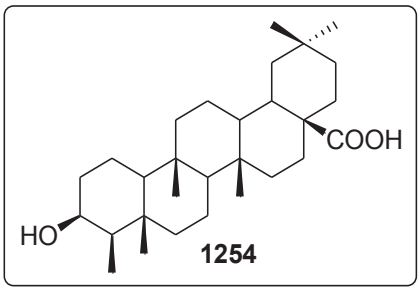
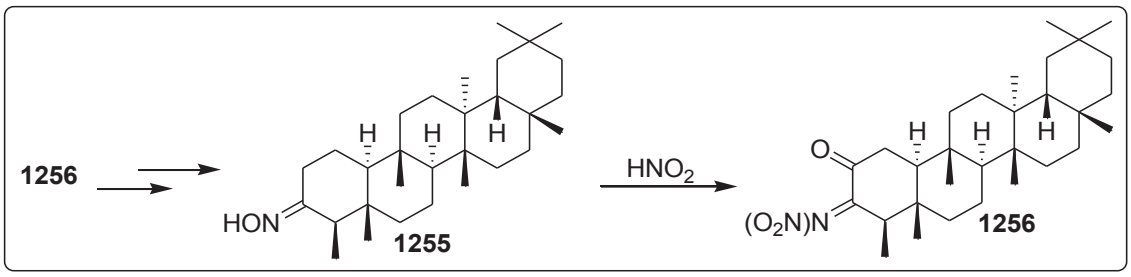


Figure 4.12 Compound **1254**.

IV.A.2.1 Oxidative transformations

Stevenson, in 1961, described a convenient isolation method for friedelin from cork smoker wash solids. He prepared its oxime (**1255**) which on treatment with nitrous acid readily yielded compound **1256** (**Scheme 4.2**) which was converted again to friedelin by heating in aqueous dioxane.[50]



Scheme 4.2 Compound **1256.**

Chromic acid oxidation of friedelin to produce friedelonic acid[8,9] and dehydrogenation of one of the epimeric secondary alcohols (derived from reduction of friedelin) by selenium at 315°C to produce 1,2,7-trimethylnaphthalene, 1,2,8-trimethylphenanthrene and 1,8-dimethylpicene were studied earlier.[7] Oxidation of friedelin (**115**) yielded a dicarboxylic acid and anhydride of the acid on pyrolysis produced norfriedelanone (**1257**). This on reflux in glacial acetic acid with selenium dioxide gave norfriedelenone, established as A(1)-norfriedel-4(23)-en-3-one (**1258**) and more drastic oxidation with selenium dioxide in dioxane at 200°C furnished norfriedelendione[51-53] which was later identified as A(4)-nor-23-norfriededel-1(10)-ene-2,3-dione (**1259**) (**Figure 4.13**).[54]

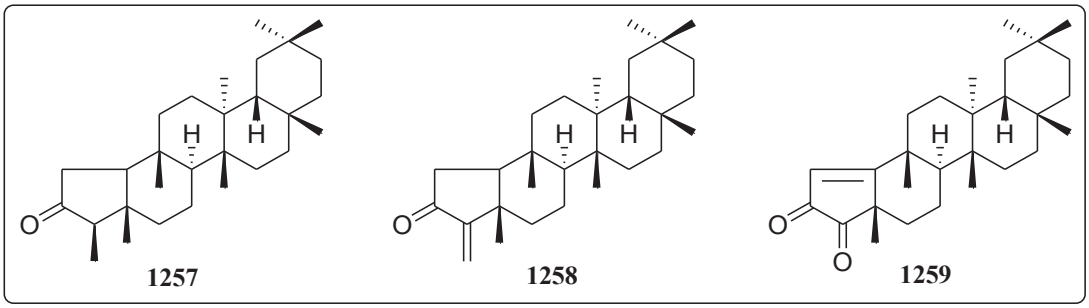
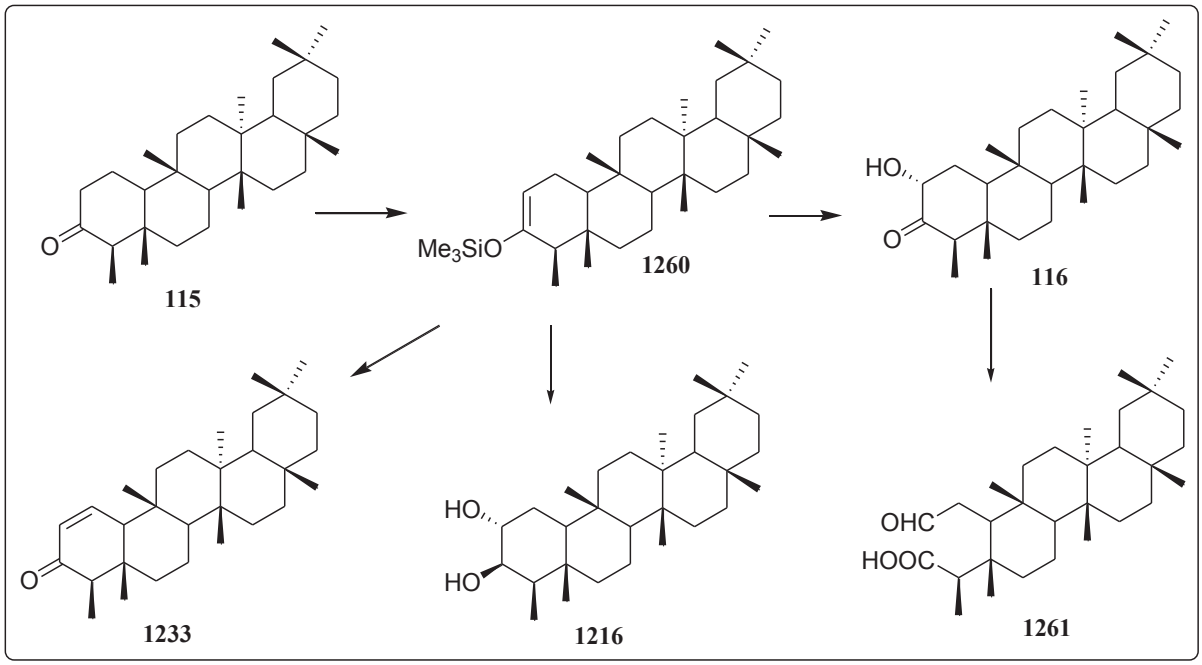


Figure 4.13 Norfriedelanone (**1257**), A(1)-norfriedel-4(23)-en-3-one (**1258**) and A(4)-nor-23-norfriededel-1(10)-ene-2:3-dione (**1259**).

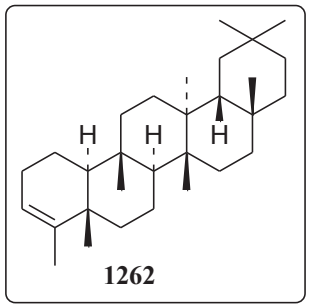
In another set of reactions, controlled silylation first transformed friedelin (**115**) into 3-trimethylsiloxyfriedel-2-ene (**1260**) in high yields. The silyl ether **1260** was then oxidized with OsO_4/NMMO to produce 2α-hydroxyfriedelan-3-one (another natural friedelane triterpenoid known as cerin, **116**) which by periodic acid oxidation resulted 2,3-secofriedelan-2-al-3-oic acid (**1261**). On the other hand, oxidation of **1260** with DDQ afforded friedel-1-en-3-one (**1233**). Compound **1260** on reductive ozonolysis furnished 2α,3β-dihydroxyfriedelane, also known as pachysandiol A (**1216**). The seco-acid **1261** was found to be a potent inhibitor of human lymphocyte proliferation (IC_{50} 10.7 μM) and of the growth of a human cancer cell line (GI_{50} 5.4-17.2 μM) (**Scheme 4.3**).[55]



Scheme 4.3 Silylation of friedelin leading to different friedelane derivatives (Ref. 78).

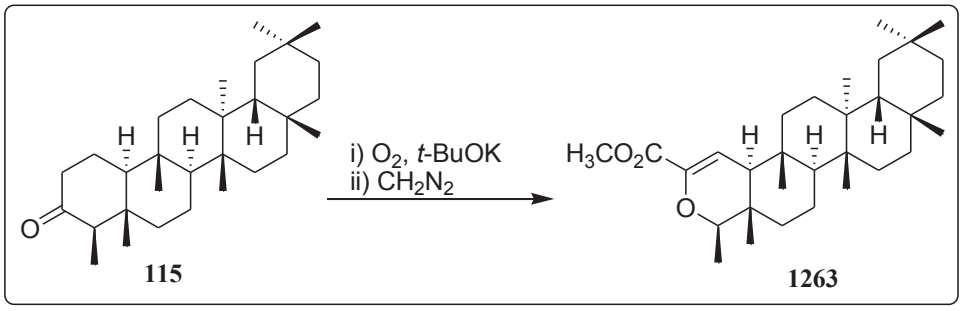
Brownlie, Spring, Stevenson and Strachan in their thorugh study with friedelin revealed that dehydration of friedelanol produces an unsaturated hydrocarbon, friedel-3-ene (**1262**) (**Figure 4.14**).[12] Again, an unsaturated ester **1263** was isolated by the oxidation of friedelin (**115**) with potassium *tert*-butoxide followed by treatment with diazomethane (**Scheme 4.4**).[56]

LTA/I_2 (Lead tetraacetate/iodine) oxidized 3β-Hydroxy friedelane (**1210**) in dry benzene to furnish a tetrahydropyridine **1264**, an iodo-ether **1265** and an α-acetoxytetrahydrofuran **1266** derivatives (**Figure 4.15**).[57]



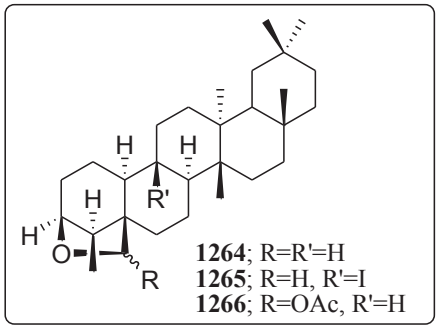
1262

Figure 4.14 Friedel-3-ene (**1262**).



115 **1263**

Scheme 4.4 Treatment of friedelin (**11**) with *t*-BuOK and diazomethane.



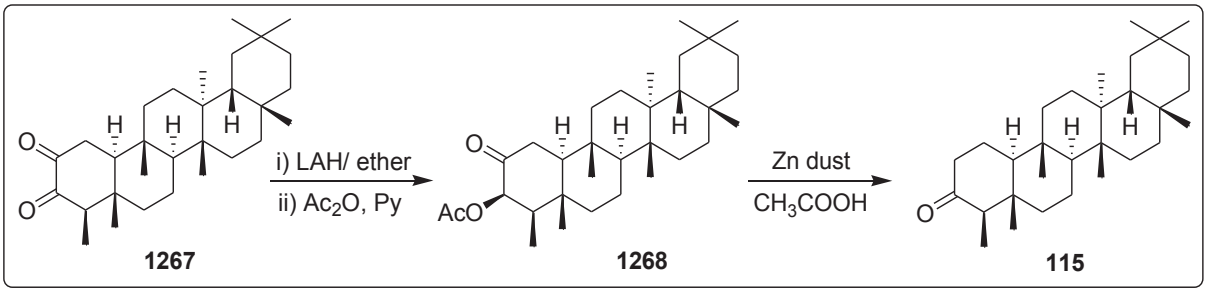
1264; R=R'=H
1265; R=H, R'=I
1266; R=OAc, R'=H

Figure 4.15 Tetrahydropyridine **1264**, iodo-ether **1265** and α-acetoxytetrahydrofuran **1266**.

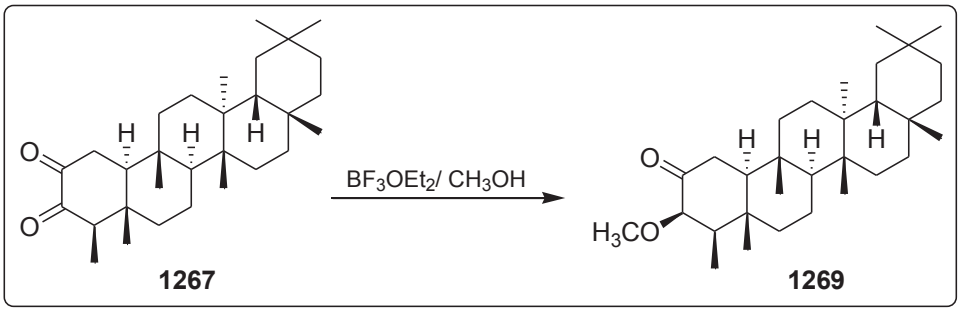
IV.A.2.2 Reductive transformations

Kane and Stevenson, in 1960, isolated friedelane-2,3-dione (**1267**) from cork smoker wash solids and they characterized it as monoacetate, monobenzoate, monomethyl and quinoxaline derivatives. Friedelane was isolated from 2,3-dione **1267** by following the Huang-Minlon reduction condition whereas selective reduction was found able to produce friedelin (**Scheme**

4.5). The monomethyl ether **1269** was obtained from friedelane-2,3-dione (**1267**) by refluxing it with boron trifluride etherate in methanol solution (**Scheme 4.6**).[58]



Scheme 4.5 Conversion of friedelane-2,3-dione (**1267**) to friedelin (**115**).

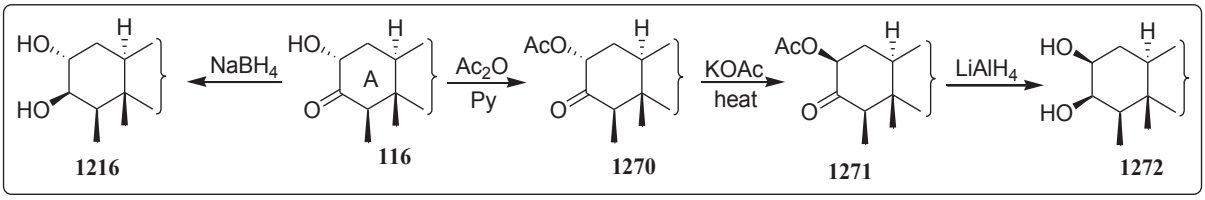


Scheme 4.6 Conversion of friedelane-2,3-dione (**1267**) to 3-methoxy-2-oxofriedelane (**1269**).

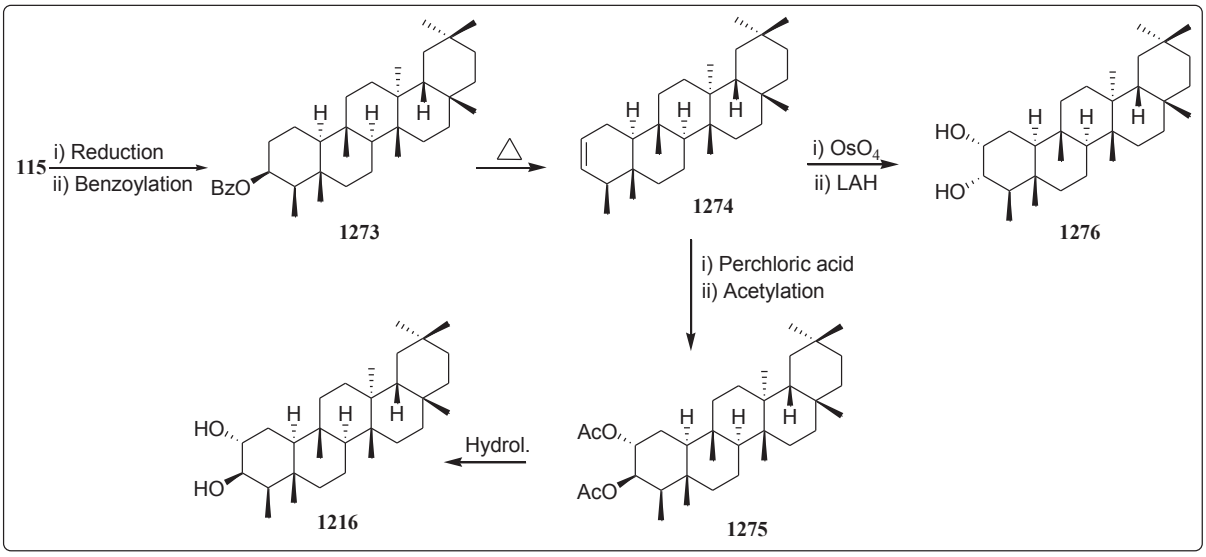
IV.A.2.3 Transformations based on both oxidation and reduction reactions

Cerin (**116**) was primarily assumed to be 2β-hydroxyfriedelin, which was later on proved, by Stevenson and his group, actually to be the 2α-hydroxy isomer.[59] They reduced cerin (**116**) with sodium borohydride and thus isolated 2α,3β-dihydroxy friedelane (**1216**) which is indeed a natural friedelane triterpenoid named as pachysandiol-A. When cerin, after acetylation, was allowed for prolonged heating with potassium acetate, 2β-acetoxyfriedelin (**1271**) was isolated which on reduction with lithium aluminium hydride produced 2β,3β-dihydroxy friedelane (**1272**). Friedelin (**115**) was also converted to friedelane-3β-yl benzoate (**1273**) by reduction followed by benzoylation. On pyrolysis, this benzoate produced friedel-2-ene (**1274**) which upon treatment with *m*CPBA, followed by perchloric acid treatment and acetylation resulted the diacetate of pachysandiol-A (**1275**). And then diol **1216** was again formed by hydrolyzing the diacetate. On the other hand, 2α,3α-dihydrxyfriedelane (**1276**) was prepared from friedel-2-ene

(**1274**) by the action of osmium tetraoxide, followed by cleavage of the ester by lithium aluminium hydride (**Scheme 4.7** and **Scheme 4.8**). Thus analyzing and comparing all the results, cerin was established as 2α-hydroxyfriedelin.[59]



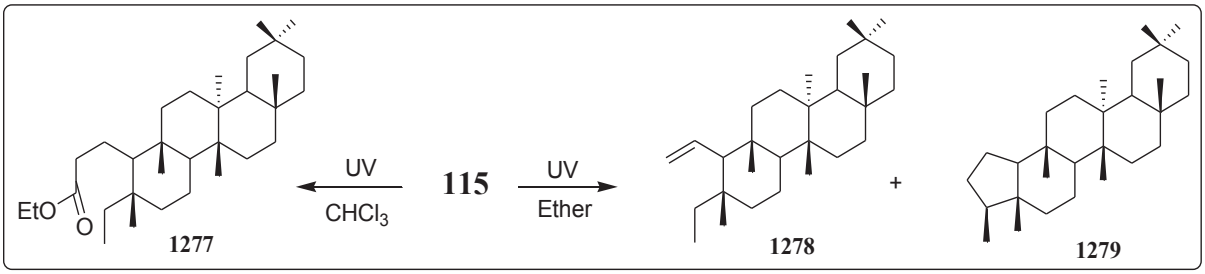
Scheme 4.7 Transformation of cerin (**116**) into different dihydroxy derivatives.



Scheme 4.8 Transformation of friedelin into different dihydroxy derivatives.

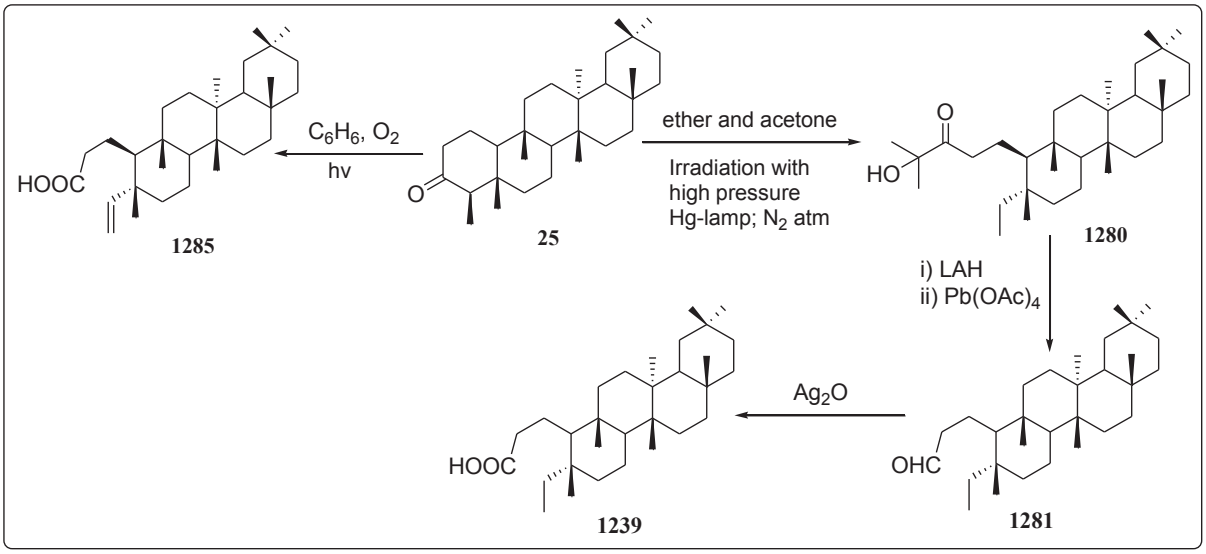
IV.A.2.4 Photochemical transformations

Stevention and his group showed that the ultraviolet irradiation of friedelin (**115**) was able to result different products depending on the solvents. In ether solution, they isolated 5-ethyl-10β-vinyl-des-A-friedelane (**1277**) and norfriedelane (**1279**) whereas in chloroform solution, ethyl 3,4-secofriedelane-3-oate (**1278**) was found to be produced. Corresponding acid and the alcohol were also produced from the ethyl ester of the seco acid **1278** by following hydrolysis and reduction, separately (**Scheme 4.9**).[60]



Scheme 4.9 Ultraviolet irradiation products of friedelin in ether and in chloroform.

Phototransformative reactions on friedelin were also carried out by many other research groups.[61] Shirasaki, Tsuyuki, Takahashi and Stevenson irradiated friedelin (**115**) with a high pressure mercury lamp under nitrogen atmosphere in a quertz vessel in ether containing acetone. The isolated product was A-seco keto-ol **1280** which was successively treated with LAH and $Pb(OAC)_4$ to result seco-aldehyde **1281** which was further oxidised with Ag_2O to yield the seco-acid **1239** and the successive transformations, in fact, confirmed compound **1280** structurally as 5α-ethyl-10β-(4-hydroxy-4-methyl-3-oxopentyl)-des-A-friedelane.[62] The other major a-ring modified friedelane triterpenoids which were produced photochemically are 2-oxo-3-oxa-friedelane (**1282**),[63] epoxyfriedelane (**1283**),[64,65] 3β-hydroxy friedelane (**1210**) and 3α-hydroxy friedelane (**1211**),[66,67]and 4-*epi*friedelin (**6**) and 4-*epi*shionone (**1284**),[68,69] and some nitrogen containing friedelanes.[70] A one-step synthesis of putranjivic acid (**1285)** was also accomplished by following a photochemical oxidation of friedelin, in benzene under oxygen (**Scheme 4.10** and **Figure 4.16**).[71]



Scheme 4.10 Photochemical reactions on friedelin (**115**).

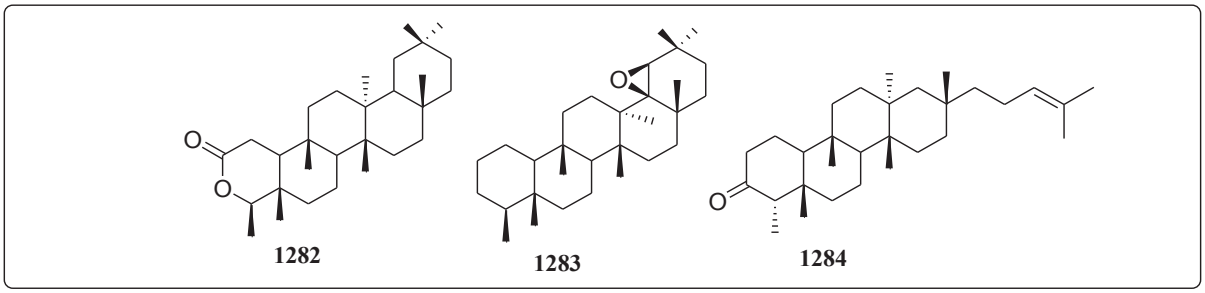


Figure 4.16 2-Oxo-3-oxa-friedelane (**1282**), epoxyfriedelane (**1283**), and 4-*epi*shionone (**1284**).

IV.A.2.5 Rearrangement-based transformations

The transformation of α-amyrine or β-amyrine (**1286**) into friedelin (**115**) was explained by a series of consecutive 1,2-rearrangements of methyl groups and hydrogens (**Figure 4.17**). Reduction of friedelin (**115**) with lithium aluminum hydride produces 3β-hydroxy friedelane (**1210**). Treatment of **1210** with hydrogen chloride in phenol at 110^{o}C caused a remarkable multi-group rearrangement which afforded olean-l3(18)-ene (**1287**). Oleanene **1287** was again prepared from α- or β-amyrine by a set of consecutive reactions viz., oxidation, Wolff-Kishner reduction and acid catalysed isomerization (**Scheme 4.11**)[72]

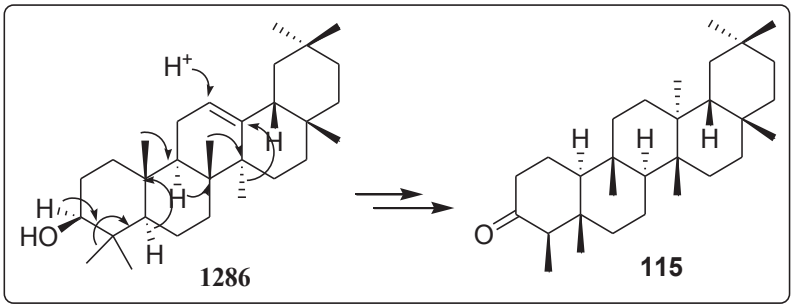
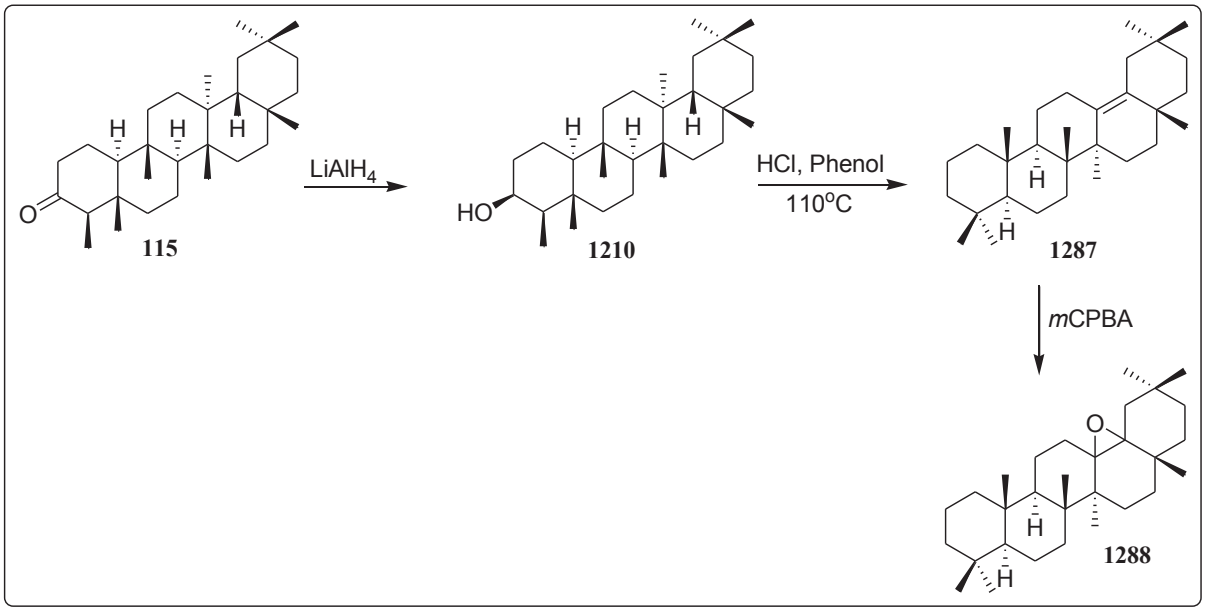


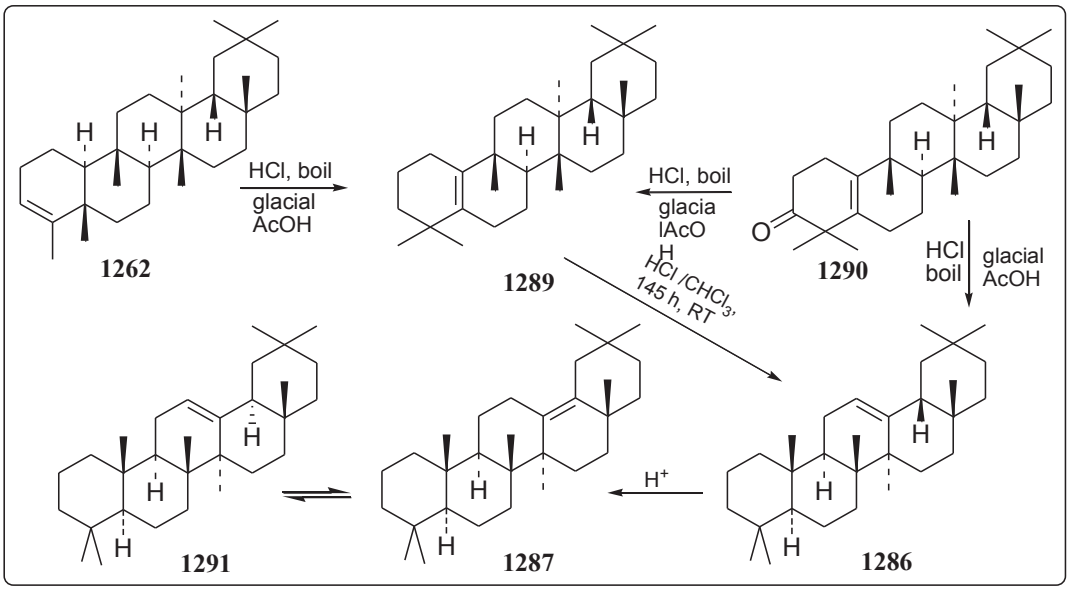
Figure 4.17 β-Amyrine (**1286,** arrows show the consecutive 1,2-rearrangements toward friedelin).

When friedel-3-ene (**1262**) in boiling acetic acid was treated with hydrogen chloride, glutin-5(10)-ene (**1289**) was obtained. This on vigorous acid treatment yielded a mixture of olean-l3(18)-ene (**1287**) and 18α-olean-12-ene (**1291**). Glutin-5(10)-en-3-one (**1290**) on several hours of treatment with HCl in boiling glacial acetic acid produced a mixture of glutin-5(10)-ene (**1289**) and olean-12-ene, i.e.; β-amyrine (**1286**). Glutin-5(10)-ene (**1289**) after 145 hrs of

treatment with HCl in chloroform at room temperature yielded olean-12-ene (**1286**), though **1286** itself remained unaffected by the same condition. (**Scheme 4.12**).[12,73,74]

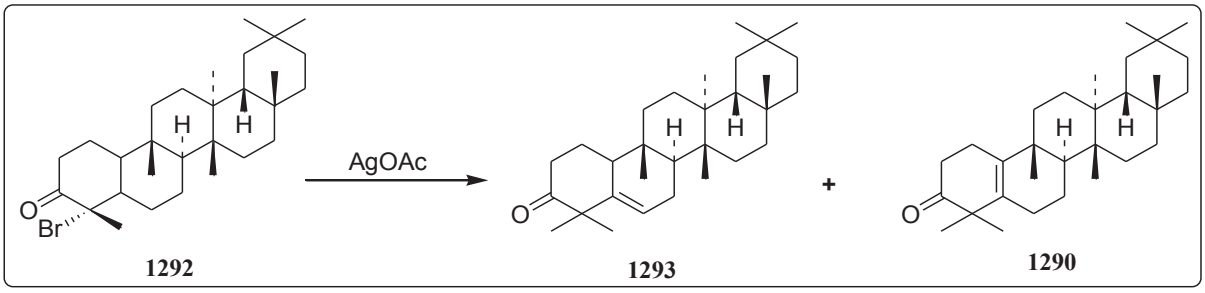


Scheme 4.11 Friedelin (**115**) to olean-l3(18)-ene (**1287**).



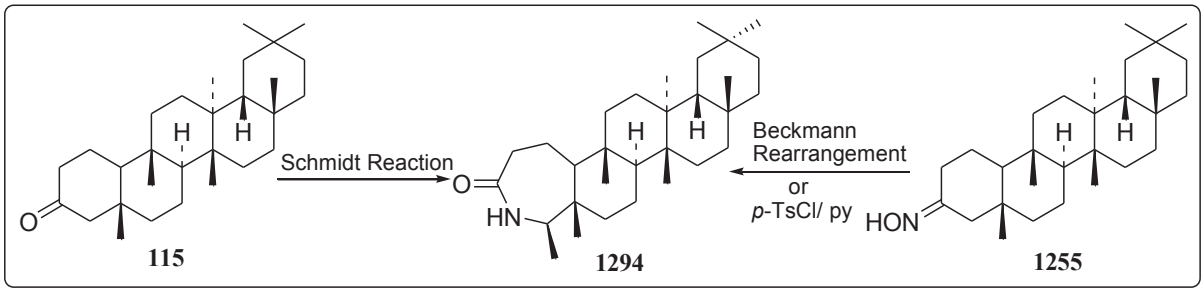
Scheme 4.12 Friedelene-oleanene rearrangement.

The action of silver acetate on 4α-bromofriedelin (**1292**) was reported to yield a a mixture of rearranged friedel-en-ones **1293** and **1290** (**Scheme 4.13**).[75]



Scheme 4.13 Molecular rearrangement of 4α-bromofriedelin (**1292**) by silver acetate.

Drake and Shrader reported the Beckmann rearrangement of friedelin oxime (**1255**)[6] and the structure was established actually as 4-aza-A-homofriedelan-3-one (**1294**) by Stevenson in the year 1963.[76] He also isolated the same product by the treatment of *p*-tolunesulfonyl chloride on the oxime in pyridine solution. The same product was also isolated by applying the Schmidt reaction condition on friedelin (**115**) (**Scheme 4.14**).[76]



Scheme 4.14 4-Aza-A-homofriedelan-3-one (**1294**) from both friedelin oxime (1**255**) and friedelin (**115**).

IV.A.2.6 Transformative reactions of bromo-friedelane triterpenoids

Friedelin (**115**) yielded 4α-bromofriedelin (**1292**) on treatment with *N*-bromosuccinimide in CCl_4,[77] but produced 2α-bromofriedelin (**1295**) by either monobromination with bromine in $CHCl_3$ in presernce of HBr[10] or, base catalysed monobromination in acetic acid or by treatment with pyridinium bromide-dibromide in acetic acid.[78] Again, friedelin (**115**) when treated with HBr in $CHCl_3$, 2α,4α-dibromo friedelin (**1296**) was produced[10] which was transformed readily into the more stable 2α,4β-dibromo isomer (**1297**) in HBr-AcOH at 20°C.[75,79] The 2α,4α-

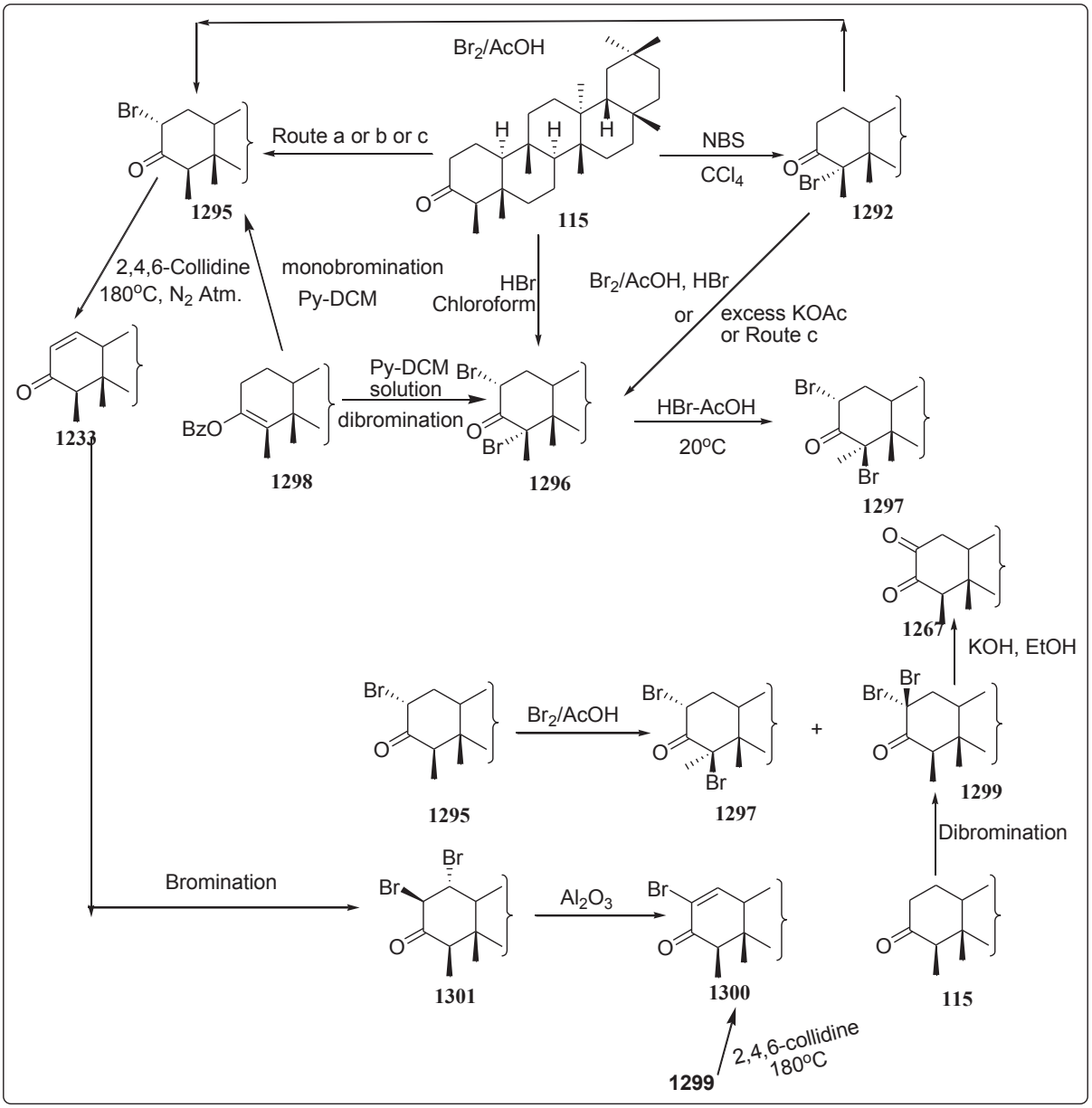
dibromo derivative **1296** was also obtained from the 4α-bromo compound **1292** by either the treatment of Br_2 in acetic acid in presence of HBr or with excess potassium acetate, and again from the enol benzoate derivative of friedelin (**1298**) by dibromination in pyridine-dichloromethane solution.[78] 2α-Bromo derivative **1295** was also the other product obtained in the last process.[78] 4α-Bromofriedelin (**1292**) when treated with Br_2 in acetic acid yielded 2α-bromofriedelin (**1295**)[78,79] which when treated again with the same reagent formed either 2α,4β-dibromo friedelin (**1297**) or 2,2-dibromo friedelin (**1299**), as was assumed by Djerassi et al.,[80] though Shoppee and Johnston obtained the latter compound by the same process and also by dibromination of friedelin (**115**).[78] This 2,2-dibromo compound when refluxed with KOH in ethanol yielded the 2,3-diketo derivative (**1267**),[77] identical with that obtained from cerin (**116**) by chromium trioxide oxidation in acetic acid.[51]Again, this 2,2-dibromo compound upon treatment with 2,4,6-collidine at 180^{o}C resulted 2α-bromo friedel-1-ene-3-one (**1300**). The same reagent under nitrogen atmosphere converted 2α-bromo derivative into friedel-1-ene-3-one (**1233**) and bromination of it followed by Al_2O_3 treatment resulted 2-bromofriedel-1-ene-3-one (**1300**) *via* 1α,2β-dibromo friedelin (**1301**).[78] All these transformations are illustrated in **Scheme 4.15**.

Pradhan et al. also reported a group of bromo- derivatives (**1299**, **1302-1306**) of friedelin, using NBS, and their associated rearrangements as shown below[81-83] (**Scheme 4.16**).

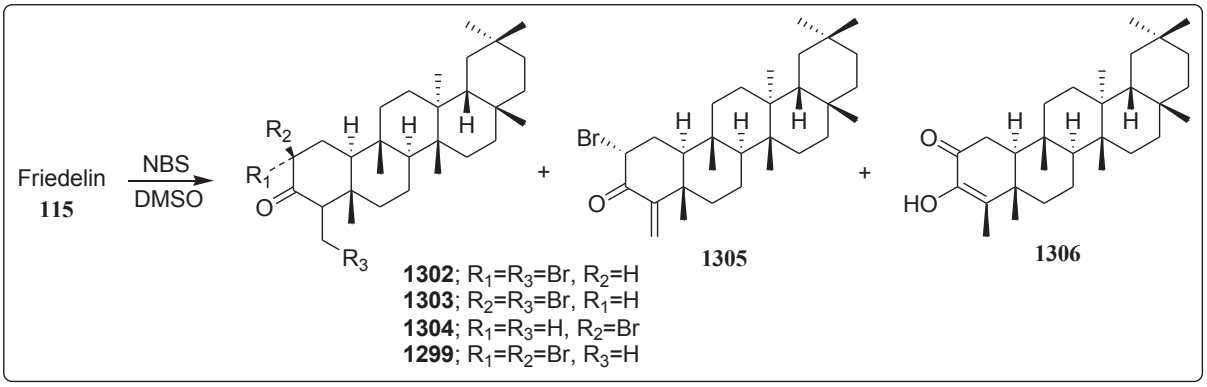
Kane and Stevenson also reported that friedel-18-ene-3-one (**1307**) was obtained by debromination of **1308** and **1309**, produced respectively from 2α-bromofriedelin (**1295**) and 4α-bromofriedelin (**1292**) by the action of NBS. And compound **1307** regenerated **1309** on treatment with NBS (**Scheme 4.17**).[77]

IV.A.2.7 Other transformations

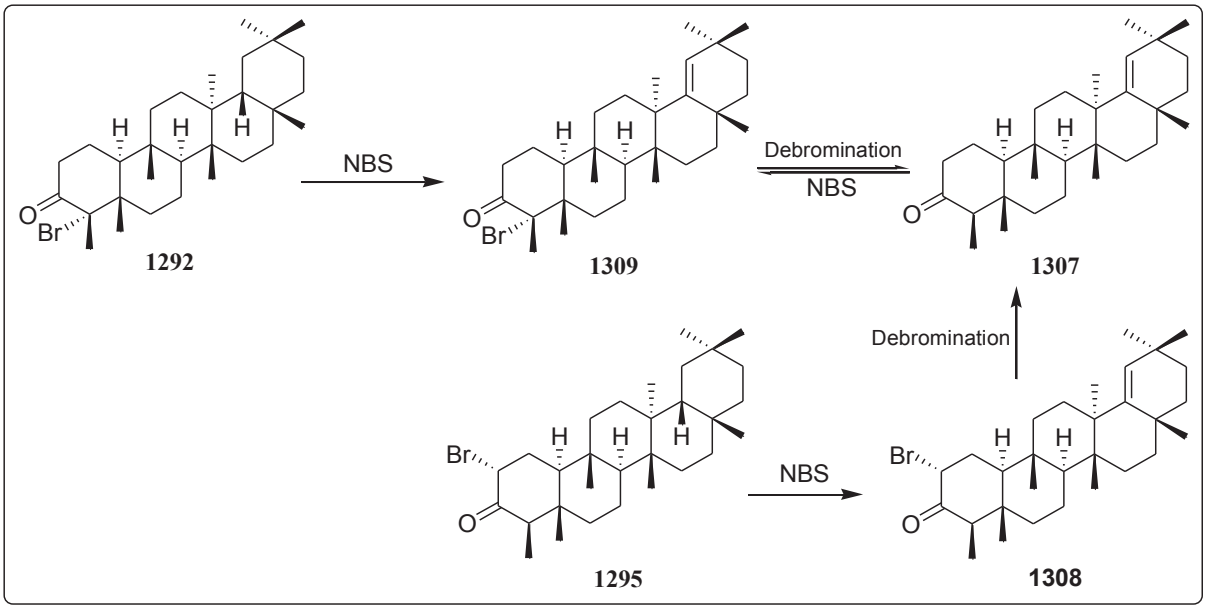
Amyrin (**1286**),[84] or a readily available tetracyclic triterpene[85] was the starting material for chemical synthesis of friedelin. A total synthesis of friedelin was accomplished successfully in 31 steps and at 0.3% yield by Ireland and Walba in 1976.[86]



Scheme 4.15 Synthetic routes of different bromo-derivatives of friedelin. [**Route a**: monobromination with Br_2 in chloroform in presence of HBr, **Route b**: base catalysed monobromination in AcOH and **Route c**: pyridinium bromide-dibromide in acetic acid.]

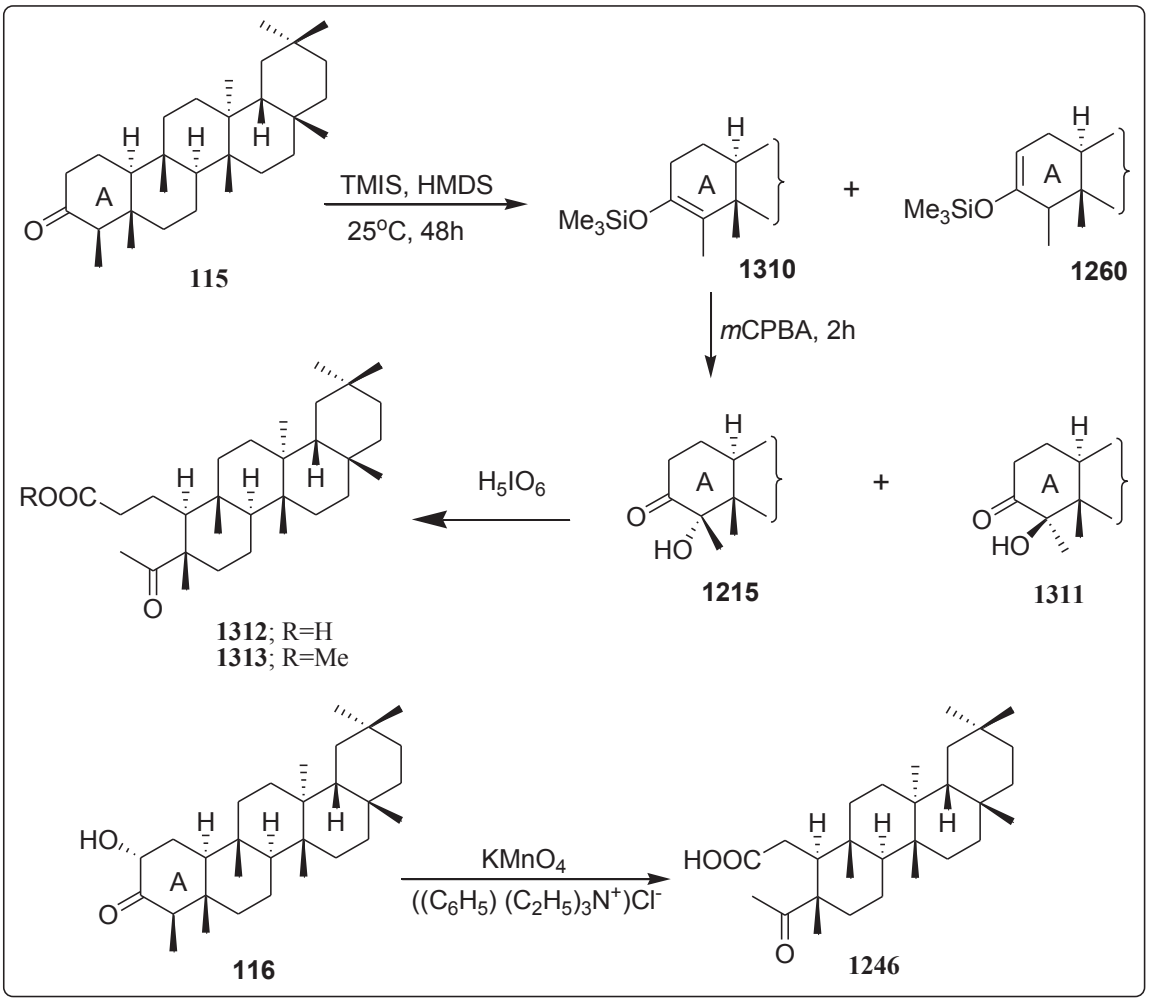


Scheme 4.16 NBS on friedelin.



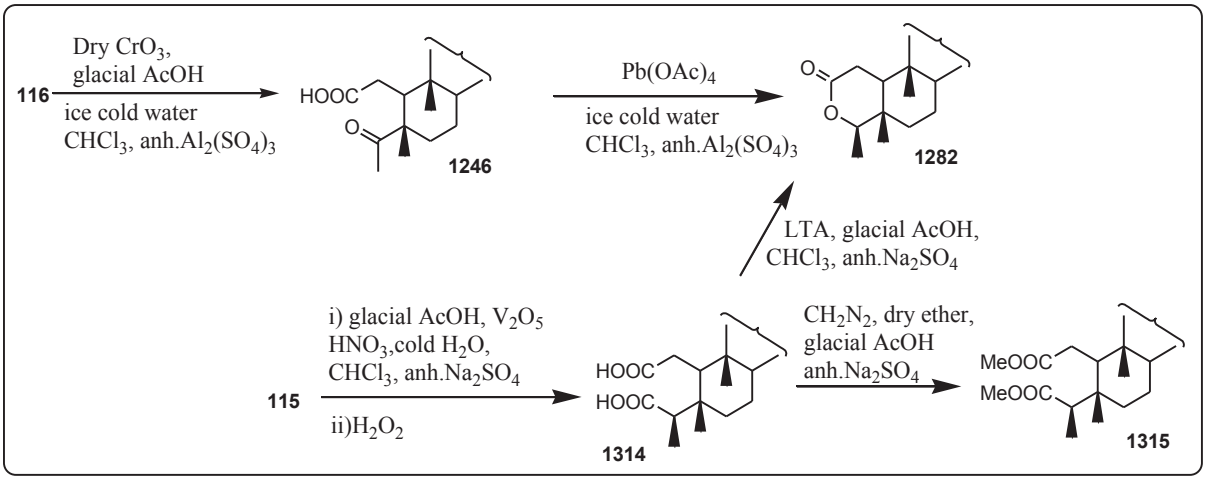
Scheme 4.17 Molecular rearrangements of bromo-derivatives of friedelin.

Moiteiro et al. synthesized secofriedelane triterpenoids stereoselectively in high yields. The ability of the compounds to inhibit the growth *in vitro* of three human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (nonsmallcell lung cancer), and SF-268 (CNS cancer) were evaluated and only compounds **11246**, **1312** and **1313** were found to possess significant growth inhibitory effects, exhibiting GI_{50} values that range from 24.6 to 32.8 μM and 10.9 to17.6 μM, respectively (**Scheme 4.18**).[87]



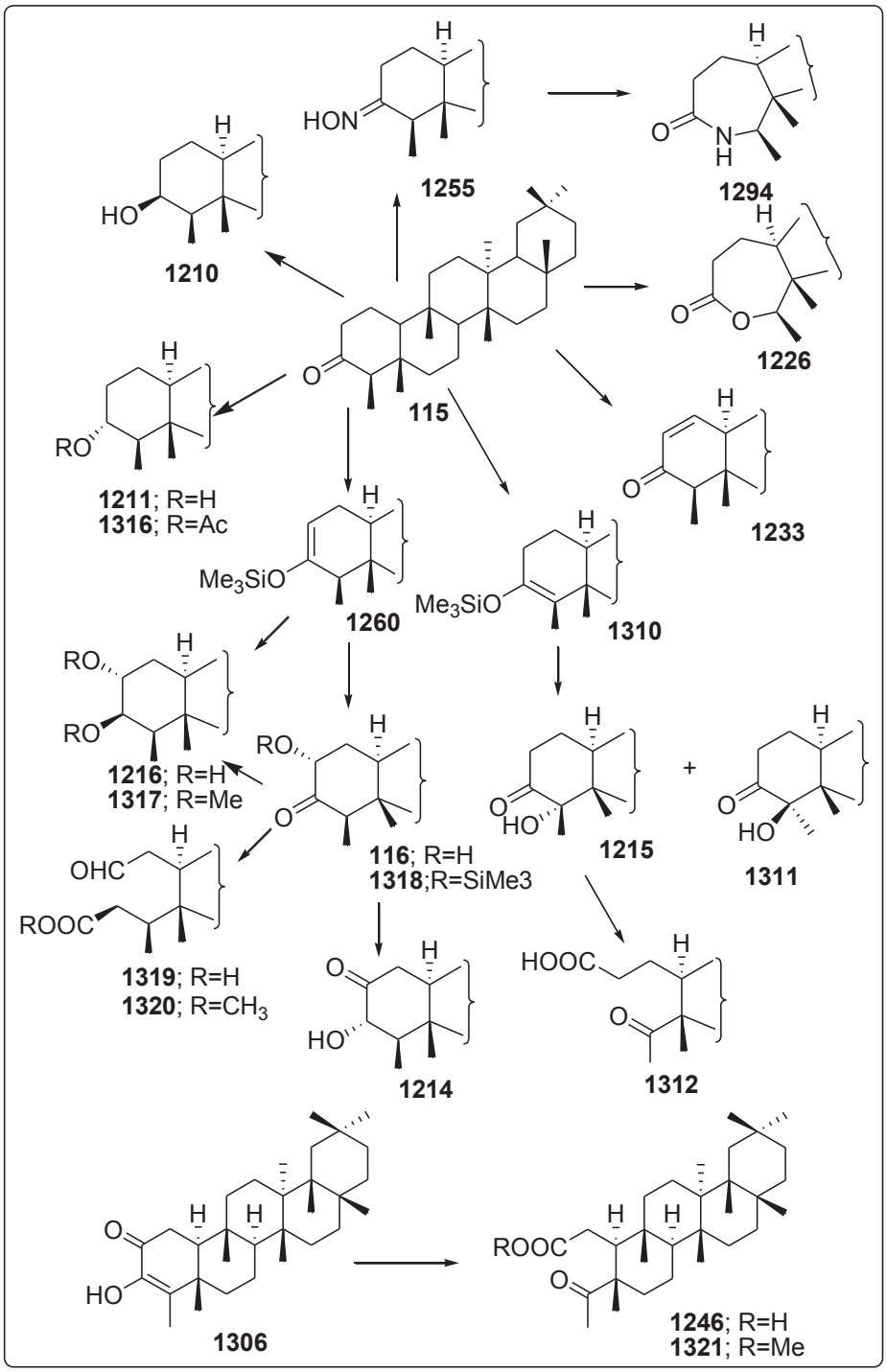
Scheme 4.18 A-ring modifications along with seco-friedelanes.

Our laboratory also has reported the synthesis of five oxygenated friedelane triterpenoids, four of them being seco derivatives. Lactone **1282** was synthesized both from cerin (**116**) and friedelin (**115**); seco dioic acid **1314** and its dimethyl ester (**1315**) were synthesised using friedelin (**115**); and seco keto acid **1246** and its methyl ester were prepared using cerin (**116**). The 3D molecular docking of the derivatives in the central catalytic domain of topoisomerase IIα (1bgw PDB for topoisomerase IIα) was also performed which described the binding nature and type of interactions between the enzyme and the synthesized friedelane triterpenoids and the topoisomerase IIα inhibitory activity was confirmed by *in vitro* experiments (**Scheme 4.19**).[88]



Scheme 4.19 Topoisomarase IIα inhibitory seco-friedelanes.

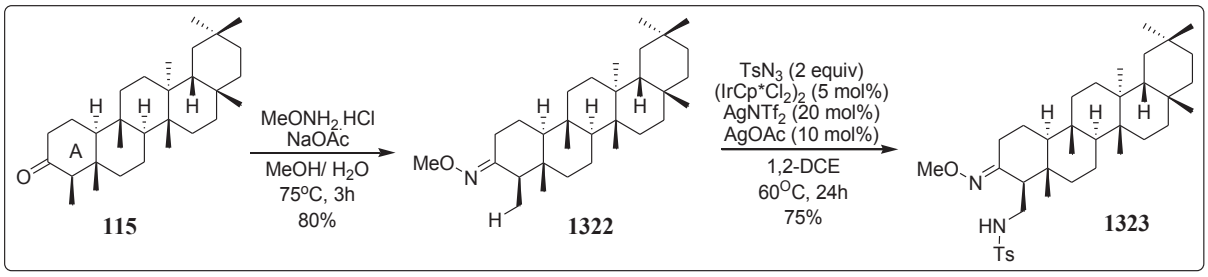
It was observed that in most of the studies, A-ring of friedelin was modified, though there are reports of changes in ring-B or even in ring C, D or E. A number of A-ring modified friedelin derivatives were found to possess potent biocidal activities as were studied by a large number of research groups. Synthesis, bioactivity screening and structure-activity relationships of various natural and synthetic triterpenoids such as friedelin (**115**), 2α-trimethylsiloxyfriedelan-3-one (**1318**), 3-hydroxyfriedel-3-en-2-one (**1306**), friedelin-2,3-lactone (**1226**), friedelin-3-oxime (**1255**) and friedelin-3,4-lactam (**1294**) were studied. Insecticidal and phytotoxic potential of these compounds, their selective cytotoxic effects on insect and mammalian cells, and their antiparasitic effects were also described. Structurally modified A-ring derivatives such as **116**, 2,3-secofriedelan-2-al-3-oic acid (**1319**), its acetylated derivative **1320**, 3β- and 3α-hydroxyfriedelane (**1210** and **1211**), 3α-hydroxyfriedel-2-one (**1214**), 4β-hydroxyfriedel-3-one (**1311**), 3,4-secofriedelan-4-oxo-3-oic-acid (**1312**), lactone **1226**, and the oxime **1255** were found to be stronger insecticides than the parent compound. Methyl-3-nor-2,4-secofriedelan-4-oxo-2-oic acid (**1246**) and its acetylated derivative **1321** also showed insecticidal activity in contrast to their inactive parent compound **1306**. The post ingestive effects and cytotoxicity of these compounds suggested a multifaceted insecticidal mode of action. These structural modifications did not result in better phytotoxic agents than the parent compounds except for lactam **1294** and yielded several moderately active antiparasite derivatives (seco acids **1319**, **1312**, **1321** and 4β-hydroxyfriedel-3-one **1311**) with cytotoxic effects on mammalian cells (**Scheme 4.20**).[89]



Scheme 4.20 Biologically active derivatives of friedelin.[2]

[2] Details of the scheme, ref. 89.

Very recently, in 2014, Kang et al. revealed a novel process of direct amidation of sp^3 C-H bonds and they applied the technique also on friedelin (**115**) (**Scheme 4.21**).[90]



Scheme 4.21 Direct amidation of unactivated 24-methyl on friedelin.

IV.A.2.8 Additional bioactivities and concluding remarks

Apart from these triterpenoids many more biologically potent derivatives of friedelane triterpenoids are also reported. Some of them are reproduced here in short.

A series of synthesized seco-friedelin triterpenoids were found to have moderate cytotoxicity and insecticidal activities.[91-93] Celastrol **117** (**Figure 4.18**) was found to have potent anti-inflammatory and neuroprotective effect and investigation was carried out for the treatment of *Parkinson's* and *Alzheimer's* diseases. Anticancer activity of this compound was also tested for different tumor cell lines, as well as in preclinical animal model.[94-102]

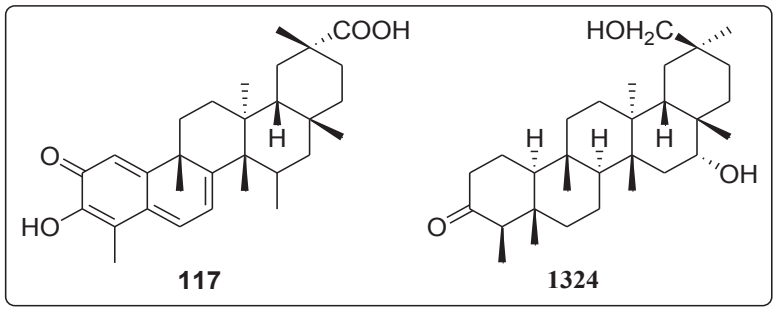


Figure 4.18 Potent A-ring modified friedelane-based drugs: Celastrol (**117**) and celasdin B (**1324**).

Another biologically important friedelane triterpenoids is celasdin B (**1324**) (**Figure 18**). From the biological evaluation, compound **1324** was found to exhibit anti-HIV replication activity in H9 lymphocyte cells with an EC_{50} value of 0.8 mg/ml.[103]

Friedelin (**115**) was found to be capable of binding the human receptors for endothelin A (ETA) and angiotensin 1 (AT1)[104] and it also showed significant protective activities under different conditions, against AA, CCl_4, $CdCl_2$ induced hepatotoxicity or in the case of cyclophosphamide, cardiotoxicity, in mouse or rat models.[105-110]

Against *Staphylococcus aureus*, Netzahualcoyone (**1325**, **Figure 4.19**) exhibited stronger inhibitory activity (with a MIC value of 1.5– 1.6 mg/ml) in comparison to some of the antibiotics used in clinical practice.[111]

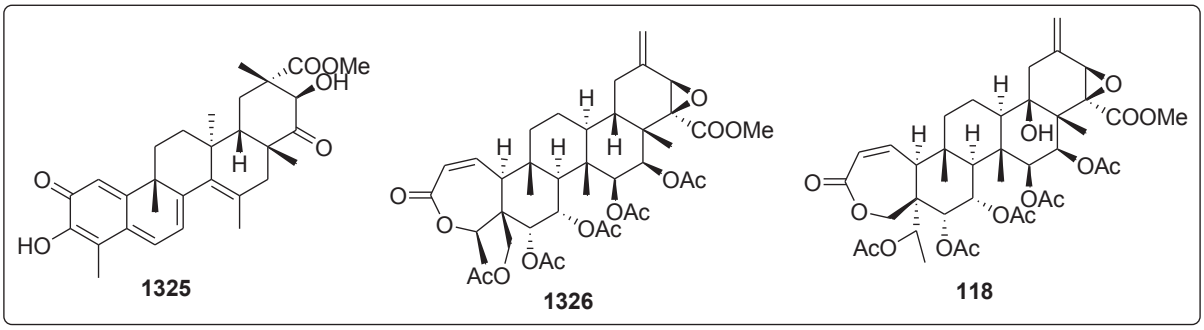


Figure 4.19 Bioactive netzahualcoyone (**1325**), compounds **1326** and correolide (**118**).

Compound **1326** was found to possess potential analgesic and potassium channel-blocking activity.[112] Correolide (**118**) was found to block KV1.3 voltagegated potassium channel with an IC_{50} value of 86 nM,[113] and the compound also inhibited human T-cell proliferation with an EC_{50} value of 307 nM (**Figure 4.19**).[113,114]

Many more natural friedelane triterpenoids showed potent biocidal activities which also include α-glucosidase inhibitory,[115] anti-inflammatory,[116] anti-HIV,[117] anti-tumor-promoting[118] activities etc.

In summary, studies have shown that the natural compound friedelin (**115**) and particularly, its derivatives have anti-cancer activity, analgesic and anti-inflammatory capability, anti-bacterial activity and can act as vascularizing agent. Some derivatives can potentially be used in phermaceuticals and functional foods for the treatment or prevention of cardiovascular and cerebrovascular diseases and tumors. Their use in cosmetics and as agro chemicals are also well pronounced.[119] And it is noteworthy to mention that the synthetic bioactive friedelane triterpenoids are mainly due to the various modifications on the A-ring of the PT, although nature has provided a number of bioactive analogues which have different functionalities distributed in all the rings.

IV.B Present work

IV.B.1 Background and abstract of the work

After the thorough review on the A-ring modified friedelane triterpenoids (as depicted above) and analyzing the highly valued potential scope of the chemical transformations associated with biological evaluation towards the practical utilizations, the author became interested in this particular field of the natural products chemistry, and hence undertook the present work as discussed below.

This chapter constitutes the syntheses of a library of A-ring modified friedelane triterpenoids. The modifications also include the all new 2-*homo*derivatives. The syntheses of the novel 2-*homo*friedelanes are based on the transformative reactions of the designed triterpenoid 3-chloro-2-formylfriedel-2-ene (**1328**) which was isolated as the major product from the reaction of friedelin (**115**) with the novel Vilsmeyer-Haack reagent. Some new derivatives of the friedelane series were also prepared from cerin (**116**, a naturally occurring PT; structurally 2α-hydroxy friedelin) as well as using one of the new derivative **1327**, structurally 3-chlorofriedel-2-ene, isolated as a side product from the key reaction. Moreover, considering the beauty of 3-chloro-2-en-al moiety, associated with the A-ring of the triterpenoid, a number of heterocycle-linked- (bonded to C3) 2-*homo*friedelane triterpenoids were synthesized.

IV.B.2 Results and Discussion

IV.B.2.1 Extraction and isolation of friedelin from *Quercus suber* bark

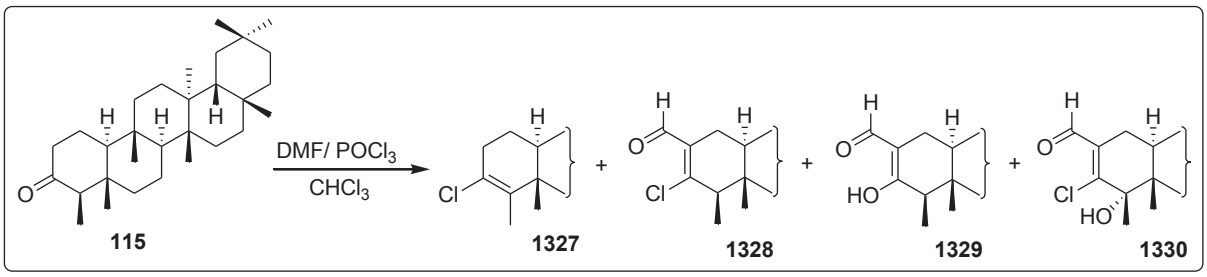
3 Kg of finely powdered cork (*Quercus suber*) was extracted with petroleum ether in a soxhlet apparatus for 72h. The crude yellowish solid obtained, after removal of the solvent by distillation, was dissolved in minimum volume of chloroform and chromatographed over silica gel column (200 g). Eluent of the column with 2% ethyl acetate in petroleum ether yielded pure white solid characterized as friedelin (**115**).

IV.B.2.2 Action of Vilsmeyer-Haack reagent on friedelin: Syntheses of 3-chlorofriedel-2-ene (1327), 3-chloro-2-formylfriedel-2-ene (1328), 3-hydroxy-2-formylfriedel-2-ene (1329) and 4α-hydroxy-3-chloro-2-formylfriedel-2-ene (1330).

Vilsmeyer-Haack reaction is a well-known transformative protocol for 2-formylation of carbonyl compounds and it uses phosphorus oxychloride along with *N,N*-dimethylformamide mixture as

the reagent. Considering the wide scope of application of the novel reagent, we targetted friedelin as the substrate, to prepare the 2-formylated and thus 2-*homo* derivative. And this derivative was indeed envisioned to be used to achieve a number of all new 2-*homo*friedelane triterpenoids by employing simple transformative reactions.

Thus first, when friedelin was treated with phosphorus oxychloride and *N*, *N*-dimethylformamide (please follow Section xyz for detailed reaction procedure), the four products isolated were characterized (please follow **section fgh** for detailed characterization) as 3-chlorofriedel-3-ene (**1327**), 3-chloro-2-formylfriedel-2-ene (**1328**), 3-hydroxy-2-formylfriedel-2-ene (**1329**) and 1α-hydroxy-3-chloro-2-formylfriedel-2-ene (**1330**). (**Scheme 4.22**)



Scheme 4.22 Action of Vilsmeyer-Haack reagent on friedelin.

Each of the products isolated (please follow section **IV.C.10** for the detailed characterizations) from the above key reaction were then utilized to achieve a library of friedelane triterpenoids having different functional/ active group distributions. Product **1327**, on further simple transformative protocols was found to result new A-ring modified friedelane triterpenoids. To add some more derivatives to this particular group of A-ring modified compounds, friedelin and cerin were again utilized. On the other hand, the products **1328**, **1329** and **1330** which belong to the all new 2-*homo*friedelane series were also used for further transformative reactions. Moreover, considering the beauty of 3-chloro-2-en-al moiety, associated with the A-ring of the triterpenoid, towards the easy access to the nucleophilic substitution at C3 as well as to the formation of heterocycles fused with the A-ring, a number of interesting heterocycle-linked- (bonded to C3) as well as heterocycle-fused (using C2-C3) *homo*friedelane triterpenoids were synthesized.

Thus, the synthesized compounds can be divided into four broad sections *viz.*,

A. A-ring modified friedelanes

B. 2-*Homo*friedelanes

C. Heterocycle-linked *homo*friedelanes.

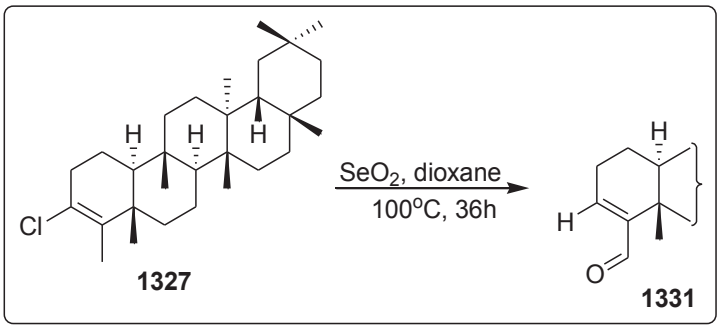
IV.B.2.2.1 A-ring modified friedelanes

According to the previous reports of the action of Vilsmeyer-Haack reagent on the ketosteroids, besides the α-formylated major product, a chloro-ene derivative was also isolated. In our case, the substrate friedelin likewise could furnish two isomeric chloro-enes viz., 3-chlorofriedel-2-ene (**1327a**) and 3-chlorofriedel-3-ene (**1327**); where in practice only the latter was isolated which can be attributed to the stability of the more substituted alkene. Next, this new derivative was used to undergo some transformative reactions to result the unprecedented derivatives. Moreover, to enrich the library of A-ring modified compounds, friedelin and cerin were transformed into some new derivatives.

IV.B.2.2.1.a Extraction and isolation of cerin (116) from *Quercus suber* bark

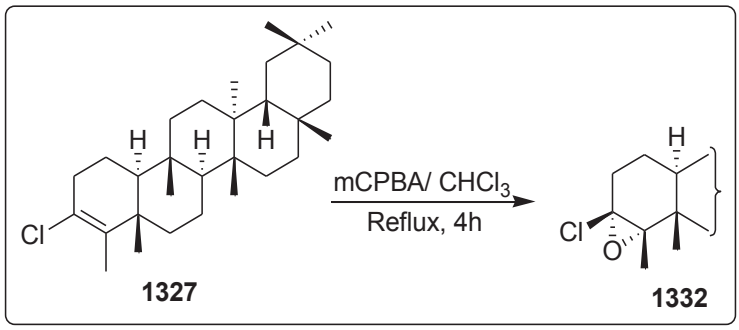
Cerin, a friedelane triterpenoid, structurally 2α-hydroxy friedelin (**116, Figure 1**)[1-2] is available from the same source where from friedelin was isolated. Ethyl acetate as eluent in the column chromatography of the cork extracts (please follow section **IV.B.2.1** for detailed extraction and isolation method) produced pure white crystalline solid characterized as cerin (m.p. 252-256^{o}C, after repeated recrystallization from $CHCl_3$).

IV.B.2.2.1.b Reaction of 3-chlorofriedel-3-ene (1327) with selenium dioxide: Besides other transformative scopes, selenium dioxide is a well known reagent for allylic hydroxylation (please follow **section lkj, (Chapter II)** for the brief review on the action of the reagent, especially on steroids). Very recently, Mugesh et al. have reported a selenium-mediated dehalogenation of halogenated nucleosides which implies to help understanding the metabolism of halogenated nucleosides in DNA and RNA.[120] When the reagent was employed on 3-chlorofriedel-3-ene (**1327**), the 23-methyl of the friedelane skeleton, an allylic one, was found to get oxidized into an aldehyde along with simultaneous dechlorination to furnish the product friedel-3-ene-23-al (**1331**). (**Scheme 4.23**)



Scheme 4.23 Synthesis of friedel-3-ene-23-al.

IV.B.2.2.1.c Reaction of 3-chlorofriedel-3-ene (1327) with *m*-CPBA: Oxidation of 3-chlorofriedel-3-ene (**1327**) with *m*-CPBA was found to result the α–epoxidation of the 3-ene functionality. Thus the compound produced was structurally 3-chloro-3α,4α-epoxyfriedelane (**1332, Scheme 4.24**).



Scheme 4.24 Oxidation of **1327** with *m*-CPBA.

IV.B.2.2.1.d Reaction of 3-chlorofriedel-3-ene (1327) with *N*-bromosuccinimide: synthesis of 24-*Nor*friedel-1, 3, 5 (10), 6-tetraene (1333): NBS is a well reagent occasionally used for allylic bromination although we were able to result the A-ring aromatization of steroids by using the same.[121, 122] Here, we aimed to achieve the corresponding 2-bromo derivative by employing NBS on 3-chlorofriedel-3-ene (**1327**), but indeed, it was our surprise to isolate the interesting A-ring aromatized titled friedelane **1333** as the only product (**Scheme 25**). There are actually a number of important biologically active aromatized friedelanes, or having their quininoid structure, available in nature.[123-128] Pristimerin (**1334**), celastrol (**117**), 6-oxopristimerol (**1335**) and demethylzeylasteral (**1336**) are some of the important compounds of this class (**Figure 4.20**).

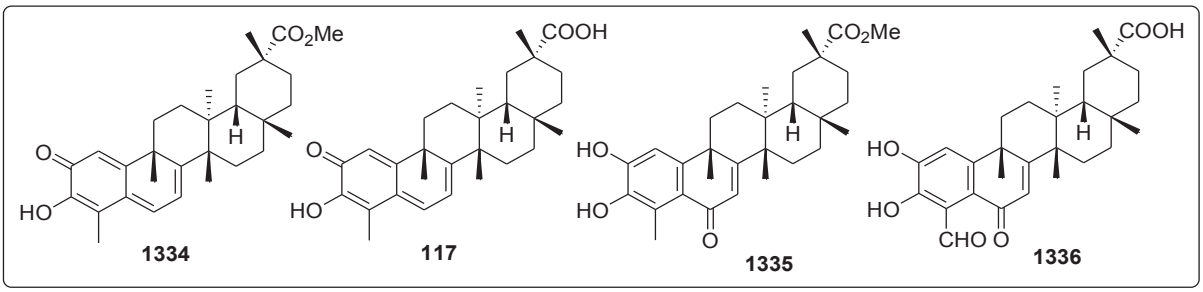
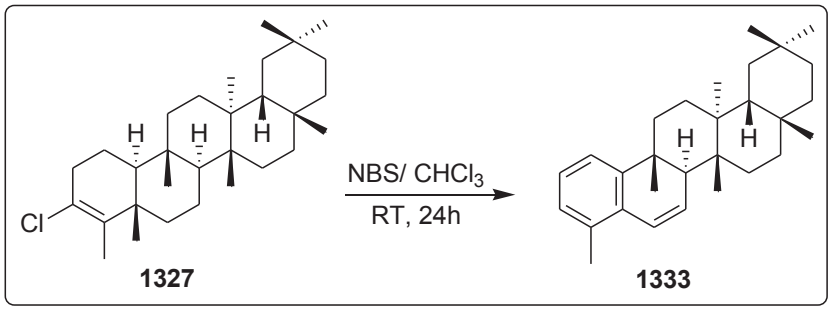
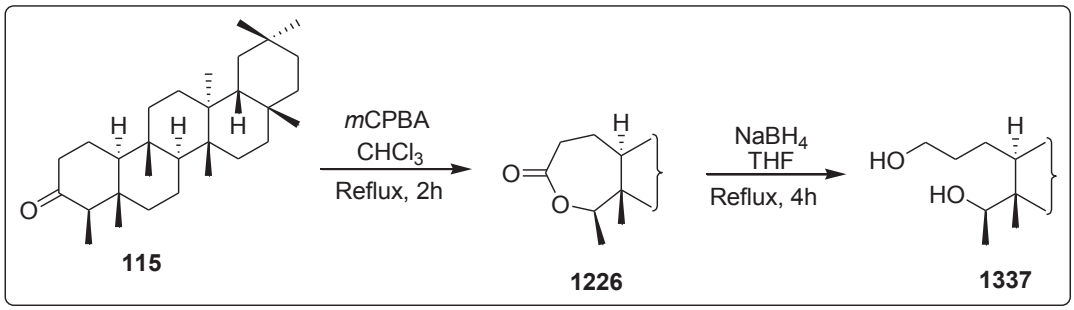


Figure 4.20 Some biologically active aromatized friedelane triterpenoids.



Scheme 4.25 Synthesis of A-ring aromatized friedelane triterpenoid by NBS.

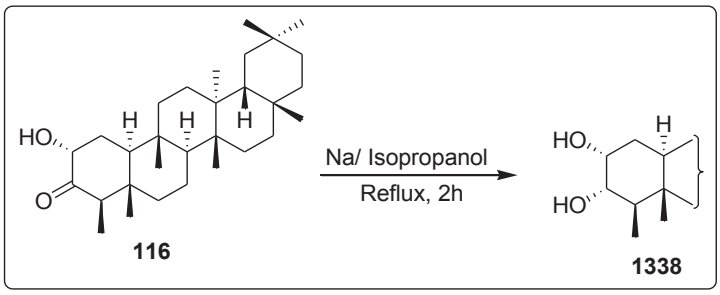
IV.B.2.2.1.e Synthesis of 3,4-*seco*friedelane-3,4-diol (1337): Friedelin was oxidized into the lactone **1226** with *m*-CPBA. The lactone was then treated with $NaBH_4$ to produce the 3,4-*seco*friedelane-3,4-diol (**1337**). (**Scheme 4.26**)



Scheme 4.26 A two-step synthesis of 3,4-*seco*friedelane-3,4-diol from friedelin.

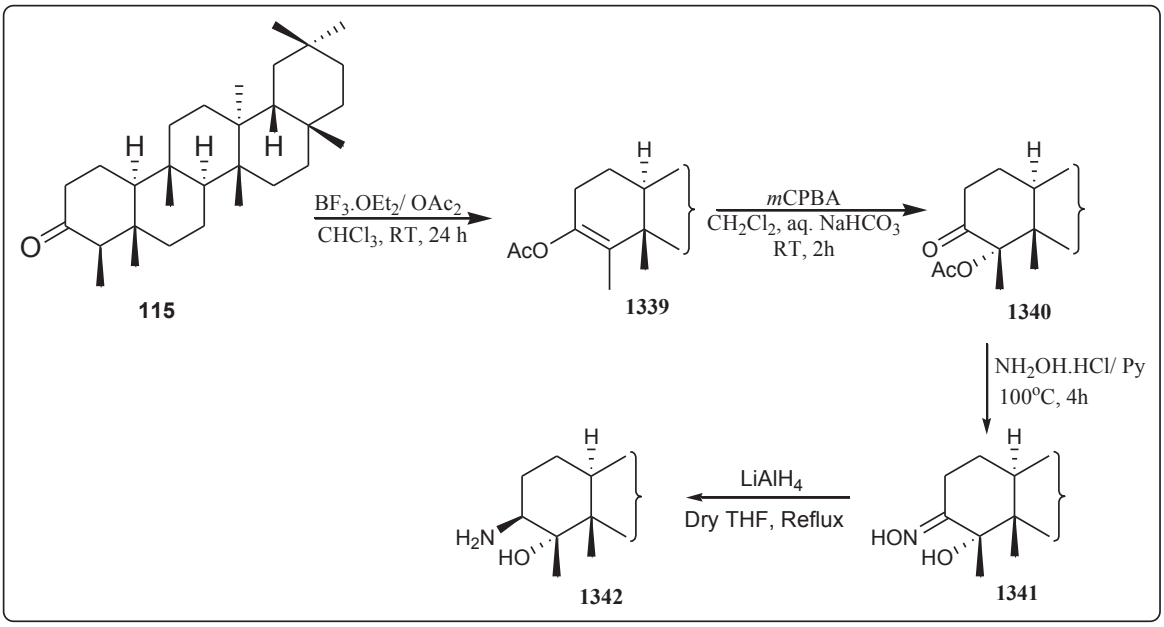
IV.B.2.2.1.f Synthesis of 3-*epi*pachysandiol A (1338): Pachysandiol A, structurally 2α,3β-dihydroxy friedelane, is a natural compound available in many plants.[129] The compound can easily be achieved by the $NaBH_4$ reduction of cerin (**116**). Here, we have employed the reduction

of cerin with sodium in alcohol to furnish actually a *cis*-diol, the 3-epimer of pachysandiol A, structurally 2α,3α-dihydroxy friedelane (**1338**, **Scheme 4.27**).



Scheme 4.27 Synthesis of 3-*epi*pachysandiol A from cerin.

IV.B.2.2.1.g Synthesis of 3β–amino–4α-hydroxyfriedelane from friedelin: The titled compound was synthesized in four steps starting from friedelin. Selective activation of the C-4 was actually the key reaction steps (step 1 and 2 here) which were achieved by following BF_3-mediated oxidation followed by *m*CPBA oxidation. Friedelin was thus transformed first into the enol acetate **1339** which, on oxidation with *m*CPBA showed the migration of the acetoxy group to C4-α to result **1340**. Oximination of the 4α-acetoxyfriedel-3-one (to furnish **1341**) followed by reduction with $LiAlH_4$ finally yielded the desired new compound 3β–amino–4α-hydroxyfriedelane (**1342**, **Scheme 4.28**).

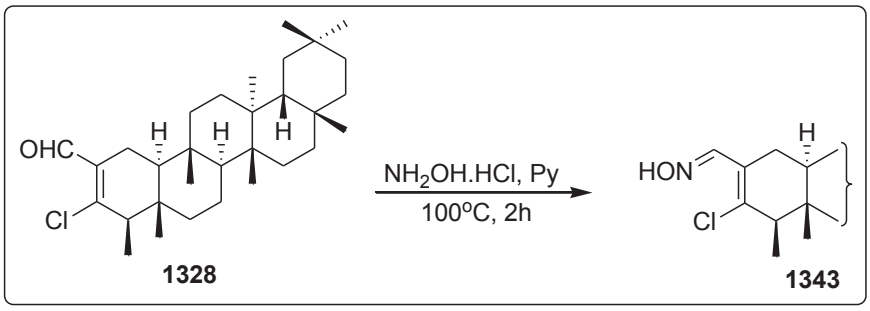


Scheme 4.28 A four-step synthesis of 3β-amino-4α-hydroxyfriedelane from friedelin.

IV.B.2.2.2 2-*Homo*friedelanes

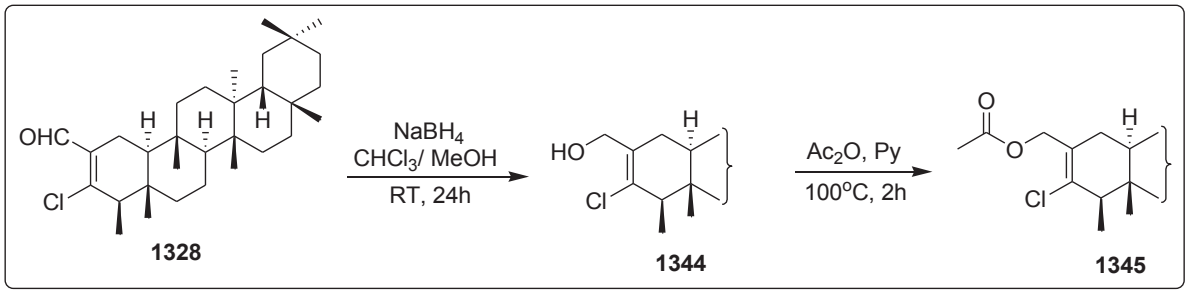
A series of 'all new' 2-*homo*friedelane triterpenoids were synthesized following two or more sequential steps starting from friedelin. The key reaction, as is mentioned earlier, was the 2-formylation of the triterpene by applying the novel Vilsmeyer-Haack reagent. As the scheme demonstrates, the reaction produced four *homo*- derivatives, **1328** being the major product (**Scheme 22**). Next, **402** was transformed into some more new derivatives to enrich the friedelane triterpenoid series.

IV.B.2.2.2.a Synthesis of 3-chlorofriedel-2-ene-2-carboxaldoxime (1343): The 2-formyl group of the 2-*homo*-derivative **1328** was transformed, by usual common procedure, with hydroxylamine hydrochloride into the corresponding oxime to furnish the titled compound (**1343**, **Scheme 4.29**).



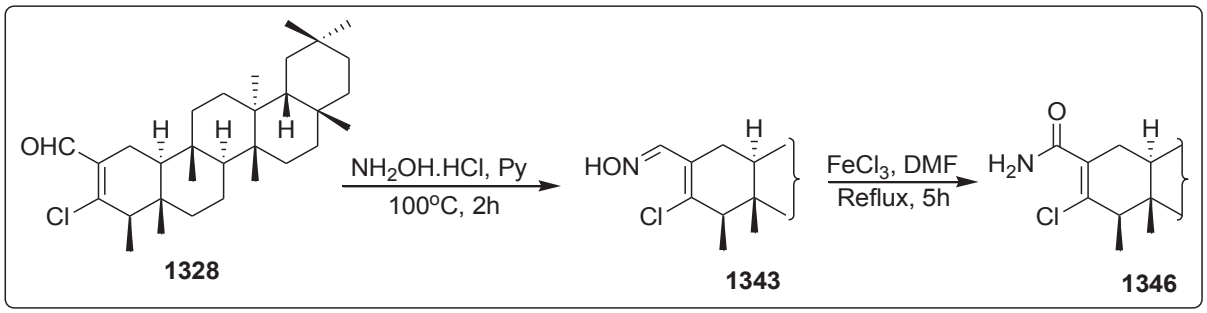
Scheme 4.29 Oximination of **1330**.

IV.B.2.2.2.b Reduction of 3-chloro-2-formylfriedel-2-ene (1328) into its 2-hydroxymethyl derivative 1344: The 2-formyl functionality of compound **1328** was reduced with $NaBH_4$ to result the allylic alcohol, 3-chloro-2-hydroxymethylfriedel-2-ene (**1344**, 92%). The 2-methanol friedelane derivative was again acetylated (with acetic anhydride) to yield 3-chloro-2-acetoxymethylfriedel-2-ene (**1345**) quantitatively (**Scheme 4.30**).



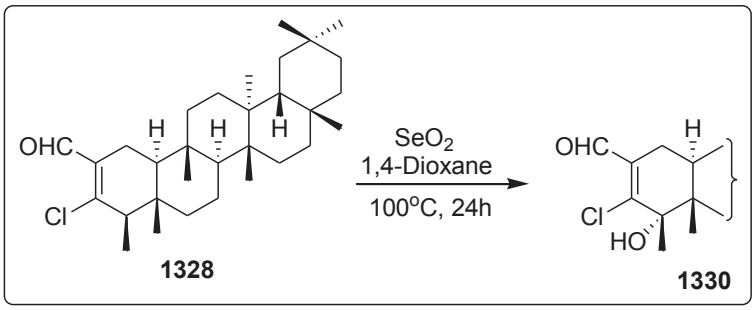
Scheme 4.30 Synthesis of 2-hydroxymethyl and its acetate derivative.

IV.B.2.2.2.c Synthesis of 3-chlorofriedel-2-ene-2-carboxamide (1346): This was synthesized from the 2-formyl derivative **1328** following two steps. First, the oxime of **1328** (**1343**, 98%) was obtained by usual procedure (with hydroxylamine hydrochloride), which after purification through recrystallisation, was allowed to reflux with anhydrous $FeCl_3$ in dry DMF (**Scheme 30**). The titled compound **1346** was isolated at 58% yield from the oxime. Though we could expect the corresponding 2-nitrile derivative in the reaction condition, formation of the 2-carboxamide derivative which is actually the Beckmann rearranged product was probably formed *via* the 2-nitrile derivative in course of the work-up procedure. Thus, from friedelin, the titled compound was synthesized in three steps. (**Scheme 4.31**)



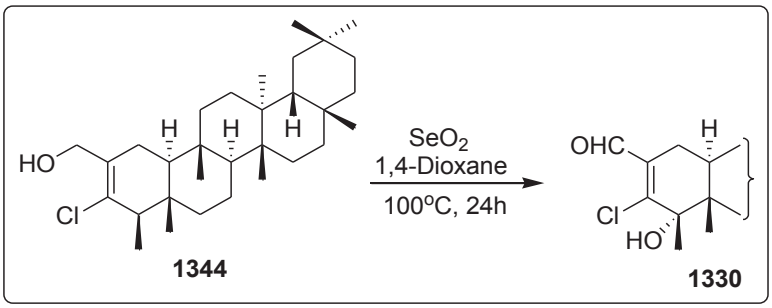
Scheme 4.31 Synthesis of 3-chlorofriedel-2-ene-2-carboxamide (**1346**).

IV.B.2.2.2.d Allylic hydroxylation of 2-formyl derivative 1328 with SeO_2: Compound **1328** possesses two allylic positions available for further functionalization (at C1 and C4), in what context selenium dioxide was employed to it for allylic hydroxylation. Among the two allylic positions available, only the C1 was found to be hydroxylated, leaving C4 completely. Thus the reaction of SeO_2 on compound **1328** furnished 4α-hydroxy-3-chloro-2-formylfriedel-2-ene (**1330, Scheme 4.32**), which was again a minor reaction product obtained from the key reaction of friedelin with the novel Vilsmeyer-Haack reagent. In this context, it may be concluded that the allylic C1 is much more reluctant towards hydroxylation, in comparison to the allylic C4.



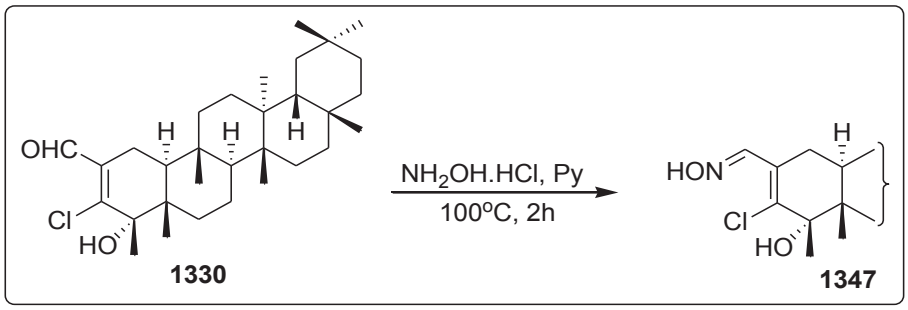
Scheme 4.32 Synthesis of 4α-hydroxy-3-chloro-2-formylfriedel-2-ene.

IV.B.2.2.2.e Transformation of 2-hydroxymethyl derivative 1344 with SeO_2: Like compound **402,** 3-chloro-2-hydroxymethylfriedel-2-ene (**1344**) also possesses two allylic positions for further functionalization (at C1 and C4). The effort to transform **1344** into the allylic hydroxylated products by using selenium dioxide resulted only the C4-α-hydroxylated **1330** where the primary allylic alcohol functionality of the reactant got simultaneously oxidized into the aldehyde group (**Scheme 4.33**).



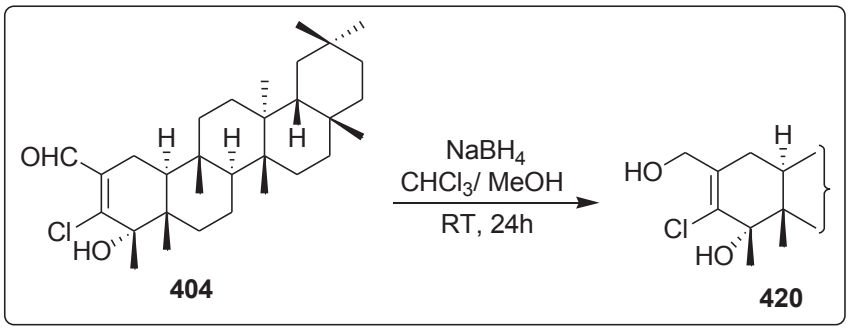
Scheme 4.33 Synthesis of 4α-hydroxy-3-chloro-2-formylfriedel-2-ene.

IV.B.2.2.2.f Preparation of the oxime derivative of 1330: The 2-formyl group of compound **1330** was transformed into the corresponding oxime (**1347**) by usual common procedure, with hydroxylamine hydrochloride. Thus the synthesized compound was 3-chloro-4α-hydroxy-2-ene-2-carboxaldoxime (**1347, Scheme 4.34**).



Scheme 4.34 Oximination of **1328**.

IV.B.2.2.2.g Synthesis of 3-chloro-4α-hydroxy-2-hydroxymethylfriedel-2-ene (1348): The aldehyde functionality of compound **1330** was reduced into the corresponding primary alcoholic group by using sodium borohydride. Thus, the titled derivative of the 2-*homo*friedelane series was obtained from **1330** at 72% yield (**Scheme 4.35).**

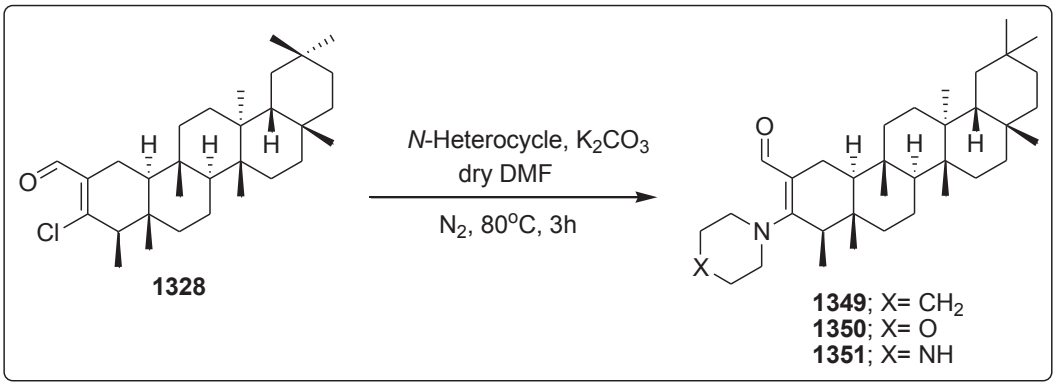


Scheme 4.35 Synthesis of 3-chloro-1α-hydroxy-2-hydroxymethylfriedel-2-ene (**1348**).

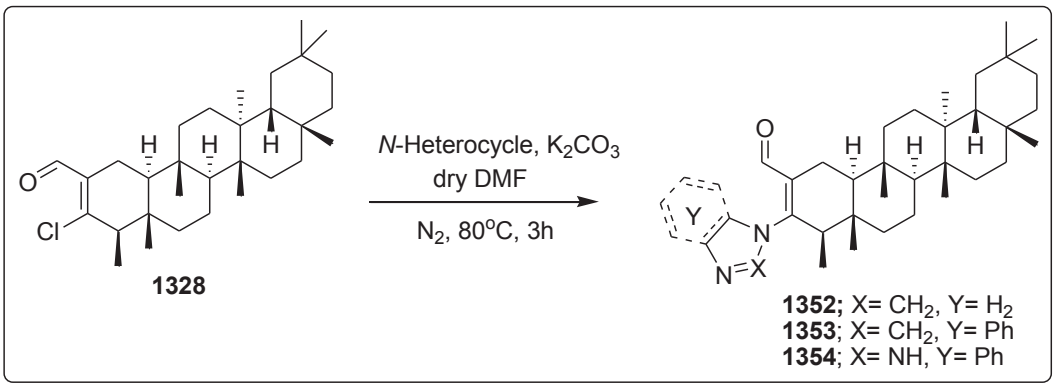
IV.B.2.2.3 Heterocycle-linked *homo*friedelanes

The C3(sp^2)-Cl of the homofriedelane **1328** is susceptible to nucleophilic substitution reactions thanks due to the associative conjugated ene-formyl functionality. Thus, some suitable nitrogen heterocycles of biological relevance were used as the nucleophiles to achieve the resultants which are, indeed, the new group of heterocycle-linked 2-*homo*friedelane derivatives. The heterocycles used for the preparation of such interesting molecules are rather simple and common, where we have used imidazole, benzimidazole and 1,2,3-benzotriazole as the aromatic *N*-heterocycles, and morpholine, piperidine and piperazine as the aliphatic *N*-heterocycles. Of note, the attempted reactions under air produced poor yields (<10%) of the desired products

leaving compound **1329** as the major yields (>75%) whereas the yield distribution was found to be reversed (approx) when the reactions were carried out under nitrogen. The reaction schemes and the products are shown below (**Scheme 4.36** and **Scheme 4.37**).



Scheme 4.36 Syntheses of aliphatic *N*-heterocycle-linked 2-*homo*friedelane derivatives.



Scheme 4.37 Syntheses of aromatic *N*-heterocycle-linked 2-*homo*friedelane derivatives.

IV.C Experimental

IV.C.1 General:

Melting points were measured in open capillary methods and were uncorrected. 1H NMR and 13C NMR spectra were recorded on BruckerAvance 300MHz FT-NMR spectrometer using 5 mm BBO probe. $CDCl_3$ or DMSO-d6 were used as solvent and TMS as reference material. Data are presented as follows: Chemical shift -in ppm on the scale relative to $\delta_{TMS} = 0$; coupling constant- *J*/Hz. Infrared spectra were recorded either in Shimudzu FT-IR 8300 Spectrometer or in Perkin Elmer FT-IR Spectrum *RX 1* Spectrometer as neat or thin films (KBr or Nujol) as indicated in the experimental procedures, and at room temperature. Frequencies are given in

wave numbers (cm-1). Mass spectra were recorded on a Qtof Micro YA263 high-resolution mass spectrometer. For column chromatography, silica gel G, 60-120 mesh was used with petroleum ether- ethyl acetate mixture as the eluent. For thin layer chromatography (TLC), freshly made silica gel plates (using silica gel for TLC and petroleum ether) were used and visualization was achieved by staining with iodine.

IV.C.2 General procedure for the Vilsmeier-Haack reaction of friedelin (115): A solution of friedelin (**115**, 1 g, 2.34 mmol) in dry chloroform (25 mL) was added dropwise to a cold and stirred solution of phosphorus oxychloride (5 mL) and dry dimethylformamide (5 mL). The mixture was allowed to attain room temperature and then refluxed under nitrogen for 6 h. It was then concentrated under reduced pressure and poured onto ice followed by extraction with chloroform (3 × 20 mL). The combined extracts were washed with brine (3 × 25 mL) and dried (Na_2SO_4), and solvent was removed to give a yellowish solid. Purification by column chromatography yielded the four products- 3-chlorofriedel-3-ene (**1327**), 3-chloro-2-formylfriedel-2-ene (**1328**), 3-hydroxy-2-formylfriedel-2-ene (**1329**) and 1α-hydroxy-3-chloro-2-formylfriedel-2-ene (**1330**).

IV.C.3 General procedure for the reduction with $NaBH_4$:

Compound (10 mg) was dissolved in CH_2Cl_2-MeOH (1:1, 10 mL) and $NaBH_4$ (1.2 equivalent) was added. The solution was stirred for 4 hours at room temperature. Sodium hydroxide (1 M, 10 mL) was added and the reaction mixture was extracted with $CHCl_3$ and after usual work-up (washed, dried, solvent evaporated), silica gel column chromatography furnished the expected pure products.

IV.C.4 General procedure for the acetylation reactions

10 mg of the compound was dissolved in pyridine (1 mL) and acetic anhydride (0.5 mL) was added to it and allowed to heat at 100^{o}C for specific time (please follow the respective Schemes for the reaction times). The reaction mixture was cooled, poured into ice cold water (50 mL), filtered and washed with cold water repeatedly and the solid was vacuum dried. The residue was column chromatographed and further recrystalised from chloroform-methanol to obtain the corresponding pure acetyl derivative.

IV.C.5 General procedure for the oximination reactions:

10 mg of the compound was dissolved in pyridine (1 mL) and hydroxylamine hydrochloride (1.5 eqv.) was added to it and allowed to heat at 100^{o}C for 4h. The reaction mixture was cooled, poured into ice cold water (50 mL), filtered and washed with water repeatedly and the solid was vacuum dried. The residue was recrystallised from chloroform-ethanol or ethanol to obtain the corresponding pure oxime derivative.

IV.C.6 Procedure for the synthesis of 3-chlorofriedel-2-ene-2-carboxamide 1346 from oxime 1343:

In a solution of oxime **1343** (20 mg, 0.04 mmol) in dry DMF (5 mL) was added anhydrous $FeCl_3$ (5 eqv) and the mixture was allowed to reflux for 5h. The reaction was cooled and water (20 mL) was added. It was then extracted with diethyl ether (3 × 15 mL) and the combined organic solvent was washed successively with water (2 × 25 mL) and brine solution (2 × 25 mL), dried (Na_2SO_4), and solvent was removed at reduced pressure to give a yellowish solid. Finally, column chromatography furnished the 2-carboxamide friedelane derivative **1346**.

IV.C.7 Oxidation of 3-chlorofriedel-2-ene (1327) with *m*CPBA:

3-Chlorofriedel-2-ene (40.0 mg, 0.09 mmol) was dissolved in chloroform (10 mL), and then *m*-CPBA (20 mg, 0.12 mmol) was added to the solution. The mixture was then allowed to reflux for 2h. The reaction was cooled, little more chloroform (10 mL) and water (15 mL) was poured and the organic layer was separated, washed with saturated solution of $NaHCO_3$ (2 x 15 mL), and with water (2 x 15 mL), and then concentrated (vaccuum) and dried (Na_2SO_4). Column chromatography followed by recrystallization yielded the desired pure compound **1332**.

IV.C.8 Allylic hydroxylation by selenium dioxide:

To a solution of **1328** (or, **1344**, 0.1 mmol) in dioxane (10 mL) was added selenium dioxide (0.15 mmol), the mixture was heated at 100^{0}C for 24h. The reaction mixture was then cooled and the black selenium deposited was filtered off through Whatman 41. To the filtrate chloroform (50 mL) was poured and was washed successively with water and then with saturated brine solution, dried over Na_2SO_4 and concentrated *in vacuo* to give a reddish gummy residue. The compounds presented therein, were then separated by column chromatography.

IV.C.9 General procedure for the syntheses of heterocycle-linked 2-*homo*friedelanes:

A mixture of compound **1328 (**0.1 mmol), suitable heterocycle (0.25 mmol), and K_2CO_3 (0.5 mmol) in dry DMF (2 mL) was heated at 80 °C under N_2 for 3 h. After cooling to room temperature, the reaction mixture was poured onto ice-cold water (30 mL), and was extracted with chlorororm (3 × 15 mL) and the combined organic solvent was washed successively with water (2 × 25 mL) and brine solution (2 × 25 mL), dried (Na_2SO_4), and solvent was removed at reduced pressure to give a yellowish solid. Finally, column chromatography furnished the heterocycle-linked 2-*homo*friedelane derivatives.

IV.C.10 Characterization of the compounds

IV.C.10.1 Friedelin (115): Eluent in column chromatography: 2% ethyl acetate in petroleum ether. White crystals, m. p. 262-263^oC (Pet. ether- ethyl acetate), (lit.[130] 262-263^oC). ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (s, 3H, Me-24), 0.87 (s, 3H, Me-25), 0.89 (s, 3H, Me-23), 0.95(s, 3H, Me-30), 1.00 (s, 6H, Me-26 and Me-29), 1.05 (s, 3H, Me-27), 1.18 (s, 3H, Me-28), 1.91- 2.02 (m, 1H, H-1), 2.20-2.47 (m, 3H, H-2 and H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.80 (C-23), 14.61 (C-24), 17.91 (C-25), 18.18 (C-7), 18.64 (C-27), 20.22 (C-26), 22.24 (C-1), 28.12 (C-20), 29.93 (C-17), 30.45 (C-12), 31.74 (C-29), 32.04 (C-28), 32.35 (C-21), 32.69 (C-15), 34.99 (C-30), 35.28 (C-19), 35.55 (C-11), 35.94 (C-16), 37.37 (C-9), 38.23 (C-14), 39.20 (C-22), 39.63 (C-13), 41.21 (C-6), 41.49 (C-2), 42.11 (C-5), 42.70 (C-18), 53.03 (C-8), 58.15 (C-4), 59.38 (C-10), 213.37 (C-3). FTIR (nujol, cm^{-1}): ν 1714, 1380, 1302, 1257, 1103, 1071, 1046, 1004, 795, 719.

IV.C.10.2 3-Chlorofriedel-3-ene (1327): Eluent in column chromatography: petroleum ether. Yield: 12%. White cube-like hard crystals, m.p. 260-262^oC. m.f. $C_{30}H_{49}Cl$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 3H, Me-24), 0.87 (m, 3H, Me-25), 0.93 (m, 12H, Me-26, Me-27, Me-29, Me-30), 1.10 (s, 3H, Me-28) 1.63 (d, 3H, J=2.1 Hz, Me-23), 1.80 (dd, 1H, *J*= 3 Hz, 12 Hz H-1), 2.23-2.36 (br m, 2H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.03 (C-24), 17.27 (C-23), 17.27, 17.54 (C-25), 17.80 (C-27), 19.04, 19.51(C-26), 27.18, 29.06, 29.55, 30.82, 31.13, 31.32 (C-29), 31.88 (C-28), 33.99, 34.26, 34.38, 34.49 (C-30), 35.07, 36.02, 37.34, 38.06, 38.27, 38.78, 39.66, 41.94, 51.72, 55.21, 125.83 (C-3), 138.20 (C-4). FTIR (neat, cm^{-1}): ν 3409, 2926, 2847, 1444, 1380, 1072, 973.

IV.C.10.3 3-Chloro-2-formylfriedel-2-ene (1328): Eluent in column chromatography: 5% ethyl acetate in petroleum ether. Yield: 52%. m.f. $C_{31}H_{49}ClO$, crystalline solid, m.p. 218°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 3H, Me-24), 0.93 (s, 3H, Me-25) 0.94 (s, 3H, Me-30), 0.99 (s, 6H, Me-26 and Me-29), 1.01 (s, 3H, Me-27), 1.14 (s, 3H, Me-28), 1.16 (d, 3H, J=2.4 Hz Me-23), 1.91-2.05 (m, 2H, H_{ax}-1 and H-10) 2.39-2.45 (m, 2H, H_{eq} and H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.77 (C-23), 14.43 (C-24), 17.39 (C-25), 18.31, 18.61 (C-27), 20.41 (C-26), 21.53, 28.18, 30.03, 30.27, 31.79 (C-29), 32.12 (C-28), 32.43, 32.80, 35.03 (C-30), 35.17, 35.31, 35.99, 36.79, 38.17, 38.17, 39.27, 39.66, 41.84, 42.75, 52.88, 53.21, 54.23, 133.08 (C-2), 155.10 (C-3), 192.18 (-CHO). FTIR (neat, cm^{-1}): ν 2932, 2855, 1675, 1611, 1394, 1232, 953.

IV.C.10.4 2-Formyl-3-hydroxy-friedel-2-ene (1329): Eluent in column chromatography: 7% ethyl acetate in petroleum ether. Yield: 10%. m.f. $C_{31}H_{50}O_2$, powdered solid, m.p. 258-260°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (s, 3H, Me-24), 0.94 (s, 3H, Me-25), 0.986 (s, 3H, Me-26), 0.994 (s, 3H, Me-29), 1.01 (s, 3H, Me-30), 1.14 (s, 3H, Me-27), 1.18 (s, 3H, Me-28), 1.79-1.85 (m, 1H, H_{ax}-1), 1.99- 2.07 (m, 3H, Me-23), 2.37- 2.52 (m, 1H, H_{eq}1), 2.64 (dd, 1H, J= 3 Hz and 18 Hz, H-4), 9.97 (d, 1H, *J*= 4.8 Hz, -CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.52 (CH_3-23), 17.63 (CH_3-24), 18.10 (CH_3-25), 18.51, 18.78 (CH_3-27), 20.10 (CH_3-26), 28.14, 28.14, 30.01, 30.20, 31.79 (CH_3-29), 32.11, 32.16, 32.74 (CH_3-28), 34.60, 34.64, 34.99 (CH_3-30), 35.31, 35.88, 36.85, 38.23, 38.42, 39.21, 39.70, 42.76, 42.76, 52.44, 54.59, 129.02 (C-2), 166.02 (C-3), 192.02 (-CHO). FTIR (KBr, cm^{-1}): ν 3443, 2933, 2863, 1687, 1587, 1462, 1383, 1282, 1177, 972, 675, 628, 573. Analysis calcd: C, 81.88; H, 11.08. Found: C, 81.40, H, 10.95.

IV.C.10.5 3-Chloro-2-formyl-4α-hydroxy-friedel-2-ene (1330): Eluent in column chromatography: 10% ethyl acetate in petroleum ether. Yield: 7%. m.f. $C_{31}H_{49}ClO_2$, powdered solid, m.p. 195°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (s, 3H, Me-25), 0.94 (s, 3H, Me-30), 0.97 (s, 3H, Me-24), 1.00 (s, 6H, Me-26 and Me-29), 1.01 (s, 3H, Me-27), 1.18 (s, 3H, Me-28), 1.40 (s, 3H, Me-23), 1.94- 2.14 (m, 3H, H-6 and H-10), 2.41 (dd, *J*= 4.2 Hz & 18.3 Hz, 2H, H-1), 10.24 (s, 1H, -CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.42 (CH_3-24), 17.89 (CH_3-25), 17.98 (CH_3-23), 18.70 (CH_3-27), 20.43 (CH_3-26), 20.66, 22.03, 28.16, 30.02, 30.26, 31.74 (CH_3-29), 32.09 (CH_3-28), 32.39, 32.76, 33.59, 35.03 (CH_3-30), 35.32, 35.40, 35.96, 36.61, 38.13, 39.26,

39.66, 42.60, 42.71, 46.43, 52.04, 78.4 (C-4), 133.7 (C-2), 153.2 (C-3) 192.8 (-CHO). FTIR (neat, cm^{-1}): ν 3480, 2926, 2855, 1675, 1373, 1113, 945.

IV.C.10.6 Friedel-3-ene-23-al (1331): Eluent in column chromatography: petroleum ether. Yield: 56%. m.f. $C_{30}H_{48}O$, White small-needle-shaped crystals. m.p. 232°C. (petroleum ether-ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (s, 3H, Me-25), 0.95 (s, 3H, Me-30), 1.00 (s, 6H, Me-26 and Me-29), 1.01 (s, 3H, Me-27), 1.15 (s, 3H, Me-24), 1.18 (s, 3H, Me-28), 2.26-2.52 (m, 3H, H-1 and H-10), 2.72 (td, *J*= 3Hz and 15 Hz, 1H, H_{eq}-2), 6.55 (d, *J*=2.7 Hz, 1H, H-3), 9.30 (s, 1H, -CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.73 (C-24), 17.96 (C-25), 18.33 (C-27), 18.62, 20.05 (C-26), 21.12, 28.19, 28.87, 30.07, 30.57, 31.83 (C-29), 32.14 (C-28), 32.27, 32.86, 35.03 (C-30), 35.39, 35.51, 36.07, 37.28, 37.54, 37.93, 38.37, 39.29, 39.77, 42.93, 53.09, 56.95, 151.84 (C-3), 151.98 (C-4), 194.23 (-CHO). FTIR (KBr, cm^{-1}): ν 3449, 2929, 2862, 2713, 1680, 1628, 1455, 1384, 1170, 1042, 991, 825, 690. ESI-MS: $[C_{30}H_{48}O + Na]^+$ requires 447.35; found 447.29. Analysis calcd: C, 84.84; H, 11.39. Found: C, 84.38, H, 11.07.

IV.C.10.7 3α,4α-Epoxy friedelane (**1332**): Eluent in column chromatography: petroleum ether. Isolated yield: 56%. White powdered solid. m.f. $C_{30}H_{50}O$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.82 (s, 3H, CH_3-25), 0.934 (s, 3H, CH_3-24), 0.944 (s, 3H, CH_3-30), 0.99 (d, *J*= 1.8 Hz, 3H, CH_3-26), 1.00 (s, 3H, CH_3-29), 1.02 (s, 3H, CH_3-27), 1.17 (s, 3H, CH_3-28), 1.26 (s, 3H, CH_3-23), 2.19 (q, J= 6.6 Hz, 1H, H_{ax}-2), 2.89 (br s, 1H, H_{eq}-2), 4.221 (t, J= 3 Hz, 1H, H-3), ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.52 (CH_3-23), 15.23 (CH_3-24), 17.68 (CH_3-25), 18.20 (CH_3-7), 18.64 (CH_3-27), 20.00 (CH_3-26), 23.81 (C-1), 28.16 (C-20), 30.01 (C-17), 30.51 (C-12), 31.79 (CH_3-29), 32.13 CH_3-28), 32.29 (C-21), 32.83 (C-15), 34.99 (CH_3-30), 35.24 (C-19), 35.31 (C-11), 36.03 (C-16), 36.41 (C-9), 38.36 (C-14), 39.25 (C-22), 39.72 (C-13), 40.73 (C-6), 41.78 (C-2), 42.87 (C-18), 50.42 (C-5), 52.83 (C-10), 53.36 (C-8), 76.88 (C-3), 102.35 (C-4). FTIR (KBr, cm^{-1}): ν 2919, 2850, 1466, 1376, 1309, 723, 655. Analysis calcd: C, 84.44; H, 11.81. Found: C, 84.66, H, 11.95.

IV.C.10.8 24-*Nor*friedel-1, 3, 5 (10), 6-tetraene (1333): Eluent in column chromatography: petroleum ether. Isolated yield: 42%. White sticky gum. m.f. $C_{29}H_{42}$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 3H, CH_3-30), 1.02 (s, 6H, Me-26 and CH_3-29), 1.03 (s, 3H, CH_3-27), 1.21 (d,

J= 2.4 Hz, CH_3-28), 1.25 (d, *J*= 4.2 Hz, CH_3-25), 2.25 (d, *J*= 3Hz, CH_3-23), 6.06 (dd, 1H, *J*= 2.7Hz and 9.9 Hz, H-7), 6.83 (dd, 1H, *J*= 3.0 Hz and 9.9 Hz, H-6), 6.92-7.17 (m, 3H, H-1, H-2 and H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.01 (C-25), 18.81 (C-27), 20.45 (C-26), 21.80, 21.85, 21.22 (C-23), 30.29, 30.96, 31.49, 31.61 (C-29), 32.09 (C-28), 32.22, 33.02, 34.77, 35.37 (C-30), 35.73, 37.69, 38.00, 38.94, 39.36, 42.83, 47.93, 119.14, 124.95, 128.98, 130.95, 131.13, 131.84, 133.87, 147.12. Analysis calcd: C, 89.16; H, 10.84. Found: C, 88.97, H, 11.01.

IV.C.10.9 Friedelin-2,3-lactone (1226): Eluent in column chromatography: 5% ethyl acetate in petroleum ether. White crystalline solid, mp: 287-289°C (lit.[89] 288-290°C), m.f. $C_{30}H_{50}O_2$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (s, 3H, Me-25), 0.89 (s, 3H, Me-24), 0.95 (s, 3H, Me-26), 0.99 (s, 6H, Me-27 and Me-30), 1.00 (s, 3H, Me- 29), 1.17 (s, 3H, Me-28), 1.20 (d, 3H, *J* = 6.3 Hz, Me-23), 1.94 (m, 1H, H-1_{ax}), 2.52 (td, 1H, *J*= 1.5, 13.0 and 13.0 Hz, H-2_{ax}), 2.63 (ddd, 1H, *J* = 1.5, 7.0 and 13.0 Hz, H-2_{eq}), 4.22 (q, 1H, *J* = 6.3 Hz, H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.45 (C-23), 16.22 (C-24), 17.90 (C-25), 18.03 (C-7), 18.55 (C-1), 18.59 (C-26), 20.20 (C-27), 28.16 (C-20), 29.98 (C-17), 30.59 (C-12), 31.75 (C-29), 32.05 (C-28), 32.35 (C-15), 32.73 (C-21), 34.35 (C-2), 35.03 (C-30), 35.29 (C-11), 35.40 (C-16), 35.95 (C-19), 38.18 (C-9), 38.37 (C-14), 38.44 (C-6), 39.22 (C-22), 39.33 (C-13), 40.76 (C-5), 42.71 (C-18), 52.72 (C-8), 63.94 (C- 10), 84.91(C-4), 175.64 (C3). FTIR: ν_{max} (KBr, cm^{-1}): 2945, 1734 (C=O), 1072 (CO), 752.

IV.C.10.10 3,4-Seco-friedelane-3,4-diol: (1337): Eluent in column chromatography: 35% ethyl acetate in petroleum ether. White powdered solid, m.p. 249°C m.f. $C_{30}H_{54}O_2$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (s, 3H, Me-24), 0.93 (s, 3H, Me-25), 0.95 (s, 3H, Me-30), 0.98 (s, 3H, Me-23), 1.00 (s, 6H, Me-26 and Me-29), 1.01 (s, 3H, Me-27), 1.18 (s, 3H, Me-28), 3.51-3.65 (m, 3H, H-3 and H-4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.37 (C-23), 17.81 (C-24), 18.02, 18.65 (C-27), 18.79(C-25), 20.16 (C-26), 21.98, 28.16, 30.00, 30.23, 31.85 (C-29), 32.10 (C-28), 32.26, 32.82, 34.94 (C-30), 35.07, 35.29, 36.06, 38.30, 39.28, 39.56, 41.91, 42.81, 52.84, 58.53, 63.25 (C-3), 75.87 (C-4). FTIR (neat, cm^{-1}): ν 3392, 2937, 2868, 1652, 1458, 1388, 1068. Analysis calcd: C, 80.65; H, 12.18. Found: C, 80.20, H, 12.01.

IV.C.10.11 3-*Epi*pachysandiol A (1338): Eluent in column chromatography: 50% ethyl acetate in petroleum ether. Yield: 62%. White needle-shaped crystals, m.p. 282- 283°C (ethyl acetate,

lit.[59] 281.5- 283 °C), m.f. $C_{30}H_{52}O_2$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (d, *J*= 6.3 Hz, 3H, CH_3-24), 0.90 (d, *J*= 6.6 Hz , 3H, CH_3-25), 0.95 (s, 1H, CH_3-30), 0.99 (s, 6H, CH_3-26 and CH_3-29), 1.00 (s, 1H, CH_3- 2), 1.17 (s, 1H, CH_3- 28), 1.26 (s, 1H, CH_3-23), 3.18 (dd, *J*= 9 Hz and 10.5 Hz, C-3), 3.38- 3.47 (m, 1H, C-2). ^{13}C NMR (75 MHz, CDCl3): δ 9.71, 14.76, 17.77, 18.15, 18.60, 20.13, 27.91, 28.15, 29.34, 30.00, 30.55, 31.76, 32.09, 32.37, 32.81, 35.00, 35.35, 35.53, 36.04, 36.96, 38.26, 38.32, 39.26, 39.70, 41.17, 42.83, 49.78, 53.12, 57.41, 77.19, 77.50. FTIR (KBr, cm^{-1}): ν 3416, 2934, 2866, 1702, 1635, 1461, 1386, 1034, 592. ESI-MS: [$C_{30}H_{48}O$ + Na^+ + H^+] requires 468.39; found 468.55. Analysis calcd: C, 81.02; H, 11.79. Found: C, 81.40, H, 11.92.

IV.C.10.12 Friedel-3-enol-acetate (**1339**): Eluent in column chromatography: 2% ethyl acetate in petroleum ether. Yield: 8-60%. m.f. $C_{32}H_{52}O_2$ white crystals, m.p. 262°C ($CHCl_3$-MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (s, 3H, Me-25), 0.95 (s, 3H, Me-30), 1.00 (s, 6H, Me-26 and Me-29), 1.01 (s, 3H, Me-27), 1.02 (s, 3H, Me-24), 1.18 (s, 3H, 28-Me), 1.59 (s, 3H, Me-23), 2.12 (s, 3H, -CH_3 of -OAc). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.55, 17.46, 18.16, 18.26, 18.67, 20.10, 20.69, 20.88, 28.20, 28.39, 30.07, 30.61, 31.83, 32.16, 32.39, 32.90, 35.04, 35.25, 35.42, 36.11, 37.08, 38.22, 38.39, 38.66, 39.31, 39.84, 42.95, 52.75, 56.10, 130.57 (C-4), 141.31 (C-3), 168.98 (>C=O of -OAc). FTIR (nujol, cm^{-1}): ν 667, 759, 1070, 1222, 1382, 1456, 1749 (>C=O of -OAc), 2337. Mass: 491.32 (M^++ Na^+), (33%), 489.31 (100%), 413.22 (13%), 301.13 (14%), 149.01 (14%), 100.10 (12%). Analysis calcd: C, 81.99; H, 11. 18. Found: C, 81.56; H, 10.89.

IV.C.10.13 4α-Acetoxyfriedel-3-one (1340): Eluent in column chromatography: 2% ethyl acetate in petroleum ether. Yield: 12-41%. m.f. $C_{32}H_{52}O_3$ white crystals, m.p. 174-176°C ($CHCl_3$-MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80 (s, 3H, Me-25), 0.86 (s, 3H, Me-24), 0.96 (s, 3H, Me-30), 1.00 (s, 6H, Me-26 and Me-29), 1.07 (s, 3H, Me-27), 1.18 (s, 3H, Me-28), 1.30 (s, 3H, Me-23), 1.93- 2.02 (m, 1H, H-1), 2.26-2.52 (m, 2H, H-2), 2.14 (-CH_3 of -OAc). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.64, 15.68, 17.95, 18.13, 18.73, 20.19, 21.50, 22.98, 28.20, 30.03, 30.55, 31.84, 32.12, 32.38, 32.85, 34.29, 35.00, 35.34, 35.95, 36.05, 37.29, 38.03, 38.32, 39.28, 39.70, 42.88, 46.05, 50.34, 52.47, 89.09 (C-4), 170.11 (-CH_3 of -OAc), 208.30 (C-3). FTIR (nujol, cm^{-1}): ν 722, 1119, 1245, 1377, 1508, 1736, 2345. ESI-MS: [$C_{30}H_{48}O$ + Na^+ + H^+] requires 508.38; found 508.54. Analysis calcd: C, 79.29; H, 10.81. Found: C, 79.52; H, 10.63.

IV.C.10.14 4α-Hydroxy friedelane-3-oxime (1341): Yield: 88%. m.f. $C_{30}H_{51}NO_2$, pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d6): δ 0.73 (s, 3H, Me-24), 0.81 (s, 3H, Me-25), 0.96 (s, 3H, Me-30), 0.99 (s, 6H, Me-26 and Me-29), 1.12 (s, 3H, Me-27), 1.17 (s, 3H, Me-28), 1.26 (s, 3H, Me-23), 1.70-2.01 (m, 3H, H-2 and H-10), 4.39 (br s, 1H, -OH), 10.38 (br s, 1H, -NOH). ^{13}C NMR (75 MHz, DMSO-d6): δ 17.16, 18.12, 18.67, 18.93, 19.85, 20.36, 28.32, 30.06, 30.59, 32.16, 32.35, 32.99, 33.75, 35.24, 35.80, 36.11, 36.97, 38.25, 39.50, 39.77, 40.05, 40.33, 40.61, 40.89, 42.90, 43.47, 49.44, 52.37, 76.62 (C-4), 161.14 (C-3). FTIR (nujol, cm^{-1}): ν 3442, 3301, 2723, 1378, 1302, 1178, 1045, 992, 944, 919, 769, 725, 572.

IV.C.10.15 3β–Amino–4α-hydroxyfriedelane **(1342):** Recrystallized from chloroform-ethanol to result pale yellow, small-flower-like crystals. m.f. $C_{30}H_{53}NO$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (s, 3H, Me-24), 0.88 (s, 3H, Me-25), 0.93 (s, 3H, Me-30), 0.95 (s, 6H, Me-29), 1.10 (s, 3H, Me-27), 1.14 (s, 3H, Me-26), 1.18 (s, 3H, Me-28), 2.08 (m, 3H, Me-23), 2.17- 2.28 (m, 1H, H-10), 2.47- 2.56 (m, 1H, H-2), 3.61- 3.83 (br hump, -OH), 5.01- 5.29 (br hump, -NH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.44 (CH_3-24), 16.81 (CH_3-25), 16.94 (CH_3-23), 17.66 (CH_3-27), 19.15 (CH_3-26), 23.78, 24.78, 27.14, 28.68, 28.96, 29.02, 30.80, 31.11, 31.32, 31.79 (CH_3-29), 33.94 (CH_3-28), 34.29, 34.36, 34.93 (CH_3-30), 37.27, 37.33, 38.23, 38.62, 41.81, 51.36, 52.26, 52.94, 54.8 (C-3), 76.20 (C-4). Analysis calcd: C, 81.20; H, 12.04, N, 3.16 Found: C, 81.40, H, 11.95, N, 3.19.

IV.C.10.16 3-Chlorofriedel-2-ene-2-carboxaldoxime (1343): Purified by recrystallization with chloroform- methanol mixture to obtain off-white needle-shaped crystals, m.p. 164^{o}C, m.f. $C_{31}H_{50}ClNO$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (s, 3H, Me-24), 0.93 (s, 3H, Me-25), 0.94 (s, 3H, Me-30), 0.99 (s, 6H, Me-26 and Me-29), 1.01 (s, 3H, Me-27), 1.09 (d, *J*= 7.2 Hz, 3H, Me-23), 1.17 (s, 3H, Me-28), 1.92 (d, *J*= 13.2 Hz, 1H, H-1), 2.13 (dt, *J*= 3.3 Hz & 12.9 Hz, 1H, H-4), 2.31-2.45 (m, 2H, H-10), 8.40 (s, 1H, -C<u>H</u>=NOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.47 (CH_3-23), 14.28 (CH_3-24), 17.39 (CH_3-25), 18.33, 18.63 (CH_3-27), 20.43 (CH_3-26), 23.09, 28.17, 30.02, 30.35, 31.77 (CH_3-29), 32.10, 32.41, 32.77 (CH_3-28), 35.06 (CH_3-30), 35.15, 35.35, 35.97, 36.73, 38.04, 38.18, 39.26, 39.65, 41.81, 42.74, 52.32, 52.87, 54.32, 126.29 (C-2), 141.69 (C-3), 150.28 (-C=NOH). FTIR (KBr, cm^{-1}): ν 3353, 2931, 2862, 1623, 1458, 1386, 1294, 1182,

1135, 985, 958, 749, 549. ESI-MS: [$C_{30}H_{48}O$ + Na^+] requires 510.34; found 510.56. Analysis calcd: C, 76.27; H, 10.32, N, 2.87. Found: C, 76.67, H, 10.67, N, 2.77.

IV.C.10.17 3-Chloro-2-hydroxymethyl-friedel-2-ene (1344): Eluent in column chromatography: 15% ethyl acetate in petroleum ether. White crystals, m.p. 244-246^oC ($CHCl_3$-methanol), m.f. $C_{31}H_{51}ClO$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 3H, Me-24), 0.79 (s, 3H, Me-25), 0.93 (s, 3H, Me-23), 0.94 (s, 3H, Me-30), 0.99 (s, 3H, Me-27), 1.01 (d, *J*=2.1 Hz, 6H, Me-26 & 29), 1.17 (d, *J*= 3 Hz, 3H, Me-28), 1.90 (dd, *J*= 3 Hz and 10.5 Hz, 1H, H-1), 2.07-2.27 (m, 3H, H-1, H-4 and H-10), 4.25 (dd, *J*= 12 Hz and 26.7 Hz, 2H, -C<u>H</u>$_2$OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.43 (CH_3-23), 14.09 (CH_3-24), 17.49 (CH_3-25), 18.37, 18.64 (CH_3-27), 20.39 (CH_3-26), 26.05, 28.19, 30.04, 30.35, 31.80 (CH_3-29), 32.12 (CH_3-28), 32.42, 32.82, 35.04 (CH_3-30), 35.33, 36.01, 36.69, 37.97, 38.20, 39.28, 39.68, 41.87, 42.77, 51.31, 52.87, 54.96, 64.07 (-CH_2OH), 132.14 (C-2), 133.10 (C-3). FTIR (KBr, cm^{-1}): ν 3384, 2938, 2864, 1662, 1461, 1385, 1183, 1133, 1045, 1007, 948, 755, 696. ESIHRMS: [$C_{30}H_{48}O$ + Na^+ + $2H^+$] requires 499.36; found 499.56. Analysis calcd: C, 78.35; H, 10.82. Found: C, 78.87, H, 10.96.

IV.C.10.18 2-Acetoxymethyl-3-chloro-friedel-2-ene (1345): Eluent in column chromatography: 2% ethyl acetate in petroleum ether. White crystals, m.p. 180-182^oC (Pet. ether- ethyl acetate), m.f. $C_{33}H_{53}ClO_2$. ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (s, 3H, Me-24), 0.92 (s, 3H, Me-25), 0.94 (s, 3H, Me-23), 1.00 (s, 3H, Me-30), 1.01 (s, 6H, Me-26 and Me-29), 1.06 (s, 3H, Me-27), 1.17 (s, 3H, Me-28), 1.90 (d, J= 13.2 Hz, 1H, H-1), 2.09 (s, 3H, -CH_3 of -OAc), 4.75 (s, 2H, -C<u>H</u>$_2$OH**).** ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.38 (CH_3-23), 14.09 (CH_3-24), 17.45 (CH_3-25), 18.33, 18.58 (CH_3-27), 20.33 (CH_3-26), 20.87, 25.67, 28.15, 30.03, 30.26, 31.82 (CH_3-29), 32.10 (CH_3-28), 32.38, 32.83, 34.96 (CH_3-30), 35.20, 35.32, 35.99, 36.66, 37.89, 38.20, 39.23, 39.67, 41.83, 42.82, 51.39, 52.83, 54.75, 65.30 (-<u>C</u>H$_2$OAc), 127.69 (C-2), 134.98 (C-3), 171.02 (CH_3 of -OAc). FTIR (KBr, cm^{-1}): ν 3444, 2933, 2866, 1745, 1459, 1383, 1225, 1026, 954, 910, 759. ESIHRMS: [$C_{30}H_{48}O$ + Na^+ + $2H^+$] requires 541.37; found 541.58. Analysis calcd: C, 76.63; H, 10.33, O, 6.19. Found: C, 76.13; H, 10.75, O, 6.05.

IV.C.10.19 3-Chlorofriedel-2-ene-2-carboxamide (1346): Eluent in column chromatography: 10% ethyl acetate in petroleum ether. Pale yellow crystals, m.p. 233-236^oC (Pet. ether- ethyl

acetate), m. f. $C_{31}H_{50}ClNO$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 3H, Me-24), 0.96 (s, 3H, Me-25), 0.97 (s, 3H, Me-23), 0.99 (s, 3H, Me-30), 1.005 (s, 3H, Me-27), 1.014 (s, 6H, Me-26 and Me-29), 1.17 (s, 3H, Me-28), 1.99 (d, *J*= 12.3 Hz, 1H, H-1), 5.08 (s, 1H, -$CONH_2$), 5.48 (s, 1H, -$CONH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7 (CH_3-24), 17.49 (CH_3-25), 17.53 (CH_3-23), 19.35 (CH_3-27), 21.57 (CH_3-26), 26.58, 27.16, 28.69, 29.03, 29.25, 30.84, 31.12, 31.37, 31.87 (CH_3-29), 33.95 (CH_3-28), 34.04, 34.29, 35.02 (CH_3-30), 36.16, 37.24, 38.24, 38.65, 38.65, 39.38, 41.83, 44.05, 51.82, 52.20, 132.02 (C-2), 153.58 (C-3), 161.70 (-$CONH_2$). Analysis calcd: C, 76.27; H, 10.32; N, 2.87; O, 3.28. Found: C, 75.87; H, 10.76; N, 2.90, O, 3.35.

IV.C.10.20 3-Chloro-4α-hydroxy-2-ene-2-carboxaldoxime (1347): Purified by recrystallization with chloroform- methanol mixture to obtain pale yellow crystals, m.p. 240°C. m.f. $C_{31}H_{50}ClNO_2$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (s, 3H, Me-25), 0.94 (s, 3H, Me-30), 0.98 (s, 3H, Me-24), 1.00 (s, 3H, Me-27), 1.01 (s, 6H, Me-26 and Me-29), 1.18 (s, 3H, Me-28), 1.35 (s, 3H, Me-23), 1.95- 2.19 (m, 4H, H-6 and H-10), 2.46 (dd, *J*= 4.5 Hz and 17.7 Hz, 2H, H-1), 8.37 (s, 1H, -C<u>H</u>=NOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.43 (CH_3-24), 17.89 (CH_3-25), 18.04 (CH_3-23), 18.72 (CH_3-27), 20.43 (CH_3-26), 21.30, 23.50, 28.17, 30.03, 30.30, 31.75 (CH_3-29), 32.09 (CH_3-28), 32.37, 32.75, 33.59, 35.03 (CH_3-30), 35.32, 35.47, 35.96, 36.59, 38.15, 39.25, 39.67, 42.56, 42.72, 46.56, 52.05, 77.97 (C-4), 128.70 (C-2), 141.20 (C-3), 150.15 (C=NOH). FTIR (KBr, cm^{-1}): ν 3422, 2939, 2868, 1627, 1459, 1385, 1295, 1181, 1073, 992, 972, 751, 696. ESI-MS: $[C_{30}H_{48}O + Na]^+$ requires 526.34; found 526.55. Analysis calcd: C, 73.85; H, 10.00; N, 2.78; O, 6.35. Found: C, 73.87; H, 10.76; N, 2.90, O, 6.00.

IV.C.10.21 3-Chloro-4α-hydroxy-2-hydroxymethylfriedel-2-ene (1348): Eluent in column chromatography: 25% ethyl acetate in petroleum ether. Pale yellow crystals, m.p. 160°C, m.f. $C_{31}H_{51}ClO_2$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (s, 3H, Me-25), 0.91 (s, 3H, Me-24), 0.95 (s, 3H, Me-30), 1.00 (s, 9H, Me-26, Me-27 and Me-29), 1.15 (s, 3H, Me-28), 1.26 (s, 3H, Me-23), 1.75 (s, 3H, Me-23), 1.87- 1.91 (m, 3H, H-1 and H-10), 4.19 (s, 1H, -C<u>H</u>$_2$OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.15 (CH_3-24), 18.14 (CH_3-25), 18.62 (CH_3-27), 19.04 (C-23), 20.05 (CH_3-26), 27.13, 28.16, 29.71, 30.02, 30.45, 31.81 (CH_3-29), 32.13 (CH_3-28), 32.26, 32.78, 35.01 (CH_3-30), 35.16, 35.30, 35.98, 36.48, 38.30, 38.47, 39.24, 39.77, 41.55, 42.83, 50.43, 52.59, 70.27 (-CH_2OH), 77.21 (C-4), 128.95 (C-2), 144.11 (C-3).

IV.C.10.22 2-Formyl-3-(1*H*-piperidin-1-yl)-friedel-2-ene (1349): Eluent in column chromatography: 10% ethyl acetate in petroleum ether. Pale yellow solid. m.f. $C_{36}H_{59}NO$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 6H, Me-24 and CH_3-30), 1.01 (s, 6H, CH_3-26 and CH_3-29), 1.03 (s, 3H, Me-25), 1.16 (s, 3H, Me-27), 1.18 (s, 3H, Me-28), 1.27 (d, *J*= 3.3 Hz, CH_3-23), 1.50- 1.55 (m, 6H, H-3′, H-4′ and H-6′), 3.25- 3.80 (m, 4H, H-2′ and H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.06 (CH_3-24), 17.64 (CH_3-25), 18.26 (CH_3-27), 18.51, 18.72 (CH_3-23), 20.12 (CH_3-26), 22.68, 24.50, 26.45, 28.17, 29.71, 30.04, 30.25 31.79 (CH_3-29), 32.14 (CH_3-28), 32.32, 32.81, 34.66, 35.00 (CH_3-30), 35.36, 35.96, 35.96, 38.12, 38.30, 38.44, 39.25, 39.74, 42.84, 46.51, 46.86, 52.53, 53.18, 54.66, 142.95, 165.84, 199.80. Analysis calcd: C, 82.85; H, 11.40; N, 2.68. Found: C, 82.10; H, 10.99; N, 2.26.

IV.C.10.23 2-Formyl-3-(1*H*-morpholin-4-yl)-friedel-2-ene (1350): Eluent in column chromatography: 10% ethyl acetate in petroleum ether. Pale yellow solid. m.p. 170^{o}C, m.f. $C_{35}H_{57}NO_2$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (s, 3H, CH_3-24), 0.94 (s, 3H, CH_3-30), 1.00 (s, 6H, CH_3-26 and CH_3-29), 1.01 (s, 6H, CH_3-25 and CH_3-27), 1.07 (s, 3H, CH_3-23), 1.18 (s, 3H, CH_3-28), 1.91-2.06 (m, 4H, H-1, H-2), 2.33- 2.37 (t, *J*= 6 Hz, 1H, H-4), 2.96 (br s, 4H, H-3′ and H-5′), 3.71 (br s, 4H, H-2′ and H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.13 (CH_3-24), 17.60 (CH_3-25), 18.14, 18.54 (CH_3-27), 19.04 (CH_3-23), 20.13 (CH_3-26), 28.14, 29.68, 30.02, 30.24, 31.76 (CH_3-29), 32.11 (CH_3-28), 32.23, 32.78, 34.60, 35.00 (CH_3-30), 35.34, 35.64, 35.95, 36.90, 38.22, 38.63, 39.24, 39.80, 40.50, 42.81, 50.34 (2), 52.54, 54.80, 66.78 (2), 141.22 (C-2), 166.66 (C-3), 198.38 (-CHO). Analysis calcd: C, 80.25; H, 10.97; N, 2.67. Found: C, 80.46; H, 11.22; N, 2.22.

IV.C.10.24 2-Formyl-3-(1*H*-piperazin-1-yl)-friedel-2-ene (1351): Eluent in column chromatography: 20% ethyl acetate in petroleum ether. White powdered solid. m.f. $C_{35}H_{58}N_2O$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (s, 3H, CH_3-24), 0.92 (s, 6H, CH_3-26 and CH_3-29), 0.93 (s, 3H, CH_3-30), 1.01 (s, 3H, Me-25), 1.11 (s, 3H, CH_3-27), 1.19 (s, 6H, CH_3-23, CH_3-28), 3.25-3.70 (m, 8H, H-2′, H-3′, H-5′ and H-6′).

IV.C.10.25 2-Formyl-3-(1*H*-imidazol-1-yl)-friedel-2-ene (1352): Eluent in column chromatography: 50% ethyl acetate in petroleum ether. Pale yellow crystal. m.p. 210^{o}C

(decomp.), m.f. $C_{34}H_{52}N_2O$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3-30), 0.99 (s, 3H, CH_3-26), 1.00 (s, 3H, CH_3-29), 1.03 (s, 3H, CH_3-27), 1.04 (s, 3H, CH_3-25), 1.19 (s, 3H, CH_3-28), 1.26 (s, 3H, CH_3-24), 1.74 (s, 3H, CH_3-23), 1.91- 2.03 (m, 1H, H-10), 2.48- 2.85 (m, 3H, H-2 and H-4), 6.83 (br s, 1H, H-4′), 7.27 (m, associated with the $CHCl_3$ peak (from $CDCl_3$), 1H, H-5′), 7.72 (br s, 1H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.16 (CH_3-24), 17.69 (C-25), 18.00, 18.56 (C-27), 19.05 (C-23), 20.15 (CH_3-26), 28.15, 29.68, 30.03, 30.19, 31.75 (CH_3-29), 32.11 (CH_3-28), 32.23, 32.75, 34.04, 34.65, 34.98 (CH_3-30), 35.36, 35.89, 37.08, 38.03, 38.29, 39.23, 39.76, 41.42, 42.81, 52.49, 54.66, 121.20, 130.49, 130.53, 130.57, 168.52, 193.35. Analysis calcd: C, 80.90; H, 10.38; N, 5.55. Found: C, 81.16; H, 10.29; N, 5.71.

IV.C.10.26 2-Formyl-3-(1*H*-benzimidazol-1-yl)-friedel-2-ene (1353): Eluent in column chromatography: 25% ethyl acetate in petroleum ether. Pale yellow crystals. m.p. 220^{o}C, m.f. $C_{38}H_{54}N_2O$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 3H, CH_3-30), 1.01 (s, 3H, CH_3-29), 1.03 (s, 3H, CH_3-26), 1.06 (s, 3H, CH_3-27), 1.20 (s, 3H, CH_3-28), 1.26 (d, *J*= 3.3 Hz, 3H, CH_3-25), 1.38 (s, 3H, CH_3-24), 1.65 (s, 3H, CH_3-23). 7.20- 7.91 (m, 4H, H-4′, H-5′, H-6′ and H-7′), 8.13 (d, *J*= 5.1 Hz, 1H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.39 (CH_3- 24), 17.78 (CH_3- 25), 18.09, 18.59 (CH_3- 27), 19.47 (CH_3- 23), 20.19 (CH_3- 26), 28.20, 29.70, 30.09, 30.25, 31.81 (CH_3- 29), 32.16 (CH_3- 28), 32.30, 32.83, 34.35, 34.74, 35.01 (CH_3- 30), 35.40, 35.95, 37.23, 37.98, 38.36, 39.27, 39.81, 41.77, 42.89, 52.55, 54.86, 109.86, 120.08 (2), 124.14, 127.96 (2), 134.50 (C-2), 145.24, 171.95 (C-3), 192.97 (-CHO). Analysis calcd: C, 82.26; H, 9.81; N, 5.05. Found: C, 82.11; H, 9.72; N, 5.13.

IV.C.10.27 2-Formyl-3-(1*H*-1, 2, 3-Benzotriazol-1-yl)-friedel-2-ene (1354): Eluent in column chromatography: 50% ethyl acetate in petroleum ether. Pale yellow crystalline solid. m.p. 237^{o}C (decomp.), m.f. $C_{37}H_{53}N_3O$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (d, *J*= 4.5 Hz, 3H, CH_3-25), 0.93 (s, 3H, CH_3-24), 0.95 (s, 3H, CH_3-30), 1.00 (s, 3H, Me-26), 1.01 (d, *J*= 1.5 Hz, CH_3- 29), 1.03 (s, 3H, CH_3-27), 1.18 (d, 3H, *J*= 2.7 Hz CH_3-28), 1.95 (s, 3H, CH_3-23), 6.84 (t, *J*= 7.5 Hz, 1H), 7.02 (d, *J*= 7.8 Hz, 1H), 7.22- 7.28 (m, 1H), 7.98 (s, 1H), 10.22 (-CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.39 (CH_3-24), 17.56 (CH_3-25), 18.24, 18.35 (CH_3-23), 18.46 (CH_3-27), 20.39 (CH_3-26), 28.19, 30.07, 30.29, 31.81 (CH_3-29), 31.90, 32.15 (CH_3-28), 32.48, 32.88, 34.99 (CH_3-30), 35.37, 35.96, 36.05, 36.81, 38.30, 39.29, 39.76, 42.87, 42.94, 52.39, 52.98, 54.34,

112.70, 120.02, 129.17, 129.26, 137.66 (C-2), 144.77, 155.01 (C-3), 192.12 (-CHO). Analysis calcd: C, 79.95; H, 9.61; N, 7.56. Found: C, 80.06; H, 9.48; N, 7.62.

IV.D Conclusion

Syntheses of a number of A-ring modified friedelane triterpenoids have been accomplished. These also include the 2-*homo* derivatives for which, as the key step, the transformation of friedelin with Vilsmeyer-Haack reagent was used. 3-Chloro-2-formylfriedel-2-ene the main product isolated from the reaction was transformed suitably into various derivatives and hence, following two or three simple steps starting from friedelin, it rendered possible to produce a library of C2,C3-, C3,C4-, and C2,C3,C4- functionalized friedelane triterpenoids. Besides, some useful methodologies were thus established during the various transformative attempts. These include a two-step aromatization of friedelin by *N*-bromosuccinimide, a one-pot dechlorination with simultaneous C-23 activation, and selective 4α-hydroxylation with simultaneous oxidation of allylic alcohol by selenium dioxide. Again, syntheses of some friedelane derivatives, *viz.*, 3β-amino-4α-hydroxy-, 2-carboxamide, 2,3-*seco*diol, 4α-hydroxy-3-chloro-2-formylfriedel-2-ene and 3-chloro-4α-hydroxy-2-hydroxymethylfriedel-2-ene, in a few steps, were found very much effective to enrich the A-ring modifications of friedelane triterpenoids. On the other hand, heterocycle-linked (to C3 of friedelanes) 2-*homo*friedelane derivatives were achieved. We believe to use these friedelane triterpenoids for future biological applications as well as to explore more interesting and usefull multifunctionalized derivatives of the particular class of pentacyclic triterpenoids.

IV.E Supporting spectra

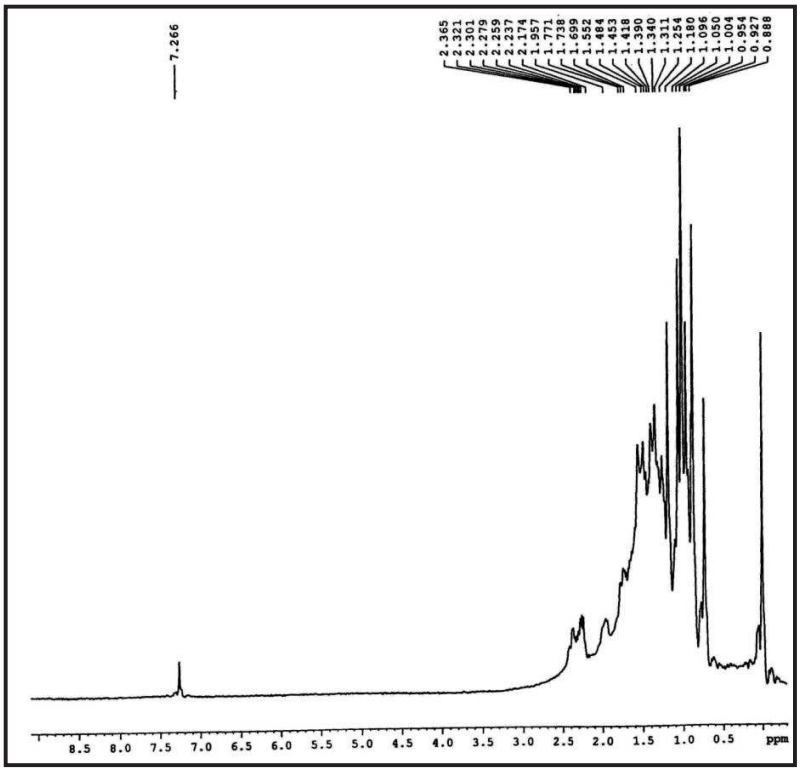


Figure 4.21 ^{1}H NMR spectrum of friedelin (**115**).

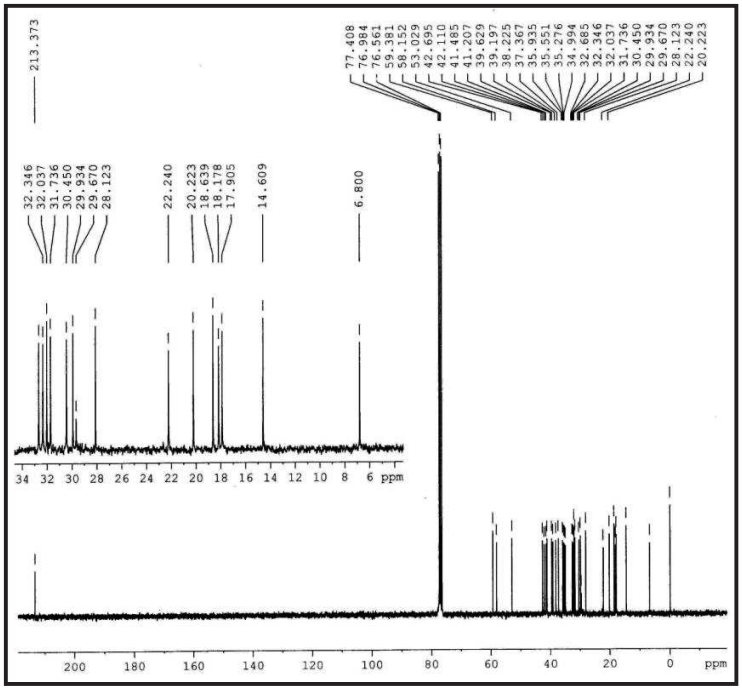


Figure 4.22 ^{13}C NMR spectrum of friedelin (**115**).

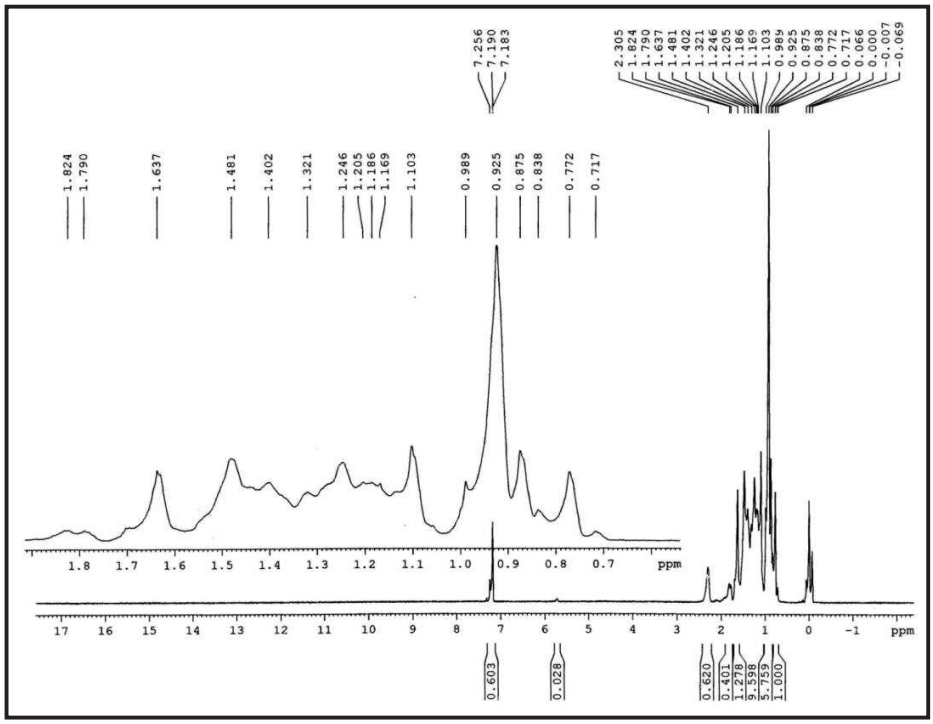


Figure 4.23 [1]H NMR spectrum of 3-chlorofriedel-3-ene (**1327**).

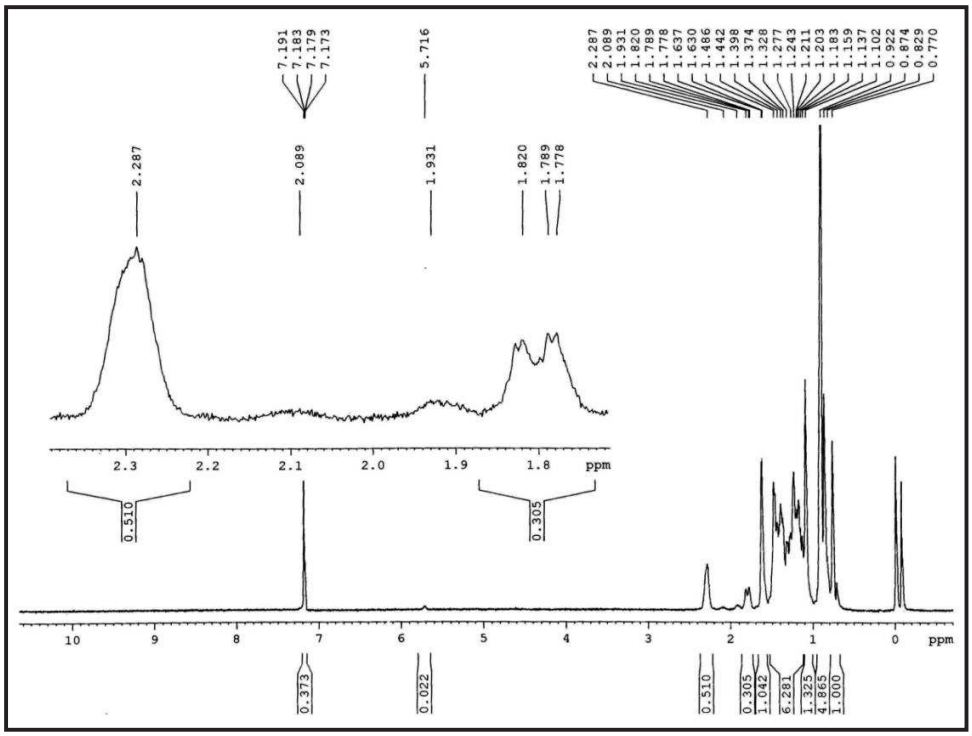


Figure 4.24 [1]H NMR spectrum (partially expanded) of 3-chlorofriedel-3-ene (**1327**).

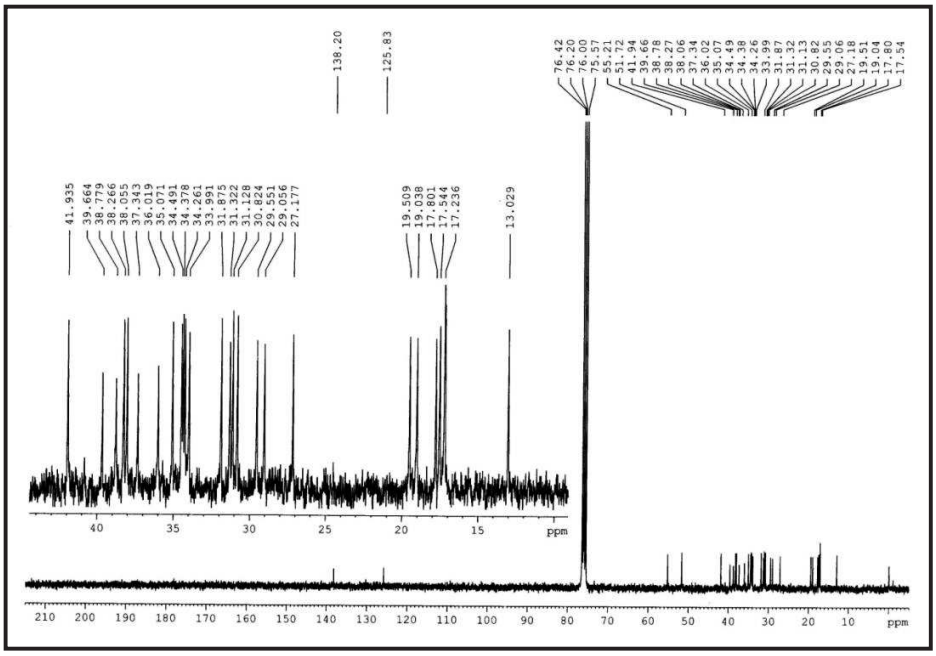


Figure 4.25 ^{13}C NMR spectrum of 3-chlorofriedel-3-ene (**1327**).

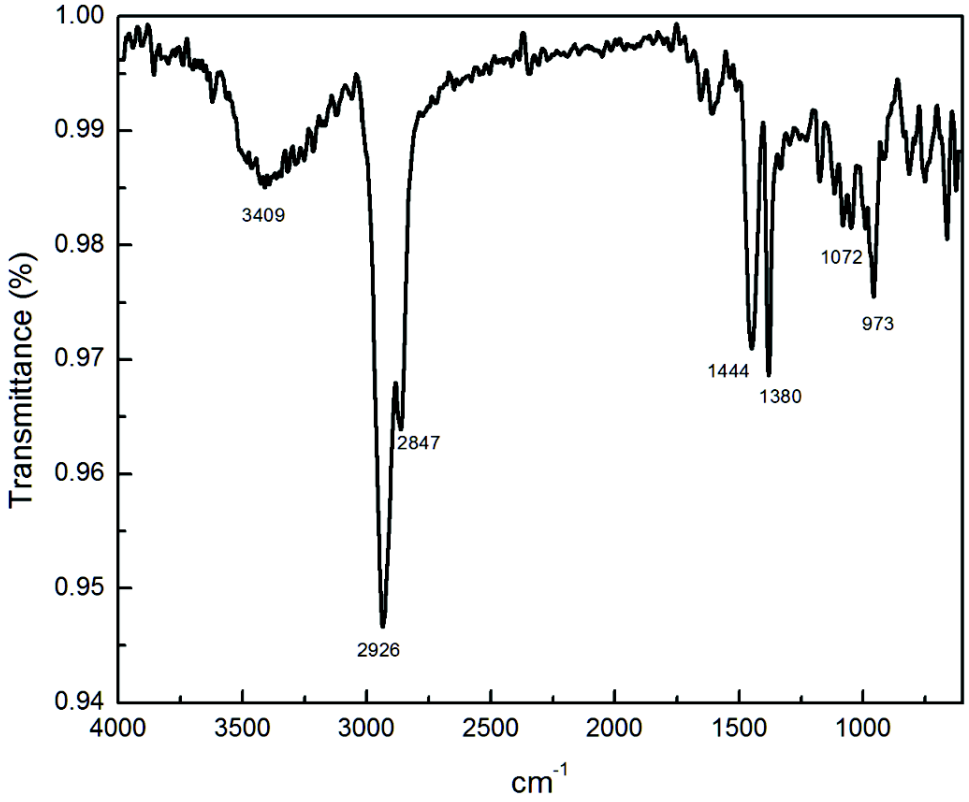


Figure 4.26 FTIR spectrum of 3-chlorofriedel-3-ene (**1327**).

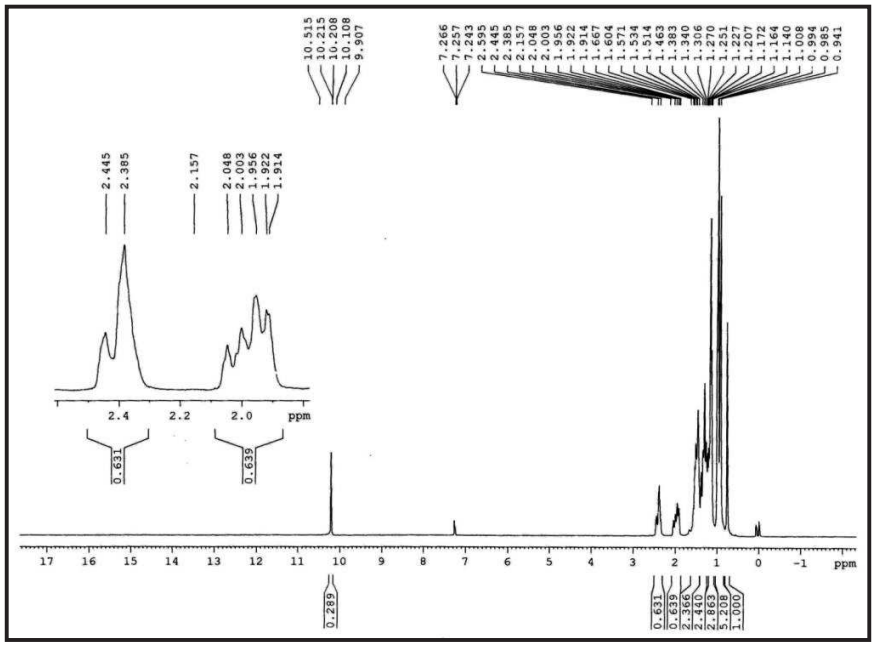


Figure 4.27 [1]H NMR spectrum of 3-chloro-2-formylfriedel-2-ene (**1328**).

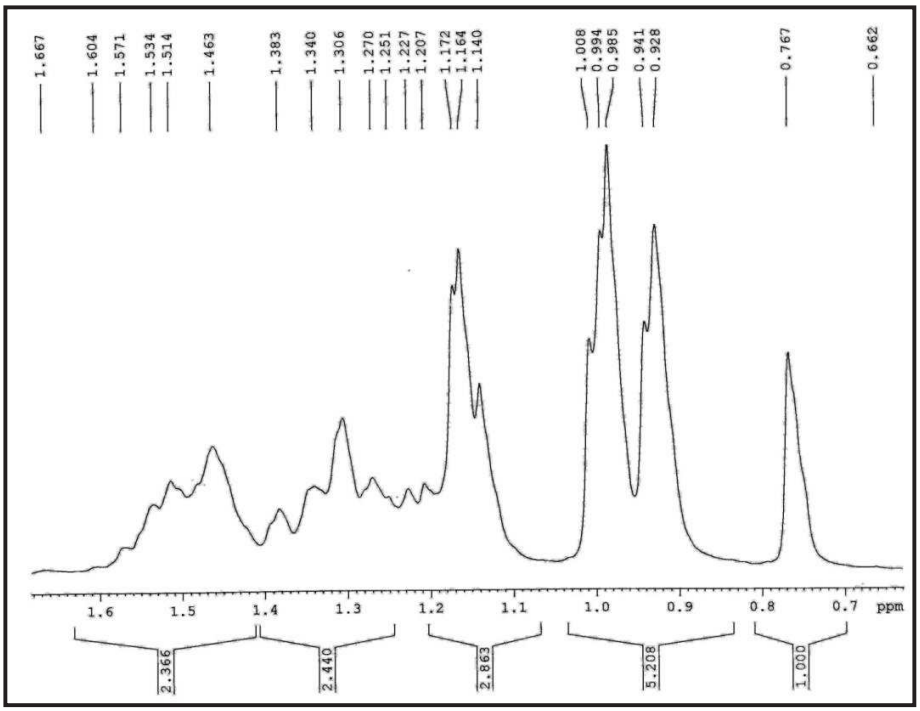


Figure 4.28 [1]H NMR spectrum (partially expanded) of 3-chloro-2-formylfriedel-2-ene (**1328**).

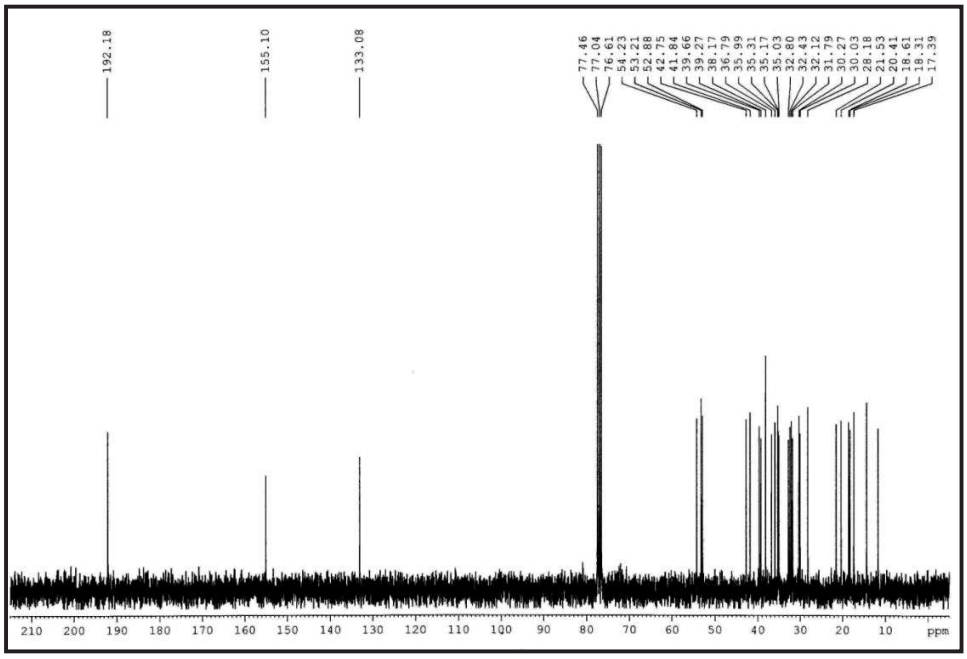


Figure 4.29 ^{13}C NMR spectrum of 3-chloro-2-formylfriedel-2-ene (**1328**).

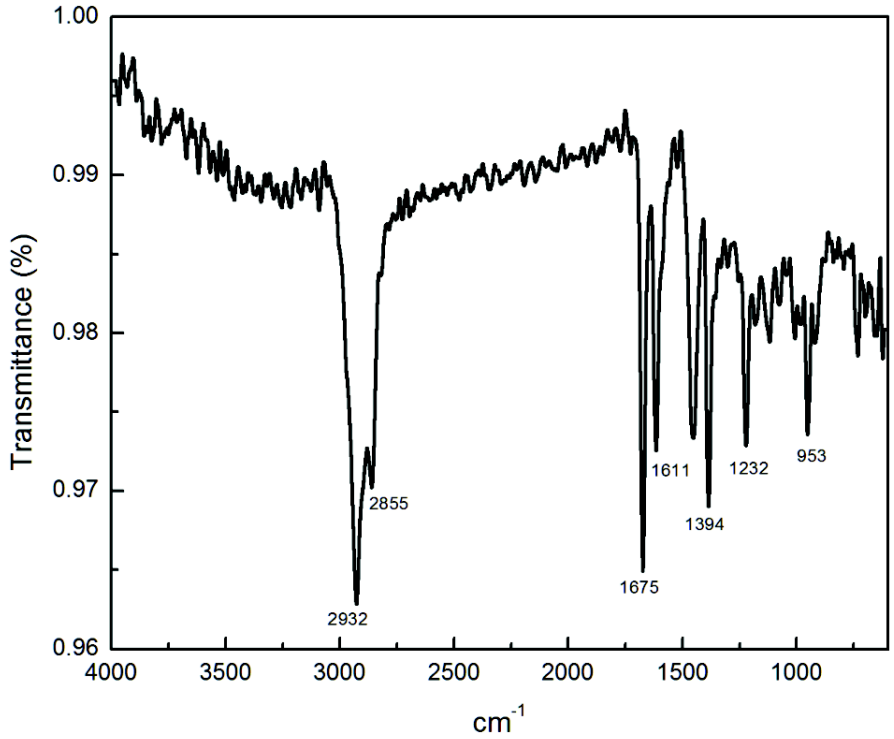


Figure 4.30 FTIR spectrum of 3-chloro-2-formylfriedel-2-ene (**1328**).

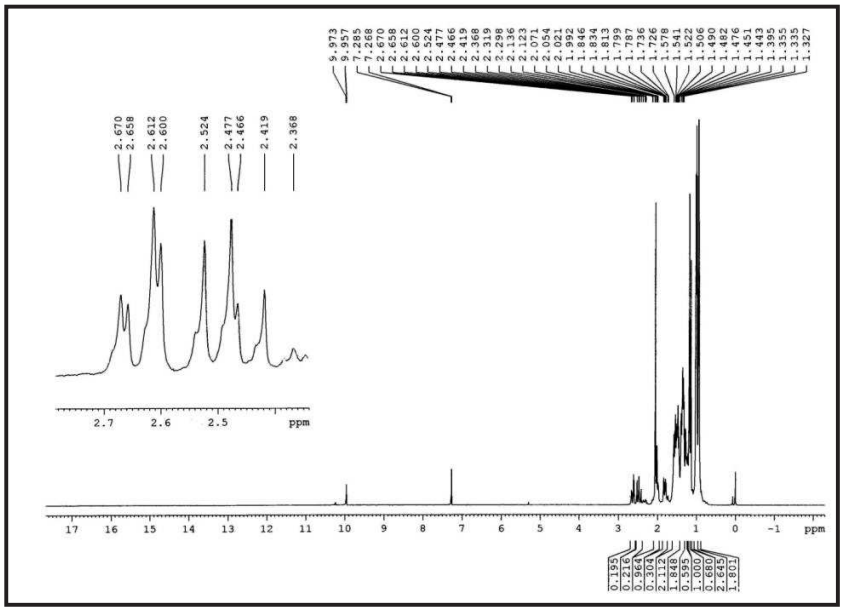


Figure 4.31 [1]H NMR spectrum of 2-formyl-3-hydroxy-friedel-2-ene (**1329**).

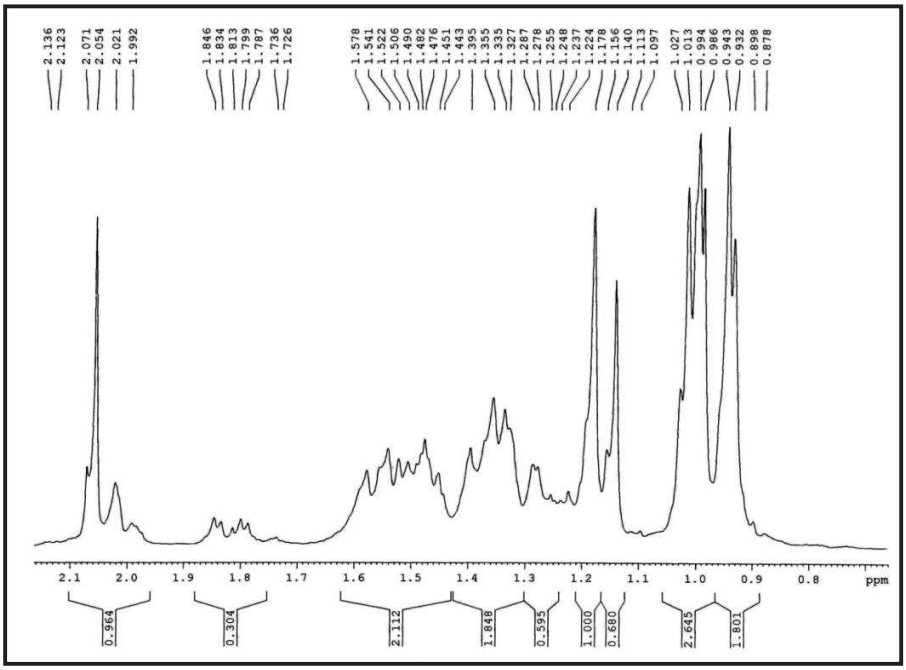


Figure 4.32 [1]H NMR spectrum (partially expanded) of 2-formyl-3-hydroxy-friedel-2-ene (**1329**).

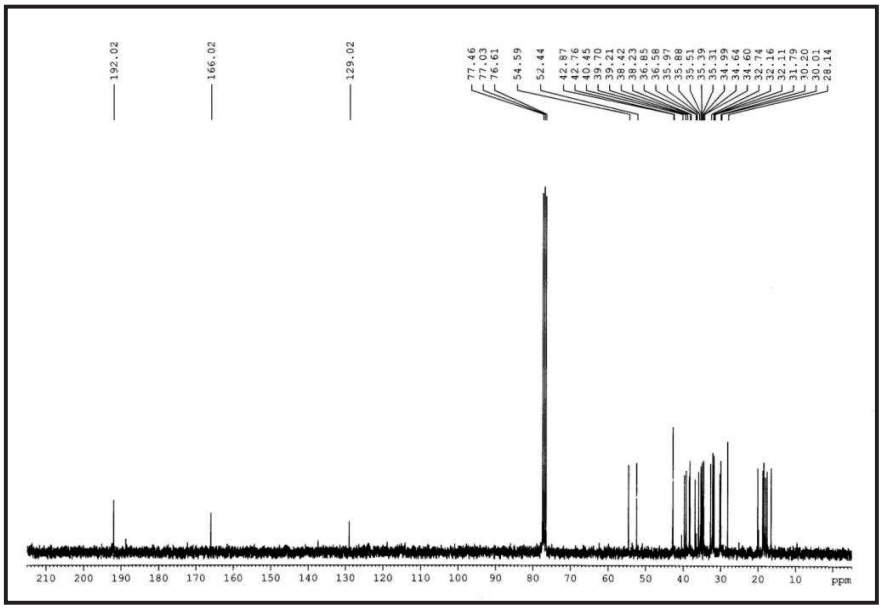


Figure 4.33 ^{13}C NMR spectrum of 2-formyl-3-hydroxy-friedel-2-ene (**1329**).

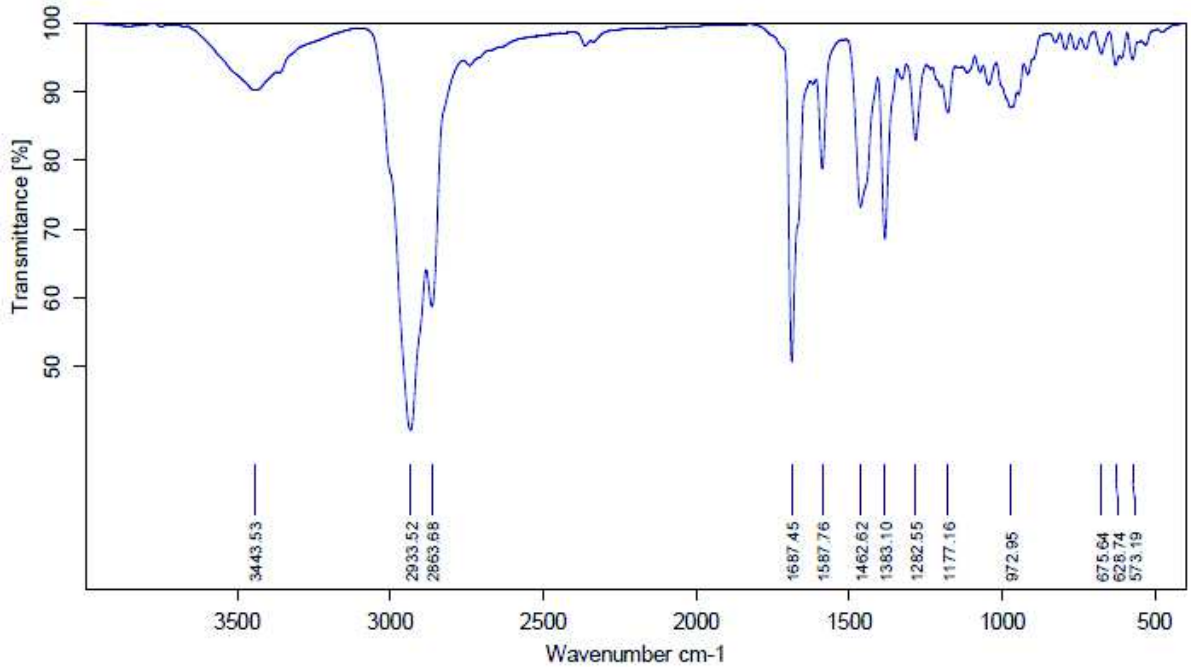


Figure 4.34 FTIR spectrum of 2-formyl-3-hydroxy-friedel-2-ene (**1329**).

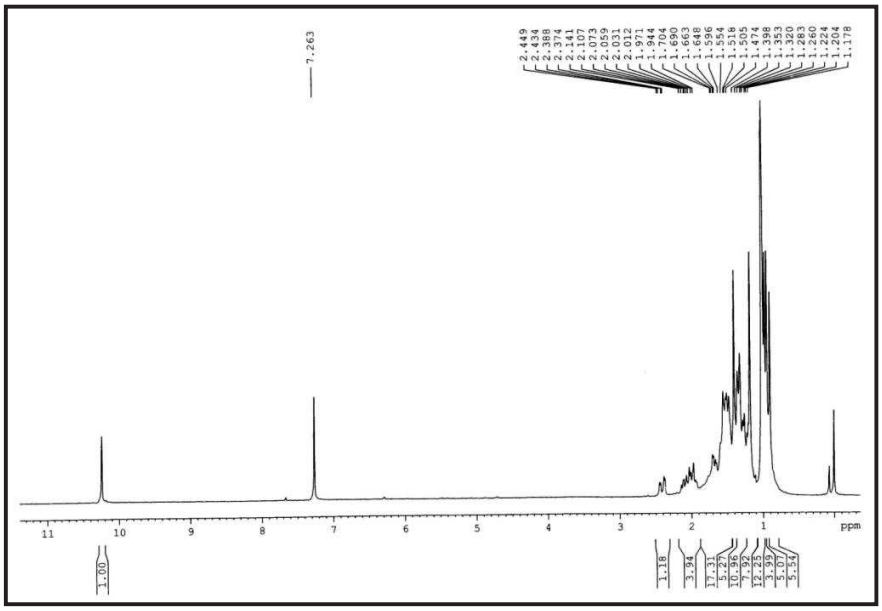


Figure 4.35 ^{1}H NMR spectrum of 3-Chloro-2-formyl-4α-hydroxy-friedel-2-ene (**1330**).

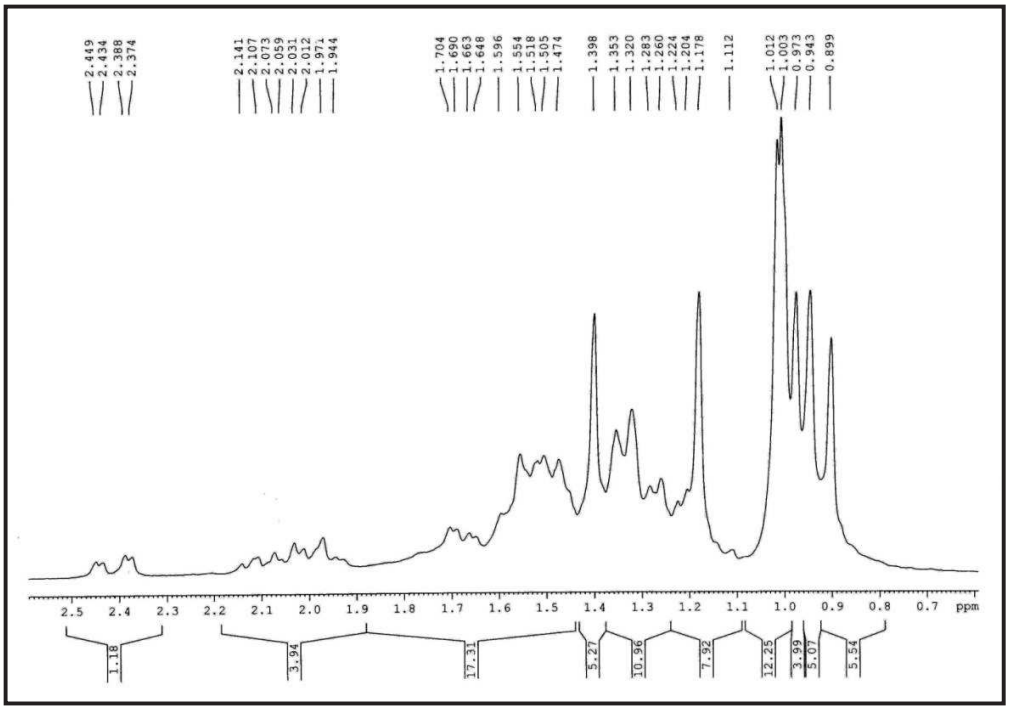


Figure 4.36 ^{1}H NMR spectrum (partially expanded) of 3-chloro-2-formyl-4α-hydroxy-friedel-2-ene (**1330**).

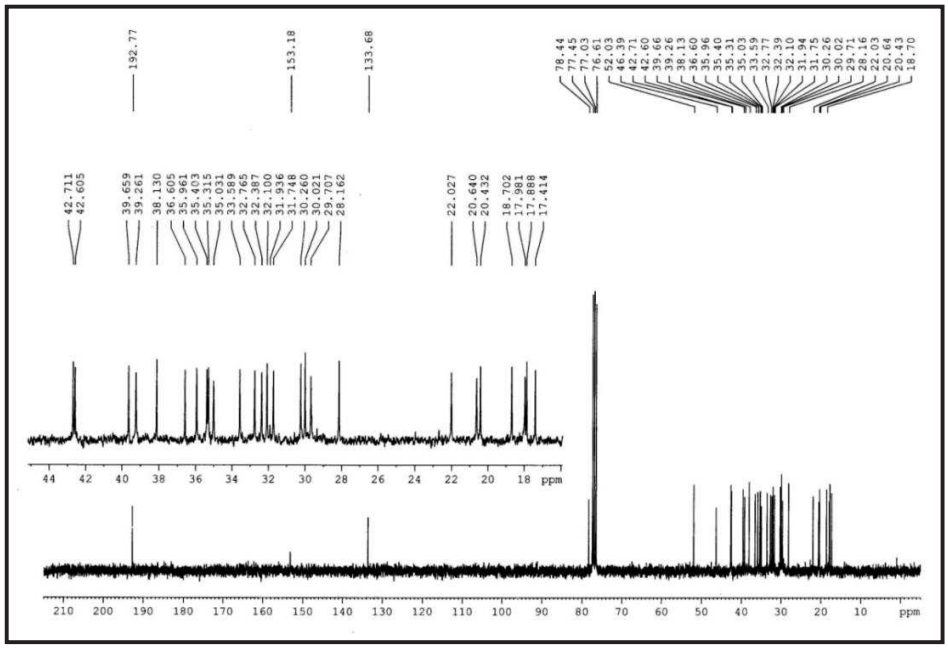


Figure 4.37 ^{13}C NMR spectrum of 3-chloro-2-formyl-4α-hydroxy-friedel-2-ene (**1330**).

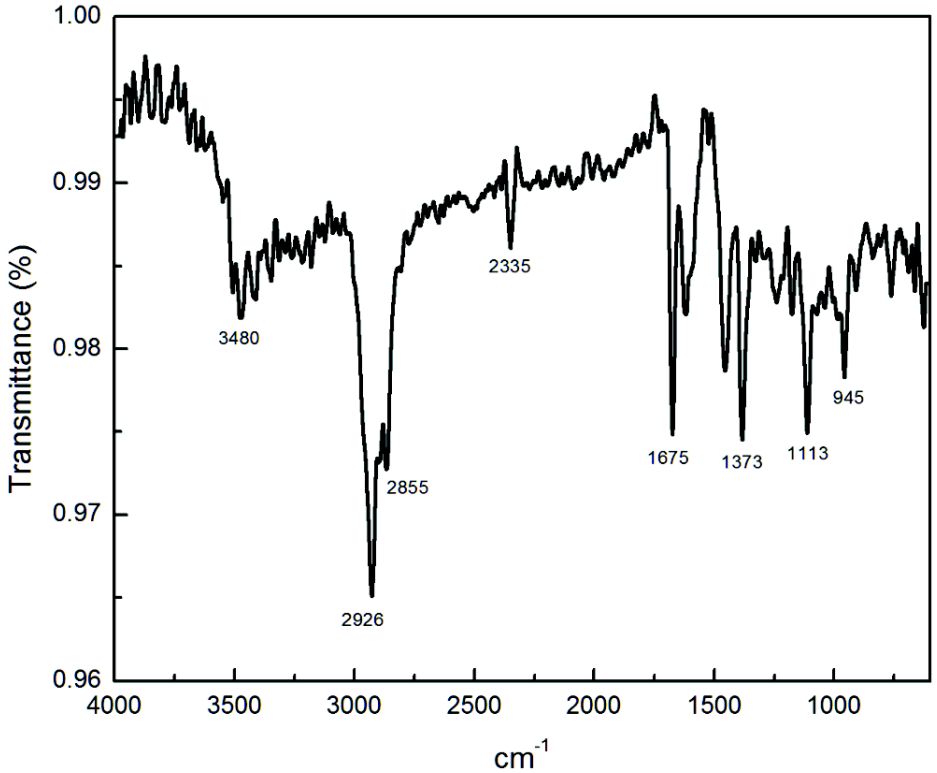


Figure 4.38 FTIR spectrum of 3-chloro-2-formyl-4α-hydroxy-friedel-2-ene (**1330**).

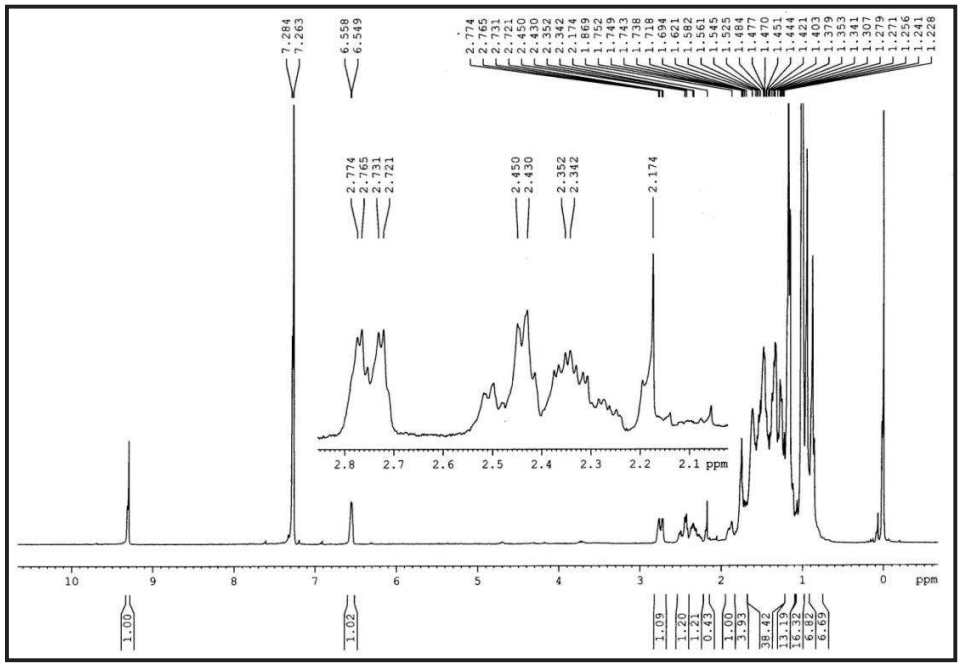


Figure 4.39 [1]H NMR spectrum of friedel-3-ene-23-al (**1331**).

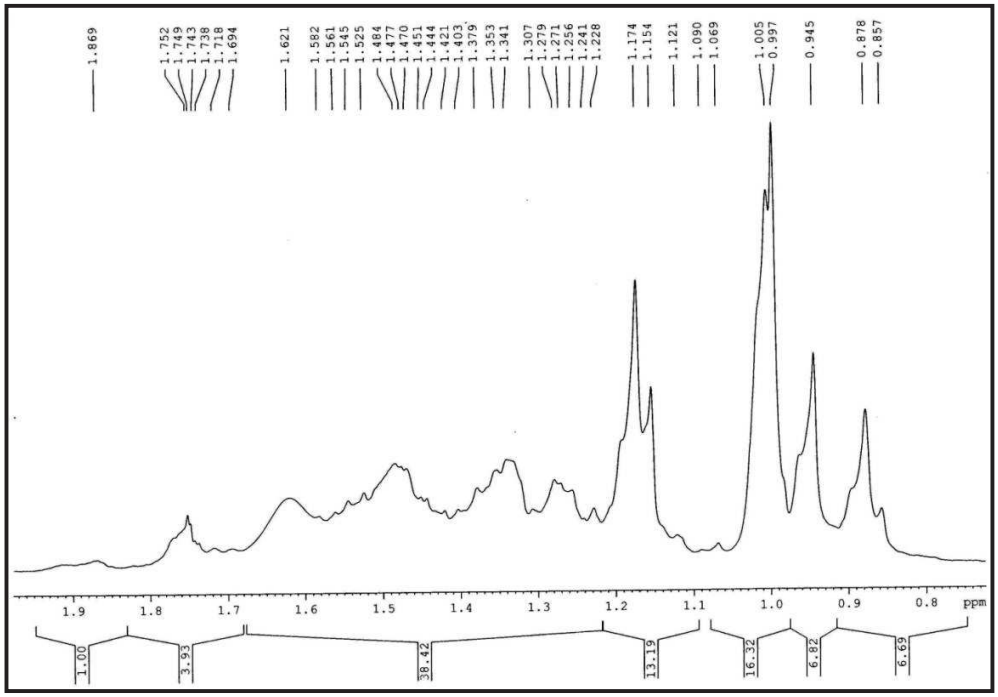


Figure 4.40 [1]H NMR spectrum (partially expanded) of friedel-3-ene-23-al (**1331**).

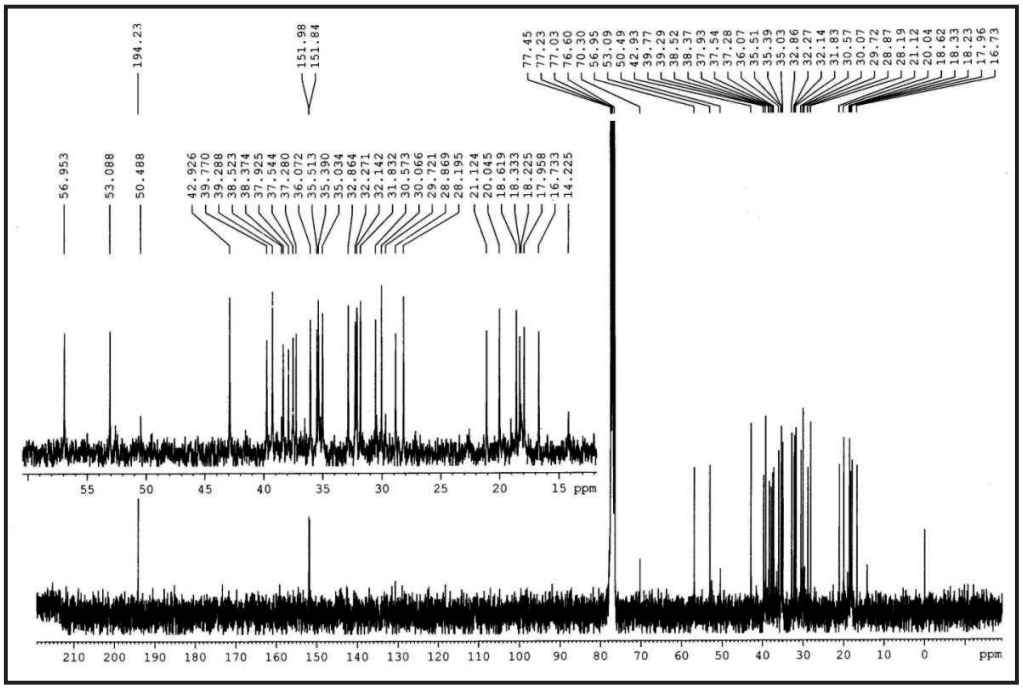


Figure 4.41 ^{13}C NMR spectrum of friedel-3-ene-23-al (**1331**).

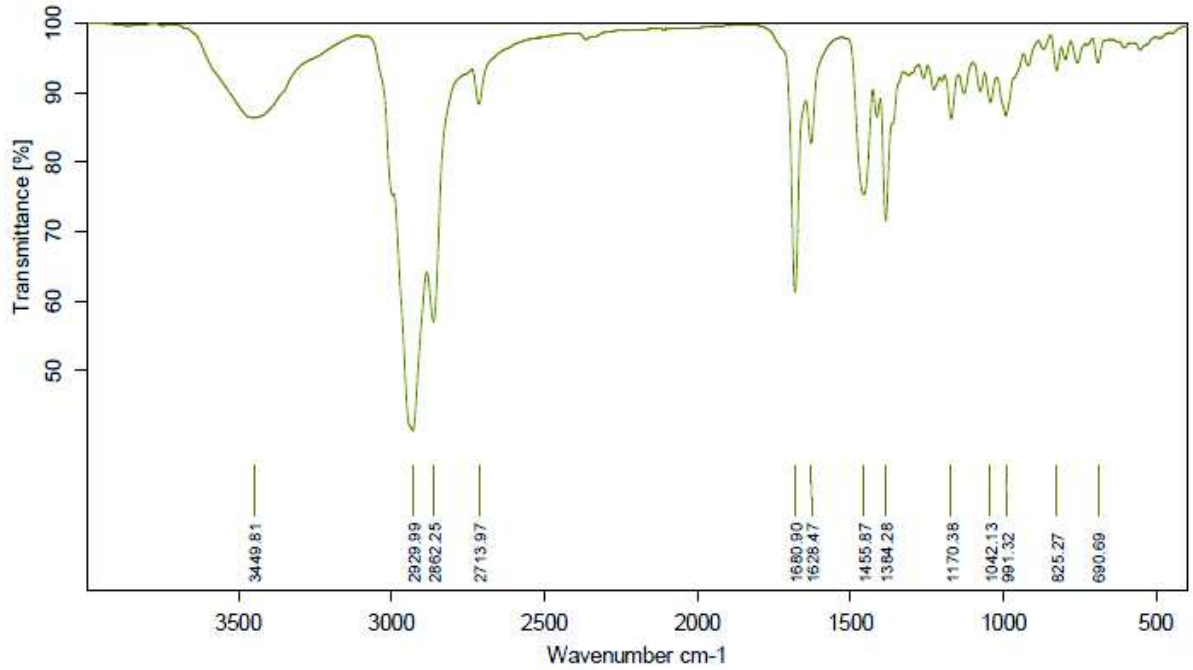


Figure 4.42 FTIR spectrum of friedel-3-ene-23-al (**1331**).

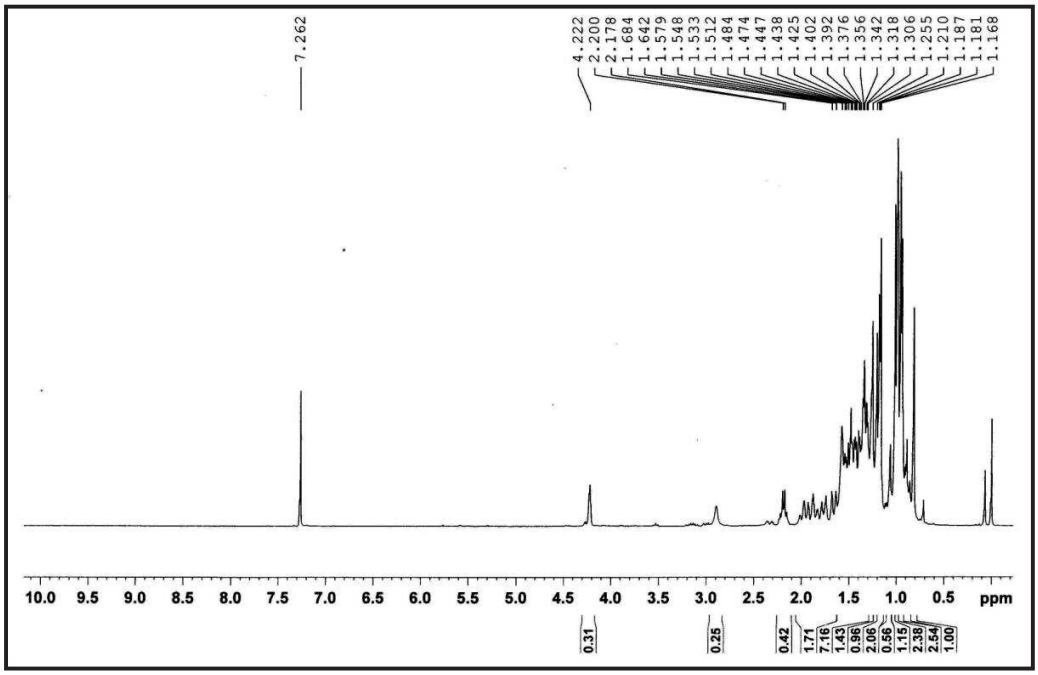


Figure **4.43** [1]H NMR spectrum of 3α,4α-epoxy friedelane(**1332**).

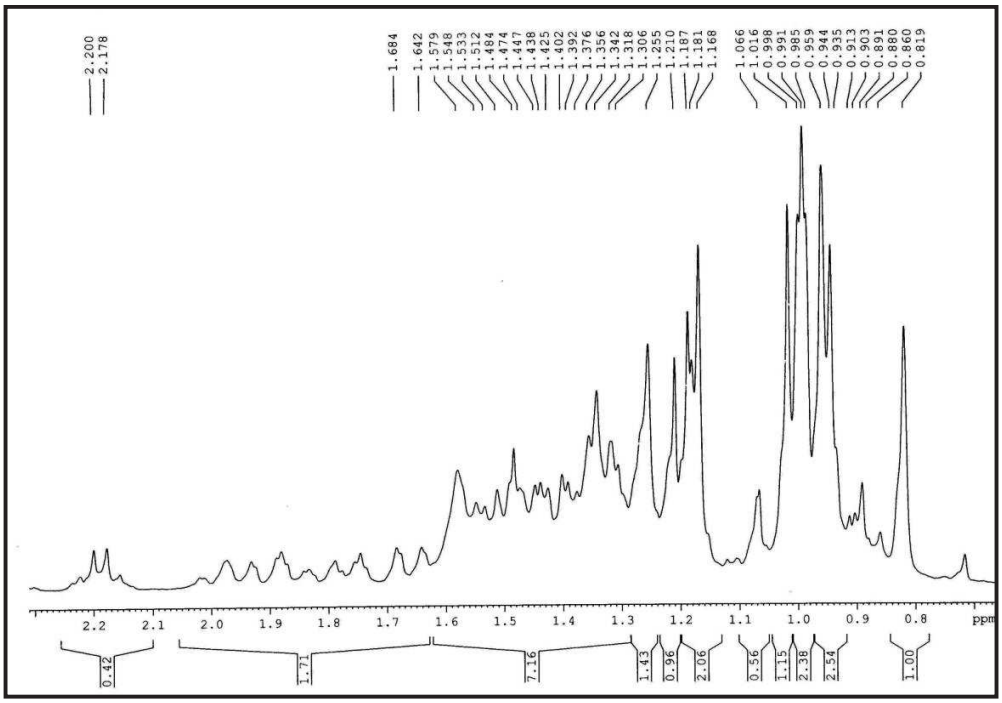


Figure **4.44** Expanded [1]H NMR spectrum of 3α,4α-epoxy friedelane(**1332**).

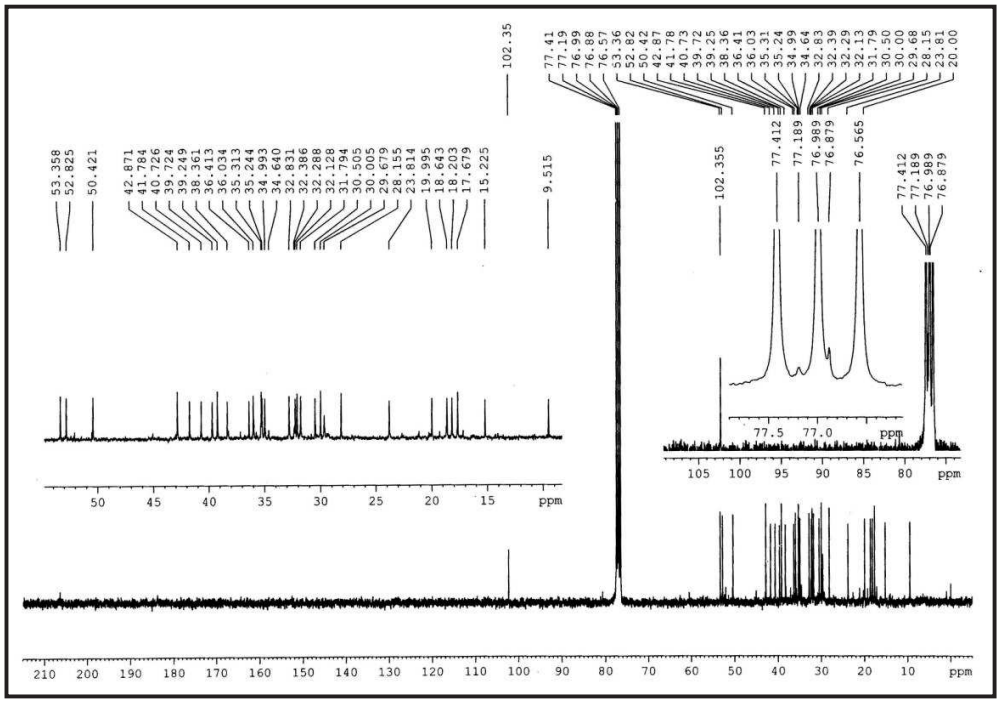


Figure **4.45** ^{13}C NMR spectrum of 3α,4α-epoxy friedelane(**1332**).

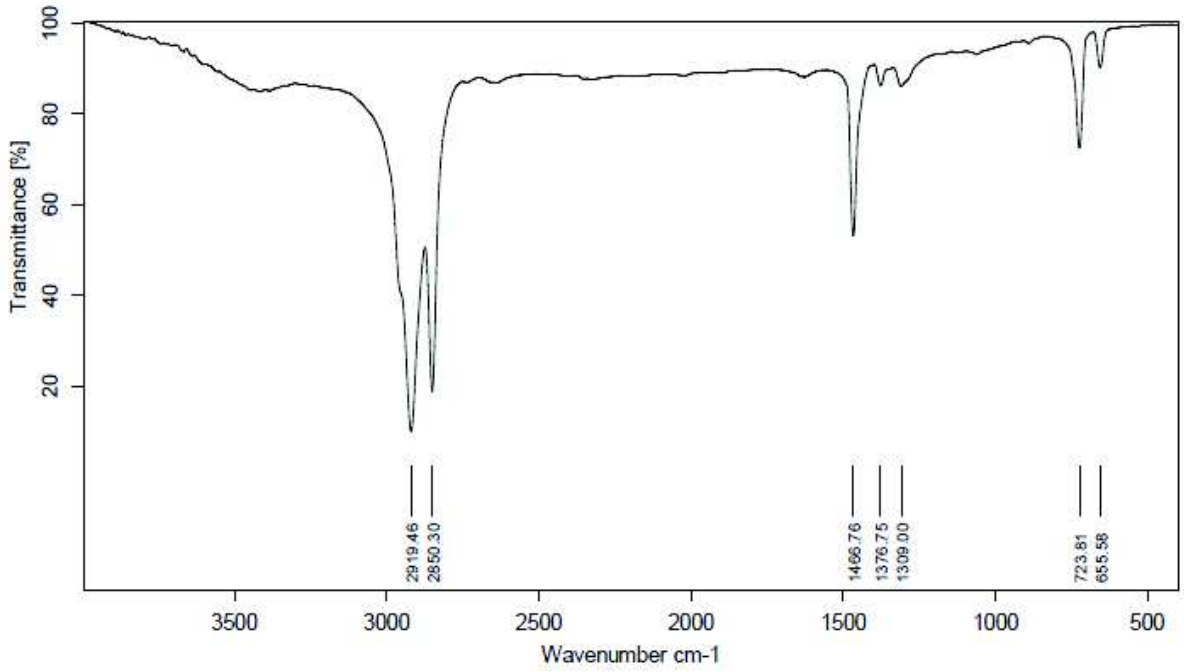


Figure 4.46 FTIR spectrum of 3α,4α-epoxy friedelane(**1332**).

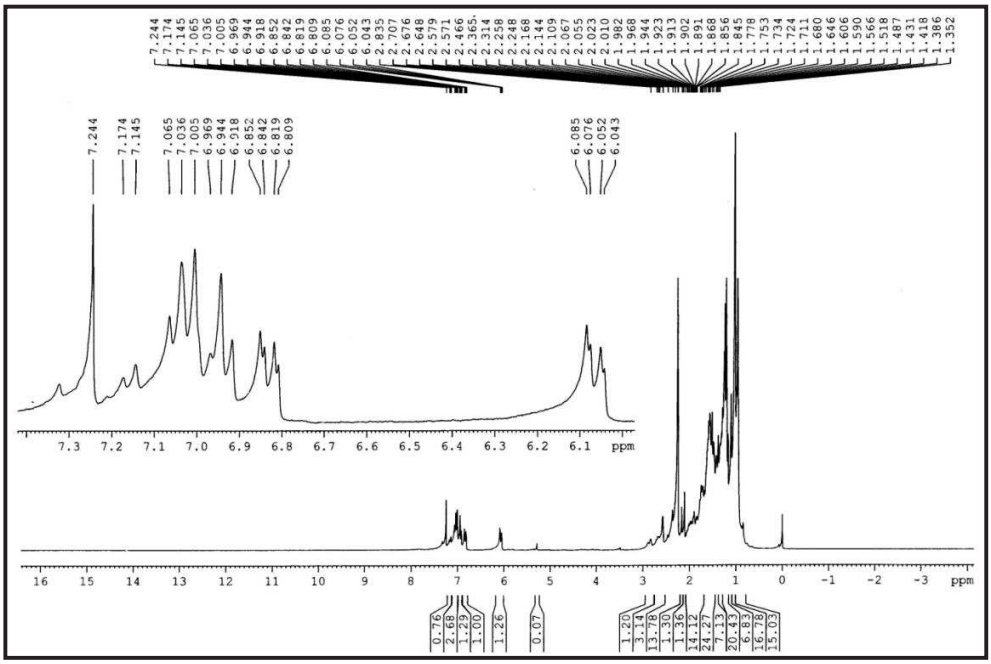


Figure 4.47 [1]H NMR spectrum of 24-*nor*friedel-1, 3, 5 (10), 6-tetraene (**1333**).

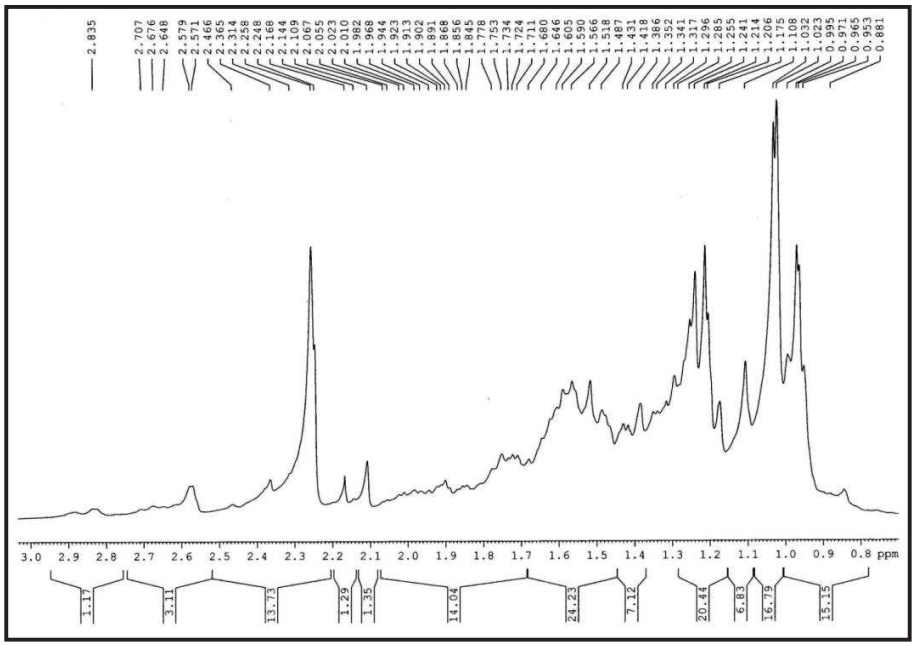


Figure 4.48 [1]H NMR spectrum (partially expanded) of 24-*nor*friedel-1, 3, 5 (10), 6-tetraene (**1333**).

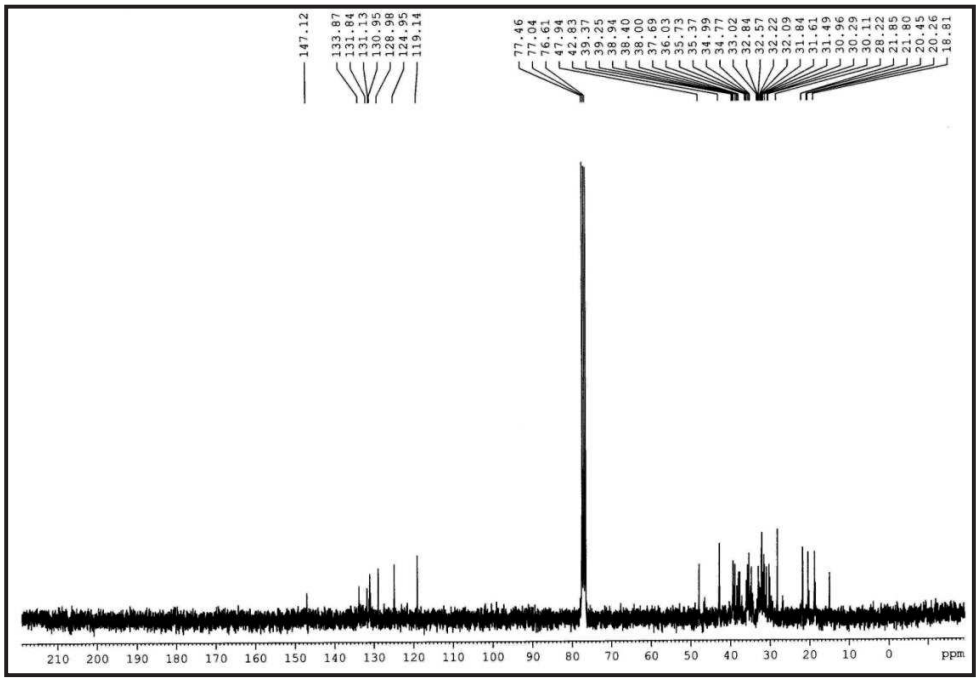


Figure 4.49 ^{13}C NMR spectrum (partially expanded) of 24-*nor*friedel-1, 3, 5 (10), 6-tetraene (**1333**).

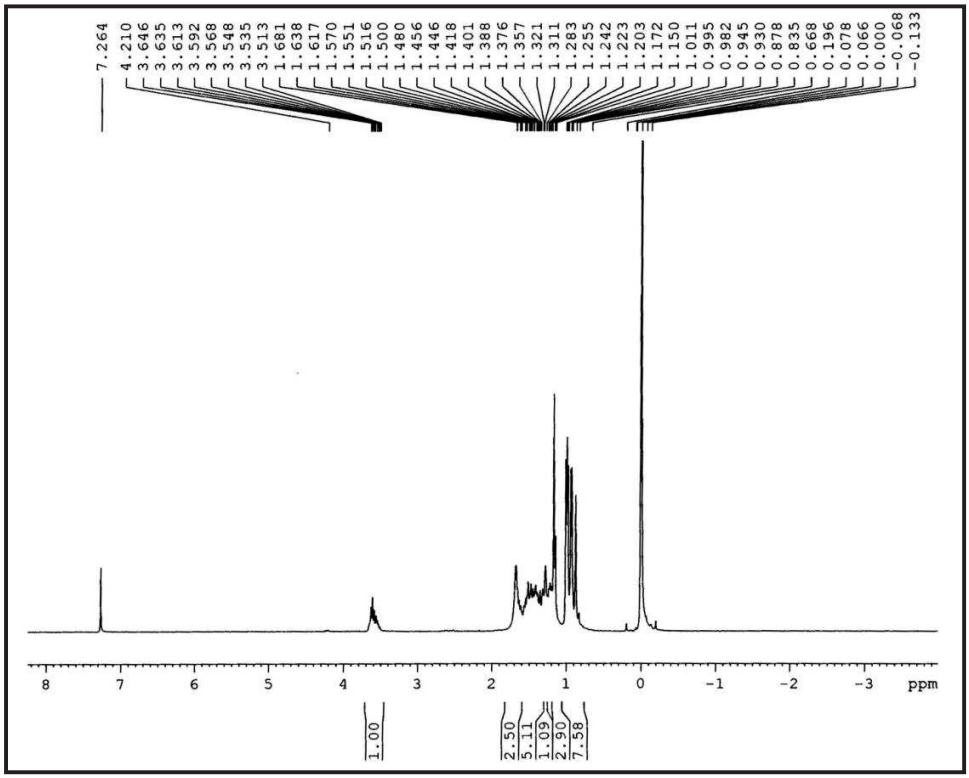


Figure 4.50 ^{1}H NMR spectrum of 3,4-seco-friedelane-3,4-diol (**1337**).

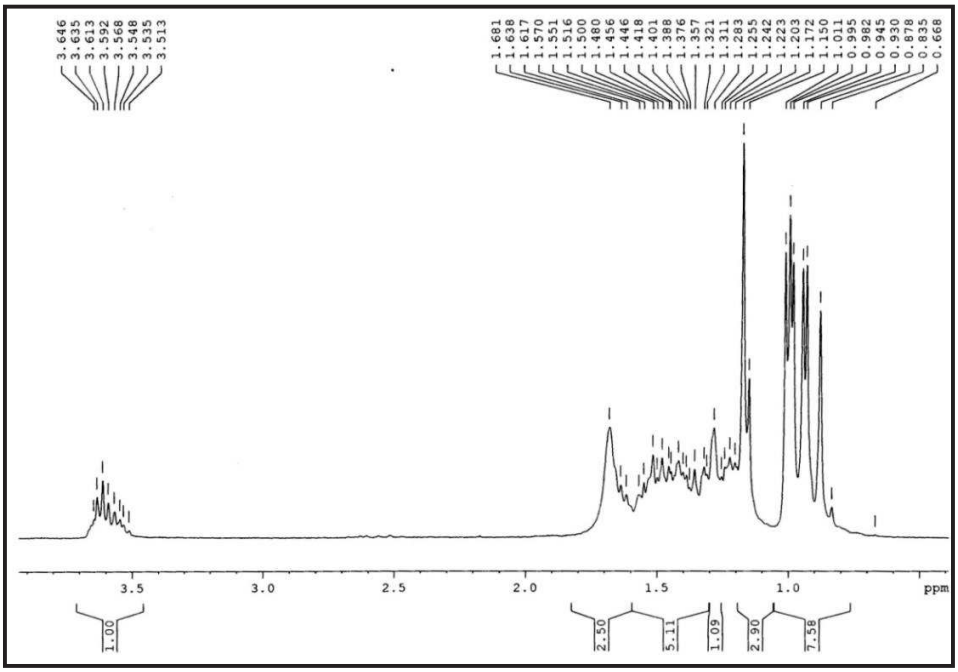


Figure 4.51 [1]H NMR spectrum (partially expanded) of 3,4-seco-friedelane-3,4-diol (**1337**).

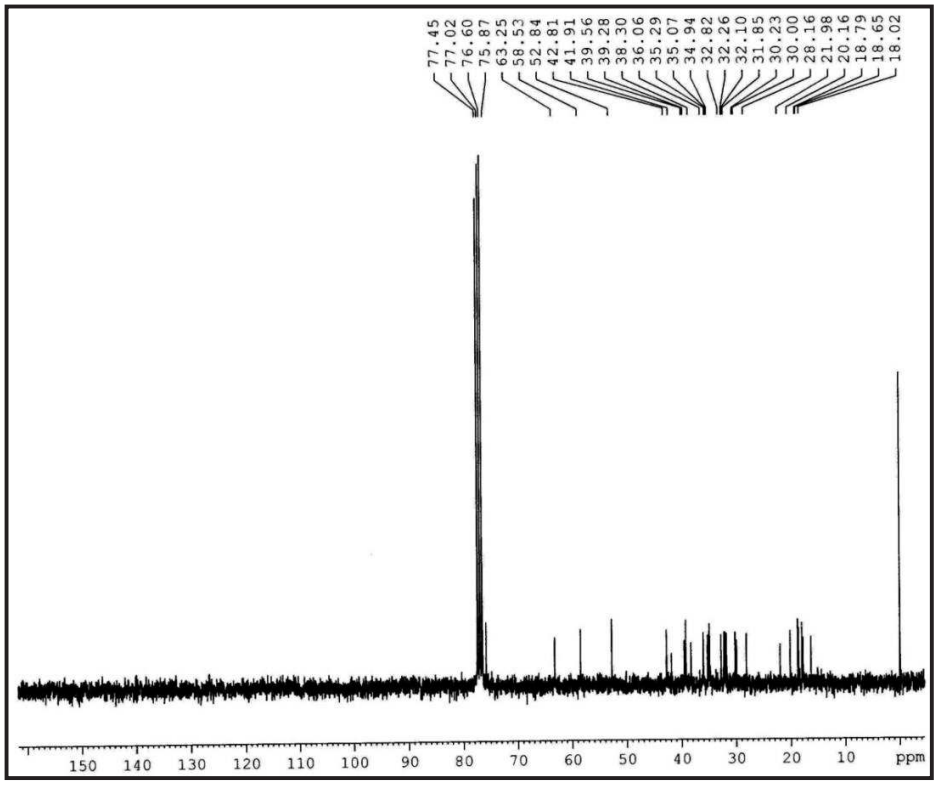


Figure 4.52 [13]C NMR spectrum of 3,4-Seco-friedelane-3,4-diol (**1337**).

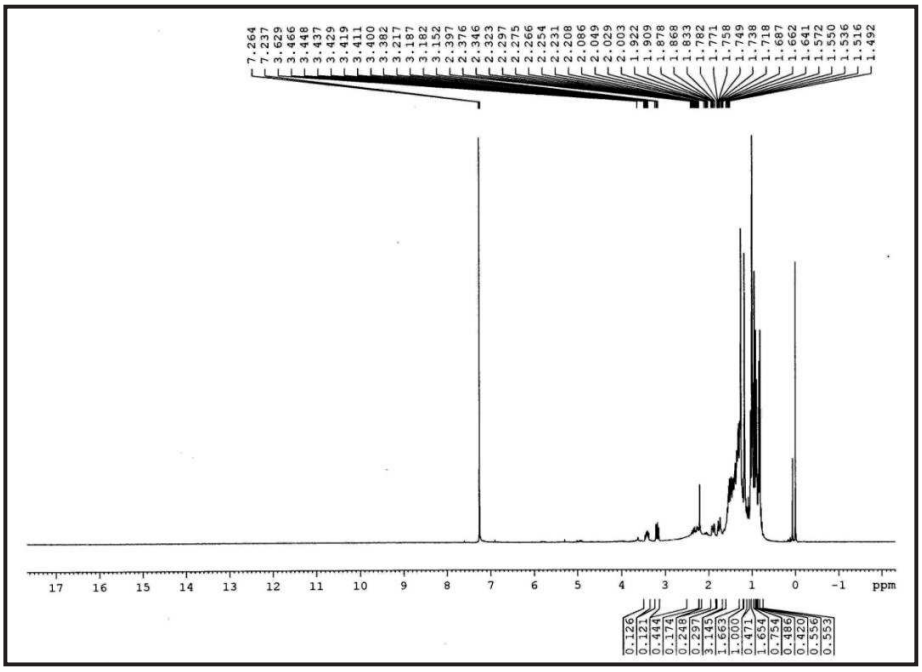


Figure 4.53 [1]H NMR spectrum of 3-*epi*pachysan diol-A (**1338**).

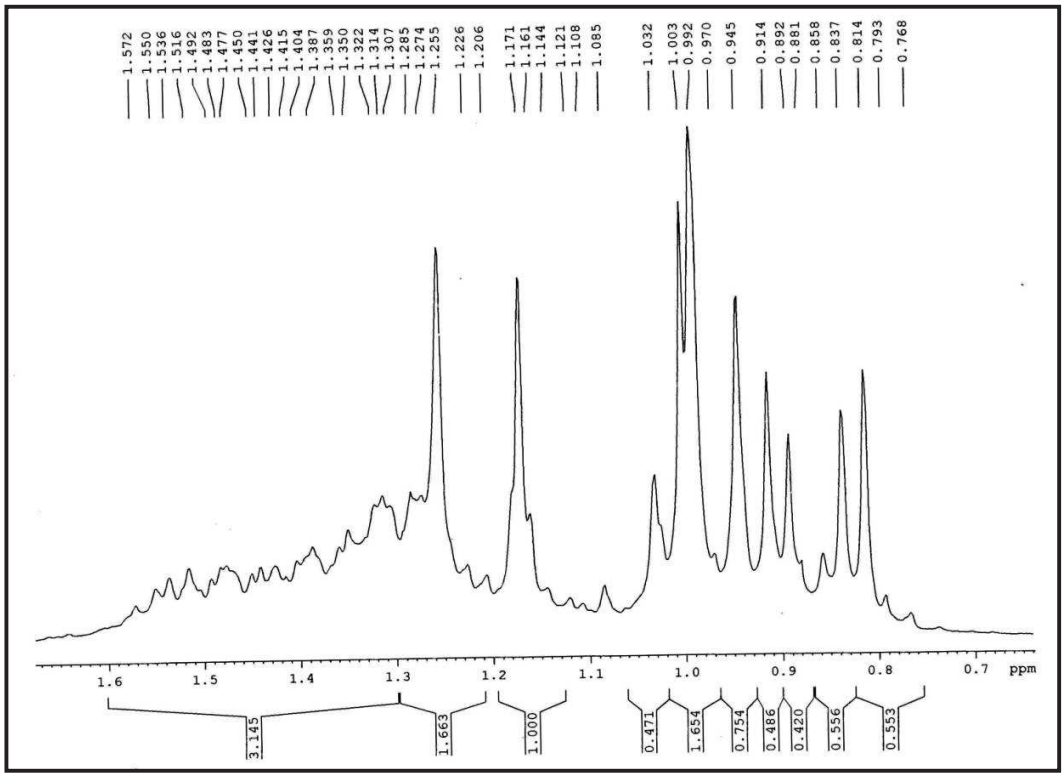


Figure 4.54 [1]H NMR spectrum (partially expanded) 3-*epi*pachysan diol-A (**1338**).

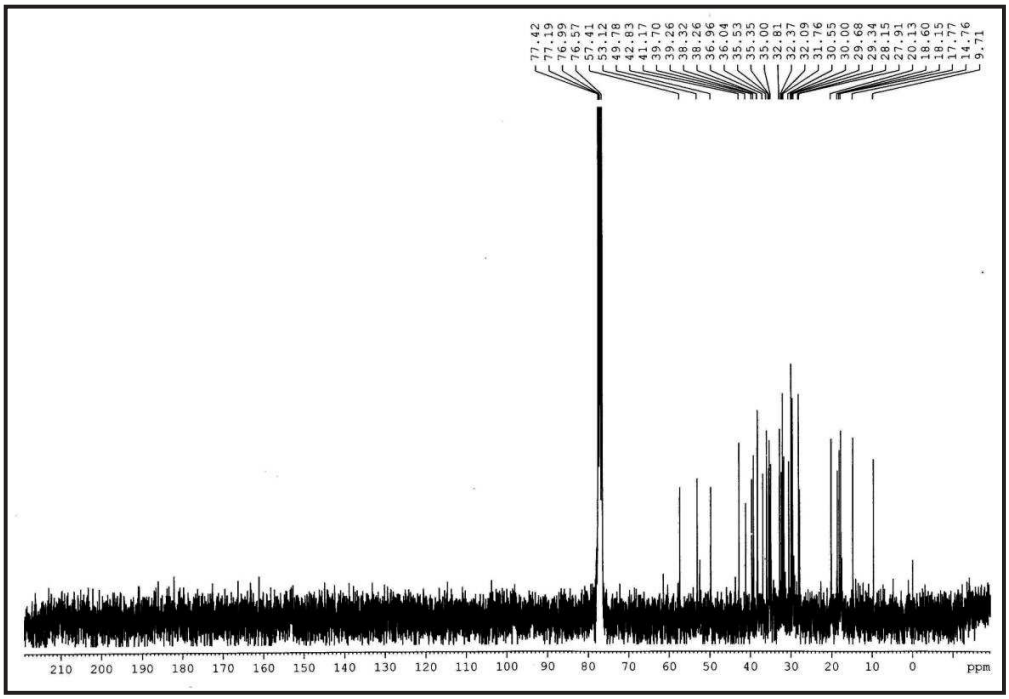


Figure 4.55 ^{13}C NMR spectrum of 3-*epi*pachysan diol-A (**1338**).

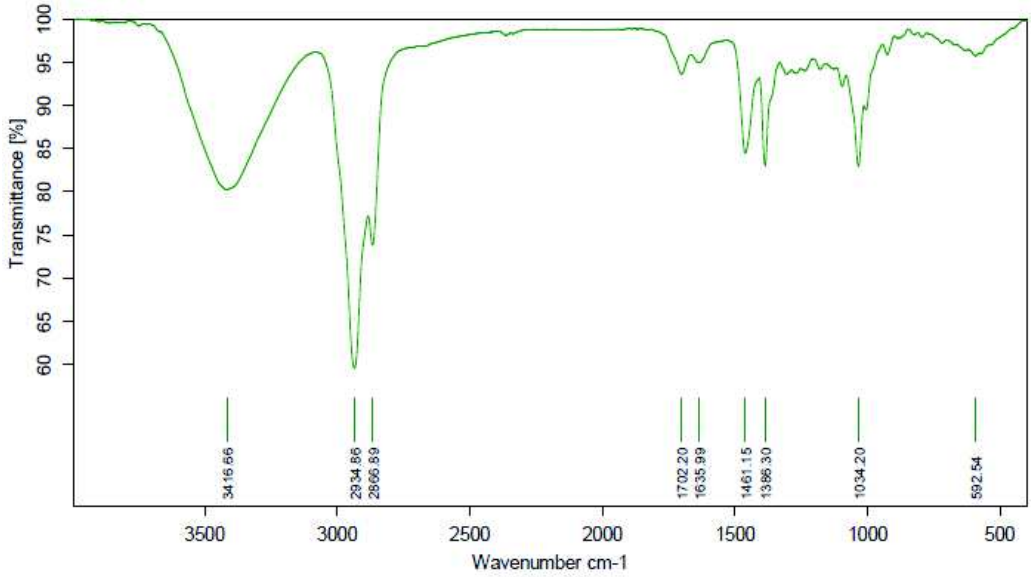


Figure 4.56 FTIR spectrum of 3-*epi*pachysan diol-A (**1338**).

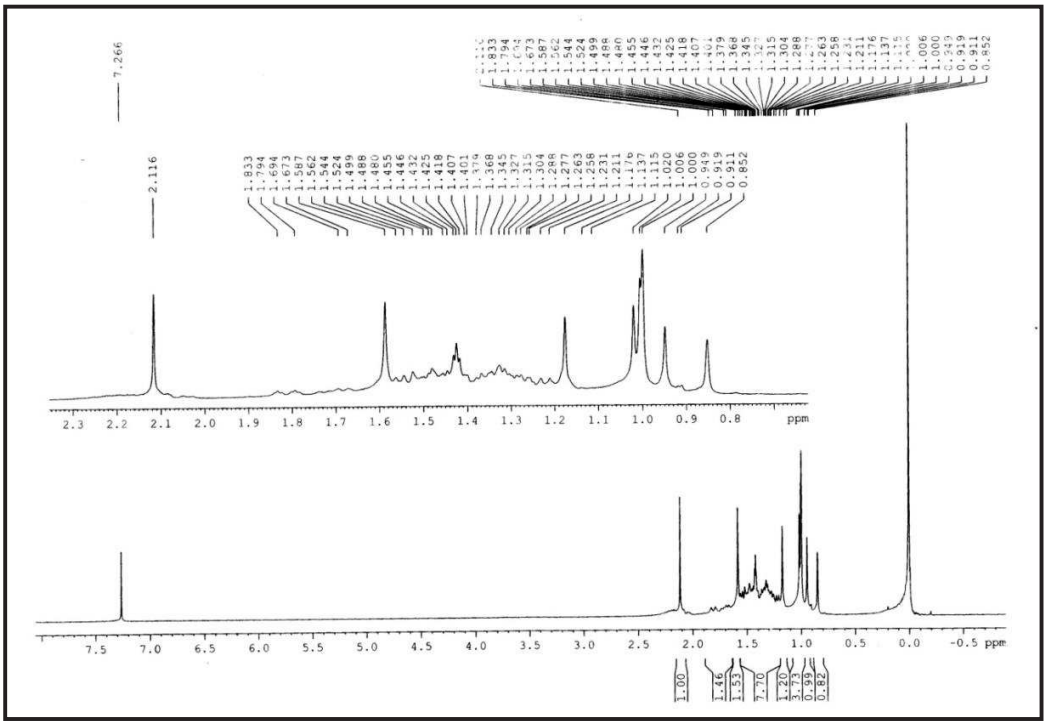


Figure 4.57 ^{1}H NMR spectrum of friedel-3-enol acetate (**1339**).

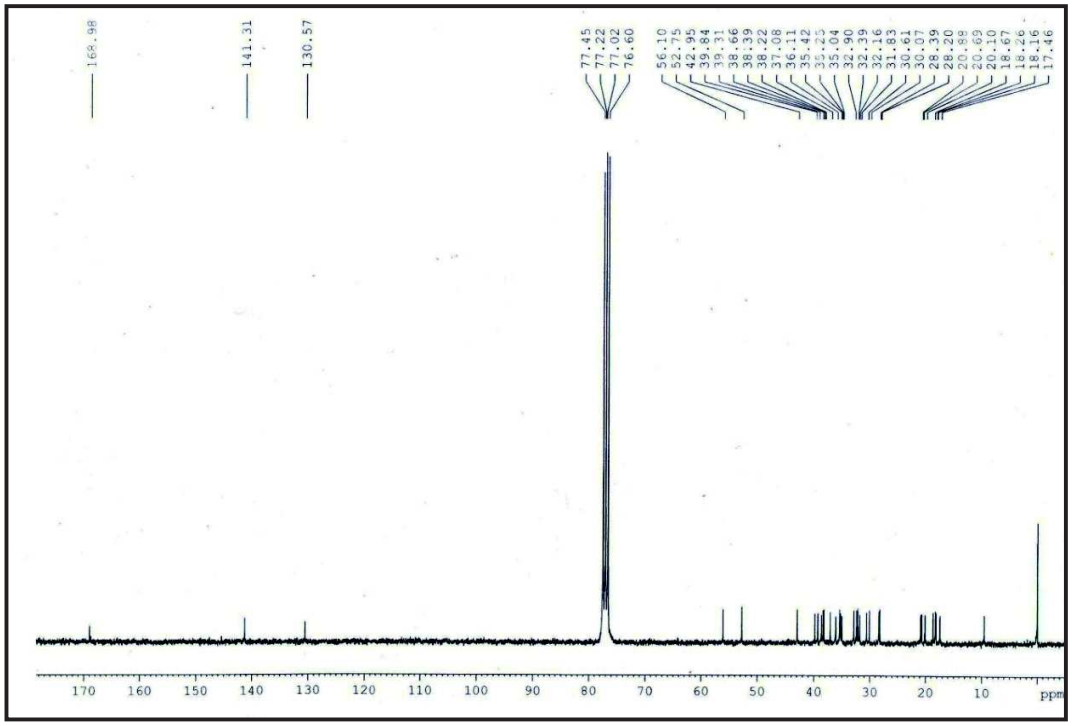


Figure 4.58 ^{13}C NMR spectrum of friedel-3-enol acetate (**1339**).

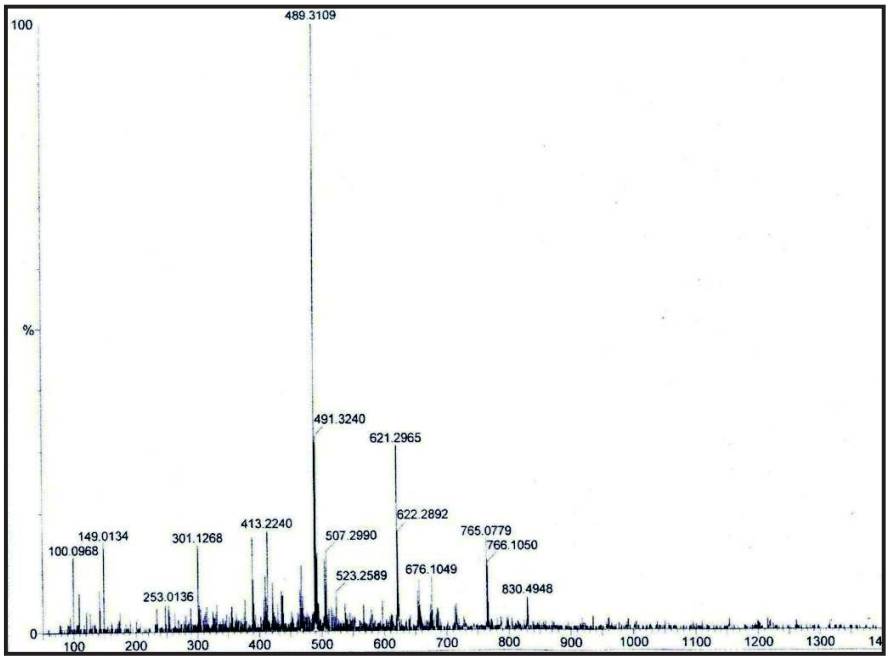


Figure 4.59 Mass spectrum of friedel-3-enol acetate (**1339**).

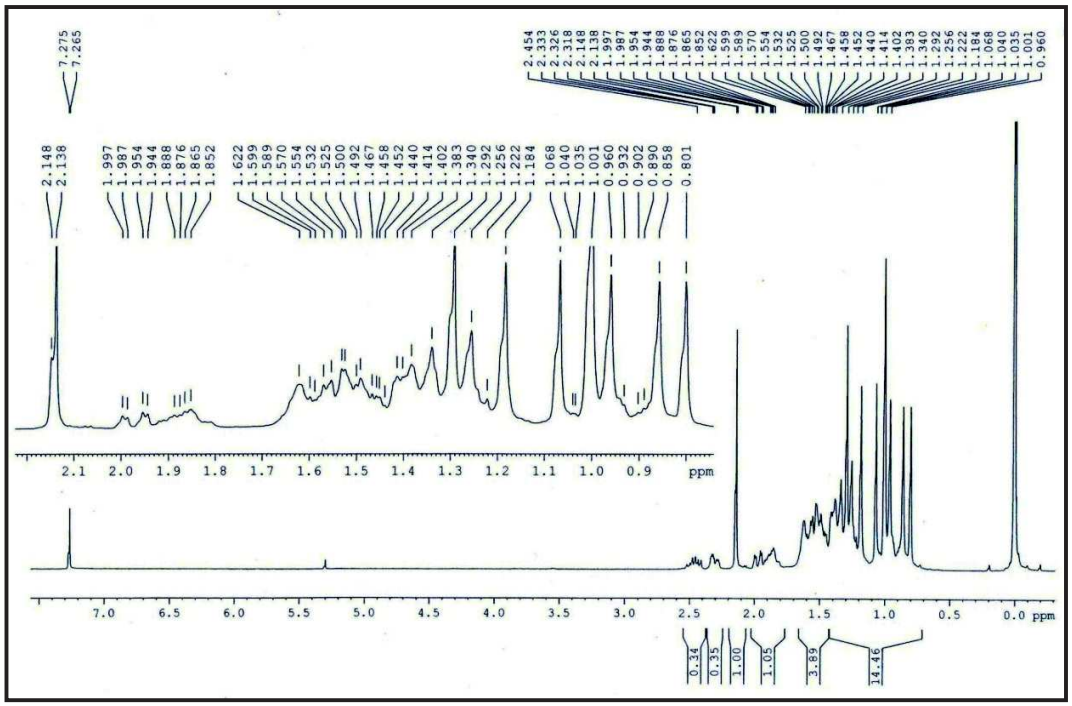


Figure 4.60 ^{1}H NMR spectrum of 4α-acetate friedel-3-one (**1340**).

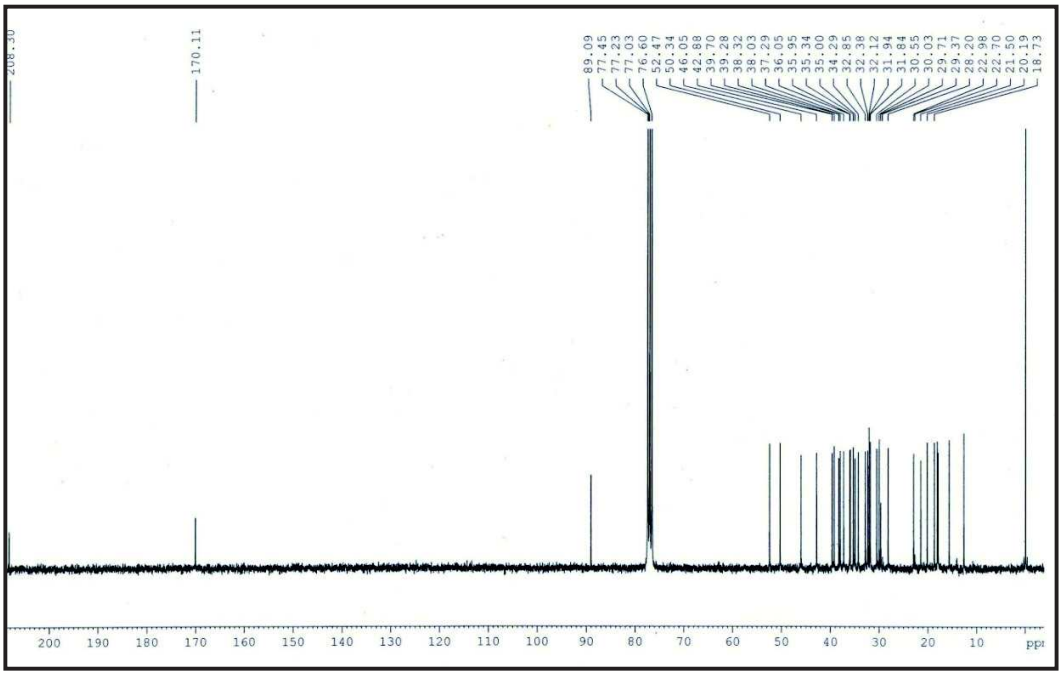


Figure 4.61 ^{13}C NMR spectrum of 4α-acetate friedel-3-one (**1340**).

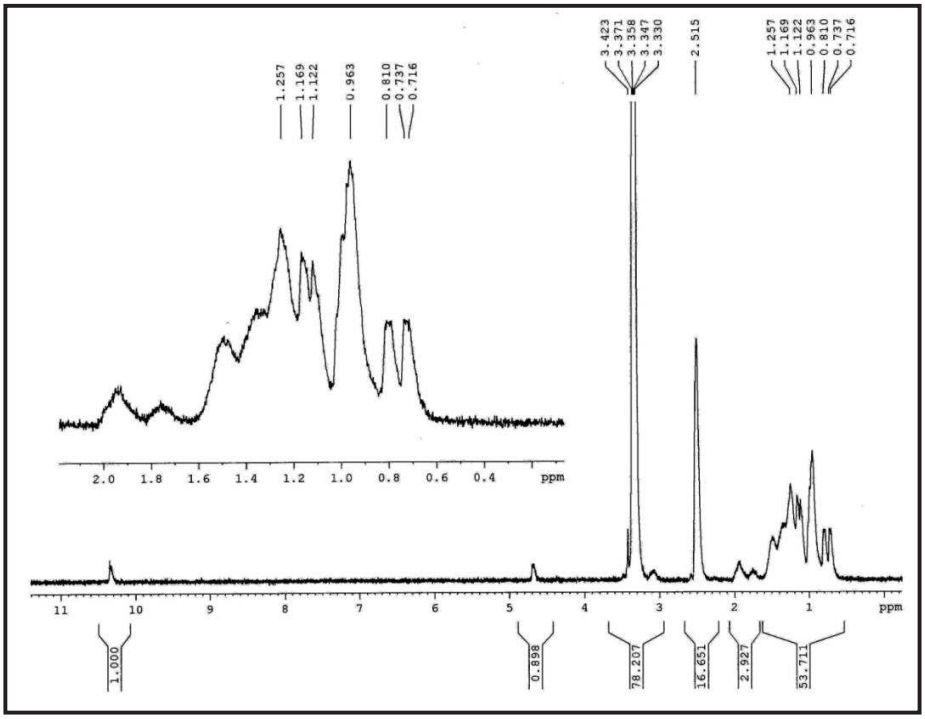


Figure 4.62 ^{1}H NMR spectrum of 4α-hydroxy friedelane-3-oxime (**1341**).

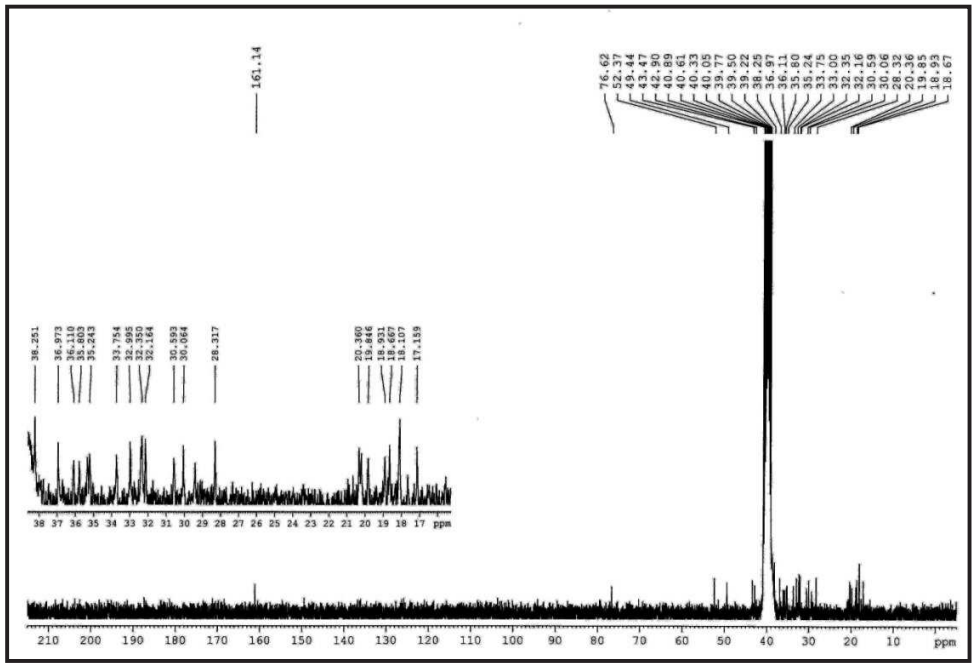


Figure 4.63 ^{13}C NMR spectrum of 4α-hydroxy friedelane-3-oxime (**1341**).

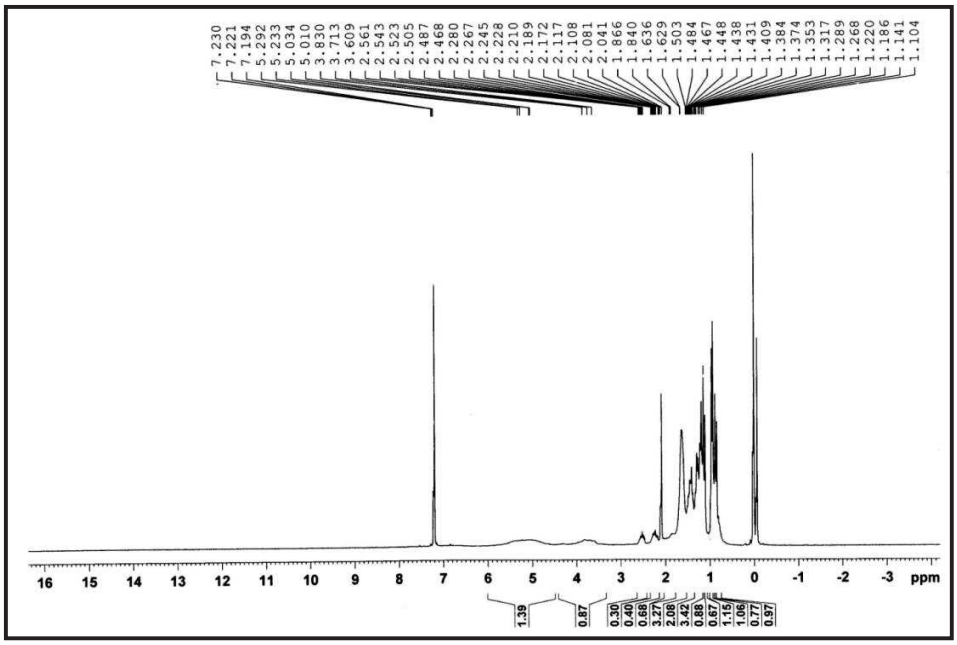


Figure 4.64 ^{1}H NMR spectrum of 3β-amino-4α-hydroxyfriedelane (**1342**).

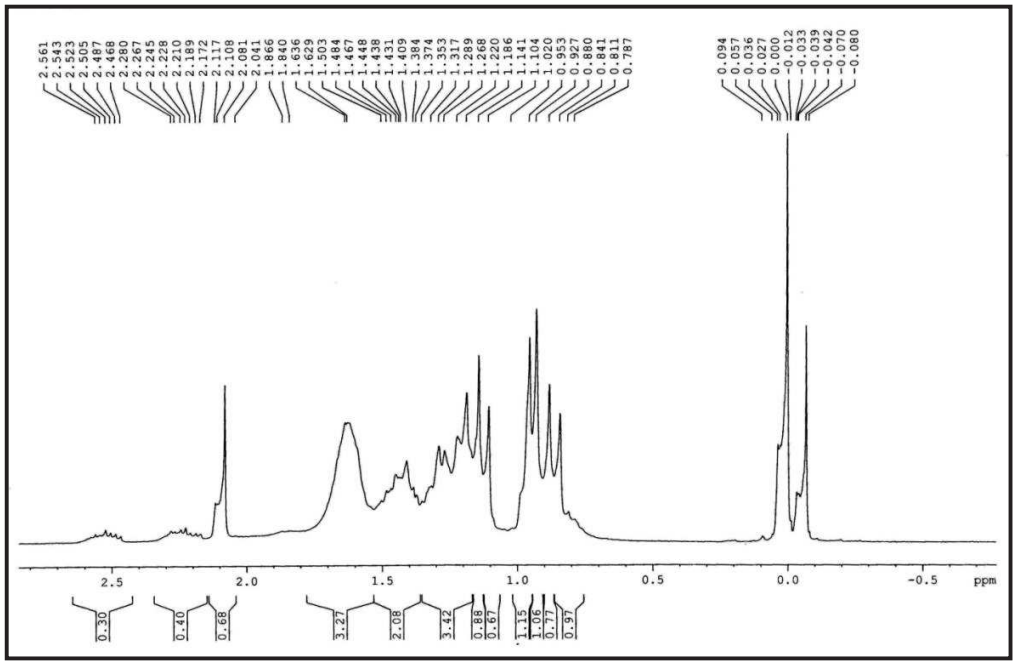


Figure 4.65 [1]H NMR spectrum (partially expanded) of 3β-amino-4α-hydroxyfriedelane (**1342**).

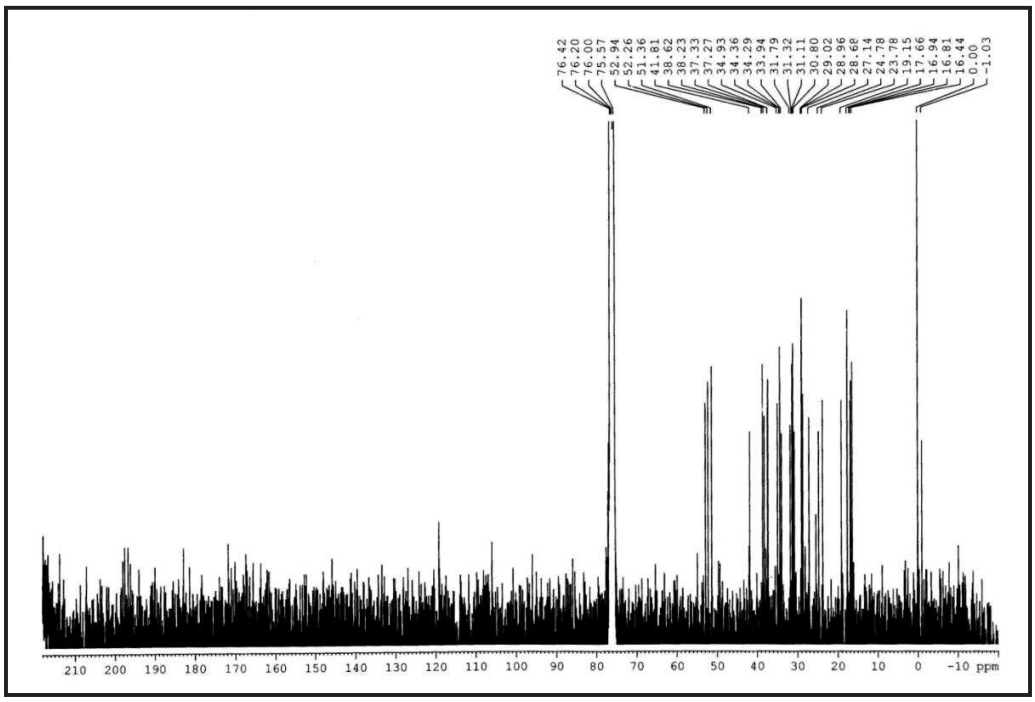


Figure 4.66 [13]C NMR spectrum of 3β-amino-4α-hydroxyfriedelane (**1342**).

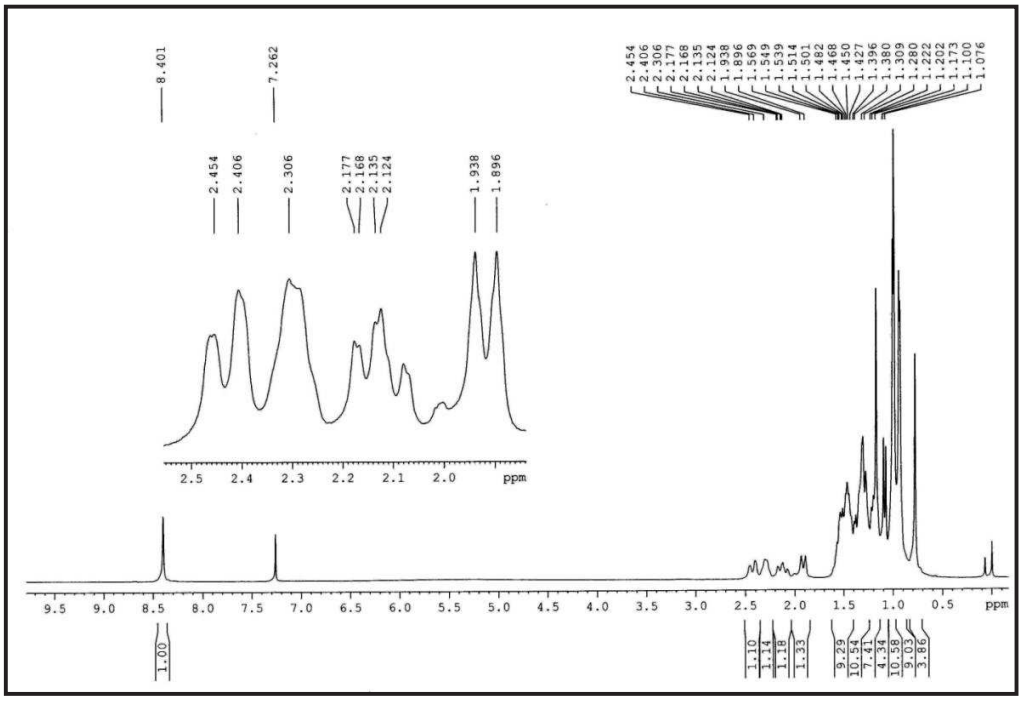


Figure 4.67 [1]H NMR spectrum of 3-chlorofriedel-2-ene-2-carboxaldoxime (**1343**).

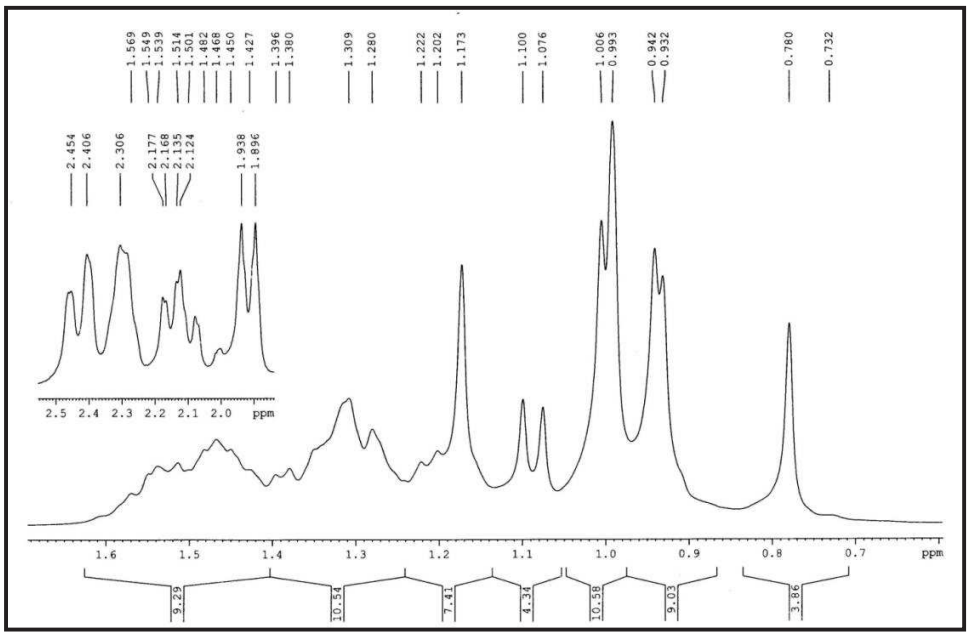


Figure 4.68 [1]H NMR spectrum (partially expanded) of 3-chlorofriedel-2-ene-2-carboxaldoxime (**1343**).

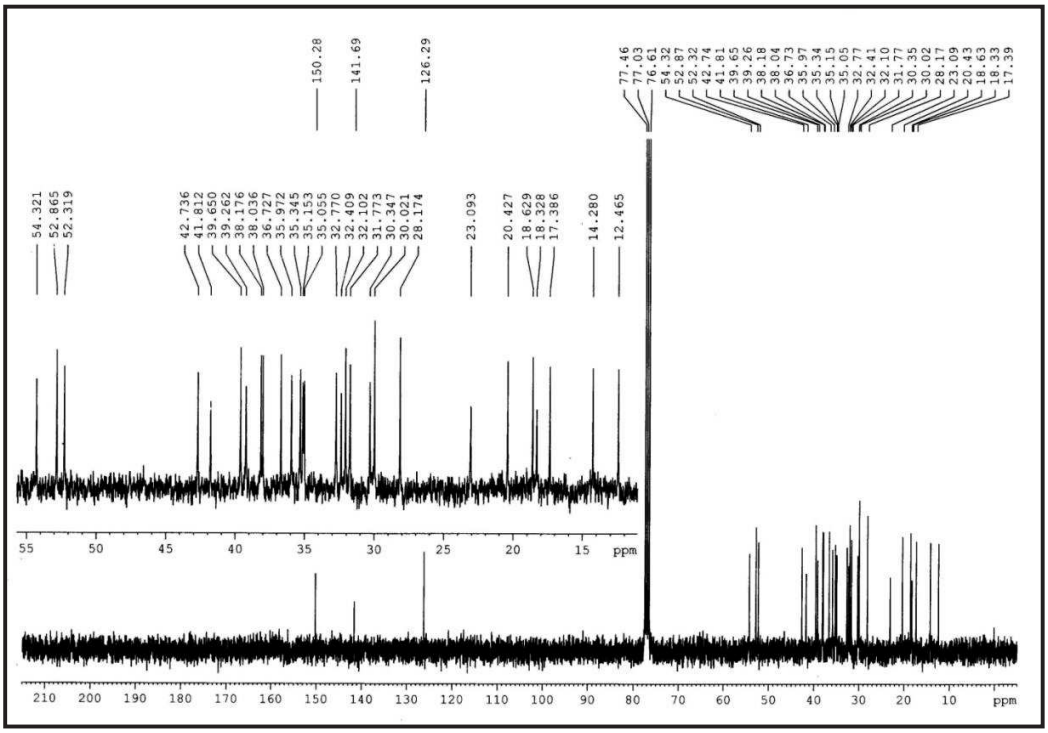


Figure 4.69 ^{13}C NMR spectrum of 3-chlorofriedel-2-ene-2-carboxaldoxime (**1343**).

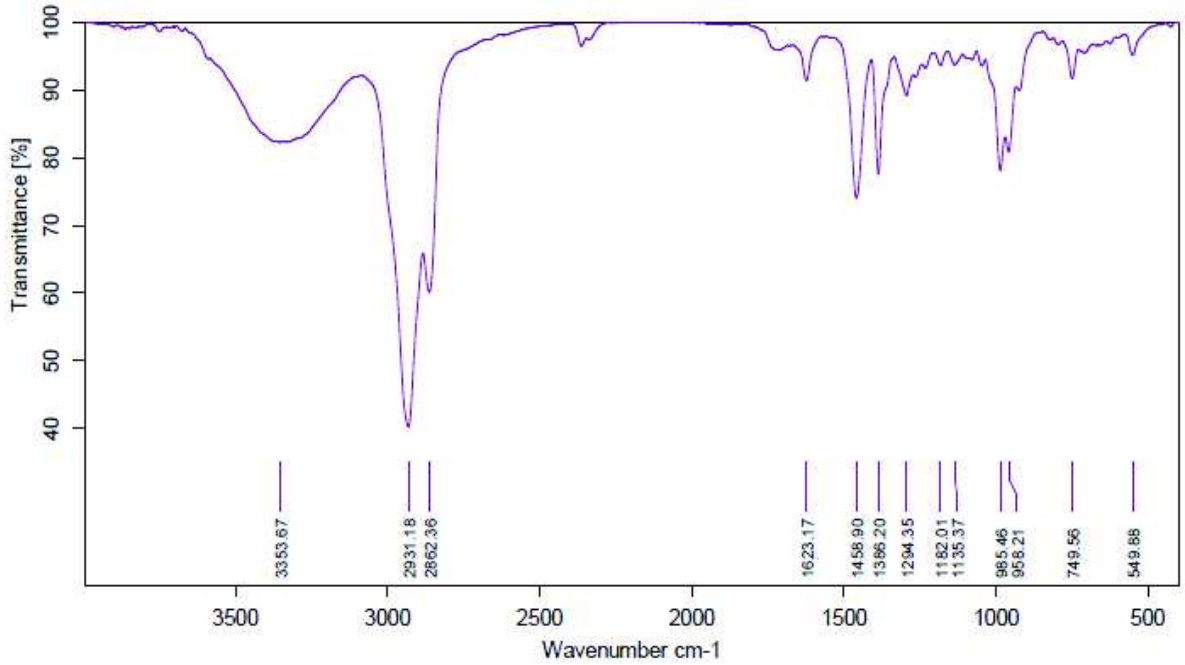


Figure 4.70 FTIR spectrum of 3-chlorofriedel-2-ene-2-carboxaldoxime (**1343**).

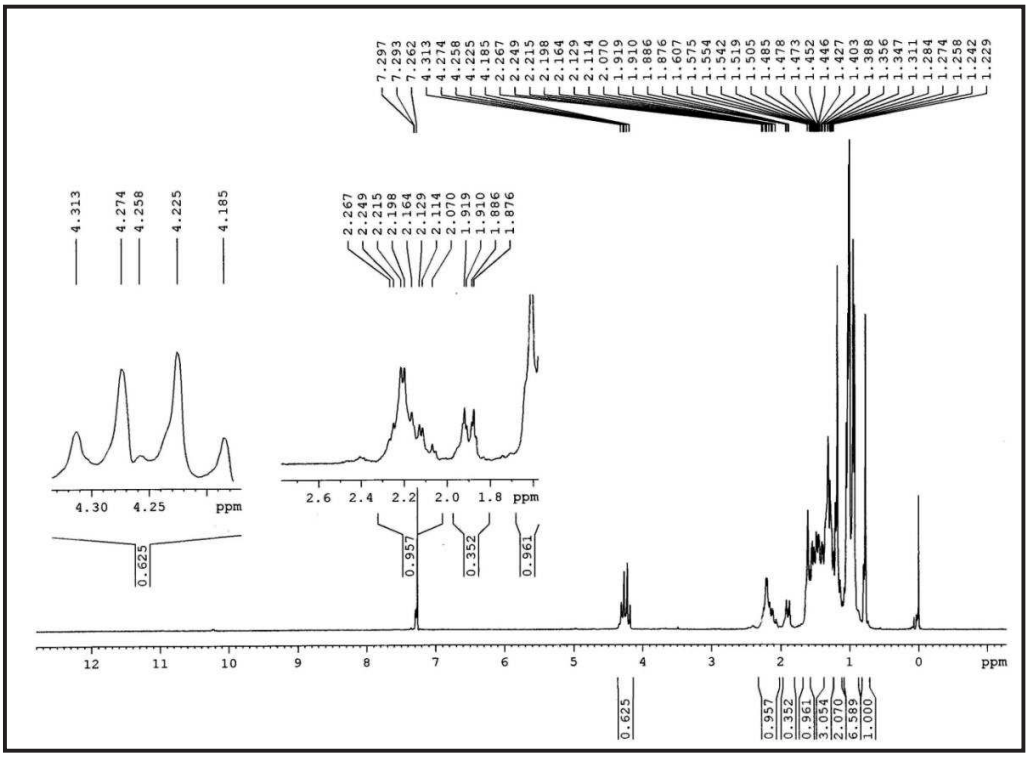


Figure 4.71 [1]H NMR spectrum of 3-chloro-2-hydroxymethyl-friedel-2-ene (**1344**).

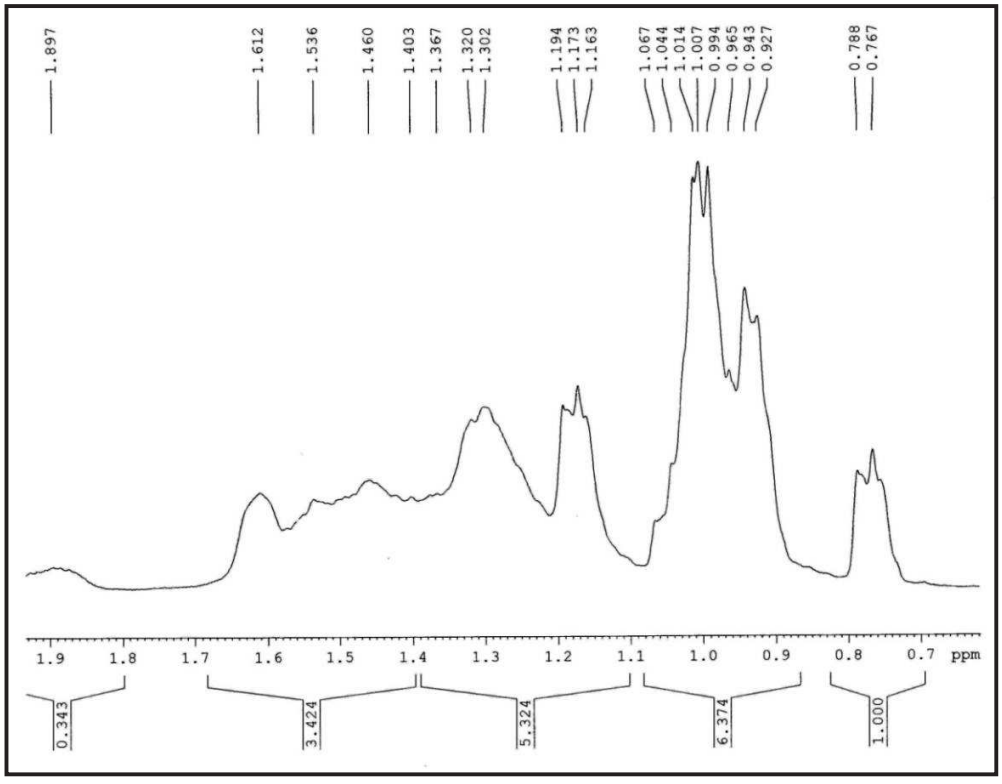


Figure 4.72 [1]H NMR spectrum (partially expanded) of 3-chloro-2-hydroxymethyl-friedel-2-ene (**1344**).

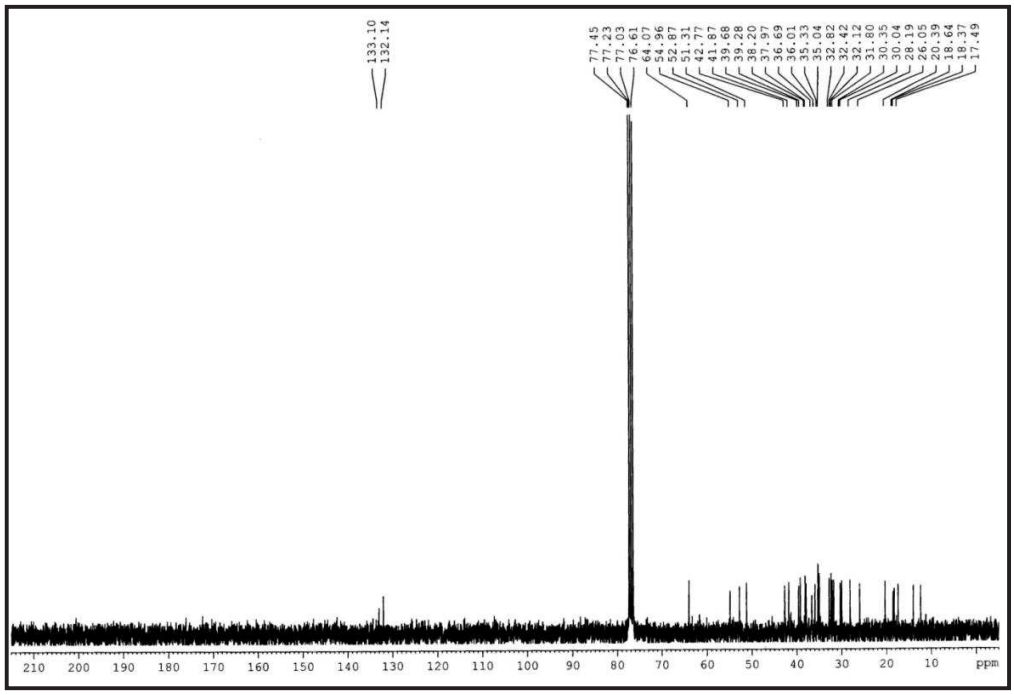


Figure 4.73 ^{13}C NMR spectrum of 3-chloro-2-hydroxymethyl-friedel-2-ene (**1344**).

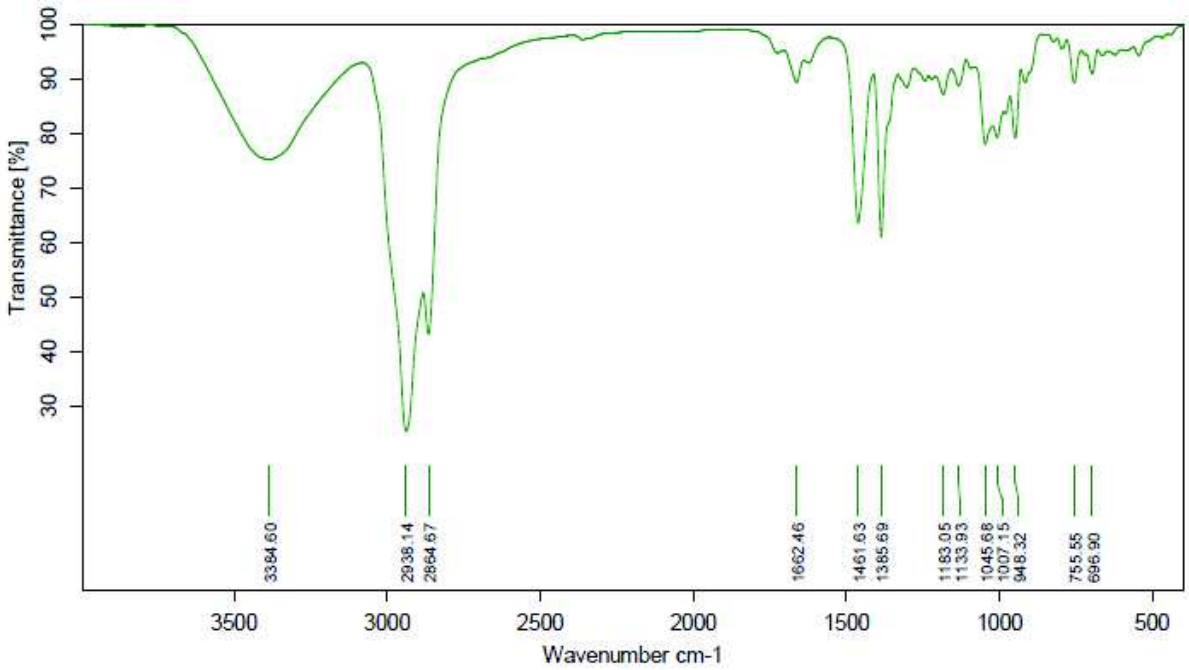


Figure 4.74 FTIR spectrum of 3-chloro-2-hydroxymethyl-friedel-2-ene (**1344**).

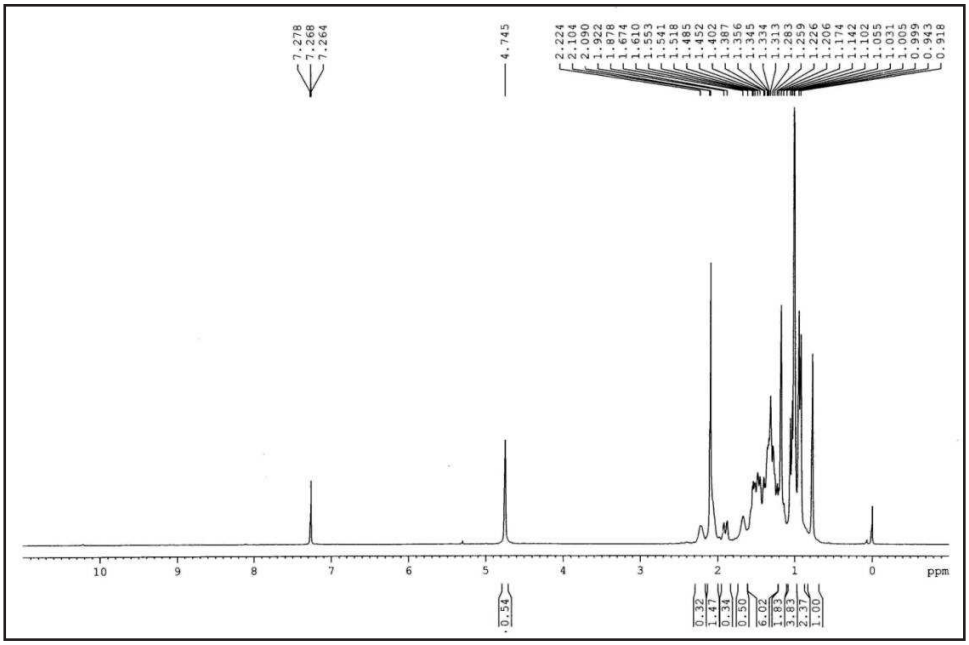


Figure 4.75 ^{1}H NMR spectrum of 2-acetoxymethyl-3-chloro-friedel-2-ene (**1345**).

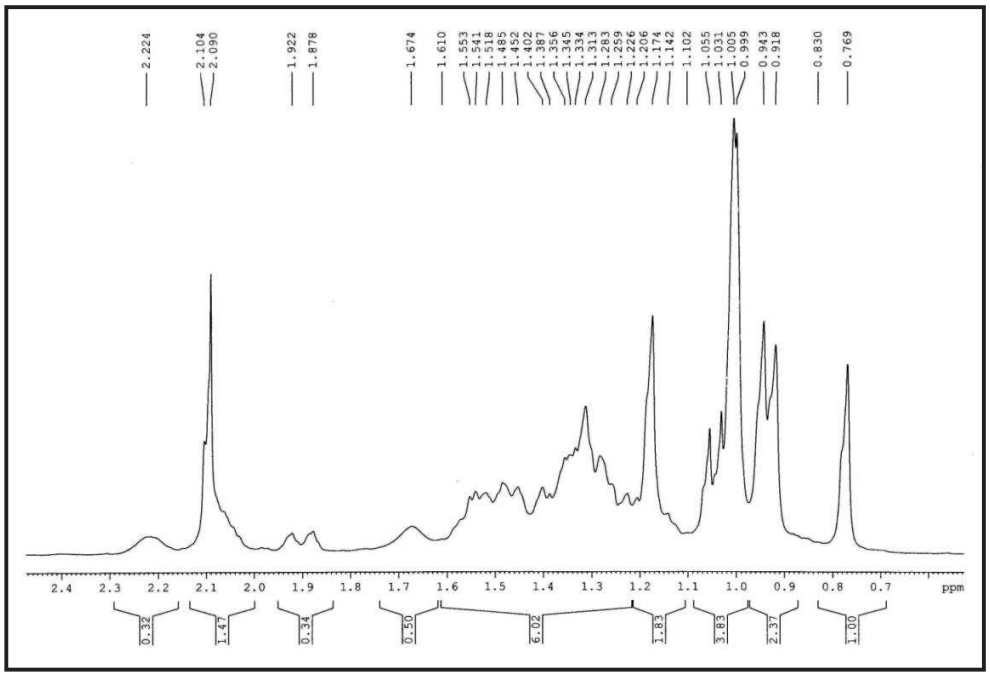


Figure 4.76 ^{1}H NMR spectrum (with partial expansion) of 2-acetoxymethyl-3-chloro-friedel-2-ene (**1345**).

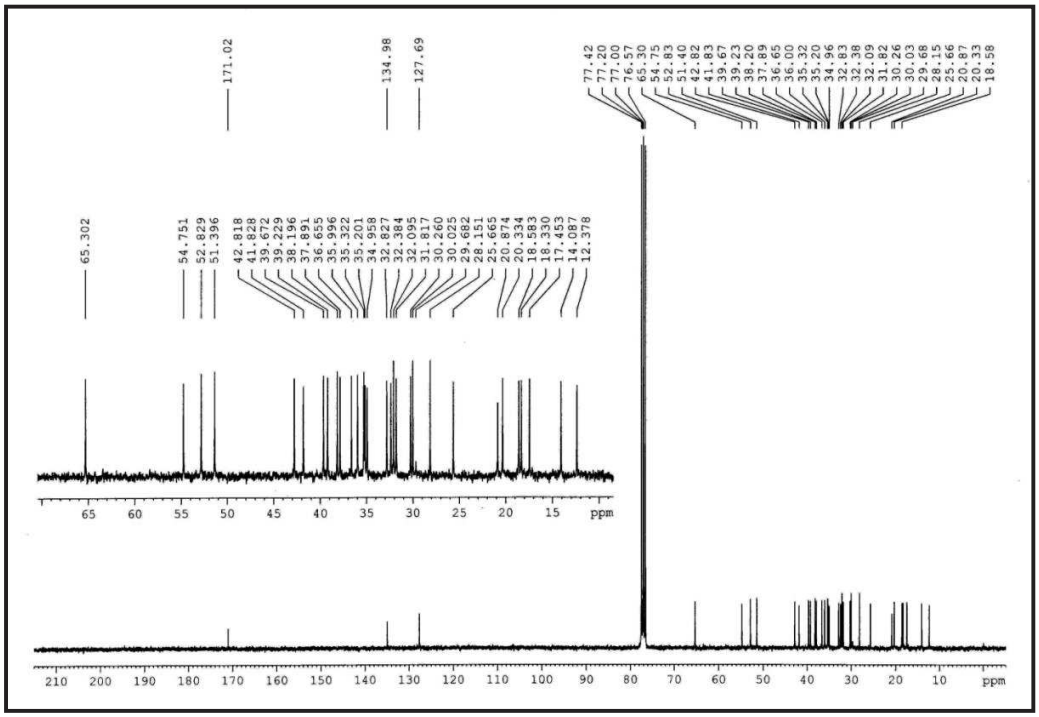


Figure 4.77 ^{13}C NMR spectrum of 2-acetoxymethyl-3-chloro-friedel-2-ene (**1345**).

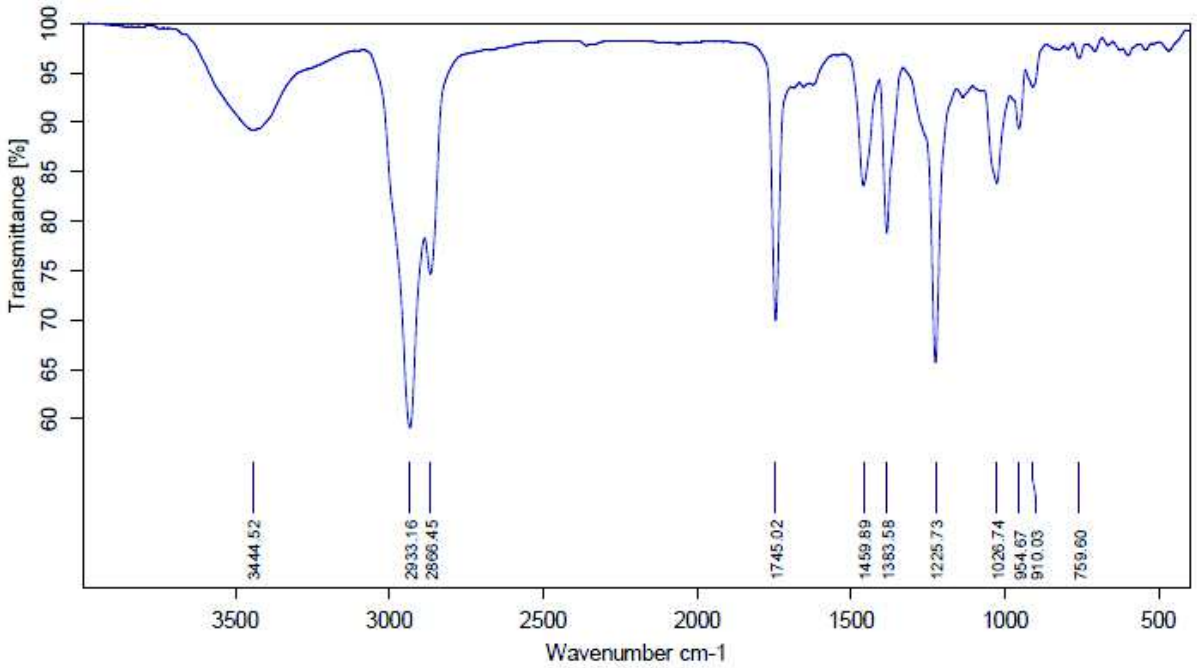


Figure 4.78 FTIR spectrum of 2-acetoxymethyl-3-chloro-friedel-2-ene (**1345**).

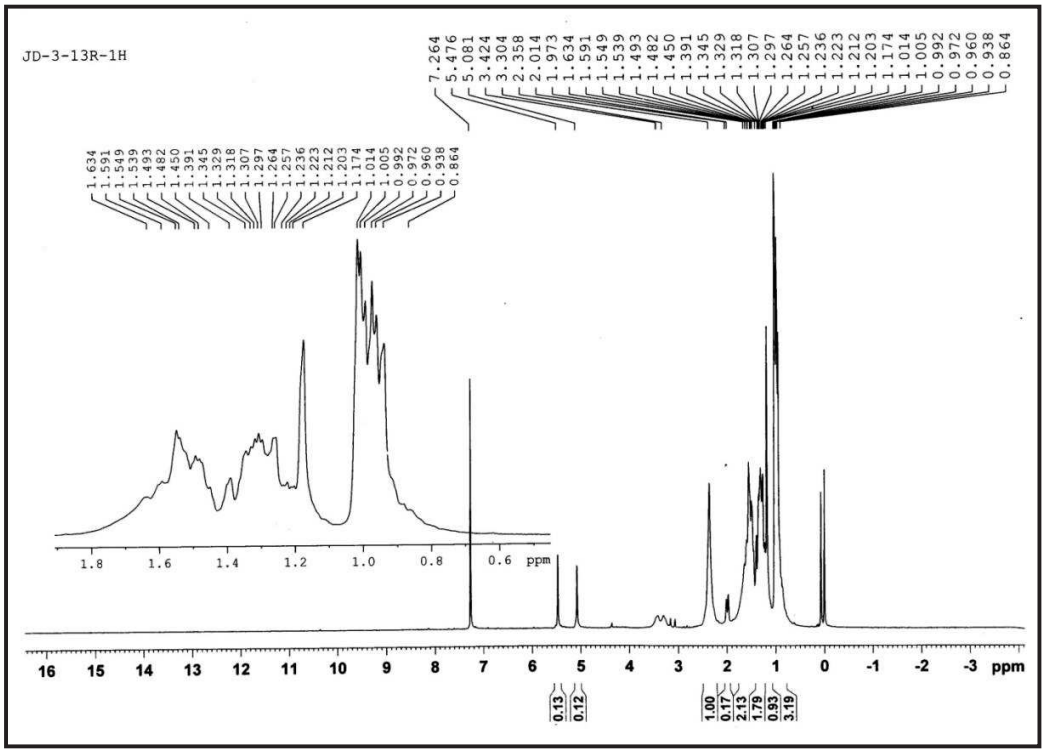


Figure 4.79 [1]H NMR spectrum of 3-chlorofriedel-2-ene-2-carboxamide (**1346**).

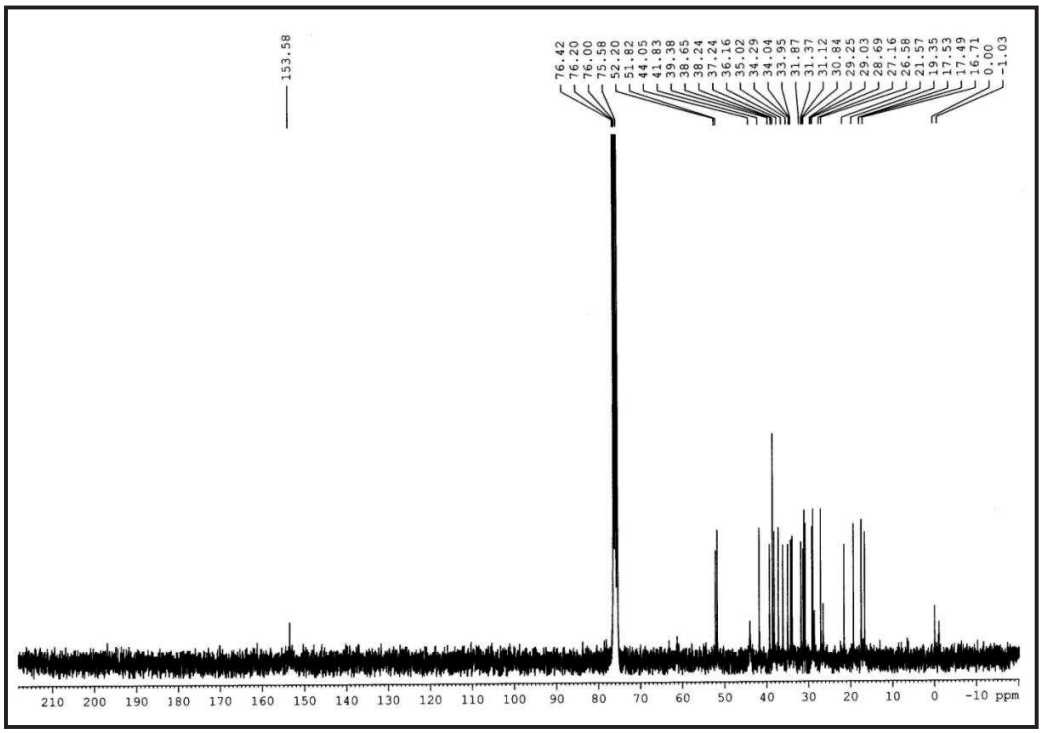


Figure 4.80 [13]C NMR spectrum of 3-chlorofriedel-2-ene-2-carboxamide (**1346**).

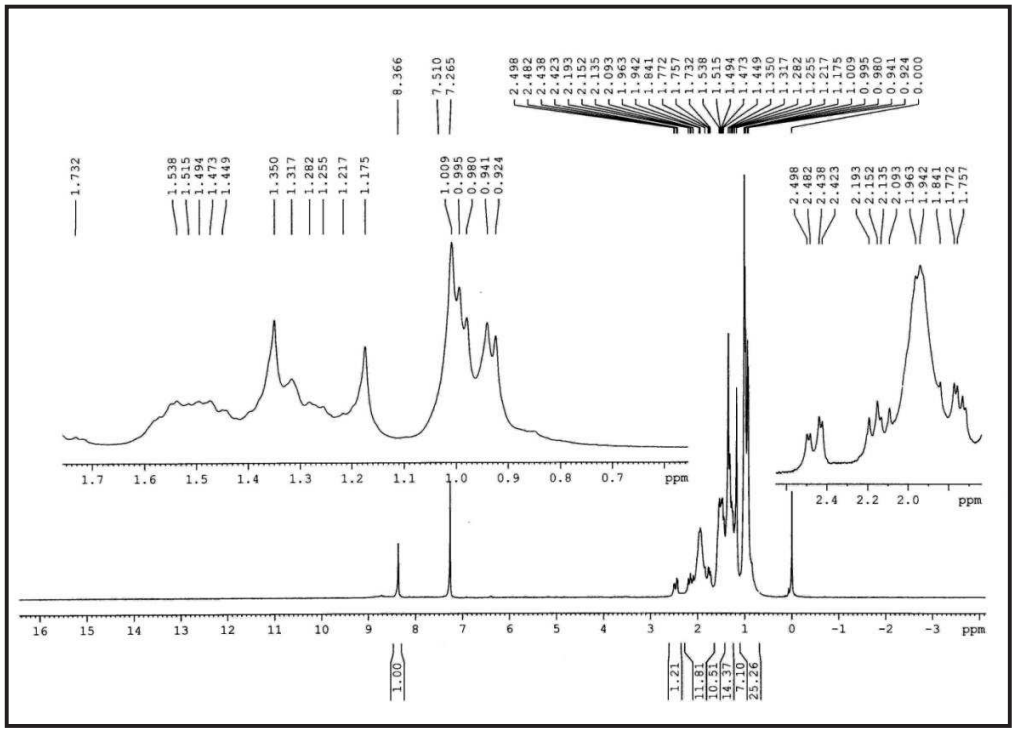


Figure 4.81 ^{1}H NMR spectrum of 3-chloro-4α-hydroxy-2-ene-2-carboxaldoxime (**1347**).

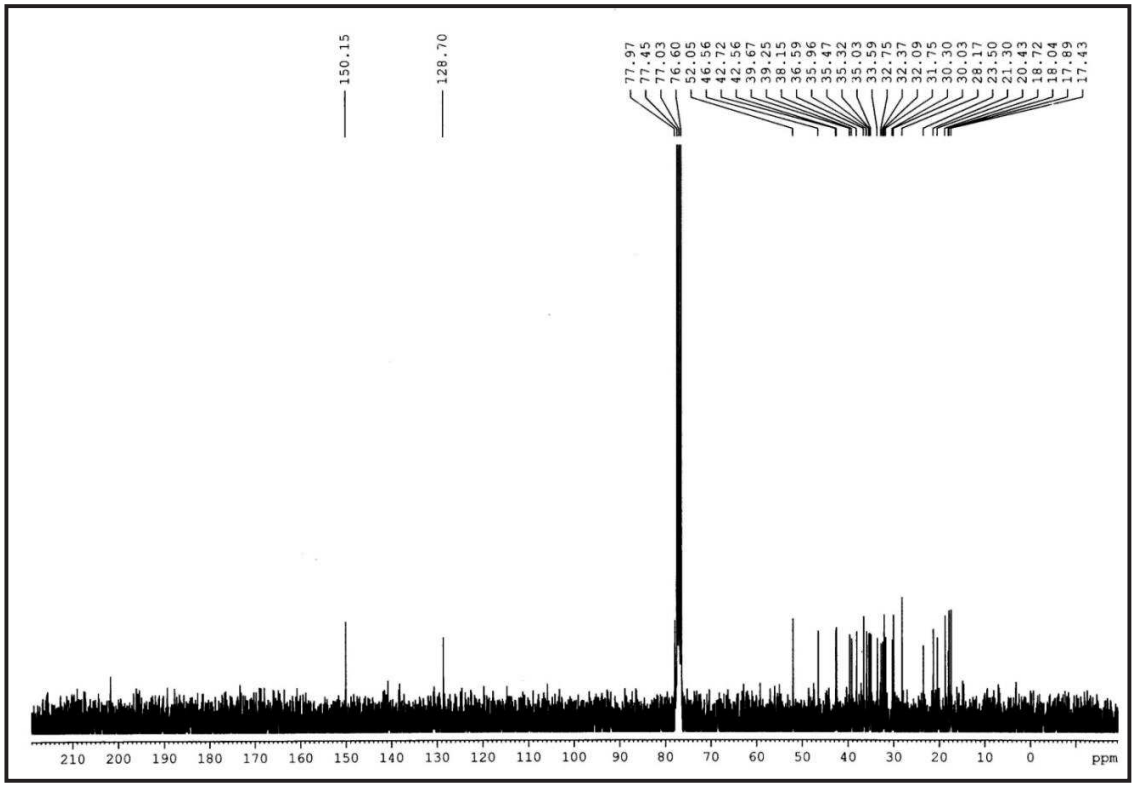


Figure 4.82 ^{13}C NMR spectrum of 3-chloro-4α-hydroxy-2-ene-2-carboxaldoxime (**1347**).

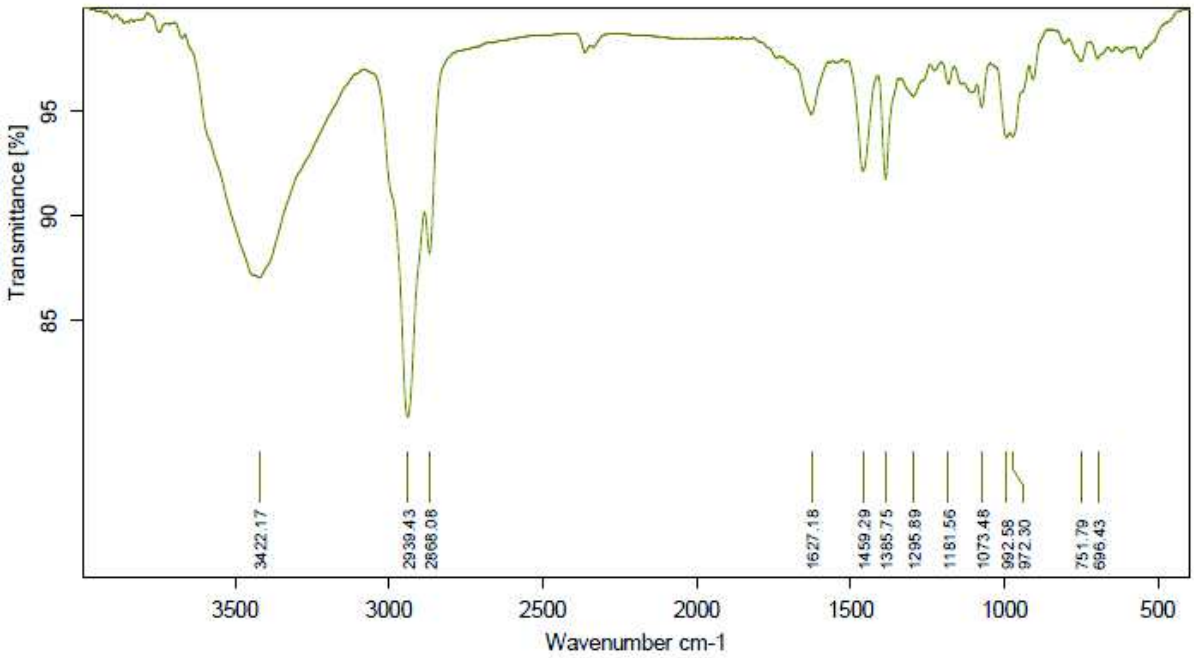


Figure 4.83 FTIR spectrum of 3-chloro-4α-hydroxy-2-ene-2-carboxaldoxime (**1347**).

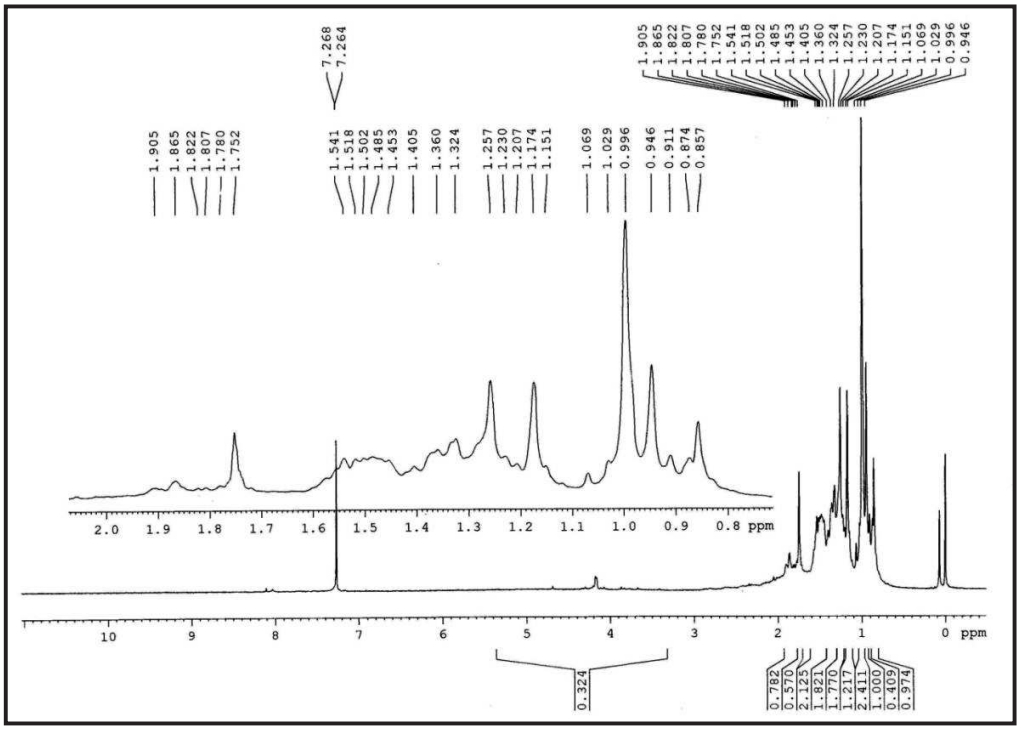


Figure 4.84 ^{1}H NMR spectrum of 2-formyl-3-chloro-4α-hydroxy-2-hydroxymethyl friedel-2-ene (**1348**).

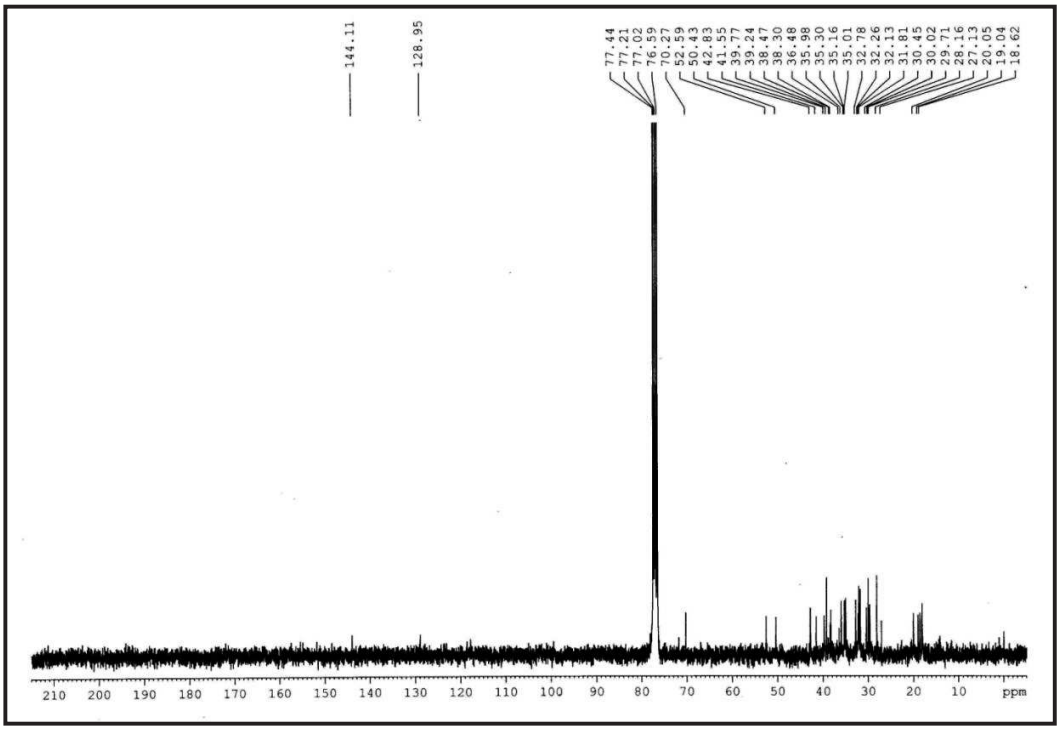


Figure 4.85 ^{13}C NMR spectrum of 2-formyl-3-chloro-4α-hydroxy-2-hydroxymethyl friedel-2-ene (**1348**).

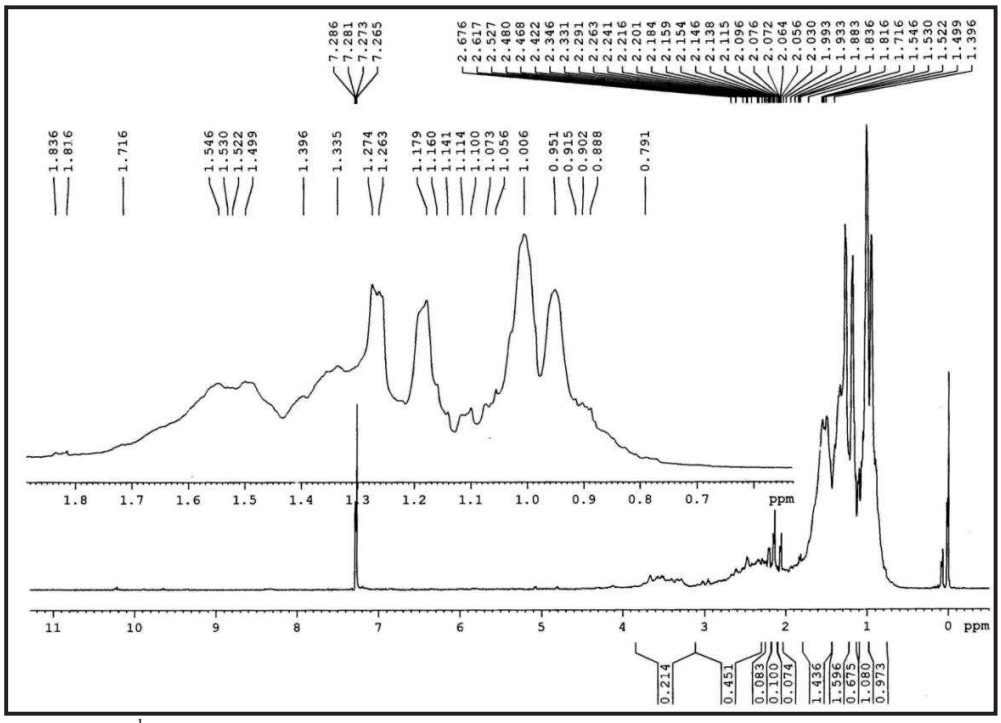


Figure 4.86 ^{1}H NMR spectrum of 2-formyl-3-(1*H*-piperidin-1-yl)-friedel-2-ene (**1349**).

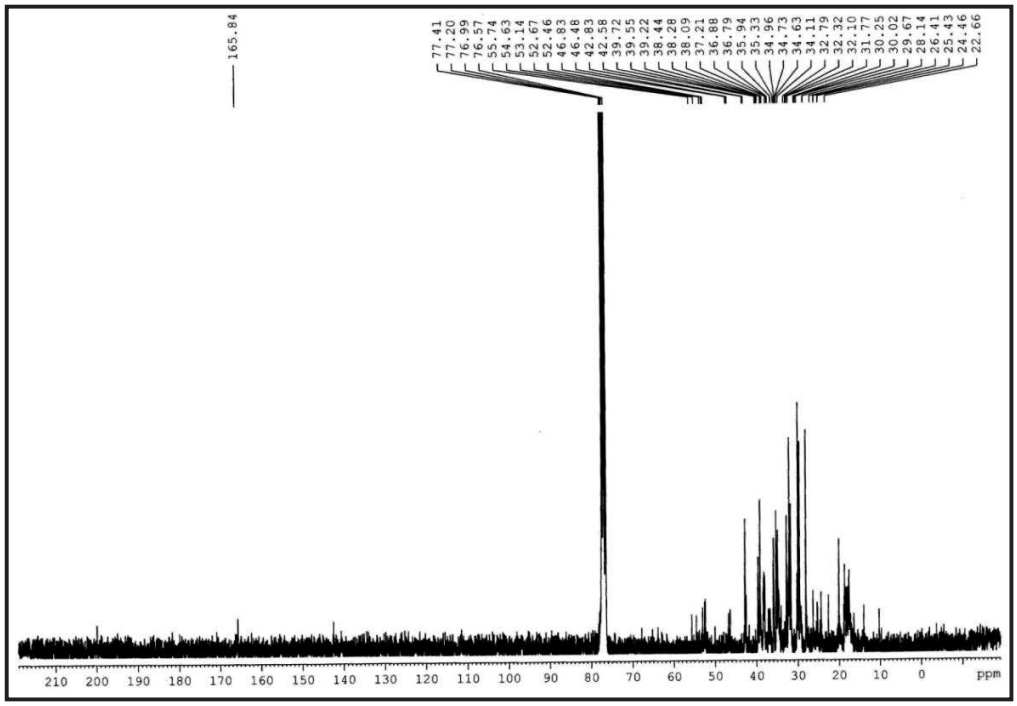


Figure 4.87 ^{13}C NMR spectrum of 2-formyl-3-(1*H*-piperidin-1-yl)-friedel-2-ene (**1349**).

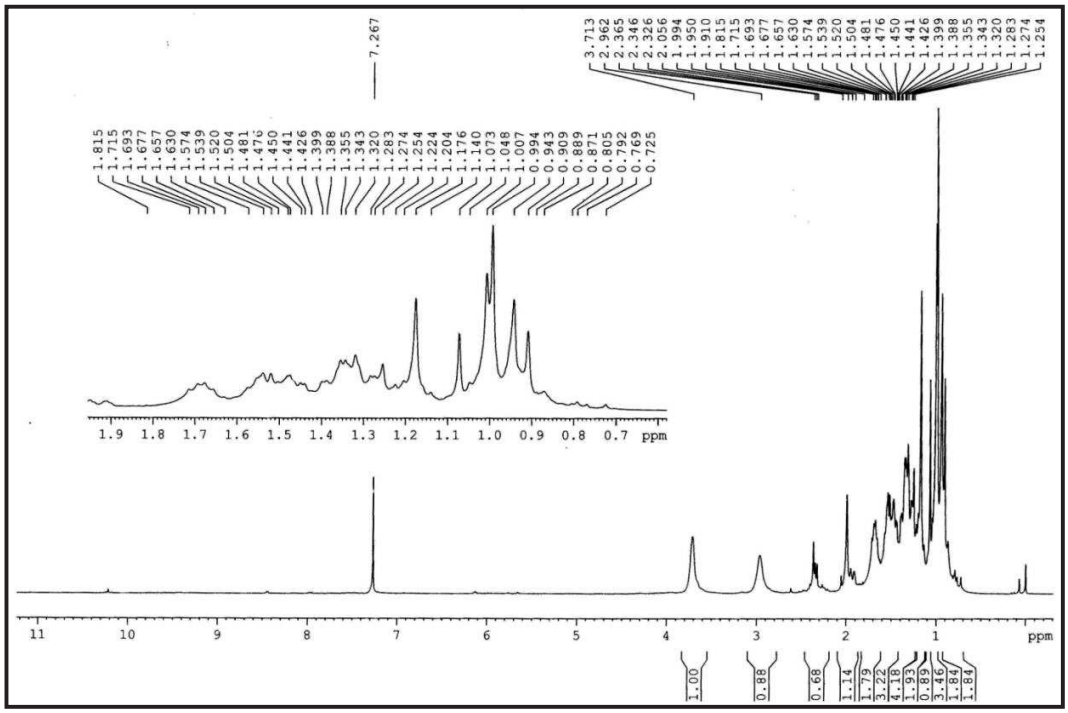


Figure 4.88 ^{1}H NMR spectrum of 2-formyl-3-(1*H*-morpholin-4-yl)-friedel-2-ene (**1350**).

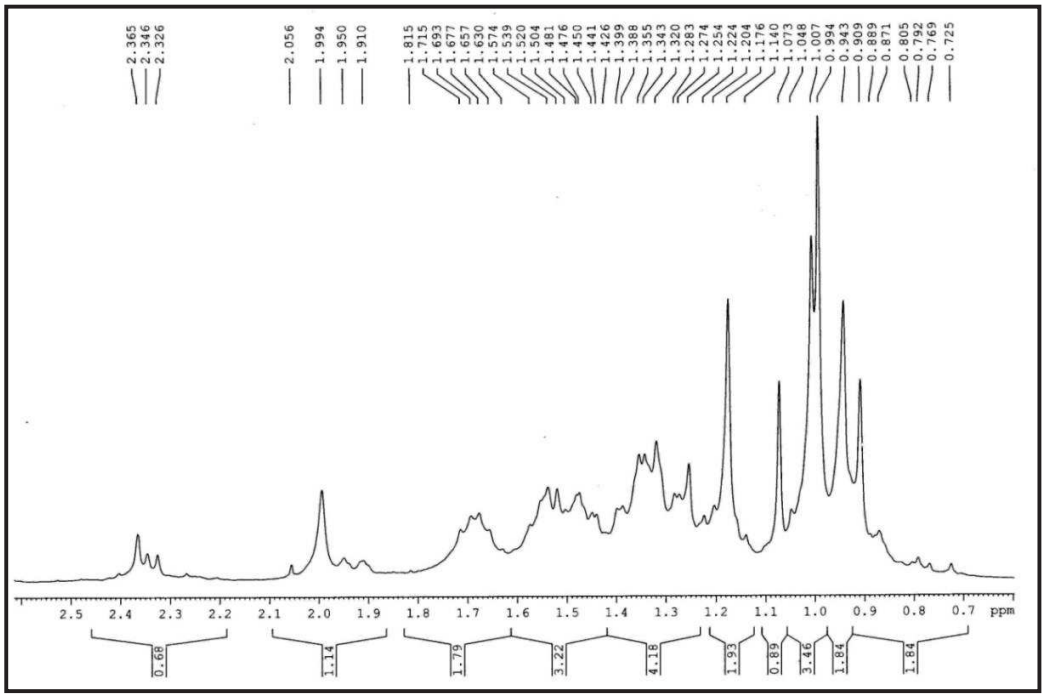


Figure 4.89 ^{1}H NMR spectrum (partially expanded) of 2-formyl-3-(1*H*-morpholin-4-yl)-friedel-2-ene (**1350**).

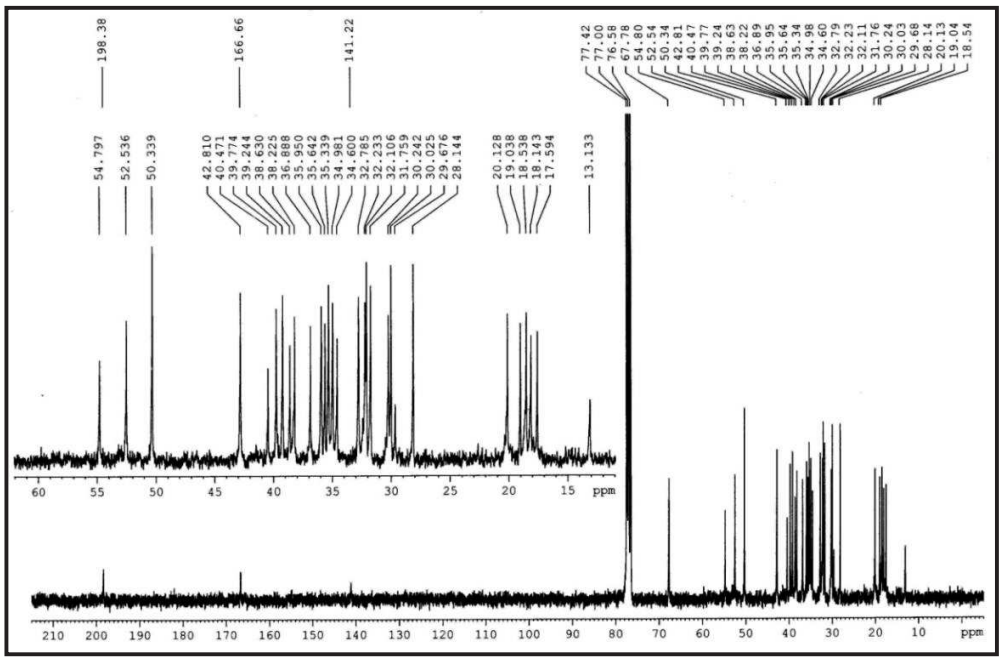


Figure 4.90 ^{13}C NMR spectrum of 2-formyl-3-(1*H*-morpholin-4-yl)-friedel-2-ene (**1350**).

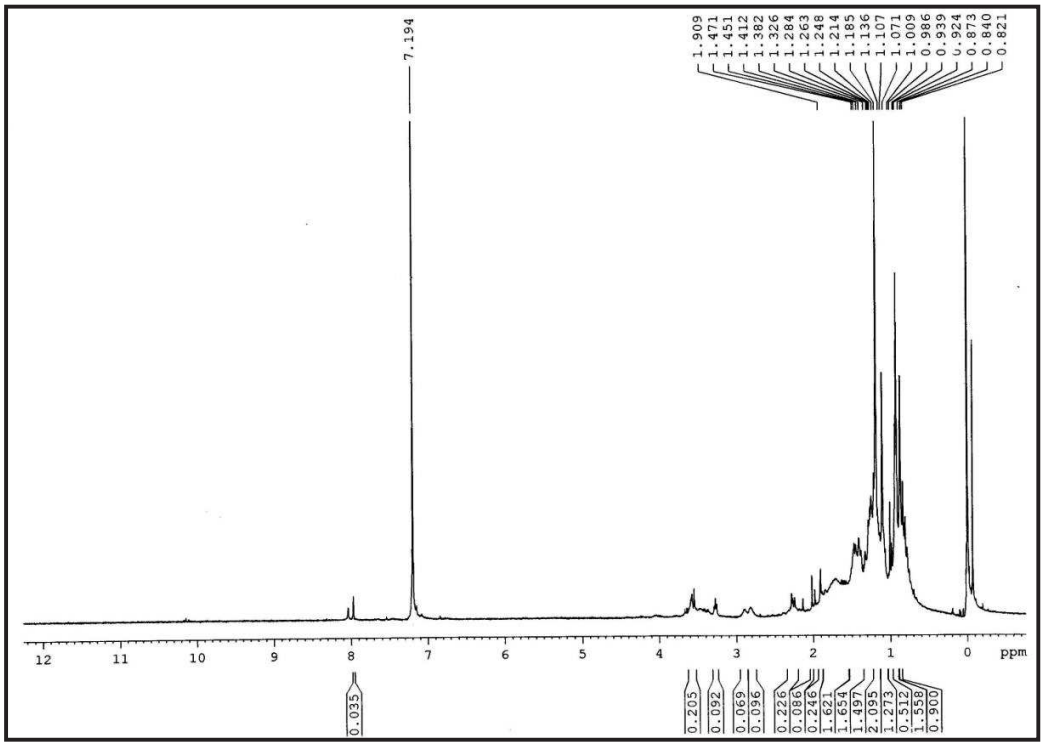


Figure 4.91 ^{1}H NMR spectrum of 2-formyl-3-(1*H*-piperazin-1-yl)-friedel-2-ene (**1351**).

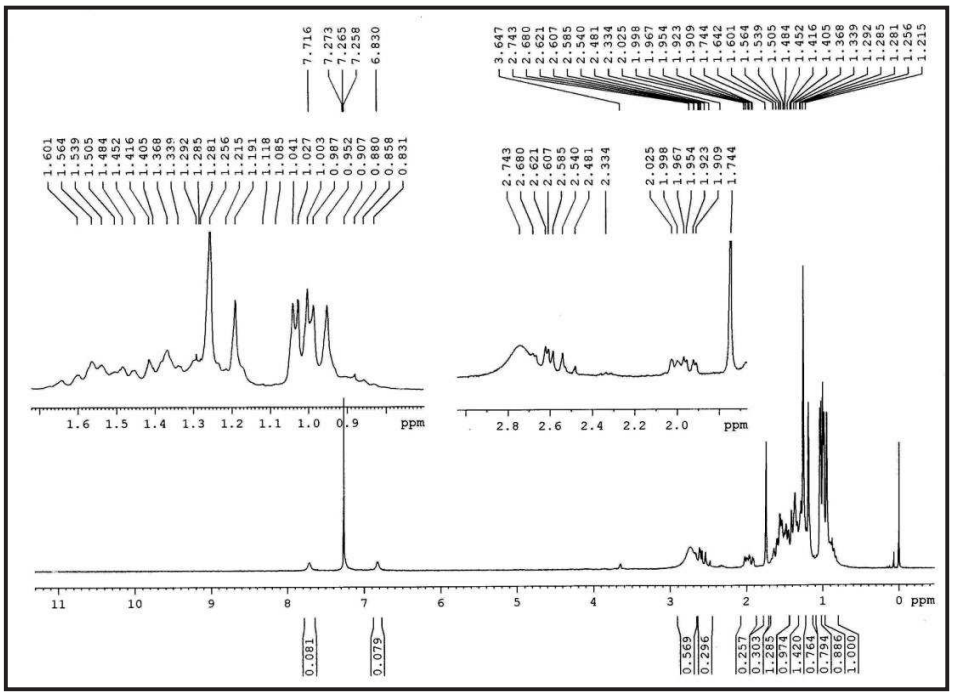


Figure 4.92 ^{1}H NMR spectrum of 2-formyl-3-(1*H*-imidazol-1-yl)-friedel-2-ene (**1352**).

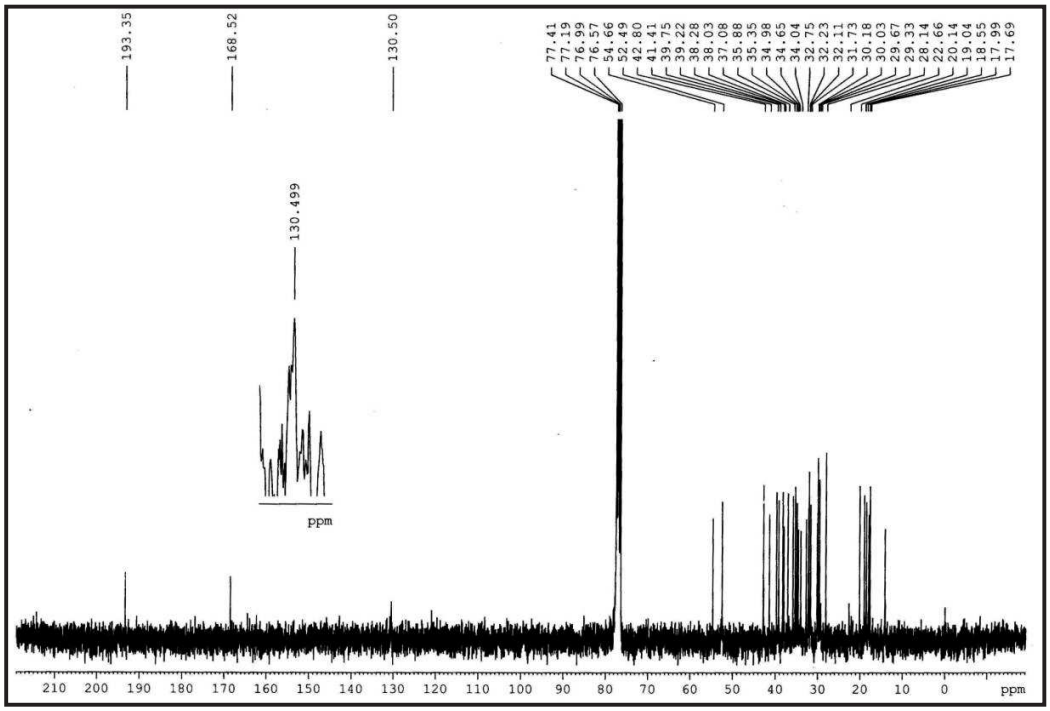


Figure 4.93 ^{13}C NMR spectrum of 2-formyl-3-(1*H*-imidazol-1-yl)-friedel-2-ene (**1352**).

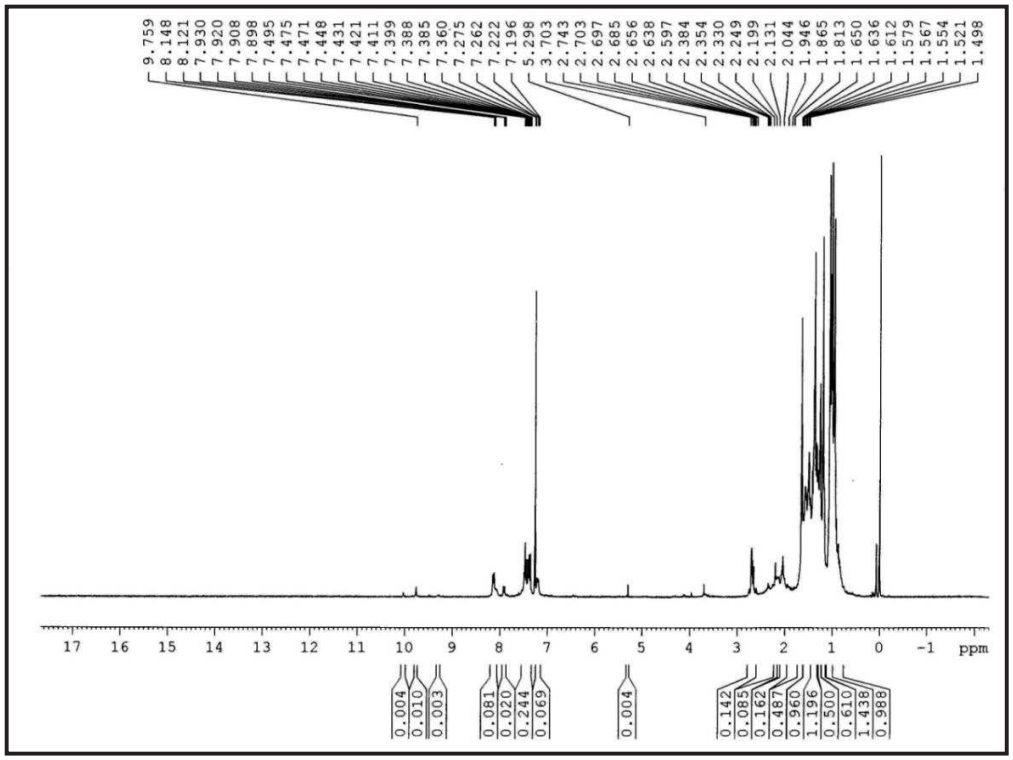


Figure 4.94 ^{1}H NMR spectrum of 2-formyl-3-(1*H*-benzimidazol-1-yl)-friedel-2-ene (**1353**).

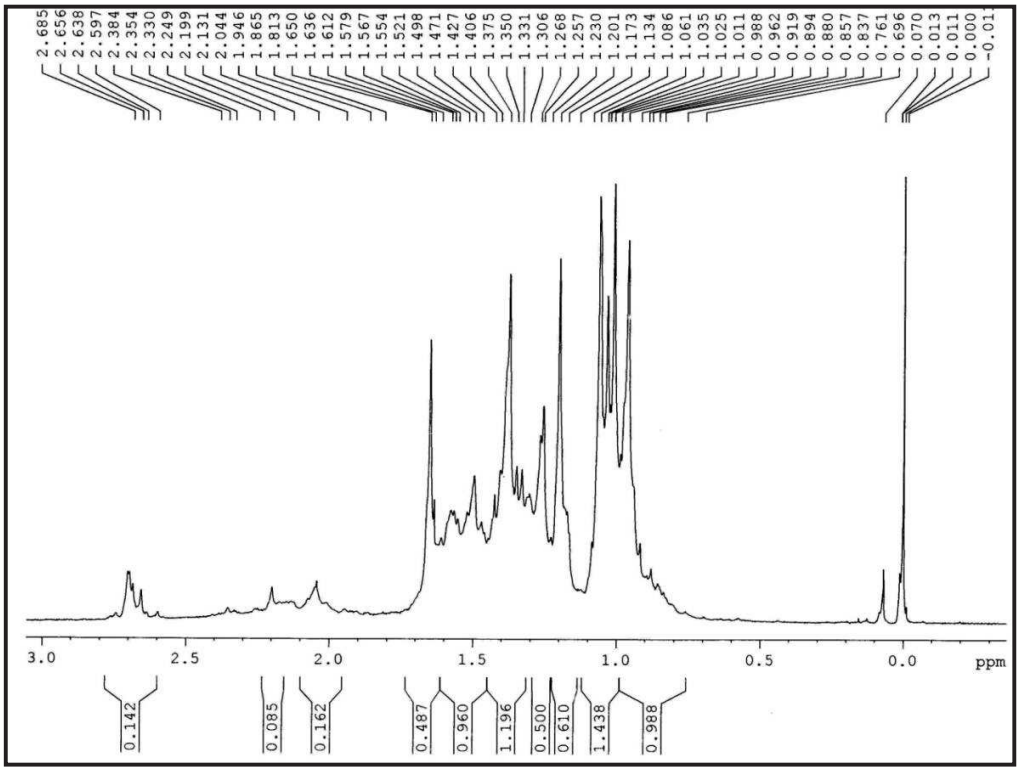


Figure 4.95 ^{1}H NMR spectrum (with partial expansion) of 2-formyl-3-(1*H*-benzimidazol-1-yl)-friedel-2-ene (**1353**).

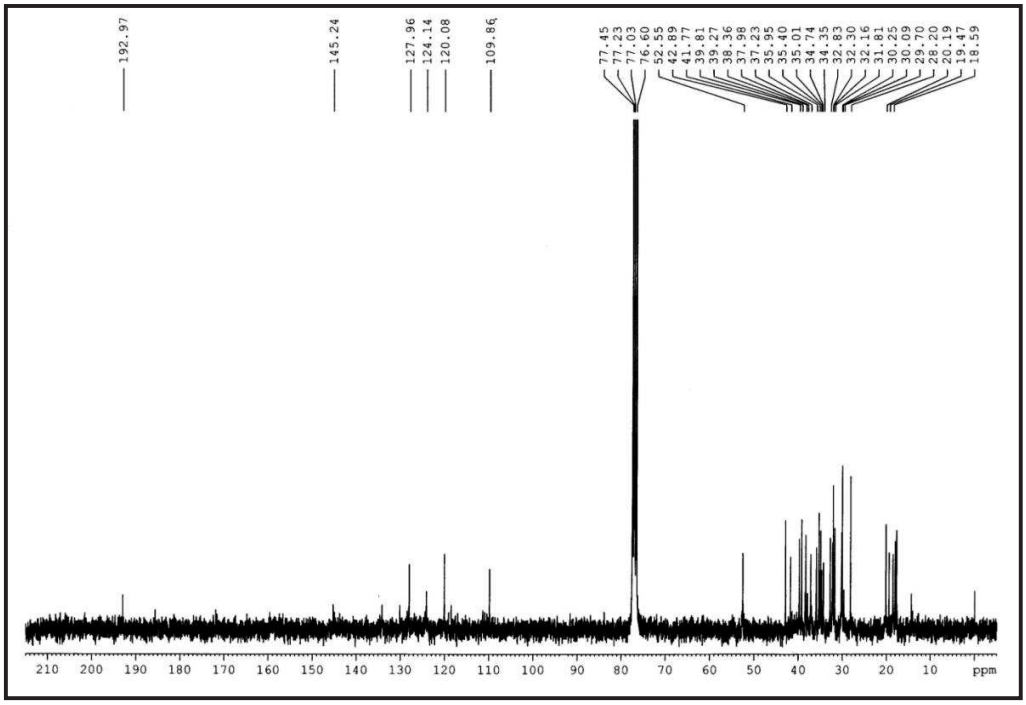


Figure 4.96 ^{13}C NMR spectrum of 2-formyl-3-(1*H*-benzimidazol-1-yl)-friedel-2-ene (**1353**).

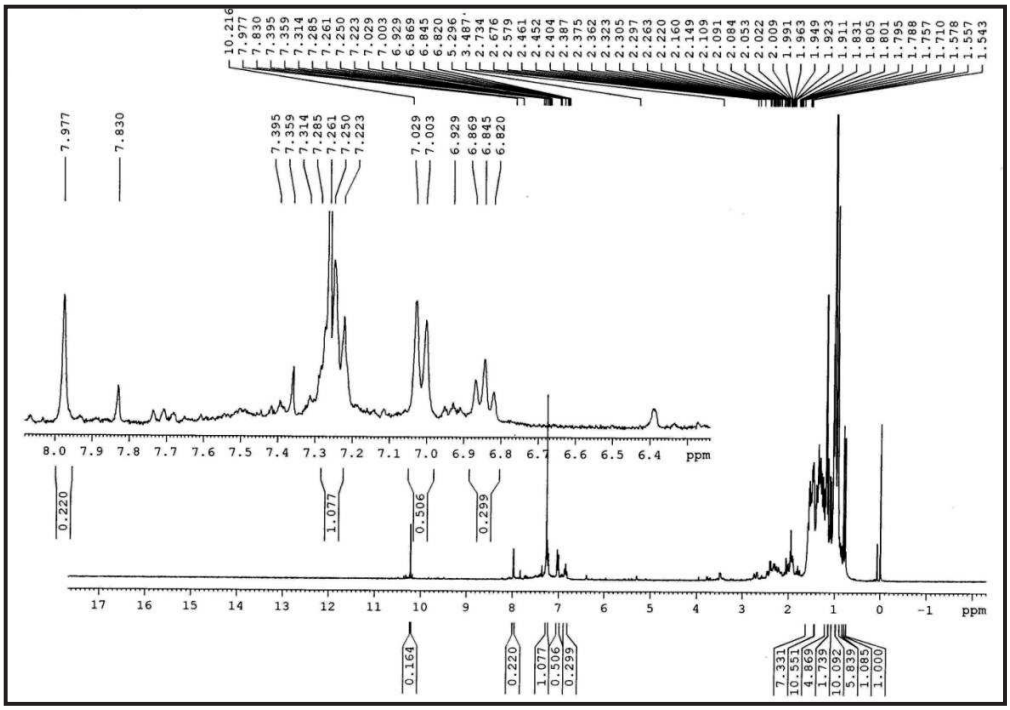


Figure 4.97 ^{1}H NMR spectrum of 2-formyl-3-(1*H*-1, 2, 3-benzotriazol-1-yl)-friedel-2-ene (**1354**).

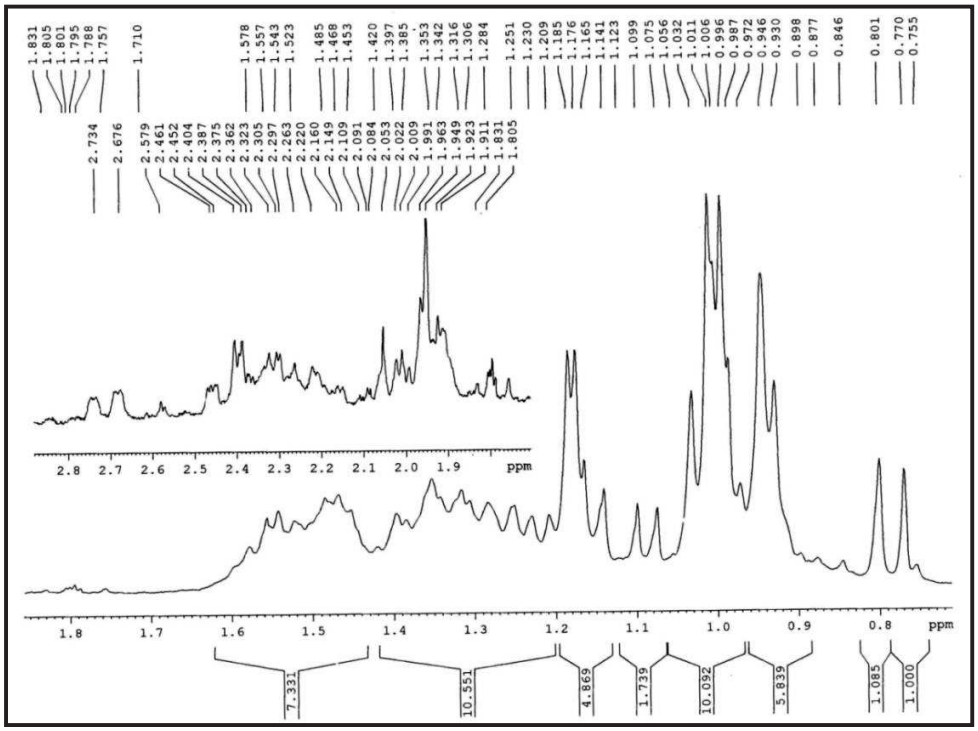


Figure 4.98 ^{1}H NMR spectrum (partially expanded) of 2-formyl-3-(1*H*-1, 2, 3-benzotriazol-1-yl)-friedel-2-ene (**1354**).

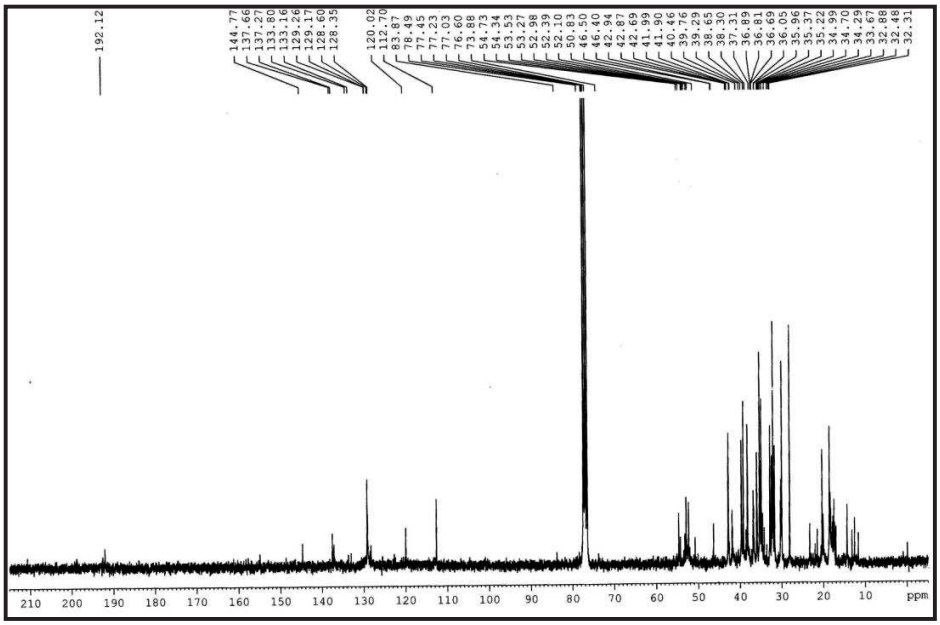


Figure 4.99 ^{13}C NMR spectrum of 2-formyl-3-(1*H*-1, 2, 3-benzotriazol-1-yl)-friedel-2-ene (**1354**).

IV.F References: The references of this chapter are provided in the **Bibliography** section of the thesis. Please follow page-372 onwards for these references.