國立交通大學

應用化學研究所

博士論文

天然物合成

Natural Product Synthesis

研究生：陳榮傑

指導教授：何子樂 博士

中華民國九十四年九月

天然物合成

Natural Product Synthesis

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指導教授：何子樂　　Advisor：Tse-Lok Ho

國 立 交 通 大 學

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論文口試推薦書

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天然物合成

Natural Product Synthesis (題目)

係由本人指導撰述，同意提付審查。

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Natural Product Synthesis

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中華民國 九十四年 九 月 五 日

天然物合成

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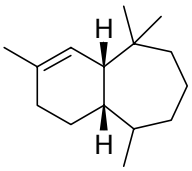
摘　　要

本論文研究計畫共分為五大部分: Intervention of Phenonium Ion in Ritter Reaction and the Synthetic Study for Argemonine，Selective C-S Bond Cleavage Reactions，β-Himachalene 的全合成，Tacamonine 的合成研究及 Calothrixin B 的合成研究。



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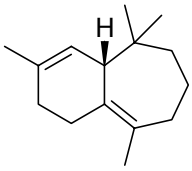

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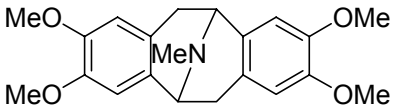
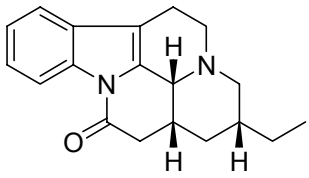


Argemonine



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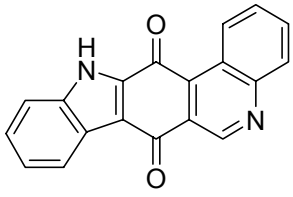

Calothrixin B

Natural Product Synthesis

student：Rong-Jie Chein Advisor : Tse-Lok Ho

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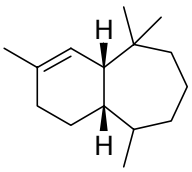
ABSTRACT

There are five topics in this dissertation : “Intervention of Phenonium Ion in Ritter Reaction and the Synthetic Study for Argemonine”, “Selective C-S Bond Cleavage Reactions”, “Total Synthesis of β-Himachalene”, “Synthetic Study for Tacamonine”, and “Synthetic Study for Calothrixin B”.



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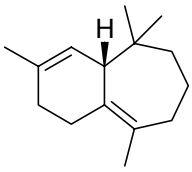

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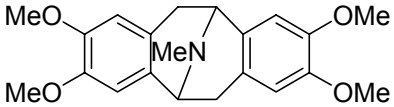
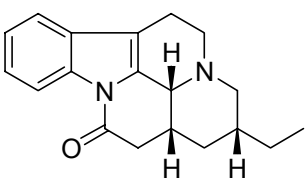
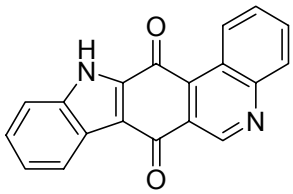


Argemonine



Tacamonine



Calothrixin B

誌謝

感謝何子樂老師的耐心教導及口試委員鍾文聖老師、蔡蘊民老師、邱勝賢老師及蒙國光老師對於論文的指導。

目錄

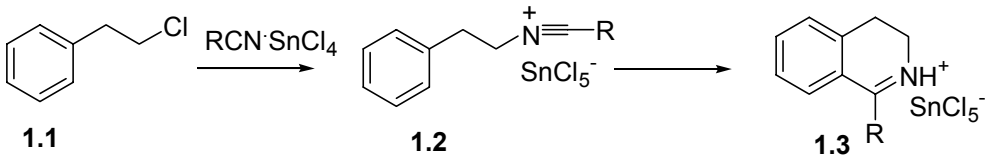
第一章 Intervention of Phenonium Ion in Ritter Reaction and the Synthetic Study for Argemonine

(1-1) 緒論

典型的Ritter 反應[1.1-1.3]是指由醇類或烯類化合物形成穩定的碳陽離子(carbocations)後，陽離子被氰類化合物捕獲，再經水解形成醯胺化合物。

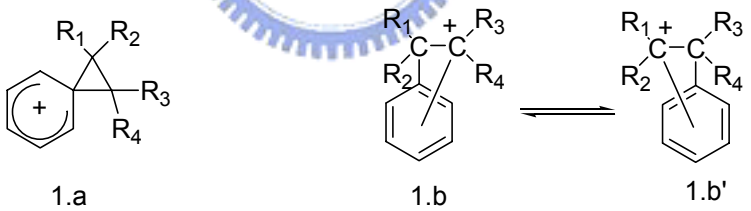
1960 年Lora-Tamayo[1.4]報導了由苯乙基氯進行Ritter型態反應生成 3,4-二氫異喹啉，如Scheme 1-1.所示。我們認為此類反應不應經由(**1.2**)中間體，因為一般的一級氯烷並不進行Ritter反應。

Scheme 1-1. Mechanism asserted by Lora-Tamayo in 1960



1.1 **1.2** **1.3**

β-芳代乙基系統的溶劑解離行為在 1960 年代的物理有機化學界是相當有爭議性的研究題材，Cram[1.5]最早提出此類反應的中間體為phenonium (σ-bridged ethylenebenzenium)離子(**1.a)** (Fig. 1-1)。但另一派學者Brown[1.6,1.7]卻認為中間體應為離子(**1.b)**和(**1.b')**間快速平衡，最後經由光譜量測的結果，證實Cram的phenonium離子理論正確。之後，Olah教授更深入研究，並有諸多論述發表[1.8,1.9]。本研究要重新探討Lora-Tamayo的報導，因我們以為phenonium離子之參與可能發展一條新的合成argemonine途徑。



1.a 1.b 1.b'

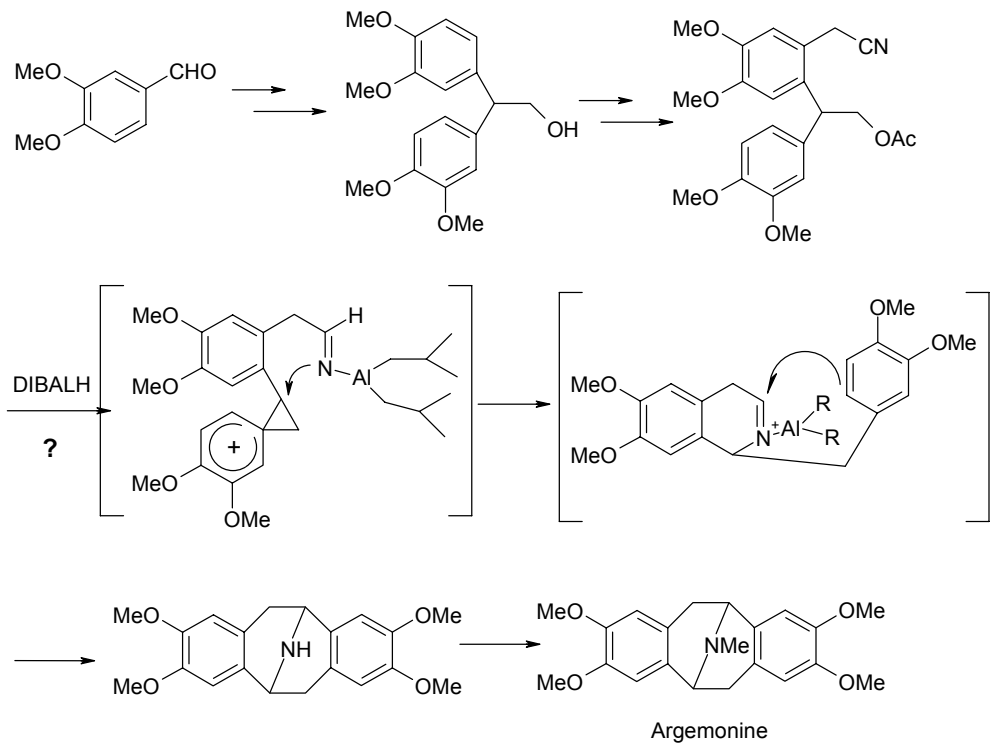
Fig. 1-1

Argemonine[1.10]（蓟罌粟鹼）是典型的pavine類生物鹼成員之一，此類擁有四環結構的天然物在結構中並包含四氫異喹啉(tetrahydroisoquinoline)為其骨架中心。近期的生化活性研究並發現此類生物鹼可抑制*herpes simplex* virus type 1 及對抗tumor necrosis factor-α (TNF-α)的產生。

Fig.1-2. Argemon (薊罌粟) （摘自www.coffeshop.pl/argemone.html 及 http://www.mazatecgarden.com/products/mazatec_garden_esoteric_herbs.htm）

此天然物擁有特殊的對稱[1.11]性結構更是引發了我們的研究興趣的原因。如Scheme 1-2.所示。

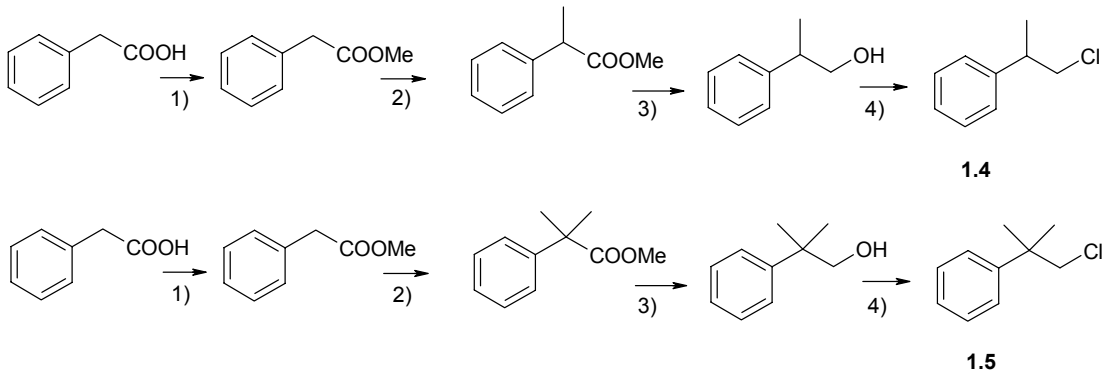
Scheme 1-2.



(1-2) 結果與討論

根據Lora-Tamayo[1.4]的報導(Scheme 1-1.)，1-氯-2-苯乙烷 (**1.1**) 在氰類化合物幫助下氯離子離去形成中間體(**1.2**)，快速環合後生成 3,4-二氫異喹啉(**1.3**)。我們認為這樣的推論較不合理，經由phenonium ion中間體而的反應機制比較可能。

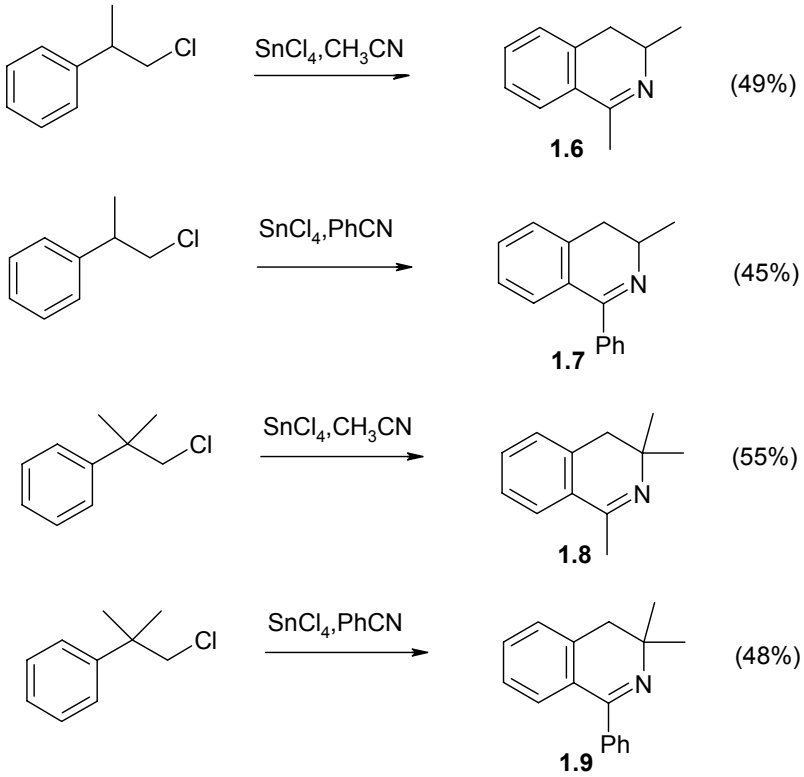
Scheme 1-3.



1) $SOCl_2$; MeOH; 2) LDA; MeI; 3) LAH; 4) $SOCl_2$

為了驗證上述想法，我們以Scheme 1-3.的步驟合成了單甲基取代(**1.4**)及雙甲基取代衍生物(**1.5**)。在Lora-Tamayo報導的條件下進行反應，得到的產物皆為 3 號碳位置甲基取代的 3,4-二氫異喹啉。藉由碳譜可判斷出我們確實得到經重排後的產物 **1.6-1.9** (Scheme 1-4.)，產物(**1.8**)的碳譜顯示有一連接氮原子的四級碳(δ 53.4) ； NOE實驗也顯示一CH_2(δ 2.63)與苯環上氫(δ 7.07)為近側關係。這樣的結果可排除Lora-Tamayo所提出.反應機制的可能性。

Scheme 1-4.

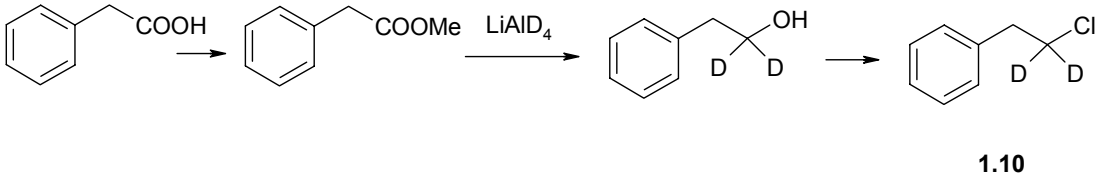


然而，除了 phenonium ion 中間體的反應機制外，還有另外一種會造成反應重排的可能性，那就是陽離子中間體形成後經由 1,2-aryl shift 產生較穩定的多取代基碳陽離子中間體再往下反應。

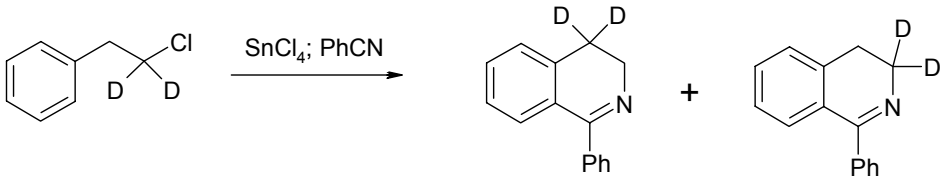
為進一步確認反應機制，我們製備了氘取代化合物(**1.10**) (Scheme 1-5.) 。以化合物(**1.10**)進行同樣反應，得到產物為一比一的 (**1.11**)及未重排產物(**1.12**)，氫譜可觀察到兩

支單峰分別位於δ 2.71 及 3.76。陽離子中間體的反應機制不應觀察到重排產物，這個結果可確認 phenonium ion (**1.13**)中間體的反應機制，也進一步說明為什麼 1-氯-2-苯乙烷(**1.1**)對此類型反應的反應性會比其他一級烷基鹵化物好的原因。

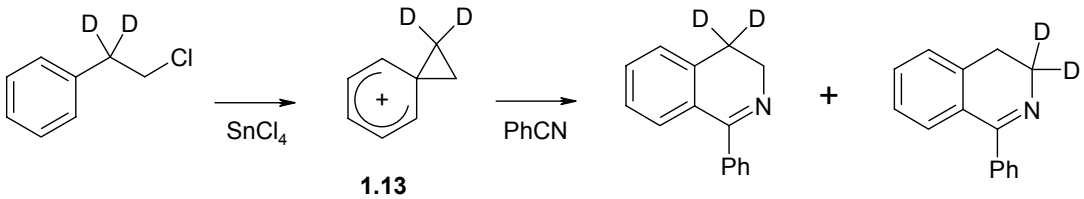
Scheme 1-5.



1.10



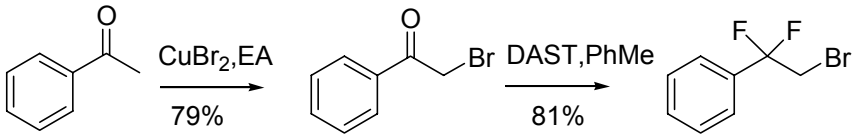
1.11 **(1 : 1)** **1.12**



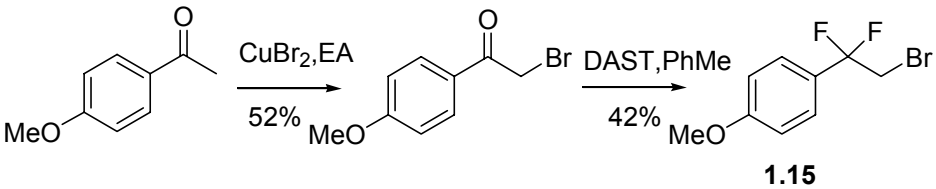
1.13

接著，我們想進一步探討陰電性強的氟原子對此類反應會有什麼影響，也就是說，是否同樣會生成含氟 phenonium 離子，又會不會與親核基(如氯化物)進行反應?

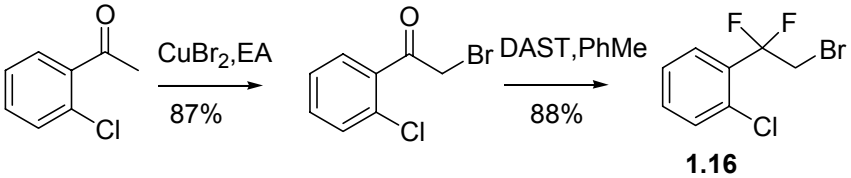
Scheme 1-6.



1.14



1.15

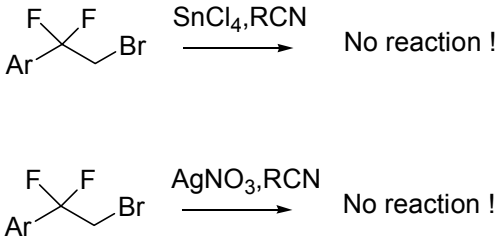


1.16

我們先將焦點置於雙氟取代化合物(**1.14**)、(**1.15**)及(**1.16**)，如Scheme 1-6.所示由溴乙酰苯(phenacyl bromide)以DAST[1.12,1.13][(diethylamino)sulfur trifluoride]試劑製備此三種雙

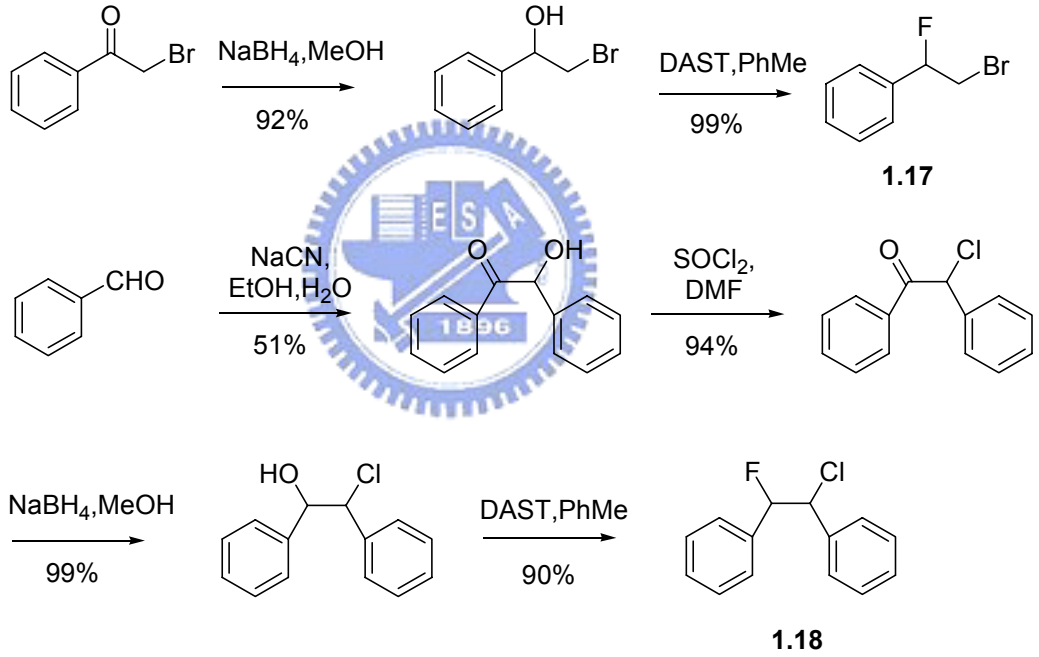
氟取代物。很快的，我們發覺這三種化合物完全不參與反應，不論是以氯化錫($SnCl_4$)或硝酸銀($AgNO_3$)處理，都只回收起始物(Scheme 1-7.)。顯然雙氟取代造成化合物幾乎完全喪失反應活性。

Scheme 1-7.



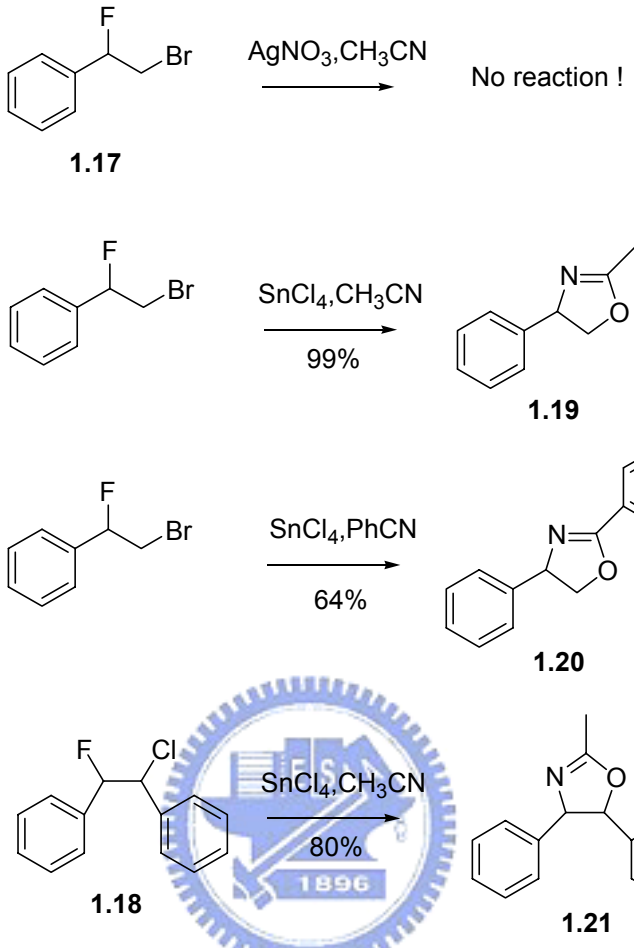
到了這個階段，我們試著降低氟原子的影響力，將雙氟取代改成單氟取代化合物(**1.17**) (Scheme 1-8.)再來觀察反應結果。

Scheme 1-8.



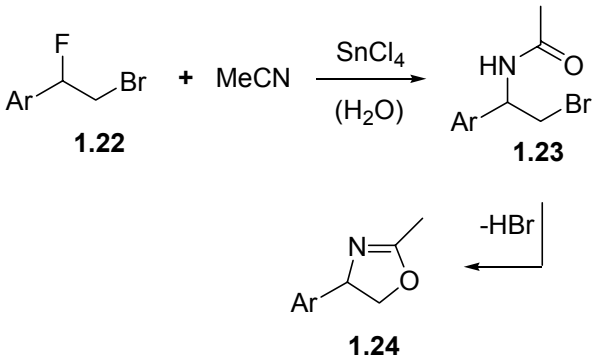
如Scheme 1-9.所示，單氟化合物(**1.17**)與氯化錫及氯甲烷加熱至 110°反應後生成2-methyl-4-phenyl-4,5-dihydrooxazole (**1.19**)，可見單一個氟原子仍舊會抑制phenonium ion的生成，也有可能是氟原子本身是較佳的路易士鹼，與氯化錫錯合後生成苄陽離子(benzylic cation)。有趣的是，若將氯化錫改成硝酸銀，則無反應發生，這應是軟硬酸鹼[1.14]配對問題使硝酸銀無法活化碳氟鍵，而碳溴鍵又被氟原子誘導影響，大大地降低了活性所致。

Scheme 1-9.



藉由室溫條件下反應的中間產物光譜可知，單氟化合物經 Ritter 反應後生成β-醯胺基 (amido) 溴化物 (**1.23**) (Scheme 1-10.)，加熱後脫除氫溴酸 (HBr) 得二氫噁唑 (dihydrooxazole)產物。氧原子的來源應是反應系統中未去除乾淨的水。我們曾嘗試加入分子篩以進一步除水，但仍無法避免此反應途徑的發生。至於 Ritter 反應中間體 N-benzylic nitrilium ion 為何不選擇我們先前所觀察到的環合反應途徑生成二氫異喹啉？我們的推論是親核中心與親電子中心因為被牢固地分隔開來，無法達成環合所需構形行所致。

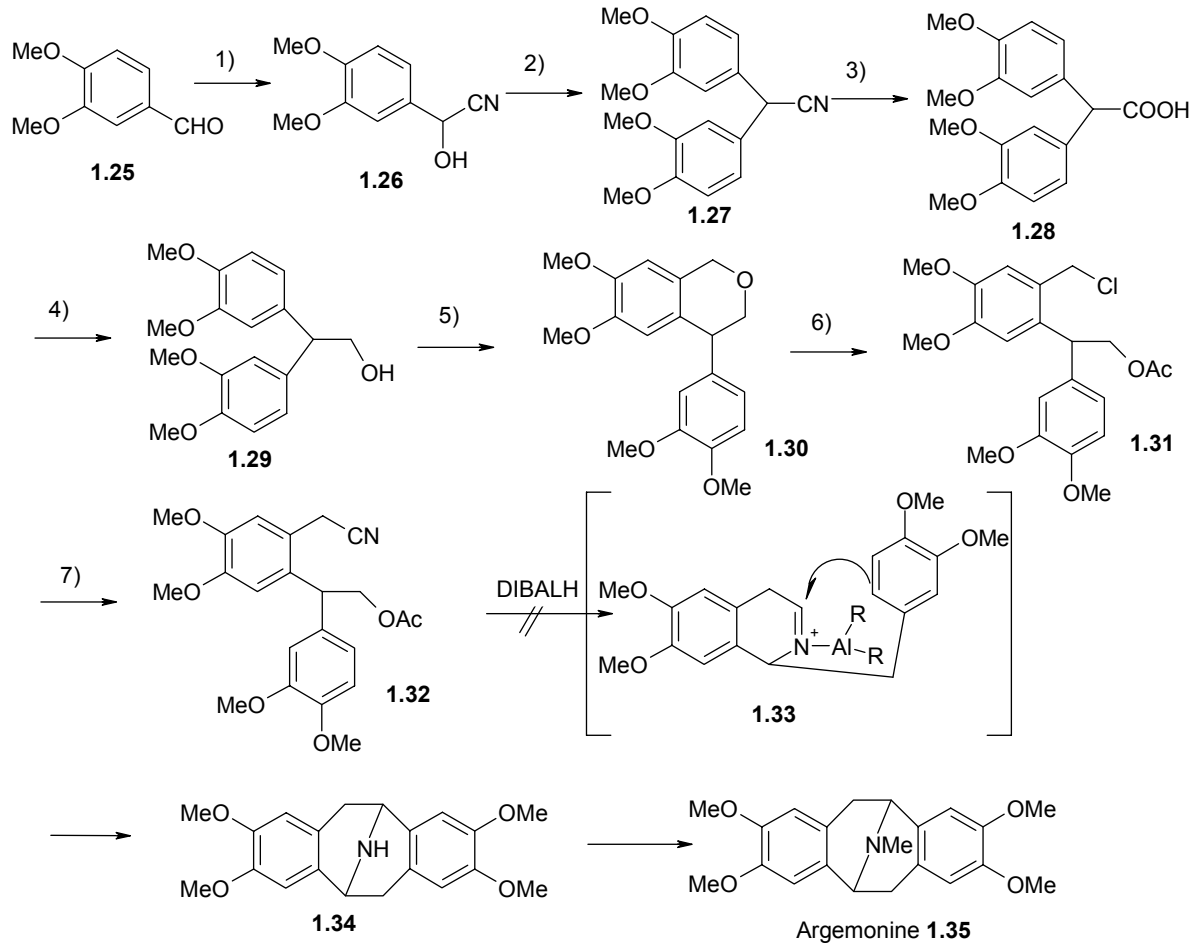
Scheme 1-10.



做了一系列的 Ritter 反應相關研究後，最終要能在實際合成上有所應用。我們選定

了 argemonine 為目標物，希望利用前述經驗及對稱中間體(**1.28**)，以 Scheme 1-11.途徑觀察由化合物(**1.32**)經中間體(**1.33**)生成四環化合物(**1.34**)的關鍵步驟是否能順利達成。可惜的是在經過許多次嘗試後，只造成化合物分解，未得到四環化合物(**1.34**)。

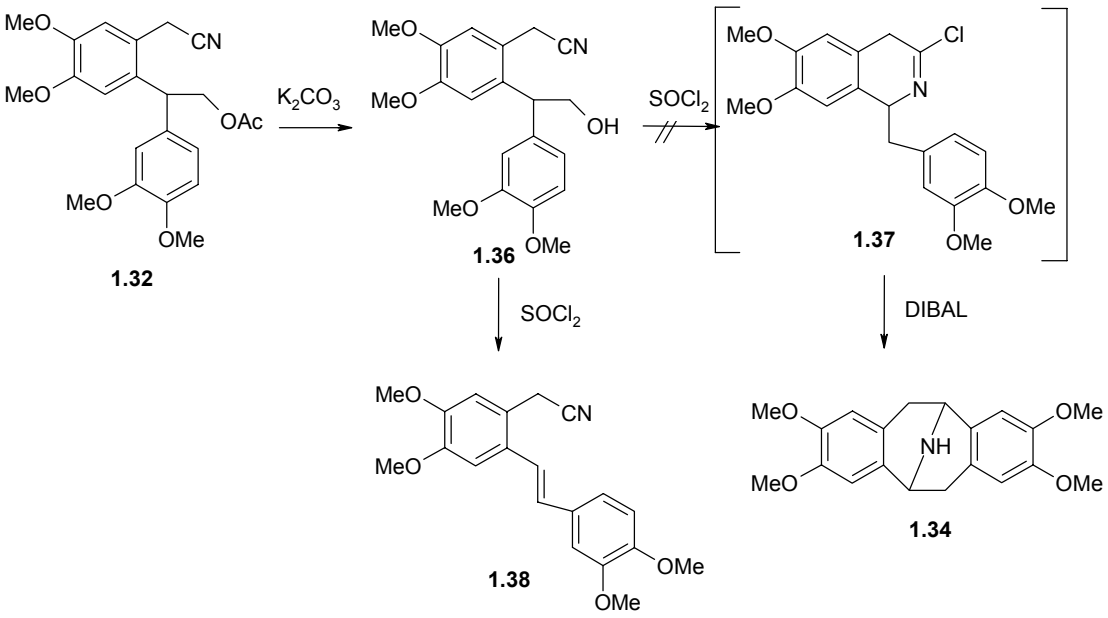
Scheme 1-11.



1) NaCN, HCl; 2) H_2SO_4, veratrole; 3) 20 % KOH/EtOH; 4) LAH; 5) CH_2O, HCl; 6) ZnCl, AcCl, CH_2Cl_2, -78^o; 7) NaCN, H_2O, CH_2Cl_2, Bu_4NBr.

又將中間體(**1.32**)水解成醇(**1.36**)後嘗試 Scheme 1-12.途徑，但產物得到的是經重排後的化合物(1.38)，仍無法取得四環化合物(**1.34**)，合成計畫就此打住。

Scheme 1-12.



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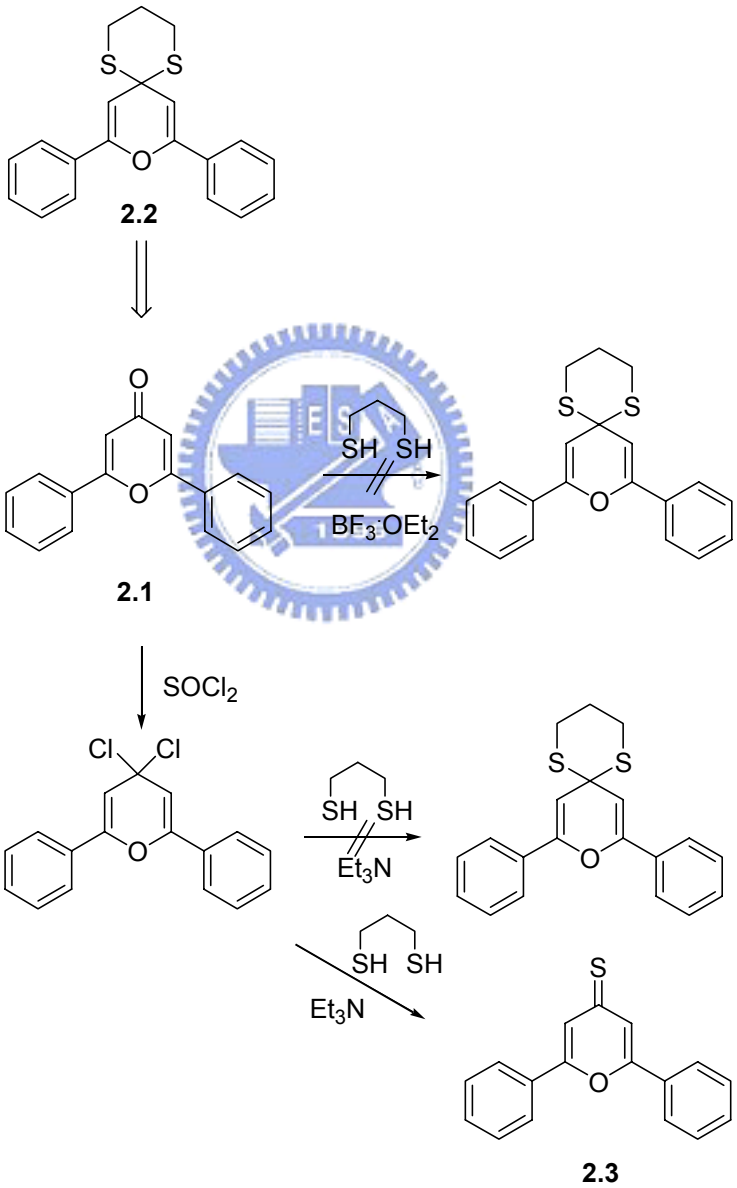
第二章 Selective C-S Bond Cleavage Reactions

(2-1) 緒論

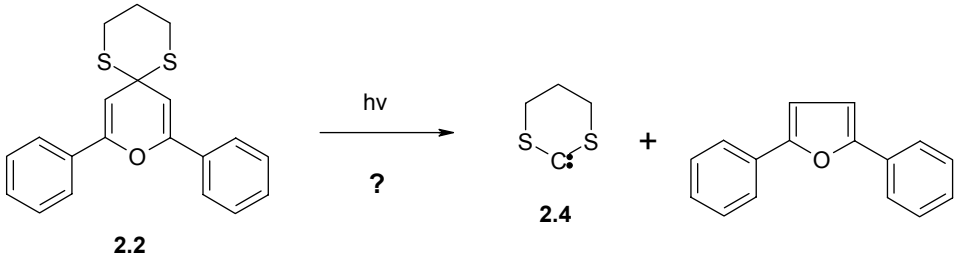
為了某些研究，我們需要合成吡喃酮[2.1](4-pyrone) (**2.1**)的dithioacetals衍生物(**2.2**)，在遍尋各文獻後卻發現全無此簡單化合物的報導。此結果出乎意料之外，但我們仍著手進行此化合物的製備。在使用各種傳統的反應後，皆無法將化合物 **2.1** 轉化成我們所需的化合物 **2.2** (Scheme 2-1.)。卻從中發現了非常罕見的結果，進而衍生出一系列的研究。

Scheme 2-1.



(2-2) 結果與討論

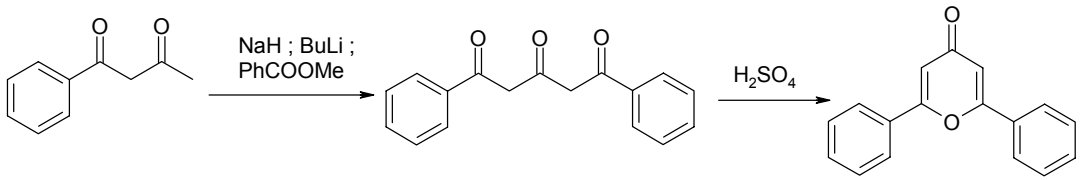
Scheme 2-2.The original proposal of our research



2.2 **2.4**

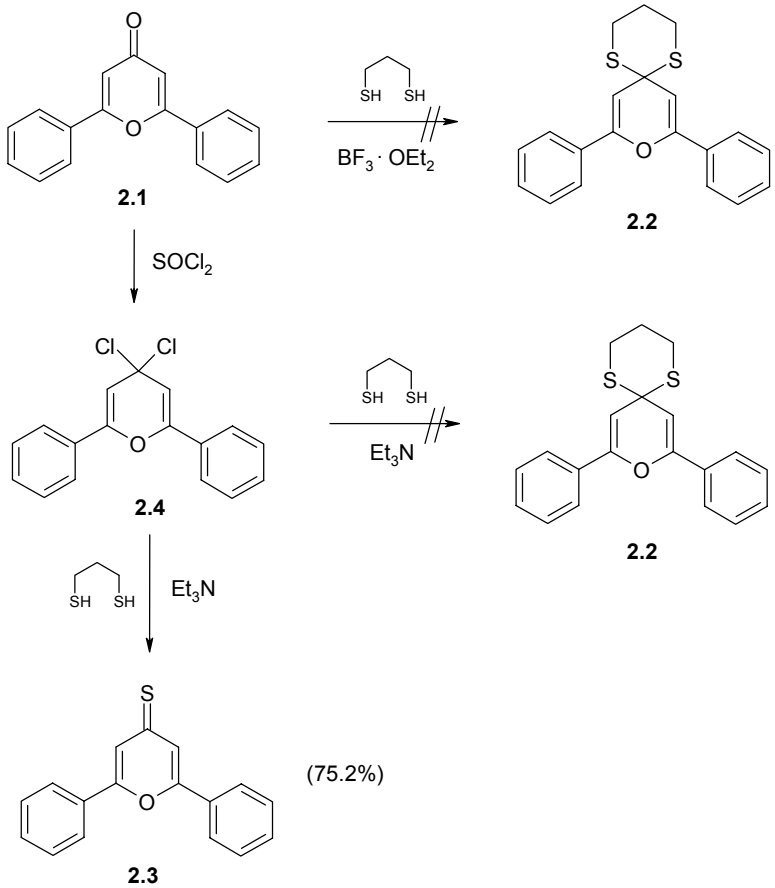
研究之初，我們是想製備化合物(**2.2**)，以其進行照光反應，觀察是否會有亞甲體(carbene) (**2.4**)生成。於是我們先合成了一些前驅物 4-吡喃酮(**2.1**) (Scheme 2-3.)。

Scheme 2-3. Synthesis of 2,6-diphenyl-4-pyrone



2.1

Scheme 2-4. Reactions of 4-pyrone with 1,3-dithiol-butane



將 4-吡喃酮(**2.1**)轉化成所需的化合物(**2.2**)過程並不順利，以典型的路易士酸催化無

法與丙二硫醇反應取得(**2.2**)。間接先以亞硫醯氯(thionyl chloride)處理後，再與丙二硫醇在鹼性條件下反應，出乎意料之外地生成硫酮化合物(**2.3**)[2.2-2.5] (Scheme 2-4.)。對於這個結果，我們的解釋是反應的中間體A或鹽A' (Fig. 2-1.)分解失去thietane或thioformaldehyde及乙烯單元所造成。為了進一步了解反應的轉換機制，我們試著以乙二硫醇及苯硫醇取代丙二硫醇進行反應，除獲得少量環硫醚(**2.6**)外，主要產物仍是硫酮化合物(**2.3**) (Scheme 2-5.)。其中，苯硫醇反應的結果令我們感到驚訝，隱含了不尋常的芳香化碳-硫鍵(C_{Ar}-S bond)的斷裂發生，副產物苯硫醚(**2.5**)及(**2.7**)的生成可為佐證(產率雖不盡理想)。

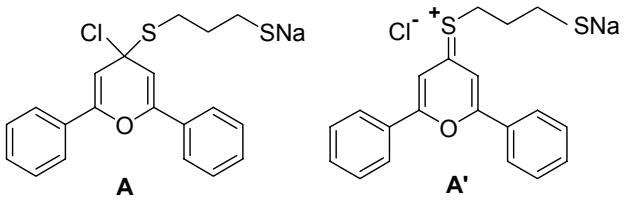
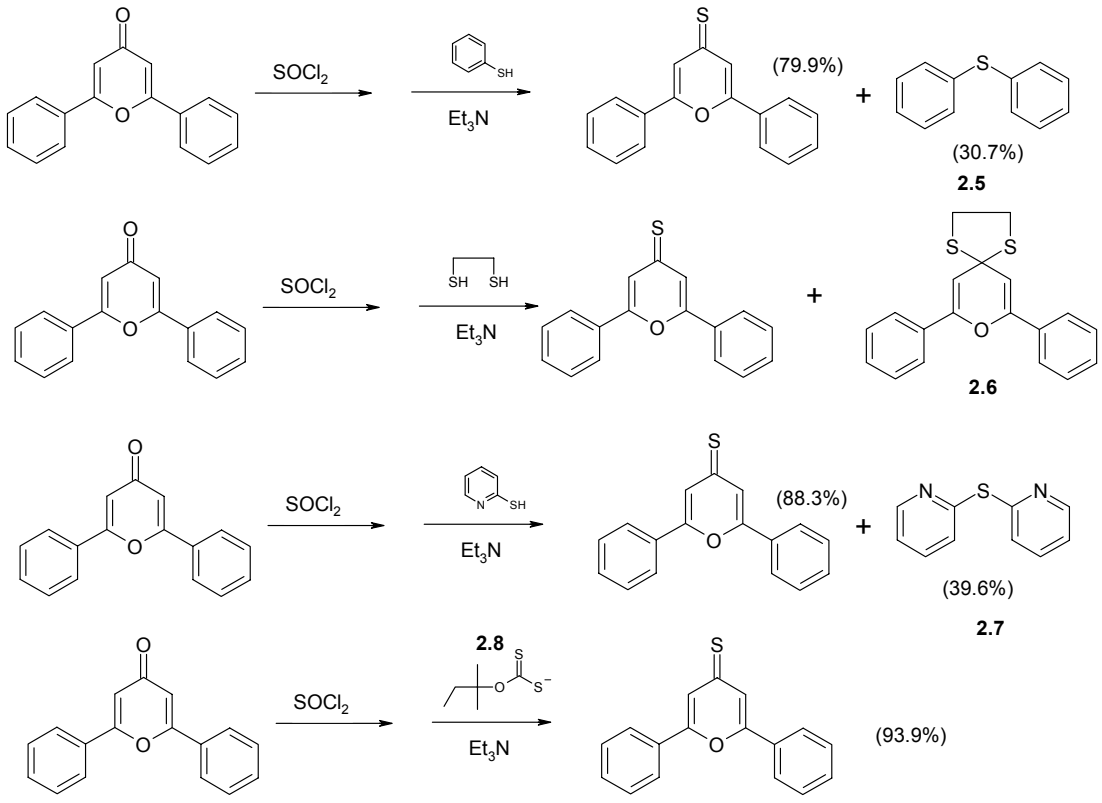
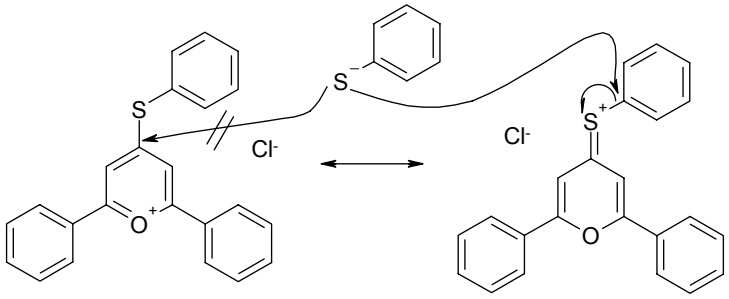


Fig. 2-1.

Scheme 2-5. Reactions of 4-pyrone with other thiol reagents



反應機構如 Fig. 2-2.所示，親核性攻擊發生於共振中間體(**2.10**)的苯環位置，而非較穩定共振中間體(**2.9**)的吡喃環碳-四位置。

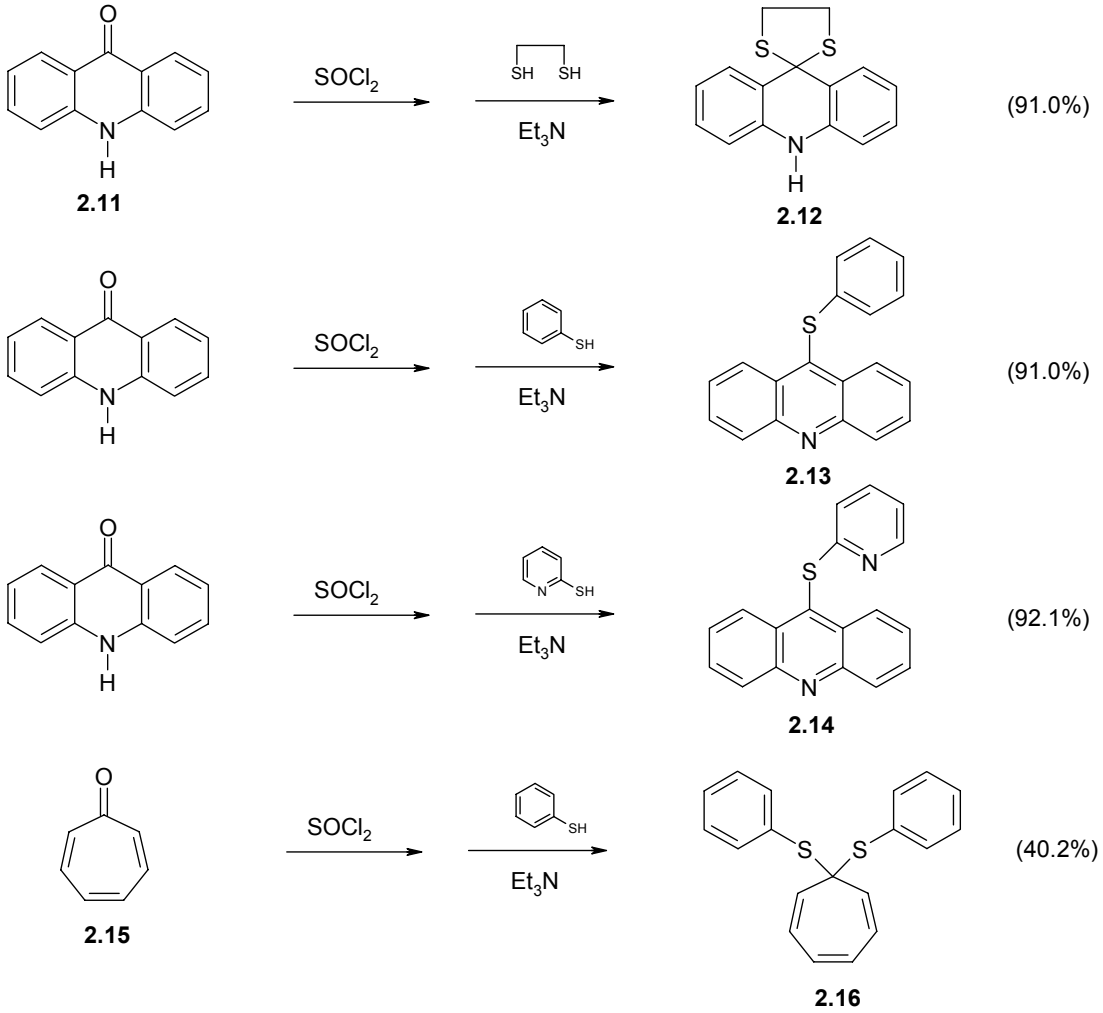


2.9 **2.10**

Fig.2-2

若以 9,10-dihydro-9-acridinone (**2.11**)或 tropone (**2.12**)取代 4-吡喃酮(**2.1**)進行反應，則只獲得一般"正常"產物，如 Scheme 2-6.所示，顯見 2,6-二苯基-4-吡喃酮 (2,6-diphenyl-4-pyrone) (**2.1**)是相當奇特的系統。

Scheme 2-6. Reactions of 9,10-dihydro-9-acridinone and tropone



2.11 **2.12** **2.13** **2.14** **2.15** **2.16**

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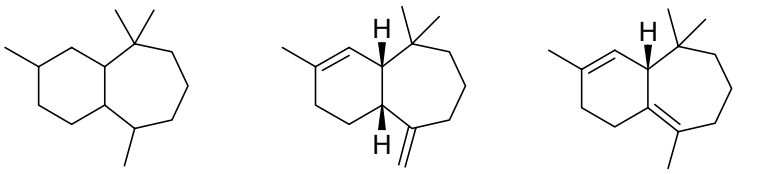
第三章 β-Himachalene 的全合成

(3-1) 緒論

具有Himachalane (Fig 3-2.)碳骨架的倍半萜類天然物，於 1952~1976 年期間陸續被報導。最早的發現是從喜瑪拉雅杉(*Cedrus deodara*, Loud.)提煉出的精油[3.1]。1961 年[3.2,3.3]分別在亞特拉斯杉(*Cedrus. atlantica*)及 *Cedrus libani* 二種杉樹中分離的是α及β-Himachalene。1968 年 Joseph和Dev[3.4]定出絕對立體結構。此等化合物 70 年代成為相當熱門的合成題材[3.5-3.9]，最近一篇全合成發表於 1997 年[3.10]。下面是已知方法之握要描述。

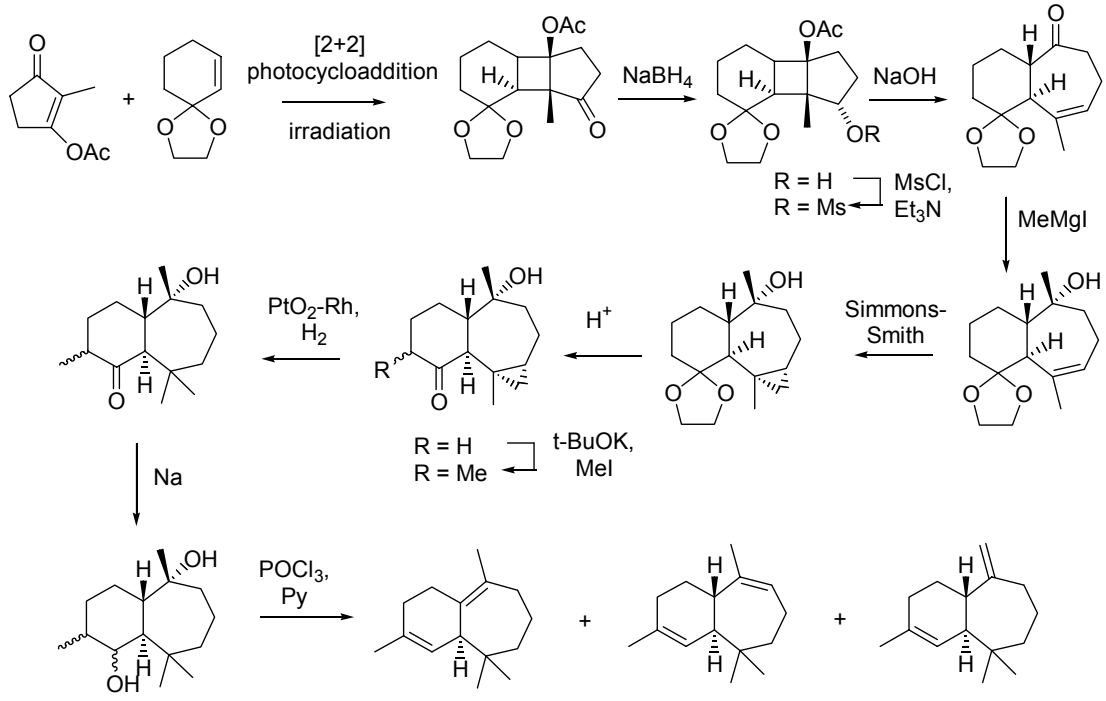
Fig. 3-1. 亞特拉斯杉(*Cedrus. atlantica*) 摘自
(http://www.boga.ruhr-uni-bochum.de/html/Cedrus_atlantica_Foto.html 及
http://www.muhlenberg.edu/cultural/graver/Collections/Conifers/Cedrus/Cedrus%20atlantica.htm)



Himachalane (-) α-himachalene (+)β-himachalene

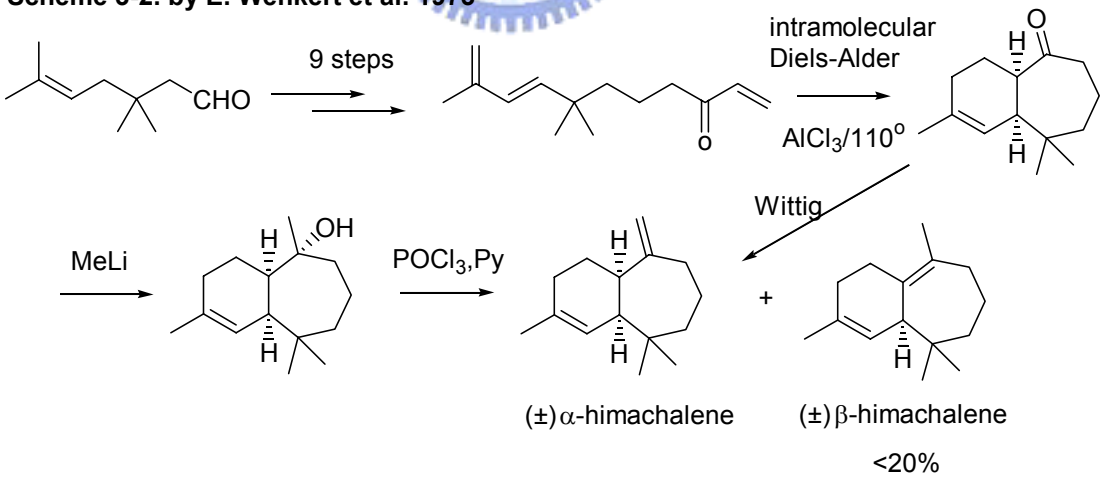
Fig. 3-2.

Scheme 3-1. by P. de Mayo et al. 1969



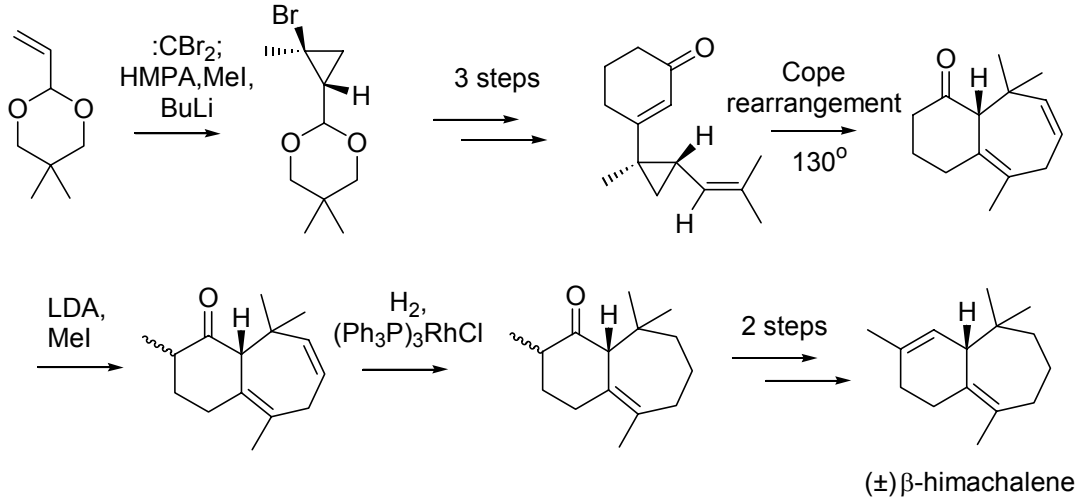
1969 年，P. de Mayo利用 2-methyl-3-oxo-1-cyclopentenyl acetate及 1,4-dioxaspiro [4.5]dec-6-ene照光進行[2+2] photocycloaddition得到四環中間體，以$NaBH_4$還原成醇後進行甲磺酸化(mesylation)，接著在鹼環境下開環生成六、七併環產物，還缺少的三個甲基分別以三種不同方法引進，共經十個步驟合成(±)β-himachalene(副產物)及另兩個主產物(±)trans-γ-himachalene和(±)trans-α-himachalene。

Scheme 3-2. by E. Wenkert et al. 1973



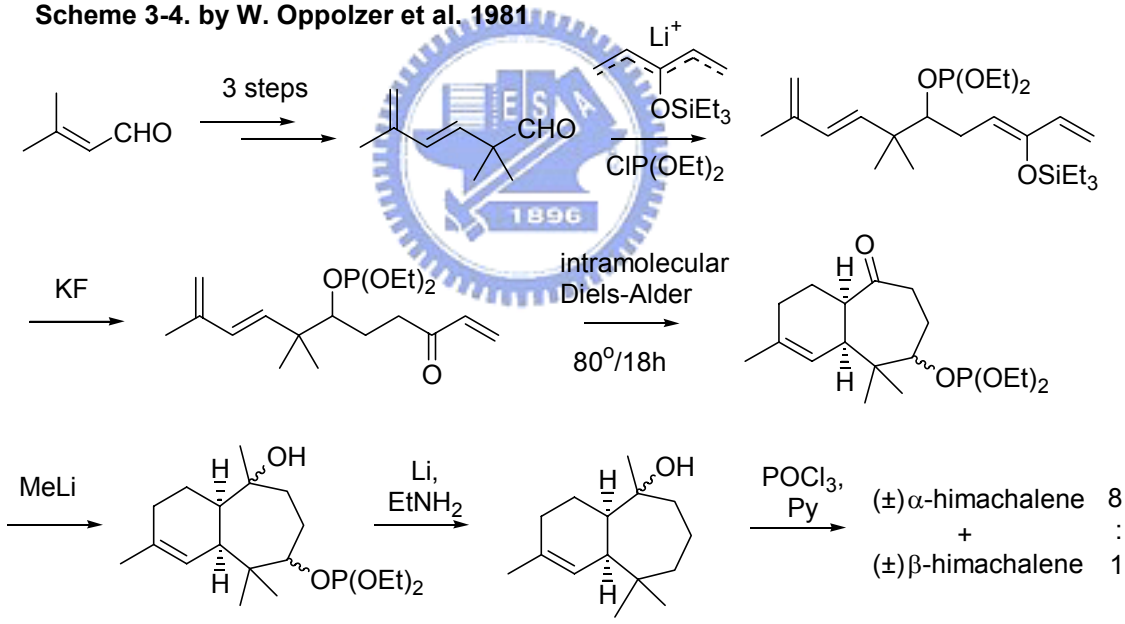
E. Wenkert 等人在 1973 年提出利用酸催化分子內(acid-catalyzed intramolecular) Diels-Alder 反應為關鍵步驟的合成途徑，以十二個步驟合成(±)α-himachalene(主產物)及(±)β-himachalene(副產物)

Scheme 3-3. by E. Piers et al. 1979



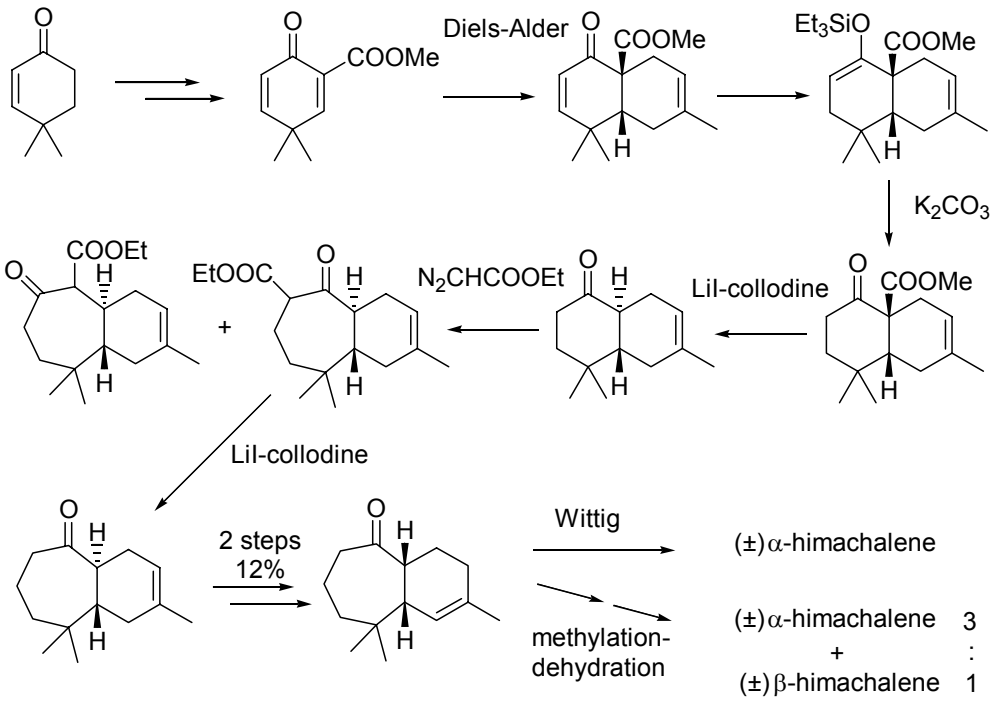
E. Piers 教授則是在 1979 年發表了九個步驟的(±)β-himachalene 合成法，以中間體 β-(2-vinylcyclopropyl)-α,β-unsaturated ketone 進行 Cope 重排反應生成六、七併環產物，在 ketone 的α位置引入甲基後，選擇性還原雙取代雙鍵得化合物，再經兩步操作合成(±)β-himachalene，總產率為 10%。

Scheme 3-4. by W. Oppolzer et al. 1981



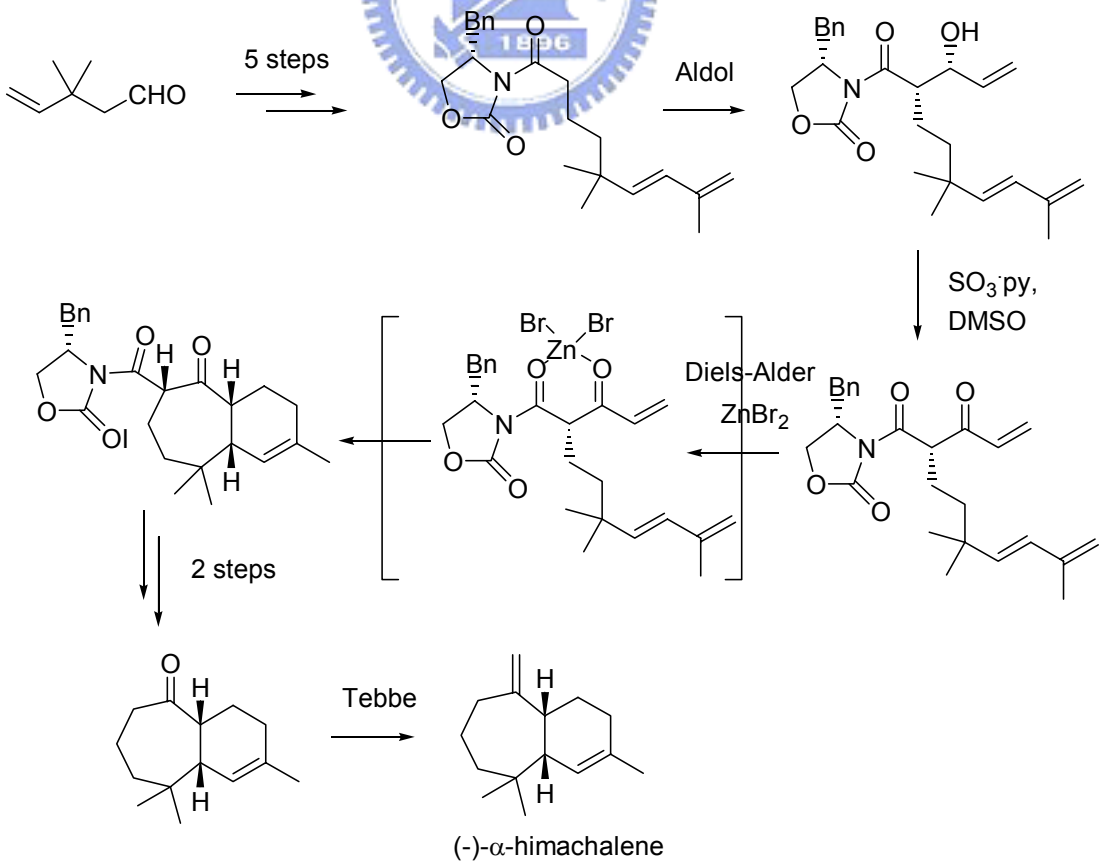
時至 1981 年，W. Oppolzer 教授改良了 E. Wenkert 的合成途徑，以較收斂的方法合成 Diels-Alder 前驅物，可在較低溫且不需路易士酸催化下進行分子內 Diels-Alder 反應，接著三步驟修飾後得主產物(±)α-himachalene 及副產物(±)β-himachalene。

Scheme 3-5. by E. N. C. Browne et al. 1981



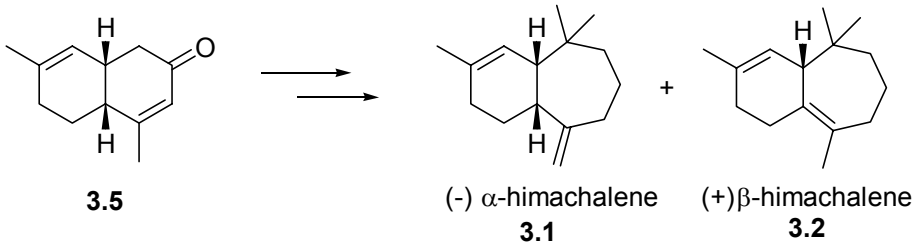
同樣在 1981 年，Liu and Browne 則是利用分子間 Diels-Alder 反應，以十一個步驟成功合成(±)α-himachalene 及(±)β-himachalene (3:1)。

Scheme 3-6. by D. A. Evans et al. 1997



直到 1997 年，Evans 教授發表了第一篇也是目前唯一一篇光學選擇性合成(-)-α-himachalene 的論文，巧妙地利用 *N*-acyl imide 作為 chiral auxiliary 先後進行 enantioselective aldol 及 enantioselective Diels-Alder 反應得光學活性中間體，兩步驟去除輔助基後再以 Tebbe 試劑[Cp2Ti(μ-Cl)(μ-CH2)AlMe2]，-40℃下處理，共十一個步驟合成(-)-α-himachalene。

至於天然物(+)-β-himachalene 則尚未有光學選擇性合成的文獻出現。

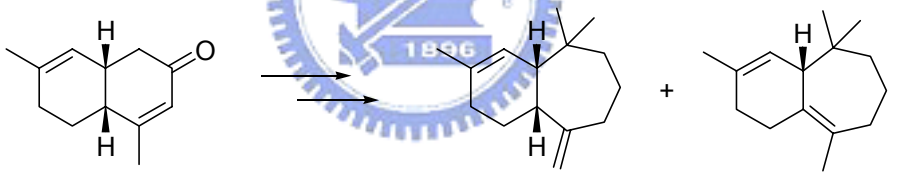


3.5 (-) α-himachalene **3.1** (+)β-himachalene **3.2**

Fig. 3-3.

我們在合成(-)-Furodysinin[3.11]時其中間物雙環烯酮已具備(-)-α及(+)-β-Himachalene 的大部份架構，尤其是環接上的絕對構形相同，故以其開始，經適當加成再行擴環，合成(-)-α-himachalene及(+)-β-Himachalene便是我們的研究方向及重點(如 Fig. 3-3 所示)。在經過多次的合成路徑修改後，成功地合成出(+)-β-Himachalene。

(3-2) 結果與討論

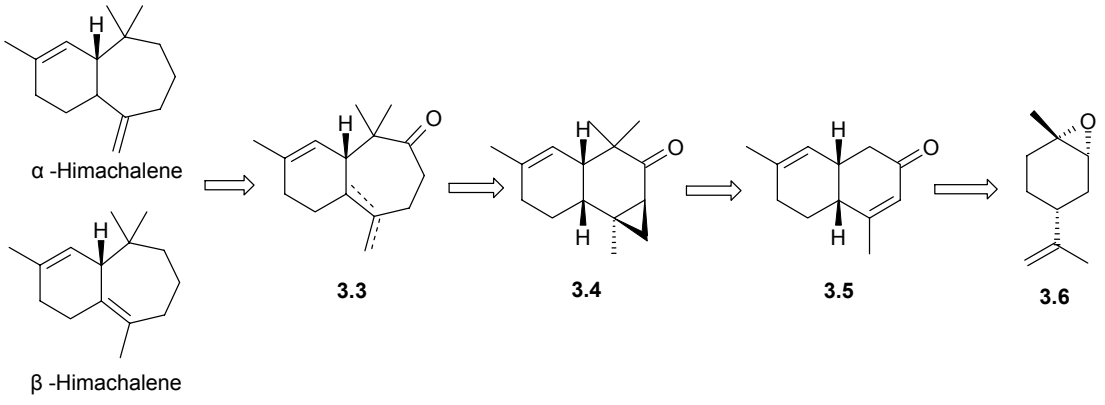


3.5 (-) α-himachalene **3.1** (+)β-himachalene **3.2**

Fig. 3-3.

由 Fig. 3-3.中三種分子結構來做比較，烯酮(**3.5**)的左側六員環及環接上立體結構皆與 α/β-Himachalene 完全相同，而右側部份官能基又極有利於改造，引發我們很高的興趣。

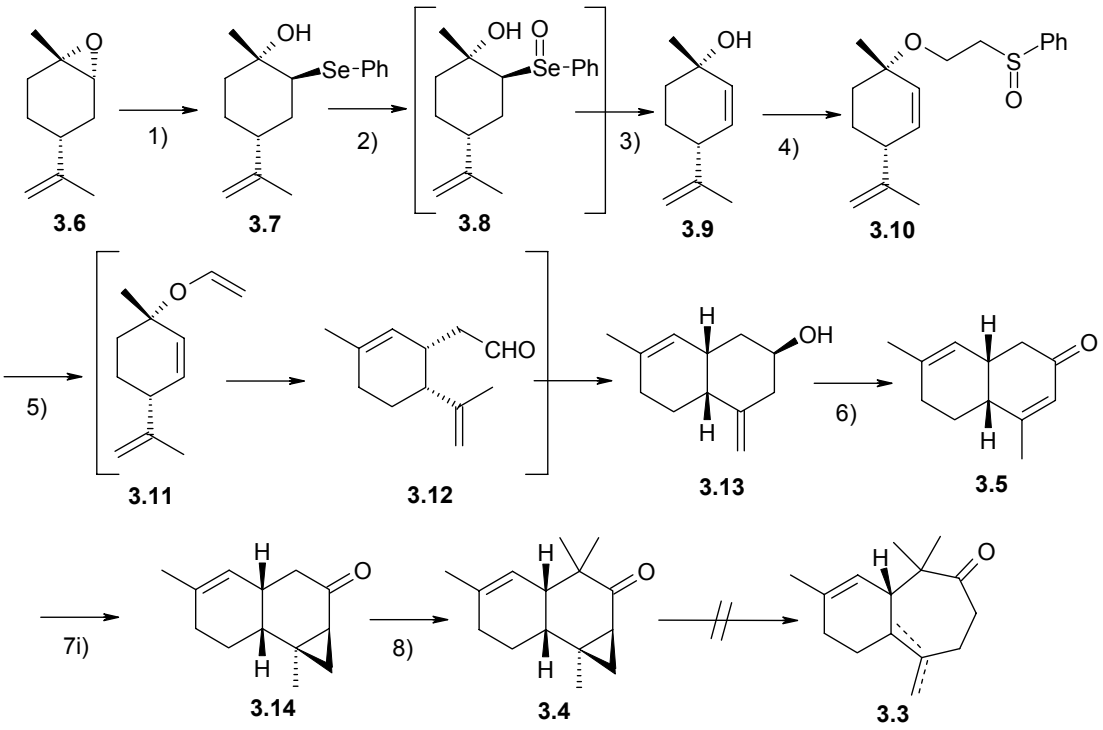
Scheme 3-7. Retrosynthesis of α /β -Himachalene



3.3 **3.4** **3.5** **3.6**

我們的合成溯徑分析是這樣的：如 Scheme 3-7.所示，根據烯酮(**3.5**)的羰基所在位置來判斷，α/β-Himachalene 的前驅物應是(**3.3**)，羰基的 α 位置易於加成甲基。而(**3.3**)即是(**3.4**)打開三員環後的產物，很明顯地只要於不飽和酮(**3.5**) 的雙鍵與另一側 α 位置適當加成，即可合成(**3.4**)，如此由烯酮 (**3.5**) 經簡短步驟應可合成 α/β-Himachalene。

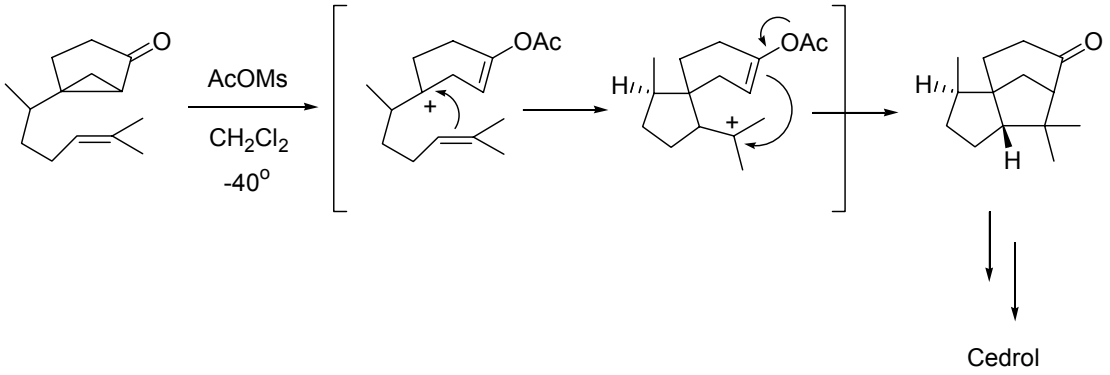
Scheme 3-8.



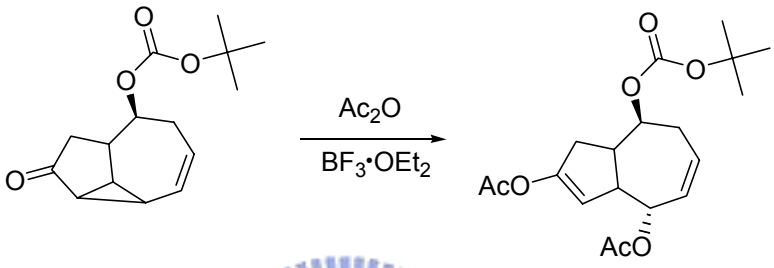
1) Ph_2Se_2, $NaBH_4$; 2) H_2O_2; 3) heating; 4) NaH; $PhSOCHCH_2$; 5) 200°; 6) Swern; 7) $Me_3SO^+I^-$, NaH, DMSO, 50°; 8) t-AmONa, THF, MeI, 60°.

由起始物右旋-反邊氧化蕈(**3.6**)開環取得二烯醇(**3.9**)的方法[3.12](Scheme 3-8.)改為以benzeneselenolate anion[3.13]打開環氧基後生成hydroxy selenide (**3.7**)，同鍋操作下經雙氧水氧化成不穩定的selenoxide (**3.8**)，隨即加熱進行脫除反應得二烯醇(**3.9**)，產率提升許多(98%)；由醇(**3.9**)經Claisen-ene聯繼反應合成烯醇(**3.13**)也有所改變，利用 2-allyloxyethyl phenyl sulfoxide[3.14] (**3.10**)作為Claisen重排反應的前驅體，直接加熱即可生成烯醇(**3.13**)，免除使用不好處理的汞鹽催化劑，產率也相對提昇且穩定許多。烯酮(**3.5**)可經由兩種途徑到(**3.4**)：一是先放入兩個甲基再加成三員環部份；另一則相反，先加成三員環後引入兩個甲基。這牽涉到策略的運用，前者需以動力學控制甲基化位置，以LDA於低溫拔除立體阻礙較小的α質子避免反應 β 位置。無法一次加成兩個甲基，要分兩次操作。若能先將三員環完成擋住一邊，就可在另一側進行熱力學控制反應。操作上較方便，更重要的是能一次放進兩個甲基。我們先將烯酮(**3.5**)與dimethyloxosulfonium methylide於 50°反應兩天，順利得到(**3.14**)(此步驟使用的試劑當量與文獻記載[3.15]稍有不同：生成dimethyloxosulfonium methylide所用的氫化鈉當量要比 trimethyloxosulfonium iodide稍微少；即在加入(**3.5**)之前要完全耗去氫化鈉，避免過量鹼造成(**3.5**)破壞及異構化發生。)。接著以$NaOAm^t$為鹼在THF中(苯不適合)進行兩次甲基化，產物的氫譜有四個甲基單峰，碳譜則有四支一級碳，果如所預期(**3.4**)。

Scheme 3-9.

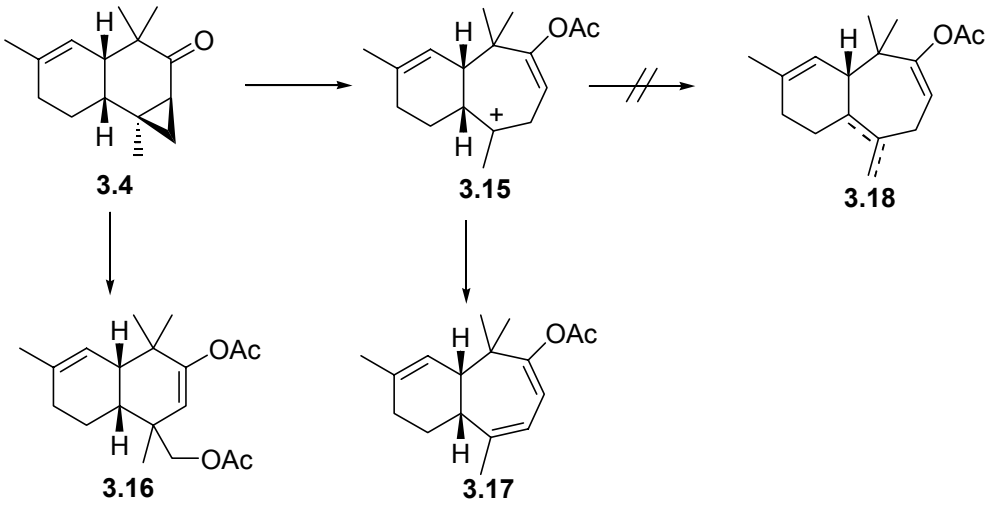


Scheme 3-10.



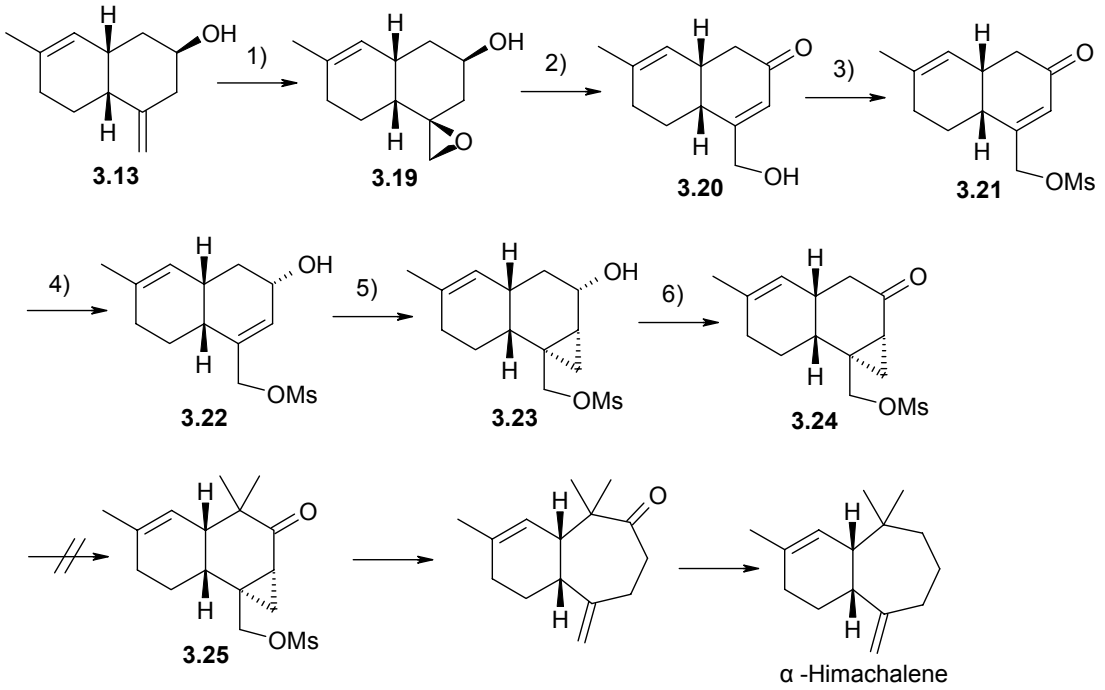
在得到(**3.4**)後我們參考了一些文獻：Corey教授在合成Cedrol[3.16]時曾進行 Scheme 3-9.的反應，利用acetyl methansulfonate於-40°下將三員環開啟，形成的陽離子再與分子內雙鍵反應。Rigby教授[3.17]則是以活性較小的路易士酸 BF_3·OEt_2開環，再藉由醋酸酐溶劑抓取陽離子中間體而生成烯酯化合物 (Scheme 3-10.)。我們先選擇較方便的後者進行(**3.4**)的開環，但反應後產物光譜於δ6.02、5.83 各出現一組雙峰可能是(**3.17**)的雙鍵氫，又δ4.06 有一組積分值較小的單峰，應是 (**3.16**) 酯基旁氫。由這結果推論陽離子中間體(**3.15**)應相當穩定，有充裕時間選擇能量較低的反應途徑。

Scheme 3-11.



接著又嘗試了Me_3SiOTf/TfOH、AcOH/H_2SO_4、AcOH/$HClO_4$、Ac_2O/AcOH等多種條件，但皆未獲得滿意的結果。

Scheme 3-12.

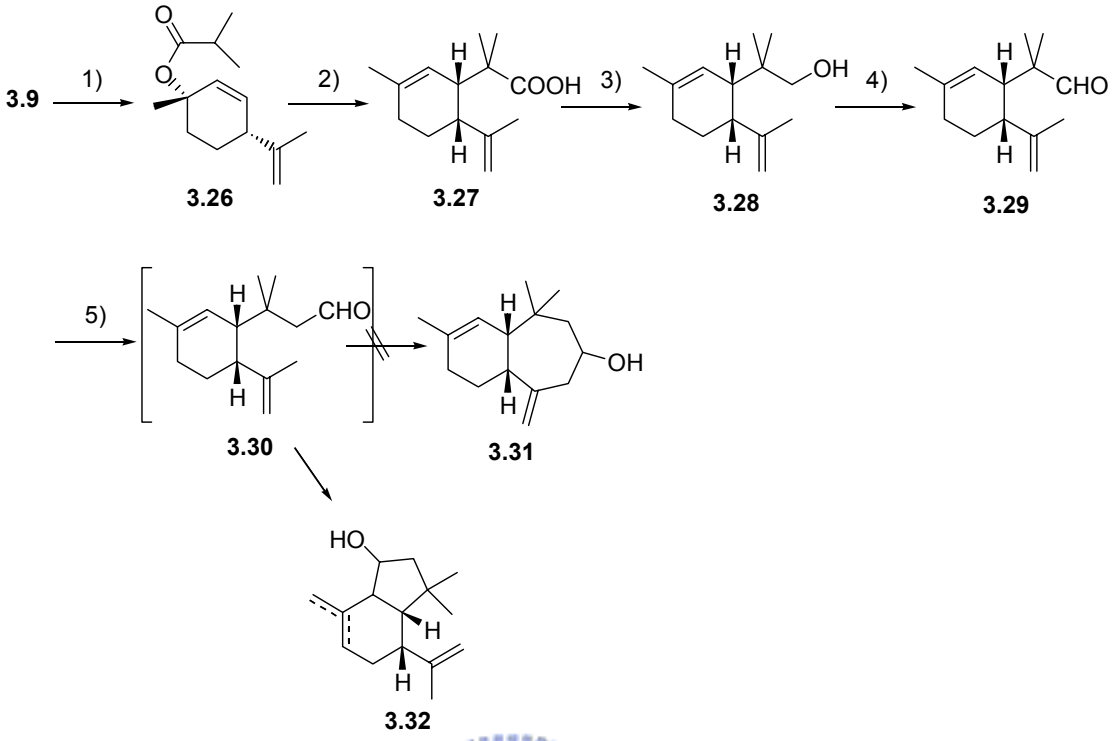


1) $Vo(acac)_2$, *t*-BuOOH; 2) Dess-Martin; 3) MsCl, Et_3N; 4) $NaBH_4$; 5) Simmons-Smith; 6) Dess-Martin

三員環開啟失敗後，我們將合成策略加以修改成 Scheme 3-12.，希望藉由離去基的幫助使能順利開環並指定雙鍵形成的位置，避免產生不希望的雙鍵異構物。但合成推進到(**3.24**)後，嘗試許多條件，只能在羰基的 α 位置引入一個甲基，卻無法順利引入第二個甲基，將反應條件激烈化的結果只導致化合物分解。另外，Scheme 3-9.的合成路徑太過冗長，主要問題在於無法在烯酮(**3.21**)的缺電子雙鍵上直接加成三員環，而需繞道重複還原氧化，實非理想。壯士斷腕，尋求其他途徑才是上策。

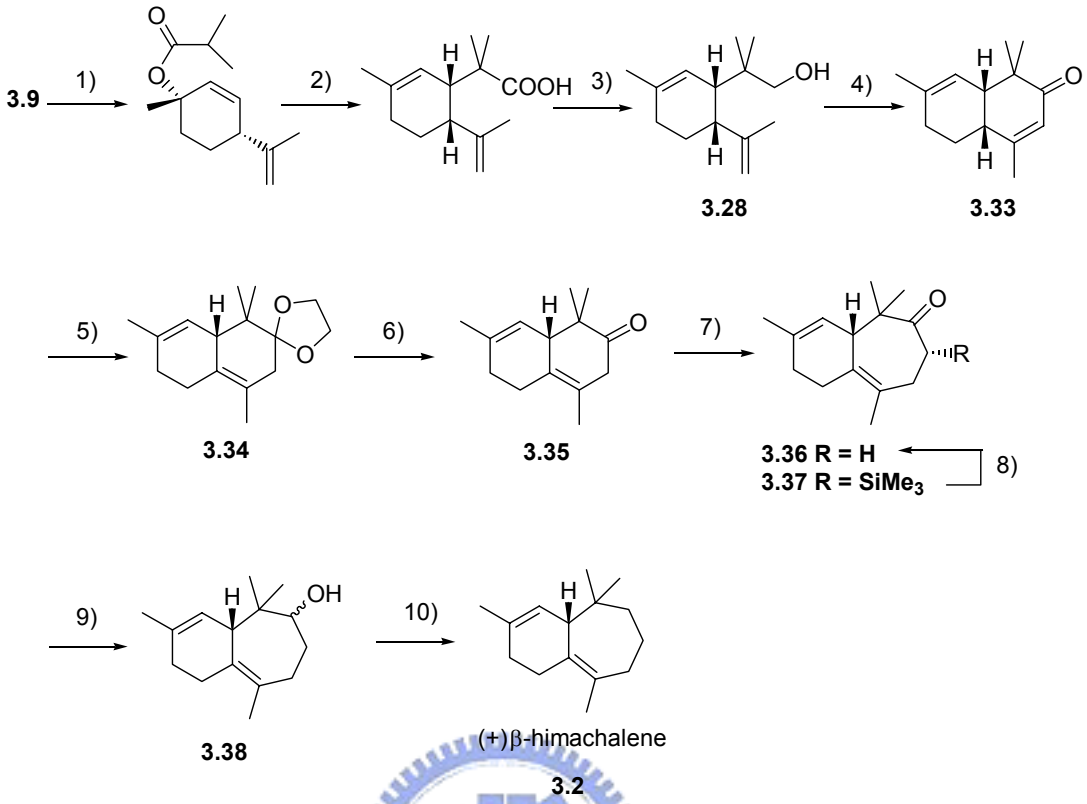
Scheme 3-13.及 Scheme 3-14.是我們下一個努力的方向，利用 Ireland-Claisen 重排反應先將兩個甲基置入(**3.27**)分子骨架內以解決 Scheme 3-10.遇到的問題。酸(**3.27**)經兩步操作得醛(**3.29**)。將醛(**3.29**)進行 Wittig 類型反應延長一個碳，水解後卻生成五、六併環產物(**3.32**)，而非我們所需的六、七併環醇(**3.31**)。

Scheme 3-13.



1) Isobutyic anhydride, Et_3N, DMAP(cat.), CH_2Cl_2, rt, 2 d, 99 %; 2) LDA, THF, -78 °, 1h, -40 °, 30 min; Me_3SiCl, -78 ° → rt; PhMe, reflux, 36 h, 68 %; 3) LAH, THF, reflux, 5 h; 4) Dess-Martin; 5) $[Ph_3PCH_2OMe]Cl$, ^tAmONa, THF, rt, 3 h; 10% HCl, THF, rt, 2.5 h.

Scheme 3-14. Total synthesis of (+)β-himachalene **3.2**



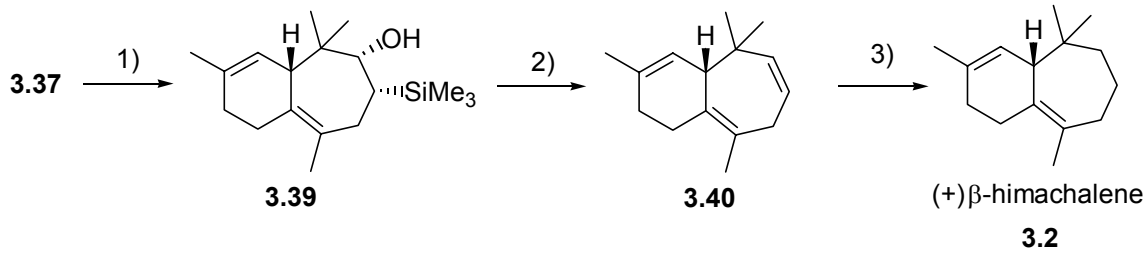
1) Isobutyic anhydride, Et_3N, DMAP(cat.), CH_2Cl_2, rt, 2 d, 99 %; 2) LDA, THF, -78 °, 1 h, -40 °, 30 min; Me_3SiCl, -78 ° → rt; PhMe, reflux, 36 h, 68 %; 3) LAH, THF, reflux, 5 h, 90 %; 4) PCC, CH_2Cl_2, rt, 24 h; TsOH, benzene, reflux, 1.5 h, 44.1 %; 5) ethylene glycol, TsOH(cat.), Dean-Stark, reflux, 24 h, 92.1 %; 6) 35 % CF_3COOH(aq), CH_2Cl_2, 10~20 °, 2 d, 98.8 %; 7) $TMSCHN_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -40 °, 2.5 h, 65.3 %; 8) TBAF, MeCN, rt, 3 h, 58.5 %; 9) $NaBH_4$, MeOH, 0 °, 1 h; 10) (i) MsCl, pyridine, DMAP(cat.), 0 ° → rt, 6 h; (ii) Li, NH_3(l), -78 °, 1 h, 44.9 % (3 steps).

合成α-Himachalene的計畫雖再次受挫，但同時進行的另一β-Himachalene合成途徑(Scheme 3-12.)終於成功，利用Corey教授報導過的氧化性陽離子環合反應(oxidative cationic cyclization reactions)[3.18]將醇(**3.28**)轉化成不飽和酮(**3.33**)。接著將不飽和酮(**3.33**)的雙鍵移至我們所需的非共軛位置(**3.35**)，其中縮酮化合物(**3.34**)的水解，在經歷多次試驗後，才找出可避免雙鍵回移的條件。在β,γ-不飽和酮(3.35)的擴環過程中，我們採用三甲基矽烷基重氮甲烷(Me_3SiCHN_2)在一當量三氟化硼反應下[3.19]，獲得兩種產物(**3.36**)及(**3.37**)，此擴環反應的位置選擇性出奇的好。矽化物(**3.37**)以TBAF處理可轉化成酮(**3.36**)。還原成醇(**3.38**)後，依循古典的方法甲磺醯基化後Birch還原，即可將羥基去除，得(+)β-himachalene (**3.2**)。測得旋光度$[\alpha]_D$ +213° (*c* 0.05 $CHCl_3$); 文獻報導[3.3,3.4] $[\alpha]_D$ +224.7°, +204 ° ($CHCl_3$)。

為改善酮(**3.36**)在硼氫化鈉還原過程沒有立體選擇性的缺憾，我們另將矽化物(**3.37**)直接以硼氫化鈉還原(Scheme 3-13.)，期望藉由巨大的三甲基矽烷基團進行立體控制，果然獲致單一產物(**3.39**)。中間體(**3.39**)在氫化鉀[3.20]處理後可進行同邊脫除反應(syn-elimination)生成三烯化合物(**3.40**)，證實了硼氫化鈉的確由立體阻礙較小的一側，也就是三甲基矽烷基團的反側進行還原，使得產物的羥基與三甲基矽烷基團位於同側。

此外我們也以NOE實驗確認了(**3.29**)的立體結構，並回推矽化物(**3.37**)。最後，選擇性還原三烯化合物(**3.40**)的雙取代雙鍵，即可完成(+)β-himachalene (**3.2**)。

Scheme 3-13.



1) $NaBH_4$, EtOH, rt, 1.5 d, 86.9 %; 2) KH, THF, rt, 24 h, 72.3 %; 3) $CoCl_2 \cdot 6H_2O$, $NaBH_4$, EtOH, rt, 24 h, 72.6 %.

我們由右旋-反邊氧化蕐(**3.7**) [(1*S*,2*R*)-epoxymenth-8-ene]共經 15 或 16 個步驟成功合成(+)-β-himachalene 總產率約為 6%，各項光譜資料皆與文獻報導一致。

(3-3) 參考文獻

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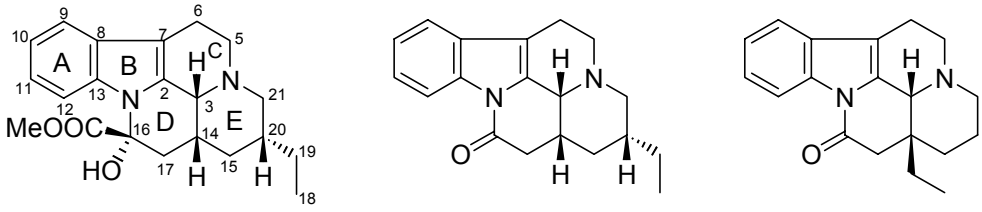
第四章 Tacamonine 的合成研究

(4-1) 緒論

Tabernaemontana eglandulosa Stapf是一種遍佈於中非森林的小型藤本植物，於夜晚開花， 薩伊地區的住民以其根部治療毒蛇的咬傷。1984 年T. A. van Beek等人[4.1]由*T. eglandulosa*的葉子和細枝中(Fig. 4-1.)，以乙醇萃取，分離出 22 種生物鹼。其中的 12 種為新發現生物鹼，tacamonine即為其中一種。有趣的是，在天然物被發現之前，G. Massiot的研究團隊[4.2]就已經早兩年以人工合成出tacamonine (早先命名為pseudovincamone)。

Fig. 4-1.Eglandulosa (摘自home.tiscali.be/ lpauwels/CATALKIN.htm)

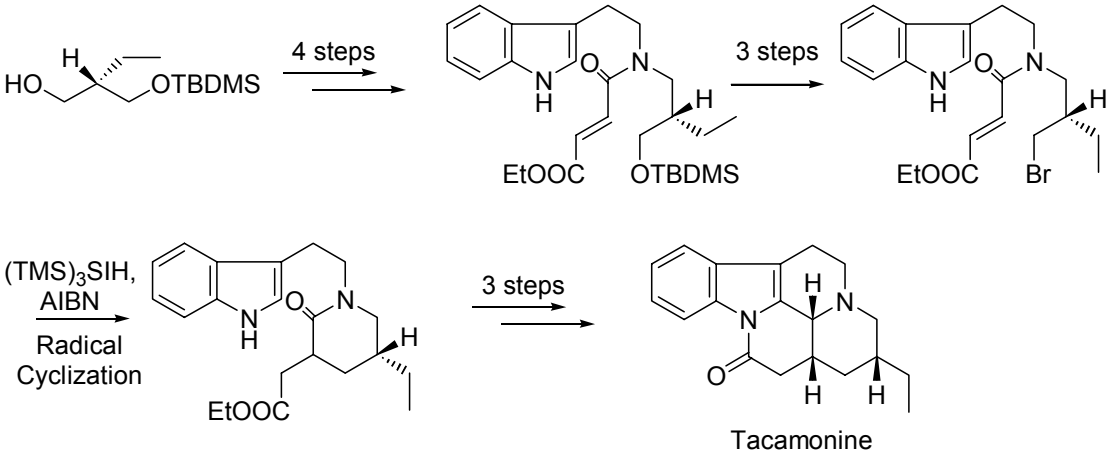
Tacamonine隸屬於tacamine (Fig. 4-2.)類indole生物鹼，eburnamonine的異構物，乙基的連接位置由五環結構中的D/E併環接點外移，產生出另一個不對稱中心，而三個三級碳上的氫立體關係皆為同側(cis)，這奇特的結構引發了我們的高度興趣。到目前為止已有四篇全合成文獻發表[4.3-4.6]。



Tacamine　　Tacamonine　　Eburnamonine

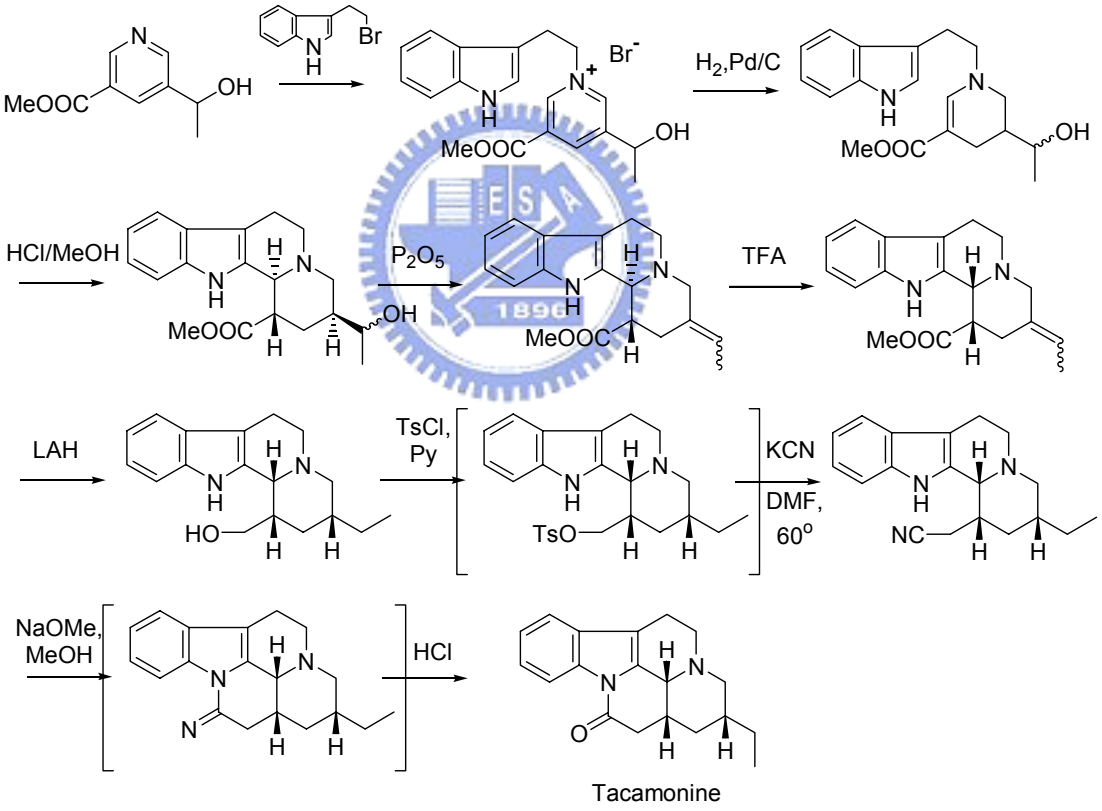
Fig. 4-2.

Scheme 4-1. by K. Fukumoto et al. 1994



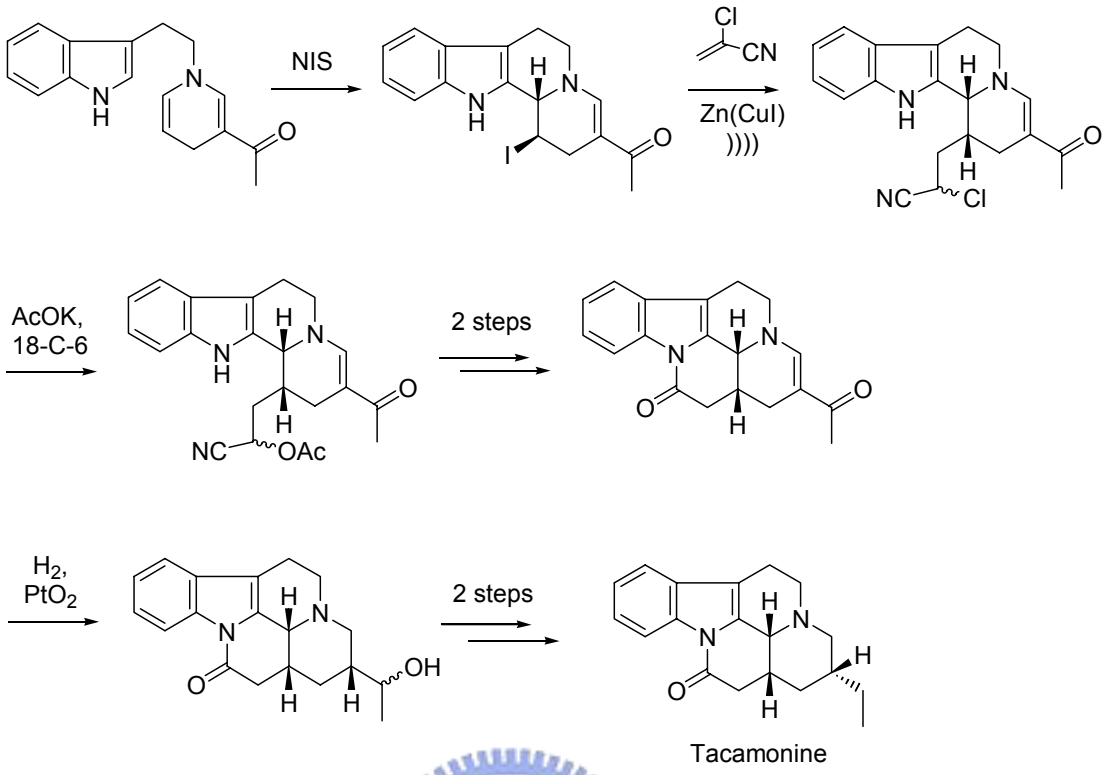
1994 年，Fukumoto[4.3]教授利用自由基環合反應(radical cyclization)，以 11 個步驟合成出tacamonine，總產率 3% (Scheme 4-1.)。

Scheme 4-2. by M. Lounasmaa et al. 1998



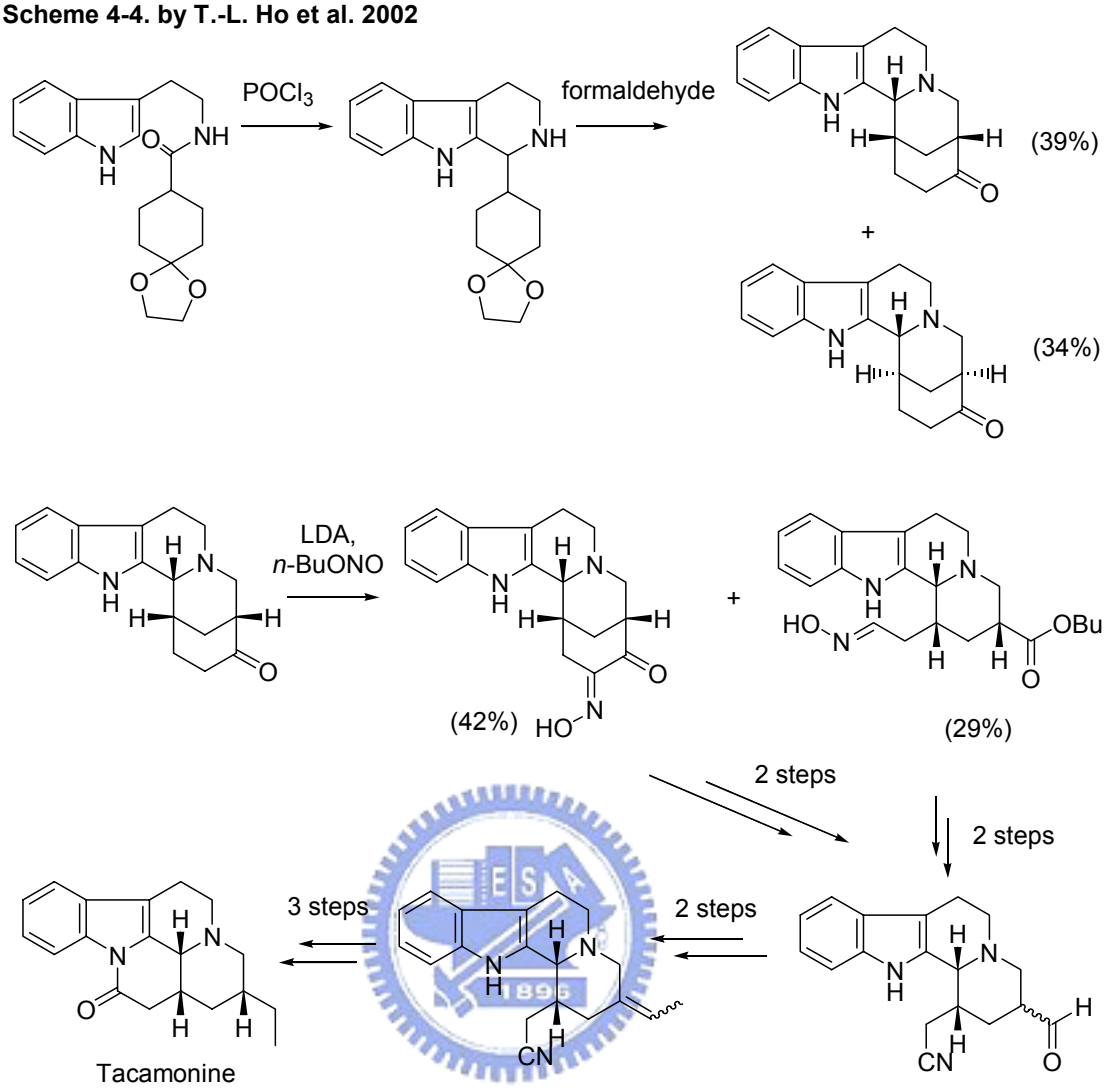
Lounasmaa[4.4]的團隊花了數年時間合成出tacamonine (Scheme 4-2.)，其中許多功夫下在三級碳上氫的異構化。

Scheme 4-3. by R. Lavilla et al. 2001



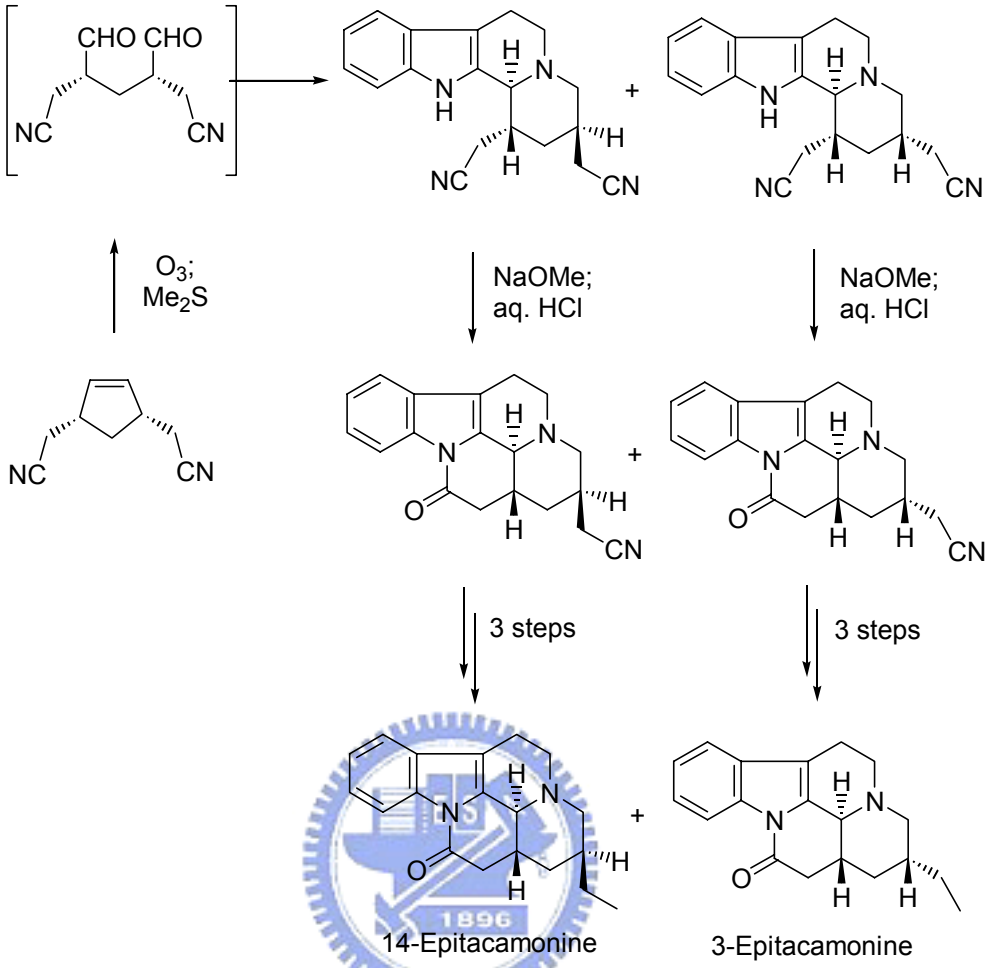
巴塞隆納大學的Lavilla[4.5]教授則在2001年以Lounasmaa於1982年合成出的中間體為起始物，再經八個合成步驟取得tacamonine，如Scheme 4-3.所示。

Scheme 4-4. by T.-L. Ho et al. 2002



本實驗室則在 2002 年[4.6]發表了tacamonine的全合成(Scheme 4-4.)。

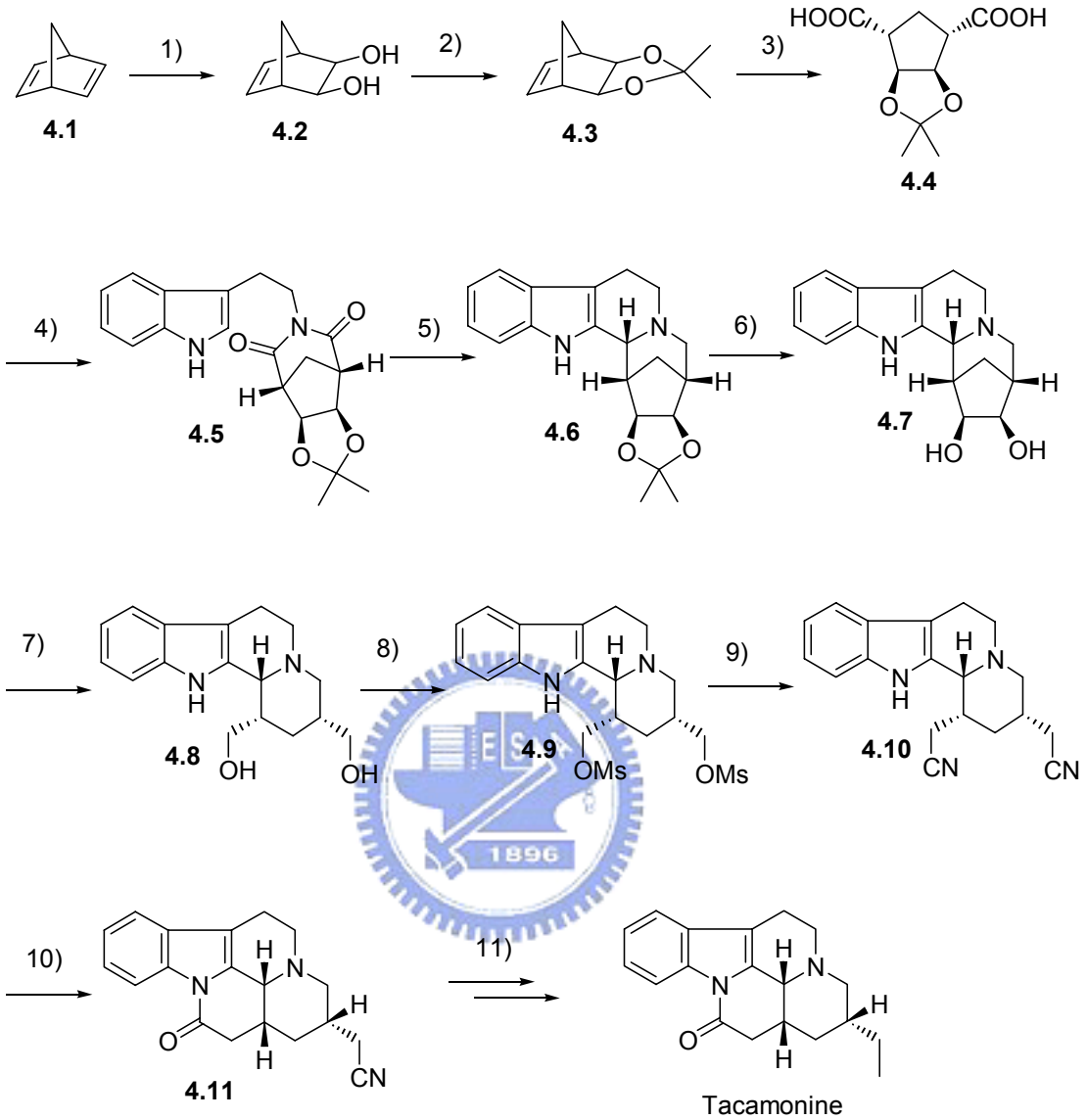
Scheme 4-5. by T.-L. Ho et al. 2001



另外，本實驗室又嘗試利用”對稱”[4.7]的概念來合成tacamonine[4.8]，雖發揮了對稱性分子的方便及簡潔性，但只達成異構物 14-epitacamonine及 3-epitacamonine的合成(Scheme 4-5.)。為彌補此美中不足之處，我們希望將此合成路徑稍做改變，一方面達成最佳的立體控制，另方面要維持對稱概念的發揮，進而展開另一合成tacamonine的計畫。

(4-2) 結果與討論

Scheme 4-6.



1)[4.9] $KMnO_4$, acetone, -78°; 2) [4.10] TsOH(cat.), acetone; 3)[4.11] $KMnO_4$, Et_2O, H_2O; 4)[4.12] ethyl chloroformate, Et_3N, tryptamine, THF; AcCl, THF; 5) Tf_2O,CH_2Cl_2; $NaBH_4$, MeOH; 6) TsOH, dioxane, H_2O, refluxed; 7) $NaIO_4$, THF, H_2O, 0°; $NaBH_4$, MeOH; 8) MsCl, Et_3N, THF, 0°; 9) NaCN, 18-crown-6, DMF, 60°; 10) NaOMe, MeOH, refluxed; HCl(conc.), 80°.

為了修正 Scheme 4-5.的立體位置問題，我們改用對稱雙酸(**4.4**)與色胺(tryptamine)接合生成亞胺(imide) (**4.5**)。亞胺(**4.5**)順序以三氟甲磺酸酐及硼氫化鈉處理後，環合生成六環產物(**4.6**)；此步驟也同時還原了內醯胺的羰基。環合過程的中間體應為(**4.13**) (Fig. 4-2)，橋環架構的影響，不論是在立體效應(steric effect)或是立體電子效應(stereoelectronic effect)上，皆有利於硼氫化鈉由另兩個同環三級碳上氫的同邊位相進行還原。也就是說，生成六環化合物(**4.6**)時，新生成的三級碳上氫必須與另兩個同環三級碳上氫位於同邊，與目標物 tacamonine 相同，解決了先前的立體控制問題。

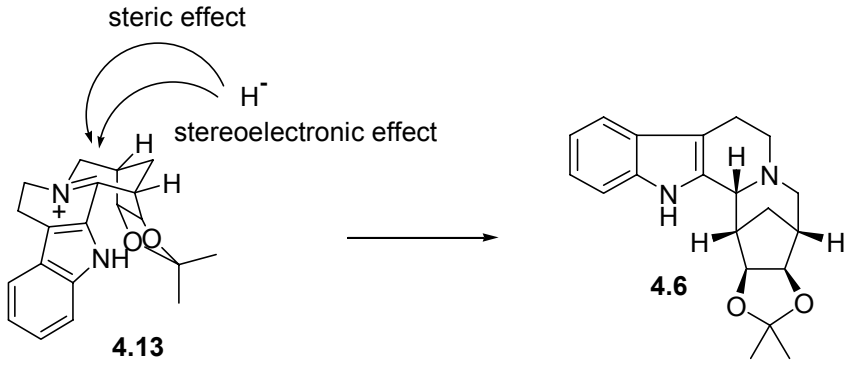


Fig. 4-2

六環化合物(**4.6**)去保護後，以$NaIO_4$切開 1,2-雙醇(**4.7**)，得到的雙醛產物不穩定，故直接還原成較穩定的 1,5-雙醇(**4.8**)。接著需將兩個側鏈各延伸一個碳，使用古典的方法先轉換成雙甲磺酸酯(**4.9**)，再以氰基取代，氰基取代反應並不順利，氰化鈉的鹼性使得主要產物為五環化合物(**4.14**)。目前以 18-冠-6-醚加入反應可抑制此問題而取得二腈(**4.10**)，但在分離上仍有問題，未取得純光譜。繼續推進至五環化合物(**4.11**)，可分離出少量純化合物並收集光譜數據。若能再大量複製並有效克服二腈(**4.10**)分離問題，則後續步驟皆為已知反應，此計畫應可順利完成。

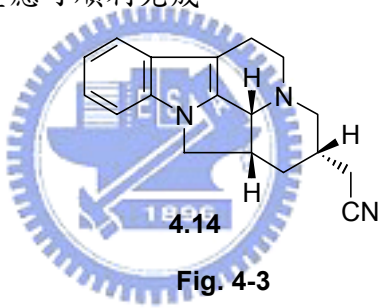
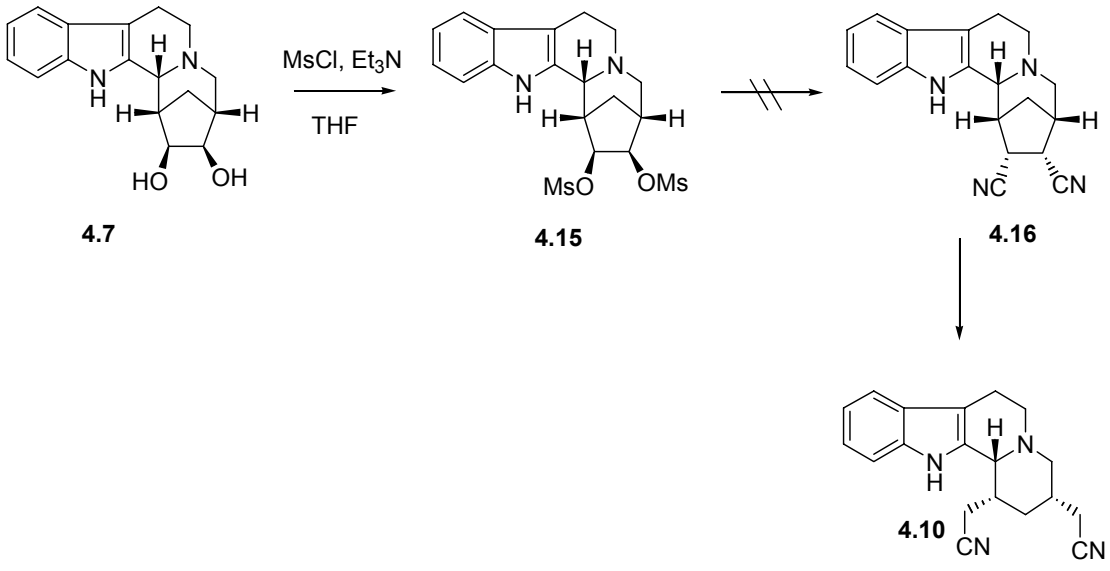


Fig. 4-3

我們也曾直接將雙醇(**4.7**)進行甲磺酸酯化反應得雙甲磺酸酯(**4.15**)，以嘗試 Scheme 4-5.所示途徑，無奈在轉化成二腈(**4.16**)時發生困難，得到雜亂的產物，故而放棄。

Scheme 4-5



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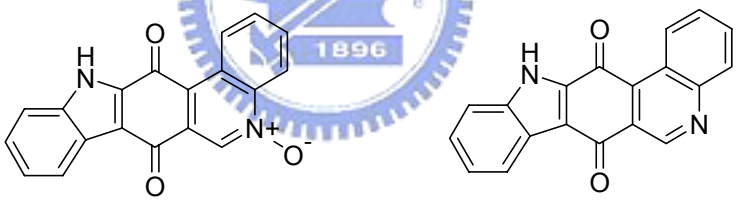
第五章 Calothrixin B 的合成研究

(5-1) 緒論

Calothrixin A及calothrixin B這兩種新奇的天然物(Fig. 5-2)，是由Rickards的研究團隊[5.1]首先在 1999 年從calothrix種藍綠藻中分離鑑定出。後其研究並發現其具有抑制瘧疾原蟲(*Plasmodium falciparum*)生長及殺死某些癌細胞的能力。有趣的是其中分子結構中包含了喹啉(quinoline),引朵(indole)及苯醌(quinone)等單元，這樣奇特的組合在生物活性的研究上被視為極具潛力的新一族天然物。第一個全合成由Kelly等人於 2000 年完成[5.2]。

Fig. 5-1. calothrix種藍綠藻 (摘自 http://protist.i.hosei.ac.jp/PDB/Images/Prokaryotes/Rivulariaceae/Calothrix_3.html,及 www-cyanosite.bio.purdue.edu/ images/images.html)



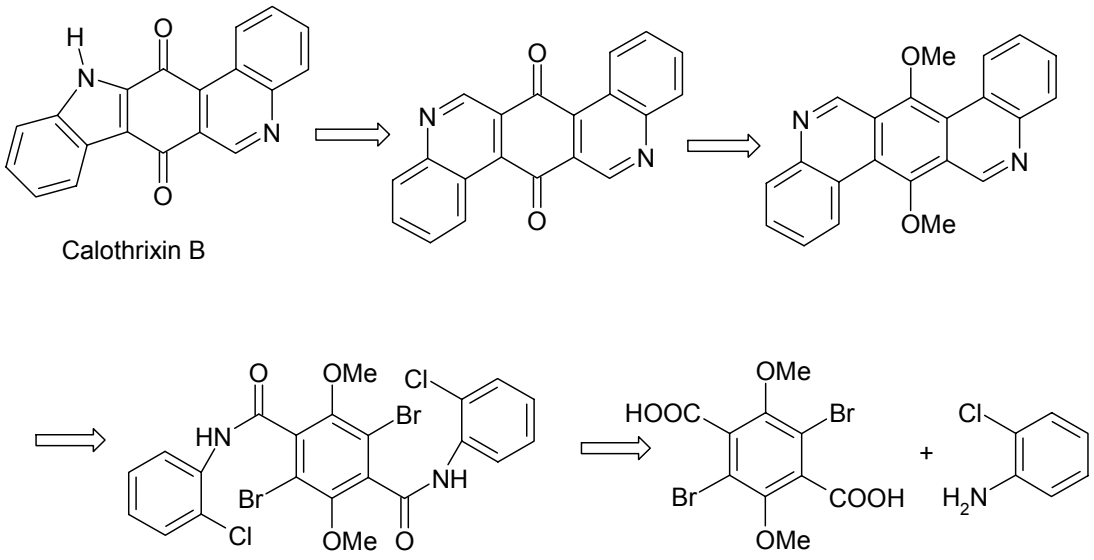
Calothrixin A　　Calothrixin B

Fig. 5-2.

我們同樣以"對稱"合成觀點出發，希望以簡短的途徑合成此天然物 calothrixin B。

(5-2) 結果與討論

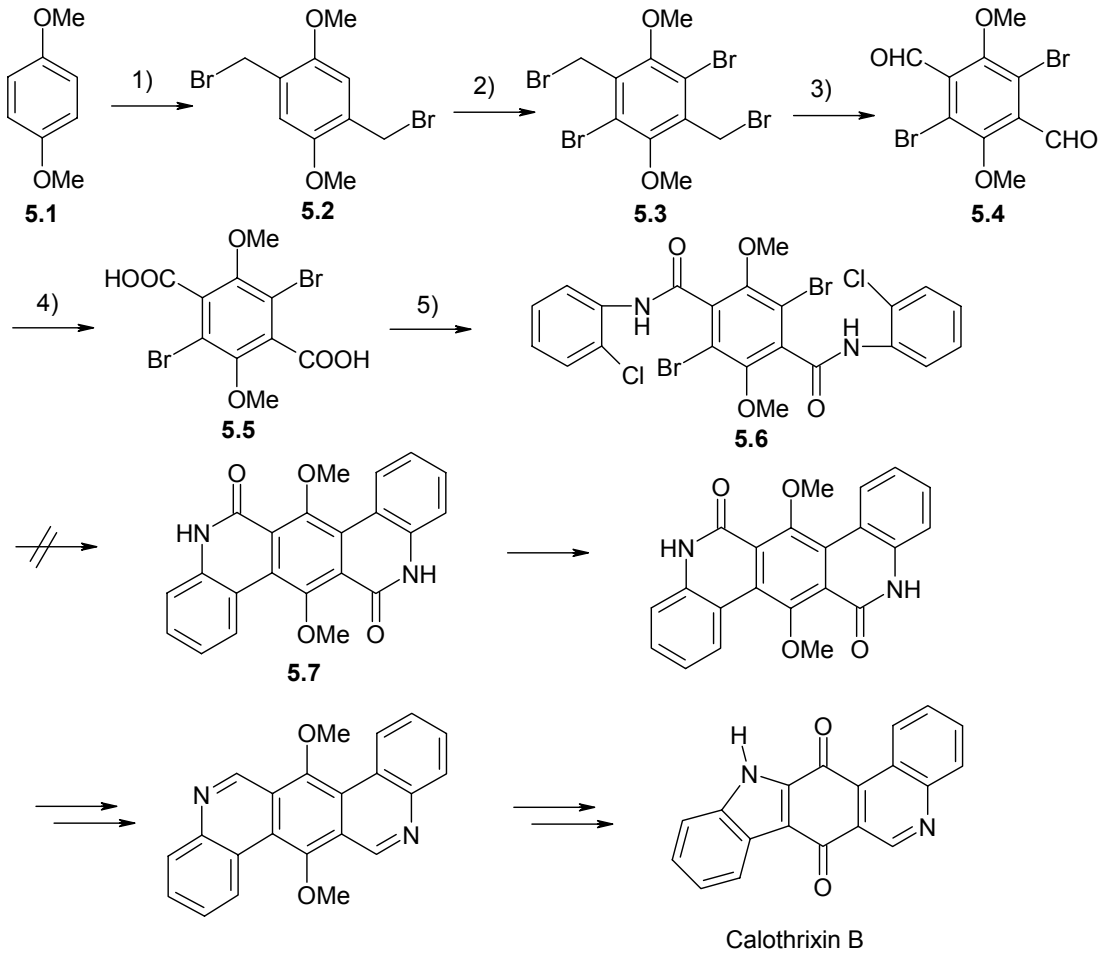
Scheme 5-1. Retreo-synthesis of calothrixin B



Calothrixin B的合成計畫如Scheme 5-2 所示，推進至化合物(**5.6**)後，嘗試許多條件[$Pd(OAc)_2$[5.3-5.5]、$Ni(COD)_2$[5.6,5.7]、$PdCl_2(PPh_3)_2$、照光]皆無法使其環化生成五環前驅物(**5.7**)，化合物(**5.6**)對許多溶劑的溶解度幾乎是不溶，也降低了反應成功的機率。

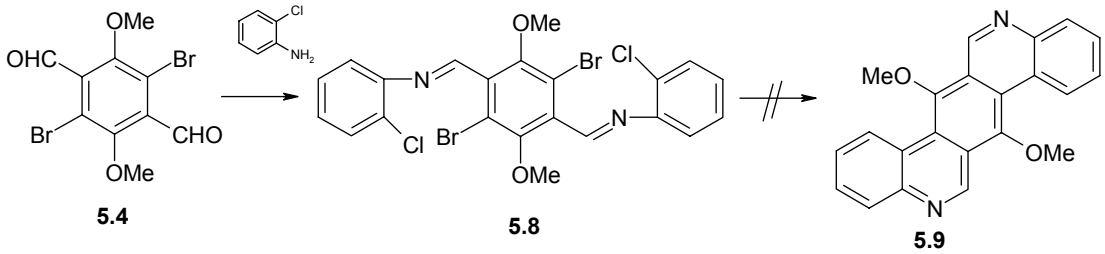
又修改路徑成Scheme 5-3.，同樣在形成五環架構時[Ullmann[5.8]、 $NiCl_2/PPh_3/Zn$[5.9]、$PdCl_2(PPh_3)_2/Bu_6Sn_2$]遇到困難。Scheme 5-4 欲以化合物(**5.4**)進行二聚化反應[5.10]，卻只回收脫氯產物(**5.16**)，無法順利完成calothrixin B計畫。

Scheme 5-2.

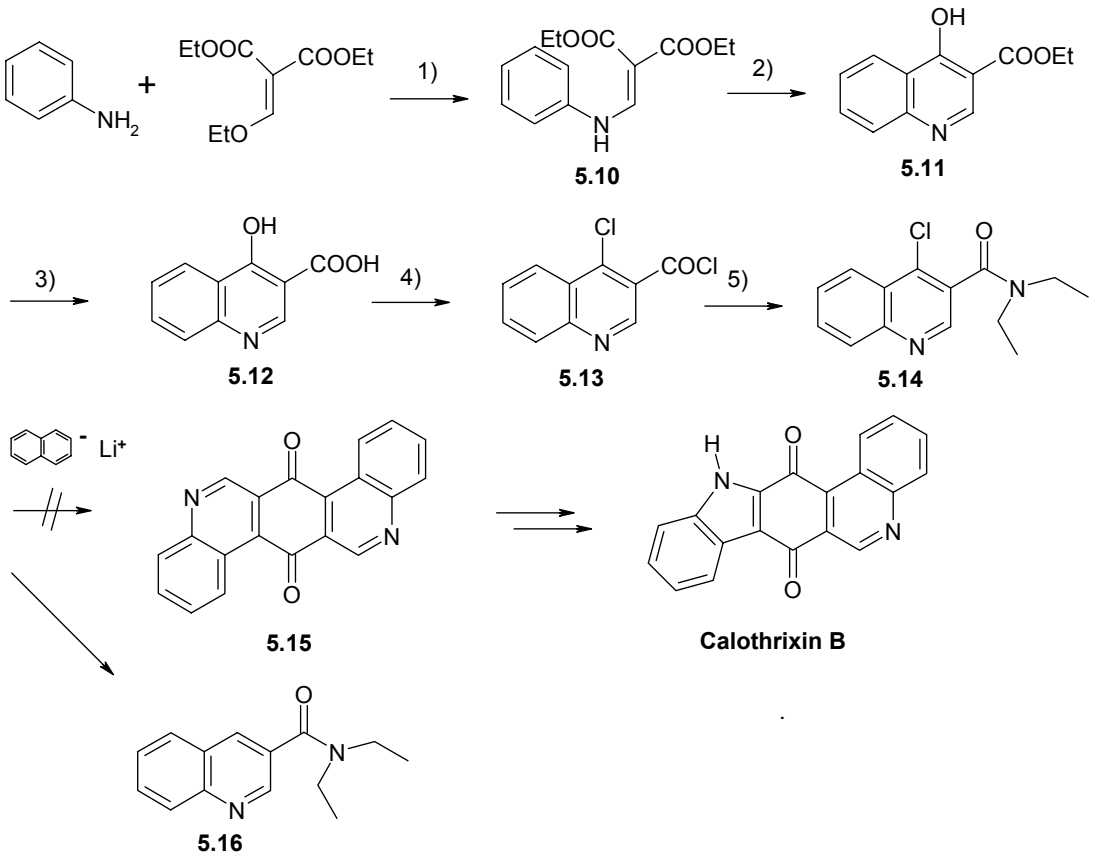


1)[5.11] $(CH_2O)n$, HBr, HOAc, 81.0 %; 2) Br_2, I(cat.), $CHCl_3$, 86.4 %; 3)[5.12] PhSeOOK, K_2HPO_4, dioxane, 82.2 %; 4)[5.13] SeO_2, 30 % H_2O_2, 98 %; 5) $SOCl_2$, CH_2Cl_2, DMF(cat.); chloroaniline, Et_3N, CH_2Cl_2, 43.4 %

Scheme 5-3.



Scheme 5-4.



1)[5.14] 100°, 58.6 %; 2)[5.14] Ph_2O, 260°, 99 %; 3)[5.15] 10 % NaOH, 87.3 %; 4) $SOCl_2$, DMF; 5) diethylamine, K_2CO_3, 82.5 % (2 steps)

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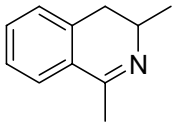
第六章 實驗步驟

General. Column chromatography (CC): *Merck* silica-gel (63-200 mesh). TLC: *Merck* silica-gel *60 F 254* plates. M.p.: uncorrected; *Laboratory Devices.* IR Spectra: *Bio-Rad FTS 165* and *FTS 3100* ; ν in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian Unity-300*; $CDCl_3$ unless otherwise indicated; δ in ppm, *J* in Hz. EI-MS: *Trio-2000* and *Jeol SX-102A*; ionization potential 70 eV. For drying organic solutions during workup of reactions, Na_2SO_4 was used. $[\alpha]_D$ was measured in $CHCl_3$.

Formation of 3,4-dihydroisoquinolines

A mixture of the phenethyl chloride and RCN (2.1 mmol each) was placed in a flask fit with a rubber septum and a condenser, $SnCl_4$ (2 mmol) was added through a syringe to the stirred mixture. After the exothermic reaction subsided, the mixture was heated in an oil bath at 110-130℃ for 3 h. It was cooled, basified with 20% NaOH and extracted with ether. The ethereal layer was extracted with 20% HCl, aqueous solution neutralized with NaOH and extracted with ether. On evaporation of the dried ethereal extract, the 3,4-dihydroisoquinoline was obtained.

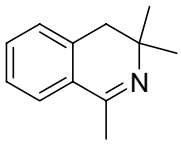


1,3-Dimethyl-3,4-dihydroisoquinoline (1.6).

1,3-Dimethyl-3,4-dihydroisoquinoline was obtained in 49% yield.

^{1}H NMR δ 1.35 (3H, d, *J* = 6.6 Hz); 2.35 (3H, *J* = 2.1, d); 2.45 (1H, *J* = 15.6 , 12.6, dd); 2.71 (1H, *J* = 15.6, 5.1, dd); 3.48-3.57 (1H, m); 7.14 (1H, *J* = 7.2, d), 7.24-7.35 (2H, m); 7.46 (1H, *J* = 7.2, d).

^{13}C NMR δ 22.0 (q); 23.3 (q); 33.4 (t); 51.8 (d); 125.2 (d); 126.8 (d); 127.5 (d); 129.3 (s); 130.5 (d); 137.2 (s); 163.4 (s).

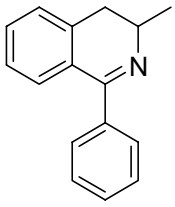


1,3,3-Trimethyl-3,4-dihydroisoquinoline (1.8).

1,3,3-Trimethyl-3,4-dihydroisoquinoline 55% yield.

^{1}H NMR δ 1.15 (6H, s); 2.32 (3H, s); 2.63 (2H, s); 7.07 (1H, *J* = 7.2, d); 7.70-7.28 (2H, m); 7.40 (1H, *J* = 7.8, d).

^{13}C NMR δ 23.1 (q); 27.8 (q); 38.6 (t); 53.4 (s); 125.0 (d); 126.5 (d); 127.9 (d); 128.4 (s); 130.4 (d); 136.1 (s); 161.0 (s).

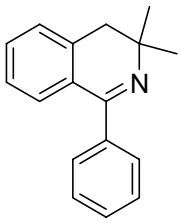


1-Phenyl-3-methyl-3,4-dihydroisoquinoline (1.7).

1-Phenyl-3-methyl-3,4-dihydroisoquinoline 45% yield.

^{1}H NMR δ 1.48 (3H, *J* = 6.9, d); 2.62 (1H, *J* = 15.6, 12.3, dd); 2.83 (1H, *J* = 15.5, 4.9, dd); 3.69-3.77 (1H, m); 7.29-7.61 (9H, m).

^{13}C NMR δ 21.6 (q); 33.4 (t); 52.7 (d); 126.4 (d); 127.3 (d); 127.5 (d); 127.8 (d); 128.0 (d); 128.4 (d); 128.5 (s); 128.8 (d); 129.1 (d); 130.6 (d); 138.4 (s); 138.9 (s); 166.2 (s).

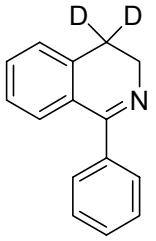


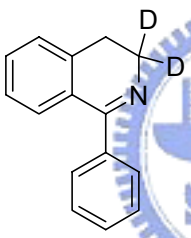
1-Phenyl-3,3-dimethyl-3,4-dihydroisoquinoline (1.9).

1-Phenyl-3,3-dimethyl-3,4-dihydroisoquinoline 48% yield.

^{1}H NMR δ 1.19 (6H, s); 2.72 (2H, s); 7.09-7.47 (9H, m).

^{13}C NMR δ 27.5 (q); 38.8 (t); 54.5 (s); 126.4 (d); 127.9 (d); 128.1 (d); 128.2 (d); 128.4 (s); 128.7 (d); 128.9 (d); 130.7 (d); 137.5 (s); 139.1 (s); 164.6 (s).

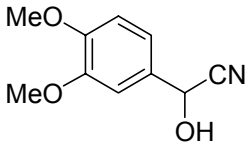




Mixture of 1-Phenyl-4,4-dideuterio-3,4-dihydro- isoquinoline (1.11) and 1-Phenyl-3,3-dideuterio-3,4-dihydroiso- quinoline (1.12).

1-Phenyl-4,4-dideuterio-3,4-dihydroisoquinoline and 1-Phenyl-3,3-dideuterio-3,4-dihydroisoquinoline (ratio 1:1).

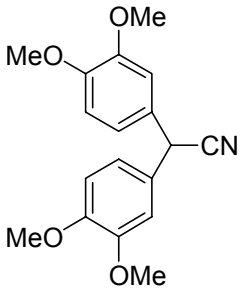
^{1}H NMR δ 2.71, 3.76 (1:1) (1H, s); 7.16-7.54 (9H, m).



2-(3,4-Dimethoxyphenyl)-2-hydroxyacetonitrile (1.26)

Under vigorous stirring conc. HCl (4.5 ml) was added in drops to a solution of veratraldehyde (5 g, 30.1 mmol) in alcohol (5 ml) which was admixed with a 10% NaCN (15 ml), cooled by ice-water, until a thick mass of small colorless crystals was formed. The crystals were collected, washed free of acid with water, then dissolved in CH_2Cl_2 and again washed with water. The organic phase was concentrated in *vacuo* to give (**1.26**) (4.2 g, 72.2 %).

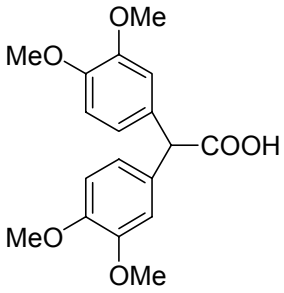
^{1}H-NMR δ 3.87 (s, 6 H); 5.45 (s, 1 H); 6.86 (d, J = 8.1, 1 H); 7.00-7.07 (m, 2 H).



2,2-Bis(3,4-dimethoxyphenyl)acetonitrile (1.27).

A suspension of finely powdered 3,4-dimethoxymandelonitrile(**1.26**) (6.8 g, 35.2 mmol) in veratrol (5.8 g, 42.0 mmol) was cooled in an ice bath, mixed with 75% H_2SO_4 (25 ml), and gradually warmed to 70^o in a water bath, while maintaining gentle stirring. The reaction was allowed to proceed for 30-40 min after complete dissolution of the reactant(s). The deep cherry-red solution was poured into ice water, extracted thrice with CH_2Cl_2, and the organic layer was washed with water. The dried, organic solution was evaporated to give (**1.27**) (7.2 g, 65.3 %).

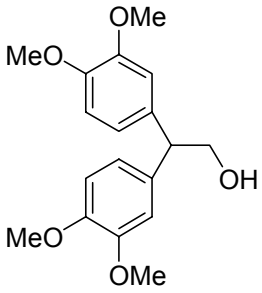
^{1}H-NMR δ 3.79 (s, 6 H); 3.83 (s, 6 H); 4.82 (s, 1 H); 6.77-6.79 (m, 6 H).



2,2-di(3,4-dimethoxyphenyl)acetic acid (1.28)

A solution of nitrile (**1.27**) (7.2 g, 23.0 mmol) in 20% alcoholic KOH (100 ml) was refluxed for 2 h. Alcohol was removed and gradually replaced with water. After about ten hours, no more ammonia was evolved. The basic solution was washed with CH_2Cl_2 and then acidified with acetic acid. An oil separated, which completed crystallized on standing (6.2 g, 81.2 %).

^{1}H-NMR δ 3.80 (s, 6 H); 3.84 (s, 6 H); 4.92 (s, 1 H); 6.79-6.84 (m, 6 H).



2,2-Bis(3,4-dimethoxyphenyl)-1-ethanol (1.29)

A soln. of acid (**1.28**) (6.2 g, 18.7 mmol) in anh. THF (30 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.4 g, 36.8 mmol) in THF (40 ml). The mixture was refluxed for 12 h, quenched with saturated NH_4Cl, and extracted with CH_2Cl_2. The org. layer was washed with brine, dried, and evaporated to afford (**1.19**) (5.9 g, 99.4 %).

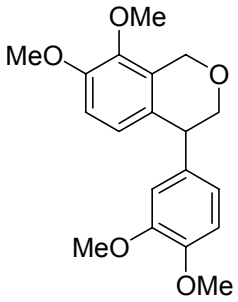
IR(neat) ν 3522, 2998, 2936, 2835, 2360, 2342, 1604, 1591, 1515, 1464, 1417, 1262, 1142, 1027, 858, 811, 764

^{1}H-NMR δ 3.81 (s, 6 H); 3.84 (s, 6 H); 3.83-3.87 (m, 2H); 4.08 (s, 2 H); 6.74 (s, 2H); 6.80 (d, *J* = 1.5, 4 H).

^{13}C-NMR δ 52.1 (d); 55.3 (q); 65.6 (t); 110.8 (d); 111.3 (d); 119.5 (d); 134.0 (s); 147.2 (s); 148.4 (s).

EI-MS: 319 (2, M+1$^{+\cdot}$), 318 (9, M$^{+\cdot}$), 288 (18), 287 (100), 273 (11).

HR-MS: 318.1469 ($C_{18}H_{22}O_5^{+\cdot}$; calc. 318.1468).



4-(3,4-dimethoxyphenyl)-7,8-dimethoxy-3,4-dihydro-1*H*-isochromene (1.30)

To a stirred solution of 2,2-bis(3,4-dimethoxyphenyl)-1-ethanol(**1.29**) (9.0 g, 28.3 mmol), dioxane (30 ml) and conc. HCl (5 ml) was added 37% formalin (2.3 g, 28.3 mmol) dropwise. During addition, HCl gas was passed through. Stirring and the introduction of HCl gas were continued for 4 h longer and then conc. HCl (20 ml) was added. After cooling the reaction mixture was extracted with CH_2Cl_2, the organic layer was washed with water, brine, dried, and evaporated in *vacuo* affording (**1.30**) (9.2 g, 98.5 %).

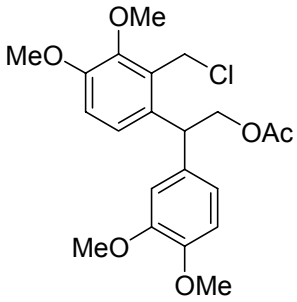
IR(neat) ν

^{1}H-NMR δ 3.68 (s, 3 H); 3.79 (s, 3 H); 3.84 (s, 3 H); 3.85 (s, 3 H); 3.98-4.02 (m, 1H); 4.07-4.12 (m, 2 H); 4.79 (q, J = 14.4, 2 H); 6.42 (s, 1H); 6.51 (s, 1H); 6.66-6.80 (m, 3 H).

^{13}C-NMR δ 43.2 (d); 55.4 (q); 67.8 (t); 72.0 (t); 106.3 (d); 110.7 (d); 111.5 (d); 111.6 (d); 120.7 (d); 126.6 (s); 127.9 (s); 135.3 (s); 147.4 (s); 148.5 (s).

EI-MS: 331 (9, M+1$^{+\cdot}$), 330 (73, M$^{+\cdot}$), 269 (100), 238 (25), 164 (23), 151 (21), 150 (40), 127 (21), 32 (23).

HR-MS: 330.1469 ($C_{19}H_{22}O_5^{+\cdot}$; calc. 330.1468).



2-[2-(chloromethyl)-3,4-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethyl acetate (1.31)

To a stirred solution of ether (**1.30**) (5.0 g, 15.2 mmol) and $ZnCl_2$ (3.0 g, 22.0 mmol) in CH_2Cl_2 (50 ml) was added acetyl chloride (5.0 g, 63.4 mmol) dropwise at -78 ^{o} under N_2. The reaction mixture was gradually warmed to 0 ^{o} and kept for 1 h. On quenching with water, the resulting mixture was extracted with CH_2Cl_2, dried, evaporated *in vacuo* and chromatographed (silica gel, 2:3 AcOEt/hexane) to give (**1.31**) (5.2 g, 84.0%).

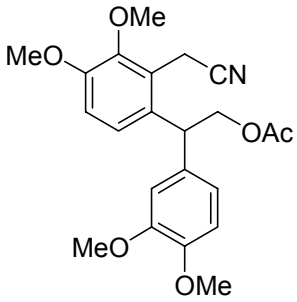
IR(neat) ν 3006, 2965, 2903, 2832, 1782, 1722, 1618, 1541, 1463, 1147, 799.

^{1}H-NMR δ 1.97 (s, 3 H); 3.78 (s, 6 H); 3.82 (s, 3 H); 3.85 (s, 3 H); 4.53-4.57 (m, 3H); 4.62-4.66 (m, 2 H); 6.68 (s, 1H); 6.74 (s, 1H); 6.77 (s, 2H); 6.82 (s, 1H).

^{13}C-NMR δ 20.5 (q), 43.7 (d); 44.1 (t); 55.3 (q); 55.4 (q); 55.5 (q); 55.6 (q); 66.1 (t); 110.7 (d); 110.8 (d); 111.4 (d); 113.3 (d); 119.3 (d); 127.6 (s); 132.5 (s); 132.7 (s); 147.2 (s); 147.5 (s); 148.6 (s); 149.0 (s); 170.5 (s).

EI-MS: 410 (3, $M+2^{+\cdot}$), 408 (8, $M^{+\cdot}$), 313 (100), 299 (70), 268 (52), 43 (28).

HR-MS: 408.1342 ($C_{21}H_{25}ClO_6^{+\cdot}$; calc. 408.1341).



2-[2-(cyanomethyl)-3,4-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethyl acetate (1.32)

A mixture of chloro-ethyl acetate (**1.31**) (2.0 g, 4.9 mmol), NaCN (0.7 g, 14.3 mmol) (pre-dissolved in 0.7 ml H_2O), Bu_4NBr (1.6 g, 4.9 mmol), and CH_2Cl_2 (20 ml) was stirred at r.t. for 4 h. The resulting solution was washed 3 times with water, dried, evaporated *in vacuo* and chromatographed (silica gel, 2:3 AcOEt/hexane) to afford (**1.32**) (1.4g, 71.7 %).

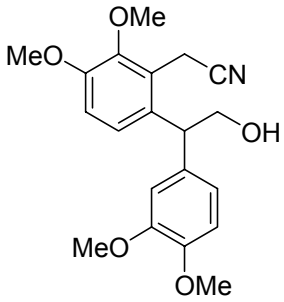
IR(neat) ν 3006, 2904, 2850, 2837, 2255, 1752, 1719, 1607, 1522, 1142, 918, 722.

^{1}H-NMR δ 1.98 (s, 3 H); 3.59 (d, *J* = 9.3, 2H); 3.78 (s, 3 H); 3.81 (s, 3 H); 3.83 (s, 3 H); 3.87 (s, 3 H); 4.34-4.38 (m, 1H); 4.44-4.50 (m, 1H); 4.55-4.61 (m, 1H); 6.65-6.68 (m, 2 H); 6.74-6.79 (m, 2H); 6.87 (s, 1H).

^{13}C-NMR δ 20.4 (q), 20.5 (t), 44.5 (d); 55.3 (q); 55.4 (q); 55.5 (q); 55.6 (q); 66.0 (t); 110.7 (d); 110.9 (d); 111.2 (d); 112.2 (d); 117.8 (s); 119.5 (d); 120.5 (s); 130.9 (s); 131.7 (s); 147.5 (s); 147.7 (s); 148.4 (s); 148.7 (s); 170.4 (s).

EI-MS: 400 (6, $M+1^{+\cdot}$), 399 (43, $M^{+\cdot}$), 339 (70), 326 (100), 324 (49), 308 (68), 299 (20), 268 (18), 43(87).

HR-MS: 399.1685 ($C_{22}H_{25}NO_6^{+\cdot}$; calc. 399.1683).



2-6-[1-(3,4-dimethoxyphenyl)-2-hydroxyethyl]-2,3-dimethoxyphenylacetonitrile (1.36)

A solution made up of cyano-ethyl acetate (**1.32**) (1.4 g, 3.5 mmol), K_2CO_3 (4.0 g), H_2O (5 ml), and MeOH (50 ml) was stirred at r.t. for 18 h. The solvent was evaporated and the residue was extracted with CH_2Cl_2. The organic layer was washed with water, dried, evaporated *in vacuo* to give (**1.36**) (1.2g, 95.8 %).

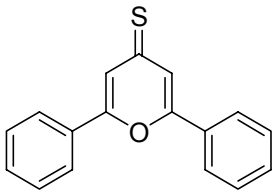
IR(neat) ν 3522, 2937, 2836, 2248, 1606, 1515, 1464, 1264, 1143, 1094, 1026, 861, 762.

^{1}H-NMR δ 3.54 (q, *J* = 28.8, 18.3, 2H); 3.77 (s, 3 H); 3.82 (s, 3 H); 3.84 (s, 3 H); 3.86 (s, 3 H); 4.06-4.17 (m, 4H); 6.65-6.68 (m, 2 H); 6.78 (d, *J* = 9.0, 1H); 6.86 (s, 1H); 6.92 (s, 1H).

^{13}C-NMR δ 20.6 (t), 47.9 (d); 55.4 (q); 55.5 (q); 55.6 (q); 55.7 (q); 65.4 (t); 110.9 (d); 111.0 (d); 111.4 (d); 112.2 (d); 118.1 (s); 119.6 (d); 120.7 (s); 131.9 (s); 132.7 (s); 147.4 (s); 147.6 (s); 148.4 (s); 148.8 (s).

EI-MS: 357 (7, $M^{+\cdot}$), 327 (20), 326 (100).

HR-MS: 357.1577 ($C_{20}H_{23}NO_5^{+\cdot}$; calc. 357.1577).



2,6-Diphenylpyran-4-thione (2.3) Method A

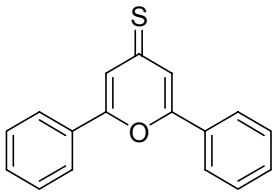
A mixture of 2,6-diphenyl-4-pyrone (50 mg, 0.2 mmol) and thionyl chloride (1 ml) was refluxed in an oil bath for 2 h, excess thionyl chloride was removed in vacuo. The yellow solid residue was dissolved in CH_2Cl_2 (2 ml) and treated with sodium *O*-*t*-amylxanthate (60 mg, 0.3 mmol) under N_2. The resulting mixture was refluxed for 15 hr, cooled, quenched with water, and extracted with CH_2Cl_2. The combined extracts were washed with water and brine, dried over Na_2SO_4, evaporated and chromatographed over silica gel (eluent: EtOAc/hex 1:9) to give 2,6-Diphenylpyran-4-thione (**2.3**) (50 mg, 93.9%) as a yellow solid.

m.p.168-170 °.

^{1}H NMR δ 7.50-7.52 (m, 6H); 7.63 (s, 2H); 7.85-7.88 (m, 4H).

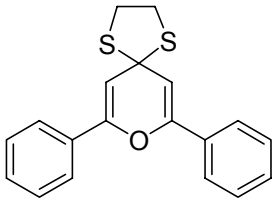
^{13}C NMR δ 121.91 (d); 126.04 (d); 129.23 (d); 130.62 (s); 131.68 (d); 156.00 (s); 201.00 (s).

HR-MS: 264.0607 ($C_{17}H_{12}OS^{+\cdot}$; calc. 264.0609).



2,6-Diphenylpyran-4-thione (2.4) Method B

A mixture of (**2.1**) (1.00 g, 4.0 mmol) and thionyl chloride (10 ml) was refluxed in an oil bath for 2 h, excess thionyl chloride was evaporated in vacuo. The resulting yellow solid residue with either 1,3-propanedithiol, benzenethiol, or 2-pyridinethiol (8.0 mmol each) were dissolved in CH_2Cl_2 (2 ml), placed under N_2, and treated with triethylamine (1.0 g, 10.0 mmol) slowly via a syringe. The reaction mixture was stirred at 50 ^{o} overnight, cooled, and poured into water. Extraction with CH_2Cl_2 was followed by back-wash with 2N NaOH, water, and brine. The organic solution was dried over Na_2SO_4, evaporated, and chromatographed over silica gel (eluent: EtOAc/hex 1:4) to afford 2,6-diphenylpyran-4-thione (**2.4**) in 75.2% (from 1,3-propanedithiol), 79.9% (from benzenethiol) and 88.3% (from 2-pyridinethiol) yield, respectively. Diphenyl sulfide (0.23 g, 30.7%) and di(2-pyridyl) sulfide (0.30 g, 39.6%) were isolated in the respective reactions.



7,9-Diphenyl-8-oxa-1,4-dithiaspiro[4.5]deca-6,9-diene (2.6)

Successive reaction of (**2.1**) (0.50 g, 2.0 mmol) with thionyl chloride and 1,2-ethanedithiol (0.44 g, 4.0 mmol) were carried in the same manner as described above (method B), silica gel chromatography (eluent: EtOAc/hex 1:9) permitted isolation of 2,6-diphenylpyran-4-thione (**2.4**) (0.20 g, 37.6%) and (**2.6**) **(**0.25 g, 38.3%).

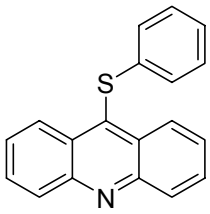
m.p.176-178 ^{o}.

IR(neat) ν 2963, 2916, 2358, 2330, 1645, 1486, 1294, 1311, 1099, 1019, 911, 798, 765.

^{1}H NMR δ 3.50 (s, 4H); 5.86 (s, 2H); 7.34-7.41 (m, 6H); 7.69-7.72 (m, 4H).

^{13}C NMR δ 41.35 (t); 61.84 (s); 102.17 (d); 124.82 (d); 128.39 (d); 128.90 (d); 133.36 (s); 147.37 (s).

HR-MS: 324.0636 ($C_{19}H_{16}OS_2^{+\cdot}$; calc. 324.0639).



9-(Phenylsulfanyl)acridine (2.13)

Dihydroacridinone (1.0 g, 5.1 mmol) was reacted with thionyl chloride (10 ml) for 6 h. The product was heated with benzenethiol (1.13 g, 10.3 mmol) and triethylamine (1.55 g, 15.3 mmol) in CH_2Cl_2 (20 ml) at 50 ^{o} overnight. Workup and chromatography over silica gel (eluent: EtOAc/hex 1:9), gave 9-(phenylsulfanyl)acridine (**2.13**) (1.34 g, 91.1%) as a yellow solid.

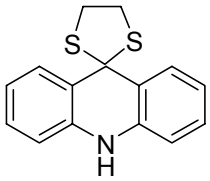
m.p.138-139 ^{o}.

IR(neat) ν 3069, 3049, 2989, 2351, 1723, 1669, 1433, 1396, 1273.

^{1}H NMR δ 6.95-7.07 (m, 5H); 7.46-7.51 (m, 2H); 7.70-7.76 (m, 2H); 8.26 (d, *J* = 9.0, 2H); 8.64 (d, *J* = 8.7, 2H).

^{13}C NMR δ 125.74 (d); 126.54 (d); 126.95 (d); 127.26 (d); 128.77 (s); 129.01 (d); 129.93 (d); 130.18 (d); 136.78 (s); 139.08 (s); 148.77 (s).

Anal. Calcd for $C_{19}H_{13}NS$: C, 79.41; H, 4.56; N, 4.88. Found: C, 79.26; H, 4.84; N, 4.82.



9,9-(Ethylendithio)acridan (2.12)

After reaction of dihydroacridinone (0.5 g, 2.6 mmol) with thionyl chloride and then 1,2-ethanedithiol (0.26 g, 2.8 mmol) in CH_2Cl_2 (10 ml) in the presence of triethylamine (0.8 g, 7.9 mmol), silica gel chromatography (eluent: EtOAc/hex 1:9) gave (**2.12**) (0.44 g, 63.3%).

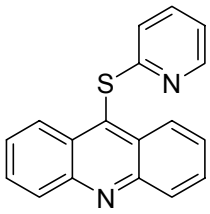
m.p.238-240 ^{o}.

IR(neat) ν 3394, 3260, 3064, 2966, 2922, 2864, 2381, 2340, 1806, 1580, 1510, 1476, 1332, 1261, 1154, 747.

^{1}H NMR δ 3.63 (4H, s); 6.66 (dd, *J* = 8.1, 1.2, 2H); 6.71 (s, 1H); 6.96-7.02 (m, 2H); 7.12-7.17 (m, 2H); 8.06 (d, *J* = 8.1, 2H).

^{13}C NMR δ 42.00 (t); 60.52 (s); 113.52 (d); 120.50 (d); 123.87 (s); 128.05 (d); 129.05 (d); 137.28 (s).

HR-MS: 271.0494 ($C_{15}H_{13}NS_2^{+\cdot}$; calc. 271.0487).



9-(2-Pyridylsulfanyl)acridine (2.14)

After reaction of dihydroacridinone (0.5 g, 2.6 mmol) with thionyl chloride and then 2-pyridinethiol (0.63 g, 5.7 mmol) in CH_2Cl_2 in the presence of triethylamine (0.8 g, 7.9 mmol), silica gel chromatography (eluent: EtOAc/hex 1:4) gave (**2.14**) (0.68 g, 92.2%).

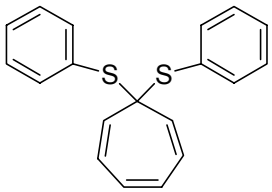
m.p.172-173 ^{o}.

IR(neat) ν 3069, 3047, 2356, 1568, 1446, 1415, 1308, 1150, 1121, 1089, 1042, 841, 747.

^{1}H NMR δ 6.35 (d, *J* = 8.1, 1H); 6.84 (dd, *J* = 7.5, 4.8, 1H); 7.13-7.18 (m, 1H); 7.46 (dd, *J* = 8.4, 7.2, 2H); 7.71 (dd, *J* = 8.5, 7.2, 2H); 8.23 (d, *J* = 9, 2H); 8.26 (d, *J* = 4.8, 1H); 8.55 (d, *J* = 8.7, 2H).

^{13}C NMR δ 120.08 (d); 120.97 (d); 126.34 (d); 127.19 (d); 128.71 (s); 129.64 (d); 130.42 (d); 136.79 (d); 137.37 (s); 148.43 (s); 149.52 (d); 159.30 (s).

Anal. Calcd for $C_{18}H_{12}N_2S$: C, 74.97; H, 4.19; N, 9.72. Found: C, 74.94; H, 4.62; N, 9.69.



1-(1λ^4-Thiopyran-1-yl)-2,4,6-cycloheptatrienyl phenyl sulfide (2.16)

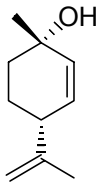
After reaction of (**2.15**) (0.3 g, 4.7 mmol) with thionyl chloride and then benzenethiol (0.62 g, 5.6 mmol) in CH_2Cl_2 (5 ml) in the presence of triethylamine (0.86 g, 8.5 mmol), silica gel chromatography (eluent: EtOAc/hex 1:9) gave (**2.16**) (0.35 g, 40.2%).

IR(neat) ν 3072, 3057, 3006, 2890, 2828, 1948, 1880, 1801, 1580, 1475, 1438, 1423, 1320, 1230, 1083, 1069, 1024, 906, 841, 738.

^{1}H NMR δ 6.23 (dd, *J* = 4.2, 2.7, 2H), 6.36 (dd, *J* = 4.2, 2.7, 2H), 7.10-7.33 (m, 12H).

^{13}C NMR δ 124.17 (d), 125.00 (s), 127.62 (d), 127.78 (d), 128.90 (d), 129.00 (d), 132.28 (d), 133.31 (s).

HR-MS: 308.0692 ($C_{19}H_{16}S_2^{+\cdot}$; calc. 308.0690).



(1*S*,4*R*)-p-Mentha-2,8-dien-1-ol (3.9).

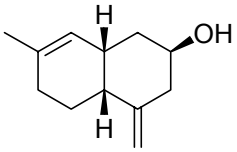
Limonene oxide (**3.6**) (5.0 g, 32.89 mmol) was mixed with 40% aq. Me_2NH (7.4 g, 164.44 mmol) in an autoclave and heated at 150 ^{o} for 18 h. After removing the excess Me_2NH the cooled reaction mixture was stirred with 30% H_2O_2 (5 ml) at r.t. during 18 h. A trace of 5% Pd/C was used to decompose any H_2O_2 left behind and the liquid was filtered, placed in a distillation vessel. Gradual heating to 150 ^{o} then 180 ^{o} formed (**3.9)** which was purified by silica gel chromatography (3.5 g, 75%).

IR: 3650-3000, 2943, 2905, 2880.

^{1}H-NMR : 1.29 (s, 3 H); 1.40-1.65 (m, 4 H); 1.73 (s, 3 H); 1.82 (m, 1 H); 2.65 (m, 1 H); 4.73 (s, 1 H); 4.77 (s, 1 H); 5.66 (d, *J* = 10.0, 1 H); 5.68 (d, *J* = 10.0, 1 H).

^{13}C-NMR:20.8 (q); 24.9 (t); 29.4 (q); 36.7 (t); 43.4 (d); 67.5 (s); 110.6 (t); 132.1 (t); 133.9 (t); 148.1 (s).

$[\alpha]_D$ = 63.9 ^{o} (*c* = 0.325).



(2*R*,4a*R*,8a*S*)-7-Methyl-4-methylene-1,2,3,4,4a,5,6,8a-octahydronaphthalen-2-ol (3.13).

To a stirred suspension of NaH (1.06 g, 26.5 mmol) in dry THF (30 ml) were added a soln. of (**3.9**) (4.0 g, 26.3 mmol) in THF (30 ml), and after 30 min., phenyl vinyl sulfoxide (8.0 g, 52.6 mmol), followed by a small amount of KH. After 3 h, moist ether was introduced, and the mixture was washed with H_2O and brine, dried and evaporated. The residue was heated with $NaHCO_3$ in decalin at 200^o for 20 h, cooled, and diluted with ether. After aq. washing, drying, evaporation *in vacuo* the residue was chromatographed to furnish (**3.13**) (2.52 g, 53.8%).

Mp. 75 ^{o}.

IR: 3230, 3073, 2925, 1645, 1430, 1325, 1240, 1180, 1055, 1008, 935, 885, 849, 812, 711.

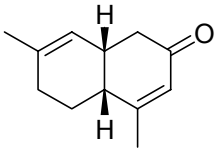
^{1}H-NMR: 1.34-1.45 (m, 3H); 1.55 (s, 3H); 1.62-1.66 (m, 1H); 1.73-1.82 (m, 1H); 1.88-1.95 (m, 1H); 2.05-2.11 (m, 1H); 2.15-2.17 (m, 1H); 2.26-2.36 (m, 3H); 3.88-3.90 (m, 1H); 4.66 (s, 1H); 4.82 (s, 1H); 5.21 (br.s 1H)).

^{13}C-NMR: 23.6 (q); 23.65 (t); 30.2 (t); 32.3 (d); 36.0 (t); 39.0 (t); 42.2 (d); 67.0 (d); 111.7 (t); 125.3 (d); 133.6 (s); 148.3 (s).

EI-MS: 178 (100, $M^{+\cdot}$), 162 (95), 145 (90).

HR-MS: 178.1361 ($C_{12}H_{18}O^{+\cdot}$; calc. 178.1358).

$[\alpha]_D$ = -10.39 ^{o} (*c* = 1).



(4a*R*,8a*S*)-4,7-Dimethyl-1,2,4a,5,6,8a-hexahydro-2-naphthalenone (3.5).

Alcohol (**3.13**) (450 mg, 2.52 mmol) was dissolved in CH_2Cl_2 (3 ml) and the sol. was added *via* a syringe into a stirred reagent prepared from oxalyl chloride (645 mg, 5 mmol in 10 ml of CH_2Cl_2) and DMSO (948 mg, 12 mmol in 3 ml of CH_2Cl_2) at -78 °. At the end of 30 min. Et_3N was added to the mixture. The cooling bath was removed after 5 min. and the reaction mixture was quenched with H_2O. The product was extracted into CH_2Cl_2, dried, evaporated, and chromatographed to afford (**3.5**) (410 mg, 92%).

Mp. 75 °.

IR: 2929, 2724, 1668, 1627, 1432, 1379, 1302, 1262.

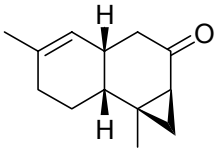
^{1}H-NMR: 1.63 (s, 3H); 1.53-1.59 (m, 1H); 1.77-1.92 (m, 1H); 2.02 (s, 3H); 2.07-2.21 (m, 3H); 2.24-2.26 (m, 1H); 2.30-2.32 (m, 1H); 2.57-2.61 (m, 1H); 5.21 (br.s 1H).

^{13}C-NMR: 22.5 (q); 22.6 (t); 23.4 (q); 30.6 (t); 34.7 (d); 39.6 (d); 40.1 (t); 123.9 (d); 126.4 (d); 134.4 (s); 164.4 (s); 198.6 (s).

EI-MS: 176 (99.5, $M^{+\cdot}$), 162 (100), 150 (70).

HR-MS: 176.1205 ($C_{12}H_{16}O^{+\cdot}$; calc. 176.1201).

$[\alpha]_D$ = +3.23 ° (*c* = 1).



(3*S*,4*R*,4a*R*,8a*S*)-4,7-Dimethyl-3,4-methylene-1,2,4a,5,6,8a-hexahydro-2-naphthalenone (3.14).

A soln. of ketone (**3.5**) (50 mg, 0.28 mmol) in DMSO (5 ml) was added to the ylide derived from [Me_3SO]I (300 mg, 1.36 mmol) and NaH (50 mg, 60% degreased by hexane) in DMSO (5 ml). After stirring at r.t. for 10 h the mixture was heated at 55 ^{o} for 2 d. The cooled reaction mixture was poured into ice-H_2O (10 ml), and extracted with ether. The org. extracts were combined, washed with H_2O, dried, and concentrated *in vacuo*. Chromatography gave (**3.14**) (40 mg, 74%).

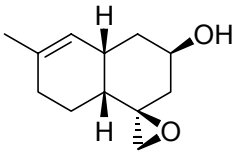
IR: 2962, 2921, 2869, 2360, 1683, 1540, 1506, 1454, 1241.

^{1}H-NMR: 0.86 (q, *J* = 10.0, 1H); 1.18 (s, 3H); 1.16-1.19 (m, 1H); 1.43 (t, *J* = 4.4, 1H); 1.56-1.58 (m, 1H); 1.60 (s, 3H); 1.79-2.00 (m, 5H); 1.98-2.33 (m, 2H); 5.29 (d, *J* = 4.5, 1H).

^{13}C-NMR: 18.9 (t); 21.2 (t); 22.7 (q); 23.4 (q); 27.7 (s); 30.0 (d); 30.7 (t); 33.5 (d); 35.8 (d); 39.7 (t);124.5 (d); 133.5 (s); 208.6 (s).

EI-MS: 190 (5, $M^{+\cdot}$), 97 (45), 85 (70), 83 (55), 71 (100), 70 (44), 69 (63).

$[\alpha]_D$ = +82.04^{o} (*c* = 1.78).



(1*R*,3*R*,4a*S*,8a*R*)-6-methyl-3,4,4a,7,8,8a-hexahydro-2H-spiro[naphthalene-1,2'-oxiran]-3-ol (3.19)

To a solution of diene-ol (**3.13**) (0.50 g, 2.80 mmol) and $VO(acac)_2$ (0.03 g, 0.11 mmol) in CH_2Cl_2 (20 ml) was slowly added t-butyl hydroperoxide (2.7M in toluene, 3.0 ml, 8.10 mmol) at 0^o under N_2. During the addition, the color of the reaction mixture turned from green to dark red. The solution was allowed to warm to r.t. and then stirring for 13 h. After addition of $Na_2SO_{3(aq)}$, the mixture was extracted with CH_2Cl_2. The extracts were combined, washed with brine, dried, concentrated, and chromatographed (silica gel, 1:9 AcOEt/hexane) to give (**3.19**) (0.45 g, 82.6 %).

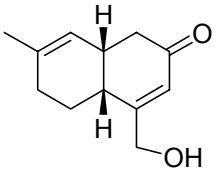
IR(neat) ν 3476, 2926, 2888, 2831, 2719, 1645, 1426, 1307, 1185, 1010, 928, 770, 736.

^{1}H-NMR δ 1.26-1.28 (m, 3 H); 1.39-1.61 (m, 3 H); 1.53 (s, 3 H); 1.75-1.92 (m, 3 H); 2.03 (dd, *J* = 15.0, 3.0, 1 H); 2.44 (s, 2 H); 2.58-2.72 (m, 1 H); 4.02 (d, *J* = 2.7, 1 H); 5.26 (d, *J* = 3.9, 1 H).

^{13}C-NMR δ 21.2 (t); 23.3 (q); 28.3 (d); 30.2 (t); 34.7 (t); 34.8 (t); 40.7 (d); 50.1 (t); 59.8 (s); 66.8 (d); 125.0 (d); 133.0 (s).

EI-MS: 194 (5, $M^{+\cdot}$), 176 (48), 163 (56), 145 (98), 131 (46), 117 (38), 107 (32), 105 (67), 91 (77), 79 (56), 77 (42), 43 (80), 41 (100), 39 (73), 32 (56).

HR-MS: 194.1310 ($C_{12}H_{18}O_2^{+\cdot}$; calc. 194.1308).



(4a*R*,8a*S*)-4-(hydroxymethyl)-7-methyl-1,2,4a,5,6,8a-hexahydro-2-naphthalenone (3.20)

A solution of epoxide (**3.19**) (0.40 g, 2.1 mmol) and Dess-Martin periodinane (1.30 g, 3.1 mmol) in CH_2Cl_2 (40 ml) was stirred at r.t. under N_2 for 12 h. The resulting mixture was poured into 1N NaOH, extracted with CH_2Cl_2, the extract was washed with 1N NaOH, water and brine, dried, concentrated, and chromatographed (silica gel, 1:4 AcOEt/hexane) to give (**3.20**) (0.33 g, 83.4 %).

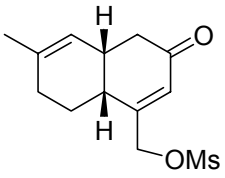
IR(neat) ν 3412, 2964, 2929, 2878, 2381, 1660, 1447, 1380, 1362, 1301, 1261, 1194, 1131, 1078, 1044, 877, 826.

^{1}H-NMR δ 1.63 (s, 3 H); 1.60-1.69 (m, 2 H); 1.92-2.04 (m, 2 H); 2.15-2.40 (m, 3 H); 2.60-2.65 (m, 1 H); 2.96 (br.s, 1 H); 4.28 (ABq, *J* = 17.1, 2 H); 5.31 (s, 1 H,); 6.09 (s, 1 H).

^{13}C-NMR δ 23.2 (t); 23.4 (q); 30.5 (t); 34.6 (d); 35.3 (d); 40.9 (t); 63.4 (t); 122.6 (d); 123.6 (d); 134.7 (s); 168.2 (s); 200.0 (s).

EI-MS: 193 (15, $M+1^{+\cdot}$), 192 (77, $M^{+\cdot}$), 174 (86), 164 (65), 159 (40), 146 (62), 133 (65), 132 (46), 131 (98), 117 (54), 105 (82), 91 (100), 79 (71), 77 (54), 55 (57).

HR-MS: 192.1151 ($C_{12}H_{16}O_2^{+\cdot}$; calc. 192.1151).



[(4a*S*,8a*R*)-6-methyl-3-oxo-3,4,4a,7,8,8a-hexahydro-1-naphthalenyl]methyl methanesulfonate (3.21)

A solution of diene-ol (**3.20**) (0.30 g, 1.6 mmol) and Et_3N (0.40 g, 4.0 mmol) in THF (10 ml) at 0^o under N_2 was stirred for 20 min, MsCl (0.30 g, 2.6 mmol) was then added. After 2 h, the reaction mixture was diluted with water, and extracted with ether. The organic layer was washed with water and brine, dried, and concentrated to give (**3.21**) (0.40 g, 94.8 %).

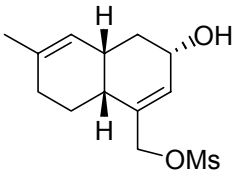
IR(neat) ν 2924, 2858, 2360, 2324, 1456, 1339, 1265, 1087, 968.

^{1}H-NMR δ 1.66 (s, 3 H); 1.82-1.85 (m, 2 H); 1.99-2.08 (m, 2 H); 2.24-2.29 (m, 1 H); 2.37-2.47 (m, 2 H); 2.65-2.69 (m, 1 H); 3.06 (s, 3 H); 4.83 (ABq, *J* = 14.4, 2 H); 5.34 (s, 1 H,); 6.06 (s, 1 H).

^{13}C-NMR δ 22.9 (t); 23.3 (q); 30.3 (t); 34.4 (d); 35.0 (d); 38.0 (q); 40.7 (t); 68.1 (t); 123.2 (d); 126.0 (d); 134.9 (s); 158.1 (s); 198.5 (s).

EI-MS: 279 (0.5, $M^{+\cdot}$), 174 (100), 159 (43), 146 (59), 133 (41), 132 (30), 131 (98), 117 (38), 105 (36), 91 (39).

HR-MS: 270.0920 ($C_{13}H_{18}O_4S^{+\cdot}$; calc. 270.0927).



[(3*S*,4a*S*,8a*R*)-3-hydroxy-6-methyl-3,4,4a,7,8,8a-hexahydro-1-naphthalenyl]methyl methanesulfonate (3.22)

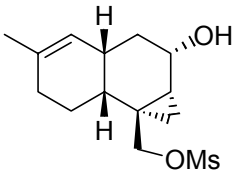
To a stirred solution of enone (**3.21**) (0.10 g, 0.37 mmol) in MeOH (1 ml) at 0 ^{o} was added $NaBH_4$ (0.05 g, 1.32 mmol) in 3 portions. After 10 min, the mixture was allowed to warm to r.t. for 1 h, quenched with water, extracted with ether, dried, and concentrated to give (**3.22**) (0.08g, 79.4%).

IR(neat) ν 3424, 2929, 2863, 1673, 1455, 1377, 1193, 1105, 1041.

^{1}H-NMR δ 1.18-1.32 (m, 2H); 1.55 (s, 3 H); 1.70-1.84 (m, 3 H); 1.89-1.96 (m, 1 H); 2.01-2.10 (m, 2 H); 2.97 (br s, 1 H); 3.18 (s, 3 H); 3.63 (d, *J* = 12.0, 1 H); 3.97 (d, *J* = 12.0, 1 H); 4.12-4.16 (m, 1 H); 5.21 (s, 1 H,); 5.59 (s, 1 H).

^{13}C-NMR δ 23.3 (q); 23.7 (t); 30.6 (t); 33.3 (d); 34.0 (d); 35.3 (t); 57.4 (q); 67.2 (d); 74.3 (t); 124.8 (d); 129.4 (d); 133.9 (s); 139.6 (s).

EI-MS: 177 (5, M-$OMs^{+\cdot}$), 176 (32), 145 (68), 143 (77), 129 (60), 107 (49), 105 (64), 95 (28), 93 (51), 91 (100), 79 (71), 77 (61), 41 (37).

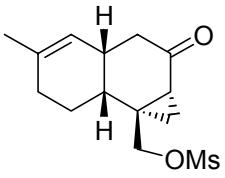


[(1a*R*,2*S*,3a*S*,7a*R*,7b*R*)-2-hydroxy-5-methyl-1a,2,3,3a,6,7,7a,7b-octahydro-1*H*-cycloprop a[*a*]naphthalen-7-yl]methyl methanesulfonate (3.23)

To a stirred solution of CH_2I_2 (100 mg, 0.37 mmol) in CH_2Cl_2 (1 ml) at 0 ^{o} under N_2 was added Et_2Zn (1M in hexane, 0.37 ml, 0.37 mmol) dropwise via a syringe, and after 10 min, a solution of enol (**3.22**) (100 mg, 0.37 mmol) in CH_2Cl_2 (1 ml). After 2 h stirring at r.t, the reaction was cooled to 0 ^{o} again, quenched with $NH_4Cl_{(sat.)}$ and extracted with CH_2Cl_2. The extract was washed with 1N brine, dried, concentrated , and chromatographed (silica gel, 1:2 AcOEt/hexane) to give (**3.23**) (60 mg, 57.1%)

^{1}H-NMR δ 0.21-0.26 (m, 1 H); 0.49 (t, *J* = 5.4, 1 H); 0.70-0.82 (m, 1 H); 1.16-1.28 (m, 3 H); 1.47-1.52 (m, 1 H); 1.57 (s, 3H); 1.82-1.87 (m, 2 H); 1.96-2.04 (m, 3 H); 2.80 (d, *J* = 9.9, 1 H); 3.26 (s, 3 H); 3.36 (d, *J* = 9.9, 1 H); 4.11-4.15 (m, 1 H); 5.10 (s, 1 H,).

^{13}C-NMR δ 7.1 (t); 23.2 (t); 23.6 (q); 24.8 (d); 28.6 (s); 30.8 (t); 30.8 (d); 32.4 (t); 34.9 (d); 58.5 (d); 68.6 (d); 80.6 (t); 124.5 (d); 134.2 (s).

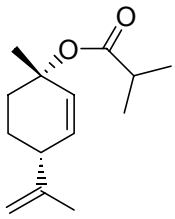


[(1a*R*,3a*S*,7a*R*,7b*R*)-5-methyl-2-oxo-1a,2,3,3a,6,7,7a,7b-octahydro-1*H*-cyclopropa[*a*]naphthalen-7-yl]methyl methanesulfonate (3.24)

A solution of hydroxyl-mesylate (**3.23**) (40 mg, 0.14 mmol) and Dess-Martin periodinane (100 mg, 0.23 mmol) in CH_2Cl_2 (5 ml) was stirred at r.t. under N_2 for 24 h, poured into 1N NaOH, extracted with CH_2Cl_2, the extract was washed with 1N NaOH, water and brine, dried, concentrated, and chromatographed (silica gel, 1:2 AcOEt/hexane) to give (**3.24**) (35 mg, 88.1 %).

^{1}H-NMR δ 0.94-0.99 (m, 1 H); 1.13 (t, *J* = 4.8, 1 H); 1.19-1.27 (m, 1 H); 1.40-1.50 (m, 1 H); 1.59 (s, 3 H); 1.65-1.70 (m, 1 H); 1.86-2.02 (m, 4 H); 2.18-2.26 (m, 1 H); 2.38-2.43 (m, 1 H); 2.96 (d, *J* = 10.5, 1 H); 3.26 (s, 3 H); 3.36 (d, *J* = 10.5, 1 H); 5.09 (s, 1 H,).

^{13}C-NMR δ 17.4 (t); 23.2 (t); 23.4 (q); 30.6 (t); 31.2 (d); 31.6 (d); 36.1 (s); 38.9 (d); 39.2 (t); 58.7 (d); 78.8 (t); 123.3 (d); 135.5 (s); 209.8 (s).



(1*S*,4*R*)-4-isopropenyl-1-methyl-2-cyclohexen-1-yl 2-methylpropanoate (3.26).

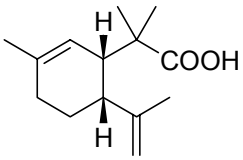
Triethylamine (20 ml), DMAP (0.20 g, 1.64 mmol), and isobutyric anhydride (15.6g, 98.60 mmol) were mixed with a solution of (1*S*,4*R*)-p-2,8-menthadien-1-ol (5.0 g, 32.89 mmol) in CH_2Cl_2 (20 ml) under N_2. After stirring at r.t. for 2 days, the mixture was poured into saturated $NaHCO_3$ solution, and washed in sequence with 1N aqueous ethylenediamine (to facilitate removal of excess anhydride), 1N HCl, H_2O, and brine. The organic solution was dried, and evaporated to give (**3.26**) (7.23 g, 99%).

IR(neat) ν 3485, 3447, 2973, 2937, 2875, 1731, 1470, 1449, 1386, 1372, 1273, 1189, 1159, 1098, 1068, 893, 863, 847, 742.

^{1}H-NMR δ 1.00 (s, 3 H); 1.02 (s, 3 H); 1.44 (s, 3 H); 1.59 (s, 3 H); 1.62-1.65 (m, 3 H); 2.00-2.05 (m, 1 H); 2.31-2.35 (m, 1 H); 2.61-2.63 (m, 1 H); 4.65 (s, 2 H); 5.57 (d, *J* = 10.2, 1 H); 6.12 (d, *J* = 10.2, 1 H).

^{13}C-NMR δ 18.4 (q); 18.6 (q); 19.8 (q); 23.9 (t); 25.3 (q); 34.2 (d); 35.2 (t); 43.2 (d); 76.3 (s); 110.3 (t); 130.4 (d); 132.9 (d); 147.4 (s); 175.4 (s).

$[\alpha]_D$ = -41.9 ^{o} ($CHCl_3$, *c* = 0.25).



2-[(1S,6R)-6-isopropenyl-3-methyl-2-cyclohexenyl]-2-methylpropanoic acid (3.27).

To a solution of LDA (prepared from diisopropylamine (5.80g, 57.32 mmol) and 1.6 M n-BuLi (28 ml, 44.8 mmol) at 0° in anh. THF (40 ml), a solution of ester (1*R*,4*S*)-4-isopropenyl-1-methyl-2-cyclohexen-1-yl 2-methylpropanoate (5.0 g, 22.52 mmol) in THF (40 ml) was added dropwise within 15 min at -78 ° under N_2. The mixture was stirred at that temp. for 1 h, warmed to -40 ° while stirring for another 30 min, cooled down again to -78 ° and then TMSCl (4.3 ml, 33.88 mmol) was added. The resulting mixture was allowed to warm up to r.t. over 30 min, and evaporated the solvent in *vacuo*. The residue was dissolved in dry toluene (90 ml) and refluxed under N_2 for 36 h. After cooling, the mixture was poured into 5% HCl, separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was concentrated, dissolved in 1N NaOH, washed with ether, acidified, extracted with CH_2Cl_2, dried, and evaporated to give (**3.27**) (3.40 g, 68.0%).

IR(neat) ν 2970, 2929, 2652, 2362, 1698, 1474, 1450, 1373, 1280, 1166, 940, 891, 740.

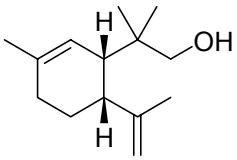
^{1}H-NMR δ 1.18 (s, 3 H); 1.19 (s, 3 H); 1.67 (s, 3 H); 1.76 (s, 3 H); 1.81-2.02 (m, 4 H); 2.36 (m, 1 H); 2.81 (s, 1 H); 4.79 (s, 2 H); 5.45 (s, 1 H).

^{13}C-NMR δ 21.9 (q); 23.7 (q); 24.3 (q); 25.7 (q); 26.0 (t); 29.3 (t); 42.8 (d); 43.1 (d); 45.7 (s); 112.6 (t); 121.2 (d); 135.9 (s); 142.7 (s); 185.1 (s).

EI-MS: 222 (15, $M^{+\cdot}$), 136 (72), 134 (100), 110 (55), 109 (51), 107 (96), 93 (89), 91 (50), 79 (47), 41 (63).

HR-MS: 222.1617 ($C_{14}H_{22}O_2^{+\cdot}$; calc. 222.1621).

$[\alpha]_D$ = 59.9 ° ($CHCl_3$, *c* = 0.125).



2-[(1*S*,6*R*)-6-isopropenyl-3-methyl-2-cyclohexenyl]-2-methyl-1-propanol (3.28).

A solution of acid (**3.27**) (3.40 g, 15.32 mmol) in anh. THF (30 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.16 g, 30.53 mmol) in THF (30 ml) at r.t. The mixture was refluxed for 5 h, cooled, quenched with saturated NH_4Cl, and extracted with ether. The organic layer was washed with brine, dried, and evaporated to afford (**3.28**) (2.87 g, 90.0%).

IR(neat) ν 3409, 2962, 2928, 1715, 1644, 1455, 1376, 1261, 1041, 889, 801, 742.

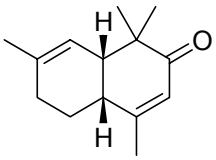
^{1}H-NMR δ 0.87 (s, 3 H); 0.91 (s, 3 H); 1.61 (s, 3 H); 1.76 (s, 3 H); 1.81-2.01 (m, 4 H); 2.14 (s, 1 H); 2.39 (m, 2 H); 3.39 (m, 2 H); 4.77 (d, *J* = 1.8, 1 H); 4.79 (d, *J* = 1.8, 1 H); 5.45 (s, 1 H).

^{13}C-NMR δ 22.9 (q); 23.1 (q); 23.7 (q); 24.2 (q); 27.6 (t); 28.2 (t); 39.0 (s); 41.6 (d); 43.8 (d); 70.7 (t); 112.1 (t); 122.5 (d); 134.8 (s); 148.6 (s).

EI-MS: 208 (10, $M^{+\cdot}$), 207 (100), 133 (56), 93 (42), 63 (56), 55 47), 43 (68), 41 (50).

HR-MS: 208.1826 ($C_{14}H_{24}O^{+\cdot}$; calc. 208.1828).

$[\alpha]_D = 49.0^{o}$ ($CHCl_3$,*c* = 0.25).



(4a*R*,8a*S*)-1,1,4,7-tetramethyl-1,2,4a,5,6,8a-hexahydro-2-naphthalenone (3.33).

PCC (14.50 g, 67.28 mmol) was added to a stirred solution of 2-[(1*R*,6*S*)-6-isopropenyl-3-methyl-2-cyclohexenyl]-2-methyl-1-propanol (**3.28**) (2.8 g, 12.61 mmol) in dry CH_2Cl_2 (100 ml). After 24 h at r.t. the reaction mixture was diluted with dry ether (150 ml) and the supernatant liquid was passed through a short pad of Florisil using ether to wash the residue. The crude product, after removal of the solvent in *vacuo*, was placed in dry benzene (100 ml), *p*-TsOH monohydrate (0.30 g) was added and the resulting solution was refluxed for 1.5 h. Isolation of the crude product by standard extractive workup followed by CC (silica gel, 1:9 AcOEt/hexane) afforded (**3.33**) (1.21g, 44.1%).

IR(neat) ν 2966, 2930, 2872, 1677, 1446, 1382, 1261, 1095, 1019, 866, 801, 737.

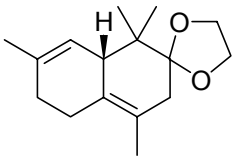
^{1}H-NMR δ 1.02 (s, 3 H); 1.11 (s, 3 H); 1.59 (s, 3 H); 1.66-1.75 (m, 2 H); 1.88-1.95 (m, 2 H); 1.89 (s, 3 H); 2.39 (s, 1 H); 2.53 (s, 1 H); 5.27 (s, 1 H); 5.71 (s, 1 H).

^{13}C-NMR δ 21.5 (q); 22.5 (q); 23.8 (q); 24.5 (q); 24.6 (t); 28.1 (t); 37.6 (s); 44.5 (d); 45.0 (d); 119.4 (d); 125.7 (d); 136.3 (s); 160.0 (s); 204.4 (s).

EI-MS: 204(81, $M^{+\cdot}$), 189 (52), 95 (88), 91 (42), 43 (54), 41 (100), 39 (58).

HR-MS: 204.1517 ($C_{14}H_{20}O^{+\cdot}$; calc. 204.1515).

$[\alpha]_D$ = -8.0 ^{o} ($CHCl_3$,*c* = 0.25).



(8a*S*)-1,1,4,7-tetramethyl-1,2,3,5,6,8a-hexahydro-2-(1,3-dioxolan-2-yl)naphthalene (3.34).

A mixture of enone (**3.33**) (1.0 g, 4.90 mmol), ethylene glycol (2.7 g, 43.55 mmol), *p*-TsOH monohydrate (30 mg), and benzene (30 mL) was refluxed in a Dean-Stark system for 24 h. The reaction mixture was poured into water and extracted with ether. The combined extracts were washed with 10% $NaHCO_3$ solution and brine, dried and concentrated to give (**3.34**) (1.12 g, 92.1%).

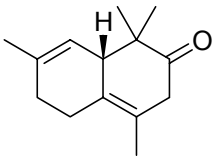
IR(neat) ν 2970, 2903, 2880, 2727, 1447, 1380, 1216, 1162, 1107, 1086, 1047, 976, 948, 847, 769.

^{1}H-NMR δ 0.72 (s, 3 H); 0.93 (s, 3 H); 1.62 (s, 3 H); 1.67 (s, 3 H); 1.92-1.98 (m, 4H); 2.24 (d, *J* = 18.3, 1 H); 2.64-2.68 (m, 1 H); 2.83 (s, 1 H); 3.83-4.00 (m, 4 H), 5.27 (s, 1 H);

^{13}C-NMR δ 18.2 (q); 18.8 (q); 19.0 (q); 23.7 (q); 26.4 (t); 31.2 (t); 39.5 (t); 40.6 (s); 46.1 (d); 65.0 (t); 65.4 (t); 111.9 (s); 121.1 (s); 121.2 (d); 128.9 (s); 135.3 (s).

EI-MS: 247 (2, M-1$^{+\cdot}$), 161 (28), 87 (30), 86 (51), 44 (58), 43 (100), 41 (35).

$[\alpha]_D$ = -12.1 ^{o} ($CHCl_3$,*c* = 0.25).



(8a*S*)-1,1,4,7-tetramethyl-1,2,3,5,6,8a-hexahydro-2-naphthalenone (3.35).

Aqueous trifluoroacetic acid (35%, 10 ml) was added to a vigorously stirred solution of ketal (**3.34**) (1.12 g, 4.51 mmol) in CH_2Cl_2 (20 ml. After maintaining at 10~20 ^{o} for 48h, the reaction mixture was diluted with ether and poured into ice-cooled $NaHCO_3$ solution. The organic phase was washed with brine, dried, and evaporated in *vacuo* affording (**3.35**) (0.91 g, 98.8%).

IR(neat) ν 2969, 2871, 2840, 1715, 1446, 1382, 1264, 1188, 1128, 853, 724.

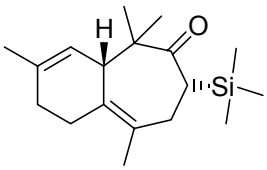
^{1}H-NMR δ 0.89 (s, 3 H); 1.10 (s, 3 H); 1.67 (s, 3 H); 1.73 (s, 3 H); 1.92-1.97 (m, 3 H); 2.63-2.66 (m, 1 H); 2.67-2.70 (m, 1 H); 2.83 (s, 1 H); 2.97 (d, *J* = 6.8, 1 H); 5.24 (s, 1 H).

^{13}C-NMR δ 17.9 (q); 19.8 (q); 20.5 (q); 23.9 (q); 26.2 (t); 30.3 (t); 44.0 (t); 47.3 (s); 47.4 (d); 119.4 (d); 121.3 (s); 129.0 (s); 137.8 (s); 214.7 (s).

EI-MS: 204 (61, $M^{+\cdot}$), 134 (100), 119 (65), 95 (69), 91 (47).

HR-MS: 204.1510 ($C_{14}H_{20}O^{+\cdot}$; calc. 204.1515).

$[\alpha]_D$ = -70.4 ^{o} ($CHCl_3$,*c* = 0.25).



(4a*S*,7*R*)-3,5,5,9-tetramethyl-7-(1,1,1-trimethylsilyl)-2,4a,5,6,7,8-hexahydro-1H-benzo[a] cyclohepten-6-one (3.37).

To a stirred solution of dienone (**3.35**) (0.60 g, 2.94 mmol) and boron trifluoride etherate (0.4 ml, 3.16 mmol) in dry CH_2Cl_2 (15 ml) was added trimethylsilyldiazomethane (2M in toluene, 1.6 ml, 3.2 mmol) at -40 ^{o} under N_2. After 2.5 h, water was added, the organic layer was washed with brine, dried and freed of solvent. The residue was chromatographed (silica gel, 1:30 AcOEt/hexane) to give (**3.37**) (0.41 g, 48.1%) and (**3.36**) (0.11 g, 17.2%).

IR(neat) ν 2963, 2908, 2727, 1695, 1464, 1447, 1378, 1247, 1096, 1051, 1031, 864, 838, 693, 615.

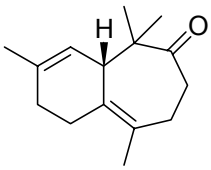
^{1}H-NMR δ 0.02 (s, 9 H); 0.84 (s, 3 H); 1.09 (s, 3 H); 1.56 (s, 3 H); 1.71 (s, 3 H); 1.78-1.91 (m, 3 H); 2.08 (dd, *J* = 16.5, 10.8, 1 H), 2.50-2.67 (m, 2 H); 2.94 (t, *J* = 9.9, 1 H); 3.58 (s, 1 H); 5.37 (s, 1 H).

^{13}C-NMR δ -2.6 (q); 17.7 (q); 20.9 (q); 23.1 (q); 24.0 (q); 27.0 (t); 30.1 (t); 35.0 (t); 35.1 (d); 44.0 (d); 55.2 (s); 118.7 (d); 126.8 (s); 132.0 (s); 136.5 (s); 218.1 (s).

EI-MS: 290 (5, $M^{+\cdot}$), 185 (52), 170 (39), 143 (30), 73 (60), 43 (100), 41 (53), 32 (75).

HR-MS: 290.2073 ($C_{18}H_{30}OSi^{+\cdot}$; calc. 290.2067).

$[\alpha]_D$ = -97.4 ^{o} ($CHCl_3$,*c* = 0.15).



(4aS)-3,5,5,9-tetramethyl-2,4a,5,6,7,8-hexahydro-1H-benzo[a]cyclohepten-6-one (3.36).

A mixture of (**3.37**) (0.25 g, 0.86 mmol) and TBAF (1M, 1.7 ml, 1.7 mmol) in CH_3CN (10 ml) was stirred at r.t. for 3 h. After removal of the solvent, the residue was subjected to CC (silica gel, 1:30 AcOEt/hexane) to give (**3.36**) (0.11 g, 58.5%).

IR(neat) ν 2966, 2927, 2910, 2728, 1706, 1465, 1448, 1381, 1248, 1081, 851.

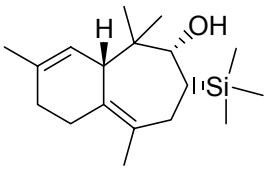
^{1}H-NMR δ 0.88 (s, 3 H); 1.15 (s, 3 H); 1.63 (s, 3 H); 1.71 (s, 3 H); 1.84-2.00 (m, 3 H); 2.10-2.16 (m, 1 H); 2.22-2.30 (m, 1 H); 2.56-2.58 (m, 1 H); 2.67 (m, 1 H); 3.04-3.13 (m, 1 H); 3.33 (s, 1 H); 5.37 (s, 1 H).

^{13}C-NMR δ 18.8 (q); 20.2 (q); 23.9 (q); 24.2 (q); 26.1 (t); 30.1 (t); 30.8 (t); 36.2 (t); 43.8 (d); 53.6 (s); 118.6 (d); 127.4 (s); 132.7 (s); 136.6 (s); 215.5 (s).

EI-MS: 218 (3, $M^{+\cdot}$), 119 (24), 105 (36), 91 (14), 55 (30), 43 (100), 41 (72), 39 (30), 32 (82).

HR-MS: 218.1669 ($C_{15}H_{22}O^{+\cdot}$; calc. 218.1671).

$[\alpha]_D$ = -86.1 ^{o} ($CHCl_3$,*c* = 0.10).



(4a*S*,6*S*,7*R*)-3,5,5,9-tetramethyl-7-(1,1,1-trimethylsilyl)-2,4a,5,6,7,8-hexahydro-1H-benzo [a]cyclohepten-6-ol (3.39).

To a solution of (**3.37**) (0.16 g, 0.55 mmol) in ethanol (2 ml) was added $NaBH_4$ (0.20 g, 5.28 mmol) in portions during 5 min. After stirring for 36 h at r.t., the reaction mixture was quenched with H_2O and extracted with ether, dried, evaporated *in vacuo* and chromatographed (silica gel, 1:30 AcOEt/hexane) to give (**3.39**) (0.14 g, 86.9%).

IR(neat) ν 3564, 2960, 2905, 1448, 1404, 1383, 1247, 1078, 1036, 995, 864, 834, 746.

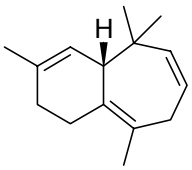
^{1}H-NMR δ 0.01(s, 9 H); 0.89 (s, 3 H); 0.94 (s, 3 H); 1.41-1.44 (m, 1 H); 1.70 (s, 3 H); 1.72 (s, 3 H); 1.83-2.02 (m, 5 H); 2.61-2.78 (m, 2 H); 3.08 (s, 1 H); 3.47 (d, *J* = 12.0, 1H); 5.34 (s, 1 H).

^{13}C-NMR δ –2.59 (q); 20.3 (q); 21.1 (q); 24.0 (q); 24.9 (d); 26.3 (t); 27.8 (q); 30.3 (t); 30.9 (t); 41.9 (s); 44.7 (d); 80.9 (d); 121.4 (d); 128.7 (s); 134.6 (s); 135.1 (s).

EI-MS: 292(2, $M^{+\cdot}$), 137 (67), 134 (38), 91 (43), 75 (38), 73 (100).

HR-MS 292.2223 ($C_{18}H_{32}OSi^{+\cdot}$; calc. 292.2224).

$[\alpha]_D = 62.2^{o}$ ($CHCl_3$,*c* = 0.15).



(4aS)-3,5,5,9-tetramethyl-2,4a,5,8-tetrahydro-1H-benzo[a]cycloheptene (3.40).

A suspension of hexane-washed potassium hydride (35%, 100 mg, 0.87 mmol) in THF (1 ml) to which was added a solution of (**3.39**) (60 mg, 0.21 mmol) in THF (2 ml). The resulting mixture was stirred for 24 h a t room temperature. Saturated NH_4Cl was added, and the resulting mixture was poured into water overlaid with ether. The organic layer was separated, washed with two portions of water, dried, concentrated, and chromatographed (silica gel, hexane) to give (**3.40**) (30 mg, 72.3%).

IR(neat) ν 3002, 2962, 2927, 2908, 2835, 1467, 1439, 1375, 1355, 1156, 980, 853, 744, 697.

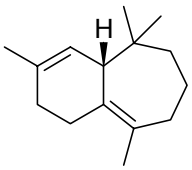
^{1}H-NMR δ 0.82 (s, 3 H); 1.07 (s, 3 H); 1.72 (s, 3 H); 1.76 (s, 3 H); 1.95-2.00 (m, 3 H); 2.11 (q, *J* = 9.0, 1 H); 2.63-2.68 (m, 1 H); 3.27-3.33 (m, 2 H); 5.15 (dd, *J* = 11.4, 3.3, 1 H); 5.44-5.52 (m, 2 H).

^{13}C-NMR δ 20.1 (q); 24.1 (q); 24.3 (q); 26.0 (t); 29.1 (q); 30.2 (t); 33.2 (t); 38.4 (s); 45.4 (d); 121.5 (d); 123.2 (d); 131.7 (s); 131.8 (s); 136.1 (s); 142.1 (d).

EI-MS: 202 (3, $M^{+\cdot}$), 104 (43), 103 (42), 91 (98), 77 (42), 44 (100).

HR-MS: 202.1722 ($C_{15}H_{22}^{+\cdot}$; calc. 202.1722).

$[\alpha]_D = 81.8^{o}$ ($CHCl_3$,*c* = 0.10).



(+)-β-Himachalene (3.2).

To a solution of (**3.36**) (100 mg, 0.46 mmol) in methanol (1 ml) was added $NaBH_4$ (50 mg, 1.32 mmol) in portions at 0 °. Stirring was continued for 1 h, quenched with H_2O, extracted with ether, dried, and evaporated *in vacuo*.

The residue and DMAP (5 mg) were dissolved in pyridine (1 ml) and MsCl (0.1 ml, 1.29 mmol) was added under N_2 at 0°. After stirring at r.t. for 6 h, the mixture was poured into ice water and extracted with CH_2Cl_2. The organic layer was washed with 10% HCl (twice), saturated $NaHCO_3$, and brine, dried and evaporated in *vacuo* affording the crude mesylate.

Li wire (80 mg, 11.53 mmol) was added to anh. NH_3(l) (15 ml) at -78 ° and the mixture was stirred until the Li metal was completely dissolved. A solution of the crude product described above in THF (3 ml) was added dropwise, the mixture was stirred at -78 ° for 1h, and the reaction was quenched by addition of solid NH_4Cl (600 mg, 11.21 mmol). Upon evaporation of the ammonia, the mixture was partitioned between H_2O and ether, aqueous layer was extracted with ether. The combined extracts was dried, evaporated in *vacuo*, and chromatographed (silica gel, hexane) to give (+)-β-himachalene (**3.2**) (42 mg, 44.9% over 3 steps).

IR(neat) ν 2962, 2911, 2853, 2726, 1646, 1447, 1376, 1361, 1187, 1155, 859, 814.

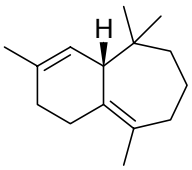
^{1}H-NMR δ 0.71 (s, 3 H); 0.95 (s, 3 H); 1.35-1.58 (m, 4 H); 1.65 (s, 3 H); 1.69 (s, 3 H); 1.83-1.95 (m, 4 H); 2.38-2.45 (m, 1 H); 2.60-2.62 (m, 1 H); 2.87 (s, 1 H); 5.40 (s, 1 H).

^{13}C-NMR δ 20.2 (q); 21.4 (t); 23.7 (q); 24.1 (q); 26.0 (t); 29.2 (q); 30.2 (t); 34.0 (t); 34.6 (s); 45.1 (t); 46.1 (d); 122.5 (d); 129.1 (s); 131.2 (s); 134.7 (s).

EI-MS: 204 (38, $M^{+\cdot}$), 133 (41), 121 (43), 119 (100), 105 (40), 93 (24), 91 (36), 55 (20), 41 (50).

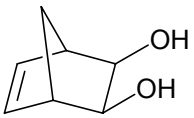
HR-MS: 204.1876 ($C_{15}H_{24}^{+\cdot}$; calc. 204.1879).

$[\alpha]_D$ = 212.3 ° ($CHCl_3$, *c* = 0.05).



(+)-β-Himachalene (3.2).

To a solution of triene (**3.40**) (30 mg, 0.15 mol) and $CoC1_2 \cdot 6H_2O$ (36 mg, 0.15 mmol) in ethanol (1 ml) under N_2 at 0^o was added $NaBH_4$ (6 mg, 0.15 mmol). The solution immediately became dark with evolution of hydrogen. The mixture was stirred under N_2 at r.t. for 24 h and poured into a 3 N HC1 solution. The aqueous solution was extracted with ether. The ether layer was dried, evaporated, and subjected to CC (silica gel, hexane) to give (+)-β-Himachalene (**3.2**) (22 mg, 72.6%)

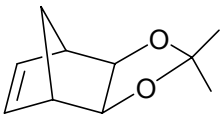


(2-exo,3-exo)-Bicyclo[2,2,1]hept-5ene-2,3-diol (4.2)

Finely powdered $KMnO_4$ (15.8 g, 100 mmol) was added, over a 10 min period, to a vigorously stirred solution of norbornadiene (23.5 g, 254 mmol) in acetone (220 ml) at –78°, after 1 h, a solution of NaOH (4.0 g,) and sodium sulfite (13 g, 103 mmol) in water (70 ml), which was precooled to 0°, was added in portions over a 5 min period. After 10 min, the thick brown-black mixture was allowed to warm to r.t. over 2 h, MnO_2 was filtered, washed with acetone (3 x 150 ml), and the filtrate was concentrated in *vacuo* below 35 ° to remove acetone. The red aqueous residue was extracted with CH_2Cl_2 (3 x 150 ml), dried, and evaporated to give a dark residue which was purified by chromatography (silica gel, EtOAc/Hex 1:1) to give diol (**4.2**) (3.41 g, 29% based on permanganate) as a white solid.

^{1}H-NMR δ 1.60 (dd, *J* = 1.8, 9.3, 1 H); 1.85 (d, *J* = 9.3, 1 H); 2.67 (d, *J* = 1.5, 2 H); 3.20 (br.s, 2 H); 3.67 (d, *J* = 1.5, 2 H); 6.01 (s, 2 H).

Y. F. Shealy, J. D. Clayton *J. Am. Chem. Soc.* **1969**, *91*, 3075-3083.

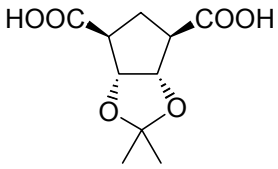


(5-exo,6-exo)-5,6-Dimethylmethylenedioxy-bicycle[2,2,1]hept-2-ene (4.3)

A solution of diol (**4.2**) (4.51 g, 35.3 mmol) and p-TsOH·$H_2$0 (0.1 g) in acetone (100 ml) was stirred at r.t. for 6 h. The solution was concentrated and chromatographed (silica gel, EtOAc/Hex 1:10) to give acetonide (**4.3**) (5.40 g, 92%) as a colorless oil.

^{1}H-NMR δ 1.32 (s, 3 H); 1.46 (s, 3 H); 1.66 (dt, *J* = 1.5, 9, 1 H); 1.95 (d, *J* = 15, 1 H); 2.74 (t, *J* = 1.5, 2 H); 4.16 (d, *J* = 1.2, 2 H); 6.02 (d, *J* = 1.5, 2 H).

M. Tanaka, M. Yoshioka, K. Sakai *Tetrahedron: Asymmetry* **1993,** *4*, 981-996.



2α,3α-[(Di methylmethylene)dioxy]-1β,4β-cyclopentanedicarboxylic acid (4.4)

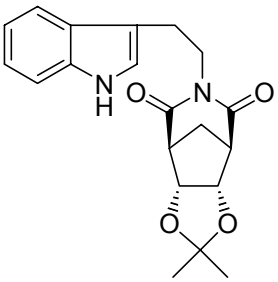
To an ice-cooled, two-phase system solution of acetonide (**4.3**) (3.70 g, 22.3 mmol) in ether (60 ml) and water (120 ml) was added $KMnO_4$ (11.6 g, 72.9 mmol) in 3 portions with efficient stirring and cooling within 1 h. The mixture was allowed to warm to r.t. and kept for 5 h. Solid Na_2SO_3 (3.2 g, 2 mmol) was added, after 10 min stirring, the suspension solution was filtered, and washed with 5% $NaHCO_3$ (5 x 50ml). The filtrate was concentrated (to about 50 ml), acidified to pH 3 with conc. HCl and extracted with EtOAc (4 x 100 ml) immediately. The combined organic solution was dried and evaporated to give diacid (**4.4**) (3.72 g, 73%) as a white solid.

m.p. 176-178^o

^{1}H NMR δ(D_6-DMSO) 1.16 (s, 3 H); 1.38 (s, 3 H); 2.07 (m, 1 H); 2.27 (m, 1 H); 2.75-2.80 (m, 2 H); 4.76 (d, *J* = 7.5, 2 H); 12.38 (br.s, 2 H).

^{13}C NMR δ(D_6-DMSO) 24.8 (q); 27.1 (q); 30.7 (t); 49.7 (d); 85.2 (d); 111.3 (s); 174.1 (s).

Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.09; H, 6.13.



(1R,2S,6R,7S)-9-[2-(1H-3-indoly)ethyl]-4,4-dimethyl-3,5-dioxa-9-azatricyclo [5.3.1.0^{2,6}]undecane-8,10-dione (4.5)

To an ice-cold solution of diacid (**4.4**) (2.0 g, 8.7 mmol) in THF (40 ml) was added triethylamine (0.88 g, 8.7 mmol) in THF (10 ml) followed by ethyl chloroformate (0.83 g, 8.7 mmol) in THF (10 ml). After stirring for 30 min, tryptamine (1.40 g, 8.7 mmol) in THF (20 ml) was added over 10 min, and the mixture warmed to r.t. and stirred for 16 h. The solvent and excess triethylamine was removed in *vacuo*, the residue was dissolved in THF (50 ml), and acetyl chloride (10 ml) was added. The reaction mixture was stirred at r.t. for 4 h, refluxed for 10 h, cooled, and filtered. The filtration was concentrated and purified by chromatography (silica gel, EtOAc/Hex 1:10 to 2:3) to give (**4.5**) as a white solid (2.5 g, 81.2 %).

m.p. 173-175 ^{o}

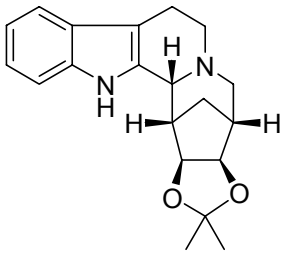
IR(neat) ν 3346, 1733, 1730, 1678, 1675, 1384, 1348

^{1}H-NMR δ 1.14 (s, 3 H); 1.39 (s, 3 H); 1.91-1.95 (m, 1 H); 2.03-2.10 (m, 1 H); 2.96-3.03 (m, 4 H); 3.97 (d, *J* = 7.2, 2 H); 4.12 (s, 2 H); 6.99 (d, *J* = 2.4, 1 H); 6.99-7.19 (m, 2 H); 7.29-7.32 (m, 1 H); 7.61-7.64 (m, 1 H); 8.12 (br.s, 1 H).

^{13}C NMR δ 22.4 (t); 23.6 (q); 25.2 (q); 26.5 (t); 39.3 (t); 50.1 (d); 80.2 (d); 111.0 (d); 111.3 (s); 111.8 (s); 118.6 (d); 119.2 (d); 121.7 (d); 122.6 (d); 127.6 (s); 135.6 (s); 172.3 (s).

EI-MS: 355 (4, M+1$^{+\cdot}$), 354 (24, M$^{+\cdot}$), 143 (100), 142 (38), 130 (55), 129 (31)

Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.84; H, 6.37; N, 8.05.



(1S,2R,16R,17R,21S)-19,19-dimethyl-18,20-dioxa-4,14-diazahexacyclo[14.5.1.$0^{2,14}$.$0^{3,11}$.$0^{5,10}$.$0^{17,21}$]docosa-3(11),5,7,9-tetraene (4.6)

A solution of Tf_2O (0.63 g, 2.2 mmol) in CH_2Cl_2 (10 ml) was added dropwise to an ice-cold solution of imide (**4.5**) (0.74 g, 2.1 mmol) in CH_2Cl_2 (10 ml). The resulting mixture was warm up to r.t., and kept for 12 h. Solvent was removed in *vacuo*, the residue was dissolved in DME (2 ml), cooled to 0 ^oC, and $NaBH_4$ (0.32 g, 8.5 mmol) was added in portions. After 4 h stirring at r.t., the reaction was quenched with water, concentrated, and then extracted with 10% MeOH/CH_2Cl_2. The organic extracts were combined, dried, evaporated under reduce pressure, and chromatographed (silica gel, EtOAc/Hex 1:9) to give a white solid (**4.6**) (0.35 g, 51.8 %).

m.p. 234-235 ^{o}

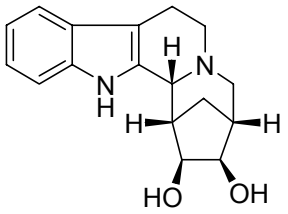
IR(neat) ν 3311, 3053, 2982, 2940, 2798, 2753, 1732, 1456, 1379, 1276, 1207, 1165, 1040, 737

^{1}H NMR δ 1.25 (s, 3 H); 1.44 (s, 3 H); 2.16-2.22 (m, 1H); 2.33 (s, 1H); 2.49-2.69 (m, 4H); 2.84-2.96 (m, 4H); 3.33 (s, 1H); 4.26 (d, *J* = 4.5, 1H); 4.54 (d, *J* = 4.5, 1H); 7.07-7.17 (m, 2H); 7.25-7.28 (m, 1H); 7.46-7.49 (m, 1H); 8.08 (br.s, 1H).

^{13}C NMR δ 21.9 (t); 23.7 (q); 25.9 (q); 32.2 (t); 40.8 (d); 52.0 (t); 57.2 (t); 61.2 (d); 80.9 (d); 83.7 (d); 108.7 (s); 109.5 (s); 111.0 (d); 117.9 (d); 119.3 (d); 121.4 (d); 127.3 (s); 133.5 (s); 135.8 (s).

EI-MS: 325 (9, $M+1^{+\cdot}$), 324 (53, $M^{+\cdot}$), 323 (100), 309 (31)

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 74.35; H, 7.57; N, 8.72.



(1S,2R,16R,17R,18S)-4,14-diazapentacyclo[14.2.1.$0^{2,14}$.$0^{1,11}$.$0^{5,10}$]nonadeca-3(11), 5,7,9-tetraene-17,18-diol (4.7)

A mixture of acetonide (**4.6**) (1.0 g, 3.1 mmol) and p-TsOH·H_2O (1.2 g, 6.3 mmol) in dioxane(8 ml) and H_2O (8 ml) was refluxed for 24 h. After removel of all solvent, the residue solid was dissolved in water, saturated with K_2CO_3 and then extracted with 10% MeOH/CH_2Cl_2. The organic layer was concentrated in *vacuo* to give (**4.7**) as a white solid (0.85 g, 97.0 %)

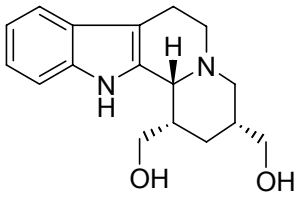
IR(neat) ν 3410, 3247, 2941, 2916, 2868, 2781, 2743, 1643, 1449, 1381, 1019, 726

^{1}H NMR δ(D_6-DMSO) 1.28 (d, *J* = 10.2, 1 H); 2.02-2.07 (m, 2 H); 2.35-2.61 (m, 5 H); 2.71-2.92 (m, 4 H); 3.18 (s, 1 H); 3.63 (d, *J* = 5.7, 1 H); 3.89 (d, *J* = 6.0, 1 H); 6.92-7.06 (m, 2 H); 7.30-7.36 (m, 2 H); 10.87 (br.s, 1 H).

^{13}C NMR δ(D_6-DMSO) 21.8 (t); 32.5 (t); 44.0 (d); 45.8(d); 52.0 (t); 58.1 (t); 62.1 (d); 72.6 (d); 75.4 (d); 109.2 (s); 111.2 (s); 117.8 (d); 119.1 (d); 121.1 (d); 127.4 (s); 134.0 (s); 136.0 (s).

EI-MS: 286 (7, M+$2^{+\cdot}$),284 (91, $M^{+\cdot}$), 283 (100), 267 (60), 169 (32), 156 (35), 44(66), 43(34).

HR-MS: 284.1551 ($C_{17}H_{20}O_2N_2^{+\cdot}$; calc. 284.1526).



[(1*S*,3*R*,12b*R*)-3-(hydroxymethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]b-carbolin-1-yl]methanol (4.8)

To a stirred solution of diol (**4.7**) (1.0 g, 3.5 mmol) in THF (15 ml) and H_2O (15 ml) at 0^o, $NaIO_4$ (3 g, 14.0 mmol) was added in portions. After 1 h stirring at 0^o, the mixture was diluted with water, extracted with 10 % MeOH/CH_2Cl_2, the combined extracts was washed with brine, dried, and evaporated in *vacuo* under 20 ^{o}. The residue was dissolved in MeOH (10 ml), cooled in an ice-bath, $NaBH_4$ (1.1 g, 29 mmol) was added in portions. After 4 h stirring at r.t., the reaction was quenched with water, extracted with 10 % MeOH/CH_2Cl_2, dried, and evaporated in *vacuo* to give (**4.8**) (0.82 g, 81.4%)

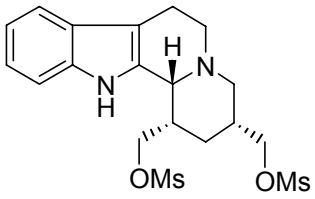
IR(neat) ν 3307, 2926, 2858, 1620, 1455, 1325, 1050, 740

^{1}H NMR δ(D_6-DMSO) 1.59-1.64 (m, 1 H); 1.74-1.76 (m, 1 H); 2.26-2.30 (m, 1 H); 2.42-2.62 (m, 3 H); 2.73-2.81 (s, 2 H); 2.96-3.00 (m, 1 H); 3.14 (d, *J* = 15.6, 2 H); 3.35-3.37 (m, 1 H); 3.65 (br.s, 1 H); 4.17-4.19 (m, 2 H); 4.55 (br.s, 1 H); 4.65 (br.s, 1 H); 6.91-7.03 (m, 2 H); 7.32 (dd, *J* = 11.6, 7.5, 2 H).

^{13}C NMR δ(D_6-DMSO) 20.1 (t); 26.2 (t); 37.6 (d); 40.3 (d); 48.7 (d); 52.8 (t); 61.9 (t); 64.5 (t); 107.3 (s); 111.1 (d); 117.4 (d); 118.3 (d); 120.4 (d); 126.8 (s); 133.8 (s); 136.1 (s).

EI-MS: 288 (8, $M+2^{+\cdot}$),286 (68, $M^{+\cdot}$), 285 (100), 255 (47), 170 (60), 169 (82).

HR-MS: 286.1684 ($C_{17}H_{22}O_2N_2^{+\cdot}$; calc. 286.1682).



((1*S*,3*R*,12b*R*)-3-[(methylsulfonyl)oxy]methyl-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]b-carbolin-1-yl)methyl methanesulfonate (4.9)

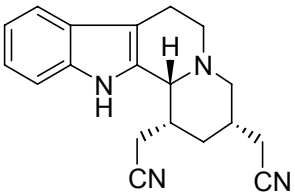
A solution of diol (**4.8**) (0.19 g, 0.7 mmol) and Et_3N (0.34 g, 3.4 mmol) in THF (3 ml) at 0^o under N_2 was stirred for 20 min, MsCl (0.30 g, 2.6 mmol) was then added. After 2 h, the reaction mixture was diluted with water, and extracted with CH_2Cl_2 dried, evaporated under reduce pressure, and chromatographed (silica gel, MeOH/ CH_2Cl_2 1:75) to give (**4.9**) (0.15g, 51.5%).

IR(neat) ν 3101, 3004, 2936, 1463, 1349, 1194, 1176, 1041, 960, 792, 750.

^{1}H-NMR δ 1.83-1.90 (m, 1 H); 2.01-2.06 (m, 1 H); 2.18 (br.s, 1 H); 2.50-2.69 (m, 4 H); 2.64 (s, 3 H); 2.81-3.01 (m, 3 H); 3.01 (s, 3 H); 3.51 (s, 1 H); 4.06-4.09 (m, 2 H); 4.16-4.22 (m, 1 H); 4.44 (t, *J* = 9.3, 1 H); 7.05-7.16 (m, 2 H); 7.33 (d, *J* = 8.1, 1 H); 7.45 (d, *J* = 8.1, 1 H); 8.46 (s, 1 H).

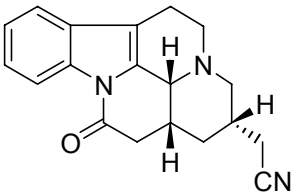
^{13}C NMR 21.0 (t); 26.2 (t); 33.4 (d); 36.1 (d); 36.5 (q); 37.0 (q); 52.9 (t); 55.7 (t); 60.9 (d); 71.0 (t); 72.3 (t); 119.9 (s); 111.0 (d); 117.9 (d); 119.3 (d); 121.5 (d); 126.7 (s); 131.4 (s); 136.4 (s).

HR-MS: 442.1233 ($C_{19}H_{26}O_6N_2S_2^{+\cdot}$; calc. 442.1233).



2-[(1*R*,3*S*,12b*R*)-1-(cyanomethyl)-1,2,3,4,6,7,12,12b-octahydropyrido[2,1-*a*]b-carbolin-3-yl]acetonitrile (4.10)

Dimesylate (**4.9**) (0.13 g, 0.3 mmol), NaCN (0.06 g, 1.2 mmol) and 18-crown-6 (0.33 g, 1.2 mmol) were heated in DMF (2 ml) at 60^{o} under N_2 for 24 h. The reaction mixture was diluted with water, and extracted with CH_2Cl_2, the combined extracts was wash twice with water, dried, evaporated under reduce pressure, and chromatographed (silica gel, MeOH/ CH_2Cl_2 1:100) to give (**4.10**) (60 mg, 66.7 %).



[(2*S*,13a*R*,13b*R*)-12-oxo-2,3,5,6,12,13,13a,13b-octahydro-1*H*-[1,7]naphthyridino[7,8,1-*lm a*]b-carbolin-2-yl]methyl cyanide (4.11)

Sodium (10 mg, 0.43 mmol) was dissolved in MeOH (1.0 ml), dinitrile (**4.10**) (60 mg, 0.20 mmol) was added and the mixture was refluxed for 4 h. The solvent was evaporated and the residue was heated in a mixture of water (1 ml) and conc. HCl (0.2 ml) at 80^{o} for 1 h. The mixture was neutralized with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried, evaporated under reduce pressure, and chromatographed (silica gel, MeOH/ CH_2Cl_2 1:100) to give (**4.11**) (55 mg, 92.0%).

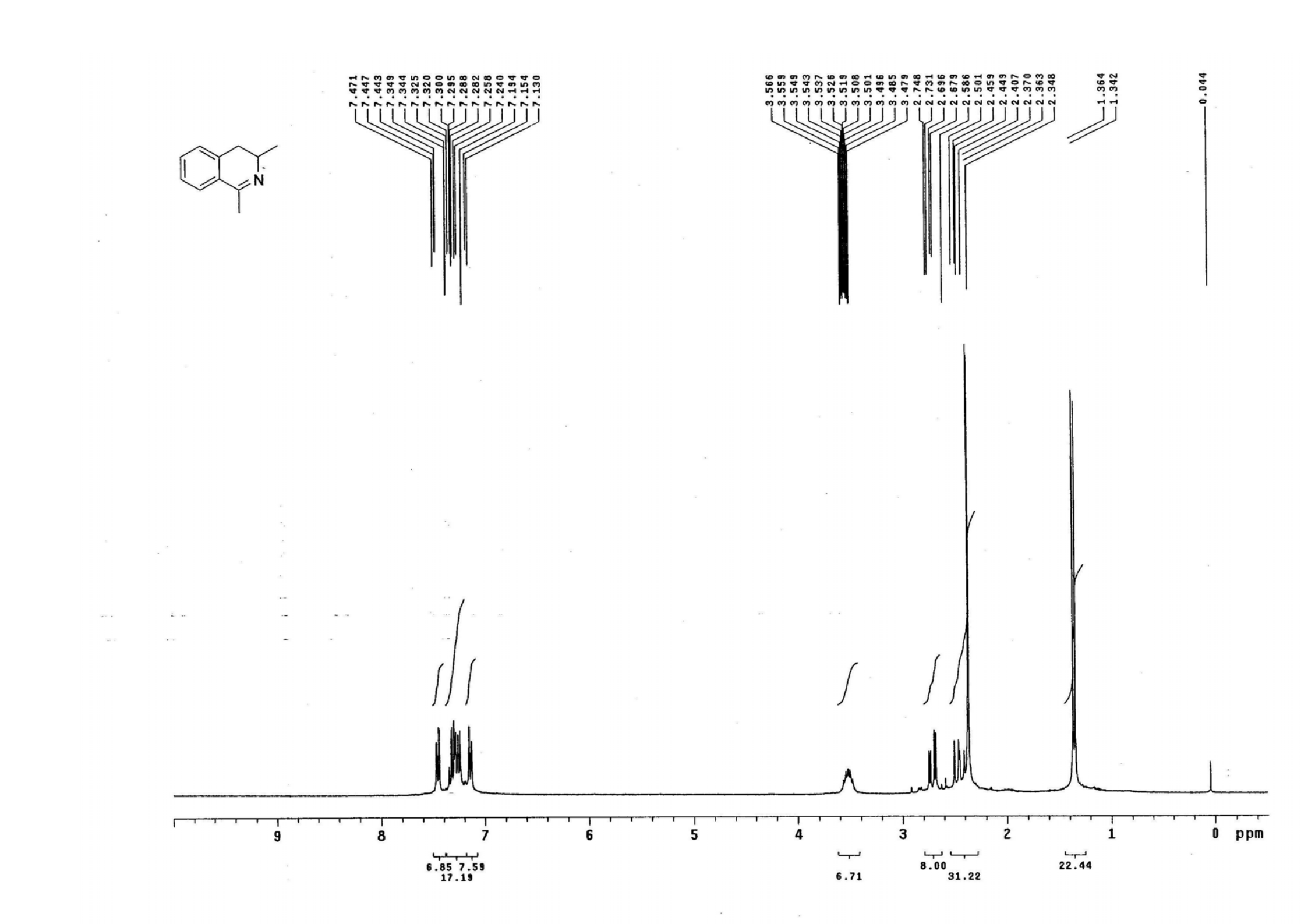
IR(neat) ν 3051, 2923, 2850, 2812, 2762, 2246, 1703, 1633, 1453, 1363, 1329, 742.

^{1}H-NMR δ 0.73 (dd, *J* = 23.7, 12.6, 1 H); 1.77-1.92 (m, 2 H); 2.10-2.34 (m, 3 H); 2.55-2.59 (m, 2 H); 2.68 (dd, *J* = 17.1, 2.1, 1 H); 2.82-2.94 (m, 2 H); 3.02 (dd, *J* = 17.1, 5.1, 1 H); 3.37 (m, 2 H); 4.33 (m, 1 H); 7.26-7.35 (m, 2 H); 7.43 (dd, *J* = 6.3, 1.8, 1 H); 8.35 (dd, *J* = 6.3, 1.8, 1 H).

^{13}C NMR 16.3 (t); 21.7 (t); 31.4 (t); 32.9 (d); 33.7 (d); 39.1 (t); 49.6 (t); 50.2 (t); 52.7 (d); 112.9 (s); 116.3 (d); 117.6 (s); 118.2 (d); 124.1 (d); 124.8 (d); 129.5 (s); 130.0 (s); 134.5 (s); 166.5 (s).

HR-MS: 305.1528 ($C_{19}H_{19}ON_3^{+\cdot}$; calc. 305.1529).

第七章 光譜附件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7.130
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3.526
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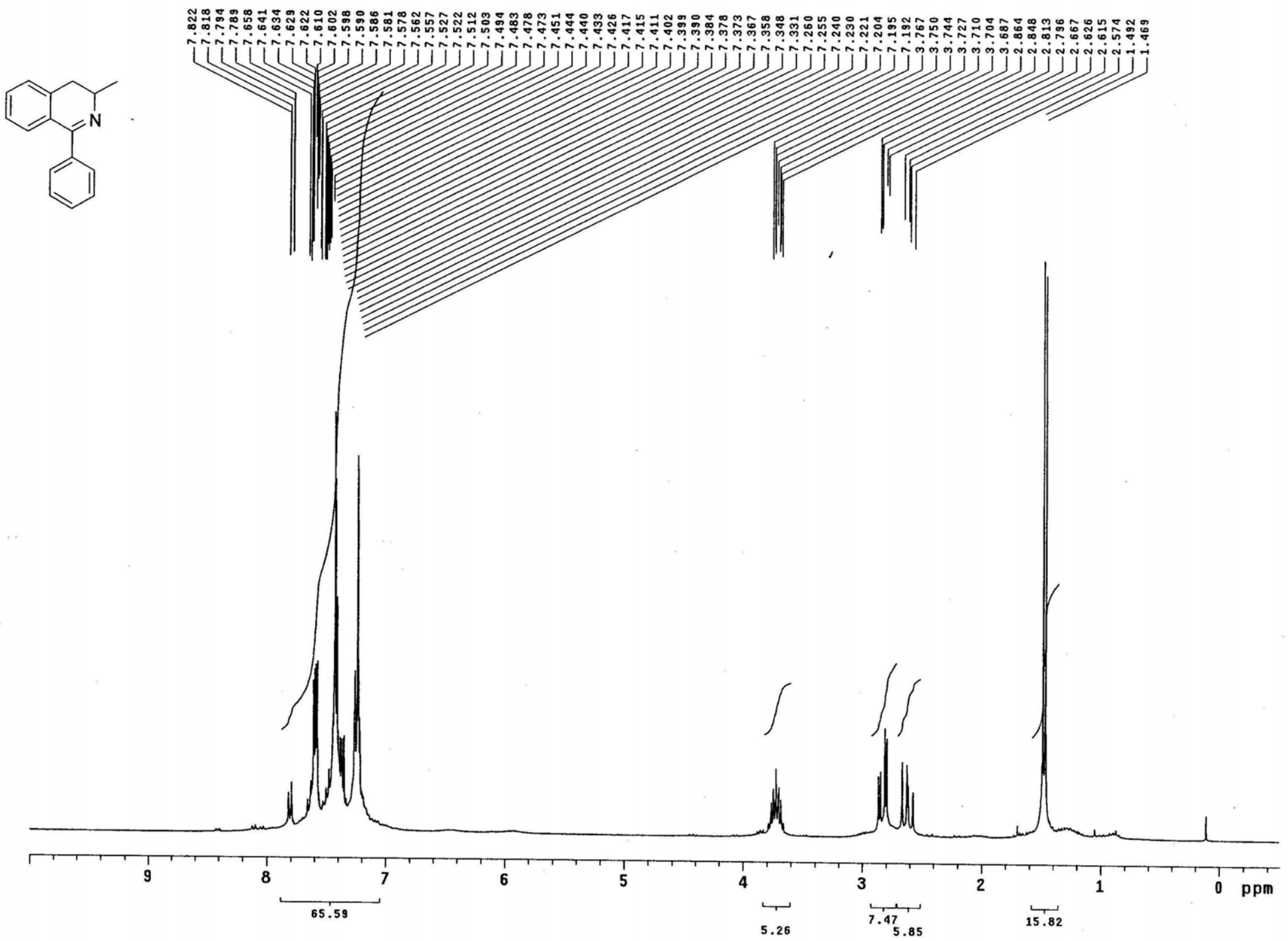
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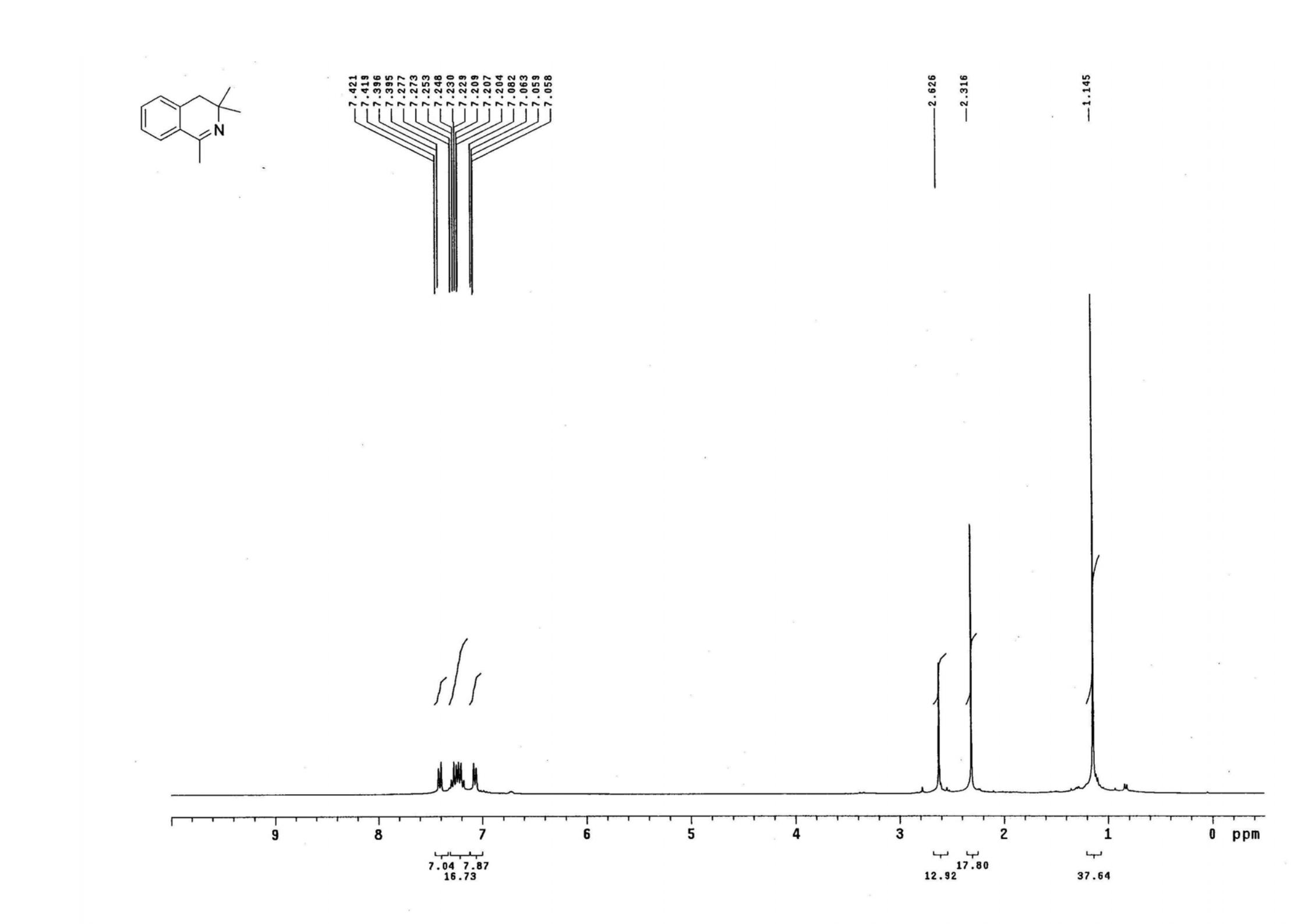
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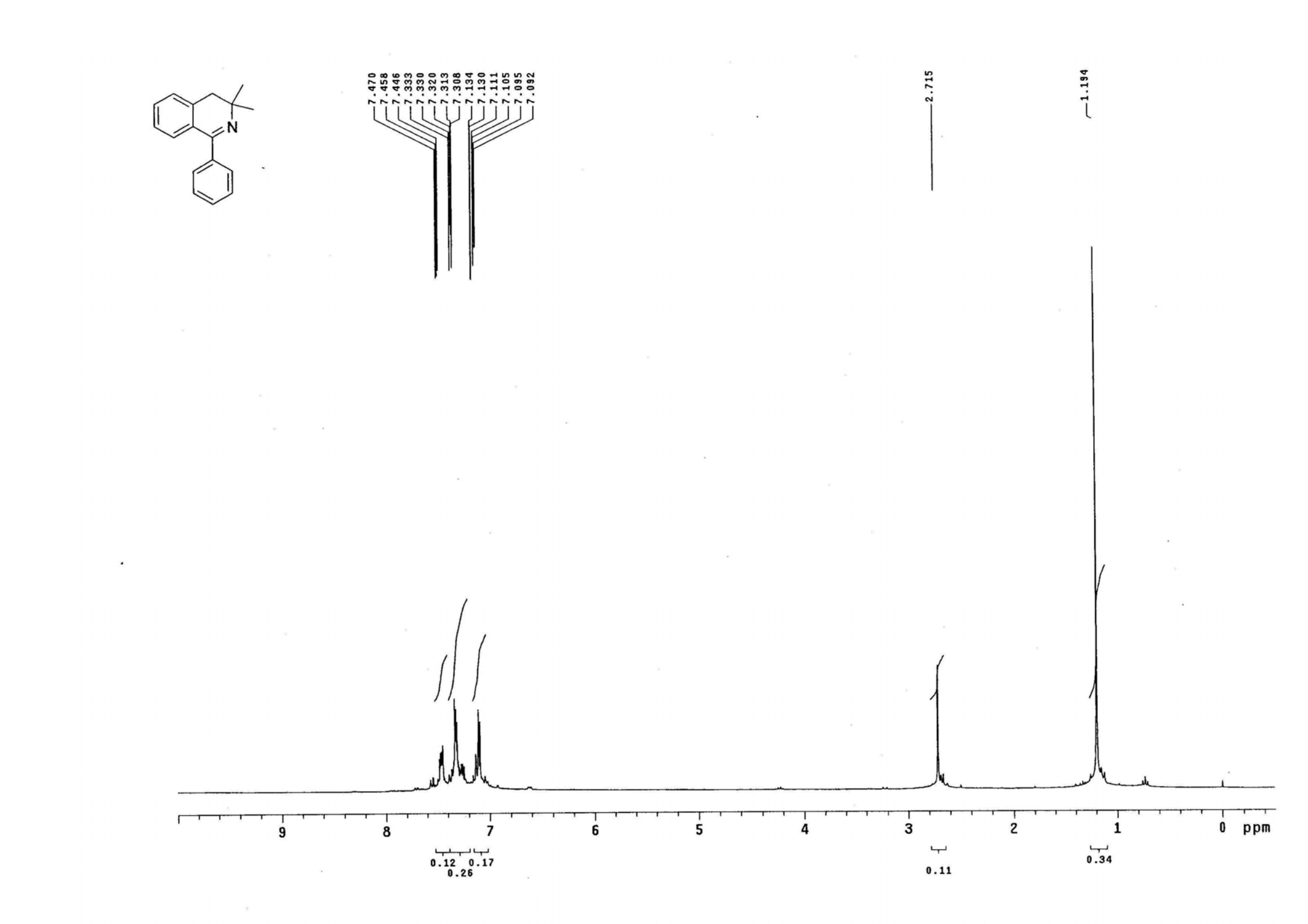
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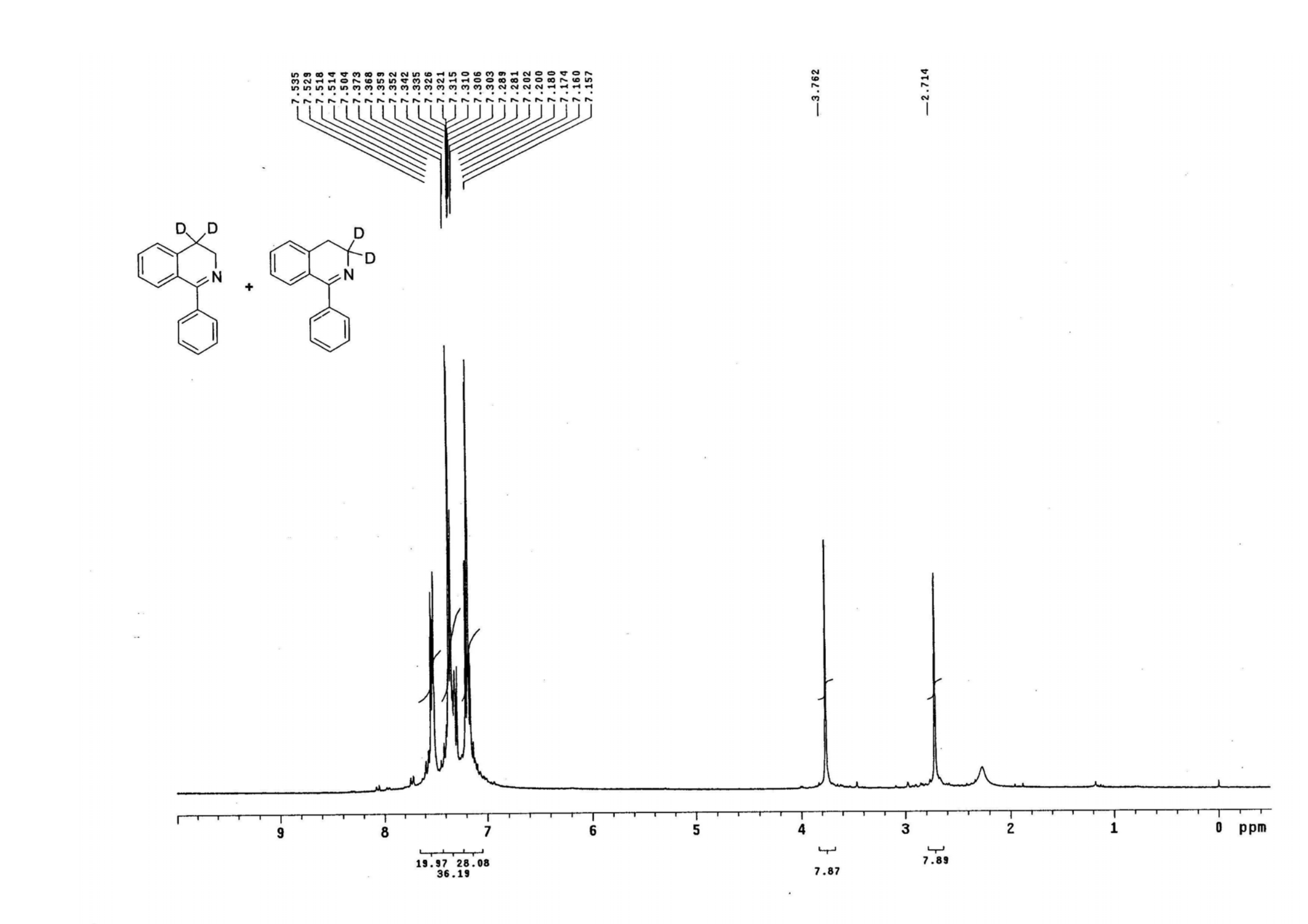
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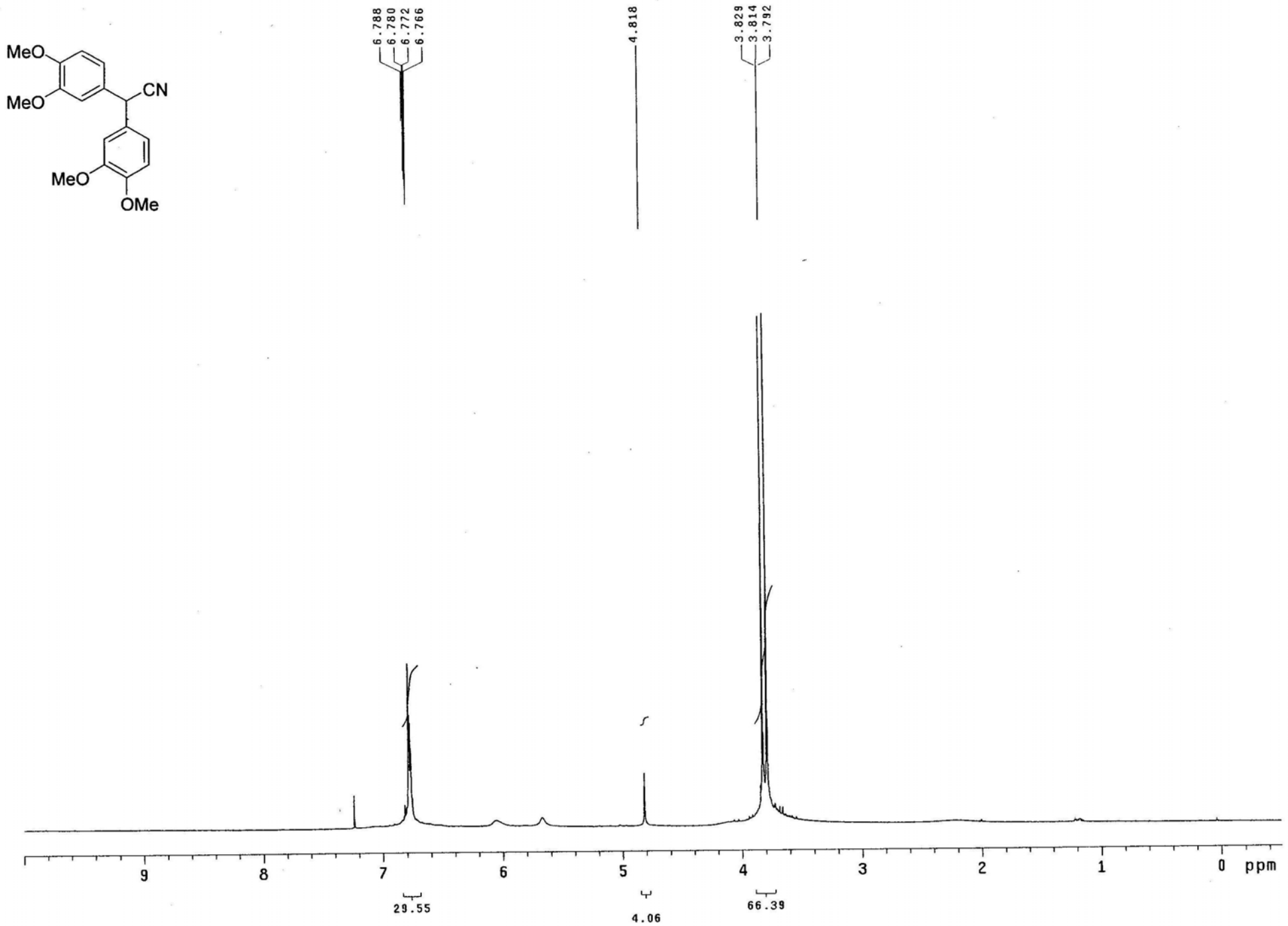
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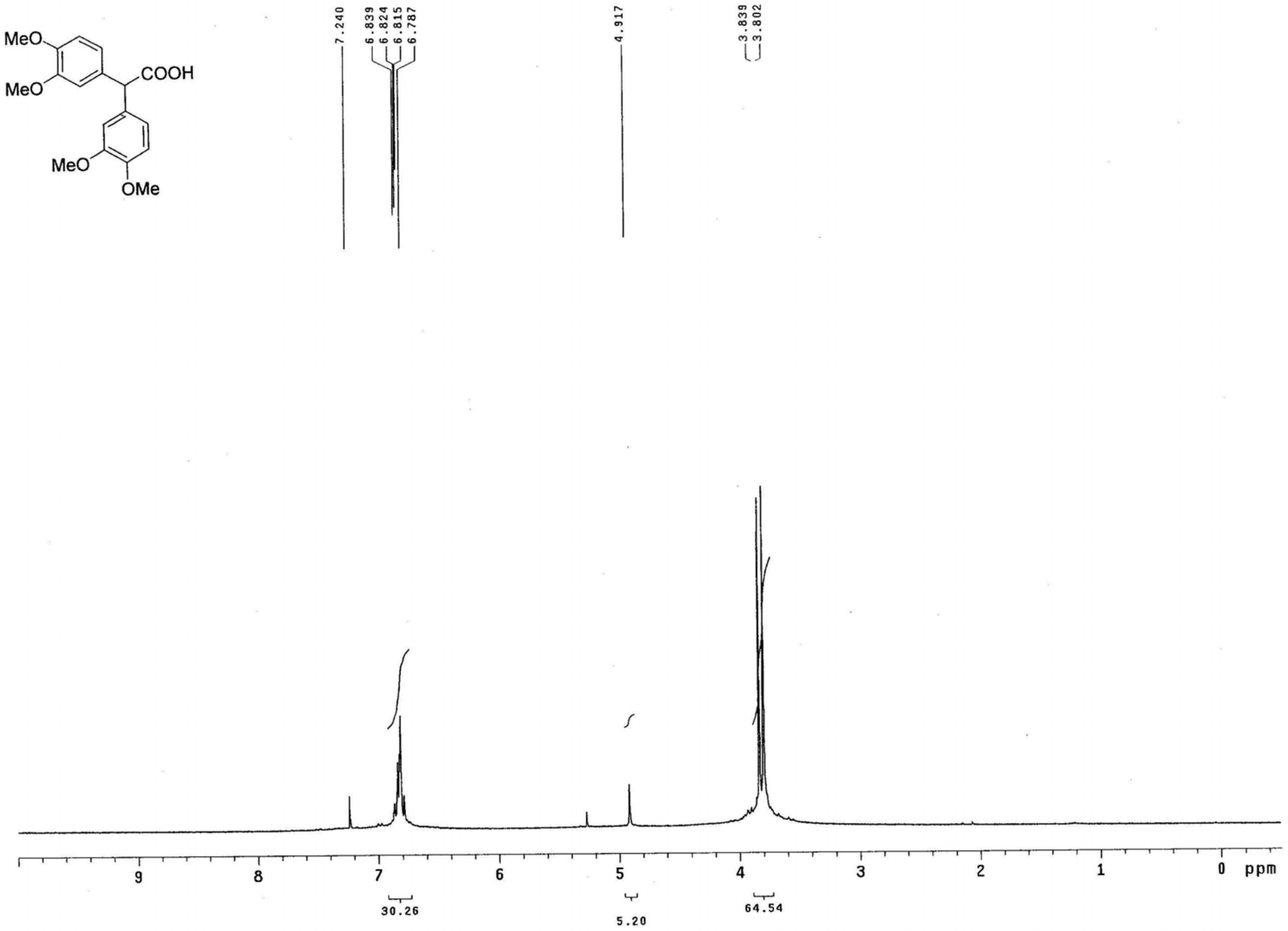
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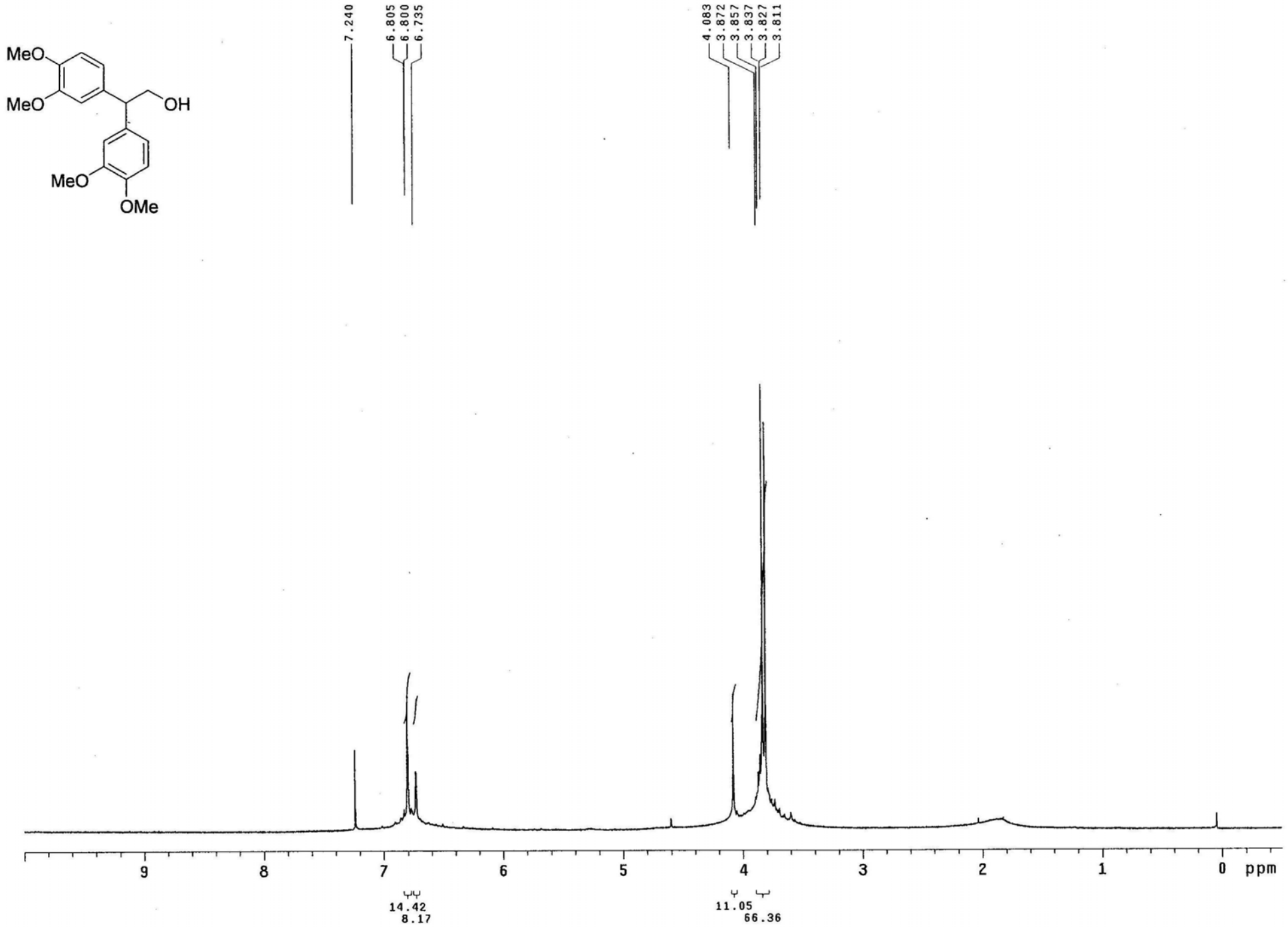
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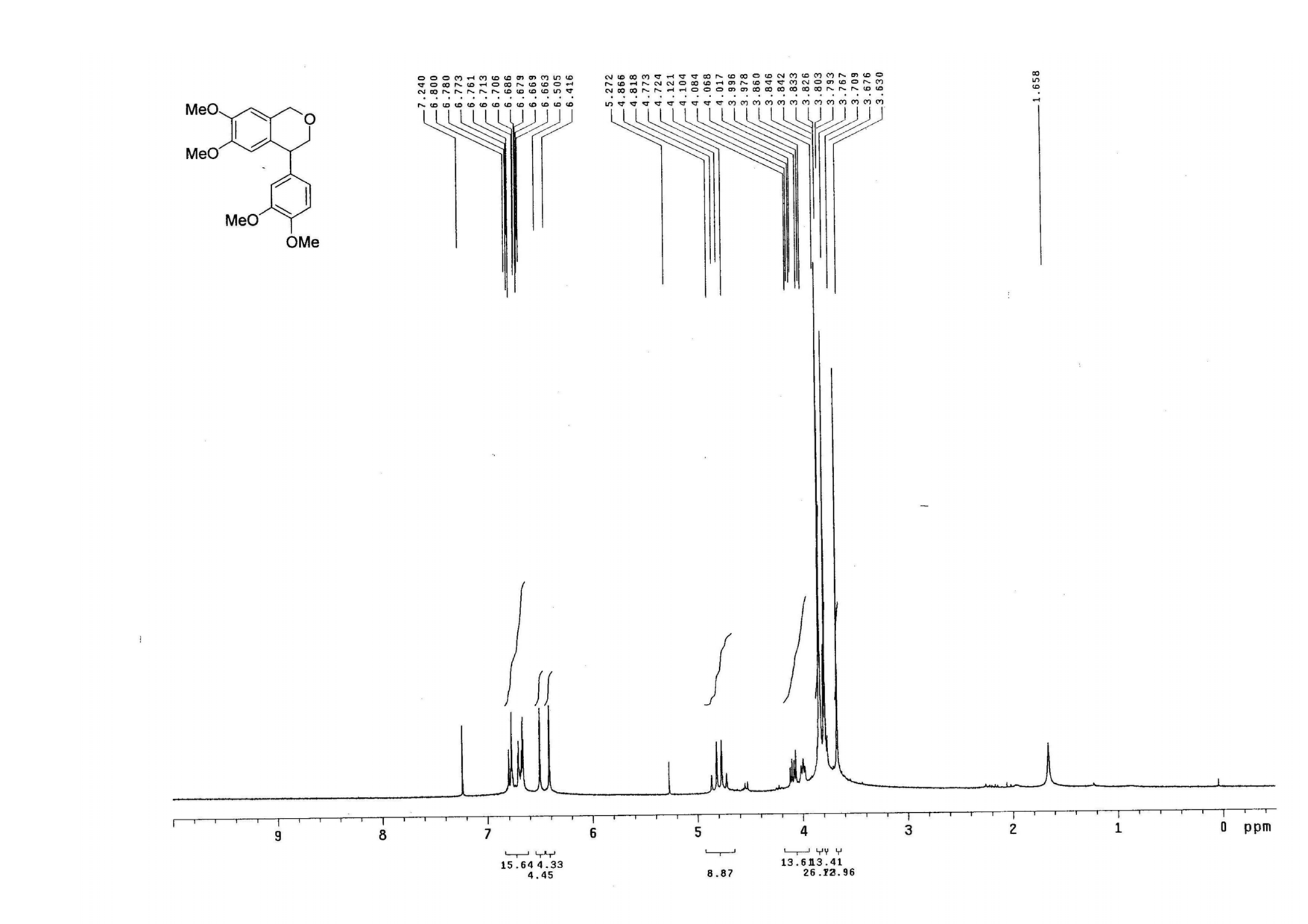
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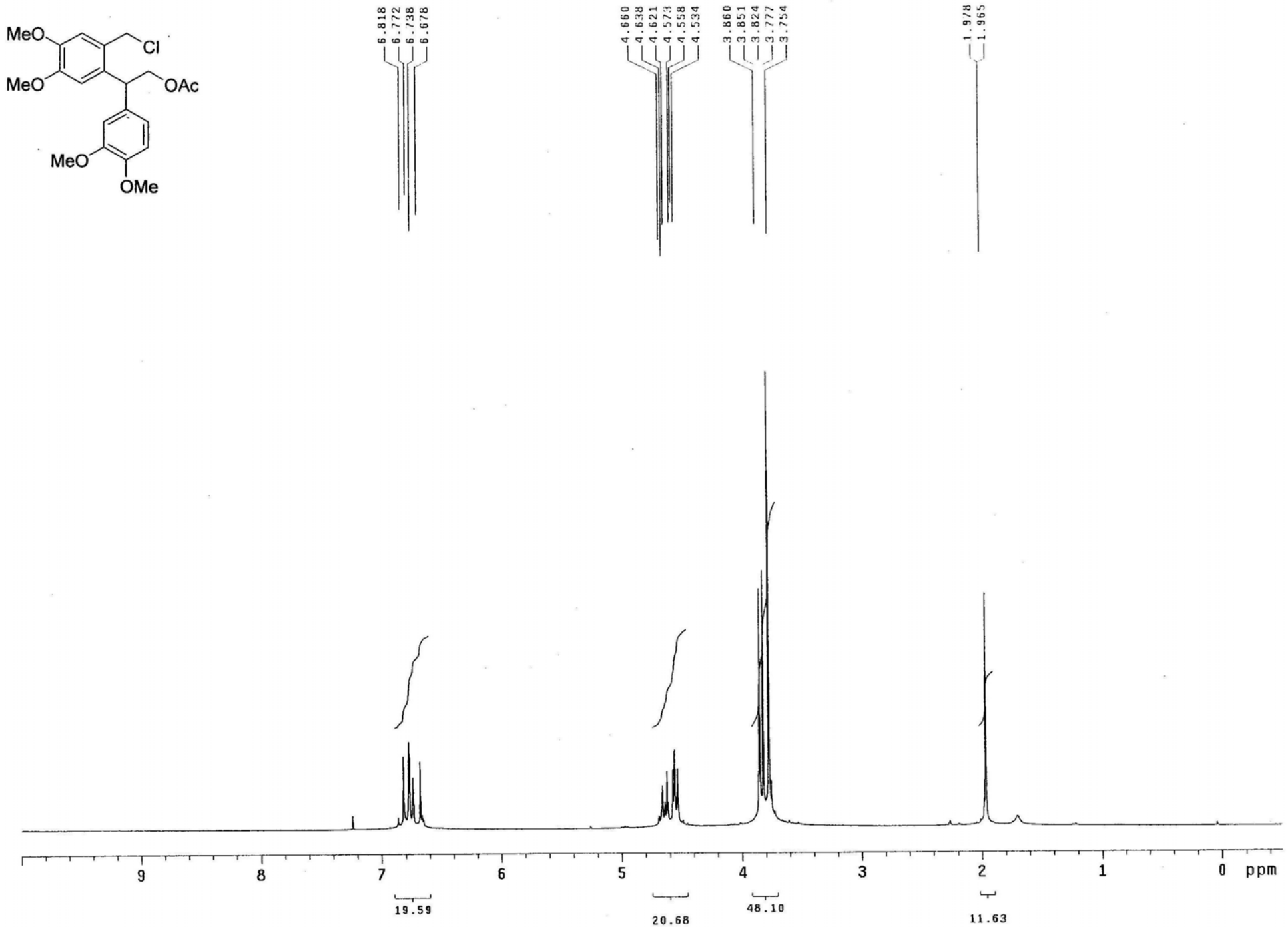
MeO
MeO
OMe
O
7.240
6.800
6.780
6.773
6.761
6.713
6.706
6.686
6.679
6.669
6.663
6.505
6.416
5.272
4.866
4.818
4.773
4.724
4.121
4.104
4.084
4.068
4.017
3.996
3.978
3.860
3.846
3.842
3.833
3.826
3.803
3.793
3.767
3.709
3.676
3.630
1.658
9
8
7
6
5
4
3
2
1
0 ppm
15.64 4.33
4.45
8.87
13.61 13.41
26.72 8.96


MeO
MeO
Cl
OAc
MeO
OMe
6.818
6.772
6.738
6.678
4.660
4.638
4.621
4.573
4.558
4.534
3.860
3.851
3.824
3.777
3.754
1.978
1.965
9
8
7
6
5
4
3
2
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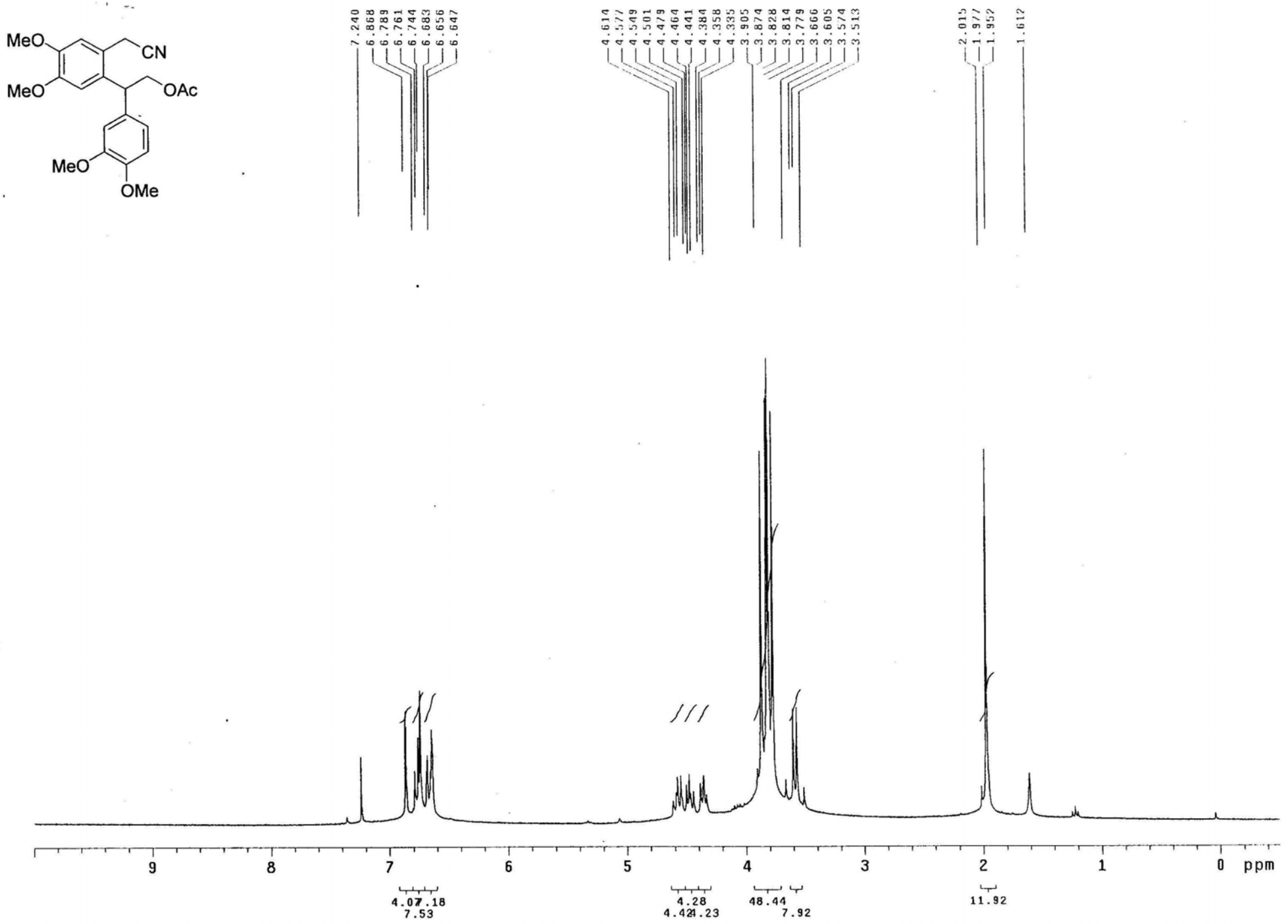
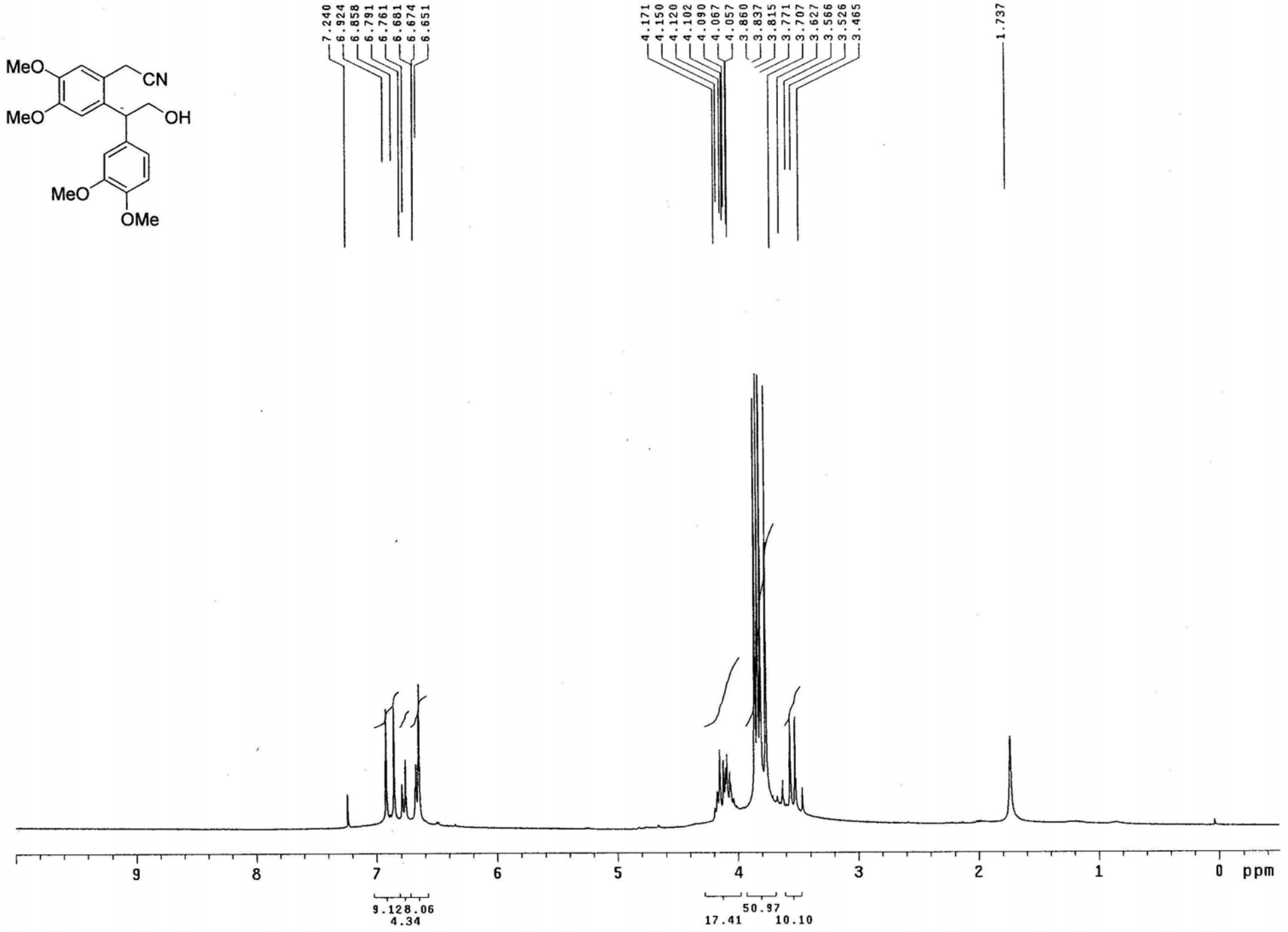
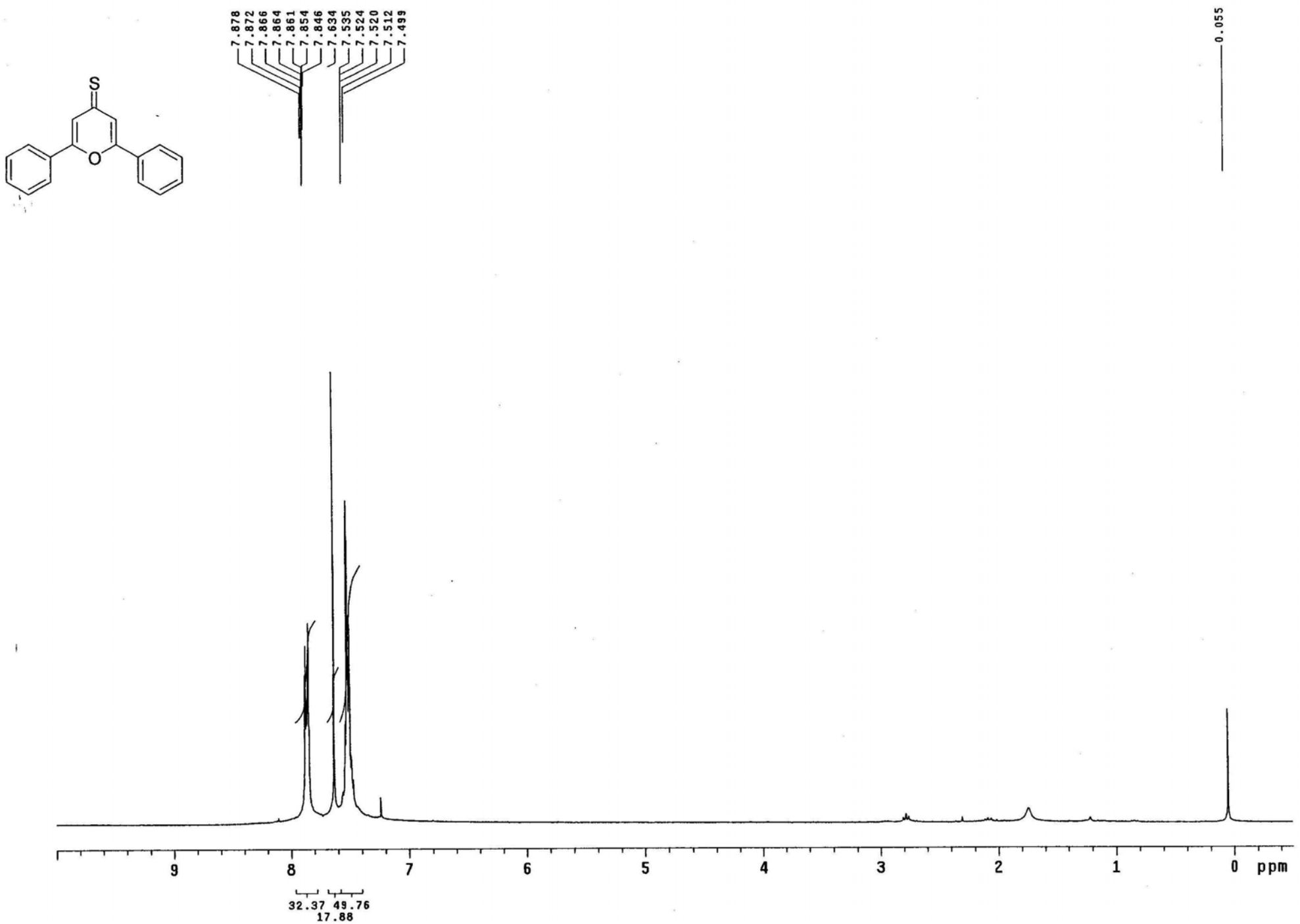
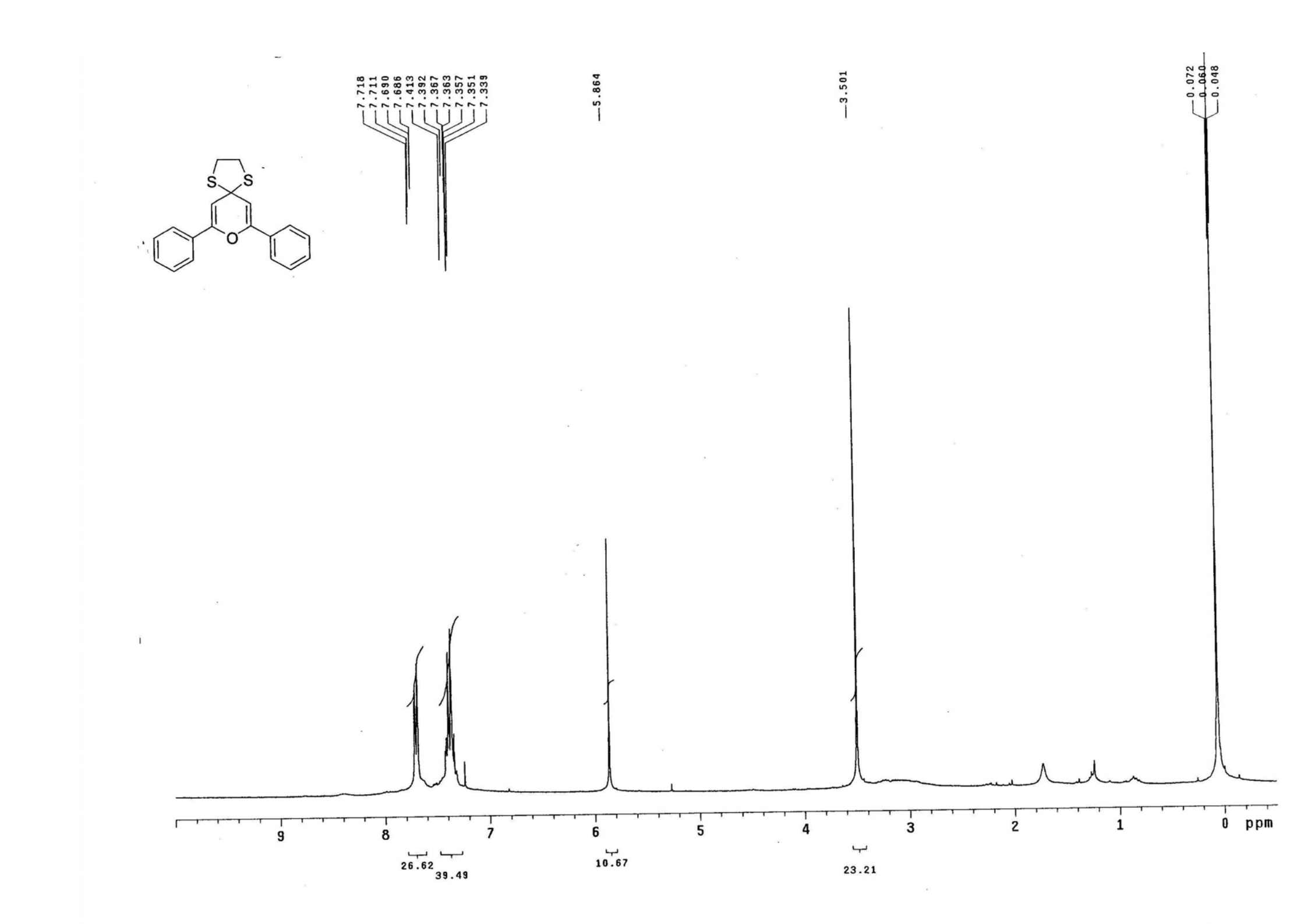
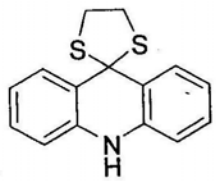
0
ppm
19.59
20.68
48.10
11.63


MeO
MeO
CN
OAc
MeO
OMe
7.240
6.868
6.789
6.761
6.744
6.683
6.656
6.647
4.614
4.577
4.549
4.501
4.479
4.464
4.441
4.384
4.358
4.335
3.905
3.874
3.828
3.814
3.779
3.666
3.605
3.574
3.513
2.015
1.977
1.952
1.612
9
8
7
6
5
4
3
2
1
0
ppm
4.07
7.18
7.53
4.28
4.42
1.23
48.44
7.92
11.92

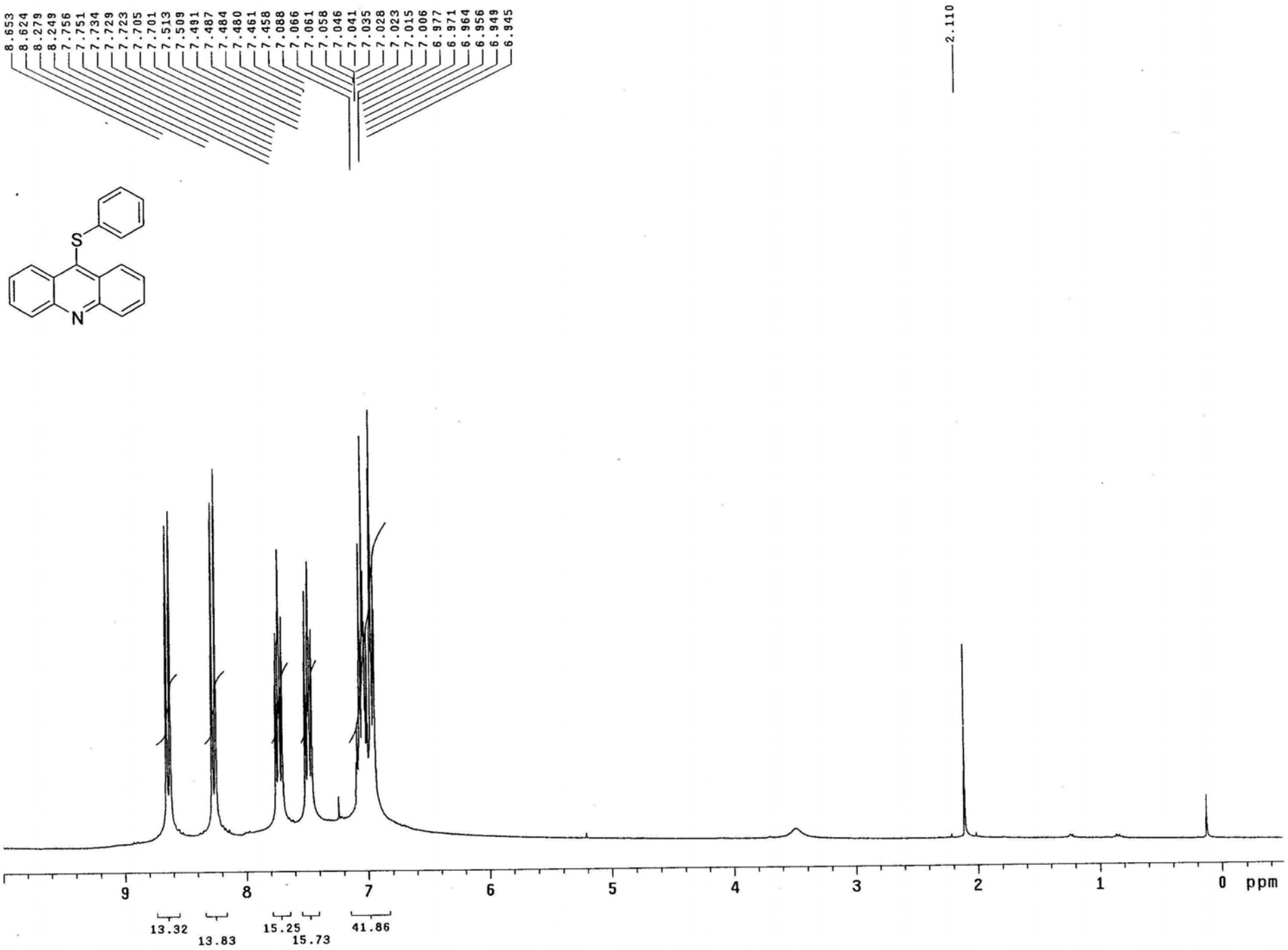

MeO
MeO
CN
OH
MeO
OMe
7.240
6.924
6.858
6.791
6.761
6.681
6.674
6.651
4.171
4.150
4.120
4.102
4.090
4.067
4.057
3.860
3.837
3.815
3.771
3.707
3.627
3.566
3.526
3.465
1.737
9
8
7
6
5
4
3
2
1
0
ppm
9.12
8.06
4.34
17.41
50.97
10.10


S
O
7.878
7.872
7.866
7.864
7.861
7.854
7.846
7.634
7.535
7.524
7.520
7.512
7.499
0.055
9
8
7
6
5
4
3
2
1
0
ppm
32.37
49.76
17.88


7.718
7.711
7.690
7.686
7.413
7.392
7.367
7.363
7.357
7.351
7.339
5.864
3.501
0.072
0.060
0.048
S
S
O
9
8
7
6
5
4
3
2
1
0 ppm
26.62
39.49
10.67
23.21


S
S
N
H

8.073
8.046
7.172
7.167
7.142
7.140
7.121
7.116
7.015
7.010
6.986
6.984
6.964
6.960
6.707
6.672
6.668
6.645
6.641
3.632
9
8
7
6
5
4
3
2
1
0 ppm
13.57
16.75
15.93
24.20
29.56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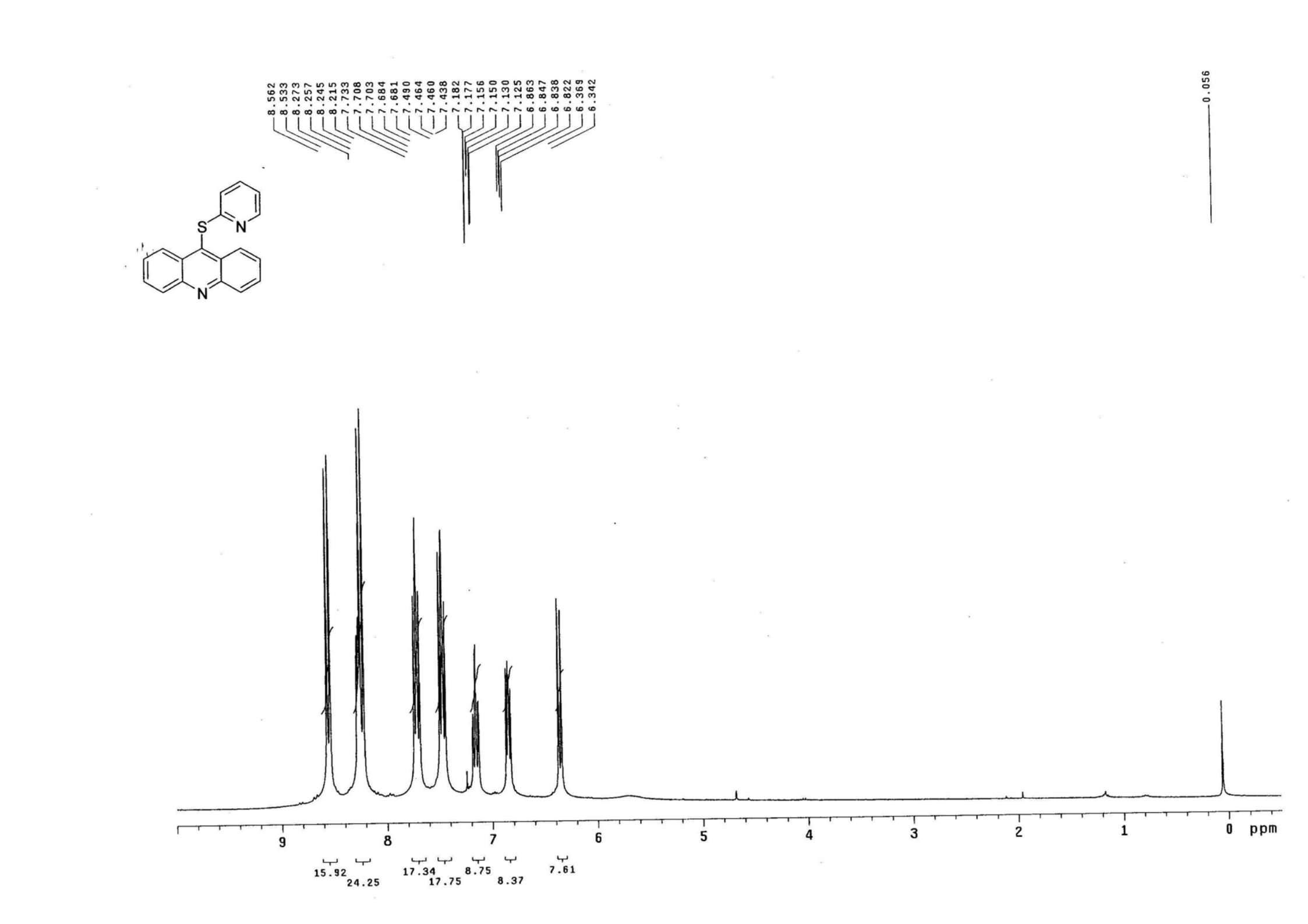
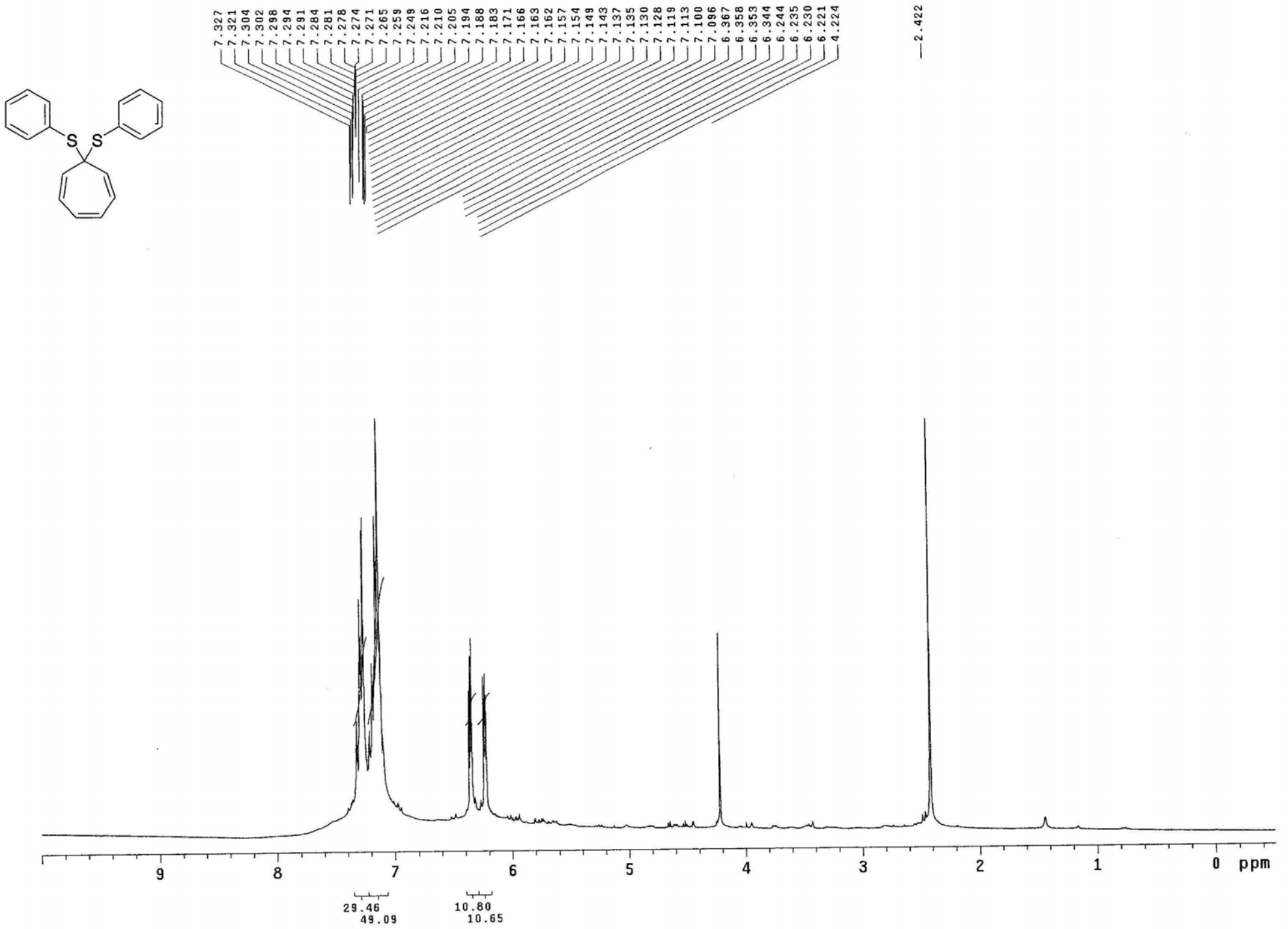
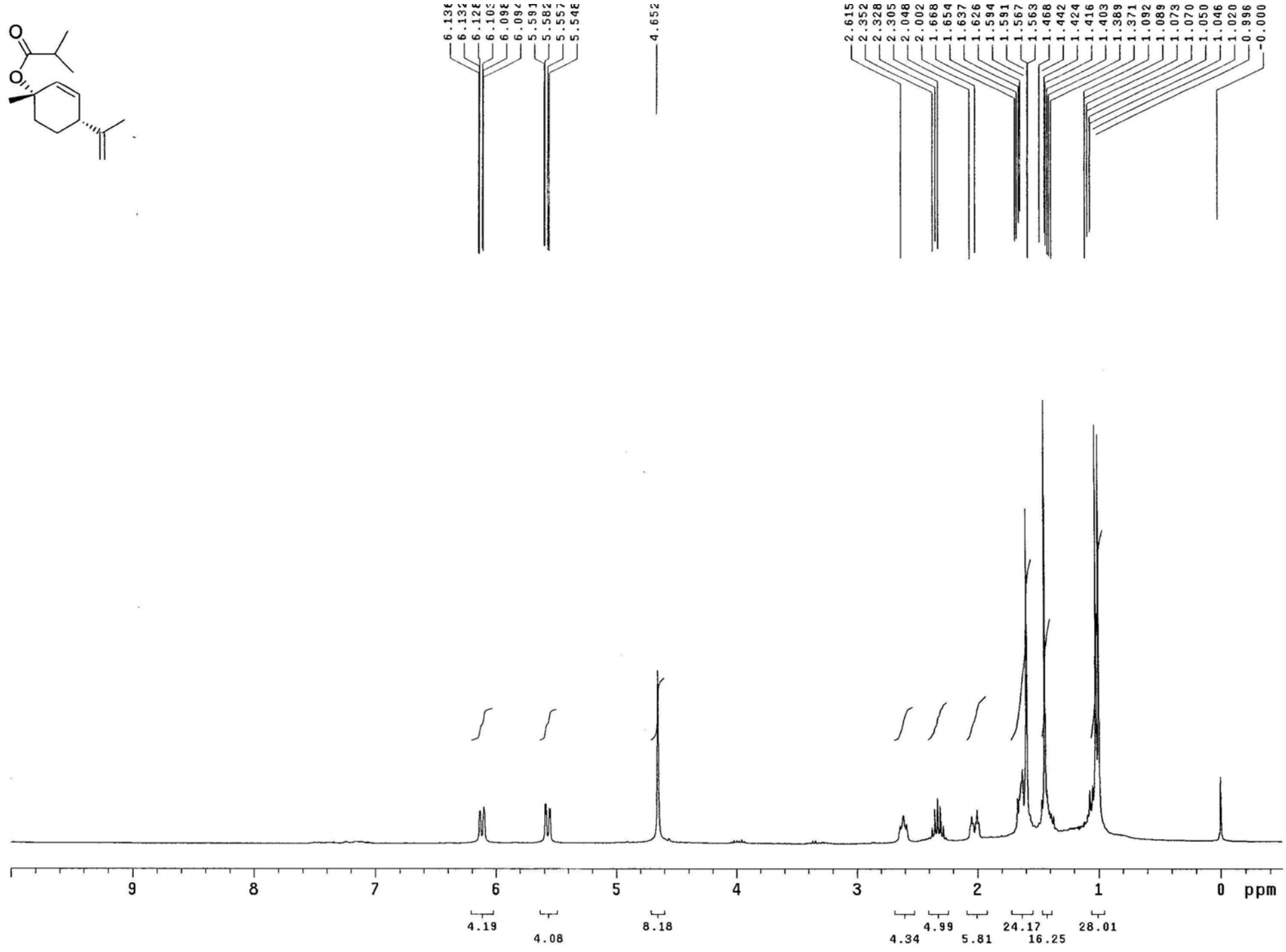
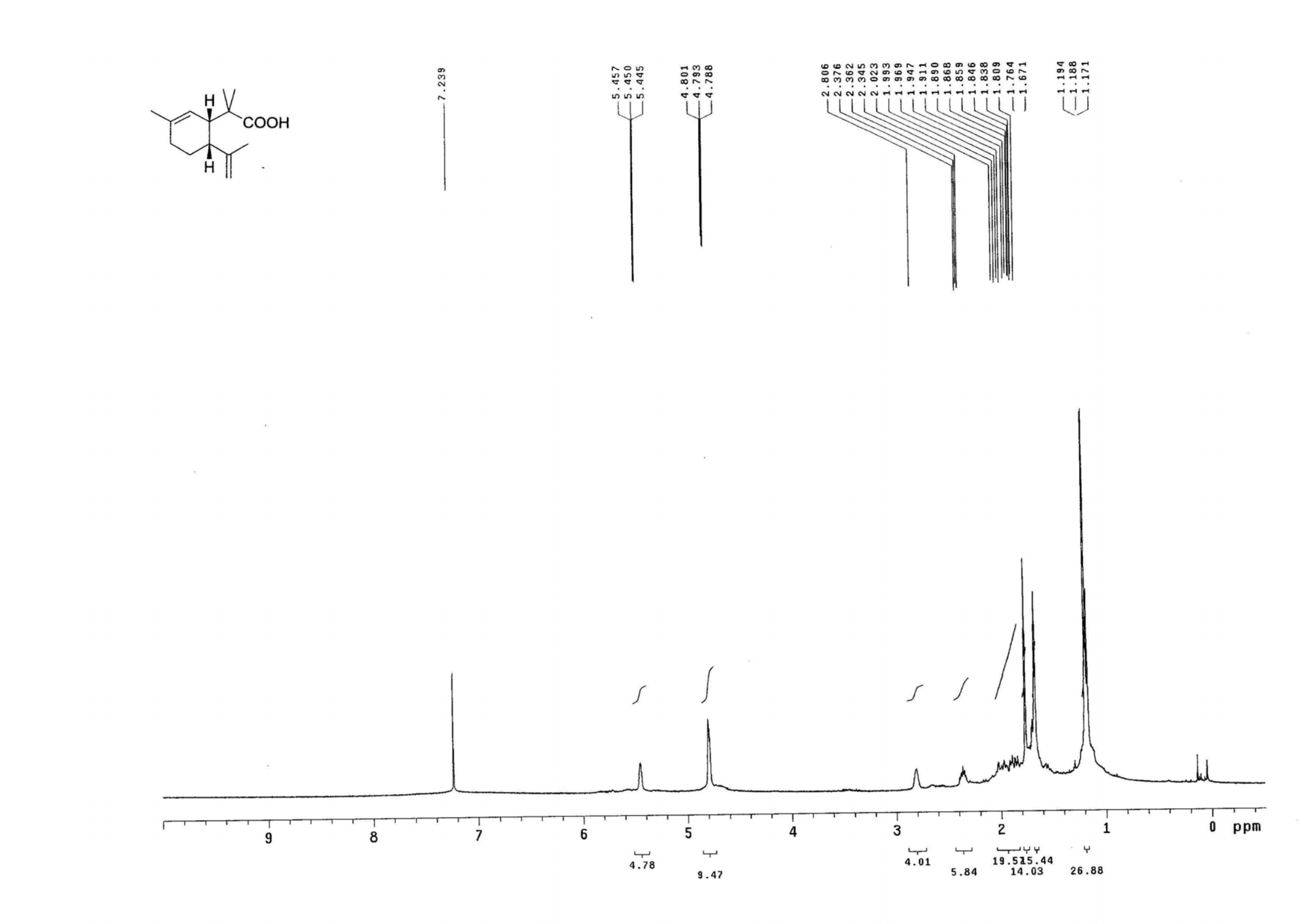
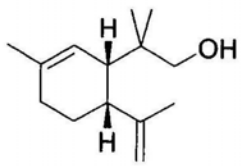
8.624
8.279
8.249
7.756
7.751
7.734
7.729
7.723
7.705
7.701
7.513
7.509
7.491
7.487
7.484
7.480
7.461
7.458
7.088
7.066
7.061
7.058
7.046
7.041
7.035
7.028
7.023
7.015
7.006
6.977
6.971
6.964
6.956
6.949
6.945
2.110
S
N
9
8
7
6
5
4
3
2
1
0 ppm
13.32
13.83
15.25
15.73
41.86


8.562
8.533
8.273
8.257
8.245
8.215
7.733
7.708
7.703
7.684
7.681
7.490
7.464
7.460
7.438
7.182
7.177
7.156
7.150
7.130
7.125
6.863
6.847
6.838
6.822
6.369
6.342
0.056
S
N
N
9
8
7
6
5
4
3
2
1
0
ppm
15.92
24.25
17.34
17.75
8.75
8.37
7.61

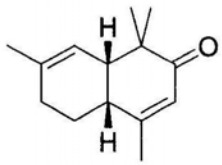

S
S
7.327
7.321
7.304
7.302
7.298
7.294
7.291
7.284
7.281
7.278
7.274
7.271
7.265
7.259
7.249
7.216
7.210
7.205
7.194
7.188
7.183
7.171
7.166
7.163
7.162
7.157
7.154
7.149
7.143
7.137
7.135
7.130
7.128
7.119
7.113
7.100
7.096
6.367
6.358
6.353
6.344
6.244
6.235
6.230
6.221
4.224
2.422
9
8
7
6
5
4
3
2
1
0 ppm
29.46
49.09
10.80
10.65


6.138
6.132
6.128
6.103
6.098
6.094
5.591
5.582
5.557
5.548
4.652
2.615
2.352
2.328
2.305
2.048
2.002
1.668
1.654
1.637
1.626
1.594
1.591
1.567
1.563
1.468
1.442
1.424
1.416
1.403
1.389
1.371
1.092
1.089
1.073
1.070
1.050
1.046
1.020
0.996
-0.000
9
8
7
6
5
4
3
2
1
0
ppm
4.19
4.08
8.18
4.34
4.99
5.81
24.17
16.25
28.01


H
COOH
H
7.239
5.457
5.450
5.445
4.801
4.793
4.788
2.806
2.376
2.362
2.345
2.023
1.993
1.969
1.947
1.911
1.890
1.868
1.859
1.846
1.838
1.809
1.764
1.671
1.194
1.188
1.171
9
8
7
6
5
4
3
2
1
0 ppm
4.78
9.47
4.01
5.84
19.52
15.44
14.03
26.88

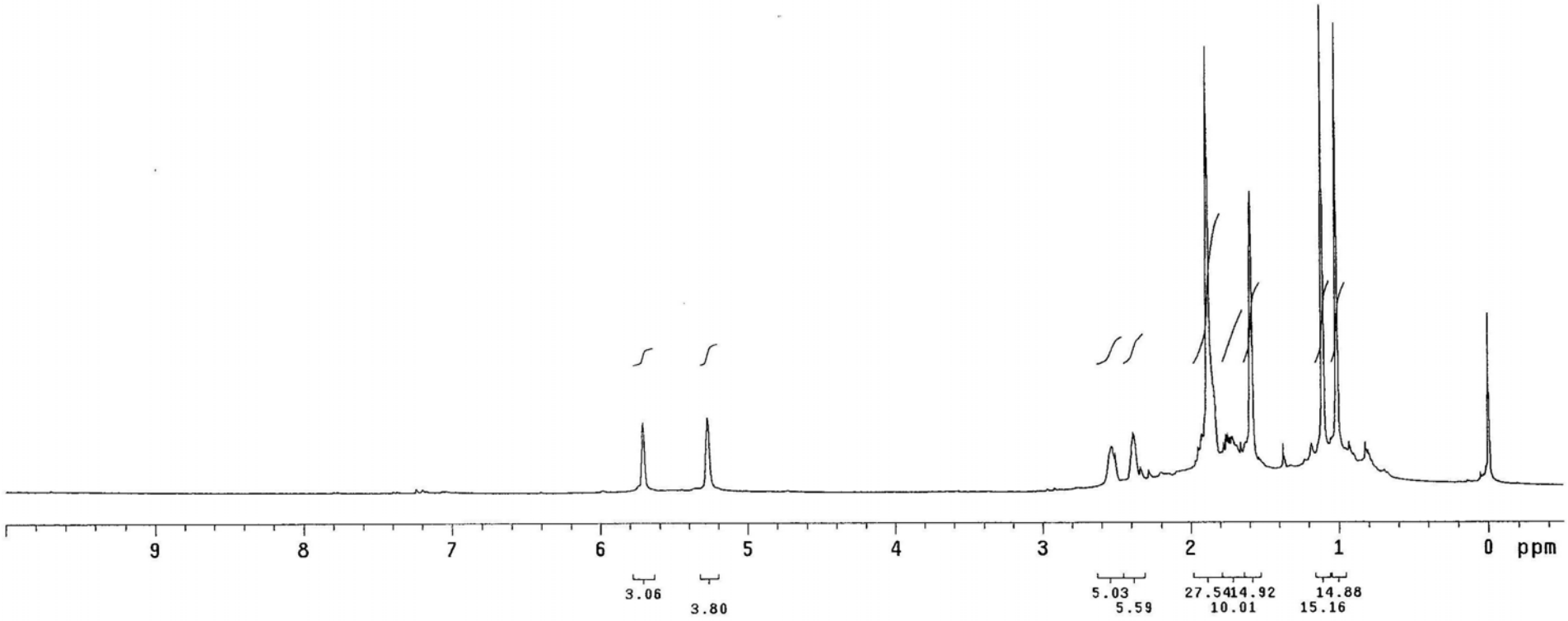

H
OH
H

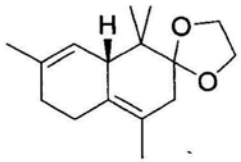
5.447
4.800
4.774
4.770
4.767
4.763
3.426
3.418
3.409
3.382
3.343
3.306
2.408
2.393
2.385
2.377
2.143
1.781
1.762
1.748
1.741
1.730
1.711
1.697
1.651
1.647
1.606
0.911
0.867
0.854
0.820
0.812
0.022
9
8
7
6
5
4
3
2
1
0
ppm
2.94
6.96
8.42
7.04
6.03
5.44
6.99
6.42
12.15
27.61



5.716
5.712
5.280
5.274
5.270

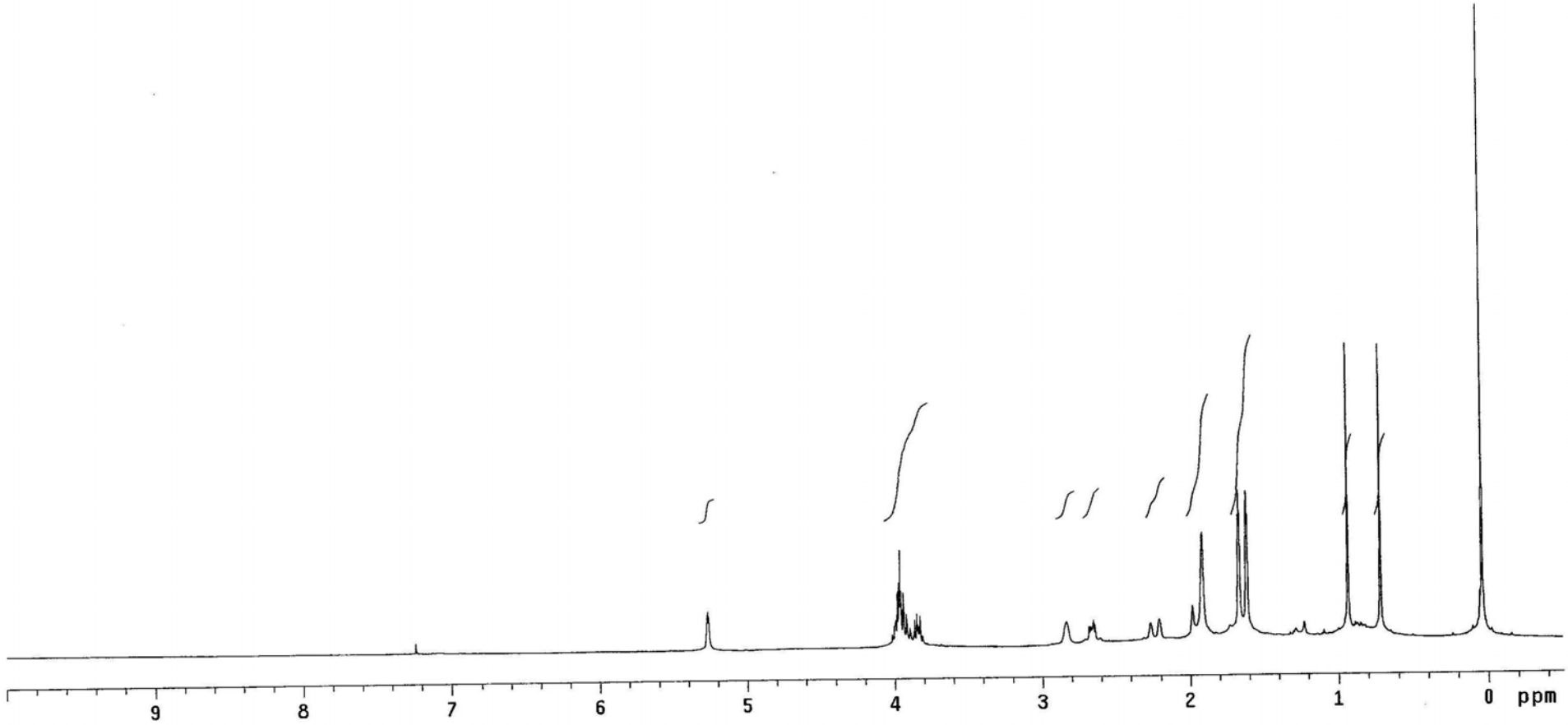
2.532
2.396
2.389
2.381
1.950
1.942
1.925
1.919
1.904
1.893
1.889
1.886
1.776
1.759
1.748
1.737
1.724
1.716
1.702
1.689
1.661
1.630
1.593
1.592
1.589
1.374
1.184
1.113
1.107
1.067
1.054
1.019
1.011
0.959
0.931
0.823
0.805
0.004

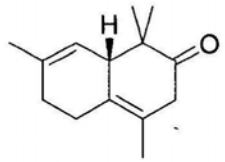




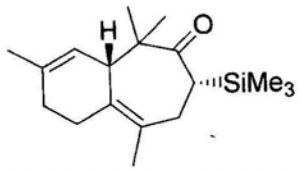
5.271
5.266
5.263
4.001
3.995
3.991
3.981
3.971
3.963
3.956
3.943
3.939
3.925
3.919
3.915
3.895
3.890
3.864
3.848
3.840
3.832
3.826
2.834
2.682
2.671
2.651
2.640
2.266
2.205
1.915
1.670
1.668
1.664
1.615

0.934
0.717
0.042

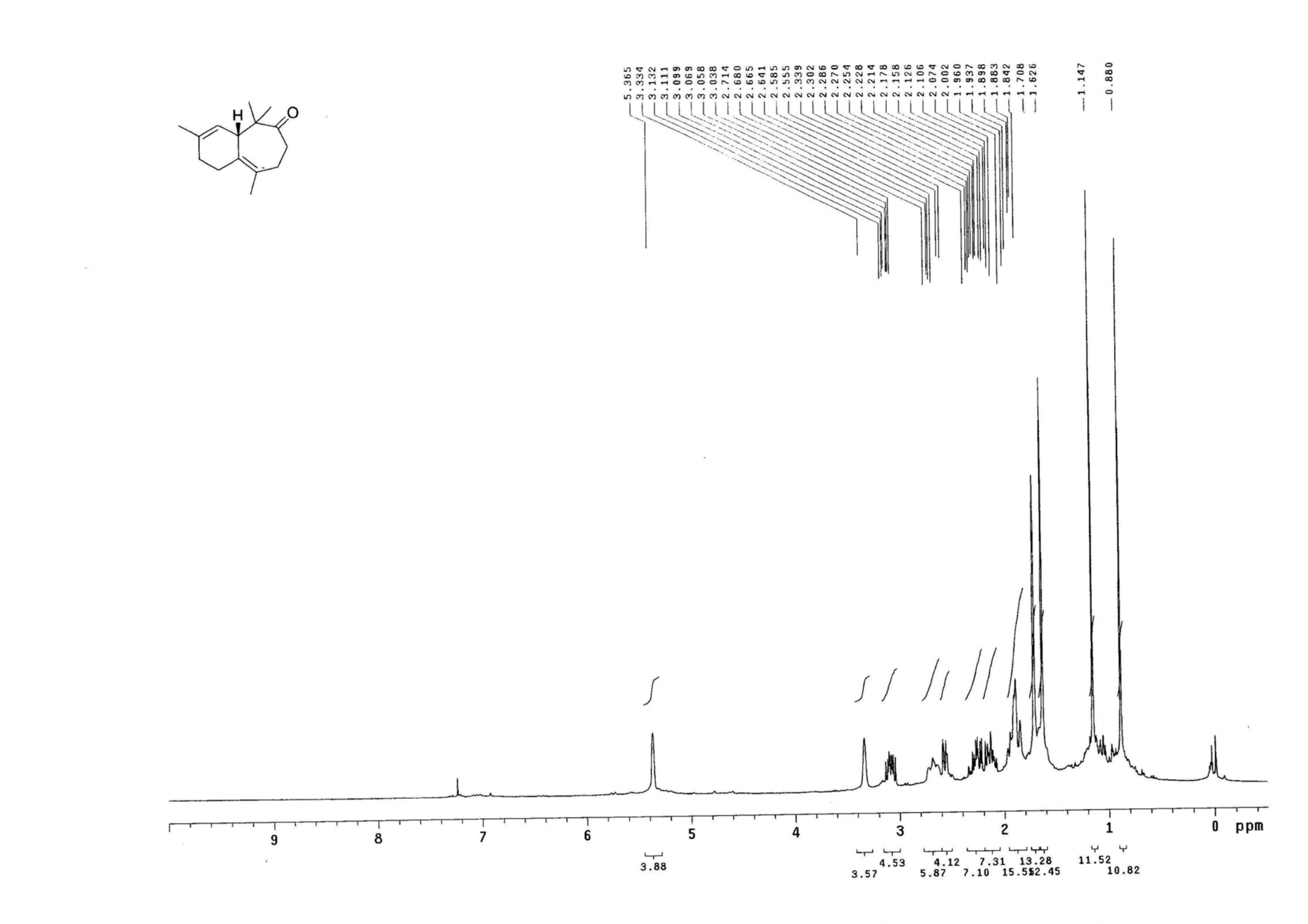


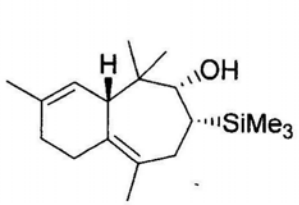

H
O

5.242
3.006
2.938
2.831
2.700
2.689
2.667
2.656
2.633
1.961
1.729
1.676
1.672
1.096
0.885
0.039
9
8
7
6
5
4
3
2
1
0
ppm

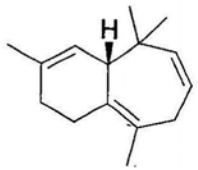

H
O
SiMe3

0.840
9
8
7
6
5
4
3
2
1
0
ppm
4.19
4.11
4.74
10.01
6.82
14.27
16.00
13.25
13.19
13.43


H
O
5.365
3.334
3.132
3.111
3.099
3.069
3.058
3.038
2.714
2.680
2.665
2.641
2.585
2.555
2.339
2.302
2.286
2.270
2.254
2.228
2.214
2.178
2.158
2.126
2.106
2.074
2.002
1.960
1.937
1.898
1.883
1.842
1.708
1.626
1.147
0.880
9
8
7
6
5
4
3
2
1
0 ppm
3.88
3.57
4.53
5.87
4.12
7.10
7.31
15.55
13.28
12.45
11.52
10.82


H
OH
SiMe3

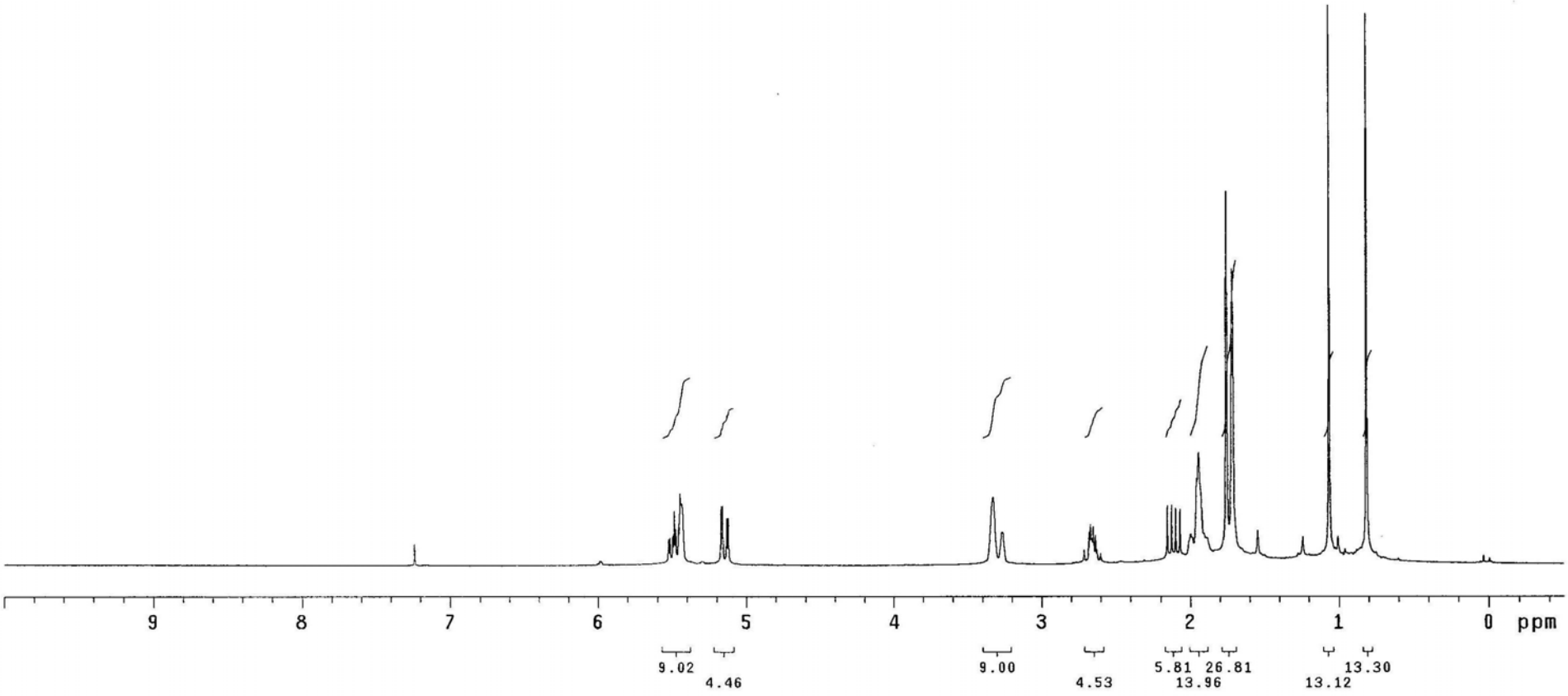
9
8
7
6
5
4
3
2
1
0
ppm
2.82
3.15
2.43
6.61
20.26
18.77
10.00
8.71
27.25

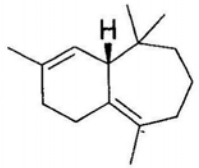


5.524
5.514
5.494
5.485
5.476
5.456
5.446
5.436
5.171
5.160
5.133
5.122

3.328
3.268
2.679
2.670
2.651
2.635
2.155
2.126
2.099
2.069
1.997
1.987
1.956
1.945
1.888
1.756
1.719

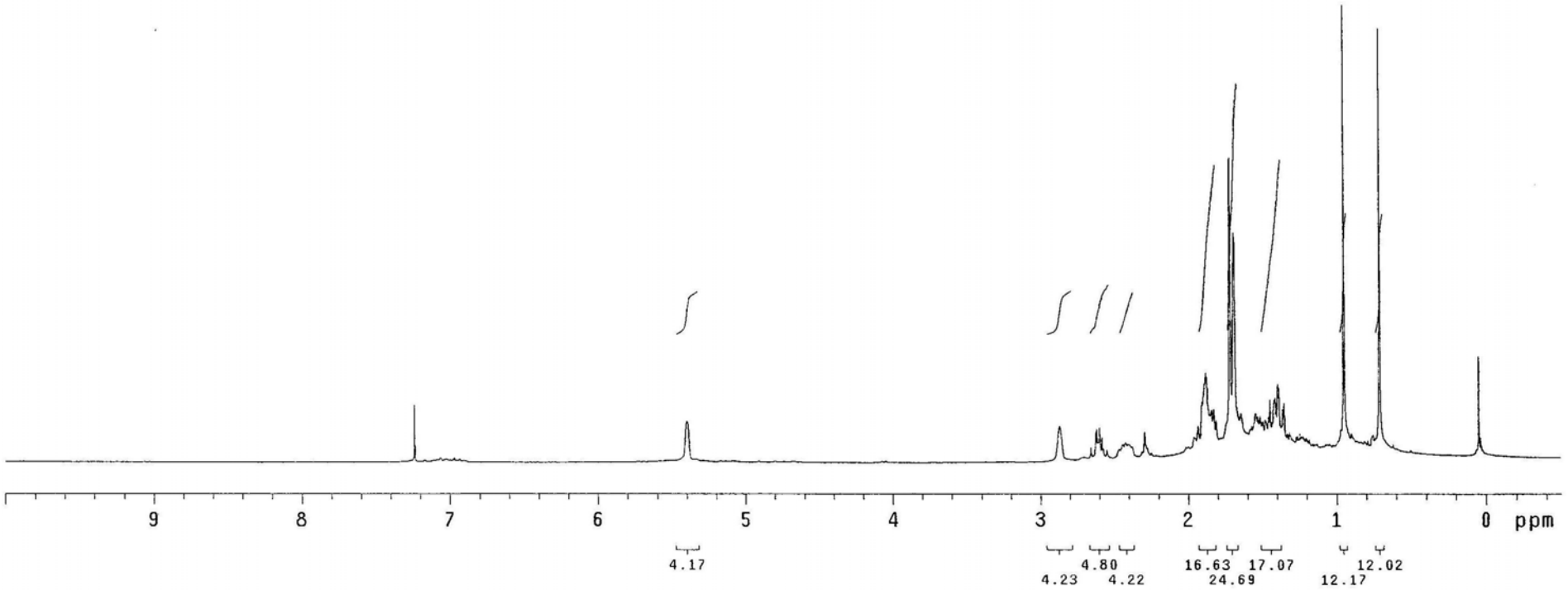
1.066
0.815

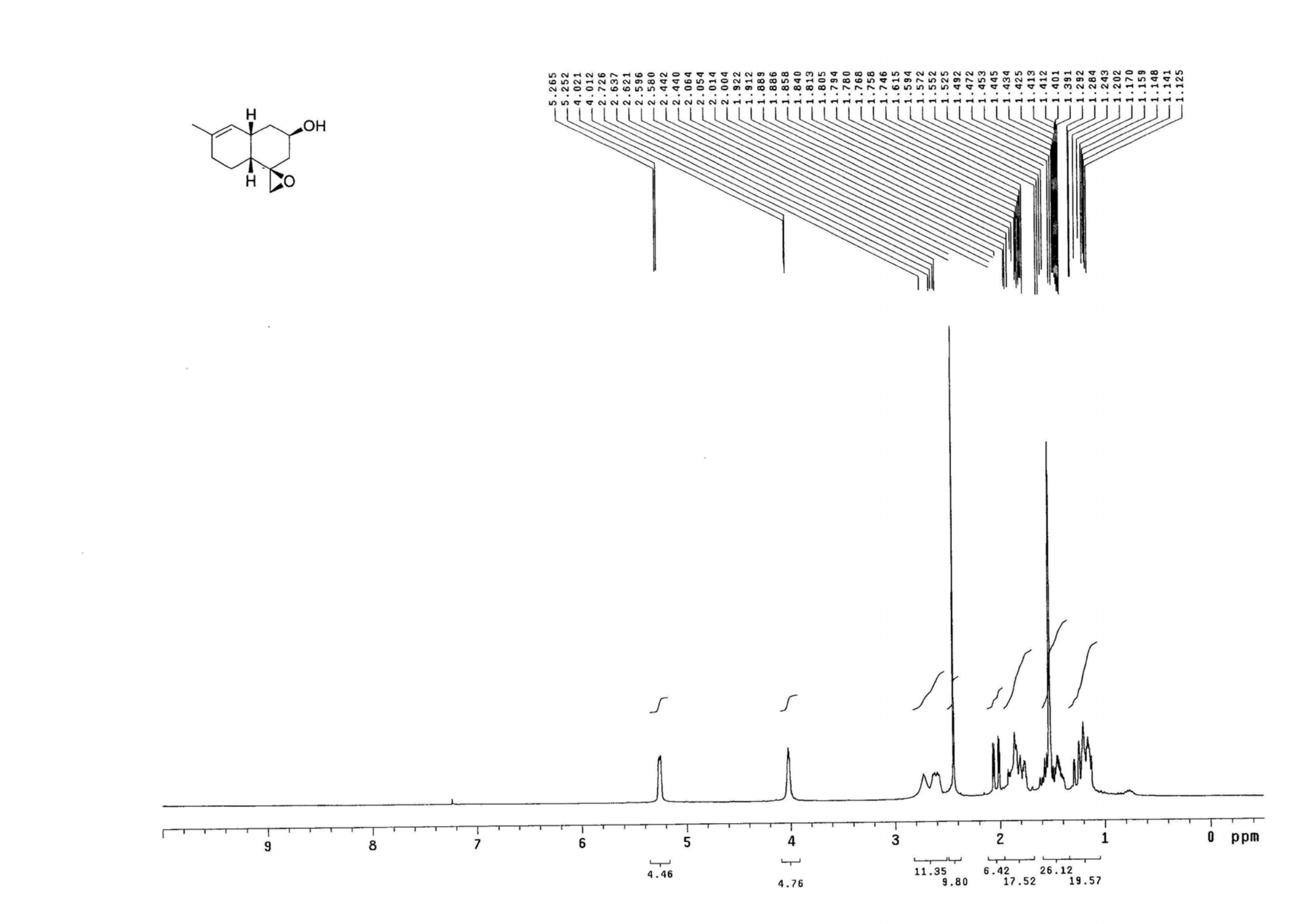


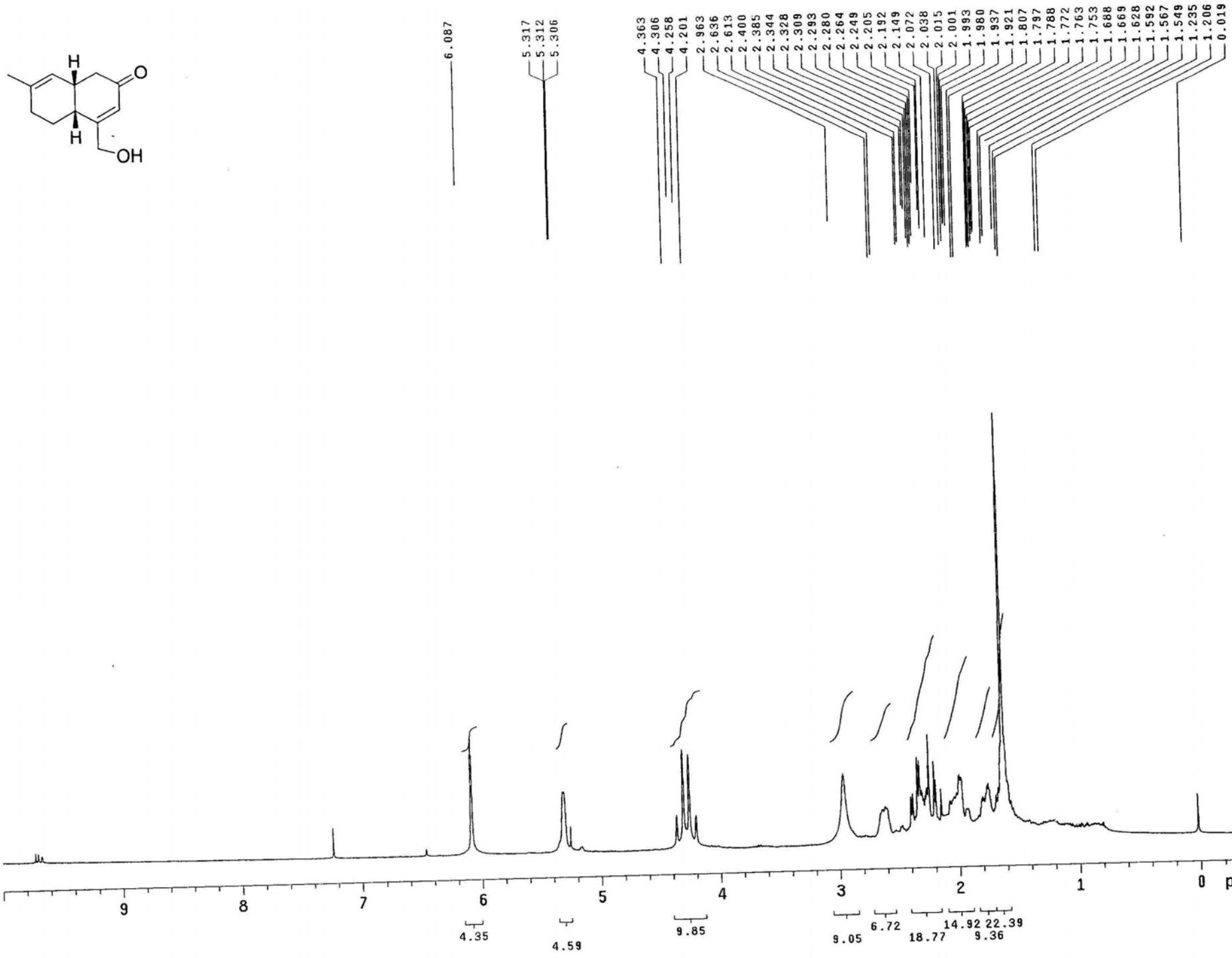


(+)β-himachalene

7.240
5.404
5.399
2.870
2.598
2.582
2.422
2.293
1.954
1.934
1.908
1.891
1.883
1.877
1.867
1.859
1.844
1.829
1.811
1.782
1.720
1.693
1.646
1.605
1.584
1.574
1.550
1.543
1.532
1.527
1.515
1.496
1.482
1.477
1.470
1.459
1.448
1.439
1.434
1.423
1.413
1.406
1.396
1.389
1.376
1.371
1.368
1.361
1.354
0.953
0.714




H
OH
H
O
5.265
5.252
4.021
4.012
2.726
2.637
2.621
2.596
2.580
2.442
2.440
2.064
2.054
2.014
2.004
1.922
1.912
1.889
1.886
1.858
1.840
1.813
1.805
1.794
1.780
1.768
1.758
1.746
1.615
1.594
1.572
1.552
1.525
1.492
1.472
1.453
1.445
1.434
1.425
1.413
1.412
1.401
1.391
1.292
1.284
1.243
1.202
1.170
1.159
1.148
1.141
1.125
9
8
7
6
5
4
3
2
1
0 ppm
4.46
4.76
11.35
9.80
6.42
17.52
26.12
19.57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O
H
OH
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4.306
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2.613
2.400
2.385
2.344
2.328
2.309
2.293
2.280
2.264
2.249
2.205
2.192
2.149
2.072
2.038
2.015
2.001
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1.980
1.937
1.921
1.807
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1.688
1.669
1.628
1.592
1.567
1.549
1.235
1.206
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9
8
7
6
5
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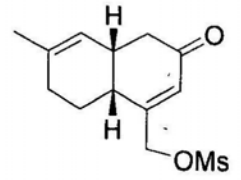
22.39


H
O
H
OMs

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2.473
2.458
2.416
2.401
2.382
2.369
2.293
2.249
2.236
2.192
2.115
2.081
2.025
1.986
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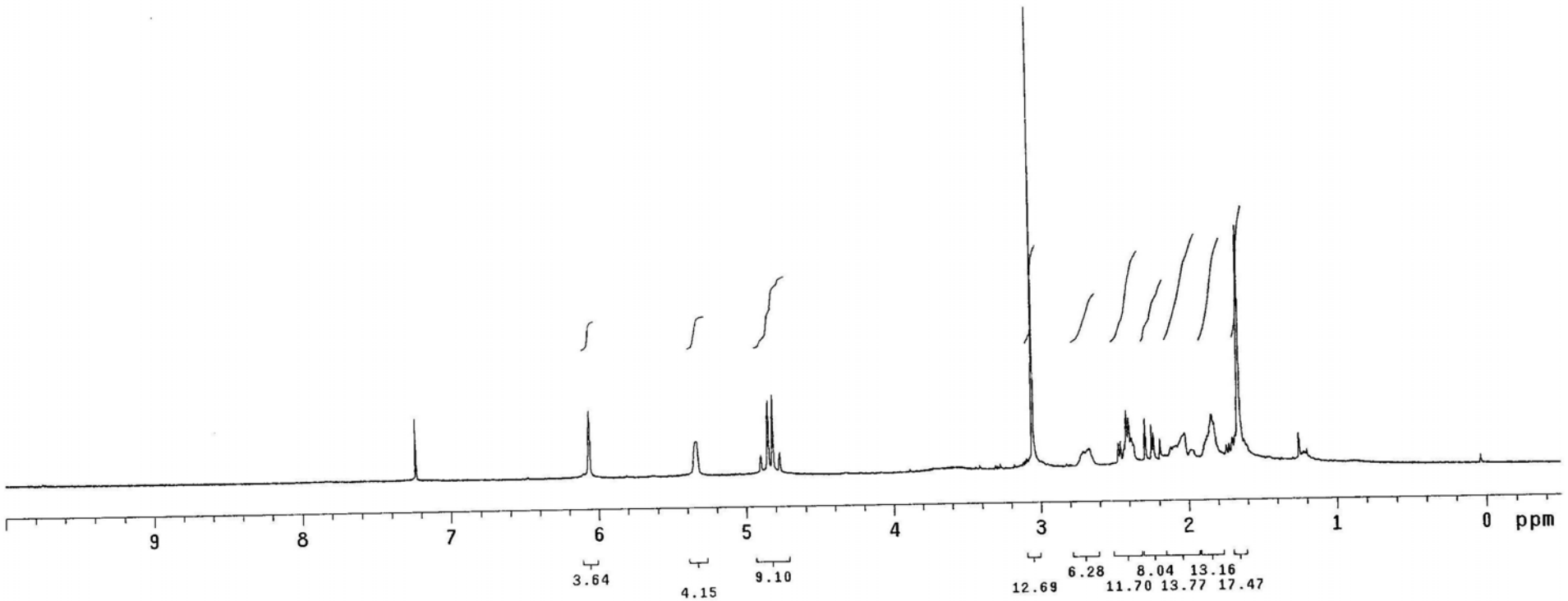
1.254


9
8
7
6
5
4
3
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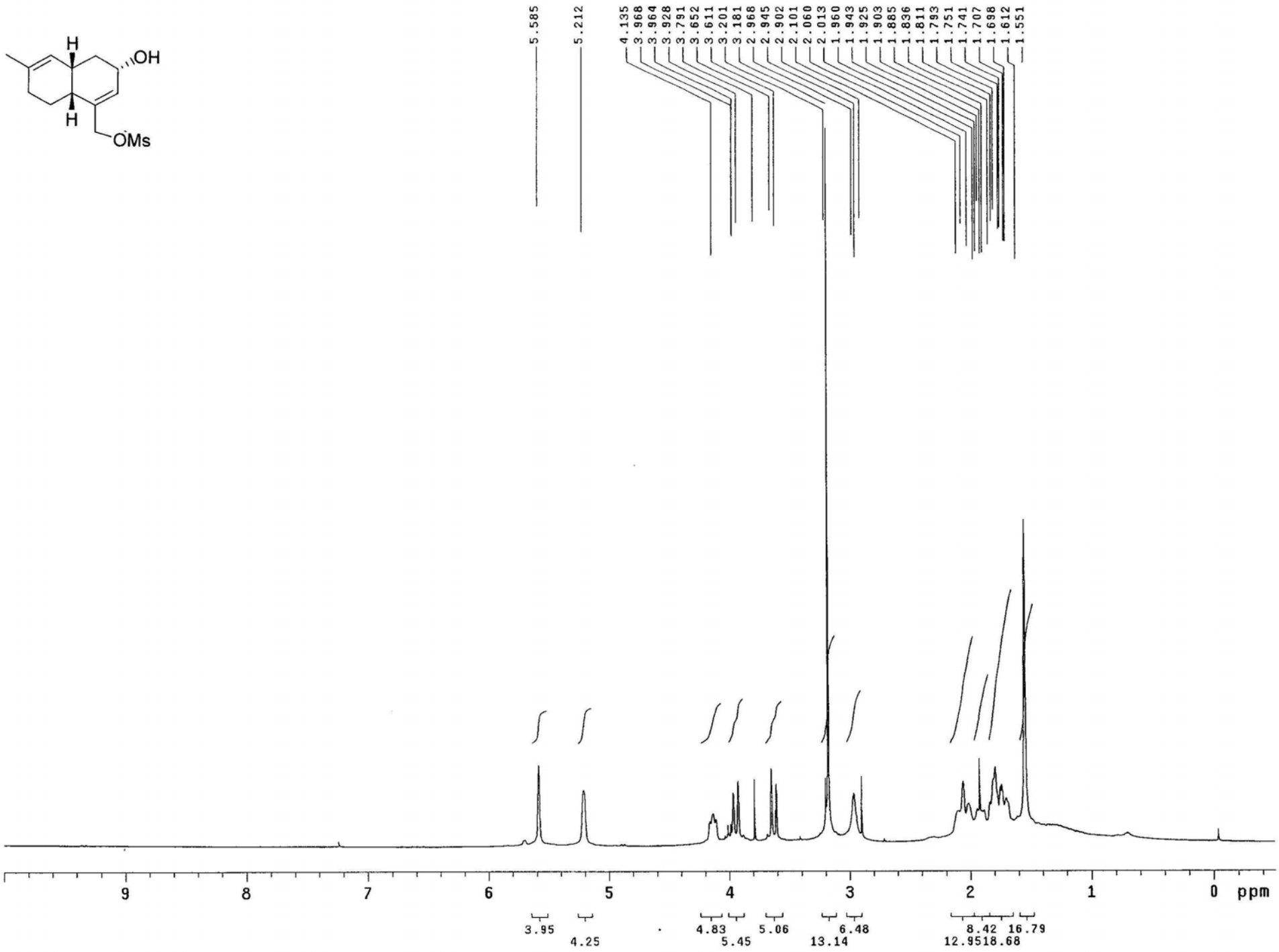
8.04
11.70
13.16
13.77
17.47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OH
H
OMs
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4.135
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3.201
3.181
2.968
2.945
2.902
2.101
2.060
2.013
1.960
1.943
1.925
1.903
1.885
1.836
1.811
1.793
1.751
1.741
1.707
1.698
1.612
1.551
9
8
7
6
5
4
3
2
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13.14
6.48
8.42
12.95
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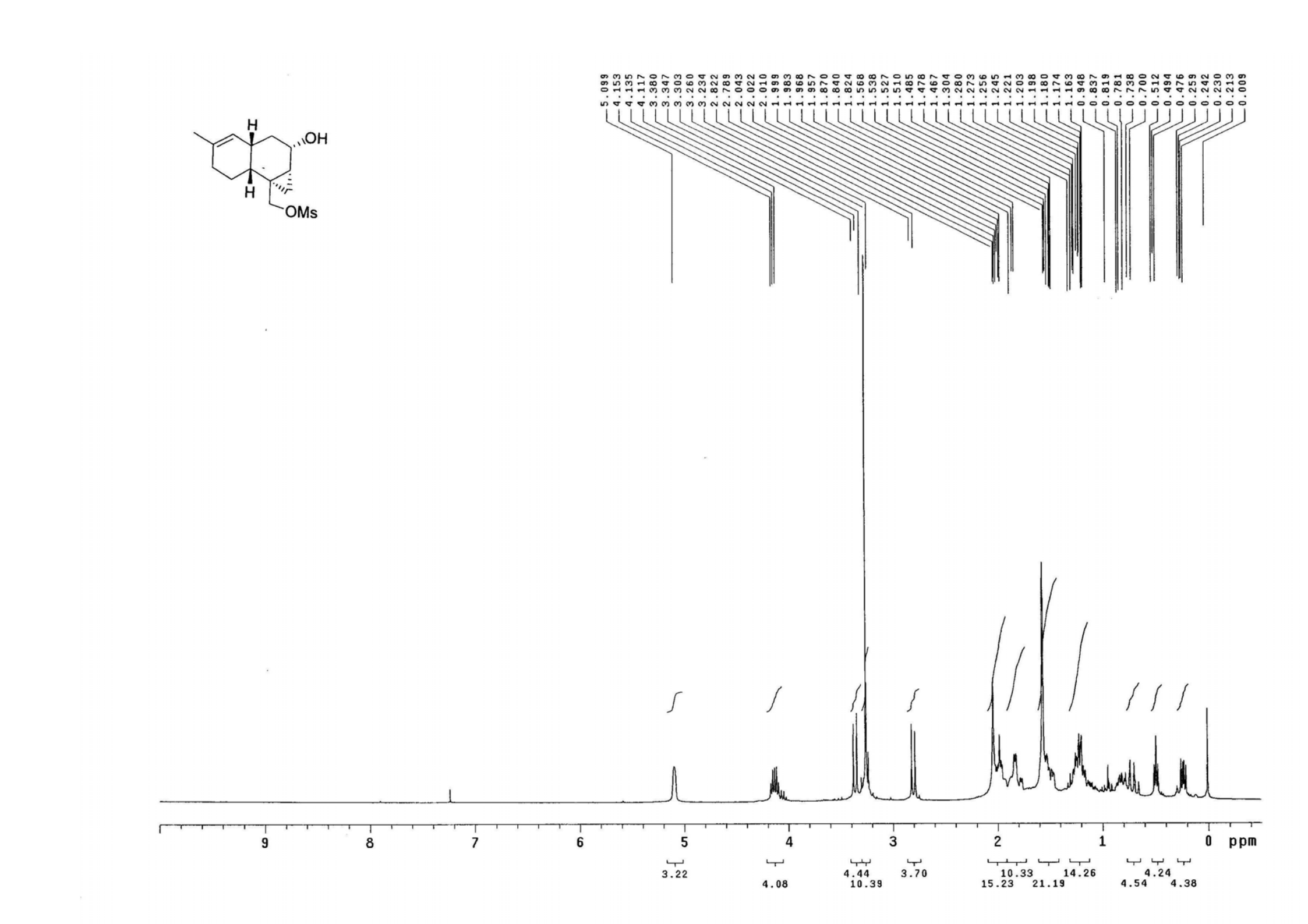
18.68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OH
H
OMs
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3.260
3.234
2.822
2.789
2.043
2.022
2.010
1.999
1.983
1.968
1.957
1.870
1.840
1.824
1.568
1.538
1.527
1.510
1.485
1.478
1.467
1.304
1.280
1.273
1.256
1.245
1.221
1.203
1.198
1.180
1.174
1.163
0.948
0.837
0.819
0.781
0.738
0.700
0.512
0.494
0.476
0.259
0.242
0.230
0.213
0.009
9
8
7
6
5
4
3
2
1
0
ppm
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10.39
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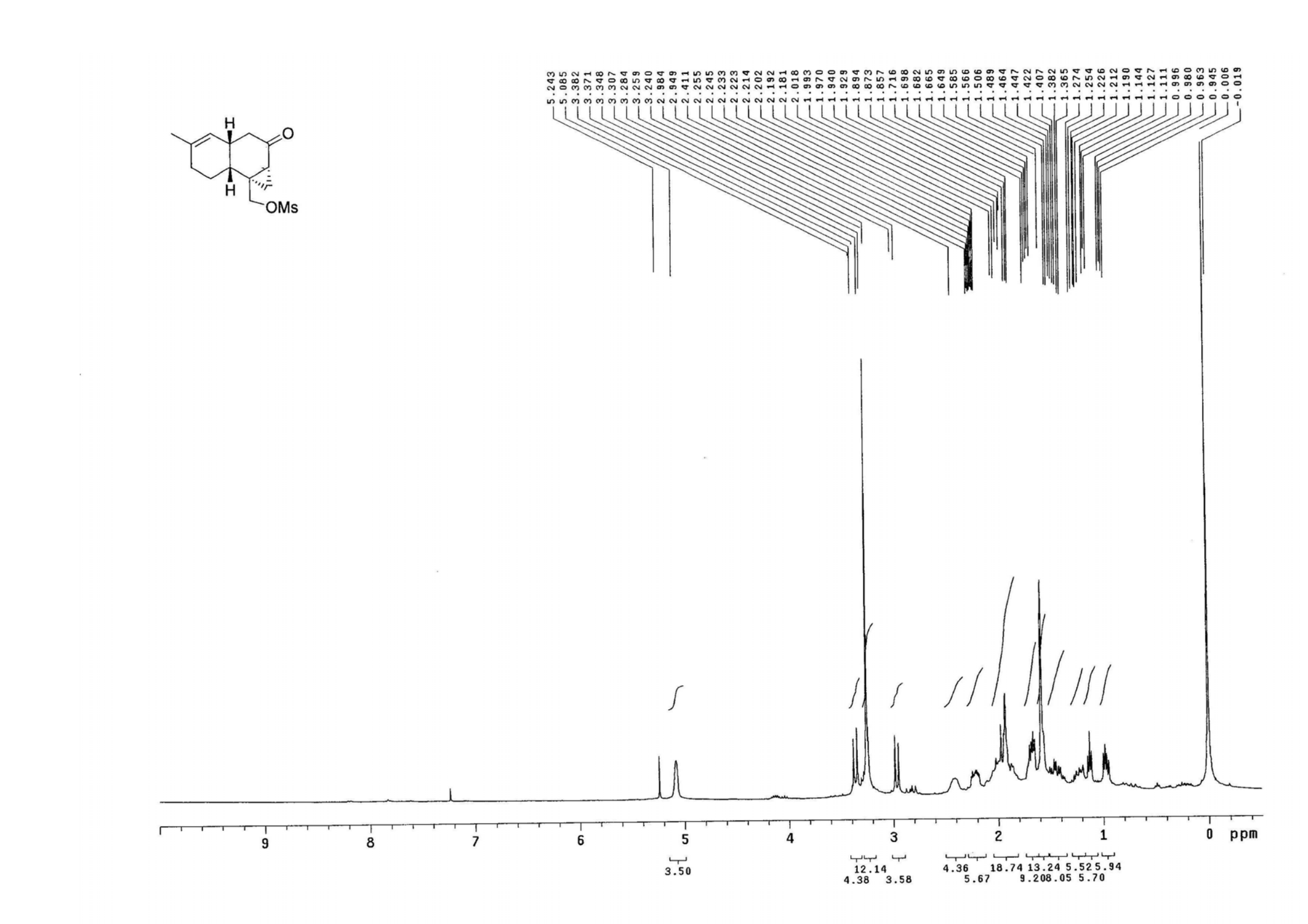
14.26
21.19
4.24
4.54
4.38


H
O
H
OMs
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2.949
2.411
2.255
2.245
2.233
2.223
2.214
2.202
2.192
2.181
2.018
1.993
1.970
1.940
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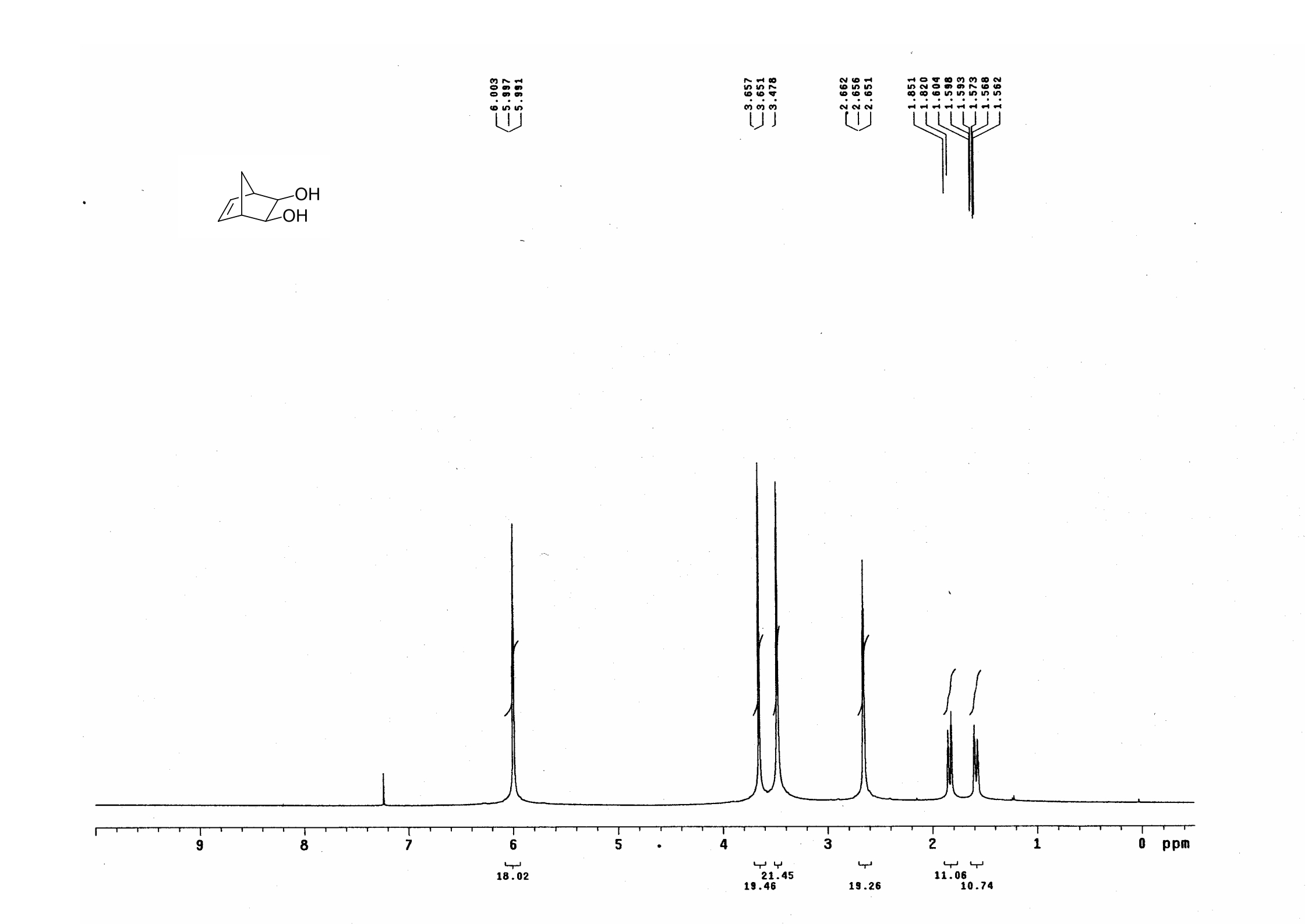
1.894
1.873
1.857
1.716
1.698
1.682
1.665
1.649
1.585
1.566
1.506
1.489
1.464
1.447
1.422
1.407
1.382
1.365
1.274
1.254
1.226
1.212
1.190
1.144
1.127
1.111
0.996
0.980
0.963
0.945
0.006
-0.019
9
8
7
6
5
4
3
2
1
0
ppm
3.50
12.14
4.38
3.58
4.36
5.67
18.74
13.24
9.20
8.05
5.52
5.70
5.94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5.991
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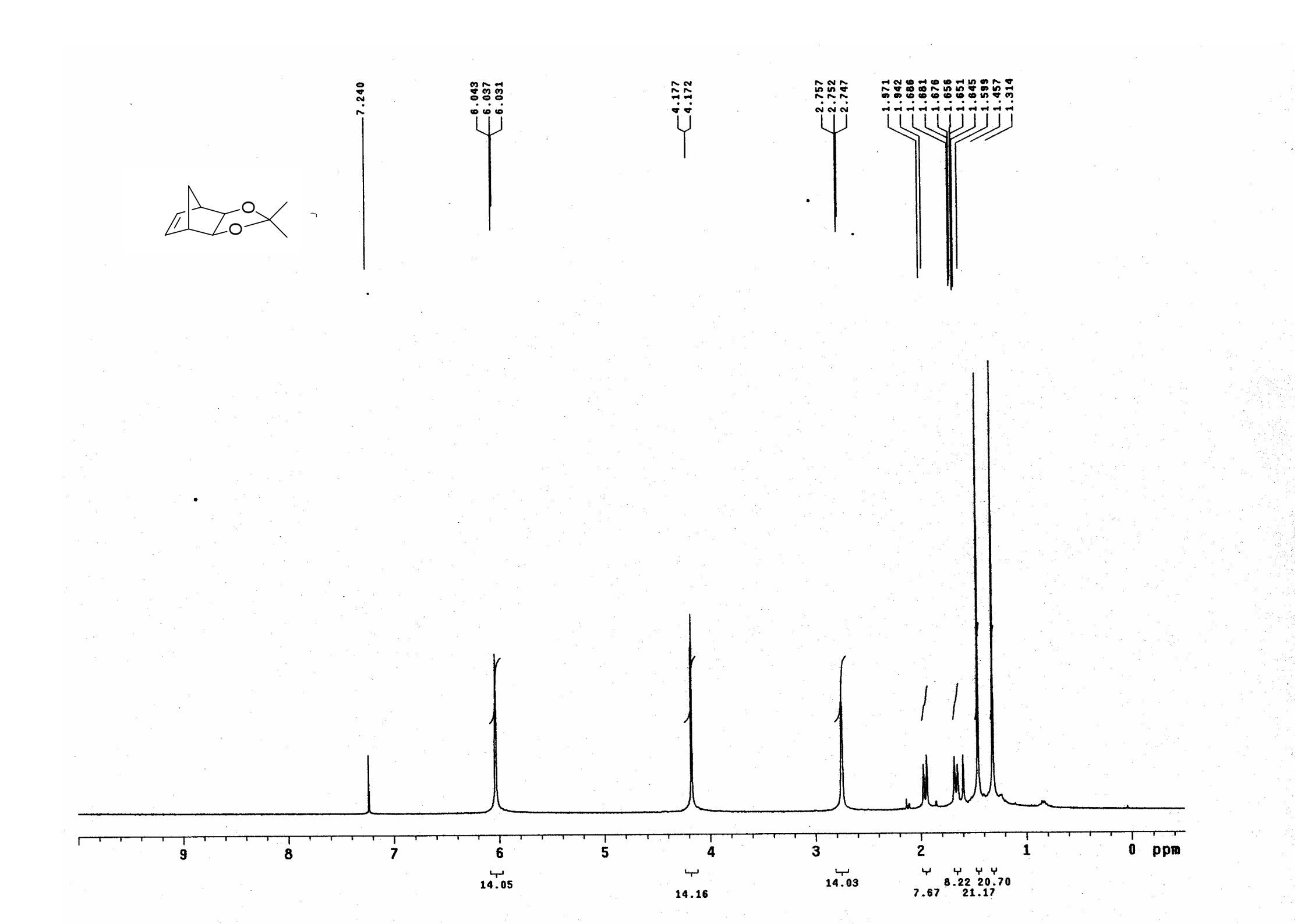
3.478
2.662
2.656
2.651
1.851
1.820
1.604
1.598
1.593
1.573
1.568
1.562
OH
OH
9
8
7
6
5
4
3
2
1
0 ppm
18.02
19.46
21.45
19.26
11.06
10.74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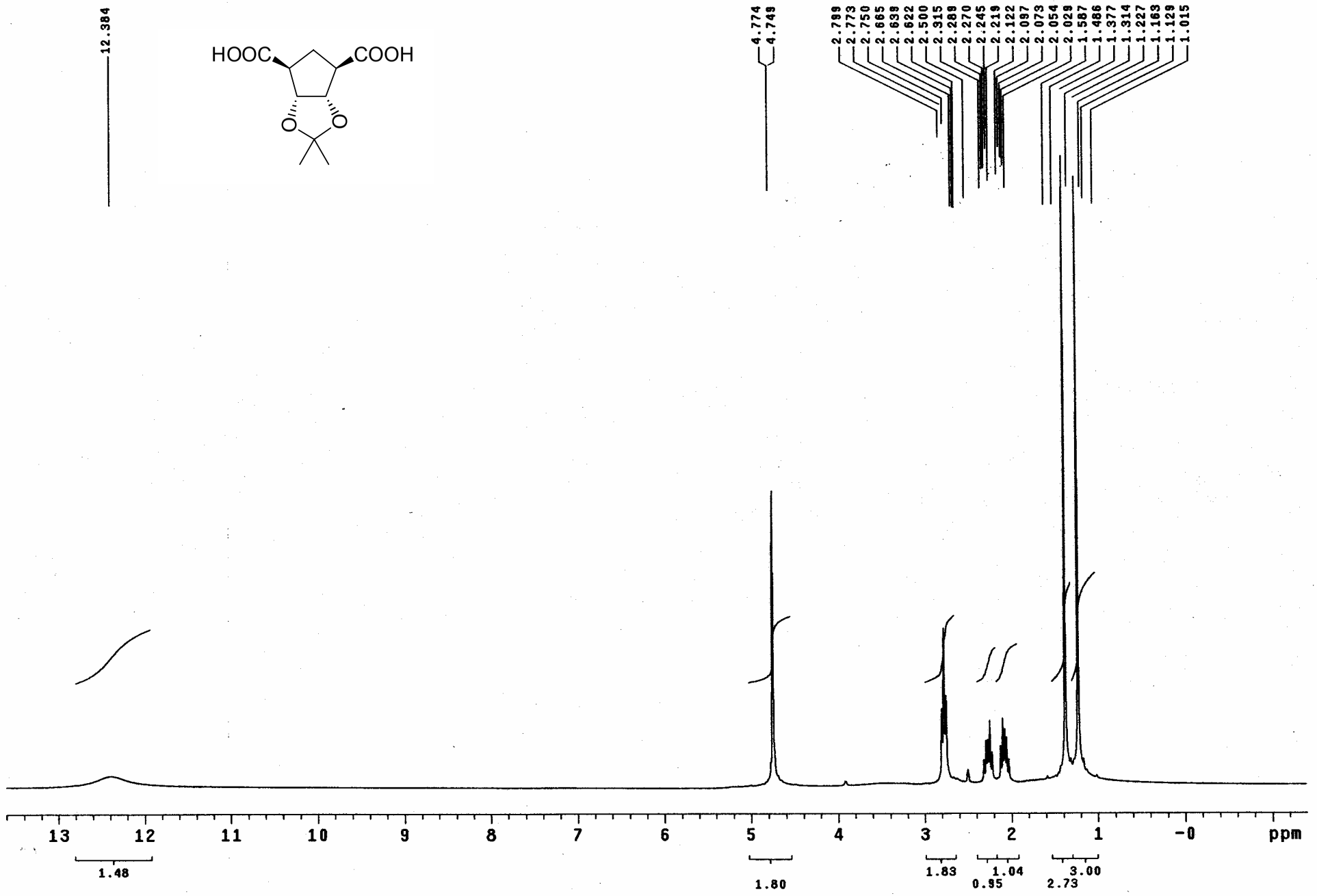
6.043
6.037
6.031
4.177
4.172
2.757
2.752
2.747
1.971
1.942
1.686
1.681
1.676
1.656
1.651
1.645
1.599
1.457
1.314
9
8
7
6
5
4
3
2
1
0 ppm
14.05
14.16
14.03
7.67
8.22
20.70
21.17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HOOC
COOH
O
O
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2.789
2.773
2.750
2.665
2.639
2.622
2.500
2.315
2.288
2.270
2.245
2.219
2.122
2.097
2.073
2.054
2.029
1.587
1.486
1.377
1.314
1.227
1.163
1.129
1.015
13
12
11
10
9
8
7
6
5
4
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2
1
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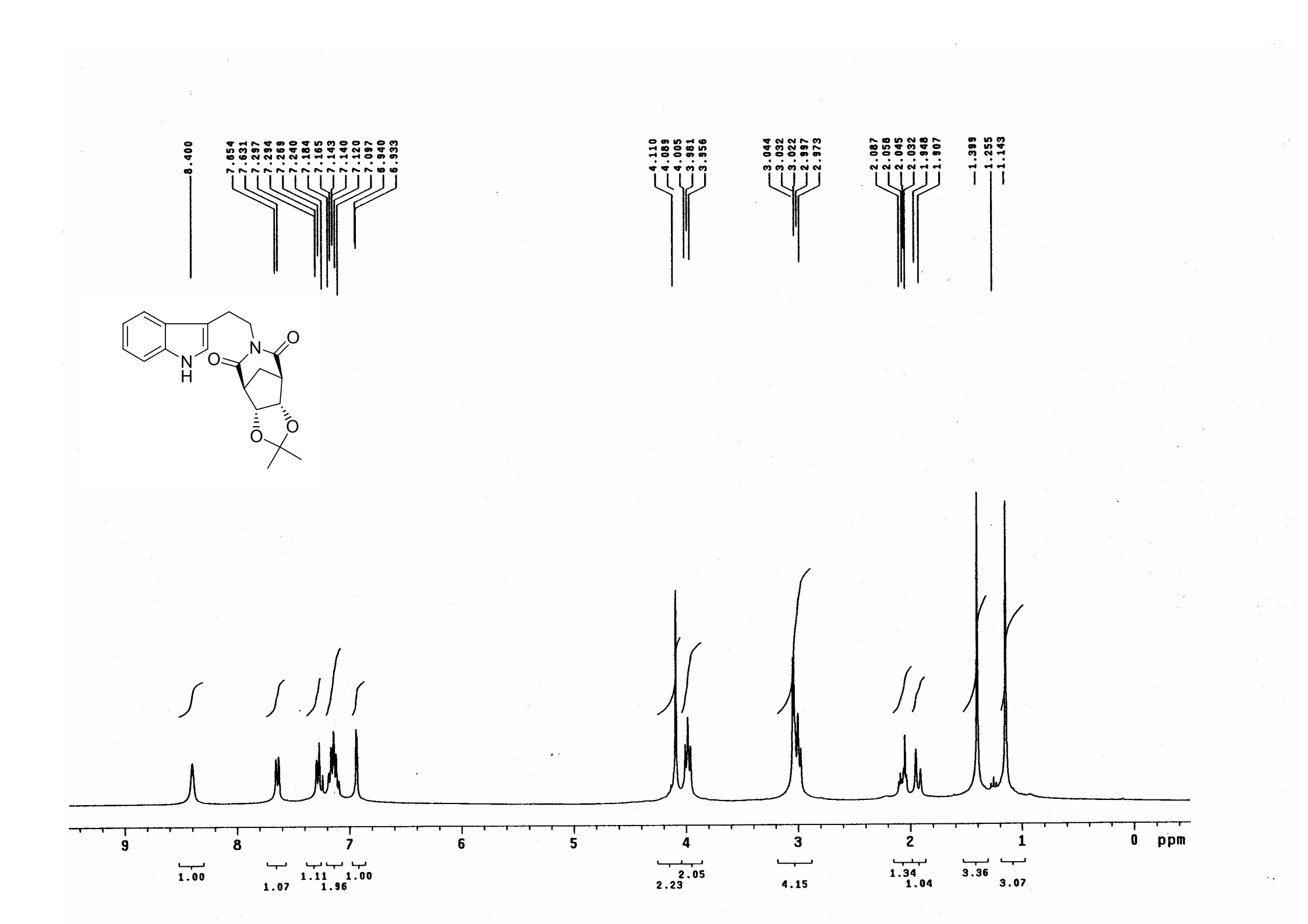
3.00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7.631
7.297
7.294
7.269
7.240
7.184
7.165
7.143
7.140
7.120
7.097
6.940
6.933
4.110
4.089
4.005
3.981
3.956
3.044
3.032
3.022
2.997
2.973
2.087
2.058
2.045
2.032
1.948
1.907
1.399
1.255
1.143
N
H
O
N
O
O
O
9
8
7
6
5
4
3
2
1
0
ppm
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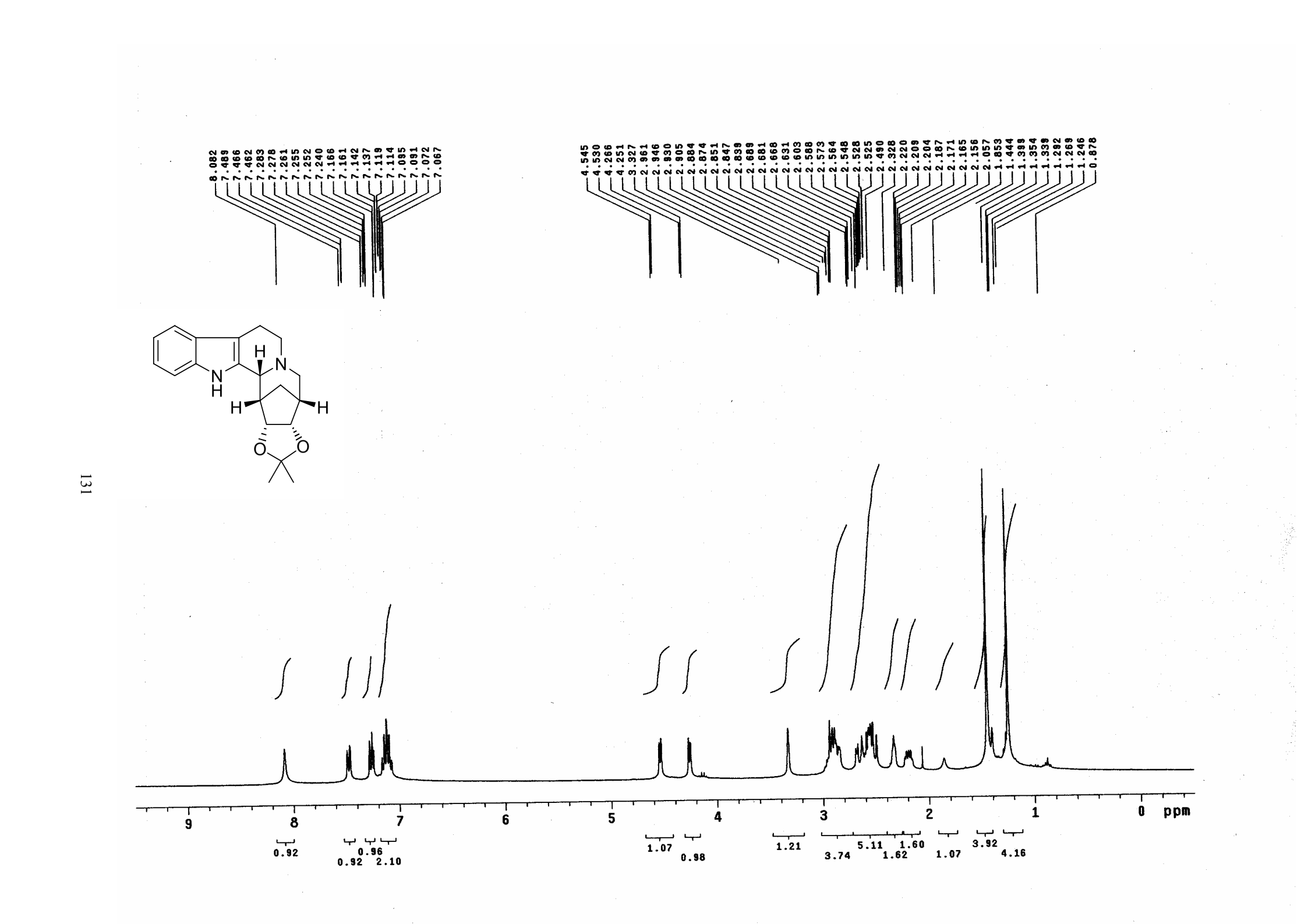
1.11
1.96
1.00
2.23
2.05
4.15
1.34
1.04
3.36
3.07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7.261
7.255
7.252
7.240
7.166
7.161
7.142
7.137
7.119
7.114
7.095
7.091
7.072
7.067
4.545
4.530
4.266
4.251
3.327
2.961
2.946
2.930
2.905
2.884
2.874
2.851
2.847
2.839
2.689
2.681
2.668
2.631
2.603
2.588
2.573
2.564
2.548
2.528
2.525
2.490
2.328
2.220
2.209
2.204
2.187
2.171
2.165
2.156
2.057
1.853
1.444
1.389
1.354
1.338
1.282
1.269
1.246
0.878
H
N
N
H
H
H
O
O
9
8
7
6
5
4
3
2
1
0
ppm
0.92
0.92
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0.98
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1.62
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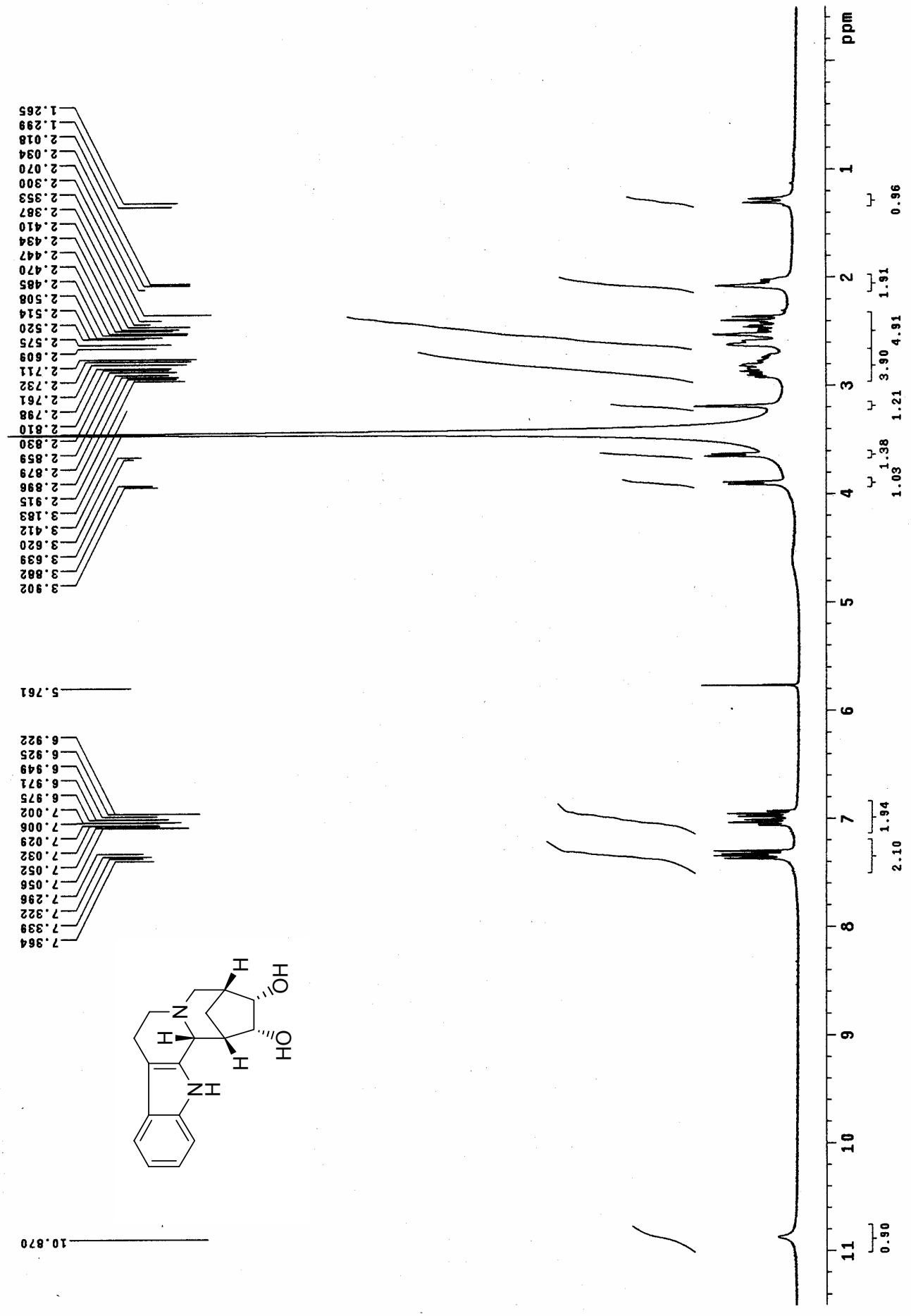
1.07
3.92
4.16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7.032
7.029
7.006
7.002
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6.971
6.949
6.925
6.922
5.761
3.902
3.882
3.639
3.620
3.412
3.183
2.915
2.896
2.879
2.859
2.830
2.810
2.798
2.761
2.732
2.711
2.609
2.575
2.520
2.514
2.508
2.485
2.470
2.447
2.434
2.410
2.387
2.353
2.300
2.070
2.034
2.018
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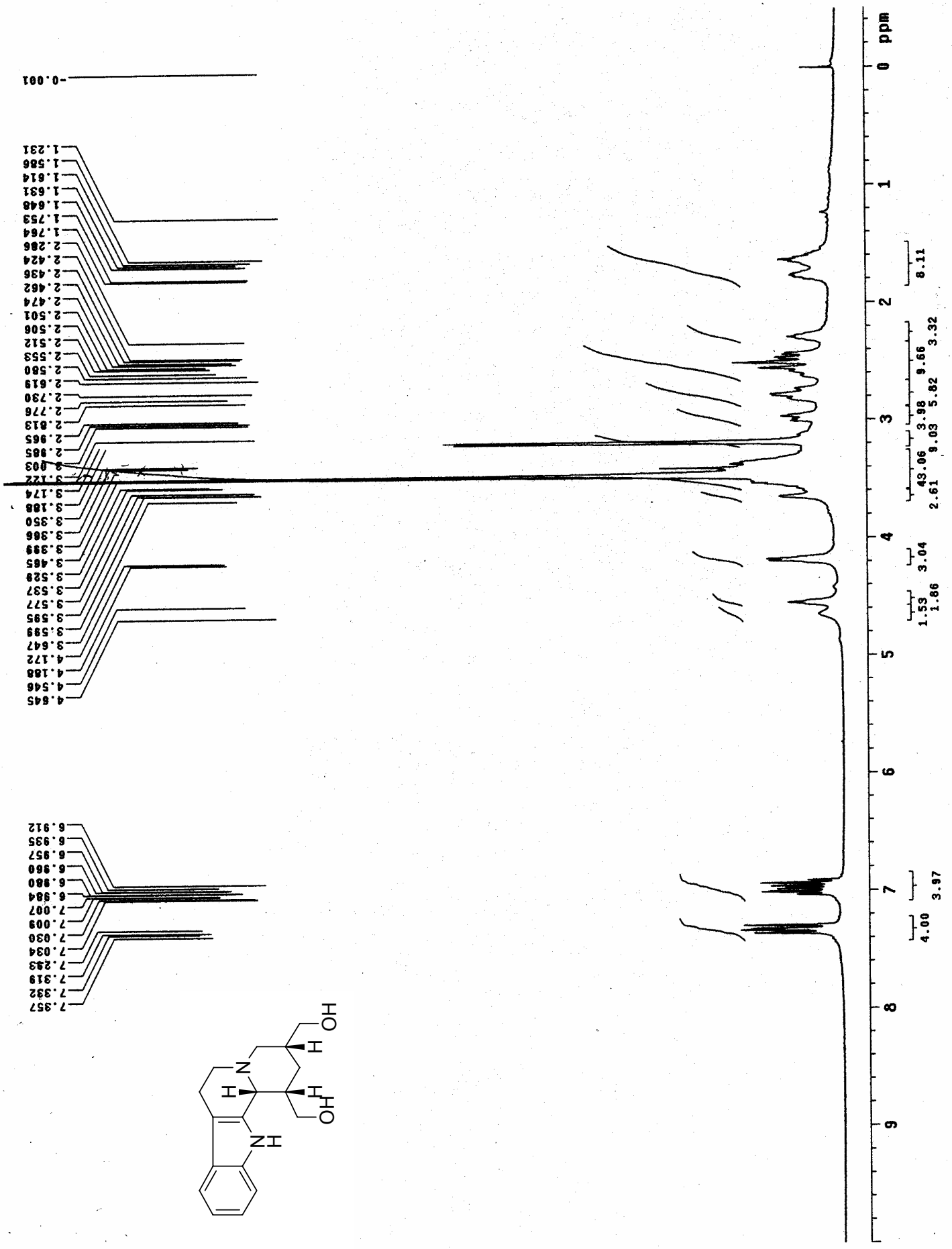
1.91
0.96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2.501
2.506
2.512
2.553
2.580
2.619
2.730
2.776
2.813
2.965
2.985
3.003
3.122
3.174
3.188
3.350
3.366
3.399
3.465
3.528
3.537
3.577
3.595
3.599
3.647
4.172
4.188
4.546
4.645
6.912
6.935
6.957
6.960
6.980
6.984
7.007
7.009
7.030
7.034
7.233
7.319
7.332
7.357
HO
H
N
H
HO
H
N
0 ppm
1
2
3
4
5
6
7
8
9
8.11
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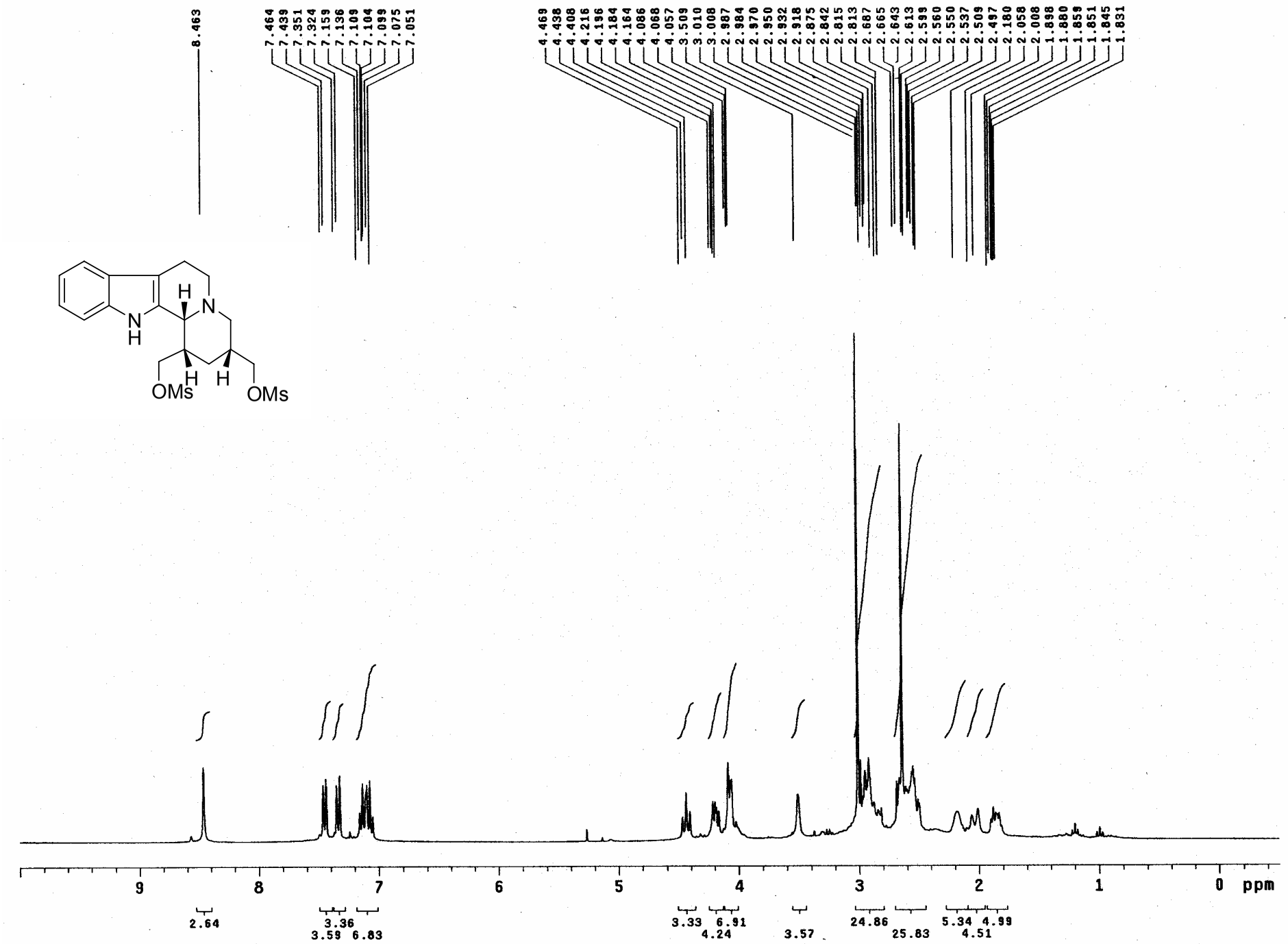
4.00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4.438
4.408
4.216
4.196
4.184
4.164
4.086
4.068
4.057
3.509
3.010
3.008
2.987
2.984
2.970
2.950
2.932
2.918
2.875
2.842
2.815
2.813
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2.665
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2.613
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1.898
1.880
1.859
1.851
1.845
1.831
H
N
N
H
H
H
OMs
OMs
9
8
7
6
5
4
3
2
1
0 ppm
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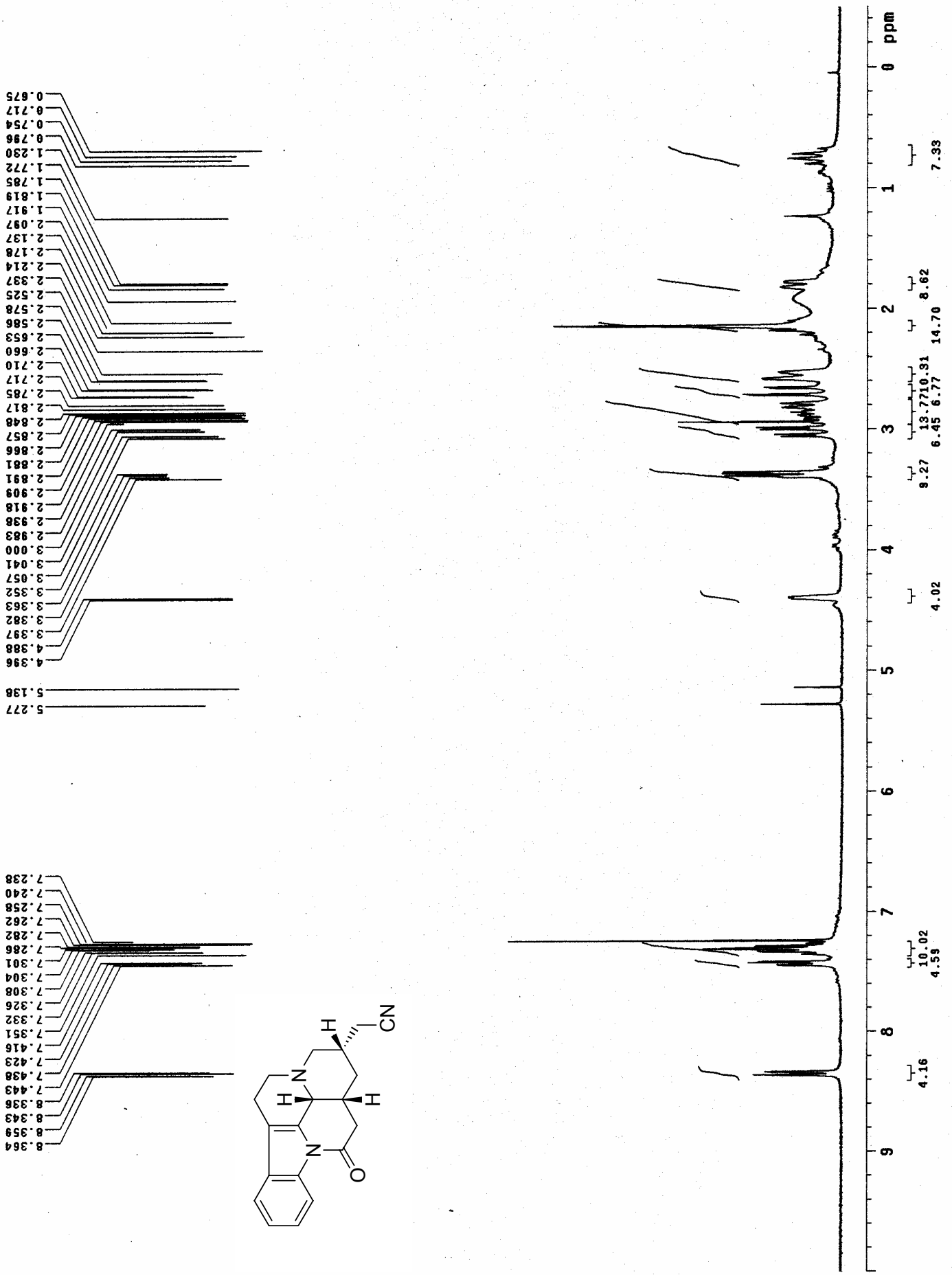
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2.214
2.337
2.525
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2.785
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2.848
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2.983
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7.423
7.438
7.443
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8.343
8.359
8.364
H
CN
N
H
H
N
O
ppm
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1
2
3
4
5
6
7
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9
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4.59
4.02
9.27
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6.45
10.31
6.77
14.70
8.62
7.33