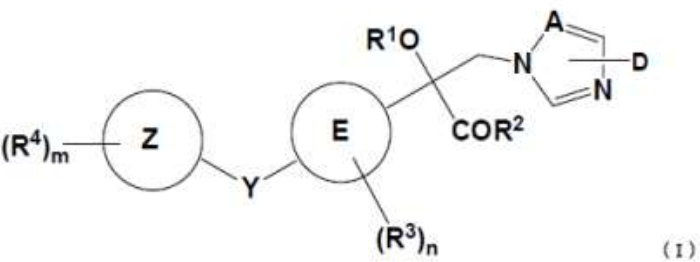
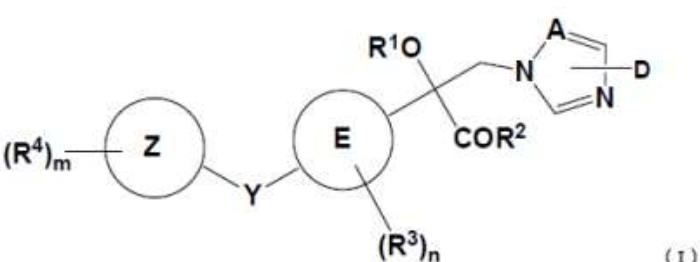


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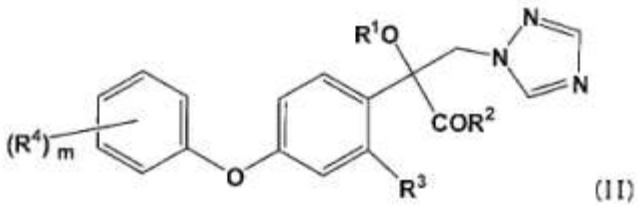
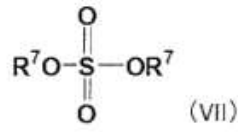
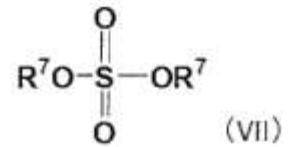
DIRECCIÓN DE NUEVAS CREACIONES
Procedimiento acelerado de exámenes de patente (PPH)

1	NÚMERO DE SOLICITUD ANTE LA SIC		
2	GLOBAL - PPH ☒ PAÍS Japón	3	PCT – PPH ☒ PAÍS Japón
4	PROSUR ☐ PAÍS	5	Alianza del Pacífico (AdP) ☐ PAÍS
6	OFICINA DE PRIMERA PRESENTACIÓN (OPP) ☐	7	OFICINA DE EXAMEN ANTERIOR (OEA) ☒
8	NÚMERO DE SOLICITUD O PUBLICACIÓN DE LA SOLICITUD (OPP) ☐ NÚMERO DE SOLICITUD EN OFICINA DE EXAMEN ANTERIOR (OEA): ☒ NÚMERO DE SOLICITUD PCT: ☒		1. PCT/JP2018/041971
9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
APELLIDOS CARO RAMÍREZ		NOMBRES Claudia Lucia	IDENTIFICACIÓN C.C .40.017.374 T.P .36.448
DIRECCIÓN Calle 94A # 11A - 32		No. TELÉFONO 3004763	
CIUDAD Bogotá		CORREO ELECTRÓNICO claudia.caro@ponsip.com	
PAÍS COLOMBIA		No. RADICACIÓN O PROTOCOLO DE PODER GENERAL NC2020/0002329	
10	CONDICIONES PARA ACCEDER A ESTE PROCESO:		
10.1. DATOS DE PRIORIDAD ☒ SI ☐ NO			
(33) PAÍS DE ORIGEN 1.Japón		CÓDIGO PAÍS JP	(31) NÚMERO 2017-218655 (32) FECHA (AAAA/MM/DD) 13/11/2017
10.2. DATOS SOLICITUD INTERNACIONAL PCT ☒ SI ☐ NO			
Solicitud Internacional No.		PCT/JP2018/041971	Fecha 13/11/2018
Publicación Internacional No.		WO/2019093522	Fecha 16/05/2019
*El solicitante presenta una copia de la(s) reivindicación(es) patentable(s) u otorgable(s) de la solicitud de la Oficina de Primera Presentación que profirió el examen de patentabilidad, junto con una traducción al castellano. ☒ SI ☐ NO			
*El solicitante presenta los resultados de búsqueda de la Oficina de Examen Anterior, junto con una traducción al castellano ☒ SI ☐ NO			
REQUISITOS PARA EL RECONOCIMIENTO DE LOS RESULTADOS DE EXÁMENES DE PATENTABILIDAD EFECTUADOS A SOLICITUDES EXTRANJERAS			
Para que la Superintendencia de Industria y Comercio pueda reconocer los resultados de exámenes de patentabilidad producidos por otras Oficinas de Propiedad Industrial se debe cumplir con las siguientes condiciones:			
(a) Al momento de solicitar el examen de patentabilidad, si el solicitante pide que se reconozcan exámenes de patentabilidad de otras oficinas extranjeras, deberá aportar junto con el pago de la tasa correspondiente, los siguientes anexos:			
(i) Copia de las resoluciones, fallos o decisiones que han sido relevantes para la determinación de la patentabilidad de la(s) solicitud(es) en la Oficina que haya proferido el examen de patentabilidad que contienen reivindicaciones patentables u otorgables que son la base de la petición, y si es del caso, su traducción al castellano. ☒ SI ☐ NO			
(ii) Copia de todas las reivindicaciones determinadas como patentables u otorgables en la Oficina que profirió el examen de patentabilidad y, si es del caso, su traducción al castellano. ☒ SI ☐ NO			
(iii) Copia de los antecedentes, información o documentos citados por el examinador de la Oficina de Primera Presentación del examen de patentabilidad, en las resoluciones, fallos o decisiones correspondientes, incluyendo la literatura no patente. Los documentos de patente deberán presentarse siempre y cuando no estén disponibles para la Superintendencia de Industria y Comercio mediante el simple acceso a bases de datos gratuitas. ☒ SI ☐ NO			
(iv) Una tabla de correspondencias de las reivindicaciones que han sido determinadas como patentables u otorgables en la solicitud de la Oficina que haya proferido el examen de patentabilidad. ☒ SI ☐ NO			
11	FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)		
			
Claudia Lucia Caro Ramirez, Representante Legal			

10 (iv)	TABLA DE CORRESPONDENCIA DE REIVINDICACIONES		
Reivindicaciones en la solicitud en Colombia		Reivindicaciones otorgables en la solicitud internacional	Explicación sobre la suficiente correspondencia ó Comentarios que explican la correspondencia
1. Un compuesto representado por la siguiente Fórmula general (I), o un N-óxido o sal agroquímicamente aceptable de estos: [Fórmula química 1]  [en la Fórmula general (I), A es N o CH; D es un hidrógeno, un grupo halógeno o SR^D; donde R^D es hidrógeno, un grupo ciano, un grupo alquilo C₁-C₆, un grupo haloalquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo haloalquenilo C₂-C₆, un grupo alquinilo C₂-C₆ o un grupo haloalquinilo C₂-C₆; R¹ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo alquinilo C₂-C₆, un grupo cicloalquilo C₃-C₈, un grupo cicloalquilo C₃-C₈- alquilo C₁-C₄, un grupo fenilo, un grupo fenil alquilo C₁-C₄, un grupo fenilalquenilo C₂-C₄, un grupo fenil-alquinilo C₂-C₄ o COXR⁵; donde R⁵ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo alquinilo C₂-C₆, un grupo cicloalquilo C₃-C₈, un grupo cicloalquilo C₃-C₈- alquilo C₁-C₄, un grupo fenilo, un grupo fenil-alquilo C₁-C₄, un grupo fenil-alquenilo C₂-C₄ o un grupo fenil-alquinilo C₂-C₄; X es un enlace simple, -O- o -NR⁶-; R⁶ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo alquinilo C₂-C₆, un grupo cicloalquilo C₃-C₈, un grupo cicloalquilo C₃-C₈-alquilo C₁-C₄, un grupo fenilo, un grupo fenil-alquilo C₁-C₄, un grupo fenil-alquenilo C₂-C₄ o un grupo fenil-alquinilo C₂-C₄; y R⁵ y R⁶ pueden formar un anillo; R² es -OR⁷ o -NR⁸R⁹; R⁷, R⁸ y R⁹ son cada uno independientemente un hidrógeno, un grupo alquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo alquinilo C₂-C₆, un grupo cicloalquilo C₃-C₈, un grupo cicloalquilo C₃-C₈-alquilo C₁-C₄, un grupo fenilo, un grupo fenil-alquilo C₁-C₄, un grupo fenil-alquenilo C₂-C₄ o un grupo fenil-alquinilo C₂-C₄, y R⁸ y R⁹ pueden formar un anillo, donde los grupos alifáticos en R¹, R², R⁵, R⁶, R⁷, R⁸, y R⁹ pueden tener 1, 2, 3 o el número máximo posible de grupos R^a iguales o diferentes,		1. 下記一般式（I）で表される化合物、又はそのN-オキシド若しくは農薬学的に許容可能な塩。 [化1]  [式（I）中、 Aは、N又はCHであり； Dは、水素、ハロゲン基又はSR^Dであり； ここで、R^Dは水素、シアノ基、C₁-C₆-アルキル基、C₁-C₆-ハロアルキル基、C₂-C₆-アルケニル基、C₂-C₆-ハロアルケニル基、C₂-C₆-アルキニル基又はC₂-C₆-ハロアルキニル基であり； R¹は、水素、C₁-C₆-アルキル基、C₂-C₆-アルケニル基、C₂-C₆-アルキニル基、C₃-C₈-シクロアルキル基、C₃-C₈-シクロアルキル-C₁-C₄-アルキル基、フェニル基、フェニル-C₁-C₄-アルキル基、フェニル-C₂-C₄-アルケニル基、フェニル-C₂-C₄-アルキニル基又はCOXR⁵であり； ここで、R⁵は、水素、C₁-C₆-アルキル基、C₂-C₆-アルケニル基、C₂-C₆-アルキニル基、C₃-C₈-シクロアルキル基、C₃-C₈-シクロアルキル-C₁-C₄-アルキル基、フェニル基、フェニル-C₁-C₄-アルキル基、フェニル-C₂-C₄-アルケニル基又はフェニル-C₂-C₄-アルキニル基であり； Xは、単結合、-O-又は-NR⁶-であり； R⁶は、水素、C₁-C₆-アルキル基、C₂-C₆-アルケニル基、C₂-C₆-アルキニル基、C₃-C₈-シクロアルキル基、C₃-C₈-シクロアルキル-C₁-C₄-アルキル基、フェニル基、フェニル-C₁-C₄-アルキル基、フェニル-C₂-C₄-アルケニル基又はフェニル-C₂-C₄-アルキニル基であり、R⁵とR⁶とは環を形成していてもよく； R²は、-OR⁷又は-NR⁸R⁹であり； R⁷、R⁸及びR⁹は、それぞれ独立に、水素、C₁-C₆-アル	Son lo mismo

y R^a se selecciona independientemente de un grupo halógeno, un grupo ciano, un grupo nitro, un grupo alcoxi C_1-C_4, y un grupo haloalcoxi C_1-C_4; R^4 es un grupo halógeno, un grupo ciano, un grupo nitro, un grupo amino, un grupo fenilo, un grupo fenil-oxi, un grupo alquilo C_1-C_4, un grupo haloalquilo C_1-C_4, un grupo alcoxi C_1-C_4, un grupo haloalcoxi C_1-C_4, un grupo alquilamino C_1-C_4, un grupo dialquilamino C_1-C_4, un grupo alquilacilamino C_1-C_4, $-SOR^{10}$ o $-SF_5$; las partes del grupo cicloalquilo o del grupo fenilo en R^1, R^2, R^5, R^6, R^7, R^8 y R^9 o la parte del grupo fenilo en R^4 pueden tener 1, 2, 3, 4, 5, o el número máximo posible de grupos R^b iguales o diferentes, y R^b se selecciona independientemente de un grupo halógeno, un grupo ciano, un grupo nitro, un grupo alquilo C_1-C_4, un grupo alcoxi C_1-C_4, un grupo haloalquilo C_1-C_4 y un grupo haloalcoxi C_1-C_4; R^3 es un grupo halógeno, un grupo ciano, un grupo nitro, un grupo fenilo, un grupo fenil-oxi, un grupo alquilo C_1-C_4, un grupo haloalquilo C_1-C_4, un grupo alcoxi C_1-C_4, un grupo haloalcoxi C_1-C_4, $-SOR^{10}$ o $-SF_5$; donde R^{10} es un grupo alquilo C_1-C_4 o un grupo haloalquilo C_1-C_4; E es un grupo fenilo o un anillo heteroaromático de 6 miembros que contiene 1 o 2 átomos de N; R^3 de n se unen a cualquier sitio de sustitución; cuando E es un grupo fenilo, entonces n es 0, 1, 2, 3 o 4 y cuando E es un anillo heteroaromático de 6 miembros que contiene 1 o 2 átomos de N, entonces n es 0, 1 o 2; Y es un átomo de oxígeno, $-CH_2O-$, $-OCH_2-$, $-NH-$, $-N(-alquilo\ C_1-C_4)$, $-N(-cicloalquilo\ C_3-C_6)-$ o $-S(O)_p-$, que se une a cualquier sitio de E; donde p es 0, 1 o 2; Z es un grupo hidrocarburo aromático que es un grupo fenilo o un grupo naftilo, o un anillo heteroaromático de 5 miembros o 6 miembros o un anillo heteroaromático de 9 miembros o 10 miembros formado por 2 anillos, que contienen de 1 a 4 heteroátomos seleccionados de O, N y S; y R^4 de m se unen a cualquier sitio de sustitución; cuando Z es un grupo hidrocarburo aromático, entonces m es 1, 2, 3, 4, o 5 y cuando Z es un anillo heteroaromático, entonces m es 0, 1, 2, 3, o 4].	キル基、C_2-C_6-アルケニル基、C_2-C_6-アルキニル基、C_3-C_8-シクロアルキル基、C_3-C_8-シクロアルキル-C_1-C_4-アルキル基、フェニル基、フェニル-C_1-C_4-アルキル基、フェニル-C_2-C_4-アルケニル基又はフェニル-C_2-C_4-アルキニル基であり、R^8とR^9とは環を形成していてもよく； ここで、R^1、R^2、R^5、R^6、R^7、R^8及びR^9における脂肪族基は、1、2、3若しくは可能な最大数の同一の又は異なる基 R^aを有していてもよく、R^aは、ハロゲン基、シアノ基、ニトロ基、C_1-C_4-アルコキシ基及びC_1-C_4-ハロアルコキシ基から互いに独立して選択され； R^4は、ハロゲン基、シアノ基、ニトロ基、アミノ基、フェニル基、フェニル-オキシ基、C_1-C_4-アルキル基、C_1-C_4-ハロアルキル基、C_1-C_4-アルコキシ基又はC_1-C_4-ハロアルコキシ基、C_1-C_4-アルキルアミノ基、C_1-C_4-ジアルキルアミノ基、C_1-C_4-アルキルアシルアミノ基、$-SOR^{10}$又は$-SF_5$であり； R^1、R^2、R^5、R^6、R^7、R^8及びR^9におけるシクロアルキル基若しくはフェニル基部分又はR^4におけるフェニル基部分は、1、2、3、4、5若しくは可能な最大数の同一の又は異なる基 R^bを有していてもよく、R^bは、ハロゲン基、シアノ基、ニトロ基、C_1-C_4-アルキル基、C_1-C_4-アルコキシ基、C_1-C_4-ハロアルキル基及びC_1-C_4-ハロアルコキシ基から互いに独立して選択され； R^3は、ハロゲン基、シアノ基、ニトロ基、フェニル基、フェニル-オキシ基、C_1-C_4-アルキル基、C_1-C_4-ハロアルキル基、C_1-C_4-アルコキシ基、C_1-C_4-ハロアルコキシ基、$-SOR^{10}$又は$-SF_5$であり； ここで、R^{10}は、C_1-C_4-アルキル基又はC_1-C_4-ハロアルキル基であり； Eは、フェニル基又はN原子を1若しくは2つ含む6員の芳香族複素環であり； R^3は任意の置換位置にn個結合しており； Eがフェニル基の場合、nは0、1、2、3又は4であり、EがN原子を1若しくは2つ含む6員の芳香族複素環である場合は、nは0、1又は2であり； Yは、Eの任意の位置に接続する酸素原子、$-CH_2O-$、$-OCH_2-$、$-NH-$、$-N(-C_1-C_4-アルキル)-$、$-N(-C_3-C_8-シクロアルキル)-$又は$-S(O)_p-$であり； pは、0、1又は2であり； Zは、フェニル基若しくはナフチル基である芳香族炭化水素基、又は、O、N若しくはSから選択されるヘテロ原子を1～4つ含む5員又は6員の芳香族複素環若しくは2環から構成される9員又は10員の芳香族複素環であり； R^4は任意の置換位置にm個結合しており；	
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	Zが芳香族炭化水素基である場合、mは1、2、3、4又は5であり、Zが芳香族複素環である場合、mは0、1、2、3又は4である]	
2. El compuesto o la sal de este de acuerdo con la reivindicación 1, en donde en la Fórmula general (I), R^1 es un hidrógeno, un grupo alquilo C_1-C_6, un grupo alquenilo C_2-C_6, un grupo alquinilo C_2-C_6 o $COXR^5$; R^2 es $-OR^7$; R^5 es un hidrógeno, un grupo alquilo C_1-C_6, un grupo alquenilo C_2-C_6 o un grupo alquinilo C_2-C_6; R^6 es un hidrógeno, un grupo alquilo C_1-C_6, un grupo alquenilo C_2-C_6 o un grupo alquinilo C_2-C_6; R^3 es un grupo halógeno, un grupo ciano, un grupo alquilo C_1-C_4, un grupo haloalquilo C_1-C_4, un grupo alcoxi C_1-C_4, $-SOR^{10}$ o $-SF_5$; y R^4 es un grupo halógeno, un grupo nitro, un grupo ciano, un grupo amino, un grupo alquilo C_1-C_4, un grupo haloalquilo C_1-C_4, un grupo alcoxi C_1-C_4, un grupo haloalcoxi C_1-C_4, un grupo alquilamino C_1-C_4, un grupo dialquilamino C_1-C_4, un grupo alquilacilamino C_1-C_4, $-SOR^{10}$ o $-SF_5$.	2. 上記一般式 (I) において、 R^1が、水素、C_1-C_6ーアルキル基、C_2-C_6ーアルケニル基、C_2-C_6ーアルキニル基又は$COXR^5$であり； R^2が、$-OR^7$であり； R^5が、水素、C_1-C_6ーアルキル基、C_2-C_6ーアルケニル基又はC_2-C_6ーアルキニル基であり； R^6が、水素、C_1-C_6ーアルキル基、C_2-C_6ーアルケニル基又はC_2-C_6ーアルキニル基である、 R^3が、ハロゲン基、シアノ基、C_1-C_4ーアルキル基、C_1-C_4ーハロアルキル基、C_1-C_4ーアルコキシ基、$-SOR^{10}$又は$-SF_5$であり； R^4が、ハロゲン基、ニトロ基、シアノ基、アミノ基、C_1-C_4ーアルキル基、C_1-C_4ーハロアルキル基、C_1-C_4ーアルコキシ基、C_1-C_4ーハロアルコキシ基、C_1-C_4ーアルキルアミノ基、C_1-C_4ージアルキルアミノ基、C_1-C_4ーアルキルシルアミノ基、$-SOR^{10}$又は$-SF_5$である、 請求項 1 に記載の化合物又はその塩。	<u>Son lo mismo</u>
3. El compuesto o la sal de este de acuerdo con la reivindicación 1 o 2, en donde en la Fórmula general (I), R^1 es un hidrógeno, un grupo alquilo C_1-C_6 o $COXR^5$; R^5 es un hidrógeno, o un grupo alquilo C_1-C_6; R^6 es un hidrógeno; R^3 es un grupo halógeno, un grupo ciano, un grupo alquilo C_1-C_4, un grupo haloalquilo C_1-C_4, un grupo alcoxi C_1-C_4, $-SOR^{10}$ o $-SF_5$; y R^4 es un grupo halógeno, un grupo nitro, un grupo ciano, un grupo amino, un grupo alquilo C_1-C_4, un grupo haloalquilo C_1-C_4, un grupo alcoxi C_1-C_4, un grupo haloalcoxi C_1-C_4, un grupo alquilamino C_1-C_4, un grupo dialquilamino C_1-C_4, un grupo alquilacilamino C_1-C_4, $-SOR^{10}$ o $-SF_5$.	3. 上記一般式 (I) において、 R^1が、水素、C_1-C_6ーアルキル基又は$COXR^5$であり； R^5が、水素又はC_1-C_6ーアルキル基であり； R^6が、水素であり； R^3が、ハロゲン基、シアノ基、C_1-C_4ーアルキル基、C_1-C_4ーハロアルキル基、C_1-C_4ーアルコキシ基、$-SOR^{10}$又は$-SF_5$であり； R^4が、ハロゲン基、ニトロ基、シアノ基、アミノ基、C_1-C_4ーアルキル基、C_1-C_4ーハロアルキル基、C_1-C_4ーアルコキシ基、C_1-C_4ーハロアルコキシ基、C_1-C_4ーアルキルアミノ基、C_1-C_4ージアルキルアミノ基、C_1-C_4ーアルキルシルアミノ基、$-SOR^{10}$又は$-SF_5$である、 請求項 1 又は 2 に記載の化合物又はその塩。	<u>Son lo mismo</u>
4. El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 3, en donde en la Fórmula general (I), R^1 es un hidrógeno, o un grupo alquilo C_1-C_6; R^7 es un grupo alquilo C_1-C_6; R^3 es un grupo halógeno, un grupo ciano, un grupo alquilo C_1-C_4, un grupo haloalquilo C_1-C_4 o un grupo alcoxi C_1-C_4; y R^4 es un grupo halógeno, un grupo ciano, un grupo alquilo C_1-C_4, un grupo haloalquilo C_1-C_4, un grupo alcoxi C_1-C_4 o un grupo haloalcoxi C_1-C_4.	4. 上記一般式 (I) において、 R^1が、水素又はC_1-C_6ーアルキル基であり； R^7が、C_1-C_6ーアルキル基であり； R^3が、ハロゲン基、シアノ基、C_1-C_4ーアルキル基、C_1-C_4ーハロアルキル基又はC_1-C_4ーアルコキシ基であり； R^4が、ハロゲン基、シアノ基、C_1-C_4ーアルキル基、C_1-C_4ーハロアルキル基、C_1-C_4ーアルコキシ基又はC_1-C_4ーハロアルコキシ基である、 請求項 1 から 3 のいずれか 1 項に記載の化合物又はその塩。	<u>Son lo mismo</u>

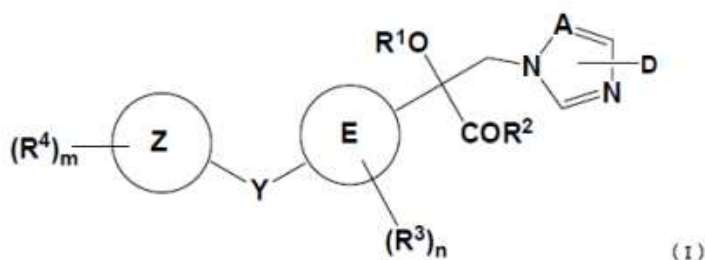
5. El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 4, en donde en la Fórmula general (I), E es un grupo fenilo.	5. 上記一般式（I）において、Eが、フェニル基である、請求項 1 から 4 のいずれか 1 項に記載される化合物又はその塩。	<u>Son lo mismo</u>
6. El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 5, en donde en la Fórmula general (I), Z es un grupo fenilo, un grupo naftilo, o un anillo heteroaromático de 5 miembros o 6 miembros que contiene de 1 a 3 heteroátomos seleccionados de N y S.	6. 上記一般式（I）において、Zが、フェニル基、ナフチル基、又はN及びSから選択されるヘテロ原子を1～3つ含む5員又は6員の芳香族複素環である、請求項 1 から 5 のいずれか 1 項に記載の化合物又はその塩。	<u>Son lo mismo</u>
7. El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 6, en donde en la Fórmula general (I), Z es un grupo fenilo.	7. 上記一般式（I）において、Zがフェニル基である、請求項 1 から 6 のいずれか 1 項に記載の化合物又はその塩。	<u>Son lo mismo</u>
8. El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 7, en donde en la Fórmula general (I), Y es un átomo de oxígeno.	8. 上記一般式（I）において、Yが酸素原子である、請求項 1 から 7 のいずれか 1 項に記載の化合物又はその塩。	<u>Son lo mismo</u>
9. El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 8, en donde en la Fórmula general (I), A es N, y D es un hidrógeno.	9. 上記一般式（I）において、AがNであり、Dが水素である、請求項 1 から 8 のいずれか 1 項に記載の化合物又はその塩。	<u>Son lo mismo</u>
10. El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 9, en donde el compuesto representado por la siguiente Fórmula general (II): [Fórmula química 2]	10. 上記化合物が、下記一般式（II）で表される化合物 [化2] 	<u>Son lo mismo</u>
11. Un método para producir un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 10, representado por la Fórmula general (I) anterior, el método comprende una etapa de convertir un compuesto representado por la siguiente Fórmula general (V) en un compuesto representado por la siguiente Fórmula general (VI) mediante el uso de un sulfato de dialquilo, que está representado por la siguiente Fórmula general (VII), o R7-LG, donde LG es un grupo saliente sustituible nucleofílicamente, y yodo y un carbonato en sulfóxido de dimetilo. [Fórmula química 3]  [Fórmula química 4]	11. 請求項 1 から 10 のいずれか 1 項に記載の上記一般式（I）で表される化合物の製造方法であって、 ジメチルスルホキシド中、下記一般式（VII）で表されるジアルキル硫酸若しくはR7-LG、ここでLGは求核的に置換可能な脱離基であり、ヨウ素及び炭酸塩を用いて、下記一般式（V）で表される化合物を、下記一般式（VI）で表される化合物に変換する工程を含む、化合物の製造方法。 [化3]  [化4]	<u>Son lo mismo</u>

(V) [Fórmula química 5] (VI)	(V) [化5] (VI)	
12. El método de producción de acuerdo con la reivindicación 11, en donde LG en R⁷-LG es un grupo halógeno.	12. R⁷-LGのLGが、ハロゲン基である、請求項 1 1 に記載の製造方法。	<u>Son lo mismo</u>
13. El método de producción para producir el compuesto representado por la Fórmula general (VI) descrita anteriormente de acuerdo con la reivindicación 11, el método comprende una etapa de convertir el compuesto representado por la Fórmula general (V) en el compuesto representado por la Fórmula general (VI) mediante el uso de R⁷-LG, donde LG es un grupo saliente sustituible nucleofílicamente, y yodo y un carbonato en sulfóxido de dimetilo.	13. 請求項 1 1 に記載の上記一般式 (V I) で表される化合物の製造方法であって、 ジメチルスルホキシド中、R⁷-LG、LGは求核的に置換可能な脱離基であり、ヨウ素及び炭酸塩を用いて、一般式 (V) で表される化合物を、一般式 (V I) で表される化合物に変換する製造方法。	<u>Son lo mismo</u>
14. Un agente químico agrícola u hortícola, o un agente protector para el material industrial que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 10, representado por la Fórmula general (I) descrita anteriormente, como un ingrediente activo.	14. 請求項 1 から 1 0 のいずれか 1 項に記載の上記一般式 (I) で表される化合物を有効成分として含有する農園芸用薬剤又は工業用材料保護剤。	<u>Son lo mismo</u>

Reivindicaciones patentables de la solicitud de la oficina de primera presentación que profirió el examen de patentabilidad.

1. 下記一般式（I）で表される化合物、又はそのN-オキシド若しくは農薬学的に許容可能な塩。

[化1]



[式（I）中、

Aは、N又はCHであり；

Dは、水素、ハロゲン基又はSR⁰であり；

ここで、R⁰は水素、シアノ基、C₁–C₆–アルキル基、C₁–C₆–ハロアルキル基、C₂–C₆–アルケニル基、C₂–C₆–ハロアルケニル基、C₂–C₆–アルキニル基又はC₂–C₆–ハロアルキニル基であり；

R¹は、水素、C₁–C₆–アルキル基、C₂–C₆–アルケニル基、C₂–C₆–アルキニル基、C₃–C₈–シクロアルキル基、C₃–C₈–シクロアルキル–C₁–C₄–アルキル基、フェニル基、フェニル–C₁–C₄–アルキル基、フェニル–C₂–C₄–アルケニル基、フェニル–C₂–C₄–アルキニル基又はCOXR⁵であり；

ここで、R⁵は、水素、C₁–C₆–アルキル基、C₂–C₆–アルケニル基、C₂–C₆–アルキニル基、C₃–C₈–シクロアルキル基、C₃–C₈–シクロアルキル–C₁–C₄–アルキル基、フェニル基、フェニル–C₁–C₄–アルキル基、フェニル–C₂–C₄–アルケニル基又はフェニル–C₂–C₄–アルキニル基であり；

Xは、単結合、–O–又は–NR⁶–であり；

R⁶は、水素、C₁–C₆–アルキル基、C₂–C₆–アルケニル基、C₂–C₆–アルキニル基、C₃–C₈–シクロアルキル基、C₃–C₈–シクロアルキル–C₁–C₄–アルキル基、フェニル基、フェニル–C₁–C₄–アルキル基、フェニル–C₂–C₄–アルケニル基又はフェニル–C₂–C₄–アルキニル基であり、R⁵とR⁶とは環を形成していてもよく；

R²は、–OR⁷又は–NR⁸R⁹であり；

R⁷、R⁸及びR⁹は、それぞれ独立に、水素、C₁–C₆–アルキル基、C₂–C₆–アルケニル基、C₂–C₆–アルキニル基、C₃–C₈–シクロアルキル基、C₃–C₈–シクロアルキル–C₁–C₄–アルキル基、フェニル基、フェニル–C₁–C₄–アルキル基、フェニル–C₂–C₄–アルケニル基又はフェニル–C₂–C₄–アルキニル基であり、R⁸とR⁹とは環を形成していてもよく；

ここで、R¹、R²、R⁵、R⁶、R⁷、R⁸及びR⁹における脂肪族基は、1、2、3若しくは可能な最大数の同一の又は異なる基R^aを有していてもよく、R^aは、ハロゲン基、シアノ基、ニトロ基、C₁–C₄–アルコキシ基及びC₁–C₄–ハロアルコキシ基から互いに独立して選択され；

R⁴は、ハロゲン基、シアノ基、ニトロ基、アミノ基、フェニル基、フェニル–オキシ基、C₁–C₄–アルキル基、C₁–C₄–ハロアルキル基、C₁–C₄–アルコキシ基又はC₁–C₄–ハロアルコキシ基、C₁–C₄–アルキルアミノ基、C₁–C₄–ジアルキルアミノ基、C₁–C₄–アルキルシルアミノ基、–SOR¹⁰又は–SF₅であり；

R¹、R²、R⁵、R⁶、R⁷、R⁸及びR⁹におけるシクロアルキル基若しくはフェニル基部分又はR⁴におけるフェニル基部分は、1、2、3、4、5若しくは可能な最大数の同一の又は異なる基R^bを有していてもよく、R^bは、ハロゲン基、シアノ基、ニトロ基、C₁–C₄–アルキル基、C₁–C₄–アルコキシ基、C₁–C₄–ハロアルキル基及びC₁–C₄–ハロアルコキシ基から互いに独立して選択され；

R³は、ハロゲン基、シアノ基、ニトロ基、フェニル基、フェニル–オキシ基、C₁–C₄–アル

キル基、 C_1-C_4 -ハロアルキル基、 C_1-C_4 -アルコキシ基、 C_1-C_4 -ハロアルコキシ基、 $-SOR^{10}$ 又は $-SF_5$ であり；

ここで、 R^{10} は、 C_1-C_4 -アルキル基又は C_1-C_4 -ハロアルキル基であり；

Eは、フェニル基又はN原子を1若しくは2つ含む6員の芳香族複素環であり；

R^3 は任意の置換位置にn個結合しており；

Eがフェニル基の場合、nは0、1、2、3又は4であり、EがN原子を1若しくは2つ含む6員の芳香族複素環である場合は、nは0、1又は2であり；

Yは、Eの任意の位置に接続する酸素原子、 $-CH_2O-$ 、 $-OCH_2-$ 、 $-NH-$ 、 $-N(C_1-C_4\text{-アルキル})-$ 、 $-N(C_3-C_6\text{-シクロアルキル})-$ 又は $-S(O)_p-$ であり；

pは、0、1又は2であり；

Zは、フェニル基若しくはナフチル基である芳香族炭化水素基、又は、O、N若しくはSから選択されるヘテロ原子を1～4つ含む5員又は6員の芳香族複素環若しくは2環から構成される9員又は10員の芳香族複素環であり；

R^4 は任意の置換位置にm個結合しており；

Zが芳香族炭化水素基である場合、mは1、2、3、4又は5であり、Zが芳香族複素環である場合、mは0、1、2、3又は4である]

2. 上記一般式 (I) において、

R^1 が、水素、 C_1-C_6 -アルキル基、 C_2-C_6 -アルケニル基、 C_2-C_6 -アルキニル基又は $COXR^5$ であり；

R^2 が、 $-OR^7$ であり；

R^5 が、水素、 C_1-C_6 -アルキル基、 C_2-C_6 -アルケニル基又は C_2-C_6 -アルキニル基であり；

R^6 が、水素、 C_1-C_6 -アルキル基、 C_2-C_6 -アルケニル基又は C_2-C_6 -アルキニル基である、

R^3 が、ハロゲン基、シアノ基、 C_1-C_4 -アルキル基、 C_1-C_4 -ハロアルキル基、 C_1-C_4 -アルコキシ基、 $-SOR^{10}$ 又は $-SF_5$ であり；

R^4 が、ハロゲン基、ニトロ基、シアノ基、アミノ基、 C_1-C_4 -アルキル基、 C_1-C_4 -ハロアルキル基、 C_1-C_4 -アルコキシ基、 C_1-C_4 -ハロアルコキシ基、 C_1-C_4 -アルキルアミノ基、 C_1-C_4 -ジアルキルアミノ基、 C_1-C_4 -アルキルアシルアミノ基、 $-SOR^{10}$ 又は $-SF_5$ である、

請求項 1 に記載の化合物又はその塩。

3. 上記一般式 (I) において、

R^1 が、水素、 C_1-C_6 -アルキル基又は $COXR^5$ であり；

R^5 が、水素又は C_1-C_6 -アルキル基であり；

R^6 が、水素であり；

R^3 が、ハロゲン基、シアノ基、 C_1-C_4 -アルキル基、 C_1-C_4 -ハロアルキル基、 C_1-C_4 -アルコキシ基、 $-SOR^{10}$ 又は $-SF_5$ であり；

R^4 が、ハロゲン基、ニトロ基、シアノ基、アミノ基、 C_1-C_4 -アルキル基、 C_1-C_4 -ハロアルキル基、 C_1-C_4 -アルコキシ基、 C_1-C_4 -ハロアルコキシ基、 C_1-C_4 -アルキルアミノ基、 C_1-C_4 -ジアルキルアミノ基、 C_1-C_4 -アルキルアシルアミノ基、 $-SOR^{10}$ 又は $-SF_5$ である、

請求項 1 又は 2 に記載の化合物又はその塩。

4. 上記一般式 (I) において、

R^1 が、水素又は C_1-C_6 -アルキル基であり；

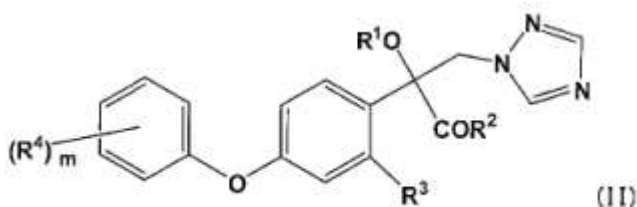
R^7 が、 C_1-C_6 -アルキル基であり；

R^3 が、ハロゲン基、シアノ基、 C_1-C_4 -アルキル基、 C_1-C_4 -ハロアルキル基又は C_1-C_4 -アルコキシ基であり；

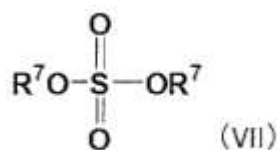
R^4 が、ハロゲン基、シアノ基、 C_1-C_4 -アルキル基、 C_1-C_4 -ハロアルキル基、 C_1-C_4 -アルコキシ基又は C_1-C_4 -ハロアルコキシ基である、

請求項 1 から 3 のいずれか 1 項に記載の化合物又はその塩。

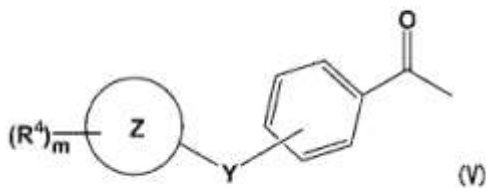
5. 上記一般式（I）において、Eが、フェニル基である、請求項1から4のいずれか1項に記載される化合物又はその塩。
6. 上記一般式（I）において、Zが、フェニル基、ナフチル基、又はN及びSから選択されるヘテロ原子を1～3つ含む5員又は6員の芳香族複素環である、請求項1から5のいずれか1項に記載の化合物又はその塩。
7. 上記一般式（I）において、Zがフェニル基である、請求項1から6のいずれか1項に記載の化合物又はその塩。
8. 上記一般式（I）において、Yが酸素原子である、請求項1から7のいずれか1項に記載の化合物又はその塩。
9. 上記一般式（I）において、AがNであり、Dが水素である、請求項1から8のいずれか1項に記載の化合物又はその塩。
10. 上記化合物が、下記一般式（II）で表される化合物
[化2]



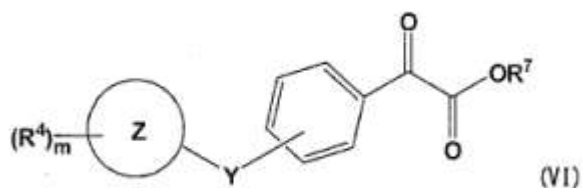
11. 請求項1から10のいずれか1項に記載の上記一般式（I）で表される化合物の製造方法であつて、
ジメチルスルホキシド中、下記一般式（VII）で表されるジアルキル硫酸若しくは R^7-LG 、ここでLGは求核的に置換可能な脱離基であり、ヨウ素及び炭酸塩を用いて、下記一般式（V）で表される化合物を、下記一般式（VI）で表される化合物に変換する工程を含む、化合物の製造方法。
[化3]



[化4]



[化5]

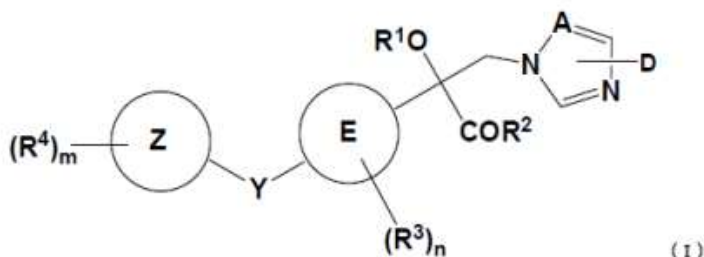


12. R^7-LG のLGが、ハロゲン基である、請求項11に記載の製造方法。
13. 請求項11に記載の上記一般式(VI)で表される化合物の製造方法であって、ジメチルスルホキシド中、 R^7-LG 、LGは求核的に置換可能な脱離基であり、ヨウ素及び炭酸塩を用いて、一般式(V)で表される化合物を、一般式(VI)で表される化合物に変換する製造方法。
14. 請求項1から10のいずれか1項に記載の上記一般式(I)で表される化合物を有効成分として含有する農園芸用薬剤又は工業用材料保護剤。

Traducción al castellano de las reivindicaciones patentables de la solicitud de la oficina de primera presentación que profirió el examen de patentabilidad.

1. Un compuesto representado por la siguiente Fórmula general (I), o un N-óxido o sal agroquímicamente aceptable de estos:

[Fórmula química 1]



[en la Fórmula general (I),

A es N o CH;

D es un hidrógeno, un grupo halógeno o SR^D;

donde R^D es hidrógeno, un grupo ciano, un grupo alquilo C₁-C₆, un grupo haloalquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo haloalquenilo C₂-C₆, un grupo alquinilo C₂-C₆ o un grupo haloalquinilo C₂-C₆; R¹ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo alquinilo C₂-C₆, un grupo cicloalquilo C₃-C₈, un grupo cicloalquilo C₃-C₈-alquilo C₁-C₄, un grupo fenilo, un grupo fenil alquilo C₁-C₄, un grupo fenilalquenilo C₂-C₄, un grupo fenil-alquinilo C₂-C₄ o COXR⁵;

donde R⁵ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo alquinilo C₂-C₆, un grupo cicloalquilo C₃-C₈, un grupo cicloalquilo C₃-C₈-alquilo C₁-C₄, un grupo fenilo, un grupo fenil-alquilo C₁-C₄, un grupo fenil-alquenilo C₂-C₄ o un grupo fenil-alquinilo C₂-C₄; X es un enlace simple, -O- o -NR⁶-;

R⁶ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo alquinilo C₂-C₆, un grupo cicloalquilo C₃-C₈, un grupo cicloalquilo C₃-C₈-alquilo C₁-C₄, un grupo fenilo, un grupo fenil-alquilo C₁-C₄, un grupo fenil-alquenilo C₂-C₄ o un grupo fenil-alquinilo C₂-C₄; y R⁵ y R⁶ pueden formar un anillo;

R² es -OR⁷ o -NR⁸R⁹;

R⁷, R⁸ y R⁹ son cada uno independientemente un hidrógeno, un grupo alquilo C₁-C₆, un grupo alquenilo C₂-C₆, un grupo alquinilo C₂-C₆, un grupo cicloalquilo C₃-C₈, un grupo cicloalquilo C₃-C₈-alquilo C₁-C₄, un grupo fenilo, un grupo fenil-alquilo C₁-C₄, un grupo fenil-alquenilo C₂-C₄ o un grupo fenilalquinilo C₂-C₄, y R⁸ y R⁹ pueden formar un anillo,

donde los grupos alifáticos en R¹, R², R⁵, R⁶, R⁷, R⁸, y R⁹ pueden tener 1, 2, 3 o el número máximo posible de grupos R^a iguales o diferentes, y R^a se selecciona independientemente de un grupo halógeno, un grupo ciano, un grupo nitro, un grupo alcoxi C₁-C₄, y un grupo haloalcoxi C₁-C₄;

R⁴ es un grupo halógeno, un grupo ciano, un grupo nitro, un grupo amino, un grupo fenilo, un grupo fenil-oxi, un grupo alquilo C₁-C₄, un grupo haloalquilo C₁-C₄, un grupo alcoxi C₁-C₄, un grupo haloalcoxi C₁-C₄, un grupo alquilamino C₁-C₄, un grupo dialquilamino C₁-C₄, un grupo alquilacilamino C₁-C₄, -SOR¹⁰ o -SF₅;

las partes del grupo cicloalquilo o del grupo fenilo en R¹, R², R⁵, R⁶, R⁷, R⁸ y R⁹ o la parte del grupo fenilo en R⁴ pueden tener 1, 2, 3, 4, 5, o el número máximo posible de grupos R^b iguales o diferentes, y R^b se selecciona independientemente de un grupo halógeno, un grupo ciano, un grupo nitro, un grupo alquilo C₁-C₄, un grupo alcoxi C₁-C₄, un grupo haloalquilo C₁-C₄ y un grupo haloalcoxi C₁-C₄;

R³ es un grupo halógeno, un grupo ciano, un grupo nitro, un grupo fenilo, un grupo fenil-oxi, un grupo alquilo C₁-C₄, un grupo haloalquilo C₁-C₄, un grupo alcoxi C₁-C₄, un grupo haloalcoxi C₁-C₄, -SOR¹⁰ o -SF₅;

donde R¹⁰ es un grupo alquilo C₁-C₄ o un grupo haloalquilo C₁-C₄;

E es un grupo fenilo o un anillo heteroaromático de 6 miembros que contiene 1 o 2 átomos de N;

R³ de n se unen a cualquier sitio de sustitución;

cuando E es un grupo fenilo, entonces n es 0, 1, 2, 3 o 4 y cuando E es un anillo heteroaromático de 6 miembros que contiene 1 o 2 átomos de N, entonces n es 0, 1 o 2;

Y es un átomo de oxígeno, -CH₂O-, -OCH₂-, -NH-, -N(-alquilo C₁-C₄), -N(-cicloalquilo C₃-C₆)- o -S(O)_p-, que se une a cualquier sitio de E;

donde p es 0, 1 o 2;

Z es un grupo hidrocarburo aromático que es un grupo fenilo o un grupo naftilo, o un anillo heteroaromático de 5 miembros o 6 miembros o un anillo heteroaromático de 9 miembros o 10 miembros formado por 2 anillos, que contienen de 1 a 4 heteroátomos seleccionados de O, N y S; y

R⁴ de m se unen a cualquier sitio de sustitución;

cuando Z es un grupo hidrocarburo aromático, entonces m es 1, 2, 3, 4, o 5 y

cuando Z es un anillo heteroaromático, entonces m es 0, 1, 2, 3, o 4].

2. *El compuesto o la sal de este de acuerdo con la reivindicación 1, en donde en la Fórmula general (I),*

R¹ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alqueno C₂-C₆, un grupo alquino C₂-C₆ o COXR⁵;

R² es -OR⁷;

R⁵ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alqueno C₂-C₆ o un grupo alquino C₂-C₆;

R⁶ es un hidrógeno, un grupo alquilo C₁-C₆, un grupo alqueno C₂-C₆ o un grupo alquino C₂-C₆;

R³ es un grupo halógeno, un grupo ciano, un grupo alquilo C₁-C₄, un grupo haloalquilo C₁-C₄, un grupo alcoxi C₁-C₄, -SOR¹⁰ o -SF₅; y

R⁴ es un grupo halógeno, un grupo nitro, un grupo ciano, un grupo amino, un grupo alquilo C₁-C₄, un grupo haloalquilo C₁-C₄, un grupo alcoxi C₁-C₄, un grupo haloalcoxi C₁-C₄, un grupo alquilamino C₁-C₄, un grupo dialquilamino C₁-C₄, un grupo alquilacilamino C₁-C₄, -SOR¹⁰ o -SF₅.

3. *El compuesto o la sal de este de acuerdo con la reivindicación 1 o 2, en donde en la Fórmula general (I),*

R¹ es un hidrógeno, un grupo alquilo C₁-C₆ o COXR⁵;

R⁵ es un hidrógeno, o un grupo alquilo C₁-C₆;

R⁶ es un hidrógeno;

R³ es un grupo halógeno, un grupo ciano, un grupo alquilo C₁-C₄, un grupo haloalquilo C₁-C₄, un grupo alcoxi C₁-C₄, -SOR¹⁰ o -SF₅; y

R⁴ es un grupo halógeno, un grupo nitro, un grupo ciano, un grupo amino, un grupo alquilo C₁-C₄, un grupo haloalquilo C₁-C₄, un grupo alcoxi C₁-C₄, un grupo haloalcoxi C₁-C₄, un grupo alquilamino C₁-C₄, un grupo dialquilamino C₁-C₄, un grupo alquilacilamino C₁-C₄, -SOR¹⁰ o -SF₅.

4. *El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 3, en donde en la Fórmula general (I),*

R¹ es un hidrógeno, o un grupo alquilo C₁-C₆;

R⁷ es un grupo alquilo C₁-C₆;

R³ es un grupo halógeno, un grupo ciano, un grupo alquilo C₁-C₄, un grupo haloalquilo C₁-C₄ o un grupo alcoxi C₁-C₄; y

R⁴ es un grupo halógeno, un grupo ciano, un grupo alquilo C₁-C₄, un grupo haloalquilo C₁-C₄, un grupo alcoxi C₁-C₄ o un grupo haloalcoxi C₁-C₄.

5. *El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 4, en donde en la Fórmula general (I), E es un grupo fenilo.*

6. *El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 5, en donde en la Fórmula general (I), Z es un grupo fenilo, un grupo naftilo, o un anillo heteroaromático de 5 miembros o 6 miembros que contiene de 1 a 3 heteroátomos seleccionados de N y S.*

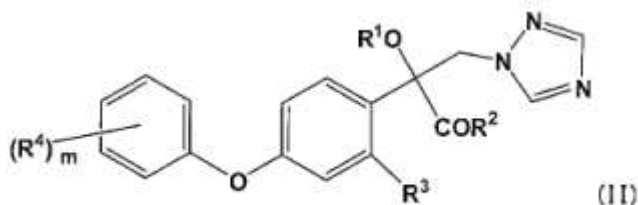
7. *El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 6, en donde en la Fórmula general (I), Z es un grupo fenilo.*

8. *El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 7, en donde en la Fórmula general (I), Y es un átomo de oxígeno.*

9. *El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 8, en donde en la Fórmula general (I), A es N, y D es un hidrógeno.*

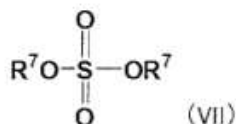
10. *El compuesto o la sal de este de acuerdo con una cualquiera de las reivindicaciones 1 a 9, en donde el compuesto representado por la siguiente Fórmula general (II):*

[Fórmula química 2]

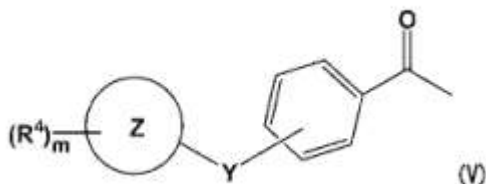


11. Un método para producir un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 10, representado por la Fórmula general (I) anterior, el método comprende una etapa de convertir un compuesto representado por la siguiente Fórmula general (V) en un compuesto representado por la siguiente Fórmula general (VI) mediante el uso de un sulfato de dialquilo, que está representado por la siguiente Fórmula general (VII), o R^7 -LG, donde LG es un grupo saliente sustituible nucleofílicamente, y yodo y un carbonato en sulfóxido de dimetilo.

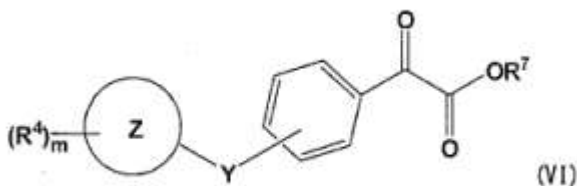
[Fórmula química 3]



[Fórmula química 4]



[Fórmula química 5]



12. El método de producción de acuerdo con la reivindicación 11, en donde LG en R^7 -LG es un grupo halógeno.

13. El método de producción para producir el compuesto representado por la Fórmula general (VI) descrita anteriormente de acuerdo con la reivindicación 11, el método comprende una etapa de convertir el compuesto representado por la Fórmula general (V) en el compuesto representado por la Fórmula general (VI) mediante el uso de R^7 -LG, donde LG es un grupo saliente sustituible nucleofílicamente, y yodo y un carbonato en sulfóxido de dimetilo.

14. Un agente químico agrícola u hortícola, o un agente protector para el material industrial que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 10, representado por la Fórmula general (I) descrita anteriormente, como un ingrediente activo.

特許協力条約

発信人 日本国特許庁（国際調査機関）

代理人 特許業務法人HARAKENZO WORLD P ATENT & TRADEMARK 様 あて名 〒530-0041 日本国大阪府大阪市北区天神橋2丁目北2番6号 大和南森町ビル		PCT 国際調査機関の見解書 (法施行規則第40条の2) [PCT規則43の2.1]	
出願人又は代理人 の書類記号 17G052W0		発送日 (日.月.年) 15.01.2019	
国際出願番号 PCT/JP2018/041971		国際出願日 (日.月.年) 13.11.2018	優先日 (日.月.年) 13.11.2017
国際特許分類 (IPC) Int.Cl. C07D249/08(2006.01)i, A01N43/653(2006.01)i, A01P3/00(2006.01)i, C07D401/06(2006.01)i, C07D401/12(2006.01)i			
出願人 (氏名又は名称) 株式会社クレハ			

1. この見解書は次の内容を含む。 ☒ 第I欄 見解の基礎 ☐ 第II欄 優先権 ☐ 第III欄 新規性、進歩性又は産業上の利用可能性についての見解の不作成 ☐ 第IV欄 発明の単一性の欠如 ☒ 第V欄 PCT規則43の2.1(a)(i)に規定する新規性、進歩性又は産業上の利用可能性についての見解、それを裏付けるための文献及び説明 ☐ 第VI欄 ある種の引用文献 ☐ 第VII欄 国際出願の欠陥 ☐ 第VIII欄 国際出願についての意見
2. 今後の手続 国際予備審査の請求がされた場合は、出願人がこの国際調査機関とは異なる国際予備審査機関を選択し、かつ、その国際予備審査機関がPCT規則66.1の2(b)の規定に基づいて国際調査機関の見解書を国際予備審査機関の見解書とみなさない旨を国際事務局に通知していた場合を除いて、この見解書は国際予備審査機関の最初の見解書とみなされる。 この見解書が上記のように国際予備審査機関の見解書とみなされる場合、様式PCT/ISA/220を送付した日から3月又は優先日から22月のうちいずれか遅く満了する期限が経過するまでに、出願人は国際予備審査機関に、適当な場合は補正書とともに、答弁書を提出することができる。 さらなる選択肢は、様式PCT/ISA/220を参照すること。

見解書を作成した日 12.12.2018			
名称及びあて先 日本国特許庁 (ISA/JP) 郵便番号100-8915 東京都千代田区霞が関三丁目4番3号	特許庁審査官 (権限のある職員) 神谷 昌克 電話番号 03-3581-1101 内線 3492	4P	8379

第 I 欄 見解の基礎

1. 言語に関し、この見解書は以下のものに基づき作成した。

- ☒ 出願時の言語による国際出願
- ☐ 出願時の言語から国際調査のための言語である _____ 語に翻訳された、この国際出願の翻訳文 (P C T 規則12.3(a)及び23.1(b))

2. ☐ この見解書は、P C T 規則 91 の規定により国際調査機関が許可した又は国際調査機関に通知された明らかな誤りの訂正を考慮して作成した (P C T 規則 43 の 2.1(b))。

3. この国際出願で開示されたヌクレオチド又はアミノ酸配列に関して、以下の配列表に基づき見解書を作成した。

- a. ☐ 出願時における国際出願の一部を構成する配列表
- ☐ 附属書C/ST.25テキストファイル形式
- ☐ 紙形式又はイメージファイル形式
- b. ☐ 国際出願とともに、P C T 規則13の3.1(a)に基づき国際調査のためにのみ提出された、附属書C/ST.25テキストファイル形式の配列表
- c. ☐ 国際出願日後に、国際調査のためにのみ提出された配列表
- ☐ 附属書C/ST.25テキストファイル形式 (P C T 規則13の3.1(a))
- ☐ 紙形式又はイメージファイル形式 (P C T 規則13の3.1(b) 及び P C T 実施細則第713号)

4. ☐ さらに、複数の版の配列表又は配列表の写しが提出され、変更後の配列表又は追加の写しに記載された情報が、出願時における配列表と同一である旨、又は出願時における国際出願の開示の範囲を超えない旨の陳述書の提出があった。

5. 補足意見：

第V欄 新規性、進歩性又は産業上の利用可能性についてのPCT規則43の2.1(a)(i)に定める見解、それを裏付ける文献及び説明

1. 見解

新規性 (N)	請求項	1-14	有
	請求項		無
進歩性 (I S)	請求項	1-14	有
	請求項		無
産業上の利用可能性 (I A)	請求項	1-14	有
	請求項		無

2. 文献及び説明

文献1 : JP 58-170770 A (インペリアル・ケミカル・インダストリーズ・ピーエルシー) 1983. 10. 07

文献2 : WO 2013/007767 A1 (BASF SE) 2013. 01. 17

文献3 : JP 59-31766 A (チバーガイギー・アクチエンゲゼルシャフト) 1984. 02. 20

文献4 : WO 93/11118 A1 (SCHERING AGROCHEMICALS LIMITED) 1993. 06. 10

文献5 : WO 2011/136268 A1 (塩野義製薬株式会社) 2011. 11. 03

文献6 : GUO, S. et al., Metal-free oxidative esterification of acetophenones with alcohols: a facile one-pot approach to α -ketoesters, RSC Advances, 2016, Vol.6, No.100, p.98422-98426, ISSN 2046-2069

文献7 : YANG, L. et al., Synthesis of Pelorol and Analogs: Activators of the Inositol 5-Phosphatase SHIP, Organic Letters, 2005, Vol.7, No.6, p.1073-1076, ISSN 1523-7060

請求項1～14に係る発明は、国際調査報告で引用された文献1～7に対して新規性及び進歩性を有する。

文献1～4には、殺カビ活性を有するトリアゾール又はイミダゾール化合物が記載されている(文献1:特許請求の範囲、実施例、文献2:請求の範囲、実施例、文献3:特許請求の範囲、実施例、文献4:請求の範囲、実施例)。文献5には、ベンジルオキシアセトフェノンをエステル化する方法が記載されている(段落[0252]～[0253])。文献6～7には、ヨウ素存在下でアセチル基をエステル化する方法が記載されている(文献6:Scheme 1-2, Table 1-2、文献7:Supporting Information p.8-9)。

しかしながら、文献1～7には、本願発明の化合物及びその中間体化合物の製造方法について記載も示唆もされていない。

TRATADO DE COOPERACIÓN DE PATENTES

De la
AUTORIDAD DE BÚSQUEDA INTERNACIONAL

Para: Harakenzo World Patent & Trademark Domicilio: Daiwa Minamimorimachi Bldg. 2-6, 2-chome-kita Tenjinbashi, Kita-ku, Osaka 530-0041, Japón		PCT CONCEPTO ESCRITO DE LA AUTORIDAD DE BÚSQUEDA INTERNATIONAL (Artículo 40bis del Reglamento de Aplicación de la Ley) (Regla 43bis.1 PCT)																	
		Fecha de correspondencia (día/mes/año) 15.01.2019																	
Referencia del expediente del solicitante o agente 17GO52WO		PARA ACCIÓN FUTURA Consulte el párrafo 2 adelante																	
Solicitud Internacional No. PCT/JP2018/041971	Fecha de presentación Internacional (día/mes/año) 13.11.2018	Fecha de prioridad (día/mes/año) 13.11.2017																	
Clasificación Internacional de Patentes (IPC) Clasificación Internacional C07D249/08 (2006.01)i, A01N43/653(2006.01)i, A01P3/00(2006.01)i, C07D401/06 (2006.01)i, C07D401/12(2006.01)i																			
Solicitante KUREHA CORPORATION																			
1. Este concepto contiene indicaciones que se relacionan con los siguientes ítems: <table border="0"> <tr> <td>☒ Casilla No. I</td> <td>Bases del concepto</td> </tr> <tr> <td>☐ Casilla No. II</td> <td>Prioridad</td> </tr> <tr> <td>☐ Casilla No. III</td> <td>No establecimiento de concepto con respecto a novedad, nivel inventivo y aplicabilidad industrial.</td> </tr> <tr> <td>☐ Casilla No. IV</td> <td>Falta de unidad de invención</td> </tr> <tr> <td>☒ Casilla No. V</td> <td>Declaración motivada en virtud de la Regla 43bis. 1 (a) (i) con respecto a novedad, nivel inventivo y aplicabilidad industrial; citas y explicaciones respaldan dicha declaración</td> </tr> <tr> <td>☐ Casilla No. VI</td> <td>Determinados documentos citados</td> </tr> <tr> <td>☐ Casilla No. VII</td> <td>Determinados defectos en la solicitud internacional</td> </tr> <tr> <td>☒ Casilla No. VIII</td> <td>Determinadas observaciones en la solicitud internacional</td> </tr> </table>				☒ Casilla No. I	Bases del concepto	☐ Casilla No. II	Prioridad	☐ Casilla No. III	No establecimiento de concepto con respecto a novedad, nivel inventivo y aplicabilidad industrial.	☐ Casilla No. IV	Falta de unidad de invención	☒ Casilla No. V	Declaración motivada en virtud de la Regla 43bis. 1 (a) (i) con respecto a novedad, nivel inventivo y aplicabilidad industrial; citas y explicaciones respaldan dicha declaración	☐ Casilla No. VI	Determinados documentos citados	☐ Casilla No. VII	Determinados defectos en la solicitud internacional	☒ Casilla No. VIII	Determinadas observaciones en la solicitud internacional
☒ Casilla No. I	Bases del concepto																		
☐ Casilla No. II	Prioridad																		
☐ Casilla No. III	No establecimiento de concepto con respecto a novedad, nivel inventivo y aplicabilidad industrial.																		
☐ Casilla No. IV	Falta de unidad de invención																		
☒ Casilla No. V	Declaración motivada en virtud de la Regla 43bis. 1 (a) (i) con respecto a novedad, nivel inventivo y aplicabilidad industrial; citas y explicaciones respaldan dicha declaración																		
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☐ Casilla No. VII	Determinados defectos en la solicitud internacional																		
☒ Casilla No. VIII	Determinadas observaciones en la solicitud internacional																		
2. ACCIÓN FUTURA Si se solicita un examen preliminar internacional, este concepto generalmente se considerará un concepto escrito de la Autoridad de Examen Preliminar Internacional ("IPEA"), excepto que esto no se aplica cuando el solicitante elige una Autoridad que no sea el IPEA y el IPEA elegido ha notificado a la Oficina Internacional de conformidad con																			

la Regla 66.1bis(b) que los conceptos escritos de esta Autoridad de Búsqueda Internacional no serán considerados de esa manera.

Si este concepto se considera, según lo dispuesto anteriormente, como un concepto escrito del IPEA, se invita al solicitante a presentar al IPEA una respuesta por escrito, cuando corresponda, con modificaciones, antes del vencimiento de 3 meses a partir de la fecha de correspondencia del Formulario PCT/ISA/220 o antes del vencimiento de 22 meses a partir de la fecha de prioridad, lo que venza más tarde.

Para más opciones, consulte el formulario PCT/ISA/220.

Fecha de terminación de este concepto	12.12.2018		
Nombre y dirección de correspondencia del ISA: JPO (ISA/JP) 3-4-3 Kasumigaseki, Chiyoda-ku, Tokyo 100-8915	Funcionario Autorizado	4P	8379
	Masakatsu Kamiya Tel 03-3581-1101, ext. 3492		

Formulario PCT/ISA/237 (portada)(enero 2015)

**CONCEPTO ESCRITO DE LA
AUTORIDAD DE BÚSQUEDA INTERNACIONAL**

Solicitud Internacional No.
PCT/JP2018/041971

Casilla No. I Base del concepto

1. Con respecto al **idioma**, este concepto se ha establecido sobre la base de:

- ☒ la solicitud internacional en el idioma en que se presentó.
- ☐ una traducción de la solicitud internacional en _____, que es el idioma de una traducción proporcionada para fines de búsqueda internacional (Reglas 12.3 (a) y 23.1 (b)).

2. ☐ Este concepto se ha establecido teniendo en cuenta la **rectificación de un error obvio** autorizado o notificado a esta Autoridad de conformidad con la Regla 91 (Regla 43*bis*.1 (a))

3. ☐ Con respecto a cualquier **secuencia de nucleótidos y/o aminoácidos** divulgada en la solicitud internacional, este concepto se ha establecido sobre la base de una lista de secuencias:

a. ☐ que forma parte de la solicitud internacional presentada:

☐ en forma de un archivo de texto Anexo C/ST.25.

☐ en papel o en forma de archivo de imagen.

b. ☐ suministrado junto con la solicitud internacional de conformidad con la Regla 13*ter*.1 (a) del PCT para fines de búsqueda internacional únicamente en forma de un archivo de texto Anexo C/ST.25.

c. ☐ suministrado después de la fecha de presentación internacional solo para fines de búsqueda internacional:

☐ en forma de un archivo de texto Anexo C/ST.25 (Regla 13*ter*.1 (a)).

☐ en papel o en forma de archivo de imagen (Regla 13*ter*.1 (b) e Instrucciones Administrativas, Sección 713).

4. ☐ Además, en el caso de que se haya archivado o proporcionado más de una versión o copia de una lista de secuencias, las declaraciones requeridas de que la información en las copias posteriores o adicionales es idéntica a la que forma parte de la solicitud tal como se presentó o no se envía más allá de la solicitud como se presentó, según corresponda, se proporcionaron.

5. Comentarios adicionales:

**CONCEPTO ESCRITO DE LA
AUTORIDAD DE BÚSQUEDA INTERNACIONAL**

Solicitud Internacional No.
PCT/JP2018/041971

Casilla No. V Declaración motivada en virtud de la Regla 43bis.1 (a) (i) con respecto a novedad, nivel inventivo o aplicabilidad industrial; citas y explicaciones respaldan dicha declaración

1. Declaración

Novedad (N)	Sí:	Reivindicaciones	<u>1-14</u>
	No:	Reivindicaciones	
Nivel Inventivo (IS)	Sí:	Reivindicaciones	<u>1-14</u>
	No:	Reivindicaciones	
Aplicabilidad Industrial (IA)	Sí:	Reivindicaciones	<u>1-14</u>
	No:	Reivindicaciones	

2. Citaciones y explicaciones

Documento 1 : JP 58-170770 A (Imperial Chemical Industries PLC) 1983. 10. 07

Documento 2 : WO 2013/007767 A1 (BASF SE) 2013. 01. 17

Documento 3 : JP 59-31766 A (Ciba-Geigy, AG) 1984. 02. 20

Documento 4: WO 93/11118 A1 (SCHERING AGROCHEMICALS LIMITED) 1993. 06. 10

Documento 5: WO 2011/136268 A1 (Shionogi & Co., Ltd.) 2011. 11. 03

Documento 6: GUO, S. et al., Metal-free oxidative esterification of acetophenones with alcohols: a facile one-pot approach to α -ketoesters, RSC Advances, 2016, Vol. 6, No. 100, p. 98422-98426, ISSN 2046-2069

Documento 7: YANG, L. et al., Synthesis of Pelorol and Analogs: Activators of the Inositol 5-Phosphatase SHIP, Organic Letters, 2005, Vol.7, No.6, p.1073-1076, ISSN 1523-7060

Las invenciones de acuerdo con las reivindicaciones 1-14 poseen novedad y nivel inventivo sobre los Documentos 1-7 citados en el Reporte de Búsqueda Internacional.

Los Documentos 1-4 divulgan un compuesto de triazol o imidazol que tiene una actividad fungicida (Documento 1: Reivindicaciones, Ejemplos, Documento 2: Reivindicaciones, Ejemplos, Documento 3: Reivindicaciones, Ejemplos, Documento 4: Reivindicaciones, Ejemplos). Documento 5 divulga un método de esterificación de benziloxiacetofenona (párrafos [0252]-[0253]. Los Documentos 6-7 divulgan un método de esterificación de un grupo acetilo en la presencia de yodo (Documento 6: Esquemas 1-2, Tablas 1-2, Documento 7: Información de respaldo p. 8-9).

Sin embargo, los Documentos 1-7 ni divulgan ni sugieren el método de producción del compuesto y un compuesto intermedio del mismo de la invención de la solicitud actual.

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Metal-free oxidative esterification of acetophenones with alcohols: a facile one-pot approach to α -ketoesters†

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Accepted 10th October 2016

DOI: 10.1039/c6ra19485k

www.rsc.org/advances

A novel and efficient oxidative esterification method for the synthesis of α -ketoesters has been developed under mild and environmentally benign conditions, which is a facile one-pot approach to α -ketoesters from commercially available acetophenones with alcohols, especially under metal-free conditions, with broad substrate scope. A possible mechanism is proposed on the basis of a series of control experiments and DMSO-¹⁸ isotopic labelling experiments.

Introduction

α -Ketoesters as an important and prevalent structural element of numerous biologically active molecules have attracted the considerable interest of chemists all over the world.¹ In addition to this biological application, α -ketoesters could also act as versatile synthetic precursors for further transformations in organic synthesis.²

Owing to these useful characters of α -ketoesters, the synthesis of α -ketoesters is a significant process and more and more novel synthetic methodologies have been developed. Traditionally, α -ketoesters could be generated from the esterification of α -ketoacyl halides and α -ketoacids,³ oxidation of α -hydroxy esters,⁴ double carbopalladative esterification⁵ or some other methods.⁶ Moreover, Jiao and co-workers reported two novel methodologies to α -ketoesters: (1) Cu-catalyzed aerobic oxidative dehydrogenative coupling of α -carbonyl aldehydes with alcohols;⁷ (2) Cu-catalyzed aerobic oxidative C–C bond cleavage of ketones.⁸ Sharada and co-workers developed an I₂-promoted cross-dehydrogenative coupling of α -carbonyl aldehydes with alcohols for the synthesis of α -ketoesters.⁹ However, these methods mentioned above suffer from some drawbacks, such as (1) the usage of expensive or impractical starting materials; (2) harsh reaction conditions; (3) low atom economy, which restrict the utility of these methods. Relatively,

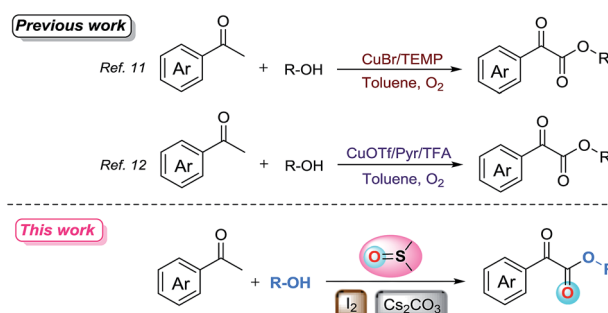
acetophenones as commercially available and cheaper starting materials were applied universally to further transformations.¹⁰ Transition-metal-catalyzed especially Cu-catalyzed aerobic oxidative esterification for the construction of α -ketoesters from acetophenones has been reported effectively in the last few years. For example, Jiao's group reported a TEMP and CuBr co-catalyzed oxygenation of acetophenones with O₂ to construct α -ketoesters.¹¹ Besides, Song's group reported a CuOTf catalyzed esterification of acetophenones with alcohols to α -ketoesters.¹² In the past decades, reactions under metal-free conditions are very popular and attract much attention in organic synthesis, such as I₂/TBHP (*tert*-butyl peroxybenzoate) system,¹³ NIS (*N*-iodosuccinimide)/TBHP system¹⁴ and I₂/IBX (2-iodoxybenzoic acid) system,¹⁵ avoiding the usage of expensive, poisonous and air-sensitive metals or organometallics. Iodine, a popular available mild Lewis acid with less toxicity and low cost, is often chosen as an alternative of toxic rare metals and transition-metal catalysts in organic synthesis.¹⁶ Previously, our group has reported an I₂-promoted aerobic oxidative coupling of acetophenones with amines to α -ketoamides under metal-free conditions.¹⁷ Referring to relative literatures, there has no

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† Electronic supplementary information (ESI) available: Experimental details, LC-ESI-MS/MS analysis, analytical data and NMR spectra of products. See DOI: 10.1039/c6ra19485k



Scheme 1 Facile one-pot approach to α -ketoesters from acetophenones under metal-free conditions.

reported work on the synthesis of α -ketoesters under metal-free conditions from acetophenones so far. Herein, we wish to develop a feasible, effective and mild method to α -ketoesters from acetophenones, which is a novel methodology to α -ketoesters from acetophenones with alcohols under metal-free conditions with broad substrate scope, employing DMSO as both important oxidant and solvent (Scheme 1).

Results and discussion

Initially, this investigation focused on the optimization of the reaction conditions and a model reaction of acetophenone **1a** (0.5 mmol) and 2-phenylethanol **2a** (1.5 mmol) was carried out in the presence of iodine as the promoter to screen a series of parameters. As listed in Table 1, effects of different oxidants on this reaction, such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl perbenzoate (TBPB), H_2O_2 , dimethylsulfoxide (DMSO), $\text{PhI}(\text{OAc})_2$ and molecular oxygen were examined under the model reaction in toluene at 50 °C, results showed that DMSO exhibited the highest reactivity to the reaction with 30% yield of the desired product **3aa** obtained (Table 1, entry 4). On this base, DMSO was examined to serve as both oxidant and solvent in the model reaction. Interestingly, a better yield of product **3aa** was obtained, demonstrating that it was actually feasible (Table 1, entry 7). Subsequently, when the model reaction was

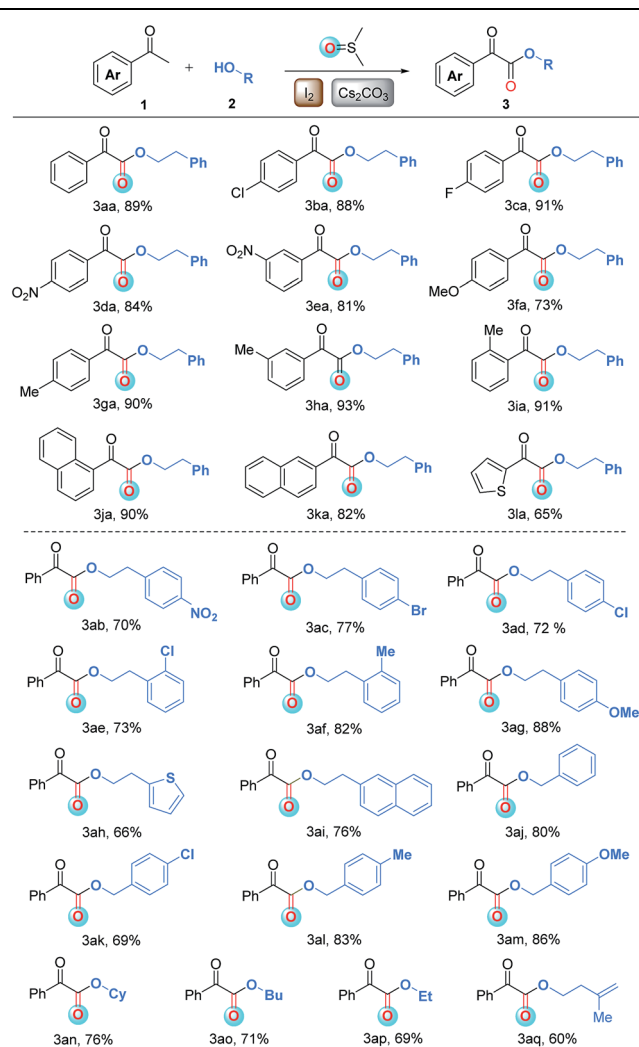
treated with a variety of bases, including inorganic and organic bases, Cs_2CO_3 exhibited the most positive effect with 68% yield of desired product isolated, while organic bases performed a little bit worse (Table 1, entry 8–12). To further improve the yield of product **3aa**, temperature of the reaction was raised to higher gradients, the best yield of 80% **3aa** was obtained at 110 °C (Table 1, entry 15). Next, different concentrations of iodine and Cs_2CO_3 were screened (Table 1, entry 17–22), the optimized reaction conditions were finally confirmed: **1a** (0.5 mmol), **2a** (1.5 mmol), 2.5 equivalents of iodine and 2.5 equivalents of Cs_2CO_3 were dissolved in 3 mL DMSO and stirred at 110 °C for 24 h, affording 89% yield of product **3aa** (Table 1, entry 21).

With the optimized reaction conditions in hands, we next probed the scope of synthesizing a series of α -ketoesters **3** applying optimized conditions and the results were summarized in Table 2. Firstly, acetophenones bearing both electron-deficient ($-\text{F}$, $-\text{Cl}$, $-\text{NO}_2$) or electron-rich substituents ($-\text{Me}$, $-\text{OMe}$) reacted well with 2-phenylethanol to produce corresponding α -ketoesters in moderate to excellent yields (Table 2, **3aa–3ia**). In addition to this feature, the results indicated that the position of these substituents on the aromatic groups had no obvious differences on the yields of corresponding products (Table 2, **3aa–3ia**). Some other aromatic rings and heterocyclic ring, such as 1-acetonaphthone, 2-acetonaphthone and 2-acetylthiophene, could also undergo the reaction with 2-

Table 1 Optimization studies of the model reaction conditions^a

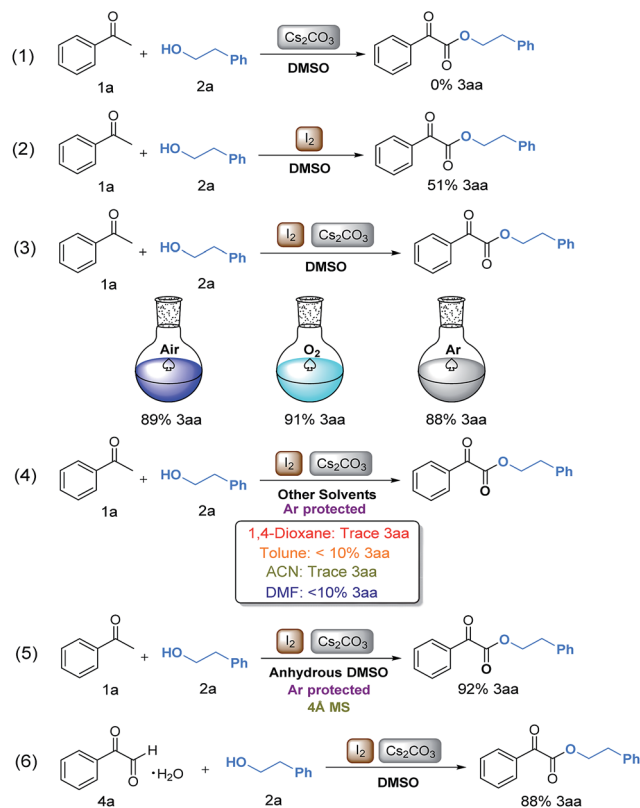
Entry	Promoter (equiv.)	Base (equiv.)	Oxidant	Solvent	Temp (°C)	Yield ^b (%)
1	I ₂ (2.0)	—	TBHP	Toluene	50	13
2	I ₂ (2.0)	—	TBPB	Toluene	50	15
3	I ₂ (2.0)	—	H ₂ O ₂	Toluene	50	<10
4	I ₂ (2.0)	—	DMSO	Toluene	50	30
5	I ₂ (2.0)	—	PhI(OAc) ₂	Toluene	50	Trace
6	I ₂ (2.0)	—	O ₂	Toluene	50	<10
7	I ₂ (2.0)	—	DMSO	—	50	44
8	I ₂ (2.0)	K ₂ CO ₃ (2.0)	DMSO	—	50	58
9	I ₂ (2.0)	Cs ₂ CO ₃ (2.0)	DMSO	—	50	68
10	I ₂ (2.0)	Et ₃ N (2.0)	DMSO	—	50	Trace
11	I ₂ (2.0)	DBU (2.0)	DMSO	—	50	49
12	I ₂ (2.0)	Pyridine (2.0)	DMSO	—	50	52
13	I ₂ (2.0)	Cs ₂ CO ₃ (2.0)	DMSO	—	70	70
14	I ₂ (2.0)	Cs ₂ CO ₃ (2.0)	DMSO	—	90	74
15	I ₂ (2.0)	Cs ₂ CO ₃ (2.0)	DMSO	—	110	80
16	I ₂ (2.0)	Cs ₂ CO ₃ (2.0)	DMSO	—	130	75
17	I ₂ (1.5)	Cs ₂ CO ₃ (2.0)	DMSO	—	110	Trace
18	I ₂ (2.5)	Cs ₂ CO ₃ (2.0)	DMSO	—	110	84
19	I ₂ (2.7)	Cs ₂ CO ₃ (2.0)	DMSO	—	110	82
20	I ₂ (2.5)	Cs ₂ CO ₃ (1.5)	DMSO	—	110	57
21	I ₂ (2.5)	Cs ₂ CO ₃ (2.5)	DMSO	—	110	89
22	I ₂ (2.5)	Cs ₂ CO ₃ (3.0)	DMSO	—	110	33

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), promoter (2.0 equiv.), base (2.0 equiv.), oxidant (2.0 mmol) in 3 mL solvent, stirred at 50 °C for 24 h in the sealed tube. ^b Yields of the isolated product.

Table 2 Substrate scope of acetophenones with alcohols^a

^a Reaction conditions: acetophenones **1** (0.5 mmol), alcohols **2** (1.5 mmol), I_2 (1.25 mmol) and Cs_2CO_3 (1.25 mmol) solved in DMSO (3 mL) were stirred at 110 °C for 24 h in the sealed tube. Yields given for isolated products after chromatography.

phenylethanol to afford desired α -ketoesters **3ja**, **3ka** and **3la** in 92%, 82% and 65% yields, respectively. Aliphatic methyl ketones, such as acetone, cyclohexanone, and methyl-ethylketone have been tested in our optimized reaction conditions. However, none of the desired products were observed. In order to further expand the universality under the optimized reaction conditions, the substrate scope of alcohols was explored, including aromatic and aliphatic alcohols. To our satisfaction, a range of 2-phenylethanols and phenylmethanols bearing different electronic variation substituents or substitution pattern were all suitable to optimized reaction conditions and produced the desired products in 69–88% yields (Table 2, **3ab–3am**). Notably, 2-thiopheneethanol as heteroaromatic ethanol could also be transformed to corresponding products **3ah** in 66% yield (Table 2, **3ah**). Besides, a variety of aliphatic alcohols were carried out under our optimized conditions. The results suggest that both primary and second aliphatic alcohols,



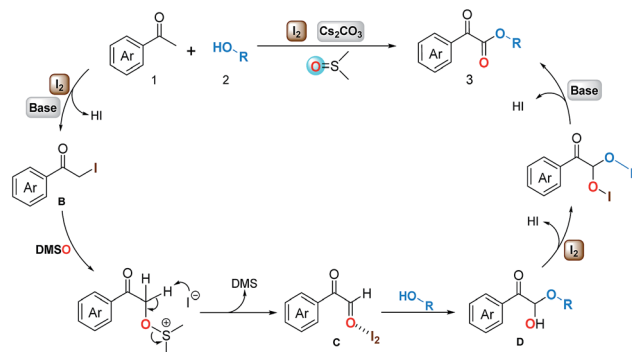
Scheme 2 Control experiments under optimized conditions.

such as cyclohexanol, *n*-butyl alcohol, ethanol and 3-methyl-3-butenol were all feasible and tolerated under this oxidative coupling reaction conditions with 60–76% yields of corresponding products obtained (Table 2, **3an–3aq**). According to the results of Table 2, this novel methodology to α -ketoesters has a board substrate scope with good yields, which implies its potential application in the last-stage functionalization of natural alcohols or some ketones with alcoholic hydroxyl group, such as cholesterol, androsterone, testosterone and the like.¹⁸

To gain deeper insight into the reaction mechanism and investigate the special role of DMSO, a series of control experiments were carried out between acetophenones **1a** and 2-phenylethanol **2a** under optimized reaction conditions (Scheme 2, experiments (1–6)). In the experiment (1), no desired product **3aa** was obtained when iodine was removed from optimized conditions. Meanwhile, the yield reduced greatly to 51% in the absence of Cs_2CO_3 (Scheme 2, experiment (2)). In the experiment (3), the parallel reactions were performed under air, O_2 and argon environment, affording similar yields of products respectively, demonstrating that aerobic conditions are not essential in this reaction process. Moreover, when the model reaction was performed in other solvents instead of DMSO, such as 1,4-dioxane, toluene, ACN and DMF, we failed to isolated the products **3aa** in an acceptable yield (Scheme 2, experiment (4)). For the purpose of ruling out the possible effect of water in the process, the same reaction was carried out in relatively dry and inert conditions with anhydrous DMSO and 4 Å MS added into the reaction conditions (experiment (5)). In

this case also, comparable yields of desired product **3aa** were observed. Next, the reaction between phenylglyoxal monohydrate **4a** and 2-phenylethanol **2a** were performed under optimized conditions as shown in experiment (6), the results showed that it could also be transformed smoothly to α -ketoesters **3aa** in 88% yield under optimized reaction conditions, indicating that phenylglyoxal monohydrate **4a** might act as the intermediate in this esterification process. Meanwhile, the results above obviously imply the significant role of DMSO in this reaction. Therefore, ^{18}O -labeled isotope experiment and ESI-MS analysis were conducted between acetophenone **1a** and 2-phenylethanol **2a** under optimized reaction conditions to further validate our conjecture (Scheme 3). When this reaction was carried out in ^{18}O -labeled DMSO replacing the general one, the ESI-MS analysis of this corresponding ^{18}O -**3aa** product clearly assigned the presence of the signal $[\text{M} + \text{Na}]^+$ and $[\text{M} + \text{K}]^+$ at 279.0906 and 295.0595 in noticeable detection, proving that DMSO served as the important oxidant in this transformation.

Based on the results above and the previous literatures reported, a plausible mechanism is proposed as shown in Scheme 4. To begin with, compound **B** is generated from the iodination of arylmethylketone and then undergoes Kornblum oxidation in the presence of DMSO, affording the key intermediate arylglyoxal (compound **C**) with the release of DMS. Next, alcoholic



Scheme 4 Possible reaction mechanism.

hydroxyl group attacks the aldehyde group of α -carbonyl aldehyde that is activated by iodine to generate the alcohol (compound **D**), which is finally oxidized by the system of I_2 and base to give desired product α -ketoesters in good yields.

Conclusion

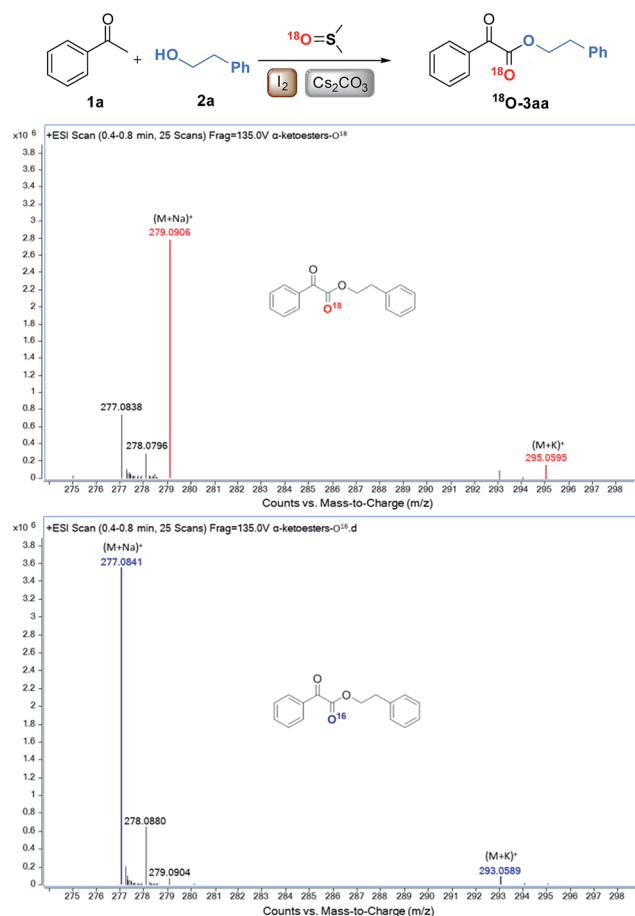
In conclusion, we have developed a novel one-pot strategy for the synthesis of functional and valuable α -ketoesters from acetophenones with alcohols in moderate to excellent yields. What's more, this facile methodology takes advantage of cheap and abundant starting materials under mildly metal-free conditions and has wide functional group universality, implying its potential value in industrialization and the last-stage functionalization of natural alcohols. Plausible mechanism was proposed based on a series of control experiments and DMSO- ^{18}O isotopic labelling experiments. Further studies on the applications of this strategy are ongoing in our group.

Acknowledgements

The research has been supported by the National Natural Science Foundation of China (Grant No. 21522604, U1463201 and 21402240); the youth in Jiangsu Province Natural Science Fund (Grant No. BK20150031, BK20130913 and BY2014005-03); a Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

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Scheme 3 ^{18}O -Labeled isotope experiment and ESI-MS analysis.

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Synthesis of Pelorol and Analogues: Activators of the Inositol 5-Phosphatase SHIP

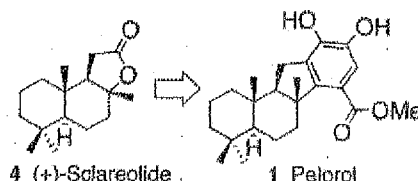
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Received December 29, 2004

ABSTRACT



A screening program designed to find new antiinflammatory agents has identified the sponge meroterpenoid pelorol (1) as an in vitro activator of the inositol-5-phosphatase SHIP. Pelorol (1) and several functional group analogues have been synthesized from sclareolide (4).

The phosphatidylinositol-3-kinase (PI3K) signaling pathway plays an important role in the regulation of many cellular functions, including survival, adhesion, movement, proliferation, differentiation, and end cell activation.¹ A key second messenger in this pathway is the membrane-associated phosphatidylinositol-3,4,5-trisphosphate (PI-3,4,5-P₃), which is present in low levels in unstimulated cells but is rapidly synthesized from PI-4,5-P₂ by PI3K in response to a diverse set of extracellular stimuli (Figure 1). To ensure that activation of the PI3K pathway is appropriately restrained, the tumor suppressor PTEN hydrolyzes PI-3,4,5-P₃ back to PI-4,5-P₂ and the Src homology 2-containing inositol 5-phosphatases SHIP, sSHIP, and SHIP2 hydrolyze it to PI-3,4-P₂.

Approximately 50% of human cancers contain biallelic inactivating mutations of the ubiquitously expressed PTEN, which illustrates the importance of these phosphatases in preventing uncontrolled cell growth. Similar to PTEN, SHIP2 is expressed in a wide variety of cell types, whereas sSHIP is restricted to stem cells and SHIP is found only in hematopoietic (blood) cells.

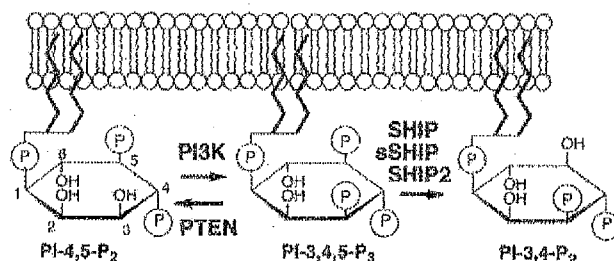


Figure 1. Enzymatic synthesis and degradation of PI-3,4,5-P₃.

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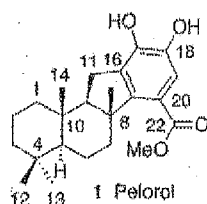
^{||} University of Amsterdam.

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Krystal and co-workers have generated mice containing a homozygous deletion of SHIP (SHIP^{-/-} mice).² These animals are viable and fertile but typically do not survive beyond 14 weeks because of a myeloproliferative disorder. Experiments with SHIP^{-/-} mice and with SHIP^{-/-} bone-marrow-derived mast cells (BMMC's) and macrophages (BMMφ's) obtained from these mice, have demonstrated that SHIP is a negative regulator of immunoglobulin E (IgE) or Steel Factor induced mast cell activation,³ a negative regulator of lipopolysaccharide (LPS) induced macrophage activation, and a negative regulator of osteoclast formation and resorptive function. As a result of this last property, SHIP^{-/-} mice suffer from severe osteoporosis.⁴ There is also evidence that SHIP acts as a tumor suppressor in both acute myelogenous leukemia (AML)⁵ and in chronic myelogenous leukemia (CML).⁶

Current attempts to develop drugs based on intervention in signaling pathways are overwhelmingly biased toward finding selective kinase inhibitors. There has been some recent interest in examining the therapeutic potential of phosphatase inhibitors,⁷ but there has been virtually no effort to explore the usefulness of small-molecule phosphatase activators. The important role of SHIP as a negative regulator of mast cell and macrophage activation, osteoclast formation, and resorptive function, as well as in AML and CML, combined with its occurrence only in hematopoietic cells, makes it an attractive drug target. We hypothesized that selective activators of SHIP would be useful experimental tools and potential drug candidates to provide proof of principle validation for a new approach to the treatment of inflammation, osteoporosis, and leukemia.

Crude extracts of marine invertebrates were screened for in vitro activation of the SHIP-catalyzed conversion of inositol-1,3,4,5-tetrakisphosphate (IP₄) to inositol-1,3,4-trisphosphate (IP₃).⁸ A MeOH extract of the sponge *Dactylospongia elegans* (Thiele, 1899), collected in Papua New Guinea,⁹ showed promising activity in the assay. Bioassay-guided fractionation of the extract identified pelorol (**1**) as the sole SHIP-activating component. Three related mero-



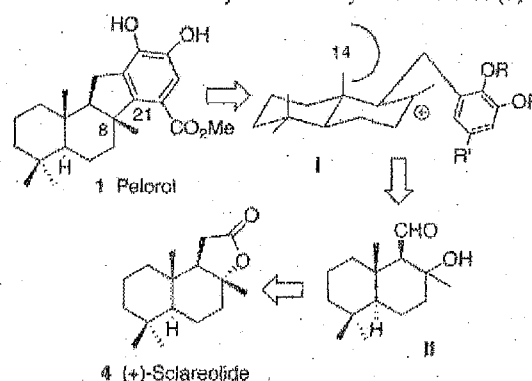
terpenoids, ilimaquinone,¹⁰ mamanuthaquinone,¹¹ and dactyloquinone A,¹² were also isolated from the *D. elegans* extract but were not active in the assay. Pelorol (**1**) was

undescribed when first isolated in our laboratory as a SHIP activator, but while further biological studies were in progress it was isolated by König's group, also from *D. elegans*,¹³ and by Schmitz's group from *Petrospongia metachromia*.¹⁰ Spectroscopic data obtained for pelorol in the current work was in complete agreement with the data reported by König and Schmitz.

The limited quantity (~10 mg) of pelorol (**1**) available from the source sponge *D. elegans* was inadequate to support detailed in vitro and in vivo evaluation of its ability to activate SHIP. To satisfy the need for additional material, confirm the absolute configuration of the natural product, and generate analogues for SAR, the total synthesis of pelorol (**1**) and analogues where the methyl ester at C-20 was replaced by methyl and ethyl residues was undertaken.

On the basis of sound biogenetic arguments, Schmitz predicted that the absolute configuration of pelorol (**1**) was 5*S*,8*R*,9*R*,10*S* as drawn. Therefore, the starting material selected for the synthesis of pelorol and analogues was the commercially available terpenoid (+)-sclareolide (**4**), which has the same absolute configurations at C-5, C-9, and C-10 as those predicted for pelorol (**1**). The synthetic plan anticipated that the key reaction would involve a biomimetic carbocation-initiated cyclization of an intermediate **I** to generate the C-8/C-21 bond (Scheme 1). Steric bulk associ-

Scheme 1. Retrosynthetic Analysis of Pelorol (**1**)



ated with the C-14 methyl was expected to cause preferential approach of the phenyl ring from the bottom face of C-8 to form the required trans B/C ring fusion. Synthetic routes to both C-8 epimers (**5** and **15**) of **II** starting from sclareolide have been reported, and the plan was to examine both as

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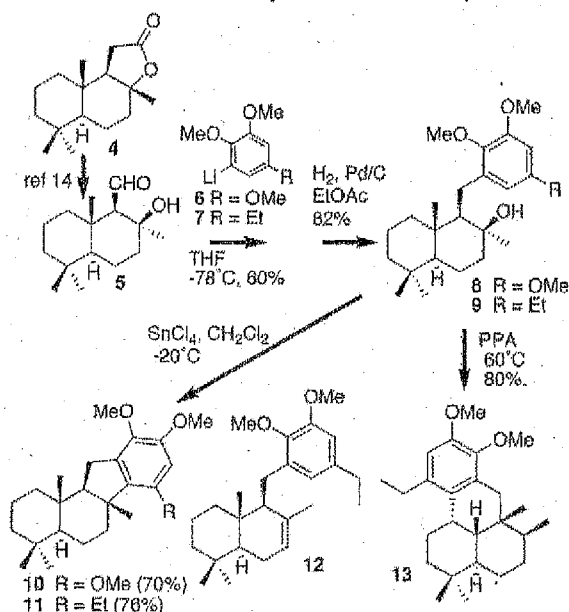
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(8) The SHIP assay was performed in 96-well microtitre plates with 10 ng of recombinant SHIP enzyme per well. SHIP enzyme was incubated with extract or DMSO for 15 min at 23 °C before addition of 200 mM inositol-1,3,4,5-tetrakisphosphate. The reaction was allowed to proceed for 20 min at 37 °C and the amount of inorganic phosphate released was then assessed by the addition of Malachite Green reagent followed by an absorbance measurement at 650 nm.

intermediates in the preparation of direct precursors to the carbocation **1** and ultimately cyclized products.

(+)-Sclareolide (**4**) was converted to the aldehyde **5** following the literature procedure (Scheme 2).¹⁴ Overman

Scheme 2. Initial Attempts at Biomimetic Cyclizations



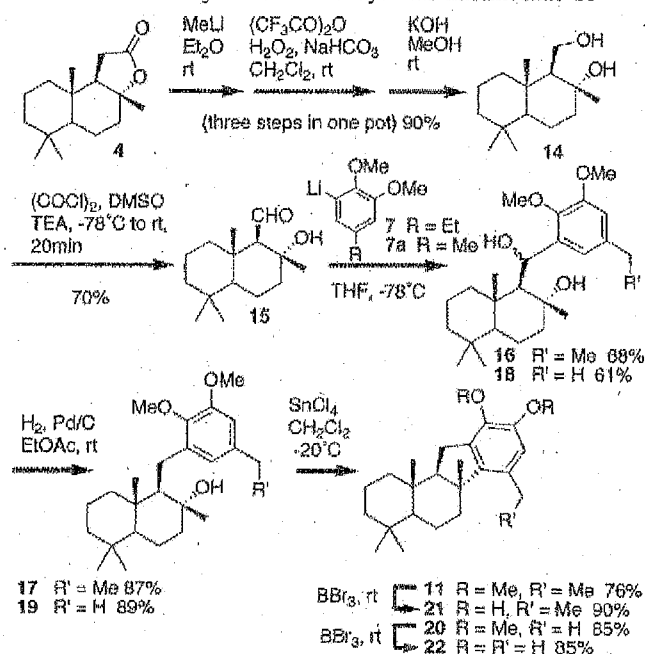
showed in his synthesis of adociasulfate that a highly nucleophilic arene was required to trap a carbocation such as **1** in preference to proton elimination to give an uncyclized olefin.¹⁵ Therefore, trimethoxyphenyllithium **6** (2 equiv) was added to aldehyde **5**, followed by hydrogenolysis of the resulting epimeric benzyl alcohols, to give the tertiary alcohol **8**. Treatment of **8** with SnCl_4 gave the cyclization product **10** having the desired stereochemistry in good yield. Unfortunately, all attempts to transform 1,2,4-trialkoxy benzene **10** or various alkyl ether analogues into polorol failed.

In an attempt to overcome this problem, the coupling reaction was repeated with dimethoxyethylphenyllithium **7** to give the tertiary alcohol **9**. Initial reactions of **9** with SnCl_4 gave variable yields of the desired product **11** and the undesired elimination product **12**, while treatment with the protic acid PPA gave only the unanticipated cyclization product **13**. We envisaged that the formation of **12** and **13** resulted from reduction of the nucleophilicity of the arene

($\text{R} = \text{Et}$ vs $\text{R} = \text{OMe}$) making the elimination reaction leading to **12** and the Wagner Meerwein rearrangements leading to **13** competitive with direct trapping of the C-8 carbocation by the arene to give the desired product **11**. After optimization of the reaction conditions, it was found that the SnCl_4 -catalyzed cyclization gave consistently high yields (~76%) for the conversion of **9** to **11**.

Although it was possible to obtain **11** via the aldehyde **5**, the preparation of **5** from sclareolide was cumbersome because it required multiple chromatographic separations and preparation of an oxidizing agent that was not commercially available.¹⁴ Therefore, we turned our attention to the aldehyde **15**, having an equatorial OH group at C-8 (Scheme 3).¹⁶ (+)-

Scheme 3. Synthesis of the Cyclized Intermediate **11**



Sclareolide (**4**) was converted to the diol **14** in excellent yield (90%) using a one-pot three-step sequence modification of the literature procedure.¹⁶ Swern oxidation cleanly oxidized the diol **14** to the aldehyde **15**.¹⁷ Reaction of **15** with phenyllithium **7** gave the epimeric benzyl alcohols **16** in good yield. Hydrogenolysis of the mixture **16** cleanly removed the benzylic alcohols to give **17**. Cyclization of **17** using SnCl_4 as a catalyst gave the desired tetracyclic intermediate **11** in high yield, without any trace of the elimination product **12**. Dimethyl ether **11** was converted to the catechol **21**, and the entire sequence was repeated with phenyllithium **7a** to give the methyl analogue **22** to provide polorol analogues for SAR.

Reaction of **11** with PCC selectively oxidized the C-22 methylene to give methyl ketone **23** in reasonable yield (Scheme 4). Treatment of **23** with I_2 in aqueous NaOH , in

(9) A voucher sample has been deposited at the Zoological Museum, University of Amsterdam (ZMA POR. 15986).

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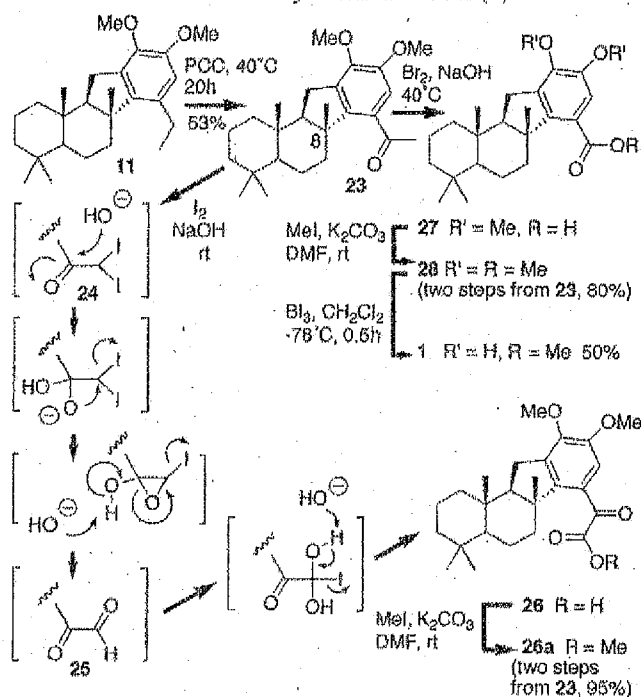
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Scheme 4. Synthesis of Pelorol (1)



an attempt to effect a haloform reaction to give benzoic acid 27, unexpectedly resulted in the near quantitative formation of the α -ketoacid 26. This anomalous result might be caused by the steric bulk of the C-8 carbon ortho to the C-22 ketone preventing the formation of a triiodinated methyl. If a diiodinated methyl ketone 24 is attacked by hydroxide to give a tetrahedral intermediate, the diiodomethyl may not be a good enough leaving group to depart in the normal fashion to give a carboxylic acid. Instead, an intramolecular S_N2 displacement of iodide can form an epoxide, which after fragmentation as shown in Scheme 4 can lead to the α -keto aldehyde 25. Oxidation of 25 via iodination of the aldehyde hydrate can generate the final α -ketoacid 26. Simply changing the halogen to Br_2 led to a clean transformation of methyl ketone 23 to the desired benzoic acid 27.

The synthesis of pelorol (1) was completed by esterification of 27 with MeI followed by selective cleavage of the phenyl methyl ethers with Br_3 at $-78^\circ C$. Synthetic pelorol (1) was identical by NMR and MS comparison with the natural product. The $[\alpha]_D$ of the synthetic material was -64° compared with values of -69° reported by König and -71° reported by Schmitz, confirming that the absolute configuration is 5*S*,8*R*,9*R*,10*S* as predicted by Schmitz.¹⁸

Pelorol (1), dimethylpelorol (28), the analogues 21 and 22, the corresponding methyl ethers 11 and 20, the trimethoxy pelorol analogue 10, and the uncyclized precursor 19 were tested for in vitro activation of SHIP and the ability to suppress degranulation and tumor necrosis factor α (TNF α) production in murine mast cells stimulated with IgE.¹⁸ Synthetic pelorol (1), the ethyl analogue 21, and the methyl analogue 22 showed significant activity in all three assays, but the methyl ethers 10, 11, 19, 20, and 28 were inactive. The relative effectiveness of the active compounds in the SHIP activation assay was $22 > 21 \approx 1$, showing that replacement of the methyl ester at C-20 in pelorol with a methyl gives enhanced activity. Lack of activity in the dimethyl ethers 20, 11, and 28 demonstrates that at least one phenol is required for activity.

Compound 22 was chosen for further evaluation because it showed biological activity greater than that of pelorol and its synthesis was shorter. Side by side evaluation of 22's ability to suppress degranulation and TNF α release in SHIP $-/-$ and SHIP $+/+$ mast cells showed that it was only active in the SHIP $+/+$ cells, indicating that it selectively targets SHIP. Compound 22 also showed positive effects comparable to the reference standard dexamethasone in a standard mouse ear edema assay for topical antiinflammatory activity and in a mouse model of septic shock.¹⁸

In summary, the sponge meroterpenoid pelorol (1) has been identified as an activator of the inositol-5-phosphatase SHIP. An efficient synthesis of pelorol (1) and several analogues has confirmed the structure and absolute configuration of the natural product and provided preliminary SAR for the SHIP-activating pharmacophore. The C-20 methyl analogue 22 has shown promising in vivo activity in two mouse models of inflammation, supporting the initial hypothesis that selective small-molecule SHIP activators should represent a new class of antiinflammatory agents.

Acknowledgment. Financial support was provided by NCIC (R.J.A.), NSERC (R.J.A.), and CIHR (R.J.A., A.M., C.O.). The authors thank M. Le Blanc for assistance with collecting *D. elegans*.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) Pure compounds were tested at 5 $\mu g/mL$. In the SHIP assay, 22 showed > 6 -fold activation, whereas 1 and 21 showed ca. 2-fold activation. See Supporting Information for experimental details of the in vivo assays. A complete description of the biological activity of pelorol and the synthetic analogues will be published elsewhere.

Supporting Information

Synthesis of Pelorol and Analogs: Activators of the Inositol 5-Phosphatase SHIP

Lu Yang,[†] David E. Williams,[†] Alice Mui,[‡] Christopher Ong,[†] Gerald Krystal,[§] Rob van Soest,[#] and
Raymond J. Andersen^{*†}

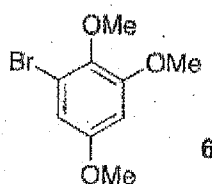
Departments of Chemistry and Earth & Ocean Sciences, University of British Columbia, Vancouver, B.C., Canada, V6T 1Z1; The Jack Bell Research Centre, Vancouver Hospital and Health Sciences Centre, Vancouver, B.C.; Terry Fox Laboratory, B.C. Cancer Control Agency, Vancouver, B.C. V5Z 1L3; Zoologisch Museum, University of Amsterdam, Amsterdam, The Netherlands

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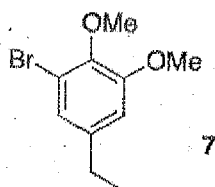
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Experimental section

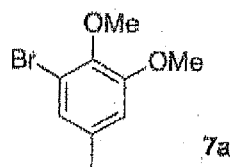
General: Starting materials and reagents were obtained from commercial sources and were used without further purification. Diethylether (Et₂O) and tetrahydrofuran (THF) were purified by distillation from sodium/benzophenone immediately before use. Dichloromethane was distilled from CaH₂ under Argon. Moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N₂. Evaporations were conducted under reduced pressure at room temperature. Analytical thin layer chromatography was performed on silica gel 60 F-254 pre-coated aluminum plates (Merck). Column chromatography was carried out on 70-230 mesh silica gel and 10 g normal phase Sepaks with the indicated solvents. Proton and carbon nuclear magnetic resonance spectra were obtained using a Bruker Avance-400 spectrometer. High resolution electrospray ionization mass spectra (HRESIMS) were obtained on ESI micromass LCT spectrometer.



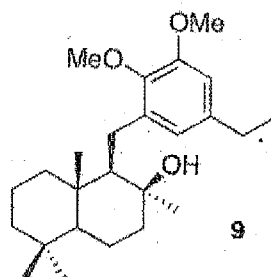
1-Bromo-2,3,5-trimethoxybenzene (6) was synthesized according to a literature procedure.¹



1-Bromo-2,3-dimethoxy-5-ethylbenzene (7). 1-bromo-2,3-dimethoxy-5-ethenylbenzene was synthesized according to literature procedure.² Hydrogenation of 1-bromo-2,3-dimethoxy-5-ethenylbenzene (5.0 g, 20.4 mmol) was carried out overnight in CH₂Cl₂ (15 mL) under H₂ (3 bars) in the presence of 5% Rh/C (800 mg). The mixture was filtered and the catalyst was washed with acetone. The filtrate and acetone washings were combined, evaporated, and dried under high vacuum to afford 4.84 g of 7 (a colorless oil, 96%) which was used in the next step without purification. ¹H NMR (CDCl₃) δ 1.20 (t, J = 7.6 Hz, 3H), 2.55 (q, J = 7.6 Hz, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 6.66 (d, J = 1.8 Hz, 1H), 6.95 (d, J = 1.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 15.4, 28.5, 56.0, 60.5, 111.5, 117.3, 123.7, 141.4, 144.4, 153.4; HRESIMS calcd for C₁₀H₁₄O₂⁸¹Br 247.0157, found 247.0157.

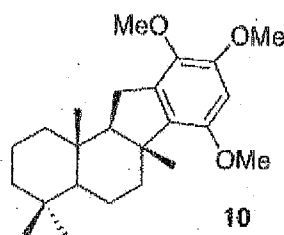


1-Bromo-2,3-dimethoxy-5-methyl benzene (7a).³ To a stirred solution of 5-bromoveratraldehyde (2.0 g, 8.7 mmol) in 1,2-dichloroethane (45.0 mL) at ambient temperature were added zinc iodide (3.9 g, 12.2 mmol) and sodium cyanoborohydride (3.8 g, 61.2 mmol). The reaction mixture was heated under gentle reflux for 20 h and then filtered through celite. The filtrate was evaporated to dryness to afford 1.5 g of **7a** (light yellow oil, 80%). ¹H NMR (CDCl₃) δ 2.26 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 6.63 (d, J = 1.4 Hz, 1H), 6.92 (d, J = 1.4 Hz, 1H); ¹³C NMR (CDCl₃) δ 20.9, 56.0, 60.4, 112.6, 117.2, 124.9, 135.0, 144.2, 153.3; HRESIMS calcd for C₉H₁₁O₂Na⁸¹Br 254.9820, found 254.9830.

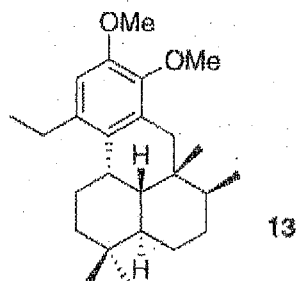


Dimethylether (9). A 1.7 M solution of t-BuLi in pentane (1.74 mL, 2.79 mmol) was added slowly to a stirred solution of **7** (627.4 mg, 2.54 mmol) in dry THF (20.0 mL) at -78°C. After stirring for 30 min, a solution of **5** (300mg, 1.26mmol) in dry THF (5.0 mL) was added. The mixture was further stirred at -78°C for 2 h after which H₂O (10.0 mL) was added and the mixture was extracted with Et₂O (120 mL, twice). The combined Et₂O extracts were washed with saturated brine, dried (MgSO₄), and concentrated to give a residue, which was chromatographed on a normal phase Sepak (8:2 Hexane/EtOAc) to give 306 mg of **9a** (white solid). ¹H NMR (CDCl₃) δ 0.87 (s, 3H), 0.88 (s, 3H), 1.03 (s, 3H), 1.21 (t, J = 7.6 Hz, 3H), 1.36 (s, 3H), 1.92 (brd, J = 12.5Hz, 1H), 2.59 (q, J = 7.7 Hz, 2H), 3.77 (s, 3H), 3.84 (s, 3H), 5.49 (s, 1H), 6.63 (d, J = 1.7Hz, 1H), 7.03 (d, J = 1.7 Hz, 1H); ¹³C NMR (CDCl₃) δ 15.7, 16.3, 18.4, 18.8, 21.8, 29.0, 32.8, 33.5, 33.8, 39.3, 39.9, 41.9, 44.1, 55.6, 55.7, 59.1, 60.0, 69.5, 75.4, 76.7, 77.0, 77.3, 110.0, 118.9, 139.2, 139.8, 143.3, 151.9; HRESIMS calcd for C₂₅H₄₀O₄Na 427.2824, found 427.2828. Hydrogenolysis of **9a** (202 mg, 0.5 mmol) was carried out overnight in EtOAc (8.0 mL) under H₂ (3 bars) in the presence of 10 % Pd/C (150 mg). The reaction mixture was filtered and concentrated to afford a brown oil, which was further purified by silica gel-column chromatography (9:1

Hexane/EtOAc) to give 165 mg of **9** (colorless oil, 85%). ^1H NMR (CDCl_3) δ 0.85 (s, 3H), 0.87 (s, 3H), 0.90 (s, 3H), 1.06 (s, 3H), 1.21 (t, $J = 7.6$ Hz, 3H), 1.73 (dt, $J = 13.1, 2.7$ Hz, 1H), 1.79 (brd, $J = 12.3$ Hz, 1H), 2.57 (q, $J = 7.5$ Hz, 2H), 2.60 (dd, $J = 15.7, 2.9$ Hz, 1H), 2.91 (dd, $J = 15.7, 7.3$ Hz, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 6.54 (d, $J = 1.8$ Hz, 1H), 6.63 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 15.2, 15.8, 18.5, 18.5, 21.9, 23.4, 28.9, 31.6, 33.4, 33.6, 39.0, 40.0, 42.0, 42.9, 55.6, 56.0, 58.9, 60.6, 73.3, 109.0, 120.5, 137.9, 139.7, 144.5, 152.4; HRESIMS calcd for $\text{C}_{25}\text{H}_{40}\text{O}_3\text{Na}$ 411.2875, found 411.2880.

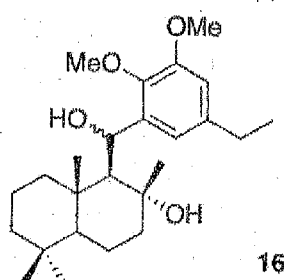


Trimethylether (10). The procedure for the preparation of **8** was the same as that used in the preparation of **9**. It afforded **8** (colorless oil, 20 mg, 60%), which was dissolved in 5 mL of CH_2Cl_2 and SnCl_4 (0.05 mL) was added slowly with stirring at -20°C under argon for 2 min. The resulting mixture was further stirred for 20 min and then diluted with CH_2Cl_2 (10 mL) and poured onto ice. The aqueous phase was extracted with CH_2Cl_2 (two x 10 mL) and the combined extracts were washed with saturated NaHCO_3 , saturated brine, and dried over MgSO_4 . Evaporation of the CH_2Cl_2 and purification of the residue by silica gel chromatography (40:1 Hexane/EtOAc) gave the trimethylether **10** (colorless oil, 14 mg, 70%). ^1H NMR (CDCl_3) δ 0.84 (s, 3H), 1.01 (s, 3H), 1.06 (s, 3H), 1.23 (s, 3H), 1.71 (dd, $J = 12.8, 6.1$ Hz, 1H), 2.40 (m, 1H), 2.50 (dd, $J = 14.7, 12.9$ Hz, 1H), 2.69 (dd, $J = 14.7, 6.2$ Hz, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 3.82 (s, 3H), 6.28 (s, 1H); ^{13}C NMR (CDCl_3) δ 16.2, 18.4, 19.5, 20.7, 21.1, 25.9, 33.1, 33.4, 37.0, 38.4, 40.2, 42.6, 46.8, 55.9, 56.3, 57.5, 60.6, 64.5, 96.3, 134.3, 136.8, 139.8, 150.9, 150.9; HRESIMS calcd for $\text{C}_{24}\text{H}_{36}\text{O}_3\text{Na}$ 395.2562, found 395.2564.

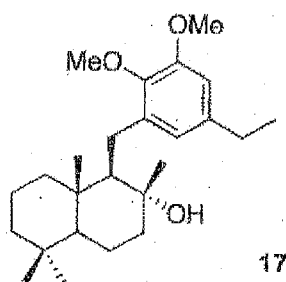


Tetracycle (13). Dimethylether **9** (100 mg, 0.26 mmol) was dissolved in 3.0 mL of polyphosphoric acid (PPA) and the mixture was heated under Argon at 60°C for 30 min. The resulting orange mixture was diluted with ice

water and extracted repeatedly with Et₂O. The combined extracts were washed with brine and concentrated to give a brown oil, which was further purified by silica gel column chromatography (20:1 Hexane/EtOAc) to give 76.3 mg of **13** (80%). The structure of **13** was elucidated by analysis of COSY, HMBC, HMQC, and ROESY data. ¹H NMR (CDCl₃) δ 0.73 (s, 3H), 0.75 (s, 3H), 0.82 (s, 3H), 0.99 (d, J = 7.2 Hz, 3H), 1.21 (t, J = 7.5 Hz, 3H), 2.13 (d, J = 18.4 Hz, 1H), 2.61 (m, 2H), 3.08 (m, 1H), 3.20 (d, J = 18.4 Hz, 1H), 3.76 (s, 3H), 3.82 (s, 3H), 6.59 (s, 1H); ¹³C NMR (CDCl₃) δ 14.8, 15.9, 20.6, 21.6, 24.4, 26.3, 27.3, 28.8, 30.5, 32.1, 32.9, 33.7, 34.7, 37.6, 38.2, 38.9, 42.1, 55.5, 59.8, 111.4, 130.2, 132.0, 138.1, 144.4, 149.4; HRESIMS calcd for C₂₅H₃₈O₂Na 393.2770, found 393.2768.

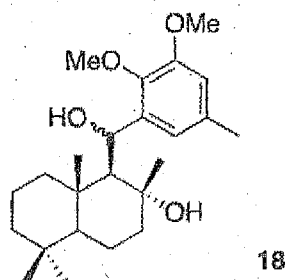


Diol (16). The procedure for the synthesis of **16** from **15** is the same as that used in the preparation of **9a** from **5** and it afforded **16** as a white solid (63%). ¹H NMR (CDCl₃) δ 0.28 (td, J = 13.1, 3.4 Hz, 1H), 0.76 (s, 3H), 0.81 (s, 3H), 1.03 (s, 3H), 1.21 (t, J = 7.6 Hz, 3H), 1.54 (s, 3H), 1.85 (dt, J = 12.2, 3.2 Hz, 1H), 2.11 (d, J = 8.4 Hz, 1H), 2.60 (q, J = 7.6 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 5.25 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 1.7 Hz, 1H), 6.90 (d, J = 1.7 Hz, 1H); ¹³C NMR (CDCl₃) δ 15.7, 15.9, 18.4, 20.0, 21.7, 25.8, 28.9, 33.3, 33.6, 38.9, 40.0, 41.5, 44.7, 55.7, 56.0, 61.3, 62.7, 69.5, 74.7, 111.0, 119.6, 140.5, 140.6, 143.5, 152.3; HRESIMS calcd for C₂₅H₄₀O₄Na 427.2824, found 427.2828.

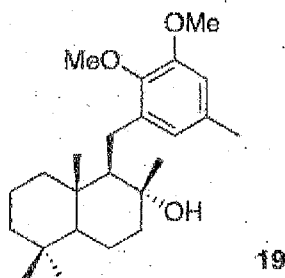


Tertiary alcohol (17). The procedure for the preparation of **17** from **16** is the same as that used in the preparation of **9** from **9a** and it afforded **17** as a colorless oil (87%). ¹H NMR (CDCl₃) δ 0.78 (s, 3H), 0.83 (s, 3H), 0.89 (s, 3H), 1.08 (td, J = 13.3, 3.8 Hz, 1H), 1.19 (t, J = 7.6 Hz, 3H), 1.26 (s, 3H), 1.82 (dt, J = 12.5, 3.2 Hz,

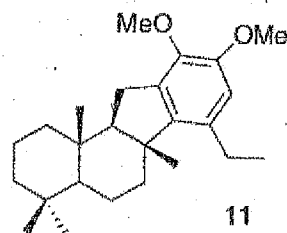
1H), 2.54 (q, $J = 7.6\text{ Hz}$, 2H), 2.81 (dd, $J = 14.5, 5.5\text{ Hz}$, 1H), 3.81 (s, 6H), 6.54 (d, $J = 1.8\text{ Hz}$, 1H), 6.64 (d, $J = 1.8\text{ Hz}$, 1H); ^{13}C NMR (CDCl_3) δ 15.4, 15.7, 18.6, 20.3, 21.6, 24.3, 25.3, 28.8, 33.3, 33.5, 39.4, 40.3, 41.8, 43.7, 55.6, 56.1, 60.6, 62.8, 73.7, 109.6, 122.0, 137.6, 140.0, 144.3, 152.3; HRESIMS calcd for $\text{C}_{25}\text{H}_{40}\text{O}_3\text{Na}$ 411.2875, found 411.2871.



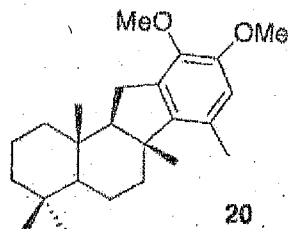
Diol (18). The procedure for the preparation of **18** from **15** was the same as that used in the preparation of **9a** from **5** and afforded **18** as a white solid (61%). ^1H NMR (CDCl_3) δ 0.27 (td, $J = 12.8, 3.1\text{ Hz}$, 1H), 0.75 (s, 3H), 0.80 (s, 3H), 1.02 (s, 3H), 1.53 (s, 3H), 1.84 (dt, $J = 12.2, 2.9\text{ Hz}$, 1H), 2.10 (d, $J = 8.5\text{ Hz}$, 1H), 2.31 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 5.26 (d, $J = 8.5\text{ Hz}$, 1H), 6.61 (d, $J = 1.5\text{ Hz}$, 1H), 6.89 (d, $J = 1.5\text{ Hz}$, 1H); ^{13}C NMR (CDCl_3) δ 15.8, 18.4, 20.0, 21.5, 21.6, 25.9, 33.2, 33.6, 38.8, 39.8, 41.5, 44.6, 55.6, 55.9, 61.4, 62.6, 69.0, 74.7, 112.1, 120.5, 134.1, 140.7, 143.3, 152.2; HRESIMS calcd for $\text{C}_{24}\text{H}_{38}\text{O}_4\text{Na}$ 413.2668, found 413.2664.



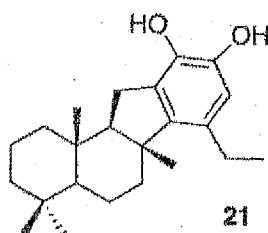
Tertiary alcohol (19). The procedure for the preparation of **19** from **18** was the same as that used in the preparation of **9** from **9a** and it afforded **19** as a colorless oil (89%). ^1H NMR (CDCl_3) δ 0.78 (s, 3H), 0.83 (s, 3H), 0.88 (s, 3H), 1.27 (s, 3H), 1.76 (brd, $J = 12.6\text{ Hz}$, 1H), 1.82 (dt, $J = 12.5, 3.2\text{ Hz}$, 1H), 2.25 (s, 3H), 2.54 (dd, $J = 14.5, 4.6\text{ Hz}$, 1H), 2.78 (dd, $J = 14.5, 5.6\text{ Hz}$, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 6.52 (d, $J = 1.7\text{ Hz}$, 1H), 6.62 (d, $J = 1.7\text{ Hz}$, 1H); ^{13}C NMR (CDCl_3) δ 15.4, 18.6, 20.3, 21.4, 21.6, 24.3, 25.0, 33.3, 33.5, 39.4, 40.3, 41.8, 43.7, 55.6, 56.1, 60.6, 62.8, 73.7, 110.8, 123.1, 129.6, 133.6, 137.7, 152.3; HRESIMS calcd for $\text{C}_{24}\text{H}_{38}\text{O}_3\text{Na}$ 397.2719, found 397.2713.



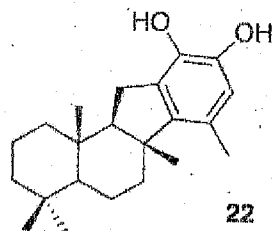
Tetracycle (11). To a stirred solution of **9** or **17** (38.8 mg, 0.1mmol) in CH_2Cl_2 (10 mL), SnCl_4 (0.1mL) was added slowly at -20°C under argon for 2 min. The resulting mixture was stirred for a further 20 min and then diluted with CH_2Cl_2 (20 mL) and poured onto ice. The aqueous phase was extracted with CH_2Cl_2 (two x 20 mL) and the combined extracts were washed with saturated NaHCO_3 , brine, and dried over MgSO_4 . Evaporation of the CH_2Cl_2 and purification of the residue by silica gel chromatography (20:1 Hexane/EtOAc) gave **11** as a colorless oil (29.5 mg, 76%). ^1H NMR (CDCl_3) δ 0.85 (s, 6H), 1.02 (s, 3H), 1.08 (s, 3H), 1.22 (t, $J = 7.6$ Hz, 3H), 2.36 (dt, $J = 12.0, 3.4$ Hz, 1H), 2.49 (dd, $J = 14.5, 13.0$ Hz, 1H), 2.56 (dd, $J = 14.5, 7.5$ Hz, 1H), 2.69 (m, 2H), 3.80 (s, 3H), 3.81 (s, 3H), 6.49 (s, 1H); ^{13}C NMR (CDCl_3) δ 16.0, 16.1, 18.3, 19.7, 21.1, 21.3, 24.7, 25.2, 33.1, 33.4, 37.1, 39.3, 40.2, 42.5, 47.9, 55.9, 57.1, 60.4, 64.3, 111.1, 133.7, 135.8, 143.6, 144.8, 150.3; HRESIMS calcd for $\text{C}_{25}\text{H}_{38}\text{O}_2\text{Na}$ 393.2770, found 393.2768.



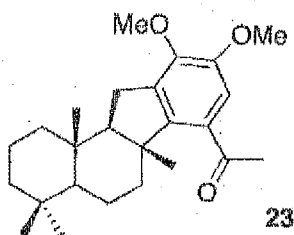
Tetracycle (20). The procedure for the preparation of **20** from **19** was the same as that used to prepare **11** from **17** and it afforded **20** as a colorless oil (85%). ^1H NMR (CDCl_3) δ 0.85 (s, 6H), 1.02 (s, 3H), 1.06 (s, 3H), 2.24 (s, 3H), 2.32 (dt, $J = 11.7, 3.1$ Hz, 1H), 2.49 (dd, $J = 14.8, 13.0$ Hz, 1H), 2.69 (dd, $J = 14.8, 6.1$ Hz, 1H), 3.47 (s, 6H), 6.41 (s, 1H); ^{13}C NMR (CDCl_3) δ 16.1, 18.3, 18.6, 19.6, 20.5, 21.1, 25.3, 33.1, 33.4, 37.1, 38.8, 40.1, 42.5, 47.6, 55.9, 57.1, 60.4, 64.4, 113.0, 127.1, 135.8, 143.7, 145.2, 150.0; HRESIMS calcd for $\text{C}_{24}\text{H}_{36}\text{O}_2\text{Na}$ 379.2613, found 379.2614.



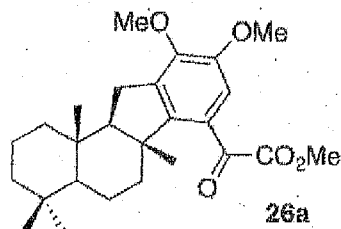
Catechol (21). To a stirred solution of 11 (38.6mg, 0.1mmol) in CH_2Cl_2 (1 mL) under Argon at 0 °C, BBr_3 in CH_2Cl_2 (2.0 mL 1M) was added and stirring was continued for 1.5 h at rt. The mixture was then poured into H_2O and extracted with CH_2Cl_2 (three x 50 mL). The combined CH_2Cl_2 extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified by silica gel flash chromatography (hexane:EtOAc 7:3) to afford 21 as a white solid (32mg, 90%). ^1H NMR (CDCl_3) δ 0.85 (s, 6H), 1.02 (s, 3H), 1.20 (s, 3H), 2.35 (dt, J = 12.2, 3.4 Hz, 1H), 2.43 (dd, J = 13.9, 13.6 Hz, 1H), 2.57 (m, 2H), 2.61 (dd, J = 14.5, 7.3 Hz, 1H), 6.47 (s, 1H); ^{13}C NMR (CDCl_3) δ 15.9, 16.1, 18.3, 19.6, 21.0, 21.3, 24.1, 24.4, 33.0, 33.3, 37.0, 40.1, 42.4, 48.0, 57.0, 64.5, 113.5, 128.4, 130.8, 137.8, 141.3, 144.7; HRESIMS calcd for $\text{C}_{23}\text{H}_{34}\text{O}_2\text{Na}$ 365.2457, found 365.2456.



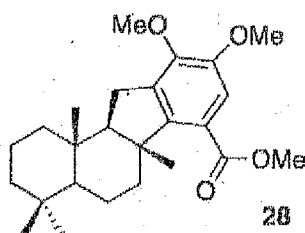
Catechol (22). The procedure for the preparation of 22 from 20 was the same as that used for the preparation of 21 from 11 and it gave 22 as a white solid (85%). ^1H NMR (CDCl_3) δ 0.85 (s, 6H), 1.02 (s, 3H), 1.04 (s, 3H), 1.74 (dd, J = 12.6, 6.4 Hz, 1H), 2.17 (s, 3H), 2.31 (dt, J = 11.6, 3.0 Hz, 1H), 2.43 (dd, J = 14.0, 12.5 Hz, 1H), 2.57 (dd, J = 14.3, 6.4 Hz, 1H), 6.40 (s, 1H); ^{13}C NMR (CDCl_3) δ 16.1, 18.2, 18.3, 19.5, 20.5, 21.1, 24.5, 33.0, 33.4, 37.0, 38.7, 40.0, 42.5, 47.8, 57.0, 64.6, 115.7, 124.1, 128.7, 138.0, 141.0, 145.2; HRESIMS calcd for $\text{C}_{22}\text{H}_{32}\text{O}_2\text{Na}$ 351.2300, found 351.2303.



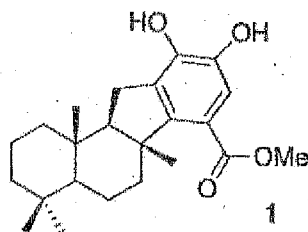
Methylketone (23). Pyridium chlorochromate (416 mg, 1.92 mmol) was added to **11** (74 mg, 0.2 mmol) dissolved in 20 mL of CH_2Cl_2 . The mixture was stirred at gentle reflux for 20 h under Argon. After cooling to rt, the reaction was diluted with Et_2O (80 mL) and the resulting dark solution was filtered through a pad of silica gel. Concentration of the filtrates and purification of the residue via silica gel chromatography (9:1 Hexane/ EtOAc) afforded 40.7 mg (53 %) of **23** as a colorless oil. ^1H NMR (CDCl_3) δ 0.82 (s, 3H), 0.84 (s, 3H), 1.03 (s, 3H), 1.22 (s, 3H), 2.31 (dt, $J = 12.5, 3.7\text{Hz}$, 1H), 2.49 (s, 3H), 2.54 (dd, $J = 14.9, 12.5\text{Hz}$, 1H), 2.69 (dd, $J = 14.9, 6.7\text{Hz}$, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 6.79 (s, 1H); ^{13}C NMR (CDCl_3) δ 16.2, 18.3, 19.4, 20.5, 21.1, 25.2, 30.2, 33.1, 33.4, 36.4, 37.1, 40.2, 42.5, 48.0, 56.2, 57.2, 60.4, 64.9, 110.1, 130.5, 137.4, 147.6, 147.9, 149.6, 201.8; HRESIMS calcd for $\text{C}_{25}\text{H}_{36}\text{O}_3\text{Na}$ 407.2562, found 407.2563.



Ketoester (26a). Methylketone **23** (15 mg, 0.04 mmol) was dissolved in 20 mL of stirring NaOH (10%) solution (containing 5 mL THF). Iodine (50 mg) was added and the mixture was stirred for an additional 20 min before being acidified by addition of 30 mL of 10% H_2SO_4 . The solution was extracted with 150 mL of Et_2O , the Et_2O was washed with brine and then concentrated to dryness to afford a residue, which was dissolved in 10 mL of DMF. Potassium carbonate (0.5g) and MeI (1.0 mL) were added to the DMF solution and stirring was continued overnight. The reaction was quenched by adding 10 mL of brine and the resulting mixture was extracted with Et_2O . The Et_2O was washed with brine, dried with MgSO_4 , and evaporated to dryness. The residue was purified by silica gel chromatography (9:1 Hexane/ EtOAc) to give 15 mg of **26a** (95%). ^1H NMR (CDCl_3) δ 0.84 (s, 3H), 0.87 (s, 3H), 1.19 (s, 3H), 1.41 (s, 3H), 1.79 (dd, $J = 11.9, 7.8\text{Hz}$, 1H), 2.41 (brd, $J = 11.9\text{Hz}$, 1H), 2.74 (dd, $J = 15.7, 12.5\text{Hz}$, 1H), 2.93 (dd, $J = 15.7, 8.1\text{Hz}$, 1H), 3.81 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 6.93 (s, 1H); ^{13}C NMR (CDCl_3) δ 18.4, 18.5, 21.9, 24.2, 24.5, 30.1, 32.9, 33.5, 36.6, 36.7, 38.4, 42.4, 47.9, 48.1, 52.8, 53.4, 56.2, 60.4, 63.2, 114.1, 118.2, 125.3, 136.4, 149.4, 150.6, 164.6, 187.4; HRESIMS calcd for $\text{C}_{26}\text{H}_{36}\text{O}_5\text{Na}$ 451.2460, found 451.2457.



Methylester (28). A solution of 0.21 g of sodium hydroxide in 2.0 mL of water was added to 0.15 mL of bromine at 0 °C over 10 minutes. To this solution was added 38 mg (0.1 mmol) of **23** in 1 mL of dioxane. After stirring at 40 °C for 30 min, the yellow solution was quenched by addition of sodium bisulfite. Following acidification with 10% H₂SO₄, the mixture was extracted with Et₂O. The Et₂O was washed with brine and dried to furnish a residue, which was dissolved in 10 mL of DMF. Potassium carbonate (1.0 g) and MeI (2.0 mL) were added to the DMF solution and stirring was continued overnight. The reaction was quenched by adding 20 mL of brine and the resulting mixture was extracted with Et₂O. The Et₂O was washed with brine, dried with MgSO₄, and evaporated to dryness. The residue was purified by silica gel column chromatography (9:1 Hexane/EtOAc) to give 32 mg of **28** (80%). ¹H NMR (CDCl₃) δ 0.83 (s, 3H), 0.84 (s, 3H), 1.04 (s, 3H), 1.22 (s, 3H), 2.44 (dt, J = 12.3, 3.4 Hz, 1H), 2.54 (dd, J = 14.3, 12.9 Hz, 1H), 2.69 (dd, J = 14.3, 6.3 Hz, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 7.00 (s, 1H); ¹³C NMR (CDCl₃) δ 16.3, 18.3, 19.5, 19.9, 21.1, 25.2, 33.1, 33.3, 36.5, 37.1, 40.2, 42.5, 48.1, 51.7, 56.1, 57.1, 60.4, 64.8, 111.6, 121.2, 137.0, 148.3, 148.7, 149.8, 168.3; HRESIMS calcd for C₂₅H₃₆O₄Na 423.2511, found 423.2513.



(-) Pelorol (1). To a solution of methyl ester **28** (5 mg, 0.013 mmol) in 2 mL of CH₂Cl₂ at -78 °C under Argon was slowly added BI₃ (60 mg) in 2 mL of CH₂Cl₂ and mixture stirred for an additional 0.5 h. The mixture was then poured into H₂O and extracted with CH₂Cl₂ (two x 50 mL). The combined CH₂Cl₂ extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified by silica gel flash chromatography (4:1 Hexane/EtOAc) to furnish **1** (2.3 mg, 50%). [α]_D^{22.8} = -63.5 (0.06, CHCl₃); ¹H NMR (CDCl₃) δ 0.83 (s, 3H), 0.84 (s, 3H), 0.97 (td, J = 12.8, 3.7 Hz, 1H), 1.04 (s, 3H), 1.21 (s, 3H), 1.66 (dd, J = 12.5, 6.4 Hz, 1H), 2.48 (dd, J = 14.6, 12.6 Hz, 1H), 2.51 (m, 1H), 2.60 (dd, J = 14.3, 6.4 Hz, 1H), 3.81 (s, 3H), 7.07 (s, 1H); ¹³C NMR (CDCl₃)

δ 16.3, 18.4, 19.5, 19.8, 21.1, 24.3, 33.0, 33.3, 36.5, 37.1, 40.2, 42.5, 48.5, 51.7, 57.1, 65.2, 114.8, 118.2, 130.0, 140.5, 143.4, 149.5, 168.0; HRESIMS calcd for $C_{23}H_{32}O_4Na$ 395.2198, found 395.2199.

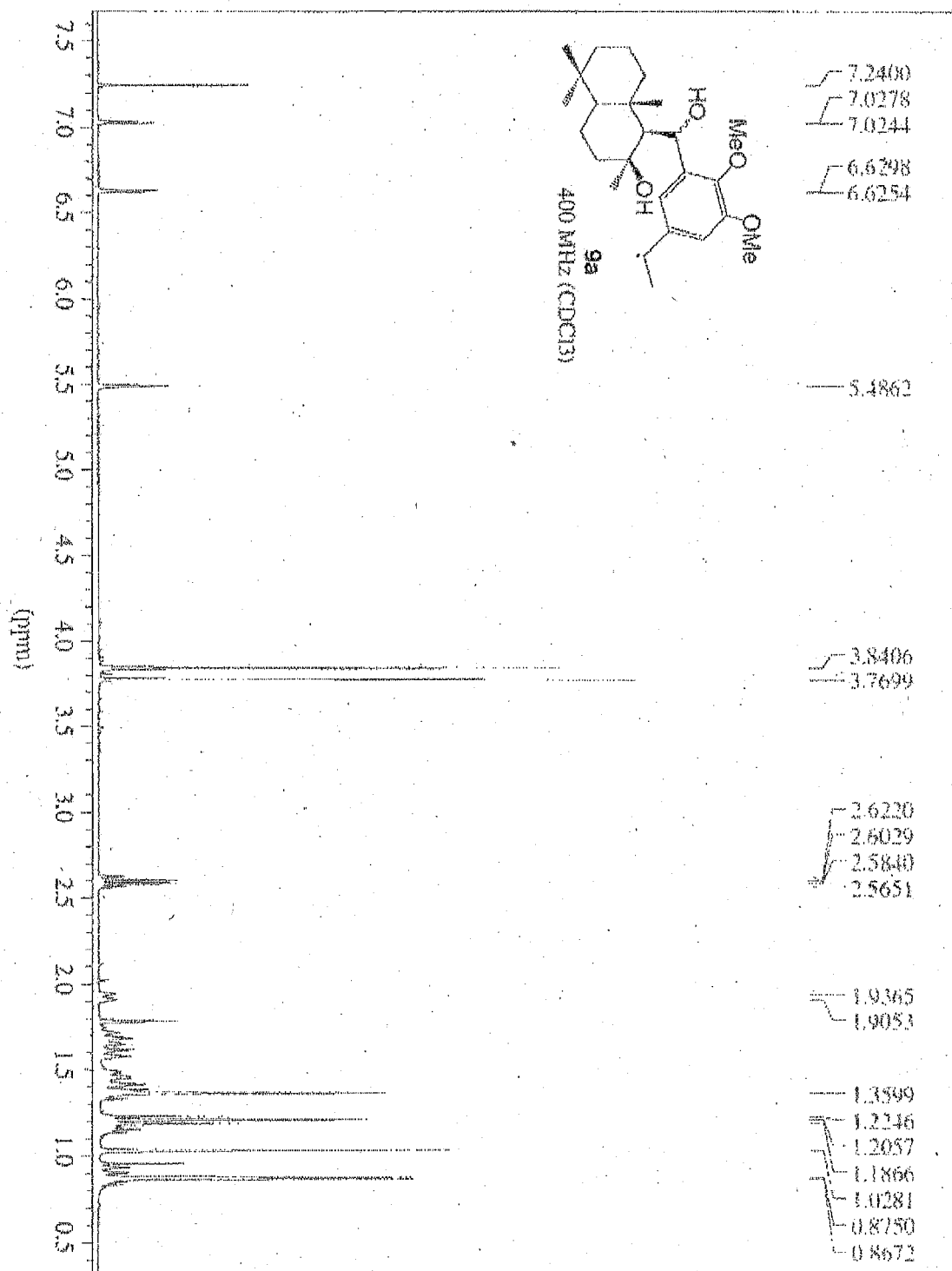
Protocol for Evaluation of Compound 22 in a Mouse Septicemia Model. Administration of the bacterial cell wall product, LPS (lipopolysaccharide), into mice results in rapid activation of macrophages to produce pro-inflammatory mediators such as $TNF\alpha$ that can be detected circulating in the blood. This is a good model of human sepsis due to bacterial infection, and can be used to assess the ability of test compounds to inhibit macrophage-dependent inflammatory processes. Mice are administered the test compound (either intra-peritoneally or orally) 30 min prior to an intra-peritoneal injection of 20 mg/kg of LPS. Blood is drawn 2 hr later for determination of plasma $TNF\alpha$ by ELISA.

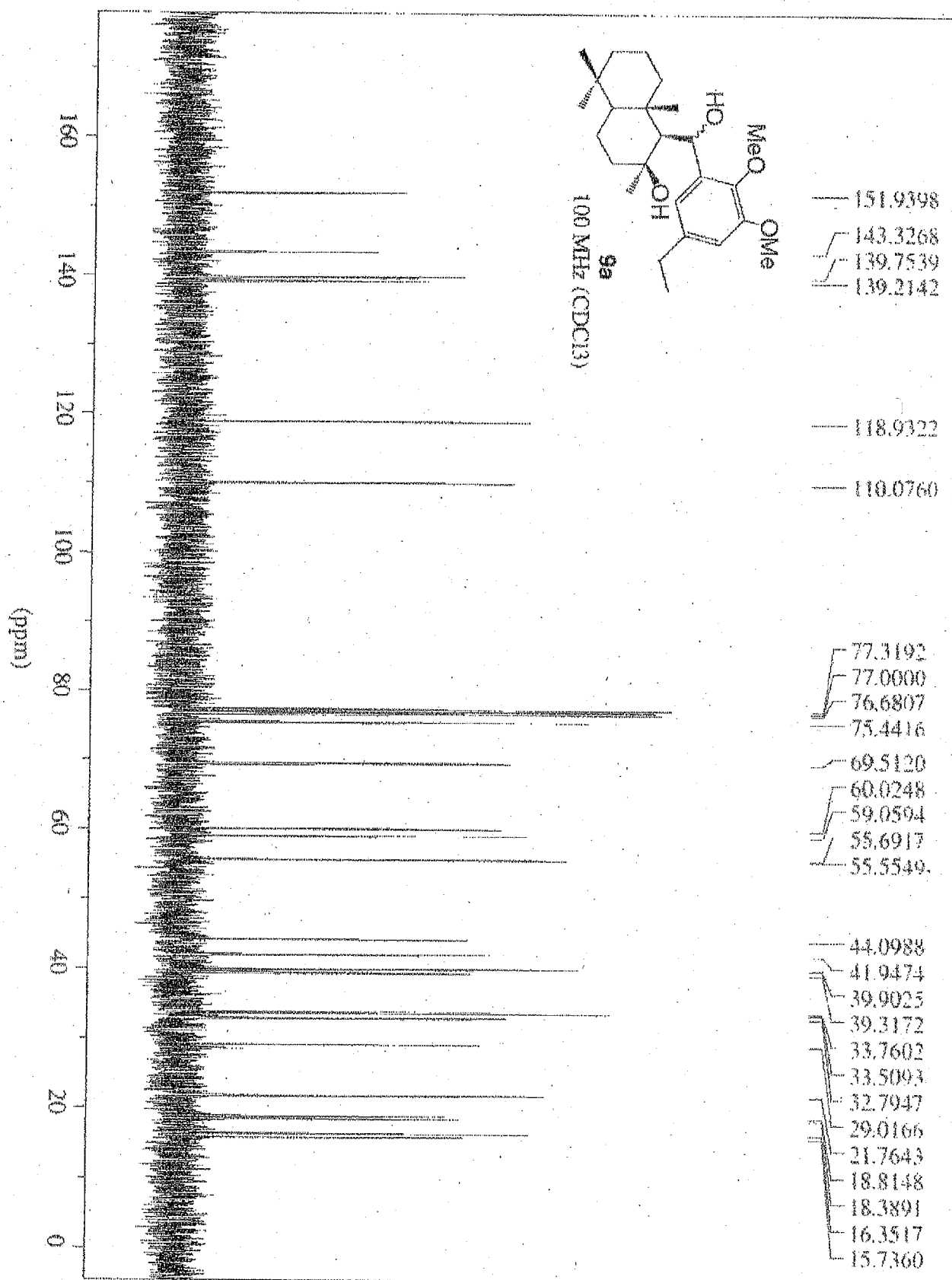
Protocol for Evaluation of Compound 22 in a Mouse Acute Anaphylaxis Model. The cutaneous anaphylaxis (or ear edema) model is a standard model of IgE (immunoglobulin E) and mast cell-dependent allergic inflammation. Mice are sensitized to the hapten DNFB (dinitrofluorobenzene) by cutaneous application of DNFB to the shaved abdomen of mice for two consecutive days. One week after the first application, tritiated thymidine (3H-Tdr) is injected intra-peritoneally. 24 hr later, test substances are painted on the left ear while the right ear receives vehicle control. 30 min after drug application, DNFB is applied to both ears to induce mast cell degranulation. This results in edema and neutrophil infiltration that can be quantitated by taking a 6 mm diameter punch from the ear for dissolution and scintillation counting. The ability of test substances to inhibit mast cell degranulation is then determined by calculating the ratio of 3H-Tdr in the test (right) ear vs the control (left) ear. One group of mice has DNFB applied only to the left ear leaving the right ear non-inflamed, in order to control for basal 3H-Tdr incorporation into ear parenchymal cells.

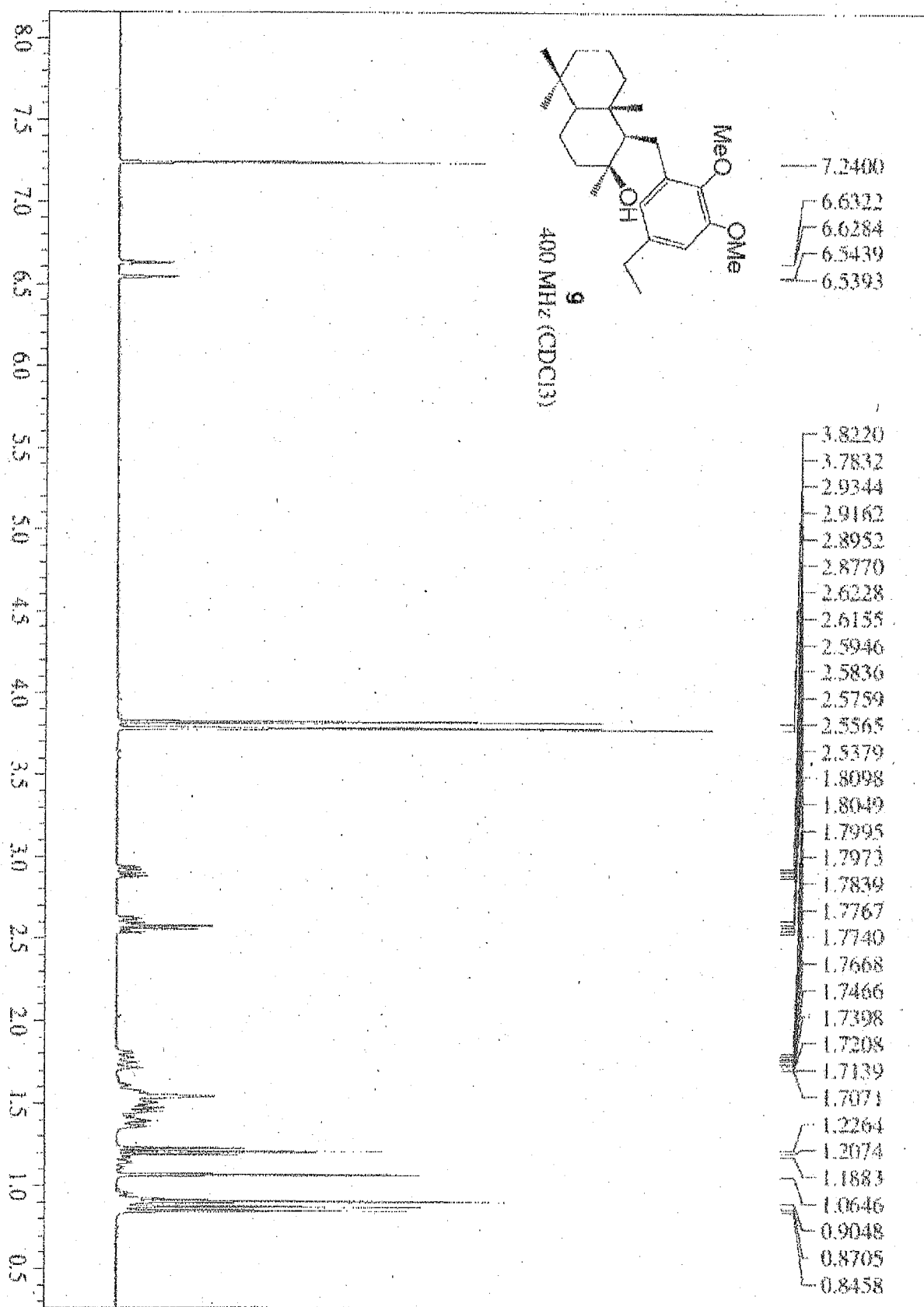
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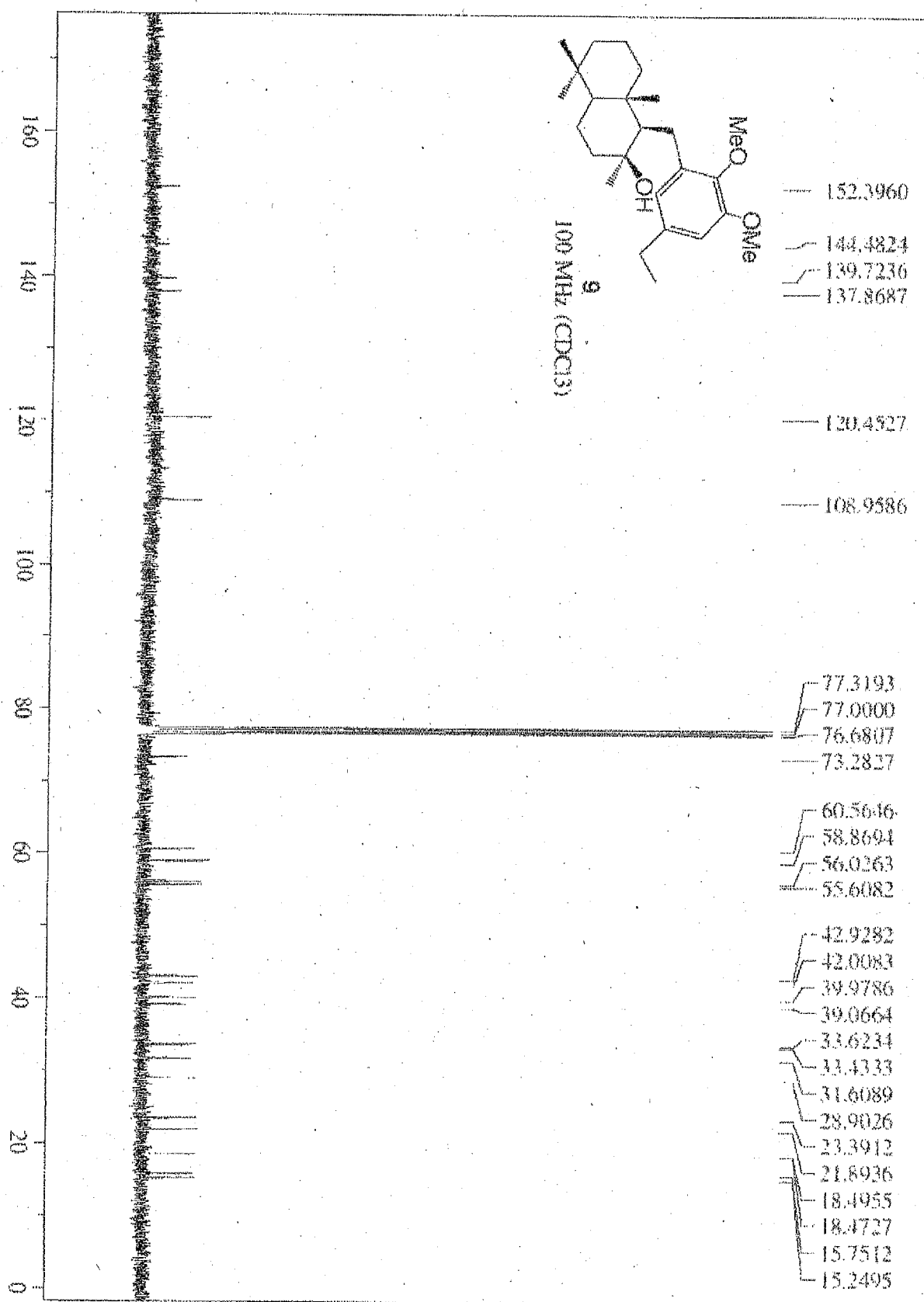
- (1) Sánchez, I.H.; Larraza, M.I.; Basurto, F.; Yañez, R.; Avila, S.; Tovar, R.; Nathan, P.J. *Tetrahedron*, **1985**, *41*, 2355-9.
- (2) Findlay, J.A.; Daljeet, A.; Murray, P.J.; Rej, R.N. *Can. J. Chem.* **1987**, *65*, 427-431.
- (3) Lau, C.K.; Dufresne, C.; Belanger, P.C.; Pietre, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038-3043.

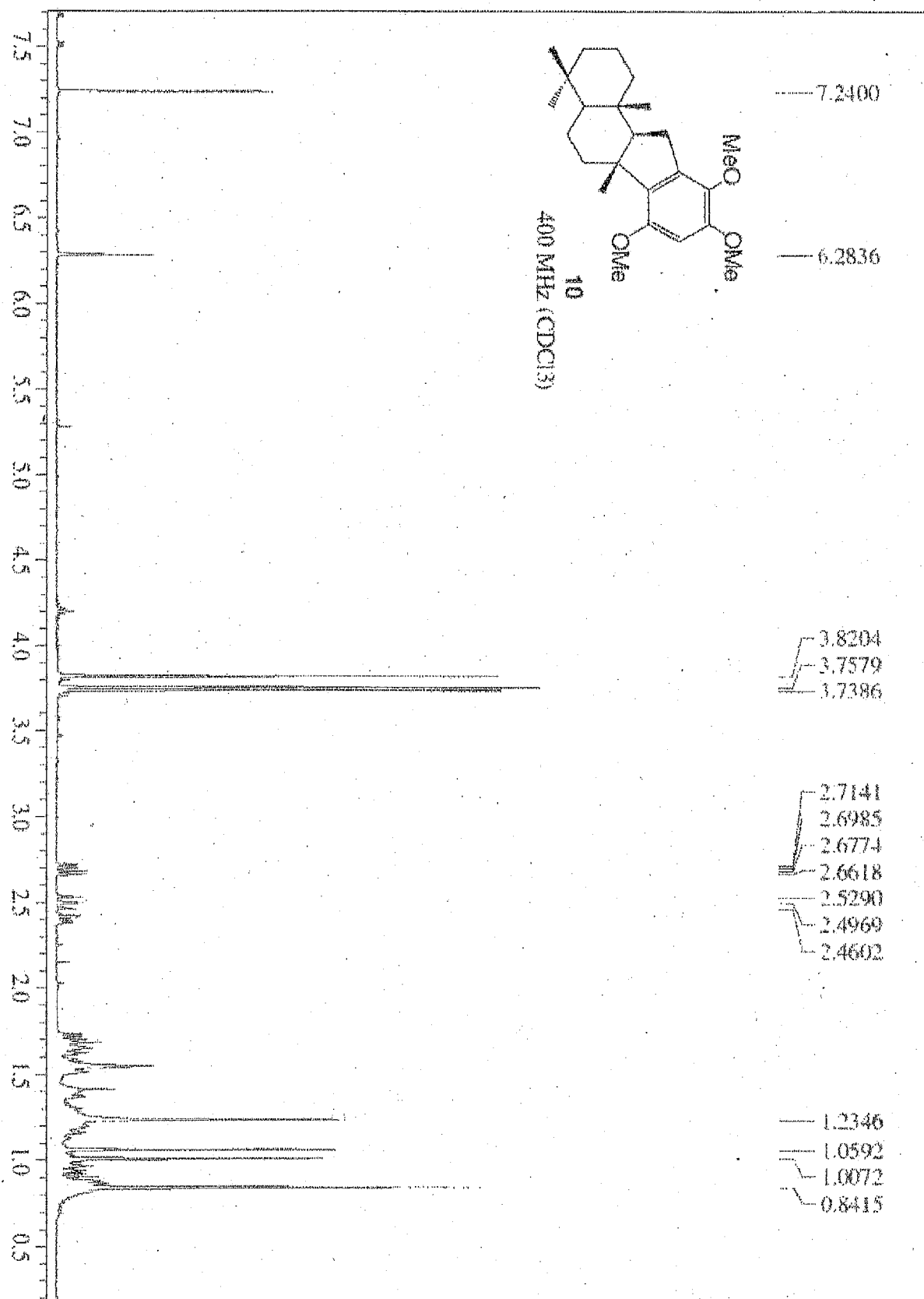
NMR Spectra

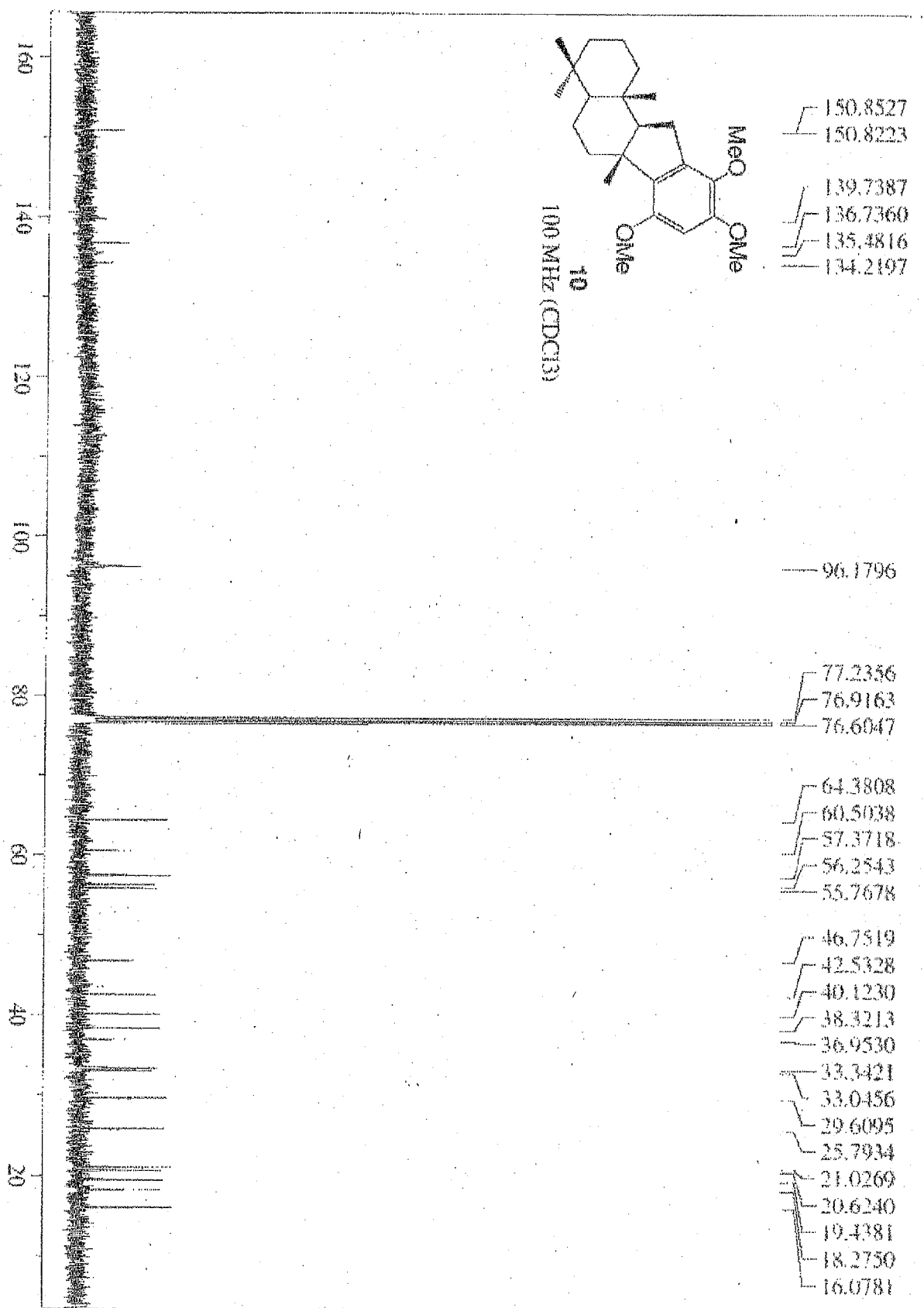


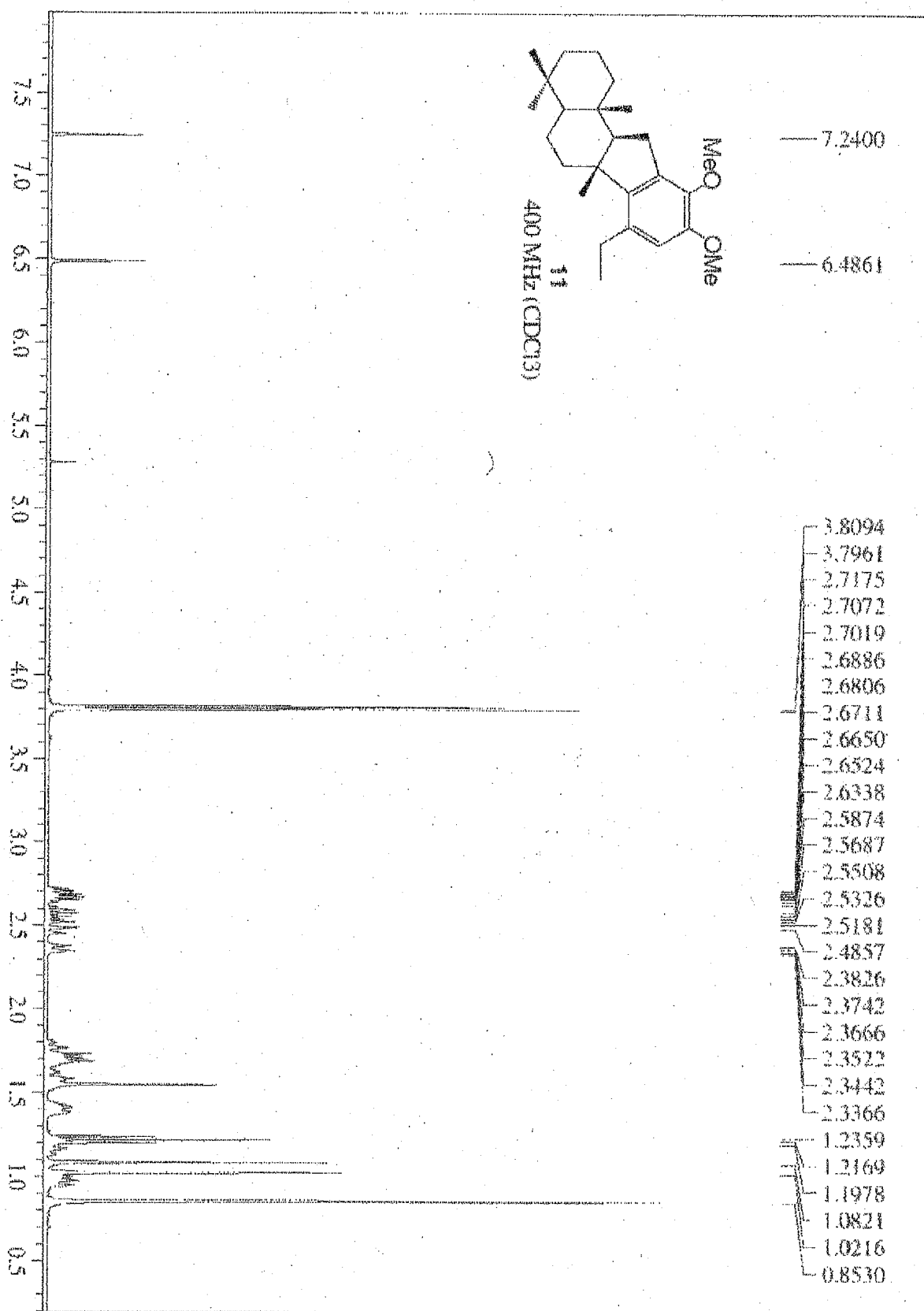


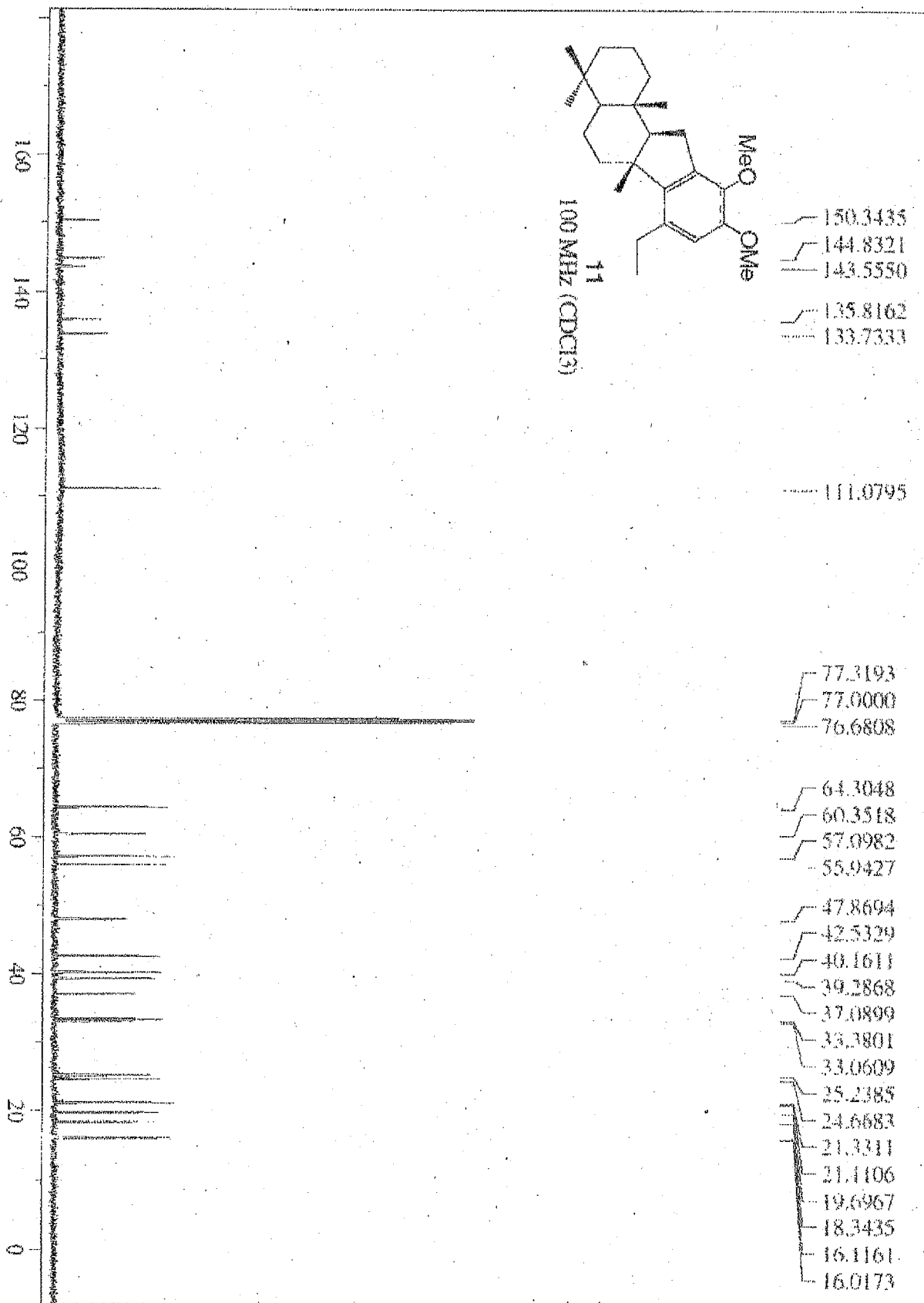


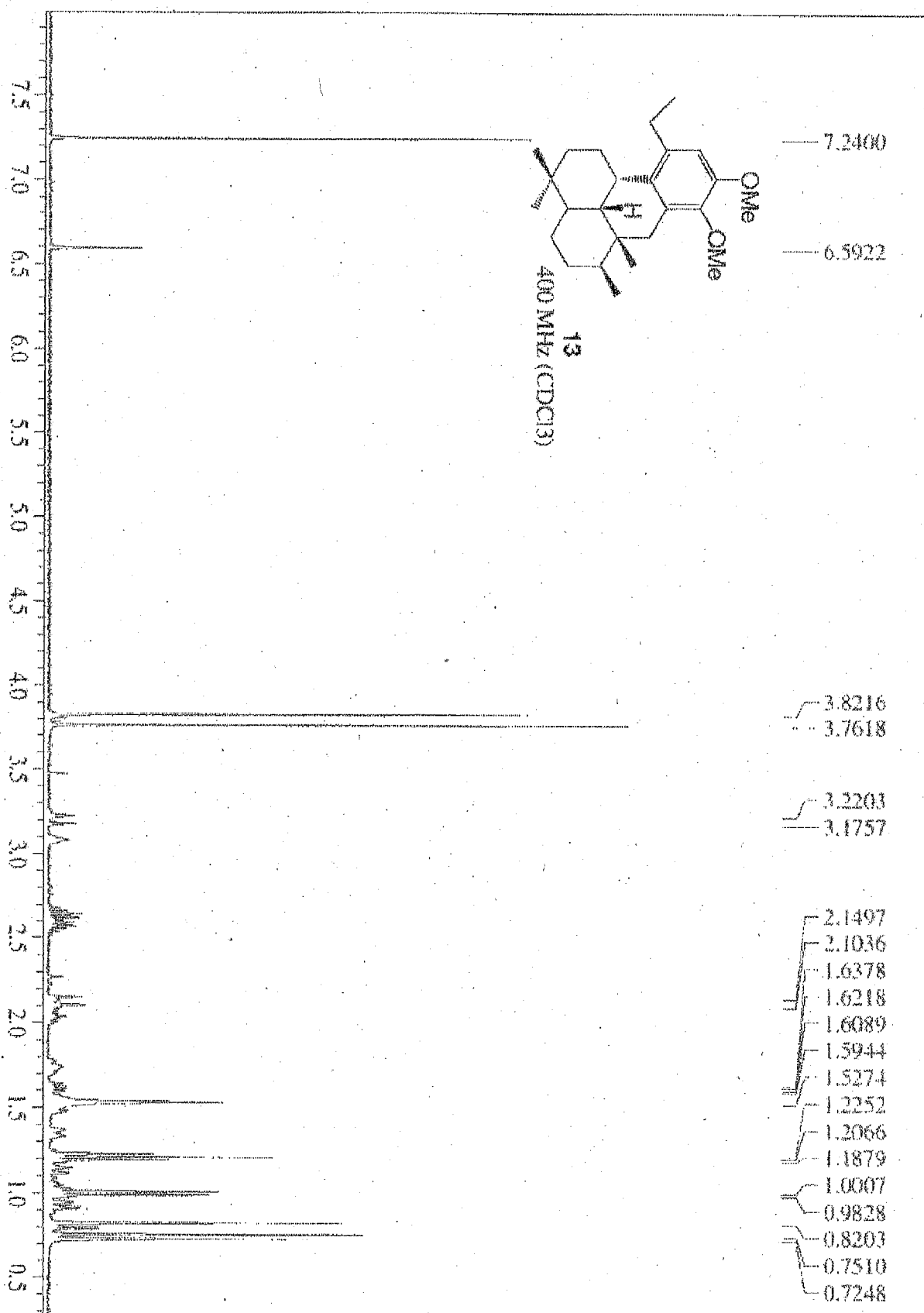


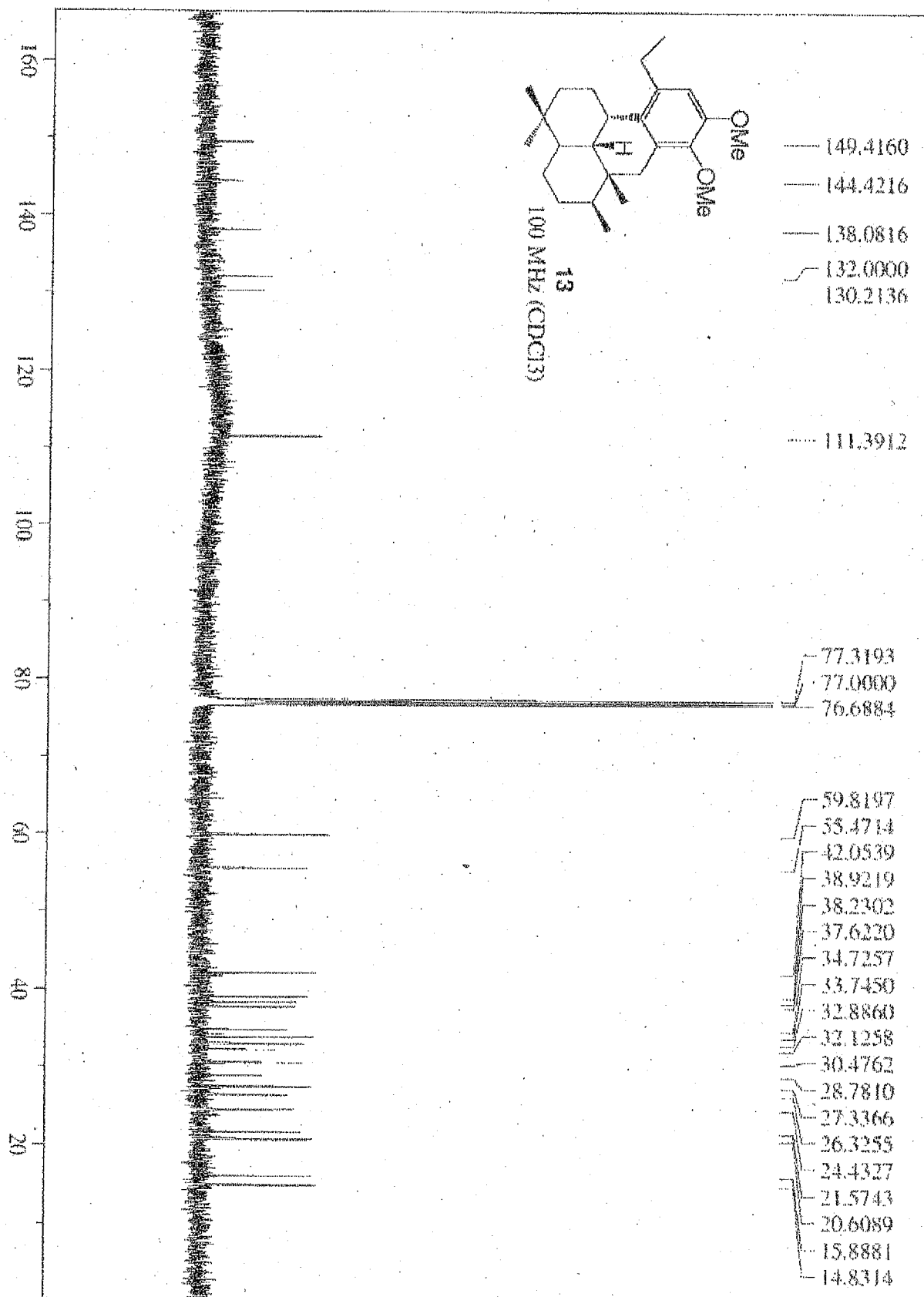


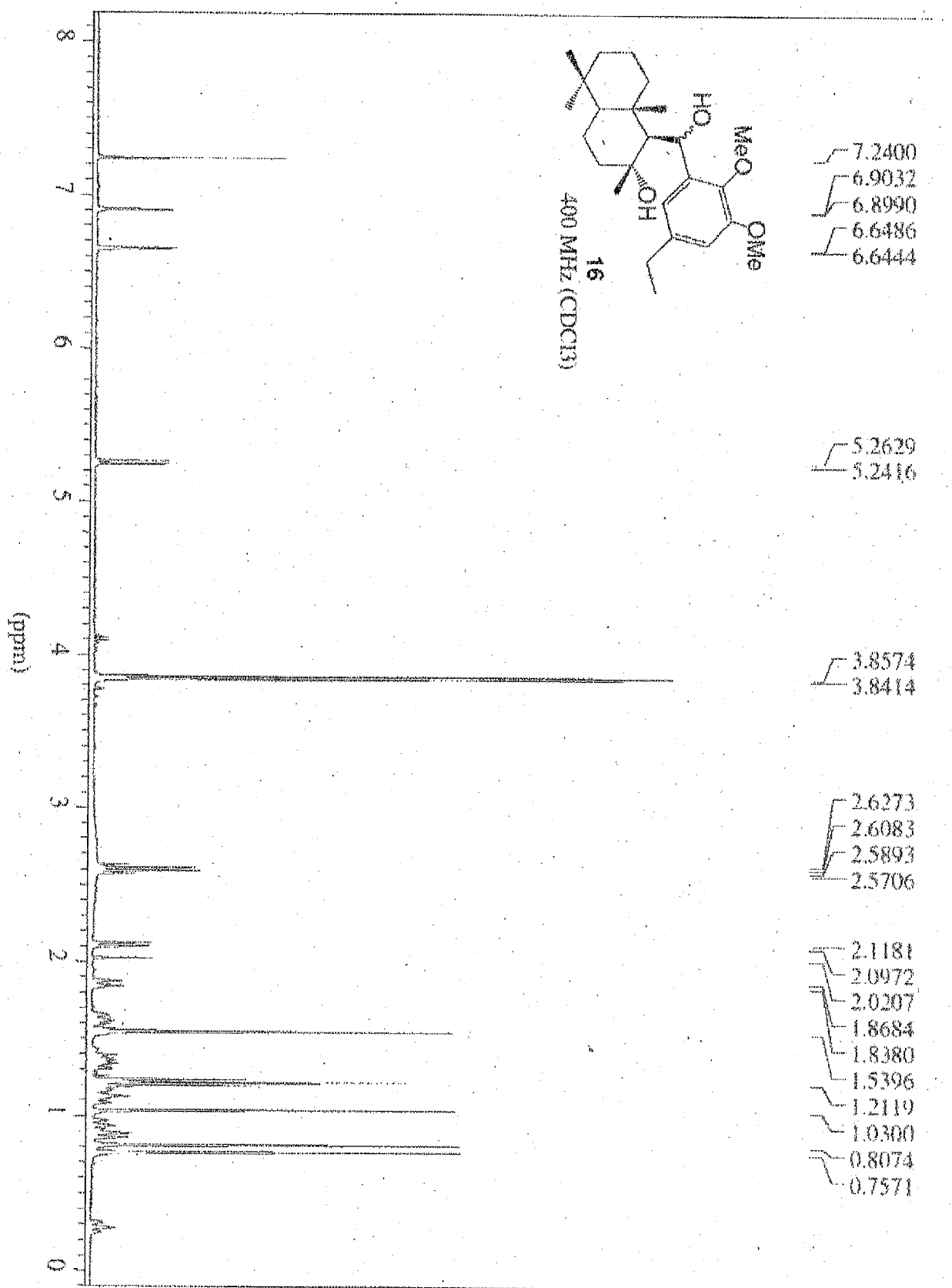


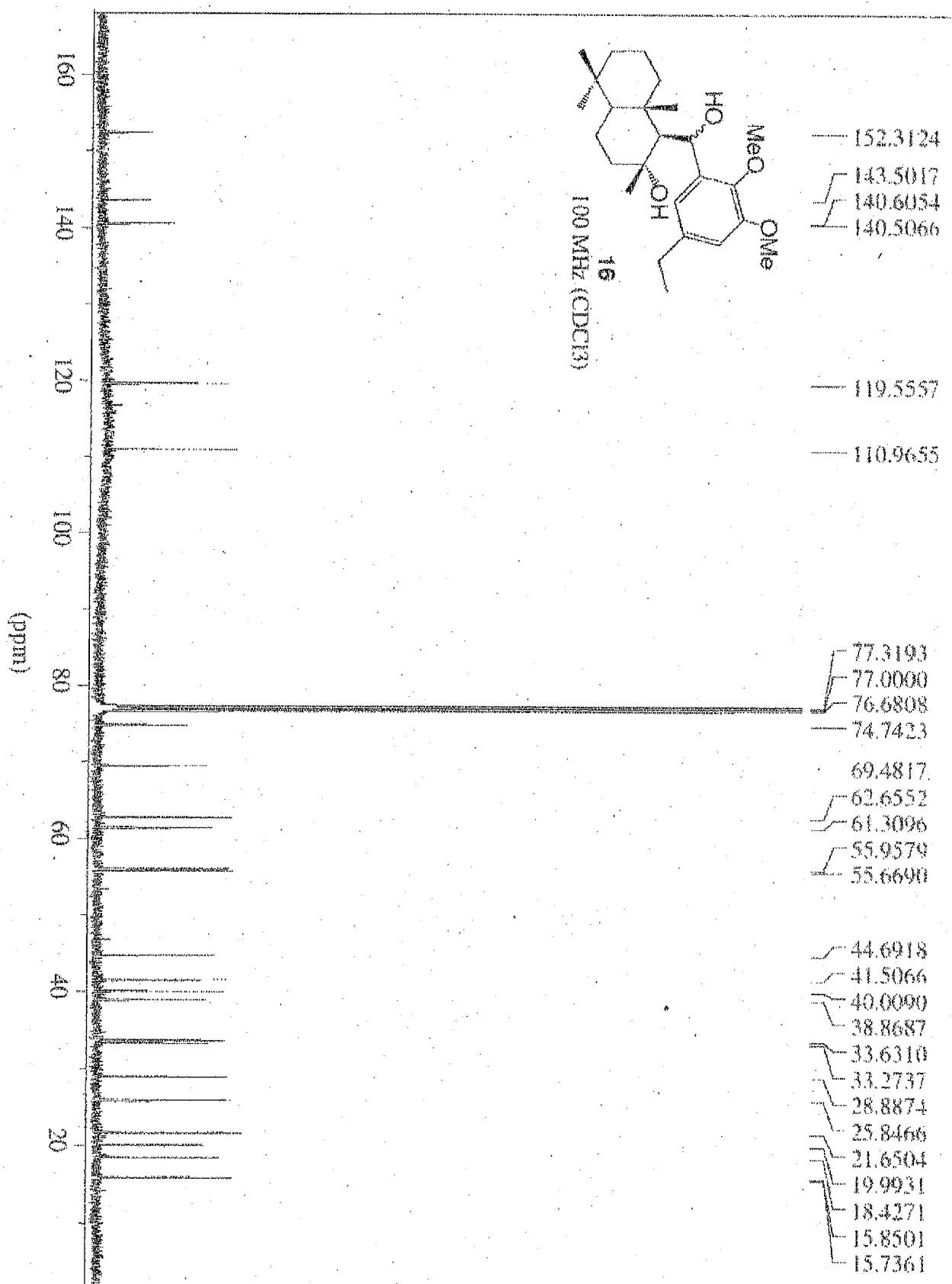


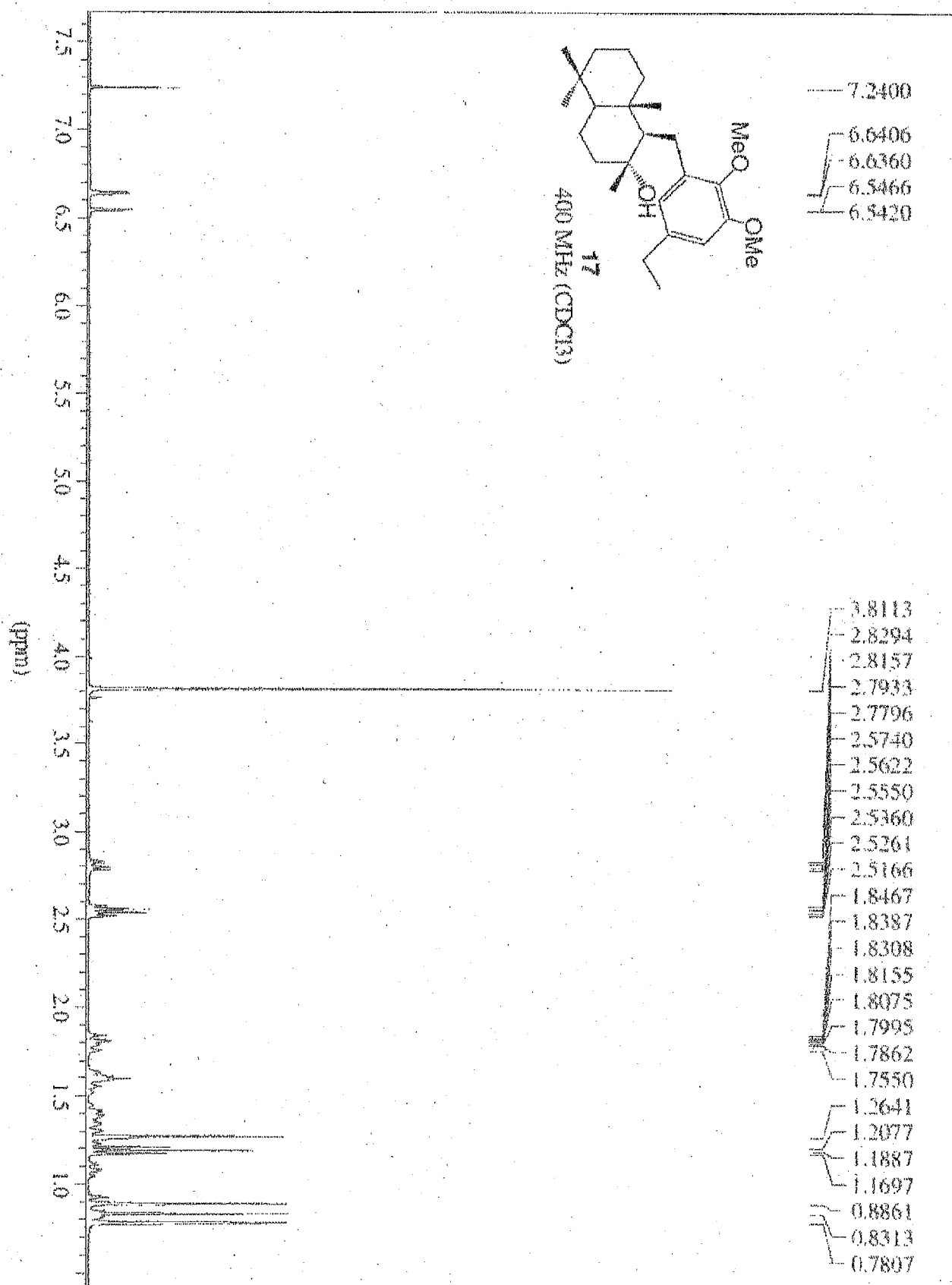


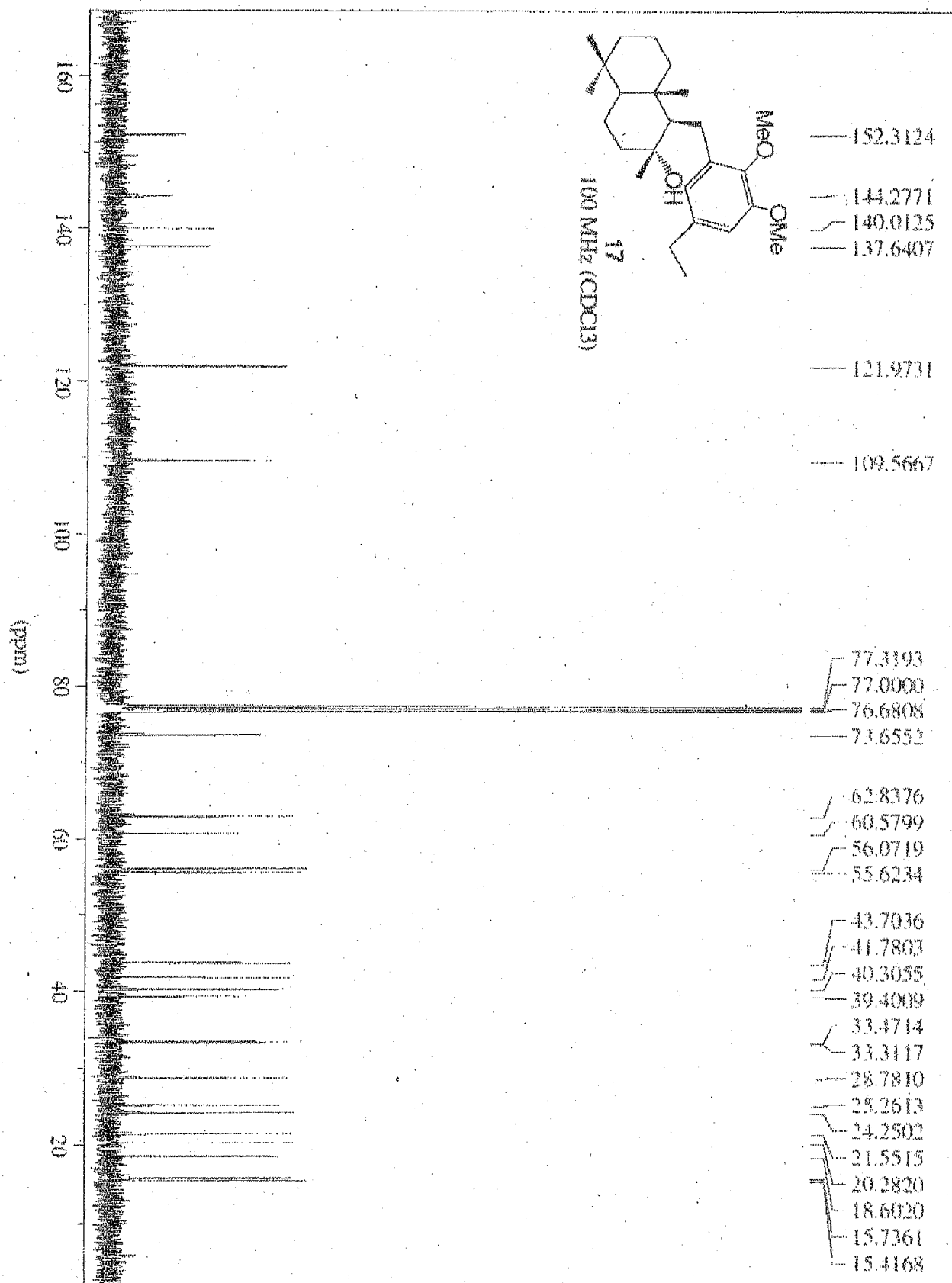


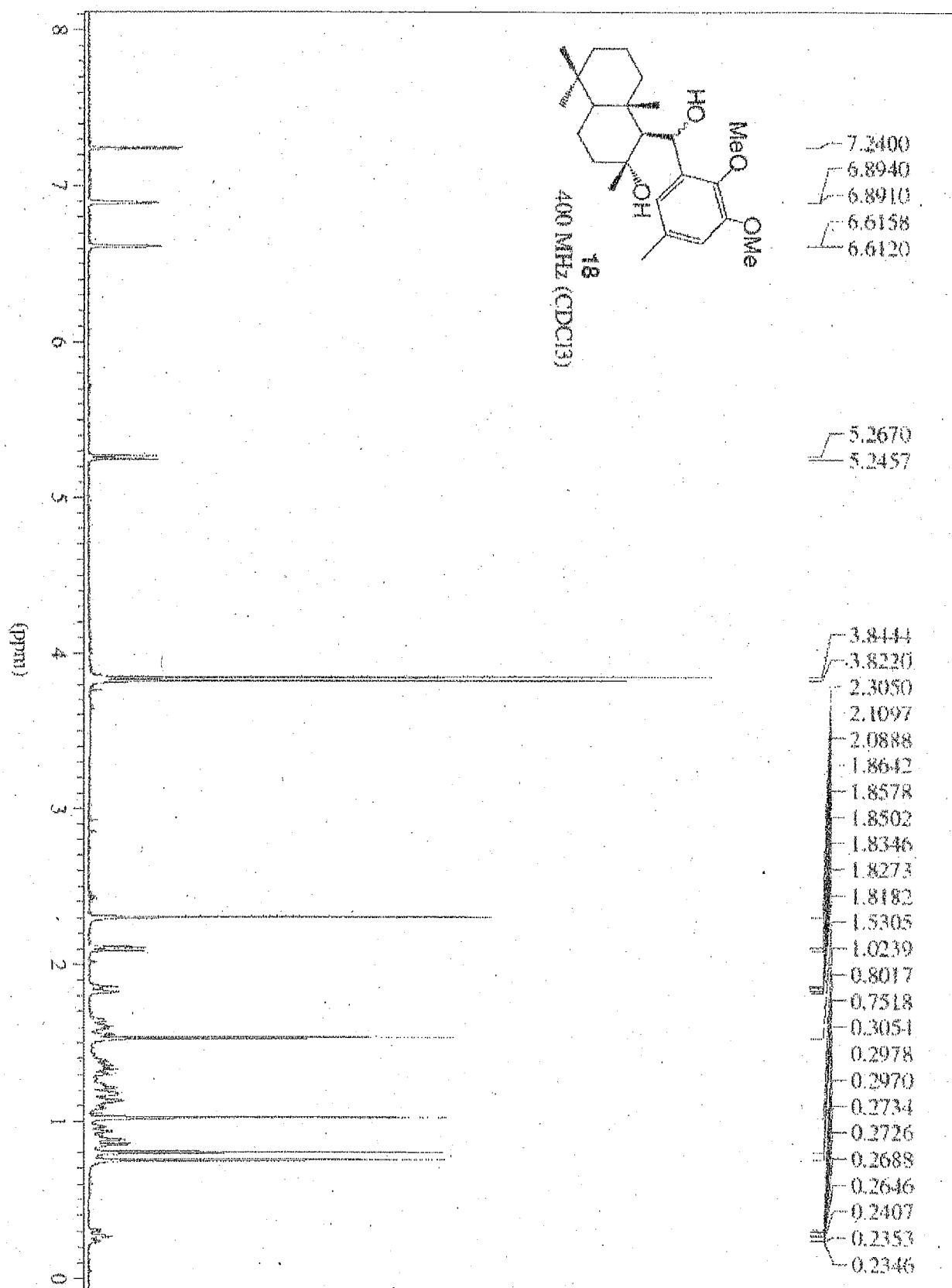


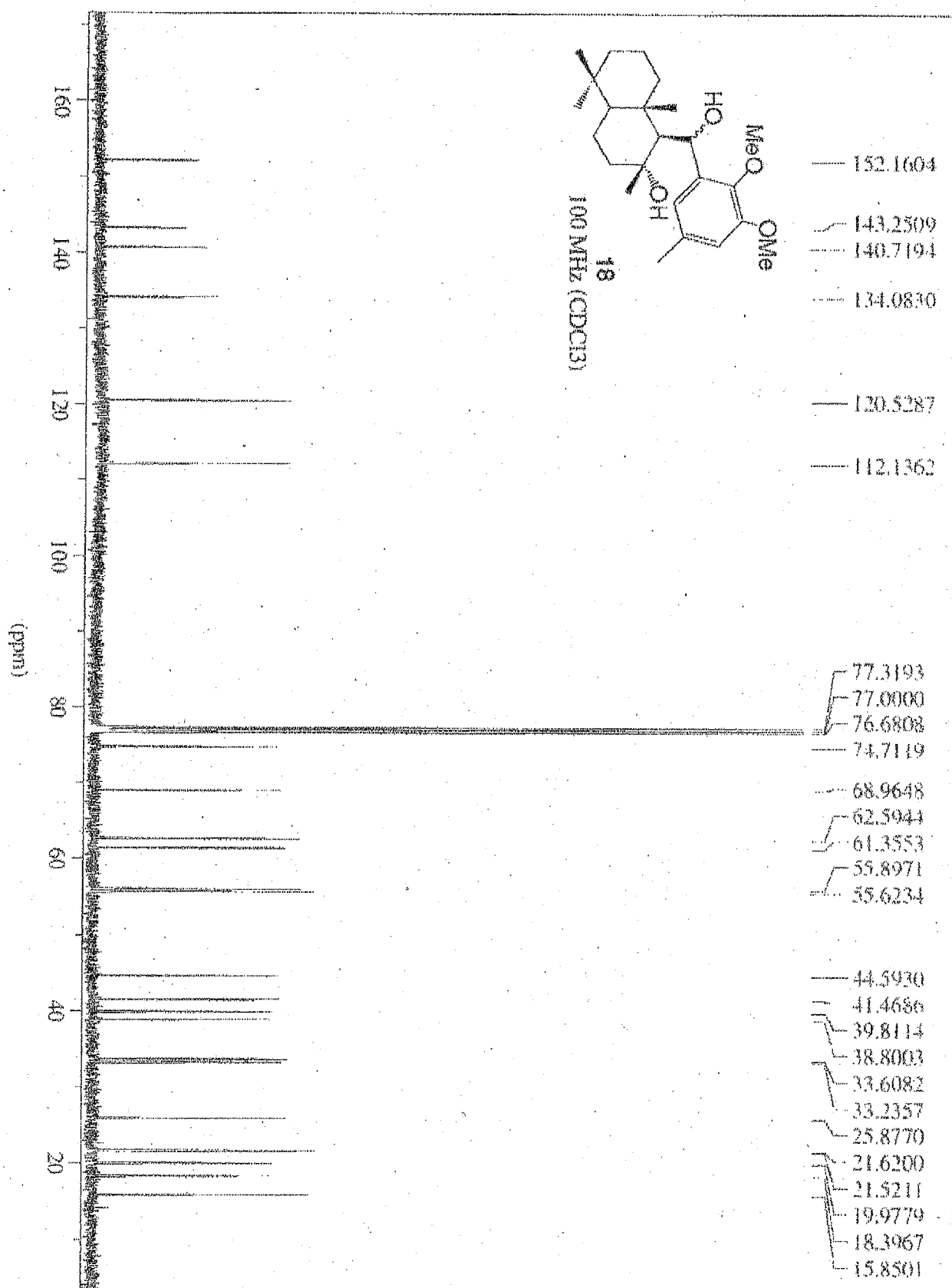


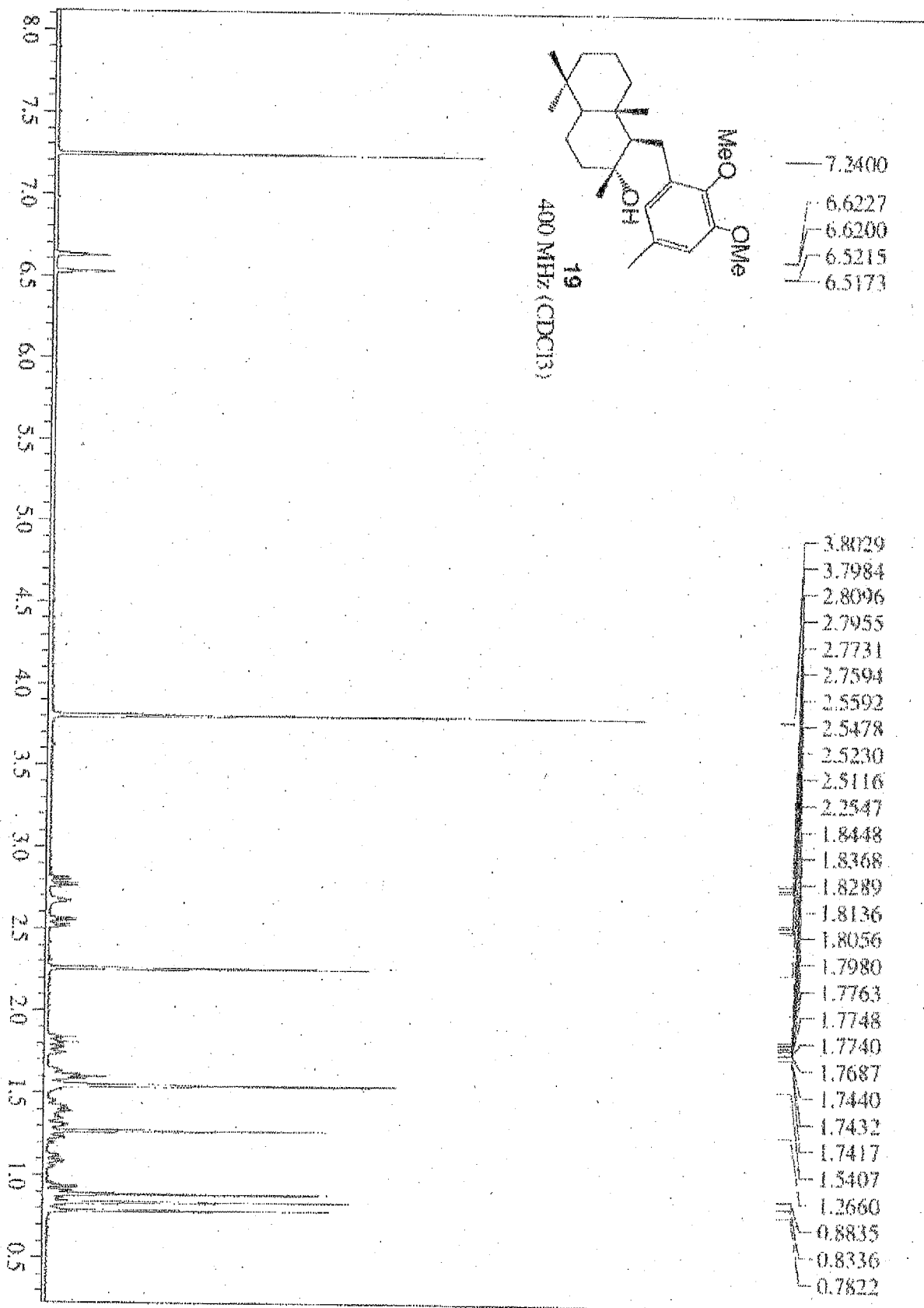


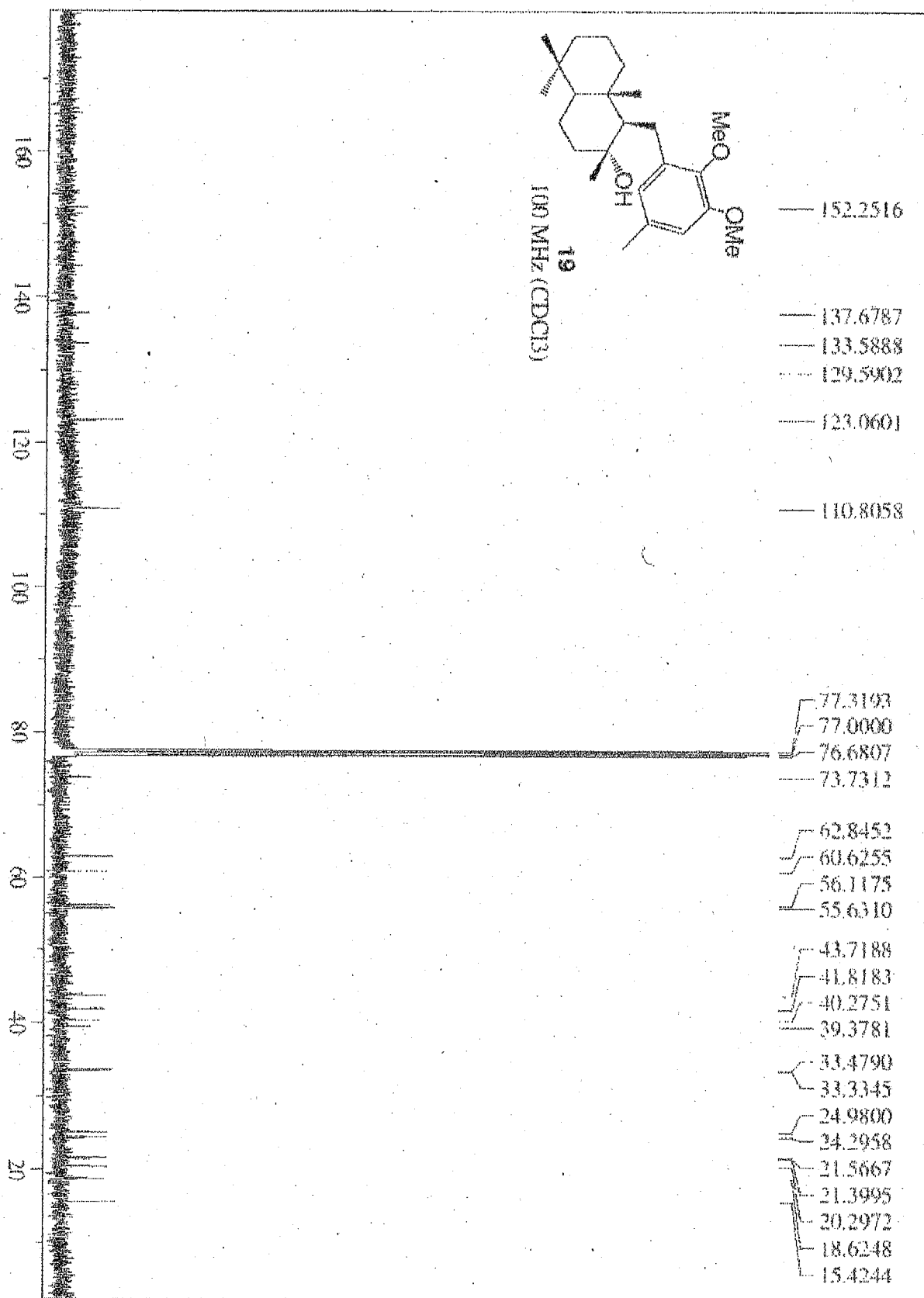


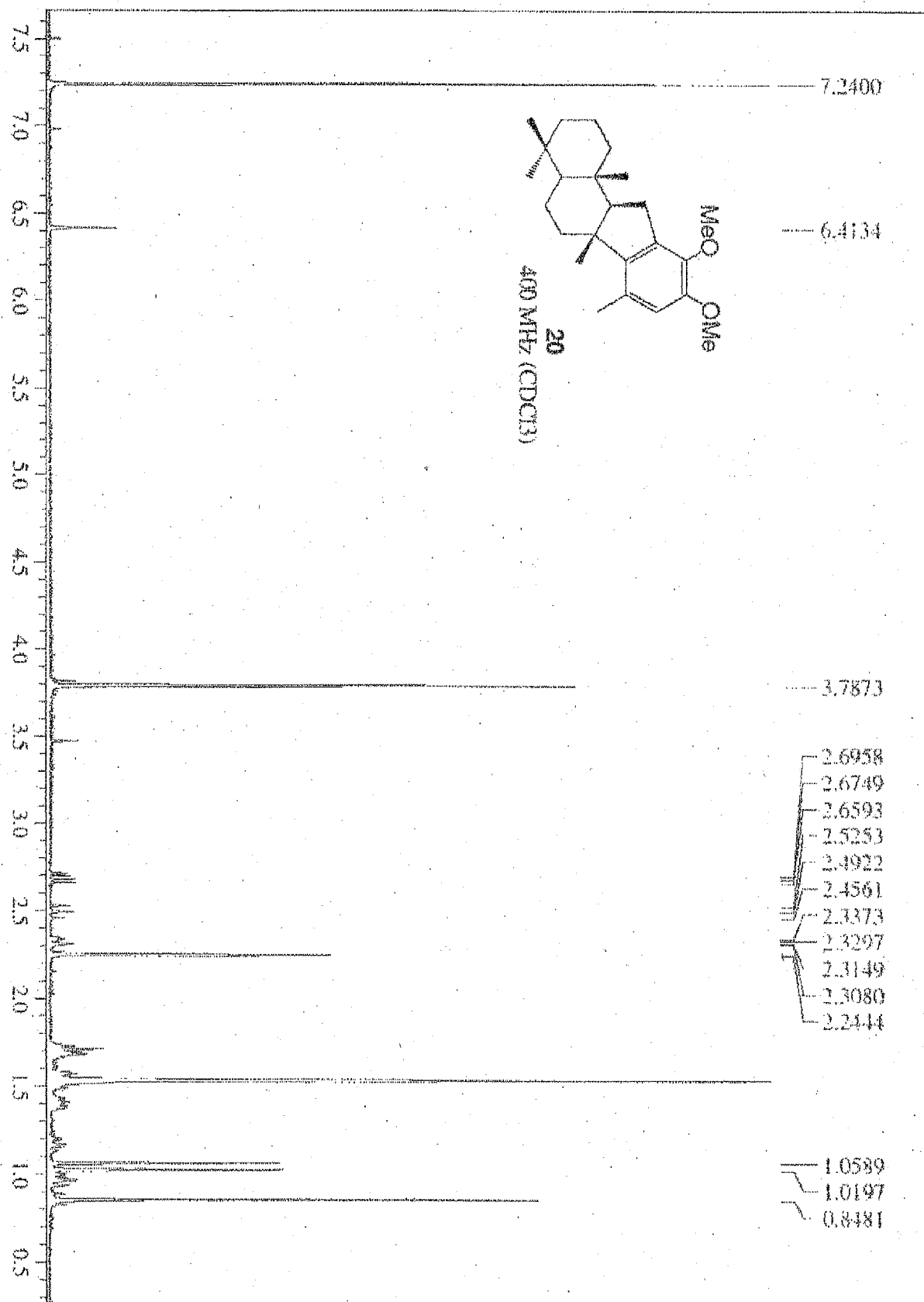


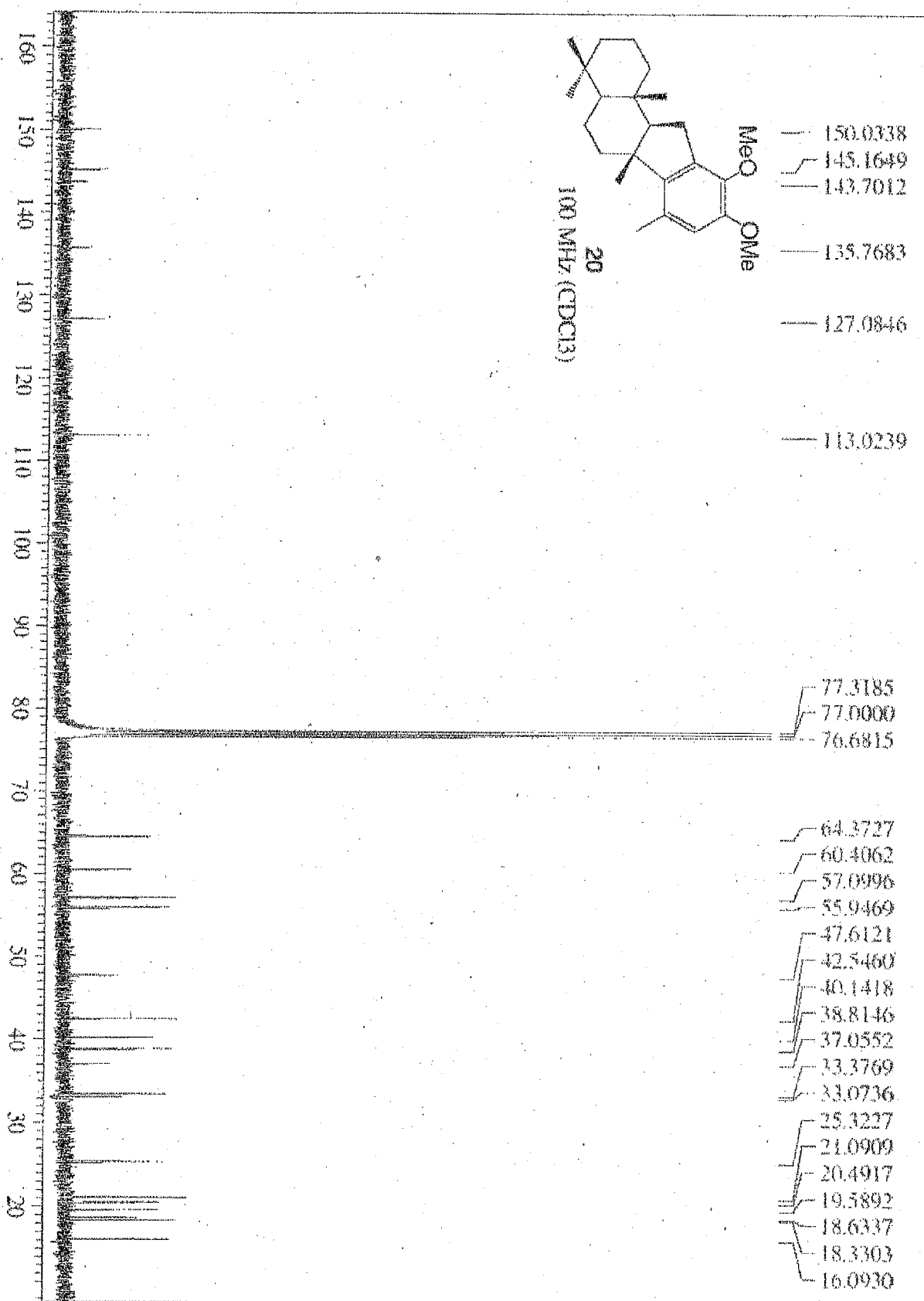


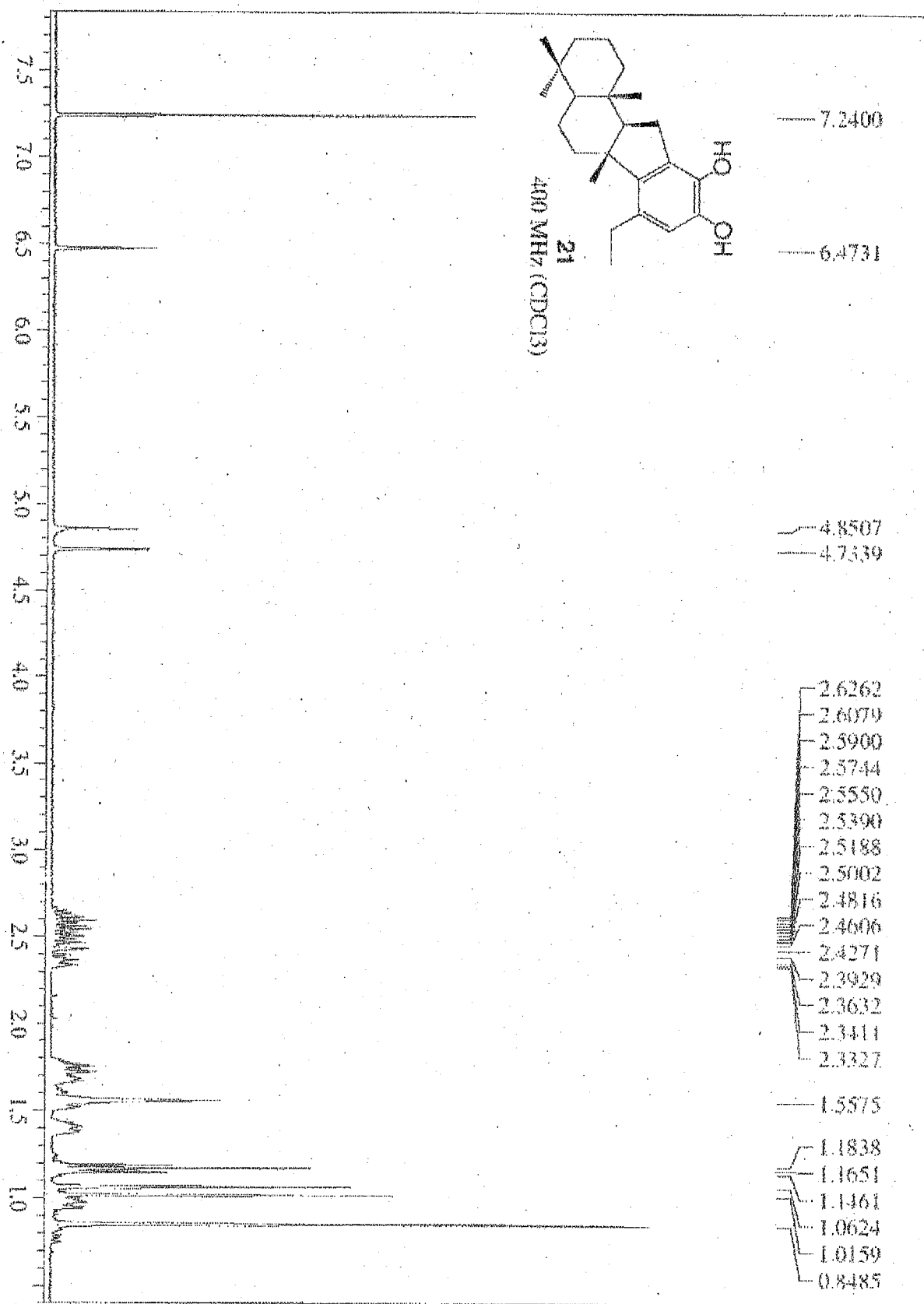


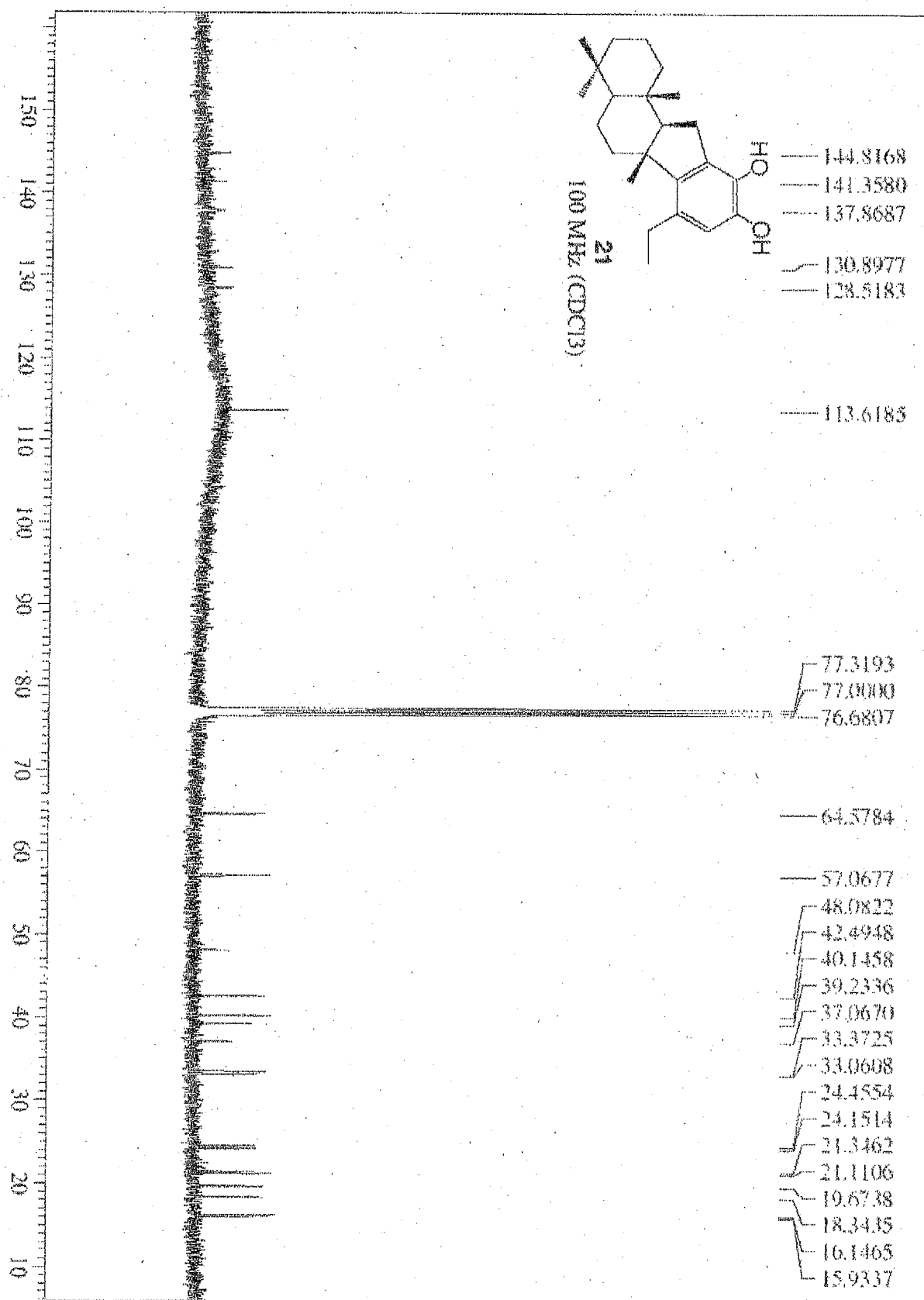


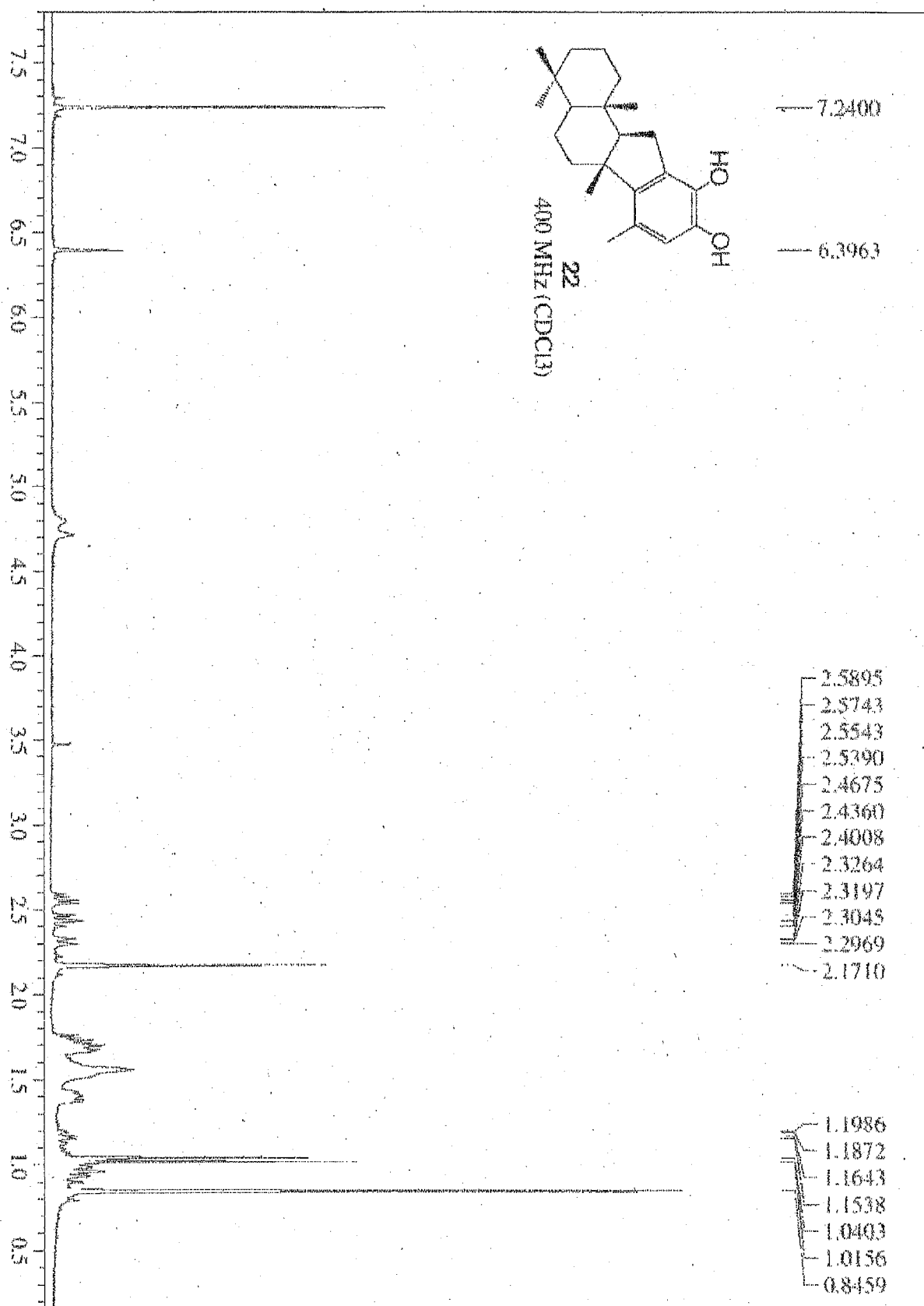


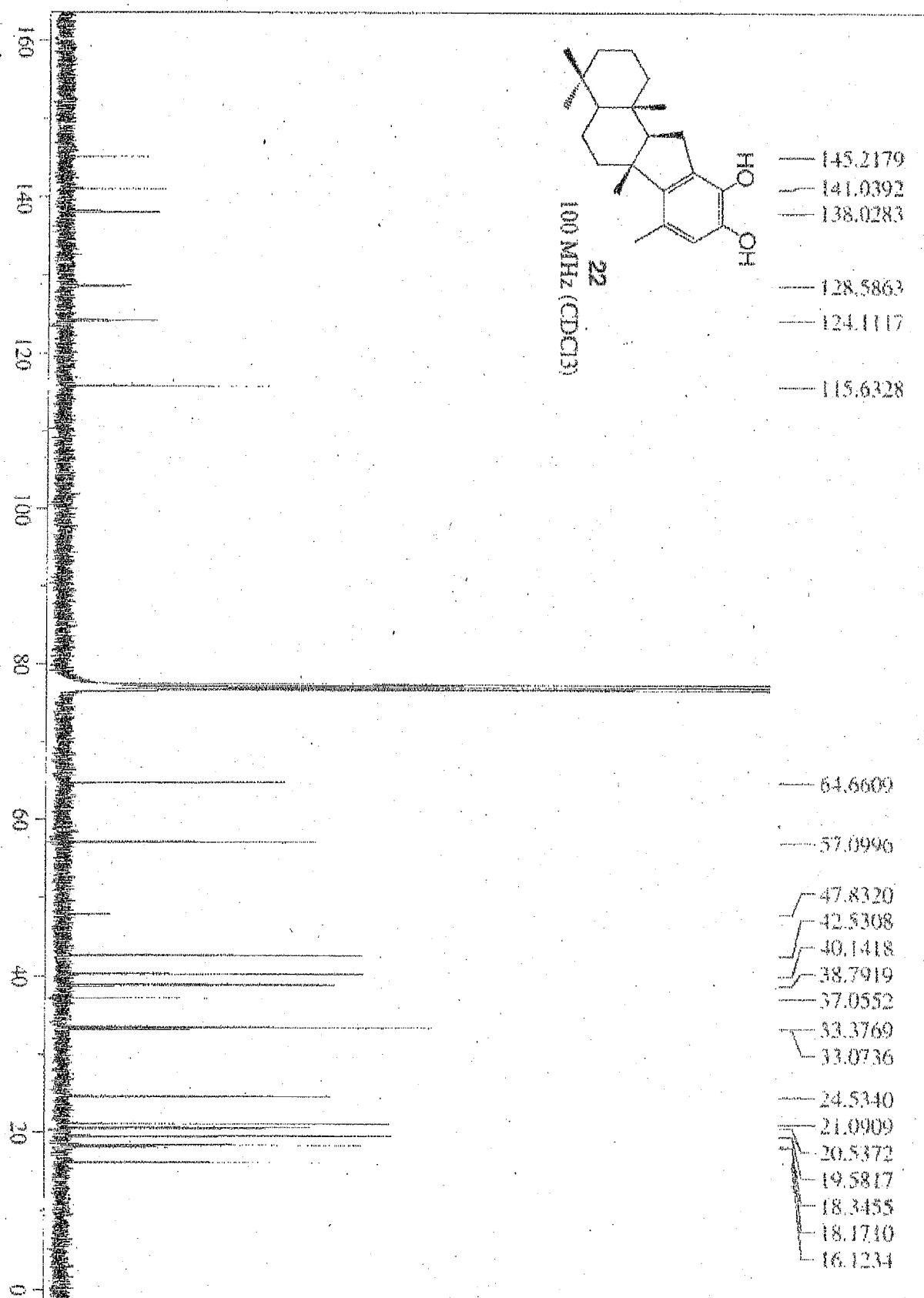


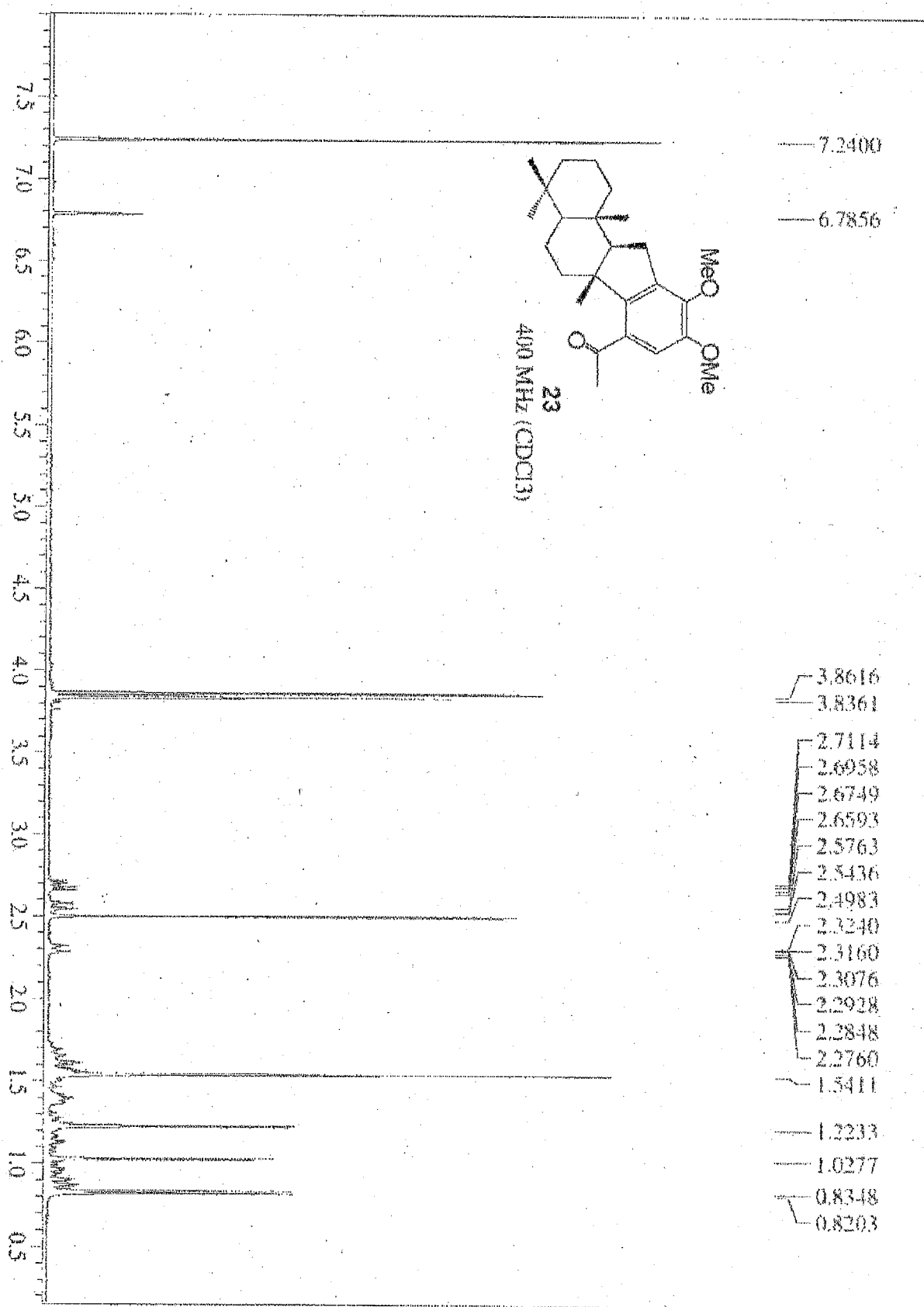


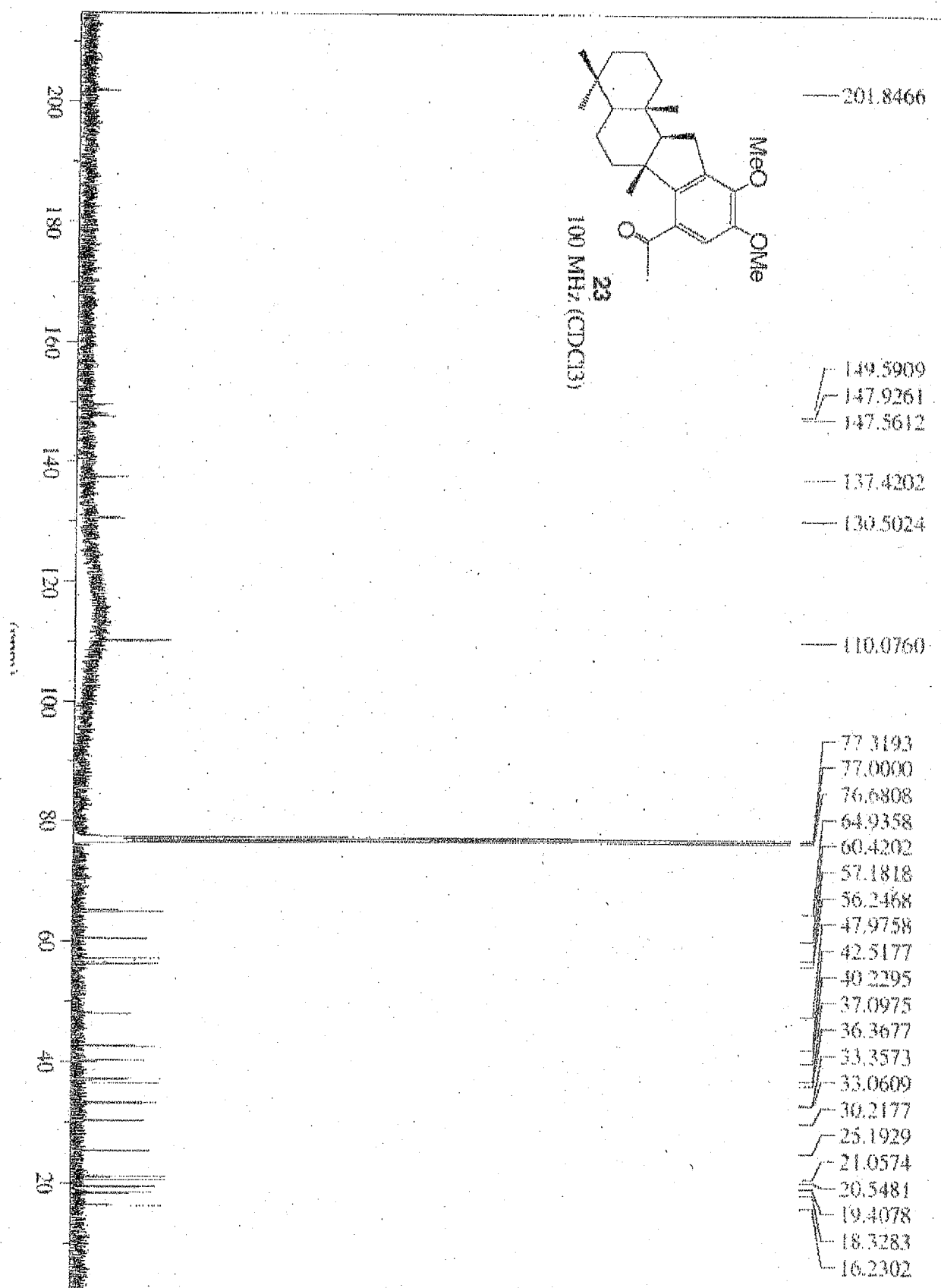


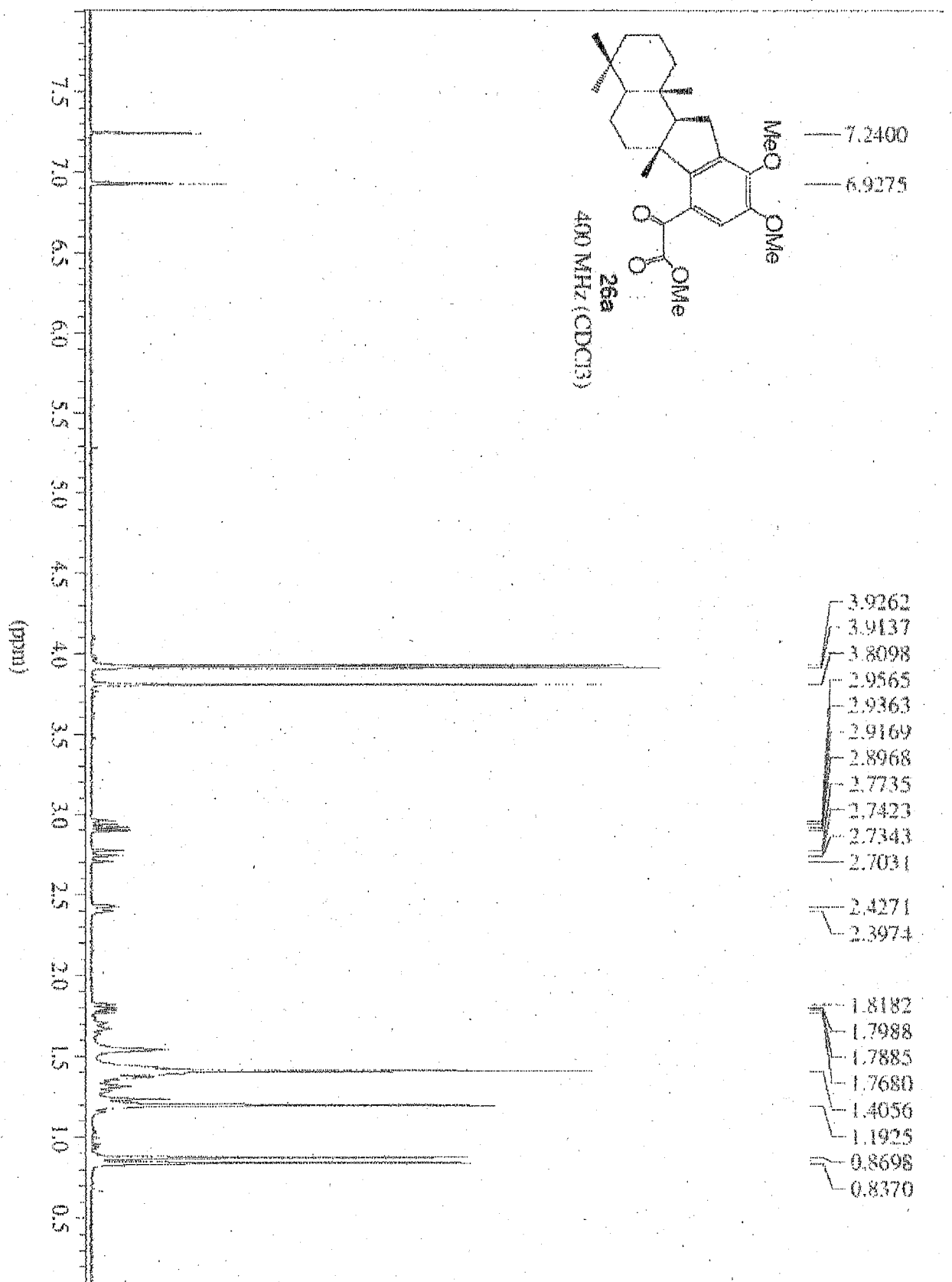


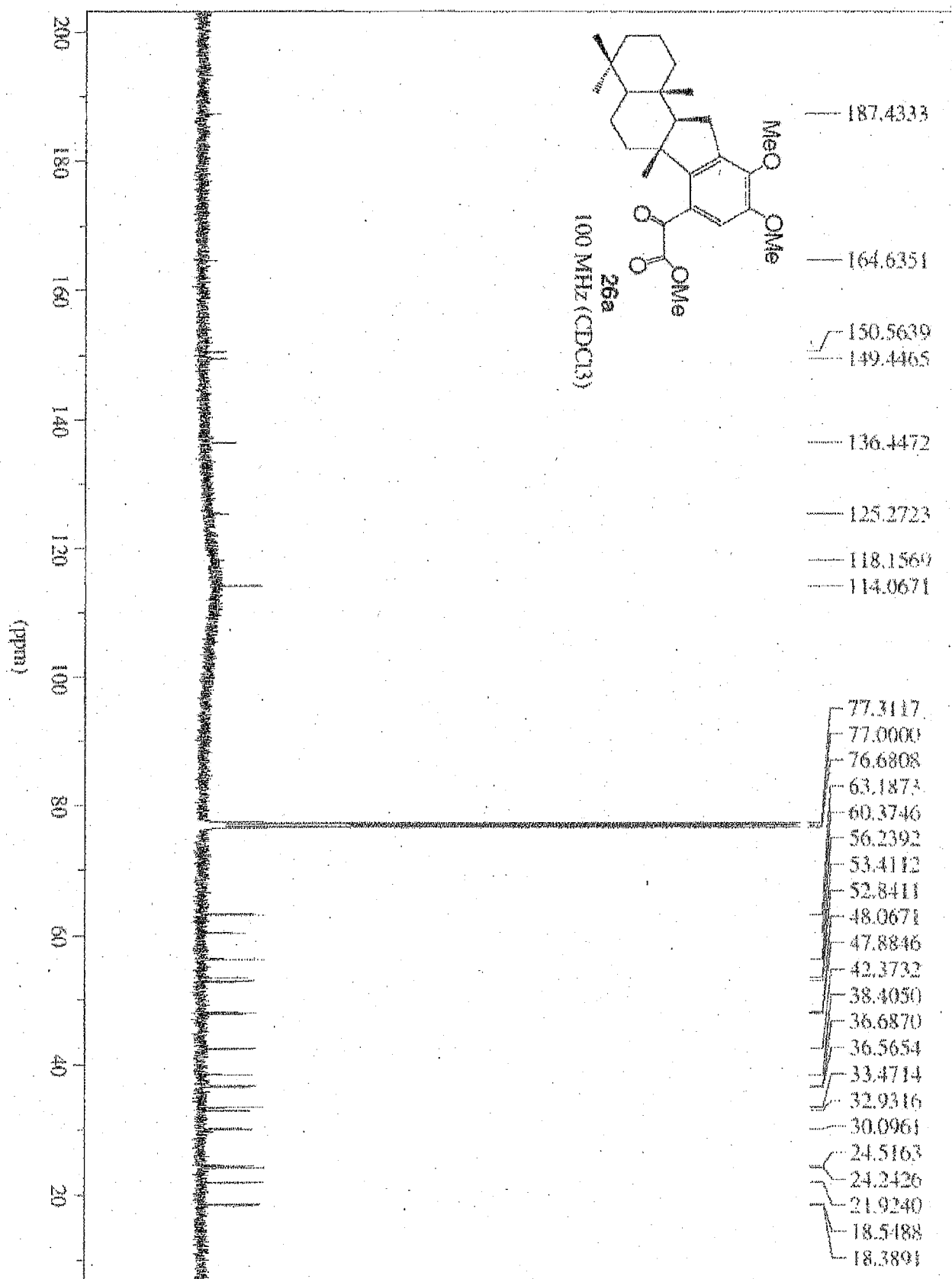


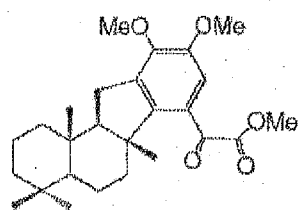




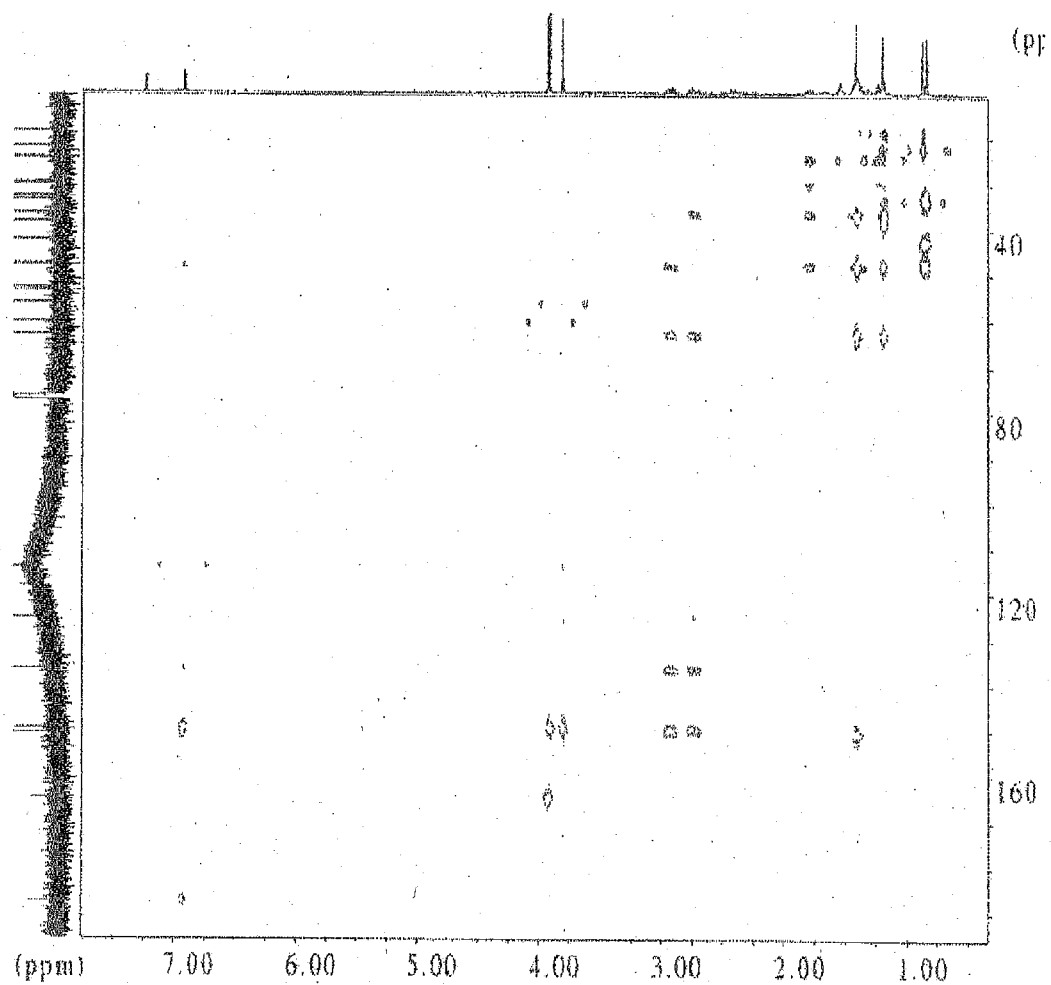


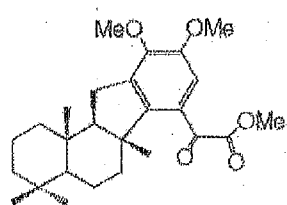




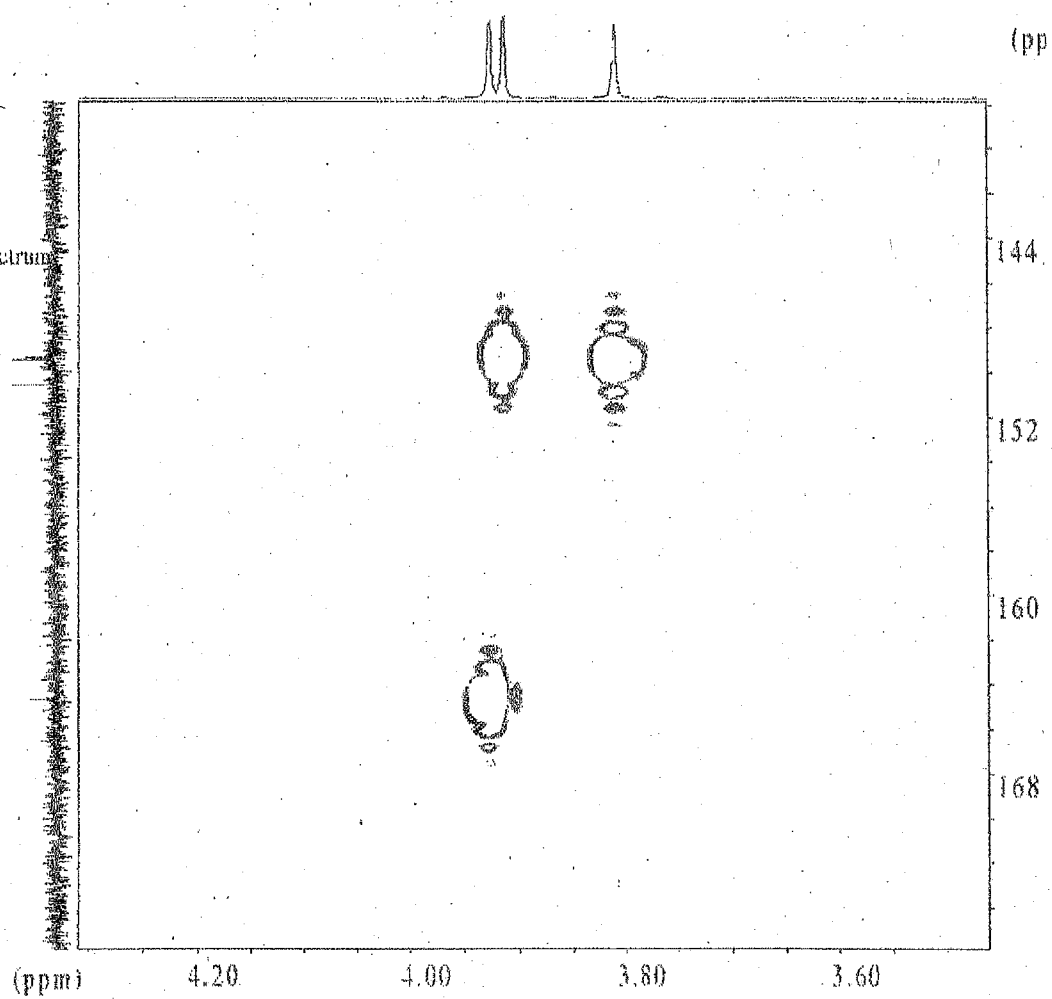


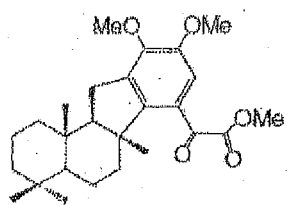
2D-HMBC spectrum of 26a
in CDCl₃



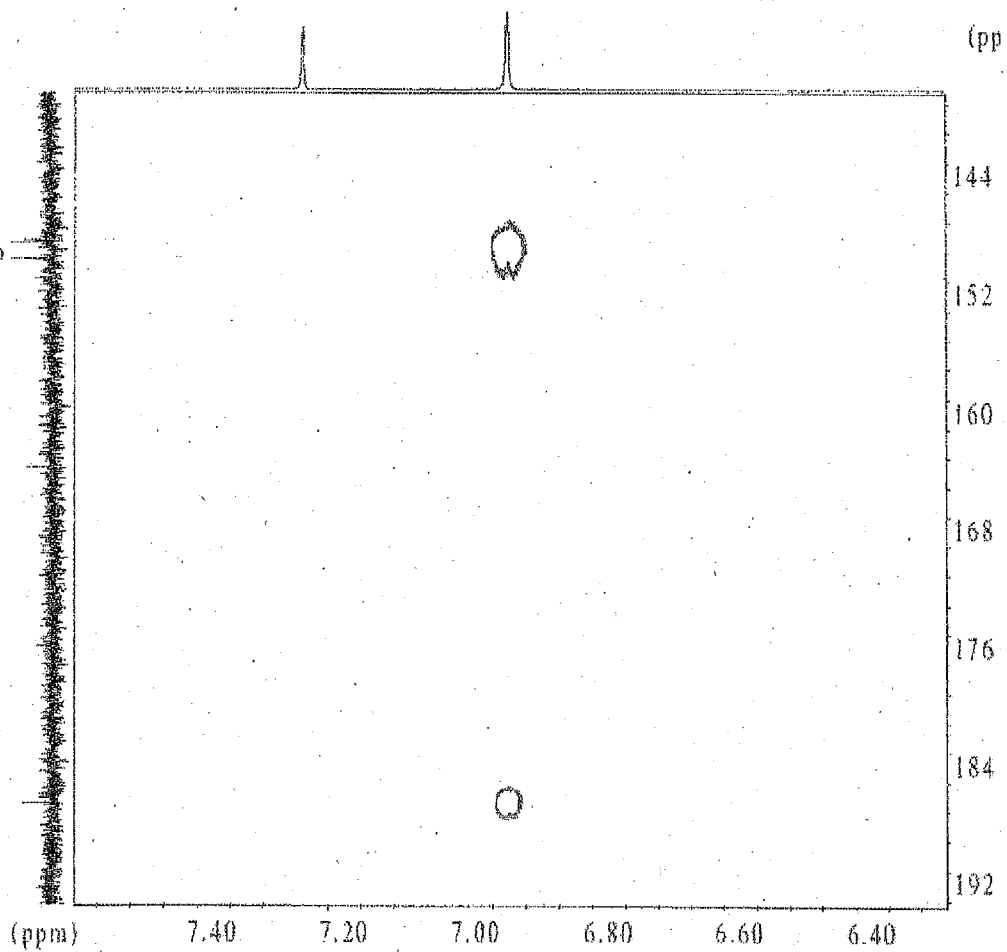


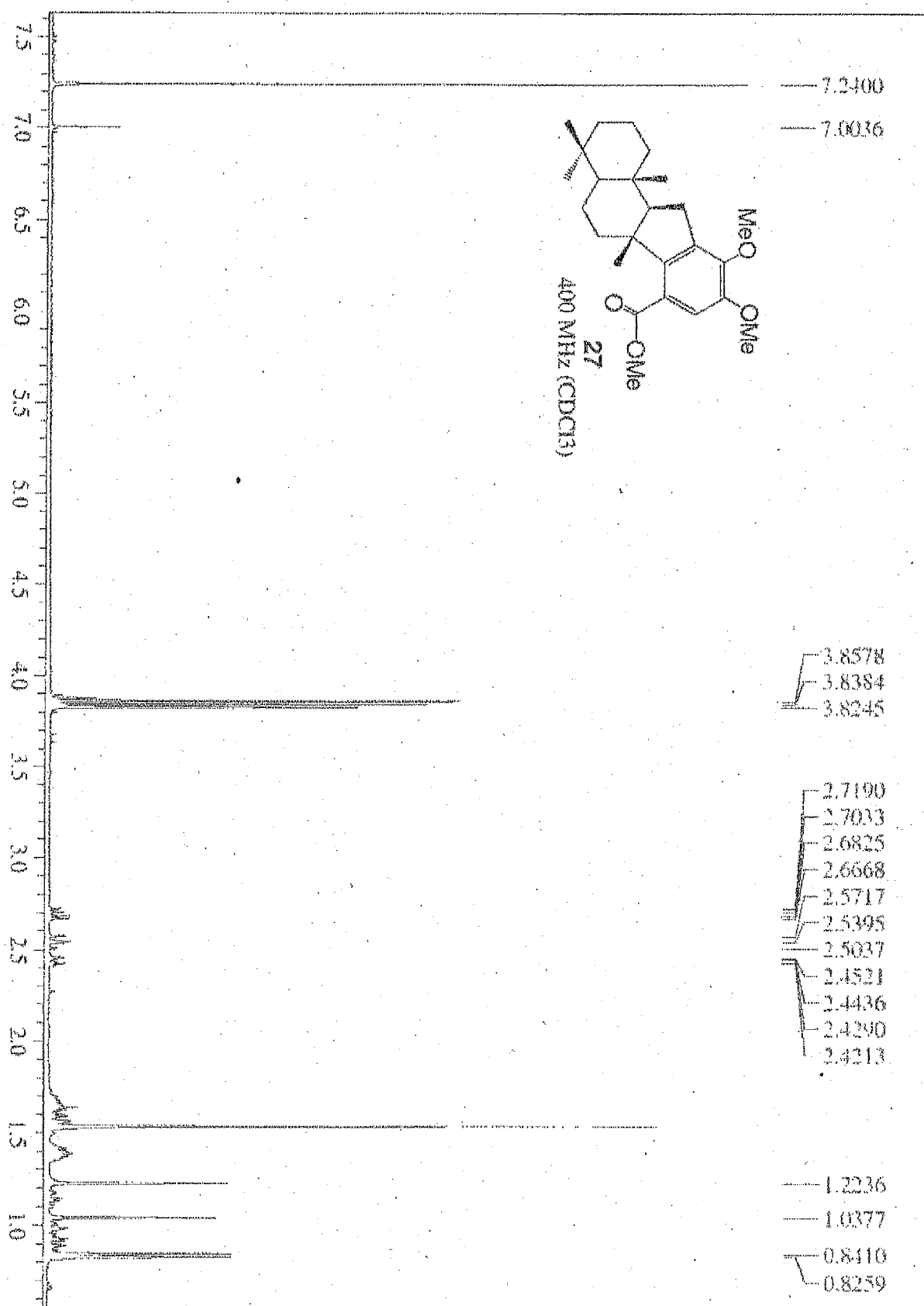
Selected region of 2D-HMBC spectrum
of **26a** in CDCl₃

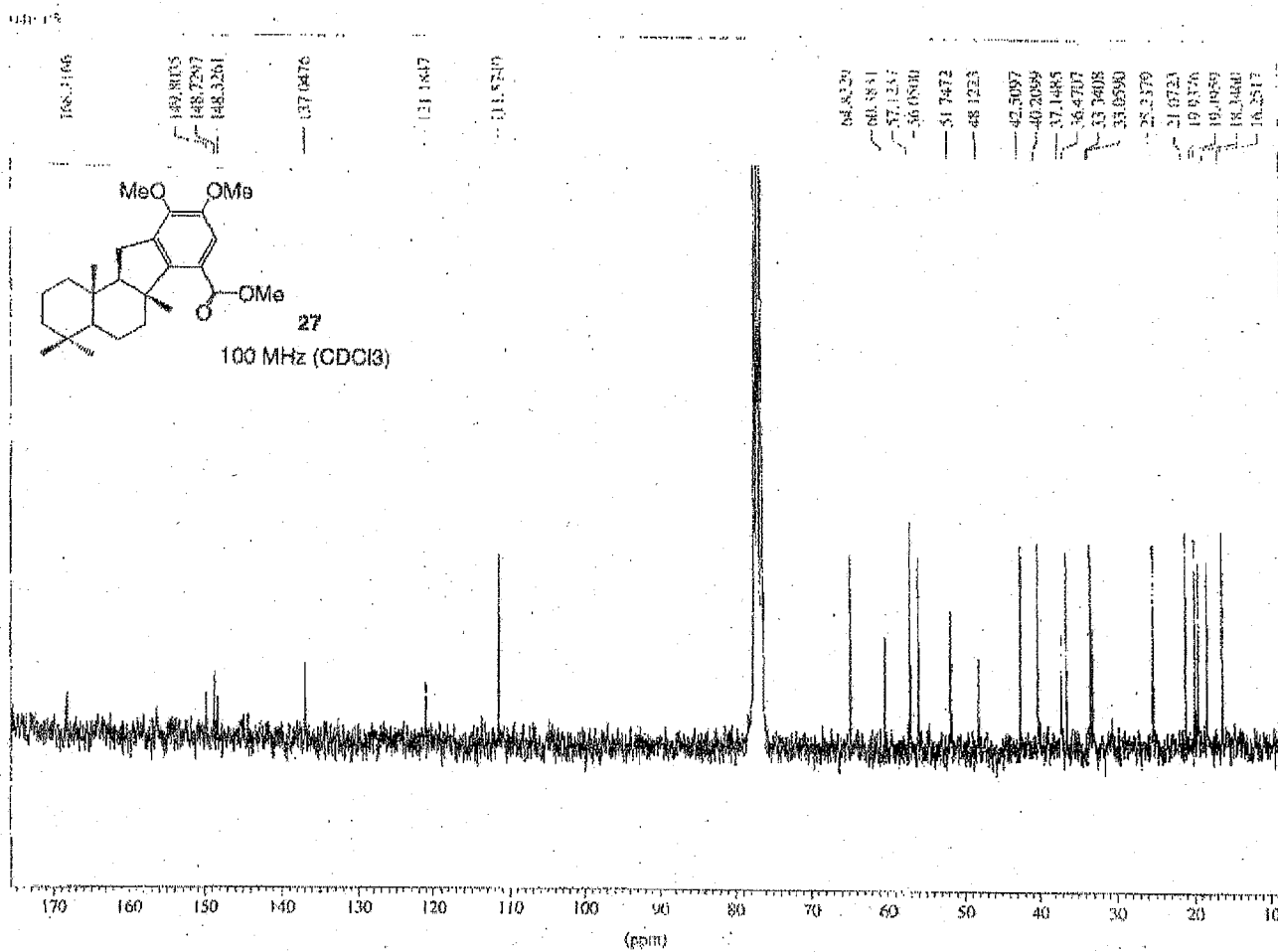


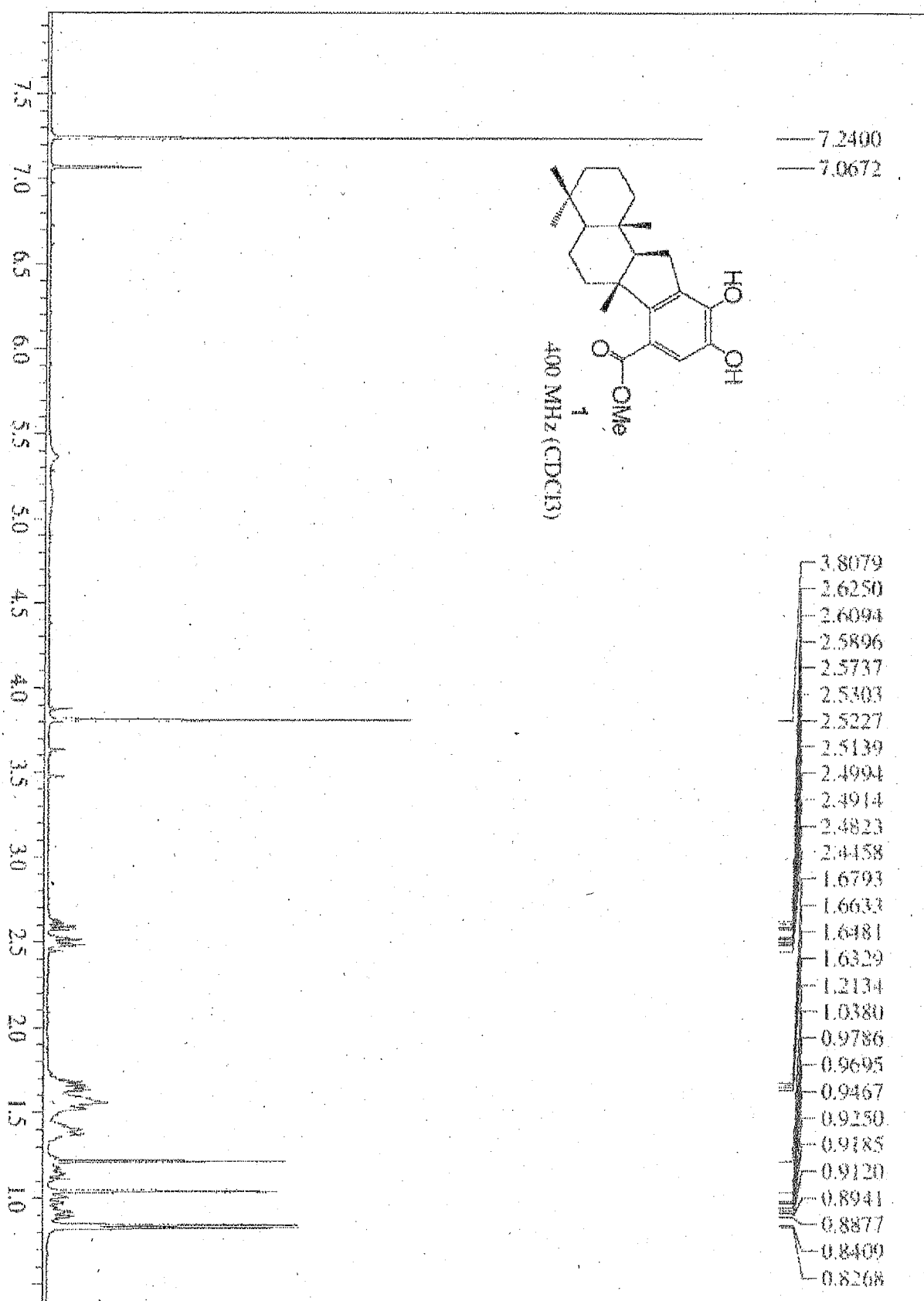


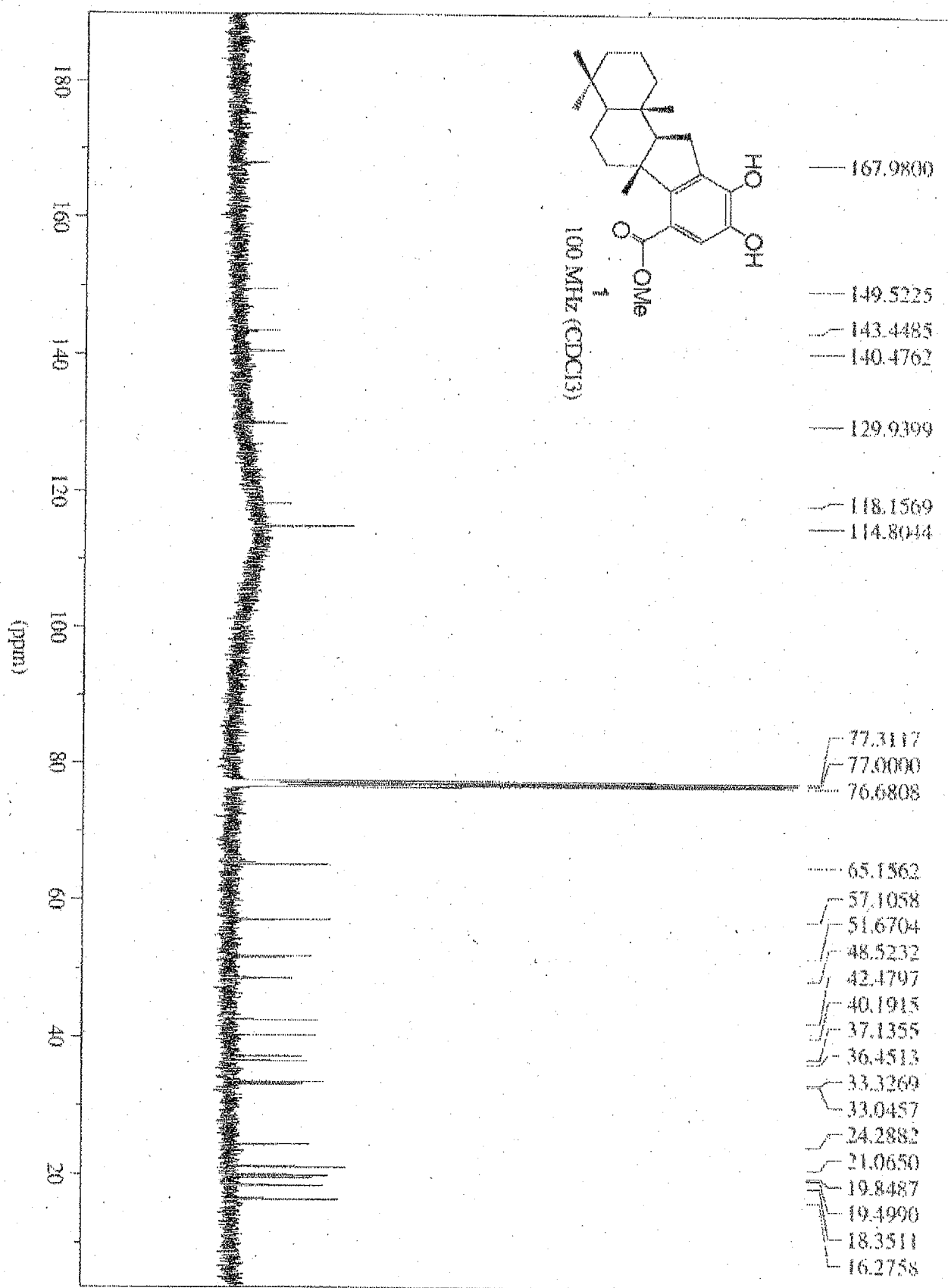
Selected region of 2D-HMBC spectrum
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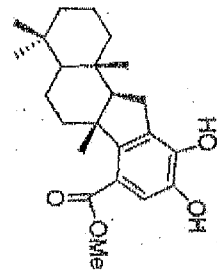












Petrolol 1
isolated from
Dactyospongia elegans

