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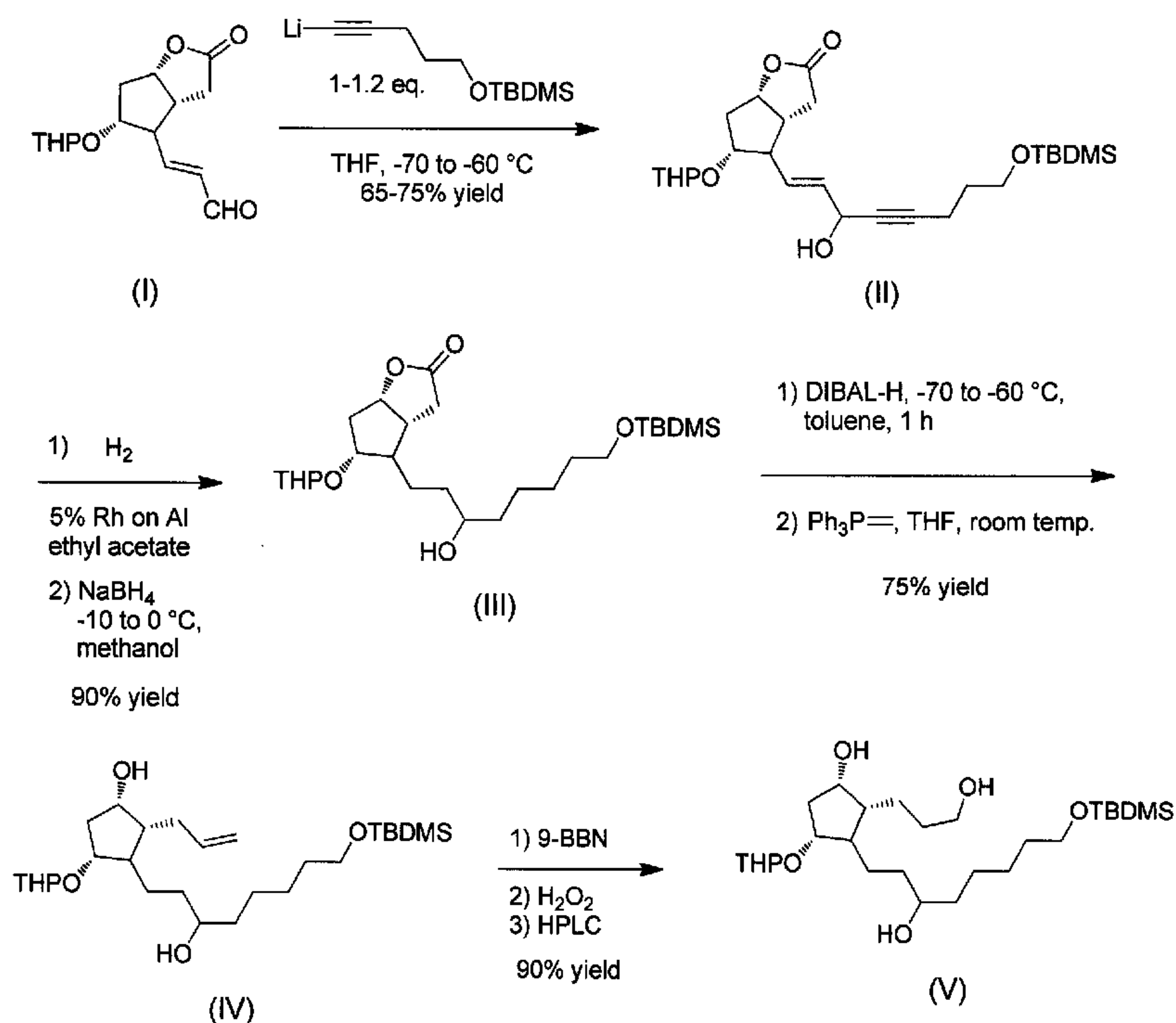
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(54) **Titre : METHODES DE FABRICATION DE METABOLITES DE TETRANOR-PROSTAGLANDINE D ET J**

(54) **Title: METHODS FOR MANUFACTURING TETRANOR-PROSTAGLANDIN D AND J METABOLITES**



(57) **Abrégé/Abstract:**

The present invention generally relates to synthetic methods for preparing tetranor-prostaglandin D and J metabolites.



ABSTRACT

[0079] The present invention generally relates to synthetic methods for preparing tetranor-prostaglandin D and J metabolites.

METHODS FOR MANUFACTURING TETRANOR-PROSTAGLANDIN D AND J METABOLITES

FIELD OF THE INVENTION

[0001] The present invention generally relates to synthetic methods for preparing tetranor-prostaglandin D and J metabolites.

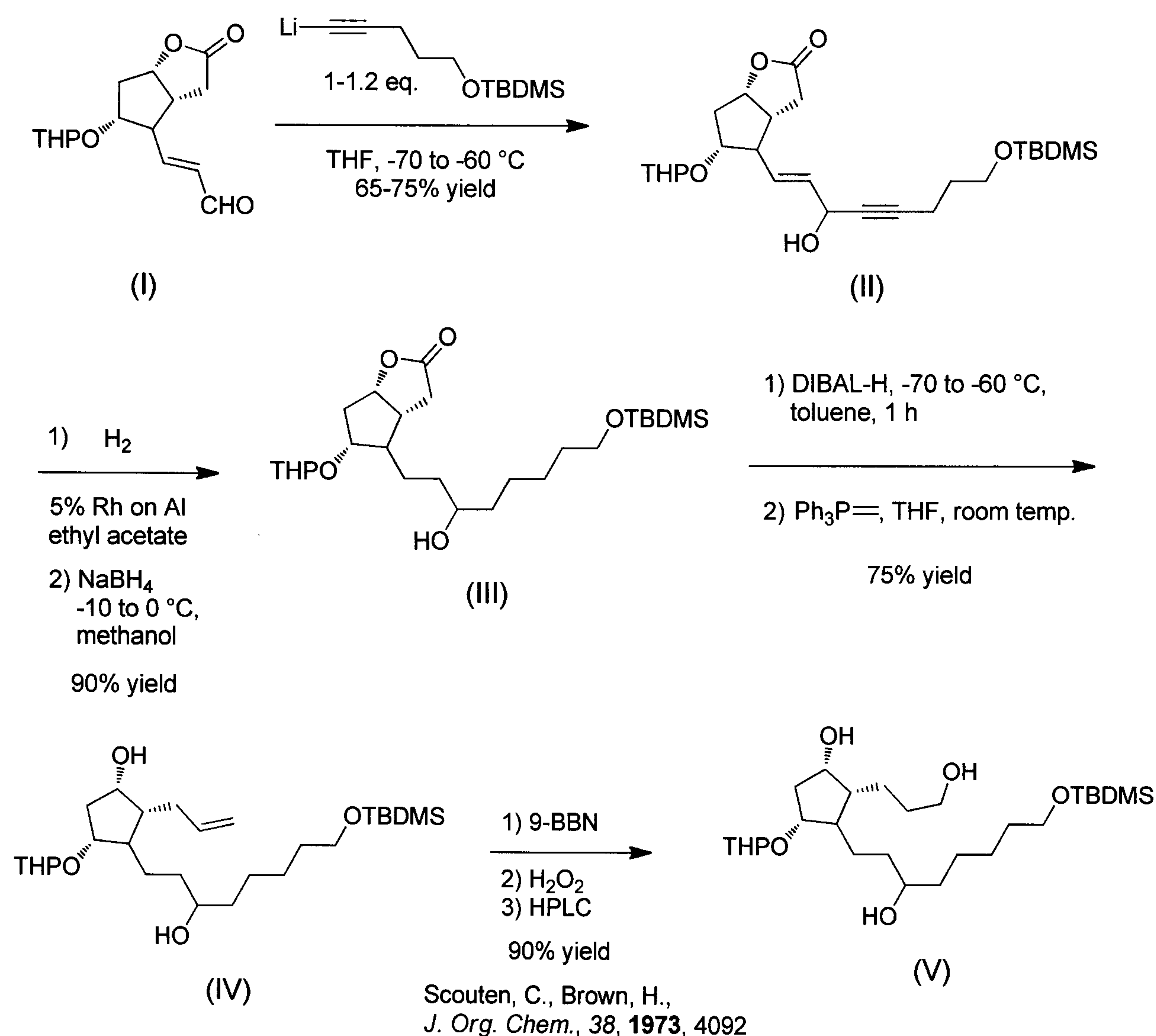
BACKGROUND OF THE INVENTION

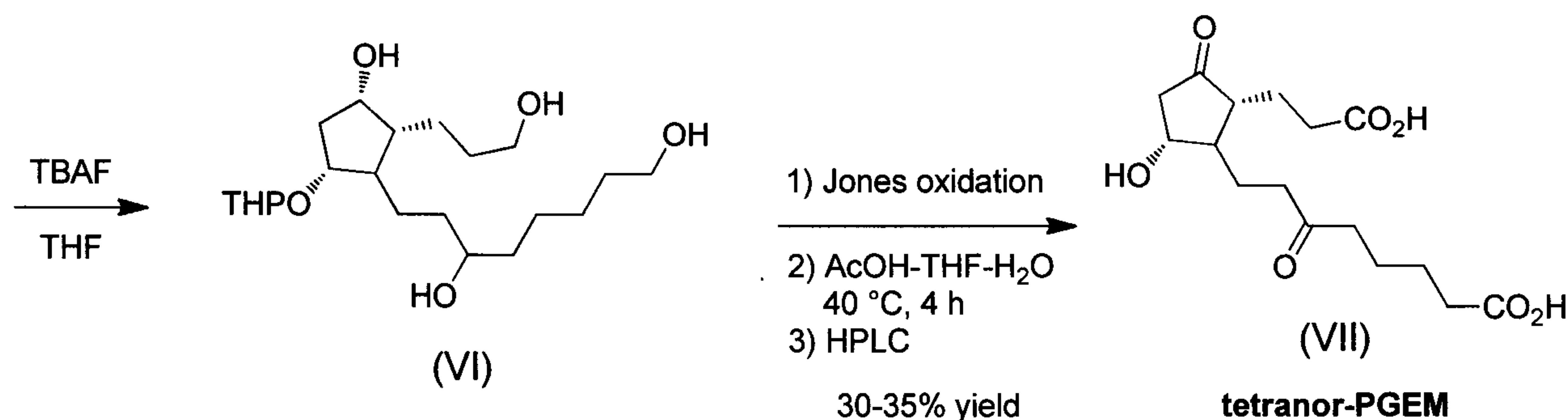
[0002] Prostaglandins are found in virtually all tissues and glands and are extremely potent mediators of a diverse group of physiological processes (Funk, C. D. *Science*, **2001**, *294*, 1871-1875). Prostaglandins can participate in a wide range of body functions, such as the contraction and relaxation of smooth muscle (Andersson, K. E., Forman, A. *Acta Pharmacol. Toxicol.*, **1978**, *43* (Suppl. 2), 90-95), the dilation and constriction of blood vessels (Abramovich, D. R., Page, K. R., Parkin, A. M. L. *Br. J. Pharmac.*, **1984**, *81*, 19-21), control of blood pressure (Anderson, R. J., Berl, T., McDonald, K. M., Schrier, R. W. *Kidney International*, **1976**, *10*, 205-215), and modulation of inflammation and immunity (Hata, A. N., Breyer, R. M. *Pharmacol. Ther.*, **2004**, *103*(2), 147-166). In general, prostaglandins and related compounds are transported out of the cells that synthesize them and affect other target cells close to their site of formation, mainly by interacting with the target cell's prostaglandin receptors to stimulate or inhibit some target cell function. They also alter the activities of the cells in which they are synthesized. The nature of these effects may vary from one cell type to another, and from the target cell type.

[0003] Prostaglandin D₂ (PGD₂) and PGE₂ are biosynthesized from the cyclooxygenase (COX) product of arachidonic acid and common prostanoid precursor prostaglandin H₂ (PGH₂) by the catalytic action of a class of prostaglandin synthases that includes the prostaglandin D synthases (PGDSs) and the PGESs, respectively. Methods and products exist for the measurement of PGD₂ and PGE₂ levels in samples derived from biological systems; however, their relative scarcity in urine due to rapid metabolism and degradation makes their use as biofluid markers for measurement of their biosyntheses impractical.

[0004] The relatively abundant PGD_2 and PGE_2 urinary metabolites tetranor-PGDM and tetranor-PGEM, respectively, are favorable quantification species for the assessment of PGD_2 and PGE_2 biosyntheses. All four species, PGD_2 , tetranor-PGDM, PGE_2 , and tetranor- PGE_2 readily dehydrate to their cyclopentenone derivatives PGJ_2 , tetranor-PGJM, PGA_2 , and tetranor-PGAM, respectively. In addition, the major urinary metabolite of the prostaglandin $\text{PGF}_{2\alpha}$ is tetranor-PGFM (Granström, E., Samuelsson, B., *J. Am. Chem. Soc.*, 91, 1969, 3398-3400.).

[0005] One synthesis of tetranor-PGEM is disclosed (Lin, C., *J. Org. Chem.*, 41(25), 1976, 4045-4047). The disclosed route began from lactone-aldehyde intermediate (I).





The disclosed route involves process for installing the prostaglandin metabolite lower chain (ω -chain) starting with (I), an intermediate that is not readily available. The ω -chain is further extended by addition of 1-dimethyl-*tert*-butylsilyloxy-4-pentynyllithium. Other than this disclosure, practical chemical syntheses of the tetranor-prostaglandin metabolites are not disclosed. Ready supplies of these important metabolites by controlled chemical processes would provide advantage over the current art of isolation through biosynthesis. Characterized standard compounds are potentially useful, for example, as assay standards or building blocks for preparing analogs for medicinal chemistry purposes. This present invention provides many practical chemical syntheses of the tetranor-prostaglandin metabolites beginning with the readily available hydroxyl-protected Corey lactone aldehyde.

SUMMARY OF THE INVENTION

[0006] The exemplary embodiments may be directed to methods for synthesizing tetranor-prostaglandin D, J, E, A, and F metabolites (tetranor-PGDM, tetranor-PGJM, tetranor-PGEM, tetranor-PGAM, and tetranor-PGFM).

[0007] The exemplary embodiments may also be directed to novel synthetic intermediates.

[0008] Other exemplary embodiments of the invention will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while disclosing exemplary embodiments of the invention, are intended for purposes of illustration only and are not intended to limit the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Figures 1-25D are compound spectra confirming the synthesis for certain compounds described in Schemes I, II and III and the Examples below.

DETAILED DESCRIPTION OF THE INVENTION

[0011] For purposes of the following detailed description, it is to be understood that the invention may assume various alternative variations and step sequences, except where expressly specified to the contrary. Moreover, other than in any operating examples, or where otherwise indicated, all numbers expressing, for example, quantities of ingredients used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0012] Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard variation found in their respective testing measurements.

[0013] Also, it should be understood that any numerical range recited herein is intended to include all sub-ranges subsumed therein. For example, a range of "1 to 10" is intended to include all sub-ranges between (and including) the recited minimum value of 1 and the recited maximum value of 10, that is, having a minimum value equal to or greater than 1 and a maximum value of equal to or less than 10.

[0014] In this application, the use of the singular includes the plural and plural encompasses singular, unless specifically stated otherwise. In addition, in this application, the use of "or" means "and/or" unless specifically stated otherwise, even though "and/or" may be explicitly used in certain instances.

[0015] Unless otherwise defined herein, scientific and technical terms used in connection with the exemplary embodiments shall have the meanings that are commonly understood by those of ordinary skill in the art.

[0016] Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclature used in connection with, and techniques of chemistry and biology described herein are those well known and commonly used in the art.

[0017] The term “protecting group” is a moiety that chemically modifies an organic functional group such that certain reaction conditions that would ordinarily cause chemical transformation of the functional group while unprotected are blocked from occurring on the protected functional group, and allowing desired chemical transformations to be carried out selectively on other functional groups that may be transformed by the reaction conditions. Protecting groups and protective group chemistry commonly used in the art is described in Greene, T.W. and Wuts, P.G.M., 1991, *Protective Groups in Organic Synthesis*, Second Edition, John Wiley & Sons, Inc., New York.

[0018] The term “THF” refers to tetrahydrofuran.

[0019] The term “DMF” refers to N,N-dimethylformamide.

[0020] The term “DHP” refers to 3,4-dihydropyran (added to hydroxyl group to form THP-O group, or THP-protected hydroxyl group).

[0021] The term “PPTS” refers to pyridinium p-toluenesulfonate.

[0022] The term “Et” as in “Et₃N”, refers to ethyl.

[0023] The term “DIBAL” refers to diisobutylaluminum.

[0024] The term “BuOK” refers to potassium butoxide, while the term “t-BuOK” refers to potassium tert-butoxide.

[0025] The term “THP” refers to tetrahydropyran.

[0026] The term “BBN” refers to borabicyclo[3.3.1]nonane, while the term “9-BBN” refers to 9-borabicyclo[3.3.1]nonane.

[0027] The term “Jones Oxidation” refers to an organic reaction for the oxidation of primary and secondary alcohols to carboxylic acids and ketones, respectively. A “Jones Reagent” is a solution of chromium trioxide in dilute sulfuric acid and acetone. A mixture of potassium dichromate and dilute sulfuric acid can also be used as the “Jones Reagent”.

[0028] The term “Ac” as in “AcOH” refers to acetyl, or $\text{CH}_3\text{-C=O}$, also written as CH_3CO , with an open valence on the carbonyl carbon atom that bonds to -OH to form acetic acid. Accordingly, the term “AcOH” refers to acetic acid, or $\text{CH}_3\text{-CO}_2\text{H}$.

[0029] The term “TBDMS” refers to tert-butyldimethylsilyl.

[0030] The term “TBDPS” refers to tert-butyldiphenylsilyl.

[0031] The term “TIPS” refers to triisopropylsilyl.

[0032] The term “TBAF” refers to tetrabutylammonium fluoride.

[0033] The term “EA” refers to ethyl acetate.

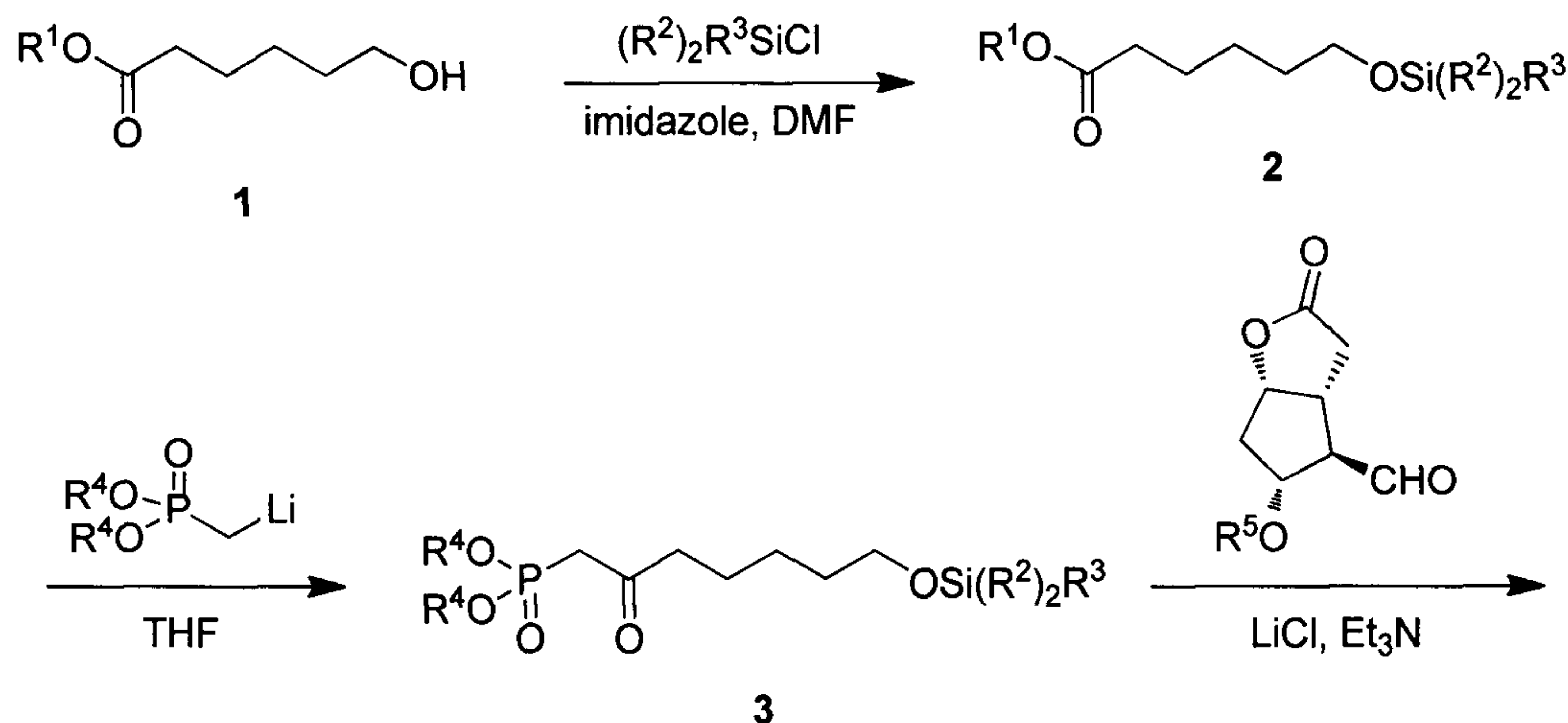
[0034] The term “ R_f ” refers to retention factor. For thin layer chromatography (TLC), R_f is defined as the distance traveled by the compound divided by the distance traveled by the solvent or solvent system (mobile phase) on the silica (stationary phase) of the TLC plate.

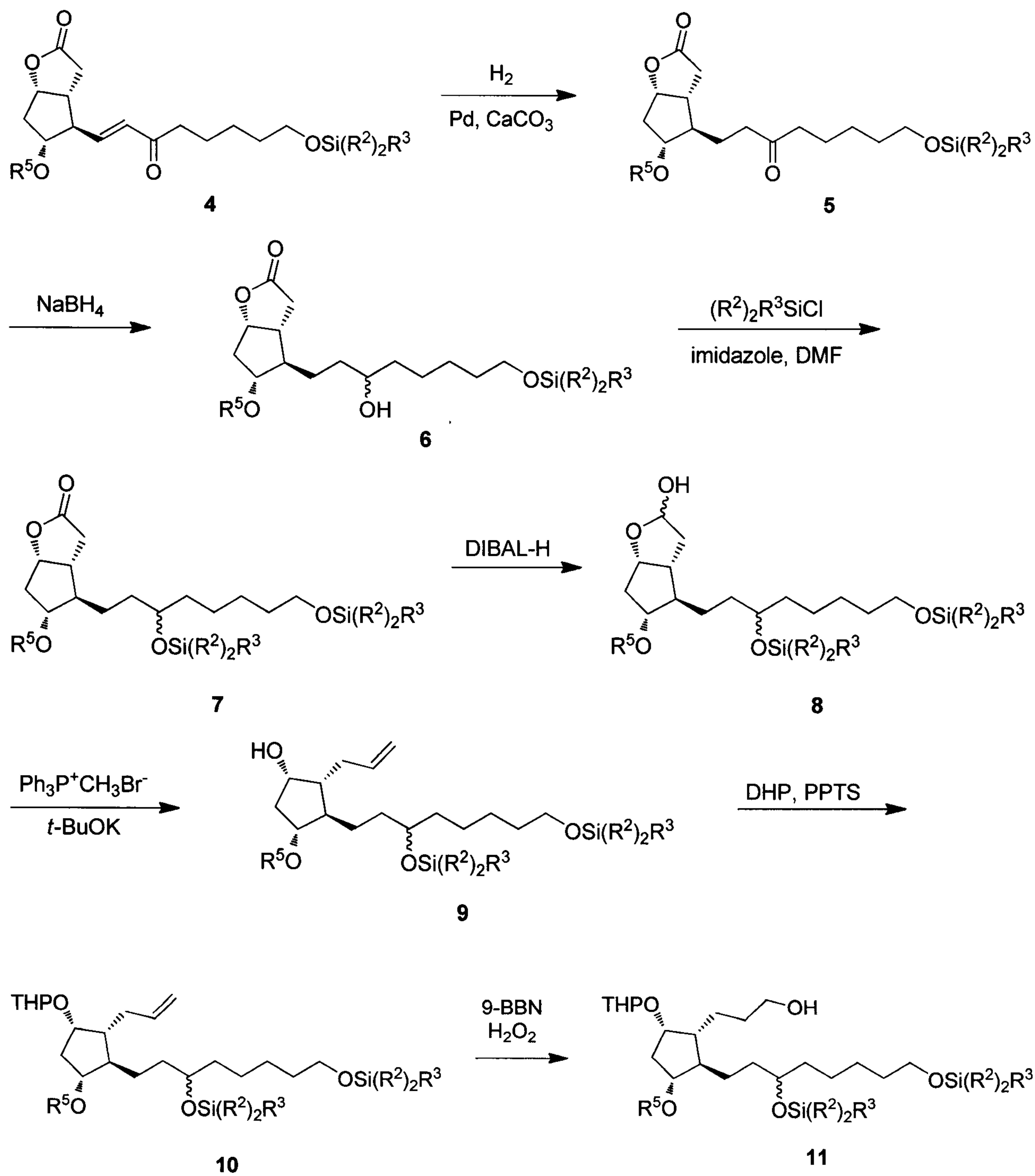
[0035] The term “PG” refers to prostaglandin.

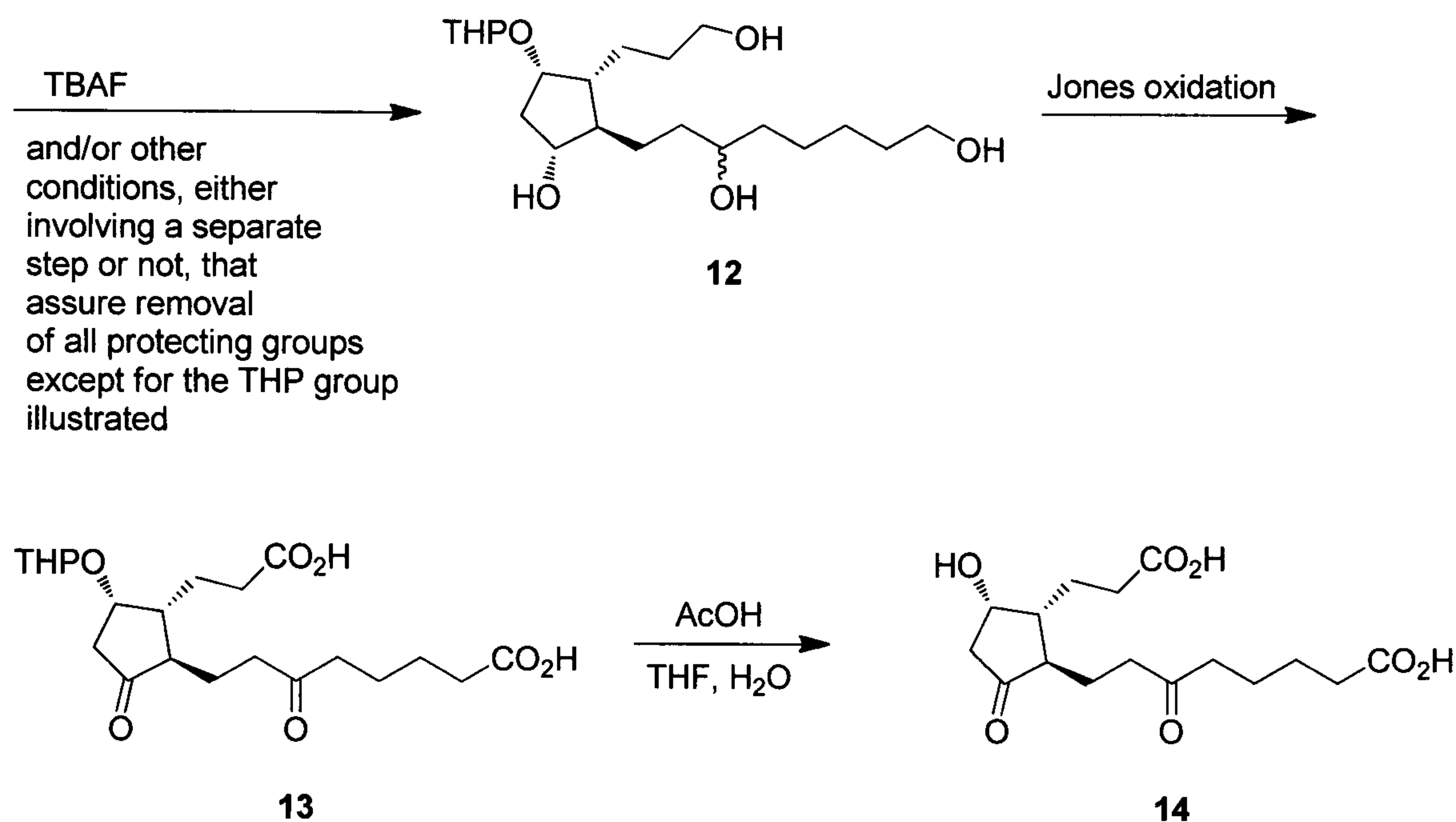
[0036] The term “TLC” refers to thin layer chromatography.

[0037] The term “Bz” refers to the benzoyl group, or Ph-C=O , also written as PhCO , with an open valence on the carbonyl carbon atom that bonds to -OH to form benzoic acid, for example.

[0038] The exemplary embodiments may be directed to a synthetic route for the preparation of tetranor-PGDM (Compound 14), comprising the reaction steps illustrated in Scheme I:





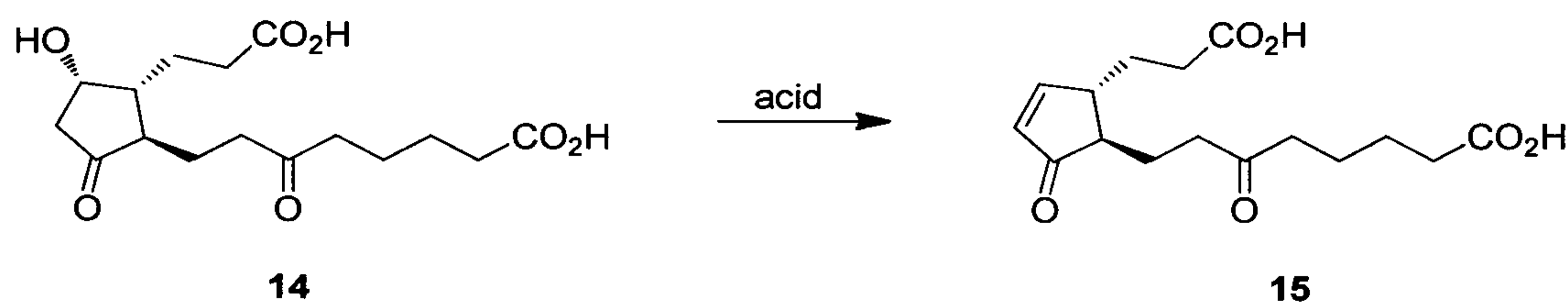


(Scheme I)

wherein R¹ is C₁₋₄ alkyl; each R² is independently C₁₋₅ alkyl or phenyl; each R³ is independently a C₁₋₄ alkyl; R⁴ is methyl or ethyl; and R⁵ is a protecting group. See Figures 1 through 12 for spectral data confirming the synthesis of certain forms of Compounds 4A, 5A, 6A, 7A, 9A, 10A, 11A, 12, 13 and 14 by the methods of Scheme I.

[0039] In certain embodiments, the protecting group R⁵ comprises *tert*-butyldimethylsilyl (TBDMS), a protecting group that is stable to all reaction conditions between its introduction to the reaction sequence illustrated in Scheme I and its required removal by appropriate deprotection conditions.

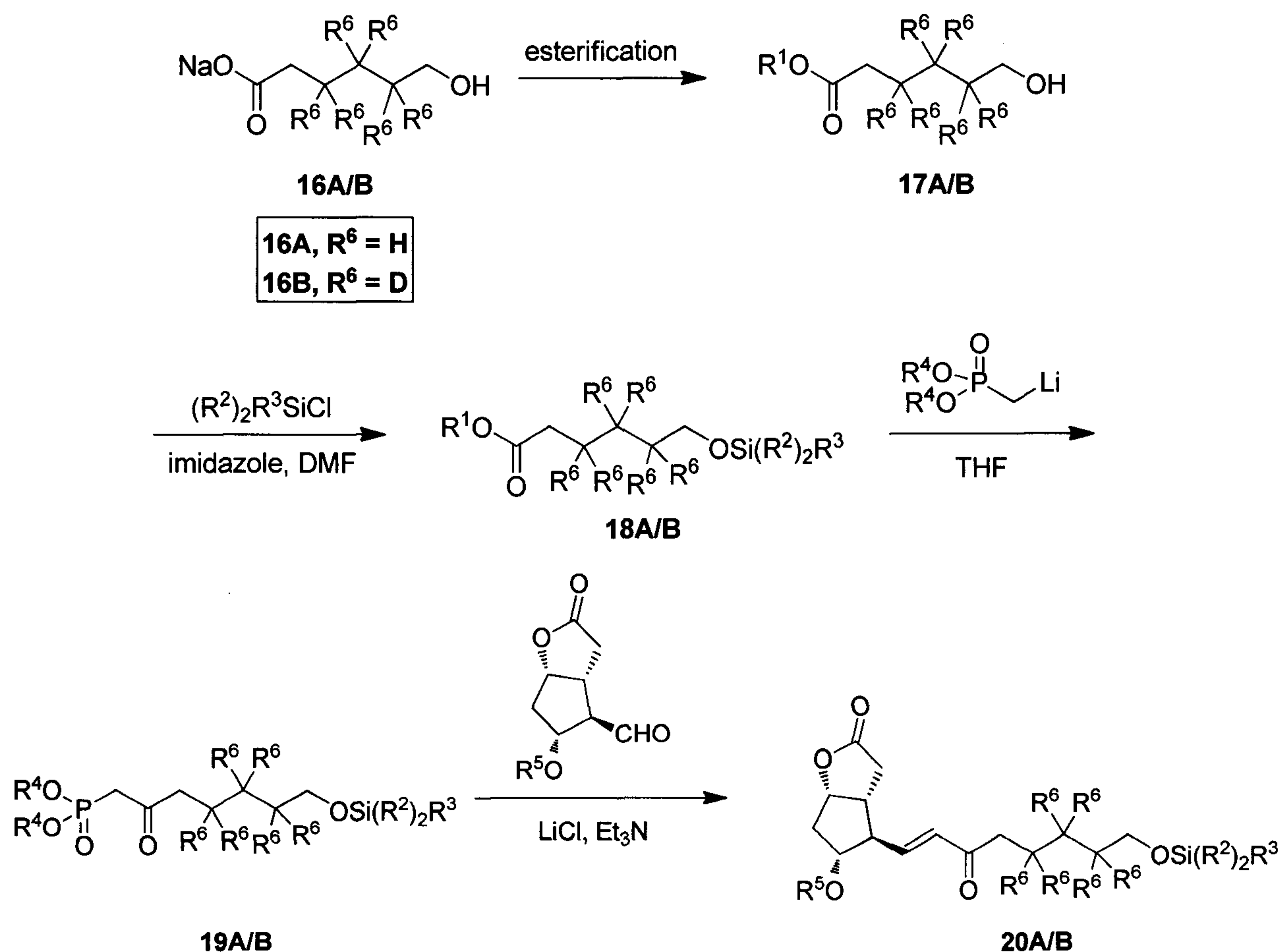
[0040] Other exemplary embodiments may be directed to a synthetic method for the preparation of Compound **15**, tetranor-PGJM, from tetranor-PGDM comprising an acid-catalyzed dehydration as illustrated in Scheme II:

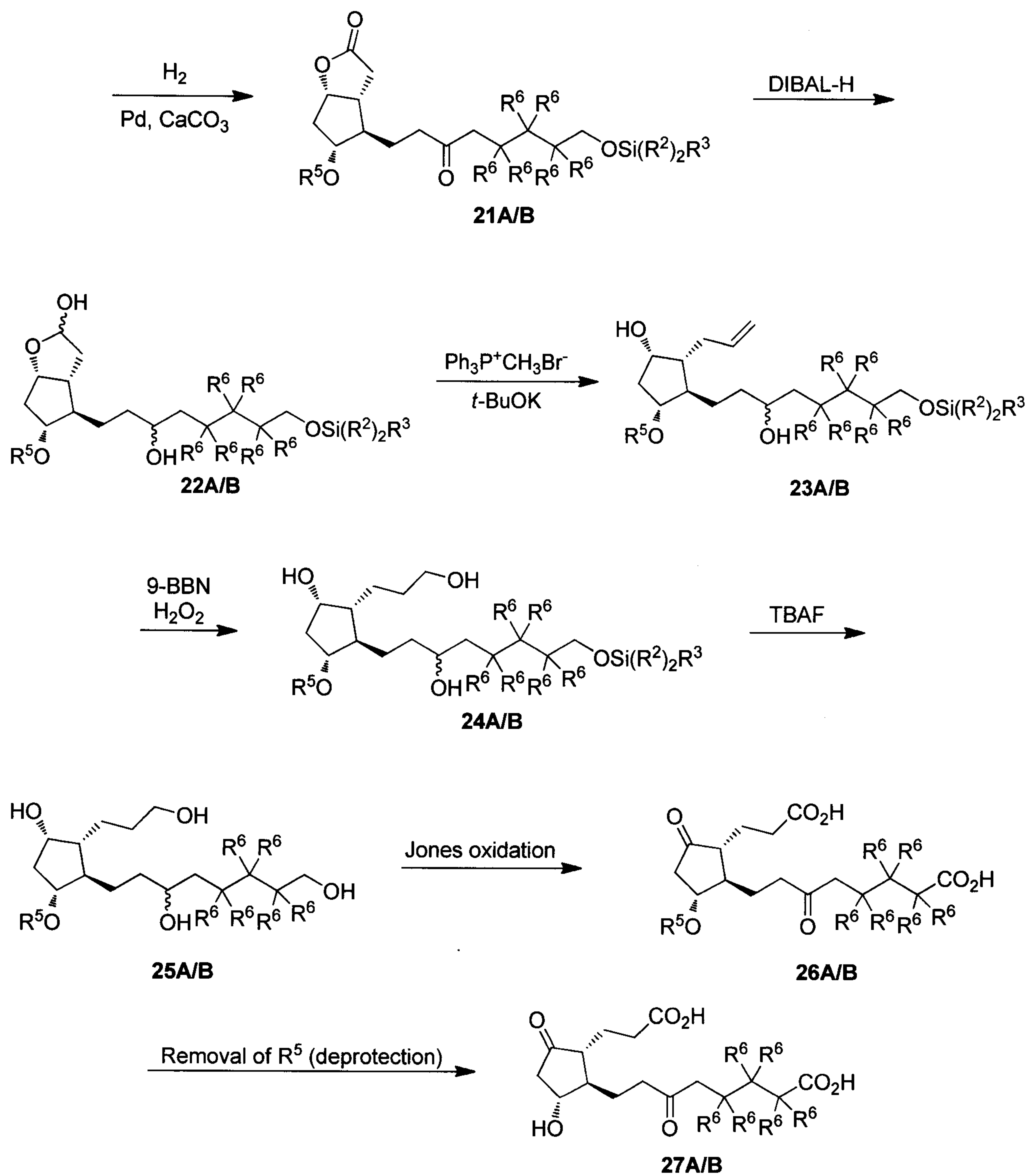


(Scheme II)

In certain embodiments, the acid comprises any organic or inorganic acid. In certain embodiments, the acid comprises acetic acid or trifluoroacetic acid. See Figures 13 and 14A-B for spectral data confirming the synthesis of Compound 15 by the methods of Scheme II.

[0041] Other exemplary embodiments may be directed to a synthetic route for the preparation of Compound 27A, tetranor-PGEM, and Compound 27B, a deuterated (D_6) analog of tetranor-PGEM, comprising the reaction steps as illustrated in Scheme III:





(Scheme III)

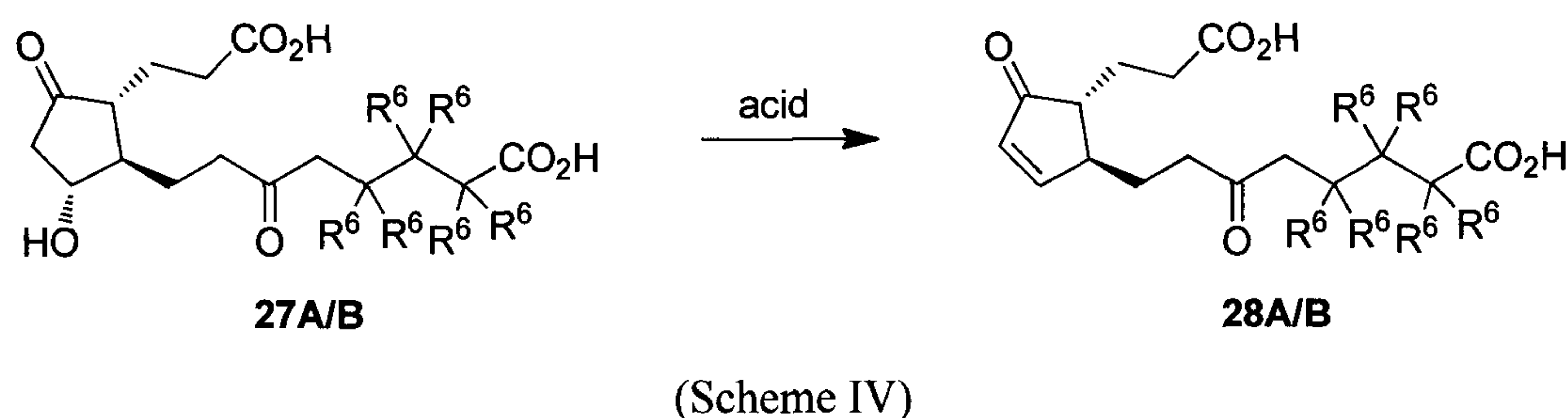
wherein R^1 is C_{1-4} alkyl; each R^2 is independently C_{1-5} alkyl or phenyl; each R^3 is independently a C_{1-4} alkyl; R^4 is methyl or ethyl; R^5 is a protecting group; and R^6 is hydrogen

or deuterium. See Figures 15-22 for spectral data confirming the synthesis of certain forms of Compounds 20A, 21A, 23A, 25A, 26A, and 27A by the methods of Scheme III.

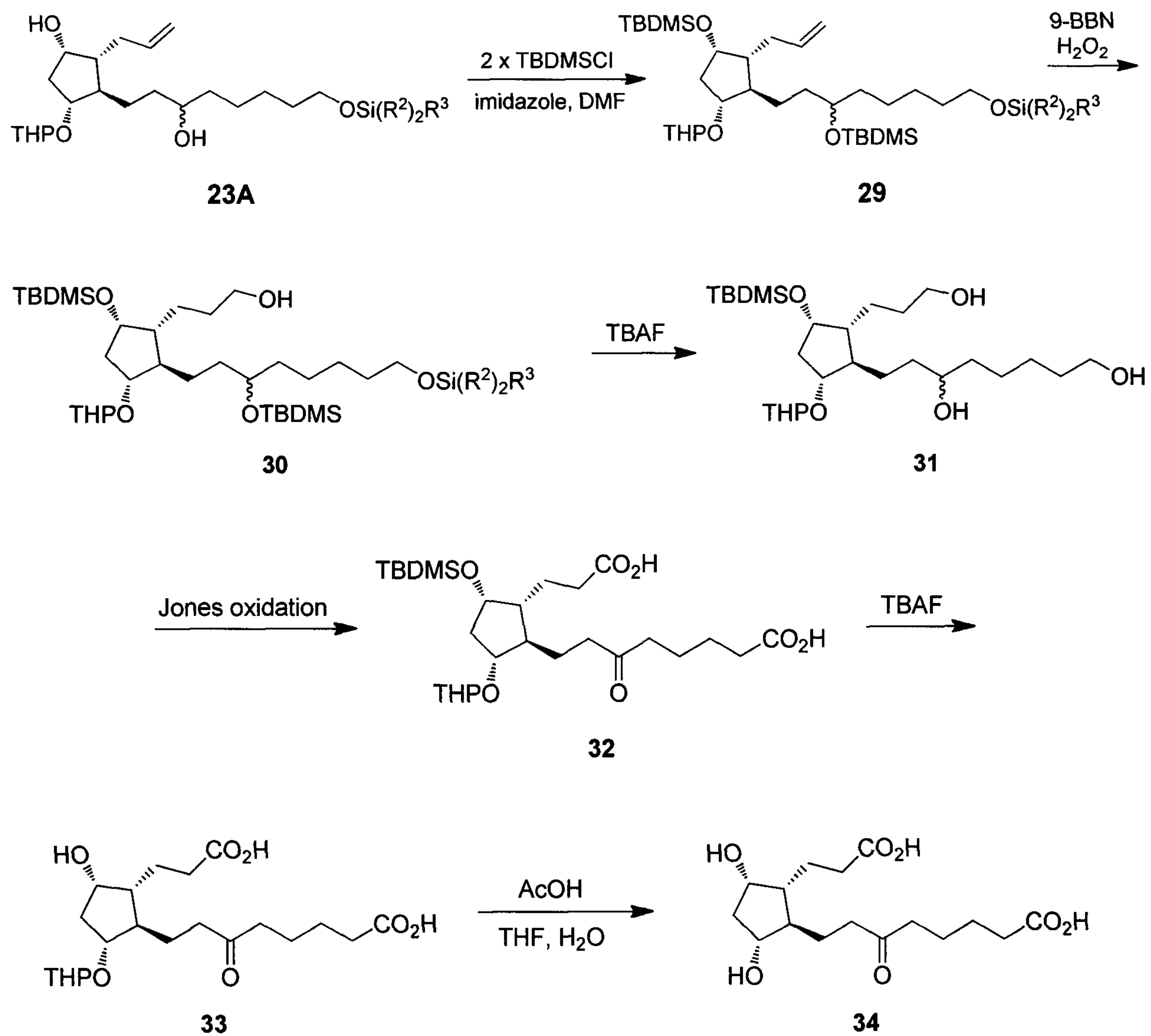
[0042] In certain embodiments, R^5 is a protecting group that survives all conditions until the final deprotection step. In certain other embodiments, R^5 is a protecting group that may be exchanged for another protecting group possessing stability under a different set of reaction conditions as required to carry out the completion of the reaction sequence or essentially the same reaction sequence as illustrated in Scheme III.

[0043] In certain of these embodiments R^5 is THP or silyl protecting group, such as, but not limited to, TBDMS, TIPS, or TBDPS. In embodiments wherein R^5 is exchanged for another protecting group, that protecting group may also be THP, TBDMS, TIPS, or a silyl protecting group, with the proviso that the exchanged protecting group is different than the protecting group for which it was exchanged.

[0044] Other exemplary embodiments may be directed to a synthetic method for the preparation of Compounds **28A** and **28B** (See Figures 23A-24 for spectral data confirming the synthesis of certain forms of Compounds 28A by the methods of Scheme IV), tetranor-PGAM and tetranor-PGAM- D_6 , respectively, comprising acid-catalyzed dehydration of the appropriate precursor Compound **27A** and **27B**, respectively, as illustrated in Scheme IV:



[0045] Other exemplary embodiments may be directed to a synthetic route for the preparation of Compound **34**, tetranor-PGFM, comprising the reaction steps illustrated in Scheme V (See Figures 25A-25D for spectral data confirming the synthesis Compound 29 by the methods of Scheme V):

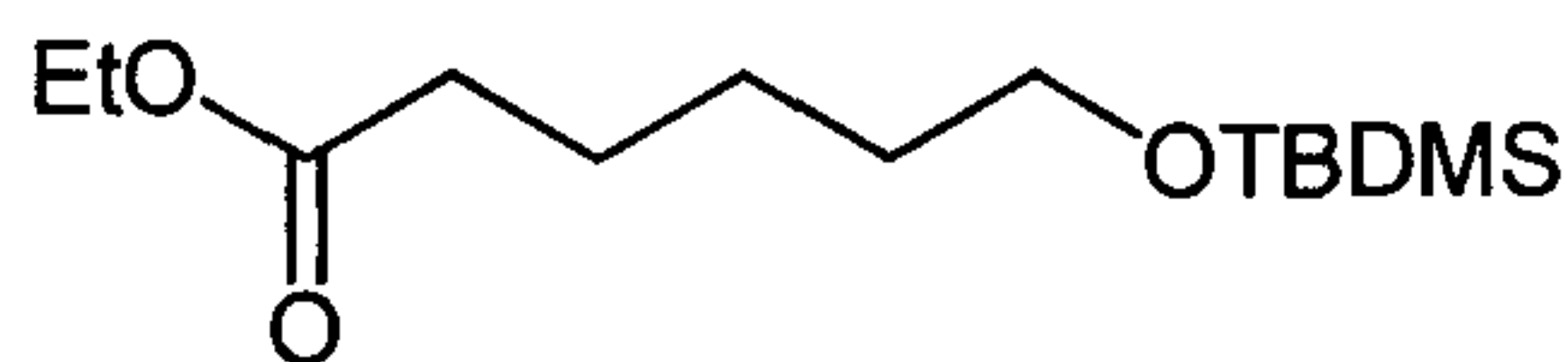


(Scheme V)

[0046]

EXAMPLES

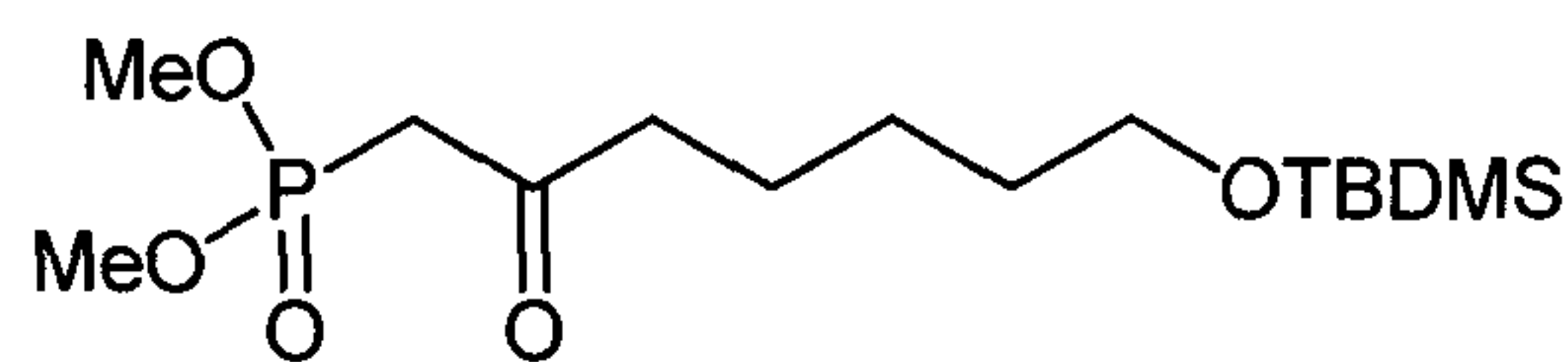
[0047] The Examples provided herein describe embodiments directed to methods for synthesizing various tetranor-PG metabolites.

Example 1: Preparation of tetranor-PGDMPreparation of Ester (2A) from 6-hydroxyhexanoate (1A)**2A**

(2, wherein **R¹** is **ethyl**,
R² is **methyl**, and
R³ is **tert-butyl**)

- 50.0 g (312.1 mmol) of ethyl 6-hydroxyhexanoate (**1A**)
- 61.15 g (405.72 mmol) of TBDMSCl;
- 42.5 g (624.2) of imidazole;
- 500 ml of DMF.

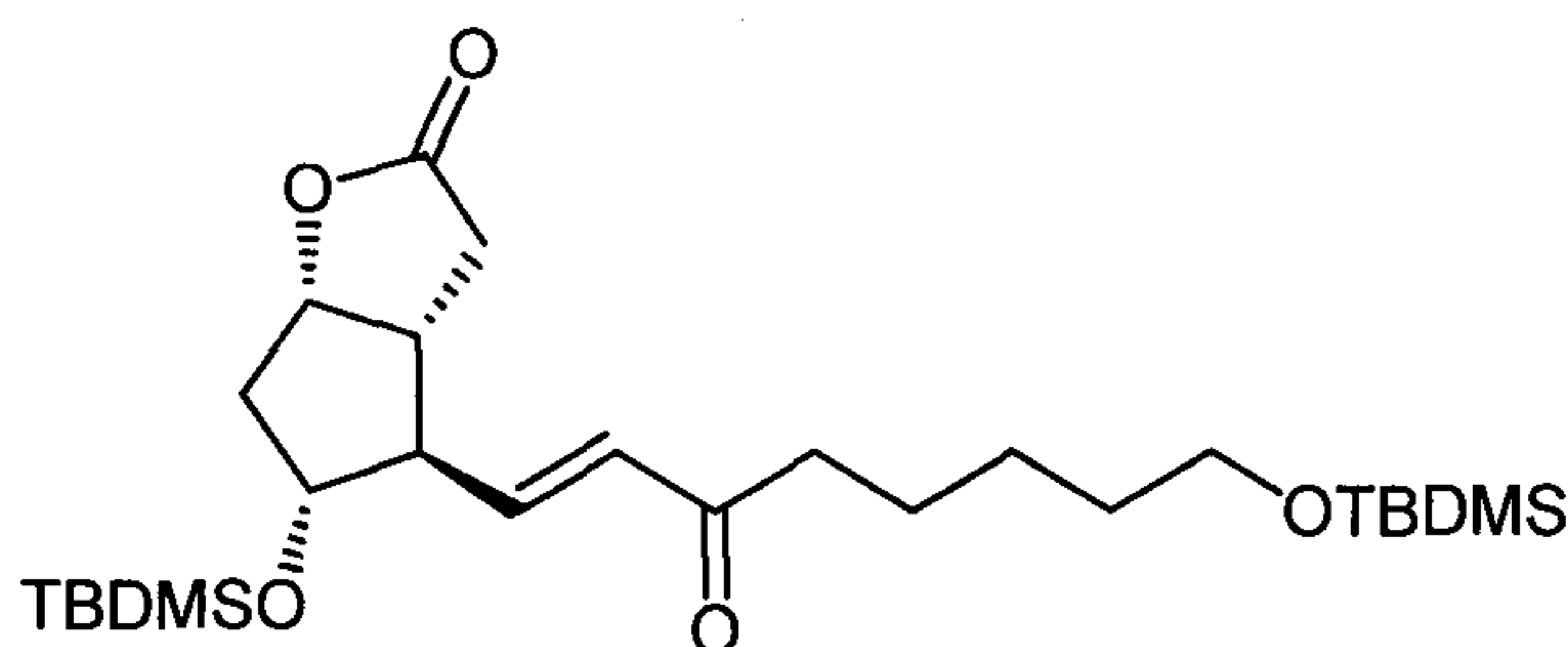
[0048] A solution of ethyl 6-hydroxyhexanoate (**1A**) in dry DMF was cooled with an ice bath and treated with TBDMSCl and imidazole portion wise for 10 minutes. The cooling bath was removed and the reaction mixture was stirred overnight (controlled by TLC, hexane – ethyl acetate 90:10). The next day the reaction mixture was treated with ice (200 g), stirred for 5 minutes, and extracted with H-EA (10:1, 800 ml, 2x200 ml). The combined organic phases were washed with water-brine (1:1, 2 x 100 ml), brine (100 ml), dried over Na₂SO₄, and evaporated. The residue was purified by flash chromatography: Silica gel (300 g), hexane (H) – ethyl acetate (EA) 100:1 – 70:1. The mass of the collected product (Ester (**2A**)) was 81.5 g (95%), TLC R_f = 0.8 (solvent system: hexane – ethyl acetate 90:10).

Preparation of Phosphonate (3A) from Ester (2A)

3A
(3, wherein R^4 is methyl)

- 41.17 g (150 mmol) of protected ester **2A**;
- 17.88 ml (165 mmol) of dimethyl methylphosphonate;
- 72.2 ml (195 mmol) of 2.7 M *n*-BuLi;
- 500 ml of THF.

[0049] A 2.5 M solution of *n*-BuLi in hexanes was added to a solution of phosphonate in dry THF (450 ml) at -75°C under a nitrogen blanket (N_2). After 3 hours, ester **2A** was added in 50 ml of dry THF to the solution and the resultant mixture (RM) was stirred 1 hour at the same temperature. The mixture was then allowed to sit overnight at room temperature. 200 ml of NH_4Cl aqueous solution was then added to the mixture and the resultant mixture was extracted with ethyl acetate (3 x 200 ml), washed with brine, dried over MgSO_4 , and evaporated. The residue remaining after evaporation was purified by flash chromatography: Silica gel (1000 g), CH_2Cl_2 -MeOH 100:1. The mass of the collected product (Phosphonate (**3A**)) was 26.2 g (57%), $R_f = 0.5$ (CH_2Cl_2 -MeOH 95:5).

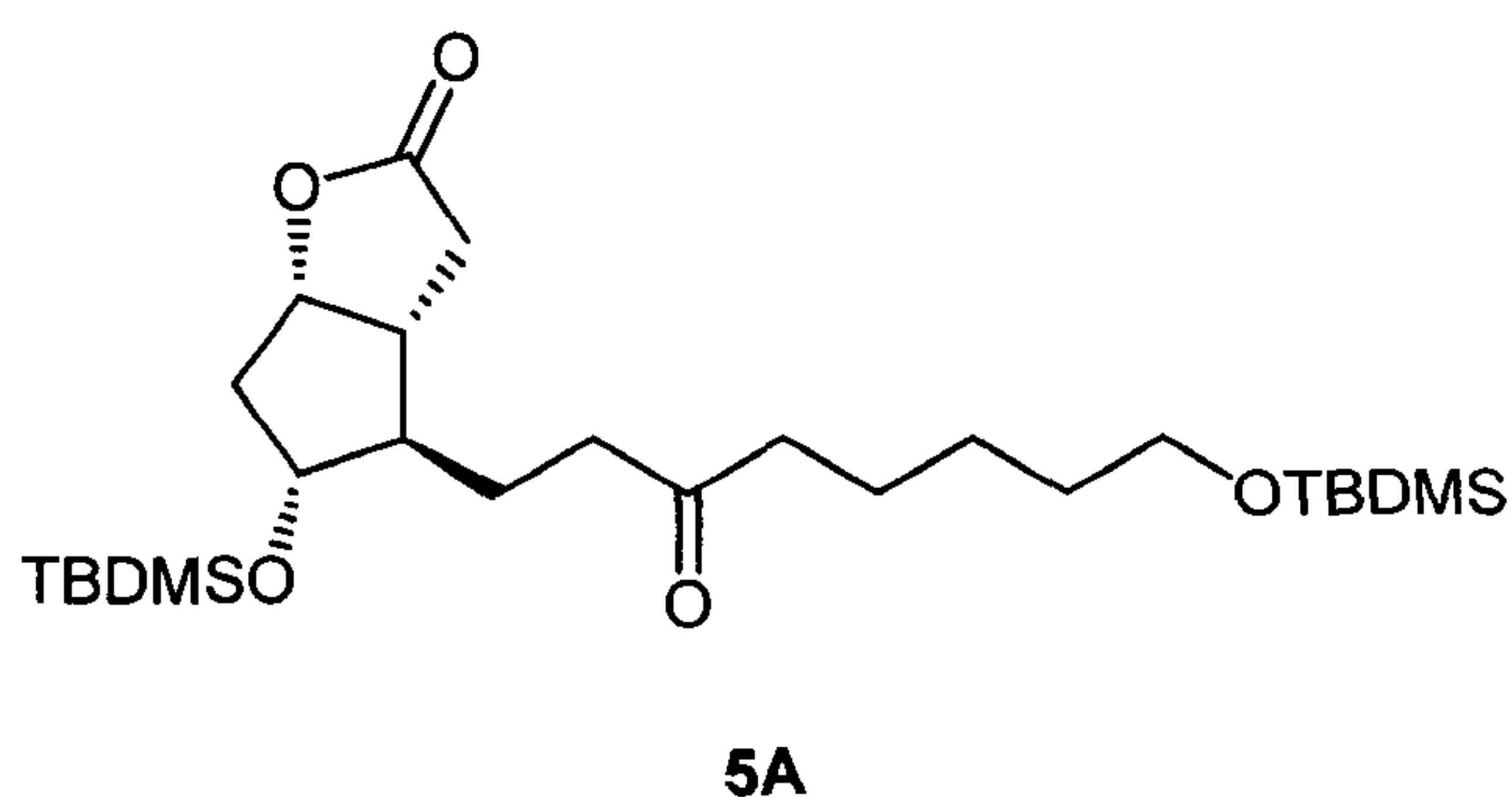
Preparation of PG-Lactone (4A) from Phosphonate (3A)

4A
(4, wherein R^5 is TBDMS)

- 23.77 g (67.4 mmol) of phosphonate **3A**;
- 18.27 g (64.23 mmol) of Corey aldehyde;
- 2.72 g (64.23 mmol) of LiCl;
- 8.95 ml (64.23 mmol) of TEA (triethyl amine);
- 300 ml of THF.

[0050] A solution of phosphonate **3A** and Corey aldehyde in dry THF was treated with LiCl and stirred at room temperature until the resultant mixture became a clear solution (10-15 minutes). The mixture was then cooled to -10°C and treated with TEA drop wise for 5 minutes under a nitrogen blanket (N₂). The resulting slurry was stirred for 1 hour at the same temperature and then the cooling bath was removed. The resultant mixture was then stirred overnight at room temperature. The next day, 100 ml of NH₄Cl aqueous solution was added to the reaction mixture and the resultant mixture was extracted with ethyl acetate. The combined organic phases were then washed with brine, dried over MgSO₄, and evaporated. The residue after evaporation was purified by flash chromatography: Silica gel (600 g), H-EA 10:1 – 5:1. The mass of the collected product (PG Lactone (**4A**) - See Figure 1) was 21.5 g (65%), R_f = 0.7 (H-EA 70:30). See Figure 1.

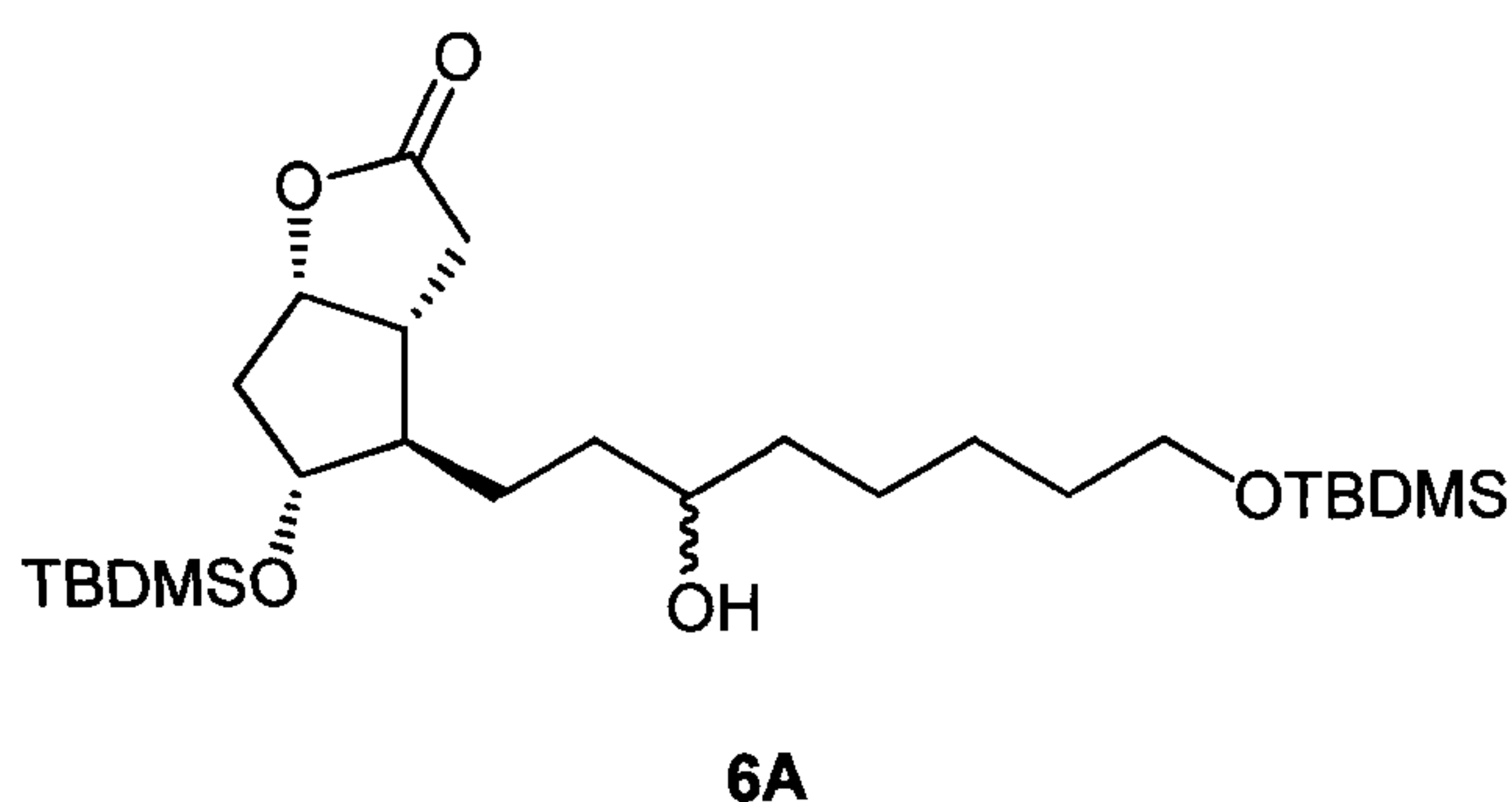
Preparation of Lactone (5A) from PG-Lactone (4A)



- 21.7 g (42.48 mmol) of PG-lactone **4A**;
- 4.0 g of Pd/CaCO₃;
- 400 ml of ethyl acetate.

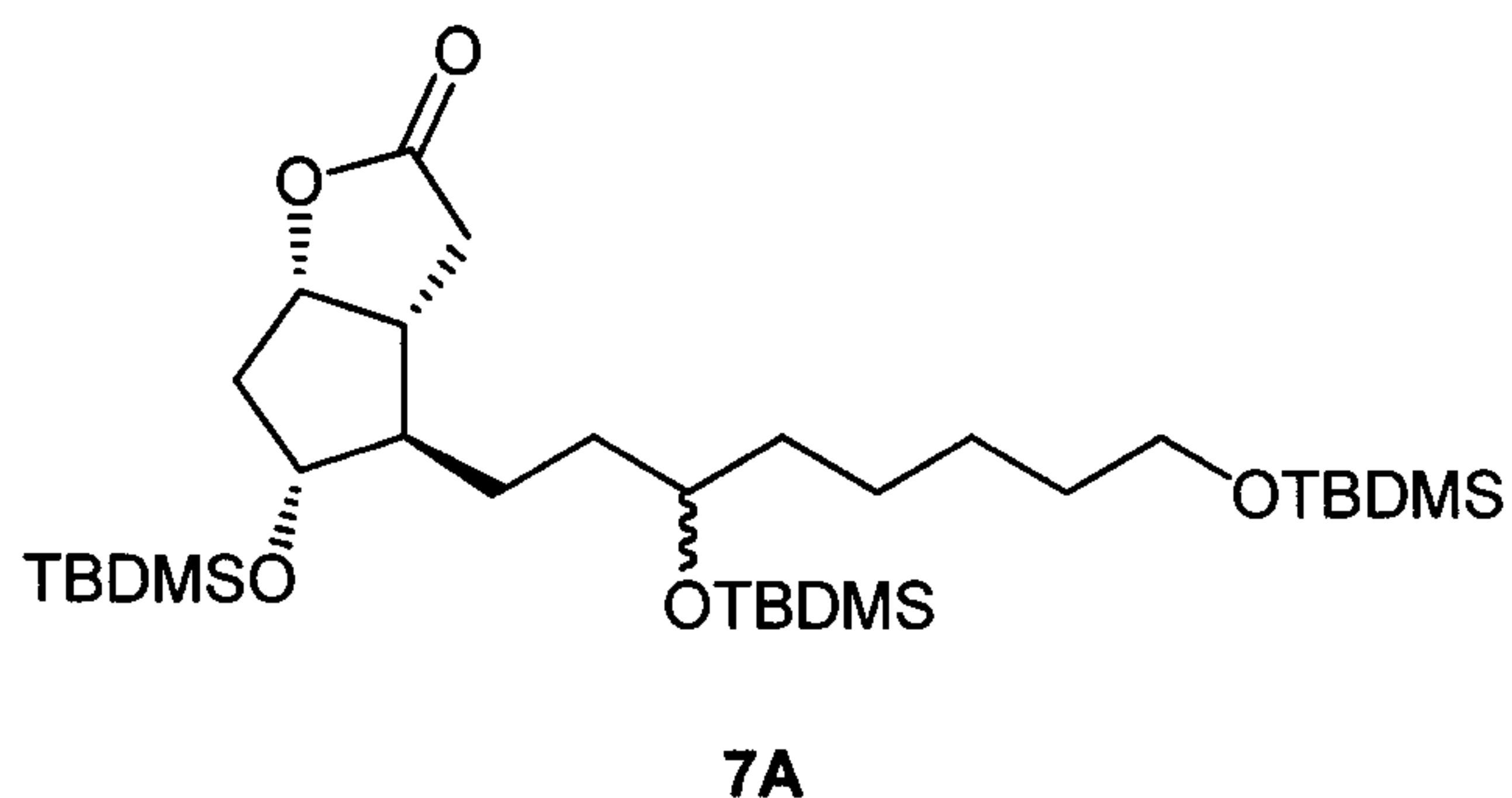
[0051] A solution of PG-lactone **4A** in ethyl acetate (EA) was treated with a catalyst and the resulting suspension was stirred under H₂ (balloon) overnight. The catalyst was then filtered through Celite, and the filtrate was evaporated and the remaining residue was used further without purification. Crude product (Lactone (**5A**) - See Figure 2) – 21.2 g, R_f = 0.75 (H-EA 65:35).

Preparation of Lactone (6A) from Lactone (5A)



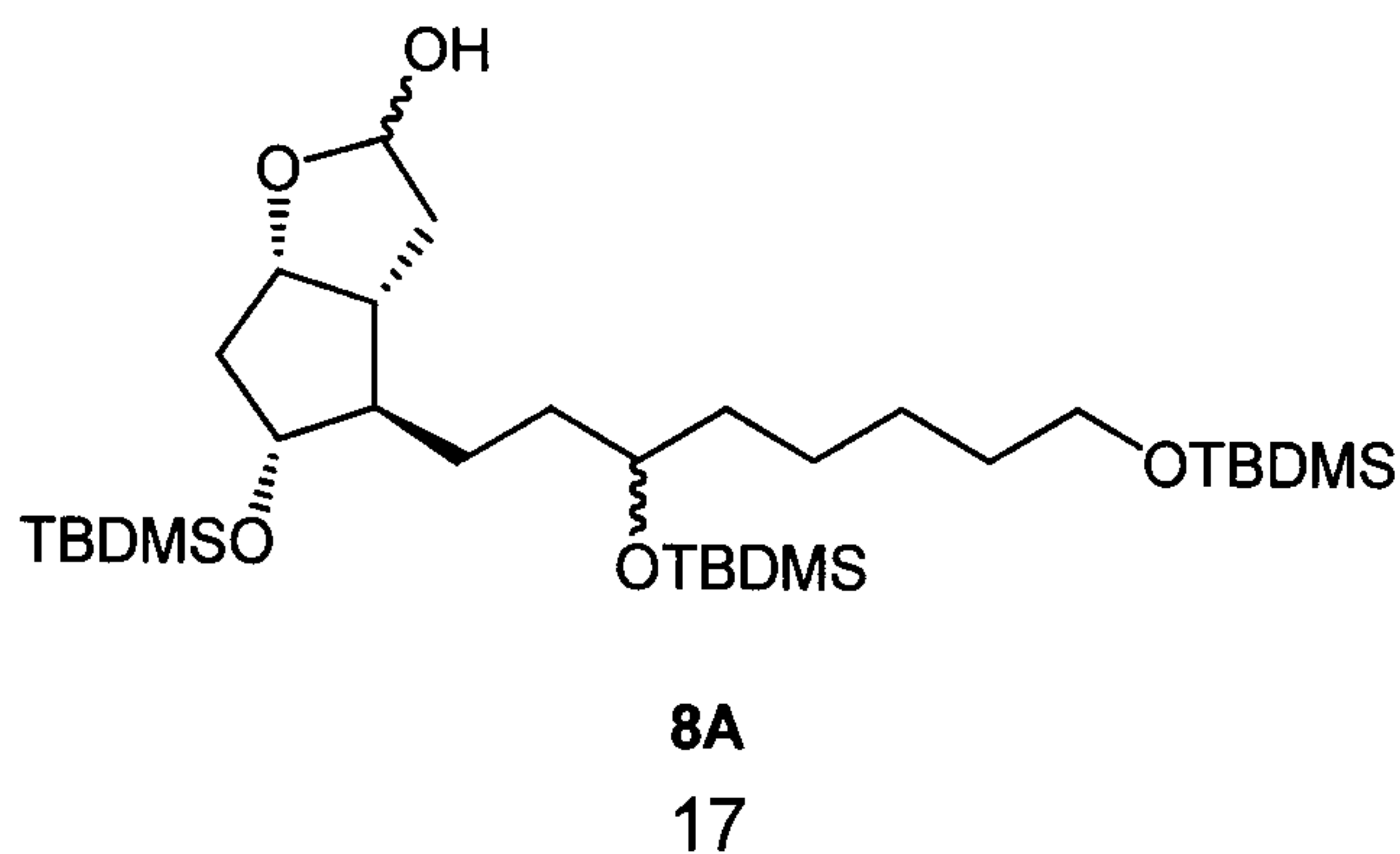
- 21.1 g (41.15 mmol) of lactone **5A**;
- 1.56 g (41.15 mmol) of NaBH₄;
- 100 ml of MeOH;

[0052] A solution of lactone **5A** in dry methanol was cooled to -7°C and treated with NaBH₄ portion wise for 30 minutes. The reaction mixture was then treated with NH₄Cl aqueous solution. The cooling bath was removed and the resultant mixture was extracted with diethyl ether. The combined organic phases were washed with brine, dried over MgSO₄, and evaporated. The residue remaining after evaporation was used further without purification. Crude product (Lactone **6A** - See Figure 3) – 21.18 g, R_f = 0.5 (H-EA 60:40).

Preparation of Lactone (7A) from Lactone (6A)

- 21.18 g (41.15 mmol) of lactone **6A**;
- 9. g (61.73 mmol) of TBDMSCl;
- 6.16 g (90.5) of imidazole;
- 300 ml of DMF.

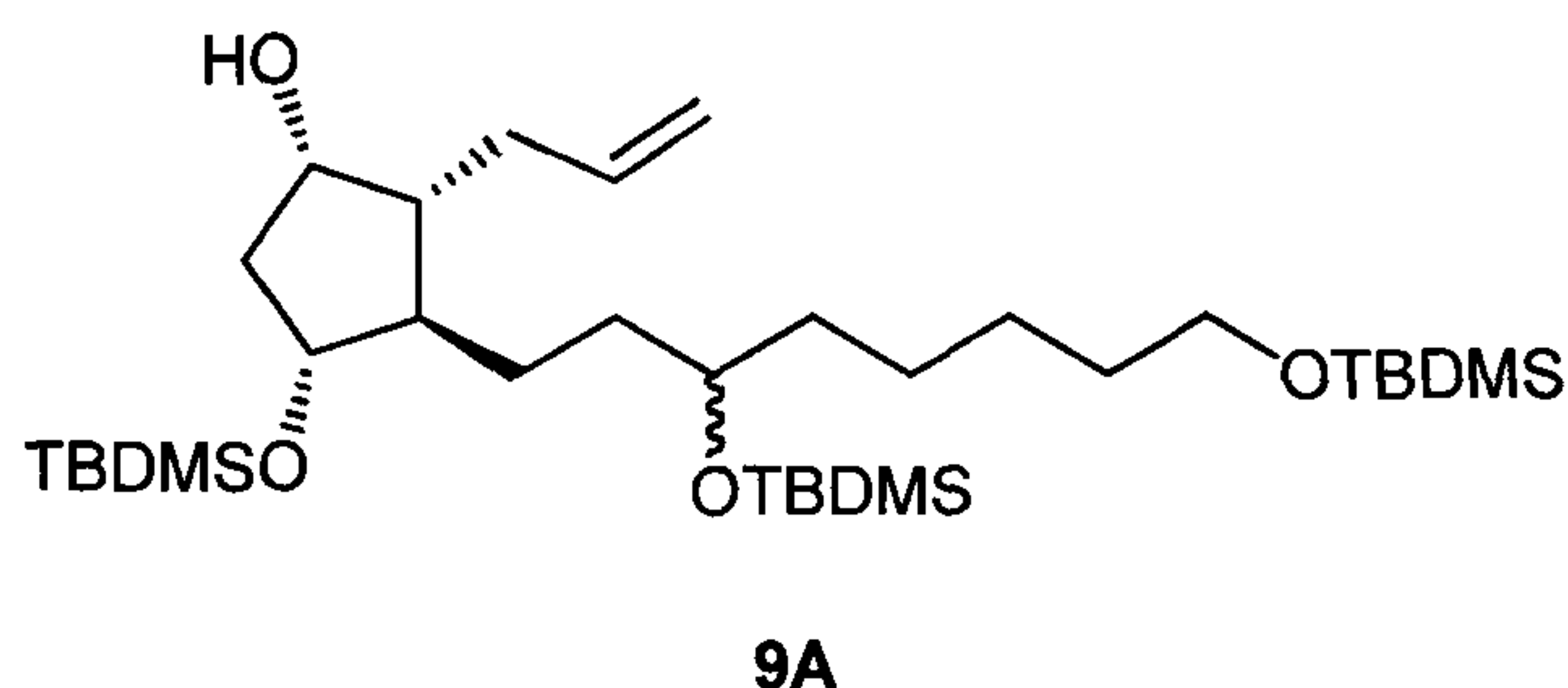
[0053] A solution of lactone **6A** in dry DMF was cooled with an ice bath and treated with TBDMSCl and imidazole portion wise for 10 minutes. The cooling bath was removed and the reaction mixture was stirred overnight (controlled by TLC, H-EA 80:20). The next day, the reaction mixture was treated with ice (200 g), stirred for 5 minutes, and extracted with ethyl acetate. The combined organic phases were washed with water-brine (1:1, 2 x 100 ml), brine (100 ml), dried over Na₂SO₄, and evaporated. The remaining residue was purified by flash chromatography: Silica gel (600 g), H-EA 50:1 – 20:1. The mass of the collected product (Lactone (**7A**) - See Figure 4) was 25.6 g (95% after 3 steps), $R_f = 0.8$ (H-EA 80:20).

Preparation of Lactone (8A) from Lactone (7A)

- 25.5 g (40.5 mmol) of lactone **7A**;
- 52.7 ml of DIBAL-H (1 M solution in toluene);
- 600 ml of toluene;
- 50 ml of THF – H₂O 7:1 mixture.

[0054] A solution of lactone **7A** in dry toluene was cooled to -70°C and DIBAL was added drop wise under a nitrogen blanket (N₂). The reaction mixture was then stirred for 1 hour and TLC (H-EA 85:15) showed no starting material. The reaction mixture was then treated with ethyl acetate (3 ml), followed with a THF-H₂O mixture. The cooling bath was removed and the reaction mixture was stirred for 2 hours. During this time a precipitate was formed, which was filtered and washed with toluene. The filtrate was then evaporated to give 27 g of pure lactol (Lactone (**8A**)), which was used for the next step without purification. $R_f = 0.5$ (H-EA 85:15).

Preparation of Olefin (9A) from Lactone (8A)

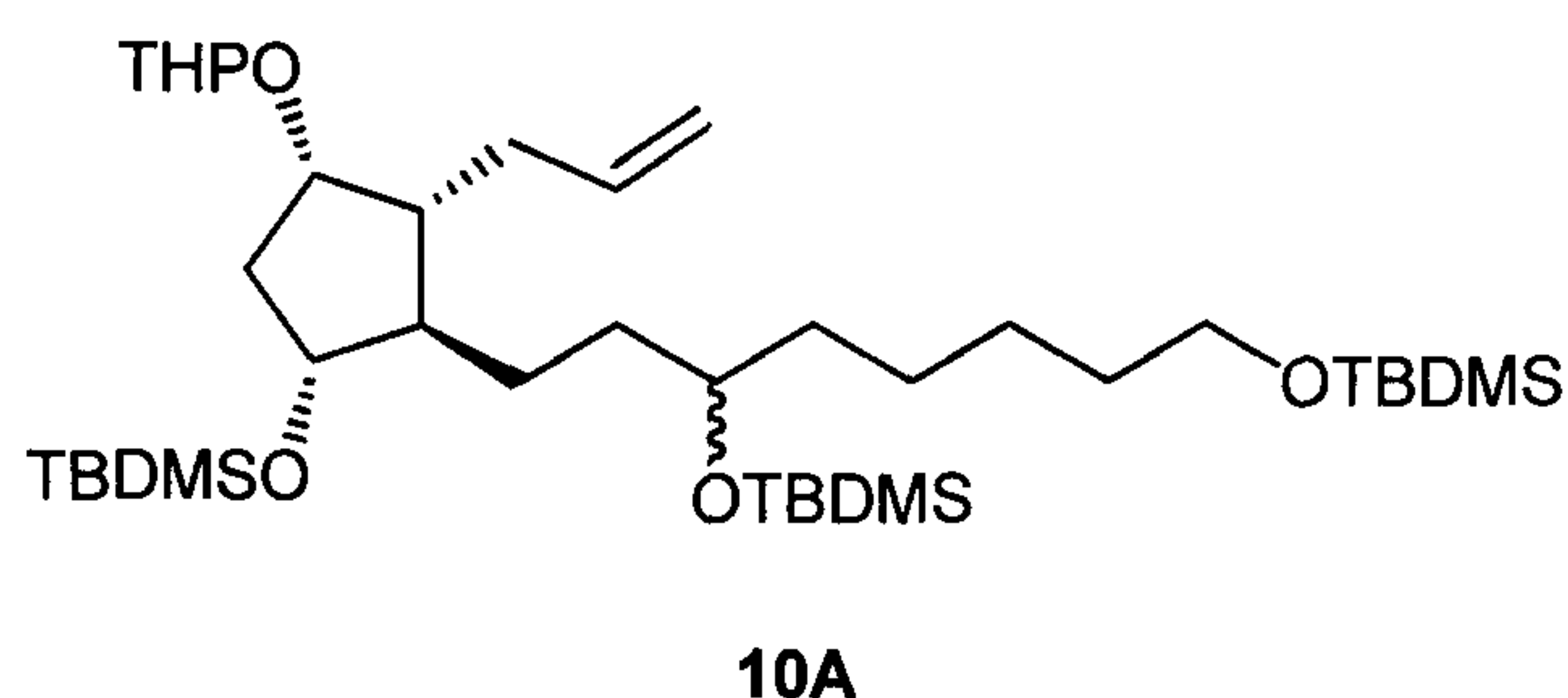


- 27.0 g (crude) (40.5 mmol) of lactol **8A**;
- 40.53 ml of *n*-BuLi (2.5 M solution in hexanes, 101.33 mmol);
- 33.3 g (93.22 mmol) of methyltriphenylphosphonium bromide;
- 500 ml of THF.

[0055] Methyltriphenylphosphonium bromide was placed in 1 liter 3-neck flame dried round bottom flask. Dry THF (450 ml) was added to the salt, and the suspension was cooled in an ice bath. While the suspension was being stirred, *n*-BuLi was added under a nitrogen (N₂) atmosphere. The ice bath was removed and the orange reaction mixture was stirred for 30 minutes at room temperature. Lactol **8A** was added (in 50 ml of dry THF) to the reaction

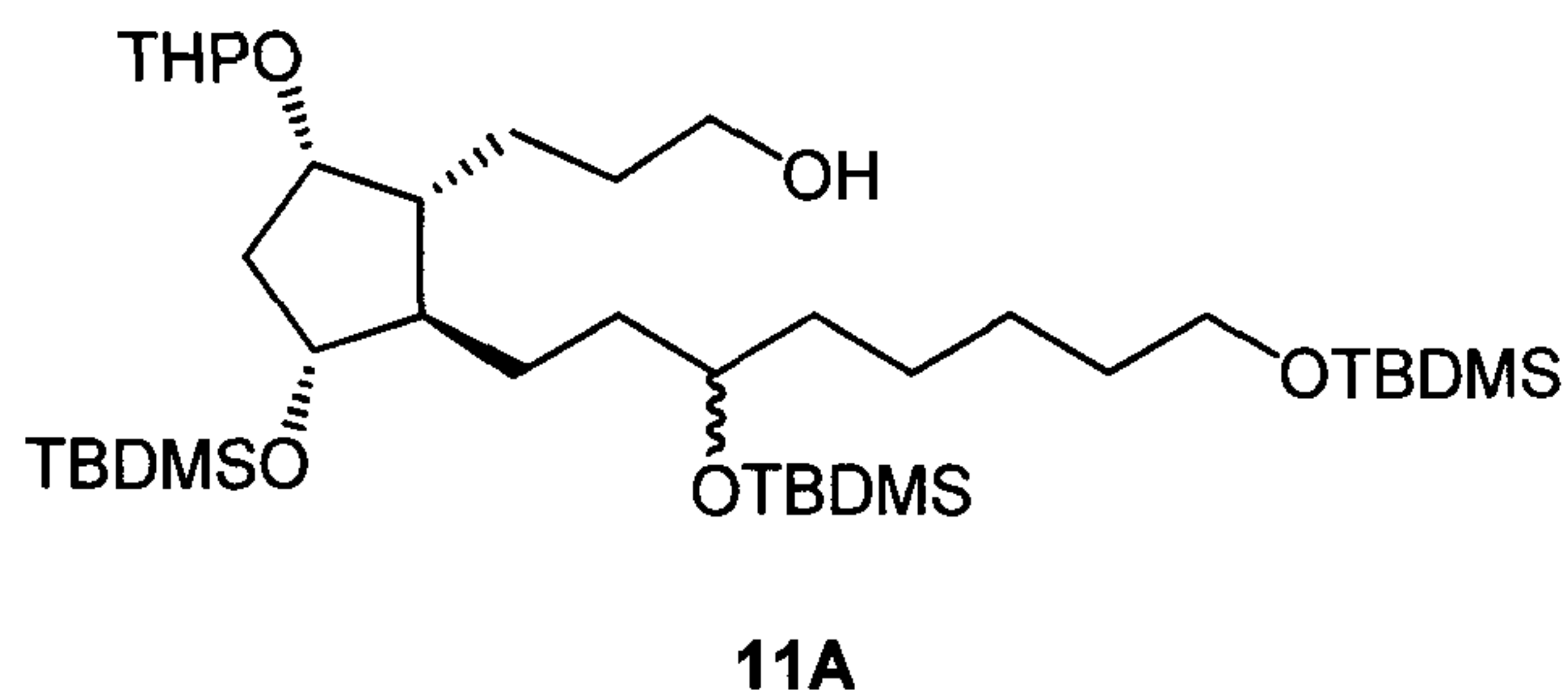
mixture and the reaction mixture was stirred overnight. The next day, the yellow reaction mixture was quenched with an aqueous solution of NH_4Cl (200 ml), stirred for 10 minutes, and diluted with 500 ml of ethyl acetate. The water phase was separated and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over MgSO_4 , and evaporated. The remaining residue was purified by flash chromatography: Silica gel (1 kg), H-EA 50:1 – 30:1. The mass of the collected product (Olefin **9A**) - See Figures 5A-5C and 6) was 22.9 g (90% after 2 steps), $R_f = 0.7$ (H-EA 95:5).

Preparation of Triol (10A) from Olefin (9A)



- 1.05 g (1.67 mmol) of olefin **9A**;
- 0.3 ml (3.33 mmol) of dihydropyran;
- 21 mg (0.08 mmol) of PPTS (pyridinium *p*-toluenesulfonate);
- 20 ml of CH_2Cl_2 .

[0056] A solution of olefin **9A** in dry CH_2Cl_2 was treated with dihydropyran and PPTS. The resulting mixture was stirred overnight at room temperature. The next day the reaction mixture was washed with an aqueous solution of NaHCO_3 and brine, dried over MgSO_4 , and evaporated. The remaining residue was purified by flash chromatography: Silica gel (24 g), H-EA 100:1 – 50:1. The mass of the collected product (Triol (**10A**)) - See Figure 7) was 0.95 g (80%, $R_f = 0.8$ (H-EA 95:5)).

Preparation of Pentaol (11A) from Triol (10A)

- 0.95 g (1.33 mmol) of triol **10A**;
- 12.0 ml of 9-BBN (0.5 M solution in THF, 6.0 mmol)
- 1.5 ml of NaOH (4 N solution);
- 1.53 ml of H₂O₂ (50%, 26.6 mmol);
- 40 ml of THF.

[0057] A solution of olefin **10A** in THF was cooled by an ice bath and 9-BBN was added drop wise under a nitrogen (N₂) blanket. After 1 hour, the cooling bath was removed and the reaction mixture was stirred for two hours. The reaction mixture was then cooled by an ice bath and NaOH was added followed by H₂O₂. The reaction mixture was stirred for two hours, diluted with ethyl acetate (100 ml), and moved to a funnel. The reaction mixture was then washed with brine (2 x 20 ml), dried over MgSO₄, and evaporated. The remaining residue was purified by flash chromatography: Silica gel (60 g), H-EA 20:1 – 10:1. The mass of the collected product (Pentaol (**11A**) - See Figures 8A-8C for spectra) was 0.72 g (75%, R_f = 0.5 (H-EA 80:20). The chemical shifts and peak heights for Figures 8B and 8C, respectively, are set out in the tables below corresponding to the peaks shown in Figures 8B and 8C:

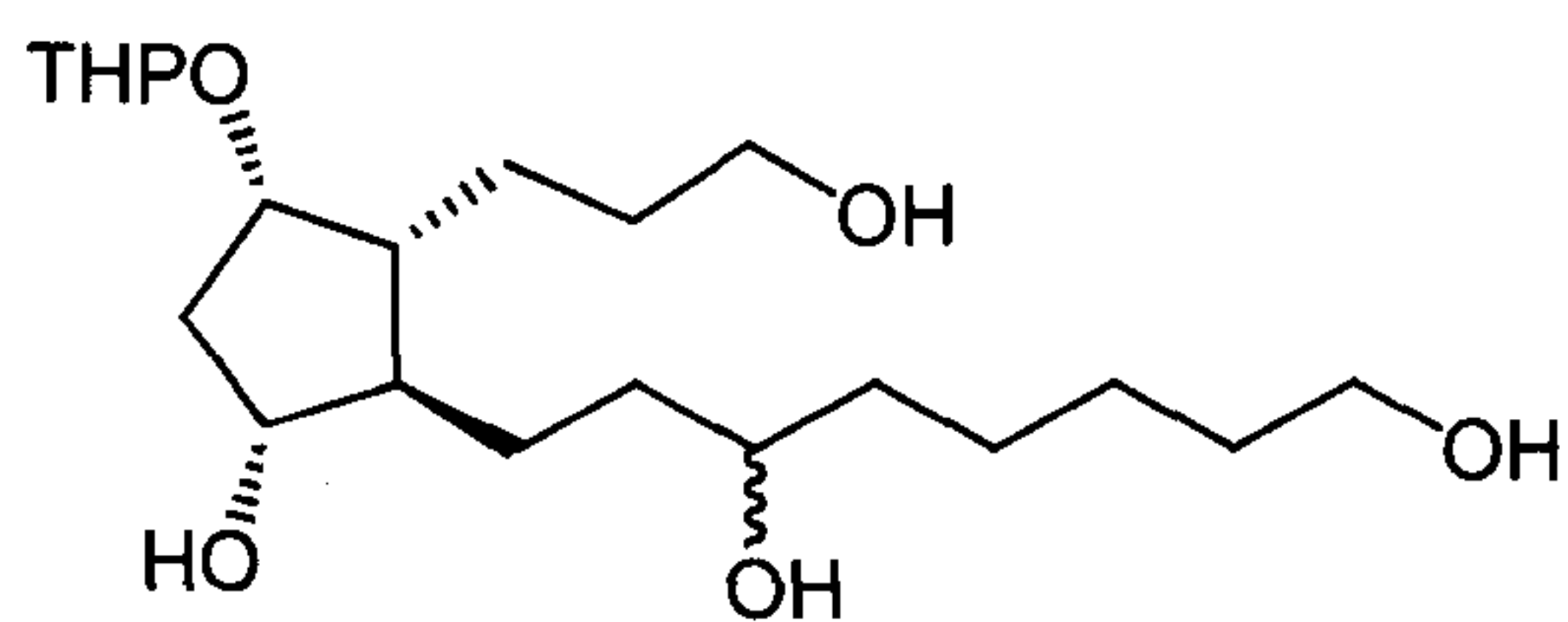
INDEX	FREQUENCY	PPM	HEIGHT
1	1840.933	4.603	26.7
2	1837.514	4.594	30.3
3	1659.525	4.149	11.2
4	1652.445	4.131	38.5
5	1648.538	4.122	13.5
6	1645.364	4.114	47.5
7	1638.284	4.096	13.7
8	1591.162	3.978	9.6
9	1585.302	3.964	17.3
10	1579.442	3.949	25.3
11	1573.094	3.933	8.6
12	1568.699	3.922	6.4
13	1556.980	3.893	5.8
14	1549.899	3.875	7.7
15	1544.772	3.862	7.4
16	1539.645	3.849	6.0
17	1524.985	3.813	6.5
18	1518.403	3.796	10.2
19	1513.276	3.784	10.2
20	1504.486	3.762	8.1
21	1497.406	3.744	14.7
22	1489.837	3.725	14.4
23	1483.245	3.708	6.6
24	1451.016	3.628	33.9
25	1446.133	3.616	78.1
26	1439.541	3.599	136.0
27	1432.949	3.583	71.7
28	1397.302	3.494	15.5
29	1392.663	3.482	12.9
30	1386.315	3.466	14.3

(FIGURE 8B)

INDEX	FREQUENCY	PPM	HEIGHT
1	1840.933	4.603	26.7
2	1837.514	4.594	30.3
3	1659.525	4.149	11.2
4	1652.445	4.131	38.5
5	1648.538	4.122	13.5
6	1645.364	4.114	47.5
7	1638.284	4.096	13.7
8	1591.162	3.978	9.6
9	1585.302	3.964	17.3
10	1579.442	3.949	25.3
11	1573.094	3.933	8.6
12	1568.699	3.922	6.4
13	1556.980	3.893	5.8
14	1549.899	3.875	7.7
15	1544.772	3.862	7.4
16	1539.645	3.849	6.0
17	1524.985	3.813	6.5
18	1518.403	3.796	10.2
19	1513.276	3.784	10.2
20	1504.486	3.762	8.1
21	1497.406	3.744	14.7
22	1489.837	3.725	14.4
23	1483.245	3.708	6.6
24	1451.016	3.628	33.9
25	1446.133	3.616	78.1
26	1439.541	3.599	136.0
27	1432.949	3.583	71.7
28	1397.302	3.494	15.5
29	1392.663	3.482	12.9
30	1386.315	3.466	14.3

(FIGURE 8C)

Preparation of Tetraol (12A) from Pentaol (11A)

**12A**

- 0.61 g (0.83 mmol) of tri-TBS pentaol **11A**;
- 5.8 ml of TBAF (1.0 M solution in THF, 5.8 mmol);
- 3 ml of THF.

[0058] TBAF was added to a solution of tri-TBS pentaol **11A** in THF, and the reaction mixture was stirred overnight. The next day 30 ml of ethyl acetate was added to the reaction mixture and the reaction mixture was then washed with brine (2 x 20 ml), dried over MgSO₄, and evaporated. The residue was purified by flash chromatography: Silica gel (24 g), CH₂Cl₂-MeOH 20:1. The mass of the collected product Tetraol (**12A**) - See Figures 9A - 9C for spectra) was 0.26 g (78%), $R_f = 0.5$ (CH₂Cl₂-MeOH 90:10). The chemical shifts and peak heights for Figures 9B and 9C, respectively are set out in the tables below corresponding to the peaks shown in Figures 9B and 9C:

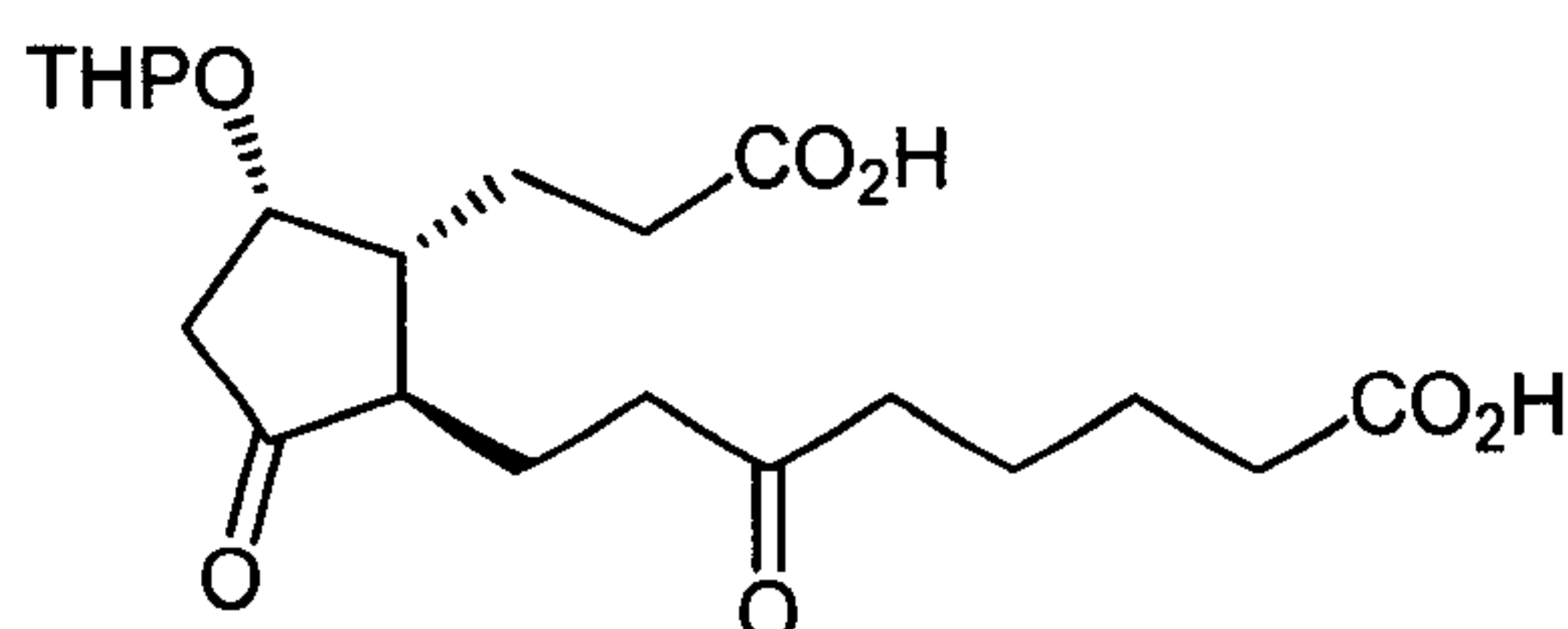
INDEX	FREQUENCY	PPM	HEIGHT
1	1867.546	4.669	4.1
2	1865.104	4.663	5.6
3	1862.663	4.657	5.3
4	1822.621	4.557	4.8
5	1695.416	4.239	5.5
6	1629.982	4.075	5.2
7	1588.720	3.972	1.5
8	1584.325	3.961	2.2
9	1579.442	3.949	2.1
10	1572.362	3.931	2.9
11	1568.211	3.921	3.4
12	1564.793	3.912	2.5
13	1556.980	3.893	3.1
14	1546.237	3.866	6.3
15	1541.110	3.853	6.0
16	1469.084	3.673	2.3
17	1464.201	3.661	5.2
18	1458.097	3.646	24.3
19	1451.505	3.629	39.5
20	1445.157	3.613	22.1
21	1409.998	3.525	4.8
22	1405.359	3.514	5.2
23	1401.453	3.504	4.7
24	1388.757	3.472	77.7
25	1345.053	3.363	11.8
26	1339.926	3.350	6.9
27	1336.507	3.342	8.8
28	1328.206	3.321	11.9

(FIGURE 9B)

INDEX	FREQUENCY	PPM	HEIGHT
1	998.596	7.497	-0.4
2	968.585	2.422	0.8
3	902.887	2.257	-0.3
4	854.300	2.136	3.9
5	841.360	2.104	4.7
6	827.199	2.068	4.9
7	799.121	1.998	-0.7
8	766.093	1.917	2.7
9	752.742	1.897	2.1
10	760.056	1.900	2.1
11	752.243	1.881	5.3
12	750.046	1.875	4.9
13	745.895	1.865	1.9
14	741.744	1.855	1.5
15	739.303	1.848	1.2
16	732.222	1.831	2.7
17	728.560	1.822	3.7
18	725.986	1.814	4.4
19	722.212	1.806	5.5
20	717.573	1.794	6.8
21	713.422	1.784	6.3
22	710.981	1.778	5.2
23	708.539	1.772	5.9
24	705.609	1.764	6.3
25	695.111	1.738	6.2
26	690.228	1.726	7.1
27	684.612	1.712	11.1
28	677.770	1.695	15.9
29	668.010	1.670	15.7
30	664.591	1.662	11.6
31	660.929	1.652	14.3
32	657.023	1.643	11.5
33	652.626	1.632	10.5
34	630.410	1.576	27.1
35	626.259	1.566	23.8
36	623.573	1.559	25.9
37	613.569	1.534	27.1
38	608.131	1.521	27.9
39	598.425	1.496	12.2

(FIGURE 9C)

Preparation of protected tetranor PGDM (13A) from Tetraol (12A)

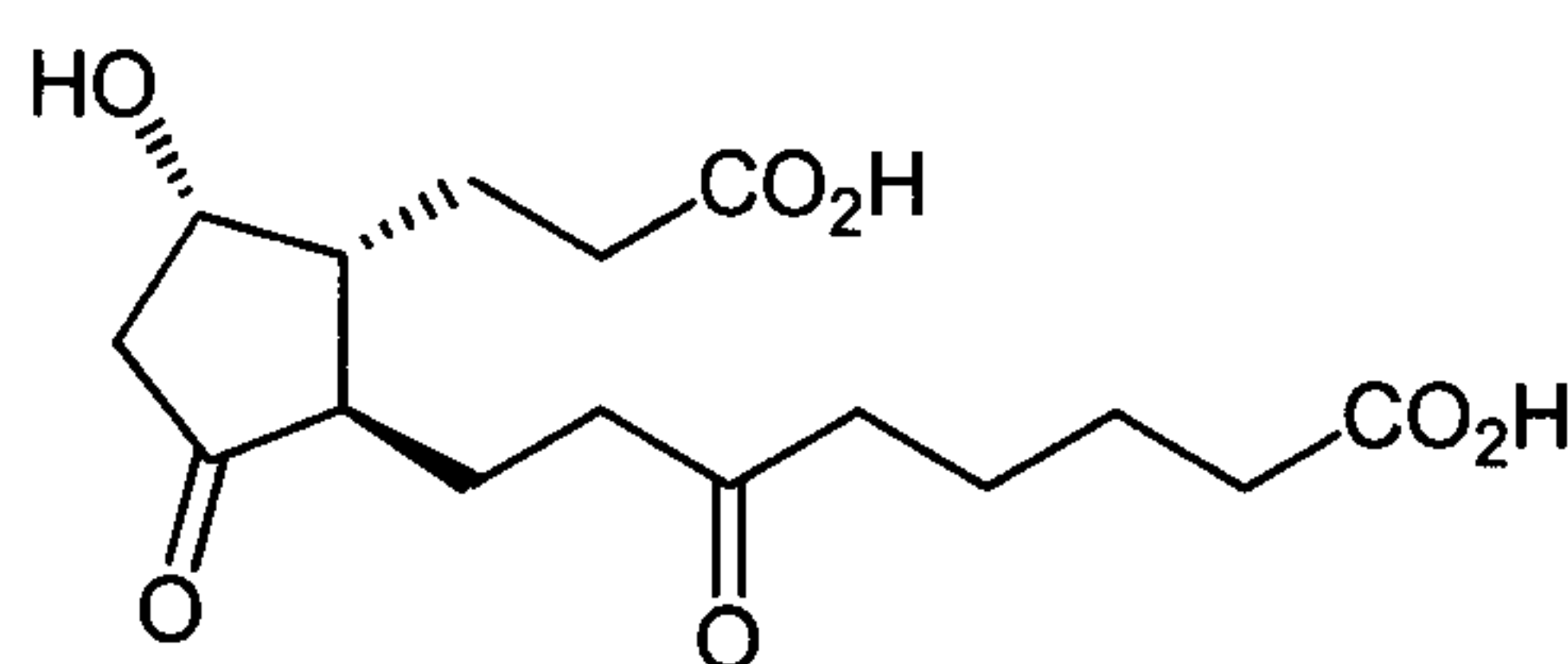
**13A**

- 255 mg (0.66 mmol) of tetraol **12A**;
- Jones Reagent (2.66 M solution in H₂O);
- 20 ml of acetone.

[0059] A solution of tetraol **12A** in acetone (10 ml) was treated with Jones Reagent (5 portions of freshly diluted with acetone in 5:1 ratio) at 0°C for 40 minutes until the color of the reaction mixture became yellow and did not disappear for 10 minutes. The reaction

mixture was then stirred for 10 minutes more, treated with 0.5 ml of *i*-PrOH, diluted with 100 ml of ethyl acetate, dried over MgSO₄, and evaporated. The residue was purified by flash chromatography: Silica gel (120 g), H - EA - HOAc 70:30:0.5. The mass of the collected product (Protected tetranor PGDM (**13A**)) was 110 mg (40%). $R_f = 0.5$ (H - EA - HOAc 15:85:1).

Preparation of Tetranor PGDM (14) from Protected Tetraol PGDM (13A)



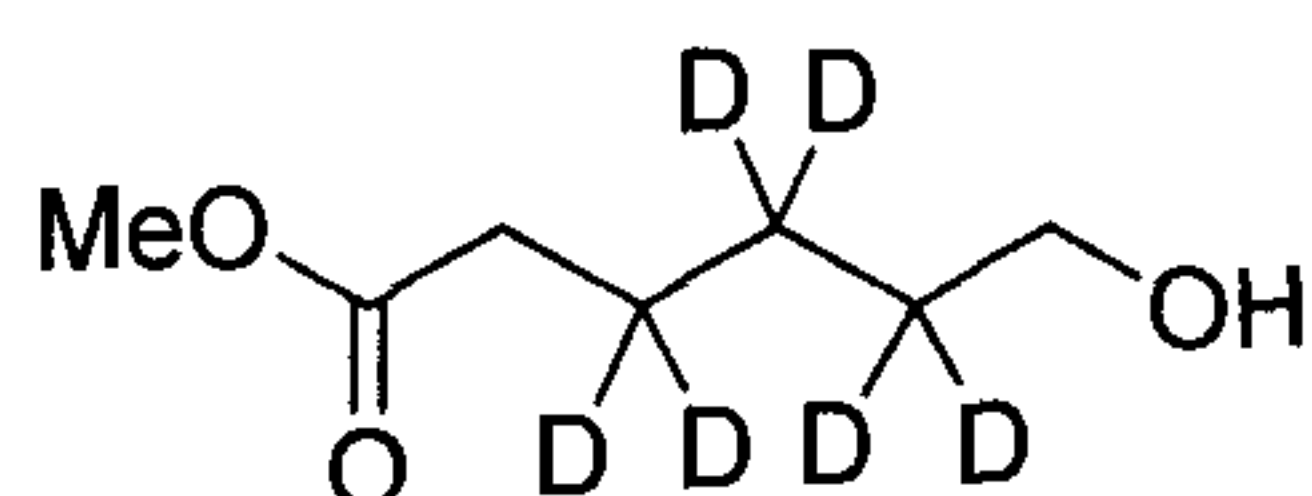
14, Tetranor-PGDM

- 180 mg (0.44 mmol) of protected tetranor PGDM;
- 0.4 ml (0.52 mmol) of 10% TFA in CH₂Cl₂
- 2 ml of CH₂Cl₂.

[0060] A solution of protected tetranor PGDM (**13A**) (in 2 ml of CH₂Cl₂) was treated with 10% TFA (in CH₂Cl₂) and stirred overnight at room temperature. The next day the remaining residue after evaporation was purified by flash chromatography: Silica gel (8 g), H - EA - HOAc 70:30:0.5 – 30:70:0.5%. The mass of the collected product (Tetranor PGDM (**14**) - See Figure 12) was 70 mg (50%). $R_f = 0.35$ (H - EA - HOAc 10:90:1).

Example 2: Preparation of tetranor-PGJM (Compound (15))

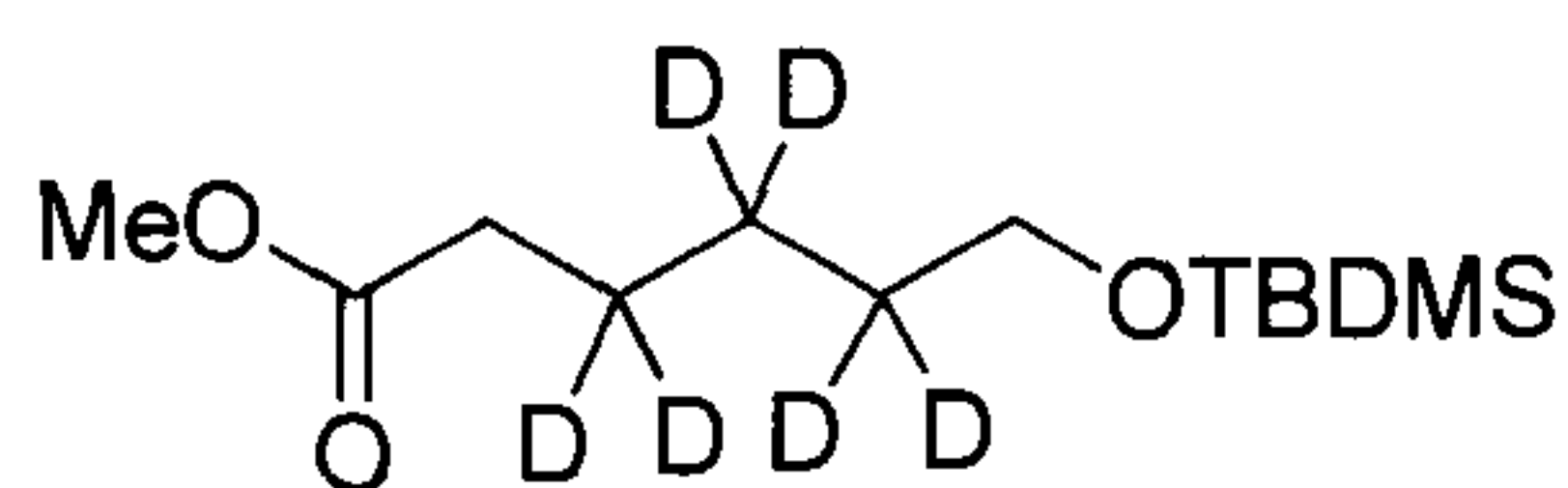
[0061] A solution of Tetranor-PGDM (Compound 14) in 2 ml of CH₂Cl₂ was treated with TFA and stirred overnight at room temperature. The next day the remaining residue after evaporation was purified by flash chromatography: Silica gel (4 g), H-EA-HOAc 60:40:0.5 – 50:50:0.5%. The mass of the collected product (Compound (**15**) - See Figures 13 and 14A-B) was 26 mg (46%). $R_f = 0.75$ (H-EA-HOAc 15:85:1)

Example 3: Preparation of tetranor-PGEM-D₆, Compound (27B)Preparation of Ester (17B-1) from Sodium Salt (16B)

17B-1
(17B, wherein R¹ is methyl)

- 2.0 g (12.49 mmol) of sodium salt **16B**;
- 5 % KHSO₄ aq. s-n;
- CH₂N₂ in ether (about 75 ml obtained from Diazald by standard procedure from Organic Synthesis).

[0062] A saturated, aqueous solution of sodium salt **16B** was treated with 5% aqueous solution of KHSO₄ until a pH of about 1 was achieved. The solution was then extracted 4 times with ethyl acetate. The organic phase was washed with brine, dried over Na₂SO₄, and evaporated. The remaining residue (1.86 g) was dissolved in 20 ml of ether and treated portion wise with an ether solution of CH₂N₂ until the color of reaction mixture became yellow. The remaining residue (ester **17B-1**) after evaporation (1.85 g, 95% yield) was used for the next step without purification.

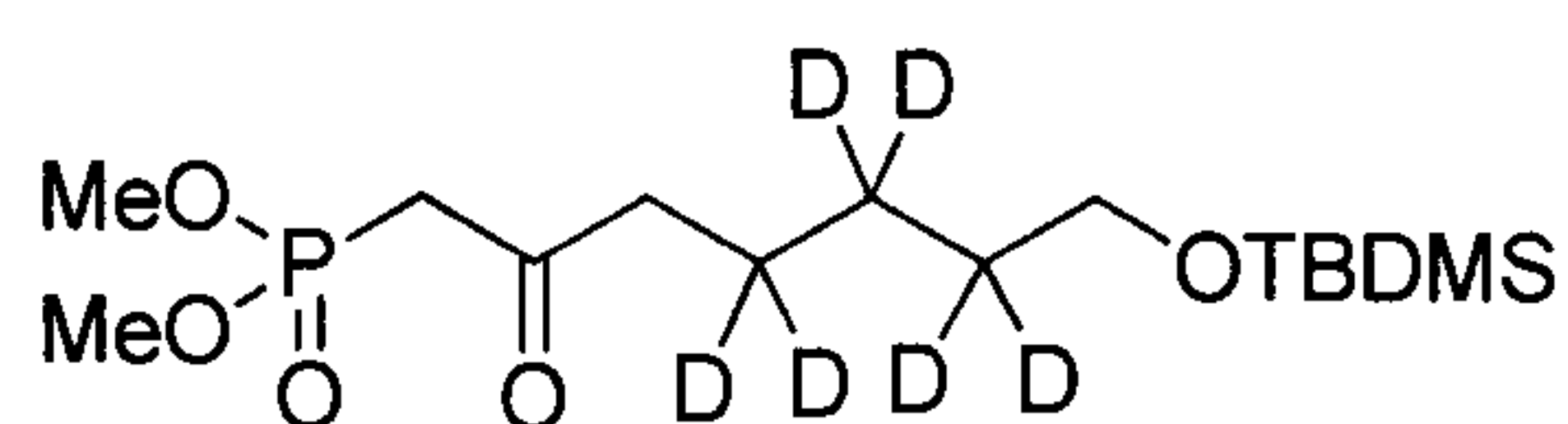
Preparation of Protected Ester (18B-1a) from Ester (17B-1)

18B-1a
(18B-1, wherein R² is methyl and R³ is *tert*-butyl)

- 1.8 g (11.8 mmol) of hydroxy ester **17B-1**;
- 2.14 g (14.2 mmol) of TBDMSCl;
- 1.00 g (14.75) of imidazole;
- 20 ml of DMF.

[0063] The ester **17B-1** was dissolved in DMF. TBDMSCl and imidazole was then added and the reaction mixture was stirred overnight (controlled by TLC, hexane – ethyl acetate 10:1). The reaction mixture was then diluted with 200 ml of ethyl acetate, washed with brine (2 x 100 ml), dried over Na₂SO₄, and evaporated. The remaining residue was purified by flash chromatography: Silica gel (250 g), hexane – ether 50:1 – 20:1. The mass of the collected product (Ester **18-B-1a(i)**) was 2.44 g (80%), R_f = 0.55 (hexane – ethyl acetate 10:1).

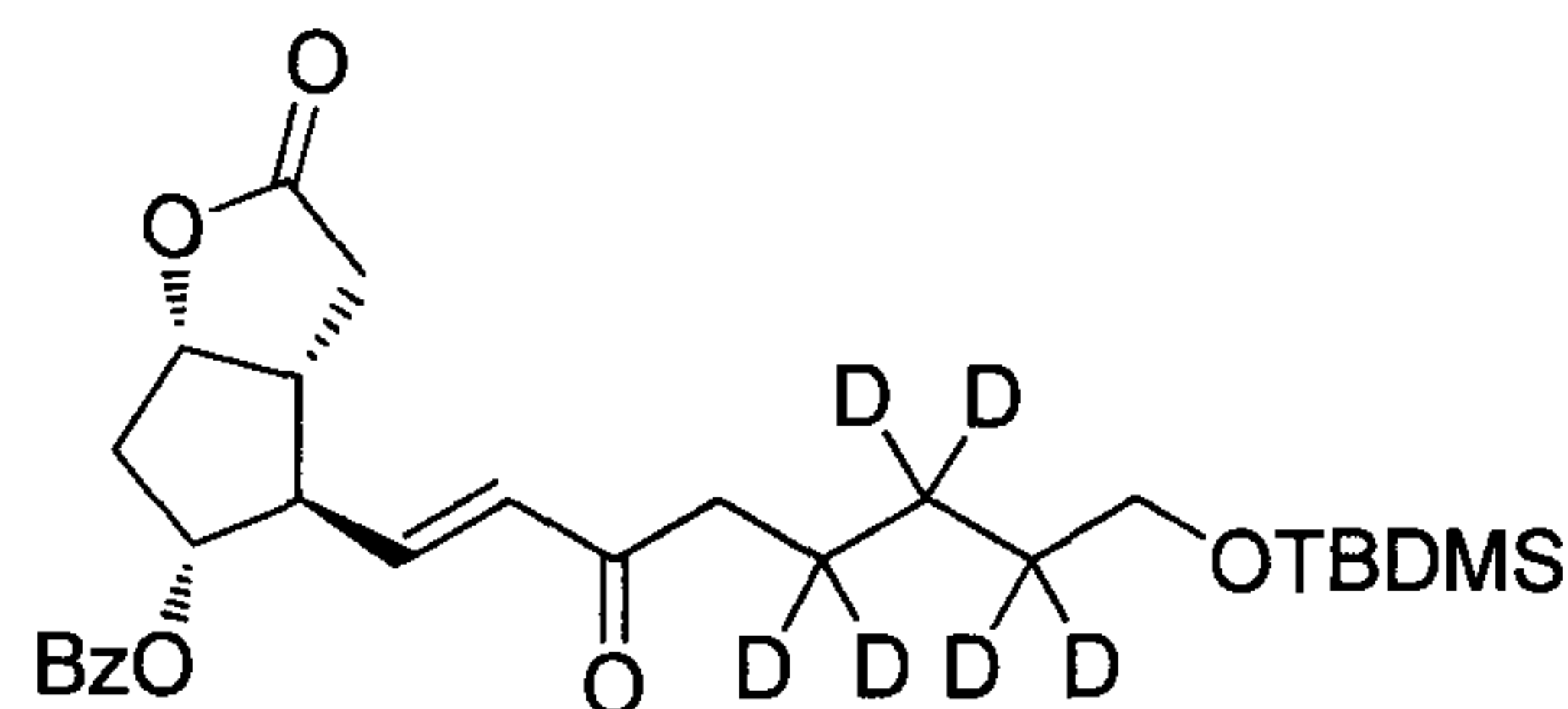
Preparation of Protected Ester (19B-1a(i)) from Protected Ester (18B-1a)



19B-1a(i)
(**19B-1a**, wherein **R⁴** is methyl)

- 2.44 g (9.16 mmol) of protected ester **18B-1a**;
- 1.02 ml (9.43 mmol) of dimethyl methylphosphonate;
- 3.66 ml (9.16 mmol) of 2.5 M *n*-BuLi;
- 50 ml of THF.

[0064] A 2.5 M solution of *n*-BuLi in hexanes was added to the solution of phosphonate in THF (45 ml) at -75°C under a nitrogen (N₂) blanket. After 40 minutes, ester **18B-1a** was added in 5 ml of THF to the reaction mixture and the reaction mixture was stirred for 1 hour at -75°C and 1 hour at room temperature. 20 ml of an aqueous solution of NH₄Cl aq. was added and the reaction mixture was extracted with ethyl acetate (3 x 100 ml), washed with brine, dried over MgSO₄, and evaporated. The remaining residue (Phosphonate (**19B-1a(i)**)) after evaporation (3.08 g, 95% yield) was used for the next step without purification.

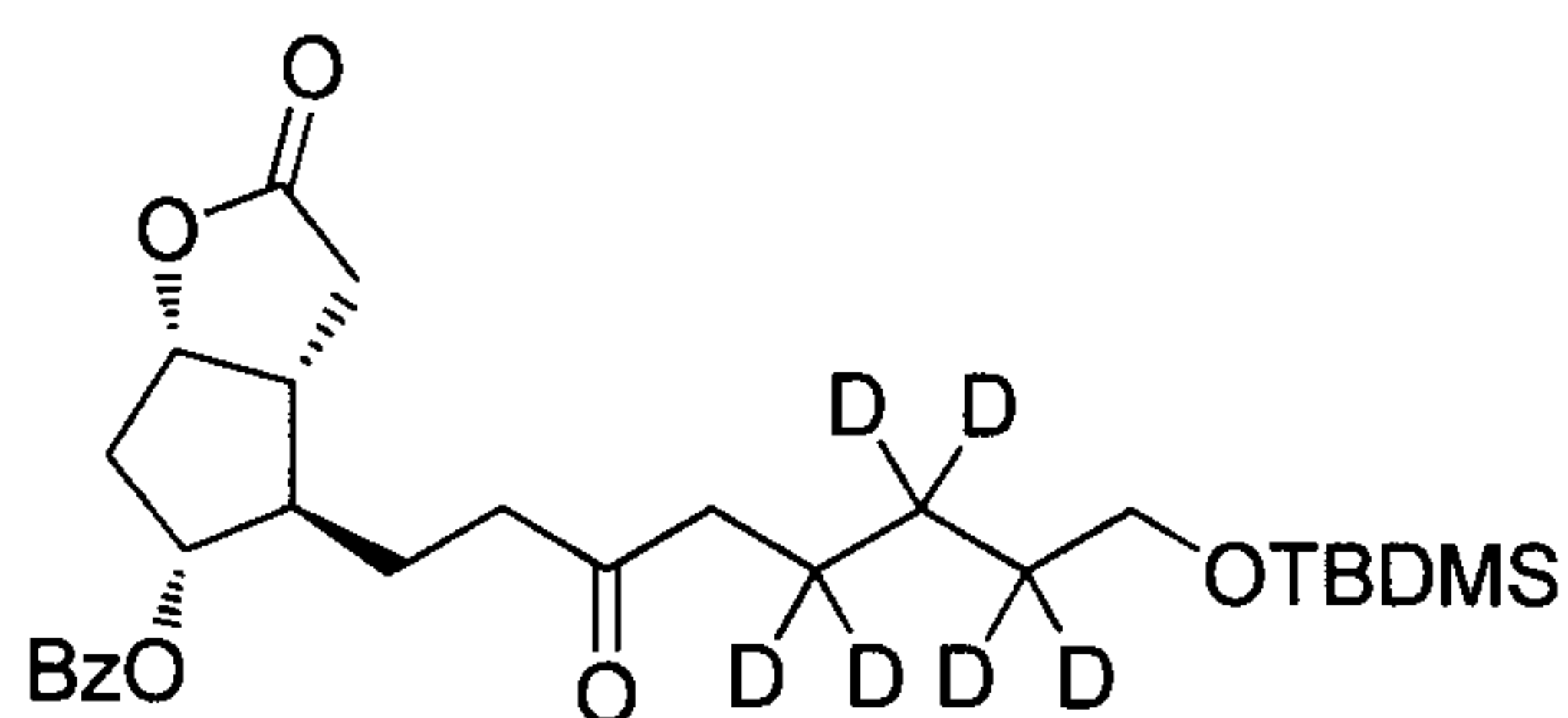
Preparation of PG-Lactone (20B-1a(i)) from Phosphonate (19B-1a(i))

20B-1a(i)
(**20B-1a**, wherein **R⁵** is benzoyl)

- 3.07 g (8.6 mmol) of phosphonate **19B-1a(i)**;
- 2.235 g (8.14 mmol) of Corey aldehyde;
- 0.37 g (8.6 mmol) of LiCl;
- 1.2 ml (8.6 mmol) of TEA (triethyl amine);
- 30 ml of THF.

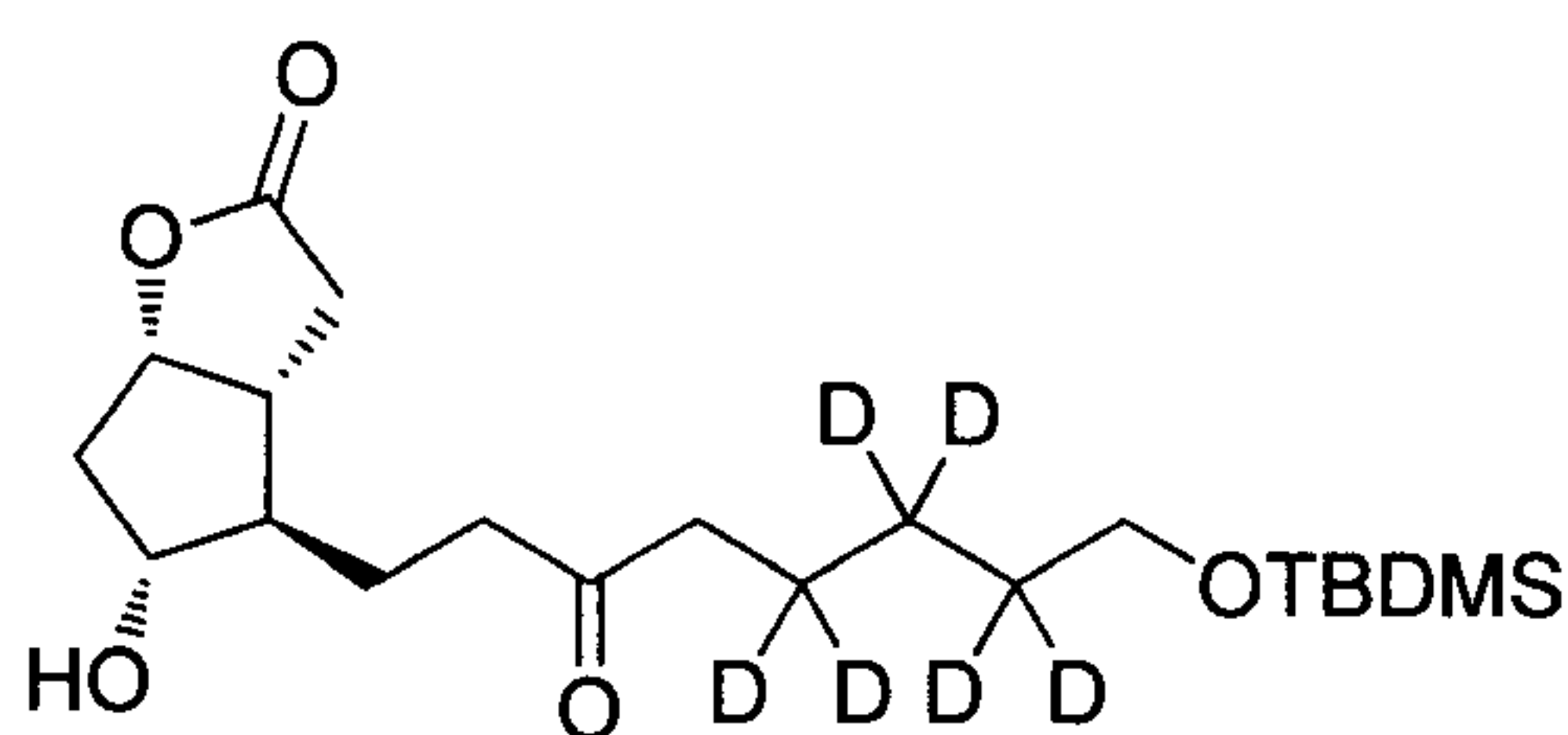
[0065] LiCl and Corey aldehyde in THF TEA* were added at -10°C under N₂ drop wise to a suspension of phosphonate **19B-1a(i)**. The reaction mixture was then stirred at -10°C, wherein the cooling bath was removed. The reaction mixture was then stirred overnight at room temperature. The next day, 10 ml of an aqueous solution of NH₄Cl was added to the reaction mixture. The reaction mixture was then extracted with ethyl acetate, washed with brine, dried over MgSO₄, and evaporated. The remaining residue after evaporation (4.48 g) was purified by flash chromatography: Silica gel (200 g), hexane – ethyl acetate 5:1 – 2:1. The mass of the collected product (PG-lactone **20B-1a(i)**) was 2.34 g (54%), R_f = 0.6 (hexane – ethyl acetate 60:40).

[0066] *Alternatively, LiCl-TEA may be used in excess (1.2-1.5 molar equivalents).

Preparation of PG-Lactone (21B-1a(i)) from PG-Lactone (20B-1a(i))**21B-1a(i)**

- 2.34 g (4.6 mmol) of PG-lactone **20B-1a(i)**;
- 0.7 g of Pd/C;
- 50 ml of ethyl acetate.

[0067] PG-lactone **20B-1a(i)** was first dissolved in ethyl acetate. The reaction flask was flashed with N₂ and a catalyst was added carefully portion wise to the reaction mixture. The reaction mixture was stirred with H₂ for two hours, resulting in the removal of about 105 ml of H₂. The catalyst was filtered off, and the reaction mixture was washed with ethyl acetate. The filtrate was evaporated and purified by flash chromatography: Silica gel (80 g), hexane – ethyl acetate 3:1 – 2:1. The mass of the collected product (PG-Lactone **21B-1a(i)**) was 2.15 g (91%), R_f = 0.55 (hexane – ethyl acetate 60:40).

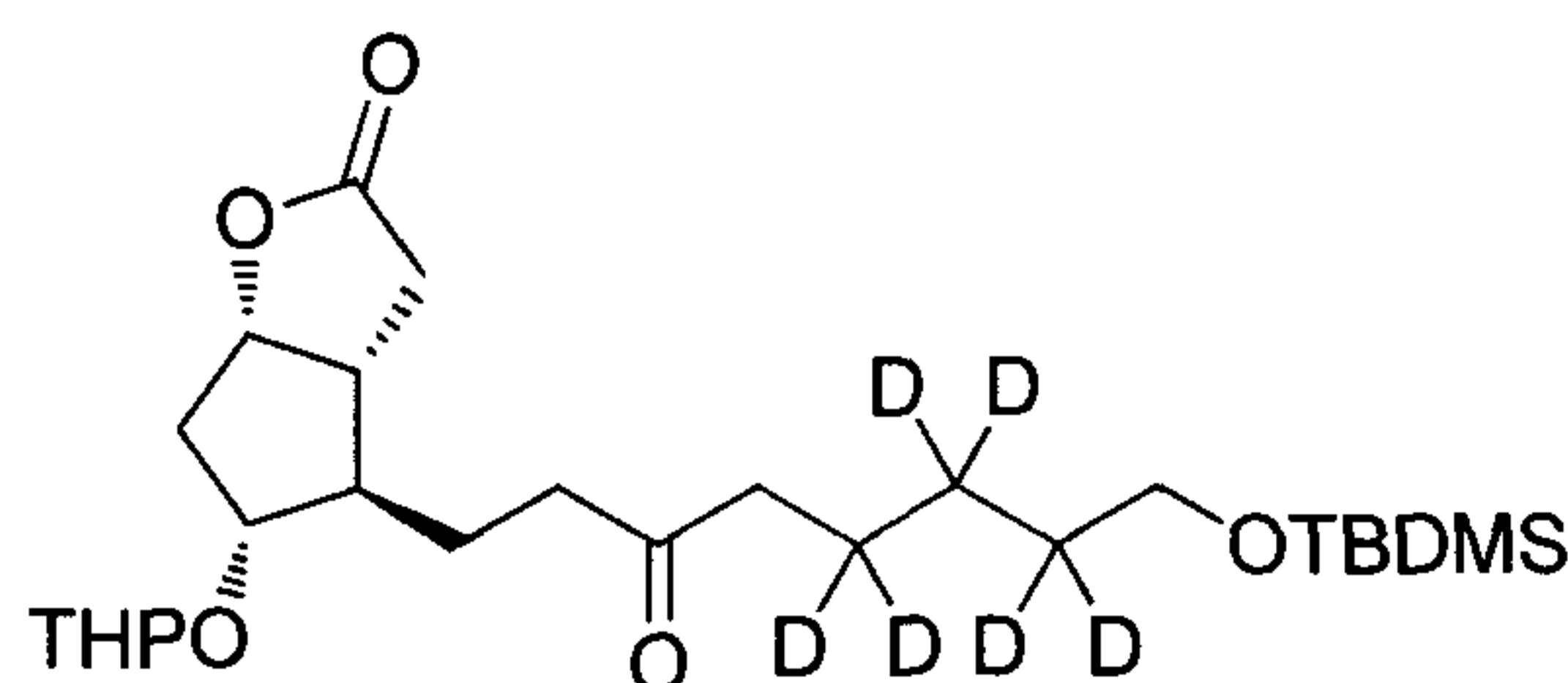
Preparation of Lactone (21B-1a(ii)) from PG-Lactone (21B-1a(i))**21B-1a(ii)**

(**21B-1a**, wherein R⁵ is hydrogen)

- 2.15 g (4.2 mmol) of PG-lactone **21B-1a(i)**;
- 0.58 g (4.2 mmol) of K₂CO₃;
- 30 ml of MeOH.

[0068] Lactone **21B-1a(i)** was dissolved in MeOH and stirred with K_2CO_3 for 5 hours (controlled by TLC, hexane – ethyl acetate 50:50). The reaction mixture was then diluted with 200 ml of ethyl acetate, washed with brine (2 x 100 ml), dried over $MgSO_4$, and evaporated. The remaining residue (2.23 g) was purified by flash chromatography: Silica gel (80 g), hexane – ethyl acetate 2:1 – 1:1. The mass of the collected product (Lactone **21B-1a(ii)**) was 1.34 g (81%), $R_f = 0.3$ (hexane – ethyl acetate 50:50).

Preparation of Lactone (21B-1a(iii)) from PG-Lactone (21B-1a(ii))



21B-1a(iii)
(**21B-1a**, wherein R^5 is tetrahydropyran-2-yl)

- 1.33 g (.22 mmol) of lactone **21B-1a(ii)**;
- 0.62 ml (6.82 mmol) of dihydropyran;
- 43 mg (0.17 mmol) of PPTS (pyridinium *p*-toluenesulfonate);
- 40 ml of CH_2Cl_2 .

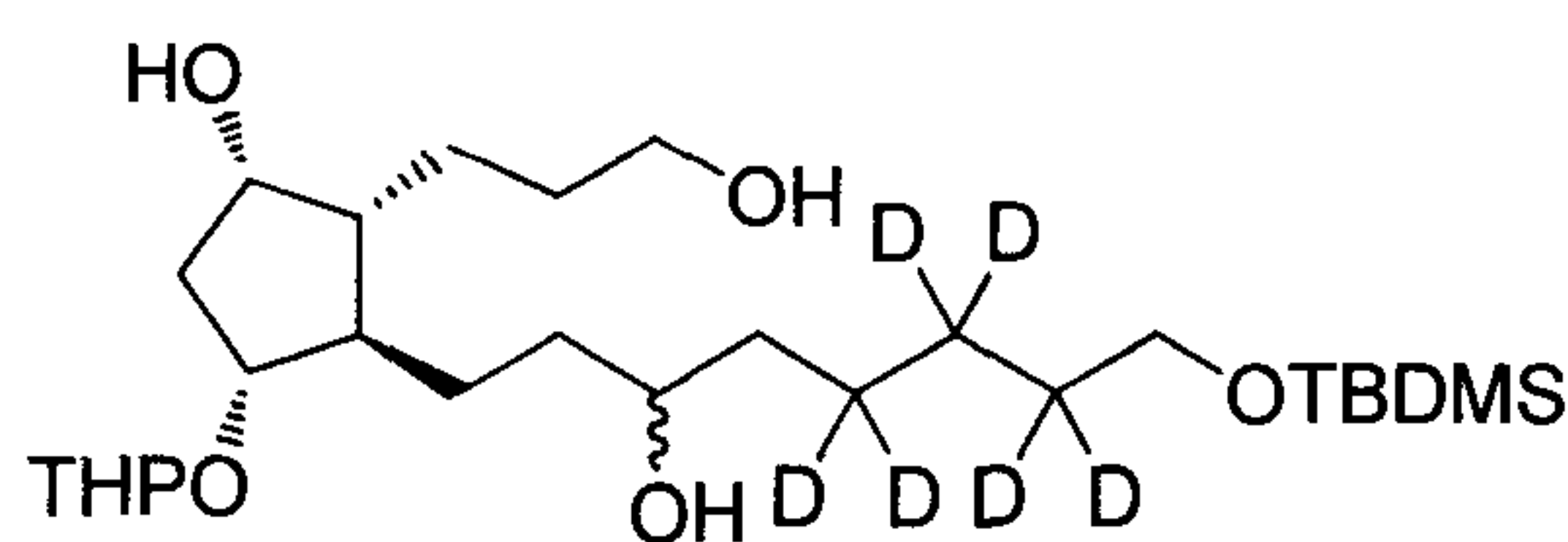
[0069] Lactone **21B-1a(ii)**, dihydropyran, PPTS and CH_2Cl were mixed together and stirred overnight. The next day the reaction mixture was washed with an aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated. The remaining residue (1.72 g) was purified by flash chromatography: Silica gel (80 g), hexane – ethyl acetate 3:1 – 1:1. The mass of the collected product (Lactone (**21B-1a(iii)**)) was 1.495 g (93%), $R_f = 0.7$ (hexane – ethyl acetate 1:1).

- 1.6 g (3.05 mmol) of lactol **22B-1a(iii)**;
- 4.3 ml of *n*-BuLi (2.5 M solution in hexanes);
- 3.8 g (10.7 mmol) of methyltriphenylphosphonium bromide;
- 50 ml of THF.

[0071] Methyltriphenylphosphonium bromide was placed in 100 ml 3-neck flame dried round bottom flask, THF was added to the salt, and the resultant, suspension was cooled by an ice bath. *n*-BuLi was added to the reaction mixture while the reaction mixture was being stirred under a nitrogen (N₂) atmosphere. The ice bath was removed and an orange reaction mixture was stirred for 30 minutes at room temperature. Lactol **22B-1a(iii)** was added in 10 ml of THF to the orange reaction mixture was stirred overnight. The next day a yellow reaction mixture was quenched with an aqueous solution of NH₄Cl, stirred for 10 minutes, and diluted with 150 ml of ethyl acetate. The water phase was separated and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over MgSO₄, and evaporated. The remaining residue (2.78 g) was purified by flash chromatography: Silica gel (80 g), hexane – ethyl acetate 3:1 – 1:1. The mass of the collected product (Olefin (**23B-1a(iii)**)) was 1.04 g (70%), *R_f* = 0.8 (CH₂Cl₂ – MeOH 20:1).

[0072] Alternatively, methyltriphenylphosphonium bromide may be used in excess up to 10 molar equivalents with corresponding excess of the *n*-BuLi base up to 11 molar equivalents.

Preparation of Triol (24B-1a(iii)) from Olefin (23B-1a(iii))

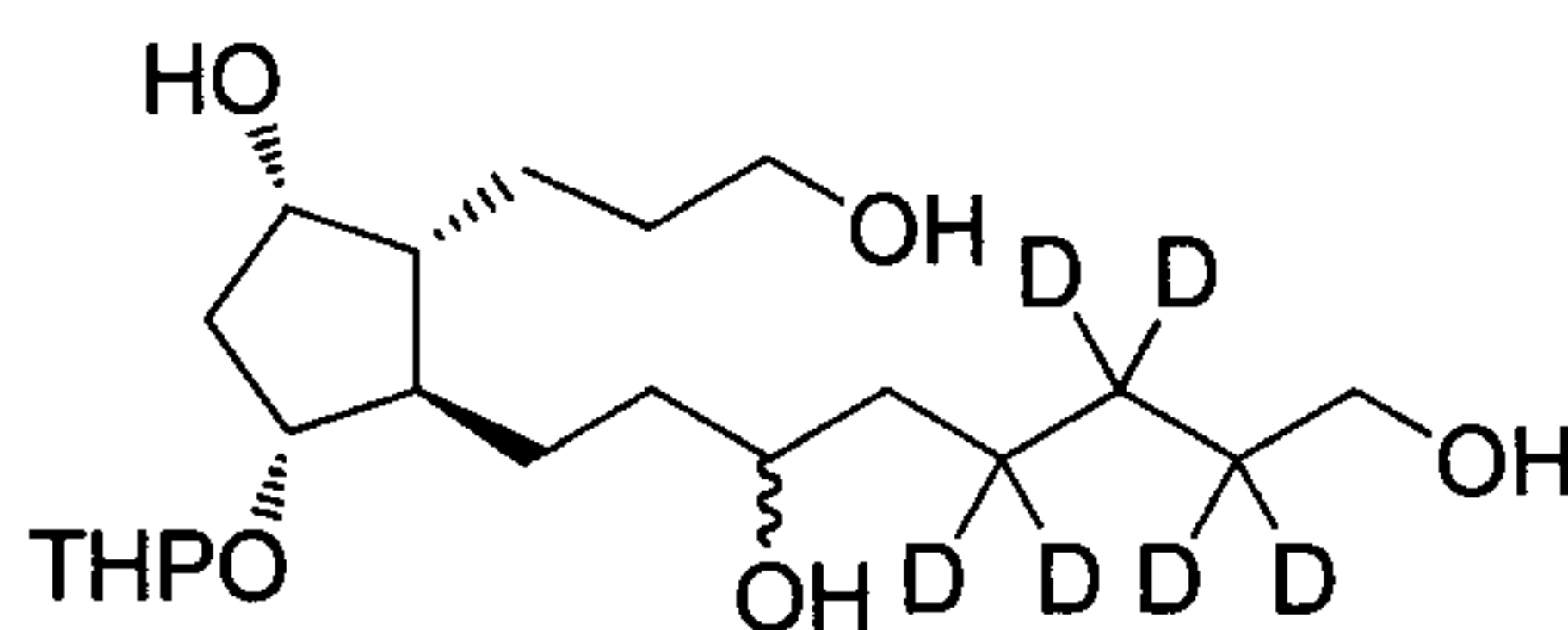


24B-1a(iii)

- 0.33 g (0.678 mmol) of olefin **23B-1a(iii)**;
- 6.1 ml of 9-BBN (0.5 M solution in THF)
- NaOH 1.0 ml (3 M solution);
- 0.8 ml of H₂O₂ (50%);
- 20 ml of THF.

[0073] A solution of olefin **23B-1a(iii)** in THF was cooled by an ice bath and 9-BBN was added drop wise to the solution under a nitrogen (N₂) blanket. After 1 hour, the cooling bath was removed and the reaction mixture was stirred for two hours. The reaction mixture was then cooled by an ice bath and NaOH was added followed by H₂O₂. The reaction mixture was stirred for two hours, diluted with ethyl acetate (100 ml) and moved to the funnel. The reaction mixture was washed with brine (2 x 20 ml), dried over MgSO₄, and evaporated. The remaining residue (0.97 g) was purified by flash chromatography: Silica gel (80 g), CH₂Cl₂ – MeOH 30:1 – 20:1. The mass of the collected product (Triol (**24B-1a(iii)**)) was 0.35 g (the yield is quantitative), which was used for the next step without purification. R_f = 0.3 (CH₂Cl₂ – MeOH 10:1).

Preparation of Tetraol (25B-1a(iii)) from Triol (24B-1a(iii))



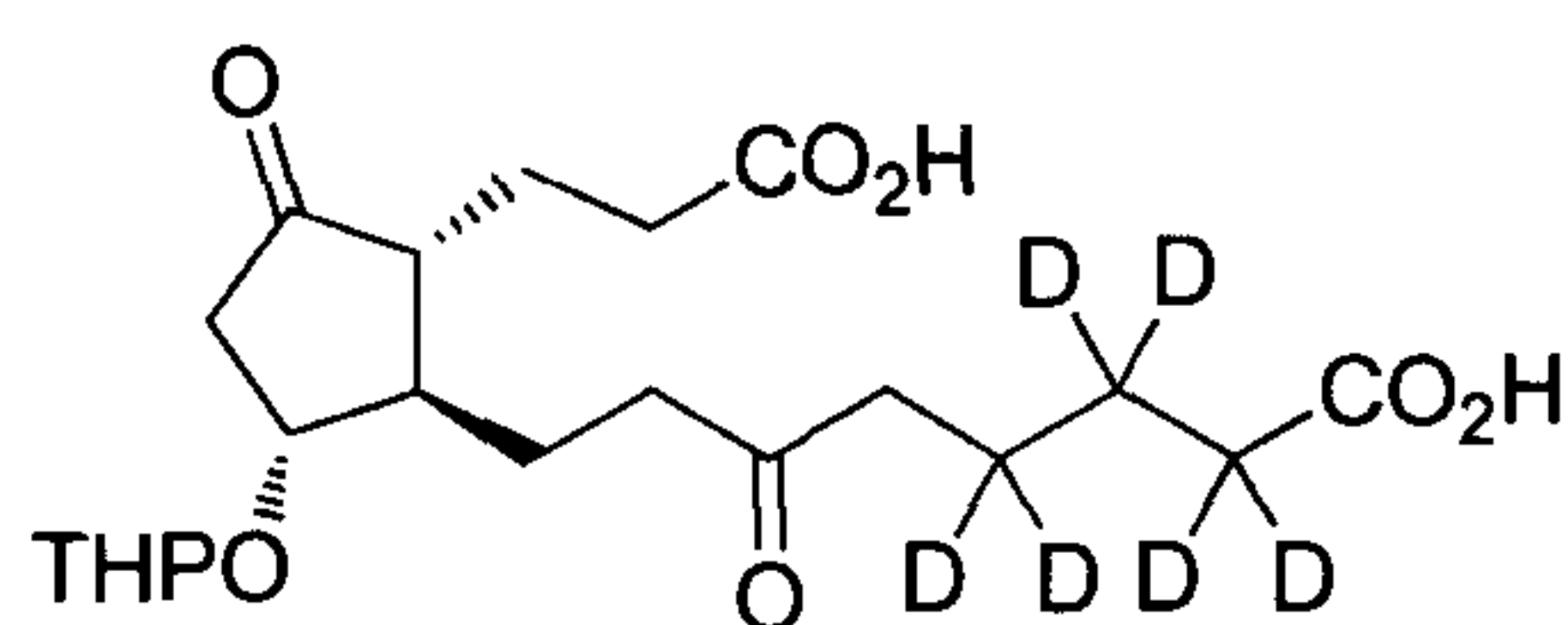
25B-1a(iii)

- 0.345 g (~ 0.678 mmol) of crude **24B-1a(iii)**;
- 1.0 ml of TBAF (1.0 M solution in THF);
- 10 ml of THF.

[0074] TBAF was added to a solution of triol **24B-1a(iii)** in THF and the reaction mixture was stirred overnight. The next day, 50 ml of ethyl acetate was added to the reaction mixture and the reaction mixture was washed with brine (2 x 20 ml), dried over MgSO₄, and evaporated. The remaining residue (0.55 g) was purified by flash chromatography: Silica gel

(60 g), MeOH – ethyl acetate - HOAc 5:95:0.5 – 20:80:0.5. The mass of the collected product (Tetraol (**25B-1a(iii)**)) was 224 mg (83% after two steps). $R_f = 0.4$ (MeOH–ethyl acetate-HOAc 5:95:1).

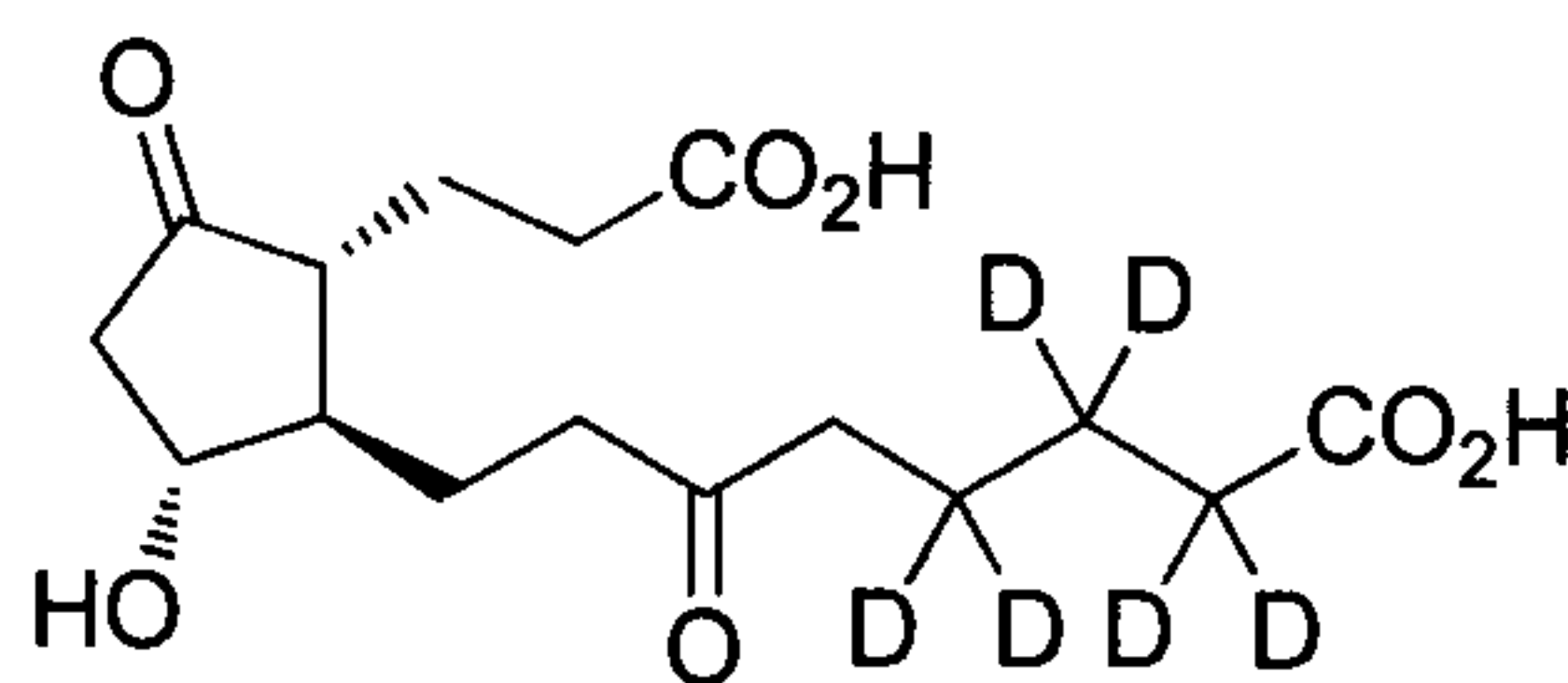
Preparation of Tetranor PGEM (**26B-1a(iii)**) from Tetraol (**25B-1a(iii)**)



26B-1a(iii)

- 214 mg (0.57 mmol) of tetraol **25B-1a(iii)**;
- Jones Reagent (2.66 M solution in H₂O);
- 70 ml of acetone.

[0075] A solution of tetraol **25B-1a(iii)** in acetone (20 ml) was treated with Jones Reagent (5 portions of freshly diluted with acetone in 50:1 ratio) at 0°C for 40 minutes until the color of the reaction material became yellow and did not disappear for 10 minutes. The reaction mixture was stirred 10 minutes more, treated with 0.5 ml of *i*-PrOH, diluted with 150 ml of ethyl acetate, dried over MgSO₄, and evaporated. The residue (0.248 g) was purified by flash chromatography: Silica gel (60 g), hexane – ethyl acetate - HOAc 60:40:0.5 – 20:80:0.5. The mass of the collected product (Tetranor PGEM (**26B-1a(iii)**)) was 46 mg (18%). $R_f = 0.57$ (hexane–ethyl acetate-HOAc 10:90:1).

Preparation of Tetranor PGAM (27(B)) from Tetranor PGEM (26B-1a(iii))**27B**

- 45 mg (0.11 mmol) of protected tetranor PGEM **26B-1a(iii)**;
- 5 ml of HOAc/THF/H₂O (4:2:1) mixture.

[0076] A solution of protected tetranor PGEM **26B-1a(iii)** (in 5ml of HOAc/THF/H₂O (4:2:1)) was stirred for two days and evaporated with toluene. The remaining residue (40 mg) was purified by flash chromatography: Silica gel (20 g), hexane – ethyl acetate - HOAc 25:75:0.5 – hexane - ethyl acetate - HOAc 10:90:0.5. The mass of the collected product (Tetranor PGAM (**27(B)**)) was 14 mg (40%). $R_f = 0.45$ (ethanol - ethyl acetate - HOAc 5:95:1).

[0077] The chemical shifts and peak heights for compound 28A as they appear in Figures 23A and 23C, respectively are set out in the tables below:

INDEX	FREQUENCY	PPM	HEIGHT
1	3029.831	7.575	7.7
2	3027.481	7.589	7.5
3	3024.155	7.581	7.4
4	3021.591	7.555	7.2
5	2906.594	7.267	35.1
6	2456.678	6.142	7.4
7	2454.848	6.138	7.0
8	2451.003	6.128	7.1
9	2448.988	6.123	6.8
10	1660.126	4.151	3.5
11	1652.385	4.133	10.8
12	1645.843	4.115	10.8
13	1638.702	4.097	3.5
14	1086.059	2.715	4.1
15	1069.212	2.673	6.4
16	1045.590	2.614	4.5
17	1034.054	2.585	4.7
18	1032.040	2.580	4.4
19	1025.814	2.565	10.3
20	1019.222	2.548	9.4
21	1012.263	2.531	3.9
22	1001.826	2.505	3.6
23	992.670	2.482	4.4
24	985.711	2.465	11.0
25	978.936	2.448	5.1
26	959.526	2.389	4.9
27	952.751	2.382	14.4
28	950.370	2.376	5.5
29	945.975	2.365	5.5
30	841.233	2.103	18.4
31	819.626	2.049	55.0
32	813.033	2.033	5.3
33	810.653	2.027	5.3
34	805.892	2.015	3.8
35	803.511	2.009	9.9
36	773.297	1.933	3.8
37	766.156	1.916	5.0
38	762.494	1.906	3.7
39	759.381	1.899	4.5

(FIGURE 23A)

INDEX	FREQUENCY	PPM	HEIGHT
1	1086.059	2.715	4.1
2	1078.734	2.697	2.6
3	1076.720	2.692	3.2
4	1069.212	2.673	6.4
5	1061.888	2.655	3.3
6	1051.633	2.629	2.4
7	1047.788	2.620	3.2
8	1045.590	2.614	4.5
9	1043.576	2.609	3.4
10	1039.547	2.595	2.5
11	1037.350	2.594	2.6
12	1034.054	2.585	4.7
13	1032.040	2.580	4.4
14	1025.814	2.565	10.3
15	1019.222	2.548	9.4
16	1012.263	2.531	3.9
17	1008.987	2.523	2.6
18	1001.826	2.505	3.6
19	995.233	2.488	3.3
20	992.670	2.482	4.4
21	985.711	2.465	11.0
22	978.936	2.448	5.1
23	959.526	2.399	4.9
24	952.751	2.382	14.4
25	950.370	2.376	5.5
26	945.975	2.365	5.5
27	870.715	2.177	2.2
28	841.233	2.103	18.4
29	818.626	2.049	55.0
30	813.033	2.036	5.3
31	810.653	2.027	5.3
32	805.892	2.015	3.8
33	803.511	2.009	3.9
34	773.297	1.933	3.8
35	769.813	1.925	2.6
36	766.156	1.916	5.0
37	762.494	1.906	3.7
38	759.381	1.899	4.5
39	755.352	1.889	4.8

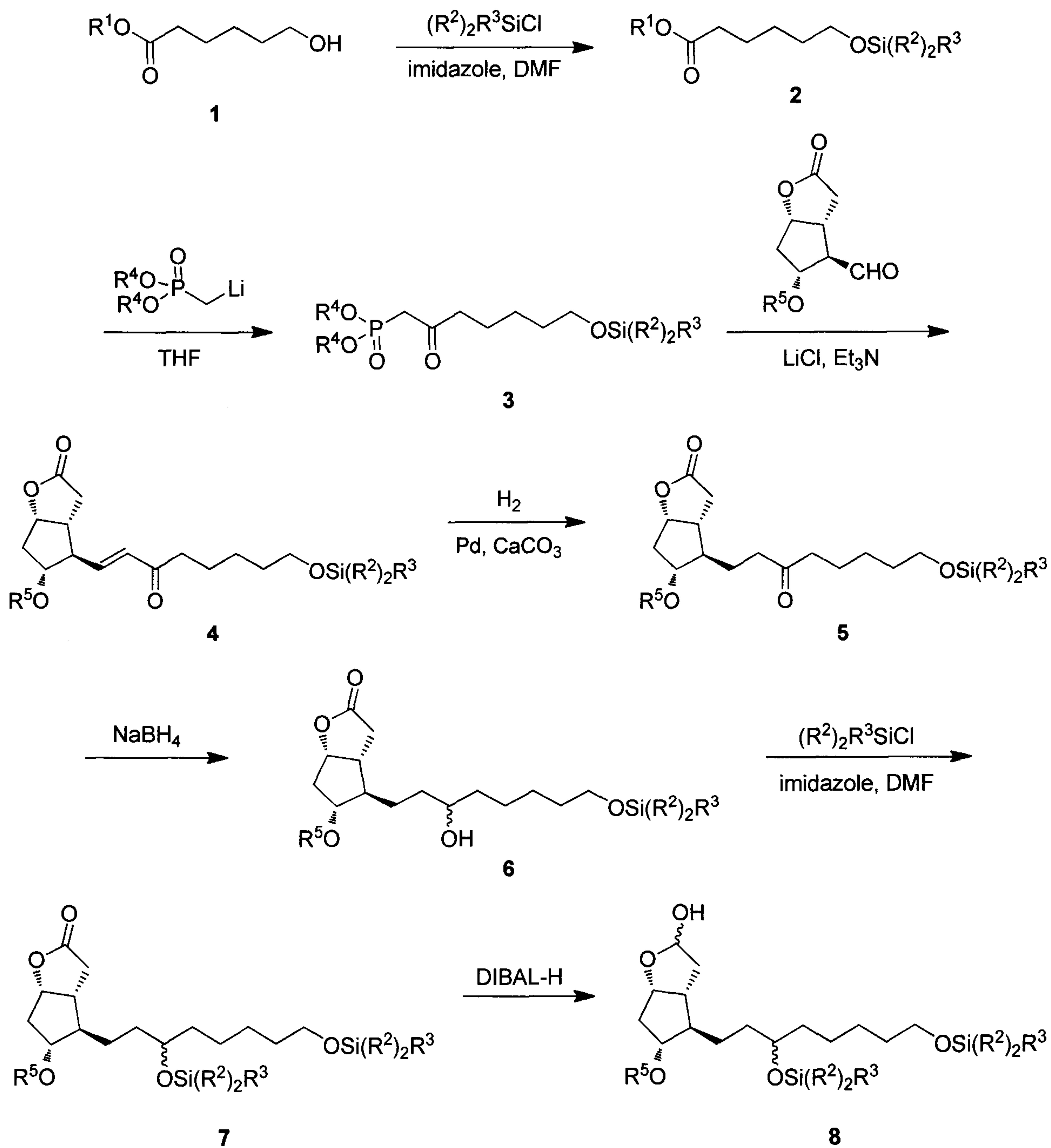
(FIGURE 23C)

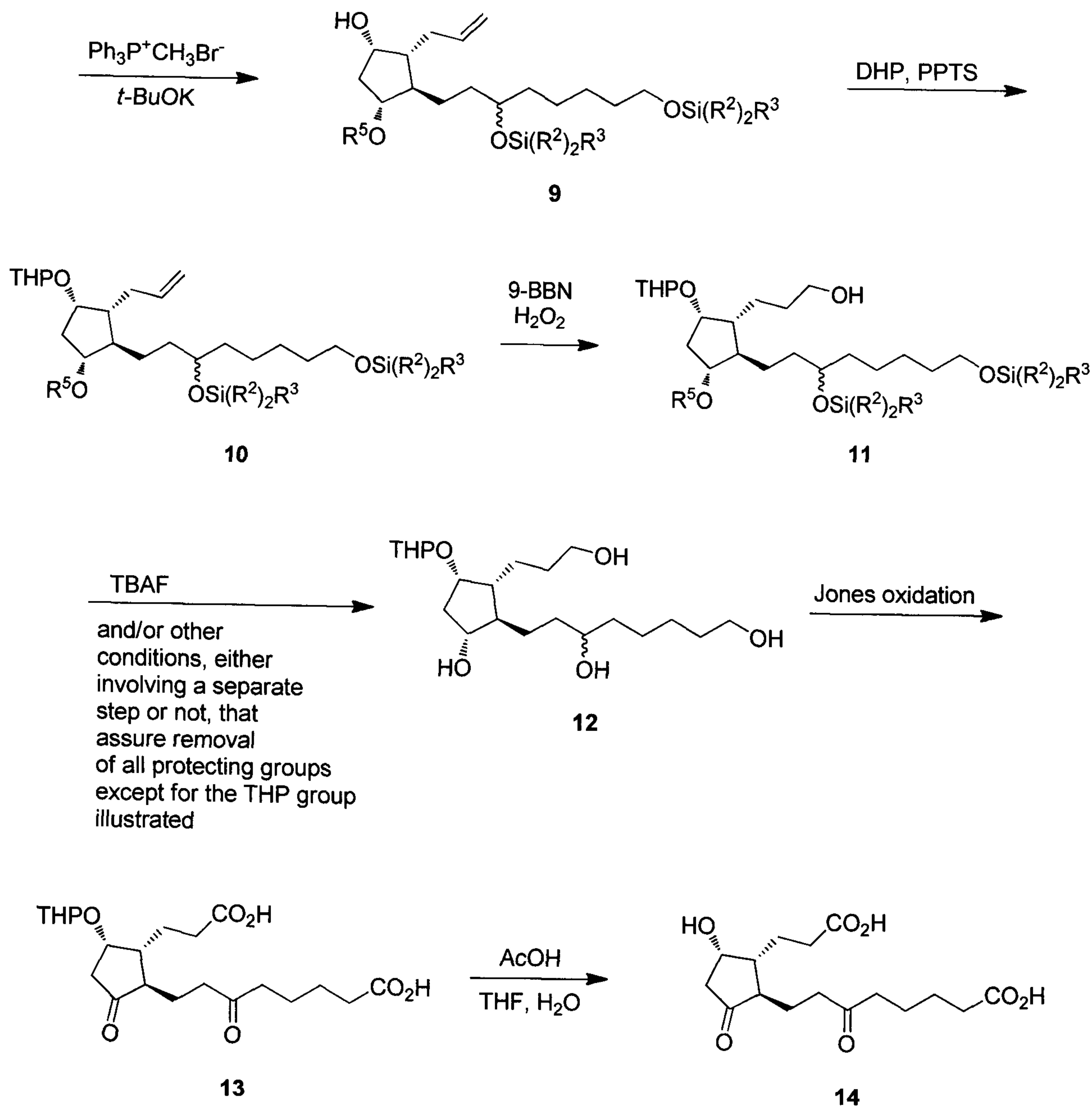
[0078] The scope of the claims should not be limited by the preferred embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

[0079]

WHAT IS CLAIMED IS:

1. A method for preparing tetranor-PGDM of formula 14 comprising the following reaction steps as shown in Scheme I:





Scheme I

wherein

DMF is N,N-dimethylformamide;

THF is tetrahydrofuran;

Et is ethyl

DIBAL is diisobutylaluminum;

t-BuOK is potassium tert-butoxide;

TBAF is tetrabutylammonium fluoride;

THP is tetrahydropyran;

Ac is acetyl;

R¹ is C₁₋₄ alkyl;

each R² is independently C₁₋₅ alkyl or phenyl;

each R³ is independently a C₁₋₄ alkyl;

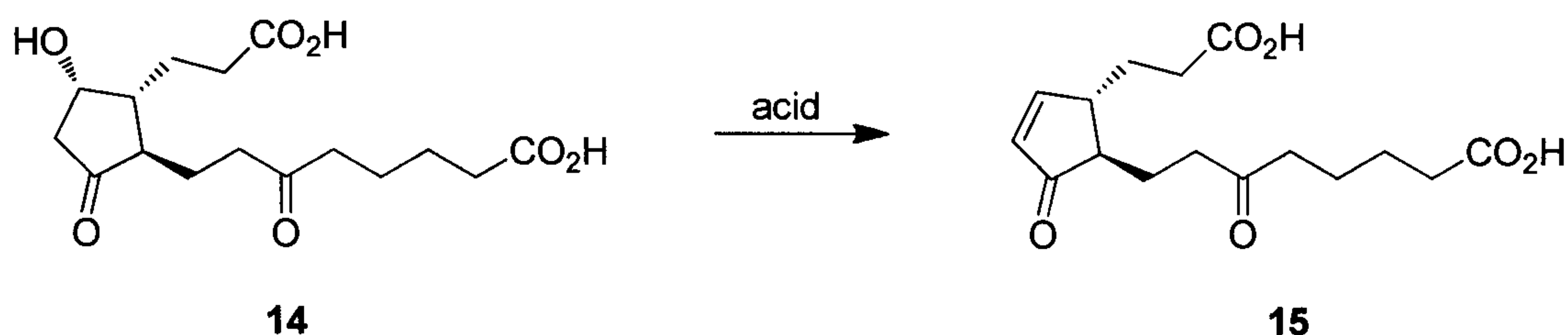
R⁴ is methyl or ethyl; and

R⁵ is a protecting group.

2. The method of Claim 1, wherein the protecting group R⁵ is *tert*-butyldimethylsilyl (TBDMS).

3. The method of Claim 1, wherein the protecting group R⁵ is stable to all reaction conditions between its introduction to the reaction sequence illustrated in Scheme I and its required removal by appropriate deprotection conditions.

4. A method for forming tetranor-PGJM of formula 15 comprising the following reaction step as shown in Scheme II:

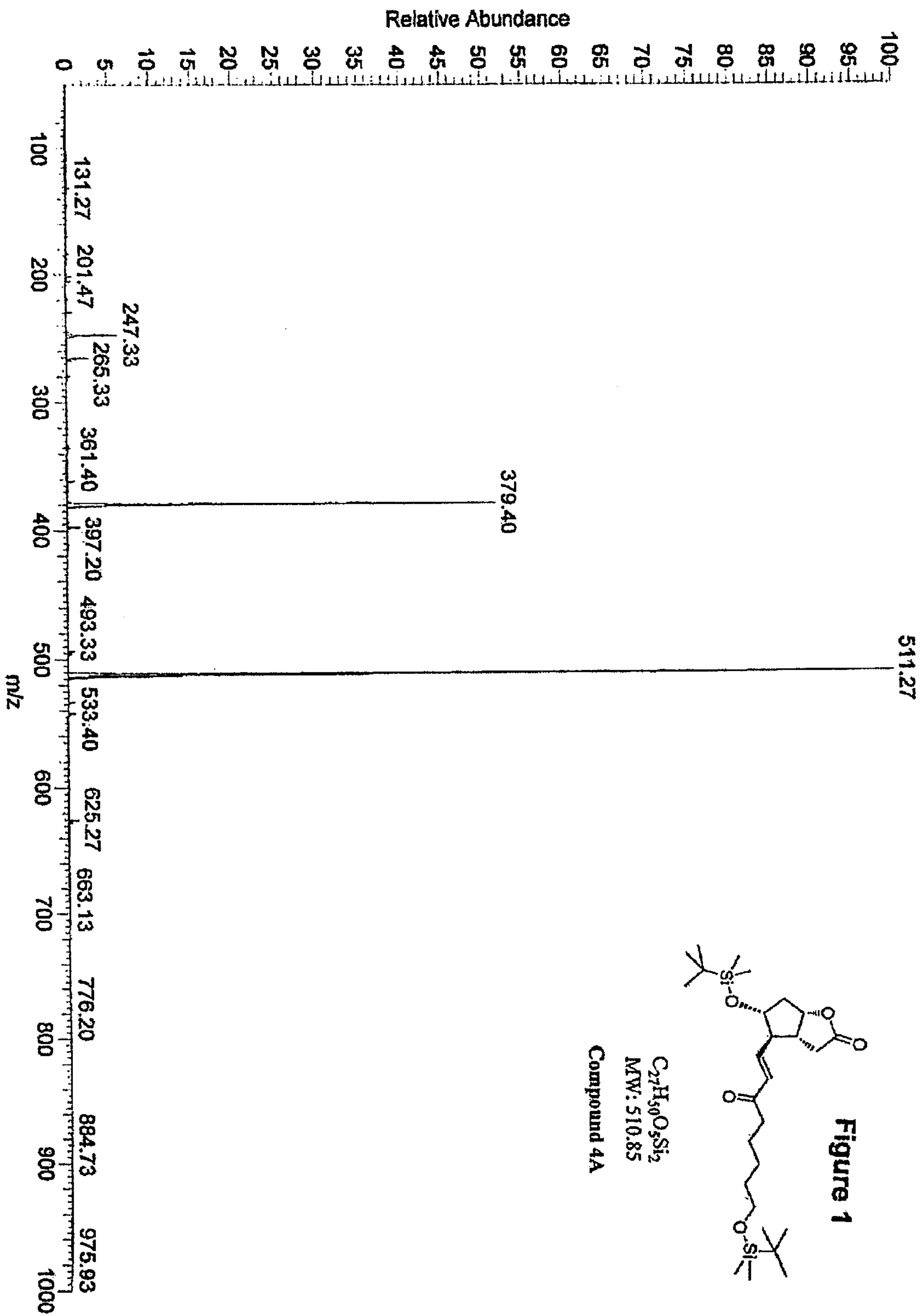


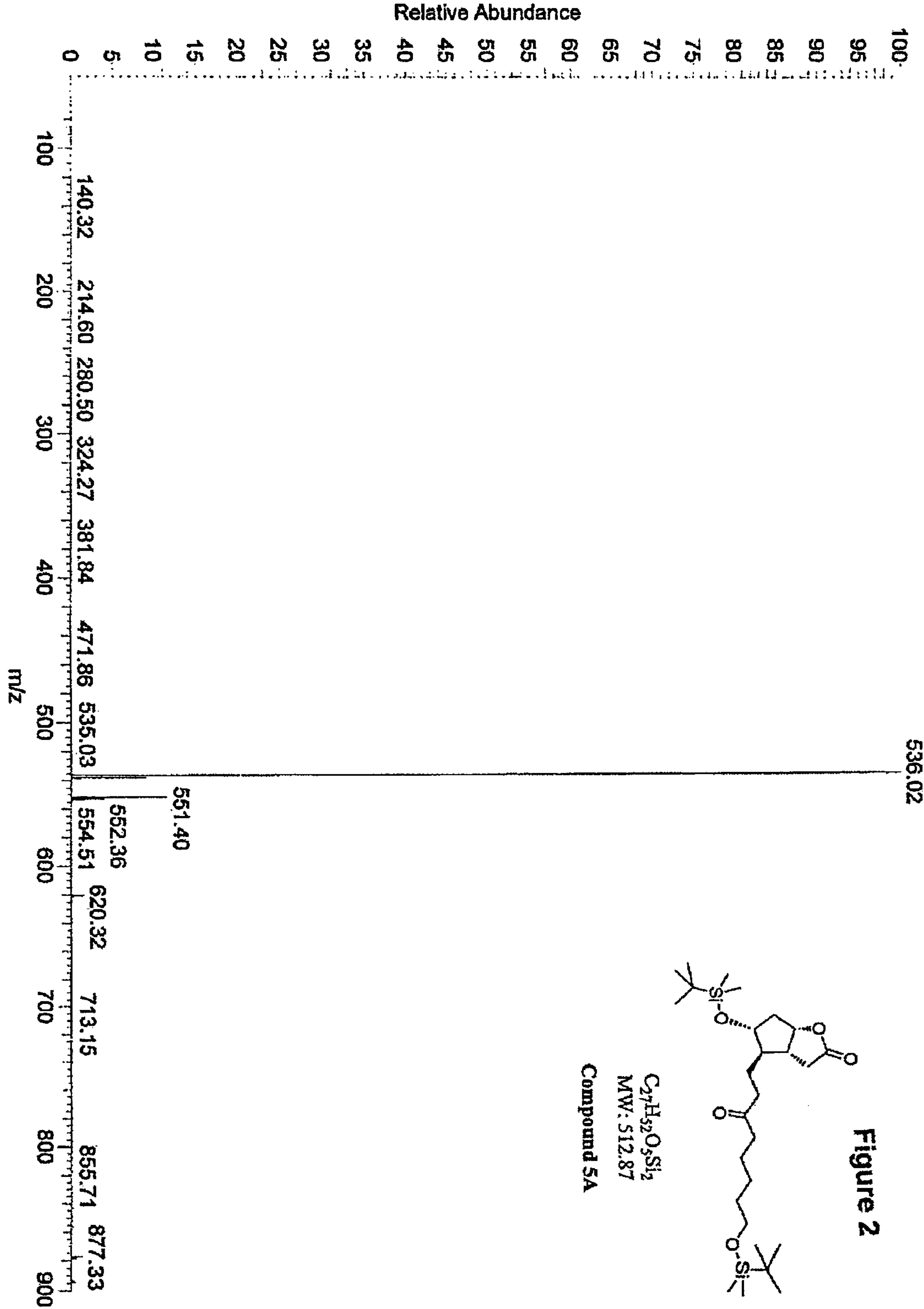
Scheme II

Comprising the steps of forming said compound 14 according to reaction Scheme I as defined in any one of claims 1 to 3 and wherein said acid comprises an organic acid or an inorganic acid.

5. The method of Claim 4, wherein said acid is acetic acid.

6. The method of Claim 4, wherein said acid is trifluoroacetic acid.





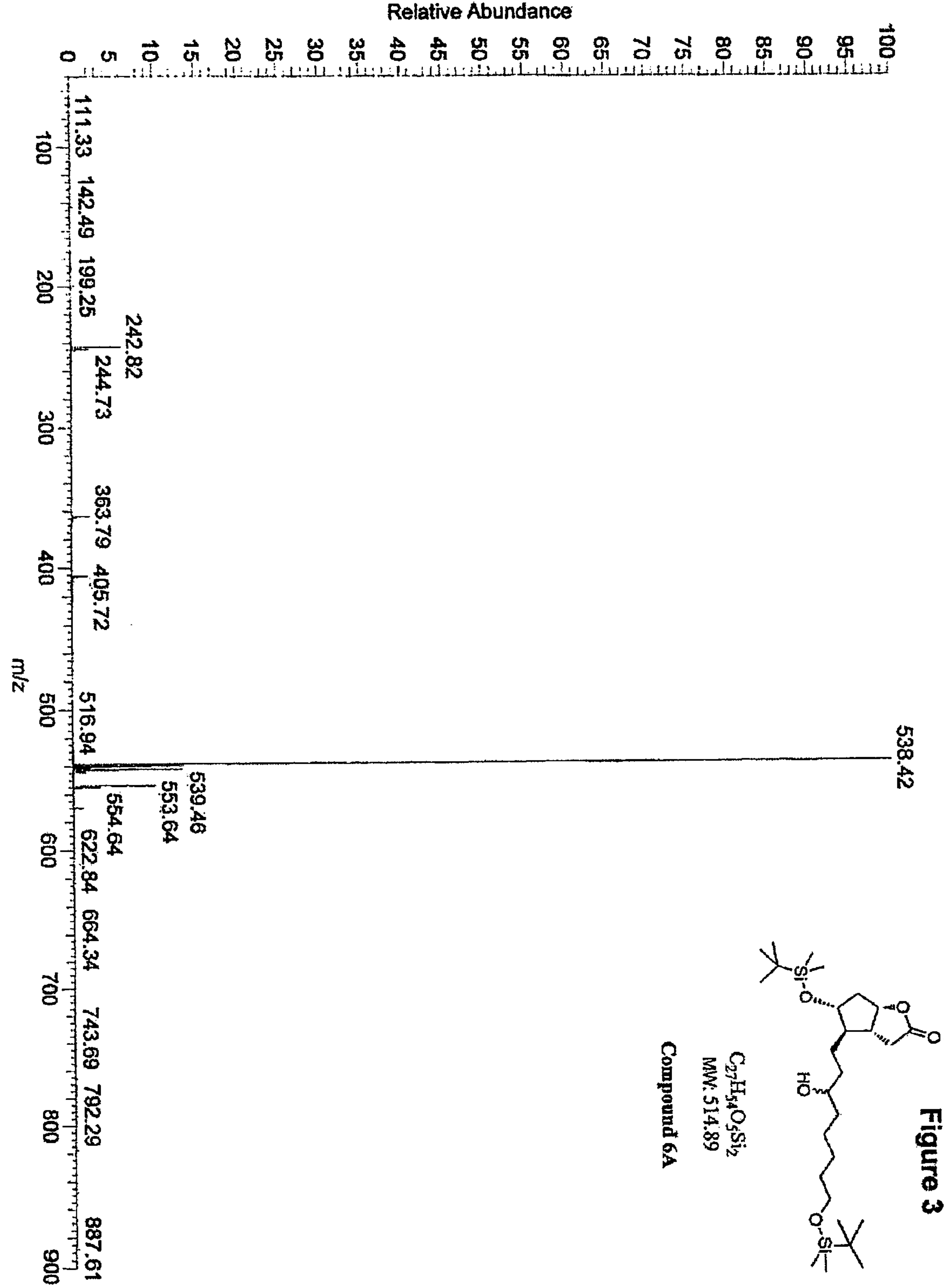
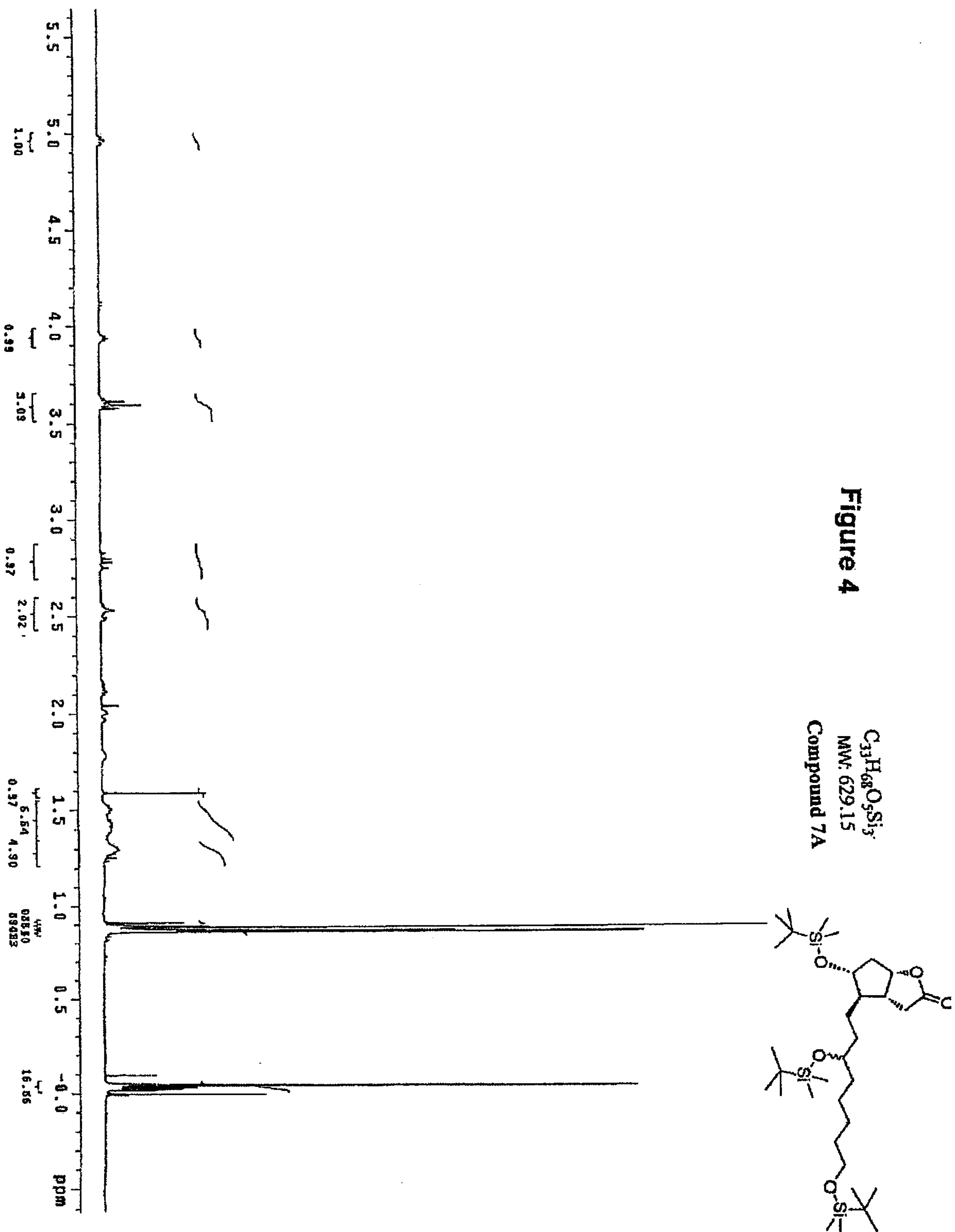


Figure 4

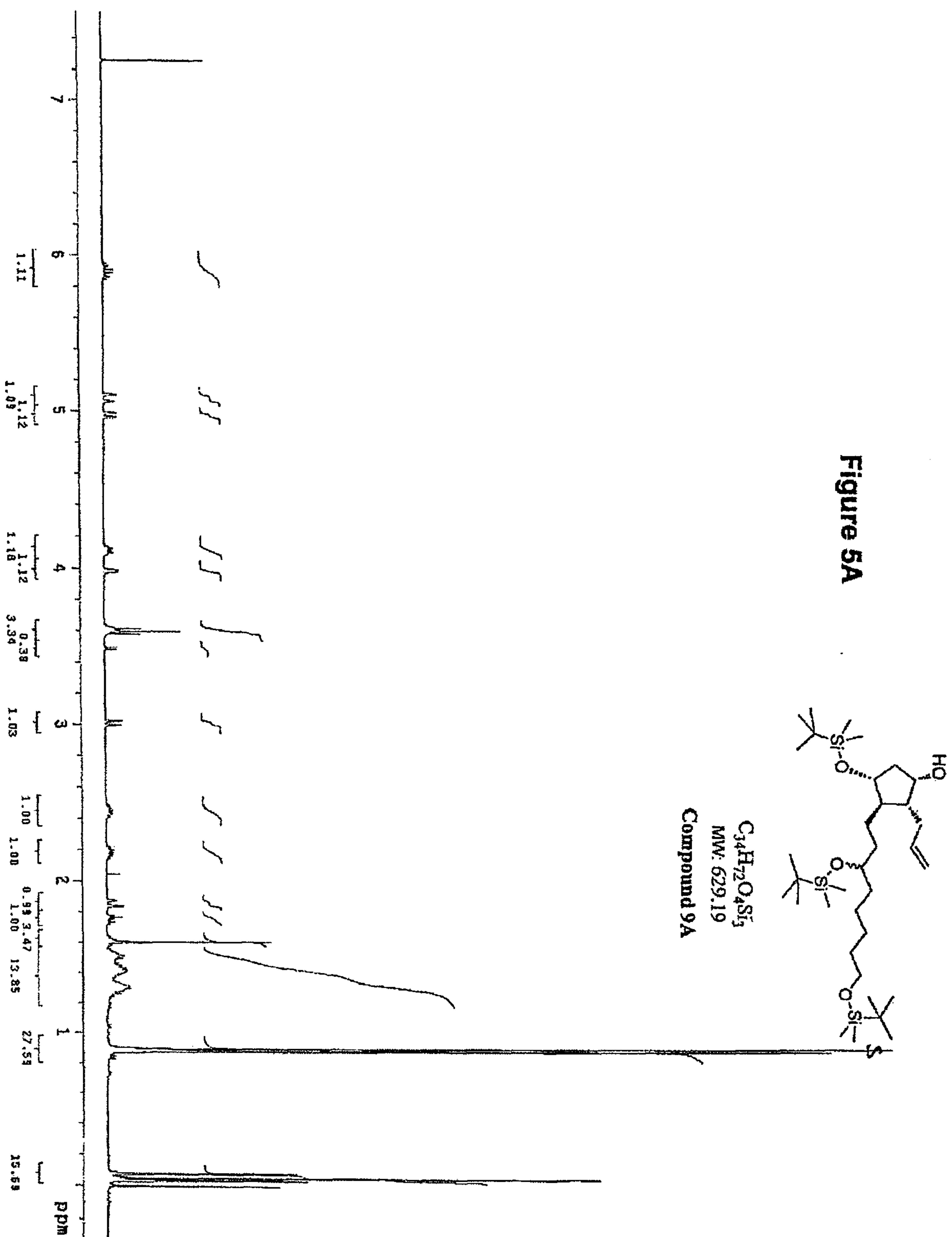
$C_{33}H_{68}O_5Si_3$
MW: 629.15
Compound 7A



FT1-B5
Solvent: CDCl3
Ambient temperature
INOVA-400 "varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 6000.2 Hz
Arrayed repetitions
OBSERVE H1, 399.9639857 MHz
DATA PROCESSING
FT size 65536
Total time 1 minute

Figure 4

Figure 5A



FF1-152-N9-15

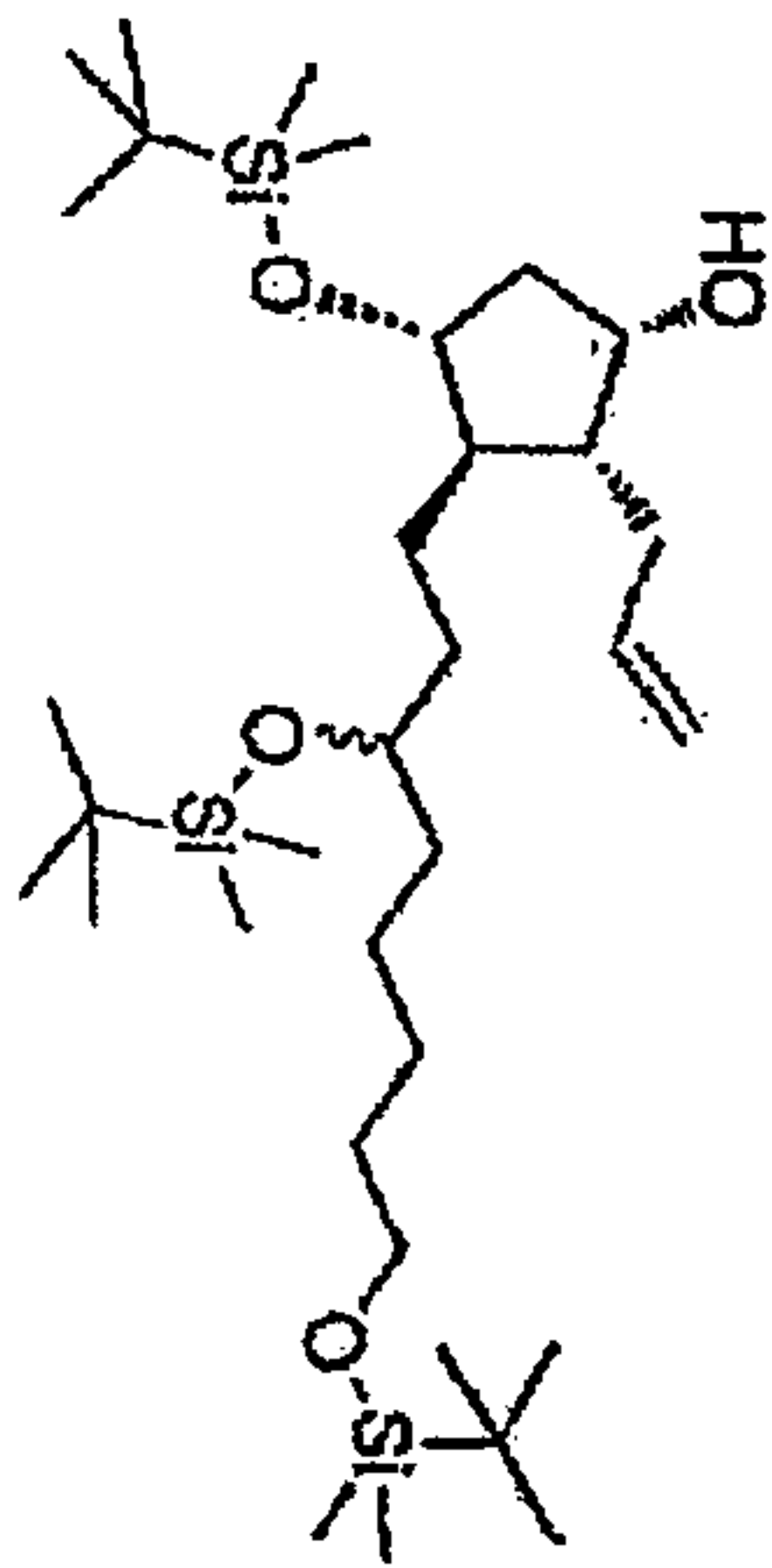
Solvent: CDCl3
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 1000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639859 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

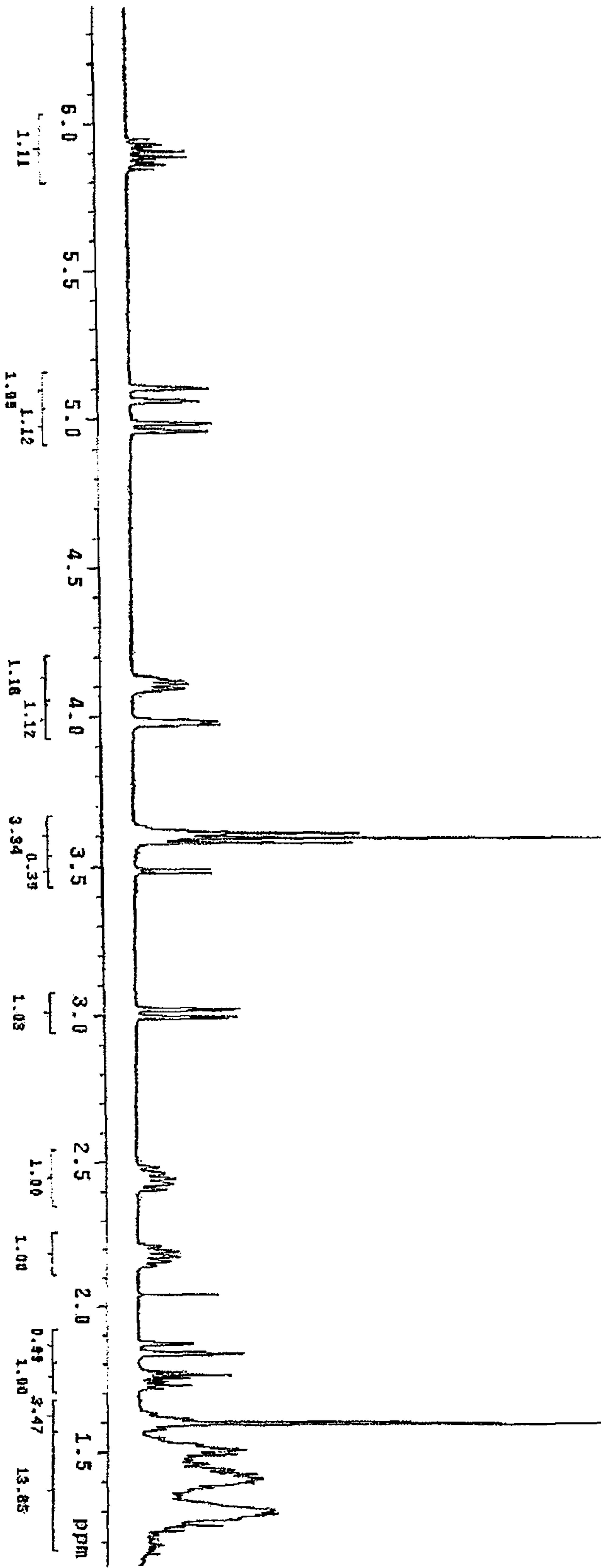
Figure 5A

Figure 5B



$C_{34}H_{72}O_4Si_3$
MW: 629.19
Compound 9A

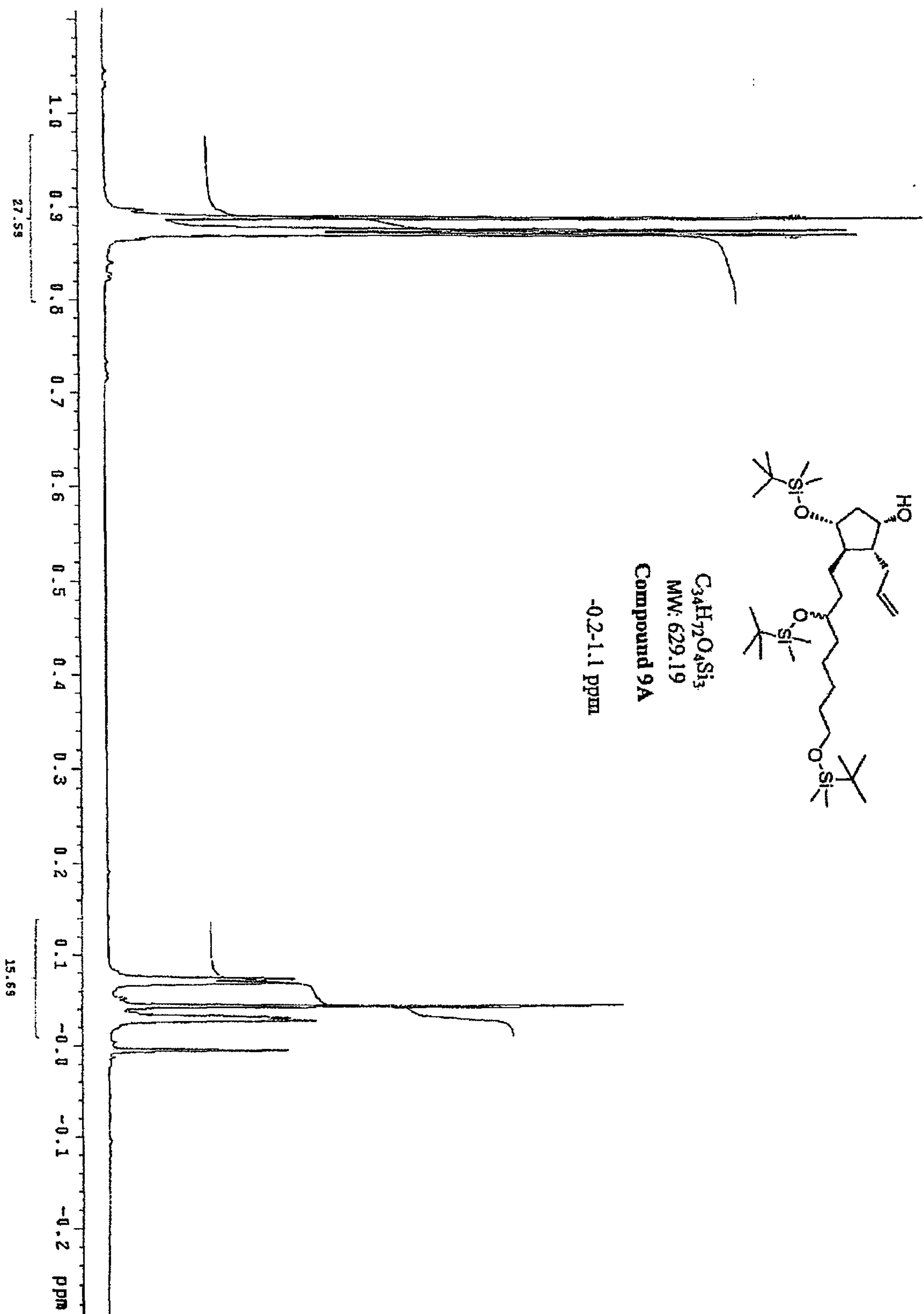
1.2-6.4 ppm



TT1-152-N8-15
Solvent: CDCl3
Ambient temperature
INOVA-400 "varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639858 MHz
DATA PROCESSING
FI size 32768
Total time 1 minute

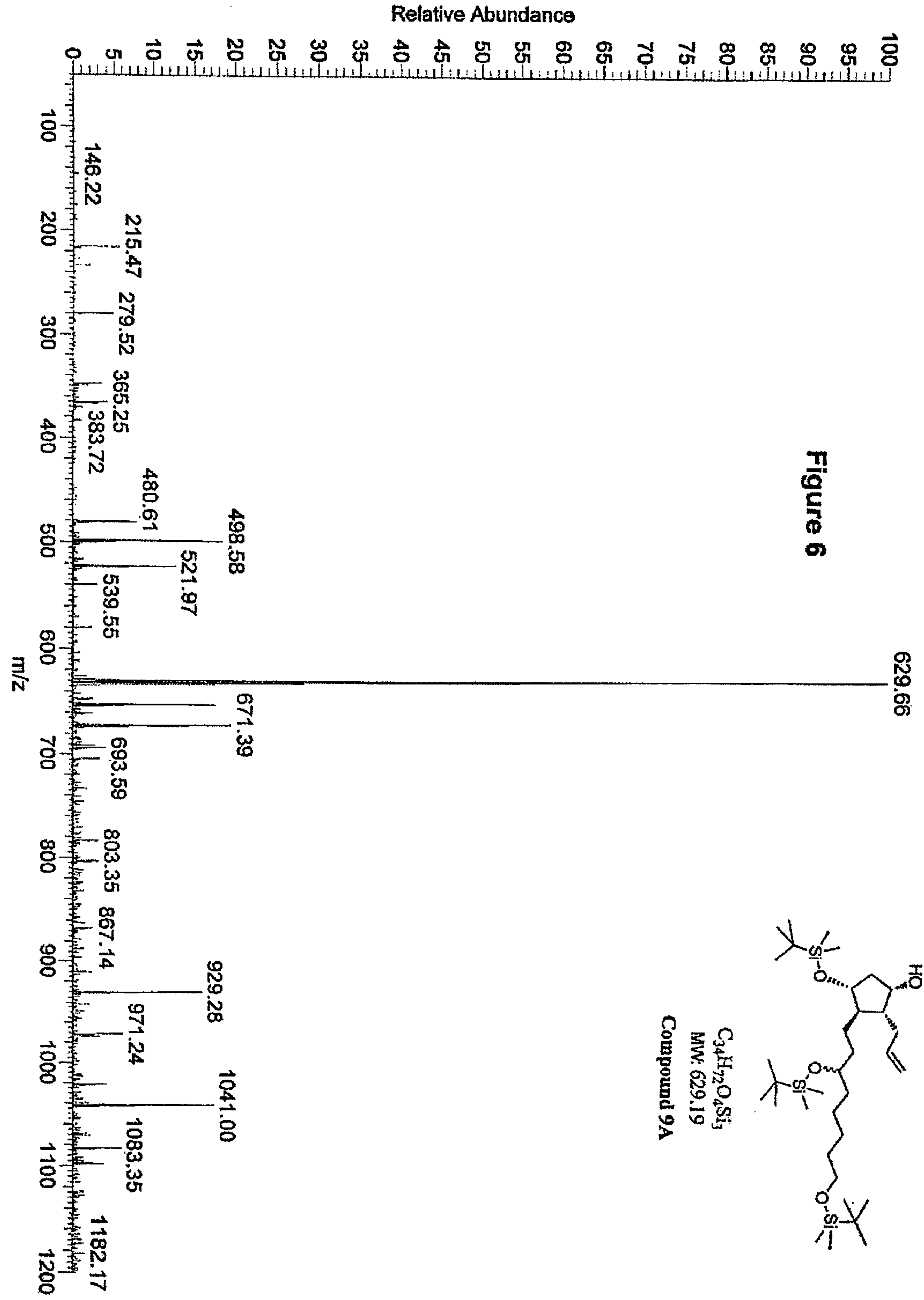
Figure 5B

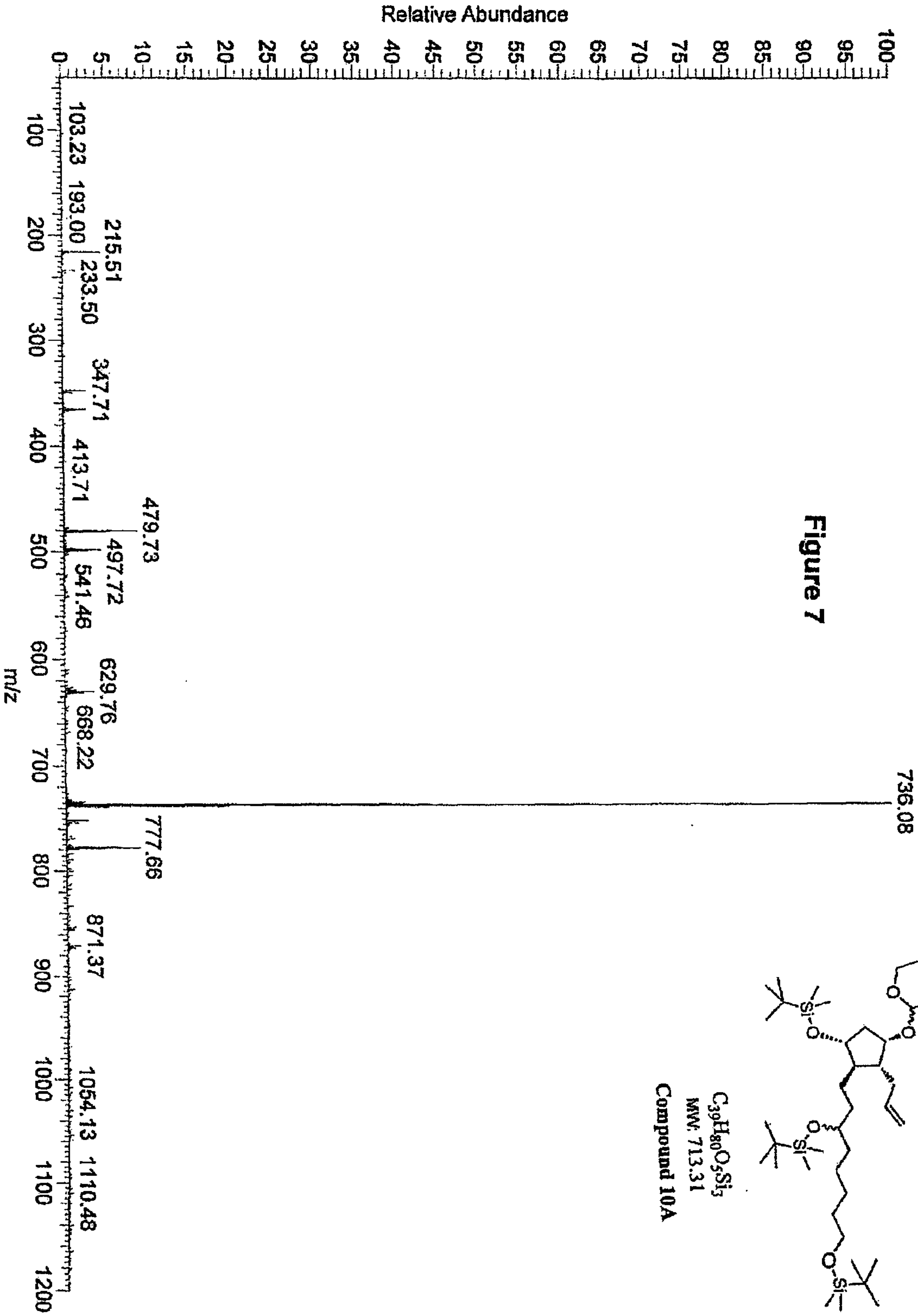
Figure 5C

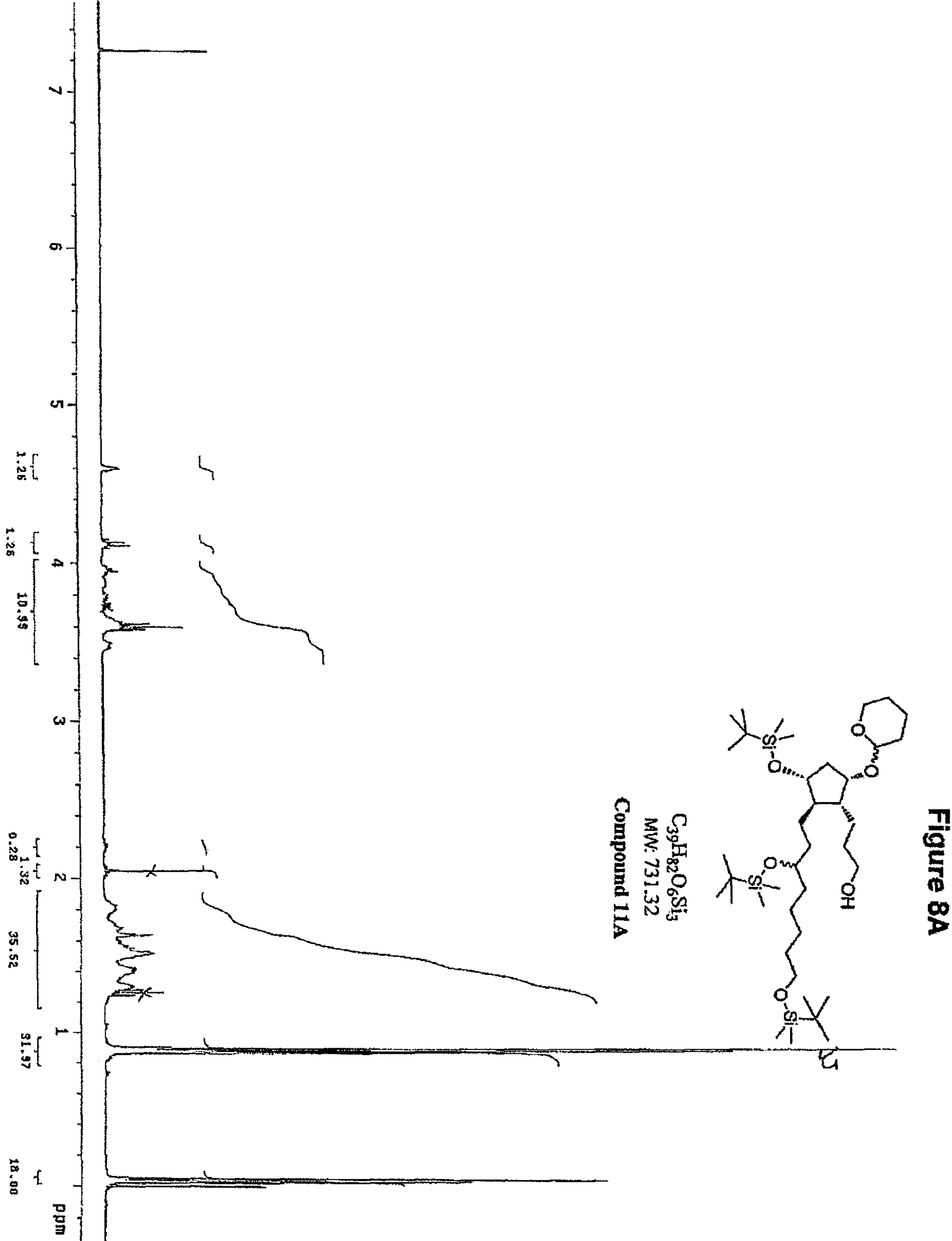


TT1-152-N8-15
Solvent: CDCl3
Ambient temperature
INOVA-400 "varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639859 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 5C







FT1-158-N17

Solvent: CCl₃
Ambient temperature
INOVA-400 "Varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639836 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 8A

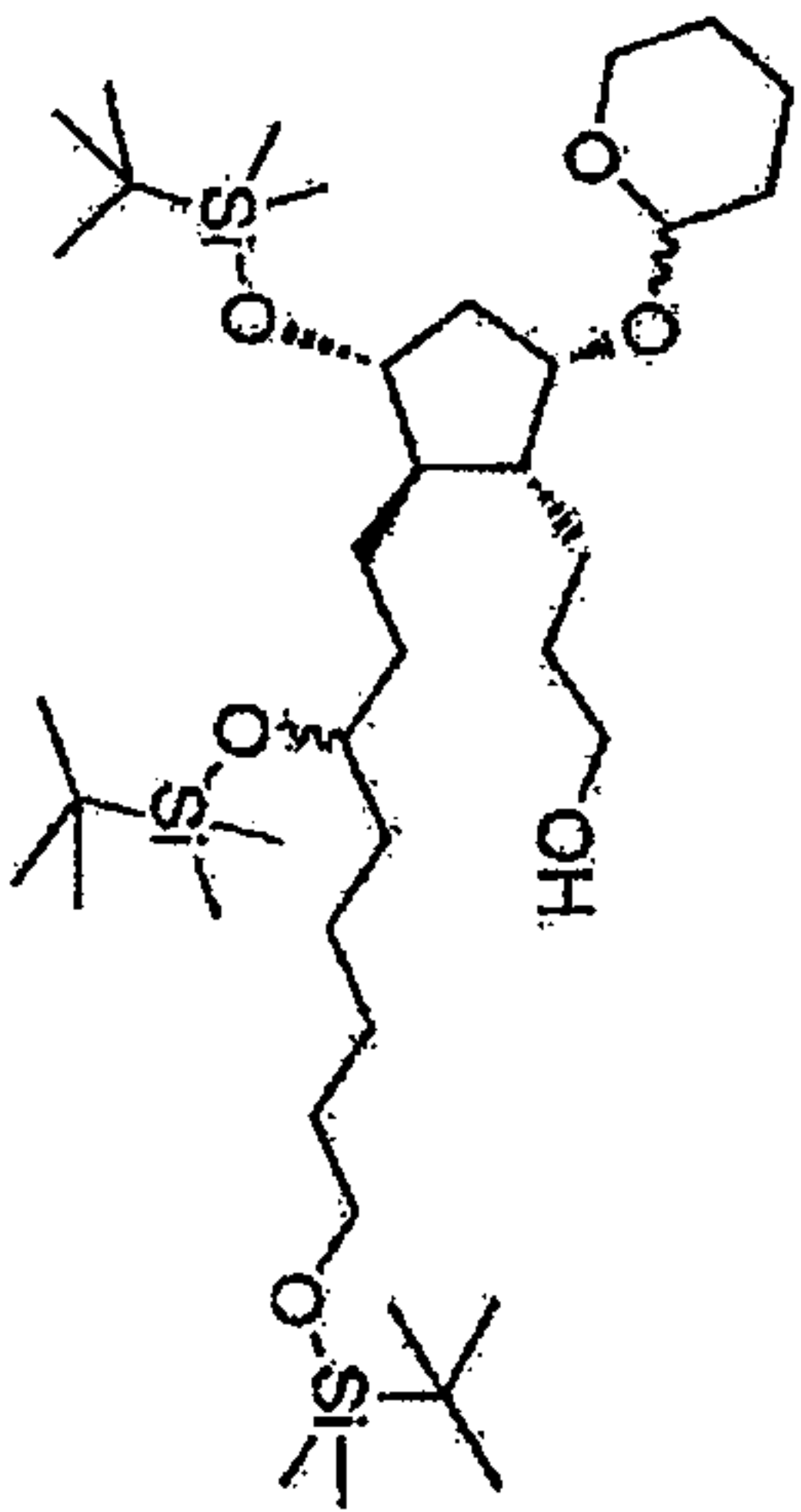
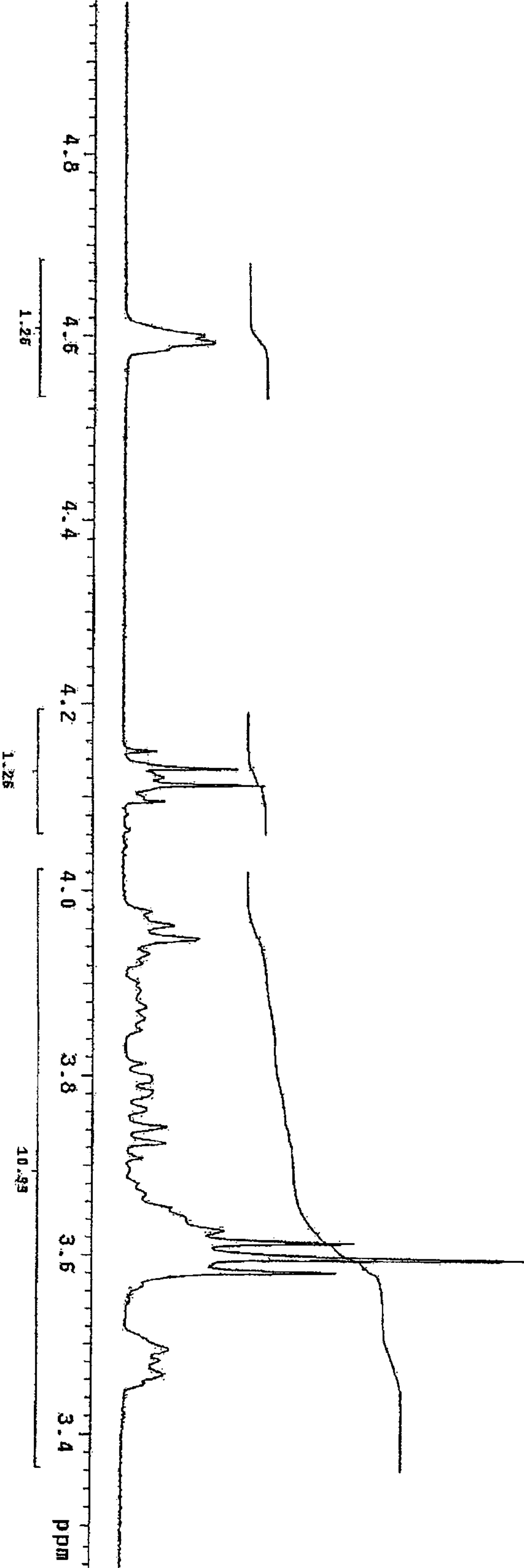


Figure 8B

$C_{39}H_{82}O_6Si_3$
MW: 731.32
Compound 11A
3.3-4.9 ppm



TT1-159-M17

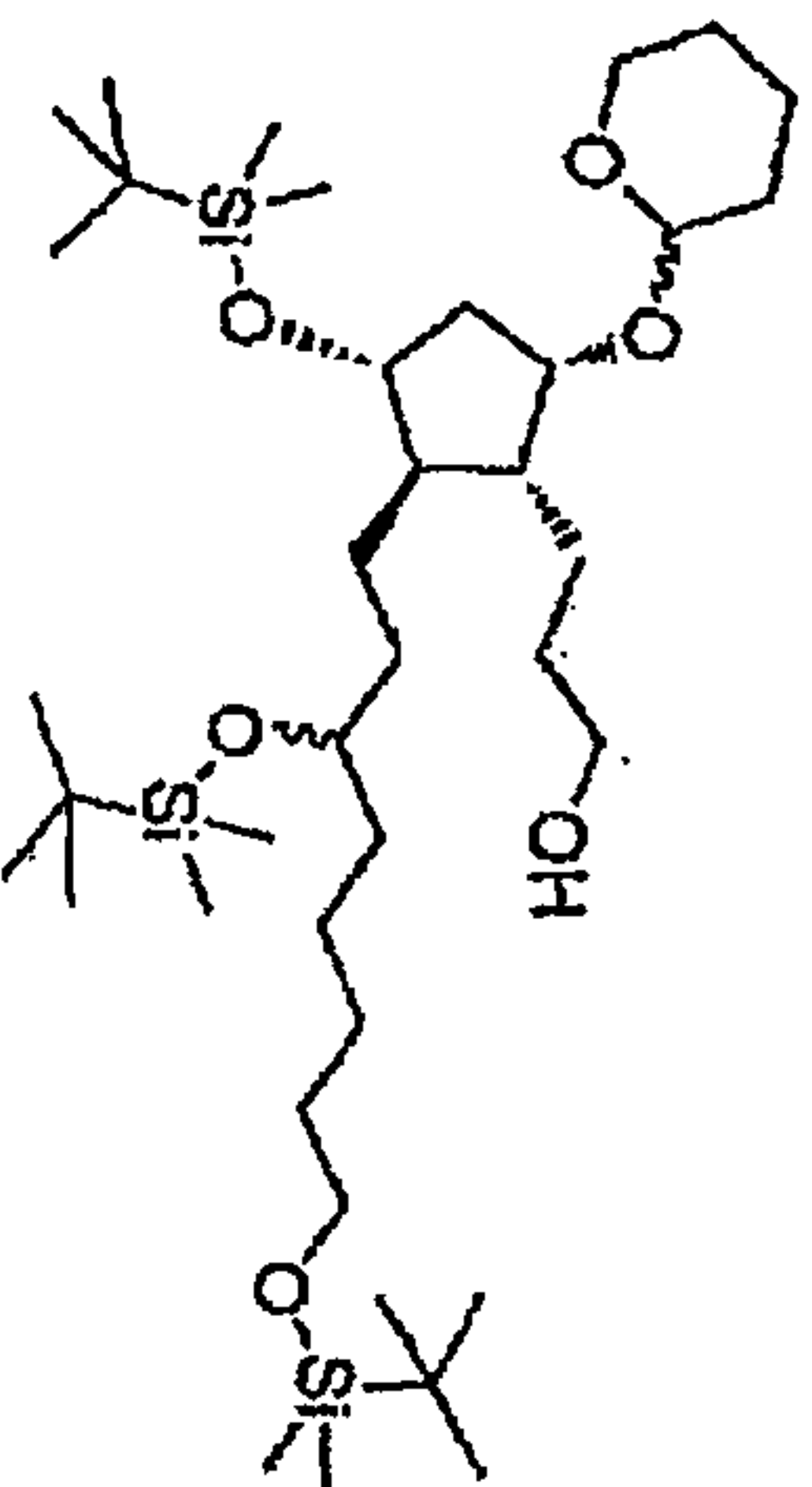
Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

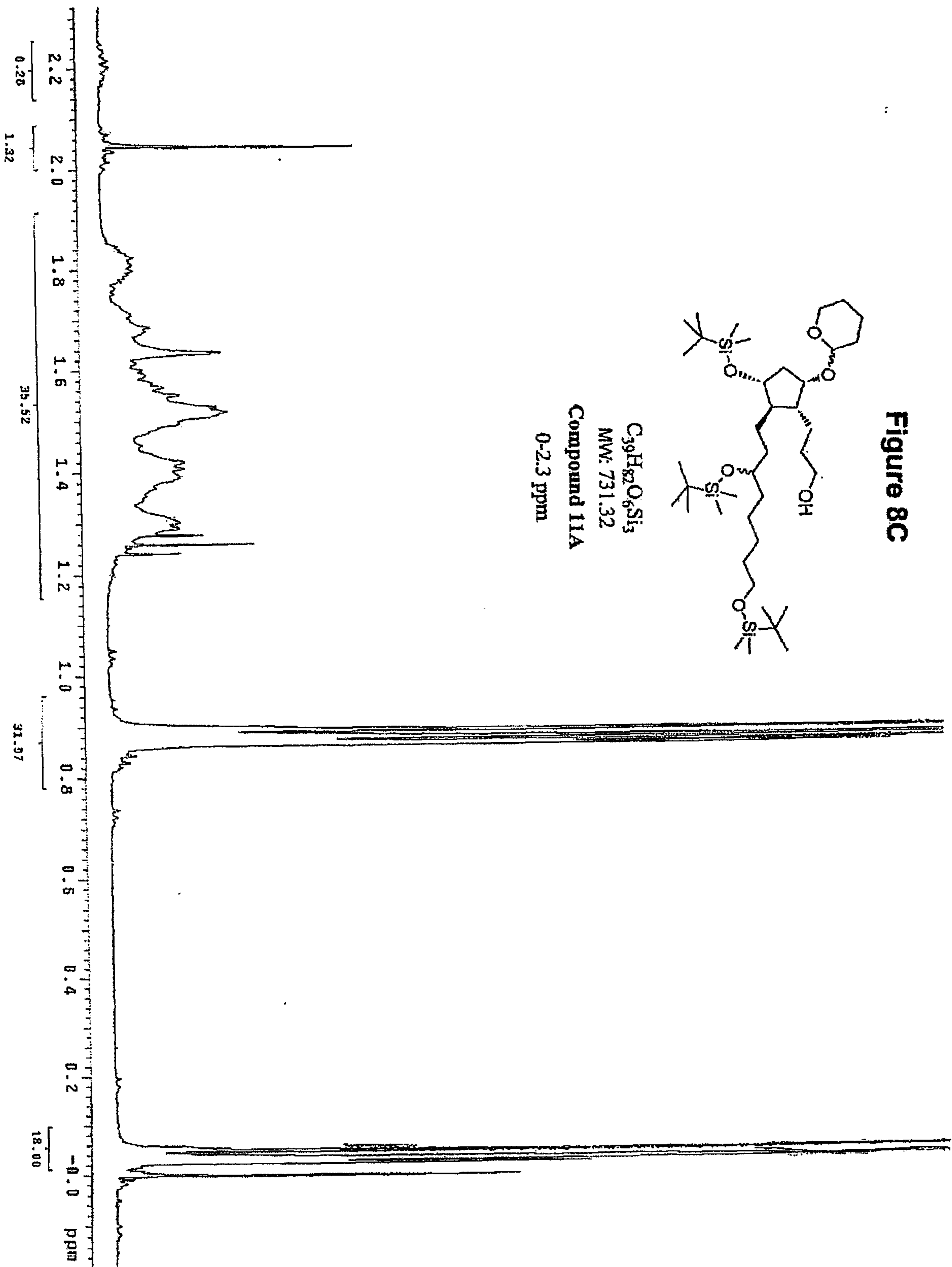
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639836 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 8B

Figure 8C

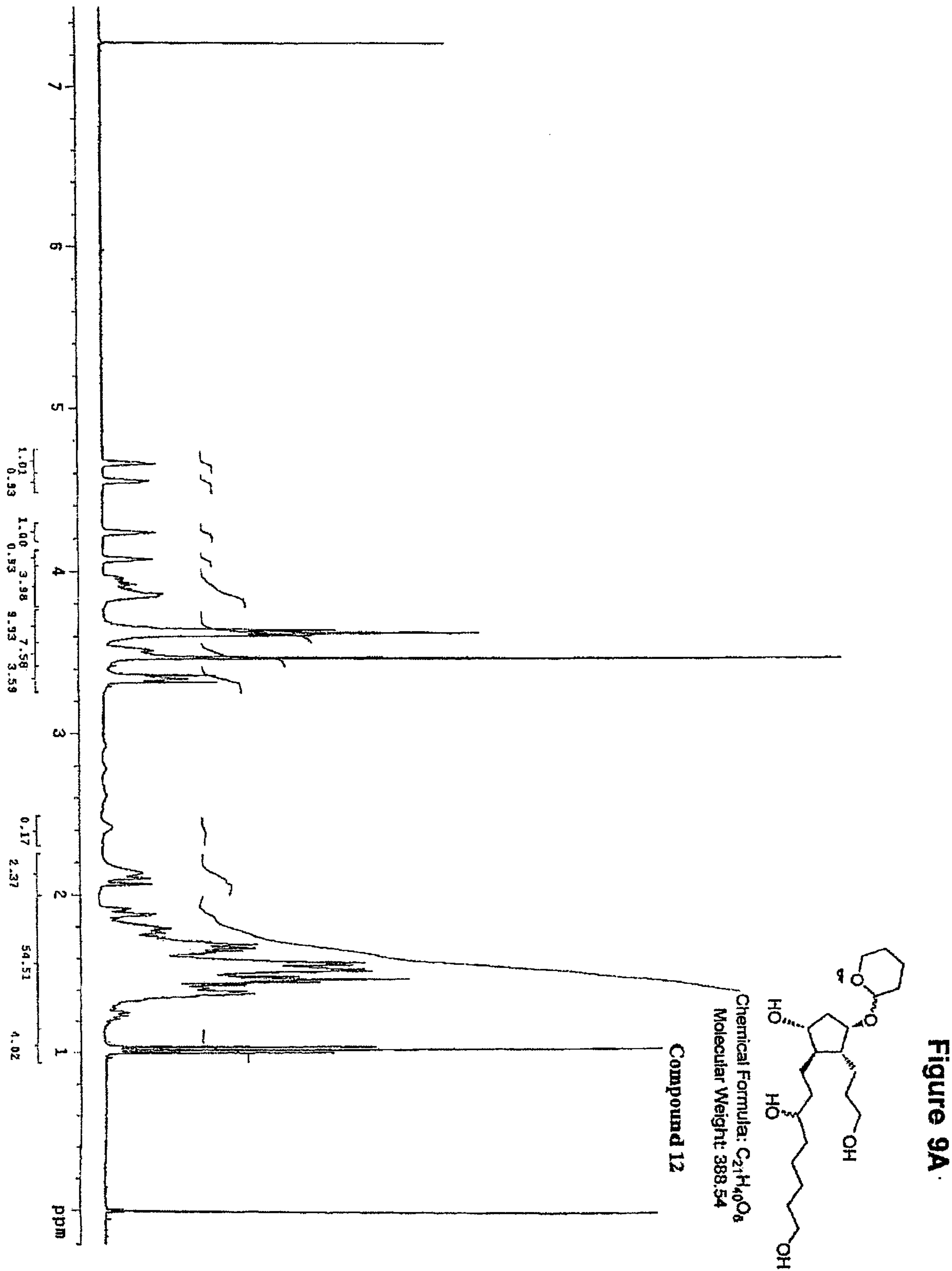


$C_{39}H_{82}O_6Si_3$
MW: 731.32
Compound 11A
0-2.3 ppm



TT1-159-N17
Solvent: CDCl3
Ambient temperature
INOVA-400 "varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1. 399.9639836 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 8C



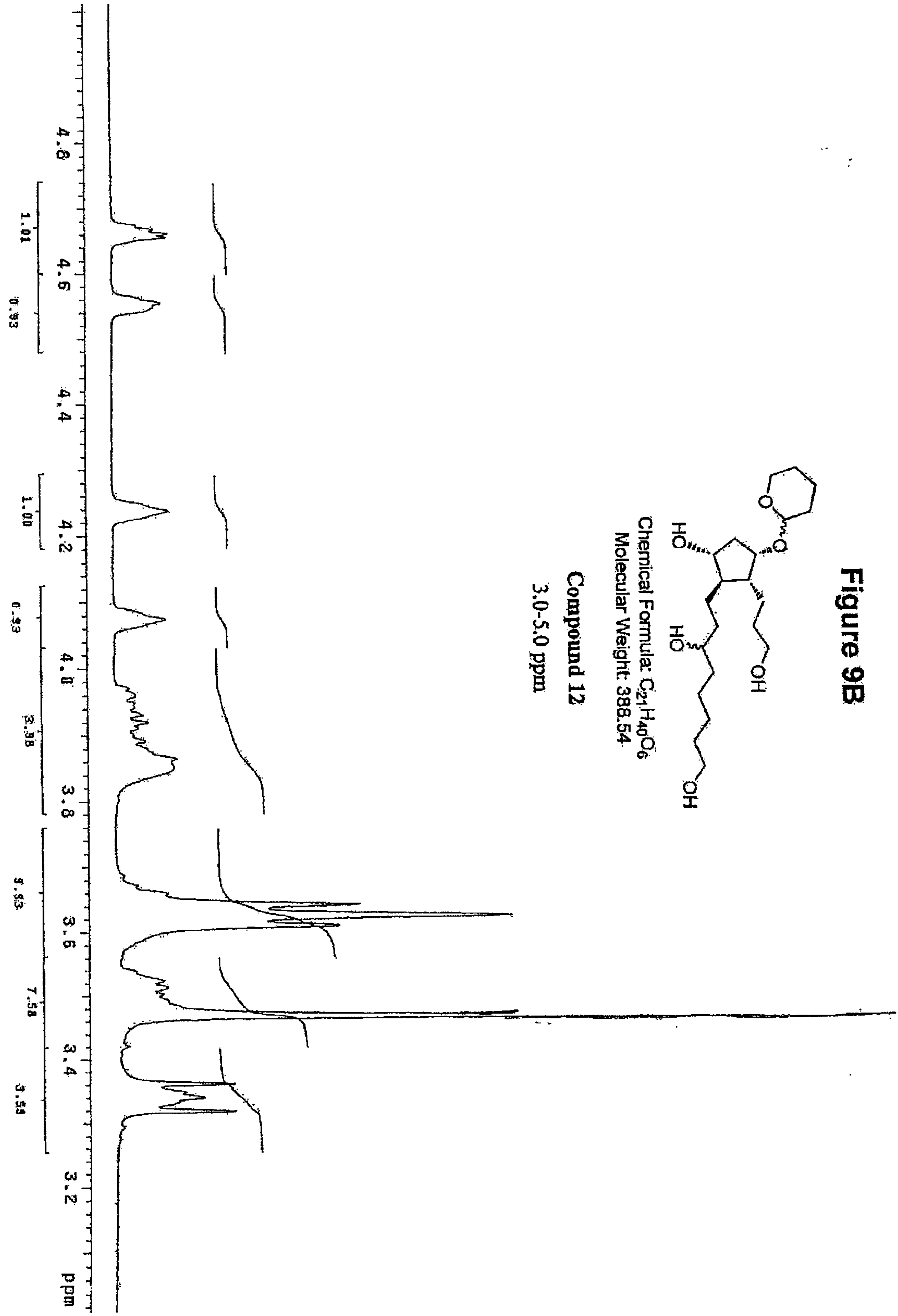
TT1-188

Solvent: CDCl₃
Ambient temperature
INOVA-400 "Varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639787 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 9A



TT1-168

Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

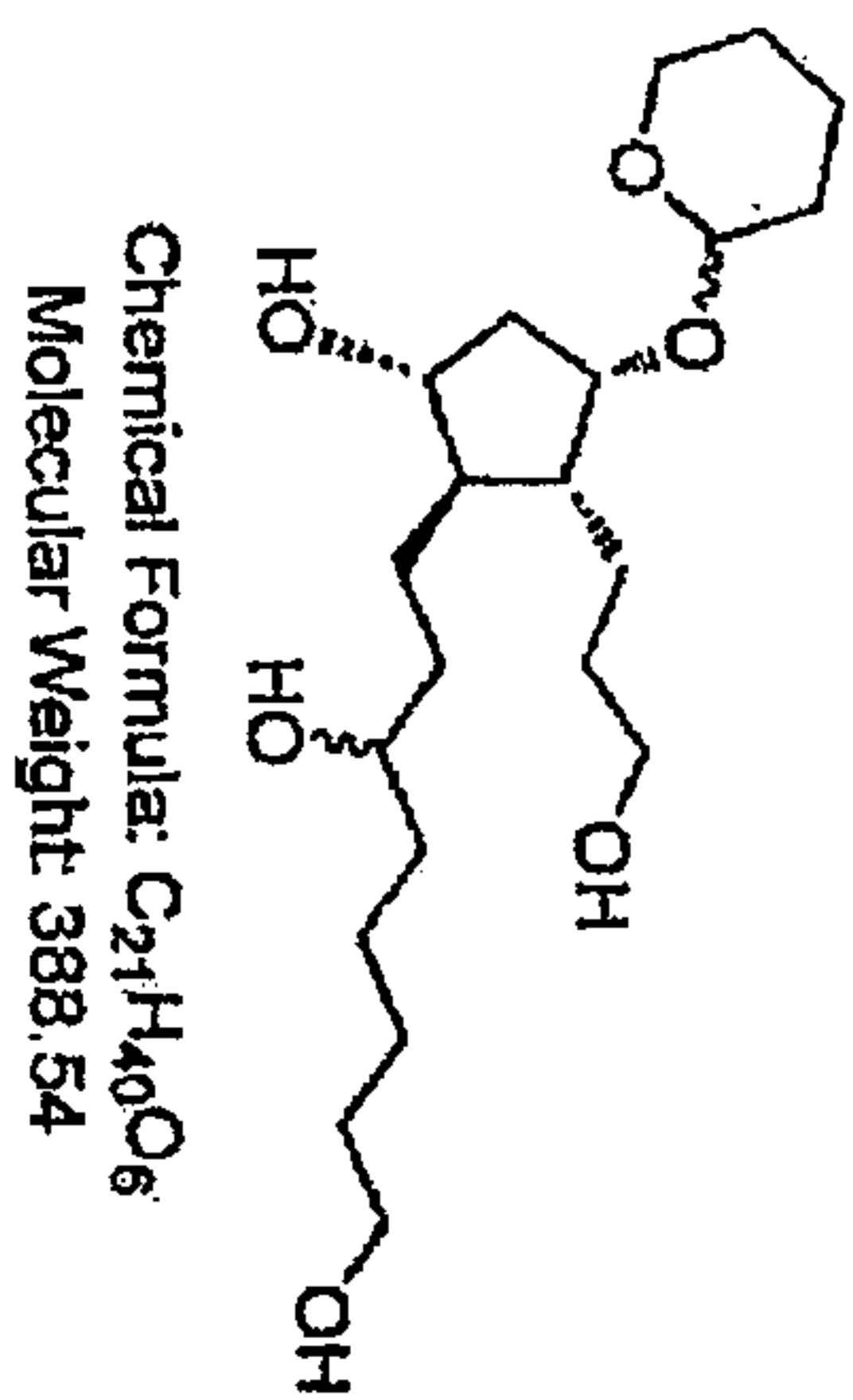
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639787 MHz

DATA PROCESSING

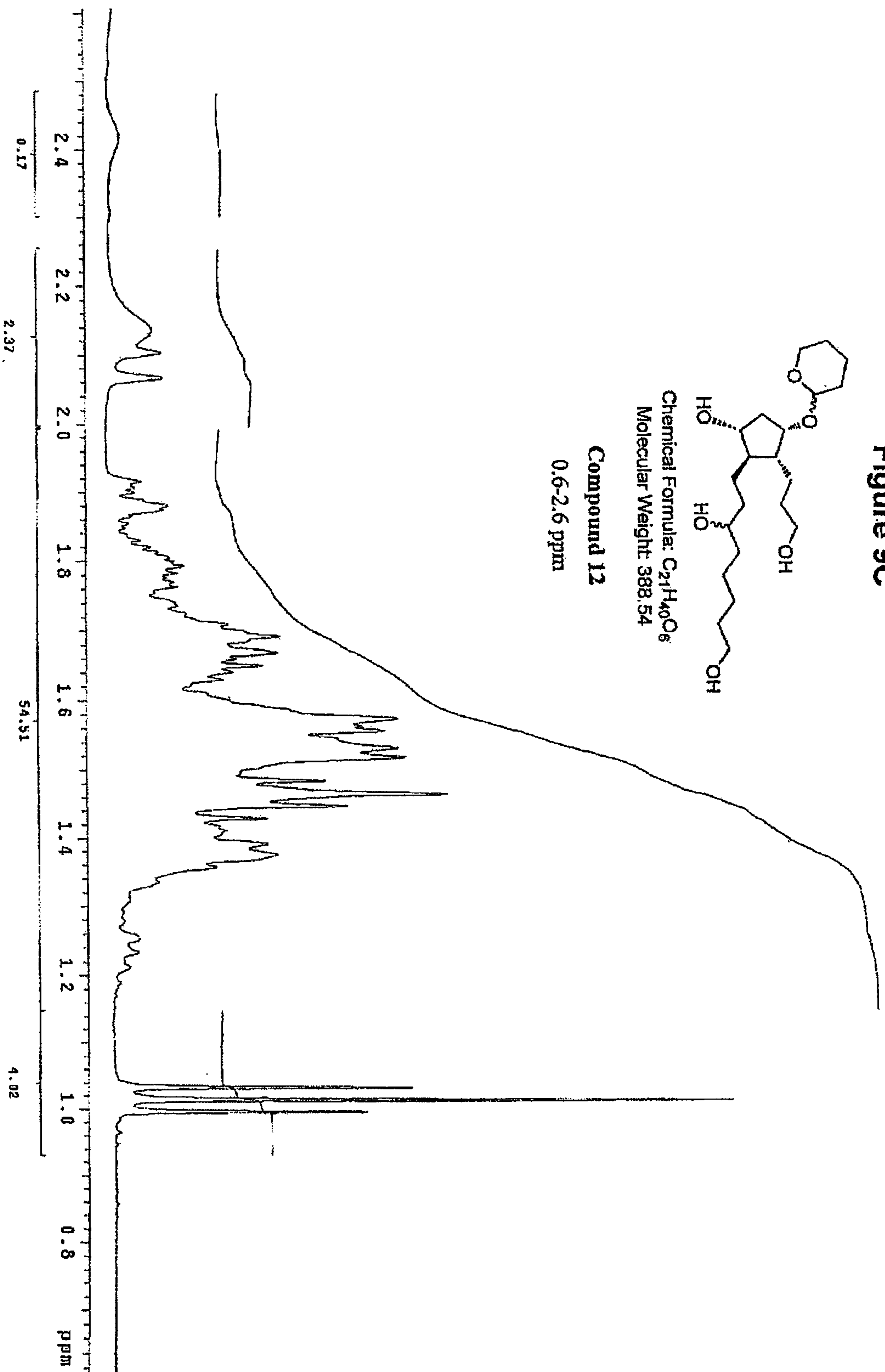
FT size 32768
Total time 1 minute

Figure 9B

Figure 9C



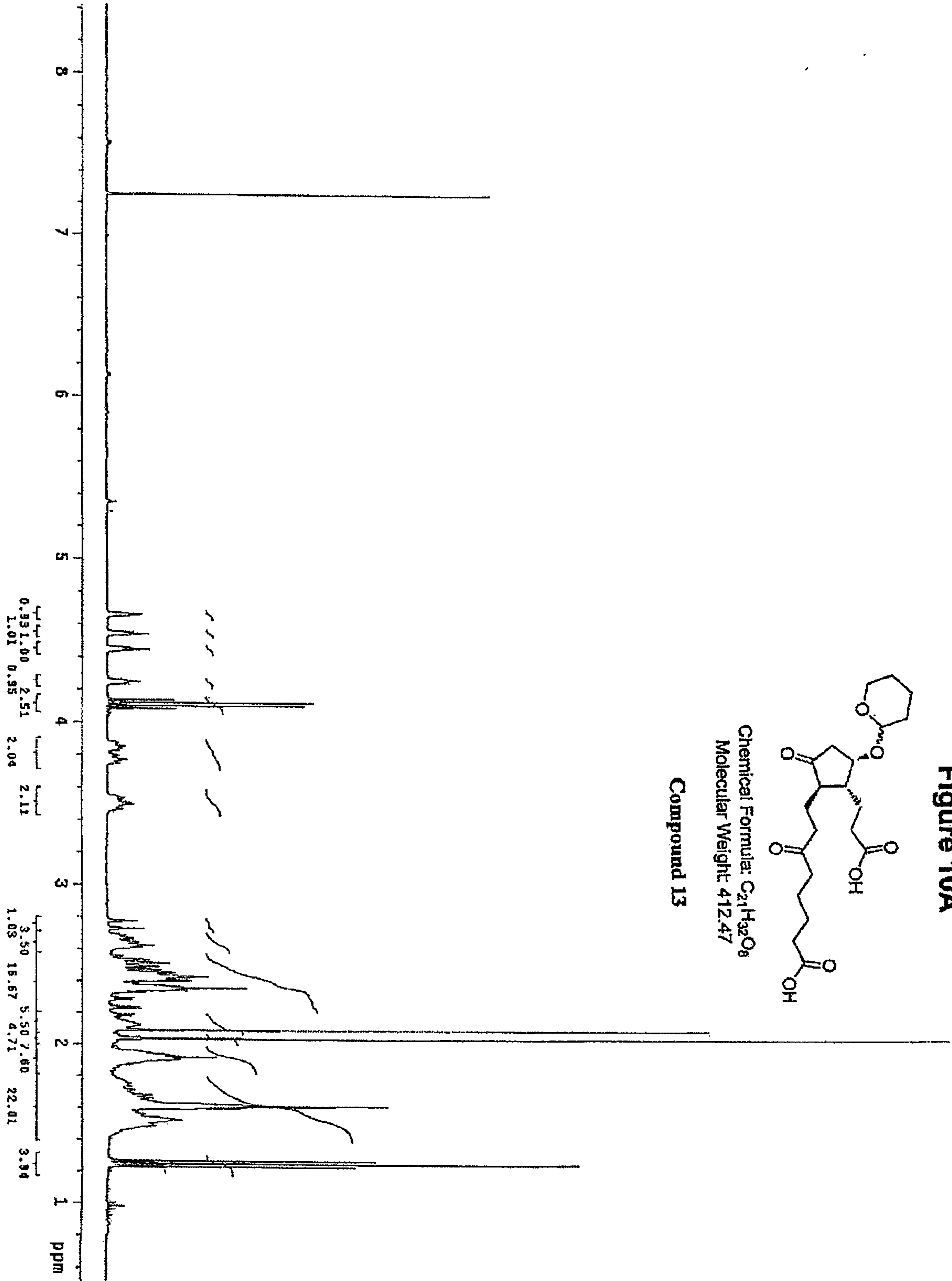
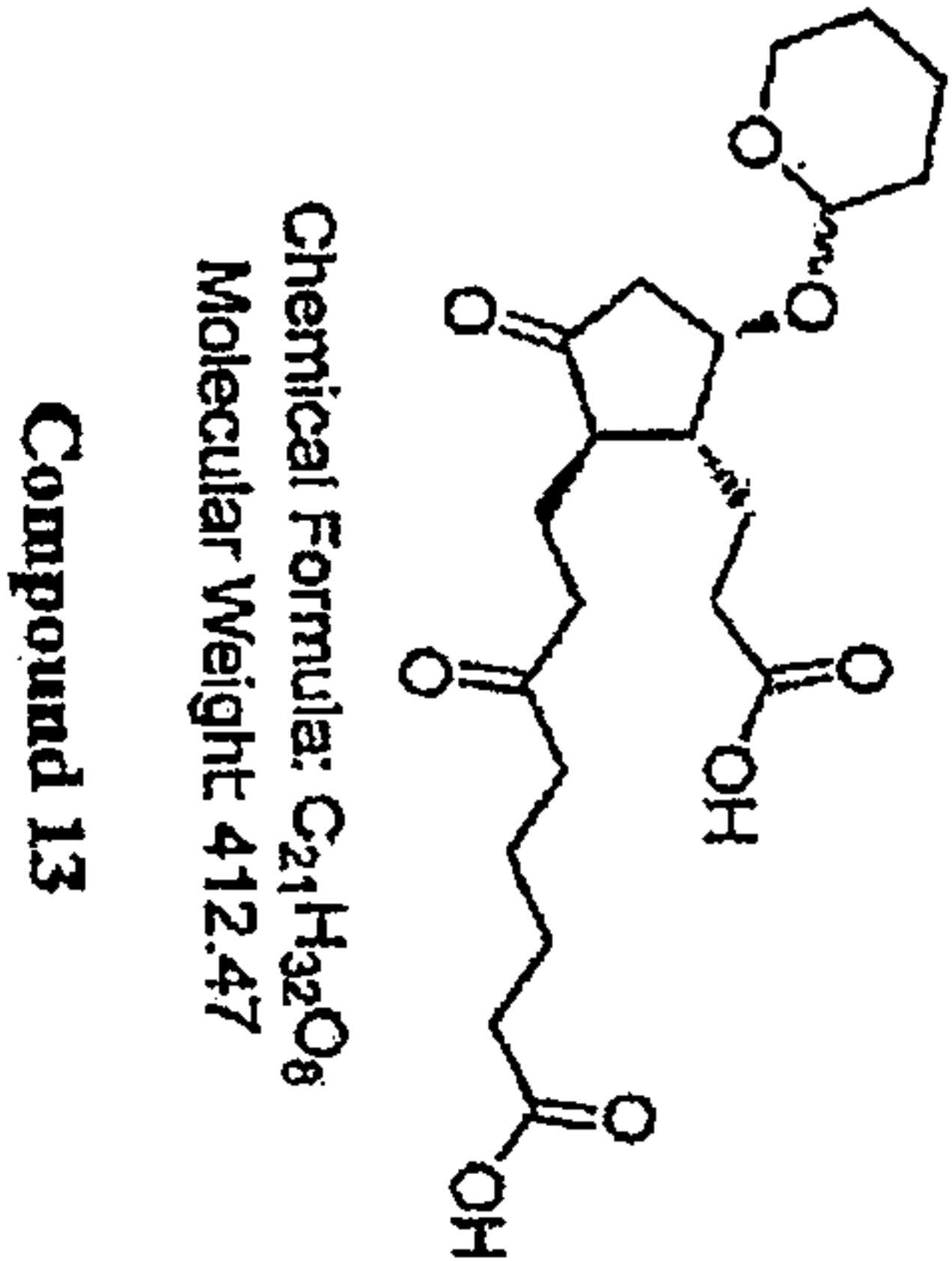
Compound 12
0.6-2.6 ppm



T11-168
Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE T11, 399.9639787 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 9C

Figure 10A



AK5-312

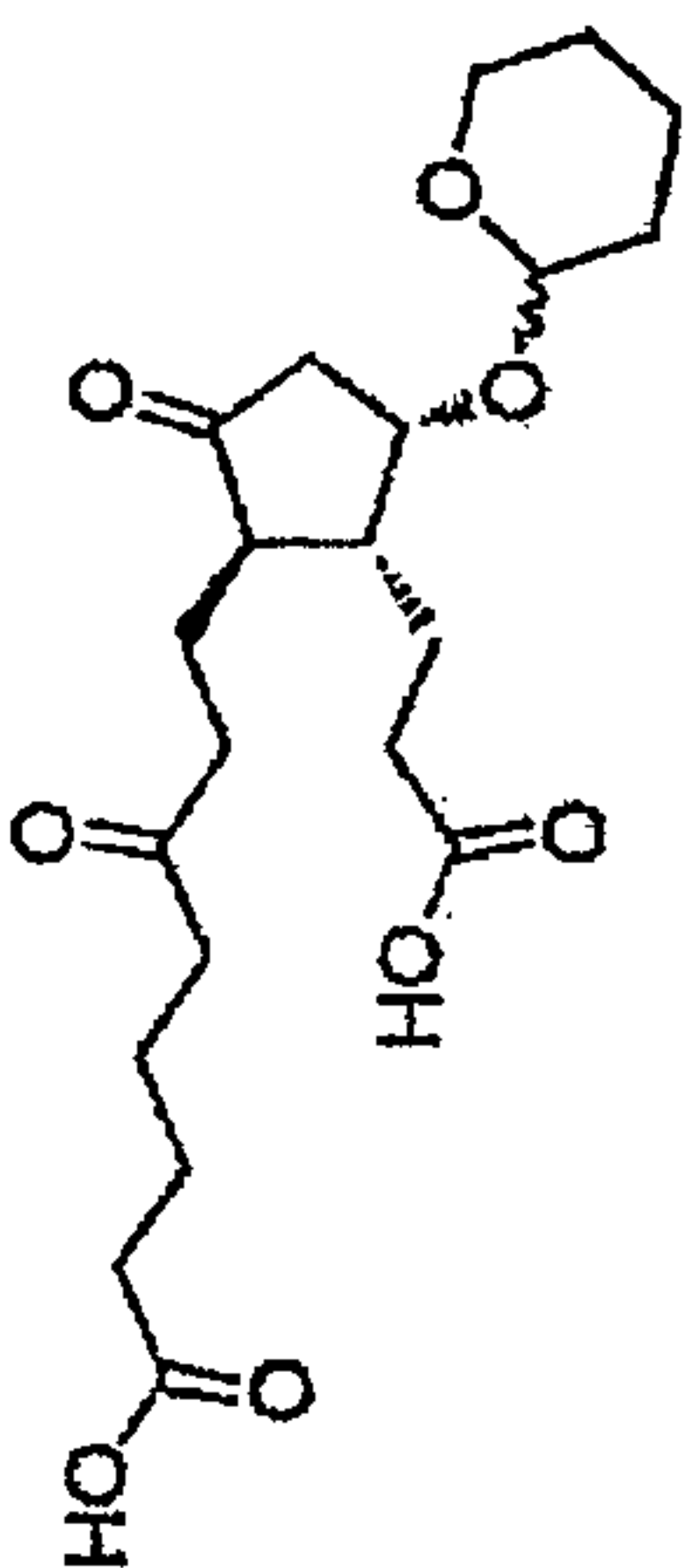
Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639874 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

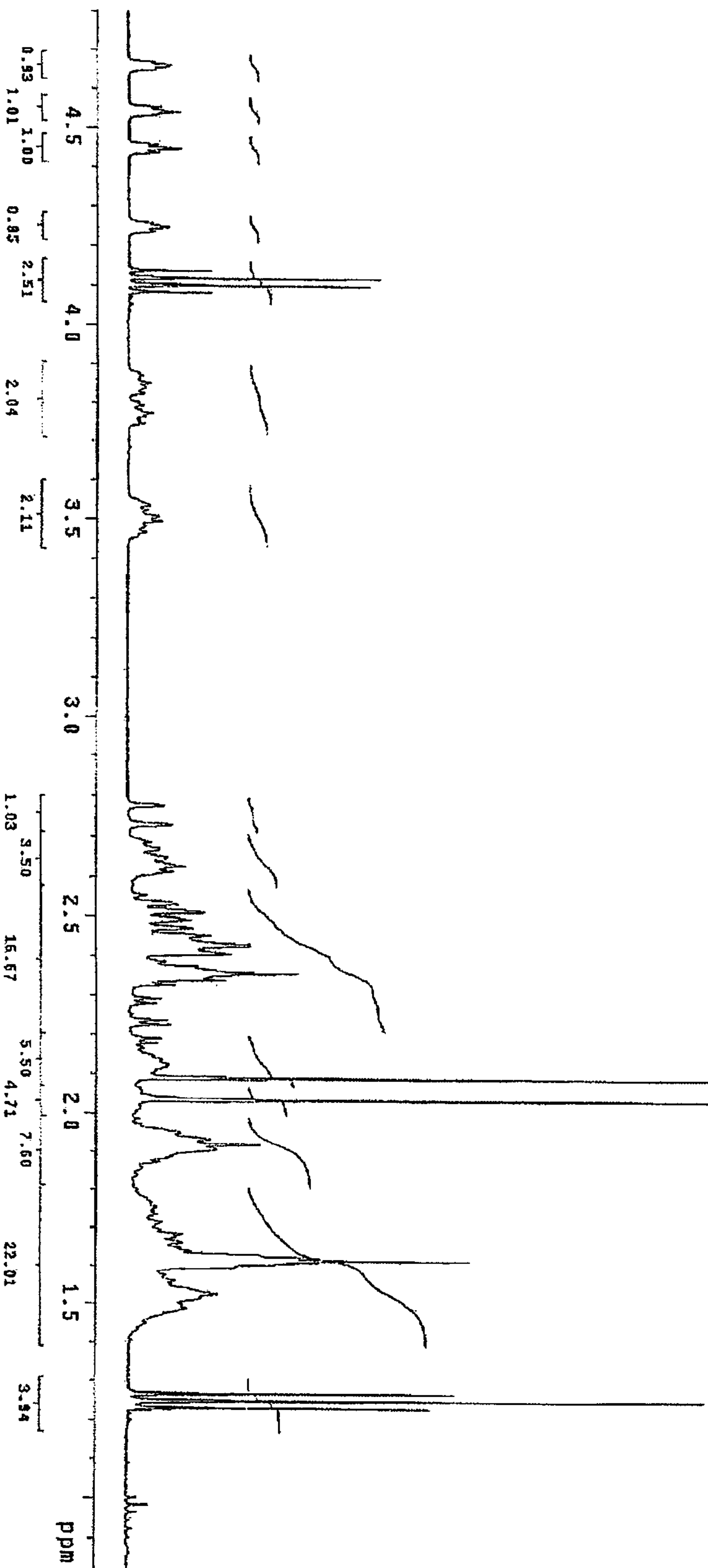
Figure 10A

Figure 10B



Chemical Formula: $C_{21}H_{32}O_8$
Molecular Weight 412.47

Compound 13
0.8-4.8 ppm



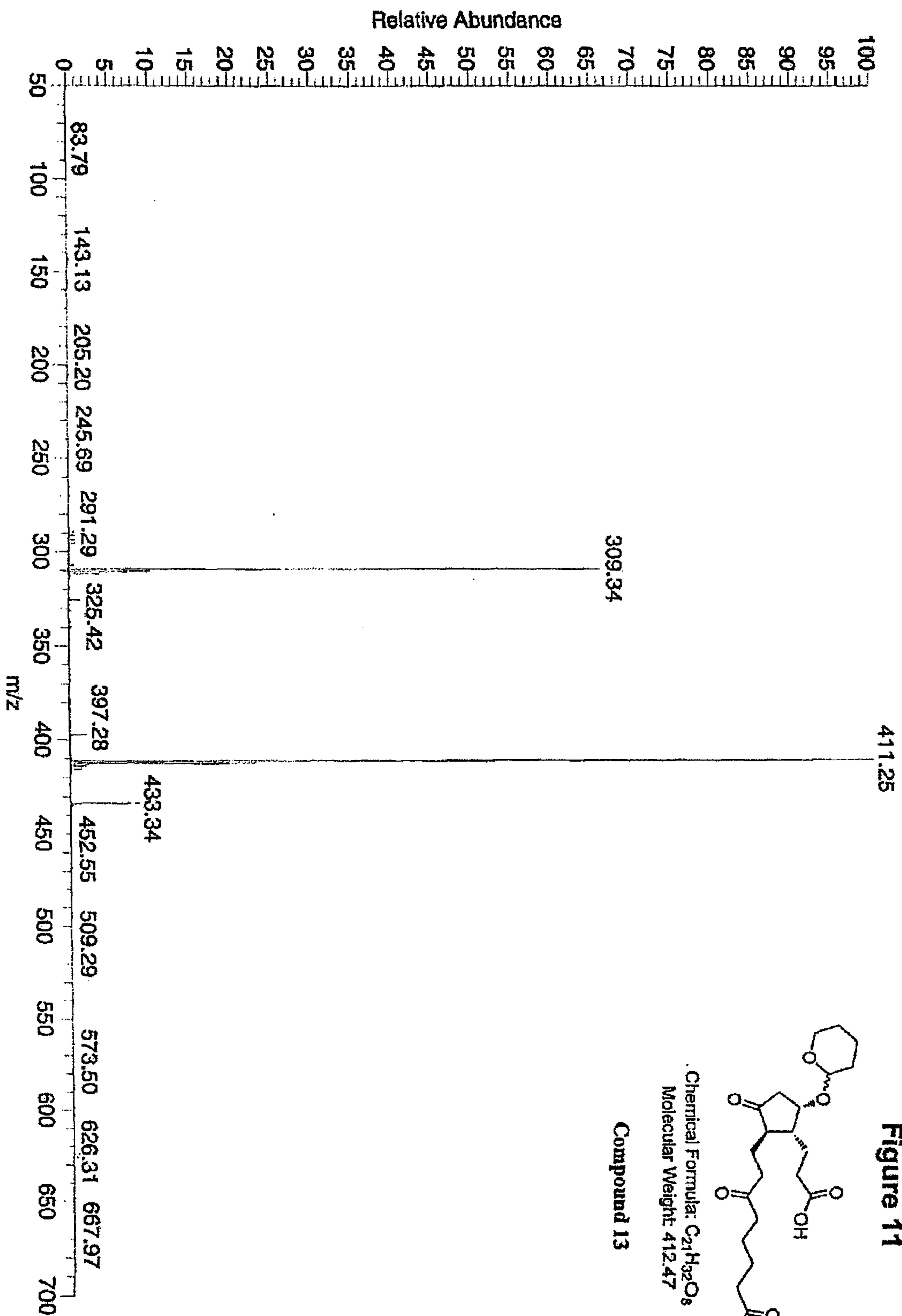
AK5-312

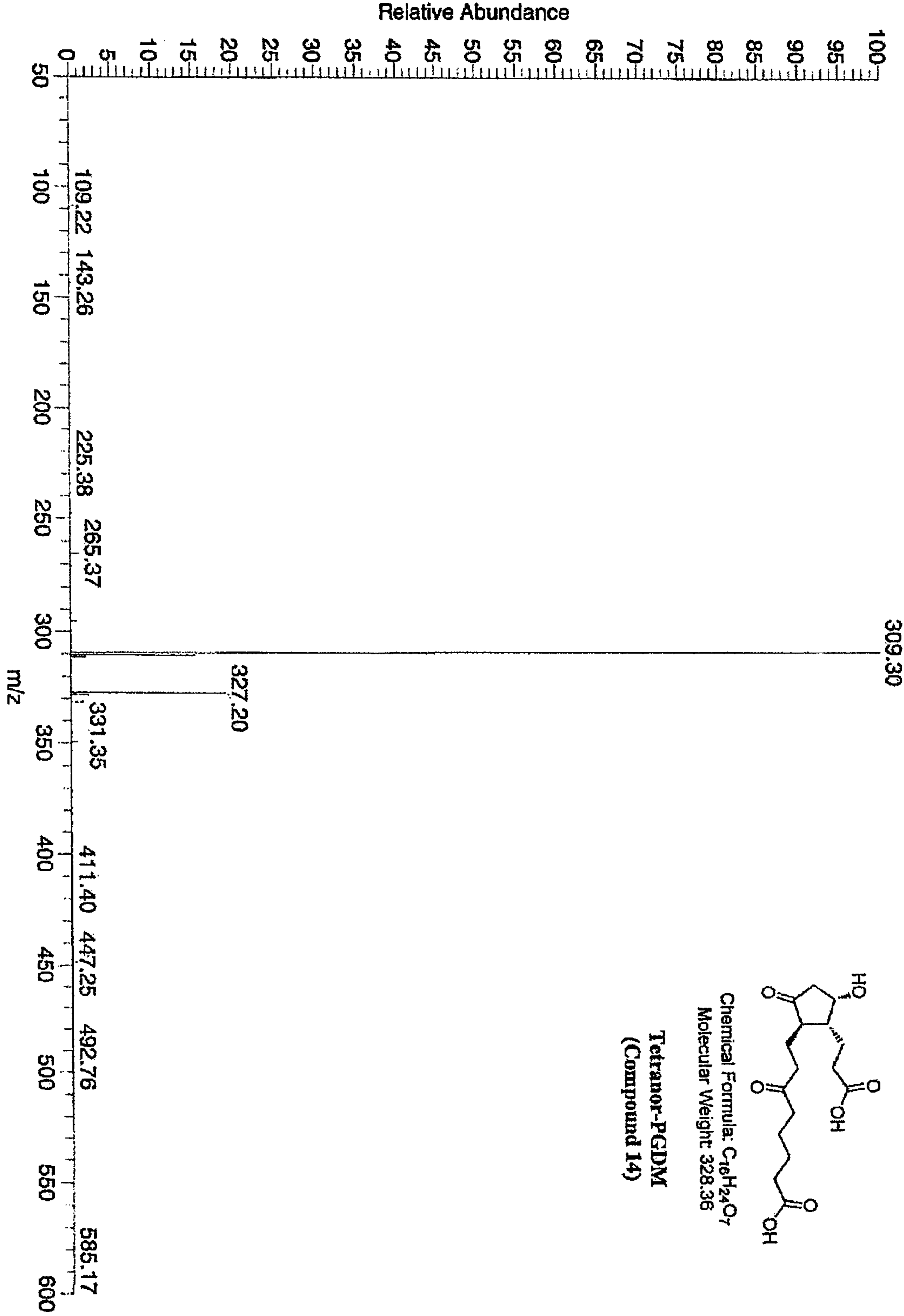
Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639874 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

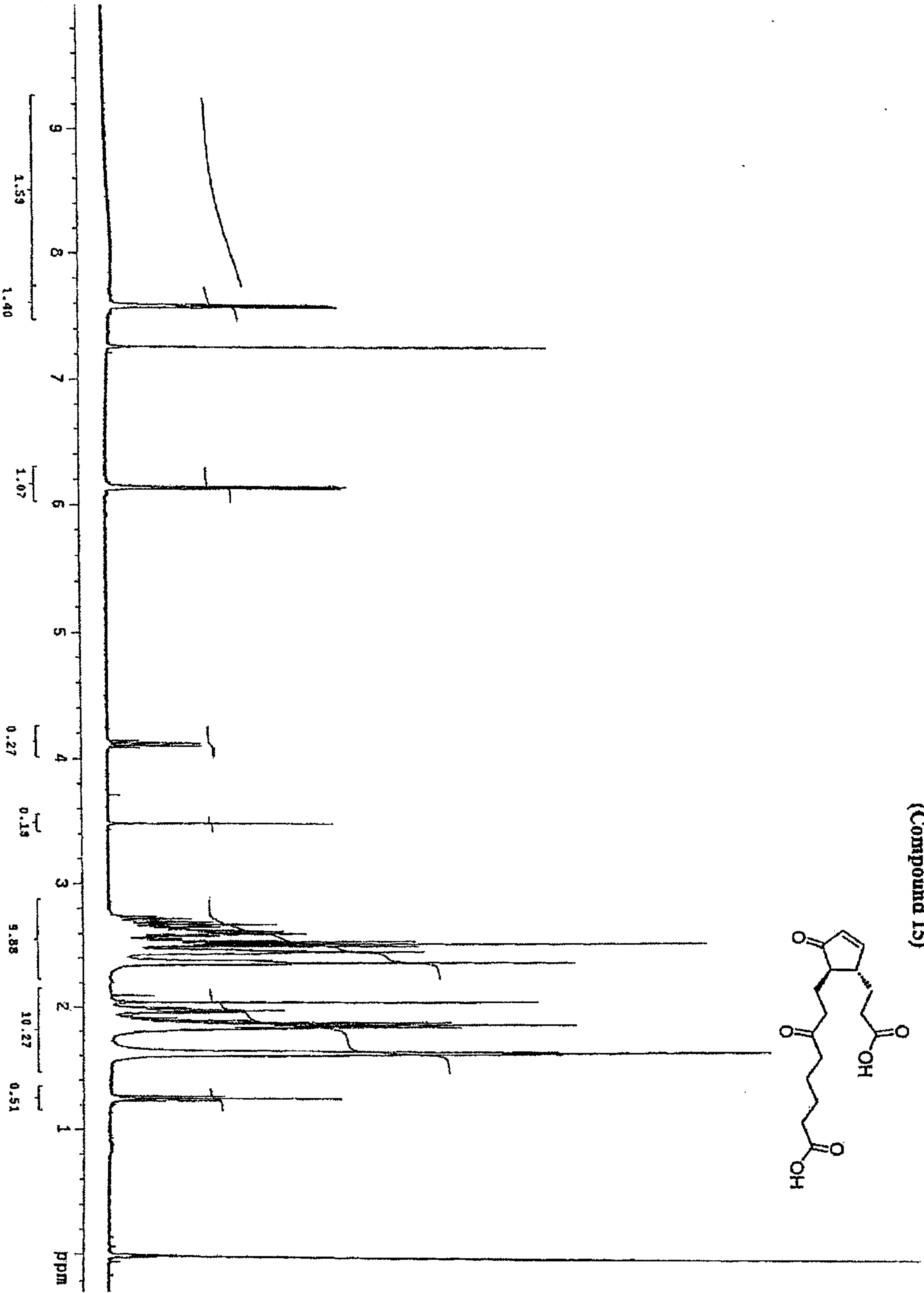
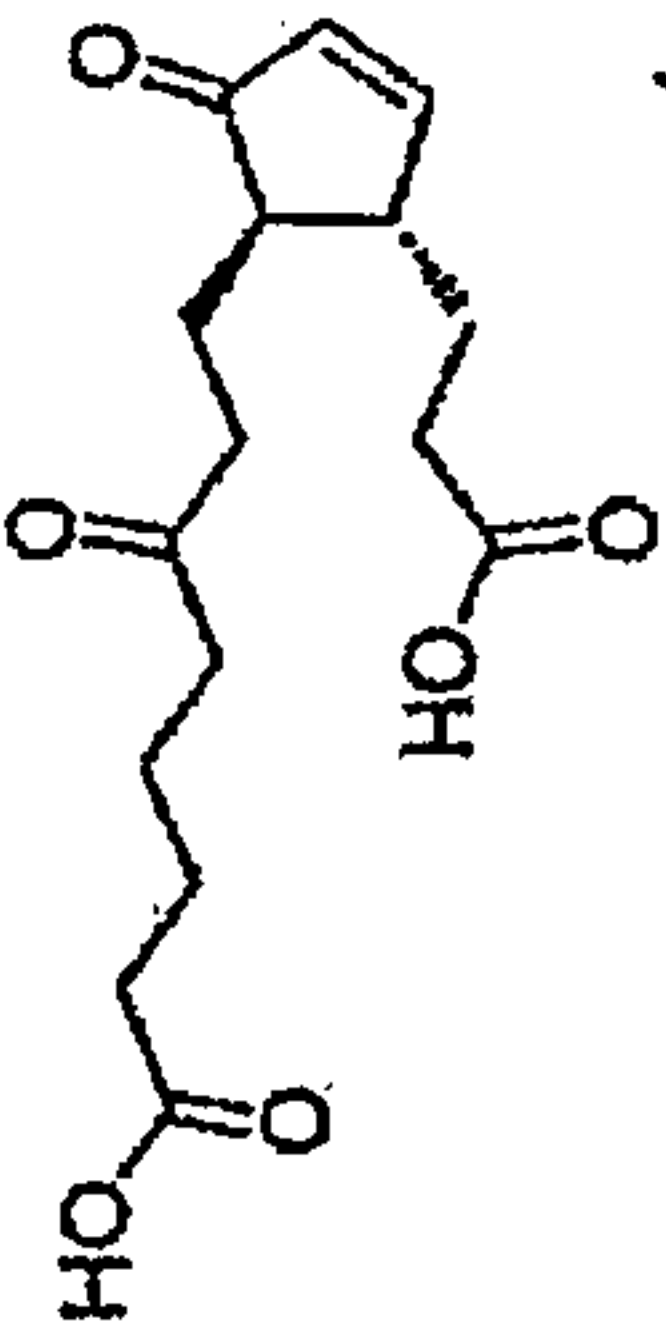
Figure 10B





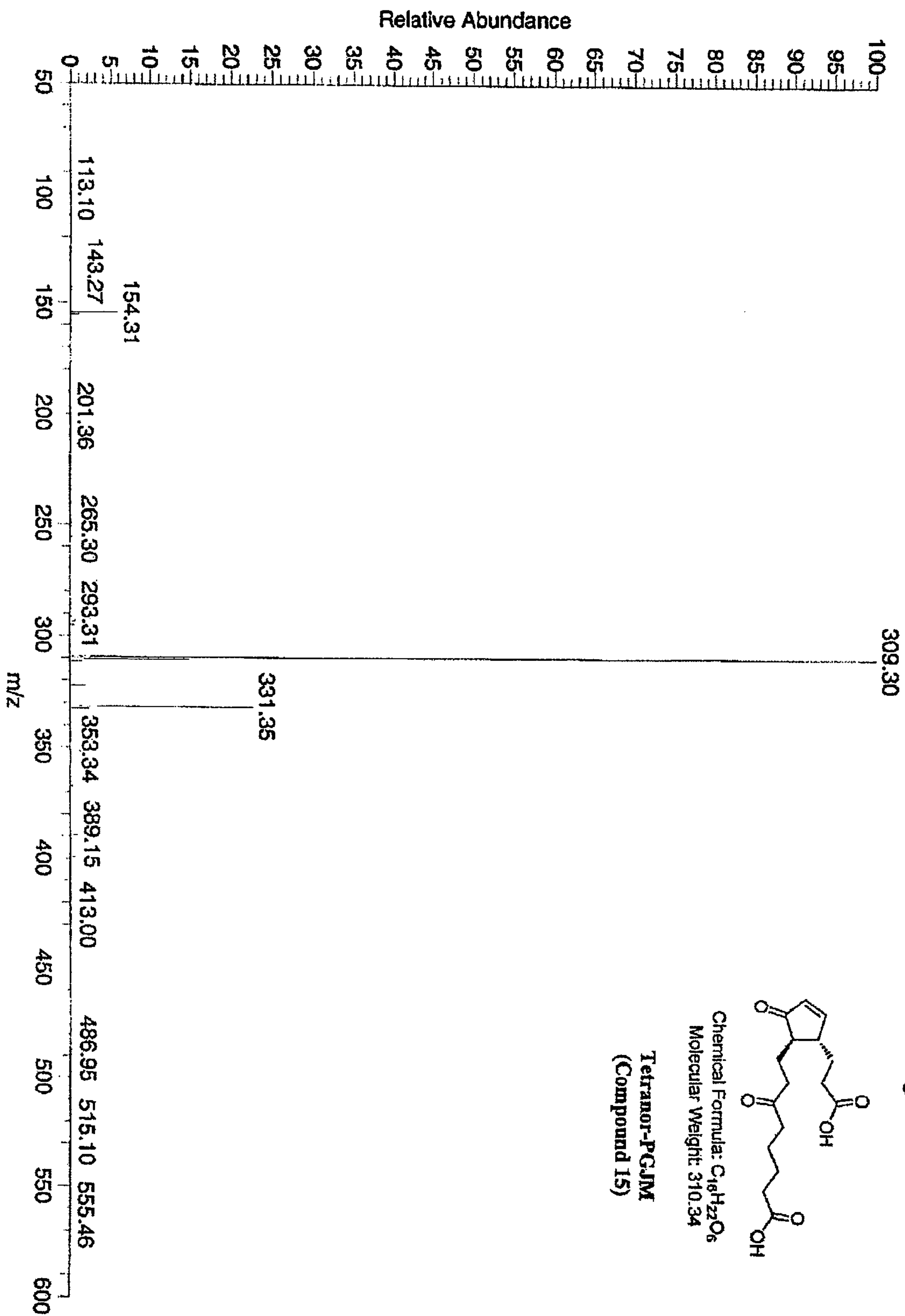
Tetranor-PGJM
(Compound 15)

Figure 13



FT1-135 H7
Solvent: CDCl3
Ambient temperature
INOVA-400 "Varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 6000.2 Hz
Arrayed repetitions
OBSERVE H1, 399.9639852 MHz
DATA PROCESSING
FT size 35536
Total time 1 minute

Figure 13



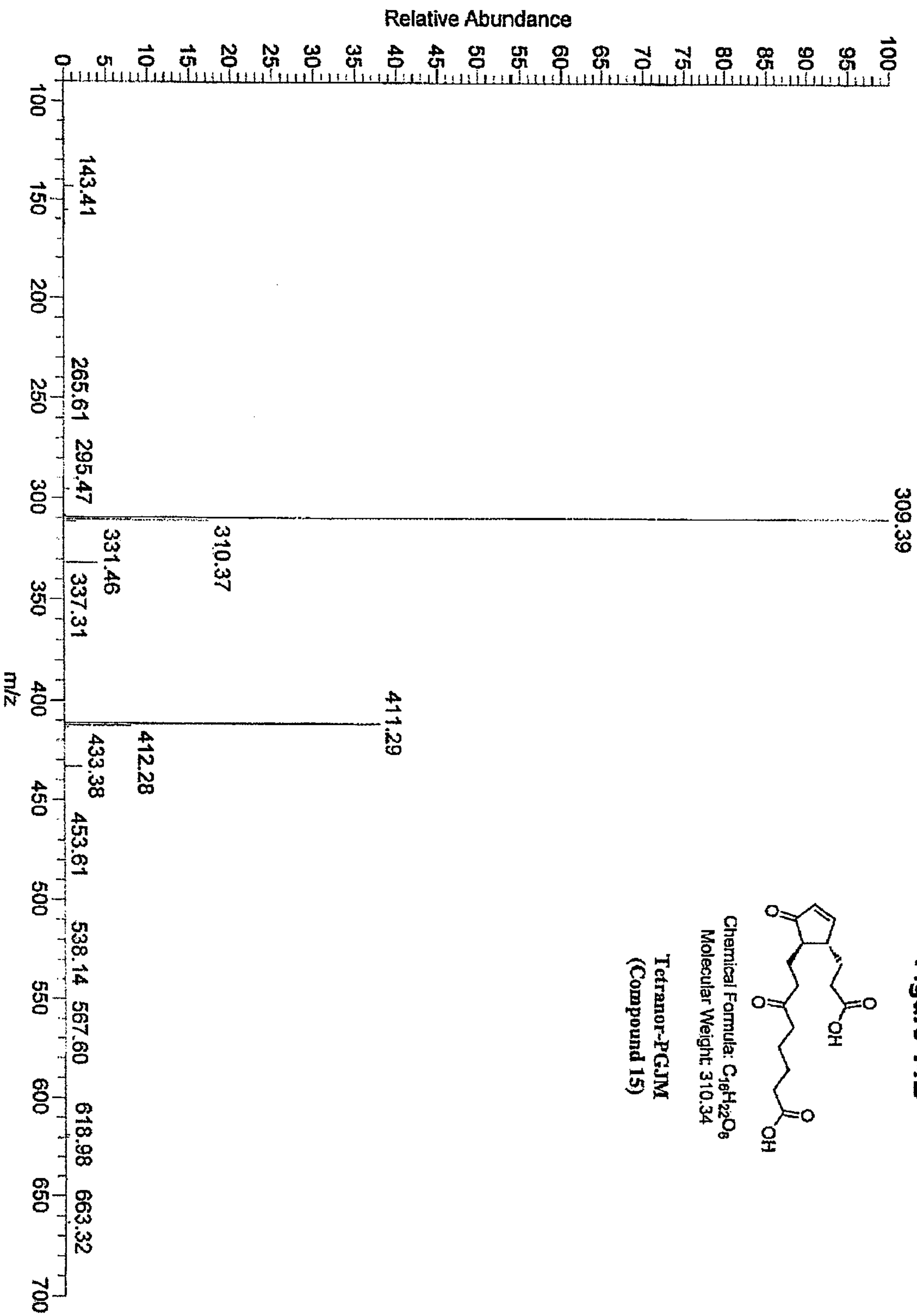
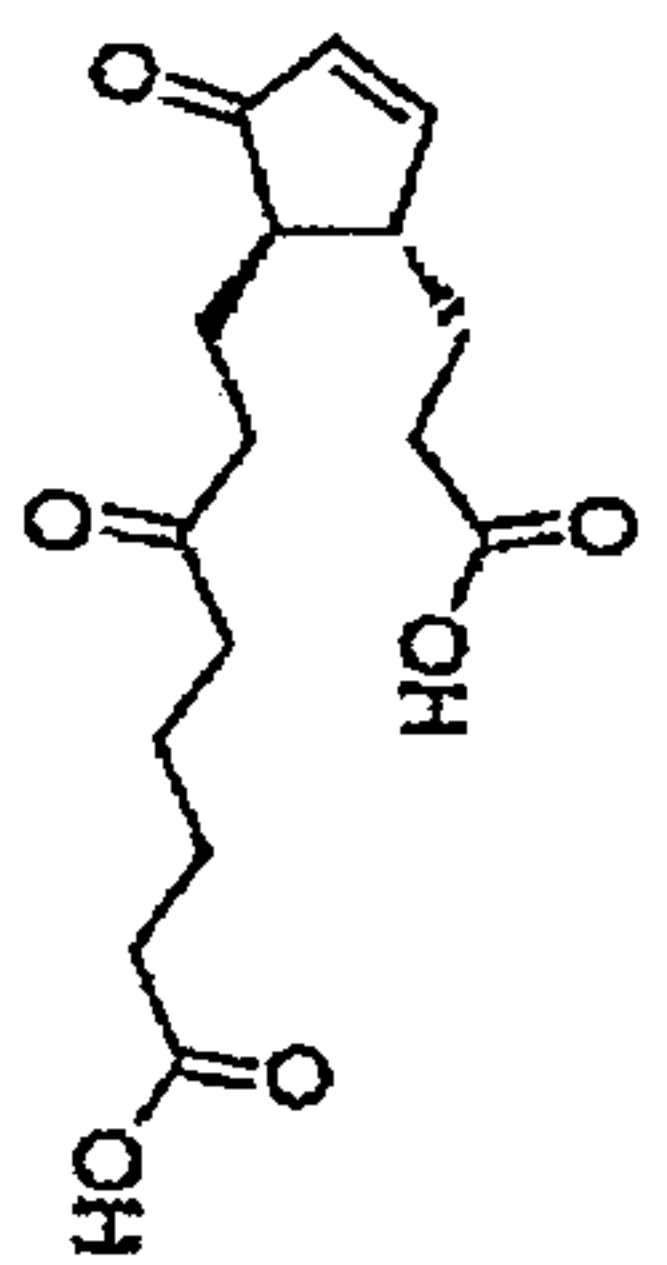
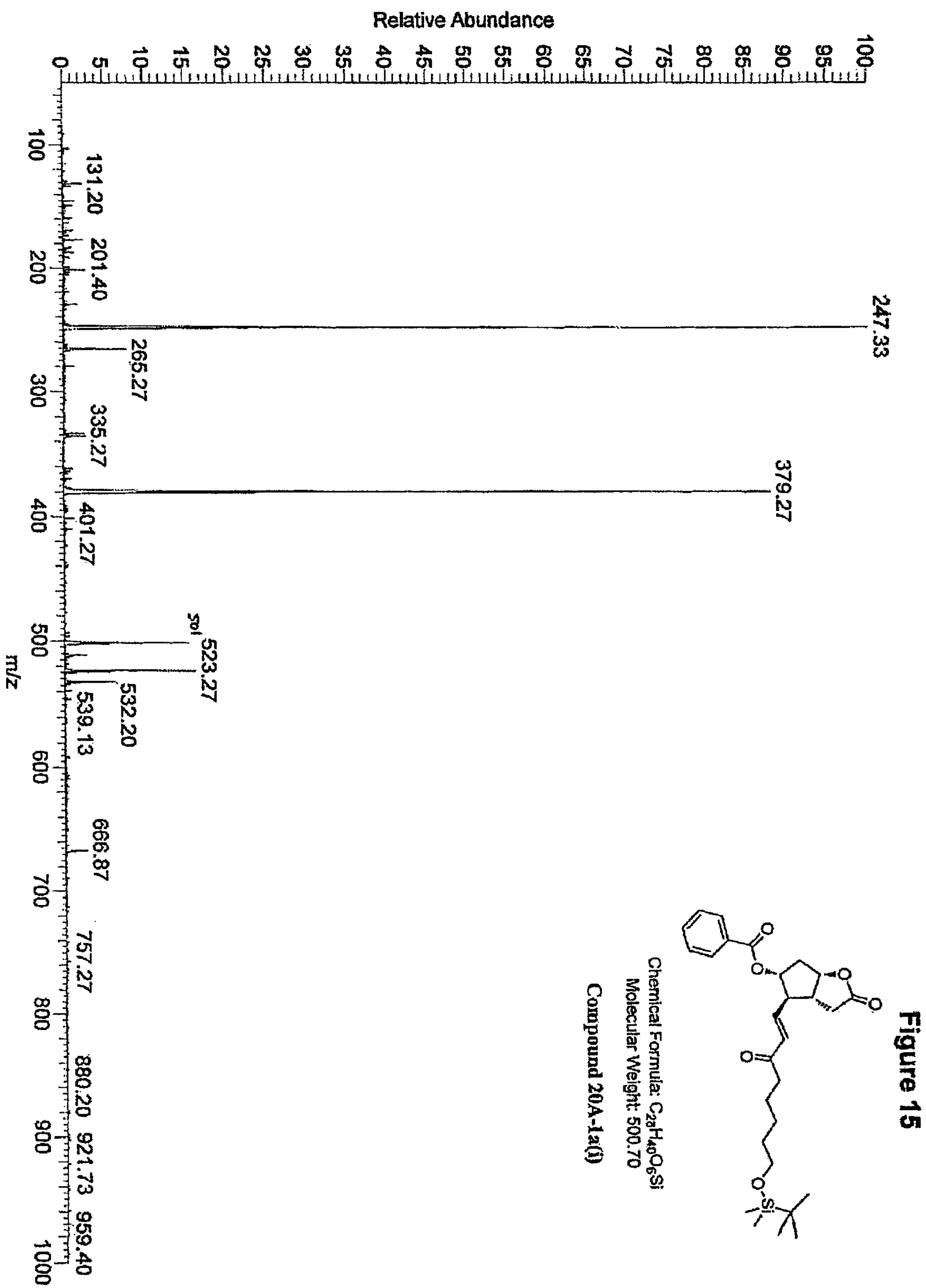


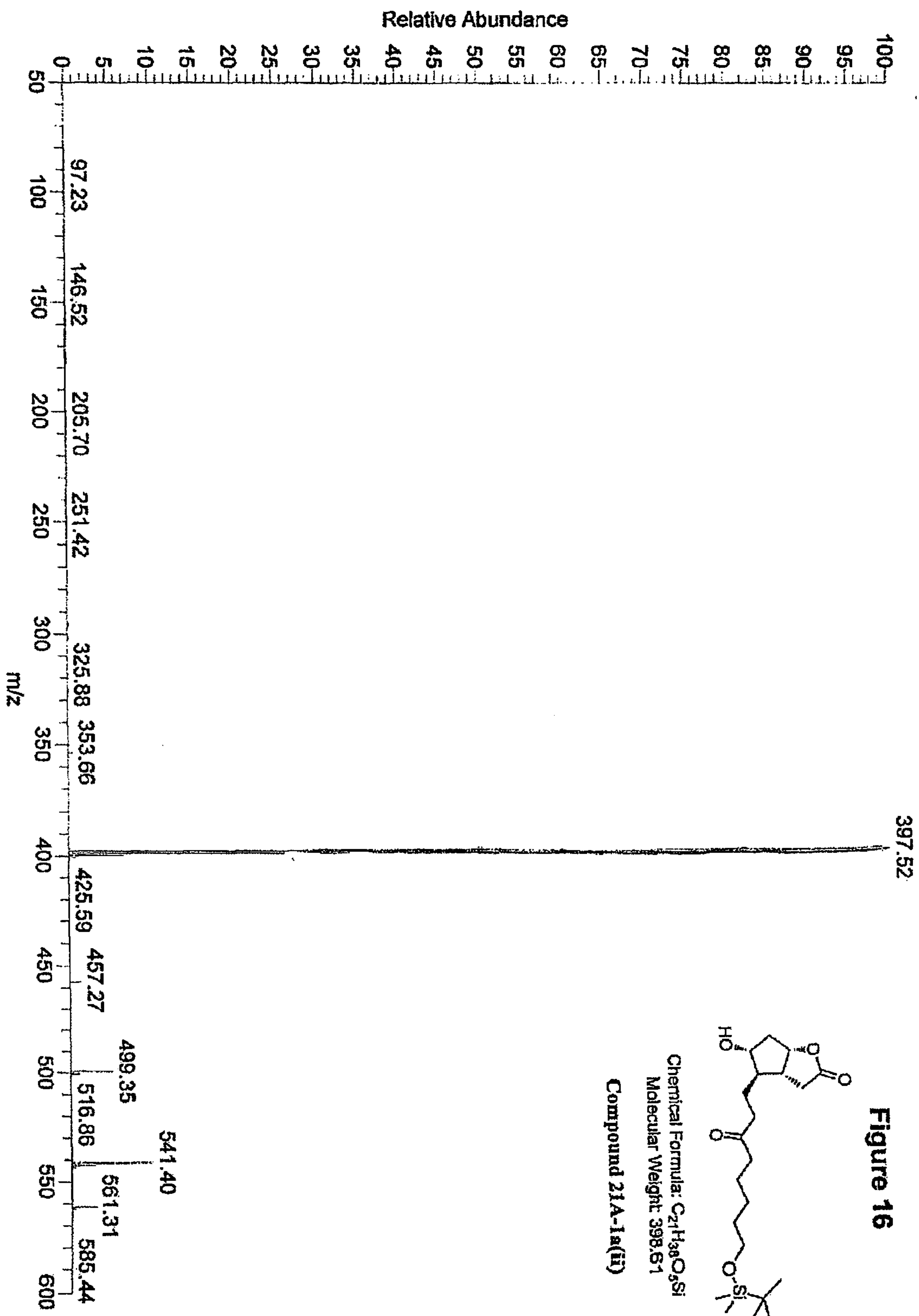
Figure 14B

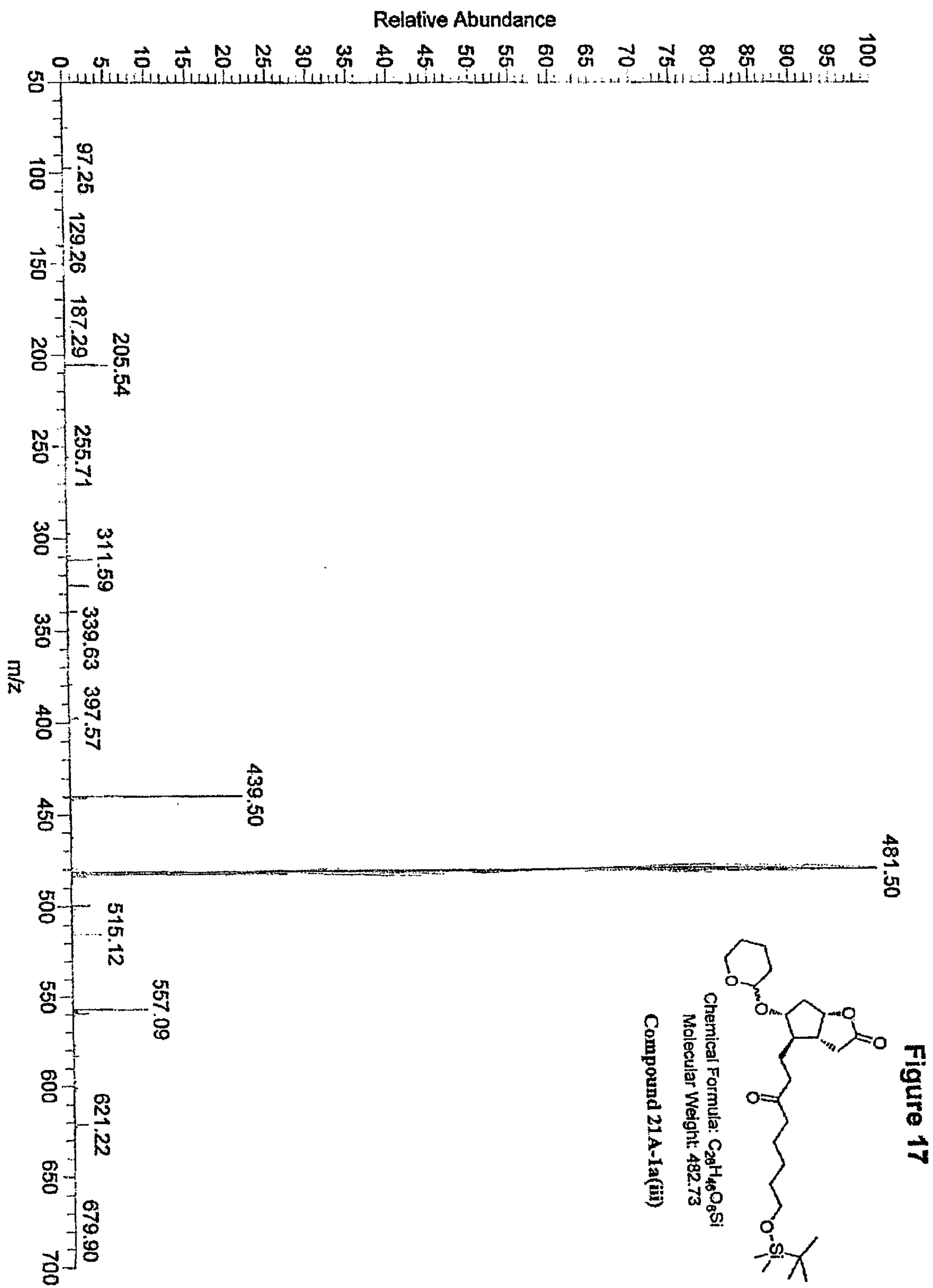


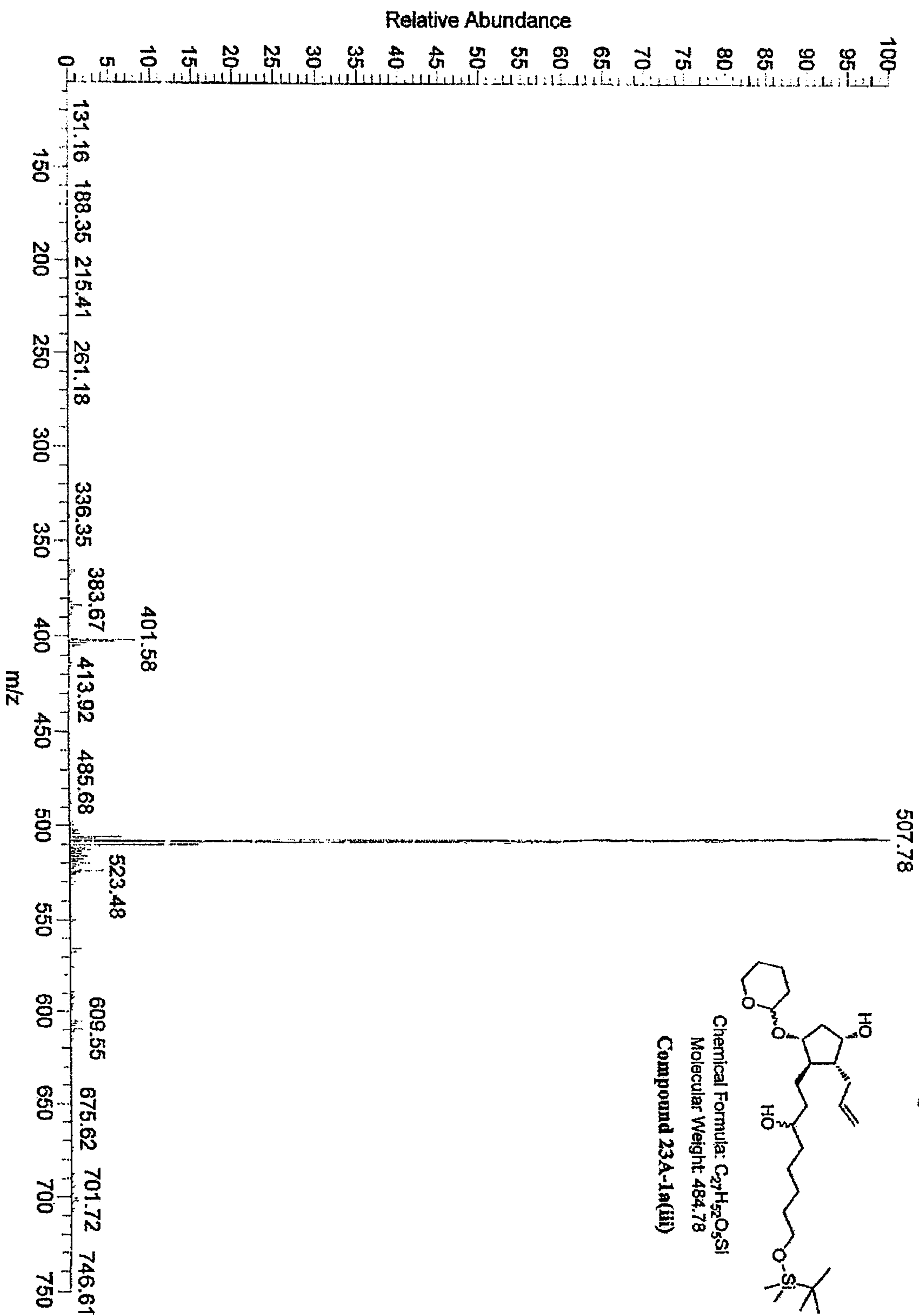
Chemical Formula: C₁₆H₂₂O₆
Molecular Weight: 310.34

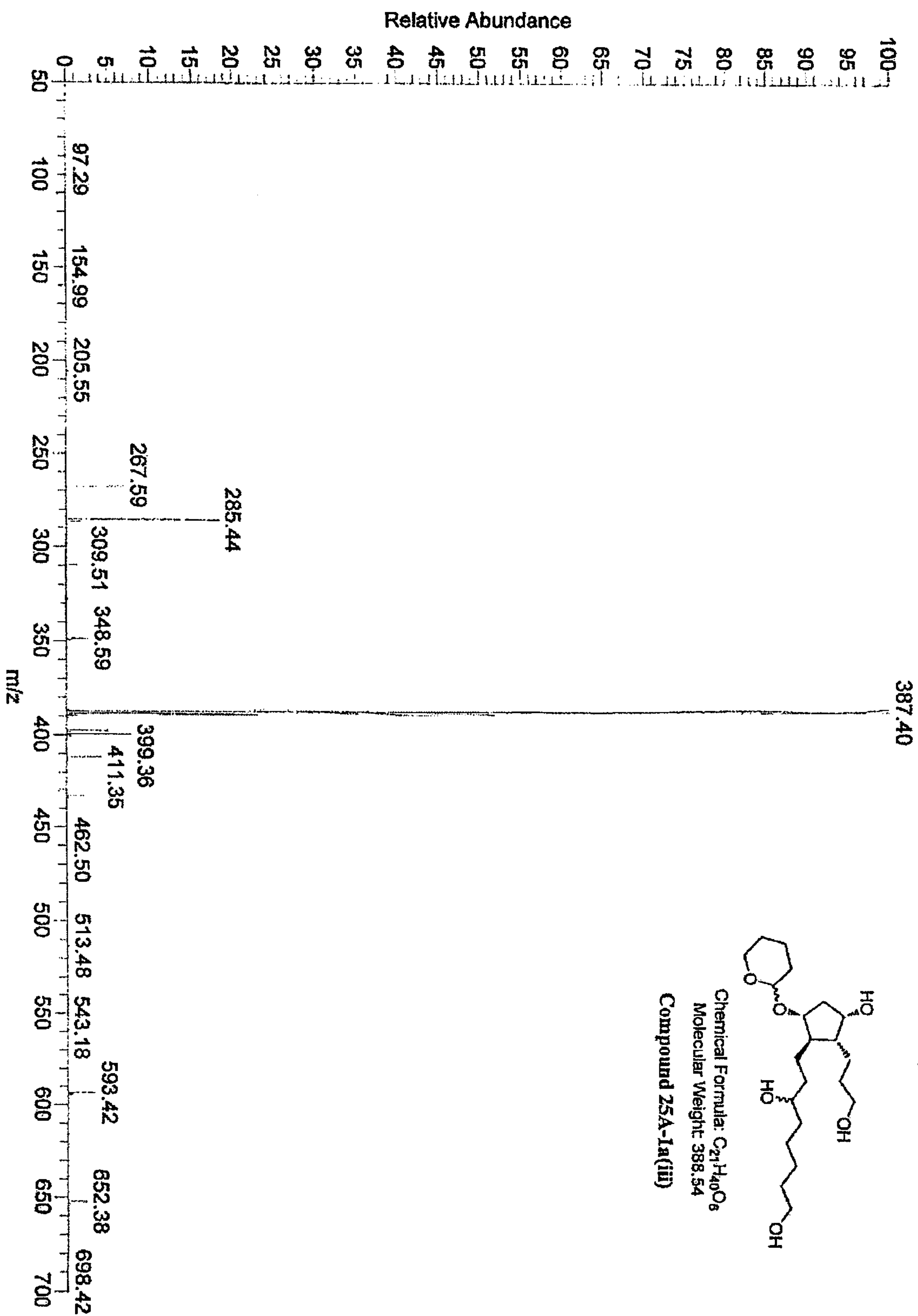
Tetranor-PGJM
(Compound 15)











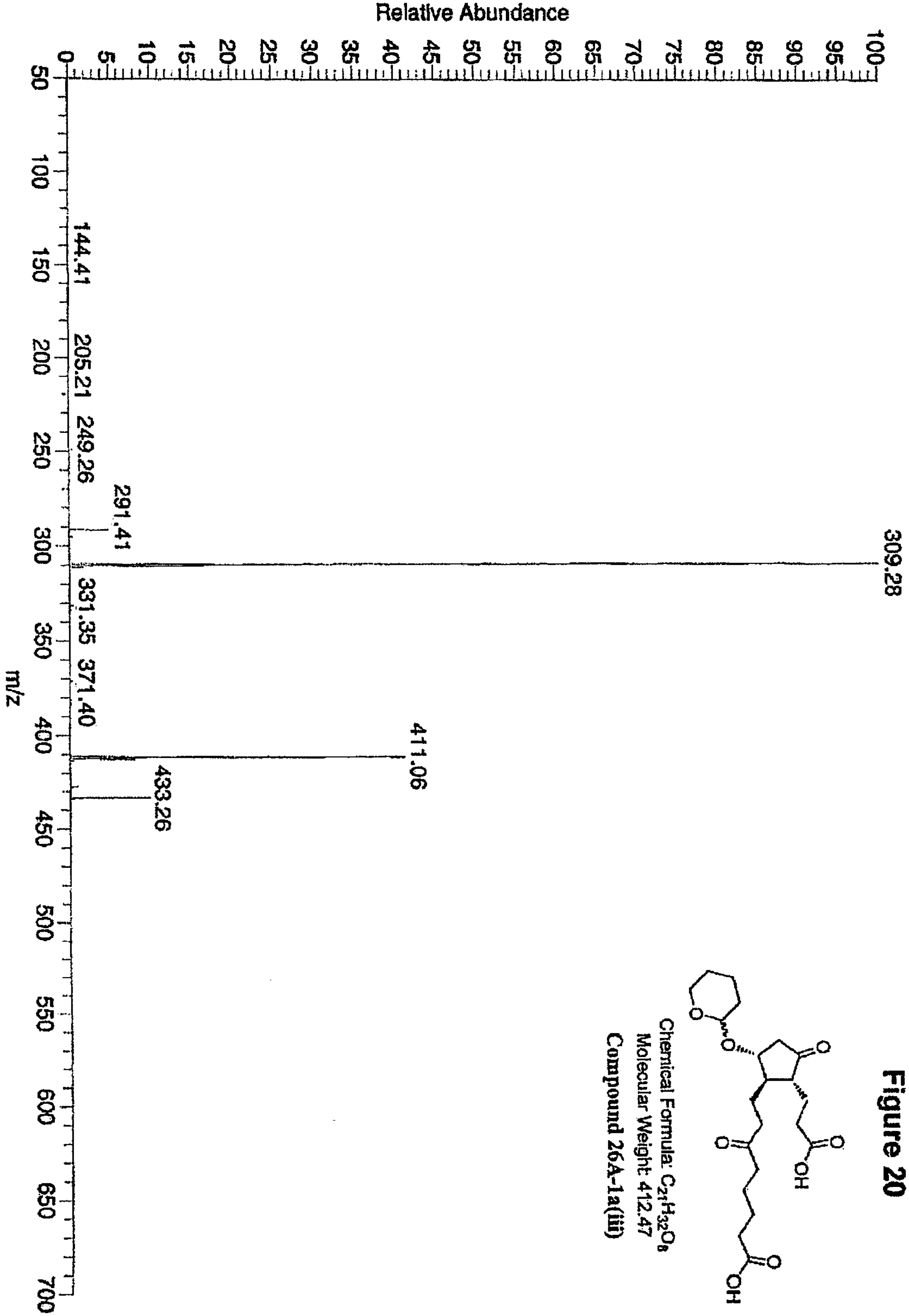
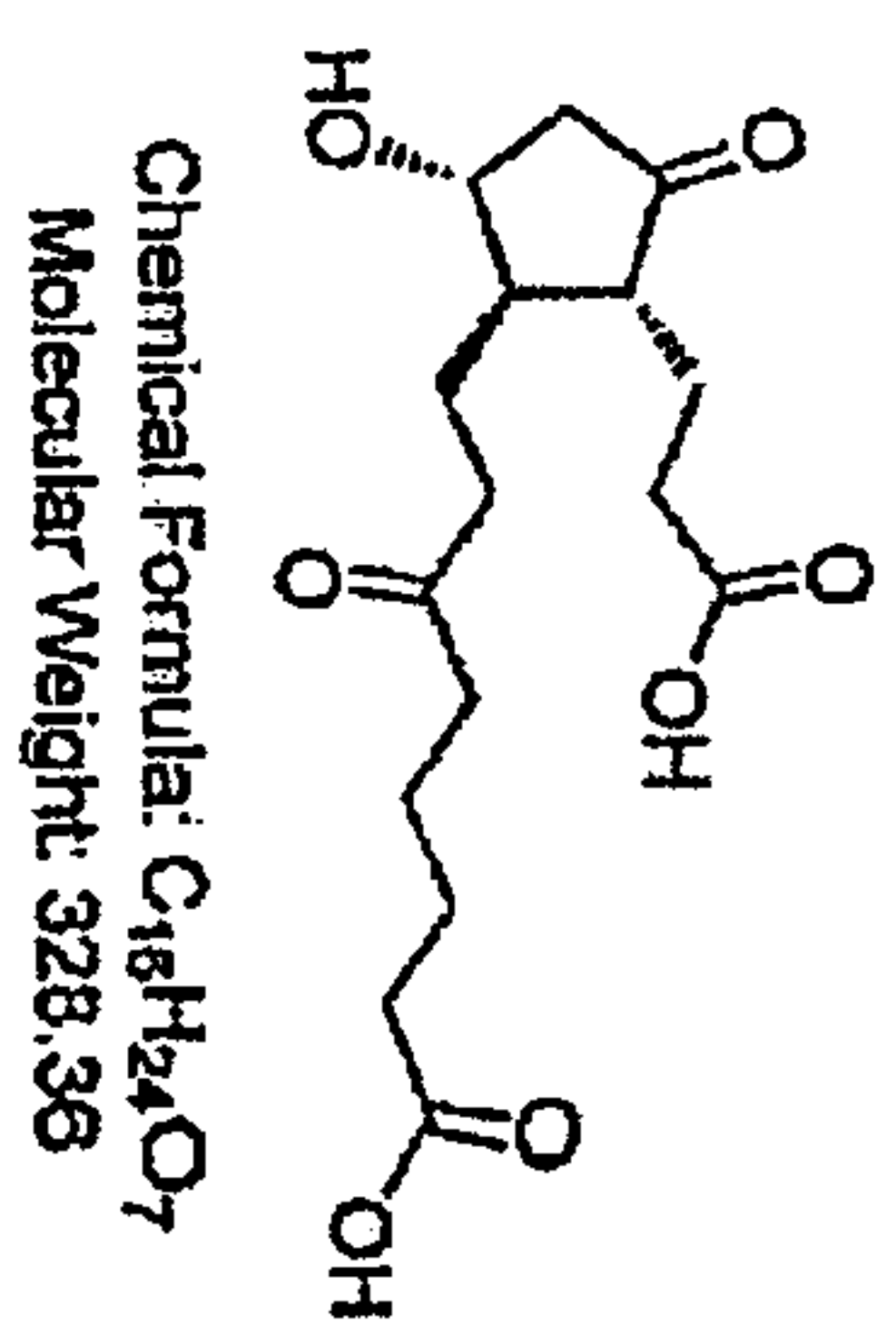
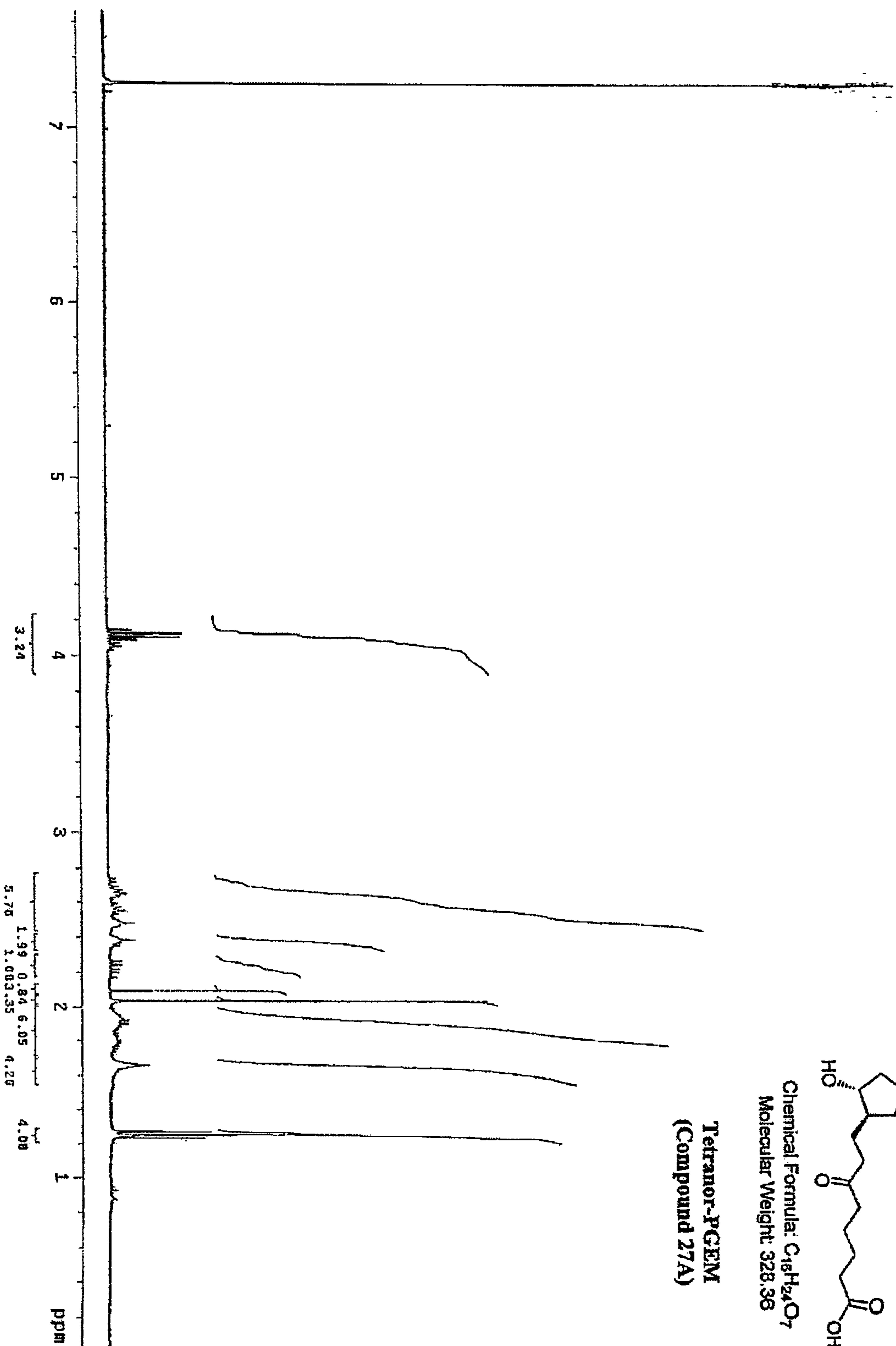


Figure 21A



**Tetranor-PGEM
(Compound 27A)**



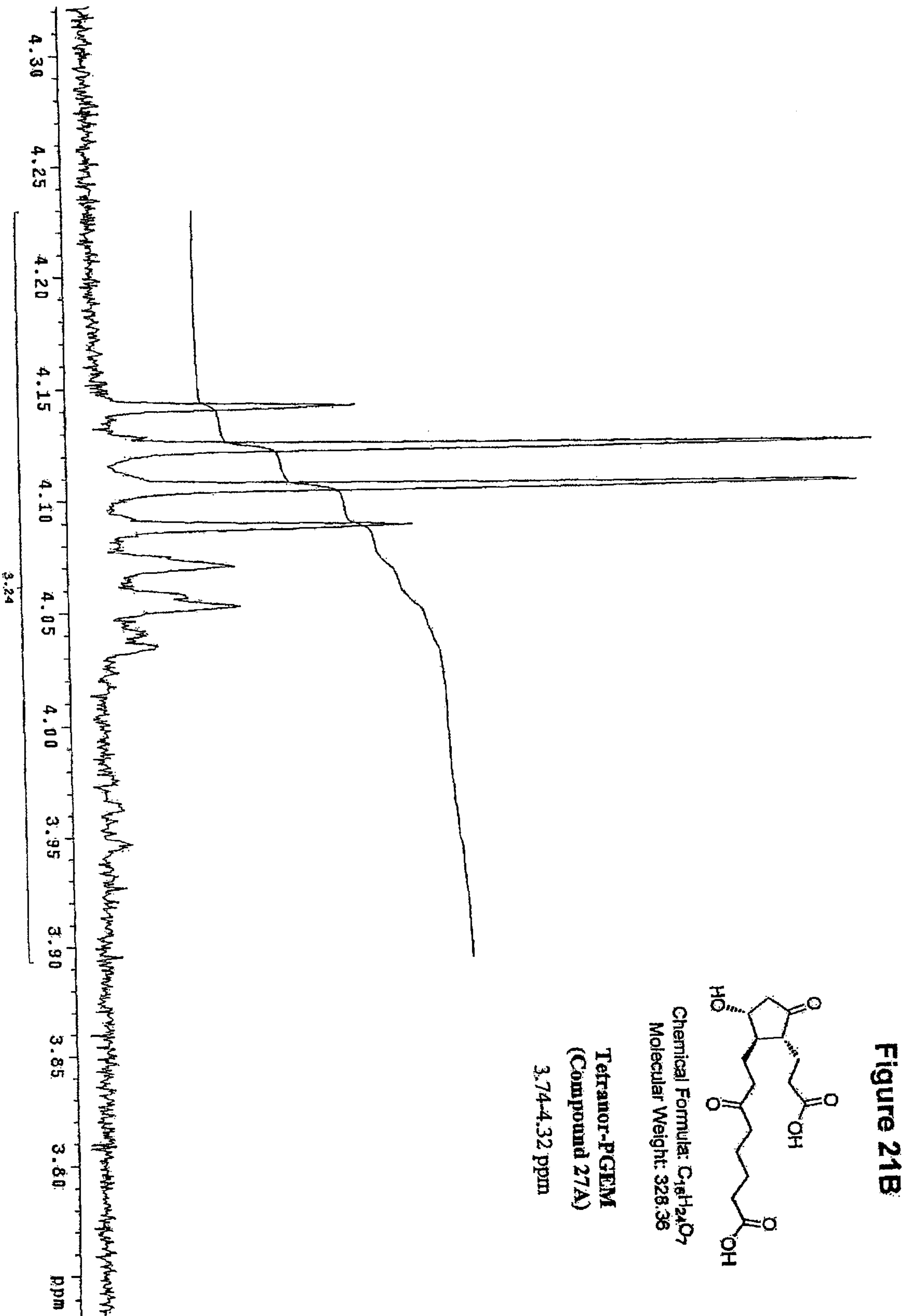
AK8-S7

Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse Arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639874 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 21A

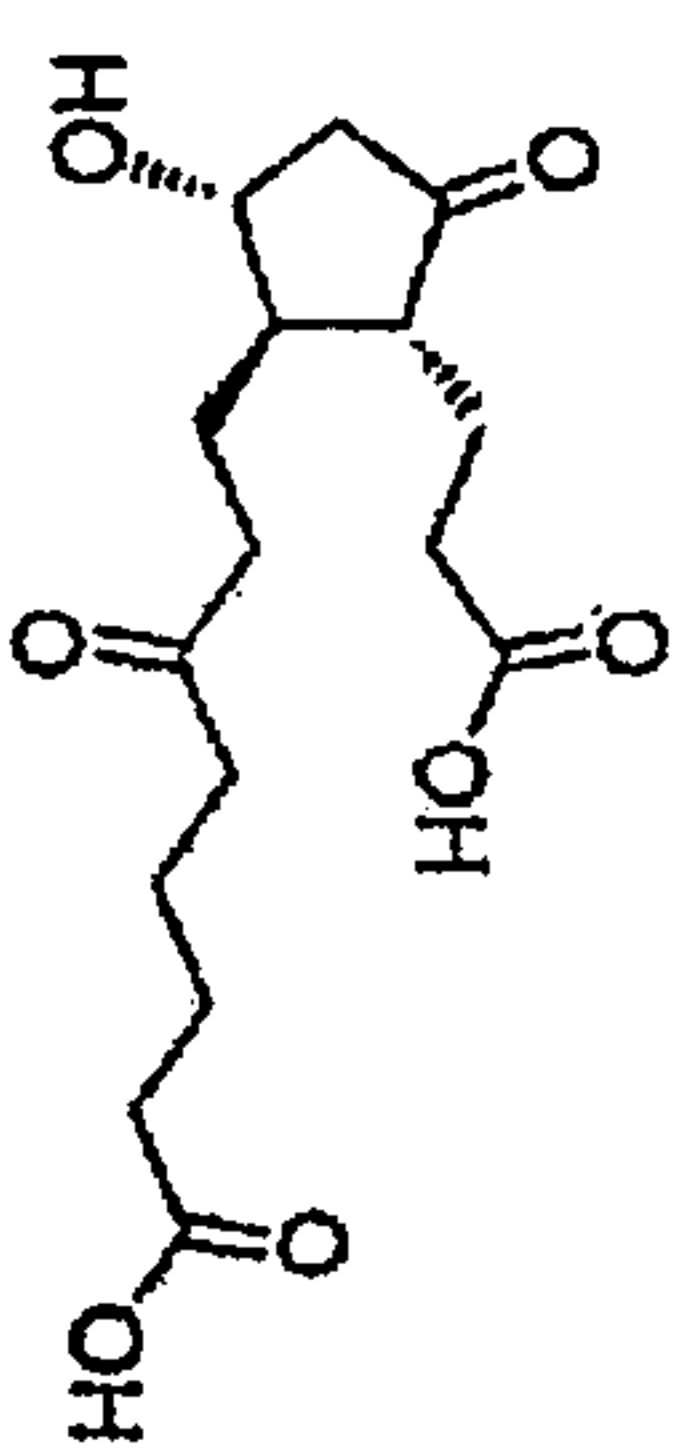


AK8-57

Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639874 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 21B

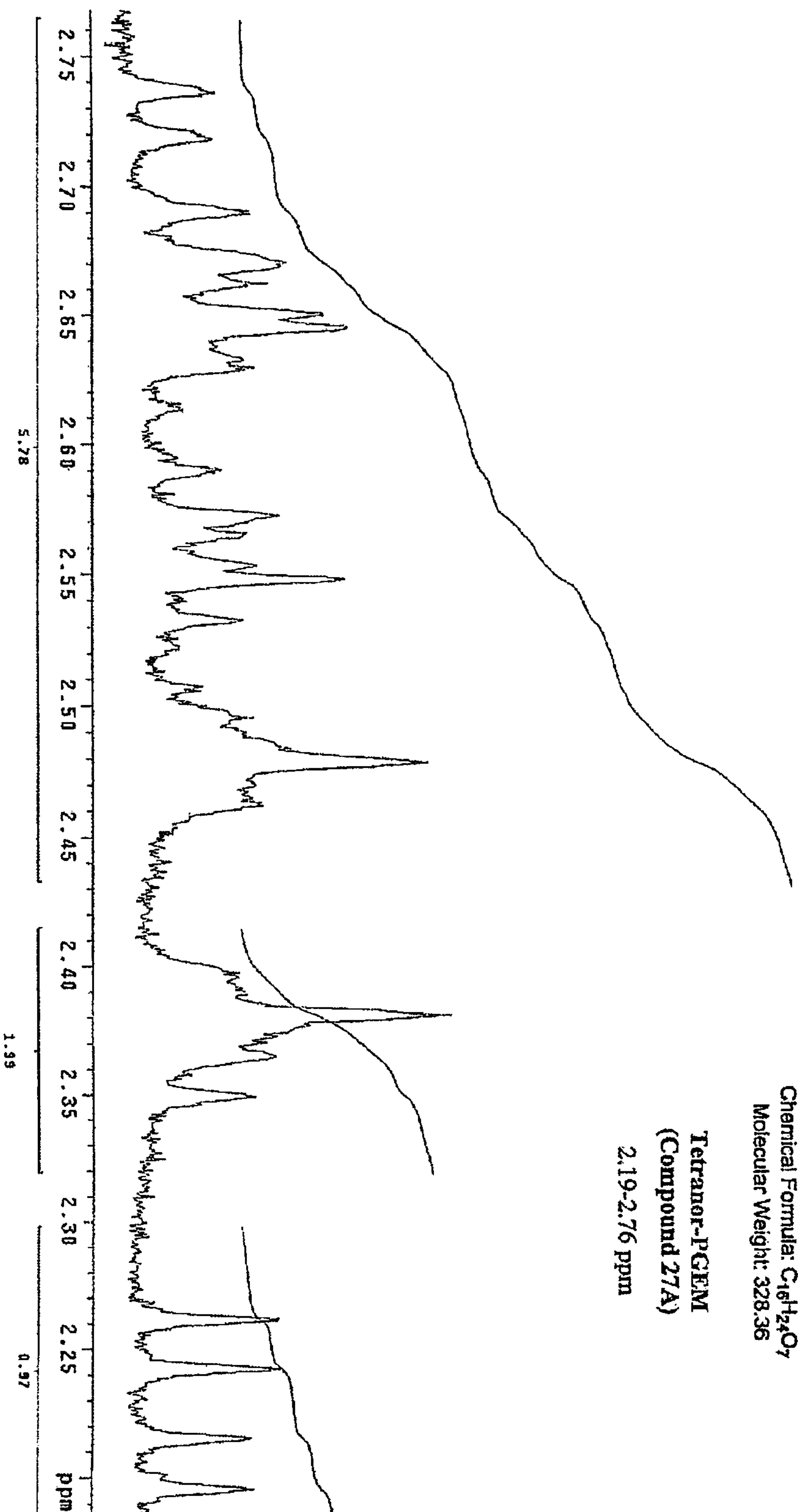
Figure 21C



Chemical Formula: $C_{16}H_{24}O_7$
Molecular Weight: 328.36

**Tetranor-PGEM
(Compound 27A)**

2.19-2.76 ppm

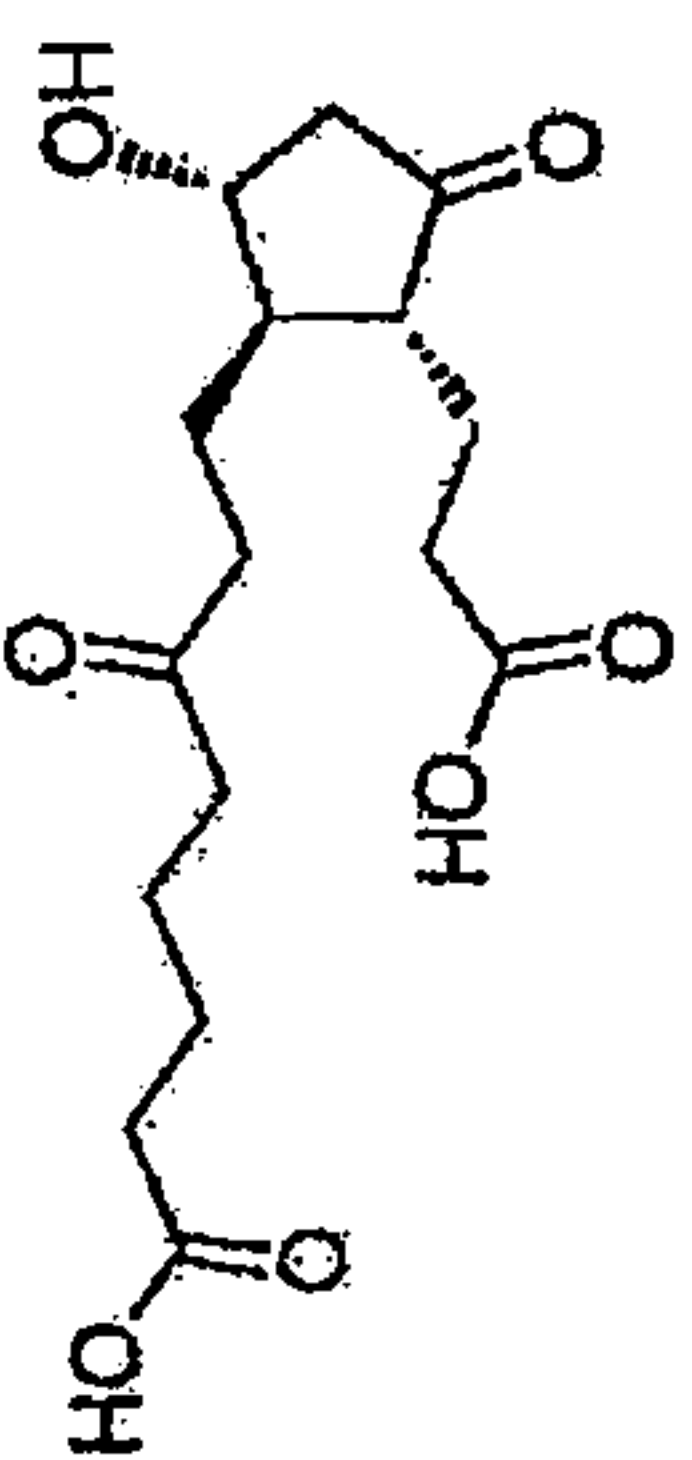


AK8-57

Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639874 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 21C

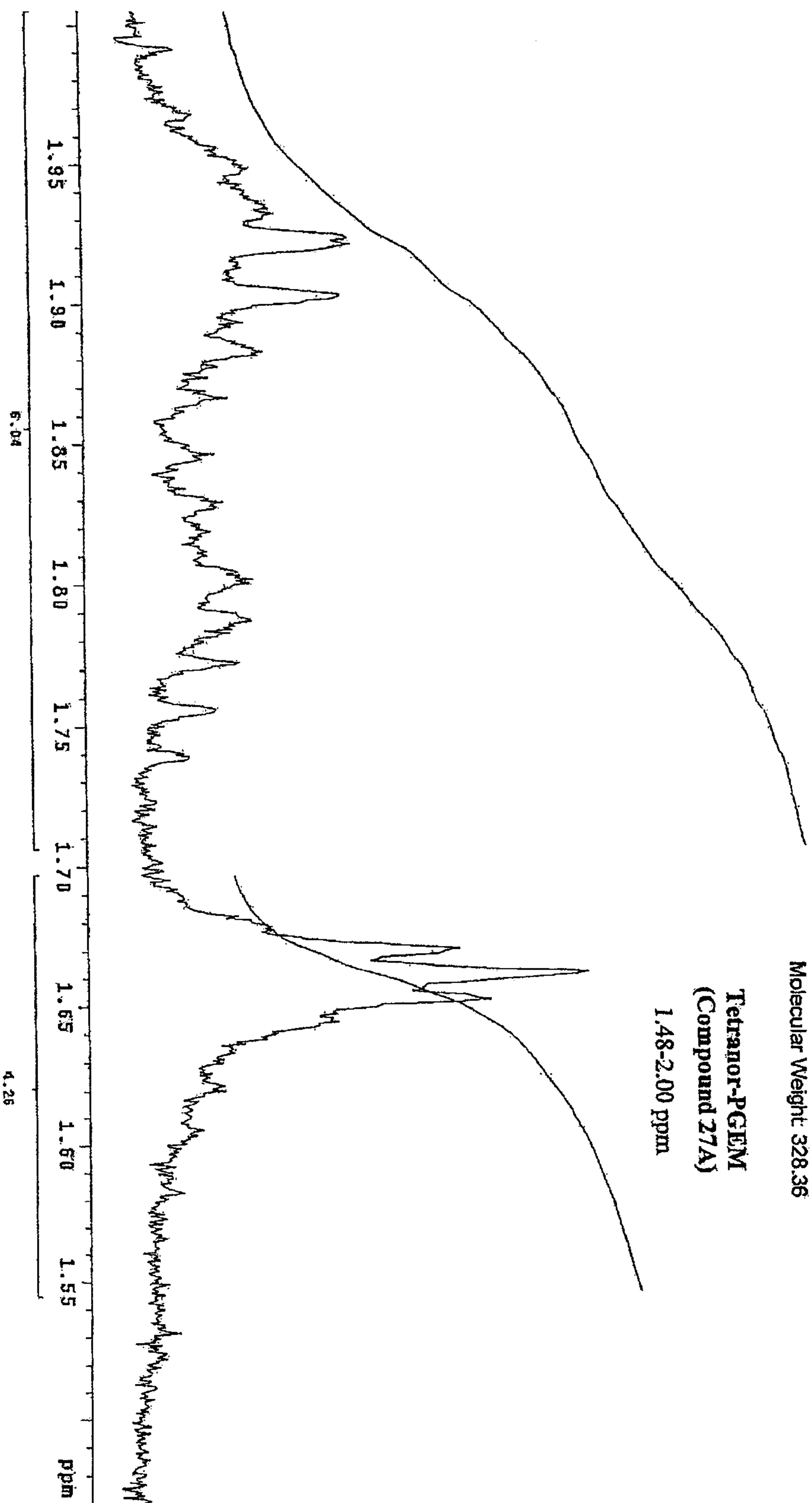
Figure 21D



Chemical Formula: $C_{16}H_{24}O_7$
Molecular Weight: 328.36

**Tetranor-PGEM
(Compound 27A)**

1.48-2.00 ppm



AK8-57

Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639874 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 21D

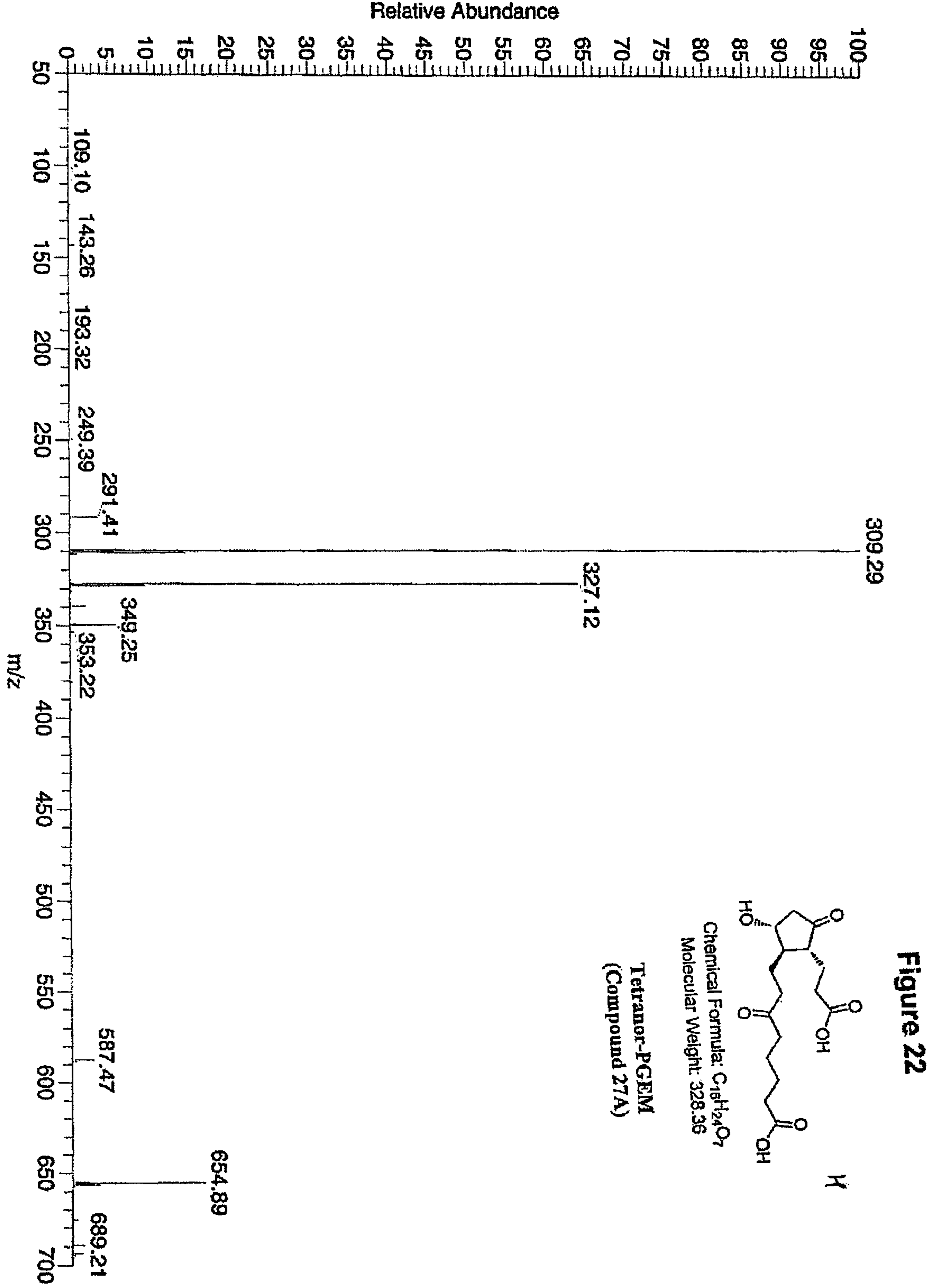
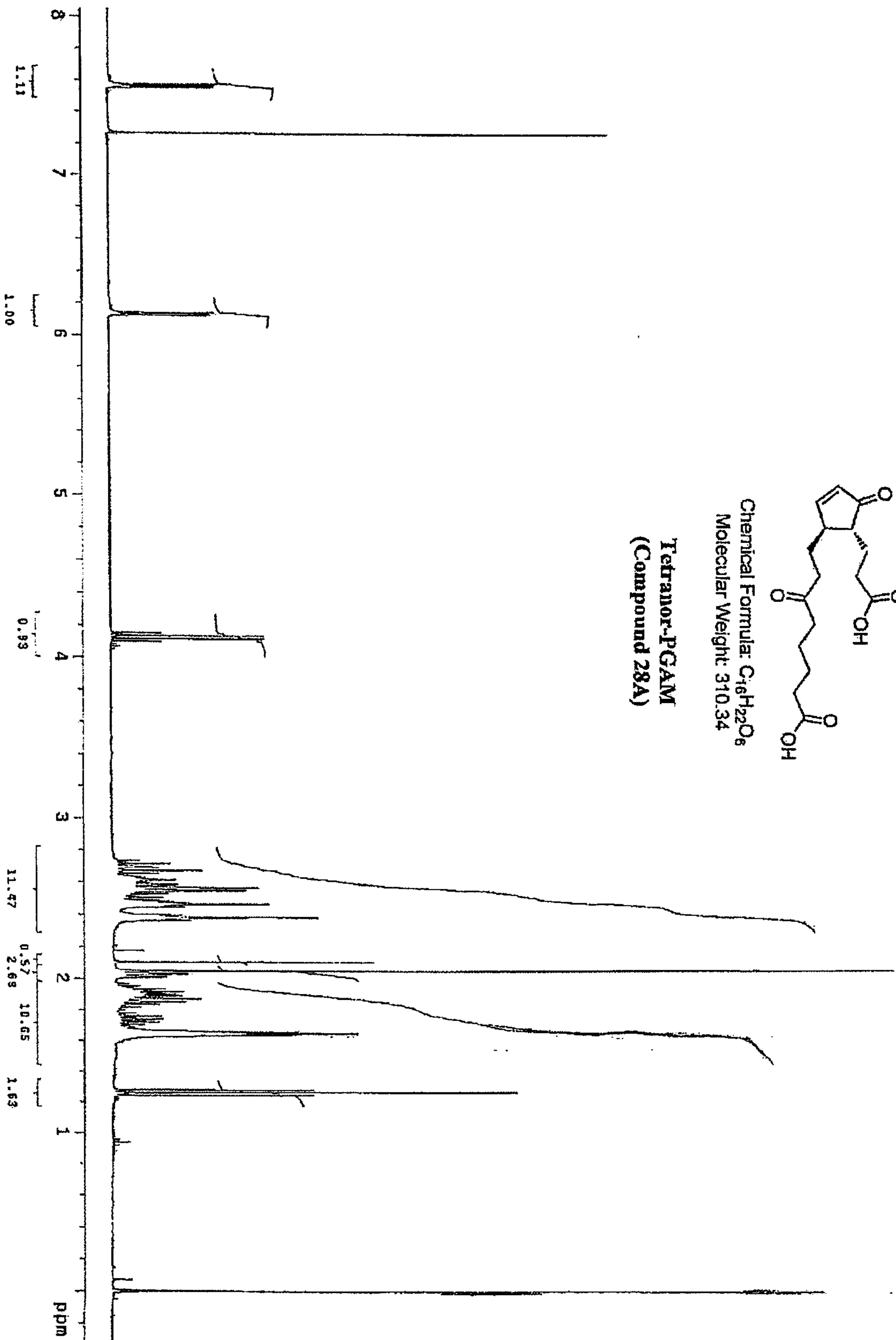
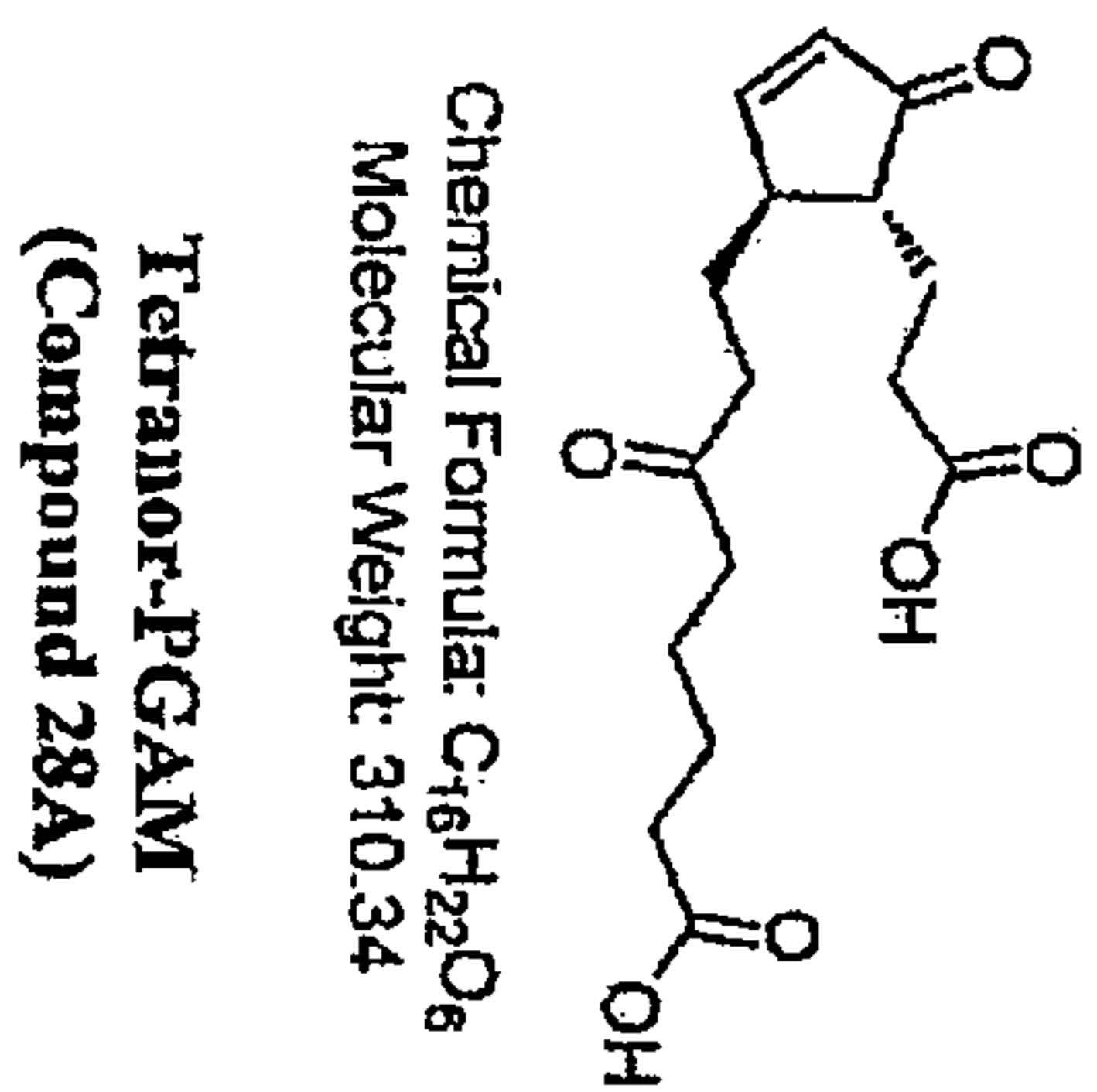
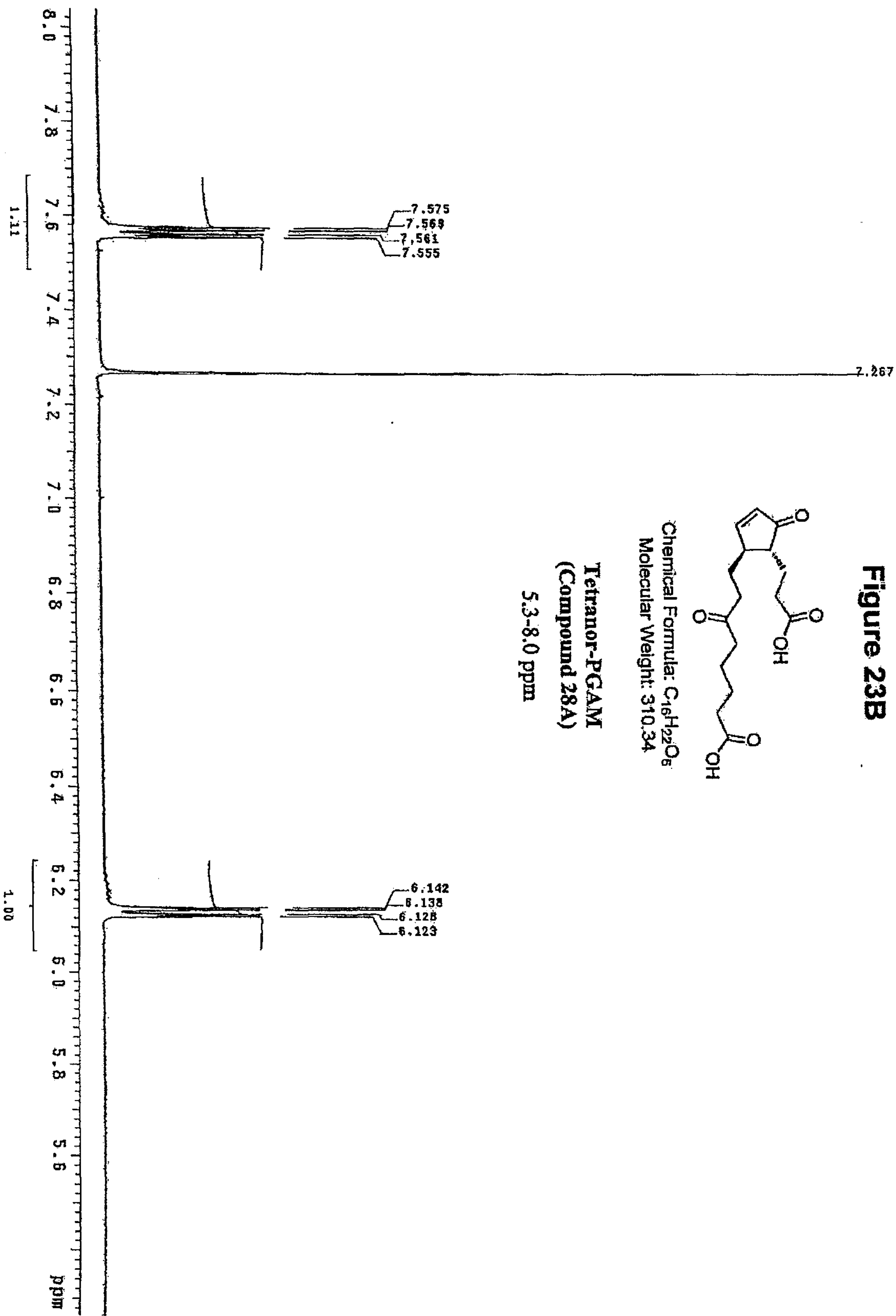


Figure 23A



AK9-150
Solvent: CDCl₃
Ambient temperature
INOVA-400 "Varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 8000.2 Hz
Arrayed repetitions
OBSERVE H1, 399.9639824 MHz
DATA PROCESSING
FT size 85536
Total time 1 minute

Figure 23A



AK9-150

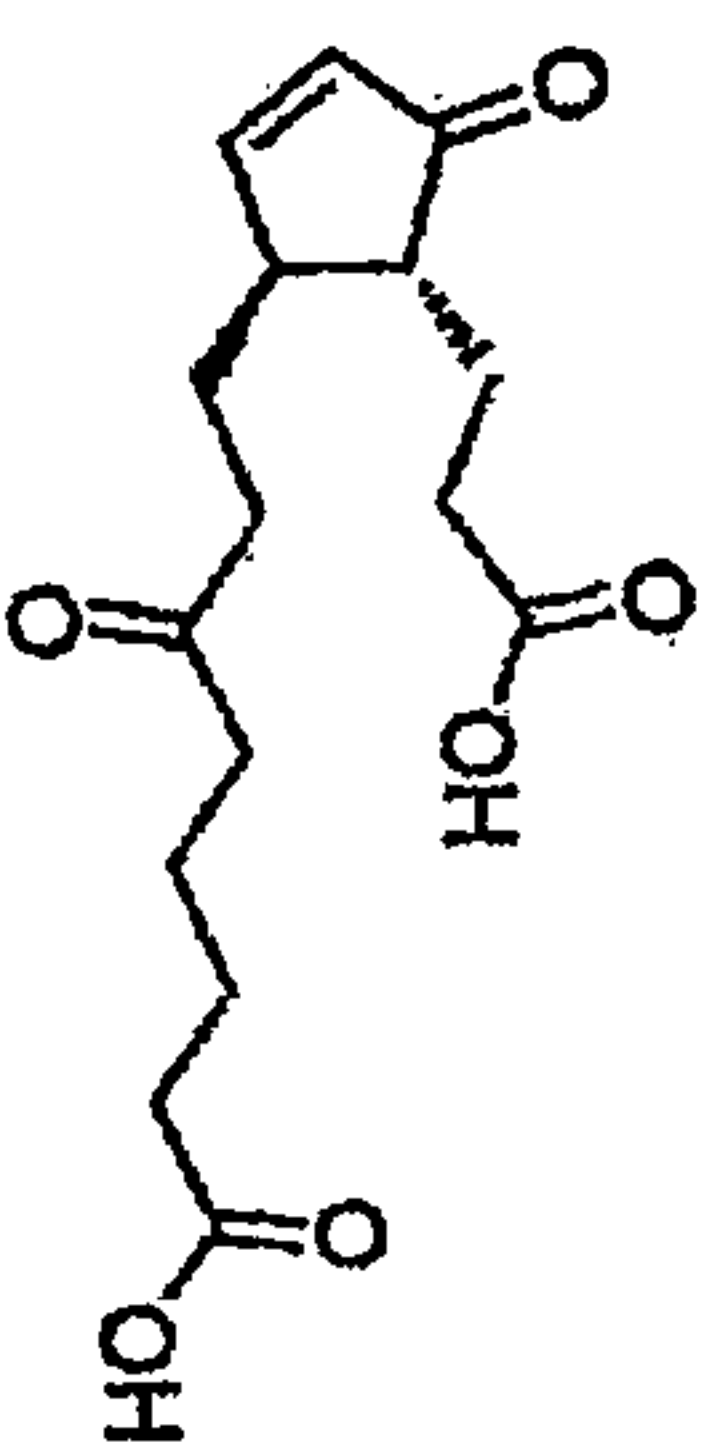
Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 6000.2 Hz
Arrayed repetitions
OBSERVE H1, 399.9639824 MHz
DATA PROCESSING
FT size 65536
Total time 1 minute

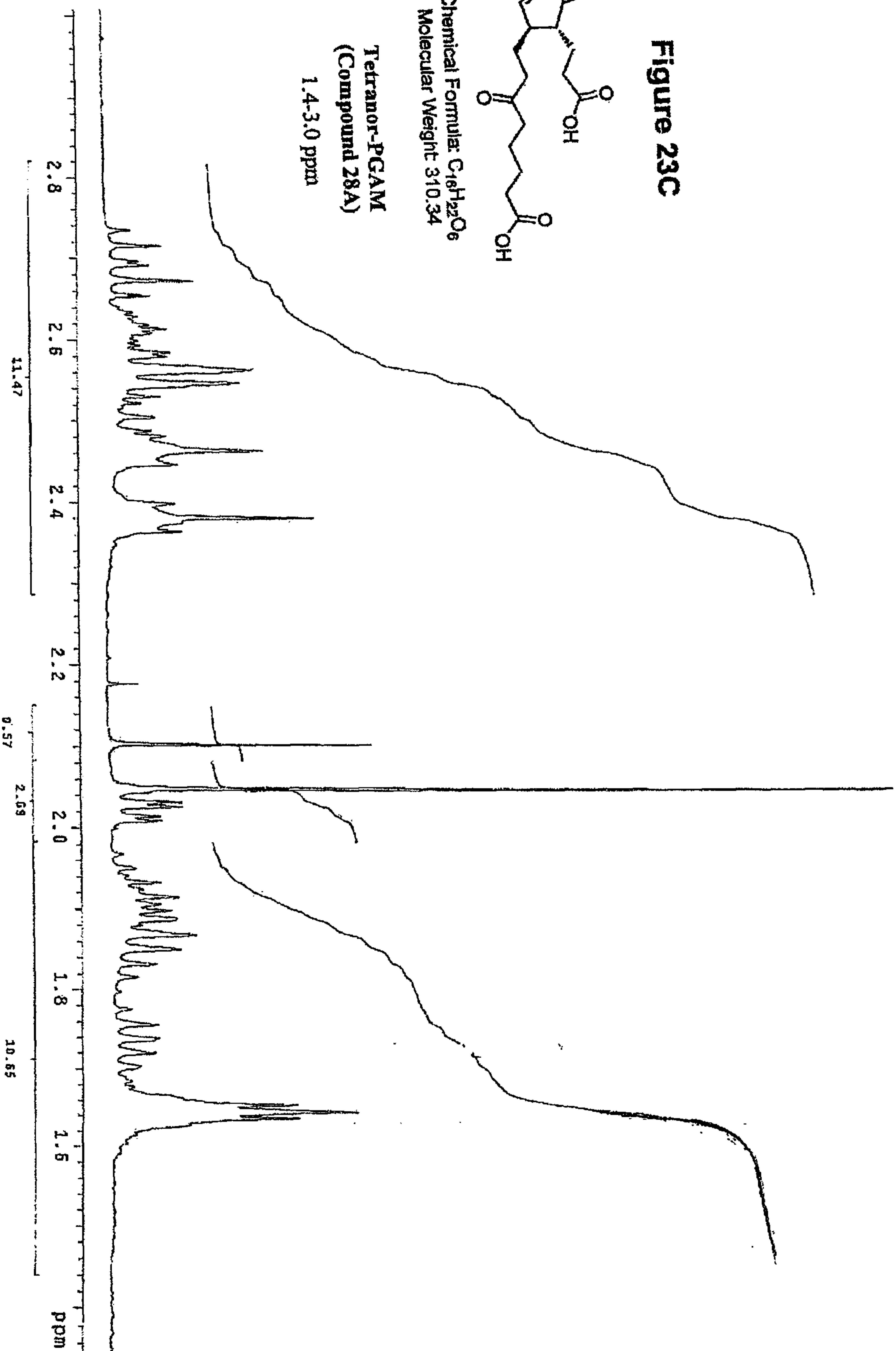
Figure 23B

Figure 23C



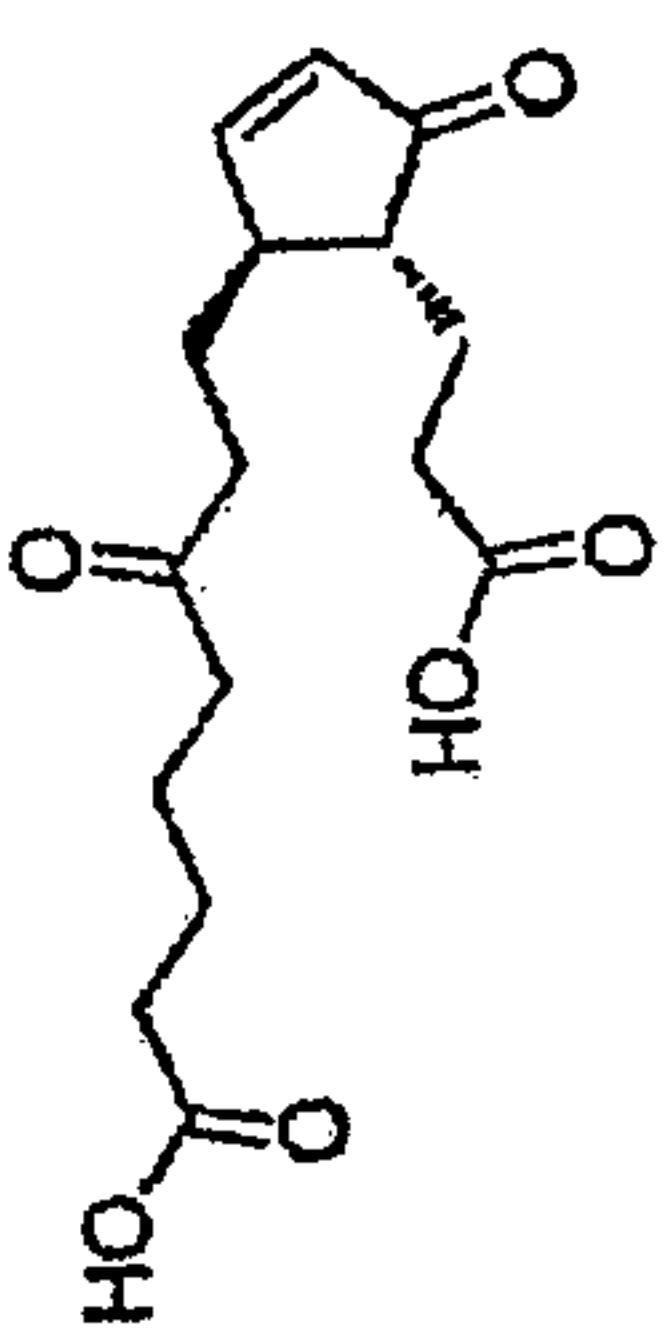
Chemical Formula: $C_{16}H_{22}O_6$
Molecular Weight: 310.34

Tetranor-PGAM
(Compound 28A)
1.4-3.0 ppm



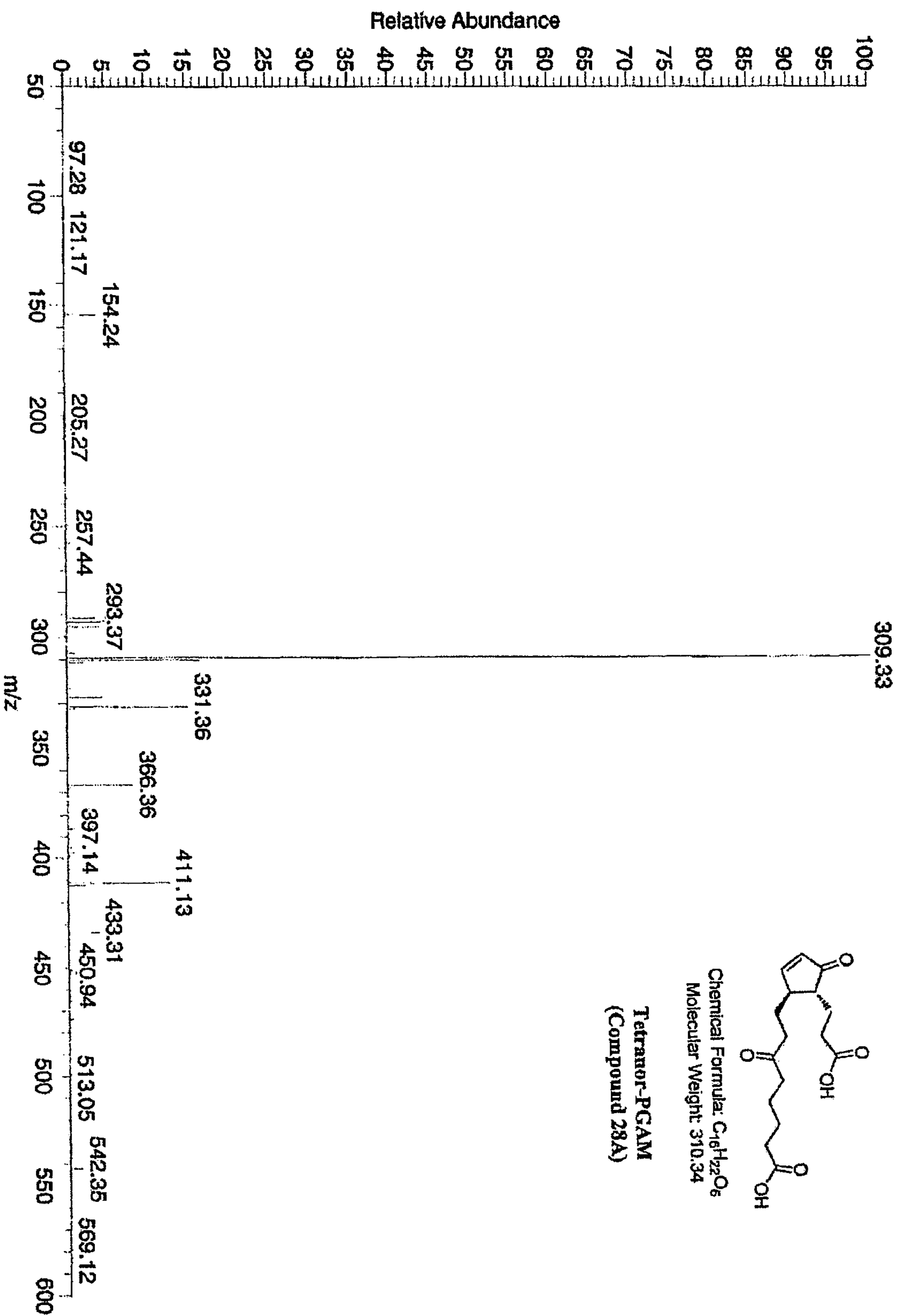
AK9-150
Solvent: CDCl3
Ambient temperature
INOVA-400 "varian2"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 6000.2 Hz
Arrayed repetitions
OBSERVE H1, 399.9039024 MHz
DATA PROCESSING
FT size 65536
Total time 1 minute

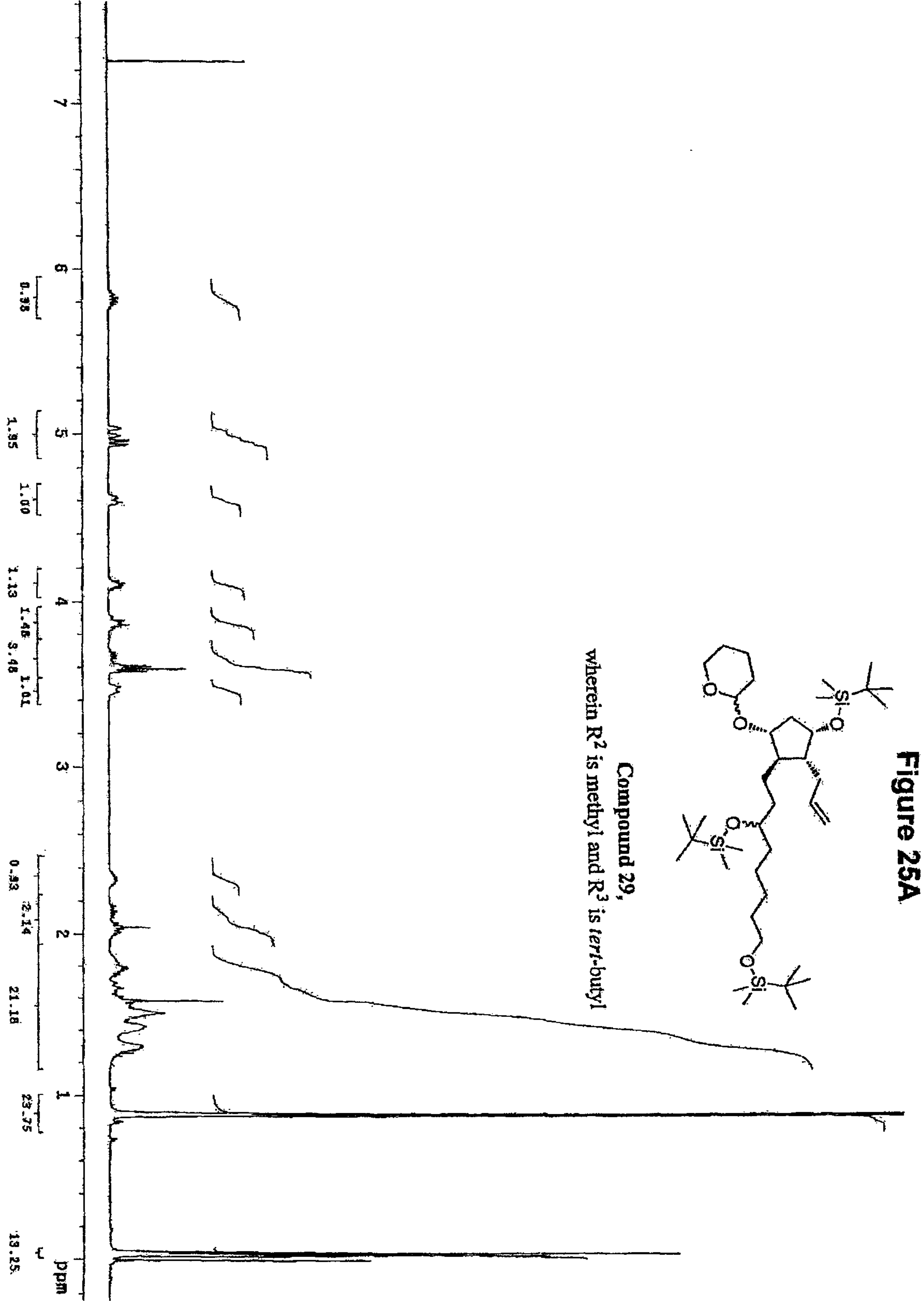
Figure 23C

Figure 24

Chemical Formula: $C_{16}H_{22}O_6$
Molecular Weight: 310.34

Tetranor-PGAM
(Compound 28A)





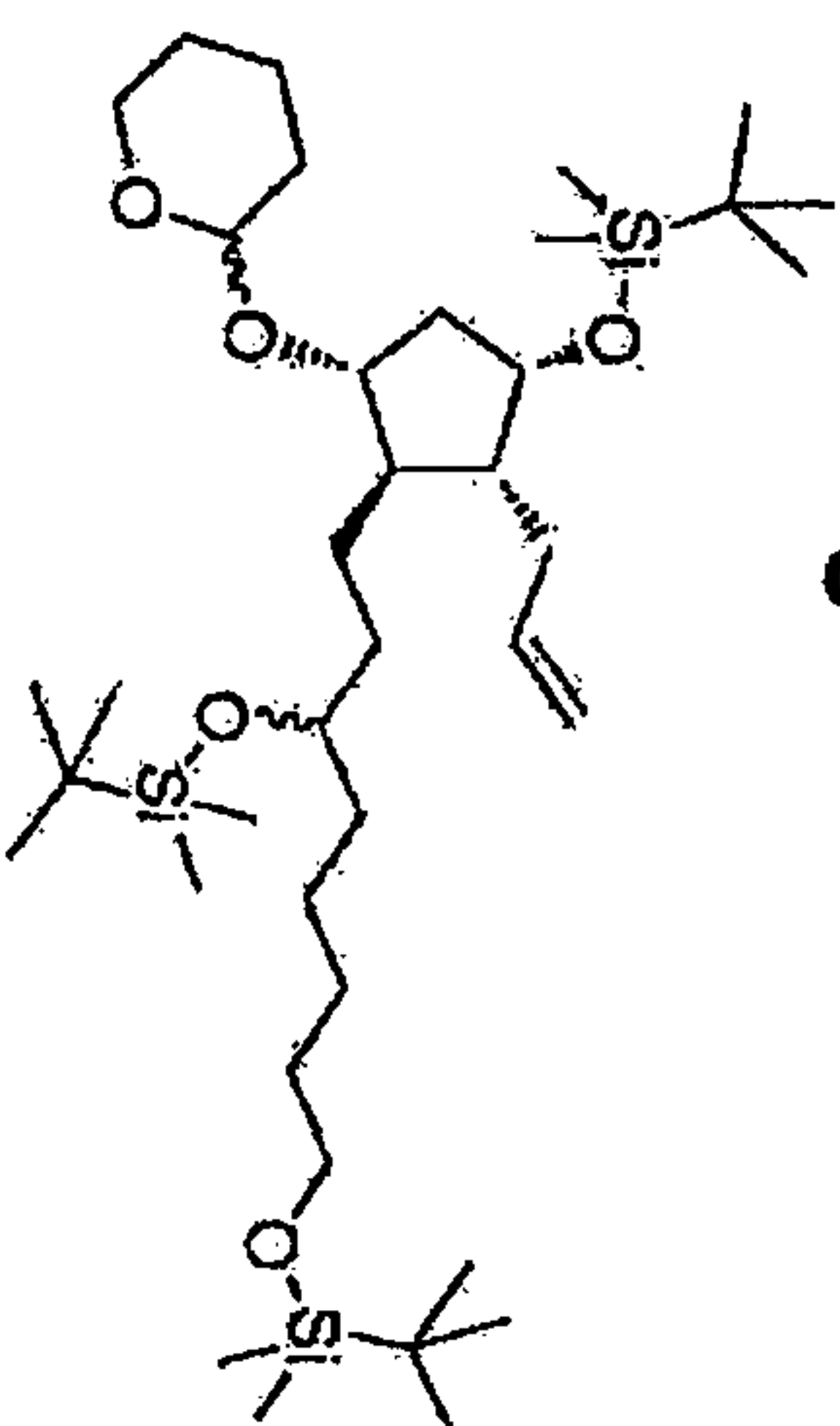
TT1-145

Solvent: CDCl₃
Ambient temperature
INDVA-400 "varian2"

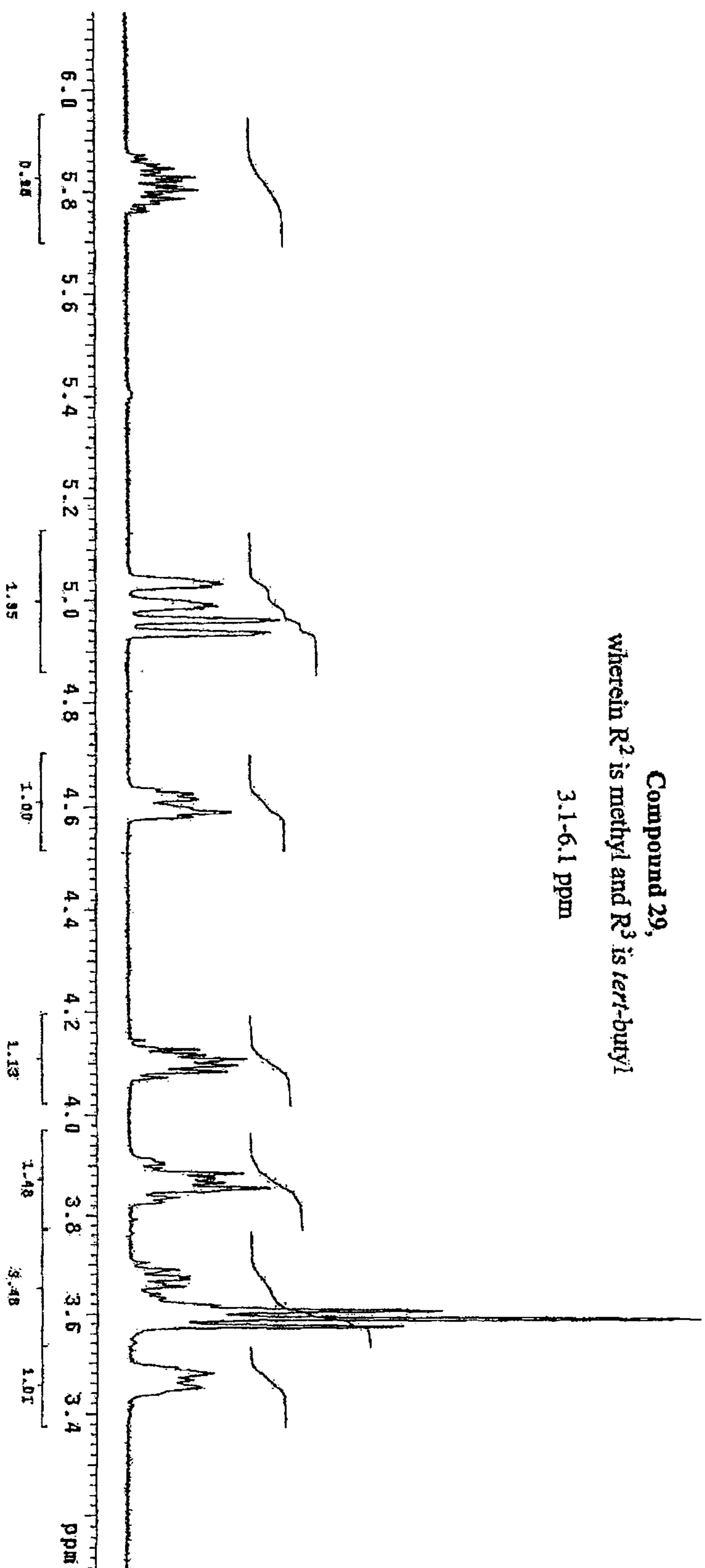
PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639858 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 25A

Figure 25B

Compound 29,
wherein R² is methyl and R³ is *tert*-butyl
3.1-6.1 ppm



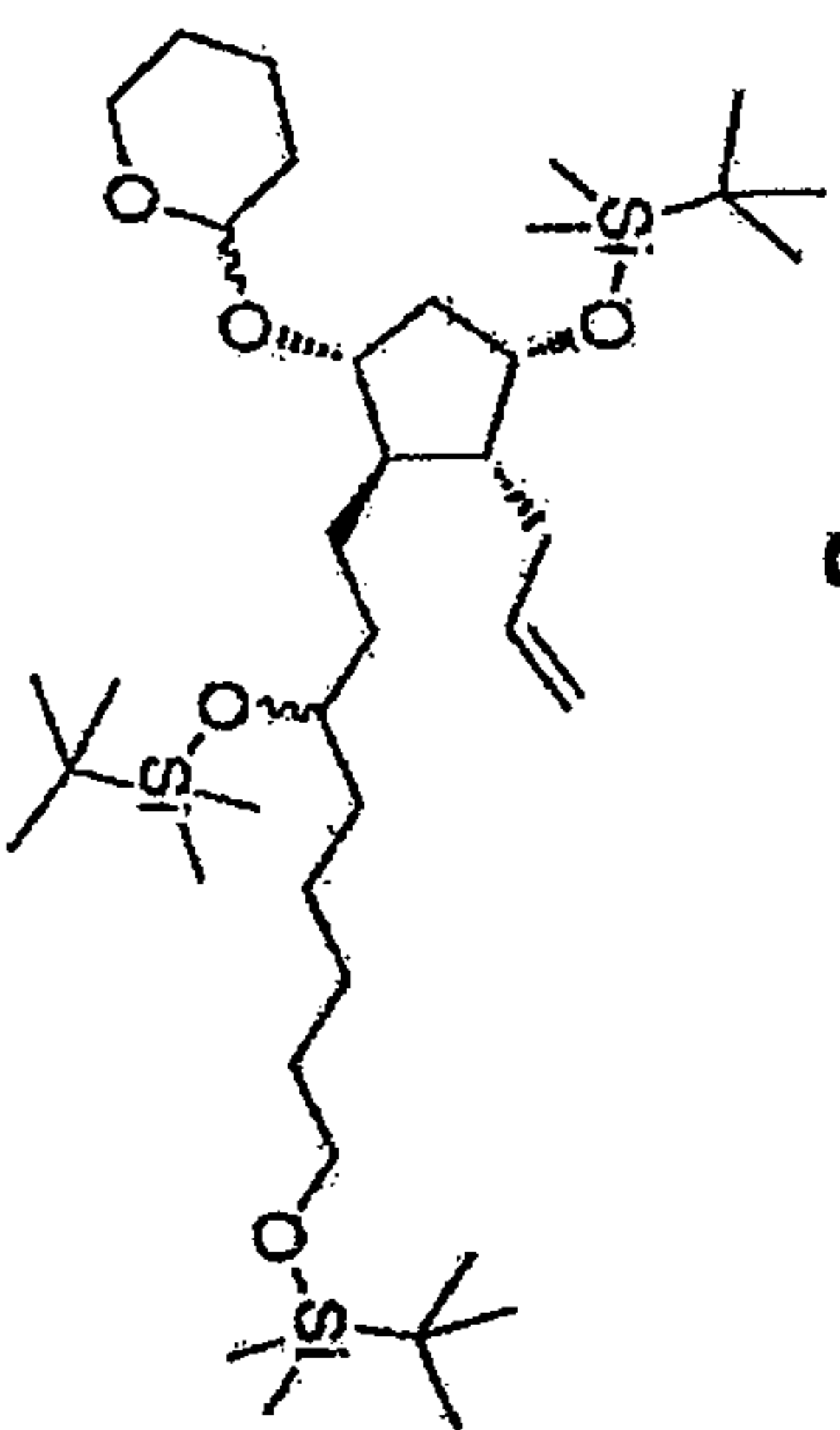
TT1-145

Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

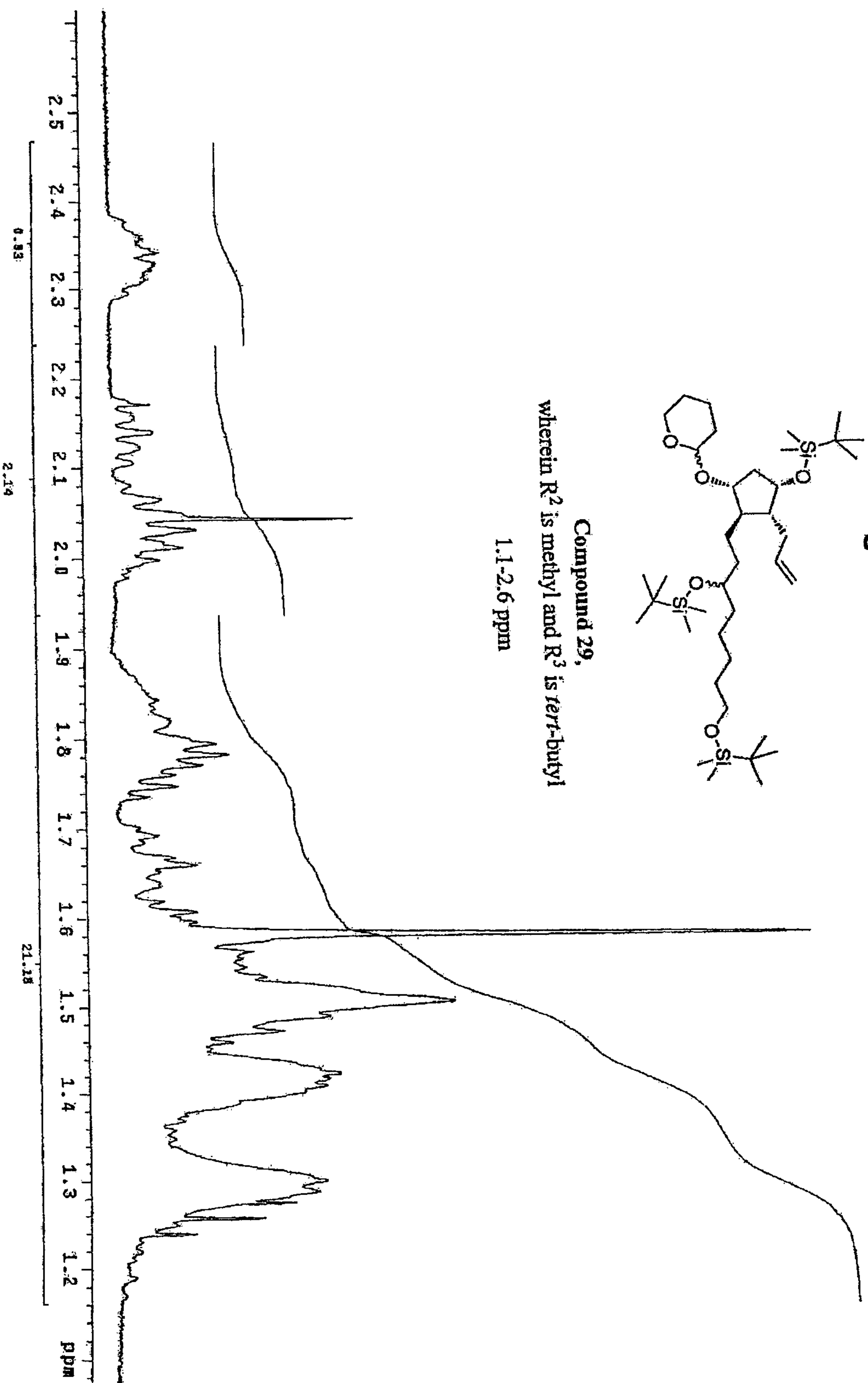
PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639858 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 25B

Figure 25C

Compound 29,
wherein R² is methyl and R³ is *tert*-butyl
1.1-2.6 ppm



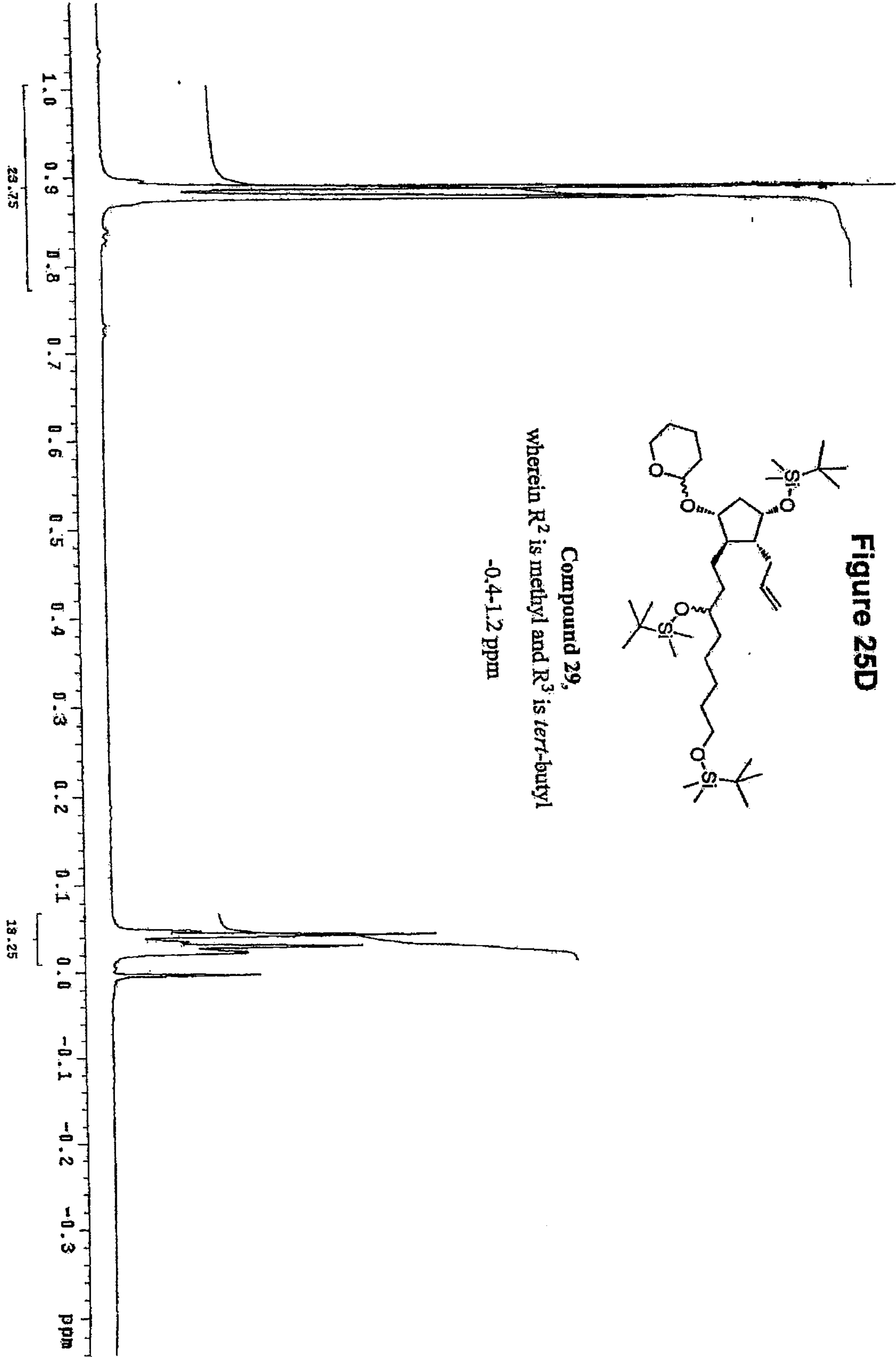
TT1-145

Solvent: CDCl₃
Ambient temperature
INOVA-400 "varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639858 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 25C



TT1-145

Solvent: CDCl₃
Ambient temperature
INOVA-400 "Varian2"

PULSE SEQUENCE

Relax. delay arrayed
1st pulse arrayed
2nd pulse 45.0 degrees
Acq. time 3.744 sec
Width 4000.0 Hz
Arrayed repetitions
OBSERVE H1, 399.9639858 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

Figure 25D

