AN ABSTRACT OF THE
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Kurt F. Sundermann for the degree of
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Abstract approved:

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A convergent synthesis of epothilone B that generates all seven of its asymmetric centers in a completely stereoselective fashion has been completed. Key reactions include an anti-Felkin aldol condensation to set the C6 and C7 stereochemistry, a directed α-hydroxylation to install the C15 (S)-hydroxyl substituent, and a Wittig condensation to join two main subunits via C-C bond formation at C9-C10. In addition, through modifications to the C9-C10 region of the macrolide, several novel and cytotoxic epothilone analogues were synthesized. Bioassay data comparing the antiproliferative activity and tubulin polymerization of the analogues with epothilone B, epothilone D, and paclitaxel showed that the synthetic analogues were less potent than their natural counterparts.

Synthesis of Epothilones and Epothilone Analogues

by

Kurt F. Sundermann

A DISSERTATION

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the requirements for the
degree of

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Approved:

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Major Professor, representing Chemistry

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Chair of the Department of Chemistry

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Dean of the Graduate School

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Kurt F. Sundermann, Author

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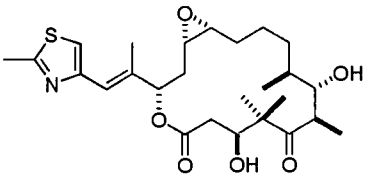
Introduction

Discovery of Epothilones

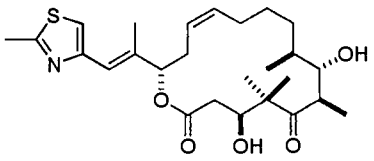
Epothilones A and B were first described as early as 1987 by the groups of Höfle et al. and Reichenbach et al. at the Gesellschaft für Biotechnologische Forschung in Germany. These novel compounds were isolated from culture extracts of the myxobacterium *Sorangium cellulosum* (Myxococcales), strain So ce90, found in a soil sample collected from the Zambesi River in South Africa. The isolation of these compounds was guided by their antifungal activity, but field experiments proved the epothilones to be too toxic as potential antifungal and pesticide agents, and as a result interest in these compounds faded until 1995.[1] In that year, Merck scientists reported that these macrolides exhibit a high level of cytotoxicity.[2] They had discovered that epothilones inhibit cellular mitosis through a mechanism of cytotoxicity similar to that of paclitaxel (Taxol) by stabilizing microtubule assemblies. Epothilone B (**2**) was particularly impressive, exhibiting a 2000-5000-fold higher potency than Taxol in multiple drug resistant cell lines. In 1996, the relative and absolute configuration of **2** was reported by Höfle and co-workers using a combination of elemental, NMR, and X-ray crystallographic analysis.[1b]

It was with this exciting background that a race to complete the first total synthesis of epothilone A and epothilone B began. The three main competitors

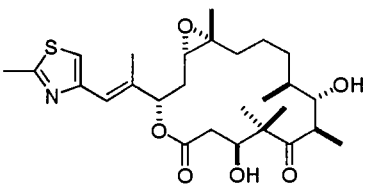
were the groups of Danishefsky, Nicolaou, and Schinzer. Late in 1996 Danishefsky[3] described the first total synthesis of epothilone A (**1**). Following a few weeks later, Nicolaou[4] and then Schinzer[5] each completed a total synthesis of epothilone A (**1**). In 1997 Danishefsky published the first total synthesis of epothilone B (**2**).[6] This was followed in a companion paper by Nicolaou's total synthesis of epothilone B (**2**).[7] It was during this synthetic race that a compound, which has been reported to possess superior qualities to either epothilone A (**1**) or B (**2**) was first discovered by Danishefsky, namely desoxyepothilone B or more commonly referred to as epothilone D (**4**).[8] Subsequently, epothilone D was isolated by Höfle and Reichenbach along with many other epothilones (**5-29**) (**Figures 1** and **2**).[9]



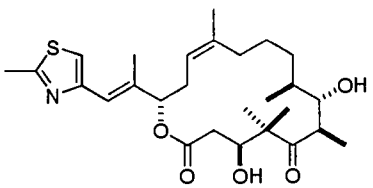
Epothilone A (**1**)



Epothilone C (**3**)

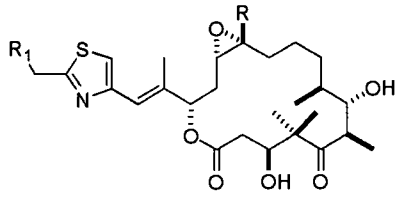


Epothilone B (**2**)

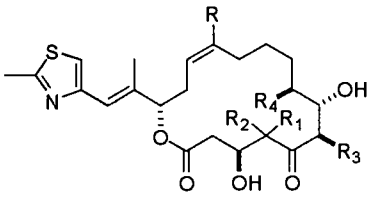


Epothilone D (**4**)

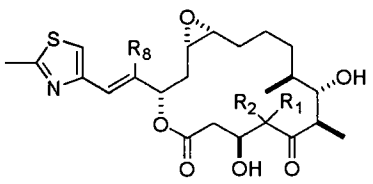
Figure 1. The Original Epothilones.



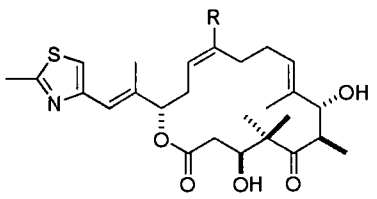
Epothilone E (**5**), R_1 = OH; R = H
Epothilone F (**6**), R_1 = OH; R = Me



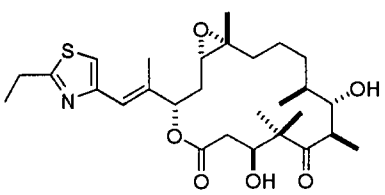
Epothilone C_1 (**16**), R_1 = H; R_2, R_3, R_4 = Me; R = H
Epothilone D_1 (**17**), R_1 = H; R_2, R_3, R_4 = Me; R = Me
Epothilone C_2 (**18**), R_2 = H; R_1, R_3, R_4 = Me; R = H
Epothilone D_2 (**19**), R_2 = H; R_1, R_3, R_4 = Me; R = Me
Epothilone C_3 (**20**), R_3 = H; R_1, R_2, R_4 = Me; R = H
Epothilone C_4 (**21**), R_4 = H; R_1, R_2, R_3 = Me; R = H



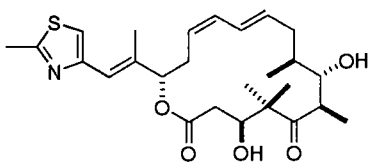
Epothilone A_1 (**7**), R_1 = H; R_2, R_8 = Me
Epothilone A_2 (**8**), R_2 = H; R_1, R_8 = Me
Epothilone A_8 (**9**), R_8 = H; R_1, R_2 = Me
Epothilone A_9 (**10**), R_1, R_2 = Me; R_8 = CH_2OH



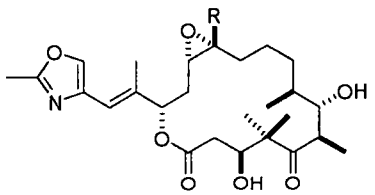
Epothilone C_5 (**22**), R = H
Epothilone D_5 (**23**), R = Me



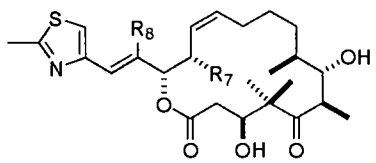
Epothilone B_{10} (**11**)



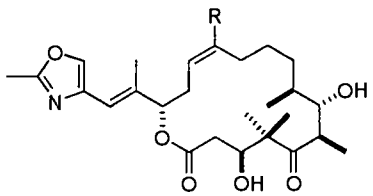
Epothilone C_6 (**24**)



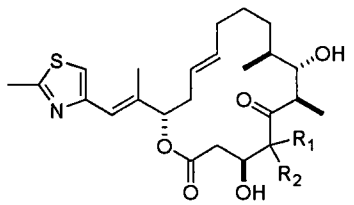
Epothilone G_1 (**12**), R = H
Epothilone G_2 (**13**), R = Me



Epothilone C_7 (**25**), R_7 = OH; R_8 = Me
Epothilone C_8 (**26**), R_7, R_8 = H
Epothilone C_9 (**27**), R_8 = CH_2OH; R_7 = H



Epothilone H_1 (**14**), R = H
Epothilone H_2 (**15**), R = Me



trans-Epothilone C_1 (**28**), R_1 = H; R_2 = Me
trans-Epothilone C_2 (**29**), R_1 = Me; R_2 = H

Figure 2. Naturally Occurring Epothilone Variants.

Bioactivity of Epothilones

The first generation epothilone drug candidates are moving through cancer clinical trials and the results are very promising. Epothilone B having successfully progressed through phase I clinical trials is currently being evaluated in phase II trials by Novartis. A lactam analog of Epothilone B (BMS-247550) has also passed phase I clinical trails and has entered into phase II. Recently phase I trials for epothilone D were initiated by Kosan Biosciences.

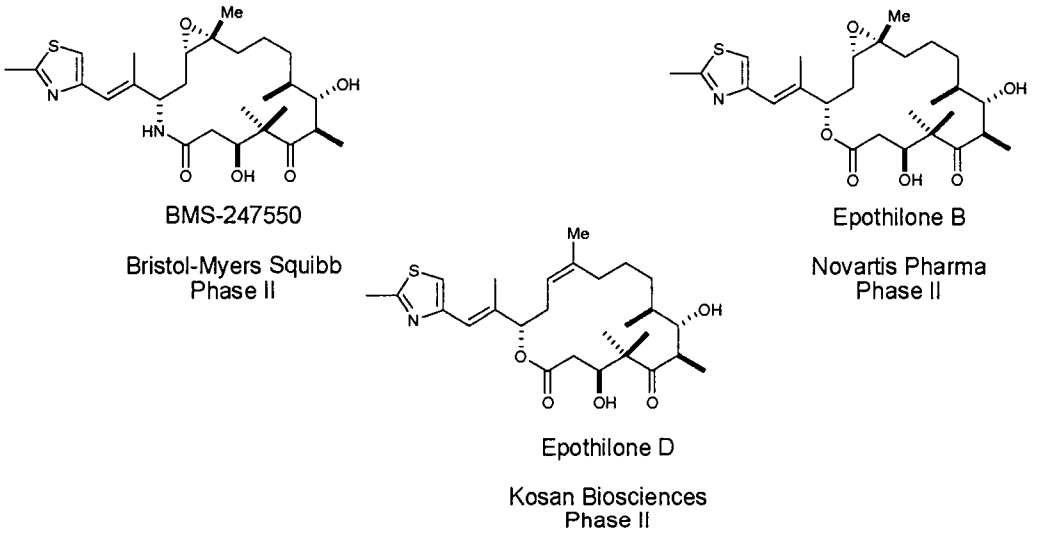


Figure 3. Epothilones and Derivatives in Clinical Trials.

Cancer is characterized by uncontrolled cell division of abnormal cells. If the growth and spreading of these cells go unchecked, other areas of the body can become invaded. For a eukaryotic cell to divide, it must successfully complete a process of nuclear division known as mitosis. A crucial role in this

phase is played by a structure called the mitotic spindle. Made up of microtubules, the spindle controls the movement of the chromatids so that each daughter cell retains an identical copy of the parent cell's genetic material (**Figure 4**).

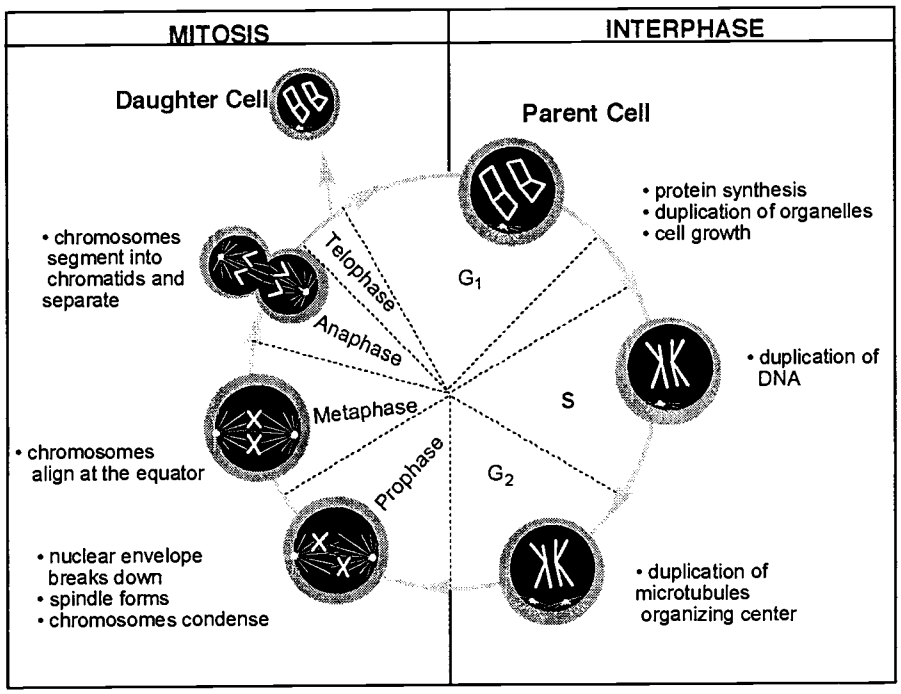


Figure 4. Eukaryotic Cell Cycle showing Mitosis

Microtubules are hollow filaments comprised of individual 55 kD globular protein subunits known as α and β tubulin. The joining of one α and one β subunit forms a heterodimer which then polymerizes to form protofilaments. Aggregation of thirteen protofilaments in a parallel arrangement leads to the formation of a microtubule which is in a constant state of flux called dynamic

instability. Substances which can perturb this equilibrium have a catastrophic effect on the mitotic cycle, and if the affected cell is unable to recover apoptosis (programmed cell death) occurs.

There are three main classes of antimitotic agents which interact with tubulin and/or microtubules. The first two classes are made up of the Vinca alkaloids such as vinblastine and vincristine and the colchicine-site binders such as colchicine and the curacins. These two classes bind to tubulin monomers and inhibit their polymerization into microtubules. The third class of antimitotic agents, which bind to fully formed microtubules, include Taxol® (paclitaxel), the epothilones and a few other naturally occurring compounds such as discodermolide, eleutherobin, and laulimalide (**Figure 5**).

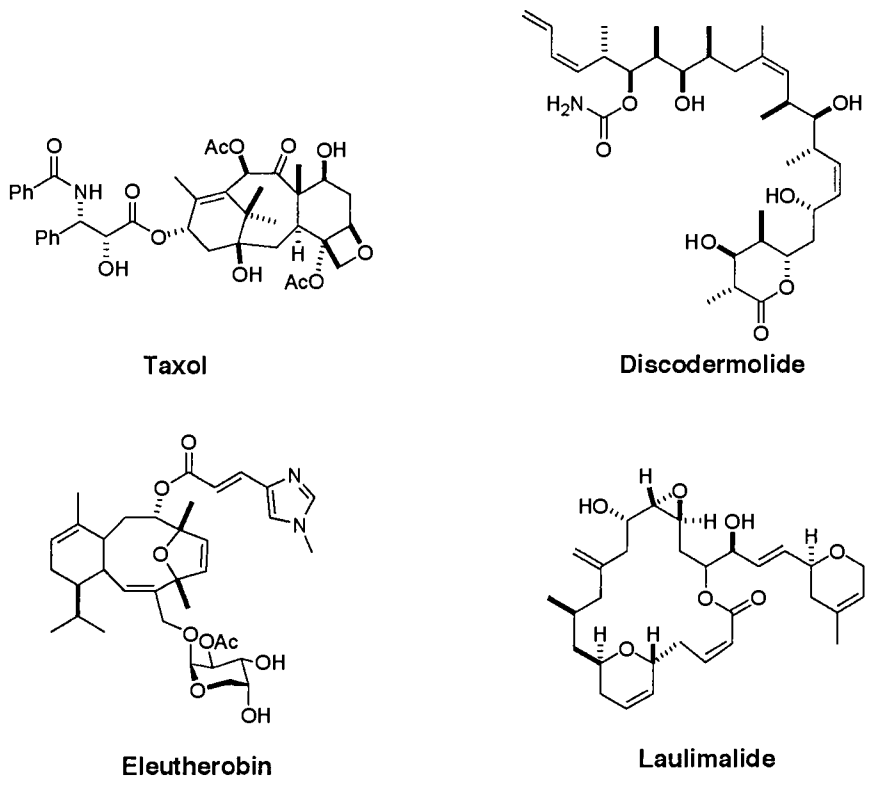


Figure 5. Microtubule-stabilizing Natural Products.

The epothilones, like Taxol® (paclitaxel), are believed to exert their cytotoxic effect by blocking the metaphase-anaphase transition of the cell cycle by means of a mechanism of action which stabilizes the microtubule assemblies and prevents their depolymerization into tubulin subunits (**Figure 6**). In vitro, both paclitaxel and epothilones are able induce tubulin polymerization in the absence of microtubule associated proteins (MAPs) and/or guanosine triphosphate (GTP) at temperatures lower than 37 °C. In fact, epothilone B (**2**) has been demonstrated to be a competitive inhibitor of [^{3}H]-paclitaxel in binding to

microtubules, being able to displace paclitaxel with an apparent K_i value of 0.71 μM. This has led to the suggestion of a common binding site shared by both paclitaxel and epothilone, and several pharmacophoric models have been proposed based on this hypothesis (*vide infra)*. What is most important for the epothilones and is in contrast to paclitaxel is that the epothilones are equally effective against drug-sensitive and multidrug-resistant cells that overexpress the P-glycoprotein efflux pump.[10]

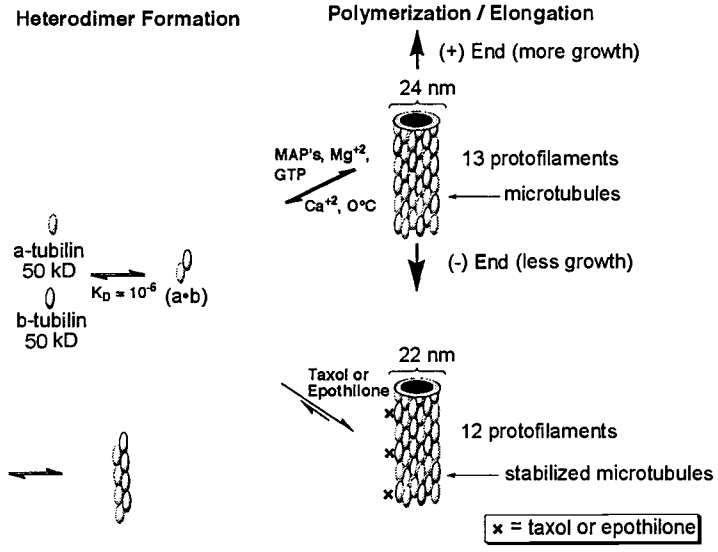
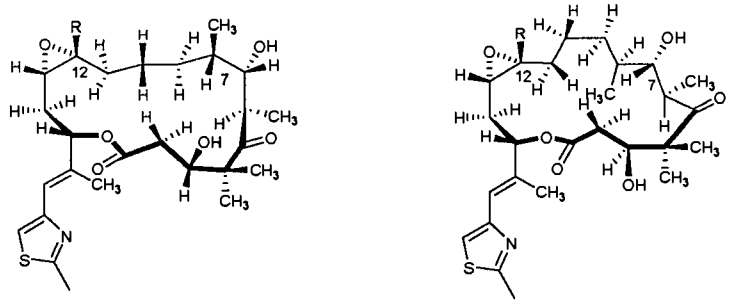


Figure 6. Microtubule Polymerization and Stablization.

Conformational Behavior

Along with the disclosure in 1996 of the relative and absolute stereochemistry of epothilone B (**2**), Hofle *et al.* concluded that the molecule's solution phase conformation was similar to its solid state conformation by

analysis of vicinal coupling constants and nuclear Overhauser enhancement measurements.[1b] Taylor supported this conclusion by independent analysis of epothilone A (**1**) using a combination of 2D NMR studies and computational modeling.[11] A second minor conformation of epothilone A (**1**) was postulated to exist, accounting for 20% of the population. The proposed solution phase major conformation of the epothilones as depicted by Hofle and Taylor is characterized by two roughly parallel anti-periplaner segments, one segment consisting of the C1-C4 region and the other the C7-C12 region. Connecting these two segments are the C5-C6 and C13-C15 portions, leading to a nearly rectangular shaped macrolactone. The minor epothilone conformation as depicted by Taylor has a triangular shape in which the C7-C12 anti-periplanar segment is reoriented towards a gauche arrangement and there is a near anti-periplanar arrangement in the C9-C5 region (**Figure 7**).



Major Conformer Minor Conformer

Figure 7. Conformations of Epothilone B.

Structure-Activity Relationships

The epothilones' remarkable biological activity has led to an enormous collection of analogs derived from fermentation, synthesis and semi-synthesis. Many of these have been evaluated in biological studies, affording a comprehensive description of structure-activity relationship.[12] For instance, an aryl side chain is crucial for activity. Replacement of the thiazole by other aromatic groups such a pyridine, or replacement of the whole side chain with a quinoline or benzothiazole has a positive effect as long as the location of the nitrogen atom is maintained. However, simple substitution of the thiazole with a phenyl group results in a 10-fold loss of antiproliferative activity. The (S) configuration at C15 is essential, inversion of this center resulting in a major loss of activity. The lactone oxygen when substituted by nitrogen to form a macrolactam reduces activity *ca.* 10-fold for drug sensitive cells, but interestingly activity drops substantially in multi-drug resistant cell lines. Elimination of the β–hydroxy lactone to form the (*E*)-C2-C3 olefin has been described as being tolerated with a *ca.* 10-fold loss of activity. However, inversion of the C3 hydroxyl has a significant negative impact on activity. Deletion of one of the C4 methyl groups is tolerated, and in the epothilone D series a 2-fold greater potency is gained. The stereochemical requirement in this structural modification has not been determined. A cyclopropane moiety in place of the *gem*-dimethyl group results in significant loss of activity. Reduction of the C5 carbonyl, simultaneous inversion of the C6 and C7 configuration, inversion of the C8 methyl group or its

removal, or replacement of this methyl substituent by a *gem*-dimethyl group all result in a substantial loss of activity. Ring contraction or expansion by deletion or insertion of methylene groups through the C9-C11 region, or incorporation of phenylene moieties through the C9-C13 region all cause a loss of activity. The C12 methyl substituent imparts *ca.* 10-fold greater activity as compared with its desmethyl congeners. Substitution by other small nonpolar substituents is tolerated but polar groups are not. Isosteres of the epoxide such as a cyclopropane or an aziridine are generally accepted and an olefin in place of the epoxide (epothilone D) reduces activity only by an order of magnitude. The stereochemistry at C12 does not have a significant impact, and both a *trans*-olefin or the corresponding epoxide are only slightly less active than epothilone B. A summary of the modifications made to the epothilone framework from which meaningful structure-activity relationships have been derived is shown in Figure 8.

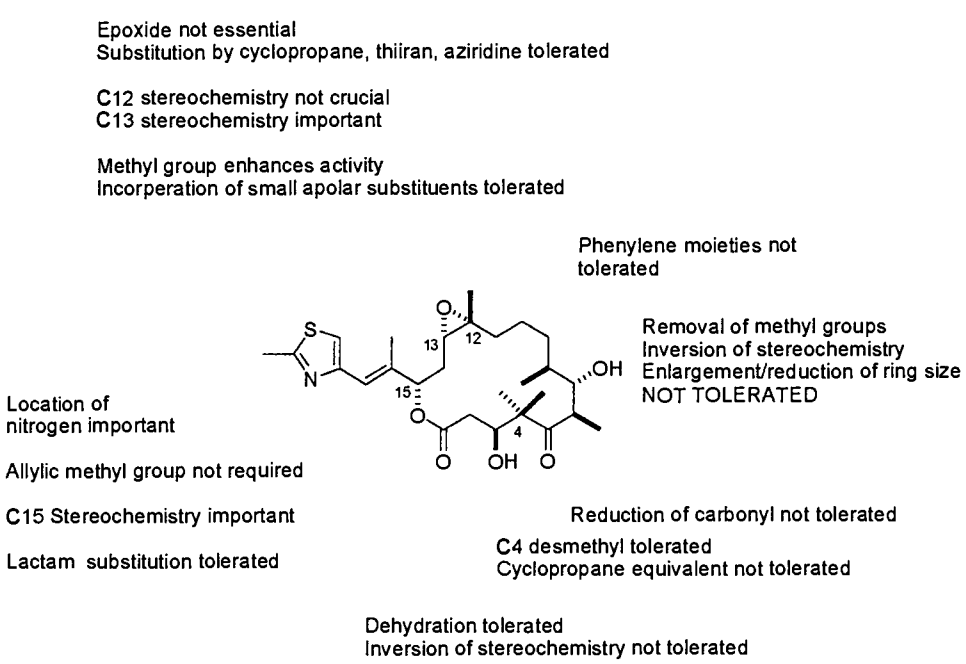
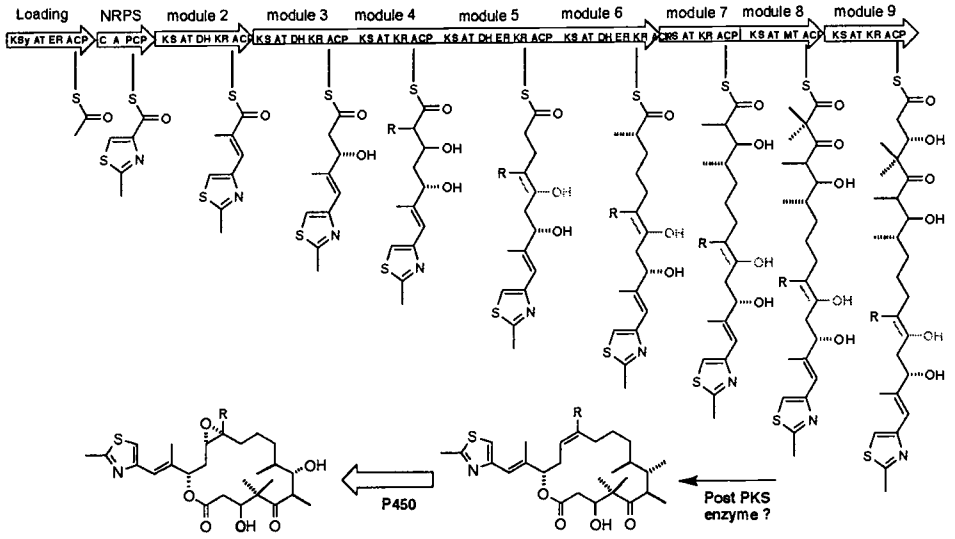


Figure 8. Structure-Activity Relationship of Epothilone B

The tubulin binding site of paclitaxel has been located on the β-subunit by means of a 3.7Å electron crystallographic structure of a tubulin/paclitaxel complex.[13] It has been proposed that epothilones and paclitaxel may share the same binding site even though the apparent structural differences between the two molecules are substantial. Several pharmacophore models have been suggested, some of which take account of other microtubule-stabilizing agents such as eleutherobin.[14] Although each of these models proposes different bioactive conformations to accommodate the published SAR data, they share the general feature of overlapping aryl groups between paclitaxel and epothilone.

Biosynthesis

The biosynthetic pathway which leads to epothilone production in *Sorangium cellulosum* has been reported to be catalyzed by a hybrid system which includes a polyketide synthase loading module, one non-ribosomal peptide synthetase module, a type I modular polyketide synthase containing eight modules, and a cytochrome P450-epoxidase.[15] The loading module is responsible for priming the biosynthesis with an acetyl group, derived from malonyl-CoA. The formation of the thiazole involves the participation of the NPRS module to incorporate a cysteine on to the acyl group. The acyltransferase which installs the C11-C12 fragment is presumed to be able to use either malonyl-CoA or methylmalonyl-CoA and thus allows for routes to both epothilone C or D. Since the dehydratase domain is absent in this module, it is unclear where and how the C11-C12 cis double bond is generated. The formation of the gem-dimethyl group involves the introduction of a methyl group from (*S*)-adenosylmethionine (**Figure 9**).



A, adenylation domain; ACP, acyl carrier protein; AT acyltransferase; C, condensation; DH, β-hydroxyacyl-thioester dehydratase; ER, enoyl reductase; KS β-ketoacyl ACP synthase; KSy, β-ketoacyl ACP synthase with the active-site cystine substituted by tyrosine; KR ketoreductase; MT (S)-adenosylmethionine-dependent methyltransferase; PCP, peptidyl carrier protein, TE thioesterase.

Figure 9. Proposed Modular Biosynthetic Pathway to Epothilones

Feeding experiments using labeled precursors have confirmed the incorporation of the biosynthetic precursors acetate, propionate, cysteine, and methylmethionine (**Figure 10**).[16]

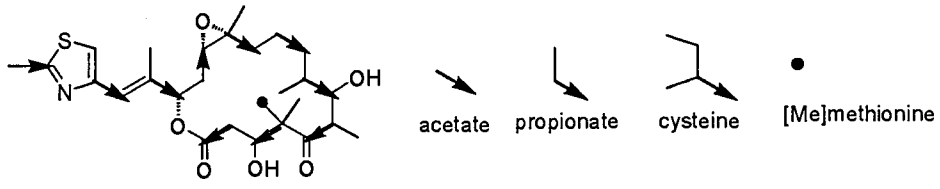


Figure 10. Precursor Incorporation into Epothilone

Synthetic Studies: 1996-2001

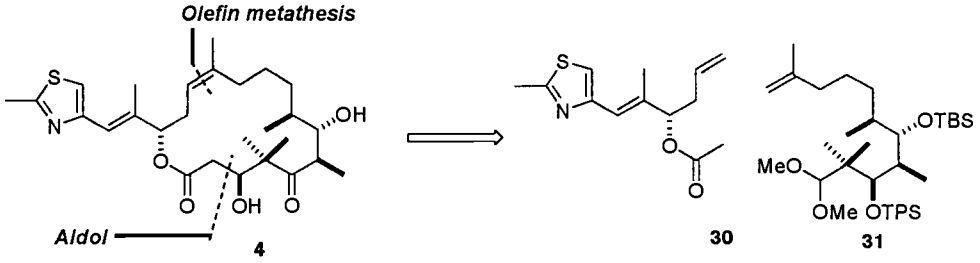
After the report of the relative and absolute stereochemistry of the epothilones was published, intense synthetic efforts were focused on these substances by academic groups as well as by pharmaceutical companies. There were two major objectives of this effort. The first goal was a concise, convergent, and fully stereocontrolled method for producing an epothilone; and the second has been to develop a library of non-natural analogues. To a large extent, the methods developed for the first goal have been exploited in the course of the second. The molecular structure of epothilone B is particularly well suited to challenge such objectives. The 16-membered macrolactone ring contains 7 stereogenic centers, an unsaturated thiazole side chain, a methyl substituted *cis*-epoxide, a *gem*-dimethyl group and a ketone. Three general synthetic strategies that join the molecule together from two subunits have been used to complete total syntheses of the epothilones. These are:

1) A macrocyclic ring-closing metathesis to form a C12-C13 olefin.
2) An organometallic mediated coupling between C11-C12 followed by a macrolactonization.
3) An aldol coupling to form the C6-C7 propionate linkage followed by a macrolactonization.

Ring-closing Metathesis Strategies

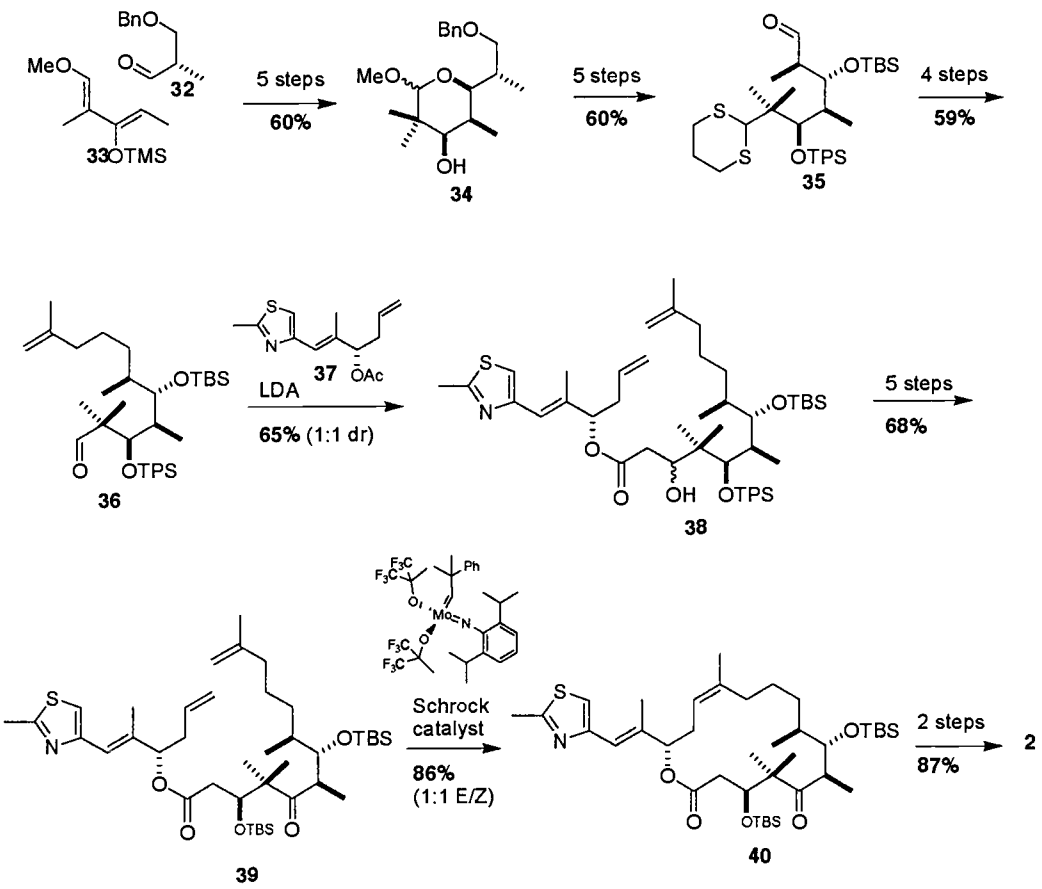
A ring-closing metathesis approach to epothilones has been reported by the groups of Danishefsky,[17] Nicolaou,[18] Schinzer,[19] Grieco,[20] Lerner[21] and Fürstner.[22] Advantages of this strategy include the rapid assembly of subunits with minimal functional group manipulation, their convergent coupling, and the ability to apply solid-phase technology. The main drawback to this strategy is that the ring-closing metathesis itself is not stereoselective and results in a mixture of *E*- and *Z*-olefins. Two variations of this approach have been used which differ in the manner whereby the two subunits are joined to form the metathesis precursor.

In Danishefsky's and Grieco's successful routes to **2** the subunits **30** and **31** were coupled using an aldol reaction prior to the ring-closing event (**Scheme 1**). This aldol coupling suffered from poor diastereoselectivity.



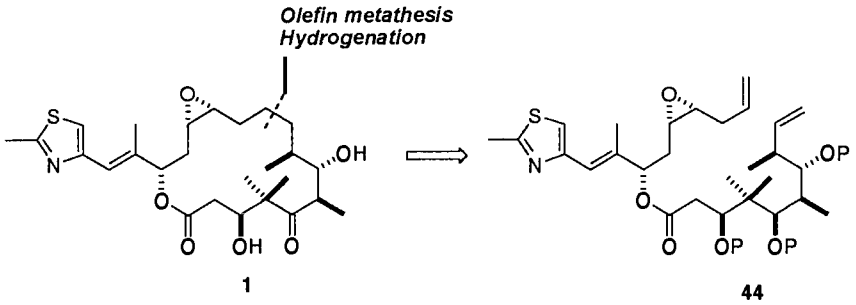
Scheme 1. Retrosynthesis of Danishefsky's and Grieco's Ring-closing Metathesis Approach.

For the synthesis of the C3-C13 fragment **31**, Danishefsky applied a Lewis acid mediated cyclocondensation between chiral aldehyde **32** and butadiene **33** to yield a dihydropyranone (**Scheme 2**). This was advanced by reduction of the carbonyl group and subsequent hydroxyl directed cyclopropanation, followed by regioselective fragmentation using *N*-iodosuccinimide and reductive deiodination, to afford the fully functionalized methyl glycoside **34**. Routine steps led to aldehyde **35** which then underwent an aldol coupling with the lithium enolate derived from acetate **37** to yield a 1:1 mixture of epimers of **38**. After an oxidation/reduction sequence and functional group manipulations, ring-closing metathesis of **39**, catalyzed by the Schrock catalyst provided **40** as a 1:1 mixture of *E* and *Z* alkenes. Separation of the mixture and deprotection gave epothilone D (**4**) which underwent epoxidation to epothilone B (**2**).



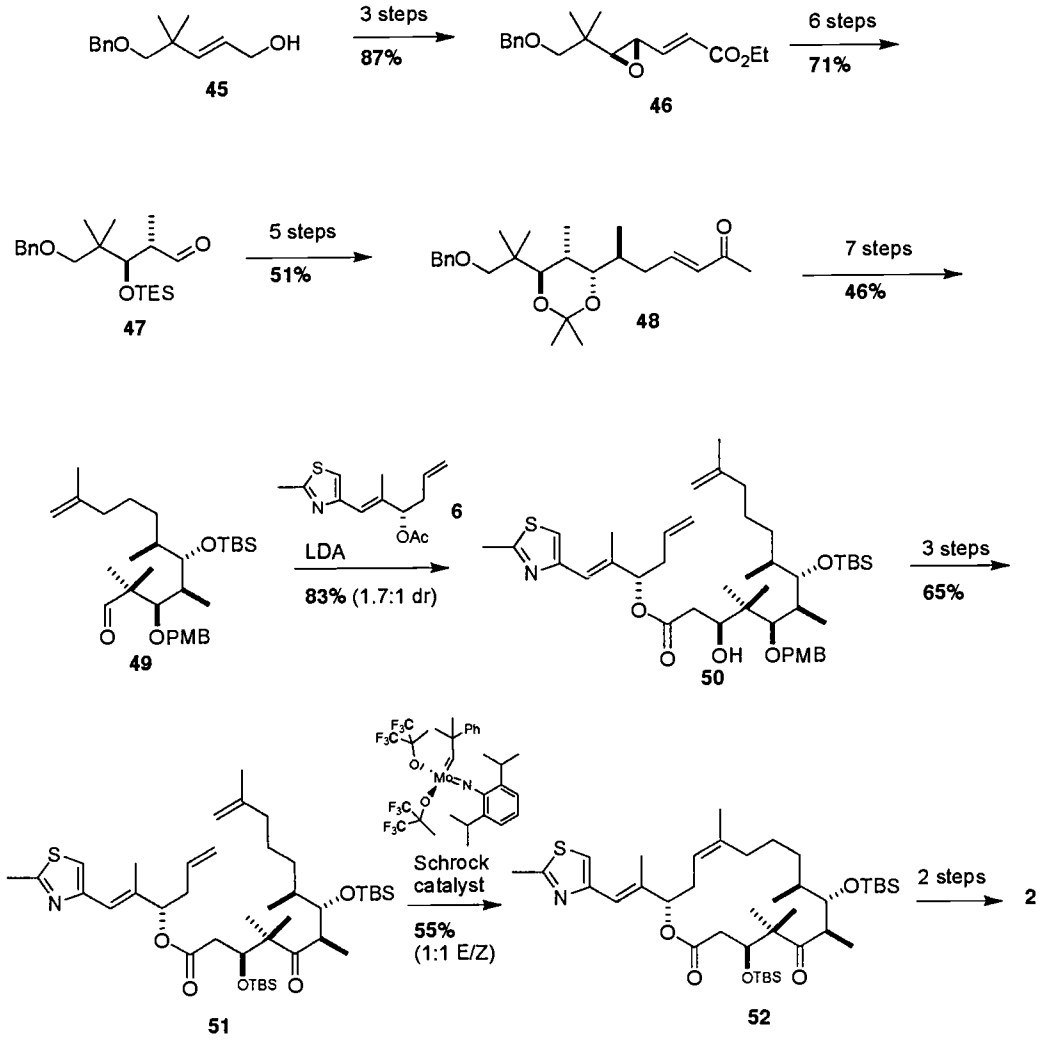
Scheme 2. Danishefsky's Ring-closing Metathesis Approach to Epothilone B.

In addition to the foregoing approach, Danishefsky attempted to utilize a ring-closing metathesis to form a C9-C10 olefin in an epothilone A precursor (**Scheme 3**). However, this strategy proved to be unsuccessful even after extensive experimentation; its failure was attributed to the dense functionalization in the C3-C8 region.



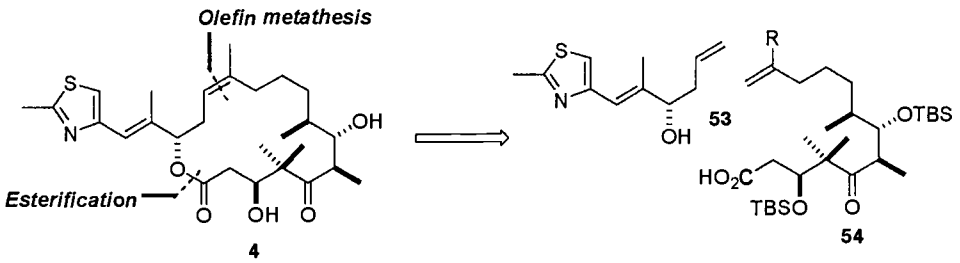
Scheme 3. Danishefsky's Failed Ring-closing Metathesis Approach.

Grieco's route to the C3-C13 subunit **31** commenced with a Sharpless asymmetric epoxidation of allylic alcohol **45** followed by oxidation and Horner olefination to yield ester **46** (**Scheme 4**). A regio- and stereocontrolled epoxide opening of **46** with trimethylaluminum, followed by protection of the resulting alcohol and functional group manipulations, led to aldehyde **47**. Crotylation using Roush's protocol set the required *syn,anti* arrangement, and routine transformations then afforded enone **48**. The enal **49** was produced by hydrogenation, Wittig olefination, debenzylation, and oxidation. Following analogous chemistry described by Danishesky, intermediate **49** was taken to epothilone B.



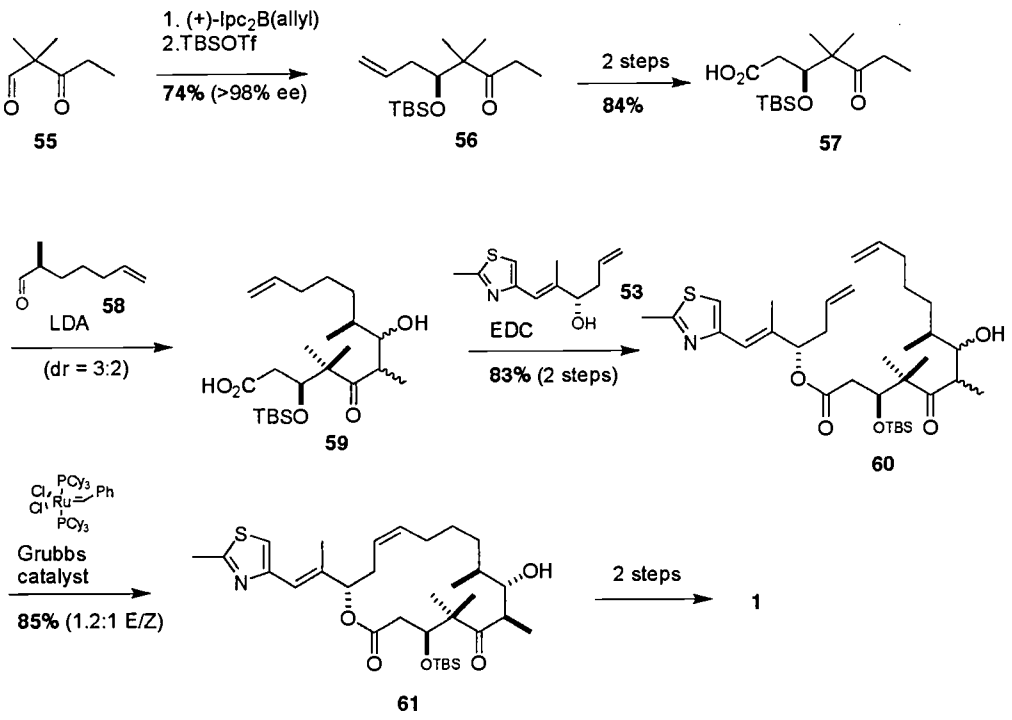
Scheme 4. Grieco's Ring-closing Metathesis Approach to Epothilone B

In each of the metathesis approaches used by Nicolaou, Schinzer, and Lerner the subunits **53** and **54** containing all the required stereogenic centers and were joined by esterification (**Scheme 5**).



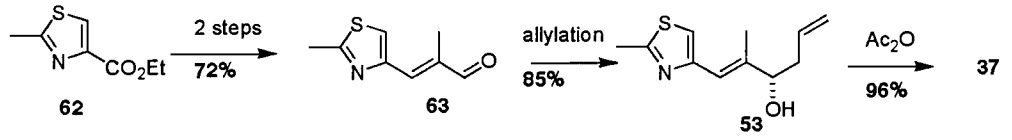
Scheme 5. Retrosynthesis of the Ring-closing Metathesis Approach used by Nicolaou, Schinzer, and Lerner.

Nicolaou's synthesis of the C1-C13 subunit **54** started with a Brown allylation of the readily available ketoaldehyde **55** to furnish **56** (**Scheme 6**). An aldol reaction between ketone **57** and aldehyde **58** yielded a 3:2 mixture of diastereomers; this mixture was treated with thiazole subunit **53** to give diene **60**. After separation of the diastereomeric mixture at this point, a ring-closing metathesis was performed with the ruthenium-based Grubbs catalyst to yield **61** as a 1.2:1 mixture of *E* and *Z* isomers. Deprotection of **61** and epoxidation completed the total synthesis of epothilone A (**1**).



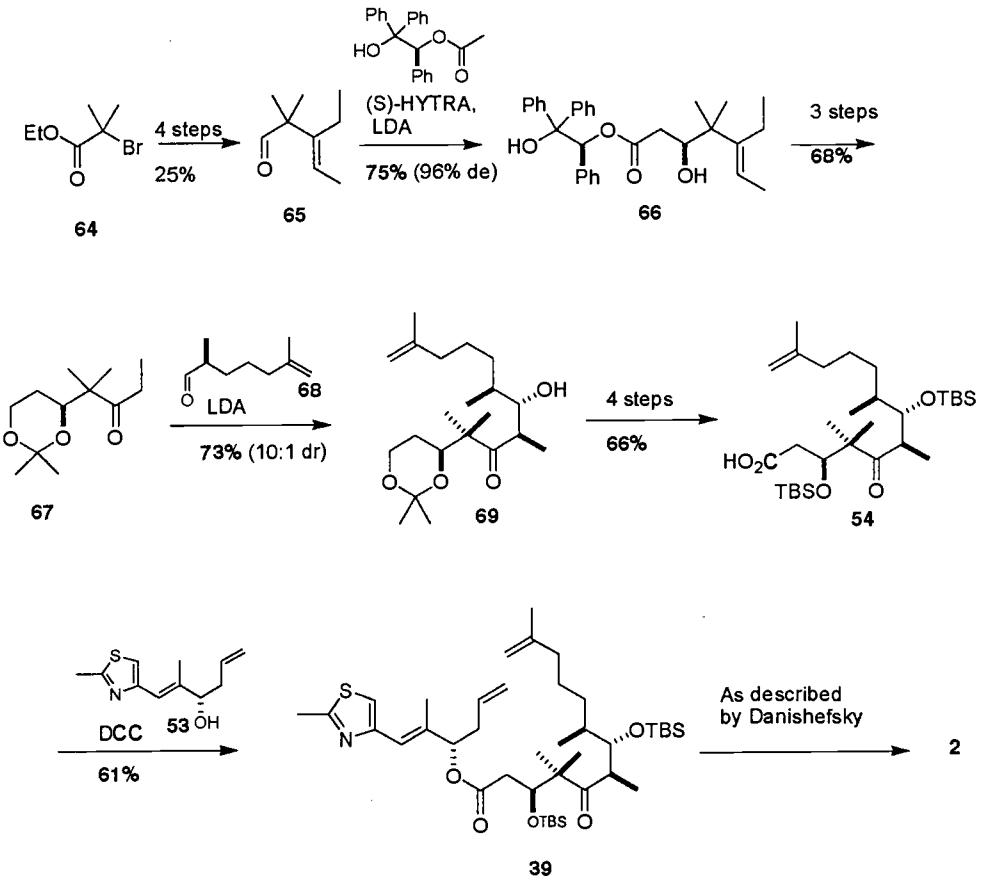
Scheme 6. Nicolaou's Ring-closing Metathesis Route to Epothilone A.

In the Nicolaou, Danishefsky and Grieco routes the thiazole subunit was prepared from 2-methylthiazolecarboxylate **62** (**Scheme 7**). Transformation to α, β-unsaturated aldehyde **63** followed by a Brown asymmetric allylation gave alcohol **53**, and treatment of **53** with acetic anhydride provided **37.** This method replaced Danishefsky's original route to **37** starting from (*R*) –glycidol.



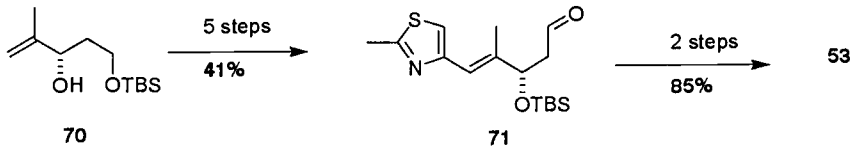
Scheme 7.

In Schinzer's preparation of the C1-C13 subunit **54**, ethyl ester **64** was advanced to aldehyde **65**, which was treated with the enolate of (*S*)-HYTRA to yield alcohol **66** in excellent diastereomeric excess (**Scheme 8**). Reduction and protection of the resultant diol as its acetal followed by ozonolysis led to ethyl ketone **67**. An aldol reaction between ketone **67** and aldehyde **68** yielded the desired adduct **69** in a 10:1 diasterometric ratio. Routine steps provided subunit **54** which eventually led to epothilone B (**2**).



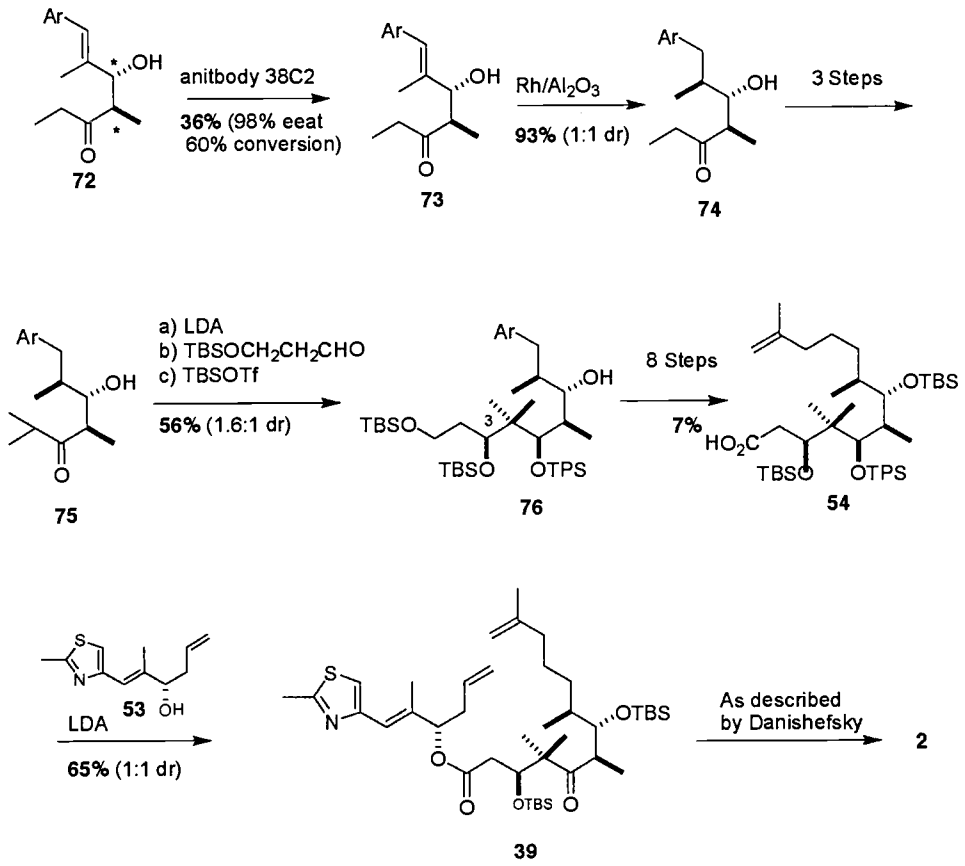
Scheme 8. Schinzer's Ring-closing Metathesis Route to Epothilone B.

Schinzer's preparation of thiazole intermediate **53** began from alcohol **70** which was obtained in 80% ee via a Sharpless kinetic resolution (**Scheme 9**). Straightforward reactions gave aldehyde **71** which then yielded **53**.



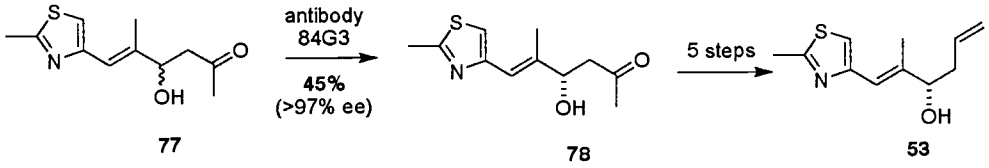
Scheme 9.

The Lerner and Sinha groups utilized an antibody-catalyzed kinetic resolution of racemic aldol product **72** followed by hydrogenation of **73** to deliver fragment **74** (**Scheme 10**). After transformation to ketone **75,** an aldol reaction was used to set the C3 stereocenter of **76** as a 1:1.6 diastereomeric mixture. Further transformations eventually led to carboxylic acid **54** which was coupled to **53** to give Danishefsky's intermediate **39.**



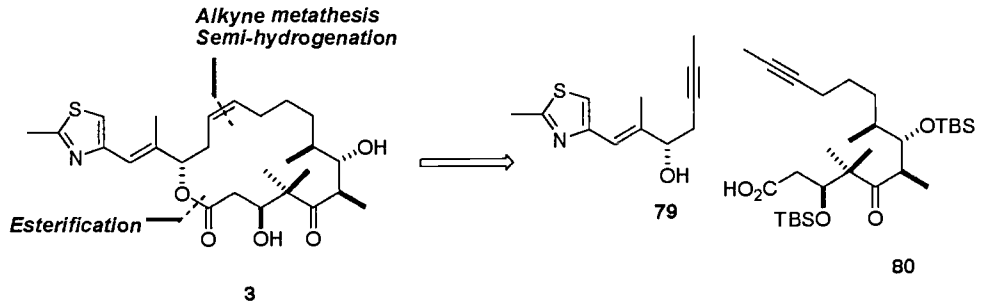
Scheme 10. The Lerner-Sinha Ring-closing Metathesis Approach to Epothilone B

The Lerner-Sinha group also made use of an antibody catalyzed kinetic resolution of racemic ketone **77** to provide the enantiomerically enriched hydroxy ketone **78** (**Scheme 11**). This then led to alcohol **53**.



Scheme 11.

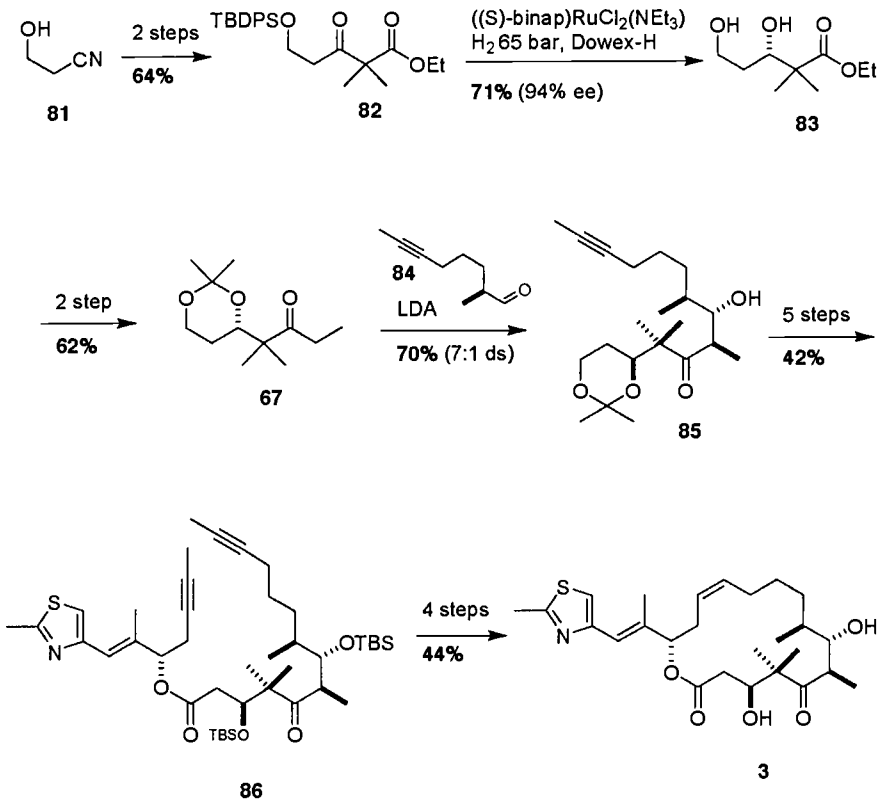
To avoid the mixture of *E*- and *Z*-olefins that had plagued other approaches to epothilones using ring-closing metatheses, Fürstner employed an alkyne metathesis followed by semi-hydrogenation to synthesize epothilone C (**3**). A retrosynthesis for this strategy is shown in **Scheme 12**.



Scheme 12. Retrosynthesis of Fürstner's Ring-closing Metathesis Approach.

Ethyl ketone **67**, efficiently prepared via a Noyori asymmetric hydrogenation of β-ketoester **82** followed by protection of the derived 1, 3-diol **83**, underwent an aldol reaction with aldehyde **84** to afford a 7:1 mixture of hydroxy ketones in which **85** was the major stereoisomer (**Scheme 13**). Subsequent chemistry provided the dialkyne **86** which, when treated with a molybdenum

amido complex, underwent macrocyclization. Semi-hydrogenation over Lindlar's catalyst, followed by deprotection and epoxidation, yielded epothilone C (**3**).

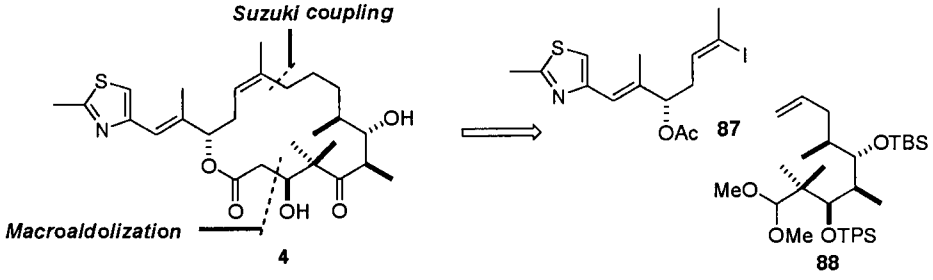


Scheme 13. Fürstner's Ring-closing Alkyne Metathesis Approach to Epothilone C

Suzuki Coupling Strategies

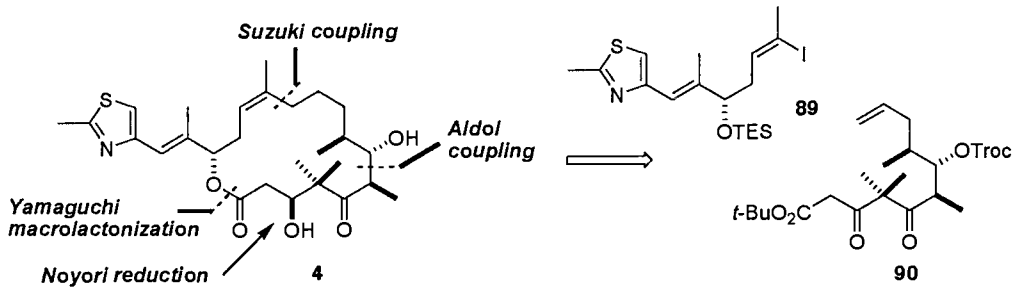
A strategy utilizing a Suzuki coupling between C11-C12 followed by a macroaldolization or a macrolactonization has been reported by three groups.

Danishefsky was the first to publish a B-alkyl Suzuki coupling of a borane derived from **88** with vinyl iodide **87** (**Scheme 14**).[23] This conjunction was followed by a macroaldolization. The fragments **87** and **88** were prepared by an extension of Danishefsky's earlier route using his metathesis strategy.



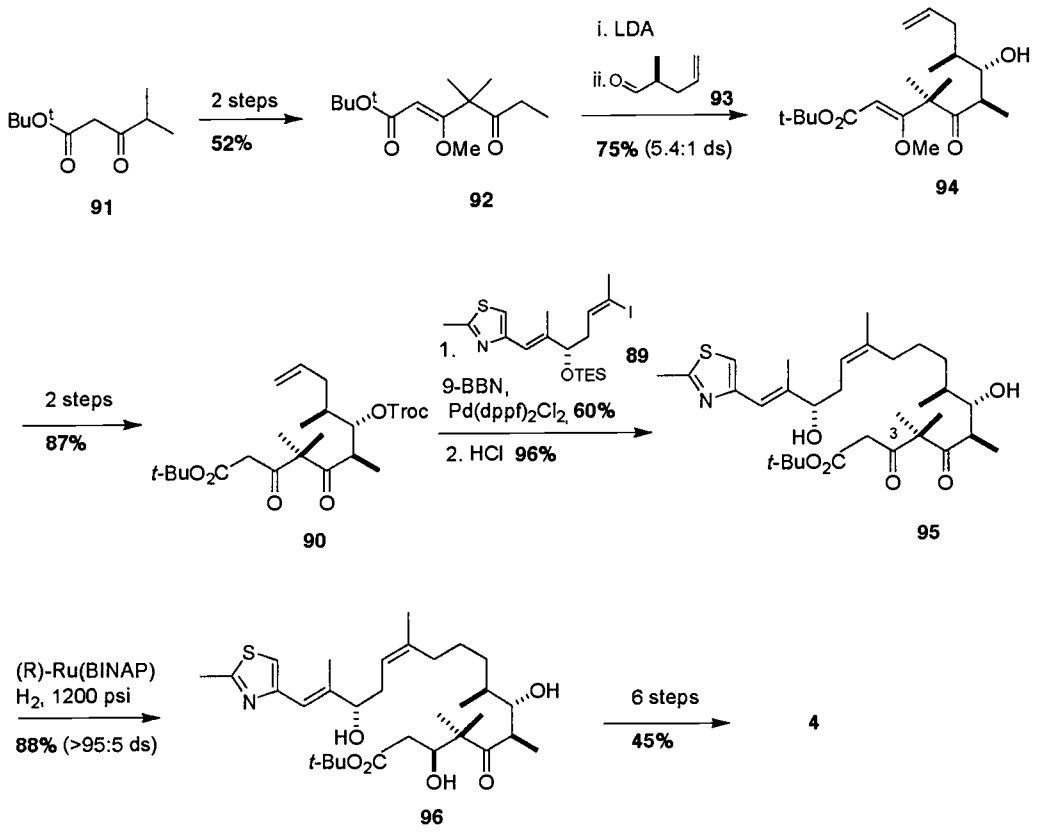
Scheme 14. Retrosynthesis of Danishefsky's Suzuki Coupling / Macroaldolization Approach.

In a revised approach to epothilone D, Danishefsky carried out a Suzuki coupling with a slightly more functionalized subunit **90** and vinyl iodide **89**.[24] The C3 ketone of **90** was reduced asymmetrically to the desired (3R) alcohol using a Noyori procedure. Final macrolactonization yielded **4**.



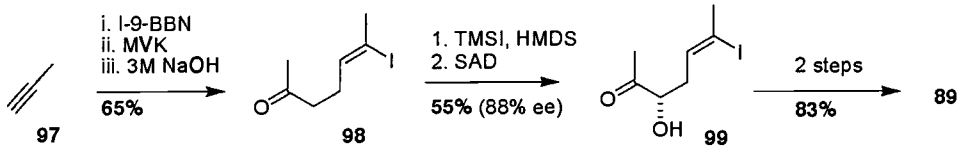
Scheme 15. Retrosynthesis of Danishefsky's Revised Suzuki Coupling Approach.

Condensation of ketoester **91** as its enol ether with propionyl chloride provided ketone **92,** and aldol coupling of **92** with aldehyde **93** yielded **94** as a 5.4:1 mixture of diastereomers. The desired stereoisomer was advanced to **90** which underwent a Suzuki coupling with vinyl iodide **89.** Deprotection then provided ester **95.** Asymmetric hydrogenation of the C3 keto moiety in **95** led to **96,** which was transformed into epothilone D (**4**).



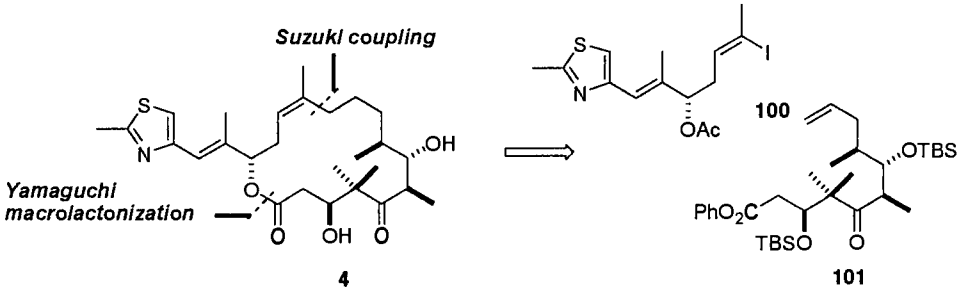
Scheme 16. Danishefsky's Revised Suzuki Coupling Approach.

The thiazole fragment **89** used for coupling with **90** was assembled from propyne (**97**) and methyl vinyl ketone via methyl ketone **98**.[25] Installation of the required (*S*) hydroxyl group was accomplished through a Sharpless asymmetric dihydroxylation of a silyl enol ether derived from **98.** The resultant α-hydroxy ketone **99** was converted to **89** using straightforward chemistry.



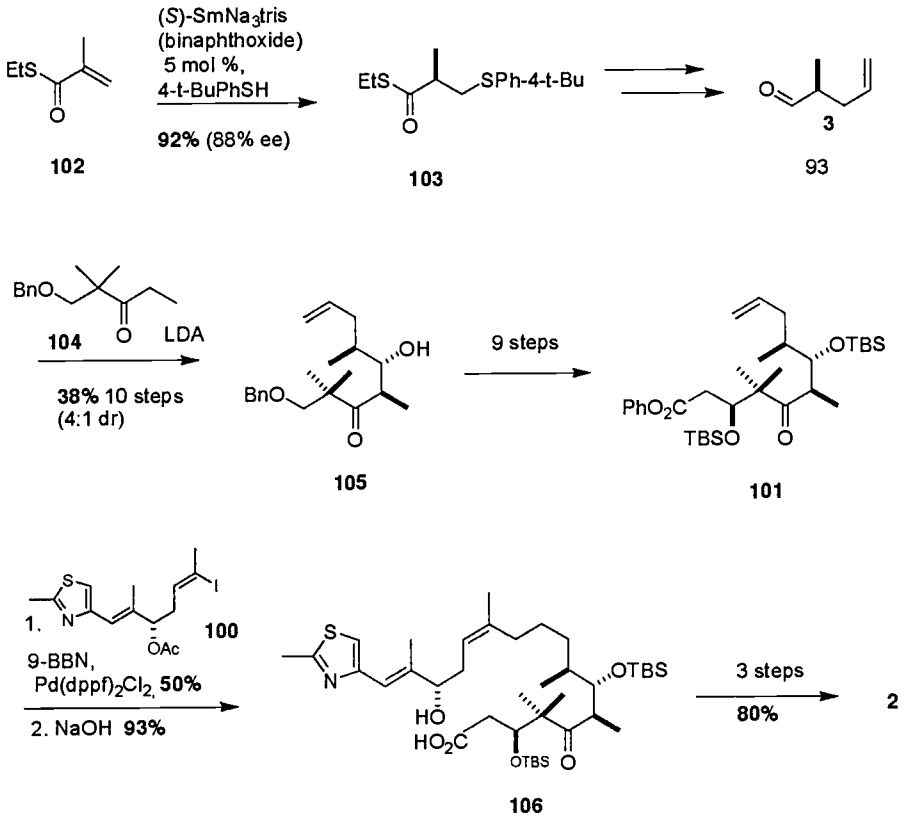
Scheme 17. Danishefsky's Revised Synthesis of the C12-C21 portion.

Shibasaki's variation of the Suzuki strategy takes advantage of the B-alkyl Suzuki coupling between vinyl iodide **100** and a fully functionalized C1-C11 propionate subunit **101**.[26] Transformation of the coupled product to a seco-acid and final macrolactonization led to epothilone D (**4**).



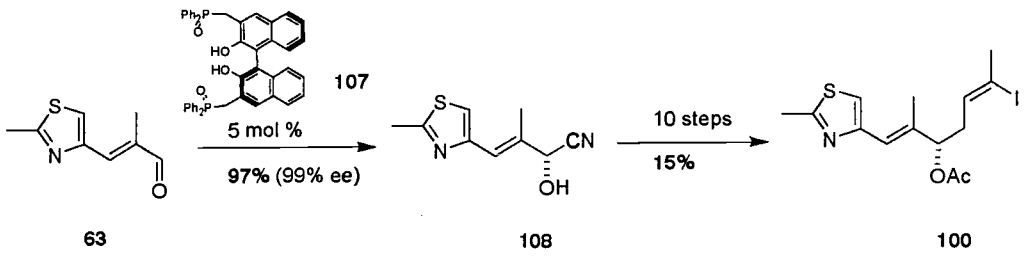
Scheme 18. Retrosynthesis of Shibasaki's Approach.

Thioester **103** was prepared by catalytic asymmetric protonation following thiol addition to the α,β–unsaturated thioester **102**. Subsequent elaboration into aldehyde **93** and aldol condensation with ketone **104** yielded **105** as a 4:1 mixture of diastereomers. Several more steps led to the desired alkene **101** which underwent Suzuki coupling with **100.** Further transformations then furnished epothilone B (**2**).



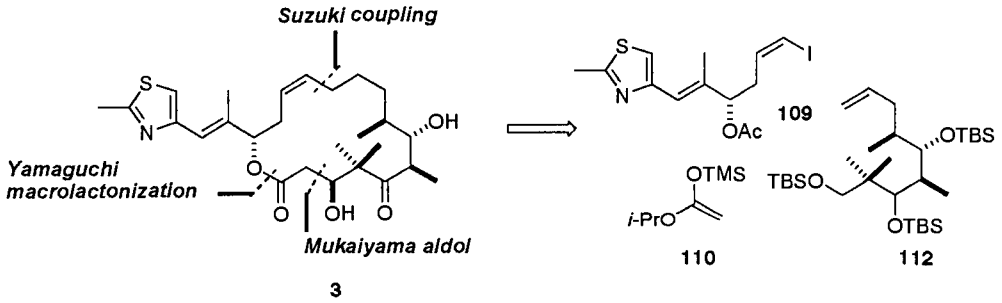
Scheme 19. Shibasaki's Approach to Epothilone B.

The thiazole fragment **100** employed in Shibasaki's route was prepared by a catalytic asymmetric cyanosilylation of the α,β-unsaturated aldehyde **63** using the bis(phosphine oxide)binaphthol-aluminum complex **107.** This gave cyanohydrin **108.**



Scheme 20. Shibasaki's Synthesis of the C12-C21 portion.

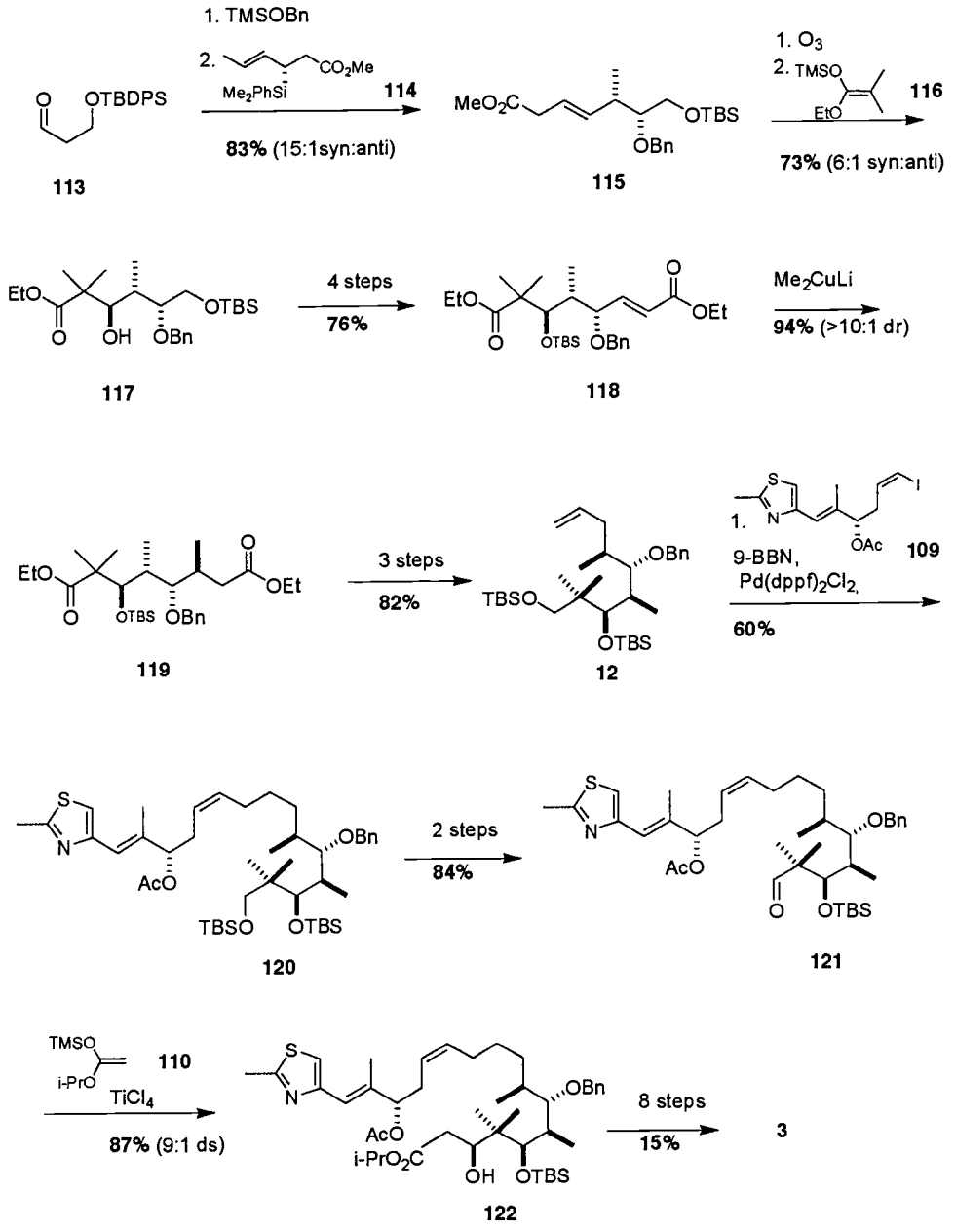
Panek's use of the Suzuki coupling accomplished a connection between vinyl iodide **109** and the C3-C11 subunit **112,** a fragment similar to that used in Danishefsky's earlier macroaldolization approach.[27] However, instead of the macroaldolization, which failed with Panek's substrate, a Mukaiyama aldol reaction using ketene actetal **110** was used prior to a Yamaguchi lactonization.



Scheme 21. Retrosynthesis of Panek's Suzuki Coupling Approach.

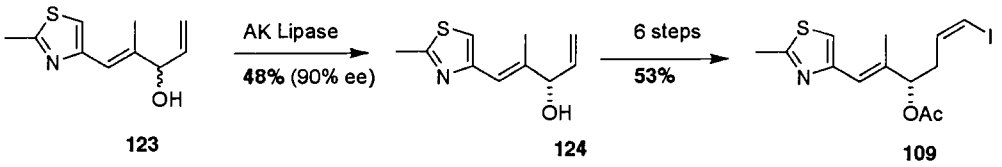
Synthesis of advanced intermediate **112** commenced with aldehyde **113** which was reacted with chiral silane **114** to give **115**. Ozonolytic cleavage of the alkene followed by a Mukaiyama aldol condensation with **116** provided ester **117**

which was advanced to diester **118.** Conjugate addition of lithium dimethylcuprate then gave **119**. Chemoselective DIBAL-H reduction of the diester **119** delivered a hydroxy aldehyde which was converted to alkene **112**, and Suzuki coupling of this substance with **109** afforded **120** and subsequently aldehyde **121.** When treated with silyl enol ether **110, 121** yielded aldol product **122**. which was taken to epothilone A (**3**).



Scheme 22. Panek's Synthesis of Epothilone A.

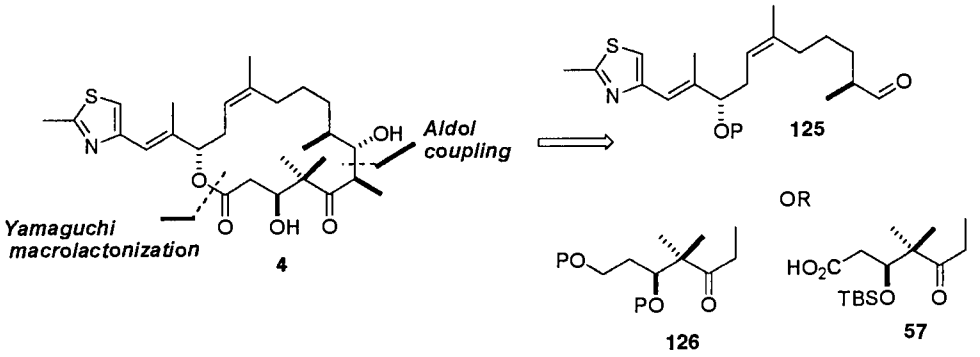
A novel aspect of Panek's synthesis of epotholine A was the preparation of the vinyl iodide **109** via a Lipase resolution of allylic alcohol **123.** This gave (S) alcohol **124** in good enantiomeric excess.



Scheme 23. Panek's Synthesis of the C12-C21 Portion of Epothilone A.

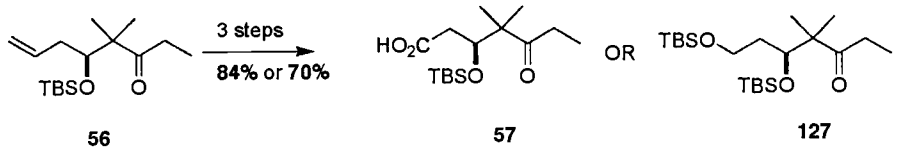
Aldol Strategies.

The most frequently used strategy of this type for epothilone synthesis is an aldol coupling of aldehyde **125** and ketone **126.** This approach has been employed successfully by Nicolaou,[28] Schinzer,[29] Mulzer,[30] Kalesse,[31] Taylor,[32] Avery,[33] and Thomas.[34] The main variation occurs with the ethyl ketone **126**. Several different protecting groups have been employed for **126**, and the keto carboxylic acid **57** has provided a further variant. The particular nature of the protecting group is believed to influence the stereochemical outcome of the aldol coupling.



Scheme 24. Common Aldol Strategies in Epothilone Synthesis.

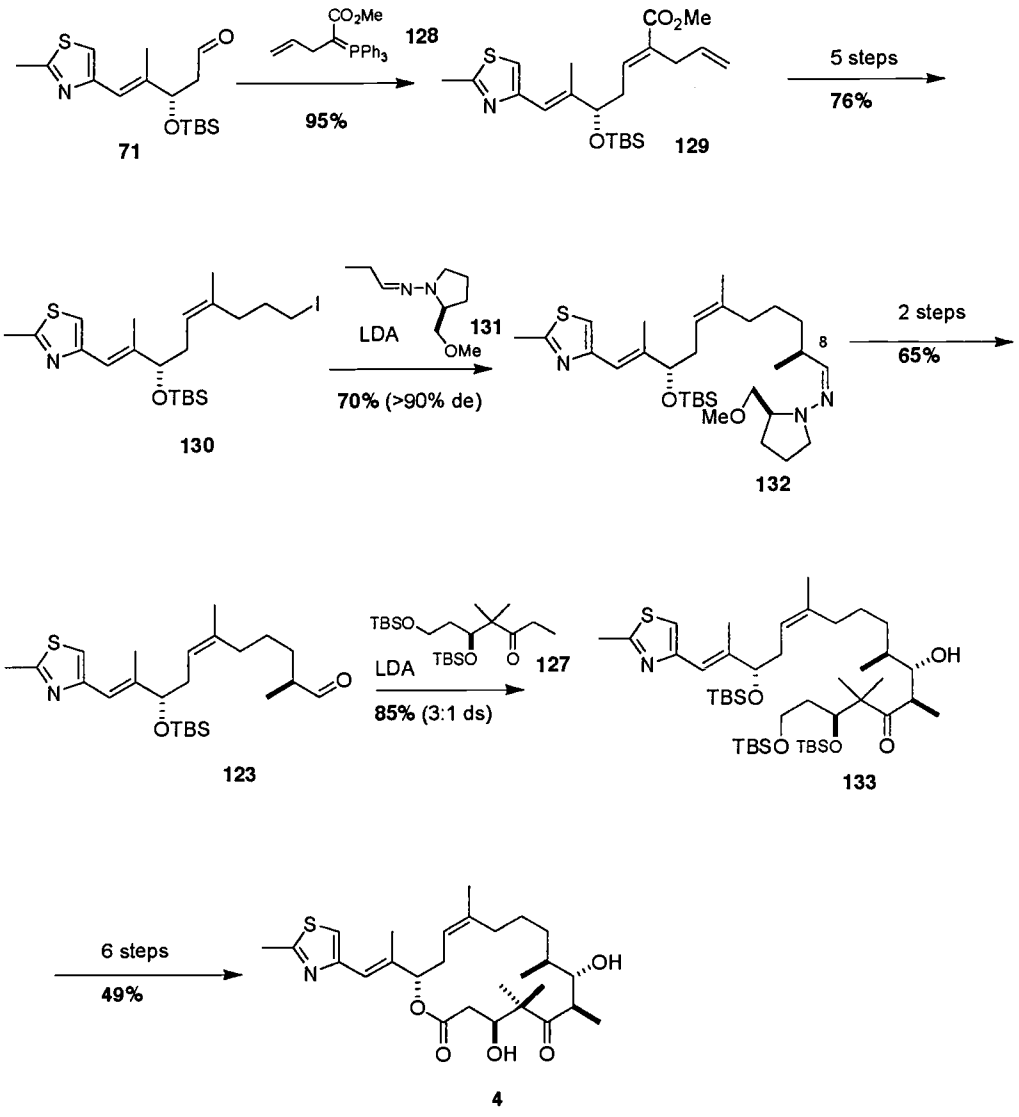
The ethyl ketones **57** and **127** used first by Nicolaou were prepared via a Brown asymmetric allylation of 2,2-dimethyl-3-oxopentanal, which gave **56.** Routine manipulations led from **56** to either **57** or **127**.



Scheme 25. Synthesis of Ethyl Ketones for Epothilones

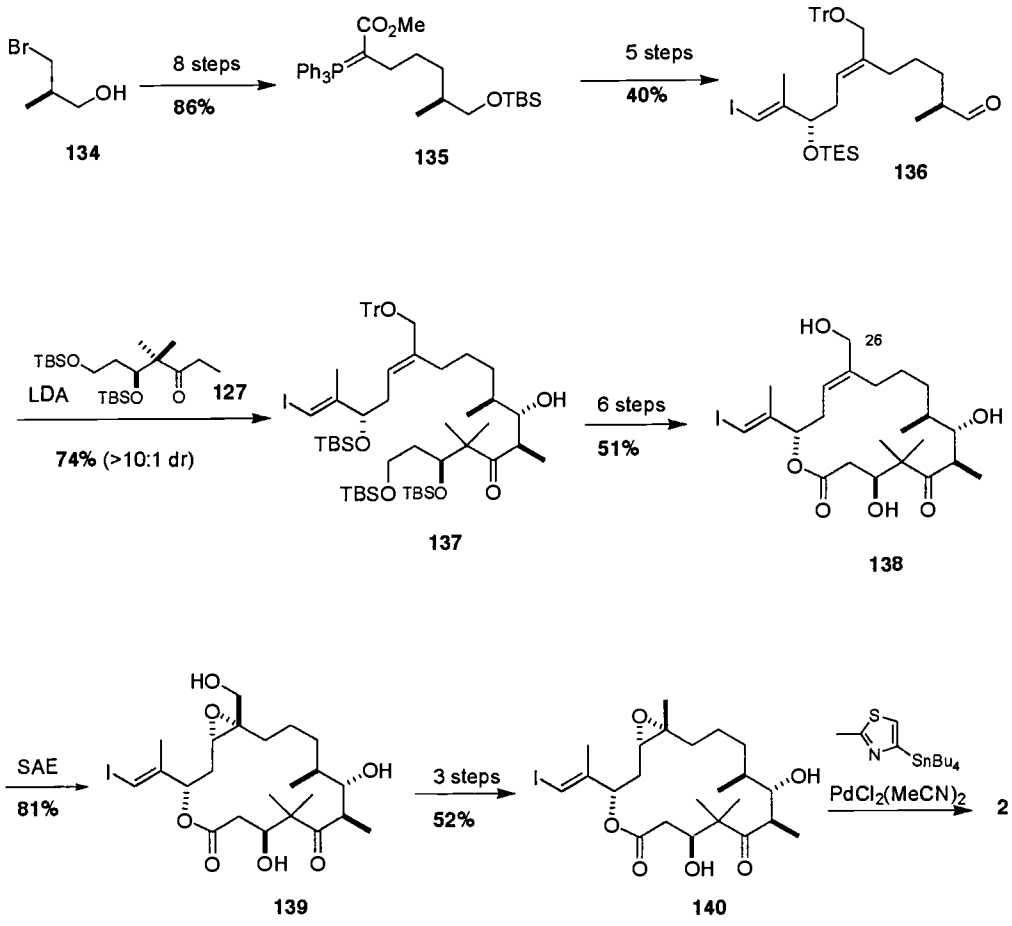
For the assembly of the C7-C21 subunit **125** Nicolaou employed a Wittig reaction of stabilized ylide **128** with aldehyde **71** to install the required trisubstituted olefin of **129.** An Ender's alkylation of **131** with iodide **130** set the (8S) methyl group in **132**. Initially, the aldol reaction between ethyl ketone **57** and aldehyde **125** resulted in a 1:1 mixture of diastereoisomers, but this poor selectivity was improved when ketone **127** was utilized and **133** was obtained as

a 3:1 mixture of diastereomers in good yield. The final steps employed the usual macrolactonization to furnish epothilone B (**2**).



Scheme 26. Nicolaou Early Aldol Approach to Epothilone B.

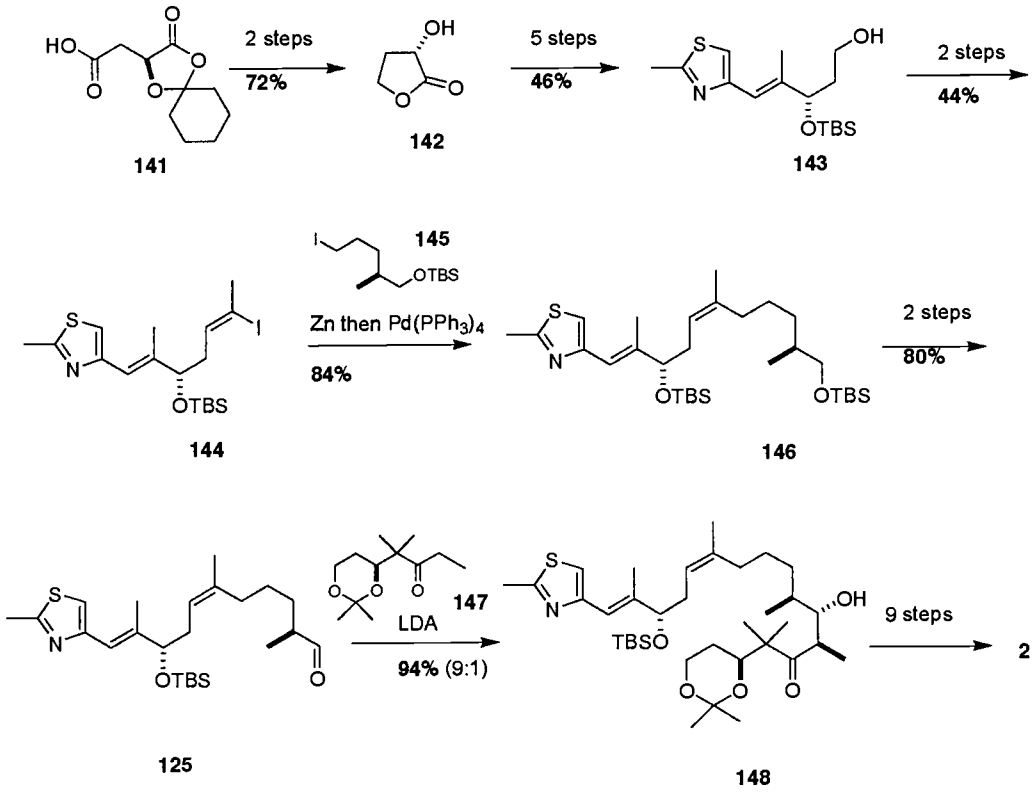
Nicolaou further refined this strategy by making use of the commercially available (2R)-3-bromo-2-methylpropanol (**134**) to assemble aldehyde **136**[35] via phosphorane **135**. This route, which employed **127** as the aldol partner for obtaining **137**, also took advantage of the C26 hydroxyl substitution to direct a Sharpless asymmetric epoxidation of **138** to yield **139.** A Stille coupling of **140** allowed attachment of a variety of aromatic groups to this scaffold in addition to the thiazole unit of **2**.



Scheme 27. Nicolaou's Revised Aldol Approach to Epothilone B.

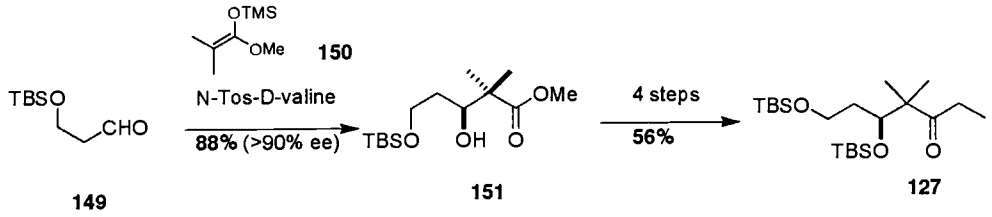
Schinzer assembled the aldehyde **125** in a quite different fashion by starting from carboxylic acid **141** and taking this substance via (2S)-2-hydroxybutyrolactone **142** to alcohol **143**. A Negishi coupling between vinyl iodide **144** and a zinc halide derived from iodide **145** gave **146** which then led to **125**. A stereoselective aldol reaction between aldehyde **125** and ethyl ketone

147 provided the desired β–hydroxy ketone **148** and an isomer in a 9:1 ratio. Straightfoward transformations then led to epothilone B (**2**).



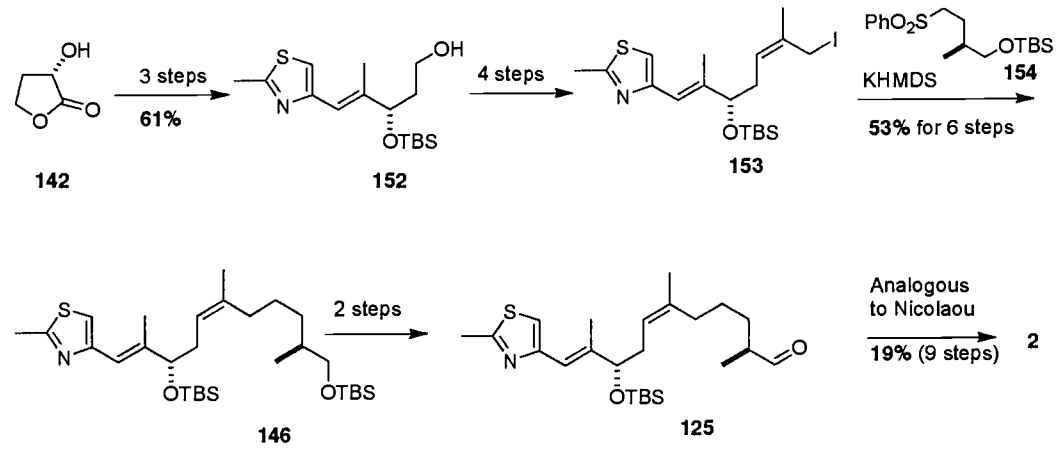
Scheme 28. Schinzer's Aldol Approach to Epothilone B.

Mulzer's synthesis of the ethyl ketone **127** featured an asymmetric Mukaiyama aldol reaction of the ketene acetal **150** and aldehyde **149** mediated by a chiral borane reagent formed by treating N-tosyl-D-valine with BH_3·THF. This gave β–hydroxyester **151** in high enantiomeric excess, which was readily converted to **127**.



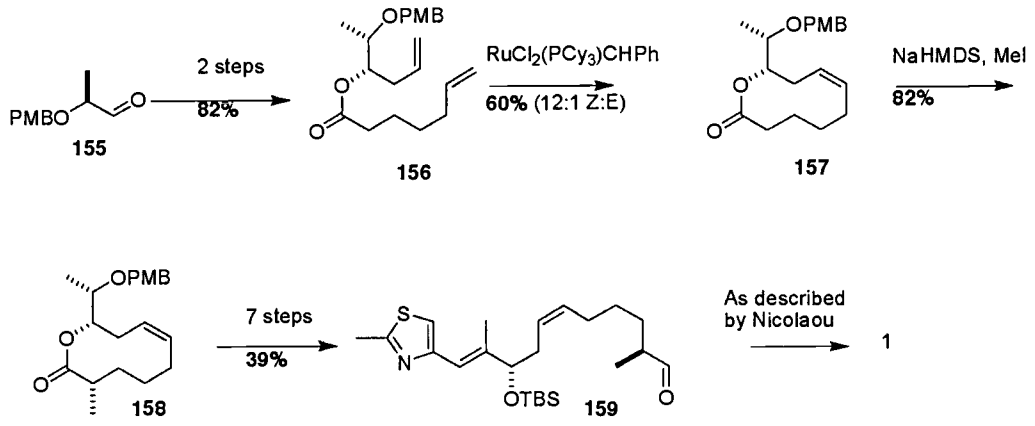
Scheme 29. Mulzer's Synthesis of Ethyl Ketone **127**.

In common with Schinzer's synthesis of aldehyde **125**, Mulzer's preparation of this compound also employed lactone **142**. The latter was transformed via alcohol **152** to an unstable allylic iodide **153**, and akylation of this substrate with the anion derived from the chiral sulfone **154** led via **146** to aldehyde **125**. This aldehyde was then processed by a route analogous to that developed by Nicolaou.



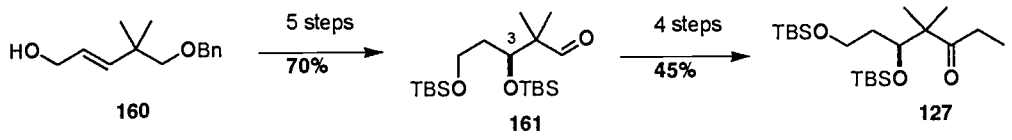
Scheme 30. Mulzer's Aldol Approach to Epothilone **B**.

The Kalesse strategy for acquiring aldehyde **159** needed for epothilone A employed a ring-closing metathesis of diene **156,** which furnished the desired Z-olefin **157** with high selectivity. Alkylation of lactone **157** yielded **158** which was advanced to aldehyde **159**. The configuration of the methyl substitutent in lactone **158** was confirmed by an independent synthesis. The aldehyde **159** was processed in an analogous manner to that employed by Nicolaou to yield epothilone A.



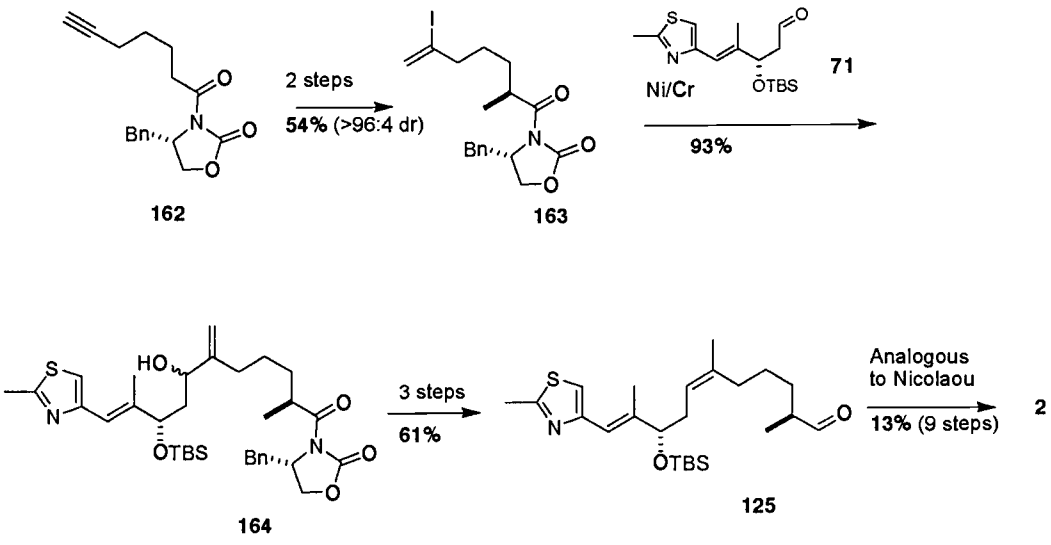
Scheme 31. The Kalesse Approach to Epothilone C.

The Kalesse group's route to ethyl ketone **127** made use of a Sharpless asymmetric dihydroxlation of **160** and subsequent Red-Al reduction of the resulting epoxide to install the C3 oxygen function of **161**. Routine chemistry from **161** produced ethyl ketone **127**.



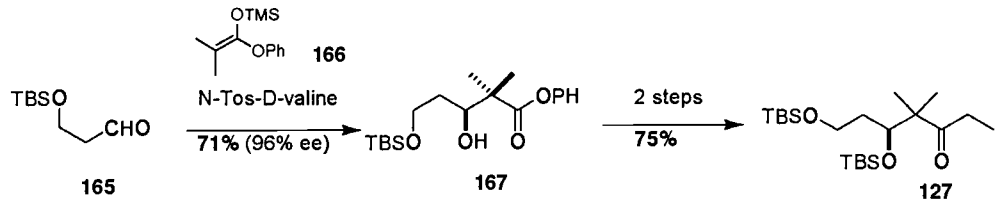
Scheme 32. The Kalesse Route to Ethyl Ketone **127**.

A recent synthesis of aldehyde **125** by Taylor utilized an efficient Nozaki-Hiyama-Kishi coupling to join vinyl iodide **163,** derived from alkyne **162,** with aldehyde **71**. A stereoselective rearrangement of the allylic alcohol **164** initiated with thionyl chloride smoothly provided the (Z)-trisubstituted double bond of **125**. This aldehyde was processed in an analogous manner to that developed by Nicolaou.



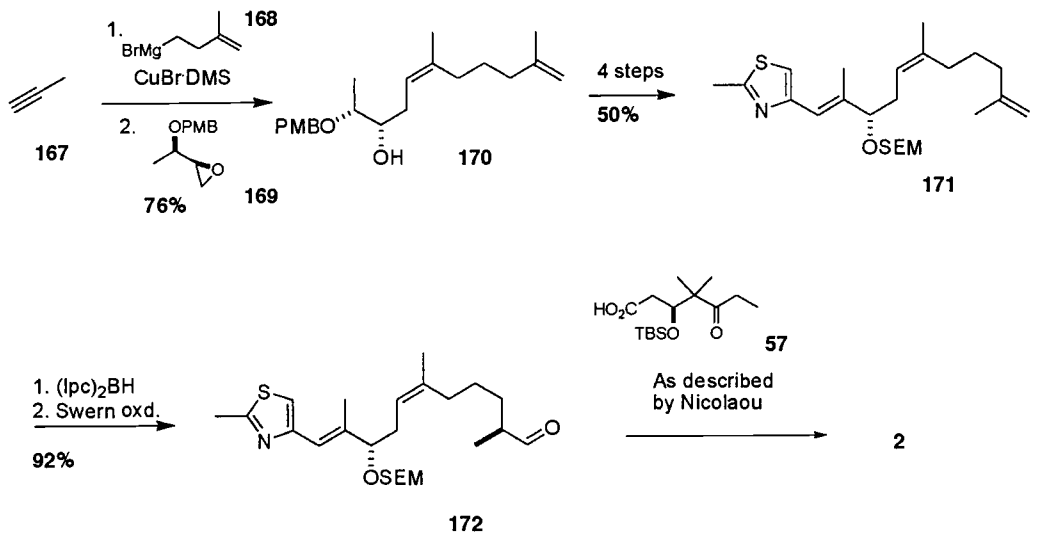
Scheme 33. Taylor's Route to Epothilone B.

Taylor's preparation of ethyl ketone **127** is essentially identical to that of Mulzer, with the exception that phenoxyketene acetal **166** was used instead of the methoxy derivative for the aldol reaction with of **165**. In addition to generating greater enantioselectivity with Kiyooka's boron reagent, the phenoxy substitution of **167** allowed direct access to the ethyl ketone **127**.



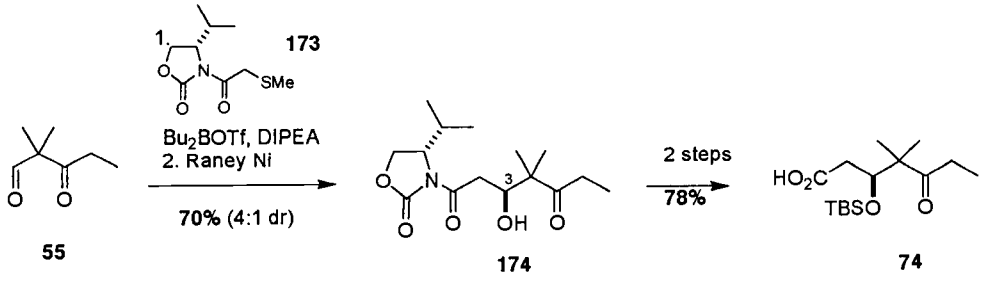
Scheme 34. Taylor's Route to Ehtyl Ketone **127**.

Avery's synthesis of aldehyde **172** began with a one-pot carbocupration of propyne and alkylation with epoxide **169** to furnish diene **170**. The terminal alkene of **171** was asymmetrically hydroborated and oxidized to give aldehyde **172**. This aldehyde was processed using Nicolaou's methodology, and eventally led to epothilone B (**2**).



Scheme 35. Avery's Approach to Epothilone B.

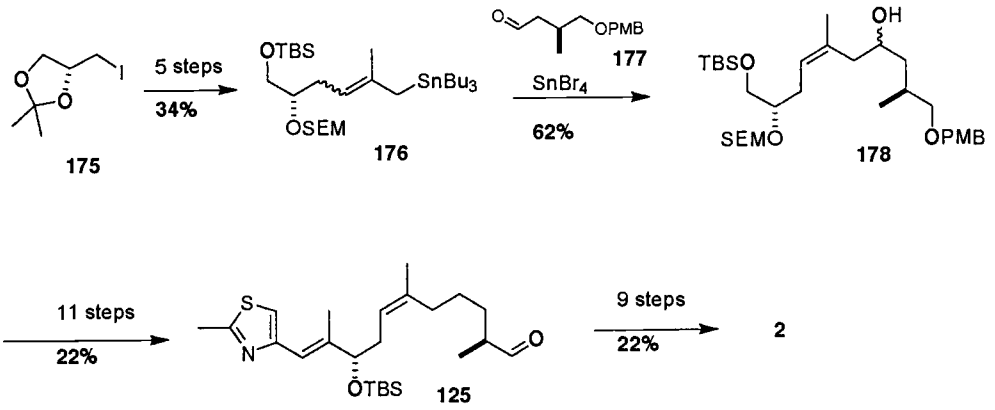
The route to ethyl ketone **74** devised by Avery set the (3*S*)-hydroxyl group as a 4:1 diastereomeric mixture via a boron-mediated aldol reaction between **55** and oxazolidinone **173**. Protection and subsequent saponification gave **74**.



Scheme 36. Avery's Route to Ethyl Ketone **74**.

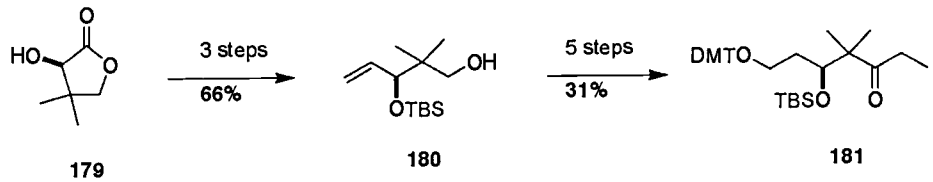
Thomas assembled aldehyde **125** by employing allyltin chemistry to set the (Z) configuration of the trisubstituted olefin. Treatment of aldehyde **177** with

allylstannane **176,** obtained from the glycerol derivative **175** yielded alcohol **178.** Further transformations delivered the required aldehyde **125** which again followed the route to epothilone B (**2**) developed by Nicolaou.



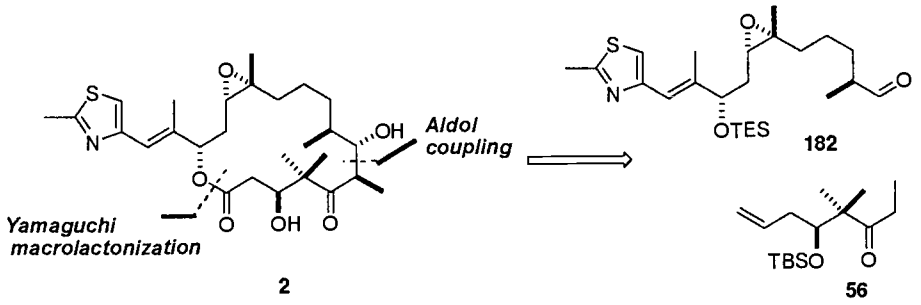
Scheme 37. The Thomas Approach to Epothilone B.

Thomas' synthesis of ethyl ketone **187** exploited the chiral starting material (R)-pantolactone (**179**) by converting this commercially available substance to **181** via alcohol **180.** The sequence proceeded smoothly with a moderate overall yield.



Scheme 38. Thomas' Route to Ethyl Ketone **181.**

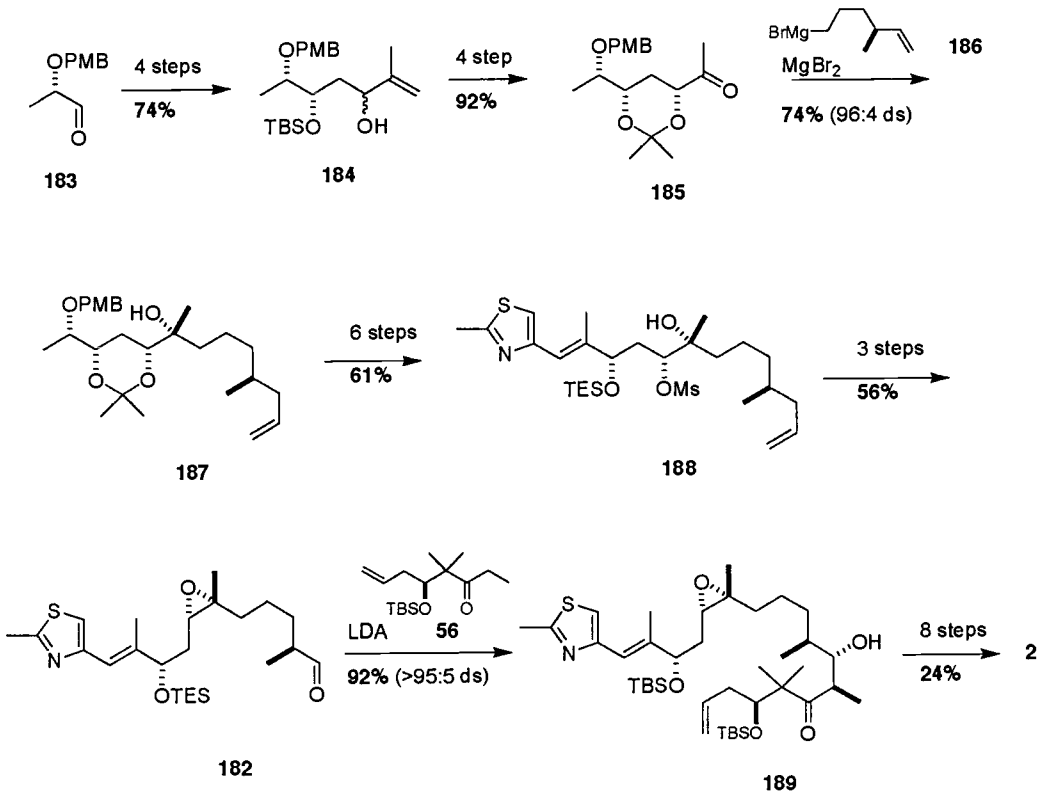
Mulzer[36] and Carreira[37] employed the same convergent aldol strategy as that pioneered by Nicolaou, but in their syntheses the aldehyde subunit **182** was functionalized with the epoxide corresponding to a direct epothilone B precursor. The aldol coupling between ethyl ketone **56** and **182** is claimed by Mulzer to show greater diastereoselectivity than the analogous reaction of **56** with aldehyde **125.** In addition, this approach avoids the somewhat variable stereoselectivity reported for the epoxidation of epothilone D (**4**) to epothilone B (**2**).



Scheme 39. Retrosynthesis of an Aldol Strategy used by Mulzer and Carreira.

Mulzer's synthesis of aldehyde **182** started with the functionalization of (*S*)-lactic acid (**183**). The resultant diastereomeric mixture **184** was enriched in the desired diastereomer via thermodynamic equilibration of methyl ketone **185.** A Grignard reaction with **186** gave tertiary alcohol **187** which was taken on to **188**. The epoxide **182,** which was derived from mesylate **188**, was treated with

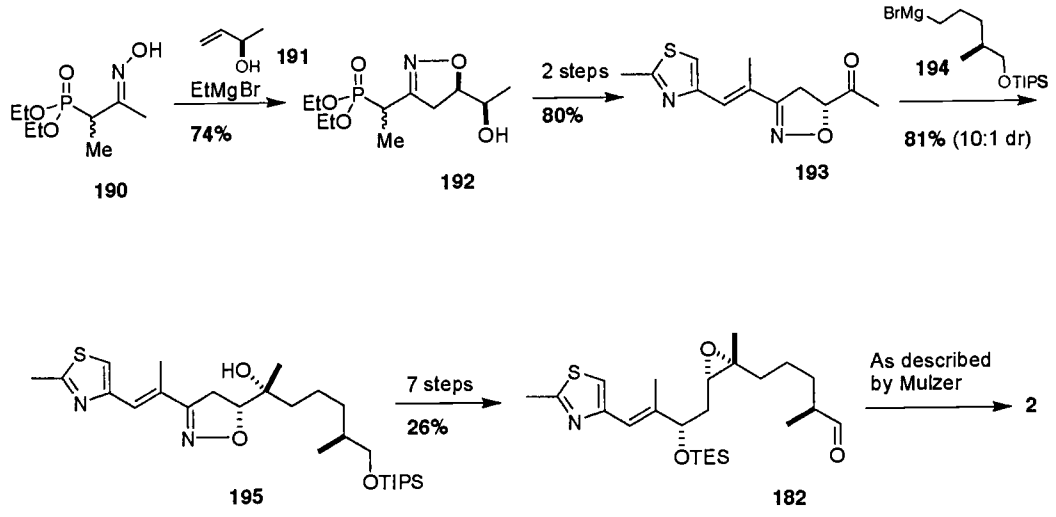
the lithium enolate of ketone **56** to give hydroxy ketone **189** in greater than a 95:5 diastereomeric ratio, and extension of this sequence led to epothilone B (**2**).



Scheme 40. Mulzer's Route to Epothilone B Using an Epoxyaldehyde.

Carreira assembled aldehyde **182** using a novel stereoselective dipolar cycloaddition of a (3*R*)-but-1-en-3-ol (**191**) with a nitrile oxide generated from oxime **190**. After elaboration of the resultant phosphonate **192**, diastereoselective reduction of the isoxazoline **193** to a diol and conversion to the desired epoxide

via a cyclic sulfite efficiently provided aldehyde **182**. This aldehyde was then processed as described by Mulzer to yield epothilone B (**2**).



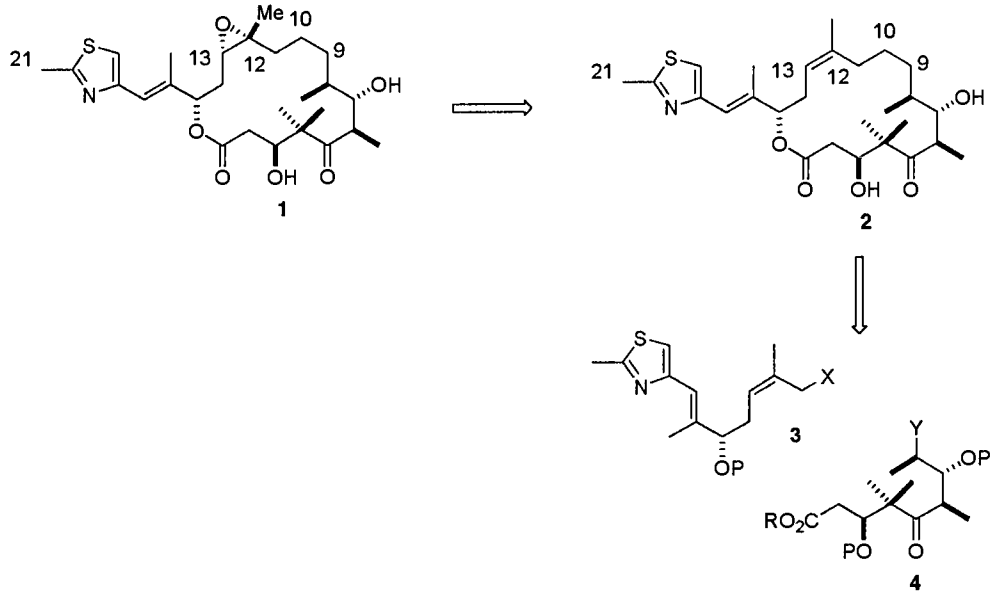
Scheme 41. Carreira's Route to Epothilone B Using an Epoxyaldehyde.

Chapter 2

Results and Discussion

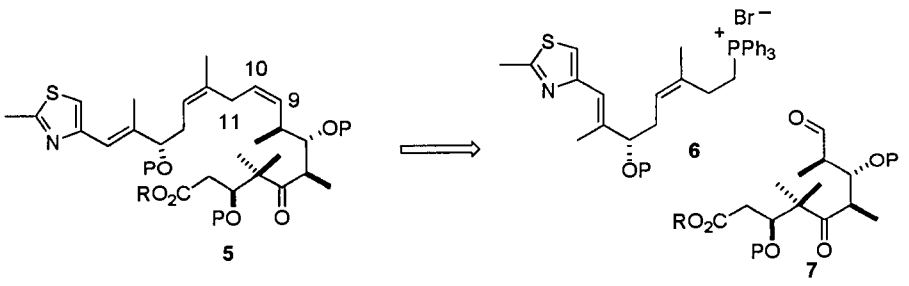
Retrosynthetic analysis

From the outset, our primary goal was the development of a synthetic route to the epothilones which would embody the highest possible degree of stereocontrol. We considered it especially important to establish clean *Z* geometry of the 12,13-trisubstituted double bond and to set in place the stereocenters at C6, C7, and C15 with complete stereochemical accuracy; at the time such a goal had not been achieved in the published routes to the epothilones. As our plan for a convergent synthesis unfolded, it became evident that an attractive means for connecting two major subunits **3** and **4** of epothilone D would be via C-C bond formation at C9-C10 (**Scheme 1**).



Scheme 1

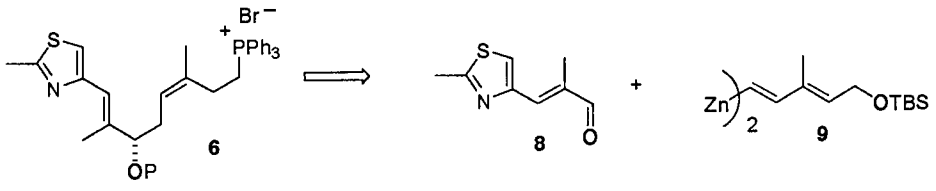
This plan would not only allow for the incorporation of functionality in a domain of the macrolide which has not been extensively explored from the viewpoint of analogue synthesis, i.e. C9-C11, but would also offer an opportunity to constrain a region of the perimeter thought to be somewhat flexible.[38] The principle of reducing flexibility and thereby limiting the unfavorable entropy loss upon binding has been widely used. Indeed, application of conformational constraints to a molecule represents a classical and significant medicinal chemistry technique that seeks to improve both structural and dynamic properties contributing to the biological potency, receptor selectivity, metabolic stability, bioavailability and efficacy of a therapeutically important compound. The first plan envisioned a Wittig olefination to connect phosphorane **6** with aldehyde **7**, thus setting in place a C9-C10 double bond as depicted in **5** (**Scheme 2**).



Scheme 2

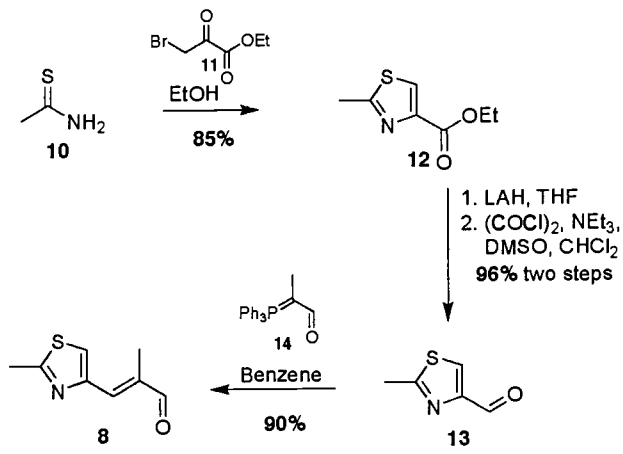
The C10-21 Subunit

Our initial approach towards the synthesis of a C10-C21 subunit relied on two key reactions to rapidly install the required carbon framework and functionality in the correct configuration. The first of these reactions depended on the ability of a chiral catalyst, 3-exo-dimethylaminoisoborneol (DAIB) to induce an asymmetric akylation of aldehyde **8** with vinylzinc species **9**, and the second key transformation rested on a selective hydrogenation of the resulting 1,3-diene to set in place the required trisubstituted olefin (**Scheme 3**).[39]



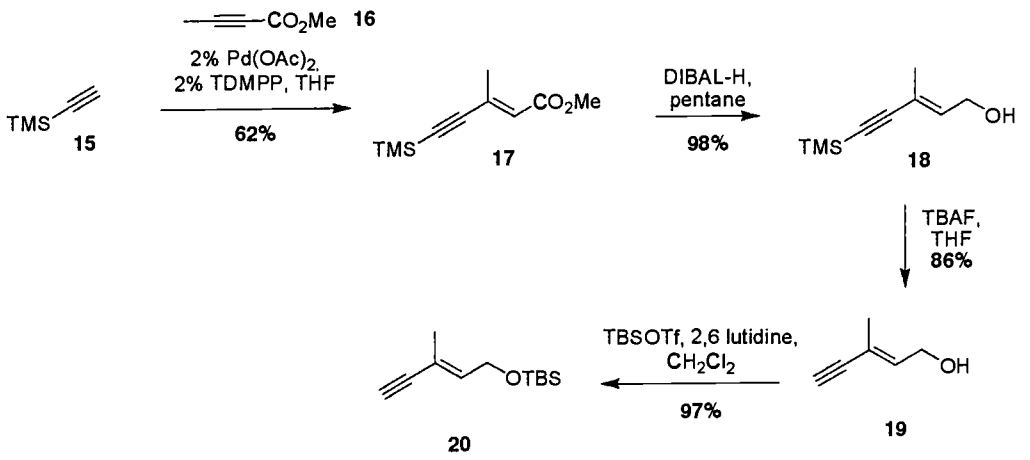
Scheme 3

Implementation of this plan began with the preparation of aldehyde **8**[40] and enyne **20**[41] according to known procedures. Aldehyde **8** was synthesized by condensing thioacetamide (**10**) and ethyl bromopyruvate (**11**) to yield thiazole **12.** Reduction of **12** with lithium aluminum hydride and Swern oxidation provided aldehyde **13.**[42] Homologation of **13** was then accomplished with the commercially available ylide **14** to afford aldehyde **8** (**Scheme 4).**



Scheme 4

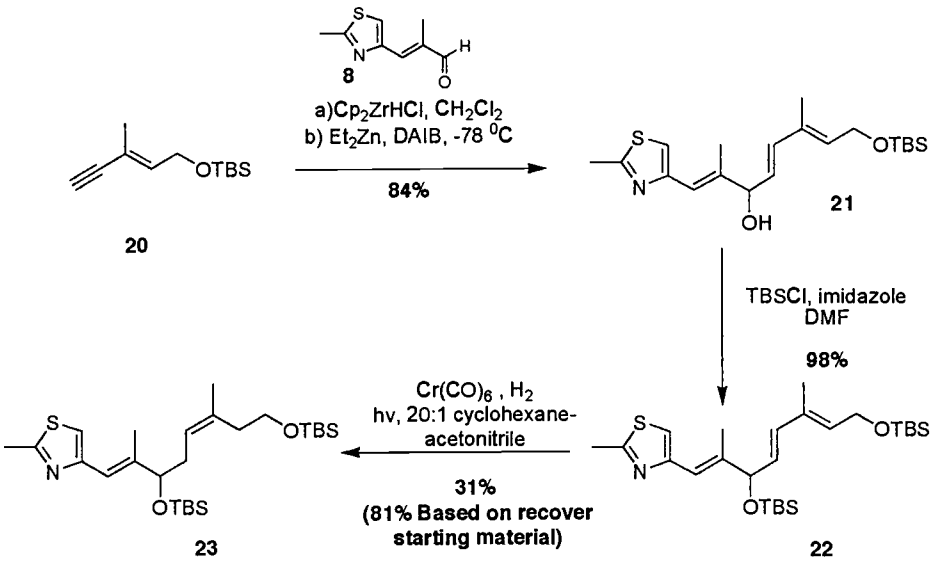
Enyne **20** was prepared by a palladium catalyzed addition of (trimethylsilyl)acetylene (**15**) to methyl-2-butynoate (**16**). Thus treatment of (trimethylsilyl)acetylene and methyl 2-butynoate with palladium acetate and tris(2,6-dimethoxyphenyl)phosphine (TDMPP) provided enyne **17**, and reduction of thioester was achieved with diisobutylaluminum hydride to give alcohol **18**. Desilylation of **18** yielded enyne **19**, and protection of this alcohol as its silyl ether **20** was accomplished using *tert*-butyldimethlysilyl trifluoromethanesulfonate (**Scheme 5**).



Scheme 5

The joining of **8** and **20** proceeded with the hydrozirconation of enyne **20** and transmetallation with diethyl zinc followed by treatment with aldehyde **8** in the presence of (-)-DAIB yielded bis-allylic alcohol **21.** However only racemic material could be obtained from this sequence. Since the zirconium manifold acted to accelerate the reaction without any asymmetric induction, attempts to couple **20** with **8** via hydroboration was tried, but this failed to deliver any coupled material. In any event, the racemic material **21** did prove useful and was carried on as planned. Protection of the secondary alcohol of **21** as its *tert*-butyldimethysilyl ether provided bis-silylether **22** which was then the subject of the second key transformation, introduction of the required Z-trisubstituted olefin. Chemoselective conversion of the conjugated diene **22** via a 1, 4 hydrogenation cleanly provided the desired trisubstituted olefin **23**. The optimal conditions for this homogenous transformation include photo-activation of chromium hexacarbonyl in a 20:1 cyclohexane-acetonitrile solution through which a gentle

stream of hydrogen was passed followed by introduction of the diene substrate. These conditions allowed the reduction of **22** to proceed smoothly at ambient temperature and pressure (**Scheme 6**).



Scheme 6

The stereochemical course of this reduction is believed to proceed through a cisoid-complexed diene system which after intramolecular delivery of hydrogen from the chromium results in the exclusive formation of a Z olefin (**Figure 1**).

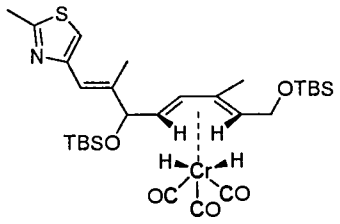
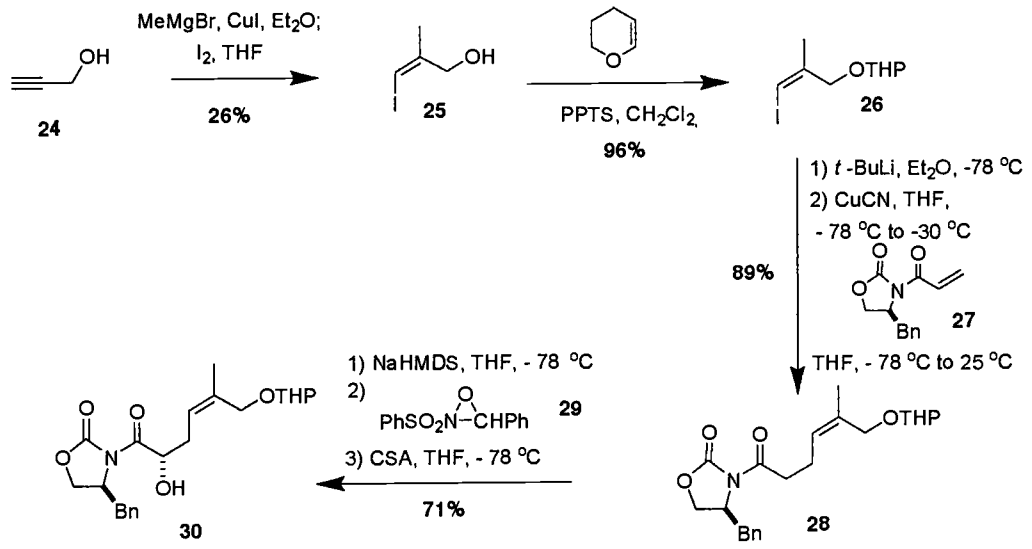


Figure 1 Cisoid-chromium complexed diene.

Although we had achieved one of the goals for our synthesis of epothilone D, namely to establish clean Z geometry of the C12-C13 double bond, our failure to generate the C15 alcohol in enantiopure form led us to revise the sythesis of the C11-C21 subunit in favor of a stereoselective route.

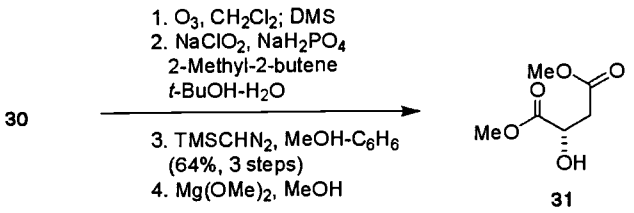
The copper-catalyzed carbomagnesiation of propargyl alcohol (**24**) has been shown to be a rare example of a trans-carbometalation which proceeds with clean regio- and stereoselectivity to give iodo alcohol **25**,[43] and although the yield of this conversion is low, the minimal cost of reagents makes this an acceptable process for constructing a functionalized trisubstituted alkene suitable for our purpose. The hydroxyl group of **25** was protected in order to permit the extension of the synthesis from this substrate. The tetrahydropyranyl ether **26**, was prepared by treating **25** with dihydropyran and an acidic catalyst. This vinyl iodide was next subjected to halogen-metal exchange using two equivalents of *tert*-butyllithium to generate irreversibly the (Z) vinyllithium species. Transmetalation with cuprous cyanide gave an alkenylcopper reagent which underwent conjugate addition to (*S*)-3-acryloyl-4-benzyloxazolidin-2-one (**27**).[44] Not only does this transformation extend the carbon backbone of fragment **26**, it also incorporates a chiral auxiliary which is exploited in the following step. Installation of the C15 hydroxyl group proceeded through the formation of the sodium enolate of oxazolidinone **28**[45] at –78 °C using sodium hexamethyldisilylazide as the base, followed by rapid addition to a precooled solution of Davis' oxaziridine **29**.[46] Quenching of the reaction with

camphorsulfonic acid afforded alcohol **30** with diastereoselectivity >98:2 (**Scheme 7**). This highly selective α-hydroxyation method is based on an Evans' protocol.[7]



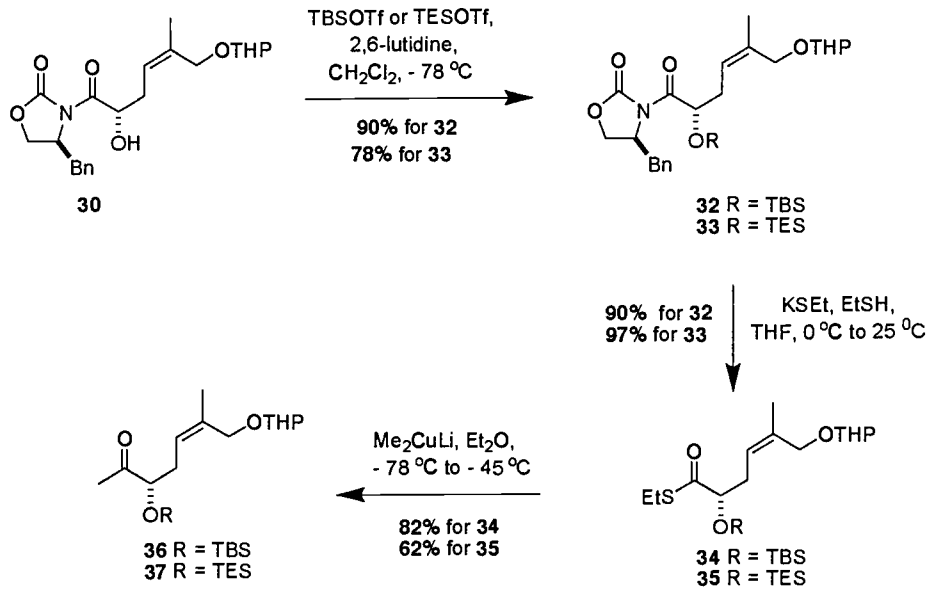
Scheme 7

The (*S*) configuration of the hydroxyl substituent in **30** was confirmed by its ozonolytic degradation to dimethyl (*S*)-maleate (**31**) (**Scheme 8**).



Scheme 8

Protection of the secondary alcohol **30** as either its *tert*-butyldimethylsilyl ether **32** or triethylsilyl ether **33** occurred as expected under standard conditions. The initial choice of the *tert*-butyldimethylsilyl protecting group was based on earlier reports that epothilone syntheses had successfully utilized this group; however, the triethylsilyl ether **33** was anticipated to be more suitable for our purpose. Cleavage of the oxazolidinone auxiliary using catalytic potassium ethanethiolate furnished the thioesters **34** and **35** in good yield and also led to >90% recovery of the chiral auxiliary. This mild cleavage method, due originally to Evans,[47] was favored over alternative methods for several reasons, including the fact that no racemization α to the thioester occurs. Both thioester **34** and **35** proved to be excellent substrates for introduction of the requisite methyl ketones **36** and **37** through reaction with lithium dimethylcuprate. The optimum conditions for this transformation occured when the cuprate was generated rapidly at 0 °C, then cooled to –50 °C before addition of the thioester substrates (**Scheme 9**).

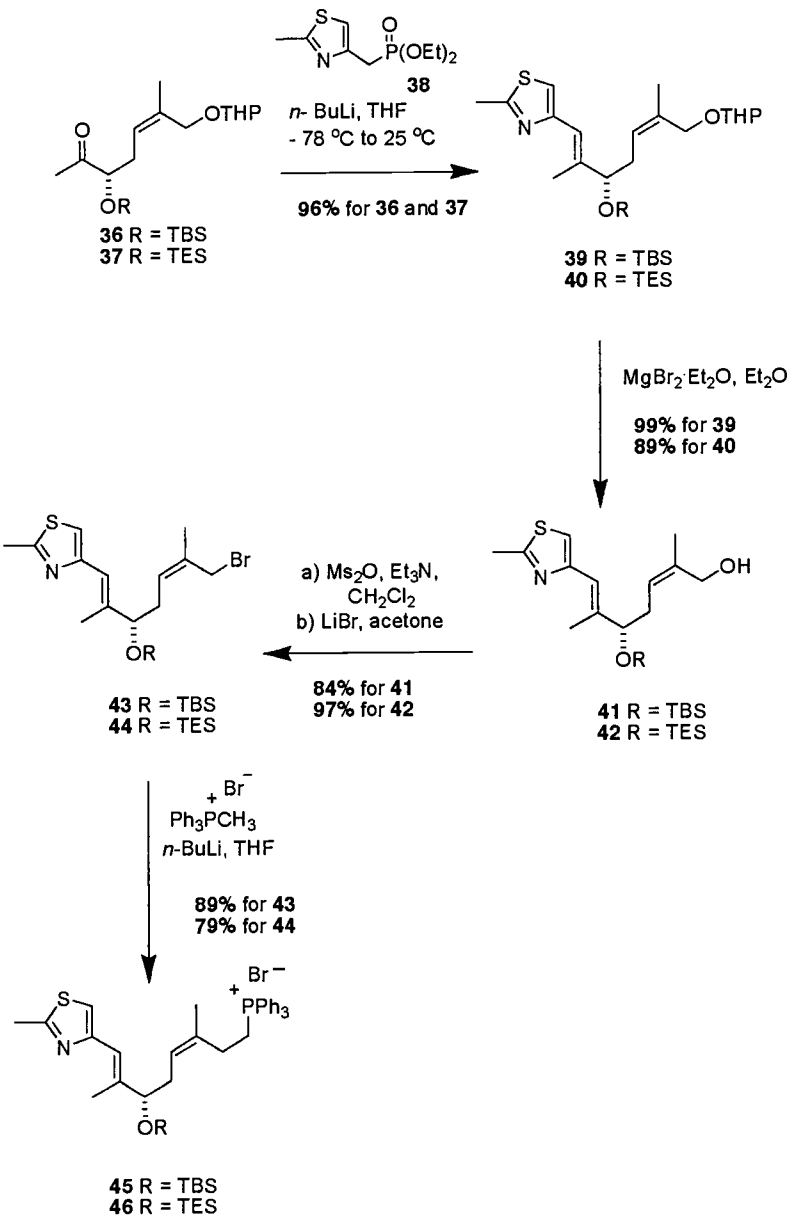


Scheme 9

Elaboration of methyl ketones **36** and **37** towards the complete thiazole side chain was our next challenge, the principal issue being installation of an (*E*)-trisubstituted olefin in this process. Wadsworth-Emmons olefination of ketones **36** and **37** with the lithium anion of the known phosphonate **38**[48] furnished the *E,Z* dienes **39** and **40**, accompanied by only a trace (<5%) of the *Z,Z* isomers. The latter was easily removed from the mixture by rapid chromatography, leading to a fully stereocontrolled preparation of **39** and **40**.

Since we next intended to functionalize **39** and **40** at the primary ether terminus, a means had to be found for removing the tetrahydropyranyl moiety without unmasking the silyl ether. Magnesium bromide in ether[49] served well for this purpose, and afforded primary alcohols **41** and **42** in high yield. Conversion

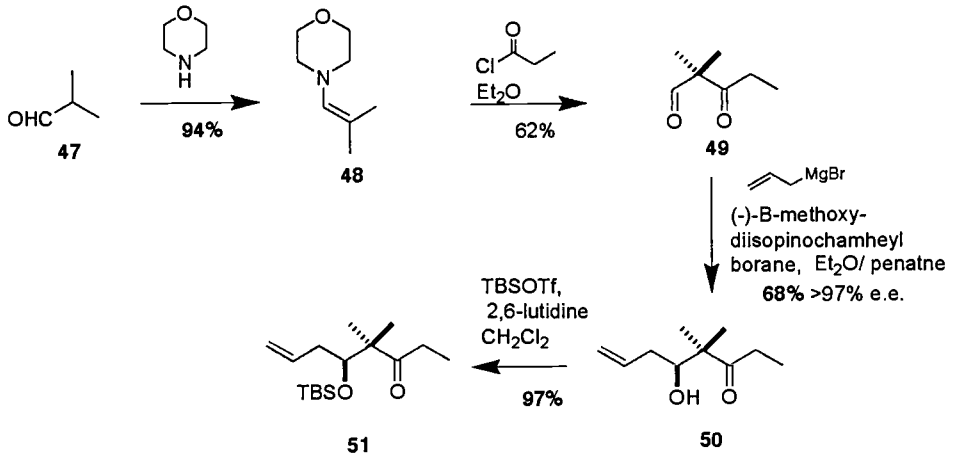
of these alcohols to their corresponding primary bromides was accomplished via their mesylates to furnish allylic bromides **43** and **44**. Homologation of these bromides to phosphonium salts **45** and **46** was accomplished by displacement with methylidenetriphenylphosphorane derived from methyltriphenylphosphonium bromide and *n*-butyllithium. (**Scheme 10**). The syntheses of **45** and **46** completed our route to the one of the two major subunits of epothilone D by a fully stereocontrolled pathway which provided a terminus at C10 in the form of a phosphonium salt suitable for connection to the second major subunit of the macrolide.


38
n- BuLi, THF
- 78 °C to 25 °C
96% for 36 and 37
36 R = TBS
37 R = TES
39 R = TBS
40 R = TES
MgBr2·Et2O, Et2O
99% for 39
89% for 40
41 R = TBS
42 R = TES
a) Ms2O, Et3N, CH2Cl2
b) LiBr, acetone
84% for 41
97% for 42
43 R = TBS
44 R = TES
Ph3PCH3
n-BuLi, THF
89% for 43
79% for 44
45 R = TBS
46 R = TES

Scheme 10

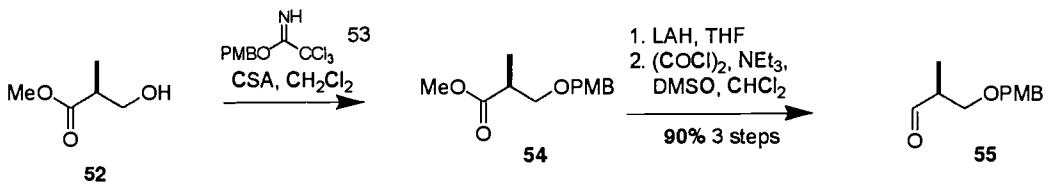
The C1-C9 Subunit

The C1-C9 subunit of the epothilone skeleton was prepared along lines similar to those employed by Mulzer[50] and Meyer[51]. Ketone **51** was prepared using a known route. Acylation of enamine **48,** derived from isobutrylaldehyde (**47**), with propionyl chloride provided keto aldehyde **49.** Allylation of **49** with Brown's allyl isopinocampheyl boron reagent[52] and protection of the resultant alcohol **50** with *tert*-butyldimethlysilyl trifluoromethanesulfonate yielded ketone **51 (Scheme 11).**[53]



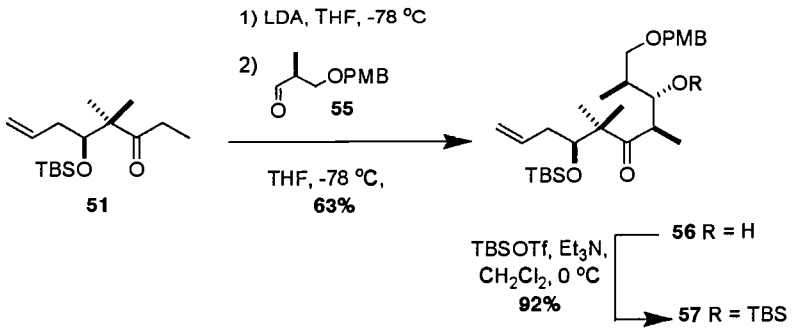
Scheme 11

Aldehyde **55** was prepared from methyl (*S*)-3-hydroxy-2-methylpropionate (**52**). Protection of alcohol **52** as its *p*-methoxybenzyl ether using **53** gave **54.** Reduction of **54** and oxidation then yielded aldehyde **55 (Scheme 12).**[54]



Scheme 12

Aldol condensation of ketone **51** with aldehyde **55** yielded anti-Felkin product **56** as the sole stereoisomer (**Scheme 13**). The optimal protocol for this coupling involved addition of a pre-cooled solution of ethyl ketone **51** in tetrahydrofuran to a solution of lithium diisopropylamide at –78 °C to form the kinetically preferred *Z*-enolate, followed by addition of a pre-cooled solution of a substoichiometric amount of aldehyde **55** in tetrahydrofuran. The reaction was quenched after 0.5 hours. These conditions probably enhance the stereochemical outcome by minimizing the retroaldol reaction typical of lithium enolates. Subsequent protection of secondary alcohol **56** as its *tert*-butyldimethylsilyl ether gave ketone **57** in 92% yield.



Scheme 13

The important role played by the *p*-methoxybenzyl ether in **55** is without question here since its replacement by a *tert*-butyldimethylsilyl ether resulted in much lower stereoselectivity in this aldol reaction. Results published by Schinzer[55] imply that there are structural component(s) of the enolate which participate in chelation to the metal cation and thereby reinforce the anti-Felkin course of this aldol reaction. The explanation proposed by Mulzer for the stereochemical outcome of this aldol reaction envisions a boat-like transition state in which a single lithium cation is coordinated to the benzyl ether, the aldehyde carbonyl, and the enolate oxygen.[12] An alternative model for the transition state of the reaction of **51** with **55** is presented in Figure 2, where *double metal chelation* involving *both* lone pairs of the aldehyde oxygen is invoked in a chair-like transition state. There is ample precedent in the literature,[56] including crystal structures of bis chelated carbonyl compounds, to support the concept of double chelation as proposed in Figure 2. In the present instance, it would be a secondary chelation placing a lithium cation between the benzyl ether oxygen atom and aldehyde carbonyl which directs addition of the *Z* enolate of **51** towards the *re* face of **55**. Whatever the true explanation for the stereoselectivity observed in the coupling of **51** with **55**, our result was most welcome since it avoided the need to remove stereoisomers of **56** from the reaction mixture.

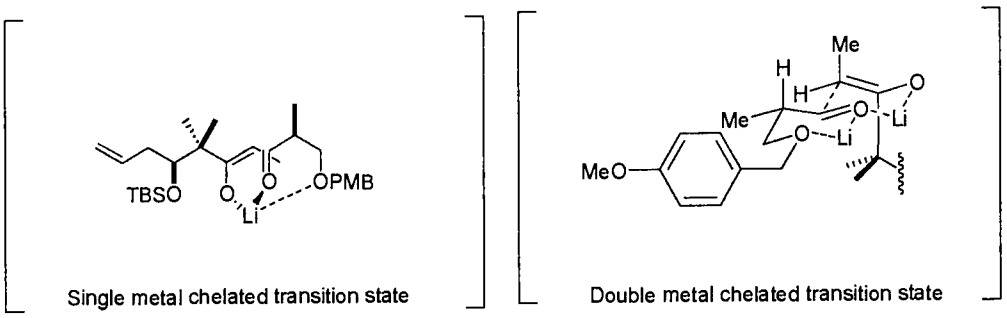
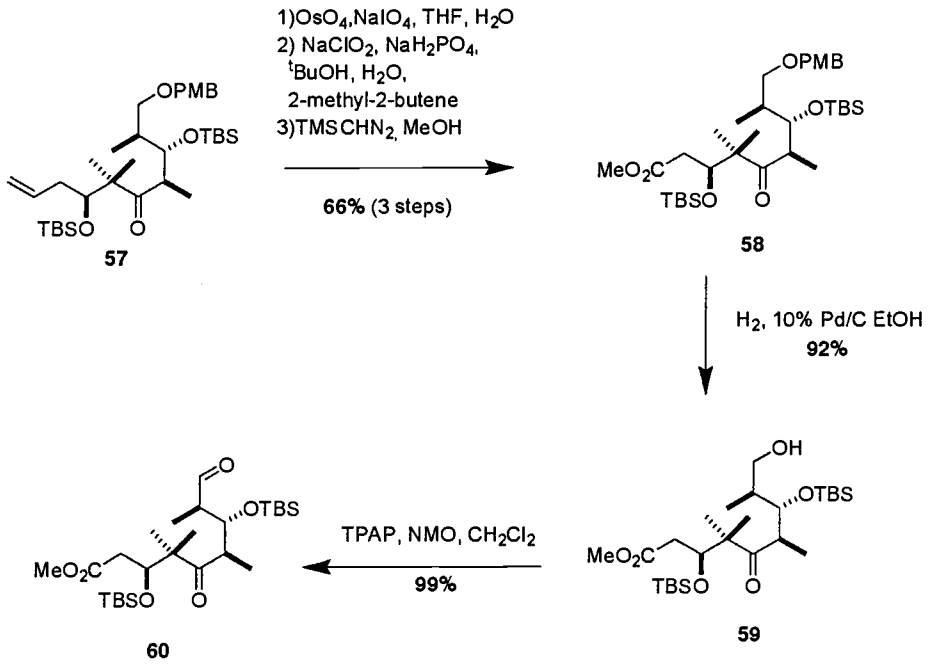


Figure 2 Possible aldol transition states of **37** with **36.**

Functional group manipulations of the differentiated terminal positions of triether **57** were now required to reveal a fragment suitable for coupling to phosphonium salt **46**. Cleavage of the terminal olefin of **57** with osmium tetraoxide and sodium periodate followed by oxidation of the resultant aldehyde to a carboxylic acid and methylation gave ester **58** in 66% yield over three steps. Removal of the *p*-methoxybenzyl protecting group was best accomplished under hydrogenation conditions using 10% palladium on carbon and delivered primary alcohol **59** in 92% yield. By contrast, Mulzer has recently reported that oxidative removal of the *p*-methoxybenzyl protecting group with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone from a substrate analogous to **58** results in an equilibrium mixture of cyclic hemiacetals which are resistant to opening.[57] Fortunately, we did not encounter this problem, and direct oxidation of alcohol **59** with a catalytic quantity of Ley's reagent[58] in the presence of *N*-methylmorpholine-*N*-oxide yielded the desired aldehyde **60** in near quantitative yield (**Scheme 14**).

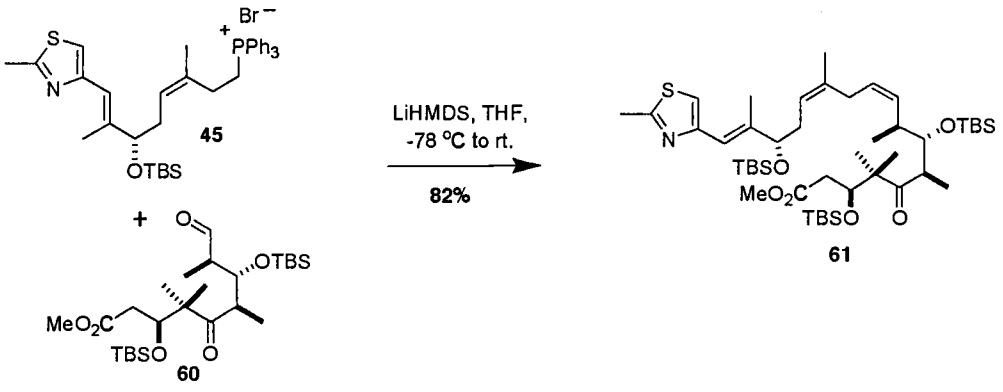


Scheme 14

Assembly of Subunits.

With both phosphonium salt **45** and aldehyde **60** in hand we could pursue our initial strategy for connecting subunits **3** and **4** via the Wittig olefination envisioned in Scheme 2. This would set in place a C9-C10 cis double bond, and it was anticipated that a triene such as **5** would provide access to an open chain precursor of epothilone D (**2**) by selective hydrogenation of the disubstituted alkene. However, it was also our intention to advance **5** towards cis 9,10-dehydroepothilone D by leaving the double bond in place so that this analogue could be evaluated against its congeners for antimitotic activity.

The Wittig reaction of **60** with the phosphorane prepared from **45** with lithium hexamethyldisilylazide, when carried out under carefully controlled conditions, afforded the pure *E,Z,Z*-triene **61** in excellent yield (**Scheme 15**).

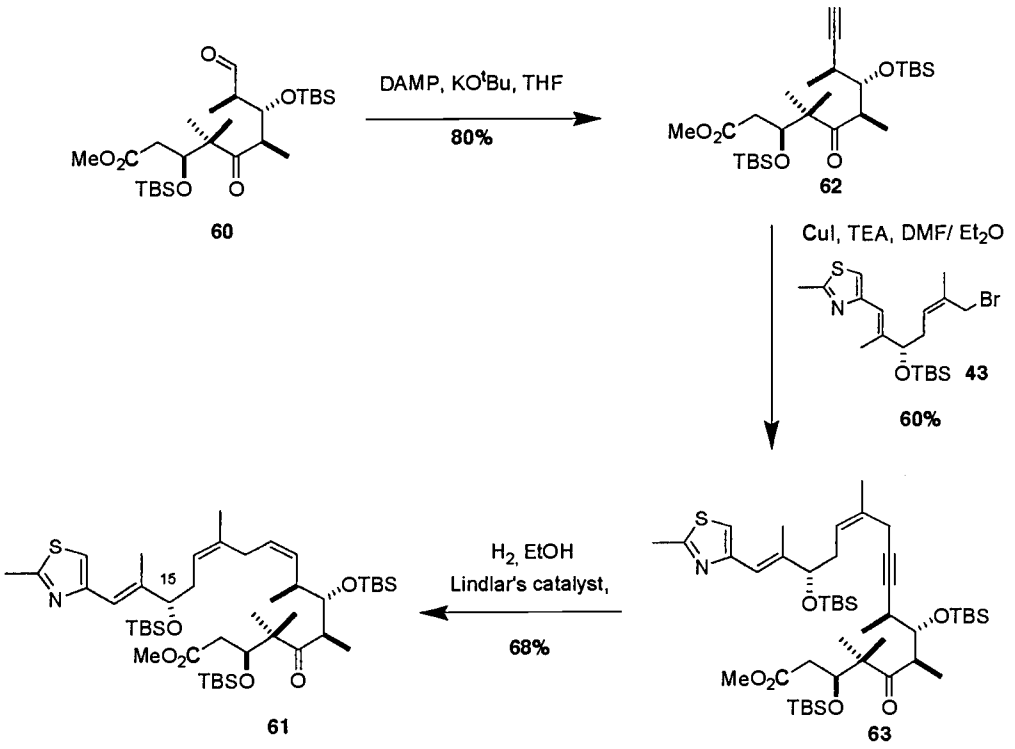


Scheme 15

Although the Wittig coupling of **45** with **60** was in most respects satisfactory, the strongly basic conditions of the reaction along with the fact that stoichiometry was difficult to control on a small scale, prompted investigation of an alternative method for linking subunits **3** and **4**. A protocol which effected direct coupling of **3** with **4** rather than preliminary homologation of the bromide **43** to **45** would confer obvious advantage, but this implied that a one-carbon homologation of aldehyde **60** would be needed. In practice, homologation of **60** was readily achieved through its condensation with dimethyl diazomethylphosphonate[59], leading to terminal alkyne **62** (**Scheme 16**).

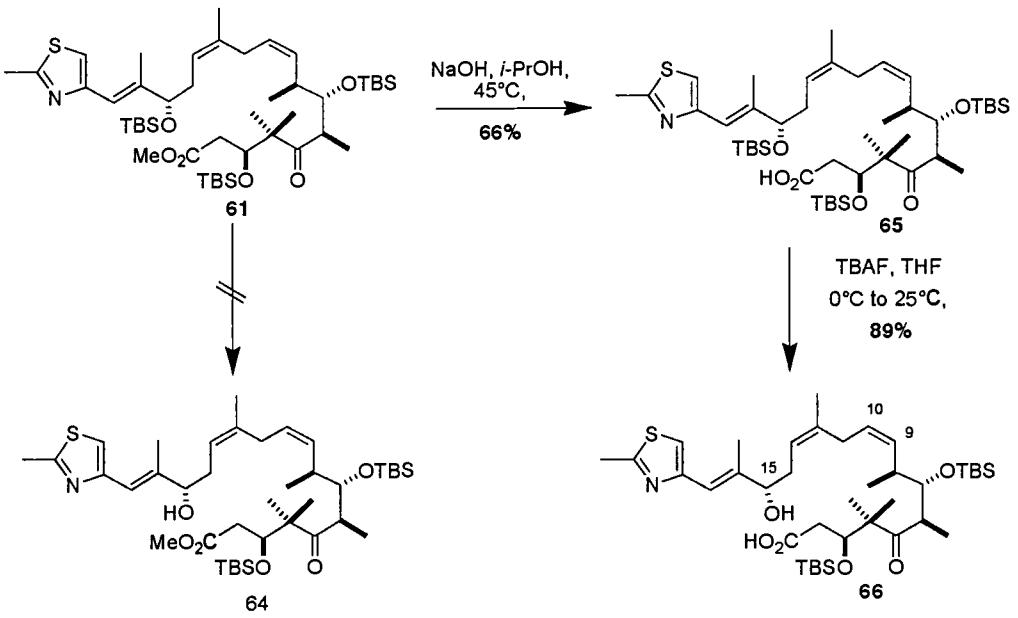
At first, it seemed plausible that a palladium-mediated coupling between allyl bromide **43** and terminal alkyne **62** should yield a dienyne with the added advantage of mild reaction conditions and minimal contamination from byproducts. The Sonogashira reaction is a widely used method for coupling 1-alkynes to aryl and vinyl halides; the reaction is typically conducted in the presence of an amine base and uses either a palladium(II) or a palladium(0) catalyst with copper(I) iodide as a cocatalyst.[60] However, attempts to employ this system to couple **43** and **62** failed to give any of the desired product. The earliest reports of this type of reaction by Stephens and Castro[61] described conditions which make use of copper(I) iodide and an amine base to effect the cross coupling of aryl halides or vinyl halides with terminal alkynes. Subsequently, modification of the original conditions were developed in which 1-alkynes were shown to couple efficiently with allyl halides. Nevertheless, extensive experimentation was still necessary to find conditions for the coupling of bromide **43** to alkyne **62**. The optimal conditions for this reaction required that two equivalents of copper acetylide be generated by treating **62** with a stoichiometric amount of copper(I) iodide and triethylamine in diethyl ether containing a minimum amount of dimethylformamide at room temperature under strictly anaerobic conditions followed by addition of allylic halide **43**.[62] The extra equivalent of alkyne could generally be recovered after the reaction was complete. These conditions afforded dienyne **63** in 60% yield along with a small amount of the conjugated diyne resulting from oxidative self-coupling.

Semihydrogenation of **63** over Lindlar's catalyst in hexane[63] gave **61** essentially identical by comparison of NMR spectra with the product obtained from Wittig coupling of **45** and **60**. The reduction of **63** was conveniently monitored by thin-layer chromatography. Although both the starting material **63** and product **61** had nearly identical R_f values, visualization by staining with *p*-anisaldehyde revealed the alkyne as a brown-red spot while the alkene was a vivid blue. Fortunately, no overreduction of **63** to the alkane was observed (**Scheme 16**).



Scheme 16

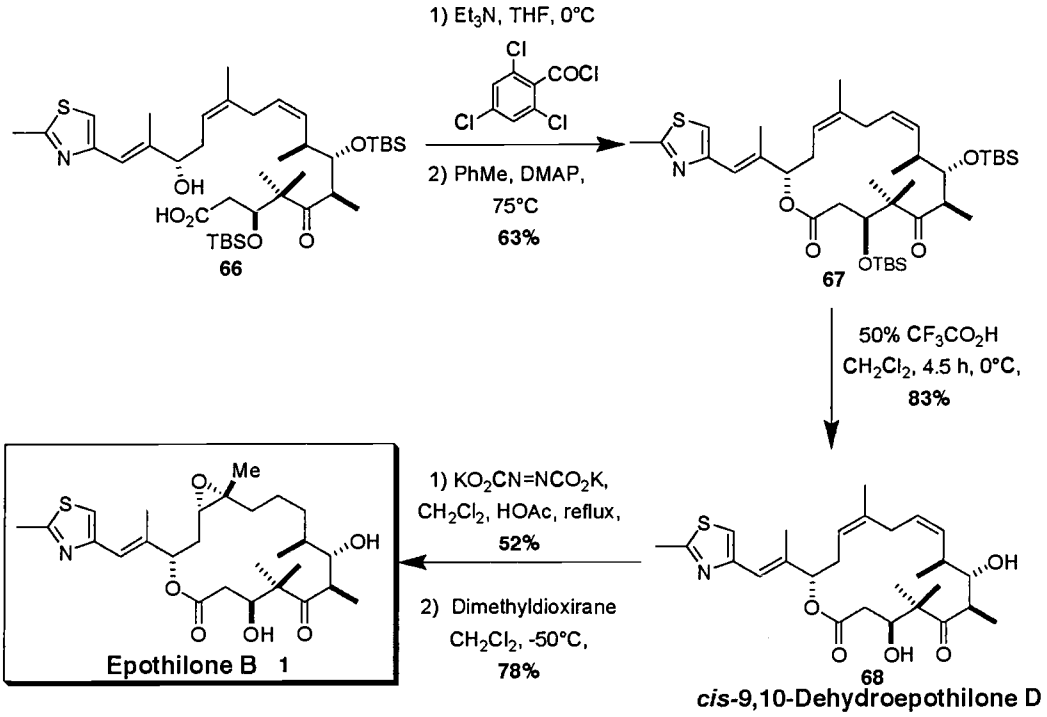
The three secondary silyl ethers of **61** are in sufficiently similar chemical environments to make selective unmasking of the ether at C15 seem implausible. Indeed, a variety of reagents known to cleave silyl ethers displayed little or no selectivity in favor of **64**. However, after saponification of **61**, the resultant carboxylic acid **65** underwent selective desilylation at C15 to afford hydroxy acid **66** in excellent yield (**Scheme 17**). A similar selective desilylation was noted by Nicolaou[14] in the case of the 9,10-dihydro version of carboxylic acid **65**. A possible explanation for the markedly different results obtained in the deprotection of ester **61** and acid **65** may involve intramolecular silyl transfer from the C15 oxygen to an intermediate carboxylate anion in the case of **65**; however, no evidence for a transient silyl ester was seen in the reaction with **65**. Nevertheless, this result suggested that the C15 hydroxyl and carboxyl centers can achieve proximity, a structural feature which augured well for the ensuing macrolactonization.



Scheme 17

It is possible that the cis-9,10 olefin encourages the carboxylic acid and C15 hydroxyl into proximity, but a "folding" effect was not manifested in the lactonization of seco acid **66**. Under Yamaguchi conditions,[64] **66** gave the bis *tert*-butyldimethylsilyl ether of 9,10-dehydroepothilone D (**67**) in a yield virtually identical with that obtained by others for macrolactonization of the 9, 10-dihydro derivative of seco acid **66**. Subsequent removal of the two remaining silyl ethers from the macrolactone with trifluoroacetic acid gave 9,10-dehydroepothilone D (**68**), but attempts to selectively hydrogenate the disubstituted olefin of **68** using Wilkinson's catalyst in order to obtain epothilone D itself were unsuccessful. However, reduction of **68** with diimide,[65] generated from dipotassium azodicarboxylate, resulted in epothilone D (**2**) in acceptable yield (**Scheme 18**).

Final epoxidation of **2** with dimethyldioxirane under conditions described by Danishefsky[66] afforded epothilone B (**1**), whose ^{1}H and ^{13}C NMR spectra exactly matched those of an authentic sample.



Scheme 18

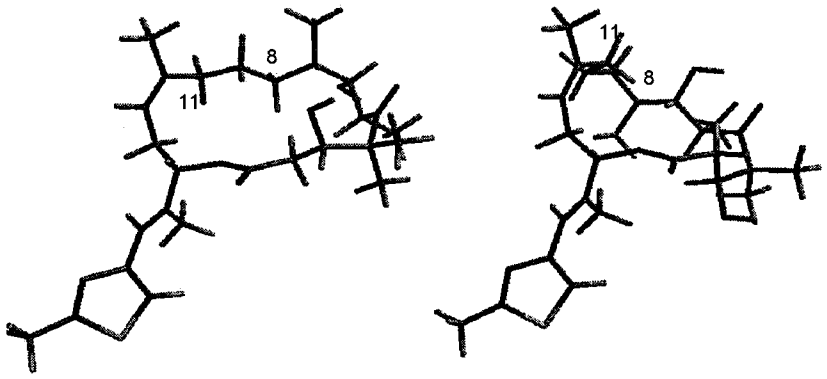
At this stage our initial goal had been met. We had completed a convergent synthesis of epothilone B via epothilone D which generated all seven of its asymmetric centers in a completely stereoselective fashion and which incorporated clean Z configuration at the 12,13-double bond. Furthermore, the C9-C10 olefin afforded us a locus at which exploratory structural modifications

could be made. The possibility of accessing a new series of epothilone analogues in which a C≡C unit across C9-C10 seemed an exciting and attainable goal since dienyne **63** was already in hand. Such an epothilone analogue would not only provide additional insight into the structural tolerance allowed for biological activity, but would also offer a unique platform on which to base modifications distinct from those that have employed the C12-C13 olefin as the point of departure. In addition, the opportunity to fashion a trans C9-C10 olefin within the epothilone framework via a cis hydrometallation of alkyne **62** followed by coupling to allyic bromide **43** seemed feasible. First, however, it was decided to examine the conformational space that would be occupied by these epothilone analogues.

Conformational Analysis of Epothilone D and 9,10-Unsaturated Analogues.

In order to gain some preliminary insight into the conformations of the proposed trans-9,10-dehydroepothilone D and 9.10-didehydroepothilone D structures, and to anticipate their bioactivities relative to epothilone D and cis 9,10-dehydroepothilone D, we decided to undertake a computational study. Energy-minimized conformations of epothilone D were calculated using a PM3 algorithm along with the crystal structure of epothilone B (**1**) as a starting geometry. The two lowest energy conformations of epothilone D, **A** and **B,** are shown in Figure **3**. Conformer **A,** in which the C8-C11 segment of the macrolide occupies an antiperiplanar orientation, corresponds closely with the solid-state

structure of epothilone B determined by X-ray crystallography. In addition, conformer **A** is also consistent with the conformations of both epothilone B[67] and epothilone A[68] that predominate in solution as suggested by NOE experiments. Conformer **B**, in which the C8-C11 segment is in a gauche arrangement, corresponds to a minor conformer of epothilone A observable in solution by NMR and which accounts for *ca* 20% of the conformer population (**Figure 3**).



A
(C8-C11 antiperiplanar)

B
(C8-C11 gauche)

Figure 3. Two predicted conformers of Epothilone D.

Conformational analysis of cis-9,10-dehydroepothilone D (**68**), trans-9,10-dehydroepothilone D , and 9,10-didehydroepothilone D, and a comparison of the strain energy of each with that of the antiperiplanar conformation of epothilone D (**A**) reveals that cis-9,10-dehydroepothilone D, trans-9,10-dehydroepothilone D , and 9,10-didehydroepothilone D, are 4.0, 1.6 and 2.0 kcal/mol higher in energy, respectively (**Figure 4**). Interestingly this comparison suggests that a linear

arrangement between C8 and C11, as in 9,10-didehydroepothilone D, imparts less overall strain to the macrolactone than the cis geometry present in cis-9,10-dehydroepothilone D. True to the homology between the antiperiplanar orientation in conformer A and that of trans-9,-10-dehydroepothilone D, the lowest calculated ring strain is embodied by trans-9,-10-dehydroepothilone D. The calculated distance of 3.86 angstroms between C8 and C11 of conformer A is ideally replicated in trans-9,10-dehydroepothilone D.

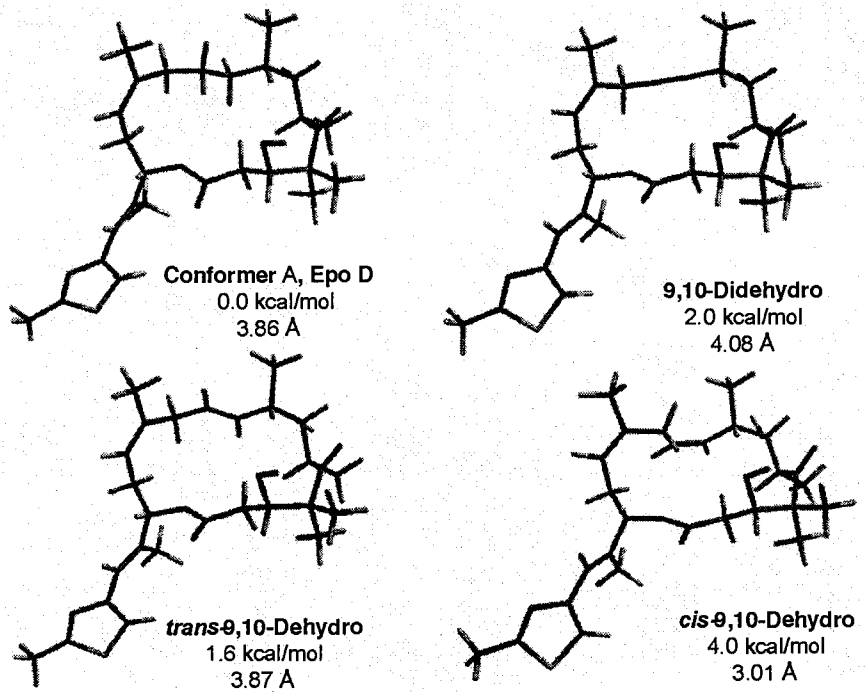


Figure 4. PM3 Geometry, Isodesmic Energy and C8-C11 distance of Conformer A of Epothilone D, cis-9,10-Dehydroepothilone D, trans-9,10-Dehydroepothilone D , and 9,10-Didehydroepothilone D

This degree of structural similarity can also be noticed in the degree of conformational distortion of cis-9,10-dehydroepothilone D, trans-9,10-dehydroepothilone D , and 9,10-didehydroepothilone D, respectively, when overlaid on conformer A of epothilone D (**Figure 5**). The overlays are arranged by fixing the superposition of the more rigid C1-C8 portion of the epothilone framework. The greatest predicted conformational deviation from conformer A occurs with cis-9,10-dehydroepothilone D, where the olefin geometry appears to distort the entire C9-C21 region (**Figure 5a**). However, in the case of trans-9,10-dehydroepothilone D, the trans-double bond allows a near perfect superposition of this portion of the structure on conformer A (**Figure 5b**). For didehydroepothilone D, the degree of distortion imparted by the 9,10-alkyne is mostly localized between the C9-C15 region of the macrolactone. Hence, based on a simple conformational rationalization, we predicted that trans-9,10-dehydroepothilone D should possess bioactivity most similar to that of epothilone D while rigidifying the macrolactone in its preferred conformation.

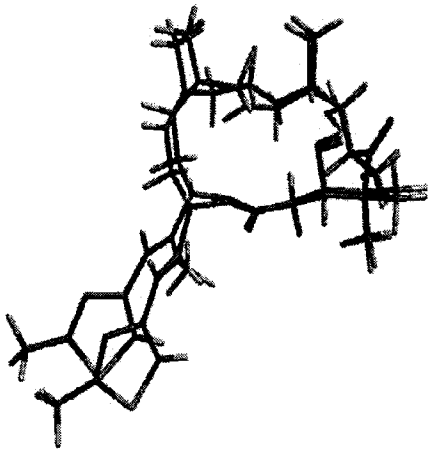


Figure 5a. Overlay of cis-9,10-Dehydroepothilone D and Conformer A of Epothilone D

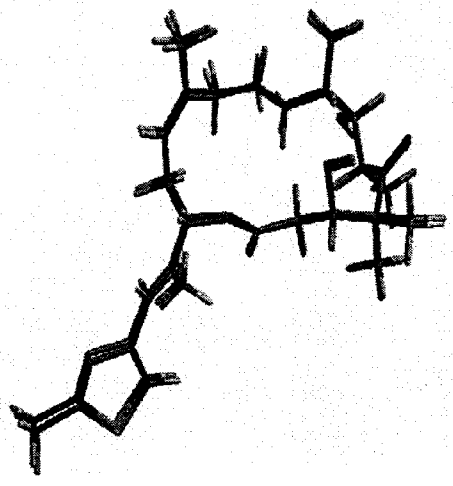


Figure 5b. Overlay of trans-9,10-Dehydroepothilone D and Conformer A of Epothilone D

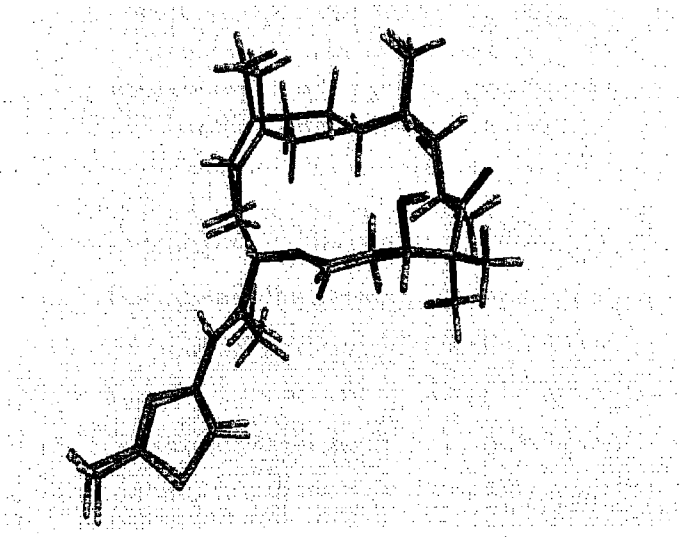
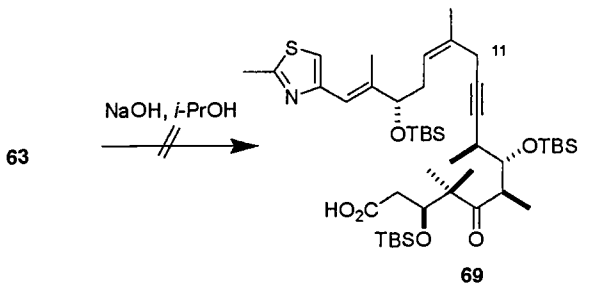


Figure 5c. Overlay of 9,10-Didehydroepothilone D and Conformer A of Epothilone D

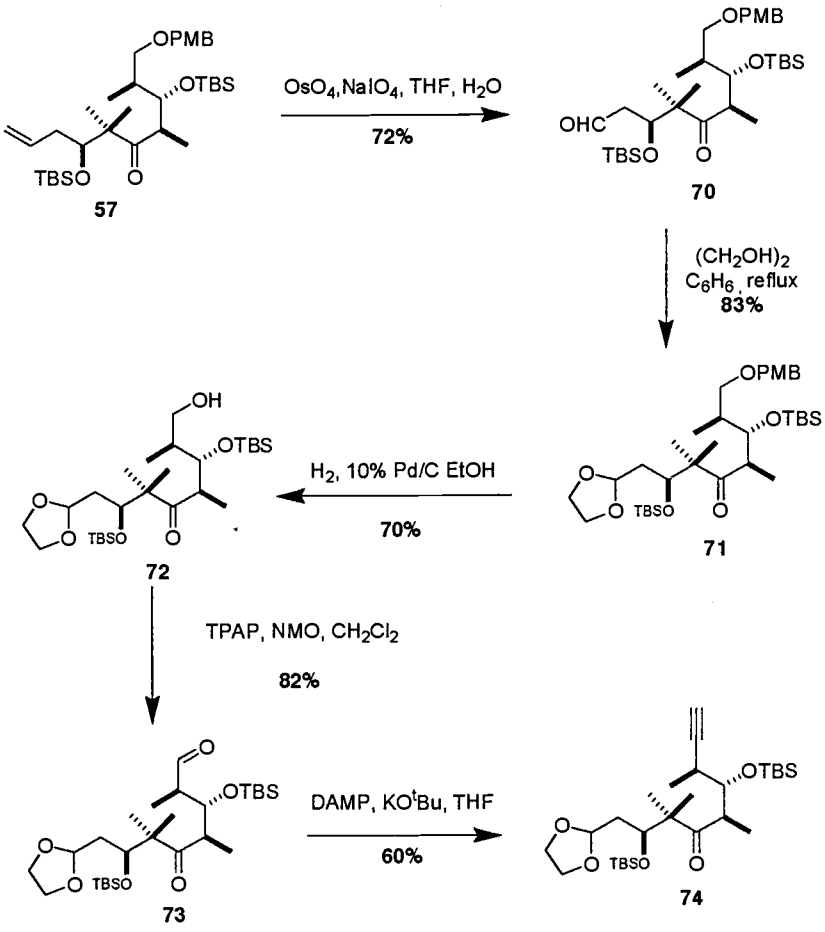
Synthetic Studies Towards trans-9,10-Dehydroepothilone D and Didehydroepothilone D.

In the course of our approach to epothilone D via **63**, we found with some disappointment that all attempts to deprotect the C15 silyl ether of **63** failed. Furthermore, attempted saponification of this ester led to rapid decomposition, thus closing another avenue from **63** (**Scheme 19**). One possible cause of the difference in reactivity of **63** as compared to triene **61** is the increased acidity of the protons at C11 in the skipped enyne moiety of **63**.



Scheme 19

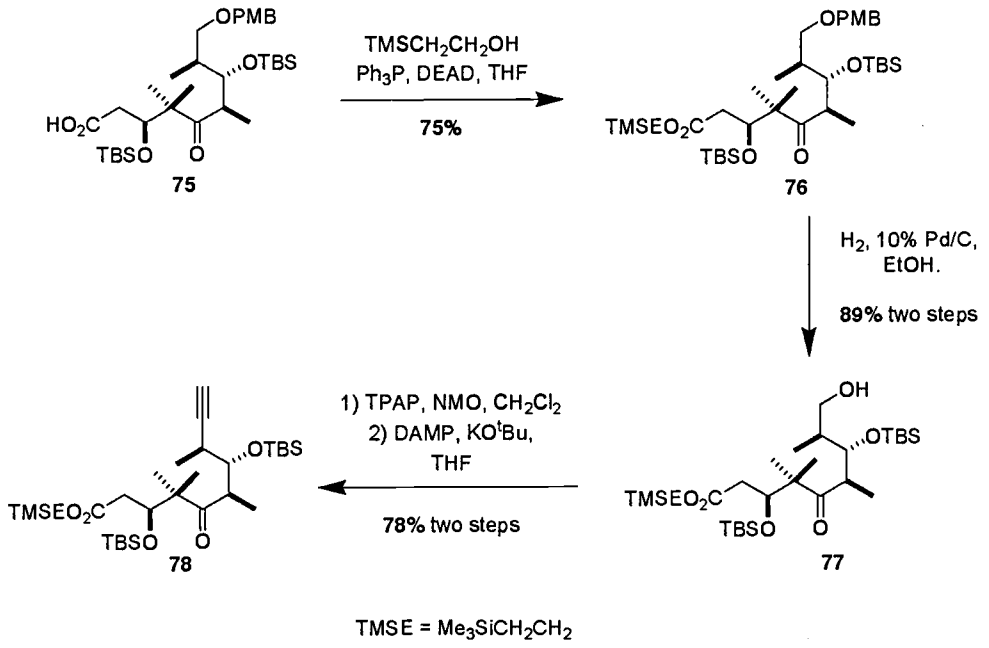
In an effort to overcome the obstacle imposed by saponification of **63**, the terminal ester of **62** was replaced by an aldehyde in the guise of acetal **74**. The latter was synthesized by oxidative cleavage of alkene **57** followed by protection of aldehyde **70** as its ethylene acetal **71**. After hydrogenolysis of **71**, the resultant alcohol **72** was oxidized to **73** which was reacted with dimethyl diazomethylphosphonate[19] to afford **74**. Disappointingly, and with no obvious explanation, **74** yielded no coupled product when treated with bromide **43** under conditions that had been successful with **62** (**Scheme 20**).



Scheme 20

Our failure with acetal **74** prompted our return to an ester terminus at the same oxidation level as that of the methyl ester but in a form which did not require such harsh conditions for its removal. A silyl ester was considered, but it seemed doubtful that such a labile protecting group would survive the conditions necessary to complete the sequence to an alkyne analogous to **74.** However, the more robust trimethylsilylethyl ester seemed a good candidate, especially since

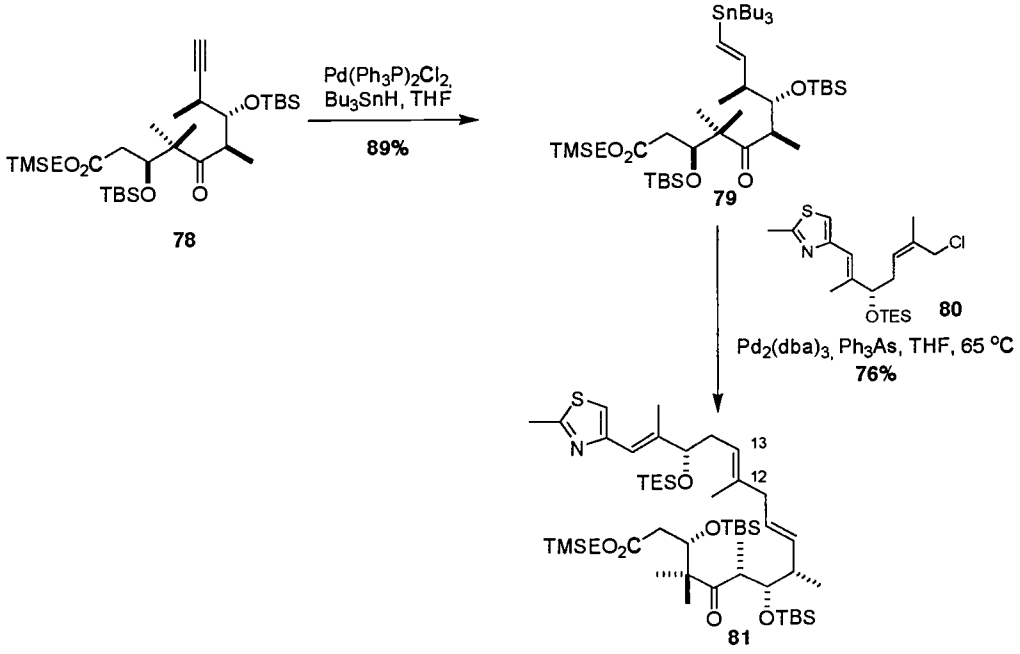
this ester might also have the added benefit of being removed concomitantly with the C15 silyl ether. This would lead directly to a seco-acid in a single step. Of course, there was still concern that deprotection at C15 would need to be selective over silyl ethers at C3 and C7. The carboxylic acid **75** derived from **57** was therefore esterified with 2-(trimethylsilyl)ethanol under Mitsunobu conditions to provide ester **76**. Hydrogenolysis of **76** removed the *p*-methoxybenzyl ether, and oxidation of the resulting alcohol **77** afforded an aldehyde, which was reacted with dimethyl diazophosphonate[19] to give terminal alkyne **78** (**Scheme 21**). Alternatively, the aldehyde from **77** was reacted with the more easily prepared Ohita-Bestmann reagent[69] to yield **78**. However, a minor amount of methyl ester arising from transesterification of **78** with the solvent was isolated when this reaction was performed under the standard basic methanol conditions.



Scheme 21

In practice, alkyne **78** functioned just as well in the modified Castro-Stephens coupling with **43** as its analogous methyl ester. However, an opportunity to attempt to create trans-9,10-dehydroepothilone D took priority at this point. Thus, hydrostannylation of alkyne **78** in the presence of a palladium dichloride catalyst furnished trans vinylstannane **79** in high yield, but our initial attempts to couple **79** with allylic bromide **43** failed to produce the expected triene. Fortunately, exchanging the bromide of **43** for chloride **80** via alcohol **42** led to a positive result, and traces of coupled product were seen in this case. Optimal conditions were eventually developed which included treating chloride **80**

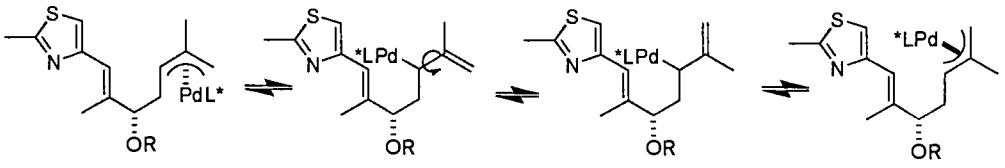
with 0.05 equivalents of the palladium catalyst and 0.3 equivalents of triphenylarsine in tetrahydrofuran followed by addition of stannane **79**.[70] Interestingly, the reaction flask needed to be briefly opened to the atmosphere for the reaction to proceed (**Scheme 22**). The unanticipated isomerization of the double bond in the coupled product was deduced by advancing this material to a known compound (*vide infra*).



Scheme 22

A possible explanation for the Z-to-*E* isomerization of the C12-C13 alkene in the Stille coupling of **79** with **80** may be found by considering the initally formed π-allyl palladium complex (**Scheme 23**). Geometrical isomerization can

potentially occur by a π to σ rearrangement, followed by rotation about the σ–alkylpalladium bond, and a subsequent σ to π rearrangement. It should be noted that the *Z* allylic chloride **80** could be recovered from the reaction with no apparent scrambling of the trisubstituted olefin and that no *E* isomer of this chloride was observed.

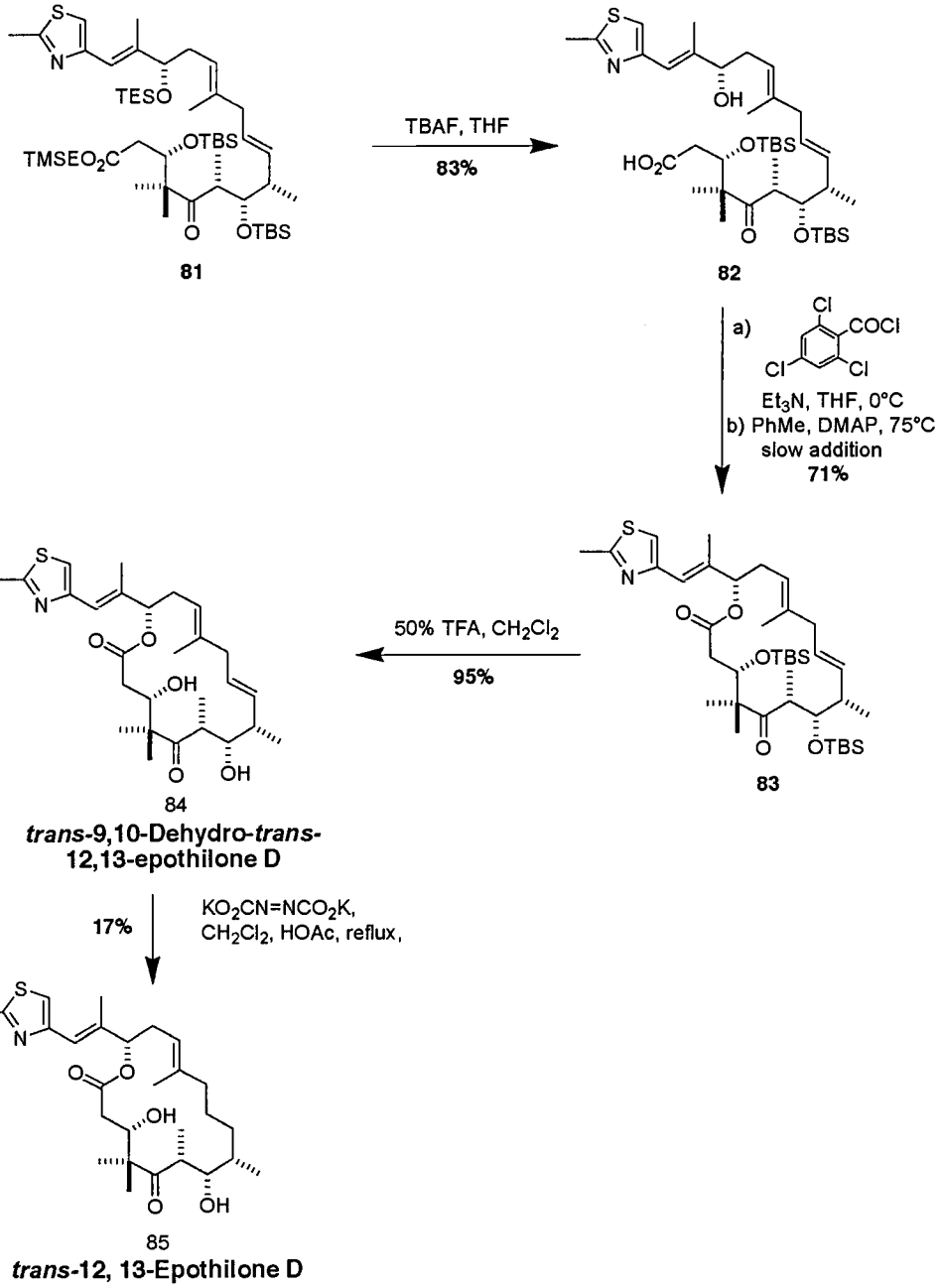


Scheme 23

Having previously developed routes to both *tert*-butyldimethylsilyl ether **41** and triethylsilyl ether **42,** optimization of the deprotection sequenced required to yield seco-acid **82** was straightforward. While selective deprotection of the C15 *tert*-butyldimethylsilyl variant only occurred in a poor and inconsistent manner, deprotection of triethylsilyl ether **81** proceeded smoothly and reproducibly to yield the hydroxyl acid **82.** The resulting seco acid **82** underwent macrolactonization to **83**, and subsequent removal of the remaining pair of *tert*-butyldimethyl ethers with trifluoroacetic acid furnished *E*-9,10-dehydro-*E*-12,13-epothilone D (**84**).

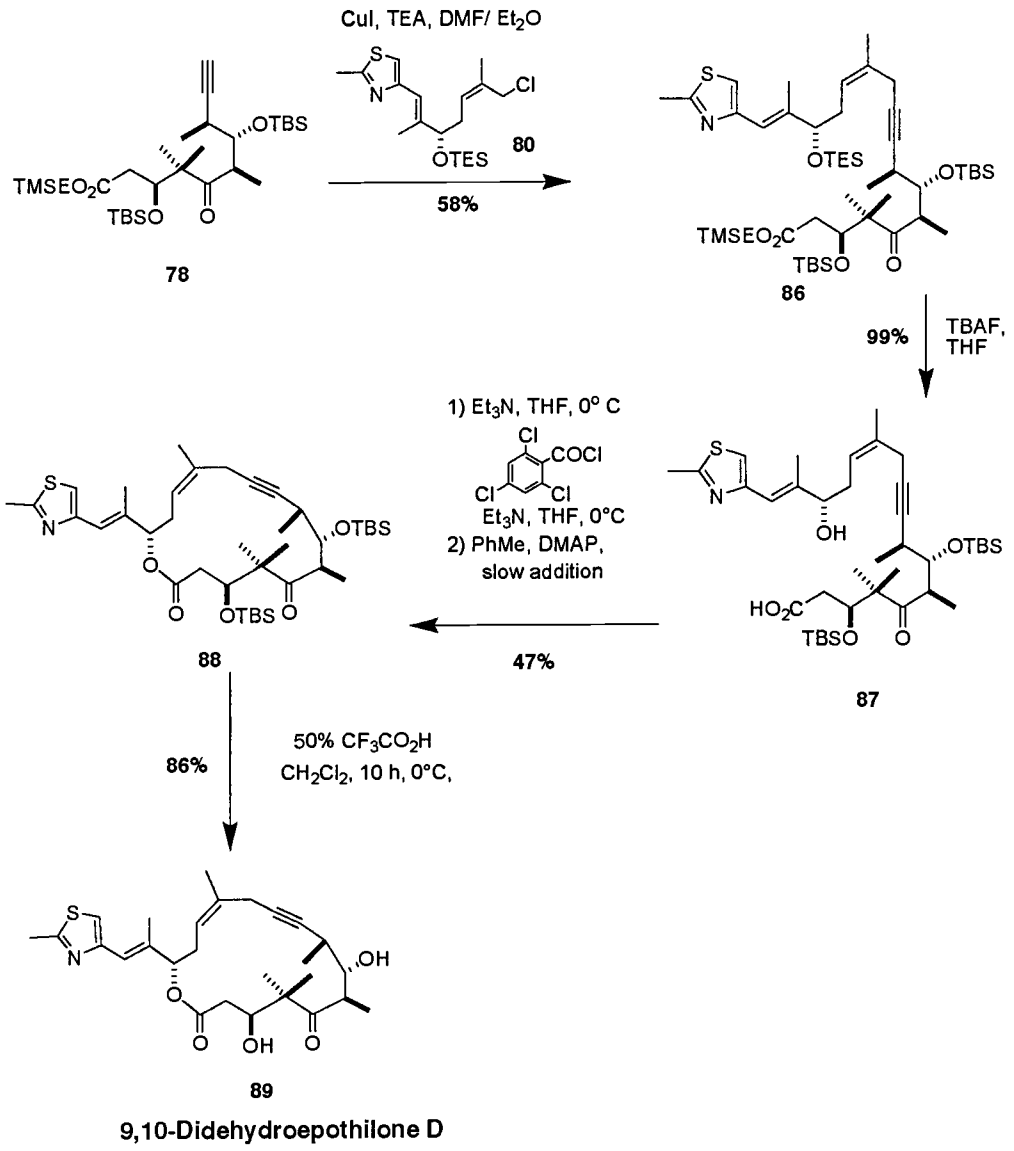
Since the structures of **81** - **84** were originally assumed to posses a C12-C13 *Z*-alkene, the correct assignment needed to be rigorously established. The most straightforward method to accomplish this would be the selective reduction of the

C9-C10 alkene which would produce epothilone D if *Z*-12,13 olefin configuration was preserved. In fact, treatment of **84** with dipotassium azodicarboxylate and acetic acid produced the known isomer *E*-12,13-epothilone D,[17] thus establishing the assignments to **81 – 84** as shown (**Scheme 24**). The identity of **85** is based upon the comparison of its NMR spectra with the published NMR spectra of *E*-12,13-epothilone D.


TESO
TMSEO2C
OTBS
O
OTBS
81
TBAF, THF
83%
OH
HO2C
OTBS
O
OTBS
82
a)
Cl
COCl
Cl
Cl
Et3N, THF, 0°C
b) PhMe, DMAP, 75°C
slow addition
71%
O
O
OTBS
O
OTBS
83
50% TFA, CH2Cl2
95%
OH
O
OH
84
trans-9,10-Dehydro-trans-
12,13-epothilone D
17%
KO2CN=NCO2K,
CH2Cl2, HOAc, reflux,
OH
O
OH
85
trans-12, 13-Epothilone D

Scheme 24

To return to alkyne **78** and complete a synthesis of 9,10-didehydroepothilne D was a relatively simple matter. The Castro-Stephens coupling of akyne **78** and allylic choride **80** yielded the expected dienyne **86**, and careful treatment of **86** with tetra-*n*-butylammonium fluoride removed both the triethylsilyl ether and trimethylsilylethyl ester in a single step. The resulting hydroxyl acid **87** underwent macrolactonization under Yamaguchi conditions to furnish **88** and subsequent cleavage of the remaining silyl ethers from **88** with trifluoroacetic acid yielded 9,10-didehydroepothilne D **89** (**Scheme 25**).



Scheme 25

Biological Data

The antiproliferative activity of **2**, **68**, **84**, **89** and paclitaxel was assessed *in vitro* using a panel of human cancer cell lines, courtesy of Novartis. As illustrated

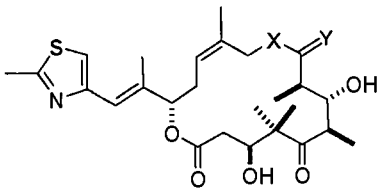
in Table 1, **68** was 20- to 30-fold less potent than natural epothilone D (**2**), and 330- to 670-fold less potent than epothilone B (**1**). Interestingly, *E*-9,10-*E*-12, 13-trans-dehydroepothilone D (**84**) showed biological activity very similar to that of 9,10-*cis* isomer **68** in spite of an apparent difference in the conformation of these two macrolactones. Thus, the average IC_{50} of **84** for growth inhibition in the cell line panel used in this study was only 1.36-fold higher than that observed for **68**. It has been noted that the isomers with a *trans*-12,13 arrangement are consistently less potent than the corresponding *cis* -12,13 olefin isomers.[71] The data for **89** reveal that it is significantly less active than either **68** or **84.** As seen for epothilones B and D, **68, 84** and **89** retain anti-proliferative activity against KB-8511 cells, a paclitaxel-resistant cell line overexpressing P-glycoprotein. While the tubulin polymerization activity of **68, 84** and **89** was lower than that of **2** (56%, 36%, <10% and 88%, respectively), it is conceivable that decreased cellular penetration may contribute to the marked reduction in antiproliferative potency observed. Taken together, these data support the proposition that the C8-C13 region of the epothilone perimeter is relatively tolerant of structural modification and suggest that the interaction of this segment of the molecule with tubulin is less stringently defined. However, it appears that a linear assembly across the C8-C11 domain as present in **89** is not well tolerated.

Substrate	Tubulin Polymerization (%)	IC_{50} KB-31 (Epidermoid) (nM)	IC_{50} KB-8511 (Epidermoid) (nM)	IC_{50} A549 (Lung) (nM)	IC_{50} HCT-116 (Colon) (nM)	IC_{50} PC3-M (Prostate) (nM)	IC_{50} MCF-7 (Breast) (nM)
1	95	0.17	0.16	0.16	0.34	0.32	0.29
2	88	1.94	1.00	4.62	4.48	7.40	2.31
68	56	59.39	28.54	109.03	101.83	146.47	72.00
84	36	103.7	70.37	108.27	109.97	146.80	95.03
89	<10	878.00	593.0				
Paclitaxel	53	2.67	841.80	5.19	4.88	6.62	3.26

Table 1 Comparison of Tubulin Polymerization Activity and Antiproliferative Activity of **1**, **2**, **68**, **84**, **89**, and Paclitaxel.

Synthesis of C10-Heteroepothilone Analogues

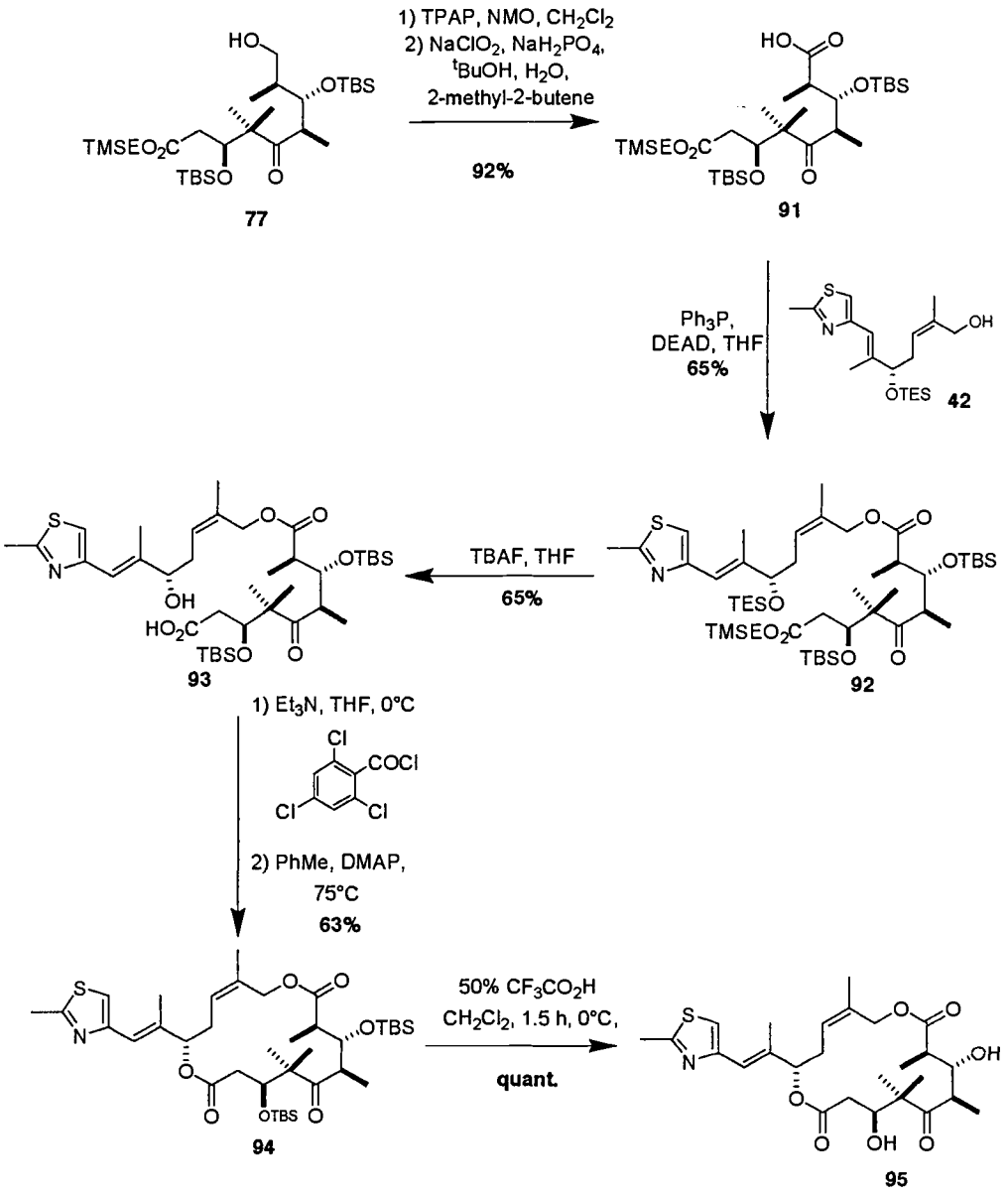
Although the synthesis of **68**, **84**, and **89** together with the data generated from them provided insight into the conformational and biological properties of the C9-C10 site in epothilones, another approach to epothilone analogues was available by modifying our original strategy. Since our previous routes to the macrolactones **68**, **84**, and **89** relied upon a one-carbon homologation to install C10, an opportunity to embed a heteroatom in its place was at hand. A heteroatom at this position could, in principle, change the conformation of the macrolactone through stereoelectronic effects and perhaps could also alter the molecule's biological profile. The most straightforward embodiment of a hetero analogue of this type is a bis-lactone compound in which C10 was replaced with an oxygen atom to form an ester linkage between C9 and C11 (**Figure 6,** X=O, Y=O).



90

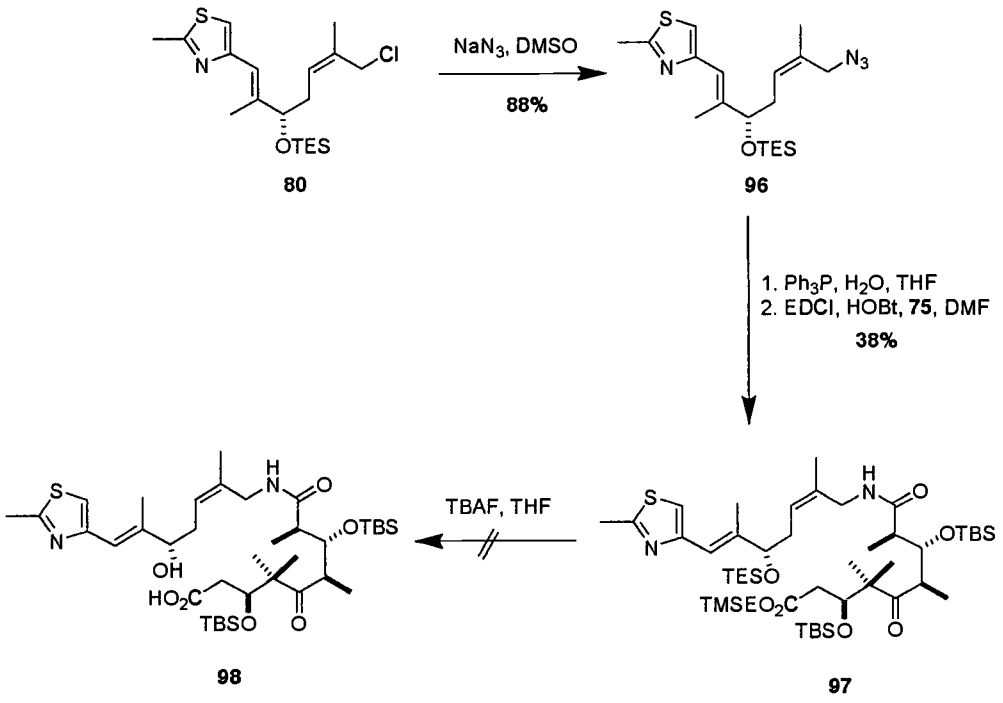
Figure 6 C10-Heteroepothilone Analogues.

Dilactone **95** seemed to be especially inviting since the necessary protecting groups were already in place for its assembly. The synthesis of dilactone **95** commenced with alcohol **77** which was oxidized to carboxylic acid **91**. Esterification of **91** with alcohol **42** under Mitsunobu conditions yielded ester **92**, from which removal of both the triethylsilyl ether and trimethylsilylethyl ester was successfully accomplished by careful treatment with tetra-*n*-butylammonium fluoride. Both *tert*-butyldimethylsilyl ethers were retained in this reaction. The resulting hydroxy acid **93** was advanced under Yamaguchi conditions to the protected dilactone **94**, and subsequent cleavage of the remaining silyl ethers from **94** with trifluoroacetic acid gave dilactone **95** (**Scheme 22**).


1) TPAP, NMO, CH_2Cl_2
2) $NaClO_2$, NaH_2PO_4,
^tBuOH, H_2O,
2-methyl-2-butene
92%
77
91
Ph_3P,
DEAD, THF
65%
42
TBAF, THF
65%
93
92
1) Et_3N, THF, 0°C
2) PhMe, DMAP,
75°C
63%
94
50% CF_3CO_2H
CH_2Cl_2, 1.5 h, 0°C,
quant.
95

Scheme 22

An amide **97**, potentially serving as an isosteric replacement of a C9-C10 *trans*-olefin, was prepared as well. Exposure of chloride **80** to sodium azide in dimethyl sulfoxide provided azide **96.** Reduction of the azide group with triphenylphosphine and coupling to carboxylic acid **91** then yielded amide **97.** However, treatment of **97** with tetra-*n*-butylammonium fluoride did not provide any selectively deprotected seco-acid, but instead led to decomposition of the starting amide, thus suggesting the need for N-protection of the potentially base sensitive amide (**Scheme 23**).



Scheme 23

The antiproliferative activity of **95** was assessed *in vitro* using two human cancer cell lines and compared against epothilone B (**1**), epothilone D (**2**) and Pacilitaxel. As illustrated in Table 1, **95** was 12- to 25-fold less potent than natural epothilone D (**2**), and 100- to 166-fold less potent than epothilone B (**1**). Interestingly, the tubulin polymerization value is somewhat lower than would be expected from the observed antiproliferative activity (**Table 2**).

Substrate	Tubulin Polymerization (%)	IC_{50} KB-31 (Epidermoid) (nM)	IC_{50} KB-8511 (Epidermoid) (nM)
1	81	0.24	0.15
2	62	1.94	1.00
95	21	25.5	25.2
Paclitaxel	39	2.9	661

Table 2. Comparison of Tubulin Polymerization Activity and Antiproliferative Activity of **1**, **2**, **95**, and Paclitaxel.

Conclusion

A convergent synthesis of epothilone B (**2**) that generates all seven of its asymmetric centers in a completely stereoselective fashion has been completed. Furthermore, the synthesis of several novel and cytotoxic epothilone analogues based on modifications to the C9-C10 region of the macrolide have been prepared by joining two advanced subunits. This strategy establishes a platform

for the future construction of a series of analogs for biological investigations and possible therapeutic use.

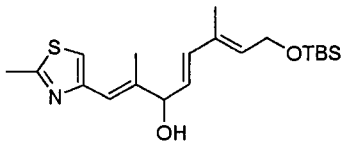
Finally, while the synthesis of trans-9,10-dehydroepothilone D was not accomplished as planned, its completion could be envisioned via a route similar to the Wittig olefination approach used to yield 9,10-cis-dehydroepothilone D.

Addendum

The synthesis and biological evaluation of trans-9,10-dehydroepothilone D was recently described from the laboratory of Professor Danishefsky. [72] This compound was distinguished with superior anti-tumor properties as compared to its parent compound epothilone D which is in phase II clinical trials.[73] It was noted, by the authors, that this compound may indeed be worthy of entering into human clinical trials.

Chapter III. Experimental Section

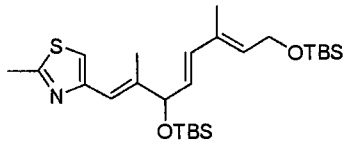
Solvents were dried by distillation immediately prior to use. Tetrahydrofuran (THF) and diethyl ether were distilled from potassium and benzophenone under an argon atmosphere. Triethylamine, diisopropylethylamine, toluene, benzene and dichloromethane were distilled from calcium hydride under argon. Acetone was distilled from calcium sulfate. Methanol and ethanol were distilled from magnesium turnings. Pyridine was distilled from barium oxide under argon. Analytical thin layer chromatography (TLC) was conducted using 1.5 x 5.0 cm precoated aluminum E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Flash chromatography was carried out using E. Merck silica gel 60 (230-400 mesh ASTM). Melting points were measured using a Büchi melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured on either a Bruker AC-300 or a Bruker AM-400 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale and coupling constants (J) are in Hz. Low resolution mass spectra (MS) were obtained using either a Varian MAT CH-7 or a Finnigan 4023 spectrometer at an ionization potential of 70 eV. High resolution mass spectra (HRMS) were recorded using a Kratos MS-50 TC spectrometer.



21

Alcohol 21: To a stirred slurry of bis(cyclopentadienyl)zirconium chloride hydride (330 mg, 1.28 mmol) in CH_2Cl_2 (1 mL) under argon at room temperature was added enyne **20** (269 mg, 1.28 mmol) in CH_2Cl_2 (3 mL). After 30 min the clear solution was cooled to - 78 °C and diethylzinc (1.47 mL, 1.0 M hexane solution) was added. After 15 min a solution of (-)-DAIB (7.5 mg, 0.06 mmol) and aldehyde **8** (246 mg, 1.28 mmol) in CH_2Cl_2 (2 mL) was added. After 14 hours the reaction was quenched with 10% aqueous sodium carbonate and the cloudy aqueous layer was extracted with ether (3x 2 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and purified by chromatgraphy (SiO_2, 30 to 50% ether in hexane) to give **21** (391 mg, 84%) as a colorless oil. IR: (thin film) 2927, 2882, 2854, 1467, 1438, 1382, 1255, 1056 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.95 (s, 1H), 6.64 (s, 1H), 6.33 (d, J = 15.6 Hz, 1H), 5.70 - 5.59 (m, 2H), 4.74 - 4.70 (m, 1H), 4.31 (d, J = 6.2 Hz, 2H), 2.70 (s, 3H), 2.01 (s, 3H) 1.73 (s, 1.73), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.8, 153.0, 141.3, 135.9, 133.6, 132.5, 128.6, 119.0, 115.9, 78, 4, 60.43, 26.2,

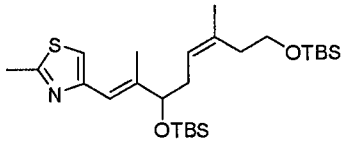
19.4, 18.6, 15.0, 12.9, -4.9; HRMS (CI) calcd. for $C_{20}H_{33}NO_2SSi$ ($M+H^+$) 380.2079, found 380.2080.



22

Triene 22: To a stirred solution of alcohol **21** (155 mg, 0.43 mmol) in DMF (0.43 mL) at 0 ^{0}C was added imidazole (51 mg, 0.75 mmol) and after 5 min tert - butyldimethylsilyl chloride (90 mg, 0.60 mmol) was added portionwise. The solution was allowed to warm to room temperature and stirred for an additional 30 min. Saturated aqueous NH_4Cl (2.5 mL) and ether (2.5 mL) were added at 0 ^{0}C and the aqueous layer was extracted with ether (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and purified by flash chromatography (SiO_2, 5% ether in hexanes) to give **22** as a colorless oil (201 mg, 98%). IR: (thin film) 2954, 2928, 2855, 2884, 2360, 1471, 1461, 1254, 1093, 1061, 1005, 835, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.93 (s, 1H), 6.58 (s, 1H), 6.28 (d, J = 15.6 Hz, 1H), 5.62 - 5.54 (m, 2H), 4.67 (d, J = 5.9 Hz, 1H), 4.39 (d, J = 6.3 Hz, 2H), 2.71 (s, 3H), 1.96 (s, 3H), 1.72 (s, 3H), 0.91 (m, 18H), 0.08 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.3, 153.2, 141.7, 133.9, 133.6, 131.2,

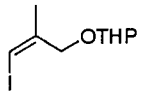
129.9, 118.1, 115.1, 78.7, 60.2, 29.6, 25.9, 25.8, 19.1, 18.3, 14.3, 12.6, -4.8, -4.9, -5.2 ;HRMS (CI) calcd. for $C_{26}H_{48}NO_2SSi$ ($M+H^+$) 494.2944, found 494.2941.



23

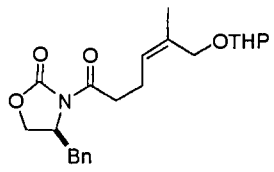
Diene 23: Through a stirred solution of $Cr(CO)_6$ (8.9 mg, 0.04 mmol) in cyclohexane (1.7 mL, freshly distilled from Na and benzophenone) and acetoniitrile (0.085 mL, freshly distilled from CaH_2 and degassed) under argon in a water cooled doubled-jacketed flask fitted with a three way tap and septa was passed a gentle stream of H_2. After 10 min. the solution was irradiated with a sun lamp for 30 min. To this yellow solution was added diene **22** (97 mg, 0.20 mmol) in 1.0 mL cyclohexane. The H_2 stream and irradiation were continued for 14 h and cyclohexane was added as needed to replace solvent loss. The reaction was concentrated and purified by flash chromatography (SiO_2, 5% ether in hexanes) to give **23** as a colorless oil (30 mg, 31%). IR: (thin film) 2954, 2927, 2885, 1470, 1255, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.92 (s, 1H), 6.45 (s, 1H), 5.21 (dd, J = 6.5, 7.1 Hz, 1H), 4.09 (t, J = 7.1 Hz, 1H), 3.62 (t, J = 7.4 Hz, 2H), 2.32-2.20 (m, 4H), 2.00 (s, 3H), 1.70 (s, 3H), 0.89 (s, 18H), 0.05 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.5, 153.5, 142.7, 133.7, 123.6, 118.9, 115.2, 79.1, 62.1,

36.1, 35.7, 26.2, 26.1, 24.4, 19.4, 18.6, 18.5, 14.1, -4.4, -4.7, -5.0; HRMS (CI) calcd. for $C_{26}H_{50}NO_2SSi$ ($M+H^+$) 496.3100, found 496.3103.



26

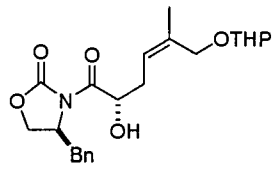
Iodide 26: To a stirred solution of **25** (1.03 g, 5.20 mmol) in CH_2Cl_2 (20 mL) was sequentially added dihydropyran (580 mg, 630 µL, 6.91 mmol) followed by pyridinium *p*-toluenesulfonate (110 mg, 0.438 mmol). After 1.5 h, the reaction was quenched with solid $NaHCO_3$ (5 g), filtered, concentrated *in vacuo,* and purified by chromatography on silica gel, eluting with 30% Et_2O / petroleum ether, to give **26** (1.42 g, 96%) as a colorless oil: IR (neat) 2940, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (s, 1H), 4.62 (t, J = 3.0 Hz, 1H), 4.26 (d, J = 12.1 Hz, 1H), 4.16 (d, J = 12.1 Hz, 1H), 3.85 - 3.95 (m, 1H), 3.5 - 3.6 (m, 1H), 1.95 (d, J = 1.5 Hz, 3H), 1.5 - 1.9 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 98.4, 75.8, 72.1, 62.5, 30.7, 25.6, 22.2, 19.6; HRMS (CI) calcd. for $C_9H_{16}IO_2$ ($M+H^+$) 283.0195, found 283.0198.



28

Alkene 28: To a stirred solution of *t*-BuLi (48 mL, 62.4 mmol, 1.3M in pentane) in Et_2O (63 mL) at -78 °C was added a solution of **26** (10.27 g, 36.4 mmol) in Et_2O (75 mL) *via* syringe pump during 20 min. After 20 min, the slurry was rapidly transferred to a precooled solution of CuCN (1.58 mg, 17.7 mmol) in THF (122 mL) at -78 °C. After 1 h at -78 °C and 5 min at -40 °C, the solution was recooled to -78 °C, and a precooled solution of **27** (3.40 g, 14.7 mmol) in THF (86 mL) was added *via* cannula. An additional amount of THF (25 mL) was added to rinse the flask. After 30 min, the solution was warmed to 0 °C, and after a further 10 min the reaction was quenched with saturated aqueous NH_4Cl (300 mL) and extracted with Et_2O (3 x 150 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with 15 - 50% Et_2O / petroleum ether, to give **28** (5.05 mg, 89%) as a colorless oil: $[\alpha]_D^{23}$ +46.1 (c 2.58, $CHCl_3$); IR (neat) 1782, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.1 - 7.4 (m, 5H), 5.40 (t, J = 7.1 Hz, 1H), 4.6 - 4.7 (m, 2H), 4.05 - 4.2 (m, 4H), 3.8 - 3.95 (m, 1H), 3.45 - 3.6 (m, 1H), 3.28 (dd, J = 3.2, 13.3 Hz, 1H), 2.9 - 3.05 (m, 2H), 2.76 (dd, J = 9.6, 13.3 Hz, 1H), 2.46 (q, J = 7.3 Hz, 2H), 1.5 - 1.9 (m, 6H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 153.6, 135.5,

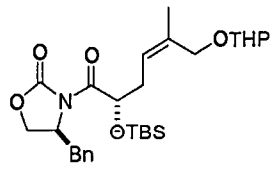
133.8, 129.6, 129.1, 127.5, 127.4, 97.8, 97.7, 66.4, 65.5, 65.4, 62.3, 55.3, 38.1, 36.0, 30.8, 25.7, 22.7, 21.9, 19.7; HRMS (FAB) calcd. for $C_{22}H_{28}NO_5$ ($M+H^+$) 386.1968, found 386.1965.



30

Alcohol 30: To a stirred solution of NaHMDS (7.6 mL, 7.6 mmol, 1M in THF) in THF (35 mL) at -78 °C was added a solution of **28** (2.482 g, 6.41 mmol) in THF (50 mL) *via* syringe pump during 30 min. An additional amount of THF (5 mL) was added to rinse the syringe. After 20 min, a precooled solution of oxaziridine **29** (2.55 g, 9.77 mmol) in THF (8 mL) was quickly added *via* cannula. After 6 min, the reaction was quenched with a solution of camphorsulfonic acid (3.54 g, 15.2 mmol) in THF (10 mL). After 2 min, saturated aqueous NH_4Cl (75 mL) was added, and the mixture was allowed to warm to room temperature and was concentrated *in vacuo* to remove THF. The aqueous layer was extracted with Et_2O (4 x 100 mL), and the dried ($MgSO_4$) extract was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with 50 - 70% Et_2O / petroleum ether, followed by further chromatography on silica gel, eluting with 2 - 4% acetone / CH_2Cl_2. The eluant was concentrated and the

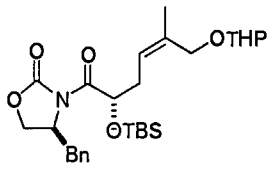
residue was triturated with 10% Et_2O / petroleum ether to give **30** (1.84 g, 71%) as a colorless foam contaminated with a small amount of phenyl sulfonamide: $[\alpha]_D^{23}$ +37.2 (c 4.00, $CHCl_3$); IR (neat) 3476, 1781, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.1 - 7.4 (m, 5H), 5.40 (m, 1H), 5.05 - 5.15 (m, 1H), 4.55 - 4.7 (m, 2H), 4.05 - 4.3 (m, 4H), 4.02 (dd, J = 3.7, 11.7 Hz, 1H), 3.8 - 3.95 (m, 1H), 3.79 (d, J = 8.6 Hz, 1H of a diastereomer), 3.66 (d, J = 8.6 Hz, 1H of a diastereomer), 3.45 - 3.6 (m, 1H), 3.31 (dt, J = 3.0, 13.5 Hz, 1H), 2.75 - 2.9 (m, 1H), 2.45 - 2.6 (m, 2H), 1.5 - 1.9 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 174.3, 153.4, 153.3, 136.2, 135.5, 135.11, 135.06, 129.6, 129.2, 127.6, 123.8, 123.1, 98.1, 96.4, 70.5, 70.4, 67.1, 67.0, 65.7, 65.0, 62.4, 61.8, 55.7, 37.7, 32.6, 30.7, 30.5, 25.6,, 22.2, 22.1, 19.7, 19.2; HRMS (CI) calcd. for $C_{22}H_{28}NO_6$ ($M+H^+$) 402.1917, found 402.1919.



32

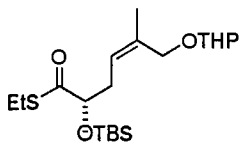
Ether 32: To a stirred solution of **30** (1.74 g, 4.32 mmol) in CH_2Cl_2 (22 mL) at -78 °C was added sequentially 2,6-lutidine (1.06 g, 1.15 mL, 9.87 mmol) followed by *t*-butyldimethylsilyl triflate (2.07 g, 1.8 mL, 7.83 mmol). After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (100 mL) and

extracted with Et_2O (4 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with 30 - 50% Et_2O / petroleum ether, to give **32** (2.06 g, 90%) as a colorless oil: $[\alpha]_D^{23}$ +32.3 (c 2.96, $CHCl_3$); IR (neat) 1782, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 - 7.4 (m, 5H), 5.35 - 5.5 (m, 2H), 4.55 - 4.7 (m, 2H), 4.05 - 4.2 (m, 2H), 4.0 - 4.15 (m, 2H), 3.8 - 3.9 (m, 1H), 3.4 - 3.5 (m, 1H), 3.36 (d, J = 13.1 Hz, 1H), 2.7 - 2.8 (m, 1H), 2.71 (dt, J = 1.6, 10.1 Hz, 1H), 2.45 - 2.55 (m, 2H), 1.5 - 1.8 (m, 9H), 0.92 (s, 9H), 0.91 (s, 9H of a diastereomer), 0.11 (s, 3H of a diastereomer), 0.10 (s, 3H of a diastereomer), 0.08 (s, 3H of a diastereomer), 0.07 (s, 3H of a diastereomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 173.7, 153.3, 135.5, 134.9, 129.6, 129.1, 127.5, 124.0, 97.6, 96.9, 71.1, 66.7, 65.5, 65.2, 62.3, 61.9, 55.8, 37.9, 34.2, 33.7, 30.8, 30.7, 26.0, 25.7, 22.0, 21.9, 19.7, 19.4, 18.5, -4.6, -4.9; HRMS (CI) calcd. for $C_{28}H_{44}NO_6Si$ ($M+H^+$) 518.2938, found 518.2908.



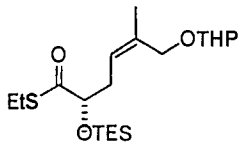
33

Ether 33: To a stirred solution of **30** (1.00 g, 2.48 mmol) in CH_2Cl_2 (25 mL) at –78 °C was added 2,6-lutidine (61 mg, 0.66 mL, 5.72 mmol). After 4 min, triethylsilyl triflate (1.19 g, 1.0 mL, 4.5 mmol) was added to the cold solution, and after 30 min the reaction was quenched with saturated aqueous NH_4Cl (60 mL) and extracted with Et_2O (3 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and the residue was purified by chromatography on silica gel, eluting with 30 - 50% Et_2O / hexane, to give **33** (1.00 g, 78%) as a colorless oil: $[\alpha]_D^{23}$ + 31.2 (*c* 1.63, $CHCl_3$); IR (neat) 1782, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 - 7.4 (m, 5H), 5.35 - 5.5 (m, 2H), 4.55 - 4.7 (m, 2H), 4.05 - 4.2 (m, 2H), 4.0 - 4.15 (m, 2H), 3.8 - 3.9 (m, 1H of a diastereomer), 3.4 - 3.5 (m, 1H of a diastereomer), 3.36 (d, J = 13.1 Hz, 1H of a diastereomer), 2.7 - 2.8 (m, 1H of a diastereomer), 2.45 - 2.55 (m, 2H), 2.46 (q, J = 7.3 Hz, 1H), 1.5 - 1.8 (m, 9H), 0.97 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 173.7, 153.3, 135.5, 134.9, 129.6, 129.1, 127.5, 124.0, 97.6, 96.9, 71.1, 66.7, 65.5, 65.2, 62.3, 61.9, 55.8, 37.9, 34.2, 33.7, 30.8, 30.7, 26.0, 25.7, 22.0, 21.9, 19.7, 19.4, 18.5, 6.7, 5.1; HRMS (CI) calcd. for $C_{28}H_{44}NO_6Si$ ($M+H^+$) 518.2938, found 518.2908.



34

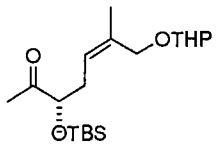
Thioester 34: To a stirred solution of ethanethiol (713 mg, 850 µL, 11.5 mmol) in THF (45 mL) was added KH (106 mg, 0.93 mmol, 35% in mineral oil). After 30 min, the mixture was cooled to 0 °C, and a solution of **32** (2.064 g, 3.99 mmol) in THF (15 mL) was added *via* cannula during 5 min. An additional amount of THF (10 mL) was added to rinse the flask. After 50 min at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (50 mL). Air was bubbled through the solution for 2 h to remove excess ethane thiol and the solution was extracted with Et_2O (4 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo,* and the residue was crystallized by the addition of 10% Et_2O / petroleum ether to yield the recovered auxillary (640 mg, 3.61 mmol, 93%) as a colorless solid. The decanted solution was chromatographed on silica gel, eluting with 10 - 30% Et_2O / petroleum ether, to give **34** (1.44 g, 90%) as a colorless oil: $[\alpha]_D^{23}$ –46.1 (c 3.50, $CHCl_3$); IR (neat) 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 - 5.5 (m, 1H), 4.55 (bs, 1H), 3.9 - 4.2 (m, 3H), 3.8 - 3.9 (m, 1H), 3.45 - 3.6 (m, 1H), 2.75 - 2.9 (m, 2H), 2.4 - 2.6 (m, 2H), 1.4 - 1.9 (m, 6H), 1.21 (t, J = 7.5 Hz, 3H), 0.93 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H of a diastereomer), 0.05 (s, 3H of a diastereomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 205.0, 135.24, 135.16, 97.9, 97.4, 78.6, 65.7, 65.5, 62.3, 62.2, 34.5, 30.8, 25.9, 25.7, 22.6, 22.1, 22.0, 19.7, 19.6, 18.4, 14.8, -4.7, -4.8; HRMS (CI) calcd. for $C_{20}H_{37}NO_4SSi$ ($M+H^+$) 401.2182, found 401.2172.



35

Thioester 35: To a stirred solution of ethanethiol (361 mg, 430 µL, 5.82 mmol) in THF (25 mL) at room temperature was added KH (55 mg, 0.48 mmol, 35% in mineral oil). After 30 min, the mixture was cooled to 0 °C and a solution of **33** (1.00 g, 1.94 mmol) in THF (10 mL) was added *via* cannula during 5 min. An additional amount of THF (5 mL) was added, and after 1 h at room temperature the reaction was quenched with saturated aqueous NH_4Cl (25 mL). Air was passed through the solution for 2 h to remove excess ethanethiol, and the mixture was extracted with Et_2O (3 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and the residue was taken up in 10% Et_2O / petroleum ether, from which 4-benzyloxazolidin-2-one crystallized as a colorless solid. The decanted solution was concentrated and the residue was purified by chromatography on silica gel, eluting with 30% Et_2O / hexane, to give the thioester **35** (730 mg, 97%) as a colorless oil: $[\alpha]_D^{23}$ –16.8 (*c* 2.73, $CHCl_3$); IR (neat) 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ5.35 - 5.5 (m, 1H), 4.55 (bs, 1H), 3.9 - 4.2 (m, 3H), 3.8 - 3.9 (m, 1H), 3.45 - 3.6 (m, 1H), 3.36 (d, J = 13.1 Hz, 1H), 2.75 - 2.9 (m, 2H), 2.4 - 2.6 (m, 2H), 1.4 - 1.9 (m, 6H), 1.21 (t, J = 7.5 Hz, 3H), 0.97 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$)

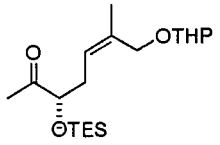
δ205.1, 205.0, 135.24, 135.16, 97.9, 97.4, 78.6, 65.7, 65.5, 62.3, 62.2, 34.5, 30.8, 25.9, 25.7, 22.6, 22.1, 22.0, 19.7, 19.6, 18.4, 14.8, 6.7, 5.1; HRMS (CI) calcd. for $C_{20}H_{37}NO_4SSi$ ($M+H^+$) 401.2182, found 401.2172.



36

Ketone 36: To a stirred solution of CuI (4.85 mg, 25.5 mmol) in Et_2O (120 mL) at 0 °C was added MeLi (33.1 mL, 23.2 mmol, 1.4M in Et_2O). After 15 min, the solution was cooled to -50 °C, and a solution of **34** (1.78 g, 4.64 mmol) in Et_2O (90 mL) was added *via* cannula. An additional amount of Et_2O (10 mL) was added to rinse the flask. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (300 mL), and the mixture was extracted with Et_2O (4 x 175 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo,* and the residue was purified by chromatography on silica gel, eluting with 15% Et_2O / petroleum ether, to give **36** (1.36 g, 82%) as a colorless oil: $[\alpha]_D^{23}$ +14.0 (c 5.00, $CHCl_3$); IR (neat) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 - 5.5 (m, 5H), 4.5 - 4.55 (m, 1H), 3.9 - 4.1 (m, 3H), 3.75 - 3.9 (m, 1H), 3.4 - 3.5 (m, 1H), 2.3 - 2.5 (m, 2H), 2.10 (s, 3H), 1.74 (s, 3H), 1.4 - 1.9 (m, 6H), 0.87 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 135.2, 135.1, 123.8, 123.5, 97.7, 97.3, 79.0, 65.5,

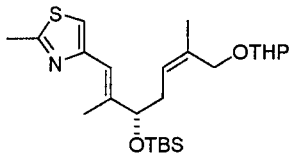
65.2, 62.2, 62.1, 33.2, 30.7, 25.8, 25.6, 25.5, 22.0, 19.6, 19.5, 18.2, -4.8, -4.9; HRMS (CI) calcd. for $C_{19}H_{37}O_4Si$ ($M+H^+$) 357.2461, found 357.2455.



37

Ketone 37: To a stirred solution of CuI (2.60 g, 13.67 mmol) in Et_2O (120 mL) at 0 °C was added MeLi (17.8 mL, 24.9 mmol, 1.4M in Et_2O). The mixture was cooled to -50 °C and a solution of the thioester **35** (960 mg, 2.49 mmol) in Et_2O (50 mL) was added *via* cannula. An additional amount of Et_2O (5 mL) was added to rinse the flask. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (200 mL), and the mixture was extracted with Et_2O (3 x 120 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and the residue was purified by chromatography on silica gel, eluting with 15% Et_2O / hexane, to give the methyl ketone **37** (548 mg, 62%) as a colorless oil: $[\alpha]_D^{23}$ –11.0 (*c* 3.26, $CHCl_3$); IR (neat) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 - 5.5 (m, 5H), 4.5 - 4.55 (m, 1H), 3.9 - 4.1 (m, 3H), 3.75 - 3.9 (m, 1H), 3.4 - 3.5 (m, 1H), 2.3 - 2.5 (m, 2H), 2.10 (s, 3H) 1.4 - 1.9 (m, 6H), 0.97 (t, J = 7.8 Hz, 9H), 0.62 (q, J = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ211.7, 135.2, 135.1, 123.8, 123.5, 97.7, 97.3, 79.0, 65.5, 65.2, 62.2, 62.1, 33.2, 30.7, 25.8, 25.6, 25.5, 22.0, 19.6, 19.5,

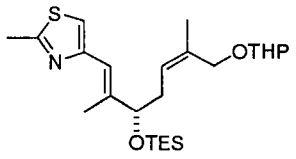
18.2, 6.7, 5.1; HRMS (CI) calcd. for $C_{19}H_{37}O_4Si$ ($M+H^+$) 357.2461, found 357.2455.



39

Thiazole 39: To a stirred solution of **38** (1.45 g, 5.82 mmol) in THF (10 mL) at -78 °C was added *n*-BuLi (3.6 mL, 5.76 mmol, 1.6 M in hexanes). After 15 min, a solution of **36** (590 mg, 1.66 mmol) in THF (7 mL) was added *via* cannula. An additional amount of THF (3 mL) was added to rinse the flask. After 30 min, the mixture was allowed to warm to room temperature during 1 h. After an additional 30 min at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the mixture was extracted with Et_2O (4 x 75 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo,* and the residue was purified by chromatography on silica gel, eluting with 10 - 20% Et_2O / petroleum ether, to give sequentially the undesired *Z* olefin isomer (40 mg, 5%) as a colorless oil followed by **39** (690 mg, 92%) as a colorless oil: *Z* diastereomer: $[\alpha]_D^{23}$ -59.2 (c 1.26, $CHCl_3$); IR (neat) 2959, 2852, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.18, (s, 1H), 5.35 - 5.5 (m, 2H), 4.55 - 4.65 (m, 1H), 4.05 - 4.15 (m, 2H), 3.8 - 3.9 (m, 1H), 3.45 - 3.6 (m, 1H), 2.68 (s, 3H), 2.4 - 2.5

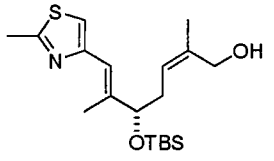
(m, 1H), 2.2 - 2.35 (m, 1H), 1.87 (d, J = 0.9 Hz, 3H), 1.76 (s, 3H), 1.4 - 1.9 (m, 6H), 0.84 (s, 9H), 0.07 (s, 3H), -0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 152.9, 143.5, 133.4, 126.7, 126.5, 118.8, 115.2, 97.9, 97.6, 70.8, 70.5, 65.9, 62.4, 62.2, 34.5 ,30.9, 26.0, 25.7, 22.1, 19.8, 19.7, 19.4, 18.5, 18.4, -4.7, -4.9. **39**: $[\alpha]_D^{23}$ +19.2 (c 3.45, $CHCl_3$); IR (neat) 2959, 1531, 1474 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.45, (s, 1H), 5.35 - 5.5 (m, 1H), 4.5 - 4.6 (m, 1H), 3.9 - 4.2 (m, 3H), 3.8 - 3.9 (m, 1H), 3.45 - 3.6 (m, 1H), 2.70 (s, 3H), 2.2 - 2.4 (m, 2H), 1.99 (d, J = 1.0 Hz, 3H), 1.76 (s, 3H) 1.4 - 1.9 (m, 6H), 0.88 (s, 9H), 0.04 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 153.4, 142.5, 142.4, 133.6, 126.2, 126.1, 119.2, 118.9, 115.3, 97.8, 97.5, 79.0, 78.9, 65.8, 65.6, 62.3, 62.2, 35.4, 35.3, 30.1, 26.9, 26.0, 25.7, 22.0, 19.7, 19.4, 18.4, 14.1, -4.5, -4.8; HRMS (CI) calcd. for $C_{24}H_{42}NO_3SSi$ ($M+H^+$) 452.2655, found 452.2645.



40

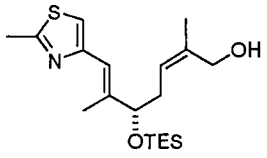
Thiazole 40: To a stirred solution of **38** (1.26 g, 5.08 mmol) in THF (9 mL) at -78 °C was added *n*-BuLi (4.7 mL, 5.00 mmol, 1.2 M in hexanes), and after 20 min, a solution of the methyl ketone **37** (520 mg, 1.45 mmol) in THF (6 mL) was

added *via* cannula. An additional amount of THF (2 mL) was added to rinse the flask. After 30 min, the solution was allowed to warm slowly to room temperature during 1 h, then was cooled at -78 °C for an additional 30 min before the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with Et_2O (3 x 65 mL), and the dried ($MgSO_4$) extract was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with 20% Et_2O / hexanes, to give thiazole **40** (627 mg, 96%) as a colorless oil: $[\alpha]_D^{23}$ –33.9 (*c* 2.56, $CHCl_3$); IR (neat) 2950, 1512, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ6.91 (s, 1H), 6.45, (s, 1H), 5.35 - 5.5 (m, 1H), 4.5 - 4.6 (m, 1H), 3.9 - 4.2 (m, 3H), 3.8 - 3.9 (m, 1H), 3.45 - 3.6 (m, 1H), 2.70 (s, 3H), 2.2 - 2.4 (m, 2H), 1.99 (d, J = 1.0 Hz, 3H), 1.4 - 1.9 (m, 6H), 0.92 (t, J = 7.9 Hz, 9H), 0.72 (q, J = 7.9 Hz, 6H);^{13}C NMR (75 MHz, $CDCl_3$,) δ164.2, 153.1, 142.5, 142.2, 133.4, 125.6, 125.5, 118.7, 118.6, 114.9, 97.4, 97.2, 78.4, 77.3, 65.4, 65.3, 62.0, 61.9, 35.0, 34.9, 30.6, 25.4, 21.7, 19.4, 19.4, 19.1, 13.8, 6.7, 4.7; HRMS (CI) calcd. for $C_{24}H_{42}NO_3SSi$ ($M+H^+$) 452.2655, found 452.2645.



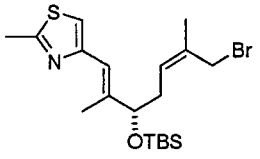
41

Alcohol 41: To a stirred solution of freshly prepared $MgBr_2$ (662 mg, 27.6 mmol of Mg, and 2.0 mL, 23.8 mmol of 1,2-dibromoethane) in Et_2O (50 mL) was added a solution of **39** (663 mg, 1.26 mmol) in Et_2O (5 mL) at room temperature followed by saturated aqueous NH_4Cl (approx. 50 µL). After 3.5 h, the solution was cooled to 0 °C and was carefully quenched with saturated aqueous NH_4Cl (50 mL). The solution was extracted with Et_2O (4 x 70 mL), and the dried ($MgSO_4$) extract was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with 30 - 50% Et_2O / petroleum ether, to give **41** (459 mg, 99%) as a colorless oil: $[\alpha]_D^{23}$ -16.8 (c 3.40, $CHCl_3$); IR (neat) 3374 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.44, (s, 1H), 5.31 (t, J = 7.7 Hz, 1H), 4.14 (d, J = 12.2 Hz, 1H), 4.1 - 4.2 (m, 1H), 4.00 (d, J = 12.2 Hz, 1H), 2.71 (s, 3H), 2.4 -2.5 (m, 1H), 2.2 - 2.3 (m, 2H), 2.00 (s, 3H), 1.80 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 153.0, 142.4, 137.7, 124.4, 119.0, 115.4, 78.4, 62.0, 35.5, 26.0, 22.2, 19.3, 18.5, 14.3, -4.5, -4.7; HRMS (CI) calcd. for $C_{19}H_{34}NO_2SSi$ 368.2080; found 368.2061.



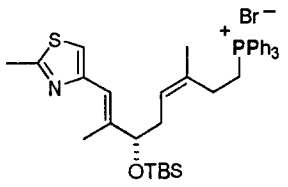
42

Alcohol 42: To a stirred solution of freshly prepared $MgBr_2$ (631 mg, 26.2 mmol of Mg, and 2.38 mL, 27.7 mmol, of 1,2-dibromoethane) in Et_2O (50 mL) at room temperature was added the thiazole **40** (556 mg, 1.20 mmol) in Et_2O (5 mL) followed by saturated aqueous NH_4Cl (approx 50 µL). After 3.5 h, the mixture was cooled to 0 °C and carefully quenched with saturated aqueous NH_4Cl (50 mL). The mixture was extracted with Et_2O (3 x 100 mL), and the dried ($MgSO_4$) extract was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with 30% Et_2O / hexanes, to give **42** (390 mg, 89%) as a colorless oil: $[\alpha]_D^{23}$ -31.0 (*c* 2.74); IR (neat) 3374 cm^1;^1H NMR (300 MHz, $CDCl_3$) δ6.92 (s, 1H), 6.44, (s, 1H), 5.31 (t, J = 7.7 Hz, 1H), 4.14 (d, J = 12.2 Hz, 1H), 4.1 - 4.2 (m, 1H), 4.00 (d, J = 12.2 Hz, 1H), 2.71 (s, 3H), 2.4 -2.5 (m, 1H), 2.2 - 2.3 (m, 2H), 2.00 (s, 3H), 1.80 (s, 3H), 0.92 (t, J = 7.9 Hz, 9H), 0.72 (q, J = 7.9 Hz, 6H);^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 153.0, 142.4, 137.7, 124.4, 119.0, 115.4, 78.4, 62.0, 61.9, 35.5, 29.9, 26.0, 22.2, 19.3, 18.5, 14.3, 6.7, 4.7; HRMS (CI) calcd. for $C_{19}H_{34}NO_2SSi$ ($M+H^+$) 368.2080, found 368.2061.



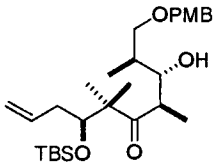
43

Bromide 43: To a stirred solution of **41** (620 mg, 1.69 mmol) in CH_2Cl_2 (5.5 mL) at 0 °C was added Et_3N (360 µL, 2.58 mmol) followed by methanesulfonic anhydride (390 mg, 2.24 mmol). After 10 min, acetone (5.5 mL) was added followed by LiBr (890 mg, 10.3 mmol). After 1.8 h at room temperature, the mixture was concentrated *in vacuo* to remove the acetone, diluted with saturated aqueous NH_4Cl (100 mL), and extracted with Et_2O (4 x 200 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with 10 - 20% Et_2O / petroleum ether, to give **43** (607 mg, 84%) as a colorless oil: $[\alpha]_D^{23}$ +65.1 (c 2.95, $CHCl_3$); IR (neat) 2949, 2930, 2852, 1479, 844 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.48, (s, 1H), 5.42 (dt, J =1.3, 7.6 Hz, H), 4.16 (dd, J = 5.4, 7.3 Hz, 1H), 4.06 (d, J = 9.5 Hz, 1H), 3.90 (d, J = 9.5 Hz, 1H), 2.71 (s, 3H), 2.3 -2.5 (m, 2H), 2.01 (d, J = 1.1 Hz, 3H), 1.83 (d, J = 1.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 153.2, 142.1, 133.3, 128.2, 119.2, 115.4, 78.1, 35.7, 32.6, 26.0, 22.2, 19.4, 18.4, 13.1, -4.5, -4.8; HRMS (CI) calcd. for $C_{19}H_{33}NO_2SSi^{81}Br$ ($M+H^+$) 430.1235, found 430.1244.



45

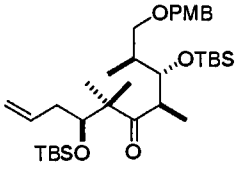
Phosphonium bromide 45: To a stirred solution of methyltriphenylphosphonium bromide (1.53 g, 4.28 mmol) in THF (16.2 mL) at -78 °C was added *n*-BuLi (2.7 mL, 4.32 mmol, 1.6M in hexanes) during 3 min. After 35 min, a precooled solution of **43** (607 mg, 1.41 mmol) in THF (7 mL) was added dropwise to the ylide during 5 min. An additional portion of THF (6 mL) was used to rinse the flask. After 15 min, the mixture was allowed to warm to -20 °C, and after an additional 20 min the reaction was quenched with MeOH and the mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with 0 - 6% MeOH / CH_2Cl_2. Dilution of the eluant with CH_2Cl_2, followed by a H_2O wash to remove excess methyltriphenylphosphonium bromide and then removal of the solvent *in vacuo*, gave **45** (890 mg, 89%) as an off-white foam: $[\alpha]_D^{23}$ +6.4 (c 1.06, $CHCl_3$); IR (neat) 2959, 2930, 2853, 1440; ^1H NMR (300 MHz, $CDCl_3$) δ 7.6 - 7.9 (m, 5H), 6.89 (s, 1H), 6.33, (s, 1H), 5.20 (m, 1H), 3.95 (m, 1H), 3.5 - 3.8 (m, 2H), 2.65 (s, 3H), 2.1 -2.3 (m, 2H), 1.88 (s, 3H), 1.83 (s, 3H), 0.78 (s, 9H), -0.07 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 153.0, 142.1, 135.6, 133.9, 130.9, 130.7, 124.7, 118.8, 117.5, 115.6, 78.2, 35.9, 26.0, 24.7, 23.7, 22.6, 21.9, 19.4, 18.3, 14.4, -4.6, -4.8; HRMS (CI) calcd. for $C_{38}H_{49}NOPSSi$ ($M+H^+$) 626.3042, found 626.3028.



56

Alcohol 56: To a stirred solution of *i*-Pr_2NH (390 µL, 2.78 mmol) in THF (0.7 mL) at –78 °C was added dropwise *n*-BuLi (1.73 mL, 2.77 mmol, 1.6M in hexanes). After 5 min, the solution was warmed to 0 °C during 45 min and then was recooled to -78 °C. To the stirred solution of LDA was added dropwise *via* cannula a precooled solution of **61** (718 mg, 2.53 mmol) in THF (0.6 mL) during 5 min. An additional amount of THF (0.4 mL) was used to rinse the flask. After an additional 50 min at -78 °C, a precooled solution of **66** (484 mg, 2.33 mmol) in THF (0.6 mL) was added dropwise *via* cannula. An additional amount of THF (0.4 mL) was used to rinse the flask. After 30 min, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (4 x 25 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo,* and the residue was purified by chromatography on silica gel, eluting with 6 - 10% Et_2O / petroleum ether, to give **56** (694 mg, 61%) as a colorless oil: $[\alpha]_D^{23}$ -25.1 (c 3.05, $CHCl_3$); IR (neat) 3483, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H) 6.86 (d, J = 8.7 Hz, 2H), 5.65 - 5.85 (m, 1H), 4.9 - 5.1 (m, 2H), 4.44 (s, 2H), 3.93 (dd, J = 4.5, 6.4 Hz, 1H), 3.80 (s, 3H), 3.55 - 3.65 (m, 3H), 3.46 (dd, J = 6.1, 8.9 Hz, 1H), 3.15 - 3.25 (m, 1H), 2.05 - 2.2 (m, 2H), 1.8 - 1.9 (m, 1H), 1.18 (s, 3H), 1.11 (s,

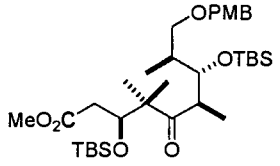
3H), 1.05 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 7.9 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.7, 159.3, 136.5, 130.9, 129.4, 116.9, 113.9, 73.2, 73.1, 72.9, 55.4, 54.4, 41.9, 39.8, 36.4, 29.9, 26.3, 23.9, 19.3, 18.4, 14.3, 10.2, -3.3, -3.8; HRMS (CI) calcd. for $C_{28}H_{49}O_5Si$ ($M+H^+$) 493.3349., found 493.3350.



57

Trisether 57: To a stirred solution of **56** (61.0 mg, 0.124 mmol) in CH_2Cl_2 (0.7 mL) at 0 °C was added sequentially Et_3N (29 mg, 40 µL, 0.287 mmol) followed by *t*-butyldimethylsilyl triflate (43.7 mg, 38 µL, 0.165 mmol) at 0 °C. After 45 min, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (4 x 25 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with 3 - 10% Et_2O / petroleum ether, to give **57** (66.5 mg, 89%) as a colorless oil: $[\alpha]_D^{23}$ -16.0 (c 2.92, $CHCl_3$); IR (neat) 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H) 6.86 (d, J = 8.6 Hz, 2H), 5.7 - 5.9 (m, 1H), 4.99 (d, J = 6.4 Hz, 1H), 4.95 (s, 1H), 4.40 (s, 2H), 3.9 - 4.0 (m, 1H), 3.85 (d, J = 7.3 Hz, 1H), 3.80 (s, 3), 3.58 (dd, J = 5.7, 9.2 Hz, 1H), 3.27 (qn, J = 7.4 Hz, 1H), 3.19 (t, J =

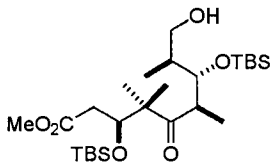
7.4 Hz, 1H) 2.0 - 2.2 (m, 2H), 1.8 - 1.9 (m, 1H), 1.13 (s, 3H), 1.04 (s, 3H), 1.02 (3H, d, J = 7.0 Hz), 0.96 (3H, d, J = 6.9 Hz), 0.891 (s, 9H), 0.887 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.2, 159.3, 137.1, 131.0, 129.5, 116.5, 113.9, 76.5, 73.1, 71.8, 55.5, 54.2, 46.2, 39.8, 38.9, 26.5, 26.3, 25.3, 18.7, 18.4, 18.0, 17.0, 16.6, -3.0, -3.3, -3.5, -3.8; HRMS (CI) calcd. for $C_{34}H_{63}O_5Si_2$ ($M+H^+$) 607.4214, found 607.4212.



58

Methyl ester 58: To a stirred solution of crude acid (1.19 mmol) in benzene (20 mL) and MeOH (2.5 mL) was added (trimethylsilyl)diazomethane (700 µL, 1.4 mmol, 2M in hexanes). After 45 min, the mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with 5 - 10% Et_2O / petroleum ether, to give **58** (502 mg, 66% from **57**) as a colorless oil: $[\alpha]_D^{23}$ -27.1 (c 1.03, $CHCl_3$); IR (neat) 1741, 1690 cm^{-1}; ^1H NMR

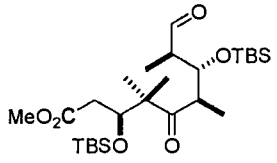
(300 MHz, $CDCl_3$) δ 7.23d, J = 8.5 Hz, 2H), 6.86d, J = 8.5 Hz, 2H), 4.39 (s, 2H), 4.3 - 4.4 (m, 1H), 3.83 (d, J = 7.8 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.58 (dd, J = 5.7, 9.1 Hz, 1H), 3.31 (dq, J = 7.2, 7.2 Hz, 1H), 3.18 (dd, J = 7.3, 9.1 Hz, 1H), 2.46 (dd, J = 3.1, 16.1 Hz, 1H), 2.26 (dd, J = 7.0, 16.1 Hz, 1H), 1.7 - 1.85 (m, 1H), 1.14 (s, 3H), 1.06 (s, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.5, 172.7, 159.3, 131.0, 129.5, 113.9, 74.1, 73.1, 71.8, 55.5, 53.6, 51.8, 46.3, 40.4, 38.9, 26.5, 26.2, 24.0, 18.8, 18.7, 18.4, 17.0, 15.7, -3.3, -3.5, -4.3, -4.4; HRMS (CI) calcd. for $C_{33}H_{63}O_7Si_2$ ($M+H^+$) 639.4112, found 639.4112.



59

Alcohol 59: To a stirred solution of **58** (290 mg, 0.455 mmol) in EtOH (7 mL) was added palladium-on-carbon (101 mg, 10% Pd), and the mixture was stirred under an atmosphere of H_2. After 45 min, the H_2 atmosphere was replaced by Ar, and the mixture was filtered through Celite (EtOH rinse). The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on silica gel, eluting with 10 - 30% Et_2O / petroleum ether, to

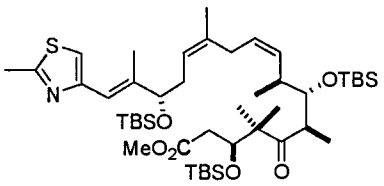
give alcohol **59** (216 mg, 0.418 mmol, 92%) as a colorless oil: $[\alpha]_D^{23}$ -13.2 (c 1.07, $CHCl_3$); IR (neat) 3538, 1743, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (dd, J = 2.9, 6.9 Hz, 1H), 3.93 (dd, J = 2.0, 7.8 Hz, 1H), 3.67 (s, 3H), 3.6 - 3.7 (m, 1H), 3.5 - 3.6 (m, 1H), 3.31 (dq, J = 7.5, 7.5 Hz, 1H), 2.43 (dd, J = 2.7, 16.3 Hz, 1H), 2.26 (dd, J = 6.9, 16.3 Hz, 1H), 1.55 - 1.65 (m, 1H), 1.22 (s, 3H), 1.13 (s, 3H), 1.09 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.4, 172.8, 78.2, 73.6, 64.9, 53.9, 51.9, 47.0, 40.3, 39.8, 29.9, 26.4, 26.2, 24.1, 19.1, 18.6, 18.4, 16.1, -3.4, -3.6, -4.3, -4.4; HRMS (CI) calcd. for $C_{26}H_{53}Si_2O_6$ ($M+H^+$) 517.3381, found 517.3361.



60

Aldehyde 60: To a stirred mixture of the alcohol obtained above (700 mg, 1.36 mmol) and powdered molecular sieves (1.5 g) in CH_2Cl_2 (35 mL) was added N-methylmorpholine-N-oxide (420 mg, 3.56 mmol) followed by tetra-*n*-propylammonium perruthenate (137.5 mg, 106 μmol). After 1 h, the mixture was diluted with 30% Et_2O / petroleum ether (100 mL) and filtered through silica gel (30% Et_2O / petroleum ether rinse). The filtrate was concentrated *in vacuo* to

give **60** (698 mg, 99%) as a colorless oil: $[\alpha]_D^{23}$ -32.1 (c 1.76, $CHCl_3$); IR (neat) 1746, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, J = 2.1 Hz, 1H), 4.41 (dd, J = 3.2, 6.9 Hz, 1H), 4.08 (dd, J = 2.1, 8.3 Hz, 1H), 3.67 (s, 3H), 3.25 (dq, J = 7.0, 7.0 Hz, 1H), 2.41 (dd, J = 3.3, 16.1 Hz, 1H), 2.2 - 2.35 (m, 2H), 1.24 (s, 3H), 1.12 (d, J = 7.1 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.09 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.090 (s, 3H), 0.085 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.0, 204.4, 172.6, 76.5, 73.9, 53.8, 51.9, 51.0, 46.8, 40.4, 29.9, 26.4, 24.0, 19.2, 18.6, 18.4, 15.9, 12.7, -3.4, -3.6, -4.3, -4.4; HRMS (CI) calcd. for $C_{26}H_{51}Si_2O_6$ ($M+H^+$) 515.3225, found 515.3218.



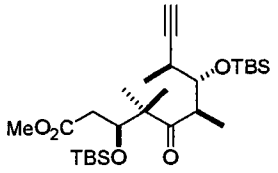
61

Triene 61 from 46: To hexamethyldisilazane (280 µL, 1.31 mmol) in THF (650 µL) at -78 °C was added *n*-BuLi (820 µL, 1.31 mmol, 1.6M in hexanes). After 5 min, the solution was warmed to 0 °C and was added dropwise to a stirred solution of **46** (930 mg, 1.32 mmol) in THF (17 mL) at -78 °C *via* cannula. After 15 min, the solution was warmed to -30 °C, and after an additional 15 min, the solution was recooled to -78 °C and added dropwise *via* cannula to a precooled solution of **60** (520 mg, 1.03 mmol) in THF (0.6 mL). The mixture was allowed to warm slowly to room temperature during 1 h. After 10 min at room

temperature, the reaction was quenched with saturated aqueous NH_4Cl (25 mL), and the solution was concentrated *in vacuo* to remove THF. The residual solution was extracted with Et_2O (4 x 50 mL), and the dried ($MgSO_4$) extract was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with 2 - 10% Et_2O / petroleum ether, to give **61** (728 mg, 0.84 mmol, 82%) as a colorless oil: $[\alpha]_D^{23}$ + 3.6 (c 1.00, $CHCl_3$); IR (neat) 1743, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.45 (s, 1H), 5.58 (t, J = 9.2 Hz, 1H), 5.2 - 5.35 (m, 1H), 5.16 (t, J = 6.6 Hz, 1H), 4.39 (dd, J = 3.1, 6.9 Hz, 1H), 4.09 (t, J = 6.6 Hz, 1H), 3.8 - 3.9 (m, 1H), 3.6 - 3.7 (m, 1H); 3.66 (s, 3H), 3.03 (qn, J = 6.7 Hz, 1H), 2.70 (s, 3H), 2.65 - 2.75 (m, 2H), 2.3 - 2.5 (m, 2H), 2.15- 2.35 (m, 3H), 1.99 (s, 3H), 1.64 (s, 3H), 1.19 (s, 3H), 1.06 (s, 3H), 1.03 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 6H), 0.04 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.0, 172.6, 164.5, 153.4, 142.5, 135.5, 131.7, 128.7, 122.2, 119.0, 115.2, 79.1, 76.1, 74.2, 53.5, 51.8, 46.4, 40.4, 37.9, 35.6, 30.9, 26.4, 26.2, 26.0, 24.0, 23.9, 19.4, 19.3, 18.7, 18.4, 14.9, 14.1, -3.3, -3.7, -4.3, -4.4, -4.7; HRMS (CI) calcd. for $C_{46}H_{86}NO_6SSi_3$ ($M+H^+$) 864.5484, found 864.5510.

From 62: To a supension of Lindlar catalyst (1.35 mg) in hexane (1 mL) was added **62**(10.0 mg, 0.011 mmol), and the mixture was stirred at room temperature under an atmosphere of H_2 for 28 h. The suspension was filtered through silica (Et_2O rinse), and the filtrate was concentrated *in vacuo*. The

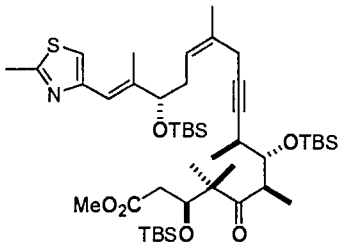
residue was purified by chromatography on silica gel, eluting with 40-60% CH_2Cl_2 / hexane to give **61** (6.8 mg, 68%) as a colorless oil: $[\alpha]_D^{23}$ + 3.7 (c 1.12, $CHCl_3$); IR (neat) 1743, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.45 (s, 1H), 5.58 (t, J = 9.2 Hz, 1H), 5.2 - 5.35 (m, 1H), 5.16 (t, J = 6.6 Hz, 1H), 4.39 (dd, J = 3.1, 6.9 Hz, 1H), 4.09 (t, J = 6.6 Hz, 1H), 3.8 - 3.9 (m, 1H), 3.6 - 3.7 (m, 1H); 3.66 (s, 3H), 3.03 (dq, J = 6.7 Hz, 1H), 2.70 (s, 3H), 2.65 - 2.75 (m, 2H), 2.3 - 2.5 (m, 2H), 2.15- 2.35 (m, 3H), 1.99 (s, 3H), 1.64 (s, 3H), 1.19 (s, 3H), 1.06 (s, 3H), 1.03 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 6H), 0.04 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.0, 172.6, 164.5, 153.4, 142.5, 135.5, 131.7, 128.7, 122.2, 119.0, 115.2, 79.1, 76.1, 74.2, 53.5, 51.8, 46.4, 40.4, 37.9, 35.6, 30.9, 26.4, 26.2, 26.0, 24.0, 23.9, 19.4, 19.3, 18.7, 18.4, 14.9, 14.1, -3.3, -3.7, -4.3, -4.4, -4.7; HRMS (CI) calcd. for $C_{46}H_{86}NO_6SSi_3$ ($M+H^+$) 864.5484, found 864.5510.



62

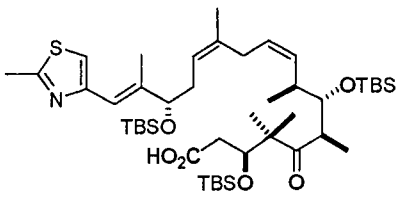
Alkyne 62: To a stirred solution of potassium *tert*-butoxide (0.27 mL, 1.0M THF solution) in THF (0.5 mL) at –78 °C was added dimethyl

(diazomethyl)phosphonate (40.2 mg, 1.25 mmol) in THF (0.5 mL). After 5 min, a solution of **60** (110 mg, 0.21 mmol) in THF (0.5 mL) was added dropwise. The mixture was stirred at –78 °C for 12 h, then was warmed to room temperature and quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted with 3 x 5 mL portions of Et_2O, and the combined extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with 5% Et_2O/hexane, to give **60** (85 mg, 80%) as colorless prisms: mp 52-54 °C; $[\alpha]_D^{23}$ –24.1 (c 1.12, $CHCl_3$); IR (neat) 1743, 1691,1472 cm^{-1};^1H NMR ($CDCl_3$, 300 MHz) δ 4.45 (dd, J = 3.1, 7.5 Hz, 1H) 3.76 (dd, J = 2.1, 6.4 Hz, 1H), 3.65 (s, 1H) 3.33 (dq, J = 7.5, 7.5 Hz, 1H) 2.40-2.26 (m, 3H), 2.06 (s, 1H), 1.24 (s, 3H)1.18 (d, J = 6.9 Hz, 3H) 1.17 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H), 0.92 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ218.6, 172.3, 85.6, 75.7, 73.3, 70.8, 53.9, 46.5, 32.1, 26.1, 23.7, 18.7, 18.5, 18.2, 15.8, -3.3, -3.9, -4.5, -4.7; HRMS (CI) calcd. for $C_{27}H_{52}Si_2O_5$ ($M+H^+$) 512.3353, found 512.3342.



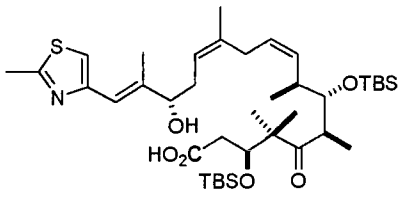
63

Enyne 63: To a stirred solution of **62** (70.0 mg, 0.135 mmol) in Et_2O (1.0 mL) and DMF (0.4 mL) at room temperature was added Et_3N (18.8 ∃L, 0.135 mmol) and CuI (25.7 mg, 0.135 mmol). After the mixture became clear (approx 5 min), a solution of **43** (29.1 mg, 0.068 mmol) in Et_2O (1.0 mL) was added. The solution was stirred for 18 h, quenched with saturated aqueous $Na_2S_2O_3$ (5 mL), and extracted with Et_2O (3 x 2 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with 50-60% CH_2Cl_2/hexanes to give **63** (35.6 mg, 60%) as a colorless oil: $[\alpha]_D^{23}$ –16.7 (*c* 1.01); IR (neat) 1743, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.91(s, 1H), 6.46 (s, 1H), 5.36 (t, J = 4.7 Hz, 1H), 4.45 (dd, J = 3.1, 6.9 Hz, 1H), 4.11 (t, J = 6.6, 1H), 3.76-3.72 (m, 1H), 3.74-3.67 (m, 1H) 3.67 (s, 3H), 3.36-3.31 (dq, J = 6.8, 6.8 Hz, 1H) 2.71 (s, 3H), 2.41-2.25 (m, 7H), 2.01 (s, 3H), 1.80 (s, 3H) 1.24 (s, 3H), 1.16 (s, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 6H), 0.04 (s, 3H), 0.01 (s, 3H), -0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ218.0, 172.4, 164.3, 153.2, 142.5, 132.2, 122.2, 118.6, 118.9, 83.1, 80.2, 78.6, 75.9, 73.5, 53.7, 51.6, 46.3, 40.4, 35.7, 32.6, 29.7, 29.2, 26.1, 26.0, 25.8, 23.8, 21.7, 19.2, 18.9, 18.4, 18.2, 16.2, 15.7, 13.9, -3.3, -3.9, -4.4, -4.6, -4.7, -4.9; HRMS (CI) calcd. for $C_{46}H_{84}NO_6SSi_3$ ($M+H^+$) 862.5327, found 862.5325.



65

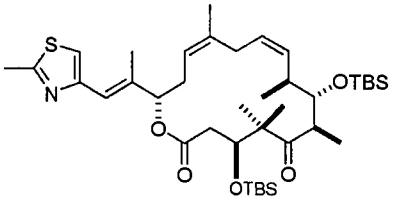
Carboxylic acid 65: To a stirred solution of **61** (51 mg, 59 μmol) in *i*-PrOH (1 mL) was added NaOH (11.5 μL, 62 μmol, 5.4M in H_2O), and the mixture was heated at 45 °C. After 16 h, the solution was concentrated, diluted with aqueous HCl (20 mL, 0.5M), and extracted with Et_2O (4 x 50 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo,* and the residue was purified by chromatography on silica gel, eluting with 5 - 20% EtOAc / hexanes, to give **65** (33 mg, 66%) as a colorless oil: IR (neat) 3500 - 2500, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.67 (s, 1H), 5.52 (t, J = 9.6 Hz, 1H), 5.3 - 5.4 (m, 1H), 5.23 (t, J = 7.4 Hz, 1H), 4.41 (dd, J = 3.3, 6.6 Hz, 1H), 3.75 - 3.85 (m, 1H), 2.9 - 3.1 (m, 2H), 2.71 (s, 3H), 2.5 - 2.8 (m, 2H), 2.1 - 2.6 (m, 4H), 1.9 - 2.1 (m, 1H), 1.93 (s, 3H), 1.71 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H), 9.94 (obscured d, 3H), 0.92 (s, 9H), 0.88 (s, 18H), 0.12 (s, 6H), 0.09 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H); HRMS (CI) calcd. for $C_{45}H_{84}NO_6SSi_3$ ($M+H^+$) 850.5327, found 850.5281.



66

Hydroxy acid 66: To a stirred solution of **65** (154 mg, 181 μmol) in THF (3.9 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (1.1 mL, 1.1 mmol, 1M in THF), and the solution was allowed to warm slowly to room temperature during 16 h. The mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl (50 mL), and extracted with EtOAc (4 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo,* and the residue was purified by chromatography on silica gel, eluting with 2 - 5% MeOH / CH_2Cl_2, to give **66** (118.5 mg, 89%) as a colorless foam: $[\alpha]_D^{23}$ -2.6 (c 3.50, $CHCl_3$); IR (neat) 3500 - 2500 , 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.70 (s, 1H), 5.56 (t, J = 10.0 Hz, 1H), 5.3 - 5.45 (m, 1H), 5.24 (t, J = 7.3 Hz, 1H), 4.35 - 4.45 (m, 1H), 4.16 (t, J = 6.2 Hz, 1H), 3.75 - 3.85 (m, 1H), 3.03 (m, 2H), 2.75 - 2.85 (m, 1H), 2.72 (s, 3H), 2.65 - 2.75 (m, 1H), 2.2 - 2.7 (m, 5H), 1.99 (s, 3H), 1.74 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.04 (d, J = 7.1 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.1, 176.0, 165.1, 152.4, 141.9, 137.5, 131.6, 127.8, 120.8, 118.8, 115.1, 77.2, 76.0, 73.5, 53.6, 46.3, 40.1, 38.0, 34.1, 30.8,

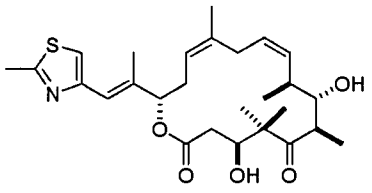
26.2, 26.0, 23.7, 23.5, 19.0, 18.9, 18.7, 18.5, 18.1, 15.0, 14.6, -3.6, -4.1, -4.2, -4.6; HRMS (CI) calcd. for $C_{39}H_{70}NO_6SSi_2$ ($M+H^+$) 736.4462, found 736.4451.



67

Lactone 67: To a stirred solution of **66** (57.2 mg, 78.0 μmol) in THF (1.3 mL) at 0 °C was added Et_3N (19 μL, 136 μmol) followed by 2,4,6-trichlorobenzoyl chloride (14 μL, 89.5 mmol). After 45 min, the mixture was diluted with THF (1 mL) and toluene (1.7 mL), and was added slowly *via* syringe pump to a stirring solution of DMAP (16.3 mg, 133 μmol) in toluene (18 mL) at 75 °C during of 3.5 h. After an additional 1 h, the solution was allowed to cool to room temperature and diluted with EtOAc. The solution was washed with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (4 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo,* and the residue was purified by chromatography on silica gel, eluting with 2 - 10% EtOAc / hexanes, to give **67** as a colorless oil (35.5 mg,

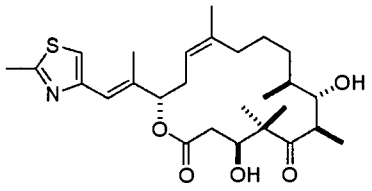
63%) contaminated with a small amount of an oligomer: IR (neat) 1738, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.50 (s, 1H), 5.65 (t, J = 10.0 Hz, 1H), 5.3 - 5.45 (m, 2H), 5.11 (t, J = 6.3 Hz, 1H), 4.45 (dd, J = 2.8, 8.0 Hz, 1H), 3.7 - 3.8 (m, 1H), 3.19 (dd, J = 9.5, 15.7 Hz, 1H), 3.0 - 3.1 (m, 1H), 2.71 (s, 3H), 2.2 - 2.7 (m, 6H), 2.09 (s, 3H), 1.74 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 1.07 (d, J = 7.1 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.0, 169.9, 164.9, 152.9, 137.8, 136.5, 130.8, 126.9, 121.1, 118.9, 116.6, 106.3, 78.1, 76.4, 73.1, 54.0, 47.4, 41.2, 39.0, 31.0, 26.4, 26.3, 26.1, 24.5, 21.3, 20.5, 19.7, 19.5, 18.9, 18.3, 15.2, 14.7, -3.4, -3.5, -4.6; HRMS (CI) calcd. for $C_{39}H_{68}NO_5SSi_2$ ($M+H^+$) 718.4357, found 718.4354.



68

***cis*-9,10-dehydroepothilone D (68):** To a stirred solution of the crude lactone **67** (16.5 mg, 23 μmol) in CH_2Cl_2 (110 μL) at 0 °C was added trifluoroacetic acid (100 μL). After 4.5 h, the mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica gel, eluting with 20 -

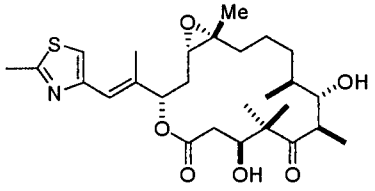
50% EtOAc / hexanes, to give **68** (9.3 mg, 83%) as a colorless oil: $[\alpha]_D^{23}$ -133.0 (c 1.30, $CHCl_3$); IR (neat) 3438, 1738, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.52 (s, 1H), 5.68 (dt, J = 7.3, 11.4 Hz, 1H), 5.57 (dd, J = 1.5, 10.2 Hz, 1H), 5.40 (t, J = 5.1 Hz, 1H), 5.15 (t, J = 7.1 Hz, 1H), 4.22 (dd, J = 2.5, 9.4 Hz, 1H), 3.7 - 3.8 (m, 1H), 3.1 - 3.2 (m, 1H), 3.04 (dd, J = 7.7, 15.3 Hz, 1H), 2.85 -2.95 (m, 1H), 2.70 (s, 3H), 2.4 - 2.7 (m, 6H), 2.06 (s, 3H), 1.72 (s, 3H), 1.27 (s, 3H), 1.1 - 1.2 (obscured d, 3H x 2), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.4, 170.7, 152.2, 138.1, 137.0, 132.3, 128.1, 119.0, 118.9, 115.7, 77.4, 74.1, 73.0, 52.7, 44.2, 39.1, 36.9, 31.4, 30.2, 29.7, 23.9, 21.8, 20.4, 19.0, 17.5, 16.0, 13.3; HRMS (CI) calcd. for $C_{27}H_{40}NO_5S$ ($M+H^+$) 490.2627, found 490.2627.



2

Epothilone D (2): To a stirred solution of **68** (6.6 mg, 13.5 μmol) in CH_2Cl_2 (2 mL) at reflux was added portionwise a large excess of dipotassium azodicarboxylate followed by acetic acid (2 equiv) until the reaction was complete by TLC (25 h). The precipitate of potassium acetate was removed periodically during the course of the reaction. The mixture was filtered through silica (Et_2O

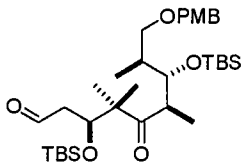
rinse), and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with EtOAc / hexanes / CH_2Cl_2 (1:4:5 - 1:1:2) , to give **2** (3.4 mg, 52 %) as a colorless oil: $[\alpha]_D^{23}$ -86.7 (c 0.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.58 (s, 1H), 5.22 (d, J = 8.8 Hz, 1H), 5.1 - 5.2 (m, 1H), 4.30 (d, J = 11.2 Hz, 1H), 3.7 - 3.8 (m, 1H), 3.4 - 3.55 (m, 1H), 3.15 (q, J = 4.8 Hz, 1H), 3.0 - 3.1 (m, 1H), 2.69 (s, 3H), 2.5 - 2.7 (m, 1H), 2.05 - 2.5 (m, 4H), 2.06 (s, 3H), 1.8 - 1.9 (m, 1H), 1.7 - 1.8 (m, 1H), 1.34 (s, 3H), 1.2 - 1.3 (m, 4H), 1.19 (d, J = 7.0 Hz, 3H), 1.07 (s, 3H), 1.01 (d, J = 6.9, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.8, 170.6, 165.2, 152.3, 139.4, 138.7, 121.1, 119.5, 115.9, 79.2, 74.4, 72.6, 53.7, 42.0, 39.9, 32.8, 32.0, 31.9, 25.6, 23.1, 19.3, 18.3, 16.1, 16.0, 13.6.



1

Epothilone B (1): To a stirred solution of **2** (1.50 mg, 3.05 μmol) in CH_2Cl_2 (400 μL) at -50 °C was added a solution of dimethyl dioxirane until all of the starting material had been consumed, as determined by TLC. The solution was concentrated *in vacuo* and the residue was purified by chromatography on

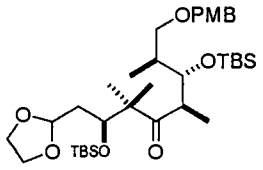
silica gel, eluting with 50 - 60% EtOAc / pentane, to give **1** (1.20 mg, 78 %) as a colorless oil: $[\alpha]_D^{23}$ –36.7 (c 0.12, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.59 (s, 1H), 5.42 (dd, J = 2.8, 7.9 Hz, 1H), 4.1 - 4.3 (m, 2H), 3.77 (bs, 1H), 3.2 - 3.35 (m, 1H), 2.81 (dd, J = 4.5, 7.6 Hz, 1H), 2.69 (s, 3H), 2.66 (bs, 1H), 2.4 - 2.55 (m, 1H), 2.36 (dd, J = 2.3, 13.6 Hz, 1H), 2.1 - 2.2 (m, 1H), 2.09 (s, 3H), 1.85 - 2.0 (m, 1H), 1.6- 1.7 (m, 1H), 1.35 - 1.55 (m, 4H), 1.37 (s, 3H), 1.28 (s, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.08 (s, 3H), 1.00 (d, J = 7.1 Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 220.6, 170.5, 165.1, 151.8, 137.5, 119.7, 116.1, 74.1, 72.9, 61.6, 61.3, 53.1, 42.9, 39.2, 36.4, 32.3, 32.1, 30.8, 29.7, 22.7, 22.3, 21.4, 19.6, 19.1, 17.0, 15.8, 13.6; HRMS (CI) calcd. for $C_{27}H_{42}NO_5S$ ($M+H^+$) 492.2784, found 492.2775.



70

Aldehyde 70:: To a stirred solution of **57** (722 mg, 1.19 mmol) in THF (9 mL) and H_2O (8.5 mL) was sequentially added OsO_4 (400 µL, 4% in H_2O) followed by $NaIO_4$ (1.065 g, 4.98 mmol). After 18 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL), and after a further 30 min, saturated aqueous NaCl (100 mL) was added. The mixture was extracted with Et_2O (4 x

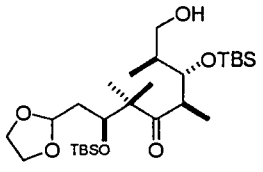
100 mL), and the dried ($MgSO_4$) extract was concentrated *in vacuo* to give aldehyde **70** as a colorless oil: $[\alpha]_D^{23}$ -13.0 (c 4.20, $CHCl_3$); IR (neat) 1725, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 1.2 Hz, 1H), 7.22 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 4.46 (t, J = 5.3 Hz, 1H), 4.39 (s, 2H), 3.82 (d, J = 7.9 Hz, 1H), 3.80 (s, 3H), 3.58 (dd, J = 6.0, 9.1 Hz, 1H), 3.27 (dq, J = 7.4, 7.4 Hz, 1H), 3.19 (dd, J = 6.9, 8.9 Hz, 1H) 2.3 - 2.5 (m, 2H), 1.6 - 1.8 (m, 1H), 1.14 (s, 3H), 1.06 (s, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 6H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.0, 201.5 159.3, 130.9, 129.5, 113.9, 76.8, 73.1, 71.7, 71.6, 55.4, 53.7, 49.7, 46.2, 38.8, 26.4, 26.1, 24.4, 18.7, 18.3, 17.0, 15.7, -3.4, -3.5, -3.9, -4.3; HRMS (CI) calcd. for $C_{33}H_{61}O_6Si_2$ ($M+H^+$) 609.4007, found 607.4005.



71

Acetal 71: To a stirred solution of aldehyde **70** (98 mg, 0.161 mmol) in benzene (10.0 mL) was added PPTS (2.0 mg, 0.008 mmol) and ethylene glycol (9.9 mL, 0.177 mmol). The reaction was refluxed for 18 hrs with azotropic removal of H_2O by use of a Dean-Stark trap. The reaction was then concetrated

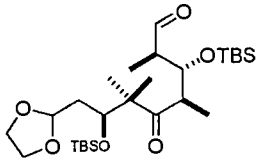
and purified by flash chromatography over silica gel (10% Et_2O / hexanes) to give acetal **71** (88 mg, 142 mmol) as a colorless oil. $[\alpha]^D_{24}$ – 12.8(c 1.65, $CHCl_3$); IR: (thin film) 2953, 2927, 2881, 2853, 1689, 1612, 1512, 1471, 1462, 1407, 1249, 1092, 774 cm^{-1};^1H NMR ($CDCl_3$, 300 MHz): δ 7.23 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.91 (dd, J = 2.9, 6.9 Hz, 1H) 4.38 (s, 2H), 4.13(dd, J = 2.0, 7.8 Hz, 1H), 3.98-3.80 (m, 5H), 3.80 (s, 3H) 3.68 (dd, J = 6.0, 9.1, 1H) 3.28 (qn, J = 7.0, 1H), 3.17(dd, J = 1.8, 7.4, 1H), 1.76-1.68 (m, 2H), 1.66-1.51 (m, 1H), 1.11 (s, 3H),1.03 (s, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.1 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 300MHz): δ 218.2, 159.0, 130.7, 129.3, 113.6, 102.5, 73.2, 72.8, 71.5, 64.6, 64.5, 60.3, 55.2 53.6, 46.0, 39.2, 38.6, 26.2, 26.1, 24.5, 18.5, 18.3 17.7, 16.8,15.4, -3.5, -3.7, -4.2; HRMS (CI) calcd. for $C_{27}H_{56}Si_2O_6$ $(M+H^+)$651.41010, found 65141124.



72

Alcohol 72: To a stirred solution of ether **71** (88 mg, 0.13 mmol) in EtOH (3.0 mL) was added palladium on carbon (45 mg, 10% Pd) followed by the introduction of an atmosphere of H_2. After 1.5 hrs. the reaction was filtered

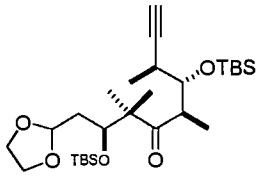
through celite (EtOH rinse), concentrated in vacuo , and purified over silica gel (10 – 30% Et_2O / hexanes) to give alcohol **72** (49 mg, 0.91 mmol, 70%) as a colorless oil. $[\alpha]^D_{24}$ –11.9 (c 2.40, $CHCl_3$); IR: (thin film) 3497, 2950, 2922, 2878, 1607, 1688, 1471, 1462, 1407, 1359, 1093, 774 cm^{-1};^1H NMR ($CDCl_3$, 300 MHz): δ 4.90 (dd, J = 2.9, 6.9 Hz, 1H) 4.15(dd, J = 2.0, 7.8 Hz, 1H) 3.98-3.79 (m, 5H), 3.69-3.66 (1H, m), 3.56-3.55 (m, 1H) 3.25 (qn, J = 7.0, 1H), 1.77-1.50 (m, 3H), 1.20 (s, 3H),1.10 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (CDCl3, 300MHz): δ 217.9, 102.5, 77.9, 64.7, 53.8, 46.6, 39.7, 39.3, 38.6, 26.9, 26.4, 25.8, 25.3, 24.9, 24.3, 18.3, 17.9, 16.1, 16.0, 15.5, 14.9, -2.7, -3.4, -3.5, -4.0, -4.1, -4.5. HRMS (CI) calcd. for $C_{27}H_{56}Si_2O_6$ Found.



73

Aldehyde 73: To a stirred solution of alcohol **72** (49 mg, 0.091 mmol) and powdered molecular sieves (0.25 g) in CH_2Cl_2 (2.5 mL) was sequentially added NMO (27.6 mg, 0.24 mmol) followed by TPAP (3.2 mg, 9.0 μmol). After 2 hrs, the reaction was filtered through silica gel (Et_2O rinse). The liquid was concentrated in vacuo to give aldehyde **73** (45 mg, 0.085 mmol, 94%) as a colorless oil. $[\alpha]_D^{24}$ -

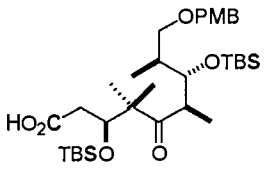
34.4 (c 2.05); IR: (thin film) 2954, 2929, 2884, 2856, 1724, 1690, 1472 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 9.73 (1H, d, J = 2.1 Hz), 4.88 (1H, dd, J = 3.0,7.3 Hz), 4.14-4.08 (m, 2H), 3.97-3.77 (m, 4H), 3.25 (1H, qn, J = 7.0 Hz), 2.30 (m, 1H), 1.73-1.70 (1H, m), 1.55-1.51 (1H, m), 1.20 (3H, s), 1.14 (3H, d, J = 7.1 Hz), 1.12 (3H, d, J = 6.9 Hz), 1.09 (3H, s), 0.89 (9H, s), 0.87 (9H, s), 0.11 (3H, s), 0.090 (3H, s), 0.085 (3H, s), 0.01 (3H, s);13C NMR (CDCl3, 75 MHz): δ 218.0, 204.4, 102.1, 76.5, 73.9, 64.4 53.8, 51.2, 46.8, 40.4, 29.9, 26.4, 24.0, 19.2, 18.6, 18.4, 15.9, 12.7, -3.4, -3.6, -4.3, -4.4; HRMS (CI) calcd. for $C_{26}H_{55}Si_2O_6$ 515.3225. Found 531.35352.



74

Alkyne 74: To a stirred solution of potassium t-butoxide (0.086 mL, 1.0 M THF soulution) in THF (0.25 mL) at –78 °C was added (diazomethyl)phosphonate (13 mg, 0.086 mmol) in THF (0.25 mL). After 5 min. a solution of aldehyde **73** (40 mg, 0.075 mmol) in THF (0.25 mL) was added dropwise. The reaction was stirred at –78 °C for 12 h, warmed to room temperature and quenched with sat. aqueous NH_4Cl. The aqueous layer was

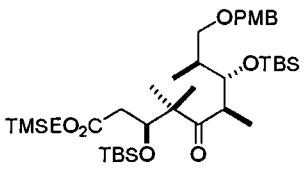
extracted with three 5 mL portions of Et_2O and the combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography (SiO_2, 5% Et_2O/hexane) to give 22 mg, 55% yield of **74** a colorless oil. $[\alpha]_D^{24}$ – 35.3(c 2.0, $CHCl_3$); IR: (thin film) 3310 2953, 2927, 2884, 2855,1692,1472,1254,1089,988, 837, 775 cm^{-1};1H NMR (CDCl3, 300 MHz): δ 4.91 (m, J = 3.1, 7.5 Hz, 1H) 4.18(dd, J = 2.1, 8.3 Hz, 1H) 3.98-3.77 (m, 5H) 3.33 (qn, J = 7.5, 1H) 2.36-2.33 (m, 1H), 2.06 (s, 1H), 1.74-1.70 (m, 2H), 1.56-1.53 (m, 1H) 1.24 (s, 3H)1.18 (d, J = 6.9 Hz, 3H) 1.17 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H), 0.93 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H). 13C NMR ($CDCl_3$, 300MHz): δ 218.6, 102.5, 85.6, 75.7, 72.7, 70.7, 64.6, 64.5, 53.9, 46.5, 39.2, 32.1, 26.1, 24.4, 18.8, 18.9, 18.32, 17.6, 15.8, -3.2, -3.7, -3.8, -4.2; HRMS (CI) calcd. for $C_{28}H_{54}Si_2O_5$ ($M+H^+$) 527.35698, found 527.35881.



75

Carboxylic acid 75: To a stirred solution of the crude aldehyde **70** prepared above in *t*-BuOH (16 mL) and H_2O (15 mL) was added 2-methyl-2-butene (3 mL) followed sequentially by NaH_2PO_4 (1.06 g, 11.6 mmol) and $NaClO_2$ (490 mg, 5.4 mmol). After 1 h, the reaction was quenched with saturated

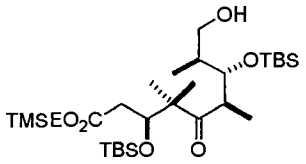
aqueous NaCl (75 mL), and the mixture was extracted with Et_2O (4 x 100 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* to give acid **75** as a colorless oil: $[\alpha]_D^{23}$ -26.8 (c 4.20, $CHCl_3$); IR (neat) 2400 - 3400, 1722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ7.23 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 4.40 (s, 2H), 4.3 - 4.4 (m, 1H), 3.82 (d, J = 7.9 Hz, 1H), 3.80 (s, 3H), 3.58 (dd, J = 5.8, 9.1 Hz, 1H), 3.32 (dq, J = 7.2, 7.2 Hz, 1H), 3.18 (dd, J = 7.2, 8.9 Hz, 1H) 2.46 (dd, J = 2.9, 16.4 Hz, 1H), 2.28 (dd, J = 6.8, 16.4 Hz, 1H), 1.7 - 1.85 (m, 1H), 1.15 (s, 3H), 1.07 (s, 3H), 1.02 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.7, 178.0, 159.3, 130.9, 129.5, 113.9, 73.8, 73.1, 71.7, 55.5, 53.7, 46.3, 40.4, 38.9, 26.4, 26.4, 26.2, 24.0, 18.7, 18.4, 17.0, 15.8, -3.3, -3.5, -4.1, -4.4; HRMS (CI) calcd. for $C_{33}H_{61}O_7Si_2$ 625.3966; found 625.3957.



76

Ester 76: To a stirred solution of **75** (195 mg, 0.32 mmol) in THF (1.5 mL) was added 2-(trimethylsilyl)ethanol (69 µL, 0.48 mmol) and triphenylphosphine (56.8 mg, 0.80 mmol). The solution was cooled to 0 °C and diethyl azodicarboxylate was added. After 1.5 h, the reaction was quenched with

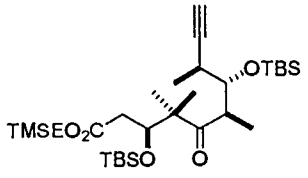
saturated aqueous NH_4Cl, and the solution was extracted with Et_2O. The extract was concentrated *in vacuo,* and the residue was purified by chromatography on silica gel, eluting with 5 - 10% Et_2O / petroleum ether, to give **76** (175 mg, 75%) as a colorless oil: $[\alpha]_D^{23}$ - 27.0 (*c* 1.03, $CHCl_3$; IR (neat) 1741, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 d, J = 8.4 Hz, 2H, 6.85 d, J = 8.4 Hz, 2H), 4.39 (s, 2H), 4.3 - 4.4 (m, 1H), 3.83 (d, J = 7.8 Hz, 1H), 3.80 (s, 3H), 3.58 (dd, J = 5.7, 9.1 Hz, 1H), 3.31 (dq, J = 7.2, 7.2 Hz, 1H), 3.18 (dd, J = 7.3, 9.1 Hz, 1H), 2.46 (dd, J = 3.1, 16.1 Hz, 1H), 2.26 (dd, J = 7.0, 16.1 Hz, 1H), 1.7 - 1.85 (m, 1H), 1.14 (s, 3H), 1.06 (s, 3H), 1.01 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H,), 0.87 (s, 9H), 0.08 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 218.5, 172.7, 159.3, 131.0, 129.5, 113.9, 74.1, 73.1, 71.8, 55.5, 53.6, 51.8, 46.3, 40.4, 38.9, 29.9, 26.5, 26.2, 24.0, 18.8, 18.7, 18.4, 17.0, 15.7, -3.3, -3.5, -4.3, -4.4; HRMS (CI) calcd. for $C_{38}H_{73}O_7Si$ ($M+H^+$) 725.4664, found 725.4666.



77

Alcohol 77: To a stirred solution of **76** (150 mg, 0.20 mmol) in EtOH (4.0 mL) was added palladium-on-carbon (55 mg, 10% Pd), and the mixture was stirred under an atmosphere of H_2. After 1 h, the H_2 atmosphere was replaced

by Ar, and the mixture was filtered through Celite (EtOH rinse). The fitrate was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with 10 - 30% Et_2O / petroleum ether, to give **77** (108 mg, 89%) as a colorless oil: $[\alpha]_D^{23}$ –8.47 (*c* 1.18, $CHCl_3$); IR (neat) 3538, 1743, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (dd, J = 2.9, 6.9 Hz, 1H), 4.17-4.11 (m, 2H) 3.93 (dd, J = 2.0, 7.8 Hz, 1H), 3.6 - 3.7 (m, 1H), 3.5 - 3.6 (m, 1H), 3.31 (dq, J = 7.5, 7.5 Hz, 1H), 2.43 (dd, J = 2.7, 16.3 Hz, 1H), 2.26 (1H, dd, J = 6.9, 16.3 Hz), 1.55 - 1.65 (1H, m), 1.22 (3H, s), 1.13 (3H, s), 1.09 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.85 (m, 2H), 0.02 (s, 9H) 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 218.4, 172.8, 78.2, 73.6, 64.9, 60.3, 53.9, 51.9, 47.0, 40.3, 39.8, 29.9, 26.4, 26.2, 24.1, 19.1, 18.6, 18.4, 17.2 16.1, -3.0, -3.4, -3.6, -4.3, -4.4.

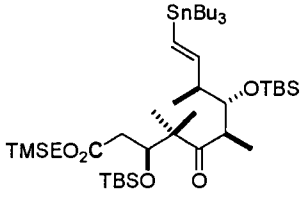


78

Alkyne 78: To a stirred mixture of **77** (200 mg, 0.33 mmol) and powdered molecular sieves (300 mg) in CH_2Cl_2 (6.0 mL) was added sequentially N-methylmorpholine-N-oxide (97 mg, 0.83 mmol) followed by tetra-*n*-propylammonium perruthenate (11.6 mg, 33 μmol). After 1.5 h, the mixture was

filtered through silica (Et_2O rinse), and the filtrate was concentrated *in vacuo* to give the crude aldehyde as a colorless oil.

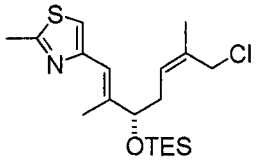
To a stirred solution of the crude aldehyde and K_2CO_3 (91 mg, 0.66 mmol) in MeOH (5.0 mL) was added dimethyl 1-diazo-2-oxopropylphosphonate (74 mg, 0.46 mmol). The solution was stirred for 4 h at room temperature, diluted with Et_2O (30 mL), washed with aqueous $NaHCO_3$ (5%), and extracted with Et_2O (3 x 30 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel, eluting with 2% Et_2O / hexanes, to give **78** (155 mg, 78%) as a colorless oil: $[\alpha]_D^{23}$ –25.1 (c 2.50, $CHCl_3$); IR (neat) 2946, 2928, 2848, 1734, 1690, 1468; ^1H NMR (300 MHz, $CDCl_3$) δ 4.45 (dd, J=3.1, 7.5 Hz, 1H), 4.11-4.16 (m, 2H), 3.76 (dd, J = 2.1, 6.4 Hz, 1H), 3.35 (dq, J = 7.3, 7.3 Hz, 1H), 2.22-2.24 (m, 3H), 2.06 (s, 1H),1.25 (s, 3H), 1.18 (d, J = 7.5 Hz, 3H), 1.17 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.95 (obscured m, 2H) 0.92 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.03 (s, 9H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.6, 172.1, 85.6, 75.7, 73.3, 70.8, 62.7, 53.8, 46.5, 40.6, 32.2, 26.1, 26.0, 18.7, 18.5, 18.2, 17.2, 15.9, -1.6, -3.3, -3.9, -4.4, -4.7; HRMS (FAB) calcd. for $C_{51}H_{63}O_5Si_3$ ($M+H^+$) 599.3983, found 599.3982.



79

Stannane 79: To a stirred solution of **78** (60.0 mg, 0.10 mmol) and bis(triphenylphosphine)palladium dichloride (1.4 mg, (0.002 mmol) in THF (0.5 mL) at room temperature was added slowly tri-*n*-butyltin hydride (32.3 μL, 0.12 mmol). After 10 min, the solution was concentrated *in vacuo,* and the residue was purified by chromatography on silica gel, eluting with 5% Et_2O / hexanes, to give **79** (79 mg, 89%) as a colorless oil: $[\alpha]_D^{23}$ –9.6 (c 1.35, $CHCl_3$); IR (neat) 2955, 2928, 2856, 1736, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (dd, J=7.5, 19.3 Hz, 1H), 5.89 (d, J=19.3 Hz, 1H), 4.43 (dd, J=3.2, 6.8 Hz, 1H), 4.15 (m, 2H), 3.85 (dd, J=1.5, 7.9 Hz, 1H), 3.07 (dq, J=7.1, 7.1 Hz, 1H), 2.40 (dd, J=3.2, 16.2 Hz, 1H), 2.23 (dd, J=6.8, 16.2 Hz, 1H), 1.45-1.53 (m, 6H), 1.23-1.37 (m, 12H), 1.19 (s, 3H), 1.09 (s, 3H), 1.03 (d, J=7.0, 3H), 1.03 (d, J=6.9, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.85-0.93 (m, 12H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.04 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.8, 172.6, 150.7,

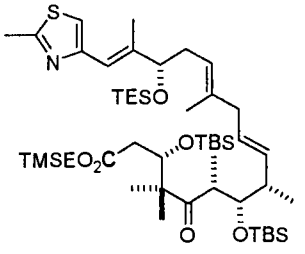
129.1, 74.0, 63.1, 53.9, 47.5, 47.1, 41.0, 29.6, 27.7, 26.6, 26.4, 24.5, 19.2, 18.9, 17.7, 15.9, 14.1, 9.9, -1.1, -2.9, -3.4, -4.0, -4.3



80

Chloride 80: To a stirred solution of **42** (35 mg, 95 μmol) in CH_2Cl_2 (0.6 mL) at 0 °C was added Et_3N (23 μL, 161 μmol) followed by methanesulfonic anhydride (21 mg, 119 □mol). After 10 min, acetone (0.6 mL) was added followed by LiCl (40 mg, 950 μmol). After 4 h at room temperature, the solution was concentrated *in vacuo* to remove acetone, diluted with saturated aqueous NH_4Cl, and extracted with Et_2O. The dried ($MgSO_4$) extract was concentrated *in vacuo* and the residue was purified by chromatography on silica gel, eluting with 10 - 20% Et_2O / petroleum ether, to give **80** (36 mg, 97%) as a colorless oil: $[\alpha]_D^{23}$ +28.1 (c 1.11, $CHCl_3$); IR (neat) 2954, 2875, 1453,1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.49 (s, 1H), 5.41 (dt, J=1.3, 7.5 Hz, 1H), 4.15 (m, 1H), 4.14 (d, J=10.8, 1H), 4.00 (d, J=10.8, 1H), 2.71 (s, 3H), 2.35 (m, 2H), 2.01 (d, J=1.2, 3H), 1.75 (d, J=1.2, 3H), 0.93 (t, J=7.69, 9H), 0.58 (q, J=7.39, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 153.5, 142.3, 133.4, 127.8, 119.4,

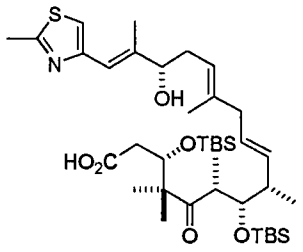
115.6, 78.4, 44.2, 35.8, 22.1, 19.6, 14.4, 7.2, 5.2; HRMS (FAB) calcd. for $C_{19}H_{33}ClNOSSi$ ($M+H^+$) 386.1741, found 386.1737.



81

Triene 81: A solution of **80** (44 mg, 114 μmol), tris(dibenzylideneactone)dipalladium-chloroform (7.1 mg, 6.8 μmol) and triphenylarsine (8.4 mg, 27 μmol) in THF (0.4 mL) was stirred at room temperature for 10 min. A solution of **62** (107 mg, 120 μmol) in THF (1.0 mL) was added, and the flask was briefly opened to the atmosphere, resealed, and heated to 65 °C. After 18 h, the mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica gel, eluting with 5% Et_2O / hexanes, to give **81** (82 mg, 76%) as a colorless oil: $[\alpha]_D^{23}$ –6.2 (c 1.23, $CHCl_3$); IR (neat) 2955, 2856, 1753, 1694, 1471 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91(s, 1H), 6.47 (s, 1H), 5.52 (dd, J=7.9, 15.6 Hz, 1H), 5.32 (dt, J=6.7, 8.5 Hz, 1H), 5.17 (t, J=7.3, 1H), 4.40 (dd, J=3.1, 6.7 Hz, 1H), 4.15-4.18 (m, 2H), 3.82 (dd, J=1.8, 7.2, 1H), 3.02 (dq, J=7.1, 7.1 Hz, 1H), 2.72 (s, 3H), 2.66 (d, J=6.6 Hz, 2H), 2.20-2.44 (m, 3H), 2.00 (s, 3H), 1.26 (s, 3H), 1.07 (s, 3H), 1.01 (d, J=7.0 Hz, 3H), 1.00 (d,

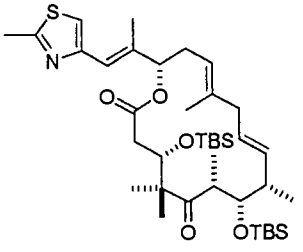
J=6.0 Hz, 3H), 0.93 (t, J=7.8 Hz, 9H), 0.91 (s, 9H), 0.87 (s, 9H), 0.58 (q, J=7.8 Hz, 6H), 0.10 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.03 (s, 9H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.5, 172.6, 164.7, 153.6, 143.0, 136.0, 133.1, 129.7, 121.9, 119.0, 115.3, 79.0, 76.8, 63.1, 53.8, 46.6, 43.8, 42.8, 40.9, 26.6, 26.4, 19.6, 18.9, 18.6, 17.7, 16.7, 14.4, 7.3, 5.5, -1.1, -3.1, -3.4, -4.0, -4.2; HRMS (FAB) calcd. for $C_{50}H_{96}NO_6SSi_4$ ($M+H^+$) 950.6036, found 950.6065.



82

Hydroxy acid 82: To a stirred solution of **81** (20 mg, 21 μmol) and powdered molecular sieves (100 mg) in THF (8.0 mL) at 0 °C was added tetra-*n*-butylammonium fluoride (16.5 mg, 63 μmol). After 6 h, the mixture was filtered through glass wool, and aqueous citric acid (pH 5, 8 mL) was added to the filtrate, which was extracted with Et_2O. The dried ($MgSO_4$) extract was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with 4% MeOH / CH_2Cl_2, to give **82** (12.8 mg, 83%) as a colorless oil: $[\alpha]_D^{23}$ –22.4 (c 2.15, $CHCl_3$); IR (neat) 3252, 2956, 2929, 2856,

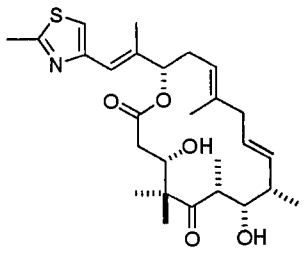
1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.58, (s, 1H), 5.54 (dd, J=7.5, 15.2 Hz, 1H), 5.38 (dt, J=6.7, 15.2 Hz, 1H), 5.20 (t, J=7.8 Hz, 1H), 4.40 (dd, J=3.2, 6.4 Hz, 1H), 4.16-4.24 (m, 1H), 3.83-3.86 (m, 1H), 3.02-3.09 (m, 1H), 2.72 (s, 3H), 2.69-2.72 (m, 2H), 2.28-2.55 (m, 5H), 1.98-2.08 (m, 2H), 2.03 (s, 3H), 1.63 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H), 1.04 (d, J=6.9 Hz, 3H), 0.97 (d, J=6.9 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.8, 175.9, 165.4, 153.0, 142.1, 138.2, 133.3, 129.5, 120.6, 119.4, 115.7, 76.9, 76.7, 73.7, 54.0, 46.8, 43.6, 42.8, 40.4, 34.6, 30.1, 26.6, 26.4, 24.2, 20.1, 19.3, 18.9, 18.6, 16.9, 14.7, -3.1, -3.5, -3.7, -4.2; HRMS (FAB) calcd. for $C_{39}H_{70}NO_6SSi_2$ ($M+H^+$) 736.4462, found 736.4466.



83

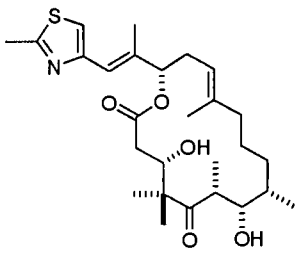
Lactone 83: To a stirred solution of **82** (22.0 mg, 30.0 μmol) in THF (0.5 mL) at 0 °C was added Et_3N (7.6 μL, 54 μmol) followed by 2,4,6-trichlorobenzoyl chloride (5.6 μL, 36 μmol). After 45 min, the mixture was diluted with THF (0.4 mL) and toluene (0.7 mL), and was added *via* syringe pump to a stirred solution

of DMAP (6.5 mg, 53 μmol) in toluene (7.2 mL) at 75 °C during 3.5 h. After an additional 1 h, the solution was allowed to cool to room temperature, diluted with EtOAc, washed with saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (4 x 40 mL). The dried ($MgSO_4$) extract was concentrated *in vacuo* and the residue was purified by chromatography on silica gel, eluting with 5% EtOAc / hexanes, to give **83** (19.4 mg, 71%) as a colorless oil: $[\alpha]_D^{23}$ –2.12 (c 1.13, $CHCl_3$); IR (neat) 2929, 2856, 1735, 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 3H), 6.54 (s, 3H), 5.44-5.46 (m, 2H), 5.28 (m, 1H), 5.22 (dd, J=3.3, 9.7, 1H), 4.63 (dd, J=3.2, 8.7, 1H), 3.90 (m, 1H), 3.16 (dq, J=6.8, 6.8 Hz, 1H), 2.71 (s, 3H), 2.20-2.71 (m, 6H), 2.14 (s, 3H), 1.68 (s, 3H), 1.10 (d, J=6.8 Hz, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.04 (d, J=7.0, 1H), 0.93 (s, 9H), 0.85 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 170.7, 165.1, 153.1, 138.7, 137.8, 133.9, 128.3, 120.3, 119.8, 116.8, 80.8, 77.7, 73.3, 55.1, 44.1, 43.1, 42.3, 42.0, 32.8, 26.6, 26.4, 21.2, 19.7, 19.1, 18.9, 18.2, 18.0, 17.2, 15.2, -2.5, -3.4, -3.8, -3.8; HRMS (FAB) calcd. for $C_{39}H_{68}NO_5SSi_2$ ($M+H^+$) 718.4357, found 718.4345.



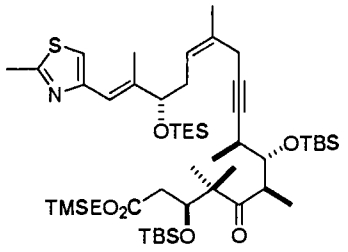
84

***trans*-9,10-Dehydro-trans-12,13,-epothilone D 84:** To a stirred solution of **83** (14.5 mg, 20 μmol) in CH_2Cl_2 (125 μL) at 0 °C was added trifluoroacetic acid (112 μL). After 8 h, the mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel, eluting with 20 - 50% EtOAc / hexanes, to give **84** (9.3 mg, 19 μmol, 95%) as a colorless waxy solid: $[\alpha]_D^{23}$ – 35.4 (c 0.50, $CHCl_3$); IR (neat) 2971, 2927, 1729, 1691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ6.98 (s, 1H), 6.55 (s, 1H), 5.53-5.48 (m, 2H), 5.38 (dd, J=2.8, 9.4 Hz, 1H), 5.23 (m, 1H), 4.23 (dd, J=4.3, 8.2 Hz, 1H), 3.71 (m, 1H), 3.27 (dq, J=5.8, 6.7 Hz, 1H), 2.27-2.77 (m, 6H), 2.72 (s, 3H), 2.11 (s, 3H), 1.69 (s, 3H), 1.26 (s, 3H), 1.17 (d, J=6.8 Hz, 3H), 1.10 (d, J=7.0 Hz, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.7, 171.0, 165.2, 152.7, 138.4, 137.8, 132.8, 129.6, 120.4, 120.2, 116.6, 79.2, 77.0, 76.4, 74.6, 72.3, 53.3, 44.7, 42.9, 40.3, 39.5, 32.6, 21.6, 20.0, 19.6, 17.8, 17.1, 15.9, 15.2; HRMS (FAB) calcd. for $C_{27}H_{40}NO_3S$ ($M+H^+$) 490.2627, found 490.2634.



85

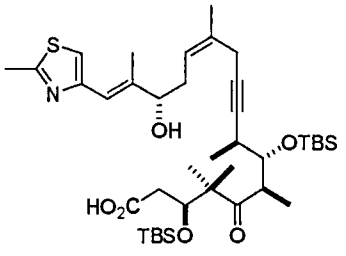
12, 13- trans-Epothilone D 85: To a stirred solution of **84** (12 mg, 25 μmol) in CH_2Cl_2 (0.5 mL) was added portionwise a large excess of dipotassium azodicarboxylate followed by acetic acid (0.5 equiv) until the reaction was complete by TLC (3 h). The mixture was filtered through silica (Et_2O rinse), and the filtrate was concentrated *in vacuo.* The residue was purified by chromatography on silica gel, eluting with 3% MeOH in CH_2Cl_2 , to give **12, 13-trans-Epothilone (85,** 2 mg, 17 %) as a colorless oil. See Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Komenecka, T.; Sorensen, E. J.; Danishefsky, S. J. J. Am. Chem. Soc. 1997, 119, 10073.



86

Enyne 86: To a stirred solution of **78** (38.0 mg, 0.063 mmol) in Et_2O (1.0 mL) and DMF (0.2 mL) at room temperature was added Et_3N (8.8 μL, 0.063 mmol) and CuI (12.0 mg, 0.063 mmol). After the mixture became clear (approx 5 min), a solution of **80** (12.2 mg, 0.315 mmol) in Et_2O (0.5 mL) was added. The solution was stirred for 18 h, quenched with saturated aqueous $Na_2S_2O_3$ (5 mL), and extracted with Et_2O (3 x 2 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo, and the residue was purified by chromatography on silica gel, eluting with 50-60% CH_2Cl_2/hexanes to give **86** (17.4 mg, 58%) as a colorless oil: $[\alpha]D^{23}$ –12.1 (c 1.74, $CHCl_3$); IR (neat) 1737, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.91(s, 1H), 6.47 (s, 1H), 5.37 (t, J = 6.7 Hz, 1H), 4.44 (dd, J = 3.2, 6.64 Hz, 1H), 4.20-4.09 (m, 3H), 3.74 (dq, J = 2.1, 11.5 Hz, 1H), 3.34 (dddd, J = 2.7, 2.7, 7.6, 7.6 Hz, 1H), 2.71 (s, 3H), 2.41-2.25 (m, 5H), 2.02 (s, 3H), 1.68 (s, 3H) 1.25 (s, 3H), 1.16 (s, 3H), 1.13 (d, J = 7.1 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.98 (obscured m, 2H), 0.94 (t, J = 8.1, 9H) 0.92 (s, 9H), 0.88 (s, 9H), 0.59 (q, J = 7.9, 9H), 0.10 (s, 3H), 0.07 (s, 6H), 0.04 (s, 9H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 219.2, 172.6, 164.7, 153.6, 142.9, 132.8, 122.4, 119.1, 115.4, 83.5, 80.6, 78.8, 76.4, 73.9, 63.9, 54.1, 41.1, 36.0, 33.0, 30.1, 26.4,

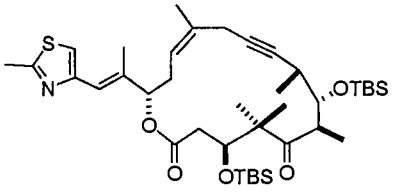
24.1, 19.6, 19.5, 19.4, 19.1, 18.9, 18.7, 18.6, 17.7, 16.1, 14.4, 7.3, 5.22, -1.1, - - 2.9, -3.5, -4.0, -4.3; HRMS (FAB) calcd. for $C_{50}H_{94}NO_6SSi_4$ ($M+H^+$) 948.58790, found 948.59258.



87

Hydroxy acid 87: To a stirred solution of **86** (8.0 mg, 8.4 μmol) and powdered molecular sieves (100 mg) in THF (1.5 mL) at 0 °C was added tetra-n-butylammonium fluoride (6.0 mg, 25 μmol). After 1 h, the mixture was filtered through glass wool, and aqueous citric acid (pH 5, 3.0 mL) was added to the filtrate, which was extracted with Et_2O. The dried ($MgSO_4$) extract was concentrated in vacuo and the residue was purified by flash chromatography on silica gel, eluting with 4% MeOH / CH_2Cl_2, to give **87** (8.2 mg, quant.) as a colorless oil: $[\alpha]D^{23}$ –0.17 (c 0.82, $CHCl_3$); IR (neat) 3338, 2954, 2929, 2856, 1713 cm^{-1}; ^1H NMR (300 MHz, 3) δ 6.96 (s, 1H), 6.58, (s, 1H), 5.50 (t, J = 6.7 Hz, 1H), 4.46 (dd, J = 2.1, 4.7 Hz, 1H), 4.20 (t, J = 4.7 H), 3.80 (dd, J = 1.1, 5.6 Hz, 1H), 3.34 (dddd, J = 5.5, 5.5, 5.5, 10.9 Hz, 1H), 2.9 (s, 1H), 2.73 (s, 3H), 2.58-2.25 (m, 5H), 2.05 (s, 3H), 1.72 (s, 3H) 1.24 (s, 3H), 1.20 (s, 3H), 1.15 (d, J

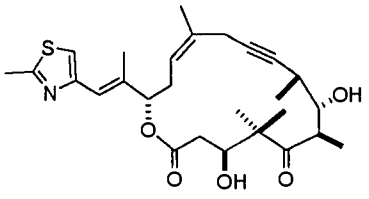
= 5.4 Hz, 3H), 1.10 (d, J = 5.2 Hz, 3H), 0.93 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.1, 175.4, 165.4, 153.0, 142.2, 134.6, 121.2, 119.3, 115.8, 84.1, 80.4, 76.4, 73.6, 54.4, 46.7, 40.4, 34.7, 33.0, 30.1, 29.6, 26.5, 26.4, 23.9, 19.2, 19.2, 18.9, 18.6, 16.9 16.4, 14.9, -2.94, -3.5, -3.6, -4.2; HRMS (FAB) calcd. for $C_{39}H_{68}NO_6SSi_2$ (M+H+) 734.43082, found 734.42877.



88

Lactone 88: To a stirred solution of **87** (8.8 mg, 12.0 μmol) in THF (0.2 mL) at 0 °C was added Et_3N (2.9 μL, 21 μmol) followed by 2,4,6-trichlorobenzoyl chloride (2.2 μL, 14 μmol). After 45 min, the mixture was diluted with THF (0.16 mL) and toluene (0.26 mL), and was added via syringe pump to a stirred solution of DMAP (2.4 mg, 20 μmol) in toluene (2.8 mL) at 75 °C during 3.5 h. After an additional 1 h, the solution was allowed to cool to room temperature, diluted with EtOAc, washed with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (4 x 20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and the residue was purified by chromatography on silica gel, eluting with 5% EtOAc / hexanes, to give **88** (4.1 mg, 47%) as a colorless oil: $[\alpha]_D^{23}$ 11.9 (c 0.41, $CHCl_3$);

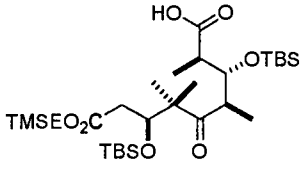
IR (neat) 2925, 2854, 1739, 1702, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 3H), 6.55 (s, 3H), 5.70 (t, J = 6.2, 1H), 5.33 (dd, J = 2.6, 11.3 1H), 4.64 (dd, J = 2.5, 8.2, 1H), 3.94 (dd, J = 2.5, 8.1 1H), 3.26 (dq, J = 7.0, 14.9 Hz, 1H), 2.71 (s, 3H), 2.70-2.35 (m, 5H), 2.15 (s, 3H), 1.66 (s, 3H), 1.16 (d, J = 7.1 Hz, 3H), 1.14 (s, 3H), 1.14 (s, 3H), 1.13 (obscured d, 1H), 0.91 (s, 9H), 0.86 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.7, 170.9, 165.1, 153.1, 139.0, 137.8, 132.9, 121.5, 120.1, 116.7, 85.5, 80.3, 79.8, 77.6, 76.4, 73.3, 55.2, 44.4, 42.5, 33.1, 32.5, 30.1, 29.0, 26.4, 26.4, 19.8, 19.7, 18.7, 18.5, 18.0, 17.4, 15.2, -2.9, -3.3, -3.8, -4.1; HRMS (FAB) calcd. for $C_{39}H_{66}NO_5SSi_2$ (M+H+) 716.42003, found 716.42093.



89

9,10-Didehydroepothilone D 89: To a stirred solution of **88** (4.1 mg, 5.7 μmol) in CH_2Cl_2 (200 μL) at 0 °C was added trifluoroacetic acid (100 μL). After 10 h, the mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel, eluting with 20 - 50% EtOAc / hexanes, to give **89** (2.4 mg, 19 μmol, 86%) as a colorless waxy solid: $[\alpha]D^{23}$ –37.9 (c 0.24, $CHCl_3$);

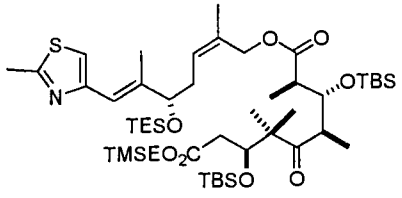
IR (neat) 3480, 2925, 1731, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.56 (s, 1H), 5.49 (t, J = 7.9, 1H), 5.38 (dd, J = 3.1, 9.9, 1H), 4.43 (dd, J = 5.6, 5.6, 1H), 3.60 (dd, J = 8.2, 8.2, 1H), 3.26 (dddd, J = 6.7, 6.7, 6.8, 15.5 Hz, 1H), 2.71 (s, 3H), 2.65-2.35 (m, 5H), 2.11 (s, 3H), 1.74 (s, 3H), 1.27 (d, J = 6.9, 3H), 1.25 (d, J = 7.1, 3H) 1.21, (s, 3H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.5, 171.1, 165.3, 152.6, 137.8, 134.5, 121.3, 120.4, 116.8, 82.7, 82.3, 79.2, 77.6, 76.6, 72.1, 53.5, 47.4, 39.8, 32.7, 31.9, 29.5, 22.2, 19.6, 19.4, 18.9, 17.0, 16.8, 15.8; HRMS (FAB) calcd. for $C_{27}H_{38}NO_5S$ (M+H+) 488.24676, found 488.24707.



91

Carboxylic acid 91: To a stirred solution of the crude aldehyde derived from **77** in t-BuOH (0.88 mL) and H_2O (0.83 mL) was added 2-methyl-2-butene (0.16mL) followed sequentially by NaH_2PO_4 (55.7 mg, 0.46 mmol) and $NaClO_2$ (27.1 mg, 0.30 mmol). After 1 h, the reaction was quenched with saturated aqueous NaCl (1.5 mL), and the mixture was extracted with Et_2O (4 x 5 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and the residue was purified by chromatography on silica gel, eluting with 20% EtOAc in hexanes to give **91**

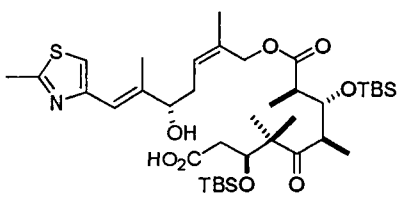
(38mg 0.061 mmol, 93%) as a colorless oil: $[\alpha]D^{23}$ -26.8 (c 1.20, $CHCl_3$); IR (neat) 2400 - 3400, 1735, 1722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (dd, J = 3.6, 6.9 Hz, 1H), 4.15 (m, 2H), 4.03 (dd, J = 2.2, 7.9 HZ, 1H), 3.36 (dq, J = 7.3, 7.3 Hz, 1H), 2.45 (td, J = 2.2, 7.4 Hz, 1H), 2.37 (d, J = 3.4 Hz, 1H), 2.26 (dd, J = 7.0, 16.1 Hz, 1H), 1.23 (d, J = 7.1 Hz, 3H) 1.22 (s, 3H), 1.14 (s, 3H), 1.11 (d, J = 6.9 Hz, 3H) 0.98 (m, 3H), 0.93 (s, 9H), 0.87 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.04 (s, 9H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.2, 177.4, 172.7, 76.6, 73.9, 63.2, 54.2, 46.8, 45.2, 40.9, 30.1, 26.4, 26.4, 24.1, 19.3, 18.7, 18.6, 17.6, 15.9, 15.6, -1.1, -3.2, -3.5, -4.0, -4.2; HRMS (CI) calcd. for C30H63O7Si3 619.38750; found 619.38817.



92

Diester 92: To a stirred solution of **91** (30.0 mg, 0.048 mmol) in THF (0.25 mL) was added 31 (20.6 mg, 0.073 mmol) and triphenylphosphine (31.4 mg, 0.12 mmol). The solution was cooled to 0 °C and diethyl azodicarboxylate (0.017mL, 0.11mmol) was added. After 4 h, the reaction was quenched with saturated aqueous NH_4Cl, and the solution was extracted with Et_2O. The extract was concentrated in vacuo, and the residue was purified by chromatography on silica

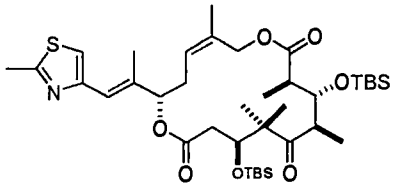
gel, eluting with 10% Et_2O / petroleum ether, to give ester **92** (30 mg, 65%) as a colorless oil: $[\alpha]D^{23}$ -20.7 (c 1.50, $CHCl_3$); IR (neat) 2954, 1735, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.46 (s, 1H), 5.42 (t, J = 7.3 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.41(dd, J = 3.0, 6.6 Hz, 1H) 4.13 (m, 3H), 3.47 (dq, J = 7.1, 7.1 Hz, 1H), 2.71 (s, 3H), 2.47-2.13 (m, 5H) 1.99 (s, 3H), 1.75 (s, 3H), 1.24 (s, 3H), 1.15 (d, J = 7.1 Hz, 3H), 1.12 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.98 (m, 3H), 0.92 (t, J = 7.7, 9H), 0.85 (s, 18H), 0.57 (q, J = 7.9 Hz, 6H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 9H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.2, 173.7, 172.6, 164.9, 153.2, 142.6, 131.9, 127.2, 119.1, 115.5, 78.5, 76.3, 74.2, 63.7, 63.1, 53.9, 45.6, 40.9, 35.5, 26.4, 24.2, 22.1, 17.7, 15.5, 15.1, 14.4, 7.2, 5.2, -1.1, -3.5, -4.0, -4.2;HRMS (CI) calcd. for $C_{49}H_{94}NO_8SSi_4$ 968.57773; found 968.57748.



93

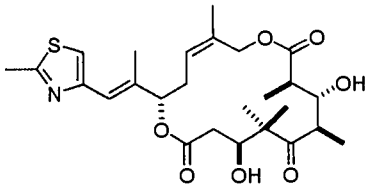
Hydroxy acid 93: To a stirred solution of **92** (30 mg, 31 μmol) and powdered molecular sieves (100 mg) in THF (5.0 mL) at 0 °C was added tetra-n-butylammonium fluoride (24.0 mg, 96 μmol). After 2 h, the mixture was filtered through glass wool, and aqueous citric acid (pH 5, 5 mL) was added to the

filtrate, which was extracted with Et_2O. The dried ($MgSO_4$) extract was concentrated in vacuo and the residue was purified by flash chromatography on silica gel, eluting with 3% MeOH / CH_2Cl_2, to give **93** (15.0 mg, 66%) as a colorless oil: $[\alpha]D^{23}$ -26.9 (c 0.75, $CHCl_3$); IR (neat) 3107, 2929, 1716, 1422 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.64 (s, 1H), 5.46 (t, J = 7.3 Hz, 1H), 4.69 (d, J = 11.8 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.42 (dd, J = 3.6, 6.3 Hz, 1H) 4.17 (t, J = 6.8 Hz, 1H), 4.09 (dd, J = 2.5, 7.7 Hz, 1H), 3.42 (dq, J = 7.4, 7.4 Hz, 1H), 2.72 (s, 3H), 2.56-2.19 (m, 5H) 2.00 (s, 3H), 1.80 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H), 1.16 (d, J = 7.1 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.4, 175.3, 173.8, 165.6, 152.8, 142.4, 133.5, 126.7, 118.9, 115.6, 76.1, 73.8, 63.8, 54.3, 45.9, 45.7, 40.6, 34.4, 26.4, 24.2, 22.2, 19.4, 19.2, 18.7, 16.1, 15.3, 13.8, -3.6, -3.7, -3.8, -4.2; HRMS (CI) calcd. for $C_{38}H_{68}O_8NSSi_2$ 754.42042; found 754.42119.



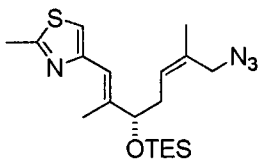
94

Dilactone 94: To a stirred solution of **93** (15.0 mg, 20.0 μmol) in THF (0.4 mL) at 0 °C was added Et_3N (4.9 μL, 35 μmol) followed by 2,4,6-trichlorobenzoyl chloride (3.6 μL, 23 μmol). After 45 min, the mixture was diluted with THF (0.3 mL) and toluene (0.4 mL), and was added via syringe pump to a stirred solution of DMAP (4.2 mg, 34 μmol) in toluene (4.6 mL) at 75 °C during 4 h. After an additional 1 h, the solution was allowed to cool to room temperature, diluted with EtOAc, washed with saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (4 x 40 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and the residue was purified by chromatography on silica gel, eluting with 5% EtOAc / hexanes, to give **94** (9.0 mg, 60%) as a colorless oil: $[\alpha]D^{23}$ -36.6 (c 0.45, $CHCl_3$); IR (neat) 2927, 1741, 1471 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 6.96 (s, 1H), 6.57 (s, 1H), 5.44 (dd, J = 5.7, 11.8 Hz, 1H), 5.34 (dd, J = 3.3, 8.8 Hz, 1H) 4.83 (d, J = 11.5 Hz, 1H), 4.46 (m, 2H), 4.02 (dd, J = 1.6, 8.7 Hz, 1H), 3.34 (dq, J = 7.4, 7.4 Hz, 1H), 2.82 (m, 1H), 2.71 (s, 3H), 2.56 (m, 3H), 2.28 (m, 1H) 2.15 (s, 3H), 1.74 (s, 3H), 1.23 (d, J = 7.4 Hz, 3H), 1.20 (d, J = 7.1 Hz, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 0.90 (s, 9H), 0.85 (s, 9H), 0.15 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 173.4, 170.8, 165.1, 152.8, 136.6, 133.7, 126.7, 121.3, 116.8, 79.2, 76.6, 73.7, 62.6, 54.2, 48.3, 45.6, 41.9, 33.3, 26.5, 25.1, 22.3, 20.4, 19.7, 18.7, 18.6, 17.4, 15.2, -3.4, -3.5, -3.7, -4.2; HRMS (CI) calcd. for $C_{38}H_{66}O_7NSSi_2$ 736.40986; found 736.40850.



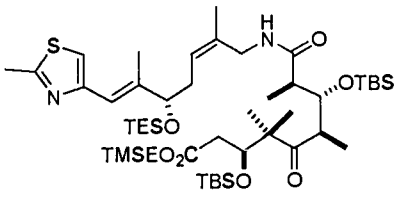
95

Dilactone 95: To a stirred solution of **94** (4.5 mg, 6 μmol) in CH_2Cl_2 (200 μL) at 0 °C was added trifluoroacetic acid (100 μL). After 8 h, the mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel, eluting with 5 - 10% MeOH / CH_2Cl_2, to give **95** (3 mg, 6 μmol, 99%) as a colorless oil: $[\alpha]D^{23}$ –40.0 (c 0.15, $CHCl_3$); IR (neat) 3503, 2924, 1732, 1458 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 7.00 (s, 1H), 6.60 (s, 1H), 5.45 (dd, J = 6.0, 11.0 Hz, 1H), 5.28 (d, J = 9.6 Hz, 1H) 5.02 (d, J = 11.2 Hz, 1H), 4.21 (d, J = 12.3 Hz, 1H), 4.02 (m, 1H), 3.77 (m, 1H), 3.46 (m, 1H), 3.23 (dq, J = 6.8, 6.8 Hz, 1H), 2.74 (s, 3H), 2.67 (m, 3H), 2.45 (m, 2H), 2.24 (m, 1H), 2.11 (s, 3H), 1.78 (s, 3H), 1.38 (d, J = 7.1 Hz, 3H), 1.31 (s, 3H) 1.27 (d, J = 6.8 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.9, 177.2, 170.9, 165.4, 152.8, 137.9, 133.6, 126.1, 120.7, 116.9, 78.9, 75.6, 73.3, 63.9, 52.7, 47.9, 41.7, 39.0, 32.7, 22.3, 21.9, 21.8, 19.6, 16.8, 16.5, 15.7; HRMS (CI) calcd. for $C_{26}H_{38}O_7NS$ 508.23690; found 508.23641.



80

Chloride 80: To a stirred solution of **80** (90 mg, 235 μmol) was added a solution of NaN_3 (0.6mL, 0.5M in DMSO) After 1 h at room temperature, the solution was diluted with H_2O and extracted with Et_2O. The dried ($MgSO_4$) extract was concentrated *in vacuo* and the residue was purified by chromatography on silica gel, eluting with 10 - 20% Et_2O / petroleum ether, to give **96** (80 mg, 88%) as a colorless oil: $[\alpha]_D^{23}$ +10.7 (c 0.7, $CHCl_3$); IR (neat) 2954, 2876, 2095,1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.47 (s, 1H), 5.49 (t, J= 7.4 Hz, 1H), 4.10 (t, J= 6.0 Hz, 1H), 3.86 (d, J=13.17, 1H), 3.69 (d, J=13.17, 1H), 2.71 (s, 3H), 2.35 (m, 2H), 2.01 (d, J=1.2, 3H), 1.75 (d, J=1.2, 3H), 0.93 (t, J=7.69, 9H), 0.58 (q, J=7.39, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 153.3, 142.3, 131.3, 127.7, 119.7, 115.6, 78.7, 51.7, 35.8, 22.7, 19.6, 14.4, 7.2, 5.2; HRMS (FAB) calcd. for $C_{19}H_{33}N_4OSSi$ ($M+H^+$) 393.2144, found 393.2137.



97

Amide 97: To a stirred solution of **96** (80.0 mg, 0.20 mmol) in THF (1.0 mL) was added H_2O (4 μL) and triphenylphosphine (56 mg, 0.22 mmol). The reaction was stirred 12 h, concentrated in vacuo, and the residue was filtered through silica gel with 3-5% MeOH / CH_2Cl_2, and then was concentrated in vacuo. To the resulting residue was added **91** (50 mg, 0.1 mmol) in DMF (0.4 mL), followed by HOBt (12 mg, 0.1 mmol) and EDCI (23 mg, 0.12 mmol). After stirring for 12 h, the reaction was diluted with EtOAc, washed with saturated aqueous NH_4Cl (5 mL), and extracted with EtOAc (4 x 5 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and the residue was purified by chromatography on silica gel, eluting with 2% MeOH / CH_2Cl_2, to give **97** (40 mg, 25%) as a colorless oil: $[\alpha]D^{23}$ -6.8 (c 1.00, $CHCl_3$); IR (neat) 3369, 2954, 1734, 1671, 1471, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.79 (t, J = 5.2 Hz, 1H) 6.47 (s, 1H), 5.32 (t, J = 7.4 Hz, 1H), 4.38 (dd, J = 3.0, 6.3 Hz, 1H) 4.13 (m, 3H), 3.98 (m, 2H), 3.75 (m, 1H) 3.22 (dq, J = 7.1, 7.1 Hz, 1H), 2.71 (s, 3H), 2.45-2.15 (m, 5H) 1.99 (s, 3H), 1.75 (s, 3H), 1.21 (d, J = 7.1 Hz, 3H), 1.20 (s, 3H), 1.11 (s, 3H), 1.06 (d, J = 7.1 Hz, 3H), 0.98 (m, 3H), 0.92 (t, J = 7.7, 9H), 0.90 (s, 9H) 0.85 (s, 9H), 0.58 (q, J = 7.8 Hz, 6H), 0.11 (s, 6H), 0.08 (s, 3H), 0.03 (s, 9H), 0.01 (s, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 218.1, 175.0, 172.6, 133.4, 125.8, 115.5, 78.6, 76.2, 74.8, 63.1, 54.0, 46.8, 46.7, 41.0, 39.9, 35.6, 30.1, 26.6, 26.5, 26.4, 24.4, 22.5, 24.4, 22.5, 19.4, 18.7, 18.6, 18.4, 17.7, 15.8, 14.4, 7.3, 5.2, -1.1, -3.0, -3.3, -4.0, -4.3;HRMS (CI) calcd. for $C_{49}H_{95}O_7N_2SSi_4$ 967.5937; found 967.5974.

Materials and Methods

The following human cancer cell lines were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA): non-small cell lung adenocarcinoma A549 (CCL 185), human colon carcinoma HCT116 (ATCC CCL 247) and estrogen-dependent breast carcinoma cell line MCF-7 (ATCC HTB 22). The human metastatic prostate carcinoma PC-3M was obtained from Dr. I. J. Fidler (MD Anderson Cancer Center, Houston, TX, USA). The human KB-31 (drug-sensitive) and KB-8511 (P-gp overexpressing, multidrug-resistant) epidermoid carcinoma cell lines were obtained from Dr. R. M. Baker, Roswell Park Memorial Institute (Buffalo, NY, USA) and have been previously described.[36]

In Vitro Tubulin Polymerization Assay. Induction of tubulin polymerization was determined using a modified version of a previously described microtubule protein centrifugation assay. Briefly, MAP-associated porcine brain tubulin was incubated with 5 μM compound for 20 min at room temperature. The samples were then centrifuged for 15 min at 14,000 rpm to separate polymerized from non-polymerized microtubule protein. The protein concentration of the

supernatant containing the remainder of non-polymerized, soluble microtubule protein was determined by the Lowry method (DC Assay Kit, Bio-Rad Laboratories, Hercules, CA) using a SpectraMaxPlus photometer (Molecular Devices, Sunnyvale, CA). The reduction in optical density at 750 nm induced by the test compound was compared to that for 25 μM epothilone B (**2**), which served as a positive control.

Determination of antiproliferative activity. Antiproliferative assays were performed as previously described. Cells were seeded at 1.5 x 10^3 cells/well into 96-well microtiter plates and incubated overnight. Compounds were added in serial dilutions on day 1. Subsequently, the cells were incubated for 3 or 4 days (allowing for at least 2 population doublings), and then were fixed with 3.3 % v/v glutaraldehyde, washed with water and stained with 0.05% w/v methylene blue. After washing, the dye was eluted with 3% HCl and the optical density was measured at 665 nm with a SpectraMax 340 photometer (Molecular Devices, Sunnyvale, CA). IC_{50} values were determined by mathematical curve-fitting using SoftPro3.0 software (Molecular Devices, Sunnyvale, CA) employing the formula $(OD_{treated}-OD_{start}) / (OD_{control}-OD_{start}) \times 100$. The IC_{50} was defined as the drug concentration which resulted in 50% net cell growth compared to control cultures at the end of the incubation period.

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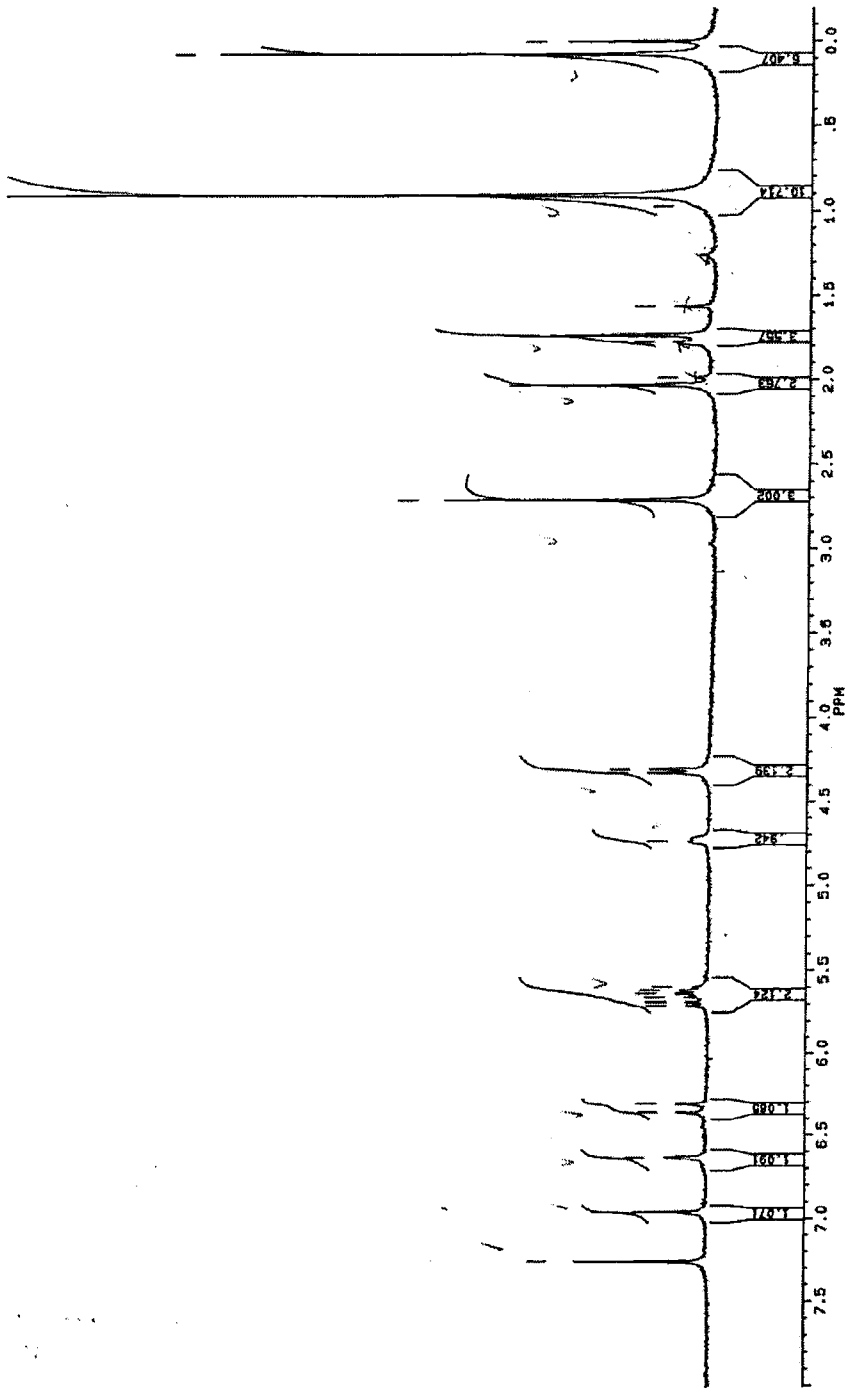
[73] For information about clinical trials of epothilone D, visit: www.kosan.com.

Appendix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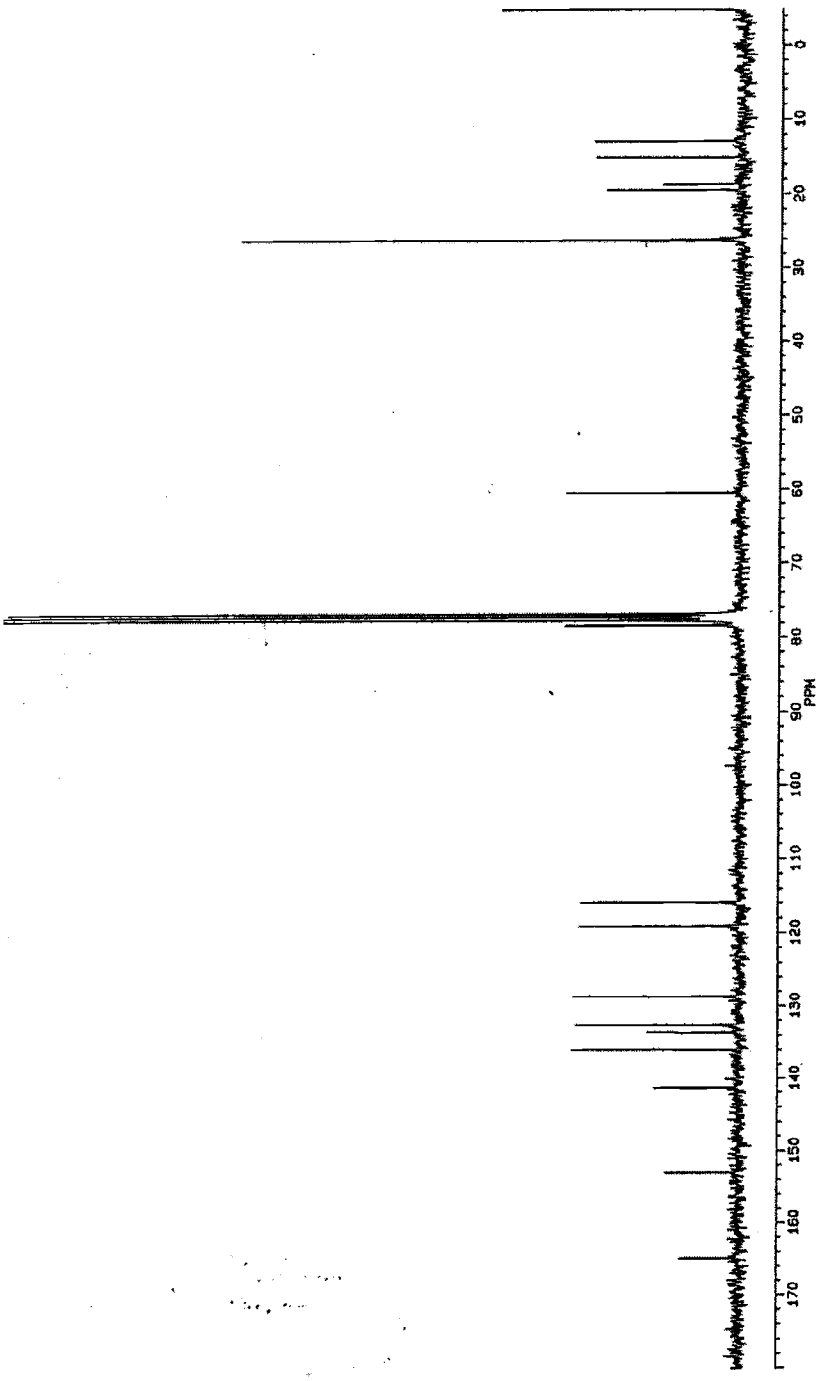

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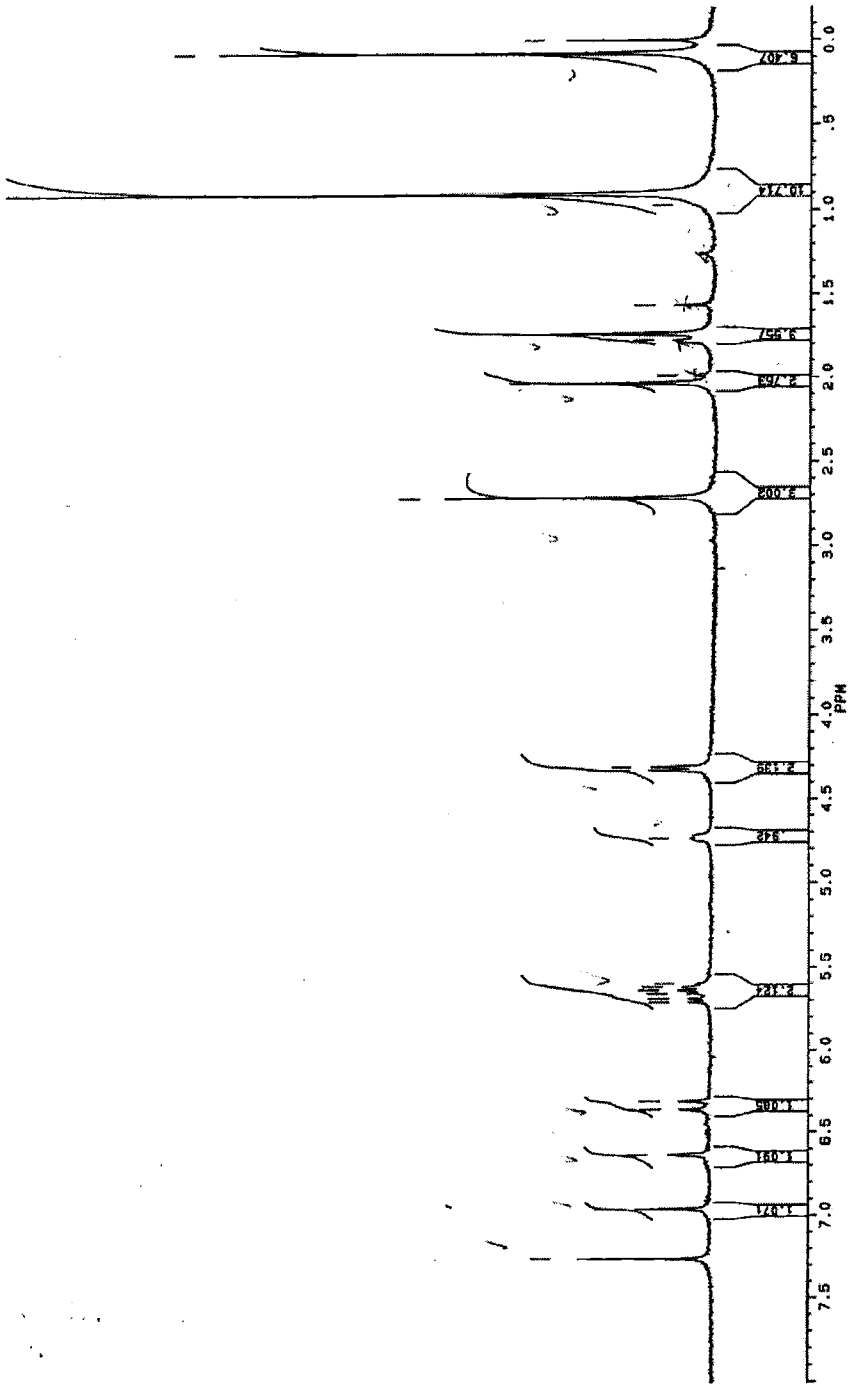

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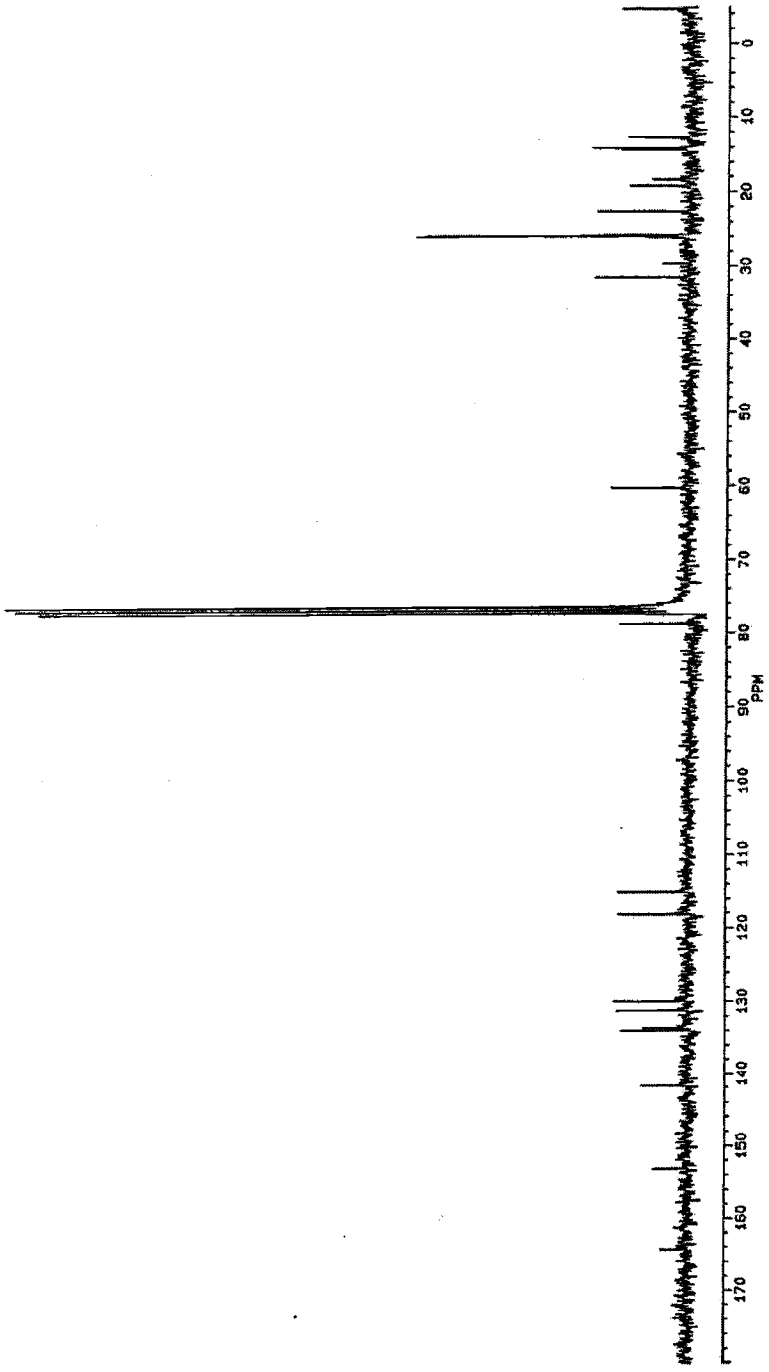

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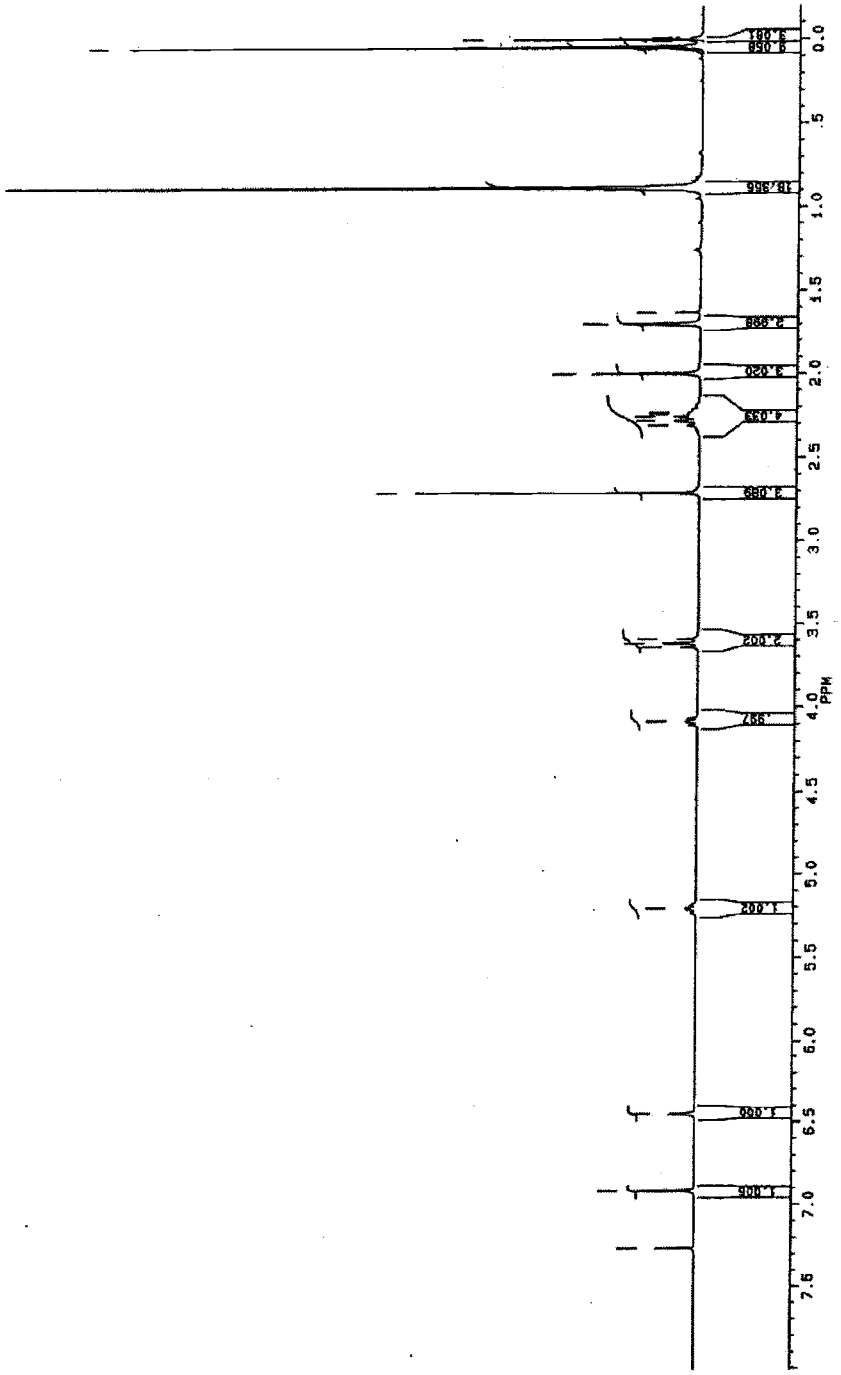

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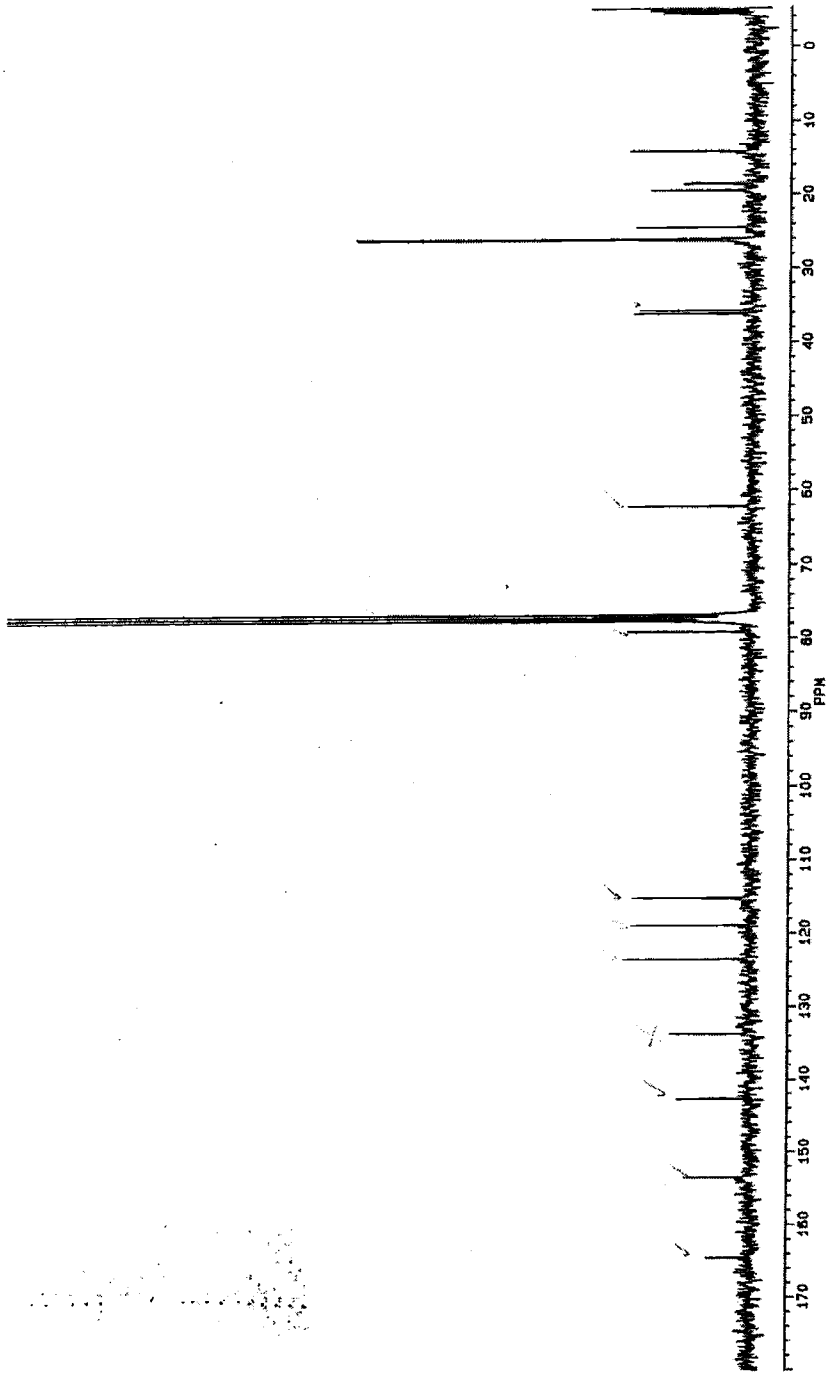

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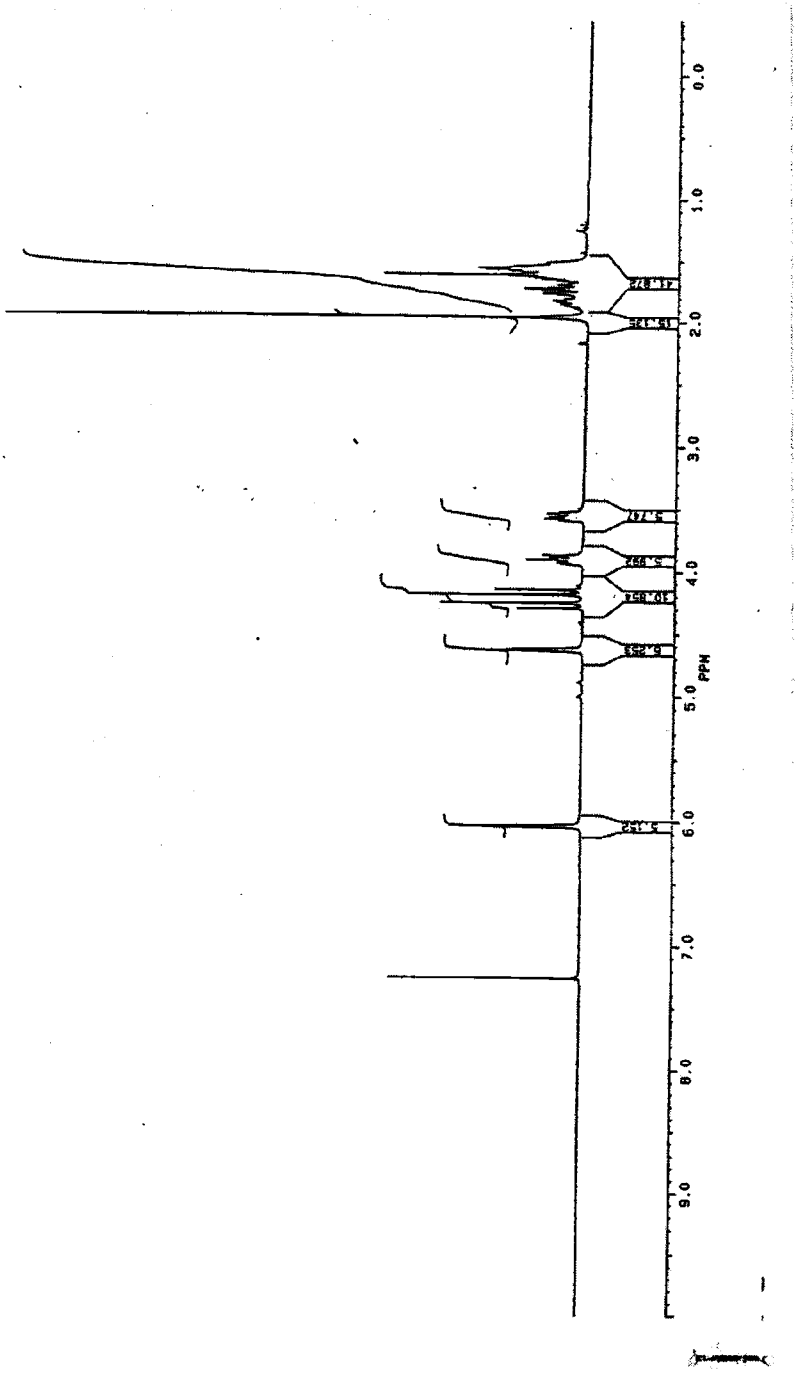

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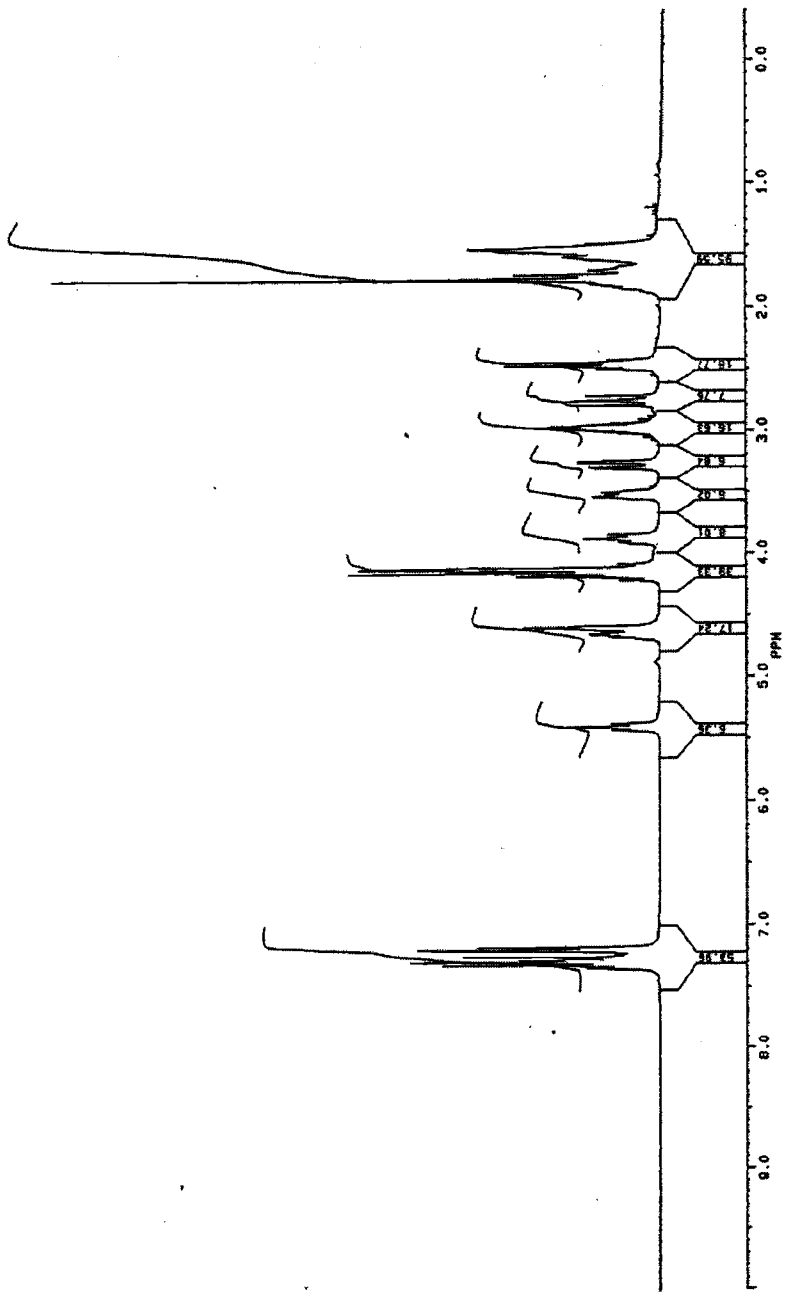

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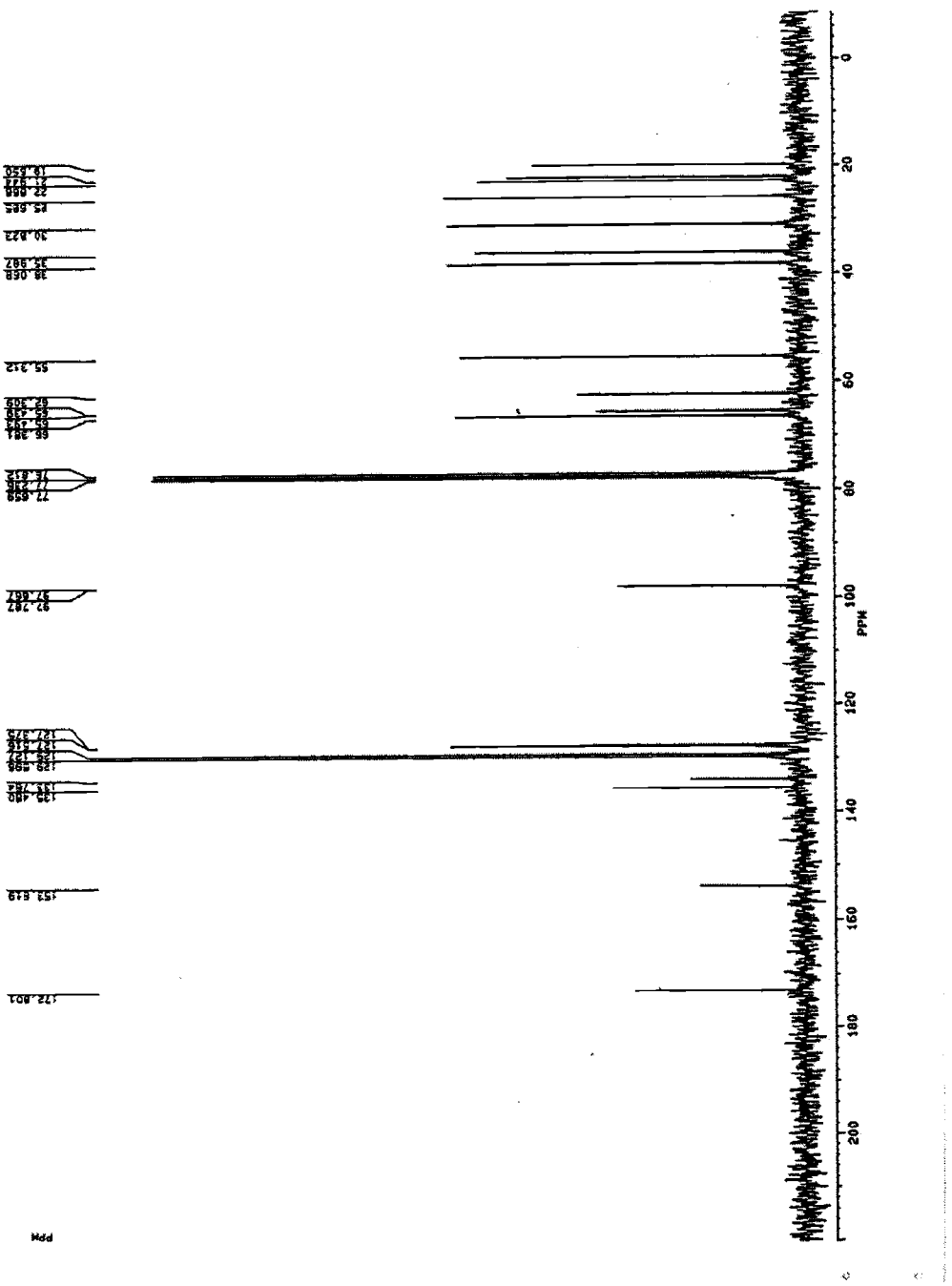

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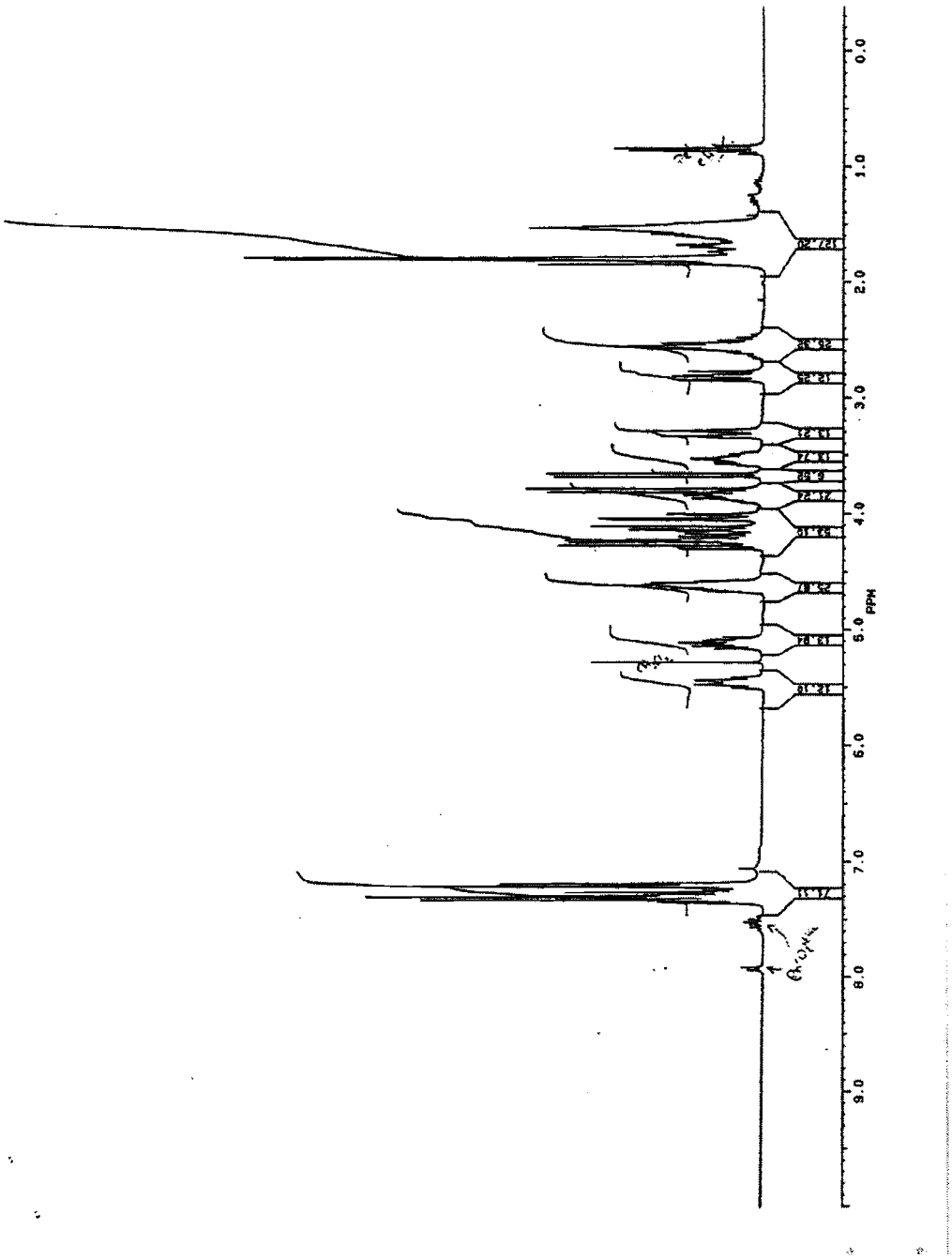

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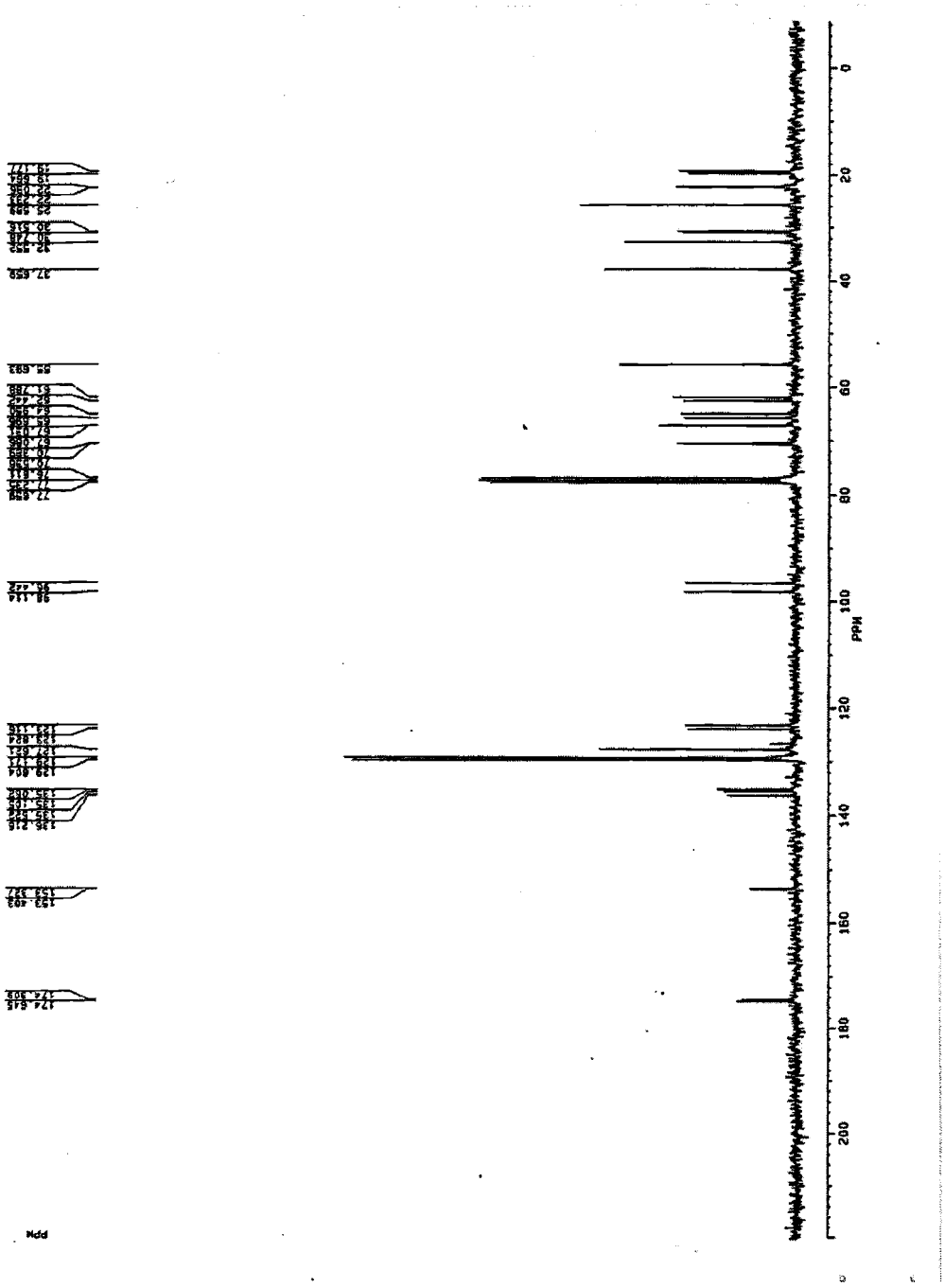

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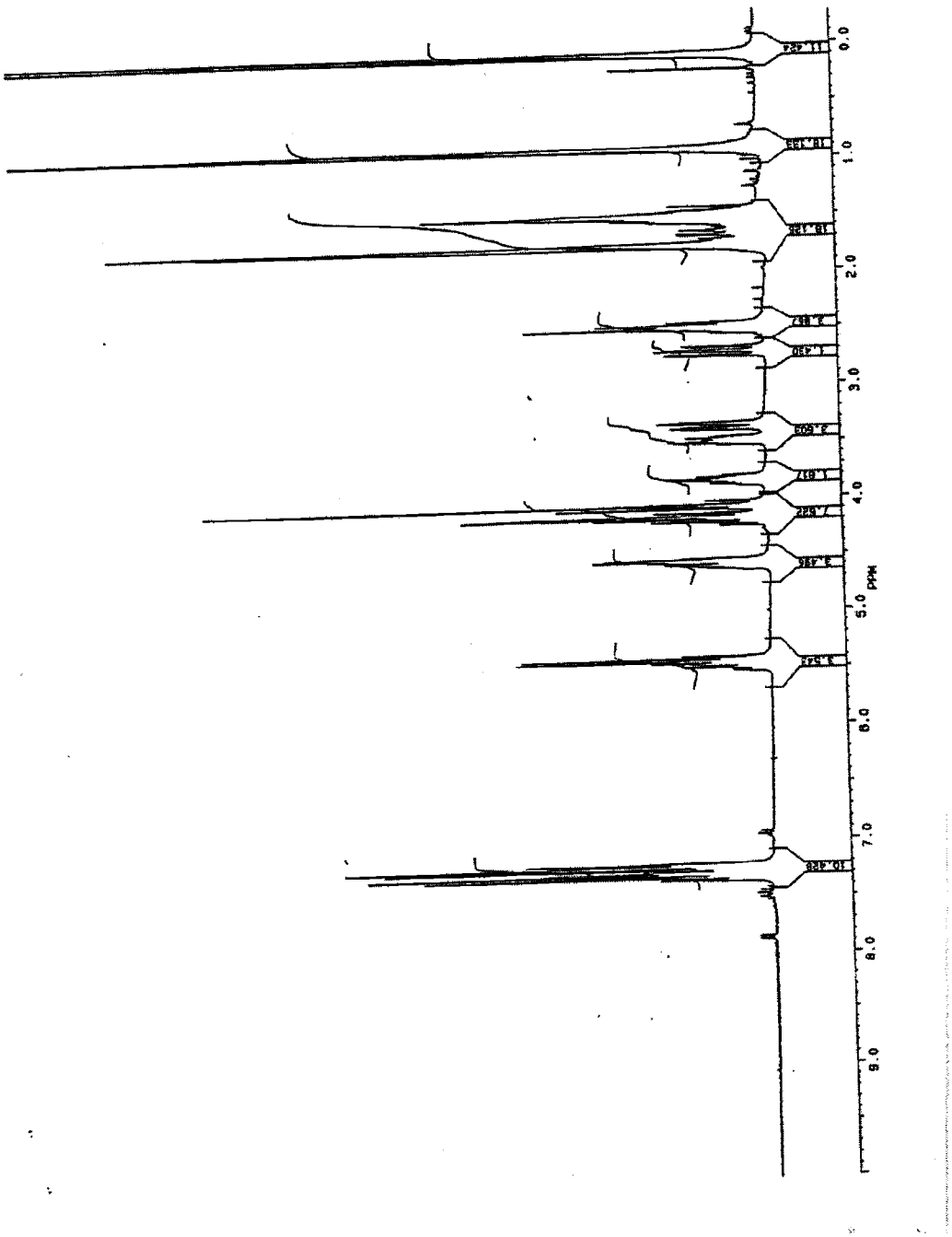

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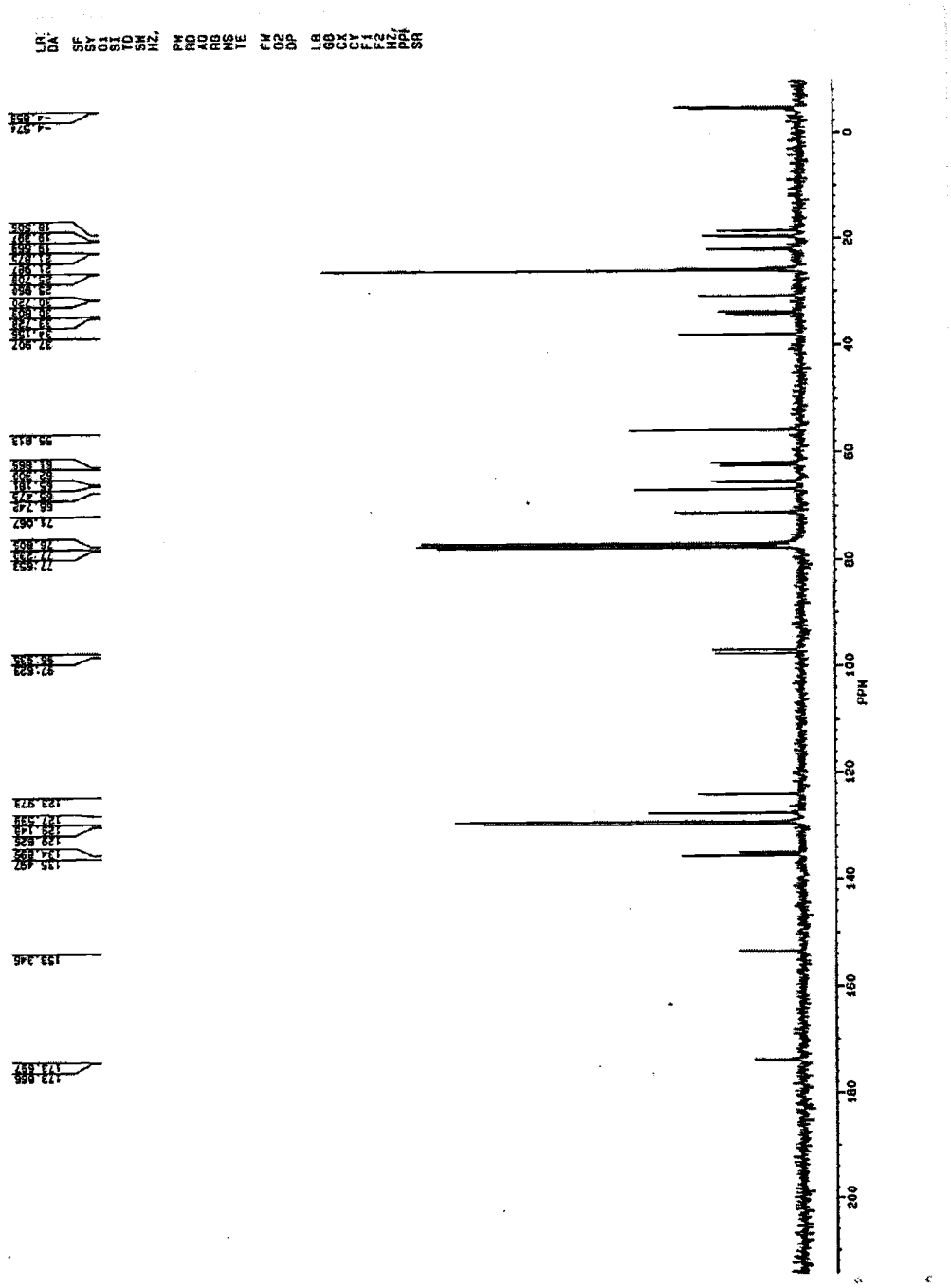

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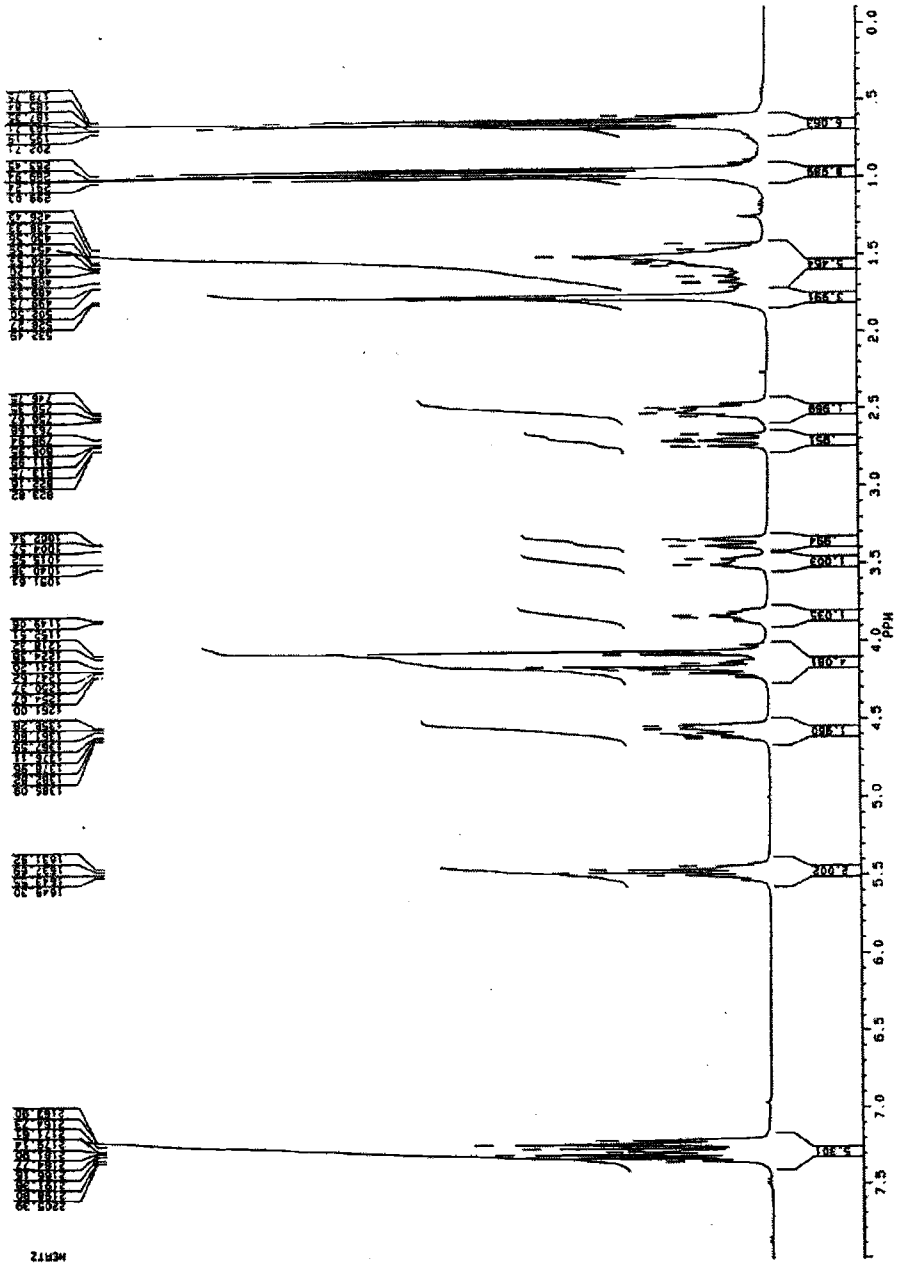

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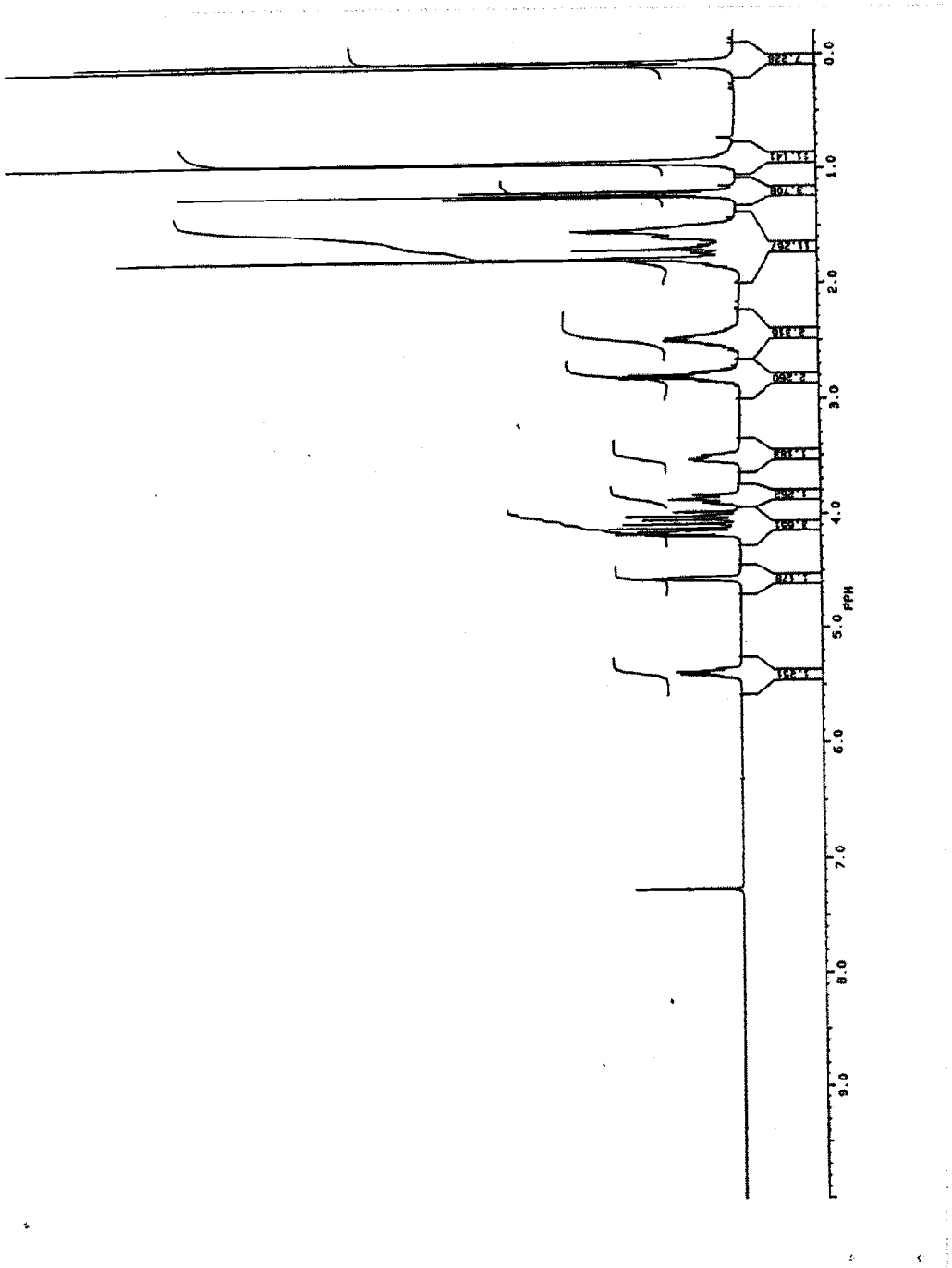

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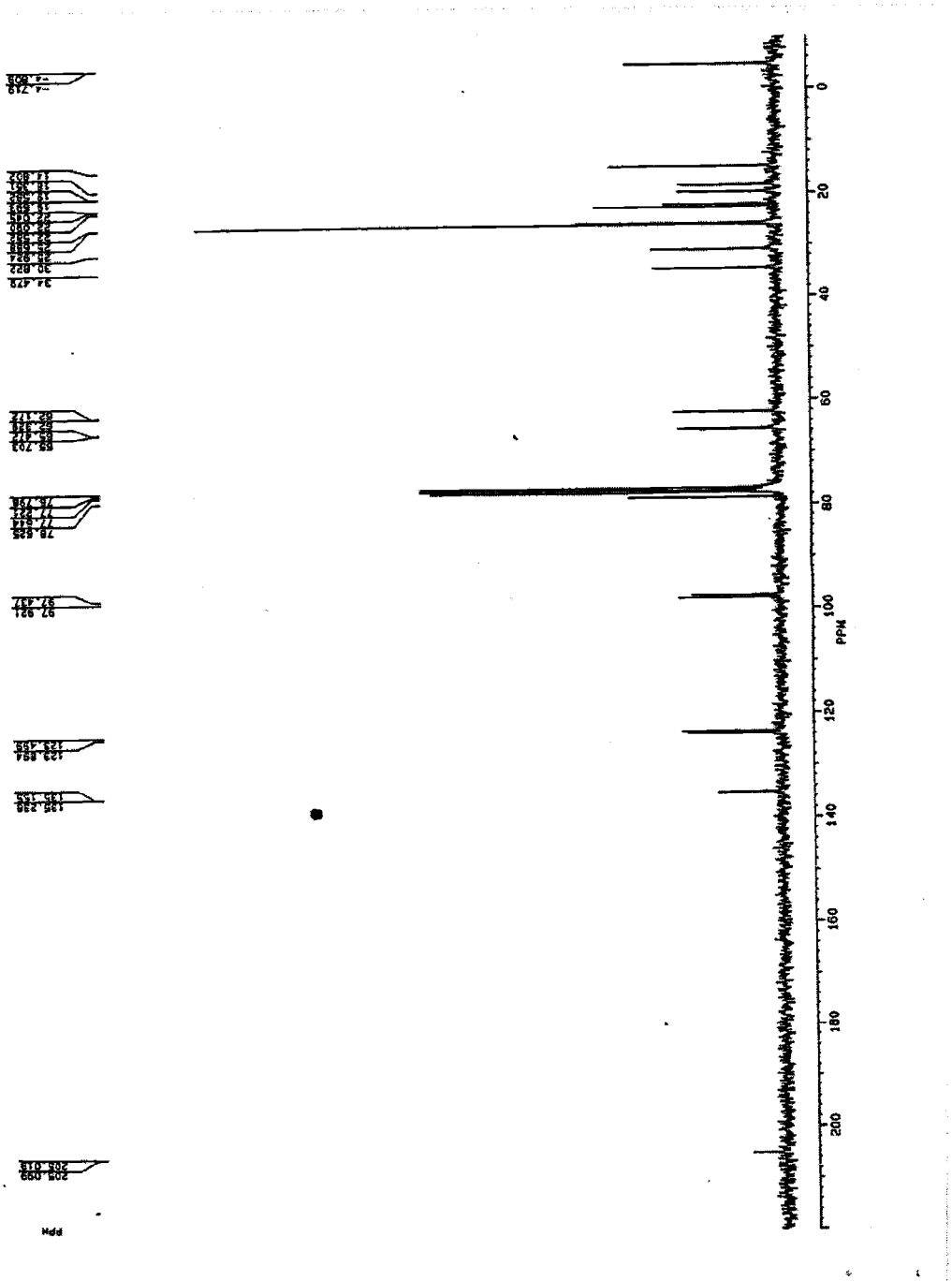
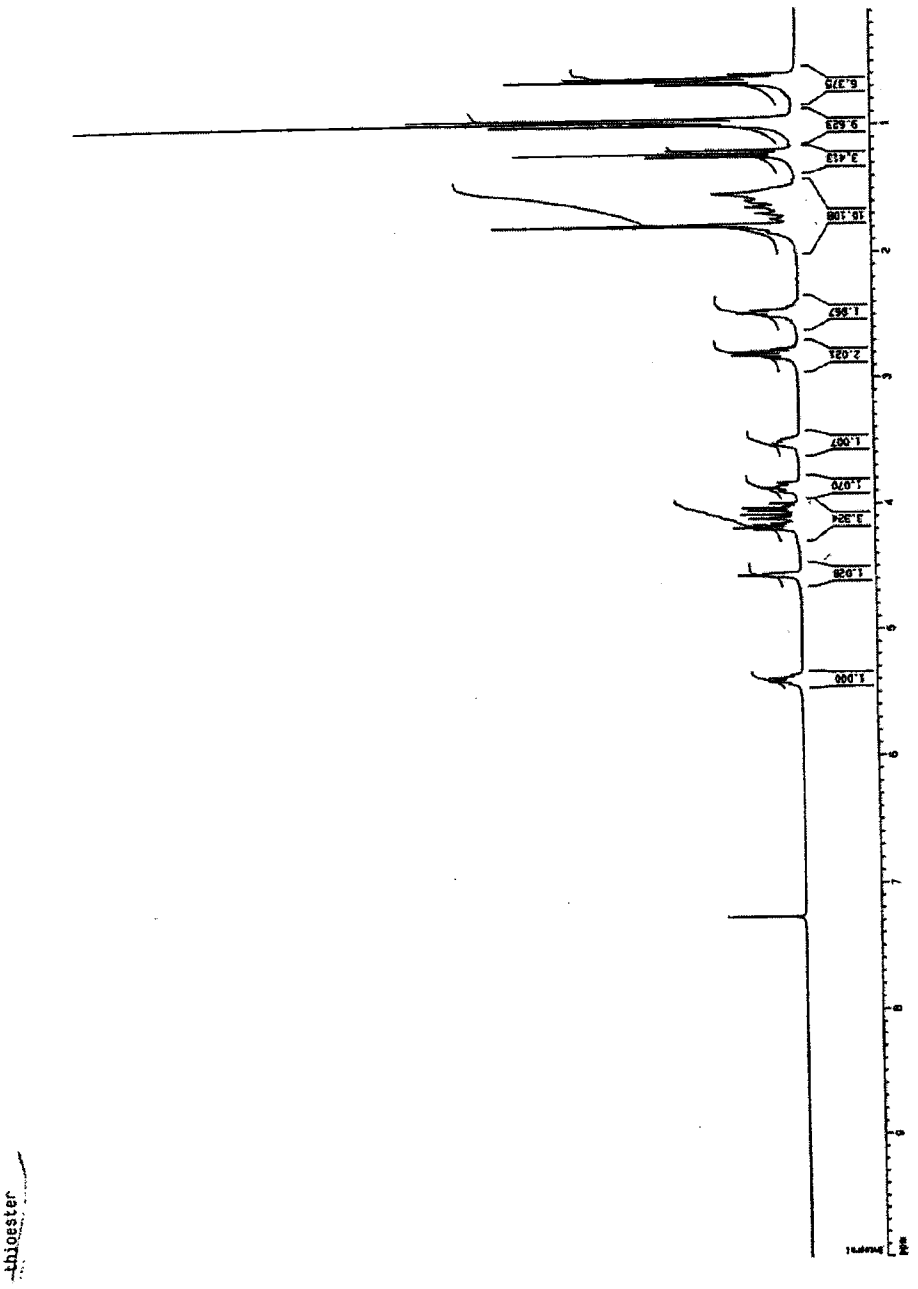
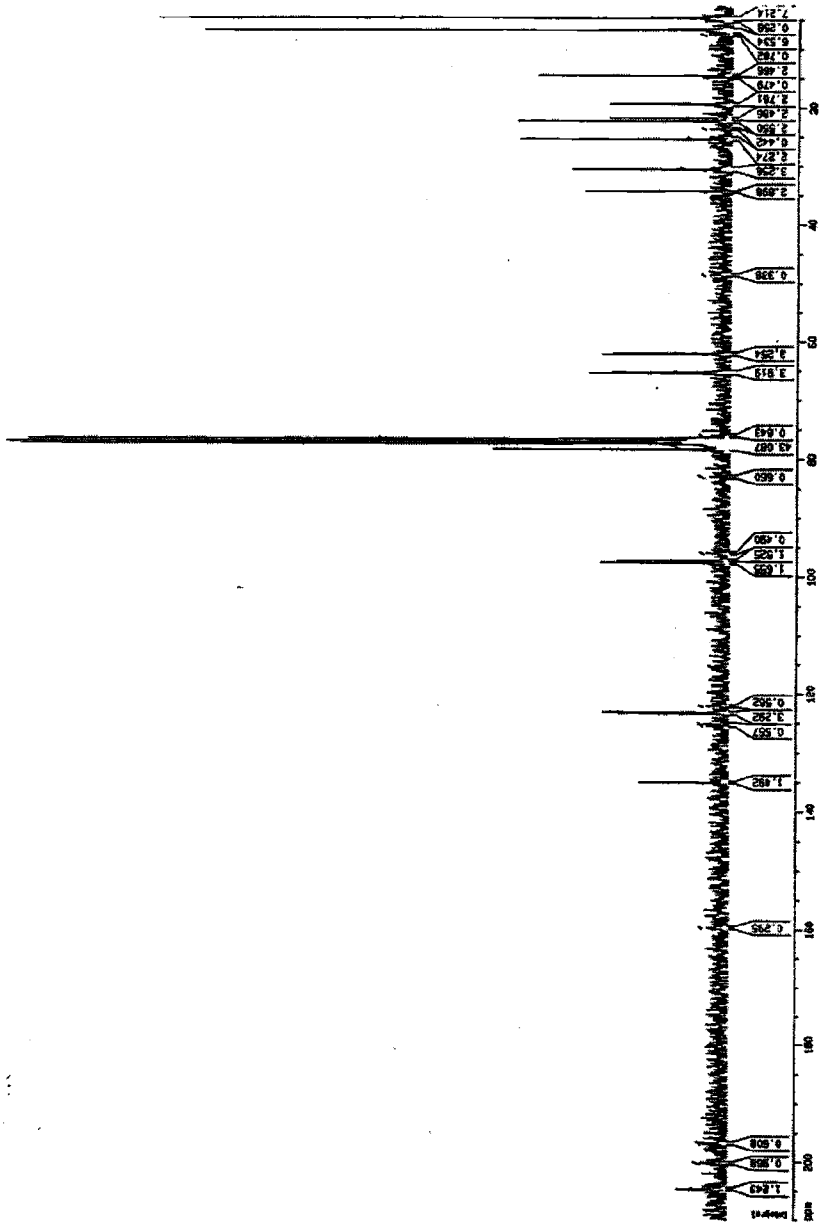


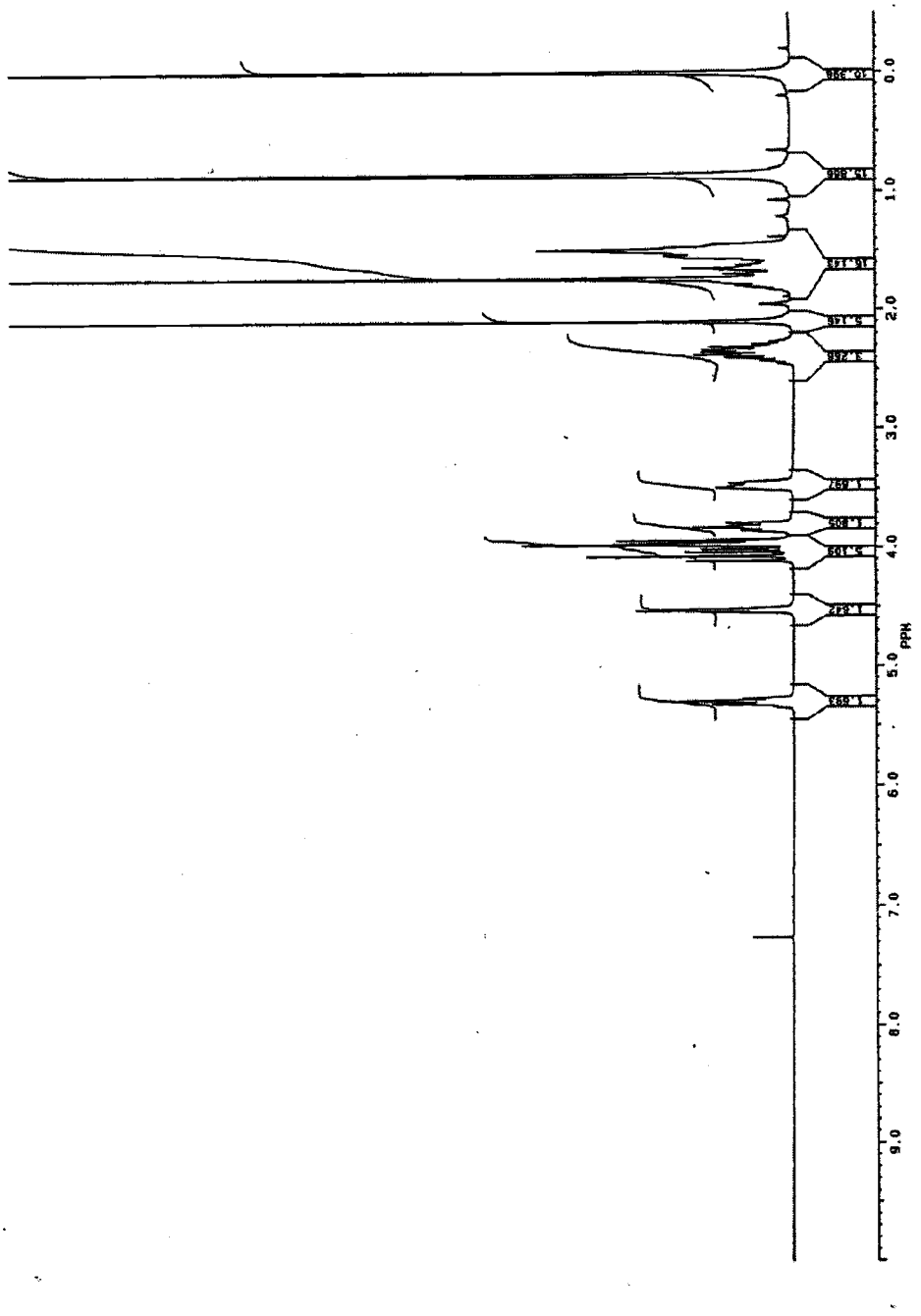
Thioester 34



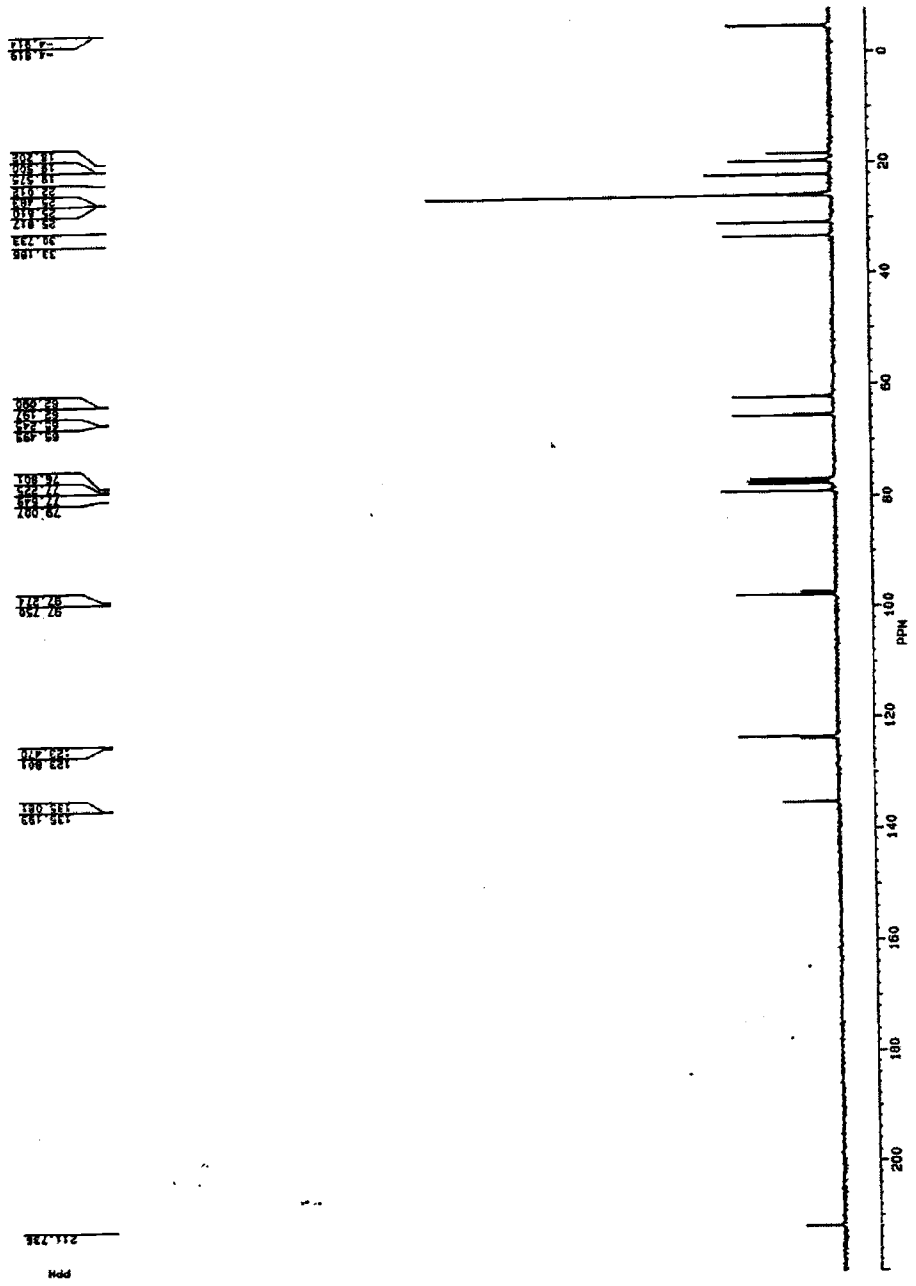
Thioester 35



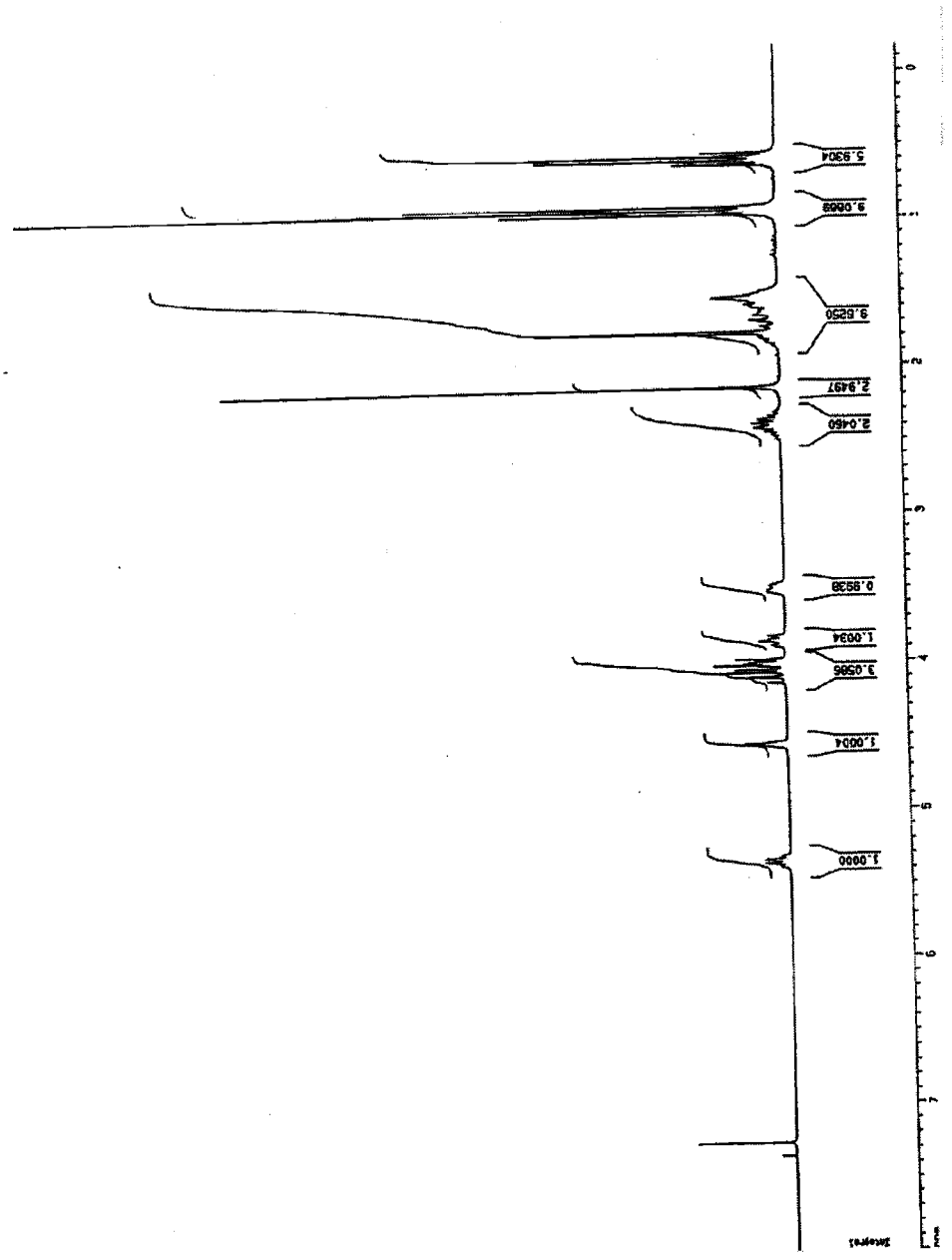
Thioester
35



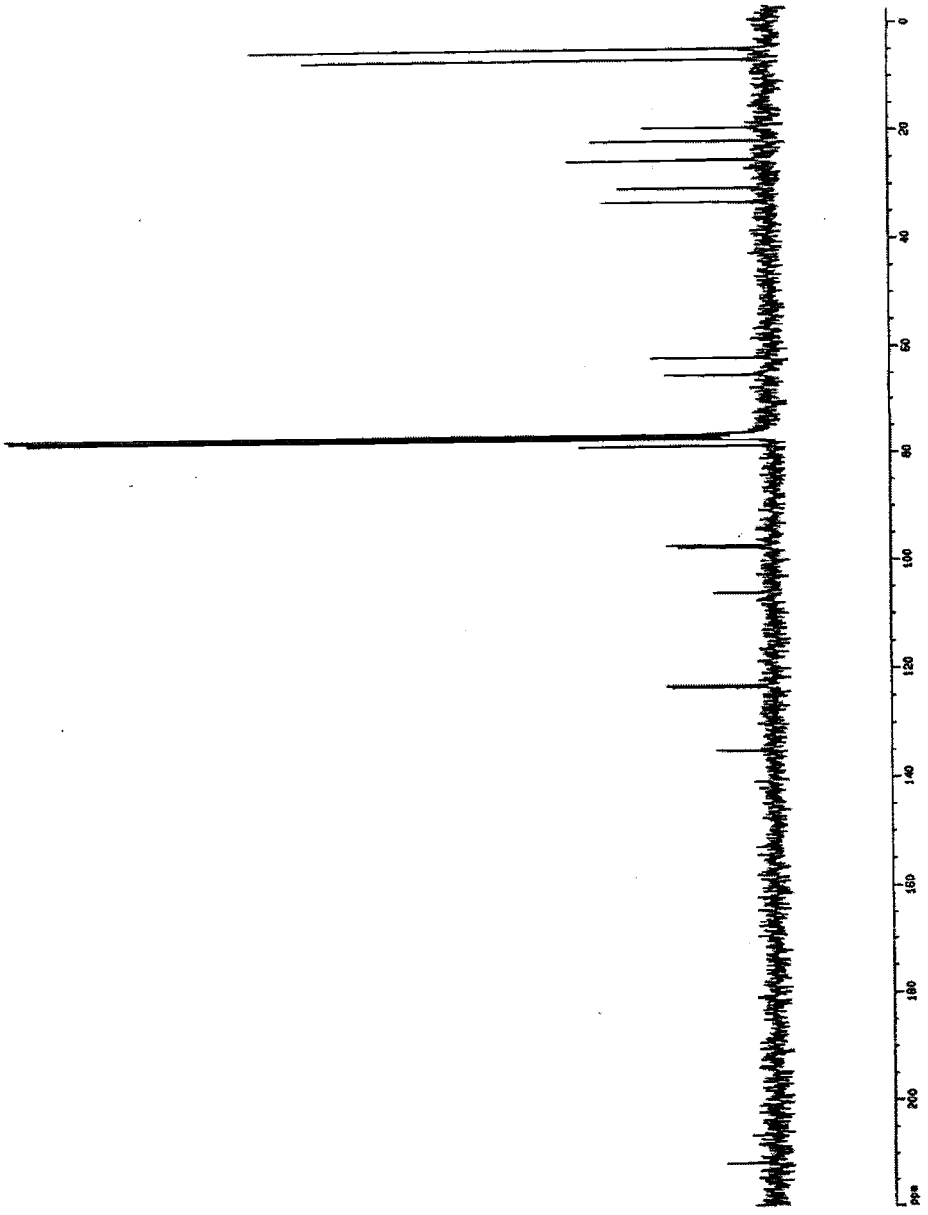
Ketone 36



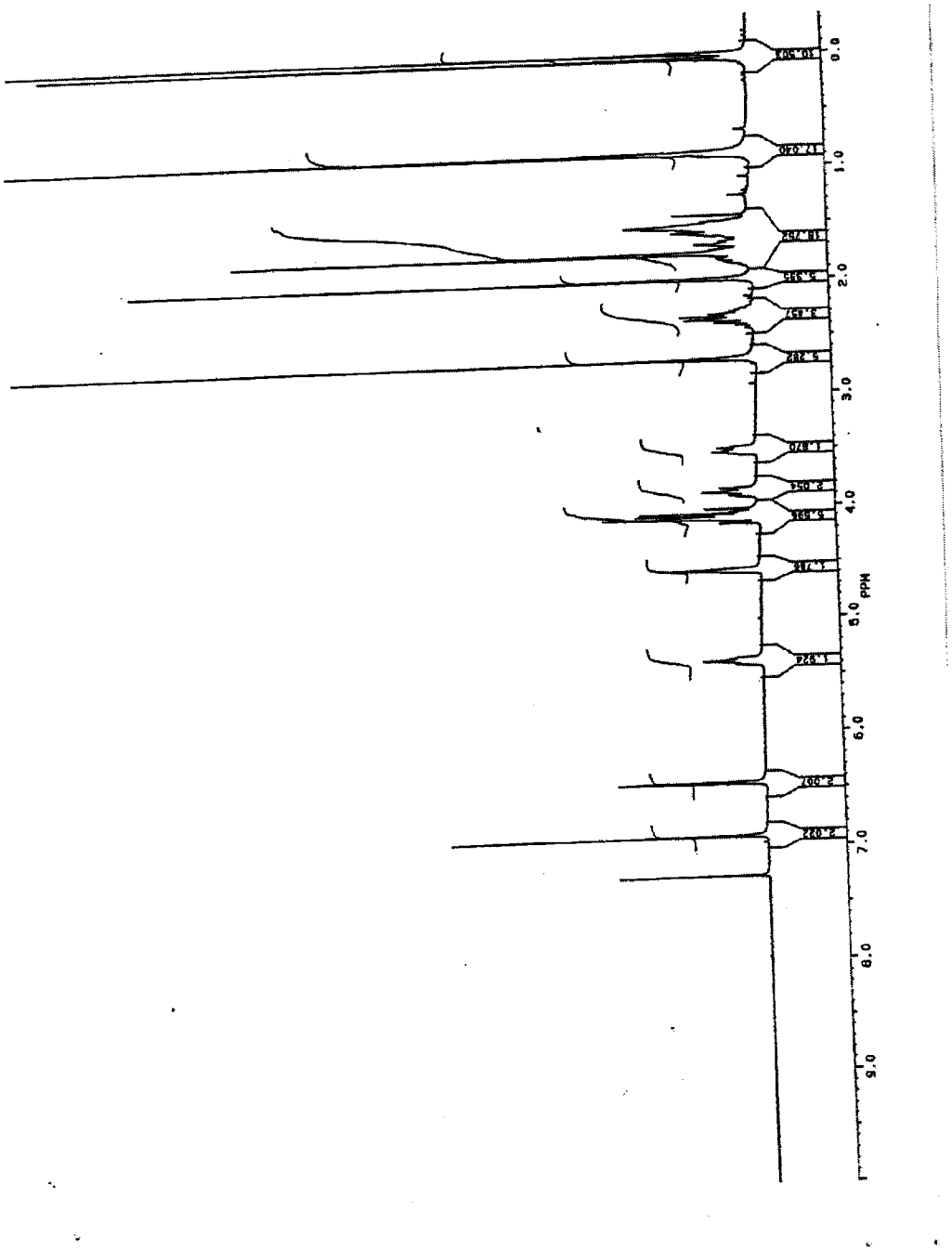
Ketone 36


5.9304
9.0609
9.8250
2.9497
2.0460
0.9538
1.0034
3.0586
1.0004
1.0000

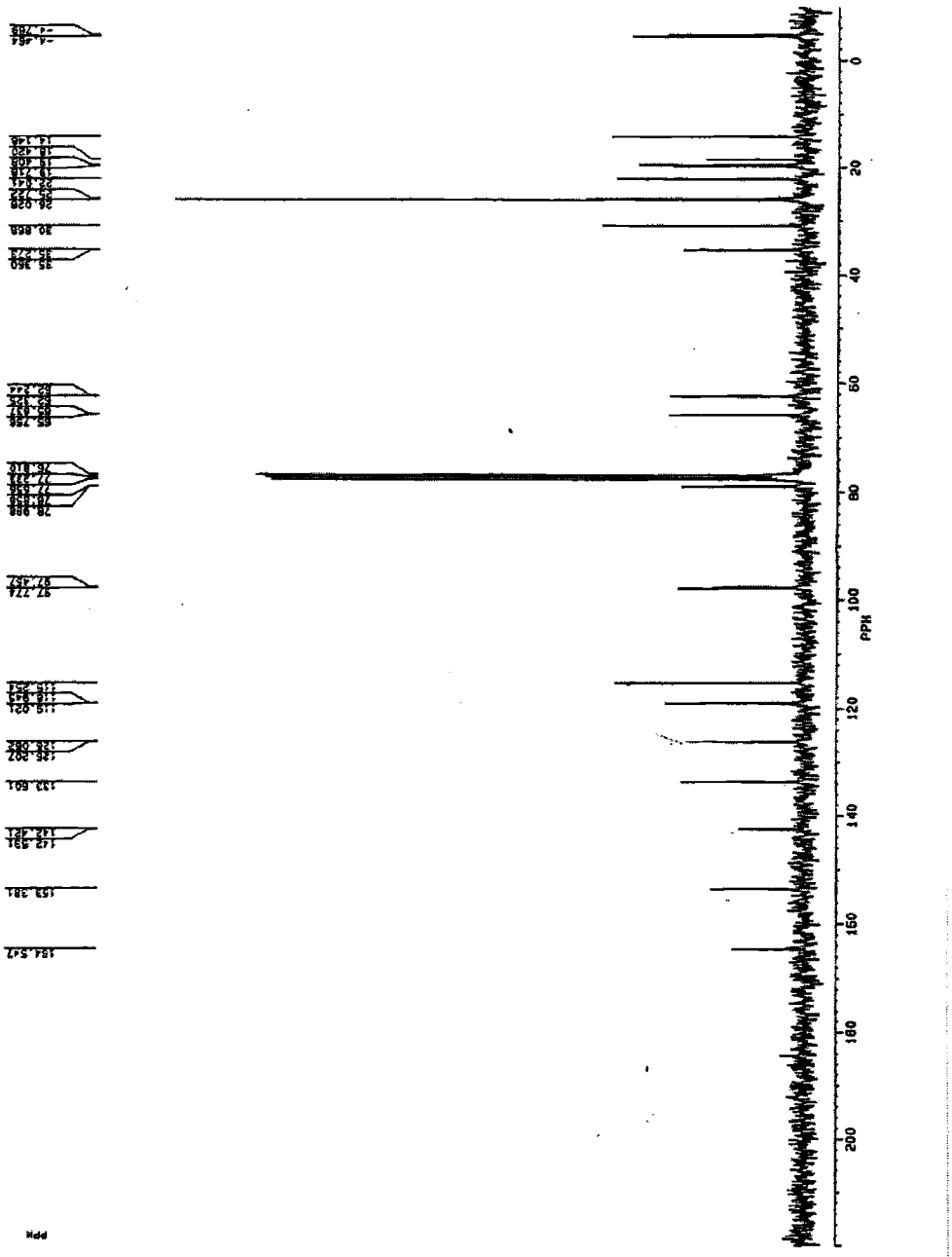
Ketone 37



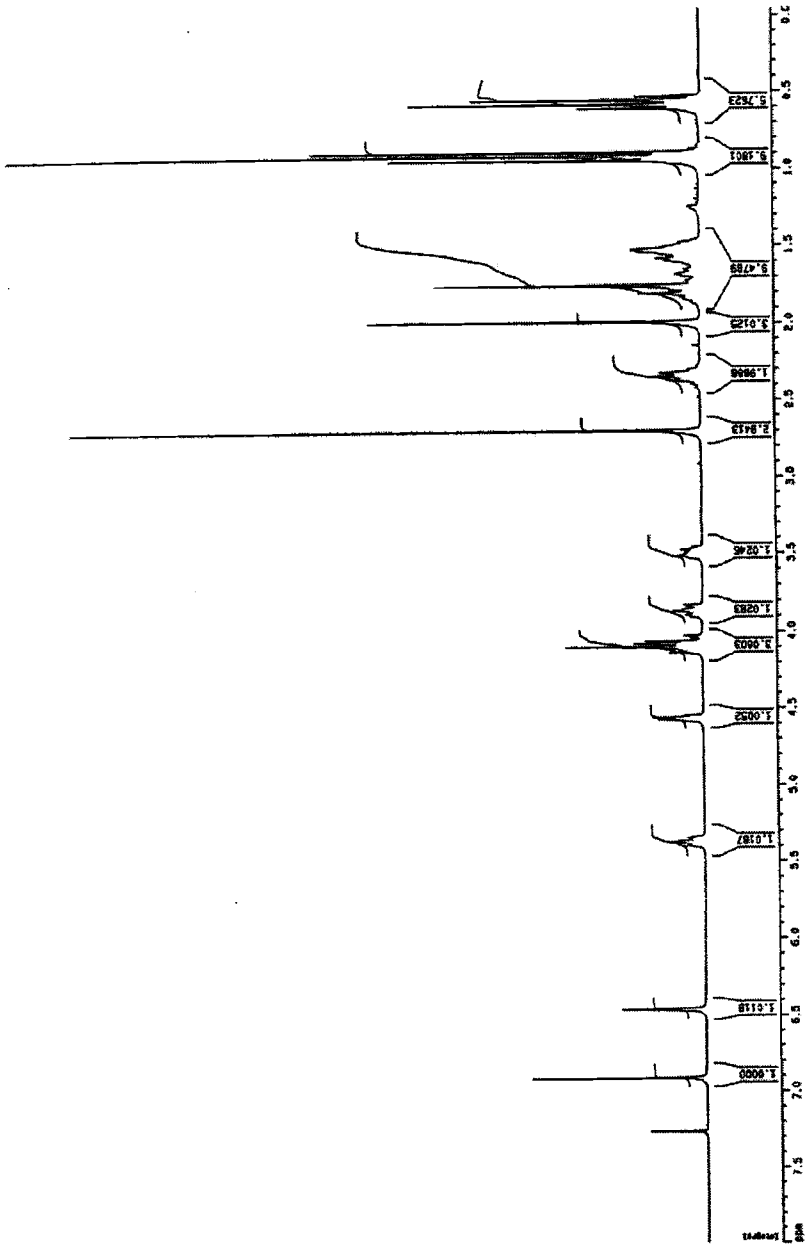
Ketone
37



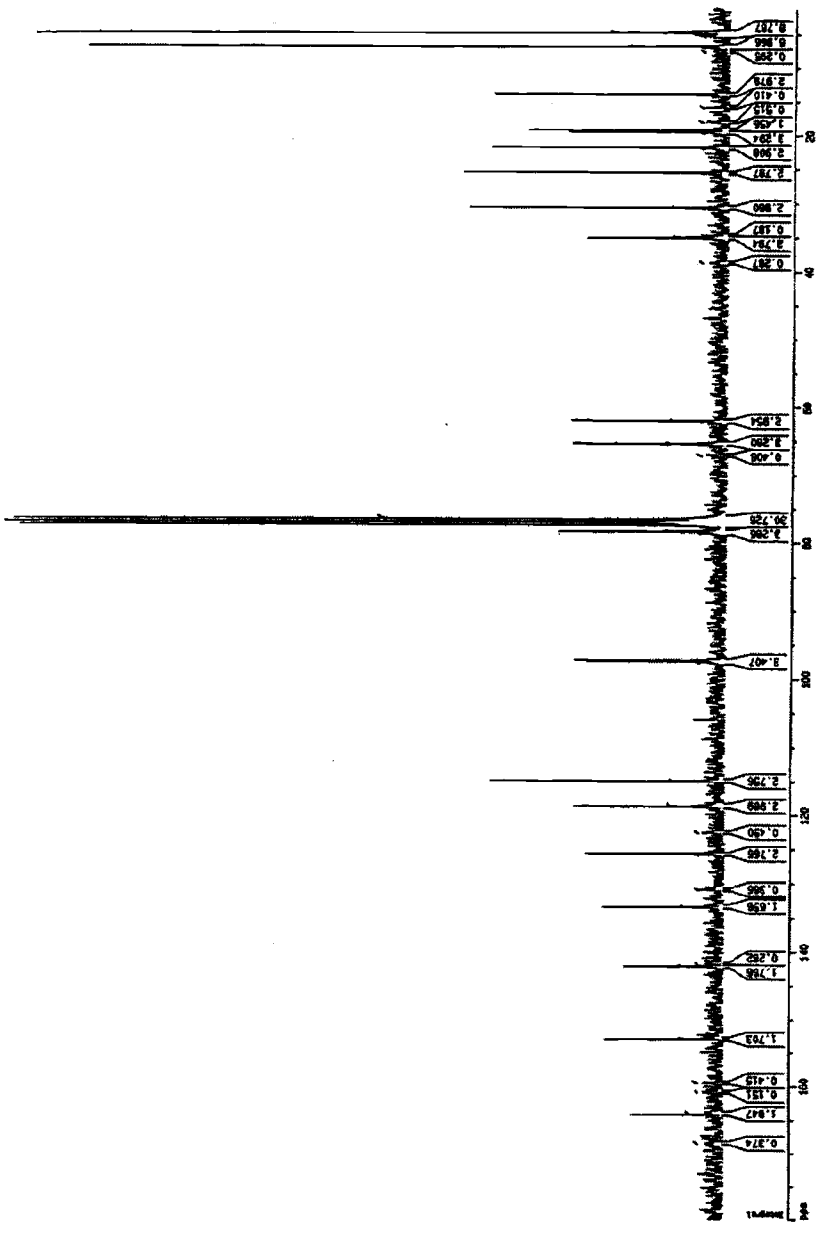
Thiazole 39



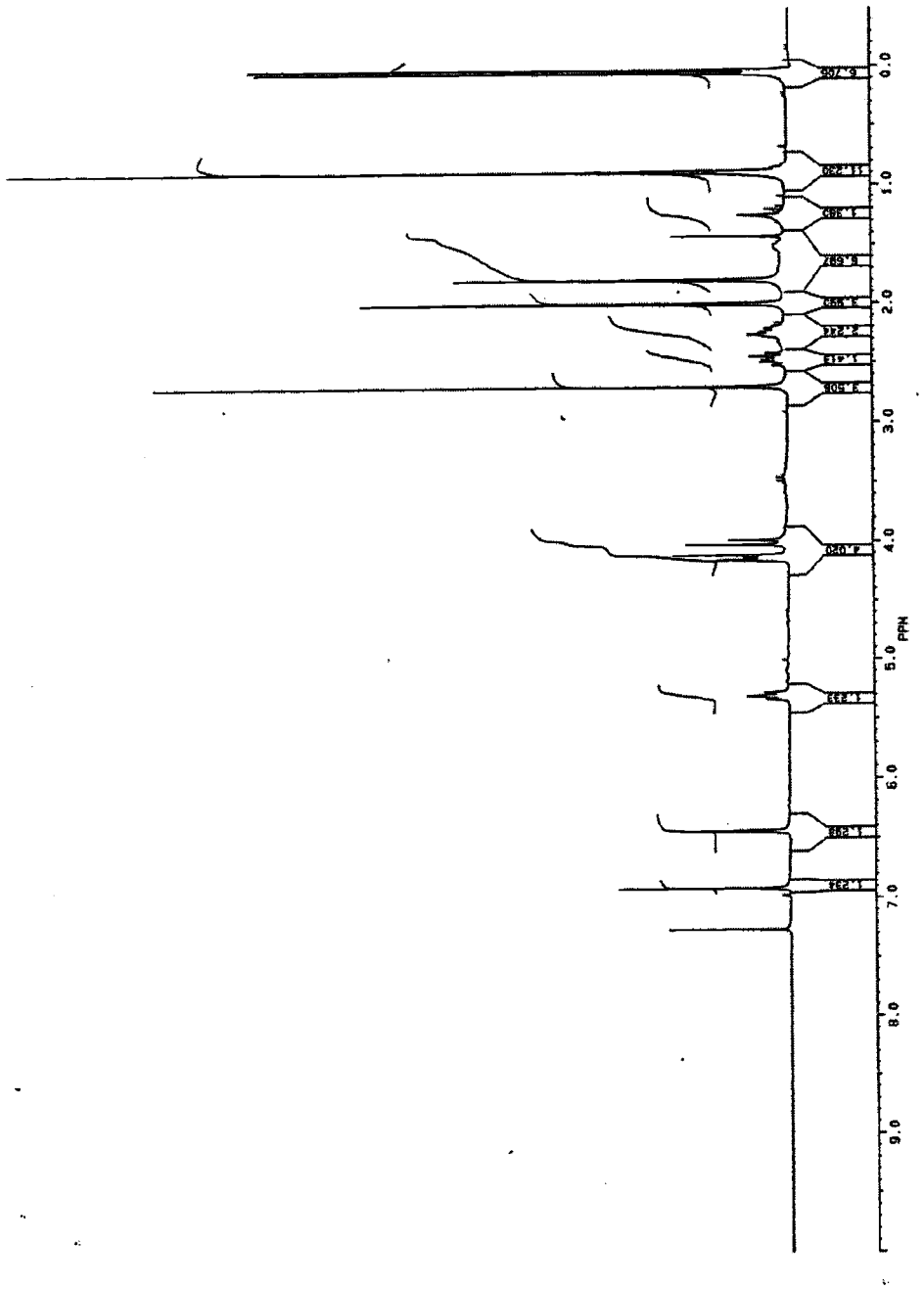
Thiazole 39



Thiazole 40



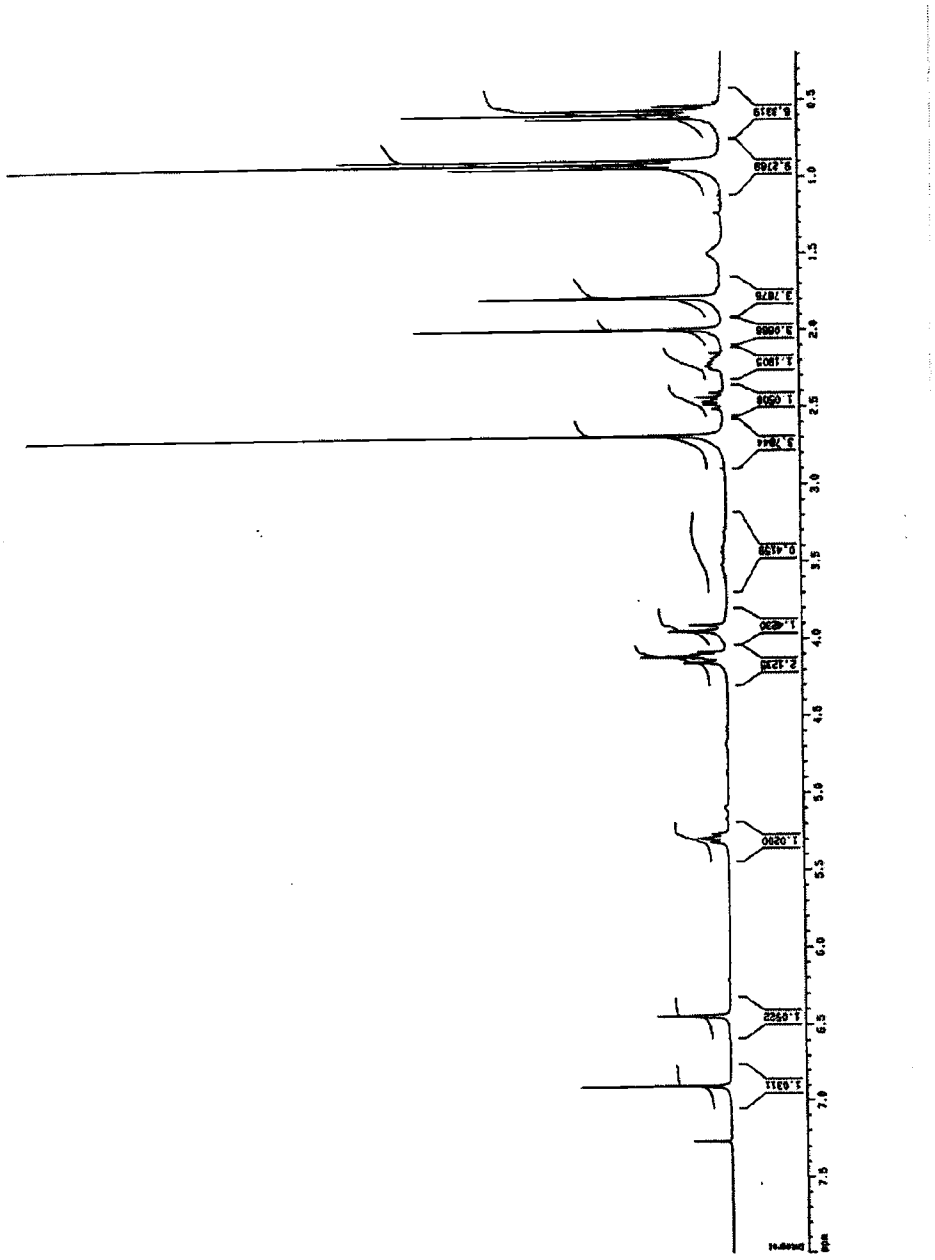
Thiazole
40



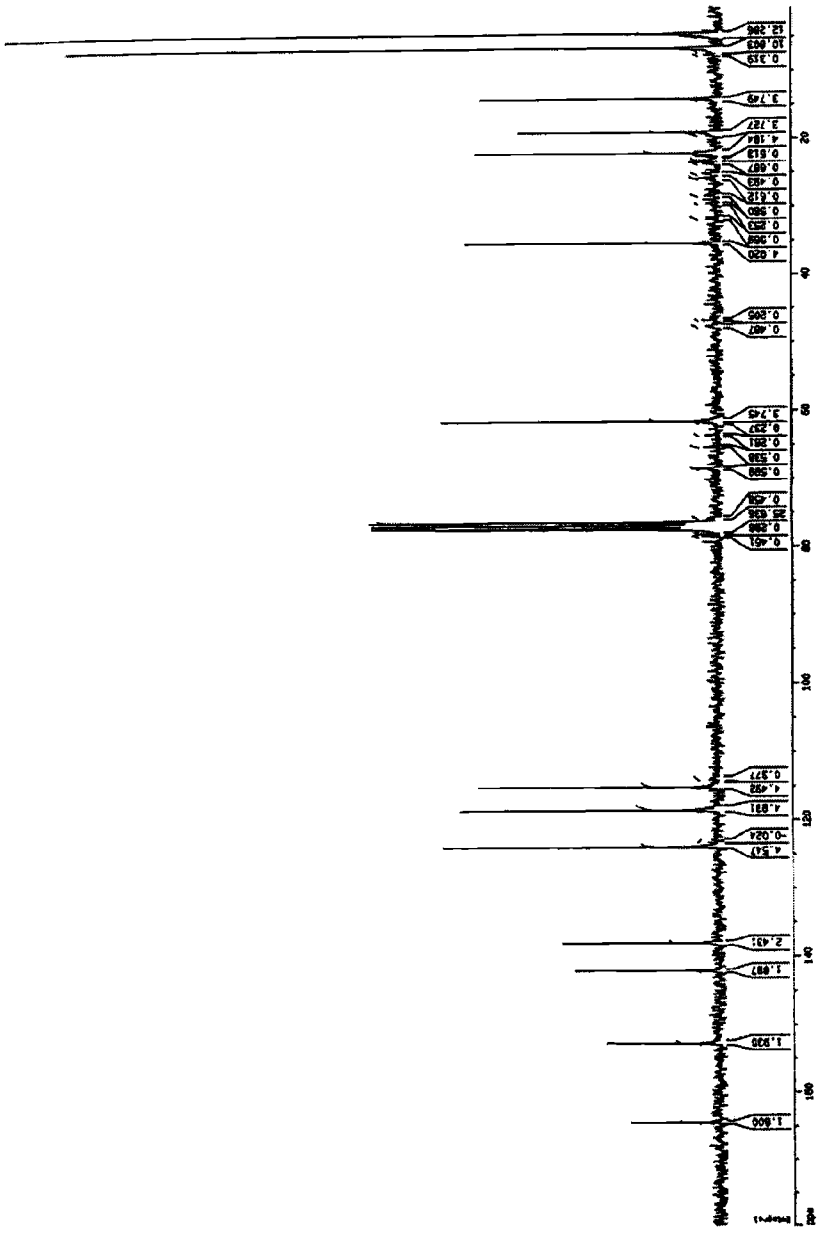
Alcohol 41

Alcohol 41

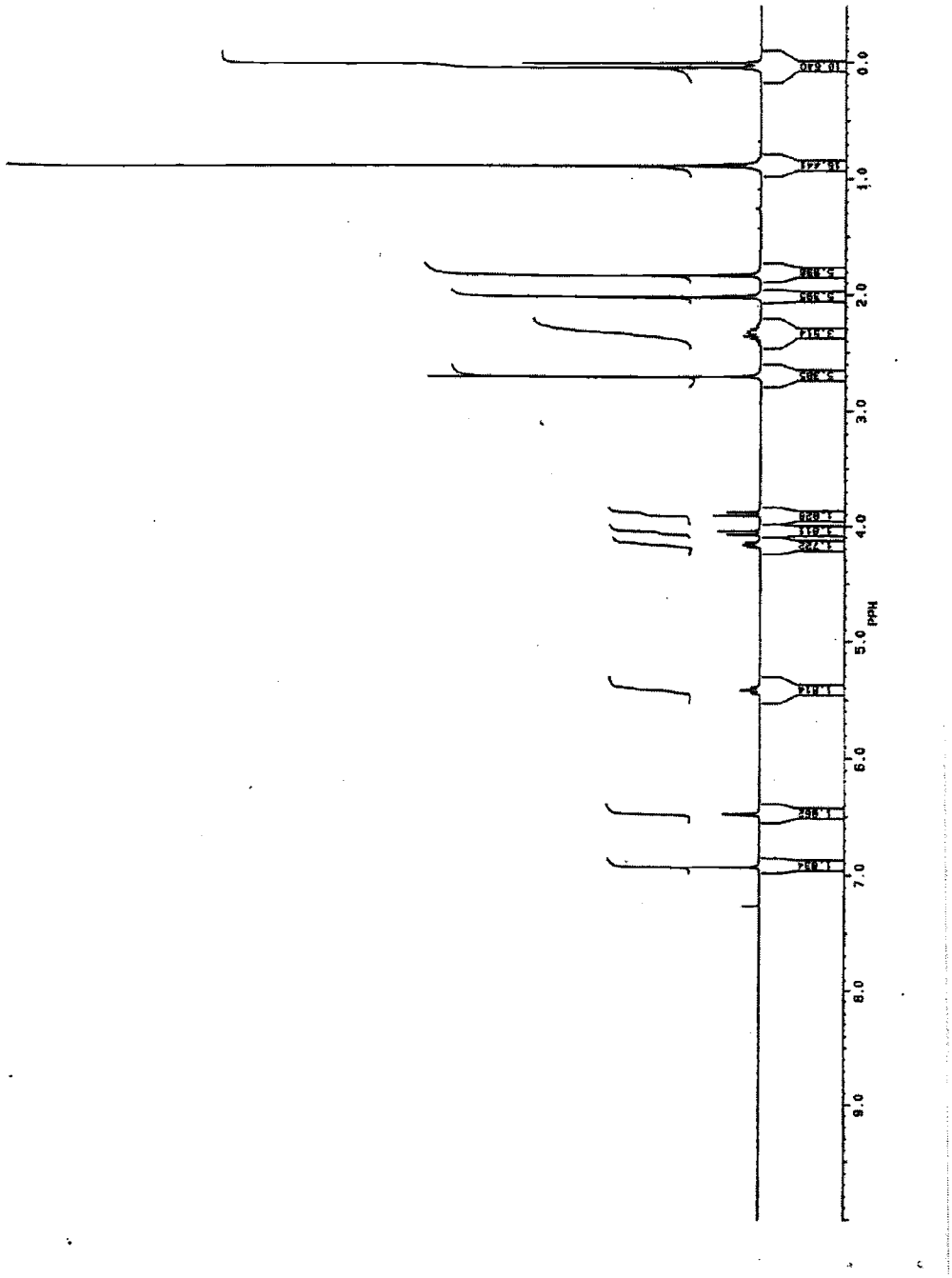
ppm
164.55
152.84
142.20
137.48
124.10
118.76
115.18
78.21
77.49
77.07
76.65
61.62
35.28
25.81
21.84
19.09
18.26
14.09
-4.74
-4.95
200
180
160
140
120
100
80
60
40
20
0



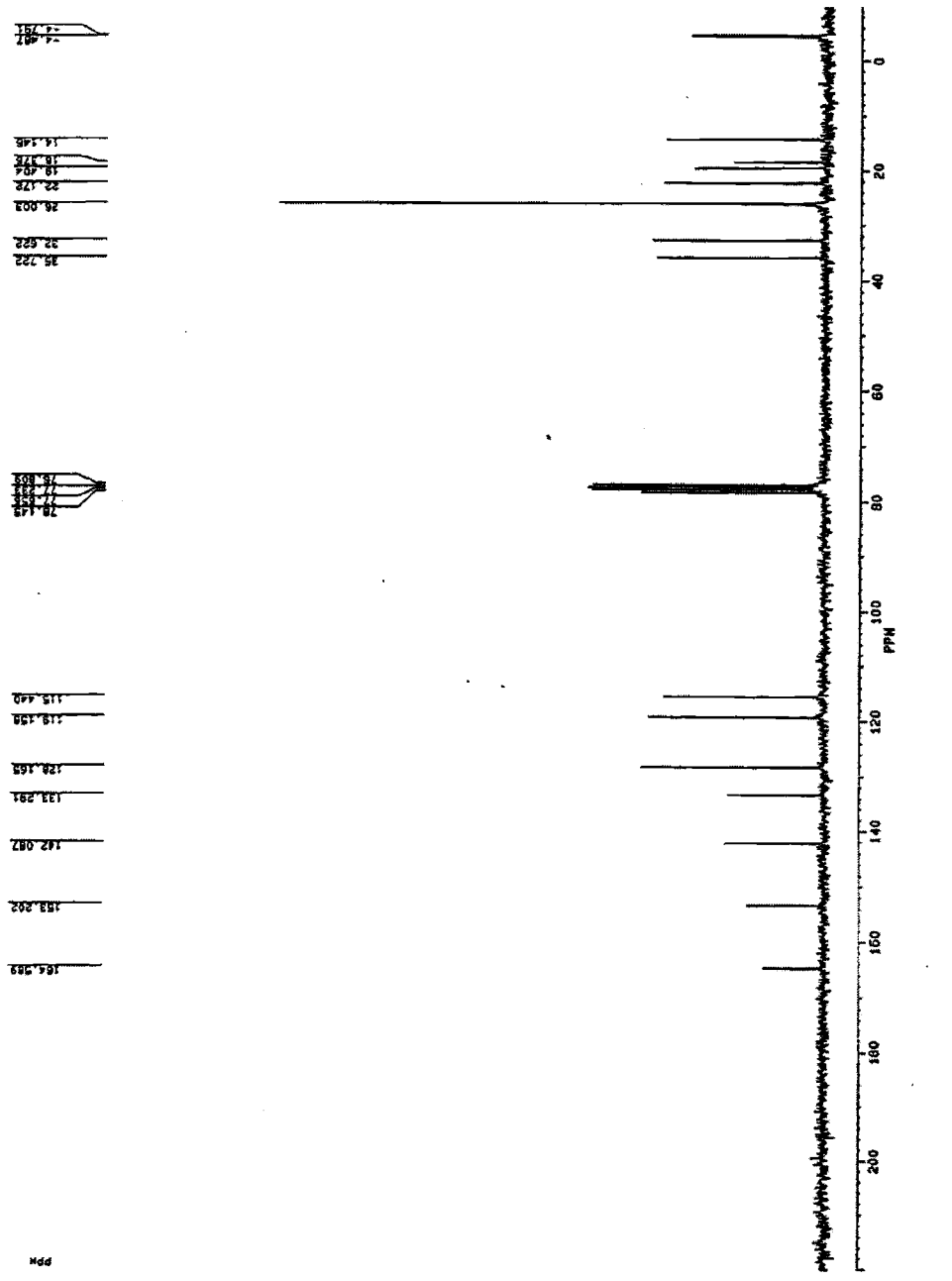
Alcohol 42



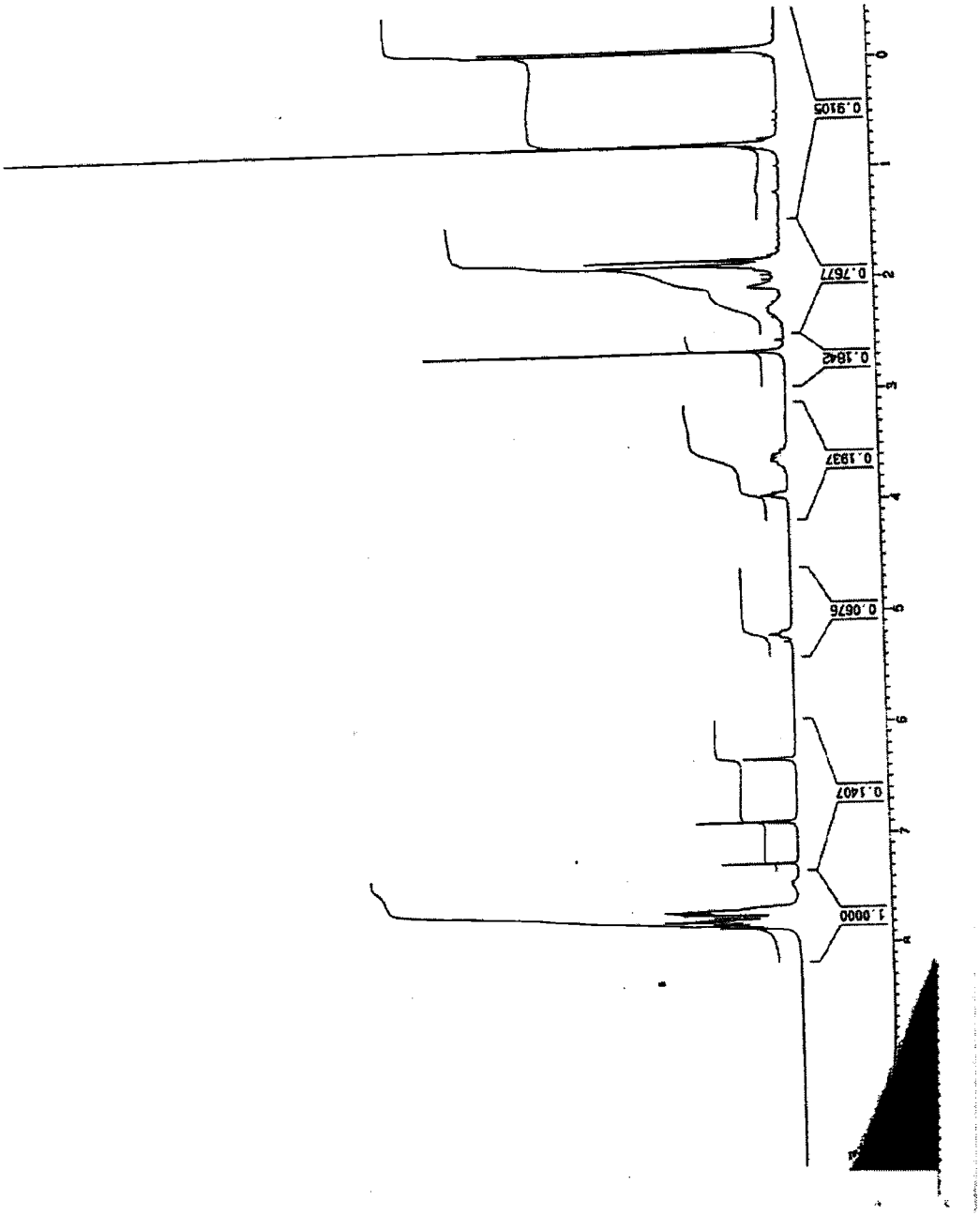
Alcohol
42



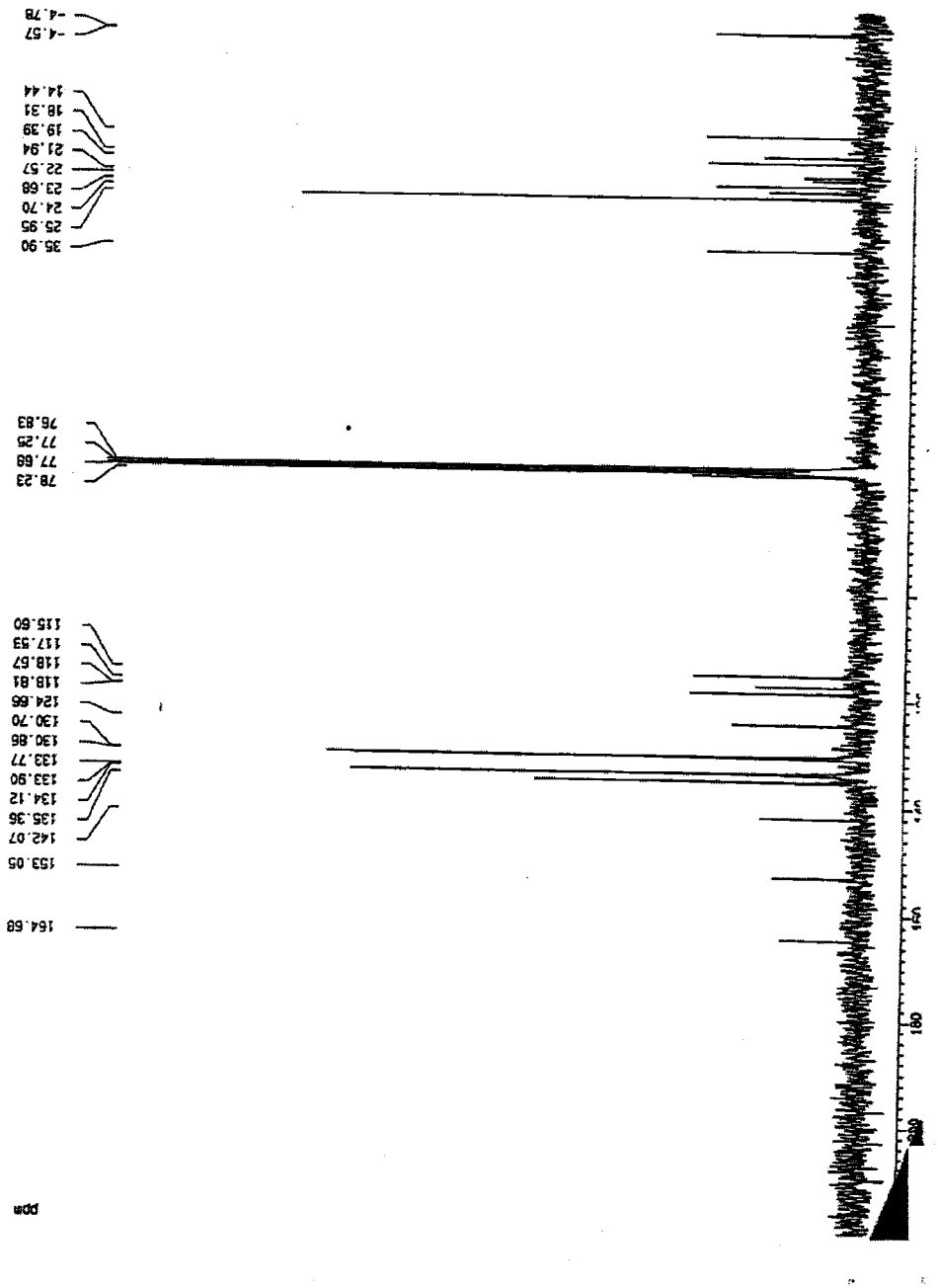
Bromide 43



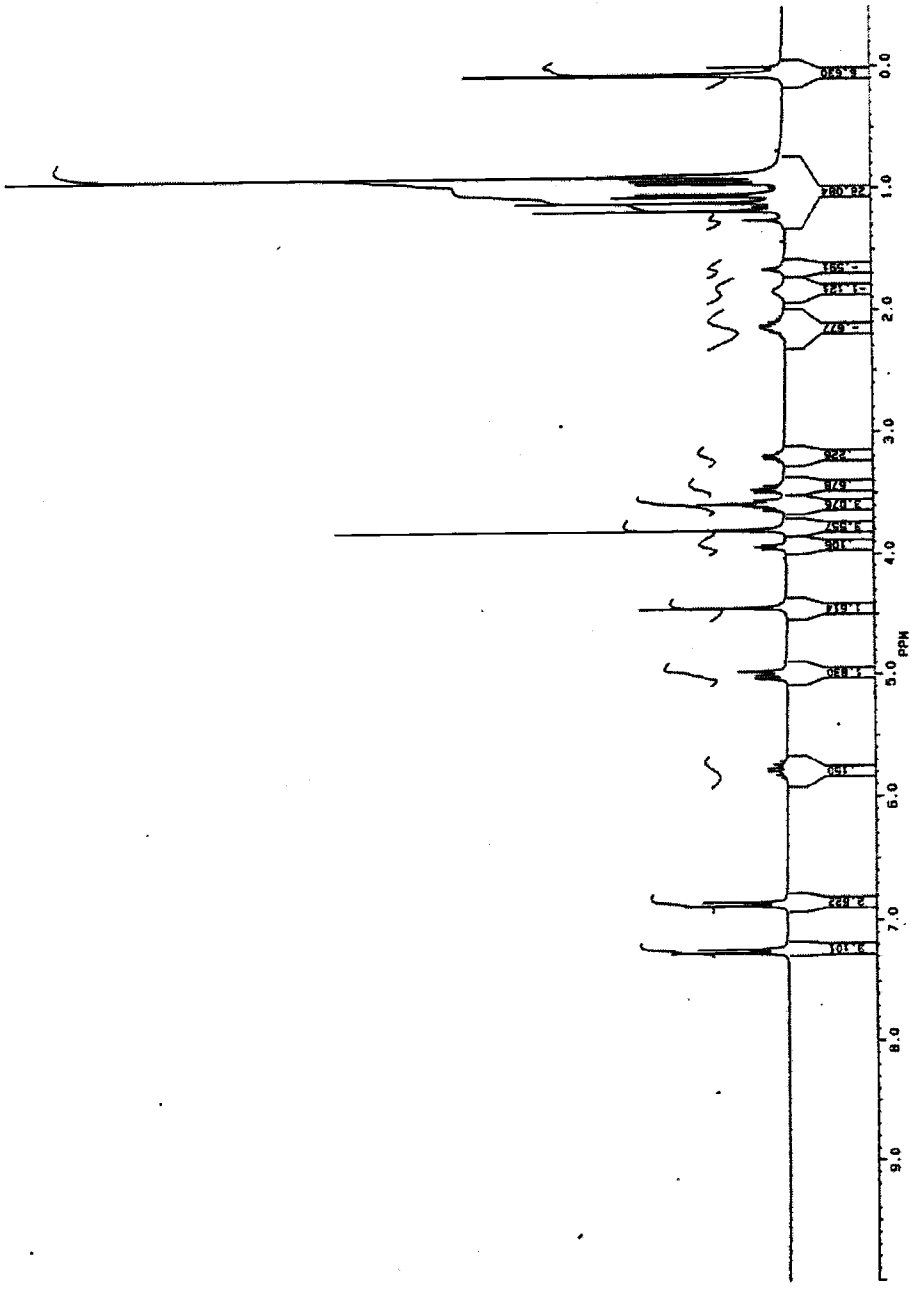
Bromide 43



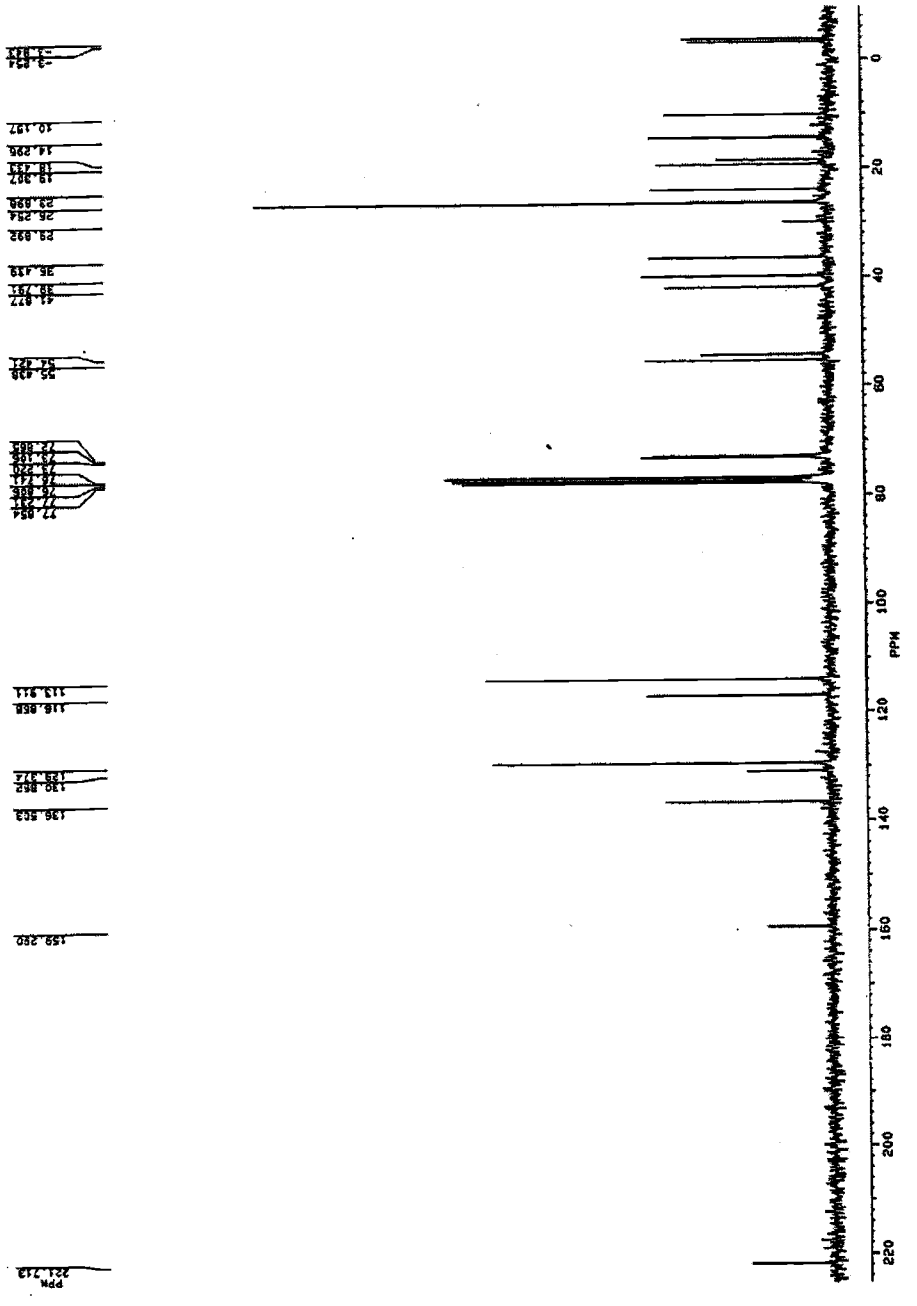
Phosphonium bromide 45



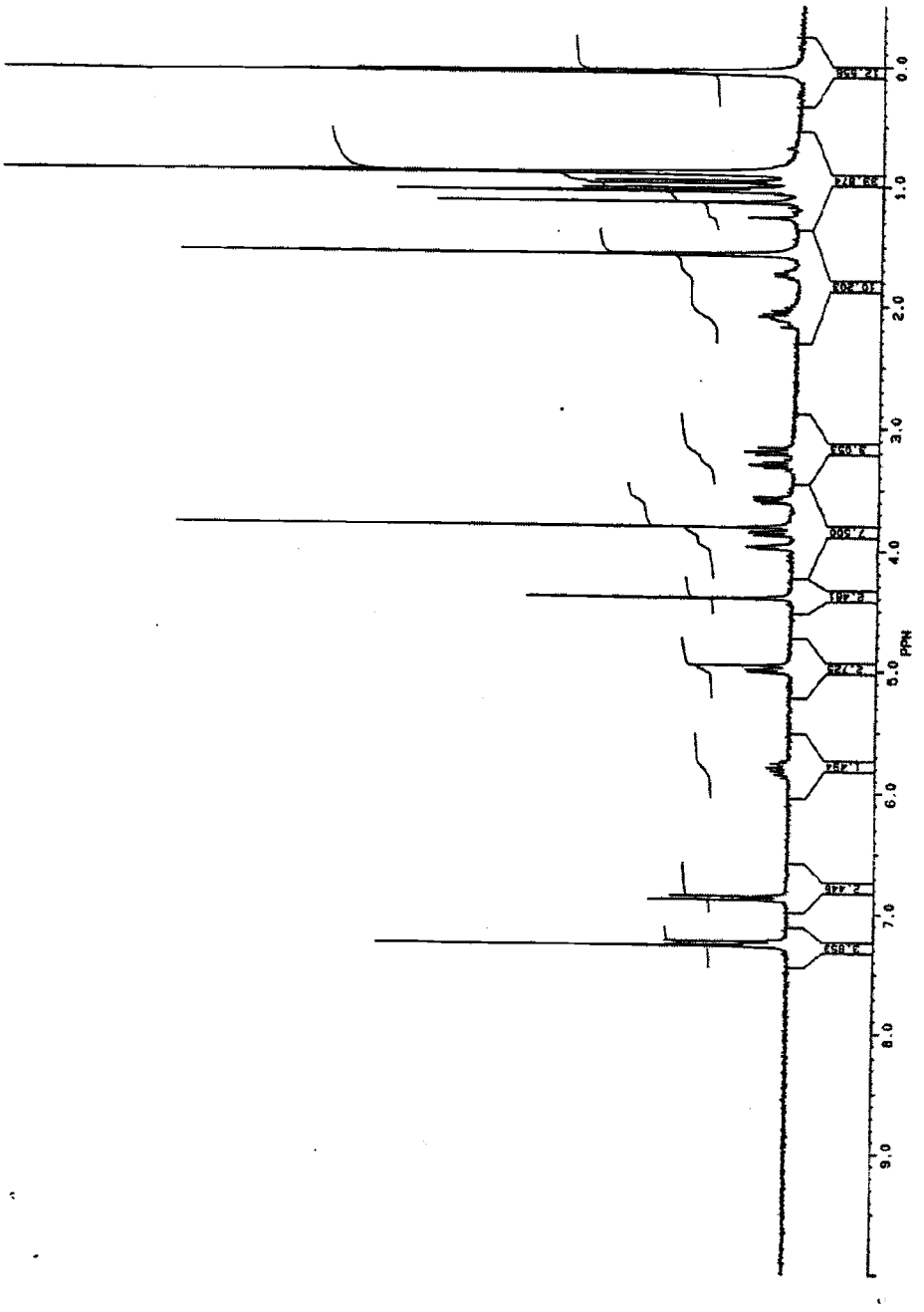
Phosphonium bromide
45



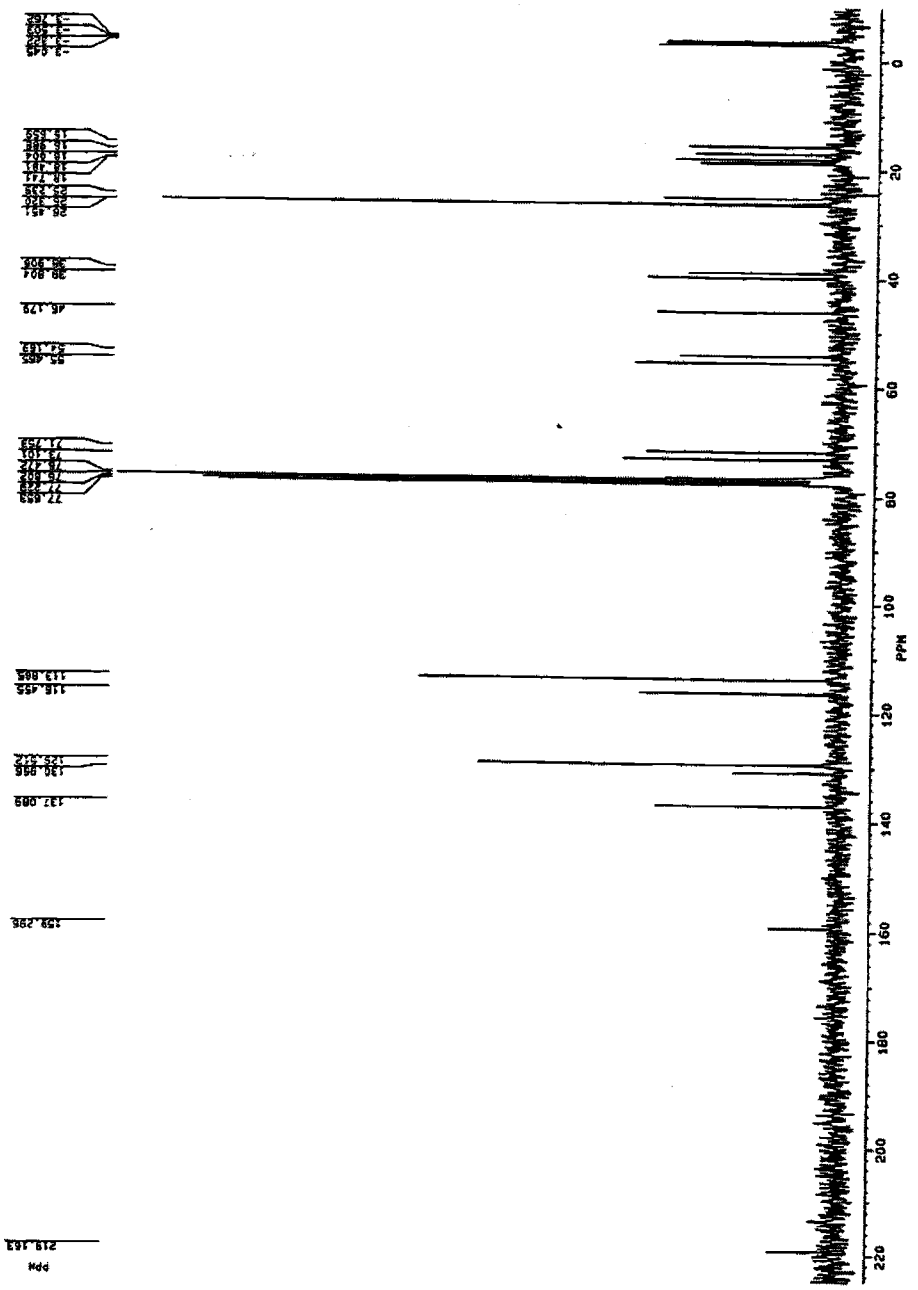
Alcohol 56



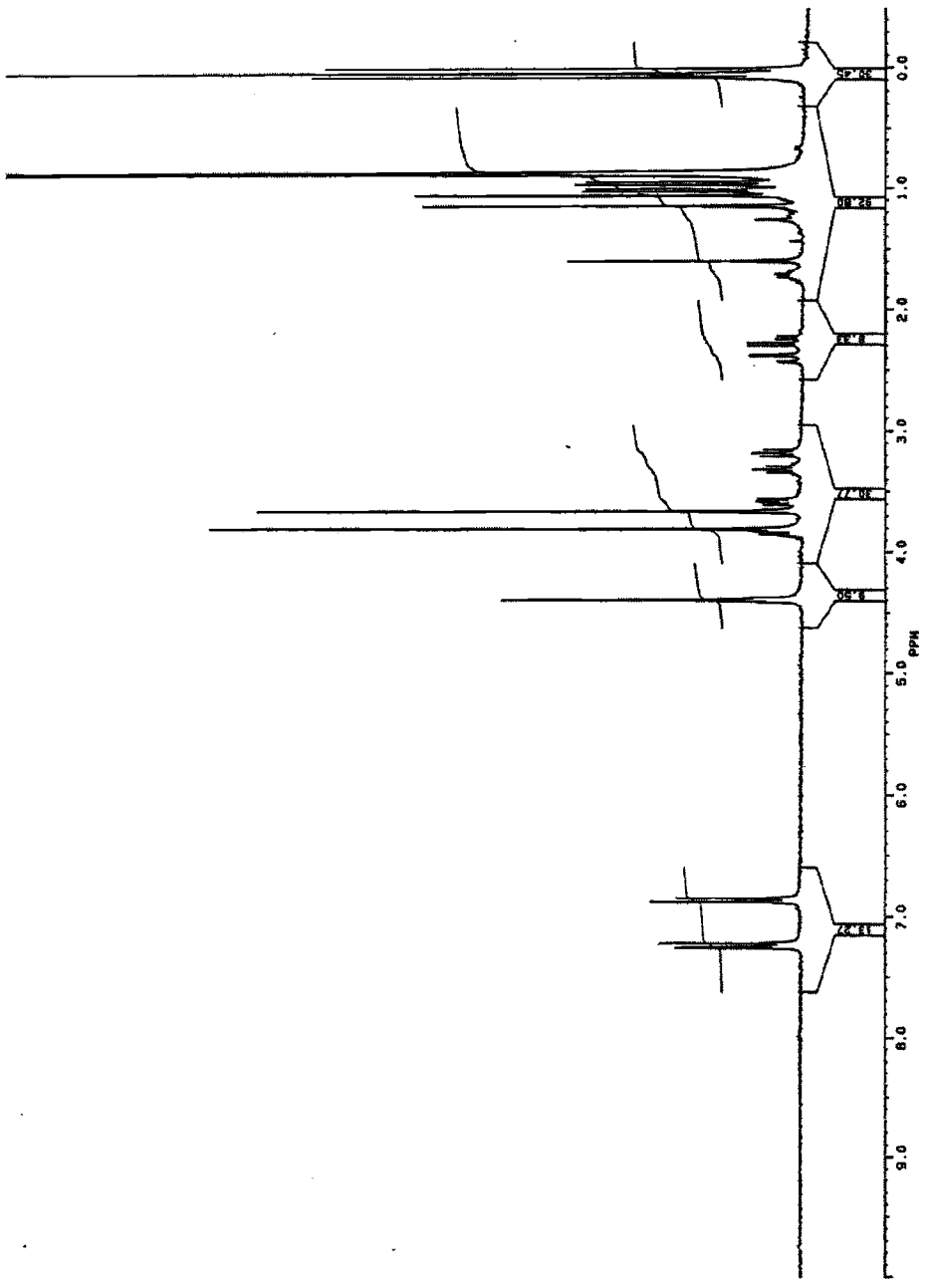
Alcohol 56



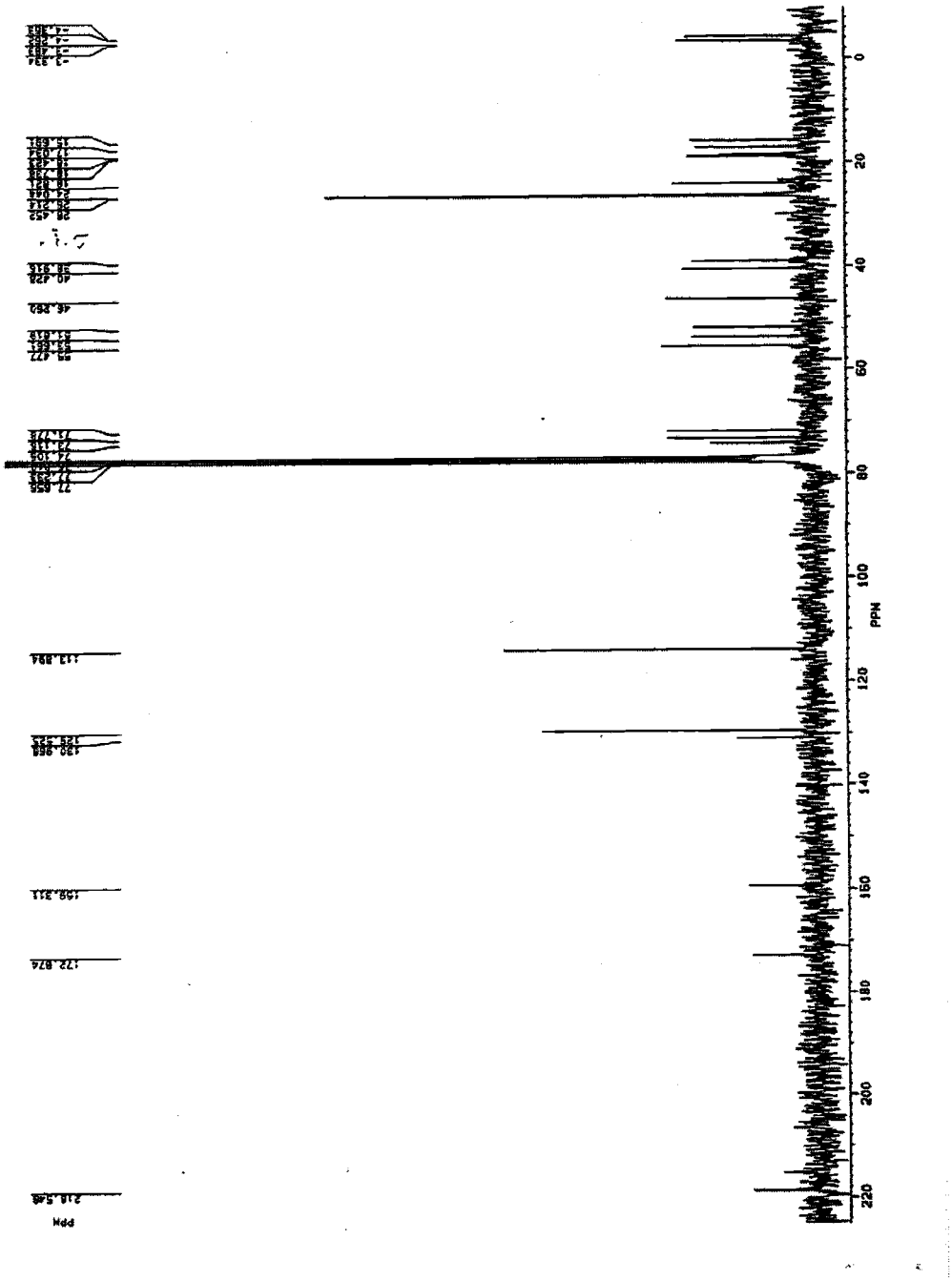
Trisether 57



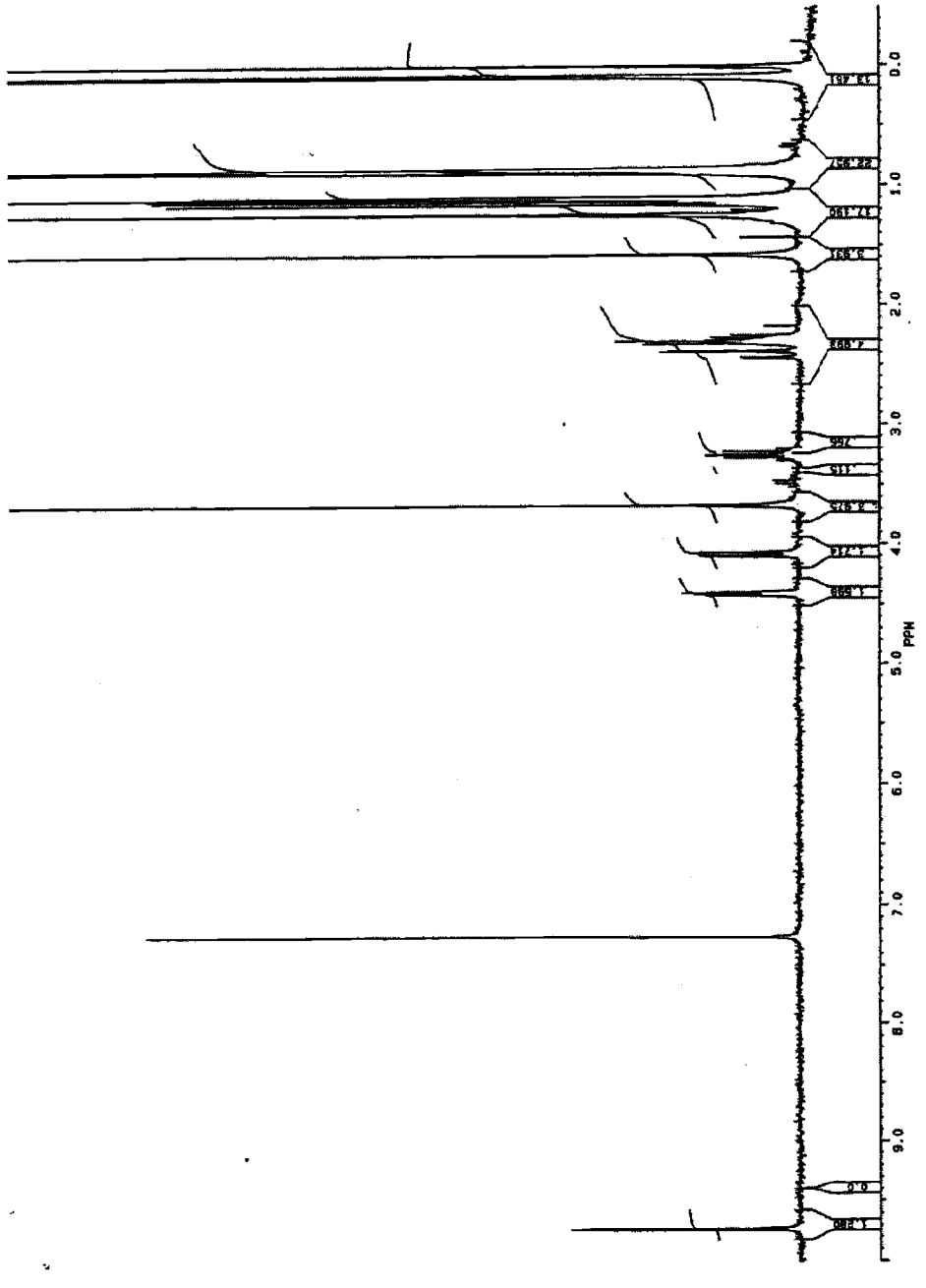
Trisether 57



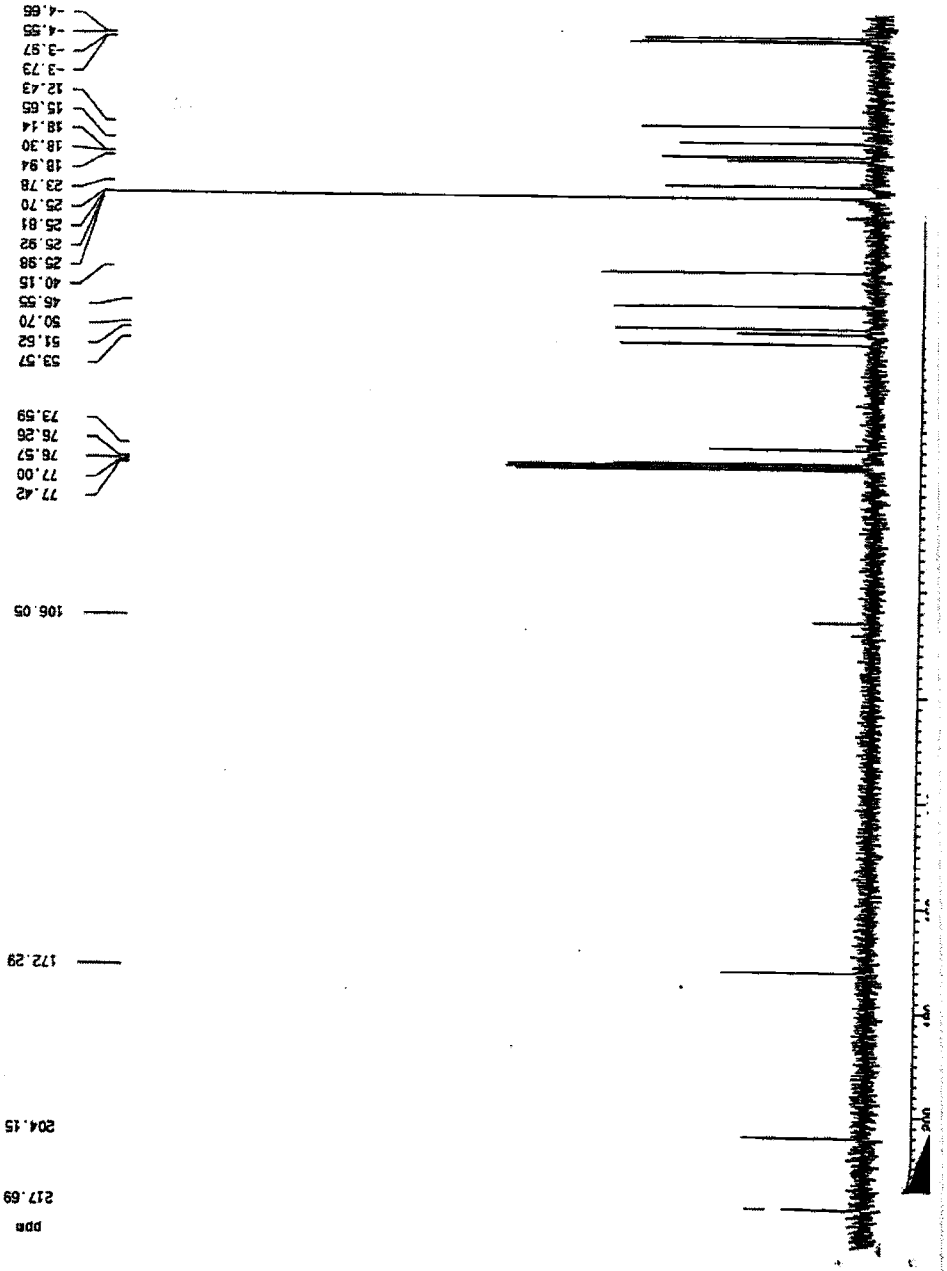
Methyl ester 58



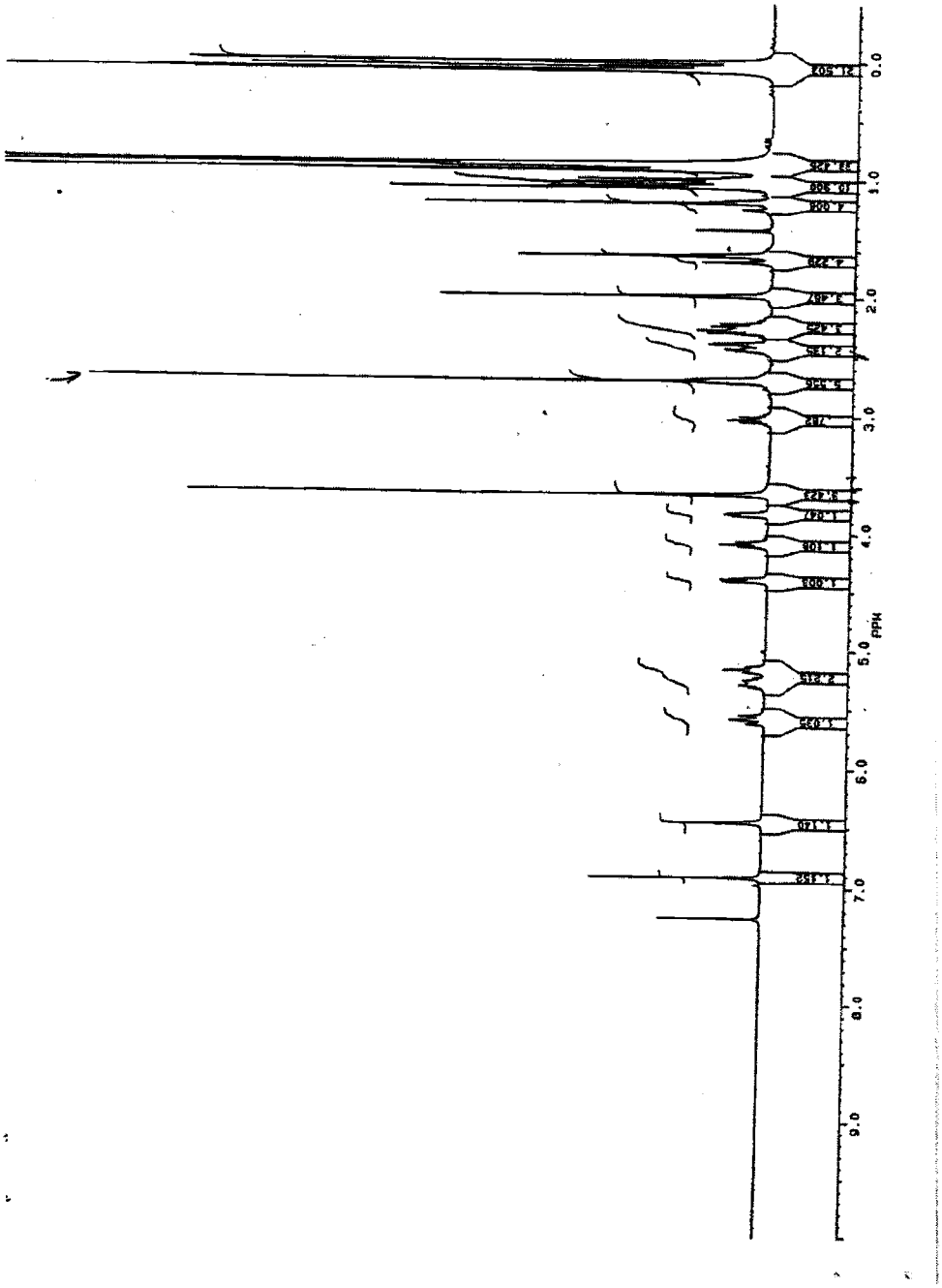
Methyl ester 58



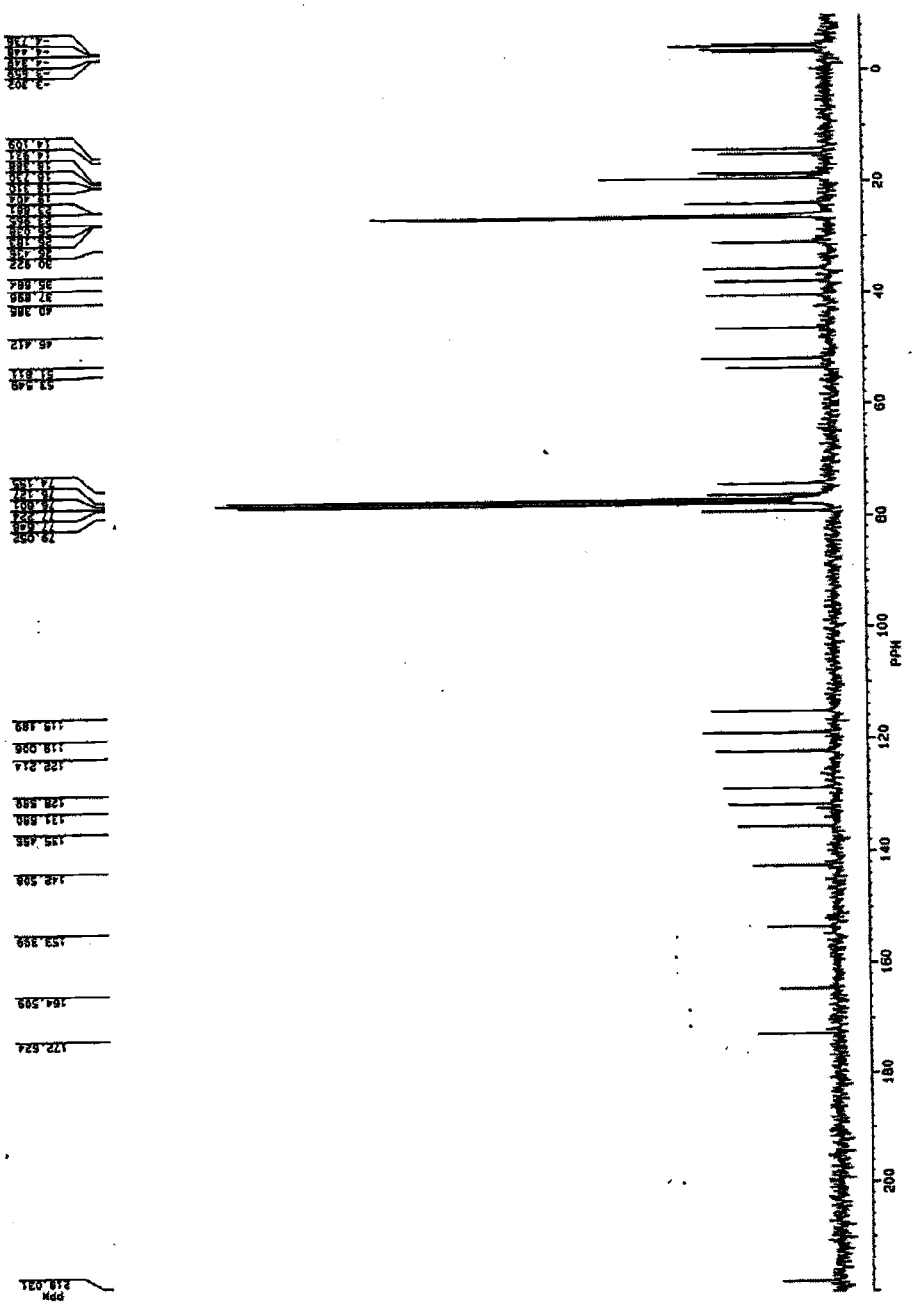
Aldehyde 60


-4.65
-4.55
-3.97
-3.73
12.43
15.65
18.14
18.30
18.94
23.78
25.70
25.81
25.92
25.98
40.15
46.55
50.70
51.62
53.57
73.59
76.26
76.57
77.00
77.42
106.05
172.29
204.15
217.69
ppm

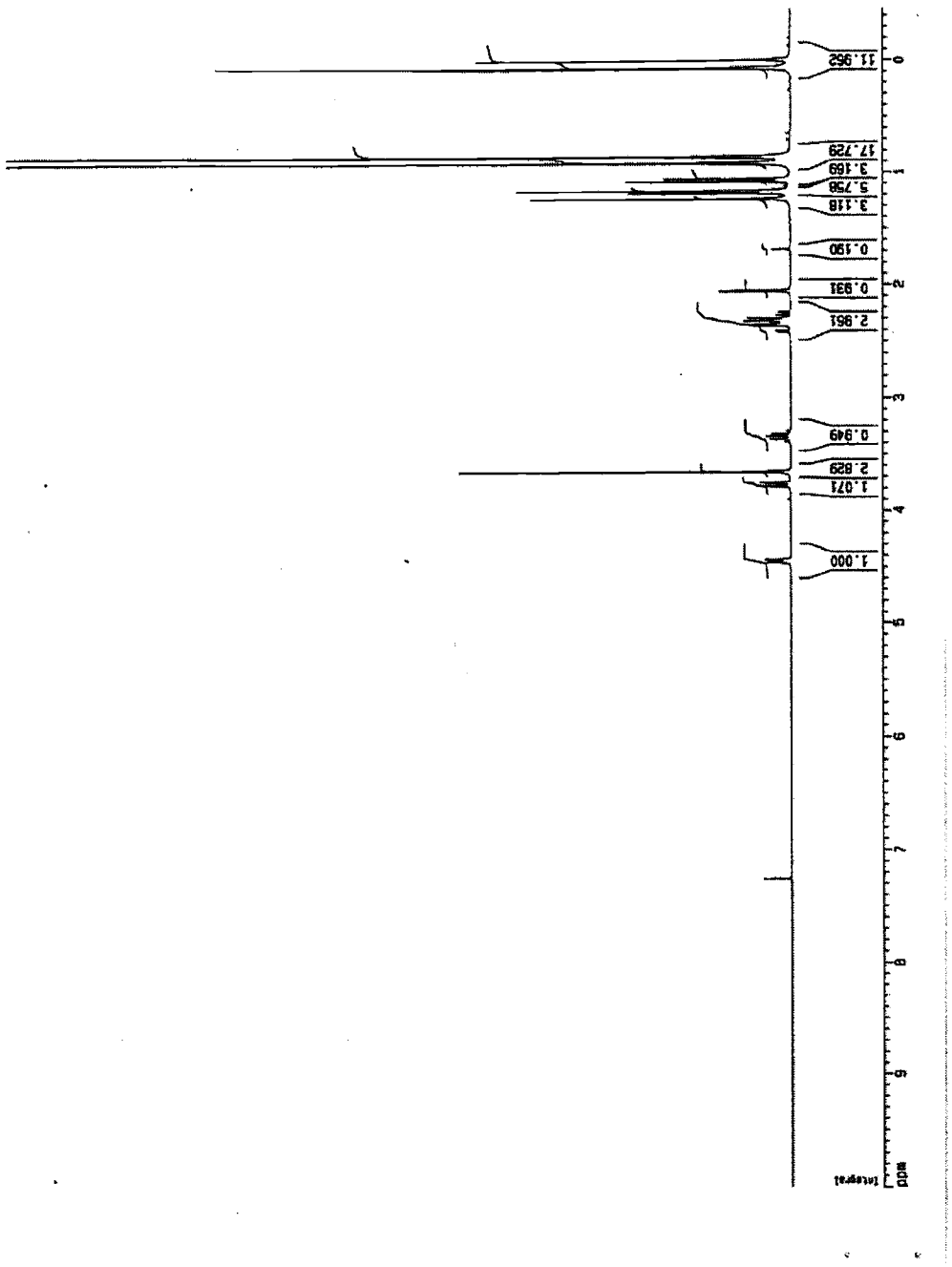
Aldehyde 60



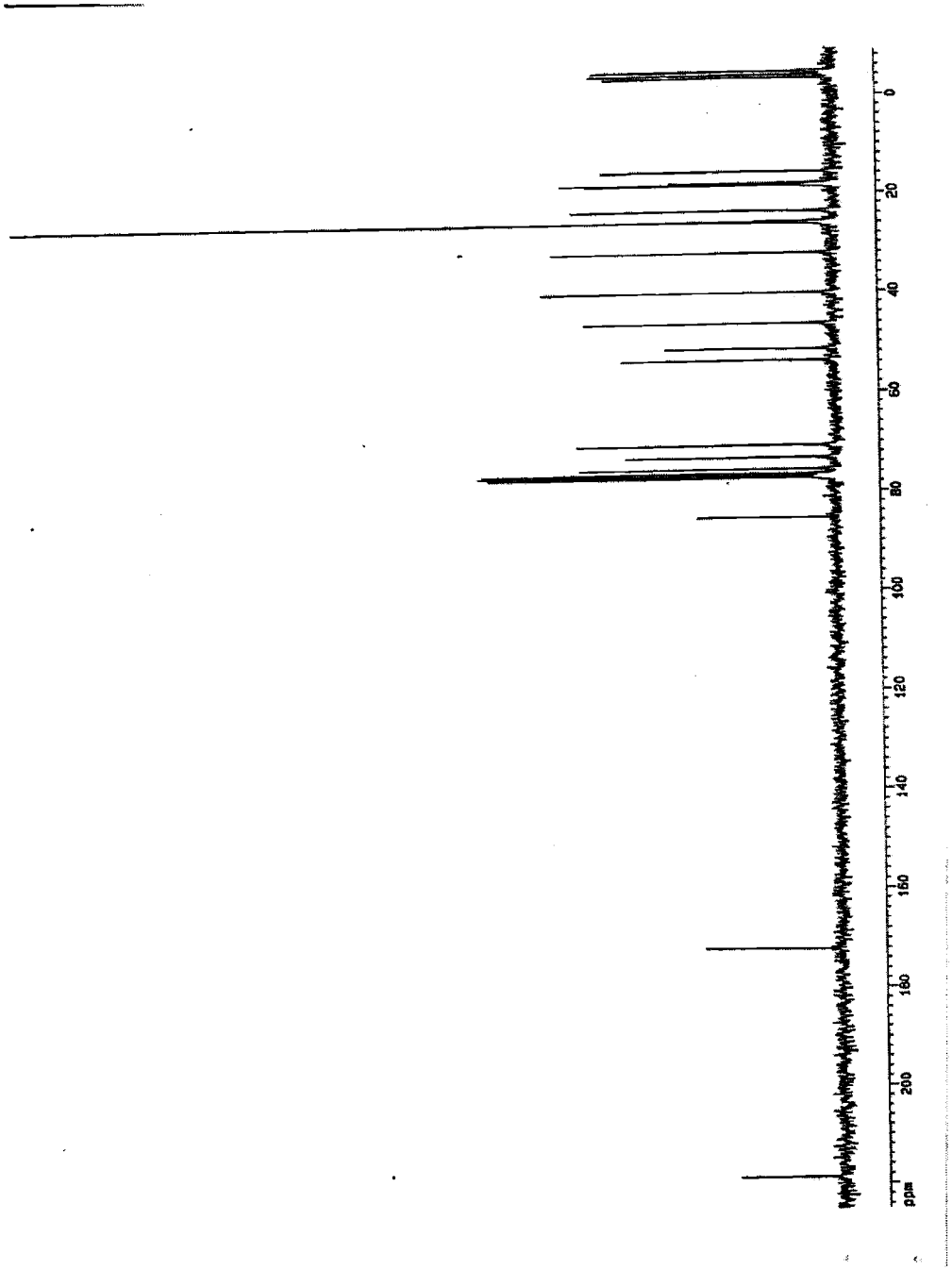
Triene 61



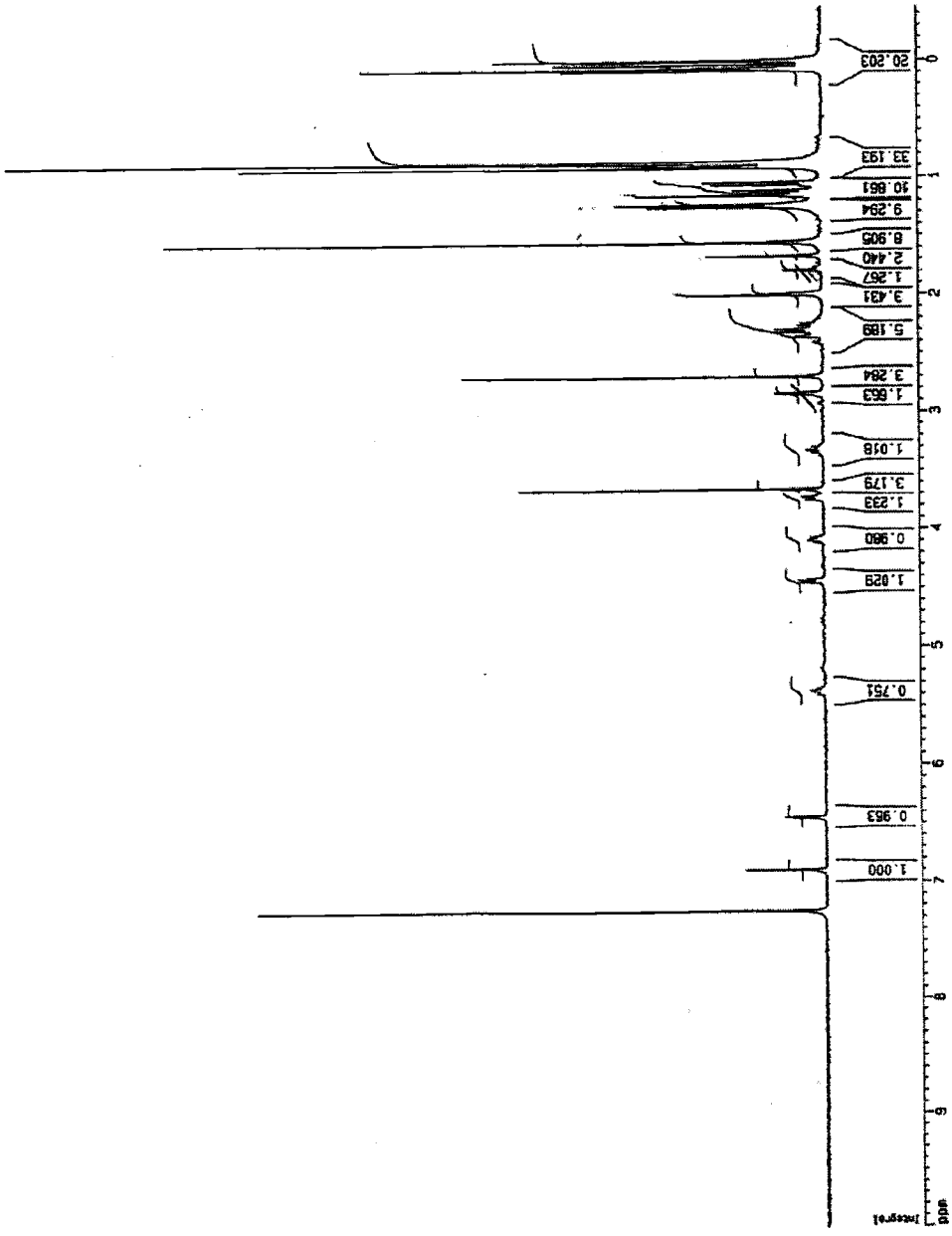
Triene 61


11.962
17.729
3.169
5.758
3.118
0.190
0.931
2.861
0.949
2.829
1.071
1.000
ppm

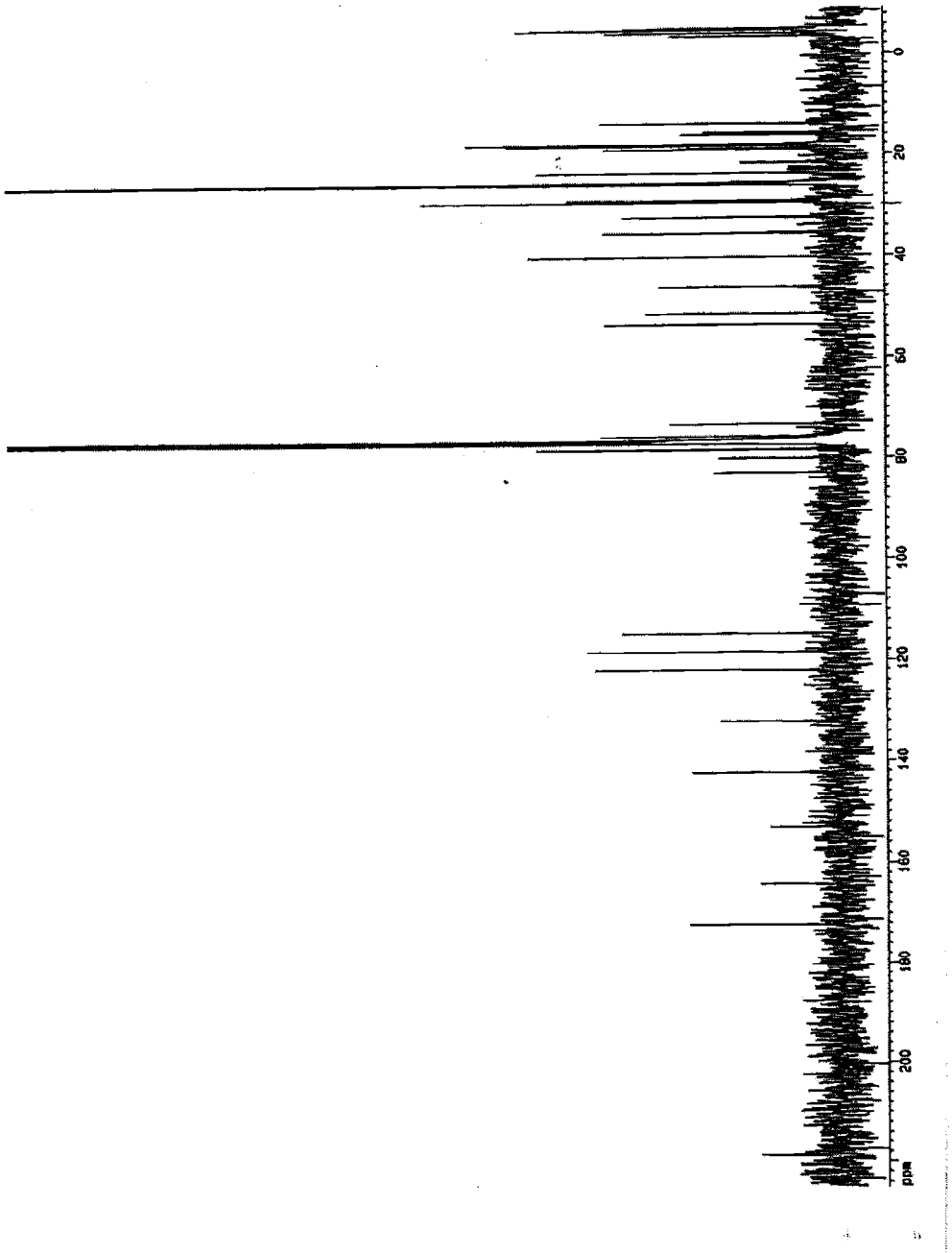
Alkyne 62



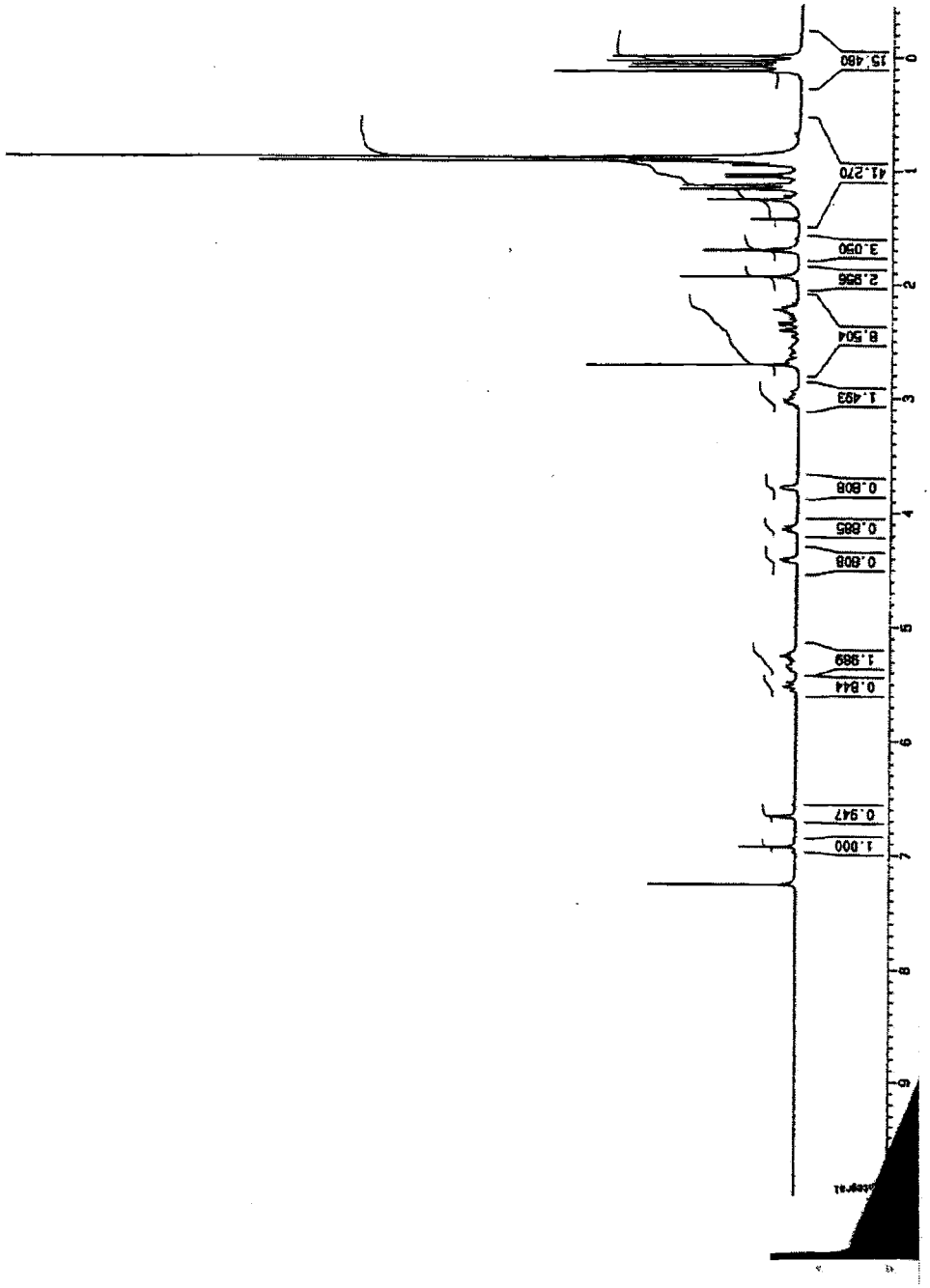
Alkyne 62


20.203
33.193
10.861
9.294
8.905
2.440
1.267
3.431
5.189
3.264
1.863
1.018
3.179
1.233
0.960
1.029
0.751
0.963
1.000
ppm

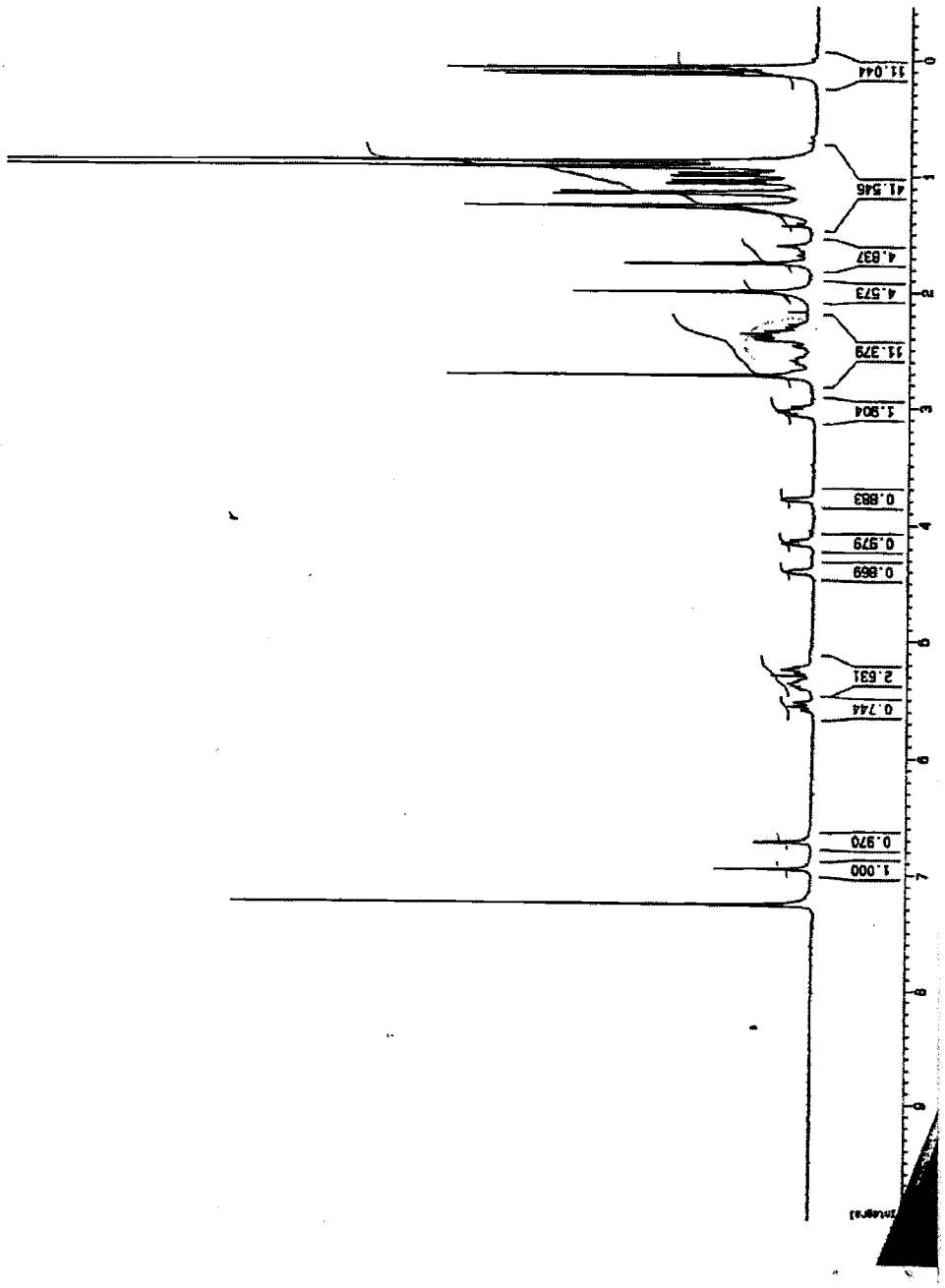
Enyne 63



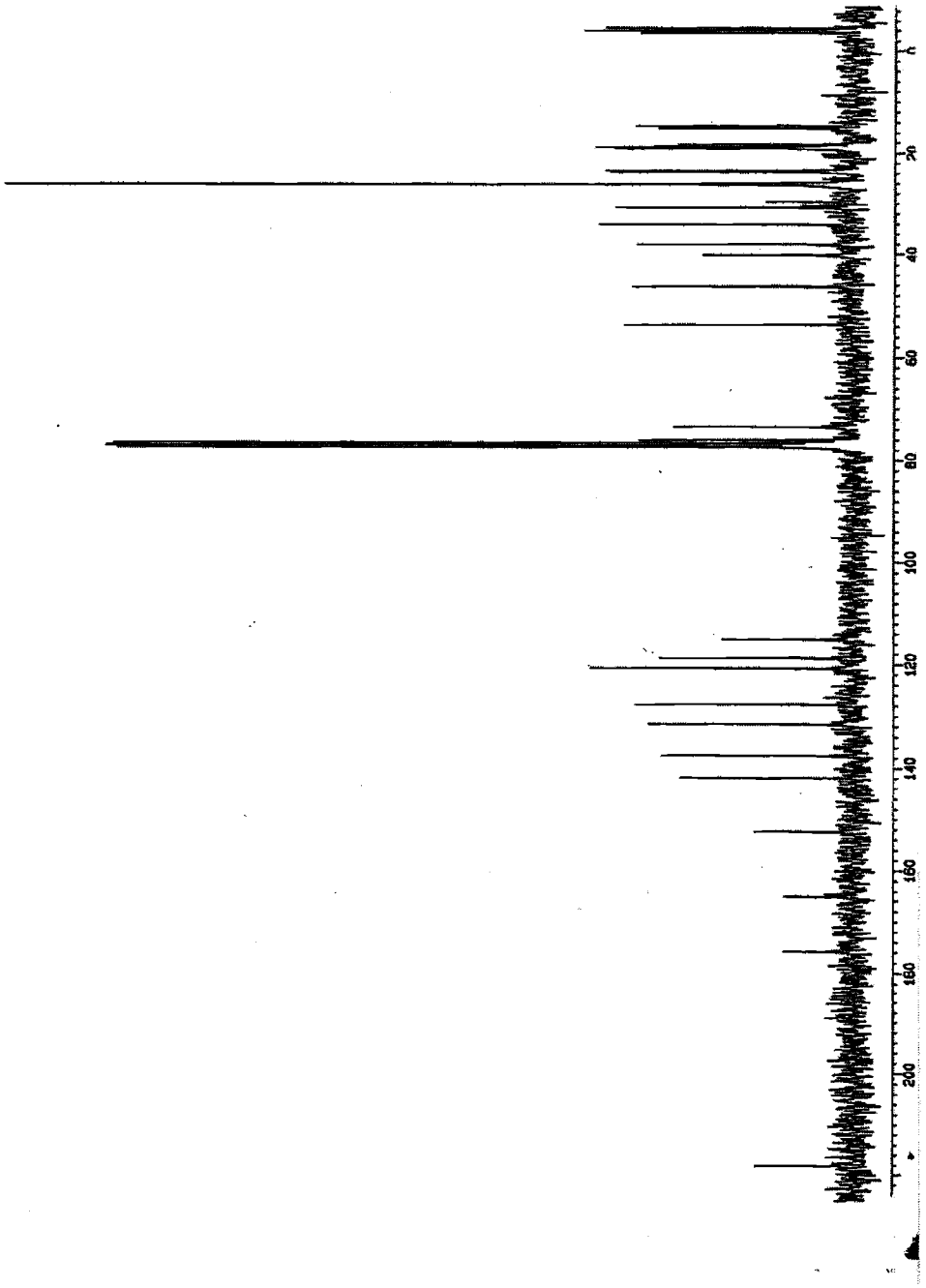
Enyne 63



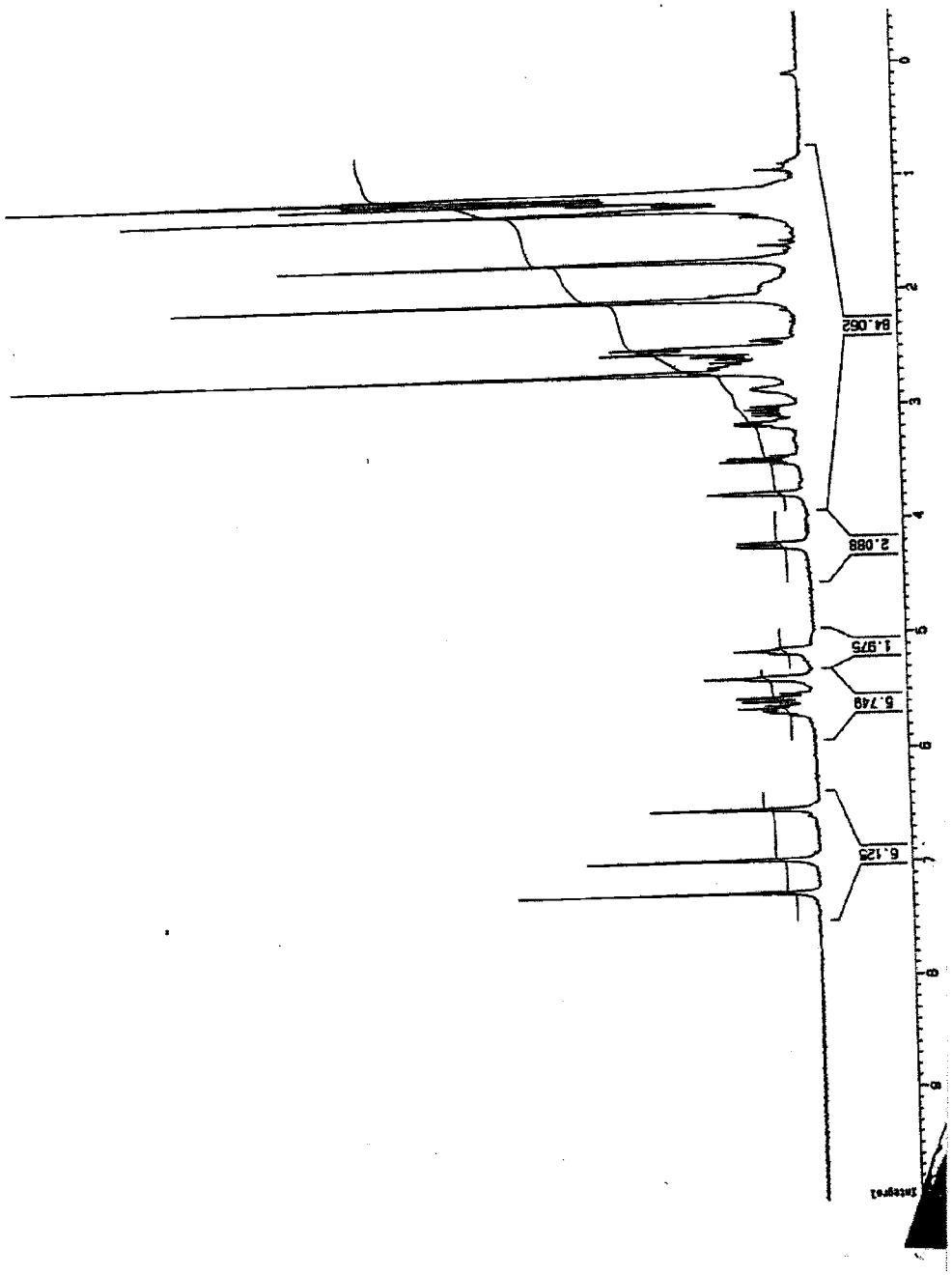
Carboxylic acid 65



Hydroxy acid 66

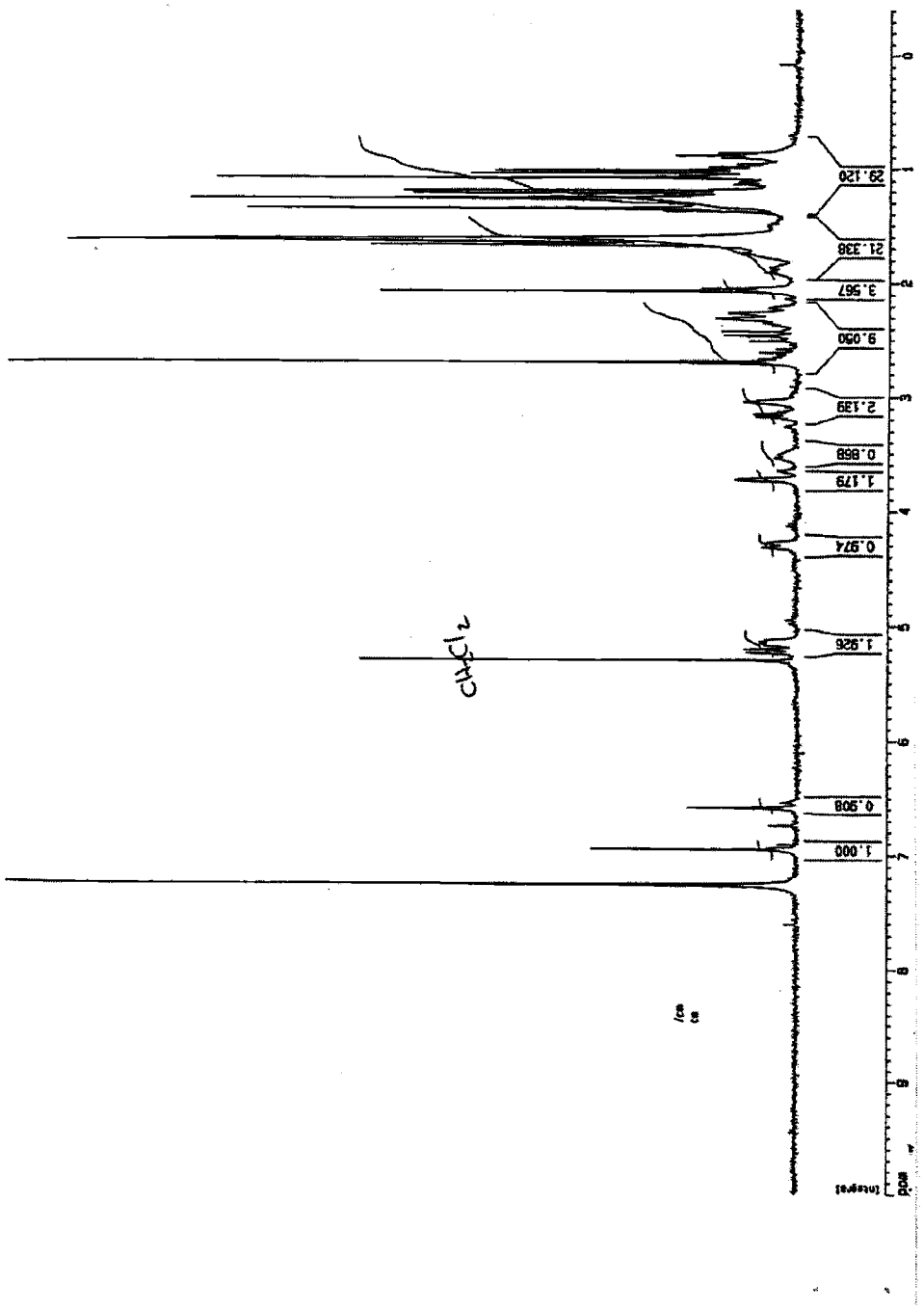


Hydroxy acid 66

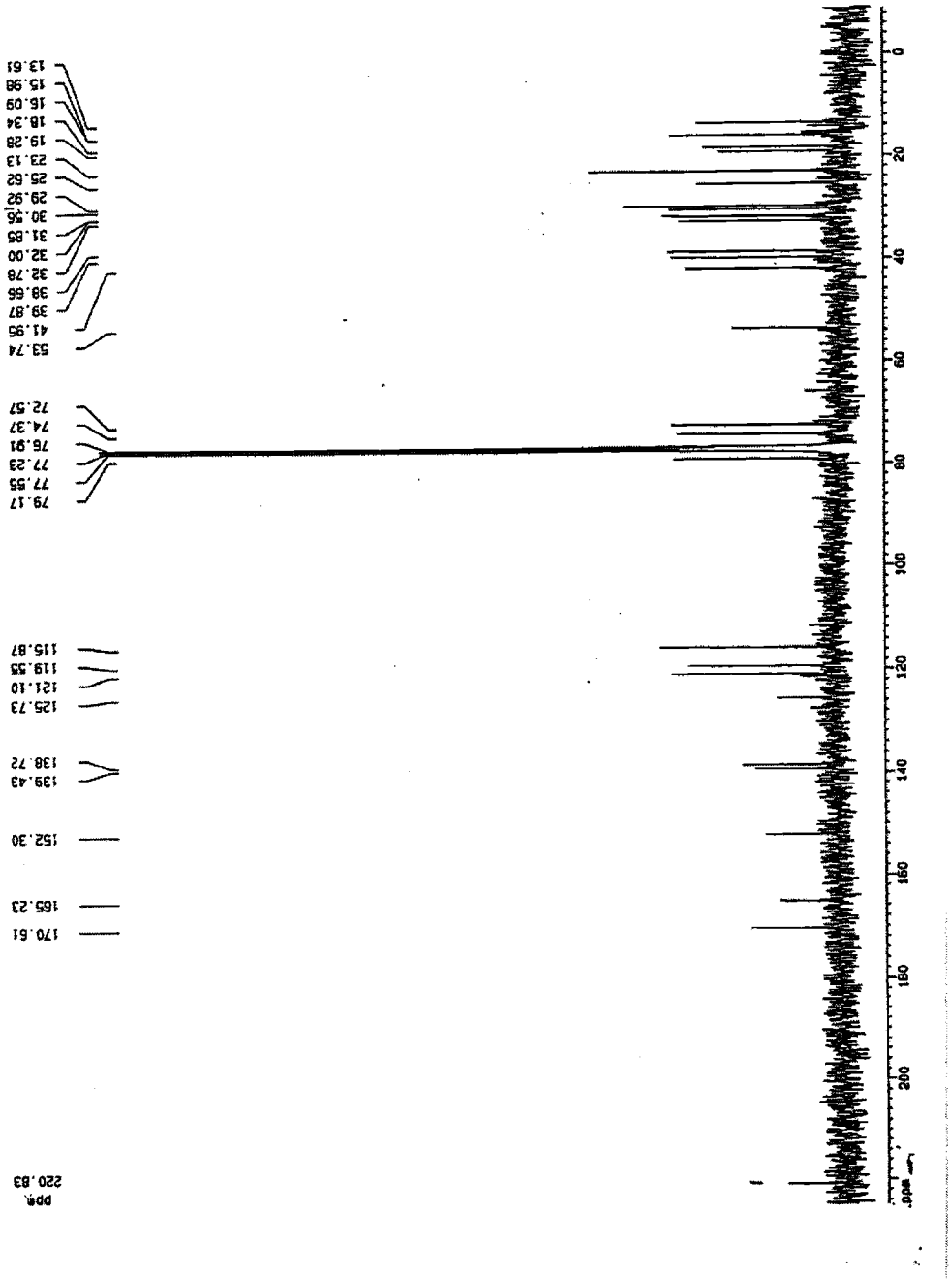


***cis*-9,10-dehydroepothilone D (68):**

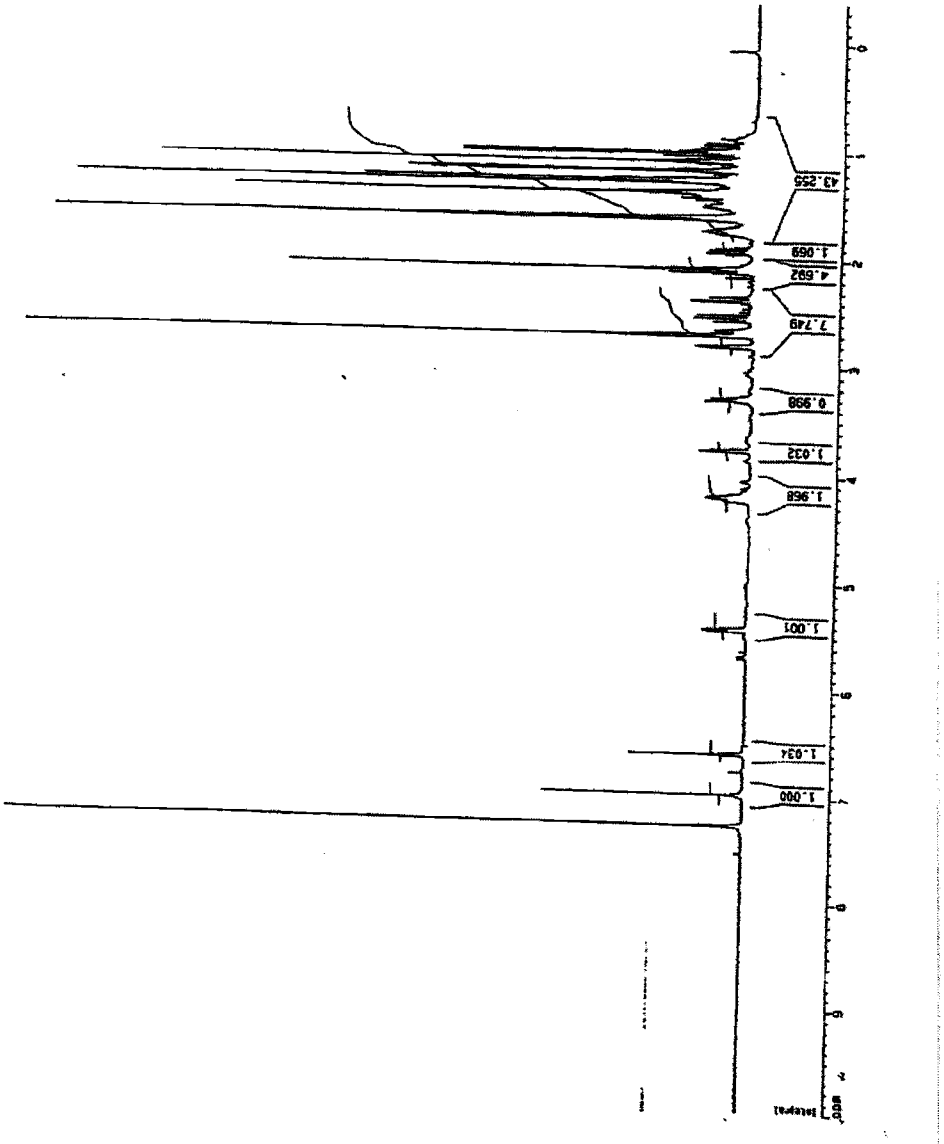
cis-9,10-dehydroepothilone D (68):



Epothilone D (2):



Epothilone D (2):

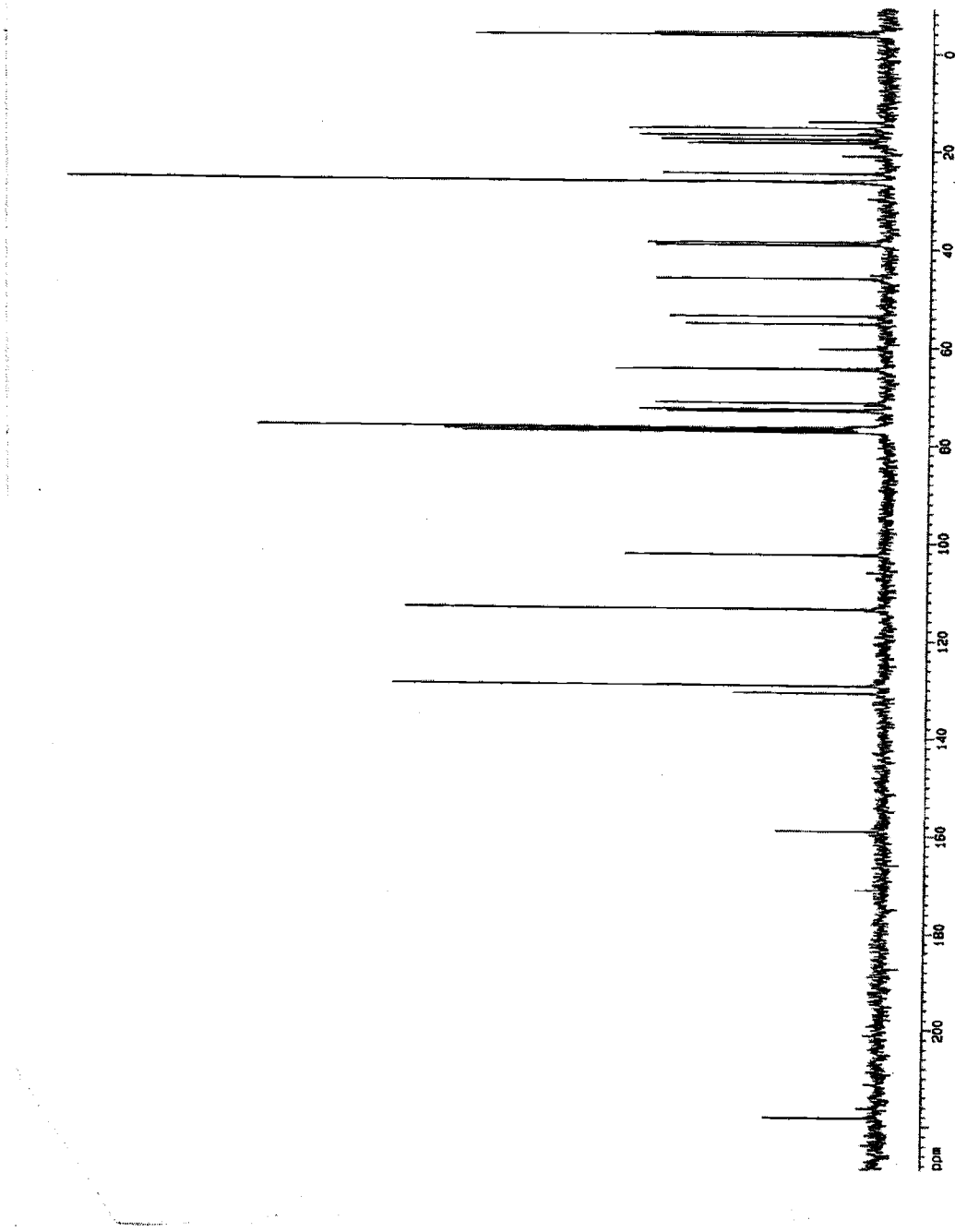


Epothilone B (1)

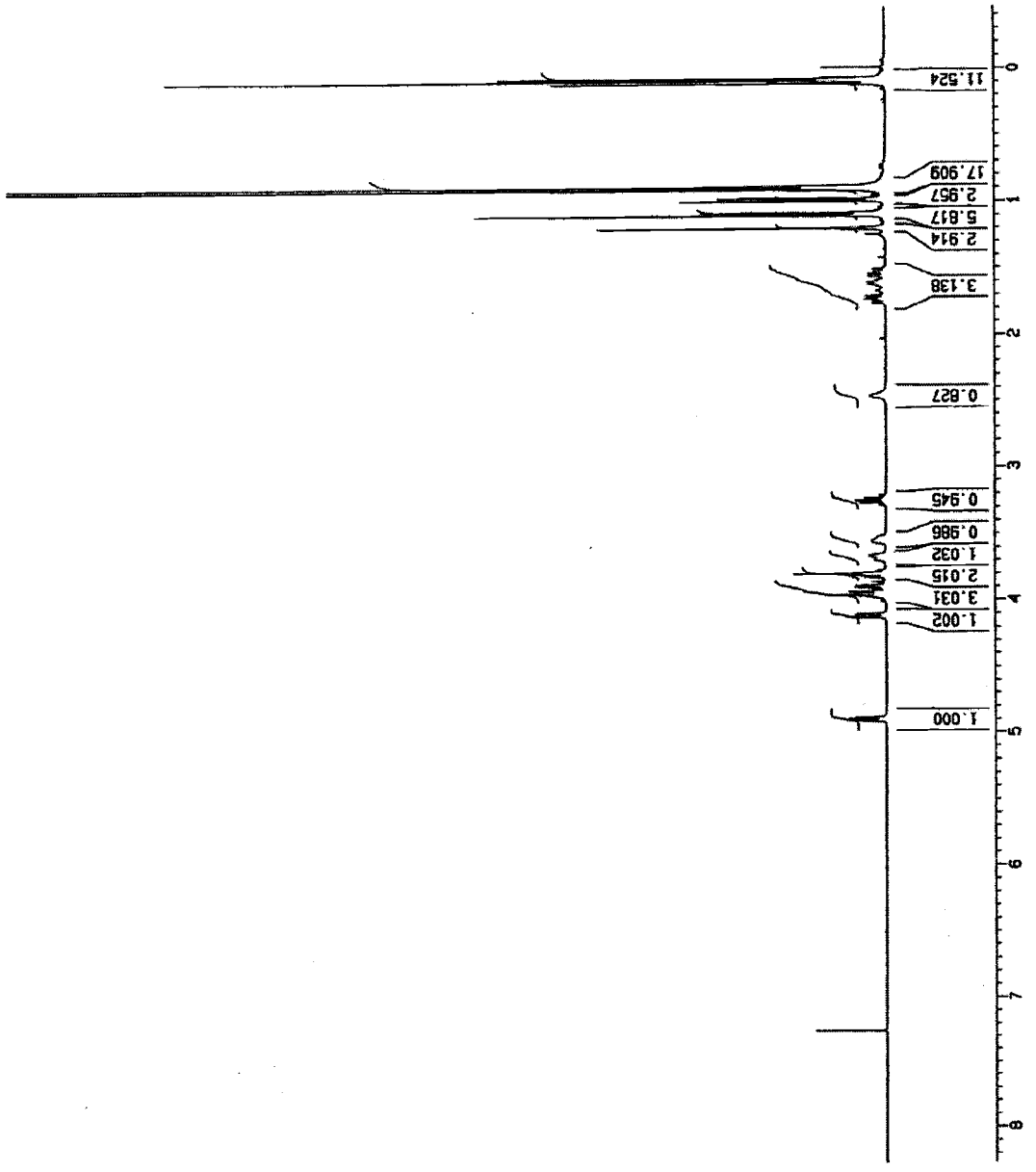
Epothilone B (1)

Acetal 71

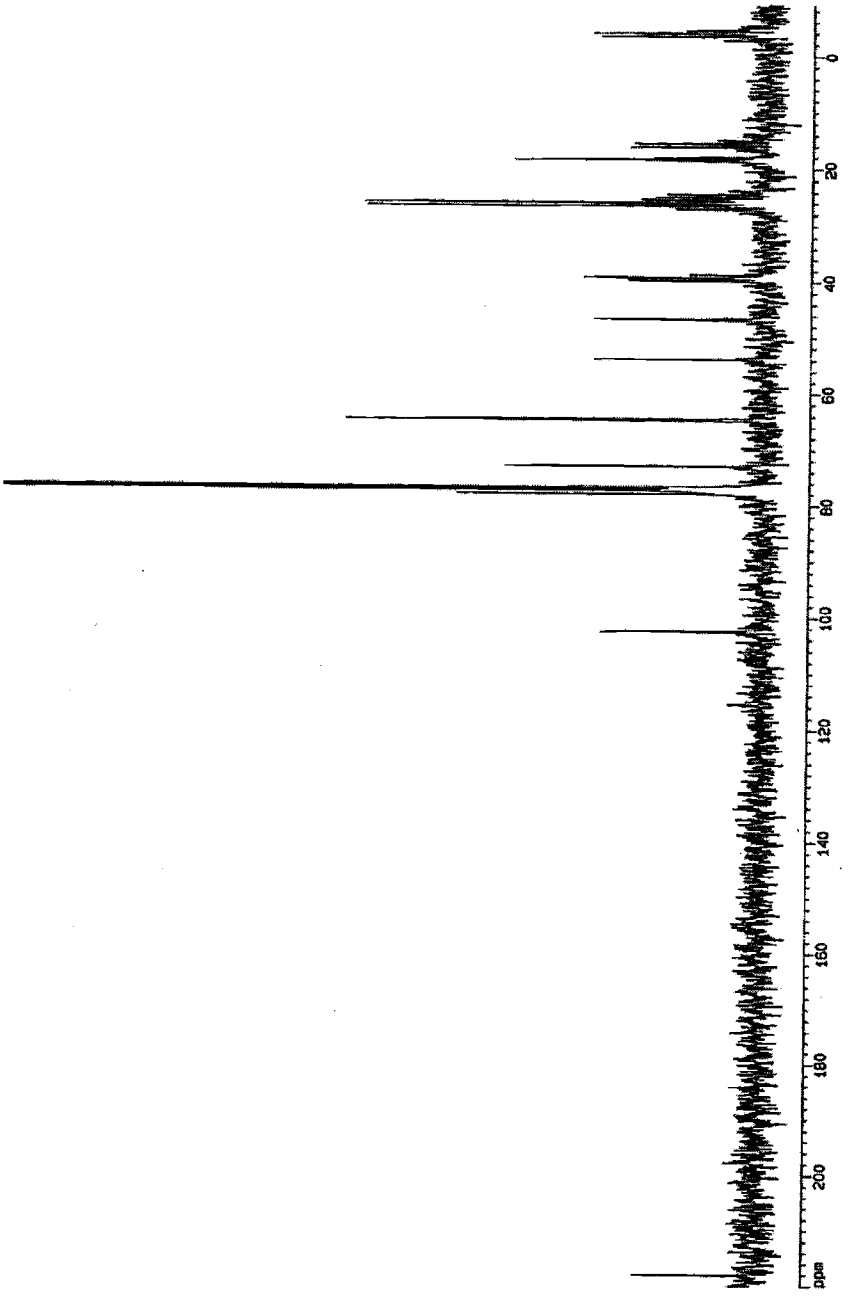
H2O
2.167
1.997
1.000
2.054
1.876
8.343
0.985
1.012
0.962
1.466
2.257
1.033
2.078
3.248
27.782
12.362
8
7
6
5
4
3
2
1
0



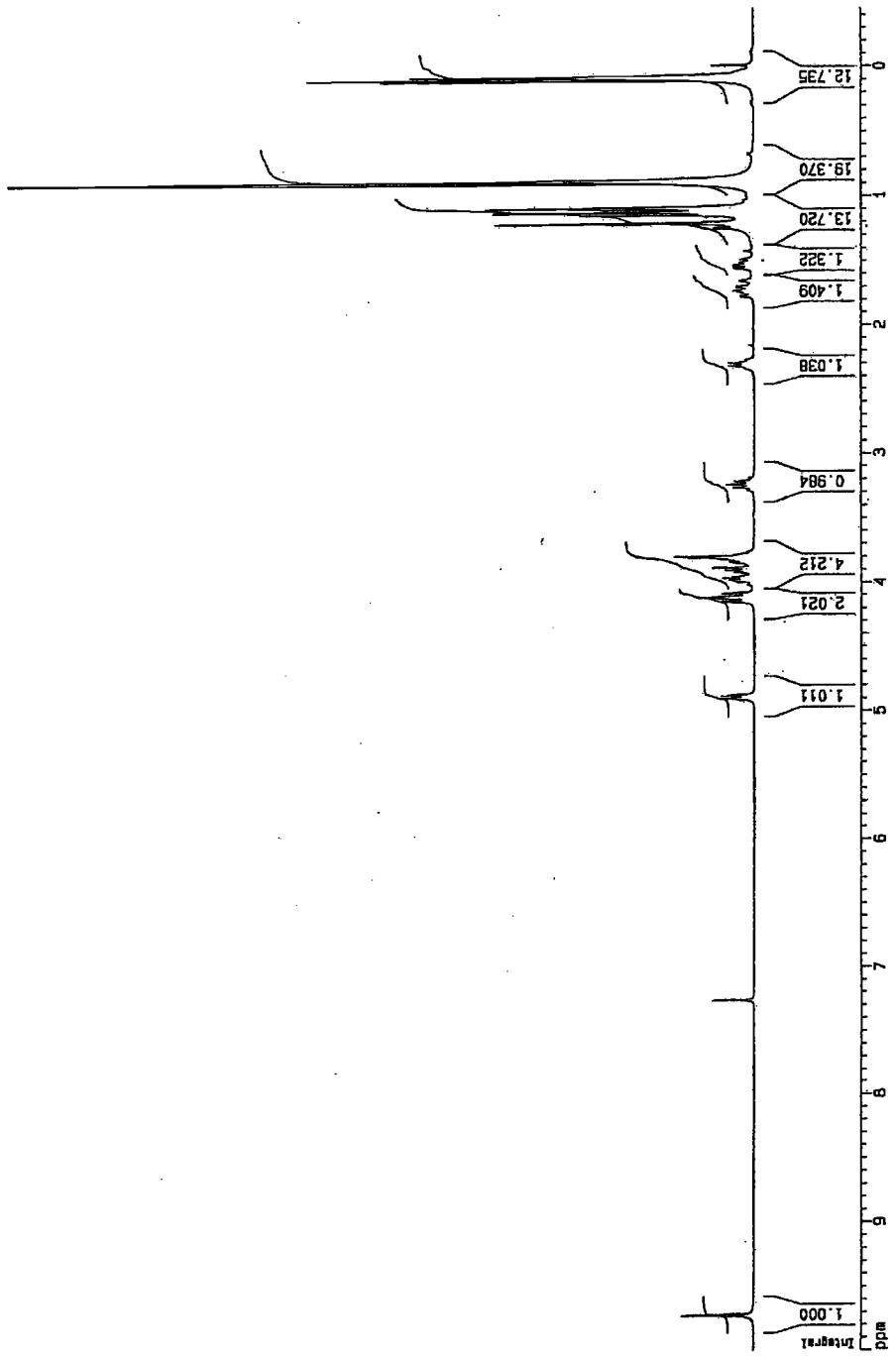
Acetal 71


11.524
17.909
2.957
5.817
2.914
3.138
0.827
0.945
0.986
1.032
2.015
3.031
1.002
1.000
0
1
2
3
4
5
6
7
8

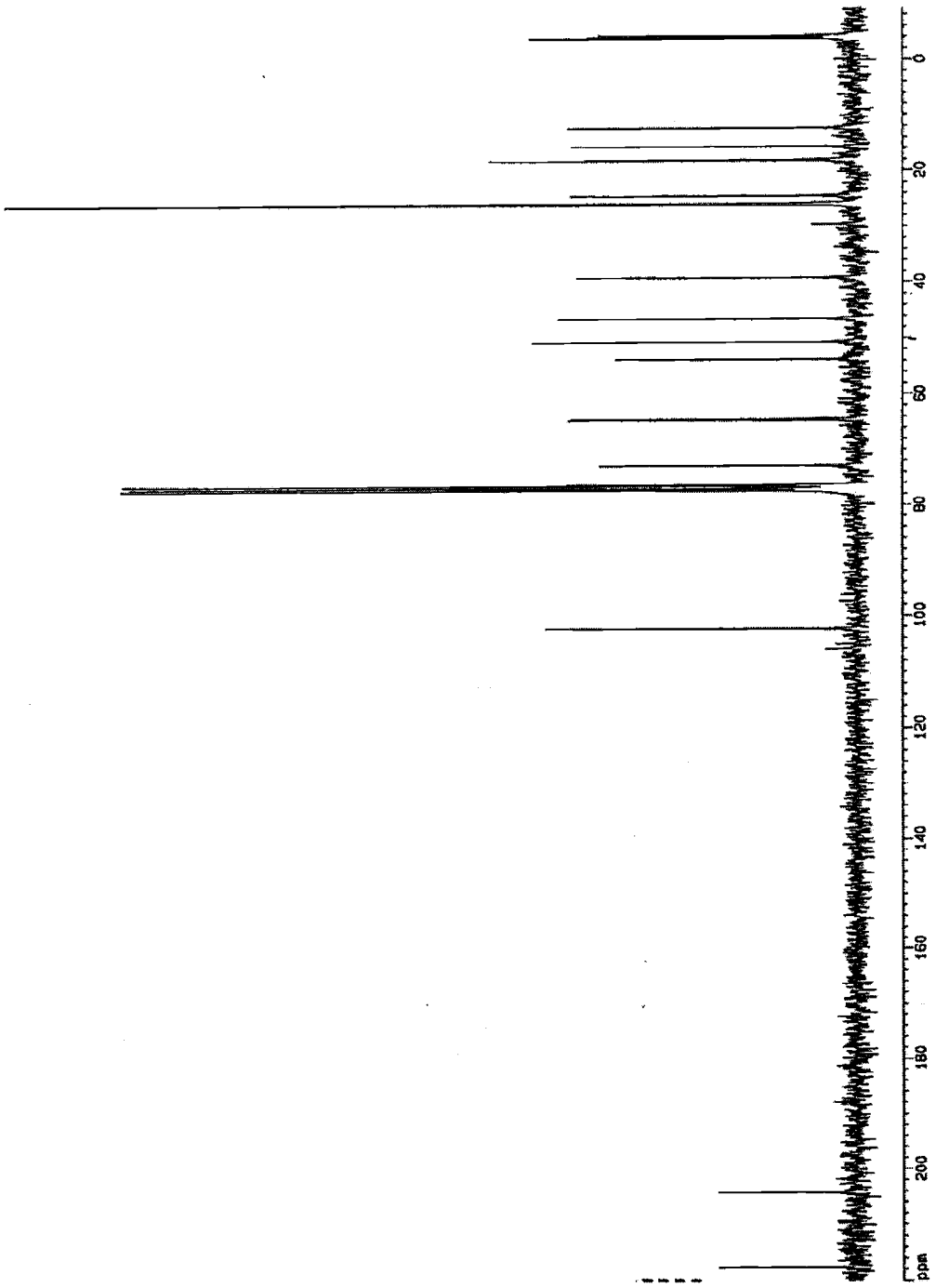
Alcohol 72



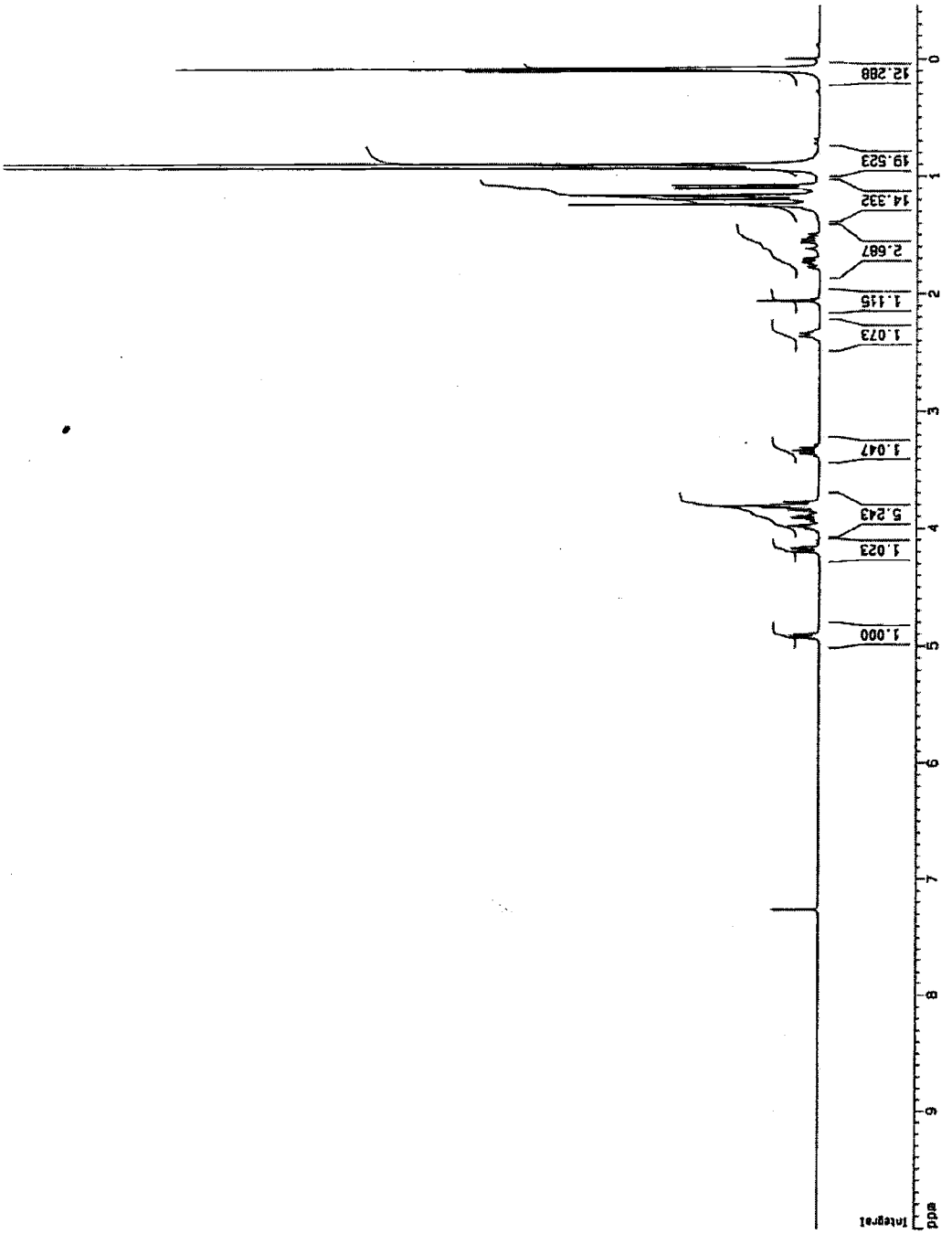
Alcohol 72


12.735
19.370
13.720
1.322
1.409
1.038
0.984
4.212
2.021
1.011
1.000
Integral
ppm

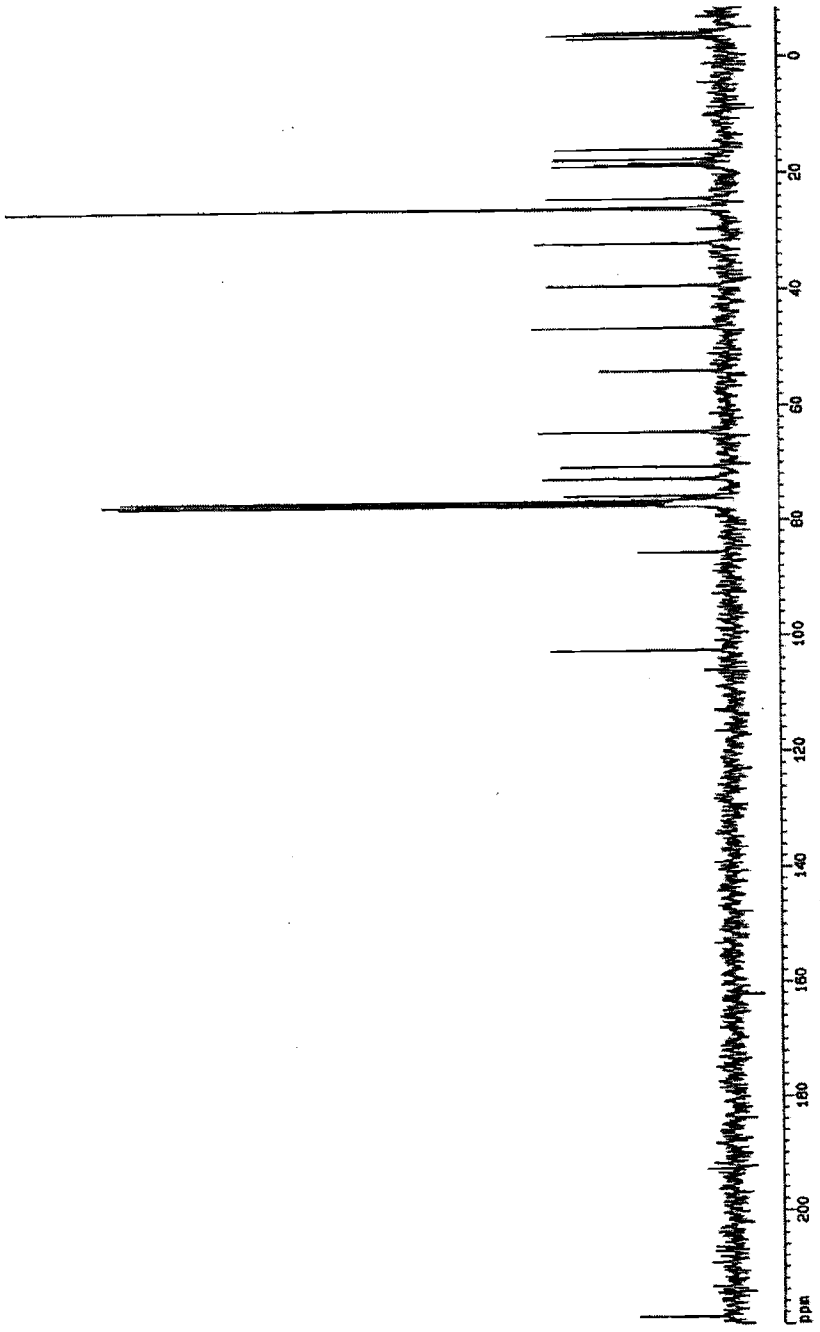
Aldehyde 73



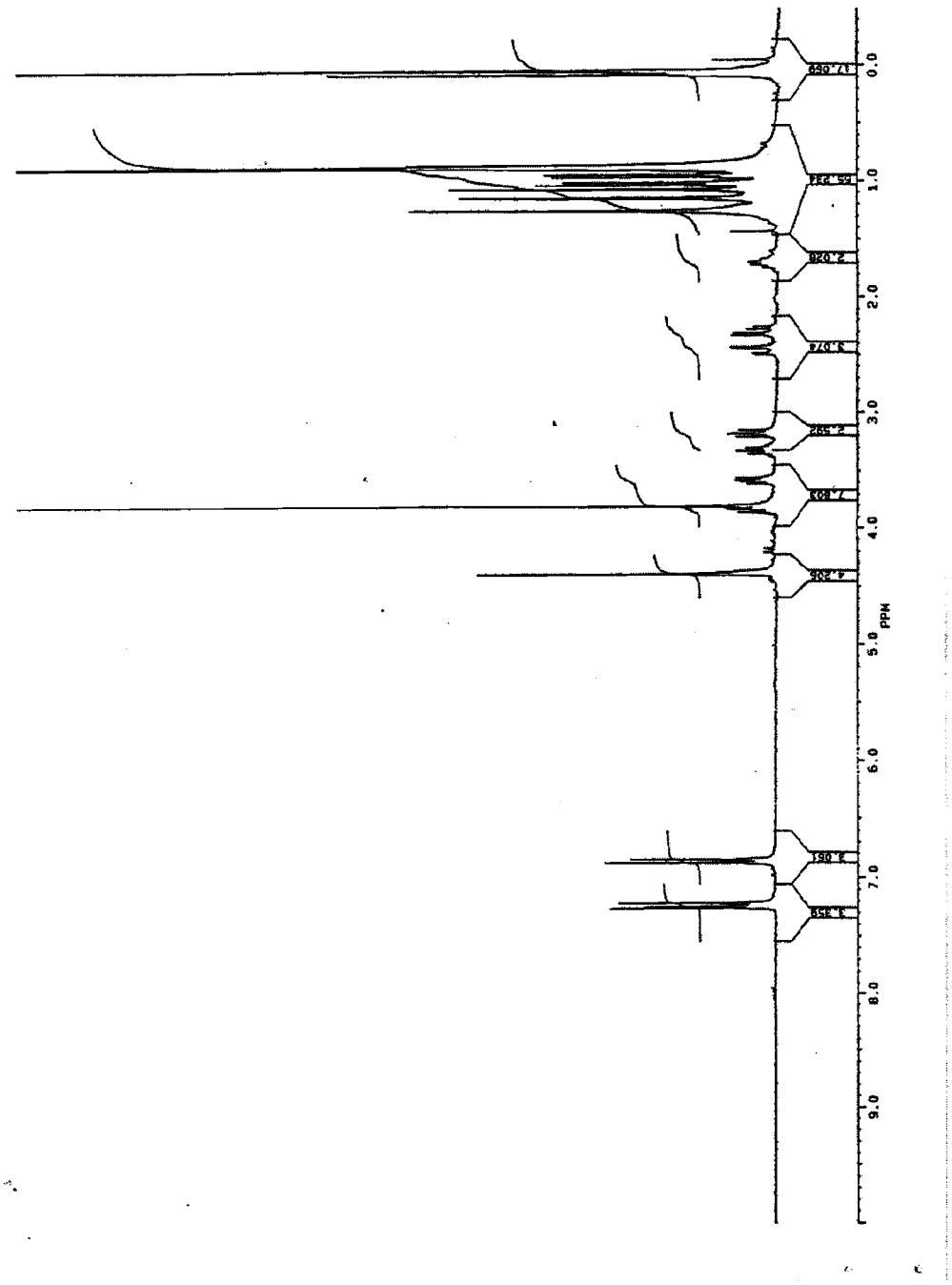
Aldehyde 73


12.288
19.523
14.332
2.687
1.115
1.073
1.047
5.243
1.023
1.000
Integral
ppm

Alkyne 74

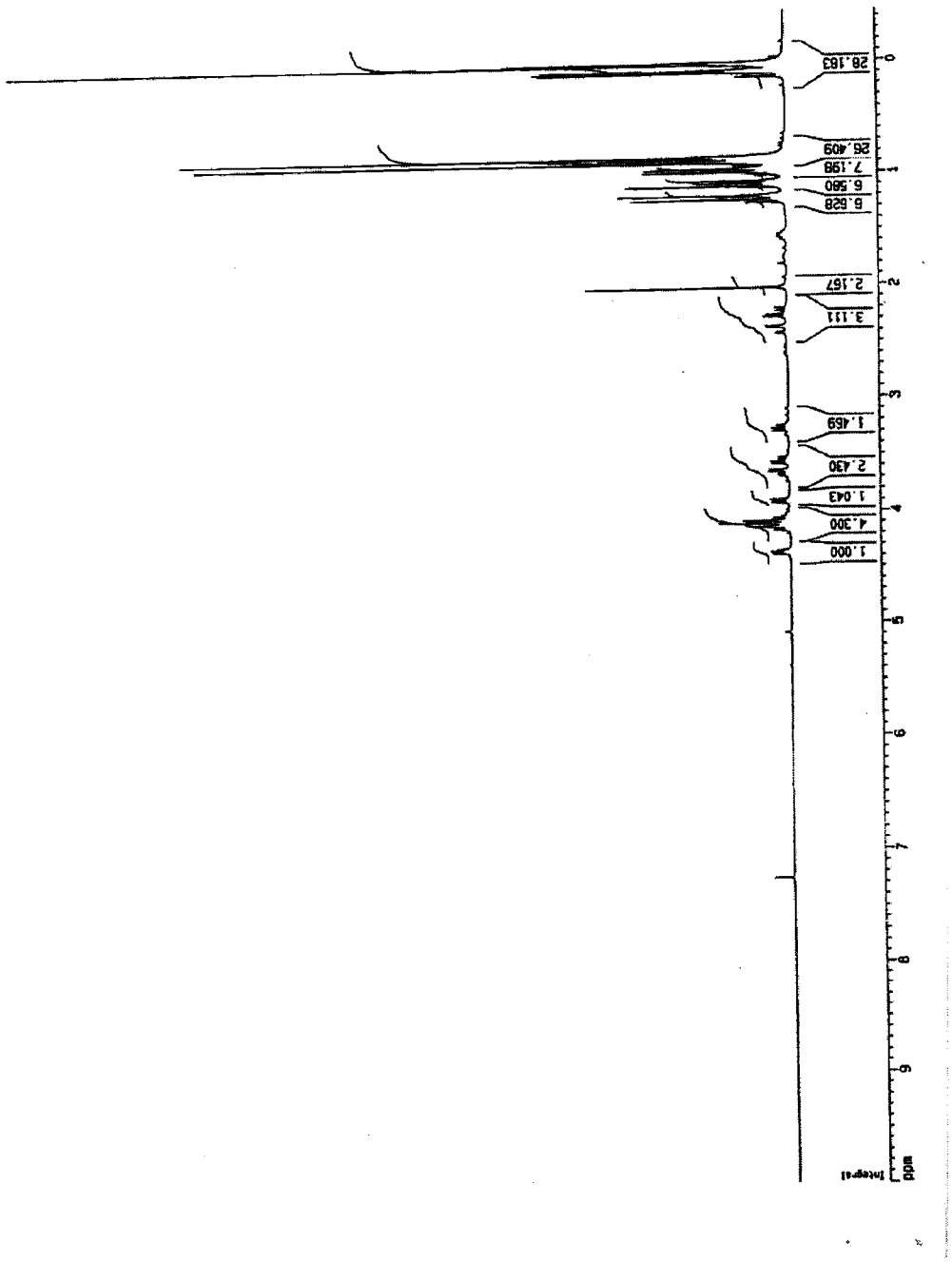


Alkyne 74



Carboxylic acid 75

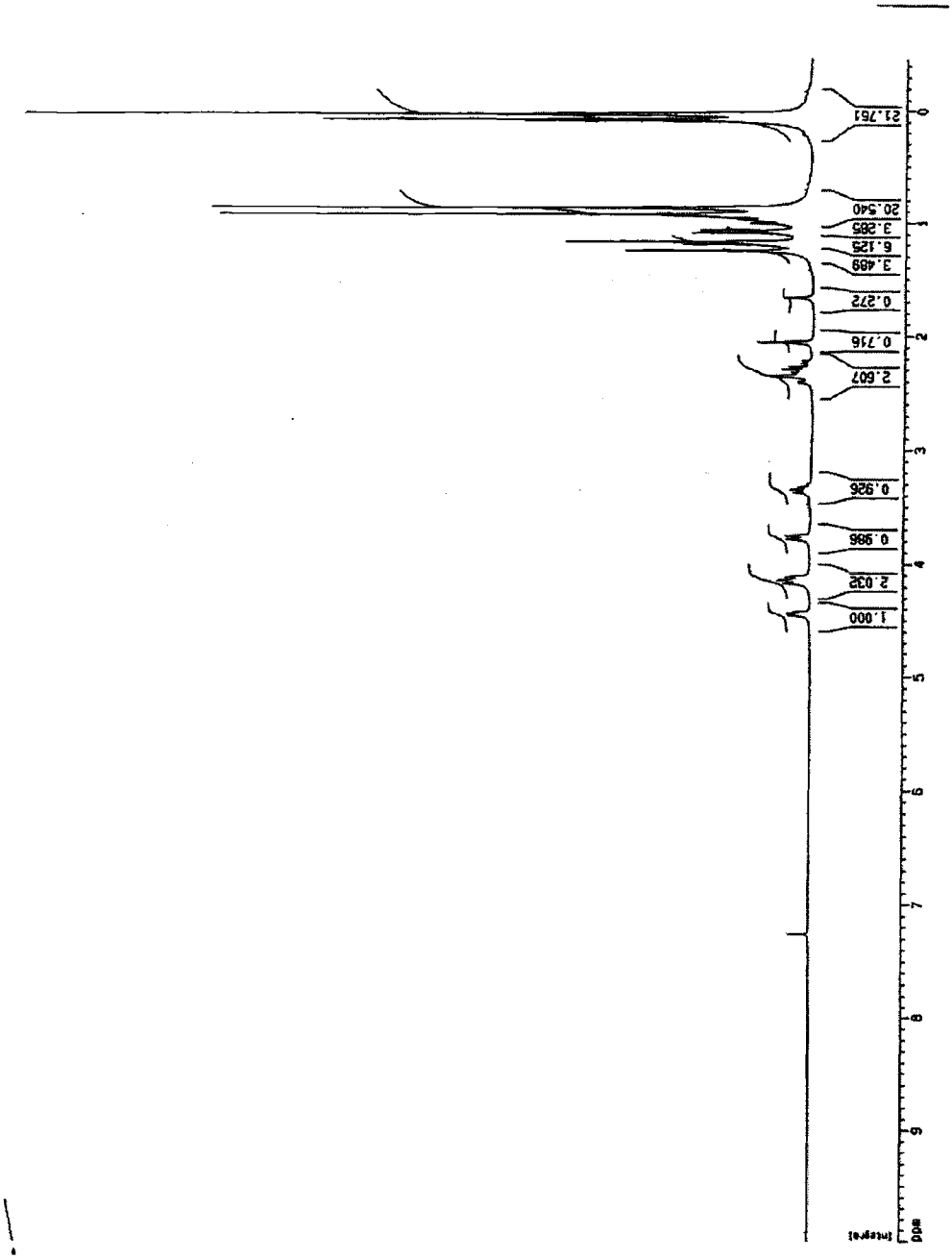
Carboxylic acid
75


28.183
26.409
7.198
6.580
6.528
2.167
3.111
1.469
2.430
1.043
4.300
1.000
ppm

Alcohol 77

Alcohol 77

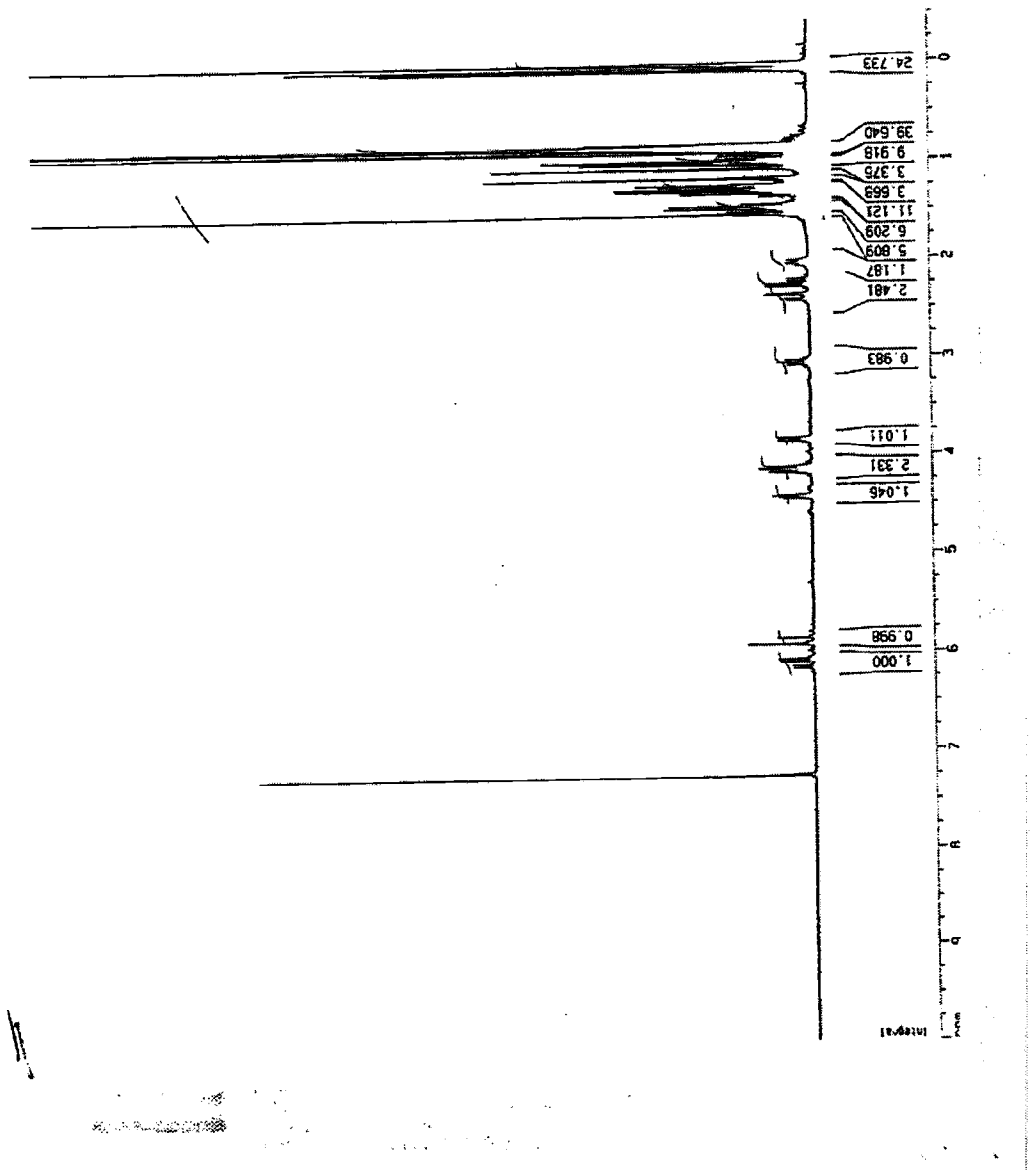
ppm
218.0
176.5
172.3
105.1
104.8
83.2
77.9
77.4
77.0
76.6
73.3
64.6
62.8
62.5
60.3
53.7
45.7
40.3
39.6
26.1
26.0
25.5
23.7
21.0
19.1
18.3
18.2
17.2
15.9
15.8
14.2
ppm
200
150
100
50


21.761
20.540
3.285
6.125
3.489
0.272
0.716
2.607
0.926
0.986
2.032
1.000

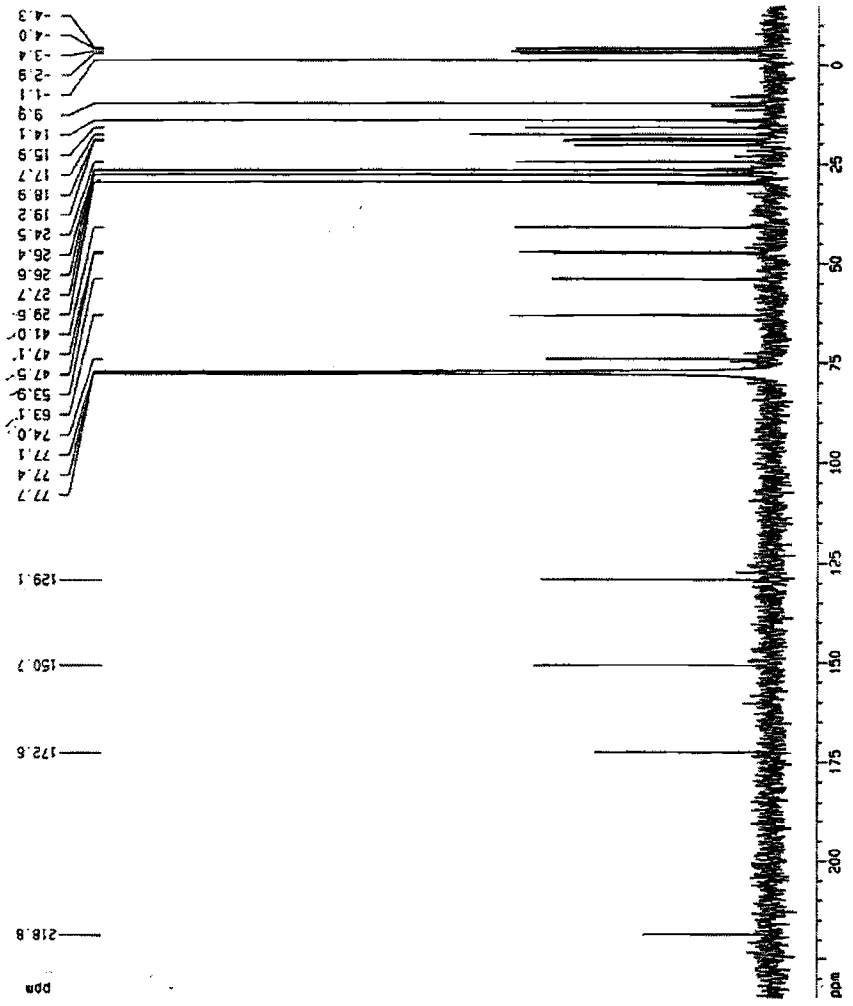
Alkyne 78

Alkyne 78

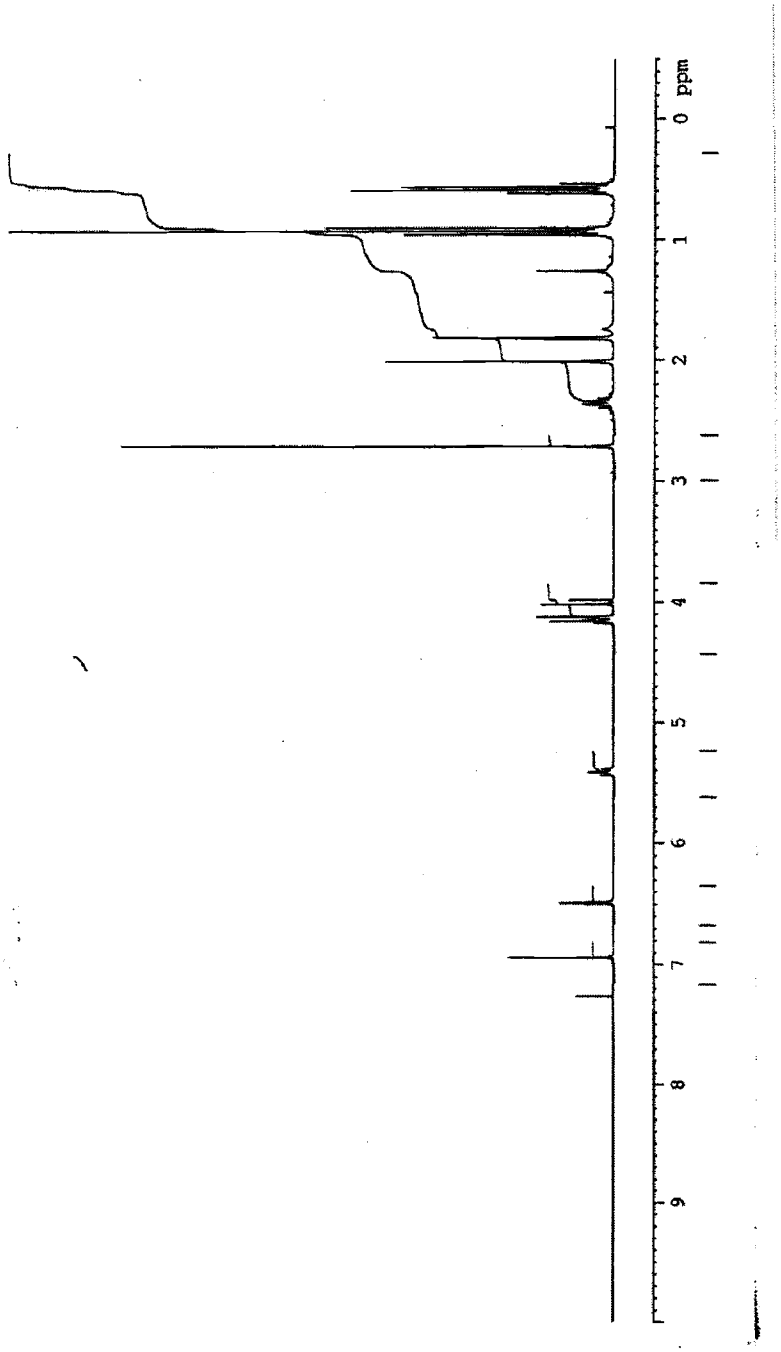
ppm
218.6
172.1
85.6
77.4
77.0
76.6
75.7
73.3
70.8
62.7
53.8
46.5
40.6
32.2
26.1
26.0
23.6
18.7
18.5
18.2
17.2
15.8
ppm
200
150
100
50


24.733
39.640
9.918
3.375
3.669
11.121
6.209
5.809
1.187
2.481
0.983
1.011
2.331
1.046
0.998
1.000

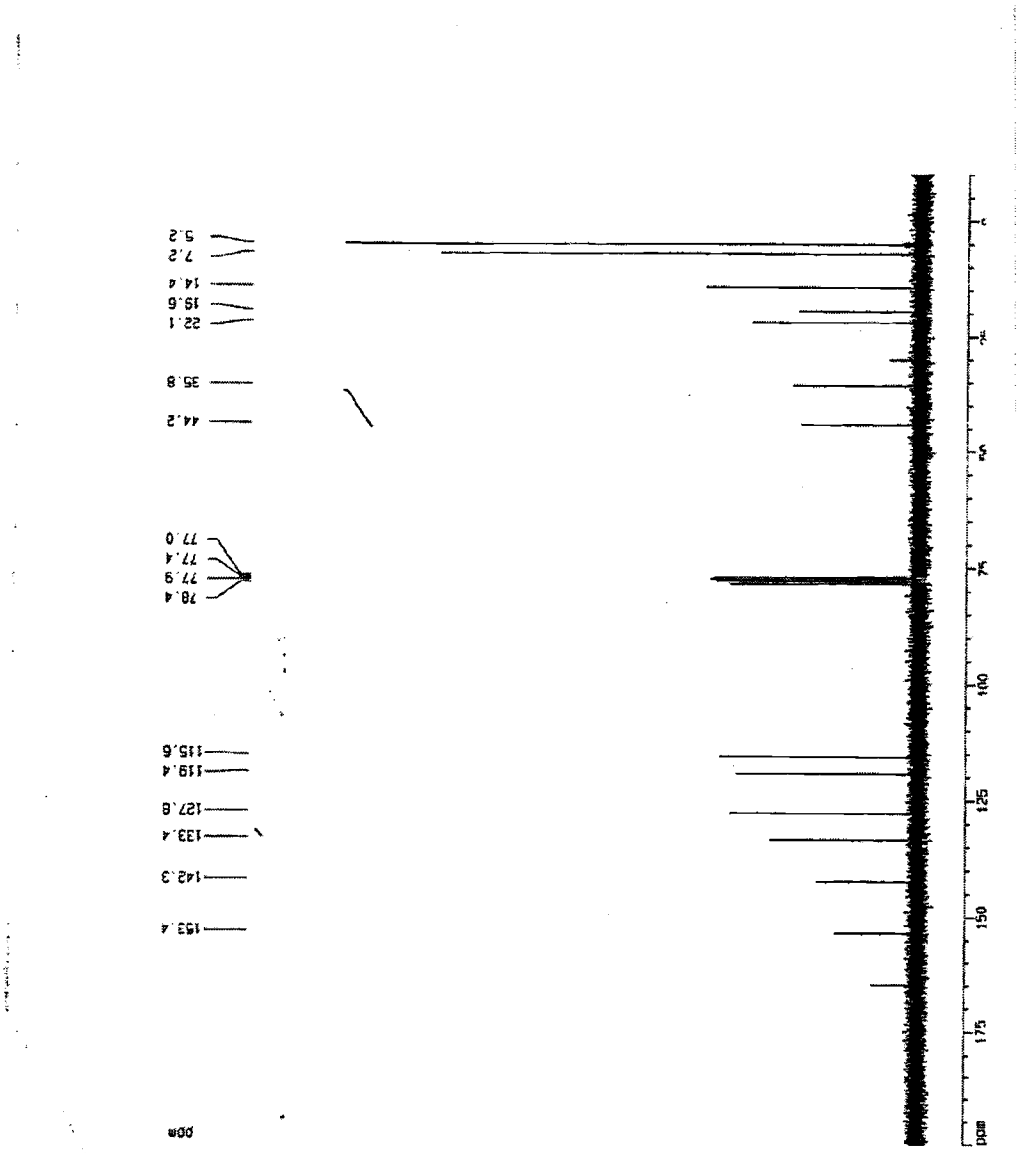
Stannane
79


-4.3
-4.0
-3.4
-2.9
-1.1
9.9
14.1
15.9
17.7
18.9
19.2
24.5
26.4
26.6
27.7
29.6
41.0
47.1
47.5
53.9
63.1
74.0
77.1
77.4
77.7
129.1
150.7
172.6
218.8
ppm
0
25
50
75
100
125
150
175
200
ppm

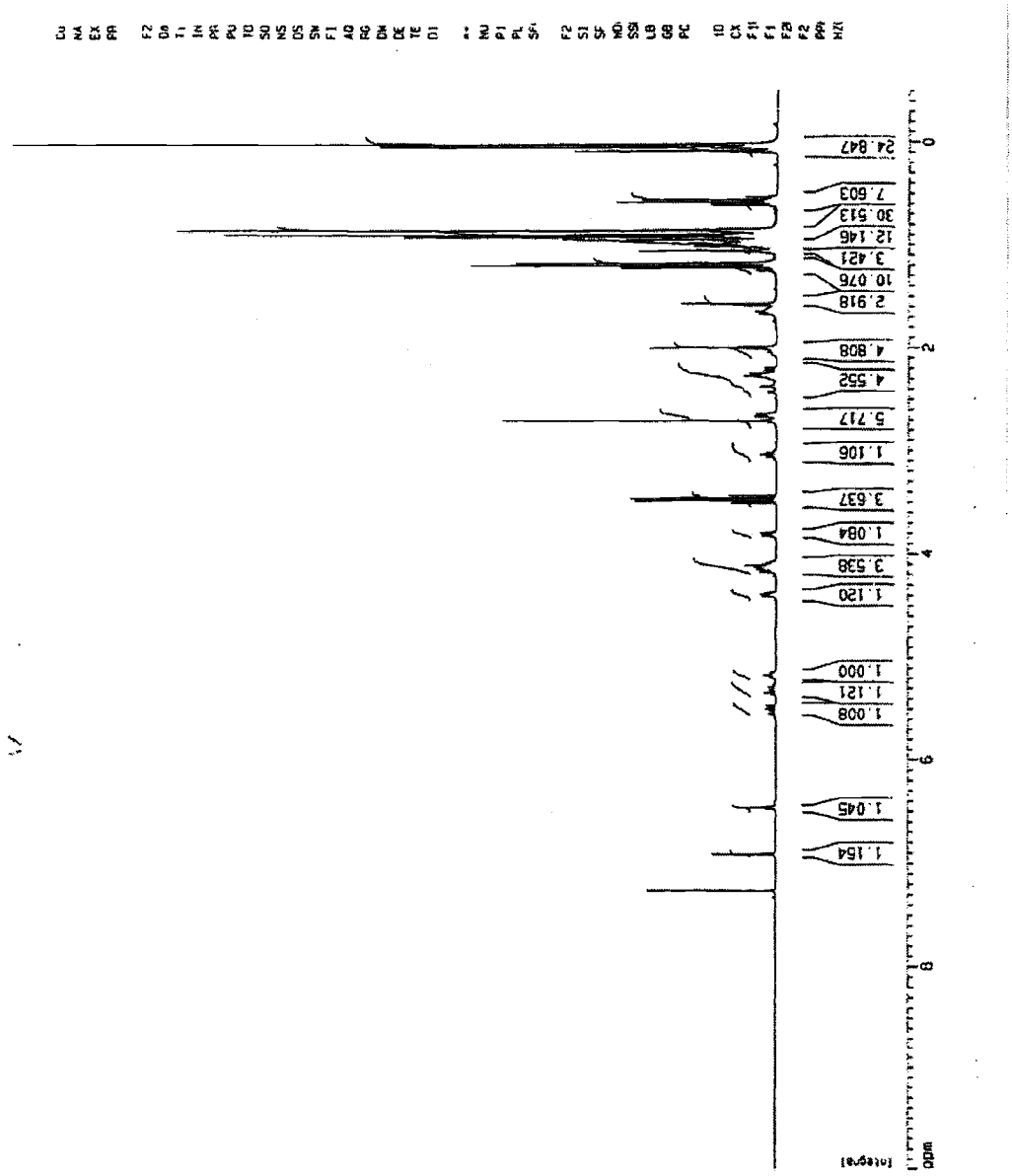
Stannane 79



Chloride 80


5.2
7.2
14.4
15.6
22.1
35.8
44.2
77.0
77.4
77.9
78.4
115.6
119.4
127.8
133.4
142.3
153.4
ppm
25
50
75
100
125
150
175
ppm

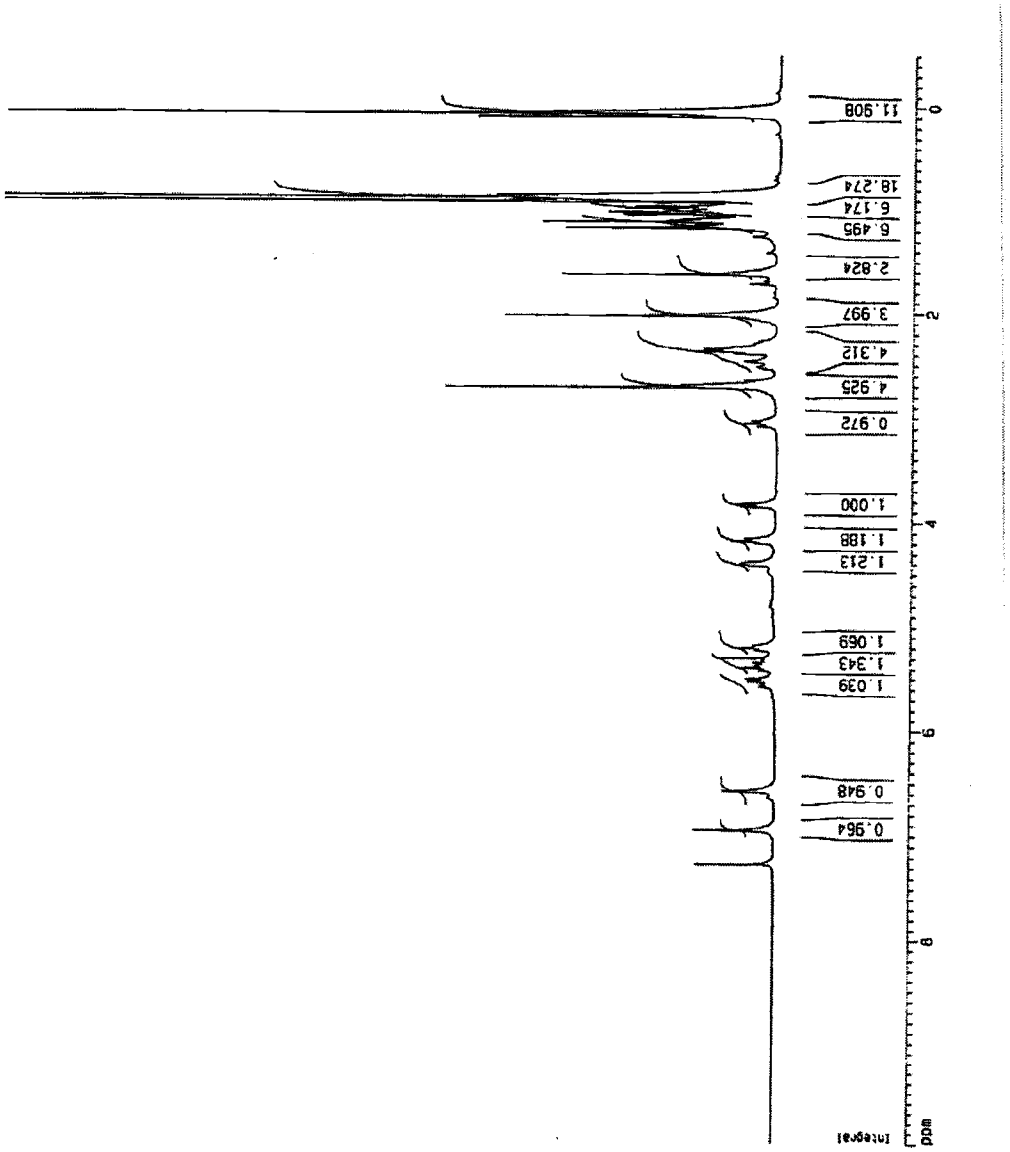
Chloride 80


24.847
7.603
30.513
12.146
3.421
10.076
2.918
4.808
4.552
5.717
1.106
3.637
1.084
3.538
1.120
1.000
1.121
1.008
1.045
1.154
ppm

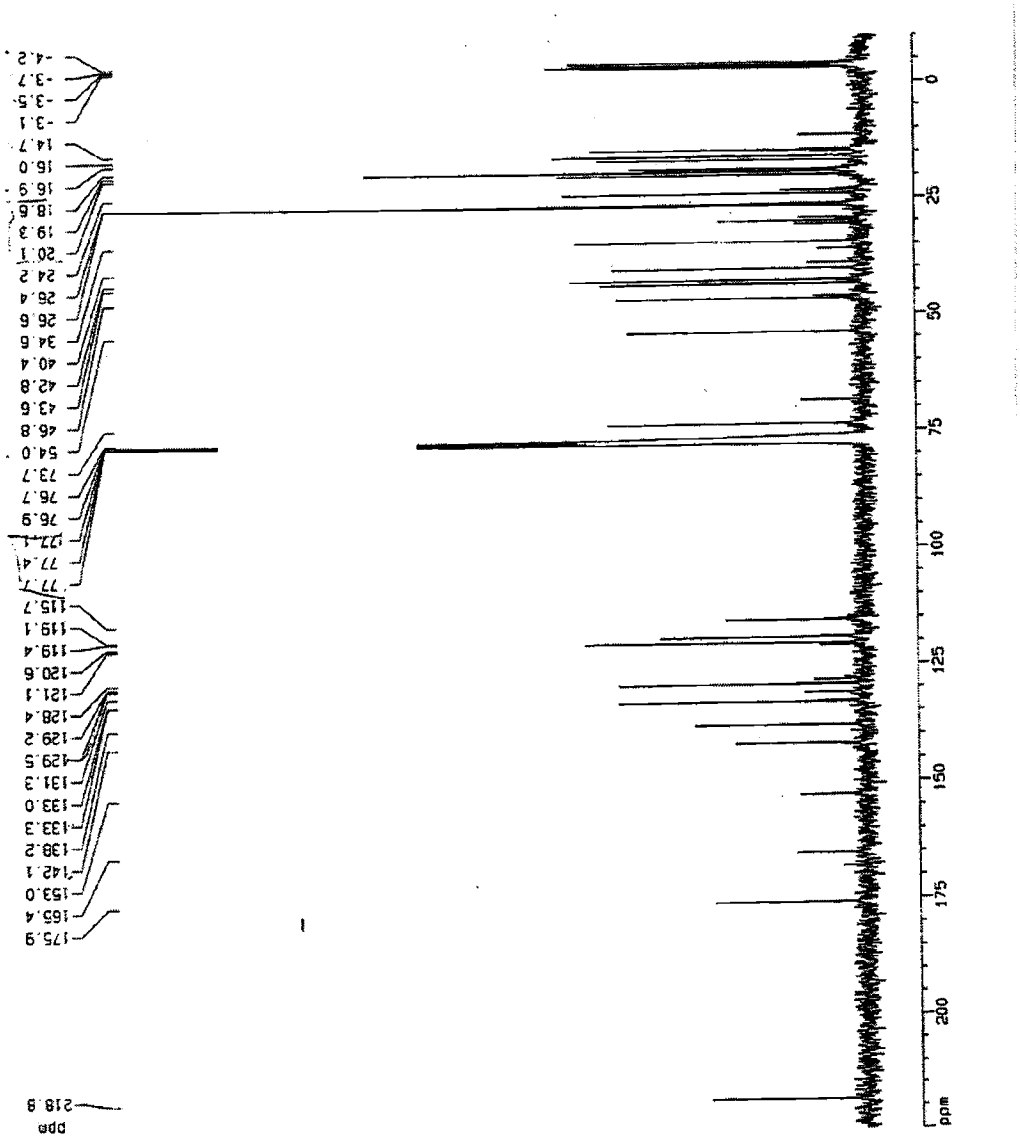
Triene 81

Triene 81

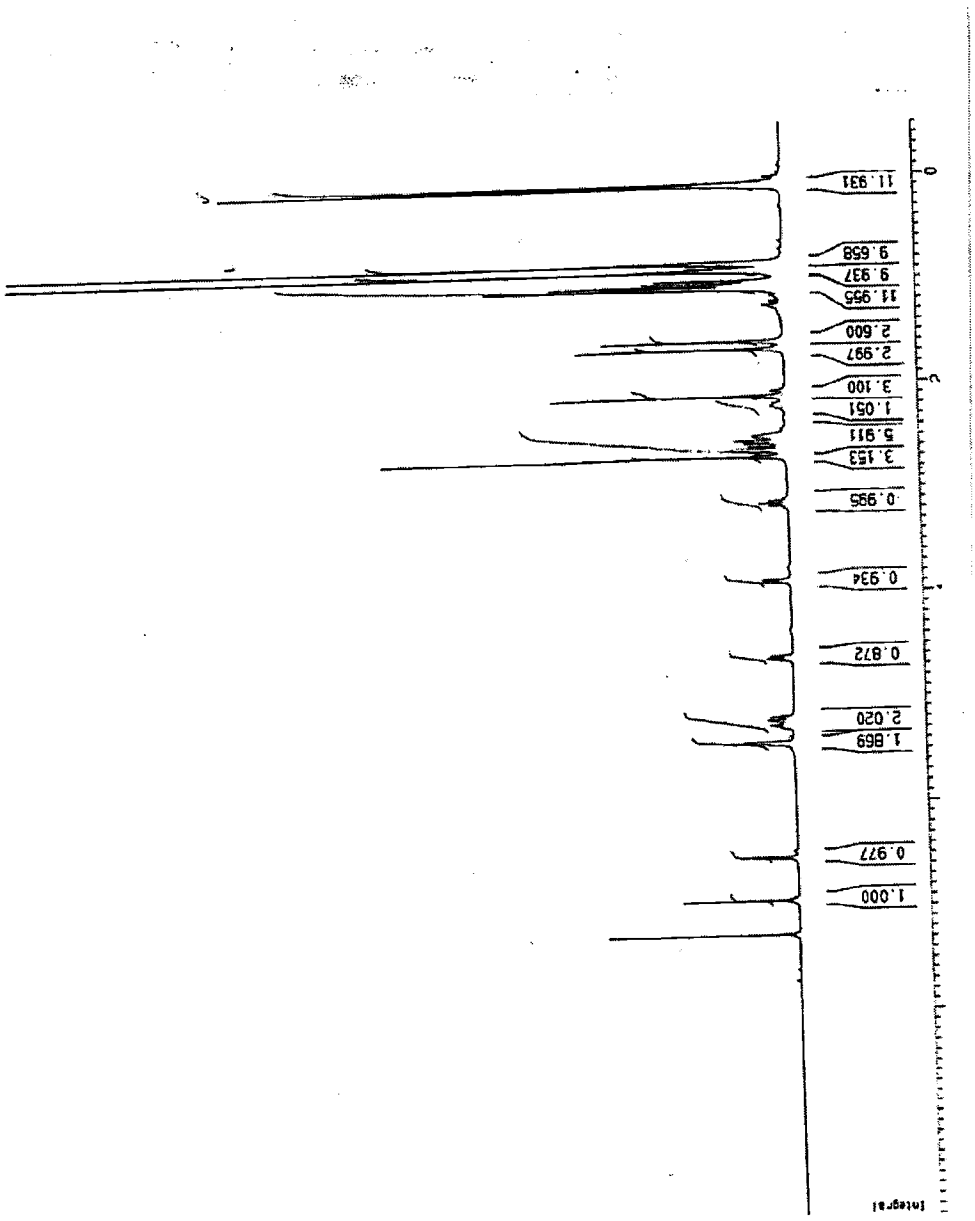
ppm
218.5
172.6
164.7
153.6
143.0
136.0
133.1
129.7
121.9
119.0
115.3
79.0
77.8
77.4
77.0
76.8
63.1
53.8
46.5
43.8
42.8
40.9
26.6
25.4
19.6
18.9
18.6
17.7
16.7
14.4
7.3
5.2
-1.1
-3.1
-3.4
-4.0
-4.2
ppm
200
175
150
125
100
75
50
25
0



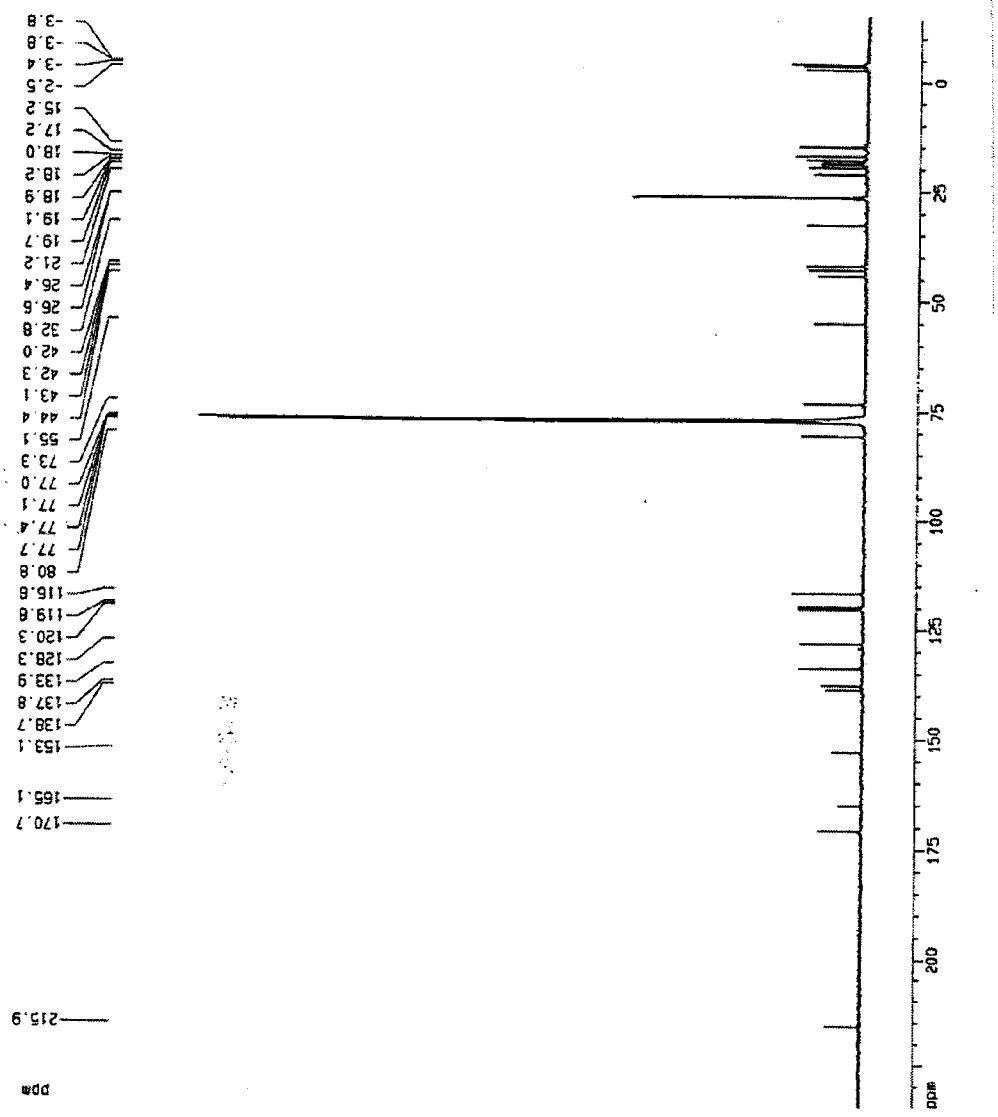
Hydroxy acid 82



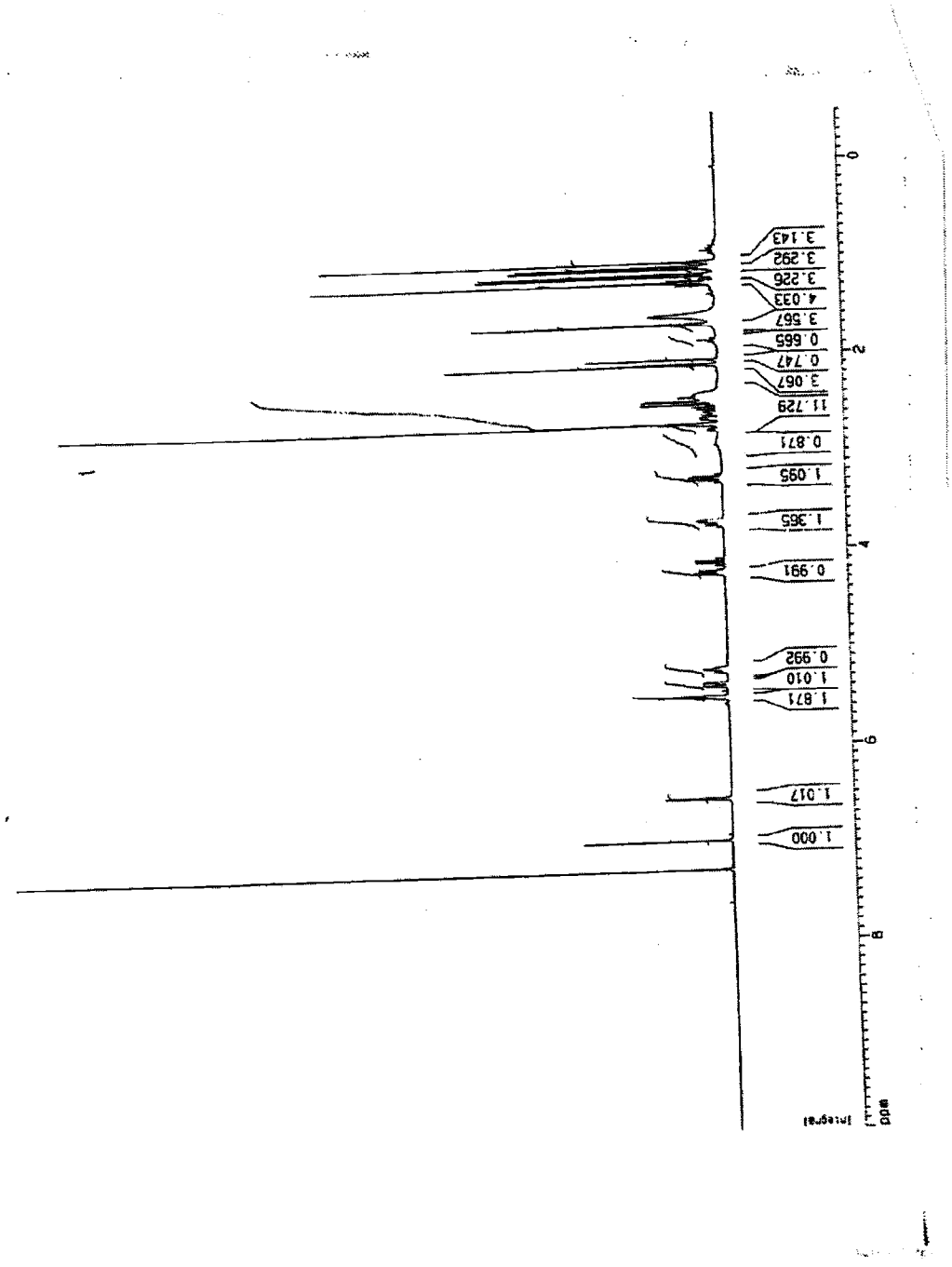
Hydroxy acid 82


11.931
9.658
9.937
11.955
2.600
2.997
3.100
1.051
5.911
3.153
0.995
0.934
0.872
2.020
1.869
0.977
1.000

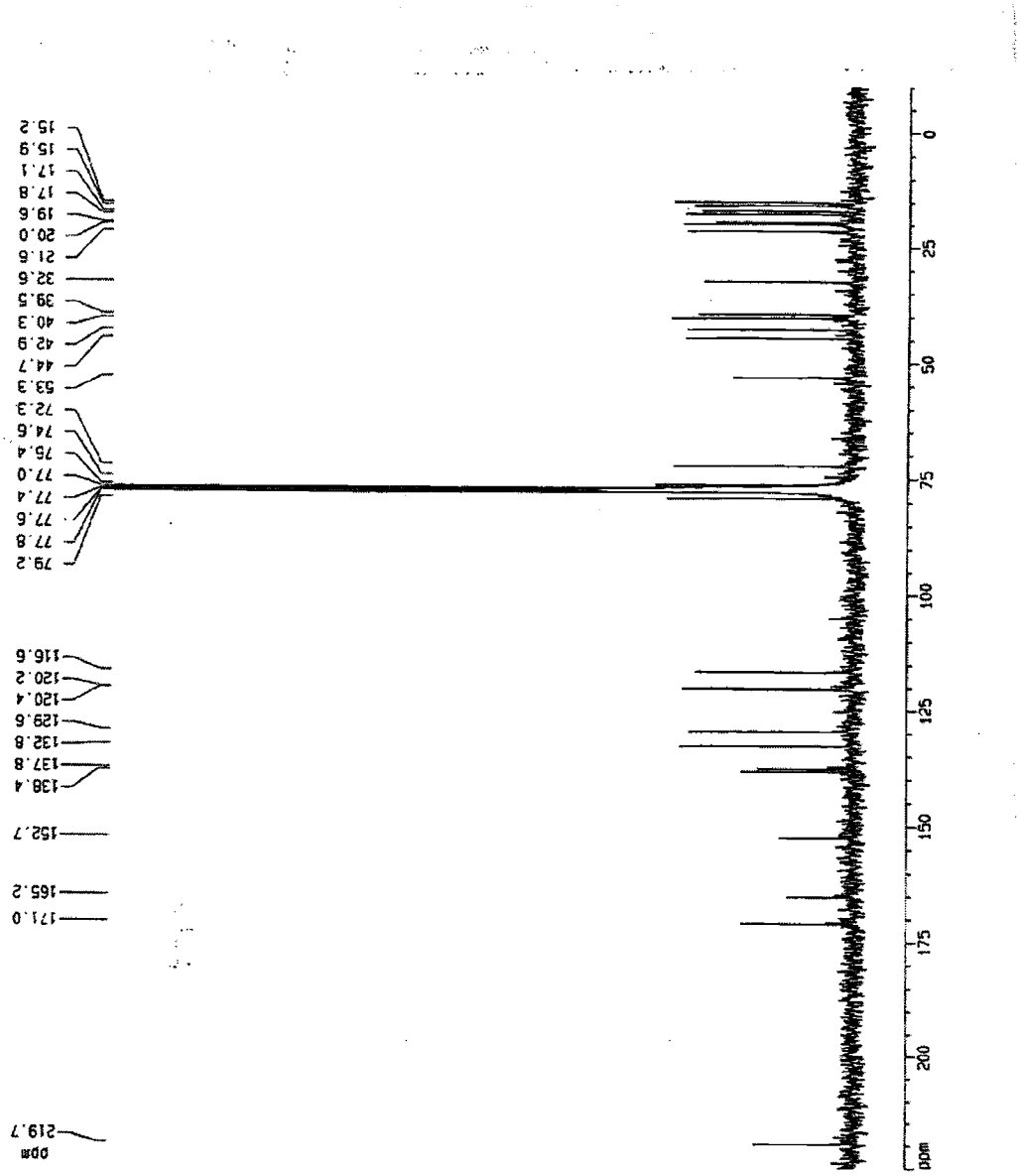
Lactone 83


-3.8
-3.8
-3.4
-2.5
15.2
17.2
18.0
18.2
18.9
19.1
19.7
21.2
26.4
26.6
32.8
42.0
42.3
43.1
44.4
55.1
73.3
77.0
77.1
77.4
77.7
80.8
116.8
119.8
120.3
128.3
133.9
137.8
138.7
153.1
165.1
170.7
215.9
ppm
0
25
50
75
100
125
150
175
200
ppm

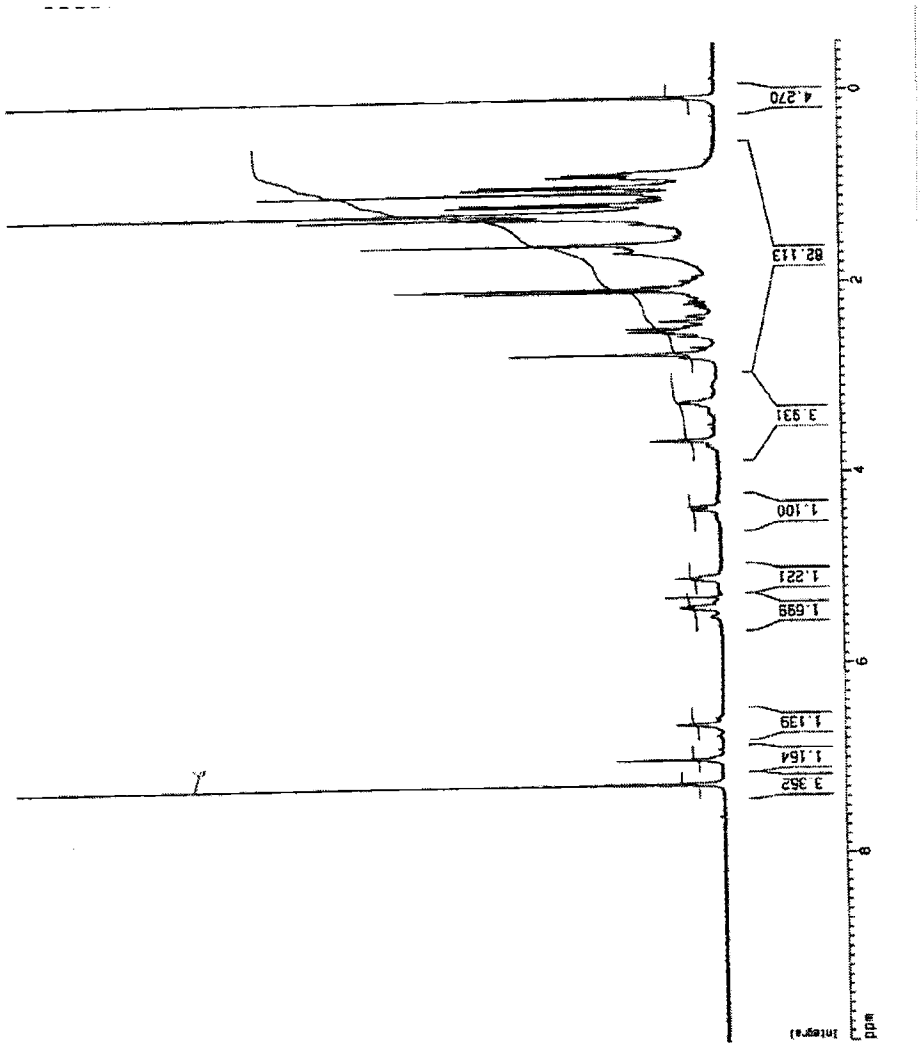
Lactone 83



***trans*-9,10-Dehydro-trans-12,13,-epothilone D 84**



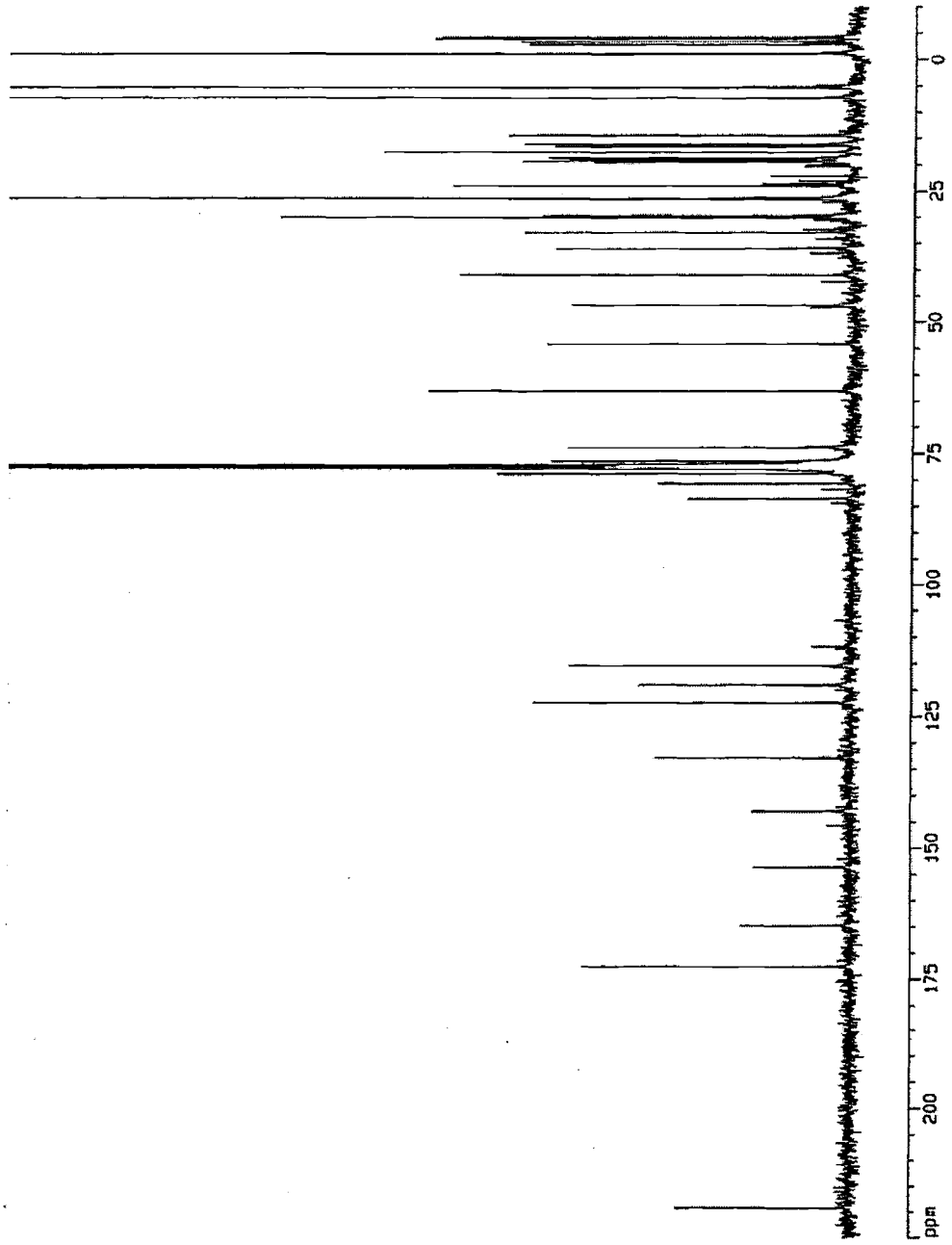
***trans*-9,10-Dehydro-trans-12,13,-epothilone D 84**



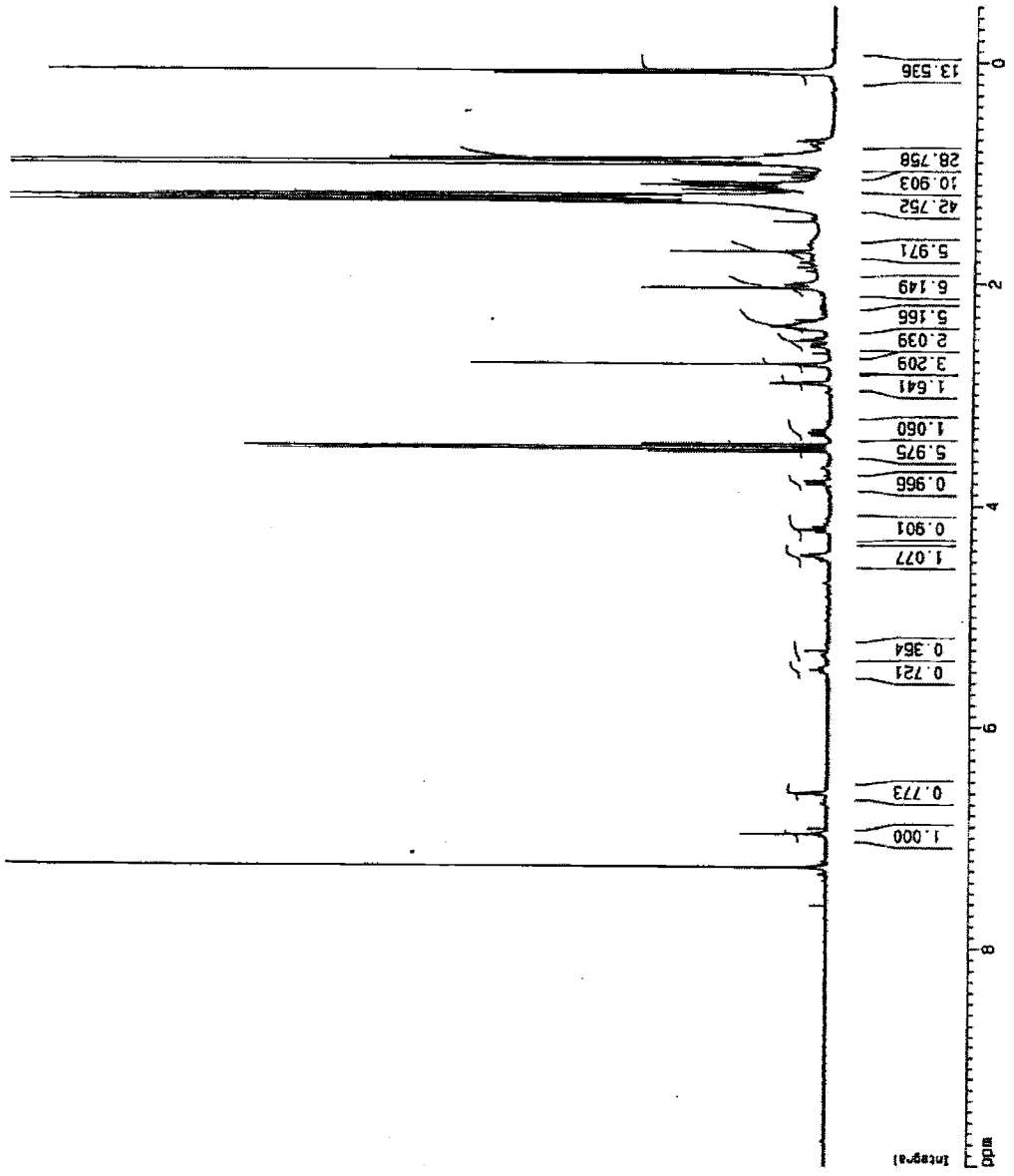
12, 13- trans-Epothilone D 85

Enyne 86

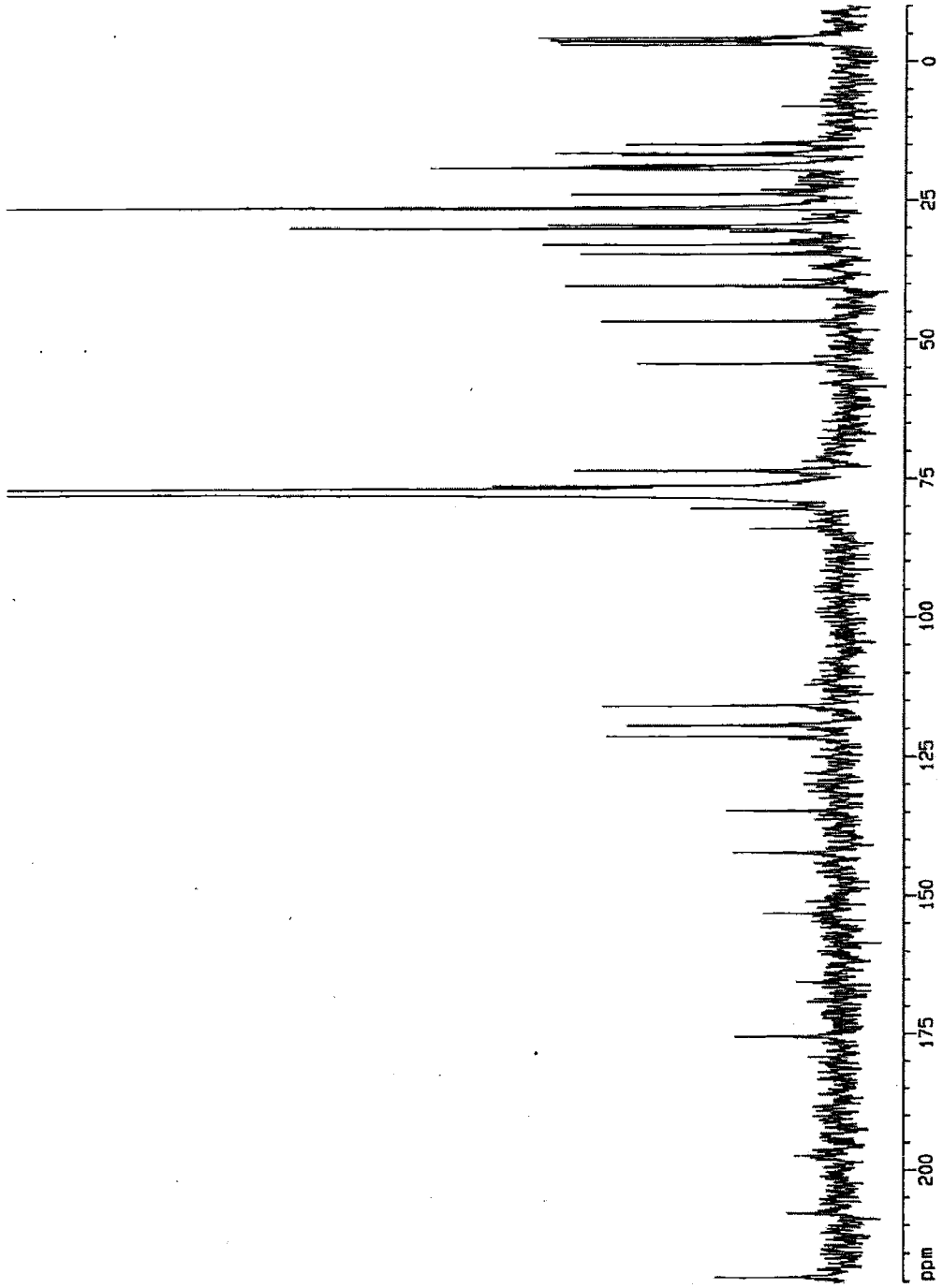
Integral
1.000
0.963
0.698
1.008
2.946
0.957
0.971
1.727
2.961
4.918
3.380
1.454
3.697
11.044
10.741
32.600
6.298
21.253
ppm
8
6
4
2
0



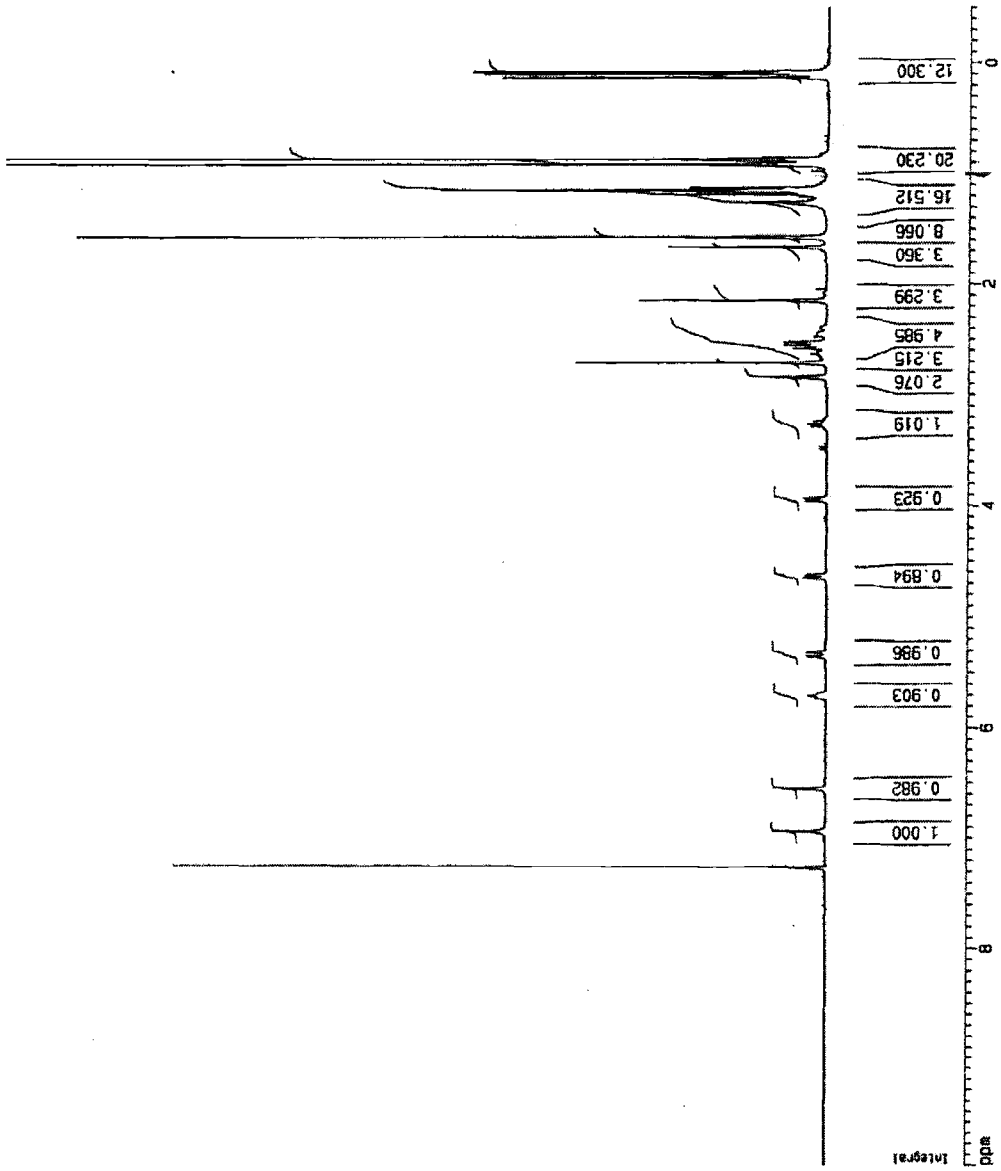
Enyne 86



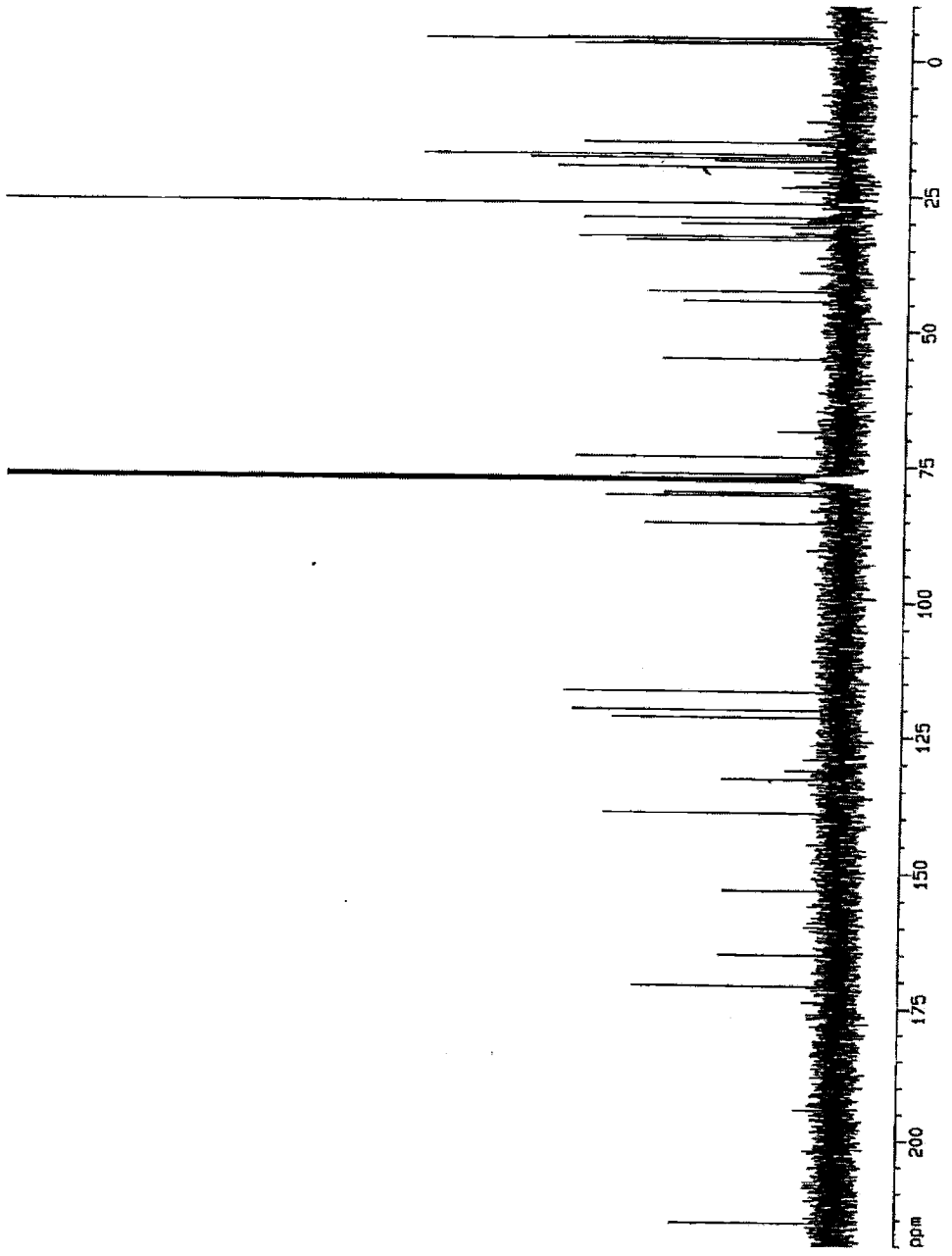
Hydroxy acid 87



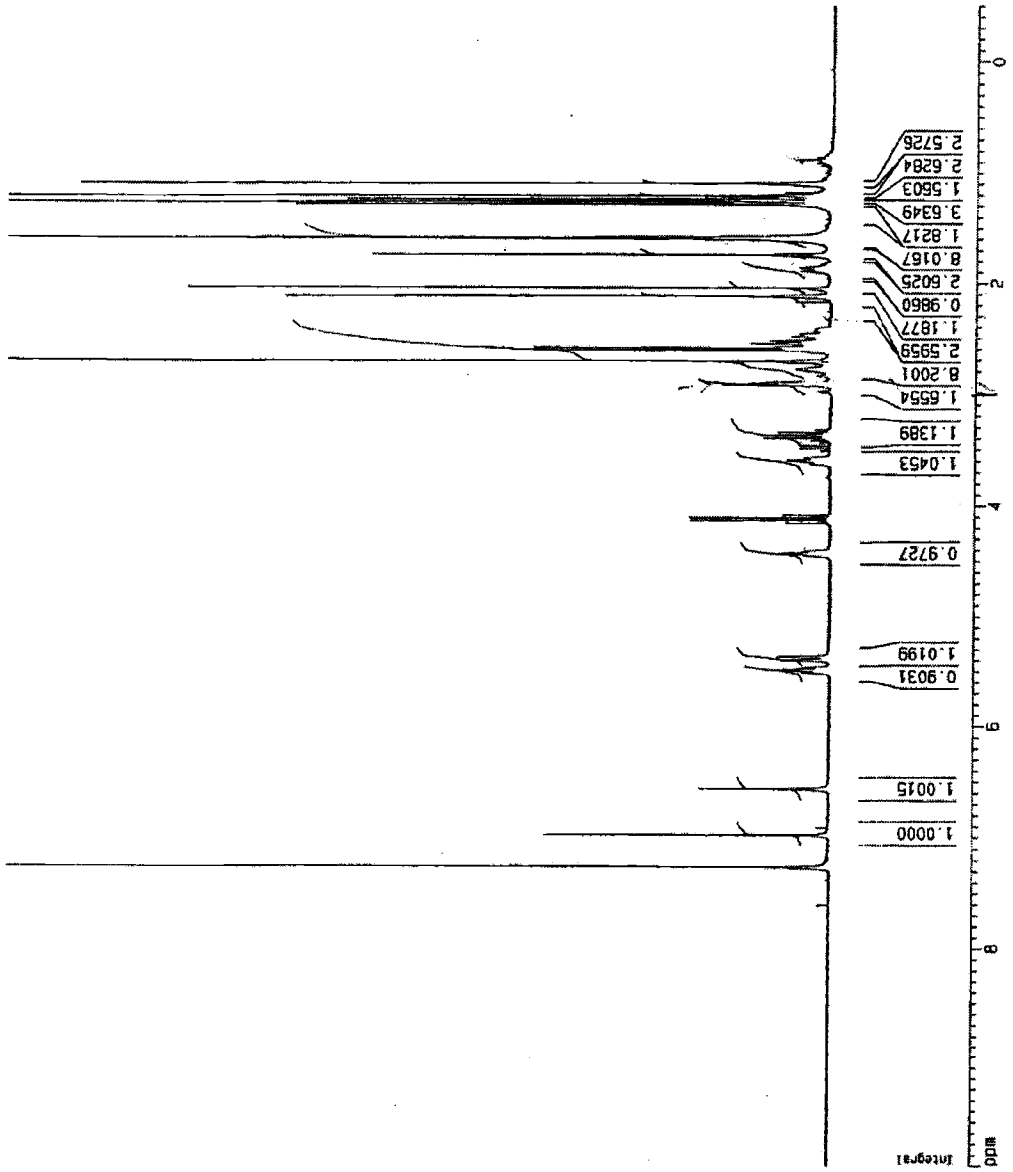
Hydroxy acid 87


12.300
20.230
16.512
8.066
3.360
3.299
4.985
3.215
2.076
1.019
0.923
0.894
0.986
0.903
0.982
1.000
Integral
ppm
0
2
4
6
8

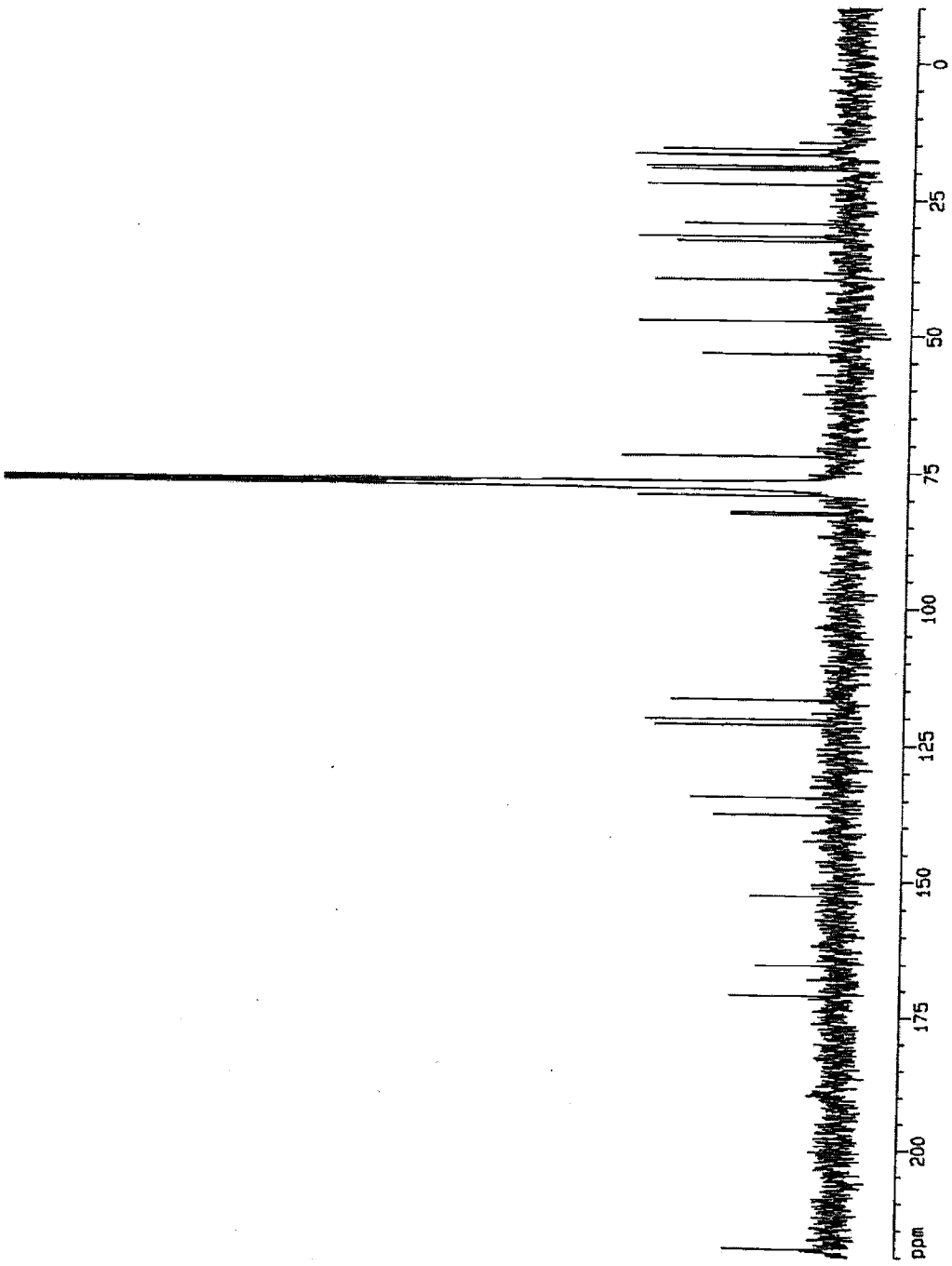
Lactone 88



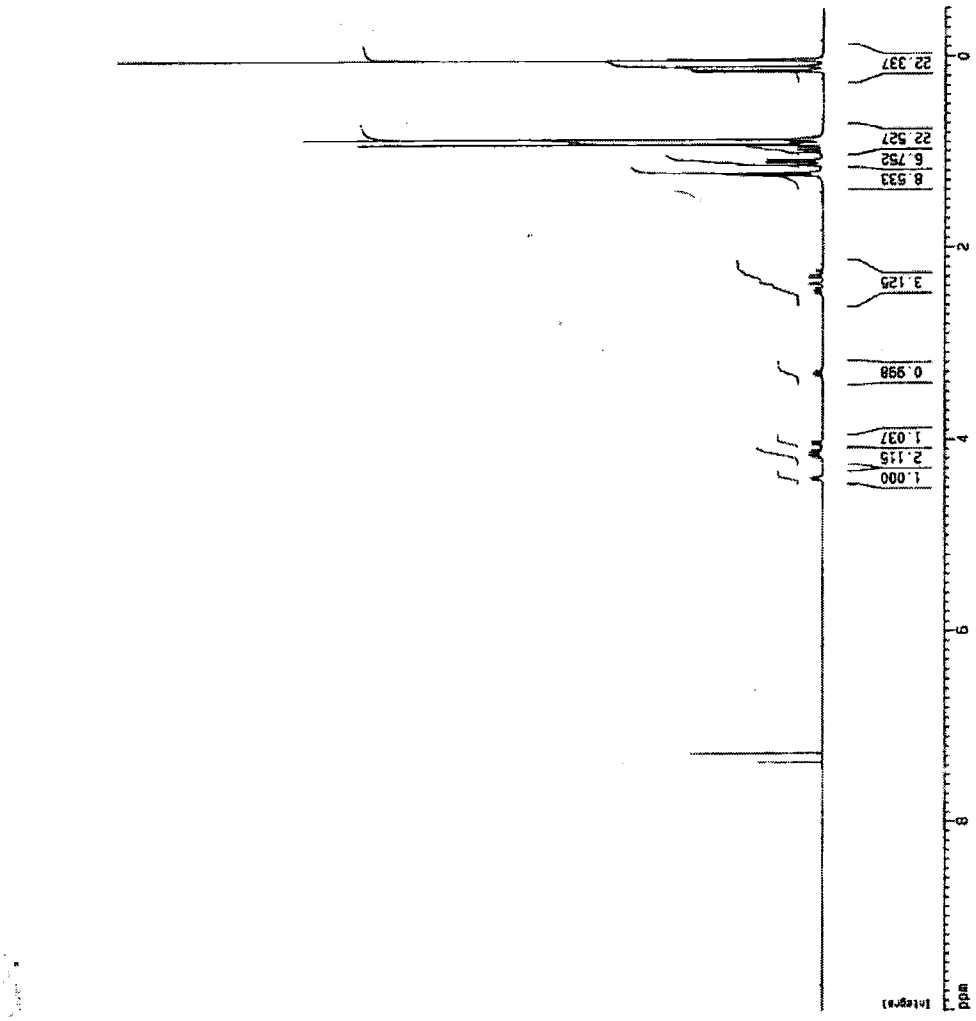
Lactone 88



9, 10-Didehydroepothilone D 89

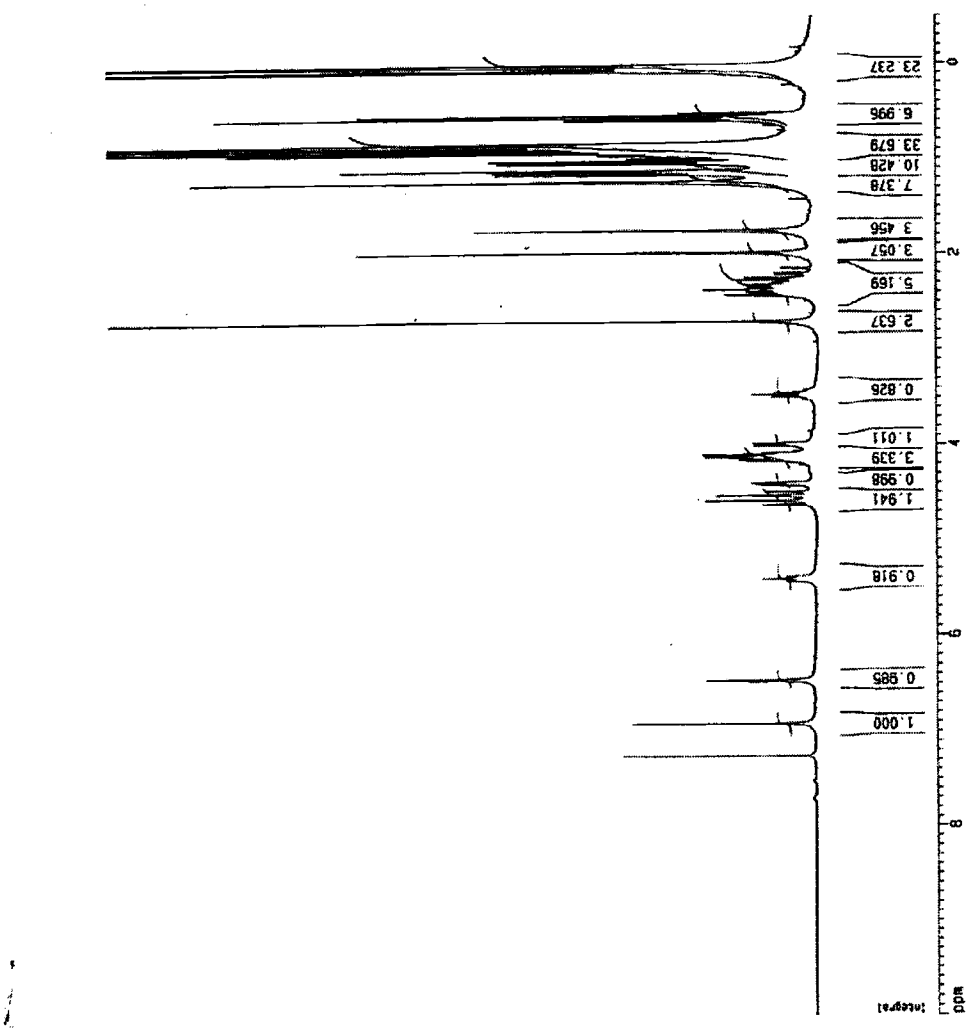


9, 10-Didehydroepothilone D 89



Carboxylic acid 91

Carboxylic acid 91


23.237
6.996
33.679
10.428
7.378
3.456
3.057
5.169
2.637
0.826
1.011
3.339
0.998
1.941
0.918
0.985
1.000
integral
ppm
0
2
4
6
8

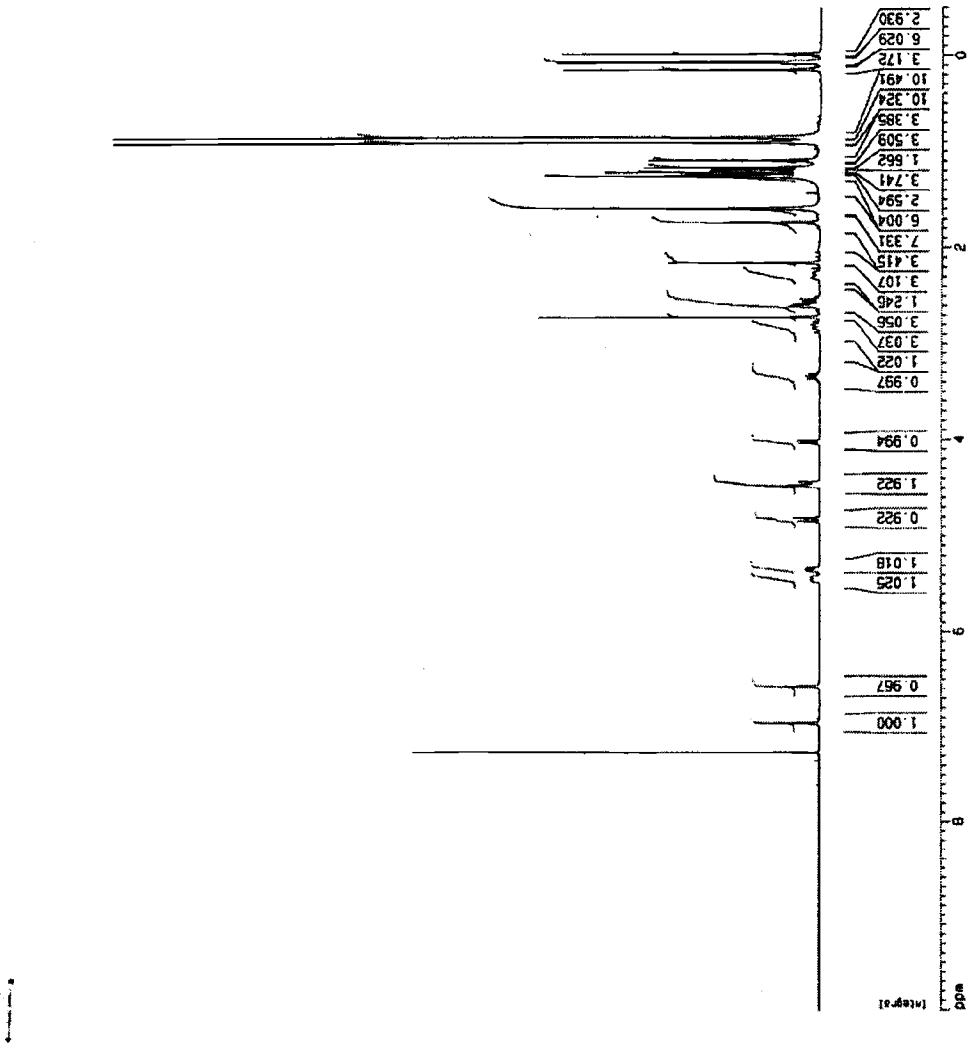
Diester 92

Diester 92

ppm
218.2
173.7
172.6
142.6
131.9
127.2
119.1
115.5
78.5
77.8
77.4
77.0
76.3
74.2
63.7
63.1
53.9
45.6
40.9
35.5
26.5
26.4
24.2
22.1
17.7
15.3
15.1
14.4
7.2
5.2
-1.1
-3.5
-4.0
-4.2
ppm
200
175
150
125
100
75
50
25
0

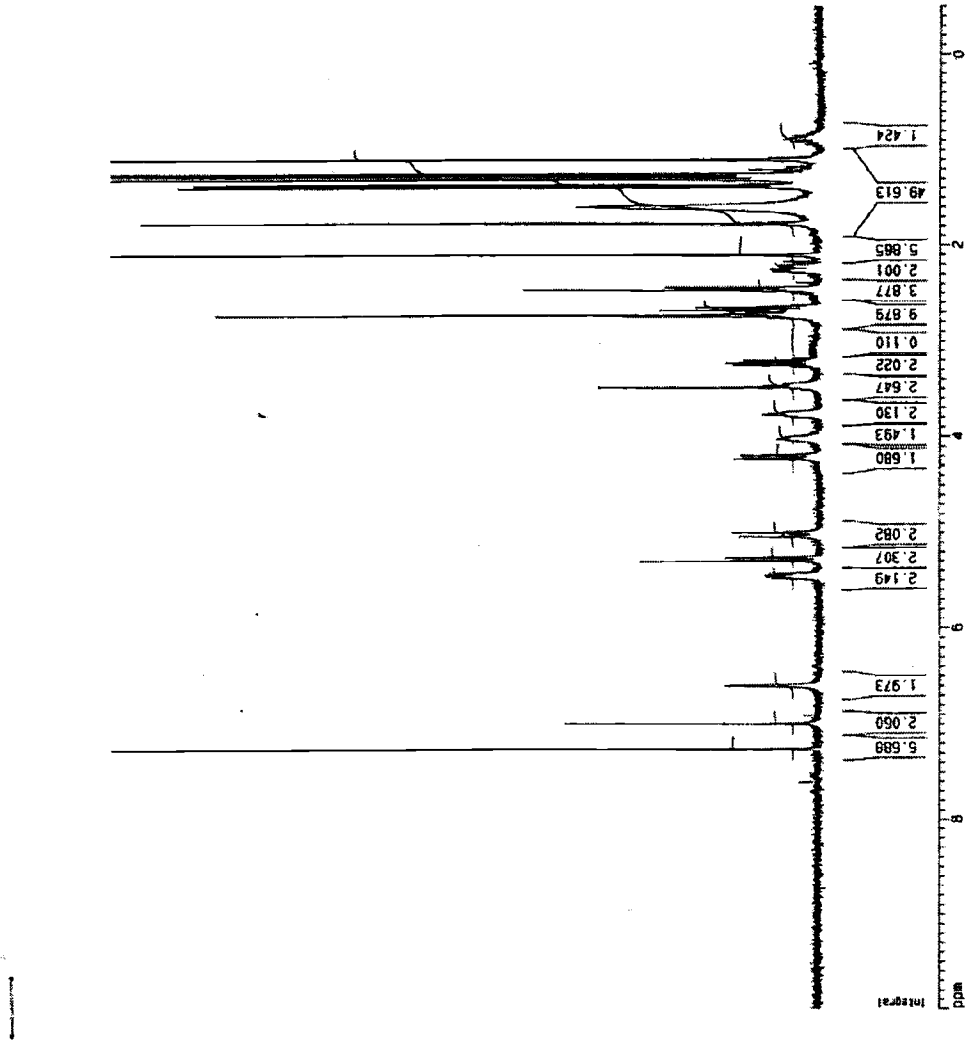
Hydroxy acid 93

Hydroxy acid 93

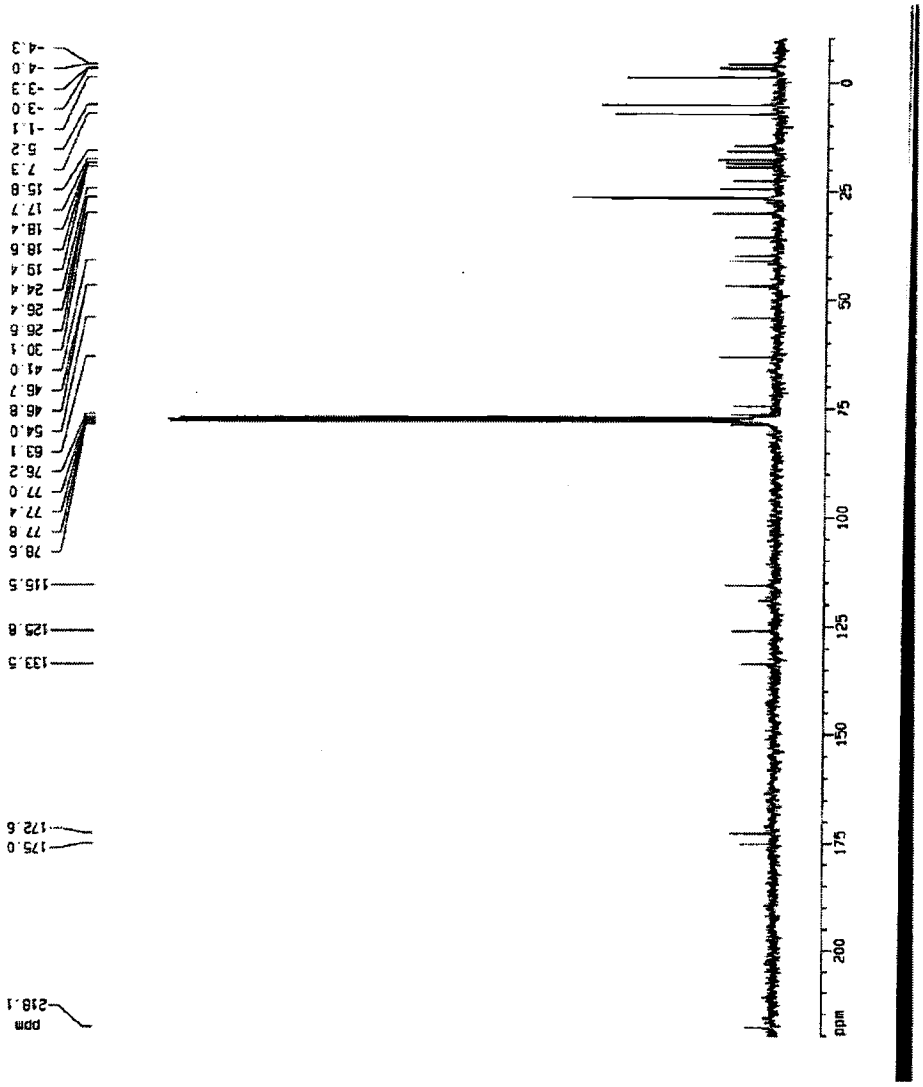


Dilactone 94

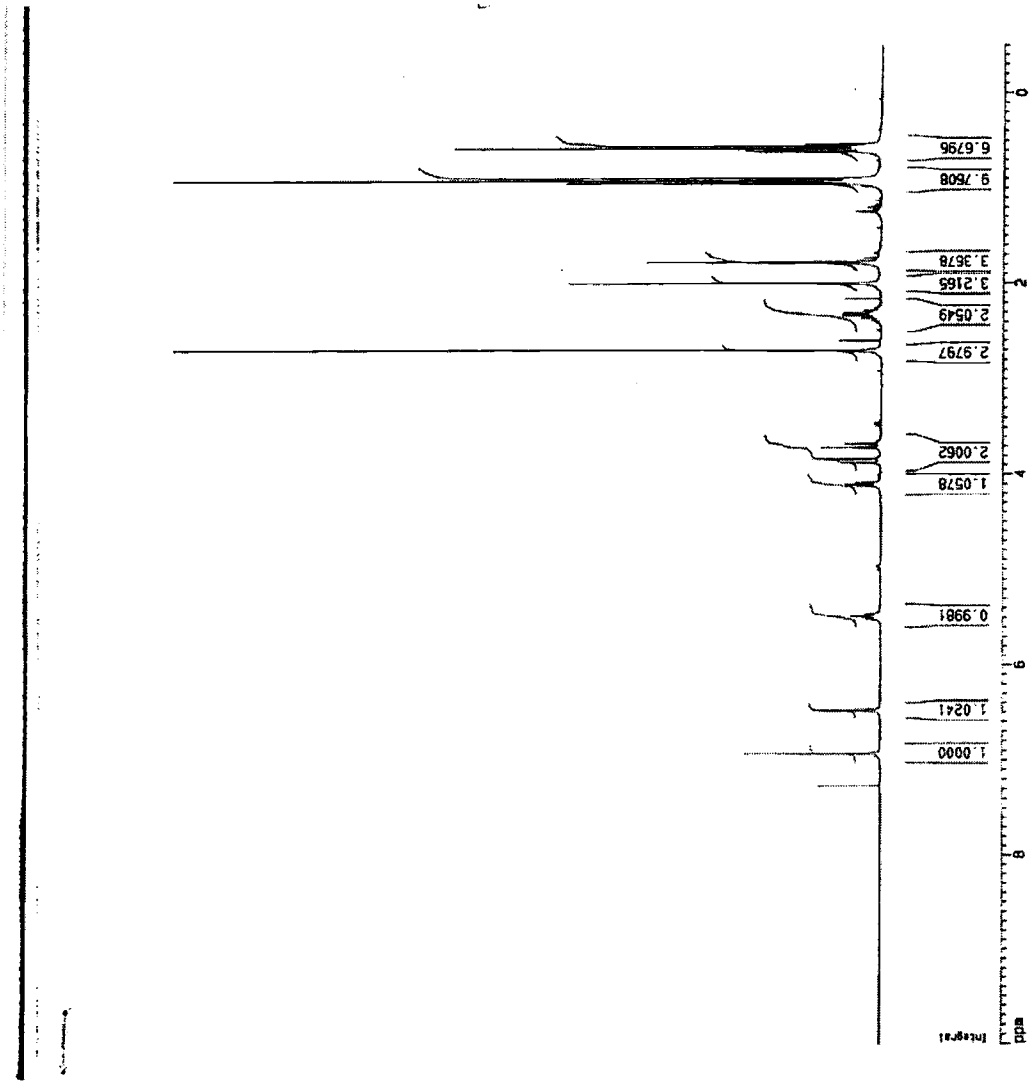
Dilactone 94



Dilactone 95



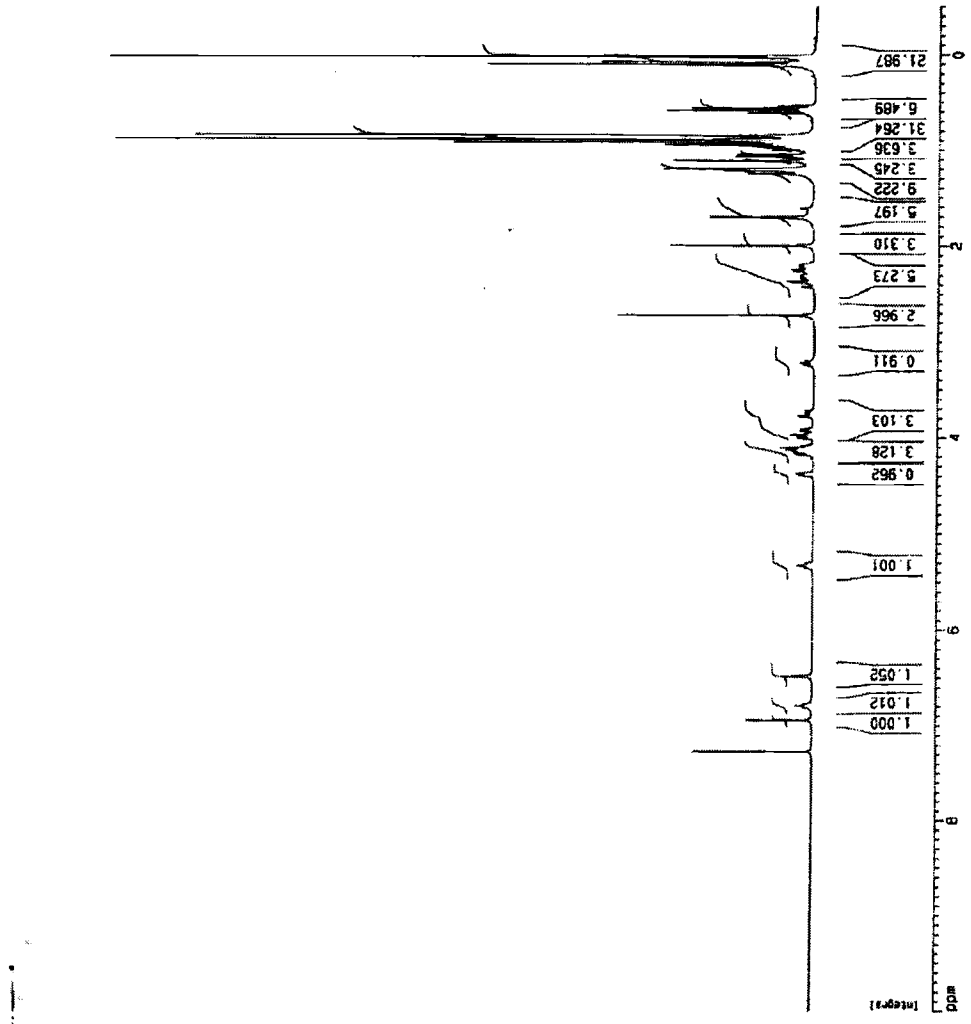
Dilactone 95


6.6796
9.7608
3.3678
3.2165
2.0549
2.9797
2.0062
1.0578
0.9981
1.0241
1.0000
Integral
ppm

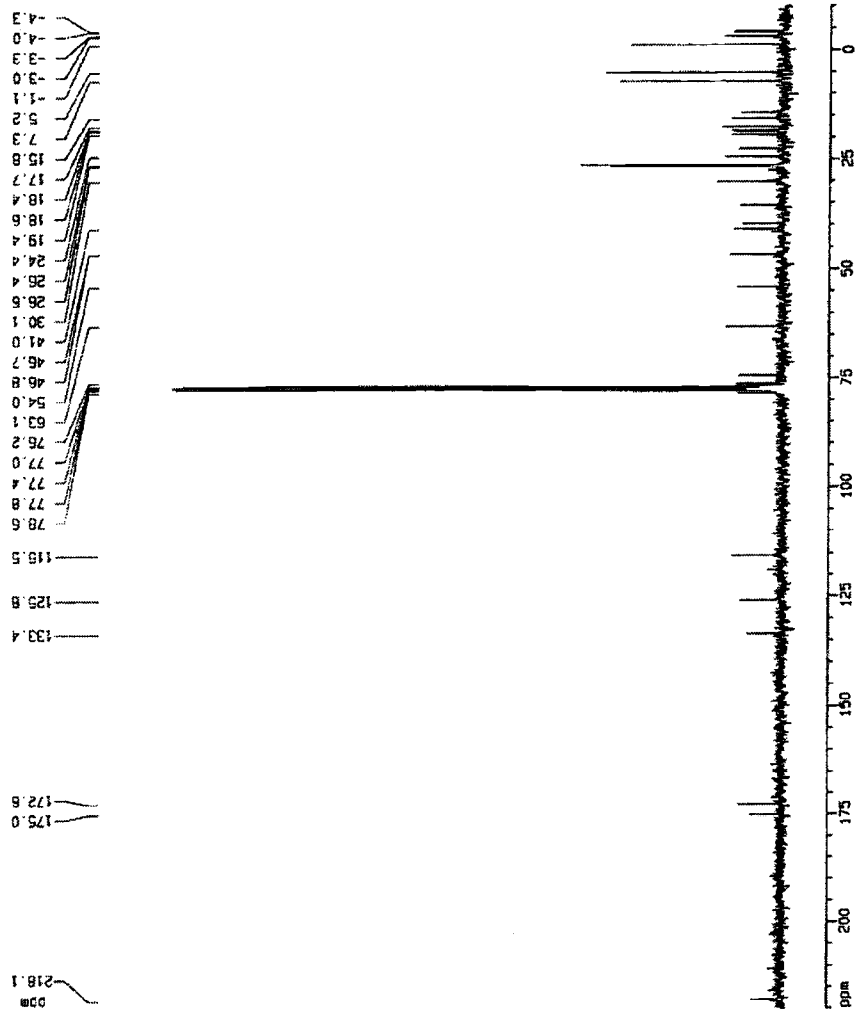
Azide 96

Azide 96

164.9
153.3
142.3
131.3
127.7
119.4
115.7
78.7
77.9
77.4
77.0
51.8
35.8
22.7
19.6
14.4
7.2
5.2
ppm
175
150
125
100
75
50
25
0


21.987
6.489
31.264
3.636
3.245
9.222
5.197
3.310
5.273
2.966
0.911
3.103
3.128
0.962
1.001
1.052
1.012
1.000
[integral]
ppm
0
2
4
6
8

Amide 97


-4.3
-4.0
-3.3
-3.0
-1.1
5.2
7.3
15.8
17.7
18.4
18.6
19.4
24.4
26.4
26.6
30.1
41.0
46.7
46.8
54.0
63.1
76.2
77.0
77.4
77.8
78.6
115.5
125.8
133.4
172.8
175.0
218.1
DSM
0
25
50
75
100
125
150
175
200
ppm

Amide 97