Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Total Synthesis of Macrodiolide Ionophores Aplasmomycin and Boromycin via Double Ring Contraction

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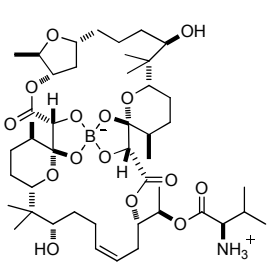
The half structure of the symmetrical macrodiolide aplasmomycin A was synthesized by alkylation of a C3-C10 α-sulfonyl ketone subunit, prepared from (*R*)-pulegone and protected as a C3 ortholactone with (2*R*,3*R*)-butanediol, by a protected 15,16-dihydroxy (12*E*)-allylic chloride representing C11-C17. The latter was obtained from (2*S*,3*R*)-1,2-epoxy-3-butanol and propargyl alcohol. Regio- and stereoselective 5-exo-trig cyclization of the ene diol moiety in this segment, mediated by *N*-bromosuccinimide, led to the (2*R*,3*S*,5*R*)-tetrahydrofuran substructure of aplasmomycin A. Attachment of an α-acetic ester at the C3 carboxylic acid and esterification of the 3'-hydroxyl group of the tetrahydrofuran as its α-bromoacetate enabled coupling of two aplasmomycin half structures as an α-acyloxy acetate. Mukaiyama macrolactonization of this hydroxy acid afforded a symmetrical 36-membered diolide. Base-mediated double Chan rearrangement of this bis α-acyloxy dilactone caused ring contraction to the 34-membered macrocycle of desboroaplasmomycin A while generating the transannular 2-hydroxy-3-hemiketal motif of the natural product in the correct configuration. Final

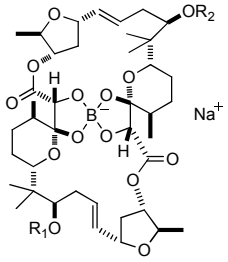
incorporation of boron into the tetraol core produced aplasmomycin A, isolated as its sodium borate. Extension of this route to the unsymmetrical macrodiolide boromycin was accomplished by modifications that included reversal of C12-C13 olefin geometry to (*Z*) for the southern half structure along with stereoselective hydride reductions of the C9 ketone that produced (9*R*) and (9*S*) alcohols for northern and southern half structures, respectively. Coupling of these half structures was made using an α-acyloxy ester linkage as for aplasmomycin A, but ring closure in this case was orchestrated via a blocked C16 alcohol that left open the C15 hydroxyl group of the southern half for Mukaiyama macrolactonization. A double Chan rearrangement of the resulting 35-membered macrocyle produced the 33-membered diolide of desborodesvalinylboromycin which had been obtained previously by degradation of natural boromycin. Insertion of boron into the tetraol core followed by esterification of the C16 alcohol with a masked D-valine and final deprotection furnished boromycin as its zwitterionic (Böeseken) complex.

Introduction

The discovery in 1967 by Huetter et al of a boron-containing macrodiolide in a culture of *Streptomyces antibioticus* brought to light the first member of a series of naturally occurring ionophores in which a borate core serves as the counterion to a sequestered alkali metal cation.[1] The compound, named boromycin (**1**), has since been encountered in several antibiotic screens where its activity against gram-positive bacteria, certain fungi, and protozoae has been evaluated.[2] The ability of **1** to encapsulate alkali metal cations and transport them across artificial membrane systems has provided a useful tool for studying the mode of action of this antibiotic. Specifically, boromycin has been shown to reduce the permeability barrier of the cytoplasmic membrane toward potassium.



1, Boromycin



2, R_1=R_2=H, Aplasmomycin A
3, R_1=H, R_2=Ac, Aplasmomycin B
4, R_1=R_2=Ac, Aplasmomycin C

Figure 1. Boromycin (**1**) and Aplasmomycins A-C (**2**-**4**)

In 1975, Kitahara and coworkers isolated three ionophores closely related to boromycin from *Streptomyces griseus* and named them aplasmomycins A (**2**), B (**3**), and C (**4**).[4] The structure of **2** was deduced by X-ray crystallographic analysis of its silver(I) complex which revealed that, in addition to the presence of a borate Böeseken complex, aplasmomycin A was a symmetrical molecule comprised of two identical halves.[5] The half structure of **2** was found to be similar to the "northern" portion of boromycin, but possessed unsaturation at C11,C12 that was absent in **1**. Boromycin itself has not yielded to X-ray crystallographic analysis, but the structure of the rubidium complex **5** of desvalinylboromycin[6] as well as the heptaol **6** in which the borate core is removed[7] have been secured by X-ray analysis. A conclusion drawn from structural comparison of **5** with **6** is that the borate is not present to give conformational rigidity to the macrocycle since the conformations of these two substances are virtually identical. Furthermore, a detailed NMR analysis of **1** and its desvalinyl derivative reveals that the solution conformation of these compounds maps closely on to their solid state structures.[8] This finding supported our view that incorporation of a borate into **6** should be facile, a hypothesis that was proven correct by partial synthesis of boromycin from **6**.[9] Although structural analysis of boromycin has not conclusively defined a role for its (*R*)-valinyl appendage, a possible function for this amino ester in the zwitterionic form is that of a "capping" device which covers an aperture housing the borate residue when **1** is not involved in active transport of an alkali metal cation.

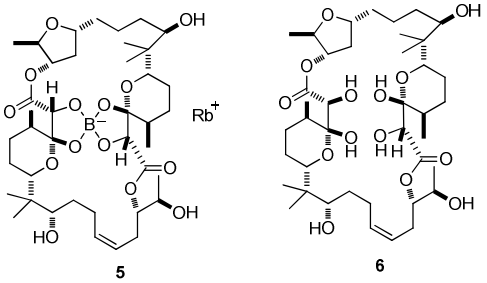
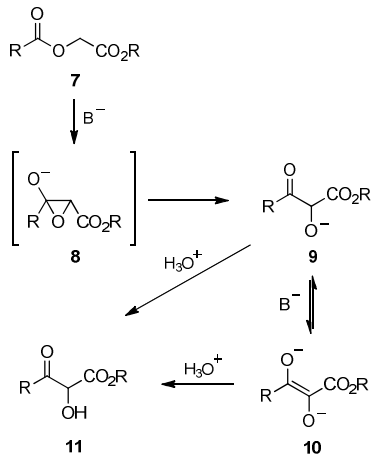


Figure 2. Rubidium Desvalinylboromycinate (**5**) and Desborodesvalinylboromycin (**6**)

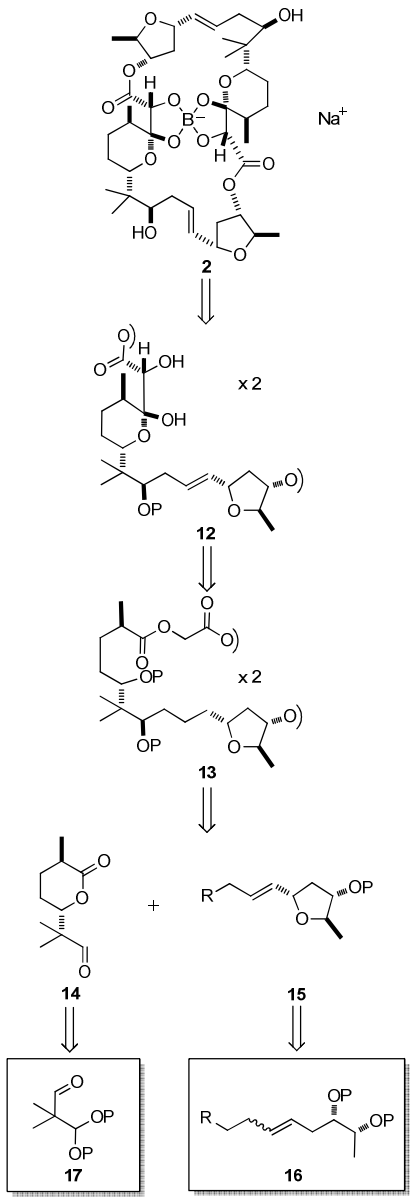
The C1-C3 unit in the half structures of both boromycin and the aplasmomycins is an α-hydroxy-β-ketal carboxylate. This moiety is also a structural feature of other natural products such as the mycalamides,[10] onnamides,[11] theopederins[12] and tartralons,[13] and it appears in oxidized form as an α-keto-β-ketal carboxylate in macrolides such as rapamycin[14] and FK-506.[15] Although several strategies for assembling the contiguous array of oxidized carbon atoms present at C1-C3 in **1** and **2** are conceivable, we were drawn to a reaction first described by Chan in which an α-acyloxy carboxylate undergoes rearrangement in a basic medium to an α-hydroxy β-keto ester.[16] The "Chan rearrangement," illustrated in Scheme 1, is presumed to involve reorganization of the enolate of ester **7** to an intermediate alkoxy epoxide **8** which collapses to α-alkoxy β-keto ester **9**. The latter was shown by Chan to undergo further deprotonation to give enediolate **10** which can be trapped, for example, as its bis silyl ether. Alternatively, **9** can lead directly to **11**. The overall sequence is formally the result of a mixed Claisen condensation of an α-hydroxy ester and appeared well suited to elaboration of the C1-C3 segment of **1** and **2**. Specifically, we programmed a route to the macrodiolide structures of **1** and **2** in which two units of **7** are incorporated into a macrocycle so that the rearrangement shown in Scheme 1 would result in a double ring contraction and thus generate the functional array at C1-C3 of each half.[17]



Scheme 1

The structural symmetry of aplasmomycin A (**2**) made this substance the more attractive target for an initial synthesis since a head-to-tail coupling of two identical half structures (Scheme 2) could be used to assemble the macrocyclic precursor for ring contraction.[18-21] The key step for setting in place the α-hydroxy-β-ketal carboxylate terminus of **12** would be double Chan rearrangement of cyclic bis α-acyloxy ester **13**.[18] The latter was foreseen as the product of alkylation of lactone aldehyde **14** by an allylic nucleophile **15** bearing an activating group (R), followed by head-to-tail coupling. While other disconnections of **13** can be envisioned, the blueprint laid out in Scheme 2 has the tactical advantage that functionality and stereocenters are more or less evenly apportioned between two major subunits. Furthermore, reversal of electrophile and nucleophile roles in the assembly process can be accommodated in this plan if our attempt to unite **14** with **15** should fail, as indeed it did. Since our eventual goal encompassed boromycin (**1**) as well as **2**, it was important that our synthesis take account of the dissymmetric nature of **1** by providing access to the southeastern quadrant of **1**. For this reason, **15** is shown fashioned in Scheme 2 from an acyclic module **16**, our intent being to execute a 5-exo-trig cyclization of this enediol to construct the tetrahydrofuran unit of aplasmomycin and the northern portion of boromycin.[22] Alternatively, **16** would remain in its acyclic cisoid form for the southern half of **1**.[23] Lactone aldehyde **14** was initially viewed as the (racemic) product of a tiglate anion addition to a protected dimethyl malondialdehyde system **17**, although an improved asymmetric route to **14** was

developed subsequently.

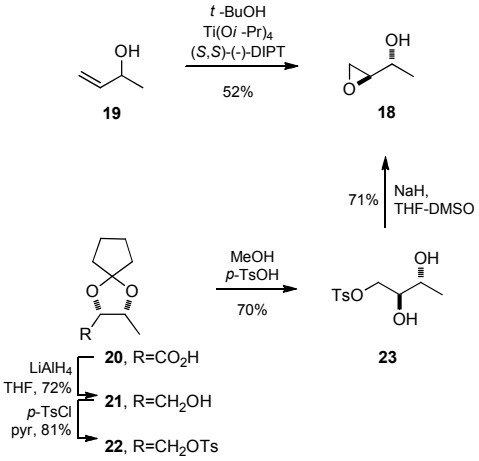


Scheme 2

Results and Discussion

Our first approach to **16** commenced from (*2S*,*3R*)-1,2-epoxy-3-butanol (**18**),[24] a substance prepared from racemic 3-buten-2-ol (**19**) by kinetic resolution using Sharpless asymmetric epoxidation[25] with (*S*,*S*)-(-)-diisopropyl tartrate as the catalyst (Scheme 3). This epoxidation accomplished preparation of (-)-**18** but proved unsatisfactory for amassing bulk material needed for a multistep synthesis. Consequently, **18** was synthesized by an alternative route from (*2R*,*3R*)-2,3-dihydroxybutyric acid, a

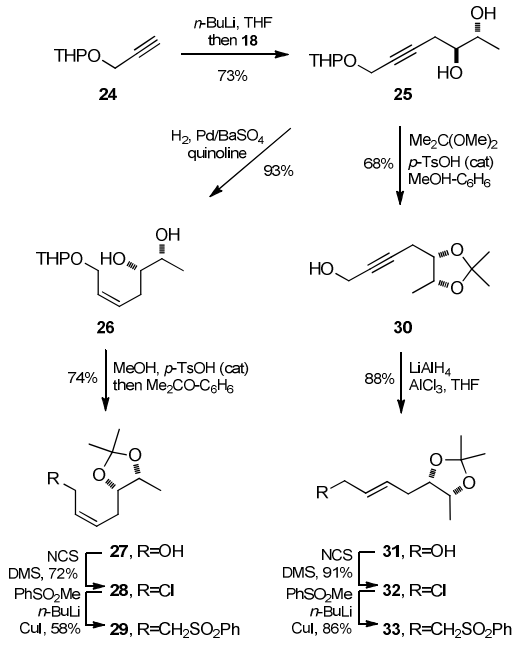
substance of proven absolute configuration[26] prepared by dihydroxylation of trans-crotonic acid[27] followed by resolution via its quinine salt. After protection of this diol as its cyclopentylidene derivative **20**, the carboxyl function was reduced and the resultant alcohol **21** was converted to its tosylate **22**. Removal of cyclopentylidene protection and treatment of diol **23** with sodium hydride in tetrahydrofuran containing a small quantity of dimethyl sulfoxide furnished **18**, identical in all respects including optical rotation with material prepared by asymmetric epoxidation of **19**.



Scheme 3

Continuation from **18** took advantage of the efficient opening of this epoxide by the lithio anion of propargyl tetrahydropyranyl ether (**24**) (Scheme 4). The resulting alkyne **25** was taken forward as a 1:1 mixture of two diastereomers along two different paths in order to obtain alkene **16** as geometrically pure cis and trans isomers. The cis isomer of **16** would be needed for the southern segment of **1**, but it was not clear *a priori* which geometrical isomer of **16** would be the preferred candidate for cyclization to the trisubstituted tetrahydrofuran of **15**. First, **25** was semi-hydrogenated under Lindlar conditions to afford cis alkene **26**. The latter was treated with methanol in the presence of an acidic catalyst and then with an acetone-benzene mixture in a sequence that cleaved the tetrahydropyranyl ether and protected the vicinal diol as acetonide **27**. At this juncture, a choice was made regarding the activating group R that would enable **15** to function as a nucleophile for coupling with aldehyde **14**. A phenylsulfonyl appendage was selected since its incorporation into **16** and its later removal from a coupled product

were likely to be straightforward. Alcohol **27** was therefore converted to allylic chloride **28** and the chloride was displaced by the anion of methyl phenyl sulfone to yield **29**.

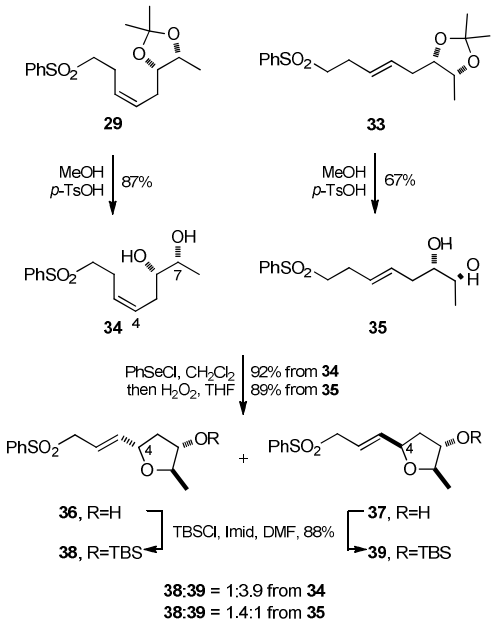


Scheme 4

We next returned to **25** in order to advance this diol towards the trans isomer of sulfone **29**, a transformation accomplished by modifying the sequence that took **26** to **27**. Diol **25** was converted to acetonide **30** under conditions that also removed the tetrahydropyranyl protection, and the resulting propargylic alcohol was reduced with lithium aluminium hydride in the presence of aluminium trichloride[28] to give trans allylic alcohol **31**. Conversion of **31** to chloride **32** followed by displacement with the anion of methyl phenylsulfone furnished **33**.

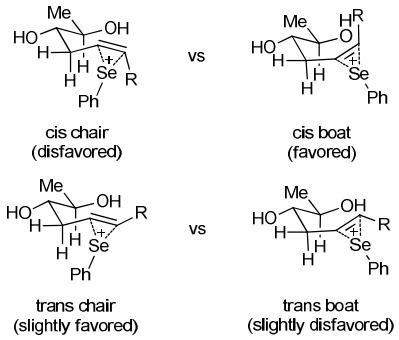
Acetonides **29** and **33** were each cleaved with methanol in the presence of a trace of acid to give diols **34** and **35** (Scheme 5) whose cyclization could now be studied for access to the trisubstituted tetrahydrofuran subunit present in **1** and **2**. Of the several modes of ring closure available to dihydroxy alkenes **34** and **35**, that involving the distal C7 hydroxyl and the proximal terminus (C4) of the olefin, a 5-exo-trig cyclization, seemed most likely on vectorial grounds;[29] however, the configuration at C5 of the resulting tetrahydrofuran was less easy to predict. A naïve assumption about the biosynthesis of **1** and **2** would suggest that, since the southern half of **1** shows the signature of **34** rather than **35**,

cyclization of the former was more likely to produce the desired (11*S*) configuration of **2**. In the event, this supposition was proven wrong. Intramolecular oxyselenation of **34** with phenylselenyl chloride followed by oxidation of the selenide with hydrogen peroxide gave a mixture of tetrahydrofurans **36** and **37** in high yield[30] and although these isomers could not be separated their *tert*-butyldimethylsilyl ethers, **38** and **39** respectively, were cleanly resolved on chromatography. From this experiment, it was deduced that the ratio **38**:**39** was 1:4 and that **34** had therefore led predominantly to the incorrect tetrahydrofuran stereoisomer **37** for **1** and **2**. An analogous sequence of phenylselenylation and selenoxide elimination, when carried out with **35**, again led to a mixture of **36** and **37**, but in this case the ratio of silyl ethers **38**:**39** was 1.5:1, indicating that the correct tetrahydrofuran configuration was slightly favored from the trans alkene precursor. Stereochemical assignment of the tetrahydrofurans **38** and **39** was facilitated by a nuclear Overhauser experiment in which enhancement of the signal due to the *tert*-butyl protons of **39** was observed when the methine proton at C5 of the tetrahydrofuran was irradiated. No corresponding enhancement was seen in **38**. It was also noticed that the methylene proton signals within the tetrahydrofuran rings of **38** and **39** exhibit markedly different chemical shifts, with those of **38** at δ 1.46 and δ 2.25 and those of **39** at δ 1.16 and δ 1.82. The proton signals of **38** agree well with the corresponding proton resonances in the NMR spectrum of aplasmomycin.



Scheme 5

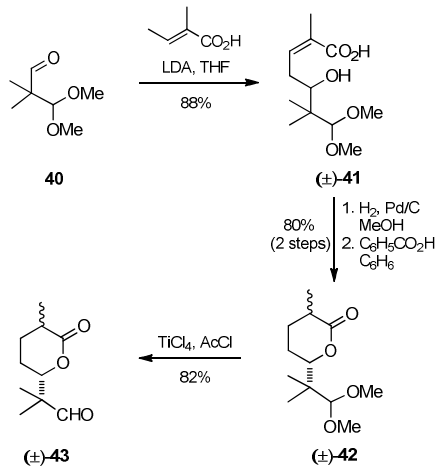
A rationale for the intramolecular oxyselenylation of **34** and **35** is presented in Scheme 6. Cyclization involving an intermediate selenium ion permits two pathways for each alkene, one proceeding through a chair-like transition state and the other via a boat. For **34**, the cis chair transition state is disfavored by a steric interaction between the R group and the pseudoaxial hydrogen of the methylene group interposed between the alkene and diol. This interaction is removed in the cis boat transition state which therefore leads to a cis-2,5-disubstituted tetrahydrofuran as the major cyclization product.[31] The energy difference between chair and boat transition states in the oxyselenation of trans alkene **35** is smaller, the (trans) boat being disfavored by an eclipsing H-H interaction between an alkene hydrogen and the pseudoaxial methylene hydrogen atom. This would give the trans chair conformer a small advantage leading to a narrow majority of **36**. The lesson taught by the chemistry in Scheme 5 was that a trans olefin analogous to **35** would be the preferred substrate for constructing the tetrahydrofuran unit of aplasmomycin and the northwestern quadrant of boromycin.



Scheme 6

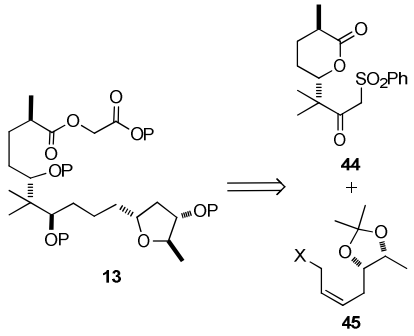
With a route to two of the quadrants of aplasmomycin settled, attention turned to the remaining pair of subunits in this diolide. The designation of **14** as the partner for coupling with allylic sulfone **38** was based on the assumption that the aldehyde function of **14** but not the lactone would react with the anion of **38,** and that selective attack would occur at the *re* face of the carbonyl to deliver an alcohol of desired (*R*) configuration. Our initial approach to lactone aldehyde **14** commenced from the monoacetal **40** of 2,2-dimethylmalondialdehyde, prepared in three steps from isobutylraldehyde (Scheme 7).[32] Exposure

of **40** to the dianion of tiglic acid produced δ-hydroxy α,β-unsaturated acid **41** which was hydrogenated and then dehydrated in benzene containing a trace of benzoic acid to yield lactone **42** as a 1:1 mixture of cis and trans isomers.[33] Cleavage of the dimethyl acetal from **42** under the anhydrous conditions described by Berkowitz[34] gave **43**. Although this lactone-aldehyde was a stereoisomeric mixture of two racemates, **43** was considered a useful test substrate for coupling with enantiopure sulfone **29**; however, no conditions could be found that led to coupling of the anion of **29** with aldehyde **43**. Instead, a deuterium exchange experiment revealed that the preformed anion of **29** had deprotonated **43** at the carbon α to the lactone carbonyl. This result implied that the quaternary carbon adjacent to the aldehyde of **43** presented too large a steric barrier for the coupling to occur.



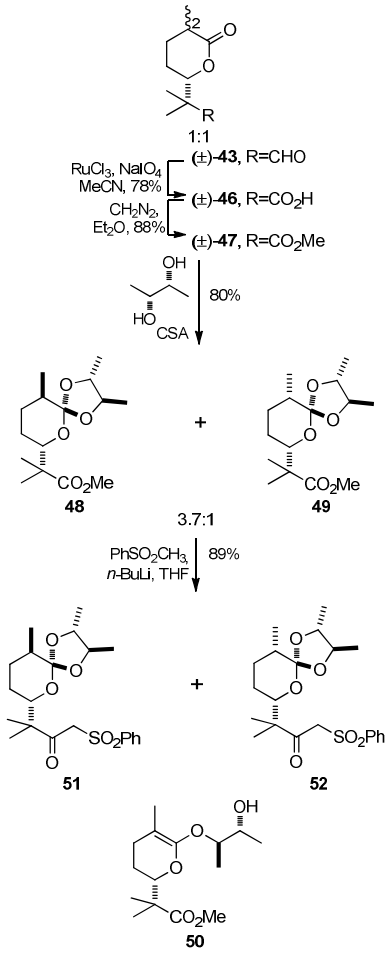
Scheme 7

Fortunately, there was a detour around this impasse requiring only modest revision of the strategy outlined in Scheme 2. The important change was reversal of the roles of electrophile and nucleophile partners in the coupling operation, so that connection would now be made between sulfone **44** and allylic halide **45** at the C10-C11 bond instead of the more sterically encumbered C9-C10 linkage (Scheme 8). There remained the question of selective deprotonation of keto sulfone **44** as well as the preparation of **44** or its surrogate in enantiopure form, but a solution to both of these problems was found in the form of an ortho lactone derivative of **44**.



Scheme 8

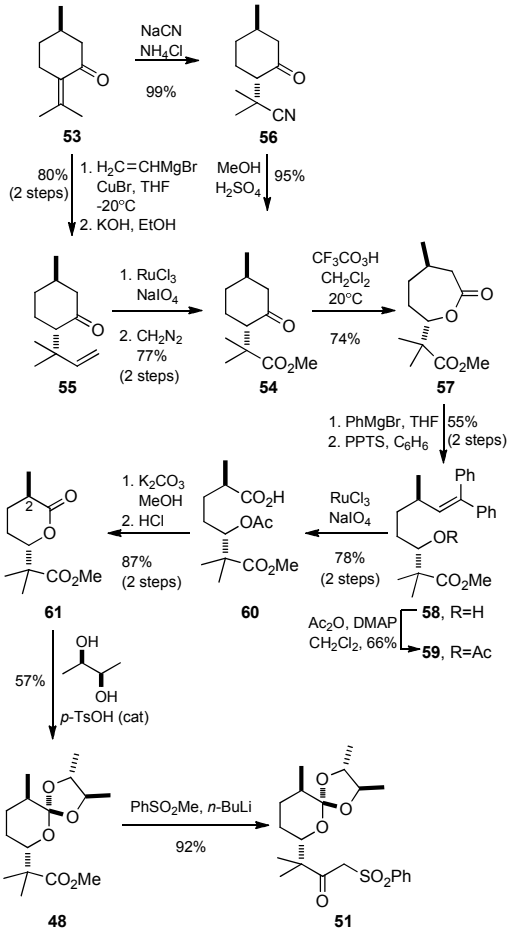
Our revised strategy for assembling quadrants of **1** and **2** began with oxidation of **43** to carboxylic acid **46** which was esterified with diazomethane to yield **47** as a 1:1 mixture of cis and trans isomers (Scheme 9). Exposure of **47** to (2*R*,3*R*)-(-)-butan-2,3-diol in the presence of a catalytic quantity of camphorsulfonic acid gave two ortho lactones **48** and **49** in the ratio 3.7:1, indicating that equilibration at the stereogenic center bearing the methyl substituent had occurred. A plausible explanation for this stereomutation involves reversible formation of ketene acetal **50**, implying that the desired stereoisomer **48** is the thermodynamically more stable epimer. Since **48** and **49** could not be separated, the mixture was subjected to condensation with the dianion of methyl phenyl sulfone under conditions described by Kondo for the formation of β-keto sulfones from esters.[31] This afforded **51** and **52** which were separated by chromatography and their configurations assigned by correlation with material prepared independently (*vide infra*).



Scheme 9

The mixture of stereoisomers produced in the sequence leading to **48** and **49** prompted a search for a new route that would lead to **47** as a single (2*R*) enantiomer in the hope that this lactone ester could be transformed with conservation of stereochemistry to **48** and thence **51**. (*R*)-(+)-Pulegone (**53**) was selected as the new point of departure and was converted to keto ester **54** via two independent pathways (Scheme 10).[35] The first route employed a copper(I) catalyzed conjugate addition of vinylmagnesium bromide to **53** to yield, after basic treatment of the mixture of cis and trans isomers, an equilibrium in favor of **55**. The vinyl group of **55** was cleaved oxidatively to yield a carboxylic acid which gave keto ester **54** upon exposure to diazomethane. A second route to **54** took advantage of the known hydrocyanation product **56**[36] of pulegone and this cleanly furnished **54** after acidic methanolysis. Baeyer-Villiger oxidation of **54** gave lactone **57** in excellent yield, and Barbier-Wieland degradation of

57 with phenylmagnesium bromide followed by acid-catalyzed dehydration[37] afforded alkenol **58** which was acetylated to yield **59**. Oxidative cleavage of alkene **59** produced carboxylic acid **60** from which the acetate was cleaved by basic methanolysis; acidification then led to enantiomerically pure δ-lactone **61**. The latter was converted to ortho lactone **48** without epimerization of the C2 methyl group under carefully controlled conditions that avoided ketene acetal **50**, and reaction of **48** with the dianion of methyl phenyl sulfone yielded **51** whose spectral properties matched those of the major isomer from the mixture of **48** and **49**.

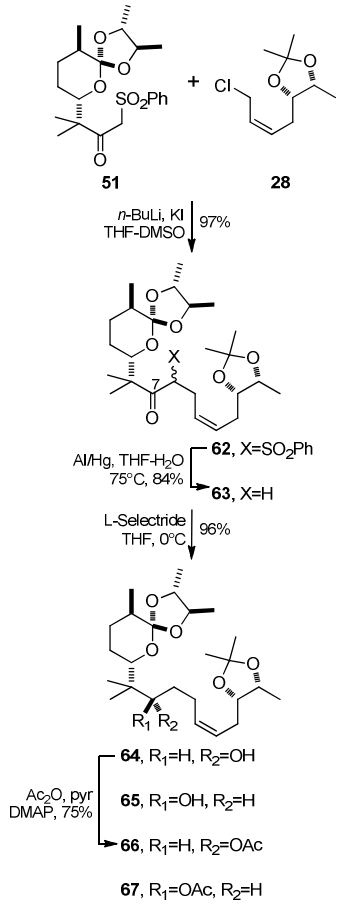


Scheme 10

With enantiopure keto sulfone **51** in hand, the most expedient path to half structures of **1** and **2** would logically be through a common intermediate, but for this strategy to be practical it was necessary to account for structural differences between boromycin and aplasmomycin. Thus, whereas aplasmomycin bears identical (9*R*) hydroxyl configurations in each half, stereochemistry at the

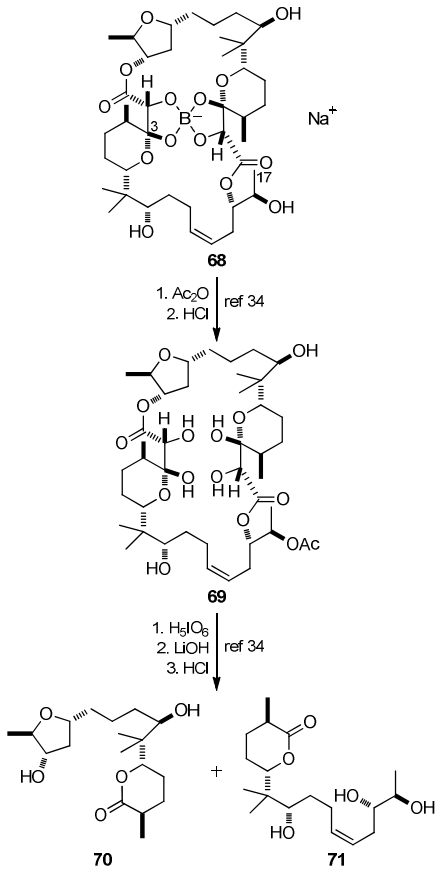
corresponding centers in boromycin is opposite, specifically (9*R*) in the northern sector and (9*S*) in the southern subunit. Also, the half structure of aplasmomycin contains a trans alkene at C11,C12 which is saturated in the northern portion of boromycin. These divergences imposed stringent requirements on methods for reduction of a C9 ketone and for constructing the tetrahydrofuran quadrants of **1** and **2** from their open chain precursor.

A first test of our revised assembly strategy was synthesis of the southern portion (C3-C17) of boromycin from keto sulfone **51** and cis allylic chloride **28**. Exposure of **51** and **28** to *n*-butyllithium in the presence of potassium iodide furnished **62** as a 1:1 mixture of two stereoisomers in nearly quantitative yield; reductive removal of the sulfonyl moiety from **62** afforded a single ketone **63** **(**Scheme 11). At this juncture, a reduction method was needed that would transform the keto group of **63** into a (7*S*) alcohol corresponding to the southern half of **1**, and several hydride reagents were investigated for this purpose. A chelation model in which a metal cation bridges the carbonyl and pyran oxygen predicted that attack at this ketone from the *si* face by a bulky reagent would be sterically impeded by the ortho lactone so that an alcohol of (*S*) configuration should be favoured. In fact, reduction of **63** with L-Selectride gave alcohols **64** and **65** in the ratio 3.5:1. The alcohols could not be separated but their acetates, **66** and **67**, were easily removed from each other by chromatography. The unwanted (7*R*) acetate **67** was returned to ketone **63** for recycling by reduction with lithium aluminium hydride to alcohol **65** and subsequent oxidation with pyridinium chlorochromate.



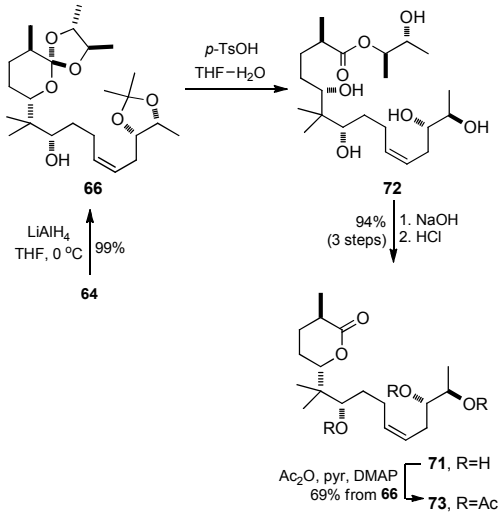
Scheme 11

Acquisition of **66** provided an opportunity to confirm our stereochemical assignments to this compound by correlation with a substance previously obtained by degradation of boromycin. Hanessian has reported that acetylation of sodium desvalinylboromycinate (**68**) obtained by saponification of **1** affords a monoacetate which, after excision of the borate core, yields hexaol **69** (Scheme 12).[38]



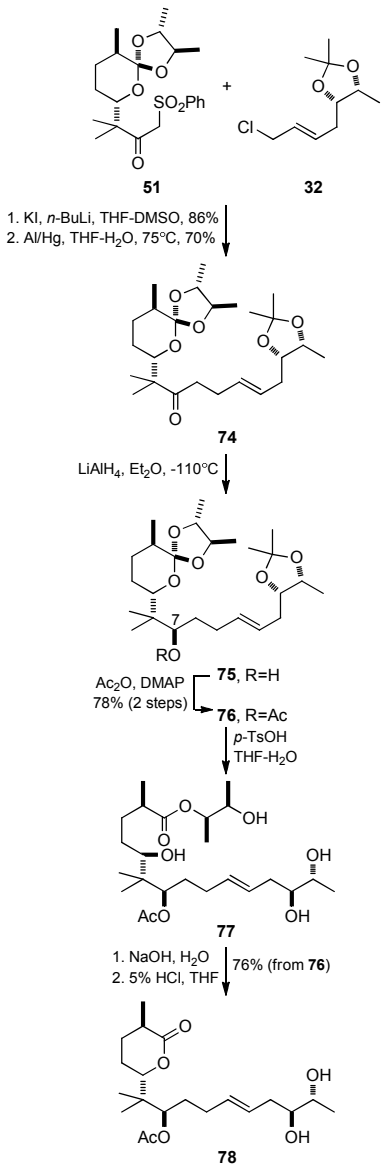
Scheme 12

Cleavage of **69** with periodic acid followed by saponification and acidification furnished lactones **70** and **71**. In order to confirm identity of our synthetic compound with boromycin degradation product **71**, acetate **66** was subjected to acidic hydrolysis to give trihydroxy ester **72** from which the acetate and dihydroxybutyl esters were cleaved by saponification (Scheme 13). Acidification produced polar δ-lactone triol **71** whose spectral properties agreed well with the same substance obtained from natural boromycin, but for rigorous proof of structural identity natural and synthetic **71** were each converted to the same triacetate **73**.



Scheme 13

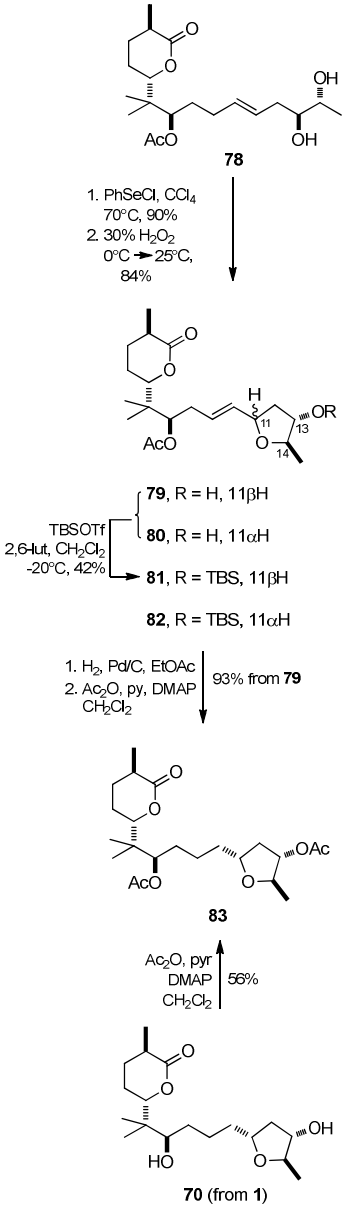
The trisubstituted tetrahydrofuran in aplasmomycin and in the northwest quadrant of boromycin was envisioned as the cyclization product of dihydroxy alkene **16** (Scheme 2), and previous studies on intramolecular oxyselenation of **34** and **35** (Scheme 5) pointed towards a trans alkene as the cyclization precursor that should favour a tetrahydrofuran with the 2,5-trans configuration present in the natural products. Our route to the half structure of **2** was therefore programmed around the alkylation of **51** shown in Scheme 11 but with trans allylic chloride **32** instead of **28**. This coupling proceeded in good yield to give ketone **74** after reductive removal of the sulfonyl group (Scheme 14). Although reduction of **74** with sodium borohydride was found to give alcohol **75** as the major epimer (7*R*:7*S* 3.5:1), a cleaner and more highly stereoselective reduction of ketone **74** was accomplished with lithium aluminium hydride at low temperature. The derived acetate **76** was obtained in good yield as the sole isomer from this reduction after purification.



Scheme 14

Acid-catalyzed hydrolysis of ortholactone **76** afforded tetrahydroxy ester **77** which, upon saponification and acidification, gave δ-lactone **78**. The latter was now our prospective candidate for cyclization to the tetrahydrofuran segment of **1** and **2**, and based on our previous experience with **35** (Scheme 5) we expected that intramolecular oxyselenation of **78** would yield a tetrahydrofuran of predominantly correct (11*R*,13*S*,14*R)* configuration. However, when **78** was treated with phenylselenyl chloride and then with hydrogen peroxide a *ca* 1:1 mixture of **79** and **80** was the result (Scheme 15). Although no other cyclization products were detected in the mixture, stereoisomeric alcohols **79** and **80** could not be separated by chromatography. Fortunately, silyl ether **81** could be removed from its

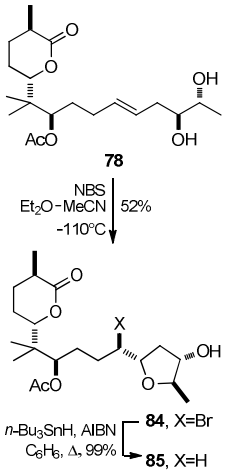
stereoisomer **82** quite easily by chromatography. Catalytic hydrogenation of the mixture of **79** and **80** gave an inseparable mixture of dihydro compounds but when this mixture was acetylated diacetate **83** could be isolated in pure form after chromatography. This compound proved to be identical with the exhaustive acetylation product from diol **70** obtained by degradation of boromycin and also with a substance prepared by Hanessian in the course of his synthetic studies on boromycin.[39] These correlations firmly secured the configuration of **79** arising from oxyselenation of **78**.



Scheme 15

Although the sequence above provided access to the northern sector of boromycin as well as the half

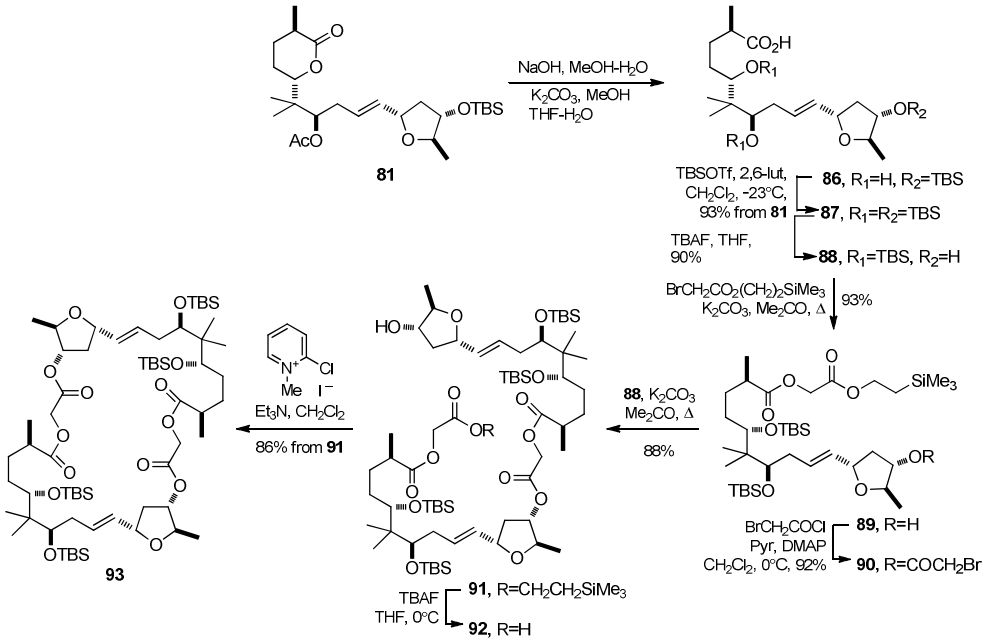
structure of aplasmomycin, a more direct entry to the tetrahydrofuran subunit of **1** than the circuitous pathway through **81** was desirable. Several electrophilic reagents including mercury(II) salts were investigated for cyclization of **78** but most produced a mixture of tetrahydrofuran epimers at C11. However, exposure of **78** to *N*-bromosuccinimide in a mixture of acetonitrile and ether at low temperature led to **84** as a single stereoisomer (Scheme 16). Reductive cleavage of the bromine substituent from **84** with tri-*n*-butylstannane was quantitative and gave **85** which was correlated with material from natural boromycin through its conversion to diacetate **83**.



Scheme 16

Synthesis of δ-lactones **71**, **79** and **85** set the stage, outlined in Scheme 2, for appending a C1-C2 unit to each of these segments and then linking the appropriate half structures through an α-acyloxy lactone bridge. The pivotal reaction at this point would be a "double Chan ring contraction" that would shrink the 34-membered cycle to a 32-membered dilactone and simultaneously install the α-hydroxy β-ketal lactone functionality present in aplasmomycin precursor **12**. Our first target was desboroaplasmomycin A, a substance available from natural **2** which we had previously converted to aplasmomycin A with trimethyl borate.[9] To this end, lactone acetate **81** was hydrolyzed under basic conditions and the resultant dihydroxy acid **86** was silylated to give tris silyl ether **87** (Scheme 17). Model experiments had shown that the secondary neopentyl-type *tert*-butyldimethylsilyl ethers in a structure such as **87** were too sterically hindered for cleavage with tetra-*n*-butylammonium fluoride, and it was therefore

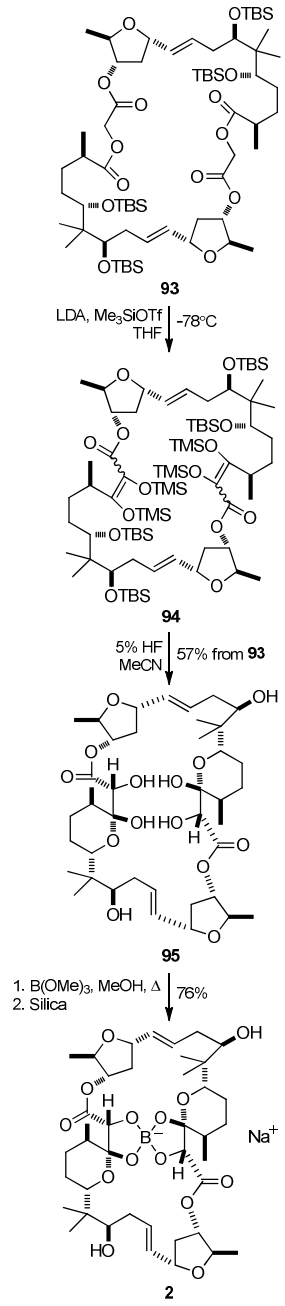
possible to remove silyl protection from the oxygen substituent on the tetrahydrofuran selectively to obtain monohydroxy carboxylic acid **88**. The potassium salt of **88** was converted to ester **89** by reaction with trimethylsilylethyl α-bromoacetate and the free hydroxyl group of **89** was esterified with α-bromoacetyl chloride. Bromoacetate **90** was then coupled with the potassium salt of carboxylic acid **88** to afford tetraester **91**. Removal of the trimethylsilylethyl ester from **91** furnished hydroxy acid **92** which underwent lactonization using Mukaiyama's protocol[40] to yield **93** in which the two-fold symmetry of the 34-membered macrocycle was apparent from the half set of proton and carbon signals displayed in its NMR spectra.



Scheme 17

Initial attempts to promote double ring contraction of **93** were not encouraging. The sequence we had envisioned, represented in Scheme 1 as **7** → **8** → **9** → **11** and which we had assumed would take place upon exposure of **93** to base, did not produce the bis α-hydroxy β-ketal lactone motif of desboroaplasmomycin. Instead, a mixture of unidentified fragmentation products appeared to be formed. However, Chan in his study of this rearrangement,[16] had shown that a second equivalent of base will convert **9** to enediolate **10** which can be trapped as a diacetate or as a bis silyl ether. This key

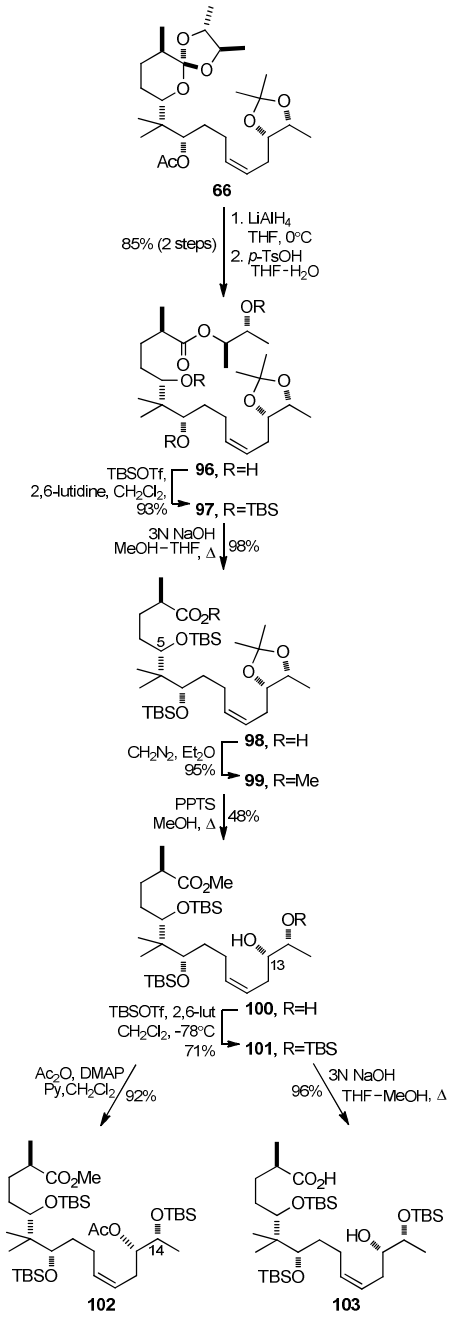
observation suggested that we should treat **93** with at least four equivalents of lithium diisopropylamide in the presence of excess trimethylsilyl triflate, and when this protocol was followed the tetrakis trimethylsilyl ether **94** was obtained as a mixture of *E* and *Z* isomers at each of the conjugated double bonds (Scheme 18). The presence of geometrical isomers complicated spectral analysis of **94** and therefore the mixture was treated directly with hydrogen fluoride in acetonitrile which resulted in cleavage of all eight silyl ethers and closure of the δ-hydroxy ketone to a cyclic hemiacetal. Remarkably, *only one stereoisomer* was produced from the sequence **93** → **95** and the compound was found to be identical in all respects with desboroaplasmomycin (**95**). This result is in line with an observation made from experiments with natural aplasmomycin and boromycin which established that the four hydroxyl substituents at C2, C2' and C3, C3' in these macrodiolides are in their most thermodynamically stable orientation. Furthermore, **95** was found to be chemically quite stable and showed no tendency to undergo retrograde aldol fragmentation that would uncouple the C2-C3 linkages in the macrocycle. Boration of **95** with trimethyl borate in methanol had already been demonstrated with naturally derived desboroaplasmomycin, and application of this protocol to synthetic **95** completed the synthesis of (+)-**2**.



Scheme 18

Extension of our synthesis of aplasmomycin to boromycin[41] required accommodation of two factors absent from our route to **2**. First, since **1** is constituted of structurally different halves, a decision had to be made that would determine which of two modes of macrocycle formation would be used to prepare our ring contraction precursor. A choice in favour of ring closure at the C15 hydroxyl substituent of the lower subunit seemed most logical, primarily because this path could proceed along lines directly analogous to the sequence that led to **93** where initial connection of half structures was made at the

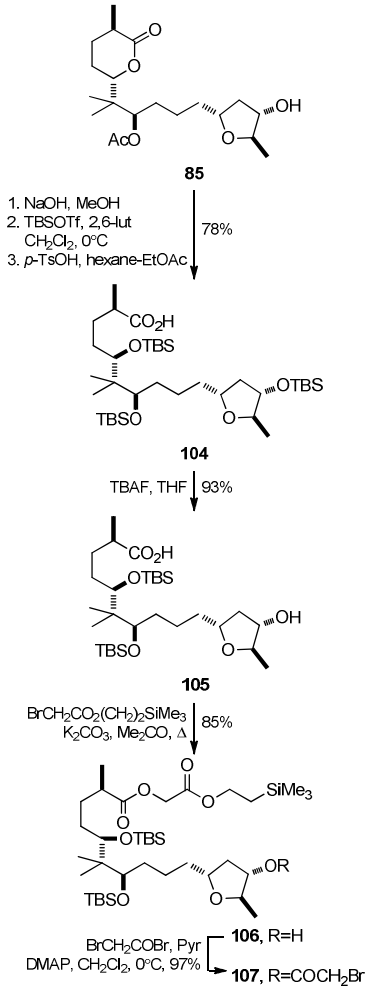
tetrahydrofuran. We had confidence from model experiments that lactonization at the C15 hydroxyl group would present no problem even if the C16 oxygen carried a protecting group, but this raised a second question regarding a distinction between hydroxyl groups at C15 and C16 in the acyclic domain of boromycin. Here, a model study with triol **71** was helpful in confirming that the more exposed alcohol at C16 could be silylated selectively.



Scheme 19

Preparation of a suitably configured southern half of boromycin for eventual coupling to the northern

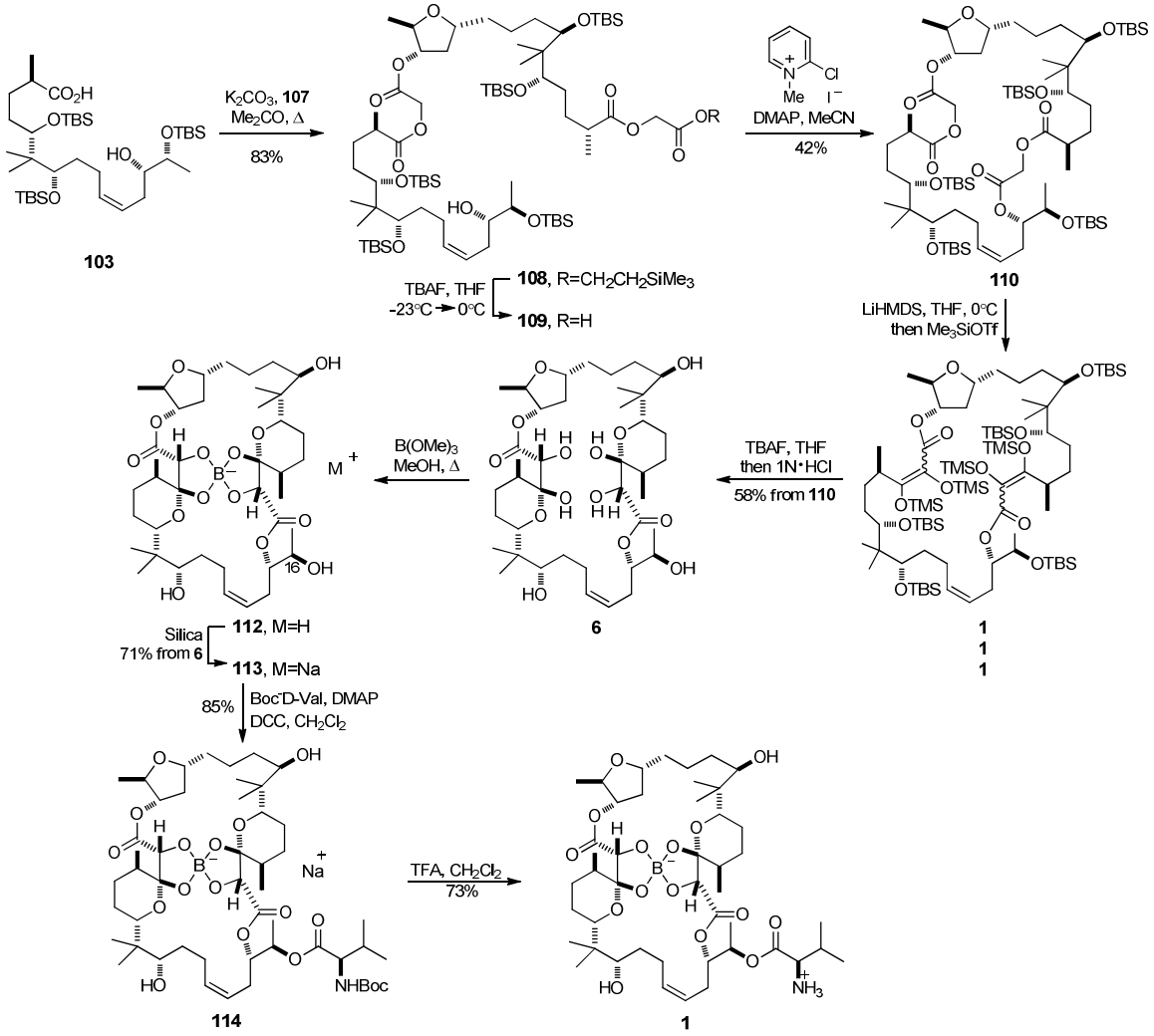
sector of **1** commenced from ortho lactone **66** (Scheme 19). After reduction of the acetate, the ortho lactone was hydrolyzed under mild conditions that left the acetonide intact. The resultant triol **96** was exhaustively silylated and ester **97** was saponified to give carboxylic acid **98**. It was intended that acetonide removal would take place at this stage but exposure of **98** to acidic methanolysis resulted in regeneration of a δ-lactone that is believed to originate from silyl transfer to the carboxyl group from the C5 silyl ether. In order to circumvent this problem, **98** was esterified with diazomethane and methyl ester **99** became the substrate for acetonide cleavage. This was accomplished in methanol at reflux in the presence of an acidic catalyst, and diol **100** was obtained in good yield. Careful silylation of **100** at low temperature gave a tris *tert*-butyldimethylsilyl ether and left one hydroxyl group unreacted. Identification of this alcohol as **101** was made by its conversion to acetate **102** in which decoupling experiments distinguished protons at C13 (δ 4.79) and C14 (δ 3.87) and confirmed that the latter was coupled to the C15 methyl protons (δ 1.14). This proved that silylation of **100** had occurred selectively at the C14 hydroxyl substituent, leaving the C13 alcohol exposed. With site selectivity of silylation of **100** assured, methyl ester **101** was saponified to provide hydroxy acid **103** as the substrate for incorporation into the lower half of **1**.



Scheme 20

The upper segment of boromycin required for connection to **103** was prepared from **85** along lines similar to those used for conversion of its unsaturated counterpart **81** to **90** (Scheme 20). Lactone acetate **85** was saponified and exhaustively silylated to give **104** after acidic cleavage of the intermediate silyl ester. Selective desilylation of the tetrahydrofuranyl silyl ether of **104** yielded hydroxy acid **105** which was primed for coupling to **103** by conversion of the carboxyl group to its trimethylsilylethyl ester **106** and then by esterification of alcohol **106** with α-bromoacetyl bromide to furnish **107**. Assembly of the macrocyclic contraction precursor for boromycin began with treatment of the potassium carboxylate from **103** with bromoacetate **107** (Scheme 21). This coupling afforded tetra ester **108** from which the 2-trimethylsilylethyl ester was cleaved selectively by exposure to tetra-*n*-butylammonium fluoride at low temperature. All of the silyl ethers were retained during this process.

Hydroxy acid **109** underwent Mukaiyama lactonization to **110**,[40] and treatment of **110** with excess lithium hexamethyldisilazide in the presence of excess trimethylsilyl triflate produced **111** as an *E/Z* mixture at each of the conjugated double bonds. The mixture was subjected to exhaustive desilylation with tetra-*n*-butylammonium fluoride which cleaved all nine of the silyl ethers from **111**, and the crude product was exposed briefly to acid. As with the formation of desboroaplasmomycin (**95)** from **93**, desborodesvalinylboromycin (**6**) was obtained as a single epimer from this sequence. The relatively nonpolar heptaol **6** was found to be identical with material previously obtained from natural boromycin after cleavage of the valinyl appendage and hydrolytic removal of the borate core. In the forward direction, **6** was converted to **112** by a previously developed sequence[9] involving exposure to dry trimethyl borate in methanol. Upon passage through silica, **112** sequestered sodium ion and yielded sodium desvalinylboromycinate (**113**) identical with the product of saponification that selectively removed the D-valine residue from **1**. Esterification of the C16 hydroxyl group of **113** with Boc-protected D-valine afforded **114** and final cleavage of Boc protection with trifluoroacetic acid gave (+)-boromycin (**1**). Zwitterion **1** is a remarkably nonpolar compound, consistent with a conformation of the molecule that folds the positively charged nitrogen atom of the valine appendage into the interior of the macrodiolide where it is held by the negative borate counterion.



Scheme 21

Conclusion

Base-promoted rearrangement of an α-acyloxy acetic ester to an α,β-enediolate, first demonstrated by Chan, has been found to constitute a powerful method for creating the α-hydroxy β-ketal lactone motif within the complex molecular architecture of aplasmomycin and boromycin. In the present context, this rearrangement was a device for ring contraction of a 34-membered macrocycle to a 32-membered diolide while simultaneously generating the core units of these boron-containing ionophoric structures in their natural configuration. Very little use has been made of this construction in complex synthesis, but it is worth noting that Chan rearrangement played a pivotal role in Holton's synthesis of taxol.[42]

Experimental

General

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran and ether were distilled from sodium and benzophenone under an argon atmosphere. Toluene, diisopropylethylamine, triethylamine, pyridine and dichloromethane were distilled over calcium hydride under argon. All solvents used for routine isolation of products and for chromatography were reagent grade. Moisture- and air-sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flame-dried under a stream of argon gas, glass syringes, and needles were oven-dried at 120 °C prior to use.

Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure. Residual solvent was removed by vacuum pump at a pressure less than 0.25 mm of mercury. Analytical thin-layer chromatography was carried out on precoated plates of silica gel of 0.2 mm layer thickness. Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 3-5% solution of phosphomolybdic acid in ethanol, a 10% solution of ammonium molybdate in water, a 1% solution of vanillin in 0.1 M sulfuric acid in methanol, or a 2.5% solution of *p*-anisaldehyde in ethanol containing 5% water, 3.5% concentrated sulfuric acid and 1% acetic acid. Column chromatography was carried out on silica gel of 230-300 mesh ASTM (40 μm particle size). Optical rotations were measured on a polarimeter at ambient temperature using a 0.9998 dm cell with 1 ml capacity. Infrared (IR) spectra were recorded on a FT-IR spectrometer. Nuclear magnetic resonance (NMR) spectra were measured at either 300 or 400 MHz for protons and at 75 or 100 MHz for carbon-13 nuclei. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the δ scale. Proton NMR data are reported in the order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (*J* in Hertz), and number of protons. Chemical ionization (CI) high- and low-resolution mass

spectra (HRMS and MS) were measured using a source temperature at 120 °C with methane gas as the ionizing source and perfluorokerosene as a reference. Electron impact (EI) mass spectra were measured at 70 eV; fast atom bombardment (FAB) mass spectra were measured using an electrospray instrument with quadrupole detection.

(2*R*,5*S*,7*R*,9*E*)-5,7-Di(*tert*-butyldimethylsilyloxy)-10-[(2'*R*,3'*S*,5'*S*)-2-methyl-3-(*tert*-butyldimethylsilyloxy)tetrahydrofuranyl]-2,6,6-trimethyldecenoic Acid (87). To a solution of **81** (54.0 mg, 0.112 mmol) in methanol (10 mL) at 0 °C was added aqueous sodium hydroxide (10%, 4 mL) and the mixture was stirred at room temperature for 24 h. The solution was cooled to 0 °C and hydrochloric acid (5%) was added until the strongly alkaline solution was weakly basic (*ca* pH 9). The mixture was evaporated to dryness under vacuum and traces of residual water were removed by azeotropic distillation with benzene to give crude dihydroxy acid **86**.

To a solution of crude **86** obtained above in methylene chloride (8 mL) at -23 °C was added 2,6-lutidine (300 μL, 2.5 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (300 μL, 1.25 mmol). The solution was stirred at -23 °C for 2 h and at 0 °C for 1 h, then was diluted with ether (10 mL). The ethereal solution was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting crude silylated product was dissolved in a mixture of absolute methanol (9 mL) and tetrahydrofuran (3 mL) at room temperature and saturated aqueous potassium carbonate was added. The mixture was stirred at room temperature for 2 h, evaporated to dryness under vacuum and the residue was taken up into brine (3 mL). The pH of the mixture was adjusted to 4-5 by addition of aqueous sodium bisulfite and the mixture was extracted with ether (15 mL). The extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was chromatographed on silica (15 g, hexanes:ethyl acetate 10:1 to 5:1) to afford **87** (72.2 mg, 93%) as a colourless oil: $[\alpha]_D^{20}$ +6.1 (*c* 0.71 $CHCl_3$); IR ($CHCl_3$) 3400-2400 (br), 2940, 2905, 2855, 1710, 1460, 1380, 1370, 1095, 830, 760, 755, 650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.02 (s, 3H), -0.01 (s, 3H), -0.00 (s, 3H), 0.01 (s, 3H), 0.02 (s, 3H), 0.03 (s, 3H), 0.74 (s, 3H),

0.81 (s, 3H), 0.86 (s, 18H), 0.87 (s, 9H), 1.14 (d, J = 7.1 Hz, 3H), 1.17 (d, J = 6.4 Hz, 3H), 1.10-1.40 (m, 3H), 1.50-1.72 (m, 2H), 1.84 (m, 1H), 2.04 (m, 1H), 2.28 (pent, J = 6.2 Hz, 1H), 2.37 (m, 1H), 2.54 (m, 1H), 3.48 (m, 1H), 3.61 (m, 1H), 3.85 (m, 2H), 4.40 (dd, J = 15.0, 7.7 Hz, 1H), 5.53 (dd, J = 15.4, 8.0 Hz, 1H), 5.67 (dt, J = 15.4, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.8, -4.6, -4.2, -3.8, -3.3, -3.1, 17.0, 18.0, 18.3, 18.4, 18.5, 18.9, 21.6, 25.7, 26.1, 26.2, 30.8, 31.6, 36.3, 39.9, 41.1, 44.3, 76.4, 77.2, 78.0, 78.2, 79.9, 131.3, 132.5, 182.1; HRMS (EI) calcd for $C_{36}H_{74}O_6Si_3$ *m/z* 686.4793, found 686.4808.

(2*R*,5*S*,7*R*,9*E*)-5,7-Di(*tert*-butyldimethylsilyloxy)-10-[(2'*R*,3'*S*,5'*S*)-3-hydroxy-2-methyltetrahydrofuranyl)-2,6,6-trimethyldecenoic Acid (88). To a solution of **87** (77.0 mg, 0.11 mmol) in tetrahydrofuran (7 mL) at room temperature was added tetra-*n*-butylammonium fluoride (1M in tetrahydrofuran, 400 μL, 0.40 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate (15 mL) and the solution was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica (10 g, hexanes:ethyl acetate 1:1) to give **88** (57.1 mg, 90%) as a viscous oil; $[\alpha]_D^{20}$ +5.2 (*c* 1.3 $CHCl_3$); IR ($CHCl_3$) 3600-2550 (br), 2960, 2940, 2905, 2860, 1730, 1710, 1470, 1370, 1090, 1085, 1070, 1055, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.79 (s, 3H), 0.82 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.12 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 6.5 Hz, 3H), 1.18-1.65 (m, 5H), 1.78 (m, 2H), 1.95 (m, 1H), 2.43 (m, 2H), 2.80 (m, 1H), 3.44 (m, 1H), 3.56 (m, 1H), 4.03 (m, 1H), 4.19 (m, 1H), 4.54 (m, 1H), 5.53 (dd, J = 15.1, 8.1 Hz, 1H), 5.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.2, -3.8, -3.4, -3.2, 17.1, 18.3, 18.4, 18.5, 18.9, 22.3, 26.1, 26.2, 30.8, 31.9, 36.4, 39.9, 40.4, 44.3, 76.6, 77.5, 77.6, 78.2, 81.1, 131.9, 132.2, 181.1; HRMS (EI) calcd for $C_{30}H_{60}O_6Si_2$ *m/z* 572.3928, found 572.3933.

2-Trimethylsilylethoxycarbonylmethyl (2*R*,5*S*,7*R*,9*E*)-5,7-Di(*tert*-butyldimethylsilyloxy)-10-[(2'*R*,3'*S*,5'*S*)-3-hydroxy-2-methyltetrahydrofuranyl]-2,6,6-trimethyldecenoate (89). To a solution of **88** (32.0 mg, 0.056 mmol) in acetone (8 mL) at room temperature was added trimethylsilylethyl 2-

bromoacetate (200 μL, 0.88 mmol) followed by anhydrous potassium carbonate (50 mg) and the mixture was heated at reflux for 40 min. The cooled mixture was diluted with ether (12 mL) and filtered, and the filtrate was concentrated under reduced pressure. The residual oil was chromatographed on silica (10 g, hexanes:ethyl acetate 8:1 to 5:1) to give **89** (37.1 mg, 93%) as a colourless oil: $[\alpha]_D^{20}$ -12.4 (*c* 0.85 $CHCl_3$); IR ($CHCl_3$) 3560-3300 (br), 2930, 2860, 1750, 1745, 1740, 1460, 1380, 1150, 1090, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.01 (s, 6H), 0.02 (s, 9H), 0.04 (s, 6H), 0.72 (s, 3H), 0.82 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 0.99 (m, 2H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.17 (d, *J* = 7.1 Hz, 3H), 1.45-1.55 (m, 2H), 1.50-1.80 (m, 3H), 1.92 (m, 1H), 2.12 (m, 1H), 2.43 (m, 3H), 3.52 (m, 1H), 3.66 (dd, *J* = 6.2, 3.9 Hz, 1H), 3.95 (m, 2H), 4.22 (m, 2H), 4.45 (dd, *J* = 14.0, 7.4 Hz, 1H), 4.52 (d, *J* = 15.7 Hz, 1H), 4.58 (d, *J* = 15.8 Hz, 1H), 5.54 (dd, *J* = 15.3, 7.2 Hz, 1H), 5.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.1, -3.8, -3.3, -3.1, -1.6, 17.1. 17.3, 18.3, 18.4, 18.6, 21.5, 26.1, 30.7, 31.4, 36.2, 39.7, 40.7, 44.3, 60.6, 63.7, 76.1, 77.0, 77.7, 77.9, 80.8, 131.2, 132.5, 167.9, 175.8; HRMS (EI) calcd for $C_{37}H_{74}O_8Si_3$ *m/z* 730.4691, found 730.4704.

2-Trimethylsilylethoxymethyl (2*R*,5*S*,7*R*,9*E*)-5,7-Di(*tert*-butyldimethylsilyloxy)-10-[(2'*R*,3'*S*,5'*S*)-3-(2-bromoacetoxy)-2-methyltetrahydrofuranyl]-2,6,6-trimethyldecenoate (90). To a solution of **89** (36.0 mg, 0.049 mmol) in methylene chloride (5 mL) containing pyridine (39.0 μL, 0.49 mmol) and a catalytic amount of 4-(dimethylamino)pyridine at 0 °C was added α-bromoacetyl chloride. After 15 min, the solution was diluted with ether (8 mL) and was washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure, and the residue was chromatographed on silica (10 g, hexanes:ethyl acetate 10:1) to give **90** (36.0 mg, 92%) as a pale yellow oil: $[\alpha]_D^{20}$ -8.0 (*c* 0.90 $CHCl_3$); IR ($CHCl_3$) 2960, 2940, 2860, 1760, 1740, 1470, 1290, 1160, 1155, 1095, 1070, 860, 840, 820, 745, 725, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.04 (s, 9H), 0.05 (s, 6H), 0.73 (s, 3H), 0.83 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 1.00 (m, 2H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.27-1.42 (m, 2H), 1.63 (m, 1H), 1.78 (m, 1H), 1.91 (m, 1H), 2.12 (m, 1H), 2.48-2.60 (m, 3H),

3.51 (m, 1H), 3.67 (m, 1H), 3.82 (s, 2H), 4.15 (dd, *J* = 6.6, 3.1 Hz, 1H), 4.22 (m, 2H), 4.50 (m, 1H), 4.52 (d, *J* = 15.8 Hz, 1H), 4.58 (d, *J* = 15.7 Hz, 1H), 4.94 (m, 1H), 5.51 (m, 1H), 5.72 (m, 1H); HRMS (EI) calcd for $C_{39}H_{75}O_9Si_3$ *m/z* 852.3882, found 852.3895.

Tetraester 91. To a solution of **90** (34.0 mg, 0.040 mmol) and **88** (20.0 mg, 0.034 mmol) in acetone (8 mL) was added anhydrous potassium carbonate (100 mg) and the mixture was heated at reflux for 2 h. After cooling to room temperature, the mixture was diluted with ether (10 mL) and filtered. The filtrate was concentrated under reduced pressure and the residual oil was chromatographed on silica (10 g, hexanes:ethyl acetate 7:1 to 4:1) to give **91** (40.1 mg, 88%) as a colourless oil: $[\alpha]_D^{20}$ -11.5 (*c* 1.02 $CHCl_3$); IR ($CHCl_3$) 2930, 2890, 1760, 1740, 1465, 1370, 1355, 1147, 1090, 1080, 1052, 970, 855, 825, 810, 790, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.01 (s, 3H), -0.01 (s, 6H), 0.01 (s, 15H), 0.02 (s, 6H), 0.04 (s, 3H), 0.72 (s, 6H), 0.82 (s, 3H), 0.83 (s, 3H), 0.86 (s, 18H), 0.87 (s, 9H), 0.88 (s, 9H), 0.99 (m, 2H), 1.89 (d, *J* = 6.1 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.1 Hz, 3H), 1.20-1.42 (m, 4H), 1.55-1.80 (m, 6H), 1.91 (m, 2H), 2.12 (m, 2H), 2.37-2.58 (m, 5H), 3.52 (m, 2H), 3.66 (m, 2H), 3.90-4.02 (m, 2H), 4.10 (m, 1H), 4.22 (m, 2H), 4.45 (m, 2H), 4.51 (d, *J* = 15.8 Hz, 1H), 4.54 (d, *J* = 15.9 Hz, 1H), 4.57 (d, *J* = 15.8 Hz, 1H), 4.61 (d, *J* = 15.9 Hz, 1H), 4.94 (m, 1H), 5.44-5.56 (m, 2H), 5.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.2, -4.1, -3.8, -3.3, -3.1, -3.0, -1.6, 17.1, 17.3, 18.3, 18.4, 18.6, 18.8, 18.9, 21.2, 21.3, 26.1, 26.2, 30.7, 31.5, 36.2, 36.3, 37.5, 39.7, 39.8, 40.7, 44.3, 60.4, 63.7, 76.1, 76.2, 77.0, 77.7, 77.9, 78.1, 78.7, 80.6, 80.8, 131.2, 131.3, 132.5, 132.6, 167.6, 167.9, 175.7, 175.8; HRMS (EI) calcd for $C_{69}H_{134}O_{15}Si_5$ *m/z* 1342.8569, found 1342.8582.

Macrolactone 93. To a solution of **91** (30.0 mg, 0.022 mmol) in tetrahydrofuran (8 mL) at -23 °C was added tetra-*n*-butylammonium fluoride (1M solution in tetrahydrofuran, 44.0 μL, 0.044 mmol). The mixture was stirred for 30 min at -23 °C, allowed to warm to room temperature and was diluted with ether (15 mL). The ethereal solution was washed with a 1:1 mixture of hydrochloric acid (1%) and brine, and the separated organic phase was dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was dried rigorously by azeotropic removal of residual

water with benzene to leave crude hydroxy acid **92**. To a solution of crude **92** in methylene chloride (12 mL) containing dry triethylamine (45 μL, 0.32 mmol) at room temperature was added 2-chloro-1-methylpyridinium iodide (45.0 mg, 0.18 mmol) and the mixture was stirred for 24 h. The mixture was diluted with ether (20 mL) and the ethereal solution was washed with water and brine. The separated organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated under vacuum to give crude **93** which was chromatographed on silica (8 g, hexanes:ethyl acetate 15:1 to 10:1) to afford **93** (23.2 mg, 86% from **91**) as a colourless oil: $[\alpha]_D^{20}$ -7.9 (*c* 0.90 $CHCl_3$); IR ($CHCl_3$) 2960, 2940, 2850, 1740, 1460, 1390, 1360, 1160, 1150, 1105, 1090, 1085, 830, 795, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.02 (s, 6H), -0.01 (s, 6H), 0.02 (s, 6H), 0.03 (s, 6H), 0.71 (s, 6H), 0.81 (s, 6H), 0.86 (s, 18H), 0.87 (s, 18H), 1.18 (d, *J* = 6.6 Hz, 6H), 1.19 (d, *J* = 6.3 Hz, 6H), 1.30-1.70 (m, 6H), 1.75 (m, 2H), 1.85 (m, 2H), 2.15 (m, 2H), 2.34-2.56 (m, 6H), 3.53 (m, 2H), 3.67 (m, 2H), 4.12 (m, 2H), 4.47 (dd, *J* =13.8, 6.7 Hz, 2H), 4.53 (d, *J* = 15.7 Hz, 2H), 4.57 (d, *J* = 15.7 Hz, 2H), 4.93 (m, 2H), 5.48 (dd, *J* = 15.3, 7.7 Hz, 2H), 5.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.3, -3.9, -3.3, -3.2, 17.1, 18.3, 18.4, 18.7, 18.9, 21.4, 26.0, 26.1, 30.4, 31.3, 36.3, 37.5, 39.6, 44.4, 60.4, 76.1, 77.0, 78.3, 78.6, 80.6, 131.2, 132.1, 167.5, 175.6; HRMS (FAB) calcd for $C_{64}H_{120}O_{14}Si_4$ *m/z* 1224.7755, found 1224.7742.

(+)-Aplasmomycin A (2). To a solution of diisopropylamine (18.2 μL, 0.13 mmol) in tetrahydrofuran (3.0 mL) at -78 °C was added *n*-butyllithium (1.5M in hexane, 116 μL, 0.13 mmol). The solution was stirred for 30 min at -78 °C, then was warmed to 0 °C and a solution of **93** (20.0 mg, 0.016 mmol) in tetrahydrofuran (1 mL) was added. The solution was stirred at 0 °C for 40 min, then was cooled to -78 °C and trimethylsilyl trifluoromethanesulfonate (37 μL, 0.193 mmol) was added. The solution was stirred at -78 °C for 20 min, diisopropylamine (20 μL, 0.13 mmol) was added, and the mixture was allowed to warm to room temperature. After 10 min, volatile materials were removed under high vacuum to leave crude **94** as a pale yellow oil. To this material dissolved in acetonitrile (1 mL) at 0 °C was added hydrofluoric acid (5%), the mixture was stirred for 10 min at this temperature

and then was allowed to warm to room temperature and was stirred for a further 3.5 h. Ethyl acetate (3 mL) was added, the resulting solution was washed with saturated sodium bicarbonate and brine and was dried over anhydrous magnesium sulfate. Removal of solvent under vacuum left a hygroscopic residue (11.4 mg, 57%), identical with desboroaplasmomycin A (**95**), which was further dried by azeotropic removal of water with benzene before its dissolution in anhydrous methanol (6 mL). To this solution at room temperature was added trimethyl borate (400 μL, 3.0 mmol) and the solution was heated at reflux for 4 h. Methanol was removed under vacuum, the residue was taken up into ether and the ethereal solution was washed with brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica (hexanes-ethyl acetate) to give pure **2** (8.8 mg, 76%) as a colorless solid that was identical with natural aplasmomycin.

Hydroxy Tetraester 108. To a solution of **103** (4.1 mg, 0.006 mmol) in acetone (1 mL) at room temperature was added solid potassium carbonate (8.0 mg, 0.06 mmol) followed by a solution of **107** (5.0 mg, 0.006 mmol) and the mixture was refluxed for 2 h. The cooled mixture was diluted with ether (5 mL) and the ethereal solution was chromatographed on silica (7 g, hexanes:ethyl acetate 5:1) to give **108 (**7.2 mg, 83%) as a colourless oil: $[\alpha]_D^{20}$ -4.4 (*c* 0.06 $CDCl_3$); IR ($CHCl_3$) 2955, 2930, 2905, 1760, 1745, 1472, 1462, 1250, 1225, 1150, 1125, 1070, 1025, 1005, 835, 815, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (br s, 39H), 0.73 (s, 3H), 0.81 (s, 3H), 0.82 (s, 3H), 0.91 (m, 48H), 1.00 (m, 2H), 1.10 (t, *J* = 6.9 Hz, 2H), 1.20 (m, 6H), 1.25-1.80 (m, 22H), 1.95 (m, 2H), 2.20 (m, 2H), 2.49 (m, 3H), 3.52 (m, 5H), 3.80 (m, 1H), 4.05 (t, *J* = 6.7 Hz, 2H), 4.23 (t, *J* = 4.5 Hz, 2H), 4.57 (m, 4H), 4.95 (m, 1H), 5.40 (dt, *J* = 8.7, 6.6 Hz, 1H), 5.47 (dt, *J* = 8.8, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.7, -4.6, -4.4, -1.7, 12.7, 16.7, 16.8, 17.2, 17.3, 18.3, 19.2, 19.3, 20.5, 23.4, 23.8, 23.9, 24.3, 25.6, 25.7, 25.8, 25.9, 28.6, 28.9, 29.3, 30.0, 30.1, 30.4, 30.5, 35.6, 36.1, 37.1, 38.5, 38.6, 39.1, 60.4, 60.5, 63.5, 69.8, 70.8, 75.0, 75.4, 75.5, 75.8, 78.1, 78.2, 78.4, 80.5, 98.2, 100.6, 100.7, 125.7, 131.7, 167.5, 167.8, 175.7, 175.9; HRMS (FAB) calcd for $C_{75}H_{152}O_{15}Si_6$ *m/z* 1460.9747, found 1460.9760.

Hydroxy Acid 109. To a solution of **108** (103 mg, 0.07 mmol) in tetrahydrofuran (10 mL) at -23 °C

was added tetra-*n*-butylammonium fluoride (1M in tetrahydrofuran, 210 μL, 0.21 mmol). The mixture was stirred at -23 °C for 30 min, then was warmed to 0 °C and stirred for a further 20 min. To this mixture was added saturated aqueous sodium chloride and the solution was stirred at 0 °C for 40 min. Ether (150 mL) was added and the separated ethereal solution was washed with brine (3 x 30 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was chromatographed on silica (15 g, hexanes:ethyl acetate 1:2) to give **109** (87 mg, 91%) as a colourless hygroscopic oil: HRMS (EI) calcd for $C_{70}H_{140}O_{15}Si_5$ *m/z* 1360.9039, found 1360.9047. This material was used immediately for the next reaction.

Macrolactone 110. To a solution of 2-chloro-1-methylpyridinium iodide (30 mg, 0.12 mmol) and 4-(*N,N*-dimethylamino)pyridine (32 mg, 0.26 mmol) in acetonitrile (45 mL) at 0 °C was added a solution of **109** (87 mg, 0.064 mmol) in acetonitrile (10 mL). The mixture was allowed to warm to room temperature and was stirred for 45 min. The mixture was concentrated under reduced pressure and the residue was taken up into ether (150 mL). The ethereal solution was washed with water and brine, and was dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was chromatographed on silica (20 g, hexanes:ethyl acetate 1:5 to 1:1) to give **110** (39 mg, 42%) as a colourless oil: $[\alpha]_D^{20}$ -7.6 (*c* 0.21 $CHCl_3$); IR ($CHCl_3$) 2970, 2945, 2940, 2935, 2890, 1760, 1745, 1470, 1465, 1255, 1150, 1100, 1070, 1005, 835, 775, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.02 (s, 6H), -0.01 (s, 6H), 0.01 (s, 6H), 0.02 (s, 6H), 0.03 (s, 6H), 0.74 (s, 3H), 0.79 (s, 3H), 0.86 (s, 6H), 0.88 (s, 9H), 0.90 (s, 18H), 0.91 (s, 18 H), 1.22 (m, 12H), 1.40-2.40 (m, 20H), 2.45 (pent, *J* = 6.8 Hz, 1H), 2.63 (m, 2H), 3.28 (m, 2H), 3.44 (m, 2H), 3.77 (m, 1H), 3.90 (m, 1H), 4.11 (m, 2H), 4.57 (m, 4H), 4.84 (m, 1H), 4.96 (m, 1H), 5.38 (dt, *J* = 8.8, 6.7 Hz, 1H), 5.44 (dt, *J* = 9.0, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.6, -4.0, -3.7, -3.5, -3.2, 17.0, 17.1, 18.1, 18.4, 18.5, 18.6, 18.7, 19.6, 20.5, 20.6, 20.7, 25.7, 25.8, 26.2, 29.7, 31.2, 33.2, 36.2, 37.0, 39.4, 39.8, 44.1, 44.3, 60.3, 60.5, 69.2, 73.4, 74.4, 78.5, 80.6, 124.3, 132.1, 167.3, 167.6, 175.6, 175.7; HRMS (FAB) calcd for $C_{70}H_{138}O_{14}Si_5$ *m/z* 1342.8933, found 1342.8921.

Desborodesvalinylboromycin (6). **A. From 110**. To a solution of lithium hexamethyldisilazide (1.6 M in tetrahydrofuran, 21.0 μL, 0.040 mmol) in tetrahydrofuran (3 mL) at 0 °C was added a solution of **110** (12.0 mg, 0.009 mmol) in tetrahydrofuran (1 mL). The solution was stirred for 30 min at 0 °C, then was cooled to -78 °C before trimethylsilyl trifluormethanesulfonate (35 μL, 0.18 mmol) was added. The solution was stirred at -78 °C for 30 min and was allowed to warm to room temperature and stirred for a further 30 min. The solvent was removed under vacuum to leave crude **111** which was subjected immediately to the next reaction.

To a solution of the crude material obtained above in acetonitrile (3 mL) at 0 °C was added hydrofluoric acid (5%, 2 mL) and the mixture was stirred for 10 min at 0 °C then at room temperature for 6 h. The mixture was diluted with ethyl acetate (3 mL), and the solution was washed with saturated sodium bicarbonate and brine and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue was chromatographed on silica (10 g, hexanes:ethyl acetate 1:2) to give **6** (4.0 mg, 58%): $[\alpha]_D^{20}$ +66.2 (*c* 0.08 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (s, 3H), 0.72 (s, 6H), 0.87 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.22 (m, 2H), 1.33 (m, 1H), 1.52-1.75 (m, 5H), 1.82 (m, 1H), 1.99 (m, 2H), 2.11 (m, 1H), 2.34 (m, 4H), 2.85 (q, *J* = 7.1 Hz, 1H), 2.99 (q, *J* = 7.0 Hz, 1H), 3.08 (t, *J* = 6.3 Hz, 1H), 3.69 (d, *J* = 8.3 Hz, 1H), 3.80 (dd, *J* = 10.5, 6.7 Hz, 2H), 4.05 (m, 2H), 4.16 (t, *J* = 6.3 Hz, 1H), 4.30 (dd, *J* = 9.6, 4.2 Hz, 1H), 4.60 (m, 1H), 4.66 (q, *J* = 6.6 Hz, 1H), 4.97 (d, *J* = 6.9 Hz, 1H), 5.10 (d, *J* = 4.7 Hz, 1H), 5.12 (t, *J* = 6.7 Hz, 1H), 5.18 (s, 2H), 5.43 (t, *J* = 6.8 Hz, 1H), 5.49 (s, 1H), 5.56 (d, *J* = 8.1 Hz, 1H), 6.30 (d, *J* = 8.1 Hz, 1H); HRMS (EI) calcd for $C_{40}H_{68}O_{14}$ *m/z* 772.4609, found 772.4593. This material was identical with **6** obtained from **1**.

B. From 1. To a solution of **1** (8.4 mg, (0.01 mmol) in methanol (1 mL) was added aqueous sodium hydroxide (20%, 100 μL) and the mixture was heated at 50 °C for 1 h. The cooled mixture was diluted with water (10 mL) and brought to pH 3 by addition of dilute hydrochloric acid (5%). The mixture was extracted with methylene chloride (4 x 10 mL) and the extract was dried over anhydrous magnesium

sulfate. Removal of the solvent under vacuum gave crude desvalinoboromycin (5.0 mg) which was taken up into benzene (1 mL). To this solution was added hydrochloric acid (6N, 0.1 mL) and the mixture was stirred at room temperature for 18 h. The solvent was removed under vacuum and the residue was chromatographed on silica (5 g, ether) to give **6** (2.5 mg, 34% from **1**) identical with material obtained from **110**.

Sodium Desvalinylboromycinate (113). To a solution of **6** (7.9mg, 0.01 mmol) in methanol (2 mL) was added trimethyl borate (100 μL, 0.75 mmol) and the mixture was heated at reflux for 4 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica (5 g, hexanes:ethyl acetate 1:1) to give **113** (5.6 mg, 71%) as a glassy solid which was used immediately for the next reaction.

Sodium *N-tert*-Butoxycarbonylboromycinate (114). To a solution of dicyclohexyl carbodiimide (4.0 mg, 0.019 mmol), 4-(*N,N*-dimethylamino)pyridine (3.5 mg, 0.03 mmol) and *tert*-butoxycarbonyl-D-valine (4.0 mg, 0.018 mmol) in methylene chloride (2 mL) at -20 °C was added a solution of **113** (5.0 mg, 0.006 mmol) in methylene chloride (1 mL). The mixture was stirred at -20 °C for 30 min, then at room temperature for 2 days. Precipitated dicyclohexyl urea was filtered off and the filtrate was chromatographed on silica (10 g, hexanes:ethyl acetate 1:1) to give **114** (5.4 mg, 85%) as a colourless amorphous solid.

(+)-Boromycin (1). To a solution of **114** (6.1 mg, 0.006 mmol) in methylene chloride (2 mL) at room temperature was added trifluoroacetic acid (0.1 mL) and the mixture was stirred for 1 h. The solution was poured into saturated aqueous sodium bicarbonate (5 mL) and the mixture was extracted with benzene (3 x 5 mL). The extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to leave a residue which was purified by chromatography on silica (10 g, hexanes:ethyl acetate 7:3) to give **1** (4.5 mg, 73%) as a colourless solid: mp 224 (dec) (lit 223-228 °C (dec)); $[\alpha]_D^{20}$ +66.1 (*c* 0.03 $CHCl_3$), lit $[\alpha]_D$ +63.5 (*c* 0.55 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H), 0.72 (s, 6H), 1.00 (m, 18H), 1.07 (d, *J* = 6.8 Hz, 3H), 1.23 (m, 2H), 1.35 (d, *J* = 6.8 Hz, 3H),

1.56 (m, 6H), 1.73 (s, 2H), 1.81 (d, J = 8.4 Hz, 2H), 1.90 (m, 2H), 2.11 (dd, J = 12.8, 7.2 Hz, 1H), 2.42 (pent, J = 5.6 Hz, 1H), 2.56 (q, J = 6.9 Hz, 1H), 2.83 (q, J = 6.8 Hz, 1H), 3.01 (dd, J = 8.3, 4.6 Hz, 1H), 3.39 (d, J = 4.5 Hz, 1H), 3.66 (d, J = 6.7 Hz, 1H), 3.78 (d, J = 6.8 Hz, 1H), 4.09 (dd, J = 6.8, 2.3 Hz, 1H), 4.15 (t, J = 6.8 Hz, 1H), 4.42 (s, 1H), 4.48 (s, 1H), 4.53 (q, J = 6.8 Hz, 1H), 4.92 (d, J = 4.6 Hz, 1H), 4.99 (d, J = 4.2 Hz, 1H), 5.13 (d, J = 6.7 Hz, 1H), 5.24 (m, 2H), 5.27 (s, 1H), 5.50 (t, J = 6.8 Hz, 1H), 5.61 (s, 1H); HRMS (FAB) calcd for $C_{45}H_{74}BNO_{15}$ *m/z* 880.5122, found 880. 5117. This material was identical with natural **1**.

Acknowledgements

We are grateful to Professor Heinz G. Floss, University of Washington, and Dr. Yoshiro Okami, Institute of Microbial Chemistry, Tokyo, for samples of natural aplasmomycin, to Professor Vladimir Prelog, ETH, Zürich, for a sample of natural boromycin, to Dr. John Hannah, Merck and Co., for the boromycin–Na^+ complex used in this work, and to Dr Subrata Shaw for assistance with the preparation of this manuscript. Financial support was provided by the National Institute for Allergy and Infectious Diseases (AI-10964), by the National Institute of General Medical Sciences (GM-50574) and by the National Science Foundation (CHE-9015466). Funds for upgrade of the Oregon State University NMR facility were provided by the National Science Foundation (CHE-9807265 and CHE-0722319) and by the M. J. Murdock Charitable Trust (Grant No. 2005265).

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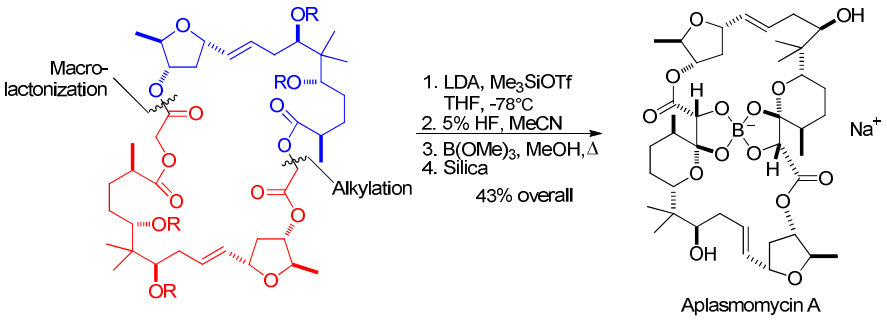
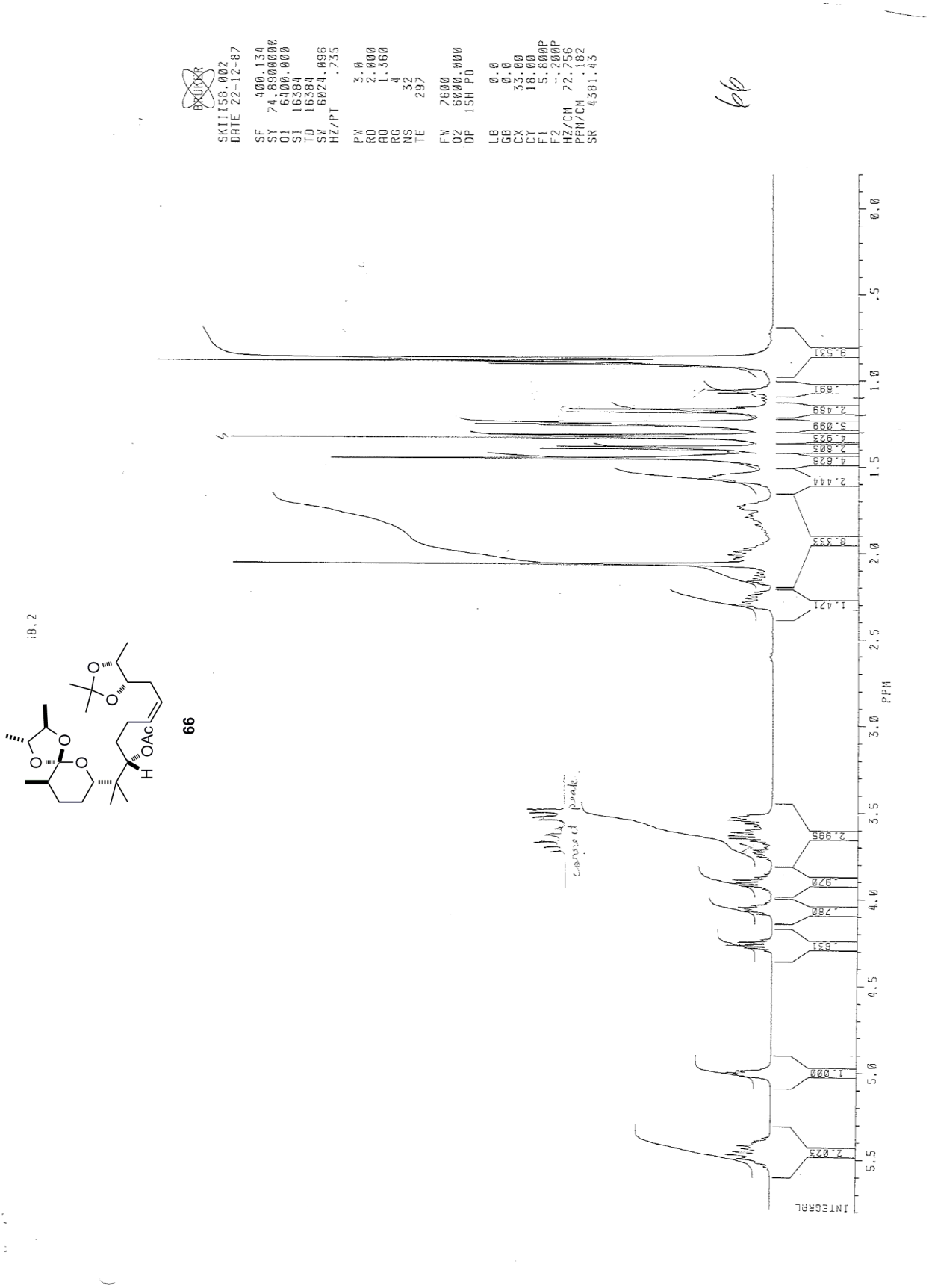
TABLE OF CONTENTS GRAPHIC

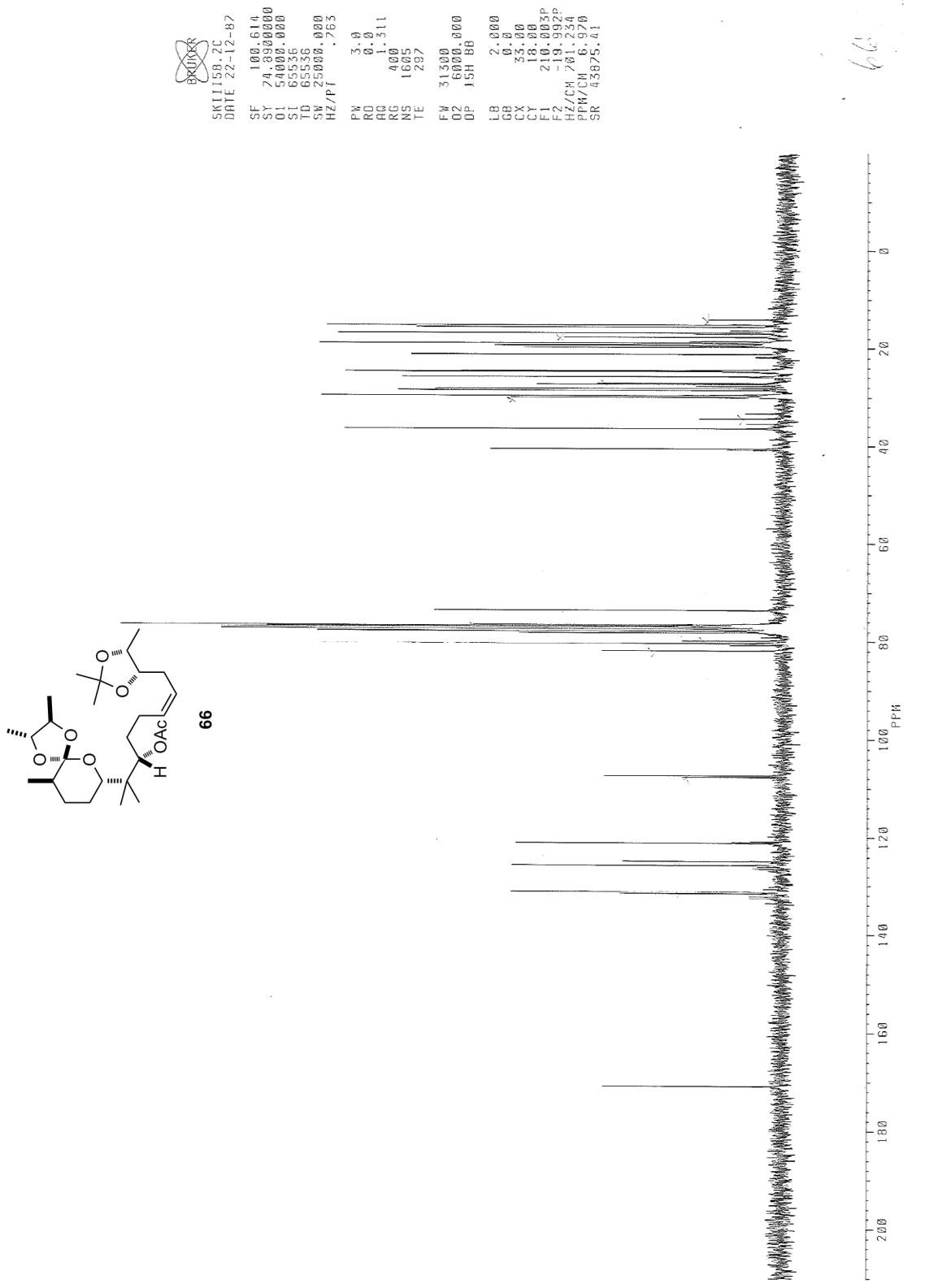
Total synthesis of macrodiolide ionophores aplasmomycin and boromycin via double ring contraction

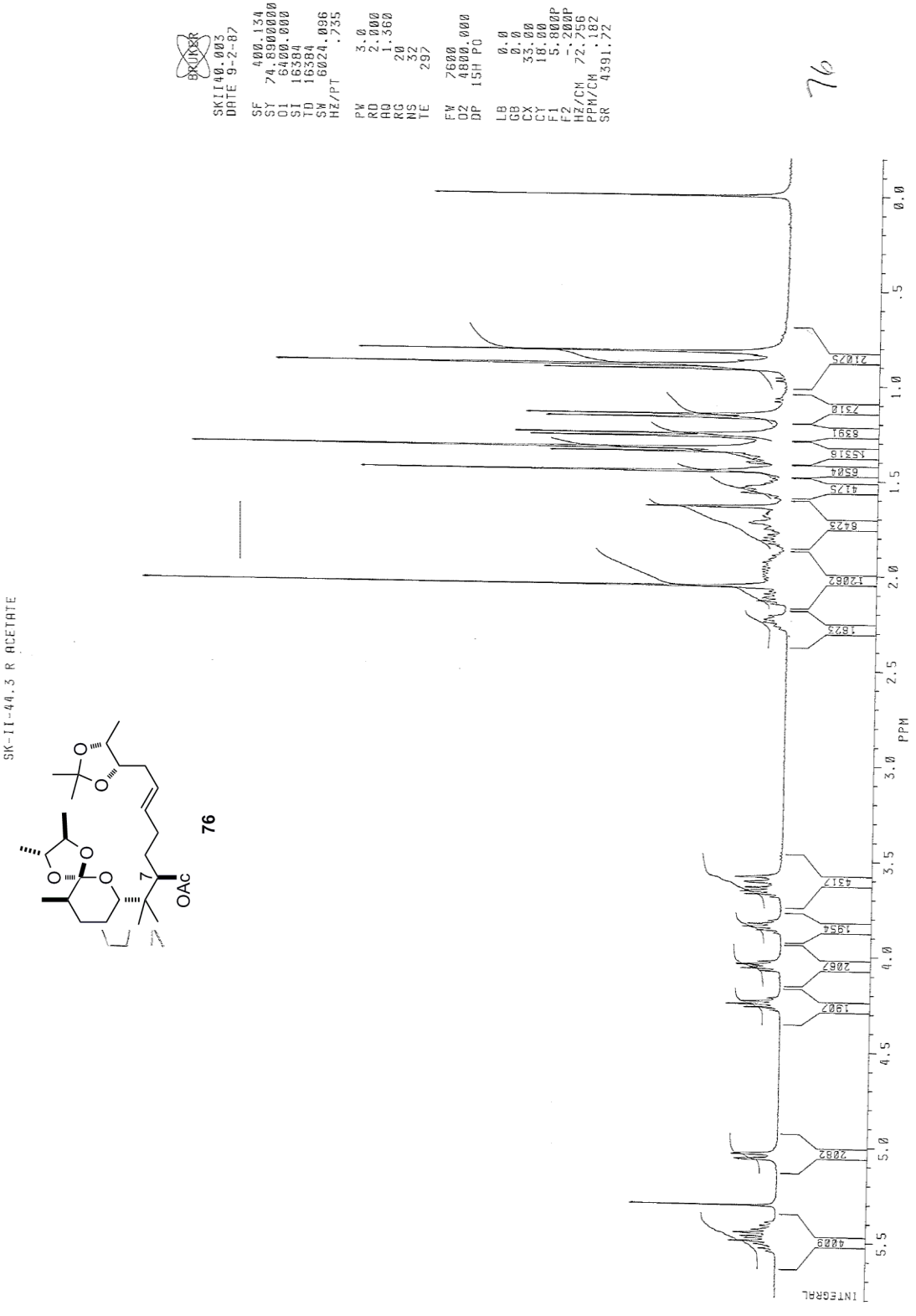
Mitchell A. Avery, Satish C. Choudhry, Om Prakash Dhingra, Brian D. Gray, Myung-chol Kang, Shen-chun Kuo, Thalathani R. Vedananda, James D. White* and Alan J. Whittle

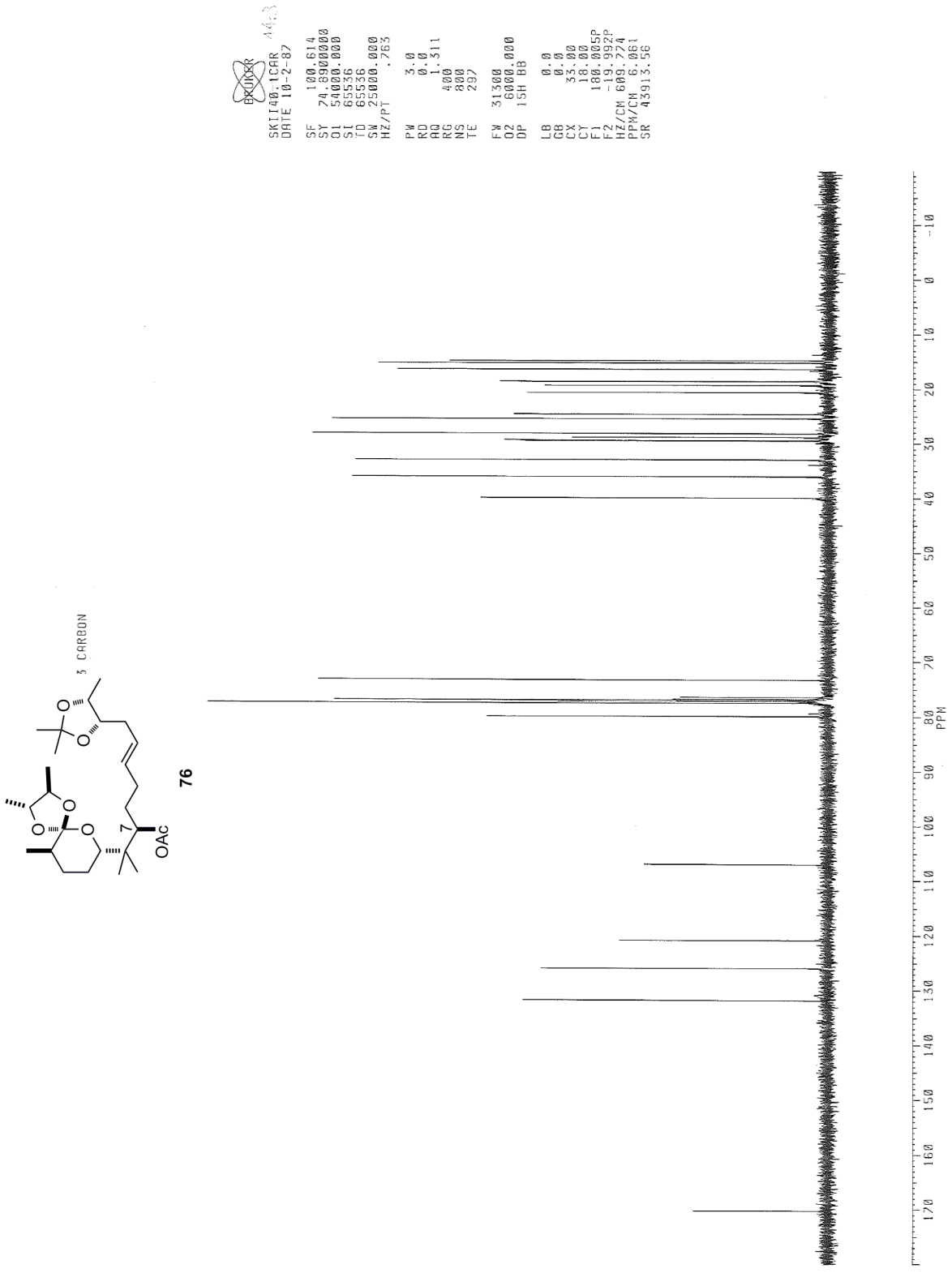
The ionophore aplasmomycin A was synthesized by double ring contraction of a symmetrical 34-membered dilactone; the unsymmetrical boromycin was synthesized using the same strategy.











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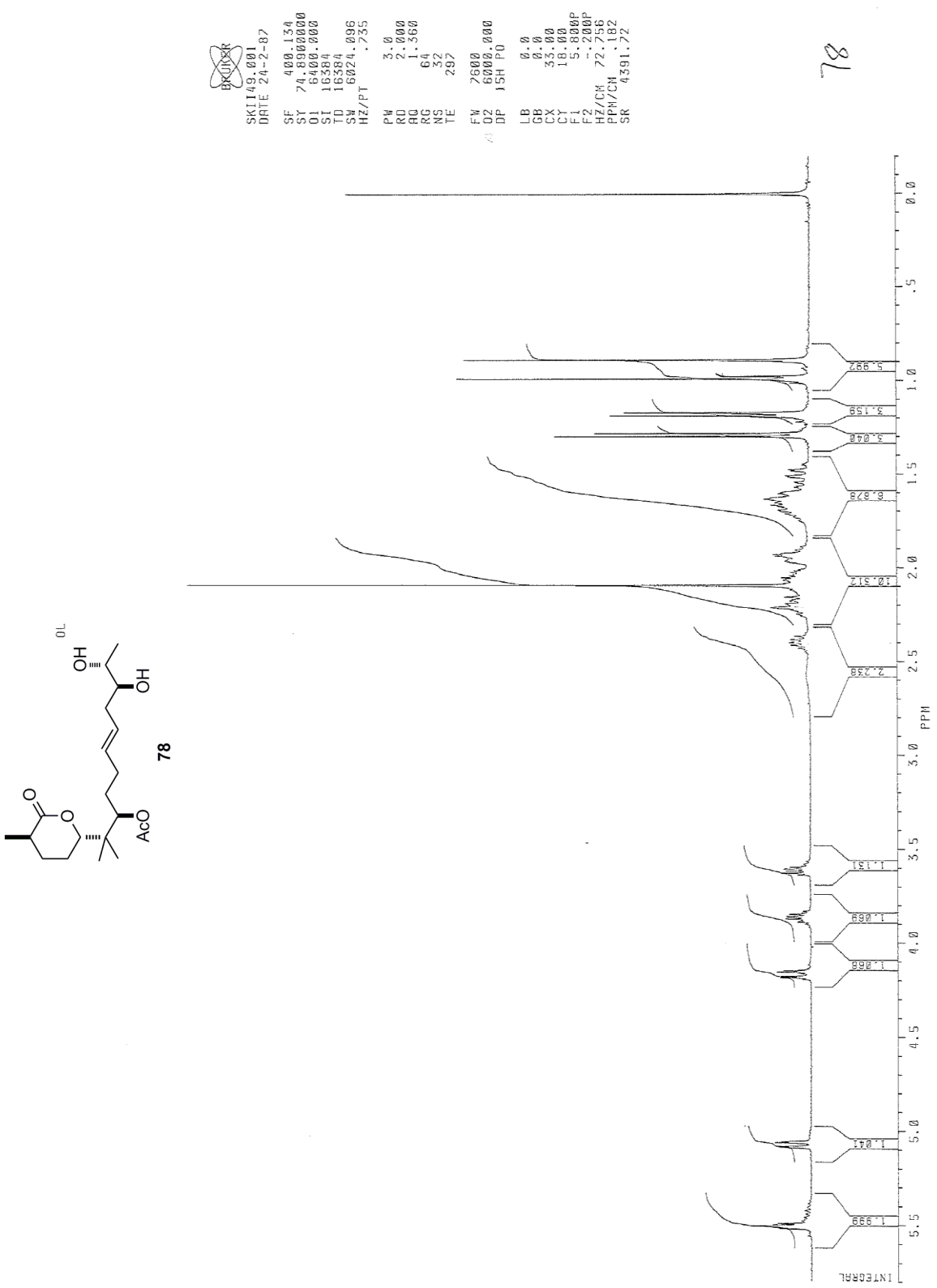

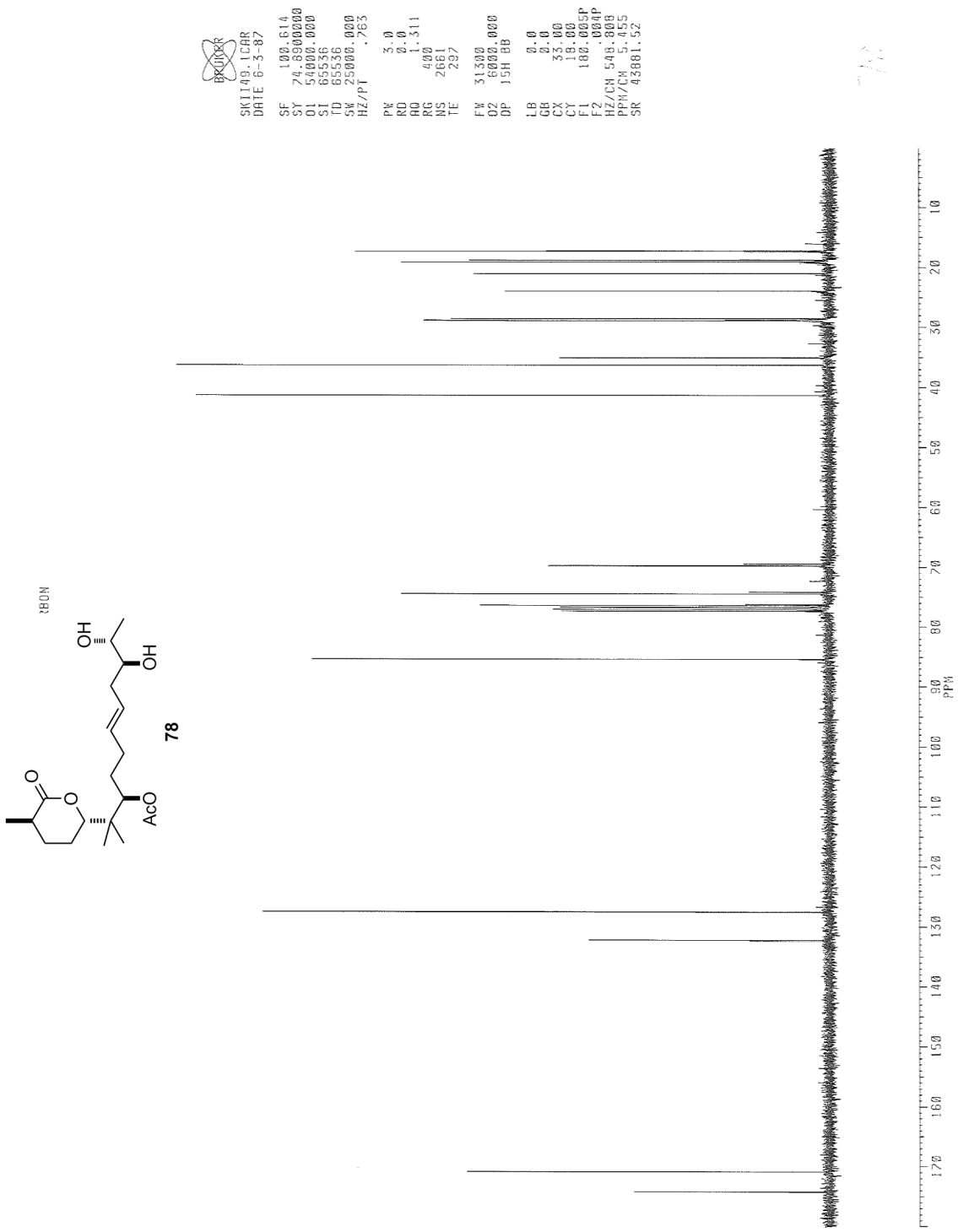

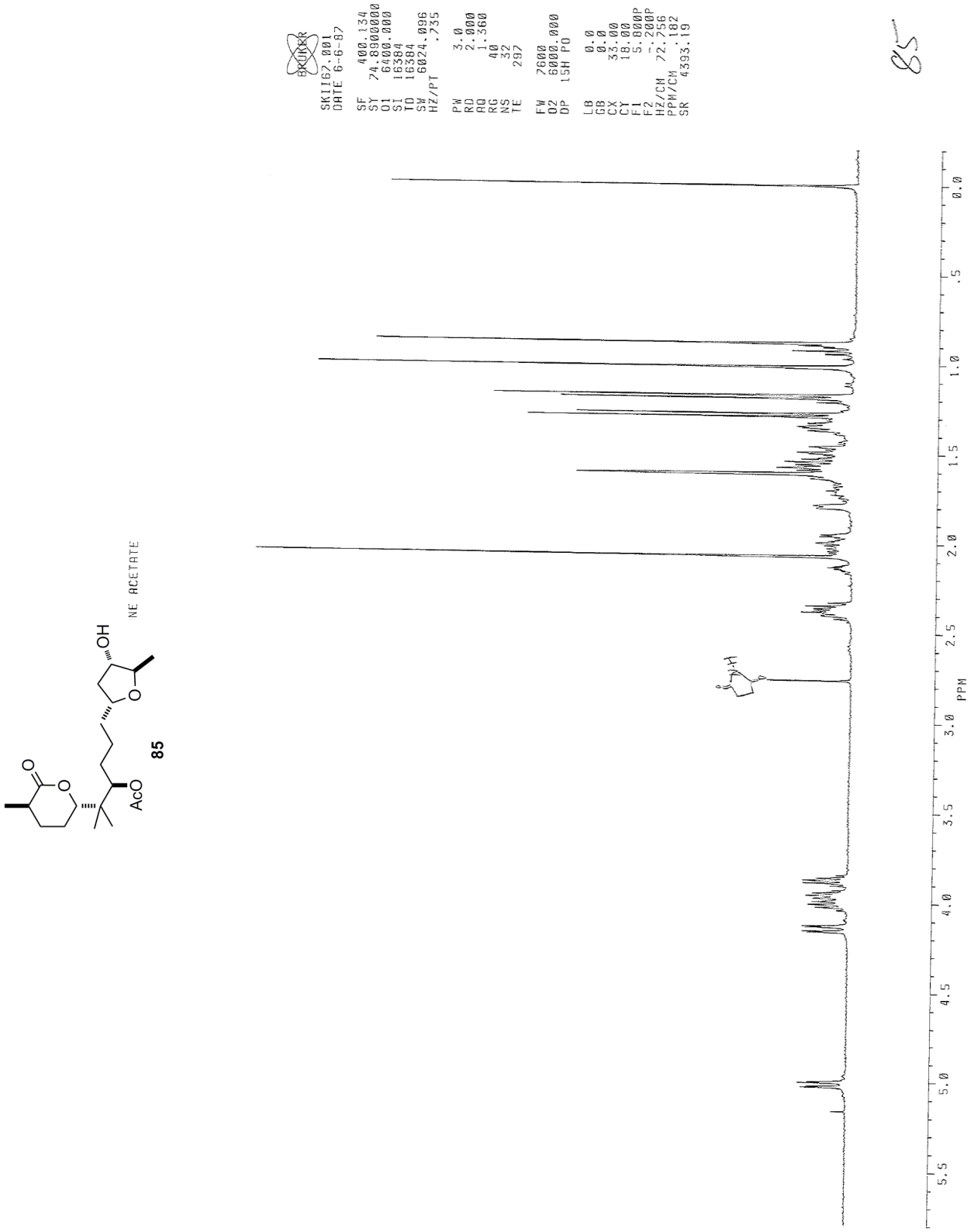

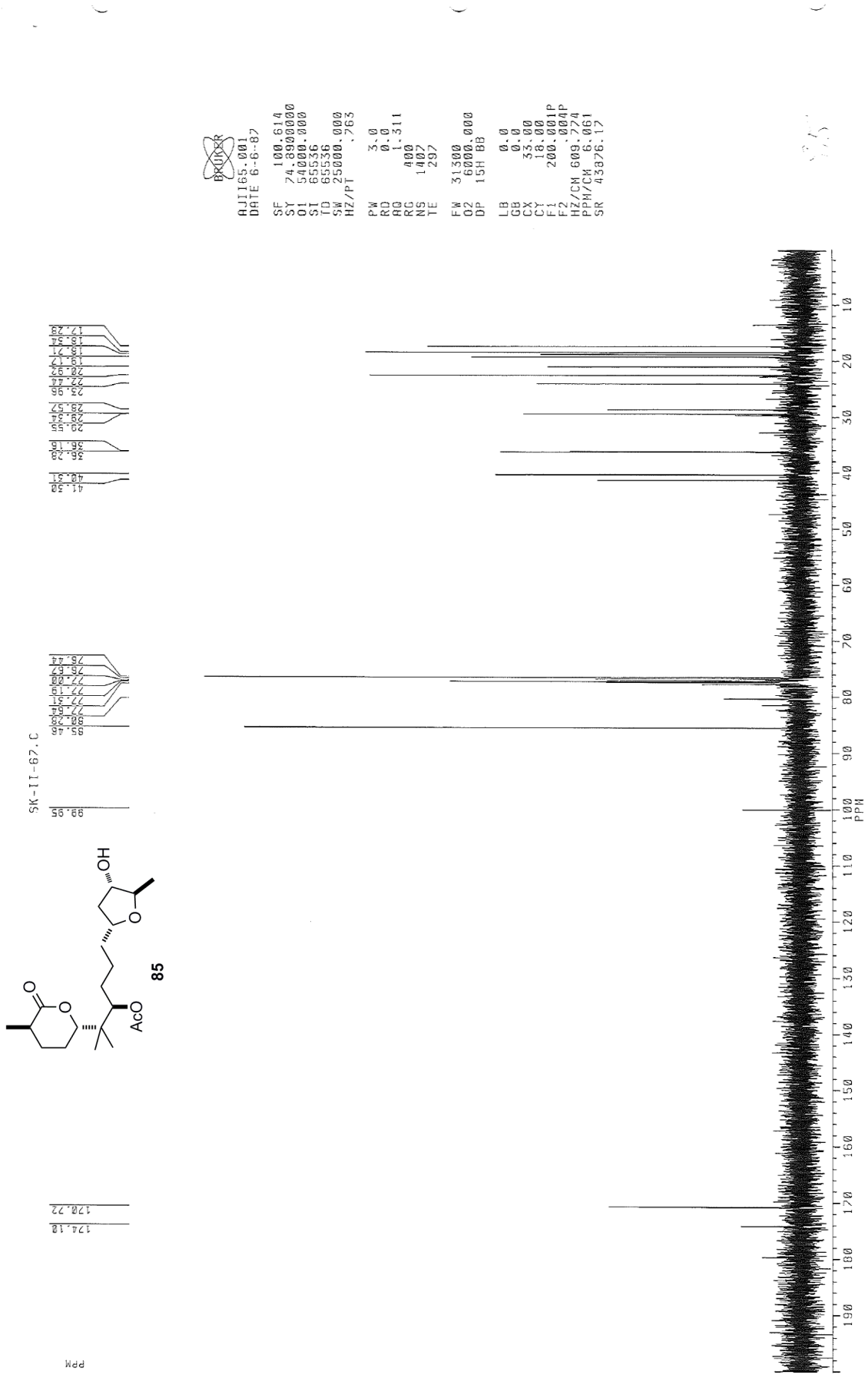

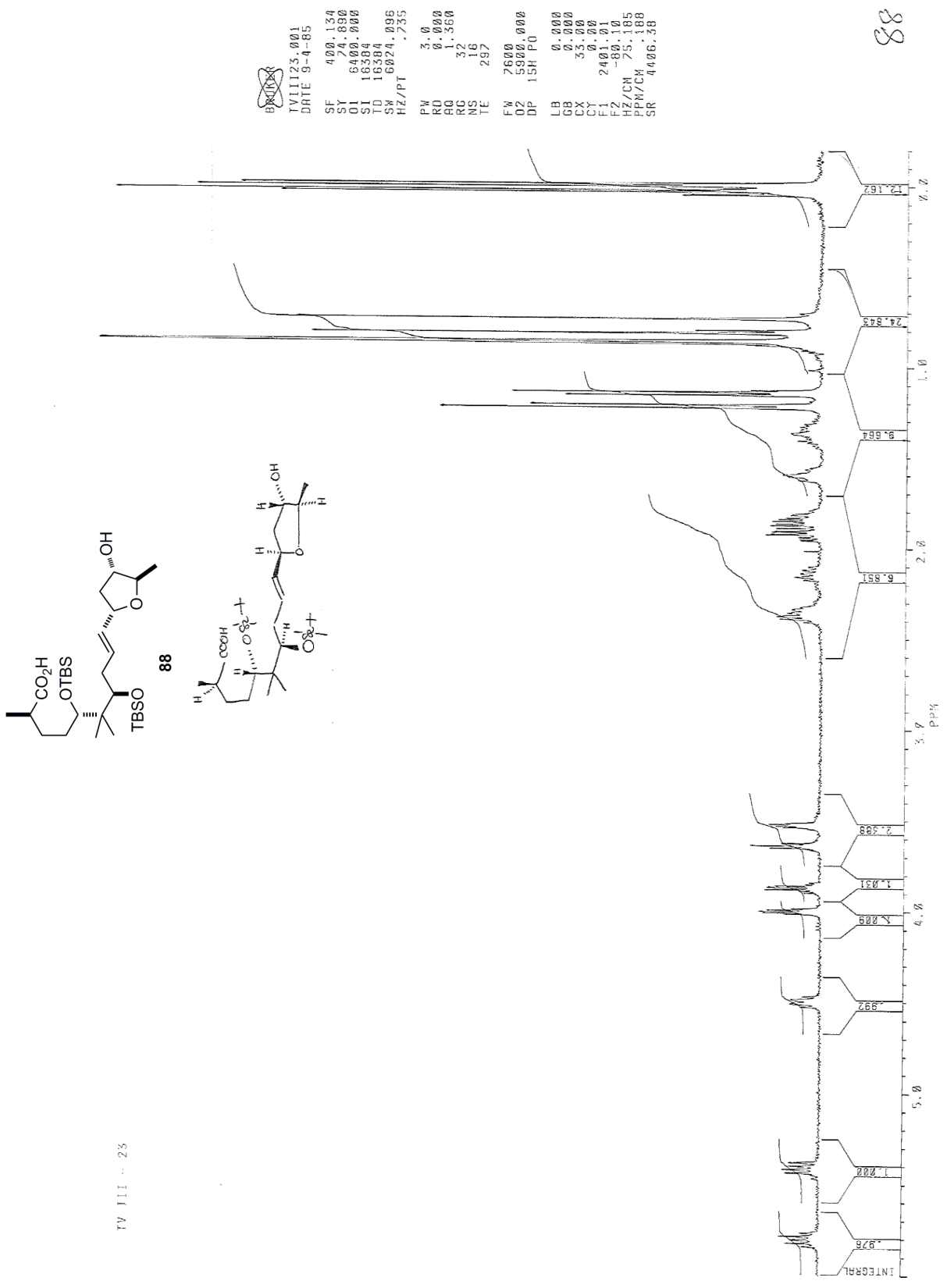

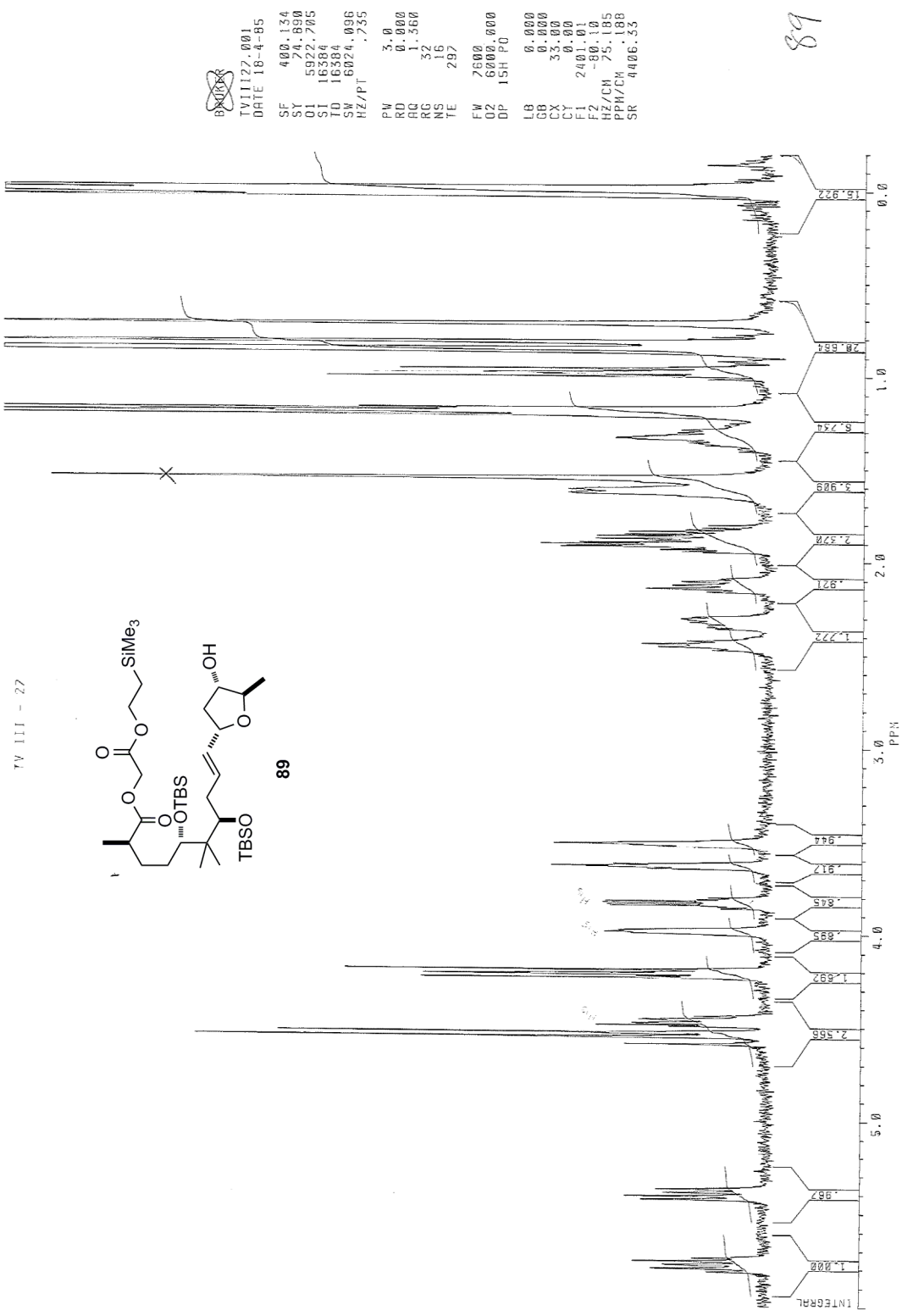

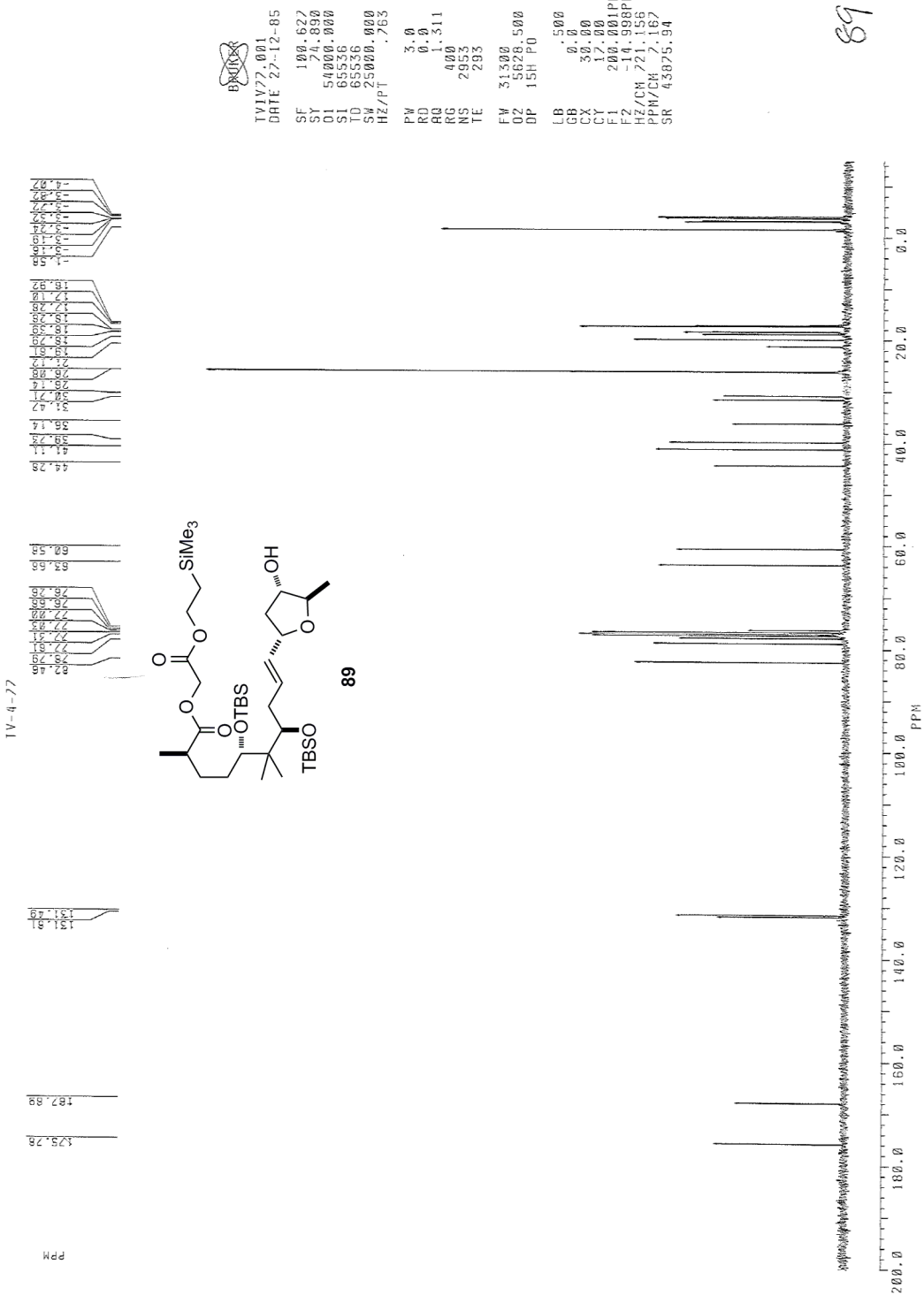

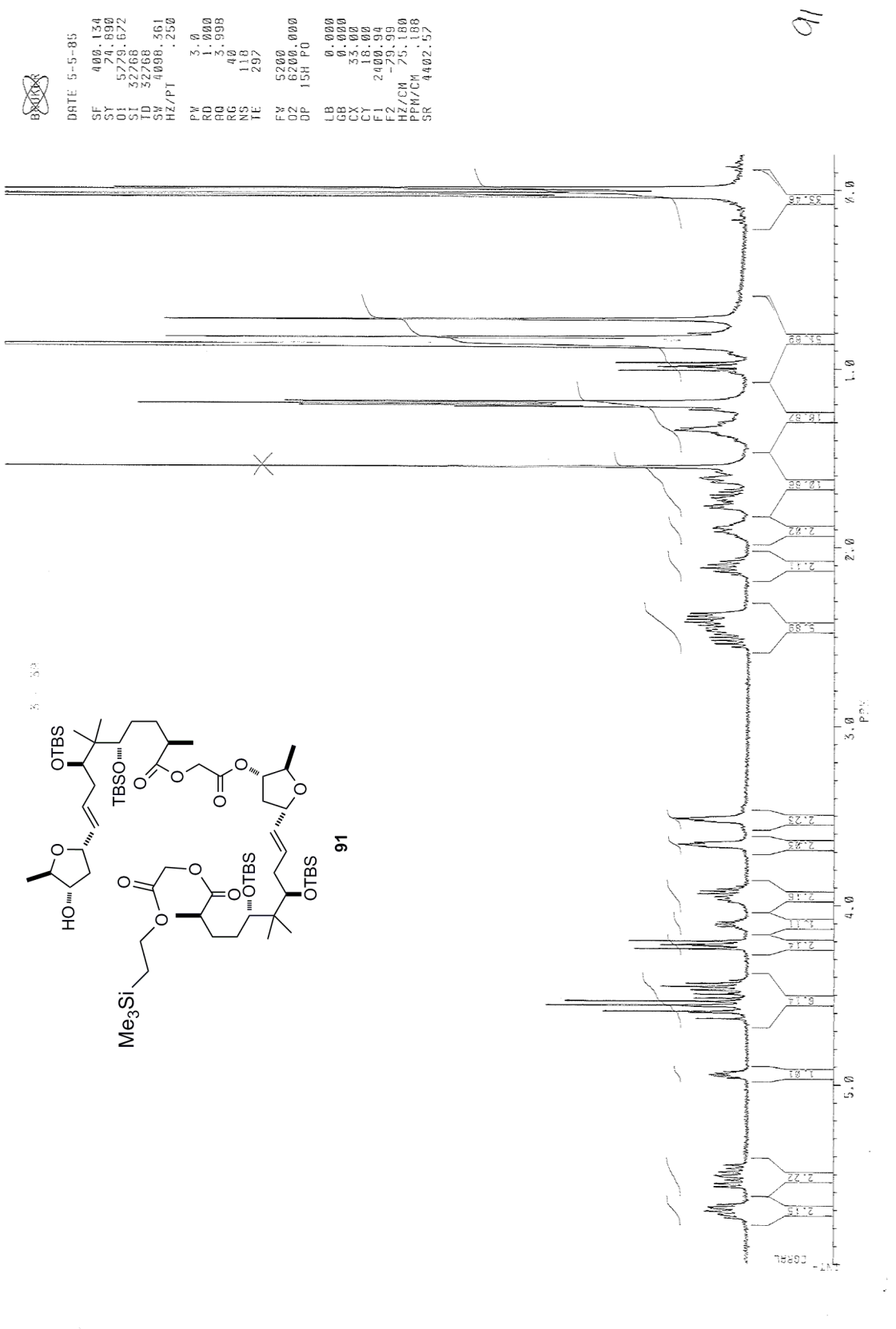

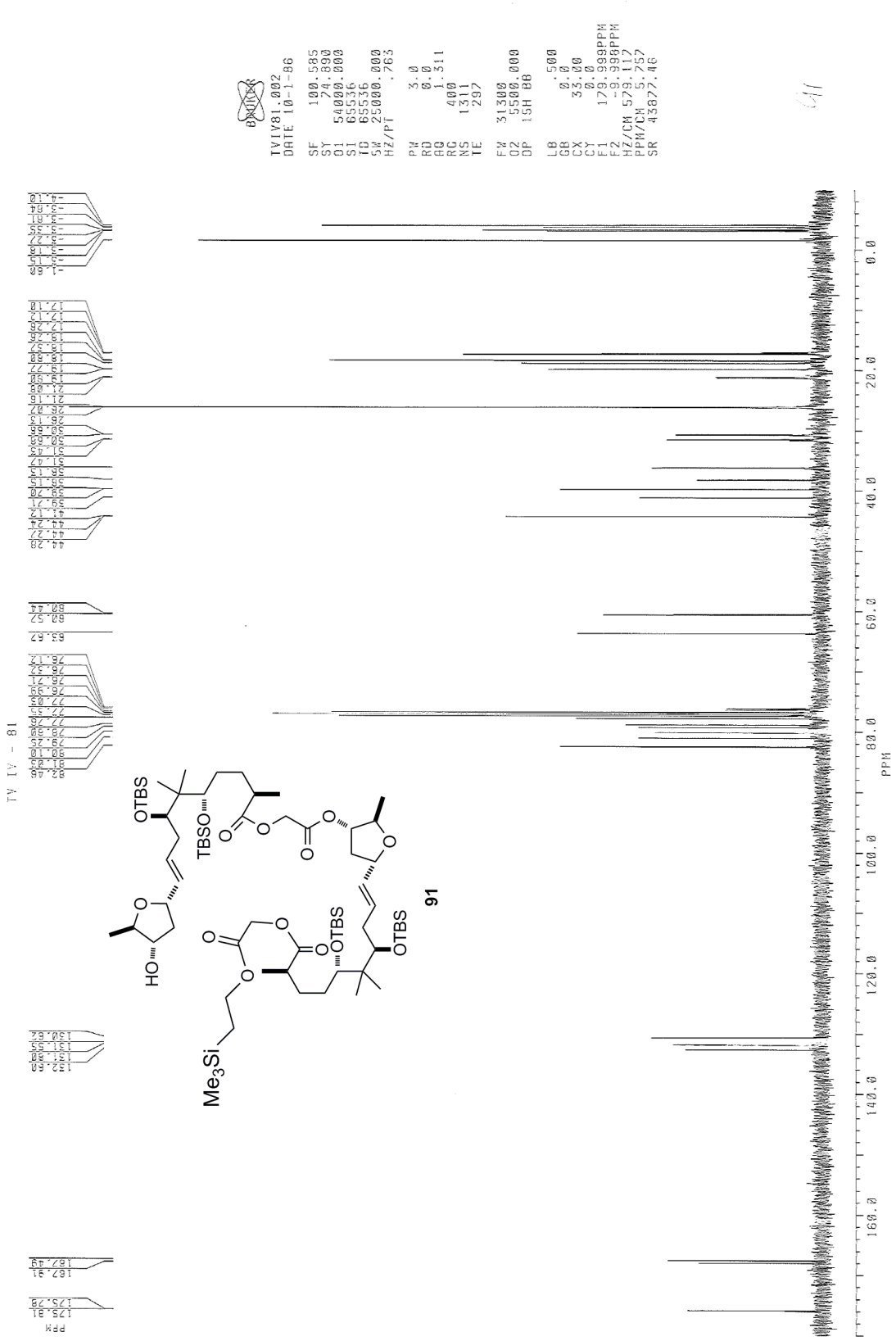

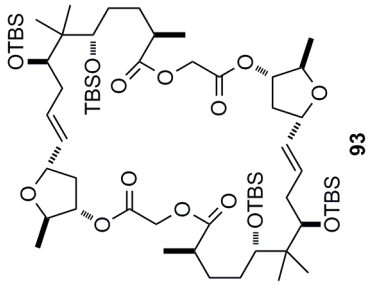

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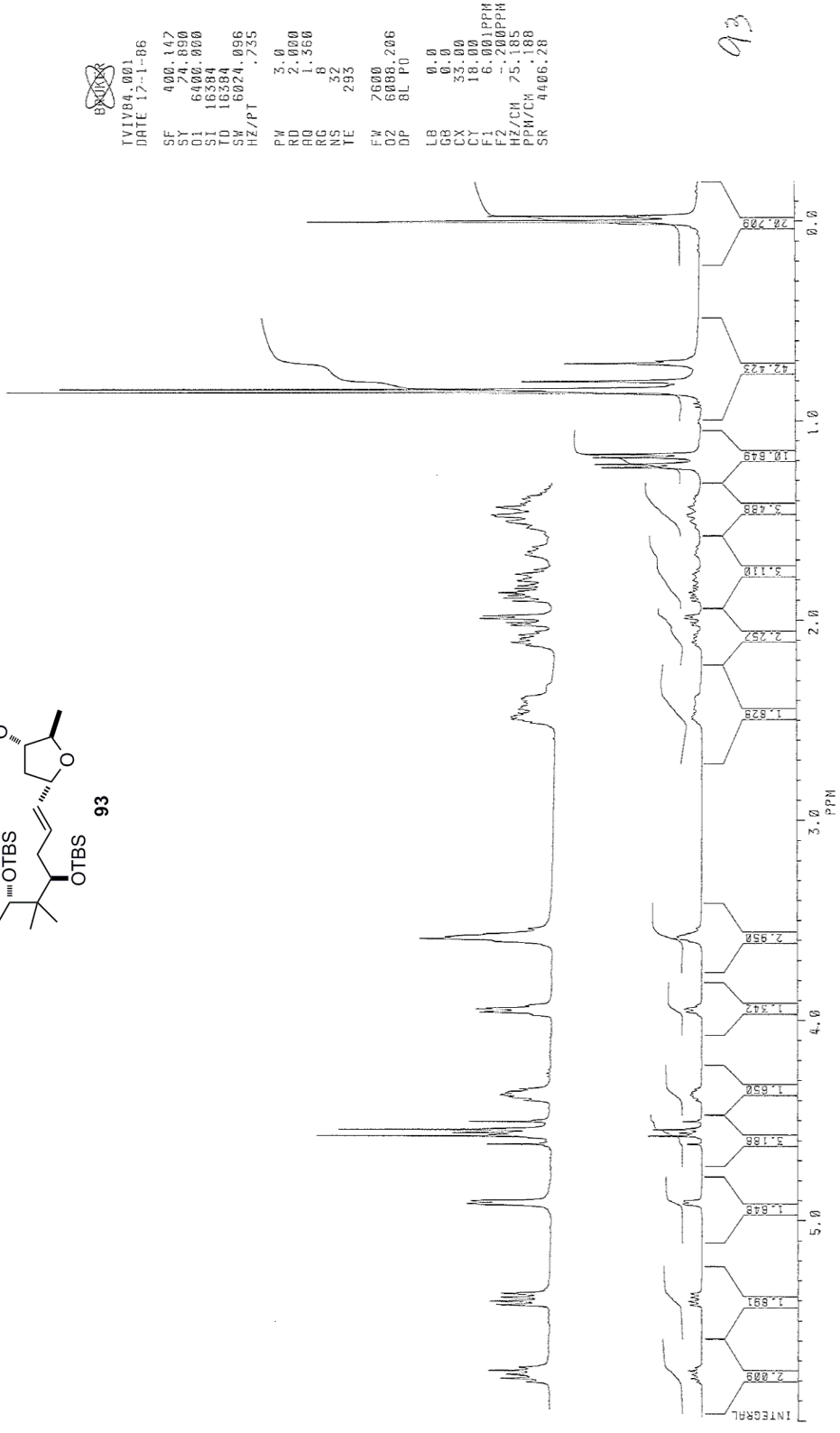

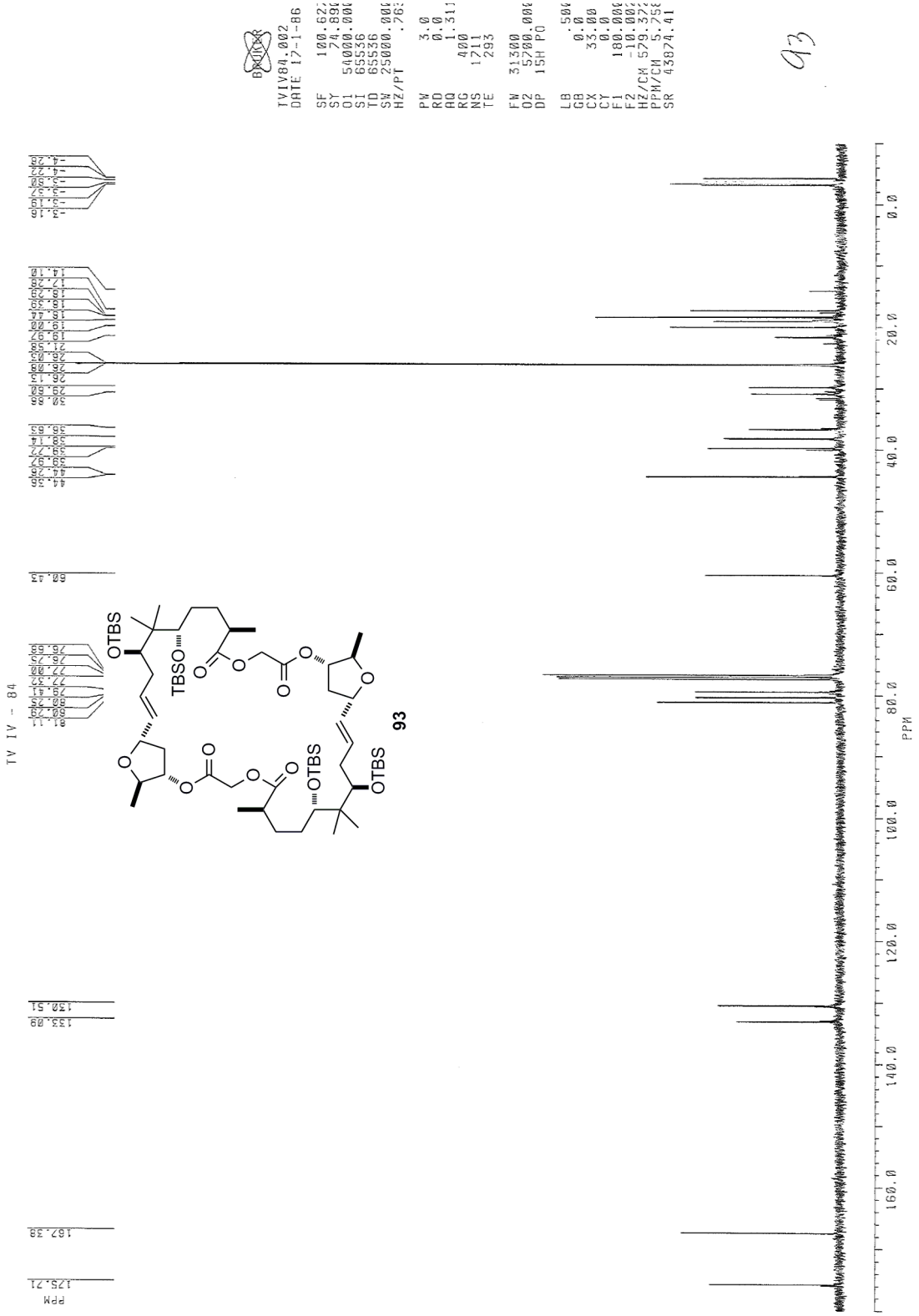

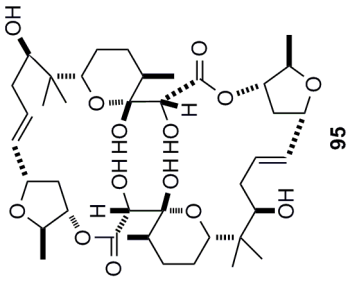

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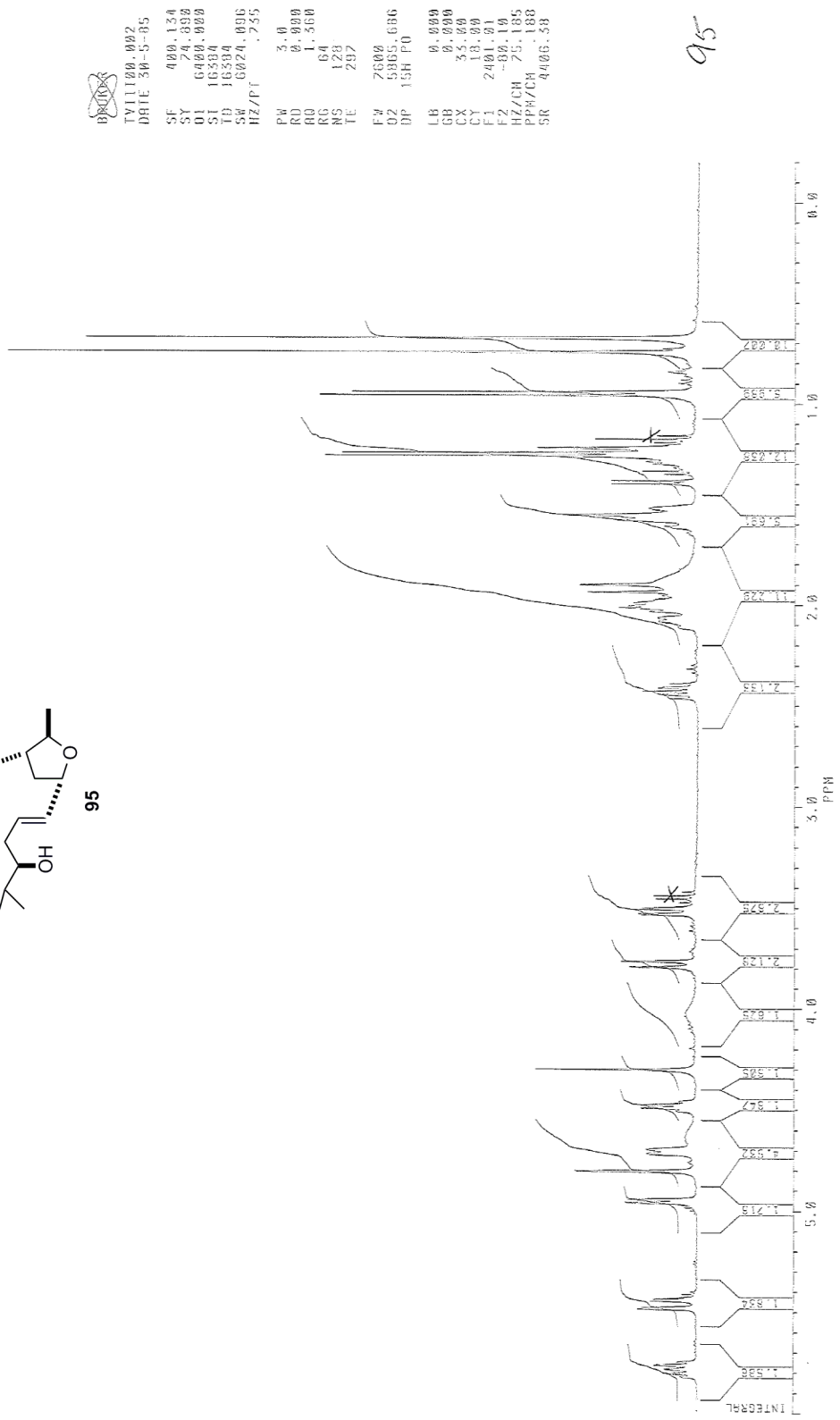

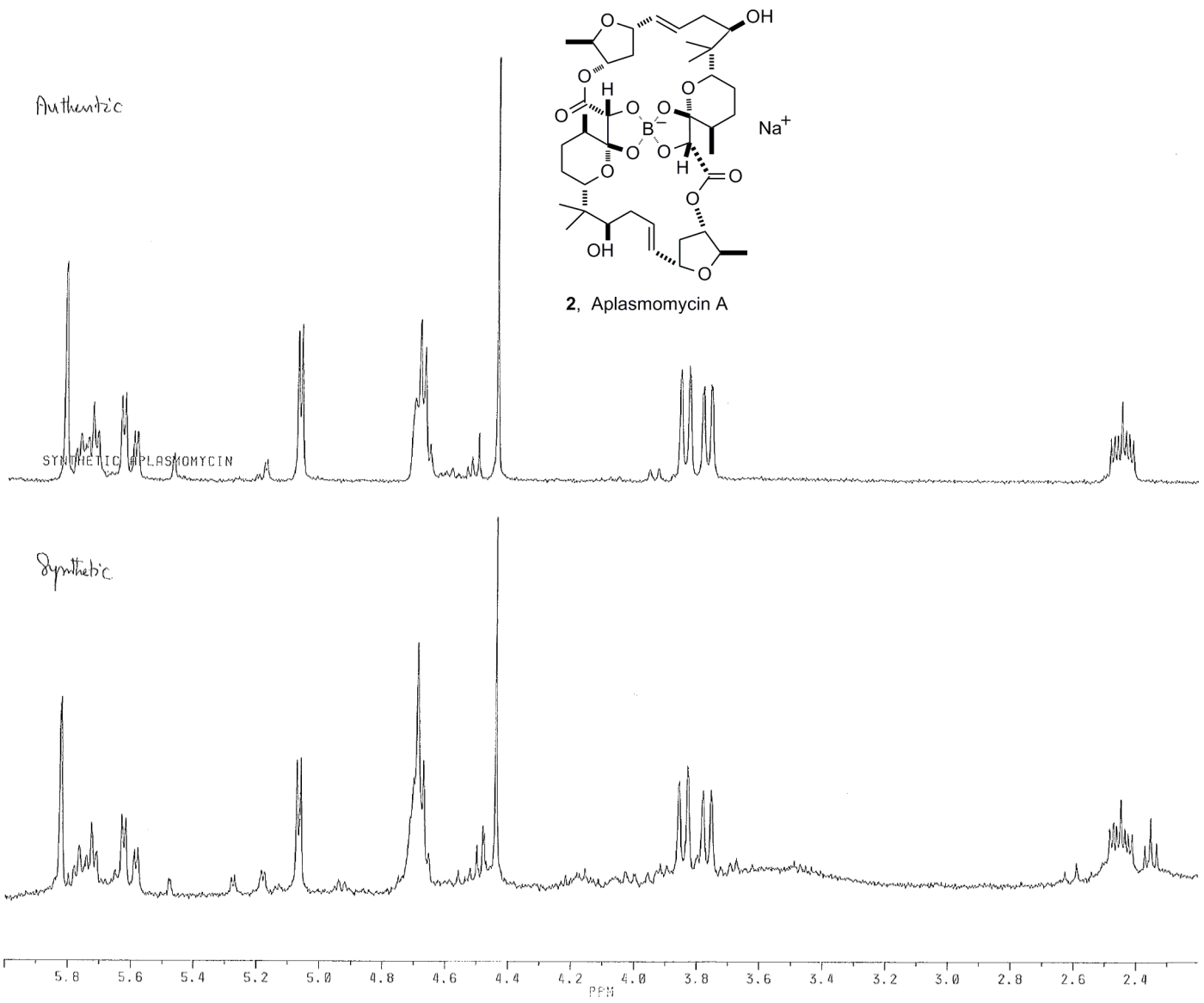

2, Aplasmomycin A

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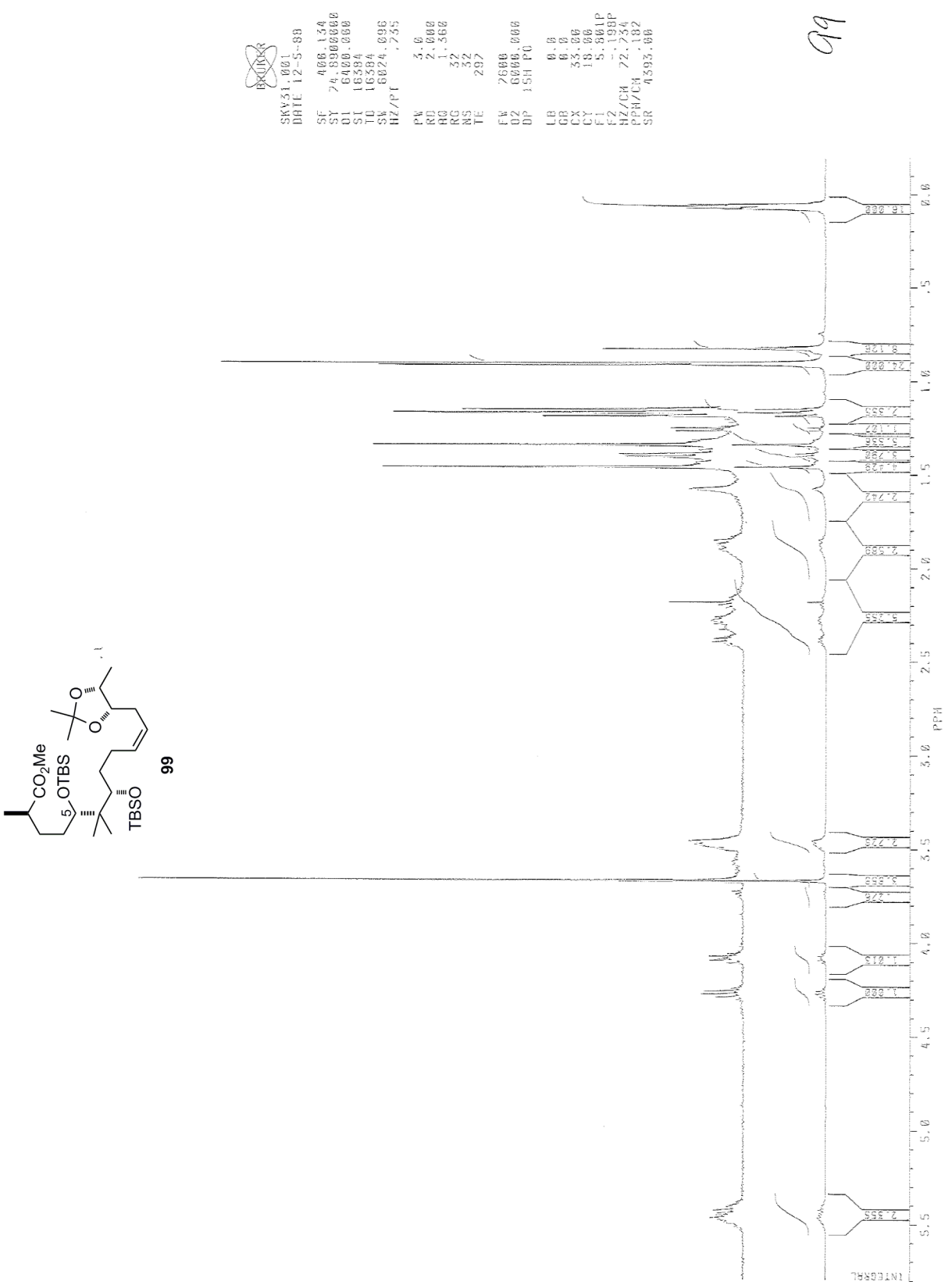

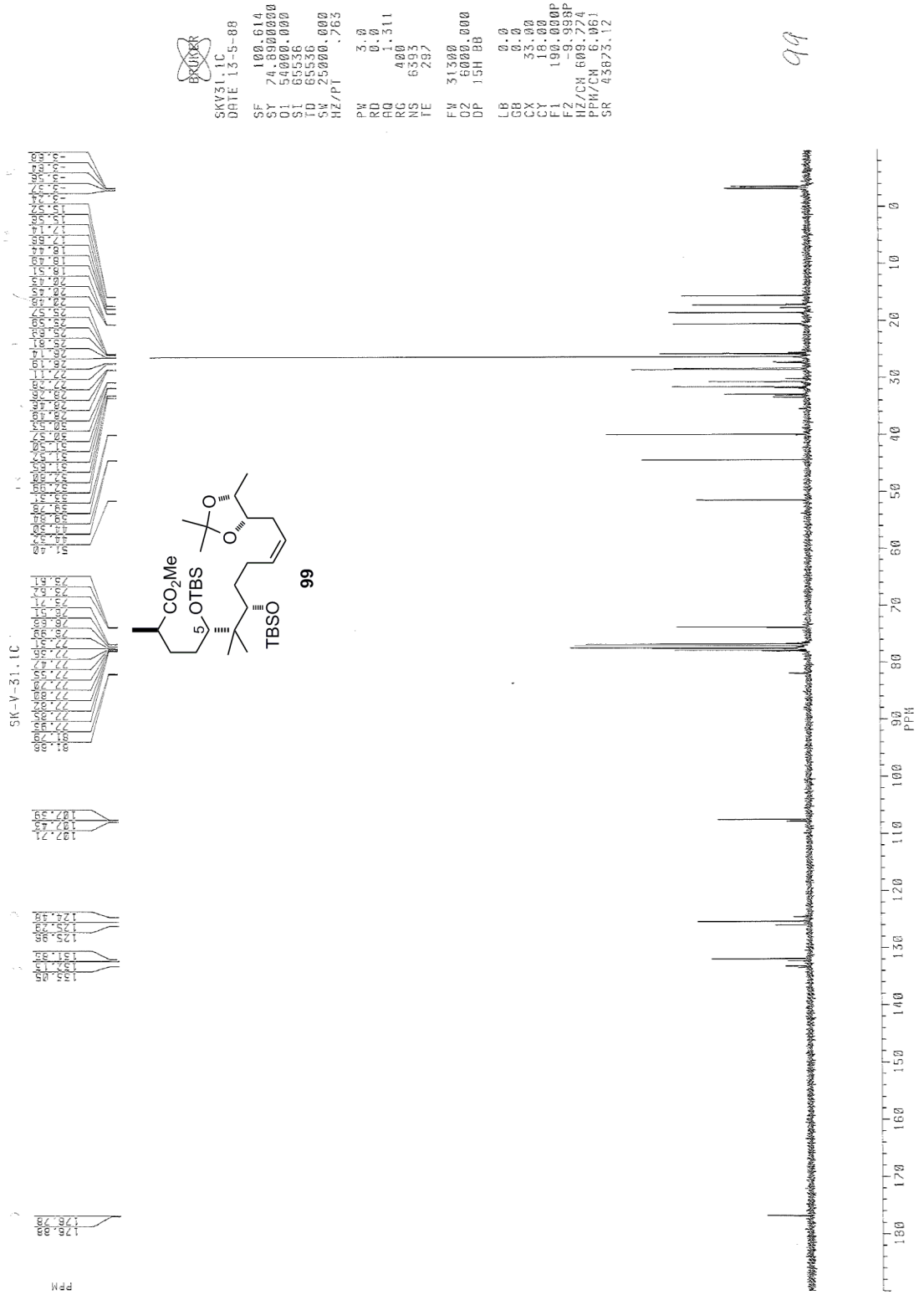

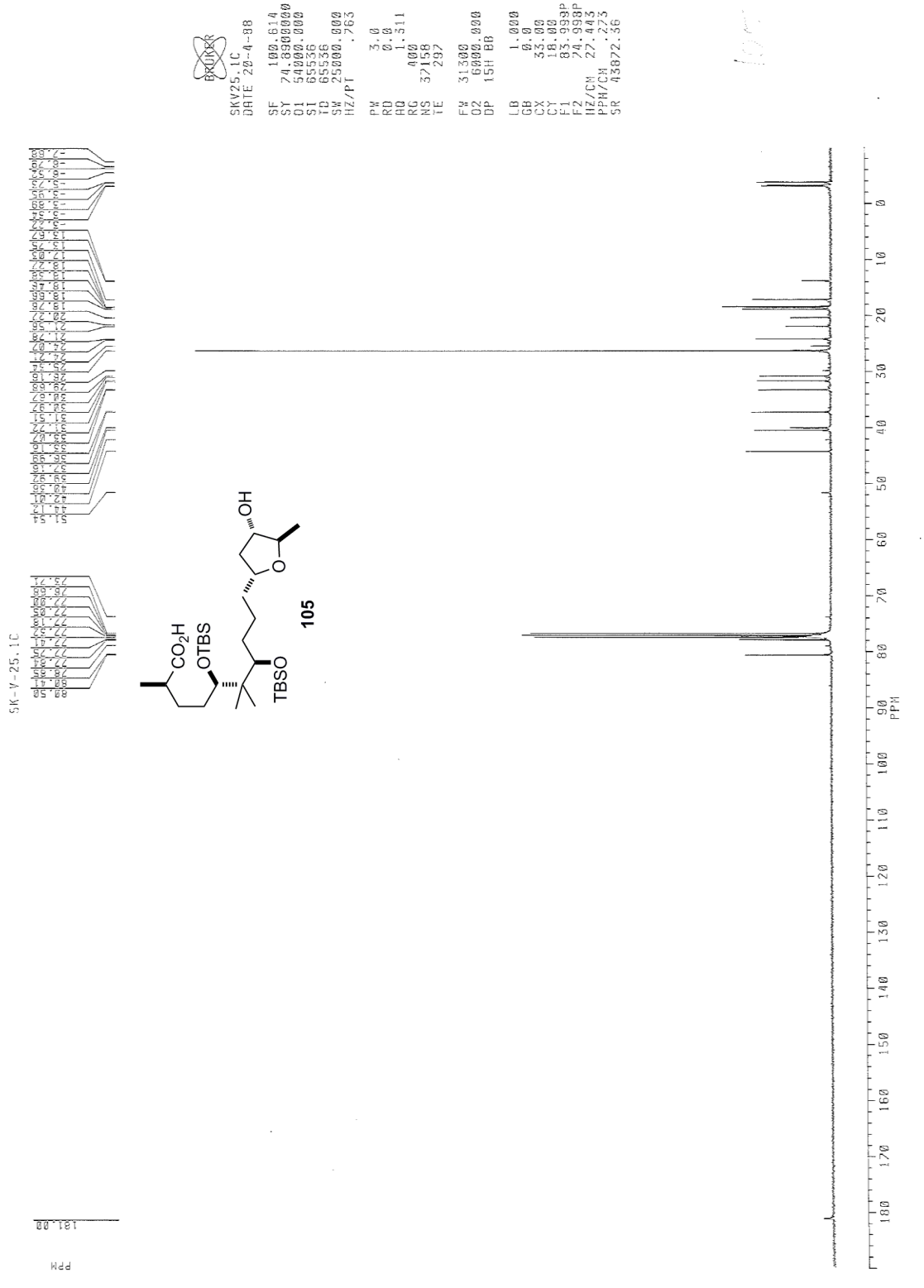

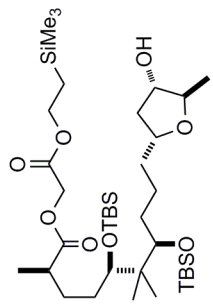

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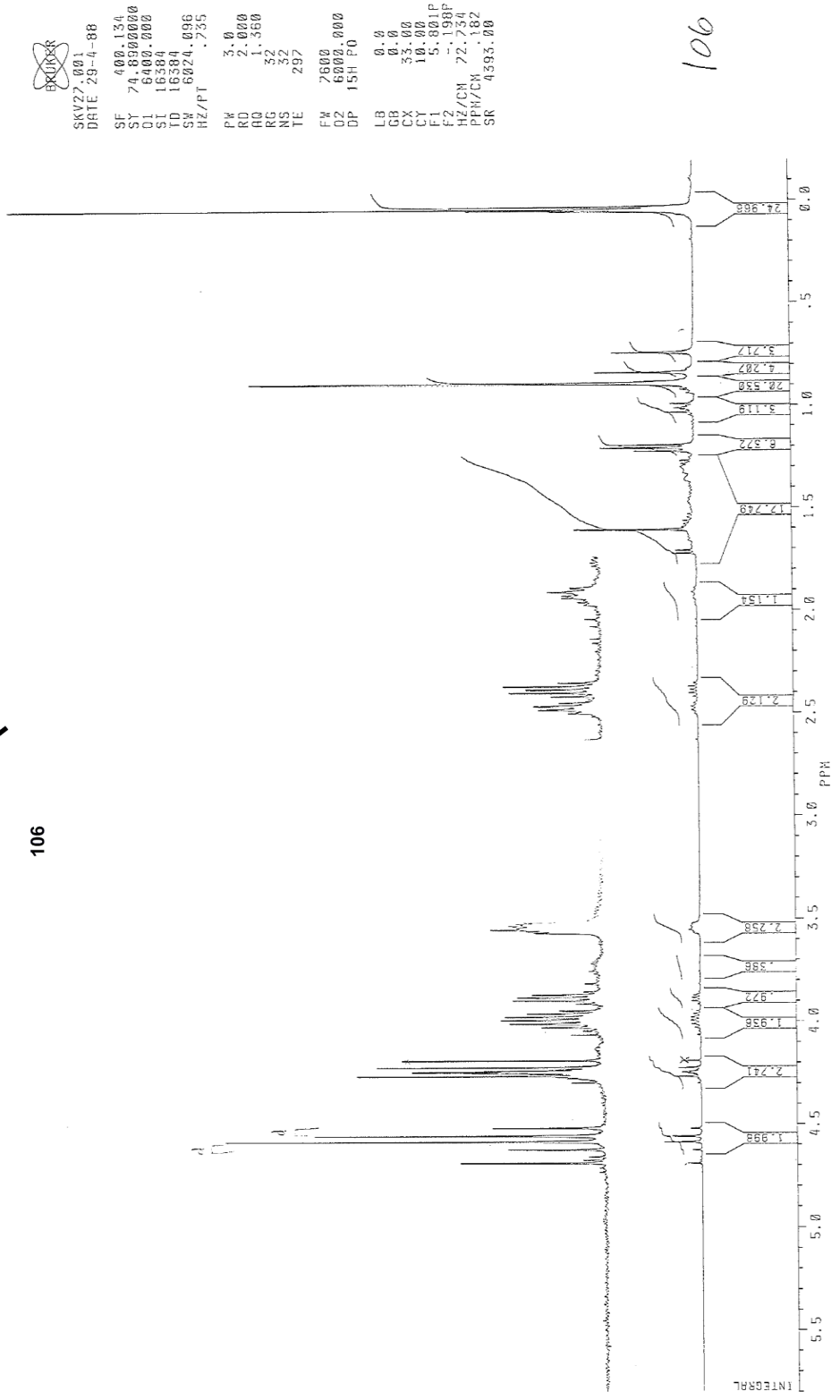

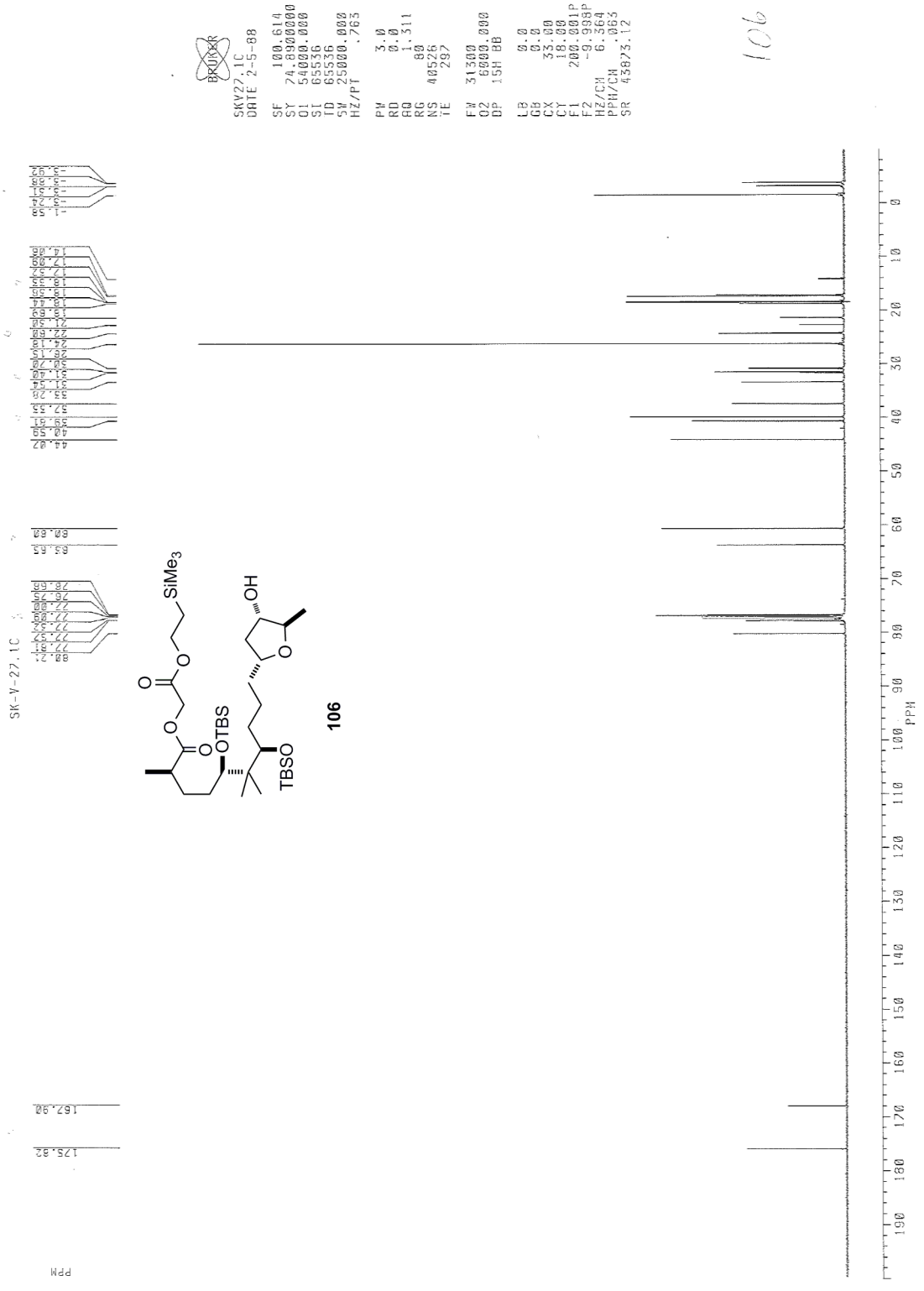

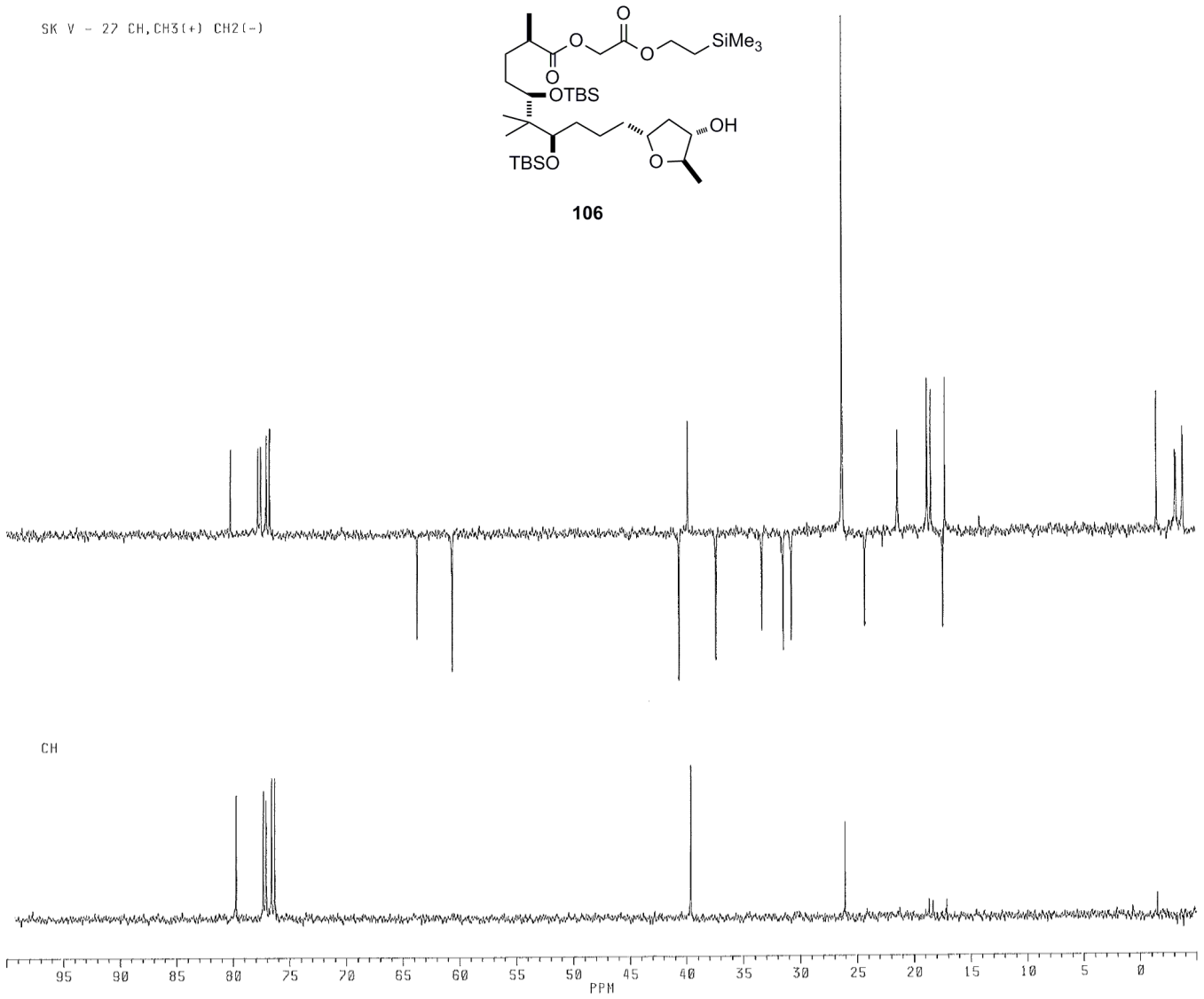

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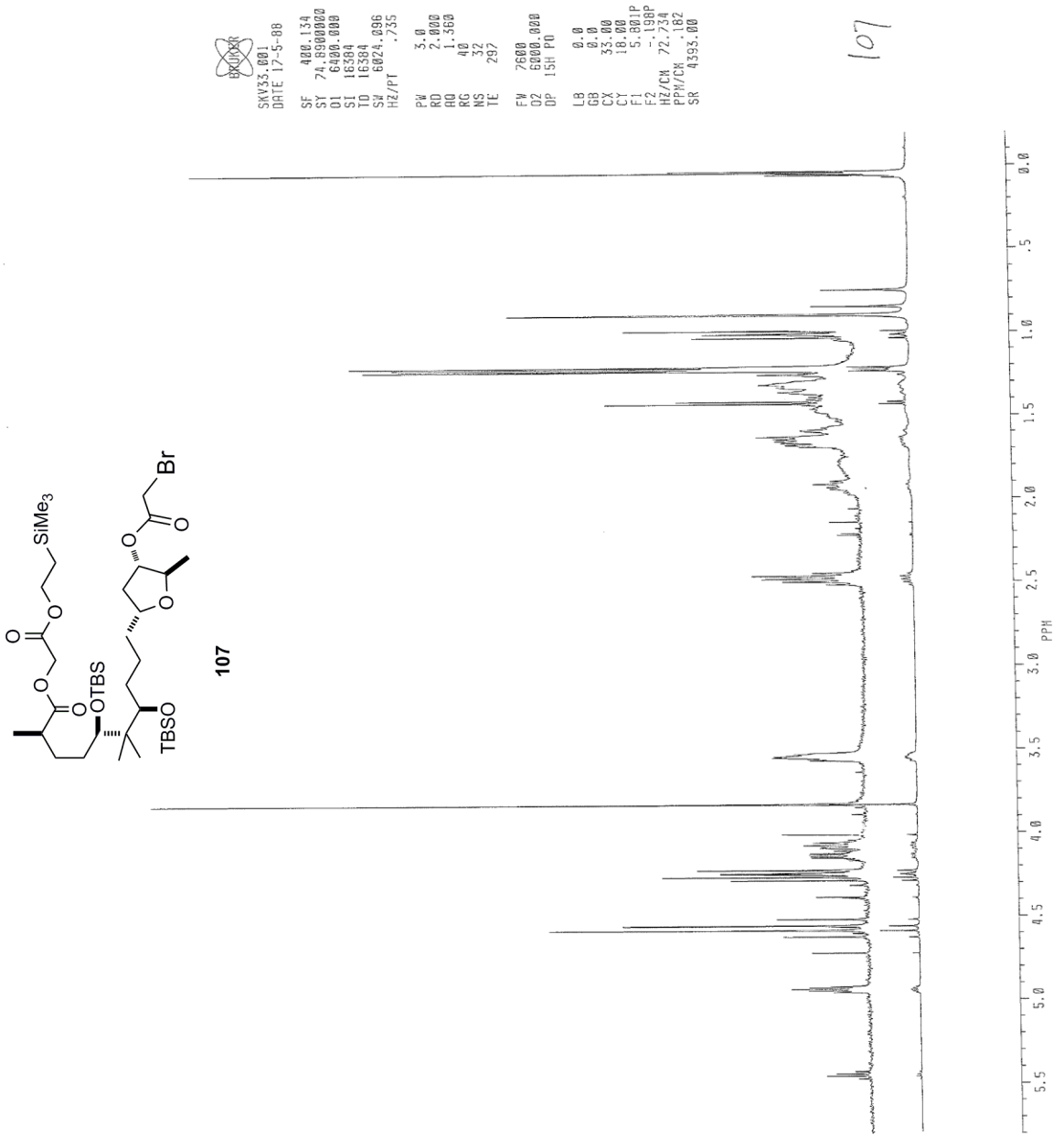

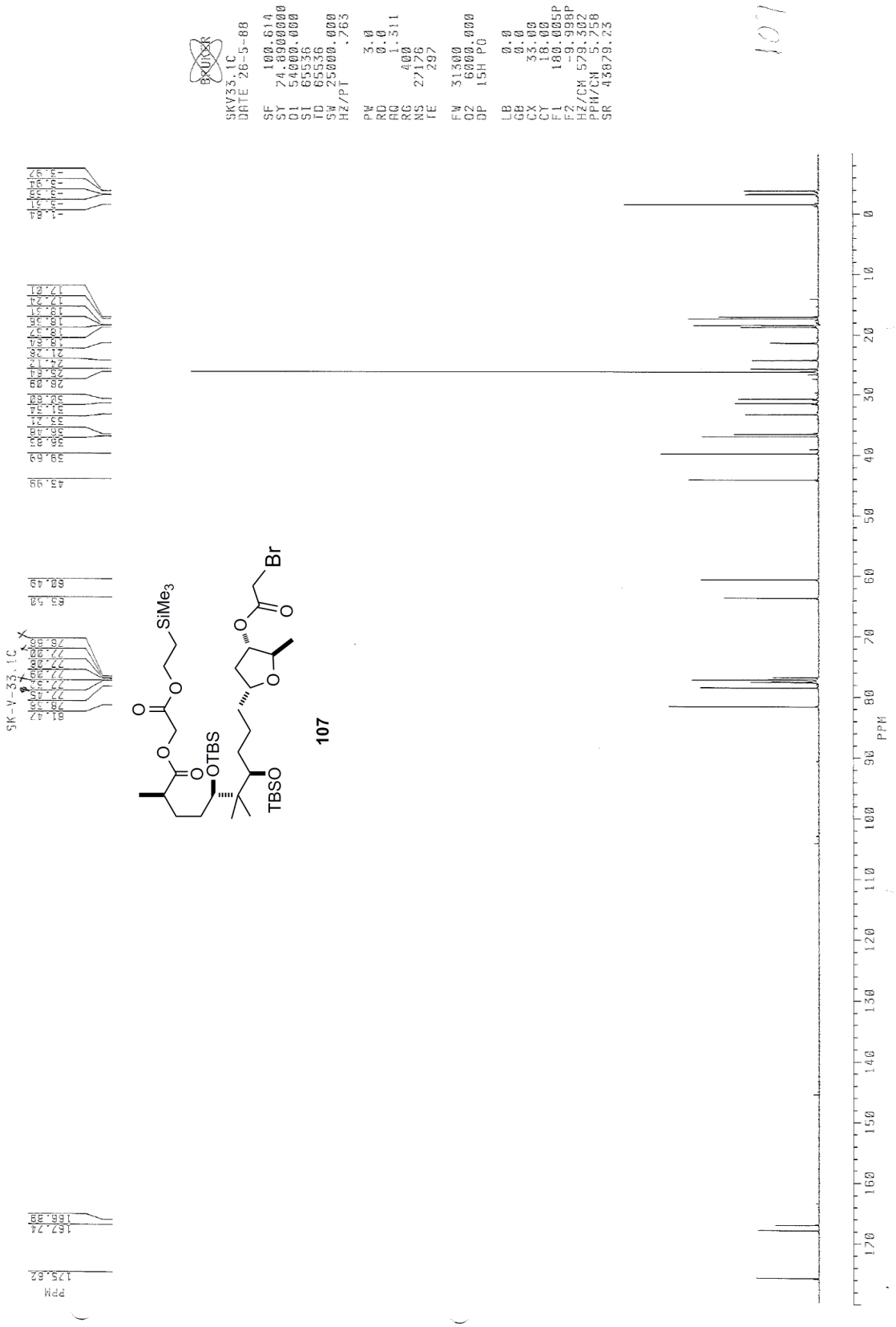

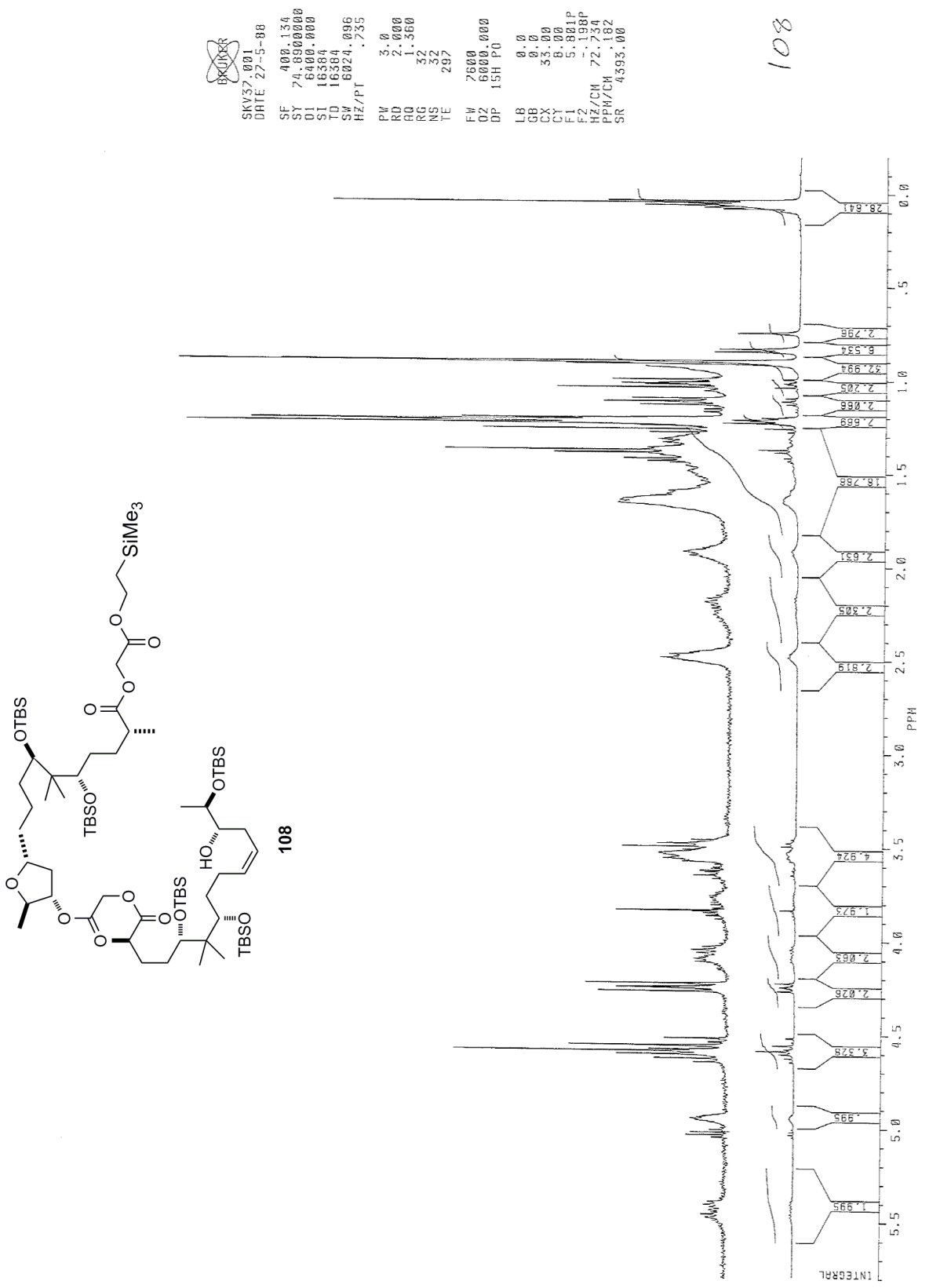

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