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PhD Thesis

Approaches to the Total Synthesis of Dictyostatin and Synthesis of *epi*-Dictyostatins

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*Non bisogna mollare mai, dottore.
Ci vuole un gran fisico per correre dietro ai sogni.*

Stefano Benni, *Elianto*

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Chapter 1

Microtubule-Stabilizing Anticancer Agents

1.1 Introduction¹

Cancer is a generic term for a group of more than 100 diseases that can affect any part of the body; other terms used are malignant tumors and neoplasms. One defining feature of cancer is the rapid creation of abnormal cells which grow beyond their usual boundaries, and which can invade adjoining parts of the body and spread to other organs, a process referred to as metastasis, which are the major cause of death.

Early detection of cancer is very important since treatment is more effective when cancer is localized. The principal methods of treatment are surgery, radiotherapy and chemotherapy. Fundamental for adequate treatment is an accurate diagnosis by means of investigations involving imaging technology (ultrasound, endoscopy, radiography) and laboratory (pathology).

A wide variety of anticancer drugs are employed nowadays for the treatment of a number of different cancers. These can be classified according to their chemical nature and mode of action. A general property which divides the anticancer drugs into two major classes, is the dependence of their action upon the specific phase in which the cancer cell is found at the point of subadministration of the drug. Thus, substances which are active only if the cell is in a specific phase of the cell cycle are named Cellular Cycle Specific (CCS), while the others are termed Cellular Cycle Nonspecific (CCNS). This characteristic has a tremendous impact on the mode of subadministration of a given drug, since, in contrast to antibacterial and antiviral drugs, substances that are able to eliminate only a fraction of the affected cells (i.e. the fraction of cells which are found in a specific phase of the cell cycle) are not very effective in the treatment of cancer. For example, a drug capable of eliminating 99.9% of a tumor mass consisting of approximately 10^{12} cells would leave 10^9 cells in the organism, a number still too large for the immune system to cope with. For this reason, a number of anticancer drugs are administered in combination with other drugs that are CCNS or specific for a different phase of the cell cycle. The effectiveness of polichemotherapy is thus at least additive and in some cases even higher than it could be expected based on the simple sum of the two actions. Another effect of the CCS chemotherapy is a decrease in the effectiveness of the treatment, as a tumor gets older, due to a decrease in the rate of reproduction and differentiation of the cells.

1.2 Microtubules as a Target for Anticancer Drugs²

1.2.1 Microtubules and Their Polymerization Dynamics

Microtubules are fibrillar structures involved in many aspects of cellular biology (transport, signaling, and mitosis). They are used by the cell to form a static structure, called the cytoskeleton, which helps to shape the cell. Microtubules are fundamental for cell division, where they play a central role through their characteristic polymerization dynamics. Microtubules are composed of α -tubulin and β -tubulin heterodimers arranged in the form of slender filamentous tubes which can be many micrometres long (**Figure 1.1**). Approximately 20% of the mass of a microtubule is made up of heterogeneous Microtubule-Associated Proteins (MAPs).

The biological functions of microtubules in all cells are determined and regulated in large part by their polymerization dynamics. The polymerization of microtubules occurs by a nucleation-elongation mechanism. The initial event in the polymerization of a microtubule is the relatively slow formation of heterodimers of α - and β -tubulin that assemble to form a short microtubule nucleus. Nucleation is followed by rapid elongation of the microtubule at both ends (by reversible non-covalent addition) to form a cylinder that is composed of tubulin heterodimers arranged head-to-tail in 13 protofilaments. Each microtubule is a left-handed helix having a so-called plus end (+), with β -tubulin facing outward, and a minus end (-), with α -tubulin facing outward. The filamentous structure of the microtubule is overlaid with MAPs, some of which appear to have a stimulatory effect on the polymerization. Microtubules are not simple equilibrium polymers: they show complex polymerization dynamics that use energy provided by the hydrolysis of GTP at that time that tubulin with bound GTP adds to the microtubule ends; these dynamics are crucial to their cellular functions.

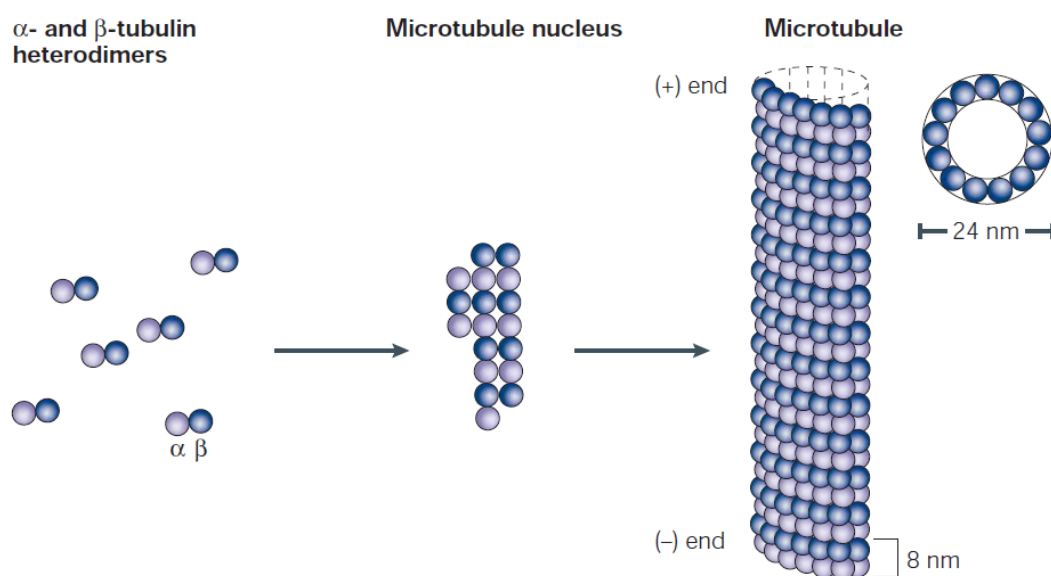


Figure 1.1 Polymerization of microtubules

1.2.2 Why Target Microtubules?

Microtubules and their uniquely rapid dynamics are extremely important in the process of mitosis, during which the duplicated chromosomes of a cell are separated into two identical sets before cleavage the cell into two daughter cells. Their importance in mitosis and cell division makes microtubules an important target for anticancer drugs. Microtubules and their dynamics are the targets of a chemically diverse group of antimitotic drugs (with various tubulin-binding sites) that have been used with great success in the treatment of cancer. In view of the success of this class of drugs, it has been argued that microtubules represent the best cancer target to be identified so far, and it seems likely that drugs of this class will continue to be important chemotherapeutic agents, even as more selective approaches are developed.³

Microtubule-targeted antimitotic drugs are usually classified into two main groups. One group, known as the microtubule-destabilizing agents, inhibits microtubule polymerization at high concentrations and includes several compounds, such as the *Vinca* alkaloids that are used clinically or are under clinical investigation for treatment of cancer. The second main group is known as the Microtubule-Stabilizing Agents (MSAs). These agents stimulate microtubule polymerization and include, among others, paclitaxel (Taxol[®], the first agent to be identified in this class), docetaxel (Taxotere[®]), the epothilones, discodermolide, dictyostatin, eleutherobins, laulimalide, and pelurosides. The classification of drugs as microtubule ‘stabilizers’ or ‘destabilizers’ is overly simplistic and can lead to confusion. The reason, is that drugs that increase or decrease microtubule polymerization at high concentrations powerfully suppress microtubule dynamics at 10–100-fold lower concentrations and, therefore, kinetically stabilize the microtubules.

1.2.3 The Mechanism of Action of Paclitaxel and Related Microtubule-Stabilizing Agents

Paclitaxel and its semi-synthetic analogue docetaxel were among the most important new additions to the chemotherapeutic arsenal in the late twentieth century. Paclitaxel, a complex molecule that was isolated from the bark of the yew tree in 1967 by Monroe Wall and Wani,⁴ underwent slow development until, in 1979, Schiff and Horwitz made the surprising discovery that, unlike the *Vinca* alkaloids, paclitaxel stimulated microtubule polymerization. The taxanes bind poorly to soluble tubulin itself, but instead bind directly with high affinity to tubulin along the length of the microtubule. The binding site for paclitaxel is in the β -subunit, and its location, which is on the inside surface of the microtubule, is known with precision because determination of the crystal structure of tubulin was carried out with the latter complexed with paclitaxel.⁵

Binding of paclitaxel to its site on the inside microtubule surface stabilizes the microtubule and increases microtubule polymerization, presumably by inducing a conformational change in the tubulin which, by an unknown mechanism, increases its affinity for neighbouring tubulin

molecules.⁶ Suppression of microtubule dynamics by paclitaxel leads to mitotic block and the cells eventually die by apoptosis.

Although other cells are also affected adversely, the main reason for cancer cells to be extremely sensitive to MSAs is that they divide more frequently than normal cells and therefore more frequently pass through a stage of vulnerability to mitotic poisons.

The clinical success of the taxanes has led to a search for other drugs that enhance microtubule polymerization. This search yielded several promising compounds. Some of these compounds compete with paclitaxel for binding to microtubules and are thought to bind at or near the taxane site (epothilones, discodermolide, eleutherobins and sarcodictyins), but others, such as laulimalide, seem to bind to unique sites on microtubules.⁷

1.3 The Use of Taxol[®] : Scope and Limitations^{2a}

1.3.1 Isolation and Syntheses of Taxol[®]

Paclitaxel (**1.1**, **Figure 1.2**) is a mitotic inhibitor used in cancer chemotherapy. It was discovered in a U.S. National Cancer Institute program in 1967 when Wall and Wani isolated it from the bark of the Pacific yew tree (*Taxus brevifolia*) and named it taxol (which was to become the trademark). From 1967 to 1993, almost all paclitaxel was derived from natural source. Consequently, early research on paclitaxel was limited by a restricted supply, due to several difficulties in obtaining the drug. The concentration of the compound in yew bark is low, and paclitaxel extraction is complex and expensive. In addition, bark collection was restricted because the Pacific yew is a limited resource located in old-growth forests which are the habitat of the endangered spotted owl.

As for total synthesis, several efforts have been devoted by the chemical community to this challenging structure, since its structural elucidation in the early 1970's. The total synthesis of paclitaxel is called one of the most hotly contested of the 1990s,⁸ with around 30 competing research groups by 1992. The number of research groups actually having reported a total synthesis stands currently at seven, with the Holton group⁹ (1994, article first accepted for publication) and the Nicolaou group¹⁰ (1994, article first published) first and second in what is called a "photo-finish". Since then, other syntheses of paclitaxel have been reported by Danishefsky¹¹ (1996), Wender¹² (1997), Kuwajima¹³ (1998), Mukaiyama¹⁴ (1998) and Takahashi¹⁵ (2006).

The commercial semisynthesis of paclitaxel, and its slightly modified version docetaxel (**1.2**), starts from 10-deacetylbaccatin III (**1.3**), isolated from the European yew (*Taxus baccata*), and is based on the addition of synthetic side chains. Currently, paclitaxel production, involves a plant cell fermentation technology.

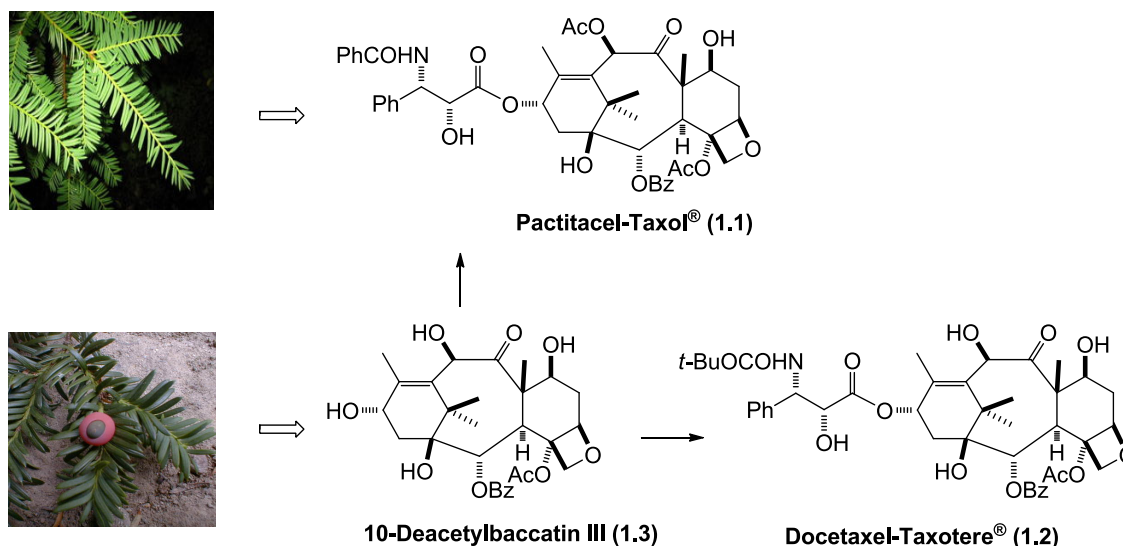


Figure 1.2 Paclitaxel (from *Taxus brevifolia*), baccatin III (from *Taxus baccata*) and synthetic docetaxel

1.3.2 Clinical Application of Taxol®

Clinical trials on Paclitaxel began in 1983. In 1989, investigators at The Johns Hopkins Oncology Center reported that the drug produced partial or complete responses (shrinking or disappearance of the tumor) in 30% of previously treated patients with advanced ovarian cancer. In 1992, the Food and Drug Administration (FDA) approved the use of paclitaxel for refractory (treatment-resistant) ovarian cancer.

Subsequently, clinical trials using paclitaxel for the treatment of advanced breast cancer demonstrated that the drug is effective against this disease. In 1994, the FDA approved the use of paclitaxel for breast cancer that has recurred within six months after the completion of initial chemotherapy and for metastatic breast cancer that is not responding to combination chemotherapy. Trials to test the effectiveness of paclitaxel against other types of cancer, including leukemia, lymphoma, cancers of the lung, colon, head and neck were also made. In the cases of ovarian cancer, paclitaxel gives a response with manageable side effects in 30-35% of cases. These results, which represent the highest reported salvage rate for ovarian cancer, are particularly significant as these patients show resistance to other therapies.

Since 1992, paclitaxel (with the registered trade name Taxol®), has developed into a 1,5 billion dollar drug, representing over 10% of the pharmaceutical sales of Bristol-Myers Squibb.¹⁶ Today, Taxol® is the drug of choice for many solid tumors, including ovarian, breast, non-small cell lung, bladder, esophagus, head and neck; and it has proven to be particularly effective at treating recurrent tumors as well as those unresponsive to previous first line therapies.

1.3.3 The Side Effects of Taxol®

Like most cancer drugs, paclitaxel has certain side effects, some of which can be serious. When Taxol® molecules bind to microtubules, they render them extremely stable and static, making cell division impossible and killing the cells as it begin to divide. Taxol® damages all rapidly dividing cells: cancer cells, but also white blood cells and hair cells. Consequently, severe side effects are experienced by people taking the drug.

The most serious and dose limiting side effect of Taxol® is depression of the bone marrow (neutropenia) which in turn diminishes the body's ability to produce the blood cells that fight infection. Reversible hair loss is a common consequence of paclitaxel treatment, as well as gastrointestinal problems, nerve damage (peripheral neuropathy), haematic and cardiac problems and other adverse effects.¹⁷

Administration of taxanes can also be hampered by hypersensitivity reactions.¹⁸ This phenomenon results from their poor solubility (Taxol® in particular) and the consequent need to dissolve in solvents such as polyoxyethylated castor oil (Cremophor EL®) or polysorbate, which are known to cause histamine release. This risk has been substantially reduced by the use of premedications, but nonetheless remains a clinical problem.

1.3.4 The Insurgence of Multiple Drug Resistance

The most severe limitation to the clinical application of Taxol® is the emergence of tumor phenotypes resistant to taxanes, as well as to other chemotherapeutic agents. This phenomenon, known as Multiple Drug Resistance (MDR), results from two mechanisms: (i) over-expression of membrane transporter proteins, on the surface of neoplastic cells, which lower the intracellular concentration of cytotoxic products; (ii) over-expression of tubulin isotypes which are less susceptible to induced polymerization and stabilization.

The first mechanism consists in the over-expression of a class of membrane transporter proteins known as ABC-transporters (ATP-dependent drug efflux pumps or ATP-binding cassettes).^{2b} These membrane pumps produce decreased intracellular drug levels and lead to cross-resistance to drugs of different chemical structures, such as paclitaxel. The first ABC-transporters to be identified was P-glycoprotein (PgP), the product of the human *MDR1* gene. Considerable efforts are underway to understand these mechanisms of resistance, to develop PgP inhibitors and microtubule-targeted drugs that are not removed by these pumps.¹⁹

The second mechanism is related to the expression of different β -tubulin isotypes,²⁰ which confer resistance or determine intrinsic insensitivity to antimetabolic drugs. In particular aberrant expression of β III-tubulin can affect the response of tumour cells to MSAs. The mechanisms underlying this behavior are currently unclear. Understanding the role of the other β -tubulin isotypes in cancer development is also at an early stage.

In sum, there is a need to develop novel taxane derivatives and newer agents to target microtubules in order to overcome this set of problems.

1.4 Natural Products with Paclitaxel-like Activity

The need for a general solution to the limitations of Taxol[®] has elicited large scale screening efforts to identify other natural product leads, which have the same mechanism of action and cytotoxicity profile. It is thought that, by acting through a common mechanism, these new leads might share Taxol[®]'s clinical benefits, but their distinct structures will endow them with unique and perhaps improved pharmacological profiles in terms of toxicity and susceptibility to resistance.

These efforts have resulted in the identification of several novel structural types (**Figure 1.3**) including the epothilones (**1.4a**, **1.4b**, **1.4c**, **1.4d**), discodermolide (**1.5**), eleutherobin (**1.6**) sarcodictyins (**1.7a**, **1.7b**), dictyostatin (**1.8** see Chapter 2), laulimalide (**1.9**), pelorusides (**1.10a**, **1.10b**) and few others.

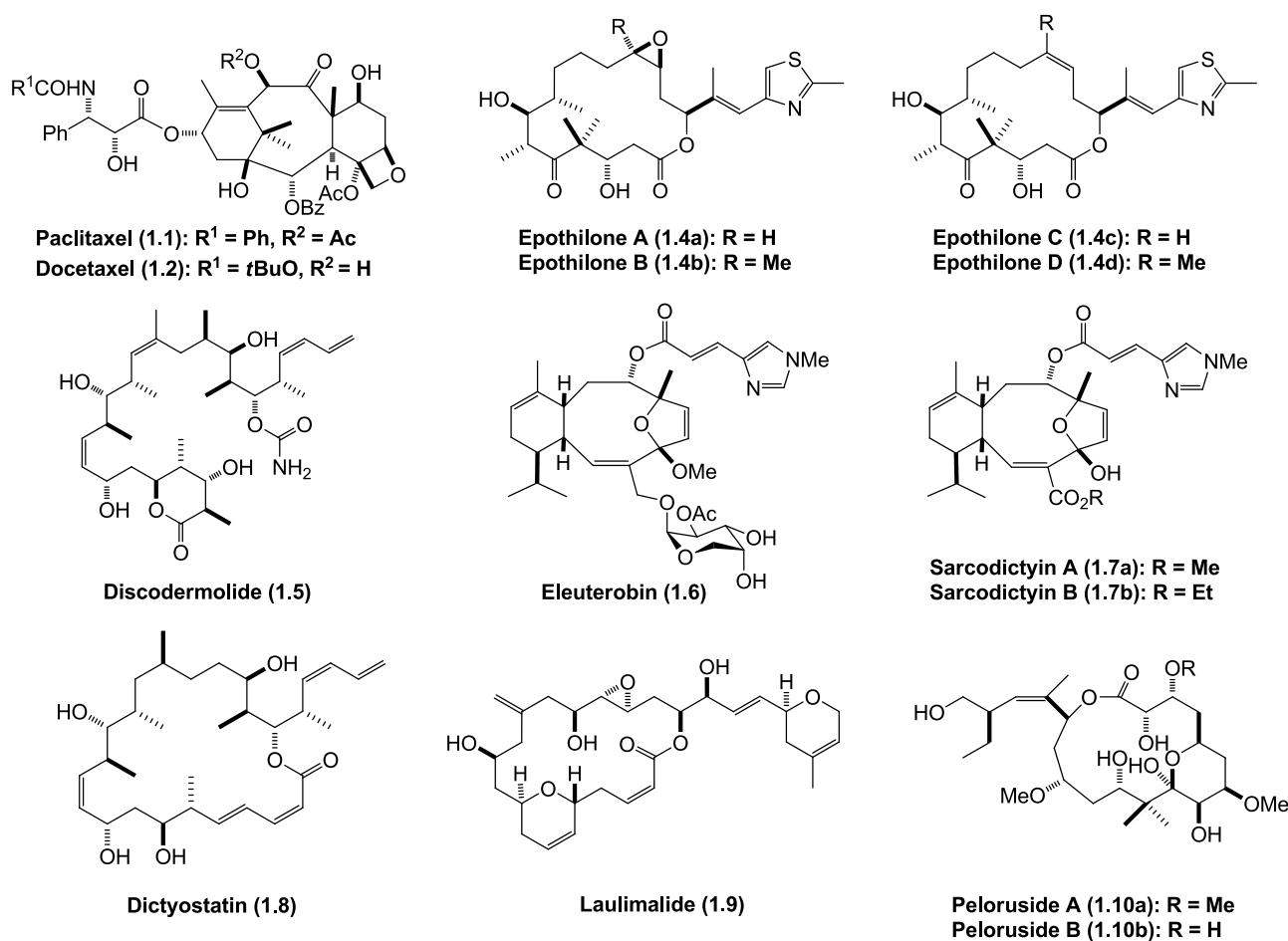


Figure 1.3 Microtubule-stabilizing anticancer agents

As is often the case for natural products extracted from marine organisms, as most of the above mentioned compounds are, natural supply is insufficient for extensive *in vitro* studies, determination of Structure-Activity Relationship (SAR), *in vivo* studies and in general for advancement to clinical trials. The need for a partially or fully synthetic approach is therefore motivated both by the scarcity as well as the fascination of their challenging molecular architecture.

1.4.1 Epothilones²¹

The epothilones (**1.4a-d**) are 16-membered macrolides named for their molecular structure, which includes an epoxide, methyl thiazole, and ketone moieties. Epothilones A, B, C and D were extracted by Höfle and Reichenbach in the 1986 from myxobacterium *Sorangium cellulosum* (**Figure 1.4**), collected on the banks of the Zambesi River.^{22,23}

Initially investigated as anti-fungal agents, epothilones A and B were proven capable of inducing tubulin polymerization and stabilizing microtubules as Taxol[®]. Both compounds compete with paclitaxel for binding to tubulin and are able to displace paclitaxel from microtubules, suggesting that they occupy the same binding site as taxanes.²⁴ Despite these similarities, analysis using electron crystallography has shown that epothilones interact with the β -subunit of tubulin through unique and independent molecular interactions.²⁵ *In vitro* studies in tumor cell lines showed that epothilone B is more active than epothilone A. Both epothilones have greater potency than paclitaxel or docetaxel *in vitro*, with mean inhibitory concentration (IC₅₀) values in the low nanomolar range. The epothilones are also active against cells that over-express Pgp,²⁶ a mechanism implicated in development of resistance to taxanes.²⁷ In addition, mutations in β -tubulin, that confer resistance to taxanes,²⁸ did not significantly alter the cytotoxicity of epothilones A and B.

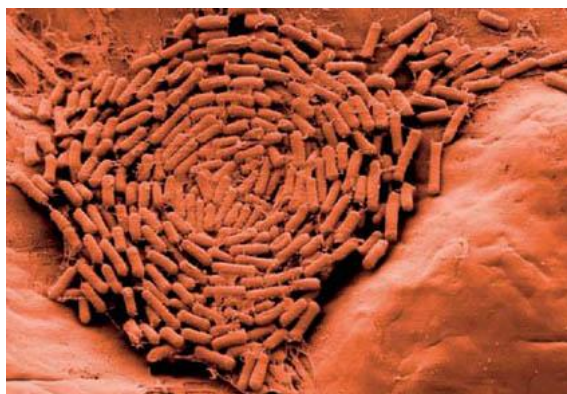


Figure 1.4 Myxobacterium *Sorangium cellulosum*

Epothilone B has been evaluated in clinical trials against a variety of solid tumors. It crosses the blood-brain barrier and has shown activity in patients with recurrent or progressive brain metastases from non small-cell lung cancer.²⁹ Epothilone D, which lacks the epoxide moiety, has shown superior *in vivo* anticancer activity relative to epothilone B. However, its clinical development has been discontinued.

Due to the high potency and clinical need for cancer treatments, epothilones have been the target of many total syntheses. The first group to publish the total synthesis of epothilones A and B was that of Danishefsky, in 1996.³⁰ Other syntheses of epothilones were published by Nicolaou,³¹ Schinzer,³² Mulzer,³³ and Carreira.³⁴ Moreover, the promising anticancer activity of epothilones and their ability to overcome resistance resulted in the synthesis of several epothilone analogs.

1.4.2 Discodermolide³⁵

Discodermolide (**1.5**) was first reported in 1990 by Gunasekera and co-workers.³⁶ Isolated from the marine sponge *Discodermia dissolute* (**Figure 1.5**), collected at a depth of 33 m off Grand Bahama Island, in the Caribbean, a combination of exhaustive extraction and chromatography afforded discodermolide in 0.002% wet weight from the frozen sponge.



Figure 1.5 Marine sponge *Discodermia dissolute*

The planar structure of this novel polyketide was elucidated through detailed NMR studies, and the relative configuration defined by single-crystal X-ray diffraction analysis. Following its initial isolation, preliminary biological evaluation revealed discodermolide to possess both potent cell growth inhibitory and immunosuppressive activity. Both the cytotoxicity exhibited against certain human cancer cell lines and binding affinity of discodermolide for tubulin are superior those of Taxol[®]. Importantly, the antiproliferative activity of discodermolide is retained in cell lines exhibiting resistance to Taxol[®]. The discodermolide binding site on tubulin was first probed through a series of competition studies with Taxol[®],³⁷ the ability of discodermolide to displace

Taxol[®] suggested it occupied an identical or similar binding site on β -tubulin. However, the identification of a synergistic potentiation of the cytotoxicity of discodermolide, when used in combination with Taxol[®], provided stronger evidence that the binding sites, in fact, overlap and are not the same.³⁸

The remarkable biological profile of discodermolide was recognized by Novartis Pharma AG and, following a huge synthetic effort to obtain sufficient drug amounts, discodermolide was progressed into phase I clinical trials in patients with advanced solid malignancies. In 2004, these trials were halted due to problems associated with severe toxicity.³⁹

A number of interesting syntheses of **1.5** have appeared in the literature,⁴⁰ namely by the groups of Smith III (the first gram-scale synthesis),⁴¹ Marshall,⁴² Schreiber,⁴³ Myles,⁴⁴ and Paterson,⁴⁵ along with several synthetic studies⁴⁶ and synthesis of analogues.⁴⁷

1.4.3 Eleutherobin and Sarcodictyins⁴⁸

Eleutherobin (**1.6**) and sarcodictyins, (**1.7a**, **1.7b**) all belong to the eleuthesides category.⁴⁹ Sarcodictyins were the founding members of this category, having been isolated in 1987 by Pietra and co-workers from the Mediterranean coral *Sarcodictyin roseum*.⁵⁰ Nine years later, Fenical and co-workers reported the isolation of eleutherobin from an *Eleutherobia* soft coral (**Figure 1.6**) found in Western Australia.⁵¹



Figure 1.6 Soft coral *Eleutherobia*

Eleutherobin has been shown to be a Pgp substrate, which does not offer any advantages over paclitaxel in the growth inhibition of MDR cell lines.⁵² In addition, the compound also exhibits reduced activity against paclitaxel-sensitive cell lines compared with paclitaxel itself. Contradictory data exist in the literature with regard to eleutherobin activity against paclitaxel-resistant cell lines that are characterized either by tubulin mutations or changes in β -tubulin isotype expression. Even in the most favorable case, however, the absolute cytotoxicity (IC₅₀) of

eleutherobin in the paclitaxel-resistant cell lines was found to be no more than twofold higher than that of paclitaxel. Sarcodictyins A and B are reported to exhibit very low resistance factors against Pgp-over-expressing human cancer cell lines,⁵³ but, at the same time, their intrinsic antiproliferative activity against drug-sensitive cells is significantly lower than that of all other MSAs.^{52c} In summary, eleutherobin and sarcodictyins as such are much less attractive antiproliferative agents than epothilones or discodermolide. However, they could still be interesting starting points for chemical derivatization or analog programs, and efforts along these lines have been reported.^{52c, 52d}

Sarcodictyins A and B have been synthesized successfully by Nicolaou and co-workers⁵⁴ who have also exploited a similar route for accessing eleutherobin.⁵⁵ A second report by Danishefsky and co-workers details an alternative access to the latter compound.⁵⁶ A formal total synthesis of eleutherobin was reported also by Gennari's group in 2005.⁵⁷ A number of other partial syntheses and alternative strategies have also been described.⁵⁸

1.4.4 Laulimalide

Although first isolated in 1988 from several different species of sponge,⁵⁹ laulimalide (**1.9**) was only recently identified as a microtubule depolymerization, inhibitor in a mechanism-based screening program.⁶⁰

Laulimalide is a potent microtubule-stabilizing agent, with IC₅₀ values against numerous drug sensitive cell lines in the low nanomolar range.⁶¹ The compound is also active against Pgp expressing MDR cell lines. While epothilones, discodermolide and eleutherobin inhibit the binding of Taxol[®] to tubulin polymer in a competitive manner, it has been shown that laulimalide binds to a different site.⁶²

After its discovery, the syntheses of several fragments of **1.9** were reported.⁶³ In the following years, total syntheses of laulimalide itself were published by Ghosh,⁶⁴ Mulzer,⁶⁵ Williams,⁶⁶ Paterson,⁶⁷ Nelson⁶⁸ and Wender,⁶⁹ along with synthesis of analogs.⁷⁰

1.4.5 Pelorusides⁷¹

Pelorusides (**1.10a**, **1.10b**) are a secondary metabolite isolated in 1999 from the marine sponge *Mycale hentscheli* (**Figure 1.7**),⁷² collected from Pelorus Sound in New Zealand.

They have potent paclitaxel-like microtubule-stabilizing activity and are cytotoxic at nanomolar concentrations.⁷³ Peloruside A (**1.10a**) was also shown to have a different binding site on the tubulin dimer to paclitaxel, but was seen to bind to the same or overlapping site with laulimalide.⁷⁴ Peloruside A has some promising advantages over paclitaxel, being more soluble and therefore not requiring the use of Cremophore EL[®] to deliver the drug to the body. This should correlate with fewer vehicle-associated side effects than paclitaxel.⁷⁵ Peloruside A is also more likely to be

effective against cells that acquire the MDR phenotype, since it remains active in cells with high PgP expression.

Tests of peloruside in animals have been very promising, with peloruside A showing no overt toxicity in mice and being more efficacious in inhibiting tumor growth than paclitaxel and docetaxel. At the present time, preclinical studies and the advancement of peloruside A into phase I clinical trials for cancer therapy are being held back due to the short supply of natural and synthetic peloruside A.

The De Brabander's group was the first to carry out a total synthesis of peloruside A.⁷⁶ This first synthesis produced the inactive enantiomer of peloruside A, but the group subsequently re-synthesized the correct, bioactive enantiomer. Since then, three other laboratories have synthesized the compound in milligram amounts⁷⁷ and several syntheses of fragments have appeared in the literature.⁷⁸ The synthetic strategies for peloruside A have been reviewed by Williams and co-workers.⁷⁹ Peloruside B (**1.10b**), has recently been synthesized by the Ghosh laboratory.⁸⁰ The relatively simple structure of pelorusides makes them suitable for the design and synthesis of analogues with improved tumor targeting and reduced tumor cross-resistance.



Figure 1.7 Marine sponge *Mycale hentscheli*

1.4.6 Other Microtubule-Stabilizing Agents

In addition to the above mentioned classes of MSAs other interesting compounds were recently reported (**Figure 1.8**).

Cyclostreptin (**1.11** originally named FR182877) was isolated by a group of Japanese scientists from *Streptomyces* sp 9885.⁸¹ Interesting, it is the only known MSA which covalently binds to tubulin.⁸² The preparation of this compound by fermentation and its activity were patented.⁸³ Total syntheses of cyclostreptin were reported by Sorensen⁸⁴ and Evans.⁸⁵

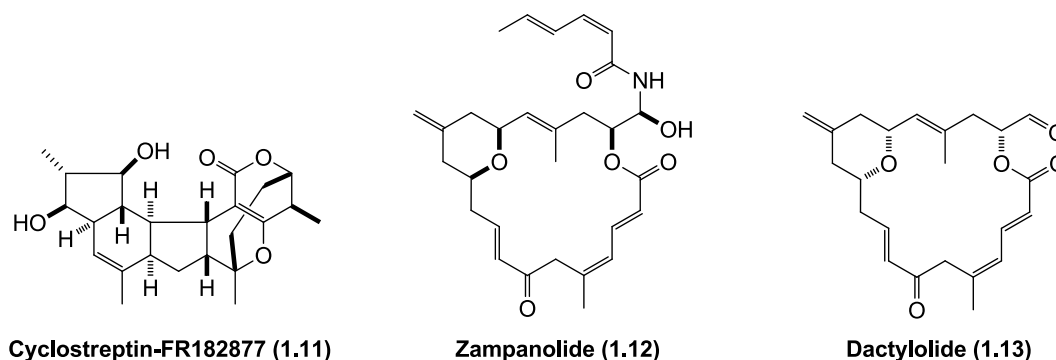


Figure 1.8 Other microtubule-stabilizing anticancer agents.

Zampanolide (**1.12**) and dactylolide (**1.13**) are structurally related polyketide-based macrolides, characterized by a highly unsaturated 20-membered macrolactone ring. Zampanolide was first isolated in 1996 by Tanaka and co-workers from the marine sponge *Fasciospongia rimosa* at Cape Zampa in Okinawa.⁸⁶ More recently, **1.12** was also isolated from the Togan sponge *Cacospongia mycofijiensis* (**Figure 1.9**) by Northcote and co-workers, who demonstrated the compound to be an efficient promotor of tubulin assembly.⁸⁷

Dactylolide was isolated in 2001 by Cutignano and co-workers from the sponge *Dactylospongia* at the Vanuatu Islands.⁸⁸ In contrast to zampanolide, dactylolide is only a moderately potent inhibitor of human cancer cell growth, with IC_{50} in the low micromolar range.

While a number of stereoselective syntheses of this two related compound have appeared in the literature,^{89,90} little work has been reported on analogue structures and their biological activity.^{89d}



Figure 1.9 Marine sponge *Cacospongia mycofijiensis*

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- ¹ Data and information reported in these paragraphs comes from the World Health Organization (WHO), American Cancer Society (ACS) and American National Cancer Institute (NCI) (web sites <http://www.who.int/en>, <http://www.cancer.org> and <http://nci.nih.gov>).
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Chapter 2

(-)-Dictyostatin

2.1 Isolation and Structure Determination

In 1994, Pettit and co-workers reported the isolation of (-)-dictyostatin (**1.8**) from a marine sponge of the genus *Spongia* sp. (family Spongiidae), collected in the Republic of Maldives, in 3.7×10^{-7} % yield (1.35 mg was obtained from 400 kg wet mass of sponges).¹ The planar gross structure, comprising an unsaturated 22-membered macrolactone ring, 11 stereogenic centers, a (2*Z*,4*E*)-dienoate moiety, a disubstituted (*Z*)-olefin and a terminal (*Z*)-diene, was determined based on the basis of the analysis of 2D NMR spectroscopic data,¹ and a partial stereostructure (**2.1**) was proposed (**Figure 2.1**).²

More recently, (-)-dictyostatin was isolated by Wright and co-workers from a *Lithistida* sponge of the family *Corallistidae* collected off the north Jamaican coast, in much higher yield (5.7 mg, 2.8×10^{-3} % of wet weight).³ Paterson and Wright subsequently proposed a full stereochemical assignment for (-)-dictyostatin, as indicated in **Figure 2.1**, based on extensive high-field NMR experiments, including application of the Murata *J*-based configuration analysis, in combination with molecular modeling.⁴ This stereochemical assignment was also based on (-)-dictyostatin being biogenetically related to (+)-discodermolide **1.5**. This stereochemical assignment was confirmed unequivocally by Paterson's total synthesis of (-)-dictyostatin⁵ and validated independently by the total synthesis of Curran,⁶ as described in §2.3.1 and §2.3.2.

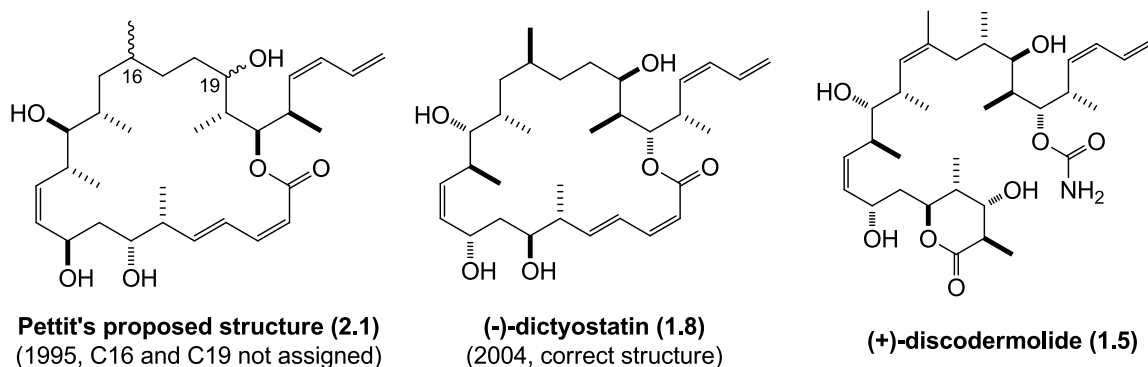


Figure 2.1 Initial and reassigned structure of (-)-dictyostatin and structure of (+)-discodermolide

2.2 The Biological Profile of (-)-Dictyostatin⁷

Upon its initial isolation, (-)-dictyostatin displayed growth inhibitory activity against a single murine P388 cell line.¹ This antiproliferative activity was not further investigated until the 2003 re-isolation, for the simple reason that natural supply was very low.³ Now, with the development of various synthetic routes to dictyostatin, a complete evaluation of the *in vitro* biological profile of (-)-dictyostatin has been possible.^{8,9}

(-)- Dictyostatin demonstrates a low nanomolar cytotoxicity, lower than that of Taxol[®], towards a range of human cell lines. Additionally, like discodermolide, retains this activity in human cell lines displaying both P-glycoprotein and β -tubulin mutation-mediated paclitaxel-resistance (**Table 2.1**).^{3,8} All three compounds bind to the same site on β -tubulin (**Figure 2.2**), with dictyostatin displaying the strongest assembly-inducing abilities.¹⁰

Compound	IC ₅₀ (nM)			
	AsPC-1 (pancreatic)	DLD-1 (colon)	PANC-1 (pancreatic)	NCI/ADR (Taxol [®] - resistant)
(-)-Dictyostatin	6.2	2.2	4.2	6.6
Taxol [®]	89	22	9.9	1300
(+)-Discodermolide	98	29	59	160

Table 2.1 Cytotoxicity of dictyostatin, Taxol[®] and discodermolide in cultured human cancer cells¹¹

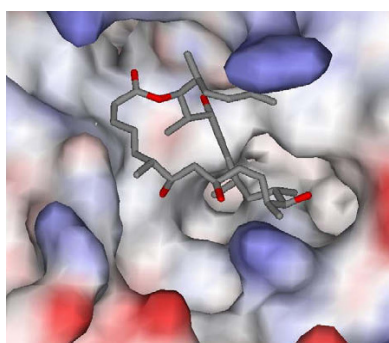


Figure 2.2 Dictyostatin docked into the taxanes binding site on β -tubulin

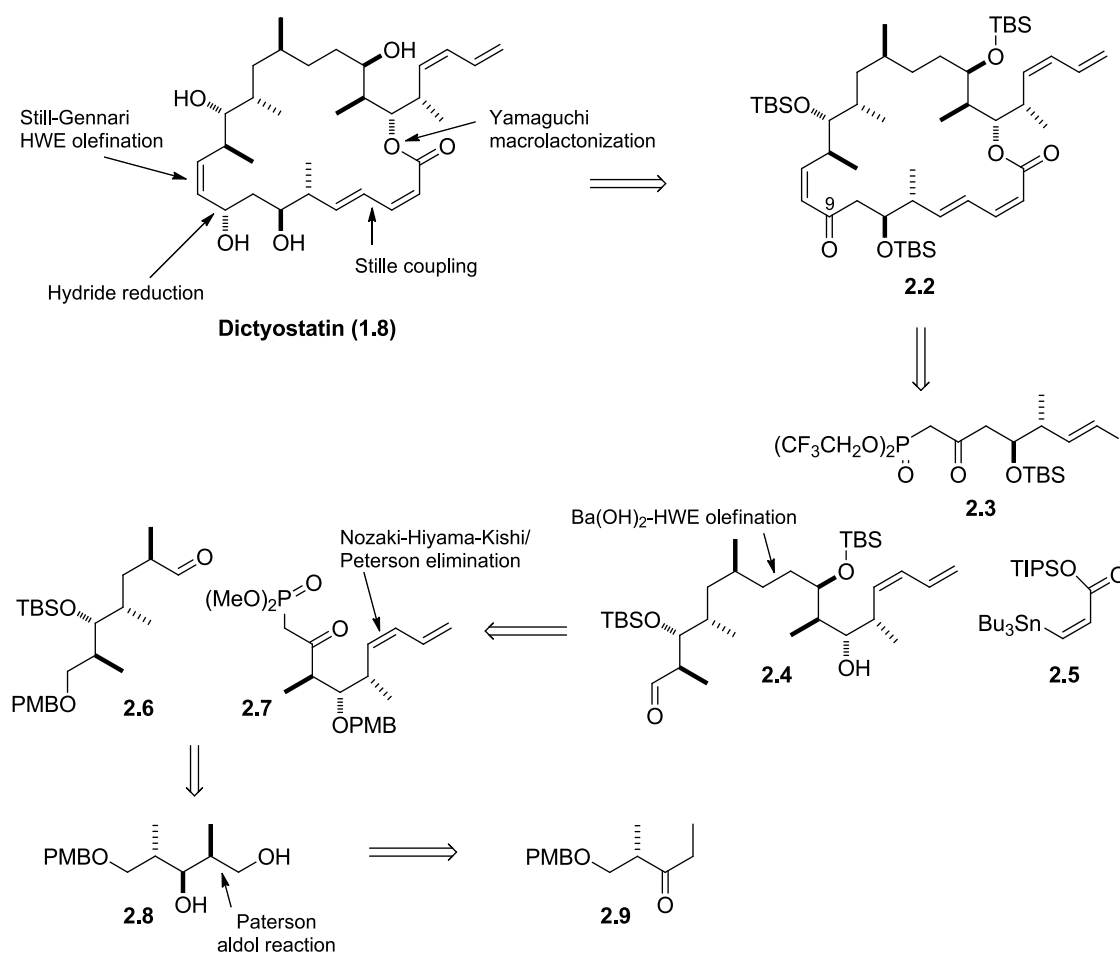
2.3 Total Syntheses of (-)-Dictyostatin

Four different total syntheses of (-)-dictyostatin (**1.8**) have been reported: in 2004, by the Paterson's group^{5,12} and the Curran's group concurrently;^{6,13,14} in 2006, by the Phillips's group,¹⁵ in 2007 by the Ramachandran's group.¹⁶

2.3.1 Paterson's Total Synthesis^{5,12}

With confidence in their stereochemical assignment, Paterson designed a highly convergent synthetic strategy for (–)-dictyostatin (shown in **Scheme 2.1**), which relied largely on substrate-directed stereoinduction. The modular synthetic approach employed by Paterson is flexible, highly convergent, and stereocontrolled, and thus offers the potential to provide useful quantities of dictyostatin as well a range of structural derivatives for SAR studies.

Two Horner-Wadsworth-Emmons (HWE) reactions were instrumental in joining the key subunits as well as providing enone substrates for stereoselective ketone reduction. The macrocyclic conformation of the 22-membered ring **2.2**, as predicted by molecular modeling studies, suggested a preference for hydride attack from the less hindered *Re*-face of the carbonyl group to create the requisite C9 stereocenter. This macrocycle was assembled by a complex Still-Gennari-type HWE coupling reaction between β -keto phosphonate **2.3** and aldehyde **2.4**, in conjunction with a Stille cross-coupling reaction with the three-carbon linking unit **2.5** to install the (*Z*)-enoate.



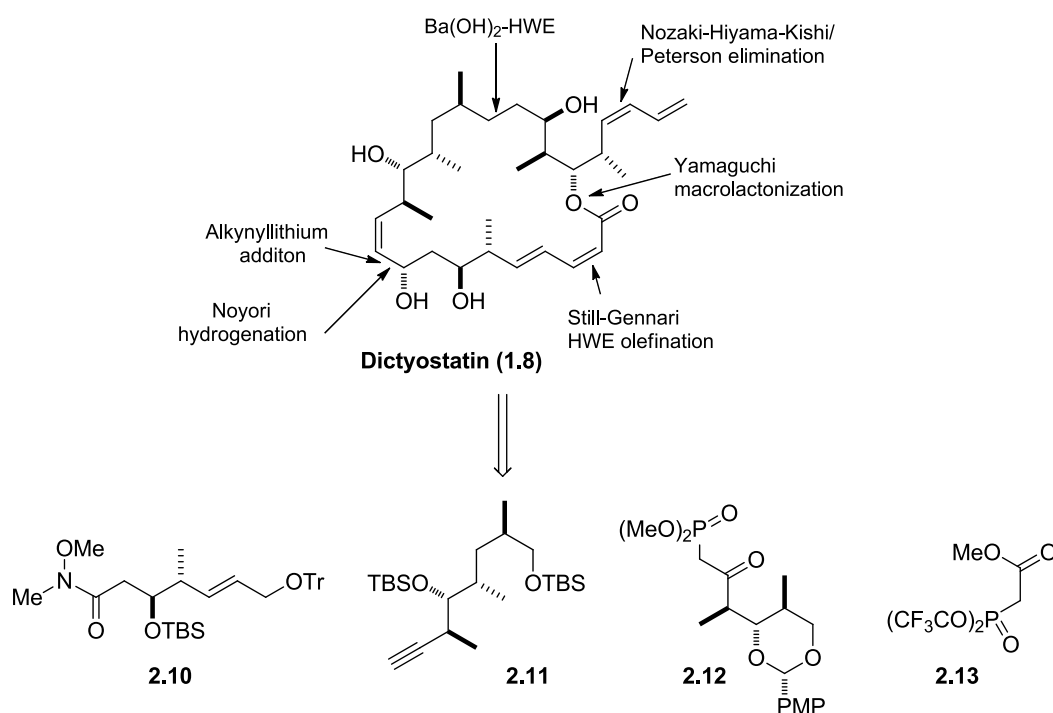
Scheme 2.1 Paterson's retrosynthetic approach

Aldehyde **2.4** was accessible by a HWE reaction between aldehyde **2.6** and phosphonate **2.7**, which has the terminal diene moiety already incorporated. Recognizing that these two subunits share an identical stereotriad, they were prepared from the common intermediate **2.8**, which was readily available in multigram quantities from ketone **2.9**, through the boron aldol methodology developed by the Paterson's group.¹⁷

2.3.2 Curran's Total Synthesis^{6,13,14}

Interestingly, the Curran's group synthesis was initiated prior to the stereochemical reassignment of dictyostatin and therefore the adopted strategy shows stereochemical flexibility in most key coupling steps. This flexibility is expected to facilitate the synthesis of a diverse range of dictyostatin analogues. Their general synthetic strategy relied upon the use of synthetic studies from earlier work towards the synthesis of discodermolide analogs.

The Curran group's approach to dictyostatin is shown in **Scheme 2.2** Strategic bond disconnections as indicated provided three key fragments: Weinreb amide **2.10**, alkyne **2.11**, and β -keto phosphonate **2.12**.



Scheme 2.2 Curran's retrosynthetic approach

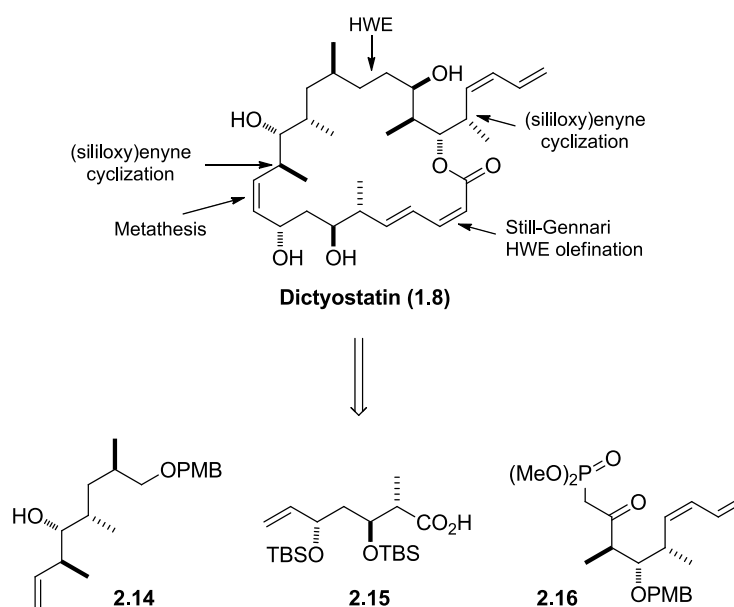
While addition of an acetylenic anion to Weinreb amide **2.10** was used to couple **2.10** and **2.11**, a HWE reaction with phosphonate **2.12** was employed to form the C17-C18 bond during construction of the macrolactone. The diene unit was introduced in the final stages of the synthesis,

based on the Paterson protocol of Nozaki-Hiyama-Kishi/Peterson olefination, as was the HWE coupling using the Still-Gennari-type phosphonate **2.13** to introduce the (*Z*)-enoate.

2.3.3 Phillips's Total Synthesis¹⁵

In contrast, the Phillips's group used the total synthesis as a showcase for their work on titanium (II)-mediated cyclization of (silyloxy)enynes as a means of constructing polypropionate stereotriads. The general utility of this methodology in the construction of polyketide natural product synthesis was evident, establishing these related stereocentres without resorting to chiral auxiliary control.

To maximize convergence, Phillips's strategy called for the union of three subunits of similar complexity (compounds **2.14**, **2.15** and **2.16**) by olefin metathesis at C10-C11, olefination at C17-C18, and a late stage macrocyclization by an intramolecular Still-Gennari HWE (**Scheme 2.3**).



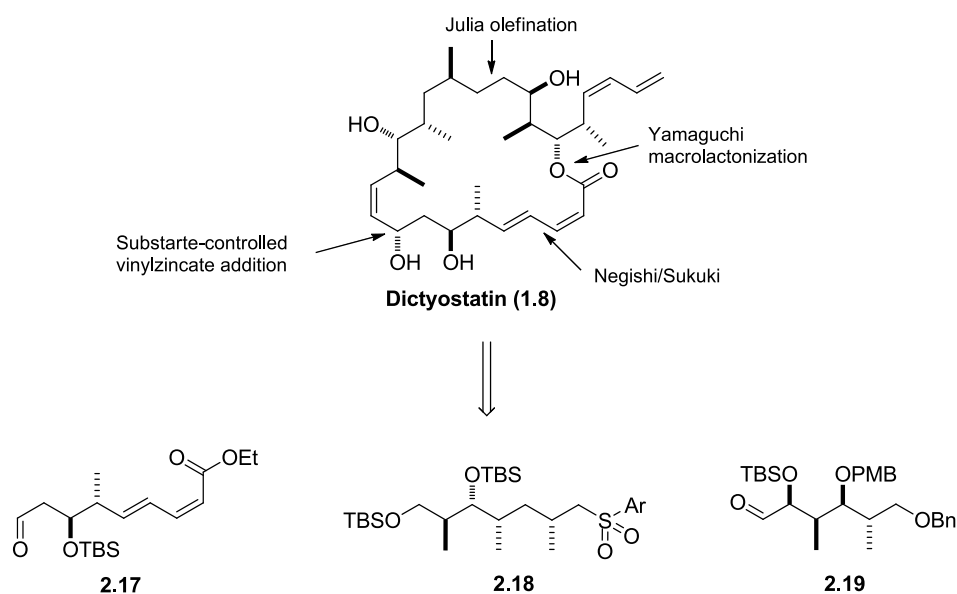
Scheme 2.3 Phillips's retrosynthetic approach

2.3.4 Ramachandran's Total Synthesis¹⁶

The most recent total synthesis from the Ramachandran's group, demonstrated their in-house developed crotylation methodology. Pinene-based chiral reagents showed the general utility of this

widely used procedure (notably used by Curran and Paterson in their total syntheses) in the synthesis of poliketide natural products.

Ramachandran's retrosynthetic analysis is illustrated in **Scheme 2.4**. Height of the eleven stereocenters were created *via* four pinene-mediated crotylboration; the Roche ester and Myers' alkylation provided two more stereocenters. The three subunits (**2.17**, **2.18** and **2.19**) were assembled *via* Julia olefination and a substrate-controlled (*Z*)-vinylzincate addition, which provided the remaining stereocenter.



Scheme 2.4 Ramachandran's retrosynthetic approach.

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Chapter 3

Analogs and Hybrids

3.1 Introduction

Along with the numerous efforts towards the total synthesis of dictyostatin already discussed, some groups have reported the synthesis of novel structural analogs (*e.g.* desmethyldictyostatins, *epi*-dictyostatins, hydrodictyostatins, dehydrodictyostatins, methoxy-dictyostatins)¹ and hybrids (discodermolide/dictyostatin and discodermolide/paclitaxel/dictyostatin)² that maintain the impressive microtubule-stabilizing activity of the parent compound. These modified structures have provided invaluable information in structure–activity relationship (SAR) studies. From a pragmatic standpoint, the identification of analogs and hybrids of reduced molecular complexity, yet retaining the biological function and potency of the parent natural products, offers a more realistic starting point for drug development by the pharmaceutical industry.³

3.2 Analogs of (-)-Dictyostatin

3.2.1 Design and Synthesis of Analogs

(-)-Dictyostatin (**1.8**) is one of the most potent microtubule-stabilizing agents discovered to date. Consequently, an increased understanding of the structure-activity relationship of (-)-dictyostatin is an important goal. Known features of the SAR of discodermolide⁴ (**1.5**) provide a starting point for addressing the SAR of dictyostatin, and the activities of synthetic analogs born during structure-assignment studies offer additional information.^{1d}

With this backdrop, there are two key portions of the dictyostatin molecule that differ significantly from discodermolide (**Figure 3.1**): (i) the bottom chain (C1-C9 region); (ii) the isolated, methyl-bearing stereocenter at C16.

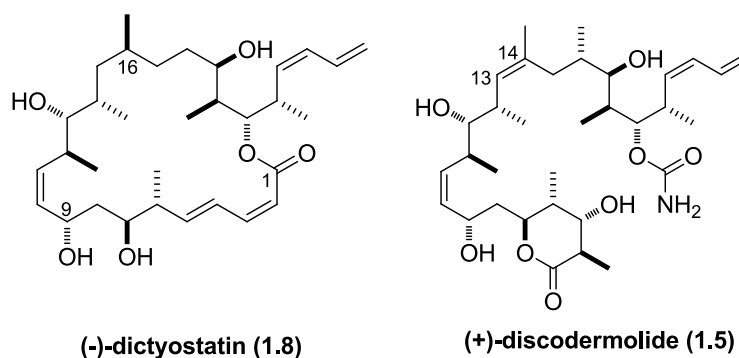


Figure 3.1 Compared structures of (-)-dictyostatin and (+)-discodermolide

The bottom chain is an interesting region for addressing structural modifications; indeed, there are many active analogs of discodermolide with modifications in this part of the molecule.⁵ It was observed that discodermolide analogues with modification of the C7 hydroxyl group (removal/methylation/acylation) displayed antiproliferative activities similar to discodermolide.⁶ Interestingly, methylation or acylation resulted in comparable and occasionally increased cytotoxicities relative to discodermolide, including in Taxol®-resistant cell lines.

The isolated stereocenter at C16 of dictyostatin is of special interest, because discodermolide does not have a corresponding stereocenter; instead, discodermolide possesses a C13-C14 (*Z*)-alkene (note that the carbon backbone of dictyostatin is two atoms longer than that of discodermolide, so C13 and C14 of discodermolide correspond to C15 and C16 of dictyostatin). The methyl group on C14 of discodermolide is not essential for biological activity; 14-desmethyldiscodermolide is a highly potent compound, as are a number of other 14-desmethyl analogues.⁷ If the C16 methyl group of dictyostatin were unnecessary, then the synthesis of such molecules would be much simpler than the parent compound, as the installation of this isolated stereocenter requires considerable effort.

On the basis of this rationale, a wide variety of dictyostatin analogs were synthesized independently by Paterson's and Curran's laboratories. A schematic overview is offered in **Figure 3.2**. Structures **3.1** to **3.19** originate from appropriate diversifications in the synthetic pathways to (-)-dictyostatin. On the contrary, compounds **3.20** to **3.24** were not deliberately devised, but are rather by-products of certain late-stage reactions (namely, HCl global deprotection affords the iso-dictyostatin series, while Yamaguchi macrolactonization leads to partial *E*-isomerization). Nevertheless, biological screening of compounds **3.20** to **3.24** broadened the understanding of the SAR for (-)-dictyostatin.

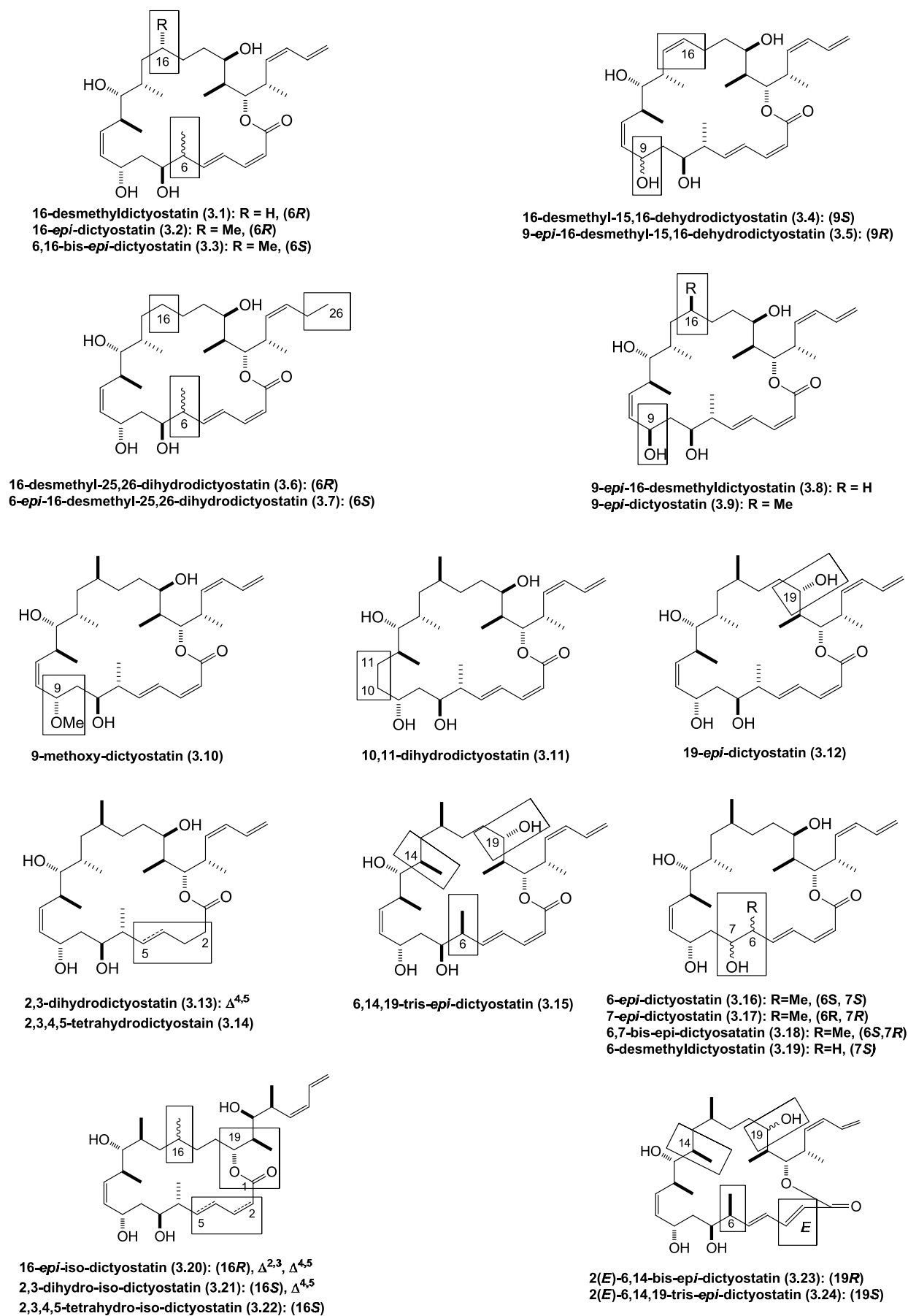


Figure 3.2 Analogs of (-)-dictyostatin

3.2.2 Biological Evaluation

In a series of cytotoxicity assays performed by Wright and co-workers (**Table 3.1**),³ the cell growth inhibitory activities (IC₅₀) of the fully synthetic dictyostatin analogs from Paterson's group were evaluated *in vitro* against four human cancer cell lines: AsPC-1 (pancreatic), DLD-1 (colon), PANC-1 (pancreatic) and NCI/ADR (ovarian, Taxol®-resistant). The latter cell line contains an over-expressed P-glycoprotein efflux pump within the cell membrane, which is responsible for its resistance to Taxol®.

Notably, the most potent analogs were 9-methoxy- (**3.10**), 2,3-dihydro- (**3.13**) and 6-desmethyldictyostatin (**3.19**), displaying low nanomolar cytotoxicity (intermediate between dictyostatin and discodermolide) in both paclitaxel-sensitive and paclitaxel-resistant cell lines. Furthermore 10, 11-dihydro- (**3.11**) and 2,3,4,5-tetrahydrodictyostatin (**3.14**) were also quite active and directly comparable to discodermolide. In contrast, low activity profiles were displayed by 9-*epi*-16-desmethyl- (**3.8**), 9-*epi*-dictyostatin (**3.9**) and the iso-series (**3.21**, **3.22**).

Compound	IC ₅₀ (nM)			
	AsPC-1 (pancreatic)	DLD-1 (colon)	PANC-1 (pancreatic)	NCI/ADR (Taxol®-resistant)
Taxol®	89	22	9.9	1300
(+)-Discodermolide	98	29	59	160
(-)-Dictyostatin	6.2	2.2	4.2	6.6
3.1	170	85	130	1500
3.8	2100	790	1500	2100
3.9	410	150	240	1100
3.10	31	2.4	9.7	8.2
3.11	43	10	18	300
3.13	94	22	42	66
3.14	118	55	64	132
3.19	56	8.1	17	43
3.21	3100	930	1900	1600
3.22	4900	1900	3200	3100

Table 3.1 Cytotoxicity of listed compounds in cultured human cancer cells (Paterson's data)³

Analogs from Curran's laboratory were examined for their antiproliferative activities against cultures of human ovarian carcinoma 1A9 cells and their paclitaxel-resistant mutants, 1A9/Ptx10 and 1A9/Ptx22 (**Table 3.2**).^{1d} Each of these resistant lines contains single mutations in the major β -tubulin gene that confer to the cells, which do not over-express drug efflux pumps, appreciable tolerance to paclitaxel.

Compound	IC ₅₀ (nM)		
	1A9 (ovarian)	1A9/Ptx10 (Taxol [®] -resistant)	1A9/Ptx22 (Taxol [®] -resistant)
Taxol[®]	0.71	64	51
(+)-Discodermolide	1.7	6.2	7.0
(-)-Dictyostatin	0.69	3.2	1.3
3.1	0.41	4.70	5.6
3.2	61	862	543
3.3	20900	50000	11560
3.4	8.3	942	62
3.5	4260	19300	4600
3.6	285	2817	445
3.7	241	4090	193
3.9	79	2160	160
3.12	21	120	43
3.15	28000	26000	30000
3.16	0.85	4.5	0.81
3.17	n.a.	n.a.	4.7
3.18	n.a.	n.a.	123
3.20	7800	44190	53760
3.23	310	780	790
3.24	25000	25000	30000

Table 3.2 Cytotoxicity of listed compounds in cultured human cancer cells (Curran's data)^{1a,1c,1d,1i}

Interestingly, 16-desmethyldictyostatin (**3.1**) exhibited superior activity on ovarian cell lines than on pancreatic and colon cell lines (compare data on **Table 3.1** and **Table 3.2** for this common analog). Enhanced cytotoxicity was also shown by 6- and 7- dictyostatin epimers (**3.16**, **3.17**), while low activity was recorded for 9-*epi*- (**3.9**, **3.5**), iso- (**3.20**) and (*2E*)-series (**3.23**, **3.24**).

3.2.3 Structure-Activity Relationship^{1c,3}

From these cytotoxicity assay results, it is possible to formulate SAR conclusions regarding the importance of the modified regions of dictyostatin structure, and hence speculate on ligand interactions with the β -tubulin binding site. SAR analysis is summarized in **Figure 3.3**.

The C16 methyl substituent, if present, must be in the (*S*) configuration. This substituent is disposable; indeed, C15-C16 (*Z*)-alkene (without the C16 methyl group) is well tolerated.

As to the bottom fragment, cytotoxicity data show the importance of C2-C3 (*Z*)-geometry as and the C2-C5 dienoate moiety (analogs with saturated C2-C5 region possess diminished biological activity). The 22-membered lactone (C1-C21 ester linkage) is essential; a 20-membered lactone (C1- C19 ester linkage) abates the desired biological action.

C6 and C7 isomers showed an intermediate activity between that of dictyostatin and discodermolide, confirming the prediction that the C6 methyl group is unlikely to contribute to a strong interaction with tubulin binding site and occupies a relatively open region. Another finding is that natural (19*R*) and (14*S*) configurations confer higher activity.

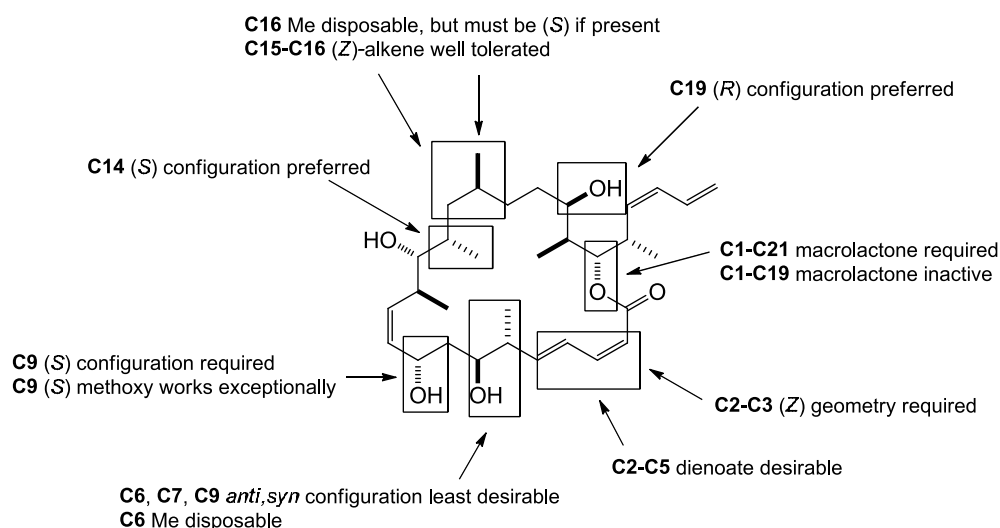


Figure 3.3 Qualitative structure-activity relationship for dictyostatin

The obtained data also clearly show that C9 must be in the (*S*) configuration. In fact, inversion of C9 configuration resulted in a substantial drop in cytotoxicity. The effect of “capping” the C9 hydroxyl group with a methyl had an insignificant effect on the binding ability of the analog. From this finding, it was proposed that the C9 hydroxyl group of dictyostatin does not act as a significant intermolecular hydrogen bond donor with proximal tubulin residues, and does not form any intermolecular hydrogen bonds, which might stabilize the bioactive conformation.

In conclusion, 9-methoxydictyostatin (**3.10**) represents the most active dictyostatin analog prepared so far, and, importantly, shows comparable cytotoxicity relative to dictyostatin against a Taxol[®]-resistant cell line.

3.3 Hybrids of (-)-Dictyostatin

3.3.1 Design and Synthesis of Hybrids

Several hybrid structures of discodermolide/dictyostatin (double hybrids) were conceived and synthesized by the Curran's and Paterson's laboratories (**Figure 3.4**).²

The first hybrid molecules (**3.25**, **3.26**) were reported in 2002 by Curran and co-workers.^{2a} They were intended to feature structural and stereochemical motifs from both discodermolide and dictyostatin. However, as a consequence of the work pre-dating the stereochemical reassignment of dictyostatin, these structures contain regions that bear little resemblance to the stereochemistry of either natural products. The acyclic hybrid-intermediates **3.27** to **3.29**, which led to **3.25** were also screened.

Recently, the bioactive conformations of dictyostatin and discodermolide were elucidated using a combination of NMR analysis, molecular modeling and docking studies.⁸ The overlay of these tubulin-bound structures revealed some striking conformational similarities. The overlap is most pronounced from the common terminal diene moiety through to C9 on dictyostatin and C7 on discodermolide, whereas there appears to be minimal spatial correlation between the δ -lactone of discodermolide and the dienolate of dictyostatin. In addition, the models for tubulin binding indicates that both discodermolide and dictyostatin occupy the taxane site and share similar interactions with the protein residues of the receptor (**Figure 3.5**).

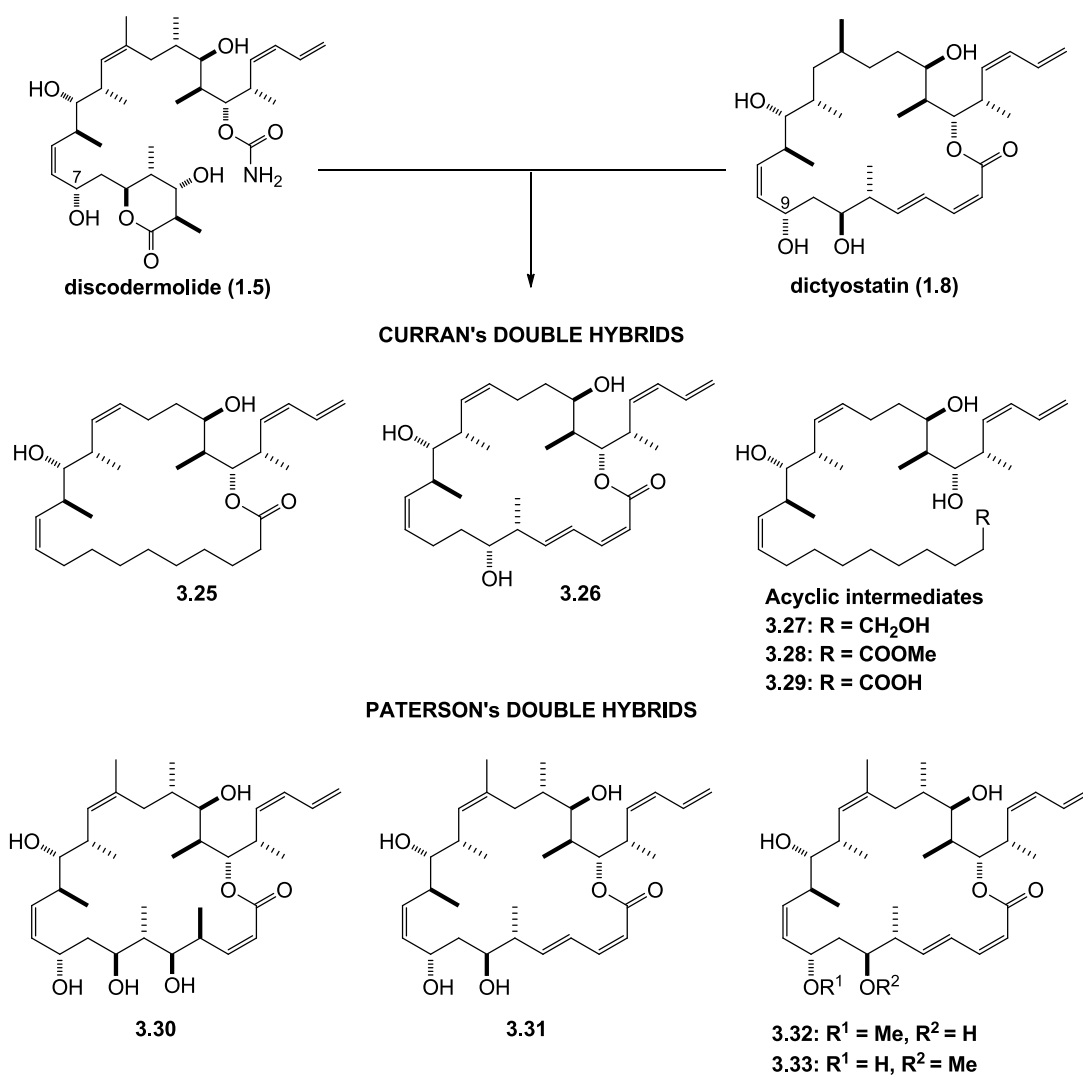


Figure 3.4 Discodermolide, dictyostatin and the resulting double hybrids

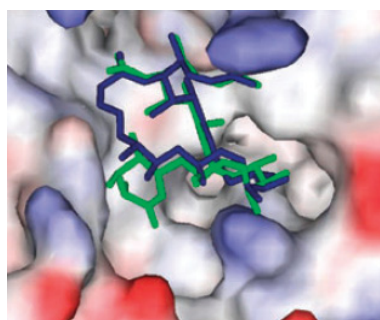


Figure 3.5 Overlay of the NMR-derived bioactive conformations of discodermolide (green) and dictyostatin (blue) at the taxane binding site on β -tubulin

With this information in hand two hybrid structures (**3.30**, **3.31**) were synthesized by Paterson and co-workers in 2007 and 2008.^{2b,2c} Furthermore, the encouraging biological results of the *O*-methylated analog **3.10** recently prompted the design and synthesis of hybrids **3.32** and **3.33**.^{2d}

Inspection of the overlaid tubulin-bound conformations of the discodermolide, paclitaxel and dictyostatin indicated that the side chain of paclitaxel occupied a region of the binding pocket that was not exploited by dictyostatin or discodermolide (**Figure 3.6**).⁸

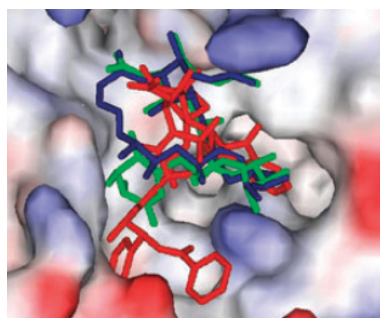


Figure 3.6 Overlay of the NMR-derived bioactive conformations of discodermolide (green), dictyostatin (blue) and paclitaxel (red) at the taxane binding site on β -tubulin

However, the C7 and C9 hydroxyls on dictyostatin were orientated to point into this vacant region. It was hypothesized that the addition of the paclitaxel (**1.1**, **Figure 3.7**) or docetaxel (**1.2**) side chain onto either of these hydroxyls would insure additional binding interactions.⁹

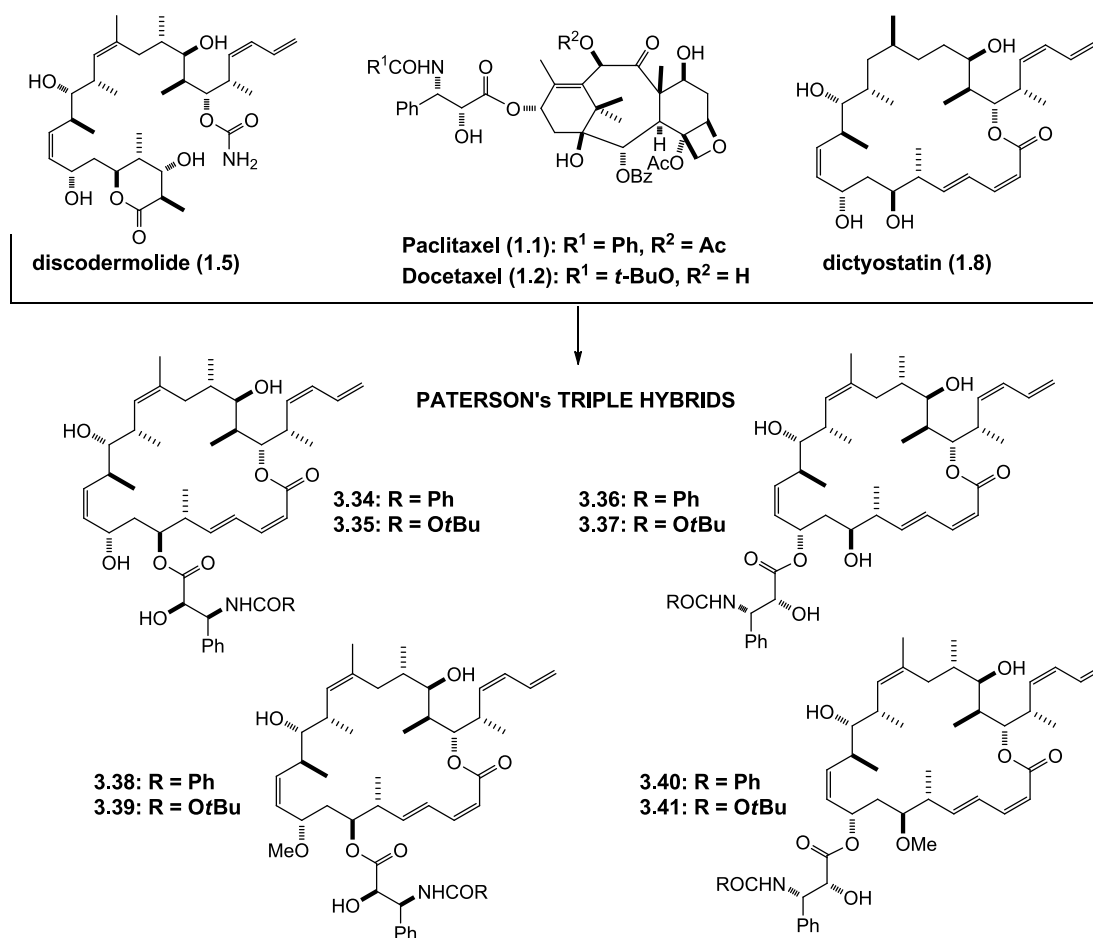


Figure 3.7. Discodermolide, taxanes, dictyostatin, and the resulting triple hybrids

Consequently Paterson and co-workers reported the synthesis of a small library of discodermolide/taxanes/dictyostatin (triple hybrids), shown in **Figure 3.7**.^{2d}

3.2.2 Biological Evaluation

The collection of double and triple hybrids was evaluated *in vitro* against several human cancer cell lines. A selection of the resulting biological data is available in **Table 3.3**.^{2,3}

Macrolactone **3.25**, non-cyclized alcohol **3.27** and ester **3.28** exhibited similar moderate activity, whereas carboxylic acid **3.29** was inactive, possibly due to poor cell membrane penetration.

Compound **3.26**, the most functionalized of Curran's hybrids, proved to be the most potent in terms of antiproliferative activity against ovarian and breast carcinoma cells.

The low cytotoxicity determined for **3.30** indicated its reduced binding affinity relative to the parent compounds. Gratifyingly a much better result was obtained with **3.31**, which displayed intermediate cytotoxicity between that of discodermolide and dictyostatin.

A similar biological activity was also recorded on **3.31** *O*-methylated derivatives: **3.32** and **3.33**.

As to triple hybrids, those bearing paclitaxel side chain, (**3.34**, **3.36**, **3.38**, **3.40**) were somewhat more active than those bearing docetaxel side chain (**3.35**, **3.37**, **3.39**, **3.41**), and the *O*-methylated triple hybrids (**3.38** to **3.41**) were less active than the non-methylated ones (**3.34** to **3.37**).

In summary, the biological data obtained on the triple hybrids library demonstrated that the polycyclic baccatin core of paclitaxel can be replaced by a macrolide template whilst maintaining pronounced cytotoxicity.

Compound	IC ₅₀ (nM)				
	PANC-1 (pancreatic)	2008 (ovarian)	HT29 (colon)	MDA-MB-231 (breast)	NCI/ADR (Taxol [®] -resistant)
Taxol[®]	9.9	n.a.	n.a.	n.a.	1300
(+)-Discodermolide	59	0.072	0.015	0.016	160
(-)-Dictyostatin	4.2	n.a.	n.a.	n.a.	6.6
3.25	n.a.	16	n.a.	27	n.a.
3.26	n.a.	1.0	n.a.	1.4	n.a.
3.27	n.a.	22	n.a.	18	n.a.
3.28	n.a.	19	n.a.	26	n.a.
3.29	n.a.	>50	n.a.	>50	n.a.
3.30	1800	n.a.	0.170	0.208	8200
3.31	12.9	n.a.	n.a.	n.a.	66.4
3.32	14	n.a.	n.a.	n.a.	n.a.
3.33	70	n.a.	n.a.	n.a.	n.a.
3.34	100	n.a.	n.a.	n.a.	n.a.
3.35	86	n.a.	n.a.	n.a.	n.a.
3.36	100	n.a.	n.a.	n.a.	n.a.
3.37	181	n.a.	n.a.	n.a.	n.a.
3.38	150	n.a.	n.a.	n.a.	n.a.
3.39	250	n.a.	n.a.	n.a.	n.a.
3.40	330	n.a.	n.a.	n.a.	n.a.
3.41	520	n.a.	n.a.	n.a.	n.a.

Table 3.3 Cytotoxicity of listed compounds in cultured human cells^{2,3}

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Chapter 4

Our Route to (-)-Dictyostatin

4.1 Introduction

The development of a practical and flexible synthesis of (-)-dictyostatin (**Figure 4.1**) is still an important goal, particularly as the natural supply is extremely scarce. With the recent withdrawal of discodermolide from clinical development,¹ the importance of dictyostatin further increases.

From a pharmaceutical perspective, also the development of (-)-dictyostatin analogs is an appealing goal, which would provide interesting opportunities for structural simplification whilst maintaining biological potency, and increase our understanding of the structure-activity relationships (SAR) of this class of antitumor agents.

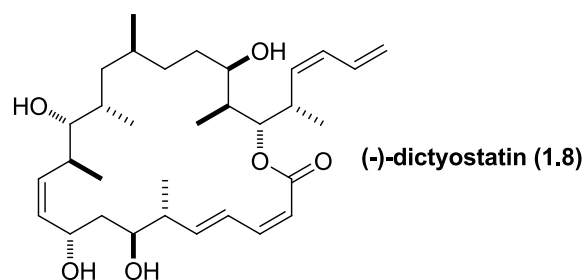


Figure 4.1 (-)-dictyostatin

4.2 Project Objectives

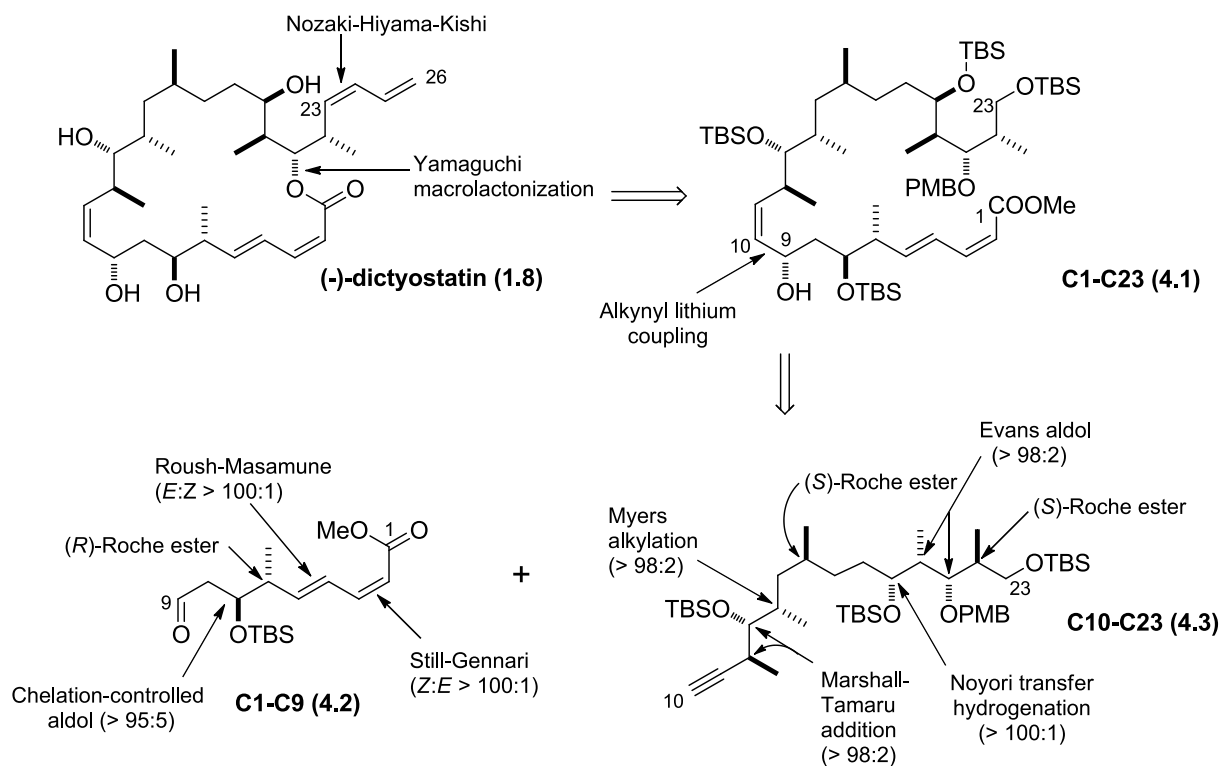
While extensive structure-activity relationship data have been established for paclitaxel and epothilones,² only limited data are available for other microtubule-stabilizing agents (MSAs). A more complete understanding of the SAR for the various natural products, through the synthesis of a broad variety of analogues, will be instrumental in the development of structurally simplified MSAs, which might then be more amenable to large-scale chemical synthesis. Of course, the

synthesis of analogues of such complex natural products requires an intricate understanding of the chemistry of these systems. This is best established initially through the total synthesis of the parent compounds themselves. In the case of (-)-dictyostatin, total synthesis is the only option to provide sufficient material for the biological profiling of the natural product itself. Therefore, the central aims of the project, of which this thesis work is part, are: (i) the synthesis and biological evaluation (effects on tubulin polymerization and antiproliferative activity) of (-)-dictyostatin; (ii) design and synthesis of analogues to establish comprehensive structure-activity relationships.

In summary, this research project could lead to a breakthrough in the design of improved MSAs and to the discovery of a new generation of anti-cancer drugs. Such an accomplishment will advance the state-of-the-art in the development of natural products as cancer therapeutic agents, and demonstrate the enabling power of modern drug design and organic synthesis to provide practical sources of such complex compounds.

4.3 Our First Retrosynthetic Approach to (-)-Dictyostatin

In our first retrosynthetic approach, the macrolide ring is disconnected in the open-chain compound C1-C23 (4.1), which is itself obtained from two key intermediates: aldehyde C1-C9 (4.2) and alkyne C10-C23 (4.3). Eight of the total eleven stereocenters and each stereogenic double-bond results from a highly stereoselective reaction, as shown in **Scheme 4.1**.



Scheme 4.1 Our first retrosynthetic approach to (-)-dictyostatin

4.4 Synthesis of Aldehyde C1-C9

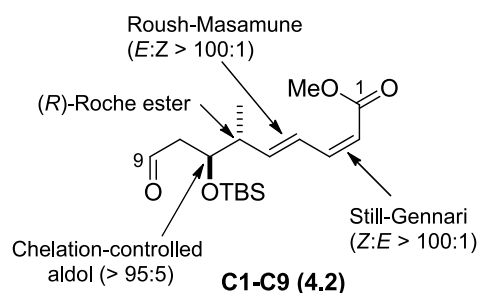
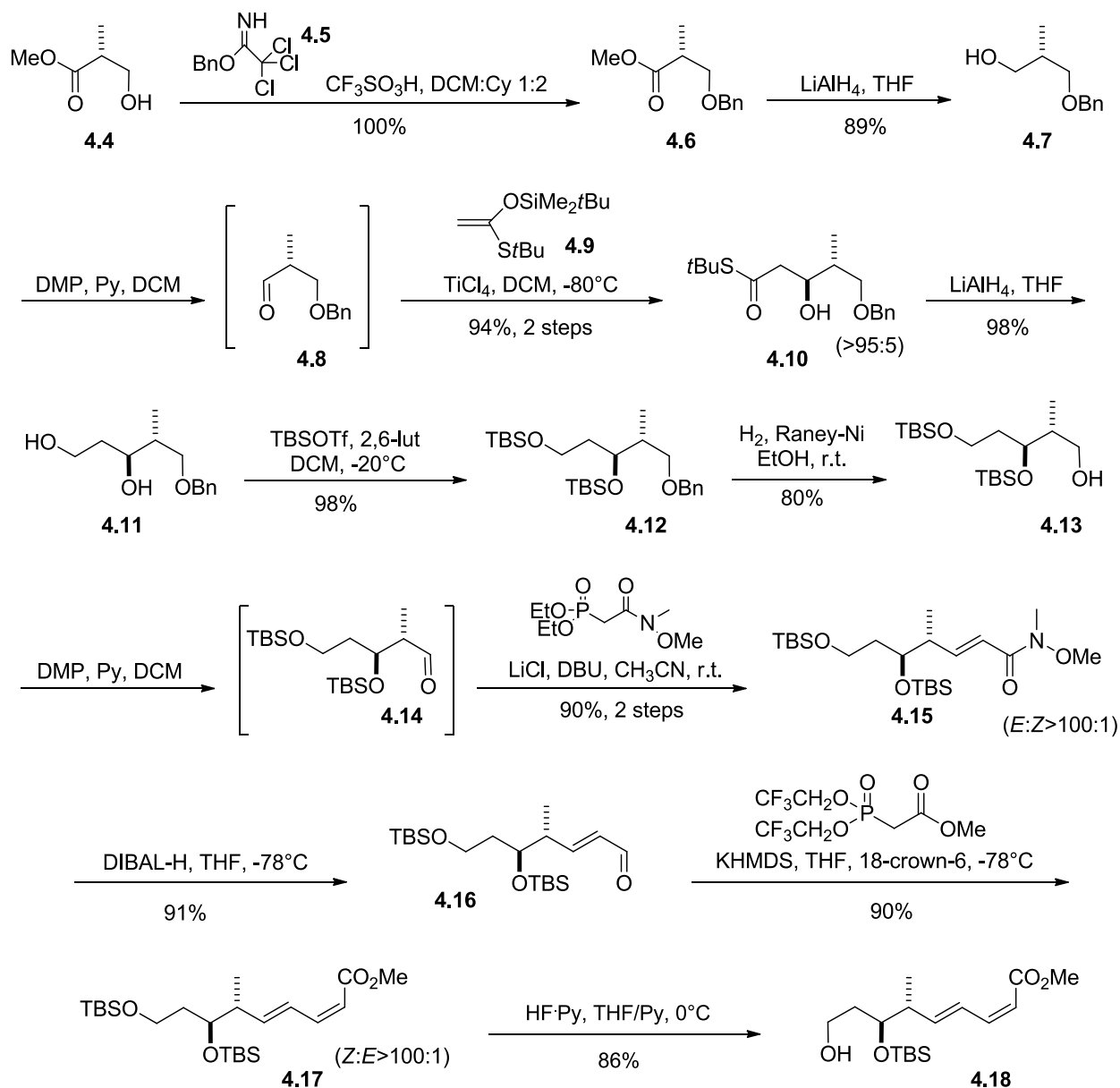


Figure 4.2 Fragment C1-C9 of (-)-dictyostatin: Aldehyde (**4.2**)

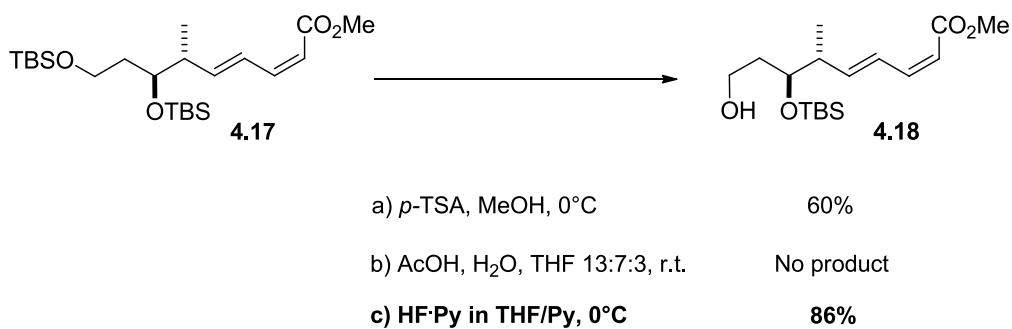
The C1–C9 fragment (**Figure 4.2**) contains two of the total eleven stereocenters and the (2*Z*,4*E*)-2,4-dienoate unit. A stereoselective synthesis of the C1–C9 fragment of (-)-dictyostatin was achieved and published in 2008³ using a TiCl₄-mediated chelation-controlled Mukaiyama-aldol reaction and two modified Horner-Wadsworth-Emmons olefinations (under Roush-Masamune and Still-Gennari conditions respectively).

The synthetic pathway (**Scheme 4.2**) started from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate [(*R*)-Roche ester, **4.4**]. Conversion of **4.4** to its benzyl ether (**4.6**) with benzyl trichloroacetimidate⁴ (**4.5**) was followed by LiAlH₄ reduction of the ester to give alcohol **4.7** in 89% overall yield.⁵ Oxidation of alcohol **4.7** with Dess-Martin periodinane (DMP)⁶ afforded aldehyde **4.8** in quantitative yield. Aldehyde **4.8** was not purified and it was immediately subjected to a TiCl₄-mediated chelation-controlled Mukaiyama aldol reaction with 1-(*tert*-butylthio)-1-(*tert*-butyldimethylsilyloxy)ethylene⁷ (**4.9**). The aldol product (**4.10**) was isolated in 94% yield, with a 97:3 diastereomeric ratio in favor of the desired stereoisomer. Although it was reported that the two diastereomers could be separated with two consecutive purifications by flash chromatography,^{7a} we still observed the presence of some epimer ($\leq 3\%$) in the ¹³C-NMR spectrum of **4.10**. However, we decided to continue our synthesis as planned, confident that the minor isomer would be removable at a later stage of the sequence. Reduction (LiAlH₄) of **4.10** gave compound **4.11** in 98% yield. Subsequent double silylation (98%) led to the fully protected triol **4.12**. Benzyl removal was accomplished by hydrogenolysis with Raney-Ni in EtOH⁸ (80%), and the resulting primary alcohol **4.13** was oxidized (DMP) to furnish aldehyde **4.14** in quantitative yield. Aldehyde **4.14** was not purified and immediately subjected to a Horner-Wadsworth-Emmons reaction with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl) phosphonate⁹ under the Roush-Masamune conditions.¹⁰ The olefination reaction afforded the Weinreb amide **4.15** in 90% yield as single isomer (*E*:*Z* > 100:1). DIBAL-H reduction gave aldehyde **4.16** (91%) which was subjected to a Still-Gennari olefination¹¹ to afford the methyl (2*Z*,4*E*)-2,4-dienoate **4.17** in 90% yield as a single isomer (*Z*:*E* > 100:1).¹² The minor (7*R*) isomer ($\leq 3\%$), originated during the Mukaiyama-aldol reaction, was removed at this stage by flash chromatography.



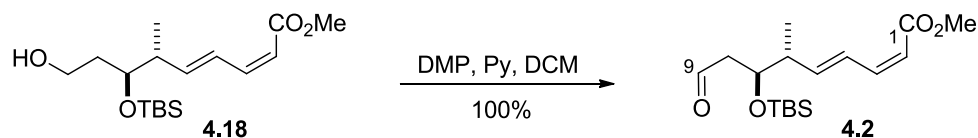
Scheme 4.2 Synthesis of aldehyde C1-C9 (4.2)

As for the final removal of the primary TBS group, three different procedures were tested (Scheme 4.3). With *p*-TSA in MeOH,¹³ selective deprotection occurred in poor yield (60%). With acetic acid in water and THF,¹⁴ no deprotection was observed. Finally, the use of the complex HF·Py¹⁵ in THF·Py¹⁵ turned out to be the best alternative: the desired alcohol **4.18** was isolated in 86% yield.



Scheme 4.3 Different procedures for the selective deprotection of the primary alcohol

The oxidation of alcohol **4.18**, was carried out with DMP (Scheme 4.4), furnishing the C1-C9 fragment of (-)-dictyostatin (**4.2**) in quantitative yield.



Scheme 4.4 Completion of the synthesis of aldehyde C1-C9 (**4.2**)

4.5 Synthesis of Alkyne C10-C23

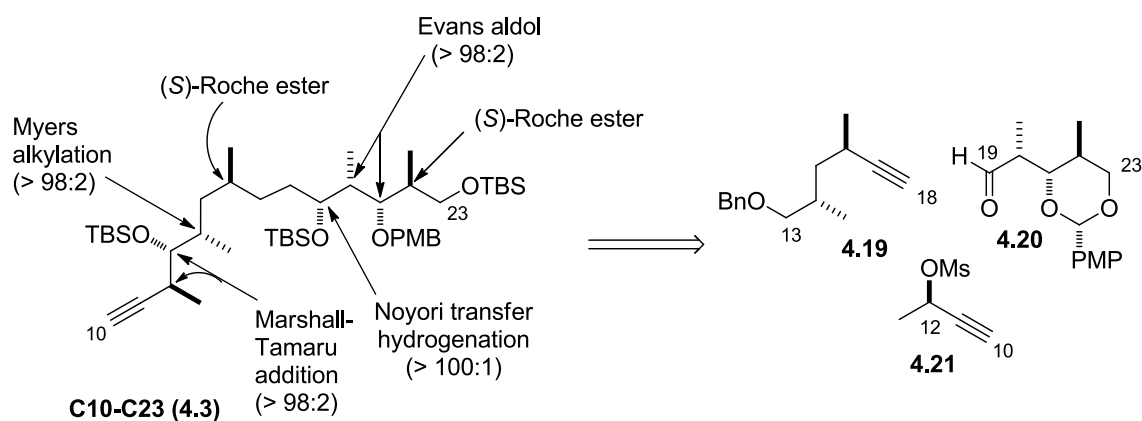


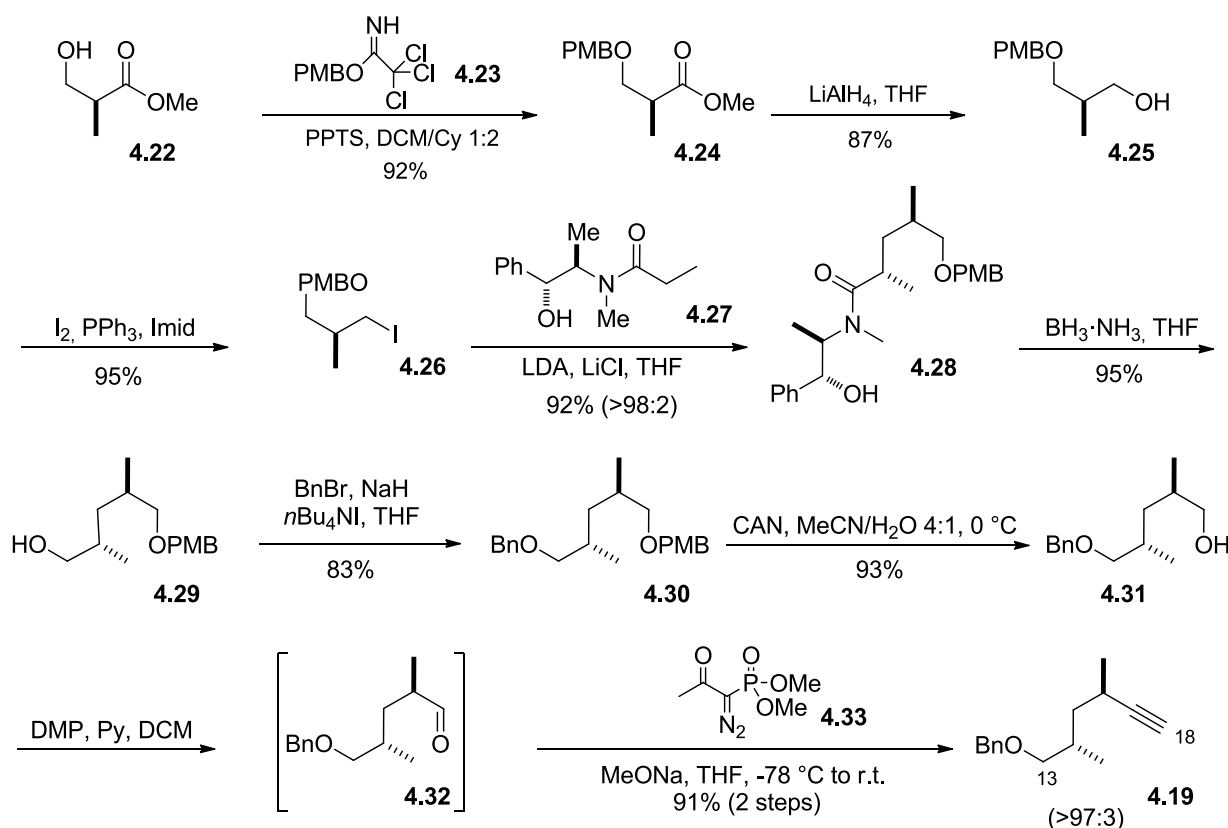
Figure 4.3 Fragment C10-C23 of (-)-dictyostatin: Alkyne (**4.3**)

The synthesis of alkyne C10-C23 (**4.3**), published by our group in 2007,¹⁶ is based on the disconnection of our target macrolide into three key fragments: alkyne C13-C18 (**4.19**), aldehyde

C19-C23 (**4.20**) and (*R*)-3-butyn-2-ol mesylate (**4.21**). The latter compound was easily obtained from commercially available (*R*)-3-butyn-2-ol in one step.

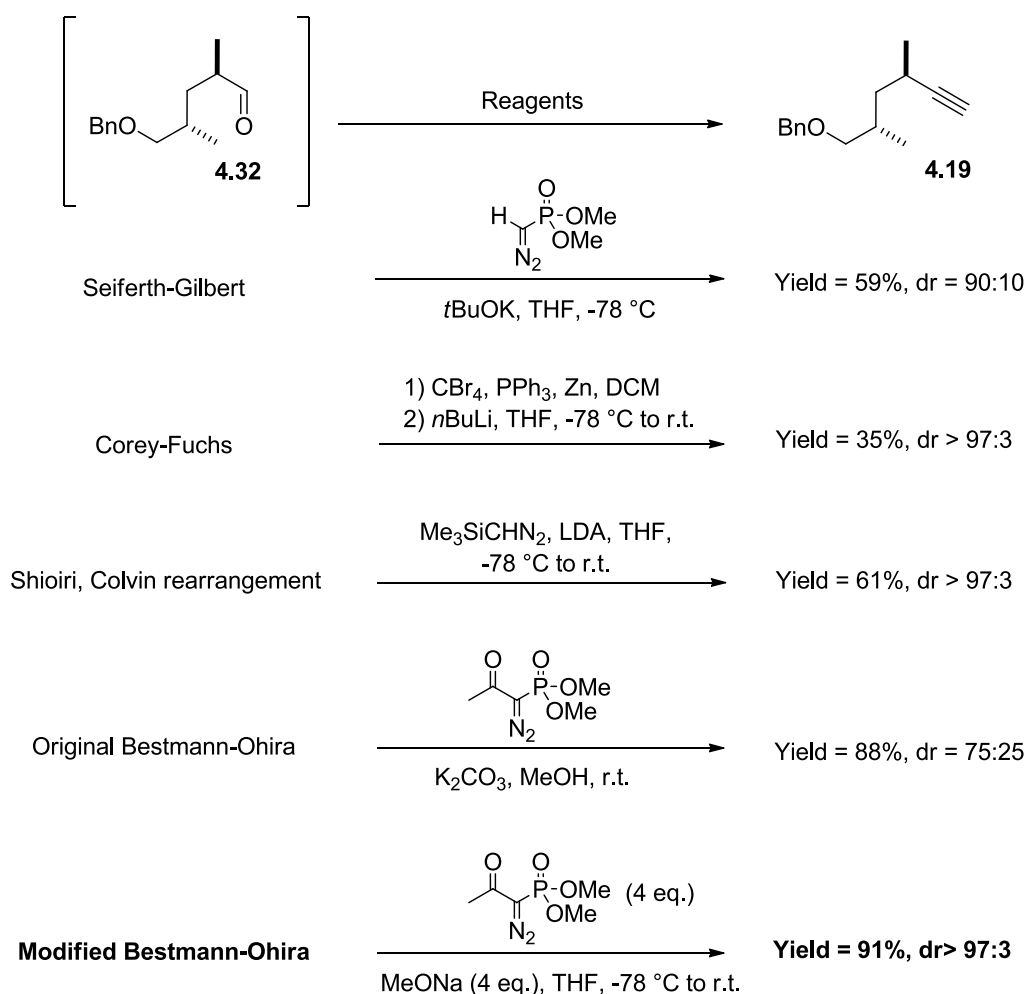
4.5.1 Synthesis of Alkyne C13-C18

We started our synthesis of alkyne **4.19** (Scheme 4.5) with the protection¹⁷ of the hydroxyl group of (*S*)-3-hydroxy-2-methylpropionate [(*S*)-Roche ester, **4.22**] with *p*-methoxybenzyl trichloroacetimidate (**4.23**), which gave compound **4.24** in 95% yield. Subsequent LiAlH₄ reduction of the ester group furnished the corresponding alcohol **4.25**, which was converted (I₂, PPh₃, imidazole)¹⁸ into iodide **4.26** in high yield (95%). Myers alkylation¹⁹ with *N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide (**4.27**) provided amide **4.28** in 92% yield and with a >98:2 diastereomeric ratio in favour of the desired diastereoisomer. Reduction with the borane-ammonia complex gave alcohol **4.29** in 95% yield. Benzyl protection (NaH, BnBr, *n*-Bu₄NI, 83%)²⁰ led to **4.30**, which, upon treatment with CAN, underwent selective removal of the PMB group over the benzyl group,²¹ to provide **4.31** in 93% yield. Dess Martin oxidation⁶ gave aldehyde **4.32**, which was not isolated, and was directly homologated to alkyne **4.19**.



Scheme 4.5 Synthesis of fragment C10-C23: alkyne C13-C18 (**4.19**)

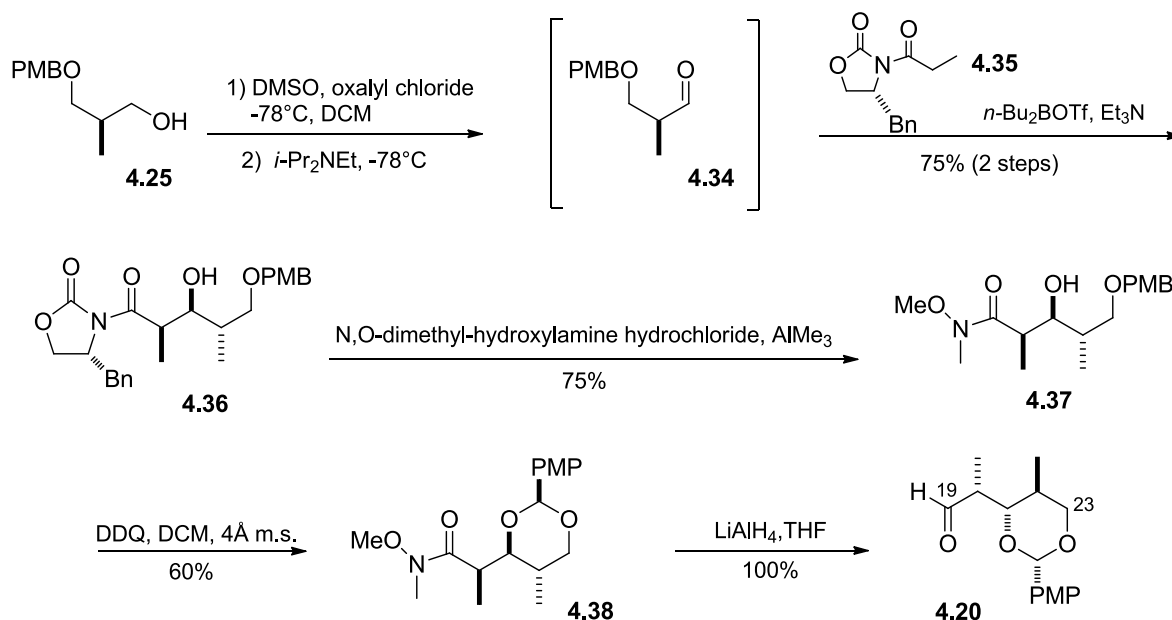
For this final alkylation, different methods were tried with the twofold purpose of avoiding epimerization at the α stereocenter and obtaining a high yield (**Scheme 4.6**). The Seifert-Gilbert procedure²² gave 10% epimerization along with a moderate yield. Corey-Fuchs dibromoolefination,²³ followed by *n*BuLi promoted elimination, resulted in no epimerization but with a very low yield. The Shioiri's lithiodiazomethane protocol²⁴ (Colvin rearrangement) led to desired alkyne **4.19** in a higher yield as a single diastereomer, but the reaction suffered the scale up and could not be reproduced with the same yield. Finally, the Ohira-Bestmann protocol²⁵ was explored. Under the original conditions, a good conversion was observed, but extensive epimerization of the α stereocenter occurred. After an in-depth investigation, it was found that the extent of epimerization could be limited by avoiding the use of a protic solvent and decreasing the amount of base. Optimal conditions²⁶ were found which allowed to obtain alkyne **4.19** in excellent yield and a diastereomeric ratio.



Scheme 4.6 Alkylation: different methods

4.5.2 Synthesis of Aldehyde C19-C23

The second key fragment was prepared according to Smith and co-workers,²⁷ as shown in **Scheme 4.7**.



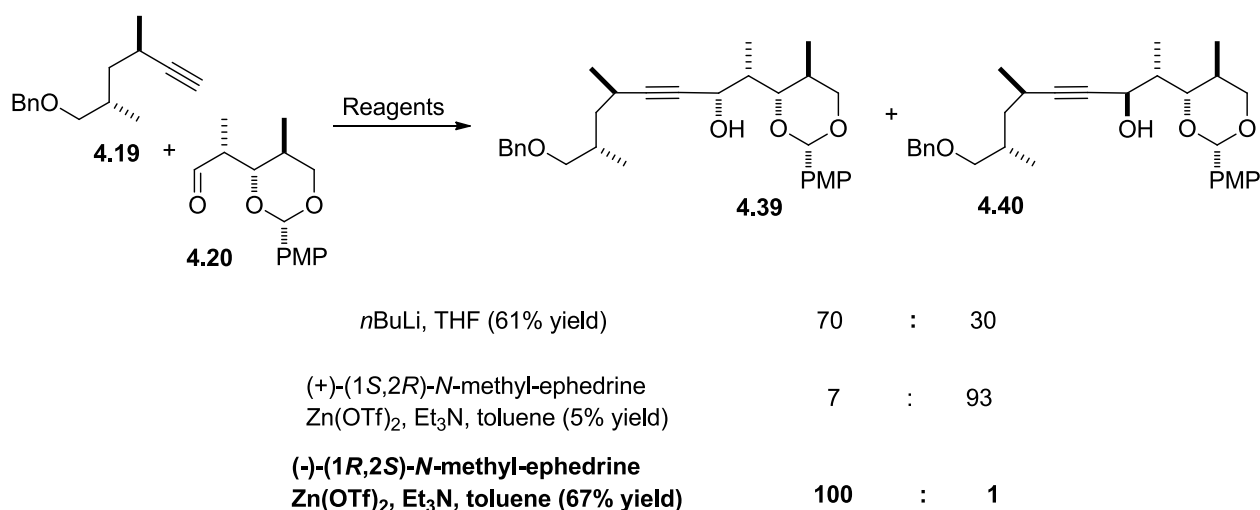
Scheme 4.7 Synthesis of fragment C10-C23: aldehyde C19-C23 (**4.20**)

Alcohol **4.25**, previously obtained in the synthesis of alkyne **4.19**, was used as starting material. The conversion of **4.25** into aldehyde **4.34** was accomplished through a Swern oxidation.²⁸ Subsequent Evans aldol condensation²⁹ with (*R*)-4-benzyl-3-propionyloxazolidin-2-one (**4.35**) gave the aldol product **4.36** with a total control of stereochemistry.²⁷ The conversion of adduct **4.36** to the Weinreb amide³⁰ **4.37** was achieved by reaction with *N,O*-dimethylhydroxylamine hydrochloride in the presence of AlMe_3 . Weinreb amide **4.37** was then treated with DDQ to give the PMP acetal³¹ **4.38**, which was reduced³² (LiAlH_4 , THF, under controlled conditions) to the desired aldehyde C19-C23 (**4.20**).

4.5.3 Completion of the Synthesis of Alkyne C10-C23

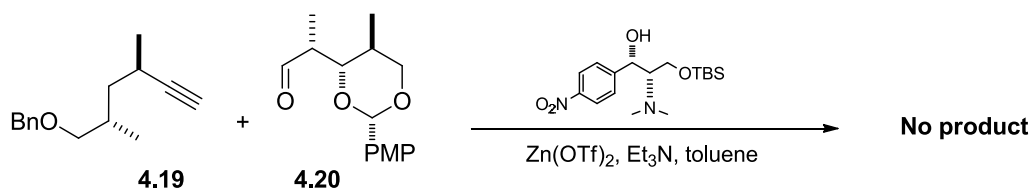
With the two key fragments **4.19** and **4.20** in our hands, we proceeded to the coupling reaction (**Scheme 4.8**). Alkyne **4.19** was treated with *n*BuLi in THF at -78°C and, then, with aldehyde **4.20** to study the intrinsic preference of the two chiral coupling partners: a mixture of the two diastereomeric propargylic alcohols **4.39** and **4.40** in a 7:3 ratio (61% yield) was obtained.

Alternatively, a Carreira asymmetric alkylation [$\text{Zn}(\text{OTf})_2$, Et_3N , toluene, r.t.]^{33,34} was carried out with either of the two enantiomers of *N*-methyl-ephedrine (**Scheme 4.8**). The reaction with (-)-(*1R,2S*)-*N*-methyl-ephedrine (matched pair) gave the desired (*S*)-alcohol **4.39** in 67% yield as a single diastereomer. In this reaction, slow addition of the aldehyde to the reaction mixture proved to be crucial to increase the yield, reducing the self-condensation of the aldehyde.³⁵ On the contrary, the Carreira coupling with (+)-(*1S,2R*)-*N*-methyl-ephedrine (mismatched pair) afforded the addition product in 5% yield, with a 93:7 diastereomeric ratio in favor of the undesired (*R*)-alcohol **4.40**.



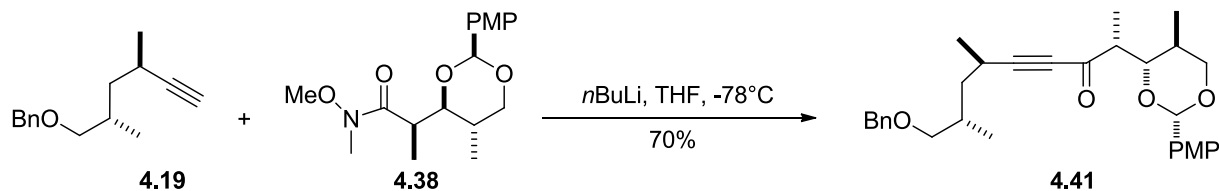
Scheme 4.8 Carreira asymmetric alkylation

Although this step was initially carried out with satisfactory results on the small scale, the protocol resulted capricious and not reproducible on a larger scale; extensive degradation of the acetal was observed in the presence of Lewis-acidic $\text{Zn}(\text{OTf})_2$. As an alternative approach, we tried a modified Carreira alkylation with a synthetic chiral aminoalcohol³⁶ instead of *N*-methyl-ephedrine (**Scheme 4.9**), but no product was obtained.



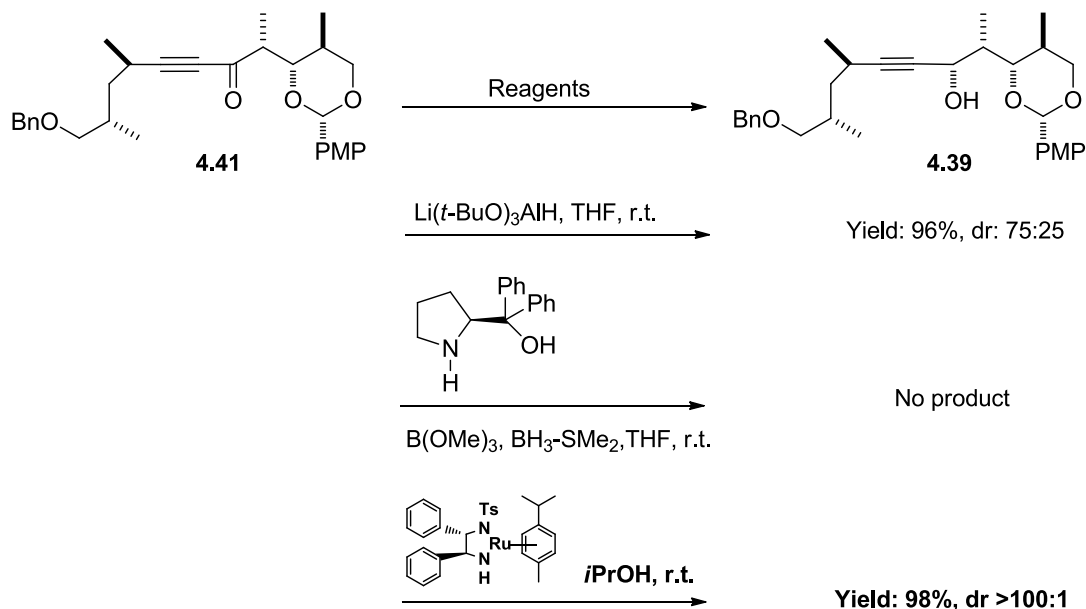
Scheme 4.9 Modified Carreira asymmetric alkylation

At this point, we changed our synthetic strategy (**Scheme 4.10**). We ran the coupling reaction ($n\text{BuLi}$, THF, -78°C) between alkyne **4.19** and Weinreb amide **4.38** (instead of aldehyde **4.20**),³⁷ which led to ynone **4.41** in 70 % yield.



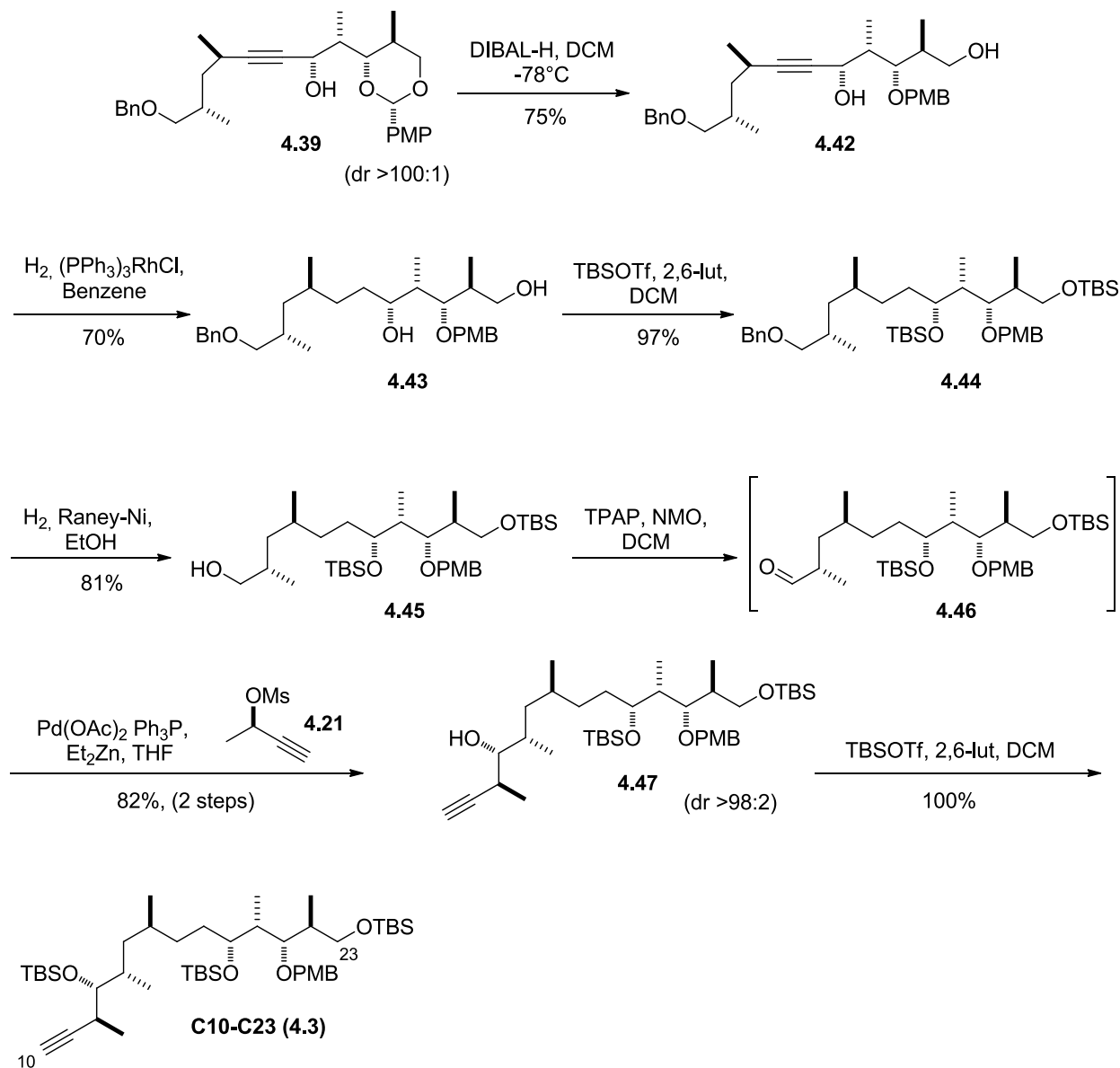
Scheme 4.10 Alternative approach for avoiding the Carreira alkylation

Afterwards, different methods for the stereoselective reduction of the ynone into the desired propargylic alcohol **4.39** were screened (**Scheme 4.11**). As a first attempt, we tried the reduction with the modified hydride $\text{Li}(t\text{-BuO})_3\text{AlH}$.¹⁵ Despite the excellent yield, the diastereomeric ratio resulted unsatisfactory (75:25). Corey's borane-mediated enantioselective reduction (CBS reduction)³⁸ with oxazaborolidines as chiral catalysts caused degradation of the ynone. The acidic environment involved in this method seems to be incompatible with our starting material. Finally, Noyori asymmetric transfer hydrogenation³⁹ [(*S,S*)-Noyori catalyst, $i\text{PrOH}$] turned out to be the best choice, giving alcohol **4.39** in a >100:1 diastereomeric ratio, with an excellent yield (98%).



Scheme 4.11 Screening of reduction methods for obtaining the propargylic alcohol **4.39**

With alcohol **4.39** in the hand we was able to complete the synthesis of key fragment C10-C23 (**4.3**) as shown in **Scheme 4.12**.

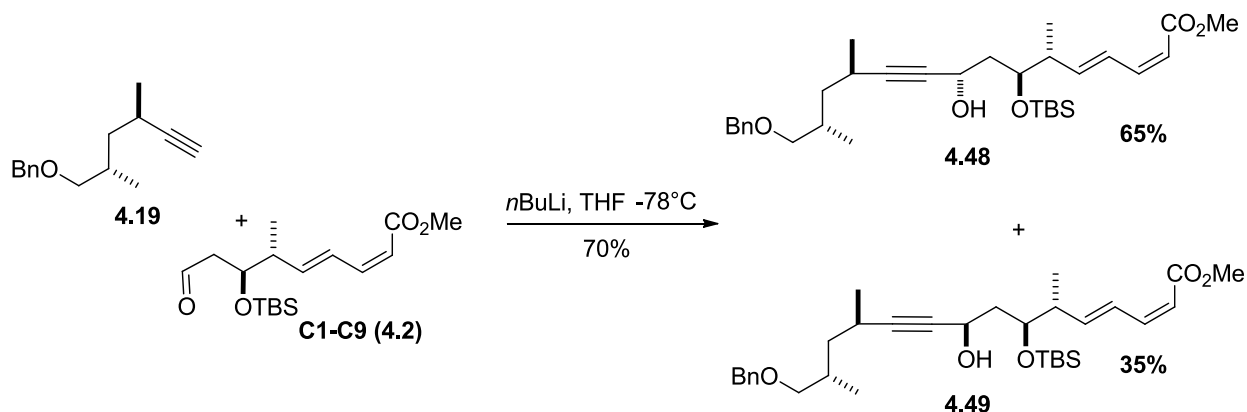


Scheme 4.12 Completion of the synthesis of fragment C10-C23 (4.3)

Acetal **4.39** was cleaved with DIBAL-H to generate the diol **4.42** in 75% yield. Hydrogenation of **4.42** (under 4 bar of hydrogen pressure) in the presence of a catalytic amount (10%) of Wilkinson's catalyst⁴⁰ afforded the desired saturated compound **4.43** (70%). Subsequent silylation (TBSOTf, 2,6-lutidine, DCM, 97%) provided the fully protected tetraol **4.44**, which was subjected to selective removal of the benzyl group over the PMB group (H_2 , Raney-Ni, EtOH, 81%)⁴¹ to obtain the primary alcohol **4.45**. TPAP/NMO oxidation⁴² of **4.45**, which furnished aldehyde **4.46**, was followed by a Marshall-Tamaru palladium-catalyzed allenylzinc addition^{43,44} with the mesylate of (*R*)-3-butyn-2-ol (**4.21**), leading to the desired alcohol **4.47** (82% over two steps) with a very high level of diastereoselectivity in favor of the desired *anti,syn* adduct (>98:2). Finally, TBS protection of alcohol **4.47** afforded quantitatively the desired key fragment C10-C23 (**4.3**) of (-)-dictyostatin (**1.8**).

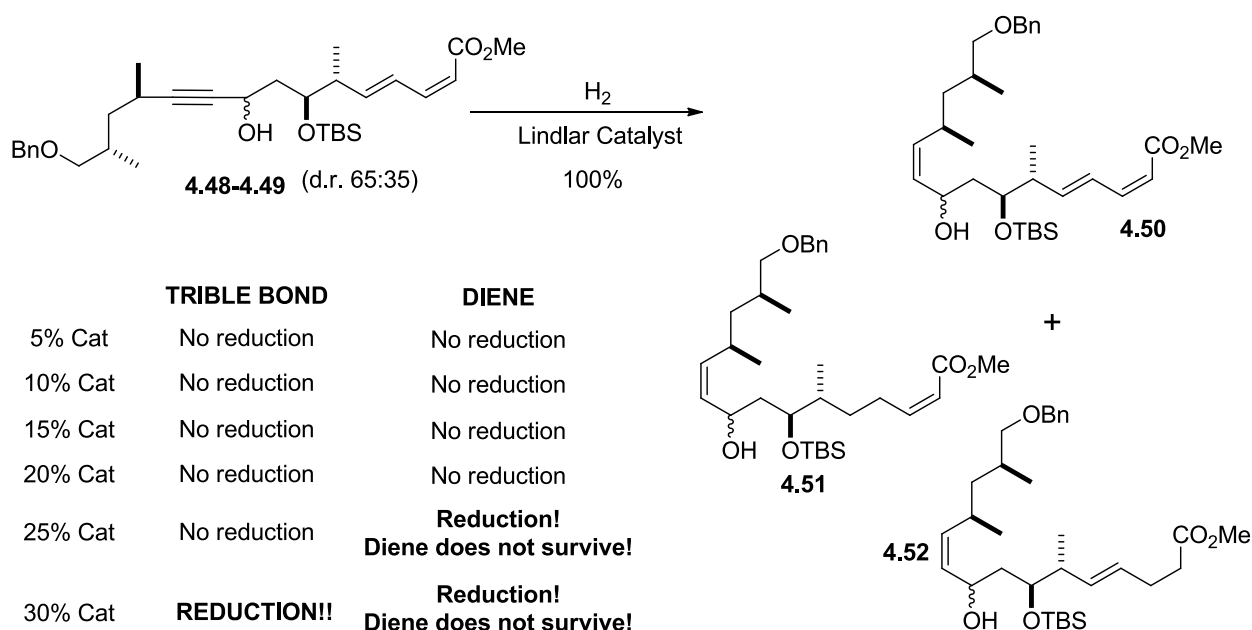
4.6 Coupling Between Two Key Fragments C1-C9 and C10-C23

Initially, we studied the coupling procedure between aldehyde C1-C9 (**4.2**) and the model alkyne **4.19** (Scheme 4.13). The formation of the alkynyl-lithium (*n*BuLi, THF, -78°C)¹⁵ and its addition to aldehyde **4.2** occurred in good yield (70%) and with an acceptable 65:35 diastereoisomeric ratio in favor of the desired product **4.48** over the undesired propargylic alcohol **4.49**.



Scheme 4.13 Coupling reaction of aldehyde **4.2** with the model alkyne **4.19**

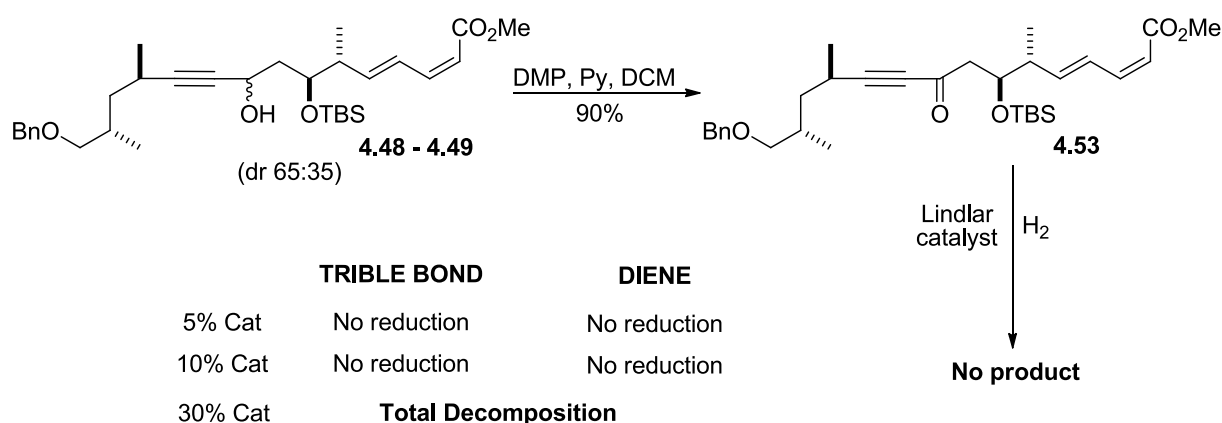
The following reaction of hydrogenation of the triple bond to (*Z*)-double bond was tried on the mixture of model propargylic alcohol **4.48** and **4.49** (Scheme 4.14).



Scheme 4.14 Reduction with Lindlar catalyst of mixture of model propargylic alcohol **4.49**

We were fearing to be unable to perform the selective reduction of the triple bond in the presence of the conjugated double bond.⁴⁵ Indeed, extensive investigation of reduction conditions failed to identify conditions that would selectively reduce the alkyne to the (*Z*)-alkene, while leaving the terminal diene intact. Hydrogenation over Lindlar catalyst⁴⁶ gave only traces of the desired product **4.50**, while the major products were over-hydrogenated compounds **4.51** and **4.52**.

We thus decided to adopt a different strategy (**Scheme 4.15**), and carry out the hydrogenation step on ynone **4.53** rather than on the propargyl alcohol. First, the mixture of propargylic alcohols **4.48** and **4.49**, derived from *n*BuLi coupling, was oxidized (DMP, Py, DCM, 90%) to give the ynone **4.53**. This compound was then hydrogenated over Lindlar catalyst in the hope of observing better results. Unfortunately, we isolated either no product or decomposition products, depending on the amount of Lindlar catalyst.

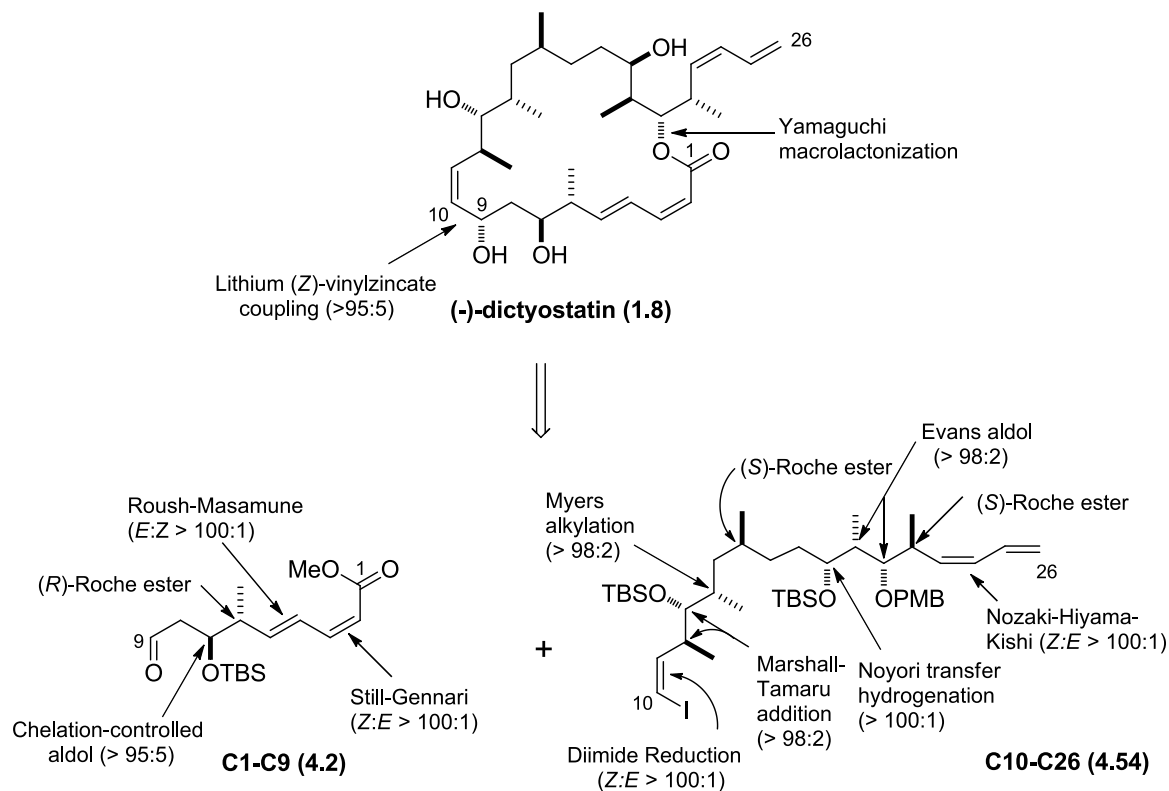


Scheme 4.15 Reduction with Lindlar catalyst of model ynone **4.53**

At this time it became evident that the reduction of the alkyne moiety in the presence of the competing terminal diene was a too high hurdle. As a consequence, we revised our retrosynthetic approach to (-)-dictyostatin (**1.8**).

4.7 Our Second Retrosynthetic Approach to (-)-Dictyostatin

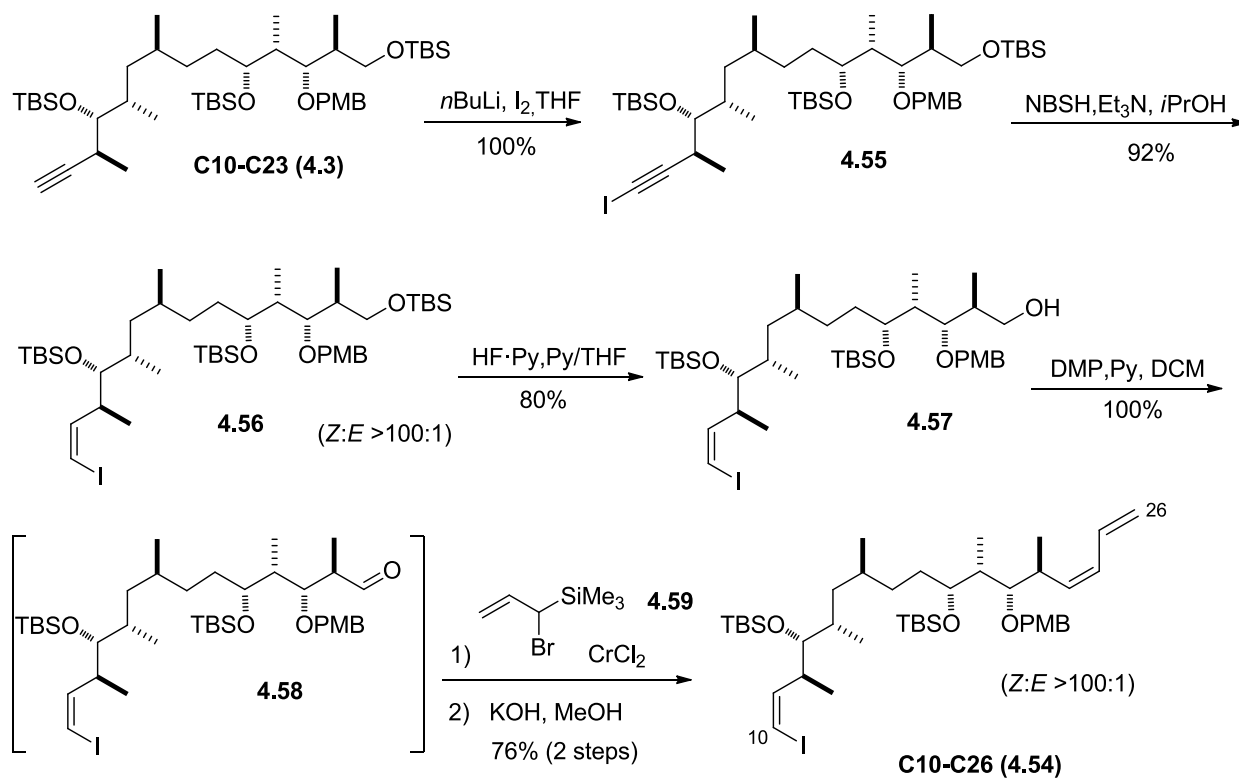
Our alternative retrosynthetic approach to (-)-dictyostatin (**Scheme 4.16**) consisted in replacing the alkyne C10-C23 (**4.3**) with the vinyl iodide C10-C26 (**4.54**). In this new strategy, adopted by Ramachandran and co-workers in their total synthesis of (-)-dictyostatin, the troublesome alkynyl lithium coupling reaction is substituted by a lithium (*Z*)-vinylzincate addition¹³.



Scheme 4.16 Our second retrosynthetic approach to (-)-dictyostatin

4.8 Synthesis of (*Z*)-Vinyl Iodide C10-C26

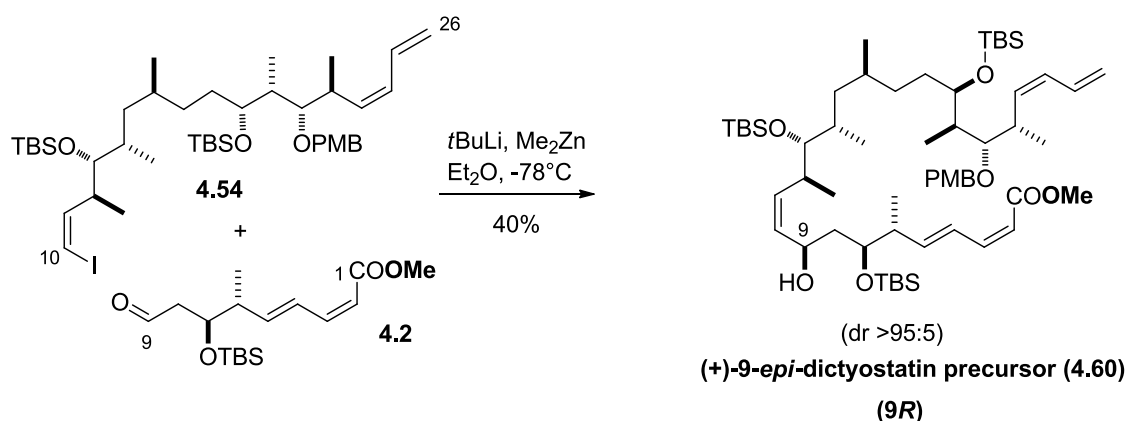
The synthesis of new key fragment C10-C26 (**4.54**), published by our group in 2010⁴⁷, starts from fragment C10-C23 (**4.3**). The alkyne was lithiated with *n*BuLi and converted into the corresponding alkynyl iodide **4.55** in quantitative yield (**Scheme 4.17**). Reduction of compound **4.55** with diimide^{15,48} (generated *in situ* from 2-nitrobenzenesulfonylhydrazide) provided (*Z*)-vinyl iodide **4.56** as a single diastereoisomer (*Z*:*E* > 100:1) in excellent yield (92%). The primary *t*-butyldimethylsilyl ether of **4.56** was selectively cleaved (HF·Py, THF/Py, 80%) to give compound **4.57**, which was converted into aldehyde **4.58** by oxidation with Dess-Martin periodinane. The latter compound was reacted with (1-bromoallyl)trimethylsilane (**4.59**) under Nozaki-Hiyama-Kishi coupling conditions (CrCl₂), followed by a Peterson elimination (KOH, MeOH)⁴⁹ to give the C10-C26 fragment (**4.54**) in good yield (76%, 2 steps) and excellent diastereoselectivity (*Z*:*E* > 100:1).⁵⁰

Scheme 4.17 Synthesis of (*Z*)-vinyl iodide C10-C26 (4.54)

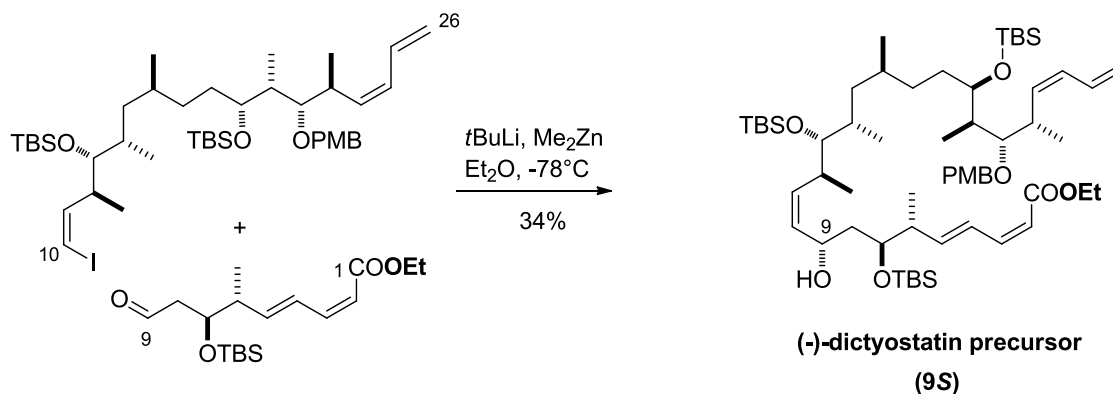
4.9 Lithium (*Z*)-Vinylzincate Addition: The Surprise

Once completed the synthesis of the fragment C10-C26 (4.54), we were ready to try its addition to the aldehyde C1-C9 (4.2). Following Ramachandran's lead,¹³ lithiation of (*Z*)-vinyl iodide 4.54 (*t*BuLi) and subsequent treatment with dimethylzinc provided the corresponding lithium (*Z*)-vinyl zincate,⁵¹ which was added to β -silyloxy aldehyde C1-C9 (4.2) to give the coupling product 4.60 in moderate yield (40%) and excellent diastereomeric ratio (>95:5, Scheme 4.18). On the basis of the structural assignment of the final product [which will not be the desired (-)-dictyostatin (1.8), but (+)-9-*epi*-dictyostatin (4.65), as described in the next sections], the stereochemistry of the newly created stereogenic center C9 in compound 4.60 turned out to be (9*R*). We found this outcome quite surprising, as the addition of the same (*Z*)-vinylzincate to a very similar aldehyde (with the ethyl ester instead of the methyl ester) was reported to give an excellent ratio in favor of the (9*S*) stereoisomer.¹³

OUR Coupling Reaction



RAMACHANDRAN'S Coupling Reaction

Scheme 4.18 Lithium (*Z*)-vinylzincate coupling reaction

The preference for the 1,3-*syn* diastereomer observed in compound **4.60** can be rationalized on the basis of the 1,3-asymmetric induction models (**Figure 4.4**) thoroughly investigated by Evans.⁵² Steric interactions in the aldehyde conformations are minimized when the β -alkyl substituent (R_β) is oriented *anti* to the $C_\alpha\text{-C=O}$ bond as in structures **A** and **B**. Usually, β -OTBS substituted aldehydes afford preferentially the 1,3-*anti* diastereomer *via* the polar model **A**, where dipoles are opposed.⁵² When aluminum Lewis acids (Me_2AlCl or MeAlCl_2) are used, exceptional chelation control reinforces the 1,3-*anti* stereochemical outcome (model **C**, axial attack).⁵³ Recently, Curran and co-workers studied the addition of a (*Z*)-vinyl lithium compound to aldehyde **4.2**, and reported a ca. 2:1 1,3-*anti* : 1,3-*syn* diastereomeric ratio.⁵⁴ Addition of other (*Z*)-vinyl lithium compounds to similar aldehydes gave 1,3-*anti* : 1,3-*syn* ratios from 1.5:1 to 1:1.6.^{15,54} Apparently, models **B** and/or **C** (equatorial attack), leading to the 1,3-*syn* diastereomer, start making a substantial impact in these addition reactions. Surprisingly, when a dimethylalkenylzincate^{51,55} is used, the stereochemical outcome is determined only by models **B** and/or **C** (equatorial attack), leading to complete selectivity in favor of the 1,3-*syn* diastereomer.

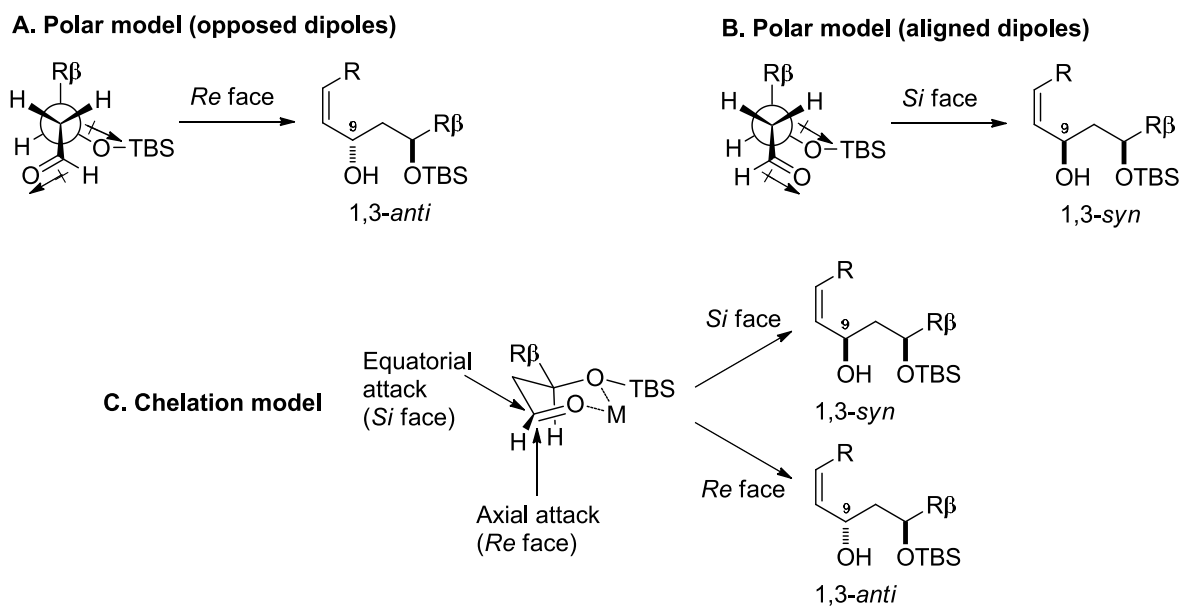
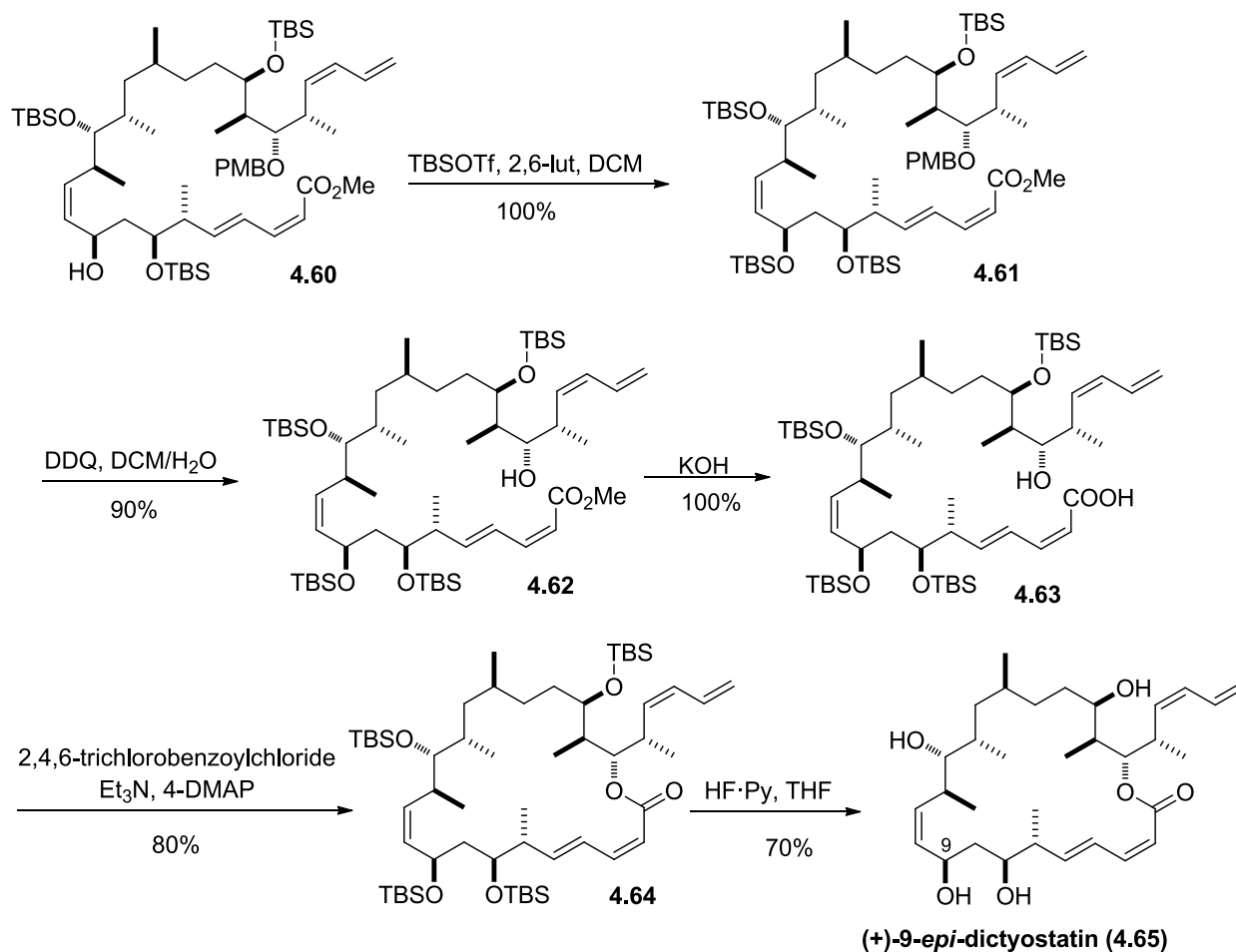


Figure 4.4 Evans's 1,3 asymmetric induction models

4.10 Completion of the Synthesis of (+)-9-*epi*-dictyostatin

As we were not yet aware of the stereochemical outcome of the (*Z*)-vinylzincate addition, we completed our synthesis as planned (**Scheme 4.19**). The secondary alcohol of compound **4.60** was silylated with TBSOTf to give the fully protected intermediate **4.61** (100%). Selective PMB removal with DDQ provided compound **4.62** (90%), which was then saponified under basic conditions (KOH) to provide *seco*-acid **4.63** (100%). Yamaguchi macrolactonization⁵⁶ gave macrolide **4.64** in good yield (80%), together with a small amount (5-10%) of the (*2E,4E*)-dienoate ($J_{\text{H}_2\text{-H}_3} = 15.2$ Hz), probably formed via a reversible Michael addition of DMAP to the (*2Z,4E*)-dienoate,⁵⁷ and which could be separated by flash chromatography. The global deprotection of the TBS groups was initially attempted with 3N HCl/MeOH in THF (2.2:1 volume ratio).¹³ However, this method caused an extensive degradation of the product. Conversely, the use of HF·Py in THF^{58,59} cleanly converted **4.64** into (+)-9-*epi*-dictyostatin **4.65** in 70% yield.



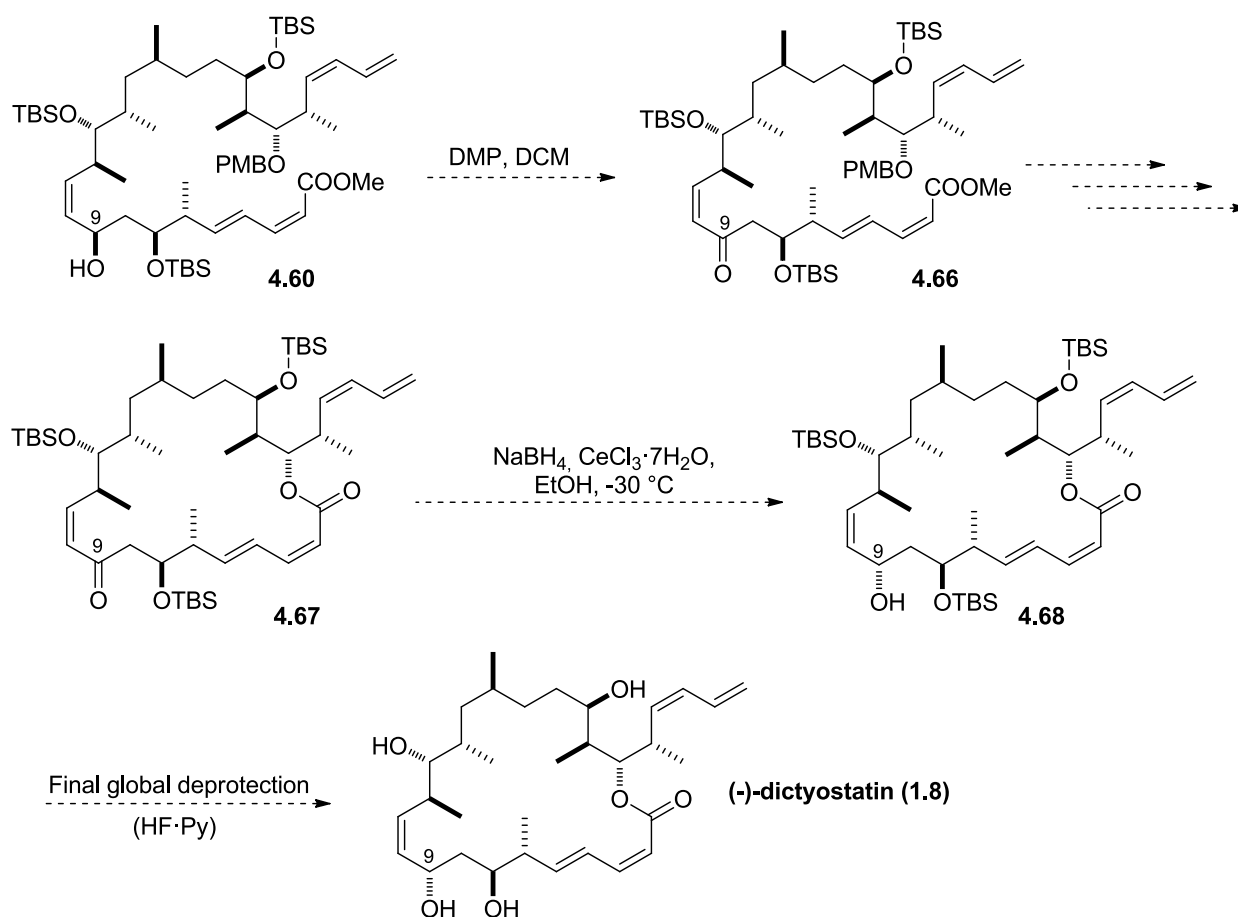
Scheme 4.19 Completion of the total synthesis of (+)-9-*epi*-dictyostatin (4.65)

Our synthetic compound **4.65** produced analytical data ($^1\text{H-NMR}$ in CD_3OD , $[\alpha]_{\text{D}}$) in disagreement with those recorded from an authentic sample of (-)-dictyostatin (**1.8**) kindly provided by Prof. Ian Paterson (University of Cambridge, UK). On the contrary, our synthetic compound **4.65** was identical ($^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ in d_6 -benzene, $[\alpha]_{\text{D}}$, HRMS, IR, R_f) to those described by Paterson⁵⁹ and Curran⁵⁴ as (+)-9-*epi*-dictyostatin (see Chapter 6 for full analytical details).

4.11 Conclusion

A highly stereoselective synthesis of (+)-9-*epi*-dictyostatin (**4.65**) has been carried out in 1.53% overall yield over 29 steps (longest linear sequence from the Roche ester). Unfortunately, unnatural configuration at C9 is known to cause a substantial drop in cytotoxicity relative to (-)-dictyostatin (**1.8**)^{54,59}. Nevertheless, compound **4.60** should be easily conveyed into the total synthesis of (-)-dictyostatin (**1.8**) by oxidation of the (9*R*)-allylic alcohol to the corresponding 9-

ketone **4.66**, completion of the synthetic sequence (as outlined in **Scheme 4.20**) and reduction of the macrocyclized enone **4.67** to the (9*S*)-allylic alcohol **4.68** (NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, EtOH , -30°C)^{59,60} immediately before final deprotection.



Scheme 4.20 Possible conveyance of **4.60** into the total synthesis of (-)-dictyostatin (**1.8**)

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Chapter 5

Our Route to 12,13-bis-*epi*-Dictyostatin

5.1 Introduction

The design and synthesis of non-natural dictyostatin analogs is an important goal for the evaluation of structure-activity relationships of this class of molecules. Although much work has been carried out in this field (as described in Chapter 3), syntheses of dictyostatin analogs modified at C12, C13 were never reported. Consequently, we decided to focus our efforts in the synthesis of dictyostatin epimers at C12 and C13. Biological screening of these new structures could be insightful to better understand the stereochemical requirements for antitumor activity.

Our synthetic route to (+)-9-*epi*-dictyostatin (**4.65**) and (-)-dictyostatin (**1.8**) is flexible enough to allow the preparation of 12,13-bis-*epi*-dictyostatin (**5.1**, Figure 5.1). The following sections delineate our preliminary activity aimed to the synthesis of **5.1**.

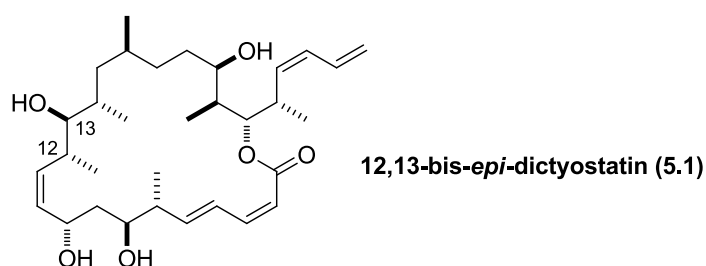
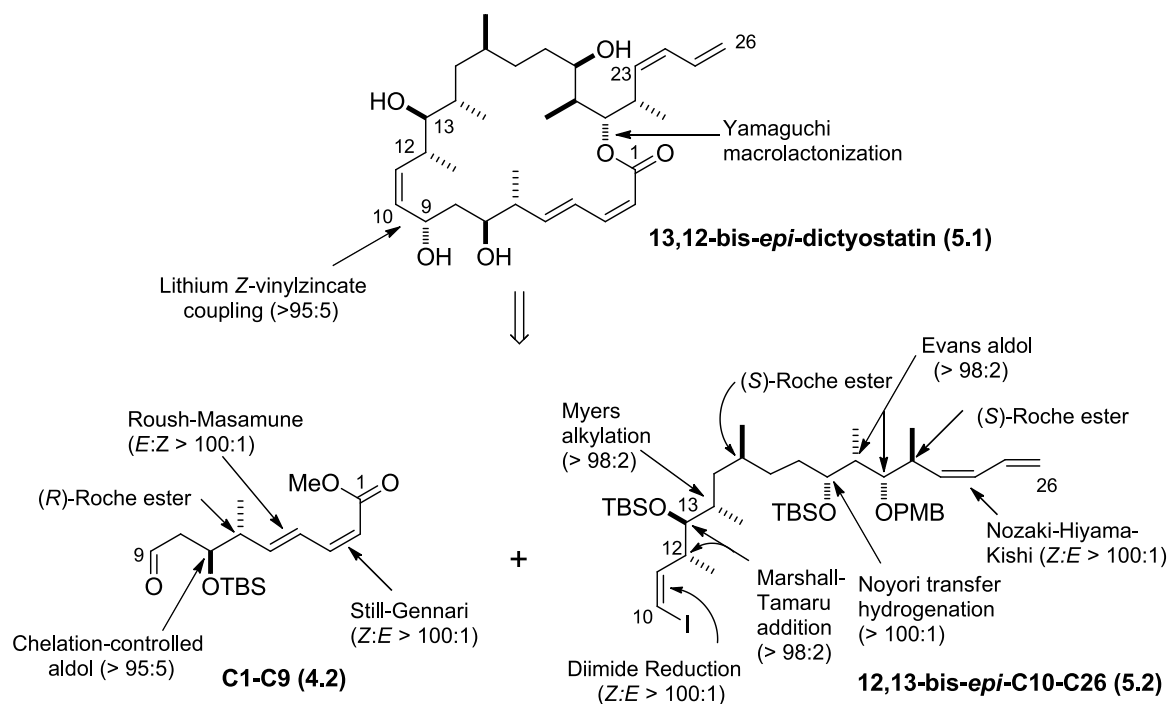


Figure 5.1 12,13-bis-*epi*-dictyostatin

5.2 Our Retrosynthetic Approach to 12,13-bis-*epi*-Dictyostatin

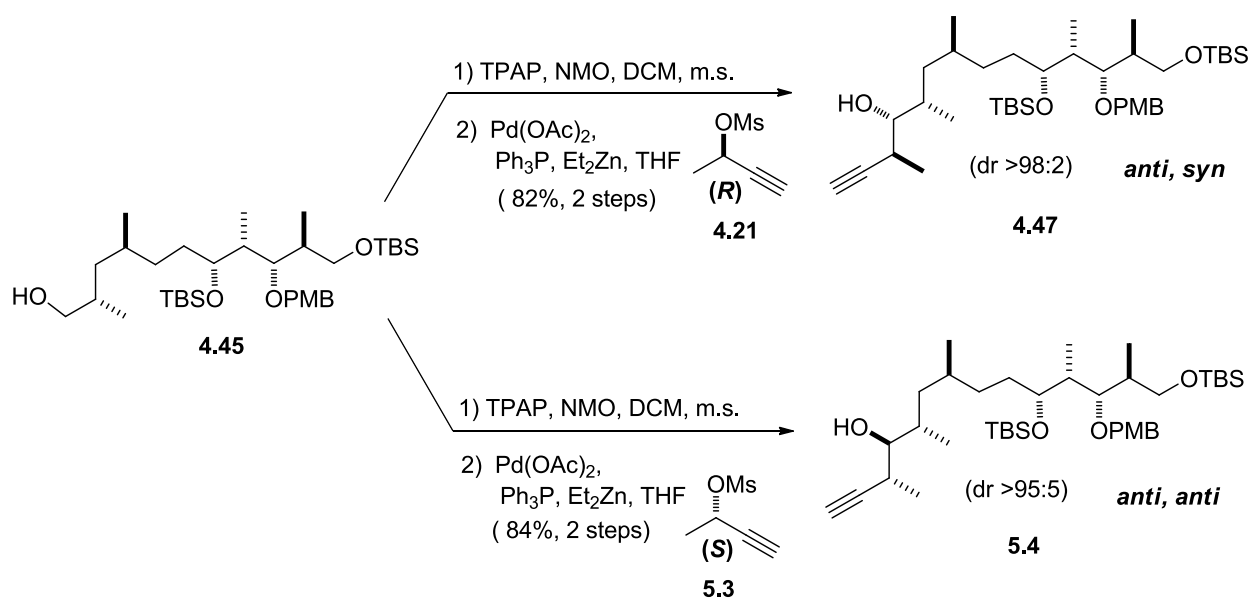
As for the synthesis of (+)-9-*epi*-dictyostatin (**4.65**), our retrosynthetic approach identified two key fragments: aldehyde C1-C9 (**4.2**) and (*Z*)-vinyl iodide bis-*epi*-C10-C26 (**5.2**) as shown in **Scheme 5.1**. For the synthesis of the former compound, see Chapter 4.



Scheme 5.1 Our retrosynthetic approach to 12,13-bis-epi-dictyostatin

5.3 Synthesis of (*Z*)-Vinyl Iodide 12,13-bis-epi-C10-C26

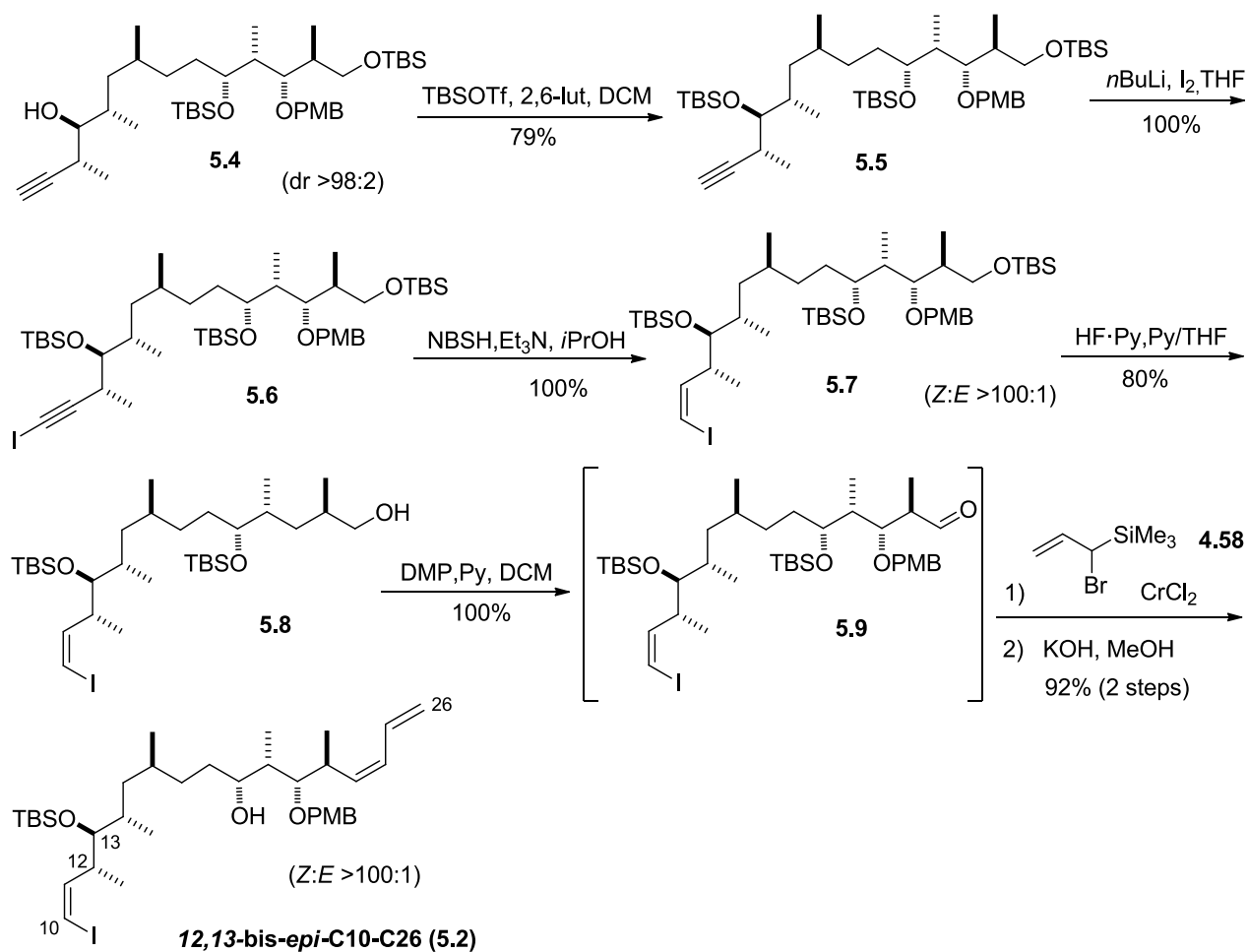
Starting from primary alcohol **4.45** (Scheme 5.2), TPAP/NMO oxidation¹ and subsequent Marshall-Tamaru palladium-catalyzed allenylzinc addition^{2,3} with the mesylate of (*R*)-3-butyn-2-ol (**4.21**), furnished alkyne **4.47** (*anti, syn* diastereomer).



Scheme 5.2. Marshall-Tamaru allenylzinc addition with two enantiomers of 3-butyn-2-ol mesylate

This compound was conveyed in the synthesis of (+)-9-*epi*-dictyostatin (**4.65**), as described in Chapter 4. The same sequence was repeated employing the mesylate of (*S*)-3-butyn-2-ol (**5.3**). This second attempt led to alkyne **5.4** (*anti, anti* diastereomer, 84% over two steps) with an excellent control of diastereoselectivity. Therefore, the use of enantiomeric 3-butyn-2-ol mesylate in a Marshall-Tamaru reaction enabled us to modify the configuration at C12 and C13, thus opening the route to 12,13-bis-*epi*-dictyostatin (**5.1**).

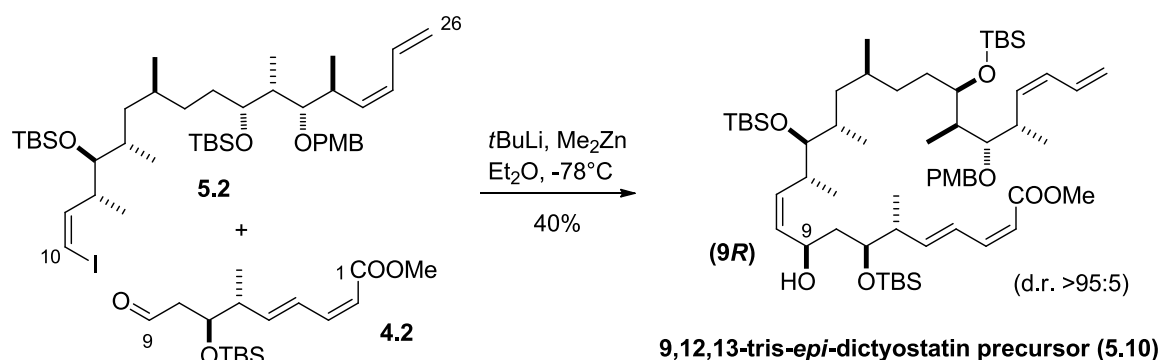
The synthesis of bis-*epi*-C10-C26 (**5.2**) was completed with an identical strategy (Scheme 5.3) to that devised for C10-C26 (**4.54**) TBS protection of Marshall-Tamaru adduct **5.4** provided alkyne **5.5** (79%), which was then lithiated with *n*BuLi and converted into the corresponding alkynyl iodide **5.6** (100%). Reduction of the latter compound with diimide^{4,5} afforded (*Z*)-vinyl iodide **5.7** quantitatively as a single diastereoisomer (*Z*:*E* > 100:1). The primary *t*-butyldimethylsilyl ether of **5.7** was selectively removed (HF·Py, THF/Py, 80%)⁴ to give alcohol **5.8**, which was oxidized to aldehyde **5.9** with Dess-Martin periodinane.⁶ Reaction with (1-bromoallyl)trimethylsilane (**4.59**) under Nozaki-Hiyama-Kishi coupling conditions (CrCl₂),⁷ followed by Peterson elimination (KOH, MeOH), provided the bis-*epi*-C10-C26 fragment (**5.2**) in high yield (92% over 2 steps) and excellent diastereocontrol of the newly formed double bond (*Z*:*E* > 100:1).⁸



Scheme 5.3 Synthesis of fragment 12,13-bis-*epi*-C10-C26 (**5.2**)

5.4 Lithium (*Z*)-Vinylzincate Addition and Completion of the Synthesis

In our hands, the lithium (*Z*)-vinylzincate addition described in §4.9 resulted (*9R*)-diastereoselective, despite what Ramachandran claimed in his total synthesis (-)-dictyostatin.⁹ Bearing this stereochemical outcome in our minds, we attempted the same coupling reaction between aldehyde C1-C9 (**4.2**) and (*Z*)-vinyl iodide 12,13-bis-*epi*-C10-C26 (**5.2**) (**Scheme 5.4**). On the basis of an *a posteriori* assessment, the new stereocenter at C9 appeared to be (*R*) once again.



Scheme 5.4 Lithium (*Z*)-vinylzincate coupling reaction

The assignment of C9 configuration was accomplished through an empirical rule described by Curran in 2007.⁴ Such rule originates from an attentive analysis of ¹H NMR spectra of some later-stage precursors of dictyostatin analogs (shown in **Figure 5.2**). Curran observed that the signal for H9 in compound α (possessing *9S* configuration) was a doublet-doublet at δ 4.5 (*J* values of 12.4 and 7.6 Hz), whereas the same signal in compound β (possessing *9R* configuration) was more closely resembling a triplet at δ 4.4 (*J* value of 8.1 Hz).

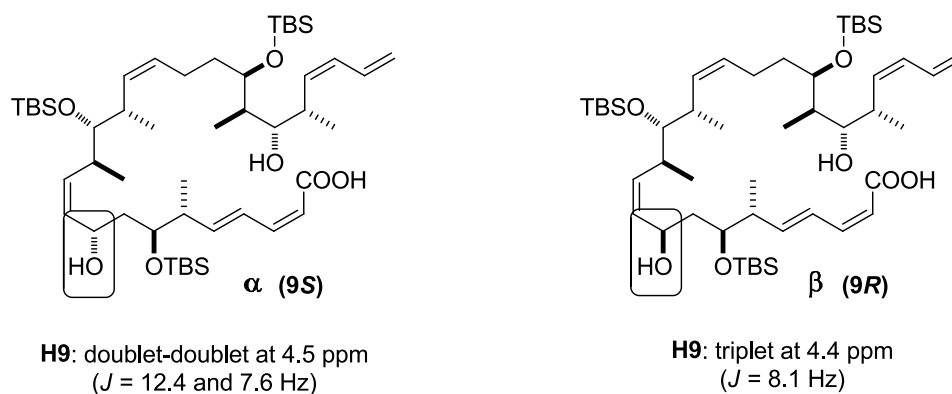
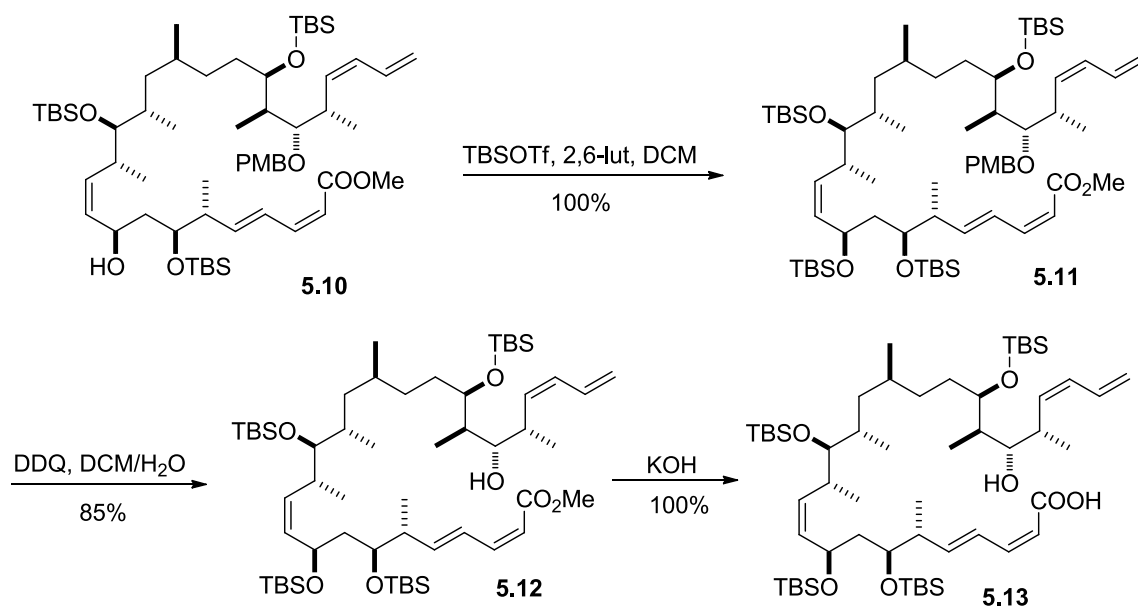


Figure 5.2 Representative compounds from which Curran derived his rule

This trend was satisfactorily verified in other similar intermediates, thus providing a straightforward and reliable method for assigning C9 configuration. However, “Curran’s rule” cannot be applied directly to compound **5.10**, because the PMB CH₂ signals would cover the area of interest (4.4-4.6 ppm). In addition, no evidence is available for the rule to be valid when the hydroxyl group on C9 is unprotected.

For these reasons, we resolved to bring a small amount of **5.10** some steps further in the synthesis (**Scheme 5.5**).



Scheme 5.5 9,12,13-tris-*epi* series

The hydroxyl moiety was silylated with TBSOTf to give the fully protected intermediate **5.11** (100%). DDQ treatment cleaved PMB selectively, providing compound **5.12** (85%), which was then saponified (KOH, 100%) to provide *seco*-acid **5.13**.

With the spectral data of this set of compounds at our disposal, we were able to ascertain the configuration at C9 through the above-mentioned empirical rule. As shown in **Figure 5.3**, compounds **5.12** and **5.13** produced triplet signals in the spectral area of interest (*right column*). This pattern is consistent with the C9 configuration being (*R*). Further evidence is provided by the analysis of ¹H NMR spectra of compounds **4.62** and **4.63** precursors of (+)-9-*epi*-dictyostatin (*left column*). Again, H9 signals are triplets, thus endorsing (9*R*) stereochemistry. Conversely, a similar intermediate, having (*S*) configuration at C9, gave rise to a characteristic doublet-doublet (*bottom*).

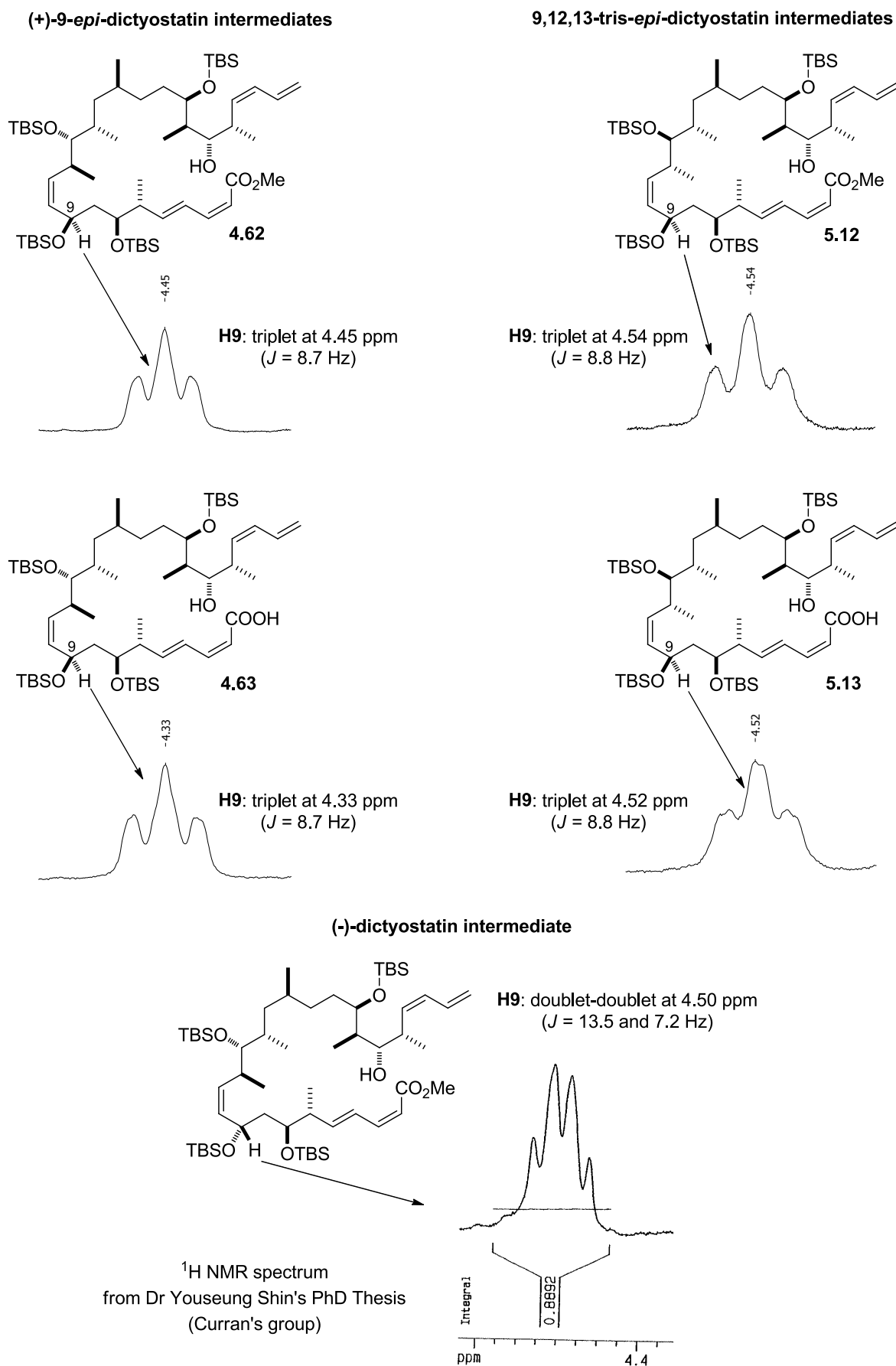


Figure 5.3 Application of “Curran’s rule” to our intermediates

5.5 Future Perspectives

Although compound **5.13** is only two steps away from 9,12,13-tris-*epi*-dictyostatin (**5.14**, **Figure 5.4**), we are not interested in completing such synthesis. As a matter of fact, (*R*) configuration at C9 turned out to inhibit biological activity in other dictyostatin analogues.^{4,10} Hence, macrolide **5.14** is likely to be worthless in a pharmaceutical scenario.

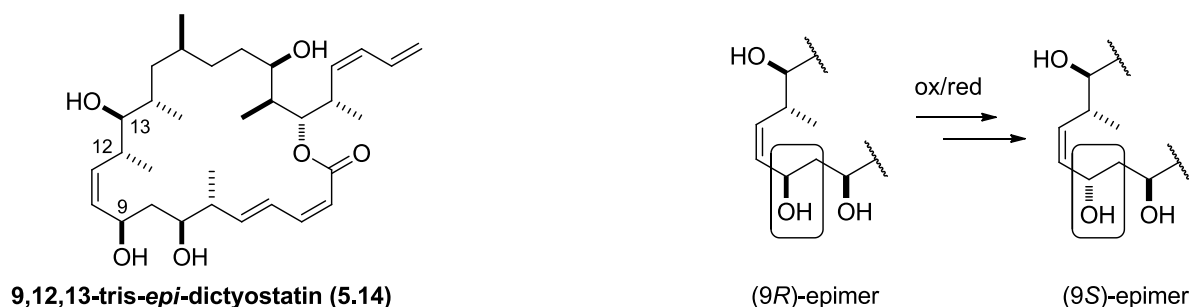


Figure 5.4 9,12,13-tris-*epi*-dictyostatin (**5.14**) and “ox/red strategy”

Nevertheless, our initial plan of synthesizing the potentially active 12,13-bis-*epi*-dictyostatin (**5.1**) is still attainable through an oxidation/reduction sequence (**Figure 5.4**). In contrast to the inversion strategy devised for compound **4.60** (see §4.11), reduction with Luche reagent (NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$)^{11,12} might not be equally reliable in the bis-*epi* series. The stereoselectivity of Luche reduction of compound **4.67** stems from a macrocyclic control whose outcome is, by chance, the desired (9*S*)-epimer. As our bis-*epi* series exhibits opposed configuration at C12 and C13, a different preferred conformation of the macrocycle might reverse the stereochemical outcome. Consequently, conceived a modified strategy capable of delivering the desired (9*S*)-epimer unambiguously. The new approach, which we wish to put into practice in the near future, is described in **Scheme 5.6**. Alcohol **5.10** will be oxidized⁴ to 9-ketone **5.15** through Dess-Martin periodinane. Subsequent reduction to the desired (9*S*)-allylic alcohol **5.16** will be carried out as a Corey’s borane-mediated enantioselective reduction (CBS reduction)¹³ with oxazaborolidines as chiral catalysts.¹⁴ The newly created 9-allylic alcohol **5.16** will be silylated with TBSOTf providing **5.17**. Selective PMB removal with DDQ will give compound **5.18**, which, after saponification (**5.19**), will undergo Yamaguchi macrolactonization (**5.20**).¹⁵ Final deprotection of **5.20** with $\text{HF} \cdot \text{Py}$ ^{10a,11} will afford our desired macrolide 12,13-bis-*epi*-dictyostatin (**5.1**).

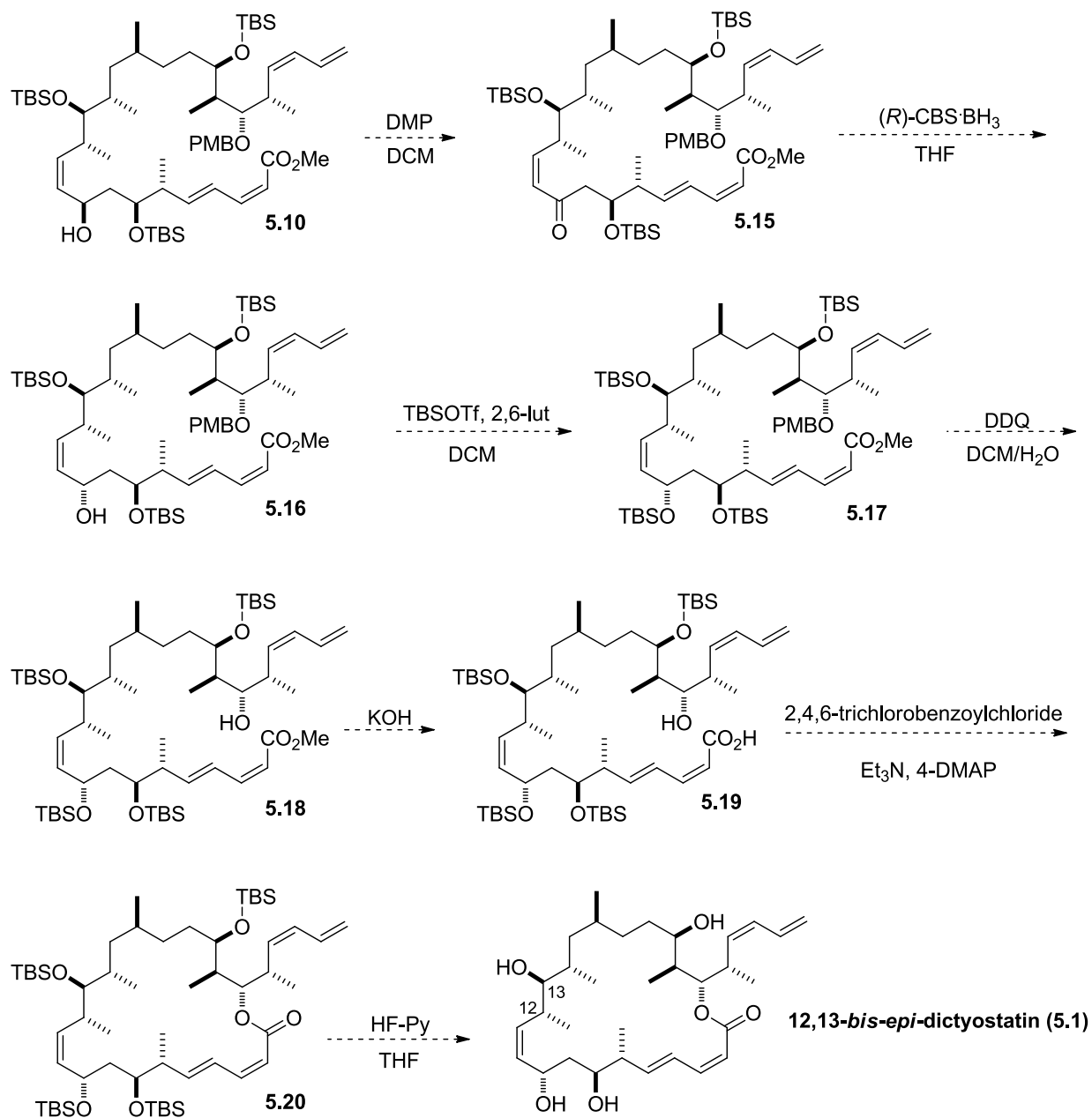


Figure 5.6 Proposed synthetic approach to 12,13-bis-*epi*-dictyostatin (5.1)

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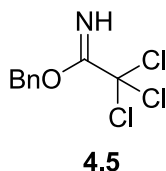
Chapter 6

Experimental Detail

6.1 General Comments

^1H (400.13 MHz) and ^{13}C (100.58 MHz) NMR spectra were recorded on a Bruker Avance-400 spectrometer. ^1H NMR chemical shifts are reported relative to TMS, and the solvent resonance was employed as the internal standard (CDCl_3 , $\delta = 7.26$). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet-doublet, td = triplet-doublet, dt = doublet-triplet, br = broad signal. ^{13}C NMR spectra were recorded with complete proton decoupling, and the chemical shifts are reported relative to TMS with the solvent resonance as the internal standard (CDCl_3 , $\delta = 77.0$). Infrared spectra were recorded on a standard FT/IR spectrophotometer. Optical rotation values were measured on an automatic polarimeter with a 1 dm cell at the sodium D line. High resolution mass spectra (HRMS) were performed on a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) – 4.7 T Magnet (Magnex) equipped with ESI source, available at C.I.G.A. (Centro Interdipartimentale Grandi Apparecchiature dell'Università degli Studi di Milano). All reactions were carried out in oven- or flame-dried glassware under nitrogen atmosphere, unless stated otherwise. All commercially available reagents were used as received. All solvents were dried by standard procedures before use. Organic extracts were dried over anhydrous Na_2SO_4 . Reactions were magnetically stirred and monitored by TLC on silica gel (60 F254 pre-coated glass plates, 0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a ceric ammonium molybdate or KMnO_4 solution. Flash chromatography was performed on silica gel (60 Å, particle size 0.040–0.062 mm) according to the procedure of Still and co-workers.¹ Yields refer to chromatographically and spectroscopically pure compounds, unless stated otherwise.

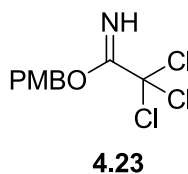
6.2 Preparation of Reagents



Benzyl 2,2,2-trichloroacetimidate (**4.5**)²

To a solution of freshly distilled benzyl alcohol (5.62 g, 52 mmol, 1 eq) in DCM (58 mL), a solution of KOH (50% in water, 58 mL) and tetrabutylammonium hydrogen sulfate (88.3 mg, 0.26 mmol, 0.005 eq) were added. The mixture was cooled to -15 °C and after 10 min under vigorous stirring, trichloroacetonitrile (5.74 mL, 57.2 mmol, 1.1 equiv) was added. After 30 min the temperature was raised to R.T. and the yellow mixture was stirred for 30 min. Phases were separated and the aqueous phase was extracted with DCM (3 x 100 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in under reduced pressure. The residue was filtered through a short plug of celite and concentration under reduced pressure gave the benzyl 2,2,2-trichloroacetimidate **4.5** (13.2 g, 100% yield) as a yellow oil which was used without further purification.

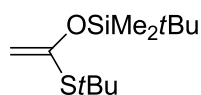
R_f 0.70 (80:20 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 5.38 (s, 2H), 7.32-7.38 (m, 5H), 8.43 (br s, 1H).



4-methoxybenzyl 2,2,2-trichloroacetimidate (**4.23**)³

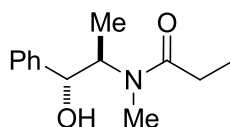
p-Methoxybenzyl alcohol (5.53 g, 40 mmol, 1 eq) was added to a suspension of NaH (60% in mineral oil; 0.16 g, 4 mmol, 0.1 eq) in Et₂O (39 mL) over 30 min at R.T. The mixture was stirred 30 min further and cooled to 0 °C. Trichloroacetonitrile (4.41 mL, 44 mmol, 1.1 eq) was then introduced over 15 min. After 2 h the solution was concentrated with the water bath temperature maintained below 40 °C. The residue was treated with a mixture of pentane (41 mL) and MeOH (0.2 mL), stirred at room temperature for 30 min, and filtered through a short plug of celite. Concentration under reduced pressure gave the trichloroimidate **4.23** (11.3 g, 100% yield) as a yellow oil which was used without further purification.

R_f 0.70 (80:20 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 3.82 (s, 3H), 5.29 (s, 2H), 6.92 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 8.37 (br s, 1H).

**4.9****1-(*tert*-butylthio)-1-(*tert*-butyldimethylsilyloxy)ethylene (4.9)⁴**

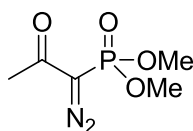
A solution of DIPA (2.1 mL, 14.7 mmol, 1 eq) in THF (18.4 mL) was treated with *n*BuLi in hexane (1.6 M, 9.2 mL, 14.7 mmol, 1 eq) at 0 °C under stirring. After 30 min at 0 °C the mixture was cooled to -78 °C and a solution of commercially available *t*-butyl-thioacetate (2.0 mL, 14.7 mmol, 1 eq) in THF (5.3 mL) was slowly added. After 30 min at -78 °C a solution of *t*-butyldimethylsilyl chloride (2.2 g, 14.7 mmol, 1 eq) in DMPU (8.2 mL) was added. Then the mixture was warmed to R.T. during 30 min, diluted with ice-cold pentane and washed with water. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude product was purified by distillation (145 °C, 20 mmHg) to give the ketene acetal **4.9** (2.7 g, 75% yield) as a colorless oil.

R_f 0.80 (80:20 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.19 (s, 6H), 0.91 (m, 9H), 1.38 (m, 9H), 4.68 (d, J = 16 Hz, 2H).

**4.27*****N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropionamide (4.27)⁵**

A 50 mL flask was charged with (1*R*,2*R*)-2-(methylamino)-1-phenylpropan-1-ol (1.0 g, 6.05 mmol, 1 eq), TEA (1.0 mL, 7.26 mmol, 1.2 eq) and DCM (12 mL). The flask was placed in a water bath, at R.T., and propionic anhydride (0.85 mL, 6.65 mmol, 1.1 eq) was added. The reaction was stirred at R.T. for 1 h and quenched with water (2 mL). The organic phase was separated and extracted with half-saturated aq. NaHCO₃ (2 x 2 mL) and 1N aq HCl (2 x 2 mL), dried and concentrated under reduced pressure to afford a white solid. Re-crystallization from toluene yielded the pure product **4.27** (1.1 g, 80% yield) as a highly viscous, yellow oil containing mixture of rotamers (minor resonances are denoted by an asterisk).

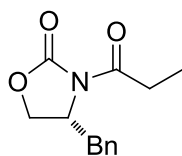
R_f 0.30 (10:20 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 1.00* (d, J = 6.8 Hz, 0.7H), 1.08-1.26* (m, 5.3H), 2.25-2.45 (m, 1.5H), 2.50-2.60* (m, 1H), 2.83 (s, 0.5H), 2.95 (s, 2.3H), 4.03* (m, 0.7H), 4.46* (m, 0.3H), 4.60* (m, 1H).

**4.33****Dimethyl (1-diazo-2-oxopropyl)phosphonate (4.33)**⁶

A solution of tosyl chloride (1.0 g, 5.25 mmol, 1 eq) and NaN₃ (341.3 mg, 5.25 mmol, 1 eq) in acetone (15 mL) and water (15 mL) was stirred at 0 °C for 2 h. Acetone was evaporated and the reaction mixture was extracted with Et₂O. The organic phase was dried and concentrated under reduced pressure to afford tosyl azide, which was used without further purification.

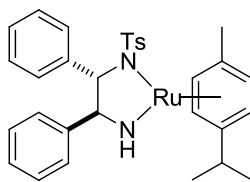
A solution of dimethyl (2-oxopropyl)phosphonate (0.72 mL, 5.25 mmol, 1 eq) in CH₃CN (5 mL) and solid K₂CO₃ (725 mg, 5.25 mmol, 1 eq) was added the crude tosyl azide (5.25 mmol, 1 eq) in CH₃CN (4 mL). The mixture was stirred overnight, then Et₂O (10 mL) was added and the solution was filtered through a short pad of celite. Purification by flash chromatography (20:80 hexane/EtOAc) afforded Bestmann-Ohira phosphonate **4.33** (453 mg, 45% yield) as a pale yellow oil.

*R*_f 0.25 (20:80 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 2.26 (s, 3H), 3.83 (d, *J* = 12.0 Hz, 6H).

**4.35****(*R*)-4-benzyl-3-propionyloxazolidin-2-one (4.35)**⁷

A solution of (*R*)-4-benzyl-oxazolidin-2-one (3.91 mg, 22.1 mmol, 1 eq) in THF (98 mL) was cooled to -78 °C and *n*BuLi in hexane (1.6 M, 15.2 mL, 24.3 mmol, 1.1 eq) was added over 15 min. After additional 30 min, a solution of propanoyl chloride (1.92 mL, 22.1 mmol, 1 eq) in THF (14 mL) was added dropwise over 10 min. The resultant mixture was stirred 2 h at -78 °C, then warmed to 0 °C and quenched by the addition of a sat. aq. NH₄Cl solution (66 mL). The layers were separated, and the aqueous phase was extracted with Et₂O. The combined organic layers were washed with water and brine, then dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (80:20 hexane/EtOAc) afforded the oxazolidinone **4.35** (5.06 g, 98% yield) as a white solid.

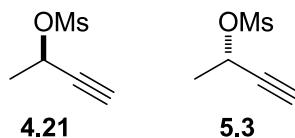
*R*_f 0.30 (80:20 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 1.23 (t, *J* = 7.6 Hz, 3H), 2.82-3.05 (m, 2H), 3.31-3.35 (dd, *J* = 3.4 Hz, 13.4 Hz, 1H), 4.18-4.25 (m, 2H), 4.67-4.73 (m, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H).



(1*S*,2*S*)-(-)-*N*-Tosyl-1,2-diphenylethane-1,2-diamine[η^6 -1-isopropyl-4-methylbenzene] ruthenium(II)] (Noyori Catalyst)⁸

A mixture of di- μ -chloro-bis[chloro(η^6 -1-isopropyl-4-methylbenzene)ruthenium(II)] (0.306 g, 0.500 mmol, 1 eq), *N*-((1*S*,2*S*)-2-amino-1,2-diphenylethyl)-4-methylbenzenesulfonamide (0.366 g, 1.00 mmol, 2 eq) and KOH (0.411 g, 7.33 mmol, 15 eq) in DCM (7 mL) was stirred at R.T. for 5 min. On addition of water (7 ml), the color changed from orange to deep purple. The purple organic layer was washed with water (7 ml), dried over CaH₂ and concentrated to dryness in vacuo to yield (*S,S*) Noyori Catalyst (0.564 g, 94%) as deep purple crystals.

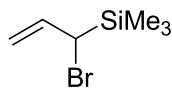
¹H NMR (400 MHz, Toluene-*d*₈): δ = 1.04 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.89 (s, 3H), 2.05 (s, 3H), 2.37 (m, 1H), 3.91 (d, *J* = 4.0 Hz, 1H), 4.71 (s, 1H), 4.94 (d, *J* = 5.0 Hz, 1H), 5.06 (d, *J* = 5.0 Hz, 1H), 5.11 (d, *J* = 5.0 Hz, 1H), 5.22 (d, *J* = 5.0 Hz, 1H), 6.42 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 2H), 7.10 (m, 10H), 7.49 (d, *J* = 8.0 Hz, 2H).



(*R*) and (*S*)-but-3-yn-2-yl methanesulfonate (4.21 and 5.3)⁹

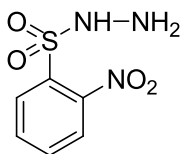
To a solution of (*R*) or (*S*)-but-3-yn-2-ol (0.2 mL, 2.5 mmol, 1 eq) in DCM (2 mL) at -78 °C TEA (1.40 mL, 10 mmol, 4 eq) and mesyl chloride (0.58 mL, 7.5 mmol, 3 eq) were added. The solution was stirred for 2 h at -78 °C (warning: starting material and final product co-spotted on TLC). After that, the mixture was quenched with sat. aq. NaHCO₃ solution. The organic phase was separated, washed with sat. aq. NaHCO₃ solution and brine, dried and concentrated under reduced pressure (>750 mbar). Purification by flash chromatography (30:10 pentane/Et₂O) afforded mesylate **4.21/5.3** (963 mg, 98% yield) as a colorless oil.

*R*_f 0.25 (30:10 pentane/ Et₂O); ¹H NMR (400 MHz, CDCl₃): δ = 1.68 (d, *J* = 6.7 Hz, 3H), 2.73 (d, *J* = 2.1 Hz, 1H), 3.15 (d, *J* = 4.5 Hz, 3H), 5.31 (qd, *J* = 6.7, 2.1 Hz, 1H).

**4.59****(1-bromoallyl)trimethylsilane (4.59)**¹⁰

To a stirred solution of DIPA (0.91 mL, 6.5 mmol, 1.3 eq) in THF (1.5 mL) at -78 °C was added *n*BuLi in hexane (1.6 M, 3.75 mL, 6.0 mmol, 1.2 eq) dropwise. After stirring at 0 °C for 30 min the solution was added to a flask containing allyl bromide (0.52 mL, 6.0 mmol, 1.2 eq) and ClSiMe₃ (0.63 mL, 5.0 mmol, 1.0 eq) in THF (1.2 mL) at -78 °C. After 2 h the reaction was quenched by the addition of sat. aq. NH₄Cl solution (3 mL) and the phases were separated. The aqueous phase was extracted with pentane and the combined organic extracts dried and concentrated under reduced pressure. Purification by flash chromatography (10:1 hexane/EtOAc) afforded compound **4.59** (590 mg, 61% yield) as a colorless oil.

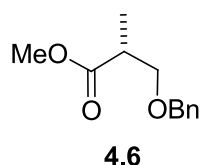
*R*_f 0.85 (10:1 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.16 (s, 9H), 3.82 (d, *J* = 9.6 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 5.19 (d, *J* = 16.8 Hz, 1H), 5.95 (m, 1H).

***o*-Nitrobenzenesulfonylhydrazide**¹¹ (NBSH)

Hydrazine monohydrate (3.0 mL, 60 mmol, 2.5 eq) was added dropwise to a solution of *o*-nitrobenzenesulfonyl chloride (5.6 g, 25 mmol, 1 eq) in THF (25 mL) at -30 °C. During the addition the reaction mixture became brown, and a white precipitate of hydrazine hydrochloride was deposited. After stirring at -30 °C for 30 min, thin-layer chromatographic analysis (TLC) indicated that the sulfonyl chloride had been consumed (10:20 hexane/EtOAc). Ethyl acetate (50 mL, 23 °C) was added to the cold reaction solution and the mixture was washed repeatedly with ice-cold 10% aq. sodium chloride solution (5 x 35 mL). The organic layer was dried at 0 °C and then was added slowly to a stirring solution of hexane (250 mL) at 23 °C over 5 min. *o*-Nitrobenzenesulfonylhydrazide precipitated within 10 min as an off-white solid and was collected by filtration. The filter cake was washed with hexane (2 x 12 mL) and then was dried under vacuum to afford pure NBSH as an off-white powder (4.4 g, 81%).

*R*_f 0.20 (1:2 hexane/EtOAc); ¹H NMR (400 MHz, CD₃CN): δ = 3.90 (br s, 2H), 5.97 (br s, 1H), 7.84 (m, 3H), 8.10 (m, 1H).

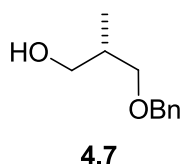
6.3 Synthesis of Aldehyde C1-C9



(*R*)-methyl-3-(benzyloxy)-2-methylpropanoate (**4.6**)

Trifluoromethanesulfonic acid (15.8 mmol, 1.4 mL, 0.7 eq) was added to a solution of (*R*)-(-)-3-hydroxy-2-methylpropanoate (Roche ester) **4.4** (2.5 mL, 22.6 mmol, 1 eq) and benzyl 2,2,2-trichloroacetimidate **4.5** (47.4 mmol, 11.97 g, 2.1 eq) in DCM/cyclohexane (1:2, 240 mL). The mixture was stirred overnight at R.T. After completion of the reaction the solution was concentrated under reduced pressure, diluted with DCM (10 mL) and washed with sat. aq. NaHCO₃ solution (50 mL). The phases were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (Na₂SO₄), and evaporated under reduced pressure. The crude product was filtered on short plug of celite and purified by flash chromatography (90:10 hexane/EtOAc) to give the the corresponding benzyl ether **4.6** (4.70 g, 100% yield) as a colorless oil.

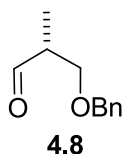
R_f 0.46 (90:10 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 1.21 (d, J = 7.2 Hz, 3H), 2.79-2.84 (m, 1H), 3.50-3.54 (m, 1H), 3.65-3.70 (m, 1H), 3.71 (s, 3H), 4.55 (s, 2H), 7.28-7.32 (m, 5H).



(*S*)-3-(benzyloxy)-2-methylpropan-1-ol (**4.7**)

A solution of PMB ether **4.6** (2.02 g, 9.7 mmol, 1 eq) in THF (16 mL) was cooled to 0 °C and added to a solution of LiAlH₄ (407 mg, 10.7 mmol, 1.1 eq) in THF (16 mL) over 30 min. The reaction mixture was gradually warmed to R.T., and stirred for 2 h. After cooling to 0 °C the mixture was quenched *via* dropwise addition of H₂O (0.27 mL), 15% NaOH (0.27 mL), and H₂O (0.82 mL). The solution was stirred for 30 min, treated with Na₂SO₄, filtered (3 mL Et₂O rinse), and concentration under reduced pressure furnished an orange oil. Purification by flash chromatography (60:40 hexane/EtOAc) afforded the corresponding PMB ether **4.7** (1.55 g, 89% yield) as a pale yellow oil.

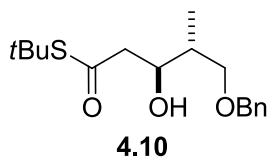
R_f 0.54 (60:40 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.91 (d, J = 7.2 Hz, 3H); 2.15-2.51 (m, 1H), 2.06 (br s, 1H), 3.37-3.46 (m, 1H), 3.48-3.58 (m, 3H), 4.55 (s, 2H), 7.21-7.34 (m, 5H).



(R)-3-(benzyloxy)-2-methylpropanal (4.8)

A solution of alcohol **4.7** (0.4 g, 2.2 mmol, 1 eq) in DCM (12.3 mL) was treated at 0 °C with Py (0.45 mL, 5.5 mmol, 2.5 eq) and DMP (1.12 g, 2.64 mmol, 1.2 eq). The reaction mixture was warmed to R.T. and stirred for 1 h. After completion of the reaction, sat. aq. NaHCO₃ solution (38.0 mL) and Na₂S₂O₃ (3.99 g, 16.1 mmol, 7.3 eq) were added. After stirring for 30 min, the phases were separated and the aqueous phase was extracted with Et₂O (3 x 40 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (Na₂SO₄), and evaporated under reduced pressure; this gave crude aldehyde **4.8** (392 mg, 100% yield) as a pale yellow oil, which was used without further purification.

R_f 0.77 (60:40 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 1.17 (d, J = 7.2 Hz, 3H), 2.65–2.73 (m, 1H), 3.66 (dd, J = 4.8 Hz, 9.2 Hz, 1H), 3.72 (dd, J = 6.8 Hz, 9.2 Hz, 1H), 4.55 (s, 2H), 7.10–7.36 (m, 5H), 9.75 (s, 1H).

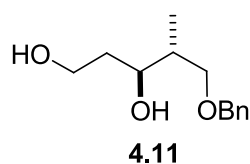


(3S,4R)-S-tert-butyl-5-(benzyloxy)-3-hydroxy-4-methylpentanethioate (4.10)

A stirring solution of aldehyde **4.8** (392 mg, 2.2 mmol, 1 eq) in (5.0 mL) was treated at -80 °C with TiCl₄ (0.49 mL, 2.2 mmol, 1 eq). After a few seconds, a solution of 1-(tert-butylthio)-1-(tert-butyltrimethylsilyloxy)ethylene **4.9** (814 mg, 3.3 mmol, 1.5 eq) in DCM (2.5 mL) was slowly added. After stirring for 2 h at -80 °C, the mixture was quenched with 1 M aq. KOH (18.0 mL). The organic phase was washed with brine (2 x 3 mL), dried (Na₂SO₄), filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (85:15 hexane/EtOAc,) to give **4.10** (642 mg, 94% yield, dr 97:3) as a colorless oil. Further purification by flash chromatography (95:5 benzene/Et₂O) did not improve the dr.

R_f 0.42 (85:15 hexane/EtOAc); $[\alpha]_D^{20} = -23.0$ ($c = 0.75$, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = 0.96 (d, J = 7.2 Hz, 3H), 1.50 (s, 9H), 1.89–1.97 (m, 1H), 2.65 (dd, J = 8.0 Hz, 15.2 Hz, 1H), 2.70 (dd, J = 4.0 Hz, 15.2 Hz, 1H), 3.52 (dd, J = 6.4 Hz, 9.6 Hz, 1H), 3.58 (dd, J = 4.8 Hz, 9.6 Hz, 1H), 4.04 (ddd, J = 4.0 Hz, 8.0 Hz, 6.4 Hz, 1H), 4.50 (s, 2H), 7.28–7.39 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ = 11.8 (epimer at C-3, <3%), 14.5, 30.4, 38.3 (epimer at C-3, <3%), 38.6, 49.0, 49.9, 70.8 (epimer at C-3, <3%), 73.0, 74.1, 74.4, 126.7, 127.2, 128.7, 138.6, 200.7; IR (neat): $\nu =$

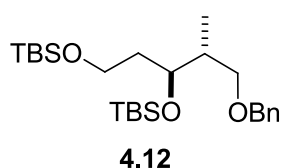
1101, 1253, 1364, 1455, 1681, 2860, 2926, 2962, 3470; HRMS (ESI): calcd. for $C_{17}H_{26}O_3SNa$: 333.4400 $[M + Na]^+$; found: 333.4425.



(3*S*,4*R*)-5-(benzyloxy)-4-methylpentane-1,3-diol (4.11)

A solution of **4.10** (500 mg, 1.6 mmol, 1 eq) in THF (4.0 mL) was added to a suspension of $LiAlH_4$ (122 mg, 3.2 mmol, 2 eq) in THF (4.0 mL) at 0 °C. The mixture was warmed to R.T. and stirred for 2 h. The solution was cooled to 0 °C and then quenched with H_2O (0.7 mL), 2 M aq. NaOH (1.4 mL), and H_2O (1.4 mL). After vigorously stirring for 1 h, the mixture was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (60:40 hexane/EtOAc), affording **4.11** (352 mg, 98% yield) as a colorless oil.

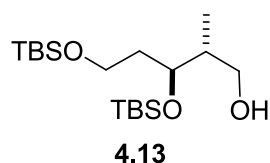
R_f 0.50 (60:40 hexane/EtOAc); $[\alpha]_D^{23} = -21.6$ ($c = 0.87$, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.8$ Hz, 3H), 1.73–1.82 (m, 2H), 1.90–2.00 (m, 1H), 2.98 (br s, 1 H), 3.50 (t, $J = 9.2$ Hz, 1H), 3.66 (dd, $J = 4.0$ Hz, $J = 9.2$ Hz, 1H), 3.79–3.89 (m, 3H), 4.55 (s, 2H), 7.28–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.1$ (epimer at C-3, <3%), 14.3, 35.8 (epimer at C-3, <3%), 36.6, 39.1, 62.3, 74.2, 75.0 (epimer at C-3, <3%), 75.9, 77.5, 128.4, 128.6, 129.2, 138.3; IR (neat): $\nu = 1028, 1057, 1071, 1364, 1454, 2877, 2924, 2958, 3388$; HRMS (ESI): calcd. for $C_{13}H_{20}O_3Na$: 247.1347 $[M + Na]^+$; found: 247.1301.



(*S*)-5-((*R*)-1-(benzyloxy)propan-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (4.12)

A solution of diol **4.11** (350 mg, 1.56 mmol, 1 eq) in DCM (39 mL) was treated at -20 °C with 2,6-lutidine (1.5 mL, 12.5 mmol, 8 eq), followed by TBSOTf (2.7 mL, 3.12 mmol, 3 eq). After stirring for 1 h, the mixture was quenched with sat. aq. NH_4Cl solution (40 mL). The phases were separated, and the aqueous phase was extracted with DCM (2 x 40 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give **4.12** (692 mg, 98% yield) as a colorless oil.

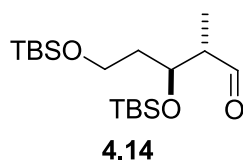
R_f 0.60 (95:5 hexane/EtOAc); $[\alpha]_D^{16} = -7.1$ ($c = 0.86$, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 0.07$ (s, 9H), 0.89–0.91 (m, 21H), 0.95 (d, $J = 6.8$ Hz, 3H), 1.60–1.67 (m, 2H), 1.99–2.05 (m, 1H), 3.31 (dd, $J = 6.8$ Hz, 9.2 Hz, 1H), 3.46 (dd, $J = 6.4$ Hz, 9.2 Hz, 1H), 3.63–3.76 (m, 2H), 3.89–3.92 (m, 1H), 4.51 (s, 2H), 7.30–7.36 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = -4.6$, -3.9 , -2.3 , 12.2 (epimer at C-3, <3%), 13.3, 18.8, 19.0, 26.5, 26.6, 36.4, 39.1 (epimer at C-3, <3%), 39.8, 60.9, 70.3 (epimer at C-3, <3%), 71.1, 73.5, 73.7, 128.0, 128.1, 129.0, 139.4; IR (neat): $\nu = 774$, 835, 1092, 1254, 1471, 2856, 2928, 2955, 3113; HRMS (ESI): calcd. for $\text{C}_{25}\text{H}_{48}\text{O}_3\text{Si}_2\text{Na}$ $[M + \text{Na}]^+$: 475.3034; found: 475.3049.



(2R,3S)-3,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpentan-1-ol (4.13)

Raney-Ni was washed with H_2O until the washings were pH neutral, and then rinsed with absolute EtOH (5 x 100 mL). A solution of **4.12** (690 mg, 1.52 mmol, 1 eq) in absolute EtOH (102 mL) was added, and the mixture was degassed and then purged with H_2 (3x). After stirring for 72 h at R.T., the reaction mixture was filtered through a short pad of celite, washed with EtOAc (2 x 100 mL), and evaporated under reduced pressure. The crude product was purified by flash chromatography (10:1 hexane/EtOAc) to afford the desired product **4.13** (441 mg, 80% yield) as a colorless oil.

R_f 0.16 (10:1 hexane/EtOAc); $[\alpha]_D^{20} = -4.0$ ($c = 1.11$, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 0.07$ (s, 6H), 0.12 (s, 6H), 0.91 (s, 9H), 0.92 (s, 9H), 1.04 (d, $J = 7.2$ Hz, 3H), 1.71–1.82 (m, 3H), 2.61 (br s, 1H), 3.55 (dd, $J = 5.6$ Hz, 11.2 Hz, 1H), 3.68 (t, $J = 6.4$ Hz, 2H), 3.80 (dd, $J = 4.0$ Hz, 11.2 Hz, 1H), 3.90–3.94 (m, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = -4.7$, -4.0 , -3.8 , 13.1 (epimer at C-3, <3%), 14.9, 18.6, 18.9, 26.5, 26.6, 38.2, 39.3, 40.5 (epimer at C-3, <3%), 60.4, 65.9, 73.4 (epimer at C-3, <3%), 74.8; IR (neat): $\nu = 775$, 836, 1094, 1255, 1472, 2858, 2885, 2929, 2956, 3366; HRMS (ESI): calcd. for $\text{C}_{18}\text{H}_{42}\text{O}_3\text{Si}_2\text{Na}$ $[M + \text{Na}]^+$: 385.2565; found: 385.2564.

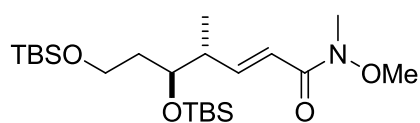


(2S,3S)-3,5-bis((tert-butyldimethylsilyl)oxy)-2-methylpentanal (4.14)

A solution of alcohol **4.13** (0.4 g, 1.1 mmol, 1 eq) in DCM (7.0 mL) was treated at 0 °C with pyridine (0.22 mL, 2.8 mmol, 2.5 eq) and DMP (0.56 g, 1.3 mmol, 1.2 eq). The reaction mixture was warmed to R.T. and stirred for 2 h. After completion of the reaction, sat. aq. NaHCO_3 solution

(18 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (2.0 g, 8.0 mmol, 7.3 eq) were added. After stirring for 30 min, the phases were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried (Na_2SO_4), and evaporated under reduced pressure; this gave crude aldehyde **4.14** (397 mg, 100% yield) as a pale yellow oil, which was used without further purification.

R_f 0.56 (90:10 hexane/EtOAc); ^1H NMR (400 MHz, CDCl_3): δ = 0.07 (s, 6H), 0.10 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.10 (d, J = 7.2 Hz, 3H), 1.75–1.82 (m, 2H), 2.58–2.59 (m, 1H), 3.70–3.73 (m, 2H), 4.17–4.19 (m, 1H), 9.76 (d, J = 1.6 Hz, 1 H).

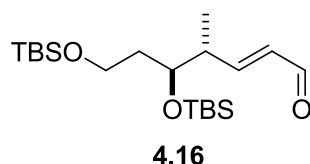


4.15

(4*R*,5*S*,*E*)-5,7-bis((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*,4-dimethylhept-2-enamide (4.15)

Diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (0.25 mL, 1.2 mmol, 1.1 eq), DBU (0.2 mL, 1.3 mmol, 1.2 eq) and aldehyde **4.14** (397 mg, 1.1 mmol, 1 eq) were added to a stirred suspension of LiCl (flame-dried under vacuum before use; 112 mg, 2.6 mmol, 2.4 eq) in MeCN (8.7 mL) at R.T.. The mixture was stirred at R.T. for 1.5 h and then quenched with H_2O (18 mL). After 15 min, EtOAc (18 mL) was added and the mixture was stirred for an additional 30 min. The two phases were separated, and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried and evaporated under reduced pressure. The crude product was purified by flash chromatography (90:10 hexane/EtOAc) to give **4.15** (441 mg, 90% yield) as a colorless oil.

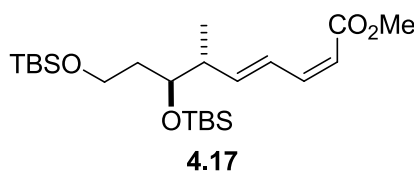
R_f 0.24 (90:10 hexane/EtOAc); $[\alpha]_D^{23} = +8.3$ (c = 0.7, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ = 0.05 (s, 6H), 0.07 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.10 (d, J = 7.2 Hz, 3H), 1.57–1.69 (m, 2H), 2.50–2.59 (m, 1H), 3.26 (s, 3H), 3.60–3.70 (m, 2H), 3.71 (s, 3H), 3.83–3.88 (m, 1H), 6.40 (d, J = 15.6 Hz, 1H), 6.97 (dd, J = 8.0 Hz, 15.6 Hz, 1H), 7.05 (dd, J = 7.2 Hz, 15.6 Hz, H-3, epimer at C-5, <3%); ^{13}C NMR (100 MHz, CDCl_3): δ = -4.7, -3.8, 15.2 (epimer at C-5 <3%), 15.6, 18.7, 18.9, 26.6, 26.7, 33.1, 37.5, 43.0, 45.1 (epimer at C-5, <3%), 60.6, 62.3, 72.8, 73.1 (epimer at C-5, <3%), 119.4, 150.2, 167.6; IR (neat): ν = 775, 836, 1099, 1255, 1382, 1471, 1636, 1666, 2857, 2886, 2895, 2929, 2955; HRMS (ESI): calcd. for $\text{C}_{22}\text{H}_{47}\text{O}_4\text{NSi}_2\text{Na}$: 468.2936 [$M + \text{Na}$] $^+$; found: 468.2328.



(4*R*,5*S*,*E*)-5,7-bis((*tert*-butyldimethylsilyl)oxy)-4-methylhept-2-enal (4.16)

A stirred solution of Weinreb amide **4.15** (400 mg, 0.9 mmol, 1 eq) in THF (9.4 mL) was treated at -78 °C with 1M DIBAL-H in hexane (2.7 mL, 2.7 mmol, 3 eq). After being stirred for 90 min at -78 °C, this solution was poured into a mixture of 1 M aq. tartaric acid (12.4 mL) and EtOAc (13.8 mL). After stirring for 1 h, the layers were separated, the aqueous phase was extracted with Et₂O (2 x 20 mL), and the combined organic extracts were washed with brine (2 x 25 mL), dried, and evaporated under reduced pressure; this gave crude aldehyde **4.16** (317 mg, 91% yield), which was used without further purification.

R_f 0.81 (60:40 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.06 (s, 6H), 0.09 (s, 6H), 0.90 (s, 9H), 0.92 (s, 9H), 1.14 (d, J = 7.2 Hz, 3H), 1.53–1.60 (m, 1H), 1.64–1.73 (m, 1H), 2.57–2.67 (m, 1H), 3.64–3.67 (m, 2H), 3.90–3.91 (m, 1H), 6.13 (dd, J = 7.6 Hz, 15.6 Hz, 1H), 6.87 (dd, J = 7.6 Hz, 15.6 Hz, 1H), 9.53 (d, J = 7.6 Hz, 1H).

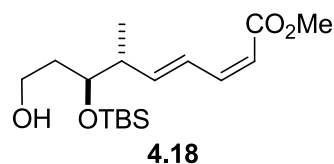


(2*Z*,4*E*,6*R*,7*S*)-methyl 7,9-bis((*tert*-butyldimethylsilyl)oxy)-6-methylnona-2,4-dienoate (4.17)

A solution of (F₃CCH₂O)₂P(O)CH₂CO₂Me (0.18 mL, 0.86 mmol, 1.2 eq) and 18-crown-6·MeCN (1.20 g, 3.9 mmol, 5 eq) in THF (15.6 mL) was cooled to -78 °C, and 0.5 M KHMDS in toluene (1.72 mL, 0.86 mmol, 1.2 eq) was added dropwise. After stirring a few minutes at -78 °C, a solution of aldehyde **4.16** (300 mg, 0.78 mmol, 1 eq) in THF (6.5 mL) was added dropwise. The mixture was stirred at -78 °C for 1 h and then treated with sat. aq. NH₄Cl solution (20 mL) and Et₂O (20 mL). The layers were separated, the aqueous phase was extracted with Et₂O (2 x 30 mL), and the combined organic extracts were washed with H₂O (2 x 40 mL), dried, and evaporated under reduced pressure. The crude product was purified by flash chromatography (100:5 hexane/EtOAc) to give the desired product **4.17** (319 mg, 90% yield) as a colorless oil.

R_f 0.35 (100:5 hexane/EtOAc); $[\alpha]_D^{24}$ = -6.4 (c = 0.35, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 0.05 (s, 6H), 0.08 (s, 6H), 0.90 (s, 9H), 0.92 (s, 9H), 1.09 (d, J = 6.9 Hz, 3H), 1.55–1.67 (m, 2H), 2.47–2.57 (m, 1H), 3.63–3.68 (m, 2H), 3.75 (s, 3H), 3.82–3.85 (m, 1H), 5.61 (d, J = 11.3 Hz, 1H), 6.06 (dd, J = 8.0 Hz, 15.2 Hz, 1H), 6.58 (t, J = 11.3 Hz, 1H), 7.37 (dd, J = 11.3 Hz, 15.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = -4.7, -3.8, 16.1, 18.8, 18.9, 26.6, 37.8, 43.4, 51.7, 60.5, 73.0, 116.0, 127.5, 146.3, 148.2, 167.6; IR (neat): ν = 775; 806, 835, 1030, 1098, 1176, 1194, 1258,

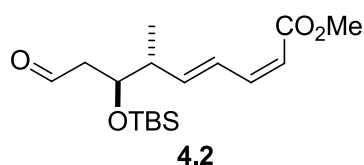
1438, 1471, 1602, 1639, 1722, 2341, 2360, 2710, 2738, 2856, 2927, 2957, 3408; HRMS (ESI): calcd. for $C_{23}H_{46}O_4Si_2Na$: 465.2827 [$M + Na$] $^+$; found: 465.2823.



(2Z,4E,6R,7S)-methyl 7-((tert-butyldimethylsilyl)oxy)-9-hydroxy-6-methylnona-2,4-dienoate (4.18)

A solution of compound **4.17** (338 mg, 0.74 mmol, 1 eq) in THF (3.8 mL) at 0 °C was treated with a solution of HF-Py in THF/Py [16.5 mL, prepared by slow addition of HF-Py (1.3 mL) to a solution of pyridine (5.0 mL) and THF (10.2 mL)]. The reaction mixture was warmed to R.T. and stirred for 8 h. After quenching the reaction by the addition of sat. aq. $NaHCO_3$ solution (30 mL), the mixture was extracted with EtOAc (4 x 20 mL). The combined organic extracts were washed with sat. aq. $CuSO_4$ (3 x 15 mL) and brine (2 x 40 mL), dried, and evaporated under reduced pressure. Purification by flash chromatography (80:20 hexane/EtOAc) afforded the alcohol **4.18** (218 mg, 86% yield) as a colorless oil.

R_f 0.20 (80:20 hexane/EtOAc); $[\alpha]_D^{24} = -14.0$ ($c = 0.2$, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$): $\delta = 0.09$ (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.09 (d, $J = 6.8$ Hz, 3H), 1.63–1.74 (m, 2H), 1.98 (br s, 1H), 2.54–2.59 (m, 1H), 3.73 (s, 3H), 3.69–3.75 (m, 2H), 3.85–3.88 (m, 1H), 5.61 (d, $J = 11.2$ Hz, 1H), 6.02 (dd, $J = 8.0$ Hz, 15.6 Hz, 1H), 6.56 (t, $J = 11.2$ Hz, 1H), 7.38 (dd, $J = 11.2$ Hz, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -3.9$, -3.7 , 15.4, 18.7, 26.5, 36.3, 43.3, 51.8, 60.7, 74.4, 116.4, 127.6, 146.0, 147.7, 167.6; IR (neat): $\nu = 775$, 837, 1005, 1031, 1082, 1176, 1197, 1256, 1439, 1601, 1637, 1719, 2857, 2885, 2929, 2954, 3418; HRMS (ESI): calcd. for $C_{17}H_{32}O_4SiNa$: 351.1962 [$M + Na$] $^+$; found: 351.1957.



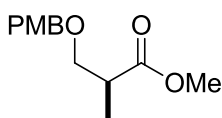
(2Z,4E,6R,7S)-methyl 7-((tert-butyldimethylsilyl)oxy)-6-methyl-9-oxonona-2,4-dienoate (4.2)

A solution of alcohol **4.18** (70 mg, 0.21 mmol, 1 eq) in DCM (1.3 mL) was treated at 0 °C with pyridine (43 μ L, 0.52 mmol, 2.5 eq) and DMP (107 mg, 0.25 mmol, 1.2 eq). The reaction mixture was warmed to R.T. and stirred for 1 h. After completion of the reaction, sat. aq. $NaHCO_3$ solution (3.5 mL) and $Na_2S_2O_3$ (380 mg, 1.53 mmol, 7.3 eq) were added. The obtained mixture was stirred for 30 min, then the phases were separated and the aqueous phase was extracted with Et_2O (3 x 4 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over Na_2SO_4 and

evaporated under reduced pressure. The crude product was purified by flash chromatography (80:20 hexane/EtOAc) to give aldehyde **4.2** (67 mg, 100% yield) as a yellow oil.

R_f 0.37 (80:20 hexane/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ = 0.07 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H), 1.12 (d, J = 6.8 Hz, 3H), 2.45-2.61 (m, 3H), 3.75 (s, 3H), 4.24 (m, 1H), 5.65 (d, J = 11.3 Hz, 1H), 6.00 (dd, J = 7.9 Hz, 15.5 Hz, 1H), 6.58 (t, J = 11.3 Hz, 1H), 7.40 (dd, J = 11.2 Hz, 15.4 Hz, 1H), 9.80 (dd, J = 1.9 Hz, 2.3 Hz, 1H).

6.4 Synthesis of Alkyne C13-C18

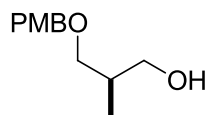


4.24

(*S*)-methyl 3-((4-methoxybenzyl)oxy)-2-methylpropanoate (**4.24**)

A solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (Roche ester) **4.22** (2.67 mg, 22.6 mmol, 1 eq) in DCM/cyclohexane (1:2, 45 mL) was cooled at 0 °C and treated with crude trichloroacetimidate **4.23** (11.3 g) and PPTS (0.29 g, 1.13 mmol, 0.05 eq) over 15 min. After 3 h, the mixture was warmed to R.T., stirred overnight, filtered through a short plug of silica and concentrated under reduced pressure. Purification of the crude product by flash chromatography (80:20 hexane/EtOAc) afforded the corresponding PMB ether **4.24** (4.95 g, 92% yield) as a pale yellow oil.

R_f 0.40 (80:20 hexane/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ = 1.19 (d, J = 7.1 Hz, 3H), 2.77-2.82 (m, 1H), 3.46-3.50 (m, 1H), 3.63-3.67 (m, 1H), 3.71 (s, 3H), 3.82 (s, 3H), 4.48 (s, 2H), 6.90 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ = 14.0, 40.2, 51.7, 55.2, 71.5, 71.7, 72.8, 113.8, 114.3, 129.2, 129.4, 130.2, 159.2, 172.3.



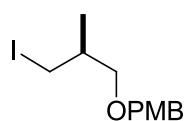
4.25

(*R*)-3-(4-Methoxy-benzyloxy)-2-methyl-propan-1-ol (**4.25**)

A solution of PMB ether **4.24** (4.95 g, 20.8 mmol, 1 eq) in THF (44 mL) was cooled to 0 °C and added to a solution of LiAlH_4 (0.87 g, 22.9 mmol, 1.1 eq) in THF (6.3 mL) over 30 min, warmed

gradually to R.T., and stirred for 2 h. The reaction mixture was then cooled to 0 °C and quenched via dropwise addition of H₂O (0.96 mL), 15% NaOH (0.96 mL), H₂O (2.4 mL). The mixture was stirred for 30 min and then treated with Na₂SO₄, filtered (3.5 mL Et₂O rinse), and concentrated under reduced pressure, furnishing an orange oil. Purification by flash chromatography (60:40 hexane/EtOAc) afforded the corresponding alcohol **4.25** (3.8 g, 87% yield) as a pale yellow oil.

R_f 0.42 (60:40 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.89 (d, J = 7.2 Hz, 3H), 2.06 (br s, 1H), 2.08 (s, 1H), 3.39-3.43 (m, 2H), 3.52-3.64 (m, 2H), 3.83 (s, 3H), 4.47 (s, 2H), 6.91 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 13.5, 35.6, 55.3, 67.9, 73.1, 75.1, 113.9, 130.0, 129.2, 159.3.

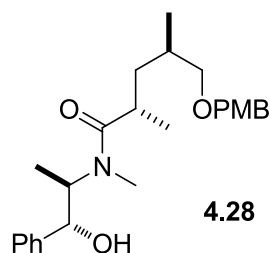


4.26

(S)-1-((3-iodo-2-methylpropoxy)methyl)-4-methoxybenzene (4.26)

Imidazole and triphenylphosphine were crystallized from EtOH prior to use. Imidazole (769 mg, 11.3 mmol, 2.5 eq), triphenylphosphine (2.96 g, 11.3 mmol, 2.5 eq) and iodine (2.29 g, 9.04 mmol, 2 eq) were added sequentially to a solution of the alcohol **4.25** (950 mg, 4.52 mmol, 1 eq) in a Et₂O/acetonitrile 2:1 mixture (90 mL). The reaction mixture was stirred for 1.5 h at R.T. and then quenched with a saturated aqueous solution of sodium thiosulfate. The organic phase was separated and the aqueous layer extracted with Et₂O (2 x 30 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. Purification of the crude product by flash chromatography (98:2 hexane/Et₂O) afforded the iodide **4.26** (1.37 g, 95% yield) as a colorless liquid.

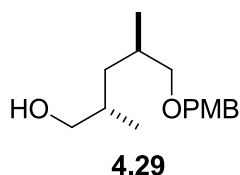
R_f 0.45 (90:10 hexane/EtOAc); $[\alpha]_D^{27} = +9.7$ (c = 0.53, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 1.00 (d, J = 6.7 Hz, 3H), 1.74-1.82 (m, 1H), 3.26-3.41 (m, 4H), 3.83 (s, 3H), 4.47 (s, 2H), 6.90 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 8.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 14.9, 18.4, 35.8, 56.0, 73.6, 74.5, 114.5, 130.0, 131.1, 159.9; IR (film): ν = 808, 1088, 1243, 1505, 1608, 2855; HRMS (FAB⁺) calcd. for C₁₂H₁₇O₂I: 320.0273 [M]⁺; found 320.0272; HRMS (ESI): calcd. for C₁₂H₁₇O₂INa: 343.01654 [M +Na]⁺; found: 343.01625.



(2*S*,4*R*)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-5-((4-methoxybenzyl)oxy)-*N*,2,4-trimethylpentanamide (4.28)

A solution of *n*BuLi in hexane (1.6 M, 7.5 mL, 12 mmol, 4.0 eq) was slowly added to a suspension of LiCl (1.6 g, 38.1 mmol, 12.7 eq, flame-dried under vacuum) and DIPA (1.8 mL, 12.9 mmol, 4.3 eq) in THF (16 mL) at 0 °C. After 30 min at 0 °C, the suspension was cooled to -78 °C. An ice-cooled solution of the Myers amide **4.27** (1.39 g, 6.3 mmol, 2.1 eq) in THF (12 mL, followed by a 2 mL rinse) was added. The mixture was stirred at -78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min. The mixture was re-cooled to 0 °C, and the iodide **4.26** (0.96 g, 3 mmol, 1 eq) was added to the solution. After 5 minutes, the ice bath was removed and the suspension stirred for 20 h at R.T. The reaction mixture was then treated with half-saturated aq. NH₄Cl solution (20 mL), and the resulting mixture was extracted with EtOAc (4 x 15 mL). The combined organic extracts were dried and concentrated under reduced pressure. Purification of the residue by flash chromatography (65:35 hexane/EtOAc) afforded the amide **4.28** as a highly viscous, yellow oil containing mixture of rotamers (1.14 g, 92% yield, minor resonances are denoted by an asterisk).

R_f 0.15 (60:40 hexane/EtOAc); $[\alpha]_D^{20} = -43.0$ ($c = 1.0$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.89$ (d, $J = 6.8$ Hz, 2.7H), 0.95* (d, $J = 6.8$ Hz, 0.3H), 0.99* (d, $J = 6.8$ Hz, 0.3H), 1.10 (d, $J = 6.8$ Hz, 2.7H), 1.13 (d, $J = 6.8$ Hz, 3H), 1.71-1.83 (m, 2H), 2.63-2.69* (m, 0.3H), 2.74-2.79 (m, 0.7H), 2.84 (s, 2.7H), 2.89* (s, 0.3H), 3.21-3.6 (m, 2H), 3.81* (s, 0.3H), 3.83 (s, 2.7H), 4.43 (s, 3H), 4.47-4.50 (m, 1H), 4.62 (t, $J = 7.2$ Hz, 1H), 6.85-7.37 (m, 9H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 15.1$, 16.2, 18.3, 18.4, 19.0, 19.7, 27.6, 31.8, 32.6*, 34.7, 34.9*, 38.8, 39.7*, 56.0, 58.8*, 73.3, 75.9*, 76.2, 76.8*, 77.2, 114.4, 127.0, 127.7*, 128.2, 129.0, 129.4*, 129.8, 130.0*, 131.4, 141.8*, 143.2, 159.7, 179.8; IR (neat): $\nu = 1041$, 1084, 1248, 1464, 1513, 1612, 1628, 1742, 2847, 2934, 3299, 3413; HRMS (ESI): calcd. for C₂₅H₃₅NaNO₄: 436.24583 [$M+Na$]⁺; found: 436.24541.

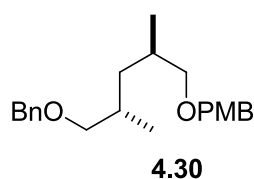


(2*S*,4*R*)-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentan-1-ol (4.29)

A solution of *n*BuLi in hexane (1.6 M, 6.6 mL, 10.6 mmol, 3.9 eq) was added to a solution of DIPA (1.6 mL, 11.4 mmol, 4.2 eq) in THF (11 mL) at 0 °C. After 30 min at 0 °C, borane-ammonia

complex (90%, 336 mg, 10.9 mmol, 4.0 eq) was added in one portion. The suspension was stirred at 0 °C for 15 min and then warmed up to 23 °C. After 15 min, the suspension was re-cooled to 0 °C and a solution of the amide **4.28** (1.13 g, 2.72 mmol, 1 eq) in THF (5 mL, followed by a 2 mL rinse) was added over 5 min. The reaction mixture was warmed to 23 °C, kept at that temperature for 2 h, and then cooled to 0 °C. The excess hydride was quenched by careful addition of 3 N aq. HCl (25 mL). The mixture was stirred for 30 min at 0 °C and then extracted with four 60 mL portions of Et₂O. The combined organic extracts were washed sequentially with 3 N aq. HCl (30 mL), 2 N aq. NaOH (20 mL), and brine (20 mL). The ether extracts were dried and concentrated under reduced pressure. Purification of the residue by flash chromatography (60:40 hexane/EtOAc) afforded the alcohol **4.29** as a colorless oil (652 mg, 95% yield).

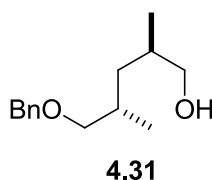
R_f 0.52 (60:40 hexane/EtOAc); $[\alpha]_D^{20} = -5.43$ ($c = 1.0$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.95$ (d, $J = 5.2$ Hz, 3H), 0.96 (d, $J = 5.2$ Hz, 3H), 0.89-0.99 (m, 1H), 1.45-1.52 (m, 1H), 1.67-1.75 (m, 1H), 1.82-1.89 (m, 1H), 1.90 (br s, 1H), 3.21-3.32 (m, 2H), 3.39-3.50 (m, 2H), 3.82 (s, 3H), 4.45 (s, 2H), 6.90 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 8.5$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 18.3, 18.8, 31.7, 33.9, 38.3, 55.9, 68.5, 73.4, 76.3, 114.4, 129.8, 131.3, 159.7$; IR (neat): $\nu =$ HRMS 1040, 1098, 1301, 1462, 1513, 1613, 2872, 2954, 3466, 3640; HRMS (ESI): calcd. for C₁₅H₂₄NaO₃: 275.16177 [$M+Na$]⁺; found: 275.16153.



1-(((2*R*,4*S*)-5-(benzyloxy)-2,4-dimethylpentyl)oxy)methyl)-4-methoxybenzene (**4.30**)

A solution of the alcohol **4.29** (563 mg, 2.23 mmol, 1 eq) in THF (2 mL) was added to a suspension of NaH (60% in mineral oil, 178.4 mg, 4.46 mmol, 2 eq) in THF (12 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1.5 h, and then re-cooled to 0 °C before adding BnBr (397 μ L, 3.34 mmol, 1.5 equiv) and *n*Bu₄NI (24.7 mg, 0.067 mmol, 0.03 eq). The reaction mixture was allowed to warm to 25 °C and stirred for 11 h. After quenching the excess NaH by the addition of MeOH (1 mL), the reaction mixture was diluted with Et₂O (20 mL), washed with a sat. aq. NH₄Cl solution (2 x 20 mL), dried and concentrated under reduced pressure. The residue was purified by flash chromatography (10:1 hexane/EtOAc) to afford the benzyl ether **4.30** (633.9 mg, 83% yield).

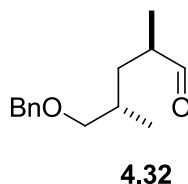
R_f 0.40 (9:1 hexane/EtOAc); $[\alpha]_D^{20} = -0.49$ ($c = 1.0$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.99$ (d, $J = 6.6$ Hz, 3H), 1.01 (d, $J = 6.6$ Hz, 3H), 1.48-1.55 (m, 1H), 1.91 (septet, $J = 6.6$ Hz, 2H), 3.20-3.27 (m, 2H), 3.34-3.41 (m, 2H), 3.84 (s, 3H), 4.46 (d, $J = 2.2$ Hz, 2H), 4.53 (d, $J = 2.2$ Hz, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 7.26-7.40 (m, 7H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 18.8, 31.7, 38.9, 56.0, 73.3, 73.7, 76.3, 76.6, 114.4, 128.1, 128.2, 129.0, 129.7, 131.6, 139.5, 159.7$; IR (neat): $\nu = 1041, 1095, 1245, 1455, 1513, 1613, 2790, 2853, 3032, 3066$; HRMS (ESI): calcd. for C₂₂H₃₀NaO₃: 365.20872 [$M+Na$]⁺; found: 365.20817.



(2*R*,4*S*)-5-(benzyloxy)-2,4-dimethylpentan-1-ol (4.31)

CAN (2.66 g, 4.86 mmol, 3 eq) was added at 0 °C, in four portions, to a solution of the PMB ether **4.30** (555 mg, 1.62 mmol, 1 eq) in CH₃CN/water 4:1 (95 mL). The temperature was maintained at 0 °C for 15 min, then the reaction mixture was warmed to R.T. After 2 h, the reaction mixture was diluted with DCM (100 mL), washed with brine (100 mL) and water (100 mL). After drying, filtering and concentrating under reduced pressure, flash chromatography (85:15 hexane/EtOAc) gave the product **4.31** as a colourless oil (334.9 mg, 93% yield).

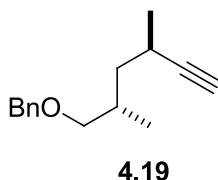
R_f 0.30 (85:15 hexane/EtOAc); $[\alpha]_D^{20} = +6.85$ ($c = 1.0$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.96$ (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 1.47-1.54 (m, 2H), 1.54 (br s, 1H), 1.68-1.78 (m, 1H), 1.83-1.93 (m, 1H), 3.25-3.37 (m, 2H), 3.42-3.54 (m, 2H), 4.52 (d, $J = 2$ Hz, 2H), 7.27-7.39 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 17.7, 18.3, 31.7, 34.0, 38.3, 68.7, 73.7, 76.5, 128.1, 128.2, 129.0, 139.3$; IR (neat): $\nu = 1028, 1097, 1362, 1455, 1496, 2872, 2926, 2957, 3488, 3640$; HRMS (ESI): calcd. for C₁₄H₂₂NaO₂: 245.15120 [$M+Na$]⁺; found: 245.15070.



(2*R*,4*S*)-5-(benzyloxy)-2,4-dimethylpentanal (4.20)

Pyridine (270 μ L, 3.34 mmol, 2.5 eq) and DMP (681 mg, 1.6 mmol, 1.2 eq) were added to a 0 °C solution of the alcohol **4.31** (298 mg, 1.34 mmol) in DCM (7.5 mL). The reaction mixture was warmed to R.T. and stirred for 1 h. The reaction was monitored by TLC and, on disappearance of the alcohol, the reaction mixture was quenched by the addition of sat. aq. NaHCO₃ solution and Na₂S₂O₃ (2.4 g, 9.76 mmol, 7.3 eq). After stirring for 30 min, the phases were separated, and the aqueous phase was extracted with Et₂O (3 x 30 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude aldehyde **4.32** was used without further purification.

R_f 0.89 (60:40 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.94$ (d, $J = 6.6$ Hz, 3H), 1.08 (d, $J = 6.9$ Hz, 3H), 1.16-1.25 (m, 1H), 1.83-1.95 (m, 2H), 2.44-2.51 (m, 1H), 3.32 (d, $J = 6.0$ Hz, 2H), 4.51 (s, 2H), 7.28-7.38 (m, 5H), 9.59 (d, $J = 2.4$ Hz, 1H).



(((2*S*,4*R*)-2,4-dimethylhex-5-yn-1-yl)oxy)methylbenzene (4.19)

SHIOIRI ALKYNYLATION

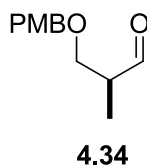
A solution of *n*BuLi in hexane (1.6 M, 1.17 mL, 1.87 mmol, 1.4 eq) was added to a solution of DIPA (262 μ L, 1.87 mmol, 1.4 eq) in THF (10 mL) at 0 °C. After 30 min at 0 °C, the mixture was cooled to -78 °C, and trimethylsilyldiazomethane in Et₂O (2.0 M, 935 μ L, 1.87 mmol, 1.4 eq) was added. After 30 min, a solution of aldehyde **4.32** (295 mg, 1.34 mmol, 1 eq) in THF (3.5 mL) was slowly added. After 1 h at -78 °C, the temperature was raised to 23 °C, and stirring was maintained overnight. The mixture was then poured into ice-cooled water, and extracted with Et₂O. The combined organic extracts were dried and concentrated under reduced pressure. The residue was purified by flash chromatography (10:1 hexane/EtOAc) to afford the alkyne **4.19** as a yellow oil (176.9 mg, 61%).

BESTMANN-OHIRA ALKYNYLATION

A solution of NaOMe (1.05 g, 19.4 mmol, 4 eq) in THF (37 mL) was cooled to -78 °C and dimethyl (1-diazo-2-oxopropyl)phosphonate **4.33** (3.73 g, 19.4 mmol, 4 eq) in THF (84 mL) was added *via* cannula. After 15 min a solution of crude aldehyde **4.32** (1.07 g, 4.85 mmol, 1 eq) in THF (25 mL) was added. The reaction mixture was stirred at -78 °C over 30 min, then the solution was slowly allowed to R.T. over 2 h. The mixture was quenched with sat. aq. NH₄Cl solution (15 mL), diluted with water and extracted with Et₂O. The organic phase was washed with brine and, after drying, filtering and concentrating under reduced pressure, flash chromatography (10:1 hexane/EtOAc) gave the alkyne **4.19** as a colorless oil (955 mg, 91% yield).

R_f 0.87 (10:1 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.98 (d, J = 6.8 Hz, 3H), 1.17-1.22 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H), 1.58-1.68 (m, 1H), 2.05 (d, J = 2.4 Hz, 1H), 2.08-2.20 (m, 1H), 2.50-2.62 (m, 1H), 3.30-3.39 (m, 2H), 4.54 (s, 2H), 7.26-7.37 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ = 16.9, 22.0, 23.8, 32.0, 41.2, 68.8, 73.3, 76.5, 89.4, 127.8, 127.9, 128.7, 139.2; HRMS (ESI): calcd. for C₁₅H₂₀NaO: 239.14064 [M +Na]⁺; found: 239.14059.

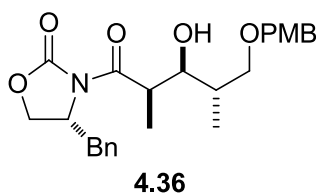
6.5 Synthesis of Aldehyde C19-C23³



(S)-3-((4-methoxybenzyl)oxy)-2-methylpropanal (4.34)

A solution of DMSO (4.24 mL, 59.7 mmol, 3.3 eq) in DCM (86.5 mL) was cooled to -78 °C and oxalyl chloride (3.92 mL, 29 mmol, 1.6 eq) was added over 30 min (internal temp <-65 °C). After additional 30 min, a solution of alcohol **4.25** (3.8 g, 18.1 mmol, 1 eq) in DCM (55.3 mL) was added dropwise over 45 min. The resulting mixture was stirred for additional 30 min at -78 °C, then DIPEA (19.1 mL, 117.6 mmol, 6.5 eq) was added over 10 min. The mixture was stirred for 30 min at -78 °C, then slowly warmed to 0 °C *via* removal of the external cooling bath. The reaction was quenched by addition to a vigorously stirred 1 M aq. KHSO₄ solution (115 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the corresponding aldehyde **4.34** (3.9 g) as a pale yellow oil, which was used without further purification.

R_f 0.63 (60:40 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 1.16 (d, J = 7.1 Hz, 3H), 2.63-2.74 (m, 1H), 3.64-3.74 (m, 2H), 4.55 (s, 2H), 7.24-7.41 (m, 5H), 9.75 (d, J = 1.5 Hz, 1H).

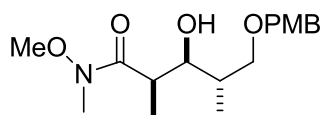


(R)-4-benzyl-3-((2R,3S,4S)-3-hydroxy-5-((4-methoxybenzyl)oxy)-2,4-dimethylpentanoyl)oxazolidin-2-one (4.36)

A solution of oxazolidinone **4.35** (4.85 g, 20.8 mmol, 1.15 eq) in DCM (55 mL) was cooled to 0 °C and *n*Bu₂BOTf in DCM (1 M, 21.7 mL 21.7 mmol, 1.2 eq) was introduced over 30 min, followed by addition of TEA (3.28 mL, 25.5 mmol, 1.3 eq) over 10 min. The mixture was stirred at 0 °C for 30 min and cooled to -78 °C. A -78 °C pre-cooled solution of aldehyde **4.34** (18.1 mmol, 1 eq) in DCM (11 mL) was added *via* syringe over 30 min. After 2 h at -78 °C and 2 h at 0 °C, the solution was quenched with pH 7 potassium phosphate monobasic sodium hydroxide buffer (0.05M, 22 mL). A solution of 30% H₂O₂ in MeOH (1:2, 56 mL) was added to the vigorously stirred reaction mixture at such a rate as to maintain temperature at 0 °C. The reaction

was stirred for 10 h at room temperature and the residue was extracted with Et₂O/DCM (10:1). The combined organic extracts were washed with sat. aq. NaHCO₃, water and brine, then dried with Na₂SO₄ and concentrated under reduced pressure. Purification of the residue by flash chromatography (70:30 hexane/EtOAc) afforded the product **4.36** as a white solid (6.0 mg, 75% yield).

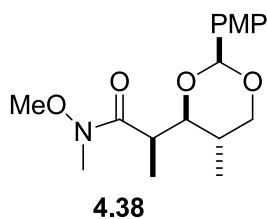
R_f 0.50 (60:40 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.96 (d, J = 7.0 Hz, 3H), 1.27 (d, J = 6.9 Hz, 3H), 1.59 (br s, 1H), 1.96-2.02 (m, 1H), 2.78 (dd, J = 13.3 Hz, 12.2 Hz, 1H), 3.35 (dd, J = 13.3 Hz, 3.0 Hz, 1H), 3.52-3.61 (m, 2H), 3.82 (s, 3H), 3.87-3.90 (m, 1H), 3.92-3.93 (m, 1H), 4.17-4.20 (m, 2H), 4.46 (s, 2H), 4.65-4.72 (m, 2H) 6.88 (d, J = 8.6 Hz, 2H), 7.22-7.37 (m, 7H); ¹³C NMR (100 MHz, CDCl₃): δ = 9.7, 13.6, 36.0, 40.7, 55.3, 55.7, 73.2, 74.7, 75.5, 113.8, 127.3, 128.6, 128.8, 129.5, 129.9, 135.4, 153.2, 159.3, 176.2.

**4.37**

(2*R*,3*S*,4*S*)-3-hydroxy-*N*-methoxy-5-((4-methoxybenzyl)oxy)-*N*,2,4-trimethylpentanamide (4.37)

A suspension of *N,O*-dimethylhydroxylamine hydrochloride (3.98 g, 40.8 mmol, 3 eq) in THF (30 mL) was cautiously treated with an AlMe₃ hexane solution (2.0 M, 20.4 mL, 40.8 mmol, 3 eq) at 0 °C over 30 min (venting bubbler is absolutely required). The resultant solution was stirred over 30 min at 0 °C and 90 min at R.T., and then cooled to -20 °C. A solution of **4.36** (6.0 g, 13.6 mmol, 1 eq) in THF (30 mL) was introduced over 10 min. After additional 2 h at -20 °C, the solution was poured slowly into a solution of 1 N aq. HCl (79 mL) and DCM (79 mL) and stirred vigorously at 0 °C for 2 h. The aqueous phase was extracted with DCM and the combined organic layers were washed with water and saturated brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (80:20 hexane/EtOAc) afforded the Weinreb amide **4.37** as a white solid (3.30 mg, 75% yield).

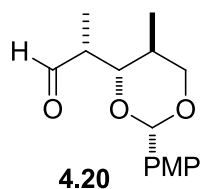
R_f 0.23 (70:30 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 1.00 (d, J = 7.2 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.85-1.93 (m, 1H), 3.06 (br s, 1H), 3.21 (s, 3H), 3.54-3.56 (dd, J = 8.8 Hz, 6Hz, 1H), 3.63-3.65 (dd, J = 8.8 Hz, 4 Hz, 1H), 3.71-3.73 (dd, J = 8.4 Hz, 3.6 Hz, 1H), 3.81 (s, 3H), 4.47 (AB system, ν_A = 4.49, ν_B = 4.45, J_{AB} = 11.6 Hz, 2H), 4.47 (s, 2H) 6.89 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 10.8, 14.7, 32.4, 36.4, 36.9, 55.7, 61.9, 73.2, 73.4, 74.3, 114.1, 114.1, 129.6, 131.0, 159.5.



(*R*)-*N*-methoxy-2-((2*S*,4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-*N*-methylpropanamide (4.38)

A vigorously stirred suspension of Weinreb amide **4.37** (3.30 g, 10.2 mmol, 1 eq) and powdered 4 Å molecular sieves (4 g) in DCM (76 mL) was treated with DDQ (4.48 g, 12.2 mmol, 1.2 eq) at -10 °C. The resultant mixture was warmed to 0 °C over 90 min and filtered through a pad of celite. The solution was diluted with hexane, washed with 1 N aq. NaOH and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (70:30 hexane/EtOAc) afforded the PMP acetal **4.38** as a white solid (1.98 mg, 60% yield).

R_f 0.22 (60:40 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.75 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.89-2.00 (m, 1H), 3.18 (s, 3H), 3.14-3.21 (m, 1H), 3.51 (t, J = 11.2 Hz, 1H), 3.69 (s, 3H), 3.78 (s, 3H), 3.82 (dd, J = 9.8 Hz, 6.4 Hz, 1H), 4.03 (dd, J = 11.3 Hz, 4.7 Hz, 1H), 5.46 (s, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 12.4, 13.0, 32.6, 33.7, 38.9, 55.2, 61.3, 72.8, 82.8, 100.7, 113.5, 127.2, 131.2, 159.7, 175.8.

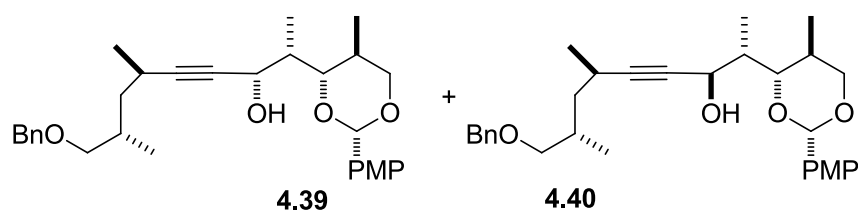


(*R*)-2-((2*S*,4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propanal (4.20)

A solution of amide **4.38** (110 mg, 0.34 mmol, 1 eq) in THF (0.68 mL) was added over 15 min to a -60 °C suspension of LiAlH₄ (20.6 mg, 0.54 mmol, 1.6 eq) in THF (2.72 mL). The resultant solution was stirred for 2 h at -60 °C, warmed to 0 °C, stirred for 1 h, and quenched via dropwise addition of glacial acetic acid (0.14 mL, 1.7 mmol, 5 eq) over 45 min. A sat. aq. sodium potassium tartrate solution (8.5 mL) was added, and the resultant solution was vigorously stirred at R.T. After 1 h, the reaction mixture was diluted with hexane (8.5 mL), and the layers were separated. The aqueous layer was extracted with DCM, and combined organic layers were washed with water, brine and sat. aq. NaHCO₃ solution. The organic phase was dried, filtered and concentrated under reduced pressure to give **4.20** as a pale yellow oil (90 mg, 100%), that was used without further purification.

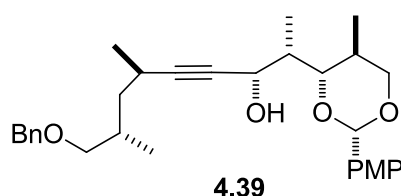
R_f 0.20 (80:20 hexane/EtOAc); ^1H NMR (400 MHz, CDCl_3): δ = 0.84 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 7.2 Hz, 3H), 2.10-2.14 (m, 1H), 2.58-2.62 (m, 1H), 3.61 (t, J = 11.2 Hz, 1H), 3.81 (s, 3H), 4.09 (dd, J = 10.0 Hz, 2.4 Hz, 1H), 4.17 (dd, J = 11.2 Hz, 4.8 Hz, 1H), 5.51 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 9.79 (s, 1H).

6.6 Synthesis of Alkyne C10-C23



(2*S*,3*S*/*R*,6*R*,8*S*)-9-(benzyloxy)-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-6,8-dimethylnon-4-yn-3-ol (4.39 and 4.40)

$n\text{BuLi}$ in hexane (1.6 M, 940 μL , 0.15 mmol, 1.5 eq) was added slowly to a stirred solution of alkyne **4.19** (25.9 mg, 0.12 mmol, 1.2 eq) in THF (2.0 mL) at -78 $^\circ\text{C}$. The yellowish solution was stirred for 90 min at -78 $^\circ\text{C}$. A solution of aldehyde **4.20** (26.4 mg, 0.10 mmol, 1 eq) in THF (0.35 mL) was added dropwise and the solution became colorless. The reaction was stirred overnight at -78 $^\circ\text{C}$ for one night. A sat. aq. NH_4Cl solution was then added, the layers were separated and the aqueous phase extracted with Et_2O (3 x 4 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (90:10 hexane/EtOAc) afforded a mixture of diastereomeric propargylic alcohols **4.39** and **4.40** in a 7:3 dr (29.3 mg, 61%) as a colorless oil. The diastereomeric ratio was determined by NMR.



(2*S*,3*S*,6*R*,8*S*)-9-(benzyloxy)-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-6,8-dimethylnon-4-yn-3-ol (4.39)

CARREIRA ASYMMETRIC ALKYNYLATION

Zinc triflate (474 mg, 1.3 mmol, 4.3 eq) was flame-dried under vacuum; (-)-N-methylephedrine (179.3 mg, 1 mmol, 3.3 eq) was added, and the flask was purged with nitrogen for 15 min. Toluene (6.6 mL) was added, followed by TEA (140 μ l, 1 mmol, 3.3 eq). After 2 h, a solution of the alkyne **4.19** (220 mg, 1 mmol, 3.3 eq) in toluene (0.4 mL) was added. After 30 min, a solution of the aldehyde **4.20** (79.3 mg, 0.3 mmol, 1 equiv) in toluene (1 mL) was slowly added through a syringe pump over 6 h. The reaction mixture was left under stirring overnight. The reaction was monitored by TLC (95:5 benzene/Et₂O). On disappearance of the aldehyde, the reaction mixture was quenched with a sat. aq. NH₄Cl solution (12 mL), and extracted with Et₂O (3 x 15 mL). The combined organic extracts were dried and concentrated under reduced pressure. Purification of the crude product by flash chromatography (80:20 hexane/EtOAc) afforded diastereoisomerically pure propargylic alcohol **4.39** (96.6 mg, 67%) as a colorless oil.

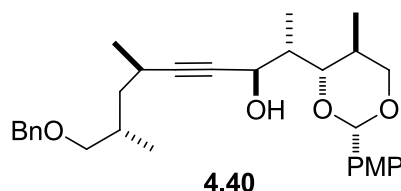
HYDRIDE REDUCTION

Li(*t*-BuO)₃AlH in THF (1M, 0.24 mL, 0.23 mmol, 3 eq), was added to a solution of **4.41** (37.2 mg, 0.078 mmol, 1 eq) in THF (0.8 mL). After 3 min of stirring at R.T. the reaction was quenched with sat. aq. NH₄Cl solution (0.11 mL) and stirred for 1 h; then it was dried, filtered and concentrated under reduced pressure. Purification of the crude product by flash chromatography (80:20 hexane/EtOAc) afforded a mixture of distereomeric propargylic alcohols **4.39** and **4.40** in a 75:25 dr (36 mg, 96%) as a colorless oil. The diastereomeric ratio was determined by NMR.

NOYORI TRANSFER HYDROGENATION

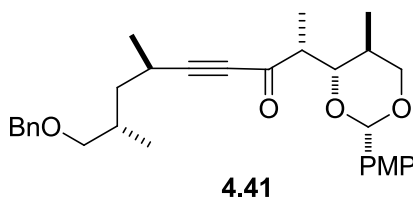
(*S,S*) Noyori Catalyst (183 mg, 0.29 mmol, 0.2 eq) was added to a solution of **4.41** (690 mg, 1.44 mmol, 1 eq) in *i*PrOH (15 mL). The reaction mixture was stirred at R.T. for 12 h. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (80:20 hexane/EtOAc) affording diastereoisomerically pure propargylic alcohol **4.39** (678 mg, 98%) as a colorless oil.

R_f 0.42 (85:15 hexane/EtOAc); $[\alpha]_D^{20} = +35.89$ ($c = 1.03$, CHCl₃); ¹H NMR (400 MHz, C₆D₆): $\delta = 0.45$ (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.12-1.22 (m, 1H), 1.25 (d, $J = 6.8$ Hz, 3H), 1.38 (d, $J = 6.8$ Hz, 3H), 1.77-1.84 (m, 1H), 1.97-2.05 (m, 2H), 2.25 (br s, 1H), 2.38-2.43 (m, 1H), 2.62-2.69 (m, 1H), 3.16-3.31 (m, 2H), 3.34 (s, 3H), 3.34-3.43 (m, 1H), 3.87 (dd, $J = 10.0$ Hz, 2.0 Hz, 1H), 4.02 (dd, $J = 11.2$ Hz, 4.8 Hz, 1H), 4.46 (s, 2H), 4.75 (d, $J = 5.6$ Hz, 1H), 5.61 (s, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 7.18-7.43 (m, 5H), 7.68 (d, $J = 8.6$ Hz, 2H); ¹³C NMR (100 MHz, C₆D₆): $\delta = 9.2, 12.1, 17.1, 22.6, 24.5, 31.2, 32.8, 41.7, 41.8, 55.2, 67.0, 73.6, 76.7, 82.7, 85.8, 89.7, 102.0, 114.3, 129.0, 132.4, 136.7, 161.2$; IR (CHCl₃): $\nu = 1462, 1518, 1615, 1732, 2851, 2874, 2933, 2969, 3024, 3040, 3501$; HRMS (ESI): calcd. for: 503.27680 [$M+Na$]⁺; found: 503.27575.



(2*S*,3*S*,6*R*,8*S*)-9-(benzyloxy)-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-6,8-dimethylnon-4-yn-3-ol (4.40)

Zinc triflate (474 mg, 1.3 mmol, 4.3 eq) was flame-dried under vacuum; (+)-*N*-methylephedrine (179.3 mg, 1 mmol, 3.3 eq) was added, and the flask was purged with nitrogen for 15 min. Toluene (6.6 mL) was added, followed by TEA (140 μ L, 1 mmol, 3.3 eq). After 2 h, a solution of the alkyne **4.19** (220 mg, 1 mmol, 3.3 eq) in toluene (0.4 mL) was added. After 30 min, a solution of the aldehyde **4.38** (79.3 mg, 0.3 mmol, 1 eq) in toluene (1 mL) was slowly added. The reaction mixture was stirred overnight and monitored by TLC (95:5 benzene/Et₂O). On disappearance of the aldehyde, the reaction mixture was quenched with a sat. aq. NH₄Cl solution (12 mL), and extracted with Et₂O (3 x 15 mL). The combined organic extracts were dried and concentrated under reduced pressure. Purification of the crude product by flash chromatography (80:20 hexane/EtOAc) afforded a mixture of diastereomeric propargylic alcohols **4.39** and **4.40** in 7:93 ratio (7.2 mg, 5%) as a colorless oil. The diastereomeric ratio was determined by NMR.

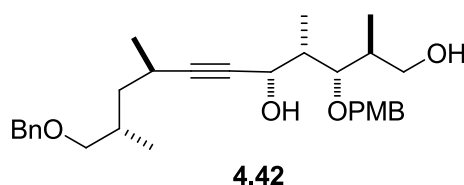


(2*R*,6*R*,8*S*)-9-(benzyloxy)-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-6,8-dimethylnon-4-yn-3-one (4.41)

Alkyne **4.19** (969.1 mg, 4.48 mmol, 1 eq) was dissolved in THF (45.2 mL) and cooled to -78 °C, then *n*BuLi in hexane (1.6 M, 45.2 mL, 1 eq) was added slowly. After 5 min, the mixture was warmed to 0 °C and stirred for 30 min. The solution was then cooled to -78 °C and Weinreb amide **4.38** (1.64 g, 5.06 mmol) in THF (2.8 mL) was added slowly. After 5 min the solution was warmed to 0 °C and stirred for 1 h. The reaction was quenched with a sat. aq. NH₄Cl solution (2.8 mL). The aqueous phase was extracted with Et₂O and the combined organic extracts were washed with brine and dried over Na₂SO₄. Filtration and concentration under reduced pressure, followed by flash chromatography (90:10 hexane/EtOAc) afforded the ynone **4.41** (1.5 g, 70% yield) as a pale yellow oil:

R_f 0.53 (80:20 hexane/EtOAc); $[\alpha]_D^{22} = +46.44$ ($c = 1.00$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.81$ (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H), 1.27 (d, $J = 6.6$ Hz, 3H), 1.27 (d, $J = 7.2$ Hz, 3H), 1.74 (ddd, $J = 14.4$ Hz, 10.5 Hz, 4.2 Hz, 1H), 2.00-2.11 (m, 2H), 2.76 (m, 2H), 3.31 (d, $J =$

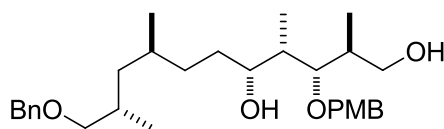
6.2 Hz, 2H) 3.55 (t, $J = 11.1$ Hz, 1H), 3.80 (s, 3H), 4.15 (dd, $J = 13.3$ Hz, 6.4 Hz, 1H), 4.23 (dd, $J = 10.1$ Hz, 2.8 Hz, 1H), 4.50 (s, 2H), 5.48 (s, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.33 (m, 7H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 8.3, 11.8, 16.5, 20.8, 24.0, 30.9, 32.0, 40.2, 49.4, 55.1, 72.8, 72.9, 75.8, 80.4, 82.8, 98.1, 100.9, 113.3, 127.3, 127.4, 128.3, 131.2, 138.8, 159.8, 188.7$; IR (neat): $\nu = 699, 737, 829, 1034, 1078, 1127, 1249, 1303, 1372, 1392, 1456, 1518, 1615, 1678, 1737, 2207, 2850, 2874, 2933, 2968$; HRMS (ESI): calcd. for $\text{C}_{30}\text{H}_{38}\text{O}_5\text{Na}$: 501.26115 $[M+\text{Na}]^+$; found: 501,26102.



(2S,3S,4S,5S,8R,10S)-11-(benzyloxy)-3-((4-methoxybenzyl)oxy)-2,4,8,10-tetramethylundec-6-yne-1,5-diol (4.42)

A solution of PMP acetal **4.39** (96.6 mg, 0.2 mmol, 1 eq) in DCM (20 ml) was cooled to -20 °C; DIBAL-H in hexane (1.0 M, 2.0 mL, 2 mmol, 10 eq) was added over 10 min. After 30 min, the temperature was raised to 0 °C, and the reaction mixture was stirred for additional 2 h. On completion of the reaction (75:25 hexane/EtOAc) the mixture was quenched with a sat. aq. solution of Rochelle's salt (2.5 ml). After 1 h under vigorous stirring, the reaction mixture was diluted with Et_2O (190 mL), washed with a sat. aq. solution of Rochelle's salt and brine, dried and concentrated under reduced pressure. The residue was purified by flash chromatography (85:15 hexane/EtOAc) to afford the product **4.42** as a pale yellow oil (72.4 mg, 75% yield).

R_f 0.13 (70:30 hexane/EtOAc); $[\alpha]_{\text{D}}^{28} = +12.55$ ($c = 1.04$, CHCl_3); ^1H NMR (400 MHz, C_6D_6): $\delta = 0.97$ (d, $J = 7.2$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 1.10-1.18 (m, 1H), 1.24 (d, $J = 6.8$ Hz, 3H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.74-1.81 (m, 1H), 2.04-2.10 (m, 2H), 2.34-2.42 (m + br s, 2H), 2.60-2.66 (m, 1H), 3.22-3.31 (m, 2H), 3.41 (s, 3H), 3.69 (dd, $J = 10.8$ Hz, 5.6 Hz, 1H), 3.81 (dd, $J = 10.8$ Hz, 4.0 Hz, 1H), 3.97-4.03 (m, 1H), 4.45 (s, 2H), 4.52 (dd, $J = 7.2$ Hz, 2.0 Hz, 2H), 4.74 (AB system, $\nu_A = 4.77$, $\nu_B = 4.71$, $J_{AB} = 10.8$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 7.19-7.43 (m, 7H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = 10.9, 15.1, 17.1, 22.5, 24.5, 32.8, 39.2, 41.8, 43.8, 55.2, 66.0, 66.6, 73.7, 75.0, 76.8, 82.9, 83.9, 90.6, 114.6, 129.0, 130.0, 131.9, 139.7, 160.1$; IR (neat): $\nu = 1263, 1455, 1514, 1613, 1730, 2874, 2932, 2963, 3024, 3048$; HRMS (ESI): calcd. for $\text{C}_{30}\text{H}_{42}\text{O}_5\text{Na}$: 505.29245 $[M+\text{Na}]^+$; found: 505.29115.

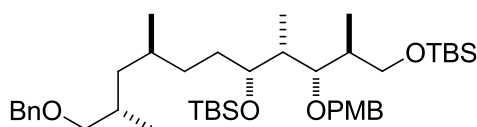


4.43

(2*S*,3*S*,4*S*,5*R*,8*S*,10*S*)-11-(benzyloxy)-3-((4-methoxybenzyl)oxy)-2,4,8,10-tetramethylundecane-1,5-diol (4.43)

Wilkinson's catalyst [Rh(PPh₃)₃Cl] (13.9 mg, 0.015 mmol, 0.1 eq) was added to a degassed solution of alkyne **4.42** (72.4 mg, 0.15 mmol, 1 eq) in benzene (6 mL) in an autoclave. The reaction mixture was purged with hydrogen, and stirred overnight under 60 psi (approximately 4 bar) of H₂ pressure. Silica gel was added to the reaction mixture and the solvent was evaporated under reduced pressure. Purification of the crude product by flash chromatography (70:30 hexane/EtOAc) afforded diol **4.43** (51.1 mg, 70% yield) as a yellowish oil.

R_f 0.13 (70:30 hexane/EtOAc); $[\alpha]_D^{28} = +14.50$ ($c = 1.00$, CHCl₃); ¹H NMR (400 MHz, C₆D₆): $\delta = 1.01$ (d, $J = 7.0$ Hz, 3H), 1.04 (d, $J = 6.4$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 3H), 1.16 (d, $J = 7.0$ Hz, 3H), 1.02-1.24 (m, 1H), 1.56-1.86 (m, 7H), 2.00-2.14 (m, 2H), 3.26 (dd, $J = 8.8$ Hz, 6.4 Hz, 1H), 3.35 (dd, $J = 8.8$ Hz, 5.6 Hz, 1H), 3.40 (s, 3H), 3.63-3.69 (m, 2H), 3.78-3.82 (m, 2H), 4.47 (d, $J = 3.0$ Hz, 2H), 4.65 (AB system, $\nu_A = 4.65$, $\nu_B = 4.59$, $J_{AB} = 10.6$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 7.19-7.44 (m, 7H); ¹³C NMR (100 MHz, C₆D₆): $\delta = 8.6$, 15.2, 18.7, 21.1, 31.1, 31.9, 33.3, 34.1, 38.6, 40.4, 42.4, 55.2, 65.6, 73.6, 74.7, 75.5, 76.5, 86.2, 114.7, 128.0, 128.1, 129.0, 130.2, 131.4, 140.0, 160.3; IR (film): $\nu = 1247$, 1301, 1374, 1455, 1514, 1613, 1738, 2871, 2928, 2955, 3442; HRMS (ESI): calcd. for C₃₀H₄₆O₅Na: 509.32375 [$M+Na$]⁺; found: 509.32290.

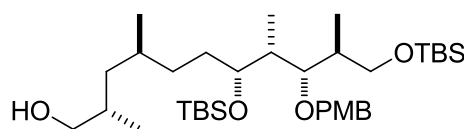


4.44

(5*R*,6*R*,7*S*,8*S*)-5-((3*S*,5*S*)-6-(benzyloxy)-3,5-dimethylhexyl)-7-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,11,11,12,12-decamethyl-4,10-dioxa-3,11-disilatridecane (4.44)

Freshly distilled 2,6-lutidine (93 μ L, 0.8 mmol, 8 eq) and TBSOTf (69 μ L, 0.3 mmol, 3 eq) were added to a stirred solution of diol **4.43** (48.6 mg, 0.1 mmol, 1 eq) in DCM (2.5 mL) at -20 °C. The reaction was monitored by TLC (80:20 hexane/EtOAc). On completion of the reaction (approximately 1.5 hours), the mixture was quenched with a sat. aq. NH₄Cl solution. The organic phase was separated and the aqueous layer extracted with DCM. The combined organic extracts were washed with brine, dried over Na₂SO₄ and evaporated under reduced pressure. Purification of the crude product by flash chromatography (80:20 hexane/EtOAc) afforded the product **4.44** (69.4 mg, 97% yield) as a colorless oil.

R_f 0.67 (80:20 hexane/EtOAc); $[\alpha]_D^{26} = +1.23$ ($c = 1.05$, CHCl_3); $^1\text{H NMR}$ (400 MHz, C_6D_6): $\delta = 0.19$ (s, 3H), 0.26 (s, 6H), 0.40 (s, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.12 (s, 9H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.18 (s, 9H), 1.21 (d, $J = 6.8$ Hz, 3H), 1.34 (d, $J = 6.8$ Hz, 3H), 1.29-1.35 (m, 1H), 1.59-1.90 (m, 6H), 2.05-2.14 (m, 3H), 3.28 (dd, $J = 8.8$ Hz, 6.4 Hz, 1H), 3.37 (dd, $J = 8.8$ Hz, 5.6 Hz, 1H), 3.42 (s, 3H), 3.77-3.85 (m, 2H), 3.93-3.99 (m, 2H), 4.48 (d, $J = 2.8$ Hz, 2H), 4.78 (AB system, $\nu_A = 4.82$, $\nu_B = 4.75$, $J_{AB} = 10.8$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 7.19-7.48 (m, 7H); $^{13}\text{C NMR}$ (100 MHz, C_6D_6): $\delta = -4.7$, -3.6, -3.4, 1.8, 11.0, 16.0, 18.7, 18.9, 21.2, 26.3, 26.7, 26.8, 31.3, 32.0, 32.2, 32.8, 39.8, 40.6, 42.3, 55.2, 65.5, 73.6, 74.7, 75.4, 76.5, 81.5, 114.5, 129.0, 129.4, 132.6, 140.0, 160.0; IR (film): $\nu = 1251$, 1360, 1462, 1514, 1586, 1613, 2856, 2928, 2955; HRMS (ESI): calcd. for $\text{C}_{42}\text{H}_{74}\text{O}_5\text{Si}_2\text{Na}$: 737.49670 $[M+\text{Na}]^+$; found: 737.49705.

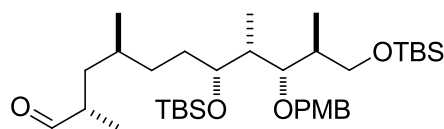


4.45

(2*S*,4*S*,7*R*,8*R*,9*S*,10*S*)-7,11-bis-(*tert*-butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzyloxy)-2,4,8,10-tetramethyl-undecan-1-ol (4.45)

Raney-Nickel was washed with water until the washings were pH neutral, and then rinsed five times with absolute EtOH. A solution of substrate **4.44** (69.4 mg, 0.097 mmol, 1 eq) in absolute EtOH (6.5 mL) was added. The mixture was accurately degassed and then purged three times with hydrogen. After stirring for 24 h, the Raney-Nickel was removed by filtration and the filtrate, after concentration under reduced pressure, was purified by flash chromatography (90:10 hexane/EtOAc) to afford alcohol **4.45** (49.1 mg, 81% yield) as a colorless oil.

R_f 0.34 (80:20 hexane/EtOAc); $[\alpha]_D^{18} = -4.72$ ($c = 1.10$, CHCl_3); $^1\text{H NMR}$ (400 MHz, C_6D_6): $\delta = 0.19$ (s, 6H), 0.25 (s, 6H), 0.93-1.04 (m, 1H), 1.01 (d, $J = 6.8$ Hz, 3H), 1.04 (d, $J = 6.0$ Hz, 3H), 1.12 (s, 9H), 1.17 (s, 9H), 1.10-1.20 (m, 2H), 1.20 (d, $J = 7.2$ Hz, 3H), 1.29 (d, $J = 7.2$ Hz, 3H), 1.42-1.90 (m, 5H), 2.09-2.15 (m, 2H), 3.27-3.32 (m, 1H), 3.39-3.43 (m, 1H), 3.44 (s, 3H), 3.76-3.84 (m, 2H), 3.91-4.00 (m, 2H), 4.77 (AB system, $\nu_A = 4.81$, $\nu_B = 4.73$, $J_{AB} = 11.2$ Hz, 2H), 6.95 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, C_6D_6): $\delta = -4.7$, -3.6, -3.4, 11.0, 16.0, 18.0, 18.9, 19.0, 21.2, 26.7, 31.3, 32.1, 32.7, 33.9, 39.8, 40.6, 41.8, 55.2, 65.5, 68.5, 74.7, 75.3, 81.4, 114.5, 129.5, 132.6, 160.0; IR (film): $\nu = 1250$, 1301, 1360, 1387, 1463, 1471, 1515, 1587, 1614, 2857, 2928, 2954, 3377; HRMS (ESI): calcd. for $\text{C}_{35}\text{H}_{69}\text{O}_5\text{Si}_2$: 625.46780 $[M+\text{H}]^+$; found: 625.46921.

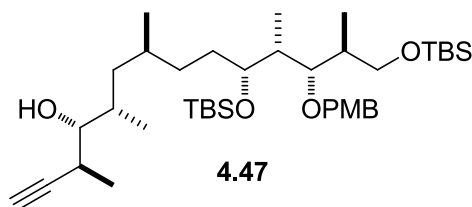


4.46

(2*S*,4*S*,7*R*,8*R*,9*S*,10*S*)-7,11-bis-(*tert*-butyl-dimethyl-silanyloxy)-9-(4-methoxy-benzyloxy)-2,4,8,10-tetramethyl-undecanal (4.46).

Solid TPAP (2.4 mg, 0.0068 mmol, 0.05 eq) was added to a stirred solution of alcohol **4.45** (84.4 mg, 0.135 mmol, 1 eq) and NMO (23.7 mg, 0.202 mmol, 1.5 eq) in DCM (0.3 mL), in presence of 4 Å molecular sieves (500 mg/mmol) at R.T. On completion of the reaction, the mixture was filtered through a pad of celite (rinsed with EtOAc). The solvent was removed under reduced pressure, and the crude aldehyde **4.46**, obtained quantitatively, was used without further purification.

R_f 0.55 (80:20 hexane/EtOAc); $^1\text{H NMR}$ (400 MHz, C_6D_6): δ = 0.18 (s, 6H), 0.38 (s, 6H), 0.98 (d, J = 7.2 Hz, 3H), 0.90-1.04 (m, 1H), 1.10 (d, J = 6.4 Hz, 3H), 1.11 (s, 9H), 1.15 (s, 9H), 1.17 (d, J = 7.2 Hz, 3H), 1.10-1.20 (m, 2H), 1.24 (d, J = 7.2 Hz, 3H), 1.21-2.12 (m, 7H), 3.46 (s, 3H), 3.75-4.04 (m, 4H), 4.76 (AB system, ν_A = 4.81, ν_B = 4.72, J_{AB} = 11.2 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 9.44 (d, J = 2.0 Hz, 1H).



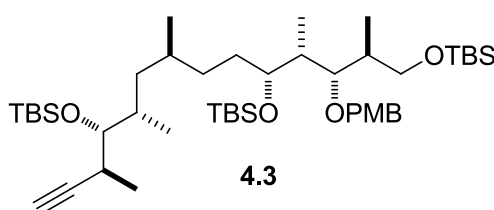
4.47

(3*S*,4*R*,5*S*,7*S*,10*R*,11*R*,12*S*,13*S*)-10,14-bis-(*tert*-butyl-dimethyl-silanyloxy)-12-(4-methoxy-benzyloxy)-3,5,7,11,13-pentamethyl-tetradec-1-yn-4-ol (4.47)

Triphenylphosphine (re-crystallized from ethanol prior to use, 1.2 mg, 0.0045 mmol, 0.05 eq), the crude aldehyde **4.47** (56.0 mg, 0.09 mmol, 1 eq) and (*R*)-mesyl-butynol **4.21** (20.0 mg, 0.135 mmol, 1.5 eq) were sequentially added to a cooled (-78 °C) solution of $\text{Pd}(\text{OAc})_2$ (1.0 mg, 0.0045 mmol, 0.05 eq) in THF (0.9 ml). Diethylzinc in hexane (1.0 M, 270 μl , 0.27 mmol, 3 eq) was added over 15 min. After 10 min., the temperature was raised to -20 °C, and the reaction mixture was stirred overnight at -20 °C. The mixture was quenched with $\text{NH}_4\text{Cl}/\text{Et}_2\text{O}$ 1:1. The Et_2O layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash chromatography (95:5 hexane/EtOAc) to afford the product **4.47** as a yellow oil (50.2 mg, 82% yield over two steps) with very high diastereoselectivity (dr > 98:2).

R_f 0.49 (80:20 hexane/EtOAc); $[\alpha]_D^{22}$ = -4.51 (c = 0.61, CHCl_3); $^1\text{H NMR}$ (400 MHz, C_6D_6): δ = 0.20 (s, 6H), 0.27 (s, 6H), 1.04 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 1.13 (s, 9H), 1.17 (d, J = 6.8 Hz, 3H), 1.18 (s, 9H), 1.22 (d, J = 6.9 Hz, 3H), 1.31 (d, J = 6.9 Hz, 3H), 1.62-1.95 (m, 9H),

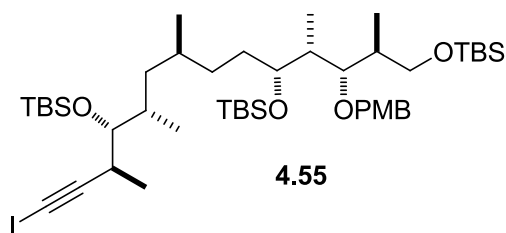
2.11-2.19 (m, 2H), 2.62-2.67 (m, 1H), 3.28 (dd, $J = 10.8$ Hz, 6.0 Hz, 1H), 3.43 (s, 3H), 3.80-3.87 (m, 2H), 3.92-4.00 (m, 2H), 4.80 (AB system, $\nu_A = 4.83$, $\nu_B = 4.77$, $J_{AB} = 10.8$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = -4.7, -3.6, -3.4, 11.1, 14.5, 16.0, 18.0, 18.9, 21.2, 26.7, 26.8, 31.0, 31.7, 32.1, 32.7, 33.6, 39.9, 40.7, 42.1, 55.2, 65.5, 71.7, 74.6, 75.5, 77.5, 81.4, 86.6, 114.5, 129.5, 132.6, 160.0$; IR (CHCl_3): $\nu = 1255, 1301, 1386, 1462, 1470, 1514, 1613, 1727, 2655, 2663, 2857, 2882, 2930, 2956, 3306$; HRMS (ESI): calcd. for $\text{C}_{39}\text{H}_{72}\text{O}_5\text{Si}_2\text{Na}$: 699.48105 $[M+\text{Na}]^+$; found: 699.48154.



(5*R*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-5-((*S*)-but-3-yn-2-yl)-11-((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (4.3)

Freshly distilled 2,6-lutidine (9.3 μl , 0.08 mmol, 4 eq) and TBSOTf (6.9 μl , 0.03 mmol, 1.5 eq) were added to a stirred solution of compound **4.47** (13.5 mg, 0.02 mmol, 1 eq) in DCM (0.5 mL) at -20 °C. On completion of the reaction (approximately 2 hours), the mixture was quenched with a sat. aq. NH_4Cl solution. The organic phase was separated and the aqueous layer extracted with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. Purification of the crude product by flash chromatography (70:30 hexane/EtOAc) afforded compound **4.3** (15.8 mg, 100% yield) as a colorless oil.

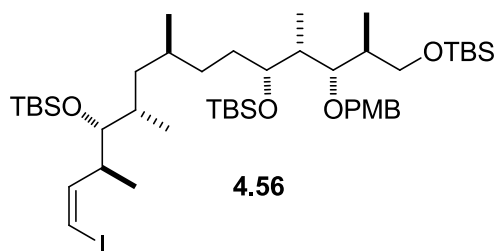
R_f 0.80 (80:20 hexane/EtOAc); $[\alpha]_D^{22} = -3.10$ ($c = 0.51$, CHCl_3); ^1H NMR (400 MHz, C_6D_6): $\delta = 0.21$ (s, 6H), 0.25 (s, 3H), 0.26 (s, 3H), 0.27 (s, 3H), 0.28 (s, 3H), 1.10 (d, $J = 7.2$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.13 (s, 9H), 1.16 (s, 9H), 1.19 (s, 9H), 1.23 (d, $J = 7.2$ Hz, 3H), 1.30 (d, $J = 6.8$ Hz, 3H), 1.31 (d, $J = 6.4$ Hz, 3H), 1.13-1.32 (m, 2H), 1.64-1.81 (m, 4H), 1.96-2.01 (m, 1H), 2.02 (d, $J = 2.4$ Hz, 1H), 2.13-2.17 (m, 3H), 2.71-2.79 (m, 1H), 3.43 (s, 3H), 3.69-4.01 (m, 5H), 4.80 (AB system, $\nu_A = 4.83$, $\nu_B = 4.77$, $J_{AB} = 10.8$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6): $\delta = -4.7, -3.6, -3.3, -3.2, -3.1, 11.0, 15.9, 16.0, 18.0, 20.9, 26.6, 26.7, 26.8, 31.4, 32.4, 32.7, 32.9, 34.1, 39.9, 40.7, 43.7, 55.2, 65.6, 71.2, 74.7, 75.4, 78.5, 81.5, 87.9, 114.5, 129.5, 132.6, 160.0$; IR (film): $\nu = 1256, 1471, 1514, 1587, 1614, 2856, 2884, 2904, 2929, 2957, 3312$; HRMS (ESI): calcd. for $\text{C}_{45}\text{H}_{86}\text{O}_5\text{Si}_3\text{Na}$: 813.56753 $[M+\text{Na}]^+$; found: 813.56718.

6.7 Synthesis of (*Z*)-Vinyl Iodide C10-C26

(5*R*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-11-(*tert*-butyldimethylsilyloxy)-5-((*S*)-4-iodobut-3-yn-2-yl)-13-(4-methoxybenzyloxy)-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (4.55)

A 1.6 M solution of *n*BuLi in hexane (0.22 mL, 0.35 mmol, 1.2 eq) was added dropwise over 5 min to a solution of alkyne **4.3** (229 mg, 0.29 mmol, 1 eq) in THF (1.5 mL) at -50 °C. After 1 h, a solution of iodine (125 mg, 0.50 mmol, 1.7 eq) in THF (0.10 mL) was added. The mixture was stirred at -50 °C for 30 min, then warmed to a R.T. over 30 min. After quenching by the addition of sat. aq. Na₂S₂O₃ solution (0.8 mL) and brine (0.8 mL), the mixture was extracted with EtOAc (3 x 3 mL) and the combined organic layers were washed with brine (2 x 4 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (9.5:0.5 hexane/EtOAc) to give the desired product **4.55** (266 mg, 100% yield) as a colorless oil.

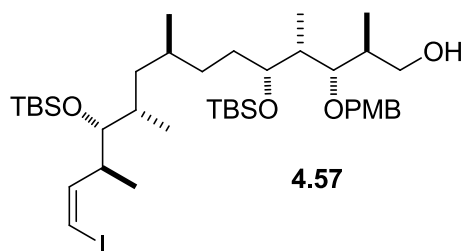
R_f 0.40 (9.5:0.5 hexane/EtOAc); $[\alpha]_D^{19} = -24$ ($c = 0.4$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.07$ (s, 9H), 0.10 (s, 6H), 0.11 (s, 3H), 0.85 (d, $J = 6.7$ Hz, 3H), 0.88 (d, $J = 6.5$ Hz, 3H), 0.93 (s, 9H), 0.93 (s, 9H), 0.94 (s, 9H), 0.94 (d, $J = 6.7$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.98-1.05 (m, 2H), 1.18 (d, $J = 7.1$ Hz, 3H), 1.27-1.50 (m, 4H), 1.63 (m, 1H), 1.81 (m, 2H), 1.91 (m, 1H), 2.76 (m, 1H), 3.48 (dd, $J = 4.3$ Hz, 6.7 Hz, 1H), 3.52 (dd, $J = 2.5$ Hz, 5.7 Hz, 1H), 3.69 (m, 3H), 3.83 (s, 3H), 4.50 (d, $J_{AB} = 10.9$ Hz, 1H, upfield part of an AB system), 4.57 (d, $J_{AB} = 10.9$ Hz, 1H, downfield part of an AB system), 6.89 (d, $J = 8.6$ Hz, 2H), 7.27 (d, $J = 8.6$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -3.7$ (CH₃), -3.6 (CH₃), -3.3 (CH₃), -3.2 (CH₃), -3.1 (CH₃), 10.8 (CH₃), 15.4 (CH₃), 16.0 (CH₃), 18.0 (CH₃), 18.9 (C₀), 19.0 (C₀), 19.6 (C₀), 20.7 (CH₃), 26.7 (CH₃), 26.8 (CH₃), 30.4 (CH₂), 31.1 (CH), 32.3 (CH₂), 32.5 (CH₂), 33.7 (CH), 35.1 (CH), 39.5 (CH), 40.3 (CH), 43.5 (CH₂), 56.0 (CH₃), 65.3 (CH₂), 74.7 (CH₂), 74.9 (CH), 78.3 (CH), 81.7 (CH), 114.4 (CH), 129.6 (CH), 132.4 (C₀), 159.6 (C₀); IR (neat): $\nu = 670, 773, 835, 939, 1078, 1171, 1250, 1301, 1361, 1387, 1462, 1514, 1613, 2856, 2928$. HRMS (ESI): calcd. for C₄₅H₈₅IO₅Si₃Na: 939.46417 [$M + Na$]⁺; found: 939.46033.



(5*R*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-11-(*tert*-butyldimethylsilyloxy)-5-((*S*,*Z*)-4-iodobut-3-en-2-yl)-13-(4-methoxybenzyloxy)-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (4.56)

A solution of iodoalkyne **4.55** (266 mg, 0.29 mmol, 1 eq) in THF (0.7 mL) and *i*PrOH (0.7 mL) at R.T. was treated with TEA (53 μ L, 0.377 mmol, 1.3 eq) and NBSH (74.0 mg, 0.34 mmol, 1.1 eq). After 12 h, additional TEA (24 μ L, 0.174 mmol, 0.6 eq) and NBSH (33.0 mg, 0.15 mmol, 0.5 eq) were added, and the mixture was stirred for 12 h. The reaction was quenched by adding water (1.7 mL) and the mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (2 x 3 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (9.5:0.5 hexane/EtOAc) to give the desired product **4.56** (245 mg, 92% yield) as a colorless oil.

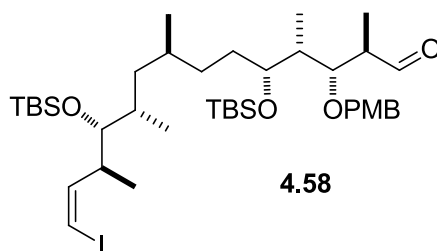
R_f 0.85 (8:2 hexane/EtOAc); $[\alpha]_D^{23} = +2.9$ ($c = 0.5$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.07$ (s, 6H), 0.08 (s, 3H), 0.09 (s, 3H), 0.10 (s, 6H), 0.86 (d, $J = 7.2$ Hz, 3H), 0.90 (d, $J = 8.0$ Hz, 3H), 0.93 (s, 30H), 0.99 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 7.0$ Hz, 3H), 1.28-1.47 (m, 6H), 1.60-1.71 (m, 2H), 1.80 (m, 1H), 1.90 (m, 1H), 2.71 (m, 1H), 3.48 (m, 2H), 3.68 (m, 3H), 3.82 (s, 3H), 4.49 (d, $J_{AB} = 10.9$ Hz, 1H, upfield part of an AB system), 4.57 (d, $J_{AB} = 10.9$ Hz, 1H, downfield part of an AB system), 6.14 (d, $J = 7.3$ Hz, 1H), 6.29 (dd, $J = 8.8$ Hz, 7.3 Hz, 1H), 6.89 (d, $J = 8.7$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -5.3$ (CH₃), -5.2 (CH₃), -4.3 (CH₃), -4.0 (CH₃), -3.7 (CH₃), -3.6 (CH₃), 10.1 (CH₃), 15.2 (CH₃), 15.8 (CH₃), 17.7 (CH₃), 18.1 (C₀), 18.3 (C₀), 18.4 (C₀), 20.5 (CH₃), 26.0 (CH₃), 26.1 (CH₃), 26.2 (CH₃), 29.7 (CH₂), 30.8 (CH), 31.1 (CH₂), 31.6 (CH₂), 35.3 (CH), 38.9 (CH), 39.6 (CH), 41.5 (CH₂), 43.5 (CH), 55.2 (CH₃), 64.6 (CH₂), 74.0 (CH₂), 74.2 (CH), 79.1 (CH), 81.1 (CH), 81.2 (CH), 113.7 (CH), 128.9 (CH), 131.6 (C₀), 144.2 (CH), 158.9 (C₀); IR (neat): $\nu = 773, 805, 835, 1079, 1256, 1377, 1462, 1514, 1611, 2855, 2927, 2956$; HRMS (ESI): calcd. for C₄₅H₈₇IO₅Si₃Na: 941.47982 [$M + Na$]⁺; found: 941.47749.



(2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*,*Z*)-5,11-bis(*tert*-butyldimethylsilyloxy)-14-iodo-3-(4-methoxybenzyloxy)-2,4,8,10,12-pentamethyltetradec-13-en-1-ol (4.57)

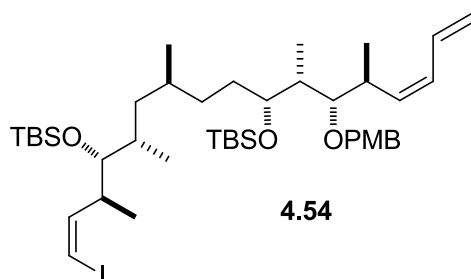
A solution of compound **4.56** (680 mg, 0.74 mmol, 1 eq) in THF (3.8 mL) at 0 °C was treated with a solution of HF·Py in THF/pyridine [16.5 mL, prepared by slow addition of commercially available 70% HF in pyridine (1.3 mL) to a mixture of pyridine (5.0 mL) and THF (10.2 mL)]. The reaction mixture was warmed to R.T. and stirred for 3 h. After quenching the reaction by addition of sat. aq. NaHCO₃ solution (30 mL), the mixture was extracted with EtOAc (4 x 20 mL). The combined organic extracts were washed with sat. aq. CuSO₄ solution (3 x 15 mL) and brine (2 x 40 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (90:10 hexane/EtOAc) to give the desired product **4.57** (477 mg, 80% yield) as a colorless oil.

R_f 0.29 (08:20 hexane/EtOAc); $[\alpha]_D^{16} = +9.6$ ($c = 0.9$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.07$ (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.88 (d, $J = 6.5$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.86-0.91 (m, 2H), 0.94 (s, 18H), 1.01 (d, $J = 7.0$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 1.13 (d, $J = 7.1$ Hz, 3H), 1.28-1.47 (m, 4H), 1.60-1.71 (m, 2H), 1.90 (m, 1H), 1.96 (m, 1H), 2.71 (m, 1H), 2.87 (br s, 1H), 3.48 (m, 2H), 3.61 (m, 2H), 3.83 (s, 3H), 3.84 (m, 1H), 4.55 (s, 2H), 6.13 (d, $J = 7.3$ Hz, 1H), 6.30 (t, $J = 7.3$ Hz, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 7.28 (d, $J = 8.6$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -3.7$ (CH₃), -3.1 (CH₃), -2.9 (CH₃), 10.7 (CH₃), 16.5 (CH₃), 16.7 (CH₃), 18.5 (CH₃), 18.8 (C₀), 19.1 (C₀), 21.2 (CH₃), 26.7 (CH₃), 26.9 (CH₃), 31.5 (CH), 32.3 (CH₂), 32.8 (CH₂), 36.2 (CH), 37.6 (CH), 41.2 (CH), 42.1 (CH₂), 44.0 (CH), 56.0 (CH₃), 65.9 (CH₂), 74.3 (CH), 76.0 (CH₂), 79.8 (CH), 81.9 (CH), 86.7 (CH), 114.6 (CH), 130.0 (CH), 131.2 (C₀), 144.8 (CH), 159.9 (C₀); IR (neat): $\nu = 773, 805, 1028, 1255, 1377, 1461, 1514, 1614, 2067, 2959, 3448$; HRMS (ESI⁺): calcd. for C₃₉H₇₃IO₅Si₂Na [$M + Na$]⁺: 827.39334; found: 827.39126.



(2*R*,3*R*,4*R*,5*R*,8*S*,10*S*,11*R*,12*S*,*Z*)-5,11-bis(*tert*-butyldimethylsilyloxy)-14-iodo-3-(4-methoxybenzyloxy)-2,4,8,10,12-pentamethyltetradec-13-enal (4.58)

A solution of alcohol **4.57** (394 mg, 0.49 mmol, 1 eq) in DCM (3.1 mL) at 0 °C was treated with pyridine (0.10 mL, 1.2 mmol, 2.5 eq) and DMP (250 mg, 0.59 mmol, 1.2 eq). The reaction mixture was warmed to R.T. and stirred for 1 h. After completion of the reaction, sat. aq. NaHCO₃ solution (8.0 mL) and Na₂S₂O₃ (888 mg, 3.6 mmol) were added. The resulting mixture was stirred for 30 min, then the phases were separated and the aqueous phase was extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried and evaporated under reduced pressure, providing the crude aldehyde **4.58**, which was used without further purification. *R_f* 0.60 (80:20 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.07 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.84-0.94 (m, 2H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.93 (s, 9H), 0.94 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.28-1.49 (m, 4H), 1.58-1.73 (m, 2H), 1.90 (m, 1H), 2.71 (m, 1H), 2.80 (m, 1H), 3.49 (dd, *J* = 3.7 Hz, 1H), 3.68 (m, 2H), 3.83 (s, 3H), 4.52 (s, 2H), 6.13 (d, *J* = 7.3 Hz, 1H), 6.30 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 9.83 (d, *J* = 2.2 Hz, 1H).



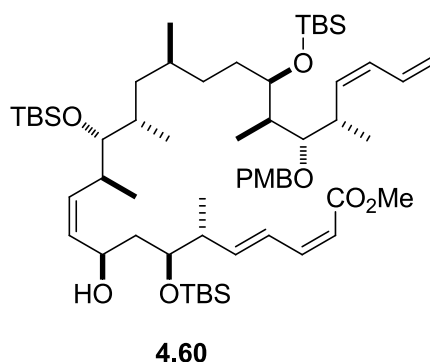
(5*R*,6*S*,8*S*,11*R*)-5-((*S*,*Z*)-4-iodobut-3-en-2-yl)-11-((2*R*,3*S*,4*S*,*Z*)-3-(4-methoxybenzyloxy)-4-methylocta-5,7-dien-2-yl)-2,2,3,3,6,8,13,13,14,14-decamethyl-4,12-dioxa-3,13-disilapentadecane (4.54)

To a slurry of CrCl₂ (301 mg, 2.45 mmol, 5 eq) in THF (4.9 mL), obtained by sonication and cooled to 0°C, freshly-prepared aldehyde **4.58** (394 mg, 0.49 mmol, 1 eq) in THF (1.7 mL) and (1-bromoallyl)trimethylsilane **4.59** (530 mg, 2.74 mmol, 5.6 eq) were added. The resulting mixture was stirred for 3h at R.T. before being re-cooled to 0°C and quenched by the addition of MeOH (2.1 mL) and 6 N aq. KOH (4.2 mL). After stirring for 20 h at R.T., the phases were separated and the aqueous layer was extracted with DCM (4 x 5 mL). The combined organic extracts were

washed with brine (2 x 15 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (100:0.5 hexane/EtOAc) to give the desired product **4.54** (308 mg, 76% yield over two steps) as a colorless oil.

R_f 0.45 (10:0.5 hexane/EtOAc); $[\alpha]_D^{22} = +22.4$ ($c = 0.2$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.04$ - 0.11 (m, 12H), 0.77 - 1.01 (m, 14 H), 0.94 (s, 9H), 0.95 (s, 9H), 1.12 (d, $J = 6.9$ Hz, 3H), 1.25 - 1.38 (m, 4H), 1.59 - 1.70 (m, 3H), 2.70 (m, 1H), 3.00 (m, 1H), 3.35 (dd, $J = 2.9$ Hz, 7.9 Hz, 1H), 3.47 (m, 1H), 3.63 (m, 1H), 3.83 (s, 3H), 4.56 (d, $J_{AB} = 10.6$ Hz, 1H, upfield part of an AB system), 4.52 (d, $J_{AB} = 10.5$ Hz, 1H, downfield part of an AB system), 5.12 (d, $J = 10.1$ Hz, 1H), 5.20 (d, $J = 16.8$ Hz, 1H), 5.60 (t, $J = 10.6$ Hz, 1H), 6.03 (t, $J = 11.1$ Hz, 1H), 6.13 (d, $J = 7.3$ Hz, 1H), 6.28 (t, $J = 7.4$ Hz, 1H), 6.60 (ddd, $J = 10.7$ Hz, 10.7 Hz, $J = 16.9$ Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -3.8$ (CH₃), -3.2 (CH₃), -3.0 (CH₃), -2.9 (CH₃), 9.9 (CH₃), 16.5 (CH₃), 18.4 (CH₃), 18.9 (C₀), 19.1 (C₀), 19.5 (CH₃), 21.1 (CH₃), 26.7 (CH₃), 26.9 (CH₃), 31.3 (CH), 31.9 (CH₂), 33.1 (CH₂), 35.9 (CH), 36.0 (CH), 41.2 (CH), 42.1 (CH₂), 44.0 (CH), 56.0 (CH₃), 73.4 (CH), 75.8 (CH₂), 79.9 (CH), 81.9 (CH), 85.2 (CH), 114.4 (CH), 117.9 (CH₂), 129.6 (CH), 129.8 (CH), 132.1 (C₀), 133.0 (CH), 135.3 (CH), 144.9 (CH), 159.7 (C₀); IR (neat): $\nu = 772$, 835 , 1039 , 1172 , 1251 , 1376 , 1462 , 1514 , 1613 , 1735 , 2855 , 2927 ; HRMS (ESI): calcd. for C₄₂H₇₅IO₄Si₂Na: 849.41408 [$M + Na$]⁺; found: 849.41248 .

6.8 Completion of the Synthesis of (+)-9-epi-Dictyostatin

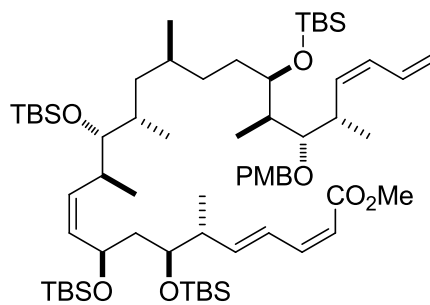


(2Z,4E,6R,7S,9R,10Z,12S,13R,14S,16S,19R,20R,21S,22S,23Z)-methyl-7,13,19-tris(tert-butylidimethylsilyloxy)-9-hydroxy-21-(4-methoxybenzyloxy)-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoate (4.60)

To a solution of *t*BuLi (1.7 M in pentane, 0.17 mL, 0.29 mmol, 2.2 eq) in Et₂O (0.2 mL) kept at -78 °C under argon atmosphere, a solution of vinyl iodide **4.54** (110 mg, 0.13 mmol, 1 eq) in Et₂O (0.4 mL) was added. After stirring for 30 min, a dimethylzinc toluene solution (2.0 M, 0.11 mL,

0.21 mmol, 1.6 eq) was added dropwise and the reaction mixture was further stirred at -78 °C for 15 min. A solution of aldehyde **4.2** (64 mg, 0.20 mmol, 1.5 eq), azeotropically dried with toluene, in Et₂O (0.6 mL) was added dropwise, and the mixture was stirred for 1 h at -78 °C. The reaction was quenched with water (2.2 mL), warmed to R.T. and diluted with Et₂O (3.6 mL). Phases were separated and the aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (10:0.5 hexane/EtOAc) to give the desired (*Z*)-allylic alcohol **4.60** (53 mg, 40% yield) as a light yellow oil. Unreacted aldehyde **4.2** (32 mg) was recovered.

R_f 0.55 (80:20 hexane/EtOAc); $[\alpha]_D^{19} = +2.6$ ($c = 1.4$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.05$ (s, 3H), 0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 9H), 0.80-0.82 (m, 1H), 0.83 (d, $J = 6.5$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.90 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.93 (s, 9H), 0.95 (s, 9H), 0.97 (d, $J = 6.8$ Hz, 3H), 1.06-1.07 (m, 1H), 1.12 (d, $J = 6.8$ Hz, 6H), 1.17-1.42 (m, 4H), 1.44-1.62 (m, 2H), 1.65-1.79 (m, 3H), 2.38 (br s, 1H), 2.63 (m, 1H), 2.71 (m, 1H), 3.01 (m, 1H), 3.34 (m, 2H), 3.64 (m, 1H), 3.74 (s, 3H), 3.82 (s, 3H), 3.88 (m, 1H), 4.49 (m, 1H), 4.51 (d, $J_{AB} = 10.6$ Hz, 1H, upfield part of an AB system), 4.58 (d, $J_{AB} = 10.6$ Hz, 1H, downfield part of an AB system), 5.12 (d, $J = 10.2$ Hz, 1H), 5.20 (dd, $J = 1.8$ Hz, 16.8 Hz, 1H), 5.40 (m, 2H), 5.61 (t, $J = 11.4$ Hz, 1H), 5.62 (d, $J = 11.4$ Hz, 1H), 6.00-6.09 (m, 2H), 6.58 (t, $J = 11.3$ Hz, 1H), 6.62 (t, $J = 10.7$ Hz, 1H), 6.89 (d, $J = 8.6$ Hz, 2H), 7.30 (d, $J = 8.6$ Hz, 2H), 7.41 (dd, $J = 11.3$ Hz, 15.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -4.4$ (CH₃), -4.4 (CH₃), -4.3 (CH₃), -3.8 (CH₃), -3.5 (CH₃), -2.7 (CH₃), 9.2 (CH₃), 14.7 (CH₃), 15.4 (CH₃), 18.1 (C₀), 18.2 (C₀), 18.6 (C₀), 18.8 (CH₃), 19.0 (CH₃), 20.2 (CH₃), 25.9 (CH₃), 26.0 (CH₃), 26.4 (CH₃), 30.3 (CH), 31.5 (CH₂), 32.4 (CH₂), 34.0 (CH), 35.2 (CH), 36.8 (CH), 40.5 (CH), 41.4 (CH₂), 42.4 (CH₂), 42.5 (CH), 51.1 (CH₃), 55.3 (CH₃), 65.3 (CH), 72.8 (CH), 73.6 (CH), 75.1 (CH₂), 79.6 (CH), 84.4 (CH), 113.7 (CH), 115.6 (CH), 117.2 (CH₂), 127.1 (CH), 128.9 (CH), 129.1 (CH), 131.4 (C₀), 132.4 (CH), 132.6 (CH), 134.6 (CH), 136.2 (CH), 145.5 (CH), 147.0 (CH), 159.0 (C₀), 166.8 (C₀); IR (neat): $\nu = 773, 836, 1075, 1174, 1251, 1377, 1462, 1514, 1613, 1637, 1720, 2855, 2926, 3503$; HRMS (ESI): calcd. for C₅₉H₁₀₆O₈Si₃Na: 1049.70877 [$M + Na$]⁺; found: 1049.70940.



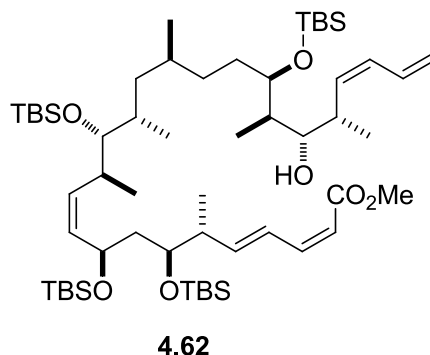
4.61

(2Z,4E,6R,7S,9R,10Z,12S,13R,14S,16S,19R,20R,21S,22S,23Z)-methyl-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-21-(4-methoxybenzyloxy)-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoate (4.61)

2,6-lutidine (18 μ L, 0.156 mmol, 4 eq) and TBSOTf (18 μ L, 0.078 mmol, 2 eq) were added dropwise to a stirred solution of **4.60** (40 mg, 0.039 mmol, 1 eq) in DCM (0.3 mL) cooled at -78 $^{\circ}$ C. After stirring at -78 $^{\circ}$ C for 1 h, the reaction was quenched by adding dropwise sat. aq. NaHCO₃ solution (1.7 mL), then it was warmed to R.T.. The mixture was diluted with DCM (11 mL), layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by flash chromatography (10:0.5 hexane/EtOAc) to give the desired product **4.61** (45 mg, 100% yield) as a pale yellow oil.

R_f 0.80 (80:20 hexane/EtOAc); $[\alpha]_D^{24} = +7.3$ ($c = 0.4$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.05$ (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.10 (s, 9H), 0.10 (s, 3H), 0.80-0.82 (m, 1H), 0.82 (d, $J = 6.1$ Hz, 3H), 0.83 (d, $J = 6.9$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.91 (s, 9H), 0.92 (s, 9H), 0.92 (s, 9H), 0.94 (s, 9H), 0.97 (d, $J = 6.8$ Hz, 3H), 1.01 (m, 1H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.27-1.42 (m, 4H), 1.46 (m, 1H), 1.62-1.72 (m, 4H), 2.49 (m, 1H), 2.59 (m, 1H), 3.00 (m, 1H), 3.34 (dd, $J = 8.0$ Hz, 3.1 Hz, 1H), 3.41 (m, 1H), 3.64 (m, 1H), 3.72 (s, 3H), 3.82 (s, 3H), 3.93 (m, 1H), 4.43 (br t, $J = 8.4$ Hz, 1H), 4.52 (d, $J_{AB} = 10.6$ Hz, 1H, upfield part of an AB system), 4.57 (d, $J_{AB} = 10.6$ Hz, 1H, downfield part of an AB system), 5.11 (d, $J = 10.2$ Hz, 1H), 5.20 (dd, $J = 1.7$ Hz, 16.9 Hz, 1H), 5.25 (dd, $J = 11.4$ Hz, 8.2 Hz, 1H), 5.47 (t, $J = 10.5$ Hz, 1H), 5.58-5.63 (m, 2H), 6.02 (t, $J = 11.0$ Hz, 1H), 6.20 (dd, $J = 15.5$ Hz, 8.9 Hz, 1H), 6.55-6.65 (m, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 7.30 (d, $J = 8.7$ Hz, 2H), 7.43 (dd, $J = 15.5$ Hz, 11.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -4.8$ (CH₃), -4.7 (CH₃), -4.3 (CH₃), -4.5 (CH₃), -4.1 (CH₃), -3.8 (CH₃), -3.5 (CH₃), 9.1 (CH₃), 14.1 (CH₃), 15.6 (CH₃), 18.0 (C₀), 18.1 (C₀), 18.2 (C₀), 18.5 (CH₃), 18.9 (CH₃), 20.5 (CH₃), 25.8 (CH₃), 26.0 (CH₃), 26.0 (CH₃), 26.2 (CH₃), 30.5 (CH), 31.7 (CH₂), 32.6 (CH₂), 35.1 (CH), 35.2 (CH), 36.5 (CH), 40.4 (CH), 40.9 (CH), 41.5 (CH₂), 44.8 (CH₂), 50.9 (CH₃), 55.3 (CH₃), 66.4 (CH), 72.4 (CH), 72.6 (CH), 75.1 (CH₂), 79.1 (CH), 84.5 (CH), 113.7 (CH), 115.0 (CH), 117.2 (CH₂), 127.4 (CH), 128.9 (CH), 129.1 (CH), 131.4 (C₀), 131.6 (CH), 132.4 (CH), 132.6 (CH), 134.6 (CH), 146.0 (CH), 147.2 (CH), 159.0 (C₀), 166.8 (C₀); IR (neat): ν

= 669, 802, 865, 1078, 1257, 1361, 1412, 1461, 1514, 1637, 719, 2856, 2928, 2961; HRMS (ESI): calcd. for C₆₅H₁₂₀O₈Si₄Na: 1163.79525 [*M* + Na]⁺; found: 1163.79601.

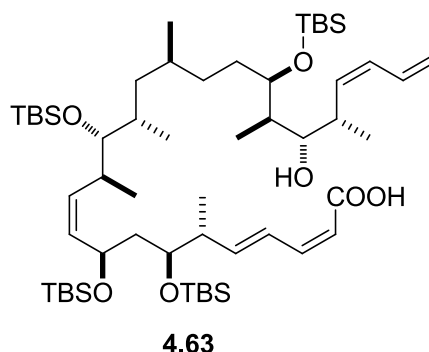


(2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-methyl-7,9,13,19-tetrakis(*tert*-butyldimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoate (4.62)

DDQ (11.6 mg, 0.051 mmol, 1.3 eq) was added to a solution of the PMB ether **4.61** (44.0 mg, 0.039 mmol, 1 eq) in DCM (1.2 mL) stirred at 0 °C in the presence of a KH₂PO₄/K₂HPO₄ buffer solution at pH 7 (0.12 mL). The reaction was stirred at 0 °C for 1 h before being quenched by dropwise addition of sat. aq. NaHCO₃ solution (19 mL). After diluting with DCM (37 mL), layers were separated and the aqueous phase was extracted with DCM (3 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give the desired product **4.62** (35.9 mg, 90% yield) as a colorless oil.

*R*_f 0.35 (90:10 hexane/EtOAc); [α]¹⁸_D = -4.1 (*c* = 0.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 0.07 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.10 (s, 12H), 0.11 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.89-0.90 (m, 6H), 0.90 (m, 1H), 0.92-0.95 (m, 39H), 0.99 (d, *J* = 6.9 Hz, 3H), 1.01-1.08 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.18-1.50 (m, 5H), 1.58-1.79 (m, 4H), 2.51 (m, 1H), 2.59 (m, 1H), 2.83 (m, 1H), 3.44 (m, 1H), 3.50 (dd, *J* = 7.3 Hz, 2.1 Hz, 1H), 3.73 (s, 3H), 3.78 (m, 1H), 3.95 (m, 1H), 4.45 (t, *J* = 8.4 Hz, 1H), 5.14 (d, *J* = 10.3 Hz, 1H), 5.21-5.29 (m, 2H), 5.48 (m, 2H), 5.60 (d, *J* = 11.3 Hz, 1H); 6.12 (t, *J* = 11.0 Hz, 1H); 6.20 (dd, *J* = 8.9 Hz, 15.5 Hz, 1H), 6.60 (t, *J* = 11.3 Hz, 1H), 6.62-6.71 (m, 1H), 7.43 (dd, *J* = 11.3 Hz, 15.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = -4.8 (CH₃), -4.7 (CH₃), -4.4 (CH₃), -4.1 (CH₃), -3.9 (CH₃), -3.8 (CH₃), -3.7 (CH₃), -3.5 (CH₃), 6.8 (CH₃), 15.7 (CH₃), 17.8 (CH₃), 18.0 (C₀), 18.1 (C₀), 18.1 (C₀), 18.5 (CH₃), 20.2 (CH₃), 20.6 (CH₃), 25.8 (CH₃), 25.9 (CH₃), 25.9 (CH₃), 26.2 (CH₃), 30.7 (CH), 31.7 (CH₂), 32.4 (CH₂), 35.5 (CH), 36.1 (CH), 36.5 (CH), 37.7 (CH), 40.9 (CH), 41.6 (CH₂), 44.8 (CH₂), 50.9 (CH₃), 66.5 (CH), 72.4 (CH), 76.8 (CH), 77.8 (CH), 79.2 (CH), 115.0 (CH), 117.2 (CH₂), 127.3 (CH), 129.9 (CH), 131.4 (CH), 132.3 (CH), 132.7 (CH), 135.4 (CH), 145.9 (CH), 147.1 (CH), 166.6 (C₀); IR (neat): ν =

799, 1020, 1093, 1260, 1412, 1461, 1601, 1637, 1720, 2855, 2927, 2961, 3447; HRMS (ESI): calcd. for $C_{57}H_{112}O_7Si_4Na$: 1043.73773 [$M + Na$] $^+$; found: 1043.73670.

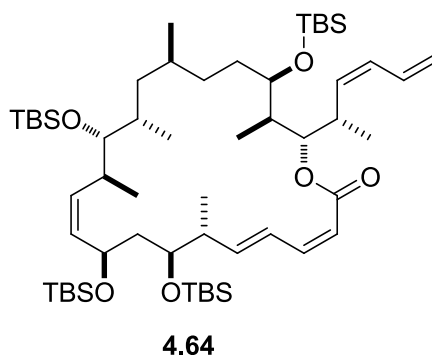


(2Z,4E,6R,7S,9R,10Z,12S,13R,14S,16S,19R,20R,21S,22S,23Z)-7,9,13,19-tetrakis(tert-butyl dimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoic acid (4.63)

To a stirred solution of the ester **4.62** (35.0 mg, 0.034 mmol, 1 eq) in THF (1.8 mL) and EtOH (4.1 mL), 1 N aq. KOH (0.33 mL) was added, and the reaction was refluxed (bath temperature: 52 °C) for 5 h. The solvent was removed under reduced pressure. The residue was diluted with Et₂O (26 mL) and sat. aq. NH₄Cl solution (8 mL); layers were separated and the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The product was purified by flash chromatography (90:10 hexane/EtOAc) to afford the *seco acid* **4.63** (34.3 mg, 100% yield) as a colorless oil.

R_f 0.26 (80:20 hexane/EtOAc); $[\alpha]_D^{32} = +3.4$ ($c = 0.2$, CHCl₃); 1H NMR (400 MHz, CDCl₃): $\delta = 0.03$ (s, 6H), 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.07 (s, 6H), 0.08 (s, 3H), 0.82 (d, $J = 7.0$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H), 0.86 (d, $J = 6.2$ Hz, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 0.89-0.92 (m, 1H), 0.90 (s, 18H), 0.92 (d, $J = 7.1$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.99-1.05 (m, 1H), 1.09 (d, $J = 6.7$ Hz, 3H), 1.22-1.46 (m, 5H), 1.60-1.66 (m, 3H), 1.73-1.76 (m, 1H), 2.43 (m, 1H), 2.56 (m, 1H), 2.78 (m, 1H), 3.41 (m, 1H), 3.53 (dd, $J = 2.7$ Hz, 7.6 Hz, 1H), 3.75 (m, 1H), 3.91 (m, 1H), 4.40 (br t, $J = 8.6$ Hz, 1H), 5.11 (d, $J = 10.2$ Hz, 1H), 5.19-5.27 (m, 2H), 5.38-5.48 (m, 2H), 5.57 (d, $J = 11.4$ Hz, 1H), 6.10 (t, $J = 11.0$ Hz, 1H), 6.22 (dd, $J = 9.0$ Hz, 15.5 Hz, 1H), 6.58-6.67 (m, 2H), 7.36 (dd, $J = 11.4$ Hz, 15.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl₃): $\delta = -4.8$ (CH₃), -4.7 (CH₃), -4.4 (CH₃), -4.1 (CH₃), -3.8 (CH₃), -3.7 (CH₃), -3.5 (CH₃), 7.4 (CH₃), 15.6 (CH₃), 17.7 (CH₃), 18.0 (C₀), 18.1 (C₀), 18.5 (C₀), 18.7 (CH₃), 20.3 (CH₃), 20.5 (CH₃), 25.8 (CH₃), 25.9 (CH₃), 26.0 (CH₃), 26.2 (CH₃), 30.7 (CH), 31.9 (CH₂), 32.0 (CH₂), 35.5 (CH), 36.2 (CH), 37.1 (CH), 38.1 (CH), 41.0 (CH), 42.3 (CH₂), 45.0 (CH₂), 66.5 (CH), 72.4 (CH), 76.5 (CH), 77.3 (CH), 79.3 (CH), 114.6 (CH), 117.8 (CH₂), 127.4 (CH), 130.1 (CH), 131.5 (CH), 132.2 (CH), 132.7 (CH), 135.1 (CH), 147.3 (CH), 147.9 (CH), 169.2 (C₀); IR (neat): $\nu = 774, 836, 1005, 1027, 1081, 1255, 1377,$

1461, 1600, 1636, 1686, 2855, 2927, 2955, 3417; HRMS (ESI): calcd. for $C_{56}H_{109}O_7Si_4$: 1005.72559 $[M - H]^-$; found: 1005.72635.

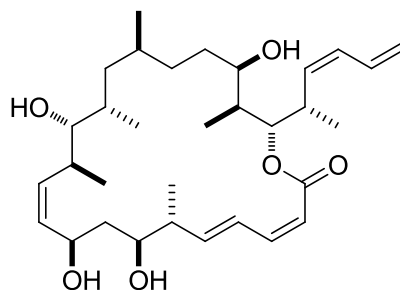


(3*Z*,5*E*,7*R*,8*S*,10*R*,11*Z*,13*S*,14*R*,15*S*,17*S*,20*R*,21*R*,22*S*)-8,10,14,20-tetrakis(*tert*-butyldimethylsilyloxy)-22-((*S,Z*)-hexa-3,5-dien-2-yl)-7,13,15,17,21-pentamethyloxacyclodocosa-3,5,11-trien-2-one (4.64)

To a solution of the *seco* acid **4.63** (18.0 mg, 0.018 mmol, 1 eq) in THF (2.2 mL) cooled to 0 °C, TEA (15 μ L, 0.108 mmol, 6 eq) and 2,4,6-trichlorobenzoyl chloride (14 μ L, 0.09 mmol, 5 eq) were added. The reaction was stirred at 0 °C for 1 h and monitored by TLC (90:10 hexane/EtOAc; R_f anhydride: 0.4) before being added to a 4-DMAP (22.0 mg, 0.18 mmol, 10 eq) solution in toluene (8.9 mL) at R.T.. The mixture was stirred at R.T. for 24 h (TLC: 97:3 hexane/EtOAc; R_f macrolactone: 0.31) and the solvent was removed under reduced pressure. The residue was diluted with Et₂O (22 mL) and water (16 mL), layers were separated and the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by flash chromatography (90:10 hexane/DCM; R_f macrolactone: 0.13) to give macrolactone **4.64** (14.0 mg, 80% yield) as a pale yellow oil.

R_f 0.31 (97:3 hexane/EtOAc); $[\alpha]_D^{21} = -19.6$ ($c = 0.1$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.04$ (s, 6H), 0.05 (s, 3H), 0.06 (s, 9H), 0.07 (s, 6H), 0.84-0.85 (m, 6H), 0.86-0.89 (m, 6H), 0.89-0.90 (br s, 27H), 0.92 (s, 9H), 1.01 (d, $J = 6.8$ Hz, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 1.11 (m, 2H), 1.15-1.32 (m, 4H), 1.38-1.55 (m, 3H), 1.62 (m, 1H), 1.78-1.86 (m, 1H), 2.41-2.47 (m, 1H), 2.47-2.54 (m, 1H), 3.05 (m, 1H), 3.41 (d, $J = 2.8$ Hz, 1H), 3.56 (m, 1H), 3.94 (m, 1H), 4.41 (t, $J = 8.8$ Hz, 1H), 5.12-5.28 (m, 4H), 5.43 (t, $J = 10.4$ Hz, 1H), 5.50-5.54 (m, 2H), 6.05 (t, $J = 11.0$ Hz, 1H), 6.16 (dd, $J = 9.1$ Hz, 15.5 Hz, 1H), 6.53 (t, $J = 11.5$ Hz, 1H), 6.61 (dt, $J = 10.6$ Hz, 16.8 Hz, 1H), 7.17 (dd, $J = 11.2$ Hz, 15.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -5.0$ (CH₃), -4.8 (CH₃), -4.4 (CH₃), -4.1 (CH₃), -3.8 (CH₃), -3.7 (CH₃), -3.3 (CH₃), 10.7 (CH₃), 14.1 (CH₃), 14.3 (CH₃), 18.0 (C₀), 18.1 (CH₃), 18.1 (C₀), 18.7 (C₀), 18.7 (CH₃), 21.2 (CH₃), 25.8 (CH₃), 25.9 (CH₃), 26.3 (CH₃), 29.5 (CH₂), 29.7 (CH₂), 30.2 (CH), 34.5 (CH), 37.9 (CH), 39.3 (CH), 40.0 (CH), 41.1 (CH), 43.8 (CH₂), 44.8 (CH₂), 66.5 (CH), 72.4 (CH), 73.1 (CH), 77.3 (CH), 81.8 (CH), 116.7 (CH), 118.1

(CH₂), 127.6 (CH), 130.0 (CH), 131.5 (CH), 132.1 (CH), 132.4 (CH), 133.4 (CH), 143.7 (CH), 146.2 (CH), 166.4 (C₀); IR (neat): ν = 662, 743, 799, 1020, 1260, 1413, 1462, 1637, 1709, 2854, 2927, 2961; HRMS (ESI): calcd. for C₅₆H₁₀₈O₆Si₄Na: 1011.71152 [*M* + Na]⁺; found: 1011.71340.



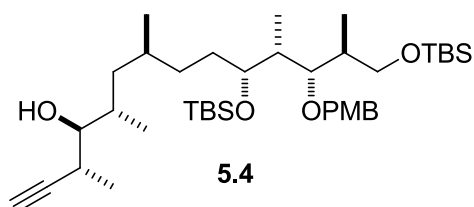
4.65

(+)-9-*epi*-Dictyostatin (4.65)

To a solution of macrolactone **4.64** (10.0 mg, 10.2 μ mol, 1 eq) in THF (1.34 mL) kept at 0 °C in a plastic vial, HF-Py (0.34 mL) was added dropwise over 2 min, and the solution was allowed to slowly warm to R.T.. The reaction was stirred for 20 h, then it was cooled to 0 °C, diluted with EtOAc (7.0 mL) and quenched with a sat. aq. NaHCO₃ solution (7.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by flash chromatography (30:70 hexane/EtOAc) to give (+)-9-*epi*-dictyostatin **4.65** (3.8 mg, 70% yield) as a white powder.

R_f 0.54 (100% EtOAc); $[\alpha]_D^{31} = +43.4$ ($c = 0.17$, CHCl₃); ¹H NMR (400 MHz, C₆D₆): 0.85 (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.5$ Hz, 3H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.99 (d, $J = 6.6$ Hz, 6H), 1.03 (d, $J = 7.0$ Hz, 3H), 1.24-1.58 (m, 7H), 1.69-1.84 (m, 3H), 1.83-1.94 (m, 2H), 2.19-2.28 (m, 1H), 2.81-2.96 (m, 2H), 3.18-3.22 (m, 1H), 3.26-3.35 (m, 1H), 3.41-3.53 (m, 2H), 3.90-3.96 (m, 1H), 4.21 (br s, 1H), 4.60 (br s, 1H), 4.98-5.02 (m, 2H), 5.09 (t, $J = 16.7$ Hz, 1H), 5.27-5.38 (m, 2H), 5.44 (dd, $J = 11.6$ Hz, 4.4 Hz, 1H), 5.56 (d, $J = 11.3$ Hz, 1H), 5.74 (dd, $J = 15.8$ Hz, 6.2 Hz, 1H), 5.98 (t, $J = 11.0$ Hz, 1H), 6.25 (t, $J = 11.3$ Hz, 1H), 6.58 (dt, $J = 16.7$ Hz, 10.6 Hz, 1H), 7.89 (dd, $J = 15.7$ Hz, 11.3 Hz, 1H); ¹³C NMR (100 MHz, C₆D₆): $\delta = 9.4$ (CH₃), 14.9 (CH₃), 16.7 (CH₃), 17.6 (CH₃), 18.5 (CH₃), 21.9 (CH₃), 30.3 (CH), 32.9 (CH₂), 33.5 (CH₂), 33.6 (CH), 35.1 (CH), 35.9 (CH), 40.7 (CH), 41.6 (CH₂), 41.7 (CH₂), 42.2 (CH), 71.1 (CH), 73.8 (CH), 74.2 (CH), 76.6 (CH), 77.7 (CH), 116.3 (CH), 118.0 (CH₂), 127.5 (CH), 130.5 (CH), 132.5 (CH), 133.1 (CH), 133.8 (CH), 133.9 (CH), 146.2 (CH), 146.9 (CH), 167.2 (C₀); IR (neat): ν = 665, 740, 804, 1019, 1380, 1415, 1460, 1602, 1637, 1685, 1709, 2927, 2961, 3380; HRMS (ESI): calcd. for C₃₂H₅₂O₆Na: 555.36561 [*M* + Na]⁺; found: 555.36537.

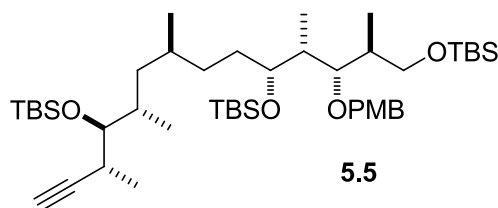
6.9 Synthesis of (Z)-Vinyl Iodide 12,13-bis-*epi*-C10-C26



(3*R*,4*S*,5*S*,7*S*,10*R*,11*R*,12*S*,13*S*)-10,14-Bis-(tert-butyl-dimethyl-silanyloxy)-12-(4-methoxy-benzyloxy)-3,5,7,11,13-pentamethyl-tetradec-1-yn-4-ol (**5.4**)

Triphenylphosphine (re-crystallized from ethanol prior to use, 0.6 mg, 0.00225 mmol, 0.05 eq), the crude aldehyde **4.46** (28.0 mg, 0.045 mmol, 1 eq) and (*S*)-mesyl-butynol **5.3** (10.0 mg, 0.0675 mmol, 1.5 eq) were sequentially added to a cooled (-78 °C) solution of Pd(OAc)₂ (0.5 mg, 0.00225 mmol, 0.05 eq) in THF (0.45 ml). Diethylzinc (1.0 M in hexane, 135 μl, 0.135 mmol, 3 eq) was added over 15 min. After 10 min, the temperature was raised to -20 °C, and the reaction mixture was stirred overnight at -20 °C. The mixture was then quenched with NH₄Cl/Et₂O 1:1. The Et₂O layer was washed with brine, dried and concentrated under reduced pressure. The residue was purified by flash chromatography (95:5 hexane/EtOAc) to afford the product **5.4** as a yellow oil (25.6 mg, 84% over two steps), with high diastereoselectivity (dr >95:5).

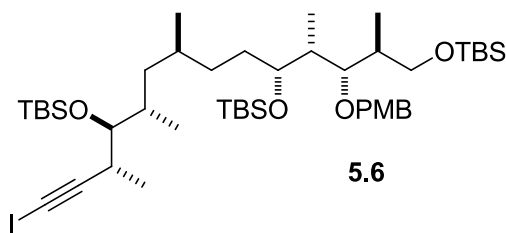
R_f 0.39 (80:20 hexane/EtOAc); $[\alpha]_D^{23} = -4.61$ ($c = 0.505$, CHCl₃); ¹H NMR (400 MHz, C₆D₆): δ = 0.20 (s, 6H), 0.26 (s, 6H), 1.00 (d, $J = 6.4$ Hz, 3H), 1.10 (d, $J = 6.8$ Hz, 3H), 1.15-1.03 (m, 1H), 1.13 (s, 9H), 1.18 (s, 9H), 1.22 (d, $J = 6.8$ Hz, 3H), 1.26 (d, $J = 6.8$ Hz, 3H), 1.30 (d, $J = 7.2$ Hz, 3H), 1.46-1.95 (m, 11H), 2.06-2.20 (m, 3H), 2.61-2.74 (m, 1H), 2.94-3.15 (m, 1H), 3.43 (s, 3H), 3.79-4.00 (m, 4H), 4.79 (AB system, $\nu_A = 4.82$, $\nu_B = 4.76$, $J_{AB} = 11.2$ Hz, 2H), 6.96 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H); ¹³C NMR (100 MHz, C₆D₆): δ = -4.7, -3.6, -3.4, 11.1, 16.0, 17.3, 18.8, 18.9, 21.9, 31.0, 31.5, 32.0, 32.1, 35.7, 39.9, 40.6, 40.8, 55.2, 65.6, 71.8, 74.6, 75.6, 79.6, 81.4, 114.5, 129.5, 132.6, 160.0; IR (film): $\nu = 1255, 1301, 1360, 1386, 1462, 1470, 1514, 1613, 1727, 2655, 2663, 2850, 2933, 2960, 3309$; HRMS (ESI): calcd. for C₃₉H₇₂O₅Si₂Na: 699.48105 [M+Na]⁺; found: 699.47937.



(5*S*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-5-((*R*)-but-3-yn-2-yl)-11-((*tert*-butyldimethylsilyl)oxy)-13-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxo-3,17-disilanonadecane (5.5)

2,6-Lutidine (0.22 mL, 1.85 mmol, 5 eq) and TBSOTf (0.26 mL, 1.11 mmol, 3 eq) were added dropwise to a stirred solution of **5.4** (252 mg, 0.37 mmol, 1 eq) in DCM (9.3 mL) cooled at 0 °C. After stirring at 0 °C for 1.5 h, the reaction was quenched by adding sat. aq. NH₄Cl solution (3.5 mL) dropwise, then it was warmed to R.T.. Layers were separated and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by flash chromatography (98:2 hexane/EtOAc) to give the desired product **5.5** (231 mg, 79% yield) as a colorless oil.

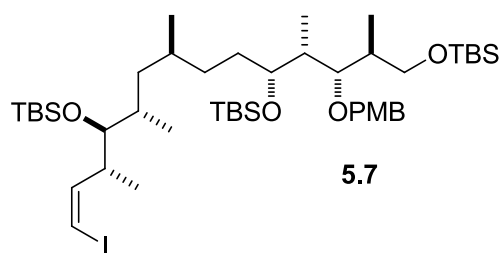
R_f 0.62 (85:15 hexane/EtOAc); $[\alpha]_D^{22} = -4.8$ ($c = 0.3$, CHCl₃); ¹H NMR (400 MHz, C₆D₆): $\delta = 0.09$ (s, 6H), 0.11 (s, 3H), 0.12 (s, 3H), 0.14 (s, 3H), 0.15 (s, 3H), 0.99 (d, $J = 6.1$ Hz, 3H), 1.01 (s, 9H), 1.05 (s, 9H), 1.06 (s, 9H), 1.11 (d, $J = 7.1$ Hz, 3H), 1.13 (d, $J = 7.1$ Hz, 3H), 1.19 (d, $J = 6.9$ Hz, 3H), 1.23 (d, $J = 7.1$ Hz, 3H), 1.28-1.35 (m, 2H), 1.50-1.58 (m, 2H), 1.59-1.70 (m, 2H), 1.79-1.86 (m, 1H), 1.90 (d, $J = 2.5$ Hz, 1H), 2.02 (m, 3H), 2.65 (m, 1H), 3.31 (s, 3H), 3.42 (dd, $J = 3.9$ Hz, 4.9 Hz, 1H), 3.69 (dd, $J = 3.9$ Hz, 6.9 Hz, 1H), 3.73 (dd, $J = 3.4$ Hz, 9.7 Hz, 1H), 3.81 (m, 1H), 3.87 (m, 1H), 4.64 (d, $J_{AB} = 11.1$ Hz, 1H, upfield part of an AB system), 4.71 (d, $J_{AB} = 11.1$ Hz, 1H, downfield part of an AB system), 6.84 (d, $J = 8.6$ Hz, 2H), 7.36 (d, $J = 8.6$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -5.3$ (CH₃), -5.2 (CH₃), -4.3 (CH₃), -4.1 (CH₃), -4.0 (CH₃), -3.9 (CH₃), 10.1 (CH₃), 15.3 (CH₃), 16.7 (CH₃), 18.1 (C₀), 18.2 (CH₃), 18.3 (C₀), 18.4 (C₀), 20.9 (CH₃), 25.9 (CH₃), 26.0 (CH₃), 26.1 (CH₃), 30.2 (CH), 30.5 (CH), 31.0 (CH₂), 31.4 (CH₂), 35.1 (CH), 38.8 (CH), 39.7 (CH), 40.3 (CH₂), 55.3 (CH₃), 64.6 (CH₂), 69.9 (CH), 73.9 (CH₂), 74.3 (CH), 78.8 (CH), 80.9 (CH), 87.3 (C₀), 113.7 (CH), 128.9 (CH), 131.6 (C₀), 158.9 (C₀); IR (neat): $\nu = 625$, 669, 774, 836, 939, 1040, 1079, 1172, 1251, 1302, 1361, 1387, 1463, 1514, 1614, 2856, 2929; HRMS (ESI): calcd. for C₄₅H₈₆O₅Si₃Na: 813.56753 [$M + Na$]⁺; found: 813.56975.



(5*S*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-11-((*tert*-butyldimethylsilyl)oxy)-5-((*R*)-4-iodobut-3-yn-2-yl)-13-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (5.6)

A solution of *n*BuLi in hexane (1.6 M, 0.22 mL, 0.35 mmol, 1.2 eq) was added dropwise over 5 min to a solution of alkyne **5.5** (231 mg, 0.29 mmol, 1 eq) in THF (1.5 mL) at -50 °C. After 1 h, a solution of iodine (125 mg, 0.50 mmol, 1.7 eq) in THF (0.1 mL) was added. The mixture was stirred at -50 °C for 30 min, then warmed to R.T. over 30 min. After quenching by the addition of a sat. aq. Na₂S₂O₃ solution (0.8 mL) and brine (0.8 mL), the mixture was extracted with EtOAc (3 x 3 mL) and the combined organic layers were washed with brine (2 x 4 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give the desired product **5.6** (268 mg, 100% yield) as a colorless oil.

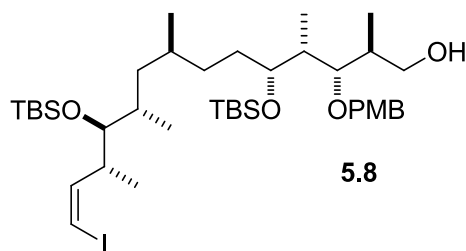
R_f 0.41 (95:5 hexane/EtOAc); $[\alpha]_D^{28} = -0.9$ ($c = 0.3$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.05$ (s, 9H), 0.06 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 9H), 0.92 (s, 9H), 0.93 (s, 9H), 0.94 (d, $J = 7.0$ Hz, 3H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 1.17 (d, $J = 7.1$ Hz, 3H), 1.28-1.33 (m, 3H), 1.35-1.44 (m, 3H), 1.58-1.62 (m, 1H), 1.73-1.82 (m, 2H), 1.89 (m, 1H), 2.76 (m, 1H), 3.40 (t, $J = 4.4$ Hz, 1H), 3.48 (dd, $J = 4.2$ Hz, 6.9 Hz, 1H), 3.61-3.70 (m, 3H), 3.80 (s, 3H), 4.48 (d, $J_{AB} = 10.9$ Hz, 1H, upfield part of an AB system), 4.56 (d, $J_{AB} = 10.9$ Hz, 1H, downfield part of an AB system), 6.87 (d, $J = 8.7$ Hz, 2H), 7.26 (d, $J = 8.6$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -5.4$ (CH₃), -5.3 (C₀), -5.2 (CH₃), -4.2 (CH₃), -4.1 (CH₃), -4.0 (CH₃), -3.9 (CH₃), 10.1 (CH₃), 15.3 (CH₃), 16.7 (CH₃), 18.1 (C₀), 18.2 (CH₃), 18.3 (C₀), 18.3 (C₀), 20.8 (CH₃), 25.9 (CH₃), 26.0 (CH₃), 26.1 (CH₃), 30.5 (CH), 31.1 (CH₂), 31.4 (CH₂), 32.5 (CH), 35.0 (CH), 38.9 (CH), 39.7 (CH), 39.9 (CH₂), 55.3 (CH₃), 64.7 (CH₂), 73.9 (CH₂), 74.4 (CH), 79.0 (CH), 80.9 (CH), 97.6 (C₀), 113.7 (CH), 128.9 (CH), 131.7 (C₀), 158.9 (C₀); IR (neat): $\nu = 670$, 773, 836, 1038, 1078, 1172, 1250, 1302, 1361, 1387, 1462, 1514, 1614, 1677, 2208, 2855, 2928, 2954; HRMS (ESI⁺): calcd. for C₄₅H₈₅IO₅Si₃Na: 939.46417 [$M + Na$]⁺; found: 939.46313.



(5*S*,6*S*,8*S*,11*R*,12*R*,13*S*,14*S*)-11-((*tert*-butyldimethylsilyl)oxy)-5-((*R,Z*)-4-iodobut-3-en-2-yl)-13-((4-methoxybenzyl)oxy)-2,2,3,3,6,8,12,14,17,17,18,18-dodecamethyl-4,16-dioxa-3,17-disilanonadecane (5.7)

A solution of iodoalkyne **5.6** (147 mg, 0.16 mmol, 1 eq) in THF (0.4 mL) and *i*PrOH (0.4 mL) at R.T. was treated with TEA (30 μ L, 0.21 mmol, 1.3 eq) and NBSH (38.0 mg, 0.18 mmol, 1.1 eq). After 12 h, additional TEA (10 μ L, 0.10 mmol, 0.6 eq) and NBSH (17.0 mg, 0.08 mmol, 0.5 eq) were added, and the mixture was stirred for 12 hours. The reaction was quenched by adding water (1.0 mL), and the mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (2 x 3 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give the desired product **5.7** (147 mg, 100% yield) as a colorless oil.

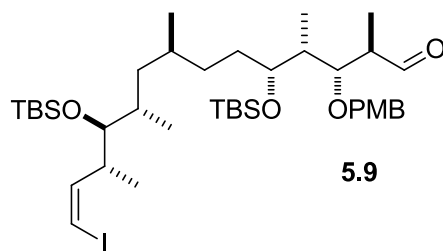
R_f 0.85 (80:20 hexane/EtOAc); $[\alpha]_D^{24} = -14.3$ ($c = 0.2$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.04$ (s, 6H), 0.05 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.81 (d, $J = 6.9$ Hz, 3H), 0.90 (d, $J = 7.1$ Hz, 3H), 0.91 (s, 12H), 0.92 (s, 9H), 0.93 (s, 9H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.99-1.02 (m, 1H), 1.22-1.32 (m, 2H), 1.36-1.49 (m, 3H), 1.58-1.62 (m, 1H), 1.66-1.73 (m, 1H), 1.78 (m, 1H), 1.88 (m, 1H), 2.68 (m, 1H), 3.46 (dd, $J = 4.1$ Hz, 6.9 Hz, 1H), 3.49 (dd, $J = 1.8$ Hz, 5.1 Hz, 1H), 3.62-3.69 (m, 3H), 3.80 (s, 3H), 4.47 (d, $J_{AB} = 10.9$ Hz, 1H, upfield part of an AB system), 4.55 (d, $J_{AB} = 10.9$ Hz, 1H, downfield part of an AB system), 6.06 (d, $J = 7.3$ Hz, 1H), 6.38 (dd, $J = 7.3$ Hz, 8.8 Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.25 (d, $J = 8.6$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -5.3$ (CH₃), -5.2 (CH₃), -4.2 (CH₃), -3.9 (CH₃), -3.7 (CH₃), 10.2 (CH₃), 15.3 (CH₃), 15.5 (CH₃), 18.2 (C₀), 18.3 (C₀), 18.8 (CH₃), 20.6 (CH₃), 26.8 (CH₃), 29.7 (CH₂), 30.5 (CH), 31.5 (CH₂), 36.5 (CH), 39.0 (CH), 39.8 (CH), 41.2 (CH₂), 41.6 (CH), 55.3 (CH₃), 64.7 (CH₂), 74.0 (CH₂), 74.3 (CH), 79.0 (CH), 80.4 (CH), 81.0 (CH), 113.7 (CH), 128.9 (CH), 131.7 (C₀), 144.2 (CH), 159.0 (C₀); IR (neat): $\nu = 773, 836, 1038, 1078, 1171, 1249, 1301, 1360, 1387, 1461, 1514, 1614, 1677, 2855, 2928, 2954$; HRMS (ESI): calcd. for C₄₅H₈₇IO₅Si₃Na: 941.47982 [$M + Na$]⁺; found: 941.47890.



(2*S*,3*S*,4*R*,5*R*,8*S*,10*S*,11*S*,12*R*,*Z*)-5,11-bis(*tert*-butyldimethylsilyloxy)-14-iodo-3-((4-methoxybenzyl)oxy)-2,4,8,10,12-pentamethyltetradec-13-en-1-ol (5.8**)**

A solution of compound **5.7** (147 mg, 0.16 mmol, 1 eq) in THF (0.8 mL) at 0 °C was treated with a solution of HF-Py in THF/pyridine [3.6 mL, prepared by slow addition of commercially available 70% HF in pyridine (0.31 mL) to a mixture of pyridine (1.1 mL) and THF (2.2 mL)]. The reaction mixture was warmed to R.T. and stirred for 4 hours. After quenching the reaction by the addition of sat. aq. NaHCO₃ solution (6 mL), the mixture was extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with sat. aq. CuSO₄ solution (3 x 10 mL) and brine (2 x 10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (90:10 hexane/EtOAc) to give the desired product **5.8** (102 mg, 80% yield) as a colorless oil.

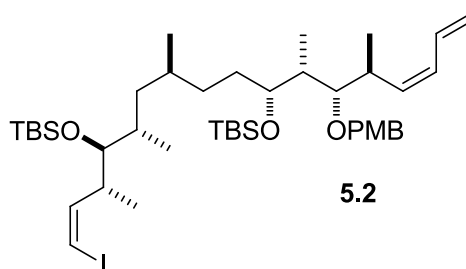
R_f 0.29 (80:20 hexane/EtOAc); $[\alpha]_D^{25} = -9.0$ ($c = 0.2$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.05$ (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.82 (d, $J = 6.9$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.91 (s, 9H), 0.92 (s, 9H), 0.98 (d, $J = 7.1$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 1.11 (d, $J = 7.0$ Hz, 3H), 1.20-1.70 (m, 8H), 1.88 (m, 1H), 1.95 (m, 1H), 2.68 (m, 1H), 3.44-3.49 (m, 2H), 3.56-3.64 (m, 2H), 3.78-3.82 (m, 1H), 3.80 (s, 3H), 4.53 (s, 2H), 6.06 (d, $J = 7.3$ Hz, 1H), 6.38 (dd, $J = 7.4$ Hz, 8.8 Hz, 1H), 6.87 (d, $J = 8.6$ Hz, 2H), 7.26 (d, $J = 8.6$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -4.4$ (CH₃), -4.2 (CH₃), -3.8 (CH₃), -3.7 (CH₃), 10.1 (CH₃), 15.5 (CH₃), 15.8 (CH₃), 18.2 (C₀), 18.3 (C₀), 18.8 (CH₃), 20.5 (CH₃), 26.0 (CH₃), 26.1 (CH₃), 30.5 (CH), 31.8 (CH₂), 31.9 (CH₂), 36.6 (CH), 37.0 (CH), 40.7 (CH), 41.1 (CH₂), 41.6 (CH), 55.3 (CH₃), 65.2 (CH₂), 73.8 (CH), 75.2 (CH₂), 79.0 (CH), 80.4 (CH), 85.9 (CH), 113.9 (CH), 129.3 (CH), 130.6 (C₀), 144.2 (CH), 159.3 (C₀); IR (neat): $\nu = 772, 806, 835, 1037, 1077, 1251, 1302, 1378, 1462, 1514, 1612, 2852, 2925, 2955, 3447$; HRMS (ESI): calcd. for C₃₉H₇₃IO₅Si₂Na [$M + Na$]⁺: 827.39334; found: 827.39306.



(2*R*,3*R*,4*R*,5*R*,8*S*,10*S*,11*S*,12*R*,*Z*)-5,11-bis((*tert*-butyldimethylsilyloxy)-14-iodo-3-((4-methoxybenzyl)oxy)-2,4,8,10,12-pentamethyltetradec-13-enal (5.9)

A solution of alcohol **5.8** (91 mg, 0.11 mmol 1 eq) in DCM (0.6 mL) was treated at 0 °C with pyridine (23 μ L, 0.28 mmol, 2.5 eq) and DMP (58 mg, 0.14 mmol, 1.2 eq). The reaction mixture was warmed to R.T. and stirred for 1 h. After completion of the reaction, sat. aq. NaHCO₃ solution (2.0 mL) and Na₂S₂O₃ (205 mg, 0.82 mmol) were added. The obtained mixture was stirred for 30 min, then the phases were separated and the aqueous phase was extracted with Et₂O (3 x 4 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried (Na₂SO₄) and evaporated under reduced pressure, providing the crude aldehyde **5.9**, which was used without further purification.

R_f 0.60 (80:20 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.82 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.92 (s, 9H), 0.98 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.27-1.36 (m, 3H), 1.38-1.43 (m, 2H), 1.53-1.69 (m, 3H), 1.87 (m, 1H), 2.67 (m, 1H), 2.78 (m, 1H), 3.48 (dd, J = 1.9 Hz, J = 5.1 Hz, 1H), 3.67 (m, 2H), 3.80 (s, 3H), 4.49 (s, 2H), 6.06 (d, J = 7.3 Hz, 1H), 6.37 (dd, J = 7.3 Hz, 8.8 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 9.80 (d, J = 2.3 Hz, 1H).

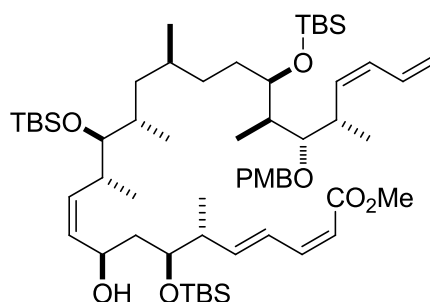


(5*S*,6*S*,8*S*,11*R*)-5-((*R*,*Z*)-4-iodobut-3-en-2-yl)-11-((2*R*,3*S*,4*S*,*Z*)-3-((4-methoxybenzyl)oxy)-4-methylocta-5,7-dien-2-yl)-2,2,3,3,6,8,13,13,14,14-decamethyl-4,12-dioxa-3,13-disilapentadecane (5.2)

To a slurry of CrCl₂ (69 mg, 0.57 mmol, 5 eq) in THF (1.1 mL), obtained by sonication and cooled to 0°C, freshly-prepared aldehyde **5.9** (0.11 mmol, 1 eq) in THF (0.4 mL) and (1-bromoallyl)trimethylsilane **4.58** (122 mg, 0.63 mmol, 5.6 eq) were added. The resulting mixture was stirred for 3 h at R.T. before being re-cooled to 0°C and quenched by the addition of MeOH

(0.5 mL) and 6 N aq. KOH (1.0 mL). After stirring for 20 h at R.T., the phases were separated and the aqueous layer was extracted with DCM (4 x 5 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (100:0.5 hexane/EtOAc) to give the desired product **5.2** (86 mg, 92% yield over two steps) as a colorless oil.

R_f 0.50 (95:5 hexane/EtOAc); $[\alpha]_D^{22} = -0.6$ ($c = 0.3$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.05$ (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.79 (d, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.3$ Hz, 3H), 0.85-0.97 (m, 2H), 0.92 (s, 9H), 0.93 (s, 9H), 0.95 (d, $J = 7.4$ Hz, 3H), 0.97 (d, $J = 7.3$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.18-1.37 (m, 4H), 1.48-1.54 (m, 1H), 1.57-1.67 (m, 2H), 2.67 (m, 1H), 2.98 (m, 1H), 3.33 (dd, $J = 3.3$ Hz, 7.8 Hz, 1H), 3.46 (dd, $J = 1.9$ Hz, 5.1 Hz, 1H), 3.61 (m, 1H), 3.80 (s, 3H), 4.49 (d, $J_{AB} = 10.6$ Hz, 1H, upfield part of an AB system), 4.56 (d, $J_{AB} = 10.6$ Hz, 1H, downfield part of an AB system), 5.10 (d, $J = 10.1$ Hz, 1H), 5.18 (dd, $J = 1.8$ Hz, 16.8 Hz, 1H), 5.58 (t, $J = 10.6$ Hz, 1H), 6.01 (t, $J = 11.1$ Hz, 1H), 6.06 (d, $J = 7.3$ Hz, 1H), 6.37 (dd, $J = 7.3$ Hz, 8.8 Hz, 1H), 6.58 (td, $J = 10.7$ Hz, 16.8 Hz, 1H), 6.87 (d, $J = 8.7$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -4.4$ (CH₃), -4.2 (CH₃), -3.7 (CH₃), -3.5 (CH₃), 9.3 (CH₃), 15.5 (CH₃), 18.2 (C₀), 18.3 (C₀), 18.7 (CH₃), 18.8 (CH₃), 20.5 (CH₃), 26.0 (CH₃), 26.1 (CH₃), 30.2 (CH), 31.6 (CH₂), 32.2 (CH₂), 35.3 (CH), 36.4 (CH), 40.6 (CH), 41.1 (CH₂), 41.6 (CH), 55.3 (CH₃), 72.8 (CH), 75.0 (CH₂), 79.1 (CH), 80.4 (CH), 84.4 (CH), 113.7 (CH), 117.2 (CH₂), 128.9 (CH), 129.1 (CH), 131.4 (C₀), 132.4 (CH), 134.6 (CH), 144.2 (CH), 159.0 (C₀); IR (neat): $\nu = 772$, 804, 835, 868, 1039, 1179, 1257, 1361, 1377, 1462, 1514, 1613, 2854, 2925, 2956; HRMS (ESI): calcd. for C₄₂H₇₅IO₄Si₂Na: 849.41408 [$M + Na$]⁺; found: 849.41270.

6.10 Synthesis of 12,13-bis-*epi*-Dictyostatin Precursors

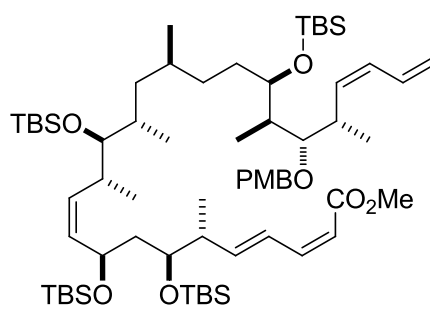
5.10

(2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*R*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-methyl 7,13,19-tris(*tert*-butyldimethylsilyloxy)-9-hydroxy-21-((4-methoxybenzyl)oxy)-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoate (5.10)

To a solution of *t*BuLi in pentane (1.7 M, 0.15 mL, 0.23 mmol, 2.2 eq) in Et₂O (0.2 mL) kept at -78 °C under argon atmosphere, a solution of vinyl iodide **5.2** (86 mg, 0.104 mmol, 1 eq) in Et₂O (0.4 mL) was added. After stirring for 30 min, dimethylzinc in toluene (2.0 M, 0.08 mL, 0.17 mmol, 1.6 eq) was added dropwise and the reaction mixture was further stirred at -78 °C for 15 min. A solution of aldehyde **4.2** (51 mg, 0.16 mmol, 1.5 eq), azeotropically dried with toluene, in Et₂O (0.5 mL) was added dropwise, and the mixture was stirred for 1 h at -78 °C. The reaction was quenched with water (2.0 mL), warmed to R.T. and diluted with Et₂O (3.0 mL). Phases were separated and the aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (10:0.3 hexane/EtOAc) to give the desired (*Z*)-allylic alcohol **5.10** (42 mg, 40% yield) as a light yellow oil.

R_f 0.41 (8:2 hexane/EtOAc); $[\alpha]_D^{29} = -10.6$ ($c = 0.2$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.04$ (s, 6H), 0.07 (s, 3H), 0.08 (s, 6H), 0.13 (s, 3H), 0.72-0.78 (m, 1H), 0.83 (d, $J = 6.4$ Hz, 3H), 0.84 (d, $J = 6.9$ Hz, 3H), 0.88-0.91 (m, 5H), 0.90 (s, 9H), 0.91 (s, 9H), 0.92 (s, 9H), 0.95 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.9$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.17-1.41 (m, 6H), 1.45-1.55 (m, 1H), 1.61-1.68 (m, 1H), 2.01 (br s, 1H), 2.55 (m, 1H), 2.69 (m, 1H), 2.98 (m, 1H), 3.30-3.34 (m, 2H), 3.61 (m, 1H), 3.72 (s, 3H), 3.80 (s, 3H), 3.95 (m, 1H), 4.49 (d, $J_{AB} = 10.6$ Hz, 1H, upfield part of an AB system), 4.54-4.59 (m, 1H), 4.55 (d, $J_{AB} = 10.8$ Hz, 1H, downfield part of an AB system), 5.09 (d, $J = 10.1$ Hz, 1H), 5.17 (dd, $J = 1.7$ Hz, 16.8 Hz, 1H), 5.33 (dd, $J = 8.8$ Hz, 10.8 Hz, 1H), 5.51-5.58 (m, 2H), 5.59 (d, $J = 11.5$ Hz, 1H), 5.96-6.06 (m, 2H), 6.53-6.62 (m, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.37 (dd, $J = 11.3$ Hz, 15.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -4.5$ (CH₃), -4.4 (CH₃), -4.3 (CH₃), -3.7 (CH₃), -3.6 (CH₃), -3.5 (CH₃), 9.3 (CH₃), 14.5 (CH₃), 16.0 (CH₃), 18.1 (C₀), 18.2 (C₀), 18.4 (C₀), 18.8 (CH₃), 20.1 (CH₃), 20.8 (CH₃), 25.9 (CH₃),

26.0 (CH₃), 26.2 (CH₃), 30.3 (CH), 31.0 (CH₂), 32.2 (CH₂), 35.0 (CH), 35.2 (CH), 35.7 (CH), 40.4 (CH₂), 40.6 (CH), 41.0 (CH₂), 43.1 (CH), 51.0 (CH₃), 55.3 (CH₃), 64.2 (CH), 72.3 (CH), 72.8 (CH), 75.0 (CH₂), 80.5 (CH), 84.4 (CH), 113.7 (CH), 115.6 (CH), 117.2 (CH₂), 126.8 (CH), 128.9 (CH), 129.1 (CH), 131.4 (CH), 131.4 (C₀), 132.4 (CH), 134.6 (CH), 135.0 (CH), 145.5 (CH), 147.2 (CH), 159.0 (C₀), 166.9 (C₀); IR (neat): $\nu = 773, 806, 836, 1039, 1080, 1174, 1252, 1377, 1462, 1514, 1602, 1638, 1721, 2855, 2926, 2955, 3427$; HRMS (ESI): calcd. for C₅₉H₁₀₆O₈Si₃Na: 1049.70877 [*M* + Na]⁺; found: 1049.70714.



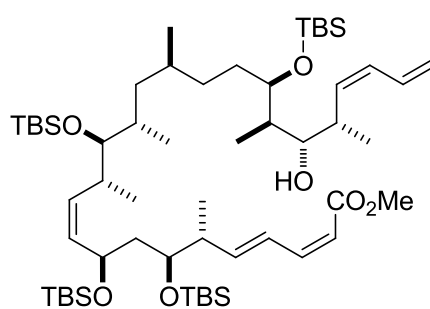
5.11

(2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*R*,13*S*,14*S*,16*S*,19*R*,20*R*,21*S*,22*S*,23*Z*)-methyl 7,9,13,19-tetrakis((*tert*-butyldimethylsilyl)oxy)-21-((4-methoxybenzyl)oxy)-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoate (5.11)

2,6-Lutidine (3 μ L, 28 μ mol, 4 eq) and TBSOTf (3 μ L, 14 μ mol, 2 eq) were added dropwise to a stirred solution of **5.10** (7.2 mg, 7 μ mol, 1 eq) in DCM (0.2 mL) cooled at -78 °C. After stirring at -78 °C for 1 h, the reaction was quenched by adding sat. aq. NaHCO₃ solution (1.0 mL) dropwise, then it was warmed to R.T.. The mixture was diluted with DCM (5 mL), layers were separated and the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by flash chromatography (95:5 hexane/EtOAc) to give the desired product **5.11** (8.0 mg, 100% yield) as a pale yellow oil.

R_f 0.80 (80:20 hexane/EtOAc); $[\alpha]_D^{29} = -14.7$ ($c = 0.4$, CHCl₃); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.02$ (s, 3H), 0.04 (s, 6H), 0.07 (s, 6H), 0.08 (s, 6H), 0.10 (s, 3H), 0.83 (d, $J = 6.8$ Hz, 6H), 0.82-0.95 (m, 8H), 0.84 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 0.92 (s, 9H), 1.04 (d, $J = 6.8$ Hz, 3H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.20-1.39 (m, 5H), 1.47-1.55 (m, 2H), 1.59-1.67 (m, 2H), 2.53 (m, 1H), 2.62 (m, 1H), 2.97 (m, 1H), 3.31-3.35 (m, 2H), 3.61 (m, 1H), 3.72 (s, 3H), 3.80 (s, 3H), 3.92 (m, 1H), 4.49-4.57 (m, 1H), 4.50 (d, $J_{AB} = 10.6$ Hz, 1H, upfield part of an AB system), 4.54 (d, $J_{AB} = 10.6$ Hz, 1H, downfield part of an AB system), 5.09 (d, $J = 10.6$ Hz, 1H), 5.17 (d, $J = 16.8$ Hz, 1H), 5.26 (dd, $J = 9.3$ Hz, 10.9 Hz, 1H), 5.55-5.62 (m, 2H), 5.59 (d, $J = 11.1$ Hz, 1H), 5.97-6.02 (m, 2H), 6.52-6.62 (m, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 7.27 (d, $J = 8.8$ Hz, 2H), 7.36 (dd, $J = 11.3$ Hz, 15.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = -4.5$ (CH₃), -4.3 (CH₃), -4.2 (CH₃), -4.1 (CH₃), -

4.0 (CH₃), -3.7 (CH₃), -3.5 (CH₃), -2.9 (CH₃), 9.2 (CH₃), 13.5 (CH₃), 16.7 (CH₃), 18.1 (C₀), 18.2 (C₀), 18.4 (C₀), 18.9 (CH₃), 20.9 (CH₃), 20.6 (CH₃), 25.8 (CH₃), 25.9 (CH₃), 26.0 (CH₃), 26.2 (CH₃), 29.7 (CH₂), 30.1 (CH), 31.6 (CH₂), 34.3 (CH), 35.1 (CH), 36.1 (CH), 40.5 (CH), 41.0 (CH₂), 43.4 (CH₂), 43.5 (CH), 51.0 (CH₃), 55.3 (CH₃), 66.7 (CH), 72.2 (CH), 72.7 (CH), 75.1 (CH₂), 80.3 (CH), 84.4 (CH), 113.6 (CH), 115.4 (CH), 117.2 (CH₂), 126.8 (CH), 128.9 (CH), 129.0 (CH), 131.3 (CH), 131.4 (C₀), 132.3 (CH), 132.4 (CH), 134.5 (CH), 145.6 (CH), 147.3 (CH), 158.9 (C₀), 166.9 (C₀); IR (neat): ν = 773, 802, 836, 1005, 1040, 1082, 1174, 1251, 1462, 1514, 1602, 1638, 1721, 2855, 2927, 2955; HRMS (ESI): calcd. for C₆₅H₁₂₀O₈Si₄Na: 1163.79525 [M + Na]⁺; found: 1163.79475.



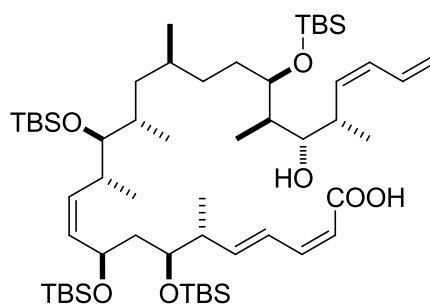
5.12

(2Z,4E,6R,7S,9R,10Z,12R,13S,14S,16S,19R,20R,21S,22S,23Z)-methyl 7,9,13,19-tetrakis((tert-butyl)dimethylsilyloxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoate (5.12)

DDQ (2.1 mg, 9 μ mol, 1.3 eq) was added to a solution of the PMB ether **5.11** (8.0 mg, 7 μ mol, 1 eq) in DCM (0.3 mL) stirred at 0 °C in the presence of a KH₂PO₄/K₂HPO₄ buffer solution at pH 7 (25 μ L). The reaction was stirred at 0 °C for 1 h before being quenched by dropwise addition of sat. aq. NaHCO₃ solution (3 mL). After diluting with DCM (7 mL), layers were separated and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography (60:40 hexane/DCM) to give the desired product **5.12** (6.1 mg, 85% yield) as a colorless oil.

R_f 0.30 (95:5 hexane/EtOAc); ¹H NMR (400 MHz, CDCl₃): δ = 0.02 (s, 3H), 0.05 (s, 9H), 0.07 (s, 3H), 0.09 (s, 6H), 0.11 (s, 3H), 0.87-0.94 (m, 11H), 0.89 (s, 9H), 0.90 (s, 9H), 0.91 (s, 9H), 0.92 (s, 9H), 0.95 (d, J = 6.7 Hz, 6H), 1.04 (d, J = 6.8 Hz, 3H), 1.25-1.34 (m, 3H), 1.38-1.44 (m, 2H), 1.50-1.71 (m, 4H), 2.35 (br s, 1H), 2.53 (m, 1H), 2.63 (m, 1H), 2.80 (m, 1H), 3.35 (m, 1H), 3.48 (dd, J = 2.2 Hz, 7.6 Hz, 1H), 3.73 (s, 3H), 3.74-3.78 (m, 1H), 3.93 (m, 1H), 4.54 (t, J = 8.8 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 5.21 (d, J = 16.9 Hz, 1H), 5.22-5.28 (m, 1H), 5.42 (t, J = 10.5 Hz, 1H), 5.56-5.63 (m, 1H), 5.59 (d, J = 11.0 Hz, 1H), 5.99 (dd, J = 7.1 Hz, 15.5 Hz, 1H), 6.09 (t, J = 11.1 Hz, 1H), 6.55 (t, J = 11.4 Hz, 1H), 6.63 (td, J = 10.8 Hz, 17.1 Hz, 1H), 7.36 (dd, J = 11.3 Hz,

15.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ = -4.4 (CH₃), -4.2 (CH₃), -4.1 (CH₃), -4.0 (CH₃), -3.8 (CH₃), -3.6 (CH₃), -2.9 (CH₃), 6.7 (CH₃), 14.1 (CH₃), 15.6 (CH₃), 17.7 (CH₃), 18.0 (C₀), 18.1 (C₀), 18.3 (C₀), 20.7 (CH₃), 20.9 (CH₃), 25.8 (CH₃), 25.9 (CH₃), 26.0 (CH₃), 26.1 (CH₃), 30.2 (CH), 30.9 (CH₂), 31.6 (CH₂), 34.2 (CH), 36.0 (CH), 36.2 (CH), 37.5 (CH), 41.1 (CH₂), 43.4 (CH₂), 43.5 (CH), 51.0 (CH₃), 66.7 (CH), 72.2 (CH), 77.3 (CH), 77.9 (CH), 80.2 (CH), 115.4 (CH), 117.7 (CH₂), 126.8 (CH), 129.8 (CH), 131.2 (CH), 132.3 (CH), 132.5 (CH), 135.4 (CH), 145.6 (CH), 147.3 (CH), 166.9 (C₀); HRMS (ESI): calcd. for C₅₇H₁₁₂O₇Si₄Na: 1043.73773 [$M + \text{Na}$]⁺; found: 1043.73677.



5.13

(2Z,4E,6R,7S,9R,10Z,12R,13S,14S,16S,19R,20R,21S,22S,23Z)-7,9,13,19-tetrakis((tert-butyldimethylsilyl)oxy)-21-hydroxy-6,12,14,16,20,22-hexamethylhexacos-2,4,10,23,25-pentaenoic acid (5.13)

To a stirred solution of the ester **5.12** (6.1 mg, 9 μmol , 1 eq) in THF (0.2 mL) and EtOH (0.5 mL), 1 N aq. KOH (40 μL) was added, and the reaction was refluxed for 6 h (bath temperature: 52 $^{\circ}\text{C}$). The solvent was removed under reduced pressure. The residue was diluted with Et₂O (2 mL) and sat. aq. NH₄Cl solution (1 mL); layers were separated and the aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic extracts were dried over Na₂SO₄ and evaporated under reduced pressure. The product was purified by flash chromatography (90:10 hexane/EtOAc) to afford the *seco* acid **5.13** (6.0 mg, 100% yield) as a colorless oil.

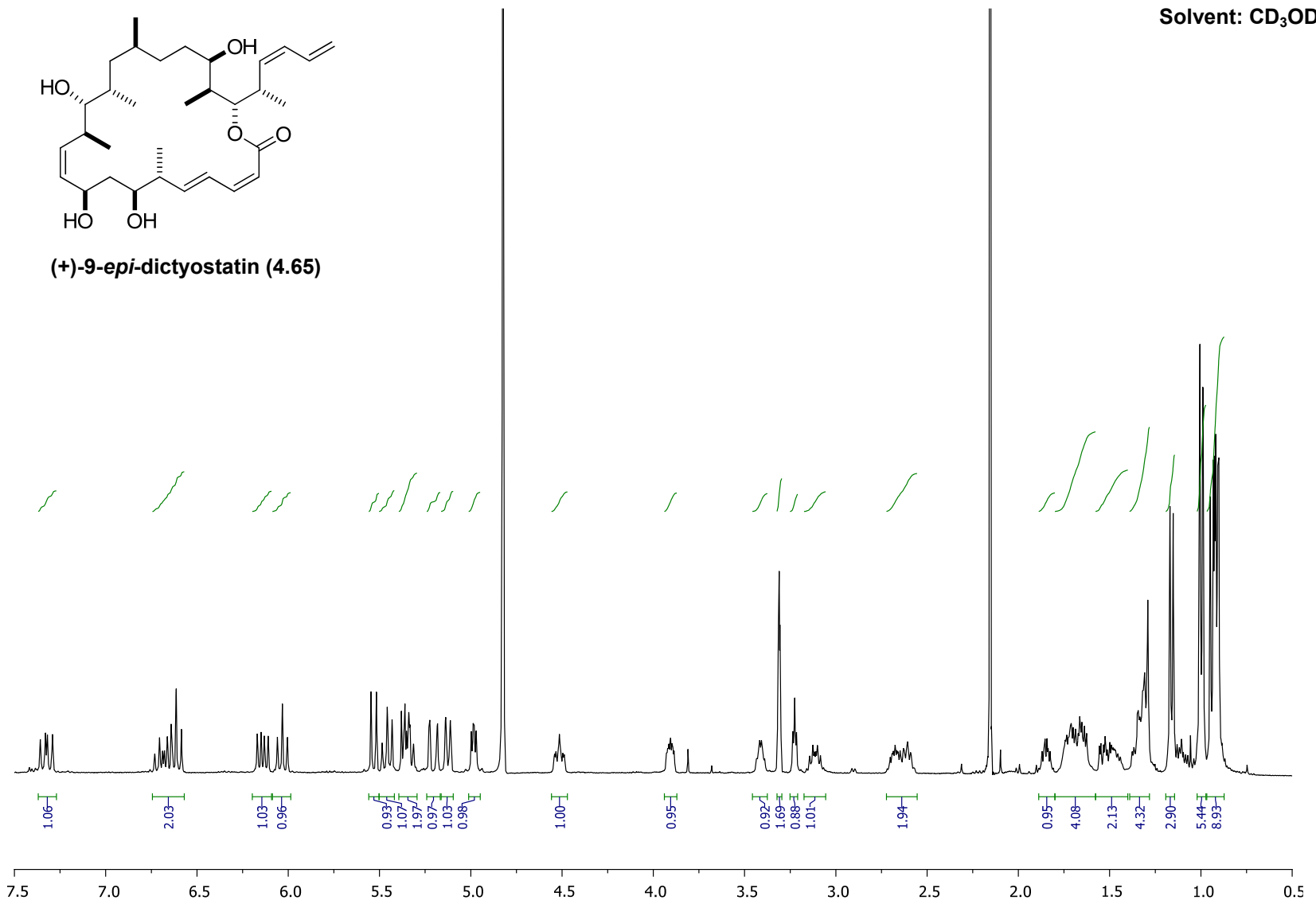
R_f 0.27 (80:20 hexane/EtOAc); ^1H NMR (400 MHz, CDCl_3): δ = 0.02 (s, 3H), 0.05 (s, 6H), 0.07 (s, 6H), 0.08 (s, 6H), 0.11 (s, 3H), 0.85 (s, 9H), 0.86-0.92 (m, 14H), 0.88 (s, 9H), 0.91 (s, 9H), 0.92 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.23-1.34 (m, 5H), 1.40-1.43 (m, 1H), 1.50-1.73 (m, 3H), 2.52 (m, 1H), 2.62 (m, 1H), 2.80 (m, 1H), 3.35 (m, 1H), 3.48 (m, 1H), 3.76 (m, 1H), 3.90 (m, 1H), 4.52 (t, J = 8.8 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 5.19-5.28 (m, 2H), 5.42 (t, J = 10.3 Hz, 1H), 5.60 (m, 2H), 6.02-6.12 (m, 2H), 6.59-6.68 (m, 2H), 7.33 (dd, J = 11.5 Hz, 15.4 Hz, 1H).

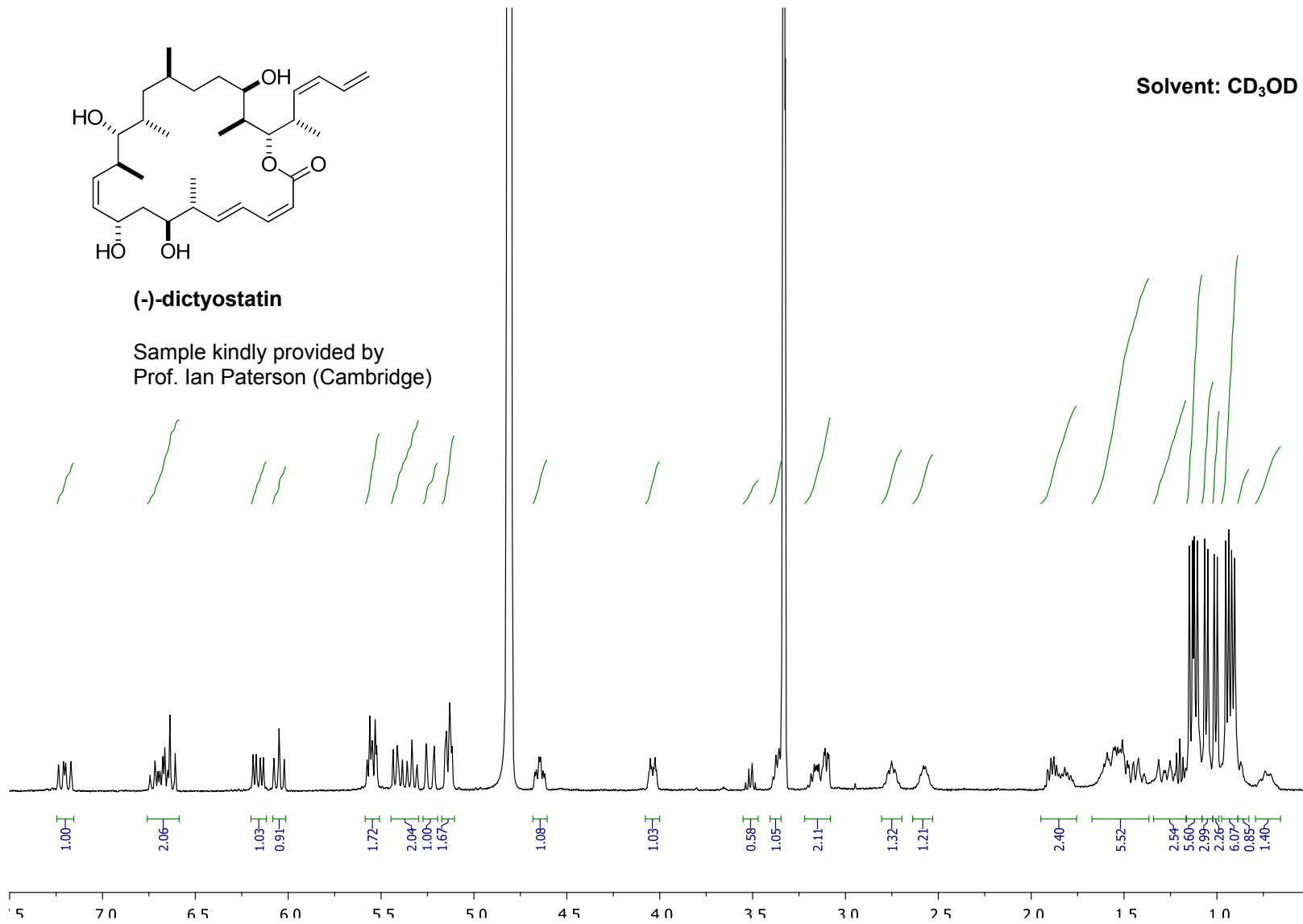
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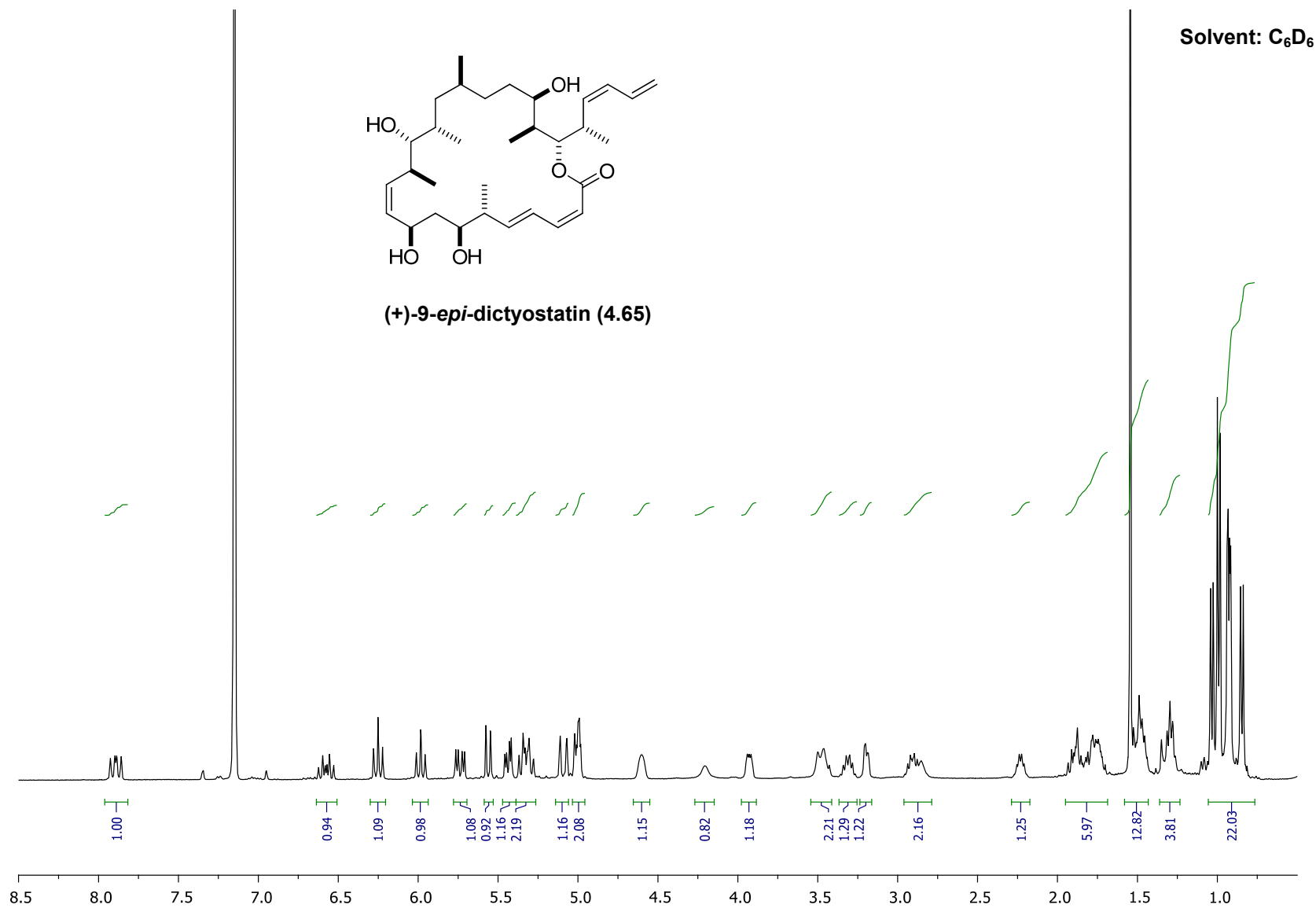
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 - ⁸ Kirkham, J. E. D.; Courtney, T. D. L.; Lee, V.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 7219.
 - ⁹ Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825.
 - ¹⁰ Gardner N. M. Ph.D. Thesis, University of Cambridge, **2008**.
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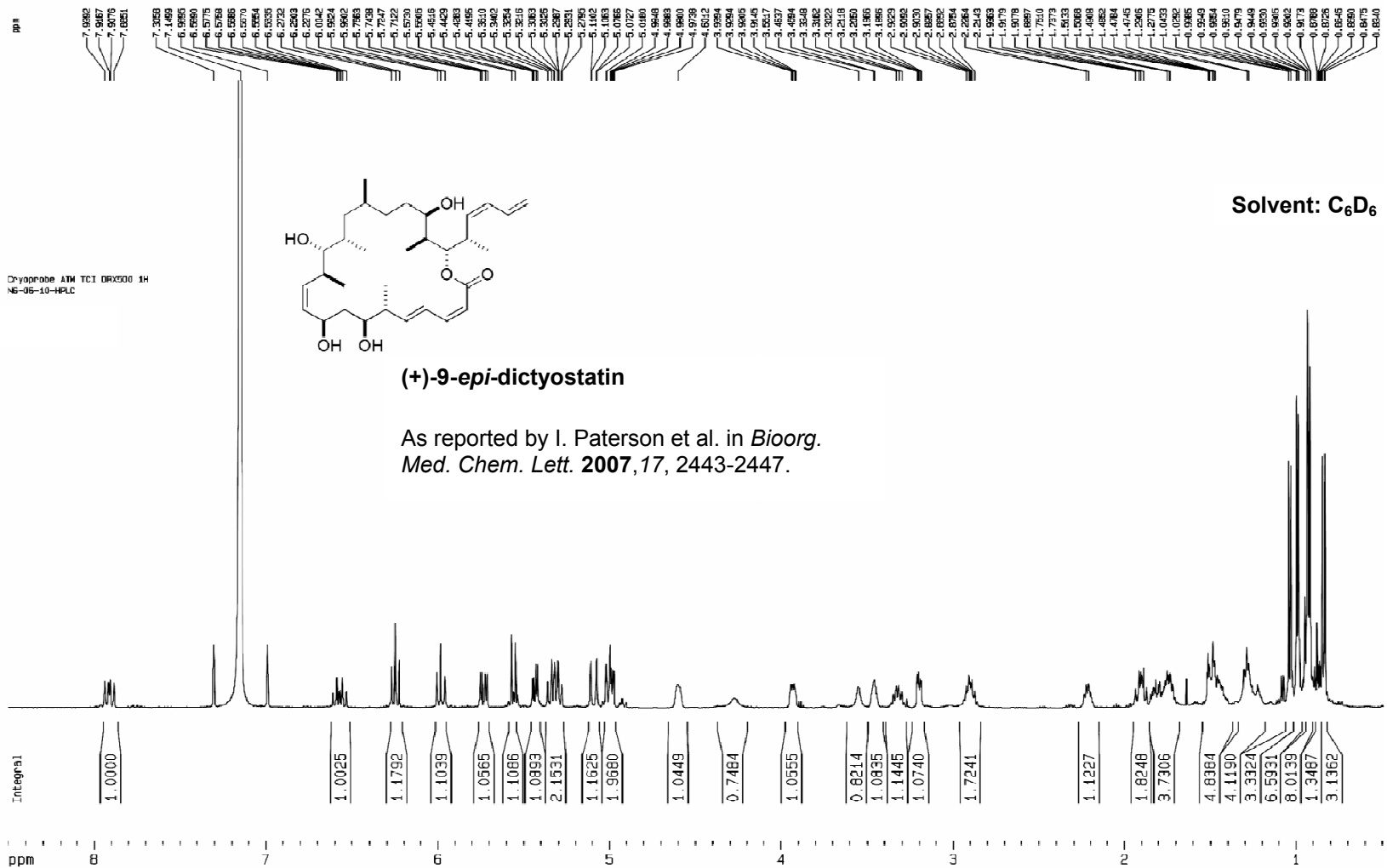
Appendix A

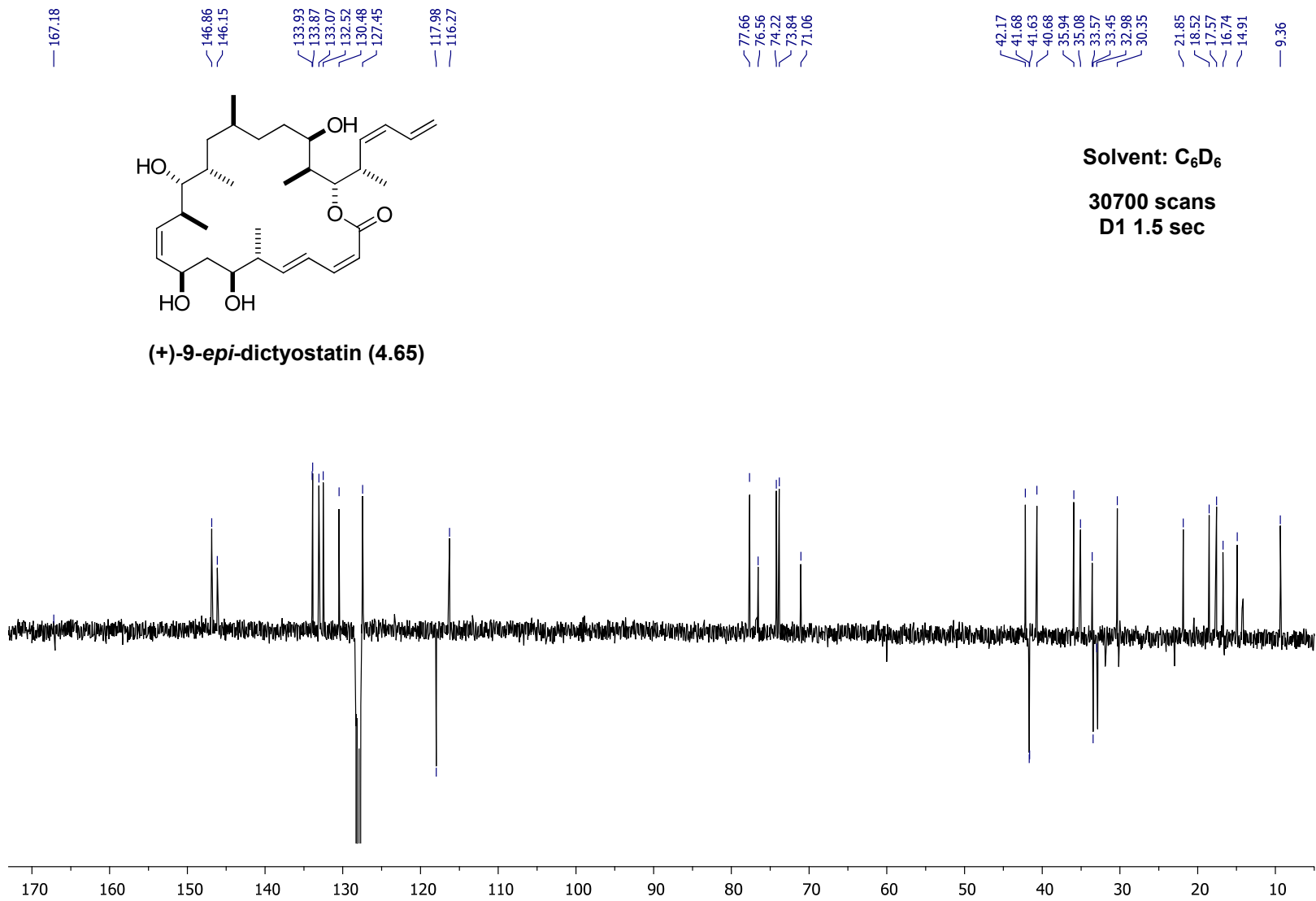
^1H and ^{13}C NMR Spectra of (+)-9-*epi*-Dictyostatin

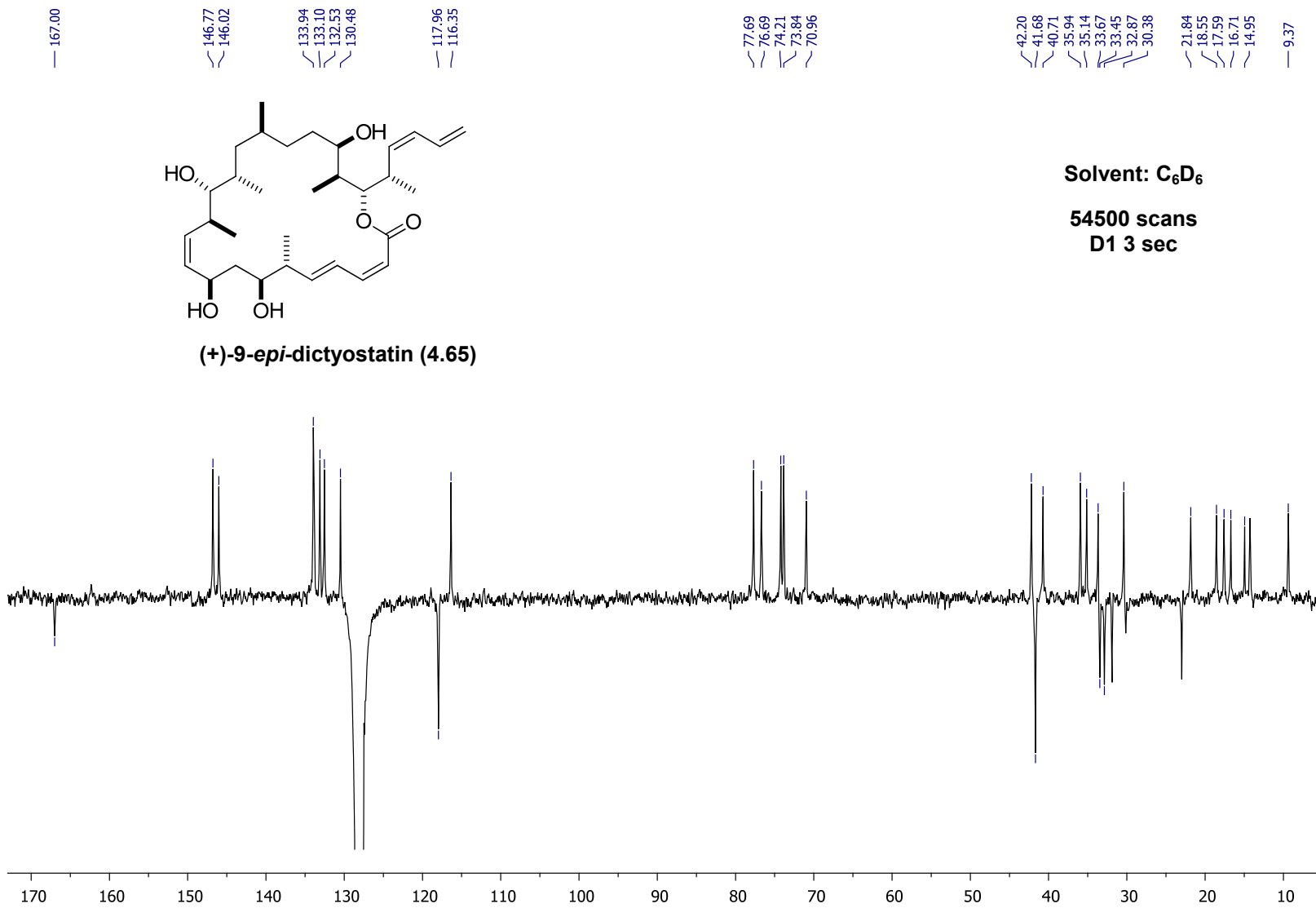


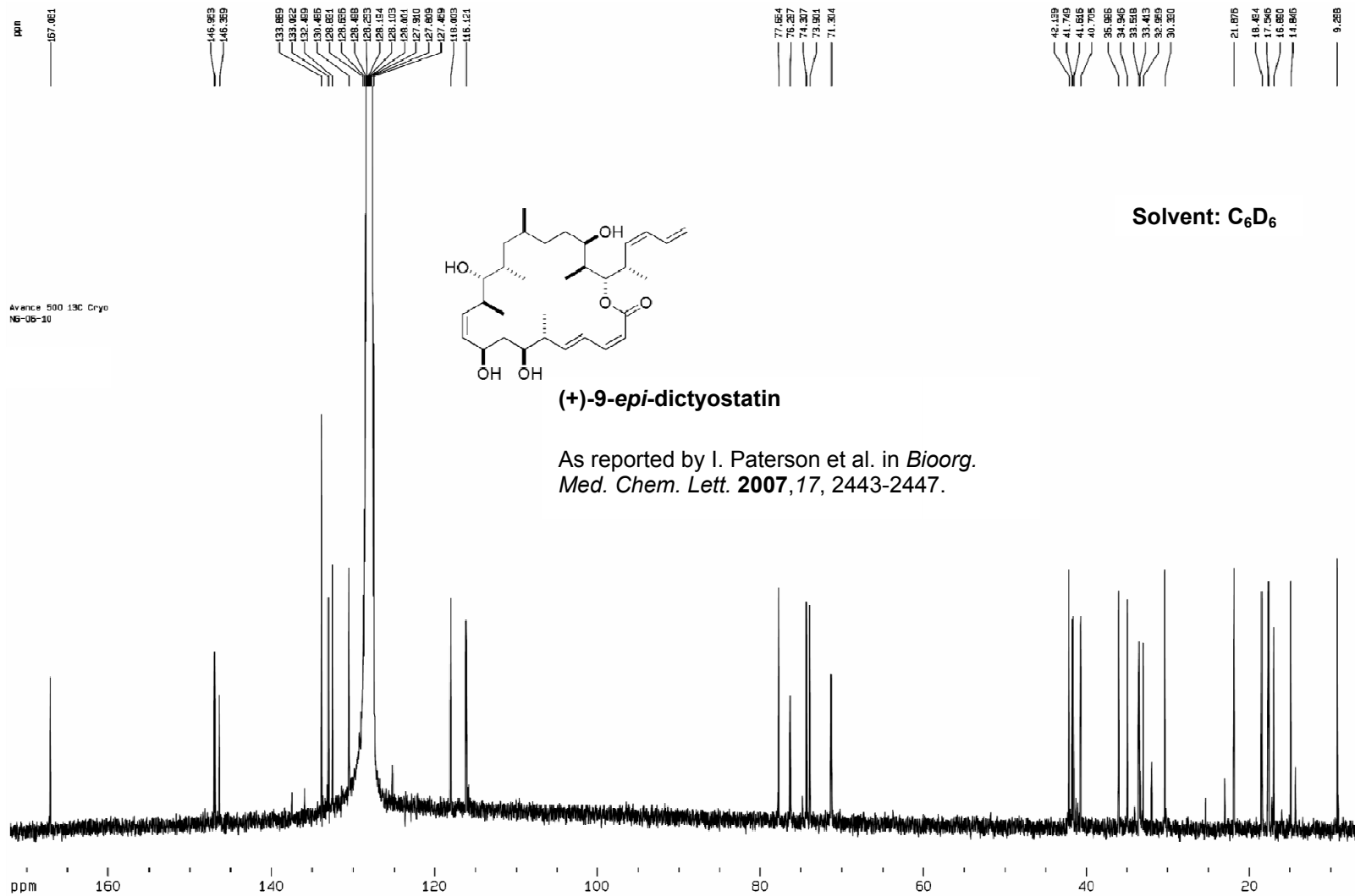








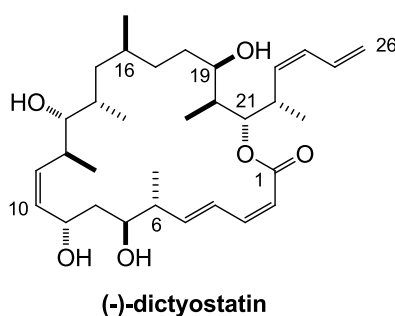




Appendix B

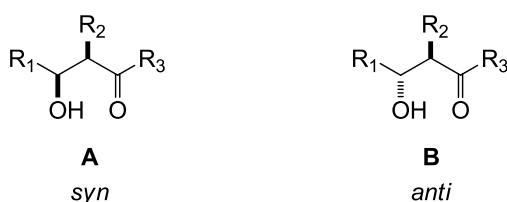
Compound Numbering

For the most part, accepted naming and numbering priorities (IUPAC) are used throughout this dissertation. The numbering system used for dictyostatin by Pettit and co-workers¹ has been adopted for dictyostatin and respective analog/hybrids of the same compound.



Nomenclature

The *syn* and *anti* convention introduced by Masamune,² for assigning the relative stereochemistry of vicinal stereocenters is used in this dissertation. A *syn* relationship refers to the two substituents both pointing into or out of a plane defined by the main chain drawn in a zig-zag conformation. Conversely, an *anti* relationship refers to the two substituents on opposite sides of the plane. The two diastereoisomers **A** and **B** are thus referred to as *syn* and *anti* respectively.



The Cahn-Ingold-Prelog priority rules, CIP system or CIP conventions³ for assigning the configuration of each stereocenter (*R* or *S* descriptor) and each double bond (*E* or *Z* descriptor) are used in this dissertation.

¹ Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc. Chem. Commun.* **1994**, 1111.

² Masamune, S.; Ali, S.; Snitman, D. L.; Garvey, D. S.; *Angew. Chem. Int. Ed.* **1980**, *19*, 557.

³ Chan, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem. Int. Ed.* **1966**, *5*, 385.

Appendix C

List of Abbreviations

1A9	Ovarian cancer cell line
1A9/Ptx10	Ovarian cancer Taxol®-resistant cell line
1A9/Ptx22	Ovarian cancer Taxol®-resistant cell line
2,6-lut	2,6-Lutidine
Ac	Acetyl
ACS	American Cancer Society
aq.	Aqueous
AsPC-1	Pancreatic cancer cell line
Bn	Benzyl
Bu	Butyl
CAN	Ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata oxazaborolidine
CCNS	Cellular Cycle Nonspecific
CCS	Cellular Cycle Specific
CM	Cross-metathesis
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DIBAL-H	Diisobutylaluminum hydride
DIPA	Diisopropylamine
DIPEA	Diisopropylethylamine
DLD-1	Colon cancer cell line
DMAP	4-Dimethylamino pyridine
DMP	Dess Martin Periodinane
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1H)-one
DMSO	Dimethylsulfoxide
dr	Diastereoisomeric ratio
EDC	1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride
Epo	Epothilone

ESI	Electrospray ionization
Et	Ethyl
FDA	Food and Drug Administration (US)
GTP	Guanosine 5'-triphosphate
h	hour
HMRS	High resolution mass spectrometry
HPLC	High Performance Liquid Chromatography
HT29	Colon cancer cell line
HWE	Horner-Wadsworth-Emmons
IC50	Mean inhibitory concentration
Imid	Imidazole
<i>i</i> Pr	Isopropyl
IR	Infra-red
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
MAP	Microtubule Associated Protein
MDR	Multiple Drug Resistance
Me	Methyl
Mes	Mesityl
min	Minutes
μ M	Micromolar
Ms	Methanesulfonyl
m.s.	Molecular Sieves
MSA	Microtubule Stabilizing Agent
MTOCs	Microtubule Organising Centres
NBSH	2-Nitrobenzenesulfonylhydrazide
NCI	National Cancer Institute (US)
NCI/ADR	Taxol [®] -resistant Cancer cell line
NMO	<i>N</i> -methylmorpholine oxide
o.n.	Over Night
OTf	Trifluoromethanesulfonate
PANC-1	Pancreatic cancer cell line
PgP	Phospho-glycoprotein
Ph	Phenyl
PMB	<i>p</i> -Methoxybenzyl
PMP	<i>p</i> -Methoxyphenyl
PPTS	Pyridinium <i>p</i> -toluenesulfonate
Pr	Propyl
<i>p</i> -TSA	<i>p</i> -Toluenesulfonic acid

Py	Pyridine
r.t. and R.T.	Room temperature
Rf	Retention factor
SAR	Structure Activity Relationship
sat.	Saturated
TBS	<i>tert</i> -Butyldimethylsilyl
TBSOTf	<i>tert</i> -Butyldimethylsilyl-trifluoromethanesulfonate
TEA	Triethylamine
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate

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Ringrazio Elena,

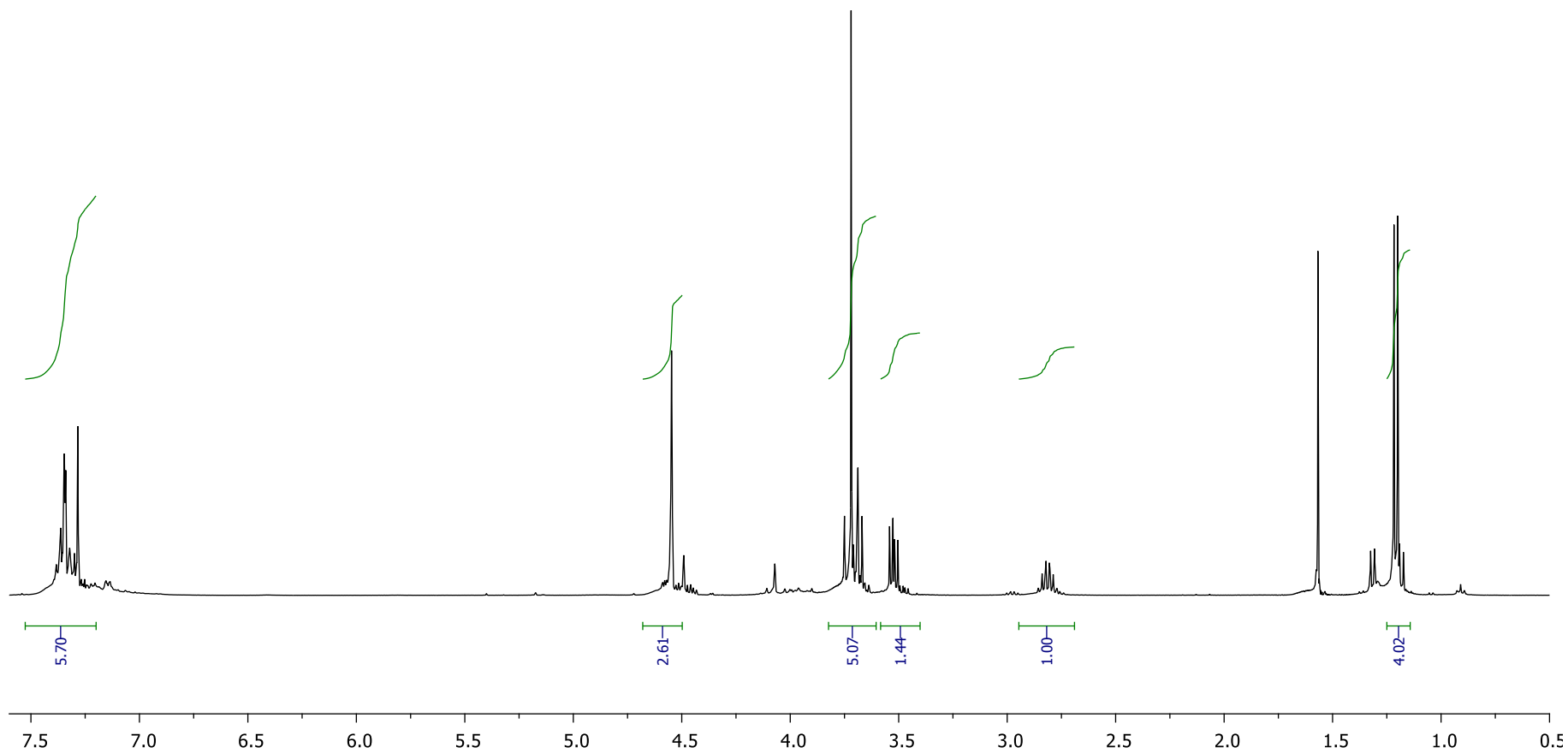
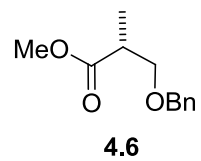
perché c'è sempre stata. In questi 3 anni come nei precedenti 25. E perché so che ci sarà nei prossimi che verranno, comunque vadano le cose.

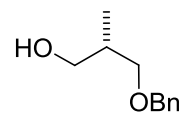
Ringrazio Elena e Max,

per il supporto psicologico, perché ora so cos'è un rivelatore al germanio, come funziona un decadimento beta e come scassinare una macchinetta delle merendine. Perché tutto quello che non è stata chimica, in questi tre anni, l'ho vissuto assieme a loro.

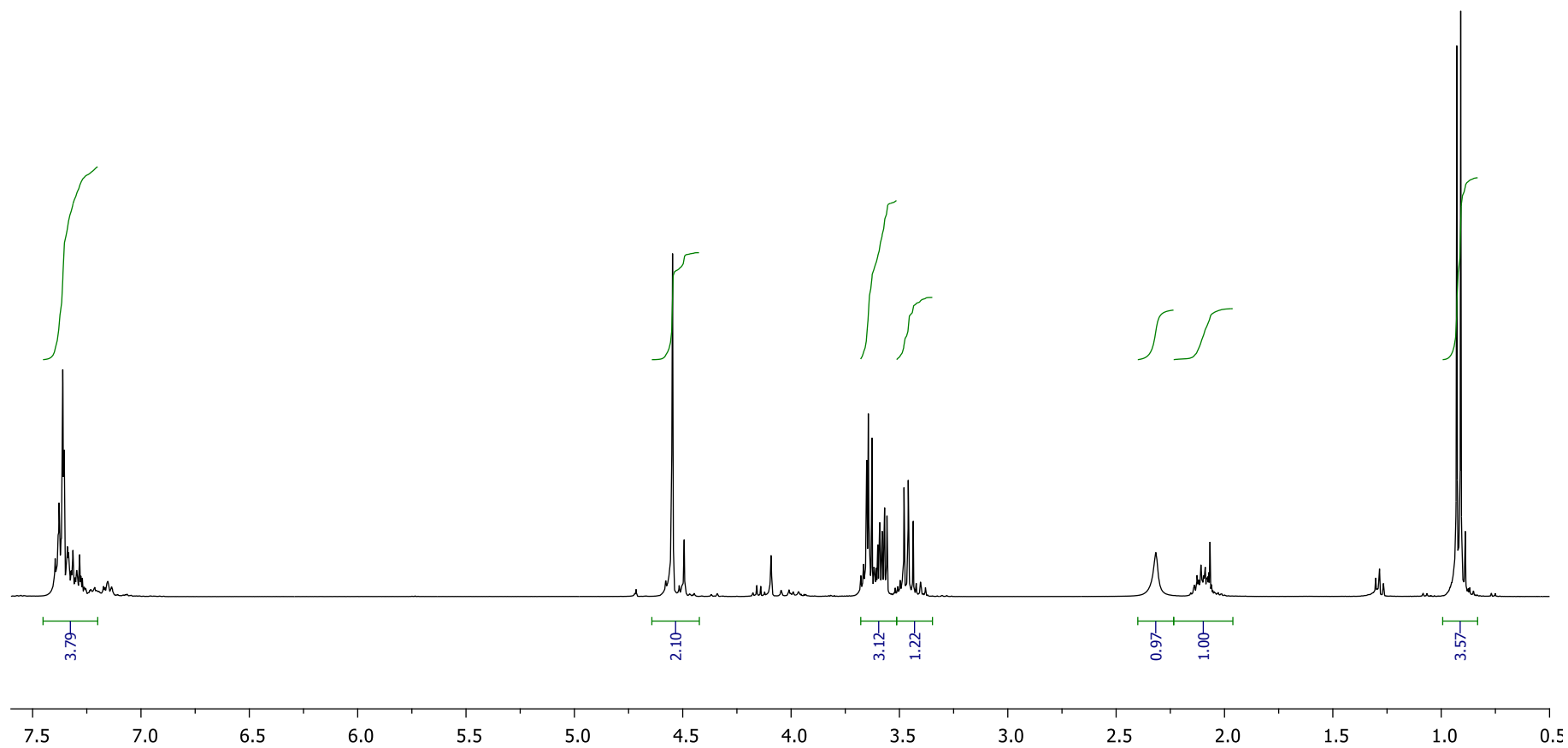
E ringrazio tutti quelli che non ho nominato personalmente ma che mi hanno riempito questo periodo e lo sanno. Perché la felicità è forse un'altra cosa, ma quello che mi è passato sotto gli occhi, in questi anni 3 anni di dottorato, non lo cambierei con nient'altro.

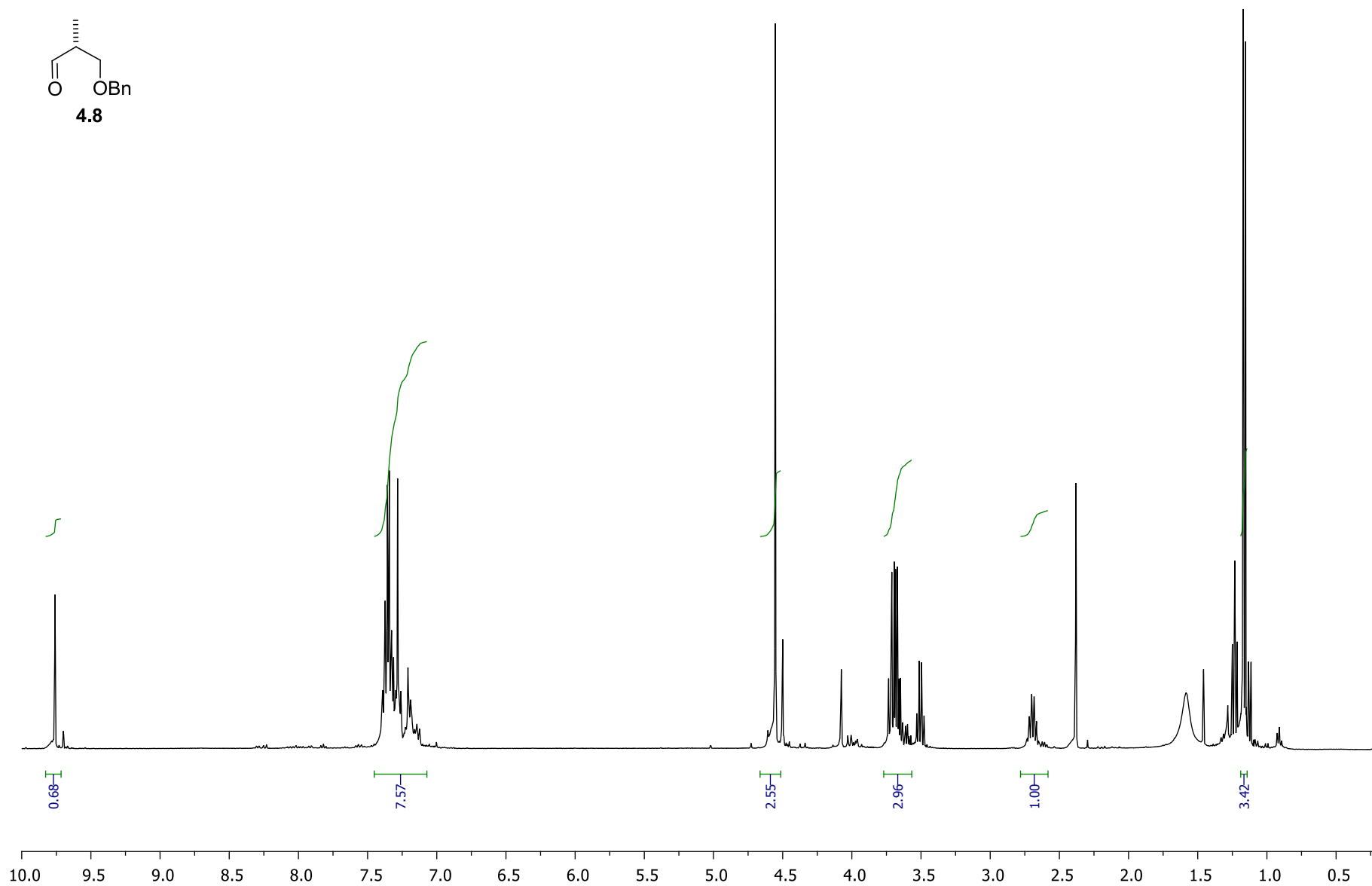
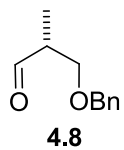
Synthesis of Aldehyde C1-C9
NMR Spectra

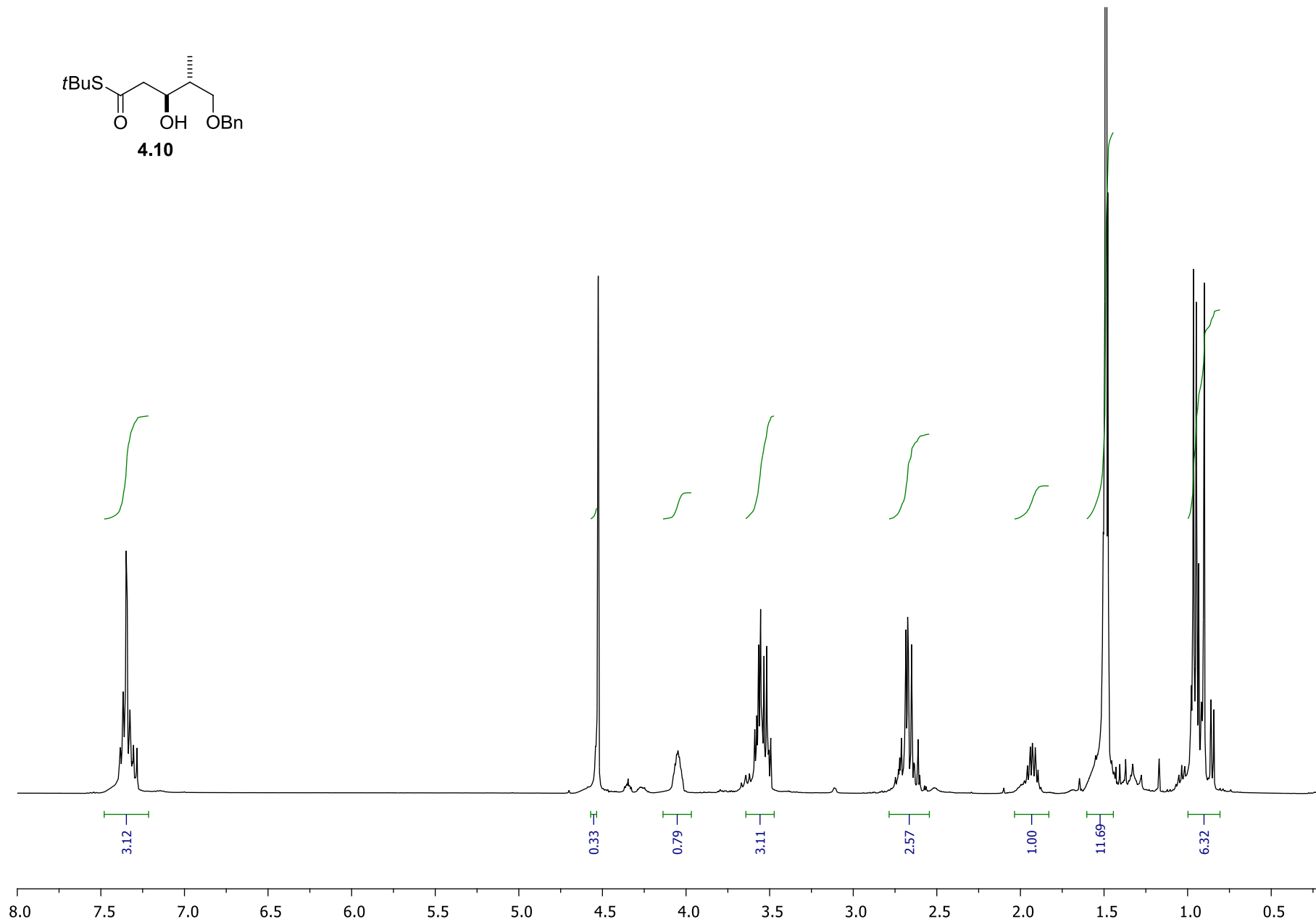
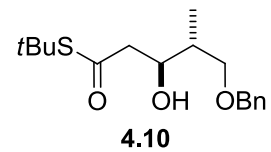




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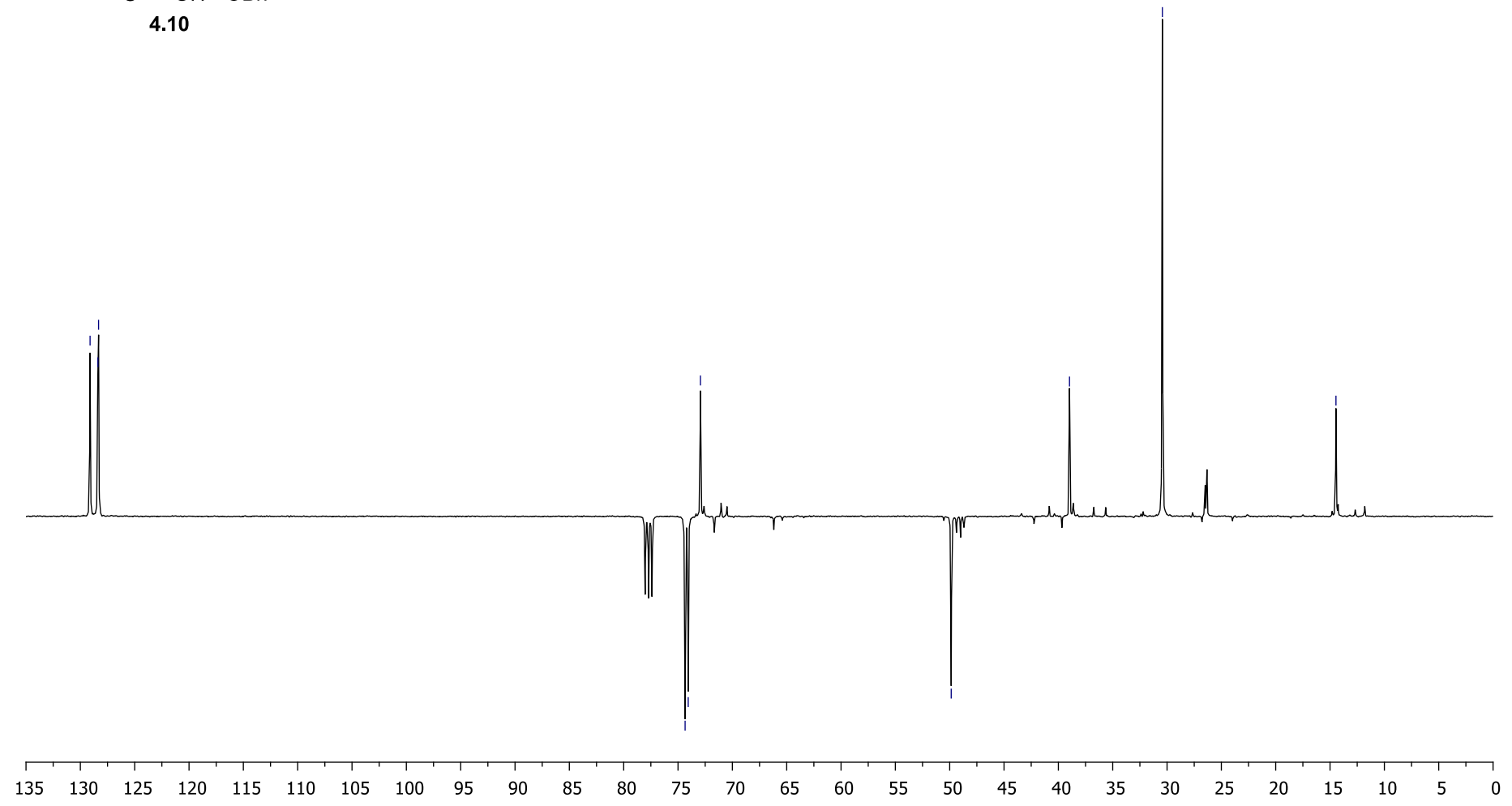
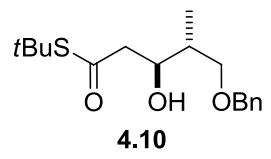
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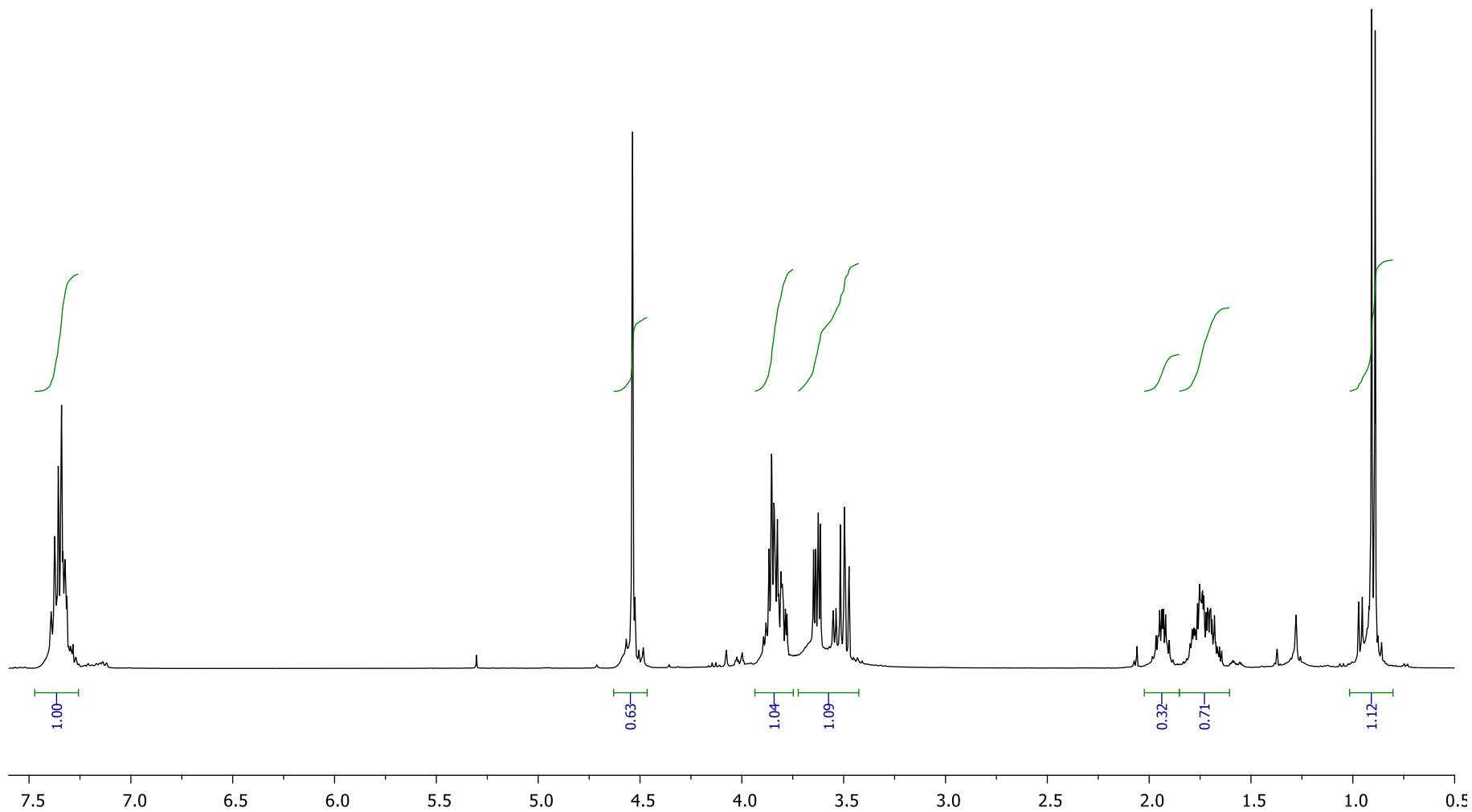
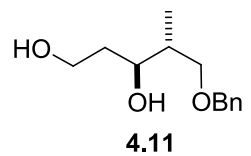
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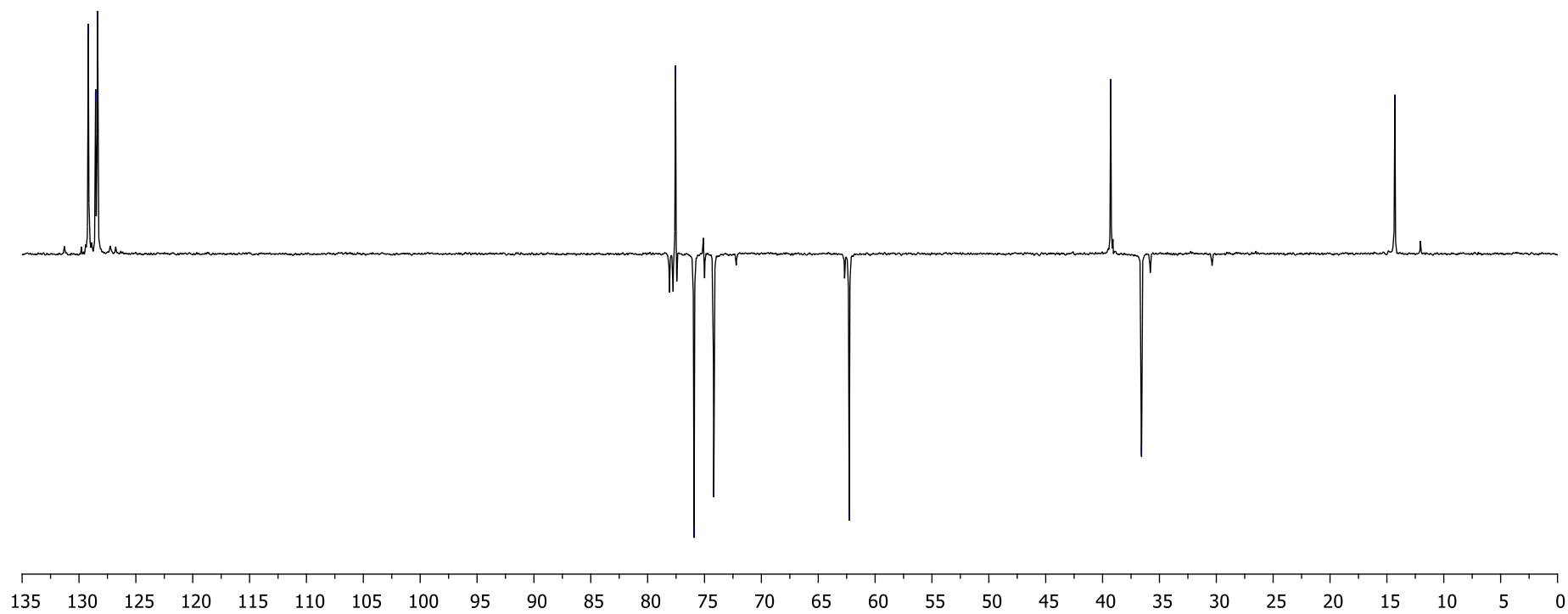
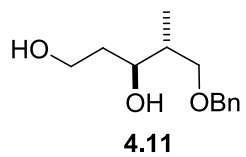
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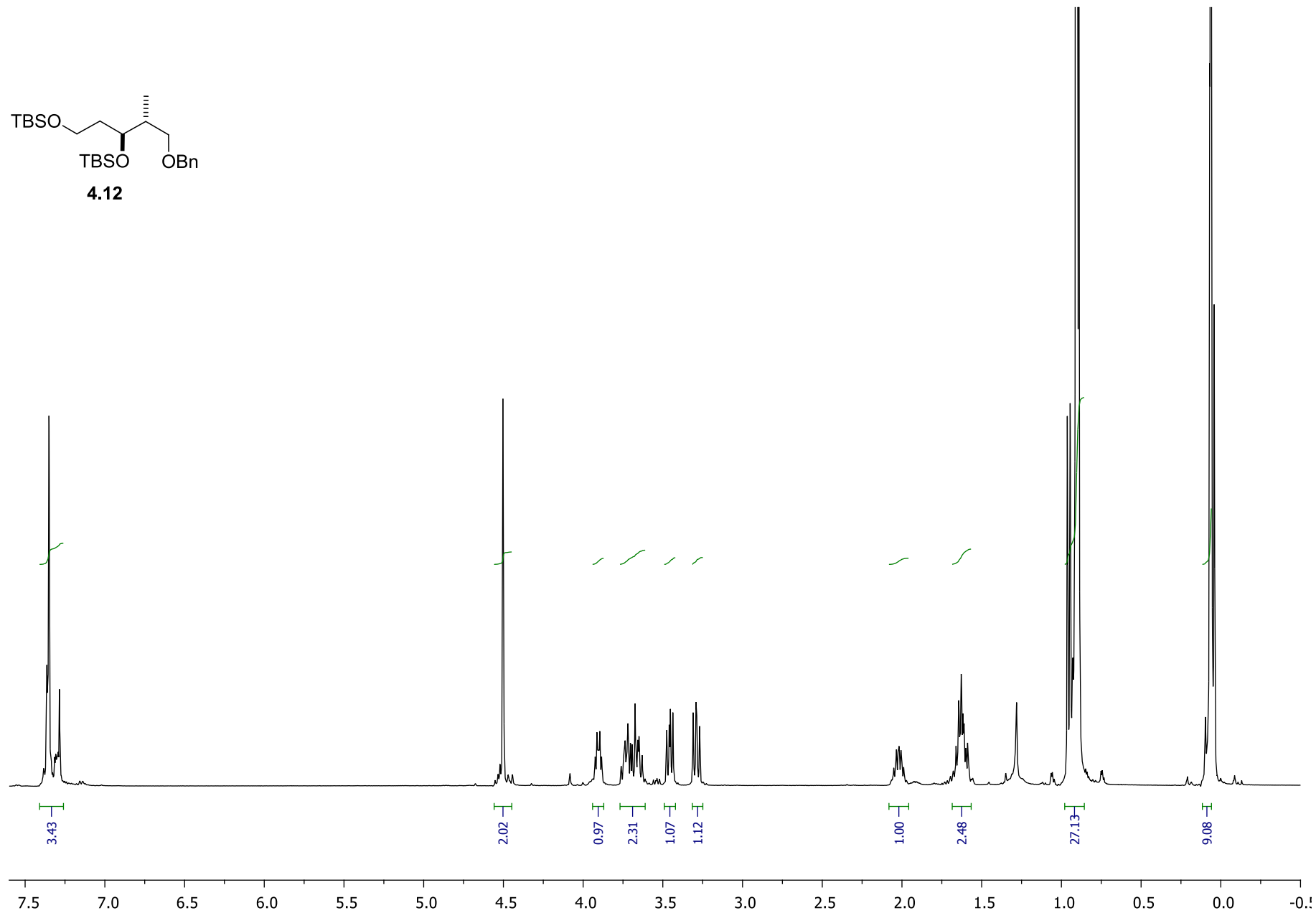
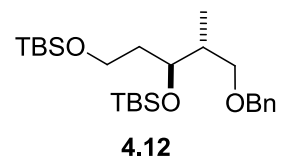
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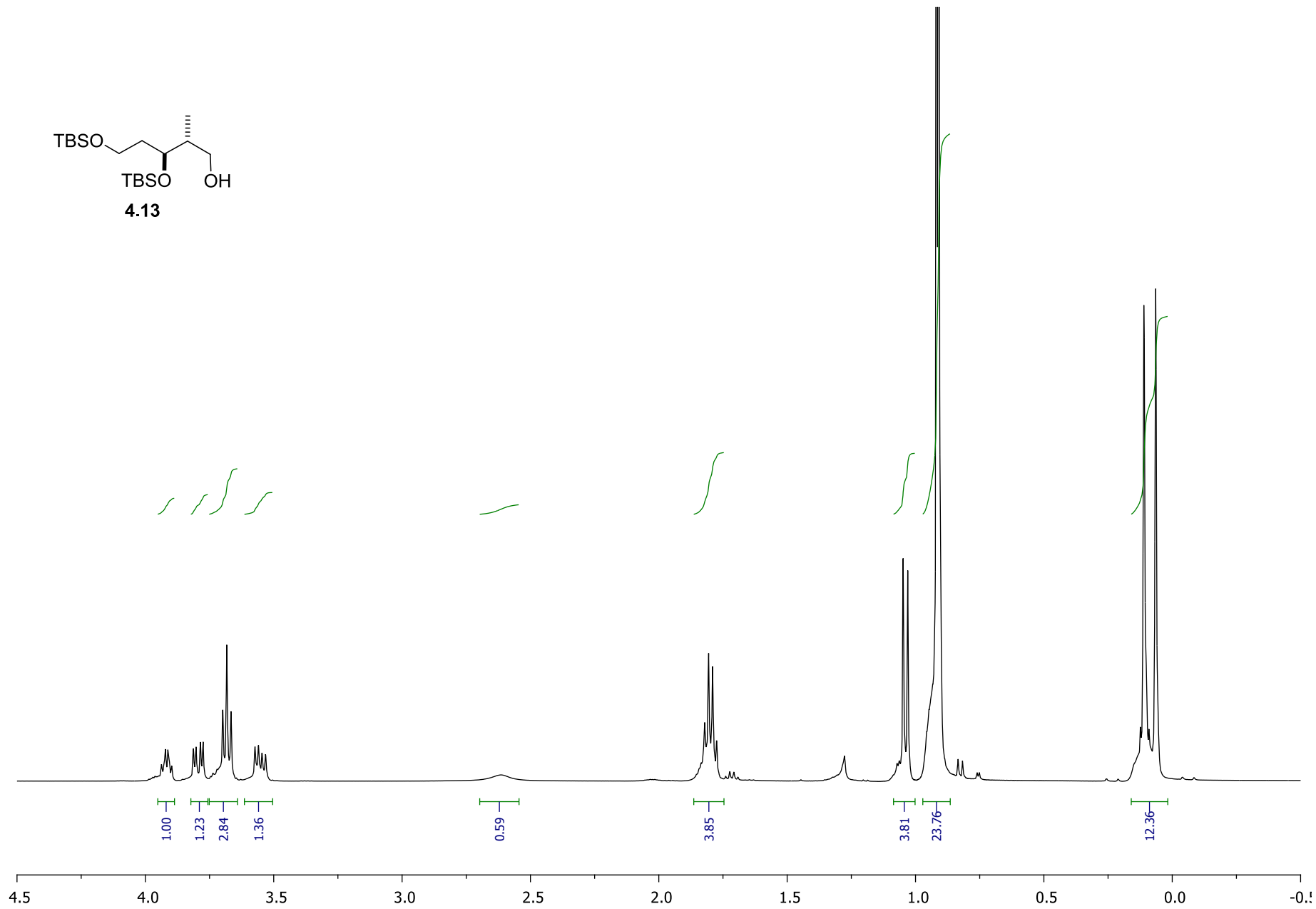
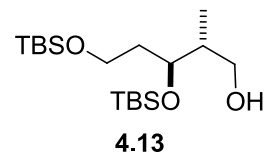
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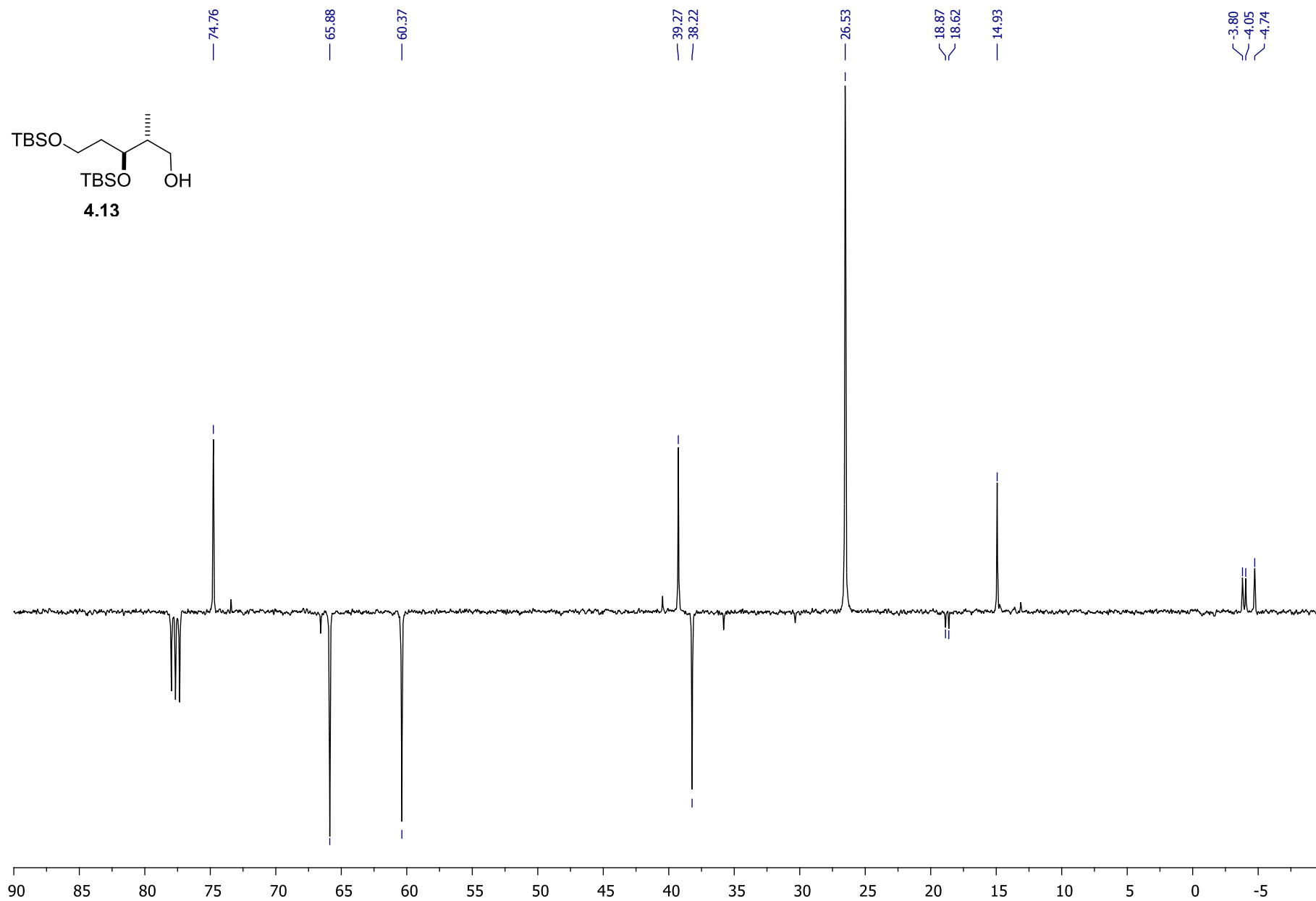
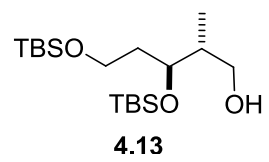
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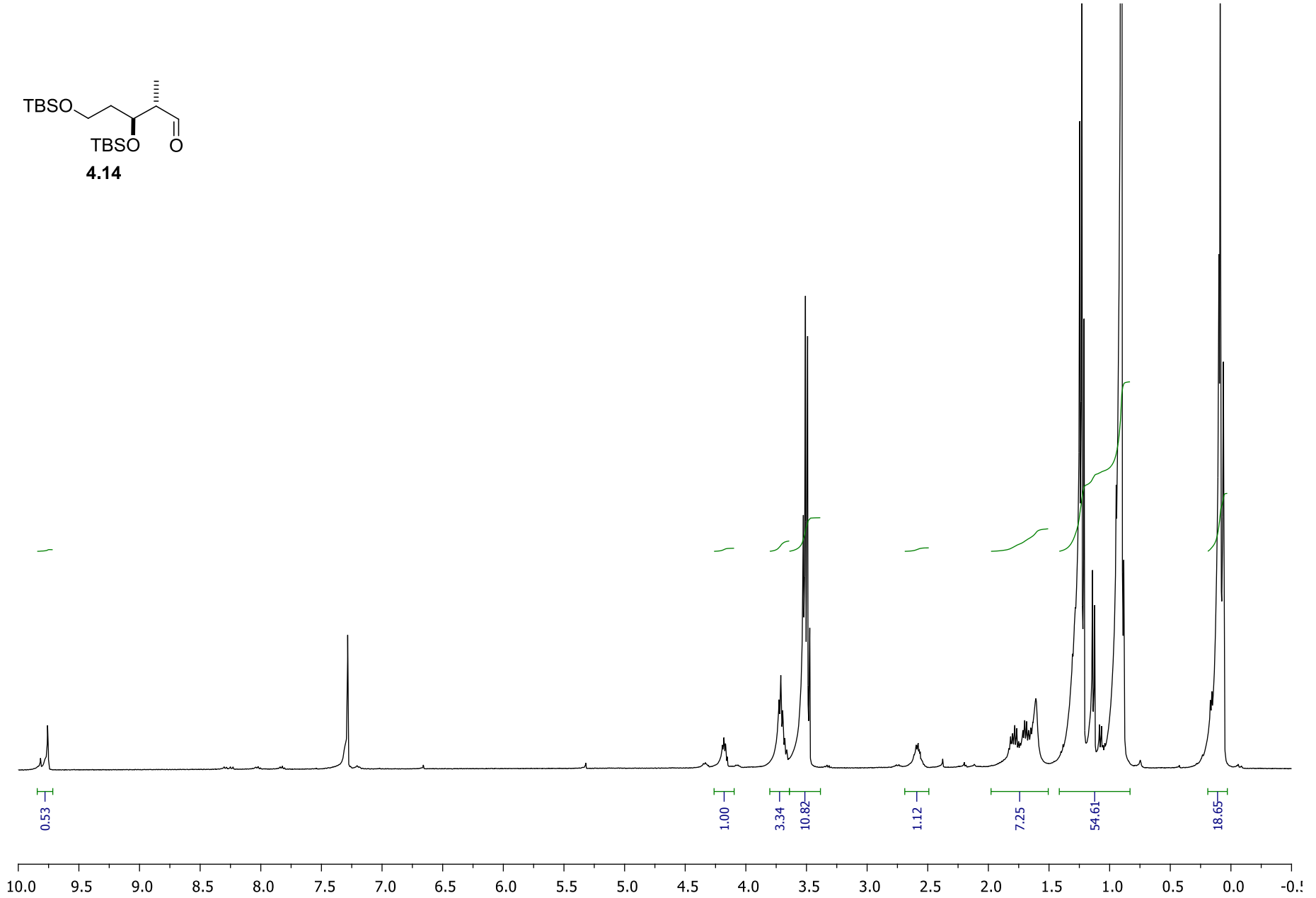
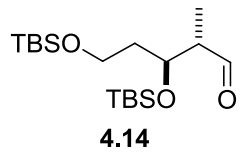
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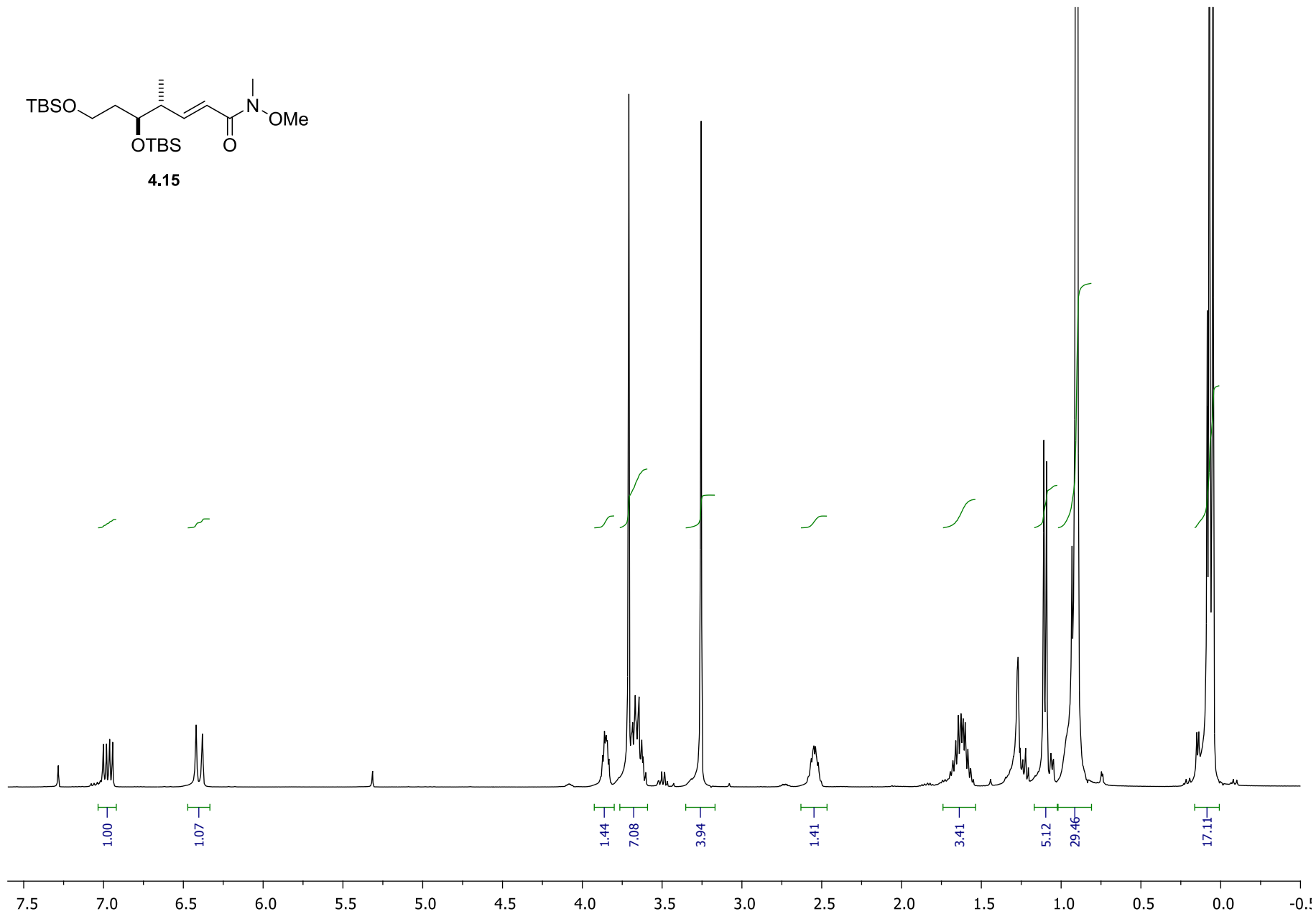
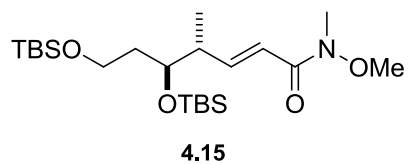


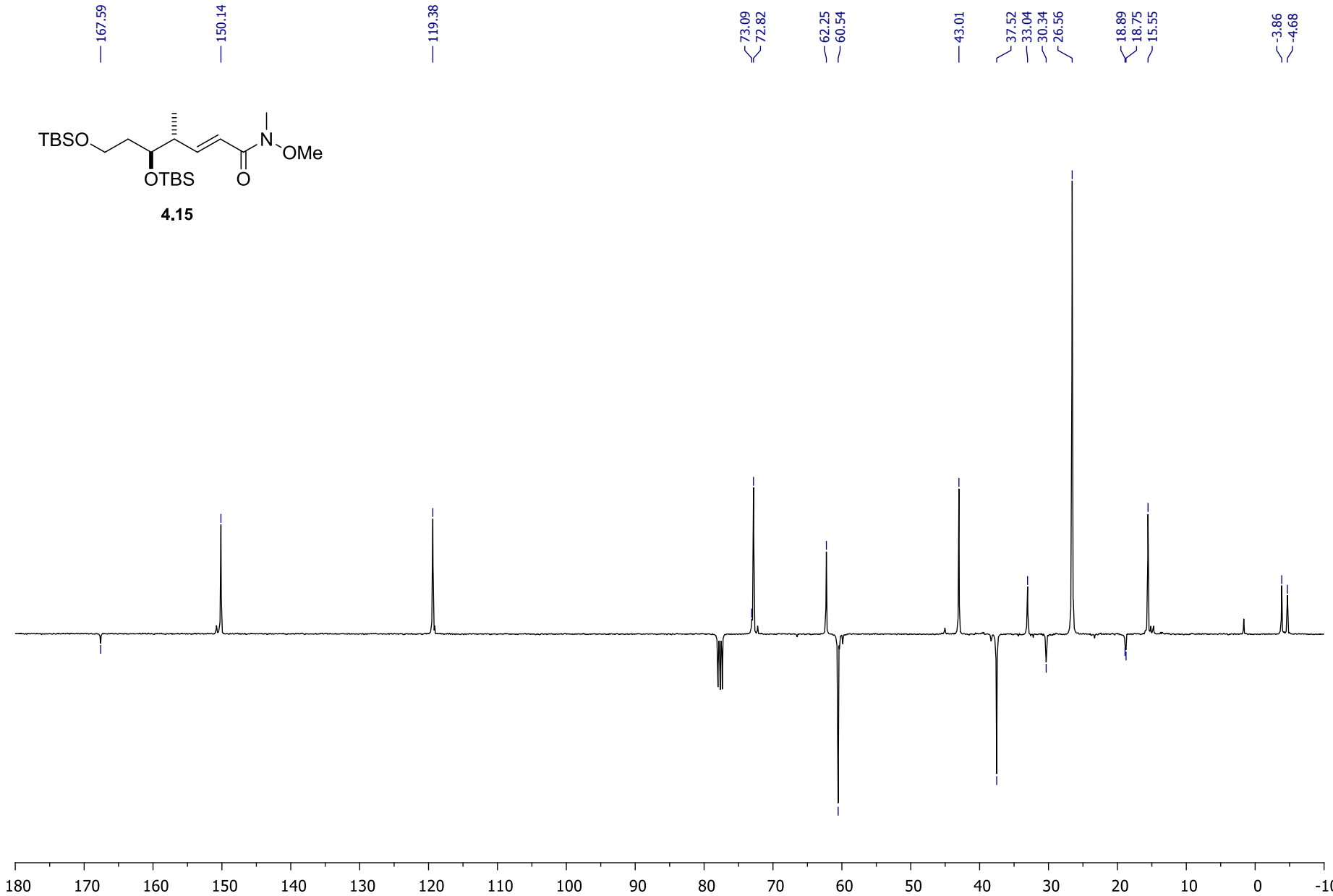
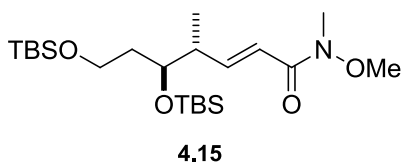


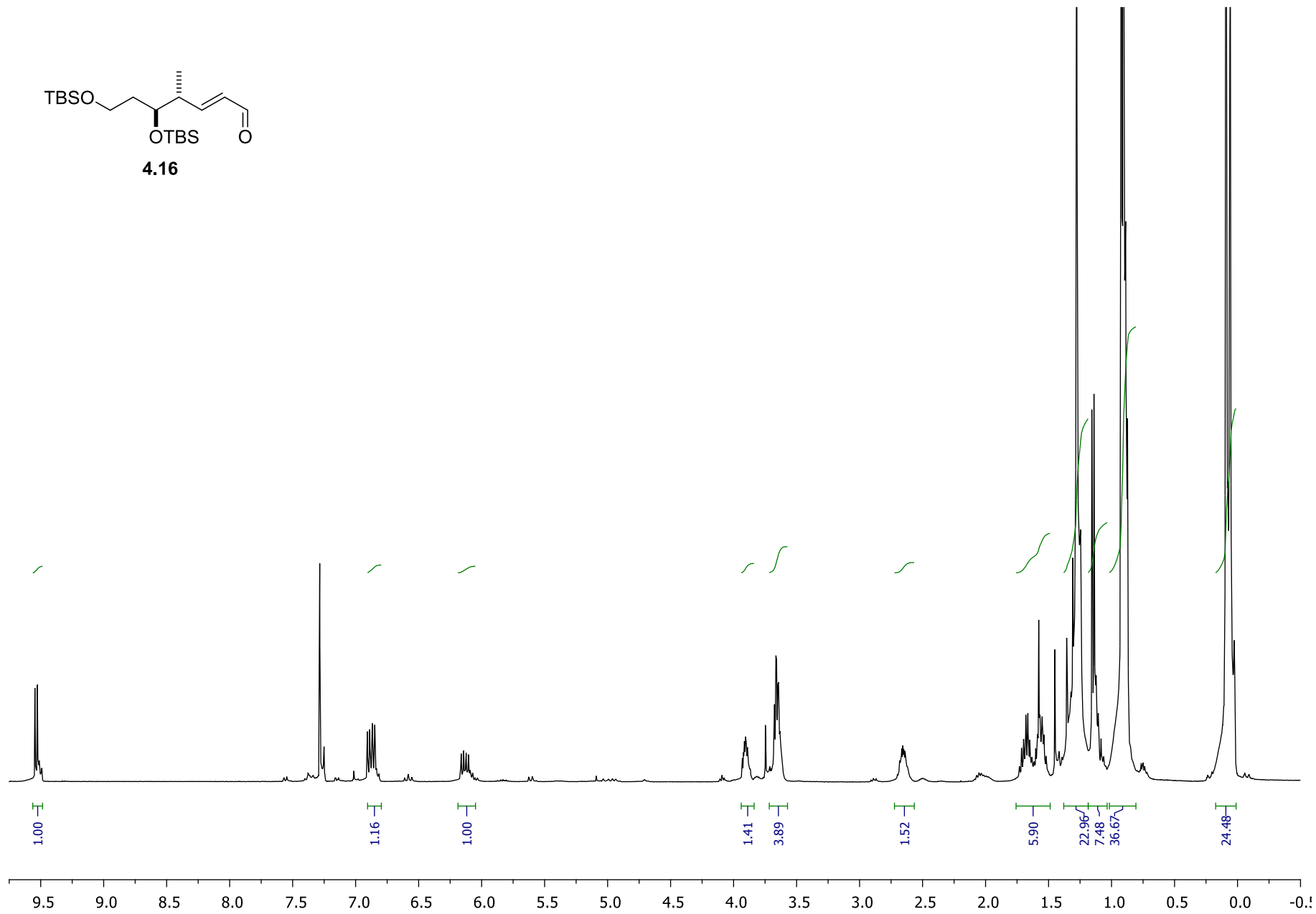
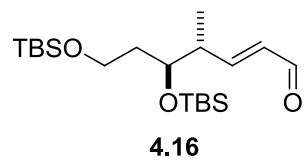


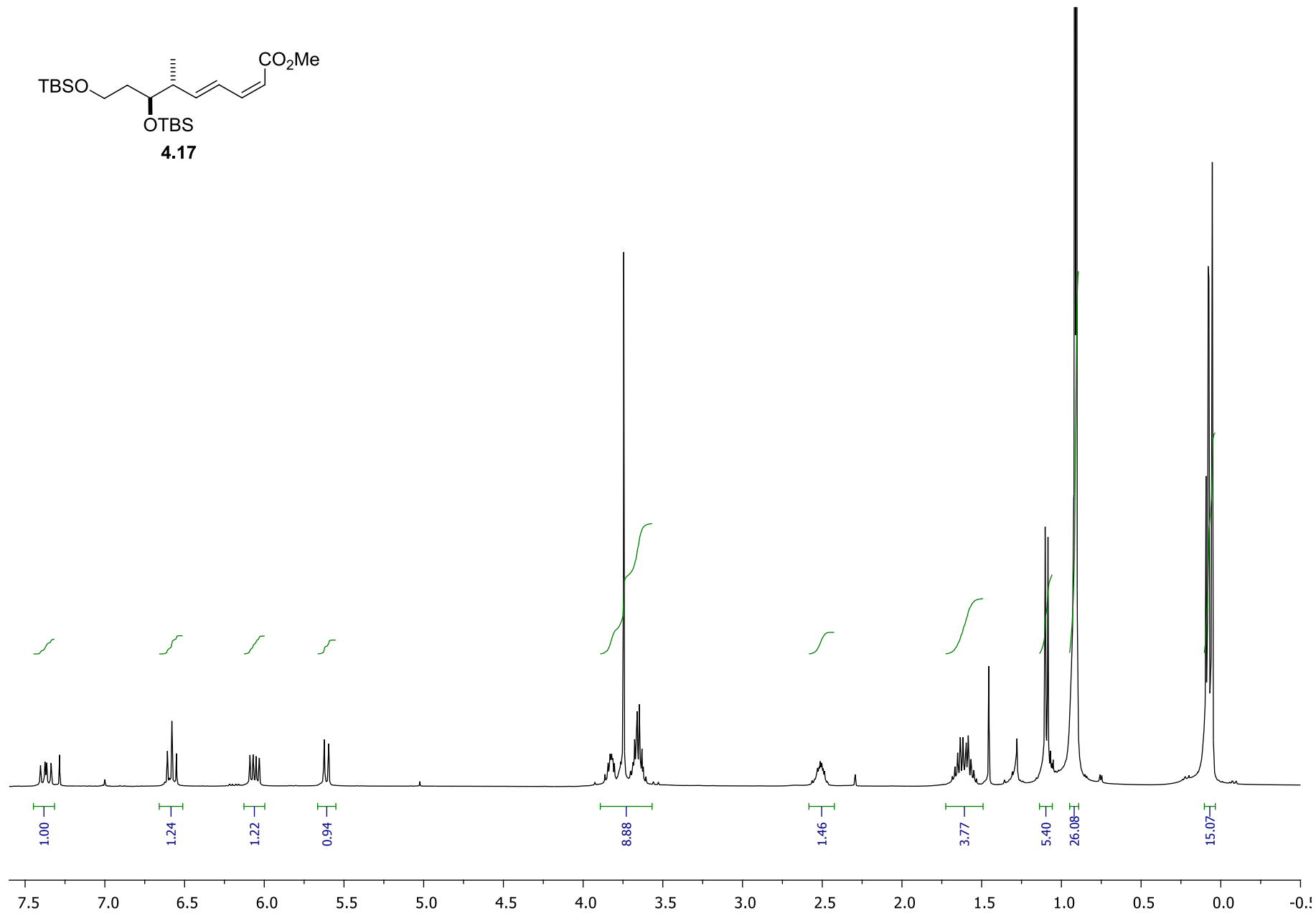
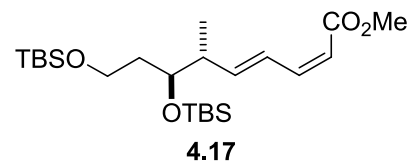


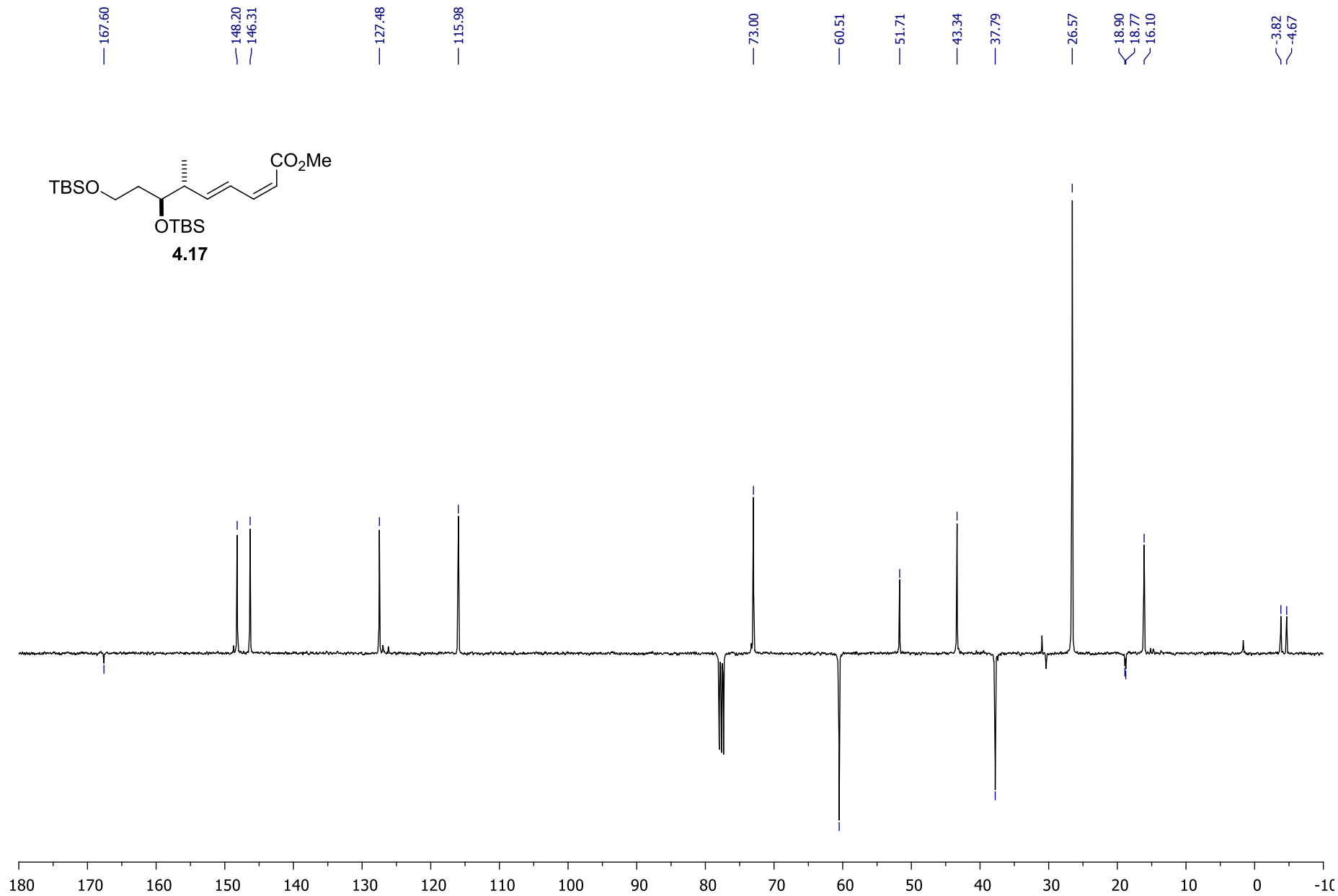
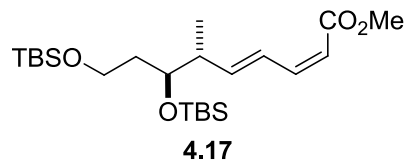


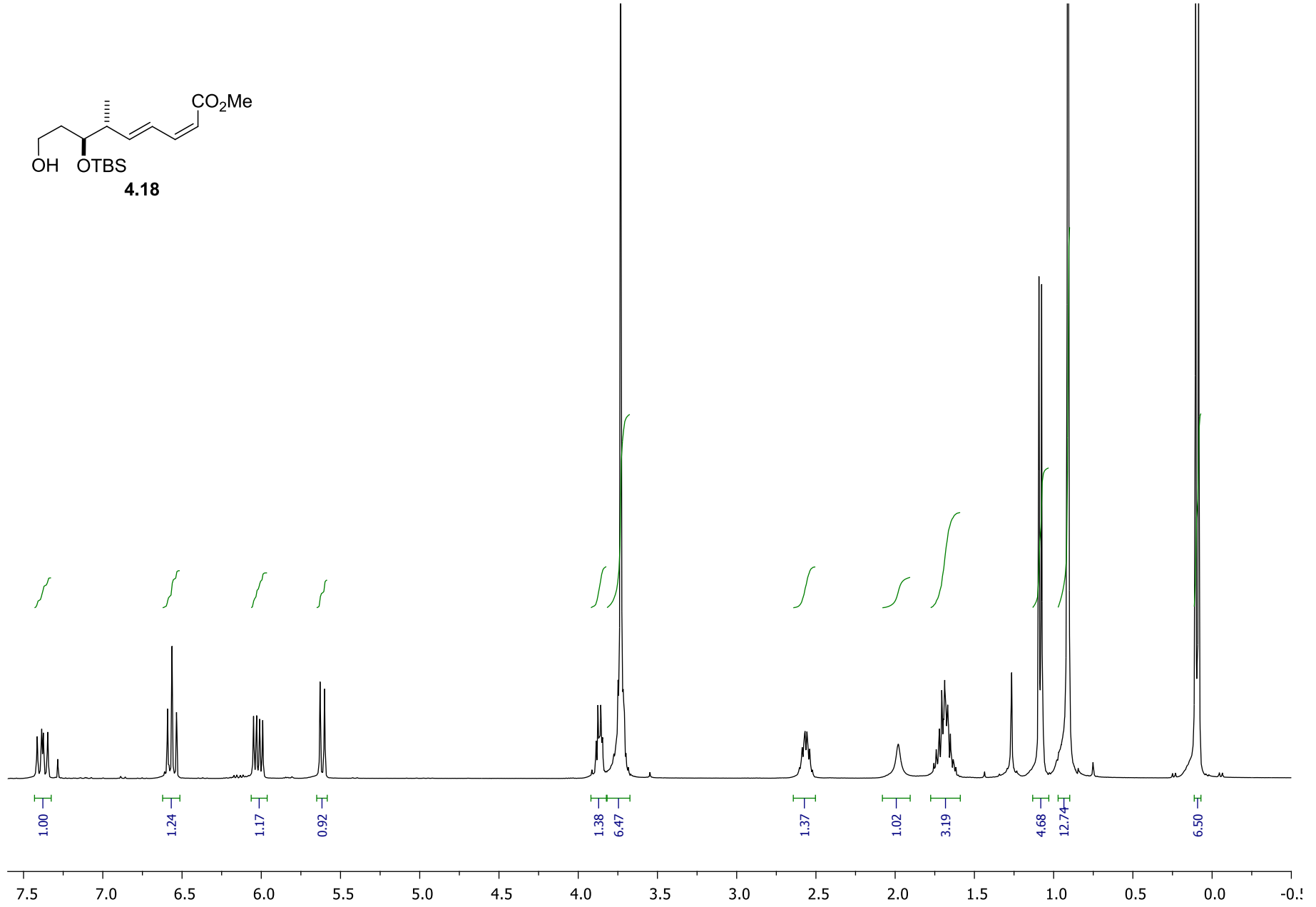
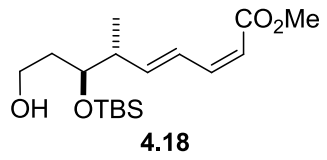


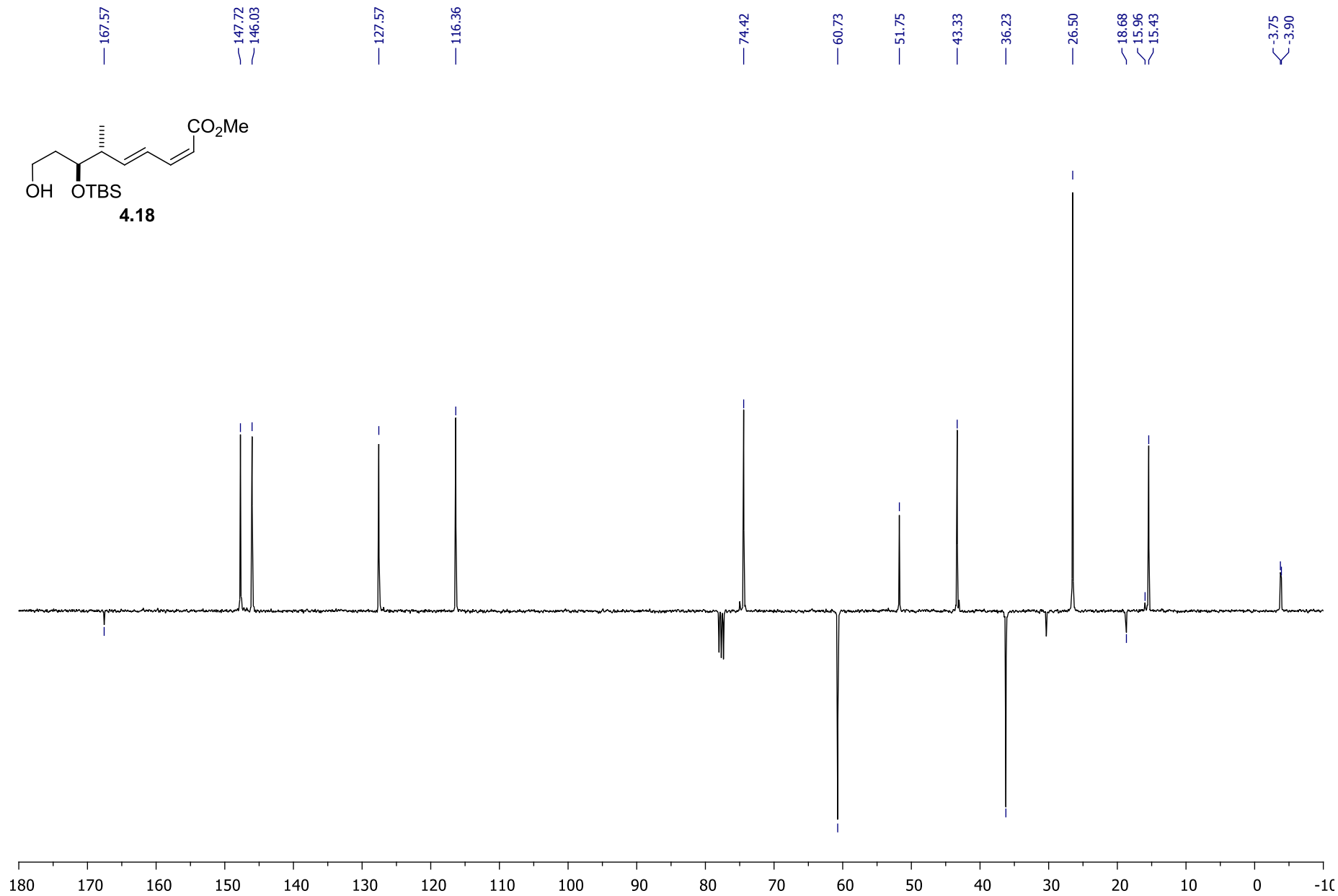
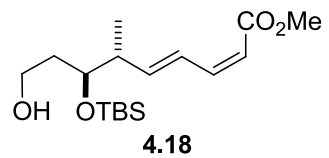


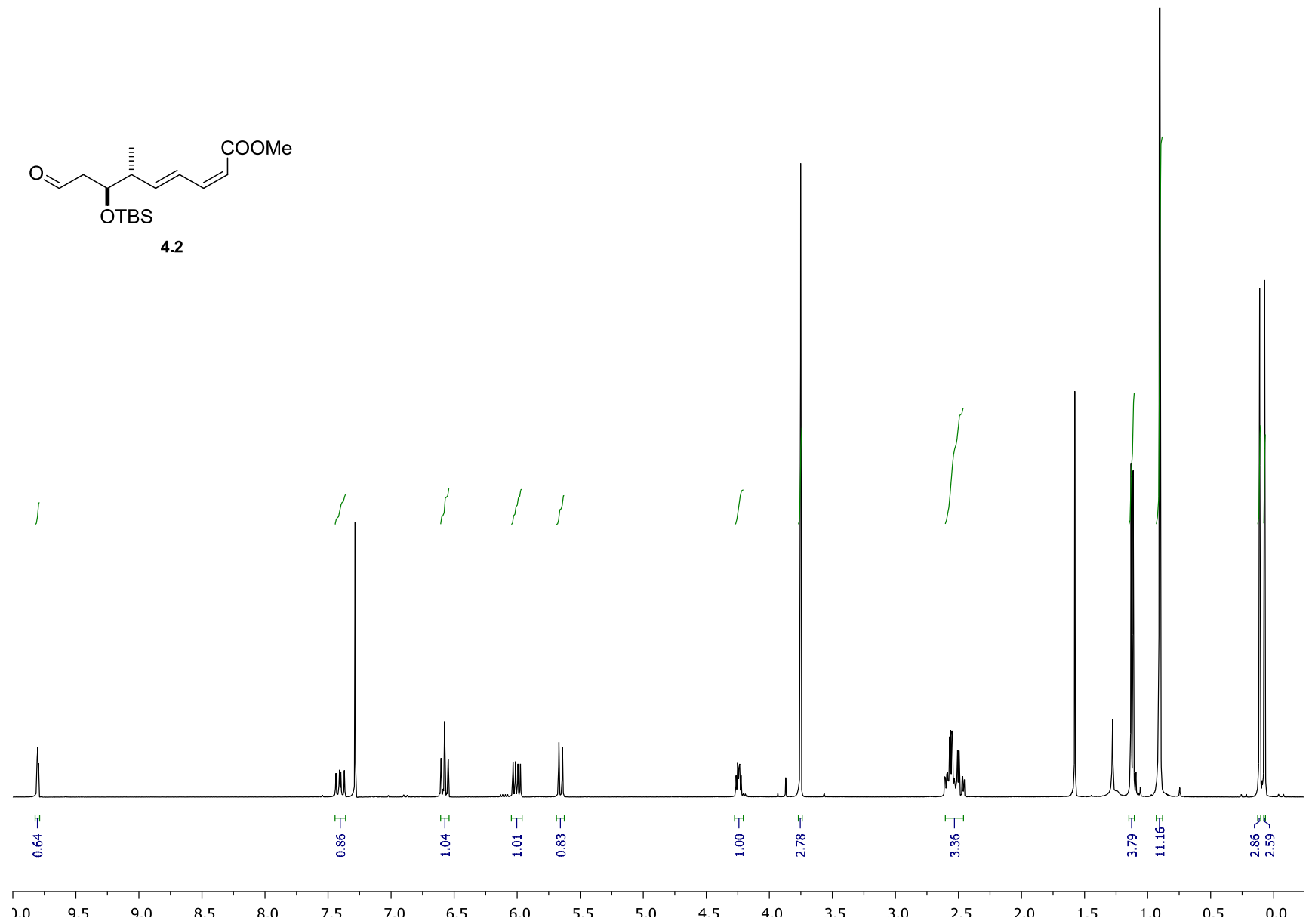
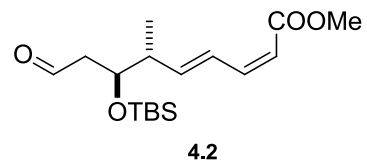






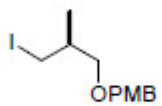




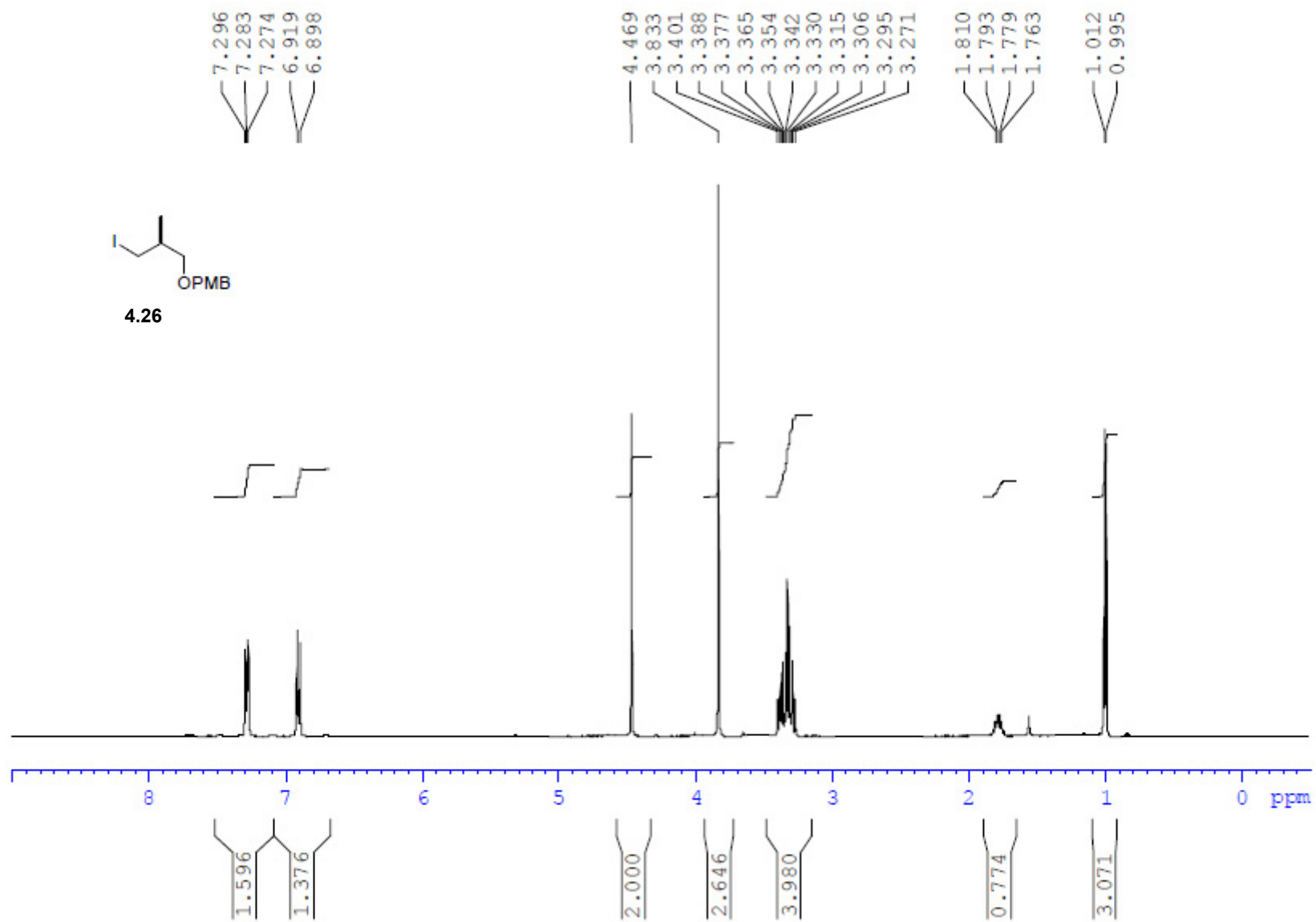


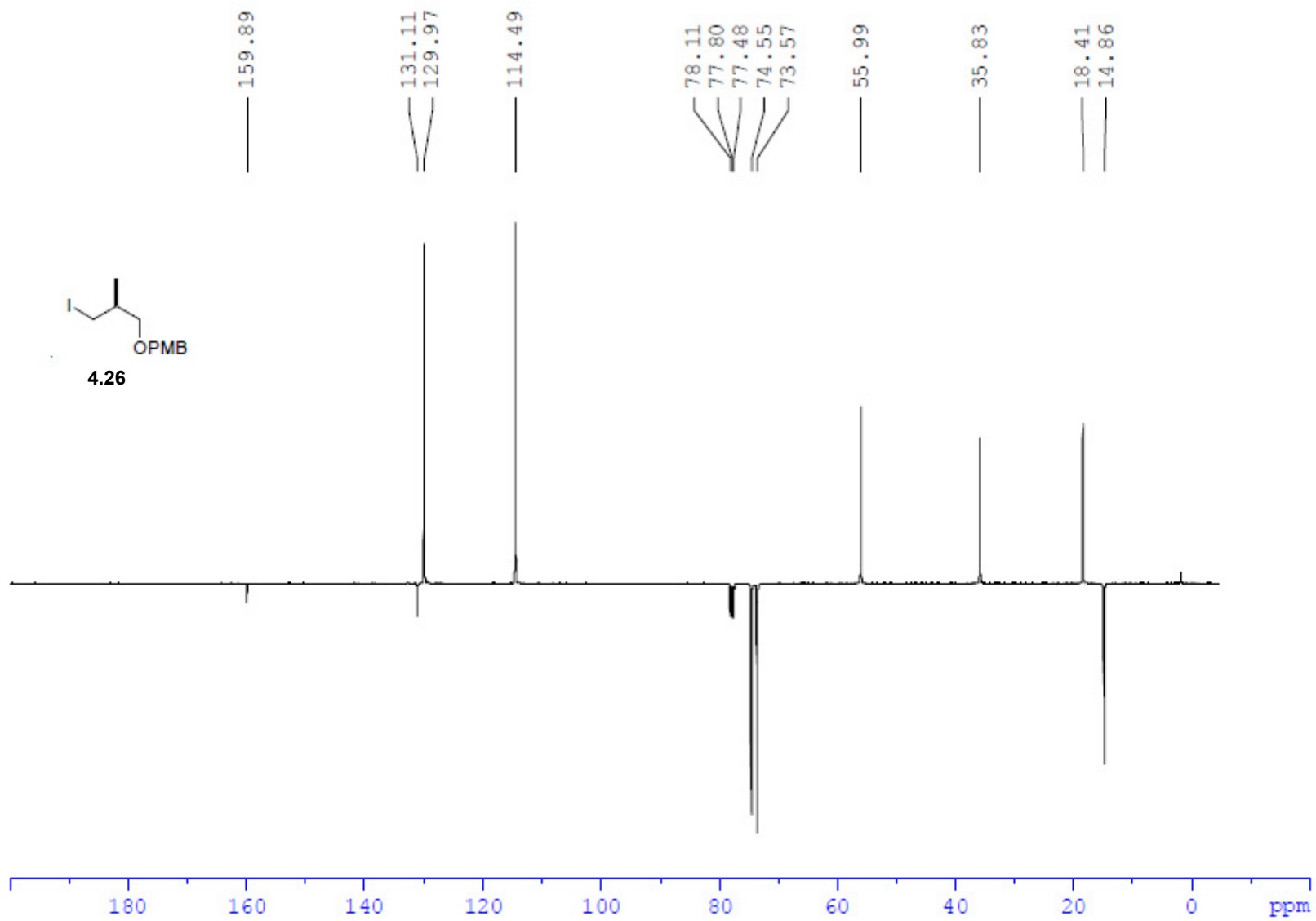
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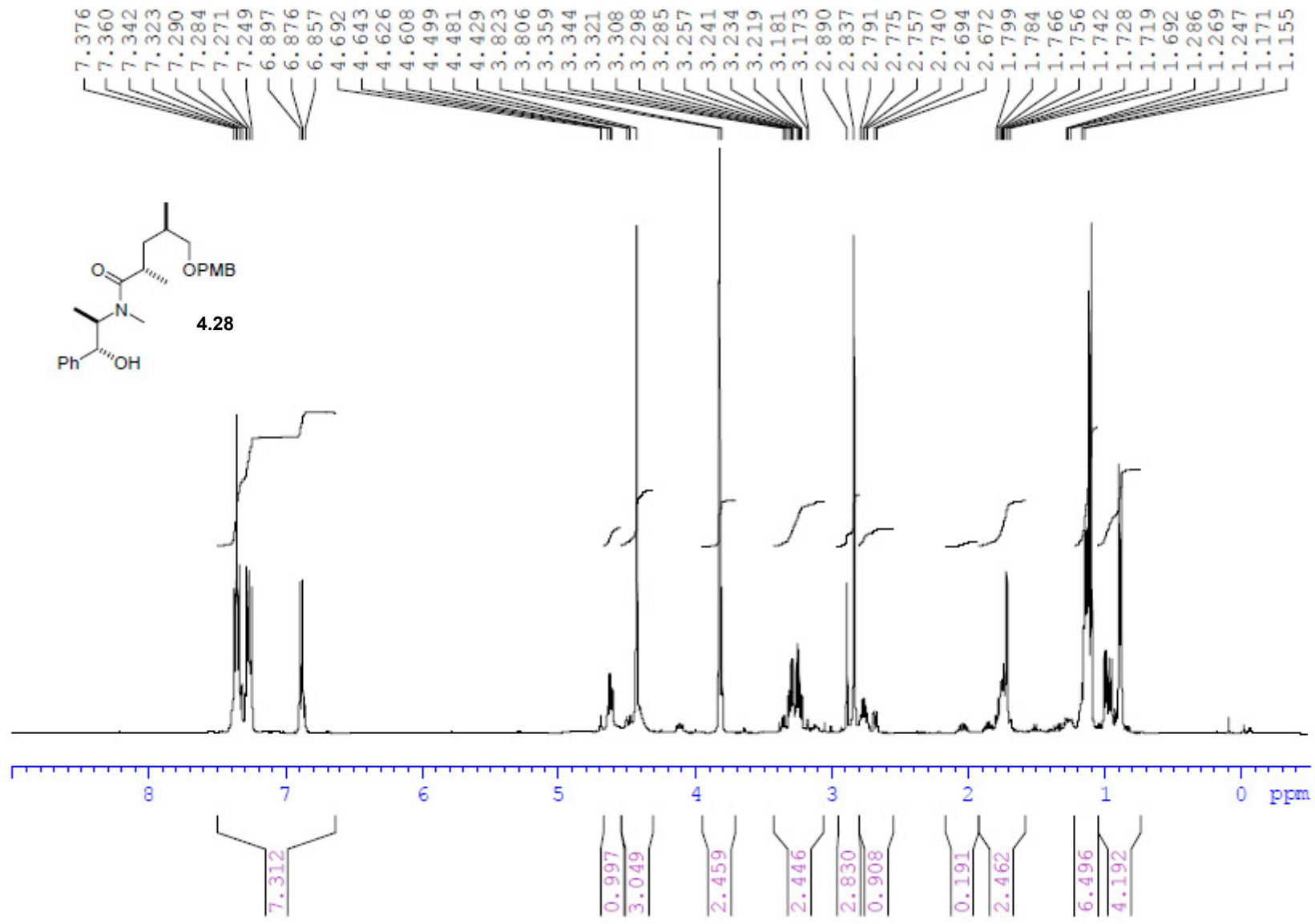
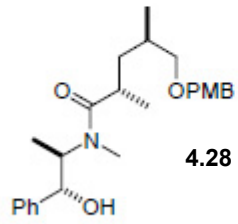
NMR Spectra

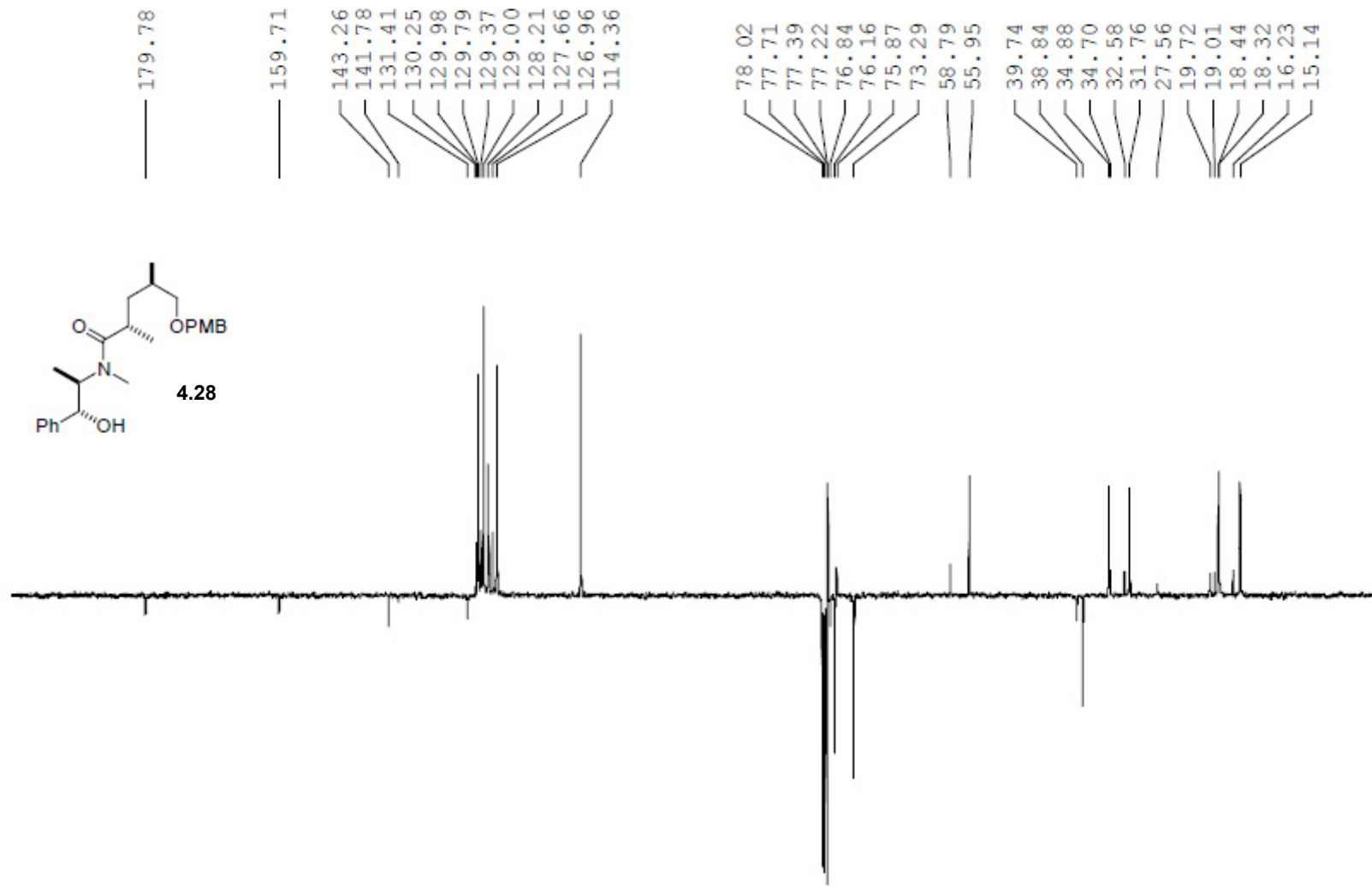
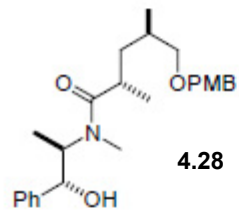


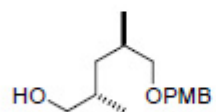
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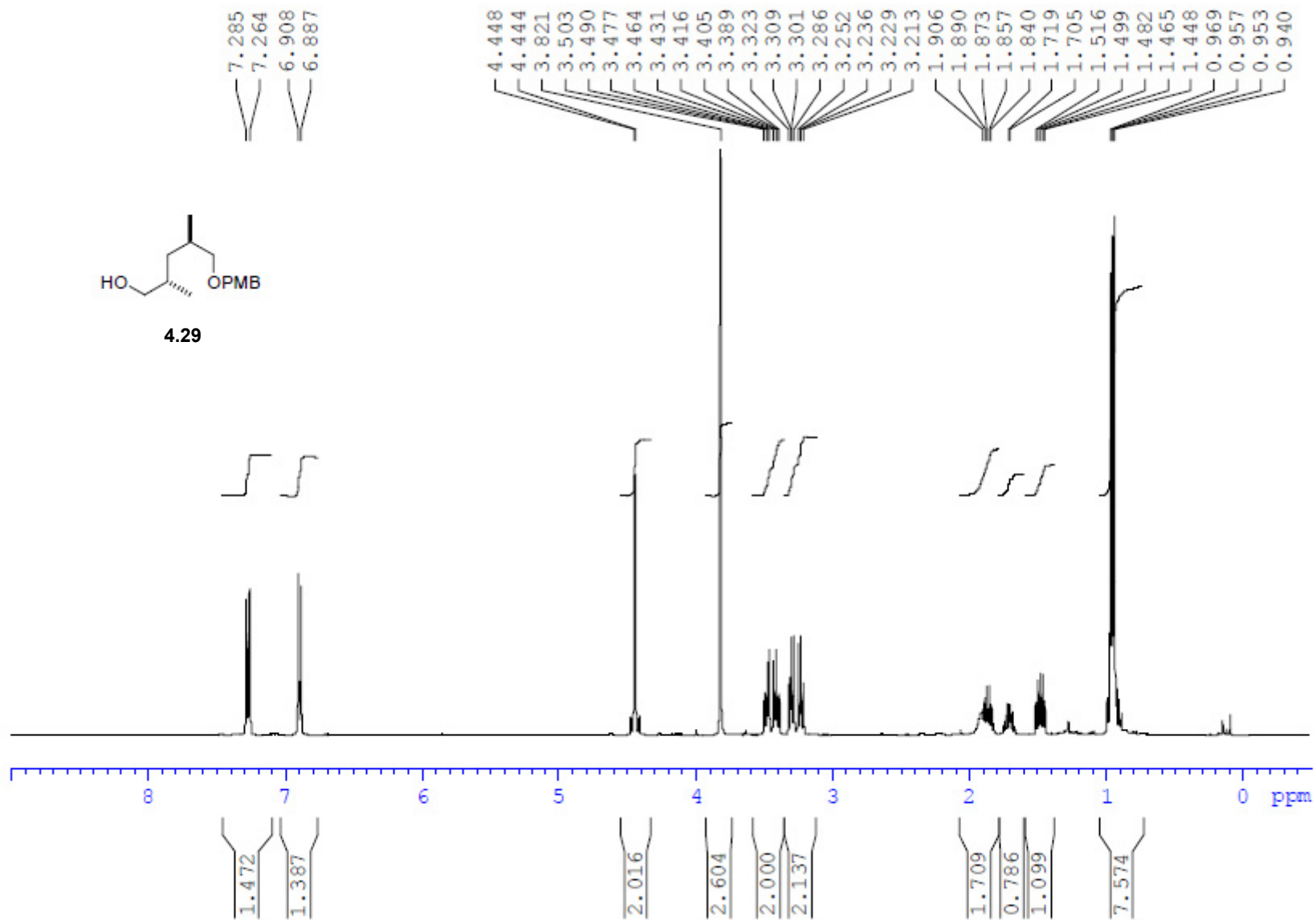


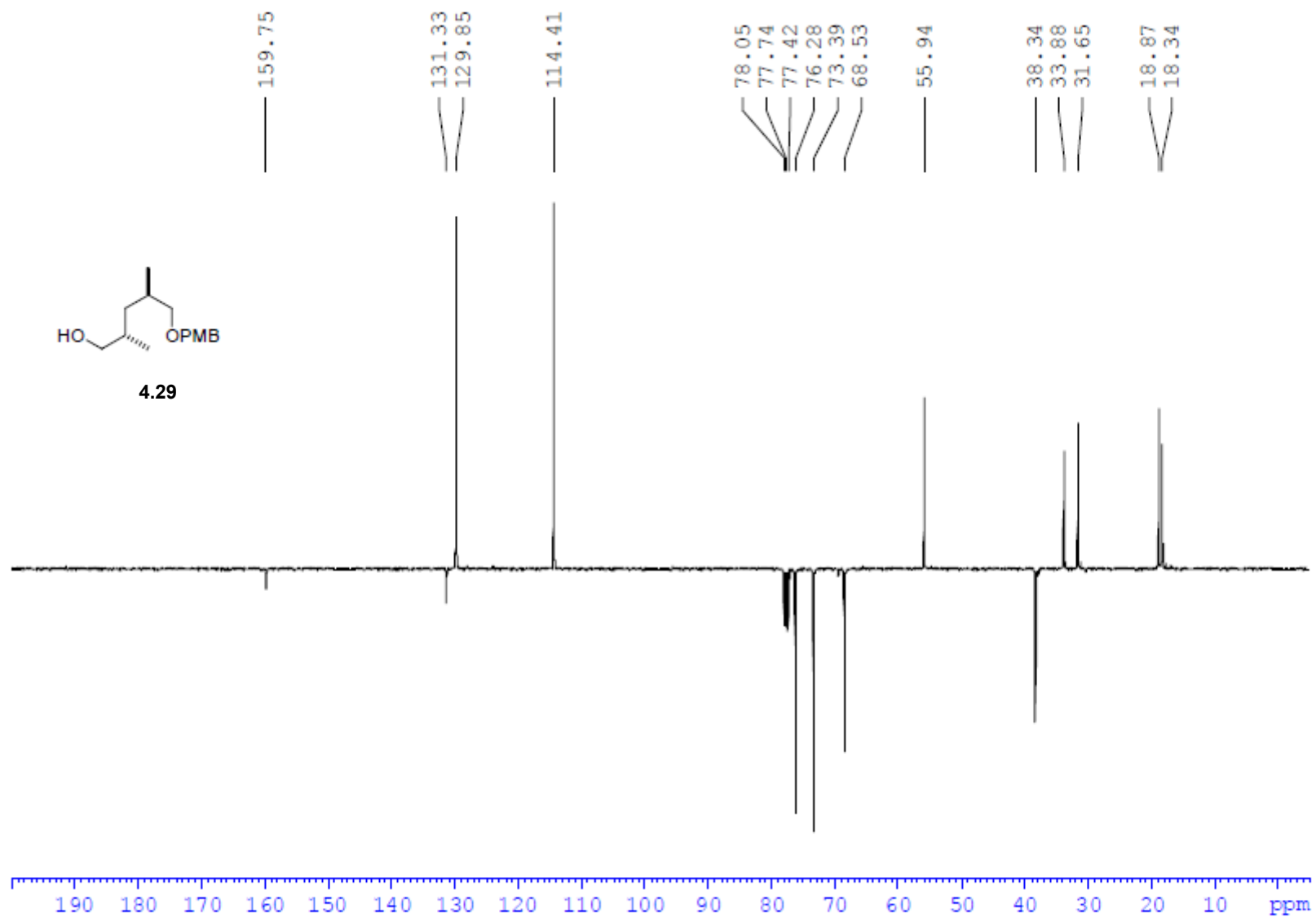


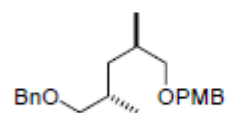




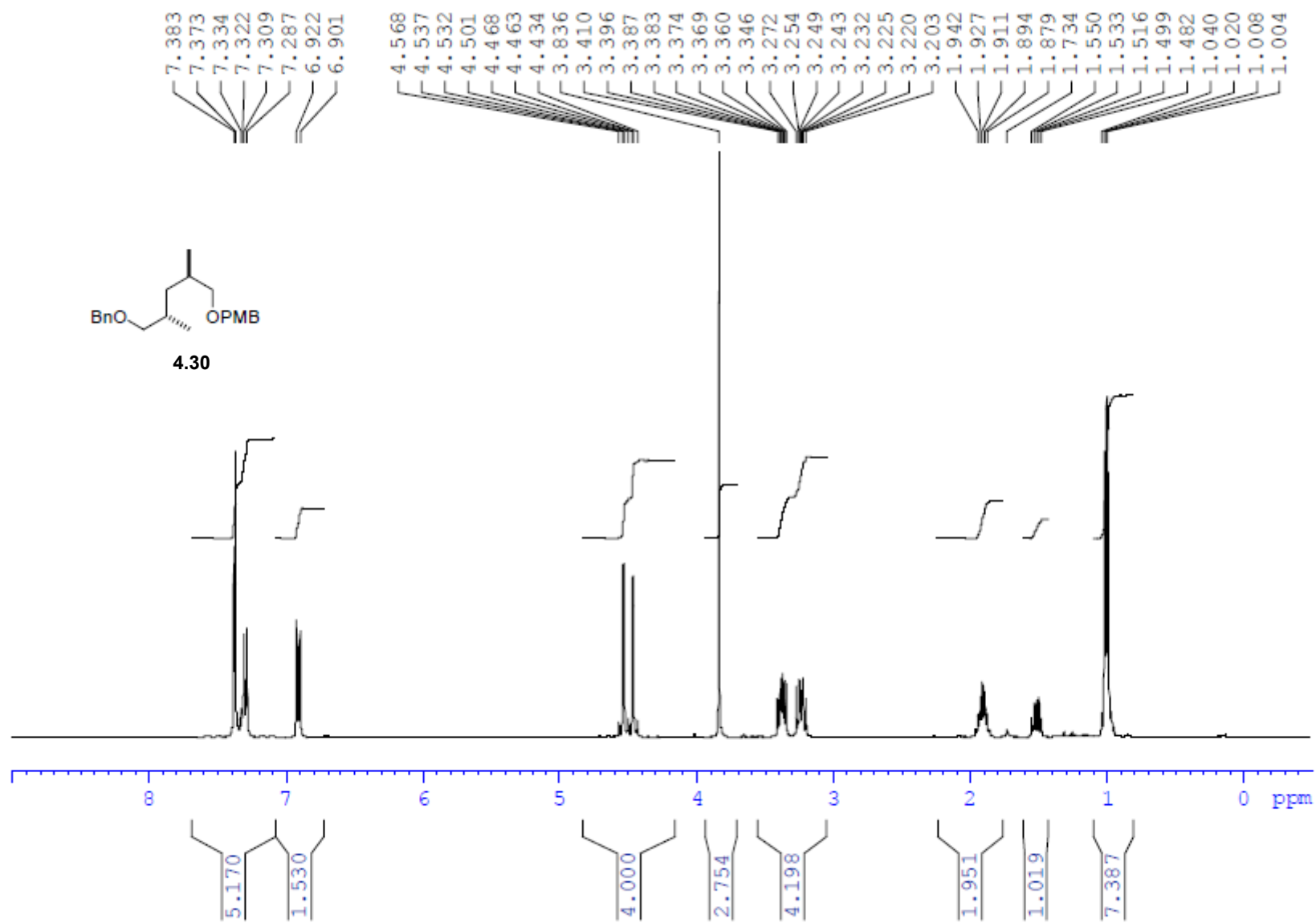
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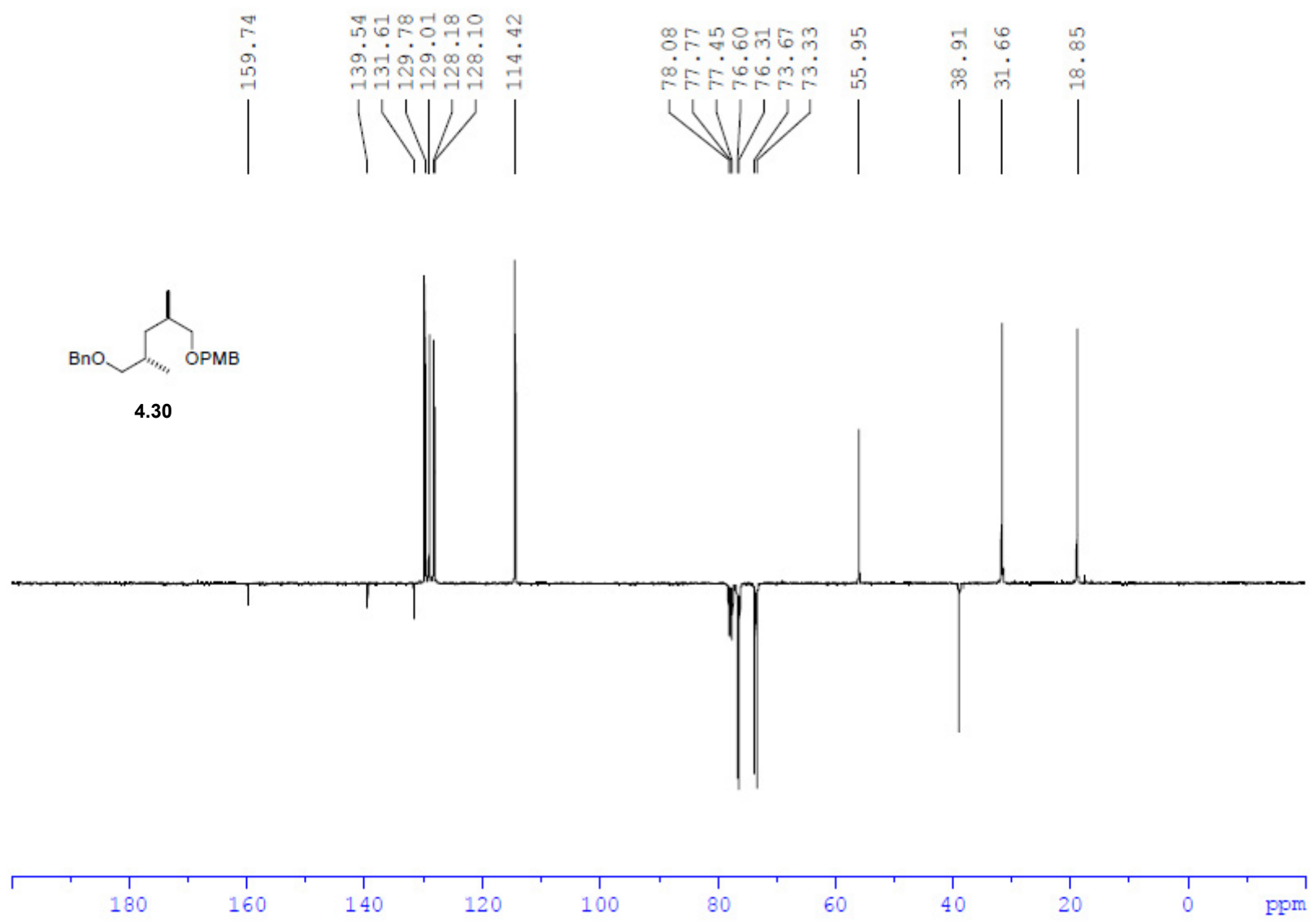


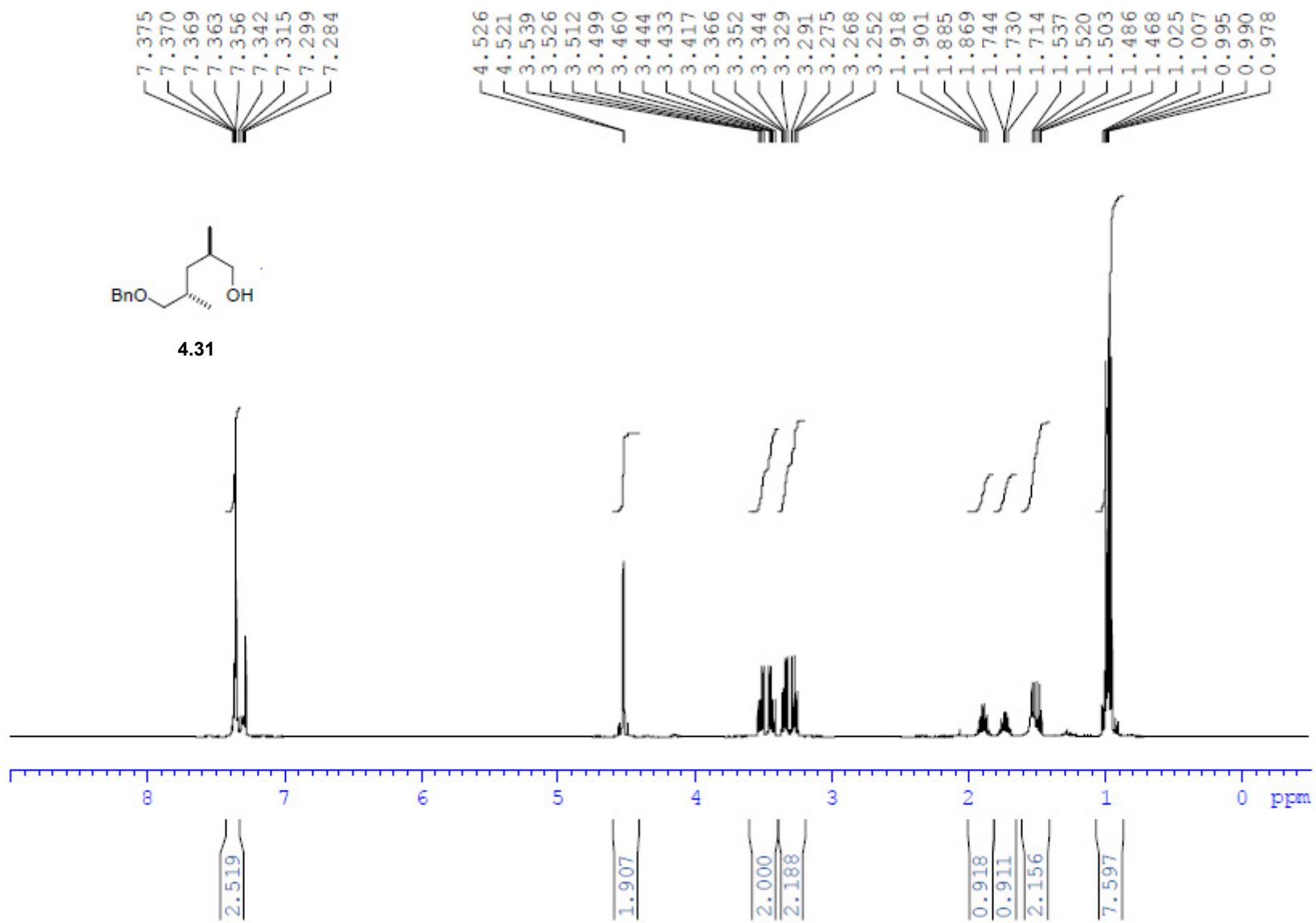


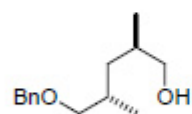


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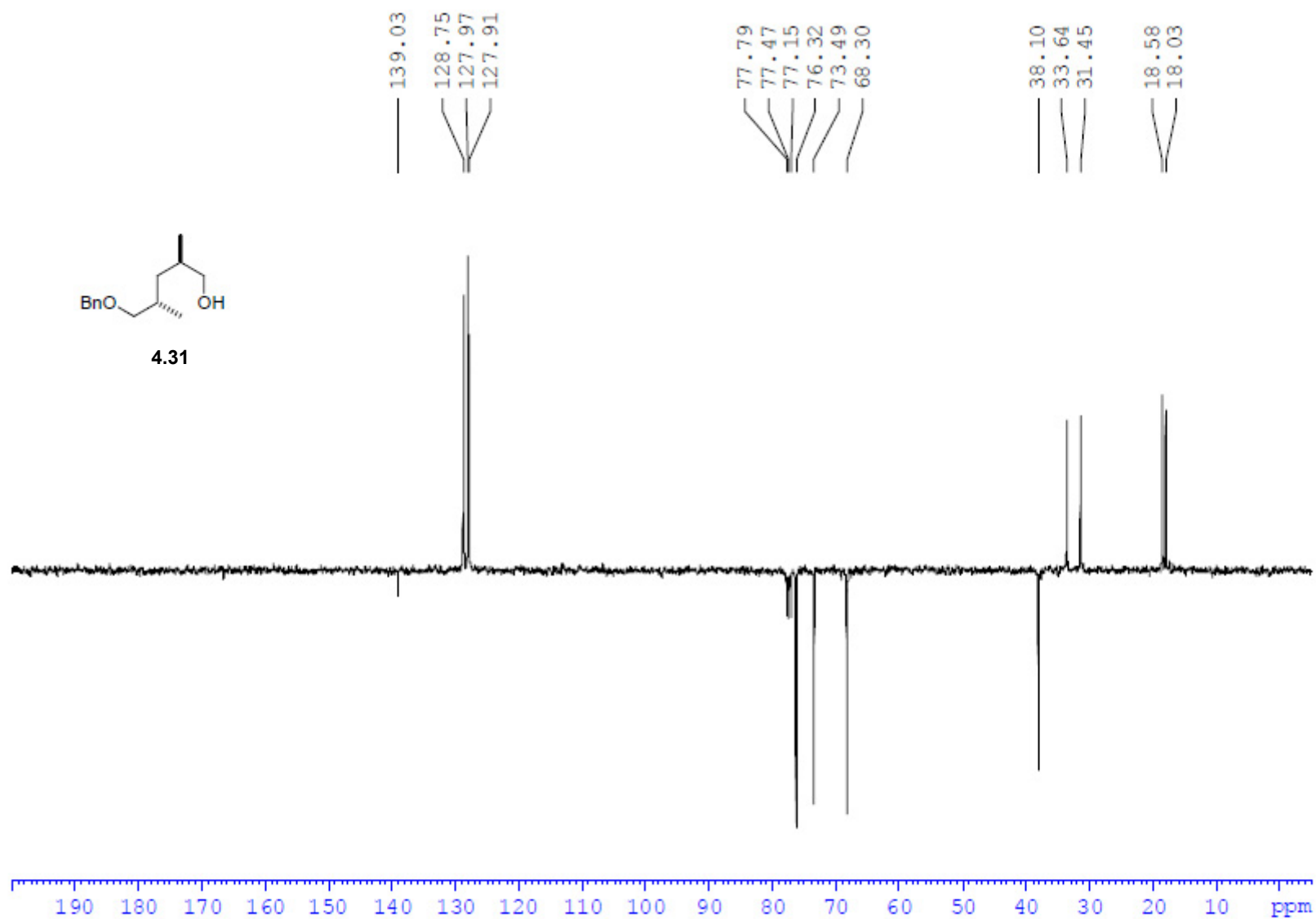


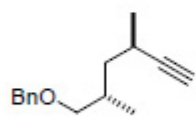




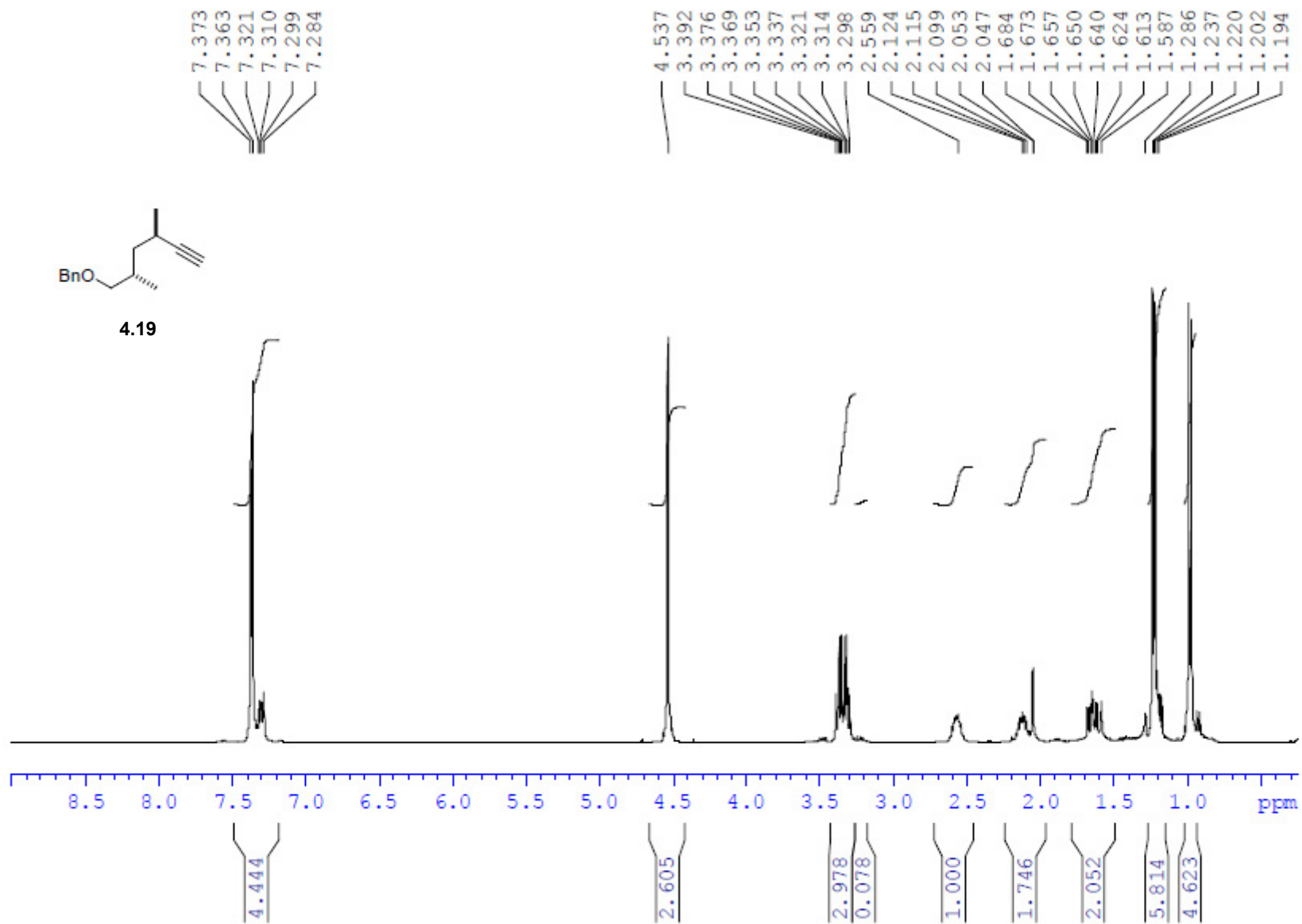


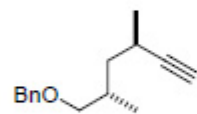
4.31



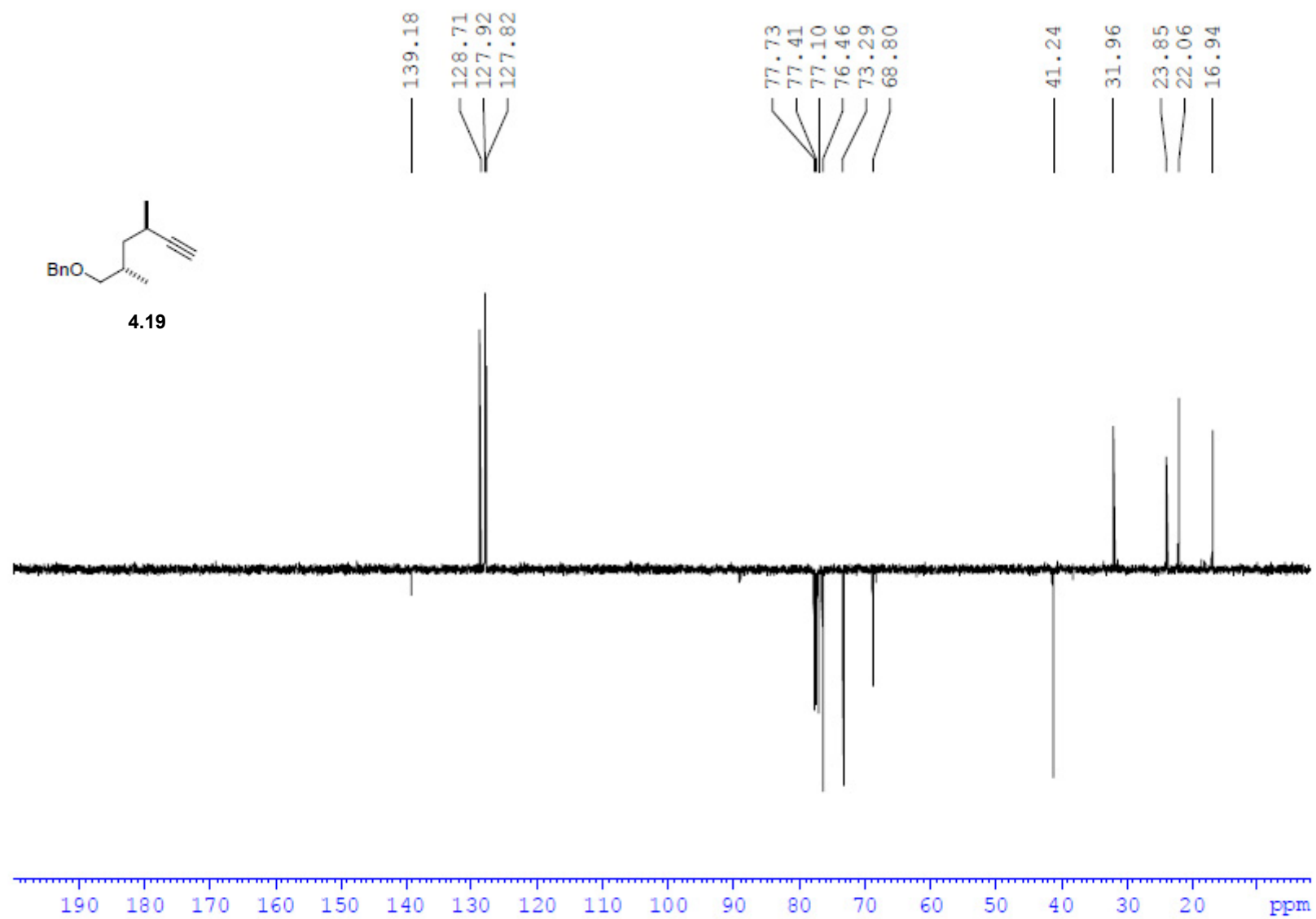


4.19



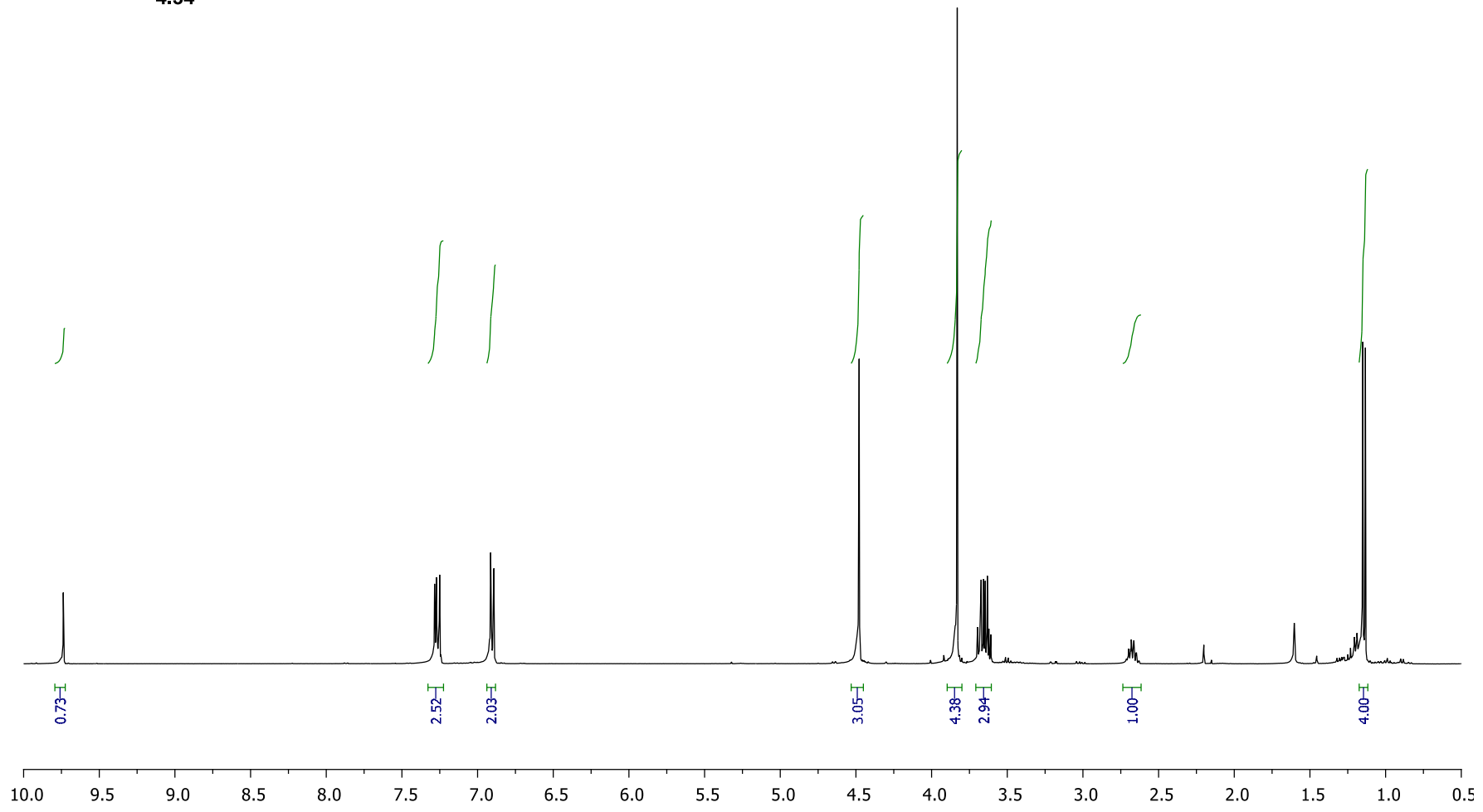
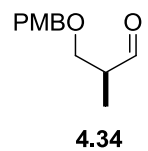


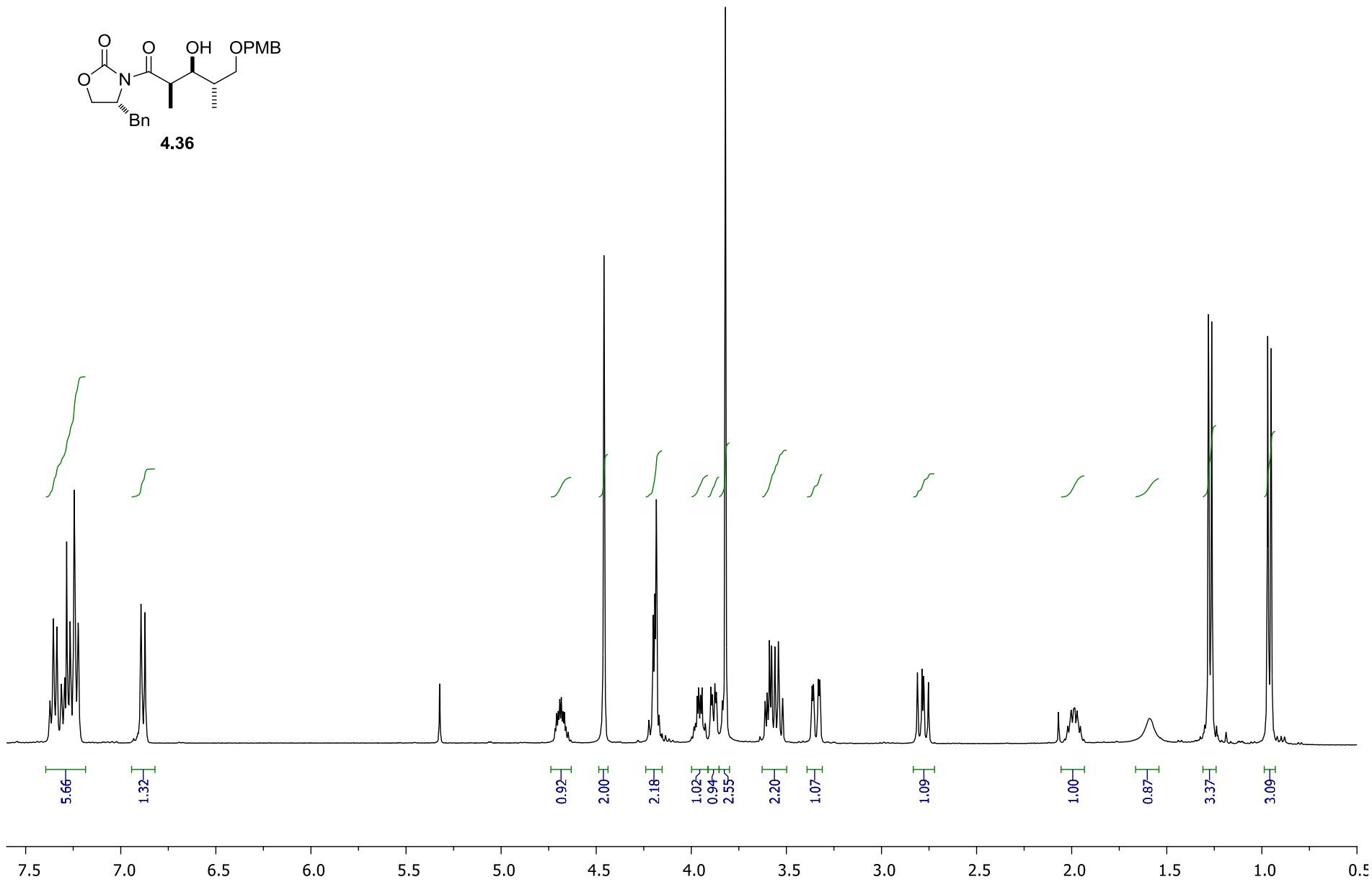
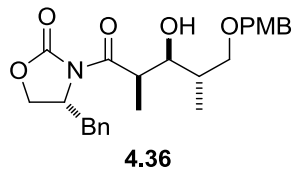
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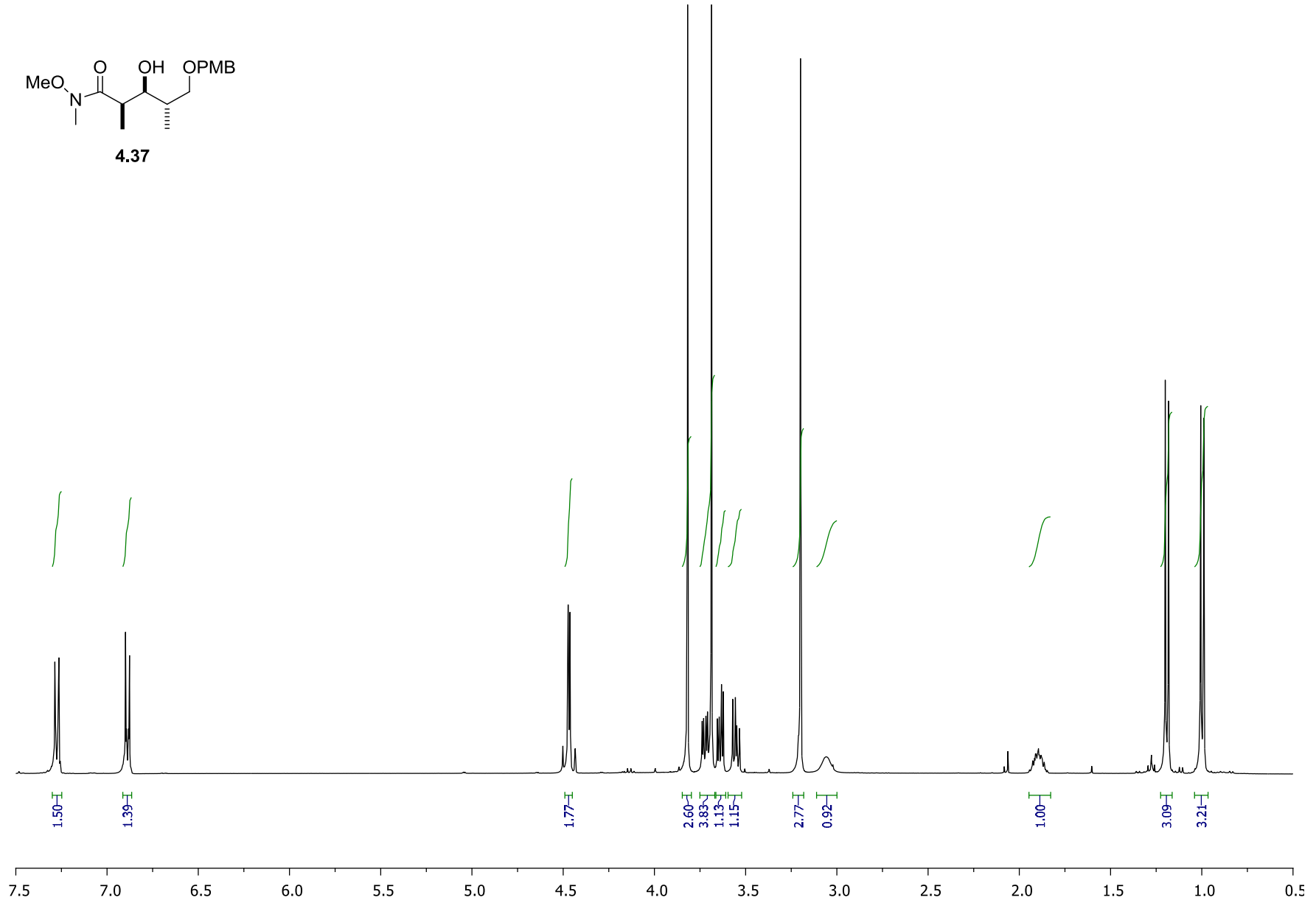
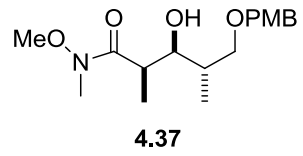


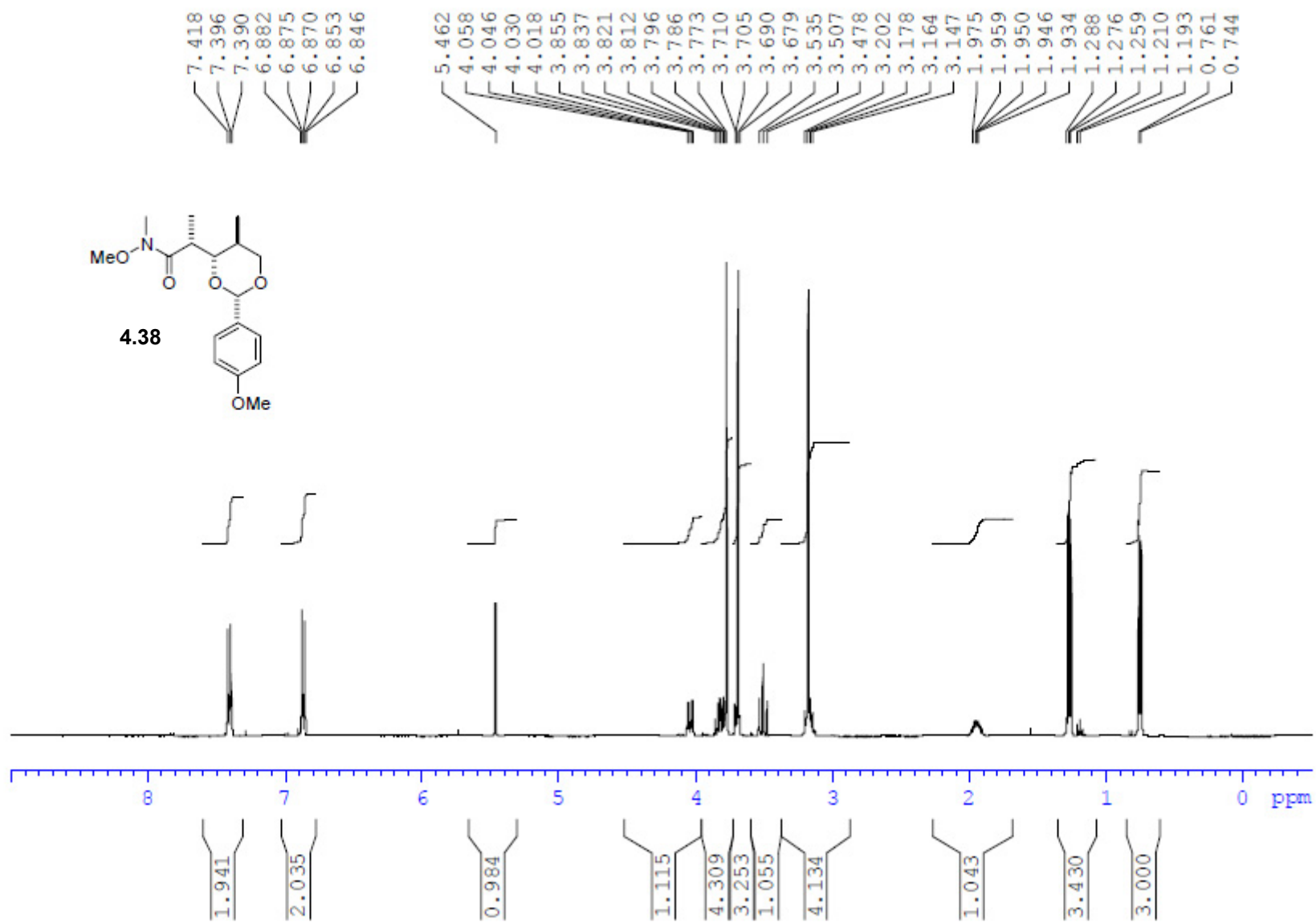
Synthesis of Aldehyde C19-C23

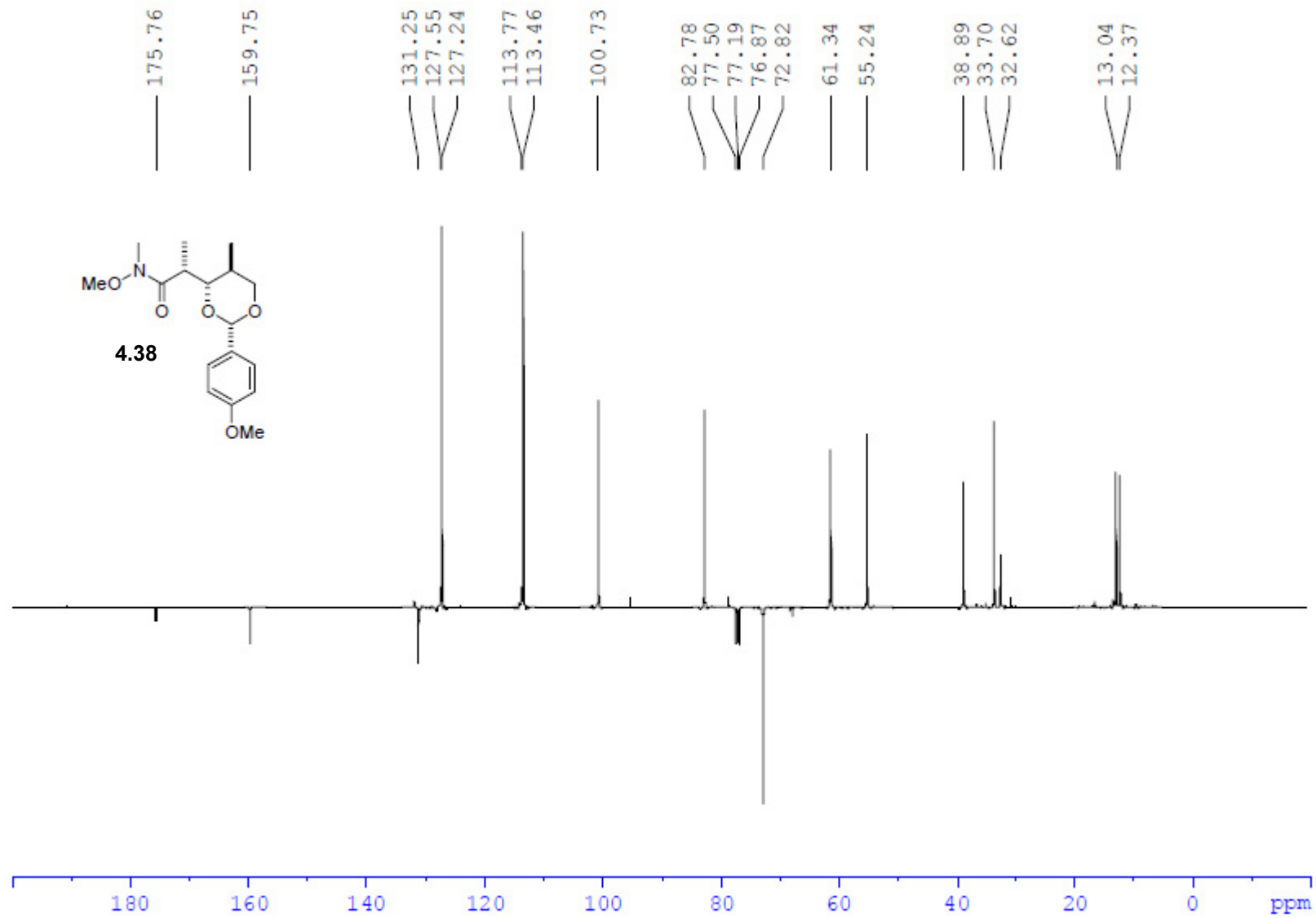
NMR Spectra

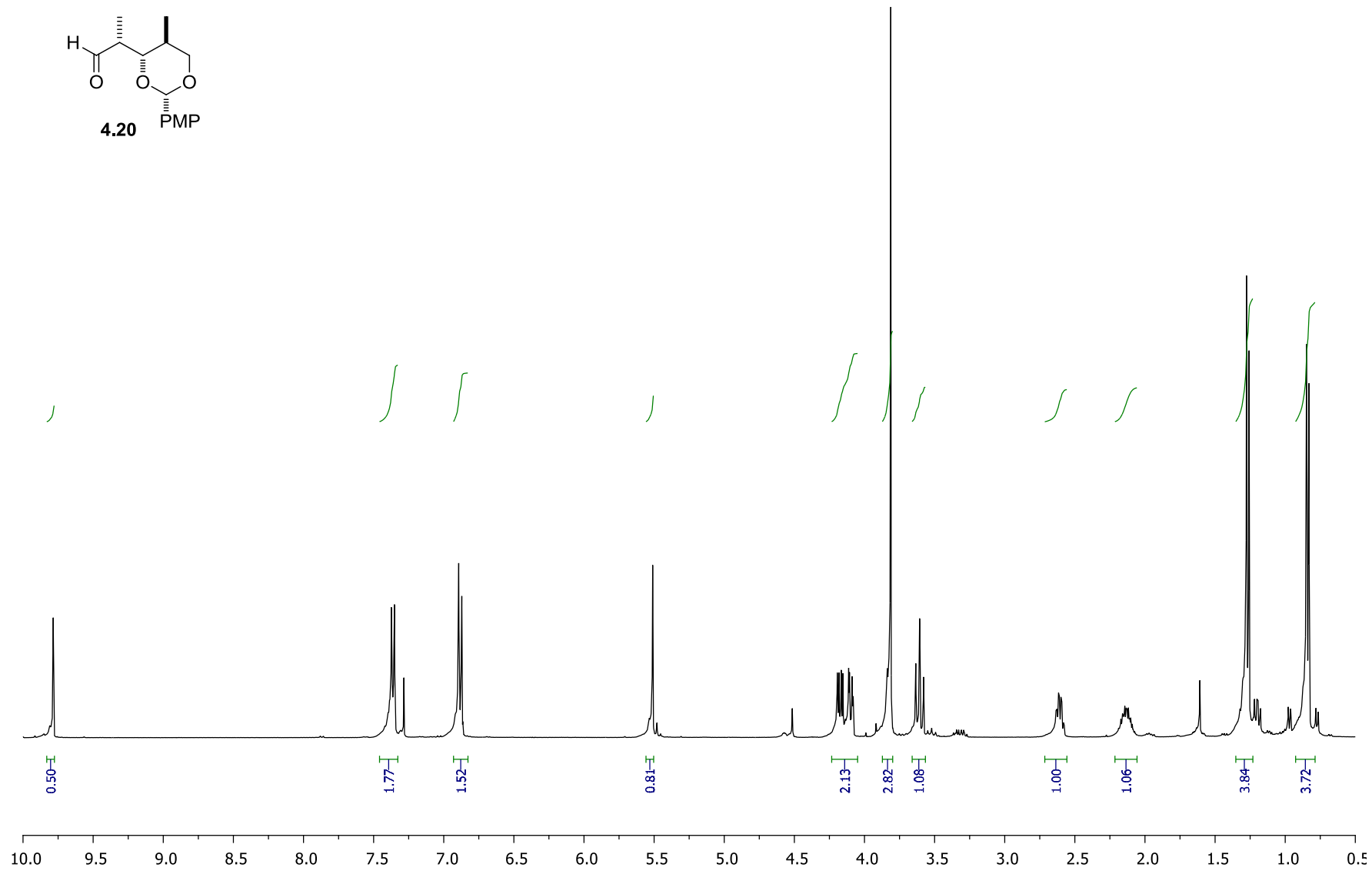
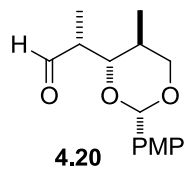








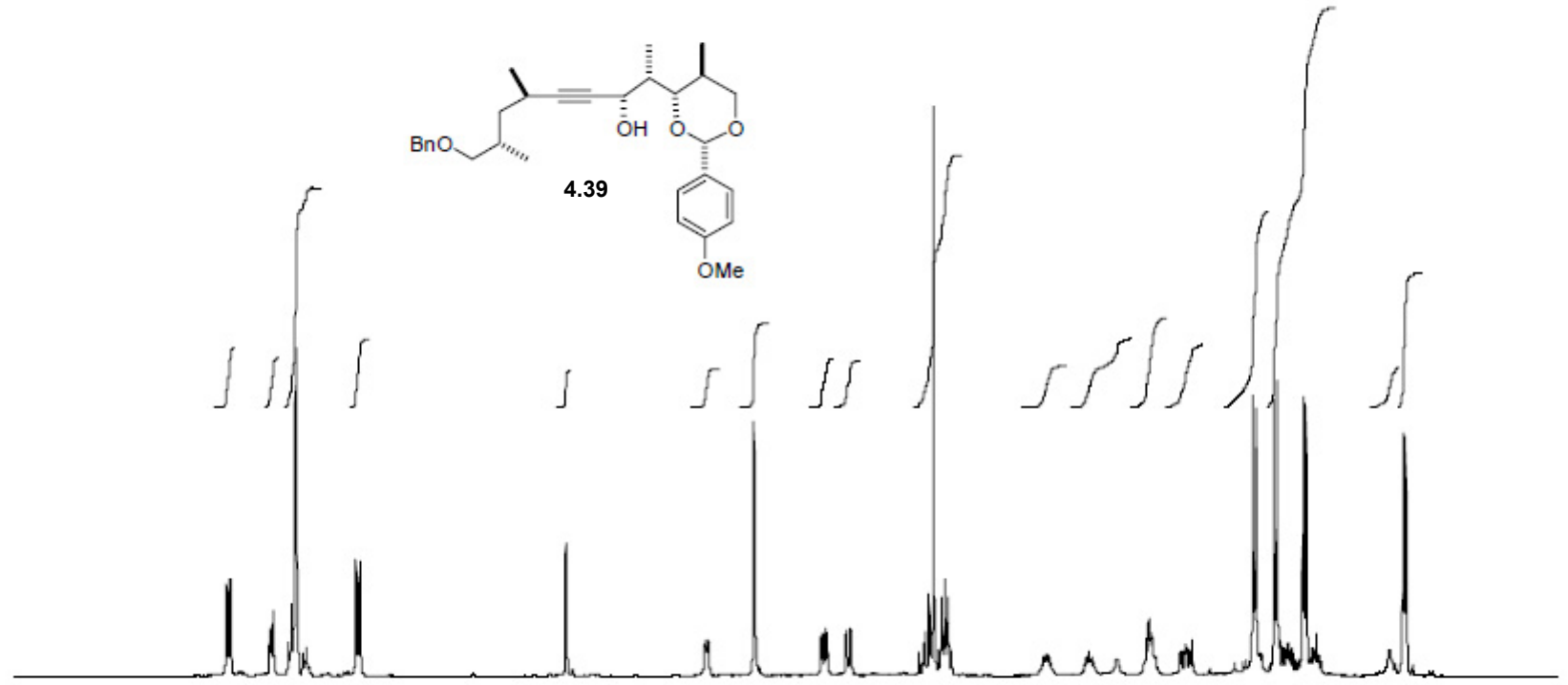
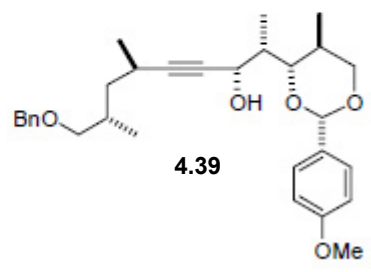




Synthesis of Alkyne C10-C23

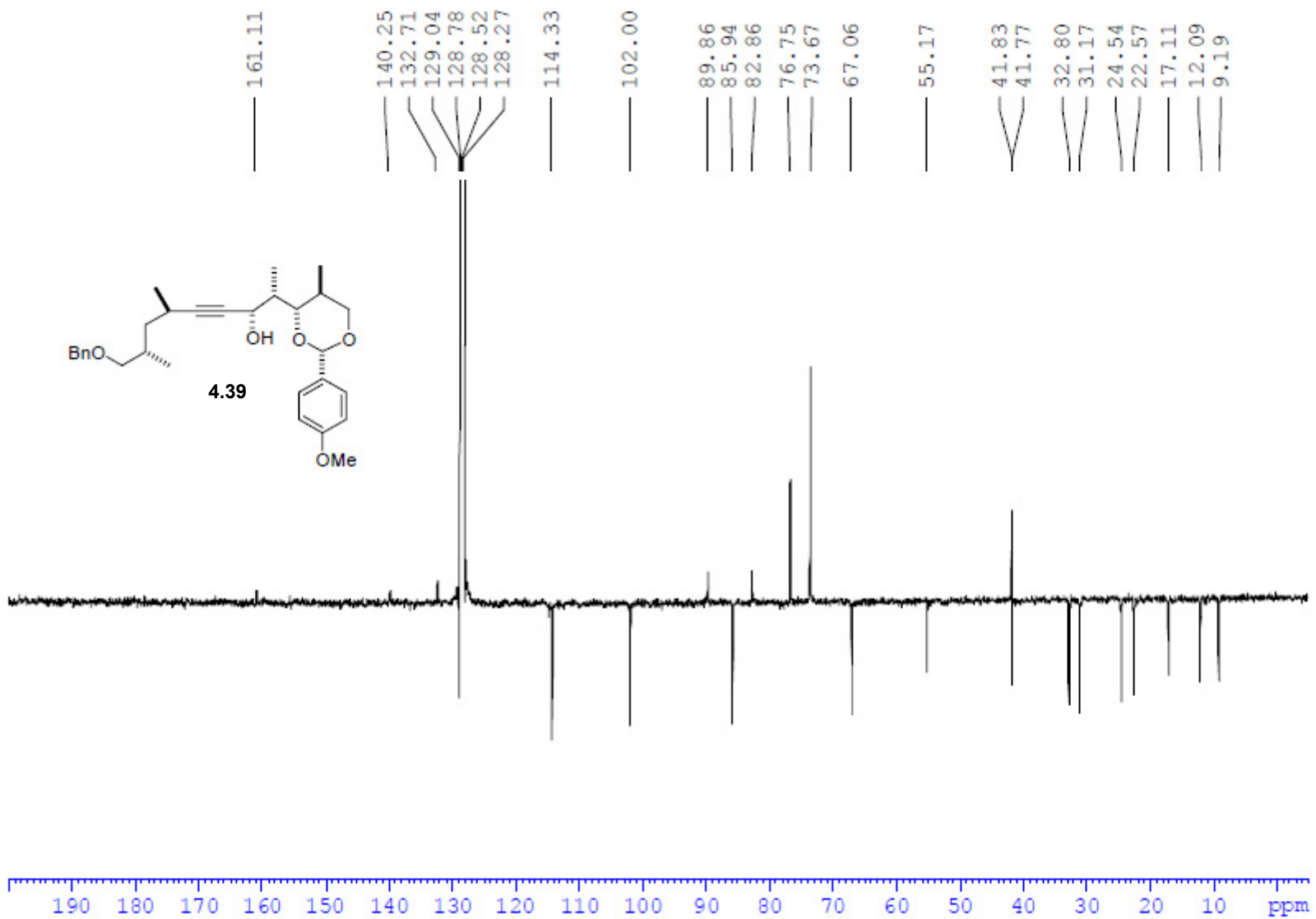
NMR Spectra

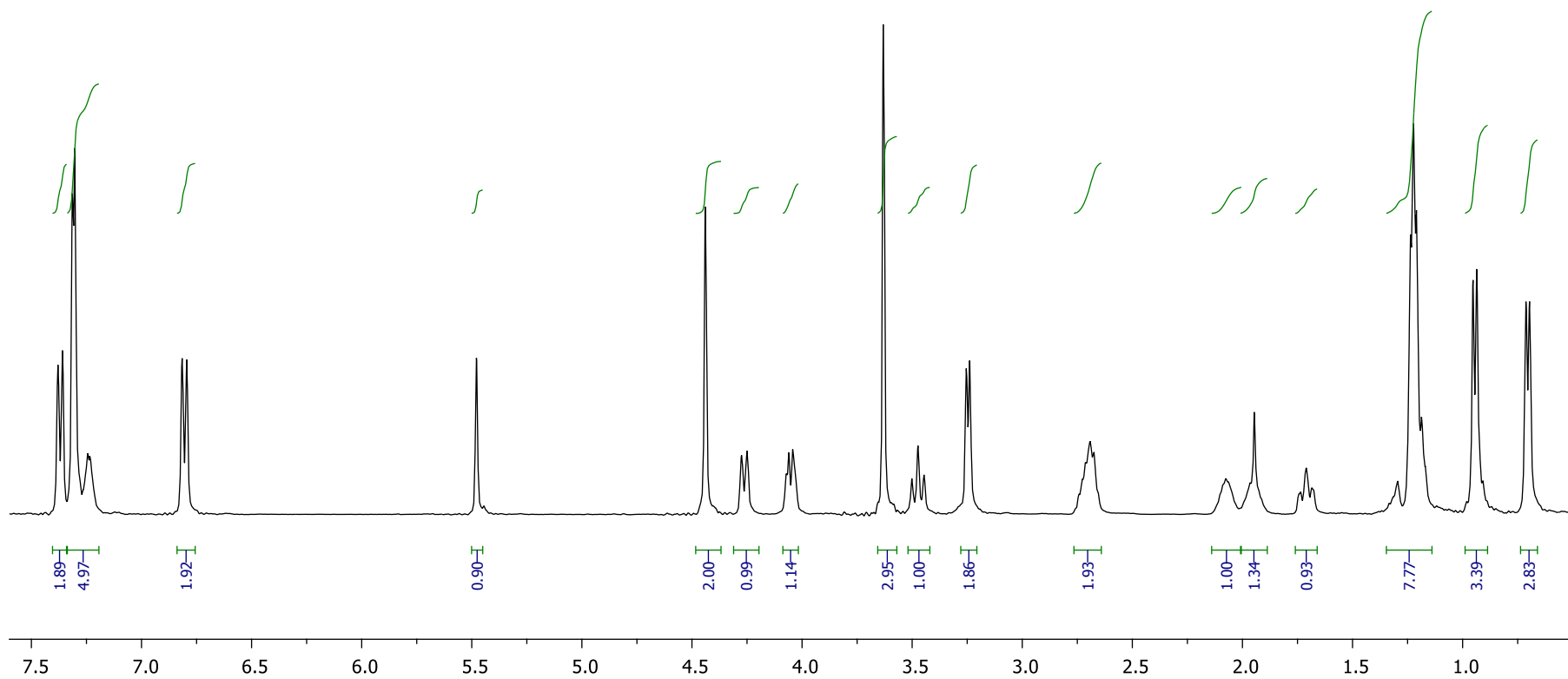
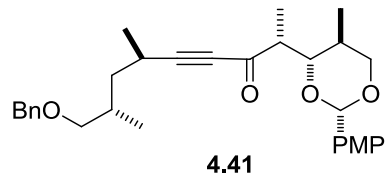
7.412
7.317
7.299
7.271
7.209
6.902
6.897
6.885
6.880
5.612
4.754
4.739
4.457
4.046
4.034
4.018
4.006
3.892
3.887
3.867
3.862
3.417
3.408
3.380
3.372
3.354
3.307
3.300
3.284
3.282
3.266
3.260
2.046
2.041
2.030
2.024
2.013
2.007
1.807
1.803
1.797
1.761
1.389
1.372
1.259
1.242
1.226
1.180
1.175
1.082
1.065
1.000
0.468
0.458
0.451

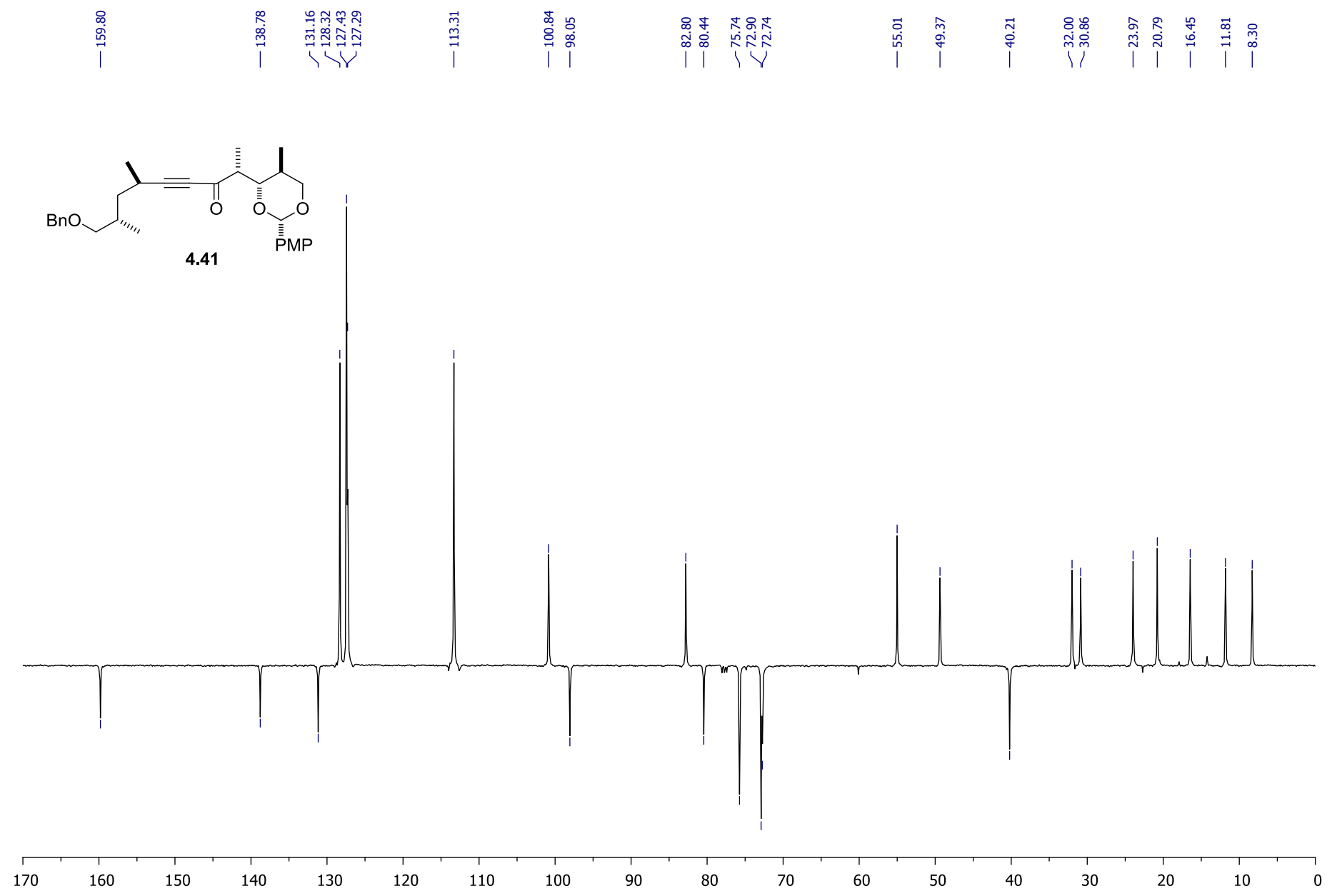
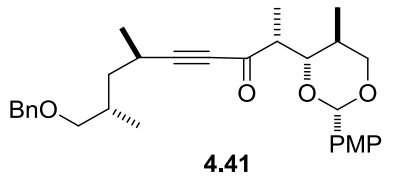


8
7
6
5
4
3
2
1
0 ppm

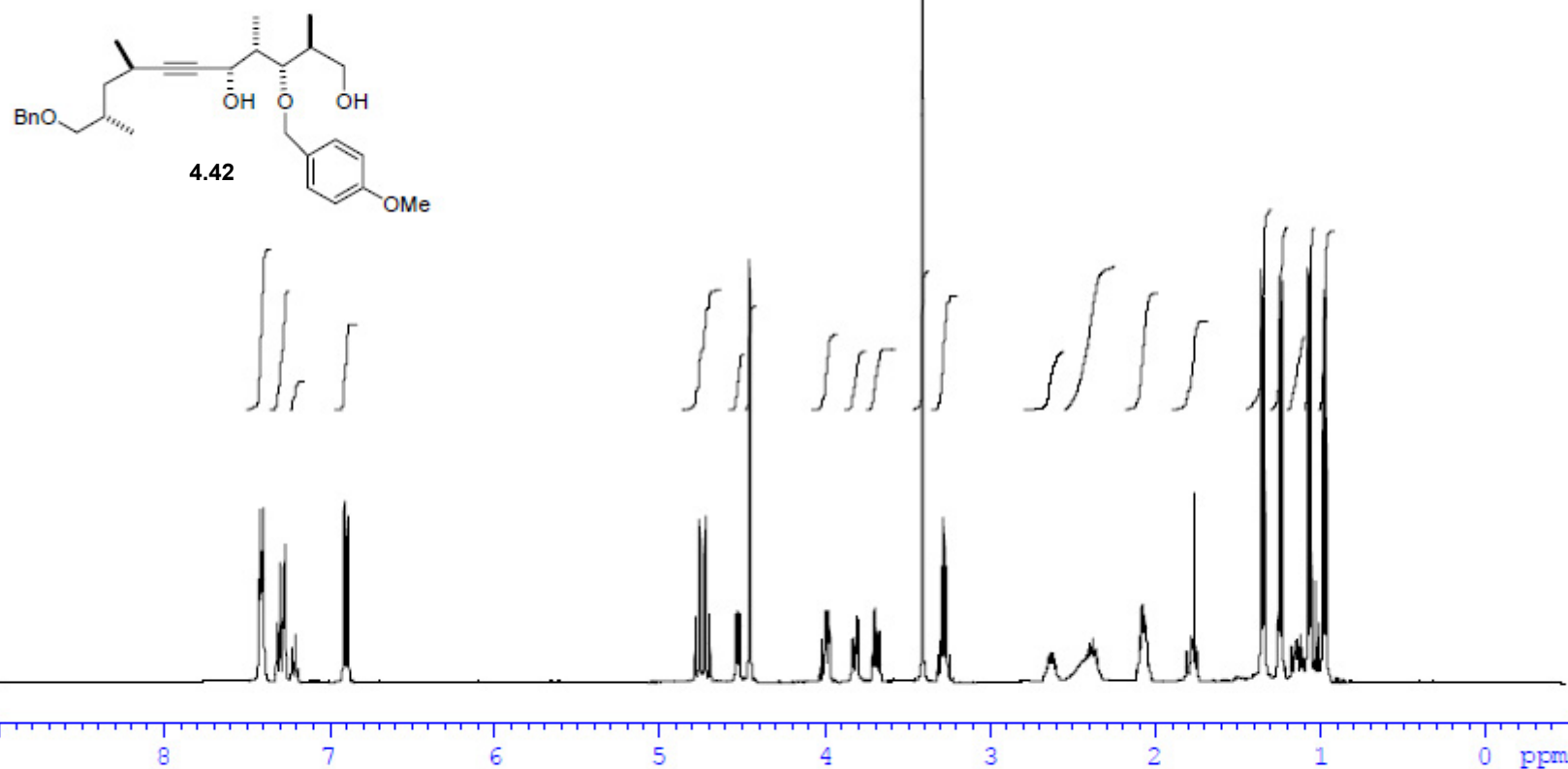
1.623
1.334
5.952
1.815
1.000
1.031
2.265
1.310
1.246
6.835
1.117
1.867
2.423
1.684
5.318
10.856
1.070
3.670



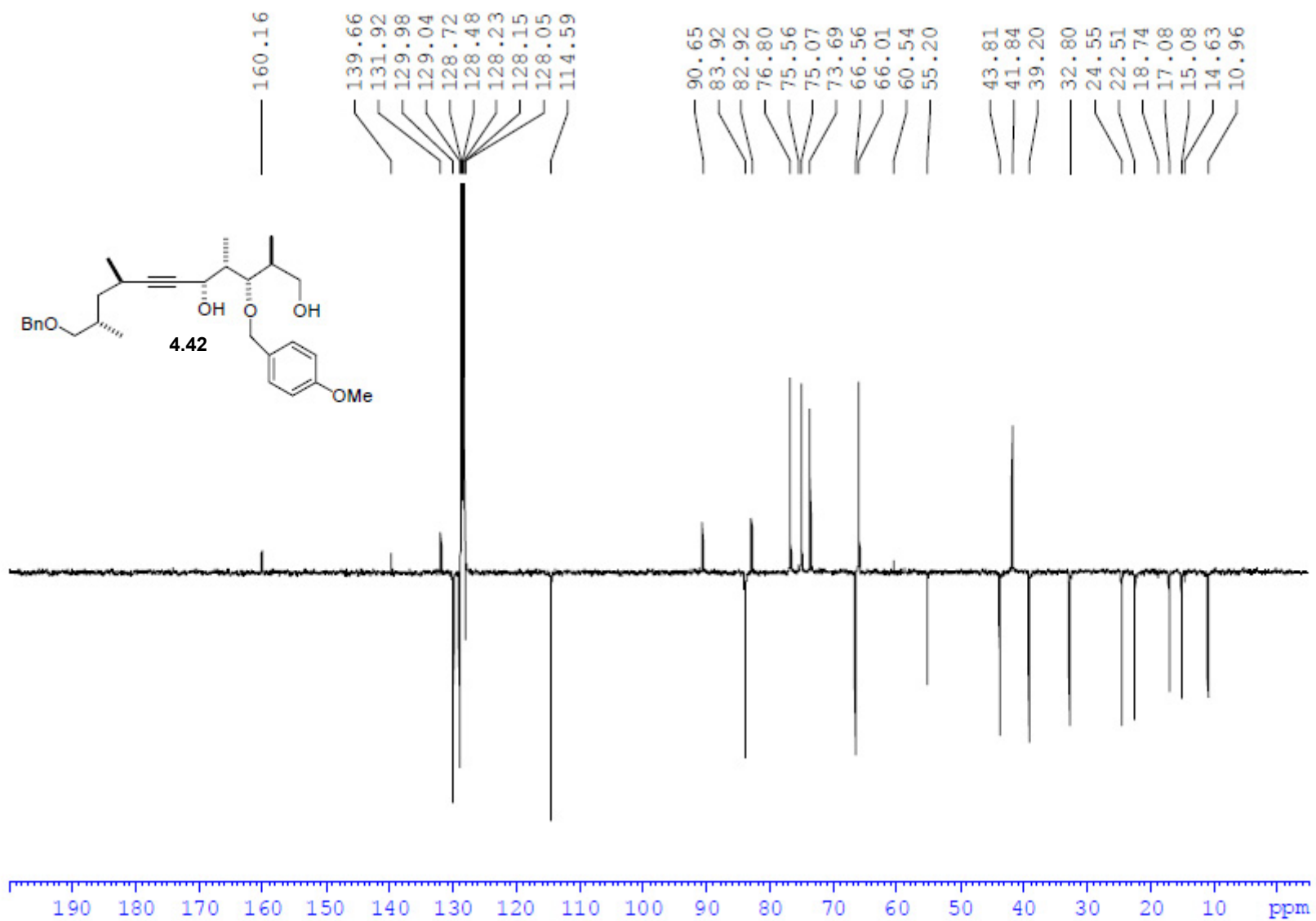


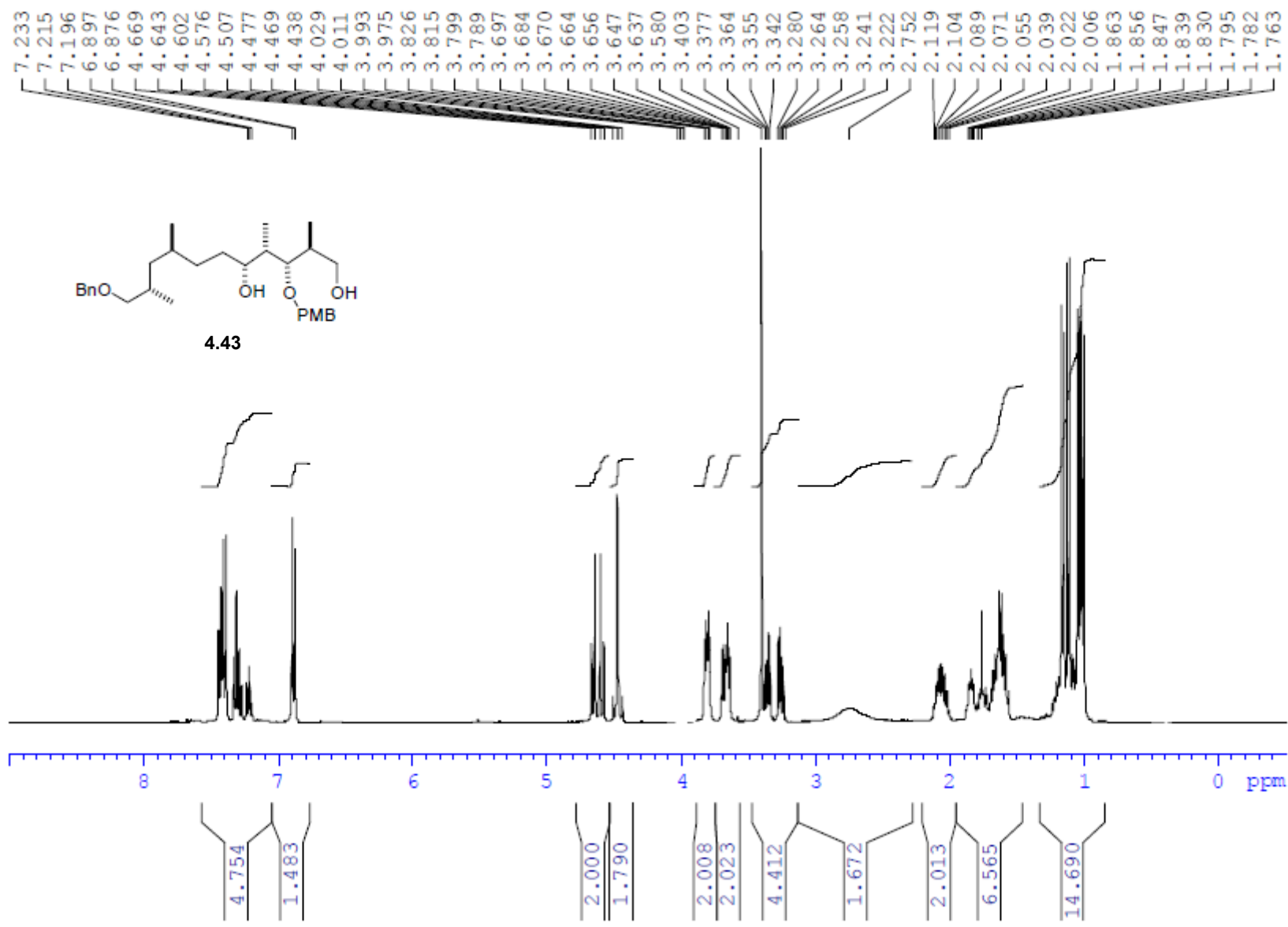


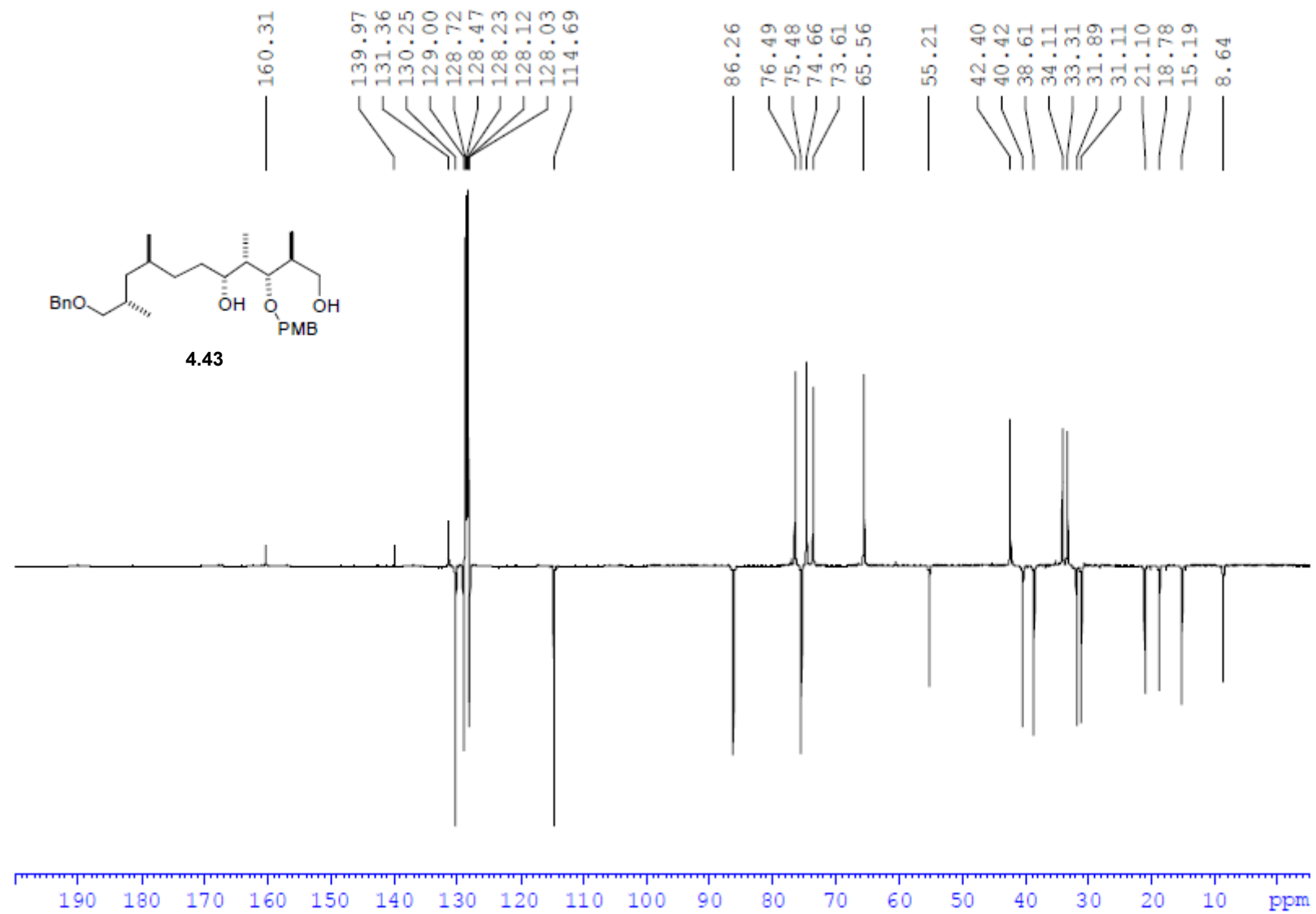
6.912
6.890
4.786
4.759
4.726
4.699
4.537
4.532
4.519
4.514
4.456
4.032
4.015
4.001
3.997
3.993
3.982
3.974
3.836
3.826
3.809
3.799
3.707
3.693
3.680
3.666
3.586
3.409
3.397
3.317
3.302
3.295
3.281
3.267
3.261
3.244
3.227
2.661
2.644
2.632
2.617
2.600
2.420
2.404
2.394
2.387
2.378
2.369
2.362
2.352
2.336
2.097
2.089
2.079
2.072

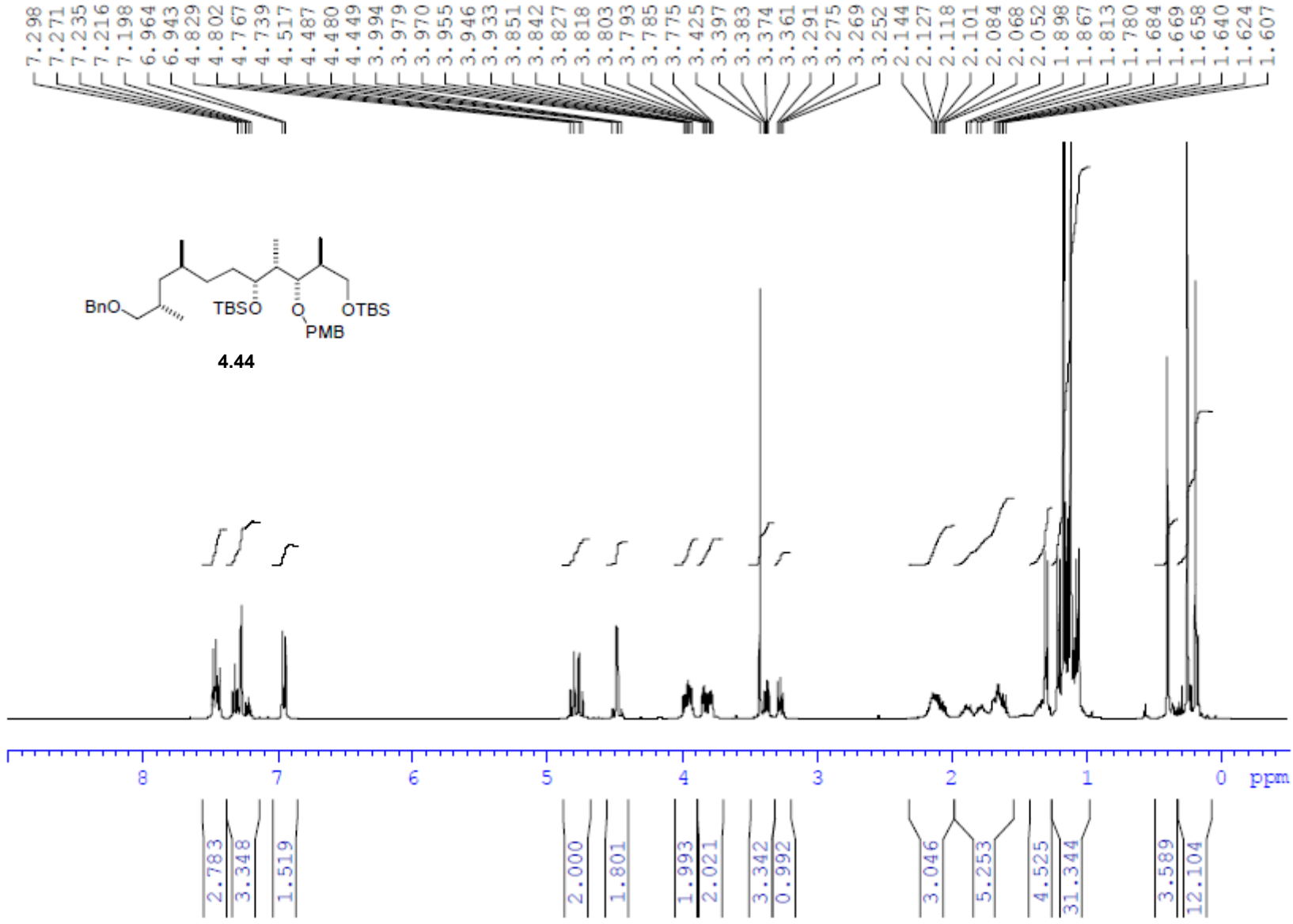


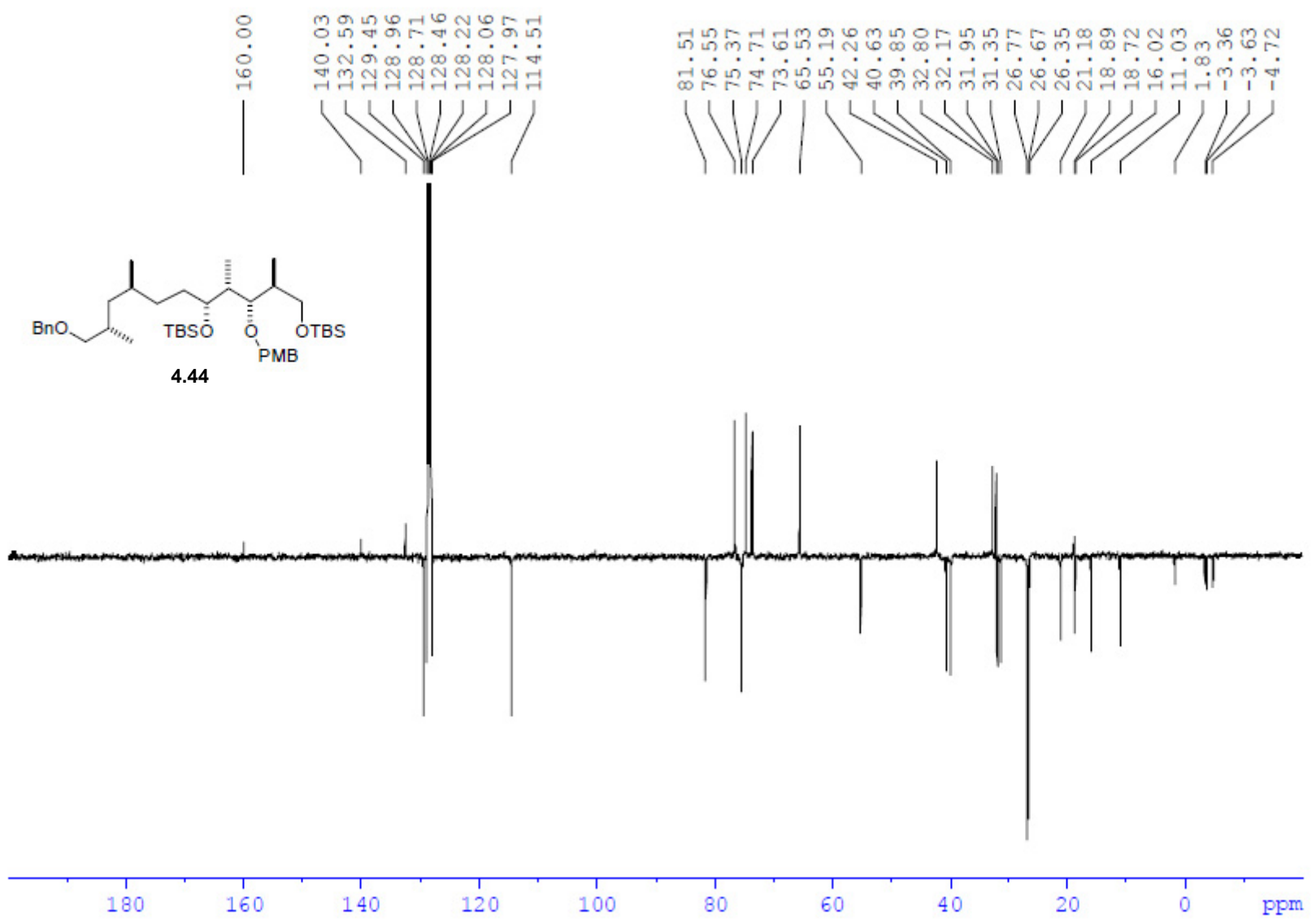
2.660
1.965
0.457
1.414
2.000
0.920
1.724
1.244
0.976
1.000
2.294
1.872
0.961
2.385
1.931
1.473
3.327
3.024
1.221
3.010
2.961

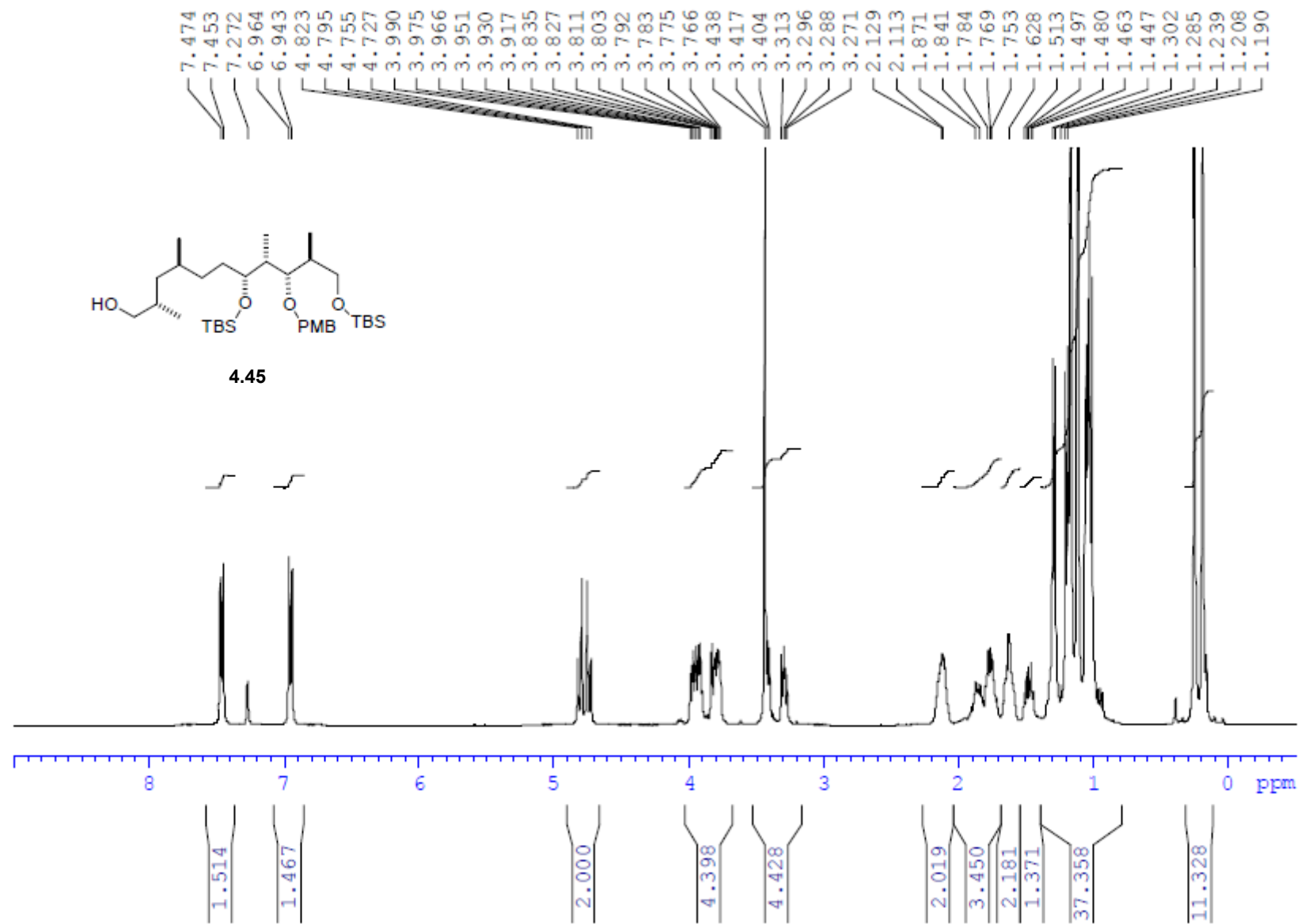


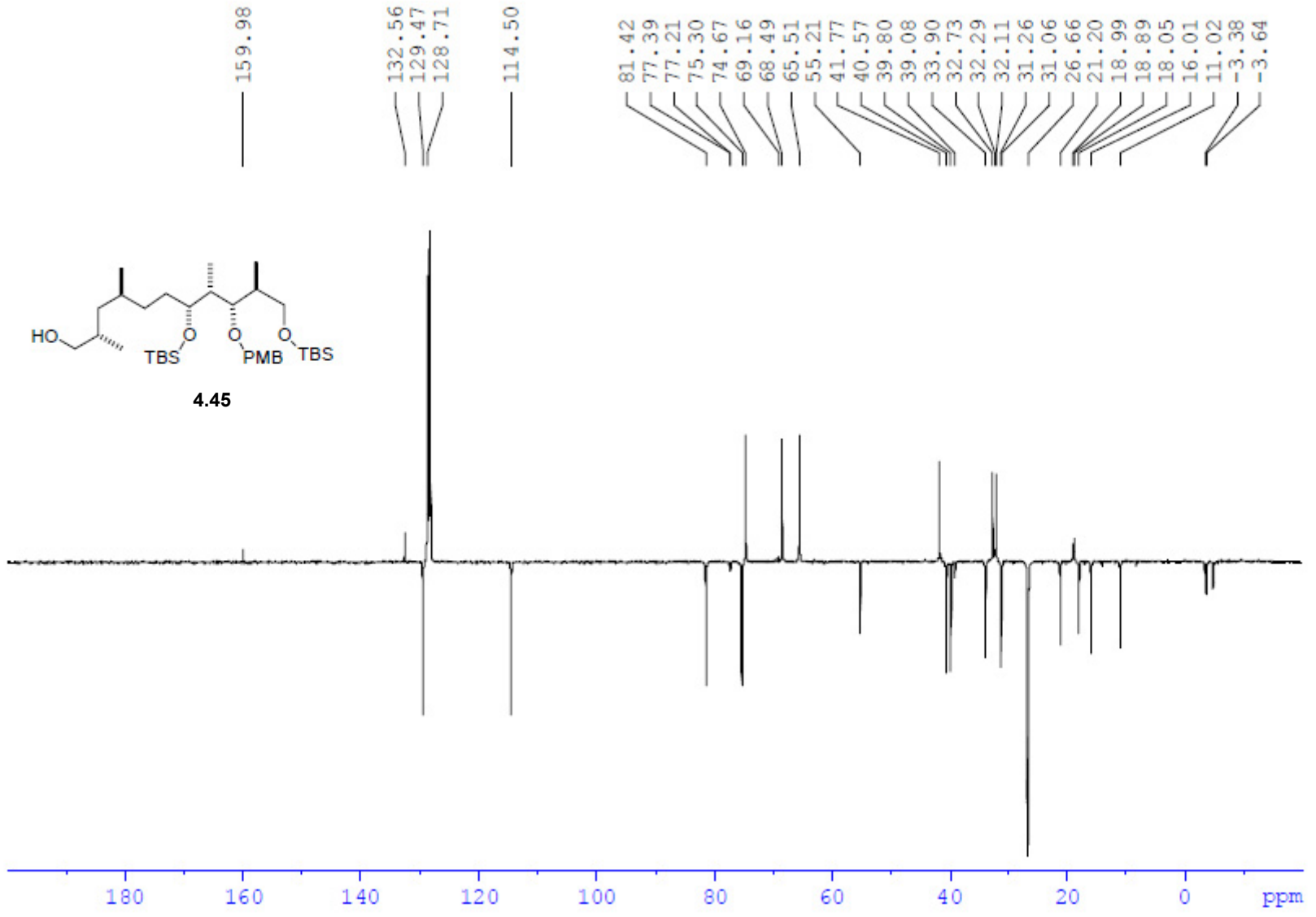


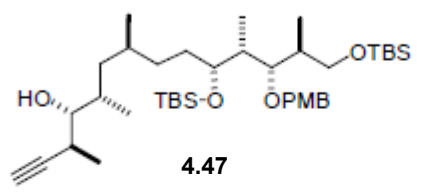
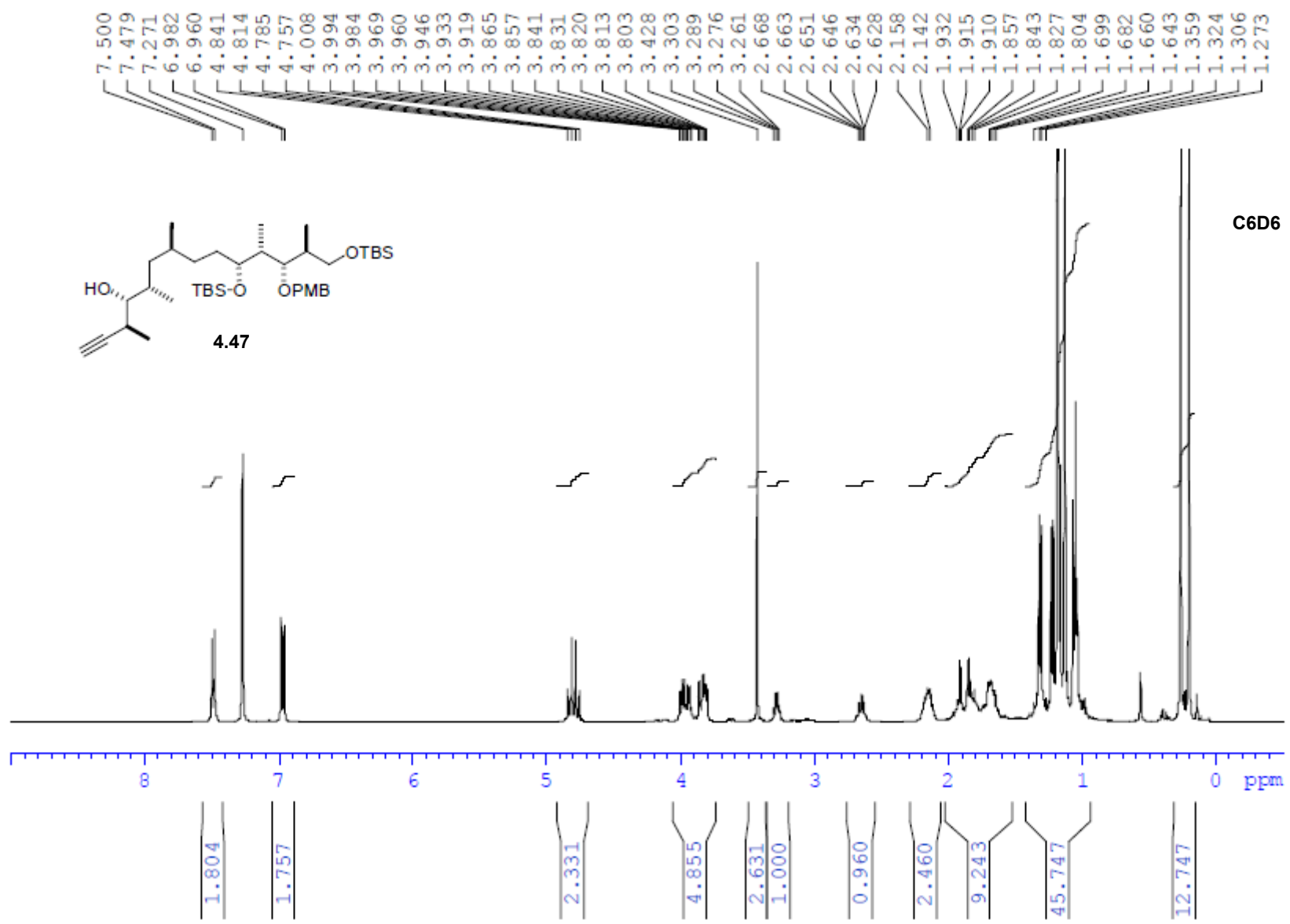




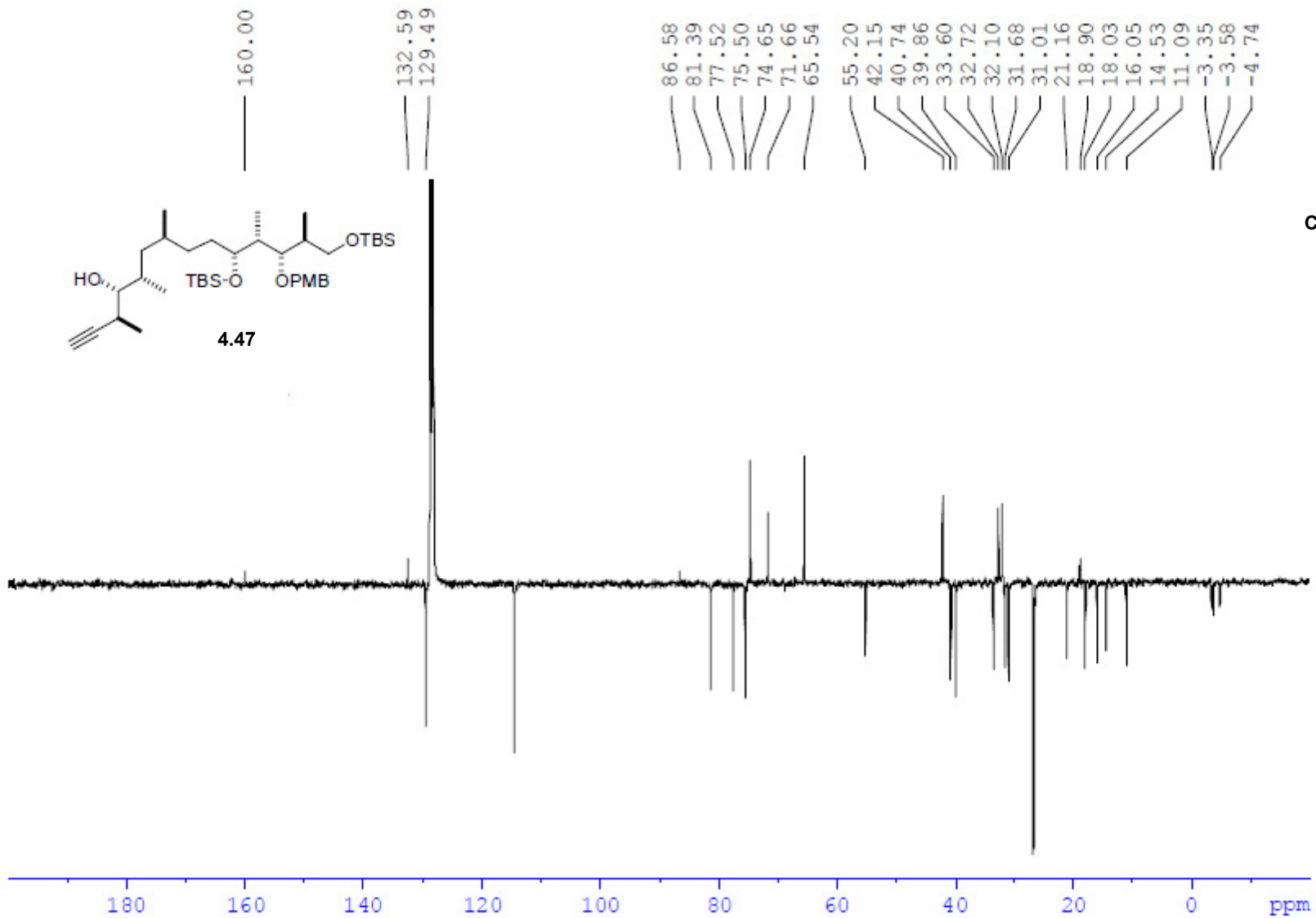




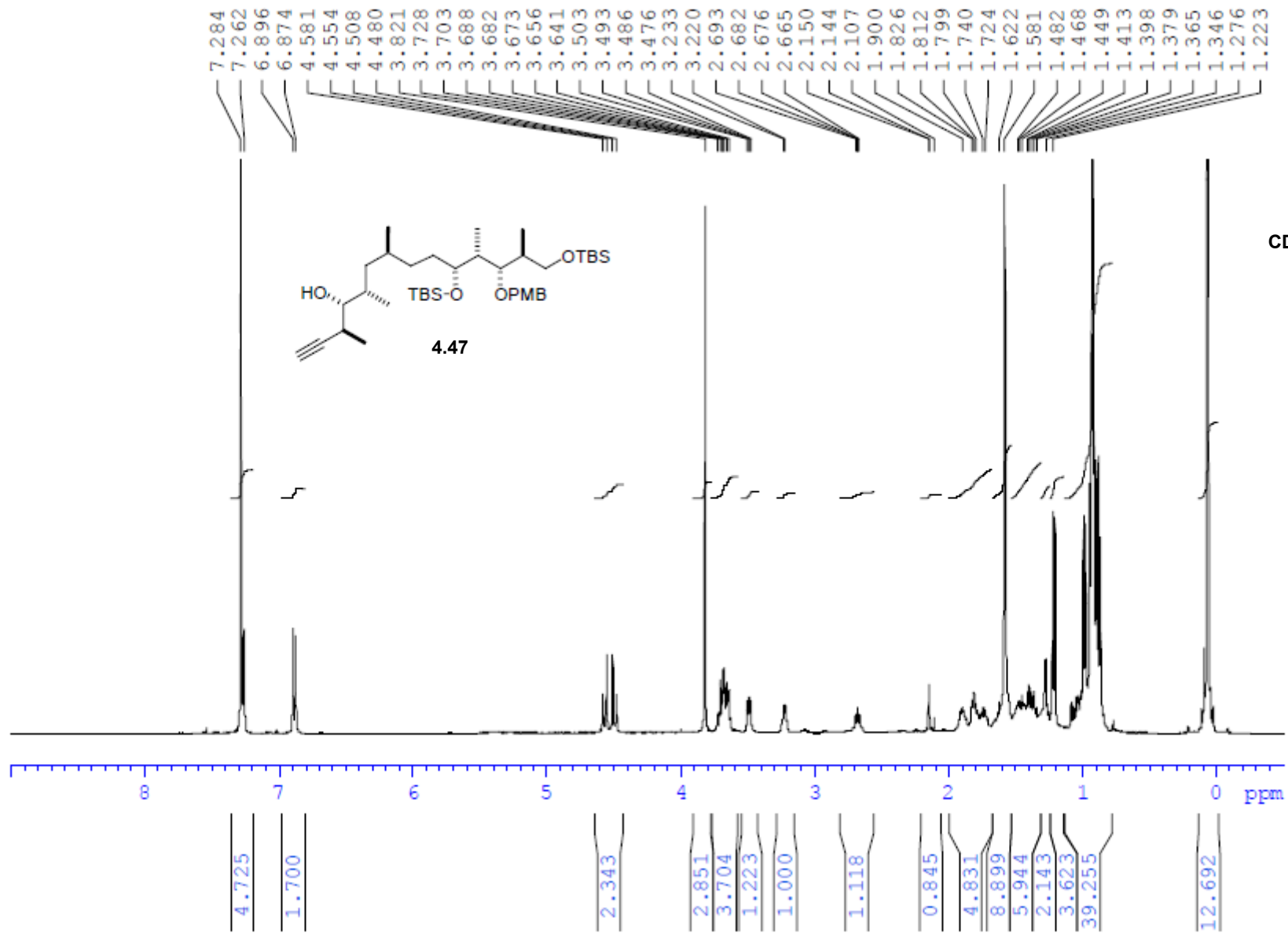


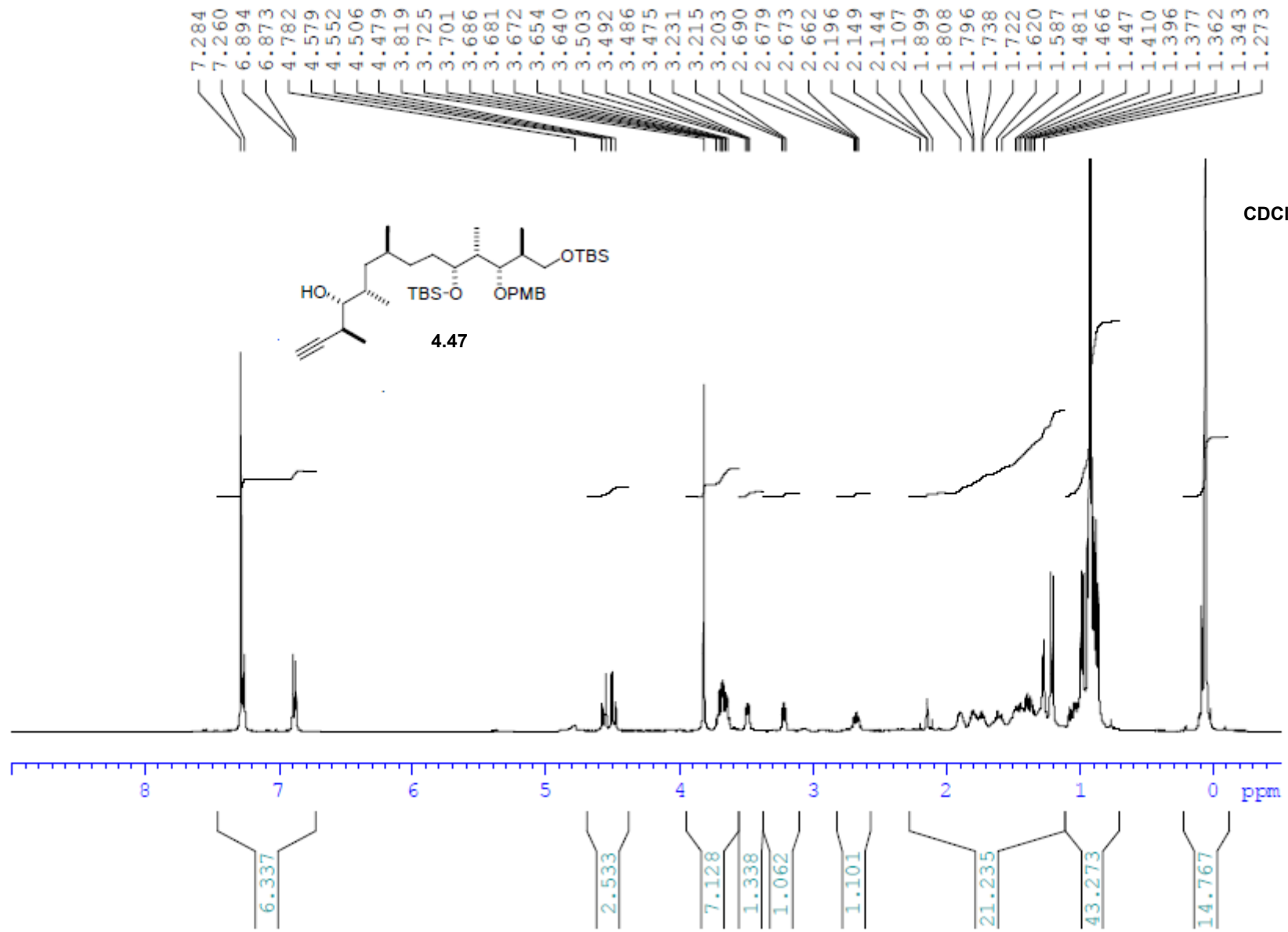


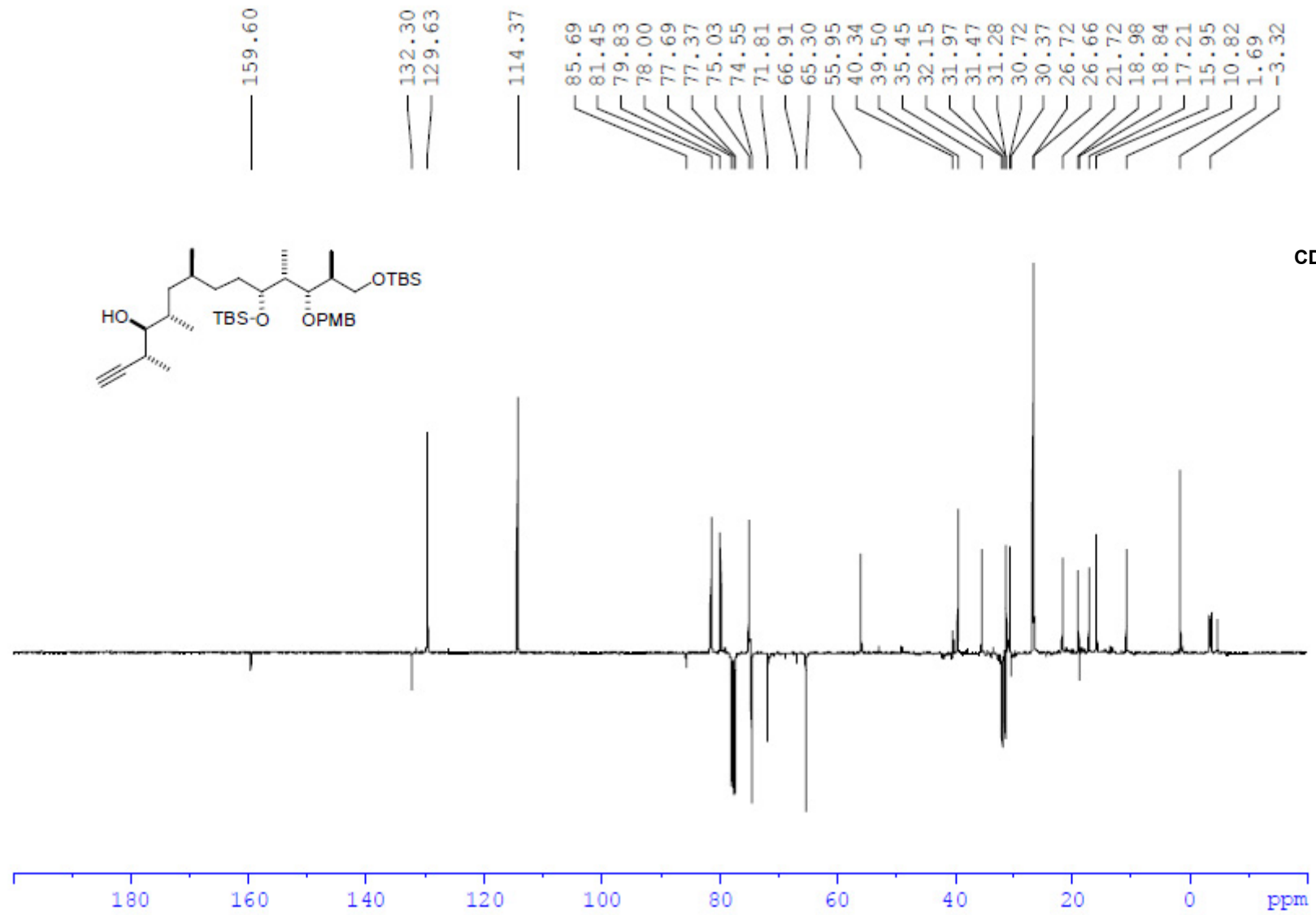
CDCl₃



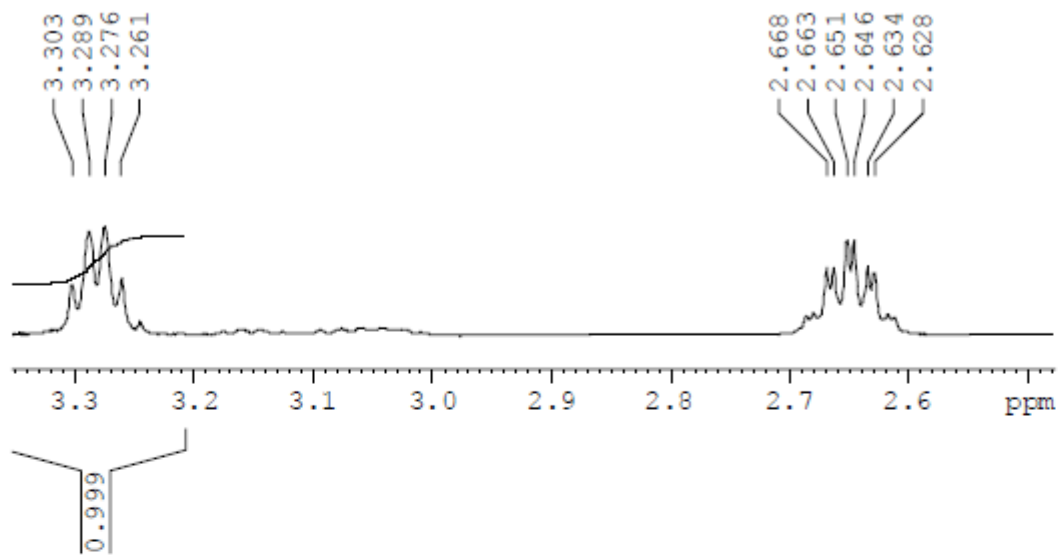
C6D6



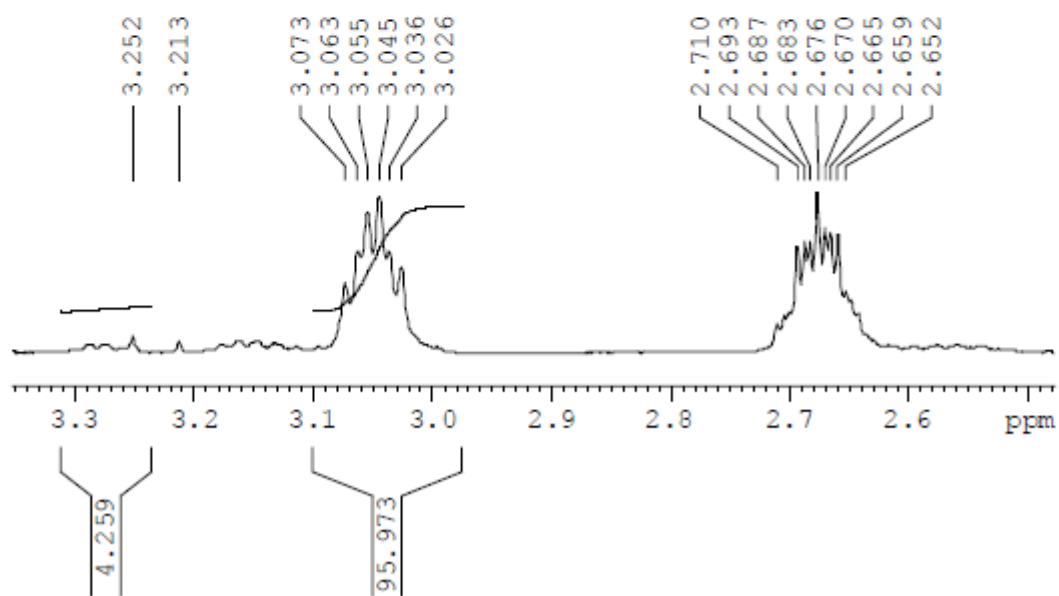
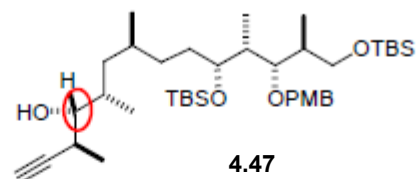




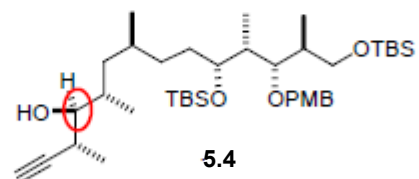
CDCl₃

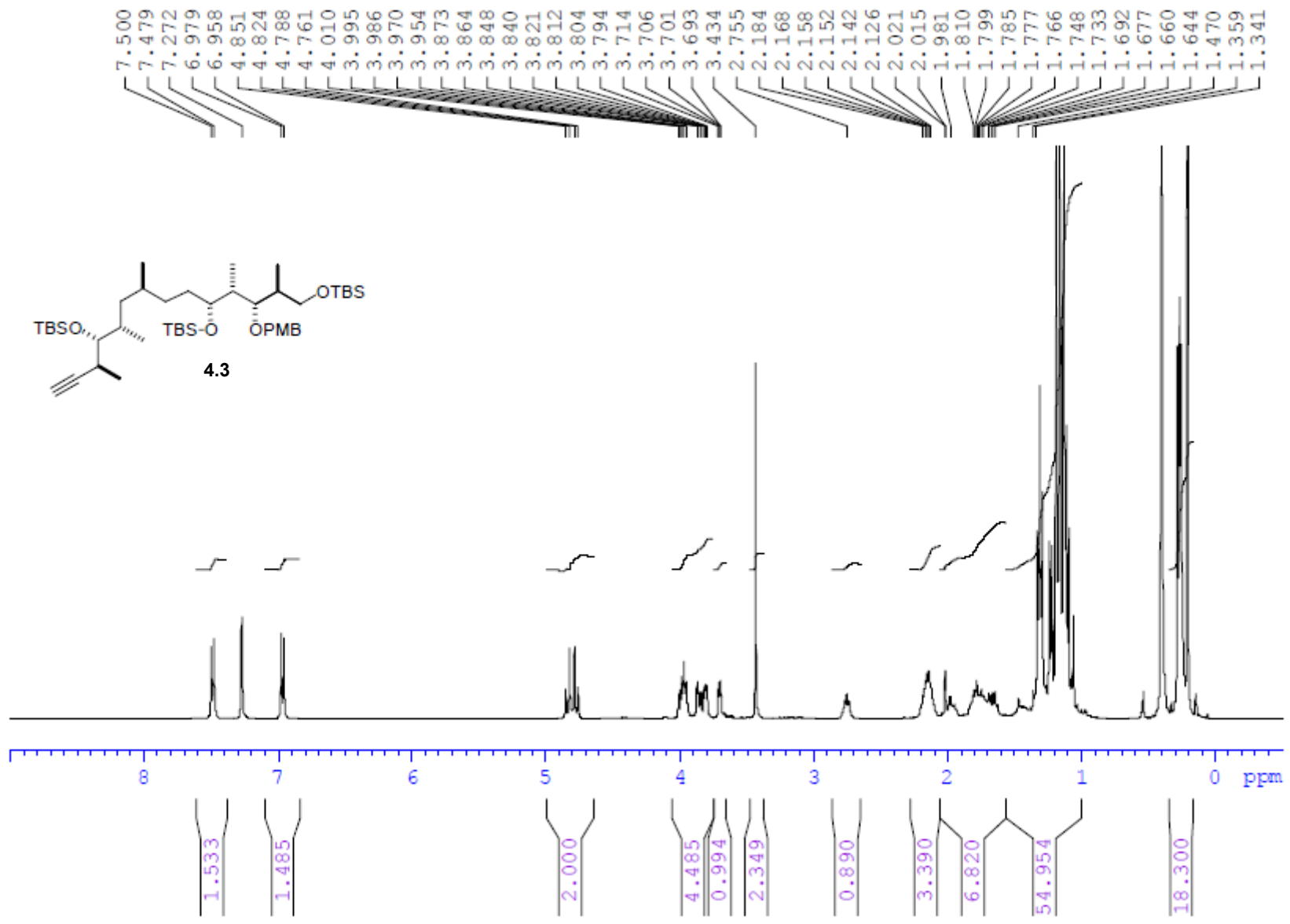


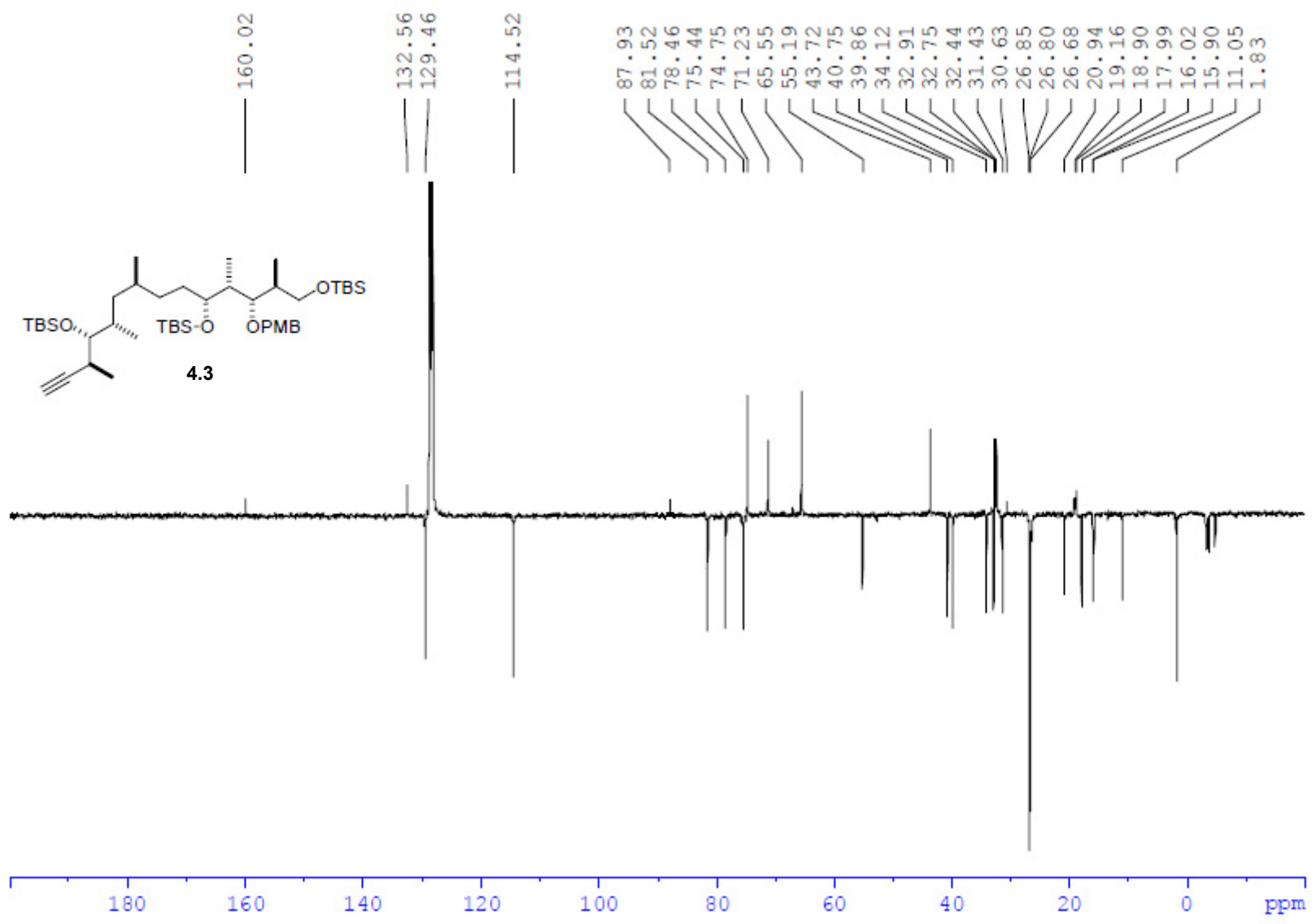
Anti, syn adduct



Anti, anti adduct

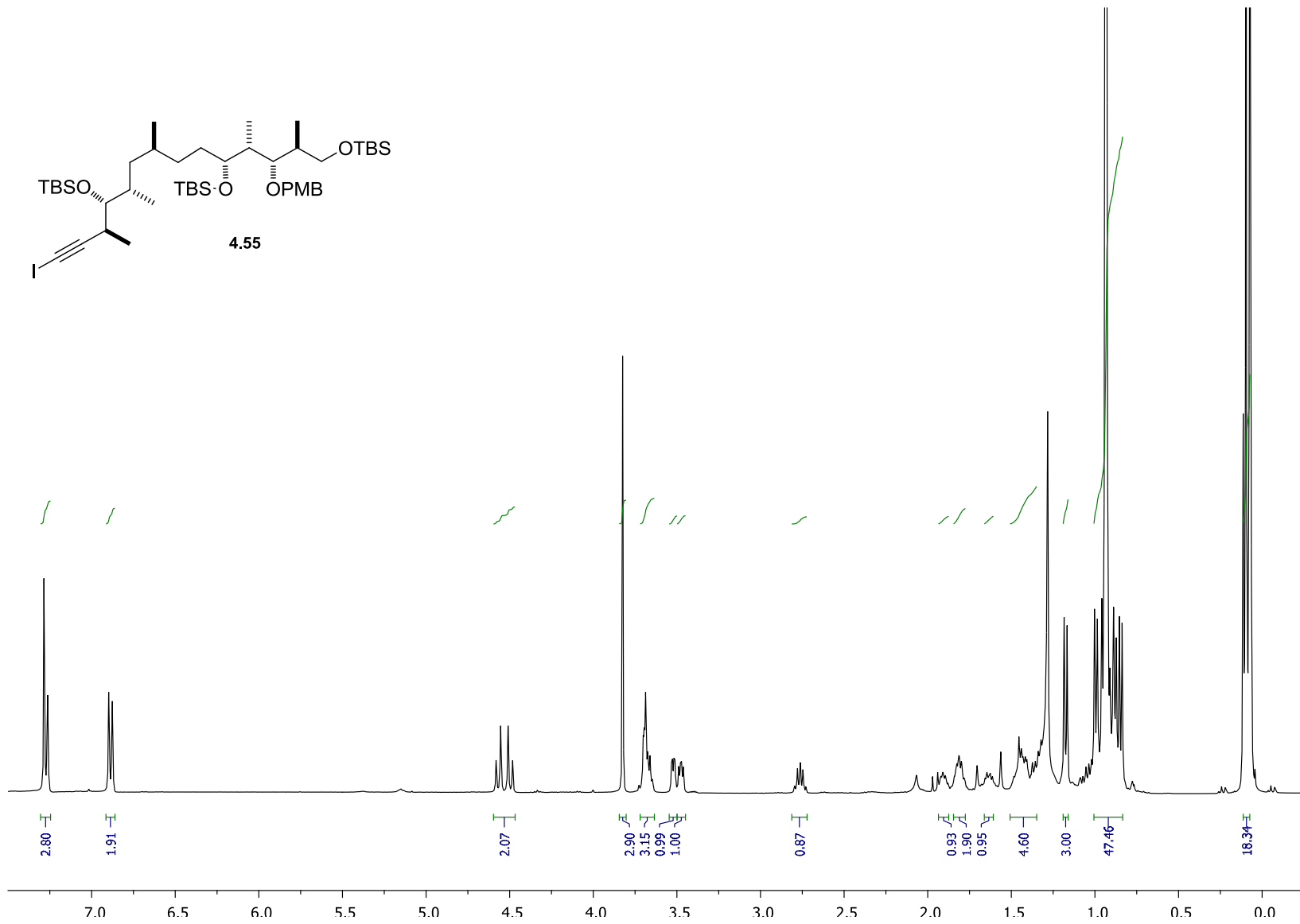
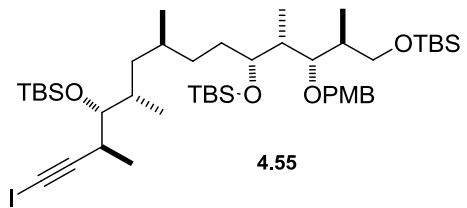


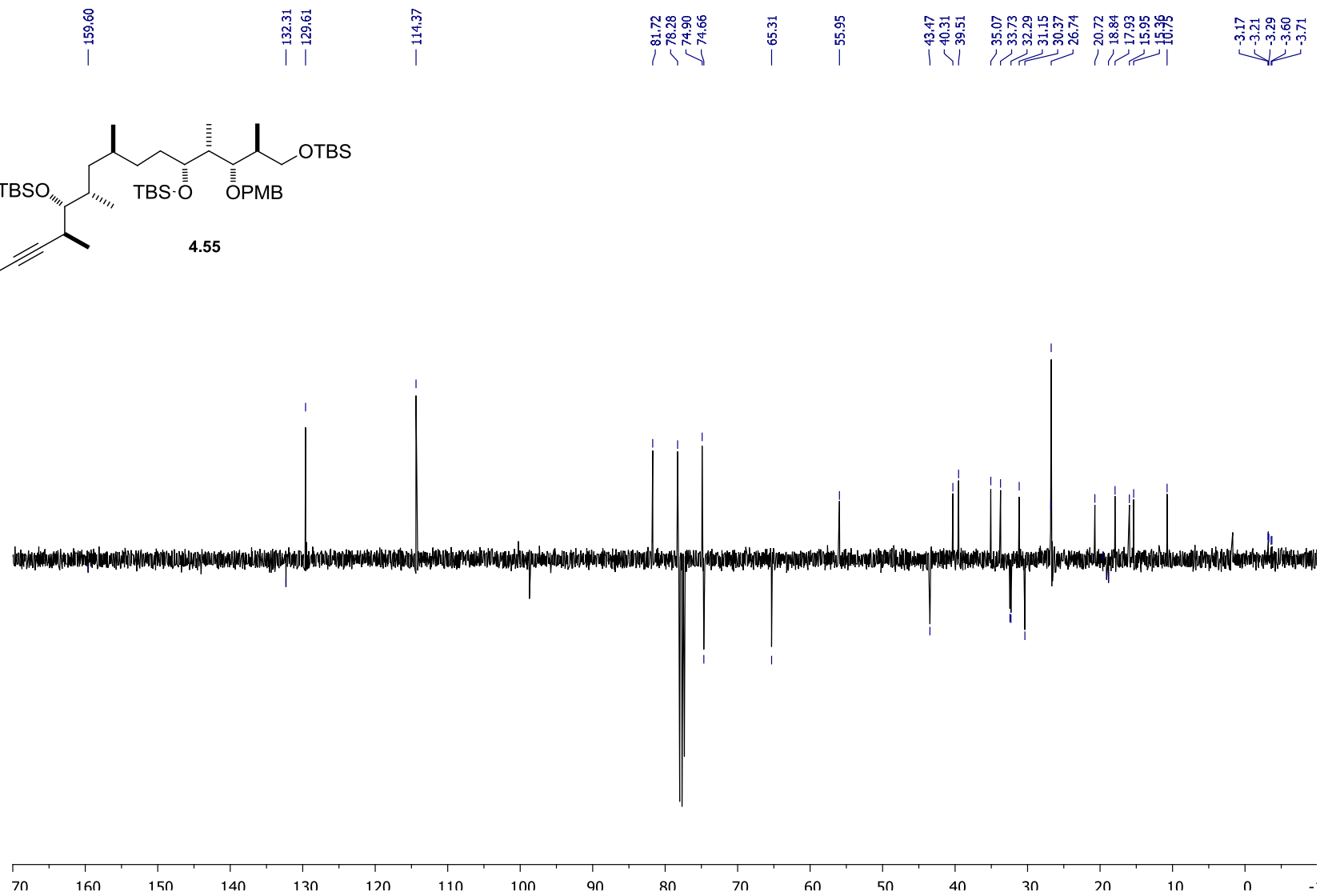
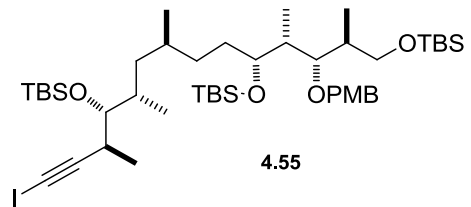


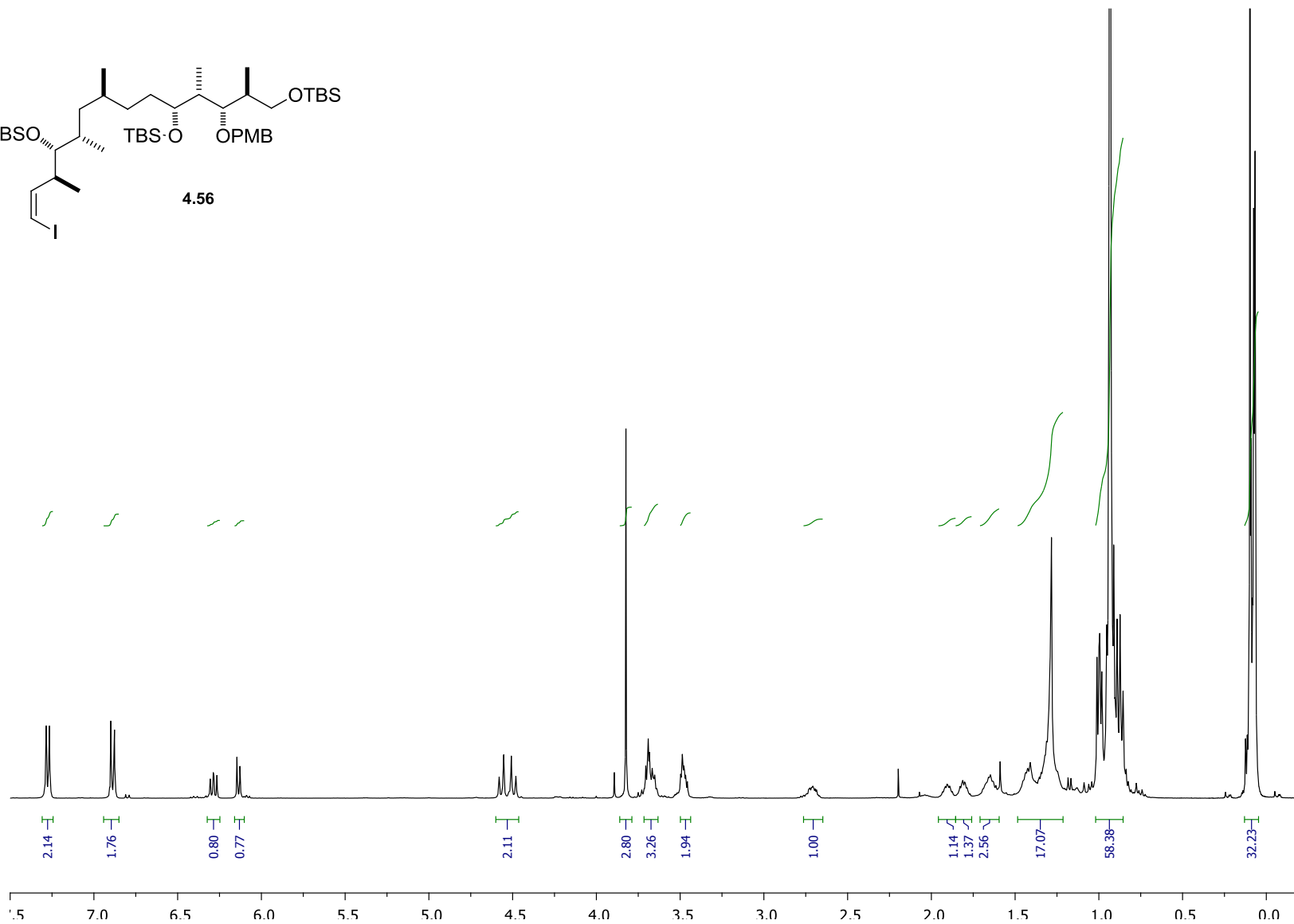
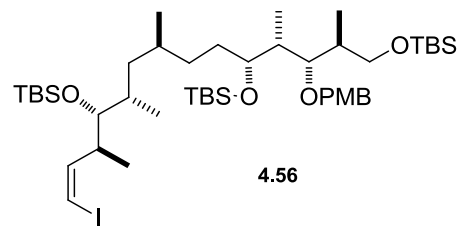


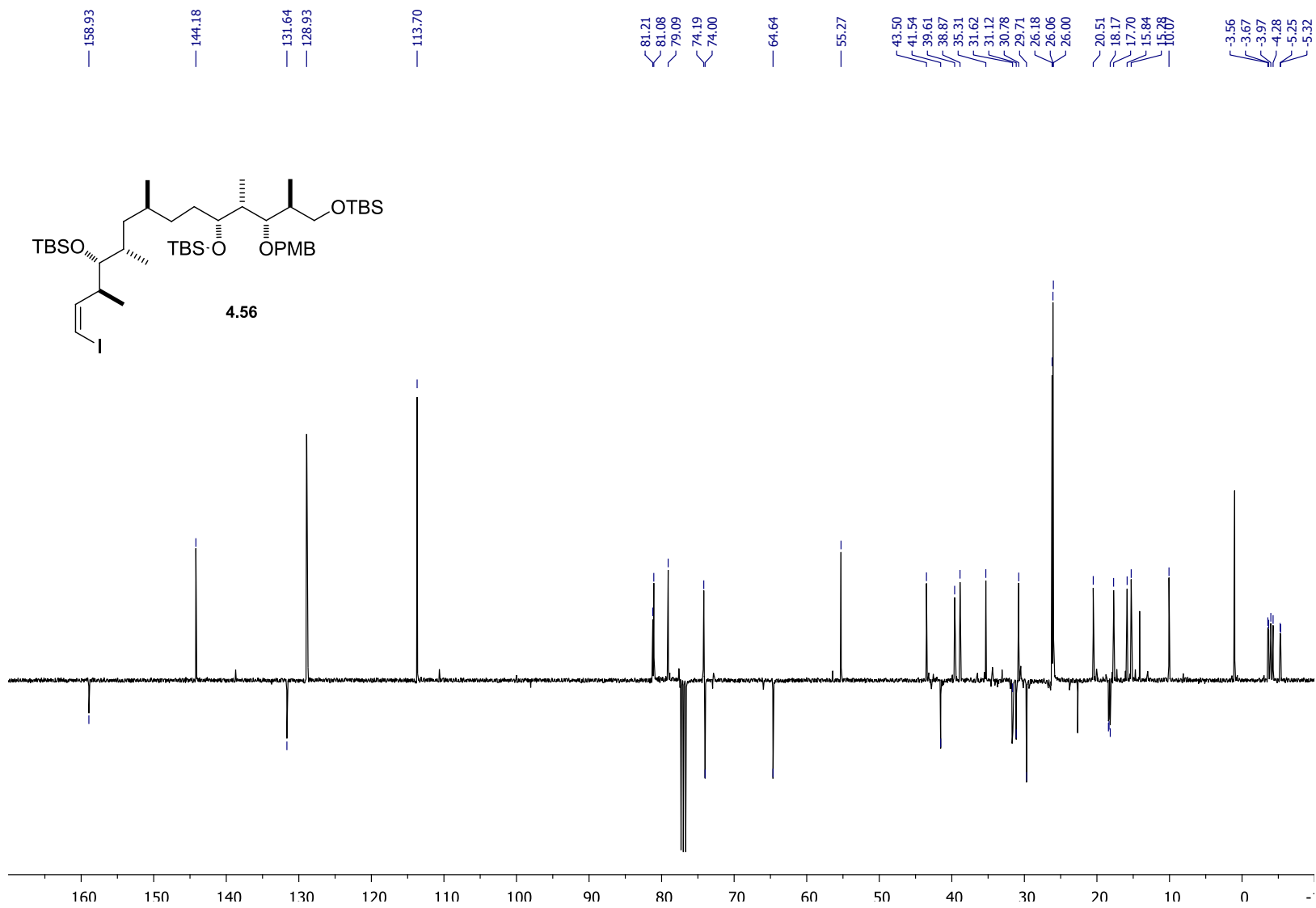
Synthesis of (Z)-Vinyl Iodide C10-C26

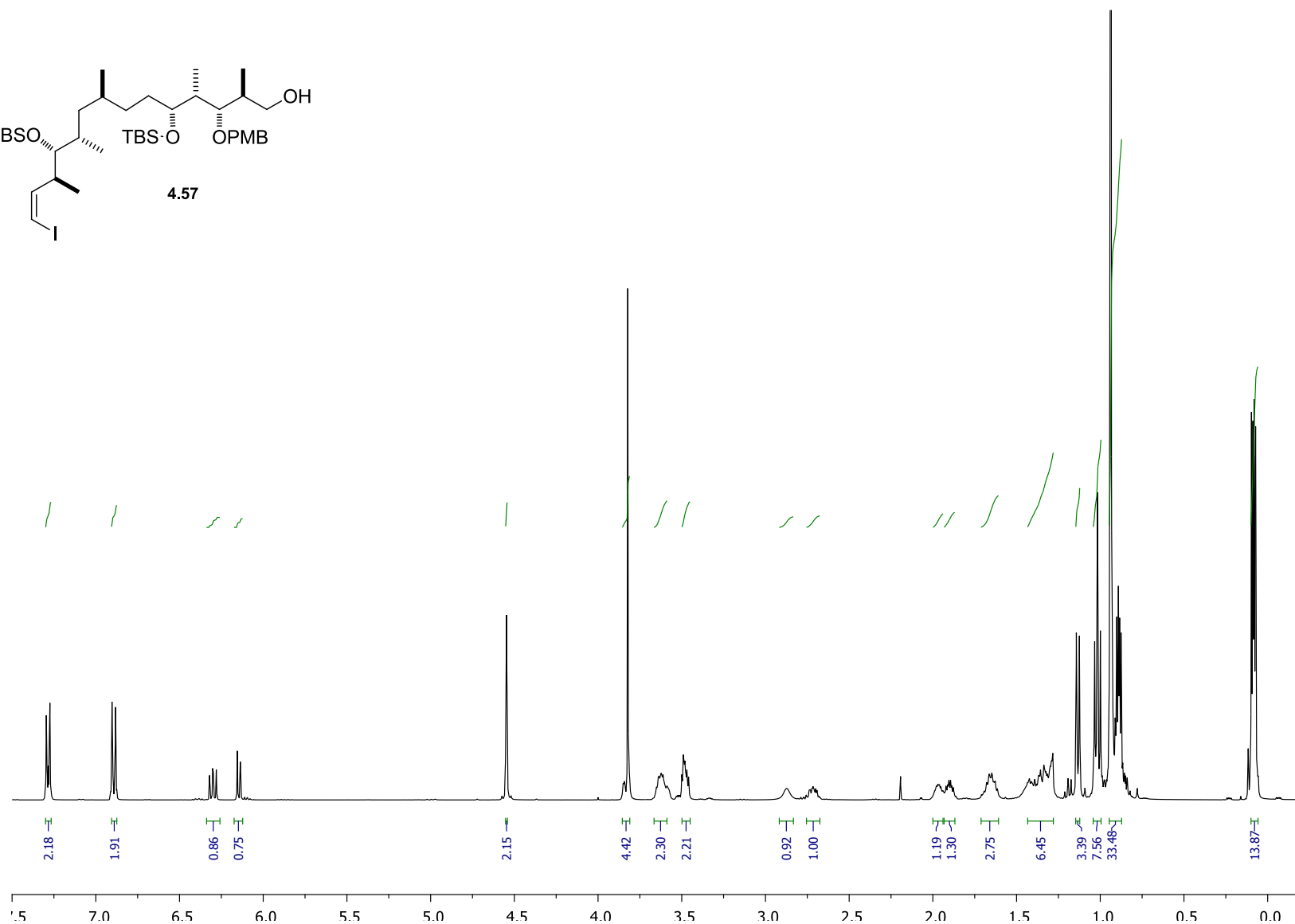
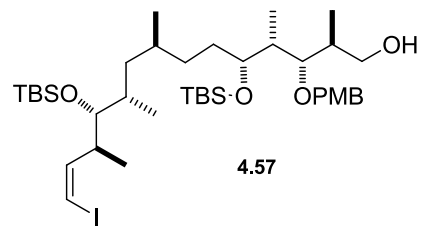
NMR Spectra

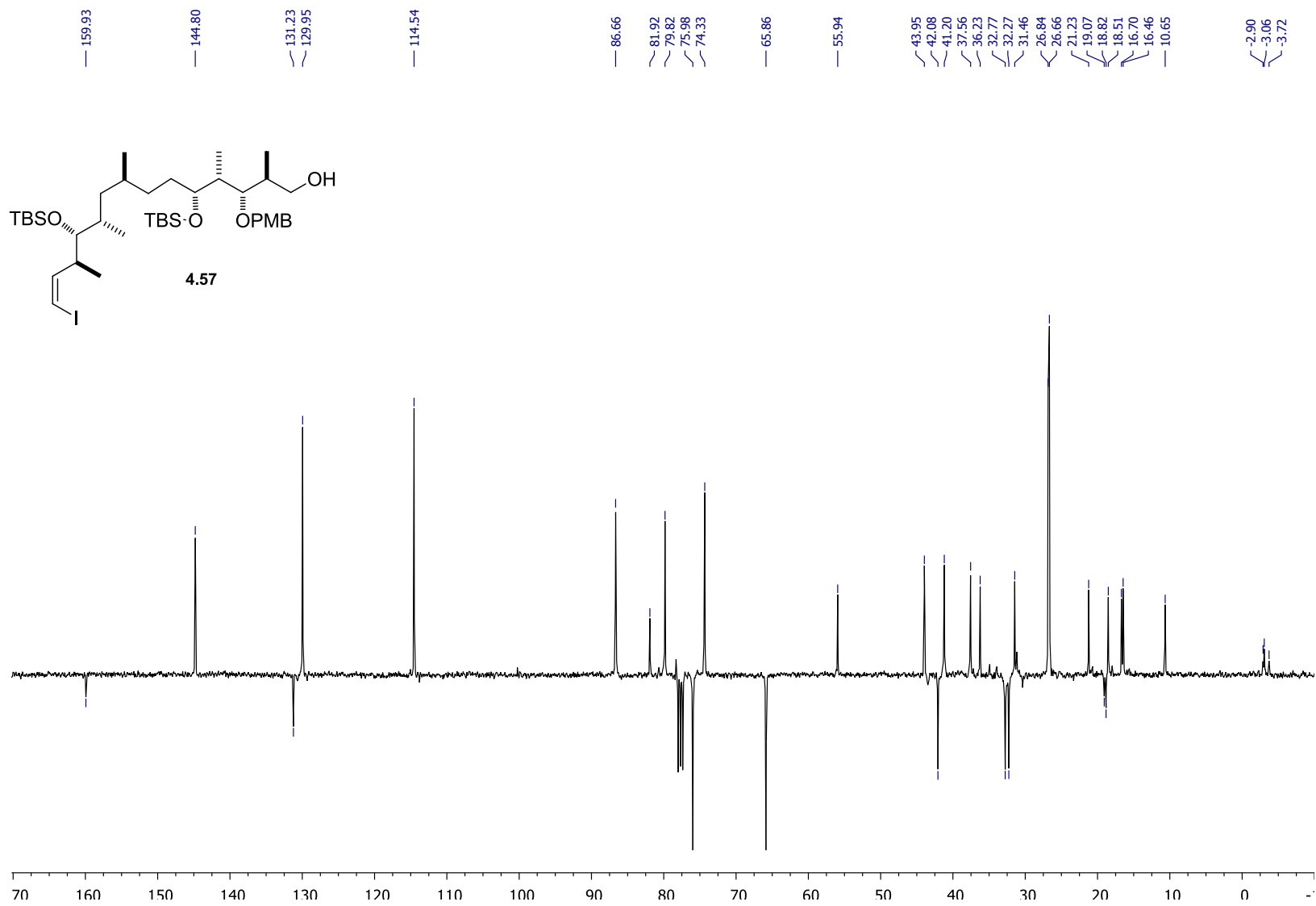


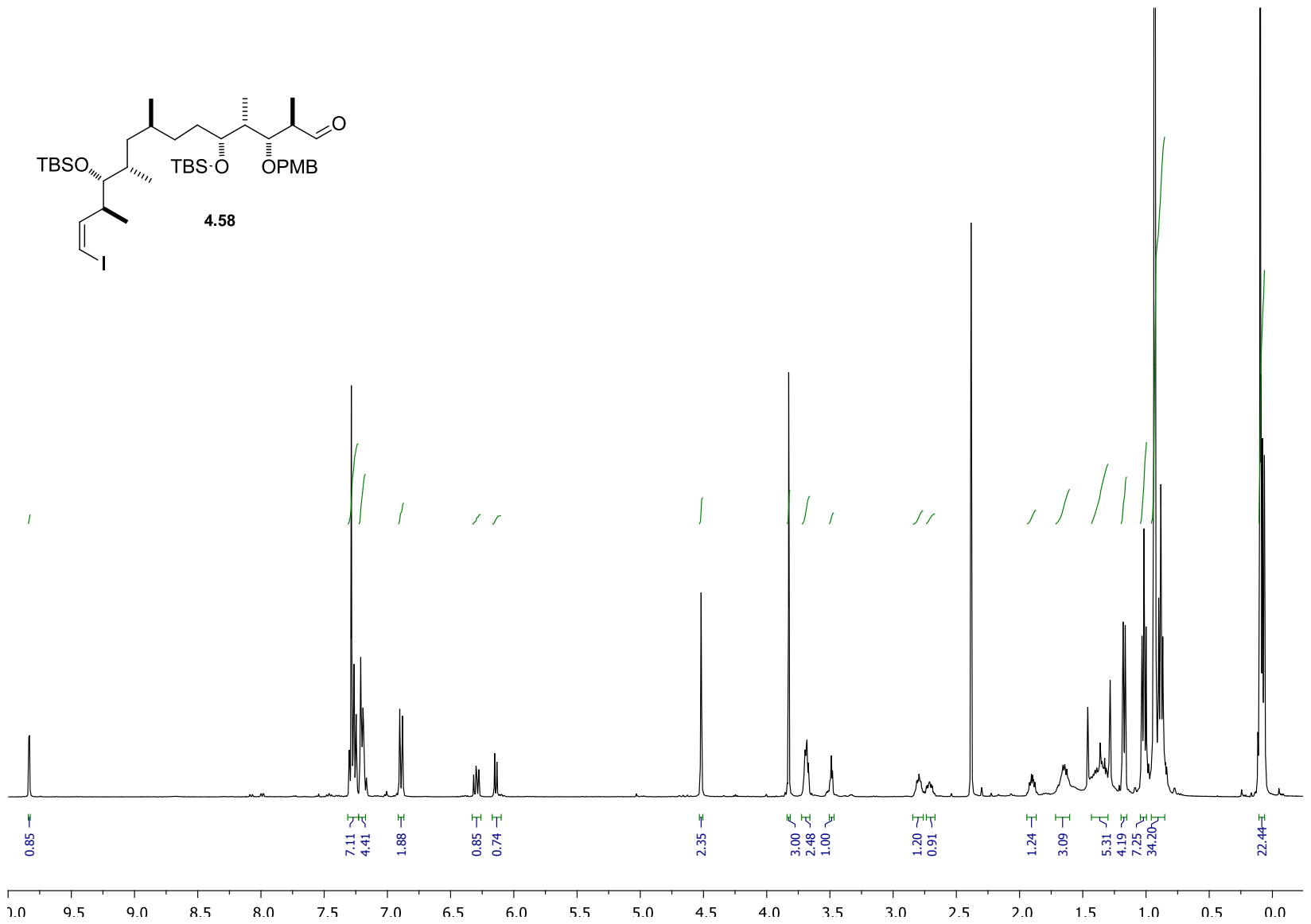
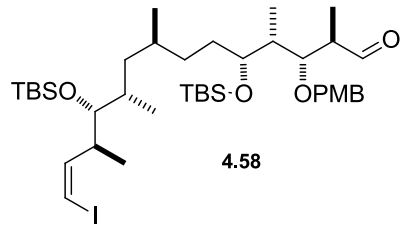


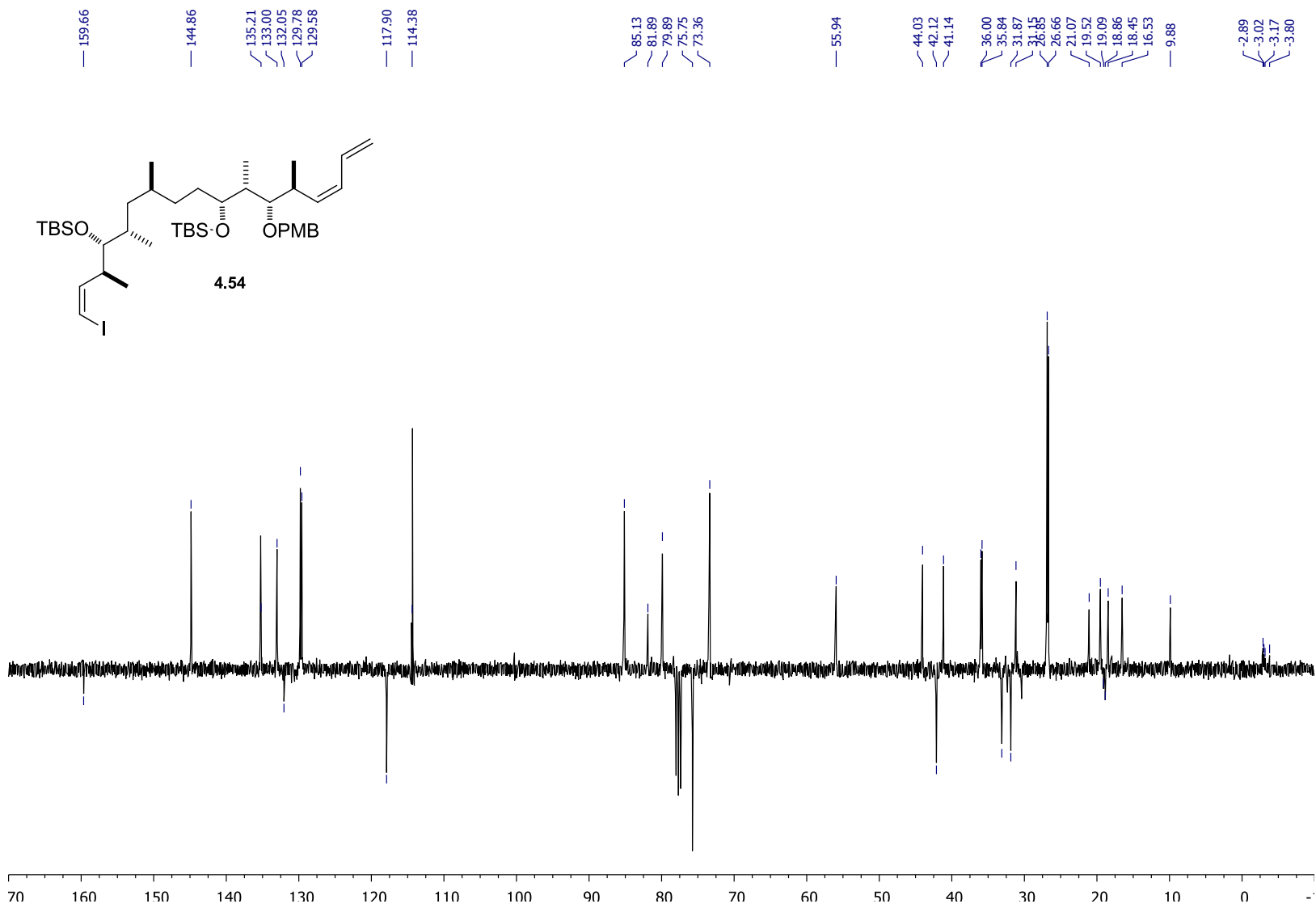




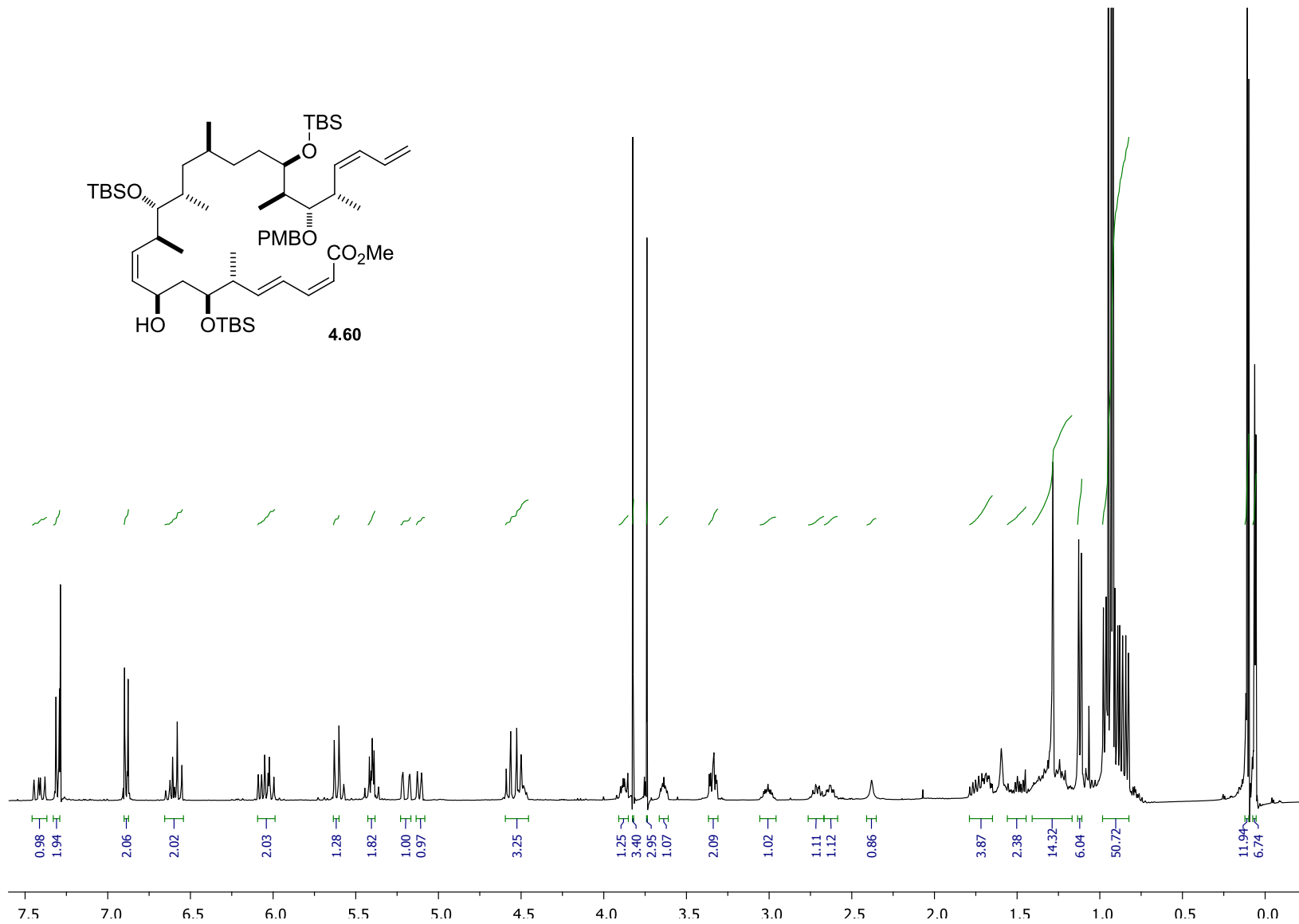
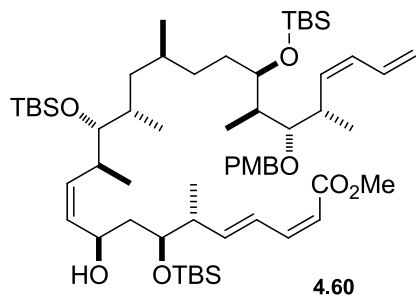


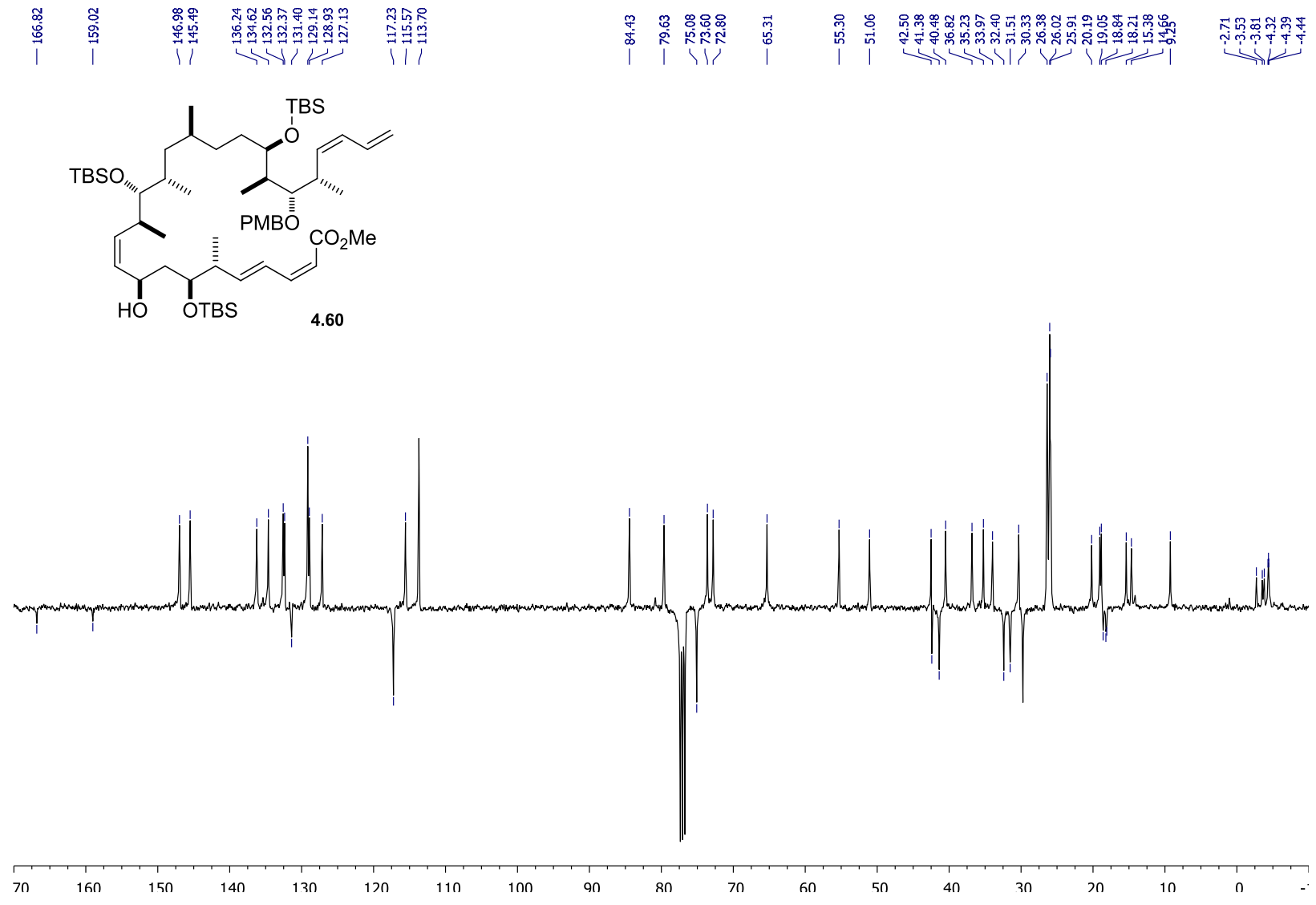


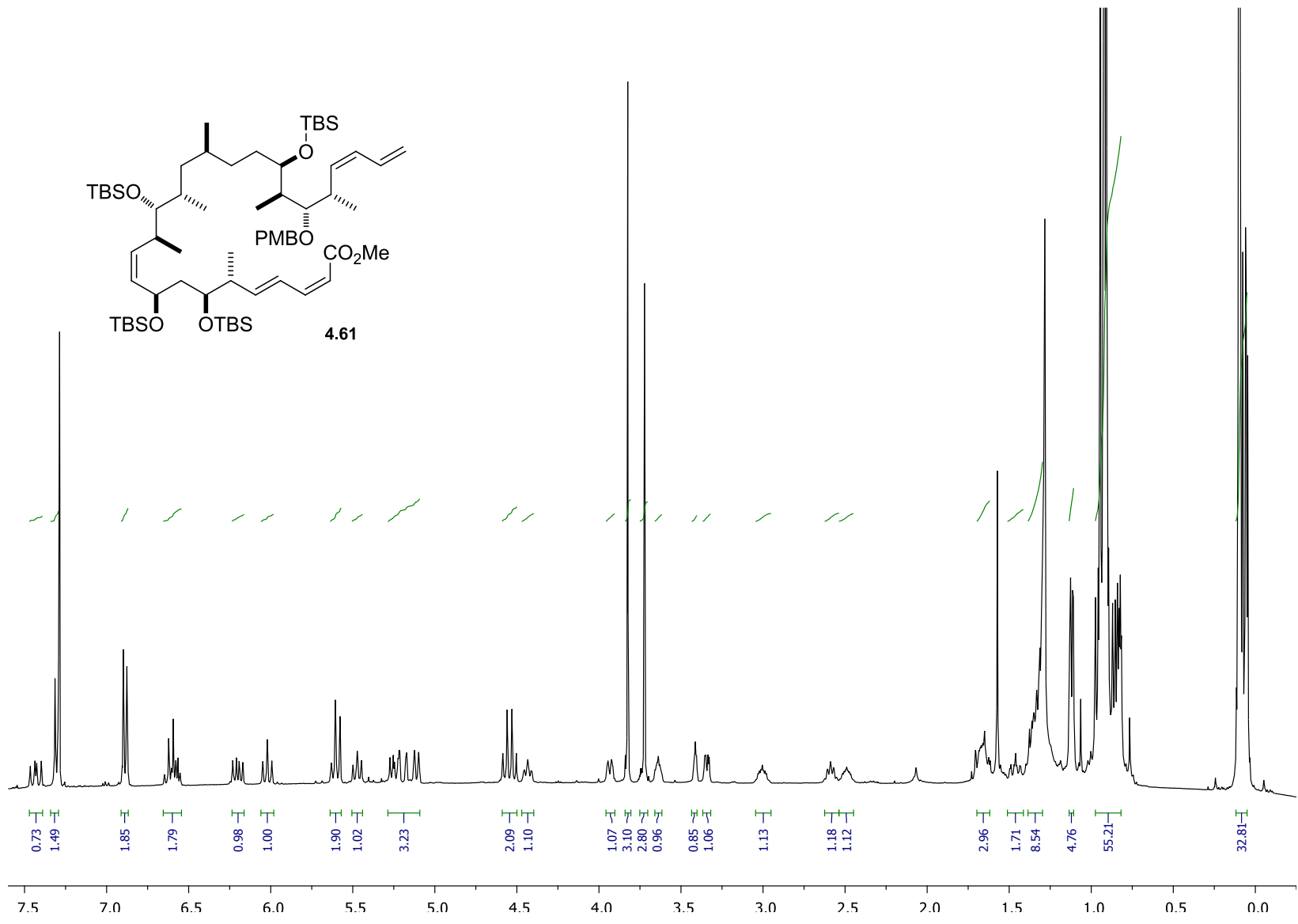


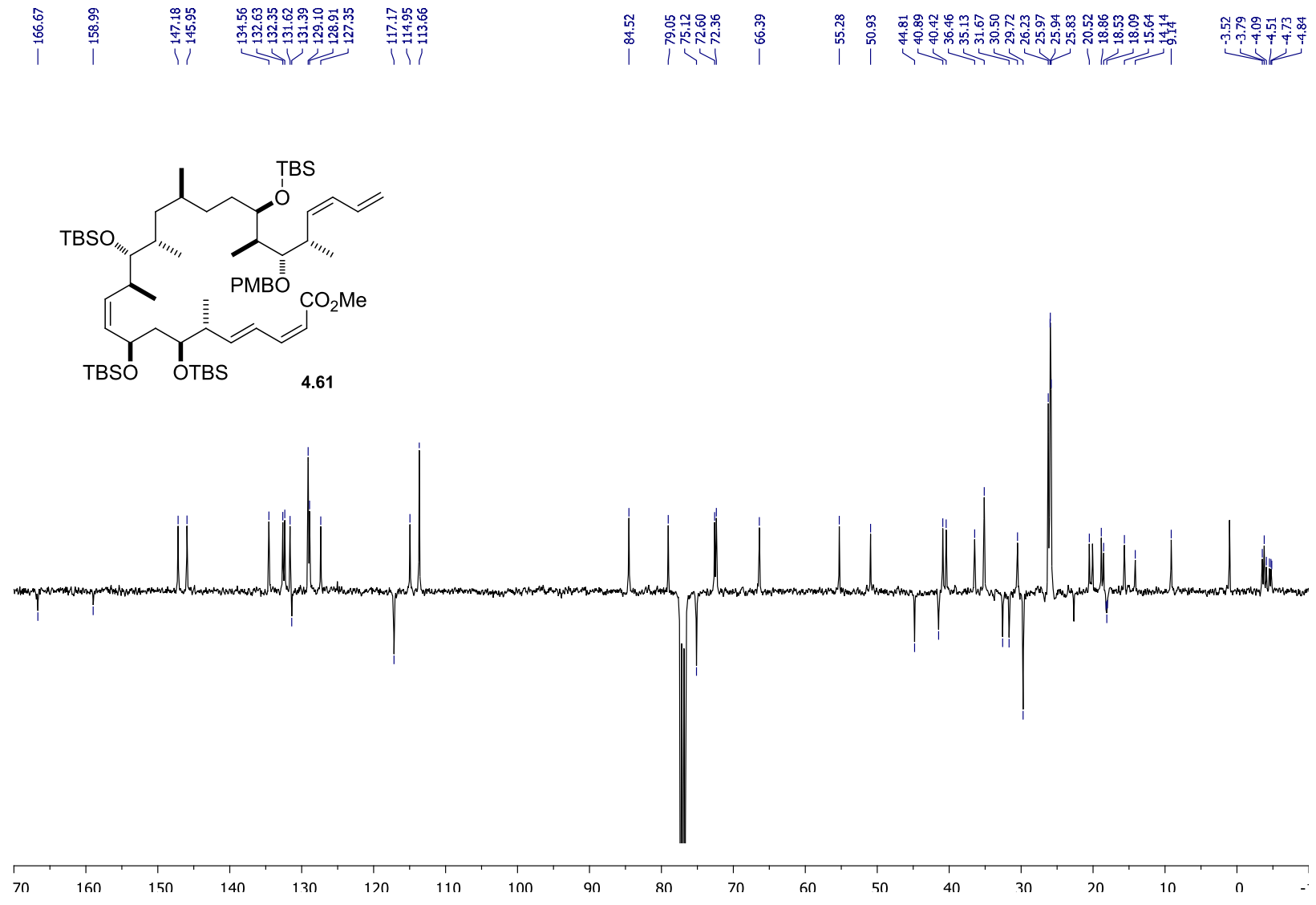


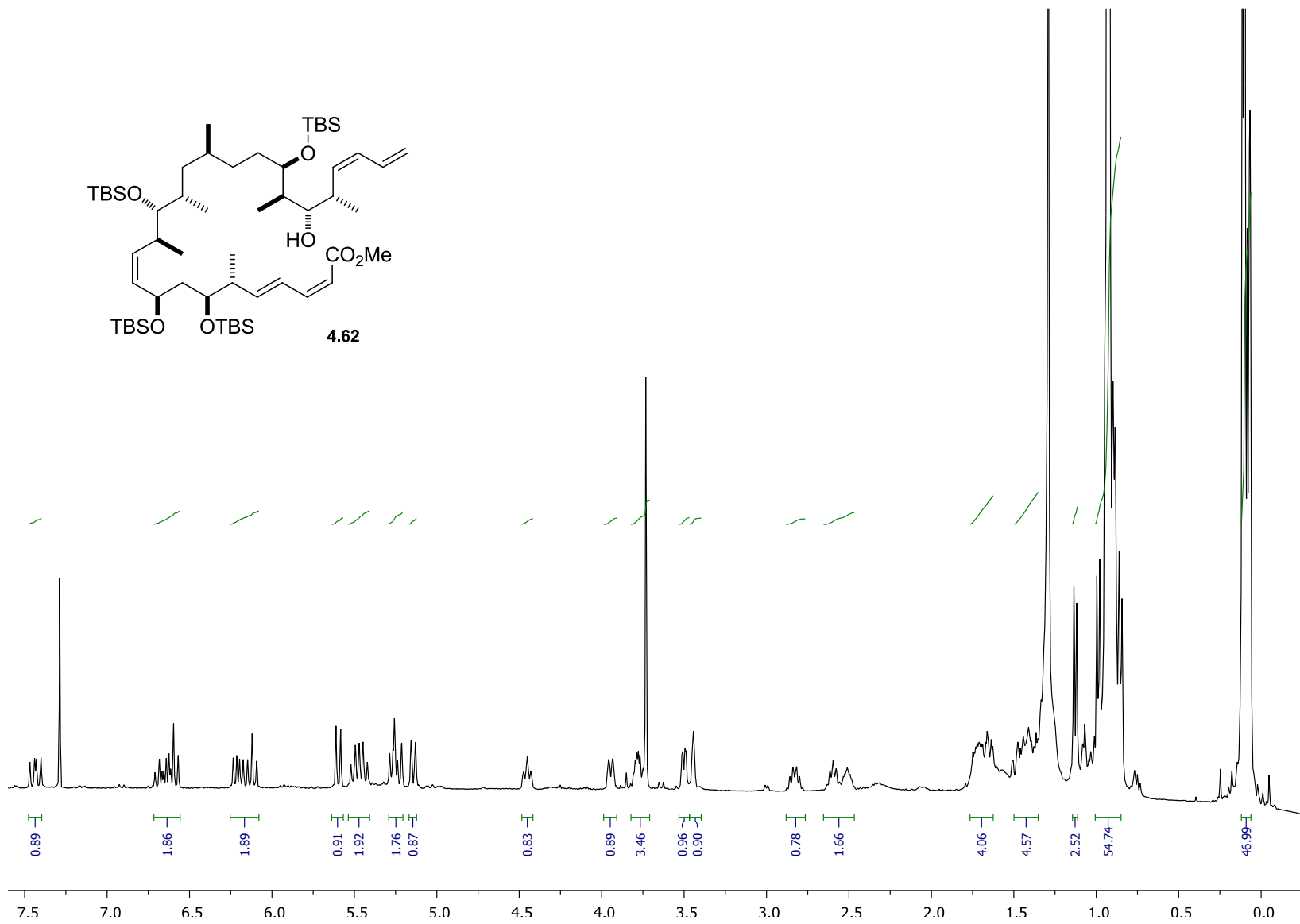
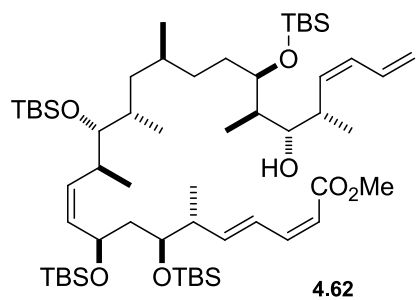
Completion of the Synthesis of (+)-9-*epi*-Dictyostatin
NMR Spectra

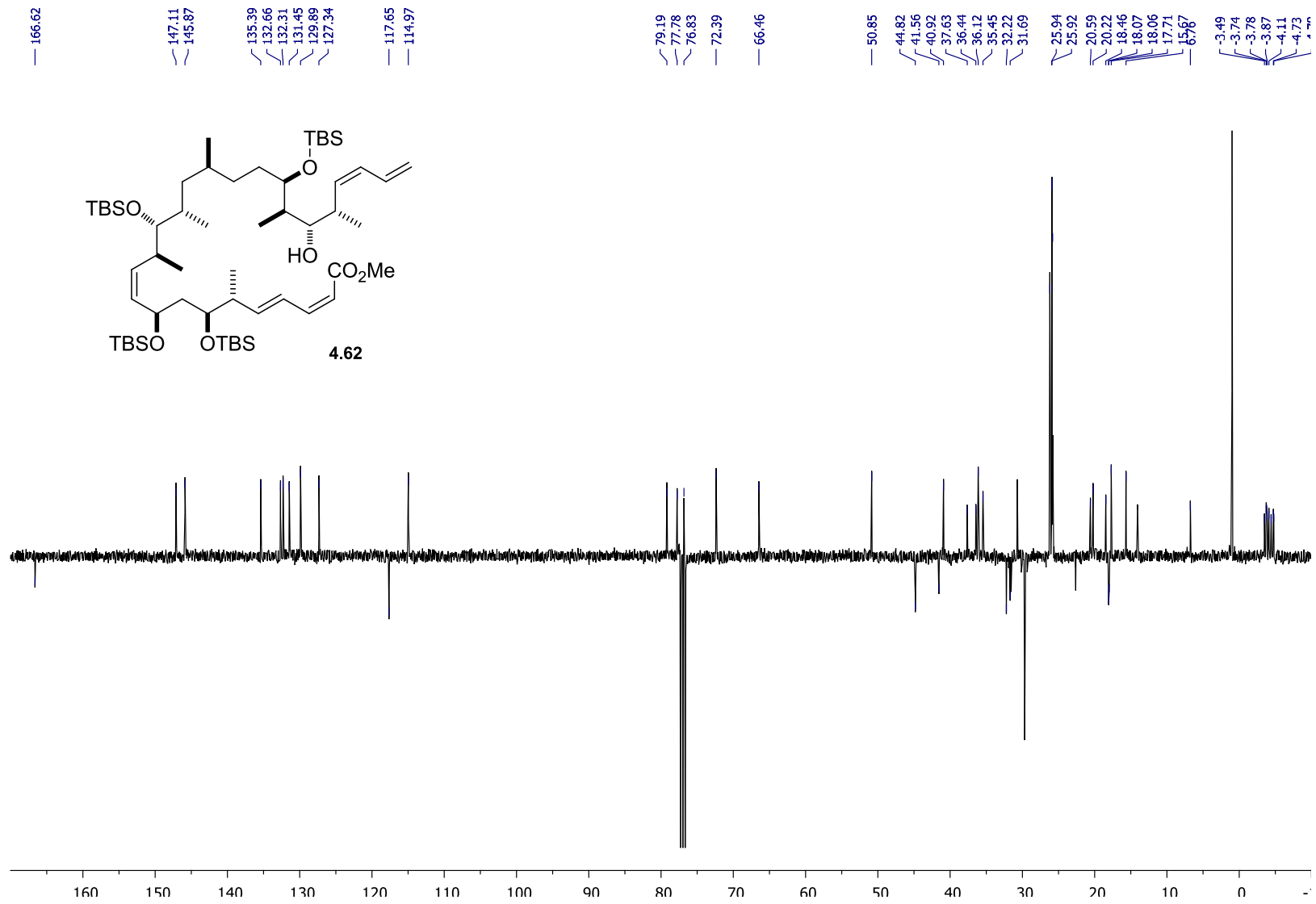


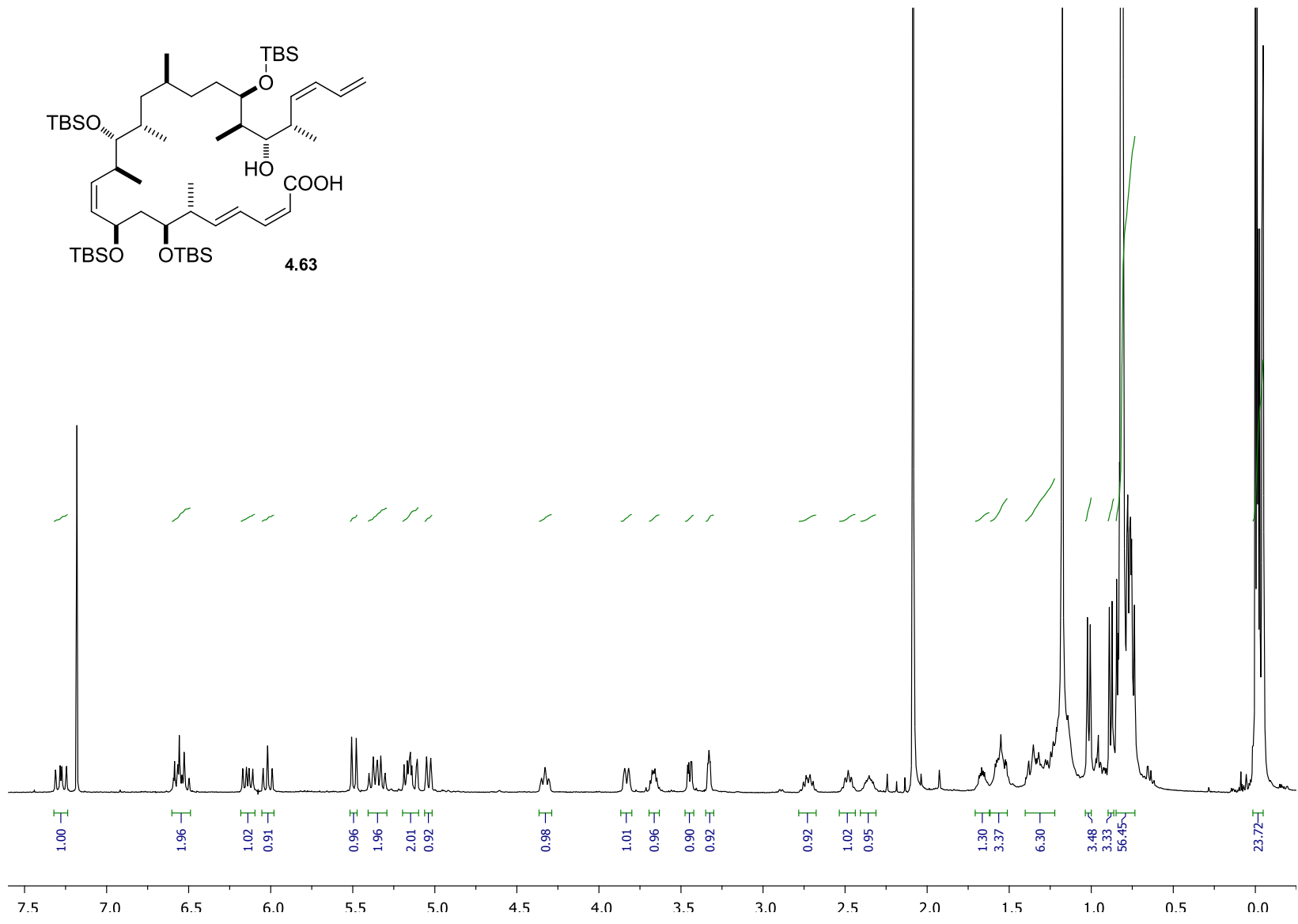
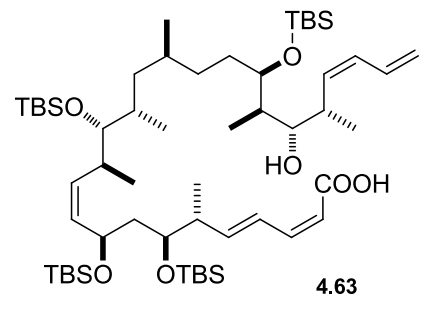


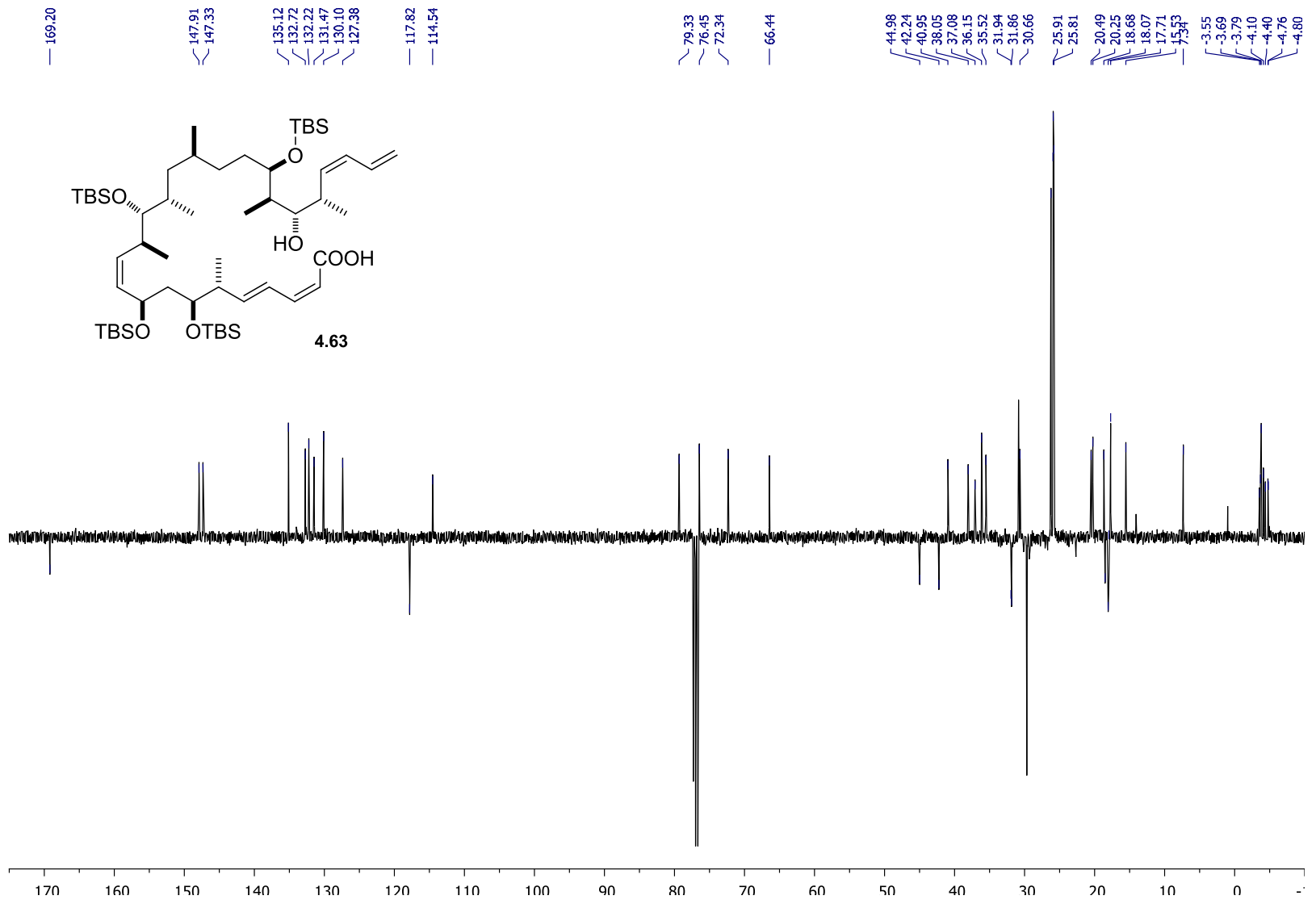


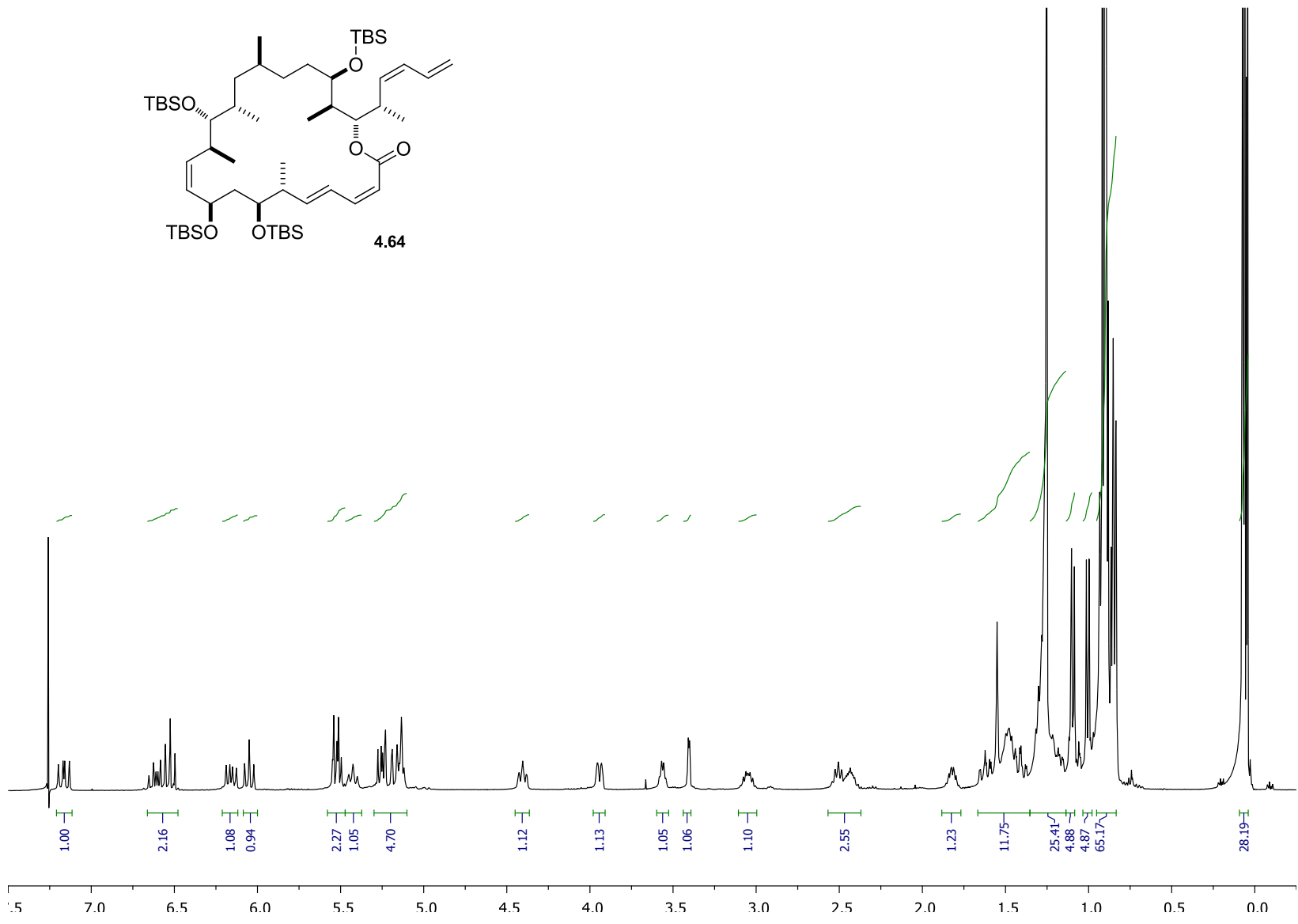
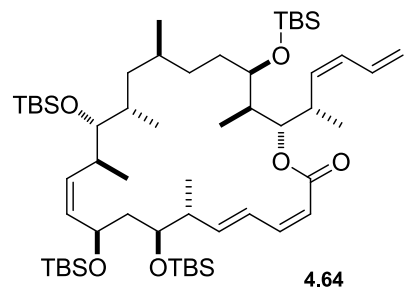


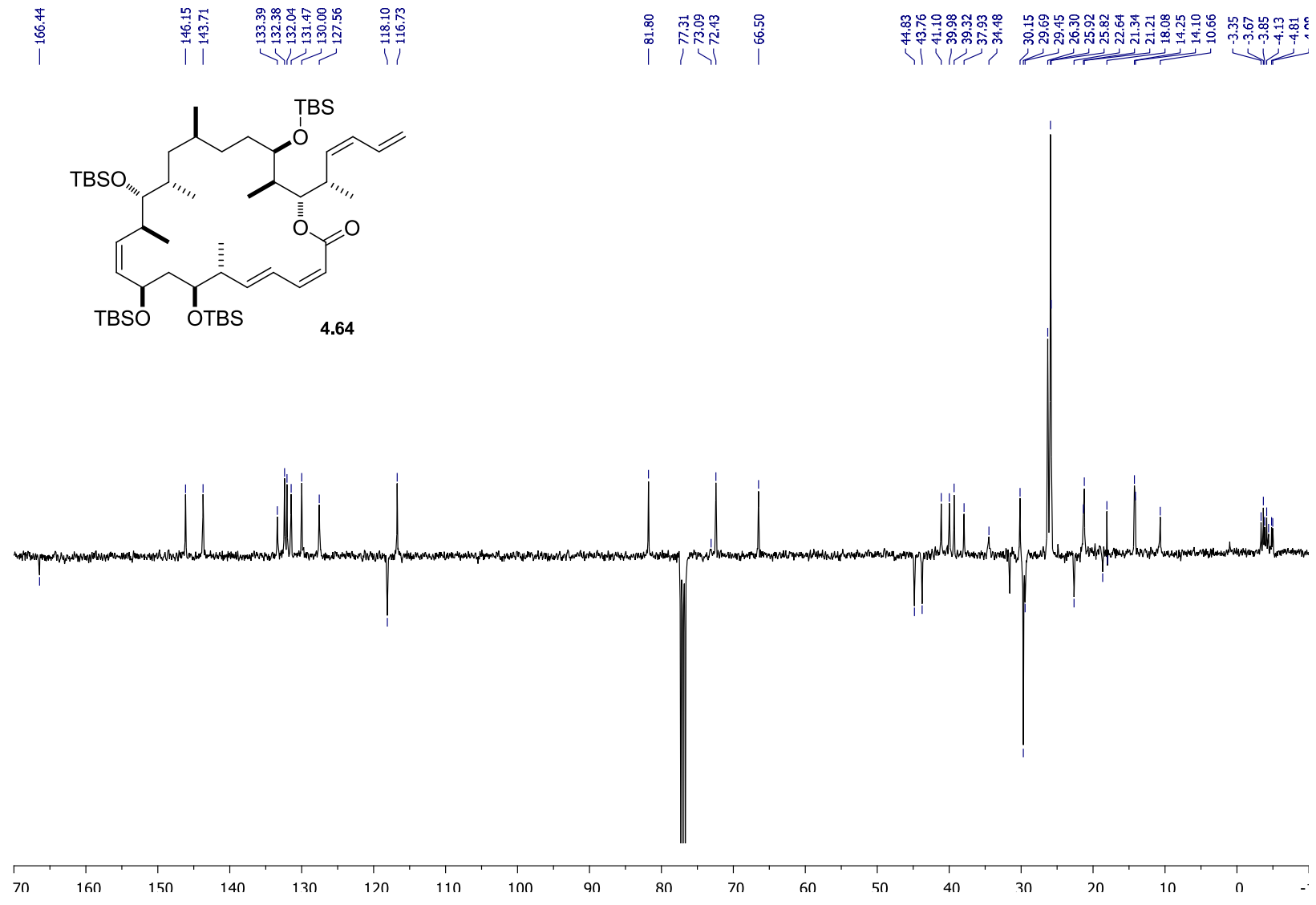


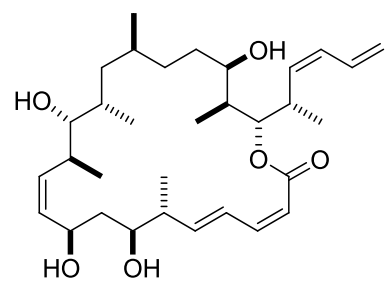






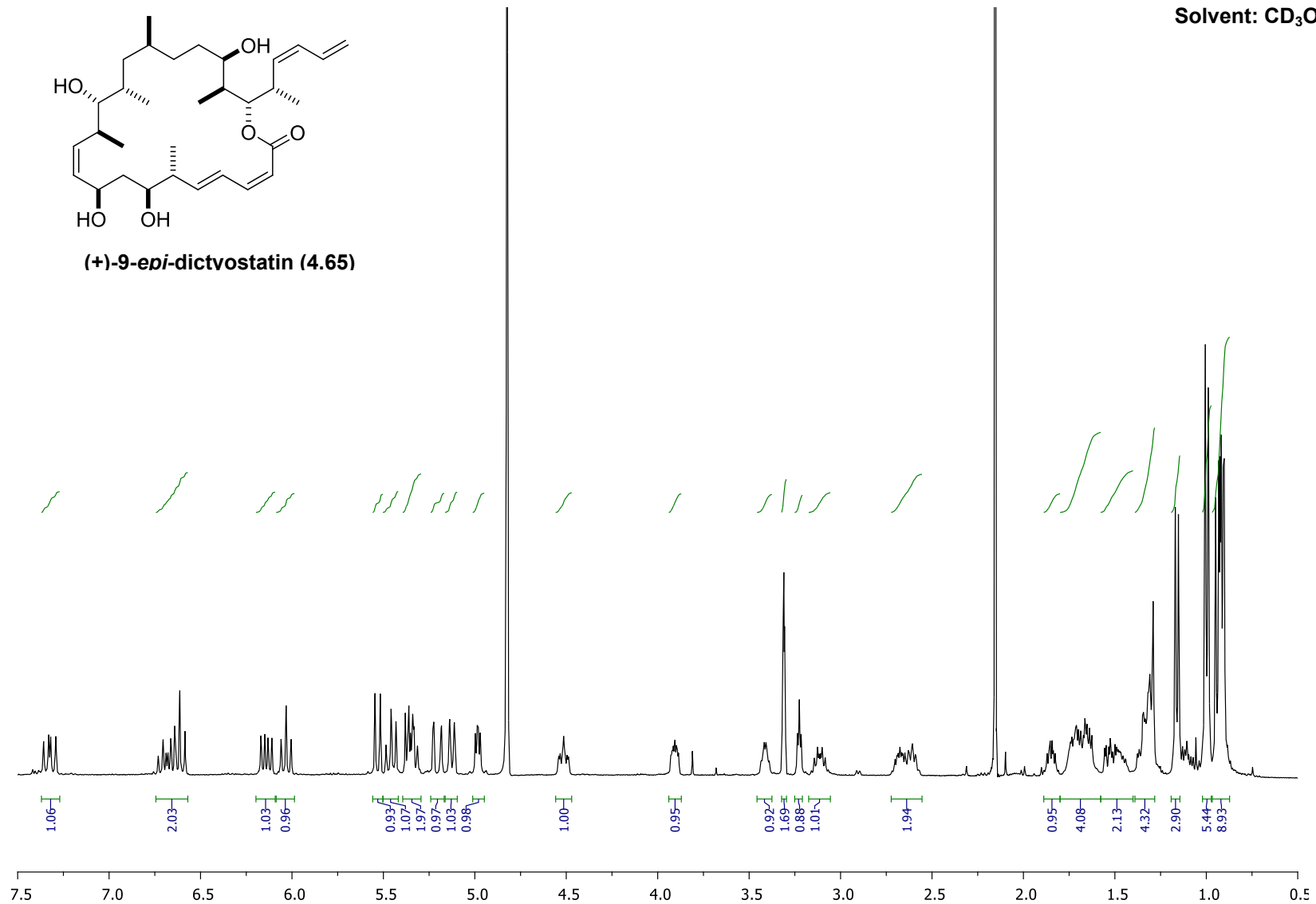


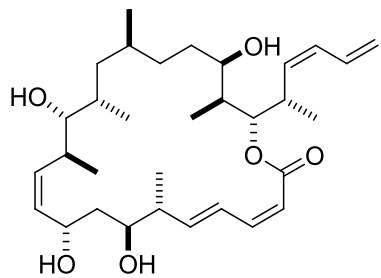




(+)-9-*epi*-dictvostatin (4.65)

Solvent: CD₃OD

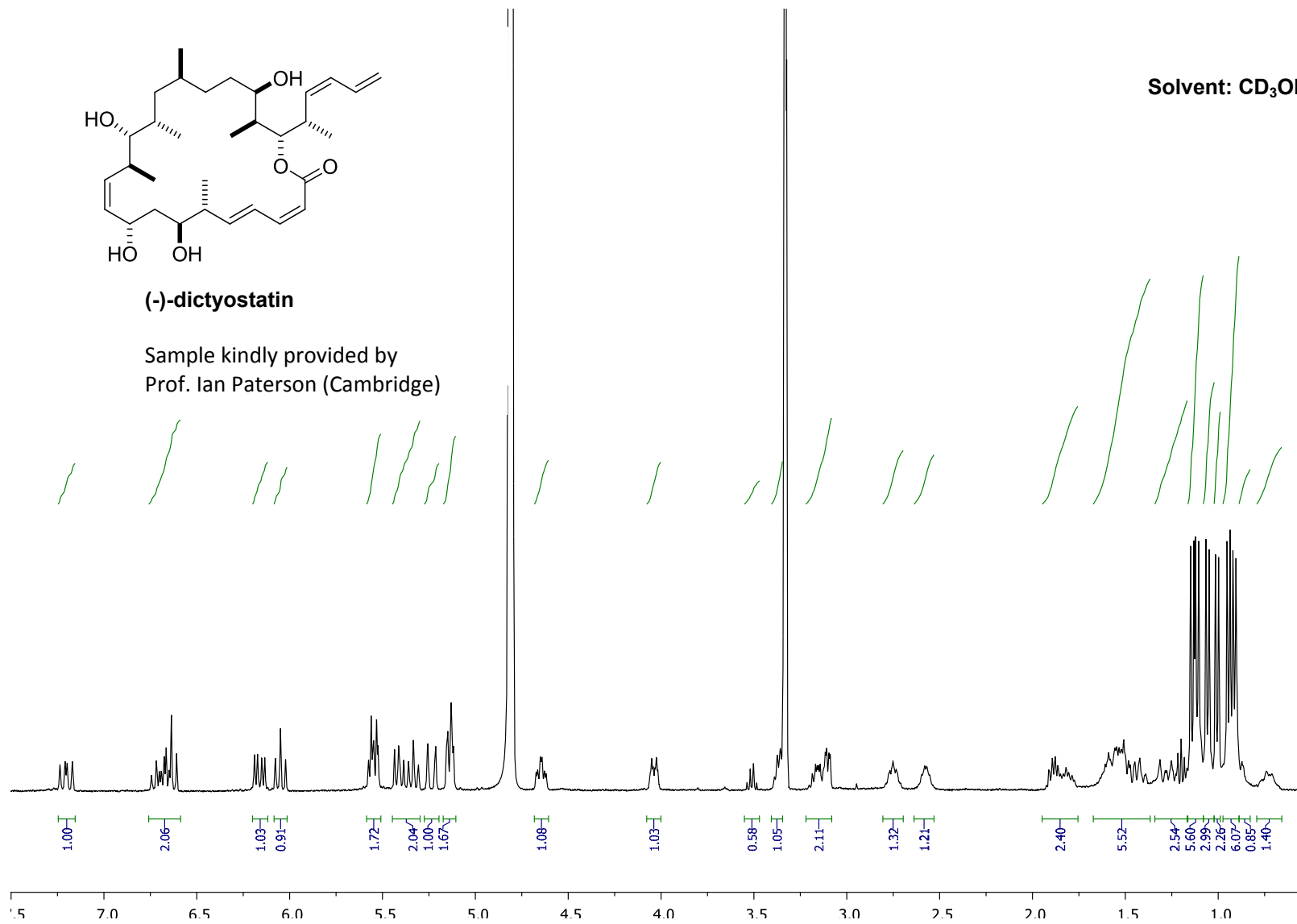


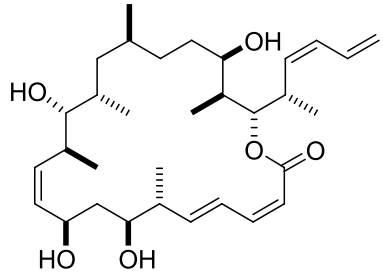


(-)-dictyostatin

Sample kindly provided by
Prof. Ian Paterson (Cambridge)

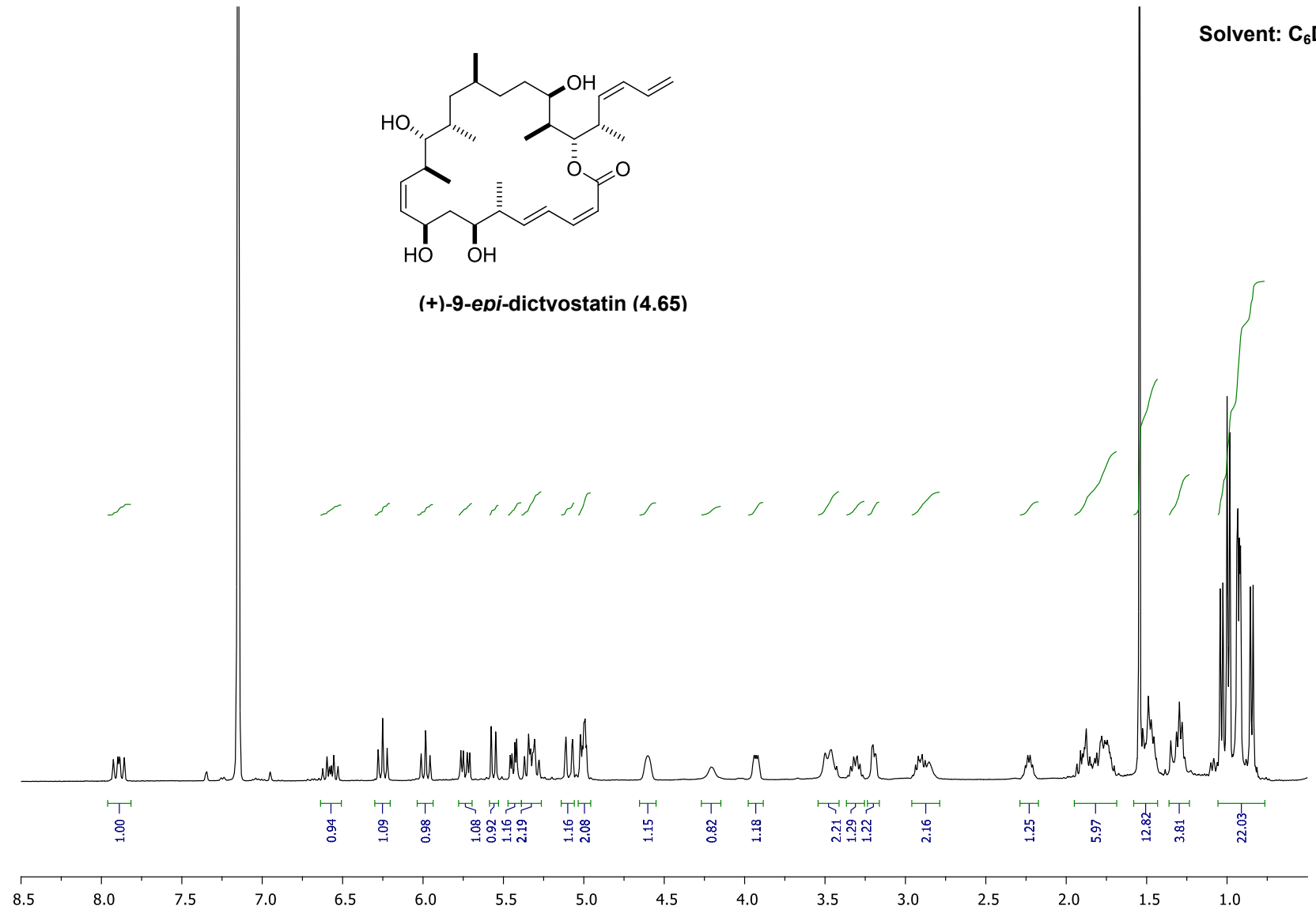
Solvent: CD₃OD

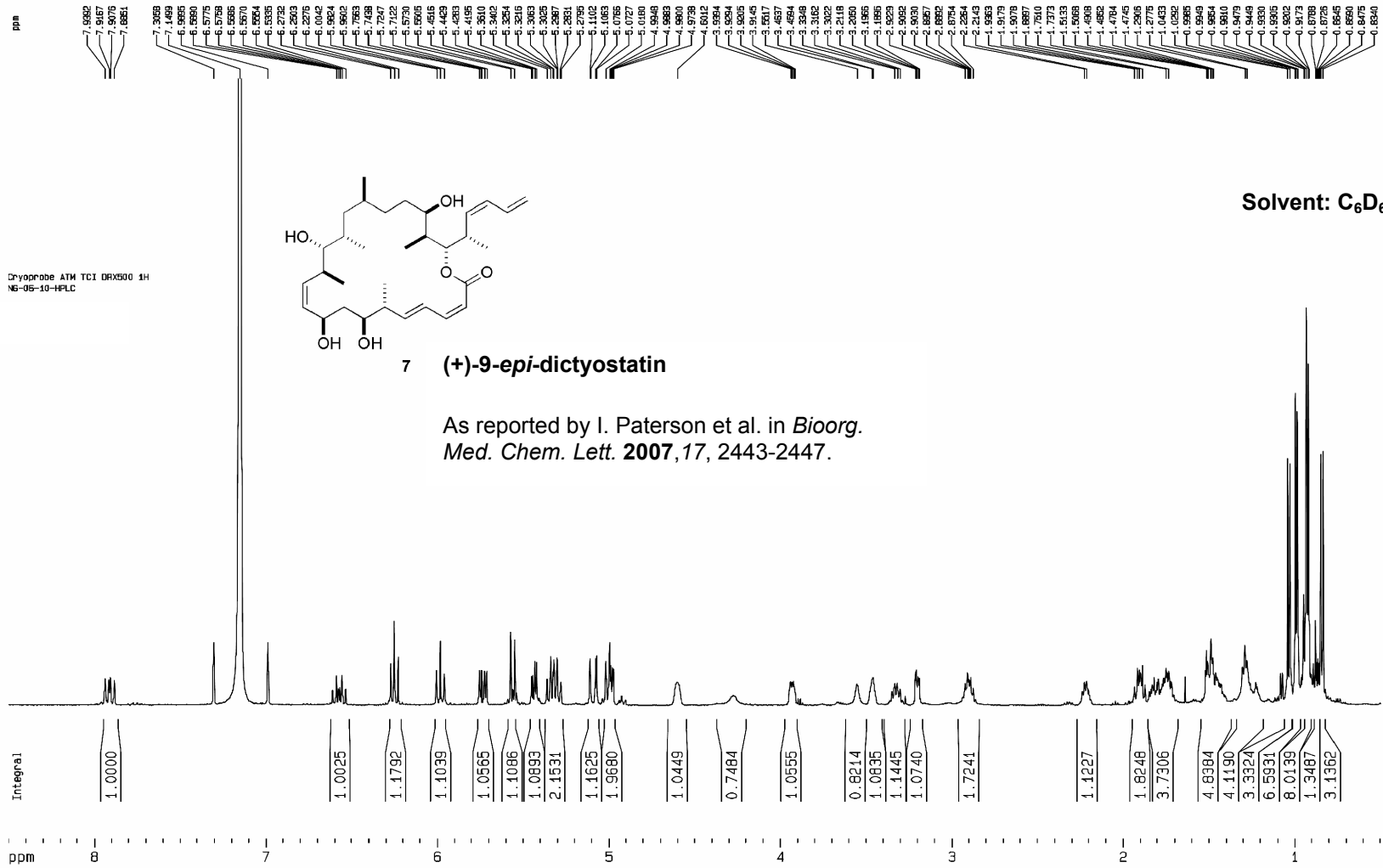


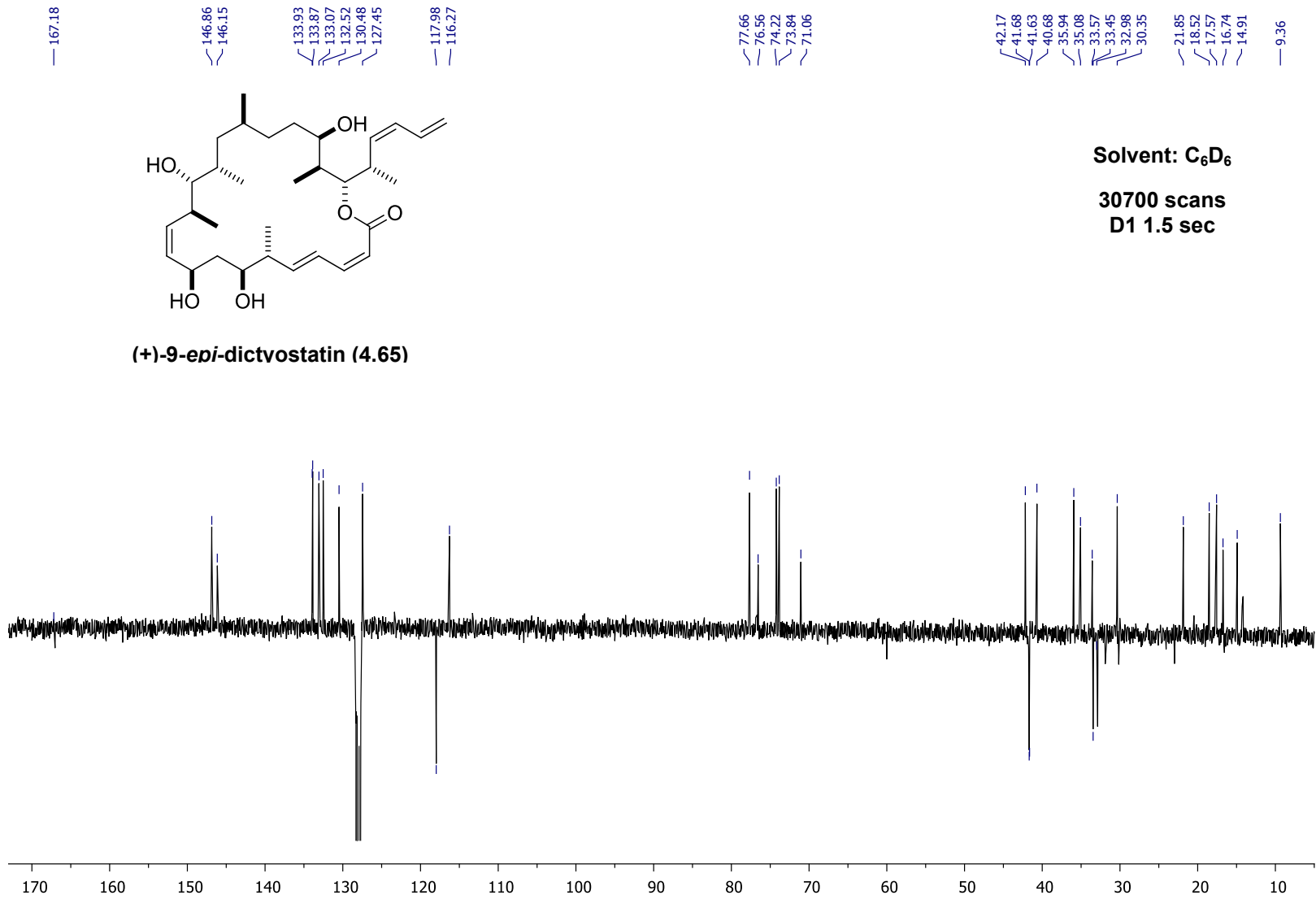


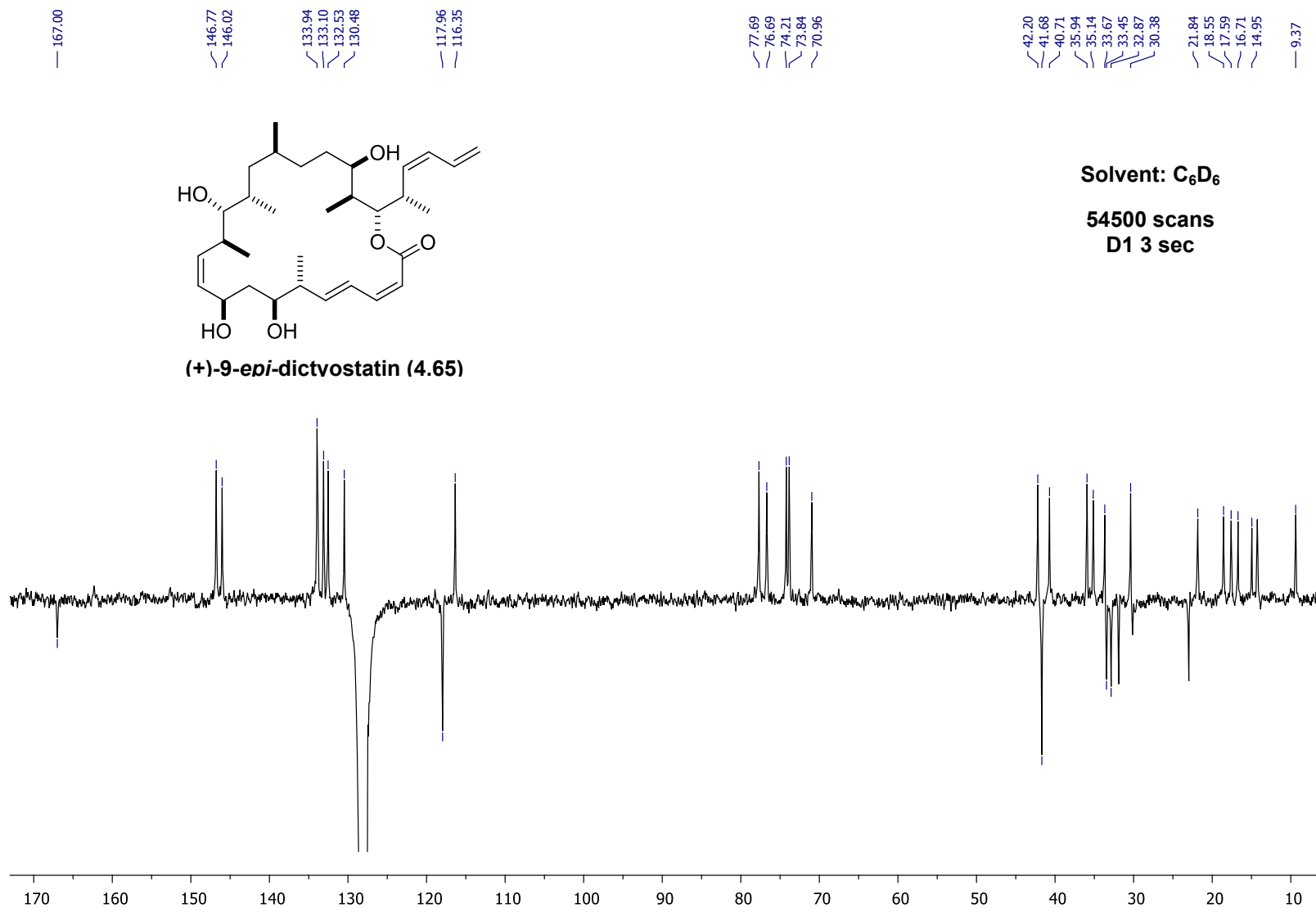
Solvent: C₆D₆

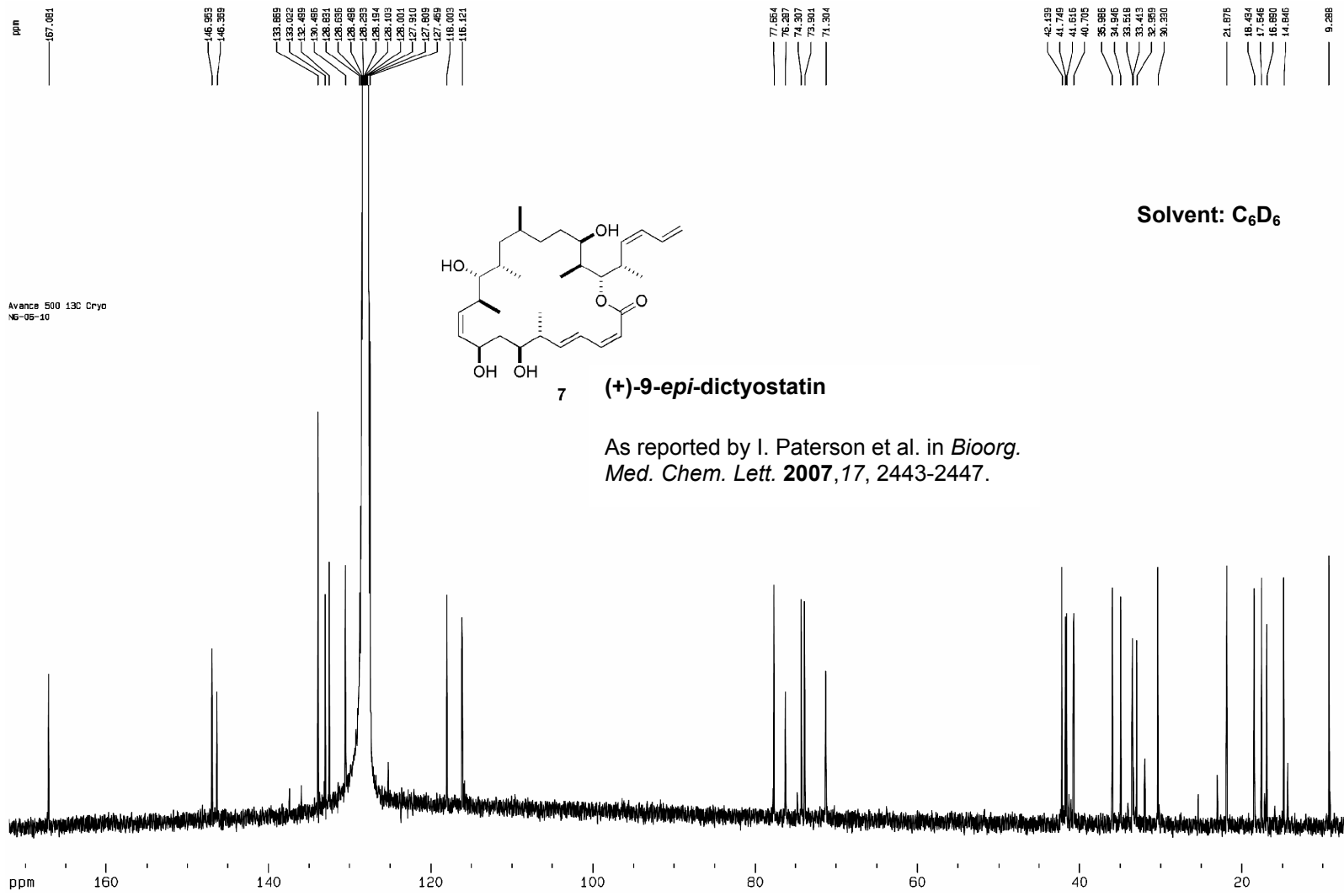
(+)-9-*epi*-dictvostatin (4.65)





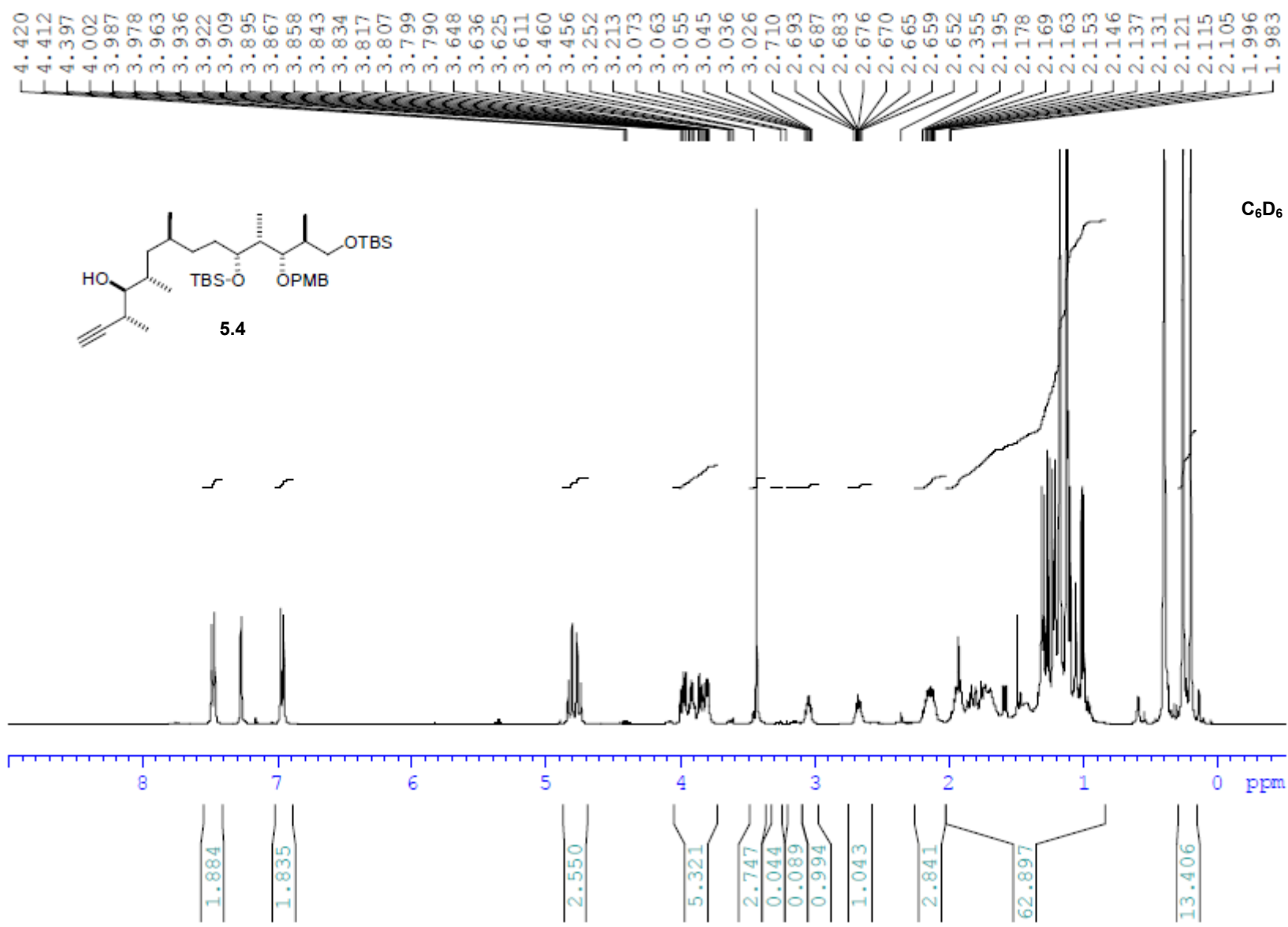


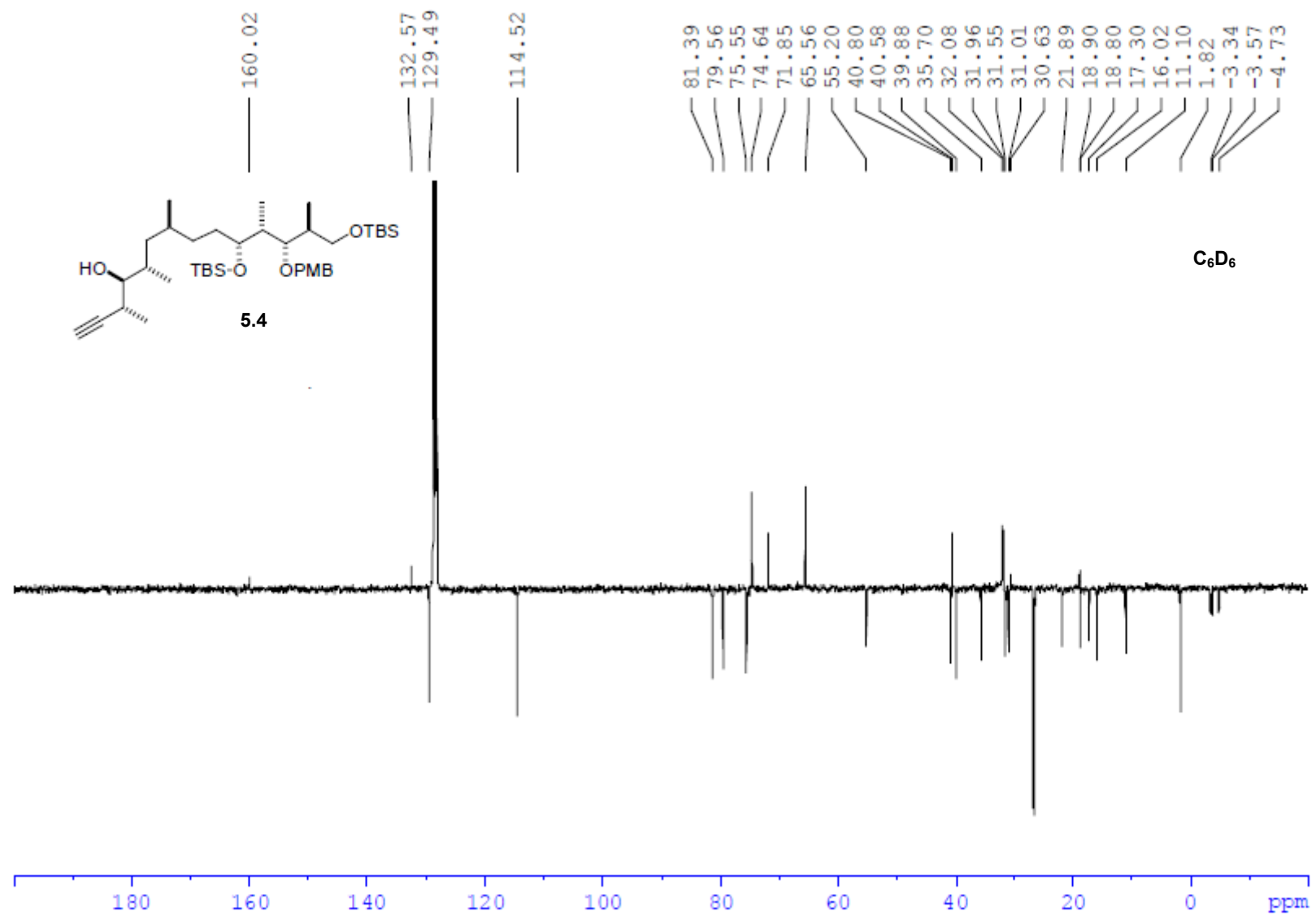


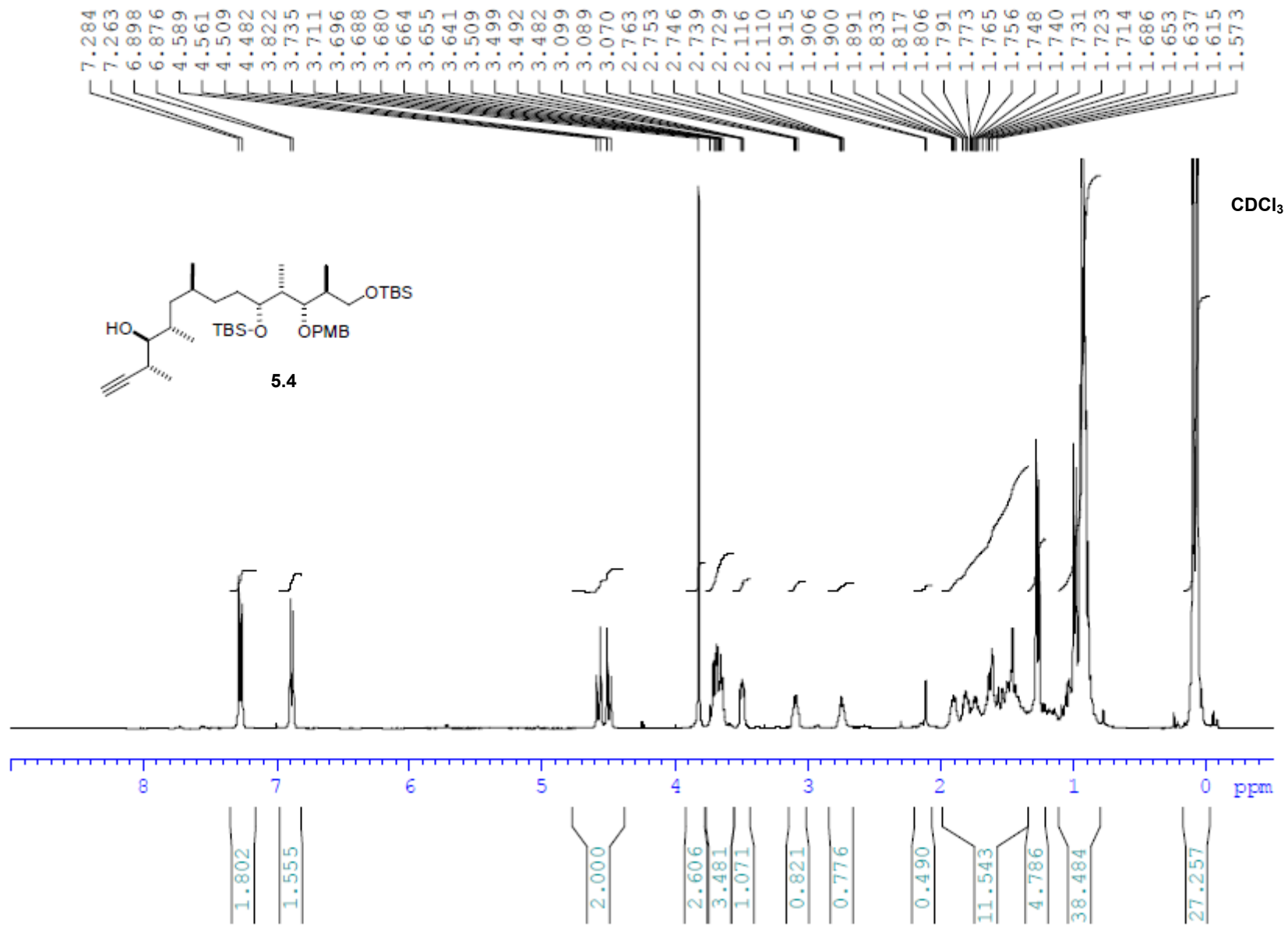


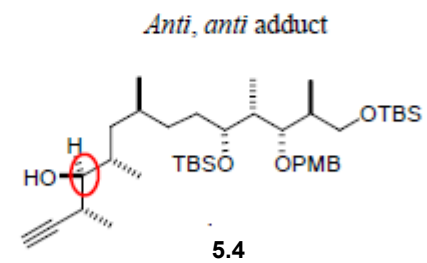
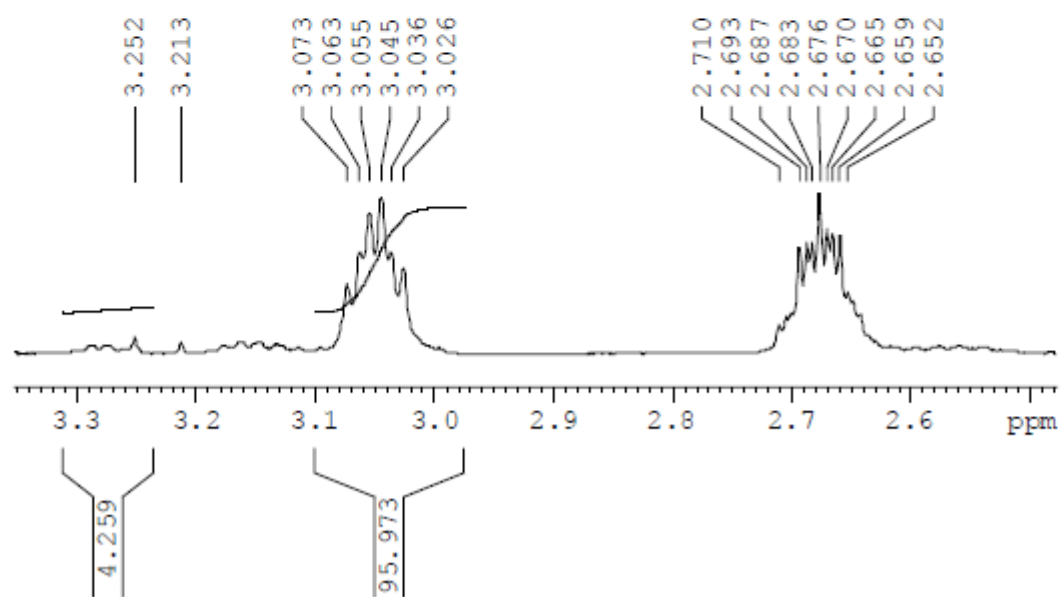
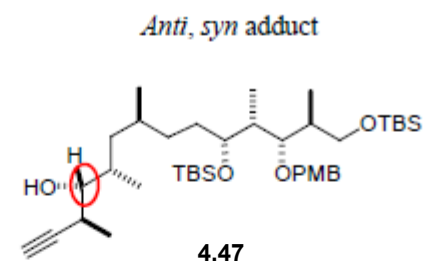
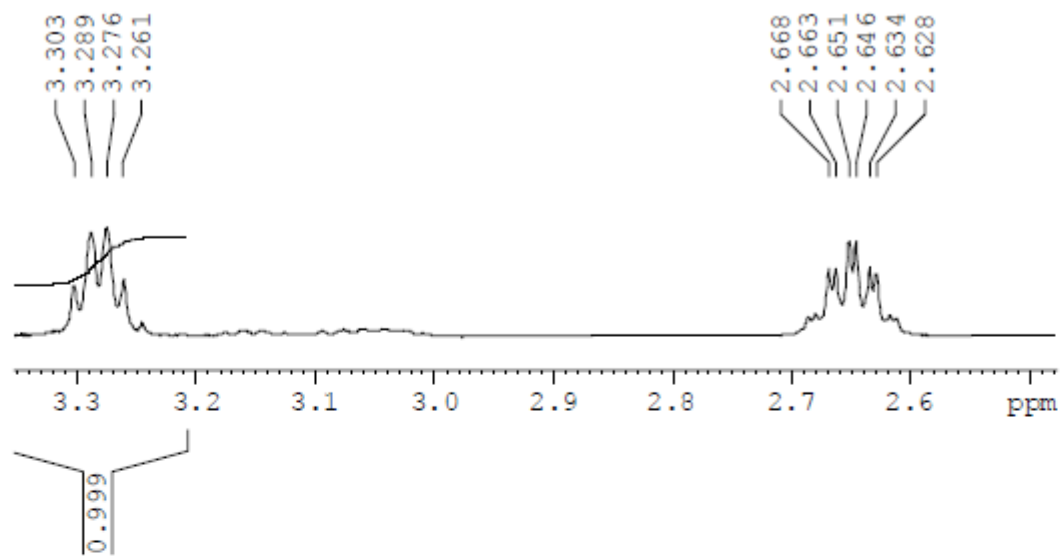
Synthesis of (Z)-Vinyl Iodide 12,13-bis-*epi*-C10-C26

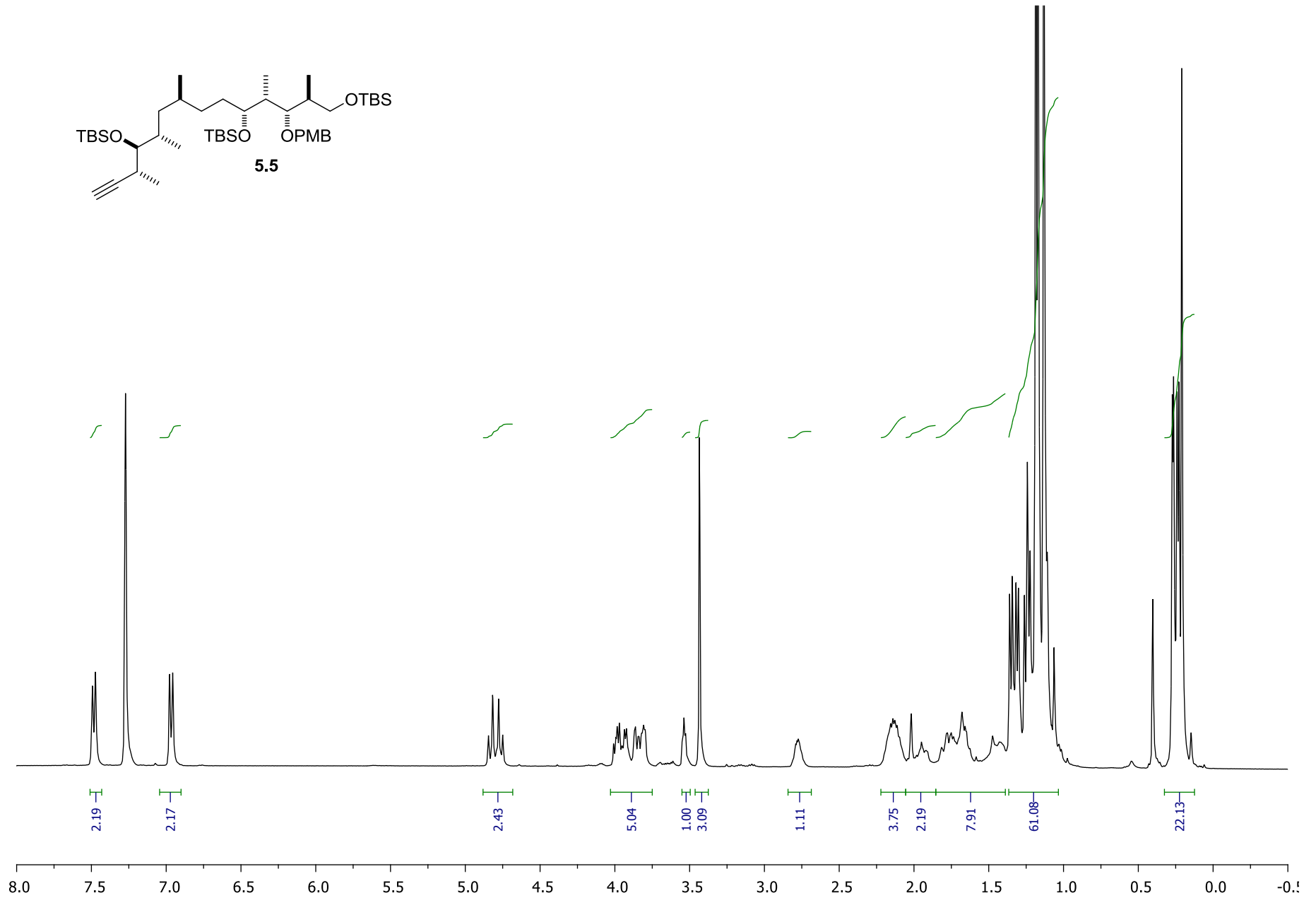
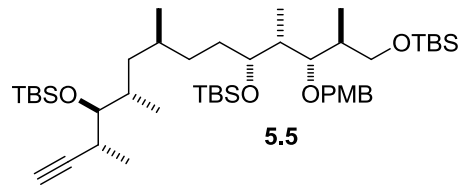
NMR Spectra

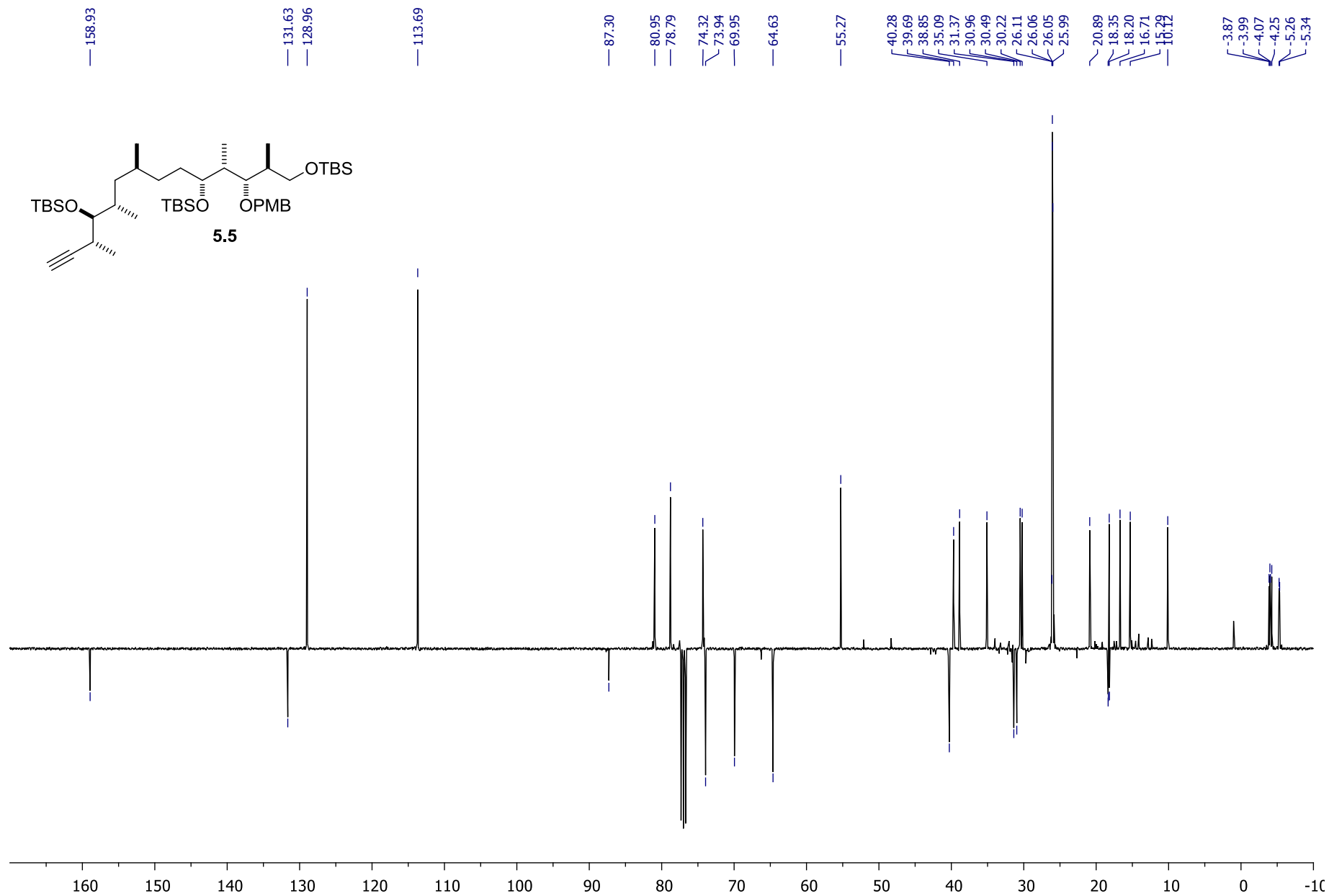
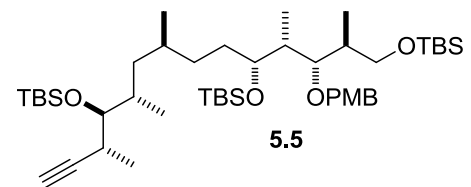


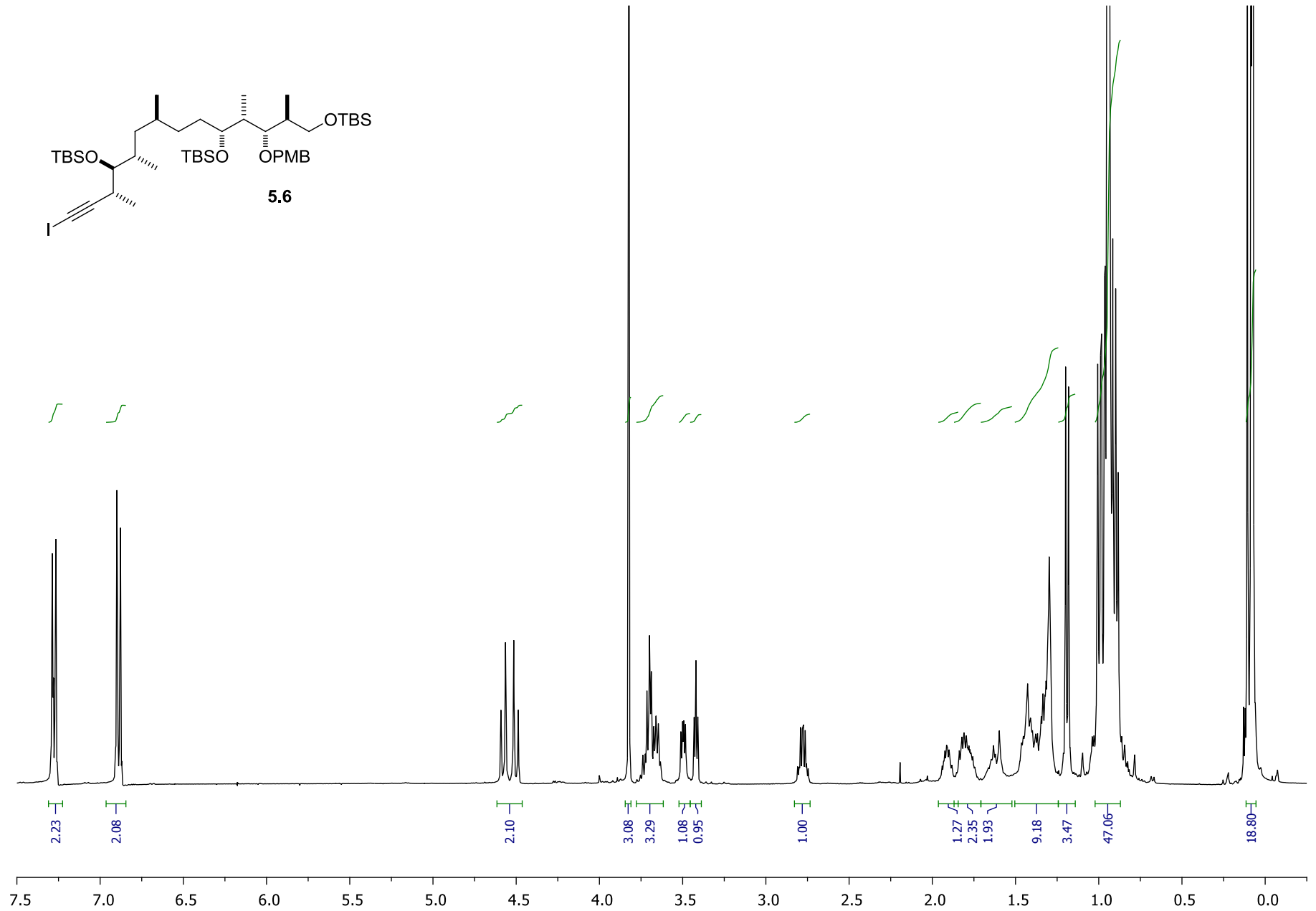
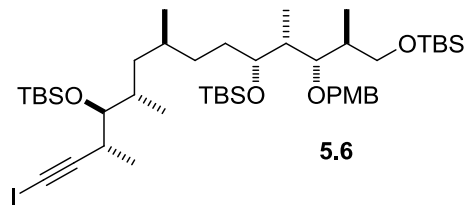


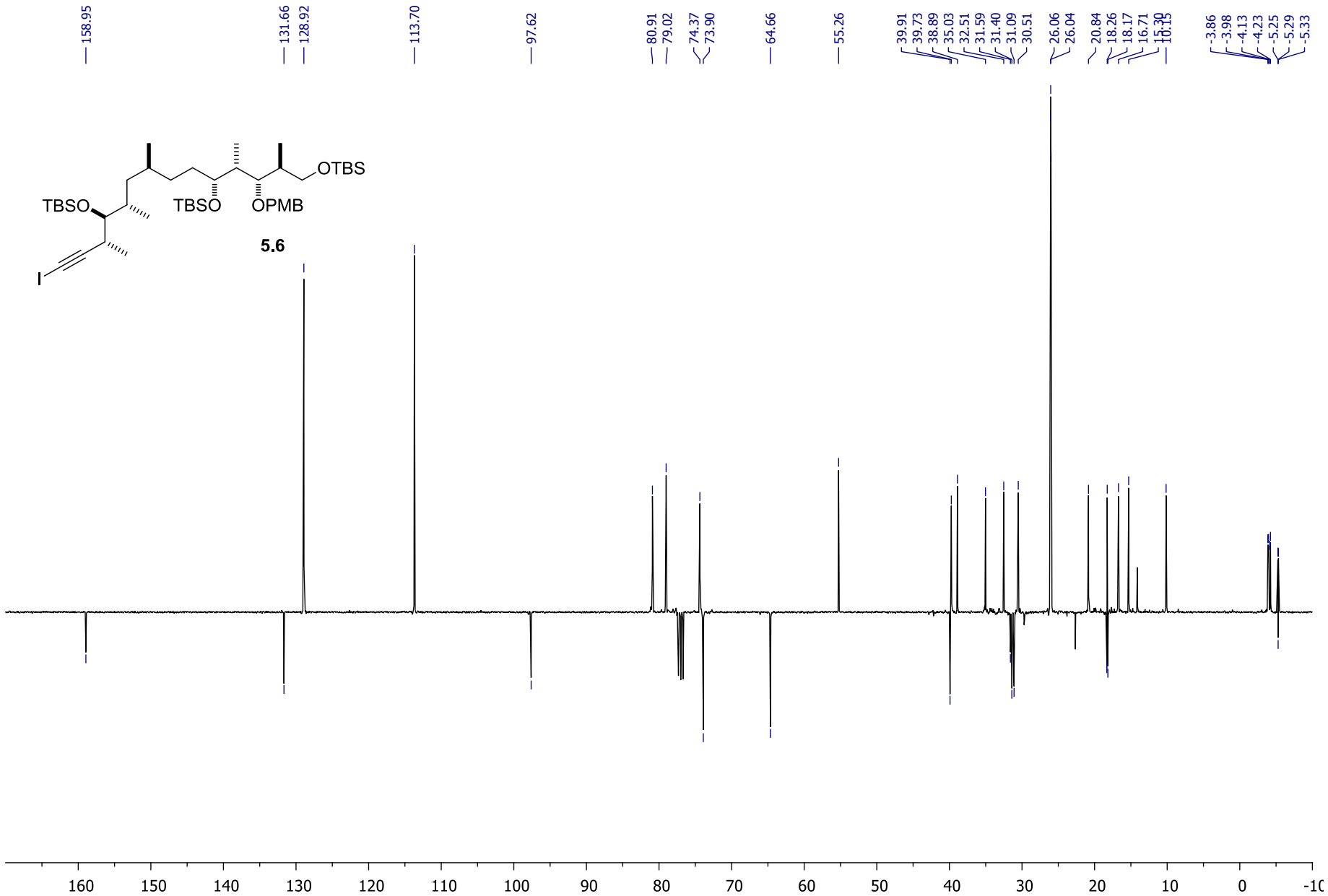


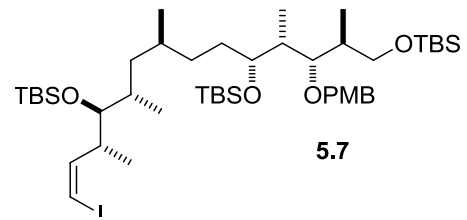




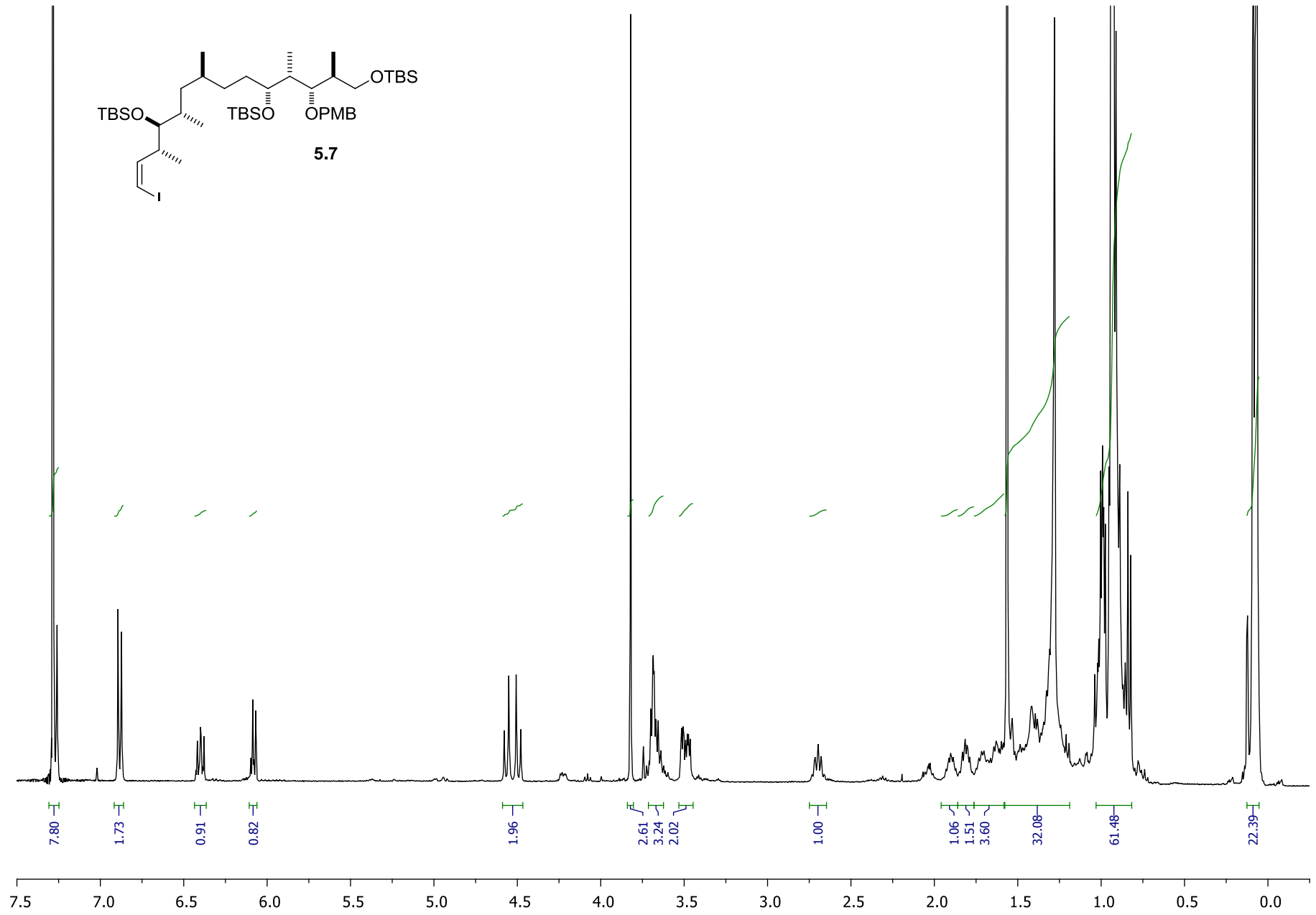


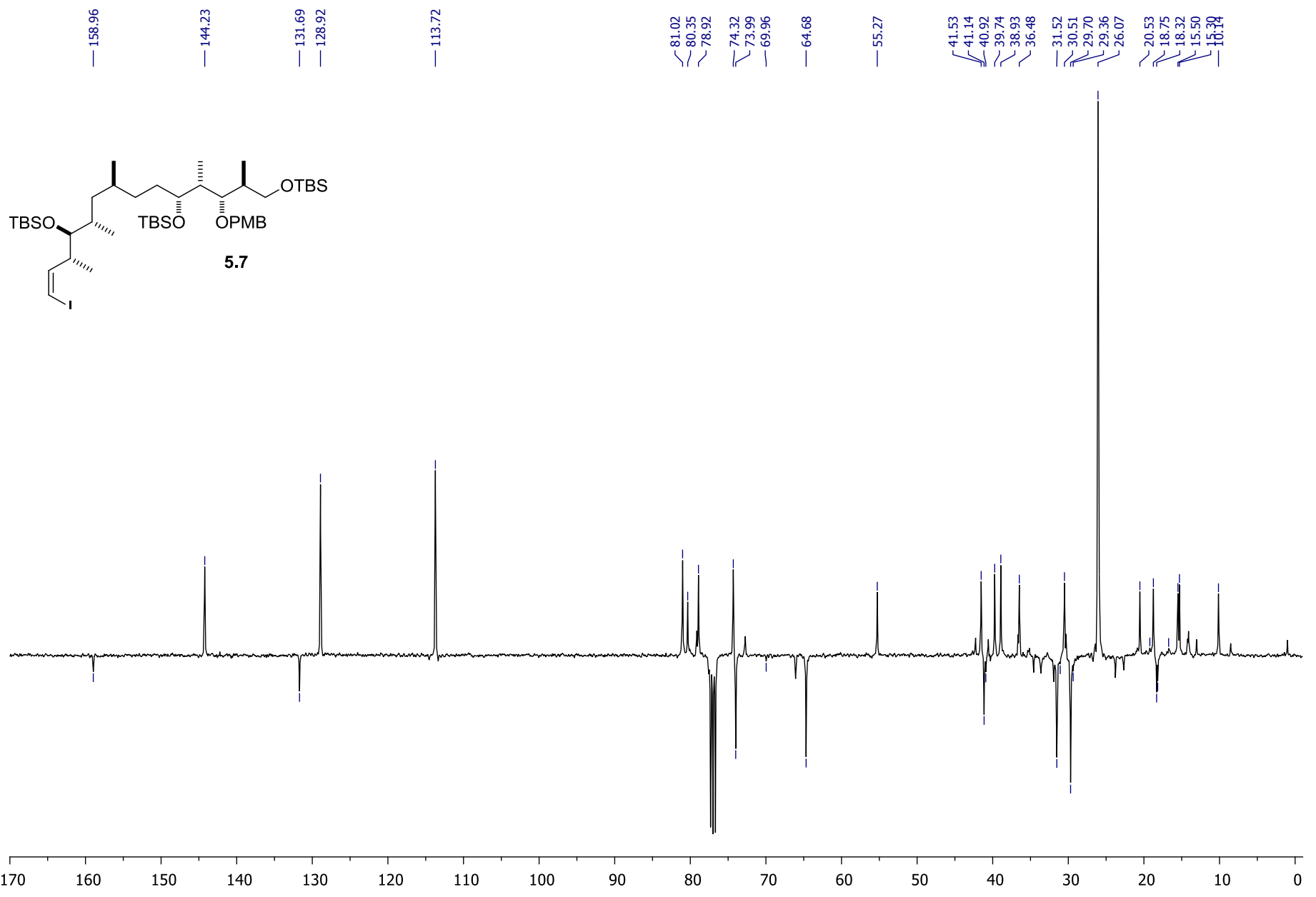


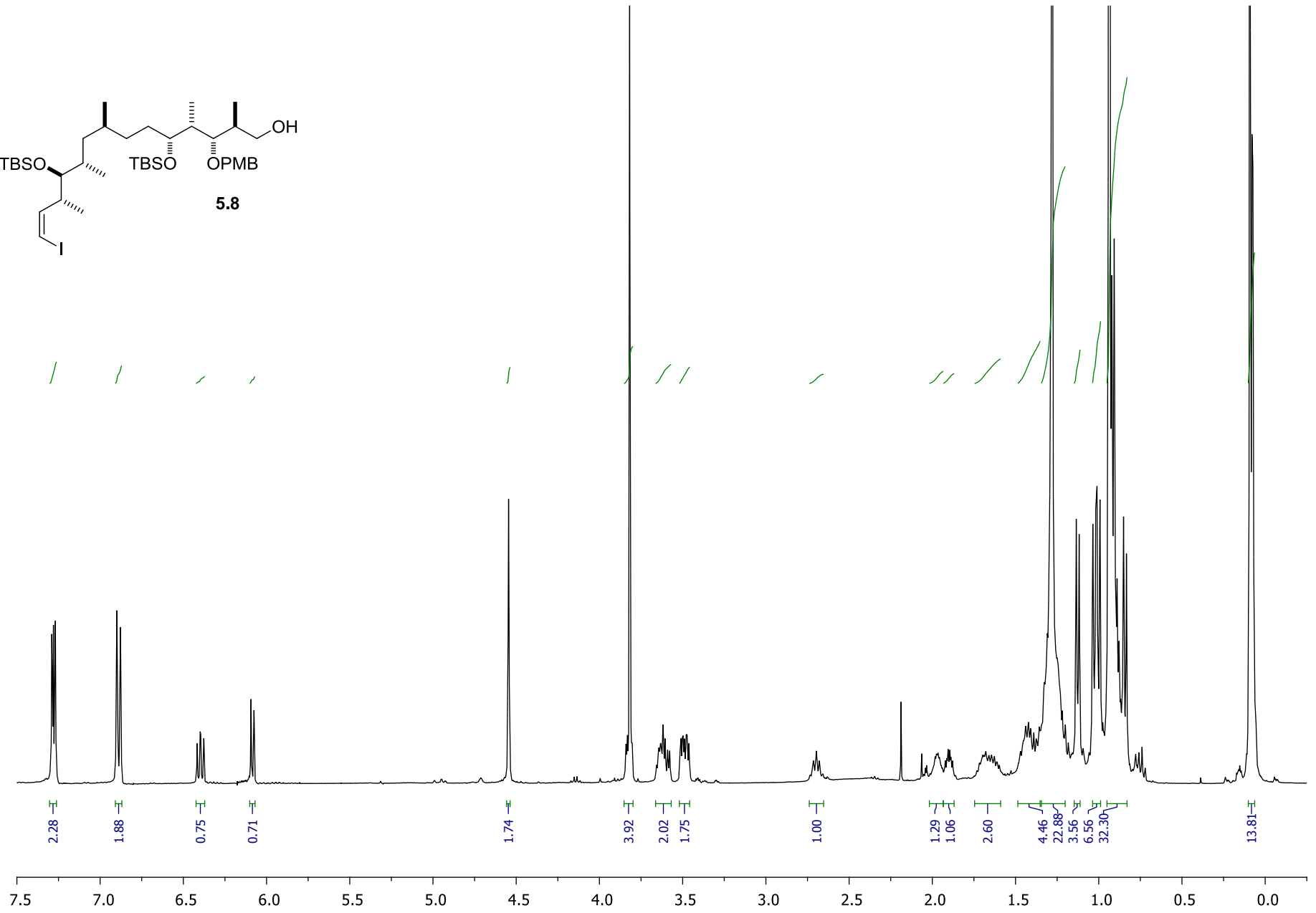
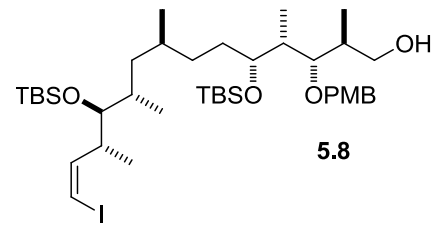


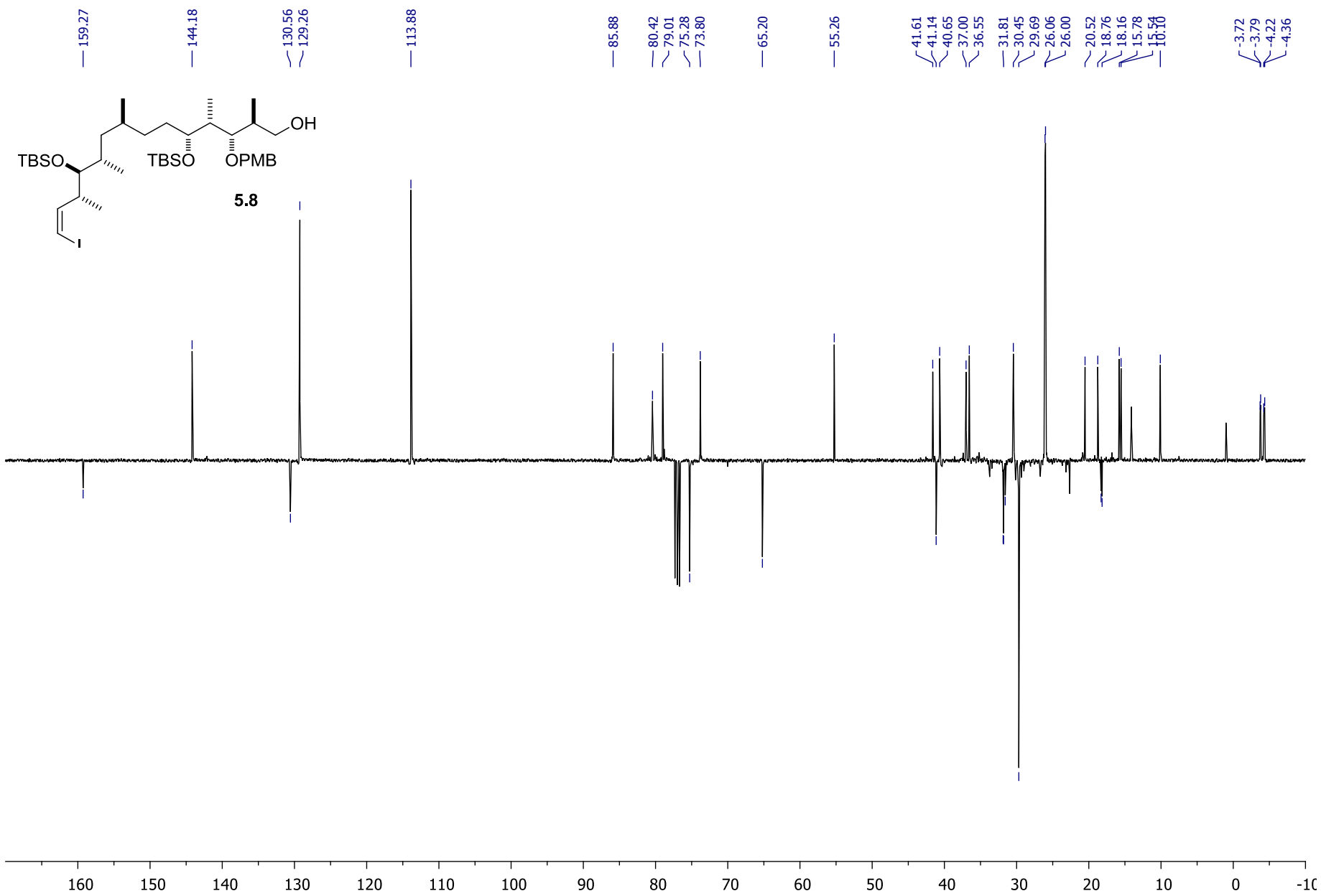


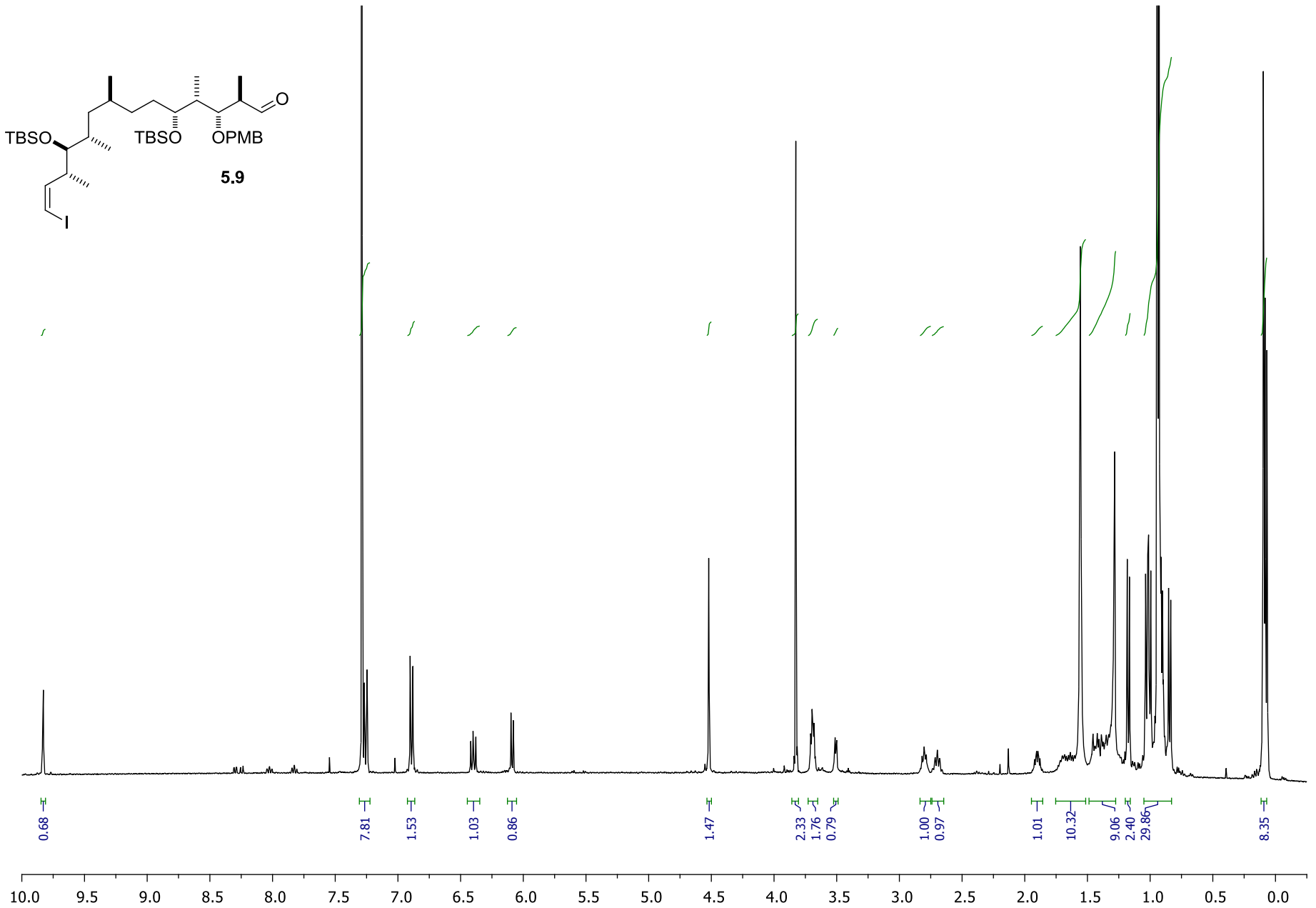
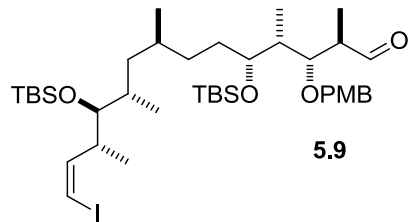
5.7

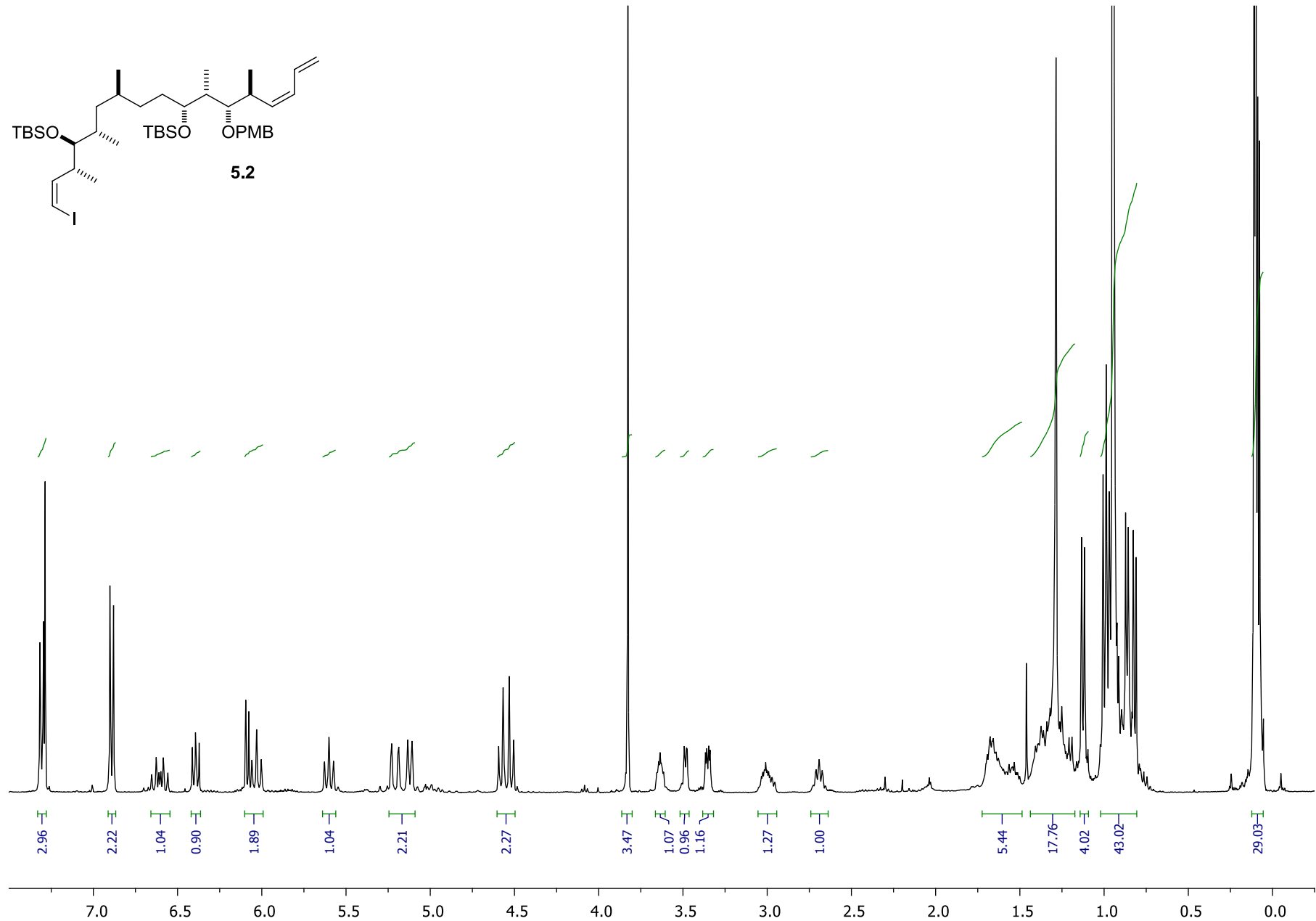
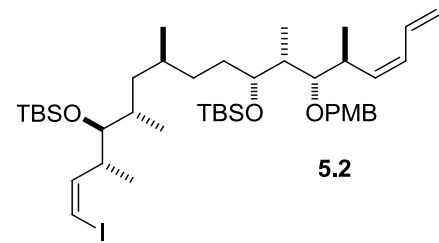


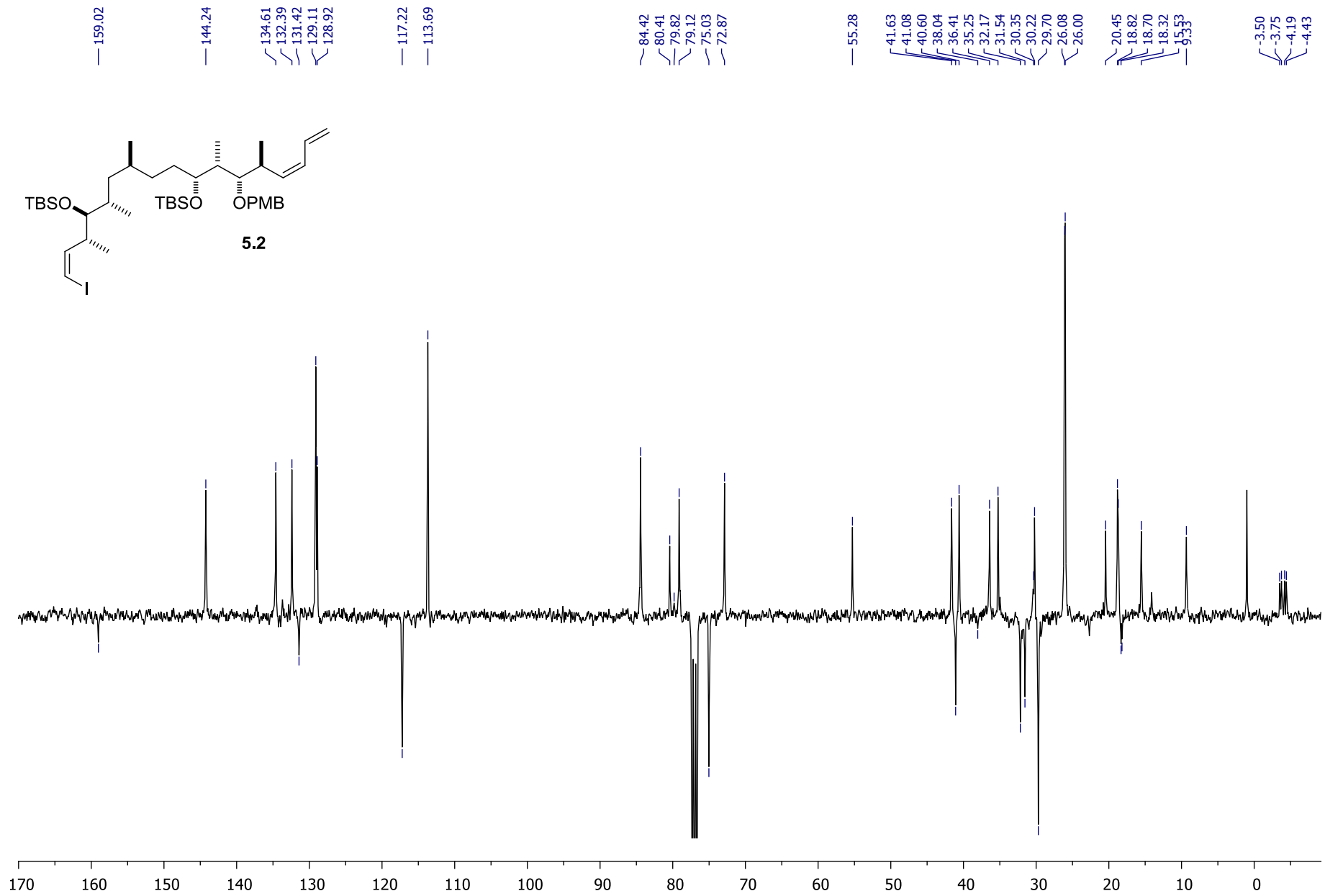
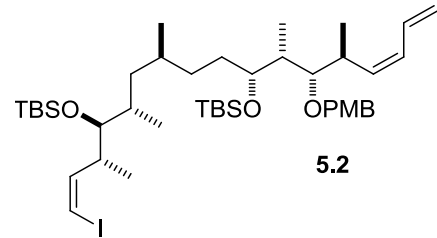






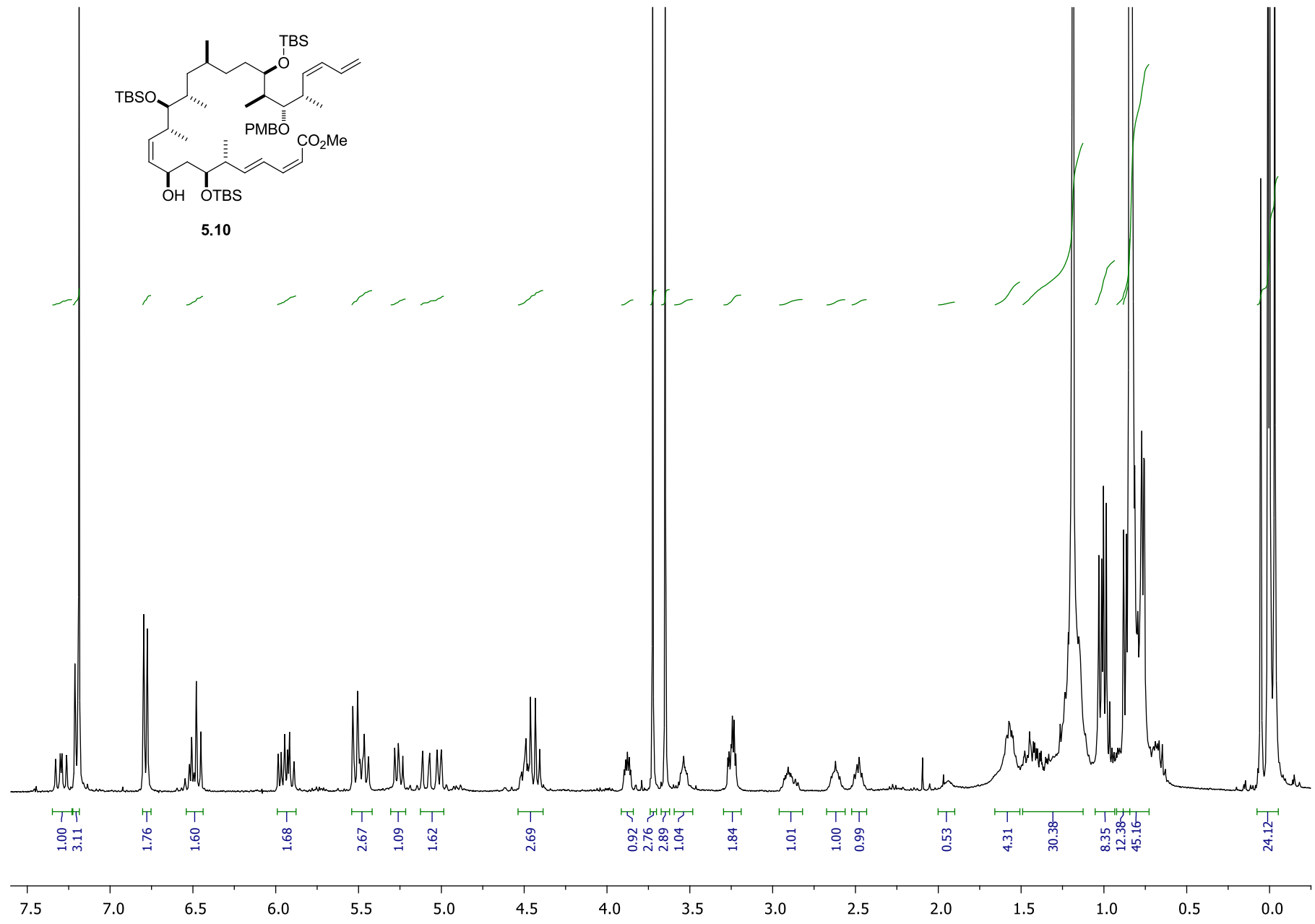
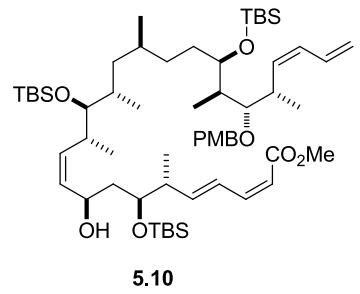


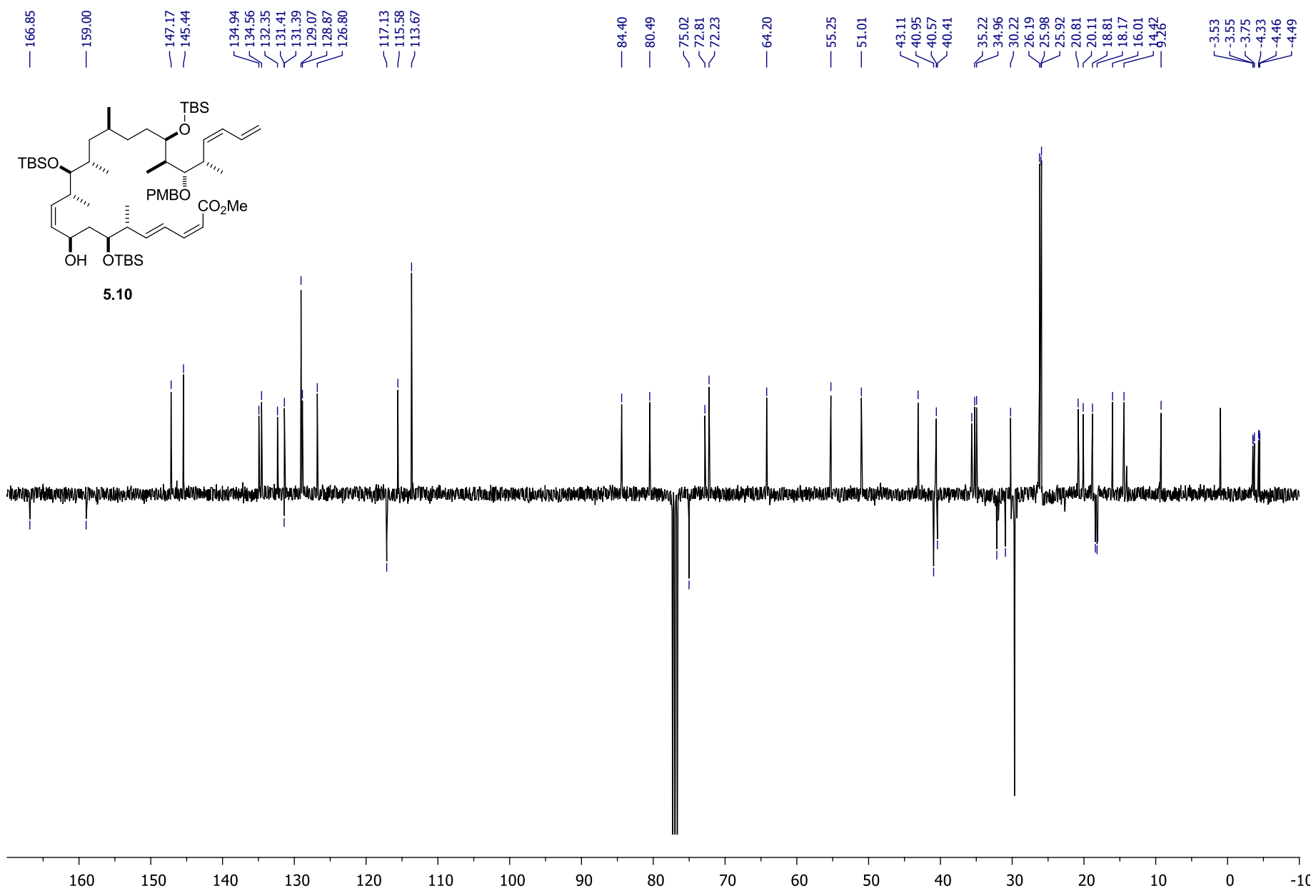


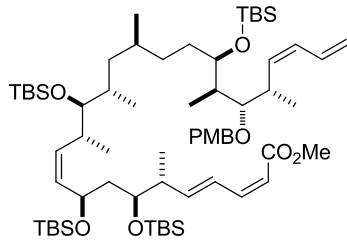


Synthesis of 12,13-bis-*epi*-Dictyostatin Precursors

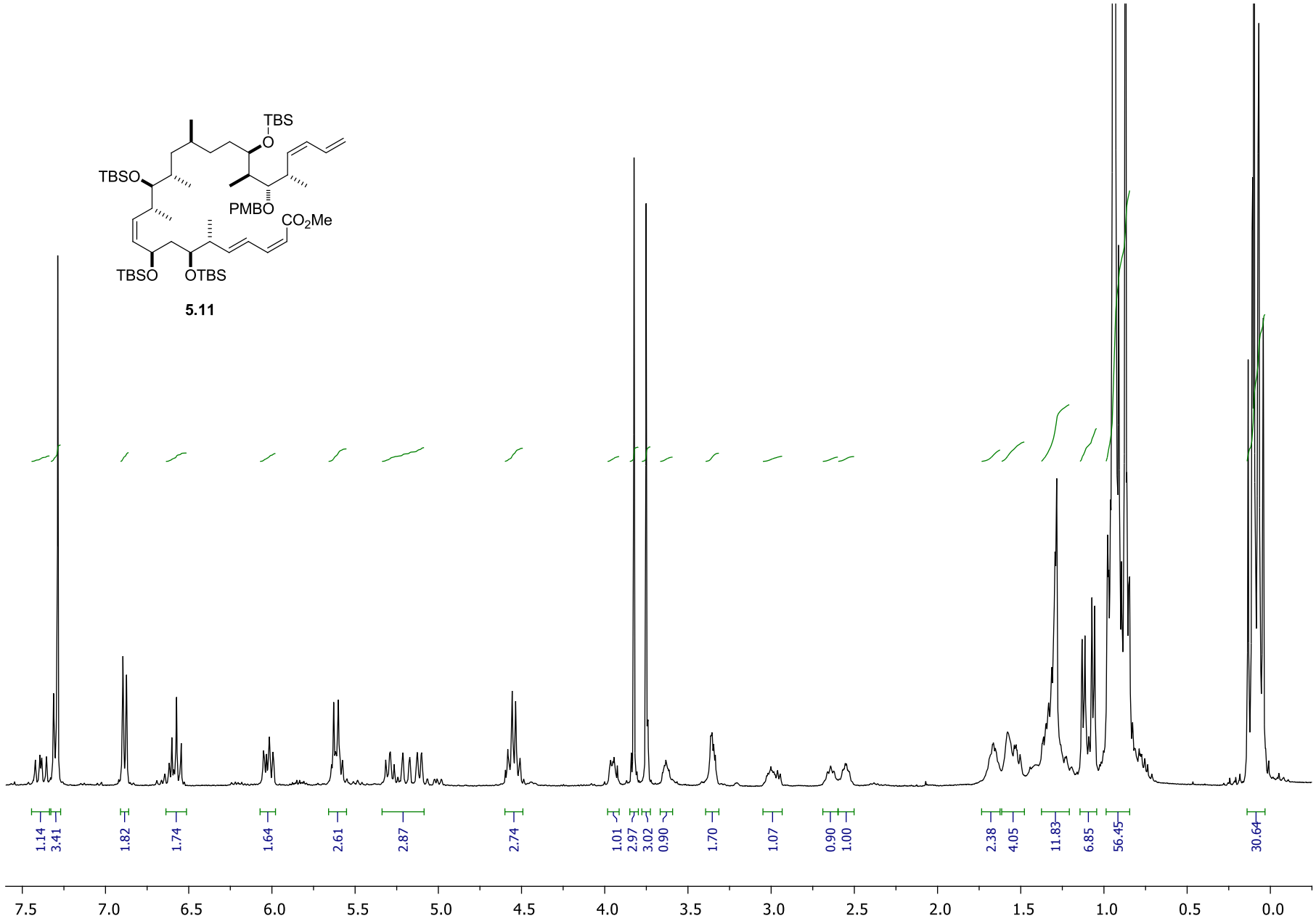
NMR Spectra

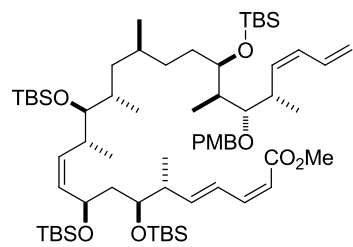




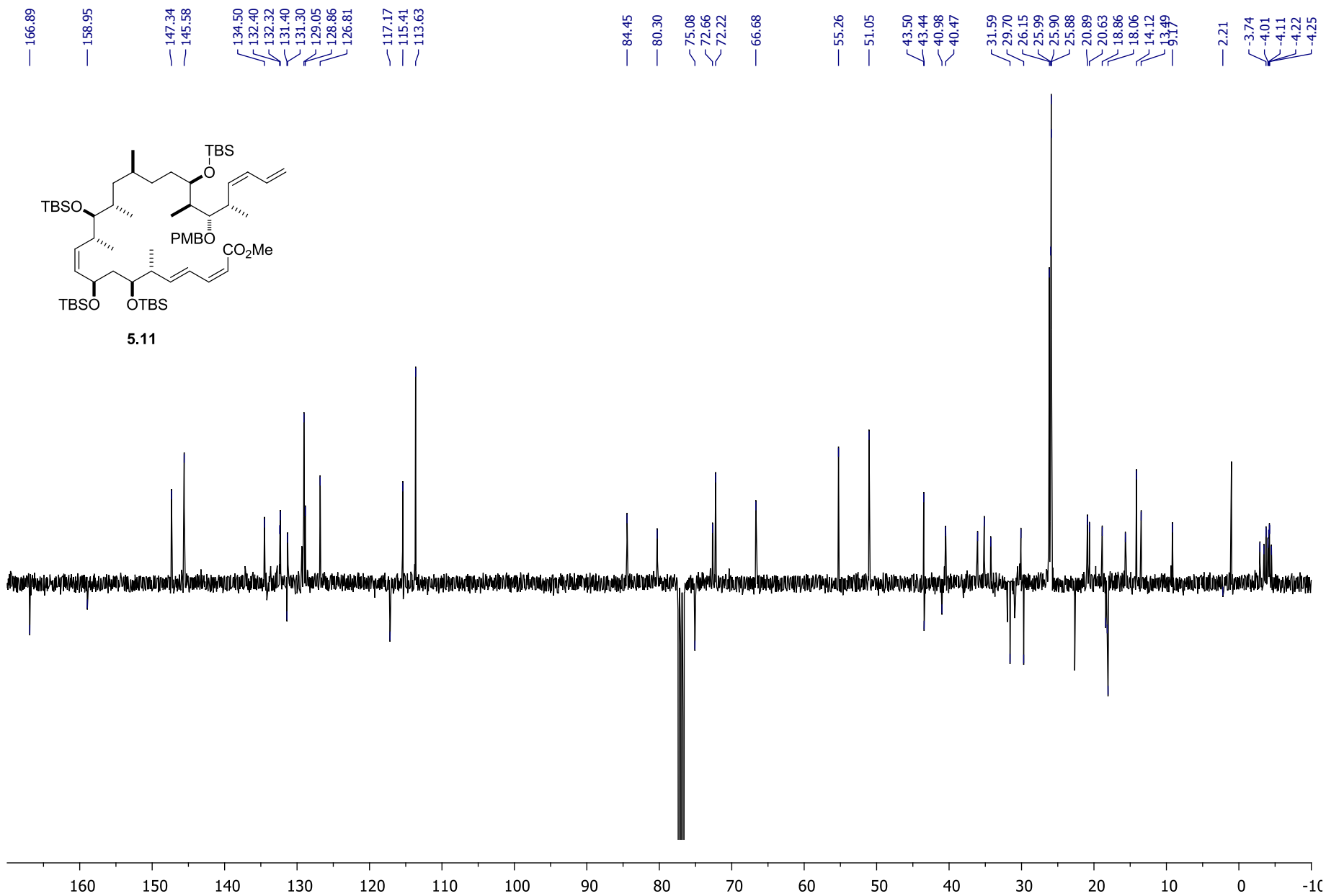


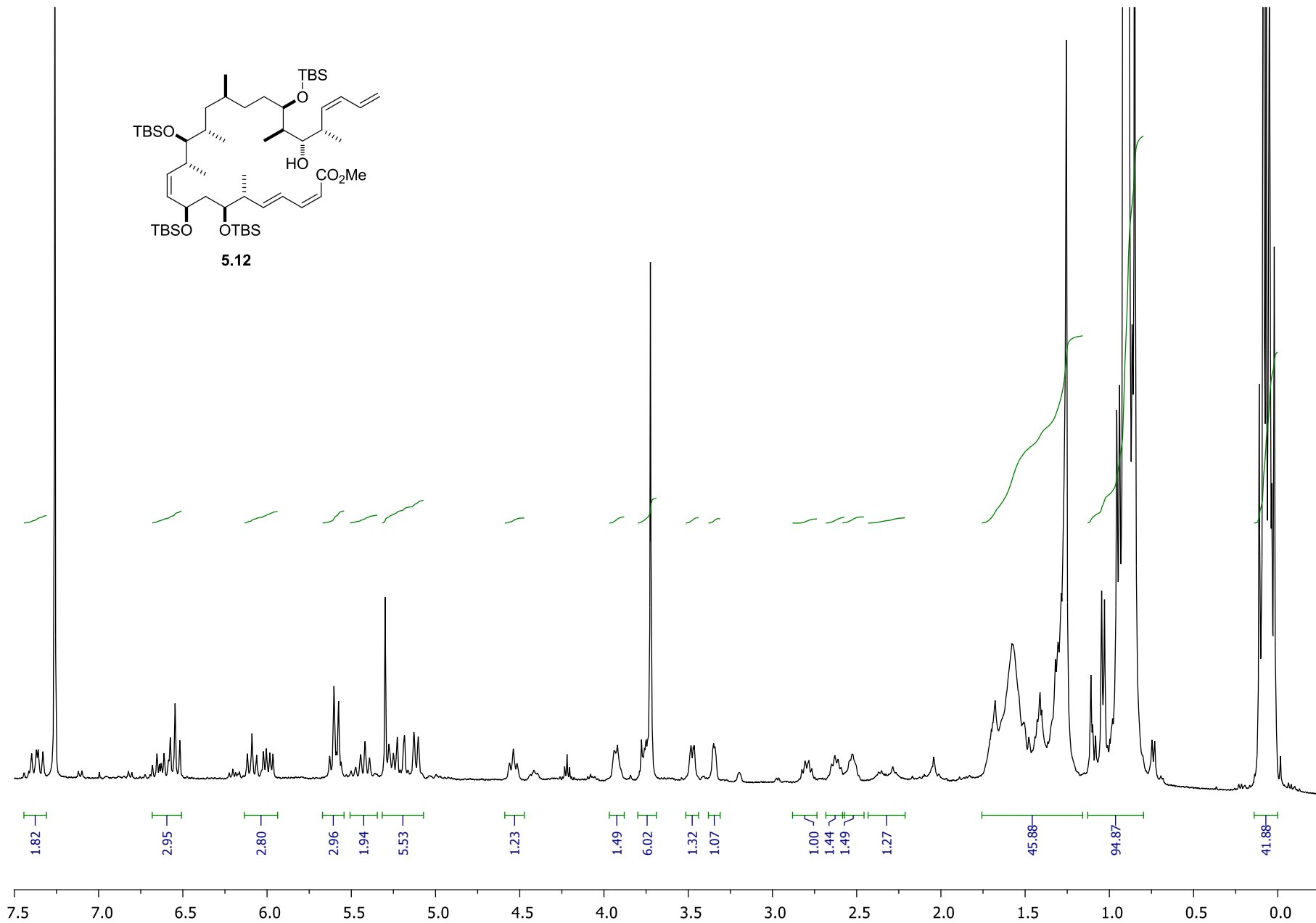
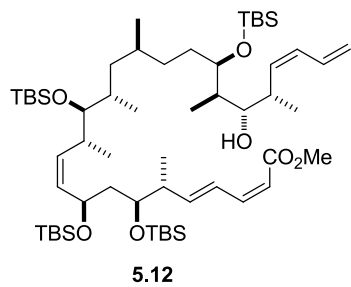
5.11





5.11





166.89

147.29
145.56

135.44
132.46
132.29
131.16
129.84
126.82

117.70
115.44

86.89

80.21
77.90

72.21

66.69

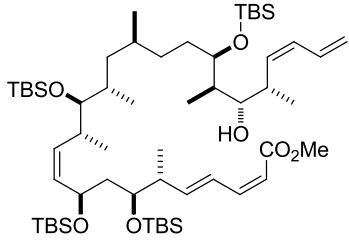
60.06

51.05

43.49
37.48
36.23
36.05
34.19
31.59
30.24
29.70
26.14
25.95
25.91
25.87

20.98
20.66
18.06
17.75
15.63
14.12
13.46
6.86

-2.89
-3.64
-3.75
-4.02
-4.06
-4.23
-4.39



5.12

