A New Synthesis of Taxol® from Baccatin III

by

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Abstract

Taxol®, an important anticancer drug, was first isolated in extremely low yield from the bark of the western yew, *Taxus brevifolia*. The clinical utility of Taxol has prompted a tremendous effort to obtain this complex molecule synthetically. Due to the chemical complexity of Taxol, its commercial production by total synthesis is not likely to be economical.

Another natural product, 10-deacetyl baccatin III, is readily available in higher yield. Several methods have been reported for the synthesis of Taxol by coupling baccatin III and the *N*-benzoyl-β-phenylisoserine side chain. A new method for the synthesis of Taxol from baccatin III is reported, and this method is compared with other methods.

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To Simge

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1. Introduction

1.1 What is cancer?

Clinically, cancer is the name given to a large family of diseases, maybe a hundred or more, that vary in age of onset, rate of growth, state of cellular differentiation, diagnostic detectability, invasiveness, metastatic potential, and response to treatment and prognosis.[1] Cancer occurs when cells become abnormal and keep dividing and forming new cells without any control or order. All organs of the body are made up of cells. Normally, cells divide to form new cells only when the body needs them. If cells divide when new ones are not needed, they form a mass of excess tissue, called a tumor. Tumors can be benign (not cancer) or malignant (cancer). The cells in the malignant tumors can damage and invade nearby tissues and organs. Cancer cells can also break away from the malignant tumor and travel through the bloodstream to form new tumors in other parts of the body. The spread of cancer is called metastasis.

Over 1 million cases of cancer occur in the United States every year, not including basal cell and squamous cell skin cancers, which add another 700,000 cases annually. Although it is considered as a disease of aging, cancer can occur at any time. On average, the diagnosis of the most common types of cancer comes at about age 67. Although cancer is relatively rare in children, it is still a leading cause of death between ages 1 and 14.

Millions of people alive today have had some type of cancer. Of these, about half are considered cured. The good news is that more and more people are now being cured of their cancers. This progress is due to better techniques of diagnosis and treatment.

[1]Ruddon, R. W. *Cancer Biology 3rd Edition*, Oxford University Press: New York, **1995**

1.2 Causes of cancer

In many cases, the causes of cancer are not clear, but both external and internal factors play a role. Cigarette smoking is a major causal factor. Other than that, diet, genetic mutation, exposure to ultraviolet (UV) light and carcinogenic chemicals may also cause cancer.

1.3 Cancer Prevention

The best way to reduce deaths from cancer is to prevent it. Medical doctors generally agree that about one-third of all human cancers are directly related to cigarette smoking.[1] For smokers, the risk of cancer is much higher than that of the nonsmokers. Excluding the UV rays of sunlight which cause skin cancer, the next most common cited cancer-causing factor is diet. The National Cancer Institute and the American Cancer Society recommend a diet low in fat, high in natural fiber, and rich in fruits and vegetables. Chemoprevention on the other hand is simply prevention with drugs. The word "drugs" is used to include dietary supplements, hormones, and vitamins etc., as well as real drugs such as aspirin and other synthetic agents used for therapeutic purposes. The number of chemopreventive agents is increasing. [2]

1.4 Cancer Treatments

Surgery is the oldest and still the most common treatment for cancer. Radiation therapy is the use of ionizing radiation to treat cancer.[3] Ionizing radiation can be delivered using photon beams and particle beams. Radiation therapy is used at some point in the treatment of more than half of all cancer cases. High-energy X-rays are used to damage cancer cells and stop them from growing and spreading. It can be used to shrink a tumor before surgery, but it is often used after surgery. Like surgery it is a local treatment; it affects the cells only in the treated area. Hormone therapy is used to keep cancer cells

[2] Kelloff, G. J.; Charles, W. B.; Winfred, F. M.; Steele, V. E. in *Cancer Cheomoprevention*, Wattenberg, L.; Lipkin, M.; Boone, C. W.; Kelloff, G. J.; Ed.; CRC Press: Florida, **1992**, 41-56

from getting the hormones they need to grow.[4] It is often used as a follow-up to surgery. Reconstructive surgery is when one part of the body is replaced with another part. Chemotherapy is the use of drugs to kill cancer cells. Unlike surgery and radiation therapy it is systemic; it works throughout the body. A single drug or a combination of drugs may be used. Chemotherapy is often used after surgery to kill any hidden cancer cells that remain in the body.

1.5 Natural Products in Cancer Chemotherapy

Drugs from plants (natural product drugs) have played a dominant role in pharmaceutical care for the treatment of various diseases, especially cancer.[5] Vincristine (Oncovin®) (**1.1**) is isolated from periwinkle (*Catharanthus roseus*). It is an antimitotic agent and is used in combination with other agents for the treatment of a wide variety of cancers, including leukemia, bladder cancer, testicular cancer[6] and lymphomas such as Hodgkin's disease.[7] Teniposide (Vumon® **1.2**), a chemical analog of the natural product podophyllotoxin (**1.3**), shows activity against Hodgkin's disease and other malignant lymphomas, pediatric refractory neuroblastoma, and brain tumors in adults.[8] The alkaloid camptothecin (**1.4**) was first isolated from the tree *Camptotheca acuminata*.[9] It has good activity against various cancers in the laboratory,[10] but is too insoluble for clinical use. Various water-soluble analogs of camptothecin (e.g., topotecan **1.5**) have been developed, however, and have found significant clinical use.

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[3] Ward, D. E. *The Cancer Handbook: A Guide for the Nonspecialist*, Cushing-Malloy: Michigan, **1994**
[4] Breast Cancer Treatments,*St. Luke's Episcopal Hospital Homepage*,www.sleh.com/fact-c01-options.html
[5] Pezzuto, J. M. *Biochemical Phramacology*, **1997**, *53*, 121-133
[6] Neuss, N.; Neuss, M. N. Therapeutic Use of Bisindole Alkaloids from Ctaharanthus' in *The Alkaloids*, Volume 37, Brossi, A.; Suffness, M.; Ed.; Academic Press: New York, **1990**, 229-239
[7] Eric, J. L.; Wen, Y. L. *Structure Activity Relationship Analysis of Anticancer Chinese Drugs and Related Plants*; Oriental Healing Arts Institute: California, **1985**
[8] Kingston, D. G. I. In *Cancer Growth and Progression*; *Cancer Growth in Man*, Wooley, P.V.; Ed.; Kluwer Academic Publishers: **1989**, 152-158
[9] Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. Plant Antitumor Agents: I. The Isolation and Structure of Camptothecin, A Novel Alkaloidal Leukemia and Tumor Inhibitor from *Camptotheca acuminata*, *J. Am. Chem. Soc.*, **1966**, *88*, 3888-3890
[10] Suffness, M.; Cordell, G. A. Antitumor Alkaloids in *The Alkaloids*, Volume 25, Brossi, A.; Ed.; Academic Press: New York, **1985**, 1-369

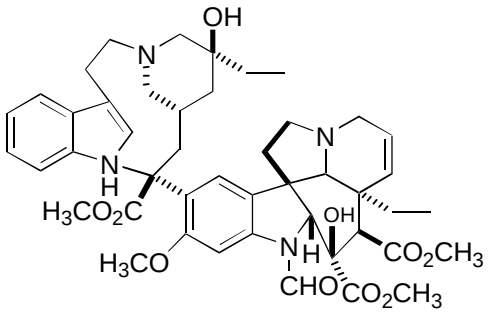

Figure 1-1 Vincristine

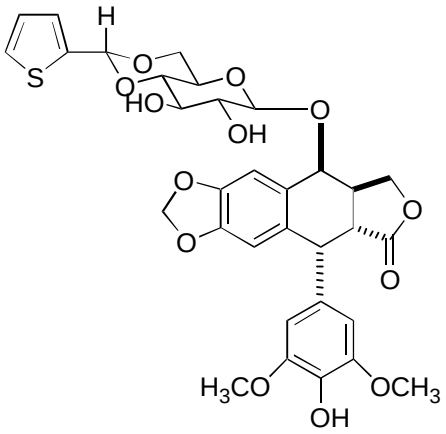

Figure 1-2 Teniposide

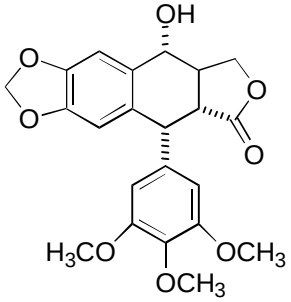

Figure 1-3 Podophyllotoxin

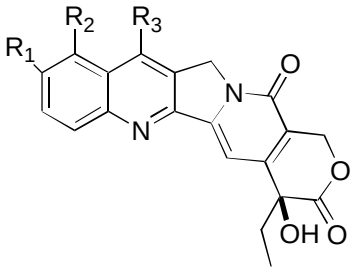

Figure 1-4 Camptothecin

$R_1 = R_2 = R_3 = H$

Figure 1-5 Topotecan

$R_1 = OH$, $R_2 = CH_2N(CH_3)_2$, $R_3 = H$

The most important member of the clinically useful natural anticancer agents is paclitaxel (Taxol®)* (**1.6**), which was first discovered in the bark of western yew (*Taxus brevifolia*). Taxol was approved by the United States Food and Drug Administration (FDA) for refractory ovarian cancer in December 1992 and for refractory breast cancer in April 1994.

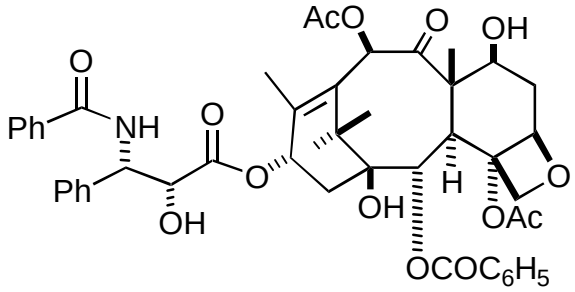

Figure 1-6 Paclitaxel

1.6 History of Taxol

Taxol was first discovered in the bark of western yew, *Taxus brevifolia* at Research Triangle Institute in North Carolina in 1967, and its chemical structure was first published in May 1971.[11] In 1979 Susan Horwitz with P. Schiff and J. Fant found the unique mechanism of action of Taxol.[12] They discovered that Taxol promoted the assembly of tubulin into stable microtubules and they explained the basis for Taxol's known action as an antimitotic drug. Although other anticancer agents, including the vinca alkaloids and the epipodophyllotoxins, are known to operate as antimitotic agents and tubulin binders, these agents acted by preventing the polymerization of tubulin into microtubules.[13] Taxol is a naturally occurring drug like discodermolide[14] (**1.7**) and

* The name Taxol, originally assigned by Dr. Wall in 1971, has been trademarked by Bristol-Myers Squibb, which offers the generic name paclitaxel instead. In this thesis the name Taxol will be capitalized in recognition of Bristol-Myers Squibb's trademark.

[11] Wani, M. C.; Taylor, H. L.; Wall, M. E. et al. Plant Antitumor Agents: VI. The Isolation and Structure of Taxol, A Novel Antileukemic and Antitumor Agent from *Taxus brevifolia*, *J. Am. Chem. Soc.*, **1971**, *93*, 2325-2327

[12] Schiff, P. B.; Fant, J.; Horwitz, S. B. Promotion of Microtubule Assembly *in vitro* by Taxol, *Nature*, **1979**, *277*, 665-667

[13] Kingston, D. G. I. History and Chemistry in *Paclitaxel in Cancer Treatment*, McGuire, W. P.; Rowinsky, E. K.; Ed.; Marcel Dekker, Inc., **1995**, *1*, 1-33

epothilones A (**1.8**) and B (**1.9**)[15] that acts by promoting the assembly of tubulin. Striking clinical results with advanced ovarian cancer were reported in 1989.[16] Also in 1989 Bristol-Myers Squibb was selected to commercialize the drug. Taxol was approved by the FDA for refractory ovarian cancer in December 1992 and for refractory breast cancer in April 1994.

Currently Taxol is being tested against a variety of different cancers. Taxol is also the best-selling anticancer drug in history, with sales of almost one billion U.S. dollars in 1997.

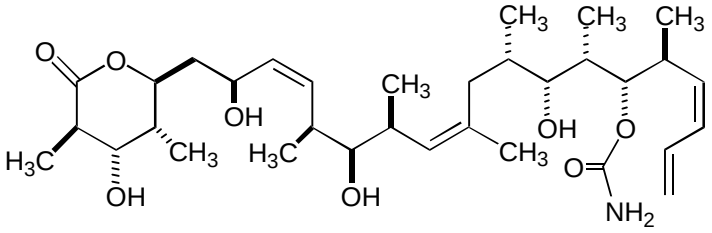

Figure 1-7 (+)-Discodermolide

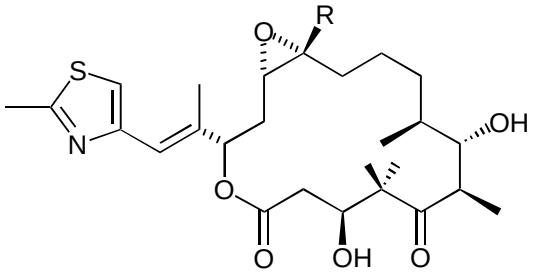

Figure 1-8 Epothilone A

R = H

Figure 1-9 Epothilone B

R = Me

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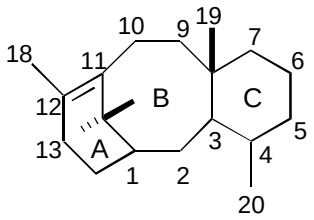
[14] Day, B. W.; Rosenkranz, H. S.; Gunasekera, S. P.; Longley, R. E.; Lin, M. C.; Hamel, E.; Kowalski, R. J.; Haar, E. Discodermolide, A Cytotoxic Marine Agent That Stabilizes Microtubules More Potently Than Taxol, *Biochemistry*, **1996**, *35*, 243-250

[15] Wessjohann, L., Epothilones: Promising Natural Products With Taxol-like Activity, *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, *No:7*, 715-718

[16] McGuire, W. P.; Rowinsky, E. K.; Rosenshein, N. B.; Grumbine, F. C.; Ettinger, D. S.; Armstrong, D. K.; Donehower, R. C., *Ann. Int. Med.*, **1989**, *111*, 273-279

1.7 Chemistry of Taxol

Chemically Taxol is classified as a taxane diterpenoid or taxoid.[13] Diterpenoids are natural products with a C-20 carbon skeleton derived biogenetically from geranylgeraniol pyrophosphate. Taxol is the most famous and most studied member of the large family of taxane diterpenoids. There are over 200 cousins of Taxol in this family, and almost all of them have the basic [9.3.1.0] pentadecene ring system (**1.A**).[17, 18]



1-A

In Taxol the A ring is essentially locked in a boat conformation, the B ring is in a chair-boat conformation, and the C ring assumes an envelope-like conformation distorted by the strained D ring fused to it.[18] Alternative taxane conformations are only produced by substantial skeletal rearrangement, e.g. D ring opening, saturation of the 11-12 double bond, or A/B ring contraction.

All known taxoids to date with one exception have been isolated from plants of the Taxaceae family and most from various *Taxus* species.[13] Taxol differs from most other taxoids in two respects. First, its taxane skeleton is esterified at the C-13 position with a complex *N*-benzoylphenylisoserine ester group, which is known as the "Taxol side-chain". The C-13 side-chain is highly flexible, rapidly samples alternative conformations, and its

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[17] Lucas, H., Über ein in den blättern von *Taxus baccata* L. Enhaltenes Alkaloid (das taxin), *Arch. Pharm.*, **1856**, *85*, 145

[17] Chiang, H. C.; Woods, M. C.; Nakadaira, Y.; Nakanishi, K. The Structures of Four New Taxinine Congeners and a Photochemical Transannular Reaction, *Chem. Commun.*, **1967**, 1201

[18] Georg, G. I.; Harriman, G. C. B.; Velde, D. G. V.; Boge, T. C.; Cheruvallath, Z. S.; Datta, A.; Hepperle, M.; Park, H.; Himes, R. H.; Jayasinghe, L. Medicinal Chemistry of Paclitaxel. Chemistry, Structure-Activity Relationships and Conformational Analysis: In *Taxane Anticancer Agents. Basic Science and Current Status*, Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M.; Ed.: American Chemical Society Symposium Series, Chapter 16, **1995**, *583*, 217-232

preferred conformation(s) depend on the medium. Second, it has an unusual fourth ring in the form of an oxetane ring attached at the C-4,5 positions, and both of these features are necessary for its biological activity. Taxol analogues in which the oxetane ring was opened such as the D-*seco*taxol (**1.10**)[19,20] were uniformly inactive in both tubulin-assembly and cytotoxicity assays.

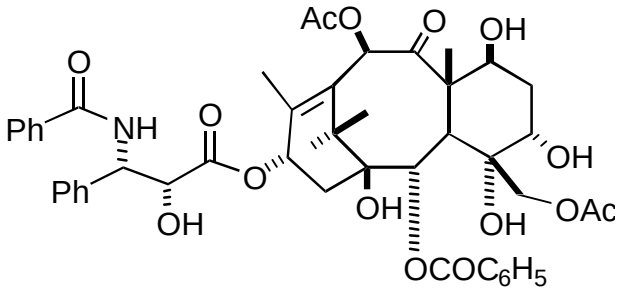


Figure 1-10 D-*seco*taxol

Although the structure of the taxoid ring system in Figure (**1.A**) looks planar on paper, it is actually like an inverted cup (**1.11**), in which the C-13 side chain is free to position itself under the mouth of the cup.[13]

[19] Kingston, D. G. I.; Samaranayake, G.; Magri, N. F.; Jitrangsri, C. Modified Taxols. V. Reaction of Taxol With Electrophilic Reagents and Preparation of a Rearranged Taxol Derivative With Tubulin Assembly Activity, *J. Org. Chem.*, **1991**, *56*, 5114

[20] Kingston, D. G. I.; Magri, N. F.; Jitrangsri, C., Synthesis and Structure-Activity Relationships of Taxol Derivatives As Anticancer Agents, in *New Trends in Natural Products Chemistry*, Atta-ur-Rahman and LeQuesne, P.W., Ed.: Elsevier, Amsterdam, **1986**, 219

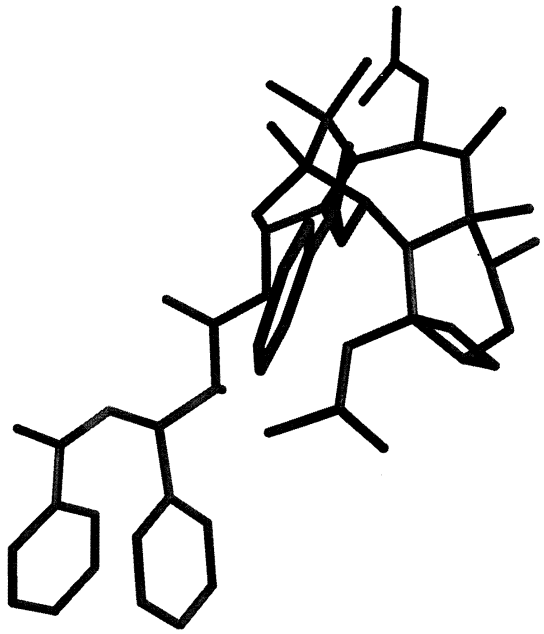
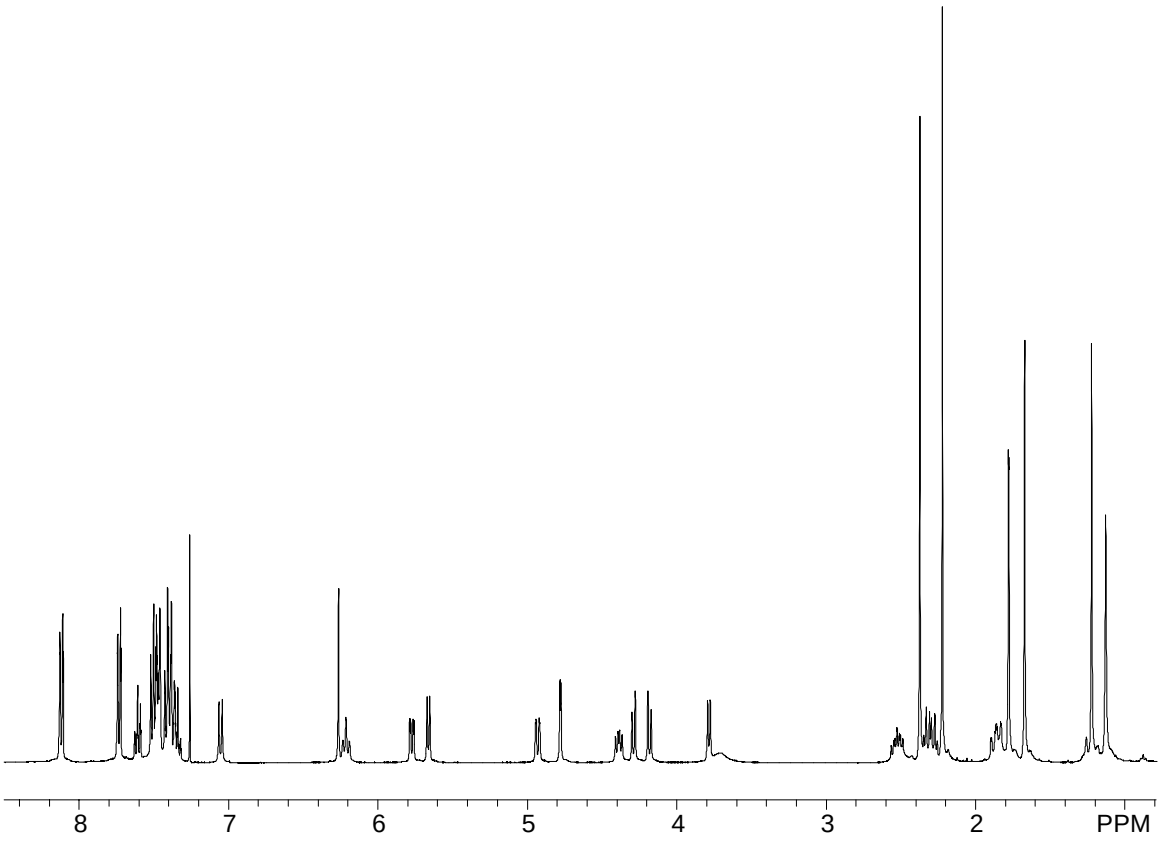


Figure 1-11 3-D Structure of Taxol

1.8 Nuclear Magnetic Resonance (NMR) Spectra of Taxol

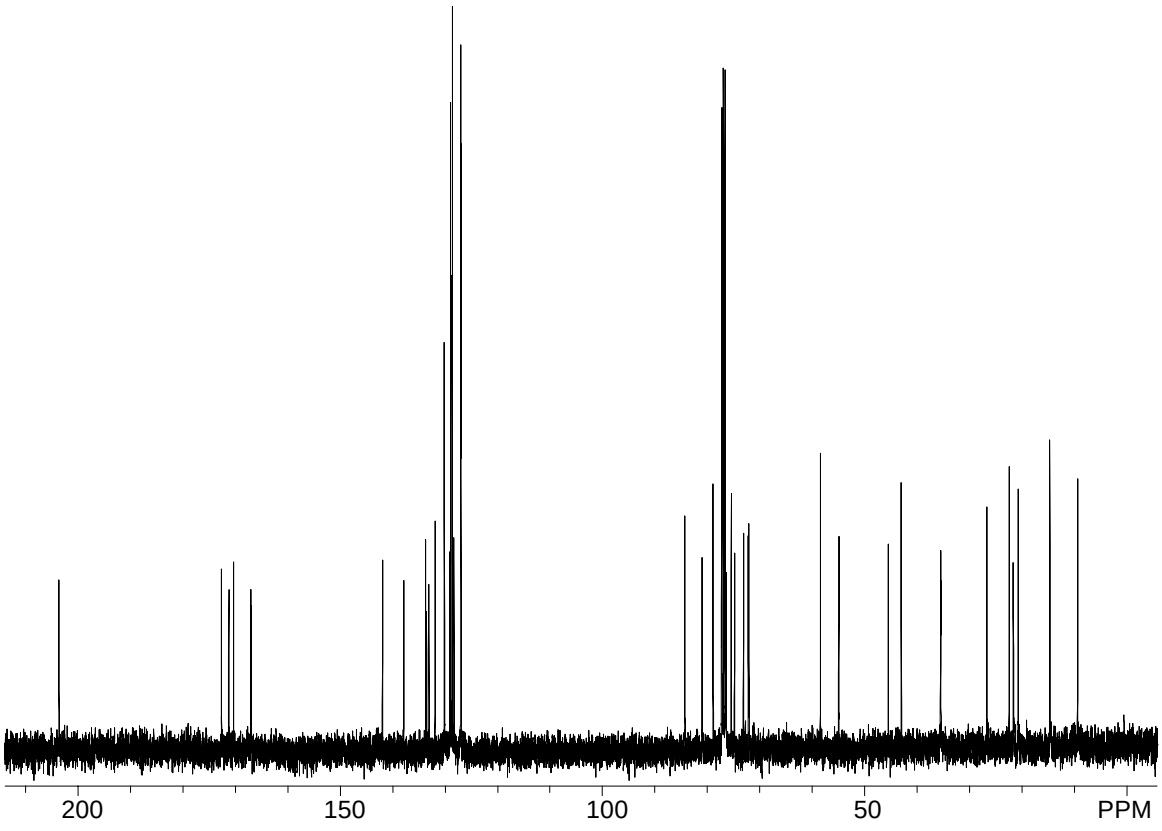
Despite the complex structure of Taxol, its proton NMR spectrum is relatively simple and can be easily assigned. Almost all of the signals are well resolved and are distributed in the region from 1.0 to 8.5 ppm. The strong three-proton signals caused by the methyl and acetate groups lie in the region between 1.0 and 2.5 ppm, together with multiplets caused by certain methylene groups. Most of the protons in the taxane skeleton and the side-chain are observed in the region between 2.5 and 7.0 ppm, and the aromatic proton signals caused by the C-2 benzoate, C-3' phenyl and C-3' benzamide groups appear between 7.0 and 8.3 ppm. The 400 MHz proton (**1.12**) and carbon (**1.13**) NMR spectra of Taxol are shown on the following pages.

1.8.1 ^{1}H-NMR Spectrum of Taxol



1-12

1.8.2 ^{13}C-NMR Spectrum of Taxol



1-13

1.9 Mechanism of Action of Taxol

Taxol was discovered because of its strong cytotoxicity and good activity in the P-388 mouse leukemia assay. The initial discovery was not followed up vigorously, however, because of the obvious supply problem in obtaining a complex natural product from the bark of a relatively scarce tree, and also because of Taxol's poor aqueous solubility. Some limited testing was carried out, however, and the first indication of Taxol's excellent activity against solid tumors was when it was shown in 1977 that it had good activity against the B16 melanoma and the MX-1 mammary xenograft in nude mice.[21,22]

Taxol's unique mechanism of action in promoting polymerization of tubulin was discovered in 1979.[12] Tubulin is the cellular protein which polymerizes reversibly to form microtubules, which constitute the mitotic spindle apparatus.[23] Microtubules are important parts of the cell essential for cell division, and they also form the cell's skeleton. Taxol binds to microtubules and stabilizes them, thus disrupting the tubulin-microtubule equilibrium and leading to mitotic spindle dysfunction. Taxol is of great interest because of this property, which until recently was unique to Taxol and related analogs. Taxol also eliminates the need for organizing centers by lowering the critical concentration of tubulin necessary for polymerization, resulting in polymerization of tubulin at many sites in addition to the organizing centers.[24] Tubulin as a pure polymer appears to be the target for Taxol, since Taxol's biochemical effects on microtubules formed from microtubule protein (including the so-called microtubule-associated proteins) are also observed with

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[21] Suffness, M. Development of antitumor Natural Products at the National Cancer Institute. *Gann Monograph on Cancer Research*, **1989**, *36*, 21

[22] Suffness, M.; Cordell, G. A. Taxus Alkaloids: In *The Alkaloids, Chemistry and Pharmacology*, Brossi, A.; Ed.: Academic Press, New York: **1985**, *25*, 6

[23] Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. The Taxane Diterpenoids: In *Progress in the Chemistry of Organic Natural Products*, Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, Ch.; Ed.: Springer-Verlag, **1993**, *61*

[24] De Brabander, M.; Geuens, G.; Nuydens, R.; Willerbords, R.; De Mey, J. Taxol Induces the Assembly of Free Microtubules in Living Cells and Blocks the Organizing Capacity of the Centrosomes and Kinetochores, *Proc. Natl. Acad. Sci. USA*, **1981**, *78*, 5608

polymer formed from pure tubulin, and Taxol can eliminate the requirement for microtubule-associated proteins in microtubule formation.[25,26]

The binding site for Taxol is different from the sites of binding of other antimitotic drugs. Taxol binds only to microtubules, while other tubulin-active drugs bind only to unpolymerized tubulin.[24] The binding of Taxol to assembled microtubules is also non-covalent and reversible.[27]

Although Taxol's anticancer activity is believed to be due to its effect on tubulin, it is also possible that this activity could be due to other mechanisms. Thus the anticancer activity of Taxol is quite different from that of other tubulin active drugs, such as vinblastine, vincristine, colchicine, podophyllotoxin and maytansine.[24] These compounds act primarily as antileukemic agents, whereas Taxol acts mainly on solid tumors. It is thus possible that the effects of Taxol on calcium ion fluxes may be involved in cellular signaling mechanisms, or that its primary action might be on tubulin/microtubule isotypes that are different form those involved in mitosis.[24]

In summary, it can be said that Taxol is a unique anticancer drug with a unique mechanism of action that no other anticancer drug in the market has.

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[25] Hamel, E.; Del Campo, A. A.; Lowe, M. C.; Lin, C. M. Interactions of Taxol, Microtubule-Associated Proteins and Guanine Nucleotides in Tubulin Polymerization, *J. Biol. Chem*, **1981**, *256*, 11887

[26] Schiff, P. B.; Horwitz, S. B. Taxol Assembles Tubulin in the Absence of Exogeneous Guanosine-5'-Triposphate or Microtubule-Associated Proteins, *Biochemistry*, **1981**, *20*, 3247

[27] Parness, J.; Horwitz, S. B. Taxol Binds of Polymerized Tubulin *in vitro*, *J. Cell. Biol.*, **1981**, *91*, 479

2. Previous Taxol and Taxol Side Chain Syntheses

Taxol can be isolated from the bark of *Taxus brevifolia* (Pacific Yew), which is a slow-growing tree that lives in the northwestern forests of the United States. For the clinical trials, more than 25,000 trees were needed, due to the low concentration of Taxol in the bark. Once the bark is removed from the tree, the tree dies. As *Taxus brevifolia* is a slow-growing tree, with trees adequate for harvesting being up to 100 years old, it is clear that the harvesting of *Taxus brevifolia* bark is not a viable long-term option for Taxol production on a large scale. It was obviously an absolute necessity to develop an improved source of this promising anticancer drug.

Various approaches to obtaining large-scale supplies of Taxol have been considered. These have included total synthesis, production by plant tissue culture, production by a Taxol-producing fungus, isolation from the needles and leaves of *Taxus* species and semi-synthesis from 10-deacetylbaccatin III. Of these approaches only the last two named have proved commercially viable, and the last one is the method used by Bristol-Myers Squibb Co., the major Taxol producer. Each of the approaches will be discussed briefly to show why this is so.

The total synthesis of Taxol has already been reported by five different research groups.[28,29,30,31,32,33] In 1994, two groups announced that they have finished the total

[28] Holton R. A.; Somoza, C.; Kim, H. B. et al. First Total Synthesis of Taxol. 1. Functionalization of the B Ring, *J. Am. Chem. Soc.*, **1994**, *116*, 1597-1598

[29] Holton R. A.; Somoza, C.; Kim, H. B. et al. First Total Synthesis of Taxol. 2. Completion of the C and D Rings, *J. Am. Chem. Soc.*, **1994**, *116*, 1599-1600

[30] Nicolaou, K. C.; Yang, Z.; Lin, J. J. et al. Total Synthesis of Taxol. *Nature*, **1994**, *367*, 630-634

[31] Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. A Total Synthesis of Taxol, *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1723-1726 and Danishefsky, S. J.; Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; DiGrandi, M. J. *J. Am. Chem. Soc.*, **1996**, *118*, 2843-2859

[32] Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancing, P. E.; Glass, T. E.; Granicher, C.; Houze, J. B.; Janichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Muhlenbach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.*, **1997**, *119*, 2755-2756 and Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancing, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.*, **1997**, *119*, 2757-2758

synthesis of Taxol: According to Holton's synthesis, a series of effective synthetic reactions were used and (-)-camphor was the starting material[29,30]; Nicolaou first constructed the A and C ring systems, then formed the B ring by a ring closure reaction.[31] In 1995, Danishefsky accomplished the total synthesis by the use of Heck cyclization.[32] In 1997, Wender reported the total synthesis by fragmentation strategy of an epoxy-alcohol, which was derived from α-pinene.[33] Also in 1997, Mukaiyama announced the total synthesis of Taxol.[34] According to his strategy, the B ring was constructed first and, the A and C rings were built onto that; either commercially available neopentyl glycol or L-serine were used as starting materials. However, due to the high complexity of the Taxol molecule, these syntheses, although they represent great achievements in synthetic organic chemistry, are far from being economical and are unlikely to become a solution to the supply problem of Taxol. But, this does not mean that synthetic approaches towards Taxol should be abandoned.

Taxol can also be isolated from the leaves of *Taxus* species, and a number of companies are using this method of production. The major advantage over the use of *Taxus brevifolia* bark is that the leaves are a renewable resource since they regenerate fairly quickly once they have been harvested.

Plant tissue-culture methods may become an important method for producing Taxol in the near future. The U. S. Department of Agriculture was the first to report tissue-culture production,[34] and this discovery was patented[35] and licensed to Phyton Catalytic (NY, USA). A second company, ESCAgenetics (CA, USA), has also announced plans for the production of Taxol, however, the details of this work are unavailable.[36]

An exciting development announced in 1993 was that Taxol could be produced by the fungus *Taxomyces andreanae*.[37] The yield was unfortunately very low (24-50 ng/l), but genetic manipulation of fungi is achieved more easily than that of plants, so it may be

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[33] Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. Asymmetric Total Synthesis of Taxol, *Proc. Japan. Acad.*, **1997**, *73*, 95-100

[34] Christen, A. A.; Bland, J.; Gibson, D. M. *Proc. Am. Assoc. Cancer Res.*,**1988**, *30*, 566.

[35] Christen, A. A.; Gibson, D. M.; Bland, J. *US Patent*, **1991**, 5019504

[36] Kingston, D. G. I. Taxol: The Chemistry and Structure-Activity Relationships of a Novel Anticancer Agent, *Trends-Biotechnol.*, **1994**, *12(6),* 222-226

possible to improve the production significantly with the help of genetic engineering. If this can be done, it would bring a new option for the production of Taxol by fermentation methods, which would have a lower cost than plant tissue culture.

The tetracyclic diterpene moiety of Taxol, 10-deacetylbaccatin III (10-DAB) (**2.1**), which is the most demanding portion of Taxol from the point of view of total synthesis, is readily available from the renewable leaves of *Taxus baccata* (European Yew). 10-DAB can be extracted from the leaves of this tree in high yields of 1g/kg.[40]

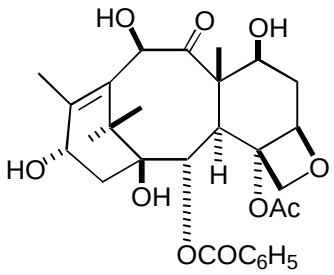

Figure 2-1 10-deacetyl-baccatin III

The removal of the leaves from the tree has no effect on the "health" of the tree and the leaves are regenerated relatively quickly, so it is unnecessary to cut down the trees to obtain the bark. The conversion of 10-DAB to Taxol is thus an excellent option for the large scale and economic synthesis of Taxol.

The first requirement of a Taxol synthesis from 10-DAB is the preparation of the Taxol side chain, *N*-benzoyl-β-phenylisoserine (**2.2**). The second requirement is the protection of the side chain 2'-OH group. The third requirement is making the proper modifications on 10-DAB, namely protection of the 7-OH group and acetylation of the 10-OH group. It was shown that[38] the 7-acetate and the 7,10-diacetate were formed in equal amounts under mild conditions (24h, 20 ^{o}C). Under more forcing conditions (48h, 60 ^{o}C), the 7,10-diacetate and the 7,10,13-triacetate were formed in equal amounts. However, under more vigorous conditions (24h, 80^{o}C), only the triacetate was formed.

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[37] Stierle, A.; Strobel, G.; Stierle, D. *Science*, **1993**, *260*, 214-216

This study proved that the order of reactivity for acetylation is 7>10>>13. In the case of more bulky protective groups, e.g. triethylsilyl group, the difference between the C-7 and C-10 hydroxyl groups; is accentuated; thus triethylsilylation of 10-DAB gave 7-triethylsilyl-10-DAB in 85% yield under optimized conditions.[39] Also, since the C-1 hydroxyl group is a tertiary hydroxyl group and is thus sterically hindered, no substitution on this group occurs under normal acetylation conditions of hydroxyl groups. Although the 7, 10 and 13 OH groups are all secondary, hydrogen bonding between 13-OH group and 4-Ac group of 10-DAB, together with the hindered location of the 13-OH group under the "cup" of the tetracyclic skeleton, makes the 13-OH group the least reactive. The final requirement is for an efficient method for the coupling the protected side chain with a protected 10-DAB, such as 7-triethylsilylbaccatin III (**2.3**).

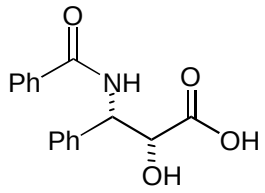


Figure 2-2 *N*-benzoyl-β-phenylisoserine

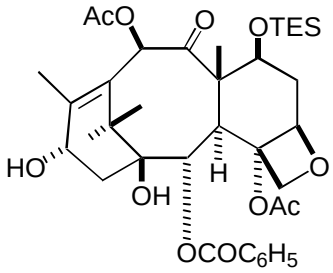


Figure 2-3 7-triethylsilylbaccatin III

[38] Gueritte-Voegelein, F.; Senilh, V.; David, B.; Guenard, D.; Potier, P. Chemical Studies of 10-deacetyl baccatin III. Hemisynthesis of Taxol Derivatives, *Tetrahedron*, **1986**, *42*, 4451

[39] Denis, J. N.; Greene, A. E.; Guenard, D.; Gueritte-Voegelein, F.; Mangatal, L.; Potier, P. Highly Efficient, Practical Approach To Natural Taxol, *J. Am. Chem. Soc.*, **1988**, *110*, 5917

Although the esterification of a secondary alcohol is not normally a challenging task, the 13-hydroxyl group of baccatin III is in a hindered environment and is hydrogen-bonded to the C-4 acetate, both features which reduce its reactivity.[13]

To overcome this problem, Potier, Greene et al. used a protected side chain (**2.4**) and forcing conditions to convert baccatin III to Taxol in 80% yield at 50% conversion and 38% overall yield without recycling.[40] They treated 7-(triethylsilyl)-baccatin III (**2.3**) with excess (2*R*,3*S*)-*N*-benzoyl-O-(1-ethoxyethyl)-3-phenylisoserine (**2.4**), (**Scheme 2-1**) in the presence of di-2-pyridyl carbonate (DPC) and 4-(dimethylamino)-pyridine (DMAP) at 73°C in toluene for 100 h and obtained the protected Taxol derivative with the yields shown above. Removal of the protecting groups with dilute HCl then gave Taxol in good yield.

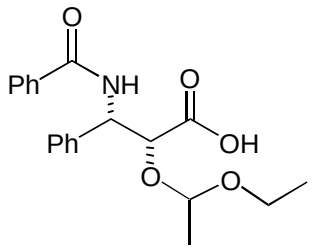
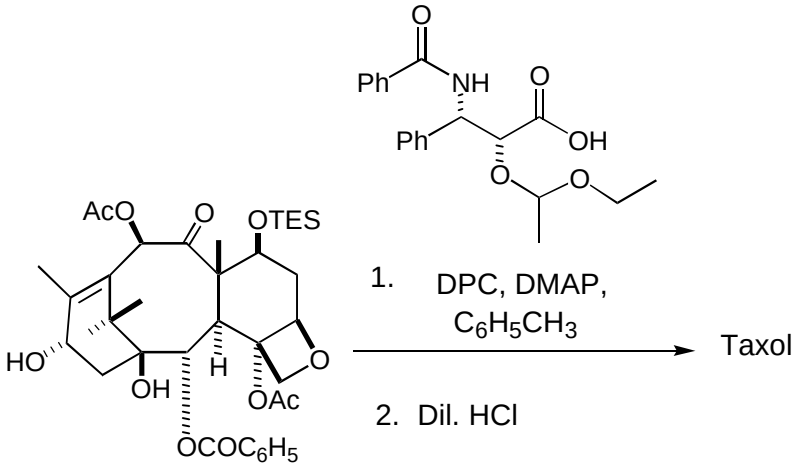


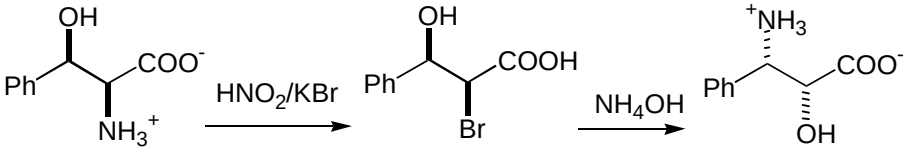
Figure 2-4 (2*R*,3*S*)-*N*-benzoyl-O-(1-ethoxyethyl)-3-phenylisoserine



2-3

Scheme 2-1

Several groups have achieved the synthesis of threo-3-phenylisoserine. In the earlier studies, mixtures of *erythro* and *threo* isomers or racemic material were observed.[40] Racemic *threo*-phenylisoserine was prepared in good yield from commercially available racemic *threo*-phenylserine (**2.5**), by reaction with nitrous acid in the presence of potassium bromide to give the α-bromo-β-hydroxycarboxylic acid **2.6**. This was then treated with aqueous ammonia to get the desired product **2.7** along with a minor product, its regioisomer (**Scheme 2-2**).[41]



2-5 **2-6** **2-7**

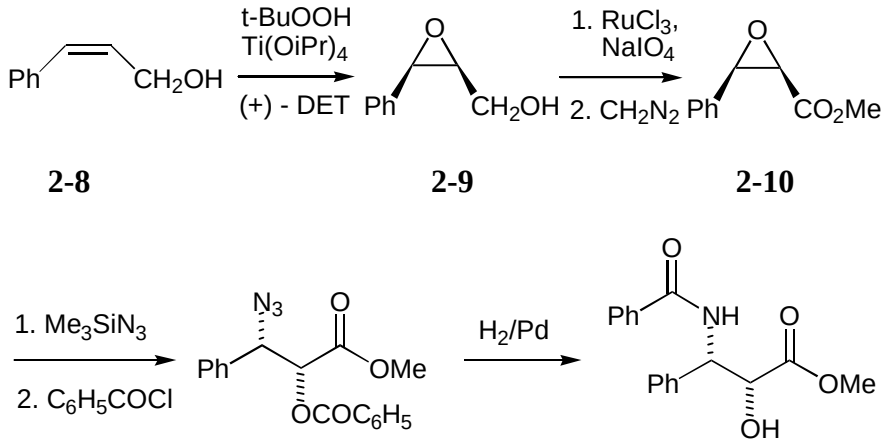
Scheme 2-2

[40] Kaji, E.; Igarashi, A.; Zen, S. The Synthetic Reactions of Aliphatic Nitro Compounds. XI. The Synthesis of β-Amino-α-hydroxycarboxylic Acids and γ-Amino-carboxylic Acids, *Bull. Chem. Soc. Jpn.*, **1976**, *49*, 3181

[41] Deamicis, C. V. Insertion Reactions of Oxacarbenes Generated Photochemically from Cyclobutanes, Ph.D. Dissertation, Stanford University, **1988**

A different strategy was shown by Hönig et al.[42] They resolved the 2-butanoyl ester of *threo*-3-azido-2-hydroxy-3-phenylpropionic acid with lipase from *Pseudomanas fluorescens*. The unhydrolysed ester, which was obtained in 35% yield and 98% enantiomeric excess, was hydrolysed and hydrogenated to (2*R*,3*S*)-phenylisoserine.

Greene et al (**Scheme 2-3**) introduced the first asymmetric synthesis of the Taxol side chain.[43] They used Sharpless asymmetric epoxidation for the conversion of *cis*-cinnamyl alcohol (**2.8**) to the epoxide **2.9** with 61% yield and 78% enantiomeric excess. Oxidation of **2.9** followed by immediate methylation resulted in methyl glycidate (**2.10**), which was then converted to an azido alcohol followed by benzoylation to give **2.11**. The desired ester **2.12** was isolated in 23% overall yield after hydrogenation of **2.11** followed by acyl migration. A benzoyl migration method was also used by Erhardt et al..[44]



2-8 **2-9** **2-10**

2-11 **2-12**

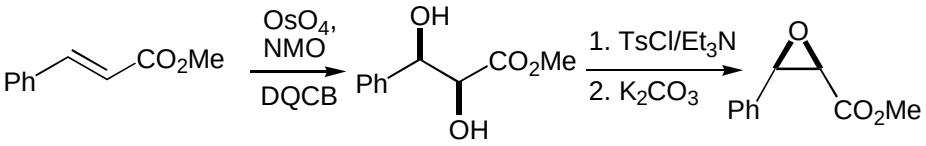
Scheme 2-3

[42] Honig, H.; Seufer-Wasserthal, P.; Weber, H. Chemo-enzymatic Synthesis of All Isomeric 3-Phenylserines and -isoserines, *Tetrahedron*, **1990**, 46, 3841

[43] Denis, J. N.; Greene, A. E.; Serra, A. A.; Luche, M. J. An Efficient, Enantioselective Synthesis of The Taxol Side Chain, *J. Org. Chem.*, **1986**, *51*, 46

[44] Erhardt, P. W.; Hu, Z. Utilization of A Benzoyl Migration To Effect An Expeditious Synthesis of The Paclitaxel C-13 Side Chain, *Org. Proc. Res.*, **1997**, *1*, 387-390

The Greene group[45] (**Scheme 2-4**) then improved the synthesis of glycidic ester **2.10**. Commercially available and fairly inexpensive methyl cinnamate (**2.13**) was converted to *cis*-diol **2.14** via Sharpless asymmetric dihydroxylation with osmium tetroxide, in the presence of *N*-methylmorpholine-*N*-oxide (NMO) and dihydroquinidine 4-chlorobenzoate (DQCB). The diol **2.14** could then be recrystallized to enantiomeric purity in 51% yield. Monotosylation of this diol gave only the C-2 tosylate, which was then converted to glycidic ester **2.10** on treatment with potassium carbonate in 35% overall yield from methyl cinnamate.



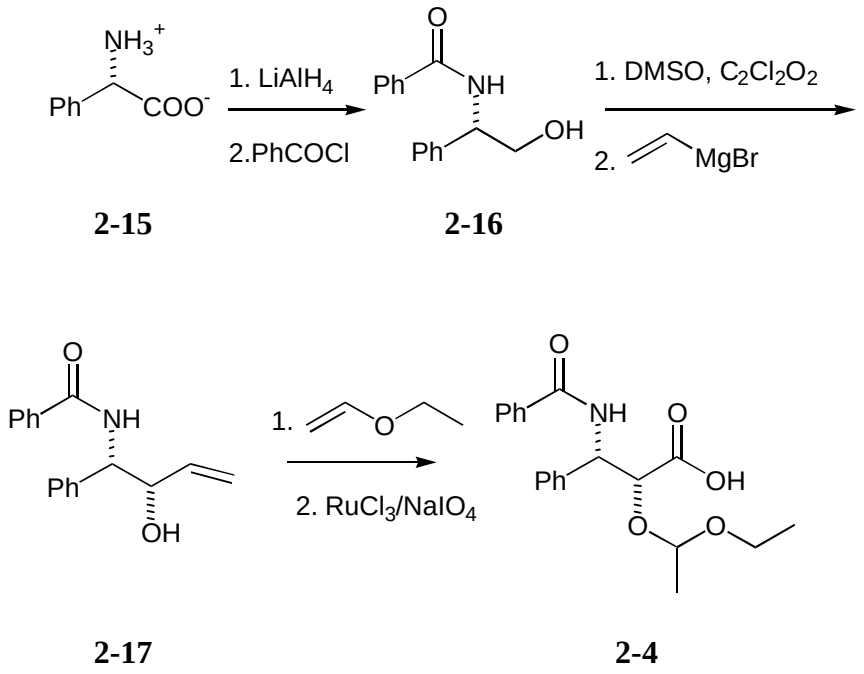
2-13 **2-14** **2-10**

Scheme 2-4

Greene and collaborators provide a third route to the Taxol and Taxotere side chains (**Scheme 2-5**).[46] In this route they start with readily available (S)-(+)-phenylglycine (**2.15**) and reduce and benzoylate it to give the amido alcohol **2.16**. Oxidation of this alcohol to the corresponding aldehyde via Swern oxidation, followed by in-situ Grignard reaction, gave the alcohol **2.17**. This alcohol was then protected with ethyl vinyl ether and oxidized to the protected acid (**2.4)** with an overall yield of 30%; a corresponding process gave the Taxotere side chain in 34% yield.

[45] Denis, J. N.; Correa, A.; Greene, A. E. An Improved Synthesis of The Taxol Side Chain and Of RP56976, *J. Org. Chem*, **1990**, *55*, 1957-1959

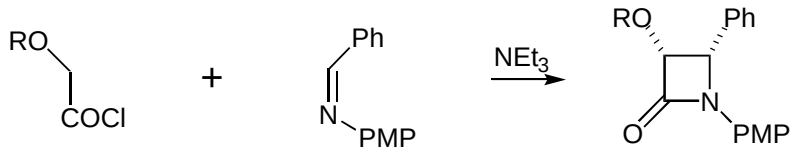
[46] Denis, J. N.; Correa, A.; Greene, A. E. Direct, Highly Efficient Synthesis from (S)-(+)-phenylglycine of The Taxol and Taxotere Side Chains, *J. Org. Chem*, **1991**, *56*, 6939



Scheme 2-5

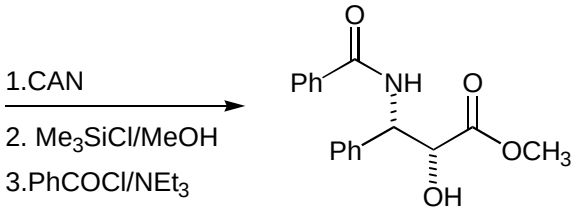
The Taxol C-13 side chain can also be prepared by various pathways using a β-lactam intermediate. One of these pathways involves the racemic *cis*-β-lactams (**2.20** or **2.22**) that is prepared by reaction of the alkoxyacyl chloride (**2.18)** or acetyloxyacyl chloride (**2.21**) with imine **2.19**. The *p*-methoxyphenyl (PMP) protecting group of **2.21** was removed with ceric ammonium nitrate (CAN), followed by ring opening and benzoylation, to give the racemic methyl ester of the side chain (**2.23)** (**Scheme 2-6**).[47]

[47] Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. Highly Stereoselective Synthesis of α-hydroxy β-amino Acids Through β-lactams: Application To The Synthesis of The Taxol and Bestatin Side Chains and Related Systems, *Tetrahedron Lett.*, **1990**, *31*, 6429



2-18 R=Me **2-19** **2-20 R=Me**

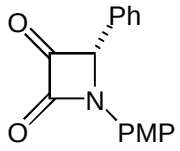
2-21 R=Ac **2-22 R=Ac**



2-23

Scheme 2-6

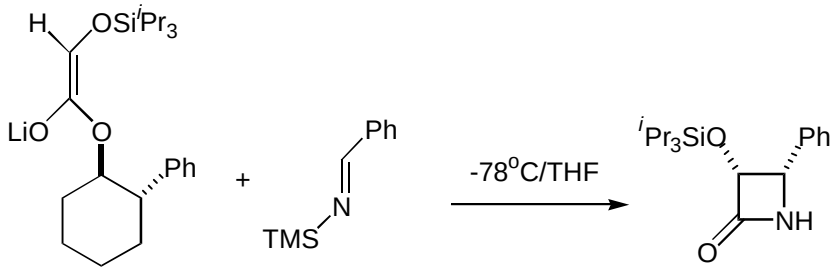
A similar route to the Taxol side chain was also described by the same authors from azetidine-2,3-dione (**2.24)** by using a different ether protecting group.



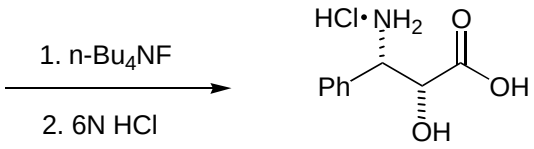
2-24

Ojima and co-workers also used β-Lactam chemistry. They developed an enantioselective synthesis of the side chain using a β-lactam.[48] In their work, lithium enolate **2.25** is condensed with the *N*-TMS-imine **2.26** to give the β-lactam **2.27** with 96-98% enantiomeric excess. The amino acid **2.28**, which was isolated after deprotection of

2.27 by fluoride ion followed by hydrolysis, was then benzoylated to give the side chain (**Scheme 2-7**).



2-25 **2-26** **2-27**



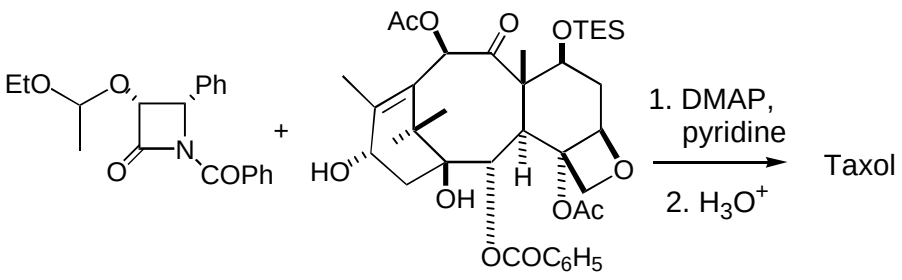
2-28

Scheme 2-7

Another β-lactam approach has been developed by Holton that uses coupling of a suitably derivatized β-lactam **2-29** with 7-(triethylsilyl)-baccatin III **(2-3)**, followed by acid hydrolysis, to give Taxol in excellent yield (**Scheme 2-8**).[49]

[48] Ojima, I.; Habus, I.; Zhao, M.; Georg, G. I.; Jayasinghe, L. R. Efficient and Practical Asymmetric Synthesis of The Taxol C-13 Side Chain, N-Benzoyl-(2R,3S)-3-phenylisoserine, and Its Analogues via Chiral 3-hydroxy-4-aryl-β-lactams Through Chiral Ester Enolate-imine Cyclocondensation, *J. Org. Chem.*, **1991**, *56*, 1681

[49] Holton, R. A. Eur. Pat. Appl. EP 400,971, 1990: *Chem. Abstr.*, **1990**, *114*, 164568q



2-29 **2-3**

Scheme 2-8

Holton's approach requires 5 equivalents of β-lactam. Furthermore, this reaction is very slow and is performed under almost neat conditions. Ojima and collaborators have developed optimal conditions for this method.[50]

The β-lactam synthon method was also used by several other groups.[51,52,53,54,55,56,57,58,59,60,61] They all tried different syntheses of different β-lactam

[50] Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. New and Efficient Approaches To The Semisynthesis of Taxol and Its C-13 Side Chain Analogs By Means Of β-Lactam Synthon Method, *Tetrahedron*, **1992**, *48*, No:34, 6985-7012

[51] Brieva, R.; Crich, J. Z.; Sih, C. J. Chemoenzymatic Synthesis of The C-13 Side Chain of Taxol: Optically Active 3-hydroxy-4-phenyl-β-lactam derivatives, *J. Org, Chem.*, **1993**, *58*, 1068-1075

[52] Georg, G. I.; Cheruvallath, Z. S.; Harriman, G. C. B.; Hepperle, M.; Park, H. An Efficient Semisynthesis of Taxol from (3R-4S)-N-benzoyl-3-[(t-butyldimethylsilyl)oxy]-4-phenyl-2-azetidinone and 7-(Triethylsilyl) baccatin III, *Biiorg. Med. Chem. Lett.*, **1993**, *3*, 2467-2470

[53] Farina, V.; Hauck, S. I.; Walker, D. G. A Simple Chiral Synthesis of The Taxol Side Chain, *Synlett.*, **1992**, *1*, 761-763

[54]Ojima, I.; Pack, Y. H.; Sun, C. M.; Brigaud, T.; Zhao, M. New and Efficient Routes To Norstatine and Its Analogs With High Enantiomeric Purity by β-lactam Synthon Method, *Tetrahedron Lett.*, **1992**, *33*, 5737-5740

[55] Ojima, I.; Pack, Y. H.; Zucco, M.; Park, Y. H.; Duclos, O.; Kuduk, S. A Highly Efficient Route To Taxotere by The β-lactam Synthon Method, *Tetrahedron Lett.*, **1993**, *34*, 4149-4152

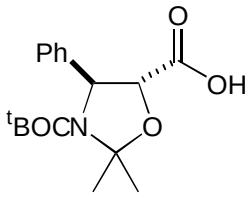
[56]Georg, G. I.; Harriman, G. C. B.; Park, H.; Himes, R. H. Taxol Photoaffinity Labels 2. Synthesis and Biological Evaluation of N-(4-Azidobenzoyl)-N-debenzoyltaxol, N-(4-azido-2,3,5,6-tetrafluorobenzoyl)-N-debenzoyl Taxol, and 7-(4-azido-2,3,5,6-tetrafluorobenzoyl)taxol, *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 487-490

[57] Ojima, I.; Zucco, M.; Duclos, O.; Kuduk, S. D.; Sun, C. M.; Park, Y. H. N-Acyl-3-hydroxy- β-lactams As Key Intermediates For Taxotere and Its Analogs, *Bioorg. Med. Chem. Lett.*, **1993**, *3*

[58] Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. Stereoselective Synthesis of Azetidin-2-ones, Precursors of Biologically Active Syn-3-amino-2-hydroxybutanoic Acids, *J. Org. Chem.*, **1993**, *58*, 4746-4748

derivatives and their coupling with suitably protected baccatin III derivatives in order to synthesize Taxol or Taxotere. Those readers interested in a more detailed discussion of the β-lactam synthon method are referred to a recently published review by Ojima and Delaloge.[62]

Another pathway involves the use of an oxazolidine derivative followed by hydrolysis and benzoylation.[63] In order to prevent undesirable epimerization at C-2' in the direct acylation process and to avoid forcing conditions, Commerçon et al. looked for a cyclic protection which, based on the stereochemistry of the side chain, would generate a less sterically hindered and thus more reactive acid. Such a cyclic compound may disfavor potential hydrogen abstraction at C-2' of an intermediately formed acid anhydride which would lead to partial epimerization at C-2' via a hypothetical ketene intermediate. They obtained such an efficient protection using an oxazolidine-type cyclization (**2.30**).



2-30

Compound **2.30** was prepared with high stereoselectivity from condensation of the boron enolate of (4*S*,5*R*)-3-bromoacetyl-4-methyl-5-phenyl-2-oxazilidinone (**2.31**) with benzaldehyde which was then converted to epoxide **2.32** in a one-pot sequence and

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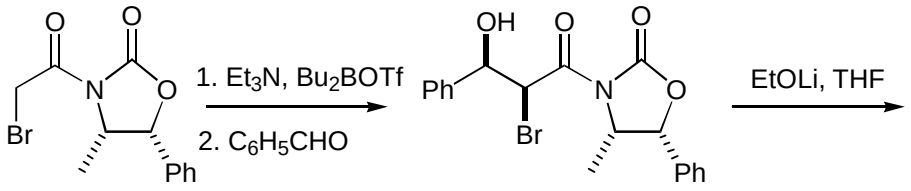
[59] Palomo, C.; Aizpurua, J. M.; Miranda, J. I.; Mielgo, A.; Odriozola, J. M. Asymmetric Synthesis of α-keto-β-lactams via [2+2] Cycloaddition Reaction- A Concise Approach To Optically Active α-hydroxy-β-lactams and β-alkyl(aryl)isoserines, *Tetrahedron Lett.*, **1993**, *34*, 6325-6328

[60] Brown, S.; Jordan, A. M.; Lawrence, N. J.; Pritchard, R. G.; McGown, A. T. A Convenient Synthesis of The Paclitaxel Side-Chain via A Diastereoselective Staudinger Reaction, *Tetrahedron Lett.*, **1998**, *39*, 3559-3562

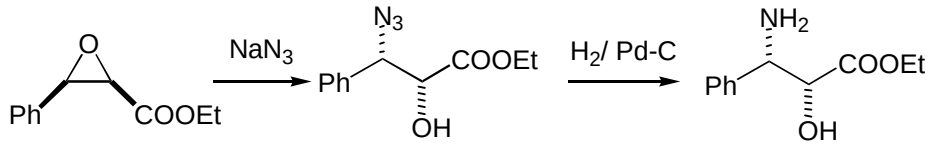
[61] Ojima, I.; Wang, T.; Delaloge, F. Extremely Stereoselective Alkylation of 3-Siloxy-β-lactams and Its Applications To The Asymmetric Syntheses Of Novel 2-alkylisoserines, Their Dipeptides and Taxoids, *Tetrahedron Lett.*, **1998**, *39*, 3663-3666

[62] Ojima, I.; Delaloge, F. Asymmetric Synthesis Of Building-blocks For Peptides and Peptidomimetics by Means of The β-lactam Synthon method, *Chem. Soc. Rev*, **1997**, *26*, 377-386

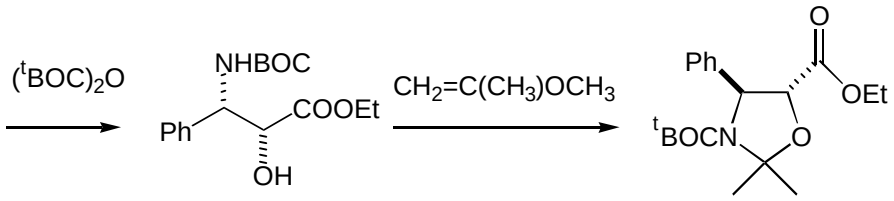
transformed through **2.33** into *N*-(^{t}BuOCO)-β-phenyl isoserinate (**2.34**) in satisfactory yields. They performed the cyclic protection with methoxypropene in the presence of a catalytic amount of pyridinium *para*-toluenesulfonate (PTSP) to give **2.35** in good yield. This was then hydrolyzed to the corresponding acid **2.30**, which was then esterified with a protected baccatin III (**2.36**) (**Scheme 2-9**).



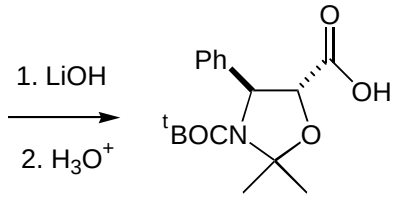
2-31



2-32 **2-33**

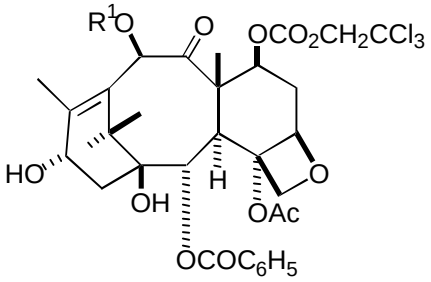


2-34 **2-35**



2-30

[63] Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. Improved Protection and Esterification of a Precursor of The Taxotere and Taxol Side Chains, *Tetrahedron Lett.*, **1992**, *33*, No:36, 5185-5188



2-36 $R^1 = CO_2CH_2CCl_3$ or Ac

Scheme 2-9

By coupling this oxazolidine derivative to a protected 10-deacetylbaccatin III they synthesized Taxotere (**2.5a**), which is also a promising anticancer agent, then converted it to Taxol by deprotection of the ^{t}BuOCO group, followed by 7-O-deprotection, benzoylation of the C-3'-NH_2 and acetylation at C-10.

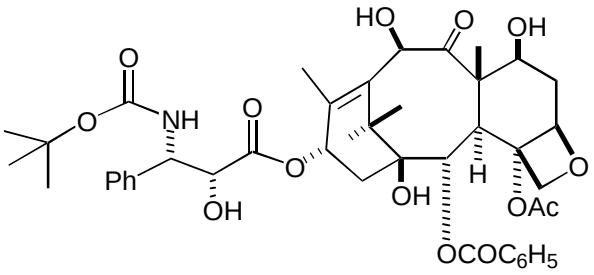
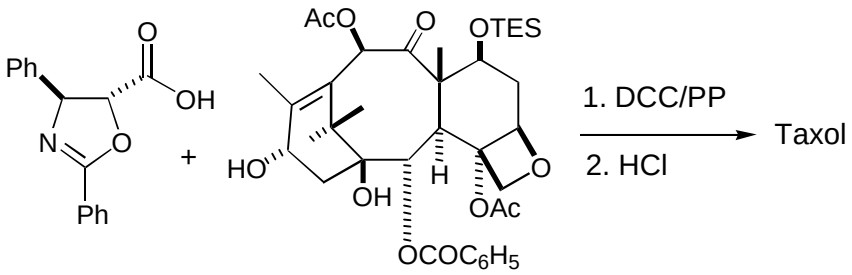


Figure 2-5a Taxotere

One other approach for the synthesis of Taxol is via an oxazoline intermediate. Kingston et al. reported that Taxol can be prepared in good yield from 7-triethylsilylbaccatin III by the simple procedure of esterification with (4*S*,5*R*)-2,4-

diphenyloxazoline-5-carboxylic acid (**2.38**) followed by hydrolysis of the resulting oxazoline ester with dilute hydrochloric acid (**Scheme 2-10**).[64]



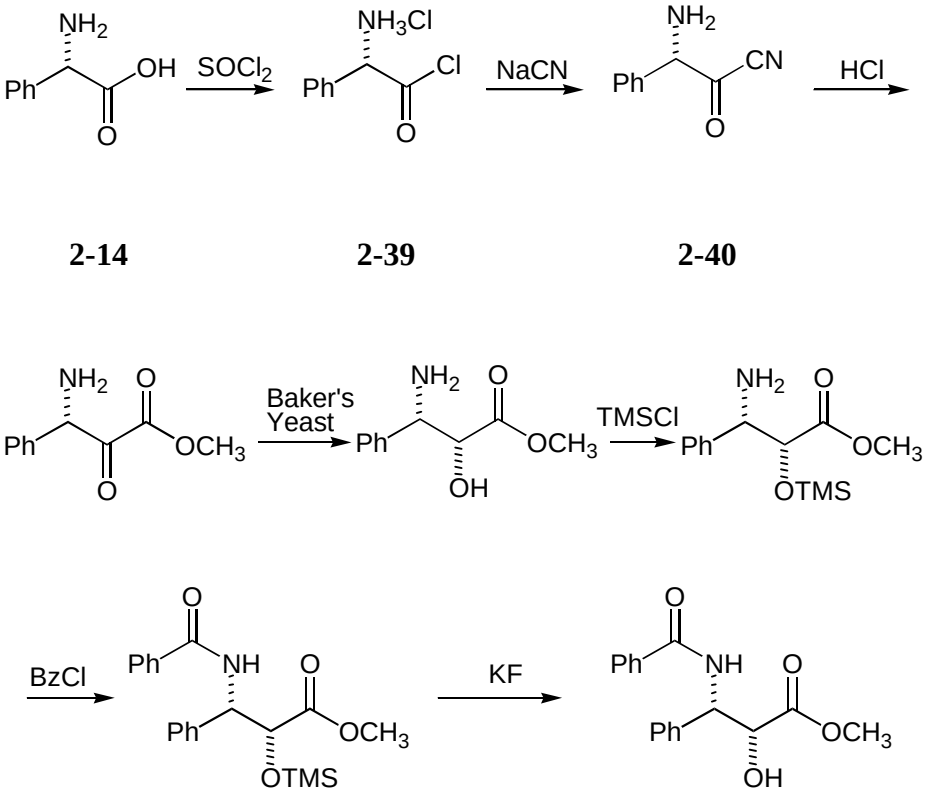
2-38 **2-3**

Scheme 2-10

A different synthesis of the Taxol side chain was developed by Kayser et al.[65] They converted unprotected phenylglycine (**2.14**) to phenylglycidylchloride hydrochloride (**2.39**) in 100% yield by treatment with thionyl chloride, which was then refluxed with a mixture of sodium cyanide and lithium carbonate in THF to give **2.40**. Alcoholysis of the nitrile was carried out with methanol in the presence of dry HCl, followed by a yeast-mediated reduction. Necessary protection of the 2'-OH group was performed with a TMS group in order to benzoylate the 3'-NH_2 group, and the TMS group was then removed to give the methyl ester of the Taxol side chain (**Scheme 2-11**).

[64] Kingston, D. G. I.; Chaudhary, A. G., Gunatilaka, A. A. L.; Middleton, M. L. Synthesis of Taxol from Baccatin III via an Oxazoline Intermediate, *Tetrahedron Lett.*, **1994**, *35*, No:26, 4483-4484

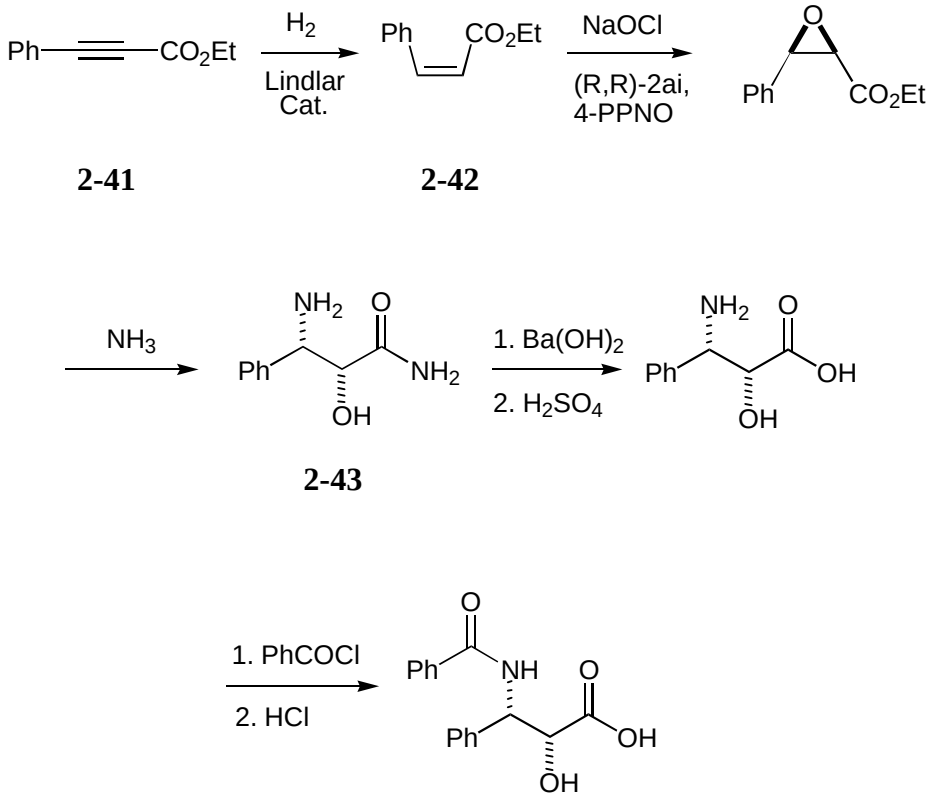
[65] Kearns, J.; Kayser, M. M. Application Of Yeast-catalyzed Reductions To Synthesis Of (2R,3S)-phenylisoserine, *Tetrahedron Lett.*, **1994**, *35*, 2845-2848



Scheme 2-11

An enantioselective synthesis of the Taxol side chain was performed by Jacobsen et al..[66] Partial hydrogenation of commercially available ethyl phenyl propiolate (**2.41**) to *cis*-ethyl cinnamate (**2.42**), followed by epoxidation to the corresponding epoxide occurred in good yield and high enantioselectivity. The *cis*-epoxide was then opened with ammonia in ethanol to generate 3-phenylisoserinamide (**2.43**) in a highly regioselective ring-opening process. Hydrolysis of the amide using $Ba(OH)_2$ in water, followed by acidification and benzoylation gave the Taxol side chain (**Scheme 2-12**)

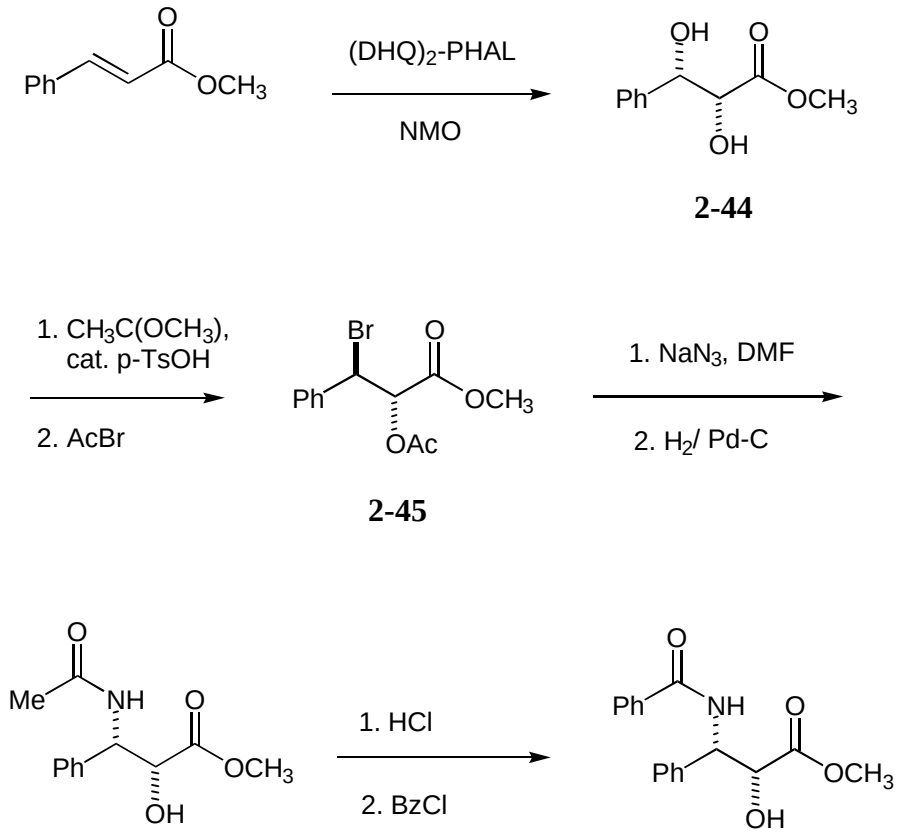
[66] Deng, L.; Jacobsen, E. N. A Practical, Highly Enantioselective Synthesis Of The Taxol Side Chain via Asymmetric Catalysis, *J. Org. Chem.*, **1992**, *57*, 4320-4323



Scheme 2-12

Sharpless and collaborators have carried out another example of enantioselective synthesis.[67] In this work, commercially available methyl cinnamate was converted to the (2*R*, 3*S*) diol **2.44** with a NMO-based asymmetric dihydroxylation reaction in the presence of ligand, $(DHQ)_2PHAL$. The diol was then converted to acetoxy bromo ester **2.45** by reaction with trimethyl orthoacetate in the presence of a catalytic amount of *p*-TsOH, followed by treatment with acetyl bromide. Ester **2.45** was converted to the Taxol side chain by treatment with sodium azide in DMF followed by hydrogenation and by acid hydrolysis and benzoylation (**Scheme 2-13**).

[67] Sharpless, K. B.; Wang, Z. M.; Kolb, H. C. Large-scale and Highly Enantioselective Synthesis of The Taxol C-13 Side Chain Through Asymmetric dihydroxylation, *J. Org. Chem.*, **1994**, *59*, 5104-5105



Scheme 2-13

Those readers interested in more detailed asymmetric aminohydroxylation methods are referred to recently published work by Sharpless et al.[68,69]

The partial synthesis of Taxol is very important when compared to that of direct isolation of Taxol from the western yew, since the availability of baccatin III or 10-DAB is greater than that of Taxol. Another advantage of the semi-synthetic approach is that various taxol analogs, such as Taxotere, which may have improved bioactivity as compared with Taxol, can also be synthesized.

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[68] Sharpless, K. B.; Tao, B.; Schlingloff, G. Reversal of Regioselection In The Asymmetric Aminohydroxylation of Cinnamates, *Tetrahedron Lett.*, **1998**, *39*, 2507-2510

[69] Sharpless, K. B.; Reddy, K. L.; Dress, K. R. *N*-chloro-*N*-sodio-2-trimethylsilyl ethyl carbamate: A New Nitrogen Source For The Catalytic Asymmetric Aminohydroxylation, *Tetrahedron Lett.*, **1998**, *39*, 3667-3670

3. Objectives

Finding lifesaving drugs is not an easy task. Millions of dollars are spent on the discovery of a promising new drug, and tens of millions of dollars are required for preclinical and clinical studies. For every 10,000 compounds screened only one or two will be approved by the FDA and find their way into pharmacies. Every penny spent on this path will be added to the price of the drug when it comes to market. This is the case for Taxol; it is not an inexpensive drug, and even today a lot of patients cannot afford to be treated with it.

As noted before, several semi-syntheses of Taxol have been reported, but most if not all of these are licensed to a small group of companies.

The objective of this work is to develop a new synthesis of Taxol from baccatin III with lower cost or higher yield or both of these, as compared with existing routes.

A second objective of this work is to find a new route that is not encumbered with patent protection so that other companies can also produce Taxol. In this way, the cost of Taxol may be reduced and Taxol may become available to treat many other people.

The objective of this work is to be useful and helpful to people on earth as much as possible.

4. Results and Discussion

4.1 Introduction

The work to be presented in this project describes a new synthesis of Taxol from baccatin III, which can be isolated as 10-deacetyl baccatin III in significant quantities (1g/kg) from the renewable needles of the European Yew, *Taxus baccata*. This is about ten times more than the amount of Taxol (0.1g/kg) that can be isolated from the bark of Pacific Yew, *Taxus brevifolia*. This is why its conversion to Taxol is an attractive but challenging option, and several methods have already been reported to accomplish this.

As noted earlier, the first requirement of a Taxol synthesis from baccatin III is the preparation of *N*-benzoyl-β-phenylisoserine, the so-called "Taxol side chain". Here, in this work a synthesis for the Taxol side chain is not proposed. Instead, previously reported methods are used to make the side chain, but a new method for the coupling of the side chain with a suitably protected baccatin III is developed.

The focus of this work is the development of new reactions that would use five-membered heterocycles. In a series of studies chiral heterocycles have been prepared that may be useful for the synthesis of the most important anticancer drug in history.

The key idea here is to find a new protecting group, a linker, which will be able to "tie back" the α-OH and β-NHCOPh groups. Why is it necessary to link the α-OH and the β-NH groups? Because, as described in the previous section, if this kind of linkage is not used, then acylation of baccatin III proceeds poorly and gives lower yields of Taxol, sometimes coupled with epimerization at the 2' position.

The discovery of a practical and useful heterocyclic system required that the system meet three important criteria:

1. The heterocyclic system should be "makeable". In other words, a suitable precursor must react easily with the side chain in high yield, in order to form the heterocyclic ring.

2. It must be able to stand up to acylation conditions. This means it must be stable during coupling with suitably protected baccatin III.

3. It must be removable easily after acylation, with high yield and of course without destroying Taxol.

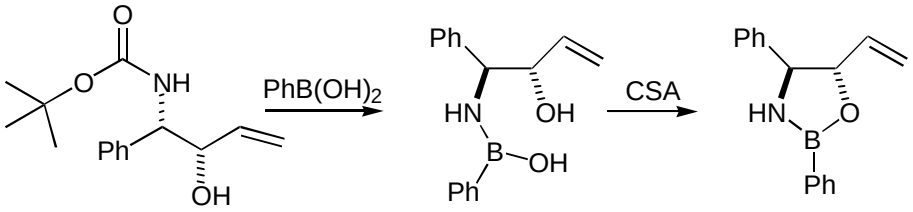
The heterocycles initially selected for this study were the cyclic boronate, the 1,3-oxazolidine-2-thione, the 2-oxo-1,2,3 oxathiazolidine or the 2,2-dioxo-1,2,3 oxathiazolidine rings.

In this study, protected forms of the Taxol side chain were investigated in order to couple the side chain to 7-triethylsilylbaccatin III, using phenylboronic acid, thiophosgene, thionyl chloride and sulfuryl chloride. The results of each of these approaches will be discussed.

4.2 Phenylboronic acid approach

The cyclic boronates of hydroxyamines have been prepared and have found use as chiral catalysts for the enantioselective reduction of ketones to chiral secondary alcohols.[70,71] A cyclic boronate protecting group was thus selected as the first linker to be investigated.

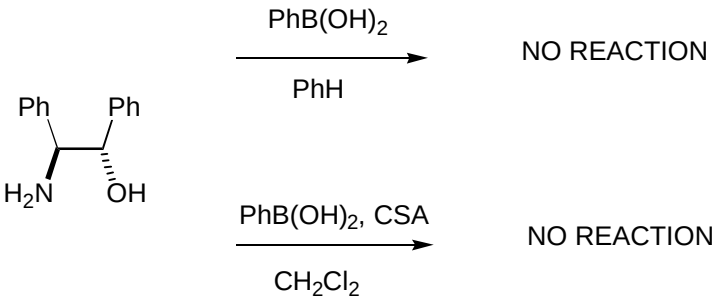
In order to synthesize the cyclic boronate, the proper starting material had to be prepared first. Thus, (+)-1,1-dimethylethyl(*N*-((1*S*,2*S*)-2-hydroxy-1-phenyl-3-butenyl)amino) methanoate (**4.1a**) and (*N*-((1*S*,2*S*)-2-hydroxy-1-phenyl-3-butenyl)benzamide (**4.1b**) were prepared using Greene's procedure.[47] Phenylboronic acid was used as reagent. However, all the attempts at the synthesis of the cyclic boronate failed. Only once and with very low yields were the compounds **4.2** and **4.3** isolated.



4-1a **4-2** **4-3**

[70] Corey, E. J.; Bakshi, R. K.; Shibata S. *J. Am. Chem. Soc*., **1987**, *109*, No: 18, 5551-5553
[71] Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C-P.; Singh, V. K. *J. Am. Chem. Soc*., **1987**, *109*, 7926-7927

Since it is neither easy nor inexpensive to make the starting material, model studies were carried out with (1*R*, 2*S*)-2-amino-1,2-diphenylethanol **(4.4**) as staring material.

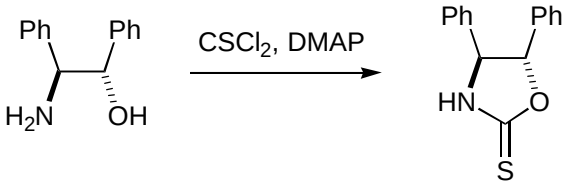


4-4

But again, all the attempts in order to make the desired cyclic boronate failed. The cyclic boronate approach was thus terminated due to the very low yield of the reaction and the presumed instability of the product. This protecting group approach thus failed to meet the first and most basic criteria for success.

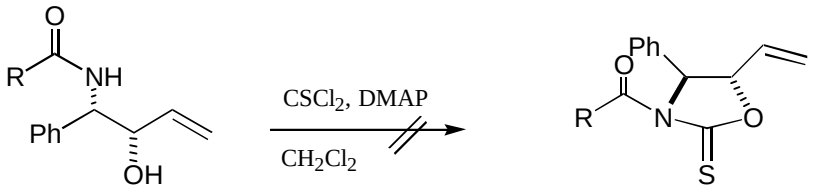
4.3 Thiophosgene approach

The second protected group selected was a cyclic 1,3-oxazolidine-2-thione. Since the carbon atom of thiophosgene is highly electrophilic, the reaction to form the desired heterocyclic product was expected to proceed smoothly. For the model studies, (1*R*,2*S*)-2-amino-1,2-diphenylethanol was used again. As expected the desired product, the cyclic 1,3-oxazolidine-2-thione (**4.5**) was readily formed.



4-5

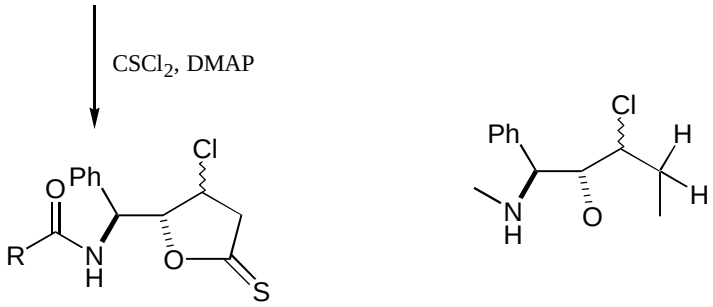
With this encouraging result from a model study the "real" compound, *N*-(2-hydroxy-1-phenylbut-3-enyl)benzamide (**4.1a**) was used as starting material. Also the same reaction conditions were tried using (*tert*-butoxy)-*N*-(2-hydroxy-1-phenylbut-3-enyl)formamide (**4.1b**).



4-1a or **4-1b** **4-6a** or **4-6b**

4-1a R = Ph

4-1b R = $(CH_3)_3CO$



4-7a R = Ph **4-7c**

4-7b R = $(CH_3)_3CO$

In both cases an unexpected product (**4.7a** or **4.7b**) was isolated in place of the expected and desired product (**4.6a** or **4.6b**).

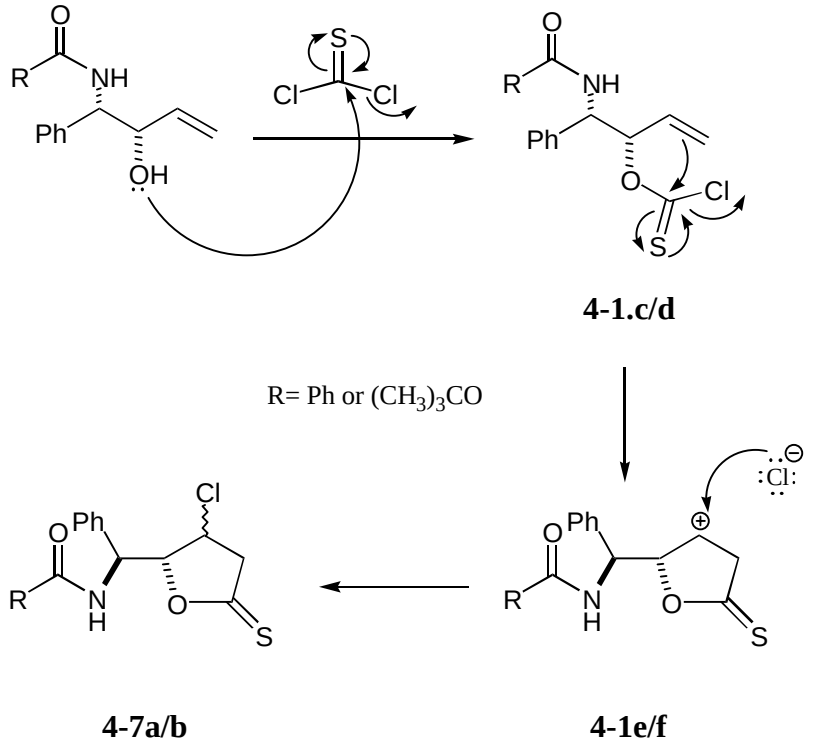
The formation of the unexpected products **4.7a** and **4.7b** was confirmed by ^{1}H-NMR and mass spectral data. Further characterization of the compounds isolated was done by ^{1}H-TOCSY, which supported the structural assignments.

The molecular formula was found to be $C_{18}H_{16}NO_2ClS$ by CIMS (*m*/*z* 346, $[M+H]^+$). A ratio of M:(M+2) of 3:1 indicated the presence of a chlorine atom in the molecule. The existence of an -NH peak at δ 6.38 ppm, together with the absence of signals for the olefinic protons in the ^{1}H-NMR spectrum of **4-7a** indicated the formation of an unexpected product. In addition to the signal for the -NH proton, signals for 3 -CH groups (δ 6.05, 5.85, 5.75) and 1-CH_2 group (δ 3.62) were observed. Correlations

observed in a ^{1}H-TOCSY experiment identified the spin system (**4.7c**). Based on the evidence the structure of **4-7a** was established as shown.

A proposed mechanism for the formation of **4.7a** from **4.1a** and **4.7b** from **4.1b** is given in **Scheme 4-1.**

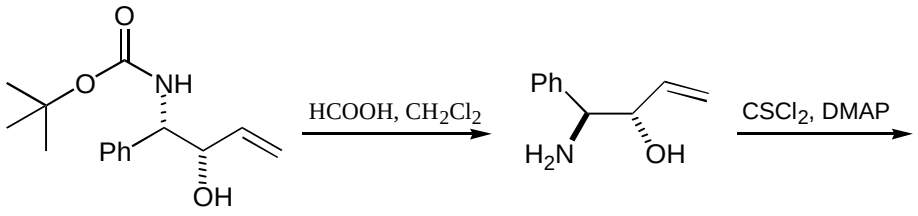
4.3.1 Proposed mechanism for the formation of unexpected products 4.7a and 4.7b



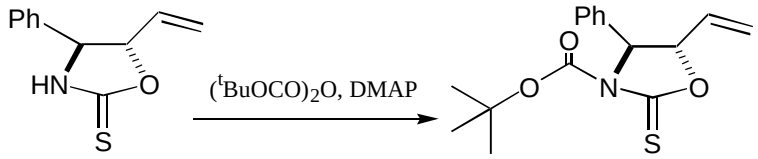
The reaction proceeds with the nucleophilic attack of the hydroxyl group on the highly electrophilic carbon of thiophosgene to form **4-1c/d**, followed by reaction of the terminal olefin to give a thiolactone type ring via a secondary carbocation intermediate **4-1e/f** on which a chlorine ion can add to give the product **4-7a** or **b**.

To overcome this problem a different route was investigated. This time the ^{t}BuOCO protecting group of (*tert*-butoxy)-*N*-(2-hydroxy-1-phenylbut-3-enyl)formamide was removed first by treatment with formic acid to give the free amine **4.9**. The cyclic

thionocarbonate was then synthesized by using the product **4.9**. The desired product **4-9.2** was isolated after reprotection of the amine as its ^{t}BOC derivative.

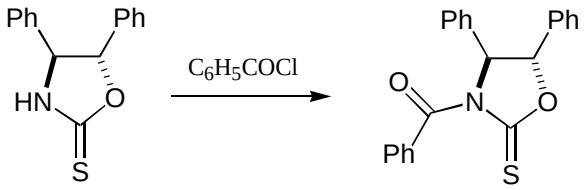


4-9



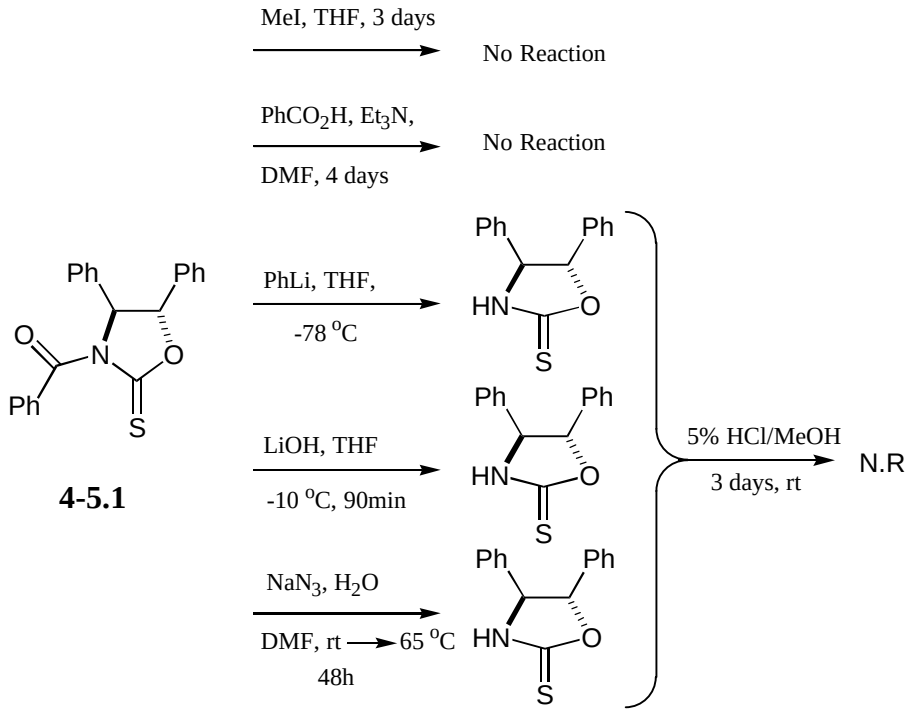
4-9.1 **4-9.2**

Up to this point it is known that the desired cyclic 1,3-oxazolidine-2-thione is makeable, and the cyclic thionocarbonate protecting group thus meets the first requirement. To find out if it also meets the last requirement, deprotection without destroying Taxol, several experiments were performed on the model compound **4-5.1**. This compound was prepared by benzoylating **4.5** so as to make the model closer to a protected Taxol derivative.

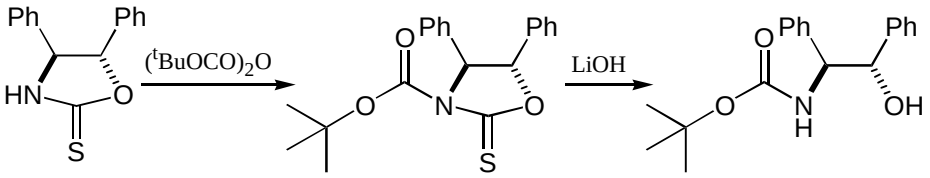


4-5 **4-5.1**

The next step was to find the best conditions for the hydrolysis of the cyclic 1,3-oxazolidine-2-thione linkage. The conditions tried and the results obtained are shown in **Scheme 4-2**.



Of all the conditions shown above, none of them was capable of hydrolyzing the cyclic 1,3-oxazolidine-2-thione linkage. The experiment was repeated with a ^{t}BOC group in place of the benzoyl group of **4-5.1**.



In the case of ^{t}BOC as the N-protecting group, ring hydrolysis was achieved on treatment with LiOH at room temperature. Regrettably these conditions would also result

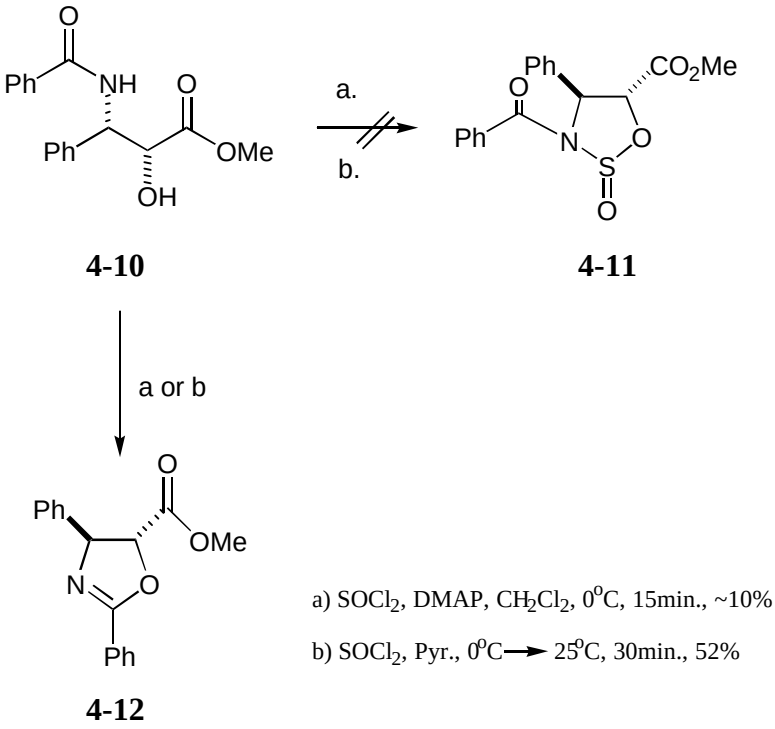
in hydrolytic removal of the side chain of Taxol, and thus could not be used in a Taxol synthesis.

In summary, the cyclic 1,3-oxazolidine-2-thione could be formed in good yield, but it could not be removed selectively under conditions that would not destroy Taxol. This group thus fails to meet requirement number 3 for a suitable protecting group, and the approach was abandoned.

4.4 Thionyl chloride approach

Before starting studies using thionyl chloride as the reagent, the starting material was replaced with the methyl ester of the Taxol side chain (**4.10**). In order to get an adequate supply of the methyl ester for the following steps of the investigation, the desired compound was synthesized in large quantity by Greene's synthesis.[46]

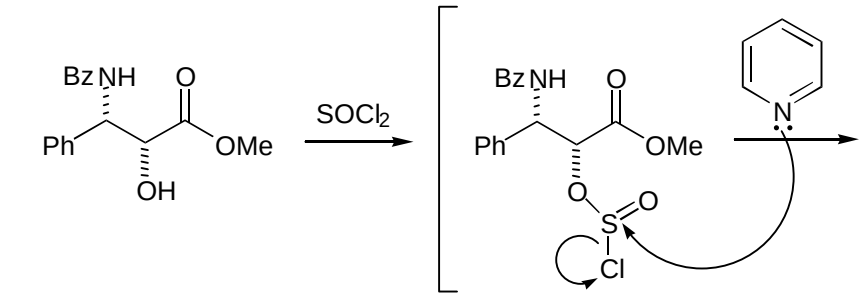
Treatment of the methyl ester of the Taxol side chain with thionyl chloride in dry dichloromethane using DMAP as catalyst gave a single product in low yield. When the reaction conditions were changed to thionyl chloride and pyridine, the yield was improved by about five fold, and the same product was formed. The ^{1}H-NMR spectrum could not distinguish between the desired product **4.11** and the alternative oxazoline **4.12**, but the mass spectrum of the product, in conjunction with its ^{1}H and ^{13}C-NMR spectra showed conclusively that the product isolated was the oxazoline **4.12**.



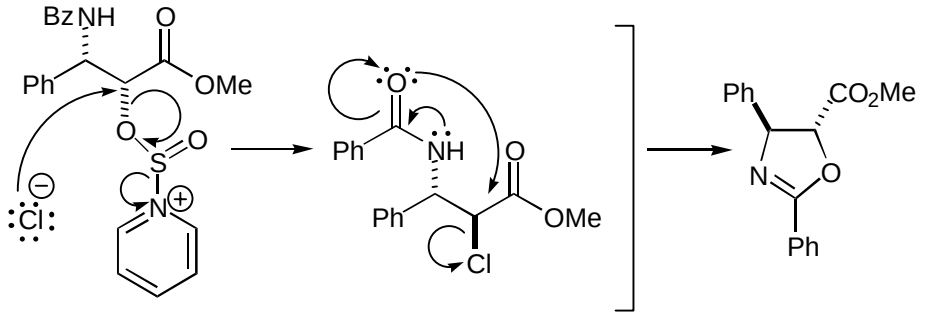
4.4.1 Proposed mechanism for the formation of the unexpected oxazoline (4.12)

Presumably, under the conditions used, thionyl chloride first converts the 2-hydroxyl group to the 2-chloride through an S_N2 reaction. Thionyl chloride is known to form chlorides from alcohols either with retention of configuration or with inversion, depending on the conditions;[72] in the case of reaction in pyridine reaction occurs with inversion. The reason for inversion is because pyridine reacts with **4-10.1** to give **4-10.2** before chlorine can attack. The freed chloride ion then attacks from the rear and the intermediate chloride adduct **4-10.3** then undergoes an intramolecular displacement through an S_N2 reaction to form the oxazoline **4.12** with overall retention of stereochemistry.

[72] March, J. *Advanced Organic Chemistry Reactions, Mechanisms and Structure 4th Edition*, John Wiley & Sons: **1992**, 326-327 and the references cited therein.



4-10 **4-10.1**

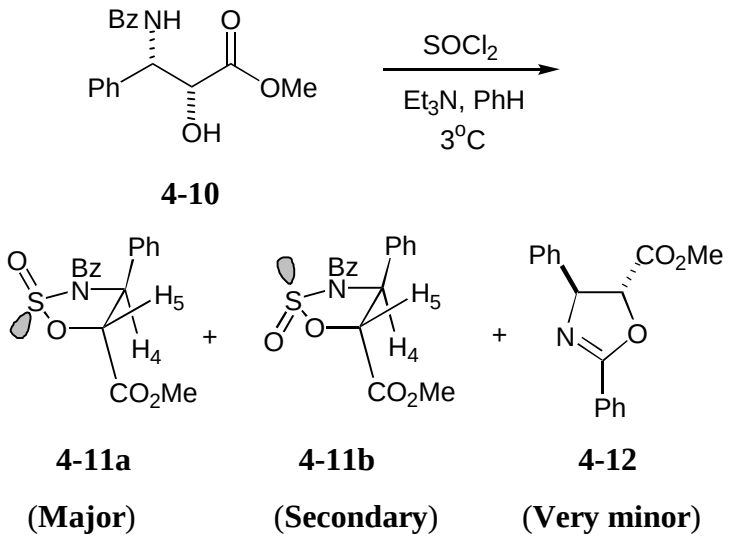


4-10.2 **4-10.3** **4-12**

The *trans* configuration of compound **4.12** was assigned by comparing the NMR data obtained with reported NMR data for *trans* oxazoline **4.12** in the literature.[73] In particular, the coupling constants of the H_4 and H_5 ($J_{H4,\ H5}$ = 6.4Hz) matched the literature data.

To avoid the formation of oxazoline **4.12**, the reaction conditions were changed to thionyl chloride/triethylamine/benzene. During the reaction under these conditions TLC (thin layer chromatography) analysis showed the formation of three products along with unreacted starting material. Isolation and identification of the new products showed that the reaction yielded a pair of isomeric 2-oxo-1,2,3-oxathiazolidines (**4.11a** and **4.11b**), one of them being the major product. The third and minor product was the known oxazoline **4.12**, which was isolated in trace amounts.

[73] Tomasini, C.; Tolomelli, A.; Gentilucci, L.; Cardillo, G. A Stereoselective Synthesis of (2*R*,3*S*)-*N*-benzoylphenylisoserine methyl ester, *J. Org. Chem.*, **1998**, *63*, 2351-2353



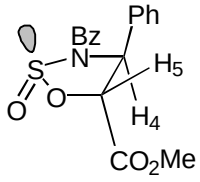
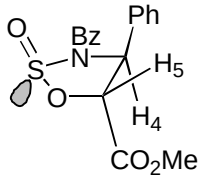
It was possible to assign the geometry of the isomeric products by NMR spectrometry. It is reported in the literature that in the case of a five-membered heterocyclic ring the sulfoxide bond (S=O) deshields the ring substituents that are *cis* to the sulfoxide bond. [74]

As shown in Table 4-1, the chemical shift of H_4 is further downfield when it is *cis* to the S=O bond, and further upfield when it is *trans*. The same trend applies to H_5 as well. Thus, the major product is assigned as **4-11a**, and the secondary product as **4-11b**.

The coupling constants of the H_4 and H_5 protons of the major product are found to be 8.8 Hz ($J_{H4,\ H5}$ = 8.8 Hz) and the coupling constants of the H_4 and H_5 of the secondary product are found to be 2.4 Hz ($J_{H4,\ H5}$ = 2.4 Hz). It is surprising that these values are so different. One possible explanation would be **4-11a** and **4-11b** are in fact *cis* and *trans* isomers at C-4 and C-5. However, this explanation cannot be correct, since as discussed below, **4-11a** and **4-11b** must only be stereoisomeric. This is because both isomers can be oxidized to the same 2,2-dioxo-1,2,3-oxathiazolidine derivative. It must thus be assumed that the different *J* values are due to subtle differences in the conformations of the 5-membered rings in **4-11a** and **4-11b**.

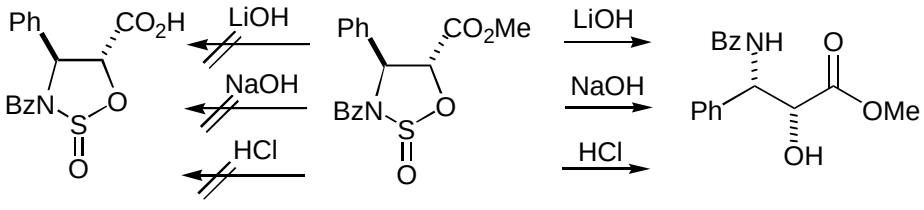
[74] Moyer, C. L.; Deyrup, J. A. 1,2,3-Oxathiazolidines-A New Heterocyclic System; *J. Org. Chem.*, **1969**, *34*, 175-179 and references cited therein.

Table 4-1 Comparison of the H_4 and H_5 chemical shifts and coupling constants

	H_4 (ppm)	H_5 (ppm)	$J_{H4,H5}$(Hz)
	6.22	5.27	2.4
	5.69	5.66	8.8

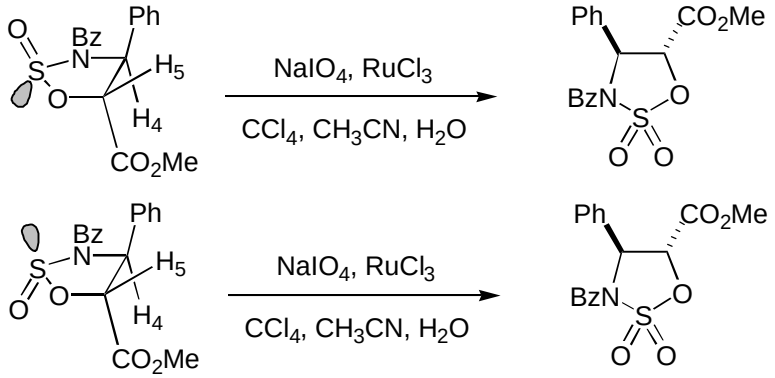
During these studies, it was discovered that one of the isomers, the major product (**4-11a**) was not soluble in ethanol. Thus, it was possible to isolate **4.11a** in pure form, without the need of further purification, by washing the crude product with ethanol after work-up. The secondary product (**4-11b**), that is the other isomer of the oxathiazolidines was not very stable and was hydrolyzed to starting material even on TLC.

The next step was the hydrolysis of the methyl ester to the corresponding carboxylic acid **4.13**. Several conditions were tried, but in all cases the sulfur linkage was broken before the methyl ester was hydrolyzed. This was contrary to literature reports that these oxathiazolidines are stable under basic conditions.[73]



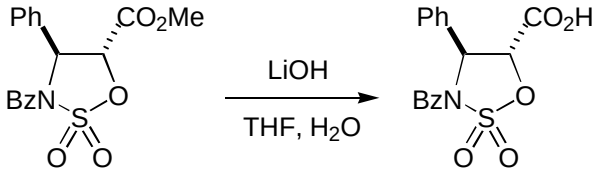
4-13 **4-11a** **4-10**

Since attempts towards the hydrolysis of the methyl ester in the presence of the mono-oxo-oxathiazolidine linkage failed, the sulfur was oxidized to the sulfone level of oxidation. This oxidation was also useful for further confirmation of the formation of the isomeric pairs **4-11a** and **4-11b** since separate oxidations of both isomers gave the same product, the 2,2-dioxo-1,2,3-oxathiazolidine (**4.14)**.



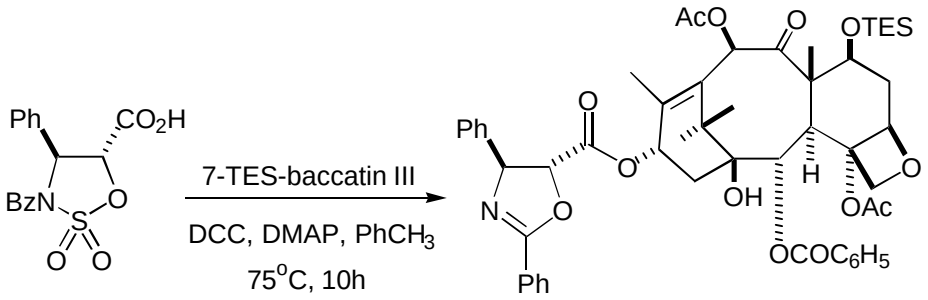
4-14

The methyl ester of the di-oxo compound was hydrolyzed to the corresponding carboxylic acid **4.15** in the presence of lithium hydroxide, and the stage was set for the coupling of **4.15** with baccatin III to give Taxol.



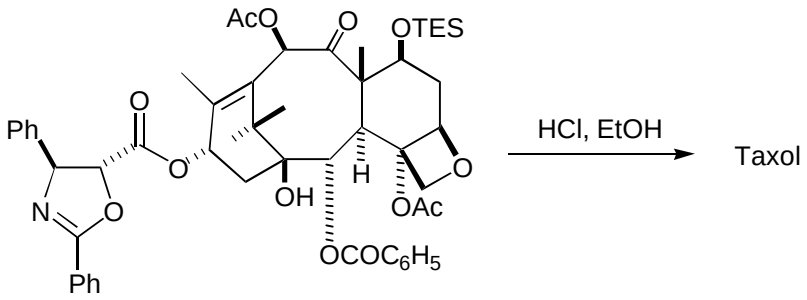
4-14 **4-15**

A dicyclohexylcarbodiimide (DCC) coupling of **4.15** to 7-triethylsilylbaccatin III in the presence of DMAP gave surprising results. During this process, the acid rearranged to the oxazoline derivative and completed the coupling to give **4.16**. The structure of **4.16** was assigned by comparison of its ^{1}H-NMR spectrum with the corresponding spectrum of the literature compound.[64]



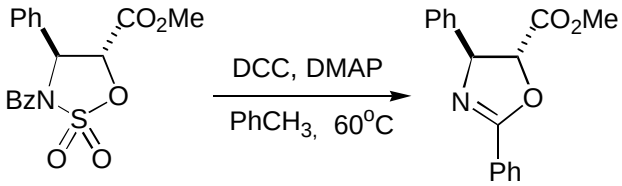
4-15 **4-16**

The unexpected product **4.16** was then converted to Taxol in the presence of hydrochloric acid, which is a known procedure.[6]



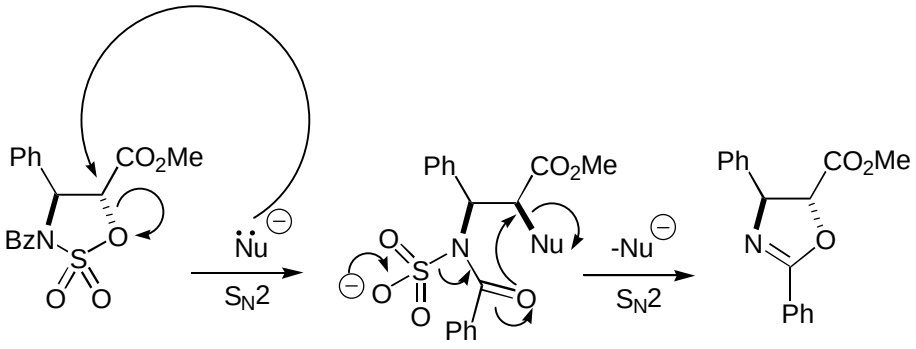
4-16

After this surprising result, a mechanistic study was performed. The methyl ester of the di-oxo compound **4.14** was subjected to the coupling conditions, but in the absence of 7-(triethylsilyl)-baccatin III. Conversion of the 2,2-dioxo-1,2,3-oxathiazolidine derivative **4.14** to *trans*-oxazoline **4.12** was observed.



4-14 **4-12**

4.4.2 Proposed mechanism for the formation of *cis* oxazoline (4.12)



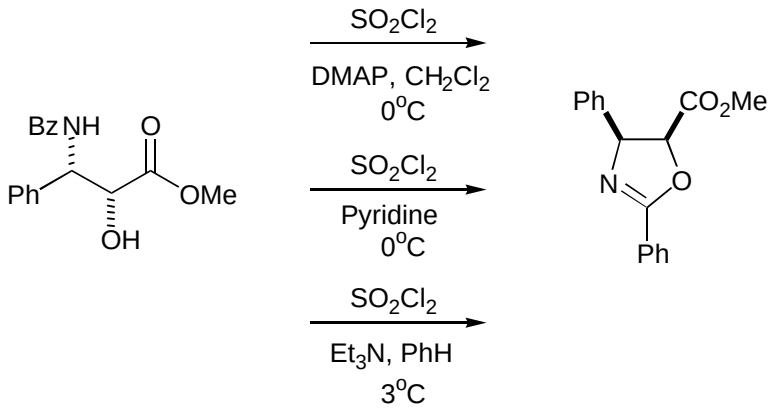
4-14a

The attack of the nucleophile on the C-2 position of **4.14**, gave **4.14a** by an S_N2 reaction, resulting inversion of configuration at this position. This is followed by intramolecular attack of the lone pair electrons of the carbonyl oxygen of the benzoyl group at C-2 with the driving force of the electrons of the negatively charged oxygen on sulfur would give the *cis* oxazoline, again by an S_N2 reaction, with overall retention of configuration.

4.5 Sulfuryl chloride approach

In order to prepare the 2,2-dioxo-1,2,3-oxathiazolidine **4.14** in one step from the methyl ester of the Taxol side chain (**4.10**), sulfuryl chloride was used as reagent. Sulfuryl chloride was introduced to the ester under the same conditions that were used for thionyl chloride. Again, the results were surprising, and the *cis*-oxazoline **4.17** was the unexpected product. The structure of product **4.17** was assigned with the help of ^{1}H-NMR, ^{13}C-NMR and mass spectral data. In particular, the coupling constant of the H_4 and H_5 protons ($J_{H4,\ H5}$ = 10.8 Hz) was consistent with that obtained by molecular modeling

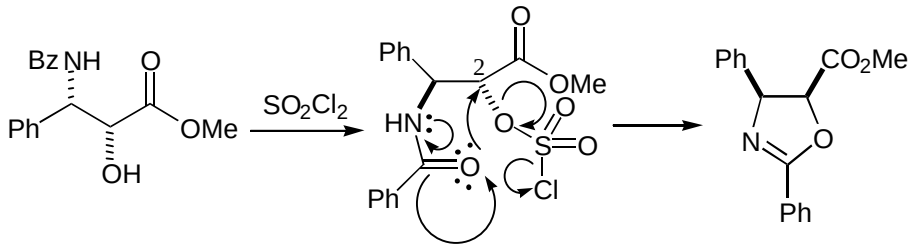
and Karplus correlation[75] for the *cis* isomer. Coupling between protons on vicinal carbon atoms depends on their dihedral angle ($\phi = H_4\text{-}C_4\text{-}C_5\text{-}H_5$). This angle was obtained from molecular modeling studies.



4-10 **4-17**

4.5.1 Proposed mechanism for the formation of *cis*-oxazoline (4.17)

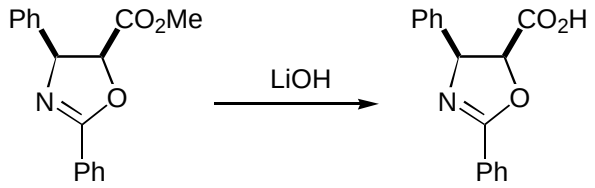
The nucleophilic addition of the -OH group to sulfuryl chloride, followed by intramolecular attack of the lone pair electrons of the carbonyl oxygen of the benzoyl group at C-2 would give the *cis* oxazoline.



4-10 **4-17**

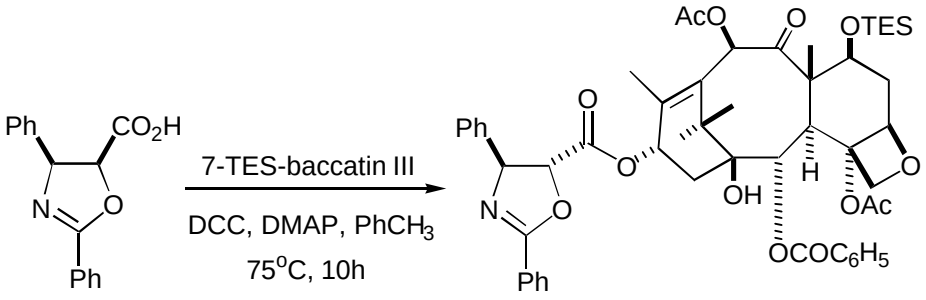
[75] Karplus, M., *J. Chem. Phys.*, **1959**, *30*, 11

The *cis*-oxazoline was then converted to its corresponding acid **4.18** in the presence of lithium hydroxide.



4-17 **4-18**

Even more surprising results were observed during the coupling of acid **4.18** with baccatin III. The *cis* oxazoline moiety was converted to the *trans* configuration in the product **4.16**.



4-18 **4-16**

The 2'-carbon thus undergoes epimerization during coupling and gives the *trans* oxazoline product.

4.5.2 Comparison of the ^{1}H-NMR Data

Table 4-2 Comparison of the ^{1}H-NMR data of methyl esters

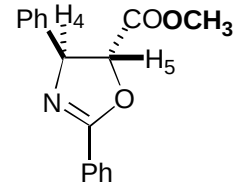
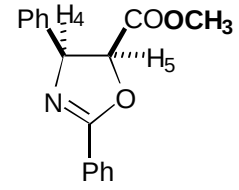
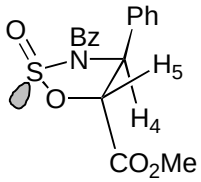
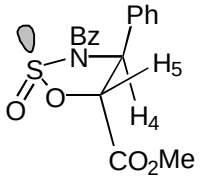
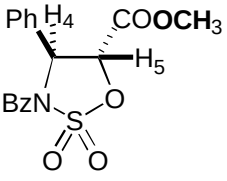
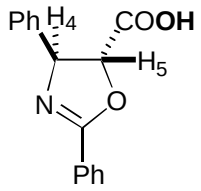
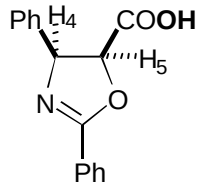
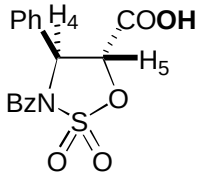
	H_4 (ppm)	H_5 (ppm)	-OCH_3 (ppm)	$J_{H4,H5}$ (Hz)
	5.47	4.93	3.87	6.4
	5.74	5.38	3.19	10.8
	5.69	5.66	3.84	8.8
	6.22	5.27	3.89	2.4
	6.03	5.16	3.87	8.4

Table 4-3 Comparison of the ^{1}H-NMR data of carboxylic acids

	H_4 (ppm)	**H_5 (ppm)**
	5.46	4.94
	5.74	5.38
	6.03	5.18

4.6 Reactions on Taxol

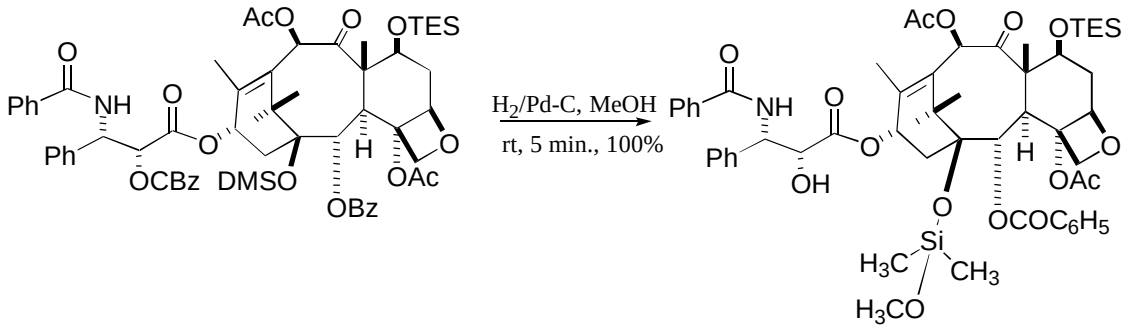
4.6.1 Synthesis of 2',3'-mono-oxo-oxathiazolidine-1-dimethylmethoxysilyl-7-triethylsilyl paclitaxel

Since the transformations and epimerizations of the protected side chains used in this study were unexpected, it was desired to compare material prepared by coupling protected side chains with 7-triethylsilylbaccatin III with material prepared directly and unambiguously from Taxol.

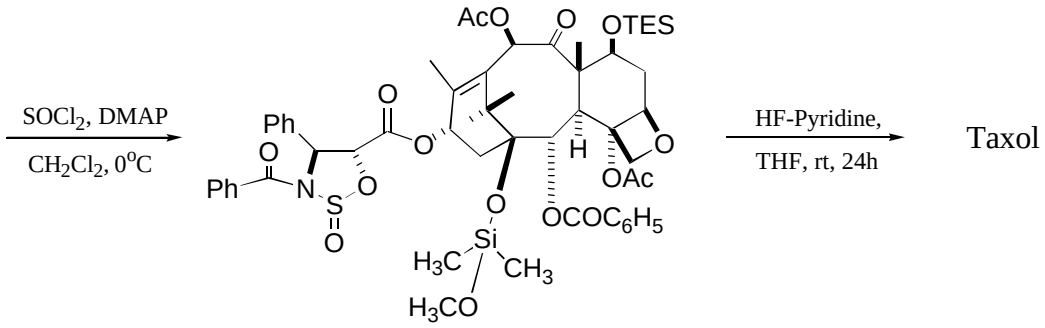
Thionyl chloride-DMAP conditions were thus used for the synthesis of the 2-oxo-1,2,3-oxathiazolidine protected side chain on the Taxol molecule. Because Taxol rearranges on treatment with thionyl chloride[76] it was necessary first to protect the C-1 hydroxyl group, with the dimethylsilyl protecting group. During the hydrogenation reaction for deprotection of the 2'-Cbz protecting group an unexpected product, 1-dimethylmethoxysilyl-7-triethylsilylpaclitaxel (**4.19**) was isolated.

Treatment of 1-dimethylmethoxysilyl-7-triethylsilylpaclitaxel (**4.19**) with thionyl chloride in the presence of DMAP gave the desired oxathiazolidine product **4.20** in high yield. This product was then hydrolyzed to Taxol by HF-pyridine in almost quantitative yield.

[76] Kingston, D. G. I., Chordia, M. D. unpublished results and Liang, X. PhD Dissertation, Virginia Tech **1996**



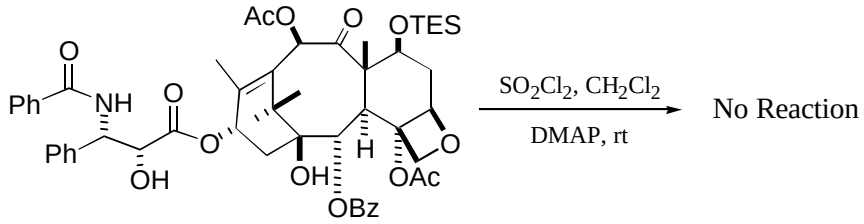
4-19



4-20

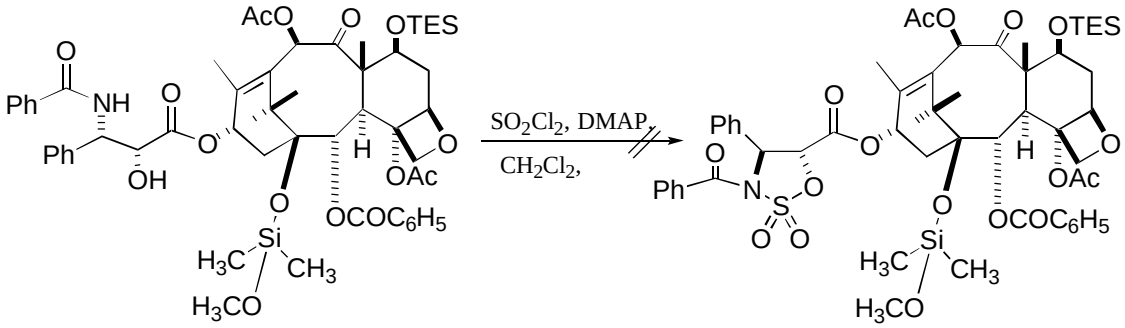
4.6.2 Sulfuryl chloride approach on Taxol

The reaction of Taxol with sulfuryl chloride, on the other hand, did not give the desired di-oxo-oxathiazolidine. The first attempt was to make the desired di-oxo product on 7-triethylsilylpaclitaxel (**4.21**), but this attempt did not work.

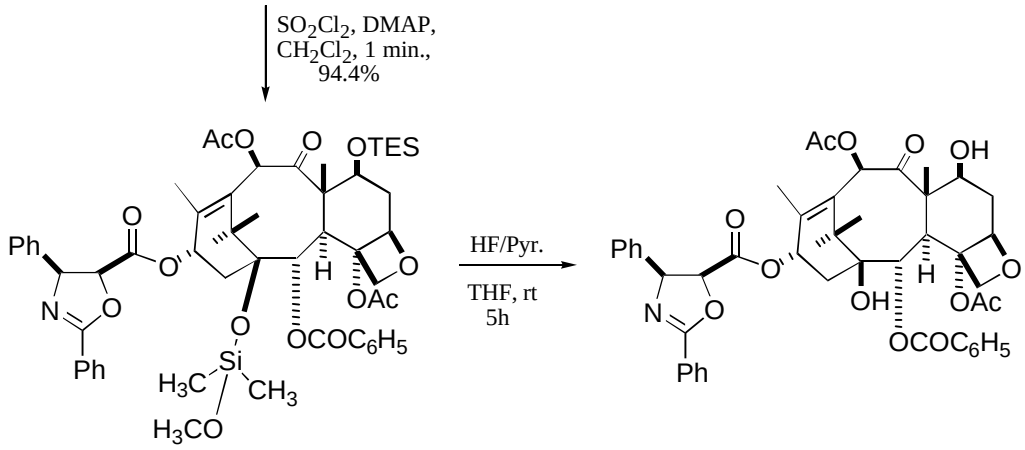


4-21

The reaction of sulfuryl chloride was then repeated with the 1-dimethylmethoxysilyl-7-triethylsilylpaclitaxel (**4.19**). This time the product was not the desired di-oxo-oxathiazolidine derivative (**4.22)**, but was instead the *cis*-oxazoline derivative of Taxol (**4.23)** which was then hydrolyzed by HF-pyridine to give (2'*S*,3'*S*)-oxazoline-paclitaxel (**4.24**). The coupling constant of the $H_{2'}$ and $H_{3'}$ protons ($J_{H2', H3'}$ = 10.8 Hz) of compound **4.24** was consistent with the *cis* oxazoline methyl ester **4.17** isolated earlier.



4-20 **4-22**



4-23 **4-24**

4.7 Conclusions

The chemistry performed allows the synthesis of the important anticancer drug, Taxol, from commercially available and fairly inexpensive starting materials and reagents and provides an alternate route to the literature routes described earlier.

With the reactions on Taxol, new Taxol analogs were isolated, and their spectral data were used for the comparison of the previously isolated Taxol analogs throughout this study.

The unexpected rearrangement of the di-oxo-oxathiazolidine side chain (**4.16**) to the coupled oxazoline derivative **4.17** prevented this work from defining a truly novel synthesis, but this problem could perhaps be circumvented by the use of different conditions or by devising a method to prepare the oxathiozolidine carboxylic acid **4.13** and couple it with a protected baccatin III derivative.

5. Experimental Section

5.1.1 General Methods:

Chemicals were obtained from Aldrich Chemical Co. and were used without further purification, unless otherwise noted. Thionyl chloride was obtained from Acros Chemical Co. All anhydrous reactions were performed in oven-dried glassware under argon. Tetrahydrofuran (THF) was distilled over sodium/benzophenone, dichloromethane was distilled over calcium hydride, and toluene was distilled over sodium prior to use. All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates (silica gel 60 GF, aluminum back) and analyzed with 254 nm UV light and/or vanillin/sulfuric acid spray and/or iodine vapor. Silica gel for column chromatography was purchased from E. Merck (230-400 mech). Preparative thin layer chromatography (PTLC) plates (silica gel 60 GF) were purchased from Analtech. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ or CD_3OD on Varian Unity 400 spectrometer (operating at 399.951 MHz for ^{1}H and 100.578 MHz for ^{13}C) and were assigned by comparison of chemical shifts and coupling constants with those of related compounds. Chemical shifts were reported as δ-values relative to tetramethylsilane (TMS) as internal reference, and coupling constants were reported in Hertz. Mass spectra (HRFABMS and LRFABMS) were obtained at Nebraska Center for Mass Spectrometry, University of Nebraska. CIMS data were obtained in the Department of Chemistry, Virginia Tech.

The phrase "worked-up in the usual way" refers to diluting the reaction mixture with an excess amount of organic solvent, washing with water and brine, drying over anhydrous sodium sulfate and evaporating the solvent in *vacuo* unless otherwise noted.

Compounds 4-1a, 4-1b, 4-10, 7-TES-baccatin III, 1-DMS-7-TES-2'CBz-Taxol and 7-TES-Taxol were prepared following the procedures that are reported in the literature, and NMR data of these compounds were identical to those in literature.

Mono-protected boronate [4-2]

To a stirred solution of 20.0 mg (0.076 mmol) of **4-1a** in benzene (1.0 ml) was added 18.0 mg (0.146 mmol) phenylboronic acid, and the mixture was refluxed 5 h under argon in the presence of powdered 4^{o}A molecular sieves. TLC showed the formation of a single product and there was no starting material left. The reaction mixture was filtered and applied on a PTLC plate (10% EtOAc/CH_2Cl_2) and the product was isolated in 35% yield. After recrystallization from EtOAc/Hexane, the new compound was identified as (**4.2**).

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.3-7.8 (m, 10H), 6.97 (d, 1H), 5.91 (m, 1H), 5.41 (d, 1H), 5.22 (d, 1H), 4.49 (dd, 1H), 2.22 (s, 1H)

^{13}C NMR ($CDCl_3$, TMS, 400 MHz) δ 137.25, 131.66, 128.84, 128.62, 127.81, 127,03, 126.82, 116.74, 75.51, 57,66

CIMS $(M+H)^+$ *m*/*z* 268

Cyclic boronate [4-3]

Compound (**4.2**) (10 mg, 0.037 mmol) was refluxed in benzene (2 ml) in the presence of 1 mg camphor sulfonic acid (CSA). The desired product (**4.3**) was isolated in 25% yield after PTLC purification (10% EtOAc/CH_2Cl_2).

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.3-8.1(m, 10H), 6.09 (m, 1H), 5.38 (dt, 1H), 5.33 (dt, 1H), 5.02 (d, 1H), 4.87 (tt, 1H)

CIMS $(M+H)^+$ *m*/*z* 250

Model studies towards the synthesis of cyclic boronate

To a stirred solution of 50.0 mg of (1*R*, 2*S*)-2-amino-1,2-diphenylethanol (**4.4**) (0.234 mmol) in benzene (2.0 ml) was added 57.0 mg (0.467 mmol) phenylboronic acid and the mixture was refluxed 10 h. under argon in the presence of powdered 4^{o}A molecular sieves. TLC analysis showed that no reaction occured. The same reaction was also tried using dichloromethane as the solvent and camphor sulfonic acid as the catalyst, but again no reaction was observed.

4,5-diphenyl-1,3-oxazolidine-2-thione [4-5]

To a stirred solution of 100.0 mg (1*R*,2*S*)-2-amino-1,2-diphenylethanol (0.469 mmol) in dry dichloromethane (3.0 ml) was added a catalytic amount of 4-(dimethylamino)-pyridine. The mixture was stirred for 5 min. and then thiophosgene (0.070 g, 0.469 mmol) was introduced at room temperature. After 5 min. TLC showed the formation of the product and the disappearance of the starting material. The reaction mixture was applied directly on a the PTLC plate (10% EtOAc/CH_2Cl_2) and the desired product was isolated in 55% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 6.9-7.13 (m, 10H), 6.17 (d, 1H, *J* = 8.8 Hz), 5.34 (d, 1H, *J* = 8.8 Hz)

CIMS $(M+H)^+$ *m*/*z* 256

Cyclic 1,3-oxazolidine-2-thione derivative [4-7b] of compound [4-1b].

To a stirred solution of 100.0 mg (0.380 mmol) starting material (**4-1b**) was added 0.111 g (0.912 mmol) of 4-(dimethylamino)-pyridine, and the mixture was stirred for 5 min. Thiophosgene (0.057g, 1 eq.) was then introduced at -10 ^oC. The reaction mixture was allowed to warm to room temperature and after 5 h. TLC showed that the reaction was completed. The reaction mixture was filtered through Celite and was applied on PTLC plate (10% EtOAc/CH_2Cl_2) and the product was isolated in 15% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.2-7.4 (m, 10H), 5.91 (dd, 1H), 5.67 (m, 1H), 5.29 (2H), 4.82 (bs, 1H), 3.62 (d, 2H), 1.43 (s, 9H)

CIMS $(M+H)^+$ *m*/*z* 342

Cyclic 1,3-oxazolidine-2-thione derivative [4-7a] of compound [4-1a].

To a stirred solution of 100.0 mg (0.380 mmol) starting material (**4-1a**) was added 0.111 g (0.912 mmol) of 4-(dimethylamino)-pyridine, and the mixture was stirred for 5 min. Thiophosgene (0.057g, 1 eq.) was then introduced at -10 ^oC. The reaction mixture was allowed to warm to room temperature and after 5 h. TLC showed that the reaction was completed. The reaction mixture was filtered through Celite and was applied on PTLC plate (10% EtOAc/CH_2Cl_2) and the product was isolated in 20% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.3-7.8 (m, 10H), 6.38 (d, 1H), 6.05 (dd, 1H), 5.85 (t, 1H), 5.75 (m, 1H), 3.62 (dd, 2H)

^{13}C NMR ($CDCl_3$, TMS, 400 MHz) δ 166.43, 165.29, 139.94, 135.00, 134.04, 131.76, 128.99, 128.64, 128.05, 127.23, 126.96, 124.37, 54.48, 35.45

CIMS $(M+H)^+$ *m*/*z* 346

1-Vinyl-2-phenyl-(1*R*,2*S*)-2-aminoethanol [4-9].

To a stirred solution of 100.0 mg (0.38 mmol) of compound (**4-1a**) in CH_2Cl_2 (3 ml) was added formic acid (1 ml) and the solution stirred at room temperature for 3 h.

During the work-up with ethyl acetate in the usual way the reaction mixture was basified with saturated aqueous sodium bicarbonate solution and concentrated to give the desired amino alcohol in 50% yield.

5-Vinyl-4-phenyl-1,3-oxazolidine-2-thione [4-9.1].

To a stirred solution of 30.0 mg (0.18 mmol) starting material (**4.9**) was added 0.065 g (0.54 mmol) of 4-(dimethylamino)-pyridine, and the mixture was stirred for 5 min. at room temperature. Thiophosgene (1 eq) was then introduced. TLC analysis showed the completion of the reaction in 1 min. The reaction mixture was applied directly on PTLC plate and the desired product was isolated I 35% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.7 (bs, 1H), 7.3-7.41 (m, 10H), 6.01 (m, 1H), 5.41 (d, 1H), 5.39 (d, 1H), 5.00 (t, 1H), 4.79 (d, 1H)

CIMS $(M+H)^+$ *m*/*z* 206

5-Vinyl-4-phenyl-3-*N*-^{t}BOC-1,3-oxazolidine-2-thione [4-9.2].

To a stirred solution of 10 mg (0.048 mmol) starting material (**4-9.1**) in CH_2Cl_2 (1 ml) was added DMAP (3 eq) and the mixture stirred for 5 min at room temperature. Di-*tert*-butyl-dicarbonate (2 eq) was then introduced. TLC analysis showed the disappearance of the starting material in 1 min. The reaction mixture was applied directly on a PTLC plate (20% EtOAc/Hexanes) and the desired product was isolated in 85% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.24-7.41 (m, 5H), 5.99 (m, 1H), 5.44 (d, 1H), 5.40 (s, 1H), 5.41 (d, 1H), 4.87 (t, 1H), 1.26 (s, 9H)

CIMS $(M+H)^+$ *m*/*z* 306

3-*N*-Benzoyl-4,5-diphenyl-1,3-oxazolidine-2-thione [4-5.1].

To a stirred solution of 25 mg (0.098 mmol) of starting material (**4.5**) in CH_2Cl_2 (1 ml) were added DMAP (cat.) and diisopropylethylamine (3 eq, 0.05 ml) at room temperature. The reaction mixture was then cooled to -10 ^oC where benzoyl chloride (1.5 eq, 0.017 ml) was introduced dropwise. TLC showed the completion of the reaction. The desired product was isolated in 90% yield after the application of the reaction mixture directly on a PTLC plate (20% EtOAc/Hexanes).

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 6.94-8.14 (m, 15H), 6.15 (d, 1H), 5.93 (d, 1H)

^{13}C NMR ($CDCl_3$, TMS, 400 MHz) δ 187.08, 170.22, 133.74-126.28, 84.92, 68.10

CIMS $(M+H)^+$ *m*/*z* 360

3-*N*-^{t}BOC-4,5-Diphenyl-1,3-oxazolidine-2-thione [4-5.2].

To a stirred solution of 10 mg (0.048 mmol) starting material (**4.5**) in CH_2Cl_2 (1 ml) was added DMAP (3 eq) and the mixture stirred for 5 min at room temperature. Di-*tert*-butyl-dicarbonate (2 eq) was then introduced. TLC analysis showed the disappearance of the starting material in 1 min. The reaction mixture was applied directly on PTLC plate (20% EtOAc/Hexanes) and the desired product was isolated in 88% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 6.81-7.14 (m, 10H), 6.01 (d, 1H), 5.66 (d, 1H)

CIMS $(M+H)^+$ *m*/*z* 356

1,2-Diphenyl-(1*R*,2*S*)-2-*N*-^{t}BOC-aminoethanol [4-5.3].

To a stirred solution of 10 mg starting material (**4-5.2**) in THF (1 ml) was introduced 1N LiOH solution at -10 ^oC. After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature where it was stirred for 24 h. TLC analysis showed the formation of a product. After the work-up, the usual way, the

crude product was applied on a PTLC plate (10% EtOAc/CH_2Cl_2) and the desired product was isolated in 57% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.02-7.39 (m, 10H), 5.30 (bs, 1H), 4.95-5.15 (2H), 2.65 (bs, 1H), 1.39 (s, 9H)

CIMS $(M+H)^+$ *m*/*z* 314

(4*S*,5*R*)-2,4-diphenyl-5-(methoxycarbonyl)-2-oxazoline [4-12].

To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-3-phenylisoserine methyl ester (25 mg, 0.08 mmol) in CH_2Cl_2 was added DMAP (7 eq). The reaction mixture was then cooled down to 0 ^oC where thionyl chloride (3 eq) was introduced dropwise. The product was isolated in 10% yield after work-up in the usual way and purification via PTLC (40%EtOAc/Hexanes).

When the reaction conditions were changed to thionyl chloride/pyridine, the yield of the reaction was increased to 53%. ^{1}H NMR, ^{13}C NMR and mass spectral data were identical with literature data.[72]

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.4 (m, 10H), 5.47 (d, 1H, *J* = 6.4 Hz), 4.93 (d, 1H, *J* = 6.4 Hz), 3.87 (s, 3H)

^{13}C NMR ($CDCl_3$, TMS, 400 MHz) δ 163.8, 141.0, 131.8, 128.7, 128.6, 128.3, 126.6, 126.4, 126.3, 83.0, 74.5, 52.6

CIMS $(M+H)^+$ *m*/*z* 282

3-*N*-benzoyl-4-phenyl-(4*S*,5*R*)-2-oxo-1,2,3-oxathiazolidine methyl esters [4-11a] and [4-11b].

To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-3-phenylisoserine methyl ester (100 mg, 0.33 mmol) in anhydrous benzene (4 ml) under argon, was added triethylamine (5 eq, 0.2 ml) and the mixture stirred for 5 min at room temperature. The reaction mixture was then cooled to 3 ^oC where thionyl chloride (4 eq, 1.336 mmol, 0.1 ml in 0.2 ml benzene) diluted in benzene was introduced dropwise over 15 minutes. TLC immediately showed the formation of 3 new compounds, along with the starting material; one of the products was the major product (**4-11a**), while one was intermediate (**4-11b**) and one was very minor

(or on some occasions) absent (**4-12**). After work-up in the usual way with ethyl acetate and saturated aqueous sodium bicarbonate, ethanol was added to the crude product to yield the major (**4-11a**)(ethanol-insoluble) product in pure form. The rest of the crude product was subjected to PTLC purification (40% EtOAc/Hexanes) to purify the other products. The two major products were identified by their spectral data as two oxathiazolidine isomers.

A total yield of 82% was obtained for both isomers of the oxathiazolidines, with 68% being the major product, 14% as the secondary product, and less then 3% being oxazoline.

Major product (**4-11a**):

Molecular Formula: $C_{17}H_{15}NO_5S$

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.35-7.74 (m, 10H), 5.69 (d, 1H, *J* = 8.8 Hz), 5.66 (d, 1H, *J* = 8.8 Hz), 3.84 (s, 3H)

^{13}C NMR ($CDCl_3$, TMS, 400 MHz) δ 167.65, 166.69, 135.517, 134.045, 132.71, 129.05, 128.91, 128.76, 127.99, 86.14, 63.40, 53.34

HRFABMS *m*/*z* 345.0746 (calcd for $C_{17}H_{15}NO_5S$, 345.0671), **LRFABMS** $(M+H)^+$ *m*/*z* 346

Secondary product (**4-11b**):

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.35-7.67 (m, 10H), 6.224 (d, 1H, *J* = 2.4 Hz), 5.273 (d, 1H, *J* = 2.4 Hz), 3.89 (s, 3H)

3-*N*-Benzoyl-4-phenyl-(4*S*,5*R*)-2,2-dioxo-1,2,3-oxathiazolidine methyl ester [4-14]

To a stirred solution of the oxathiazolidine (**4-11a** or **4-11b**) in $CH_3CN/CCl_4/H_2O$ (1:1:2) solvent system at room temperature was added an excess amount of $NaIO_4$ and a catalytic amount of $RuCl_3$. The reaction mixture was stirred for 45 min. The reaction mixture was filtered through sand/Celite/silica gel and after work-up in the usual way with EtOAc, the crude product was isolated via PTLC (40% EtOAc/Hexanes) in 91% yield. The same product was obtained from both (**4-11a)** and (**4-11b**).

Molecular Formula: $C_{17}H_{15}NO_6S$

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.38-7.83 (m, 10H), 6.03 (d, 1H, *J* = 8.4 Hz), 5.16 (d, 1H, *J* = 8.4 Hz), 3.87 (s, 3H)

^{13}C NMR ($CDCl_3$, TMS, 400 MHz) δ 166.49, 164.73, 135.07, 133.41, 132.47, 129.56, 129.28, 128.71, 128.46, 127.25, 78.38, 62.98, 53.71

HRFABMS *m*/*z* 361.0699 (calcd for $C_{17}H_{15}NO_6S$, 361.0620), **LRFABMS** $(M+H)^+$ *m*/*z* 362.0

3-*N*-Benzoyl-4-phenyl-(4*S*,5*R*)-2,2-dioxo-1,2,3-oxathiazolidine carboxylic acid. [4-15]

To a stirred solution of 40 mg (0.11 mmol) starting material (**4.14**) in THF (2 ml) was added 500 µL water and the mixture stirred for 5 min. LiOH (3 eq, 8 mg, 0.33 mmol) was then introduced and the reaction mixture was stirred for 45 min. When the TLC showed the disappearance of starting material, the reaction mixture was diluted with EtOAc, acidified with dil. HCl and usual work-up procedure was performed. The crude product was applied on a PTLC plate (10% MeOH/CH_2Cl_2) in order to give the desired acid in 92% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.38-7.79 (m, 10H), 7.14 (bs, 1H), 6.03 (d, *J* = 8.0 Hz), 5.18 (d, 1H, *J* = 8.0 Hz)

^{13}C NMR ($CDCl_3$, TMS, 400 MHz) δ 167.60, 166.79, 135.06, 133.49, 132.31, 129.62, 129.29, 128.75, 128.43, 127.31, 78.16, 62.89

Acylation of 7-triethylsilylbaccatin III with acid (4.15) and isolation of (2'*S*,3'*R*)-oxazoline-7-triethylsilylpaclitaxel [4.16].

To a stirred emulsion of the acid (**4.15**) in anhydrous toluene was added 1 eq of DMAP, 4 eq of DCC and the mixture stirred under argon for 5 minutes. 7-triethylsilylbaccatin III (0.25 eq) was then introduced and the reaction mixture was warmed to 75^{o}C and stirred overnight. TLC showed the formation of a new product. The work-up was performed in the usual way with EtOAc after the filtration of the reaction mixture through Celite. The product (**4.16**) was isolated via PTLC (40%EtOAc/Hexane) in 30% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.37-8.23 (m, 15H), 6.42 (s, 1H, H_{10}), 6.18 (t, 1H, H_{13}), 5.68 (d, 1H, $H_{3'}$), 5.60 (d, 1H, H_2), 4.93-4.96 (m, 2H, $H_{2',5}$), 4.50 (dd, 1H, H_7), 4.29 (d, 1H, H_{20}), 4.14 (d, 1H, H_{20}), 3.84 (d, 1H, H_3), 2.54 (m, 1H, H_6), 2.23-2.40 (m, 2H, $H_{14,14}$), 2.16 (s, 3H, $Me_{4\text{-}Ac}$), 2.08 (s, 3H, $Me_{10\text{-}Ac}$), 2.06 (t, 1H, H_6), 1.68 (s, 3H, Me_{18}),

1.58 (s, 3H, Me_{19}), 1.24 (s, 3H, Me_{17}), 1.19 (s, 3H, Me_{16}), 0.92 (t, 9H, 3x$Me_{7\text{-TES}}$), 0.56 (q, 6H, 3x$CH_{2\ 7\text{-TES}}$),

HRFABMS $(M+H)^+$ *m/z* 950.4166 (calcd for $C_{53}H_{63}NO_{13}Si$, 949.4070), **LRFABMS** $(M+H)^+$ *m/z* 950.5

Conversion of 3-*N*-benzoyl-4-phenyl-(4*S*,5*R*)-2,2-dioxo-1,2,3-oxathiazolidine methyl ester (4-14) to (4*S*,5*R*)-2,4-diphenyl-5-(methoxycarbonyl)-2-oxazoline (4-12).

To a stirred emulsion of 10 mg compound **4.14** in anhydrous toluene was added 1 eq of DMAP, 4 eq of DCC and the mixture stirred under argon for 5 minutes. 7-triethylsilylbaccatin III (0.25 eq) was then introduced and the reaction mixture was warmed to 60 ^oC and stirred overnight. TLC showed the formation of a new product. The work-up was performed in the usual way with EtOAc after the filtration of the reaction mixture through Celite. The product (**4.12**) was isolated via PTLC (40%EtOAc/Hexane) in 20% yield.

Spectral data are shown above.

(4*S*,5*S*)-2,4-diphenyl-5-(methoxycarbonyl)-2-oxazoline [4-17].

To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-3-phenylisoserine methyl ester (25 mg, 0.08 mmol) in CH_2Cl_2 was added DMAP (7 eq). The reaction mixture was then cooled to 0 ^oC and sulfuryl chloride (3 eq) was introduced dropwise. The product, isolated after work-up in the usual way and purification via PTLC in 65% yield, was the *cis*-oxazoline (**4.17**).

The same product was also isolated when the reaction conditions were changed to sulfuryl chloride/pyridine or sulfuryl chloride/triethylamine/benzene.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.22-8.11 (m, 10H), 5.74 (d, 1H, *J* = 10.8 Hz), 5.38 (d, 1H, *J* = 10.8 Hz), 3.198 (s, 3H)

^{13}C NMR ($CDCl_3$, TMS, 400 MHz) δ 168.45, 164.73, 136.86, 131.92, 128.66, 128.41, 128.11, 128.06, 127.70, 126.69, 81.04, 73.45, 51.54

CIMS $(M+H)^+$ *m/z* 282

(4*S*,5*S*)-2,4-diphenyl-2-oxazoline-carboxylic acid [4-18].

To a stirred solution of the 40 mg (0.11 mmol) starting material (**4.17**) in EtOH (2 ml) was added 500 µl water and stirred for 5 min. 3 eq of LiOH (8 mg, 0.33 mmol) was then introduced and the reaction mixture was stirred for 45 min. When the TLC showed the disappearance of starting material, the reaction mixture was diluted with EtOAc, acidified with dil. HCl and the usual work-up procedure was performed. The crude product was applied on a PTLC plate (10% MeOH/CH_2Cl_2) to give the desired acid in 92% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.22-8.11 (m, 10H), 5.74 (d, 1H) 5.38 (d, 1H), **CIMS** $(M+H)^+$ *m*/*z* 268

1-dimethylmethoxysilyl-7-triethylsilylpaclitaxel [4-19].

To a stirred solution of 70 mg 2'-Cbz-1-dimethylsilyl-7-triethylsilylpaclitaxel in 5 ml methanol was added catalytic amount of 5% palladium on activated carbon (Pd-C) and the reaction mixture was stirred under hydrogen atmosphere for 5 min. TLC analysis showed the formation of a new product and disappearance of the starting material. The reaction mixture was then filtered through silica gel, concentrated and applied on a PTLC plate (40% EtOAc/Hexanes) to give the product in almost quantitative yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.34-8.14 (m, 15H), 7.01 (d, 1H, 3'-NH), 6.41 (s, 1H, H_{10}), 6.22 (t, 1H, H_{13}), 5.85 (d, 1H, $H_{3'}$, J = 8.8 Hz), 5.76 (d, 1H, H_2), 4.91 (d, 1H, $H_{2'}$, J = 8.8 Hz), 4.82 (s, 1H, H_5), 4.41 (dd, 1H, H_7), 4.27 (d, 1H, H_{20}), 4.22 (d, 1H, H_{20}), 3.80 (d, 1H, H_3), 3.05 (s, 3H, -OMe), 2.50-2.52 (m, 2H, H_6 and H_{14}), 2.41 (s, 3H, $Me_{4\text{-}Ac}$), 2.39 (m, 1H, H_{14}), 2.17 (s, 3H, $Me_{10\text{-}Ac}$), 1.92 (s, 3H, Me_{18}), 1.88 (t, 1H, H_6), 1.68 (s, 3H, Me_{19}), 1.23 (s, 3H, Me_{17}), 1.16 (s, 3H, Me_{16}), 0.91 (t, 9H, $3xMe_{7\text{-}TES}$), 0.56 (q, 6H, $3xCH_{2\ 7\text{-}TES}$), -0.146 (s, 3H, $Me_{1\text{-}Si}$), -0.236 (s, 3H, $Me_{1\text{-}Si}$)

Molecular Formula:

HRFABMS *m*/*z* 1056.4571 (calcd for $C_{56}H_{73}NO_{15}Si_2$, 1055.4519), **LRFABMS** $(M+H)^+$ *m*/*z* 1056.5

2',3'-Oxo-oxathiozilidine-1-dimethylmethoxysilyl-7-triethylsilylpaclitaxel [4-20].

To a stirred solution of 1-dimethylmethoxysilyl-7-triethylsilylpaclitaxel (12 mg) in CH_2Cl_2 was added 3 eq of DMAP and stirred for 5 min. Thionyl chloride (2 eq) was then introduced at 0 ^oC. TLC showed the formation of a new compound in 1 min. 8 mg of the desired product along with 2 mg of starting material isolated via PTLC (40% EtOAc/Hexanes) in 66% yield after the work-up in the usual way with EtOAc.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.44-8.05 (m, 15H), 6.41 (s, 1H, H_{10}), 6.29 (t, 1H, H_{13}), 5.78 (d, 1H, $H_{3'}$, J = 9.6 Hz), 5.73 (d, 1H, H_2), 5.69 (d, 1H, $H_{2'}$, J = 9.6 Hz), 4.85 (d, 1H, H_5), 4.40 (dd, 1H, H_7), 4.20 (d, 1H, H_{20}), 4.16 (d, 1H, H_{20}), 3.75 (d, 1H, H_3), 3.07 (s, 3H, -OMe), 2.40-2.50 (m, 2H, H_6 and H_{14}), 2.28 (d, 1H, H_{14}), 2.18 (s, 3H, $Me_{4\text{-}Ac}$), 2.02 (s, 3H, $Me_{10\text{-}Ac}$), 1.91 (s, 3H, Me_{18}), 1.85 (t, 1H, H_6), 1.65 (s, 3H, Me_{19}), 1.23 (s, 3H, Me_{17}), 1.18 (s, 3H, Me_{16}), 0.9 (t, 9H, 3x$Me_{7\text{-}TES}$), 0.55 (q, 6H, 3x$CH_{2\ 7\text{-}TES}$), -0.056 (s, 3H, $Me_{1\text{-}Si}$), -0.214 (s, 3H, $Me_{1\text{-}Si}$)

Molecular Formula: $C_{56}H_{71}NO_{16}SSi_2$

HRFABMS *m/z* 1101.4083 (calcd for $C_{56}H_{71}NO_{16}SSi_2$, 1101.4032), **LRFABMS** $(M+H)^+$ *m/z* 1101.5

Deprotection of 2',3'-oxo-oxathiozilidine-1-dimethylmethoxysilyl-7-triethylsilyl paclitaxel (4.20)

To a stirred solution of 5 mg ($4.5x10^{-3}$ mmol) compound (**4.20**) in THF, in a Teflon vial was added dropwise 8μL of HF-pyridine via a plastic syringe at room temperature. The reaction was allowed to stir at room temperature for 24 h. TLC analysis showed the disappearance of the starting material. After the work-up with EtOAc, $NaHCO_3$, H_2O, the crude product was applied on a PTLC plate (40% EtOAc/Hexanes) to give Taxol, identical with the natural product in all respects, in 53% yield along with 7-TES-Taxol (13% yield).

(2'*S*,3'*S*)-Oxazoline-1-dimethylmethoxysilyl-7-triethylsilylpaclitaxel [4-23].

To a stirred solution of 1-dimethylmethoxysilyl-7-triethylsilylpaclitaxel (10 mg) in CH_2Cl_2 was added 3 eq of DMAP and the mixture stirred for 5 min. Sulfuryl chloride (2 eq) was then introduced at 0 ^oC. TLC showed the formation of a new compound. The product was isolated via PTLC (40% EtOAc/Hexanes) in 95% yield after the work-up in the usual way with EtOAc.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.29-8.13 (m, 15H), 6.30 (s, 1H, H_{10}), 5.80 (d, 1H, $H_{3'}$, *J* = 10.8 Hz), 5.69 (d, 1H, H_2), 5.53 (t, 1H, H_{13}), 5.45 (d, 1H, $H_{2'}$, *J* = 10.8 Hz), 4.91 (d, 1H, H_5), 4.35 (dd, 1H, H_7), 4.24 (d, 1H, H_{20}), 4.17 (d, 1H, H_{20}), 3.66 (d, 1H, H_3), 3.06 (s, 3H, -OMe), 2.49 (m, 1H, H_6), 2.37 (m, 1H, H_{14}), 2.29 (s, 3H, $Me_{4\text{-}Ac}$), 2.15 (s, 3H, $Me_{10\text{-}Ac}$), 2.12 (d, 1H, H_{14}), 1.86 (t, 1H, H_6), 1.64 (s, 3H, Me_{18}), 1.48 (s, 3H, Me_{19}), 1.16 (s, 3H, Me_{17}), 0.98 (s, 3H, Me_{16}), 0.93 (t, 9H, 3x$Me_{7\text{-}TES}$), 0.58 (q, 6H, 3x$CH_{2\ 7\text{-}TES}$), -0.13 (s, 3H, $Me_{1\text{-}Si}$), -0.22 (s, 3H, $Me_{1\text{-}Si}$)

HRFABMS *m/z* 1044.4621 $(M+Li)^+$ (calcd for $C_{56}H_{71}NO_{14}Si_2$, 1037.4414) **LRFABMS** *m/z* 1037.5

(2'*S*,3'*S*)-Oxazolinepaclitaxel [4-24].

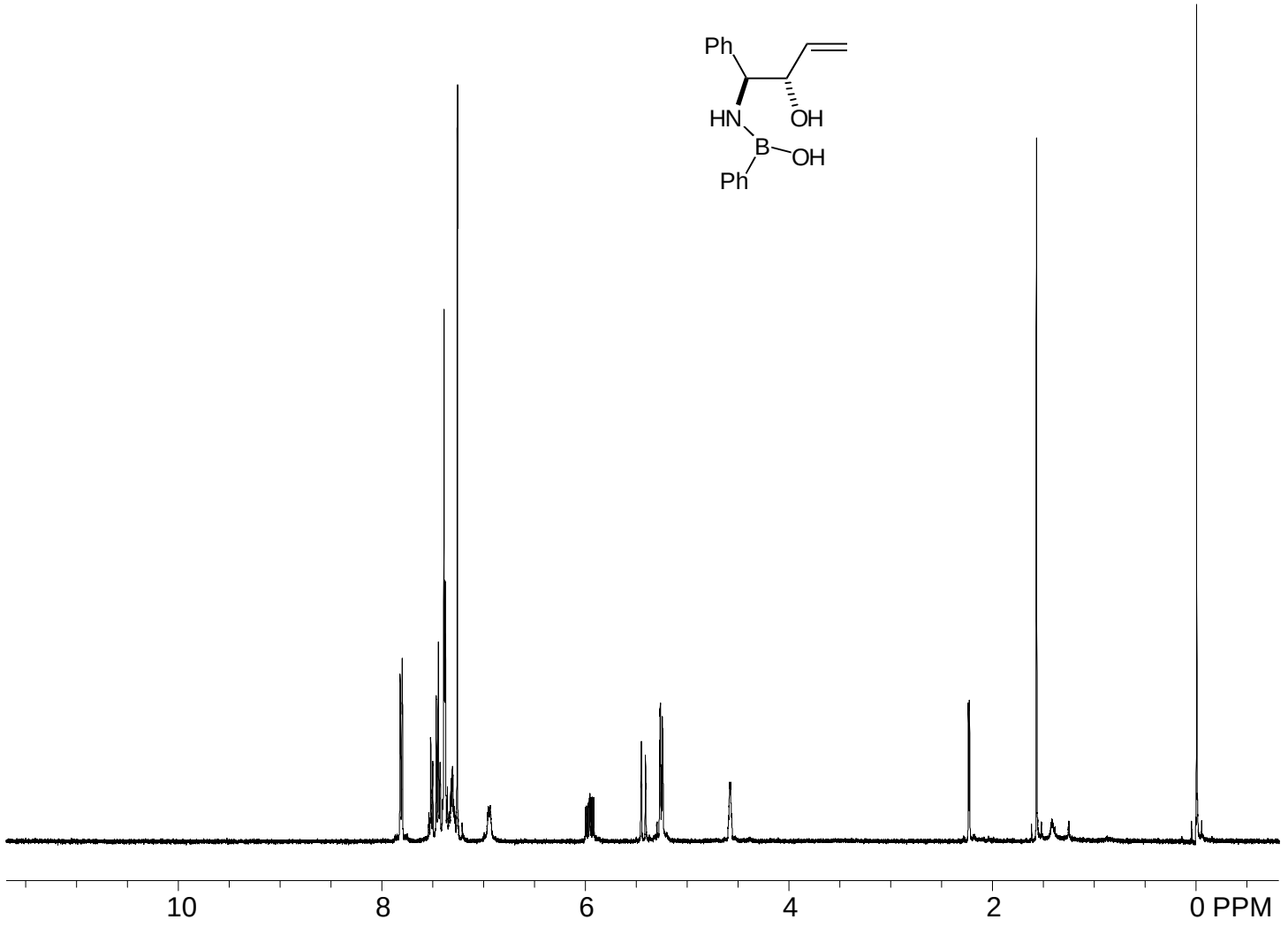
To a stirred solution of 7 mg ($6.8x10^{-3}$ mmol) compound (**4.23**) in THF, in a Teflon vial was added dropwise 5μL of HF-pyridine via a plastic syringe at room temperature. The reaction was allowed to stir at room temperature for 5 h. TLC analysis showed the disappearance of the starting material. After the work-up with EtOAc, $NaHCO_3$, H_2O, the crude product was applied on a PTLC plate (40% EtOAc/Hexanes) to give (**4.24**), in 53% yield.

^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.30-8.13 (m, 15H), 6.15 (s, 1H, H_{10}), 5.80 (d, 1H, $H_{3'}$, *J* = 10.8 Hz), 5.71 (t, 1H, H_{13}), 5.59 (d, 1H, H_2), 5.45 (d, 1H, $H_{2'}$, *J* = 10.8 Hz), 4.93 (d, 1H, H_5), 4.36 (m, 1H, H_7), 4.26 (d, 1H, H_{20}), 4.12 (d, 1H, H_{20}), 3.64 (d, 1H, H_3), 2.55 (m, 1H, H_6), 2.44 (s, 1H, 7-OH), 2.228 (s, 3H, $Me_{4\text{-}Ac}$), 2.225 (s, 3H, $Me_{10\text{-}Ac}$), 1.97 (d, 1H, H_{14}), 1.95 (d, 1H, H_{14}), 1.85 (t, 1H, H_6), 1.63 (s, 3H, Me_{18}), 1.38 (s, 3H, Me_{19}), 1.09 (s, 3H, Me_{17}), 1.06 (s, 3H, Me_{16})

LRFABMS (M^+) *m/z* 835.3

6. Appendix

^{1}H-NMR spectra of the selected compounds are shown. Detailed assignments for protons and carbons are given in the experimental section.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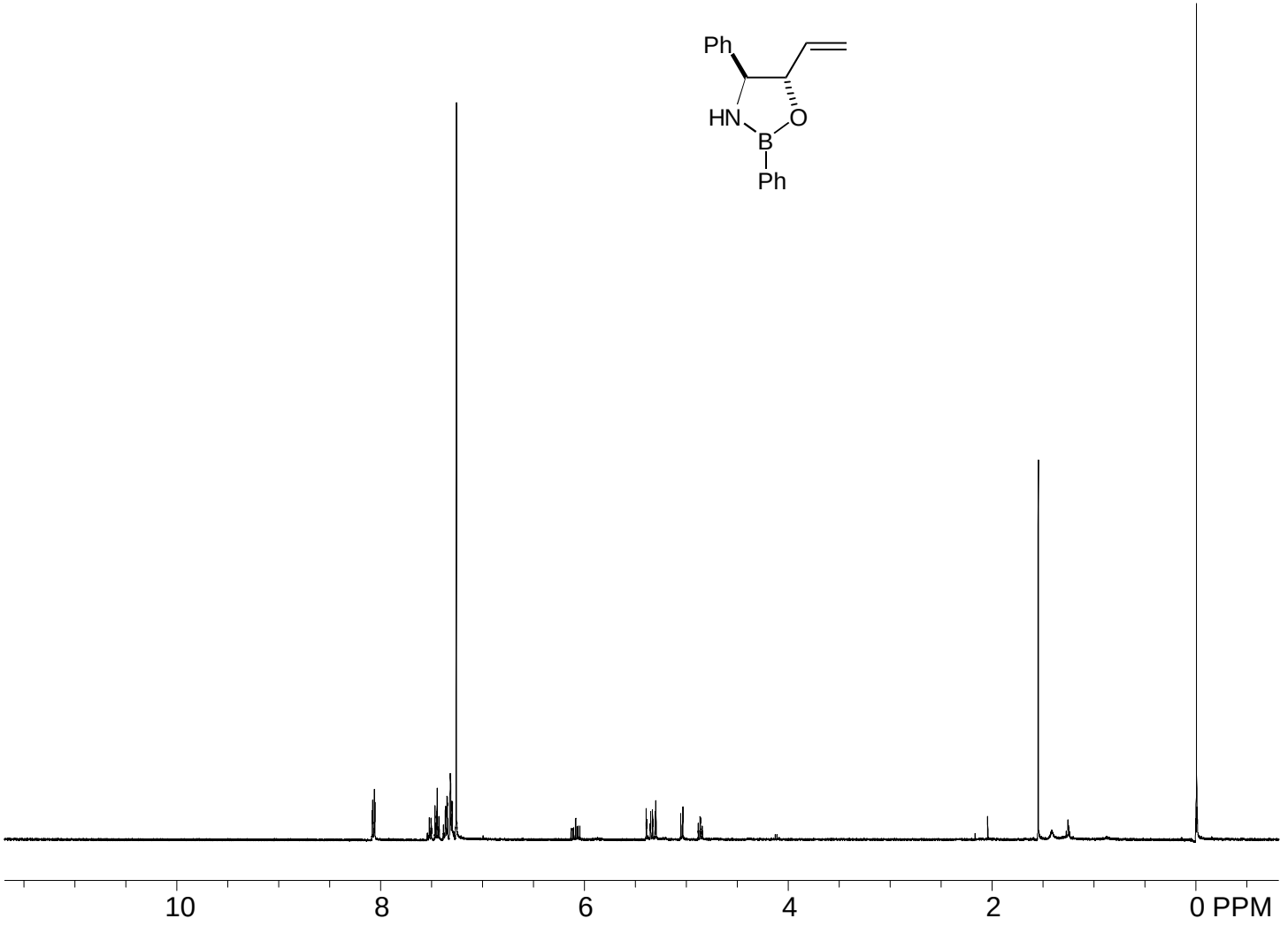
2
0 PPM



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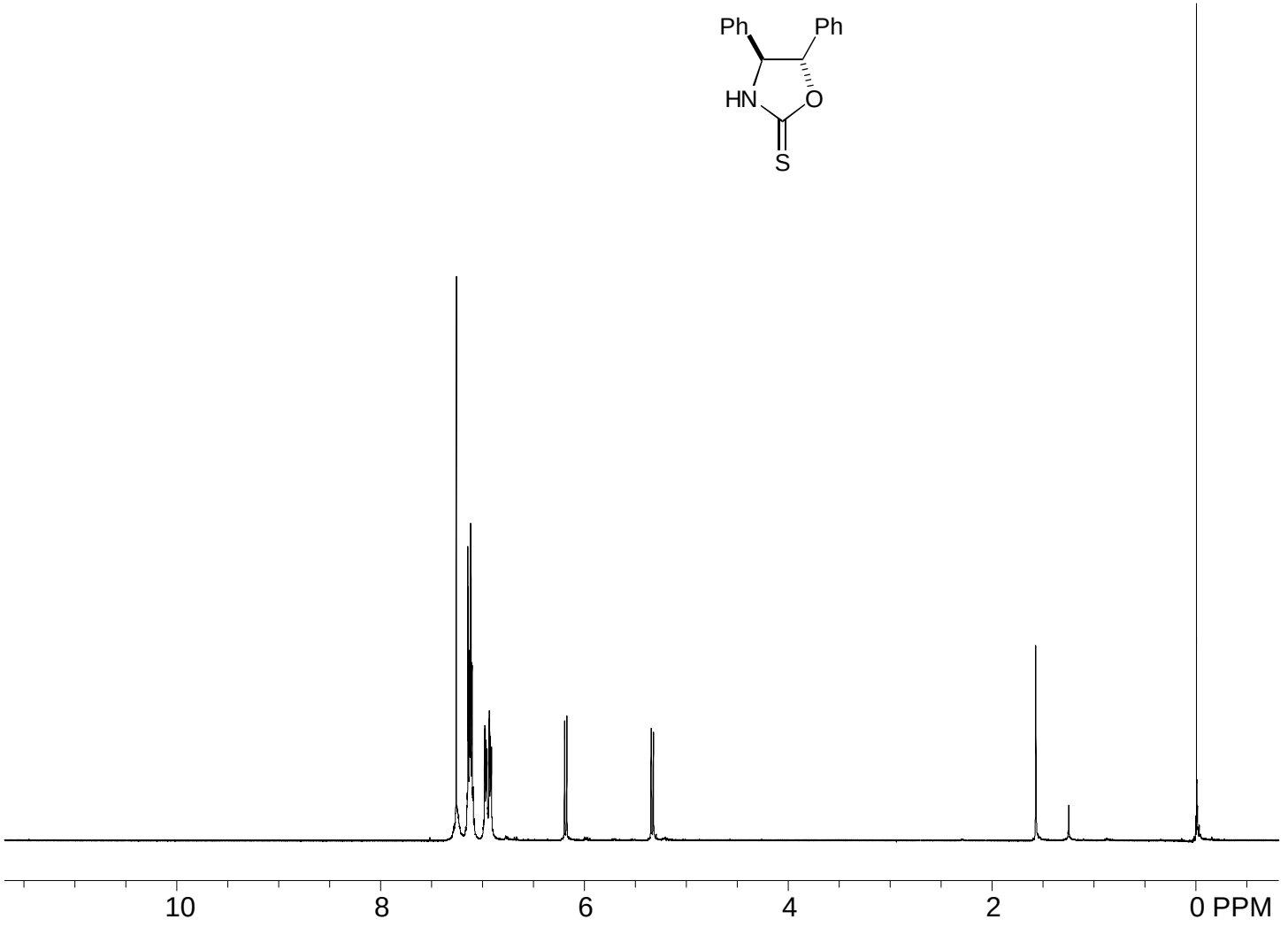
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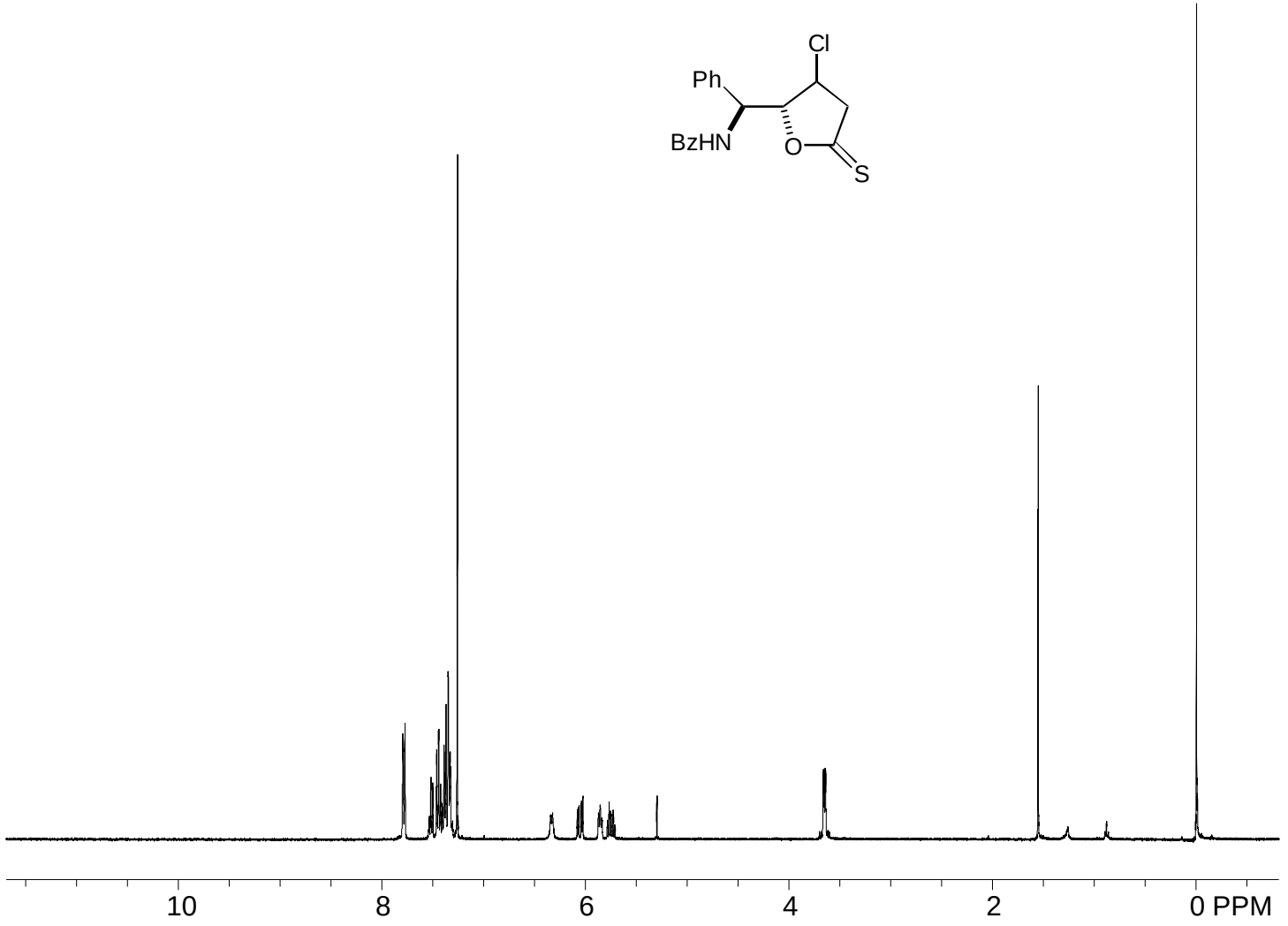
Ph
HN
O
S
10
8
6
4
2
0 PPM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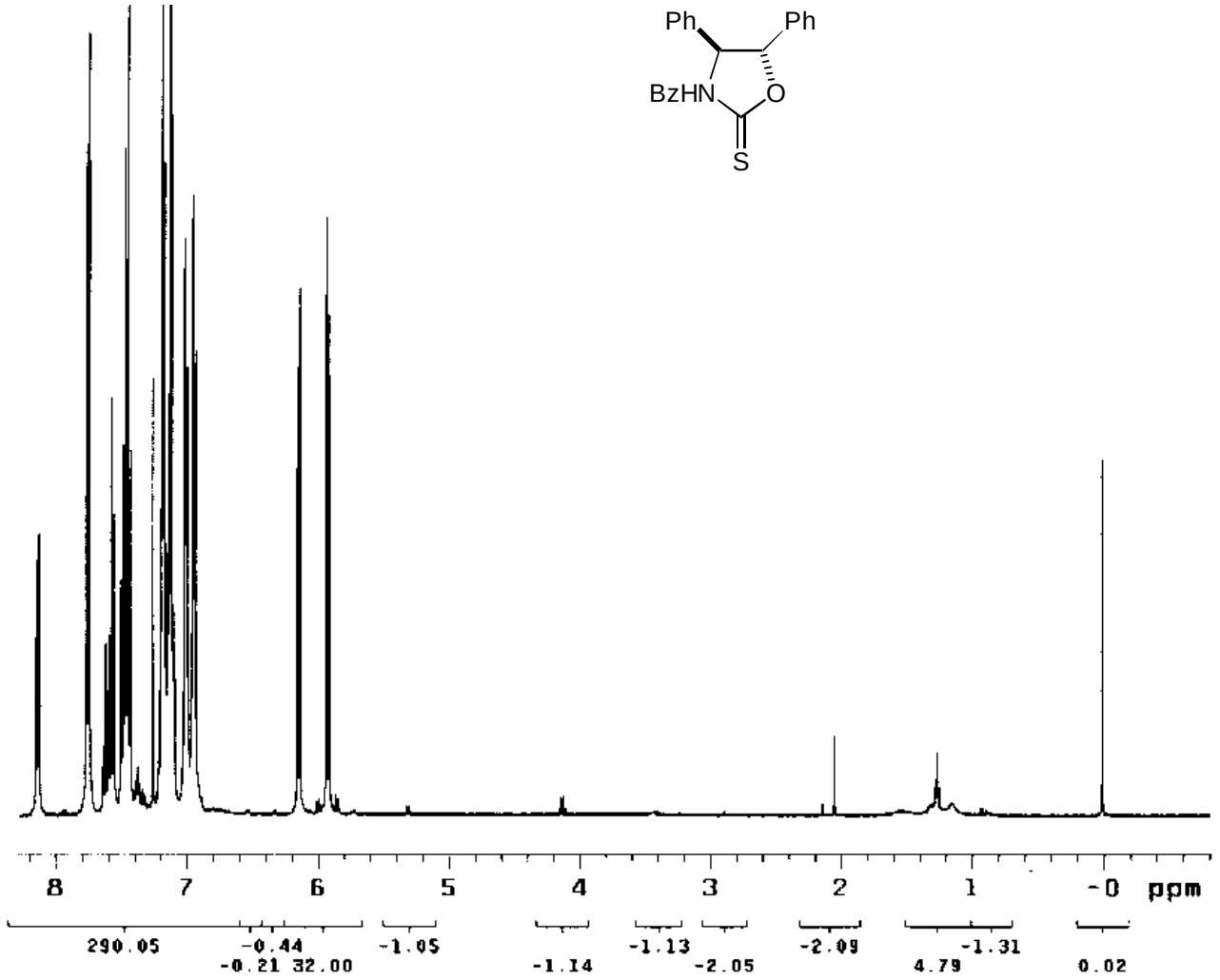
Ph
BzHN
O
S
10
8
6
4
2
0 PPM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Ph
BzHN
O
S
8
7
6
5
4
3
2
1
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32.00
-1.05
-1.14
-1.13
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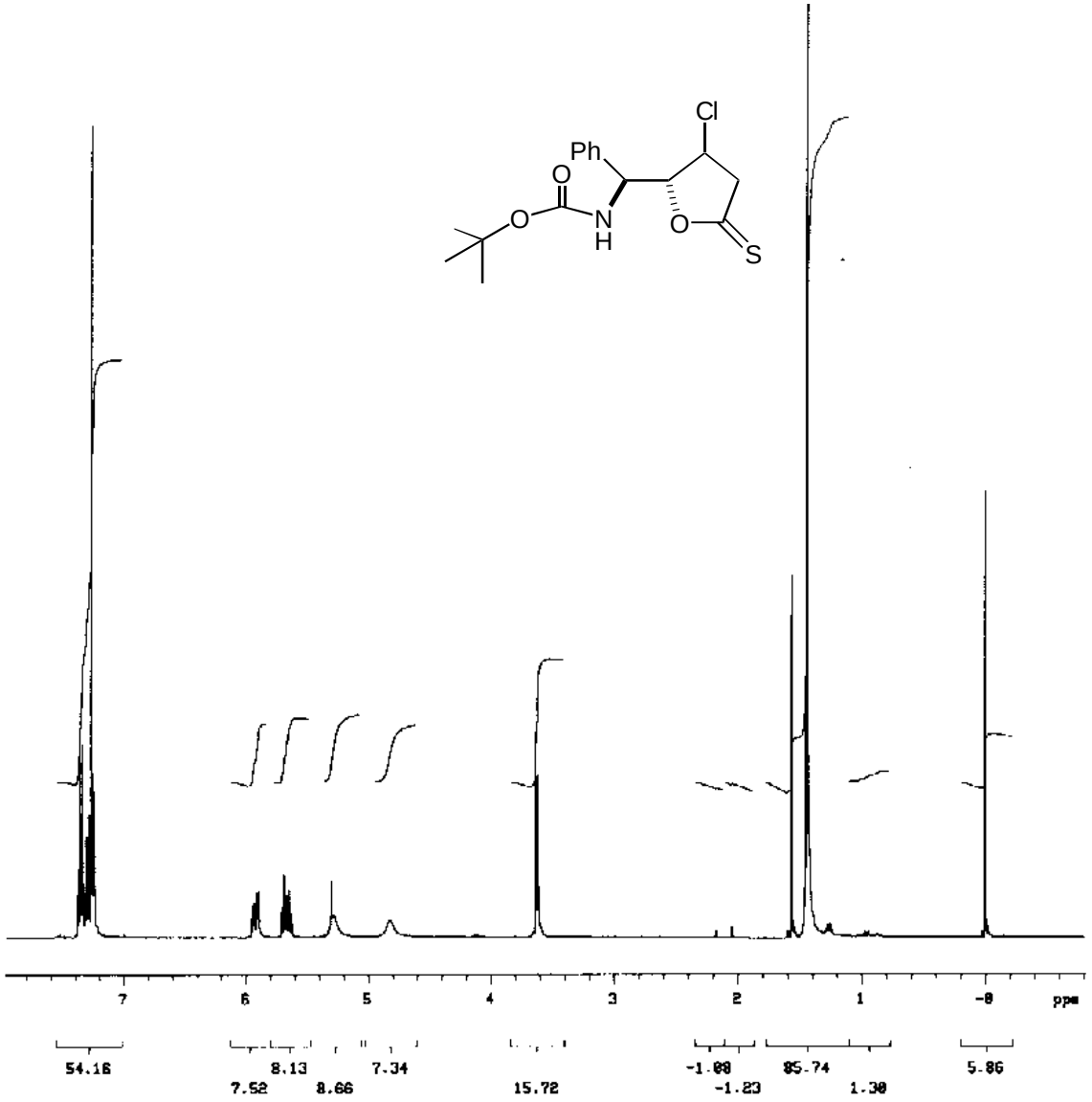
-2.09
-1.31
4.79
0.02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N
H
O
S
7
6
5
4
3
2
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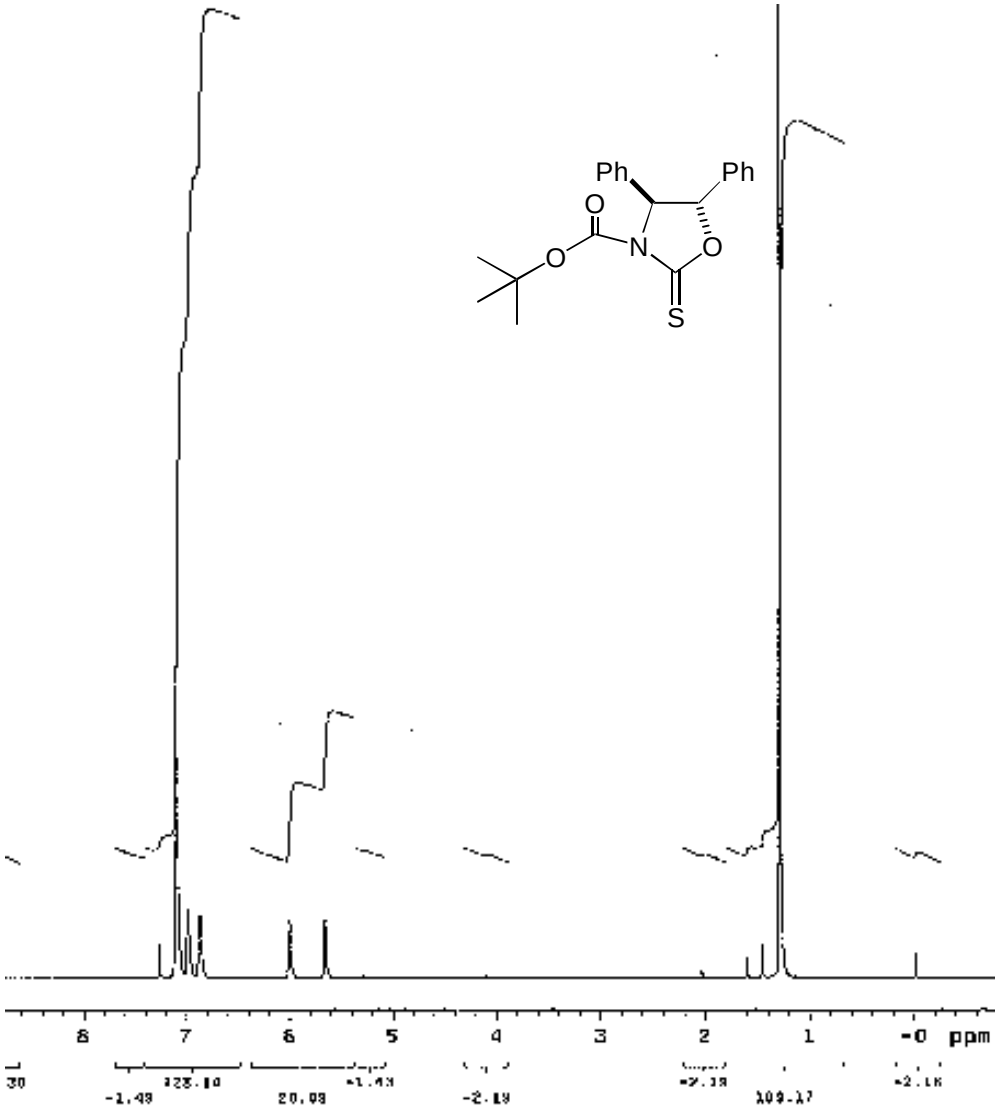
7.34
7.52
8.66
15.72
-1.08
-1.23
85.74
1.30
5.86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Ph
O
O
N
O
S
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6
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4
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2
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0
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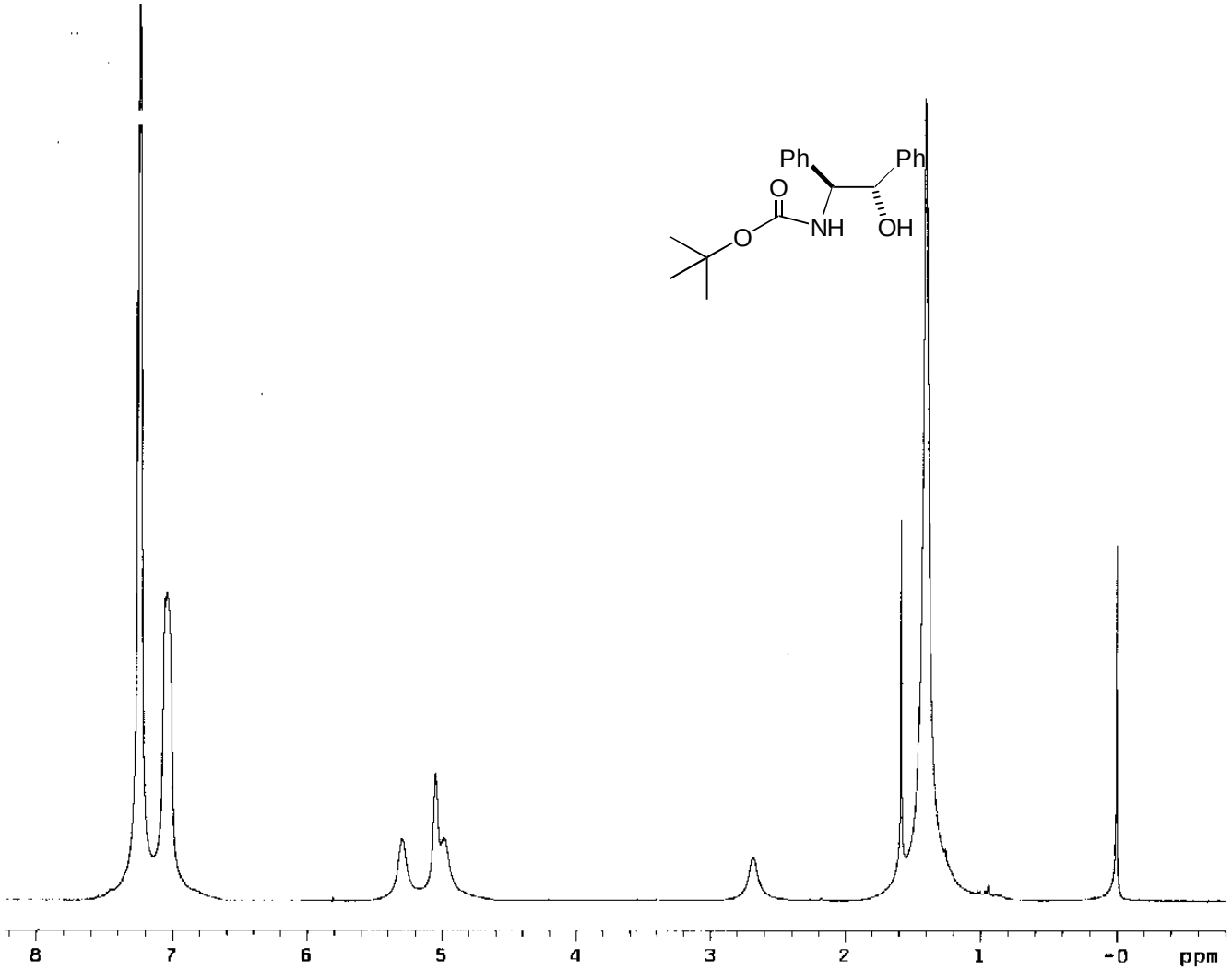
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Ph
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OH
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6
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3
2
1
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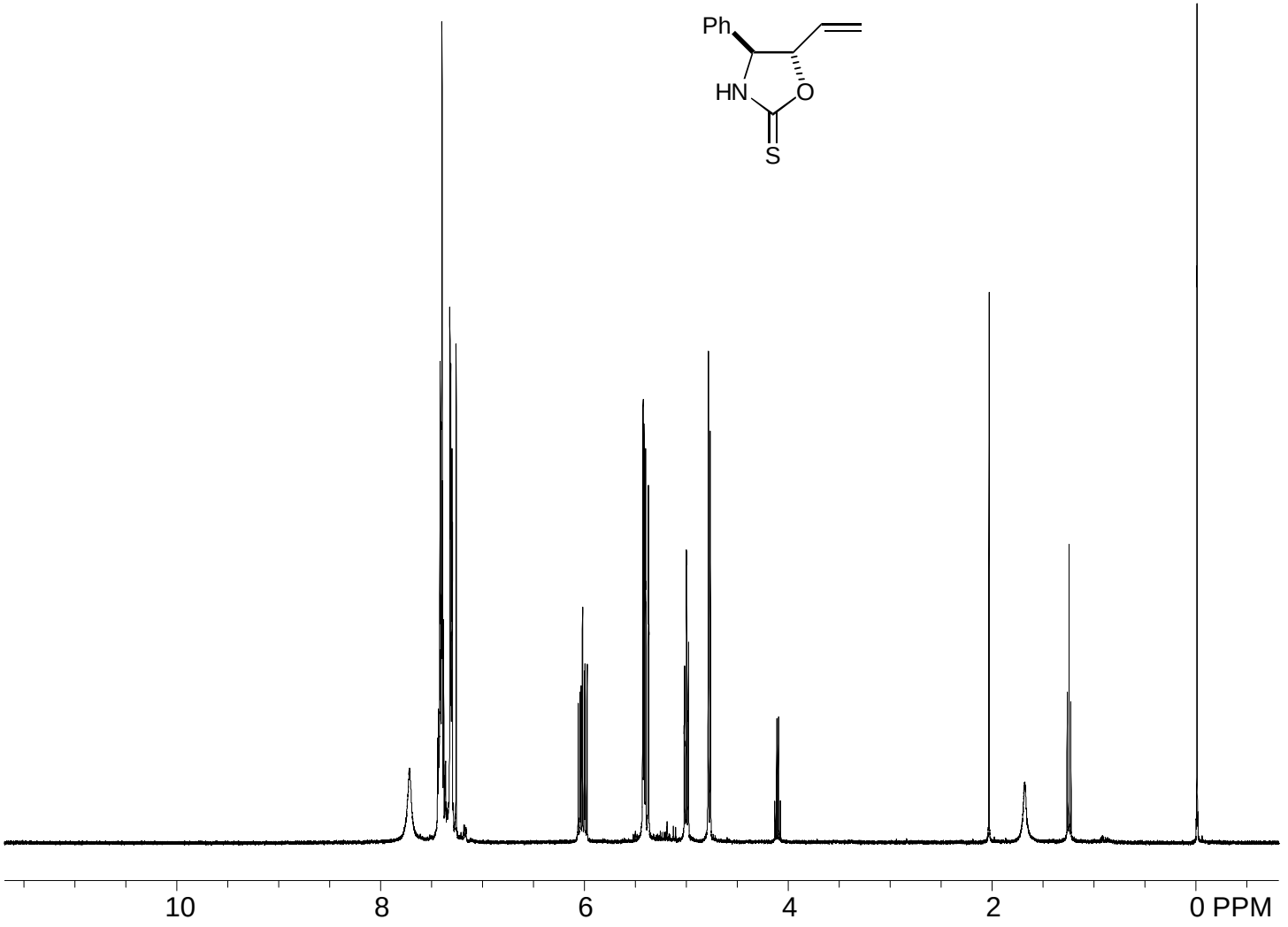
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O
S
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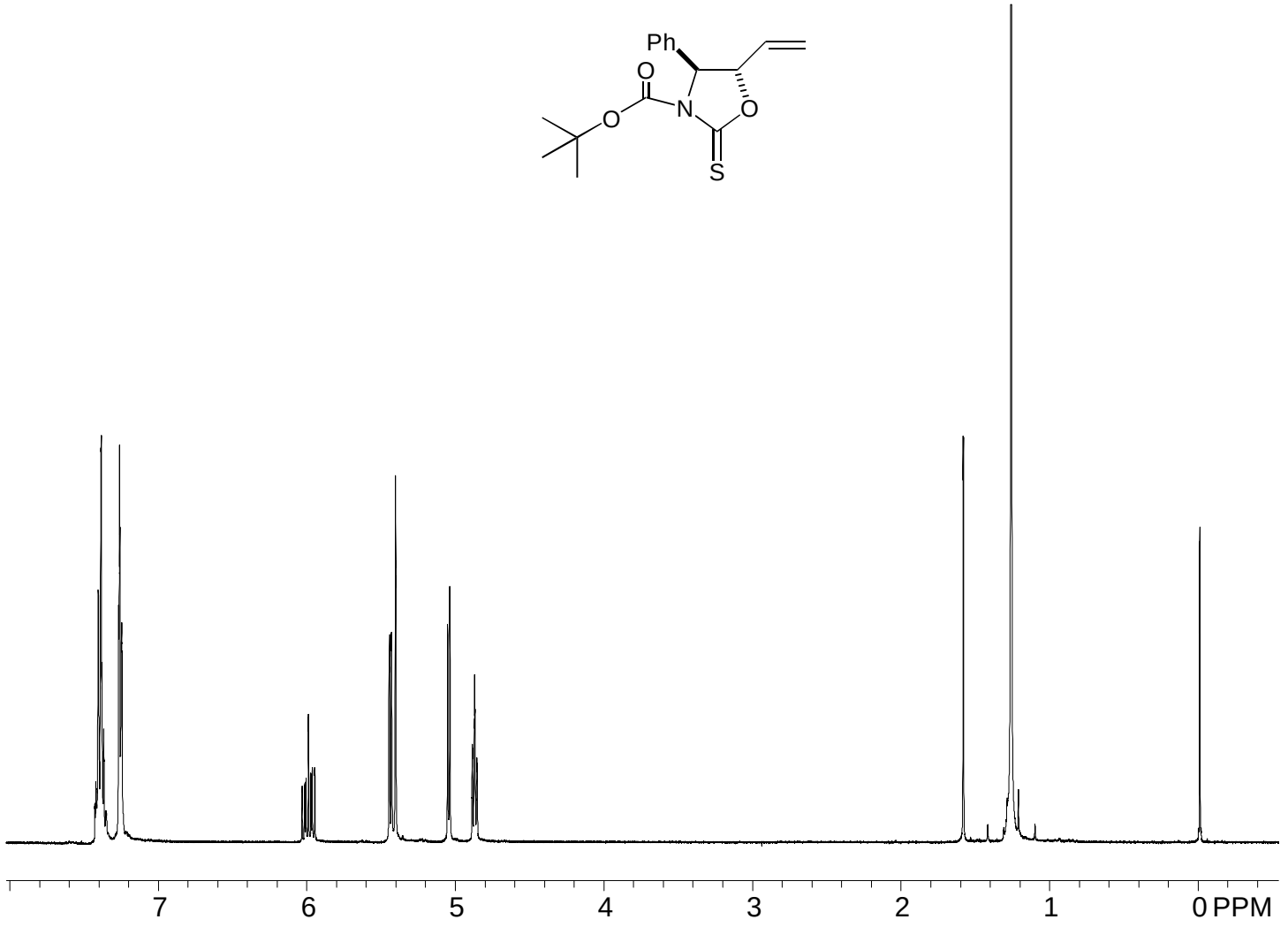
8
6
4
2
0 PPM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S
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2
1
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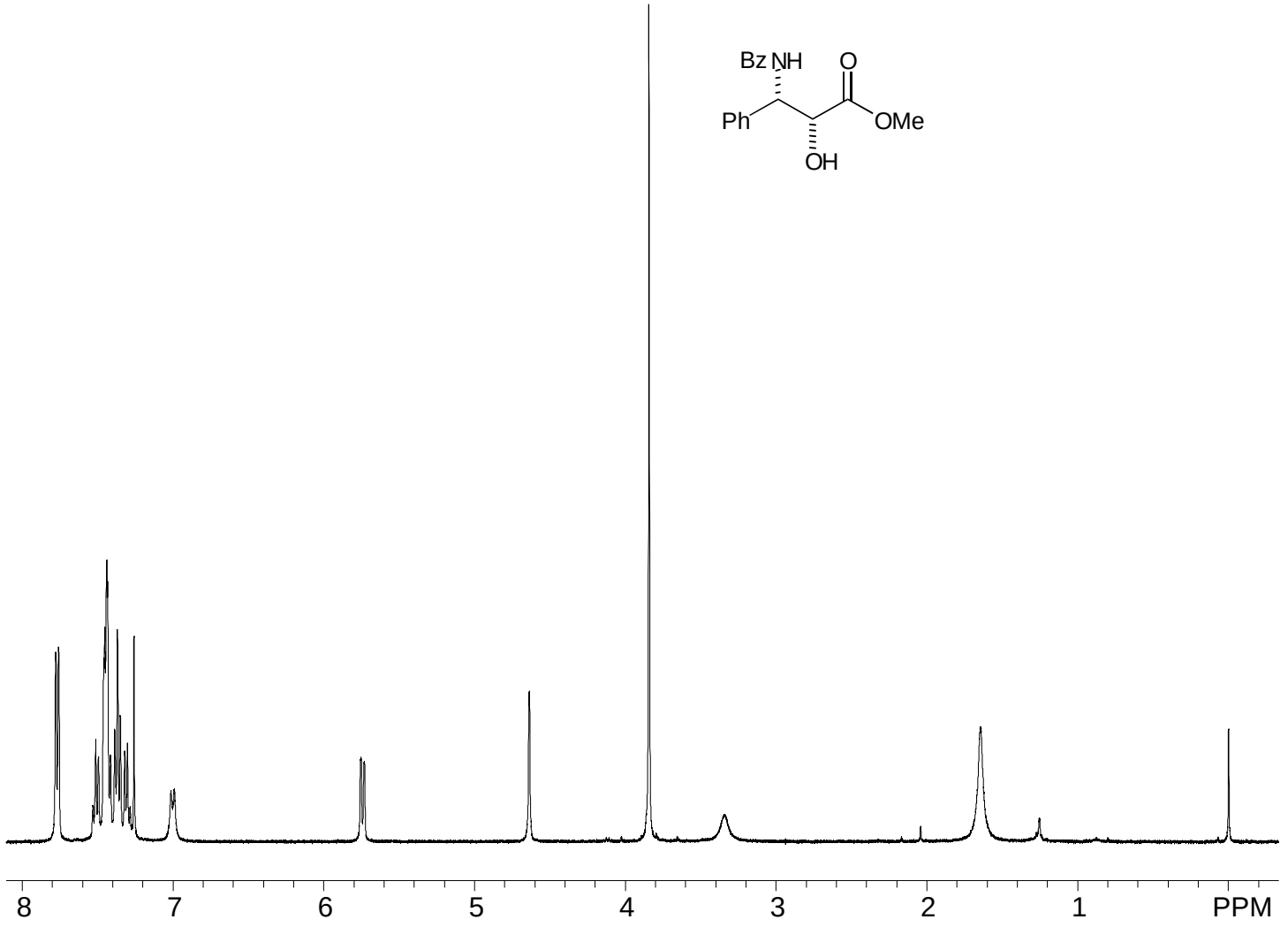
Bz NH
O
Ph
OMe
OH
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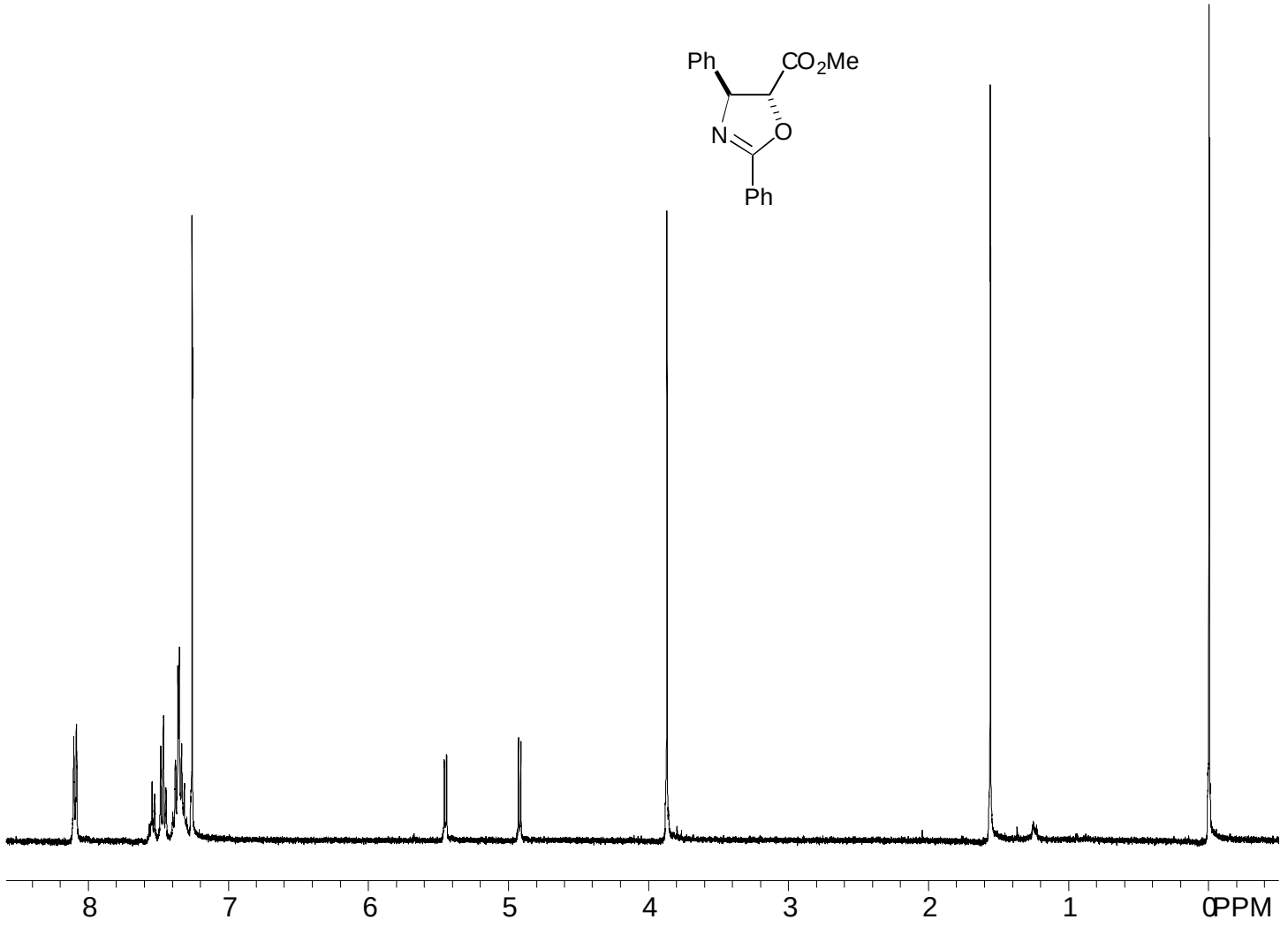
7
6
5
4
3
2
1
PPM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5
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3
2
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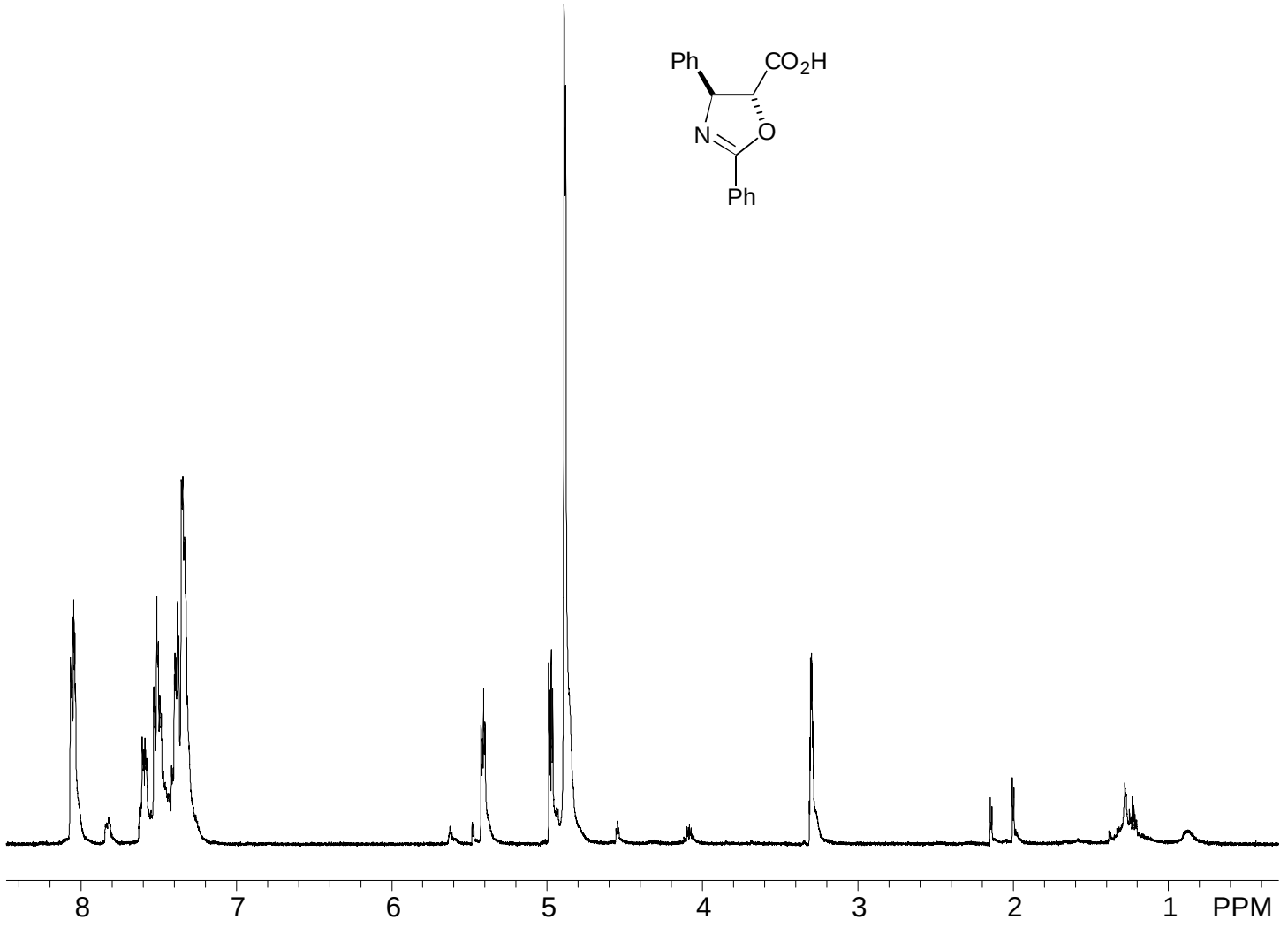
PPM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O
Ph
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6
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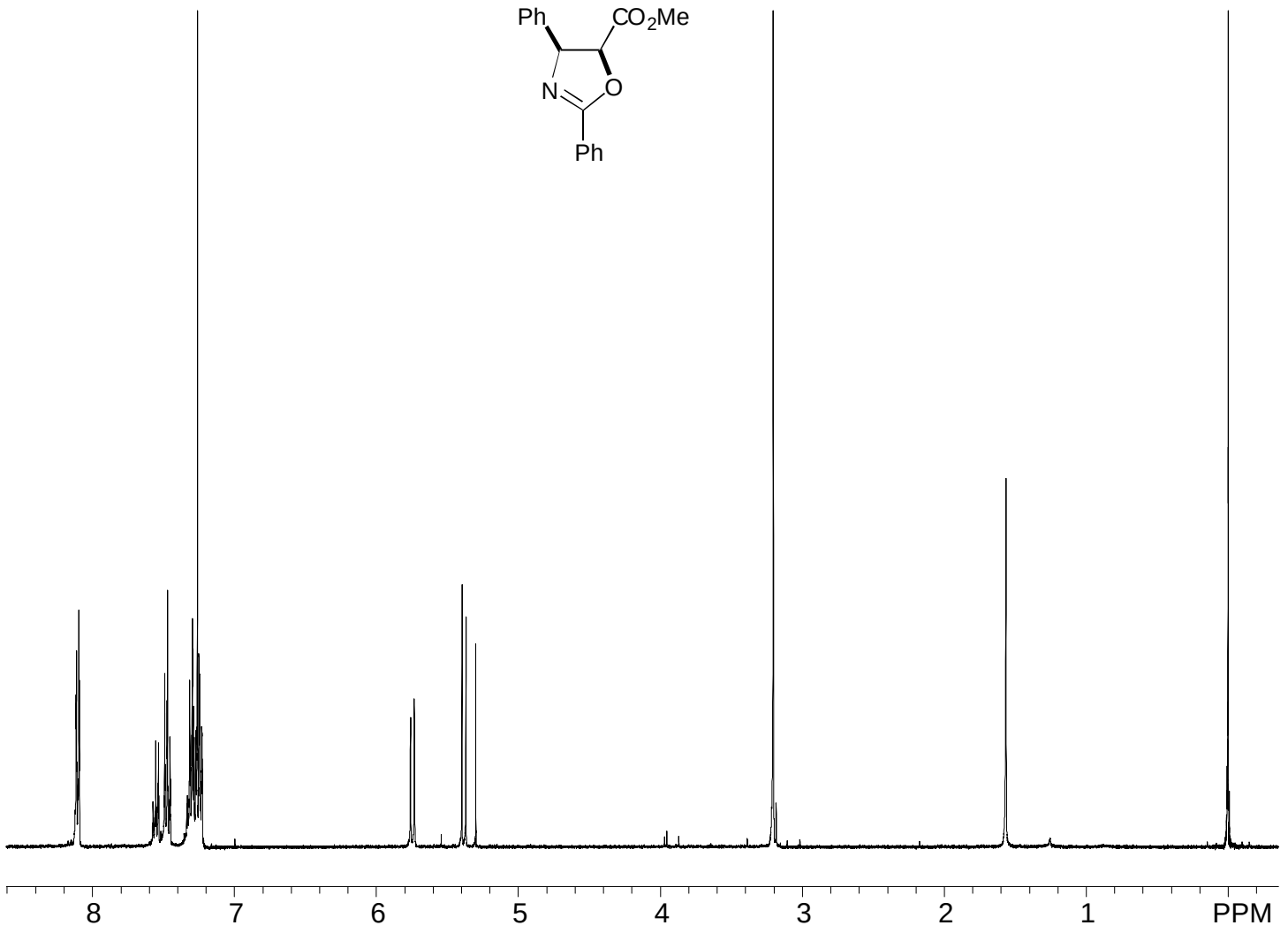
3
2
1
PPM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6
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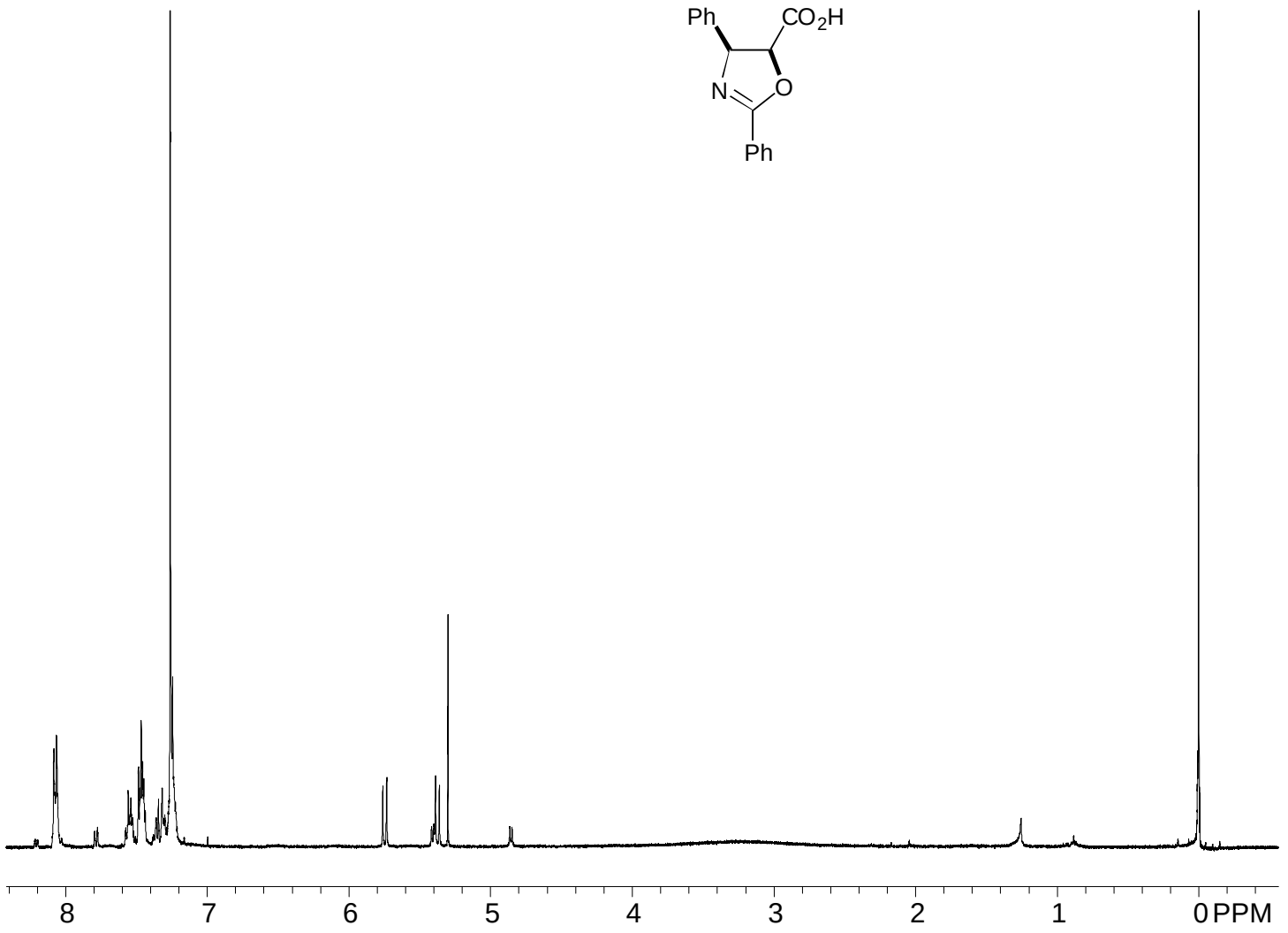
4
3
2
1
PPM


Ph
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Ph
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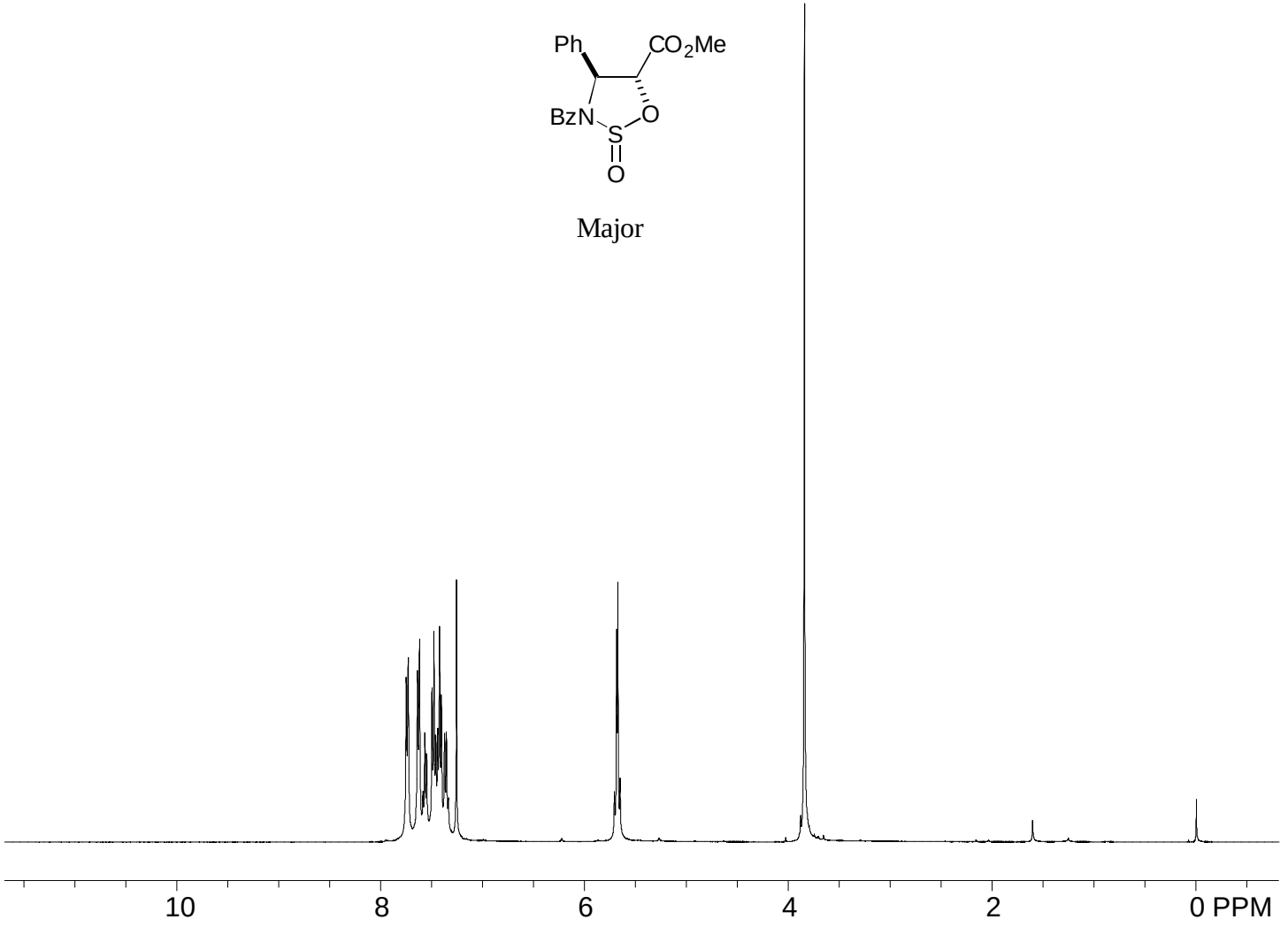
6
5
4
3
2
1
0 PPM


Ph
CO2Me
BzN
S
O
O
Major
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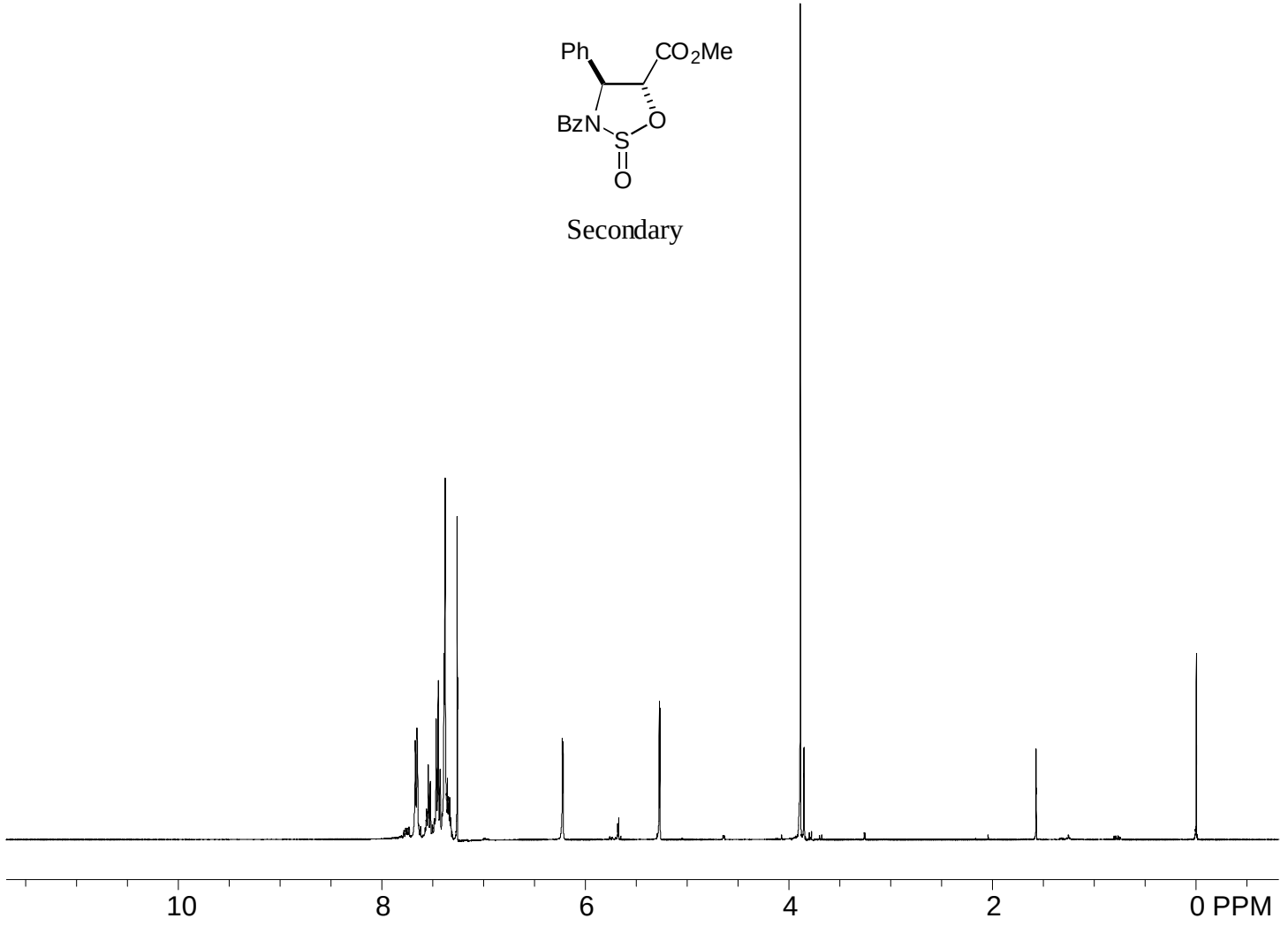
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S
O
O
Secondary
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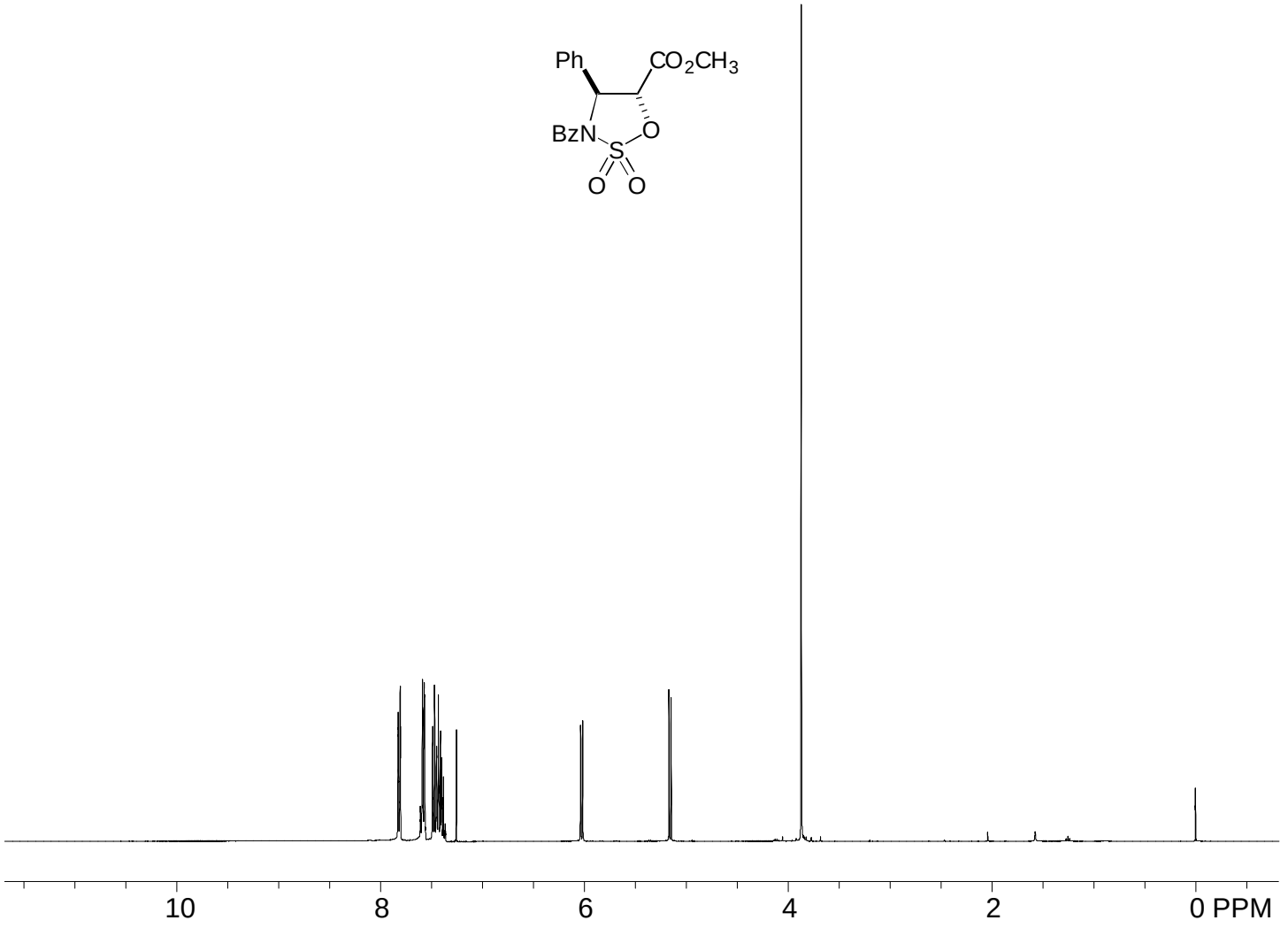
6
4
2
0 PPM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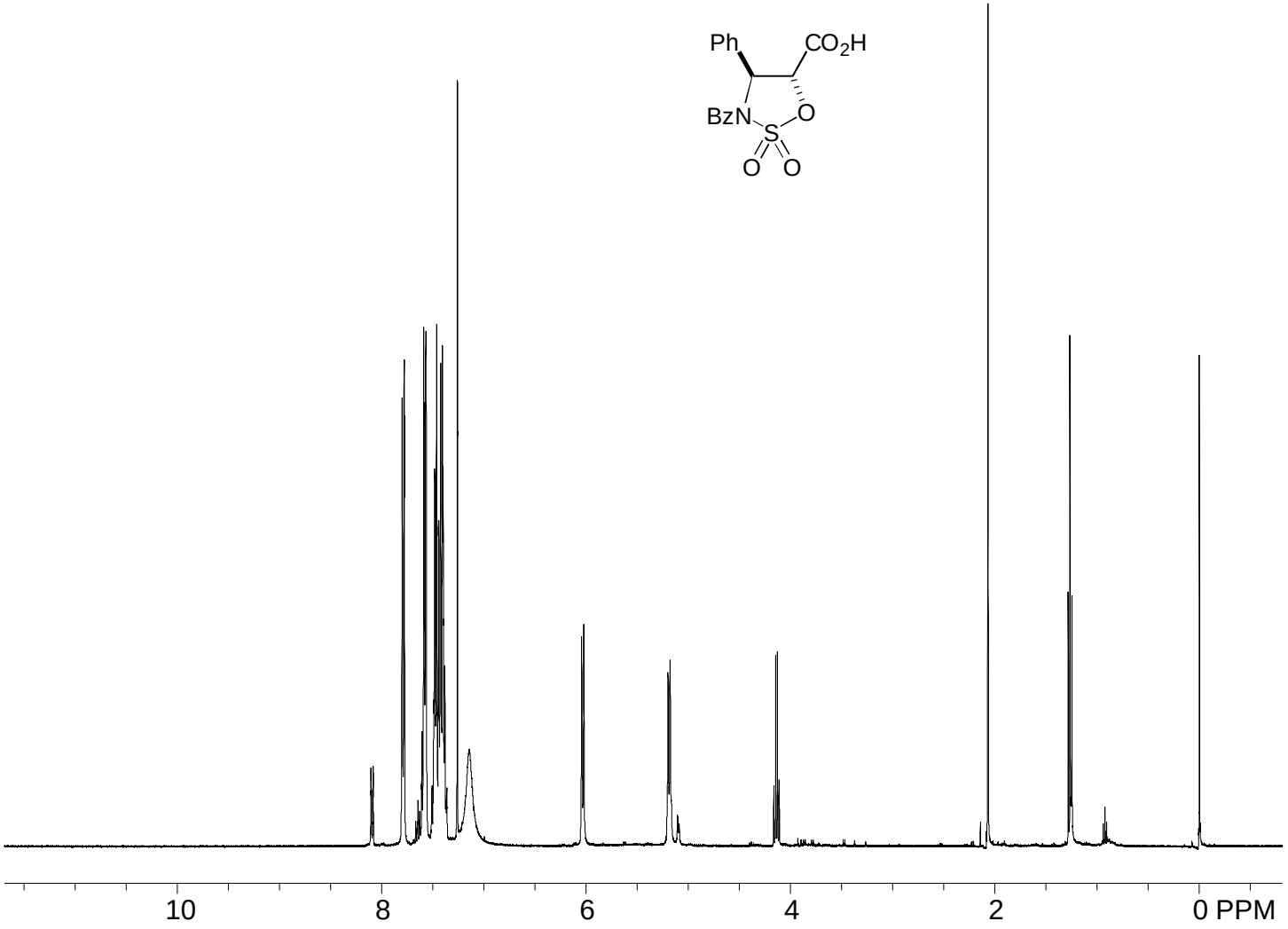
BzN
S
O
O
O
10
8
6
4
2
0 PPM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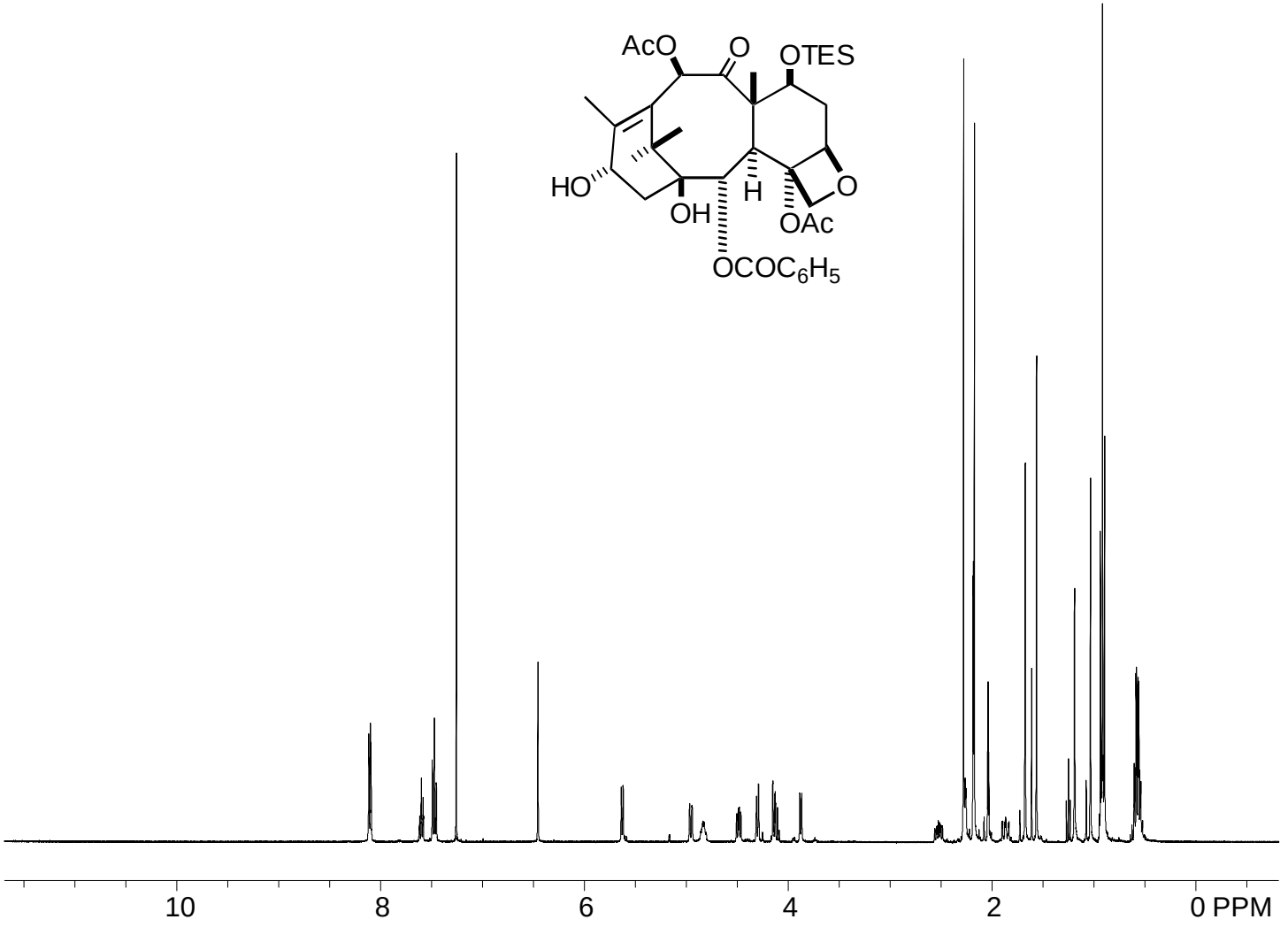
CO2H
BzN
S
O
O
O
10
8
6
4
2
0 PPM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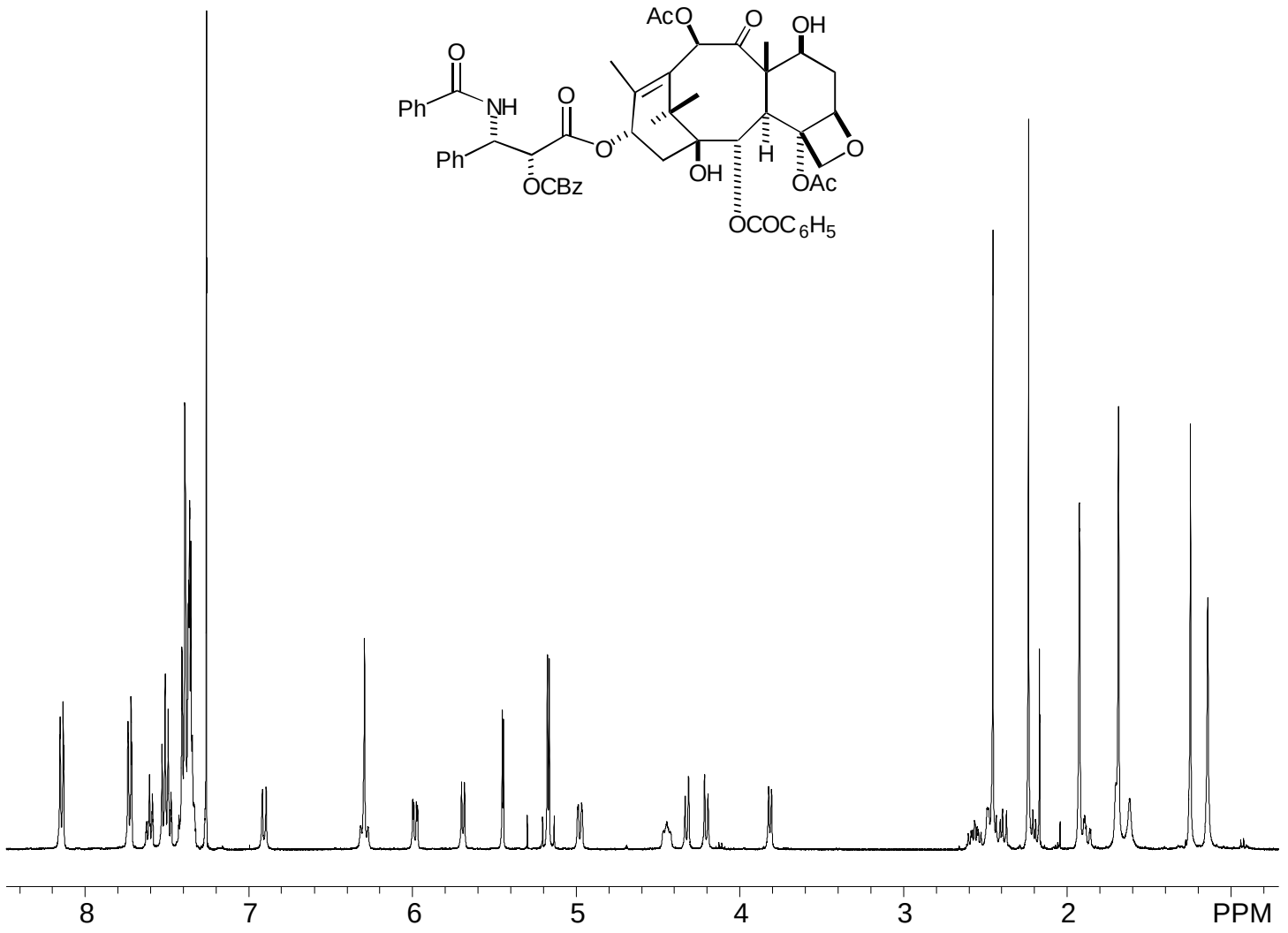
HO
OH
H
O
OAc
OCOC6H5
10
8
6
4
2
0 PPM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OH
O
Ph
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OH
H
O
OAc
OCOC6H5
8
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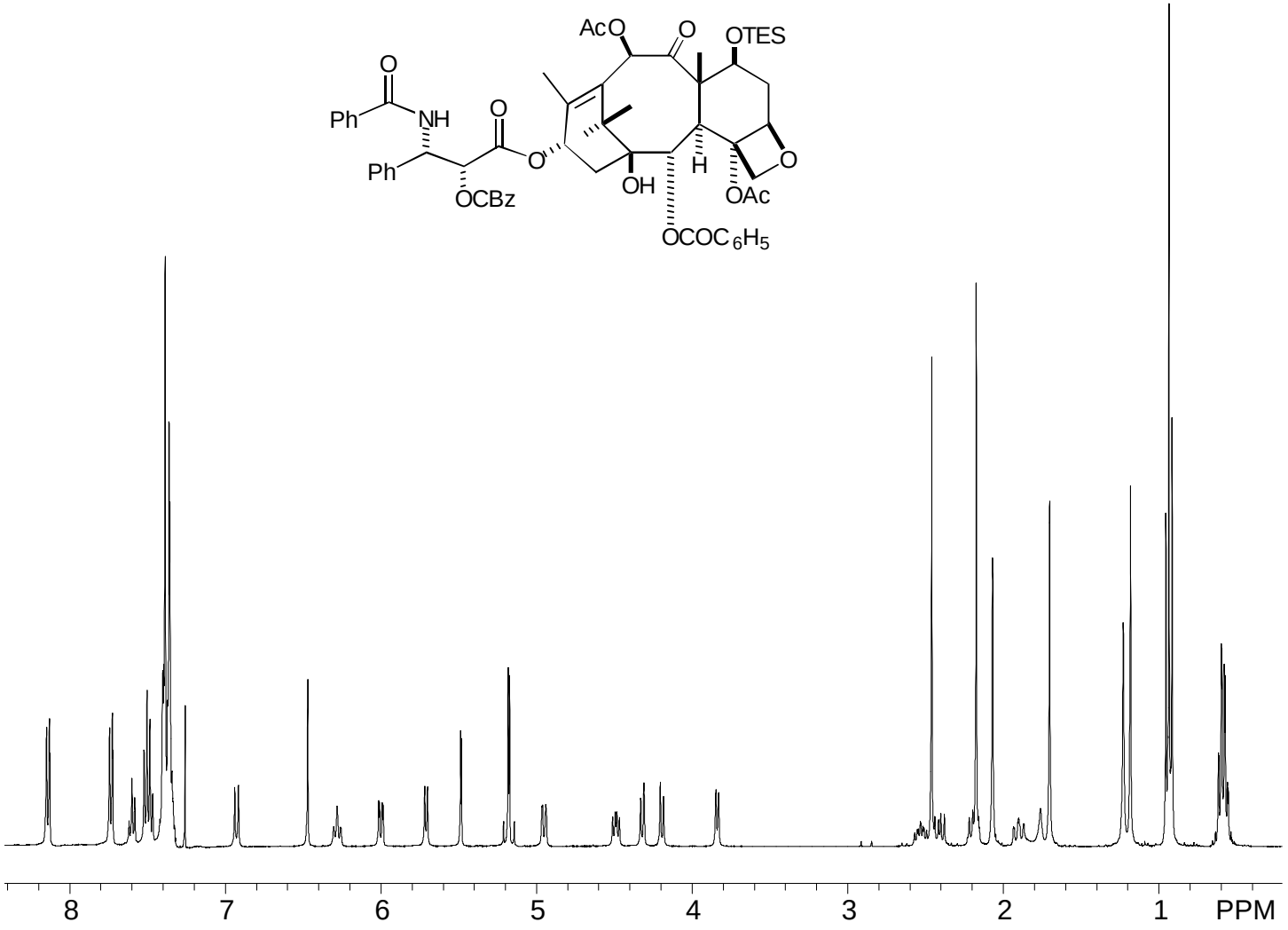
5
4
3
2
PPM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OTES
O
Ph
NH
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OH
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OAc
OCOC6H5
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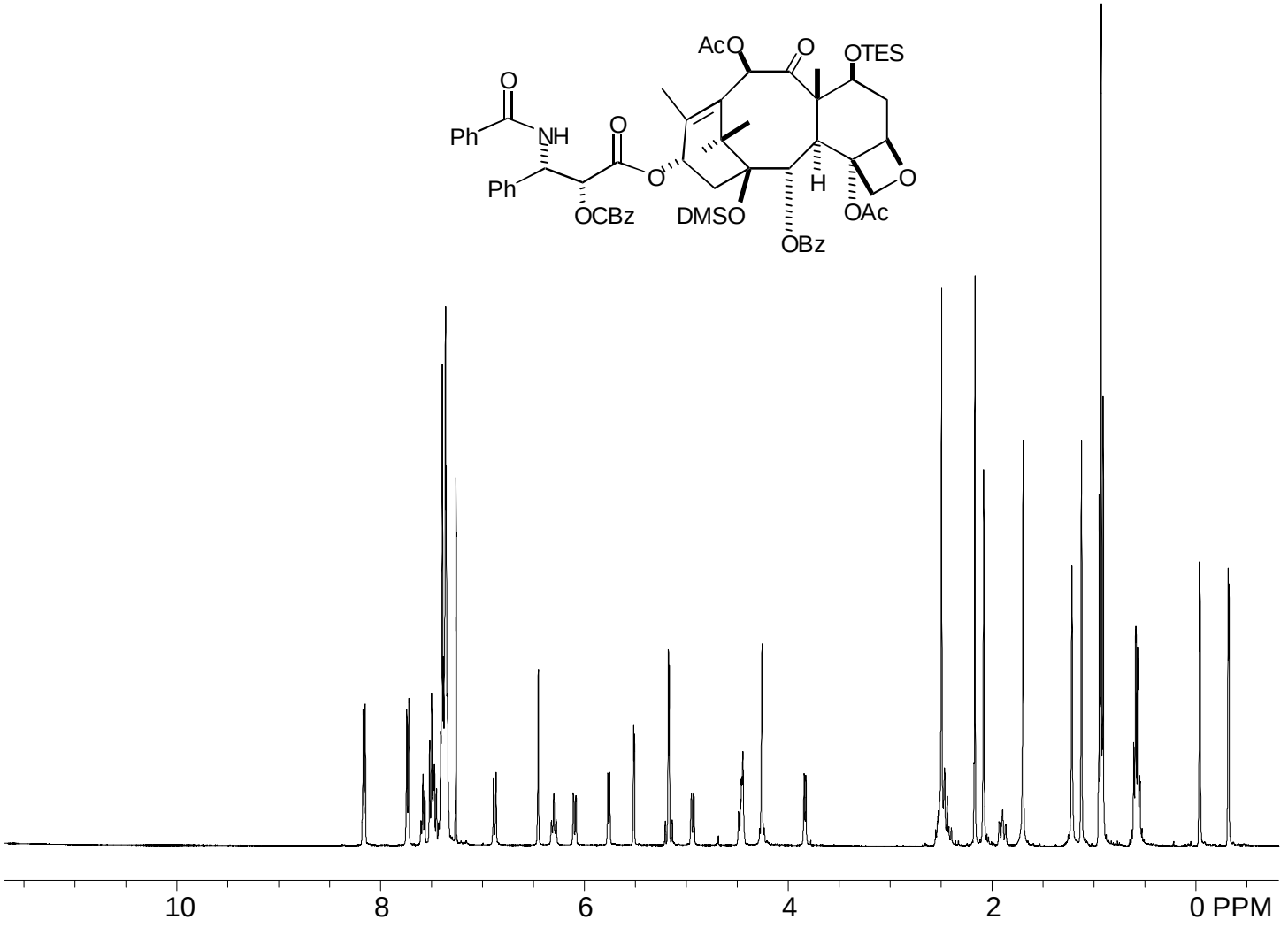
1
PPM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Ph
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H
O
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OBz
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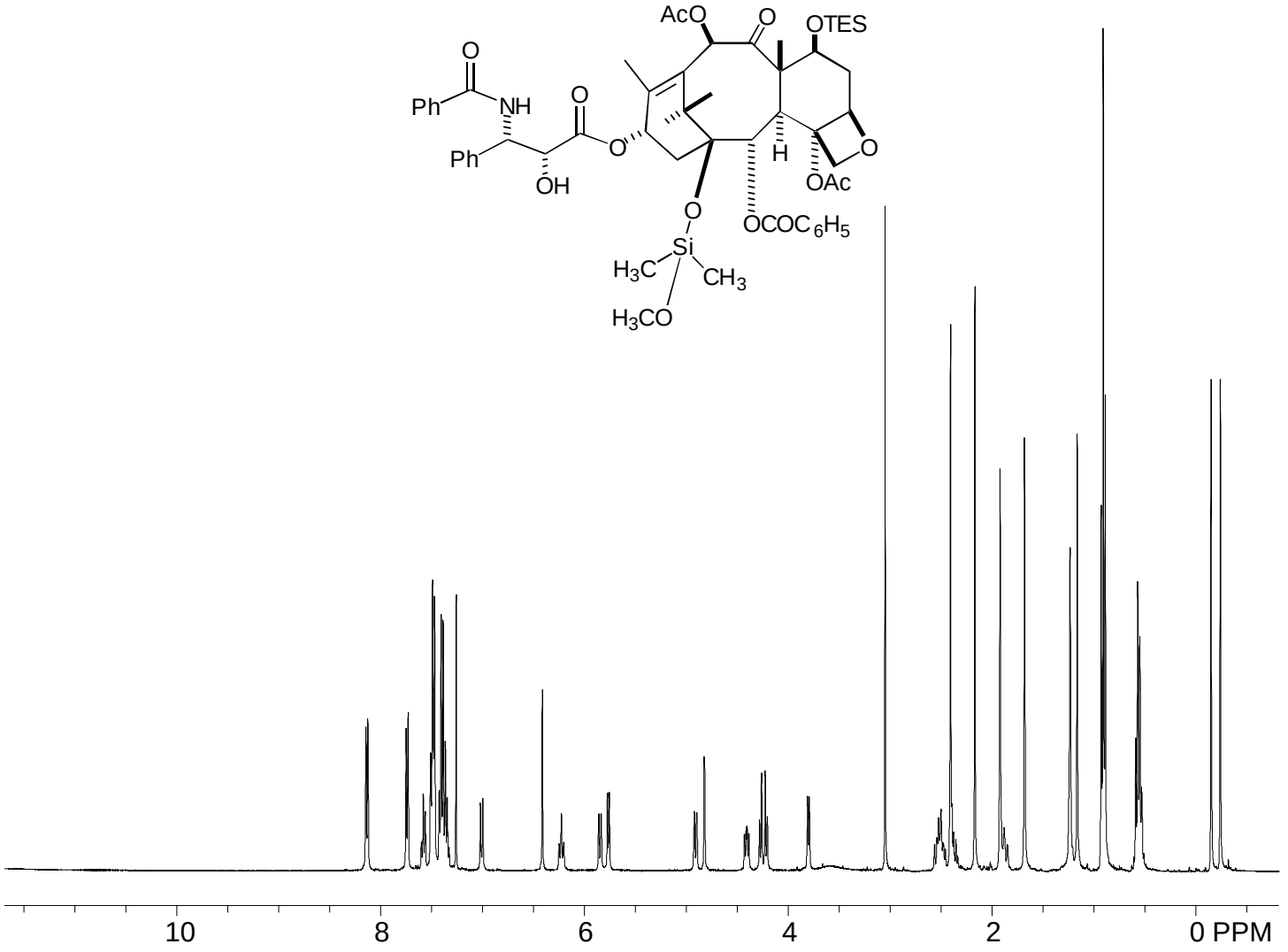
0 PPM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O
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NH
O
Ph
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O
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CH3
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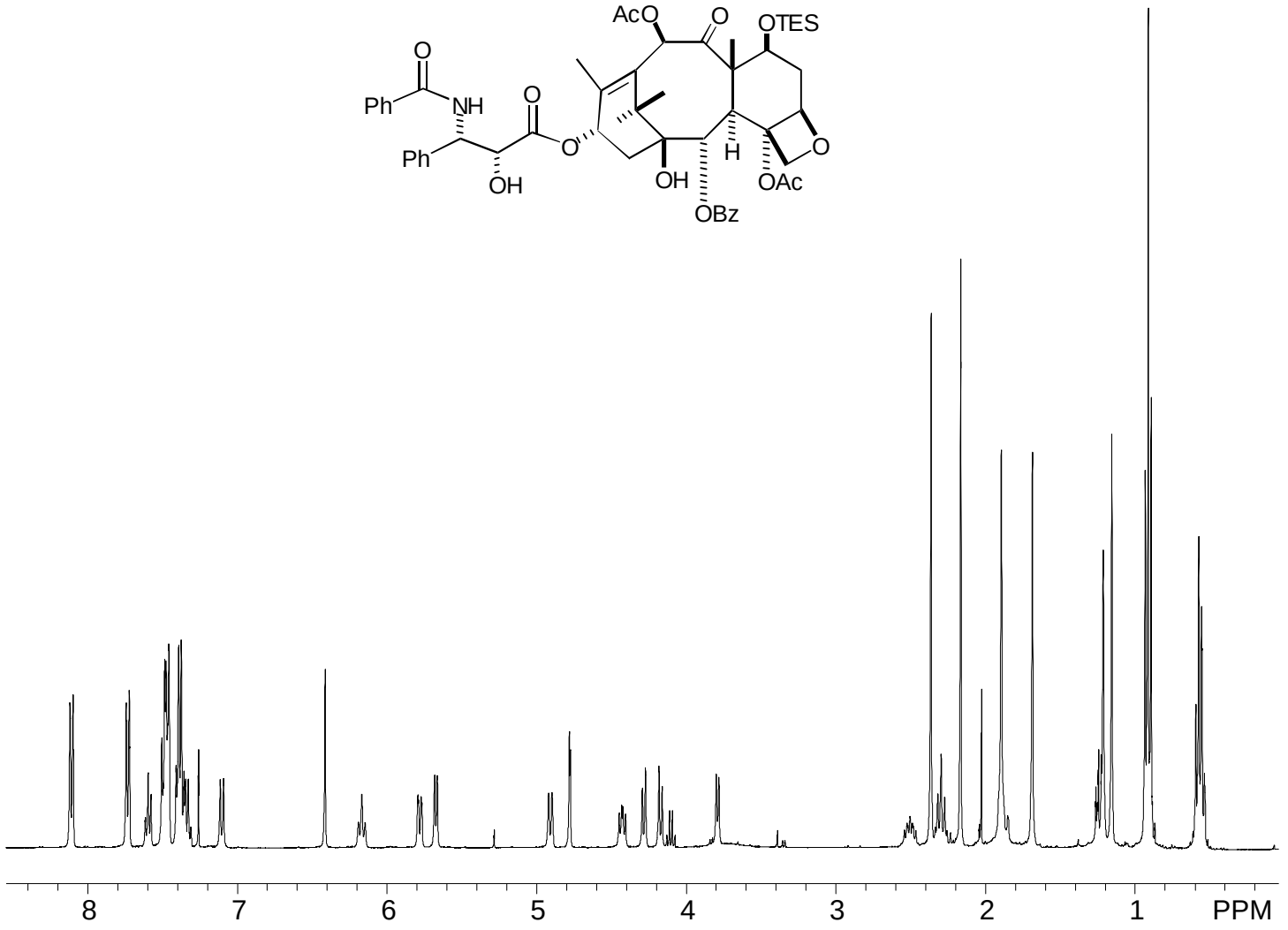
8
6
4
2
0 PPM


AcO
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OTES
O
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NH
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Ph
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OH
OH
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OAc
OBz
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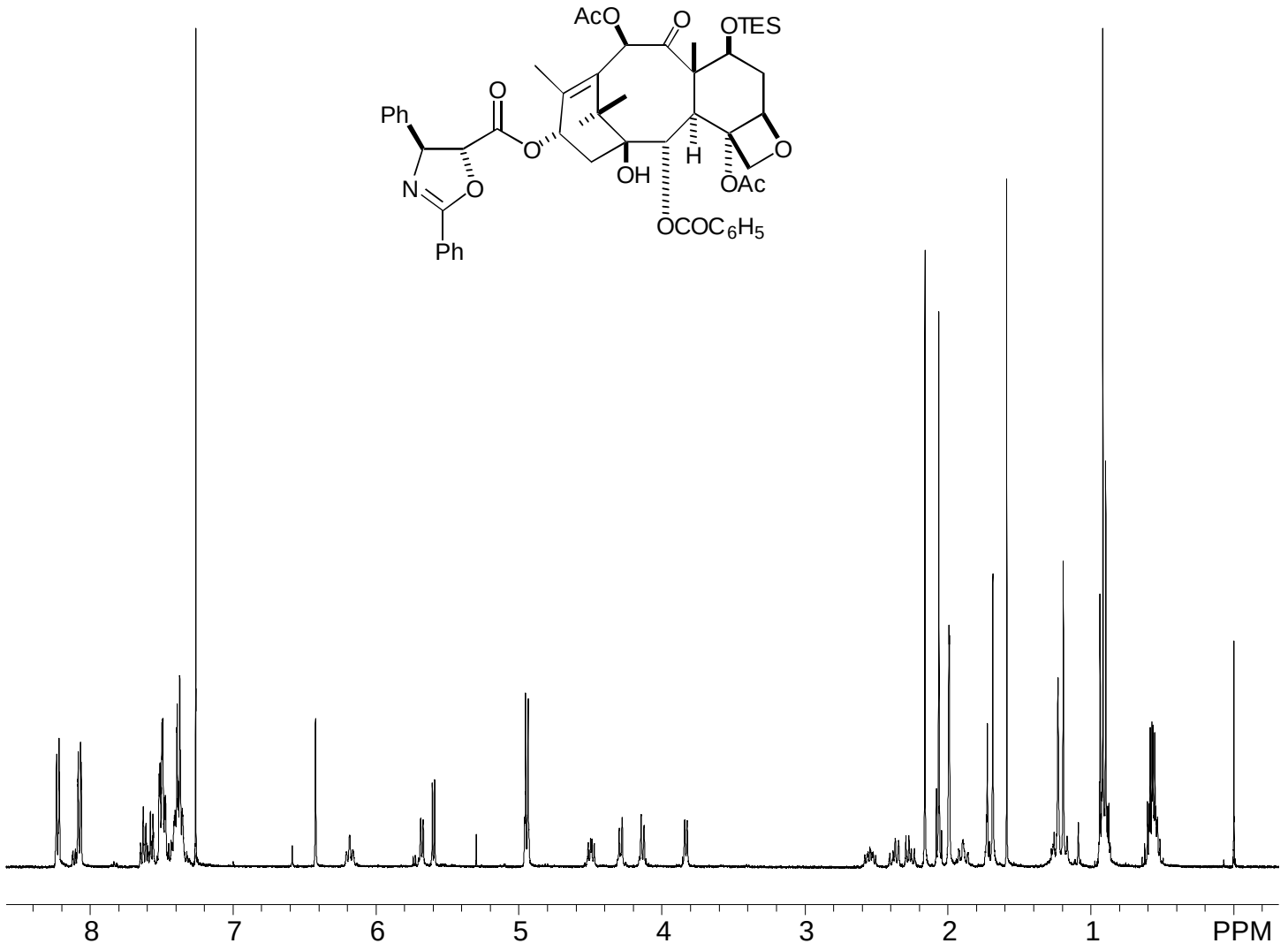
2
1
PPM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OTES
Ph
O
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OAc
O
OCOC6H5
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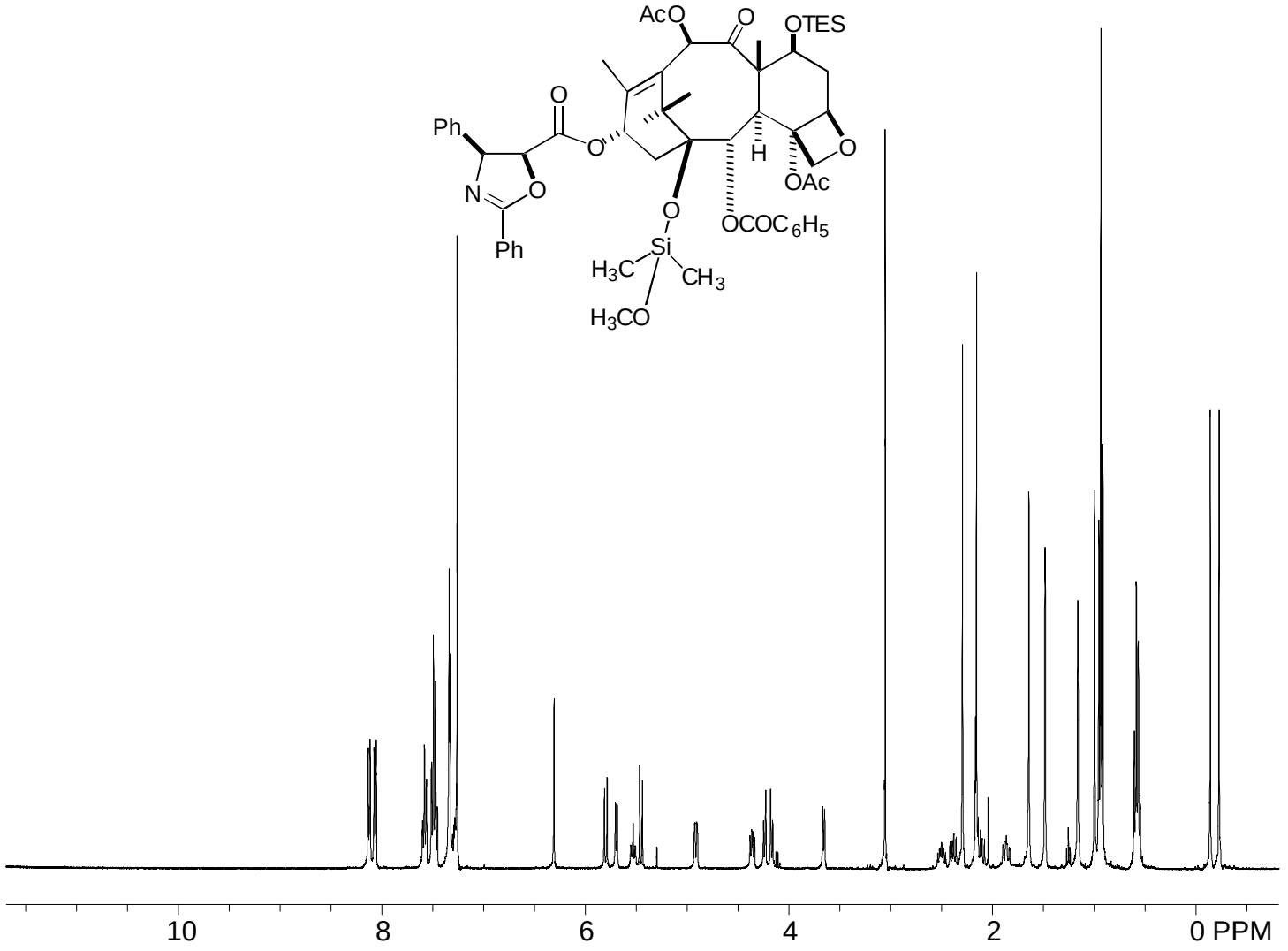
PPM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CH3
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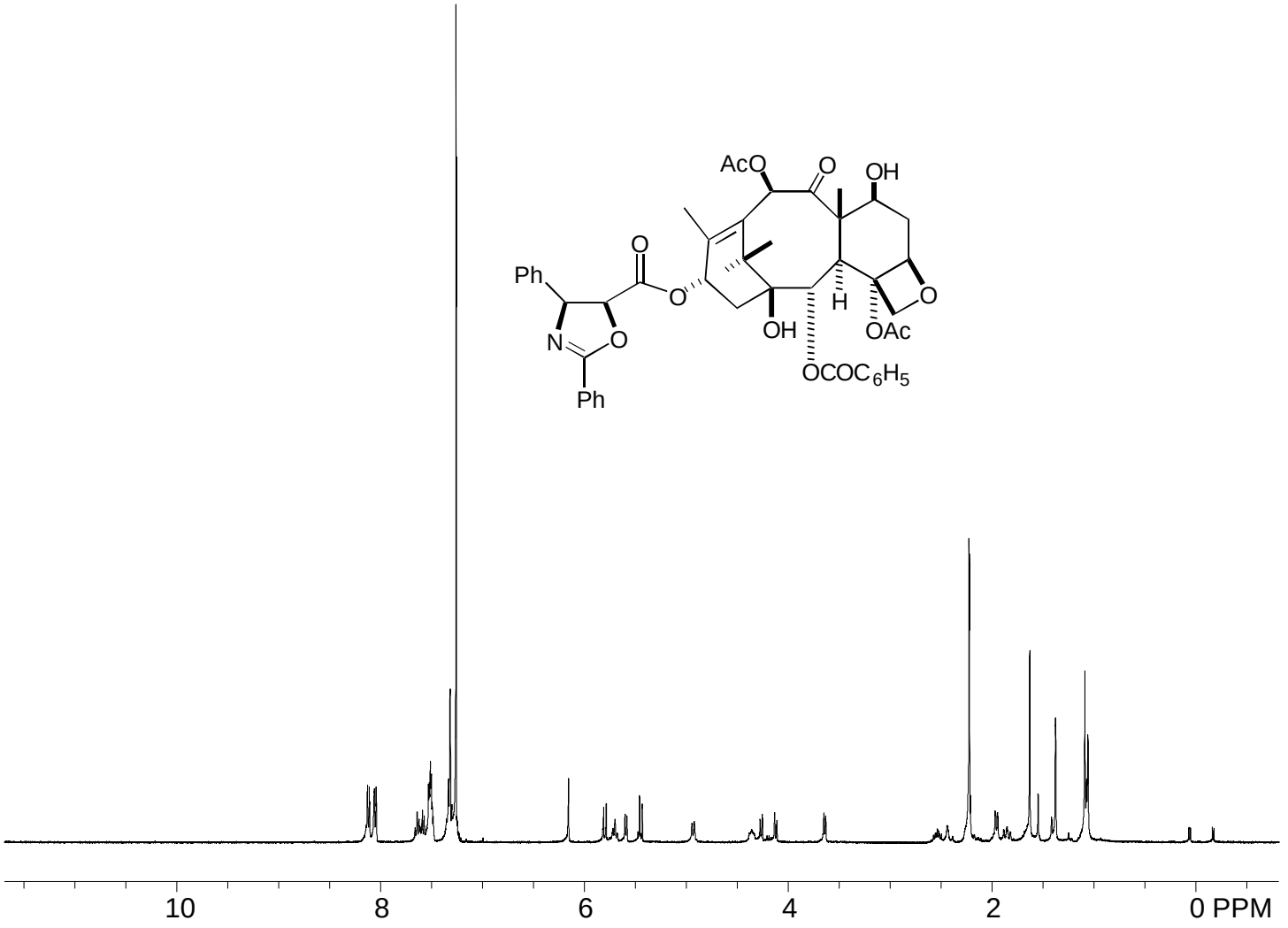
0 PPM


AcO
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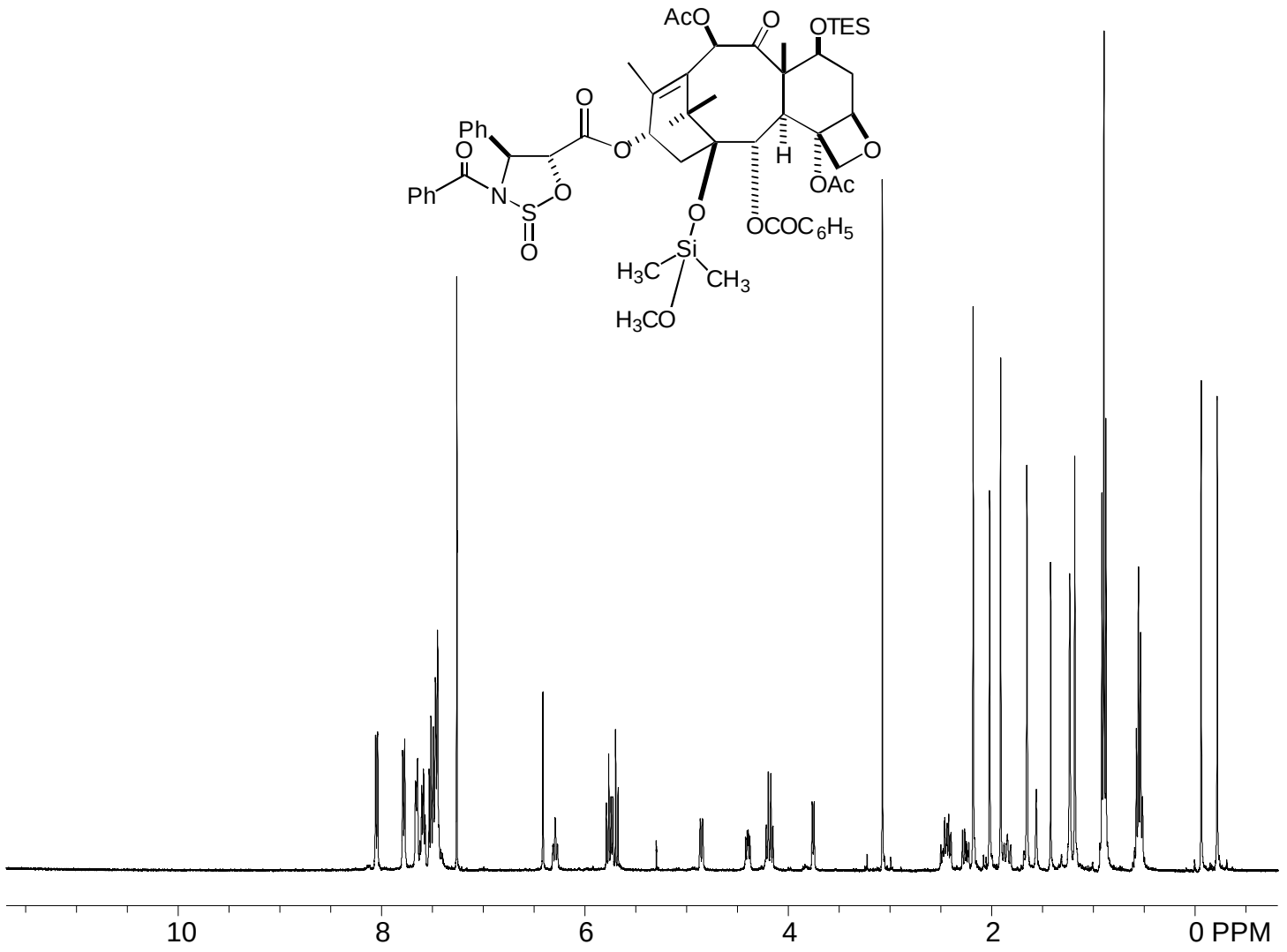
AcO
O
OTES
Ph
O
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O
H
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Ph
N
S
O
O
OAc
O
OCOC6H5
Si
H3C
CH3
H3CO
10
8
6
4
2
0 PPM

7. Vita

Erkan Baloglu was born to Mr. and Mrs. Ali Baloglu on August 11, 1971 in Istanbul, Turkey. He graduated with Honors from Ozel Dost High School, Istanbul, Turkey in June 1989. He started his education in chemistry in the Department of Chemistry at Istanbul Technical University in October 1990, where he graduated with a Bachelor of Science degree in Chemistry in February 1995.

In August 1995, 6 days after his marriage to Mrs. Simge Baloglu, he came to the United States and began his graduate studies in organic chemistry in the Department of Chemistry, Virginia Tech, Blacksburg, VA. During his time there, he held graduate teaching and research assistantships for the Department of Chemistry. He also served as head teaching assistant. In May 1998, he received the graduate student teaching award. In August 1998, he completed the requirements for the degree of Master of Science in Chemistry.

The author will begin studies for his degree of Doctor of Philosophy in Chemistry in the Department of Chemistry at Virginia Tech. The author is a member of the American Chemical Society, American Chemical Society Organic Division, IUPAC and Istanbul Technical University Alumni Association.