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Synthesis of Taxane Cyclization Precursors

by

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ABSTRACT

In order to elucidate the mechanism of the biosynthesis of the taxane framework, a bicyclic diterpenoid designated isoverticillene (**21**) has been synthesized. The molecule is a hydrocarbon containing a *cis*-fused bridgehead that possibly favors the formation of the taxane framework through an electrophilic π transannular cyclization. The key step in the synthesis of isoverticillene is the cyclization of a 12-membered ring through a palladium-catalyzed intramolecular allylation of a γ-sulfonyl-α,β-unsaturated ketone. This synthesis also features the use of readily available chiral starting material, (1*S*)-(+)-10-camphorsulfonic acid (**37**), and involves selective methods of forming *E* tri-substituted double bonds. Because an advanced intermediate in the synthesis also serves as an entry point to verticillene (**16**), the first enantioselective synthesis of the putative taxane biosynthetic precursor, (+)-verticillene (**16**), has also been achieved.

Thesis Supervisor: Scott C. Virgil

Title: Assistant Professor of Chemistry

To my parents.

Acknowledgments

These past five years at MIT have been enjoyable and rewarding, and they could not have been such without the presence of these important people in my life.

My parents, though some three thousand miles away, have loved and supported me all this time as if they had been living next door.

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My long-time roommate and friend Andy Fung shared with me much fun time of dinning out, watching movies and listening to foreign-language music. Terrence Ho and I have been partners in world travel. I would never have visited South America if I have not met this great friend in Montreal four summers ago.

Past and present friends of my Tuesday-night fellowship have been loving and caring in a way that only a brother or a sister would. They have lifted burdens from my heart in times of stress and have put smiles on my face in times of sorrow.

Lastly, the David and Lucile Packard Foundation has been a generous source of funding for my education at MIT and the research presented in this thesis.

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Chapter 1. Introduction — Taxol and its Biosynthesis

Tremendous interests in the chemical compound taxol (paclitaxel)[1] have been generated over the past decade, due mainly to the molecule's interesting structure (**1**, Scheme 1) and its efficacy as an anti-cancer drug.[2] The scarce supply of taxol from its natural sources and the potential of a large demand for the drug have also intensified research efforts in areas such as its large-scale production through semi-synthesis from more abundant taxane metabolites and through biological means such as cell culture. Such biology-oriented endeavors would benefit greatly from a fundamental understanding of the biogenesis of taxol and its natural analogs. It not only helps to answer the intriguing question of how taxol arises in nature, but can also aid the development of a long-term solution to the problem of supplying taxol.[3]

1.1 Historical background

Taxol was first discovered during screenings of bark samples collected by Barclay from the conifer *Taxus brevifolia* Nutt. (the Pacific yew) in the Oregonian forests in the

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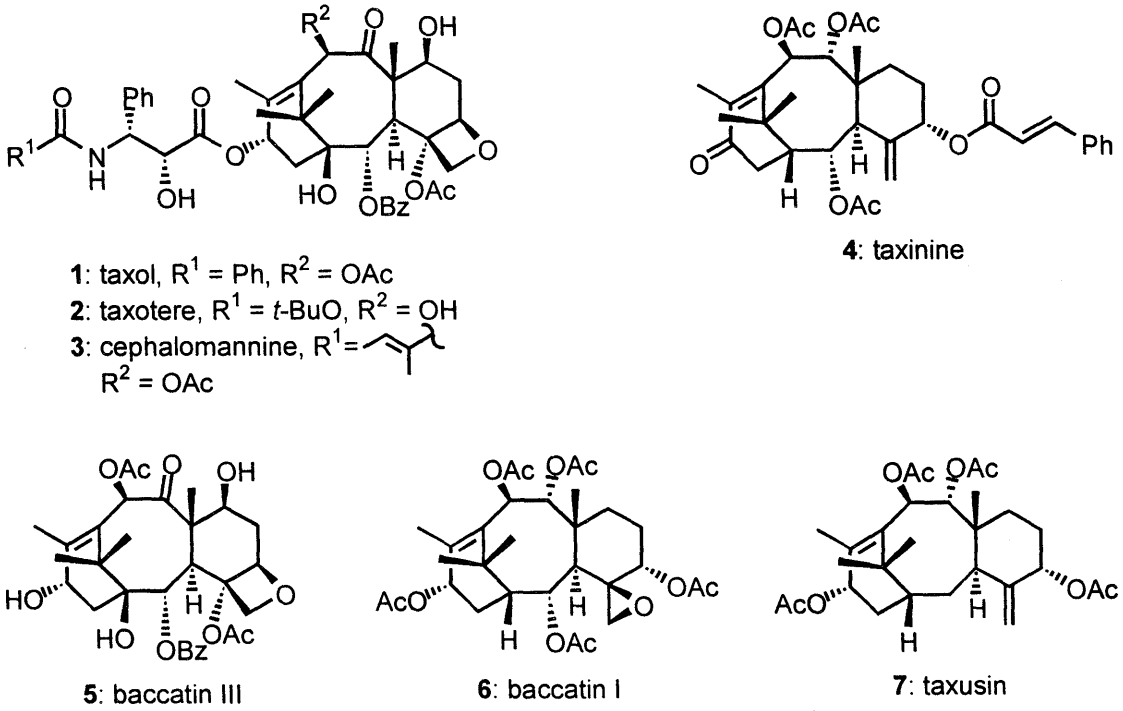
[1] Taxol is a registered trademark of Bristol-Myers Squibb. The generic name of the molecule is paclitaxel. The much more familiar name taxol will be used in this paper in lieu of paclitaxel.

[2] For reviews of taxol, see: (a) *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, 1995. (b) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15. (c) Kinsgton, D. G. I. *Pharmac. Ther.* **1991**, *52*, 1.

[3] Hassler, S., Ed. *Nature Biotechnology* **1996**, *14*, 1055.

1960's.[4] Noted for its potent activity against leukemia and various tumor cell lines, taxol was isolated and identified in 1971 at the National Cancer Institute.[5] The structure of this cytotoxic compound was determined to be a highly oxygenated diterpenoid,[6] belonging to a class of natural products called taxanes, found in various species of the *Taxus* plant family (Scheme 1).[7]

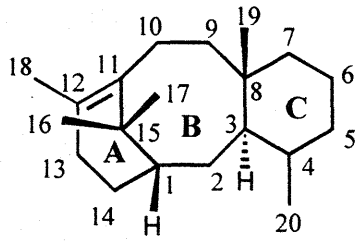


Scheme 1. Taxol and other taxane analogs.

Taxol and other taxane analogs (**2**-**7**) share a common tricyclic carbon framework (Scheme 2). The unique taxane ring-system consists of the bridged

[4] Junod, T. *Life* **1992**, *15*, 71.
[5] Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.
[6] Diterpenoids are compounds containing a C_{20} skeleton, made up of four isoprene units.

bicyclo[5.3.1]undecane system of the A-B portion of the molecule, and the *trans*-fused bicyclo[6.4.0]dodecane system of the B-C portion. This novel arrangement is further complicated by the bridgehead double bond in the A-ring and the geminal methyl groups at C15. The overall result is a very compact and rigid scaffold, on which the extensive oxygen functionality, the eleven stereocenters, the oxetane moiety and the C13 side chain of taxol are built. Such complexity of taxol's framework and functionality has presented a great challenge to the synthetic chemist, but efforts have ultimately resulted in several impressive total syntheses[8] that have become milestones in the field of organic synthesis.



Scheme 2. Taxane framework and numbering system.

Interests in taxol were greatly heightened when its unique mechanism of action

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[7] (a) Lythgoe, B. *The Alkaloids* **1968**, *10*, 597. (b) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Nozoe, S. *Natural Products Chemistry*; Kodansha-Academic Press: Tokyo, 1974; Vol. 1, pp. 281. (c) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425.

[8] (a) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Nicolaou, K. C.; Zang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630; and also: Nicolaou,, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Coulandouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. (c) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1723; and also: Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bommann, W. G.; Alaimo, C. A.; Coburn, C. A.; Digrandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, 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.

was determined in 1979.[9] For years, it was believed that taxol shared its mode of action with the potent and well-studied anti-cancer agents, vinca alkaloids and colchicine, both of which act upon microtubules. These drugs stabilize microtubule formation so that mitosis is disrupted and the dividing cancer cell experiences cell-cycle arrest and ensuing cell-death. Microtubules are intracellular structures that are responsible for many cellular functions including the formation of the cytoskeleton, the transmission of cellular signals,[10] the positioning of organelles,[11] and the movement of the cell.[12] Microtubules also play a crucial role during mitosis. They form spindle fibers,[13] which align[14] and then partition[15] the newly duplicated chromosomes of the mother cell, so that each of the daughter nuclei would contain one set of the genetic materials.

Microtubules are formed by the polymerization of small protein subunits called tubulin.[16] Microtubules and tubulin are in a dynamic equilibrium, and the delicate balance[17] between the assembly and disassembly of tubulin is critical for the dynamic functions of microtubules, including those during mitosis. Taxol has the unique property of stabilizing microtubules through complexation to tubulin dimers.[18] Microtubules formed by taxol-bound tubulin are resistant to depolymerization, adversely affecting the dynamics of microtubule equilibrium. Cancer cells treated with taxol are unable to undergo mitosis because of the apparent absence of mitotic spindle fibers and the

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[9] Horwitz, S. B.; Fant, J.; Schiff, P. B. *Nature* **1979**, *277*, 665.
[10] Rasenick, M. M.; Wang, N.; Yan, K. *Adv. Second Messenger Phosphoprotein Res.* **1990**, *24*, 381.
[11] Cooper, M. S.; Cornell-Bell, A. H.; Chernjawsky, A.; Dani, J. W.; Smith, S. J. *Cell* **1990**, *61*, 135.
[12] Scholey, J. M. *Nature* **1990**, *343*, 118.
[13] (a) McIntosh, J. R.; Koonce, M. P. *Science* **1989**, *249*, 622. (b) Kuriyama, R.; Nislow, C. *BioEssays* **1992**, *14*, 81.
[14] McIntosh, J. R.; Pfarr, C. M. *J. Cell Biol.* **1991**, *115*, 577.
[15] Gorbsky, G. *BioEssays* **1992**, *14*, 73.
[16] Sullivan, K. F. *Annu. Rev. Cell Biol.* **1988**, *4*, 687.
[17] Purich, D. L.; Kristofferson, D. *Adv. Protein Chem.* **1984**, *36*, 133.
[18] Horwitz, S. B.; Fant, J.; Schiff, P. B. *Nature* **1979**, *277*, 665.

presence of abnormal, microtubule bundles.[19]

Because of taxol's efficacy as an anti-cancer drug, the past decade has seen a dramatic increase in demand for the drug. Taxol was recently approved by the Food and Drug Administration (FDA) for the treatment of the ovarian and the breast cancer. And as taxol's use will likely increase, both in the treatment of earlier stages of cancer and in the treatment of additional cancer types,[20] the issue of taxol supply will become more serious.

To meet the demand of taxol, extraction from its natural sources is not a sustainable solution because of the low taxol content in the Pacific yew, as well as other *Taxus* species.[21] For example, to obtain the two grams of taxol needed to treat one typical patient requires at least 20 kilograms of Pacific yew bark, which translates to a cost of over $10,000 and the death of about 12 mature yew trees each year.[22] Widespread harvest of yew bark will no doubt pose a threat on the delicate environment of the Pacific Northwest.

Because the production of taxol by total synthesis is not viable on an industrial scale due to low yield and the number of steps, taxol is currently manufactured following a semi-synthesis[23] in which the 10-deacetyl derivative (**8**) of baccatin III is coupled with an enantiomerically pure synthetic β-lactam fragment **9** (Scheme 3).[24] Similarly, taxotere[25] (**2**), a synthetic analog of taxol also approved by the FDA as an anti-cancer

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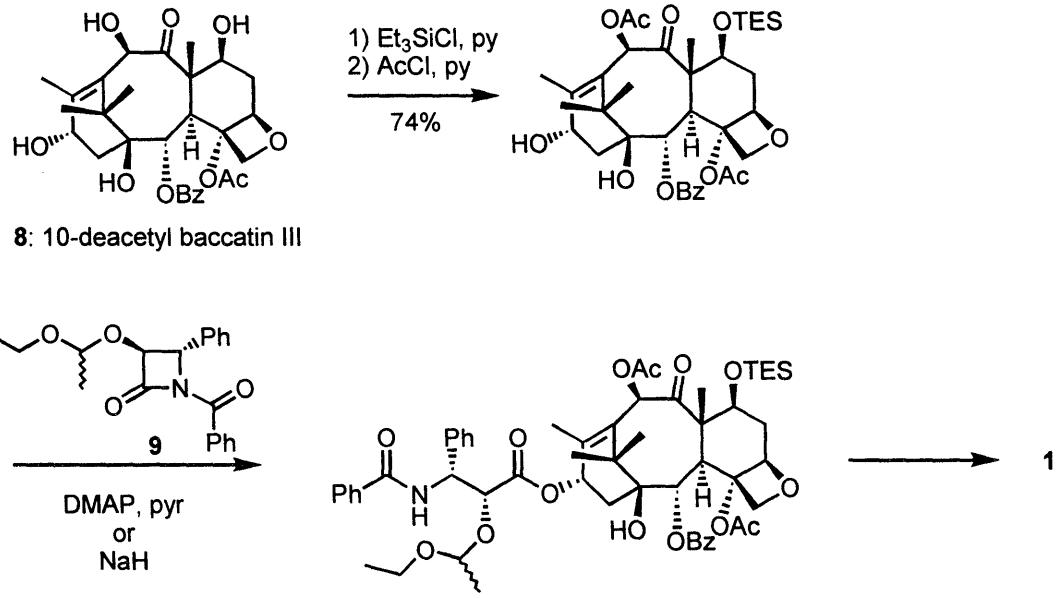
[19] Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*,1561.
[20] Slichenmeyer, W. J.; Von Hoff, D. D. *Anti-Cancer Drugs* **1991**, *2*, 519.
[21] (a) Whiterup, L. M.; Look, S. A.; Stasko, M. W.; Ghiorzi, T. J.; Muschik, G. M.; Cragg, G. M. *J. Nat. Prod.* **1990**, *53*, 1249. (b) Vidensek, N.; Lim, P.; Campbell, A.; Carlson, C. *J. Nat. Prod.* **1990**, *53*, 1249.
[22] Hartzell, H. *The Yew Tree*; Hugolosi Press: Eugene, OR, 1991.
[23] Holton, R. A. *Workshop on Taxol and Taxus: Current and Future Perspectives*; National Institute of Cancer: Bethesda, MD, 1990.
[24] (a) Holton, R. A. Eur. Pat. App. 400971, 1990. (b) Ojima, I.; Habus, I.; Zhao, M.; Georg, G.; Jayasinghe ,L. R. *J. Org. Chem.* **1991**, *56*, 1681. (c) Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.
[25] Taxotere is a registered trademark of Rhone-Poulenc. The generic name for the compound is docetaxel.

drug, is produced on a large scale from the coupling of **8** and a synthetic side chain.[26] A taxane possessing almost all of the functionality of taxol, baccatin III can be extracted[27] in larger quantities (1 in 3000 kg) from the renewable needles and twigs of a much more common shrub, the European yew (*Taxus baccata*). Because harvesting from these plantation-grown plants do not result in their deaths, the environmental impact is far less.



Scheme 3. Holton-Ojima semi-synthesis of taxol.

Perhaps the most promising means of solving the problem of taxol supply is plant-cell culture. Cells cultured from the callus tissue of *T. brevifolia* have been shown to be capable of producing taxol as a major secretion product.[28] The possibility of using other *Taxus* species has also been actively pursued. Recently, a plant-cell signal transducer

[26] Colin, M.; Guénard, D.; Guéritte-Voegelein, F.; Poiter, P. U.S. Pat. App. 4924012, 1991.
[27] McCormick, D. *Bio/Technology* **1993**, *11*, 26.

methyl jasmonate has been used to induce a five-fold increase in taxol production and a 20-fold increase in baccatin III production from cells cultured from *Taxus media* (a cross between the European yew and the Japanese yew, *Taxus cuspidata*), as well as significant increases from cells cultured from *T. brevifolia* and *T. baccata*.[29]

In addition, indigenous to the Pacific yew and the Himalayan yew (*Taxus wallachiana*), the fungi *Taxomyces andreanane*[30] and *Pestalotiopsis microspora*[31], respectively, have also been isolated and cultured to produce taxol. These findings could potentially lead to fermentation technology for large-scale taxol production. Whether the fungi generate taxol the same way as *T. brevifolia* remains to be investigated.

In comparison to the total volume of output in taxol research, relatively little has been reported on the biosynthesis of taxol. Studies of taxine, isolated from *T. baccata*, have shown that its side chain, (3*R*)-dimethylamino-3-phenylpriopinate, or Winterstein's acid, comes from phenylalanine.[32] It is therefore probable that taxol's own C13 side-chain is similarly formed from phenylalanine.[2c] It has also been suggested the side chain is not attached as an intact unit, but as phenylisoserine, followed by subsequent benzoylation.[33] As to taxol's characteristic oxetanyl D-ring, it is likely formed from the rearrangement of the epoxide of allylic acetate **10** (Scheme 4), a moiety contained in baccatin I (**6**).[34] Model studies have yet to confirm these hypotheses.

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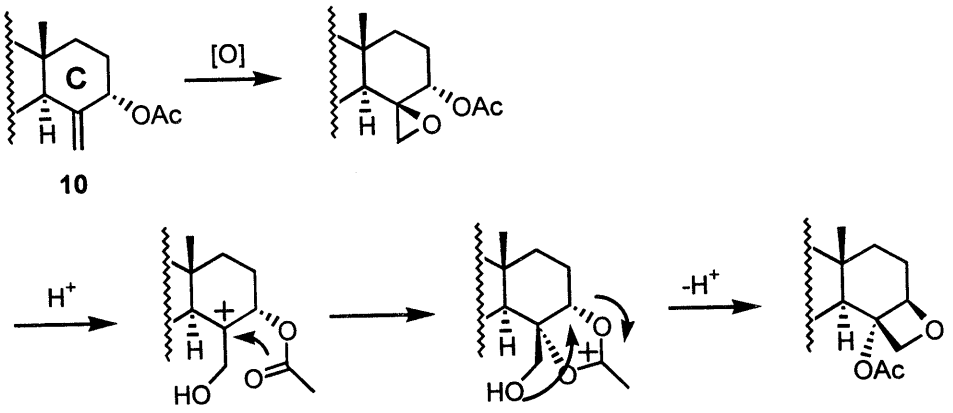
[28] Christen, A. A.; Gibson, D. M.; Bland, J. U.S. Pat. App. 5019504, 1992.
[29] Yukimune, Y.; Tabata, H.; Higashi, Y.; Hara, Y. *Nature Biotechnology* **1996**, *14*, 1129.
[30] (a) Stierle, A.; Strobel, G.; Stierle, D. *Science* **1993**, *260*, 214. (b) Stone, R. *Science* **1993**, *260*, 154.
[31] Strobel, G.; Yang, X.; Sears, J.; Kramer, R.; Sidhu, R., S.; Hess, W. M. *Microbiology* **1996**, *142*, 435.
[32] Leete, E.; Bodem, G. B. *Tetrahedron Lett.* **1966**, 3925. (b) Platt, R. V.; Opie, C. T.; Haslam, E. *Phytochemistry* **1984**, *23*, 2211.
[33] Fleming, P. E.; Knaggs, A. R.; He, X.-G.; Mocek, U.; Floss, H. G. *J. Am. Chem. Soc.* **1994**, *116*, 4137.
[34] Swindell, C. S.; Britcher, S. F. *J. Org. Chem.* **1986**, *51*, 793. (b) Francl, M. M.; Hansell, G.; Patel B. P.; Swindell, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3535. (c) Guéritte-Voegelein, F.; Guénard, D.; Potier, P. *J. Nat. Prod.* **1987**, *50*, 9.



Scheme 4. Postulated mechanism of D-ring formation in taxol biosynthesis.

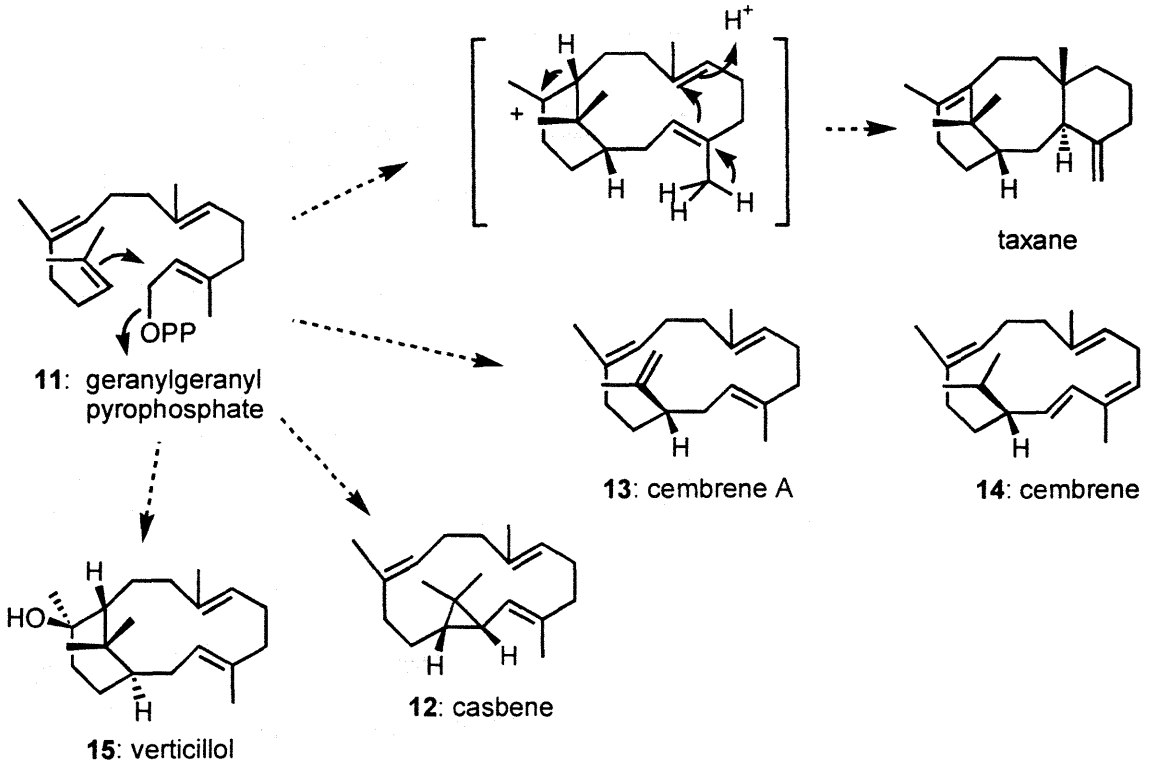
Among all of the questions revolving around taxol biogenesis, perhaps the most intriguing one is the formation of the unprecedented tricyclic carbon framework. What is its origin? Are the rings in taxol all generated in one enzymatic step? Is the framework constructed before oxygenation occurs, or does taxol arise from already functionalized precursor? Do other naturally occurring taxanes such as taxusin (**7**) share the same biogenetic pathway as taxol? Attempt to answer some of these questions have formed the basis of several studies reported in the past decade, as well as the one presented in this thesis.

1.2 Biosynthesis of taxol's carbon framework

When the first taxanes were studied in the early 1960's, Lythgoe *et al.*[35]

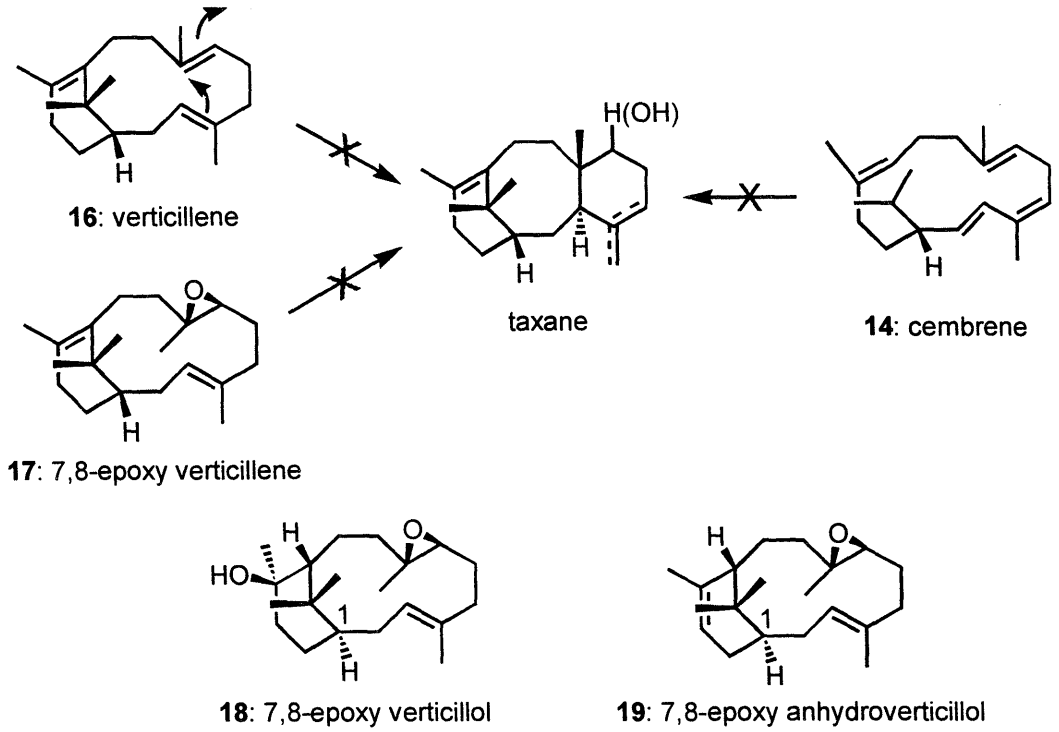
[35] Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc. (C)* **1966**, 1933.

hypothesized that the carbon skeleton arises from geranylgeranyl pyrophosphate (**11**),[36] a universal diterpenoid precursor composed of four isoprene units. It was proposed that through a series of intramolecular electrophilic π cyclization reactions, initiated by the ionization of the pyrophosphate group of **11**, the tricyclic framework of taxane is generated (Scheme 5). Similar biogenesis of other cyclic diterpenoid natural products, such as casbene (**12**), cembrenes[37] (**13**, **14**) and verticillol[38] (**15**) have been suggested by others (Scheme 5).



Scheme 5. Geranylgeranyl pyrophosphate as a common precursor to cyclic diterpenoids.

[36] West, C. A. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, pp. 375-411.
[37] Dauben, W. G.; Thiessen, W. E., Resnick, P. *J. Am. Chem. Soc.* **1962**, *84*, 2015.
[38] Erdtman, H.; Norin, T.; Sumimoto, M.; Morrison, A. *Tetrahedron Lett.* **1964**, 3879.



Scheme 6. Unsuccessful attempts to form taxane framework *via* transannular cyclization.

It was not until twenty years later when Lythgoe's hypothesis was first investigated in the laboratory. Pattenden *et al.* prepared a putative taxane precursor, designated verticillene (**16**, Scheme 6), in order to study its possible role in the proposed mechanism of taxane biosynthesis.[39] The initial goal was to elicit an electrophilic transannular cyclization[40] of the bicyclic verticillene to form the tricyclic taxane framework. However, under various acidic conditions, verticillene did not undergo the expected cyclization. In another attempt, verticillene was converted to the 7,8-epoxide (**17**) and was ionized by Lewis acid to initiate the desired electrophilic cyclization. Once

[39] Begley, M. J.; Jackson, C. B.; Pattenden, G. *Tetrahedron* **1990**, *46*, 4907.

again, the reaction failed to give any cyclized product (Scheme 6).

A few natural products have also been investigated for their likely role as a taxane biosynthetic precursor (Scheme 6). Model studies on the acid-catalyzed transannular cyclization of cembrene (**14**) by Dauben *et al.* failed to yield any product with a taxane skeleton.[41] A constituent of the wood of the conifer *Sciadopitys verticillata*, verticillol[42] (**15**) is structurally similar to verticillene (**16**). It should be noted, however, that naturally occurring (+)-verticillol is "enantiomeric" to taxanes, having the opposite configuration at C1. Unfortunately, reaction of the epoxy derivatives (**18**, **19**) of verticillol with Lewis acid did not result in transannular cyclization.[39]

1.3 A closer look at the mechanism and its intermediates in taxadiene formation

While the frustrating failure to elicit the desired cyclization in cembrene, verticillene or its derivatives did not rule out their possible role in taxane biosynthesis, it prompted a closer look at other possible intermediates in the proposed mechanism as likely cyclization precursors (Scheme 7). Because the cascade of cyclization reactions is initiated by the ionization of geranylgeranyl pyrophosphate (**11**), the initial steps in the mechanism would most likely be the formation of the C1-C15 and the C15-C11 bonds to give a bicyclic carbocation **20**.

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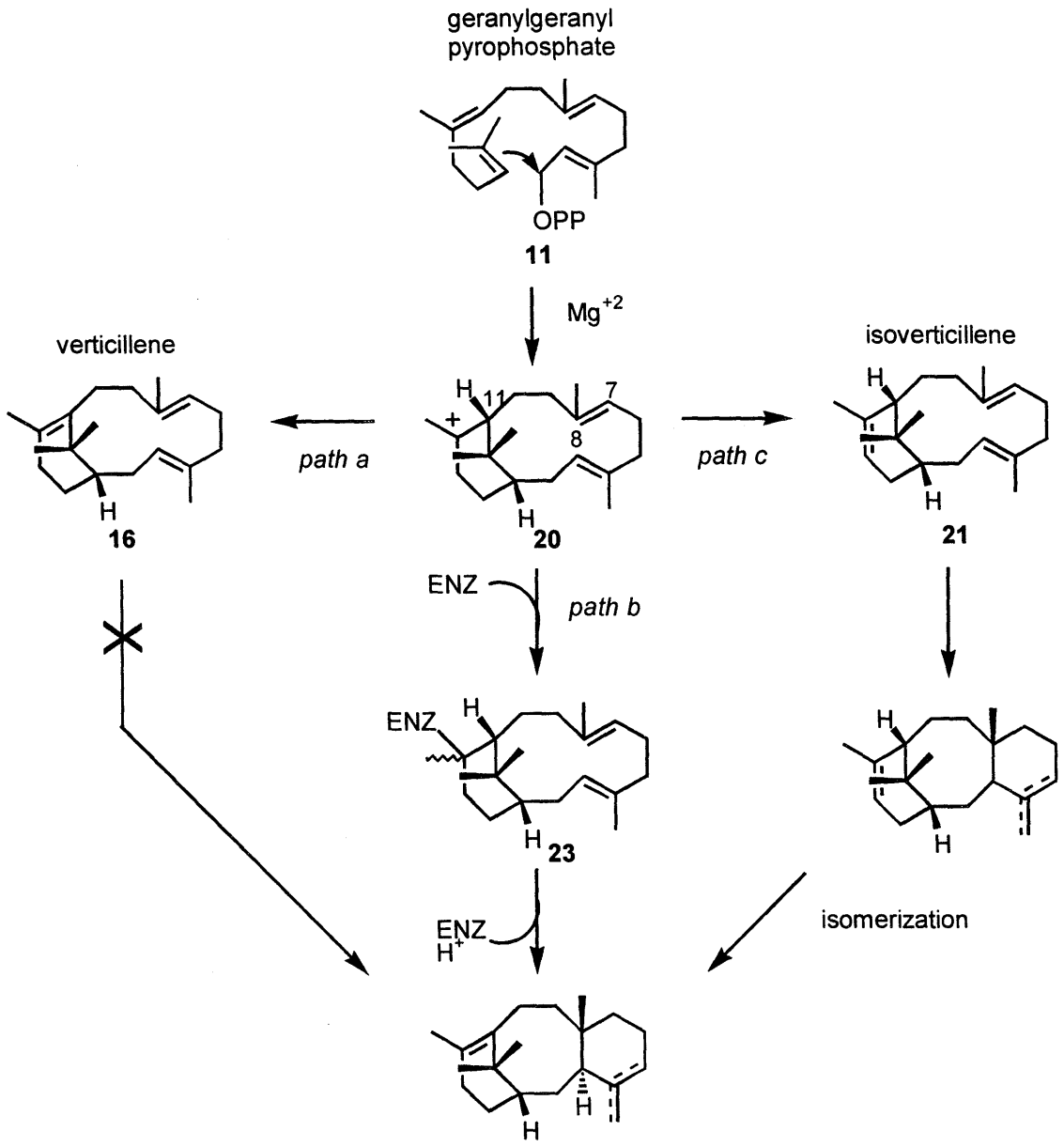
[40] For a review of transannular cyclization see: Harrowven, D. A.; Pattenden, G. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: London, 1991; Vol. 3, pp. 379-411.
[41] Dauben, W. G.; Hubbell, J. P.; Oberhansli, P.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 669.
[42] Karlsson, B.; Pilotti, A.-M.; Söderholm, A.-C.; Norin, T.; Sundin, S.; Sumimoto, M. *Tetrahedron* **1978**, *34*, 2349.



Scheme 7. Possible alternative mechanisms of taxadiene formation.

Three possible scenarios describe the subsequent fate of carbocation **20**. In the most direct one (*path a* in Scheme 7), **20** is deprotonated at C11 to give verticillene (**16**), which then undergoes the hypothetical transannular cyclization to give taxadiene. It is also possible (*path b* in Scheme 7) that carbocation **20** remains enzyme-bound and

undergoes transannular cyclization before deprotonation at C11 to give taxadiene. A third and more indirect possibility (*path c* in Scheme 7) is the deprotonation of **20** at C13 to give an isomer of verticillene, designated as isoverticillene (**21**). Transannular cyclization of isoverticillene provides a taxadiene isomer, whose C12-C13 double bond would be repositioned at C11-C12 in a subsequent isomerization step.

One crucial difference between the latter two pathways and the first is the three-dimensional shape of the transannular cyclization precursor as defined by the geometry at the bridgehead. Verticillene (**16**) has a double bond at the C11-C12 position. The bridgehead at C11 is therefore planar, making the 12-membered ring rounder and more "open" (Scheme 8). Enzyme-bound **23** and isoverticillene (**21**), on the other hand, have a pyrimidalized center at C11. The relative bridgehead stereochemistry being *cis*, the more oblong **23** and **21** seem more favorably poised to undergo transannular cyclization than either verticillene (**16**) or verticillol (**15**).

Simple molecular modeling[43] shows that the distances between C3 and C8 (the atoms to be joined by a σ bond) in verticillene (**16**) and isoverticillene (**21**) are significantly different: 3.8 Å and 3.0 Å, respectively (Scheme 8). A similar comparison can be made between the corresponding cationic intermediates, **22** and **24**, in which the C7 position is protonated and the C8 position is the reacting sp^2 center. The C3-C8 distances for **22** and **24** are 3.7 Å and 2.9 Å, respectively.

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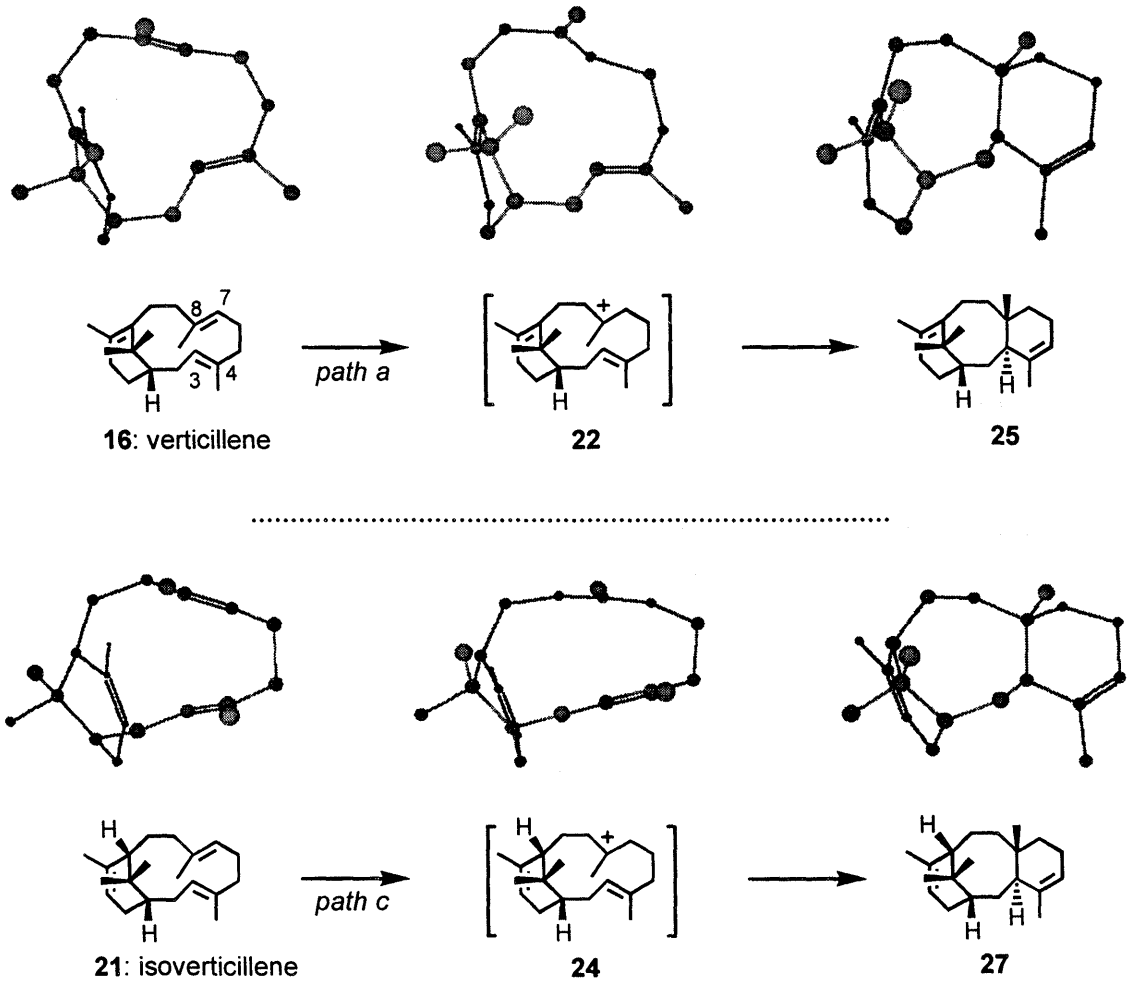
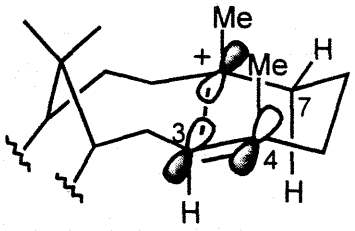
[43] Structures **16**, **21**, **22**, **24**, **25**, **27** were modeled using MM2 on Chem3D Plus (Macintosh Version 3.1) by CambridgeSoft Corp. Structures **16**, **21**, **22**, **24** were built first as conformers most resembling the cyclized products **25**, **27**. Structures **16**, **21**, **22**, **24** were then modified through energy-minimization. The choice and comparisons of these energy-minimized structures were made under the crude assumption that the transition state of the transannular cyclization reaction would be product-like, and the cyclization precursors/intermediates would most likely undergo reaction *via* conformations that most resemble the cyclized products.



Scheme 8. Energy-minimized conformations of possible taxane cyclization precursors.[43]

More important than the difference in proximity, however, is the difference in the orientation of the C3-C4 and C7-C8 double bonds. This is because the π orbital of the C3-C4 double bond must interact with the p-orbital of C8 in order to form the C3-C8 σ bond (Scheme 9). In verticillene (**16**), the planes containing the relevant double bonds are virtually orthogonal to each other, and the C3-C4 π orbital in cationic intermediate **22** is not at all pointing towards C8 (Scheme 8). Modeling suggests if the C3-C4 double

bond of either **16** or **22** were to be re-oriented for optimal orbital overlap with C8, the molecule has to be distorted such that the C3-C8 distance becomes even greater.



Scheme 9. Formation of C3-C8 bond *via* electrophilic cyclization.

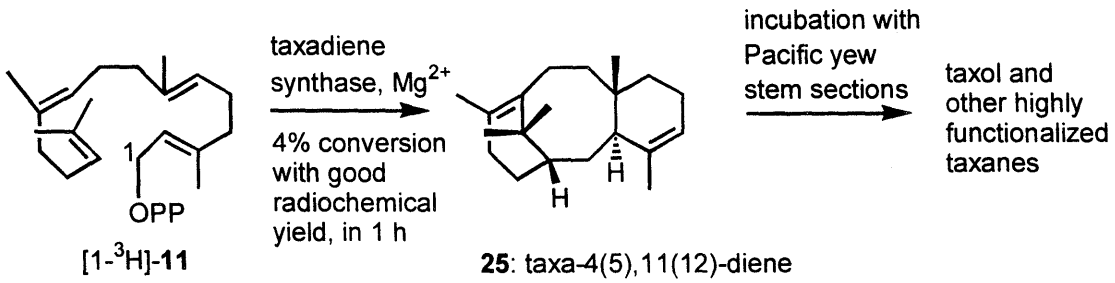
On the other hand, in isoverticillene (**21**) the planes containing the C3-C4 and the C7-C8 double bonds are virtually parallel to each other. The C3-C4 π orbital in the corresponding cationic intermediate **24** is also poised to interact with the C8 center. It seems quite possible that the significant difference in the geometry of **16** and **21** could decide their ability to undergo transannular cyclization, and that isoverticillene could serve as a precursor to taxane structures.

1.4 Recent development in the elucidation of taxane biosynthesis

Shortly after initial studies of isoverticillene had commenced, Croteau *et al.* reported in 1995 and 1996 a series of impressive findings on the biogenesis of taxol.

In initial studies, cell-free extracts prepared from the stem section of *T. brevifolia* saplings were incubated with ^{3}H-labeled geranylgeranyl pyrophosphate (**11**, Scheme

10).[44] The result was a 4% conversion to a ^{3}H-containing hydrocarbon as the major product. A sufficient amount of this product was isolated and its structure was identified to be taxa-4(5),11(12)-diene **25**, a natural product itself found (<0.0001% by weight) in the bark of *T. breviolia*. Taxadiene **25** was subsequently incubated with cell cultured from the yew stem sections, affording in good radiochemical yield highly-functionalized taxane metabolites, including 10-deacetyl baccatin III and taxol itself. These results have not only identified taxadiene **25** as an intermediate in taxane biosynthesis, but have also confirmed the formation of the taxane framework from geranylgeranyl pyrophosphate as the first committed step, preceding any oxygenation and side-chain acylation.



Scheme 10. Enzyme catalyzed formation of first taxadiene intermediate.

The enzyme responsible for catalyzing taxadiene formation was later purified and characterized.[45] Taxadiene synthase is a monomeric protein of molecular weight of 79 kDa. It is in many ways, such as size and a divalent metal-ion requirement, similar to other diterpenoid cyclases such as casbene synthase[46] in castor bean and abietadiene

[44] Koepp, A. E.; Hezari, M.; Zajicek, J.; Vogel, B. S.; LaFever, R. E.; Lewis, N. G.; Croteau, R. *J. Biol. Chem.* **1995**, *270*, 8686.
[45] Hezari, M.; Lewis, N. G.; Croteau, R. *Arch. Biochem. Biophys.* **1995**, *322*, 437.
[46] Dueber, M. T.; Adolf, W.; West, C. A. *Plant Physiol.* **1978**, *62*, 598.

synthases[47] in conifers. Taxadiene synthase has very low activity levels, and the reaction it catalyzes is very likely the rate-determining step in taxol biosynthesis. Croteau *et al.* have recently cloned[48] the cDNA for taxadiene synthase, providing further information of the enzyme.

While these recent results describe the first step of taxane biosynthesis for the first time at the enzyme level, the mechanistic course of taxadiene synthase is yet to be elucidated. In a subsequent, more detailed mechanistic study,[49] Croteau *et al.* was unable to detect in the taxadiene synthase reaction the formation of any intermediates such as cembrene A (**13**), casbene (**12**) or verticillene (**16**), nor were they able to convert these potential olefinic intermediates into taxa-4(5),11(12)-diene (**25**) at detectable levels *via* incubation with taxadiene synthase. These results, however, do not rule out any enzyme-bound olefinic intermediate.

Two important findings resulted from studies of the reaction of various ^{2}H-labeled geranylgeranyl pyrophophates with taxadiene synthase.[49] Using mass spectrometry analysis, Croteau *et al.* concluded that taxa-4(5),11(12)-diene (**25**) is formed without the initial formation of taxa-4(20),11(12)-diene (**28**, Scheme 11). Contrary to general belief, deprotonation of the final cationic intermediate **29** occurs at C5, not at C20.

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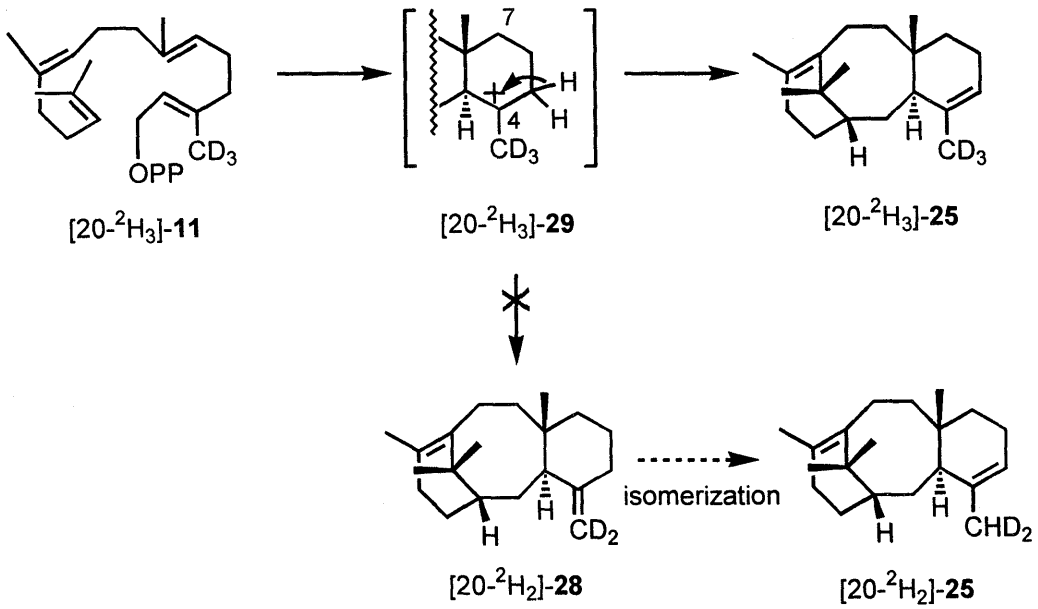
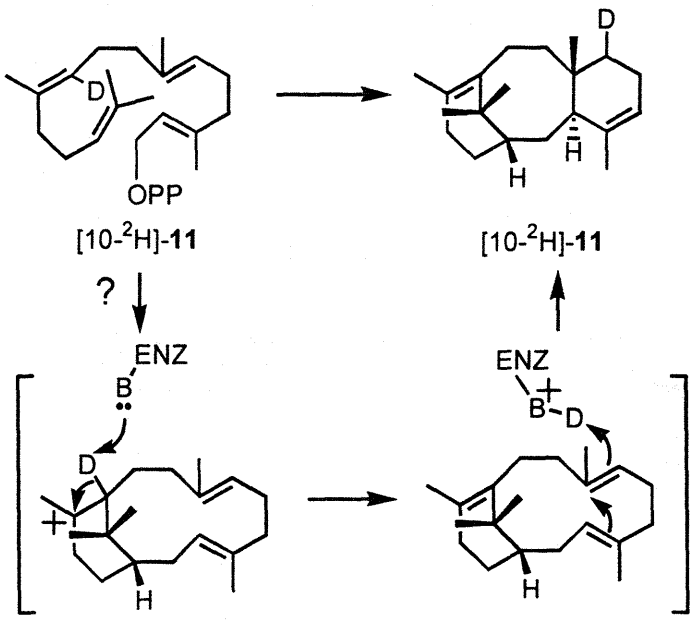
[47] LaFever, R. E.; Stofer Voge, B.; Croteau, R. *Arch. Biochm. Biophys.* **1994**, *313*, 139.
[48] Wildung, M. R.; Croteau, R. *J. Biol. Chem.* **1996**, *271*, 9201.
[49] Lin, X.; Hezari, M.; Koepp, A. E.; Floss, H. G.; Croteau, R. *Biochemistry* **1996**, *35*, 2968.



Scheme 11. Mechanism of formation of C4-C5 double bond.

In addition, when incubated with taxadiene synthase, deuterium in [10-^{2}H]-geranylgeranyl pyrophosphate was transferred to the C7 position in taxadiene, suggesting either: 1) a direct intramolecular proton transfer, or 2) an indirect transfer mediated by a protein residue at the enzyme active site (Scheme 12).[49]

In spite of Croteau's recent findings, it is still uncertain whether the geometry of the transannular cyclization precursor as defined by the bridgehead stereochemistry is crucial for the formation of taxadiene intermediate. The feasibility of transannular cyclization of isoverticillene is yet to be evaluated.



Scheme 12. Intramolecular deuterium transfer in taxadiene formation.[49]

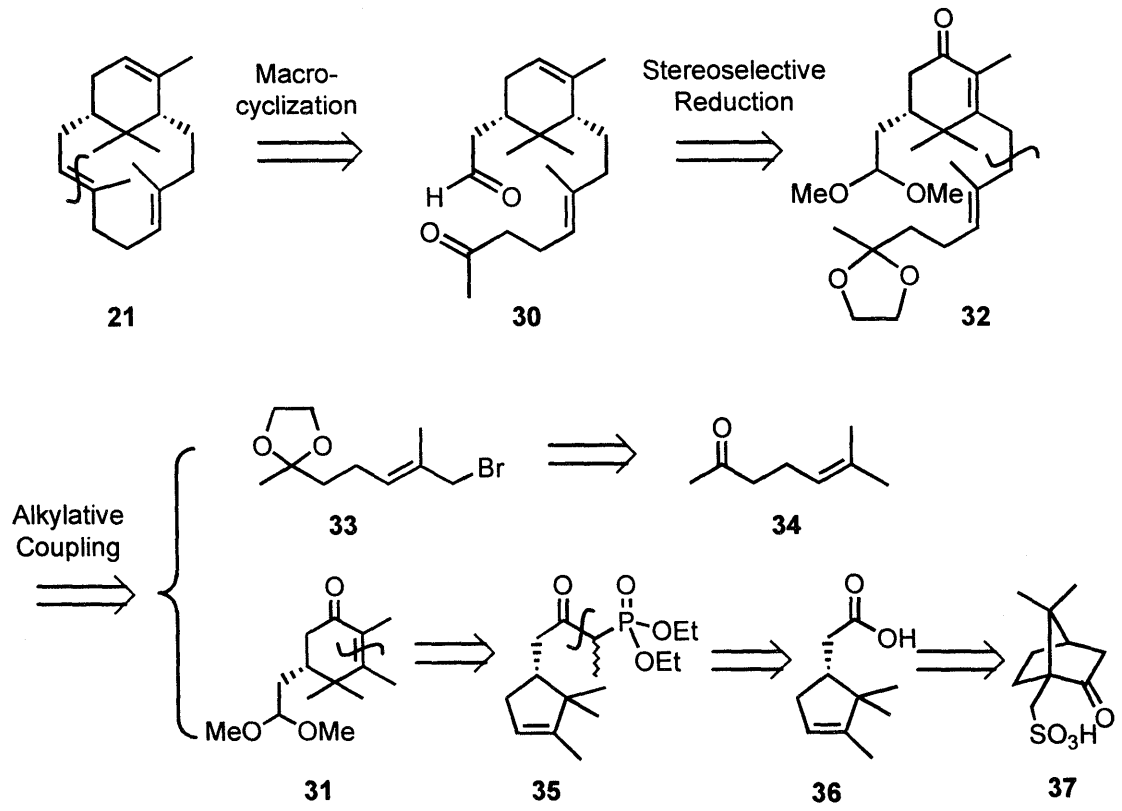
Chapter 2. Efforts towards the Synthesis of Isoverticillene — the McMurry Cyclization Approach

To study the possible role of isoverticillene in taxane biosynthesis as described in the previous chapter, it was necessary to synthesize the molecule in order to evaluate its ability to undergo transannular cyclization to form the taxane carbon framework. While it was possible to modify existing syntheses[39,49] of racemic verticillene to achieve our goal, the execution of an original and efficient enantioselective synthesis of isoverticillene would prove a challenging and fruitful endeavor. Described in the following two chapters are efforts towards the total synthesis of enantiomerically pure isoverticillene.

2.1 Retrosynthetic analysis

Isoverticillene (**21**) is a bridged bicyclo[9.3.1] hydrocarbon, composed of a six-membered ring, a 12-membered macrocycle, two important stereocenters at the bridgehead, and three carbon-carbon double bonds as its only functional groups.

When planning the synthesis of this seemingly simple compound, difficulty of constructing the 12-membered ring was anticipated. As suggested by molecular modeling,[43] the presence of the two *E* double bonds and the geminal methyl groups at C15 causes the macrocyclic portion of isoverticillene to be considerably more rigid and strained than in the case of a simple bicyclo[9.3.1] alkane.



Scheme 13. Retrosynthetic analysis of isoverticillene synthesis.

Many methods have been devised to construct macrocyclic compounds.[50] Used successfully in examples of medium- and large-ring syntheses,[51] the McMurry carbonyl coupling reaction[52] was expected to be a good way to effect the potentially difficult macrocyclization. This would be especially convenient, because, unlike other intramolecular coupling reactions requiring reactive partners of opposite "polarities" to be

[50] For reviews on syntheses of macrocyclic compounds, see: (a) Roxburg, C. J. *Tetrahedron* **1995**, *51*, 9767. (b) Meng, Q.; Hesse, M. In *Topics in Current Chemistry*, Weber, E., Vögtle, F., Eds.; Springer-Verlag: Berlin, 1991; Vol. 161, 107. (c) Ho, T.-L. *Carbocycle Construction in Terpene Synthesis*; VCH Publishers: New York, 1988; pp. 240-247.

[51] For examples of macrocylization using the McMurry coupling reaction, see ref. 52, references therein, and: (a) Li, W.; Mao, J.; Li, Y.; Li, Y. *Org. Prep. Proc. Intl.* 1994, 26, 445. (b) Li, Y.; Li, W.; Li, Y. *J. Chem. Soc., Perkin Trans.1* **1993**, 2653. (c) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942.

on the same molecule, the McMurry reaction would require only one type of functionality (the carbonyl) simplifying the task of functional group manipulation in preparing the macrocyclization precursor. This key step was to be left towards the end of the synthesis in order to avoid potential problems caused by the early presence of the rigid and possibly sensitive macrocycle. Therefore, the first disconnection in the retrosynthetic analysis (Scheme 13) was made at the C3-C4 double bonds to give a ketoaldehyde intermediate (**30**).

Ketoaldehyde **30** was further disconnected to give a cyclohexenone "core" (**31**) and a side-chain fragment (**33**). While the α,β-unsaturated ketone of **31** could be used as a handle in its coupling with the side chain *via* an alkylation reaction, this same enone functionality could be exploited later in the alkylation product (**32**) to set the stereochemistry at C11 of isoverticillene through the use of diastereoselective methods such as the Ireland dissolving-metal reduction.

While side-chain fragment **33** could be synthesized from commercially available heptenone (**34**) in three steps, cyclohexenone **31** would be synthesized from ketophosphonate **35**, which itself would be derived from (*R*)-campholenic acid (**36**). The five-membered ring of **35** would first be opened by ozonolysis; the acyclic product would then be re-cyclized by a Horner-Wadsworth-Emmons reaction to give six-membered **31**. (*R*)-Campholenic acid (**36**), in turn, could be prepared in enantiomerically pure form from commercially available (1*S*)-(+)-10-camphorsulfonic acid (**32**).

This synthetic plan features a convergent approach and the utility of an inexpensive starting material that is readily available in enantiomerically pure form.

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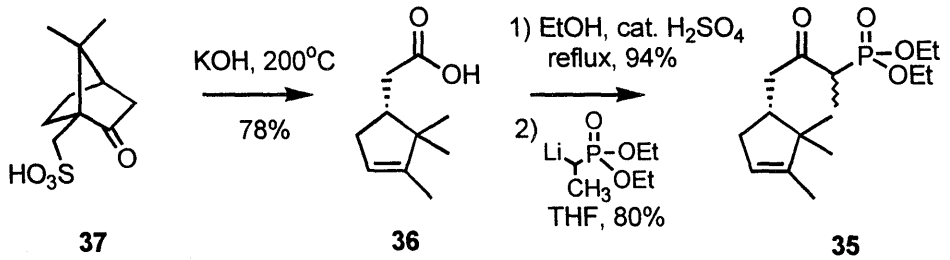
[52] For a review, see: Lectka, T. In *Active Metals: Preparation, Characterization, Application*; Fürstner, A., ed. VCH Publishers: New York, 1996.

2.2 Synthesis of cyclohexenone core and side-chain fragment

For the preparation of cyclohexenone **31**, (1*S*)-(+)-10-camphorsulfonic acid (**37**) was converted to (*R*)-campholenic acid **36** in 78% yield through an alkali fusion reaction (Scheme 14).[53] Acid **36** was first converted to the ethyl ester through an acid-catalyzed esterification reaction in 94% yield. The product was then reacted with the lithium anion of diethyl ethanephosphonate to give a good yield (80%) of an inseparable diastereomeric mixture of ketophosphonate **35**.

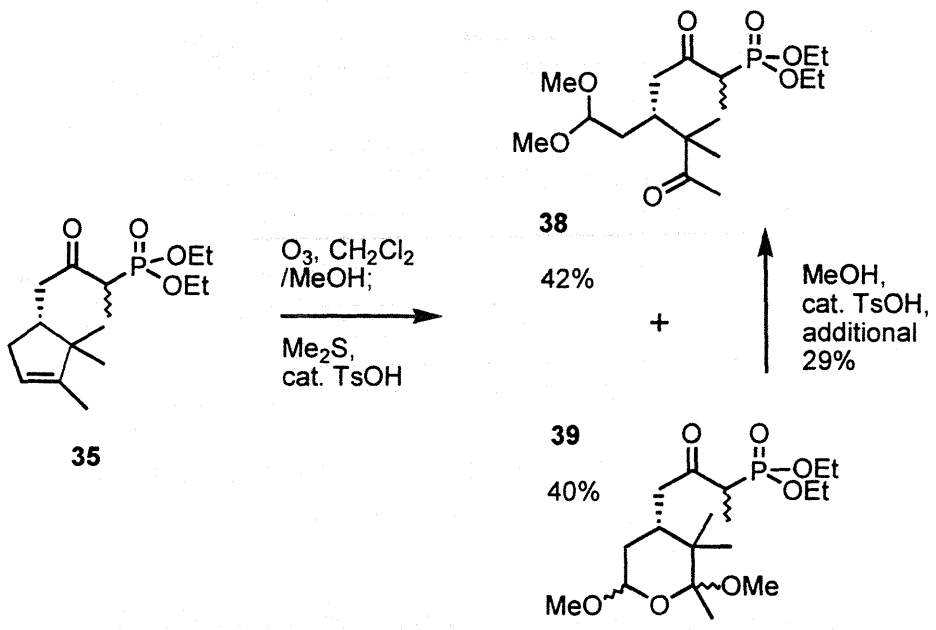


Scheme 14. Enantioselective synthesis of ketophosphonate **35**.

The mixture of diastereomers of ketophosphonate **35** was then subjected to ozonolysis conditions in methanol and dichloromethane. Upon reduction of the α-hydroxy hypdroperoxide intermediate in the presence of a catalytic amount of toluenesulfonic acid,[54] an equilibrium mixture of the acyclic acetal **38** and the cyclic acetal **39** was obtained (Scheme 15). In **38**, the newly formed aldehyde was protected, while the other carbonyl was exposed to react later with the phosphonate moiety. On the

[53] Crist, B. V.; Rodgers, S. L.; Lighter, D. A. *J. Am. Chem. Soc.* **1982**, *104*, 6040.

other hand, **39** could not undergo subsequent reaction; but upon treatment with acid in methanol, **39** could be re-equilibrated into another mixture containing the desired acyclic acetal **38**.

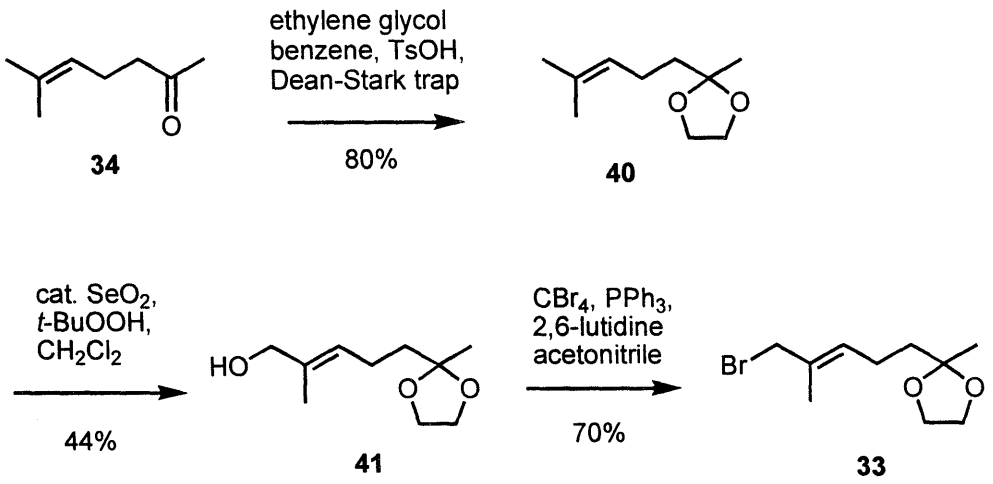


Scheme 15. Ozonolysis of cyclopentenyl ring.

The isomeric mixture of acyclic acetal **38** was then treated with sodium hydride in the Horner-Wadsworth-Emmons reaction to afford cyclohexenone **31** in good yield (80%).[55] Because of the difficulty of separating the acyclic acetal **38** from the cyclic acetal **39** after ozonolysis, it became more practical to take the mixture of **38** and **39** through the Horner-Wadsworth-Emmons reaction. Since **39** was inert under these

[54] Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.
[55] Grieco, P. A.; Pogonowski *Synthesis* **1973**, 425. For a review, see: Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.

reaction conditions, it could be recovered afterwards and separated easily by chromatography from the much less polar **31**.

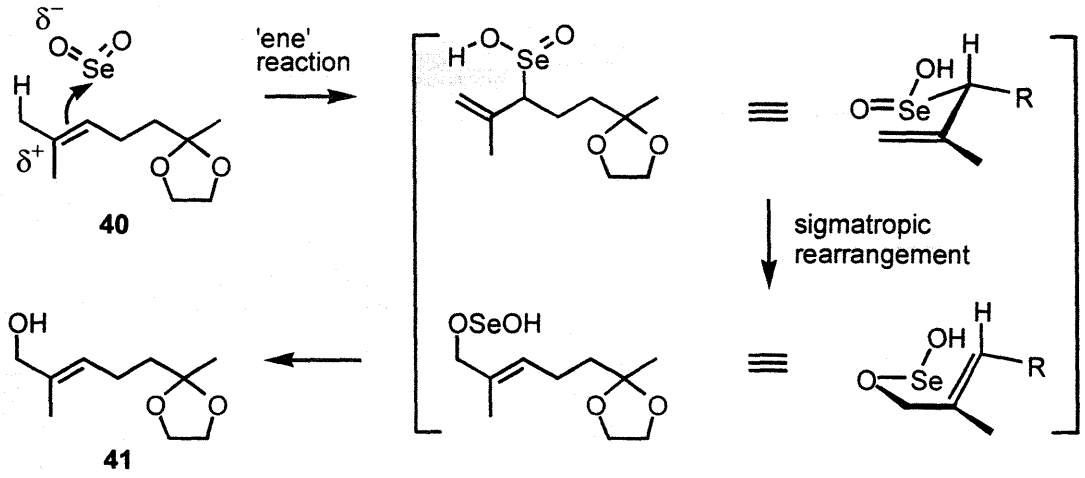


Scheme 16. Synthesis of side chain fragment.

For the synthesis of side-chain fragment **33** (Scheme 16), 2-methyl-2-hepten-6-one (**34**) was first protected as the ethylene ketal (**40**). Subsequent hydroxylation using catalytic selenium dioxide in the presence of *tert*-butylhydroperoxide resulted in 44% yield of the desired *E*-allylic alcohol **41**.[56] While there was substantial amount (19%) of the over-oxidized *E*-α,β-unsaturated aldehyde product, which could be reduced by sodium borohydride to generate **41**, no *Z*-allylic alcohol or the "internally" hydroxylated product could be isolated from the hydroxylation reaction. This well-documented regioselectivity was a consequence of: 1) the electrophilic character of the initial "ene" reaction in which selenium dioxide reacted at the less substituted side of the double bond; and 2) in the subsequent 2,3-sigmatropic rearrangement of the organoselenium

[56] Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

intermediate (**42**), the adoption of an energetically favored five-membered conformation in which the side-chain was in the pseudoequatorial position (Scheme 17).[57]



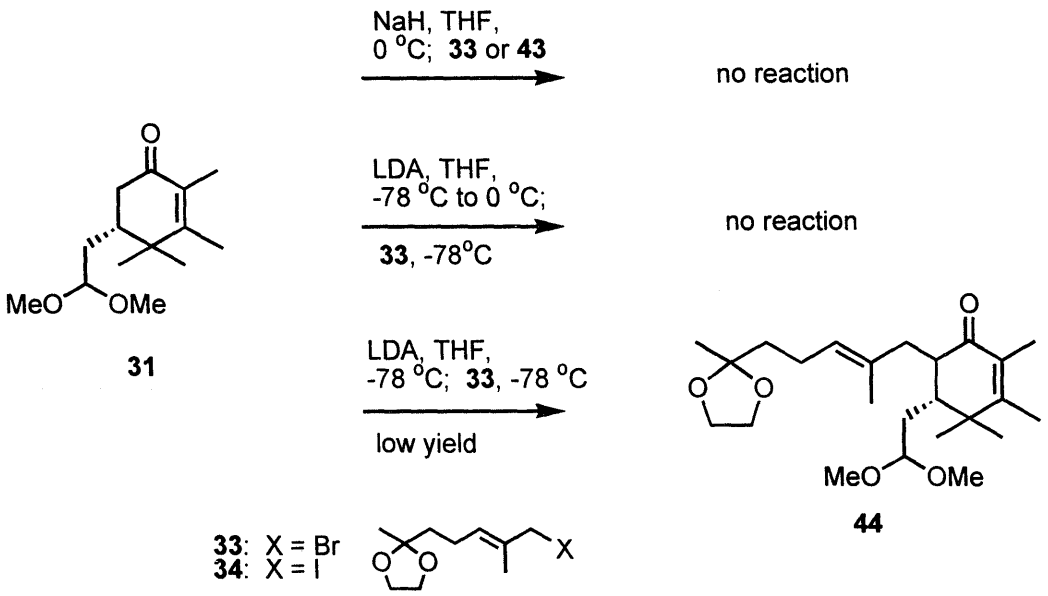
Scheme 17. Regioselective allylic hydroxylation by selenium dioxide.

2.3 Efforts towards the direct alkylation of cyclohexenone intermediate

Initial studies of the direct alkylation of cyclohexenone **31** with side-chain fragment **33** were unsuccessful (Scheme 18). Enolate of **31** generated by sodium hydride at 0 °C did not react with either bromide **33** or iodide **43** under various conditions. When **31** was treated with lithium diisopropylamide at -78 °C followed by slow addition of bromide **33** at -78 °C, only a small amount of the α'-alkylation product (**44**) was isolated. If the alkylating agent was added *after* the reaction mixture had been allowed to warm up to room temperature, however, no reaction was observed. These results

[57] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990;
(continued on next page)

suggested that while the kinetic enolate was only slightly reactive towards alkylation at the α' position, the thermodynamic enolate was completely inert.



Scheme 18. Attempts of direct γ-alkylation of cyclohexenone **31**.

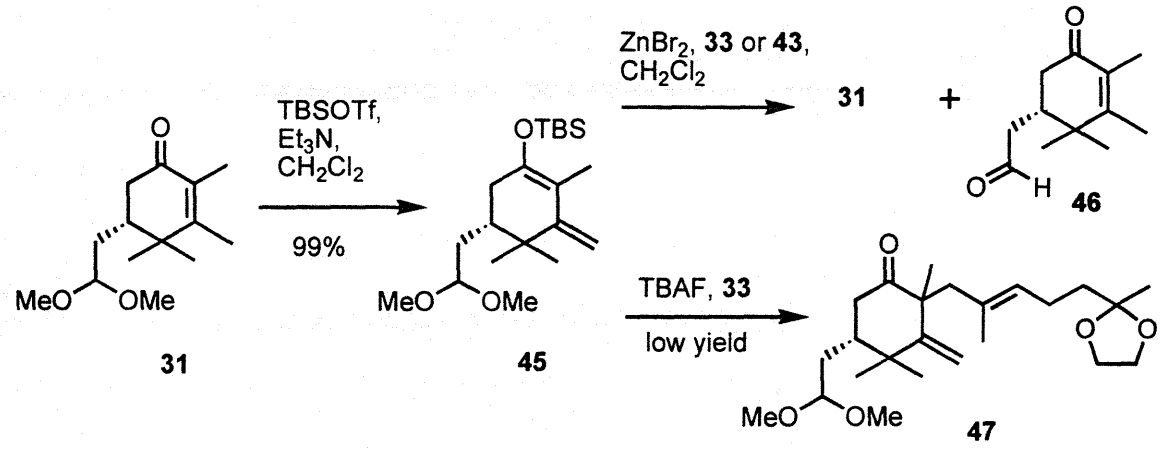
An alternative approach to the direct alkylation of cyclohexenone **31** would be the generation of a reactive enolate from a silyl enol ether derivative in the presence of the alkylating agent (Scheme 19).[58] Cyclohexenone **31** was first converted in near-quantitative yield (99%) to the *tert*-butyldimethylsilyl enol ether (**45**) using triethylamine and *tert*-butyldimethylsilyl trifluoromethanesulfonate. Silyl enol ether **45** was then treated with zinc bromide in the presence of bromide **33** or iodide **43**.[59] Unfortunately, in both cases, only the hydrolyzed products (**31**, **46**) were recovered upon work-up.

Part B, pp. 660-661.

[58] For a review, see: Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181.

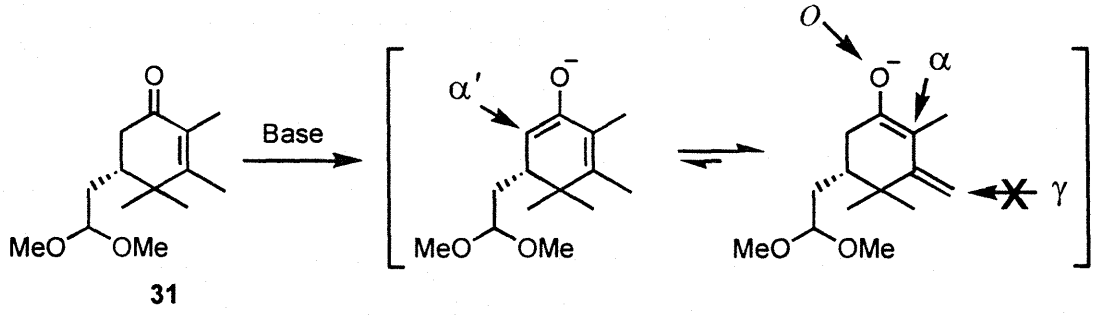
[59] Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, *34*, 3209.

Interestingly, when **45** was treated with tetrabutylammonium flouride,[60] a small amount of the α-alkylated product (**47**) was isolated.



Scheme 19. Attempts of alkylation of silyl enol ether.

While the unfavorable course of these reactions could be partly explained in our particular case by steric hindrance at the γ site, the problem of γ-alkylation of an α,β-unsaturated ketone is a general one and lies in the unfavorable electronic properties of the dienolate anion.[61]



Scheme 20. Regioselectivity of alkylation of α,β-unsaturated ketone

[60] Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025.
[61] Gompper, R.; Wagner, H.-U. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 321.

When a typical α,β-unsaturated ketone such as cyclohexenone **31** is treated with base, the resulting dienolate becomes an ambident nucleophile, and electrophilic attack can theoretically occur at four possible positions: the oxygen, the α' carbon, the α carbon and the γ carbon (Scheme 20). O-alkylation has been known to occur when "hard" electrophiles such as sulfonates, silyl halides or carboxylic anhydrides are used. In the case when a kinetic enolate is generated, C-alkylation occurs at the α' carbon if it is not severely hindered.

In the case of the thermodynamic dienolate, C-alkylation and protonation almost always occur at the α carbon even when: 1) it is already mono-alkylated and/or quite congested;[62] and 2) γ-alkylation would give the more thermodynamically favored conjugated product. (While alkylation does occur at the γ position in some intramolecular cases where the geometry of the molecule is overwhelmingly favorable,[63] intermolecular cases are rarely achieved.[64]) This kinetic phenomenon has been attributed to the greater π-electron population at the α position than the γ position,[61,63,65] as suggested by theoretical calculations on dienolates[61] and other similar dienyl systems such as methyl butadienyl ether[66] and cyclohexadienyl radical.[67]

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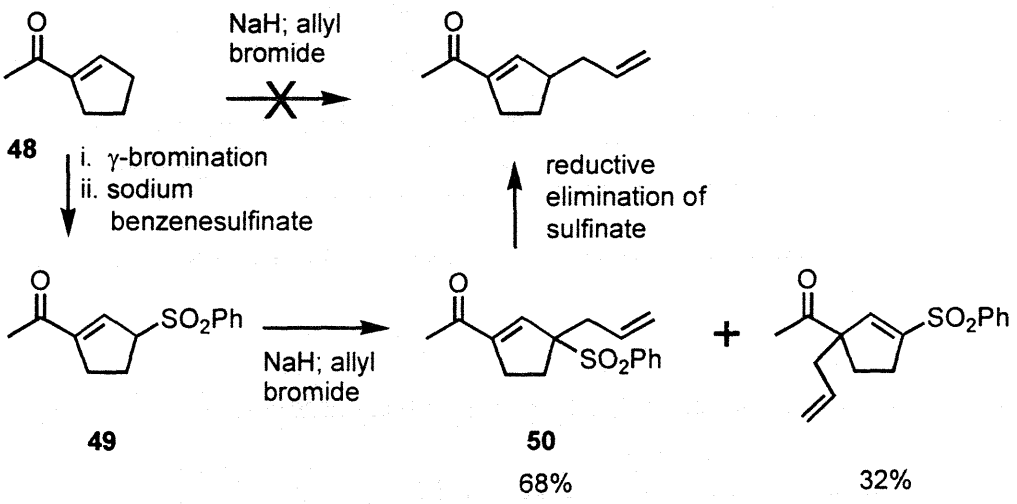
[62] (a) Ando, M.; Buchi, G.; Ohmuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880. (b) Schroepfer, G. J., Jr.; Parish, E. J.; Kandutsch, A. A. *J. Am. Chem. Soc.* **1977**, *99*, 5494.
[63] Piers, E.; Zbozny, M.; Wigfield, D. C. *Can. J. Chem.* **1979**, *57*, 1064
[64] Conia, J. M. *Rec. Chem. Prog.* **1963**, *24*, 43.
[65] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley and Sons: Chichester, Englnad, 1976; pp. 45-46.
[66] Rogers, N. A. J.; Sattar, A. *Tetrahedron Lett.* **1965**, 1471.
[67] (a) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *38*, 773. (b) Colpa, J. P.; de Boer, E. *Mol. Phys.* **1963**, *7*, 333.

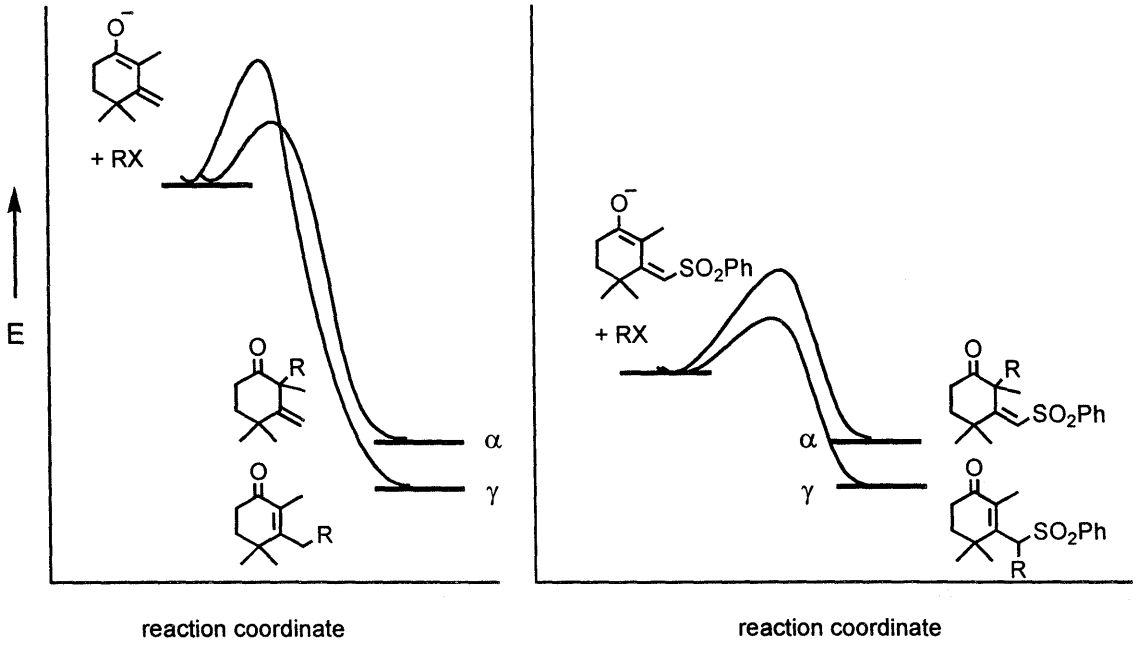
2.4 Sulfone-directed γ-alkylation of α,β-unsaturated ketone

To solve the regioselectivity problem of γ-alkylation of α,β-unsaturated ketones, Lansbury *et al.* have developed a general strategy of using an arylsulfonyl directing group.[68] When such a directing group was in place at the γ carbon, the regioselectivity of enone alkylation could be reversed to favor the γ site to varying degrees. For example, while alkylation of acetylcyclopentene (**48**) by allyl bromide would result exclusively in the α-allylation product, the sodium anion of 1-acetyl-3-(phenylsulfonyl)cyclopentene (**49**) reacted with allyl bromide to give predominantly the γ-allylation product (**50**, Scheme 21). Similar γ selectivity was observed when other types of alkylating agents were used.



Scheme 21. Regioselectivity of directed alkylation of α,β-unsaturated ketone.[68]

[68] Lansbury, P. T.; Erwin, R. W.; Jeffrey, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 1602



Scheme 22. Explanation of the regioselectivity of the directed alkylation using the Hammond postulate.

To explain this reversal of regioselectivity, Lansbury *et al.*[68] invoked the Hammond postulate (Scheme 22). It was hypothesized that in a series of increasingly stabilized conjugated anionic systems, the transition state of the alkylation reaction occurs "later" on the reaction coordinate, and becomes more product-like. Hence, the thermodynamic stability of alkylation products will have a greater influence on the relative stability of the transition states and, in turn, on the relative rates of the pathways leading to the different products. The substantial stability of sulfone-stabilized anions is evident in the increased acidity of β-ketosulfones. And since the conjugated γ-alkylation product is more thermodynamically stable than the de-conjugated α-alkylation product, the transition state of the γ-alkylation pathway is likely lower in energy than in the case

without the directing group; hence, γ-alkylation product could be observed in these cases.[69]

While this strategy of directed alkylation of α,β-unsaturated ketone is quite general except in cases with severe steric hindrance at the γ position, this method has not been widely used because of the difficulty and inefficiency of installing the γ-directing group. The original sequence of reactions (Scheme 21) involves first the functionalization of the α,β-unsaturated ketone *via* the γ-bromo compound, followed by a substitution reaction with sodium benzenesulfinate to give the γ-aryl sulfone product. The inefficiency lies in the bromination reaction, in which the reaction of the dienolate using *N*-bromosuccinimide gives low yield and poor regioselective control.

2.5 Modified approach to the γ-alkylation of cyclohexenone intermediate

As it would be useful to incorporate the directed alkylation strategy into the synthesis of isoverticillene, it was decided to first improve the protocol of installing the γ-directing group.

To synthesize the γ-sulfonyl-α,β-unsaturated ketone, the γ position was to be functionalized selectively as the alcohol, which is then converted to a leaving group before being reacted with sodium benzenesulfinate.

To hydroxylate cyclohexenone **31**, we first attempted to oxidize silyl enol ether **45** with *m*-chloroperbenzoic acid.[70] But the yield of the desired compound was low (37%).

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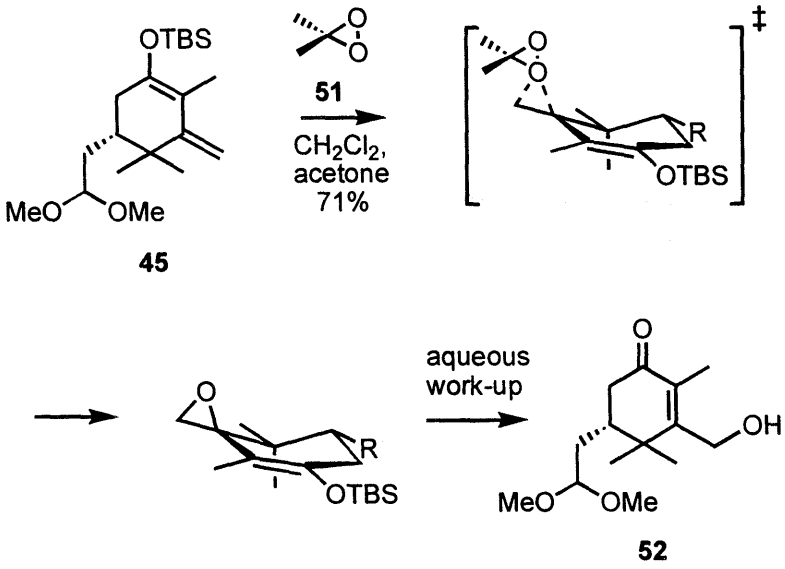
[69] Piers *et al.* (ref. 65) used a similar argument to explain the predominant γ alkylation in his intramolecular examples in which cyclization is substantially energetically unfavorable, resulting in a "later" transition state.

[70] Hassner, A., Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

The labile silyl enol ether was easily hydrolyzed in solution with peroxyacid, and the oxidant, like *N*-bromosuccinimide, was not very selective towards reacting with the β,γ-double bond of **45**.



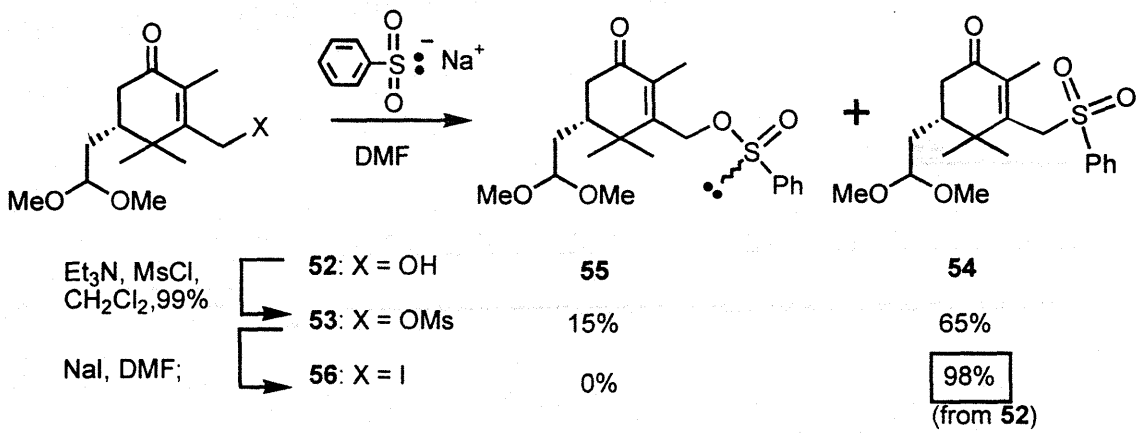
Scheme 23. Regioselective hydroxylation of silyl dienol ether.

The solution to the problem was found in the increasingly popular oxidizing agent, dimethyldioxirane (**51**).[71] Not only does dimethyldioxirane react in neutral conditions, it is also very sensitive to steric effects. As suggested by both theoretical[72] and experimental studies,[73] dimethyldioxirane oxidation goes through an ordered, Bartlett-type "butterfly" transition state.[74] Therefore, in the case of silyl enol ether **45**, it

[71] For reviews of dioxiranes as oxidants, see: (a) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205.
[72] Bach, R. D.; André, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1985**, *107*, 4549.
[73] Murray, R. W.; Shiang, D. L. *J. Chem. Soc., Perkin Trans.2* **1990**, 349.
[74] Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311.

would be possible to oxidize selectively the less hindered terminally-substituted β,γ-double bond, rather than the one flanked by a methyl group and a bulky siloxy group (Scheme 23).

Indeed, prepared as an acetone solution from oxone[75] ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) and acetone,[76] dimethyldioxirane reacted efficiently and cleanly at -78 °C with silyl enol ether **45** to give 71% yield (99% based on recovered starting material **45**) of the desired alcohol **52**.[77] The initial product of the reaction was the β,γ-epoxide,[78] but this labile intermediate was readily hydrolyzed *in situ* by trace water or upon work-up to give **52**.



Scheme 24. Sulfonylation of γ-hydroxy-α,β-unsaturated ketone.

With the γ-functionalized intermediate in hand, we next converted alcohol **52** to the mesylate (**53**) in near-quantitative yield (Scheme 24). When **53** was reacted with sodium benzenesulfinate in *N,N*-dimethylformamide, the desired S-alkylated sulfone **54** was obtained in 65% yield, along with 15% of the O-alkylated sulfinate **55**. (Sulfinate

[75] Oxone is a registered trademark of Du Pont.
[76] Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847.
[77] Adam, W.; Hadjiarapoglou, L.; Jäger, V.; Klicic, J.; Seidel, B.; Wang, X. *Chem. Ber.* **1991**, *124*, 2361.

55 was isolated as a mixture of diastereomers, as evident in its ^{1}H NMR spectrum.) We next converted mesylate **53** to the iodide (**56**) in *N,N*-dimethylformamide, followed by treatment with sodium benzenesulfinate in the same reaction vessel. In this instance, a much higher yield (98% from the alcohol) of sulfone **54** was obtained.

This improvement could be explained by the "hard and soft acids and bases" (HSAB) principle,[79] first introduced by Pearson *et al.*[80] Initially, the principle classified and successfully predicted thermodynamically favorable interactions between inorganic acids and bases of similar "hardness" or "softness." It was later applied in organic chemistry[81] to qualitatively explain kinetic phenomenon in reactions involving nucleophiles (Lewis bases) and electrophiles (Lewis acids). "Hard" and "soft" acids and bases were initially classified empirically according to their polarizability and polarity. Thus, a "soft" Lewis base has a diffuse and polarizable electron population, whereas a "hard" one contains a "tight" electronegative atom with a high charge density. In an explanation offered by Fleming,[82] a soft nucleophile has a high-energy HOMO and a soft electrophile has a low-energy LUMO, whereas a hard nucleophile has a low-energy HOMO and a hard electrophile has a high-energy LUMO. Hence, a soft nucleophile favors reaction with a soft electrophile because their frontier orbitals are closer in energy. On the other hand, a "hard" nucleophiles is more reactive towards a "hard" electrophile because there is a large coulombic attraction between reaction centers of high charge density.

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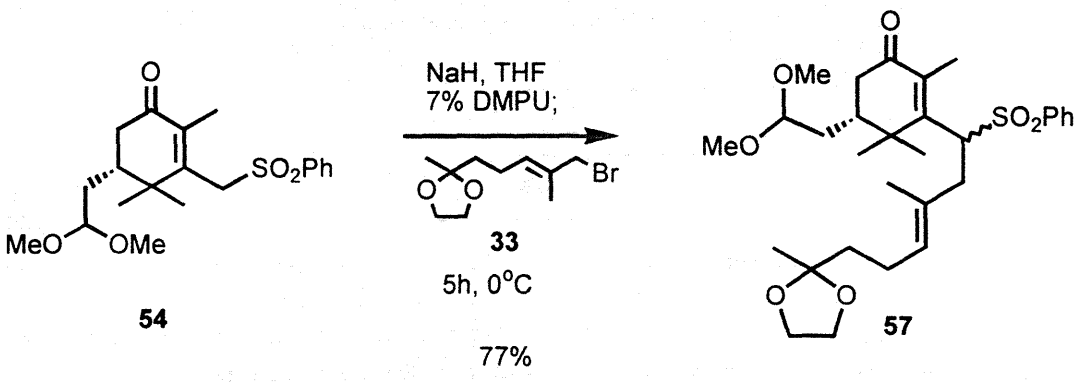
[78] Chenault, H. K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 4249.
[79] For reviews, see: (a) Pearson, R. G. *J. Chem. Ed.* **1968**, *45*, 581. (b) Ho, T.-L. *Chem. Rev.* **1975**, *75*, 1.
[80] Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533.
[81] (a) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827. (b) Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977.
[82] See ref. 67; pp. 34-47.

In our particular case, benzenesulfinate anion is an ambident nucleophile. Since the oxygen atoms are more electronegative, the charge density on them is higher, making them the "harder" nucleophilic sites than sulfur. Mesylate **53** is a hard electrophile because the C-O bond is polarized, causing the carbon center to be more electropositive than in the case of a bromide or an iodide. Therefore, by changing the electrophile from the "hard" mesylate **53** to the "soft" allylic iodide **56**, reaction at the "softer" sulfur site of benzenesulfinate was preferred.

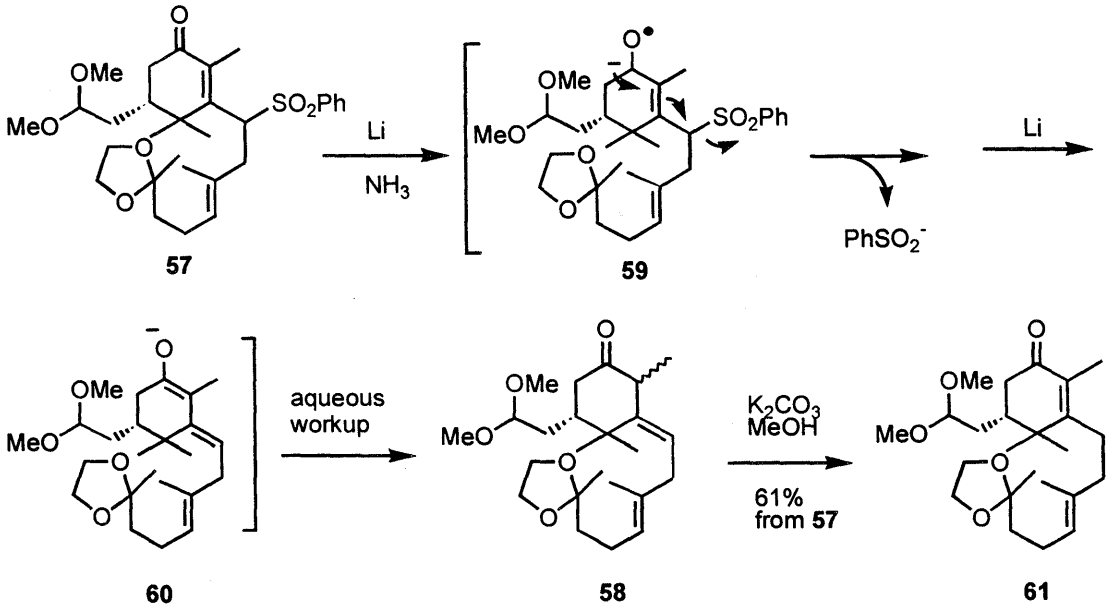
The sequence of reactions described here represents a marked improvement over the old method of installing the γ-directing group. While the typical yield of a γ-sulfonyl compound from the α,β-unsaturated ketone in the old two-step sequence ranged from 10 to 43%,[68] our three-step sequence gave an overall yield of 70%.



Scheme 25. Directed γ-alkylation of α,β-unsaturated ketone.

With the γ-directing group in place, the alkylative coupling of the cyclohexenone core and the side-chain fragment was once again attempted. Sulfone **54** was treated with

sodium hydride in tetrahydrofuran and co-solvent[83] *N,N'*-dimethylpropyleneurea, followed by the addition of bromide **33**. After five hours at 0°C, the reaction afforded a good yield (77%) of enone **57** as the only alkylation product (Scheme 25). As suggested by its ^{1}H NMR spectrum, the isolated product was an approximately 1:1 diastereomeric mixture. The presence of the co-solvent *N,N'*-dimethylpropyleneurea (7% by total volume) was absolutely necessary for the reaction to occur at a reasonable rate to avoid the onset of the decomposition of bromide (**33**). (When iodide **43** was used as the alkylating agent, some double-bond isomerization occurred during alkylation, resulting in a higher yield (83%) of both *E* and *Z* isomers of the γ-alkylation product.)



57 **59** **60** **58** **61**

Scheme 26. Reductive removal of sulfonyl directing group.

[83] Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385.

The sulfonyl group of alkylation product **57** was then reductively removed using dissolving-metal conditions (Scheme 26).[68,84] Reaction of the diastereomeric mixture of **57** with excess lithium in liquid ammonia resulted in ketone **58**. The ^{1}H NMR spectrum of the isolated product suggested it was a mixture of diastereomers at C12. In this reaction, the formation of the initial radical anion (**59**) was followed by the elimination of sulfinate ion. Subsequent reduction by another electron from lithium metal resulted in dienolate **60**. However, because protonation of **60** during work-up occurred at the kinetically favorable α position as explained earlier, the initial product was the de-conjugated ketone **58**. Without further purification the crude mixture of **58** was reacted under basic methanolic conditions to afford the desired enone (**61**) as a single isomer in 61% yield.

With a total yield of 30% in five synthetic operations, this sequence of reactions demonstrated the ability of using a directing group to alkylate an α,β-unsaturated ketone at a site that was not only sterically hindered, but also electronically unfavorable.

2.6 Stereoselective reduction of cyclohexenone

Having the side-chain fragment attached, the next task was to reduce the enone **61** stereoselectively. Two considerations made the use of the Ireland dissolving-metal reduction[85] a good choice for this transformation. First, this sequence would transpose the enone double bond in **61** to the desired C12-C13 position.

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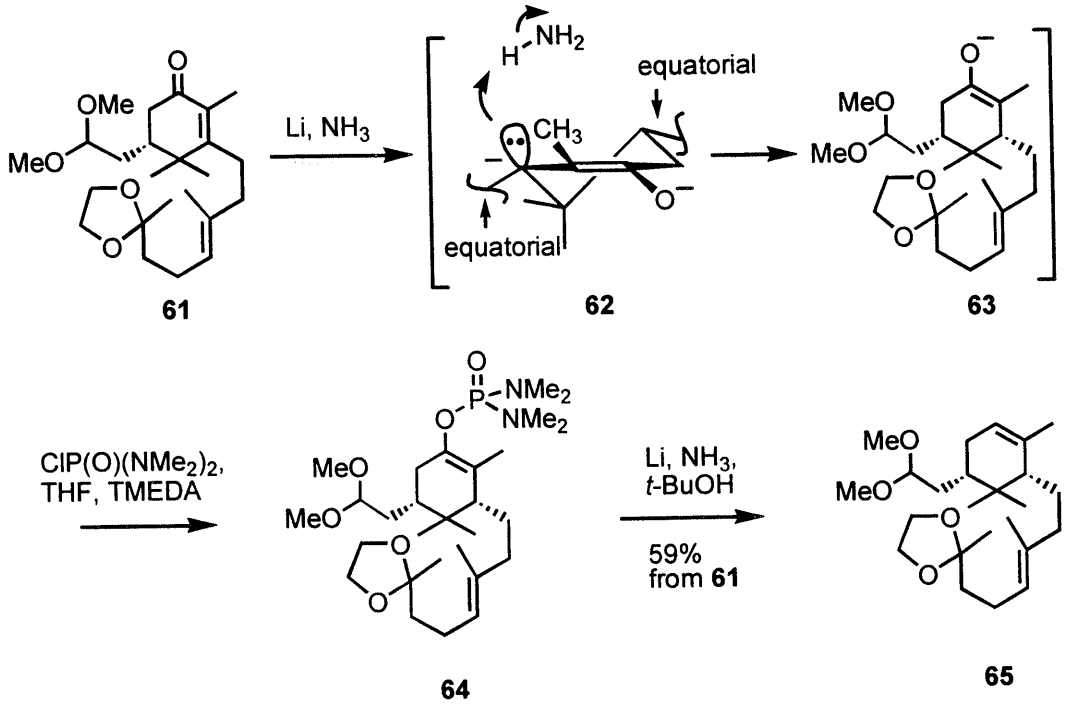
[84] Caine, D. *Org. React.* **1976**, *23*, 1.

[85] (a) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098. (b) Ireland, R. E.; Pfister, G. *Tetrahedron Lett.* **1969**, 2145.

More importantly, the predominant diastereomer of the reduction product was predicted to have the desired *cis* relative stereochemistry. In the mechanism of the dissolving-metal reduction (Scheme 27), two electrons from lithium are added into the conjugated cyclohexenone system resulting in a dianion intermediate (**62**). Subsequent protonation by ammonia usually occurs perpendicular to the enolate system of the most thermodynamically favorable conformation of dianion **62**.[86] Thus, we anticipated axial protonation at the β carbon of the most stable half-chair conformer of **62** (with the two alkyl side-chains in the pseudoequatorial positions) to afford the desired stereoisomer of enolate **63**.



Scheme 27. Stereoselective reduction of α,β-unsaturated ketone.

[86] See ref. 59; pp. 254-255.

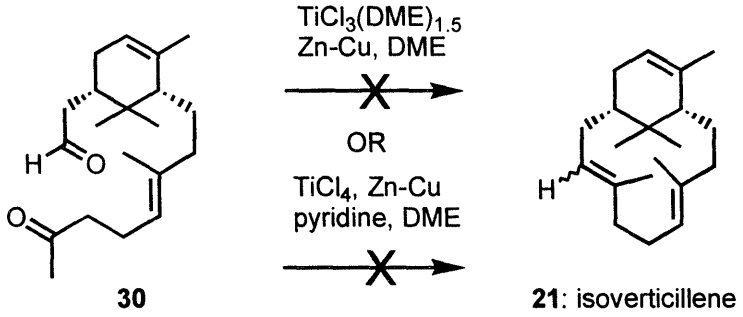
When the first lithium reduction reaction was carried out, the resulting enolate (**63**) was trapped with tetramethylphosphorodiamidic chloride using Ireland's procedure to give phosphoramidate **64** (Scheme 27).[85a] Without further purification, the crude product was subjected to the second lithium reduction reaction in the presence of a proton source. The result was a 59% yield of an approximately 10:1 diastereomeric mixture (based on ^{1}H NMR integration) of the desired deoxygenated product **65**. Because the diastereomers could not be separated by chromatographic means and the stereochemistry of the products could not be determined unambiguously from the ^{1}H NMR spectrum, the diastereomeric mixture was carried on to test the feasibility of the McMurry cyclization.

2.7 Efforts towards the McMurry coupling reaction

For the final and key McMurry coupling reaction of the synthesis, the diastereomeric mixture of deoxygenated product **65** was first treated with catalytic amount of acid in acetone in a trans-ketalization reaction to unmask the carbonyl functionalities to give ketoaldehyde **30**.

In a standard protocol of the McMurry coupling reaction (Scheme 28), ketoaldehyde **30** was heated at reflux temperature in dimethoxyethane along with the solvent complex of titanium(III) chloride ($TiCl_3(DME)_{1.5}$) and zinc-copper couple.[87] Unfortunately no desired cyclization product could be isolated. The rate of addition, the choice of solvent and the temperature of reaction were modified in different ways. Unfortunately, in almost all cases, a complex mixture of products was obtained without

any discernible major product. A streak on the thin-layer-chromatography plate in these reactions suggested either substantial decomposition or polymerization of the starting ketoaldehyde under reaction conditions. To eliminate the possibility of the presence of any trace acid generated from the inadvertent hydrolysis of $TiCl_3(DME)_{1.5}$, another procedure using pyridine as a proton scavenger, titanium(IV) chloride and zinc-copper couple was attempted (Scheme 28).[88] Again, none of the desired product could be isolated.



Scheme 28. Unsuccessful McMurry coupling reactions.

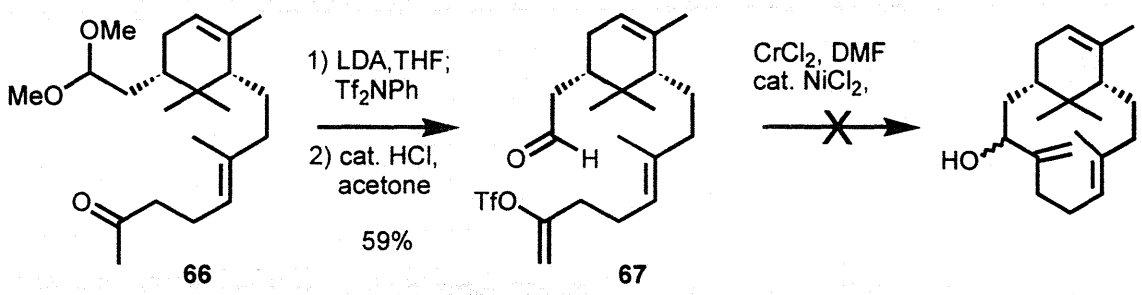
After many disappointing trials, it became apparent the McMurry coupling reaction was not suitable for this macrocyclization step. It is not clear why this well-tested macrocyclization method has failed in this synthesis. It is conjectured that the reactive radical nature of the reaction might have been responsible in part for the substantial amount of intermolecular reaction between molecules that are very unwilling to react intramolecularly. Also, the high temperature requisite for the deoxygenation

[87] McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748.
[88] Li, Y.; Li, W.; Li. Y. *Synth. Commun.* **1994**, *24*, 721.

reaction might have been incompatible with the starting material or any initially formed cyclization product.

2.8 The challenge of the macrocyclization

The frustrating failure to effect the macrocyclization using well-tested methods such as the McMurry carbonyl coupling reaction underlines the difficulty in constructing the verticillenic macrocycle. Not only is there an unfavorable entropy change in bringing the ends of a long alkyl chain together, there is also a considerable enthalpic barrier in forming the strained 12-membered ring of the product.

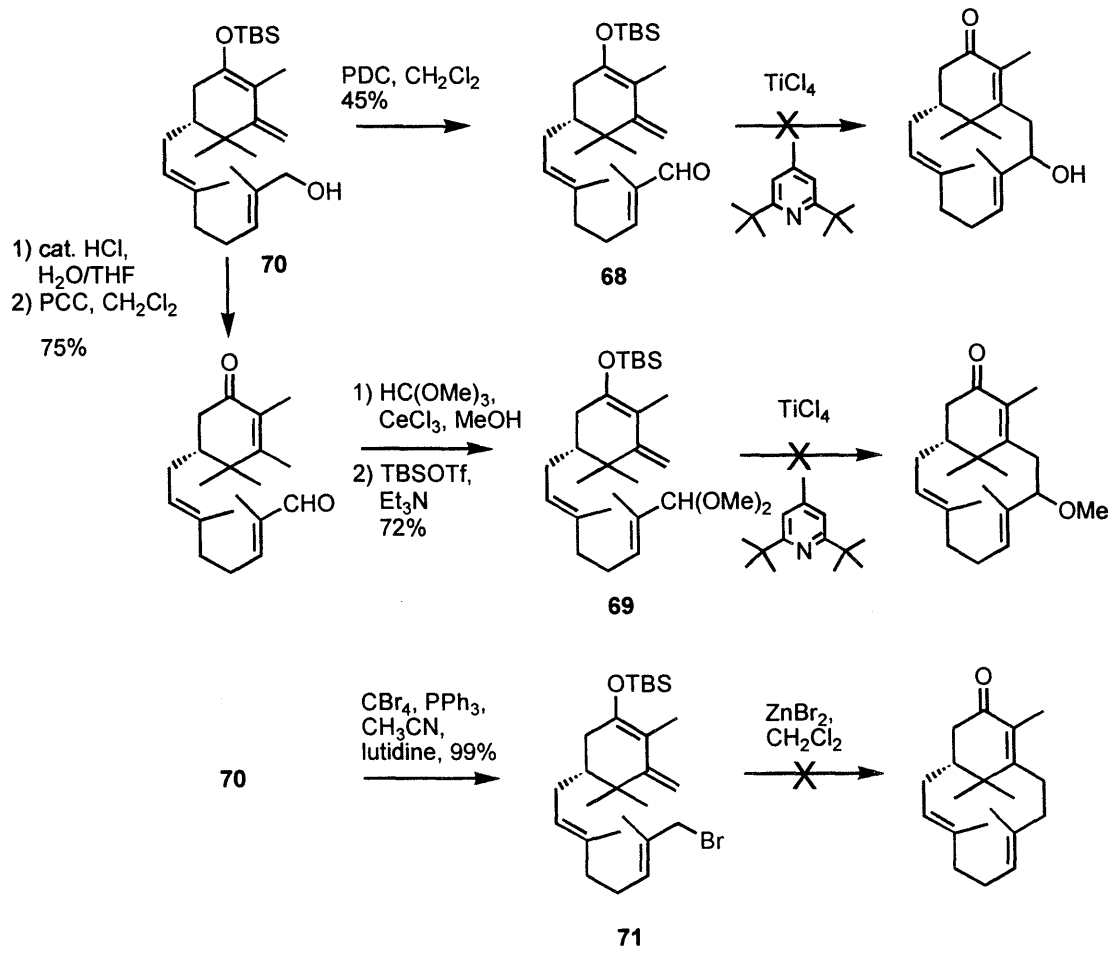


Scheme 29. Macrocyclization attempt using Nozaki-Kishi reaction.

Below is a brief summary of other unsuccessful efforts in carrying out the macrocyclization using methods that have precedents in other macrocycle syntheses. For example, in an attempt to apply intramolecularly the milder chromium-assisted Nozaki-Kishi reaction,[89,90] ketone **66** was first converted to enol triflate **67** in 59% yield (Scheme

[89] For a review, see: Cintas, P. *Synthesis* **1992**, 248.

29).[91] Disappointingly, when **67** was treated with chromium(II) chloride in the presence of a catalytic amount of nickel(II) chloride,[92] no intramolecular aldehyde addition was observed.



Scheme 30. Unsuccessful macrocyclization of silyl enol ethers.

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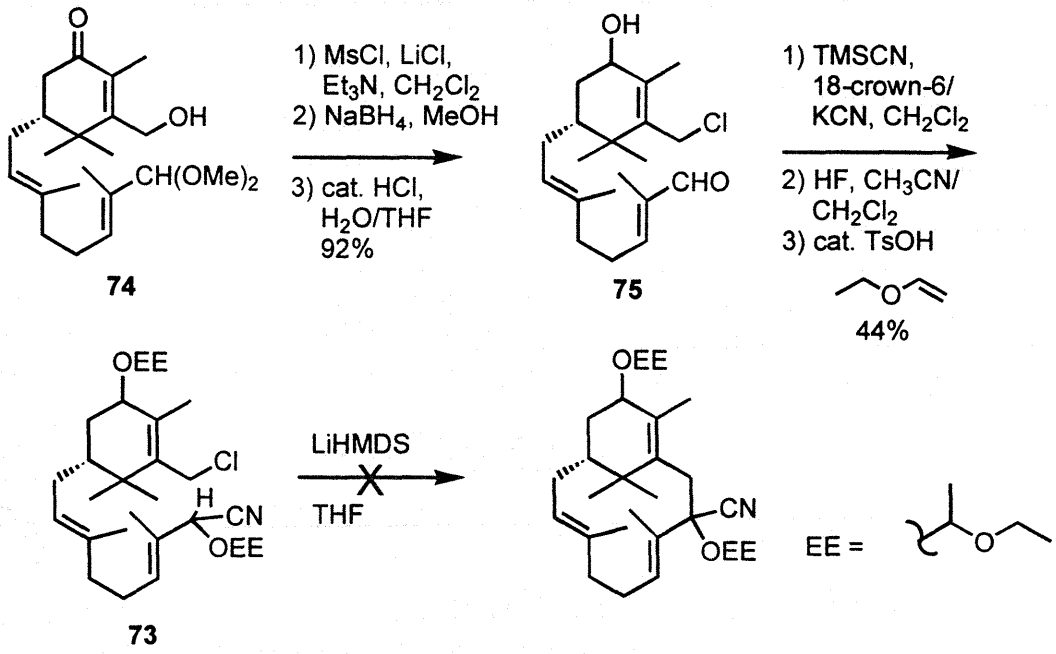
[90] For recent examples of macrocyclization using the Nozaki-Kishi reaction, see: (a) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735. (b) Roe, M. B.; Whittaker, M.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 8103. (c) Buszek, K. R., Jeong, Y. *Synth. Commun.* **1994**, *24*, 2461.

[91] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

[92] Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.

In an attempt to effect an intramolecular Mukaiyama aldol reaction, treatment of aldehyde **68** or acetal **69** (prepared from allylic alcohol **70**[93] *via* several functional group interchanges) with Lewis acid titanium(IV) chloride gave no cyclization products (Scheme 30).[94,95] Also, direct intramolecular γ-alkylation of silyl enol ether-bromide **71** in the presence of zinc(II) bromide[59] failed to give any cyclization product (Scheme 30).



Scheme 31. Attempted intramolecular alkylation of protected cyanohydrin.

In another attempt, cyanohydrin **73** was synthesized in seven steps from acetal **74** to be used in an intramolecular alkylation reaction (Scheme 31).[96] Prepared from γ-

[93] The synthesis of ## is described in Chapter 3.

[94] (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1975**, 319.

[95] For examples of macrocyclization using Mukaiyama-type aldol reaction, see: (a) Furukawa, T.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron* **1992**, *48*, 6975. (b) Satoh, T.; Kaneko, Y.; Okuda, T.; Uwaya, S.; Yamakawa, K. *Chem. Pharm. Bull.* **1984**, *32*, 3452.

[96] For examples of macrocyclization using cyanohydrins, see: (a) Takayanagi, H.; Kitano, Y.; Morinaka, Y. *J. Org. Chem.* **1994**, *59*, 2700. (b) Takahashi, T.; Nemoto, H.; Kanda Y.; Tsuji, J.; Fukazawa, Y.; Okajima,

(continued on next page)

hydroxylation of acetal **69**, **74** was converted to the γ-chloroenone, followed by 1,2-reduction of the enone and hydrolysis of the acetal, affording a high yield (92%) of aldehyde **75**. The stereochemistry at C13 of **75** was not established but its ^{1}H NMR indicated only a single diastereomer in the isolated product. Formation of the trimethylsilyl cyanohydrin, followed by the re-protection of both hydroxyl moieties as the ethoxyethyl ether gave protected cyanohydrin **73** in an overall yield of 44%.[96b] Unfortunately, slow addition of **73** into a solution of lithium bis(trimethylsilyl)amide did not yield any macrocyclization product.

2.9 Summary

Despite the inability to cyclize the 12-membered ring of verticillene using the McMurry coupling reaction as well as several other methods known to be effective in macrocycle formation, the synthetic efforts described here have not been entirely fruitless. Not only have we learned the limitations posed by the structure of the molecule, but we have also developed several strategies that can be used in later attempts to synthesize isoverticillene and other verticillenic compounds. These strategies include: 1) the use of (1*S*)-(+)-10-camphorsulfonic acid (**37**) as a readily available chiral starting material for the enantioselective synthesis of the cyclohexyl "core;" 2) the sulfone-directed alkylation of the enone moiety for the regioselective attachment of an alkyl side-chain; and 3) the

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T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499. (c) Takahashi, T.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 4695.

use of the enone moiety as a handle for the functional group manipulation at the C10, C11, C12 and C13 positions of the molecule.

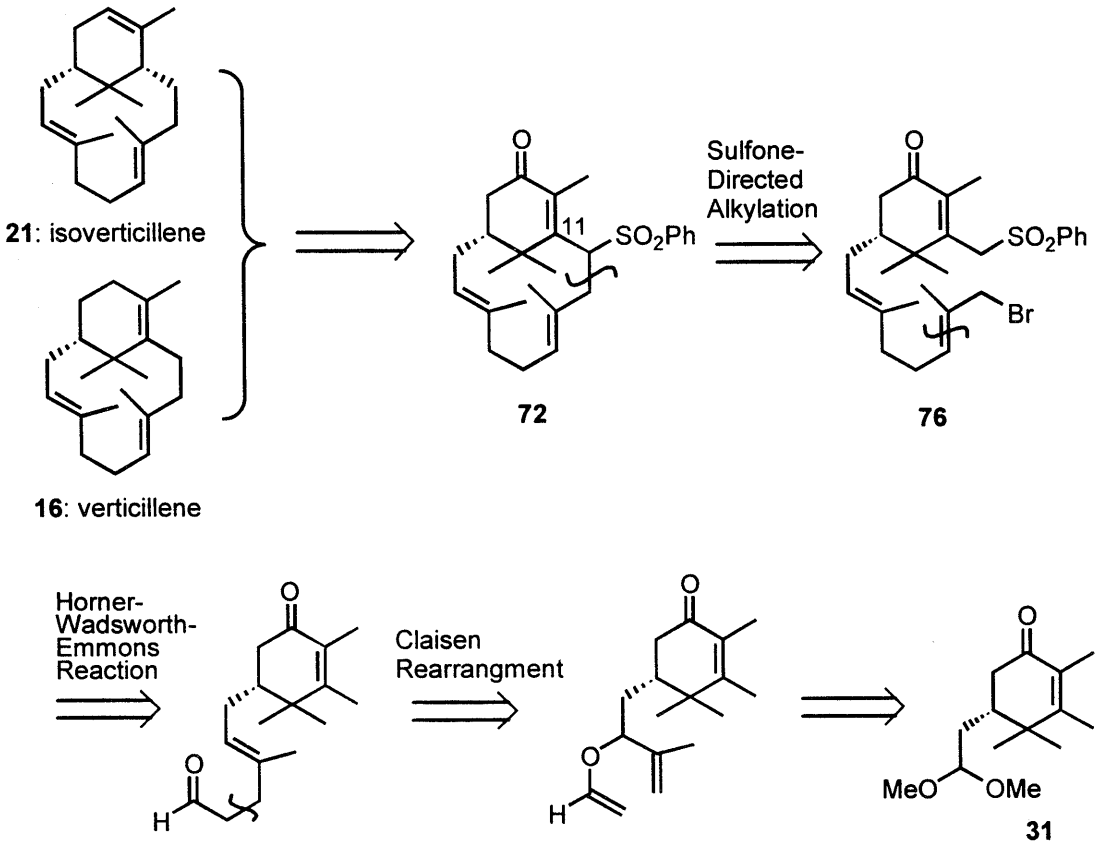
Chapter 3. Synthesis of Isoverticillene and Verticillene — the Successful Alkylative Cyclization Approach

Described in the previous chapter was a convergent plan for the synthesis of isoverticillene (**21**), whose key McMurry cyclization reaction failed to afford the target molecule in the last step. After a number of other unsuccessful attempts to effect the difficult macrocyclization and with the number of remaining options dwindling, it was decided next to take advantage of the success of the intermolecular directed alkylation approach and to apply it *intra*molecularly to the construction of the 12-membered ring.

3.1 Modified synthetic plan

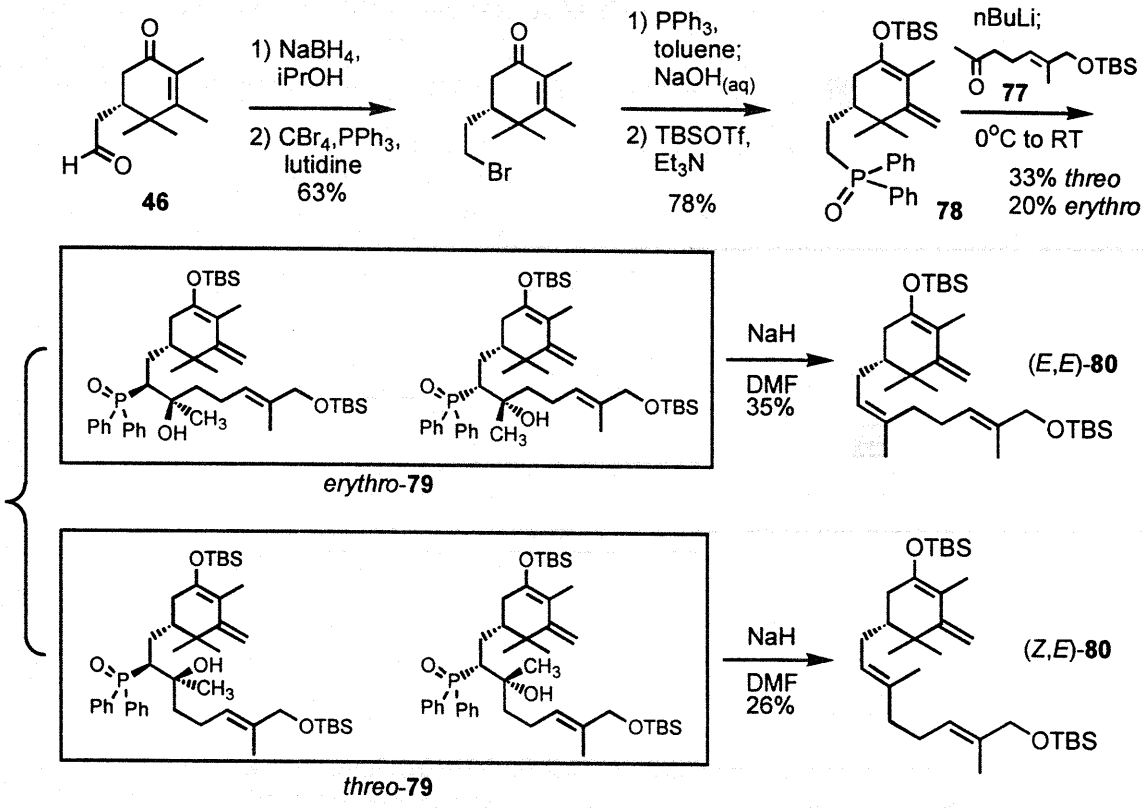
To incorporate the directed alkylative cyclization approach into the synthesis of isoverticillene (**21**), it was necessary to make a few modifications. In the modified plan (Scheme 32), macrocyclization would be achieved by an intramolecular alkylation of sulfone-bromide **76**. The directing group and the stereochemistry at C11 (bridgehead) would be installed using the same methods as in the previous synthesis. The same cyclohexenone intermediate (**31**) from the original synthesis would also be used here. On the other hand, the side-chain would need to be built from the opposite direction in a more linear fashion so that the geometry of its double bonds could be controlled. This would be achieved using a Horner-Wadsworth-Emmons reaction and a Claisen rearrangement reaction because each would favor the formation of the *E* isomer of the corresponding tri-substituted double bonds.

One important feature of this synthetic plan is that, unlike the previous synthesis, the modified route include advanced intermediates, such as cyclized sulfonyl enone **72**, which could serve as immediate precursors to not only isoverticillene (**21**) but also verticillene (**16**) and (-)-verticillol (*ent*-**15**). If successful, the plan could lead to the first enantioselective syntheses of these compounds.



Scheme 32. Retrosynthetic analysis of modified synthesis of isoverticillene.

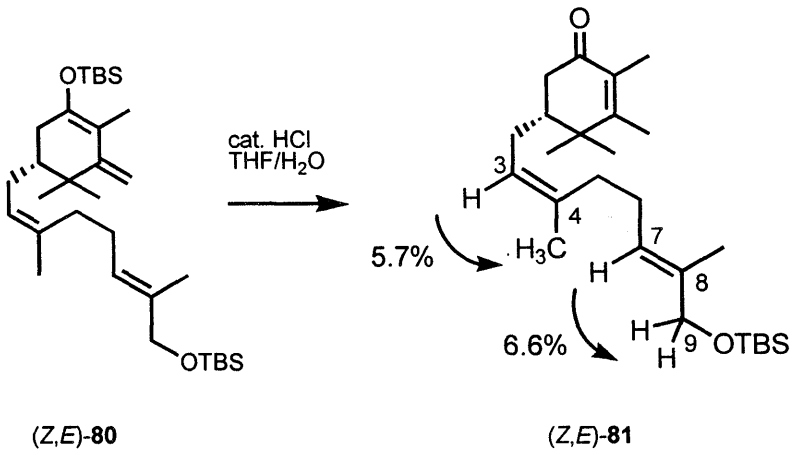
3.2 Initial efforts towards the construction of side chain



Scheme 33. Side-chain construction — Horner-Wittig reaction.

In earlier studies, the side chain in intermediates such as sulfone-bromide **76** was attached to cyclohexenone **31** using a more convergent but less efficient approach. In a Horner-Wittig reaction, heptenone fragment **77** (prepared from 2-methyl-2-hepten-6-one (**34**) in a similar way as described in Section 2.2) was reacted with the lithium anion of phosphine oxide **78** (synthesized *via* several functional group interchanges from aldehyde **46**) to give a diastereomeric mixture of the coupled β-hydroxyphosphine oxide **79**

(Scheme 33).[97] The *threo* and *erythro* diastereomers were then separated by column chromatography, so that in the subsequent stereospecific base-induced *syn* elimination, pure (*E,E*)- and (*Z,E*)-isomers of the olefinic product **80** could be obtained separately. Unfortunately, the yields of these reactions were low, and the selectivity for the *threo* diastereomer of adduct **79** and hence the desired (*E,E*)-isomer of **80** was poor.



Scheme 34. nOe difference studies on geometry of side-chain double bonds.

To determine the geometry of the side-chain double bonds in olefinic product **80**, silyl enol ether (*Z,E*)-**80** was hydrolyzed, so that nOe difference studies could be performed on the product (*Z,E*)-**81** (Scheme 34). When the C7 vinyl proton of enone (*Z,E*)-**81** was irradiated, a 6.6% nOe was observed to the carbinol protons at C9 and none to the protons on the neighboring C8 methyl group, suggesting an *E* double bond at C7-C8. This was expected because in the synthesis of side-chain fragment heptenone **77**, the selenium-dioxide-catalyzed allylic hydroxylation of ketal **40** resulted exclusively the *E*

[97] (a) Warren, S.; Buss, A. D. *J. Chem. Soc., Perkin Trans.1* **1985**, 2307. (b) Warren, S.; Buss, A. D. *Tetrahedron Lett.* **1983**, *24*, 111.

allylic alcohol **41** (Section 2.2). When the C3 vinyl proton of (*Z*,*E*)-**81** was irradiated, an 5.7% nOe was observed to the neighboring C4 methylene methyl protons; this is consistent with a *Z* double bond at C3-C4. From these results it was inferred that the other isomer of olefinic product **80** obtained from the Horner-Wittig reaction was the (*E*,*E*)-isomer.

3.3 Current approach to the side chain construction

In the current, more efficient and selective synthesis of the side-chain, the aldehyde moiety of cyclohexenone **31** was first deprotected (Scheme 35). A propenyl group was then selectively added to the aldehyde through the Nozaki-Kishi reaction using chromium(II) chloride and 2-bromopropene.[98] Known for its chemoselectivity towards aldehydes over ketones, the reaction gave good yield (81%) of a mixture of diastereomers of the desired product **82**. When carried out on a large scale, however, the chromium-assisted reaction becomes somewhat impractical because a large excess (minimum of four equivalents) of the expensive chromium(II) chloride was required. This also made work-up rather difficult. In an attempt to reduce the amount of chromium metal used in the reaction, a procedure using chromium(II) chloride as a catalyst and manganese as the stoichiometric reducing agent was attempted,[99] but the yield was poor.

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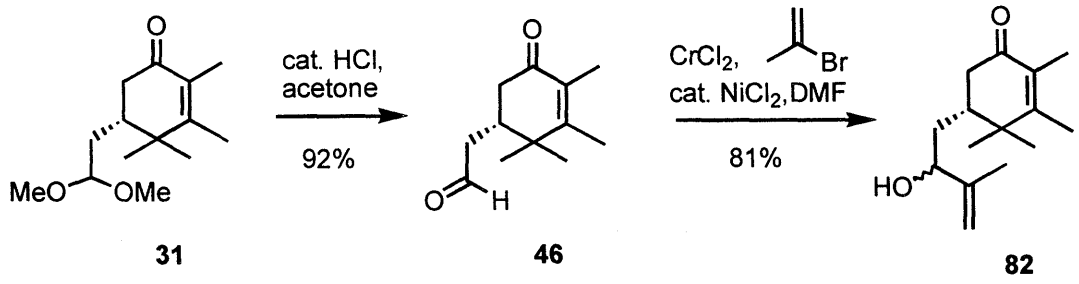
[98] Takai, K.; Sakogawa, K.; Kataoku, Y.; Oshima, K.; Utimoto, K. *Org. Synth.* **1994**, *72*, 180.
[99] Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533.



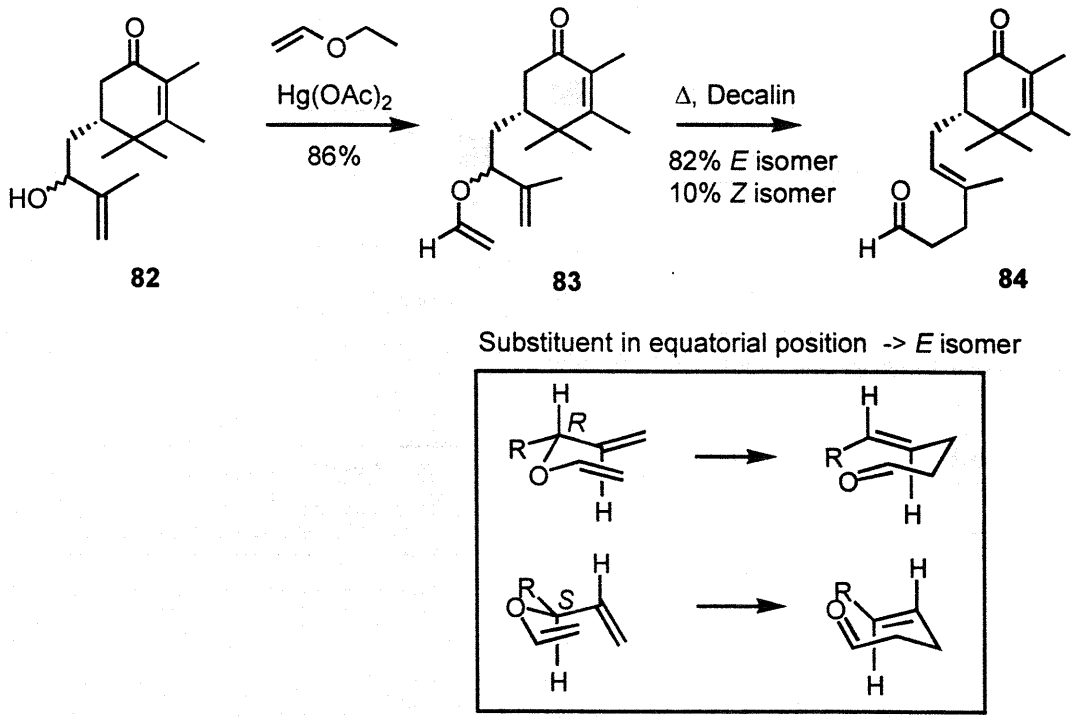
31 **46** **82**

Scheme 35. Construction of side-chain — the Nozaki-Kishi reaction.

In another attempt, aldehyde **46** was reacted with the Grignard reagent propenyl magnesium bromide. The result was a moderately selective addition of propenyl group to the aldehyde to give a moderate yield of allylic alcohol **82**. This became a good substitute for the Nozaki-Kishi reaction in larger-scale cases.

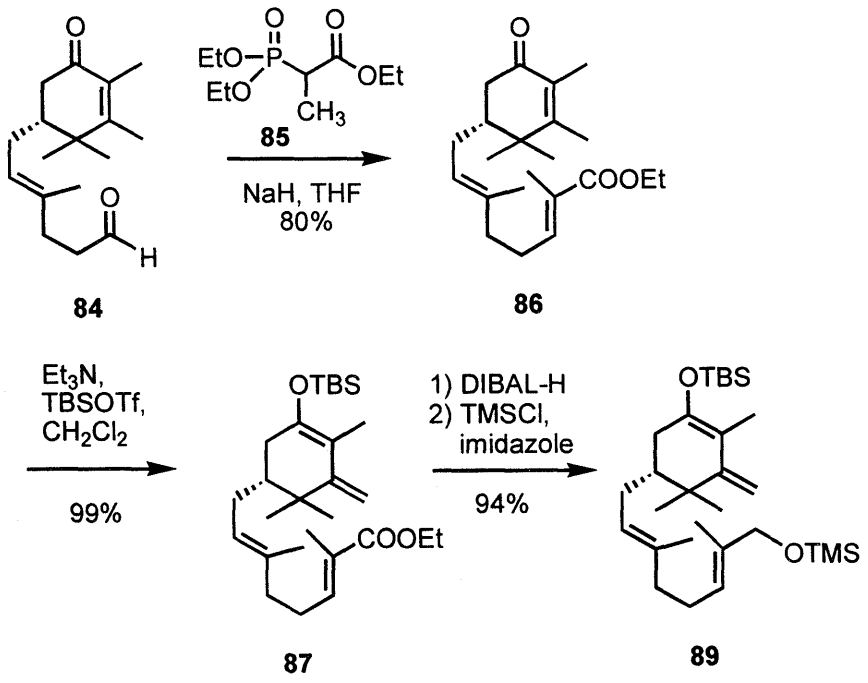
To set up the molecule for the Claisen rearrangement, the diastereomers of allylic alcohol **82** were then converted to the corresponding vinyl ether **83** through a mercury(II) catalyzed trans-etherification reaction (Scheme 36). Heating allylic alcohol **82** at reflux temperature in ethyl vinyl ether with occasional addition of mercury(II) acetate afforded in good yield (86%) the Claisen rearrangement precursor, vinyl ether **83**.[100]

[100] (a) Dauben, W. G.; Dietsche, T. J. *J. Org. Chem.* **1972**, *37*, 1212. (b) Burgstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198. (c) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828.



Scheme 36. Side-chain construction — the Claisen rearrangement.

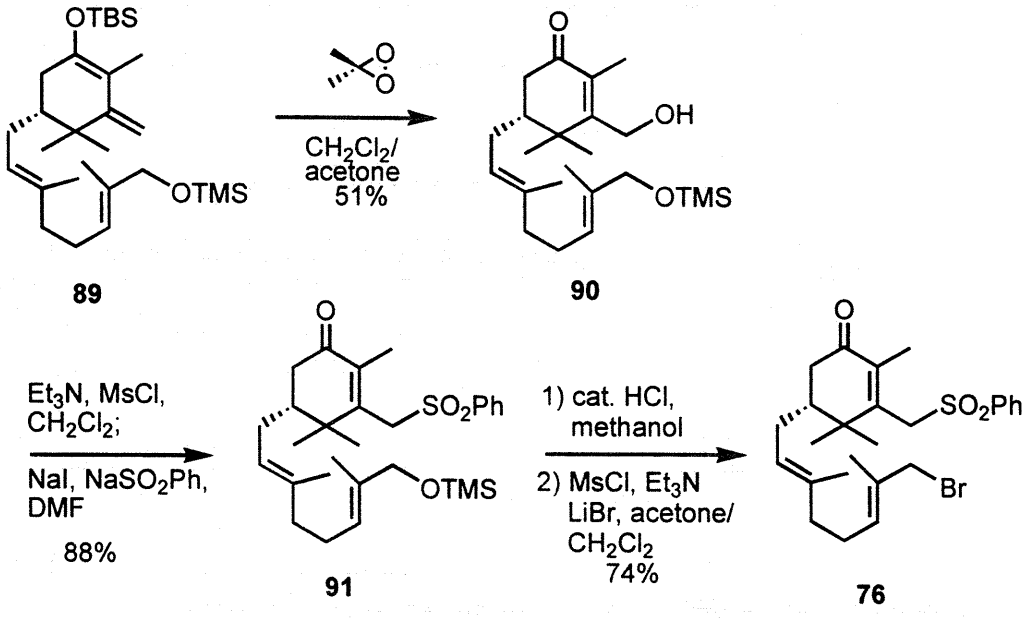
The diastereomeric mixture of vinyl ether **83** was then heated to 200 °C in decahydronaphthalene for two hours to give predominantly the *E* isomer (82%) of the desired aldehyde **84** (Scheme 36).[100a,b] When the diastereomers of the starting vinyl ether **83** were heated separately, the *E*-to-*Z* ratio of the aldehyde product from either reaction is similar (~ 8:1). This selectivity for the *E* isomer could be explained by the preferred six-membered half-chair conformation during the transition state of the 3,3-sigmatropic rearrangement reaction. In *both* diastereomers of **83**, there is a slight preference for the alkyl substituent (R-group in Scheme 36) to be in the pseudoequatorial position, resulting in a predominance of the *E* isomer of aldehyde **84**.



Scheme 37. Side-chain construction — the Horner-Wadsworth-Emmons reaction

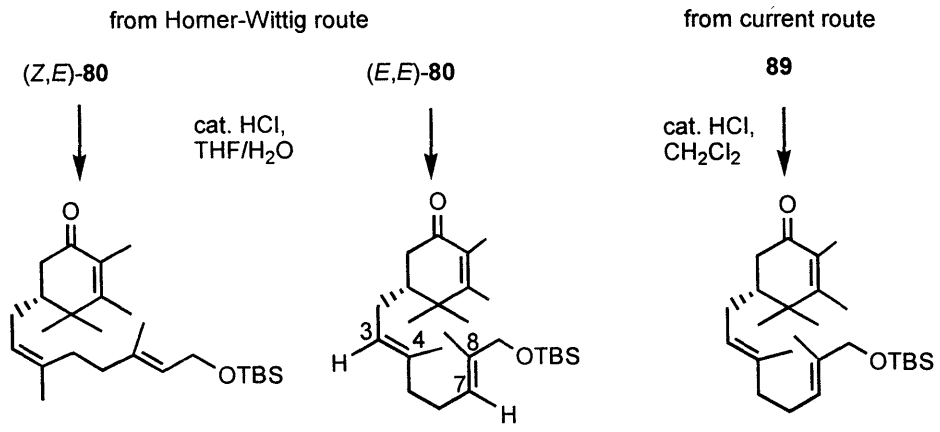
Next, the side chain of aldehyde **84** was further extended through a Horner-Wadsworth-Emmons reaction (Scheme 37). When the sodium anion of triethyl 2-phosphonopropionate (**85**) was reacted with aldehyde **84**, a good yield (80%) of the *E* isomer of the α,β-unsaturated ethyl ester **86** was obtained.

Before further elaboration of the side-chain, the enone moiety of **86** was protected as the silyl enol ether, which would also serve the purpose of introducing the γ-directing group. Treatment of **86** with *tert*-butyldimethylsilyl trifluoromethanesulfonate in the presence of triethylamine again provided near-quantitative yield of silyl enol ether **87**. The ester moiety of **87** was then reduced with diisobutylaluminum hydride at -78 °C to afford the alcohol **70** before being protected as the trimethylsilyl ether (**89**, Scheme 37). This protection was necessary to distinguish this hydroxyl group from the one to be generated later at the γ position of the enone.



Scheme 38. Preparation of alkylative cyclization precursor.

To set up the nucleophilic portion of the molecule for the alkylative cyclization reaction, γ-hydroxylation of the α,β-unsaturated ketone was accomplished as before by reacting silyl enol ether **89** with dimethyldioxirane to give alcohol **90** (Scheme 38). The yield (51%) of the oxidation was somewhat lower because of the labile trimethylsilyl protecting group. Alcohol **90** was then converted to the mesylate. The mesylate was then converted to sulfone **91** through *in situ* generation of the iodide and subsequent reaction with sodium benzenesulfinate. As described in the previous chapter, the γ-iodide was anticipated to be selective for S-alkylation with sulfinate anion. The yield of sulfone **91** from this three-step sequence was 88%. For the electrophilic portion of the intramolecular reaction precursor, the trimethylsilyl protecting group of **91** was hydrolyzed with catalytic amount of acid in methanol, and the resulting alcohol was converted into sulfone-bromide **76** in 74% yield *via* the mesylate.



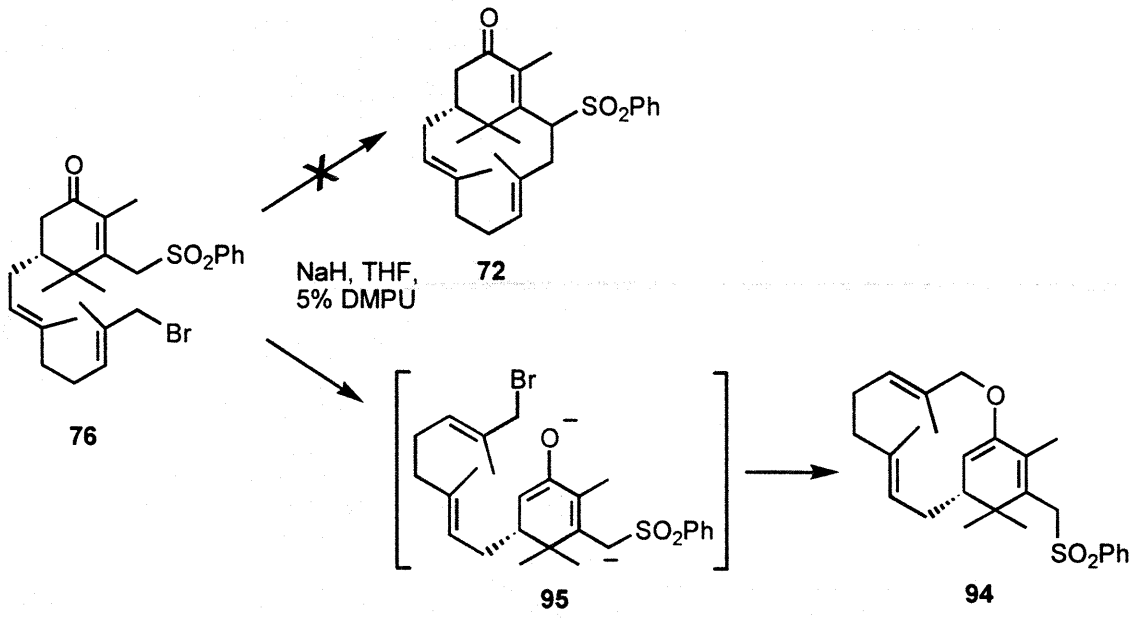
	(Z,E)-81	(E,E)-81	81
	δ	δ	δ
C3 vinyl	5.07	5.08	5.08
C4 methyl	1.69	1.59	1.59
C7 vinyl	5.38	5.36	5.36
C8 methyl	1.60	1.59	1.59 ppm
			Assignment → *E,E*

Scheme 39. Comparison of ^{1}H NMR spectra of geometric isomers of olefin **81**.

In order to confirm the double-bond geometry in the intermediates following the Horner-Wadsworth-Emmons reaction, silyl enol ether **89** was treated with catalytic amount of hydrochloric acid in dichloromethane to give enone **81**, so that its ^{1}H NMR spectrum could be compared to those of enones (*E,E*)-**81** and (*Z,E*)-**81** synthesized using the Horner-Wittig approach (Section 3.2). The ^{1}H NMR spectrum of **81** was identical to that of (*E,E*)-**81** and is significantly different from that of (*Z,E*)-**81** (Scheme 39), confirming the assignment of the double-bond geometry in the intermediates in the current synthesis.

3.4 Initial studies on directed alkylative cyclization

With the cyclization precursor **76** in hand, we once again attempted the difficult macrocyclization. Using similar conditions as in the intermolecular case, sulfone-bromide **76** was added over ten hours *via* a syringe pump into a suspension of sodium hydride in tetrahydrofuran and co-solvent *N,N'*-dimethylpropyleneurea at both room and reflux temperature. While the reactions proceeded to give a complex mixture of polar compounds, only one non-polar product could be isolated in low yield in each case.

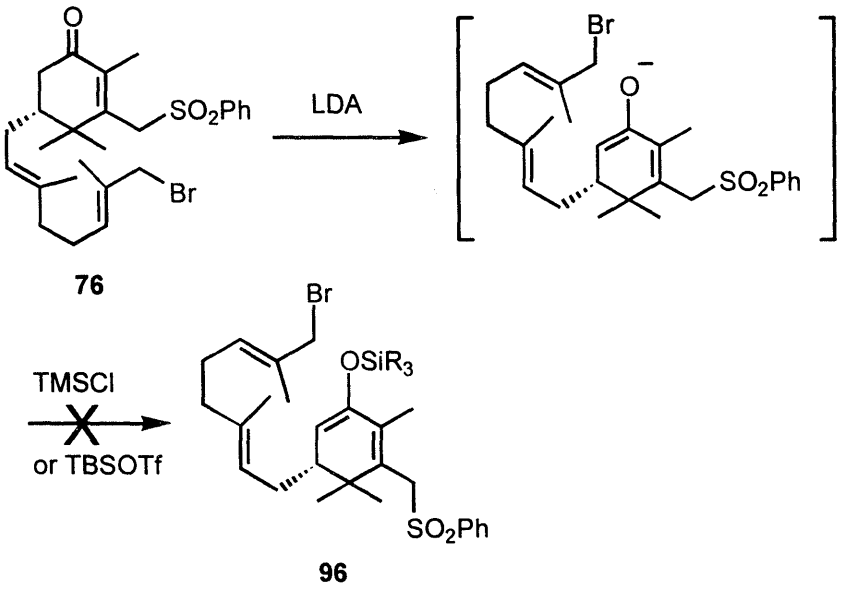


Scheme 40. Unexpected formation of cyclic enol ether.

The ^{1}H NMR spectrum of this product shows the presence of one extra vinyl proton, as well as the presence of *both* protons α to the sulfonyl group. Along with the absence of a carbonyl absorption peak in the IR spectrum, this suggested that the product was not the γ-alkylation product (**72**) but the cyclic enol ether (**94**), a result of O-

alkylation of dianion **95** (Scheme 40). While both O- and C-γ-alkylation would result in a 12-membered macrocycle, the side chain apparently favored attack at the less sterically hindered oxygen site.

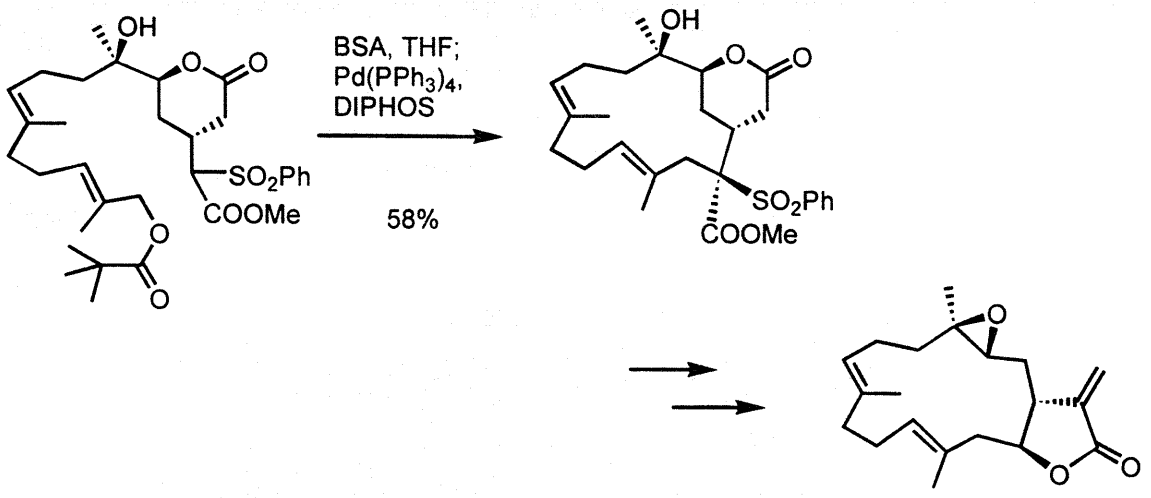
To solve this regioselective problem, we initially attempted the straightforward solution of blocking the oxygen site by a bulky siloxy group as in silyl enol ether **96** (Scheme 41). Unfortunately, reaction of the kinetic enolate of sulfone-bromide **76** with trimethylsilyl chloride[101] at -78 °C was inefficient, and the silyl enol ether product (**96**) was too labile to survive work-up. The reaction of the kinetic enolate of **76** with *tert*-butyldimethylsilyl trifluoromethanesulfonate at -78 °C also did not afford any desired silyl enol ether.



Scheme 41. Unsuccessful O-silylation of enone.

[101] House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

We next turned to the possibility of using the palladium-catalyzed allylation reaction to effect the recalcitrant macrocyclization. It had been demonstrated that π-allylpalladium complexes generated from various allylic functionalities such as allylic acetates react well with "soft" nucleophiles such as anions of malonates and β-carboxysulfones to form C-alkylation products.[102] Because the delocalized π-allyl palladium complex is a "softer" electrophile, this method has the potential to favor C-alkylation over O-alkylation of an enolate. Furthermore, the use of π-allylpalladium alkylation in macrocyclic construction have been documented.[103] For example, the 14-membered macrocycle in soft-coral terpenoid isolobophytolide (**97**) was constructed in good yield using this strategy (Scheme 42).[104]



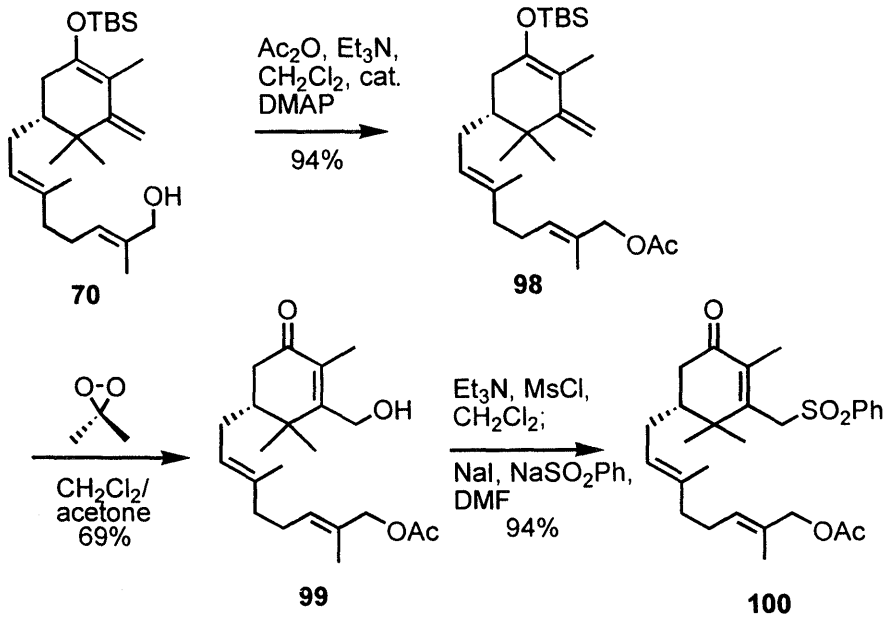
97: isolobophytolide

Scheme 42. Synthesis of isolobophytolide macrocycle using palladium-catalyzed allylation.

[102] For reviews, see: (a) Trost, B. M. *Science* **1983**, *219*, 245. (b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.
[103] (a) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.
[104] Marshall, J. A.; Andrews, R. C.; Lebioda, L. *J. Org. Chem.* **1987**, *52*, 2378.

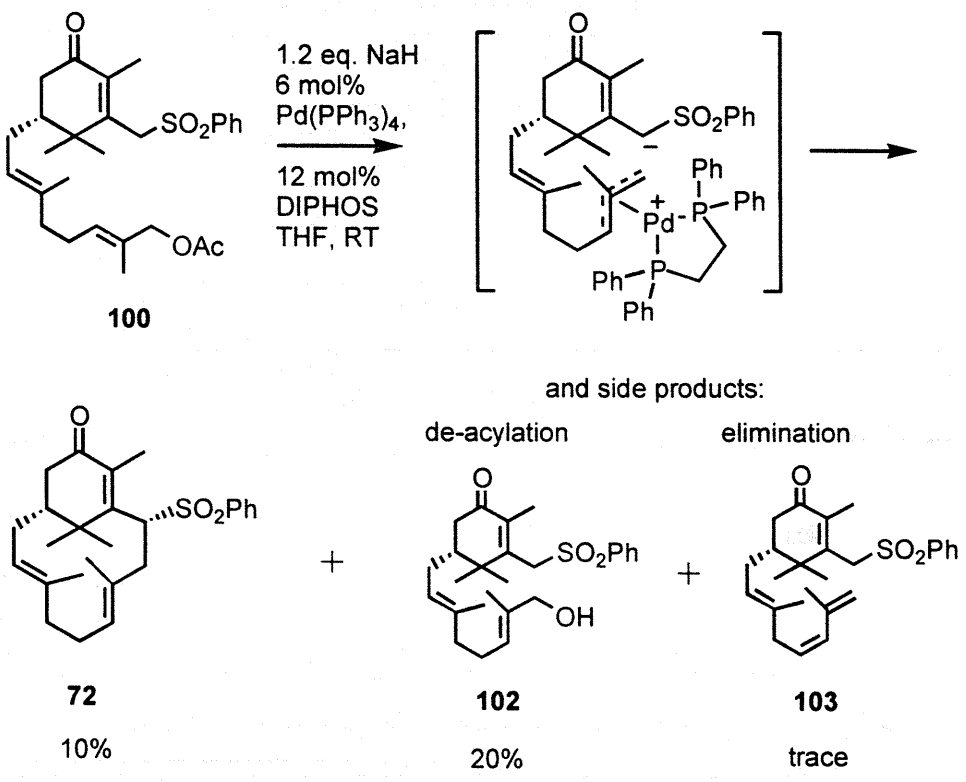
3.5 Palladium catalyzed directed alkylative cyclization

Synthesis of the palladium-catalyzed allylation precursor began with the conversion of alcohol **70** to acetate **98** (Scheme 43). The acetate moiety served the purposes of: 1) distinguishing this hydroxyl group from the one generated in the next step; and 2) being an effective precursor to the π-allylpalladium complex during the cyclization step. The dual function of the acetate shortened the synthesis by removing two subsequent steps of deprotecting and acylating the allylic alcohol moiety. In addition, with the more stable acetate protecting group, the reaction of silyl enol ether **98** with dimethyldioxirane (**51**) resulted in a higher yield (69%) than in the case of trimethylsilyl-protected **89** (51%). Alcohol **99** was subsequently converted to the γ-sulfonyl-α,β-unsaturated ketone (**100**) as before in high yield (Scheme 43).



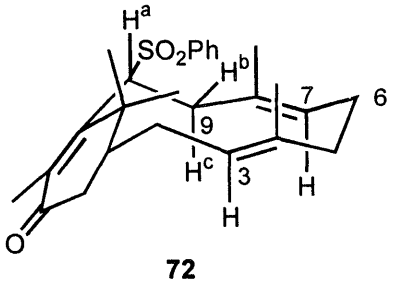
Scheme 43. Synthesis of acetate substrate for palladium-catalyzed allylation.

Initial studies of the allylation reaction demonstrated that, albeit in low yield (10%), cyclization did indeed occur when acetate **100** was stirred with sodium hydride, 6 mol% of tetrakis(triphenylphosphine)palladium(0) and 12 mol% of the auxiliary ligand 1,2-bis(diphenylphosphino)ethane at room temperature (Scheme 44). Spectroscopic data of the isolated product were consistent with a single diastereomer of the intramolecularly γ-alkylated product **72**. In addition, careful analysis of the ^{1}H NMR and COSY spectra of cyclized sulfonyl enone **72** allowed a preliminary determination of the C10 stereochemistry based on proton-proton coupling constants between C10 proton and its neighboring C9 methylene protons (Scheme 45).



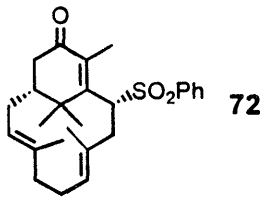
Scheme 44. Palladium-catalyzed alkylative cyclization of acetate.

It is interesting to note that the rigidity of the newly formed macrocycle is reflected in the distinct coupling patterns and the more scattered resonances in the ^{1}H NMR spectra of subsequent intermediates (Scheme 45). For example, in cyclized sulfonyl enone **72** as well as subsequent cyclized intermediates, the vinyl proton at C7 no longer couples to the C6 methylene protons equally. Instead of appearing as a triplet in the NMR spectra of the acyclic precursors, the resonance of C7-*H* in **72** appears as a doublet of doublet, suggesting it couples differently to the diastereotopic protons at C6. This same phenomenon can also be observed with the vinyl proton at C3.

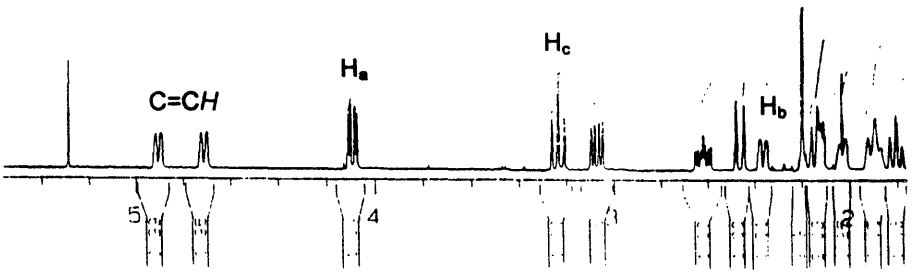


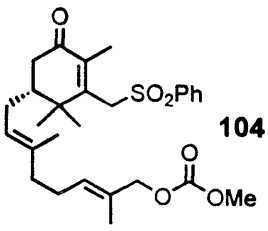
J_{HaHb} = 3.9 Hz
J_{HaHc} = 12.7 Hz

72

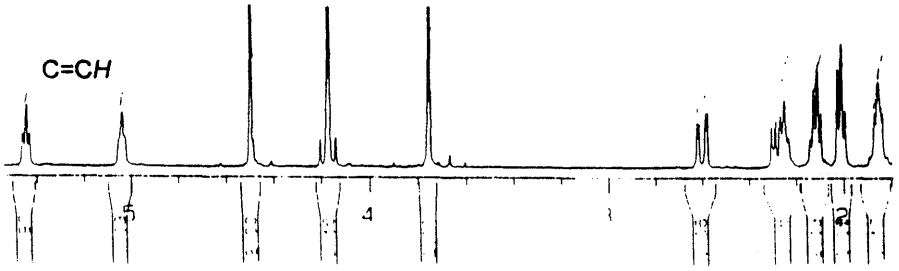


72





104

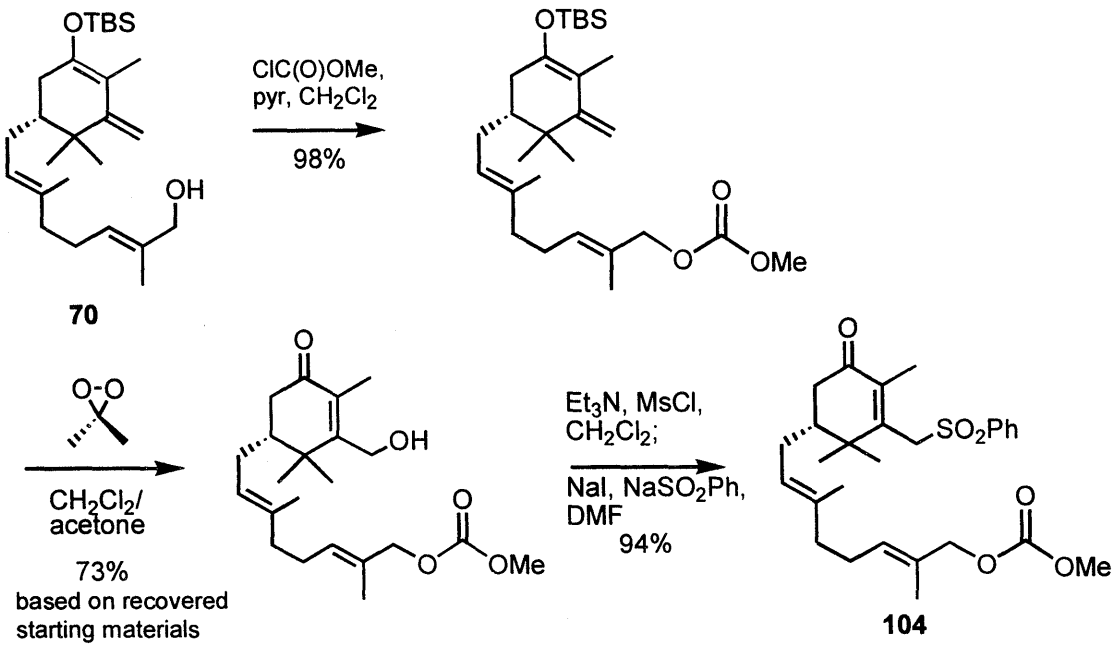


Scheme 45

In an attempt to explain the dramatic difference in regioselectivity between the palladium-assisted reaction and the direct alkylation of sulfone-bromide **76** (Section 3.4), we once again invoked the "hard and soft acids and bases" (HSAB) principle (Section 2.5). The mono-anions of **76** and **100** each have three nucleophilic sites, with the most electronegative oxygen being the "hardest," and the γ carbon next to the stabilizing sulfone group being the "softest." Because reactions between "like" partners are kinetically favored, the relative "softness" of the delocalized π-allylpalladium cation probably made it possible for alkylation to occur at carbon rather than oxygen.

While this palladium-catalyzed cyclization reaction represented a triumph over the major obstacle in the synthesis, several modifications had to be made to improve the yield. The major side reactions (Scheme 44) were the facile hydrolysis of the acetate moiety to give allylic alcohol **102**, and the elimination of the π-allylpalladium complex species to give diene **103**. First, to avoid elimination it was found necessary that: 1) the reaction mixture was not to be heated; 2) little or no excess of the base was to be used; and 3) the base was allowed to be mostly consumed by the sulfone substrate before the addition of palladium catalysts. Unfortunately, by allowing more time for deprotonation, one allowed more time for the hydrolysis of the acetate moiety.

In an attempt to slow down the rate of acetate hydrolysis, milder base 1,8-diazabicyclo[4.3.0]undec-7-ene and silylating agent *N,O*-bis(trimethylsilyl)acetamide were used instead of sodium hydride. Unfortunately, no reaction occurred when either of these milder reagents was used at room temperature; and when the reaction mixtures were heated, only the elimination product **103** was obtained.

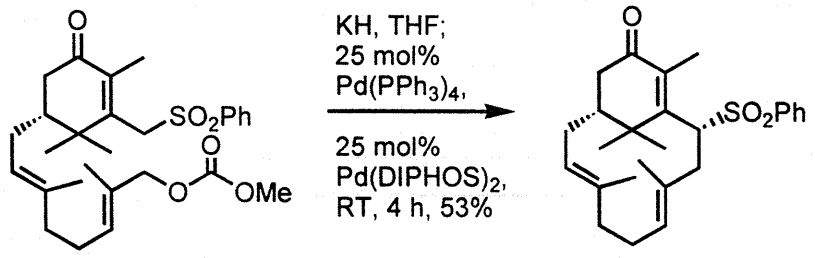


Scheme 46. Synthesis of carbonate macrocyclization precursor.

A partial solution to the hydrolysis problem was found in the more robust carbonate **104**, the synthesis of which (Scheme 46) was similar to that of the acetate (**100**). While carbonate **104** reacted similarly with palladium to give cyclized sulfonyl enone **72**,[105] the carbonate moiety was also stable in the presence of potassium hydride for at least one hour before allylic alcohol **102** began to appear. Unlike the case of acetate **100**, the stability of carbonate **104** allowed enough time for hydride to react completely with the sulfone before the onset of hydrolysis of the protecting group.

Because the subsequent cyclization reaction itself was slow at room temperature, hydrolysis still posed a problem after the initial reaction with metal hydride. It was therefore necessary to use 50 mol% of the palladium catalysts so that the cyclization reaction could compete favorably with the rate of carbonate hydrolysis. The use of 20

mol% of catalysts, for example, slowed down the cyclization reaction enough that hydrolyzed product was recovered after six hours in nearly 30% yield.



104 **72**

Scheme 47. Optimized conditions for palladium-catalyzed alkylative cyclization.

The reaction conditions for this difficult macrocyclization were later optimized as follows (Scheme 47): carbonate **104** was first treated with potassium hydride for 45 minutes in tetrahydrofuran, followed by the addition of 25 mol% tetrakis-(triphenylphosphine)palladium(0) and 25 mol% bis[bis(diphenylphosphino)ethane]-palladium(0). After four hours at room temperature, a 53% yield of the desired cyclized sulfonyl enone **72** was obtained. The purpose of using bis[bis(diphenylphosphino)-ethane]palladium(0) as a co-catalyst was to minimize the presence of excess free phosphine ligand, while maintaining a one-to-one ratio between the auxiliary ligand bis(diphenylphosphino)ethane and palladium.

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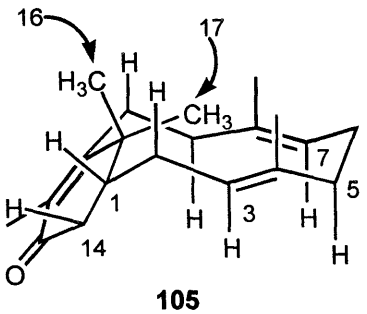
[105] Tsuji, E.; Shimizu, I. Minami, I. Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809.



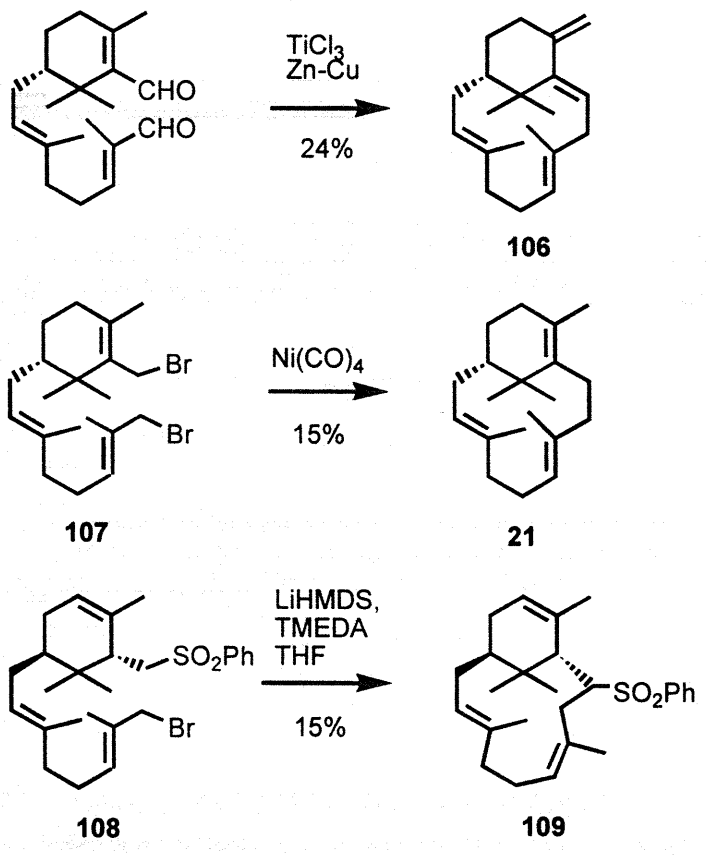
105

cross peaks between:

C3-H and C5-H	$C16H_3$ and C14-H
C7-H and C9-H	$C17H_3$ and C1-H
$C16H_3$ and C1-H	$C17H_3$ and C2-H
$C16H_3$ and C10-H	$C17H_3$ and C10-H

Scheme 48. Structure of macrocyclic enone based on NOESY data.

In order to determine whether the C7-C8 double bond of cyclized sulfonyl enone **72** remained in the *E* configuration during the macrocyclization step, a NOESY experiment was performed on enone **105**, which was prepared by the removal of the directing group of **72** through the reductive elimination of sulfinate using excess lithium in ammonia as discussed earlier. Along with results from a COSY experiment, the NOESY spectrum identified several protons in close proximity with each other through magnetization exchange. A cross peak was observed between C7-*H* and one of the adjacent C9-H_2 protons, but *not* between the former and the C8-CH_3 protons (Scheme 48). Similarly, a cross peak was observed between C3-*H* and one of the adjacent C5-H_2 protons, but *not* between the former and the C4-CH_3 protons. These provided evidence for the *E* configuration at both the C3-C4 and C7-C8 double bonds. (As discussed earlier in Section 3.3, the geometry at the C3-C4 double bonds had been previously established as the *E* isomer by nOe difference experiments.) In addition, other cross peaks between the geminal methyl groups with adjacent protons on the macrocycle further confirmed the structure of cyclized enone **105**.



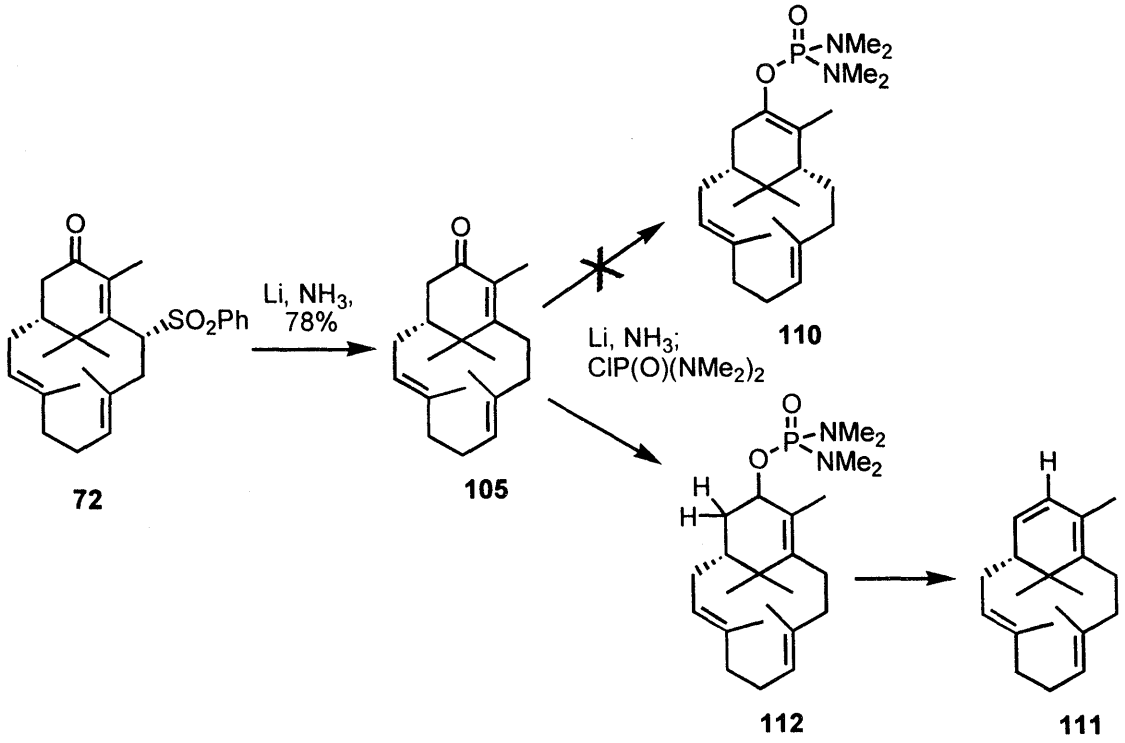
Scheme 49. Previous attempts of verticillenic macrocyclization.

The yield of the macrocyclization reaction (53%) compared well with previous attempts of cyclization of similar verticillenic macrocycle (Scheme 49). In the ten-step synthesis of verticillene Pattenden *et al.*,[39] the key McMurry coupling reaction afforded a 24% yield of an unexpected cyclized product. In the 12-step synthesis by Croteau *et al.*,[49] the cyclization was achieved in 15% yield through a nickel(0) coupling reaction of a dibromo precursor (**107**). In the synthesis of anhydroverticillol by Kato *et al.*,[106] alkylation of bromo sulfone **108** afforded 15% yield of the cyclized but isomerized (7*Z*)-product (**109**).

[106] Kumagai, T.; Ise, F.; Ueyhara, T.; Kato, T. *Chem. Lett.* **1981**, 25.

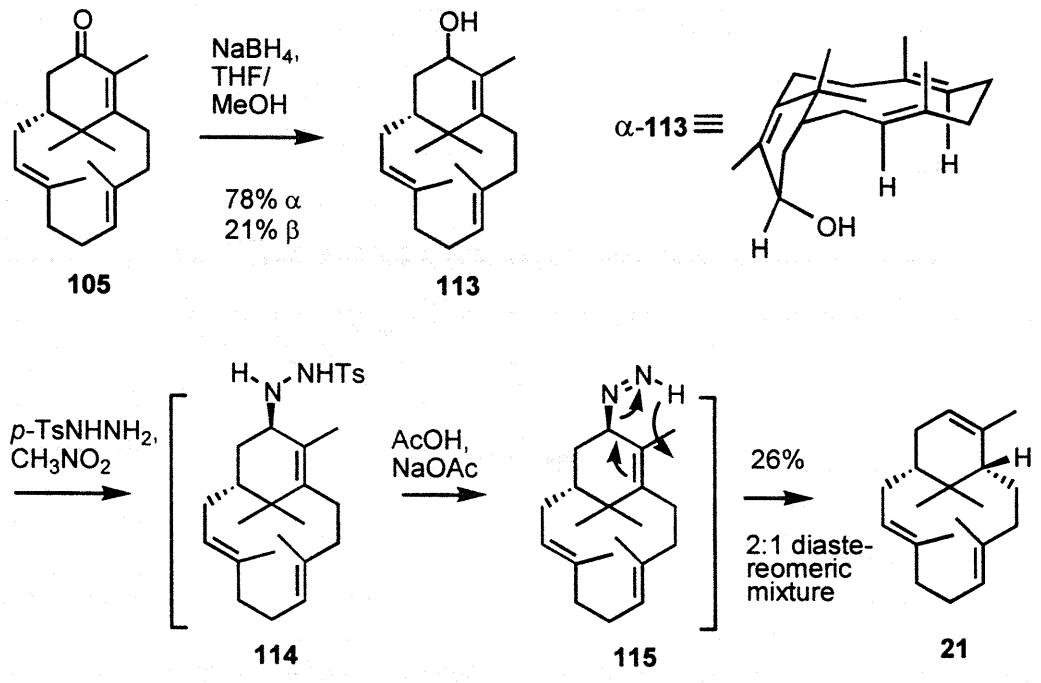
3.6 Completion of the synthesis of isoverticillene and verticillene

After the reductive removal of the sulfone group in sulfonyl enone **72** (Scheme 50), enone **105** was to be reduced and deoxygenated using Ireland's procedure of dissolving-metal reduction as described in the previous chapter. However, the initial reduction of enone **105** failed to produce the expected phosphoramidate product (**110**). Spectroscopic data of the product suggested that the isolated product was diene **111**. This product was probably formed by the 1,2-reduction of enone **105** and the subsequent elimination of phosphoramidate **112**.



Scheme 50. Dissolving-metal reduction of directing group and enone.

As an alternative to the final functional group transformation, enone **105** was first reduced by sodium borohydride in tetrahydrofuran and methanol in near-quantitative yield to give a 3.5:1 diastereomeric mixture of allylic alcohol **113** (Scheme 51). In the ^{1}H NMR spectrum of the major stereoisomer of **113**, the unusual down-field shift of one of the vinyl proton resonances seemed to suggested the major isomer had an α hydroxyl group that pointed into the 12-membered ring, deshielding one of the vinylic protons on the ring. This explanation was supported by the idea that hydride was preferably delivered from the more accessible convex side of the molecule.



Scheme 51. Completion of the synthesis of isoverticillene.

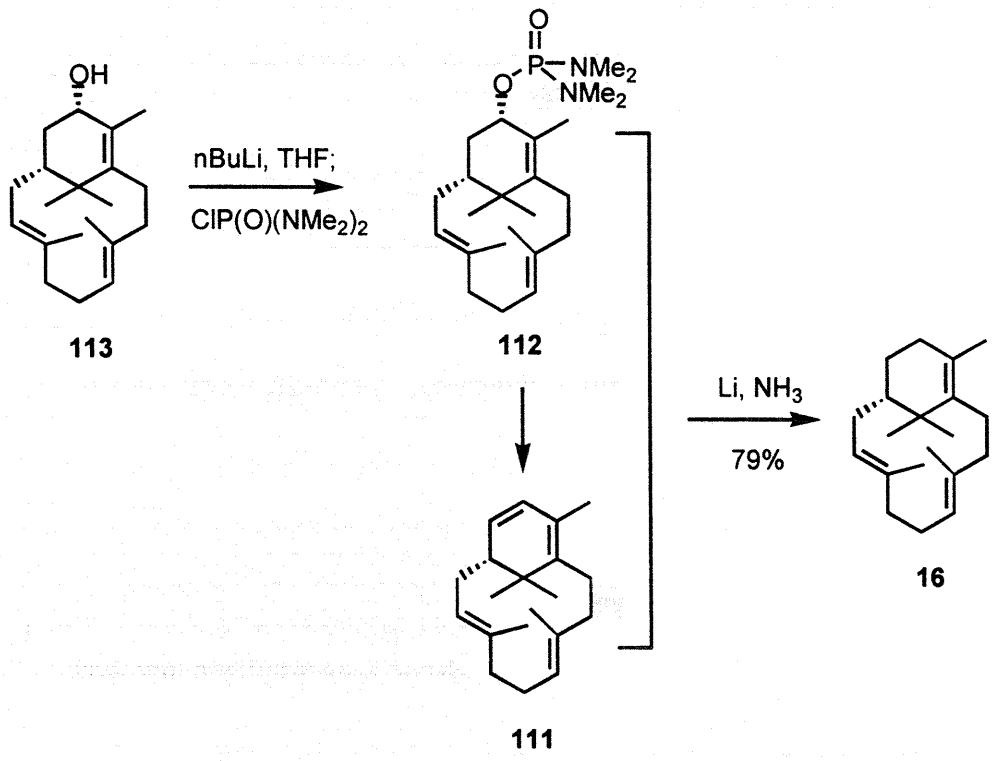
For the subsequent allyl diazene rearrangement reaction,[107] alcohol **113** was first converted to the toluenesulfonyl hydrazine **114** using *p*-toluenesulfonhydrazide in tetrahydrofuran and nitromethane (Scheme 51). Because the reaction most likely involves ionization of the C13 center, and because *p*-toluenesulfonhydrazide probably preferentially approaches at C13 from the molecule's convex side, the predominant product was anticipated to be the β-substituted toluenesulfonyl hydrazine **114**. Mechanistically, decomposition of allyl toluenesulfonyl hydrazine intermediates produces alkenes which have undergone stereoselective transposition *via* a retro-"ene" reaction of the diimide intermediate such as **115**. Therefore, the predicted β-stereochemistry of toluenesulfonyl hydrazine **114** was believed to result in the desired *cis*-fused isomer of isoverticillene (**21**).

Experimentally, using *either* diastereomer of the starting alcohol **113**, the product of the allyl diazene rearrangement was obtained as a 2:1 mixture of diastereomers (based on ^{1}H NMR integration). The very non-polar mixture was efficiently separated by column chromatography using silver-nitrate-impregnated silica gel. The isolated yields of the two diastereomers were 18% and 7.8%. Unfortunately, their stereochemistries at C11 could not be determined by NMR means. Based on mechanistic considerations of the formation of the toluenesulfonyl hydrazine intermediate (**114**), however, it is very likely the major isomer from the allyl diazene rearrangement reaction is the correct stereoisomer of isoverticillene (**21**).

Attempts to improve the stereochemical outcome of this reaction is underway. In addition, because of the stereospecificity of the allyl diazene rearrangement reaction, the stereochemistry of the major isomeric product from this reaction could be deduced if the

[107] Hutchins, R. O.; Kacher, M.; Rua L. *J. Org. Chem.* **1975**, *40*, 923.

stereochemistry of the major isomer of starting hydrazine **114** could be determined by spectroscopic means. NMR studies such as nOe difference experiments of toluenesulfonyl hydrazine **114** will be conducted to determine the stereochemistry at C13.



Scheme 52. Completion of the synthesis of verticillene

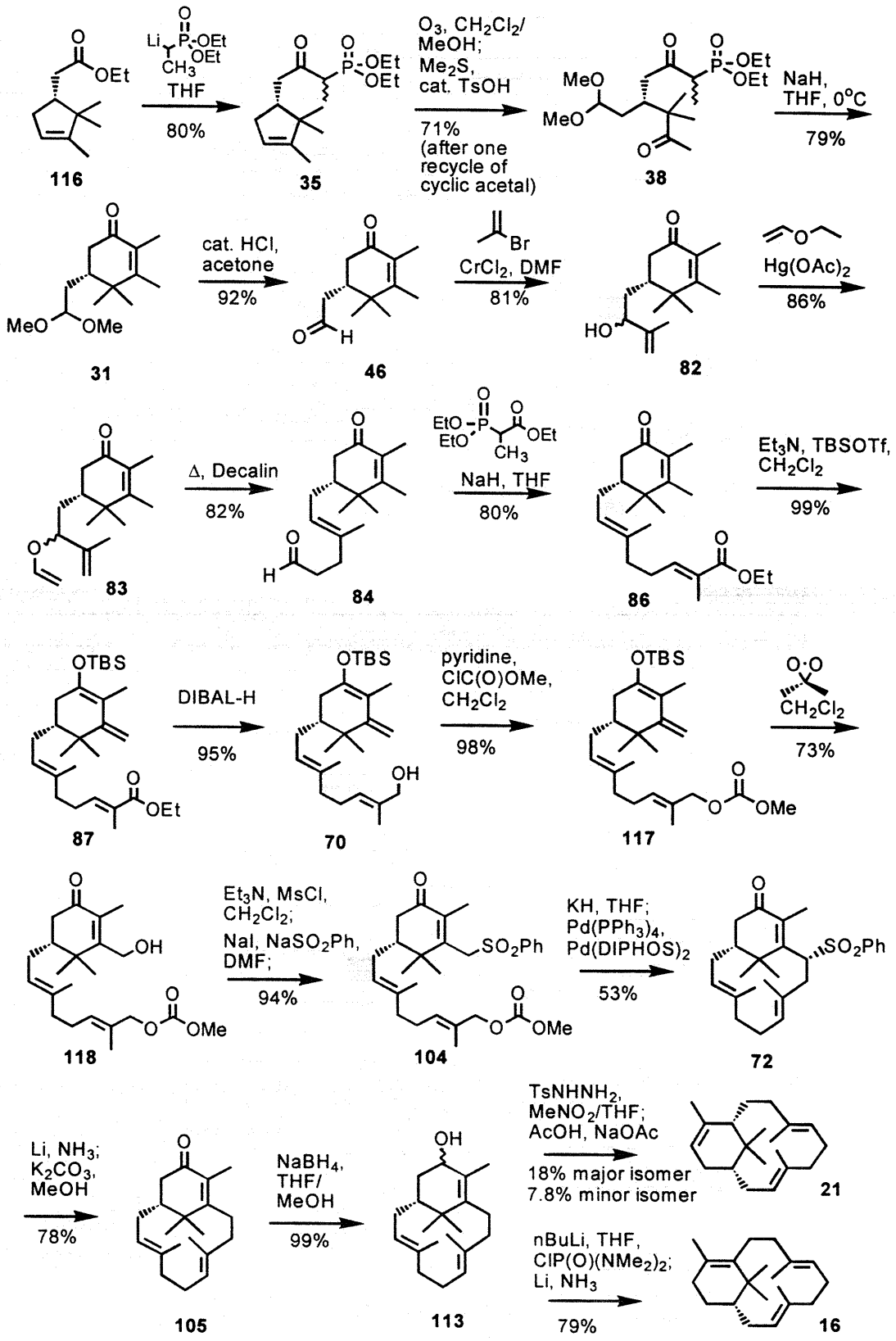
For the completion of the synthesis of verticillene (**16**), the major isomer of **113** was deoxygenated using Ireland's protocol (Scheme 52).[85a] Alcohol **113** was first converted to the phosphoramidate **112** with *n*-butyllithium and tetramethylphosphorodiamidic chloride. Addition of the reaction mixture containing both **112** and elimination product **111** to excess lithium in liquid ammonia afforded a 71% yield of verticillene (**16**). Since diene **111** could not be found in the final product mixture, it was very likely that the conjugated diene of **111** had also been reduced to give

verticillene. Spectroscopic data of **16**, including ^{1}H NMR, ^{13}C NMR and DEPT, are identical to those reported by Pattenden *et al.*[39] In addition, this synthesis afforded enantiomerically pure verticillene having an optical rotation of $[\alpha]^{22}_{D}$ +72.8°.

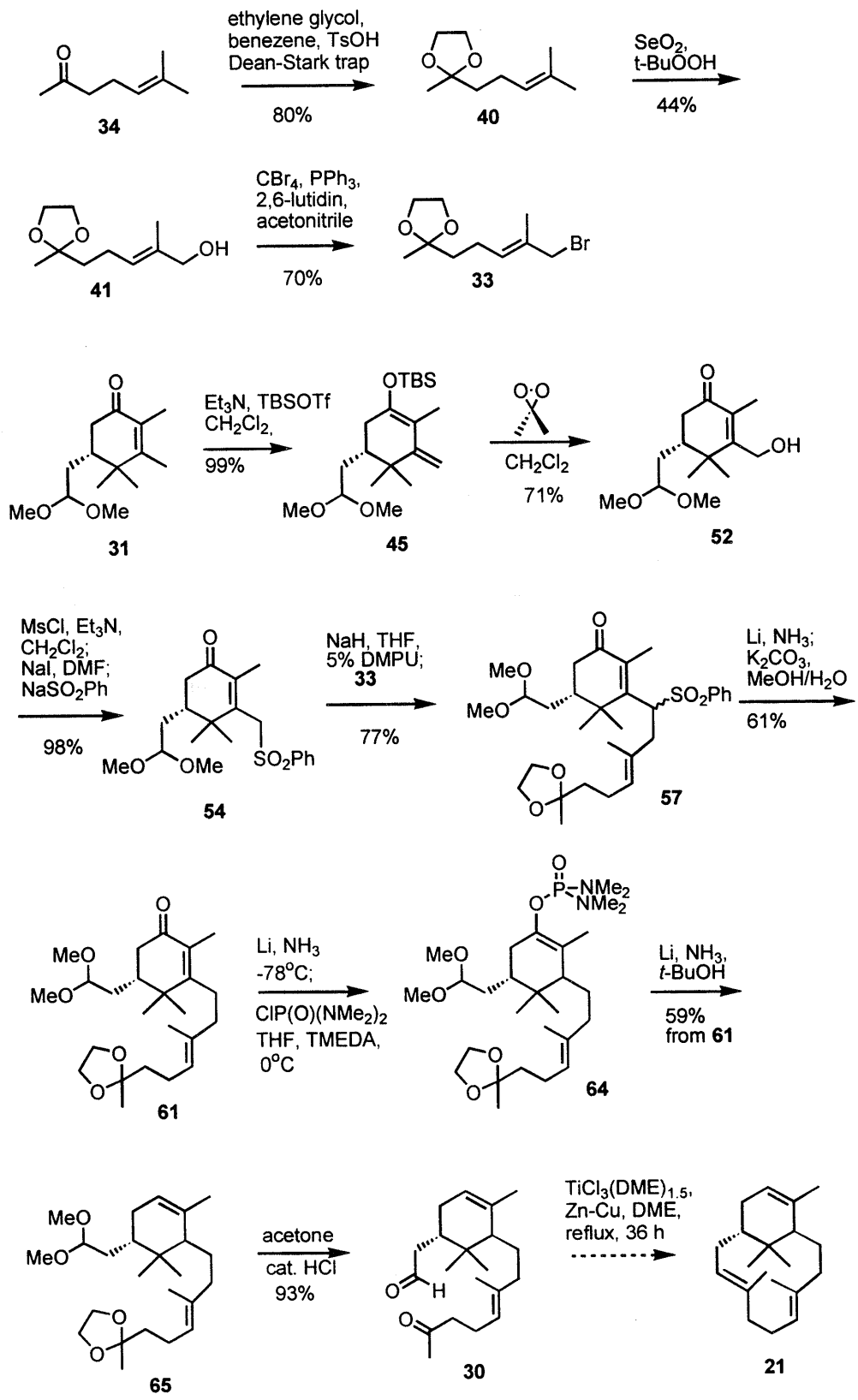
3.7 Summary

Through the efficient application of existing methodology in organic synthesis and the development of an efficient sulfone-directed allylation, we have overcome the major obstacle of forming the 12-membered verticillenic macrocycle. We have further applied our strategy to the stereoselective synthesis of isoverticillene. In addition, the first enantioselective synthesis of (+)-verticillene was successfully achieved. The enone moiety in cyclized enone **105** had provided a convenient handle for its modification into different verticillenic analogs.

In summary, the modified synthesis of isoverticillene involved a total of 19 operations starting from (*R*)-ethyl campholenate (**116**), with an overall yield of 0.78% assuming the major isomer of the final reaction is the correct stereoisomer (Scheme 53); this is compared to the 13 steps and 8.0% overall yield of the incomplete synthesis (excluding the final McMurry cyclization) described in the previous chapter (Scheme 54). The synthesis of verticillene involved a total of 19 operations starting from (*R*)-ethyl compholenate (**116**), with an overall yield of 3.0%.



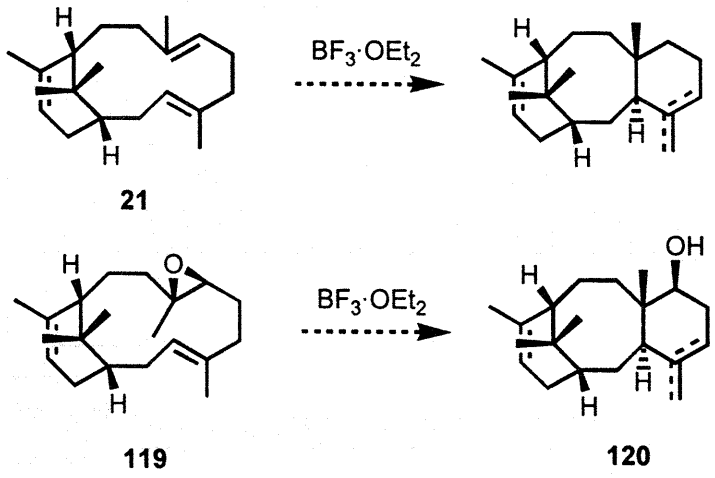
Scheme 53. Summary of reactions — synthesis of isoverticillene and verticillene



Scheme 54. Summary of reactions — the McMurry coupling approach to isoverticillene.

Chapter 4. Future Prospects

Because isoverticillene (**21**) was synthesized as a mixture of diastereomers, the immediate goal would be to optimize the allyl diazene rearrangement reaction, so that the yield of the desired diastereomer could be maximized. With isomerically pure isoverticillene at hand, the next task would be to evaluate its ability to undergo transannular cyclization as proposed to give the taxane carbon framework. Using procedures developed for other similar electrophilic transannular cyclization reactions,[108] isoverticillene could be cyclized through reaction with a Lewis acid catalyst. It could also be epoxidized at C7-C8, so that the transannular cyclization of epoxide **119** would be facilitated by the ionization of the epoxy moiety to form taxadienol **120** (Scheme 55).



Scheme 55. Proposed Lewis acid-catalyzed transannular cyclization of isoverticillene and 7,8-epoxy isoverticillene.

Isotopically labeled isoverticillene could be tested *in vitro* and *in vivo* experiments as a probe for the mechanism of taxadiene synthase. In addition, with enantiomerically pure verticillene at hand, its possible role as a substrate for taxadiene synthase could also be re-investigated, because prior studies[49] were conducted with racemic verticillene.

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[108] For a recent example, see: Williams, D. R.; Coleman, P. J. *Tetrahedron Lett.* **1995**, *36*, 39. See also ref. 40 and references therein.

Experimental Section

General Procedures

Reaction mixtures were stirred magnetically unless otherwise noted. All moisture and/or air sensitive reactions were carried out under a positive pressure of argon, and were performed in glassware that was oven-dried. Solvents and liquid reagents were transferred *via* syringe or cannula unless otherwise noted. Reactions were monitored by thin-layer chromatography. Organic solvents were removed through concentration on a Büchi rotary evaporator at 20 - 40 mmHg.

Materials

Commercial solvents and reagents were used without further purification with the following exceptions:

Solvents:

Acetonitrile was distilled under argon from calcium hydride.

Benzene was distilled under argon from calcium hydride.

Dichloromethane was distilled under nitrogen from phosphorous pentoxide.

N,*N*-Dimethylformamide was stored over activated 4Å molecular sieves.

Dimethyl sulfoxide was distilled at 20 mm Hg from calcium hydride.

Tetrahydrofuran was distilled under nitrogen from sodium benzophenone ketyl.

Toluene was distilled under nitrogen from sodium.

Reagents:

n-Butyllithium was titrated prior to use with *sec*-butyl alcohol in tetrahydrofuran at 0 °C using 1,10-phenanthroline as an indicator.[109]

Chromium(II) chloride was purchased in anhydrous form from Alfa Aesar.

Dimethyldioxirane was prepared by stirring acetone (64 mL), water (88 mL), sodium bicarbonate (48 g) and oxone (100 g) under house vacuum (~ 40 mmHg), while condensing the reagent in a cold-finger at -78 °C. The condensate was dried over magnesium sulfate and filtered to give a 0.06-0.08 M solution (20 mL) of dimethyldioxirane.[76]

N,N'-Dimethylpropyleneurea was distilled at 0.5 mmHg from calcium hydride and was stored over activated 4Å molecular sieves.

Ethyl vinyl ether was distilled from calcium hydride and was stored at -20 °C.

Lithium metal was stored under mineral oil, and was washed with hexanes, cut into small pieces and flattened before use.

Bis[1,2-bis(diphenylphosphino)ethane]palladium(0) was prepared by first completely dissolving palladium(II) chloride (0.177 g, 1.0 mmol) and 1,2-bis(diphenylphosphino)ethane (1.0 g, 2.5 mmol) in dimethyl sulfoxide (12 mL) at 160 °C. Two minutes after the oil bath was removed, hydrazine hydrate (0.20 mL, 4.0 mmol) was added. The reaction mixture was then allowed to cool down to room temperature in the dark overnight for crystallization to complete. The resulting orange crystals were collected on a fritted funnel under argon, washed successively with ethanol (3 x 4 mL)

[109] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

and ether (3 x 5 mL), and dried overnight under vacuum. The reagent was stored in the dark at -20 °C under argon.[110]

Mercury(II) acetate was recrystallized from absolute ethanol and 0.025% acetic acid.

Methanesulfonyl chloride was distilled at 20 mmHg.

Ozone was generated from a Welsbach ozone generator using the settings described in the experimental procedure.

Pyridine was distilled under argon from calcium hydride.

Tetrakis(triphenylphosphine)palladium(0) was prepared by first completely dissolving palladium(II) chloride (0.18 g, 1.0 mmol) and triphenylphosphine (1.31 g, 5.0 mmol) in dimethyl sulfoxide (12 mL) at 140 °C. Two minutes after the oil bath was removed, hydrazine hydrate (0.20 mL, 4.0 mmol) was added. The reaction mixture was then allowed to cool down to room temperature in the dark over 6 h. The resulting yellow crystals were collected on a fritted funnel under argon, washed successively with ethanol (3 x 4 mL) and ether (3 x 5 mL), and dried overnight under vacuum. The reagent was stored in the dark at -20 °C under argon.[110]

N,*N*,*N*′,*N*′-Tetramethylethylenediamine was distilled from calcium hydride under argon.

Tetramethylphosphorodiamidic chloride was distilled at 30 mmHg and was stored under argon at -20 °C.

Triethylamine was distilled under nitrogen from calcium hydride.

Triphenylphosphine was recrystallized from hexanes.

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[110] Cotton, F. A. *Inorg. Synth.* **1972**, *13*, 121.

Chromatography

Column chromatography was performed using Merck 230-400 mesh silica gel. HPLC grade solvents were used.

Thin layer chromatography was performed using Merck pre-coated, glass-backed 0.25 mm silica gel 60 plates, assimilated with 254-nm fluorescent indicator. The plates were observed by illumination with an ultraviolet lamp and by staining with an ethanolic solution of *p*-anisaldehyde (2%) with concentrated sulfuric acid (5%) and acetic acid (1.5%).

Instrumentation

Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

Optical rotations were determined using a Perkin-Elmer 241 polarimeter using a sodium lamp (D line) at 20 °C. Concentration (*c*) is indicated as units of 10 mg/mL.

^{1}H NMR spectroscopy was conducted on a Bruker AC 250 MHz spectrometer, a Varian XL 300 MHz spectrometer, a Varian Unity 300 MHz spectrometer or a Varian VXR 500 MHz spectrometer. Chemical shifts are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane, using the residual chloroform signal (δ 7.26) as a standard. Multiplicities are reported in the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet), dd (doublet of doublet), *etc.*

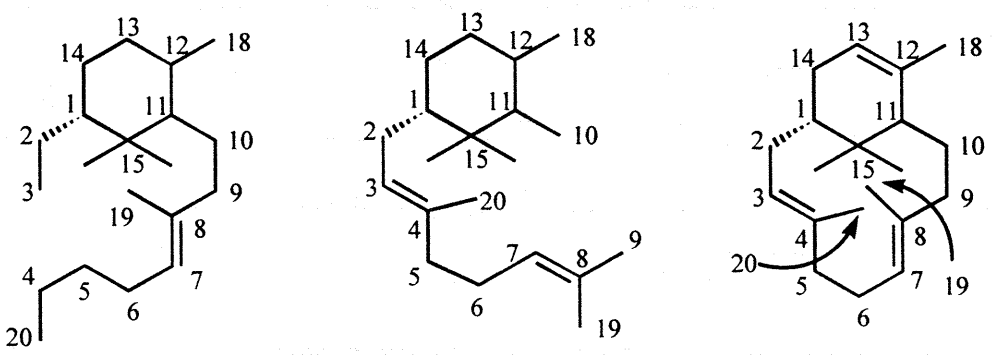
^{13}C NMR were recorded on a Varian XL 300 MHz spectrometer, a Varian Unity 300 MHz spectrometer or a Varian VXR 500 MHz spectrometer. The deuteriochloroform signal (δ 77.0) was used as a standard.

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. Broad absorption peaks are denoted with the letter "b" in parentheses.

Electron ionization mass spectra (EIMS) were recorded on a Hewlett-Packard 5971 mass spectrometer, equipped with a Hewlett-Packard 5890 Series II gas chromatograph (HP-1 column). Spectra were recorded in units of mass to charge ratio (*m/z*).

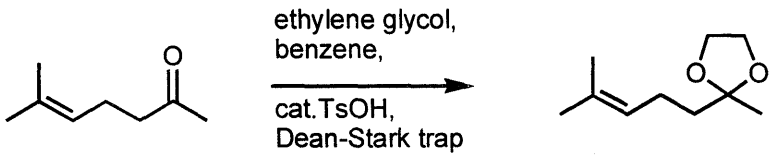
High resolution mass spectra (HRMS) were recorded on a Finnigan MAT 8200 mass spectrometer by the MIT Spectroscopy Lab.

Elemental analyses (Anal.) were performed by Galbraith Laboratories at Knoxville, Tennessee.



The conventional numbering scheme for taxane structures will be used in the characterization of the intermediates described herein. For the purpose of a consistent representation, the same numbering scheme will be applied in cases where the verticillenic macrocycle is not intact.

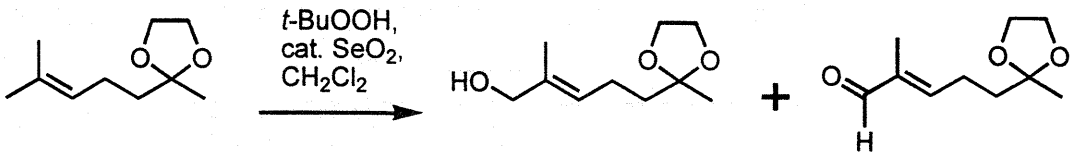
Experimental Procedures



34 80% **40**

Ketal 40:

Heptenone **34** (5 g, 40 mmol) was dissolved in benzene (50 mL) along with ethylene glycol (10 mL, 180 mmol) and a catalytic amount of *p*-toluenesulfonic acid (10 mg, 0.05 mmol) in a flask equipped with a Dean-Stark trap and a reflux condenser. The mixture was heated to reflux temperature and stirred overnight. After cooling down to room temperature, cold saturated sodium bicarbonate solution (50 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ether (3 x 40 mL). The combined organic layers were dried quickly over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 97:3 hexanes-ethyl acetate with 1% triethylamine) to yield 5.4 g (80%) of ketal **40.** R_f 0.61 (9:1 hexanes-ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.08 (m, 1H, C=C-*H*), 3.91 (m, 4H, ketal), 2.04 (m, 2H, C=C-CH_2), 1.65 (s, 3H, C=C-CH_3), 1.61-1.65 (m, 2H), 1.58 (s, 3H, C=C-CH_3), 1.29 (s, 3H). IR (film) 2981, 2931, 2878, 1673, 1450, 1377, 1252, 1220, 1137, 1059, 947, 864 cm^{-1}.



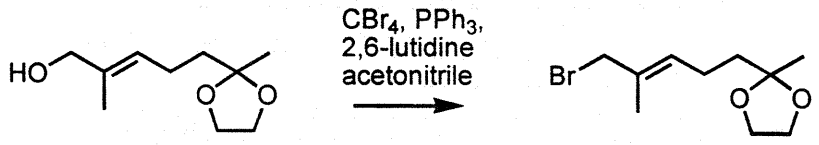
40 **41** **121**

44% 19%

Allylic alcohol 41:

tert-Butylhydroperoxide in aqueous solution (70%, 11 mL, 82 mmol) was added to dichloromethane (50 mL) and was dried by adding cautiously anhydrous magnesium sulfate. This was filtered directly into a solution of alkene **40** (4.0 g, 24 mmol) in dichloromethane (20 mL) at room temperature. Selenium dioxide (52 mg, 0.47 mmol) was added to the reaction mixture, which was then stirred at room temperature for 24 h. More selenium dioxide (52 mg, 0.47 mmol) was added the next day, and the reaction mixture was stirred for an additional 8 h. At -78 °C, dimethyl sulfide (7.3 mL, 100 mmol) was added to the reaction mixture, which was then allowed to stirred overnight at room temperature. Solvents were removed *in vacuo*. The residue was diluted with saturated sodium bicarbonate solution (70 mL) and extracted with ether (5 x 40 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 7:3 hexanes-ethyl acetate, then increasing solvent polarity to 1:1 hexanes-ethyl acetate with 1% methanol) to yield 1.9 g (44%) of allylic alcohol **41** and 0.9 g (19%) of the over-oxidized α,β-unsaturated aldehyde. Analytical data for allylic alcohol **41**: R_f 0.32 (55:45 hexanes-ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.39 (qt, J = 1.3, 7.1 Hz, 1H, C=C-*H*), 3.97 (d, J = 5.6 Hz, 2H, C=C-CH_2-OH), 3.92 (m, 4H, ketal), 2.14 (m, 2H, C=C-CH_2), 1.64-1.71 (m, 3H, C=C-CH_2, and -O*H*), 1.66 (s, 3H, C=C-CH_3), 1.31 (s,

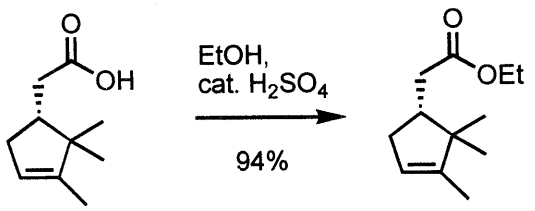
3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 125.5, 109.8, 68.6, 64.6, 38.6, 23.7, 22.2, 13.5. IR (film) 3417, 2982, 2938, 2877, 1450, 1377, 1347, 1252, 1220, 1137, 1080, 1056, 948, 863 cm^{-1}. HRMS (EI) Calcd for $C_{10}H_{18}O_3$ (M^+): 182.12560. Found: 186.12566.



41 70% **33**

Allylic bromide 33:

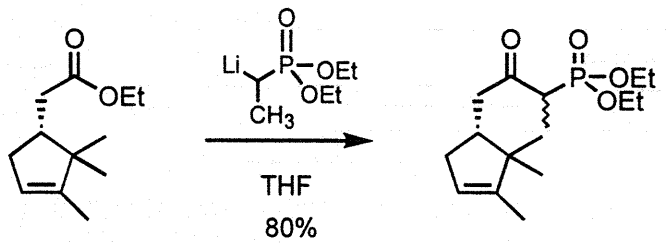
Allylic alcohol 41 (0.30 g, 1.6 mmol) was dissolved in acetonitrile, along with triphenylphosphine (0.85 g, 3.2 mmol) and 2,6-lutidine (0.24 mL, 2.1 mmol). The reaction mixture was cooled to 0 °C, followed by the addition of tetrabromomethane (1.1 g, 3.2 mmol). The reaction mixture was stirred at room temperature for 15 min before cold saturated sodium bicarbonate solution (15 mL) was added. Solvent was removed *in vacuo*, and the aqueous residue was extracted with hexanes (5 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was immediately purified by column chromatography (silica, 9:1 hexanes-ethyl acetate) to afford 0.28 g (70%) of allylic bromide **33**. R_f 0.63 (3:1 hexanes-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (t, J = 7.5 Hz, 1H, C=C-*H*), 3.96 (s, 2H, C=C-CH_2-Br), 3.90-3.96 (m, 4H, ketal), 2.12 (m, 2H, C=C-CH_2), 1.75 (s, 3H, C=C-CH_3), 1.68 (m, 2H, C=C-CH_2), 1.31 (s, 3H). IR (film) 2981, 2879, 1660, 1446, 1377, 1207, 1130, 1103, 1055, 947, 865 cm^{-1}.



36 **116**

Ester 116:

(*R*)-Campholenic acid **36** (14 g, 83 mmol) was dissolved in ethanol (250 mL), followed by the addition of 5 drops of concentrated sulfuric acid. The reaction mixture was heated to reflux temperature overnight. At 0 °C, saturated sodium bicarbonate solution (5 mL) was added to the reaction mixture. Ethanol was removed *in vacuo* and the residue was further diluted with more saturated sodium bicarbonate solution (75 mL). This was extracted with ether (4 x 50 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give 15 g (94%) of the desired ethyl ester **116**. R_f 0.54 (3:2 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +12.1° (*c* 1.46, acetone). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (dq, 1H, *J* = 1.7, 2.7 Hz, 1H, C=C-*H*), 4.12 (q, *J* = 7.2 Hz, 2H, O-CH_2), 2.38 (m, 1H, O=C-CH_2), 2.34 (m, 1H, O=C-CH_2), 2.24 (m, 1H, C=C-CH_2), 2.22 (m, 1H, C=C-CH_2), 1.89 (dddd, *J* = 2.4, 4.9, 8.8, 18.0 Hz, 1H, O=C-CH_2-C*H*), 1.59 (td, *J* = 1.7, 2.4 Hz, 3H, C=C-CH_3), 1.24 (t, *J* = 7.2 Hz, 3H, O-CH_2-CH_3), 0.97 (s, 3H, *gem*-CH_3), 0.76 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 147.9, 121.6, 60.1, 46.7, 16.4, 35.5, 35.4, 25.5, 19.8, 14.2, 12.5. IR (film) 3038, 2957, 2934, 2867, 2839, 1737, 1465, 1445, 1374, 1362, 1295, 1252, 1186, 1142, 1031, 798 cm^{-1}. EIMS Calcd for $C_{12}H_{20}O_2$ (M^+): 196.15. Found: *m/z* 196.15 (M^+), 181.15 $(M\text{-}CH_3)^+$, 151.10 $(M\text{-}OCH_2CH_3)^+$.

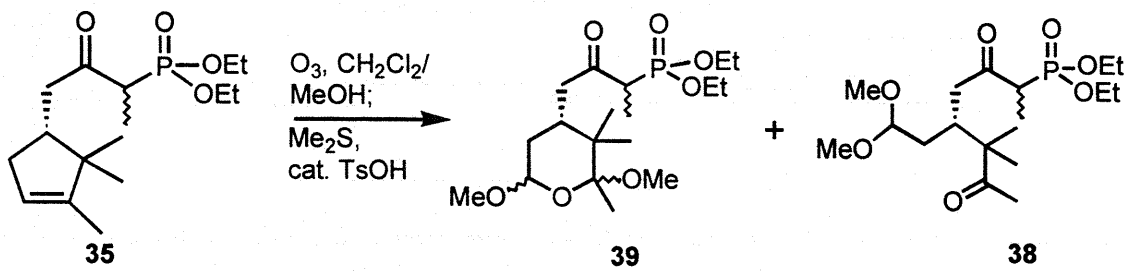


116 **35**

Ketophosphonate 35:

Diethyl ethanephosphonate (28.9 g, 174 mmol) in tetrahydrofuran (400 mL) was cooled to -78 °C. To this was added over 10 min *n*-butyllithium (73 mL, 2.30 M in hexanes). The mixture was stirred for 1 h with gradual warming to 0 °C. Ester **116** (15 g, 80 mmol) in tetrahydrofuran (40 mL) was transferred *via* a cannula to the reaction flask at -78 °C. The reaction mixture was stirred for 30 min. Saturated aqueous sodium bicarbonate solution (50 mL) was added and the reaction mixture was allowed to warm up to room temperature. Solvent was removed *in vacuo*; the residue was diluted with water (100 mL) and then extracted with ether (5 x 80 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give a yellow oil. The crude product was purified by fractional distillation at reduced pressure (161 °C, 0.5 mmHg) to afford 20 g (80%) as an inseparable diastereomeric mixture of ketophosphonate **35**. R_f 0.33 (6:4 hexanes-ethyl acetate). Analytical data for diastereomeric mixture (numbers in brackets represent two different resonances for the two diastereomers): ^{1}H NMR (250 MHz, $CDCl_3$) δ {5.19, 5.18} (s, 1H, C=C-C*H*), 4.03-4.16 (m, 4H, P-OCH_2), {3.28, 3.18} (dq, J_{HH} = 7.0, J_{HP} = 11.1 Hz, 1H, P-C*H*), {2.82, 2.60} (dd, J = 3.5, 16.8 Hz, 1H, CH_2-C=O), {2.76, 2.55} (dd, J = 16.8, 10.3 Hz, 1H, CH_2-C=O), 2.33-2.42 (m, 1H), 2.15-2.28 (m, 1H), 1.70-1.85 (m, 1H), {1.57, 1.56} (s, 3H, C=C-CH_3), {1.32, 1.30} (dd, J_{HH} = 7.0, J_{HP} = 18.0 Hz, 3H, P-CHCH_3), 1.30 (t, J = 7.0

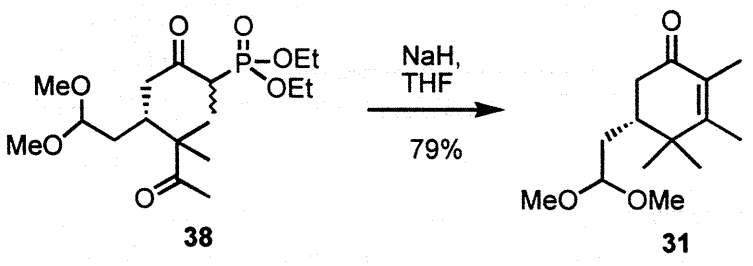
Hz, 6H, P-OCH_2CH_3), {0.952, 0.945} (s, 3H, *gem*-CH_3), {0.76, 0.75} (s, 3H, *gem*-CH_3). IR (film) 3036, 2981, 2955, 2909, 2867, 1715, 1651, 1457, 1374, 1305, 1253, 1053, 1026 cm^{-1}. EIMS Calcd for $C_{16}H_{29}O_4P$ (M^+): 316.18. Found: *m/z* 316.15 (M^+), 301.10 ($M-CH_3)^+$, 271.05 ($M-OCH_2CH_3)^+$.



Ozonolysis of ketophosphonate 35:

Ketophosphonate **35** (6.3 g, 20 mmol) was dissolved in methanol (100 mL) and dichloromethane (100 mL), and was cooled to -78 °C. Ozone (generator settings at 2.0 S.L.P.M., 90 V at 0.4 kg/cm^2) was bubbled through the solution at -78 °C for 15 min until the reaction mixture became slightly blue. Argon was then passed through the reaction mixture for 20 min until the blue hue had mostly disappeared. At -78 °C, anhydrous methyl sulfide (29 mL, 400 mmol) was added with caution, followed by the addition of a catalytic amount of *p*-toluenesulfonic acid (5 mg) to induce subsequent acetal formation. The reaction mixture was allowed to warm slowly to room temperature, and was stirred for a total of 40 h. Solvents were then removed *in vacuo*. The residue was diluted with water (50 mL) and saturated sodium bicarbonate solution (100 mL), and was extracted with ether (10 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give 27 g (96%) of a mixture of isomers of cyclic acetal **39** (higher R_f) and acyclic acetal **38** (lower R_f). This mixture could be used in the next reaction without further purification. Alternatively, it was purified by column chromatography (silica, 6:4 hexanes-ethyl acetate with 1% triethylamine and 1% methanol, then increasing solvent polarity to 45:55 hexanes-ethyl acetate with 1% triethylamine and 1% methanol); several fractions containing both **38** and **39** were combined and re-purified by column chromatography. Pure cyclic acetal **39**

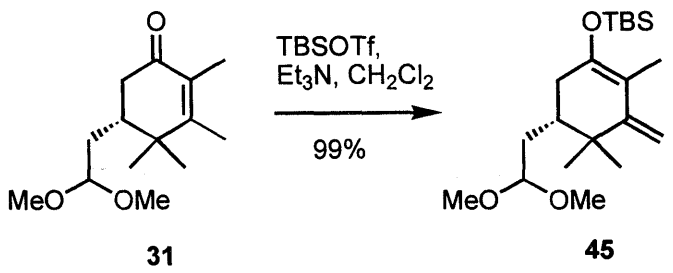
was then dissolved in methanol (50 mL), followed by the addition of a catalytic amount of *p*-toluenesulfonic acid (5 mg). The reaction mixture was stirred overnight at room temperature. Methanol was removed *in vacuo*. The residue was then diluted with cold saturated sodium bicarbonate solution (30 mL), and was extracted with ether (6 x 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give another equilibrium mixture of **38** and **39**. This was purified by column chromatography using conditions described above. After one recycle, a total of 5.5 g (71%) of acyclic acetal **38** was isolated. R_f 0.45 (15:85 hexanes-ethyl acetate). Analytical data for diastereomeric mixture **38** (numbers in brackets represent two different resonances for the two diastereomers): ^{1}H NMR (250 MHz, $CDCl_3$) δ {4.28, 4.27} (m, 1H, C*H*(OMe)$_2$), 4.07-4.16 (m, 4H, P-OC*H*$_2$), {3.30, 3.26} (s, 3H, OC*H*$_3$), {3.24, 3.18} (s, 3H, OC*H*$_3$), 3.10-3.30 (m, 1H, P-C*H*), 2.50-2.86 (m, 3H), 2.12 (s, 3H, C=C-C*H*$_3$), 1.46-1.54 (m, 1H), 1.39 (m, 9H, P-OCH$_2$C*H*$_3$ and P-CHC*H*$_3$), 1.35 (m, 1H), {1.04, 1.02} (s, 3H, *gem*-C*H*$_3$), {1.00, 0.97} (s, 3H, *gem*-C*H*$_3$).



38 31

Cyclohexenone 31:

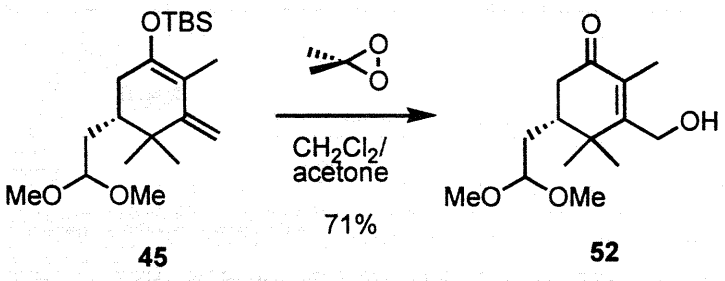
Sodium hydride (0.52 g, 20 mmol) was suspended in tetrahydrofuran (100 mL) and was cooled to 0 °C. Acyclic acetal **38** (6.2 g, 16 mmol) in tetrahydrofuran (50 mL) was transferred to the sodium hydride suspension. The reaction mixture was then warmed to room temperature and was stirred overnight. Saturated sodium bicarbonate solution (50 mL) was added to the reaction mixture. Solvent was removed *in vacuo*, and the aqueous residue was extracted with ether (6 x 40 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 7:3 hexanes-ethyl acetate, then increasing solvent polarity to 15:85 hexanes-ethyl acetate with 1% methanol) to afford 3.0 g (79%) of α,β-unsaturated ketone **31**. R_f 0.46 (7:3 hexanes-ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.39 (dd, J = 3.8, 7.7 Hz, 1H, C*H*(OMe)$_2$), 3.31 (s, 3H, OC*H*$_3$), 3.28 (s, 3H, OC*H*$_3$), 2.56 (dd, J = 4.2, 16.8 Hz, 1H, C*H*$_2$-C=O), 2.23 (dd, J = 11.9, 16.8 Hz, 1H, C*H*$_2$-C=O), 1.85 (ddd, J = 2.1, 7.6, 13.8 Hz, 1H, C*H*$_2$-CHC(OMe)$_2$), 1.91 (m, 1H, C*H*-CH$_2$C=O), 1.85 (s, 3H), 1.72 (s, 3H), 1.34 (ddd, J = 3.7, 10.5, 14.4 Hz, 1H, C*H*$_2$-CHC(OMe)$_2$), 1.14 (s, 3H, *gem*-C*H*$_3$), 0.99 (s, 3H, *gem*-C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 161.6, 130.2, 103.4, 53.5, 52.5, 39.5, 39.4, 39.2, 33.3, 25.4, 20.0, 16.7, 11.5. IR (film) 2967, 2830, 1665, 1613, 1465, 1375, 1329, 1241, 1193, 1129, 1057 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.33, H, 9.82.



31 **45**

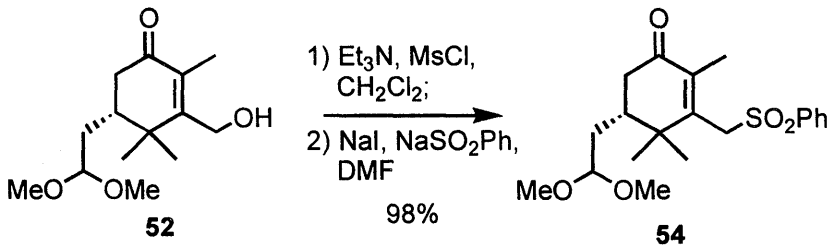
Silyl enol ether 45:

Cyclohexenone **31** (4.8 g, 20 mmol) was dissolved in dichloromethane (100 mL) and triethylamine (20 mL, 143 mmol) was added. At 0 °C, *tert*-butyldimethylsilyl trifluoromethanesulfonate (5 mL, 22 mmol) was added dropwise to the reaction mixture, which was then stirred for another 10 min. Ice-cooled saturated sodium bicarbonate solution (80 mL) was added to the reaction mixture at 0 °C. Solvent was removed *in vacuo* and the aqueous residue was extracted with ether (4 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 95:5 hexanes-ethyl acetate with 1% triethylamine) to 7.1 g (99%) of silyl enol ether **45.** R_f 0.91 (95:5 hexanes-ethyl acetate with 1% triethylamine). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.80 (s, 1H, C=C-CH_2), 4.77 (s, 1H, C=C-CH_2), 4.41 (dd, J = 4.6, 7.0 Hz, 1H, CH(OMe)$_2$), 3.31 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3), 1.74 (m, 1H), 1.74 (s, 3H, C=C-CH_3), 1.55-1.65 (m, 2H), 1.31 (dd, J = 4.4, 14.2 Hz, 1H), 1.25 (m, 1H), 1.07 (s, 3H, *gem*-CH_3), 1.02 (s, 3H, *gem*-CH_3), 0.97 (s, 9H, Si-C(CH_3)$_3$), 0.15 (s, 3H, Si-CH_3), 0.13 (s, 3H, Si-CH_3).



γ-Hydroxy-α,β-unsaturated ketone 52:

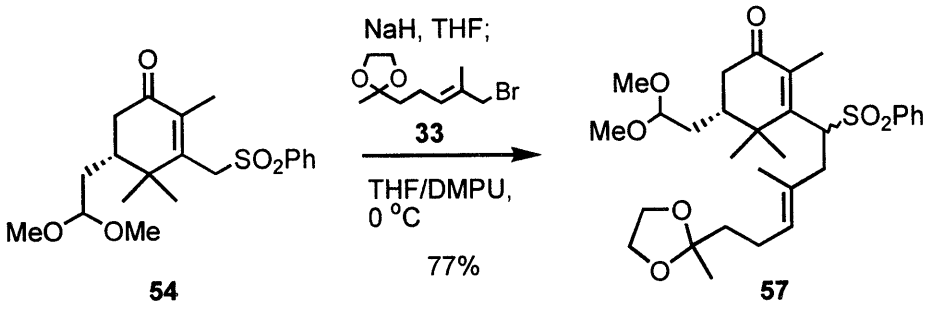
Enol ether **45** (0.411 g, 1.16 mmol) was dissolved in dichloromethane (10 mL) and was cooled to -78 °C. A freshly prepared solution of dimethyldioxirane in acetone (25 mL, ~ 0.03 M) was cooled to -78 °C and was transferred to the enol ether solution *via* a cannula. The cloudy solution was then allowed to warm to room temperature. Solvents were removed *in vacuo* and the residue was immediately dissolved in ice-cooled saturated sodium bicarbonate solution (40 mL). The aqueous mixture was extracted with ether (4 x 20 mL); combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 1:1 hexanes-ethyl acetate, then increasing polarity of solvents to 2:3 hexanes-ethyl acetate with 1% methanol) to yield 0.21 g (71%) of alcohol **52**. R_f 0.22 (11:9 hexanes-ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.41 (dd, J = 4.0, 7.5 Hz, 1H, C*H*(OMe)$_2$), 4.34 (m, 2H, C*H*$_2$OH), 3.33 (s, 3H, OC*H*$_3$), 3.30 (s, 3H, OC*H*$_3$), 2.61 (dd, J = 4.1, 16.7 Hz, 1H, C*H*$_2$-C=O), 2.29 (dd, J = 11.9, 16.7 Hz, 1H, C*H*$_2$-C=O), 2.05-1.87 (m, 2H), 1.88 (s, 3H, C*H*$_3$-C-C=O), 1.47 (t, J = 6.2 Hz, 1H, -O*H*), 1.36 (ddd, J = 4.0, 10.5, 14.4, Hz, 1H, C*H*$_2$-CHC(OMe)$_2$), 1.25 (s, 3H, *gem*-C*H*$_3$), 1.06 (s, 3H, *gem*-C*H*$_3$).



γ-Sulfonyl-α,β-unsaturated ketone 54:

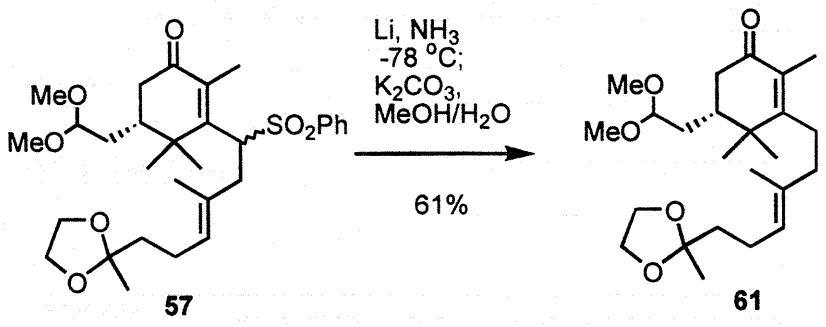
Alcohol **52** (1.7 g, 6.8 mmol) and triethylamine (1.4 mL, 10 mmol) were dissolved in dichloromethane (35 mL) and cooled to 0 °C. Methanesulfonyl chloride (0.63 mL, 8.1 mmol) was added to the reaction mixture. After 10 min of stirring at 0 °C, ice-cooled saturated sodium bicarbonate solution (30 mL) was added. Solvent was removed *in vacuo*, and the residue was extracted with ether (4 x 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give mesylate **53** as a colorless oil. R_f 0.66 (95:5 dichloromethane-ether). ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.87 (s, 2H, C*H*$_2$-OSO$_2$Me), 4.40 (dd, *J* = 3.7, 7.3 Hz, 1H, C*H*(OMe)$_2$), 3.32 (s, 3H, OC*H*$_3$), 3.29 (s, 3H, OC*H*$_3$), 3.06 (s, 3H, OSO$_2$-C*H*$_3$), 2.64 (dd, *J* = 4.0, 16.8 Hz, 1H, C*H*$_2$-C=O), 2.31 (dd, *J* = 11.3, 16.8 Hz, 1H, C*H*$_2$-C=O), 1.99 (m, 1H, C*H*-CH$_2$C=O), 1.88 (m, 1H, C*H*$_2$-CHC(OMe)$_2$), 1.83 (s, 3H, C*H*$_3$-C-C=O), 1.35 (ddd, *J* = 3.7, 10.2, 13.5 Hz, 1H, C*H*$_2$-CHC(OMe)$_2$), 1.23 (s, 3H, *gem*-C*H*$_3$), 1.06 (s, 3H, *gem*-C*H*$_3$). Mesylate **53** was then re-dissolved in *N*,*N*-dimethylformamide (40 mL) and was cooled to 0 °C. Sodium iodide (1.1 g, 7.5 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 30 min, the reaction mixture was cooled to 0 °C and sodium bezenesulfinate (1.2 g, 7.5 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 2 h before saturated sodium bicarbonate solution (50 mL) was added. The aqueous mixture was extracted with ether (5 x 50 mL) and the

combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 6:4 hexanes-ethyl acetate) to afford 2.56 g (98%) of sulfonyl enone **54.** R_f 0.51 (55:45 hexanes-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.1 Hz, 2H, C2'-*H* and C6'-*H*), 7.68 (t, J = 7.4 Hz, 1H, C4'-*H*), 7.59 (t, J = 7.5 Hz, 2H, C3'-*H* and C5'-*H*), 4.39 (dd, J = 4.0, 7.4 Hz, 1H, C*H*$(OMe)_2$), 4.17 (s, 2H, PhO_2S-CH_2), 3.31 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 2.71 (dd, J = 4.6, 17.5 Hz, 1H, CH_2-C=O), 2.38 (dd, J = 9.8, 17.6 Hz, 1H, CH_2-C=O), 2.01-2.06 (m, 1H), 1.91 (ddd, J = 2.5, 7.4, 14.0 Hz, 1H, CH_2-CHC$(OMe)_2$), 1.78 (s, 3H, CH_3-C-C=O), 1.39 (ddd, J = 4.0, 10.6, 14.2 Hz, 1H, CH_2-CHC$(OMe)_2$), 1.30 (s, 3H, *gem*-CH_3), 1.15 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 149.8, 141.0, 138.1, 133.9, 129.5, 127.6, 103.1, 58.9, 53.5, 52.4, 40.0, 39.3, 39.0, 33.0, 26.5, 22.0, 13.3. IR (film) 3061, 2939, 2831, 1669, 1649, 1447, 1370, 1319, 1509, 1150, 1127, 1084, 1057 cm^{-1}.



γ-Alkylation product 57:

Sulfone **54** (1.85 g, 4.86 mmol) was dissolved in tetrahydrofuran (40 mL). At 0 °C, sodium hydride (150 mg, 6.1 mmol) was added to the solution, and the reaction mixture was stirred at 0 °C for 1 h. *N,N'*-Dimethylpropyleneurea (4 mL) was then added to the reaction mixture, followed by the addition of bromide **33** (1.21 g, 4.86 mmol) in tetrahydrofuran (15 mL). The reaction mixture was stirred for 5 h at 0 °C. The reaction was then quenched at 0 °C with saturated sodium bicarbonate (40 mL). Solvent was then removed *in vacuo* before the aqueous layer was extracted with ether (4 x 30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography twice (silica, first column: 7:3 hexanes-ethyl acetate with 1% triethylamine, then increasing solvent polarity to 6:4 hexanes-ethyl acetate with 1% methanol; second column: 99:1 dichloromethane-ethyl ether with 1% triethylamine, then increasing solvent polarity to 99:1 dichloromethane-ethyl ether with 1% methanol) to yield 2.1 g (77%) of alkylation product **57** as an inseparable mixture of diastereomers. R_f 0.31 (9:1 dichloromethane-ethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.93 (m, 2H, C2'-*H* and C6'-*H*), 7.59-7.69 (m, 1H, C4'-*H*), 7.50-7.58 (m, 2H, C3'-*H* and C5'-*H*), 5.14 (m, 1H, C=C-*H*), 4.36 (m, 1H, C*H*$(OMe)_2$), 4.14 (m, 1H, PhO_2S-C*H*), 3.89 (m, 4H, ketal), 3.29 (m, 6H, OCH_3).

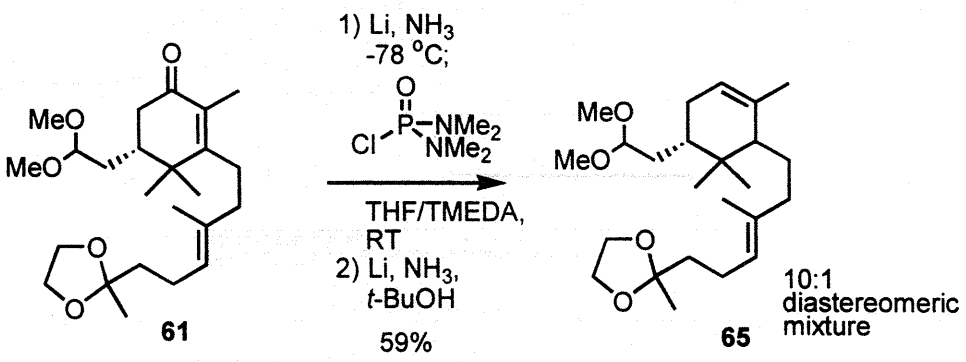


57 61

Enone 61:

Ammonia (~ 200 mL) was condensed at -78 °C in an oven-dried flask equipped with a glass-covered magnetic stir-bar, followed by the addition of small flattened pieces of lithium wire (0.53 g, 76 mmol), which dissolved into a blue solution after 15 min. Sulfone **57** (1.9 g, 3.4 mmol) in tetrahydrofuran (10 mL) was transferred to the reaction flask *via* a cannula. The reaction mixture was stirred at -78 °C for 10 min before quenching with solid ammonium chloride in small portions until blue color disappeared. After the ammonia has evaporated, water (50 mL) was added. The aqueous mixture was extracted with ether (4 x 40 mL) and the combined organic layers were concentrated to give a crude mixture of the conjugated and de-conjugated enones. This was re-dissolved in methanol (40 mL) and water (60 mL). Solid potassium carbonate (~ 3 g) was added, and the reaction mixture was stirred at 45 °C for 3 h. Saturated sodium bicarbonate solution (40 mL) was added and methanol was removed *in vacuo*. The residue was extracted with ether (4 x 30 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica, 8:2 hexanes-ethyl acetate, then increasing solvent polarity to 55:45 hexanes-ethyl acetate) to give 850 mg (61%) of α,β-unsaturated ketone **61**. R_f 0.27 (7:3 hexanes-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.18 (t, J = 7.2

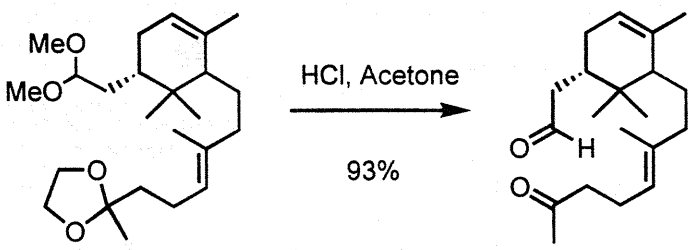
Hz, 1H, C=C*H*), 4.39 (dd J = 3.9, 7.5 Hz, 1H), C*H*$(OMe)_2$), 3.93 (m, 4H, ketal), 3.32 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 2.58 (dd, J = 4.3, 16.9 Hz, 1H, CH_2-C=O), 2.24 (dd, J = 11.4, 16.9 Hz, 1H, CH_2-C=O), 2.24 (m, 2H), 2.03-2.13 (m, 4H), 1.84,-1.98 (m, 2H), 1.77 (s, 3H, C=C-CH_3), 1.68 (m, 2H), 1.66 (s, 3H, C=C-CH_3), 1.33 (m, 1H), 1.32 (s, 3H, ketal-C-CH_3), 1.19 (s, 3H, *gem*-CH_3), 1.01 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 164.8, 134.7, 130.9, 124.6, 109.8, 103.3, 64.6 (2 carbons), 53.6, 52.5, 39.8, 39.2, 39.0, 38.3, 33.2, 30.2, 25.7, 23.8, 22.6, 20.6, 15.9, 11.5. IR (film) 2967, 2831, 1664, 1607, 1473, 1448, 1375, 1336, 1200, 1129, 1057, 962, 948 cm^{-1}



Alkene 65:

Ammonia (~ 45 mL) was condensed at -78 °C in an oven-dried flask equipped with a glass-covered magnetic stir-bar, followed by the addition of small flattened pieces of lithium wire (36 mg, 5.2 mmol), which dissolved into a blue solution after 15 min. Enone **61** (0.23 g, 0.56 mmol) in tetrahydrofuran (10 mL) was transferred to the reaction flask *via* a cannula. The reaction mixture was stirred for 1.5 h at -78 °C and was then quenched at -78 °C by adding *via* a syringe a few drops of isoprene, just enough to cause the blue color to disappear. After more tetrahydrofuran (3 mL) was added, the reaction mixture was allowed to warm to room temperature under argon, and ammonia was evaporated through an oil bubbler. After the reaction mixture had reached room temperature, residual ammonia was removed *in vacuo* by evacuating the reaction flask with the vacuum pump for 10 min. The vacuum was then replaced with argon, before *N*,*N*,*N*',*N*'-tetramethylethylenediamine (2 mL) and tetramethylphosphorodiamidic chloride (0.80 mL, 5.4 mmol) were added sequentially. The reaction mixture was stirred at room temperature overnight. Water (20 mL) was added, and solvent was removed *in vacuo*. The aqueous residue was extracted with ether (6 x 20 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the crude phosphoramidate product. R_f 0.43 (55:45 hexanes-ethyl acetate).

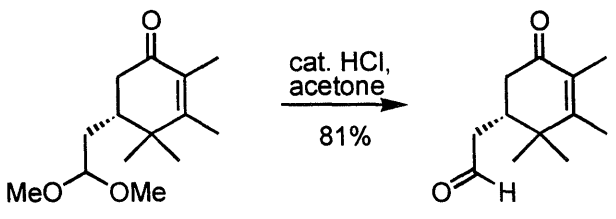
In another oven-dried flask equipped with in a glass-covered magnetic stir-bar, ammonia (~ 30 mL) was condensed at -78 °C, followed by the addition of small flattened pieces of lithium wire (45 mg, 6.5 mmol), which dissolved into a blue solution after 15 min. *tert*-Butyl alcohol (110 mg, 1.4 mmol) was added to the reaction mixture, followed by the addition of the crude phosphoramidate in tetrahydrofuran (10 mL). The reaction mixture was allowed to stir without external cooling for 1 h before being quenched by careful addition of solid ammonium chloride until the blue color disappeared. Water (20 mL) was added, and the solvent was removed. The aqueous residue was extracted with ether (4 x 20 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 8:2 hexanes-ethyl acetate) to afford 132 mg (59%) of alkene **65**. Analytical data for the major diastereomer: R_f 0.80 (55:45 hexanes-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (bs, 1H, C12=C13-*H*), 5.13 (m, 1H, C7=C8-*H*), 4.41 (dd, J = 3.8, 8.0 Hz, 1H, C*H*(OMe)$_2$), 3.92 (m, 4H, ketal), 3.31 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 1.98-2.20 (m, 2H), 1.81-1.97 (m, 4H), 1.59-1.69 (m, 4H), 1.69 (s, 3H), 1.61 (s, 3H), 1.31-1.50 (m, 2H), 1.31 (s, 3H), 1.20-1.31 (m, 2H), 0.92 (s, 3H, *gem*-CH_3), 0.68 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) 136.8, 136.0, 124.5, 121.2, 110.3, 104.0, 65.0, 53.6, 52.0, 50.4, 42.6, 40.0, 39.4, 36.3, 33.2, 29.3, 27.6, 26.7, 24.2, 23.0, 22.9, 16.4, 16.2. IR (film) 2960, 2830, 1446, 1376, 1250, 1194, 1126, 1058, 947, 912, 864 cm^{-1}.



65 **30**

Ketoaldehyde 30:

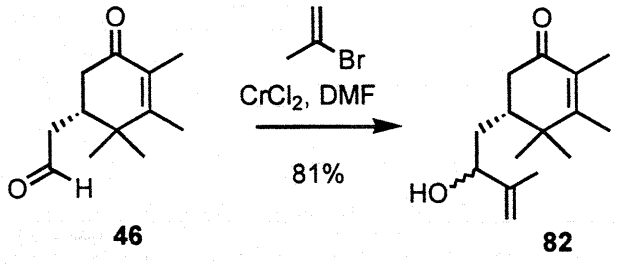
Alkene **65** (132 mg, 0.334 mmol) was dissolved in acetone (20 mL), followed by the addition of catalytic amount of concentrated hydrochloric acid (5 drops). The reaction was allowed to proceed at -20 °C for 24 h. At 0 °C, saturated sodium bicarbonate solution (20 mL) was added, and the solvent was removed *in vacuo*. The aqueous residue was extracted with ether (4 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 8:2 hexanes-ethyl acetate) to yield 95 mg (93%) of ketoaldehyde **30.** R_f 0.35 (8:2 hexanes-ethyl acetate). ^{1}H NMR (500 MHz, C_6D_6) δ 9.32 (dd, J = 1.2, 2.7 Hz, 1H, C*H*O), 5.18 (bs, 1H, C12=C13-*H*), 5.10 (t, J = 7.1 Hz, 1H, C7=C8-*H*), 2.21 (dt, J = 7.2, 7.2 Hz, 2H, O=C-CH_2), 2.11 (m, 1H), 2.06 (ddd, J = 1.2, 3.7, 15.9 Hz, 1H, CH_2-CHO), 1.97 (t, J = 7.3 Hz, 2H, O=C-C-CH_2), 1.88 (m, 1H), 1.82 (m, 1H), 1.74 (dddd, J = 3.9, 5.3, 9.3, 9.3 Hz, 1H, C1-*H*), 1.59-1.68 (m, 2H), 1.64 (s, 3H, C=C-CH_3), 1.60 (s, 3H, O=C-CH_3), 1.53 (s, 3H, C=C-CH_3), 1.51-1.45 (m, 2H), 1.25 (m, 1H), 0.68 (s, 3H, *gem*-CH_3), 0.52 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 189.5, 136.65, 136.63, 122.9, 120.3, 50.0, 45.6, 43.7, 42.1, 38.5, 35.7, 29.8, 29.6, 27.3, 26.8, 22.5, 22.4, 16.4, 16.0.



31 **46**

Aldehyde 46:

Acetal **31** (5.3 g, 22 mmol) was dissolved in acetone (400 mL), followed by the addition of six drops of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature overnight, and was then warmed to 50 °C for 4 h to drive the reaction to completion. At room temperature, saturated sodium bicarbonate solution (75 mL) was added, and acetone was removed *in vacuo*. The aqueous residue was extracted with ether (5 x 50 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 3:1 hexanes-ethyl acetate) to afford 3.9 g (92%) of aldehyde **46.** R_f 0.72 (7:3 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +33.9° (*c* 1.37, acetone). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H, C*H*O), 2.63 (d, *J* = 17.1 Hz, 1H), 2.42-2.49 (m, 2H), 2.28 (dd, *J* = 9.3, 17.1 Hz, 1H), 2.22 (dd, *J* = 11.7, 17.6 Hz, 1H), 1.84 (s, 3H, C=C-C*H*$_3$), 1.70 (s, 3H, C=C-C*H*$_3$), 1.13 (s, 3H, *gem*-C*H*$_3$), 0.99 (s, 3H, *gem*-C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 196.5, 160.6, 130.4, 45.1, 39.6, 38.9, 37.9, 25.6, 20.7, 16.5, 11.4. IR (film) 2971, 2725, 1723, 1662, 1612, 1467, 1419, 1374, 1330, 1096, 1076, 1054 cm^{-1}. EIMS Calcd for $C_{12}H_{18}O_2$ (M^+): 194.13. Found: 194.10 (M^+), 179.05 (M-CH_3)$^+$.

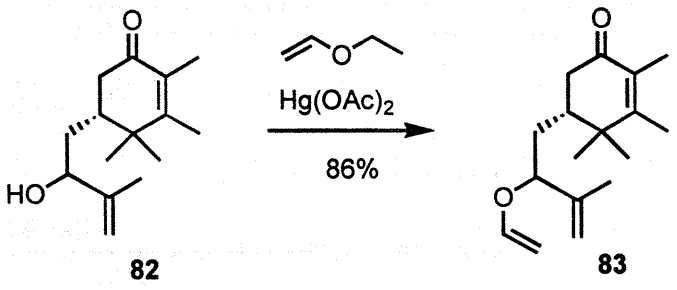


46 **82**

Allylic alcohol 82:

Anhydrous chromium(II) chloride (9.9 g, 80 mmol) was dissolved in ice-cooled *N,N*-dimethylformamide (150 mL). Aldehyde **46** (3.9 g, 20 mmol) and 2-bromopropene (3.6 mL, 40 mmol) were dissolved in *N,N*-dimethylformamide (10 mL), and this solution was transferred to the green chromium(II) chloride solution *via* a cannula. Two small crystals of nickel(II) chloride hexahydrate were added to the reaction mixture, which was then stirred at room temperature for 5 h. Saturated ammonium chloride solution (250 mL) was added to the reaction mixture, and the aqueous mixture was stirred at room temperature for 30 min. It was then extracted with ether (15 x 100 mL); combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 8:2 hexanes-ethyl acetate, then increasing solvent polarity to 1:1 hexanes-ethyl acetate) to give a total of 3.8 g (81%) of the diastereomers of allylic alcohol **82**. Analytical data for the mixture of diastereomers: IR (film) 3422(b), 3071, 2973, 1652, 1616, 1448, 1374, 1333, 1244, 1219, 1096, 1076, 1026, 967, 900 cm^{-1}. Analytical data for the higher R_f product: R_f 0.78 (7:3 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +44.4° (*c* 1.55, acetone). ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (m, 1H, HO-CH-C=CH_2), 4.80 (m, 1H, HO-CH-C=CH_2), 4.06 (m, 1H, HO-C*H*), 2.59 (dd, *J* = 3.9, 16.3 Hz, 1H, CH_2C=O), 2.23 (dd, *J* = 11.7, 16.3 Hz, 1H, CH_2C=O), 2.08 (dddd, *J* = 2.1, 3.9, 10.4, 11.7 Hz, 1H, C1-*H*), 1.86 (s, 3H, C=C-CH_3),

1.73 (s, 3H, C=C-CH_3), 1.71 (s, 3H, C=C-CH_3), 1.66-1.71 (m, 1H), 1.26 (ddd, J = 2.8, 10.4, 13.2 Hz, 1H, HO-CH-CH_2), 1.16 (s, 3H, *gem*-CH_3), 0.99 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 162.4, 148.2, 129.9, 109.9, 72.4, 39.3, 39.2, 38.5, 35.8, 25.2, 19.7, 17.9, 16.6, 11.3. Analytical data for the lower R_f product: R_f 0.56 (7:3 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +31.4° (*c* 1.30, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 1H, HO-CH-C=CH_2), 4.85 (m, 1H, HO-CH-C=CH_2), 4.16 (dd, J = 5.1, 8.8 Hz, 1H, HO-C*H*), 2.57 (dd, J = 4.3, 17.0 Hz, 1H, CH_2C=O), 2.26 (dd, J = 12.1, 17.0 Hz, 1H, CH_2C=O), 1.86 (s, 3H, C=C-CH_3), 1.81 (ddd, J = 2.1, 9.2, 13.4 Hz, 1H, HO-CH-CH_2), 1.73 (s, 3H, C=C-CH_3), 1.70 (d, J = 0.9 Hz, 3H, C=C-CH_3), 1.65-1.70 (m, 1H, C1-*H*), 1.40 (ddd, J = 5.5, 10.6, 13.4 Hz, 1H, HO-CH-CH_2), 1.13 (s, 3H, *gem*-CH_3), 1.02 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 161.9, 146.1, 130.1, 113.3, 75.2, 40.5, 39.4, 39.2, 34.7, 25.3, 19.8, 16.7. 16.0, 11.5. HRMS calculated for $C_{15}H_{24}O_2$ (M^+): 236.17762. Found: 236.17755.

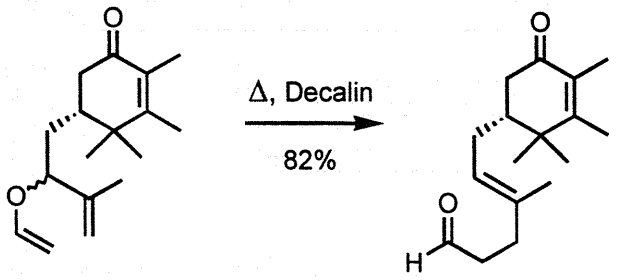


82 83

Vinyl ether 83

Procedures were identical for the reaction of either diastereomer of allylic alcohol **82.** Lower-R_f diastereomer of alcohol **82** (0.489 g, 2.07 mmol) was dissolved in freshly distilled ethyl vinyl ether (20 mL) and was heated to reflux temperature. Mercury(II) acetate (30 mg, 0.094 mmol) was added to the reaction mixture. The reaction mixture was stirred for four days at reflux temperature, and additional mercury(II) acetate (10 mg, 0.031 mmol) was added every 2 to 3 h, 4 to 5 times a day. After the reaction mixture has cooled to room temperature, glacial acetic acid (0.1 mL) was added to the reaction mixture and was stirred for another 3 h. Petroleum ether (20 mL) was then added to the reaction mixture, which was then washed with potassium hydroxide solution (5% aqueous, 2 x 20 mL). The organic layer was then dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 95:5 hexanes-ethyl acetate with 1% triethylamine) to give 0.469 g (86%) of isomerically pure vinyl ether **83.** Using the same procedure, the higher-R_f alcohol (0.333 mg, 1.41 mmol) afforded 0.286 g (77%) of the corresponding vinyl ether **83**. Analytical data for the product diastereomer obtained from the higher-R_f starting alcohol **82**: R_f 0.22 (95:5 hexanes-ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.21 (dd, J = 6.6, 14.1 Hz, 1H, O-C*H*=CH_2), 4.89 (m, 2H, O-CH-C=CH_2), 4.22 (dd, J = 1.6, 14.1 Hz, 1H, O-CH=CH_2), 4.08 (dd, J = 10.3, 3.04 Hz, 1H, O-C*H*-C=CH_2), 3.95 (dd, J =

1.6, 6.6 Hz, 1H, O-CH=CH_2), 2.55 (dd, J = 4.2, 16.6 Hz, 1H, CH_2C=O), 2.22 (dd, J = 11.7, 16.6 Hz, 1H, CH_2C=O), 2.01 (m, 1H, C1-*H*), 1.92 (ddd, J = 2.2, 10.3, 14.1 Hz, 1H, O-CH-CH_2), 1.86 (s, 3H, C=C-CH_3), 1.73 (s, 3H, C=C-CH_3), 1.65 (s, 3H, C=C-CH_3), 1.22 (ddd, J = 3.0, 7.3, 14.1 Hz, 1H, O-CH-CH_2), 1.16 (s, 3H, *gem*-CH_3), 0.99 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 161.9, 150.4, 144.5, 130.1, 112.7, 88.9, 80.5, 39.4, 39.3, 38.8, 34.9, 25.3, 19.9, 17.3, 16.7, 11.4. IR (film) 3115, 2973, 1664, 1636, 1617, 1465, 1458, 1437, 1375, 1328, 1237, 1193, 1166, 1075, 1053, 903 cm^{-1}. Analytical data for the product diastereomer obtained from the lower-R_f starting alcohol **82**: R_f 0.22 (95:5 hexanes-ethyl acetate). ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.25 (dd, J = 6.6, 14.1 Hz, 1H, O-C*H*=CH_2), 4.98 (s, 1H, O-CH-C=CH_2), 4.94 (s, 1H, O-CH-C=CH_2), 4.31 (dd, J = 1.4, 14.1 Hz, 1H, O-C*H*-C=CH_2), 4.16 (dd, J = 5.4, 9.2 Hz, 1H, O-CH=CH_2), 4.01 (dd, J = 1.4, 6.6 Hz, 1H, O-CH=CH_2), 2.56 (dd, J = 4.2, 16.9 Hz, 1H, CH_2C=O), 2.27 (dd, J = 11.9, 16.9 Hz, 1H, CH_2C=O), 1.87 (s, 3H, C=C-CH_3), 1.86 (ddd, J = 1.9, 9.3, 15.9 Hz, 1H, O-CH-CH_2), 1.74 (s, 3H, C=C-CH_3), 1.64-1.74 (m, 1H, C1-*H*), 1.64 (s, 3H, C=C-CH_3), 1.51 (ddd, J = 5.4, 10.7, 15.9 Hz, 1H, O-CH-CH_2), 1.13 (s, 3H, *gem*-CH_3), 1.02 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 161.7, 149.8, 142.9, 130.2, 115.3, 89.3, 82.8, 40.1, 39.4, 39.1, 33.1, 25.3, 19.8, 16.7, 15.8, 11.5. IR (film) 3115, 3073, 2973, 1666, 1636, 1617, 1465, 1448, 1375, 1319, 1192, 1177, 1074, 1049, 908 cm^{-1}.

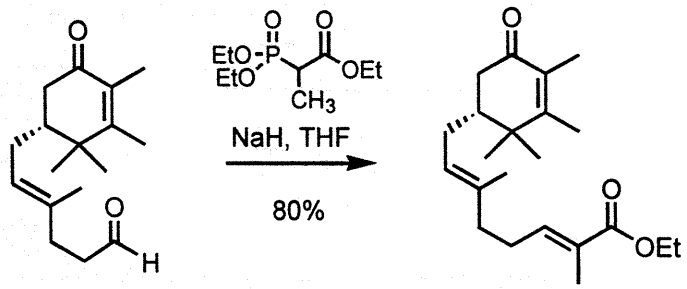


83 **84**

Aldehyde 84:

Anhydrous decahydronaphthalene (10 mL) was deoxygenated by passing argon through the solvent for 30 min. Diastereomeric mixture of vinyl ether **83** (1.7 g, 6.5 mmol) was placed in an oven-dried round-bottom flask fitted with an oven-dried reflux condenser, whose ground-glass joints were sealed with vacuum grease. The apparatus was then evacuated and filled with argon three times before decahydronaphthalene was added to dissolve **83**. The reaction mixture was heated under argon to 200 °C and stirred at that temperature for 2 h. After the reaction mixture was cooled to room temperature, the solution was directly purified by column chromatography (silica, hexanes and then 85:15 hexanes-ethyl acetate). Fractions containing mixture of *E* and *Z* isomers of aldehyde **84** were combined and separated by column chromatography. Along with 140 mg (8%) of the *Z* isomer, a total of 1.39 g (82%) of the pure *E* isomer of **84** was isolated. Analytical data for *E* isomer: R_f 0.52 (7:3 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +0.67° (*c* 0.89, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (t, *J* = 1.8 Hz, 1H, C*H*O), 5.05 (t, *J* = 7.2 Hz, 1H, C=C*H*), 2.47 (t, *J* = 7.5 Hz, 2H, CH_2-CHO), 2.40 (dd, *J* = 16.4, 4.1 Hz, 1H, CH_2C=O), 2.26 (dt, *J* = 7.5, 1.8 Hz, 2H, C5-*H*), 2.19 (m, 1H), 2.10 (dd, *J* = 16.4, 11.2 Hz, 1H, CH_2C=O), 1.83 (s, 3H, C=C-CH_3), 1.82 (m, 1H), 1.73 (m, 1H), 1.69 (s, 3H, C=C-CH_3), 1.54 (s, 3H, C=C-CH_3), 1.13 (s, 3H, *gem*-CH_3), 0.99 (s, 3H, *gem*-CH_3). ^{13}C NMR (75

MHz, $CDCl_3$) δ 202.1, 198.0, 161.5, 134.8, 130.1, 123.4, 44.2, 42.0, 39.4, 38.4, 31.6, 28.3, 25.5, 19.9, 16.5, 16.1, 11.3. IR (film) 2972, 2938, 2721, 1724, 1663, 1612, 1465, 1437, 1327, 1240, 1075 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.68; H, 10.01.

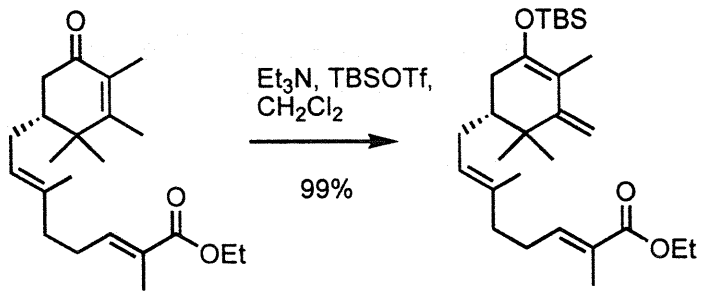


84 **86**

α,β-Unsaturated ester 86:

Sodium hydride (93 mg, 3.9 mmol) was suspended in tetrahydrofuran (25 mL) and was cooled to 0 °C. Triethyl 2-phosphonopropionate (0.83 mL, 3.9 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min until it turned clear. Aldehyde **84** (0.925 g, 3.53 mmol) in tetrahydrofuran (25 mL) was transferred to the reaction mixture *via* a cannula. The reaction mixture was stirred at 0 °C for 15 min before being warmed up to room temperature. After 3 h, the reaction mixture was kept at -20 °C overnight. Saturated sodium bicarbonate solution (40 mL) was added at 0 °C, and the solvent was removed *in vacuo*. Aqueous residue was extracted with ether (5 x 30 mL); combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product mixture was purified by column chromatography (silica, 9:1 hexanes-ethyl acetate) twice to afford 0.98 g (80%) of isomerically pure ester **86**, along with 0.16 g (13%) of the *Z* isomer. Analytical data for (*E*)-**86**: R_f 0.61 (9:1 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +39.7° (*c* 1.37, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (dq, *J* = 7.1, 1.2 Hz, 1H, C8=C7-*H*), 5.08 (t, *J* = 6.9 Hz, 1H, C4=C3-*H*), 4.16 (q, *J* = 7.1 Hz, 2H, OCH_2), 2.46 (dd, *J* = 16.9, 4.0 Hz, 1H, CH_2C=O), 2.26 (m, 2H, C6-*H*), 2.20 (m, 1H), 2.14 (dd, *J* = 11.2, 16.8 Hz, 1H, CH_2C=O), 2.08 (t, *J* = 7.2 Hz, 2H), 1.86 (s, 3H, C=C-CH_3), 1.81 (s, 3H, C=C-CH_3), 1.72-1.85 (m, 2H), 1.73 (s, 3H, C=C-CH_3), 1.57 (s, 3H,

C=C-CH_3), 1.26 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.17 (s, 3H, *gem*-CH_3), 1.02 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 168.0, 161.4, 141.4, 135.7, 130.1, 127.7, 123.2, 60.2, 44.3, 39.5, 38.5, 38.2, 28.4, 27.1, 25.6, 20.0, 16.5, 16.0, 14.1, 12.2, 11.3. IR (film) 2974, 1713, 1668, 1612, 1464, 1446, 1373, 1327, 1270, 1180, 1123, 1079, 1036 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.32; H, 10.10.

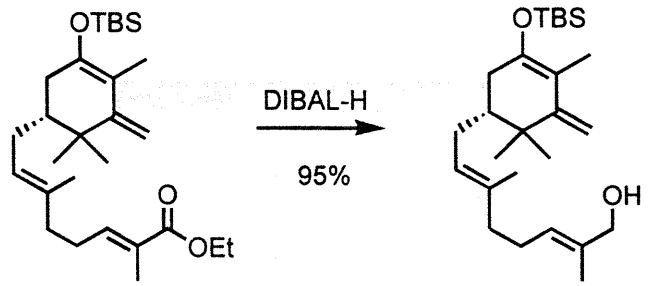


86 **87**

Silyl enol ether 87:

Enone **86** (2.5 g, 7.2 mmol) was dissolved in dichloromethane (70 mL) along with triethylamine (10 mL, 72 mmol). The mixture was cooled to 0°C, followed by the addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.3 mL, 14 mmol). The reaction mixture was stirred at 0 °C for 10 min before being quenched with ice-cooled saturated sodium bicarbonate solution (50 mL). Solvent was removed *in vacuo*, and the residue was extracted with ether (4 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 95:5 hexanes-ethyl acetate with 1% triethylamine) to yield 3.3 g (99%) of silyl dienol ether **87.** R_f 0.79 (9:1 hexanes-ethyl acetate with 1% triethylamine). $[\alpha]^{22}_D$ -32.0° (*c* 0.99, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (tq, *J* = 7.3, 1.3 Hz, 1H, C8=C7-*H*), 5.12 (t, *J* = 7.09 Hz, 1H, C4=C3-*H*), 4.79 (s, 1H, C10=C9-*H*), 4.76 (s, 1H, C10=C9-*H*), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2), 2.30 (dd, *J* = 5.4, 17.3 Hz, 1H, C14-*H*), 2.24 (m, 2H), 2.09 (t, *J* = 7.74 Hz, 2H), 2.06 (m, 1H), 1.92 (ddq, *J* = 17.5, 5.5, 1.6 Hz, 1H, C14-*H*), 1.82 (d, *J* = 1.14 Hz, 3H, C=C-CH_3), 1.74 (t, *J* = 1.6 Hz, 3H, C=C-CH_3), 1.74 (m, 1H), 1.57 (s, 3H, C=C-CH_3), 1.44, (ddt, *J* = 3.3, 10.8, 5.5 Hz, 1H, C1-*H*), 1.28 (t, *J* = 7.2 Hz, 3H, OCH$_2$CH_3), 1.10 (s, 3H, *gem*-CH_3), 1.03 (s, 3H, *gem*-CH_3), 0.95 (s, 9H, Si-C(CH_3)$_3$), 0.12 (s, 3H, Si-CH_3), 0.11 (s, 3H, Si-

CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 153.7, 146.5, 141.7, 135.0, 127.8, 124.7, 112.7, 103.3, 60.3, 44.1, 38.5, 37.5, 32.9, 27.9, 27.5, 25.8, 25.7, 24.4, 18.2, 16.1, 14.3, 12.3, 11.9, -3.6, -3.7. IR (film) 3100, 2930, 2858, 1713, 1645, 1601, 1472, 1468, 1379, 1381, 1259, 1226, 1178, 1116, 1081, 1039, 1006, 938, 926, 838, 779 cm^{-1}.

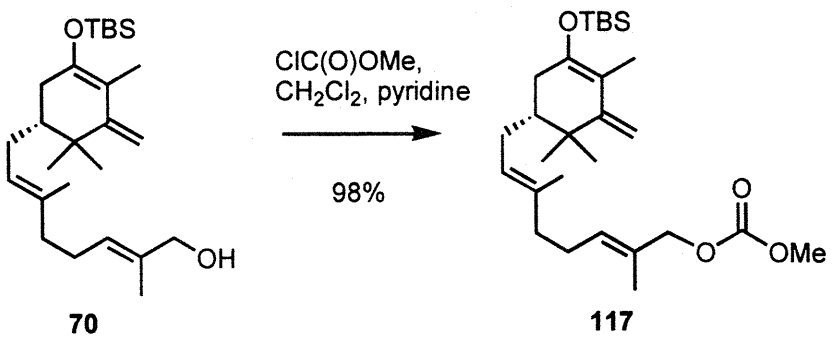


87 70

Alcohol 70:

Ester **87** (171 mg, 0.371 mmol) was dissolved in dichloromethane (15 mL) and was cooled to -78 °C. Diisobutylaluminum hydride in toluene (1.50 mL, 1.50 M) was added, and the reaction mixture was stirred at -78° C for 2.5 h. The reaction was quenched slowly with methanol at -78°C. Concentrated sodium potassium tartrate solution (10 mL) was added, and the reaction mixture was warmed to room temperature and stirred for 1 h. Saturated sodium bicarbonate solution (10 mL) was added and the organic solvents were removed *in vacuo*. The aqueous residue was extracted with ether (4 x 20 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 85:15 hexanes-ethyl acetate with 1% triethylamine) to yield 147 mg (95%) of alcohol **70.** R_f 0.57 (8:2 hexanes-ethyl acetate with 1% triethylamine). $[\alpha]^{22}_D$ -34.9° (*c* 1.15, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (tq, *J* = 1.2, 6.9 Hz, 1H, C8=C7-*H*), 5.10 (ddq, *J* = 8.6, 6.0, 1.2 Hz, 1H, C4=C3-*H*), 4.80 (s, 1H, C10=C9-*H*), 4.77 (s, 1H, C10=C9-*H*), 3.99 (d, *J* = 6.0 Hz, 2H, HO-CH_2), 2.30 (ddq, *J* = 5.5, 17.5, 1.7 Hz, 1H, C14-*H*), 1.99-2.17 (m, 5H), 1.93 (ddq, *J* = 5.7, 17.5, 1.6 Hz, 1H, C14-*H*), 1.74 (t, *J* = 1.6 Hz, 3H, C=C-CH_3), 1.74 (m, 1H), 1.66 (s, 3H, C=C-CH_3), 1.57 (s, 3H, C=C-CH_3), 1.44 (ddt, *J* = 3.5, 10.8, 5.6 Hz, 1H, C1-*H*), 1.10 (s, 3H, *gem*-CH_3), 1.03 (s, 3H, *gem*-CH_3),

0.95 (s, 9H, Si-C(CH_3)$_3$), 0.13 (s, 3H, Si-CH_3), 0.12 (s, 3H, Si-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 146.6, 135.7, 134.8, 126.1, 124.0, 112.7, 103.2, 69.0, 44.1, 39.5, 37.5, 32.9, 27.8 (3 carbons), 26.4, 25.8 (2 carbons), 24.3, 18.2, 16.1, 13.6, 11.9, -3.6, -3.7. IR (film) 3322(b), 3102, 2928, 1645, 1601, 1472, 1463, 1379, 1353, 1309, 1258, 1226, 1177, 1115, 1006, 938 cm^{-1}.

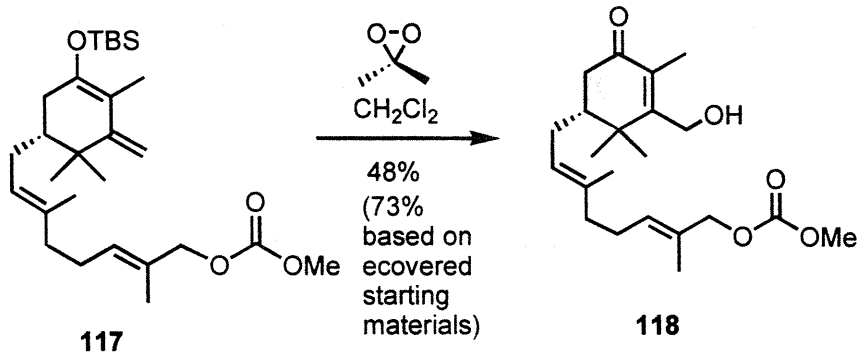


70 **117**

Carbonate 117:

Allylic alcohol **70** (2.54 g, 6.21 mmol) was dissolved in dichloromethane (40 mL) along with pyridine (0.65 mL, 8.1 mmol). The mixture was cooled to 0 °C before methyl chloroformate (0.58 mL, 7.5 mmol) was added. The reaction mixture was stirred at room temperature for 6 h before cold saturated sodium bicarbonate solution (40 mL) was added. Solvent was removed *in vacuo*, and the aqueous residue was extracted with ether (4 x 40 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 95:5 hexanes-ethyl acetate with 1% triethylamine) to give 2.9 g (98%) of the carbonate **117**. R_f 0.35 (95:5 hexanes-ethyl acetate with 1% triethylamine). $[\alpha]^{22}_D$ -29.9° (*c* 1.39, acetone). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 (t, *J* = 6.8 Hz, 1H, C8=C7-*H*), 5.09 (t, *J* = 7.1 Hz, 1H, C4=C3-*H*), 4.79 (s, 1H, C10=C9-*H*), 4.76 (s, 1H, C10=C9-*H*), 4.50 (s, 2H, OCH_2), 3.77 (s, 3H, OCH_3), 2.30 (dd, *J* = 3.5, 17.5 Hz, 1H, C14-*H*), 2.04-2.17 (m, 3H), 2.01 (t, *J* = 7.3 Hz, 2H, C14-*H*), 1.92 (dd, *J* = 5.5, 17.5, 1H), 1.74 (s, 3H, C=C-CH_3), 1.69-1.74 (m, 1H), 1.67 (s, 3H, C=C-CH_3), 1.56 (s, 3H, C=C-CH_3), 1.44 (dddd, *J* = 3.5, 5.5, 5.5, 10.8 Hz, 1H, C1-*H*), 1.10 (s, 3H, *gem*-CH_3), 1.03 (s, 3H, *gem*-CH_3), 0.95 (s, 9H, SiC-(CH_3)$_3$), 0.13 (s, 3H, Si-CH_3), 0.11 (s, 3H, Si-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 153.8, 146.6, 135.5, 130.3, 129.5, 124.3, 112.7, 103.2,

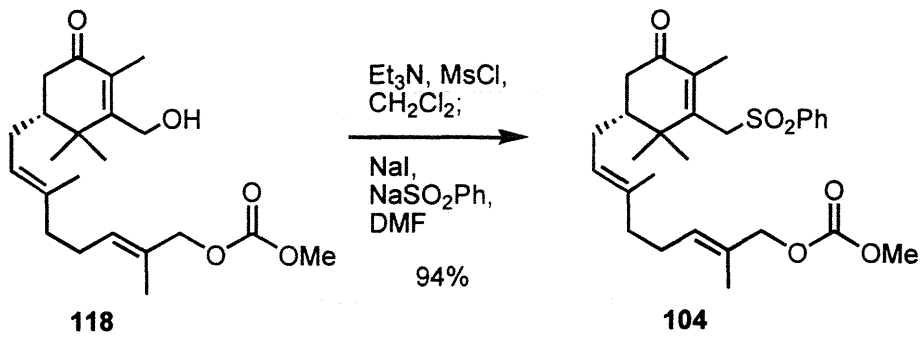
73.8, 54.6, 44.1, 39.2, 37.5, 32.9, 27.9 (3 carbons), 26.6, 25.8 (2 carbons), 24.4, 18.2, 16.1, 13.8, 11.9, -3.6, -3.7. IR (film) 3101, 2956, 2929, 2858, 1752, 1643, 1601, 1442, 1376, 1353, 1271, 1177, 1115, 1006, 945, 838 cm^{-1}. HRMS (FAB, 3-NBA) Calcd for $C_{28}H_{48}O_4Si$ $(M+H)^+$: 477.34002. Found: 477.33941.



γ-Hydoxy-α,β-unsaturated ketone 118:

Silyl dienol ether **117** (2.9 g, 6.1 mmol) was dissolved in dichloromethane (80 mL) and was cooled to -78 °C . A freshly prepared solution of dimethyldioxirane in acetone (150 mL, ~ 0.02 M) cooled to -78 °C was transferred slowly *via* a cannula to the reaction mixture, which was then warmed to room temperature. Saturated sodium bicarbonate solution (70 mL) was added and solvents were removed *in vacuo*. The aqueous residue was extracted with ether (6 x 50 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 7:3 hexanes-ethyl acetate) to give 1.0 g (34%) of starting silyl dienol ether **118**, and 1.1 g (48%) of γ-hydoxy-α,β-unsaturated ketone **118**. R_f 0.59 (7:3 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +37.0° (*c* 1.77, acetone). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (t, *J* = 6.84 Hz, 1H, C8=C7-*H*), 5.05 (m, 1H, C4=C3-*H*), 4.50 (s, 2H, OCH_2), 4.35 (d, *J* = 11.7 Hz, 1H, PhO_2S-CH_2), 4.32 (d, *J* = 11.7 Hz, 1H, PhO_2S-CH_2), 3.76 (s, 3H, OCH_3), 2.49 (dd, *J* = 3.7, 16.9 Hz, 1H, CH_2C=O), 2.24 (m, 1H), 2.18 (dd, *J* = 11.7, 16.9 Hz, 1H, CH_2C=O), 2.12 (t, *J* = 7.57, 2H), 2.02 (m, 2H), 1.87 (s, 3H, CH_3-C-C=O), 1.81 (dd, *J* = 8.3, 13.2 Hz, 1H), 1.77 (m, 1H), 1.66 (s, 3H, C=C-CH_3), 1.60 (bs, 1H, O*H*), 1.57 (s, 3H, C=C-CH_3), 1.27 (s, 3H, *gem*-CH_3), 1.08 (s, 3H, *gem*-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 159.9, 155.6, 136.4, 133.2, 130.0, 129.5, 122.6, 73.8, 59.7, 54.7, 44.7, 39.1, 38.7, 28.4, 26.3, 25.6, 20.4, 16.3, 14.3, 14.0, 11.5. IR (film) 3452(b), 2958, 1749, 1669, 1443, 1375, 1327, 1271, 998, 943 cm^{-1}. Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.43; H, 9.33.

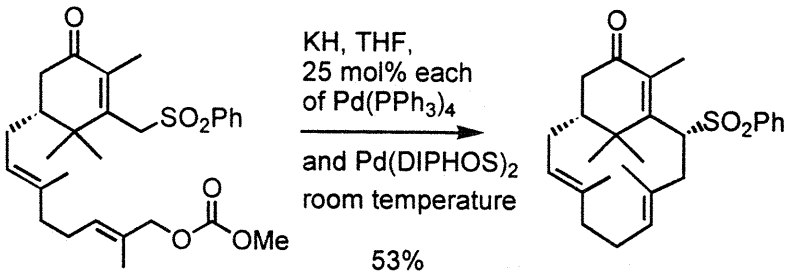


118 **104**

Sulfone 104:

γ-Hydoxy-α,β-unsaturated ketone **118** (1.1 g, 2.9 mmol) was dissolved in dichloromethane (40 mL) and was cooled to 0 °C. To this solution was added triethylamine (0.61 mL, 4.4 mmol) and then methanesulfonyl chloride (0.27 mL, 3.5 mmol). The reaction mixture was stirred for 10 min at 0 °C, followed by the addition of ice-cooled saturated sodium bicarbonate solution (25 mL). Solvents were removed *in vacuo* and the aqueous residue was extracted with ether (4 x 30 mL). The ombined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give the crude mesylate as a colorless oil. This oil was re-dissolved in *N,N*-dimethylformamide (50 mL) and was cooled to 0 °C. Solid sodium iodide (520 mg, 3.5 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 45 min, the reaction mixture was again cooled to 0 °C and sodium benzenesulfinate (530 mg, 3.2 mmol) was added. The reaction mixture was stirred at 0 °C overnight. Saturated sodium bicarbonate (75 mL) was added and the aqueous mixture was extracted with ether (5 x 50 mL). Combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give a colorless oil. This is purified by column chromatography (silica, 7:3 hexanes-ethyl acetate) to yield 1.4 g (94%) of sulfone **104.** R_f 0.31 (7:3 hexanes-ethyl acetate). $[\alpha]^{22}_D$ -13.2° (*c* 1.46, acetone). ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.3 Hz, 2H, C2'-*H* and C6'-*H*), 7.67 (t, *J* = 7.3 Hz, 1H, C4'-*H*), 7.58 (t, *J* = 7.3 Hz, 2H, C3'-*H* and C5'-*H*), 5.45 (t, *J* = 6.6 Hz, 1H, C8=C7-*H*), 5.04 (t, *J* = 6.4 Hz, 1H, C4=C3-*H*), 4.50 (s, 2H, OCH_2), 4.18 (d, *J* = 14.2 Hz, 1H, PhO_2S-CH_2), 4.16 (d, *J* = 14.2 Hz, 1H, PhO_2S-CH_2), 3.76 (s, 3H, OCH_3), 2.60 (dd, *J* = 3.9, 17.6 Hz, 1H, CH_2C=O), 2.28 (dd, *J* = 9.3, 17.6 Hz, 1H, CH_2C=O), 2.25 (m, 1H), 2.12 (dt, *J* = 7.6, 7.6 Hz, 2H), 2.01 (t, *J* = 7.6, 2H), 1.84-1.87 (m, 2H), 1.76 (s, 3H, CH_3-C-C=O), 1.66 (d, *J* = 1.0 Hz, 3H, C=C-CH_3), 1.55 (d, *J* = 1.0 Hz, 3H, C=C-CH_3), 1.31 (s, 3H, *gem*-CH_3), 1.18 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 156.2, 150.2, 141.8, 138.7, 137.1, 134.4, 130.5, 130.2, 130.0, 128.2, 123.0, 74.2, 59.5, 55.1, 45.4, 39.8, 39.5, 39.2, 28.9, 27.5, 26.7, 22.8, 16.6, 14.3, 13.9. IR (film) 3064, 2956, 1749, 1670, 1604, 1585, 1446, 1370, 1321, 1309, 1271, 1151, 1084, 941 cm^{-1}. HRMS (EI) Calcd for $C_{28}H_{38}O_6S$ (M^+): 502.23891. Found: 502.23900.

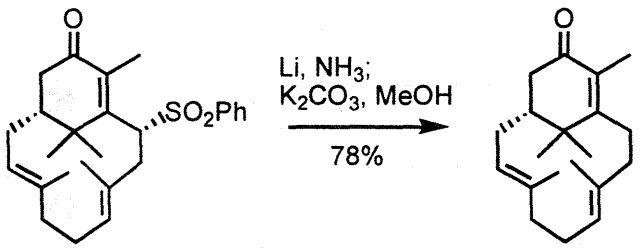


104 **72**

Macrocyclic sulfone 72:

Bis[1,2-bis(diphenylphosphino)ethane]palladium(0) (0.247 g, 0.274 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.316 g, 0.274 mmol) were dissolved in tetrahydrofuran (90 mL), and the yellow solution was stirred at room temperature in the dark for 45 min. Carbonate **104** (0.550 g, 1.09 mmol) was dissolved in tetrahydrofuran (70 mL) in an oven-dried flask. At 0 °C, potassium hydride (44 mg, 1.1 mmol) was added. The reaction mixture was then warmed to room temperature. After 45 min, when most of the gas evolution had ceased, the solution of catalysts was transferred to the reaction mixture *via* a cannula. The reaction mixture was stirred at room temperature for another 4 h before saturated sodium bicarbonate solution (50 mL) was added. Solvent was removed *in vacuo*, and the aqueous residue was extracted with dichloromethane (4 x 30 mL). Combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give a red oil. The crude product was purified by column chromatography (silica, 65:35 hexane-ethyl acetate). Fractions containing co-eluting elimination product was purified again once more by column chromatography using a different solvent system (silica, 95:5 dichloromethane-ether) A total of 250 mg (53%) of the desired cyclized sulfonyl enone **72** was isolated as a white solid. m.p. 152-153 °C. R_f 0.70 (55:45 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +99.1° (*c* 1.27, acetone). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.93 (d, *J* = 7.3 Hz, 2H, C2'-*H* and C6'-*H*), 7.68 (t, *J* = 7.3 Hz, 1H, C4'-*H*), 7.60 (t, *J* = 7.8 Hz, 2H, C3'-*H* and C5'-*H*), 4.91 (dd, *J* = 1.9, 11.7 Hz, 1H, C8=C7-*H*), 4.72 (d, *J* = 11.2 Hz, 1H, C4=C3-*H*), 4.09 (dd, *J* = 3.9, 12.7 Hz, 1H, PhO_2S-C*H*), 3.24 (t, *J* = 13.2 Hz, 1H, C9-*H*), 3.07 (dd, *J* = 7.3, 16.6 Hz, 1H, CH_2C=O), 2.62 (ddd, *J* = 5.4, 12.0, 15.4 Hz, 1H, C2-*H*), 2.46 (dd, *J* = 1.2, 16.4 Hz, 1H, CH_2C=O), 2.37 (ddd, *J* = 1.9, 3.8, 13.3 Hz, 1H, C9-*H*), 2.20 (s, 3H, CH_3-C-C=O), 2.11-2.16 (m, 2H, C1-*H* and C6-*H*), 2.04 (bd, *J* = 11.2 Hz, 1H, C5-*H*), 1.87-1.93 (m, 2H, C2-*H* and C6-*H*), 1.81 (ddd, *J* = 3.2, 12.8, 12.8 Hz, 1H, C5-*H*), 1.44 (s, 3H, C8-CH_3), 1.40 (s, 3H, *gem*-CH_3), 1.31 (s, 3H, C4-CH_3), 0.90 (s, 3H, *gem*-CH_3). COSY (500 MHz, $CDCl_3$) experiment was performed to determine coupling partners. ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 149.8, 141.3, 138.5, 133.6, 132.5, 132.0, 129.4, 128.0, 127.7, 122.9, 67.0, 45.4, 41.8, 39.7, 39.4, 39.0, 33.4, 31.1, 25.6, 25.1, 16.5, 15.8, 15.5. IR (film) 3063, 2966, 2915, 2854, 1670, 1606, 1584, 1446, 1306, 1147, 1083, 915 cm^{-1}. HRMS (EI) Calcd for $C_{26}H_{34}O_3S$ (M^+): 426.22287. Found: 426.22294.

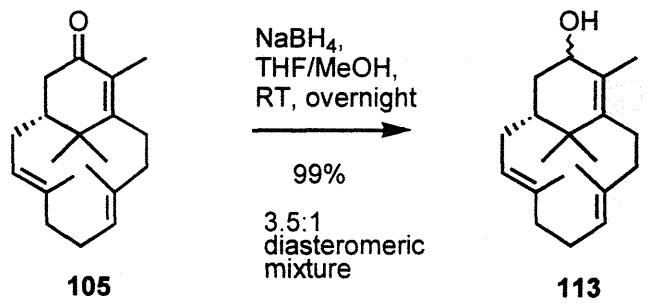


72 **105**

Enone 105:

Ammonia (~ 40 mL) was condensed at -78 °C in an oven-dried flask equipped with a glass-covered magnetic stir-bar, followed by the addition of small flattened pieces of lithium wire (55 mg, 7.9 mmol), which slowly dissolved into a blue solution after 15 min. Sulfonyl enone **72** (23 mg, 0.054 mmol) in tetrahydrofuran (2 mL) was transferred to the reaction flask *via* a cannula. The reaction mixture was stirred at -78 °C for 10 min before quenching with solid ammonium chloride in small portions until blue color disappeared. After the ammonia had evaporated, saturated ammonium chloride solution (3 mL) and water (3 mL) were added. The aqueous mixture was extracted with ether (4 x 15 mL) and the combined organic layers were concentrated to give a crude mixture of the conjugated and de-conjugated enones. This was re-dissolved in methanol (10 mL) and water (5 mL). Solid potassium carbonate (~ 1 g) was added, and the reaction mixture was stirred at room temperature for 2 h. Saturated ammonium chloride solution (5 mL) was added and methanol was removed *in vacuo*. Residue was extracted with ether (4 x 15 mL); combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography (silica, 9:1 hexanes-ethyl acetate) to give 12 mg (78%) of α,β-unsaturated ketone **105** as a white solid. m.p. 151-153 °C. R_f 0.59 (7:3 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +98.9° (*c* 1.5, acetone). ^{1}H

NMR (500 MHz, $CDCl_3$) δ 4.79 (d, *J* = 11.7 Hz, 1H, C4=C3-*H*), 4.69 (dd, *J* = 11.7, 3.4 Hz, 1H, C8=C7-*H*), 2.95 (dd, *J* = 17.1, 7.8 Hz, 1H, CH_2C=O), 2.66 (dt, *J* = 4.9, 13.2 Hz, 1H, C9-*H*), 2.65 (m, 1H, C2-*H*), 2.49 (dt, *J* = 4.6, 13.8 Hz, 1H, C10-*H*), 2.42 (dd, *J* = 1.5, 17.1 Hz, 1H, CH_2C=O), 2.34 (dt, *J* = 14.4, 4.3 Hz, 1H, C10-*H*), 2.18 (ddt, *J* = 2.9, 13.7, 11.7 Hz, 1H, C6-*H*), 2.00-2.09 (m, 3H, C1-*H*, C5-*H* and C9-*H*), 1.87-1.92 (m, 2H, C2-*H* and C6-*H*), 1.85 (s, 3H, CH_3-C-C=O), 1.79 (dt, *J* = 3.2, 12.8 Hz, 1H, C5-*H*), 1.54 (s, 3H, C8-CH_3), 1.48 (s, 3H, C4-CH_3), 1.15 (s, 3H, *gem*-CH_3), 1.01 (s, 3H, *gem*-CH_3). COSY (500 MHz, $CDCl_3$) experiment was performed to determine coupling partners. NOESY (500 MHz, $CDCl_3$) experiment was performed to determine double-bond geometry. ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 163.4, 132.12, 132.07, 131.6, 128.7, 123.1, 44.5, 41.7, 39.7, 38.9, 36.4, 33.9, 30.6, 28.3, 25.6, 24.5, 16.5, 15.5, 13.6. IR (film) 3060, 2950, 2907, 2849, 1664, 1604, 1477, 1448, 1375, 1357, 1299, 1041, 1030, 914 cm^{-1}. HRMS (EI) Calcd for $C_{20}H_{30}O$ (M^+): 286.22967. Found: 286.22952.

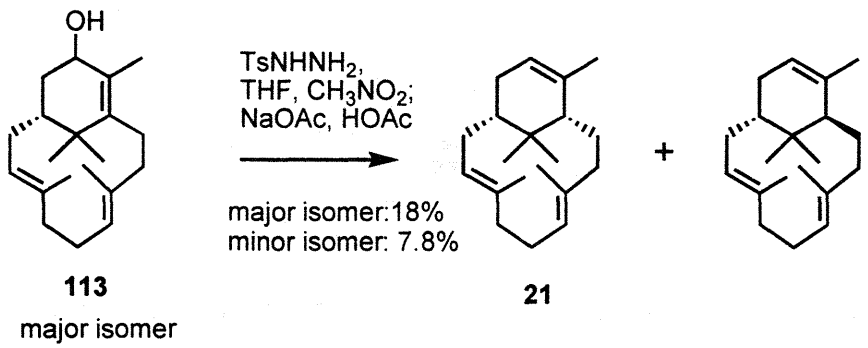


105 **113**

Alcohol 113:

Enone **105** (23 mg, 0.12 mmol) was dissolved in tetrahydrofuran (20 mL) and methanol (1 mL), followed by the addition of sodium borohydride (50 mg, 1.3 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated sodium bicarbonate solution (20 mL). Solvents were removed and the aqueous residue was extracted with ether (3 x 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, 9:1 hexanes-ethylacetate) to give 18 mg (78%) of the major diastereomer of alcohol **113** and 5 mg (21%) of the minor diastereomer, both as white solids. Analytical data for the minor diastereomer: m.p. 126-7 °C. R_f 0.39 (8:2 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +78° (*c* 0.51, tetrahydrofuran). ^{1}H NMR (500 MHz, C_6D_6) δ 4.99 (d, *J* = 11.2 Hz, 1H, C=C*H*), 4.77 (d, *J* = 11.2 Hz, 1H, C=C*H*), 4.11 (t, *J* = 8.6 Hz, 1H, HO-C*H*), 2.63 (dt, *J* = 5.1, 13.1 Hz, 1H), 2.55 (dddd, *J* = 1.7, 6.4, 12.2, 15.4 Hz, 1H), 2.12-2.21 (m, 2H), 2.06 (dd, *J* = 13.7, 4.2 Hz, 1H), 2.01 (m, 1H), 1.99 (dt, *J* = 1.5, 5.8 Hz, 1H), 1.79-1.92 (m, 5H), 1.83 (s, 3H, C=C-CH_3), 1.55 (tt, *J* = 2.7, 5.9 Hz, 1H), 1.49 (t, *J* = 1.5 Hz, 3H, C=C-CH_3), 1.46 (t, *J* = 1.5 Hz, 3H, C=C-CH_3), 0.99 (s, 3H, *gem*-CH_3), 0.78 (s, 3H, *gem*-CH_3). IR (film) 3302(b), 2966, 2908, 2849, 1450 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H,

11.18. Found: C, 82.45; H, 11.19. Analytical data for the major diastereomer: m.p. 120-123 °C. R_f 0.54 (8:2 hexanes-ethyl acetate). $[\alpha]^{22}_D$ +12° (*c* 1.8, tetrahydrofuran). ^{1}H NMR (500 MHz, C_6D_6) δ 5.94 (ddd, *J* = 1.2, 8.6, 6.8 Hz, 1H, C=C*H*), 4.95 (d, *J* = 11.2 Hz, 1H, C=C*H*), 3.66 (t, *J* = 5.6 Hz, 1H, HO-C*H*), 2.53 (dt, *J* = 4.9, 13.2 Hz, 1H), 2.47 (dd, *J* = 7.8, 15.6 Hz, 1H), 2.28 (ddt, *J* = 1.0, 15.1, 6.8 Hz, 1H), 2.19 (dt, *J* = 12.2, 11.2 Hz, 1H), 2.13 (dt, *J* = 4.4, 13.9 Hz, 1H), 2.00-2.08 (m, 3H), 1.86-1.93 (m, 3H), 1.78 (s, 3H, C=C-CH_3), 1.62 (d, *J* = 14.7 Hz, 1H), 1.59 (bs, 1H, O*H*), 1.52 (tt, *J* = 2.0, 6.8 Hz, 1H), 1.50 (s, 6H, C=C-CH_3), 0.87 (s, 3H, *gem*-CH_3), 0.86 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, C_6D_6) δ 140.3, 132.6, 132.0, 130.3, 129.6, 127.3, 69.7, 42.4, 39.1, 38.6, 38.2, 36.5, 34.0, 32.7, 27.0, 26.7, 25.2, 20.7, 17.2, 17.0. IR (film) 3454, 2968, 2910, 2853, 1649, 1473, 1445, 1383, 1358, 1114, 1009, 974, 961 cm^{-1}. HRMS (EI) Calcd for $C_{20}H_{32}O$ (M^+): 288.24532. Found: 288.24529.



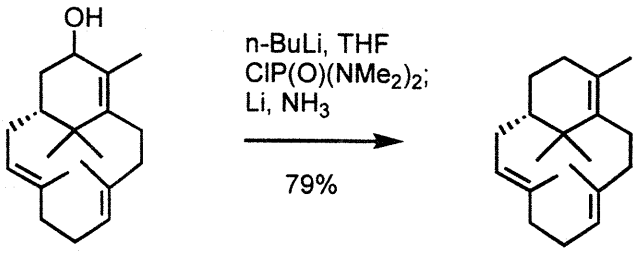
113
major isomer

21

Isoverticillene (21):

Alcohol **113** (major isomer from the previous step, 18 mg, 0.062 mmol) was dissolved in tetrahydrofuran (1 mL) and nitromethane (1 mL). At 0 °C, excess *p*-toluenesulfonhydrazide (200 mg, 1.3 mmol) was added to the reaction mixture, which was then stirred for 4 h at room temperature. When all of the starting material had been consumed and a more polar spot was observed on the TLC plate (R_f 0.34, 8:2 hexanes-ethyl acetate), the reaction mixture was partitioned between cold saturated sodium bicarbonate (20 mL) and ether (20 mL). Combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was quickly purified by column chromatography (silica, 9:1 hexanes-ethyl acetate) to remove any elimination diene product **111**, as well as excess unreacted *p*-toluenesulfonhydrazide. The isolated product was an approximately 2:1 mixture of the α- and β-substituted tosylhydrazines **114** based on ^{1}H NMR integration. (A similar diastereomeric ratio was observed when the minor isomer of starting alcohol **113** was used.) The mixture of tosylhydrazines **114** was re-dissolved in tetrahydrofuran (5 mL) followed by the addition of a solution of sodium acetate (0.5 g) in glacial acetic acid (10 mL). The reaction mixture was then heated to 40 °C over 5 h. Some gas evolution was observed. A sodium hydroxide solution (3M, 20 mL) was then added to neutralize the acid, followed by the

extraction of the aqueous layer with hexanes (3 x 20 mL). Combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was first purified by column chromatography (silica, hexanes) to give 5.0 mg (30%) of an approximately 2:1 mixture of diastereomers containing isoverticillene (**21**) (based on ^{1}H NMR integration). This mixture was then separated by column chromatography (silver nitrate/silica, 95:5 hexanes-ethyl acetate) to give 3.0 mg (18%) of the major diastereomer. R_f 0.72 (hexanes). The minor diastereomer was obtained in 1.3 mg (7.8%). R_f 0.75 (hexanes). Analytical data for major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (dd, J = 3.4, 8.8 Hz, 1H, C=C*H*), 5.21 (t, J = 2.9 Hz, 1H, C12=C13-*H*), 5.10 (dd, J = 4.4, 10.7 Hz, 1H, C=C*H*), 2.26-2.34 (m, 2H), 2.19-2.24 (m, 2H), 2.01-2.13 (m, 2H), 1.92 (m, 1H), 1.77 (dt, J = 12.7, 9.8 Hz, 1H), 1.74 (m, 1H), 1.69 (m, 3H, C=C-CH_3), 1.62 (s, 3H, C=C-CH_3), 1.59 (m, 1H), 1.40 (s, 3H, C=C-CH_3), 1.39-1.41 (m, 2H), 1.31 (s, 3H, *gem*-CH_3), 0.91 (s, 3H, *gem*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 138.0, 133.1, 127.2, 123.8, 118.8, 50.0, 41.2. 40.3, 38.9, 38.8 (2 carbons), 35.1, 33.8, 31.5, 30.3, 24.5, 23.7, 17.2, 15.5. IR (film) 3026, 2955, 2919, 2861, 1662, 1443, 1385, 1361 cm^{-1}.



113
major isomer

16

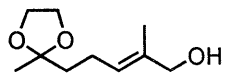
(+)-Verticillene (16):

Alcohol **113** (major isomer from the previous step, 15 mg, 0.052 mmol) was dissolved in tetrahydrofuran (5 mL). 1,10-Phenanthroline was added as an indicator. The solution was cooled to 0 °C before *n*-butyllithium (2.43 M in hexanes) was added dropwise until the reaction mixture turned completely red. Tetramethylphosphorodiamidic chloride (0.15 mL, 1.0 mmol) was added to the reaction mixture, which was then stirred at room temperature. Because the reaction mixture slowly turned from red to yellow, more *n*-butyllithium was added dropwise at 0 °C until the reaction mixture turned red again, followed by the addition of another portion of tetramethylphosphorodiamidic chloride (0.10 mL, 0.68 mmol). The reaction mixture was once again stirred at room temperature. This procedure was repeated once more until a total of 4 h had elapsed, and most of the starting material had been consumed. In a separate flask equipped with a glass-covered stir-bar, was condensed ammonia (~ 40 mL) at -78 °C. Flattened pieces of lithium wire (90 mg, 13 mmol) were added to the liquid ammonia, followed by the transfer of the alcohol/tetrahydrofuran solution *via* a cannula . The cooling bath was removed and the reaction mixture was allowed to stir at ammonia's boiling point for 1.5 h, before being quenched with solid ammonium chloride. The ammonia was evaporated, followed by the addition of water (20 mL). The aqueous layer was extracted with ether (3 x 20 mL), and

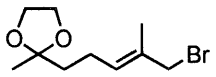
the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (silica, hexanes) to give 11 mg (79%) of verticillene. R_f 0.64 (hexanes). $[\alpha]^{22}_D$ +72.8° (*c* 1.1, acetone). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (d, *J* = 12.2 Hz, 1H, C=C*H*), 4.69 (d, *J* = 10.7 Hz, 1H, C=C*H*), 2.64 (dddd, *J* = 1.5, 6.4, 13.7, 15.6 Hz, 1H), 2.46 (dt, *J* = 6.6, 12.1 Hz, 1H), 2.30 (m, 1H), 2.11-2.22 (m, 4H), 2.05 (m, 1H), 1.81-1.98 (m, 5H), 1.67 (s, 3H, C=C-CH_3), 1.53-1.60 (m, 2H), 1.52 (s, 3H, C=C-CH_3), 1.50 (s, 3H, C=C-CH_3), 0.95 (s, 3H, *gem*-CH_3), 0.85 (s, 3H, *gem*-CH_3). ^{13}C NMR and DEPT (125 MHz, $CDCl_3$) δ 136.0, 132.8, 131.5, 128.5 (CH), 126.8 (CH), 126.3, 42.8 (CH), 40.2 (CH_2), 38.5 (CH_2), 37.0, 34.1 (CH_2), 32.8 (CH_3), 31.4 (CH_2), 27.5 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 24.5 (CH_3), 21.7 (CH_3), 16.6 (CH_3), 15.4 (CH_3). IR (film) 3056, 2966, 2911, 2849, 1661, 1471, 1444, 1383, 1372, 1363, 1214, 1198, 1171, 1149, 1109, 1094, 1058, 897, 835, 825, 811 cm^{-1}. HRMS (EI) Calcd for $C_{20}H_{32}$ (M^+): 272.25040. Found: 272.25032.

Selected Spectra

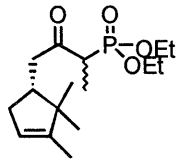
Index to Selected Spectra



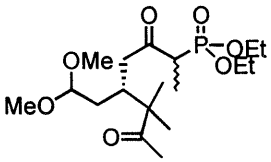
41 ^{1}H NMR p. 144



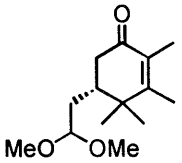
33 ^{1}H NMR p. 145



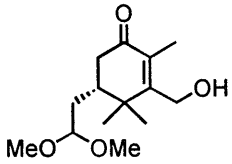
35 ^{1}H NMR p. 146



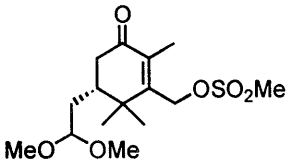
38 ^{1}H NMR p. 147



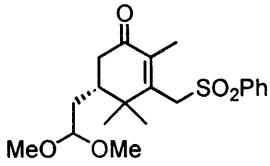
31 ^{1}H NMR p. 148



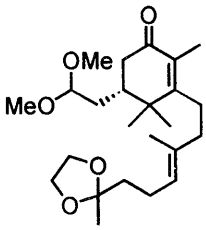
52 ^{1}H NMR p. 149



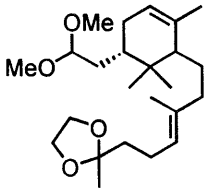
55 ^{1}H NMR p. 150



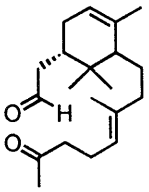
54 ^{1}H NMR p. 151



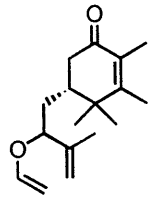
61 ^{1}H NMR p.152



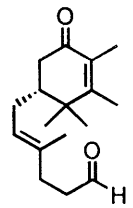
65 ^{1}H NMR p. 153



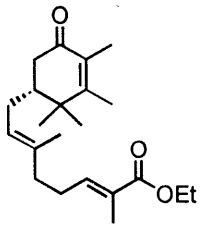
30 ^{1}H NMR p. 154



83 diastereomer a: ^{1}H NMR p. 155
diastereomer b: ^{1}H NMR p. 156



84 ^{1}H NMR p. 157



86 ^{1}H NMR p. 158

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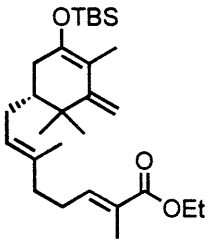
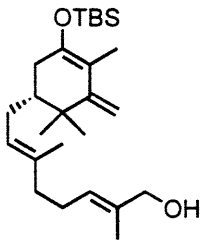


87 ^{1}H NMR p. 159



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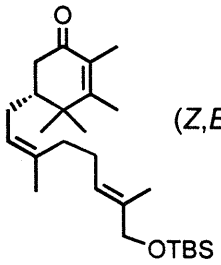
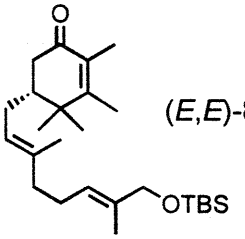
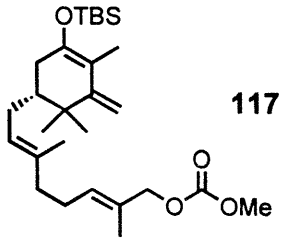


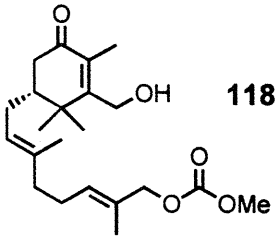
(*Z*,*E*)-**81** ^{1}H NMR p. 161
nOe difference p. 162



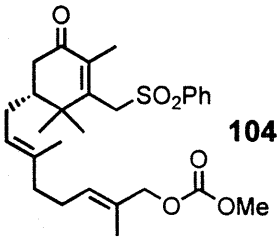
(*E*,*E*)-**81** ^{1}H NMR p. 163



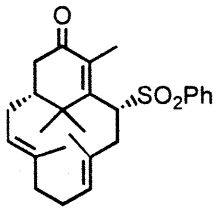
117 ^{1}H NMR p. 164



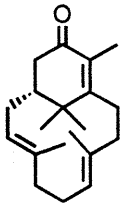
118 ^{1}H NMR p. 165



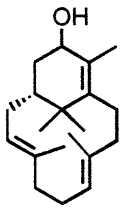
104 ^{1}H NMR p. 166



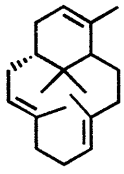
72 ^{1}H NMR p. 167
COSY p. 168



105 ^{1}H NMR p. 169
COSY p. 170
NOESY p. 171



113 major diastereomer:
^{1}H NMR p. 172
minor diastereomer:
^{1}H NMR p. 173



21 major diastereomer:
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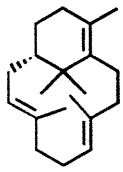
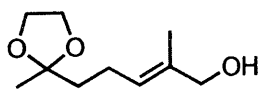


16 ^{1}H NMR p. 175
^{13}C NMR p. 176
DEPT p. 176



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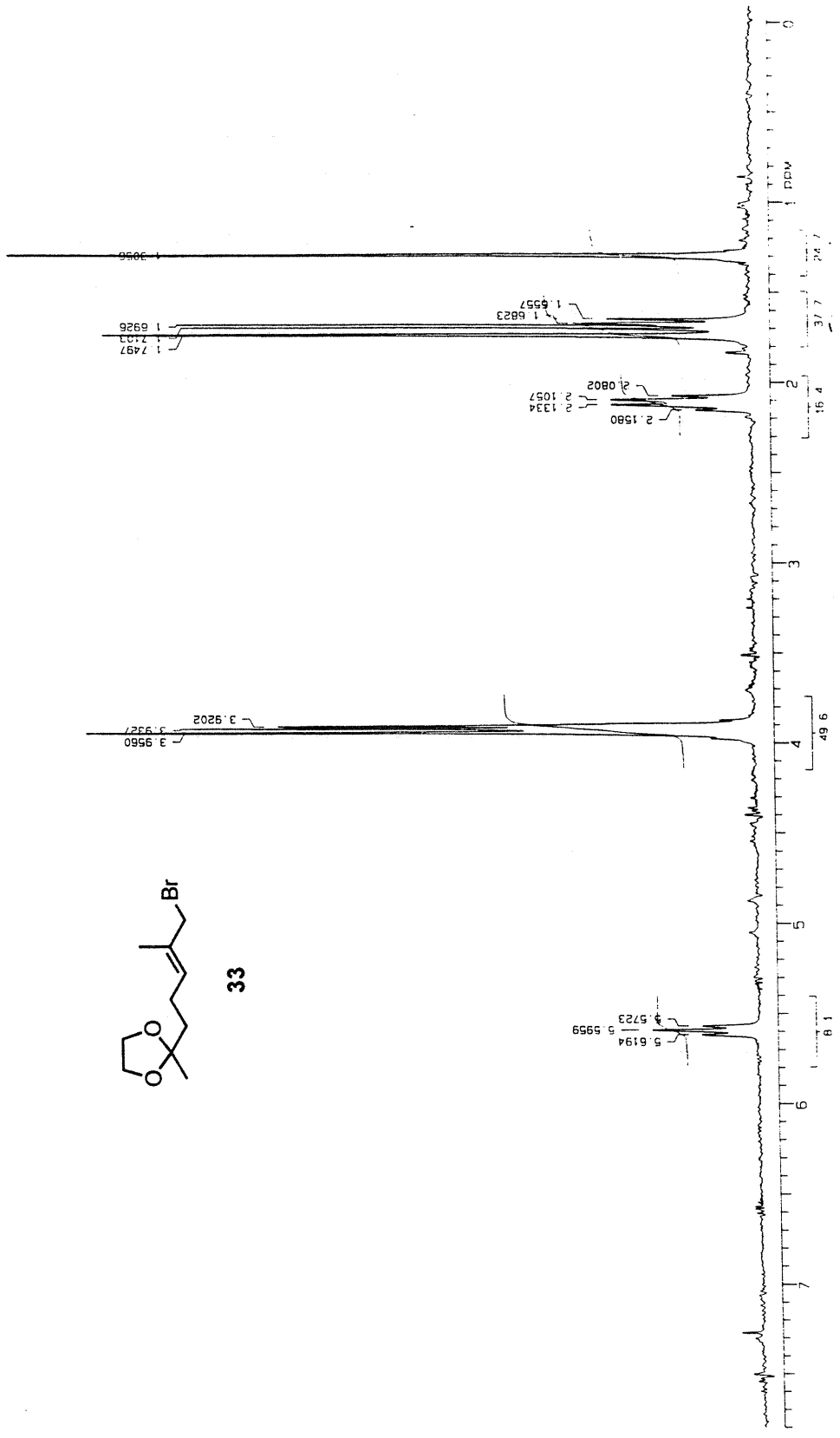
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2.1057
2.0802
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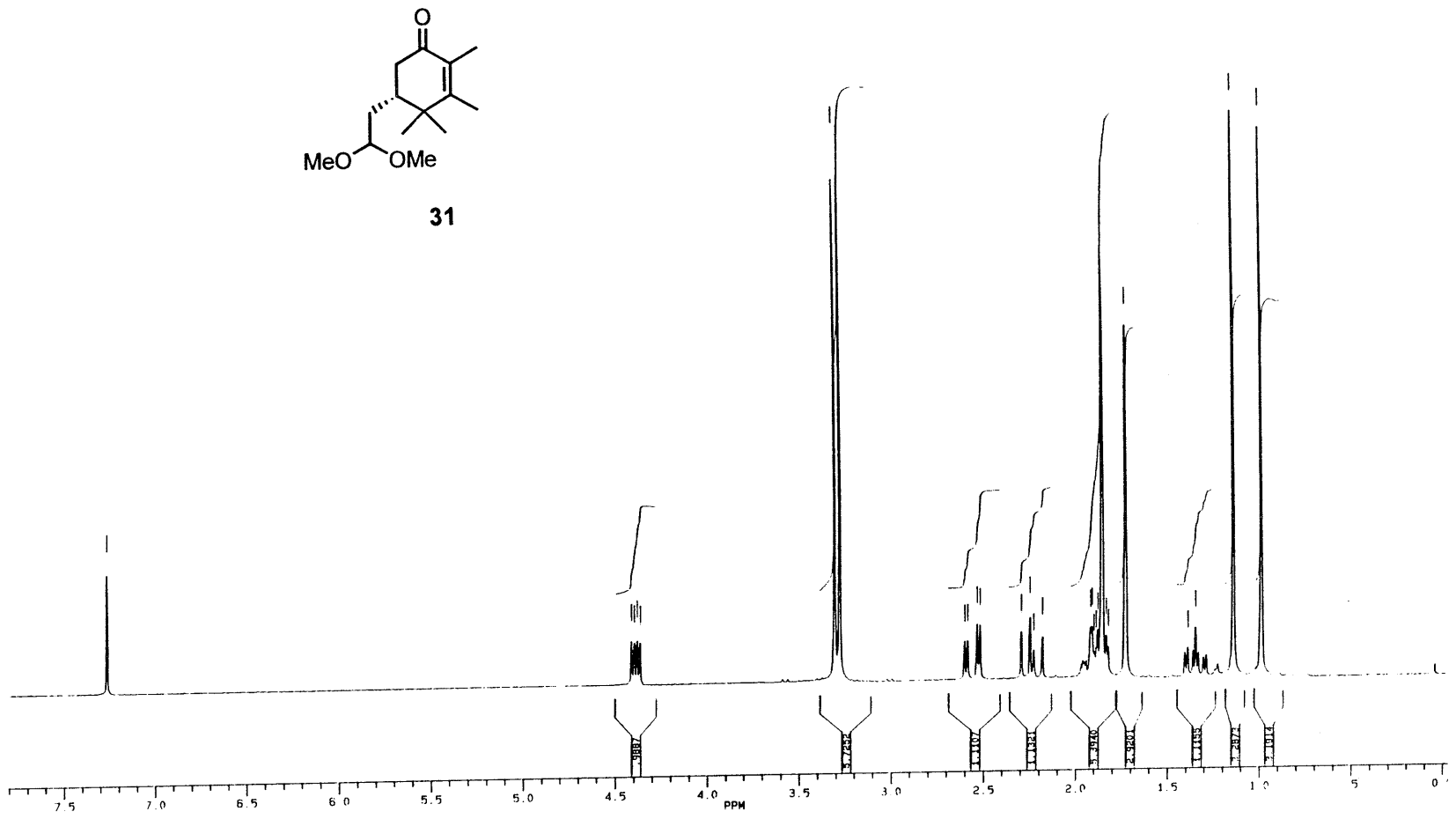
1.7173
1.6926
1.6823
1.6557
1.3956
ppm

35

38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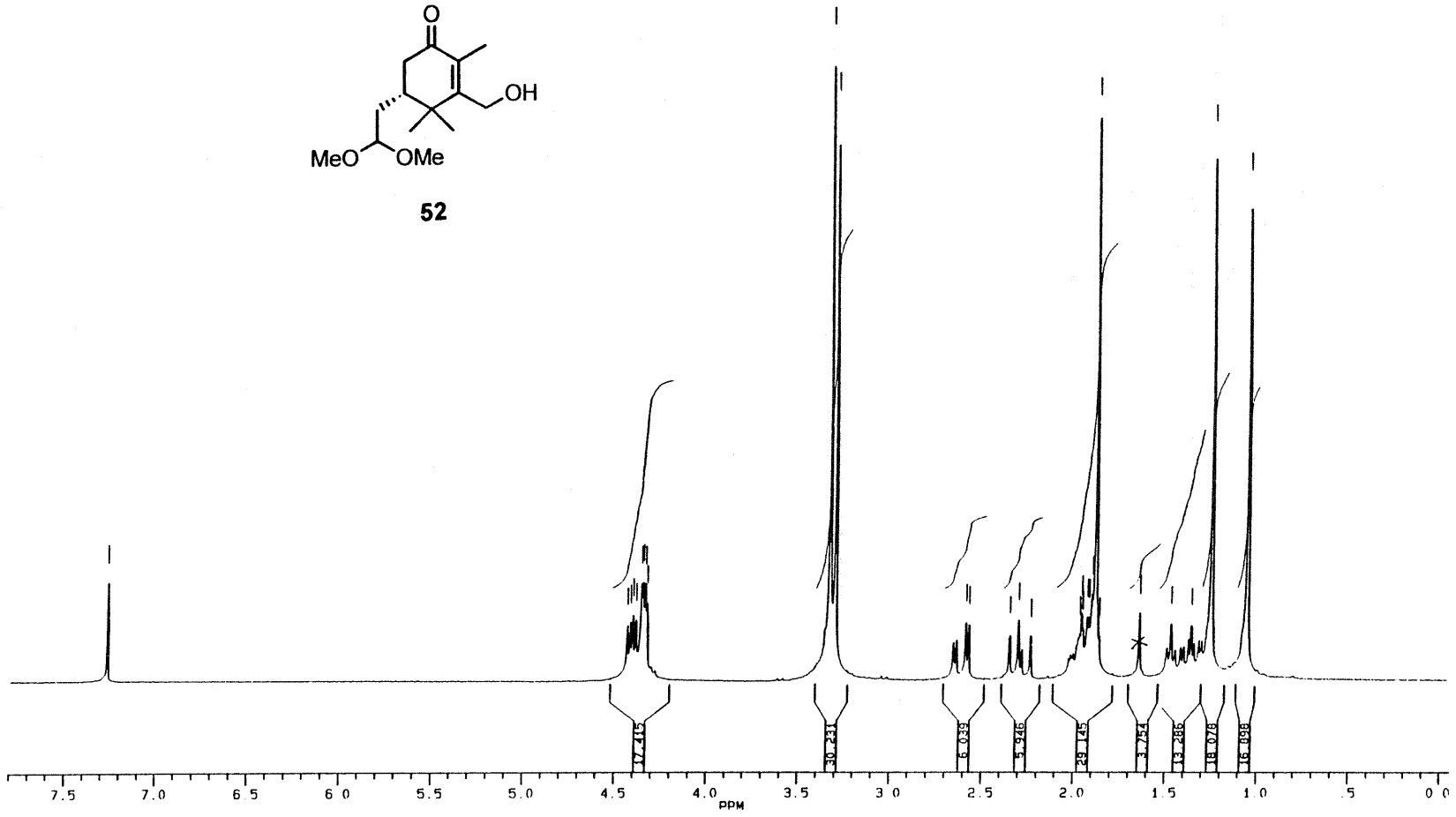
OMe
31
PPM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OMe
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16.898
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7.0
6.5
6.0
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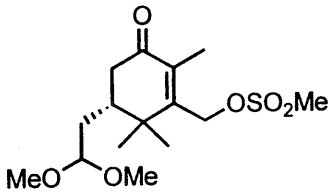

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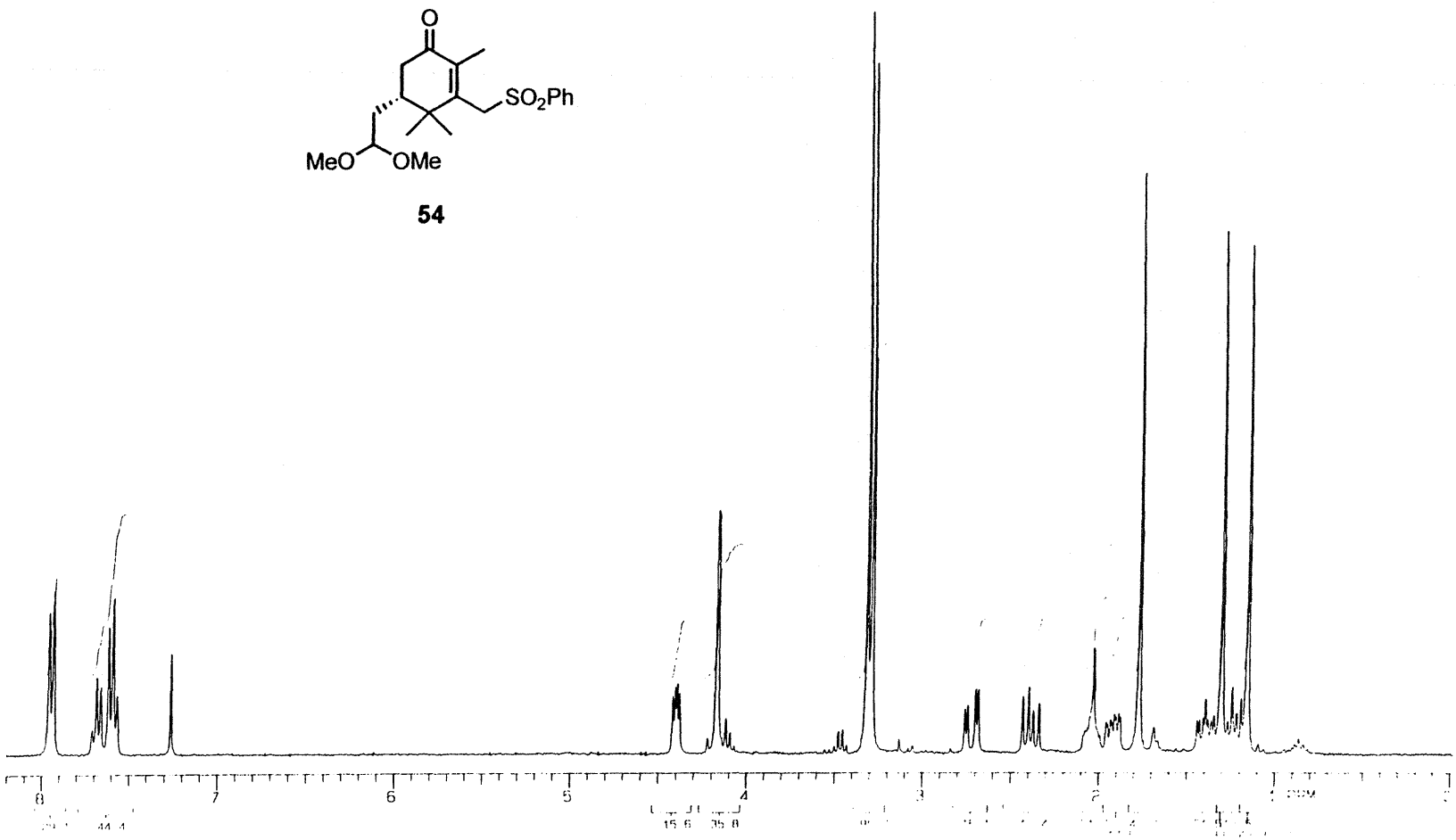
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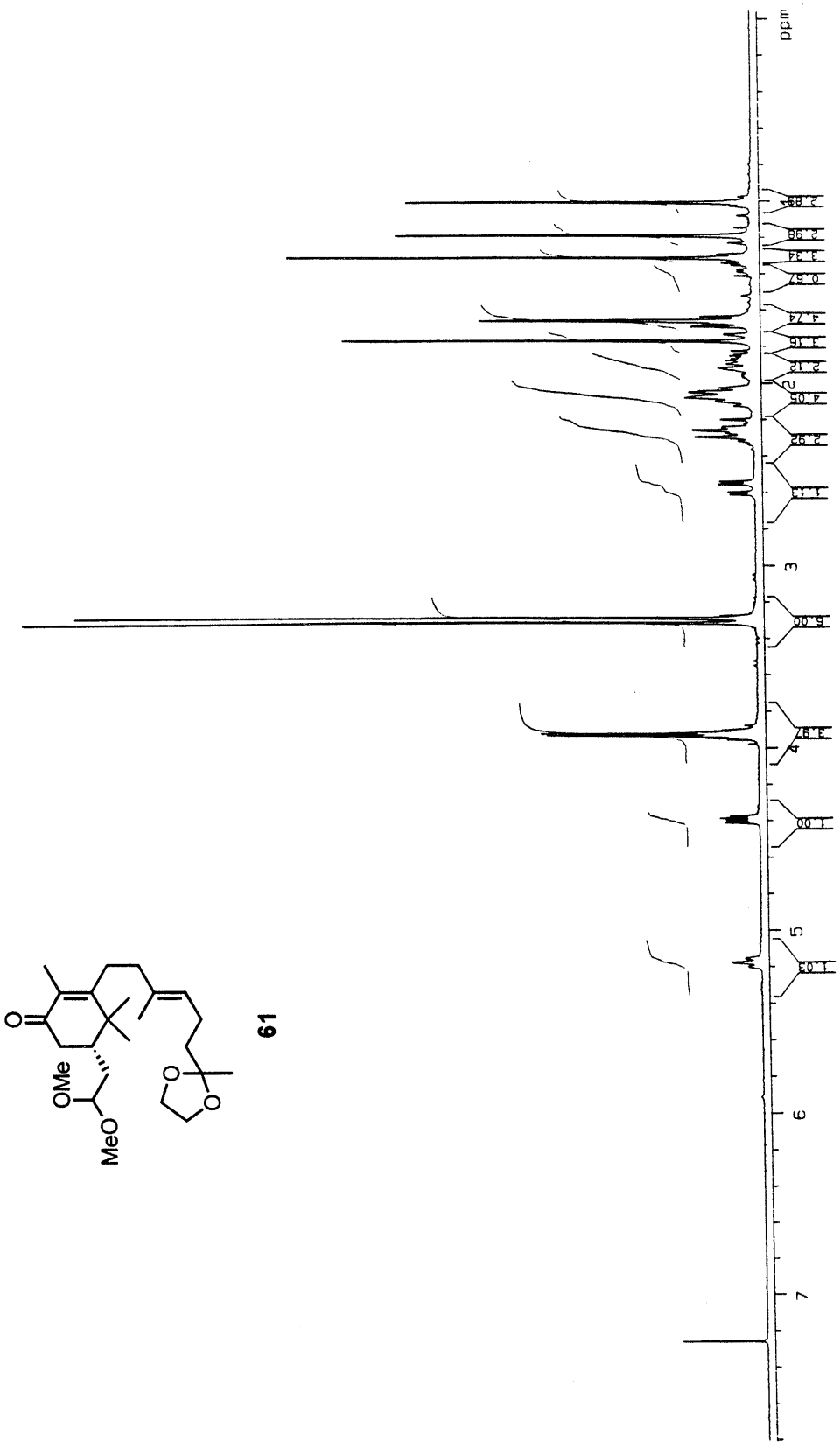
6
5
4
3
2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4
5
6
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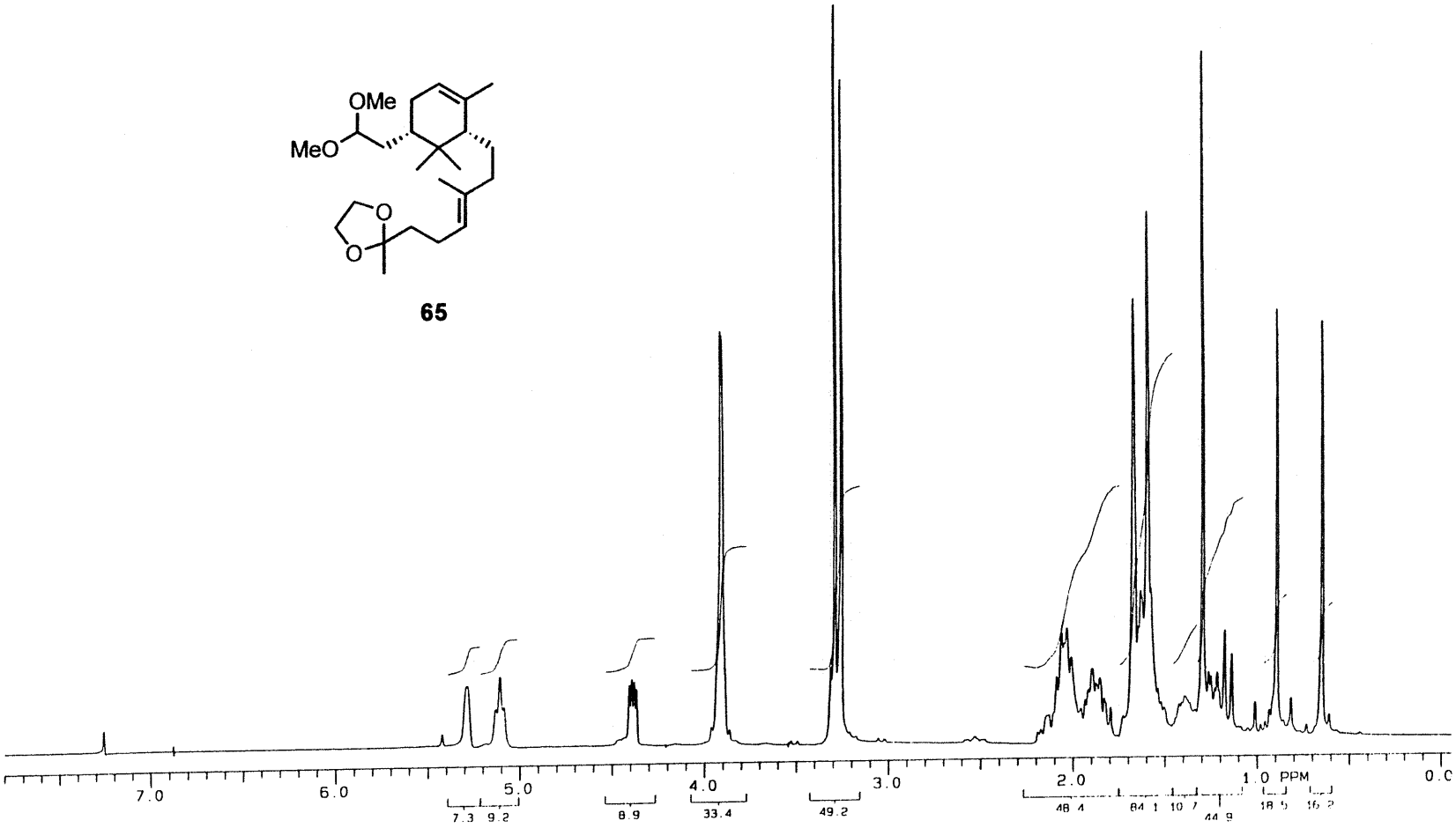
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48.4
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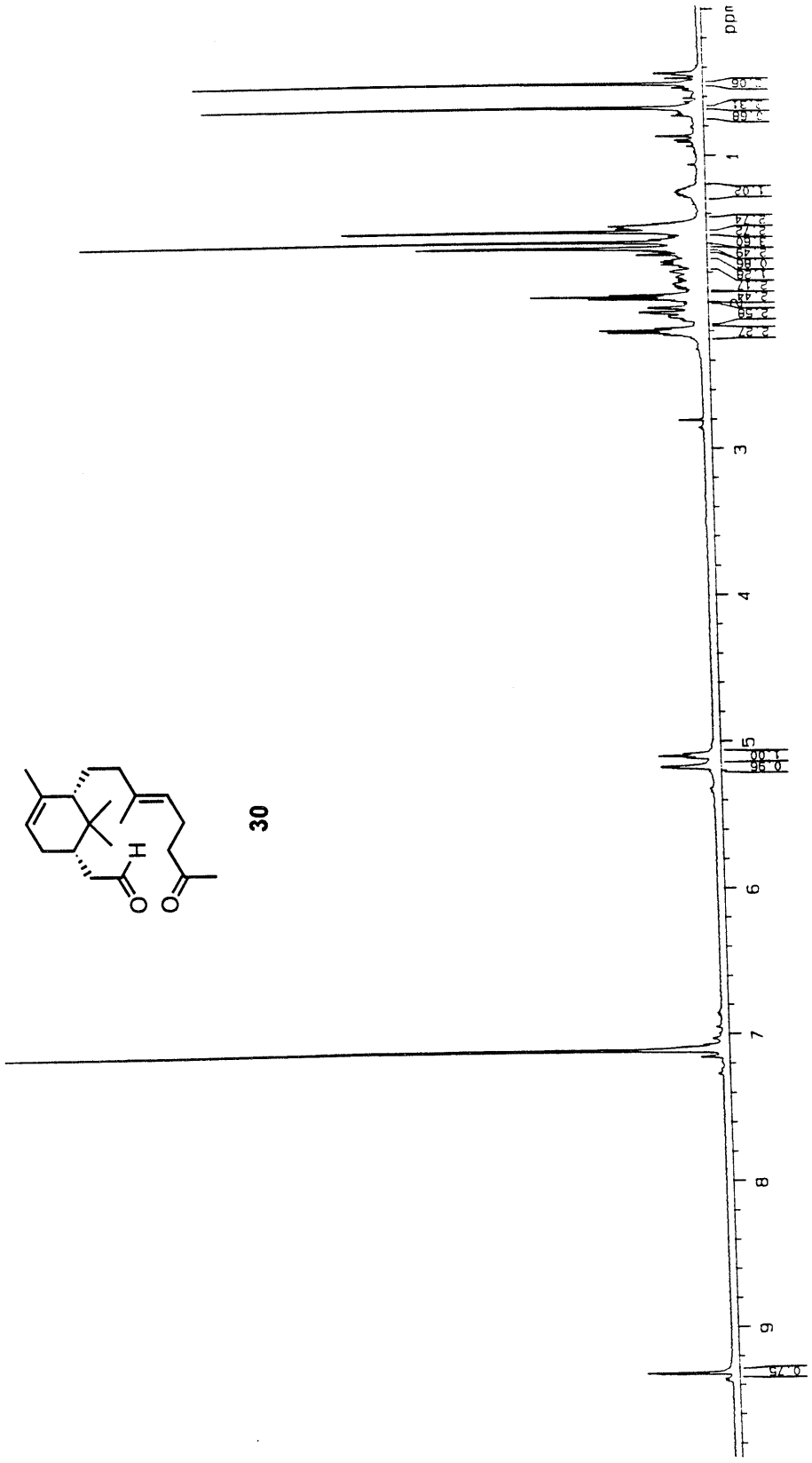
44.9

65



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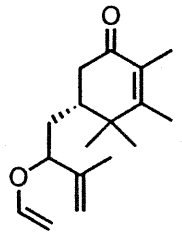
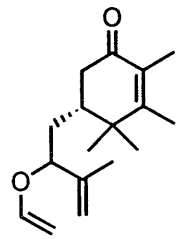


83

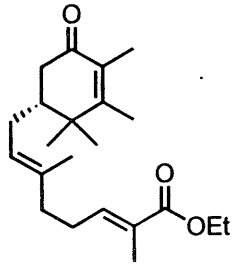
diastereomer a



83

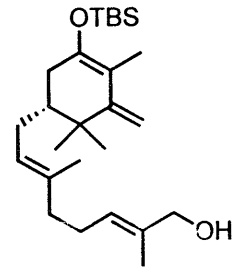
diastereomer b

84



86

87



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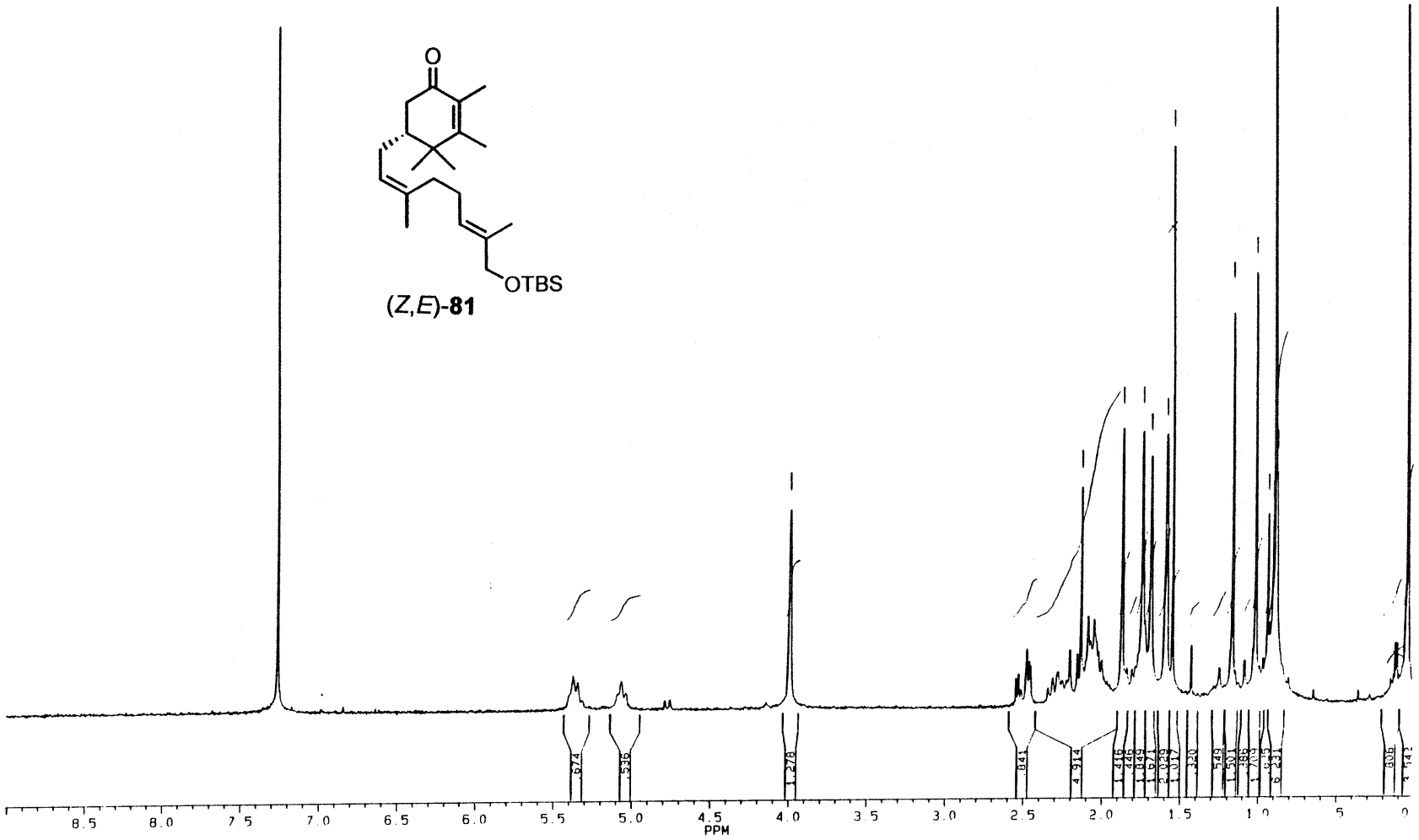
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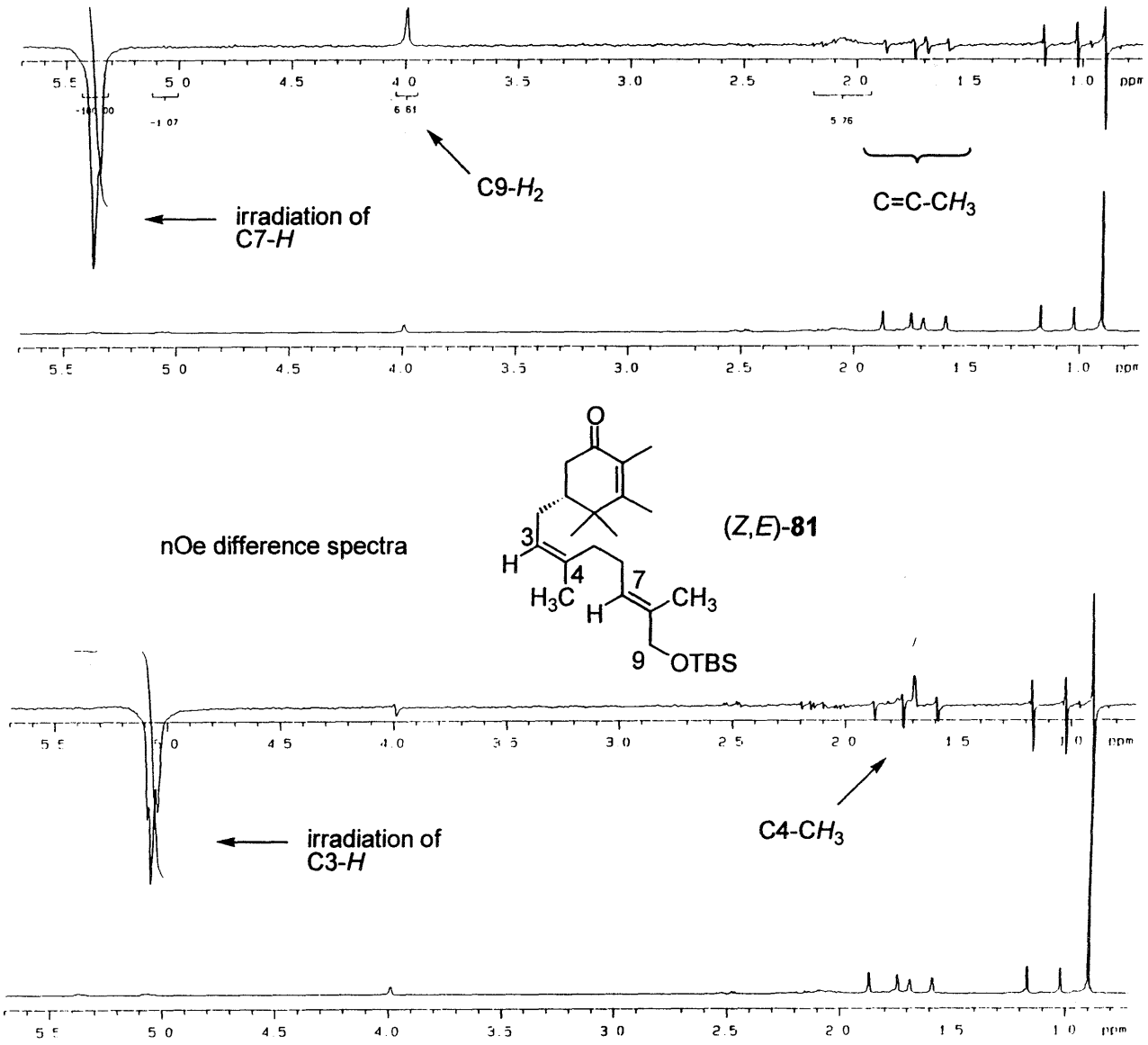
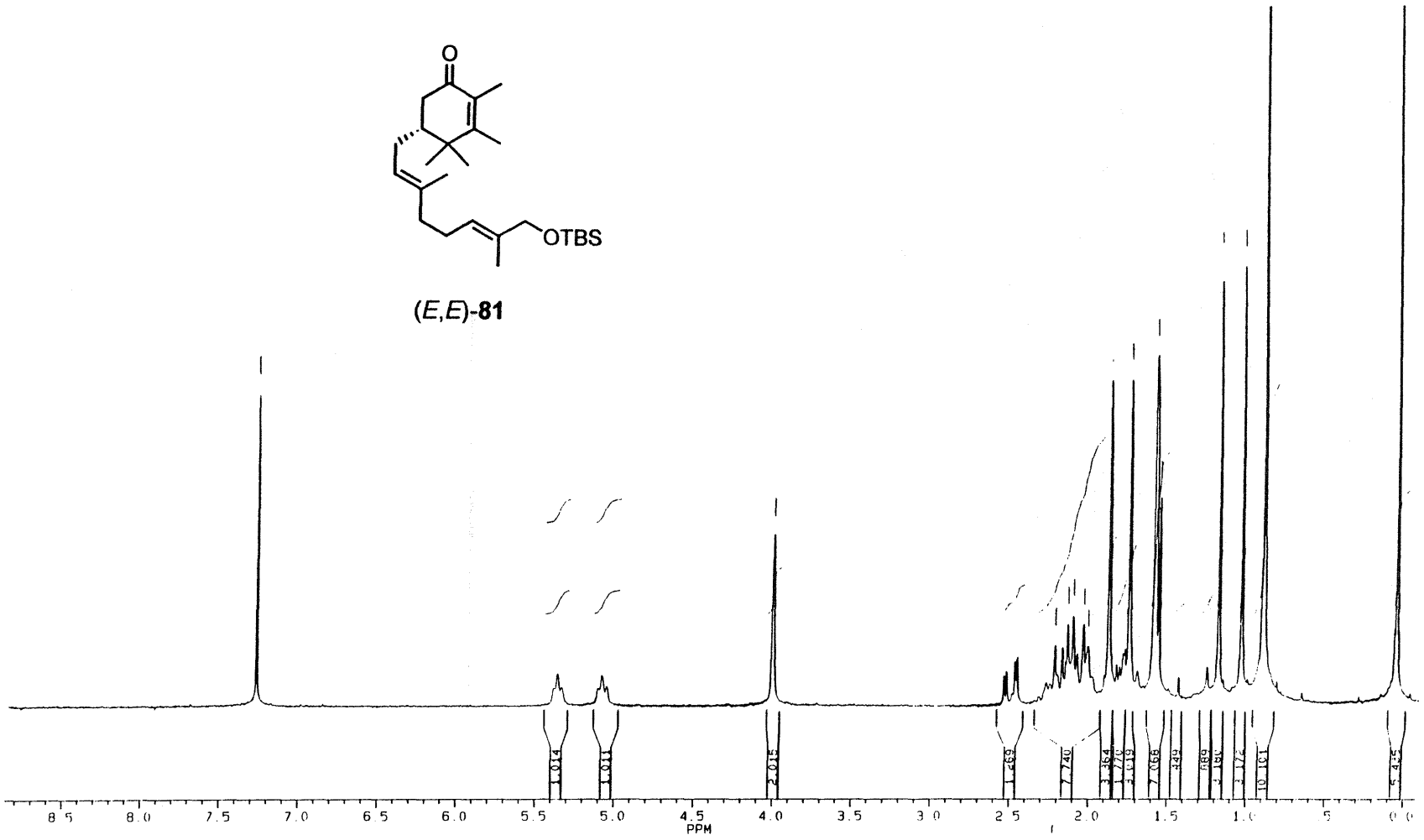
4.0
3.5
3.0
2.5
2.0
1.5
1.0
5
0
PPM


C9-H_2
irradiation of C7-H
C=C-CH_3
nOe difference spectra
(Z,E)-81
irradiation of C3-H
C4-CH_3
OTBS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OTBS
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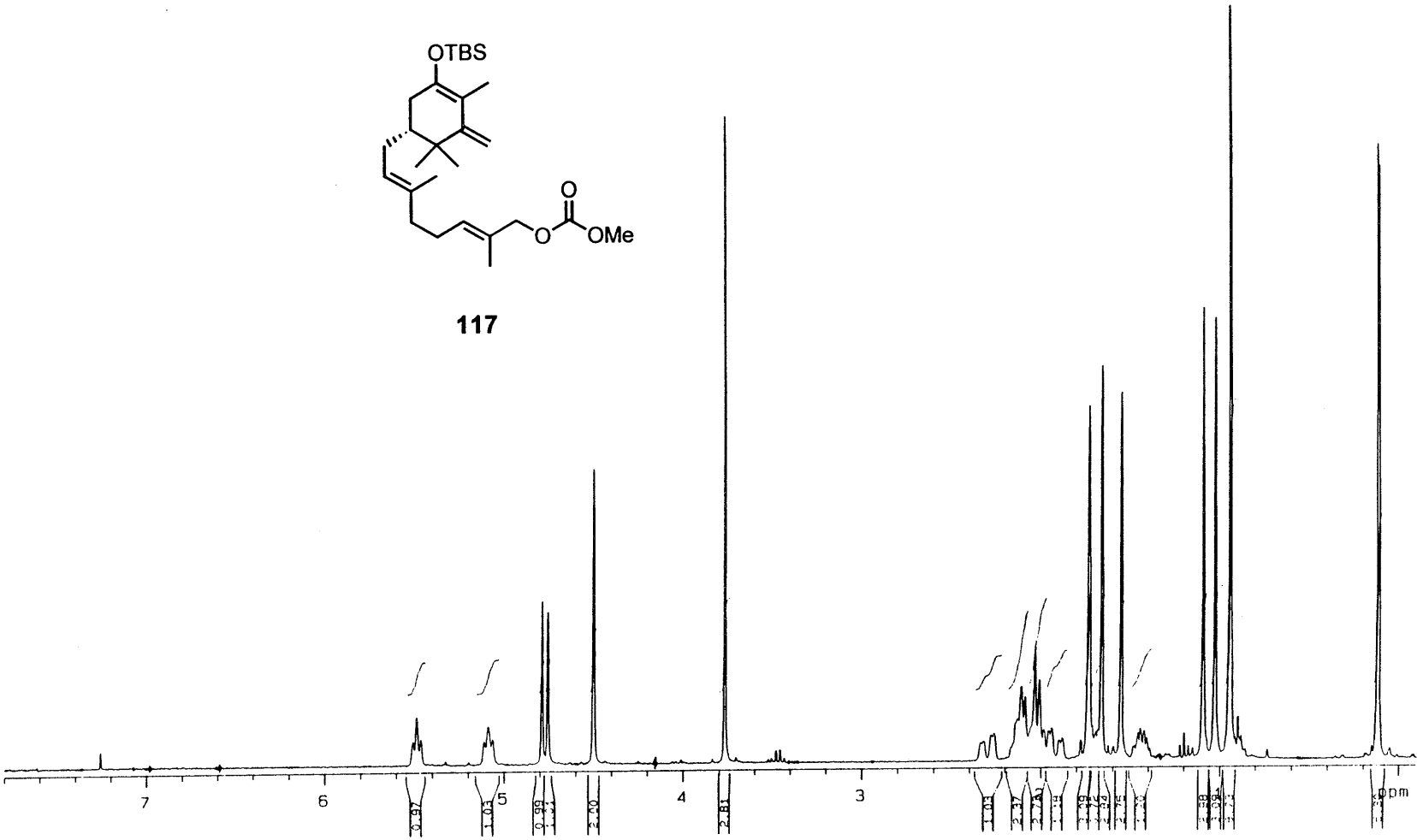
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM



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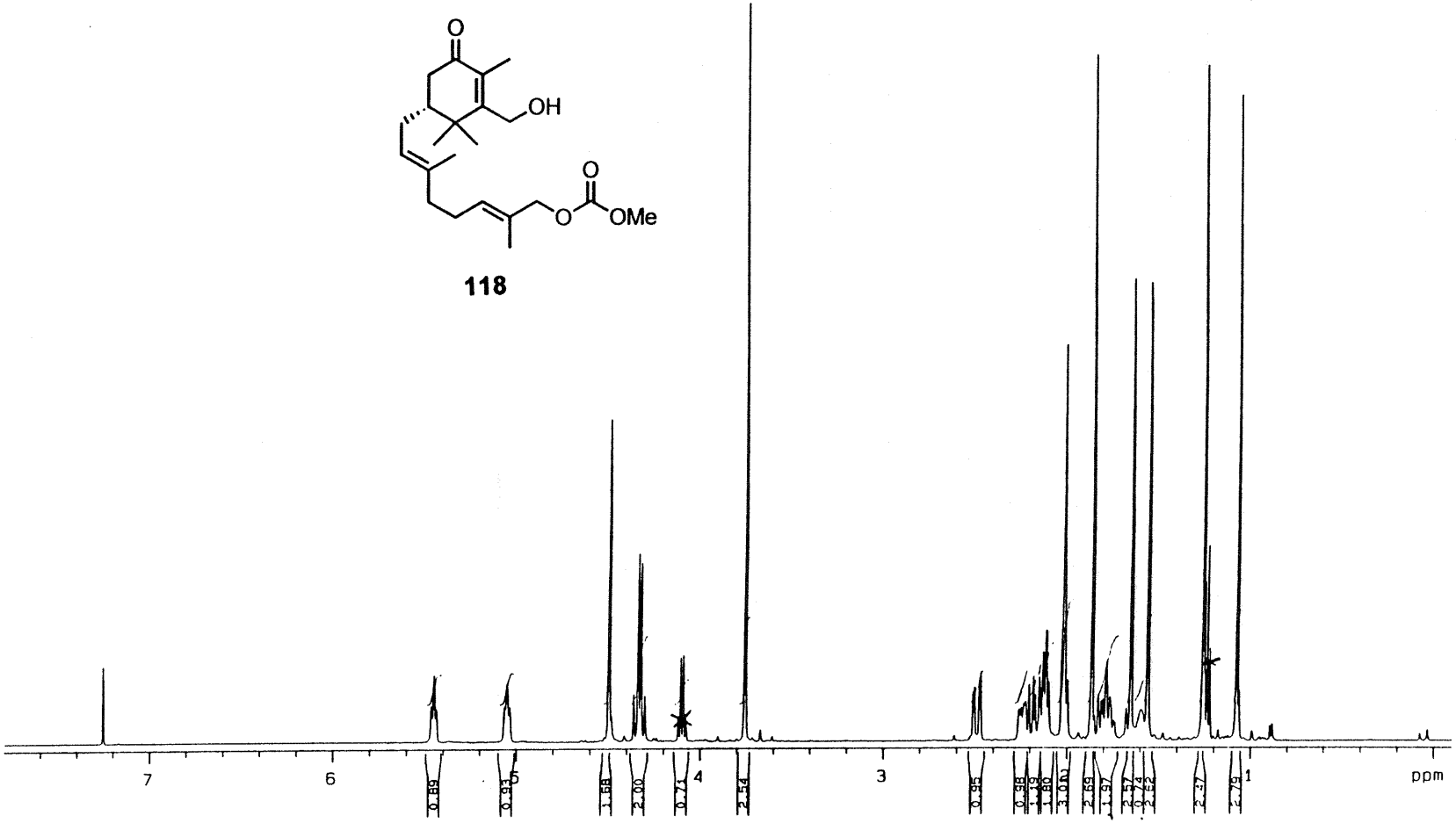
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O
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3
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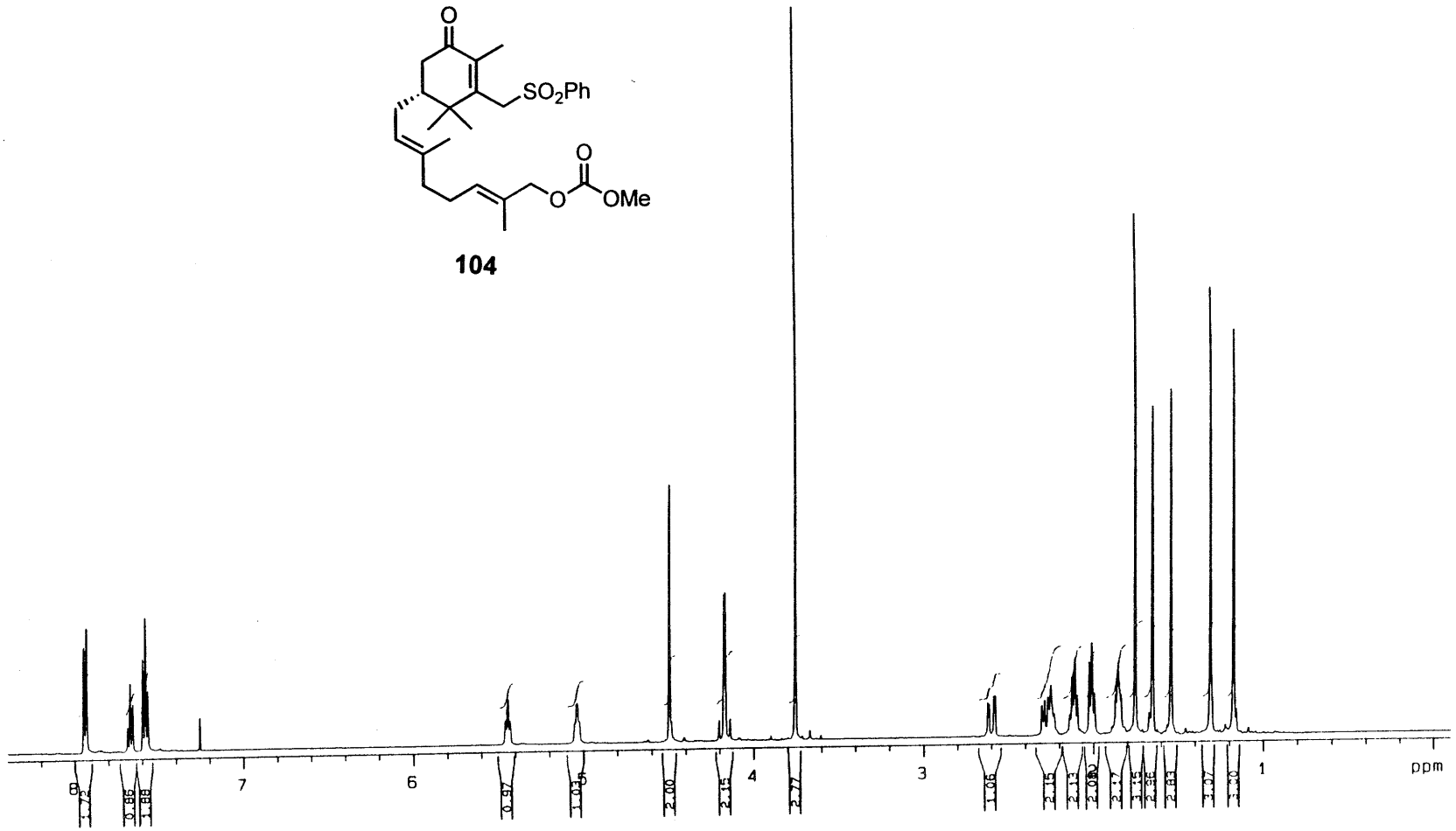
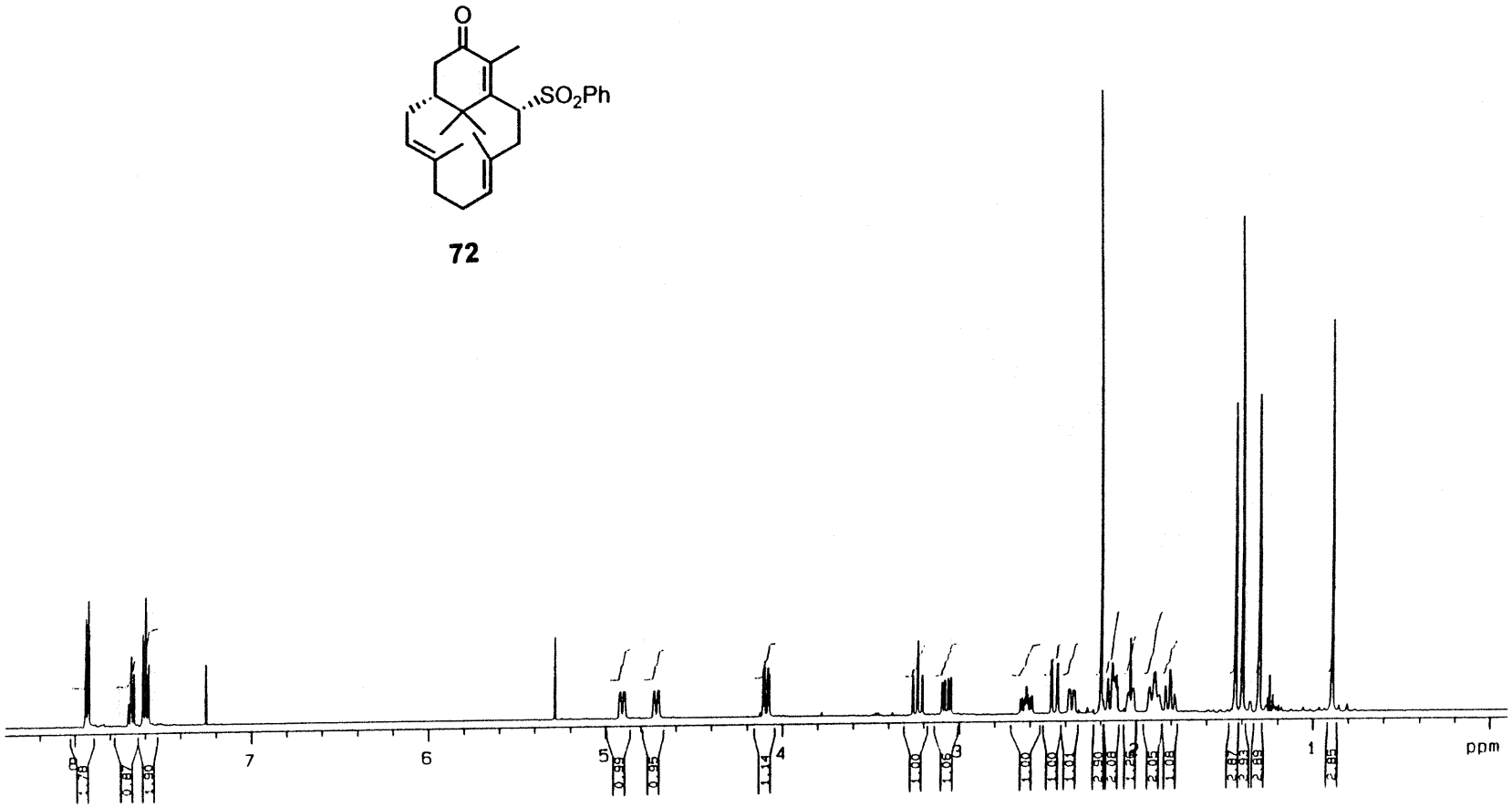
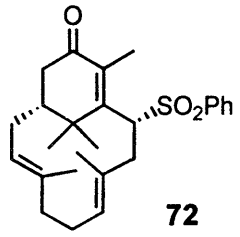
0.71
2.84
0.95
0.88
1.00
2.69
11.97
2.57
2.74
2.82
2.37
2.79

118

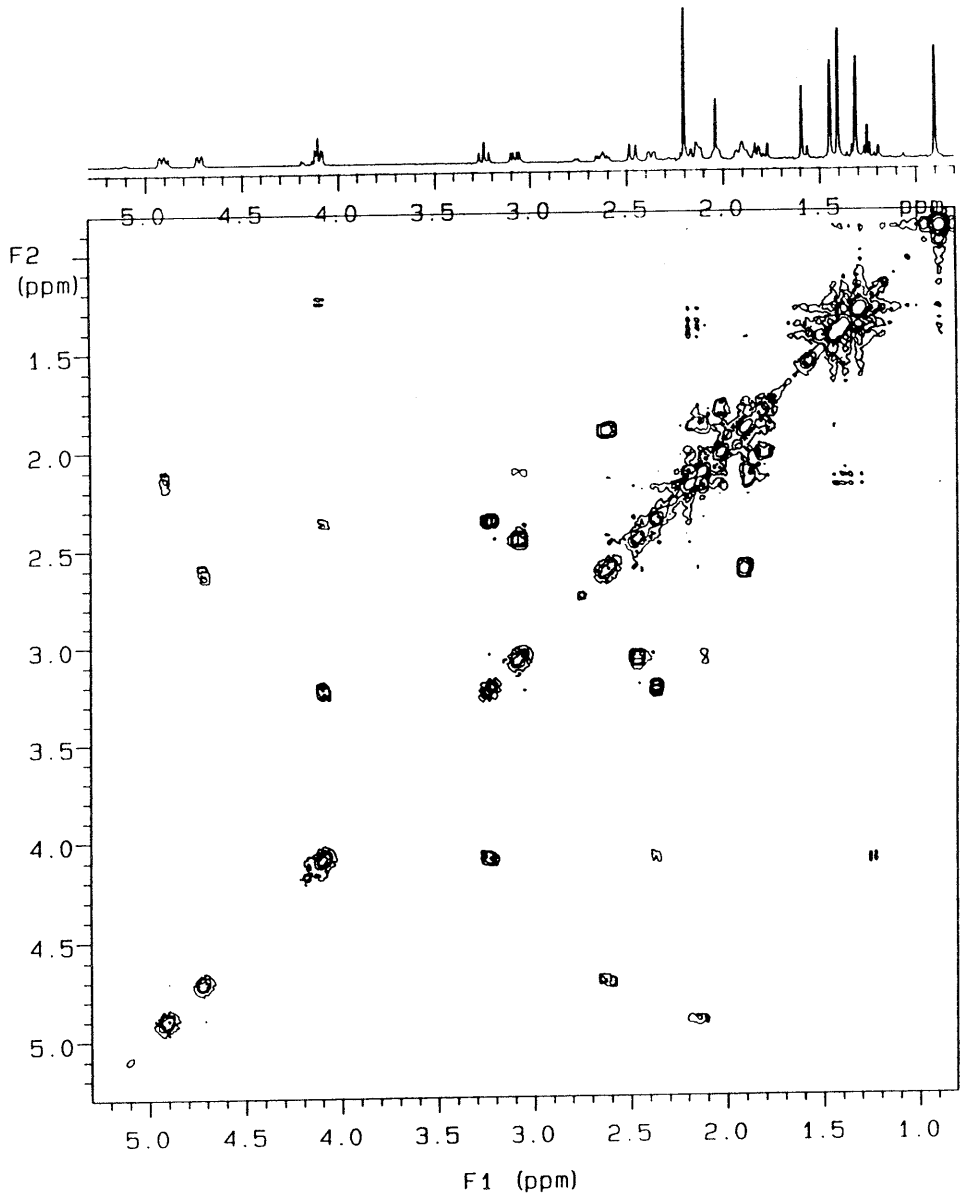

O
SO2Ph
O
O
OMe
104
8
7
6
5
4
3
1
ppm

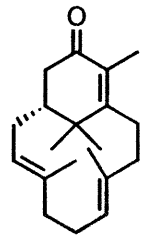

O
SO2Ph
72
7
6
5
4
3
1
ppm



72

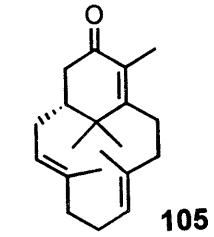
COSY spectrum





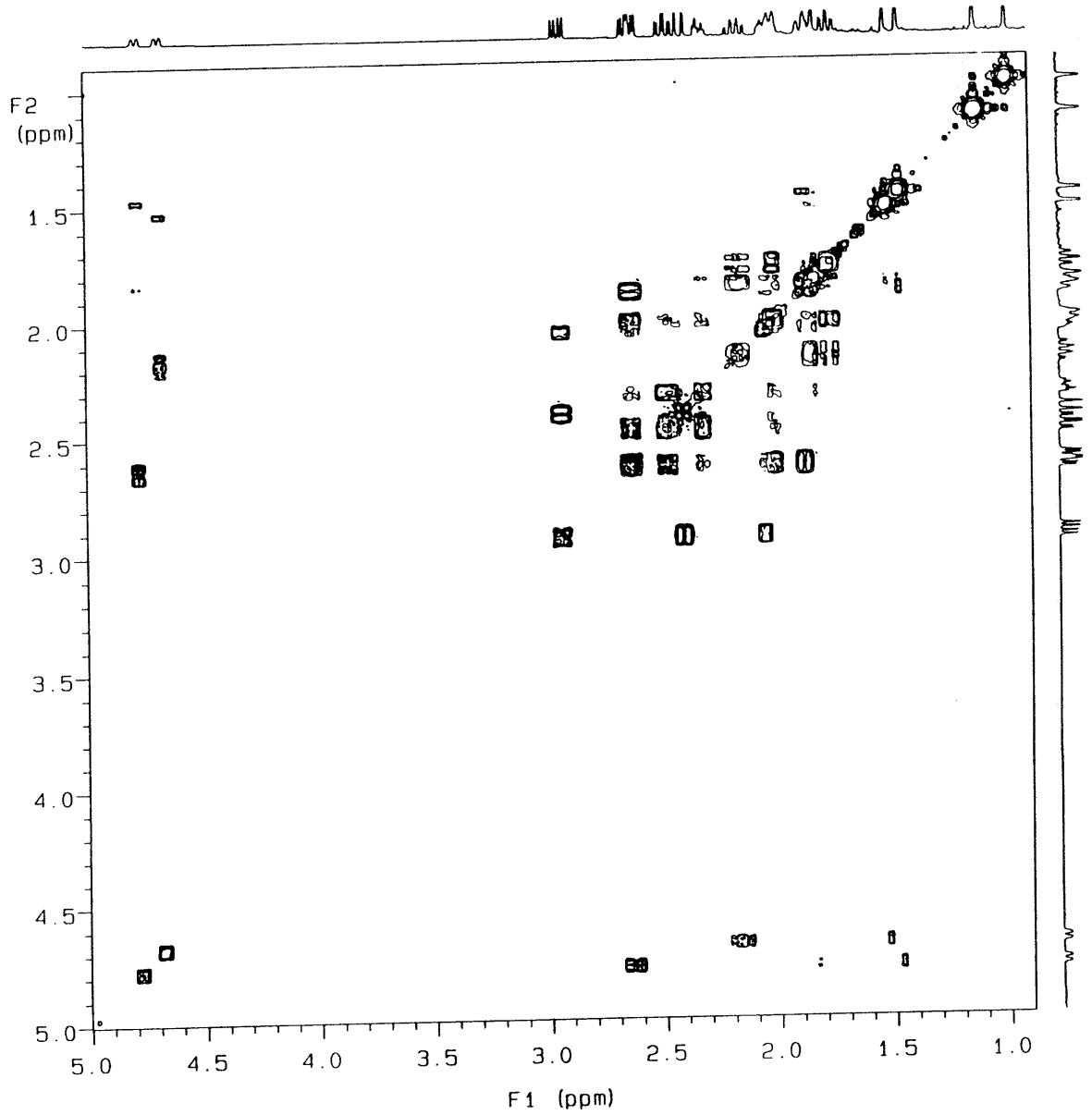
105

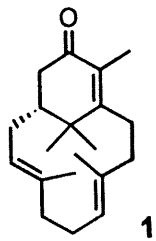
7
6
5
4
3
ppm
0.87
0.99
1.00
2.05
1.13
1.04
1.10
1.16
1.28
2.25
3.05
1.41
2.70
2.71
2.99
2.95



105

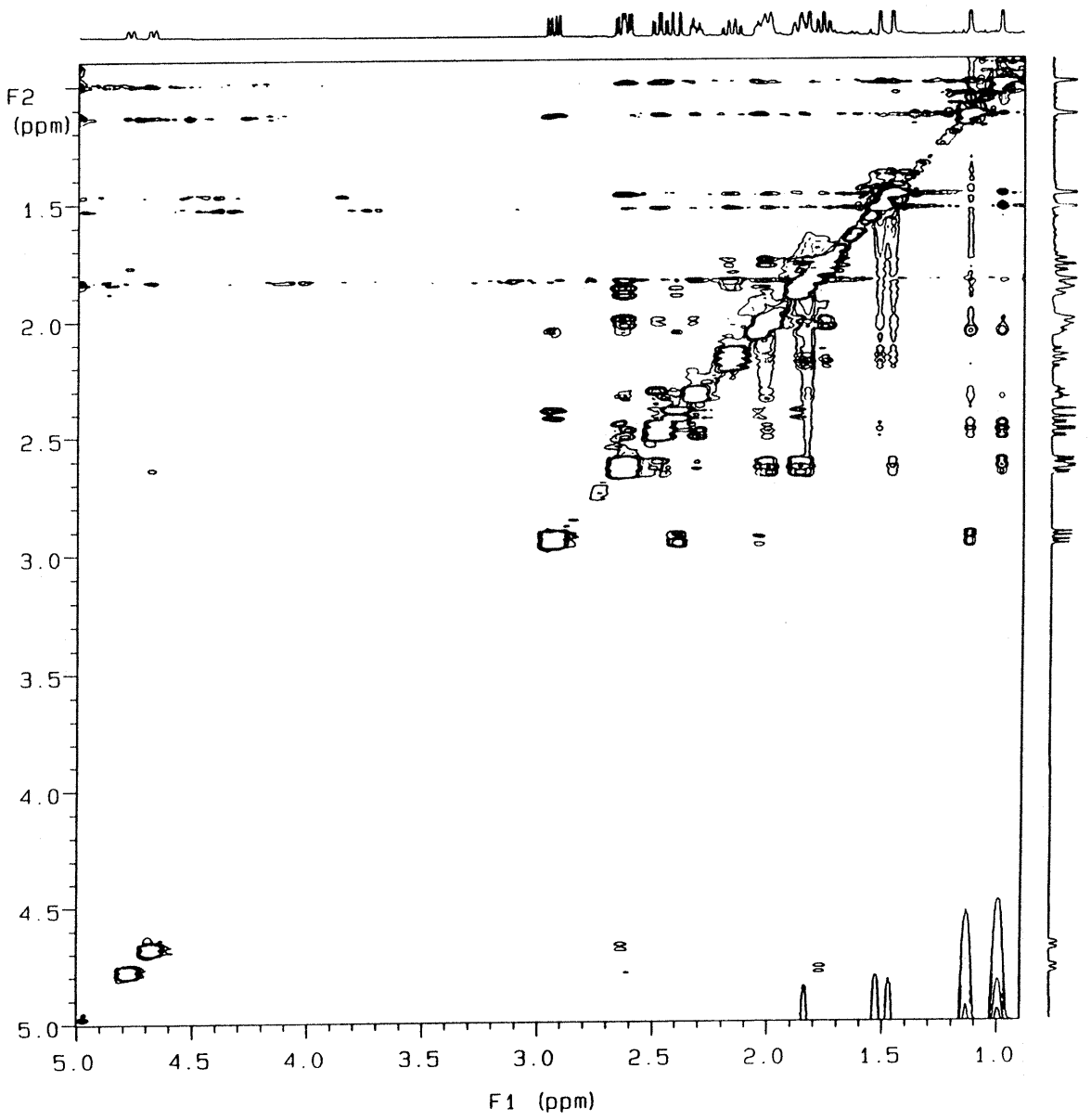
COSY spectrum

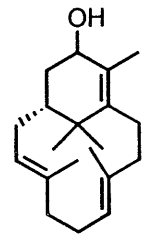




105

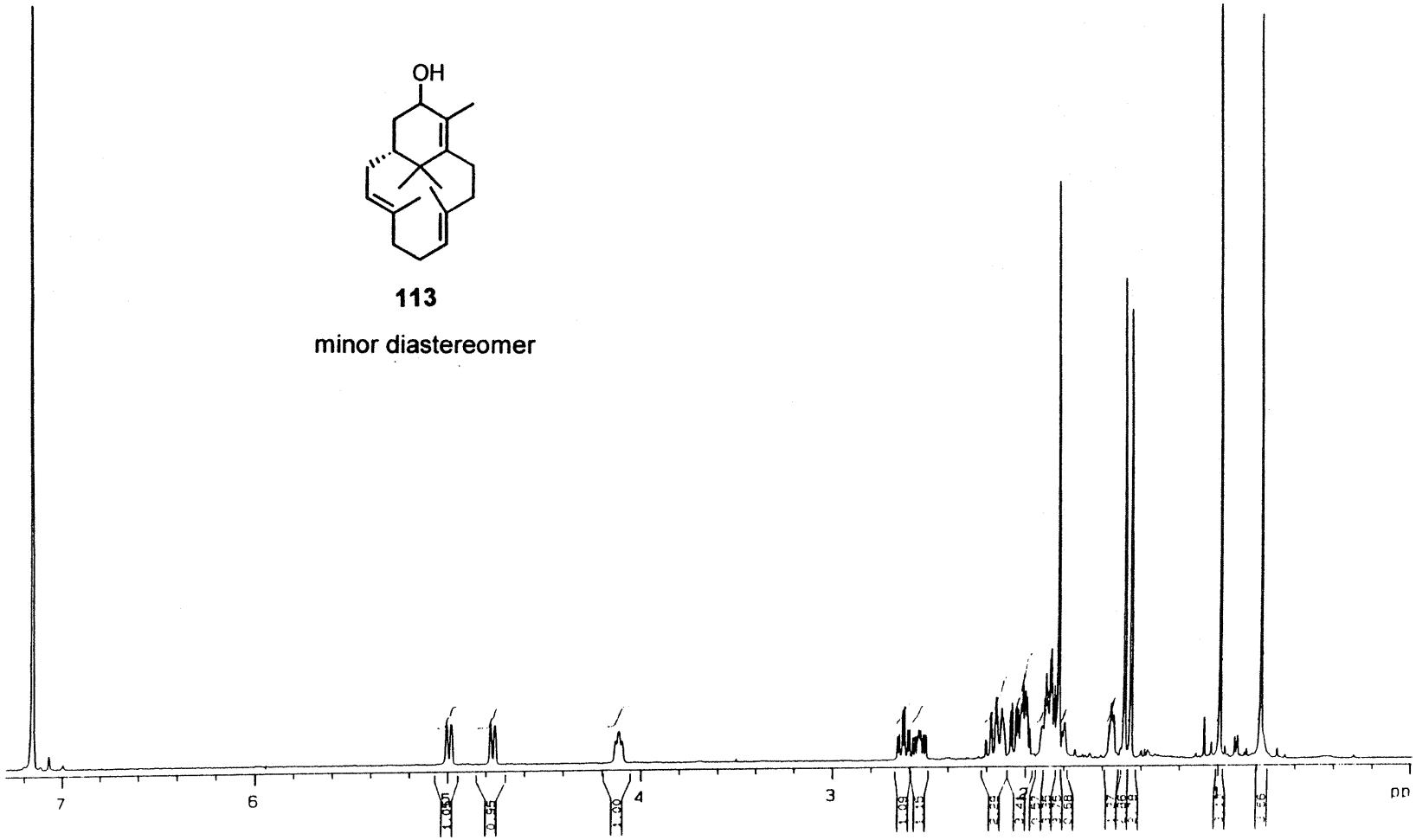
NOESY spectrum

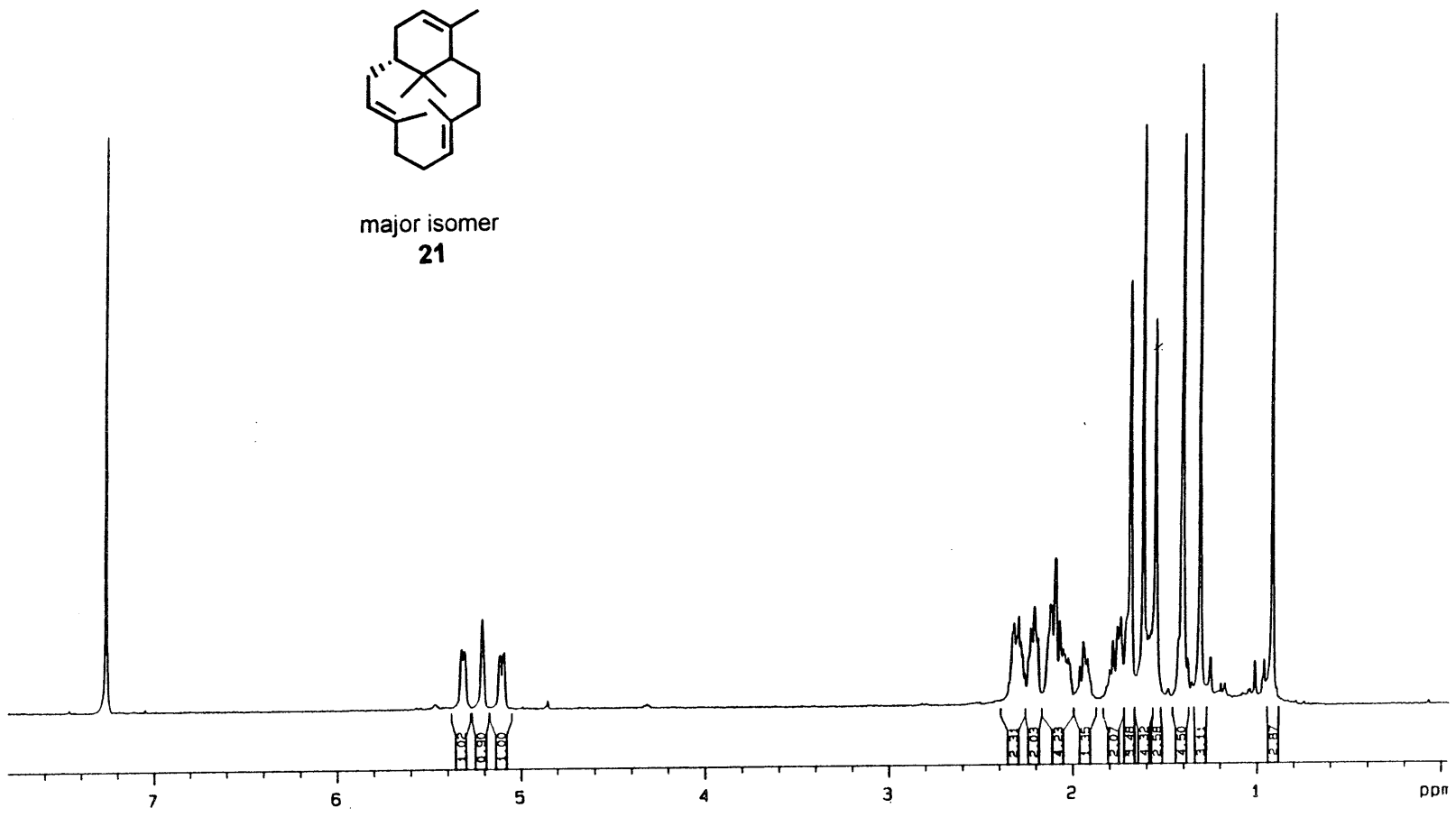


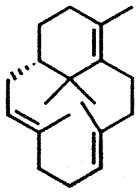


113

major diastereomer

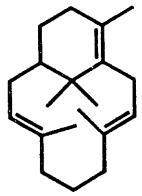

OH
113
minor diastereomer
7
6
4
3
2
1
ppm


major isomer
21
7
6
5
4
3
2
1
ppm



16

0.94
0.91
1.00
1.00
1.06
4.09
1.08
5.15
2.87
2.92
2.50
2.69
3.18
4.23
7
6
5
4
3
2
1
ppm



16

^{13}C NMR and DEPT spectra

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