AN ABSTRACT OF THE DISSERTATION OF

M Sundaram Shanmugham for the degree of Doctor of Philosophy in Chemistry presented on January 13, 2004

Title: SYNTHESIS OF FURANOEREMOPHILANE SESQUITERPENOIDS

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Abstract approved: _____

James D. White

Two approaches to the tricyclic core of the furanoeremophilane sesquiterpenoids are described. The first approach entails a projected Diels-Alder/retro Diels-Alder reaction of an acetylenic oxazole **64**. Construction of the pivotal aldehyde **67** commenced from ketone **68**. The acetylenic moiety was then introduced *via* a Felkin-Ahn addition of lithiopropyne to aldehyde **67**. The final conversion of the cyclohexanone **83** to the acetylenic triflate **65** was unsuccessful. Attempts at addition of lithiated 2-methyloxazole **88** to ketone **83** were also unsuccessful.

The second approach exploited a new annulation strategy. The aldehyde **64** was advanced to the 2, 4, 6-triisopropylbenzene sulfonylhydrazone **102** and a Shapiro reaction of **102** then provided alcohol **96**. The furyl stananne **114** was readily prepared via a six-step sequence from

acetylacetaldehyde dimethyl acetal **106**. Unification of allylic bromide **90** and stannane **114** was accomplished through a Stille cross coupling methodology and the resulting product **113** was advanced to the aldehyde **116**. However, attempts at further oxidation of this aldehyde to the required acid **89** failed. An alternative furyl stananne **124** with a *tert*-butyldimethylsilyl substituent at the C2 position was prepared from 3-furoic acid. An analogous sequence to that used with **113** led to aldehyde **131** which was successfully cyclized with the aid of trimethylsilyl trifluromethanesulfonate and 2, 6-lutidine to the tricyclic structure **132**. Oxidation of the epimeric mixture of alcohols, followed by stereoselective reduction and removal of the *tert*-butyldimethylsilyl group from alcohol **134,** gave (±)-6β-hydroxyeuroposin (**4**). Oxidation experiments with **134** were shown to convert the furan in this structure to a butenolide characteristic of the eremophilenolides.

SYNTHESIS OF FURANOEREMOPHILANE SESQUITERPENOIDS

By

M Sundaram Shanmugham

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Dedicated With Love

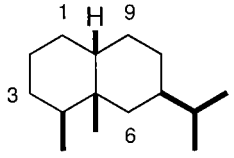
To My Parents

SYNTHESIS OF FURANOEREMOPHILANE SESQUITERPENOIDS

Chapter I.

Introduction

Plants of the *Senecio, Petasites* and *Ligularia* families are a rich source of chemically and biologically interesting secondary metabolites. The most frequently encountered natural products from plants of these families are sesquiterpenoids with structures based on the eremophilane framework **1**. In these natural products, the eremophilane nucleus (**Figure 1.1**) can exist at several oxidation levels, and members of the class are often found bearing a fused furan or a modified furan ring.

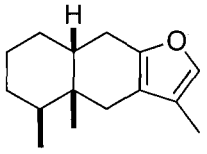


1

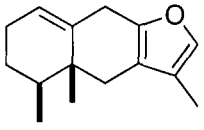
Figure 1.1: The eremophilane framework

The so-called furanoeremophilanes (**Figure 1.2**) represent a large subset of the eremophilane sesquiterpeniods.[1] Members of this family were first isolated as early as 1960 and to date, over two hundred furanoeremophilanes have been reported. The simplest member of the group, furanoeremophilane (**2**), was isolated from the roots of *Petasites officinalis*, and its initial characterization by Novotny and coworkers was built upon extensive degradation studies.[2]

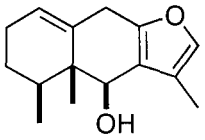
Since the initial discovery of furanoeremophilane (**2**), a vast array of novel furanoeremophilane structures has been reported. Euryopsin (**3**), a dehydroderivative of **2**, was isolated from *Senecio othonaβ* and has been proposed as the biogenetic precursor of 6β-hydroxyeuryopsin (**4**), a recently isolated sesquiterpenoid from the aerial part of *Senecio toluccanus*.[4]



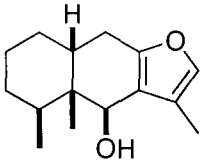
2: Furanoeremophilane



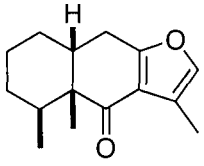
3: Euryopsin



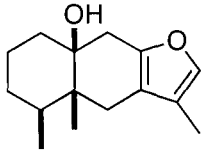
4: 6β-Hydroxyeuryopsin



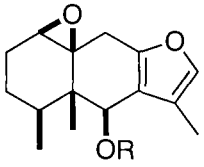
5: Petasalbine



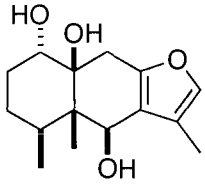
6: Ligularone



7: Tetradymol



8: Senemorin
R = angelate
9: R = H



10: Euryopsol

Figure 1.2: Furanoeremophilanes

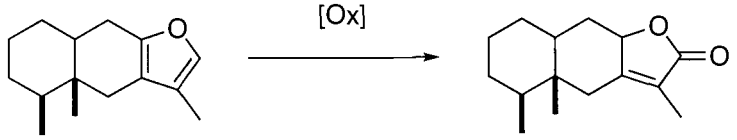
A large number of hydroxylated and keto derivatives of furanoeremophilanes have been isolated, the oxgenation pattern on the furanoeremophilane framework being highly specific to the species of plant from which the compound originated. For instance, petasalbine (**5**) and its oxidized form, ligularone (**6**), were isolated from *Petasites albus*.[5] The characterization of these simple natural products was based upon spectroscopic studies, and the stereochemistry of the secondary alcohol in petasalbine (**5**) was based upon its reactivity profile towards acetylation. During synthetic studies on this furanoeremophilane, petasalbine (**5**) was readily acetylated in the presence of acetic anhydride. However, 6-epipetasalbine failed to undergo acetylation due to the hindered nature of the alcohol and this result confirmed the stereochemical assignment to petasalbine (**5**).

The most notorious of the furanoeremophilanes, tetradymol (**7**), is a toxic substance isolated from *Tetradymia glabrata*, a plant implicated in the poisoning of sheep.[6]

Structural assignment to the more complex furanoeremophilanes has been aided by extensive synthetic studies. For instance, the epoxy-furanoeremophilane senemorin (**8**, R = angelate) was initially isolated from the roots of *Senecio nemorensis*[7] and provided alcohol **9** upon hydrolysis of the ester. The same alcohol **9**, was later isolated from the roots of *Ligularia fischeri*.[8] The stereochemistry of the epoxide in senemorin (**8**) was established

via alkaline hydrolysis, which afforded euryopsol (**10**), a substance previously isolated from the resin of *Euryops floribundus*.[9]

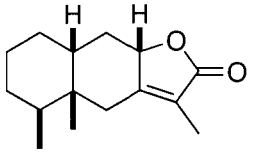
Mild oxidation of the furanoeremophilane nucleus generally leads to the corresponding butenolactone, a transformation that has proven useful in structural determination (**Scheme 1**).



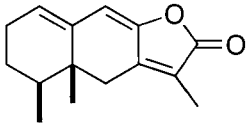
Furanoeremophilane Eremophilenolide

Scheme 1

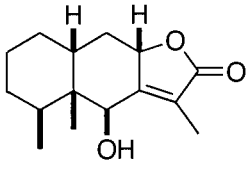
These lactone-based eremophilanes are also isolated as natural products and are collectively known as eremophilenolides (**Figure 1.3**).



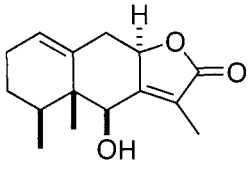
11: Eremophilenolide



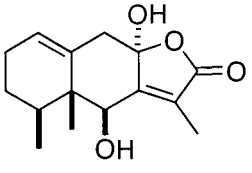
12: Ligularenolide



13: 6β-Hydroxy eremophilenolide



14: Toluccanolide A



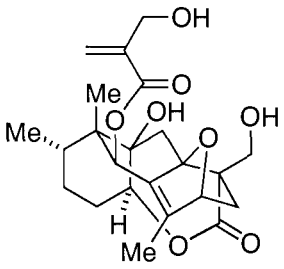
15: Toluccanolide C

Figure 1.3: Eremophilenolides

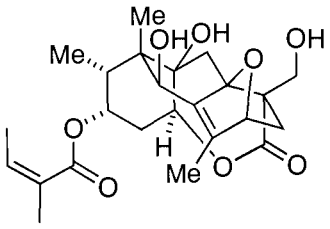
The simplest member of this group, eremophilenolide (**11**), was isolated from *Petasites officinalis* together with furanoeremophilane (**2**). The structural assignment to **11** and many other eremophilenolides was drawn primarily from degradation studies.[2] Ligularenolide (**12**) was isolated from the roots of *Ligularia sibirica*, which is extensively used in traditional Chinese medicine.[10] Another member of this family, 6β-hydroxyeremophilenolide (**13**), was isolated from *Petasites albus* and has been proposed as an oxidation product of petasalbine (**5**).[11] Indeed, Minato has reported the oxidative conversion of petasalbine (**5**) to 6β-hydroxyeremophilenolide (**13**).[12] A related series, the toluccanolides, were isolated from extracts of *Senecio toluccanus,* the same species that produces 6β-hydroxyeuryposin (**4**).[13] Toluccanolide A (**14**) was isolated from the aerial part of the plant and its structural assignment was based upon comparison with synthetic material prepared by Kitagawa.[14] The structure of toluccanolide C (**15**) was confirmed by means of X-ray crystallographic analysis.[13]

Extracts of *Ligularia* species are extensively used in traditional Chinese medicine and, as such, these plants are considered to be a rich source of valuable bioactive metabolites. During a screening program designed to identify these bioactive compounds, a small family of novel eremophilanes were isolated and were collectively designated as ligulaverins (**Figure 1.4**).[15] These substances possess a highly unusual structure, with the major metabolite, ligulaverin A (**16**) being unique. The structure of ligulaverin A was

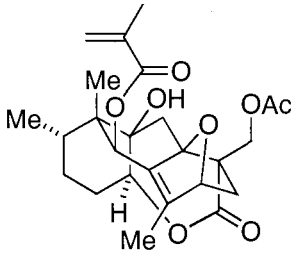
established by a combination of spectroscopic studies and X-ray crystallographic analysis.[16]



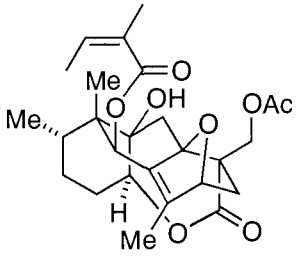
16: Ligulaverin A



17: Ligulaverin B



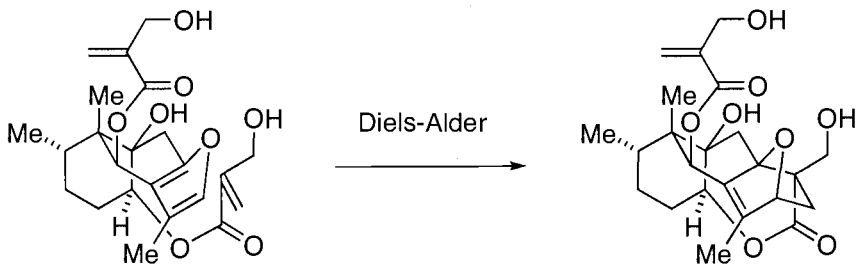
18: Ligulaverin C



19: Ligulaverin D

Figure 1.4: Ligulaverins

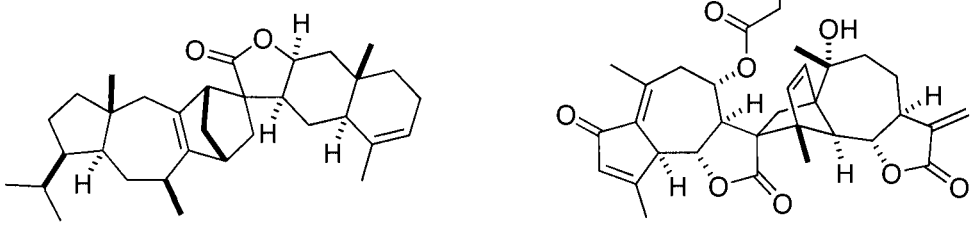
The unusual molecular structure of ligulaverin A has prompted Rankin to offer a provocative hypothesis to explain its formation via an enzymatic intramolecular Diels-Alder reaction (**Scheme 2**) of triol **20**.



20 **16**: Ligulaverin A

Scheme 2

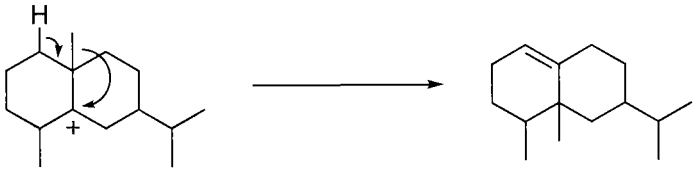
Interestingly, the ligulaverins represent a growing family of secondary metabolites that are believed to originate *via* an enzyme catalyzed Diels-Alder reaction.[17] Although a Diels-Alder biogenesis has been proposed for certain members of the eudesmanolide and guaianolide families of sesquiterpenoids (**Figure 1.5**), there are other isoprenoid structures whose natural origin can be envisioned *via* a Diels-Alder pathway. For instance, the liverwort *Plagiochila moritziana* produces plagiospirolides A (**21**), a Diels-Alder adduct of eudesmanolide.[18] Arteminolide (**22**), isolated from the aerial parts of *Artemisia sylvatica,* may be considered a Diels-Alder adduct of guaianolide.[19]



21: Plagiospirolides A **22**: Arteminolide

Figure 1.5: Isoprenoids presumably formed via Diels-Alder cycloaddition

The eremophilanes were also the first sesquiterpenoids whose structures were found to violate Ruzicka's Isoprene Rule. In order, to account for the failure of the eremophilane skeleton to conform to the Isoprene Rule, Robinson proposed that the eremophilane skeleton originated from a eudesmanoid structure (obeying the Isoprene Rule), which had experienced a suprafacial 1, 2 migration of an angular methyl group to the adjacent angular position (**Scheme 3**).[20]

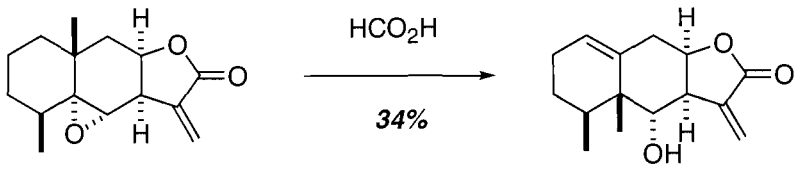


eudesmane skeleton

eremophilane skeleton

Scheme 3

This biogenetic equivalent of a Wagner-Meerwein rearrangement would presumably be triggered by a transient carbocation and would be terminated by loss of a proton to leave a double bond that is characteristic of many natural eremophilanes. To date, only one example of a methyl migration corresponding to the eudesmane to eremophilane transformation has been observed in the laboratory. In 1972, Kitagawa and coworkers reported the conversion of dihydroalantolactone 5α, 6α-epoxide (**23**) to the eremophilane alcohol **24**,[9] but this interesting reaction remains the sole illustration supporting this important biogenetic hypothesis (**Scheme 4**)



23 24

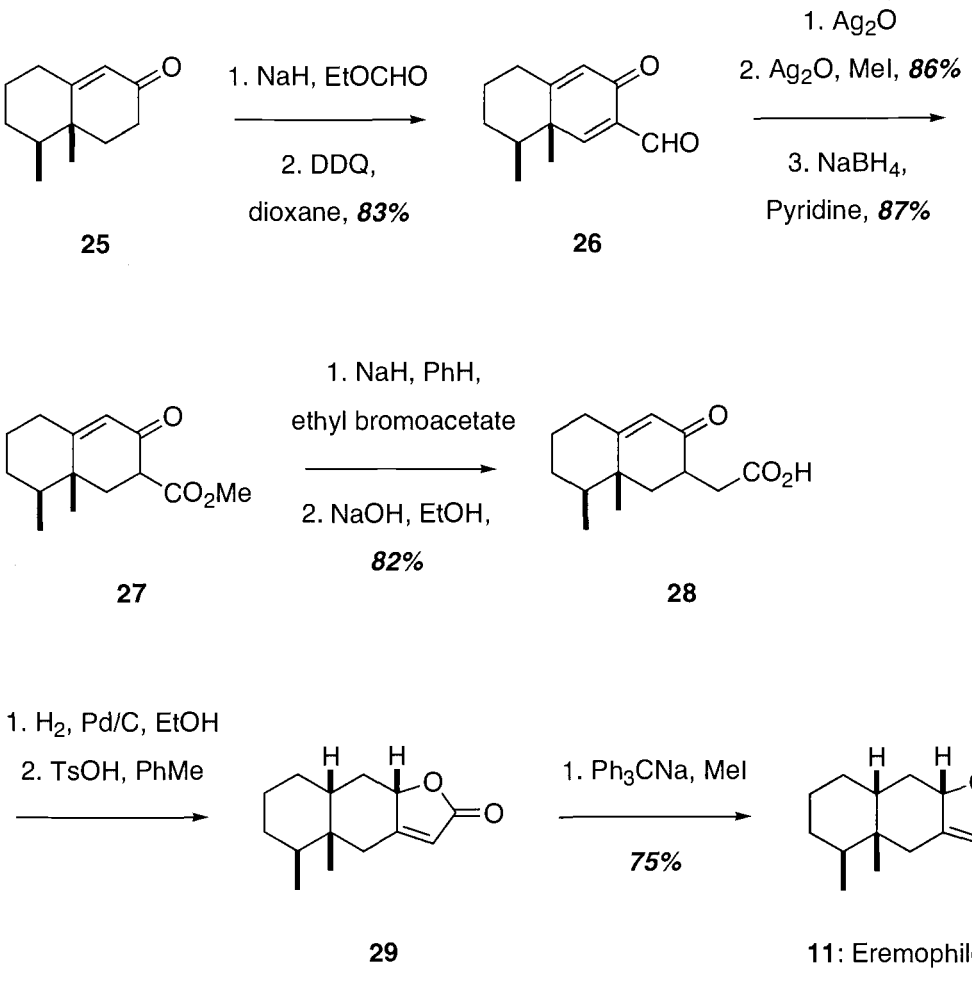
Scheme 4

Alcohol **24** was subsequently converted by Kitagawa into 6β-hydroxyeuroposin (**4**), and thus provided the first *in vitro* correlation between an eudesmanoid and eremophilanoid sesquiterpene.

The furanoeremophilanes have invited a broad range of effort directed towards their total synthesis, and several conceptually different approaches to this family of natural products have been reported.[21] The synthesis of eremophilenolide (**11**) by Piers in 1971 was the first of many successful routes to the furanoeremophilanes.[22] This pioneering endeavor fully confirmed the structural and stereochemical assignment previously made by Novetny to this natural product. Pier's approach took advantage of a Robinson annulation as the key step to install the C5 quaternary center and the *cis*- oriented vicinal methyl groups (**Scheme 5**). Condensation of the resulting enone **25** with ethyl formate followed by dehydrogenation with 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ) provided dienone **26**.

Oxidation of aldehyde **26** with silver oxide was followed by esterification of the resultant carboxylic acid with methyl iodide, and subsequent reduction of the cross-conjugated keto-ester with sodium borohydride afforded **27**.

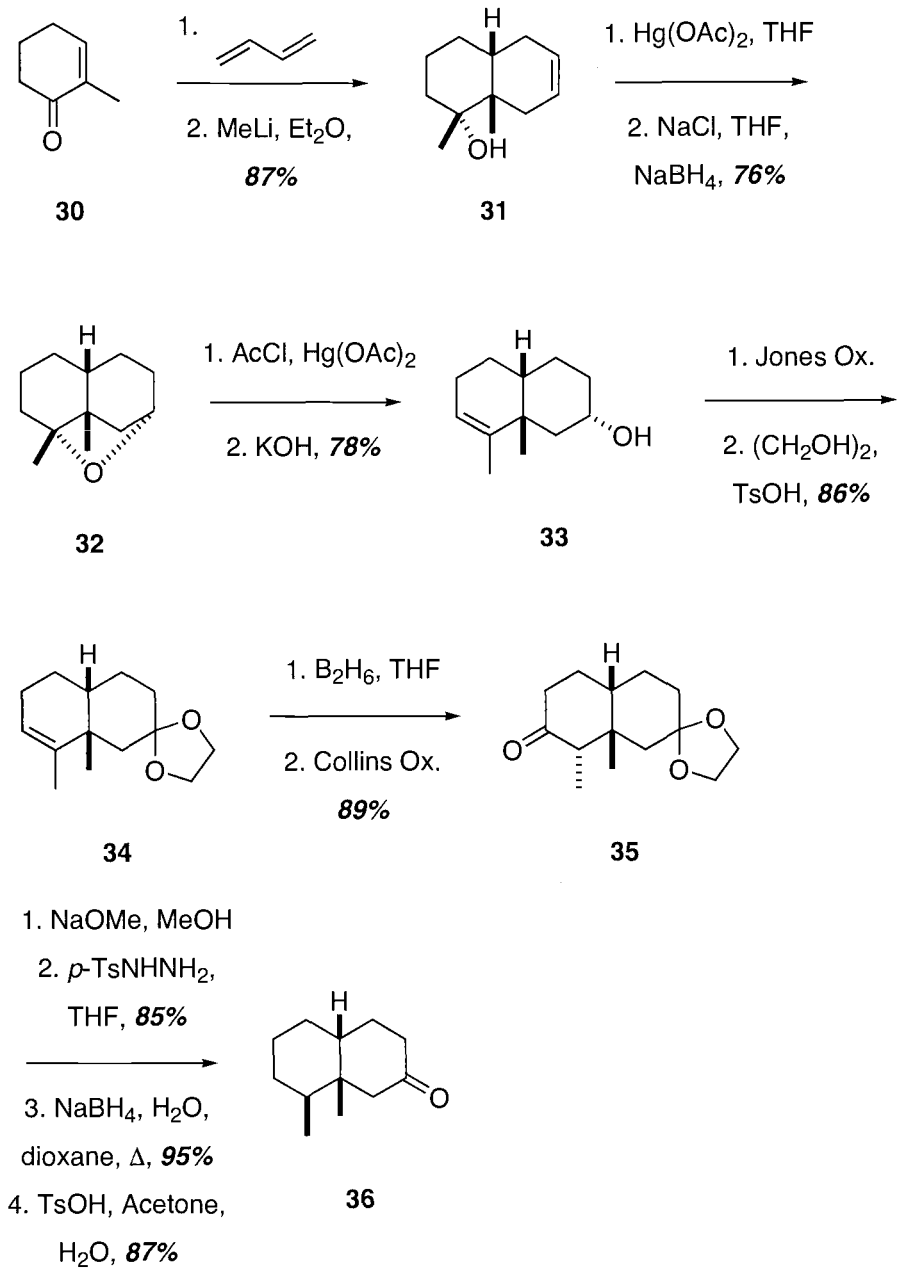
Alkylation of this ketoester followed by decarboxylation yielded the ketoacid **28**.



Scheme 5 Pier's synthesis of Eremophilenolide

Hydrogenation of the enone, and treatment of the saturated ketoacid with *p*-toluenesulfonic acid in refluxing toluene furnished (±)-11-desmethyleremophilenolide **29**. A final methylation of the α, β-unsaturated lactone **29** with trityl sodium and methyl iodide afforded (±)-eremophilenolide **11**.

The approach used by Kitahara to fashion the decalin skeleton of the eremophilanes exploited a bimolecular Diels-Alder reaction.(**Scheme 6**)[23]

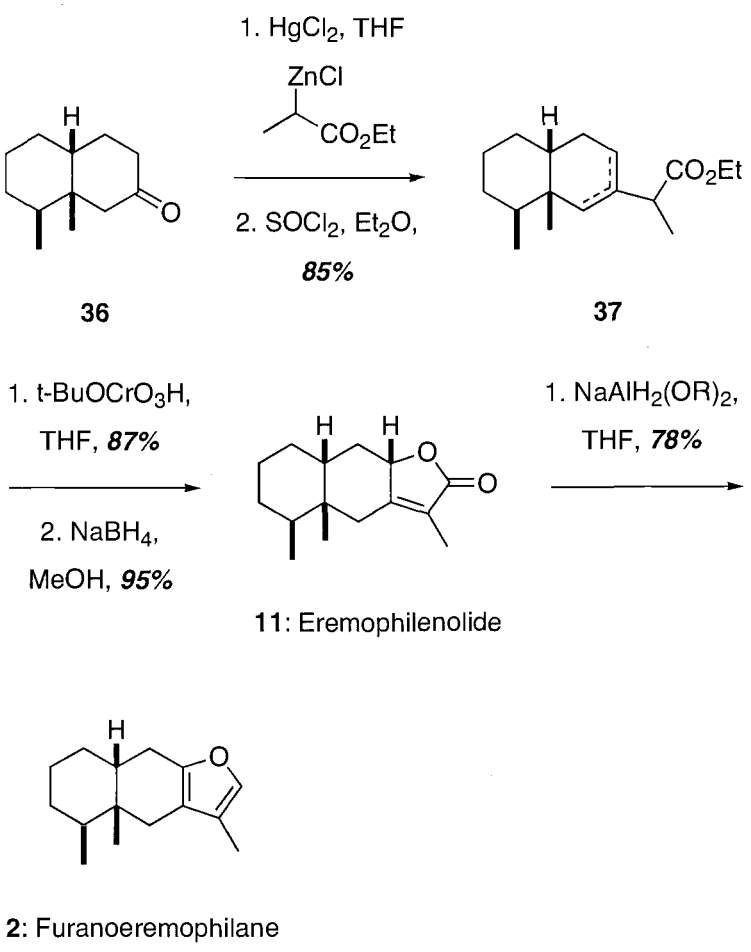


30 **31** **32** **33** **34** **35** **36**

Scheme 6 Kitahara's approach to Eremophilenolide

Diels-Alder cycloaddition of cyclohexenone **30** and butadiene allowed the installation of the C5 quatenary center, and addition of methyllithium to the resulting ketone yielded the tertiary alcohol **31** as the major stereoisomer. Intramolecular oxymercuration provided the means for separation of the major product. Cleavage of the cyclic ether, oxidation, and dioxalane formation yielded **34** which was converted into ketone **35** by a hydroboration-oxidation sequence. The resulting α-methyl ketone was epimerized under basic conditions. Bamford-Stevens deoxygenation and removal of the dioxalane blocking group then gave decalone **36**.

The late-stage installation of the furan residue commenced with a Reformatsky reaction (**Scheme 7**). Allylic oxidation of **37**, followed by stereoselective reduction, gave eremophilenolide (**11**) and final semi-reduction of the butenolide followed by acid-catalyzed dehydration provided furanoeremophilane (**2**).

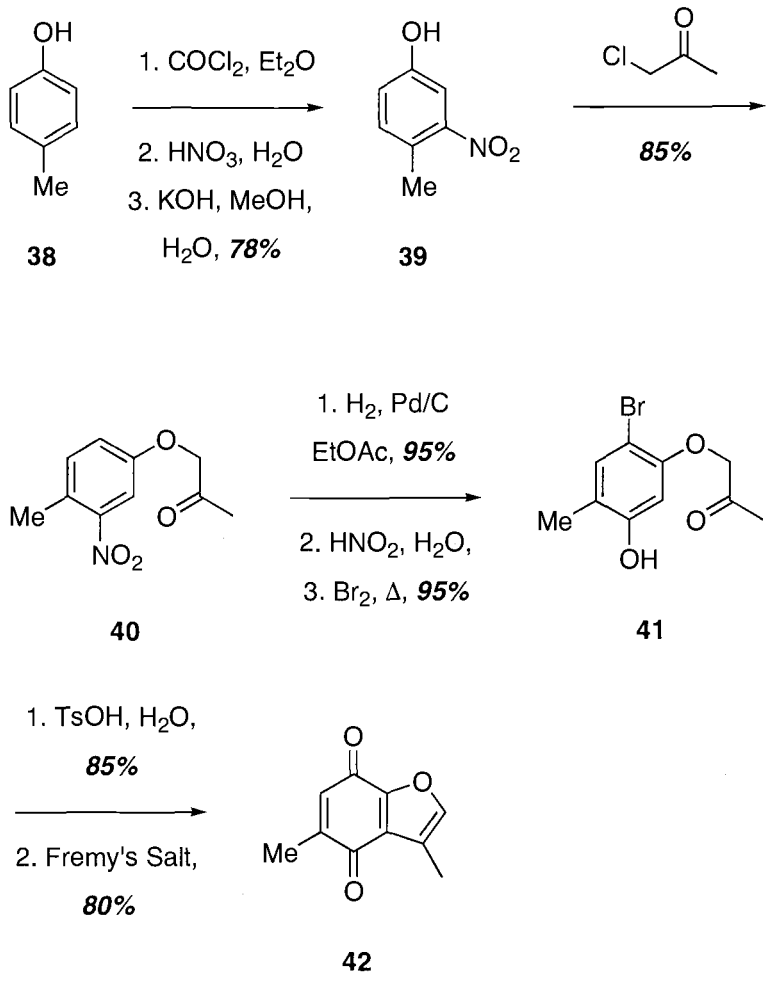


Scheme 7 Kitahara's synthesis of Furanoeremophilane

A different strategy to assemble the furanoeremophilane framework was reported by Bohlmann[24] and by Yamakawa.[25]

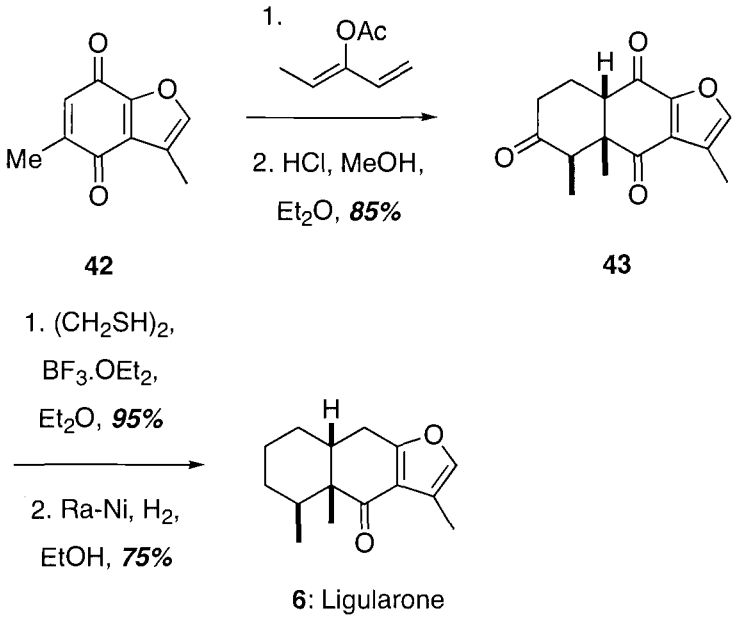
In Bohlmann's synthesis, *p*-cresol **38** was reacted with phosgene and the resulting carbonate was nitrated. Hydrolysis of the bis-nitro carbonate yielded **39** (**Scheme 8**). The latter was alkylated with chloroacetone to give ketone **40**, and reduction of the nitro group followed by bromination of the resulting phenol afforded **41**. Formation of the pivotal furanoquinone **42** was

accomplished by an acid-catalyzed dehydration and final oxidation of the resulting benzofuran.



Scheme 8 Bohlmann's approach to Ligularone

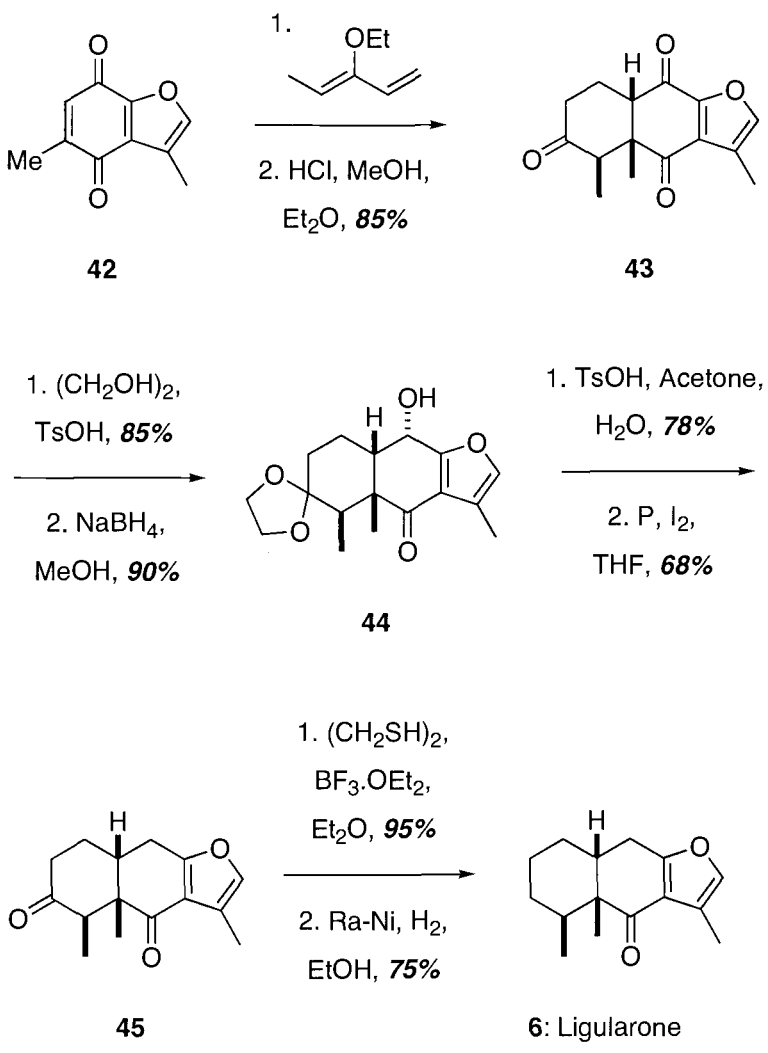
Construction of the furanoeremophilane core from **42** commenced with a Diels-Alder reaction of the furanoquinone with 3-acetoxy-1, 3-pentadiene (**Scheme 9**). After acidic hydrolysis of the cycloadduct, the resulting trione **43** was condensed with ethanedithiol to give a bis-thioketal which was reduced with Raney nickel to (±)-ligularone (**6**).



Scheme 9 Bohlmann's synthesis of Ligularone

In a related approach to (±)-ligularone (**6**) by Yamakawa, furanoquinone **42** was reacted with 3-ethoxy-1, 3-pentadiene (**Scheme 10**).[25] The resulting adduct was hydrolyzed and the triketone **43** was converted to a monodioxalane.

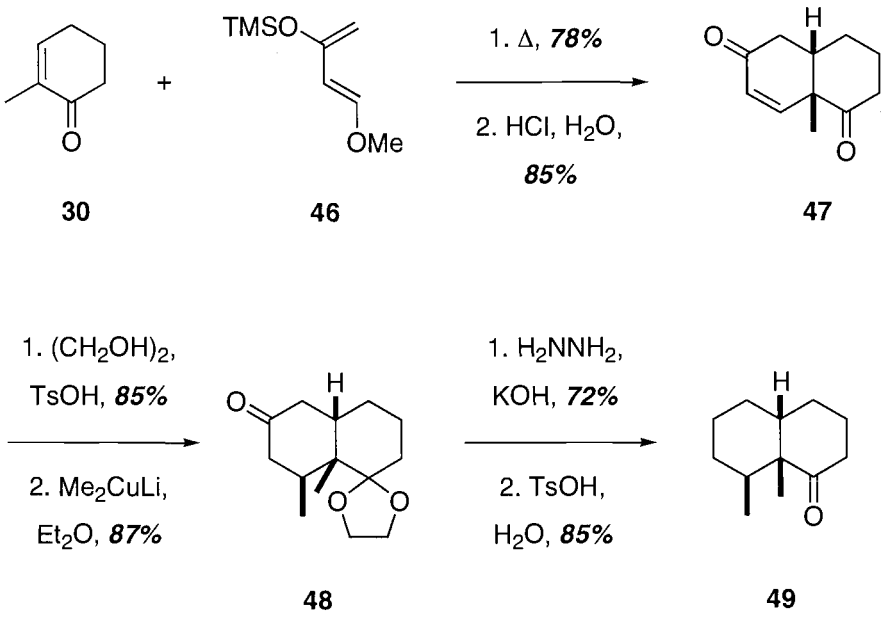
The less hindered of the remaining pair of ketones was reduced with sodium borohydride, and deoxygenation of the resulting furanyl alcohol provided **45**. Final conversion of **45** to (±)-ligularone was accomplished by a strategy identical to that employed by Bohlmann and coworkers.



Scheme 10 Yamakawa's synthesis of Ligularone

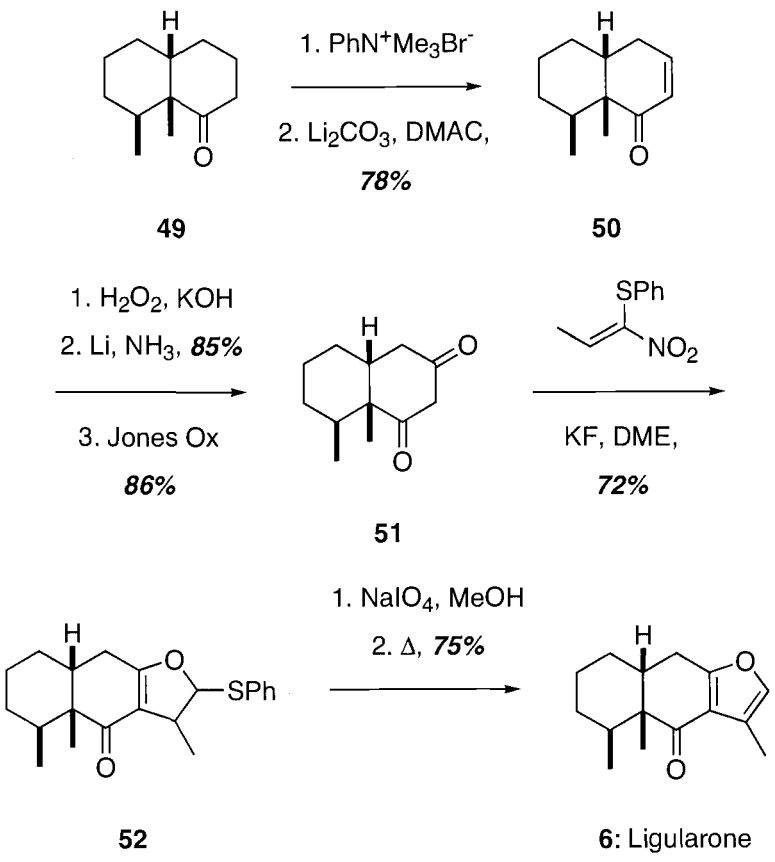
The approach of Yoshikoshi to (±)-ligularone (**6**) also exploits a Diels-Alder cycloaddition to install the C5 quaternary center[26] (**Scheme 11**). 2-Methylcyclohex-2-enone (**30**) was reacted with the Danishefsky diene **46**, and the resulting adduct was hydrolyzed to provide enone **47**. After selective ketalization of the non-conjugated carbonyl, the enone was treated with lithium dimethylcuprate to produce **48** in which addition to the convex face of the enone had occurred. Ketone **48** was subjected to Wolff-Kishner reduction and

the dioxalane was then removed under acidic conditions to give the decalone **49**.



Scheme 11 Yoshikoshi's approach to Ligularone

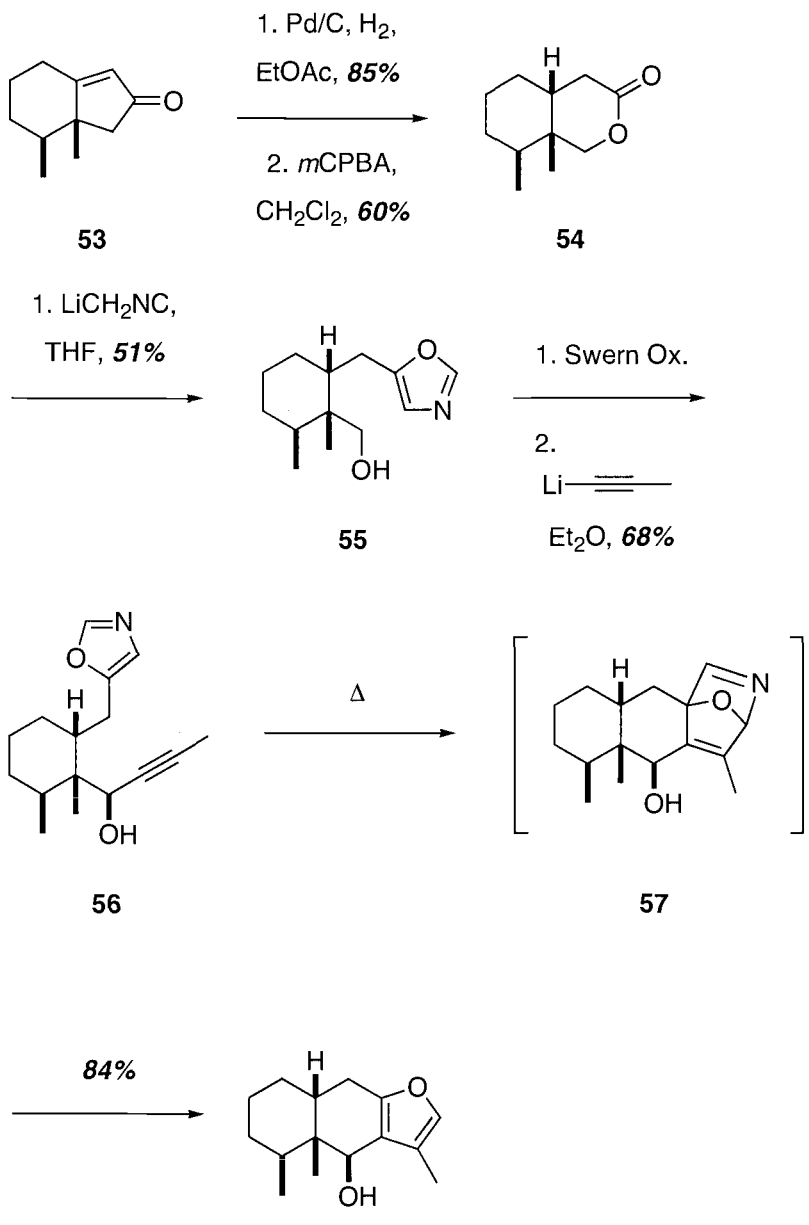
Installation of the furan moiety in Yoshikoshi's synthesis commenced with conversion of the decalone **49** to enone **50** via elimination of the α-bromoketone. Base catalyzed epoxidation of **50** was followed by a dissolving metal reduction, and the resulting mixture of diols was oxidized to the 1, 3-dione **51**. Michael addition of **51** to (*Z*)-1-nitro-1-thiophenylpropene, followed by condensation, with loss of the nitro group furnished the dihydrofuran **52**. Final oxidation of the thiophenyl substituent and thermolysis of the resulting sulfoxide furnished (±)-ligularone (**6**).



Scheme 12 Yoshikoshi's synthesis of Ligularone

The approach used by Jacobi to assemble the furanoeremophilane skeleton employed an elegant Diels-Alder/retro-Diels-Alder strategy[27] (Bis-heteroannulation) (**Scheme 13**).[28]

The Jacobi synthesis of petasalbine (**5**) commenced from enone **53**, previously utilized by Evans[29] in his bakkenolide synthesis (**Scheme 13**). Hydrogenation of **53** followed by a regioselective Baeyer-Villiger oxidation produced lactone **54**. This lactone underwent a modified Schollkopf reaction to give the oxazole **55**.

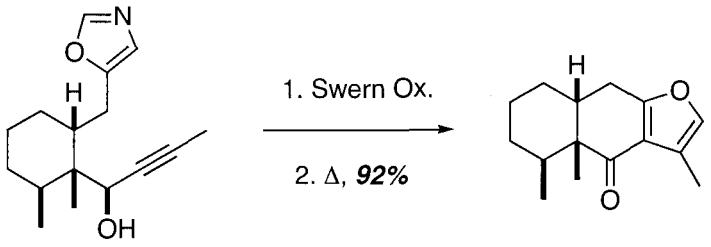


Scheme 13 Jacobi's synthesis of Petasalbine

The resulting primary alcohol was oxidized to an aldehyde which after a Felkin addition by 1-lithiopropyne afforded the pivotal oxazole-acetylene **56**. Pyrolysis of **56** in dichlorobenzene caused an intramolecular Diels-Alder addition of the alkyne to the oxazole and a subsequent retro-Diels-Alder

fragmentation of **57** with the loss of hydrogen cyanide. The result was a remarkably efficient synthesis of (±)-petasalbine (**5**).

In an extension of this methodology, Jacobi showed that Swern oxidation of alcohol **56**, followed by thermolysis of the resulting ketone, produced (±)-ligularone (**6**) (**Scheme 14**).

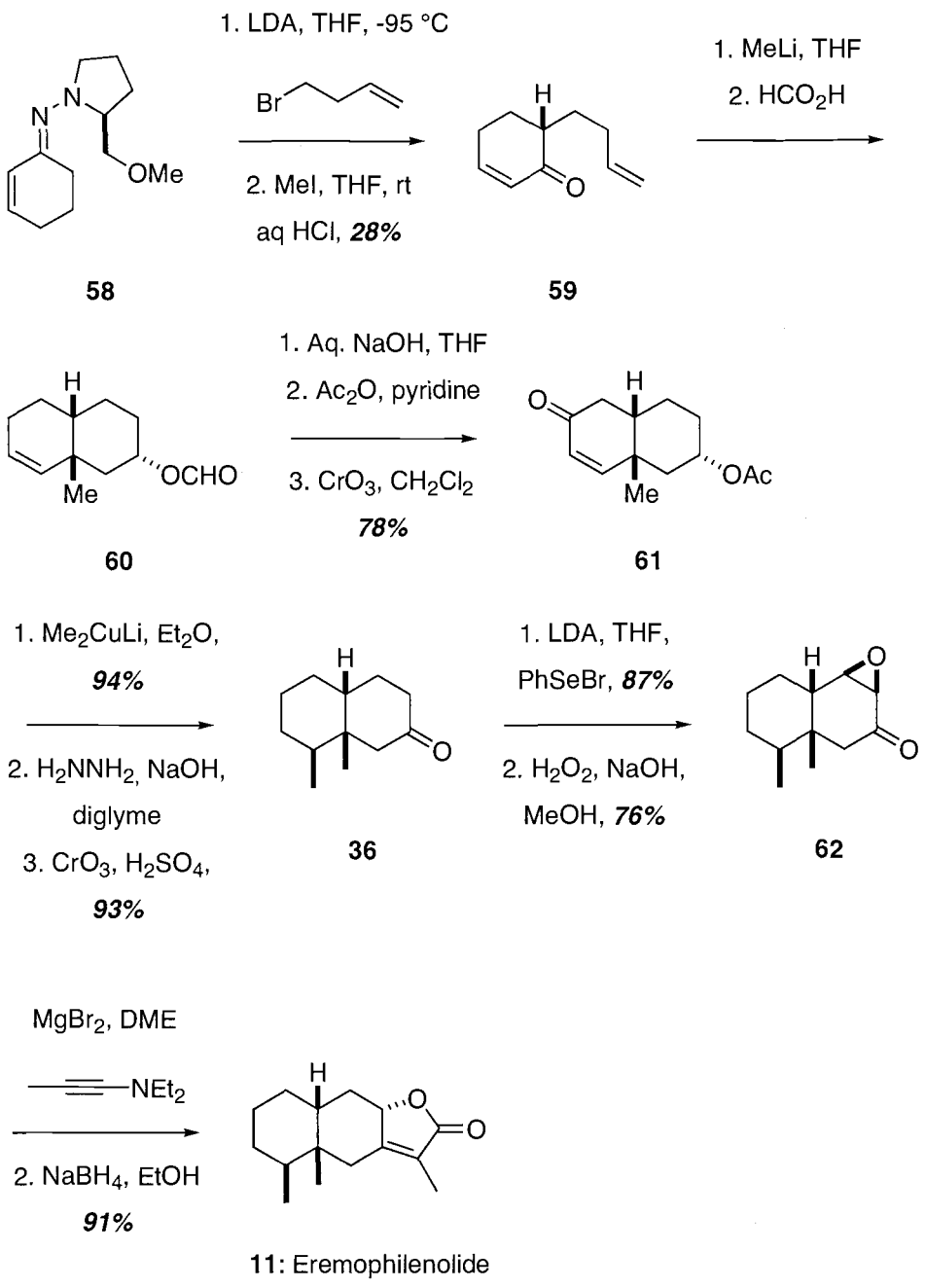


56 **6:** Ligularone

Scheme 14 Jacobi's synthesis of Ligularone

The first asymmetric synthesis of a furanoeremophilane was reported by Pennanen,[30] who employed chemistry developed by Enders[31] to introduce asymmetry in the course of an alkylation of cyclohexenone (**Scheme 15**).

Alkylation of the SAMP hydrazone **58** of cyclohexenone with 1-bromo-3-butene led to (*S*)-6-(3-butenyl)cyclohex-2-enone (**59**) after removal of the chiral auxiliary. The enone **59** was converted to the known decalin **60** using methodology reported by Marshall in his synthesis of fukinone.[32] The vicinal methyl group was introduced into enone **61** by an approach similar to Yoshikoshi's and gave ketone **36**. Phenylselenation of **36** followed by oxidation with basic hydrogen peroxide resulted in the formation of epoxyketone **62**.



Scheme 15 Pennanen's synthesis of Eremophilenolide

Lewis-acid mediated addition of 1-dimethylaminopropyne provided an unsaturated amide and also triggered an epoxide-carbonyl rearrangement. Final reduction of the resultant ketone and lactonization yielded (+)-

eremophilenolide (**11**) whose absolute configuration matched that of the natural material.

In summary, several conceptually different approaches to the furanoeremophilane sesquiterpenoids have been reported. It is noteworthy that most of these approaches have relied upon classical annulation methods and have employed a strategy in which the furan is appended to a preformed decalin platform in the latter stages of the synthesis.

Reference

1. Pinder, A. R. In *Progress in the chemistry of Organic Natural Products*, W. Herz, H. Grisebach, G. W. Kirby, Ed., Wien Springer Verlag: New York, **1977**, *34*, 81.
2. Novotny, L.; Herout, V.; Sorm, F. *Tetrahedron Lett.* **1961**, 697.
3. Bohlmann, F.; Knoll, K. H.; Zdero, C.; Mahanta, P. K.; Grenz, M.; Suwita, A.; Ehlers, D.; Van, N. L.; Abraham, W. R. Natu, A. R. *Phytochemistry* **1977**, *16*, 965.
4. Arciniegas, A.; Perez-Castorena, A. L.; Parada, G.; Villasenor, J. I.; De Vivar, R. *Revista Latinoamericana de Quimica* **2000**, *28*, 131.
5. Ishii, H.; Tozyo, T.; Minato, H. *Tetrahedron* **1965**, *21*, 2605.
6. Jennings, P. W.; Reeder, S. K.; Hurley, J. C.; Caughlan, C. N.; Smith, G. D. *J. Org. Chem.* **1974**, *39*, 3392.
7. Novotny, L.; Krojidlo, M.; Samek, Z.; Kohoutova, J.; Sorm, F. *Collect. Czech. Chem. Commum.* **1973**, *38*, 739.
8. (a) Moriyama, Y.; Sato, T.; Nagano, H.; Tanahashi, Y.; Takahashi, T. *Chem. Lett.* **1972**, 637. (b) Sato, T.; Moriyama, Y.; Nagano, H.; Tanahashi, Y.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 112.
9. Eagle, G. A.; Rivett, D. E. A.; Williams, D. H.; Wilson, R. G. *Tetrahedron* **1969**, *25*, 5227.

10. Ishizaki, Y.; Tanahashi, Y.; Takahashi, T.; Kazuo, T. *Tetrahedron* **1970**, *26*, 5387.

11. Novotny, L.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commum.* **1964**, *29*, 2189.

12. Ishii, H.; Tozyo, T.; Minato, H. *J. Chem. Soc. C* **1966**, 1545.

13. Perez, A-L.; Vidales, P.; Cardenas, J.; Romo de Vivar, A. *Phytochemistry* **1991**, *30*, 905.

14. Kitagawa, I.; Shibuya, H.; Kawai, M. *Chem. Pharm. Bull.* **1977**, *25*, 2638.

15. Zhao, Y.; Parsons, S.; Baxter, R. L.; Jia, Z-J.; Sun, H-D.; Rankin, D. W. H. *Chem. Commun.* **1996**, *21*, 2473.

16. Zhao, Y.; Parsons, S.; Baxter, R. L.; Jia, Z-J.; Sun, H-D.; Rankin, D. W. H. *Tetrahedron* **1997**, *53*, 6195.

17. (a) Ichihara, A.; Oikawa, H. In *Comprehensive Natural Products Chemistry*; Sankawa, U., Ed.; Barton, D., Nakanishi, K., Meth-Cohn, O., Series Eds.; Polyketides and Other Secondary Metabolites, Vol 1; Elsevier: New York, 1999; 367. (b) Laschat, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 289.

18. Sporle, J.; Becker, H.; Gupta, M. P.; Veith, M.; Huch, V. *Tetrahedron* **1989**, *45*, 5003.

19. Lee, S. H.; Kim, M. J.; Bok, S. H.; Lee, H.; Kwon, B. M. *J. Org. Chem.* **1998**, *63*, 7113.

20. Robinson, R. In *The Structural Relations of Natural Products*. Oxford University Press: London, **1955**, 12.

21. For introductory discussions in furanoeremophilanes synthesis. Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, In *The Total Synthesis of Natural Products,* J. ApSimon Ed., Wiley: New York, **1983**, *5*, 202.

22. Piers, E.; Geraghty, M. B.; Smillie, R. D. *Chem Commun.* **1971**, 614.

23. Nagakura, I.; Maeda, S.; Ueno, M.; Funamizu, M.; Kitahara, Y. *Chem Lett.* **1975**, 1143.

24. Bohlmann, F.; Forster, H-J.; Fischer, C. H. *Justus Liebigs Ann. Chem.* **1976**, 1487.

25. Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1977**, *25*, 2535.

26. Miyashita, M.; Kumazawa, T.; YoshiKoshi, A. *Chem. Lett.* **1979**, 163.

27. (a) Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (b) Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, Bradley, A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585.

28. (a) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7749. (d) Jacobi, P. A. In *Advances in Hetercyclic Natural Product Synthesis*; JAI: New York, **1992**, 251.

29. Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453.

30. (a) Pennanen, S. I. *Acta Chem. Scand.* **1980**, *34*, 261. (b) Pennanen, S. I. *Acta Chem. Scand.* **1981**, *35*, 555.

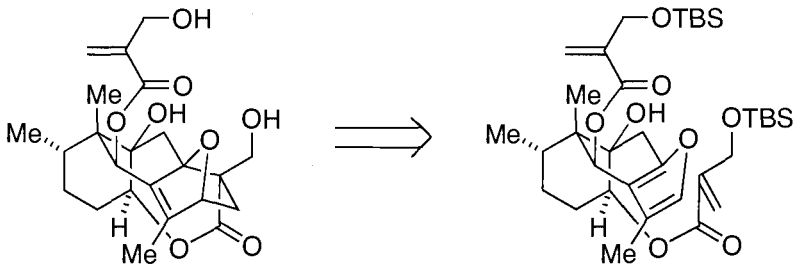
31. Enders, D.; Eichenauer, H.; Bas, U.; Schubert, H.; Kremer, K. A. M. *Tetrahedron* **1984**, *40*, 1345.

32. Marshall, J. A.; Cohen, G. M. *J. Org. Chem.* **1971**, *36*, 877.

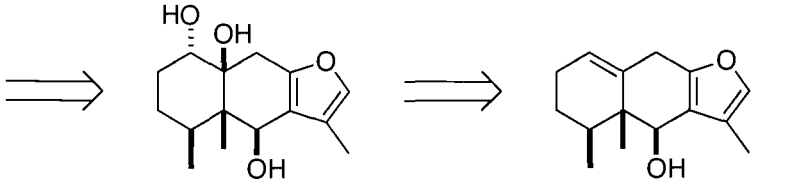
Chapter II.

Bis-Heteroannulation Approach to the Furanoeremophilane

The unique and complex architecture of furanoeremophilanes, such as the ligulaverins, coupled with their largely unexplored potential in medicine or as tools for biological studies make these natural products attractive targets for total synthesis. Further, our interest in developing a synthetic approach to the furanoeremophilane skeleton was inspired in part by the intriguing biosynthesis of the ligulaverins. Our initial synthetic plan for ligulaverin A (**16**) was patterned along biomimetic lines and is depicted in **Scheme 16**.



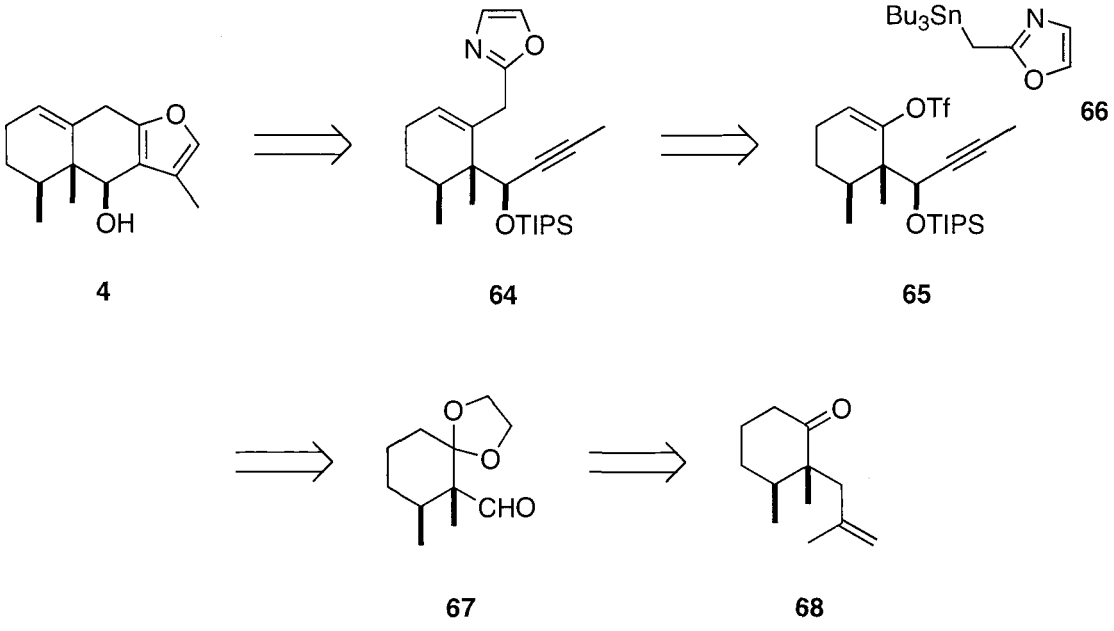
16: Ligulaverin A **63**



10: Euryopsol **4**: 6β-hydroxyeuryopsin

Scheme 16

The central disconnection in our planned synthesis of ligulaverin A (**16**) is designed around its presumed biosynthesis involving an intramolecular Diels-Alder reaction. This led to the initial goal of constructing a protected version of the cycloaddition precursor **63**.[1] A further disconnection of the α-hydroxymethacrylate side chain anchors our approach to a natural furanoeremophilane, euroypsol (**10**).[2] Access to the *trans* diol moiety of euroypsol (**10**) was envisioned from the tricyclic olefin, 6β-hydroxyeuryopsin (**4**). As such, 6β-hydroxyeuryopsin (**4**) emerged as the primary focus of our planning exercise. At the outset of our synthesis, several strategies were considered for gaining access to 6β-hydroxyeuryopsin (**4**). Initially, our preferred route was based upon Jacobi's bis-heteroannulation methodology.[3] (**Scheme 17**)

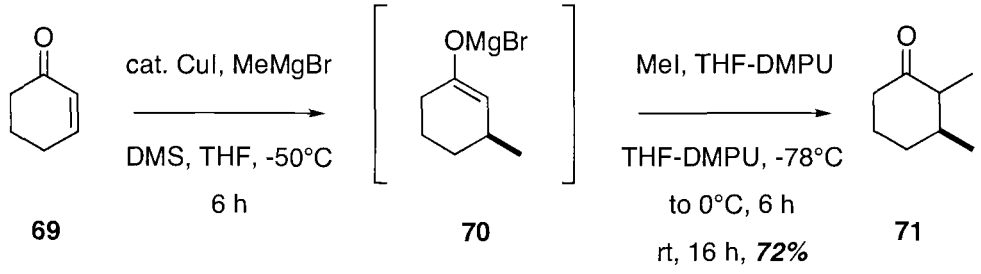


Scheme 17

According to this precept, our synthetic plan for 6β-hydroxyeuryopsin (**4**), would involve the pivotal bis-heteroannulation precursor **64** which would originate from a Stille cross coupling[4] of the triflate **65** with the readily available oxazole stannane **66**. The vinyl triflate **65** would, in turn, originate from the known ketone **68**[5] *via* aldehyde **67**.

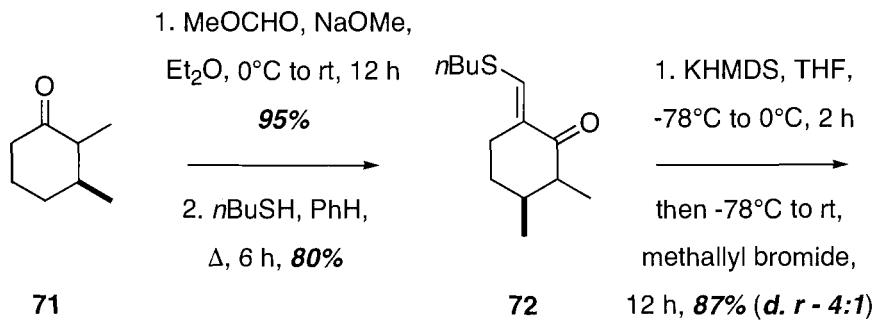
Based on this analysis, our studies initially focused on a convenient pathway for the preparation of the vinyl triflate **65** in racemic form. Critical to the success of our synthetic plan was the early installation of the vicinal methyl groups in the required *cis* orientation. Another important consideration in our plan for the synthesis of ketone **68** was that the approach could, in principle, be extended towards an asymmetric synthesis.

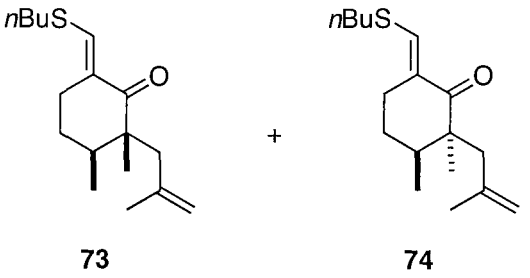
With these constraints in mind, our synthesis of **68** commenced with the copper catalyzed conjugate addition of methylmagnesium bromide to cyclohex-2-enone **69**.[5] Alkylation of the transient magnesium enolate **70** with methyl iodide provided the feedstock ketone **71** as 4:1 mixture of *trans-cis* isomers (**Scheme 18**).[6]



Scheme 18

Our next goal was the installation of the vicinal *cis*-dimethyl group present in the natural product. Our plan to accomplish this goal involved the use of Ireland's regioselective alkylation methodology.[7] In the event, the kinetic enolate of ketone **71** was formylated and the resulting hydroxymethylene ketone was converted to the vinylogous thiolester **72**.[8] Alkylation of the potassium enolate of thiolester **72** with methallyl bromide provided **73** and **74** in the ratio 4:1 respectively (**Scheme 19**).[9]

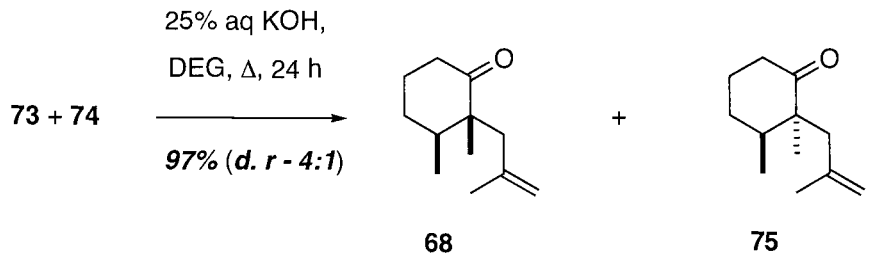




Scheme 19

As a consequence of the alkylation of **72**, we achieved two important goals. The potentially problematic C5 quaternary center and the desired *cis*-oriented methyl substituents were introduced in a highly efficient manner.

Final hydrolytic removal of the *n*-butylthiomethylene blocking group was readily accomplished with the aid of a 25% aqueous solution of potassium hydroxide in refluxing diethylene glycol (DEG) (**Scheme 20**).



68 **75**

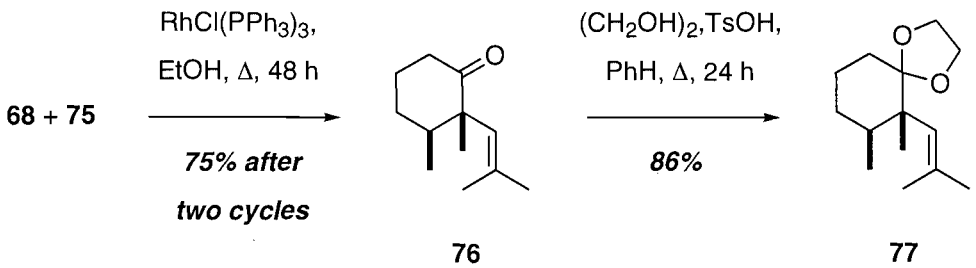
Scheme 20

This short sequence, previously employed by Piers in his synthesis of aristolone,[8] under optimal conditions provided multigram quantities of the ketone **68** and set the stage for further elaboration to the required vinyl triflate **65**. The inseparable mixture of ketone **68** and **75** was used as such.

At this juncture, several objectives had to be met to complete the conversion of ketone **68** to the aldehyde **67**. These tasks included protection of the sterically hindered ketone, isomerization of the *exo* methylene function and oxidative cleavage of the resulting ancillary trisubstitued olefin. Although, these operations could be viewed as seemingly simple tasks, meeting these goals in practice proved to be extremely challenging. Fortunately, the ketone **68** allowed a degree of flexibility in our strategy for elaboration to aldehyde **67**.

Our studies initially focused upon the isomerization of the *exo* methylene group to its *endo* isomer. The use of transition metal complexes for isomerization of olefins has good precedent, and several metal complexes,

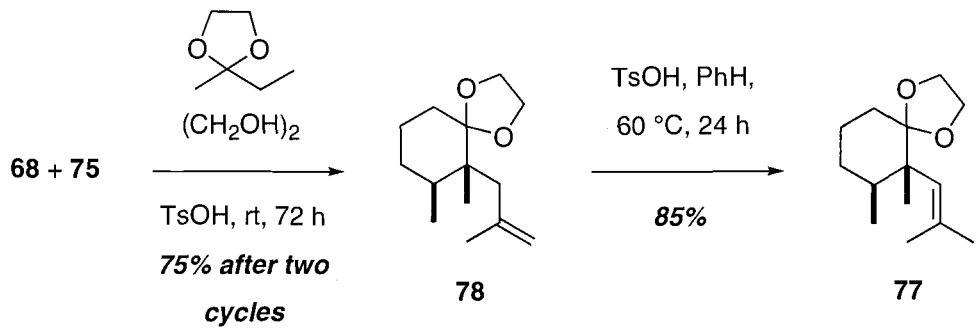
primarily rhodium and palladium complexes have been developed for this transformation.[10] After screening a variety of metal complexes, Wilkinson's catalyst (chlorotristriphenylphosphinorhodium), was found to be an effective catalyst for this isomerization. For this reaction, the mixture of ketone **68** and **75** were heated at reflux in ethanol for 48 h to effect a smooth isomerization (**Scheme 21**). The product, ketone **76**, was carefully purified by silica gel chromatography to yield a single isomer. The recovered ketones **68** and **75** were resubjected to the isomerization conditions and after two cycles provided ketone **76** in good overall yield. The next phase of this endeavor was the installation of the ketone blocking group. Protection of ketone **76** proved to be extremely difficult, presumably reflecting steric hinderance by the neighboring quaternary center. The ketal **77** was eventually prepared using forcing conditions over a longer period than is usually required for ketalization.



Scheme 21

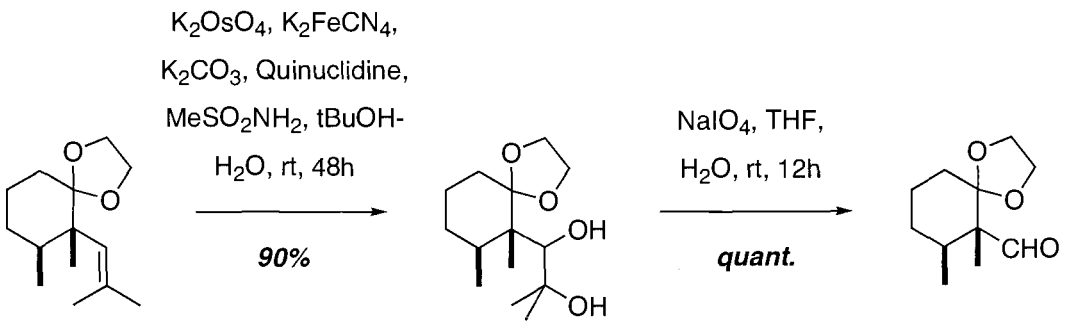
Although this sequence proved amenable to moderate scale up (~1.0 g), the isomerization was erratic on a larger scale. In particular, the isomerization was highly dependent upon the source and age of the rhodium catalyst and often resulted in poor conversion.

Eventually, these problems became an insurmountable obstacle on a preparative scale, and an alternative plan was sought. The sequence (**Scheme 22**) that proved to be most convenient on a preparative scale started with transketalization of the ketone **68**.[11] The resulting pure ketal **78** was smoothly isomerized to the trisubstituted olefin **77** with a catalytic amount of *p*-toluenesulfonic acid in benzene. This transformation proved to be very clean and the product was routinely used without further purification.



Scheme 22

Ozonolysis of **77**, followed by a reductive workup, was initially used to cleave the trisubstituted olefin to aldehyde **67**,[12] but unfortunately the reaction was erratic with respect to yield. A workable alternative to ozonolysis proved to be a two-step Lemieux-Johnson procedure[13] (**Scheme 23**). Osmylation of **77** was effected using the Tsuji-Sharpless two-phase protocol.[14] The reaction required the use of 5% potassium osmate and quinuclidine as the ligand to furnish the diol **79** in excellent yield. Cleavage of the glycol **79** was then readily accomplished with an excess of sodium periodate,[15] or alternatively with lead tetraacetate.[16]

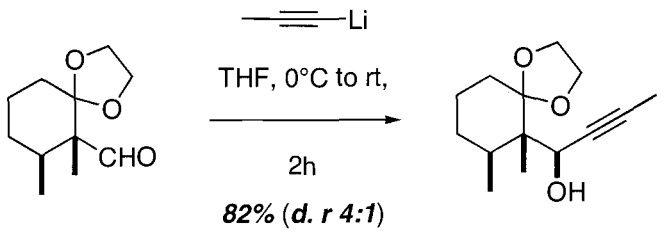


77 **79** **67**

Scheme 23

This route, which requires eight steps from cyclohexenone **69** to provide aldehyde **67**, was hardly ideal. However, it sufficed for our purposes.

With aldehyde **67** in hand, our attention turned to the next phase of our plan. The stereoselective addition of nucleophiles to α-chiral aldehyde has developed into an important tool for the construction of stereogenic alcohols.[17] As anticipated from a stereochemical analysis based upon the Felkin-Ahn principle, addition of 1-lithiopropyne to aldehyde **67** afforded the desired alcohol **80** as a readily separable crystalline solid in good yield. (**Scheme 24**)



67 **80**

Scheme 24

X-ray diffraction analysis of **80** fully confirmed the relative stereochemistry as shown (**Figure 2.1**).

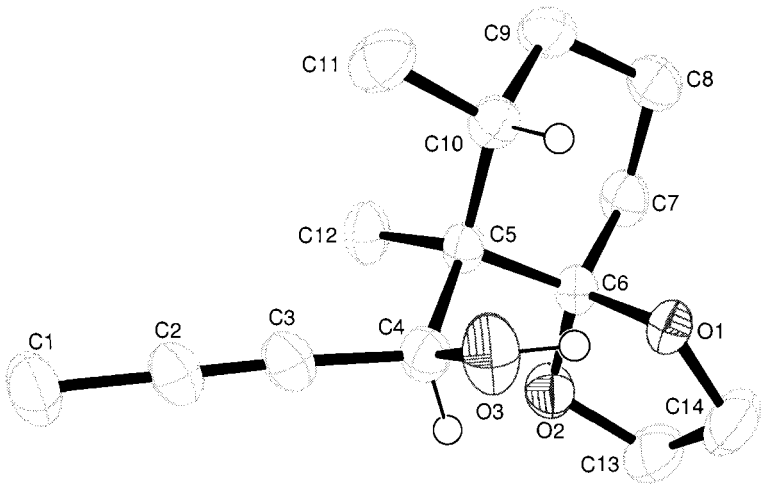
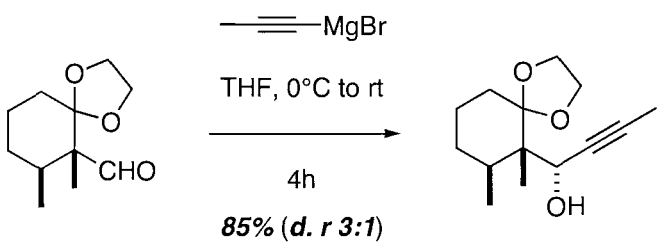


Figure 2.1

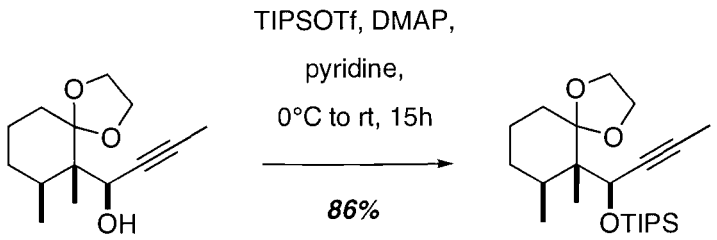
The stereoselectivity observed from the reaction of **67** to give **80** is likely due to stereoelectronic effects (the Felkin-Ahn argument) as suggested by Jacobi, whose synthesis of petasalbine (**5**) also featured such a stereoselective lithiopropyne addition. Interestingly, the use of propynylmagnesium bromide[18] with **67** resulted in reversal of the alcohol configuration in **80** (**Scheme 25**). This observation is consistent with a chelation-controlled model for the addition.



67 **81**

Scheme 25

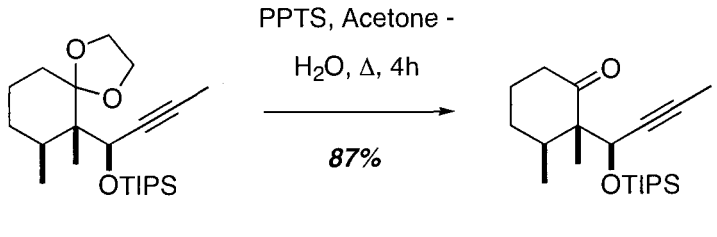
The secondary alcohol **80** was smoothly converted to the triisopropylsilyl ether **82** (**Scheme 26**) in a reaction which required the use of a stoichiometric amount of 4-dimethylaminopyridine (DMAP).[19] Inspection of the ^{13}C NMR spectrum of **82** revealed the presence of two sets of signals for the acetylene region presumably due to conformational isomers resulting from restricted rotation around the proximal quaternary center. This observation was confirmed by desilylation of **82**, which cleanly produced alcohol **80**.



80 **82**

Scheme 26

Removal of the ketone blocking group was smoothly effected under mild acidic conditions in refluxing aqueous acetone (**Scheme 27**).[20]

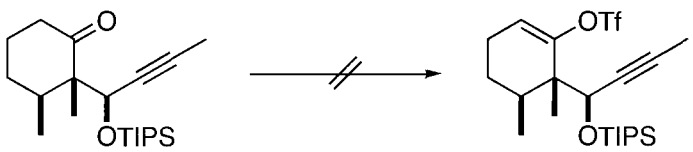


82 **83**

Scheme 27

With a reliable synthesis of ketone **83** completed, our next task was its conversion to vinyl triflate **65**. Initial attempts at triflation of the potassium

enolate[21] of ketone **83** with Comins reagent[22] yielded an unidentified product. Likewise, attempts to form the lithium enolate of **83** with lithium diisopropylamide (LDA) proved unsuccessful since deuterium exchange studies revealed no incorporation of deuterium into ketone **83**. The use of triflic anhydride and 2, 6-di-*tert*-butylpyridine as reported by Snider[23] resulted in complete decomposition of **83** (**Scheme 28**).

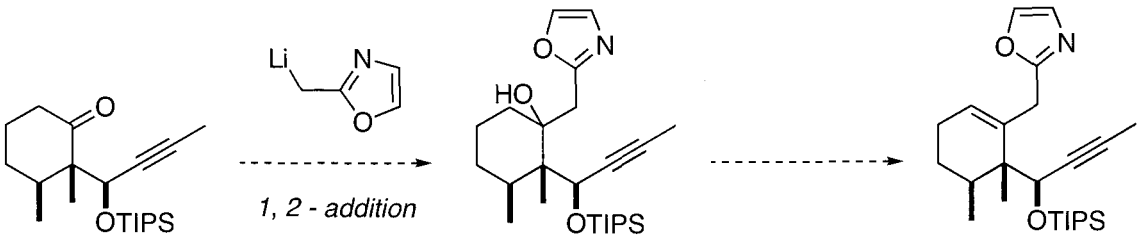


83 **65**

Scheme 28

These negative results suggested that there was steric hindrance, associated with the presence of the quaternary center and the adjacent secondary triisopropylsilyl ether, which prevented the final conversion of **83** to **65**.

These discouraging results prompted us to investigate a new approach to a furanoeremophilane precursor (**Scheme 29**). This new plan involved 1, 2-addition of lithiated 2-methyloxazole to the previously prepared ketone **83**, and draws precedence from studies by Evans during his synthesis of phorboxazole A.[24]

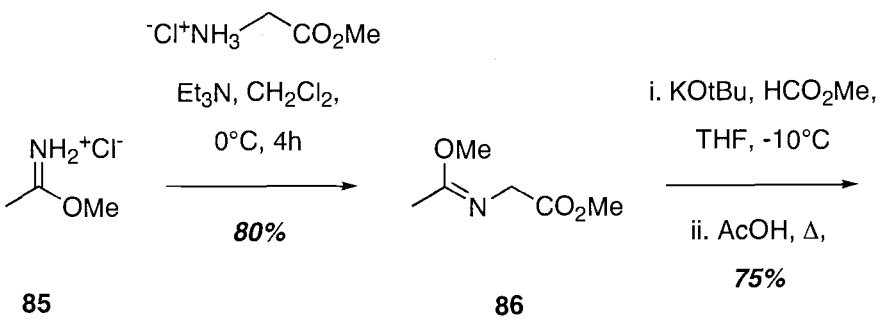


83 **84** **64**

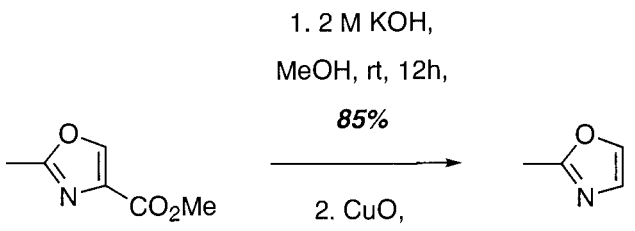
Scheme 29

With this design concept in mind, the requiste 2-methyoxazole (**88**) was prepared by a known route and is outlined in **Scheme 30**.[25]

The synthesis of 2-methyoxazole (**88**) commenced with the condensation of methyl acetimidate hydrochloride **85** with glycine methyl ester in the presence of triethylamine. The resulting ester **86** was formylated and the resulting potassium salt of the ester was treated with hot glacial acetic acid to provide the oxazole **87** in good yield. Ester **87** was saponified and decarboxylated[26] to yield 2-methyloxazole (**88**).



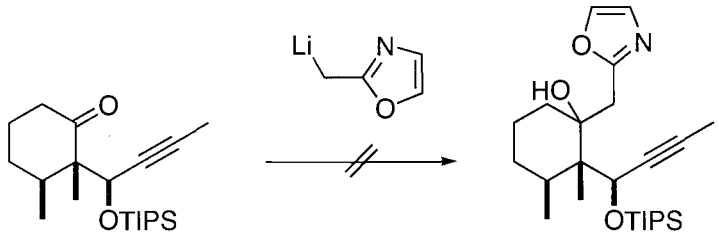
85 **86**



87 **88**

Scheme 30

Selective metalation of the oxazole **88** was effected using lithium diethylamide and provided a bright yellow solution of 2-lithiomethyloxazole. However, much to our disappointment, the lithiated oxazole showed no inclination to undergo addition to ketone **83** (**Scheme 31**).



83 **84**

Scheme 31

Attempts to enhance the reactivity of the ketone **83** by the use of cerium salts also proved unsuccessful.[27]

This negative outcome provided further testimony to the high risk associated with attempts to conduct chemistry proximal to a quaternary center, and mandated that a new strategy be devised for extending our route to the furanoeremophilane system.

Experimental Section

General Experimental

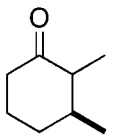
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone under an argon atmosphere. Acetonitrile, dichloromethane, diisoproylamine and triethylamine were distilled from calcium hydride under argon. All solvents used for routine isolation of products and for chromatography were reagent grade. Moisture and air sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flame dried under a stream of dry argon, and glass syringes were oven dried at 120 °C and cooled in a dessicator over anhydrous calcium sulfate prior to use. Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure.

Analytical thin layer chromatography (TLC) was performed using precoated glass E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light, and/or by heating the plate after dipping in a 3% solution of vanillin in 0.2 M sulfuric acid in ethanol or a 1% solution of potassium permanganate in 0.02% 1N sodium hydroxide in water. Flash chromatography was preformed on E. Merck silica gel 60 (230-400

mesh ASTM). Radial chromatography was preformed on individually prepared rotors with layer thickness of 1, 2, or 4 mm using a Chromatotron manufactured by Harrison Research, Palo Alto, California.

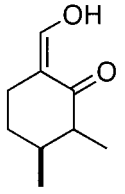
Melting points were measured using a Buchi melting point apparatus, and are uncorrected. Infared (IR) spectra were recorded with Nicolet 5DXB FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a Bruker AC-300 or a Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) using the δ scale. ^{1}H NMR spectral data are reported in the order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant (*J*) in Hertz (Hz), and number of protons.

Chemical ionization (CI) high and low resolution mass spectroscopy (HRMS and MS) were obtained using a Kratos MS-50 spectrometer with a source of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtain using a Varian MAT311 or a Siemens P4 spectrometer and these data were interpreted using the direct methods program contained in the SHELXTL (silicon Graphics/Unix) software package.



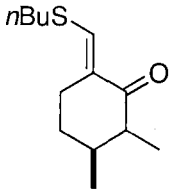
***Cis*- and *trans*-2, 3-dimethylcyclohexanone (71).** To a suspension of cuprous (I) iodide (1.22 g, 6.4 mmol, 3.2 mol % vs substrate) in THF (185 mL) at -78 °C under argon was added dimethyl sulfide (30 mL). To the resulting clear solution was added a 3M solution of methyl magnesium bromide in Et_2O (74 mL, 0.22 mol). A solution of 2-cyclohexen-1-one **69** (19.22 g, 0.20 mol) in THF (30 mL) was added dropwise over 80 min at -50 °C and the mixture was stirred for 6 h at -50 °C. The resulting suspension was cooled to -78 °C and MeI (63 mL, 1.0 mol) was rapidly added followed by freshly distilled DMPU/THF (120 mL, 1:1). The resulting suspension was warmed to 0 °C over 6 h and stirred at room temperature for 18 h. The resulting mixture was poured into 20% aqueous ammonium hydroxide (200 mL), filtered through Celite and extracted with Et_2O (5 x 100 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (1500 g, Et_2O-hexanes, 1:4) afforded 18.65 g (74%) of the title compound as a clear oil. A small sample of the pure *trans* isomer was isolated for spectroscopic purposes: IR (neat) 2958, 2930, 2871, 1709, 1455, 1373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 7 Hz, 3H), 1.01 (d, J = 7 Hz, 3H), 1.35 - 1.48 (m, 2H), 1.54 - 1.66 (m, 1H), 1.77 - 1.82

(m, 1H), 1.94 - 2.04 (m, 2H), 2.24 (dddd, J = 2, 3, 5, 14 Hz, 1H), 2.33 (dddd, J = 1, 1, 6, 13 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 21.1, 26.5, 34.6, 41.5, 41.9, 52.2, 213.6; MS (CI) *m/z* 126 (M+), 111, 95, 81; HRMS (CI) *m/z* 126.1043 (calcd for $C_8H_{14}O$: 126.1044).



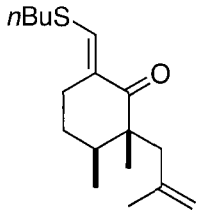
6-Hydroxymethylene-2, 3-dimethylcyclohexanone. To an ice-cooled suspension of sodium methoxide (5.40 g, 100.0 mmol) in Et_2O (80 mL) under argon was added 2, 3-dimethylcyclohexanone **71** (5.05 g, 40.0 mmol) and the resulting mixture was stirred for 10 min. Ethyl formate (5.50 mL, 68.0 mmol) was added and the mixture was allowed to warm to ambient temperature and stirred for 12 h. The mixture was diluted with water (50 mL) and separated. The ethereal layer was extracted with 10% aqueous NaOH (2 x 20 mL). The combined aqueous layer and alkaline extract was cooled, acidified with 6M HCl, and extracted with Et_2O (5 x 20 mL). The combined organic phase was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting oil (5.92 g, 96%) was used without further purification. A small sample was purified for spectroscopic analysis: IR (neat) 2960, 2930, 2855, 1639, 1590, 1455, 1365, 1329, 1229, 1179, 1150 cm-

1; ^{1}H NMR (400 MHz, $CDCl_3$) (major isomer) δ 1.00 (d, *J* = 7 Hz, 3H), 1.20 (d, *J* = 7 Hz, 3H), 1.23 - 1.35 (m, 1H), 1.39 - 1.53 (m, 1H), 1.74 - 1.80 (m, 1H), 2.01 (q, *J* = 7 Hz, 1H), 2.24 - 2.39 (m, 2H), 8.62 (d, *J* = 3 Hz, 1H), 14.59 (d, *J* = 3 Hz, 1H); (minor isomer) δ 0.91 (d, *J* = 7 Hz, 3H), 1.08 (d, *J* = 7 Hz, 3H), 1.46 - 1.53 (m, 1H), 1.55 - 1.63 (m, 1H), 1.82 - 1.95 (m, 1H), 2.31 - 2.47 (m, 3H), 8.66 (d, *J* = 3 Hz, 1H), 14.44 (d, *J* = 3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 16.1, 20.5, 22.7, 30.2, 35.5, 43.5, 108.3, 187.8, 188.1; (minor isomer) δ 12.8, 17.0, 22.4, 26.8, 31.3, 40.3, 107.6, 188.4, 188.5.



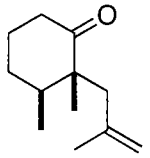
6-*n*-Butylthiomethylene-2, 3-dimethylcyclohexanone (72). A solution of the above hydroxymethylene ketone (5.92 g, 38.4 mmol), *n*-butyl mercaptan (5.22 mL, 48.8 mmol) and *p*-TsOH (20 mg) in anhydrous PhH (90 mL) was refluxed under an argon atmosphere using a Dean-Stark separator for 3 h. The cooled solution was diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (800 g, Et_2O-Hexanes, 1:4) produced 7.58 g (87%) of the titled compound as a

yellow oil: IR (neat) 2957, 2929, 2872, 1544, 1456, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.88 (d, *J* = 7 Hz, 3H), 0.90 (t, *J* = 7 Hz, 3H), 1.02 (t, *J* = 7 Hz, 3H), 1.14 (d, *J* = 7 Hz, 2H), 1.39 (q, *J* = 7 Hz, 3H), 1.54 - 1.71 (m, 3H), 1.80 - 1.89 (m, 1H), 2.21 - 2.30 (m, 1H), 2.35 - 2.43 (m, 1H), 2.45 - 2.53 (m, 1H), 2.80 (t, *J* = 7 Hz, 2H), 7.45 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 13.5, 14.3, 20.7, 21.5, 26.5, 30.2, 32.6, 34.1, 36.1, 49.9, 130.1, 141.6, 198.6; (minor isomer) δ 12.3, 15.2, 24.9, 27.5, 33.2, 47.2, 129.9, 141.3, 199.4; MS (FAB) *m/z* 227 (M+-1), 211, 197, 169; HRMS (CI) *m/z* 227.1465 (calcd for $C_{13}H_{23}OS$: 227.1469).



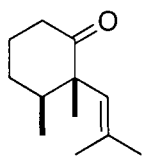
6-((butylthio)methylene)-2,3-dimethyl-2-(2-methylallyl) cyclohex-anone (73). To a solution of 6-thiomethylene 2, 3-dimethylcyclohexanone **72** (6.79 g, 30.0 mmol) in THF (54 mL) at -78°C under argon was added a 0.5M solution of KHMDS (66 mL, 33.0 mmol) and the mixture was stirred for 1 h at 0°C. The resulting red solution was cooled to -78°C and 3-bromo-2-methylpropene (7 mL, 70 mmol) was added. The resulting mixture was slowly allowed to warm to room temperature and stirred for 12 h. The mixture was diluted with saturated

aqueous NH_4Cl and extracted with Et_2O (3 x 100 mL). The extract was washed saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (800g, Et_2O:Hexane, 1:4) afforded 7.40g (88%) of the titled compound as a colorless oil: IR (neat) 3071, 2960, 2930, 2874, 1660, 1541, 1451, 1296, 1151, 890, 810 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major diastereomer) δ 0.90 (d, *J* = 7 Hz, 3H), 0.90 (t, *J* = 7 Hz, 3H), 0.95 (s, 3H), 1.40 (sextet, *J* = 7 Hz, 2H), 1.49 (s, 3H), 1.50 - 1.68 (m, 4H), 1.90 - 1.98 (m, 1H), 2.09 (d, *J* = 14 Hz, 1H), 2.12 - 2.31 (m, 1Hz), 2.44 - 2.51 (m, 1H), 2.79 - 2.87 (m, 3H), 4.61 (m, 1H), 4.72 (m, 1H), 7.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer) δ 13.9, 16.4, 21.0, 22.0, 24.3, 26.7, 27.1, 33.0, 34.2, 34.7, 45.5, 49.7, 114.7, 130.2, 143.5, 143.6, 201.3; MS (FAB) *m/z* 281 (M+H), 265, 223, 211, 191, 161; HRMS (FAB) *m/z* 281.1937 (calcd for $C_{17}H_{29}OS$: 281.1939).



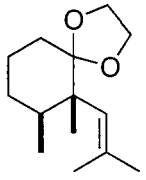
2, 3-Dimethyl-2-(2-methallyl)cyclohexanone (68). To a solution of 2, 3-dimethyl-2-methallyl-6-*n*-butylthiomethylenecyclohexanones (9.81 g, 35.0 mmol) in diethylene glycol (60 mL) under argon was added a solution of 25% aqueous KOH (56 mL). The resulting solution was heated to reflux for 24 h. The

cooled solution was diluted with Et_2O (100 mL) and H_2O (100 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic phase was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (800 g, Et_2O-Hexanes, 1:9) produced 5.68 g (90%) of the titled compound (4:1 mixture of diastereomers) as a colorless oil: IR (neat) 3073, 2939, 2876, 1704, 1458, 1380, 890 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (major diastereomer) δ 0.89 (d, J = 7 Hz, 3H), 0.97 (s, 3H), 1.45 - 1.53 (m, 1H), 1.59 (s, 3H), 1.71 -1.78 (m, 1H), 1.84 - 1.96 (m, 3H), 2.29 - 2.36 (m, 2H), 2.45 - 2.52 (m, 1H), 2.63 (d, J = 14 Hz, 1H), 4.63 (m, 1H), 4.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer) δ 16.2, 20.1, 23.9, 24.6, 29.2, 38.7, 38.8, 44.7, 52.4, 114.9, 143.3, 216.1; (minor diastereomer) δ 16.1, 20.6, 24.2, 27.0, 29.9, 39.4, 40.28, 45.4, 52.9, 114.8, 142.5, 216.5; MS (CI) *m/z* 181 (M+1), 165, 147, 137, 125, 109; HRMS (CI) *m/z* 180.1513 (calcd for $C_{12}H_{20}O$: 180.1514).



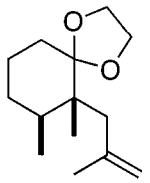
2, 3-Dimethyl-2-(2-methylprop-1-enyl)cyclohexanone (76). To a solution of cyclohexanones **68** and **75** (2.16 g, 12.0 mmol) in 10% aqueous EtOH (80 mL) under argon was added $RhCl(PPh_3)_3$ (1.12 g, 0.12 mmol, 10 mol % vs

substrate). The resulting red solution was heated to reflux (bath temperature above 128 °C) for 72 h. The solvent was removed *via* distillation and residue was diluted with ether (100 mL), washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (250 g, Et_2O-Hexanes, 1:19) produced 1.18 g (55%) of the title compound as a clear oil: IR (neat) 2965, 2929, 2874, 1704, 1451, 1384, 1371, 1308 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 7 Hz, 3H), 1.03 (s, 3H), 1.36 (dddd, J = 2, 4, 4, 4 Hz, 1H), 1.38 (d, J = 1 Hz, 3H), 1.67 (d, J = 1 Hz, 3H), 1.78 - 1.87 (m, 1H), 2.00 - 2.09 (m, 1H), 2.09 - 2.16 (m, 1H), 2.59 - 2.67 (m, 1H), 5.35 (t, J = 1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 18.7, 21.0, 24.1, 27.3, 29.0, 39.5, 45.2, 54.8, 132.6, 134.0, 216.6; MS (CI) *m/z* 180 (M+), 165, 137, 109, 95; HRMS (CI) *m/z* 180.1513 (calcd for $C_{12}H_{20}O$: 180.1514).



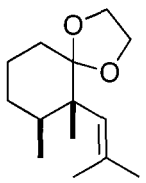
6, 7-Dimethyl-6-(2-methylpropenyl)-1, 4-dioxaspiro[4.5]decane (77). To a solution of cyclohexanone **76** (1.20 g, 6.65 mmol), in anhydrous PhH (100 mL) at ambient temperature under argon were added ethylene glycol (7.40 mL, 0.13 mmol) and ppts (0.5 g, 30 % mol vs substrate). The resulting biphasic mixture was heated to refluxed under an argon atmosphere for 24 h with a Dean-Stark

water separator. The cooled solution was diluted with Et_2O (10 mL), washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (200 g, Et_2O-Hexanes, 1:4) produced 1.28 g (86%) of the title compound **77** as a clear oil: IR (neat) 3070, 2953, 2880, 1639, 1543, 1460, 1373, 1189, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, *J* = 7 Hz, 3H), 1.14 (s, 3H), 1.21 - 1.27 (m, 1H), 1.35 - 1.49 (m, 2H), 1.51 - 1.59 (m, 3H), 1.70 (d, *J* = 1 Hz, 3 H), 1.76 (d, *J* = 1 Hz, 3H), 1.82 - 1.92 (m, 1H), 3.78 - 3.86 (m, 4H), 4.99 (t, *J* = 1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 16.8, 19.7, 23.0, 29.0, 29.5, 32.0, 40.0, 48.2, 65.4, 65.8, 114.8, 131.9, 132.9; MS (CI) *m/z* 224(M^+), 209, 181, 163, 153, 139, 121; HRMS (CI) *m/z* 224.1771 (calcd for $C_{14}H_{24}O$:224.1776).



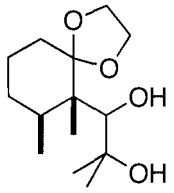
6, 7-Dimethyl-6-(2-methally)-1, 4-dioxaspiro[4. 5] decane (78). To a solution of cyclohexanones **68** and **75** (18.02 g, 0.1 mol) in 2-ethyl-2-methyl-1, 3-dioxolane (580.0 g, 5.0 mol) at room temperature under argon was added ethylene glycol (62.0 g, 1.0 mmol) and TsOH (19.0 g, 0.1 mol). The resulting mixture was stirred for 76 h. The mixture was diluted with Et_2O (300 mL),

washed with saturated $NaHCO_3$, and concentrated under reduced pressure. Chromatography of the residue on silica (600g, Et_2O-Hexanes, 1:19) afforded (6.4 g, 28%) of the titled compound as a clear oil: IR (neat) 3070, 2952, 2882, 1638, 1463, 1442, 1382, 1212, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 7 Hz, 3H), 1.01 (s, 3H), 1.23 - 1.31 (m, 1H), 1.46 - 1.61 (m, 5H), 1.78 - 1.86 (m, 1H), 1.82 (s, 3H), 2.20 (d, J = 14 Hz, 1H), 2.28 (d, J = 14 Hz, 1H), 3.82 - 3.95 (m, 4H), 4.63 (m, 1H), 4.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.6, 22.1, 25.2, 30.2, 30.4, 38.4, 44.4, 45.6, 64.1, 64.4, 113.3, 113.7, 146.3; MS (CI) *m/z* 224(M+), 209, 181, 163, 153, 139, 121; HRMS (CI) *m/z* 224.1771 (calcd for $C_{14}H_{24}O$: 224.1776).



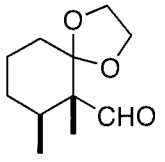
6, 7-Dimethyl-6-(2-methylpropenyl)-1, 4-dioxaspiro[4.5]decane (77). To a solution of ketal **78** (6.40 g, 28.55 mmol) in anhydrous benzene (100 mL) at ambient temperature under argon was added $TsOH.H_2O$ (0.27 g, 5 % mol vs substrate). The resulting solution was warmed to 60°C for 24 h. The cooled solution was diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and

concentrated under reduced pressure to afford **77** as a clear oil. The material was used without further purification.



1-(6, 7-Dimethyl 1, 4-dioxa-spiro[4.5]dec-6-yl)-2-methylpropane-1, 2-diol (79). To a mixture of K_2OsO_4 (8 mg, 0.02 mmol), $K_3Fe(CN)_6$ (0.494 g, 1.50 mmol), K_2CO_3 (0.208g, 1.50 mmol), quinuclidine (0.168 g, 1.50 mmol) and methanesulfonamide (0.142 g, 1.50 mmol) in H_2O (2.5 mL) at ambient temperature under argon was added a solution of ketal **77** (0.112 g, 0.50 mmol) in *tert*-BuOH (2.5 mL). The mixture was stirred for 48 h and treated with Na_2SO_3 (0.756 g, 6.0 mmol). The resulting mixture was stirred for 1 h and diluted with Et_2O (10 mL) and H_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (30 g, Et_2O-Hexanes, 1:1) produced 0.104 g (80%) of the titled compound as a clear oil: IR (neat) 3485, 2932, 1466, 1177, 1097, 1039, 921 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J = 7 Hz, 3H), 1.03 (s, 3H), 1.26 (s, 3H), 1.31 - 1.49 (m, 4H), 1.33 (s, 3H), 1.50 -

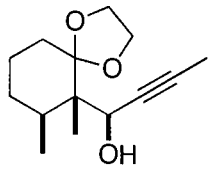
1.56 (m, 1H), 1.69 - 1.73 (m, 1H), 2.47 - 2.56 (m, 1H), 3.36 (d, J = 11 Hz, 1H), 3.51 - 3.54 (m, 2H), 3.91 - 3.95 (m, 1H), 3.97 - 4.07 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 22.3, 28.6, 29.6, 29.8, 30.3, 36.2, 48.7, 62.7, 62.9, 74.9, 82.6, 116.0; MS (CI) *m/z* 257 (M^++1), 240, 199, 170, 155, 138, 109; HRMS (CI) *m/z* 257.1751 (calcd for $C_{14}H_{25}O_4$: 257.1752).



6, 7-Dimethyl-1, 4-dioxa-spiro[4.5]decane-6-carbaldehyde (67). To a solution of diol **79** (0.129 g, 0.50 mmol) in anhydrous CH_2Cl_2 (2.3 mL) at 0 °C under argon was added solid Na_2CO_3 (0.159 g, 1.50 mmol) and $Pb(OAc)_4$ (0.255 g, 0.58 mmol). The mixture was stirred for 10 min at 0 °C, filtered and concentrated under reduced pressure. The resulting oil (0.100 g, 100%) was used without further purification. A small sample was purified for spectroscopic analysis.

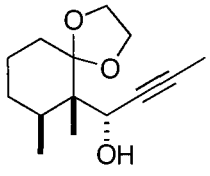
Alternate procedure. To a solution of diol **79** (1.29 g, 5.0 mmol) in THF/H_2O (1:1, 50 ml) at ambient temperature under argon was added solid $NaIO_4$ (10.69 g, 50.0 mmol). The resulting solution was stirred for 12 h at room temperature. The reaction mixture was diluted with Et_2O (100 mL) and H_2O (100 mL). The phases were separated and the aqueous phase was extracted

with Et_2O (3 x 20 mL). The combined organic phase was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting oil (1.00 g, 100%) was used without further purification. IR (neat) 2956, 2933, 2883, 1725, 1181, 1104, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, J = 7 Hz, 3H), 1.05 (s, 3H), 1.17 - 1.25 (m, 1H), 1.52 - 1.60 (m, 1H), 1.60 - 1.68 (m, 1H), 2.35 - 2.44 (m, 1H), 3.89 - 3.97 (m, 4H), 9.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 14.5, 16.7, 22.6, 28.8, 30.7, 33.1, 56.8, 64.9, 65.1, 113.3, 207.6; MS (CI) *m/z* 199 (M+-1), 185, 169, 141, 127, 113, 99; HRMS (CI) *m/z* 199.1337 (calcd for $C_{11}H_{19}O_3$: 199.1334).



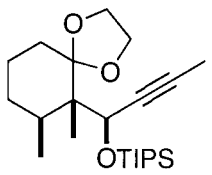
1-(6, 7-Dimethyl-1, 4-dioxa-spiro[4.5]dec-6-yl)-but-2-yn-1-ol (80). To a solution of propyne (3 mL) in anhydrous THF (0.72 mL) at -78 °C under argon was added a 1.73M solution of *n*-butyllithium (0.58 mL, 1.00 mmol). The mixture was stirred for 1 h at -78 °C. A solution of aldehyde **67** (0.049 g, 0.25 mmol) in anhydrous THF (0.5 mL) at -78 °C was added to the solution of 1-lithio-1-propyne. The resulting mixture was allowed to warm to room temperature over 3 h and stirred at room temperature for 2 h. The reaction mixture was diluted with pH 7 buffer (5 mL) and extracted with Et_2O (2 x 10 mL), dried over

anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (30 g, Et_2O-Hexanes, 2:3) afforded 0.032 g (54%) of the titled compound as a white solid and 0.011 g (18%) of the epimeric alcohol as a clear oil: m.p 111-112 °C; IR (KBr) 3523, 3426, 2958, 2929, 1384, 1262, 1178, 1105, 1057, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.07 (d, *J* = 7 Hz, 3H), 1.24 - 1.44 (m, 3H), 1.53 - 1.61 (m, 3H), 1.82 (dd, *J* = 1, 2 Hz, 3H), 2.19 - 2.28 (m, 1H), 3.78 (d, *J* = 2 Hz, 3H), 3.91 - 4.08 (m, 2H), 4.04 - 4.12 (m, 2H), 4.71 (q, *J* = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.1, 14.3, 17.2, 22.9, 30.2, 30.4, 33.3, 48.1, 64.2, 64.6, 66.0, 79.8, 82.4, 115.4; MS (CI) *m/z* 238 (M^+), 221, 193, 180, 170, 155, 111, 99; HRMS (CI) *m/z* 238.1567 (calcd for $C_{14}H_{22}O_3$: 238.1568).



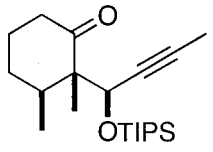
1-(6, 7-Dimethyl-1, 4-dioxa-spiro[4.5]dec-6-yl)-but-2-yn-1-ol (81). To a solution of aldehyde **67** (0.100 g, 0.50 mmol) in anhydrous THF (5.5 mL) at 0 °C under argon was added a 0.36M solution of propynylmagnesium bromide (4.0 mL, 1.44 mmol). The mixture was stirred for 2 h at 0 °C and at ambient temperature for 2 h. The reaction mixture was treated with pH 7 buffer (10 mL) and extracted with Et_2O (2 x 10 mL), dried over anhydrous $MgSO_4$, and

concentrated under reduced pressure. Chromatography of the residue on silica (30 g, Et_2O-Hexanes, 2:3) afforded 0.064 g (54%) of the titled compound as a clear oil and 0.034 g (29%) of the epimeric alcohol as a white solid: IR (neat) 3489, 2923, 2858, 2360, 1463, 1185, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 7 Hz, 3H), 1.00 (s, 3H), 1.20 - 1.31 (m, 1H), 1.42 - 1.51 (m, 2H), 1.52 - 1.61 (m, 3H), 1.84 (d, *J* = 2 Hz, 3H), 2.21 - 2.30 (m, 1H), 3.91 - 3.99 (m, 2H), 4.04 - 4.12 (m, 2H), 4.25 (d, *J* = 8 Hz, 1H), 4.41 (d, *J* = 6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.3, 13.4, 16.2, 22.1, 29.8, 31.9, 34.5, 48.0, 64.0, 64.5, 67.4, 80.0, 81.0, 115.4; MS (CI) *m/z* 238 (M+), 221, 170, 99; HRMS (CI) *m/z* 238.1557 (calcd for $C_{14}H_{22}O_3$: 238.1568).



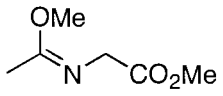
[1-(6, 7-Dimethyl-1, 4-dioxa-spiro[4.5]dec-6-yl)-but-2-ynyloxy]-triisopropyl-silane (82). To a solution of alcohol **80** (0.026 g, 0.10 mmol) in anhydrous pyridine (0.3 mL) at 0 °C under argon was added DMAP (0.022 g, 0.18 mmol) and TIPSOTf (0.20 mL, 0.74 mmol). The mixture was warmed to ambient temperature and stirred for 15 h. MeOH (1.0 mL) was added and stirred for 15 min. The resulting mixture was diluted with Et_2O (10 mL), washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over

anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (18 g, Et_2O-Hexanes, 1:4) afforded 0.034 g (86%) of the titled compound as a clear oil: IR (neat) 2953, 2866, 2230, 1463, 1382, 1185, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.63 - 0.77 (m, 1H), 0.95 -1.11 (m, 2H), 1.37 - 1.67 (m, 7H), 1.83 (d, *J* = 2 Hz, 3H), 2.32 - 2.40 (m, 1H), 3.85 - 3.98 (m, 4H), 4.53 (q, *J* = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.3, 12.6, 13.0, 13.3, 13.4, 14.7, 17.6, 18.1, 18.2, 18.3, 18.6, 18.7, 23.0, 30.7, 31.2, 35.6, 50.3, 50.5, 64.8, 66.2, 66.4, 80.1, 81.7, 113.7; MS (CI) *m/z* 394 (M^+), 351, 283, 225, 205, 183, 141, 131, 84; HRMS (CI) *m/z* 394.2900 (calcd for $C_{23}H_{42}O_3Si$: 394.2903).



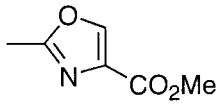
2, 3 -Dimethyl-2-(1-triisopropylsilanyloxy-but-2-ynyl)-cyclohexanone (83). To a solution of ketal **82** (0.026 g, 0.06 mmol) in 10% aqueous acetone (0.70 mL) at 0 °C under argon was added PPTS (0.005 g, 0.02 mmol). The resulting solution was heated to reflux for 3 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (1.0 mL) and extracted with Et_2O (2 x 10 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica

(18 g, Et_2O-Hexanes, 1:19) afforded 0.019 g (86%) of the titled compound as a clear oil: IR (neat) 2942, 2866, 2228, 1709, 1461, 1081, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 - 0.80 (m, 1H), 0.95 -1.22 (m, 25H), 1.38 - 1.51 (m, 2H), 1.76 (t, *J* = 2 Hz, 3H), 1.75 - 1.99 (m, 3H), 2.26 - 2.40 (m, 2H), 2.46 - 2.54 (m, 1H), 5.06 & 5.15 (q, *J* = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.9, 13.0, 13.3, 13.4, 14.6, 15.2, 15.2, 16.6, 17.5, 18.1, 18.2, 18.5, 18.6, 19.3, 23.3, 23.3, 29.1, 29.2, 30.1, 35.6, 39.8, 59.2, 59.4, 65.9, 66.0, 79.2, 79.3, 83.0, 83.2, 213.7, 213.8; MS (CI) *m/z* 350 (M^+), 335, 307, 265, 239, 225, 211, 183; HRMS (CI) *m/z* 350.2635 (calcd for $C_{21}H_{38}O_2Si$: 350.2641).



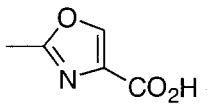
Methyl α-[(Methoxyethylidene)-amino]-acetate (86). To a suspension of methyl acetimidate hydrochloride **85** (20.0 g, 182 mmol) in CH_2Cl_2 at 0 °C under argon was added glycine methyl ester hydrochloride (23.0 g, 182 mmol) and the mixture was stirred for 45 min at 0 °C. A solution of triethylamine (25.4 mL, 182 mmol) in CH_2Cl_2 (22 mL) was added with a syringe pump over 150 min at 0 °C. The mixture was slowly allowed to warm to room temperature and the stirring was continued for 5 h. The mixture was diluted with pH 7 buffered water (60 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic phase was washed with pH

7 buffered water, saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by distillation (61 - 65 °C at 14.0 mmHg) afforded 19.02 g (72%) of the titled compound as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 1.81 (s, 3H), 3.61 (s, 3H), 3.66 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 51.3, 52.2, 53.0, 165.5, 171.1.



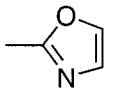
2-Methyl-oxazol-4-yl-carbonic acid Methyl Ester (87). To a solution of potassium *tert*-butoxide (7.63 g, 68 mmol) in THF (200 mL) at –10 °C under argon was added *via* syringe pump a solution of methyl α-[(methoxyethylidene)-amino]-acetate **86** (9.87 g, 68 mmol) and methyl formate (5.05 mL, 81.6 mmol) in THF (50 mL). After 1 h at -10 °C, anhydrous Et_2O (750 mL) was added *via* a cannula resulting in the formation of a yellowish precipitate. After 2 h at 0 °C the suspension was filtered through a Schlenck tube under argon. The resulting pale yellow filter cake was washed under argon with anhydrous Et_2O (3 x 40 mL), dried under an argon stream and reduced pressure. The crude potassium salt was used directly for the next step. To refluxing glacial acetic acid (15 mL) was added the crude potassium salt and the resulting dark solution was refluxed for 1.5 h and cooled to ambient temperature. The mixture was carefully

poured into saturated aqueous $NaHCO_3$ (50 mL). The pH value of the solution was adjusted to 8 by further addition of solid $NaHCO_3$. The aqueous mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Distillation (120 - 122 °C at 14.0 mmHg) of the residue afforded 4.32 g (75%) of the titled compound: IR (film) 3149, 3087, 2959, 1730, 1578, 1317, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.79 (s, 3H), 8.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 52.3, 133.5, 144.1, 161.9, 162.7; MS (CI) *m/z* 141 (M+), 110, 95, 82; HRMS (CI) *m/z* 141.0426 (calcd for $C_6H_7O_3N$: 141.0426).



2-Methyloxazole-4-carboxylic Acid. To methyl ester **87** (2.82 g, 20.0 mmol) at room temperature under argon was added a 4M aqueous solution of KOH (6.0 mL). The resulting mixture was heated at reflux for 1 h. The resulting clear solution was cooled to 0 °C and neutralized with a 6M aqueous solution of HCl (4.0 mL). The resulting fine needles were filtered, washed with cold water, Et_2O and dried to afford 2.34 g (92%) of the titled compound: m. p. 183-184 °C (Lit. 183-184 °C); IR (KBr) 3162, 3123, 2827, 2690, 2543, 1725, 1650, 1585 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.48 (s, 3H), 8.37 (s, 1H); ^{13}C NMR (100 MHz,

CD_3OD) δ 10.8, 131.9, 143.2, 161.2, 161.8; MS (CI) *m/z* 127 (M+), 110, 99, 85; HRMS (CI) *m/z* 127.0268 (calcd. for $C_5H_5O_3N$: 127.0269).



2-Methyloxazole (88). To a solution of the above acid (1.52 g, 12.0 mmol) in quinoline (6.4 mL) at room temperature under argon was added copper oxide (0.094 g, 1.2 mmol). The resulting dark suspension was heated to 180 °C for 1 h. Distillation (81 – 83 °C) of the resulting suspension afforded 0.78 g (78%) of the titled compound as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 6.89 (s, 1H), 7.44 (d, *J* = 1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 127.3, 138.7, 162.0.

Reference

1. Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

2. Eagle, G. A.; Rivett, D. E. A.; Williams, D. H.; Wilson, R. G. *Tetrahedron* **1969**, *25*, 5227.

3. Jacobi, P. A. In *Advances in Heterocyclic Natural Product Synthesis*; JAI: New York, **1992**, 251.

4. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1996**, *50*, 1.

5. Boeckman, R. K. *J. Org. Chem.* **1973**, *38*, 4450.

6. Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253.

7. Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615.

8. (a) Piers, E.; Britton, R. W.; De Waal, W. *Can. J. Chem.* **1969**, *47*, 831. (b) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453.

9. Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687.

10. (a) Golborn, P.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2870. (b) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.

11. (a) Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, A.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773. (b) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308.

12. Pappas, J. J.; Keaveney, W. P.; Edward, G.; Berger, M. *Tetrahedron Lett.* **1966**, *36*, 4273.

13. Vorbruggen, H.; Bennua, B. *Synthesis* **1988**, 925.

14. (a) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem*, **1990**, *55*, 766. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K-S.; Kwong, H-L.; Morikawa, K.; Wang, Z-M.; Xu, D.; Zhang, X-L. *J. Org. Chem.* **1992**, *57*, 2768.

15. Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

16. Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.

17. Smith, A. B.; Chen, S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 10935.

18. Chan, K-K.; Cohen, N.; Noble, J. P.; Specian, A. C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497.

19. Burke, S. D.; Austad, B. C.; Hart, A. C. *J. Org. Chem.* **1998**, *63*, 6770.

20. Sterzycki, R. *Synthesis* **1979**, *16*, 724.

21. Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043.

22. Comins, D. L.; Dehghani, *Tetrahedron* **1992**, 6299.

23. Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569.

24. Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87.

25. (a) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.*, **1947**, 96. (b) Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Raeder, M.; Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2415. (c) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Synth.* **2002**, *79*, 244.

26. Wiley, R. H.; Smith, N. R. *Org. Synth.* **1955**, *23*, 731.

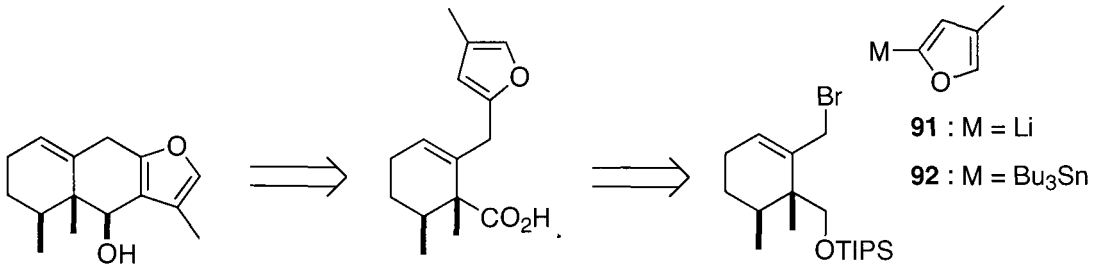
27. (a) Inamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Inamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

Chapter III.

A Classical Annulation Approach to the Furanoeremophilanes

The series of negative results from our initial approach to the furanoeremophilane sesquiterpenoids underscored two important points. First, late stage installation of the trisubstituted olefin appeared to be highly problematic due to the steric hindrance of the adjacent quaternary center. Furthermore, a coupling reaction in spatial proximity to the quaternary methyl group was also going to be an extremely difficult operation.

With these problems in mind, we developed a totally revised approach to our target, 6β-hydroxyeuryopsin (**4**, **Scheme 32**). Our new strategy foresaw the incorporation of the furan ring onto a preexisting matrix wherein the trisubstituted olefin was already in place.

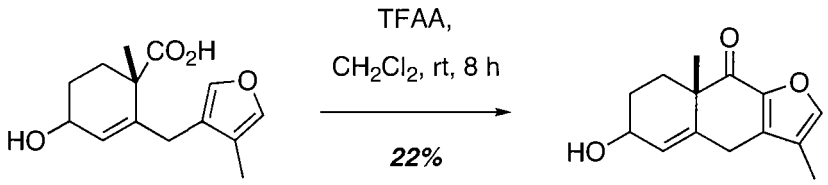


4: 6β-Hydroxyeuryopsin **89** **90**

Scheme 32

More specifically, in this stepwise approach the central six-membered ring in **4** would be constructed by exploiting the inherent reactivity of the furan moiety, which would actively participate in the ring closing exercise.

Interestingly, this annulation strategy has evolved into the cornerstone of several syntheses, and Wong's approach towards the furanoeudesmanes provides a noteworthy example (**Scheme 33**).[1]

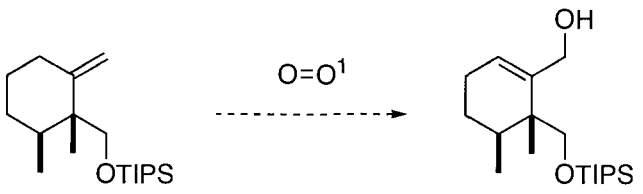


93 **94**

Scheme 33

Further, the critical union of the allylic bromide **90** and furan fragments **91** or **92** can be envisioned as arising from either alkylation chemistry for **91** or Stille cross-coupling methodology for **92**. It was hoped that this bond forming strategy would circumvent the problem associated with fragment coupling in proximity to the quaternary center.

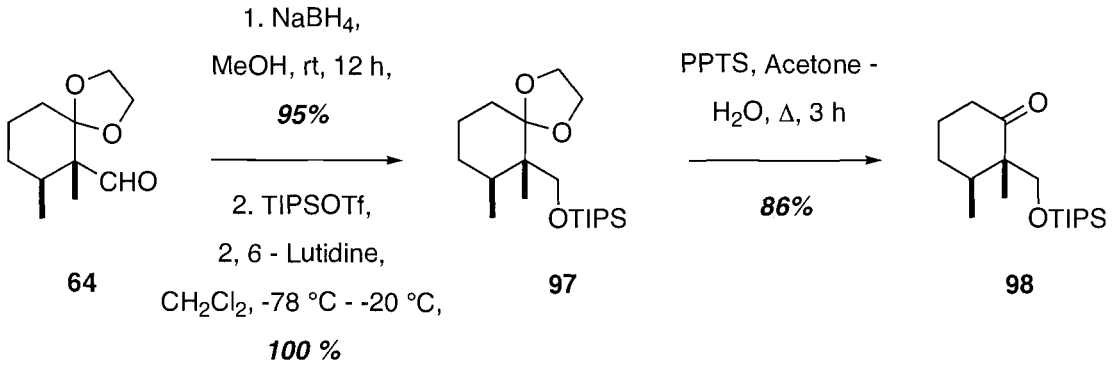
With this plan in mind, we undertook a series of initiatives aimed at preparing the allylic alcohol **96** which we were confident could be converted to bromide **90**. Our initial focus turned to the use of singlet oxygen to effect an allylic transposition of the *exo*-methylene group in **95** (**Scheme 33**) with accompanying formation of alcohol **96**.[2]



95 **96**

Scheme 33

Our new approach commenced from the previously prepared aldehyde **64** which was reduced with sodium borohydride, and the resulting alcohol was converted to the triisopropylsilyl ether **97**.[3] Acidic hydrolysis of the ketal **97** using pyridinium *p*-toluenesulfonate in aqueous acetone provided the ketone **98** (**Scheme 34**).



64 **97** **98**

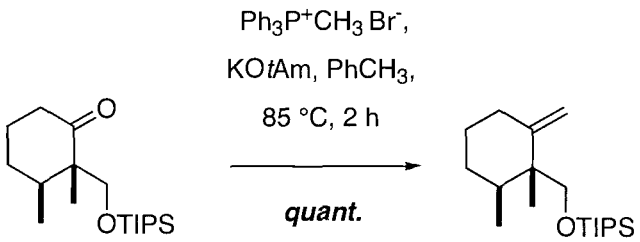
Scheme 34

Our next task was methylenation of the sterically hindered ketone **98**. Several methods for olefination of a sterically hindered ketone have been reported, and our initial olefination studies focused on employing Takai's methylenation reagent derived from dibromomethane, zinc dust and titanium tetrachloride.[4] This mild reagent was found to be effective in the bis-olefination

of two sterically encumbered ketones in Katoh's synthesis of 8-O-methylpopolohuanone E.[5] However, prolonged exposure of ketone **98** to an excess of the Takai reagent, prepared according to the procedure reported by Katoh, produced only a low yield (< 10%) of the desired olefin **95**.

The limited success of the Takai olefination of ketone **98** was somewhat discouraging and forced us to search for an alternative method for converting this ketone **98** to the *exo*-olefin **95**. Our attention was thus drawn towards a high temperature Wittig olefination procedure reported by Smith during his synthesis of (±)-modhephene.[6]

In the event, exposure of ketone **98** to a preheated solution of methylenetriphenylphosphorane, generated with potassium *tert*-amylate, gave the desired product **95** in excellent yield (**Scheme 35**).[7]

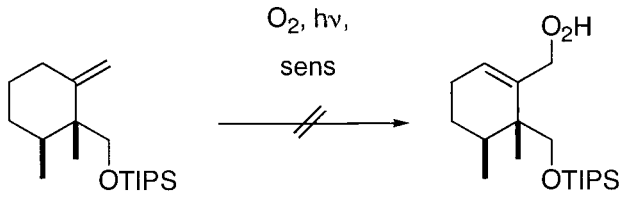


98 **95**

Scheme 35

It was now possible to address the question of whether **95** would be reactive towards singlet oxygen. Disappointingly, prolonged irradiation of olefin **95** in the presence of oxygen with a 300 Watt lamp using Rose Bengal or

tetraphenylporphine as photosensitizer yielded none of the desired hydroperoxide product (**Scheme 36**).



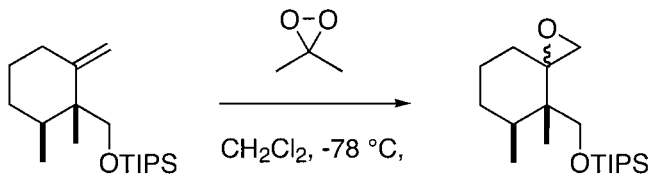
95 **99**

Scheme 36

Although the conversion of an *exo* olefin analogous to **95** to an allylic alcohol is judged to have good precedent,[8] it is unclear whether the failure of **95** to react in the expected manner was due to electronic effects or to steric effects.[9] However, as singlet oxygen is very sensitive to steric effects, the lack of reactivity of olefin **95** may be attributed to steric influences in the substrate.[10]

At this juncture, we turned to an alternative strategy for preparing allylic alcohol **96**. It was decided that a more fruitful approach would lie in epoxidation of the *exo* double bond, thereby setting the stage for an epoxide fragmentation, which would lead directly to allylic alcohol **96**.

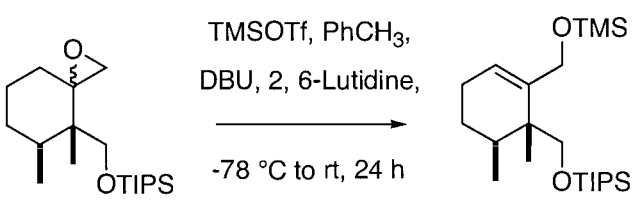
Epoxidation of olefin **95** was readily accomplished with dimethyl dioxirane (DMDO) in dichloromethane at low temperature.[11] The product **100** was isolated as a 3:2 mixture of diastereoisomers and was used as such in the subsequent reactions (**Scheme 37**).



95 **100**

Scheme 37

Our initial attempts, using lithium diisopropylamide[12] or diethylaluminum 2,2,6,6-tetramethylpiperidinide[13] to bring about fragmentation of **100** met with failure, presumably due to the high degree of steric hindrance around the epoxide afforded by the proximal quaternary center. Success was finally realized by employing trimethylsilyl trifluromethanesulfonate (TMSOTf) and 1, 8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in the presence of 2, 6-lutidine.[14] However, the reaction proved to be sluggish and gave the silylated alcohol **101** in low yield (**Scheme 38**).



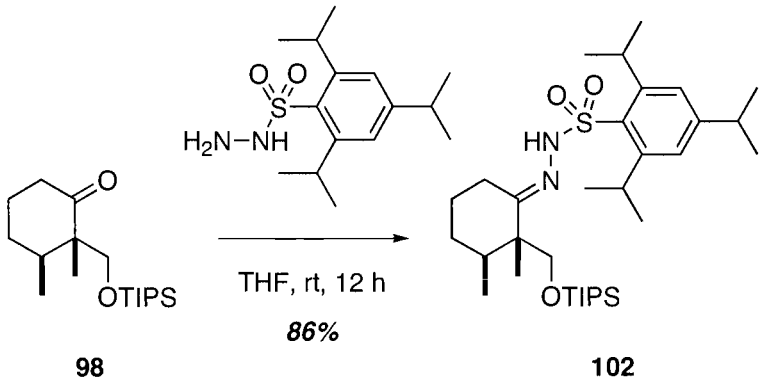
100 **101**

Scheme 38

In view of the foregoing difficulties, we sought a new route to the allylic alcohol **96**, for which we returned to ketone **98**. An ideal solution to our problem appeared to be the Shapiro reaction.[15] The classical reaction

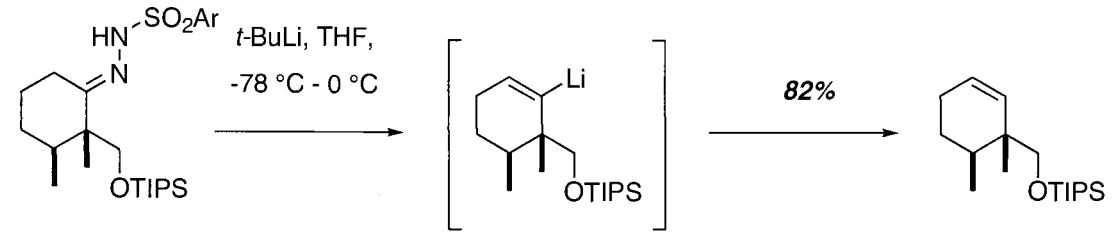
discovered by Shapiro has been used primarily for the formation of an olefin from the tosylsulfonyl hydrazone derivative of a ketone. In subsequent studies with 2, 4, 6-triisopropylbenzenesulfonylhydrazones, Bond and Chamberlin discovered that the intermediate vinyllithium species could be stabilized by the use of tetramethylethylenediamine (TMEDA) and trapped with a variety of externally added electrophiles.[16]

Our initial concern with this approach was the preparation of the required 2, 4, 6-triisopropylbenzenesulfonylhydrazone of the hindered ketone **98**. However, much to our delight, condensation of 2, 4, 6-triisopropylbenzene sulfonylhydrazine[17] with ketone **98** proved to be straightforward and furnished hydrazone **102** in excellent yield (**Scheme 39**).



Scheme 39

Initial studies with hydrazone **102** were encouraging. Thus, treatment of **102** with *tert*-butyllithium in tetrahydrofuran (THF) smoothly generated the vinyllithium intermediate **103**, which was protonated by the solvent to give the cyclohexene derivative **104** in high yield (**Scheme 40**).



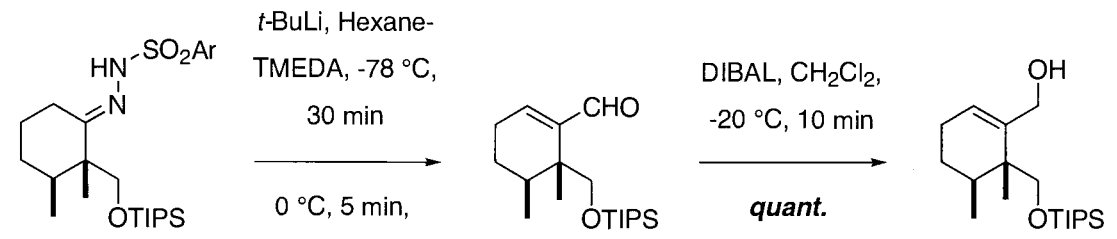
102: Ar = 2, 4, 6 - triisopropylbenzene

103

104

Scheme 40

Furthermore, when the same reaction of **93** was conducted with *tert*-butyllithium in tetramethylethylenediamine (TMEDA) using hexane as the solvent and the mixture was quenched with dimethylformamide (DMF), the α, β-unsaturated aldehyde **105** was obtained in good yield. The aldehyde was reduced with diisobutylaluminium hydride (DIBAL) to afford the allylic alcohol **96** quantitatively (**Scheme 41**).



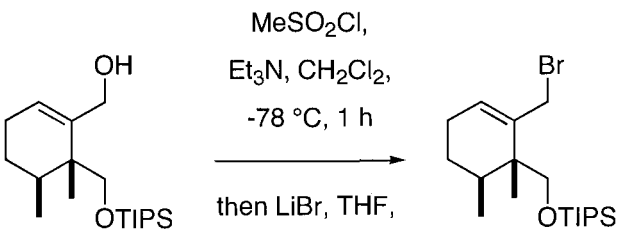
102: Ar = 2, 4, 6 - triisopropylbenzene

105

96

Scheme 41

The final conversion of alcohol **96** to the allylic bromide **90** proved to be uneventful. Thus, allylic alcohol **96** was first converted to its mesylate with methanesulfonyl chloride and the mesylate was treated with anhydrous lithium bromide to furnish the allylic bromide **90** in excellent yield (**Scheme 42**).[18]

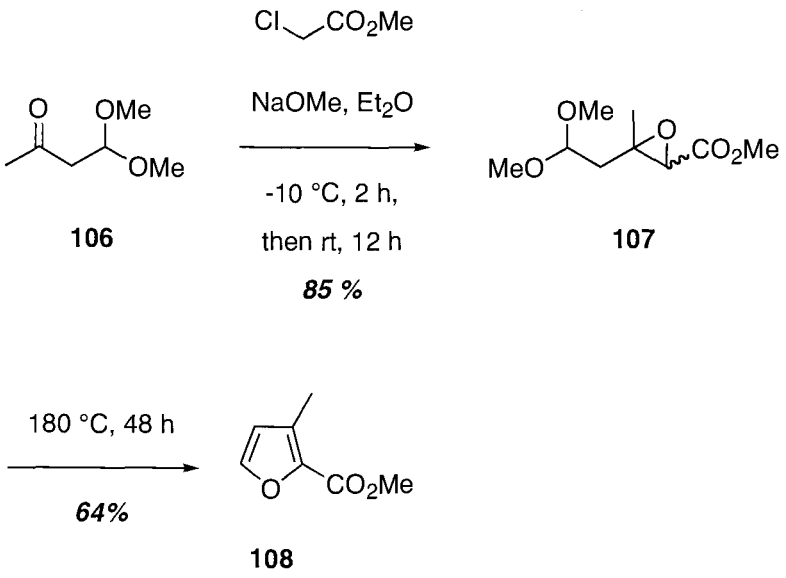


96 **90**

Scheme 42

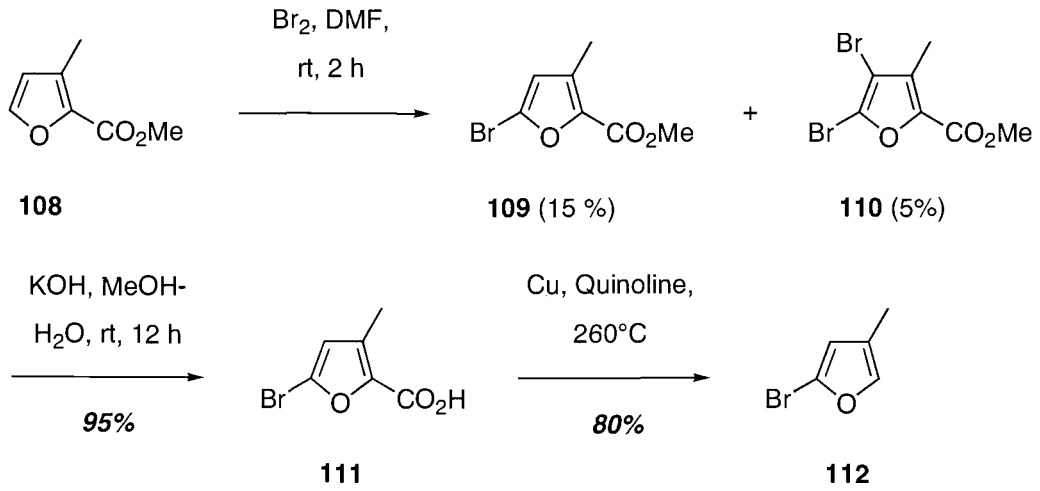
With a viable route to the allylic bromide **90** secured, our attention turned to the preparation of the lithiated furan fragment **91** required for coupling with **90**. 2-Lithio-4-methylfuran (**91**) has found application in several syntheses to date,[19] the regioselective lithiation being generally accomplished through a halogen-lithium exchange reaction.[20]

The synthesis of **91** commenced with a Darzens condensation of methyl α-chloroacetate with ketone **106** which provided glycidic ester **107** as a 1:1 mixture of stereoisomers. Subsequent pyrolysis of the glycidic ester mixture with the continuous removal of methanol yielded methyl 3-methylfuran-2-carboxylate (**108**) (**Scheme 43**).[21]



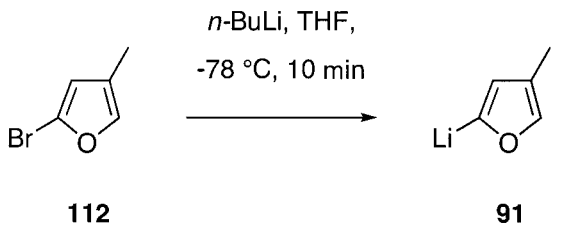
Scheme 43

Exposure of furan **108** to bromine in dimethylformamide (DMF) afforded the monobrominated furan **109**, together with the dibromofuran **110** in low yield. Unfortunately, attempts to improve the yield of this bromination using pyridinium perbromide[22] or N-bromosuccinimde[23] (NBS) were unsuccessful. After careful separation by silica gel chromatography, pure monobromofuran **109** was obtained. This ester was saponified, and a copper promoted decarboxylation furnished the required bromofuran **112** (**Scheme 44**).



Scheme 44

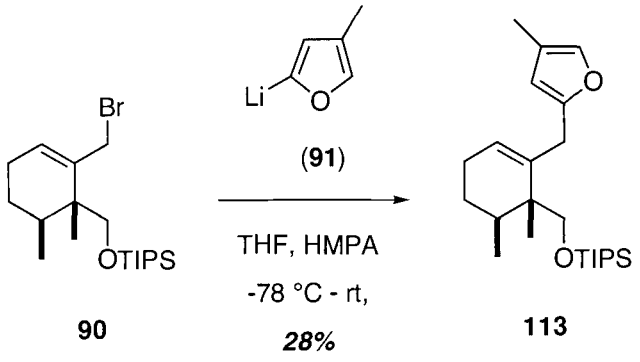
With the two fragments **90** and **112** in hand, our focus now turned to developing an efficient coupling strategy. Initially, our attention was drawn towards a direct alkylation strategy, as employed by Knight during his synthesis of pleraplysillin-2.[20] Formation of the 2-lithio-4-methylfuran (**91**) was smoothly effected by a halogen-lithium exchange of bromofuran **112** with *n*-butyllithium in tetrahydrofuran (THF) at low temperature (**Scheme 45**).



Scheme 45

The resulting bright yellow solution of 2-lithio-4-methylfuran (**91**) was used immediately in subsequent reactions. Initial studies with the lithiated furan **91** were discouraging since the bromide **90** proved to be unreactive with

91. However, with the addition of hexamethylphosphorus triamide (HMPA) to the reaction mixture, a modest yield of the coupled product **113** was obtained (**Scheme 46**).[24]



90 **113**

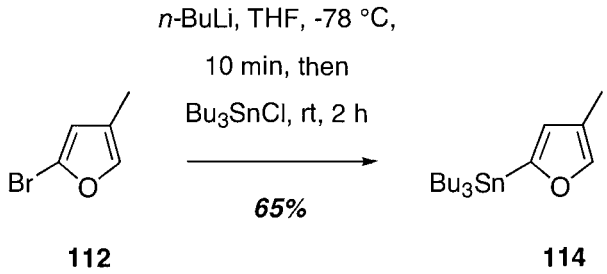
Scheme 46

The reaction of **90** with **91** was plagued by a large number of unidentifiable side products. Further, the coupled product **113** proved to be unstable, which was consistent with observations reported by Knight during his synthesis of pleraplysillin-2.[20]

Even as these alkylation studies were in progress, efforts directed toward an alternative coupling strategy were initiated. The Stille cross coupling, which has evolved into an extremely powerful method for the assembly of natural products,[25] appeared to offer an attractive option for preparing **113**.

With a Stille coupling strategy in mind, a route to the furylstannane required for this reaction was devised from the bromofuran **112**. After halogen-metal exchange of **112** with *n*-butyllithium, the resulting lithiofuran **91** was

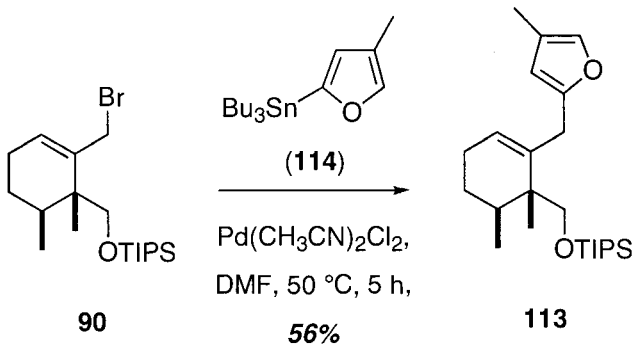
quenched with tributyltin chloride to provide the furylstannane **114** (**Scheme 47**)



112 **114**

Scheme 47

Considerable experimentation was needed to establish that ligandless conditions, as recommended for Stille coupling of sterically demanding substrates, were the most effective for the preparation of **113**.[26] In the event, exposure of a mixture of bromide **90** and stannane **114** to palladium bis(acetonitrile) dichloride complex in dimethylformamide (DMF) resulted in the formation of the coupled product **113** in good yield (**Scheme 48**).

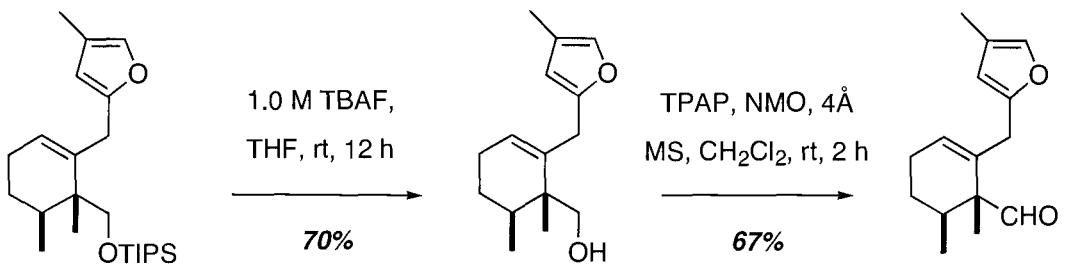


90 **113**

Scheme 48

Unfortunately, the coupling yields deteriorated when the reaction was conducted on scales larger than a hundred milligrams, presumably due to the

inherent lability of the furan. As a consequence of the instability of the coupled product, subsequent steps in this sequence were conducted in rapid progression. First, the triisopropylsilyl (TIPS) protecting group was removed from **113** with the aid of a 1M solution of tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF), and the resulting alcohol **115** was then oxidized to aldehyde **116** with catalytic tetra-*n*-propylammonium perruthenate (TPAP)[27] and stoichiometric N-methylmorpholine-N-oxide (NMO) (**Scheme 49**).

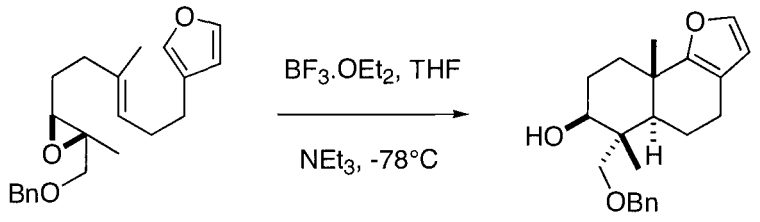


113 **115** **116**

Scheme 49

Our initial goal was to convert **116** to carboxylic acid **89**, and considerable experimentation was devoted to bringing about the further oxidation of this sensitive aldehyde. Unfortunately, the oxidation proved to be highly problematic and the variety of conditions which were explored, all met with failure. However, with the aldehyde **116** in hand, a unique opportunity for examining a Lewis-acid catalyzed cyclization of this material became available. To date, several examples of Lewis-acid catalyzed annulations involving a furan have been reported.[28] An example of such an annulation

process is found in a furan-terminated cationic cyclization of **117** reported by Tanis, which proceeded in good yield and with excellent stereocontrol to give the tricyclic structure **118** (**Scheme 50**).[29]

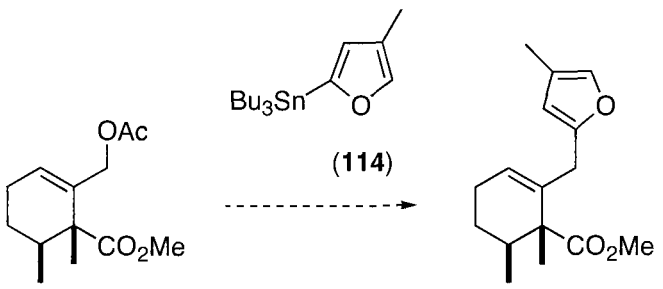


117 **118**

Scheme 50

Disappointingly, the application of numerous Lewis acidic conditions to the attempted cyclization of **116** proved to be unsuccessful, leading primarily to polymers resulting from decomposition of the labile furan.

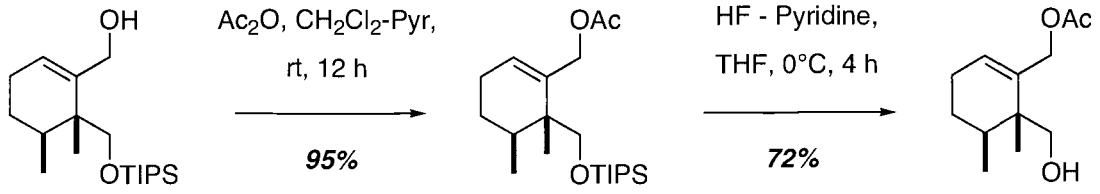
In view of this failure and the difficulties encountered with oxidation of aldehyde **116**, we began a search for a new approach to carboxylic acid **89**. The success of our Stille coupling strategy with **90** and **114** suggested that the carbonyl oxidation level required for cyclization at the 3-position of the furan could be preinstalled into the coupling fragment, and with this approach in mind we chose the allylic acetate **119** as the coupling partner for the stannane **114** (**Scheme 51**).



119 **120**

Scheme 51

The synthesis of the allylic acetate **119** commenced from the previously prepared allylic alcohol **96**. The alcohol **96** was smoothly converted to its acetate **121** with acetic anhydride and the triisopropylsilyl (TIPS) group was removed with hydrogen fluoride-pyridine to yield primary alcohol **122** (**Scheme 52**).

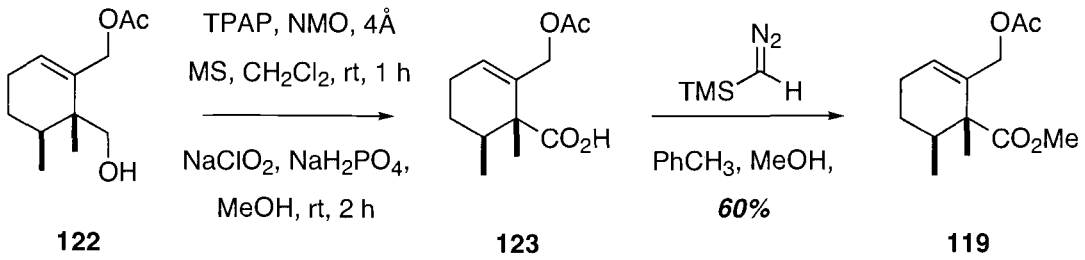


96 **121** **122**

Scheme 52

It was discovered that the alcohol **122** was prone to acetate migration under the conditions of its preparation, and therefore it was immediately oxidized to the aldehyde with tetra-*n*-propylammonium perruthenate (TPAP) and N-methylmorpholine-N-oxide (NMO). Further oxidation of the aldehyde with sodium chlorite was uneventful, and the resulting carboxylic acid **123** was

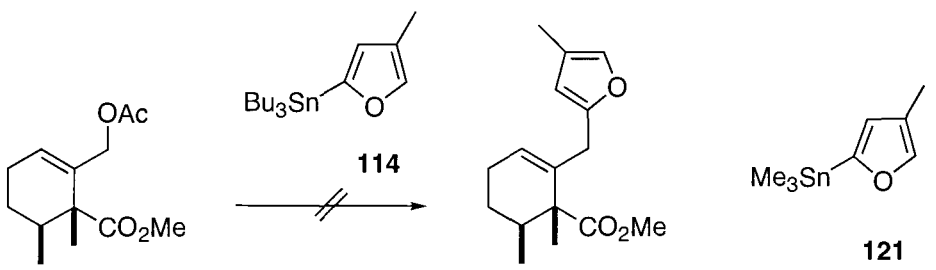
converted to its methyl ester **119** with trimethylsilyl diazomethane (**Scheme 53**).



122 **123** **119**

Scheme 53

With the allylic acetate **119** in hand, coupling studies were conducted with stannanes **114** and **121**. Unfortunately, attempts at a palladium-catalyzed Stille reaction of **119** with the stannane **121** under various conditions gave no coupled product (**Scheme 54**). In several instances, spectroscopic examination of the recovered material suggested that the acetate **110** had survived intact, but in all of the coupling attempts the stannane component, **114** or **121**, was destroyed.



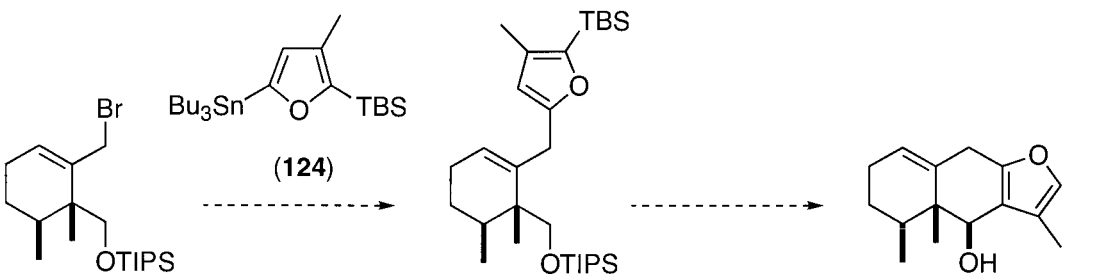
119 **114** **120** **121**

Scheme 54

It was surmised from these results that the failure of the coupling reactions attempted with **119** and **114** was due to the inherent instability of the furan component towards the relatively harsh reaction conditions, and that a more stable version of the furan partner would be needed for a successful coupling with **110**.

This conclusion suggested that the problems encountered in our Stille reaction could be alleviated by the introduction of a stabilizing substituent into the furan. Interestingly, recent studies by Bornowski have shown that the placement of a removable silyl group at C-2 introduces a significant degree of stability into 3-methylfuran.[30] This strategy was used to good effect in his synthesis of athanasin.[31]

Based upon this finding, a new approach to the Stille coupling was devised in which a potentially removable silyl substituent was incorporated at C-2 of the furan component (**Scheme 55**).

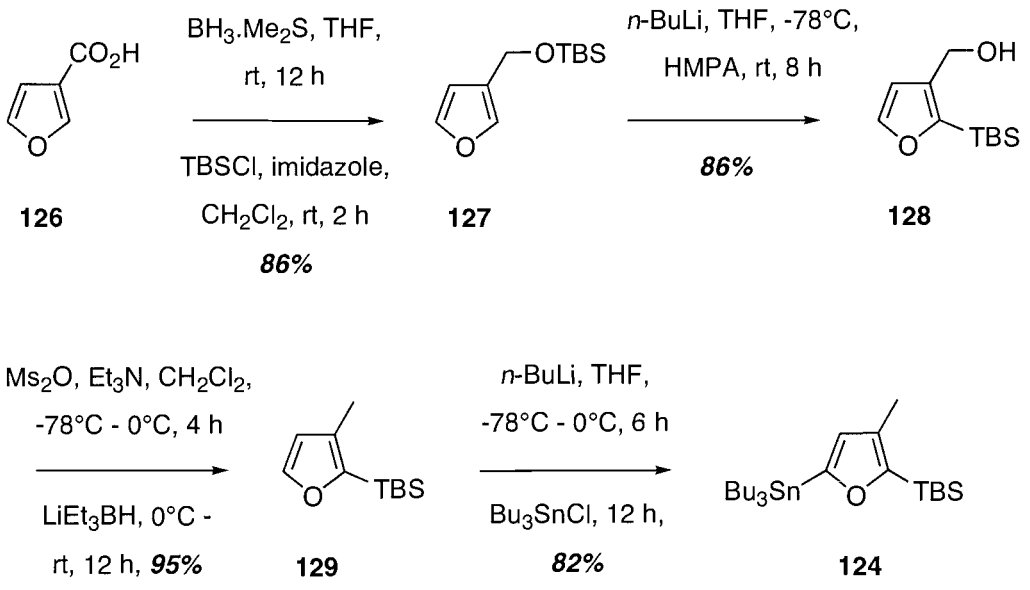


90 **125** **4**: 6β-Hydroxyeuryopsin

Scheme 55

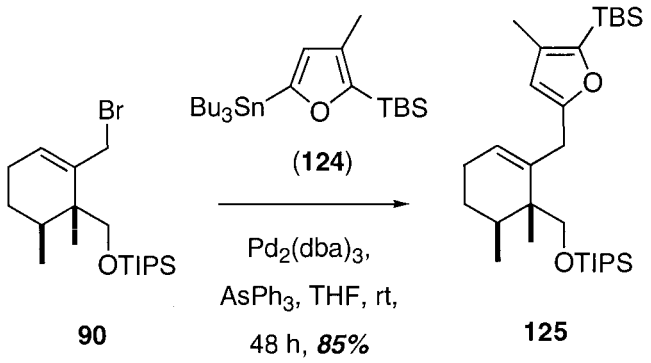
It was hoped that this structural change would lead to a stable series of intermediates, which would permit the elaboration to the furanoeremophilane core structure of **4**. The selection of the robust *tert*-butyldimethylsilyl (TBS) substituent for this purpose, as in furan **124**, would also allow the selective cleavage of the triisopropylsilyl (TIPS) ether from the coupled product **125**.

Our synthesis of furyl stannane **124** commenced from 3-furoic acid (**126**). Borane reduction[32] followed by silylation of the resulting primary alcohol provided *tert*-butyldimethylsilyl ether **127** and set the stage for a retro-Brook rearrangement that would lead to **128**. For this purpose, the silyl ether **127** was treated with *n*-butyllithium and hexamethylphosphoramide (HMPA) in tetrahydrofuran which smoothly effected a retro-Brook rearrangement to produce the disubstituted furan **128**.[33] Deoxygenation of the primary alcohol of **120** was accomplished by conversion to its mesylate and reduction with lithium triethylborohydride (Super Hydride). Conversion of **129** to the furylstannane **124** was completed *via* lithiation at C-5 of the furan with *n*-butyllithium and quenching of the lithiofuran with tributyltin chloride.



Scheme 56

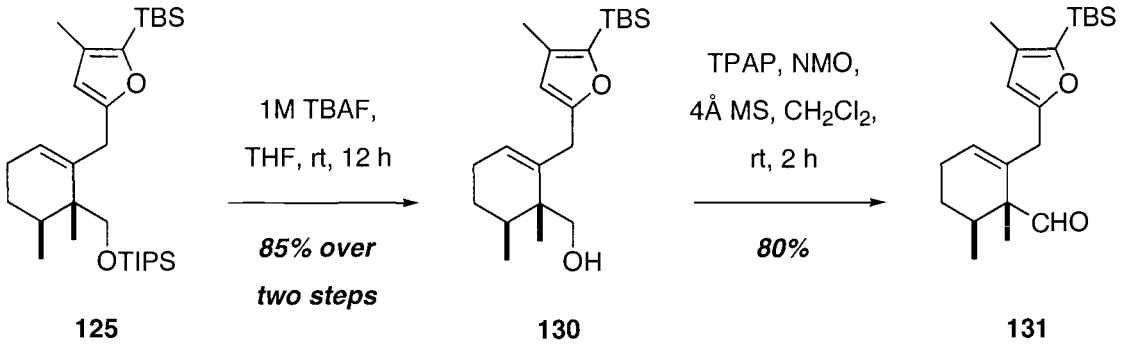
To our delight, the Stille coupling of bromide **90** with stannane **124** proved to be straightforward and gave **125** in good yield (**Scheme 57**). The coupling was best effected with tris(dibenzylideneacetone)dipalladium as the catalyst and triphenylarsine as the carrier ligand.[34]



Scheme 57

In the reaction of **90** with **124**, varying amounts of 2–*tert*-butyl-dimethylsilyl-3-methyfuran (**129**) were obtained resulting from destannylation of **124**, and consequently an excess of stannane component **124** was essential for achieving optimal conversion to **125**. It is noteworthy that the use of a similar stannane to **124** in a Stille reaction resulted mainly in homo-coupling to furnish a dimeric furan linked at the C-2 positions.[35] No dimeric structure of this type was encountered in our reaction with **124**.

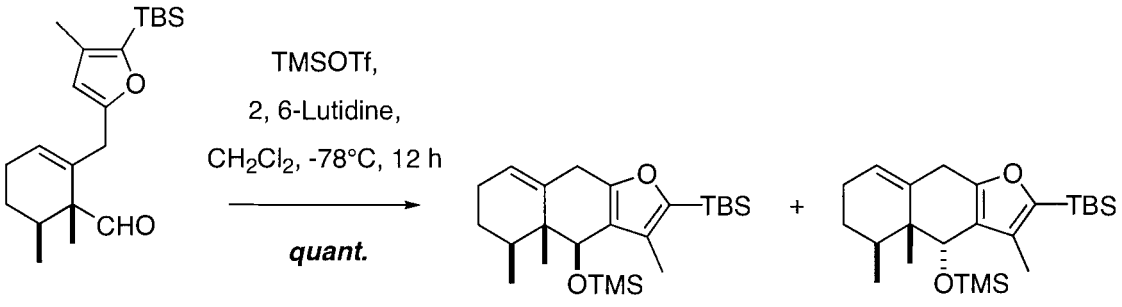
The conversion of coupled product **125** to aldehyde **131** was uneventful. As in the sequence previously described with **113**, the triisopropylsilyl (TIPS) protecting group was removed from **125** with the aid of a 1M solution of tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF),[36] and the resulting alcohol **130** was oxidized to aldehyde **131** with tetra-*n*-propylammonium perruthenate (TPAP) and N-methylmorpholine-N-oxide (NMO) (**Scheme 58**).



125 **130** **131**

Scheme 58

The availability of aldehyde **131** now enabled us to explore a Lewis-acid mediated cyclization approach to the furanoeremophilane nucleus. However, initial studies with this aldehyde proved to be somewhat discouraging. Thus, exposure of **131** to boron trifluoride etherate ($BF_3.OEt_2$) or diethylaluminum chloride (Et_2AlCl) resulted in complete decomposition. Happily, a successful cyclization was finally realized by using trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of 2, 6-lutidine. The tricyclic product was isolated in quantitative yield as a 4:1 mixture of trimethylsilyl (TMS) ether stereoisomers **132** and **133** respectively. These stereoisomers were inseparable and the mixture was therefore carried forward in the hope that their configuration could be established at a later stage.



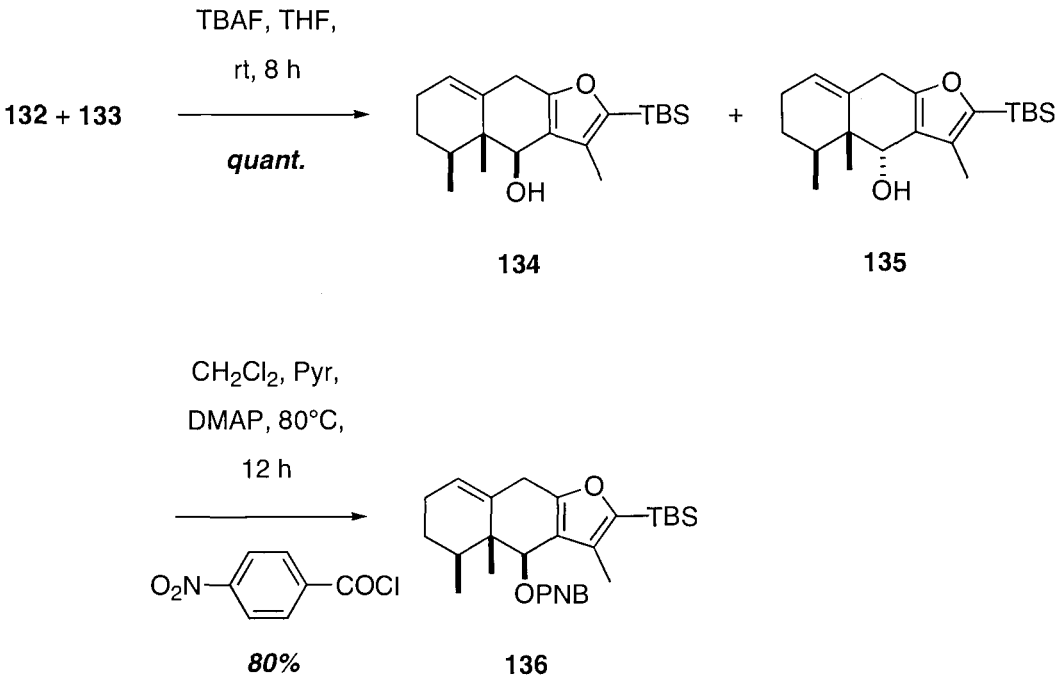
131 **132** **133**

Scheme 59

It is noteworthy that this annulation pathway is the first demonstration of a nucleophilic addition of a furan to an aldehyde. It also represents a unique approach to the furanoeremophilane skeleton in constructing the central

carbocyclic ring as the last ring-forming event. All other routes build a fused furan on to a preexisting decalin platform. There is no doubt that the silyl substituent on the furan **131** plays a pivotal role in its cyclization to **132** and **133** by suppressing the side reactions which take place at the furan when this substituent is absent.

The trimethylsilyl (TMS) group was cleaved from the mixture of **132** and **133** with a 1M solution of tetra-*n*-butylammonium fluoride (TBAF), but attempts to separate the resulting epimeric mixture of alcohols **134** and **135** were also unsuccessful. However, the alcohol mixture **134** and **135**, upon treatment with *p*-nitrobenzoyl chloride yielded a crystalline *p*-nitrobenzoate derivative **136** of the major alcohol.[37]



Scheme 60

After purification of this ester, X-ray diffraction analysis established its stereochemistry as shown in **136,** thereby confirming the configuration assigned to alcohol **134** (**Figure 3.1**).

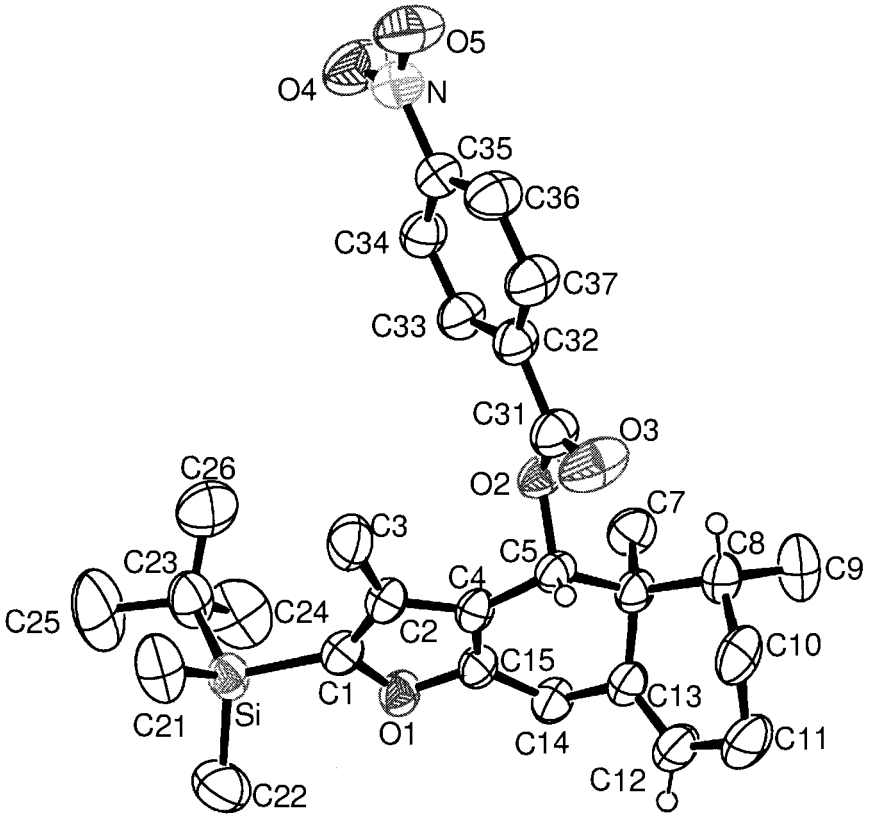
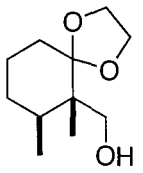


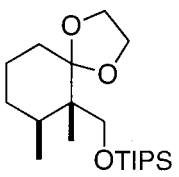
Figure 3.1

Thus, the major alcohol **134** from the cyclization of **131** possesses the relative stereochemistry corresponding to natural 6β-hydroxyeuryopsin (**4**). The successful construction of the core framework of the furanoeremophilane system now provided an opportunity the stage for elaboration of several naturally occurring members of this sesquiterpene family.

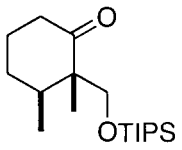
Experimental



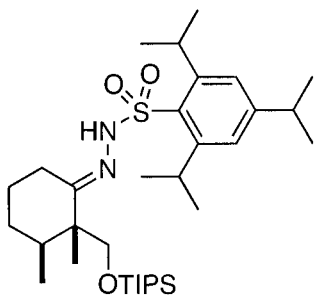
(6, 7-Dimethyl-1, 4-dioxa-spiro[4.5]dec-6-yl)-methanol To a solution of aldehyde **64** (0.49 g, 2.5 mmol) in methanol (2.5 mL) at ambient temperature under argon was added a solution of $NaBH_4$ (0.07 g, 1.85 mmol) in 5 mL of 2M NaOH and 45 mL of H_2O. The resulting mixture was stirred at ambient temperature for 12 h. The resulting mixture was diluted with Et_2O (100 mL), washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (180 g, Et_2O-Hexanes, 2:3) afforded 0.40 g (95%) of the titled compound as a clear oil: IR (neat) 3537, 2931, 2881, 1461, 1412, 1185, 1122, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 3H), 0.87 (d, 3H), 1.21 - 1.33 (m, 1H), 1.42 - 1.61 (m, 5H), 2.08 - 2.15 (m, 1H), 3.17 (d, J = 7 Hz, 1H), 3.30 (dd, J = 7, 11 Hz, 1H), 3.76 (d, J = 11 Hz, 1H), 3.91 - 4.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 15.8, 23.0, 29.5, 30.3, 32.7, 45.1, 64.3, 64.8, 65.8, 115.4; MS (CI) *m/z* 200, 183, 169, 157, 141, 127, 113; HRMS (CI) *m/z* 200.1412 (calcd for $C_{11}H_{20}O_3$: 200.1412).



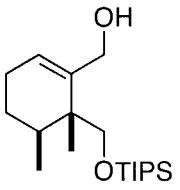
(6, 7-Dimethyl-1, 4-dioxa-spiro[4.5]dec-6-ylmethoxy)-triisopropyl-silane (97). To a solution of alcohol (0.40 g, 2.0 mmol) in CH_2Cl_2 (0.25 mL) at –78°C under argon was added a solution of TIPSOTf (1.32 ml, 2.2 mmol) and 2, 6-lutidine (2.0 mL). The resulting mixture was warmed to -20 over 4h. The resulting mixture was diluted with Et_2O (100 mL), washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (150 g, Et_2O-Hexanes, 1:19) afforded 0.71 g (100%) of the titled compound as a clear oil: IR (neat) 2942, 2866, 1463, 1381, 1189, 1090, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 – 1.00 (m, 6H), 1.00 – 1.12 (m, 18H), 1.19 - 1.31 (m, 1H), 1.38 - 1.61 (m, 8H), 1.85 – 1.19 (m, 1H), 3.75 (s, 2H), 3.80 – 3.98 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 12.4, 17.2, 18.2, 22.5, 30.5, 31.0, 37.5, 46.9, 64.8, 67.6, 113.6; MS (FAB) *m/z* 357, 313, 295, 283, 269, 241, 227, 199; HRMS (FAB) *m/z* 357.2824 (calcd for $C_{20}H_{41}O_3Si$: 357.2825).



2, 3-Dimethyl-2-triisopropylsilanyloxymethyl-cyclohexanone (98). To a solution of ketal (0.71 g, 2.0 mmol) in 10% aqueous acetone (25 mL) at 0 °C under argon was added PPTS (0.05 g, 0.2 mmol). The resulting solution was heated to reflux for 3 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (1.0 mL) and extracted with Et_2O (2 x 10 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (100 g, Et_2O-Hexanes, 1:19) afforded 0.53 g (86%) of the titled compound as a clear oil: IR (neat) 2941, 2866, 1712, 1463, 1104, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 3H), 0.90 (d, *J* = 7 Hz, 3H), 0.97 - 1.10 (m, 21H), 1.43 - 1.61 (m, 1H), 1.67 – 1.91 (m, 4H), 2.22 – 2.42 (m, 4H), 3.60 (d, *J* = 7 Hz, 1H), 3.98 (d, *J* = 7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 15.8, 16.0, 18.0, 18.4, 23.8, 29.2, 35.0, 39.1, 54.6, 66.7, 214.7; MS (CI) *m/z* 313, 295, 269, 239, 227, 199; HRMS (CI) *m/z* 313.2562 (calcd for $C_{18}H_{37}O_2Si$: 313.2562).

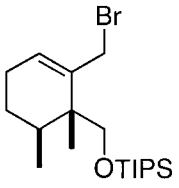


***N*-(2, 3-Dimethyl-2-triisopropylsilanyloxymethyl-cyclohexylidene)-*N'*-(2, 4, 6-triisopropyl-phenyl)-hydrazine (102).** To a solution of ketone **98** (0.53 g, 1.62 mmol) in THF (10 mL) at ambient temperature under argon was added trisylhydrazine (1.5 g, 1.8 mmol). The resulting solution was stirred at ambient temperature for 12 h. The mixture was concentrated under reduced pressure. Chromatography of the residue on silica (100 g, Et_2O-Hexanes, 1:19) afforded 0.56 g (86%) of the titled compound as a clear oil: IR (neat) 3243, 2958, 2866, 1600, 1563, 1462, 1425 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 7 Hz, 3H), 0.88 (s, 3H), 0.91 - 1.05 (m, 21H), 1.28 (m, 21H), 1.57 – 1.71 (m, 2H), 1.75 – 1.85 (m, 1H), 1.98 - 2.12 (m, 2H), 2.32 – 2.42 (m, 1H), 2.90 (q, J = 5 Hz, 1H), 3.48 (d, J = 7 Hz, 1H), 3.78 (d, J = 7 Hz, 1H), 4.20 (m, 1H), 7.11 (s, 2H), 7.45 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 12.9, 15.9, 18.0, 18.4, 19.5, 20.9, 23.5, 24.0, 25.2, 28.4, 30.2, 34.5, 34.6, 48.6, 69.5, 123.8, 131.9, 151.5, 153.3, 161.8; MS (CI) *m/z* 593, 549, 482, 392, 325, 295, 236; HRMS (CI) *m/z* 593.4174 (calcd for $C_{33}H_{61}O_3SiSN_2$: 593.4172).



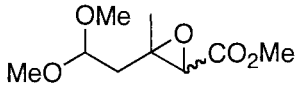
(5, 6-Dimethyl-6-triisopropylsilanyloxymethyl-cyclohex-1-enyl)-methanol (96) To a solution of hydrazone **102** (1.2 g, 2.0 mmol) in 10% TMEDA-Hexanes (25 mL) under argon at –78°C was added a 1.73 M solution of *tert*-butyllithium (2.31 mL, 4.0 mmol). The resulting solution was stirred at –78 °C for 30 mins and warmed to 0 °C for 5 mins. The resulting orange solution was cooled to –78 °C and DMF (1.0 mL) was added. The resulting solution was warmed to room temperature and stirred for 2 h. The mixture was diluted with Et_2O:H_2O (100 mL) and extracted with Et_2O (2 x 10 mL). The ether extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. To a solution of the residue in CH_2Cl_2 (10 mL) under argon at –78°C was added a 1.0M solution of DIBAL (2.0 mL, 2.0 mmol). The resulting solution was warmed to –20 °C over 30 mins. The solution was cooled to –78 °C and 0.5M solution of Rochelle's Salt (5 mL) was added. The resulting mixture was warmed to room temperature and stirred for 12 h. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The ether extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (100 g, Et_2O-Hexanes, 2:8)

afforded 0.56 g (85%) of the titled compound as a clear oil: IR (neat) 3354, 2942, 2866, 1659, 1463, 1433, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, J = 7 Hz, 3H), 0.87 (s, 3H), 1.05 – 1.15 (m, 21H), 1.30 – 1.42 (m, 1H), 1.52 – 1.62 (m, 1H), 1.82 – 1.95 (m, 1H), 2.00 - 2.08 (m, 2H), 3.05 (m, 1H), 3.65 (s, 2H), 3.9 (m, 1H), 4.2 (d, *J* = 4 Hz, 1H), 5.82 (t, *J* = 3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 16.3, 17.7, 18.4, 24.7, 26.8, 33.0, 42.8, 65.3, 69.2, 129.1, 142.0; MS (CI) *m/z* 327, 309, 283, 239; HRMS (CI) *m/z* 326.2637 (calcd for $C_{19}H_{38}O_2Si$: 326.2641).



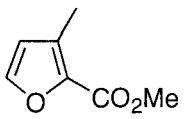
(2-Bromomethyl-1, 6-dimethyl-cyclohex-2-enylmethoxy)-triisopropyl-silane (90). To a solution of alcohol **96** (0.33 g, 1.0 mmol) in CH_2Cl_2 (10 mL) under argon at –78°C was added Et_3N and Ms_2O. The resulting solution was warmed to –20°C over 6h. The solution was cooled to –78°C and H_2O (5 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined ether extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. To a solution of the residue in THF (5 mL) under argon at room temperature was added LiBr (0.69 g. 10.0 mmol). The resulting solution

was stirred at room temperature for 12 h. The mixture was diluted with Et_2O and H_2O (100 mL, 1:1). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 mL). The ether extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (50 g, Et_2O-Hexanes, 1:19) afforded 0.37 g (95%) of the titled compound as a clear oil: IR (neat) 2959, 2941, 2865, 1463, 1098, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J* = 7 Hz, 3H), 0.95 – 1.15 (m, 21H), 1.30 – 1.42 (m, 1H), 1.52 – 1.62 (m, 1H), 1.82 – 1.95 (m, 1H), 2.00 - 2.2 (m, 2H), 3.72 (m, 2H), 4.15 (q, *J* = 7 Hz, 2H), 6.02 (t, *J* = 3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 16.3, 19.7, 24.6, 26.0, 30.0, 32.2, 36.0, 43.6, 68.8, 133.2, 148.2; MS (CI) *m/z* 389, 347, 309, 182; HRMS (CI) *m/z* 387.1718 (calcd for $C_{19}H_{36}BrOSi$: 387.1718).



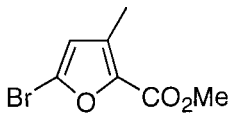
Methyl 5, 5-dimethoxy-3-methyl-2, 3-epoxypentanoate (107). To a solution of methyl chloroaceate (174g, 1.6 mol) and 4, 4-dimethoxy-2-butanone **106** (132g, 1.0 mol) in Et_2O (800 mL) under argon at –10 °C was added NaOEt (86g, 1.6 mol) *via* a powder addition funnel. During the addition, the temperature of the mixture was maintained below –5 °C. The resulting mixture was stirred at –10 °C for 2 h and then warmed to room temperature for 12 h.

The mixture was cooled to 0 °C and diluted with 10% aqueous acetic acid (200 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 200 mL). The combined ether layer was washed with saturated $NaHCO_3$ until the washings are no longer acidic. The ether layer was washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to afford a nearly quantitative yield of the crude glycidic ester as a 1:1 mixture of isomers. A small sample was purified by distillation (b. p – 78 - 80 at 0.45 mmHg): IR (neat) 2954, 2834, 1754, 1440, 1409, 1384, 1294 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.43 (s, 3H), 1.70 – 1.87 (m, 1H), 1.94 – 2.05 (m, 3H), 3.27 – 3.33 (m, 12H), 3.43 (s, 1H), 3.75 – 3.78 (m, 6H), 4.48 – 4.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 23.1, 36.0, 41.1, 52.6, 52.7, 53.1, 53.8, 54.7, 58.8, 59.4, 60.5, 60.8, 102.1, 102.6, 169.1, 169.2; MS (CI) *m/z* 203 (M+H)+, 187, 173, 155, 141, 113; HRMS (CI) *m/z* 203.0917 (calcd. for $C_9H_{15}O_5$:203.0919).

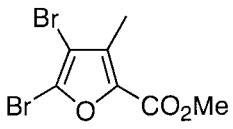


Methyl 3-methyl-2-furoate (108). Crude ester **107** (51.0g, 0.25 mol) was heated to 180 °C under argon for 48 h with the continuous removal of methanol. Chromatography of the residue on silica (400 g, EtOAc-Hexanes,

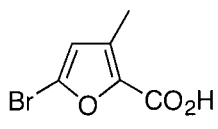
1:4) gave 22.4 g (64%) as a clear oil: IR (neat) 3143, 2999, 2954, 1712, 1602, 1490, 1440, 1406, 1295, 1196, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.79 (s, 3H), 6.25 (m, 1H), 7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 51.8, 115.4, 131.4 140.5, 145.2, 160.2; MS (CI) *m/z* 140(M+), 127, 109, 97; HRMS (CI) *m/z* 140.0476 (calcd for $C_7H_8O_3$: 140.0473).



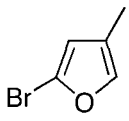
Methyl 5-bromo-3-methyl-2-furoate (109). To a solution of ester **108** (14.0 g, 0.1 mol) in DMF (20 mL) under argon at 0°C was added bromine (10.3 mL, 0.2 mol). The resulting dark mixture was stirred for 3h. The mixture was diluted with Et_2O (100 mL) and the ethereal solution was washed with saturated Na_2SO_3 solution (50 mL), saturated NaCl solution (50 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (800 g, EtOAc-Hexanes, 1:9) afforded 3.27 g (15%) as a yellow solid: M. p – 61°C; IR (neat) 2953, 1714, 1601, 1480, 1438, 1397, 1292 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.85 (s, 3H), 6.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 52.1, 117.3, 126.8, 134.0, 142.5; MS (CI) *m/z* 217(M+), 203, 187, 171, 147; HRMS (CI) *m/z* 217.9578 (calcd for $C_7H_7O_3Br$: 217.9578).



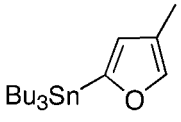
Methyl 4, 5-dibromo-3-methyl-2-furoate (110). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 11.6, 52.4, 108.4, 127.5, 133.1, 142.1, 158.7; MS (CI) *m/z* 297(M+-+1), 282, 266, 240; HRMS (CI) *m/z* 295.8677 (calcd for $C_7H_6O_3Br_2$: 295.8683).



5-Bromo-3-methyl-2-furoic acid (111). To a solution of methyl ester **109** (2.62 g, 12.0 mmol) in MeOH/H_2O (30:3 mL) under argon at room temperature was added KOH (1.35 g, 24.0 mmol). The resulting solution was stirred for 12 h and diluted with H_2O (50 mL). The resulting solution was extracted with Et_2O (2 x 50 mL) and the aqueous layer was cooled and acidified was 1N HCl. The resulting precipitate was filtered and dried over P_2O_5 to afford 2.32 g (95%) of the titled compound. M. p. – 160 - 161 °C (Lit. M. p. – 160 - 162 °C); ^{1}H NMR (300 MHz, DMSO) δ 2.31 (s, 3H), 4.94 (bs, 1H), 6.47 (s, 1H); ^{13}C NMR (300 MHz, DMSO) δ 10.6, 117.1, 126.6, 133.7, 143.0, 160.4; MS (CI) m/z 204 (M+), 189; HRMS (CI) m/z 203.9421 (calcd for $C_6H_5O_3Br$: 203.9422).

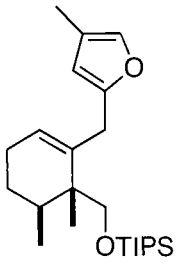


2-Bromo-3-methyl-furan (112). To a solution of acid (2.04 g, 10.0 mmol) in quinoline (5 mL) at room temperature under argon was added copper metal (0.42 g, 6.6 mmol). The resulting suspension was heated to 260°C and distillation (B. p - 140 - 144 °C (lit 138 - 144°C)) afforded 1.28 g (80%) of the titled compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 6.12 (s, 1H), 7.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.2, 114.0, 122.1, 123.4, 141.3.



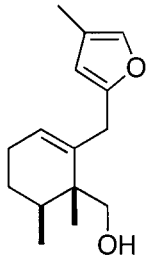
2-Tributylstannyl-4-methyl furan (114). To a solution of bromofuran **112** (0.80 g, 5.0 mmol) in THF (16 mL) at –78 °C under argon was added a 1.63 M solution of *n*-butyllithium (3.1 mL, 4.8 mmol) in hexanes. The resulting solution was allowed to warm to –50 °C over 6 h. The resulting solution was cooled to –78 °C and Bu_3SnCl (1.30 mL, 4.8 mmol) was added. The resulting solution was warmed to room temperature and stirred for 12 h. The mixture was diluted with Et_2O/H_2O (1:1, 100 mL), the layers were separated, and the aqueous

layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on silica (100g, Et_2O;Et_3N:hexanes, 1:1;18) gave 1.23 g (65%) of the titled compound as a colorless solid: IR (neat) 2957, 2926, 2871, 2853, 1463, 1376, 1101, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 – 0.92 (m, 9H), 1.04 – 1.15 (m, 9H), 1.25 – 1.40 (m, 6H), 1.51 – 1.59 (m, 6H), 2.05 (s, 3H), 6.40 (s, 1H), 7.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9, 10.4, 14.1, 27.6, 29.4, 119.8, 124.6, 144.4, 163.1; MS (CI) *m/z* 371 (M+), 315, 259, 200; HRMS (CI) *m/z* 370.1470 (Calcd for $C_{17}H_{32}OSn$: 370.1469).



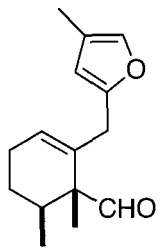
[1, 6-Dimethyl-2-(4-methyl-furan-2-ylmethyl)-cyclohex-2-enylmethoxy]-triisopropyl-silane (113). To a solution of bromide **90** (0.110g, 0.4 mmol) and stannane **114** (0.40g, 1.6 mmol) in DMF at ambient temperature under argon was added $Pd(CH_3CN)_2Cl_2$. The resulting solution was warmed to 50°C for 6 h. The reaction mixture was diluted with H_2O (20 mL) and Et_2O (30 mL) was added. The layers were separated and the aqueous layer was extracted with

Et_2O (2 x 20 mL). The combined ether layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on silica (150 g, Et_2O-Hexanes, 1:19) afforded 0. 055 g (56%) of the titled compound as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 – 0.99 (m, 6H), 1.09 (m, 21H), 1.32 – 1.52 (m, 2H), 2.02 (s, 3H), 2.02 – 2.10 (m, 3H), 3.29 – 3.39 (m, 2H), 3.44 – 3.52 (m, 1H), 3.61 – 3.69 (m, 1H), 5.34 (m, 1H), 5.91 (s, 1H), 7.11 (s, 1H) MS (FAB) *m/z* 390 (M+), 347, 307, 289; HRMS (FAB) *m/z* 390.2944 (Calcd for $C_{24}H_{42}O_2Si$: 390.2954).

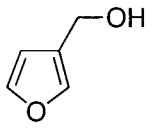


[1, 6-Dimethyl-2-(4-methyl-furan-2-ylmethyl)-cyclohex-2-enyl]-methanol (115). To a solution of silyl ether **113** (0.048 g, 0.12 mmol) in THF (1 mL) at ambient temperature under argon was added a 1.0M solution of TBAF (0.5 ml). The resulting dark solution was stirred for 12 h. The reaction mixture was diluted with H_2O (20 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined ether layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the

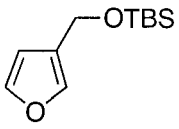
residue on silica (100 g, Et_2O-Hexanes, 1:1) afforded 0. 019 g (70%) of the titled compound as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (s, 3H), 0.95 (d, *J* = 7 Hz, 1H), 1.32 – 1.48 (m, 2H), 2.05 (s, 3H), 2.05 – 2.12 (m, 4H), 3.32 (s, 2H), 3.45 (dd, *J* = 10, 7 Hz, 1H), 3.62 (dd, *J* = 8, 3 Hz, 1H), 5.64 (t, *J* = 2 Hz, 1H), 5.96 (s, 1H), 7. 05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 16.4, 17.1, 25.6, 27.0, 31.0, 32.5, 43.7, 66.2, 109.7, 121.1, 129.5, 138.1, 138.3, 155.2.



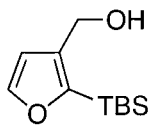
1, 6-Dimethyl-2-(4-methyl-furan-2-ylmethyl)-cyclohex-2-ene carbaldehyde (116). To a solution of alcohol **115** (10.0 mg, 0.02 mmol) in CH_2Cl_2 (1 ml) at ambient temperature under argon was added 4Å MS (25 mg), TPAP (3 mg) and NMO (10 mg). The resulting green suspension was stirred for 2 h, filtered and concentrated under reduced pressure. Chromatography of the residue on silica (5 g, Et_2O-Hexanes, 1:19) afforded the title compound (6.6 mg, 67 %) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0. 80 (s, 3H), 1.02 (s, 3H), 1.42 – 1.48 (m, 1H), 1.54 – 1.70 (m, 1H), 1.95 (s, 3H), 1.85 – 2.02 (m, 4H), 3.12 (q, J = 8Hz, 2H), 5.67 (t, J = 2 Hz, 1H), 5.86 (s, 1H), 7. 05 (s, 1H), 9.21 (s, 1H).



Furan-3-methanol. To a solution of 3-furoic acid **126** (2.24 g, 20.0 mmol) in THF (10 mL) at 0 °C under argon was added a 2M solution of borane-dimethyl sulphide in THF (12 mL, 24.0 mmol). The resulting mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was carefully diluted with H_2O (20 mL) and solid NaCl and $NaCO_3$ (1:1, 20 g) was added. The mixture was extracted with Et_2O (2 x 10 mL), washed with saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on silica (300 g, Et_2O-Hexanes, 1:1) afforded 1.56 g (80%) of the titled compound as a clear oil: IR (neat) 3335, 2928, 2880, 1504, 1388, 1157, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (bs, 1H), 4.44 (s, 2H), 6.37 (m, 1H), 7.34 - 7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.6, 110.2, 125.6, 140.3, 143.8; MS (CI) *m/z* 98 (M^+), 95; HRMS (CI) *m/z* 98.0366 (calcd for $C_5H_6O_2$: 98.0368).

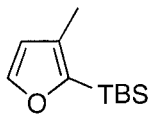


3-(*tert*-Butyldimethylsilyloxy)methylfuran (127). To a solution of 3-(hydroxymethyl)furan (2.94 g, 30.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C under argon was added imidazole (2.45 g, 36.0 mmol). After dissolution of the imidazole, solid *tert*-butyldimethylsilyl chloride (5.43 g, 36.0 mmol) was added, and after 10 min the mixture was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with Et_2O/H_2O (1:1, 100 mL). The layers were separated, and the aqueous layer was extracted with ether (3 x 25 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on silica (300 g, Et_2O-Hexanes, 1:19) afford 6.36 g (100%) of the silyl ether: IR (neat) 2956, 2930, 2858, 1502, 1472, 1463, 1255, 1093, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.93 (s, 9H), 4.61 (d, J = 1 Hz, 2H), 6.37 (m, 1H), 7.35 – 7.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.8, 18.8, 26.3, 57.8, 110.0, 126.1, 139.7, 143.5; MS (CI) *m/z* 212(M+), 197, 155, 137, 125, 111, 99, 89; HRMS (CI) *m/z* 212.1235 (calcd for $C_{11}H_{20}O_2Si$: 212.1232).



2-*tert*-Butyldimethylsilyl-3-(hydroxymethyl)furan (128). To a solution of 3-(*tert*-butyldimethylsilyloxy)methylfuran **127** (4.24 g, 20.0 mmol) in THF (40 mL)

under argon at –78 °C was added a 1.6M solution of *n*-butyllithium (12.5 mL, 22.0 mmol) in hexanes and hexamethylphosphoramide (HMPA) (3.94 mL, 22.0 mmol). The resulting mixture was allowed to warm to room temperature over 6 h and stirred at room temperature for 12 h. The mixture was diluted with Et_2O/H_2O (1:1, 100 mL), the layers were separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic extracts was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (300 g, EtOAc:hexanes 2:3) gave 3.35 g (79%) of the titled compound as a colorless solid: M. p. – 44 - 45 °C IR (neat) 3322, 2953, 2929, 2857, 1471, 1412, 1390, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 6H), 0.90 (s, 9H), 2.12 (bs, 1H), 4.55 (s, 2H), 6.46 (d, J = 1 Hz, 1H), 7.57 (d, J = 1Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3, 17.7, 26.7, 57.4, 110.9, 136.3, 147.1, 155.2; MS (CI) *m/z* 213 $(M+H)^+$, 195, 155, 127, 99; HRMS (CI) *m/z* 195.1207 (Calcd for $C_{11}H_{19}OSi$: 195.1205).

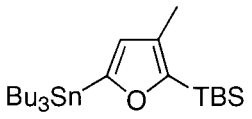


2-(*tert*-Butyldimethylsilyl)-3-methylfuran (129). To a solution of alcohol (2.12 g, 10.0 mmol) in CH_2Cl_2 (40 mL) at –78 °C under argon was added

Ms_2O (2.09 g, 12.0 mmol) and Et_3N (1.7 mL, 12.0 mmol). The resulting mixture was stirred at –78 °C for 1 hr and at 0 °C for 4 hr. The reaction mixture was carefully diluted with Et_2O/H_2O (1:1, 100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts are washed with aqueous saturated NaCl, dried over anhydrous Na_2SO_4 and concentration under reduced pressure to afford 3.54 g (100%) of the methanesulfonate which was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 6H), 0.91 (s, 9H), 2.95 (s, 3H), 5.19 (s, 2H), 6.51 (m, 1H), 7.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 17.7, 26.7, 38.8, 64.2, 111.6, 129.2, 147.6, 158.9.

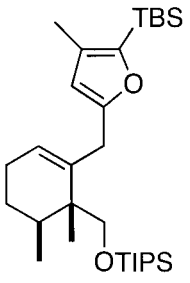
To a solution of methanesulfonate (3.54 g, 10.0 mmol) in THF (40 mL) at 0 °C under argon was added a 1M solution of lithium triethylborohydride (20 mL, 20.0 mmol) in THF. After 10 min, the cooling bath was removed and the solution was allowed to stir at room temperature for 24 hr. The reaction mixture was carefully diluted with Et_2O/H_2O (1:1, 100 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic extracts are washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentration under reduced pressure. Purification of the crude product by flash chromatography on silica (150 g, Et_2O:hexanes, 1:19) provides 1.86 g (95%) of 2-(*tert*-butyldimethylsilyl)-3-methylfuran **129** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 6H), 0.91

(s, 9H), 2.13 (s, 3H), 6.23 (m, 1H), 7.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 11.8, 18.2, 26.8, 113.1, 131.1, 146.3, 153.7; MS (CI) *m/z* 196 (M+), 181, 139, 125, 111; HRMS (CI) *m/z* 196.1277 (calcd for $C_{11}H_{20}OSi$: 196.1283).



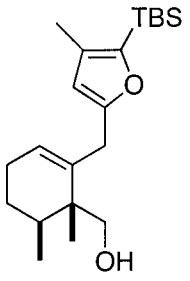
2-Tri-n-butylstannane-5-(*tert*-butyldimethylsilyl)-4-methylfuran (124). To a solution of furan **129** (0.78 g, 4.0 mmol) in THF (8 mL) at –78 °C under argon was added a 1.6M solution of *n*-butyllithium (3.0 mL, 4.8 mmol) in hexanes. The resulting solution was allowed to warm to room temperature over 6 h. The resulting solution was cooled to –78 °C and Bu_3SnCl (1.30 mL, 4.8 mmol) was added. The resulting solution was warmed to room temperature and stirred for 12 h. The mixture was diluted with Et_2O/H_2O (1:1, 100 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts was washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on silica (100g, Et_2O;Et_3N:hexanes, 1:1;18) gave 1.84 g (95%) of the titled compound as a colorless solid: ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 6H), 0.86 – 0.92 (m, 6H), 0.90 (s, 9H), 1.04 (t, *J* = 8 Hz, 6H), 1.26 – 1.39 (m, 9H), 1.51 – 1.59 (m, 6H), 2.12 (s, 3H), 6.38 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ –5.4, 10.5, 11.6, 14.1, 18.3, 27.3, 28.0, 29.4, 124.9, 131.0, 158.4, 164.9; MS (CI) *m/z* 486 $(M+H)^+$, 429, 373, 315, 291; HRMS (CI) *m/z* 486.2349 (Calcd for $C_{23}H_{46}OSiSn$: 486.2340).



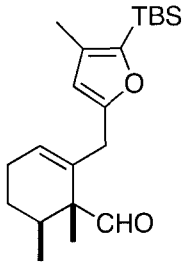
2-(*tert*-Butyl-dimethyl-silanyl)-5-(5, 6-dimethyl-6-triisopropylsilanyloxy-methyl-cyclohex-1-enylmethyl)-3-methyl-furan (125). To a solution of bromide **90** (0.110 g, 0.28 mmol) and stannane **125** (0.58 g, 1.12 mmol) in THF (0.112 mL) at ambient temperature under argon was added $Pd_2(dba)_3$ (0.08 g) and $AsPh_3$ (0.08 g). The resulting dark solution was stirred for 48 h. The reaction mixture was diluted with H_2O (20 mL) and Et_2O (30 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined ether layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on silica (150 g, Et_2O-Hexanes, 1:19) afforded 0. 12 g (85%) of the titled compound as a clear oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.29 (s, 6H), 0.88 (s, 3H), 0.90 (d, *J* = 7 Hz, 3H), 0.92 (s, 9H), 1.01 – 1.15

(m, 21H), 1.32 – 1.52 (m, 2H), 1.60 – 1.70 (m, 2H), 1.95 - 2.05 (m, 3H), 2.12 (s, 3H), 3.31 – 3.36 (m, 2H), 3.44 – 3.52 (m, 1H), 3.61 – 3.69 (m, 1H), 5.34 (m, 1H), 5.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 12.5, 13.1, 13.9, 16.2, 17.6, 18.2, 18.5, 19.3, 24.6, 26.8, 31.9, 32.1, 43.4, 67.6, 67.9, 110.3, 125.8, 132.6, 139.3, 151.5, 159.4; MS (CI) *m/z* 504 (M^+), 461, 317, 273; HRMS (FAB) *m/z* 504.3810 (Calcd for $C_{30}H_{56}O_2Si_s$: 504.3818).



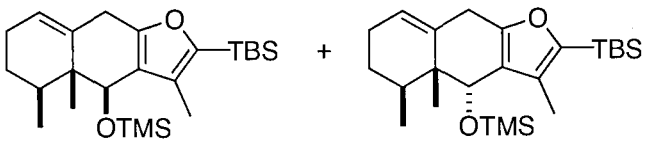
{2-[5-(*tert*-Butyl-dimethyl-silanyl)-4-methyl-furan-2-ylmethyl]-1, 6-dimethylcyclohex-2-enyl}-methanol (130). To a solution of silyl ether **125** (0.12 g, 0.24 mmol) in THF (5 mL) at ambient temperature under argon was added a 1.0M solution of TBAF (2.5 ml). The resulting dark solution was stirred for 12 h. The reaction mixture was diluted with H_2O (20 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined ether layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue on silica (100 g, Et_2O-Hexanes, 1:1) afforded 0. 083 g (100%) of the titled compound as a clear oil:

IR (neat) 3383, 2954, 2926, 2856, 1599, 1470, 1462, 1249, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 6H), 0.81 (s, 3H), 0.90 (s, 9H), 0.95 (d, *J* = 7 Hz, 1H), 1.36 – 1.50 (m, 2H), 2.05 – 2.13 (m, 3H), 2.13 (s, 3H), 3.32 (s, 2H), 3.45 (dd, *J* = 10, 7 Hz, 1H), 3.66 (dd, *J* = 8, 2 Hz, 1H), 5.69 (t, *J* = 2 Hz, 1H), 5.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.6, 12.2, 16.4, 17.1, 18.0, 25.6, 26.9, 27.1, 31.2, 32.8, 43.9, 66.1, 110.1, 130.1, 133.1, 138.1, 138.1, 152. 8, 158.8; MS (CI) *m/z* 348 (M^+), 317, 291, 273, 261, 245, 215, 199, 183, 169; HRMS (CI) *m/z* 348.2483 (Calcd for $C_{21}H_{36}O_2Si$: 348.2484).



2-[5-(*tert*-Butyl-dimethyl-silanyl)-4-methyl-furan-2-ylmethyl]-1, 6-dimethyl-cyclohex-2-enecarbaldehyde (131). To a solution of alcohol **130** (0.083 g, 0.24 mmol) in CH_2Cl_2 (25 mL) at ambient temperature under argon was added tetra-*n*-propylammonium perruthenate (0.050 g), N-methylmorpholine N-oxide (0.40g) and freshly activated 4Å molecular sieves (0.050 g). The resulting green suspension was stirred for 2 h, filtered and concentrated under reduced pressure. Chromatography of the residue on silica (50g, Et_2O-Hexanes, 1:19) afforded the title compound (0.066 mg, 80%) as a colorless oil: IR (neat) 2954,

2927, 2856, 1725, 1470, 1461, 1249 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 6H), 0.81 (d, *J* = 7 Hz, 1H), 0.94 (s, 9H), 1.05 (s, 3H), 1.40 (m, 1H), 1.56 (m, 1H), 1.95 (m, 1H), 2.10 (s, 3H), 2.18 (m, 2H), 3.12 (q, *J* = 7 Hz, 2H), 5.69 (t, *J* = 2 Hz, 1H), 5.96 (s, 1H), 9.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 11.9, 13.5, 16.5, 18.1, 25.6, 25.7, 26.8, 32.5, 55.8, 110.8, 128.9, 132.6, 134.3, 152.3, 157.3, 204.9; MS (CI) *m/z* 346 (M+), 331, 317, 289, 261, 245, 215, 205, 183, 167; HRMS (CI) *m/z* 346.2323 (Calcd for $C_{21}H_{34}O_2Si$: 348.2328).



TMSOTf-Mediated Cyclization. To a solution of aldehyde **131** (0.063 g, 10.0 mmol) in CH_2Cl_2 (3 mL) at –78 °C under argon was added 2, 6-lutidine (0.23 mL, 12.0 mmol) and TMSOTf (0.160 mL, 12.0 mmol). The resulting mixture was stirred at –78 °C for 12 h. The reaction mixture was carefully diluted with H_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts are washed with aqueous saturated NaCl, dried over anhydrous Na_2SO_4 and concentration under reduced pressure. Chromatography of the residue on silica (50g, Et_2O-Hexanes, 1:19) afforded the title compound (0.072 mg, 100%) as a colorless

oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (Major Isomer) 0.25 (s, 3H), 0.28 (s, 3H), 0.30 (s, 6H), 0.96 (s, 9H), 1.04 (d, *J* = 7 Hz, 3H), 1.08 (s, 3H), 1.46 – 1.60 (m, 1H), 1.80 – 1.95 (m, 2H), 2.15 (s, 3H), 2.95 (d, *J* = 7 Hz, 1H), 3.45 (d, *J* = 7 Hz, 1H), 4.86 (s, 1H), 5.62 (d, *J* = 2Hz, 1H).

Reference

1. (a) Yick, C-Y.; Tsang, T-K.; Wong, H. N. C. *Tetrahedron* **2003**, *59*, 325. (b) Chakraborty, A.; Kar, G. K.; Ray, J. K. *Tetrahedron* **1997**, *53*, 2989.
2. Frimer, A. A. *Chem. Rev.* **1979**, *79*, 359.
3. Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.
4. (a) Takai, K.; Hotta, Y.; Ohsima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417. (b) Takai, K.; Hotta, Y.; Ohsima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698.
5. Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. *Org. Lett.* **2001**, *3*, 2701.
6. Smith, A. B.; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845.
7. White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 9912.
8. Bell, R. A.; Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1966**, *31*, 2536.
9. Foote, C. S.; Denny, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 5162.
10. Gollnick, K. *Advan. Photochem.* **1968**, *6*, 1.
11. (a) Stachel, S. J.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6785. (b) Murray, R. W.; Singh, M. *Organic Syn. Coll. Vol. 9*, 288.

12. Leonard, J.; Bennett, L.; Mahmood, A. *Tetrahedron Lett.* **1999**, *40*, 3965.

13. Reese, C. B.; Risius, A. C. *J. Org. Chem.* **1989**, *54*, 3515.

14. (a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738. (b) Rizzo, C. J.; Smith, A. B. *Tetrahedron Lett.* **1988**, *29*, 2793.

15. Shapiro, R. H. *Org. React.* **1975**, *23*, 405.

16. Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

17. Bourgeois, D.; Lallemand, J-Y.; Pancrazi, A.; Prunet, J. *Synlett* **1999**, *10*, 1555.

18. Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233.

19. Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1974**, *38*, 2157.

20. Knight, D. W.; Rustidge, D. C. *J. Chem. Soc. (C)* **1986**, 679.

21. (a) Burness, D. M. *J. Org. Chem.* **1956**, *21*, 102. (b) Burness, D. M. *Org. Synth.* **1959**, *39*, 49.

22. Reeves, W. P.; King, R. M. *Synthetic Comm.* **1993**, *23*, 855.

23. Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328.

24. Mori, K.; Komatsu, M. *Tetrahedron* **1987**, *43*, 3409.

25. (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* 1996, 50, 1.

26. (a) Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551. (b) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 6299.

27. (a) Griffith, W. P.; Ley, S. J.; Whitcombe, G. P.; White, A. D. *Chem. Comm.* **1987**, 1625. (b) Griffith, W. P.; Ley, S. J. *Aldrichimica Acta.* **1990**, *23*, 13.

28. (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (b) Tanis, S. P.; Dixon, L. A.; Herrinton, P. M. *Tetrahedron Lett.* **1985**, *26*, 5347. (c) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.

29. Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1988**, *53*, 4929.

30. Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron* 19 , *46*, 1199.

31. Bojack, G.; Bornowski, H. *Tetrahedron* 19 , *47*, 9179.

32. Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786.

33. (a) Bures, E.; Spinazze, P. G.; Beese, G.; Hunt, I. R.; Rogers, C.; Keay, B. *J. Org. Chem.* **1997**, *62*, 8741. (b) Bures, E.; Nieman, J. A.; Yu, S.; Spinazze, P. G.; Bontront, J-L. J.; Hunt, I. R.; Rauk, A.; Keay, B. *J. Org. Chem.* **1997**, *62*, 8750.

34. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

35. Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492.

36. Kwon, O.; Su, D-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*. 1880.

37. Paquette, L. A.; Montgomery, F. J.; Wang, T-Z. *J. Org. Chem.* **1995**, *60*, 7857.

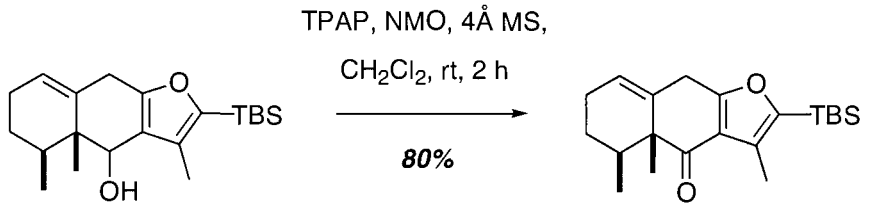
Chapter IV.

Routes to Furanoeremophilanes and Eremophilenolides

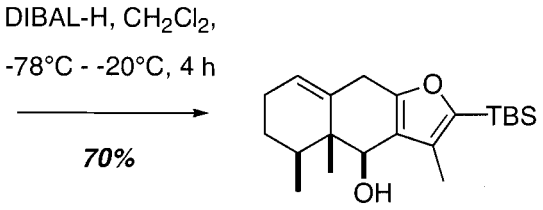
With a route to a substance possessing the furanoeremophilane framework completed, attention now turned to extending our approach to specific members of this terpenoid family, including 6β-hydroxyeuryopsin (**4**) and euryopsol (**10**).

Since the task of separating alcohols **134** and **135** proved to be an insurmountable problem, recourse was made to an oxidation-reduction sequence[1] with the goal of obtaining a single isomer for further studies. Oxidation of the mixture of alcohols **134** and **135** proceeded smoothly with catalytic tetra-*n*-propylammonium perruthenate (TPAP) and stoichoimetric N-methylmorpholine-N-oxide (NMO)[2] to give ketone **137** as a single compound in high yield.

Reduction of ketone **137** was examined with several reducing agents with the hope that a pure alcohol with the desired β configuration would be obtained. Eventually, it was found that the use of diisobutylaluminum hydride (DIBAL) produced a single isomer,[3] whose ^{1}H NMR spectrum corresponded to the major product **134** from the cyclization of aldehyde **131** (**Scheme 61**).



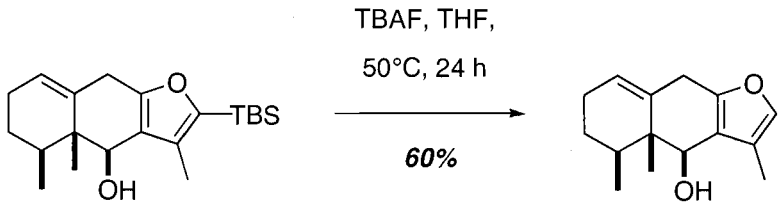
134 + 135 **137**



134

Scheme 61

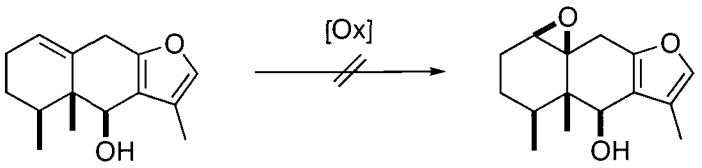
Removal of the *tert*-butyldimethyl (TBS) substituent from the furan of **134** proved to be challenging, but was achieved under strenuous conditions[4] using a 2M solution of tetra-*n*-butylammonium fluoride (TBAF) in tetrahydrofuran (THF). These conditions provided racemic 6β-hydroxyeuropsin (**4**), identical by spectral comparison with the natural terpenoid isolated by De Vivar (**Scheme 62**).[5]



134 **4**: 6β-Hydroxyeuryopsin

Scheme 62

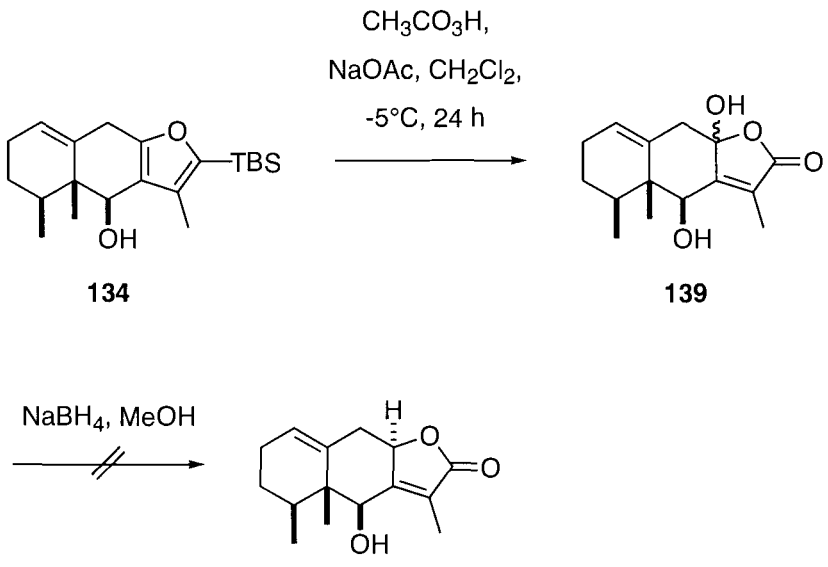
The availability of synthetic 6β-hydroxyeuropsin (**4**) now afforded an opportunity to examine the hydroxylation of the trisubstituted olefin as a means for obtaining euryopsol (**10**). Inspection of a molecular model of the tricyclic structure **4** suggested that attack by an oxidizing agent would occur from the β-face. However, initial attempts at epoxidizing the hindered olefin of **4** with *meta*-chloroperoxybenzoic acid (mCPBA) or dimethyl dioxirane (DMDO) only resulted in its decomposition (**Scheme 63**)



4: 6β-Hydroxyeuryopsin **138**

Scheme 63

Closer examination of the crude mixture from these oxidations suggested that reaction was occurring at the furan rather than the double bond. In following up this observation, it was found that prolonged exposure of alcohol **134** to peracetic acid under buffered conditions yielded a mixture of epimeric butenolides **139** that clearly indicated oxidation had taken place at the furan ring (**Scheme 64**).[6] Unfortunately, attempts to reduce this mixture of lactones **139** to tolulaccanolide A (**14**) led to a complex mixture of products.[7]

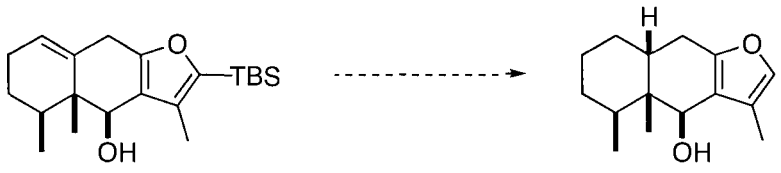


134 **139**

14: Toluccanolide A

Scheme 64

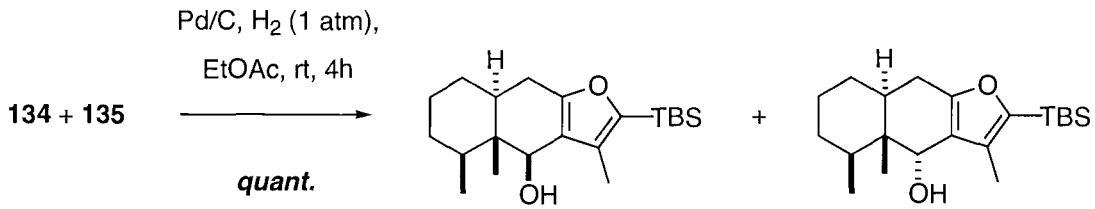
In a further extension of our studies based upon the reactivity of **134**, we attempted the elaboration of this core structure towards several other naturally occurring members of the furanoeremophilane family. Specifically, we conjectured that stereoselective hydrogenation of **134** followed by desilylation would provide petasalbine (**5**) (**Scheme 65**), and further oxidation of the secondary alcohol to a ketone would lead to ligularone (**6**).



134 **5**: Petasalbine

Scheme 65

Catalytic hydrogenation of the mixture of alcohols **134** and **135**, using palladium-on-carbon, cleanly provided two products in excellent yield (**Scheme 67**). The products were readily separable and it was clear from their NMR spectra that both were the result of saturation of the trisubstituted double bond. However, upon removal of the TBS group, neither product corresponded spectroscopically to petasalbine (**5**), and we were led to conclude that hydrogenation of **134** and **135** occurred in each case from the α face. Thus, the proposed structures of the products from hydrogenation of **134** and **135** are **140** and **141**, respectively.



140 **141**

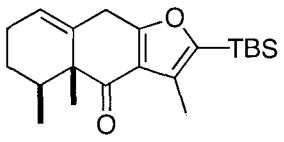
Scheme 67

The outcome of the hydrogenation of **134** and **135** suggests that steric hindrance by the quaternary center overrides any conformational preference for delivery of the reagent from the β face of these structures.

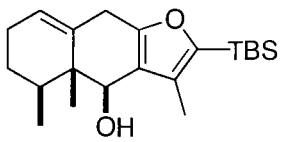
In summary, we have developed a new approach to the core structure of the furanoeremophilane sesquiterpenoids. The approach was applied successfully to a synthesis of (±)-6β-hydroxyeuryopsin (**4**), but failed to deliver

euryopsol (**10**) or petasalbine (**5**). It was discovered that mild oxidation of the furan portion of the furanoeremophilane nucleus leads to a butenolide which potentially affords entry to eremophilenolides, such as tolucanolide A (**14**).

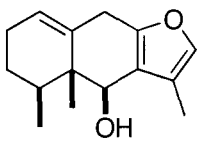
Experimental



11-(*tert*-Butyldimethylsilyl)-6-ketofuranoeremophil-1(10)-ene (137). To a solution of alcohols **134** and **135** (8.0 mg, 0.01 mmol) in CH_2Cl_2 (1 ml) at ambient temperature under argon was added 4Å MS (25 mg), TPAP (1 mg) and NMO (10 mg). The resulting green suspension was stirred for 2 h, filtered and concentrated under reduced pressure. Chromatography of the residue on silica (10 g, EtOAc-Hexanes, 1:19) afforded the title compound (5.0 mg, 80%) as a colorless oil. IR (neat) 2953, 2928, 2856, 1679, 1650, 1607, 1431, 1412, 1251, 836, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 6H), 0.91 (s, 9H), 1.15 (d, *J* = 7 Hz, 3H), 1.21 (s, 3H), 1.39 - 1.55 (m, 2H), 1.90 - 2.07 (m, 2H), 2.26 (s, 3H), 2.36 - 2.43 (m, 1H), 3.32 (d, *J* = 8 Hz, 1H), 3.71 (dq, *J* = 1, 8 hz, 1H), 5.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.3, 10.8, 17.8, 18.1, 19.9, 24.0, 26.8, 29.0, 31.9, 32.7, 51.3, 119.3, 126.7, 131.3, 135.9, 154.8, 168.0, 200.2; MS (CI) 344 (M+), 329, 287, 259, 217, 189, 97 HRMS (CI) m/z 344.2174 (calcd for $C_{21}H_{32}O_2Si$) 344.2172.



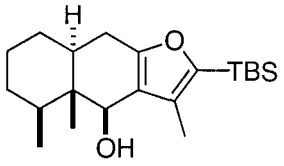
11-(*tert*-Butyldimethylsilyl)-6β-hydroxyeuropoysin (134). To a solution of ketone (16.0 mg, 0.046 mmol) in CH_2Cl_2 (0.4 mL) at -78°C under argon was added a 1.0M solution of DIBAL (0.096 mL, 0.096 mmol). The reaction mixture was allowed to warm to -20°C over 4 h. The resulting solution was recooled to –78°C and was quenched with 0.5M Rochelle salt. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined ether layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (10g, Et_2O-Hexanes, 1:9) afforded 11.0 mg (70%) of the titled compound as a colorless oil: IR (neat) 3423, 2951, 2926, 2855, 1461, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 6H), 0.94 (s, 9H), 1.03 (s, 3H), 1.06 (d, *J* = 7 Hz, 3 H), 1.43 - 1.53 (m, 2H), 1.70 - 1.78 (m, 1H), 1.89 - 1.95 (m, 1H), 2.02 - 2.16 (m, 2H), 2.18 (s, 3H), 3.02 (d, *J* = 7 Hz, 1H), 3.45 (d, *J* = 7 Hz, 1H), 4.69 (d, *J* = 8 Hz, 1H), 5.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 15.7, 16.2, 18.1, 22.5, 26.9, 27.3, 30.1, 32.0, 33.6, 43.5, 73.7, 120.3, 123.9, 132.2, 137.4, 152.9, 154.6; MS (CI) *m/z* 346(M^+), 329, 289, 259, 229, 219, 197; HRMS (CI) *m/z* 346.2325 (calcd for $C_{21}H_{34}O_2Si$: 346.2328).



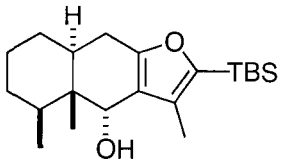
6β-hydroxyeuryopsin (4). To a solution of alcohol (2.0 mg, 0.006 mmol) in THF (0.2 mL) under argon was added solid TBAF (0.060 g, 0.23 mmol). The resulting red solution was heated to 55°C for 24 h. The resulting solution was diluted with ether and water. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined ether layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue on silica (1g, Et_2O-Hexanes, 1:9) afforded 0.8 mg (60%) of the titled compound: ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.06 (d, J = 7 Hz, 3 H), 1.40 - 1.50 (m, 2H), 1.70 - 1.78 (m, 1H), 1.89 - 1.95 (m, 1H), 2.02 - 2.16 (m, 2H), 2.05 (s, 3H), 2.97 (d, *J* = 7 Hz, 1H), 3.42 (d, *J* = 7 Hz, 1H), 4.67 (d, *J* = 8 Hz, 1H), 5.65 (m, 1H), 7.05 (s, 1H).

Hydrogenation of 134 and 135. To a solution of alcohol (10 mg, 0.02 mmol) in EtOAc (1 mL) was added palladium on carbon (4 mg). The resulting suspension was hydrogenated at 1 atm over a period of 6 h. The resulting suspension was concentrated under reduced pressure. Chromatography of

the residue on silica (10g, Et_2O-Hexanes, 1:9) afforded 7 mg (70%) of **140** as a colorless oil and 3 mg (30%) of **141** as a crystalline solid:



Major Product **140:** IR (neat) 2951, 2925, 2855, 1637, 1462, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 6H), 0.80 (s, 3H) 0.96 (s, 9H), 1.18 (d, J = 7 Hz, 3 H), 1.43 - 1.53 (m, 2H), 1.70 - 1.78 (m, 1H), 1.89 - 1.95 (m, 1H), 2.02 - 2.16 (m, 2H), 2.15 (s, 3H), 2.30 – 2.45 (m, 2H), 4.55 (d, *J* = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.4, 11.1, 18.1, 18.9, 26.7, 26.9, 28.5, 30.1, 32.5, 42.6, 43.3, 44.1, 120.1, 132.0, 152.2, 154.8; MS (CI) *m/z* 346(M^+), 329, 289, 259, 229, 219, 197; HRMS (CI) *m/z* 348.2490 (calcd for $C_{21}H_{36}O_2Si$: 348.2484).



Minor Product **141:** ^1H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 6H), 0.80 (s, 3H) 0.96 (s, 9H), 1.18 (d, *J* = 7 Hz, 3 H), 1.43 - 1.53 (m, 2H), 1.70 - 1.78 (m, 1H), 1.89 - 1.95 (m, 1H), 2.02 - 2.16 (m, 2H), 2.15 (s, 3H), 2.30 – 2.45 (m, 2H), 4.38

(d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, 9.6, 10.2, 15.7, 18.1, 18.9, 26.5, 26.9, 28.8, 30.0, 31.2, 35.4, 36.0, 41.4, 66.3, 68.9, 120.6, 131.5, 152.1, 155.7; MS (CI) *m/z* 348(M^+), 291, 273, 263, 238, 217; HRMS (CI) *m/z* 348.2474 (calcd for $C_{21}H_{36}O_2Si$: 348.2484).

Reference

1. Kitagawa, I.; Yamazoe, Y.; Shibuya, H.; Takeda, R.; Takeno, H.; Yosioka, I. *Chem. Pharm. Bull.* **1974**, *22*, 2662.

2. (a) Griffith, W. P.; Ley, S. J.; Whitcombe, G. P.; White, A. D. *Chem. Comm.* **1987**, 1625. (b) Griffith, W. P.; Ley, S. J. *Aldrichimica Acta.* **1990**, *23*, 13.

3. Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.

4. Paquette, L. A.; Maleczka, R. E. *J. Org. Chem.* **1992**, *57*, 7118.

5. Arciniegas, A.; Perez-Castorena, A. L.; Parada, G.; Villasenor, J. I.; De Vivar, R. *Revista Latinoamericana de Quimica*, **2000**, *28*, 131.

6. Ishii, H.; Tozyo, T.; Minato, H. *J. Chem. Soc. (C)*, **1966**, 1545.

7. Horii, Z-I.; Yoneda, E.; Tanaka, T.; Iwata, C. *Chem. Pharm. Bull.* **1977**, *25*, 2784.

Chapter V.

General Conclusion

The studies described in this dissertation outline a conceptually new approach to the furanoeremophilane sesquiterpeniods. Central to success of our approach was the discovery of two pivotal reactions. A highly efficient Stille cross coupling of the fragments provide the key intermediate for our TMSOTf mediated annulation.

The approach allowed for the first total synthesis of 6β-hydroxyeuroposin in twenty-one steps from cyclohexenone. Further, with the core framework now secured, the stage is set for future studies directed towards other members of the furanoerermophilane family.

Bibliography

Arciniegas, A.; Perez-Castorena, A. L.; Parada, G.; Villasenor, J. I.; De Vivar, R. *Revista Latinoamericana de Quimica*, **2000**, *28*, 131.

Bell, R. A.; Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1966**, *31*, 2536.

Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551.

Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron*, 46, 1199.

Boeckman, R. K. *J. Org. Chem.* **1973**, *38*, 4450.

Bohlmann, F.; Forster, H-J.; Fischer, C. H. *Justus Liebigs Ann. Chem* **1976**, 1487.

Bohlmann, F.; Knoll, K. H.; Zdero, C.; Mahanta, P. K.; Grenz, M.; Suwita, A.; Ehlers, D.; Van, N. L.; Abraham, W. R. Natu, A. R. *Phytochemistry* **1977**, *16*, 965.

Bojack, G.; Bornowski, H. *J. Org. Chem*, **1985**, *50*, 9179.

Bojack, G.; Bornowski, H. *Tetrahedron*, 47, 9179.

Bosch, M. P.; Camps, F.; Coll, J.; Guerrero, A.; Tatsuoka, T.; Meinwald, J. *J. Org. Chem.* **1986**, *51*, 773.

Bourgeois, D.; Lallemand, J-Y.; Pancrazi, A.; Prunet, J. *Synlett*, **1999**, *10*, 1555.

Bures, E.; Nieman, J. A.; Yu, S.; Spinazze, P. G.; Bontront, J-L. J.; Hunt, I. R.; Rauk, A.; Keay, B. *J. Org. Chem.* **1997**, *62*, 8750.

Bures, E.; Spinazze, P. G.; Beese, G.; Hunt, I. R.; Rogers, C.; Keay, B. *J. Org. Chem.* **1997**, *62*, 8741.

Burke, S. D.; Austad, B. C.; Hart, A. C. *J. Org. Chem.* **1998**, *63*, 6770.

Burness, D. M. *J. Org. Chem.* **1956**, *21*, 102.

Burness, D. M. *Org. Synth.* **1959**, *39*, 49.

Chakraborty, A.; Kar, G. K.; Ray, J. K. *Tetrahedron* **1997**, *53*, 2989.

Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

Chan, K-K.; Cohen, N.; Noble, J. P.; Specian, A. C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497.

Chattopadhyay, S. K.; Kempson, J.; McNeil, A.; Pattenden, G.; Raeder, M.; Rippon, D. E.; Waite, D. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2415.

Comins, D. L.; Dehghani, *Tetrahedron* **1992**, 6299.

Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.*, **1947**, 96.

Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328.

Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozpeikar, B. *Tetrahedron* **1974**, *38*, 2157.

Eagle, G. A.; Rivett, D. E. A.; Williams, D. H.; Wilson, R. G. *Tetrahedron* **1969**, *25*, 5227.

Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87.

Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033.

Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453.

Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1996**, *50*, 1.

Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *32*, 6299.

Foote, C. S.; Denny, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 5162.

Frimer, A. A. *Chem. Rev.* **1979**, *79*, 359.

Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5253.

Golborn, P.; Scheinmann, F. *J. Chem. Soc. Perkin Trans. 1* **1973**, 2870.

Gollnick, K. *Advan. Photochem.* **1968**, *6*, 1.

Griffith, W. P.; Ley, S. J.; Whitcombe, G. P.; White, A. D. *Chem. Comm.* **1987**, 1625.

Griffith, W. P.; Ley, S. J. *Aldrichimica Acta.* **1990**, *23*, 13.

Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308.

Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, In *The Total Synthesis of Natural Products,* J. ApSimon Ed., Wiley: New York, **1983**, *5*, 202.

Ichihara, A.; Oikawa, H. In *Comprehensive Natural Products Chemistry*; Sankawa, U., Ed.; Barton, D., Nakanishi, K., Meth-Cohn, O., Series Eds.; Polyketides and Other Secondary Metabolites, Vol 1; Elsevier: New York, 1999; 367.

Inamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

Inamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615.

Ishii, H.; Tozyo, T.; Minato, H. *J. Chem. Soc. (C)* **1966**, 1545.

Ishii, H.; Tozyo, T.; Minato, H. *Tetrahedron*, **1965**, *21*, 2605.

Ishizaki, Y.; Tanahashi, Y.; Takahashi, T.; Kazuo, T. *Tetrahedron*, **1970**, *26*, 5387.

Jacobi, P. A. In *Advances in Hetercyclic Natural Product Synthesis*; JAI: New York, 1992, 251.

Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7749.

Jacobi, P. A.; Craig, T. A.; Walker, D. G.; Arrick, Bradley, A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984**, *106*, 5585.

Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611.

Jennings, P. W.; Reeder, S. K.; Hurley, J. C.; Caughlan, C. N.; Smith, G. D. *J. Org. Chem.*, **1974**, *39*, 3392.

Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687.

Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron*, **1997**, *53*, 14179.

Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. *Org. Lett.* **2001**, *3*, 2701.

Kitagawa, I.; Shibuya, H.; Kawai, M. *Chem. Pharm. Bull.* **1977**, *25*, 2638.

Kitagawa, I.; Yamazoe, Y.; Shibuya, H.; Takeda, R.; Takeno, H.; Yosioka, I. *Chem. Pharm. Bull.* **1974**, *22*, 2662.

Kitagawa, I.; Yamazoe, Y.; Shibuya, H.; Takeda, R.; Takeno, H.; Yosioka, I. *Chem. Pharm. Bull.* **1976**, *24*, 56.

Knight, D. W.; Rustidge, D. C. *J. Chem. Soc. (C)*, **1996**, 679.

Kwon, O.; Su, D-S.; Meng, D.; Deng, W.; D'Amico, D. C.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **1998**, *37*. 1880.

Laschat, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 289.

Lee, S. H.; Kim, M. J.; Bok, S. H.; Lee, H.; Kwon, B. M. *J. Org. Chem.* **1998**, *63*, 7113.

Leonard, J.; Bennett, L.; Mahmood, A. *Tetrahedron Lett.* **1999**, *40*, 3965.

Marshall, J. A.; Cohen, G. M. *J. Org. Chem.* **1971**, *36*, 877.

Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem*, **1990**, *55*, 766.

Miyashita, M.; Kumazawa, T.; YoshiKoshi, A. *Chem. Lett.* **1979**, 163.

Mori, K.; Komatsu, M. *Tetrahedron*, **1987**, *43*, 3409.

Moriyama, Y.; Sato, T.; Nagano, H.; Tanahashi, Y.; Takahashi, T. *Chemistry Lett.* **1972**, 637.

Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.

Murray, R. W.; Singh, M. *Organic Syn. Coll. Vol. 9*, 288.

Nagakura, I.; Maeda, S.; Ueno, M.; Funamizu, M.; Kitahara, Y. *Chem Lett.* **1975**, 1143.

Novotny, L.; Herout, V.; Sorm, F. *Tetrahedron Lett.* **1961**, 697.

Novotny, L.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1964**, *29*, 2189.

Novotny, L.; Krojidlo, M.; Samek, Z.; Kohoutova, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1973**, *38*, 739.

Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233.

Pappas, J. J.; Keaveney, W. P.; Edward, G.; Berger, M. *Tetrahedron Lett.* **1966**, *36*, 4273.

Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492.

Paquette, L. A.; Maleczka, R. E. *J. Org. Chem.* **1992**, *57*, 7118.

Paquette, L. A.; Montgomery, F. J.; Wang, T-Z. *J. Org. Chem.* **1995**, *60*, 7857.

Pennanen, S. I. *Acta Chem. Scand.* **1980**, *34*, 261.

Pennanen, S. I. *Acta Chem. Scand.* **1981**, *35*, 555.

Perez, A-L.; Vidales, P.; Cardenas, J.; Romo de Vivar, A. *Phytochemistry*, **1991**, *30*, 905.

Piers, E.; Britton, R. W.; De Waal, W. *Can. J. Chem.* **1969**, *47*, 831.

Piers, E.; Geraghty, M. B.; Smillie, R. D. *Chem Commun.* **1971**, 614.

Pinder, A. R. In *Progress in the chemistry of Organic Natural Products*, W. Herz, H. Grisebach, G. W. Kirby, Ed., Wien Springer Verlag: New York, **1977**, *34*, 81.

Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043.

Reese, C. B.; Risius, A. C. *J. Org. Chem.* **1989**, *54*, 3515.

Reeves, W. P.; King, R. M. *Synthetic Comm.* **1993**, *23*, 855.

Rizzo, C. J.; Smith, A. B. *Tetrahedron Lett.* **1988**, *29*, 2793.

Robinson, R. In *The Structural Relations of Natural Products*. Oxford University Press: London, **1955**, 12.

Sato, T.; Moriyama, Y.; Nagano, H.; Tanahashi, Y.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 112.

Shapiro, R. H. *Org. React.* **1975**, *23*, 405.

Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K-S.; Kwong, H-L.; Morikawa, K.; Wang, Z-M.; Xu, D.; Zhang, X-L. *J. Org. Chem.* **1992**, *57*, 2768.

Smith, A. B.; Chen, S.-Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1997**, *119*, 10935.

Smith, A. B.; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845.

Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569.

Sporle, J.; Becker, H.; Gupta, M. P.; Veith, M.; Huch, V. *Tetrahedron*, **1989**, *45*, 5003.

Stachel, S. J.; Danishefsky, S. J. *Tetrahedron Lett.* **2001**, *42*, 6785.

Sterzycki, R. *Synthesis*, **1979**, *16*, 724.

Stille, J. K. *Angew. Chem.Int. Engl.* **1986**, *25*, 508.

Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139.

Takai, K.; Hotta, Y.; Ohsima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.

Takai, K.; Hotta, Y.; Ohsima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698.

Tanis, S. P.; Dixon, L. A.; Herrinton, P. M. *Tetrahedron Lett.* **1985**, *26*, 5347.

Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572.

Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1988**, *53*, 4929.

Vorbruggen, H.; Bennua, B. *Synthesis* **1988**, 925.

White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Synth.* **2002**, *79*, 244.

White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 9912.

Wiley, R. H.; Smith, N. R. *Org. Synth.* **1955**, *23*, 731.

Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.

Yick, C-Y.; Tsang, T-K.; Wong, H. N. C. *Tetrahedron*, **2003**, *59*, 325.

Yoon, N. M.; Pak, C. S.; Brown, H. C.; Krishnamurthy, S.; Stocky, T. P. *J. Org. Chem.* **1973**, *38*, 2786.

Zhao, Y.; Parsons, S.; Baxter, R. L.; Jia, Z-J.; Sun, H-D.; Rankin, D. W. H. *Chem. Comm.* **1996**, *21*, 2473.

Zhao, Y.; Parsons, S.; Baxter, R. L.; Jia, Z-J.; Sun, H-D.; Rankin, D. W. H. *Tetrahedron* **1997**, *53*, 6195.

Appendices

APPENDIX A

SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON

ALCOHOL 80

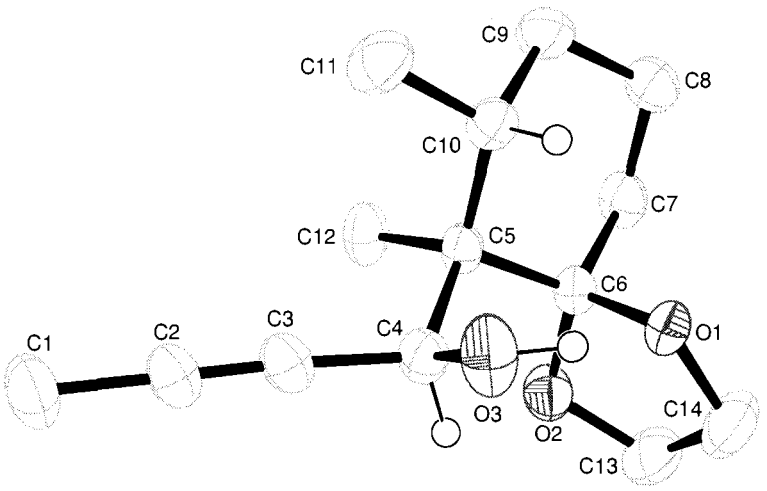


Table A.1 Crystal data and structure refinement for alcohol 80.

Empirical formula	$C_{14}H_{22}O_3$
Formula weight	238.32
Temperature	290(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1/a$ (non-standard setting of #14)
Unit cell dimensions	a = 7.411(1) Å α = 90°.
	b = 22.785(1) Å β = 93.97°.
	c = 7.666(1) Å γ = 90°.
Volume	1291.37(6) $Å^3$
Z	4
Density (calculated)	1.226 Mg/m^3
Absorption coefficient	0.677 mm^{-1}
F(000)	520
Crystal size	0.30 x 0.20 x 0.20 mm^3
Theta range for data collection	3.88 to 67.76°.
Index ranges	-8<=h<=7, -27<=k<=27, -9<=l<=9
Reflections collected	4370
Independent reflections	2190 [R(int) = 0.0265]
Completeness to theta = 67.76°	93.4 %
Max. and min. transmission	0.8765 and 0.8227
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2190 / 30 / 186
Goodness-of-fit on F^2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1256
R indices (all data)	R1 = 0.0490, wR2 = 0.1287
Extinction coefficient	0.0051(8)

Largest diff. peak and hole 0.291 and -0.251 e.Å^{-3}

Table A.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for alcohol 80.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9819(3)	2850(1)	9979(2)	51(1)
C(2)	9069(2)	3253(1)	8643(2)	40(1)
C(3)	8442(2)	3580(1)	7554(2)	38(1)
C(4)	7795(2)	3995(1)	6185(2)	36(1)
C(5)	6545(2)	3721(1)	4664(2)	28(1)
C(6)	6768(2)	4099(1)	3010(2)	29(1)
C(7)	5509(2)	3923(1)	1441(2)	38(1)
C(8)	3551(2)	3932(1)	1883(2)	44(1)
C(9)	3275(2)	3552(1)	3474(2)	43(1)
C(10)	4521(2)	3735(1)	5064(2)	33(1)
C(11)	4099(3)	3380(1)	6675(2)	48(1)
C(12)	7205(2)	3096(1)	4312(2)	40(1)
C(13)	8945(3)	4623(1)	1735(3)	53(1)
C(14)	7628(3)	5046(1)	2426(3)	60(1)
O(1)	6470(1)	4704(1)	3436(1)	34(1)
O(2)	8596(1)	4078(1)	2572(1)	40(1)
O(3)	6985(2)	4475(1)	7049(2)	51(1)

Table A.3 Bond lengths [Å] and angles [°] for alcohol 80.

C(1)-C(2)	1.457(2)	C(3)-C(2)-C(1)	179.4(2)
C(2)-C(3)	1.189(2)	C(2)-C(3)-C(4)	176.06(18)
C(3)-C(4)	1.469(2)	O(3)-C(4)-C(3)	106.75(12)
C(4)-O(3)	1.4307(19)	O(3)-C(4)-C(5)	113.82(13)
C(4)-C(5)	1.5680(19)	C(3)-C(4)-C(5)	114.89(12)
C(5)-C(12)	1.5345(19)	C(12)-C(5)-C(6)	108.53(11)
C(5)-C(6)	1.5509(18)	C(12)-C(5)-C(10)	112.24(12)
C(5)-C(10)	1.553(2)	C(6)-C(5)-C(10)	107.99(11)
C(6)-O(2)	1.4189(18)	C(12)-C(5)-C(4)	108.78(11)
C(6)-O(1)	1.4387(16)	C(6)-C(5)-C(4)	107.19(11)
C(6)-C(7)	1.523(2)	C(10)-C(5)-C(4)	111.93(11)
C(7)-C(8)	1.513(2)	O(2)-C(6)-O(1)	104.46(11)
C(8)-C(9)	1.521(2)	O(2)-C(6)-C(7)	110.29(11)
C(9)-C(10)	1.535(2)	O(1)-C(6)-C(7)	109.57(11)
C(10)-C(11)	1.527(2)	O(2)-C(6)-C(5)	109.43(11)
C(13)-O(2)	1.430(2)	O(1)-C(6)-C(5)	108.69(10)
C(13)-C(14)	1.493(3)	C(7)-C(6)-C(5)	113.95(12)
C(14)-O(1)	1.425(2)	C(8)-C(7)-C(6)	111.35(12)
		C(7)-C(8)-C(9)	110.89(13)
		C(8)-C(9)-C(10)	112.04(13)
		C(11)-C(10)-C(9)	110.68(13)
		C(11)-C(10)-C(5)	113.79(13)
		C(9)-C(10)-C(5)	111.94(12)
		O(2)-C(13)-C(14)	104.95(13)
		O(1)-C(14)-C(13)	105.90(14)
		C(14)-O(1)-C(6)	107.01(12)
		C(6)-O(2)-C(13)	106.39(12)

Symmetry transformations used to generate equivalent atoms:

Table A.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for alcohol 80.

The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	57(1)	53(1)	42(1)	8(1)	-13(1)	8(1)
C(2)	42(1)	44(1)	33(1)	0(1)	-6(1)	5(1)
C(3)	39(1)	44(1)	31(1)	0(1)	-5(1)	2(1)
C(4)	43(1)	33(1)	30(1)	1(1)	-7(1)	-2(1)
C(5)	35(1)	24(1)	25(1)	0(1)	-3(1)	0(1)
C(6)	33(1)	27(1)	28(1)	1(1)	1(1)	3(1)
C(7)	49(1)	39(1)	26(1)	1(1)	-5(1)	0(1)
C(8)	43(1)	48(1)	38(1)	3(1)	-14(1)	-5(1)
C(9)	38(1)	47(1)	42(1)	1(1)	-6(1)	-10(1)
C(10)	37(1)	32(1)	31(1)	-1(1)	1(1)	-3(1)
C(11)	54(1)	53(1)	37(1)	5(1)	6(1)	-13(1)
C(12)	55(1)	28(1)	37(1)	-1(1)	-3(1)	8(1)
C(13)	50(1)	52(1)	58(1)	12(1)	15(1)	-7(1)
C(14)	62(1)	40(1)	81(1)	20(1)	20(1)	-4(1)
O(1)	40(1)	25(1)	38(1)	4(1)	3(1)	1(1)
O(2)	37(1)	43(1)	41(1)	7(1)	8(1)	6(1)
O(3)	80(1)	33(1)	39(1)	-9(1)	-20(1)	7(1)

Table A.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for alcohol 80.

	x	y	z	U(eq)
H(1A)	9670(60)	2991(17)	11180(30)	62(2)
H(1B)	11130(30)	2808(18)	9820(50)	62(2)
H(1C)	9250(50)	2461(11)	9800(50)	62(2)
H(1D)	8780(40)	2668(18)	10550(50)	62(2)
H(1E)	10500(50)	2526(15)	9460(50)	62(2)
H(1F)	10610(50)	3043(16)	10910(40)	62(2)
H(4)	8840(30)	4147(4)	5673(13)	62(2)
H(7A)	5677(4)	4202(4)	448(15)	62(2)
H(7B)	5833(5)	3518(6)	1048(6)	62(2)
H(8A)	2756(13)	3782(2)	845(16)	62(2)
H(8B)	3175(7)	4352(7)	2128(4)	62(2)
H(9A)	3506(4)	3152(6)	3197(5)	62(2)
H(9B)	2050(20)	3582(1)	3761(5)	62(2)
H(10)	4240(7)	4133(10)	5307(6)	62(2)
H(11A)	2792(16)	3408(1)	6851(3)	62(2)
H(11B)	4803(9)	3538(2)	7714(13)	62(2)
H(11C)	4428(5)	2965(5)	6504(3)	62(2)
H(12A)	7067(3)	2854(3)	5335(12)	62(2)
H(12B)	8470(15)	3108(1)	4060(4)	62(2)
H(12C)	6494(9)	2932(2)	3319(12)	62(2)
H(13A)	8751(4)	4587(1)	460(20)	62(2)
H(13B)	10200(20)	4753(2)	2028(5)	62(2)
H(14A)	8263(10)	5345(5)	3158(11)	62(2)
H(14B)	6928(11)	5242(3)	1462(15)	62(2)
H(3)	6530(30)	4721(8)	6280(20)	62(2)

Table A.6. Torsion angles [°] for alcohol 80.

C(1)-C(2)-C(3)-C(4)	-170(100)	C(7)-C(6)-O(1)-C(14)	-88.41(16)
C(2)-C(3)-C(4)-O(3)	-110(2)	C(5)-C(6)-O(1)-C(14)	146.48(14)
C(2)-C(3)-C(4)-C(5)	123(2)	O(1)-C(6)-O(2)-C(13)	-34.34(14)
O(3)-C(4)-C(5)-C(12)	-158.94(13)	C(7)-C(6)-O(2)-C(13)	83.31(15)
C(3)-C(4)-C(5)-C(12)	-35.43(18)	C(5)-C(6)-O(2)-C(13)	-150.57(13)
O(3)-C(4)-C(5)-C(6)	83.90(15)	C(14)-C(13)-O(2)-C(6)	25.55(19)
C(3)-C(4)-C(5)-C(6)	-152.60(13)	O(2)-C(6)-O(1)-C(14)	29.74(15)
O(3)-C(4)-C(5)-C(10)	-34.34(17)	C(13)-C(14)-O(1)-C(6)	-13.9(2)
C(3)-C(4)-C(5)-C(10)	89.17(16)	O(2)-C(13)-C(14)-O(1)	-7.0(2)
C(12)-C(5)-C(6)-O(2)	-56.07(14)	C(4)-C(5)-C(10)-C(9)	171.51(12)
C(10)-C(5)-C(6)-O(2)	-177.98(11)	C(6)-C(5)-C(10)-C(9)	53.75(15)
C(4)-C(5)-C(6)-O(2)	61.26(14)	C(12)-C(5)-C(10)-C(9)	-65.84(15)
C(12)-C(5)-C(6)-O(1)	-169.57(12)	C(4)-C(5)-C(10)-C(11)	-62.08(16)
C(10)-C(5)-C(6)-O(1)	68.52(13)	C(6)-C(5)-C(10)-C(11)	-179.84(12)
C(4)-C(5)-C(6)-O(1)	-52.24(14)	C(12)-C(5)-C(10)-C(11)	60.57(16)
C(12)-C(5)-C(6)-C(7)	67.93(16)	C(8)-C(9)-C(10)-C(5)	-56.69(18)
C(10)-C(5)-C(6)-C(7)	-53.98(15)	C(8)-C(9)-C(10)-C(11)	175.22(14)
C(4)-C(5)-C(6)-C(7)	-174.74(12)	C(7)-C(8)-C(9)-C(10)	55.88(18)
O(2)-C(6)-C(7)-C(8)	179.06(12)	C(6)-C(7)-C(8)-C(9)	-54.55(17)
O(1)-C(6)-C(7)-C(8)	-66.48(15)	C(5)-C(6)-C(7)-C(8)	55.53(16)

Symmetry transformations used to generate equivalent atoms:

Table A. 7. Hydrogen bonds for alcohol 80 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(1)	0.87	2.18	2.8188(15)	130.8

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y+1,-z+1

APPENDIX B

SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON

BENZOATE 136

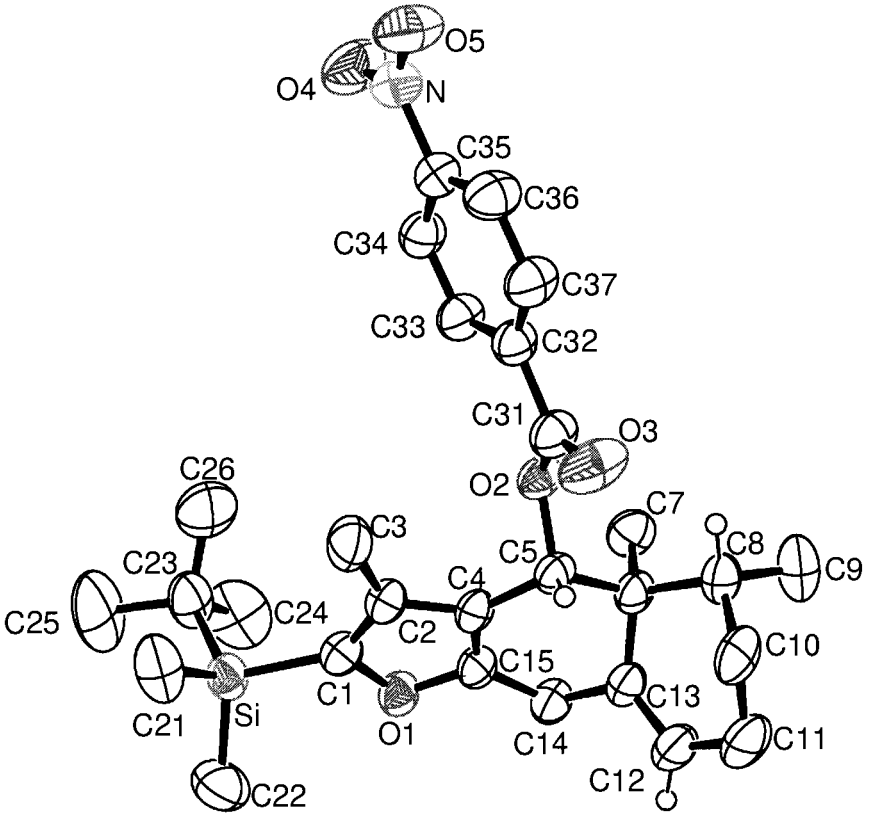


Table B.1. Crystal data and structure refinement for benzoate 136.

Empirical formula	$C_{26}H_{37}NO_5Si$	
Formula weight	495.68	
Temperature	293(2) K	
Wavelength	1.54180 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.479(2) Å	a= 98.68(3)°.
	b = 8.389(3) Å	b= 99.07(3)°.
	c = 22.545(9) Å	g = 91.40(3)°.
Volume	1379.1(8) $Å^3$	
Z	2	
Density (calculated)	1.194 Mg/m^3	
Absorption coefficient	1.045 mm^{-1}	
F(000)	532	
Crystal size	0.2 x 0.2 x 0.1 mm^3	
Theta range for data collection	2.01 to 67.29°.	
Index ranges	-1<=h<=8, -9<=k<=9, -26<=l<=26	
Reflections collected	5964	
Independent reflections	4750 [R(int) = 0.0279]	
Completeness to theta = 67.29°	96.5 %	
Absorption correction	Semi-empirical (Psi-scans)	
Max. and min. transmission	0.6589 and 0.1885	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4750 / 0 / 324	
Goodness-of-fit on F^2	1.086	
Final R indices [I>2sigma(I)]	R1 = 0.0639, wR2 = 0.1853	
R indices (all data)	R1 = 0.0803, wR2 = 0.2000	

Largest diff. peak and hole 0.264 and -0.378 e.Å^{-3}

Table B. 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for benzoate 136.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	10291(3)	5453(3)	1318(1)	50(1)
O(2)	12447(3)	5461(3)	3299(1)	46(1)
O(3)	14939(3)	4314(4)	3709(1)	79(1)
N	8946(5)	1979(4)	5184(1)	62(1)
O(4)	7318(4)	2150(4)	5098(2)	89(1)
O(5)	9696(4)	1267(4)	5576(1)	85(1)
C(1)	9928(4)	3916(4)	1457(2)	50(1)
C(2)	10899(4)	3806(4)	2014(2)	47(1)
C(3)	10955(6)	2383(5)	2341(2)	67(1)
C(4)	11914(4)	5305(4)	2226(1)	43(1)
C(5)	13284(4)	5836(4)	2786(1)	42(1)
C(6)	13825(4)	7657(4)	2869(1)	45(1)
C(7)	12302(5)	8626(4)	3113(2)	57(1)
C(8)	15642(4)	8046(4)	3316(2)	56(1)
C(9)	15976(6)	9832(5)	3579(2)	84(1)
C(10)	17234(4)	7441(5)	3005(2)	67(1)
C(11)	17406(5)	8291(6)	2467(2)	76(1)
C(12)	15595(5)	8337(5)	2079(2)	62(1)
C(13)	14027(4)	8042(4)	2242(2)	48(1)
C(14)	12292(4)	7862(4)	1779(2)	51(1)
C(15)	11505(4)	6235(4)	1794(1)	45(1)
Si	8234(1)	2590(1)	881(1)	53(1)
C(21)	8718(6)	437(5)	894(2)	81(1)
C(22)	8412(7)	3081(7)	119(2)	92(2)
C(23)	5893(5)	2980(5)	1064(2)	72(1)

C(24)	5445(8)	4709(7)	992(3)	109(2)
C(25)	4482(6)	1801(9)	644(3)	135(3)
C(26)	5842(7)	2769(7)	1725(2)	98(2)
C(31)	13356(5)	4595(4)	3687(2)	53(1)
C(32)	12178(4)	3987(4)	4088(2)	49(1)
C(33)	10299(4)	4121(4)	3985(2)	53(1)
C(34)	9235(5)	3461(4)	4343(2)	54(1)
C(35)	10058(5)	2695(4)	4798(2)	52(1)
C(36)	11913(5)	2559(5)	4916(2)	62(1)
C(37)	12962(5)	3218(5)	4555(2)	60(1)

Table B.3. Bond lengths [Å] and angles [°] for benzoate 136

O(1)-C(15)	1.362(4)	C(15)-O(1)-C(1)	106.6(2)
O(1)-C(1)	1.402(4)	C(31)-O(2)-C(5)	118.6(2)
O(2)-C(31)	1.336(4)	O(5)-N-O(4)	123.2(3)
O(2)-C(5)	1.469(4)	O(5)-N-C(35)	118.6(3)
O(3)-C(31)	1.208(4)	O(4)-N-C(35)	118.2(3)
N-O(5)	1.215(4)	C(2)-C(1)-O(1)	108.4(3)
N-O(4)	1.218(4)	C(2)-C(1)-Si	136.1(3)
N-C(35)	1.474(5)	O(1)-C(1)-Si	115.5(2)
C(1)-C(2)	1.365(5)	C(1)-C(2)-C(4)	107.2(3)
C(1)-Si	1.873(3)	C(1)-C(2)-C(3)	127.1(3)
C(2)-C(4)	1.429(4)	C(4)-C(2)-C(3)	125.6(3)
C(2)-C(3)	1.493(5)	C(15)-C(4)-C(2)	106.6(3)
C(4)-C(15)	1.341(4)	C(15)-C(4)-C(5)	122.4(3)
C(4)-C(5)	1.497(4)	C(2)-C(4)-C(5)	130.9(3)
C(5)-C(6)	1.547(4)	O(2)-C(5)-C(4)	106.2(2)
C(6)-C(13)	1.525(4)	O(2)-C(5)-C(6)	110.7(2)
C(6)-C(7)	1.538(5)	C(4)-C(5)-C(6)	112.2(3)
C(6)-C(8)	1.555(4)	C(13)-C(6)-C(7)	109.9(3)
C(8)-C(9)	1.525(5)	C(13)-C(6)-C(5)	106.8(3)
C(8)-C(10)	1.533(5)	C(7)-C(6)-C(5)	108.8(3)
C(10)-C(11)	1.518(6)	C(13)-C(6)-C(8)	110.4(3)
C(11)-C(12)	1.498(5)	C(7)-C(6)-C(8)	110.4(3)
C(12)-C(13)	1.312(5)	C(5)-C(6)-C(8)	110.4(3)
C(13)-C(14)	1.521(4)	C(9)-C(8)-C(10)	110.0(3)
C(14)-C(15)	1.480(5)	C(9)-C(8)-C(6)	113.7(3)
Si-C(22)	1.849(5)	C(10)-C(8)-C(6)	110.3(3)
Si-C(21)	1.855(4)	C(11)-C(10)-C(8)	111.3(3)
Si-C(23)	1.887(4)	C(12)-C(11)-C(10)	110.6(3)
C(23)-C(24)	1.523(7)	C(13)-C(12)-C(11)	125.1(4)
C(23)-C(25)	1.530(6)	C(12)-C(13)-C(14)	120.5(3)
C(23)-C(26)	1.533(7)	C(12)-C(13)-C(6)	123.7(3)
C(31)-C(32)	1.490(5)	C(14)-C(13)-C(6)	115.4(3)

C(32)-C(37)	1.377(5)	C(15)-C(14)-C(13)	105.0(3)
C(32)-C(33)	1.398(5)	C(4)-C(15)-O(1)	111.2(3)
C(33)-C(34)	1.382(5)	C(4)-C(15)-C(14)	127.6(3)
C(34)-C(35)	1.363(5)	O(1)-C(15)-C(14)	121.1(3)
C(35)-C(36)	1.382(5)	C(22)-Si-C(21)	109.0(2)
C(36)-C(37)	1.379(5)	C(22)-Si-C(1)	108.5(2)
		C(21)-Si-C(1)	110.14(18)
C(22)-Si-C(23)	110.4(2)	O(2)-C(31)-C(32)	112.0(3)
C(21)-Si-C(23)	110.0(2)	C(37)-C(32)-C(33)	119.6(3)
C(1)-Si-C(23)	108.76(17)	C(37)-C(32)-C(31)	118.8(3)
C(24)-C(23)-C(25)	109.9(4)	C(33)-C(32)-C(31)	121.6(3)
C(24)-C(23)-C(26)	108.4(4)	C(34)-C(33)-C(32)	120.1(3)
C(25)-C(23)-C(26)	109.0(5)	C(35)-C(34)-C(33)	118.7(3)
C(24)-C(23)-Si	109.4(3)	C(34)-C(35)-C(36)	122.7(3)
C(25)-C(23)-Si	110.6(3)	C(34)-C(35)-N	119.5(3)
C(26)-C(23)-Si	109.6(3)	C(36)-C(35)-N	117.8(3)
O(3)-C(31)-O(2)	124.5(3)	C(37)-C(36)-C(35)	118.2(3)
O(3)-C(31)-C(32)	123.5(3)	C(32)-C(37)-C(36)	120.8(3)

Symmetry transformations used to generate equivalent atoms:

Table B.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for benzoate 136.

The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	38(1)	57(1)	53(1)	10(1)	1(1)	-2(1)
O(2)	33(1)	58(1)	52(1)	18(1)	7(1)	2(1)
O(3)	36(1)	122(2)	94(2)	57(2)	15(1)	19(1)
N	62(2)	71(2)	55(2)	11(2)	16(2)	-3(2)
O(4)	53(2)	126(3)	98(2)	41(2)	22(2)	-5(2)
O(5)	81(2)	114(3)	74(2)	45(2)	25(2)	7(2)
C(1)	40(2)	56(2)	55(2)	8(2)	10(2)	-3(1)
C(2)	37(2)	50(2)	54(2)	8(1)	7(1)	-2(1)
C(3)	75(3)	54(2)	68(2)	11(2)	2(2)	-14(2)
C(4)	27(1)	49(2)	52(2)	8(1)	6(1)	-1(1)
C(5)	32(2)	49(2)	47(2)	11(1)	7(1)	0(1)
C(6)	29(2)	51(2)	53(2)	7(1)	7(1)	-2(1)
C(7)	47(2)	60(2)	67(2)	9(2)	16(2)	8(2)
C(8)	40(2)	63(2)	58(2)	6(2)	-1(2)	-10(2)
C(9)	74(3)	71(3)	92(3)	-10(2)	-8(2)	-17(2)
C(10)	27(2)	84(3)	87(3)	15(2)	1(2)	-6(2)
C(11)	37(2)	104(3)	87(3)	17(2)	15(2)	-11(2)
C(12)	47(2)	75(2)	66(2)	16(2)	13(2)	-11(2)
C(13)	38(2)	49(2)	56(2)	8(1)	9(1)	-5(1)
C(14)	44(2)	53(2)	56(2)	15(2)	4(2)	-3(1)
C(15)	29(2)	53(2)	51(2)	6(1)	5(1)	0(1)
Si	37(1)	60(1)	56(1)	-4(1)	5(1)	-1(1)
C(21)	64(3)	69(3)	96(3)	-15(2)	-4(2)	8(2)
C(22)	84(3)	129(4)	56(2)	2(2)	7(2)	-5(3)
C(23)	43(2)	79(3)	83(3)	-14(2)	7(2)	1(2)
C(24)	85(4)	108(4)	129(5)	3(3)	14(3)	46(3)

C(25)	40(3)	164(6)	167(6)	-63(5)	2(3)	-13(3)
C(26)	71(3)	114(4)	114(4)	4(3)	45(3)	2(3)
C(31)	41(2)	64(2)	56(2)	19(2)	4(2)	0(2)
C(32)	42(2)	55(2)	51(2)	14(1)	5(1)	0(1)
C(33)	40(2)	64(2)	56(2)	19(2)	4(2)	2(2)
C(34)	40(2)	65(2)	57(2)	12(2)	9(2)	-1(2)
C(35)	49(2)	56(2)	50(2)	9(2)	12(2)	-4(2)
C(36)	52(2)	80(3)	59(2)	29(2)	7(2)	7(2)
C(37)	41(2)	80(3)	64(2)	26(2)	5(2)	4(2)

Table B. 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for benzoate 136.

	x	y	z	U(eq)
H(3A)	10302	1477	2079	100
H(3B)	10406	2635	2699	100
H(3C)	12192	2123	2455	100
H(5)	14368	5213	2761	51
H(7A)	12478	9740	3074	86
H(7B)	12327	8533	3533	86
H(7C)	11152	8208	2883	86
H(8)	15596	7453	3656	67
H(9A)	15866	10460	3254	126
H(9B)	17173	10010	3813	126
H(9C)	15099	10152	3837	126
H(10A)	18348	7628	3297	80
H(10B)	17054	6287	2867	80
H(11A)	17904	9384	2613	91
H(11B)	18232	7728	2227	91
H(12)	15580	8595	1691	74
H(14A)	11464	8687	1890	61
H(14B)	12553	7948	1377	61
H(21A)	8031	-215	541	122
H(21B)	8384	114	1254	122
H(21C)	9988	298	894	122
H(22A)	8144	4190	107	137
H(22B)	7564	2398	-183	137
H(22C)	9620	2910	37	137
H(24A)	5523	4874	585	163
H(24B)	6292	5444	1274	163
H(24C)	4239	4898	1072	163
H(25A)	3300	2018	742	202

H(25B)	4760	715	697	202
H(25C)	4502	1929	229	202
H(26A)	6598	3603	1994	147
H(26B)	6278	1733	1792	147
H(26C)	4619	2837	1803	147
H(33)	9765	4655	3675	63
H(34)	7983	3538	4276	64
H(36)	12440	2038	5231	75
H(37)	14214	3143	4627	72

Table B.6. Torsion angles [°] for benzoate 136.

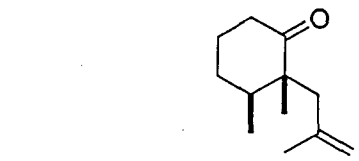
C(15)-O(1)-C(1)-C(2)	0.9(4)	C(7)-C(6)-C(13)-C(12)	134.9(4)
C(15)-O(1)-C(1)-Si	178.6(2)	C(5)-C(6)-C(13)-C(12)	-107.2(4)
O(1)-C(1)-C(2)-C(4)	-0.7(4)	C(8)-C(6)-C(13)-C(12)	12.8(5)
Si-C(1)-C(2)-C(4)	-177.6(3)	C(7)-C(6)-C(13)-C(14)	-52.4(4)
O(1)-C(1)-C(2)-C(3)	-179.1(3)	C(5)-C(6)-C(13)-C(14)	65.5(3)
Si-C(1)-C(2)-C(3)	4.0(6)	C(8)-C(6)-C(13)-C(14)	-174.4(3)
C(1)-C(2)-C(4)-C(15)	0.2(4)	C(12)-C(13)-C(14)-C(15)	122.1(4)
C(3)-C(2)-C(4)-C(15)	178.6(3)	C(6)-C(13)-C(14)-C(15)	-50.9(4)
C(1)-C(2)-C(4)-C(5)	-176.0(3)	C(2)-C(4)-C(15)-O(1)	0.4(4)
C(3)-C(2)-C(4)-C(5)	2.4(6)	C(5)-C(4)-C(15)-O(1)	177.0(3)
C(31)-O(2)-C(5)-C(4)	127.4(3)	C(2)-C(4)-C(15)-C(14)	-175.8(3)
C(31)-O(2)-C(5)-C(6)	-110.5(3)	C(5)-C(4)-C(15)-C(14)	0.8(5)
C(15)-C(4)-C(5)-O(2)	133.5(3)	C(1)-O(1)-C(15)-C(4)	-0.8(3)
C(2)-C(4)-C(5)-O(2)	-50.7(4)	C(1)-O(1)-C(15)-C(14)	175.6(3)
C(15)-C(4)-C(5)-C(6)	12.5(4)	C(13)-C(14)-C(15)-C(4)	16.9(5)
C(2)-C(4)-C(5)-C(6)	-171.8(3)	C(13)-C(14)-C(15)-O(1)	-158.9(3)
O(2)-C(5)-C(6)-C(13)	-160.1(2)	C(2)-C(1)-Si-C(22)	-151.5(4)
C(4)-C(5)-C(6)-C(13)	-41.7(3)	O(1)-C(1)-Si-C(22)	31.8(3)
O(2)-C(5)-C(6)-C(7)	-41.5(3)	C(2)-C(1)-Si-C(21)	-32.1(4)
C(4)-C(5)-C(6)-C(7)	77.0(3)	O(1)-C(1)-Si-C(21)	151.1(3)
O(2)-C(5)-C(6)-C(8)	79.9(3)	C(2)-C(1)-Si-C(23)	88.4(4)
C(4)-C(5)-C(6)-C(8)	-161.7(3)	O(1)-C(1)-Si-C(23)	-88.3(3)
C(13)-C(6)-C(8)-C(9)	80.4(4)	C(22)-Si-C(23)-C(24)	-54.3(4)
C(7)-C(6)-C(8)-C(9)	-41.3(4)	C(21)-Si-C(23)-C(24)	-174.7(3)
C(5)-C(6)-C(8)-C(9)	-161.7(3)	C(1)-Si-C(23)-C(24)	64.7(4)
C(13)-C(6)-C(8)-C(10)	-43.6(4)	C(22)-Si-C(23)-C(25)	66.9(5)
C(7)-C(6)-C(8)-C(10)	-165.4(3)	C(21)-Si-C(23)-C(25)	-53.5(5)
C(5)-C(6)-C(8)-C(10)	74.2(4)	C(1)-Si-C(23)-C(25)	-174.2(4)
C(9)-C(8)-C(10)-C(11)	-63.4(4)	C(22)-Si-C(23)-C(26)	-173.0(3)
C(6)-C(8)-C(10)-C(11)	62.7(4)	C(21)-Si-C(23)-C(26)	66.6(4)
C(8)-C(10)-C(11)-C(12)	-46.5(5)	C(1)-Si-C(23)-C(26)	-54.1(4)

C(10)-C(11)-C(12)-C(13)	14.9(6)	C(5)-O(2)-C(31)-O(3)	12.7(5)
C(11)-C(12)-C(13)-C(6)	2.1(6)	C(5)-O(2)-C(31)-C(32)	-166.4(3)
C(5)-O(2)-C(31)-C(32)	-166.4(3)	O(5)-N-C(35)-C(34)	178.3(4)
O(3)-C(31)-C(32)-C(37)	7.7(6)	O(4)-N-C(35)-C(34)	-2.8(5)
O(2)-C(31)-C(32)-C(37)	-173.2(3)	O(5)-N-C(35)-C(36)	-1.9(5)
O(3)-C(31)-C(32)-C(33)	-169.7(4)	O(4)-N-C(35)-C(36)	177.1(4)
O(2)-C(31)-C(32)-C(33)	9.3(5)	C(34)-C(35)-C(36)-C(37)	-0.5(6)
C(37)-C(32)-C(33)-C(34)	-1.1(5)	N-C(35)-C(36)-C(37)	179.6(3)
C(31)-C(32)-C(33)-C(34)	176.3(3)	C(33)-C(32)-C(37)-C(36)	1.0(6)
C(32)-C(33)-C(34)-C(35)	0.5(5)	C(31)-C(32)-C(37)-C(36)	-176.5(4)
C(33)-C(34)-C(35)-C(36)	0.4(6)	C(35)-C(36)-C(37)-C(32)	-0.2(6)
C(33)-C(34)-C(35)-N	-179.8(3)		

Symmetry transformations used to generate equivalent atoms:

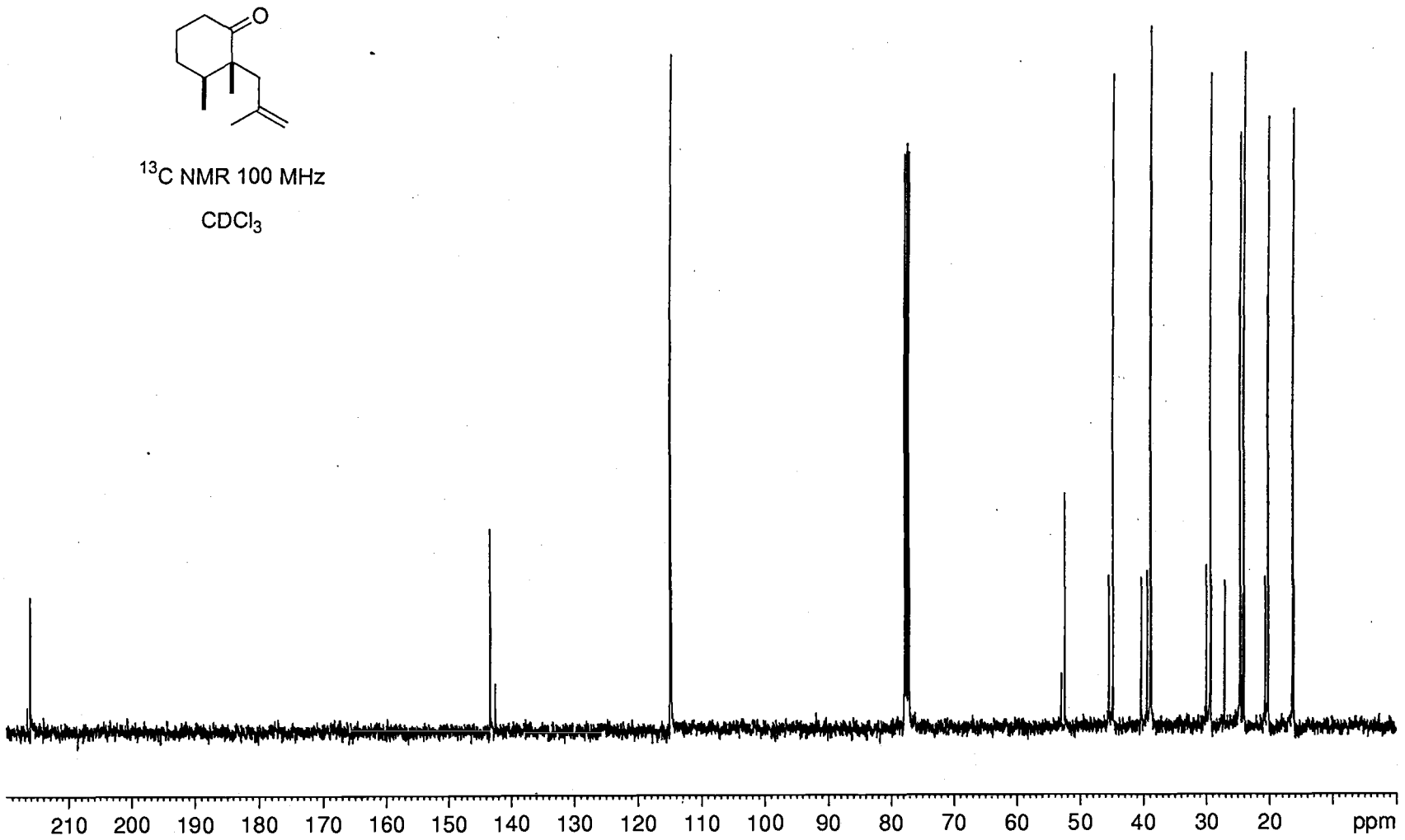
APPENDIX A

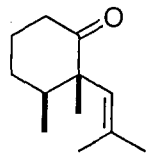
SELECT NMR SPECTRA



^{1}H NMR 400 MHz

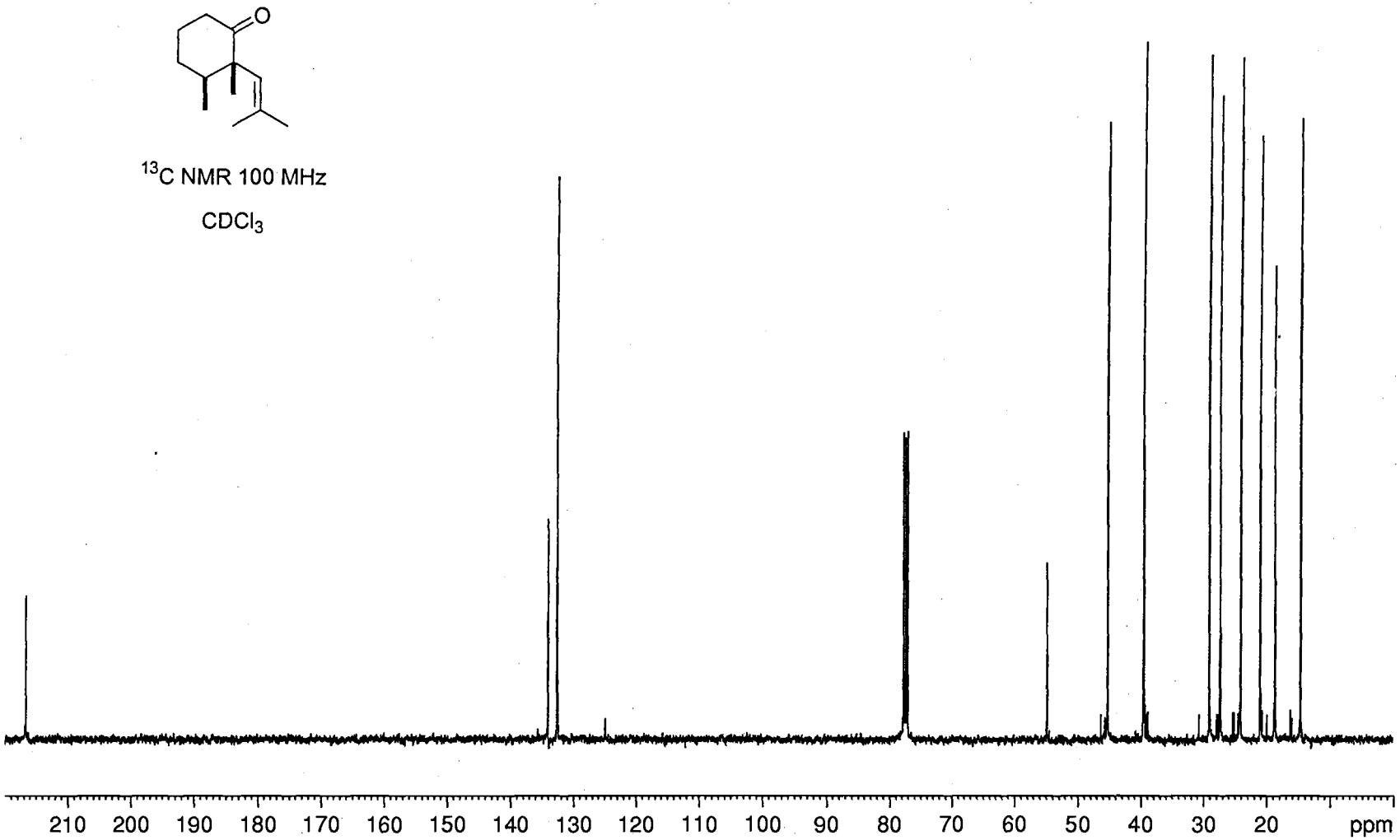
$CDCl_3$

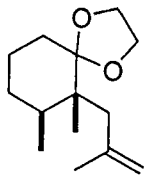

O
^{13}C NMR 100 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



^{1}H NMR 400 MHz

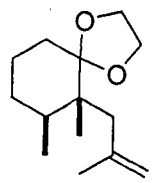
$CDCl_3$


O
^{13}C NMR 100 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



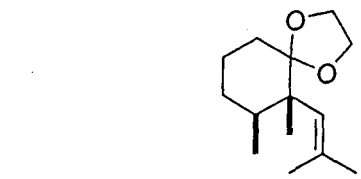
^{1}H NMR 400 MHz

$CDCl_3$



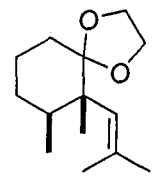
^{13}C NMR 100 MHz

$CDCl_3$



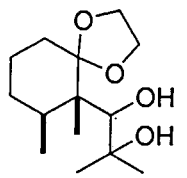
^{1}H NMR 400 MHz

$CDCl_3$



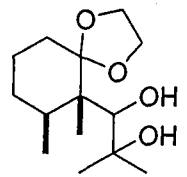
^{13}C NMR 100 MHz

$CDCl_3$



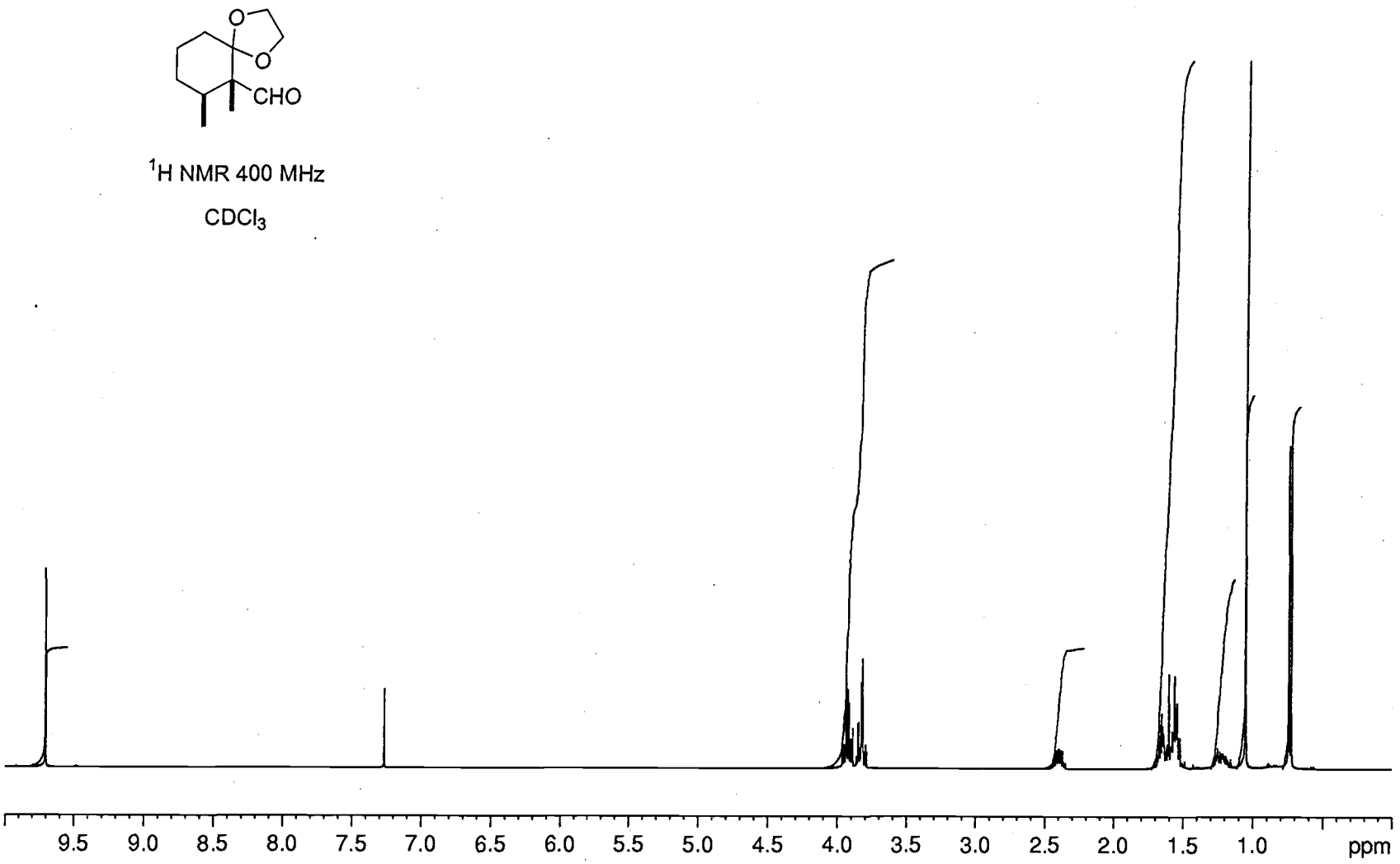
^{1}H NMR 400 MHz

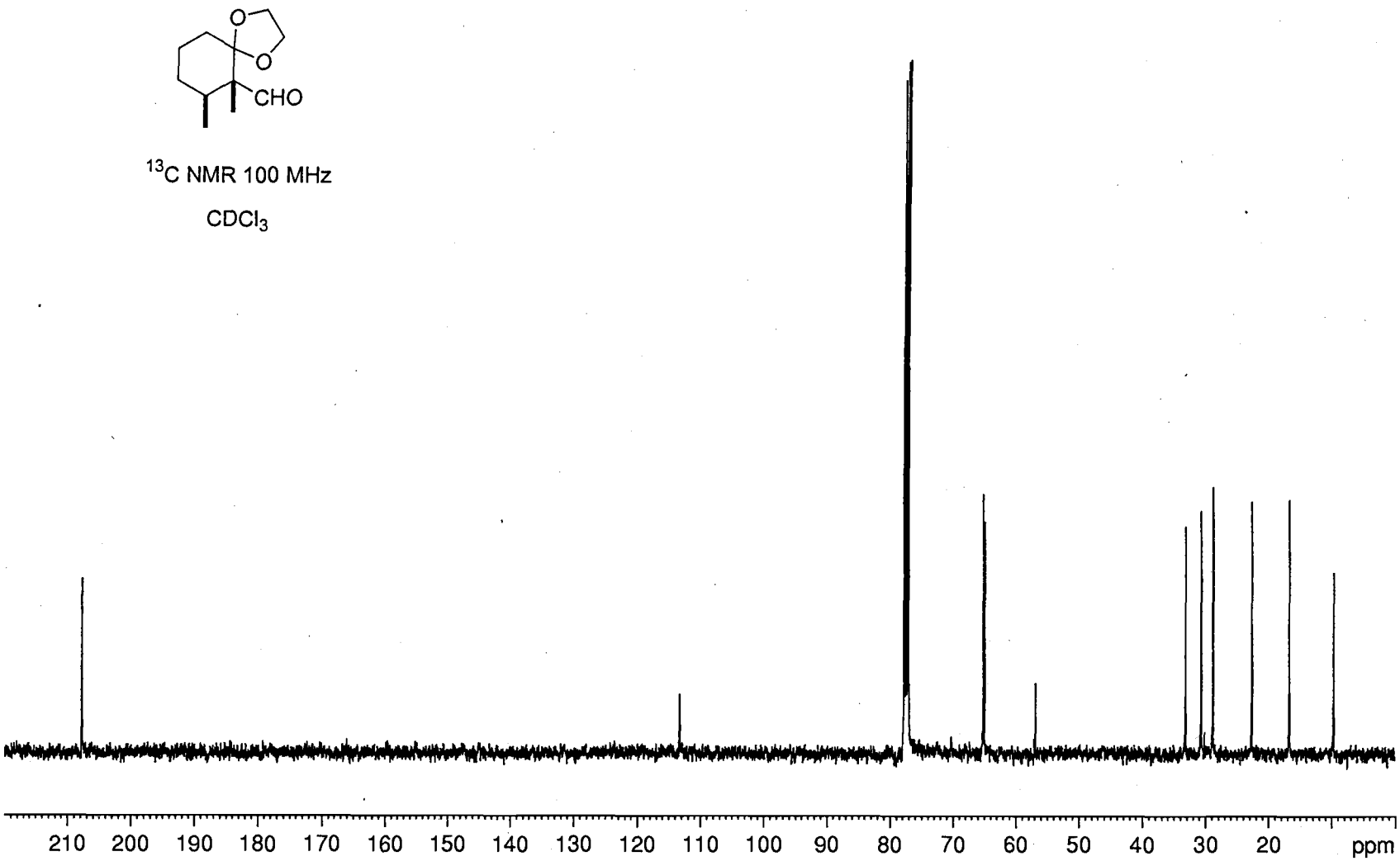
$CDCl_3$

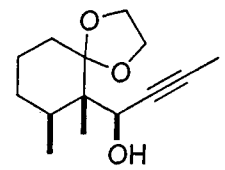


^{13}C NMR 100 MHz

$CDCl_3$

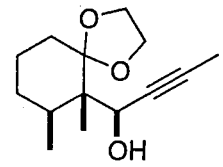

O
O
CHO
^{1}H NMR 400 MHz
$CDCl_3$
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


O
O
CHO
^{13}C NMR 100 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



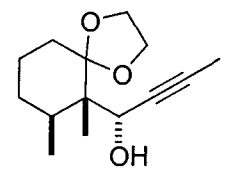
^{1}H NMR 400 MHz

$CDCl_3$



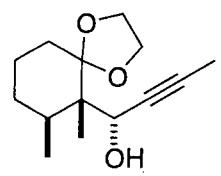
^{13}C NMR 100 MHz

$CDCl_3$



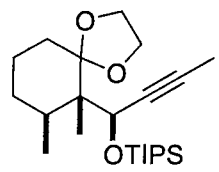
^{1}H NMR 400 MHz

$CDCl_3$



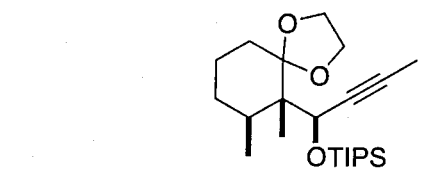
^{13}C NMR 100 MHz

$CDCl_3$



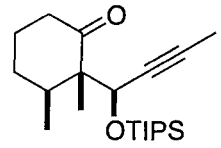
^{1}H NMR 400 MHz

$CDCl_3$



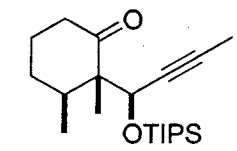
^{13}C NMR 100 MHz

$CDCl_3$



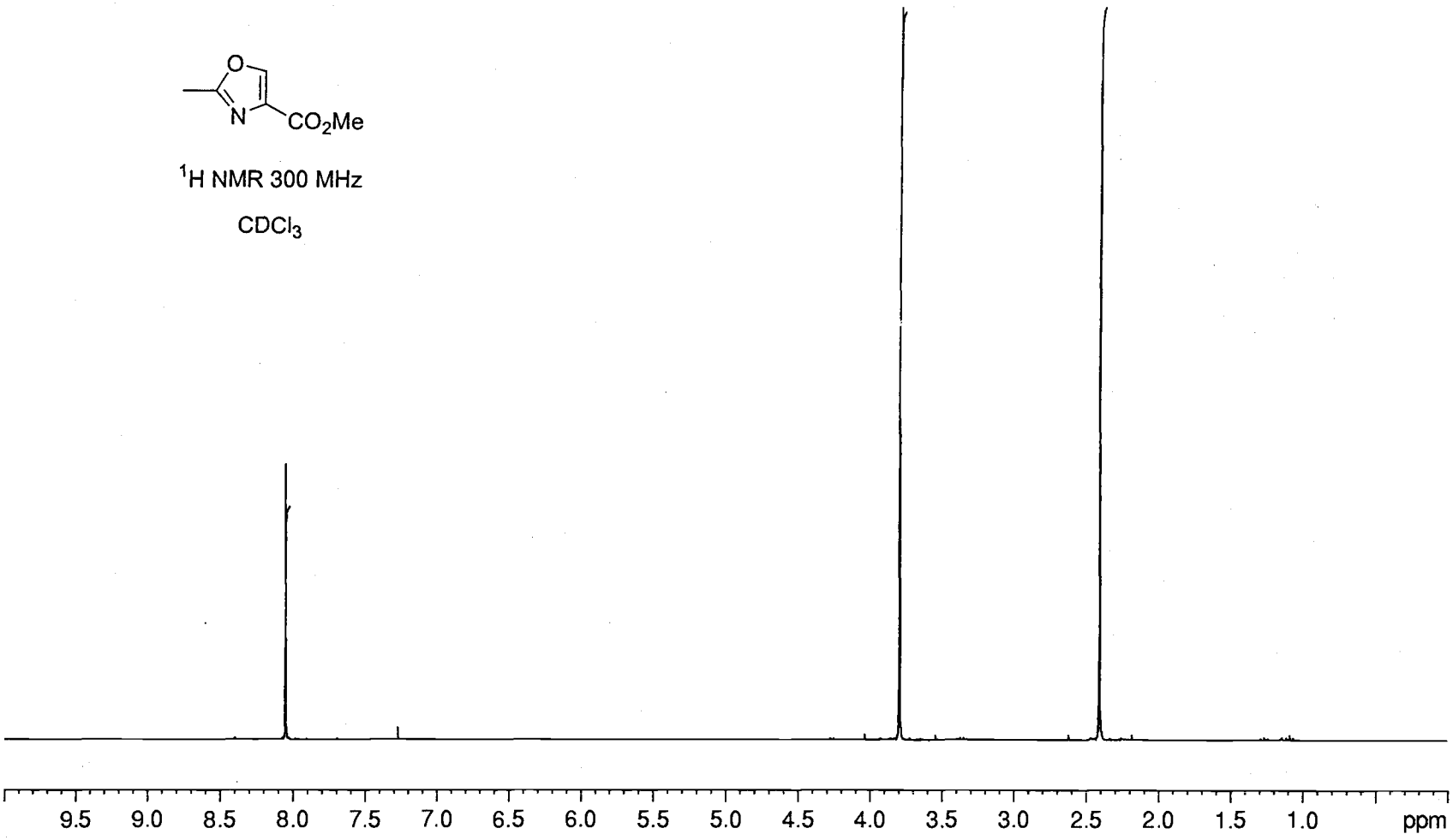
^{1}H NMR 400 MHz

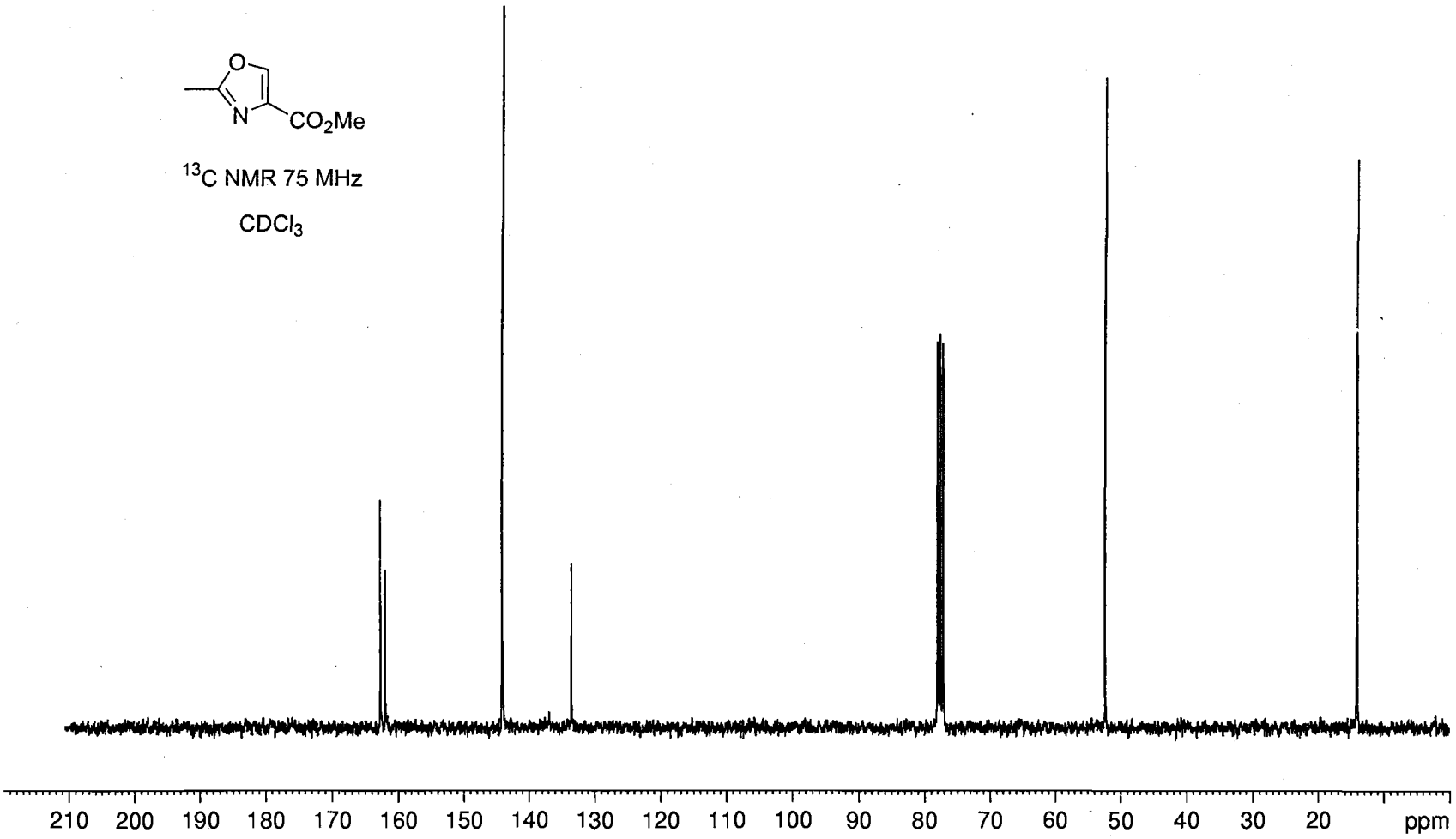
$CDCl_3$

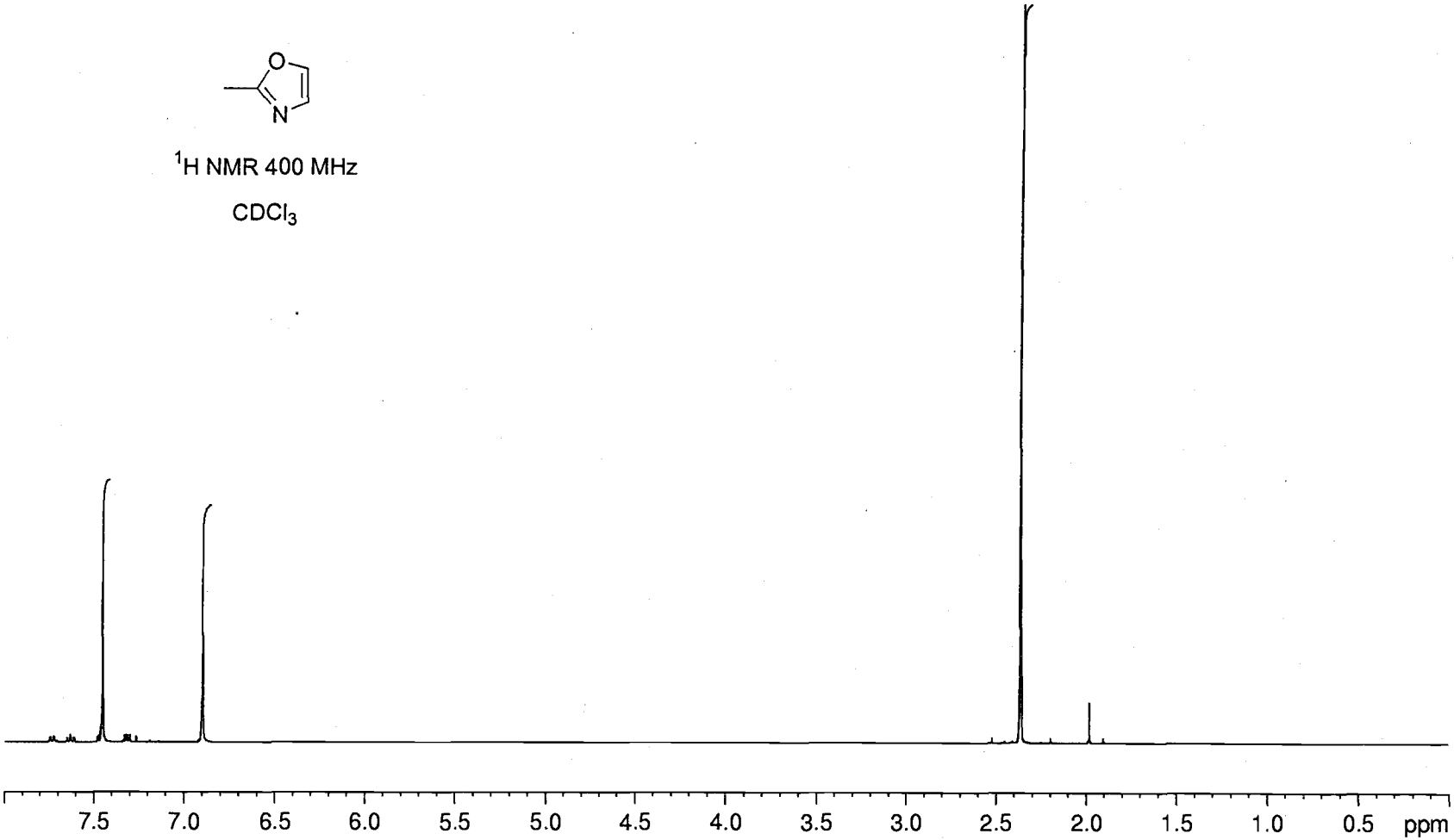


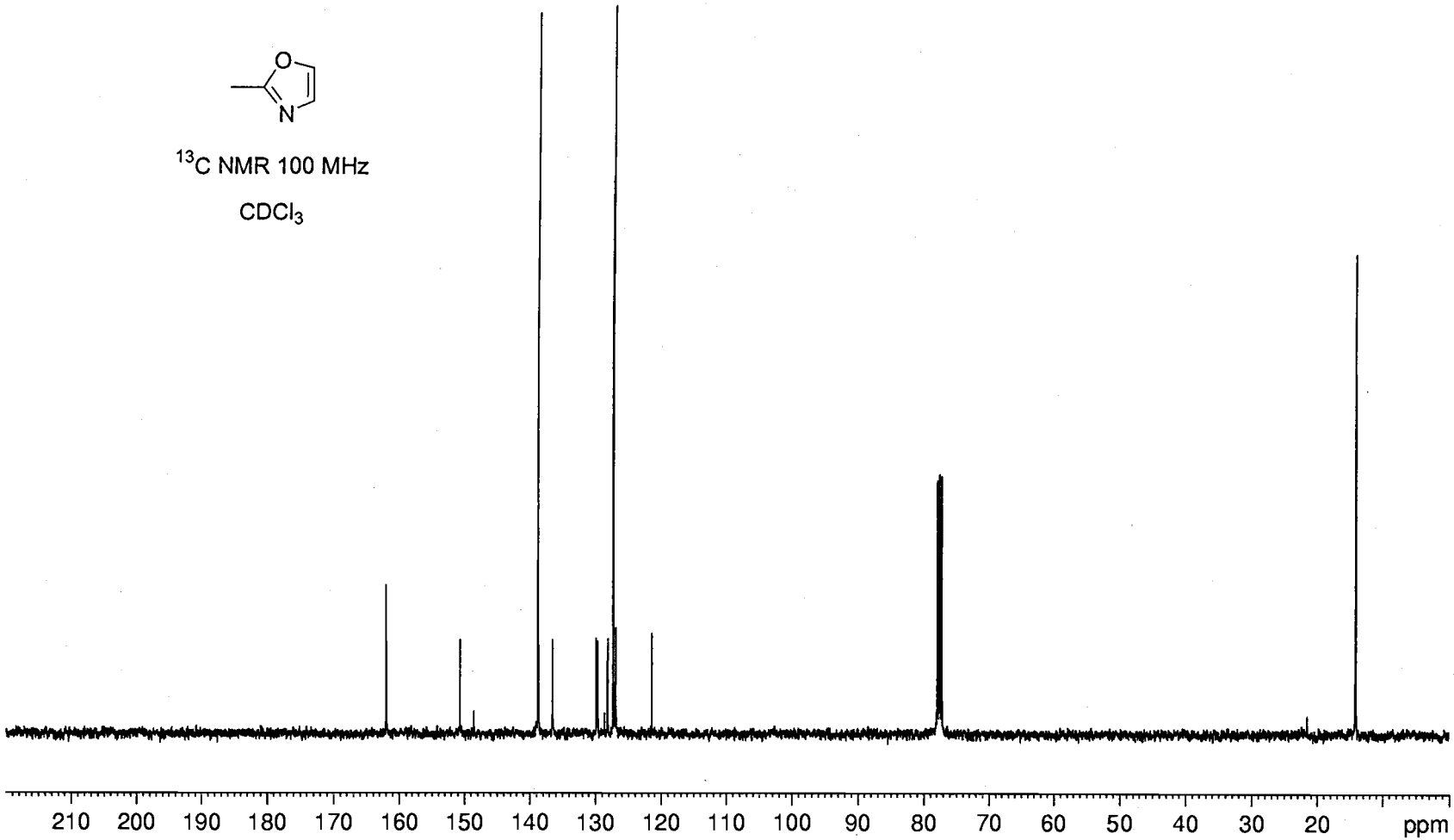
^{13}C NMR 100 MHz

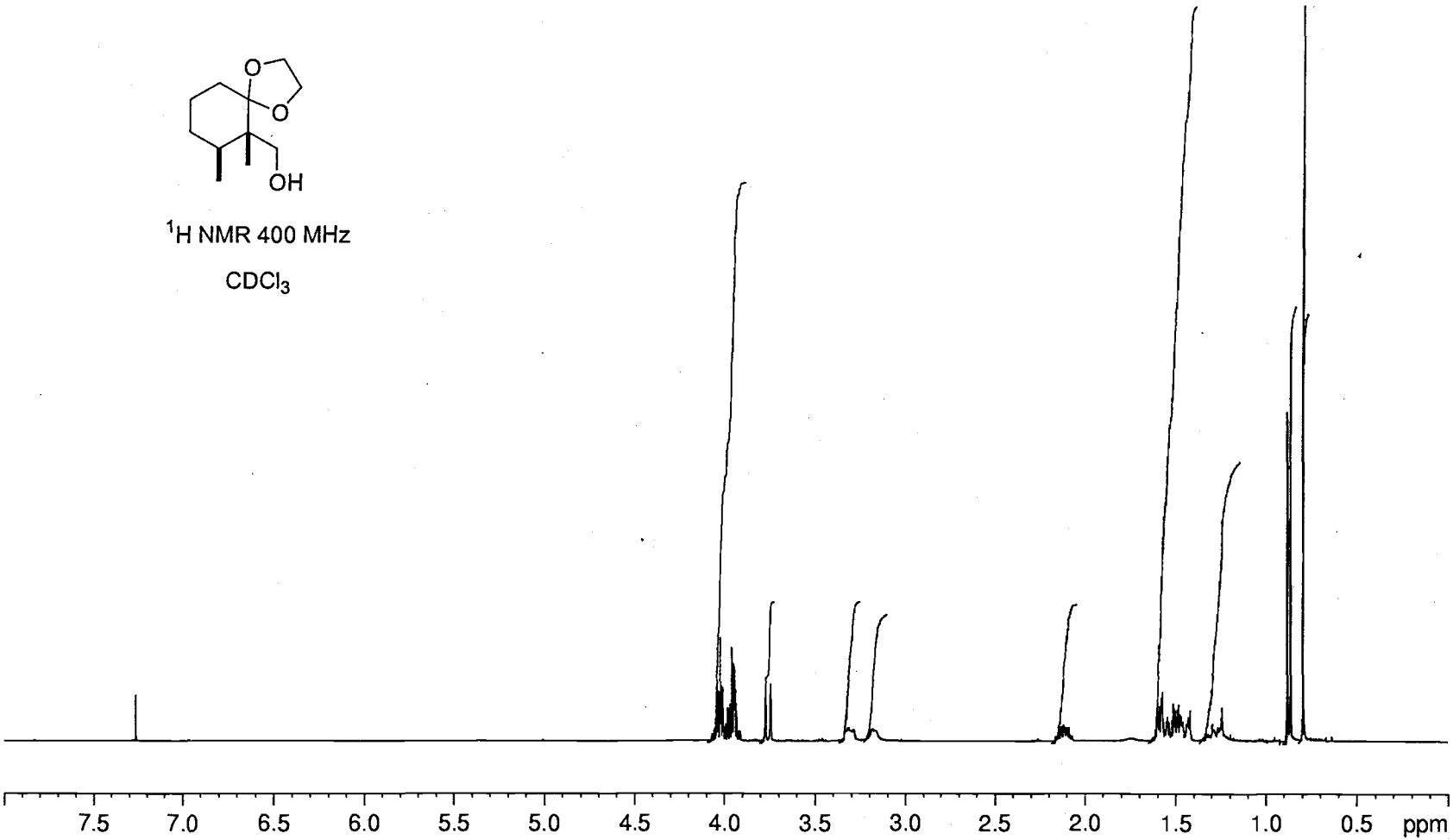
$CDCl_3$

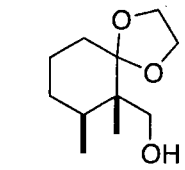

O
N
CO2Me
1H NMR 300 MHz
CDCl3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


O
N
CO2Me
13C NMR 75 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


O
N
^{1}H NMR 400 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

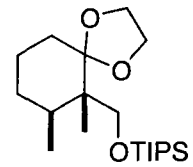

O
N
^{13}C NMR 100 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


O
O
OH
^{1}H NMR 400 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



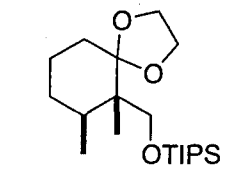
^{13}C NMR 100 MHz

$CDCl_3$



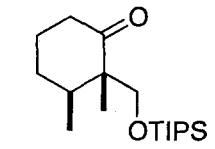
^{1}H NMR 400 MHz

$CDCl_3$



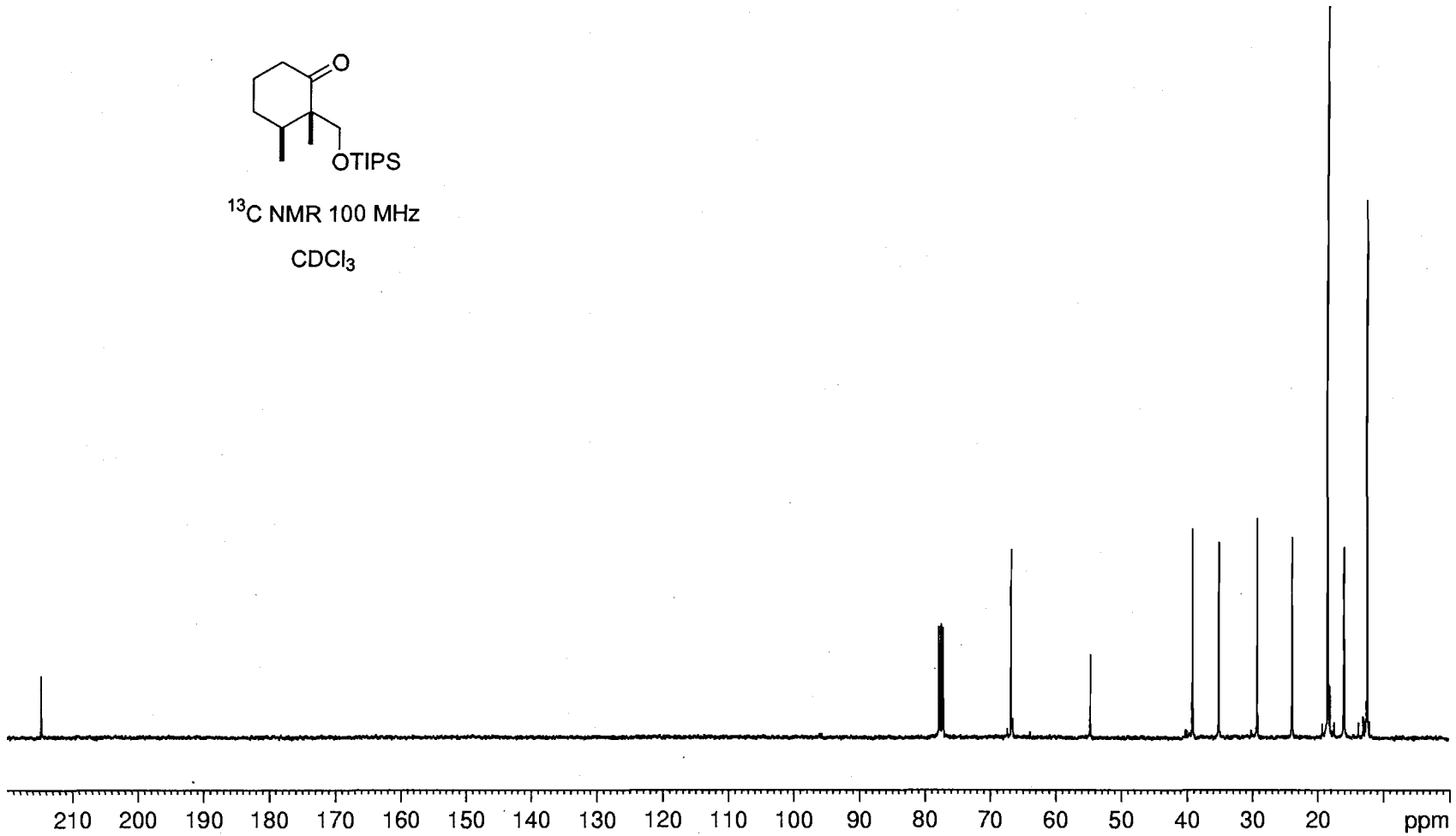
^{13}C NMR 100 MHz

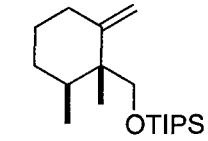
$CDCl_3$



^{1}H NMR 400 MHz

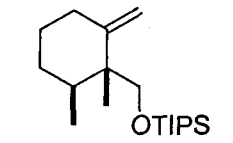
$CDCl_3$


O
OTIPS
^{13}C NMR 100 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



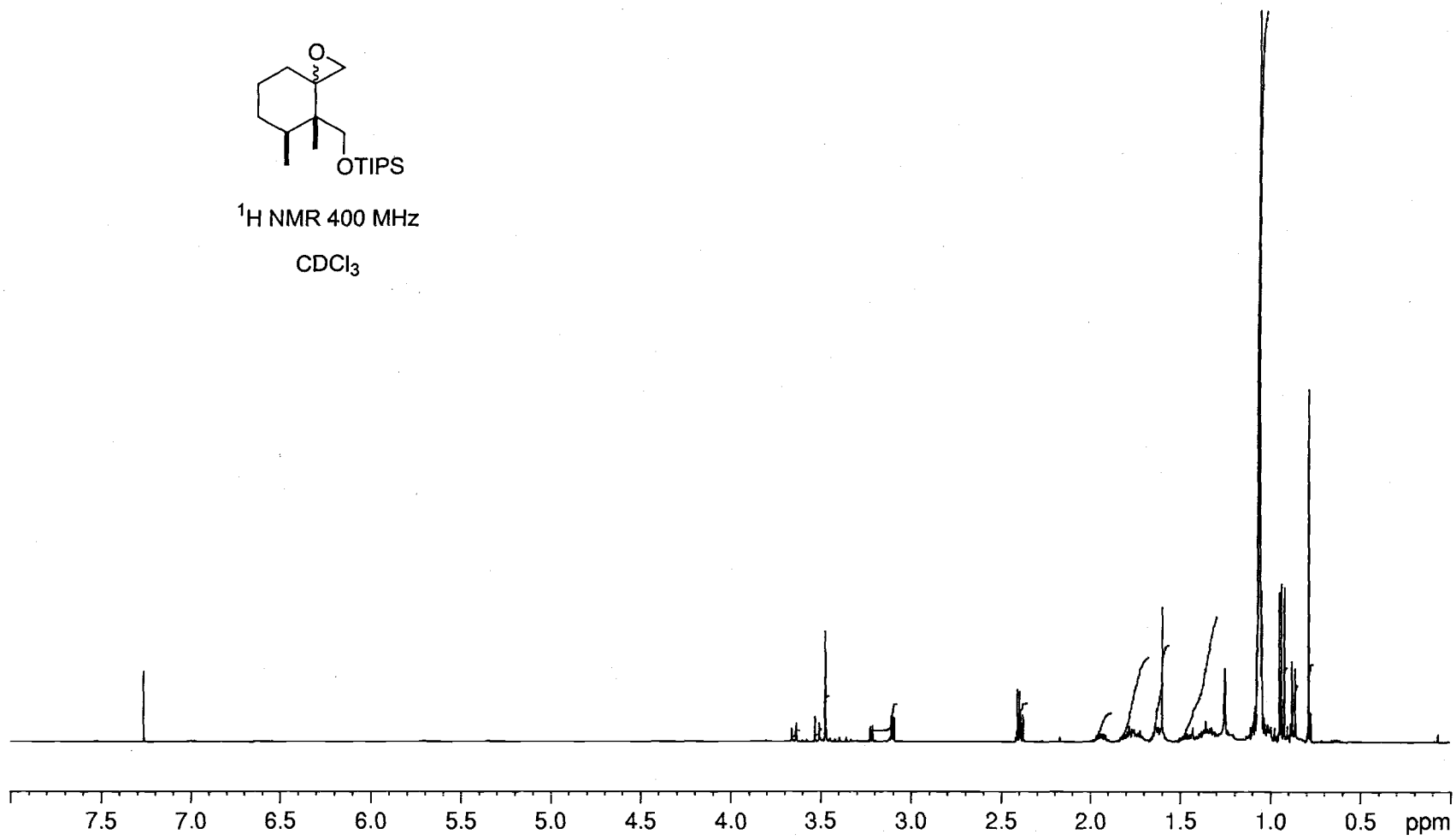
^{1}H NMR 400 MHz

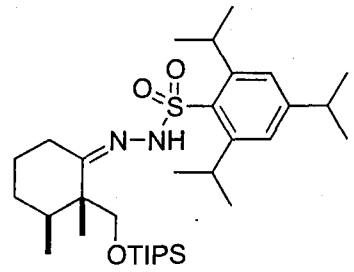
$CDCl_3$



^{13}C NMR 100 MHz

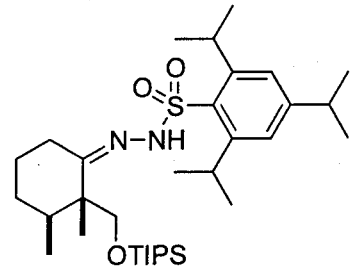
$CDCl_3$


O
OTIPS
^{1}H NMR 400 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



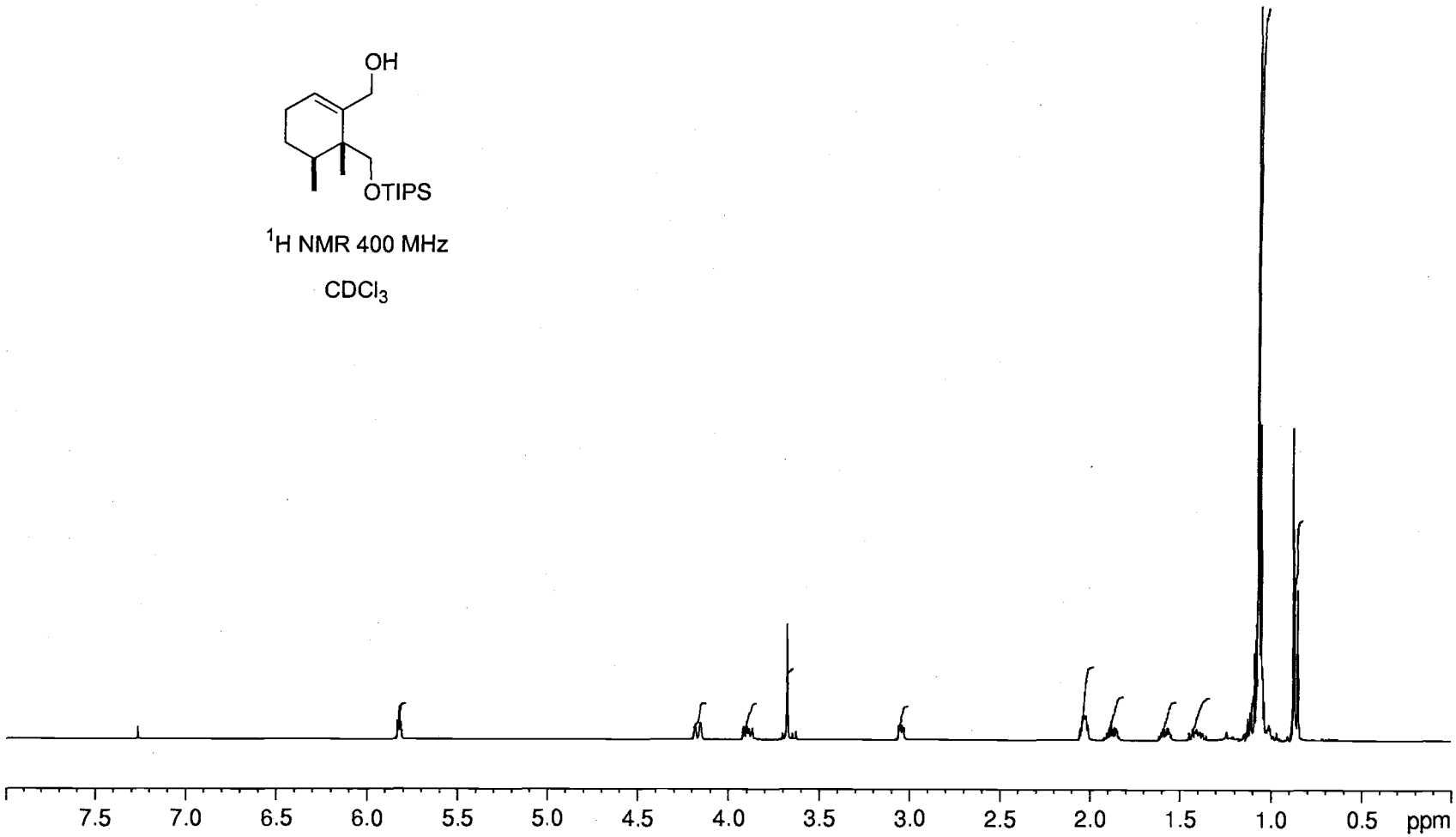
^{1}H NMR 400 MHz

$CDCl_3$



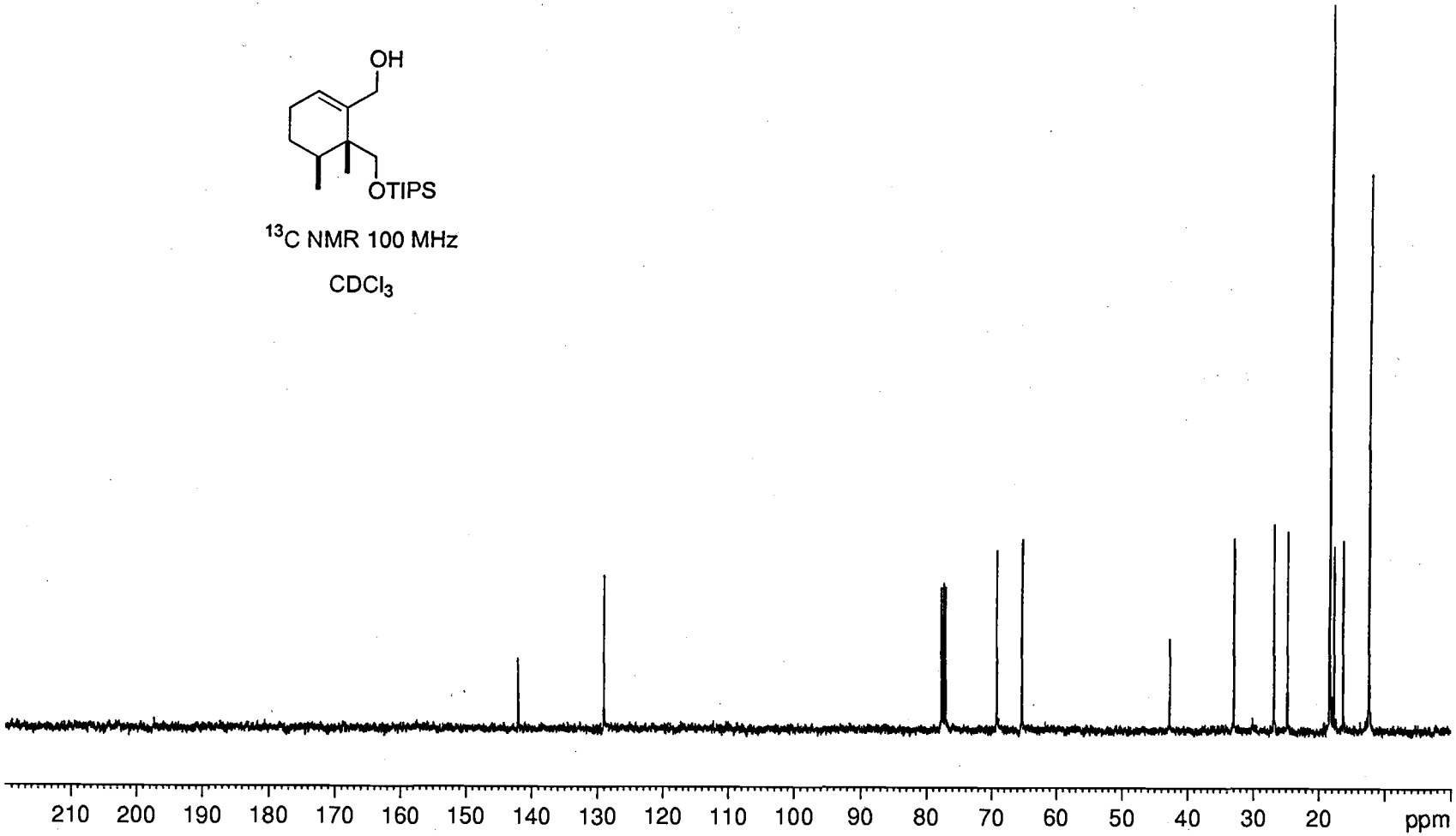
^{13}C NMR 100 MHz

$CDCl_3$



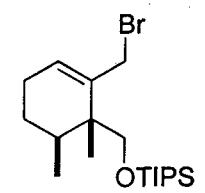
^{1}H NMR 400 MHz

$CDCl_3$



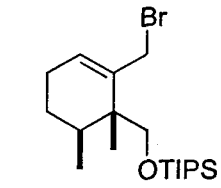
^{13}C NMR 100 MHz

$CDCl_3$



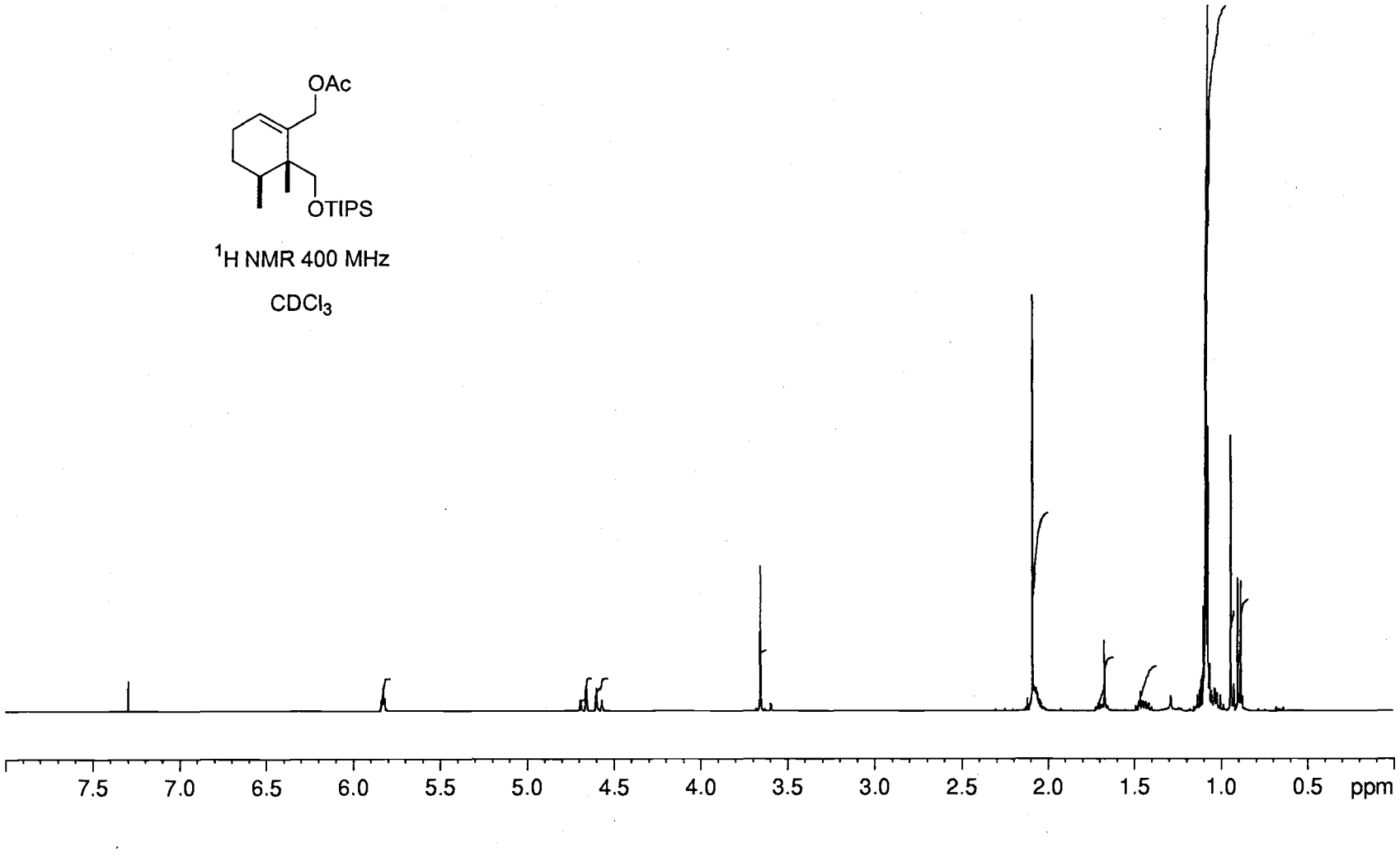
^{1}H NMR 400 MHz

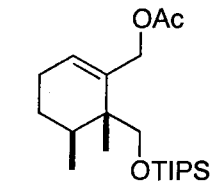
$CDCl_3$



^{13}C NMR 100 MHz

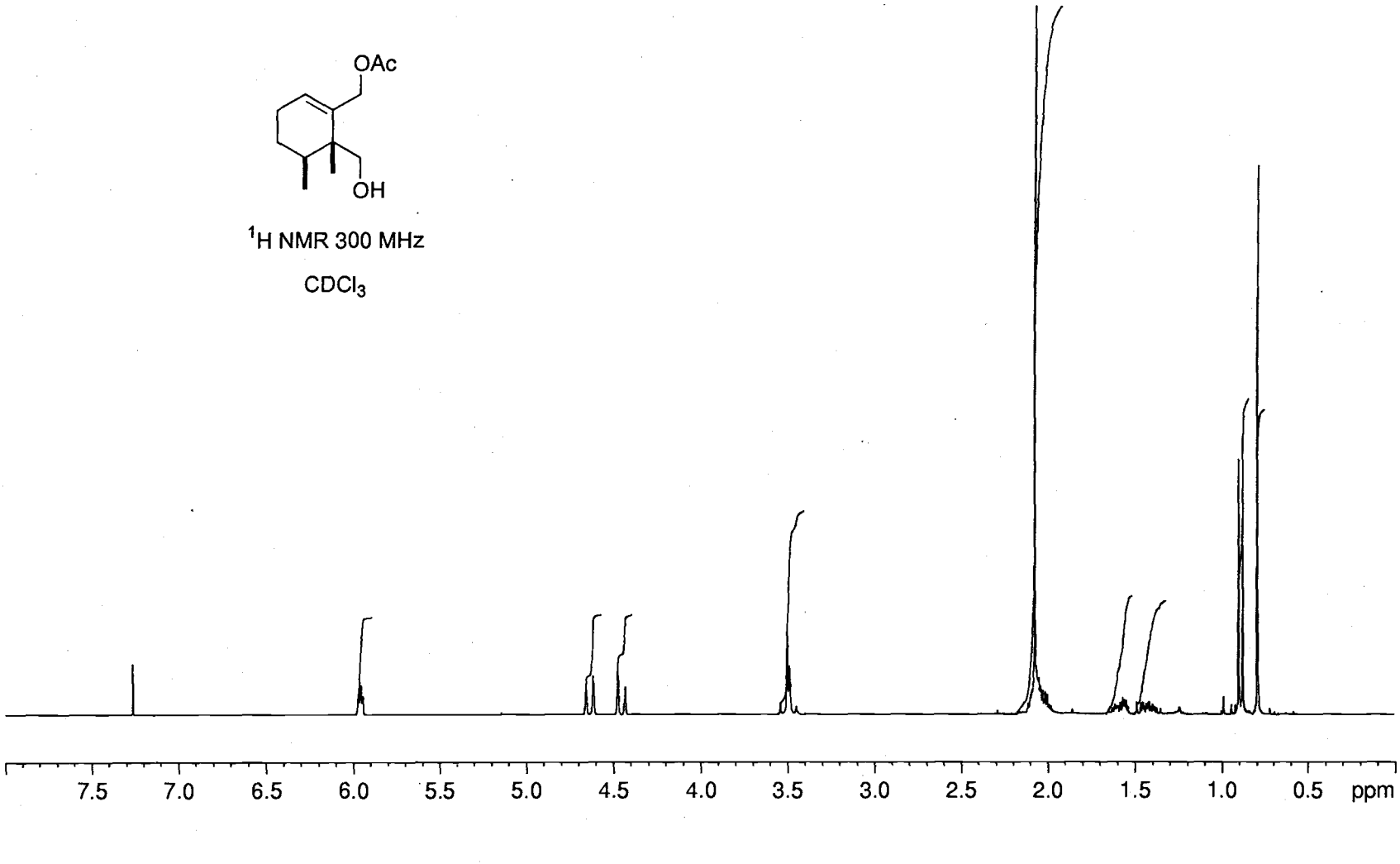
$CDCl_3$

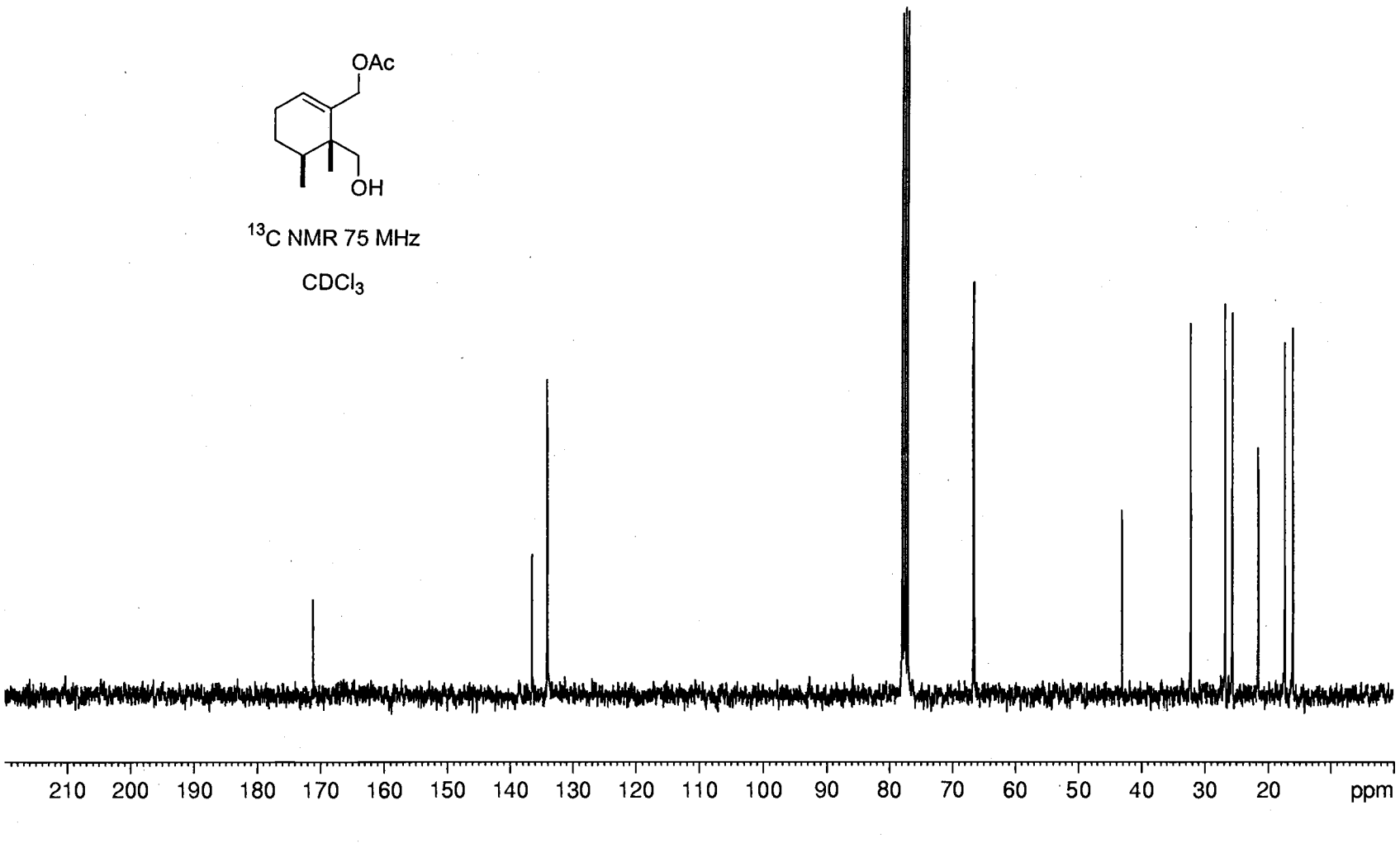

OAc
OTIPS
^{1}H NMR 400 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

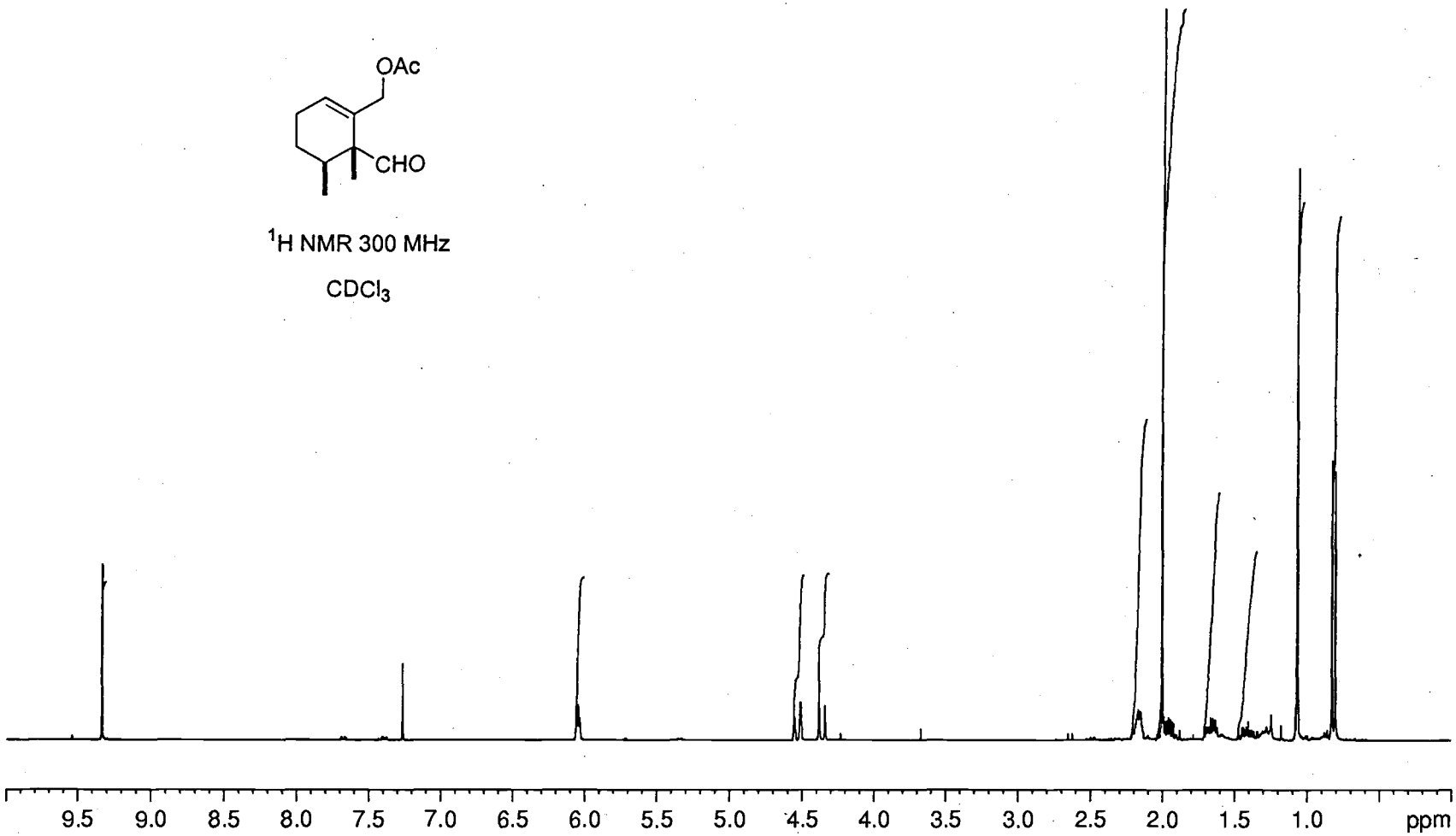


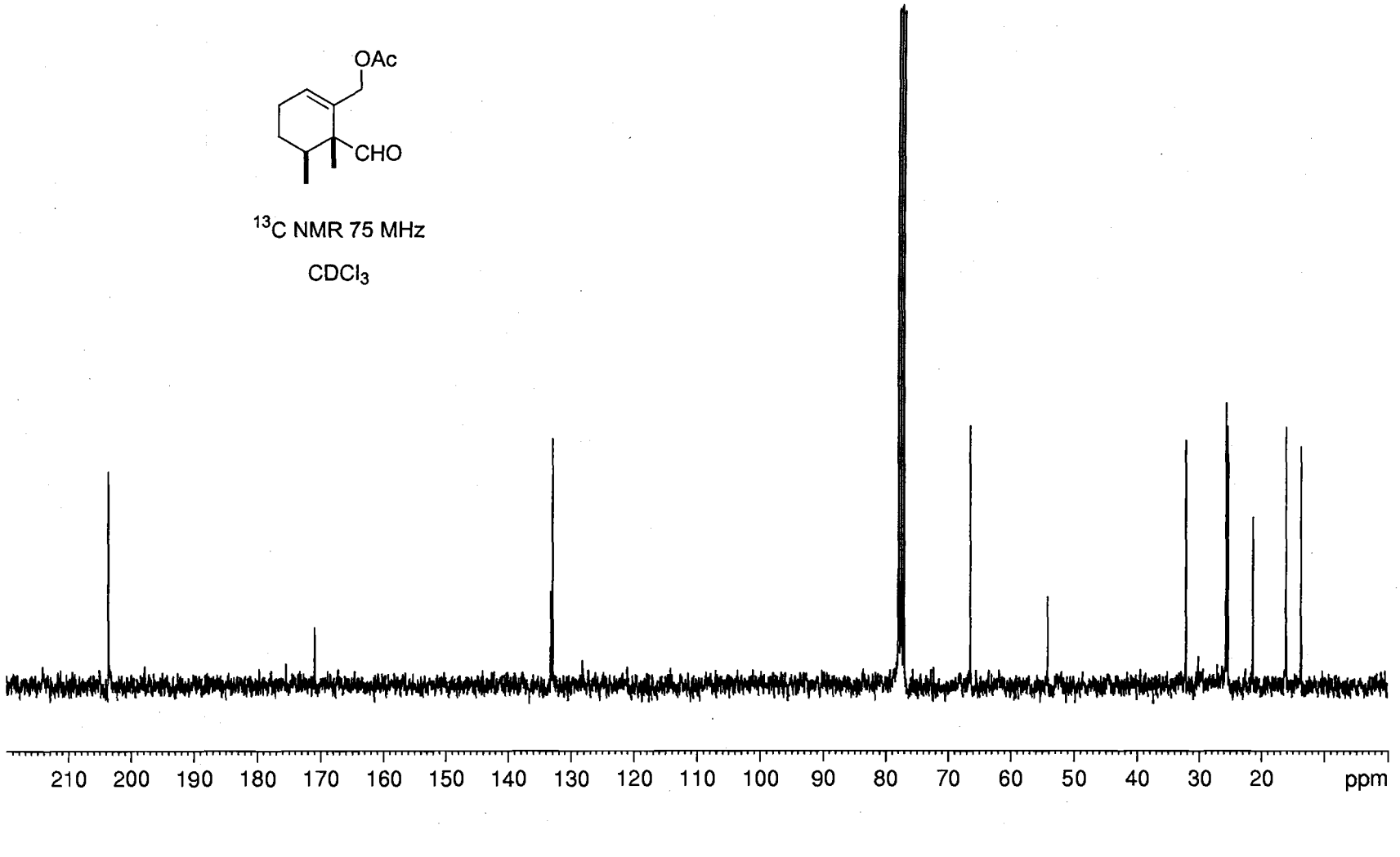
^{13}C NMR 100 MHz

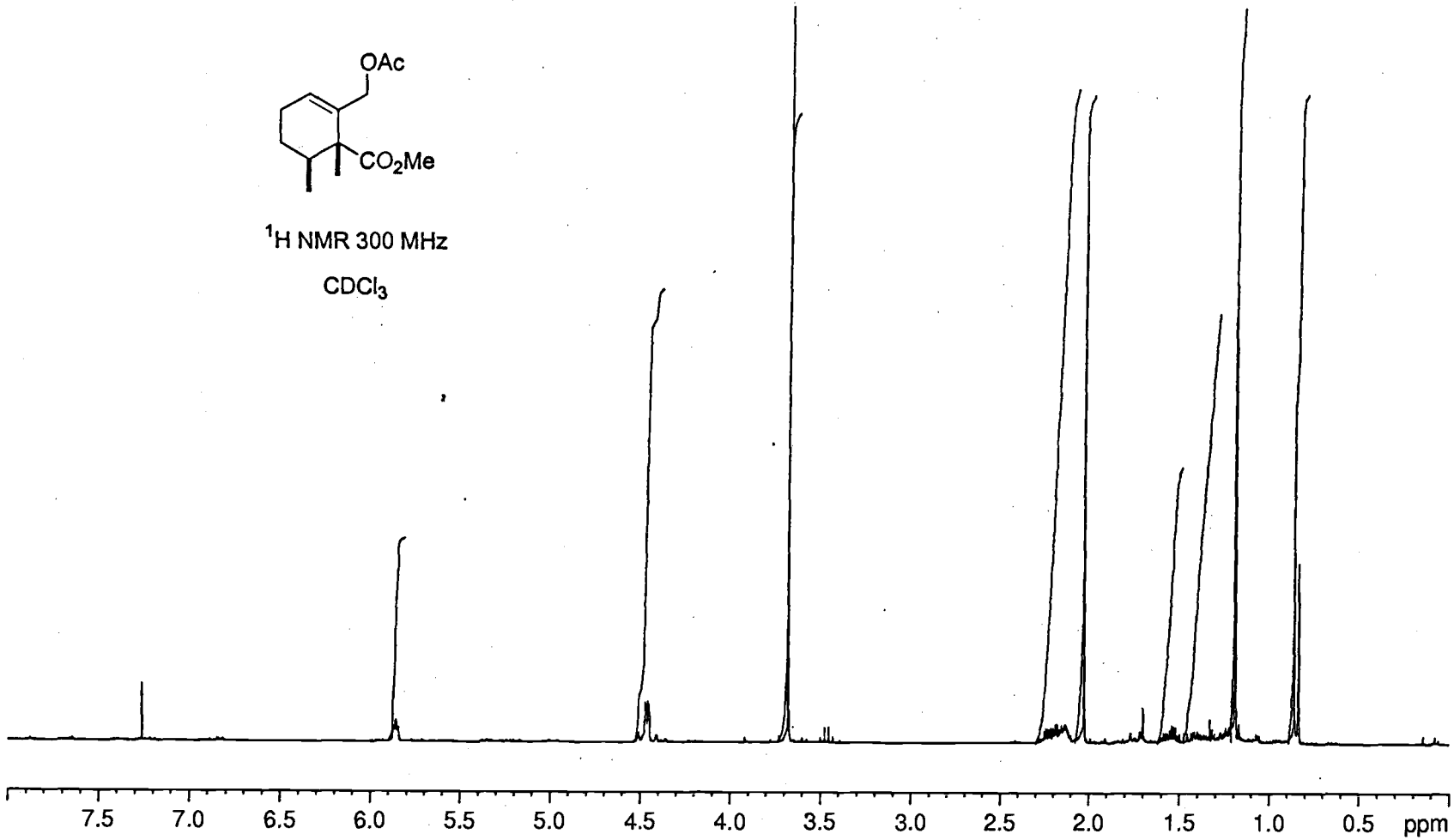
$CDCl_3$

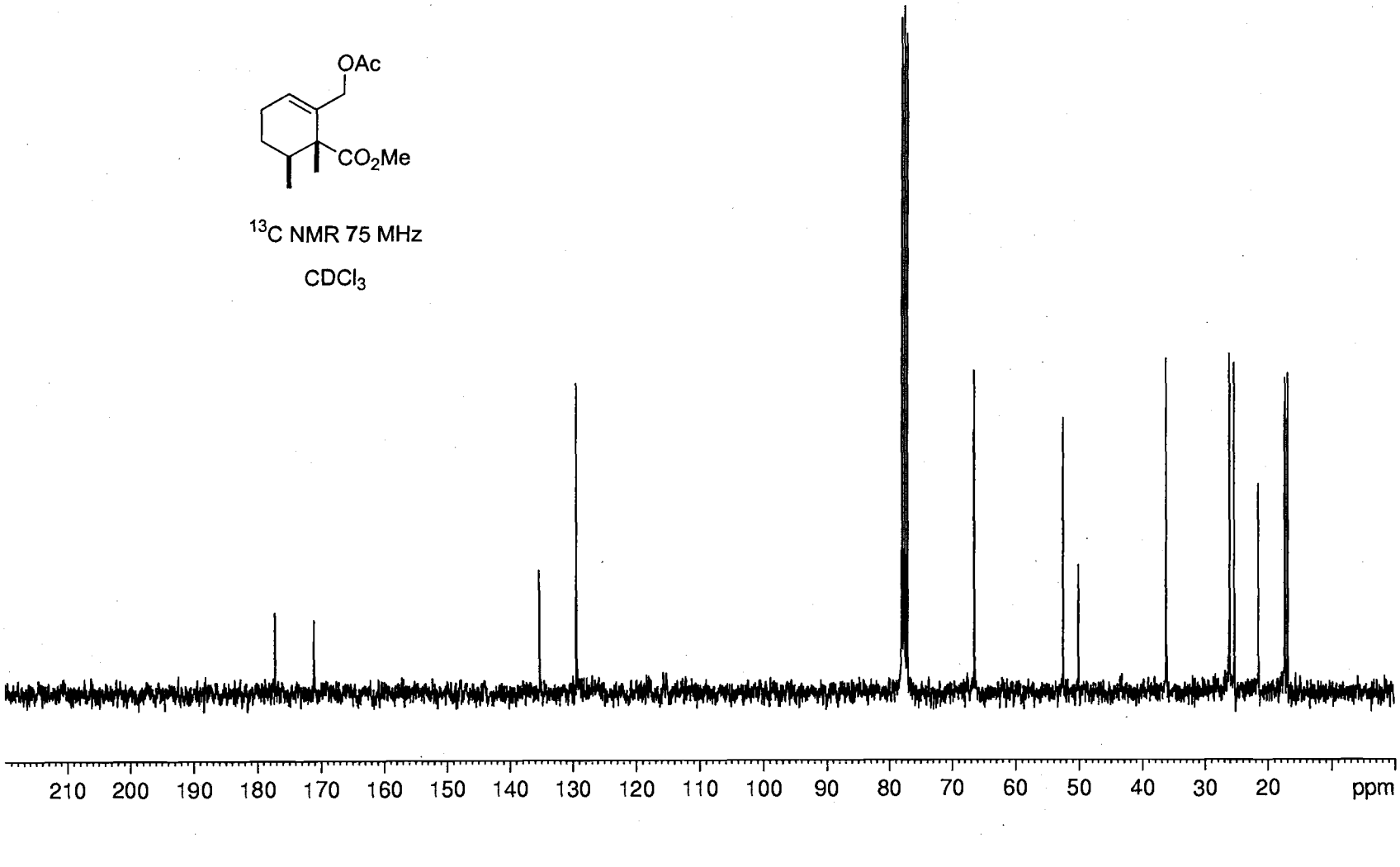

OAc
OH
^{1}H NMR 300 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

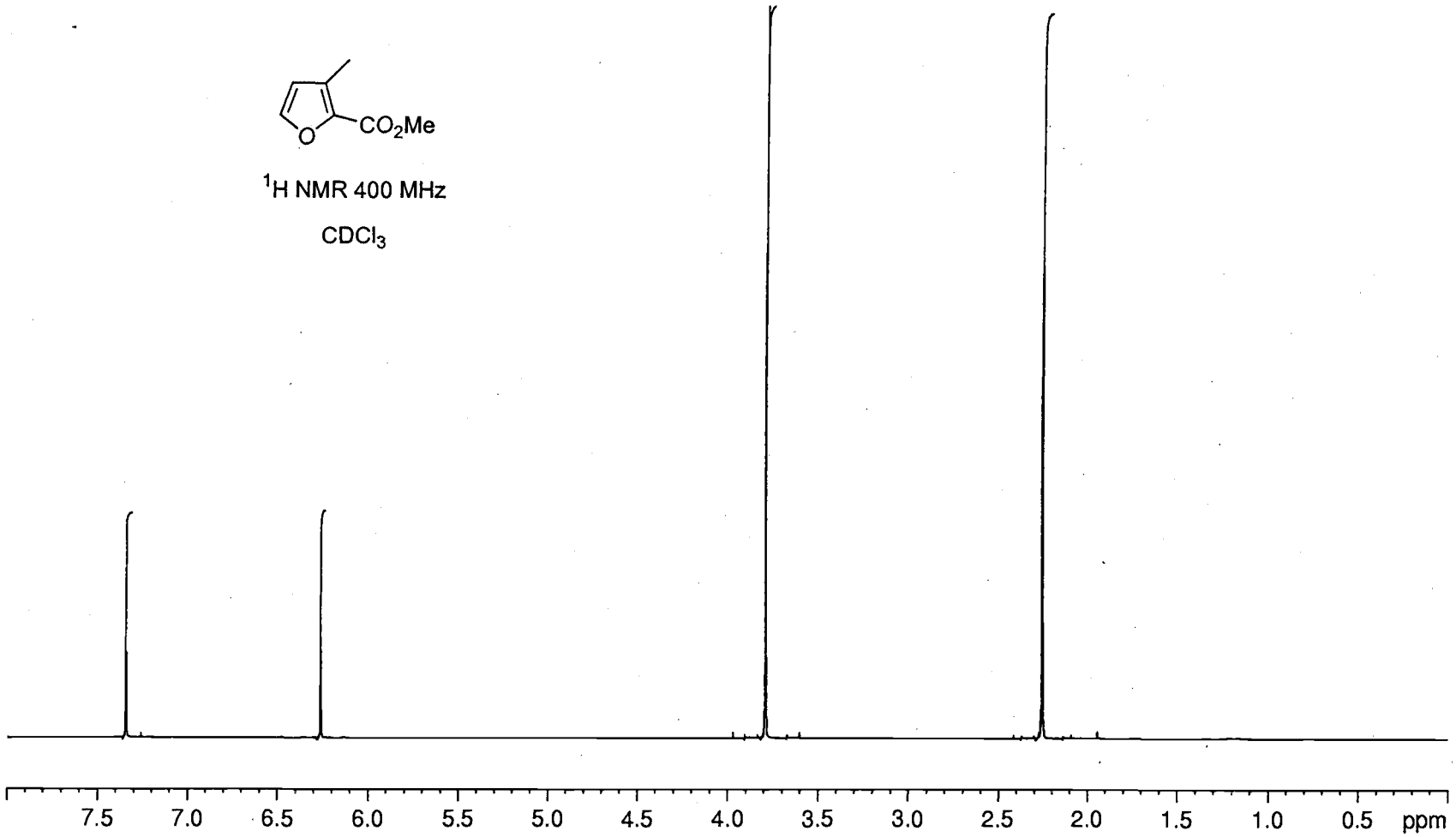

OAc
OH
^{13}C NMR 75 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

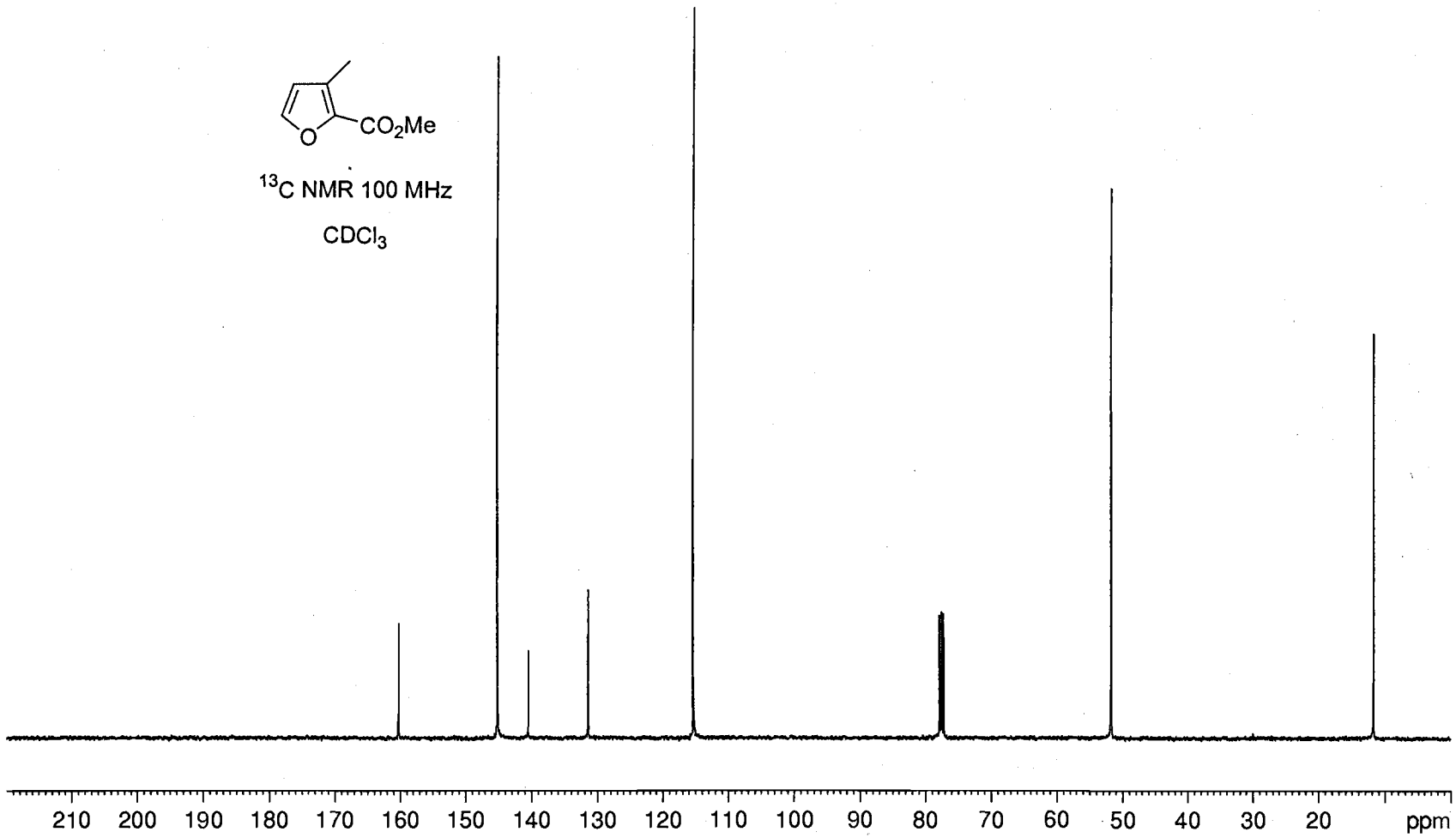

OAc
CHO
^{1}H NMR 300 MHz
$CDCl_3$
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

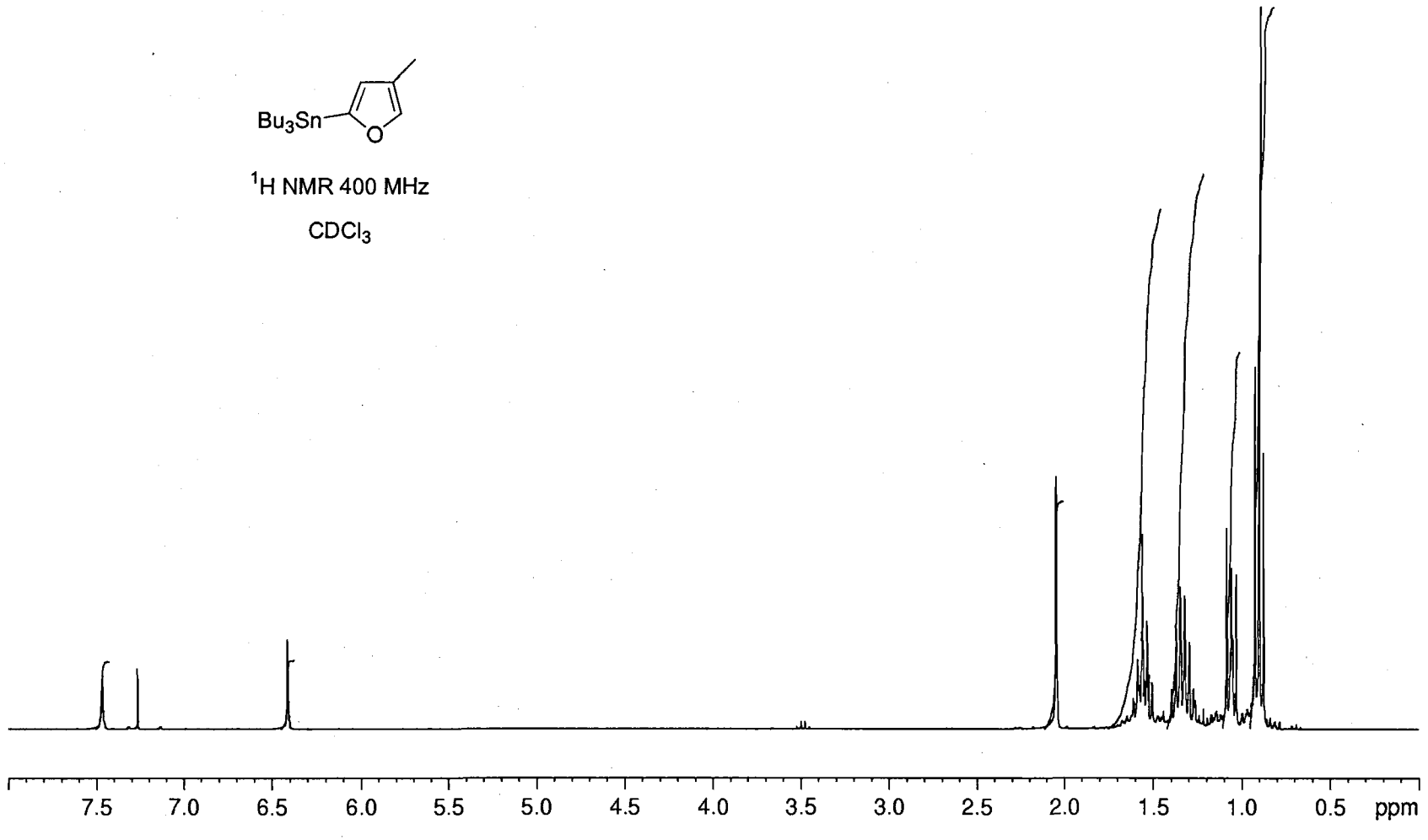

OAc
CHO
^{13}C NMR 75 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

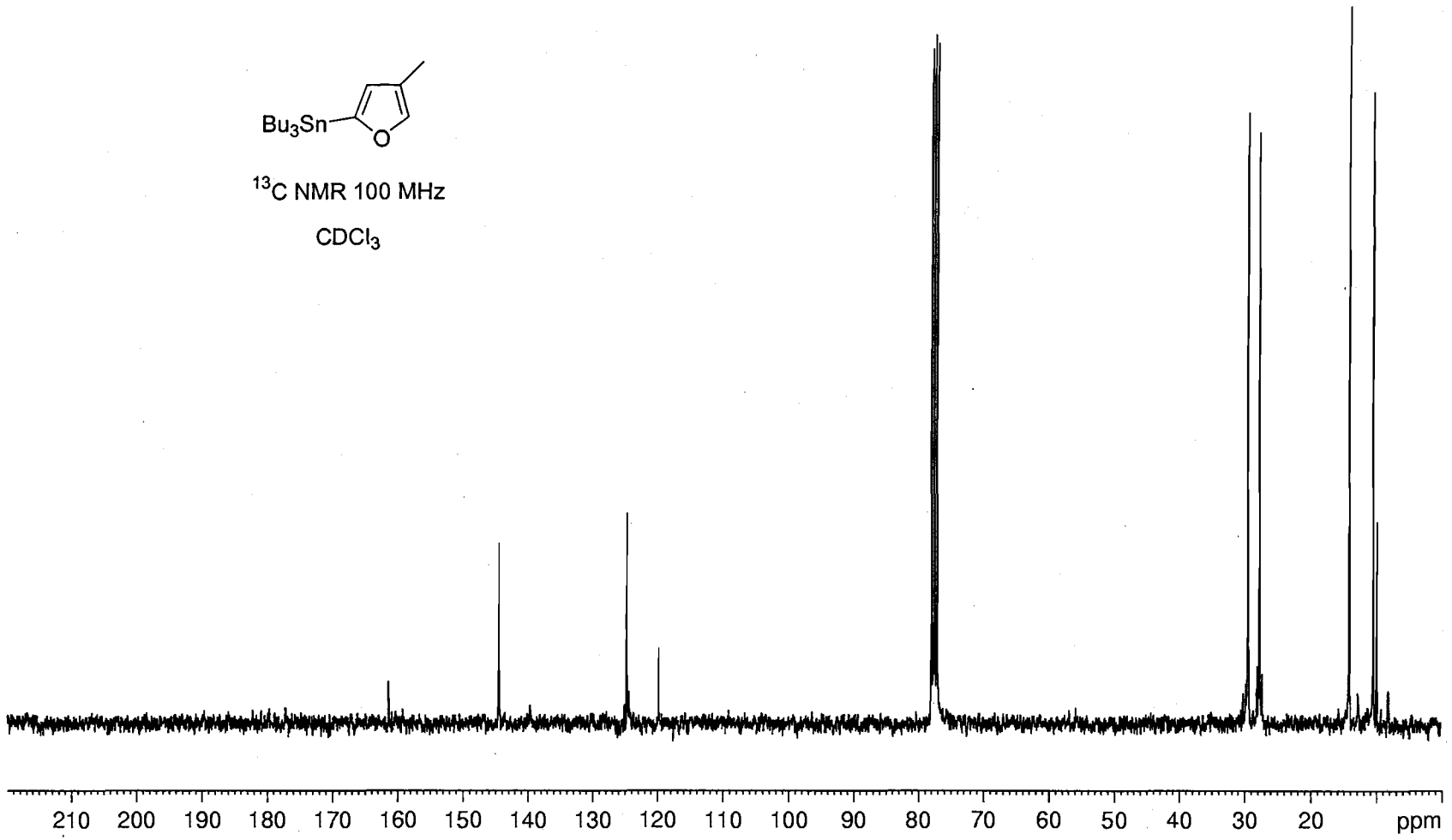

OAc
CO2Me
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

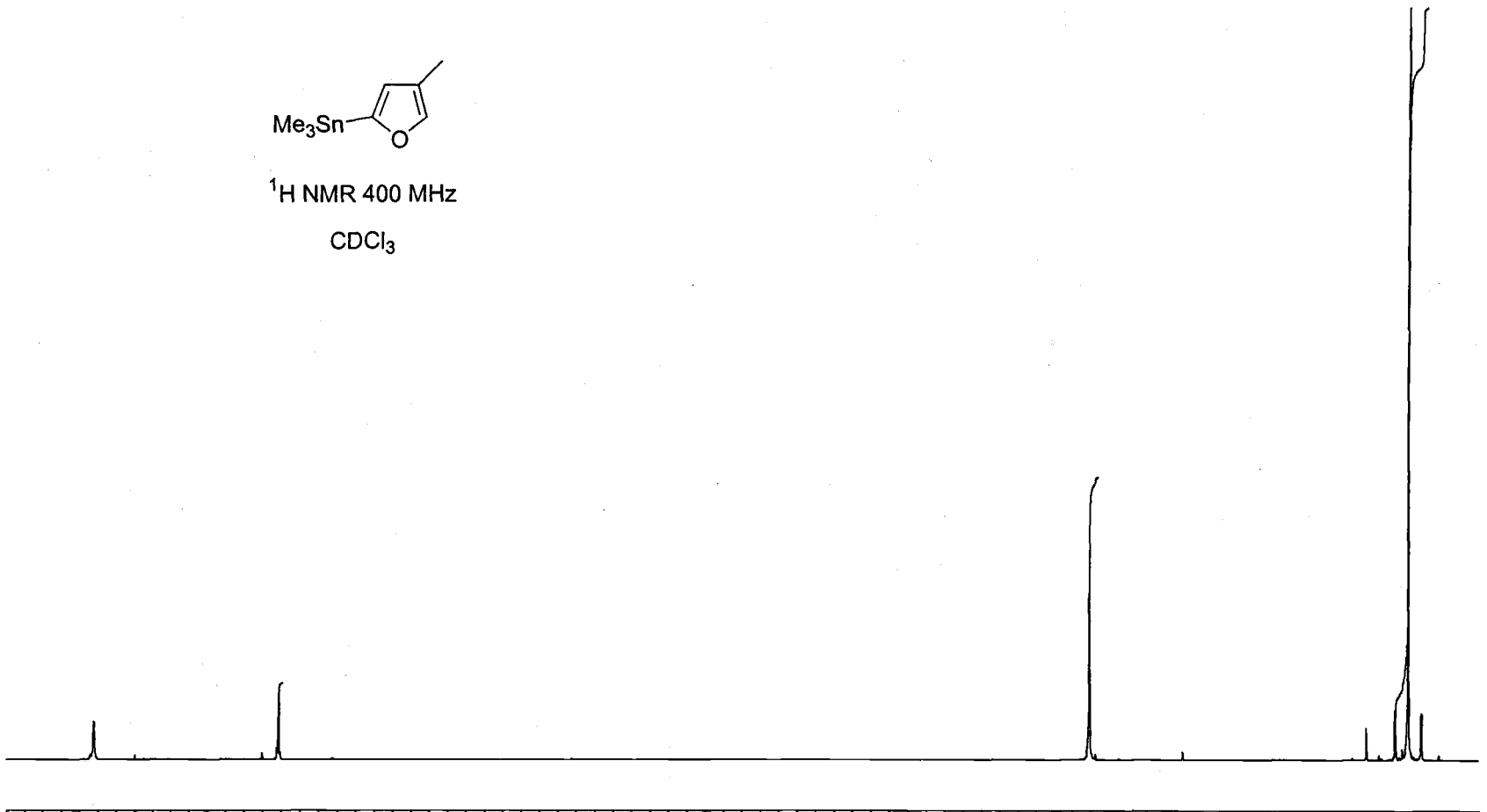

OAc
CO2Me
13C NMR 75 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

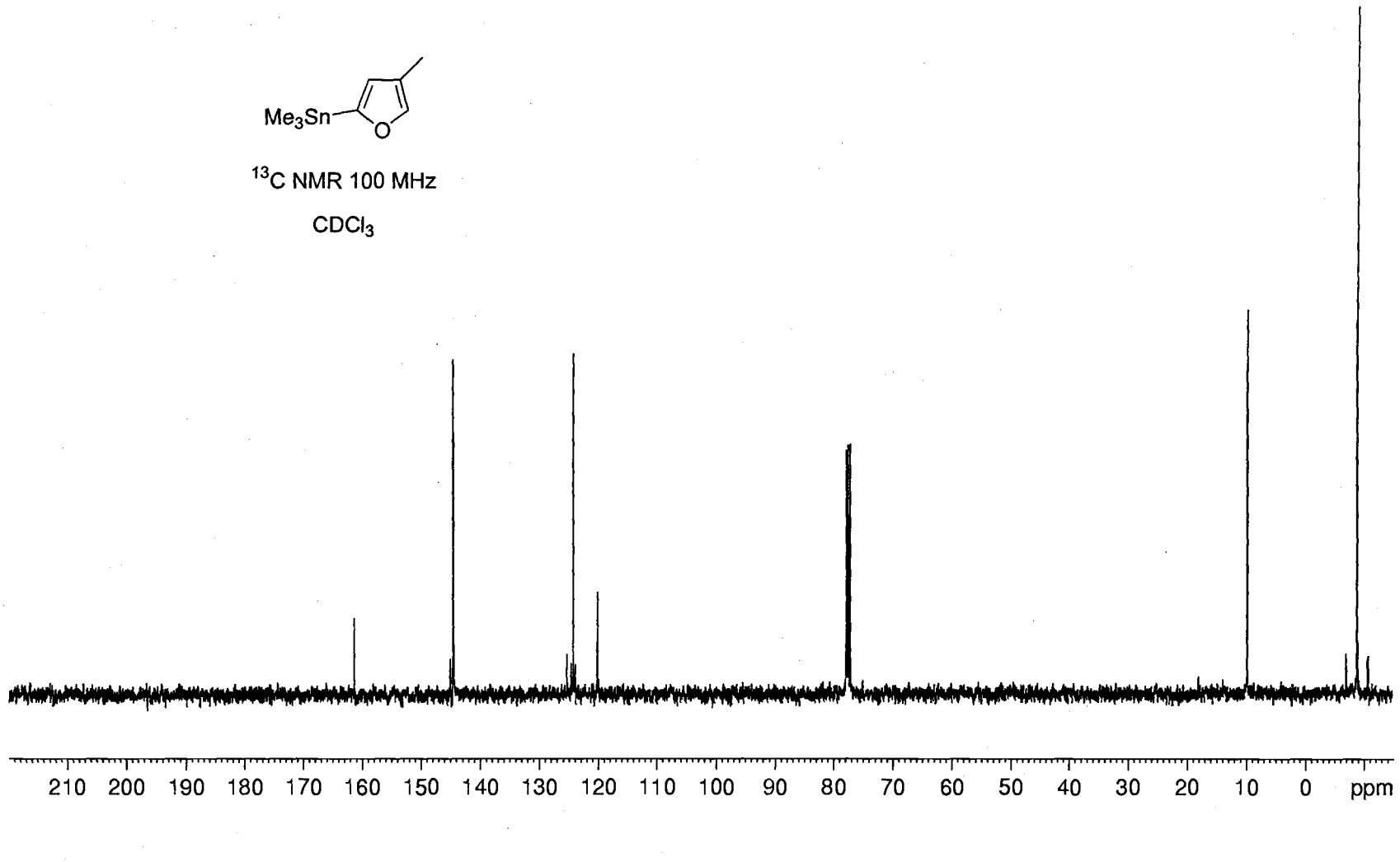

CO2Me
O
1H NMR 400 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

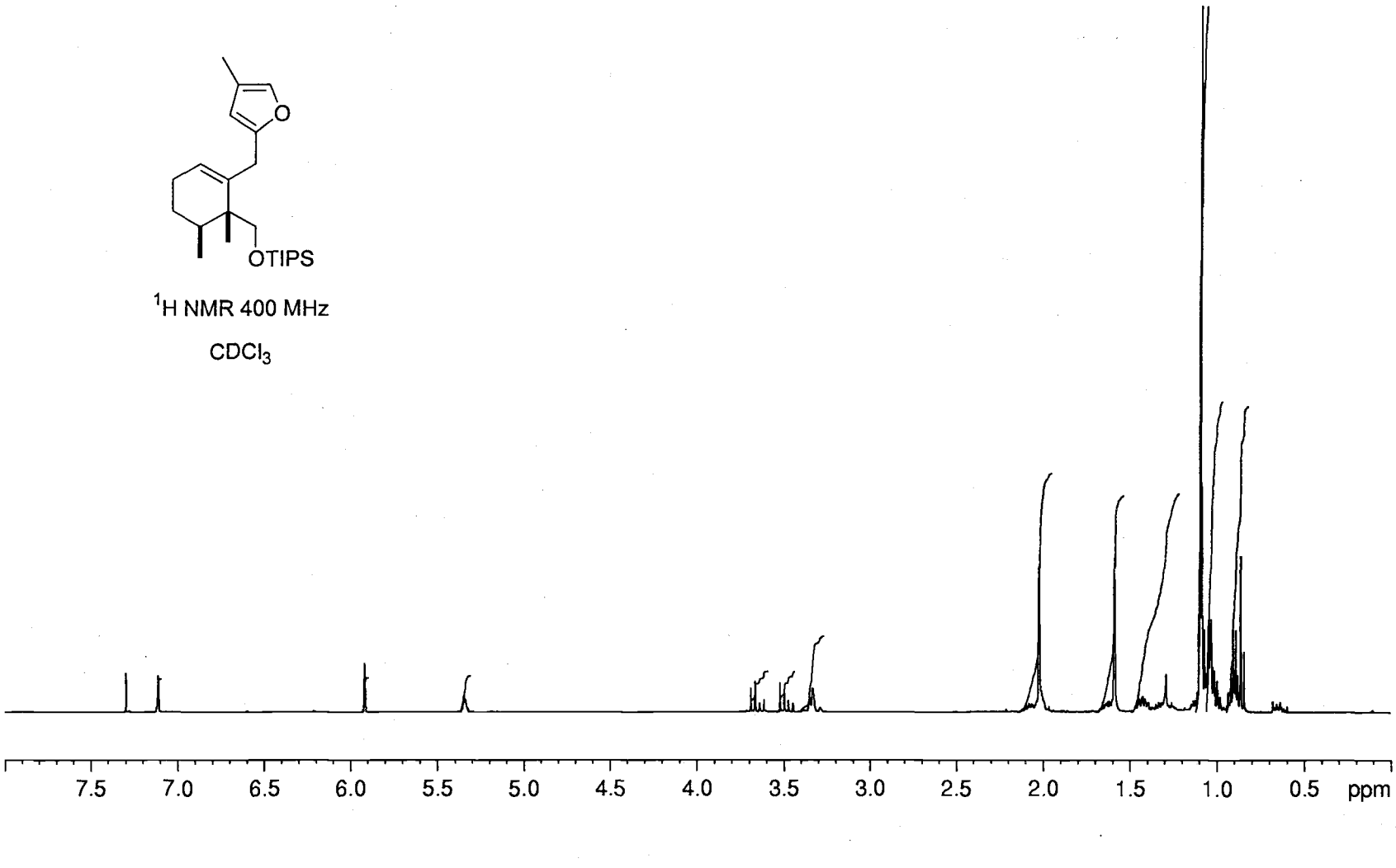

CO2Me
O
13C NMR 100 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

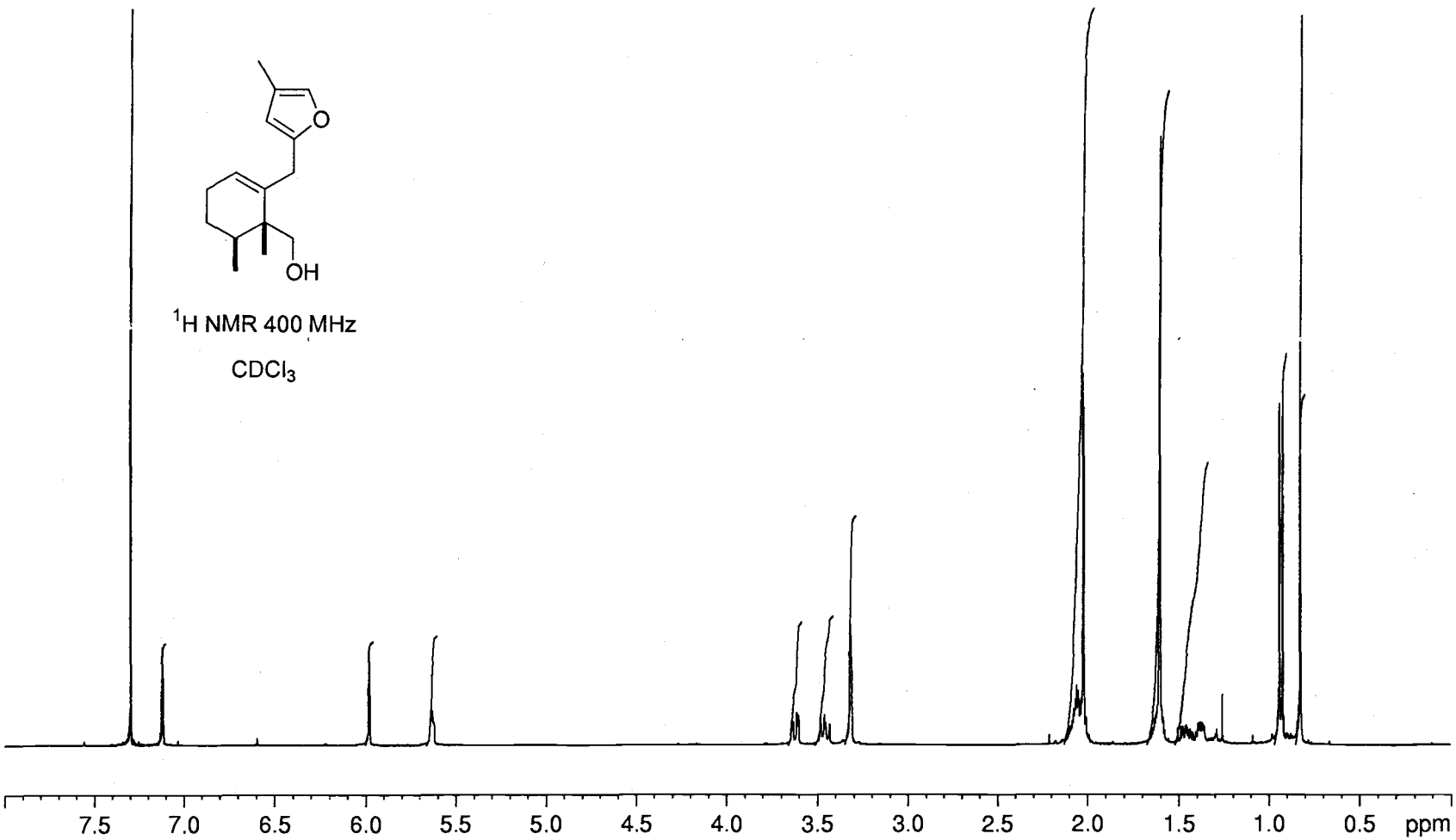

Bu3Sn
O
1H NMR 400 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

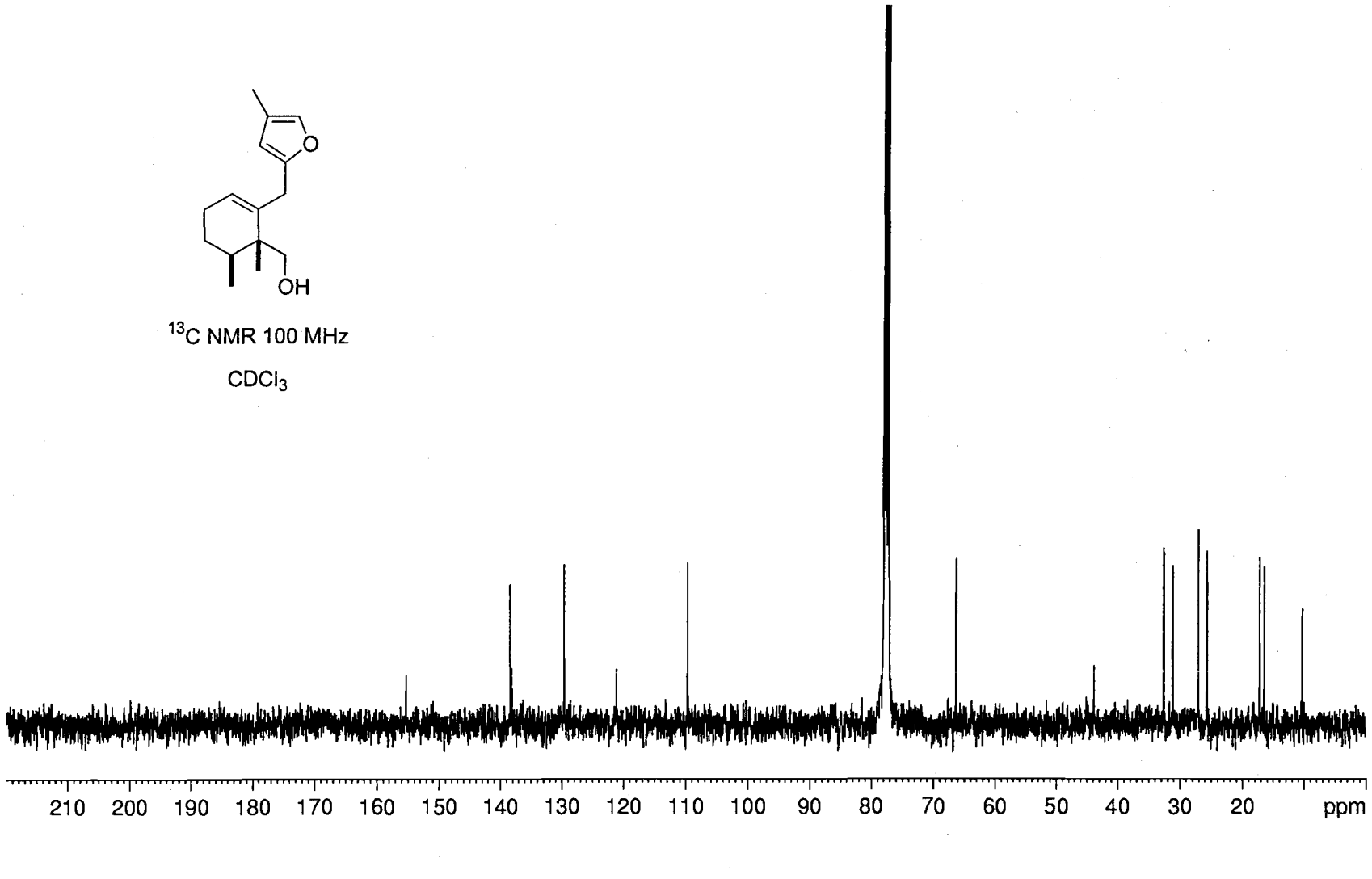

Bu3Sn
O
13C NMR 100 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

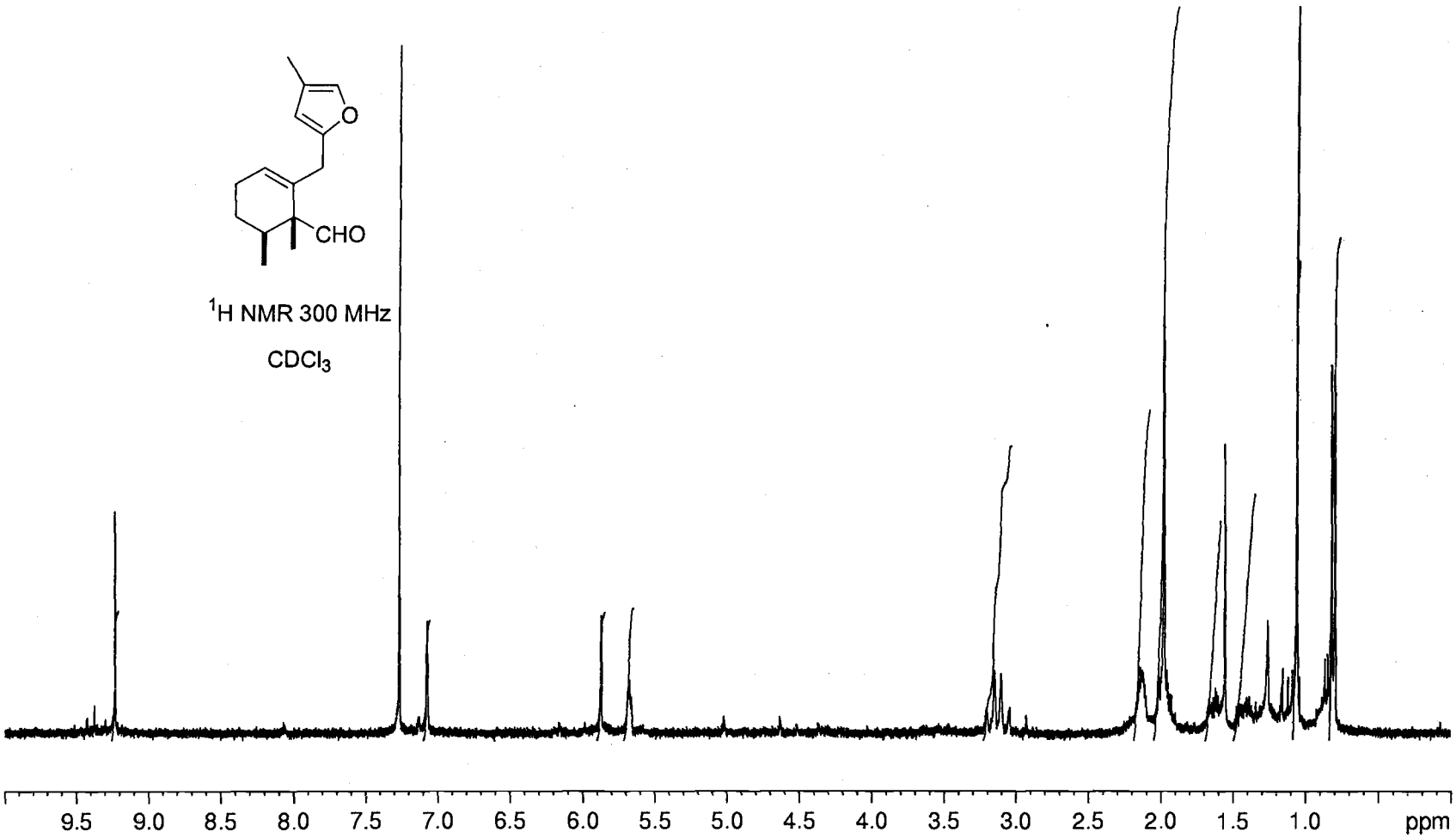

Me3Sn
O
1H NMR 400 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

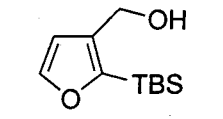

Me3Sn
O
13C NMR 100 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


O
OTIPS
^{1}H NMR 400 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


O
OH
^{1}H NMR 400 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

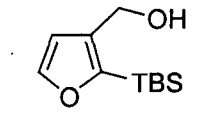

O
OH
^{13}C NMR 100 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


O
CHO
^{1}H NMR 300 MHz
$CDCl_3$
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



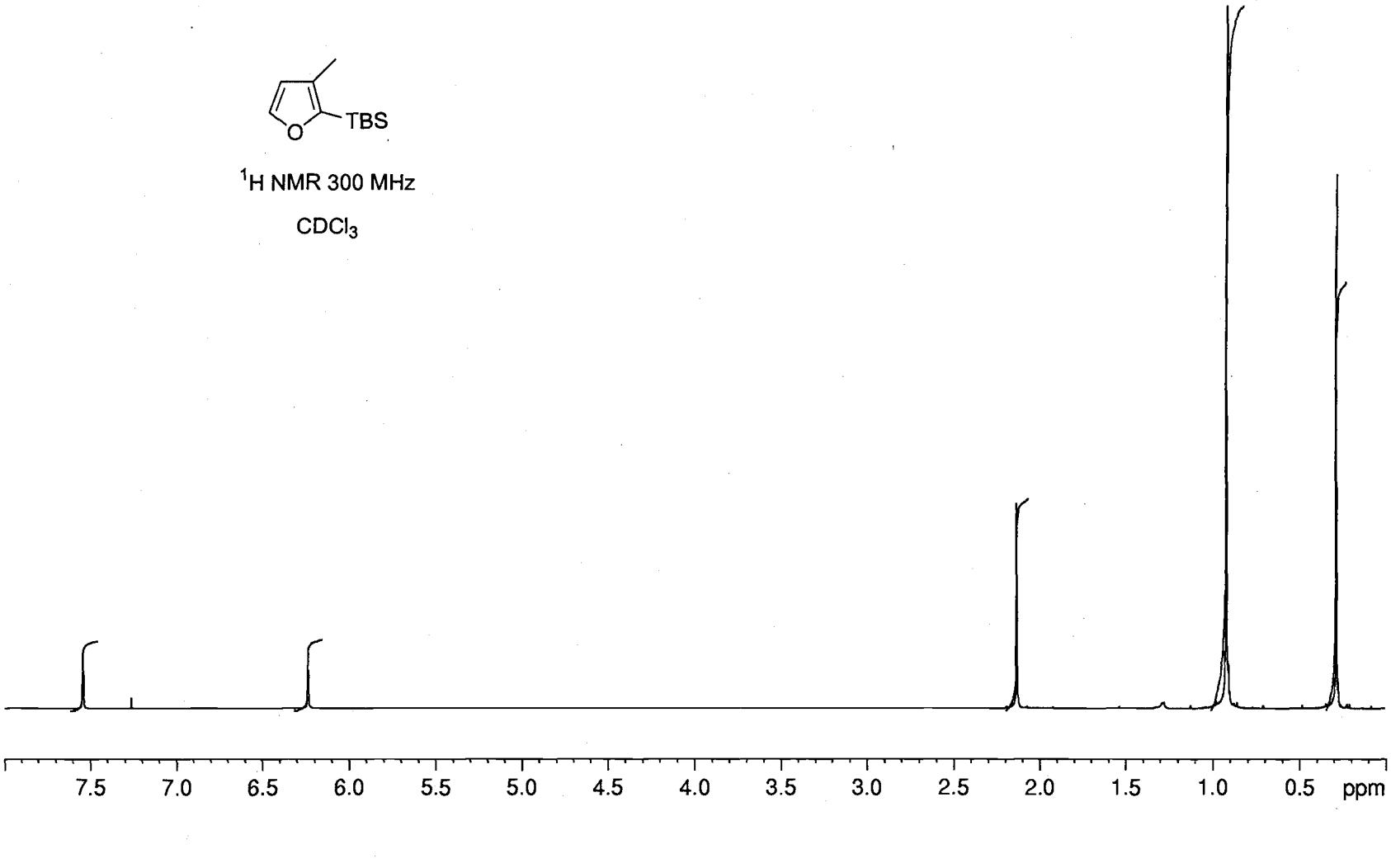
^{1}H NMR 300 MHz

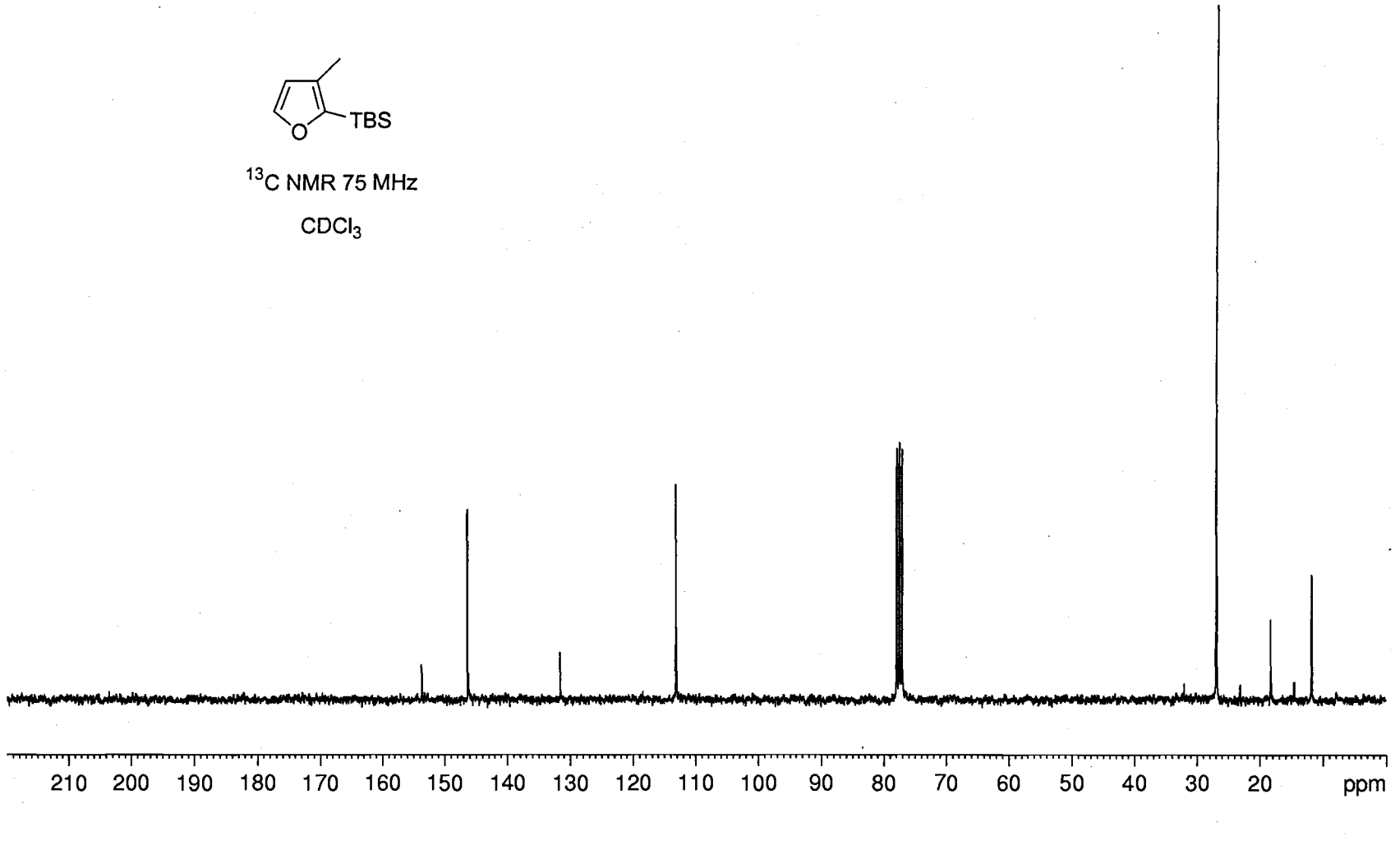
$CDCl_3$

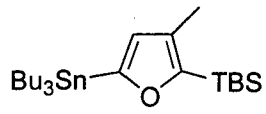


^{13}C NMR 75 MHz

$CDCl_3$

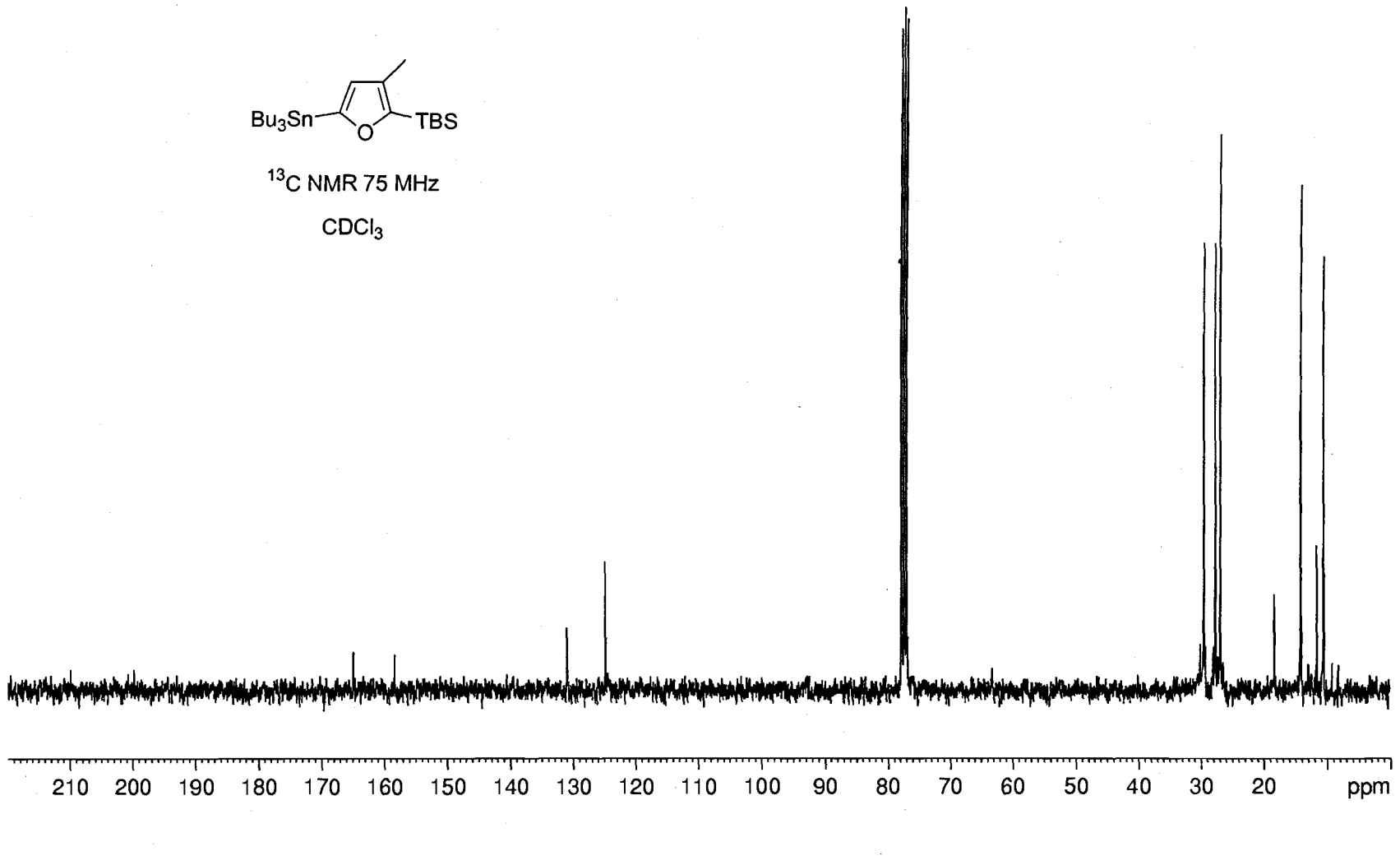

TBS
O
^{1}H NMR 300 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

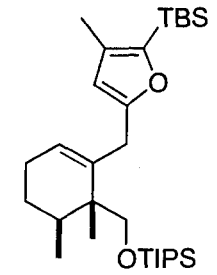

TBS
O
^{13}C NMR 75 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



^1H NMR 300 MHz

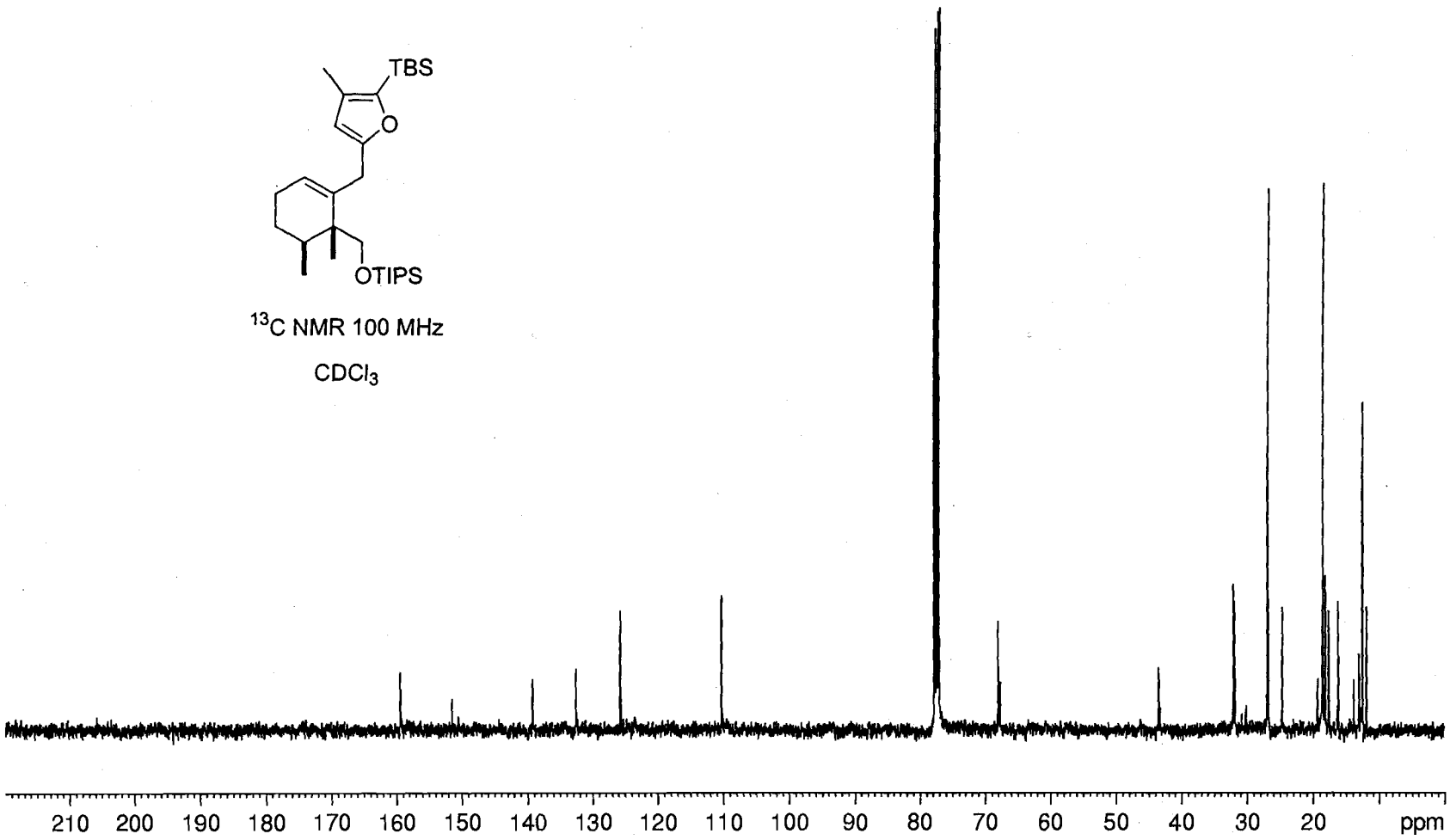
$CDCl_3$

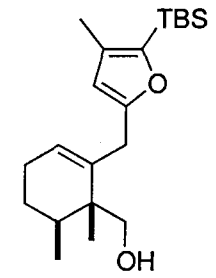

Bu3Sn
TBS
O
13C NMR 75 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



^{1}H NMR 400 MHz

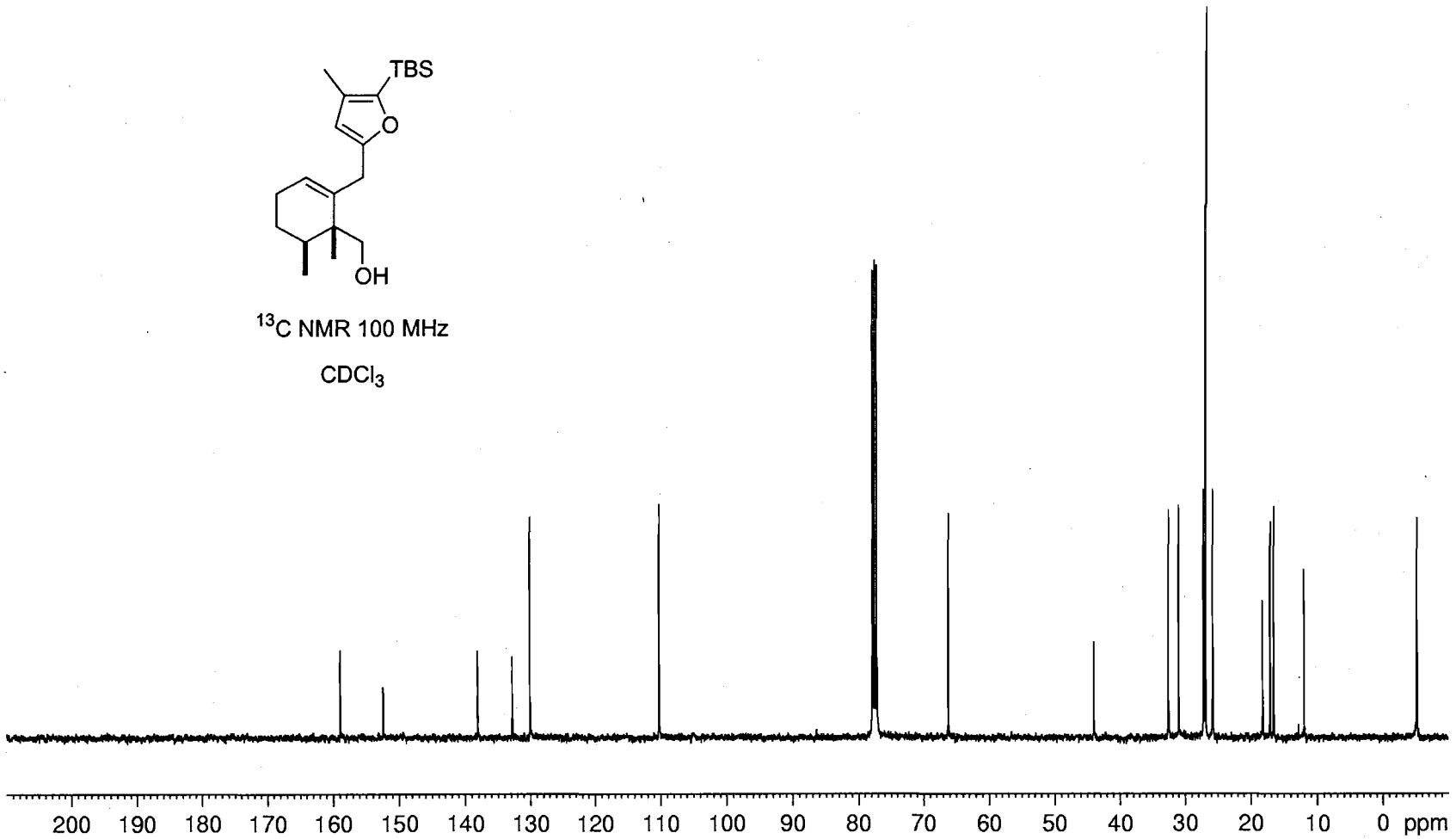
$CDCl_3$

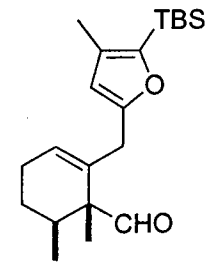

TBS
O
OTIPS
^{13}C NMR 100 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



^{1}H NMR 400 MHz

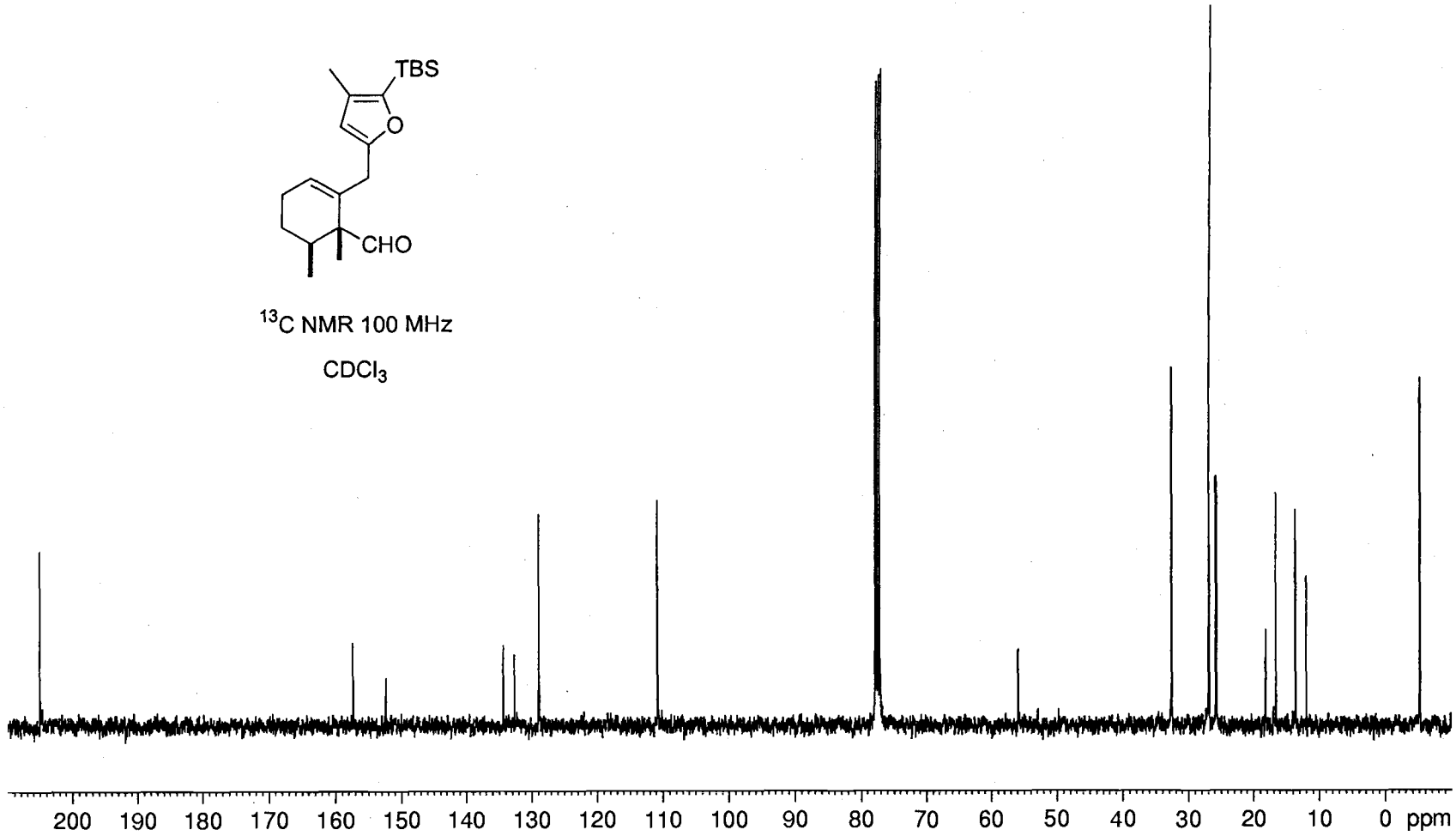
$CDCl_3$

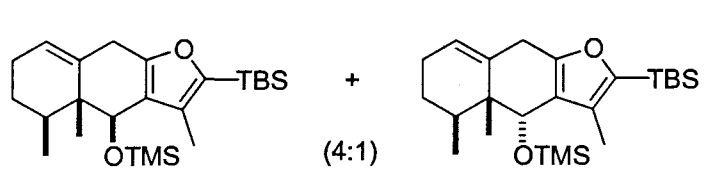

TBS
O
OH
^{13}C NMR 100 MHz
$CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



^{1}H NMR 400 MHz

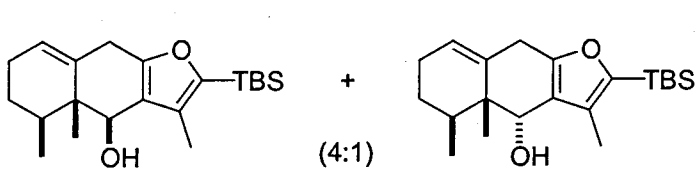
$CDCl_3$


TBS
O
CHO
^{13}C NMR 100 MHz
$CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



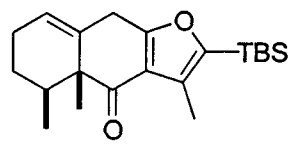
^{1}H NMR 400 MHz

$CDCl_3$



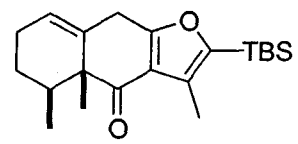
^{1}H NMR 400 MHz

$CDCl_3$



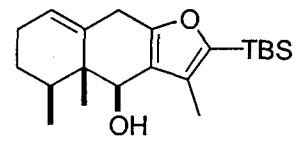
^{1}H NMR 300 MHz

$CDCl_3$



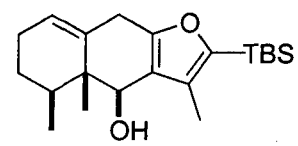
^{13}C NMR 75 MHz

$CDCl_3$



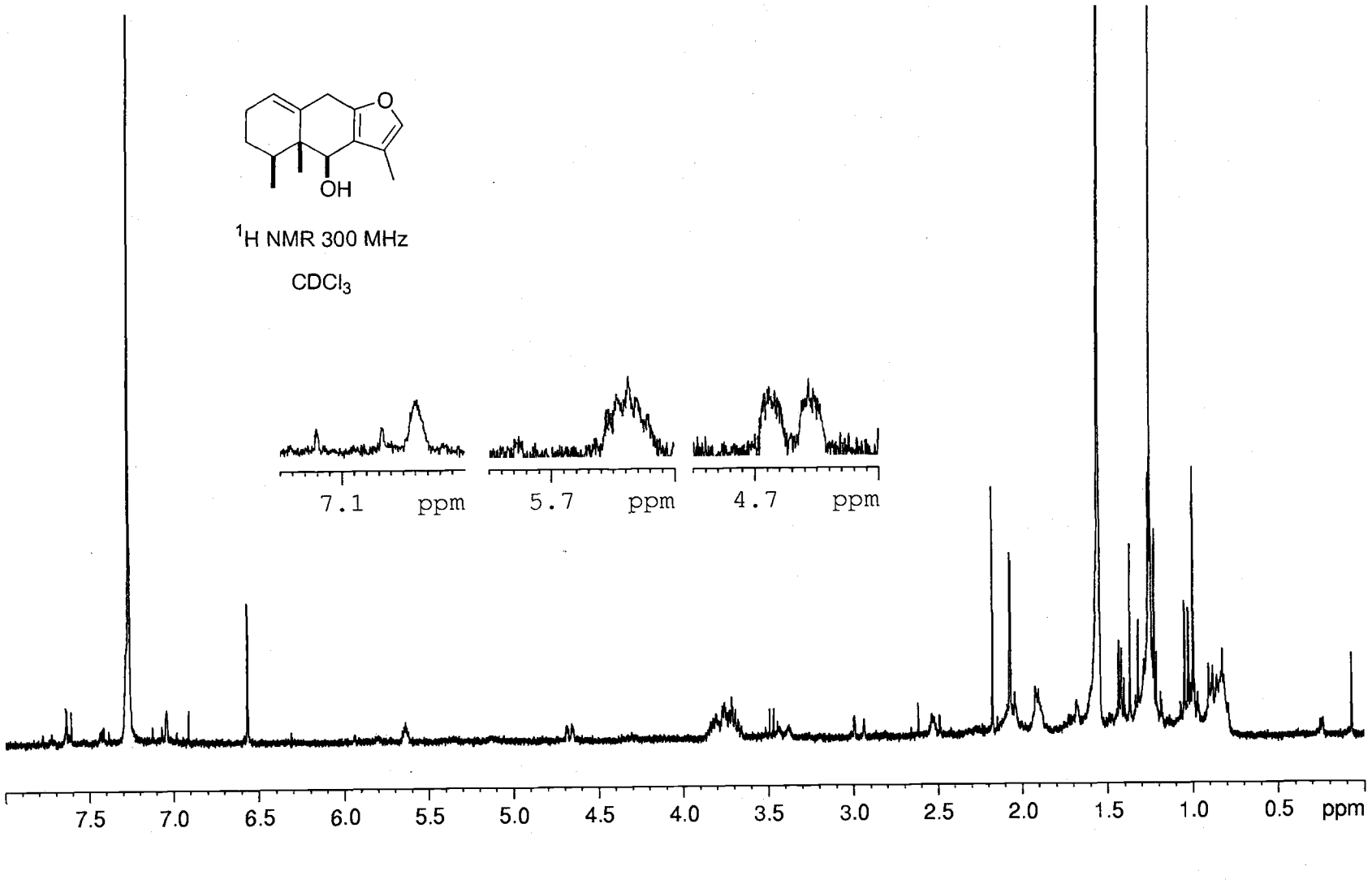
^{1}H NMR 400 MHz

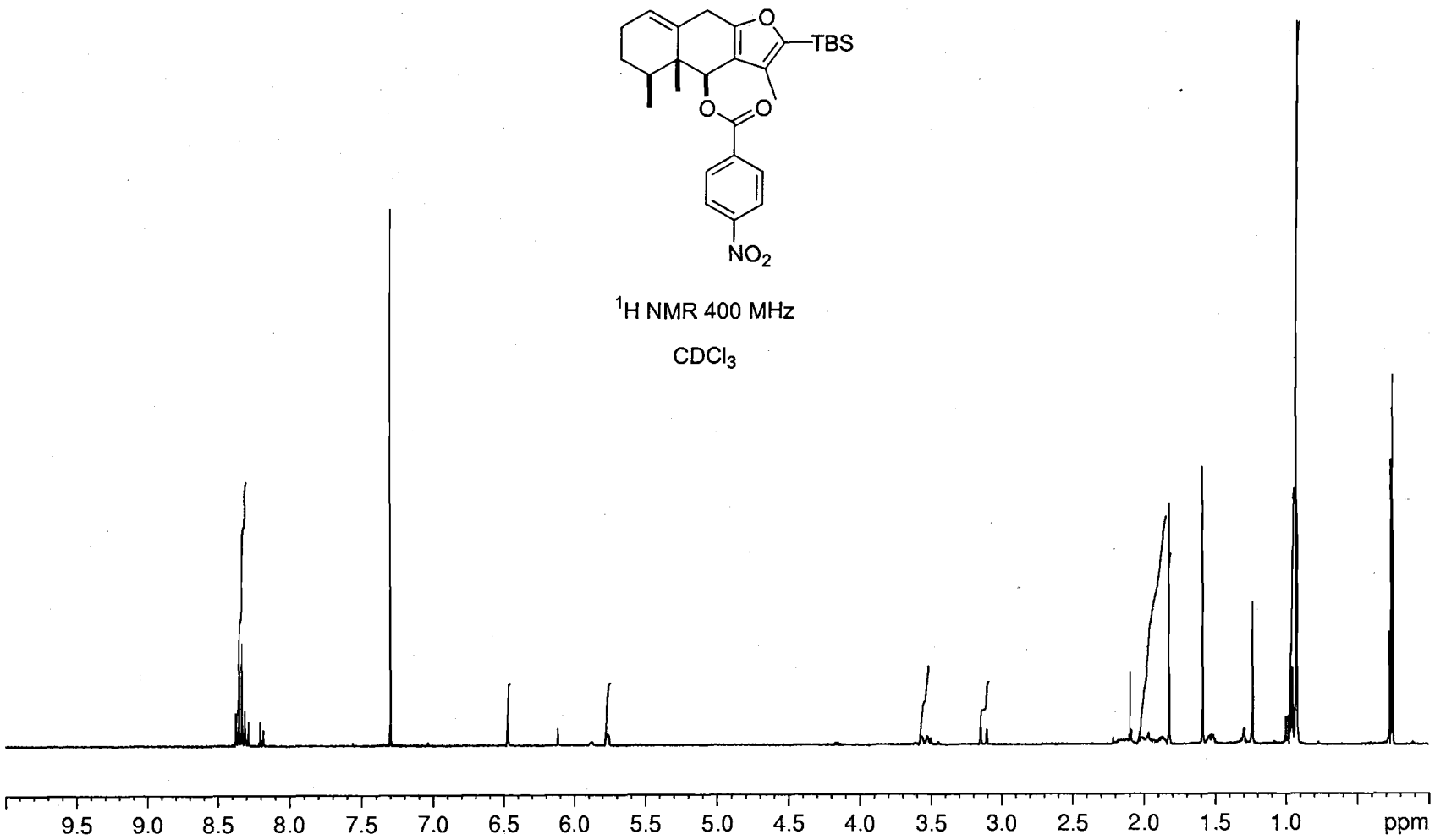
$CDCl_3$

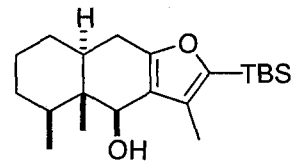


^{13}C NMR 100 MHz

$CDCl_3$

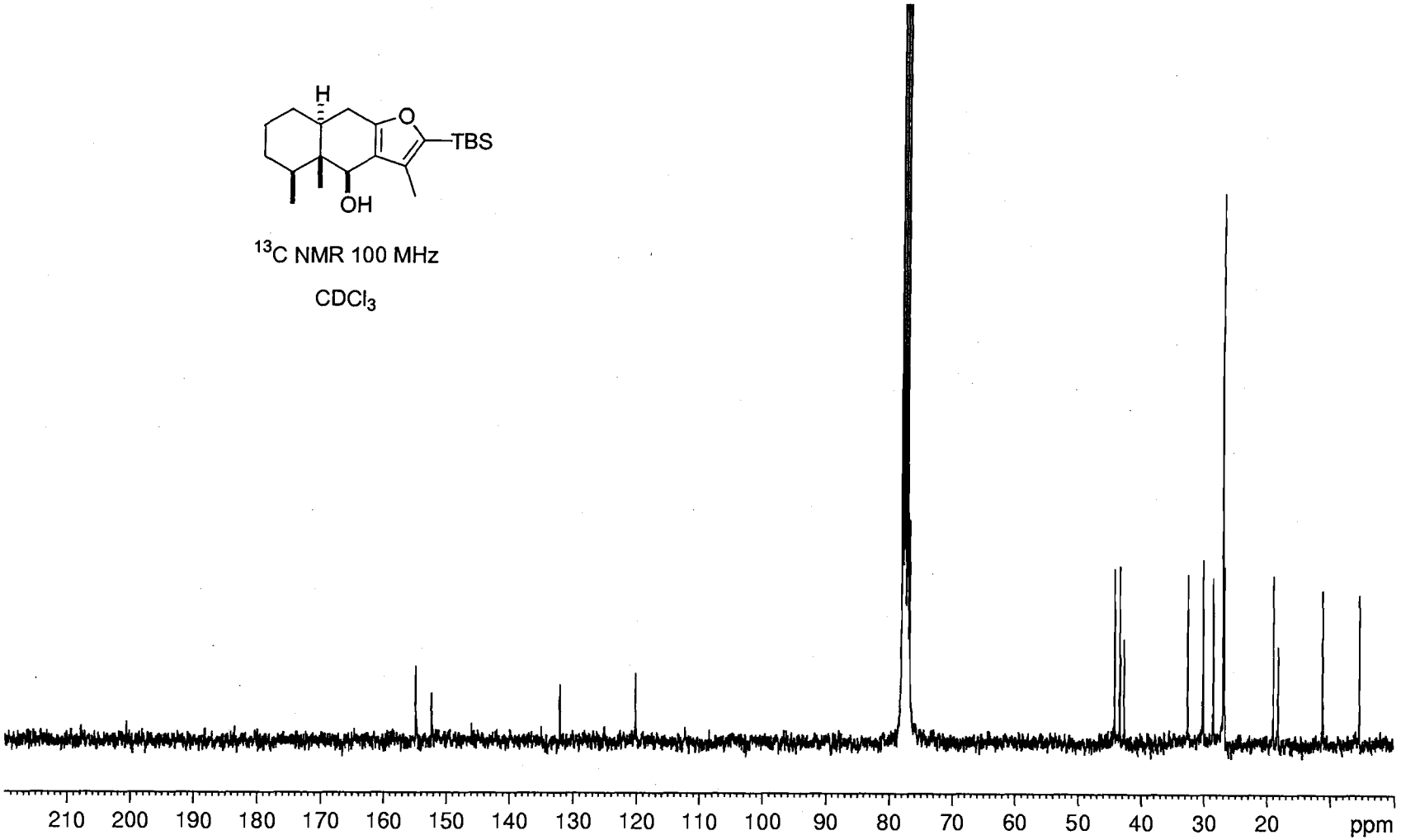

O
OH
^{1}H NMR 300 MHz
$CDCl_3$
7.1 ppm
5.7 ppm
4.7 ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

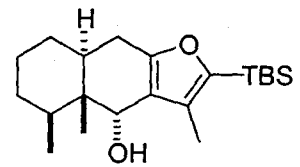

TBS
O
O
O
NO2
1H NMR 400 MHz
CDCl3
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



^{1}H NMR 400 MHz

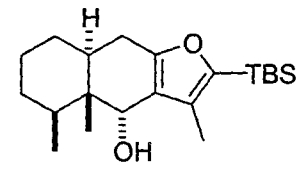
$CDCl_3$


H
O
TBS
OH
^{13}C NMR 100 MHz
$CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



^{1}H NMR 400 MHz

$CDCl_3$



^{13}C NMR 100 MHz

$CDCl_3$