I. **Nickel-Catalyzed, Intermolecular Reductive Couplings of Alkynes and Aldehydes**

II. **Enantioselective Synthesis of (–)-Terpestacin and Structural Revision of Siccanol Using Catalytic Stereoselective Fragment Couplings and Macrocyclizations**

by

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Massachusetts Institute of Technology

May 2004 [June 2004]

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May 11, 2004

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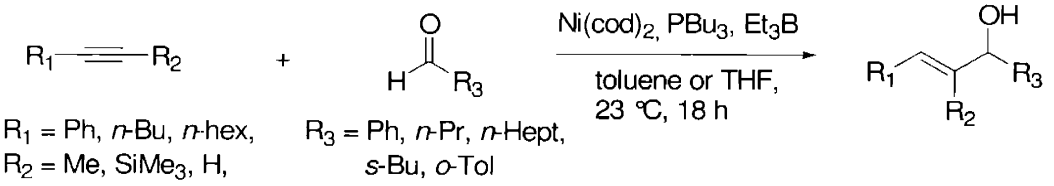
To Mom and Dad, Joseph, and my love Vicky

ABSTRACT

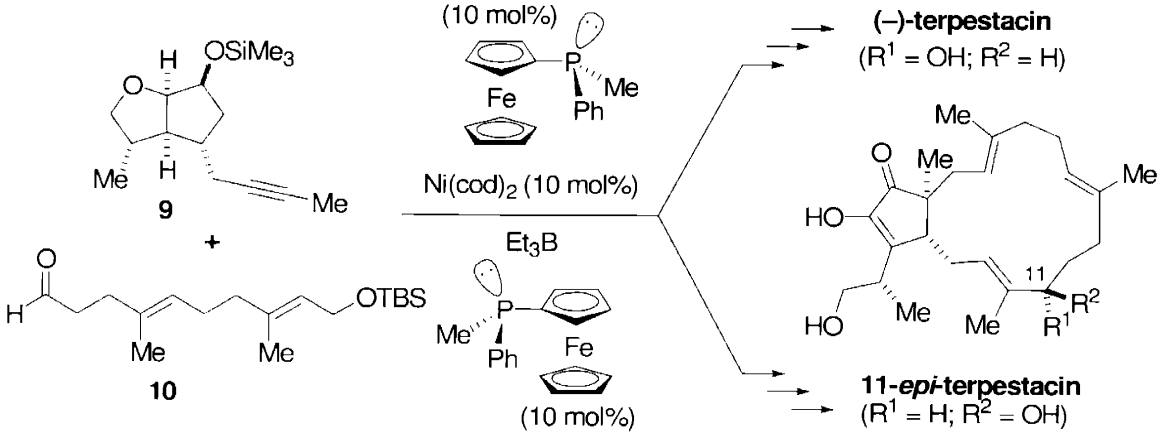
I. Nickel-Catalyzed Intermolecular Reductive Coupling of Alkynes and Aldehydes

Alkynes and aldehydes were coupled reductively in a single catalytic reaction to yield di- and trisubstituted allylic alcohols with high stereoselectivity and regioselectivity. In most cases, a 1:1 ratio of alkyne to aldehyde was sufficient for efficient coupling. The yield and regioselectivity were strongly dependent on the phosphine ligand, but the allylic alcohols formed were invariably the products of cis addition to the alkyne.



II. Enantioselective Synthesis of (–)-Terpestacin and Structural Revision of Siccanol Using Catalytic Stereoselective Fragment Couplings and Macrocyclizations

(–)-Terpestacin (**1**), (naturally occurring enantiomer) and (+)-11-*epi*-terpestacin (**2**) were prepared using catalyst-controlled, stereoselective intermolecular reductive couplings of alkyne **9** and aldehyde **10**. Related to enantioselective methods developed in our laboratory, these stereoselective fragment couplings were instrumental in confirming that "siccanol" is *not* 11-*epi*-terpestacin, but in fact is (–)-terpestacin itself.



Thesis Supervisor: Timothy F. Jamison

Title: Assistant Professor of Chemistry

Preface

Portions of this thesis have appeared in the following articles that were co-written by the author:

Highly Selective Catalytic Intermolecular Reductive Coupling of Alkynes and Aldehydes

Org. Lett. **2000**, *2*, 4221-4223.

Huang, W.-S.; Chan, J.; Jamison, T. F.

Synthesis of (–)-Terpestacin via Catalytic, Stereoselective Fragment Coupling: Siccanol is (–)-Terpestacin Not 11-*epi*-Terpestacin

J. Am. Chem. Soc. **2003**, *125*, 11514-11515.

Chan, J.; Jamison, T. F.

Enantioselective Synthesis of (–)-Terpestacin and Structural Revision of Siccanol Using Catalytic Stereoselective Fragment Couplings and Macrocyclizations

Submitted for Publication

Acknowledgments

"Choose a job you love and you will never have to work a day in your life"

- *Confucius*

It has been an interesting five years being a graduate student at MIT. Never in my life have I met so many people that are so proud and passionate at what they do. These five years have been very difficult for me and I would not have made it without the support of many friends and family.

First and foremost, I would like to thank my father, whose support for me has been unwavering all my life. His ability to listen, and his great words of wisdom have guided me through many difficult times in graduate school.

I would like to thank Tim for being a wonderful mentor, particularly in the lab during my early years. I've had the rewarding experience of witnessing the development of a research group from the beginning. Looking back, I feel that life could have been a lot worse given the fact that I was working for "an assistant professor at MIT". Without doubt, Tim made the best of the situation. For that, I am very, very grateful.

I have been fortunate to have met some wonderful lab mates and friends over the years. Wei-Sheng (our first post-doc), Heffron, Chudi, Sejal, and Carmela (Molly), made the day to day work in the lab pleasant. I would also like to thank "introductory yield" MOZ for "telling it like it is" and I wish Karen, Jim, Victor and Cici all the best. Ivory and Ryo have been two of my closest friends in graduate school. I would like to thank them both for the great times -- especially the lunch conversations over Gooseberry's.

From my time in Toronto, it was Professor Rob Batey who provided my first opportunity to work in a lab and really stimulated my interest in the organic chemistry. I'd like to thank Dr. Bruce MacKay for being a wonderful mentor during my undergraduate years.

Last but not least, I'd like to thank Vicky for always being there for me, for putting everything in perspective, and for showing me balance. How wonderful life is when she's in my world.

Table of Contents

Abbreviations

Ac	acetyl
Acac	acetylacetonate
Bu	butyl
cod	cyclooctadiene
coe	cyclooctene
Cy	cyclohexyl
DCC	*N,N'*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DMAP	4-dimethylaminopyridine
DMF	*N,N'*-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
Fs	farnesyl
g	grams
h	hour
Hex	hexyl
Hept	heptyl
i-Pr	isopropyl
KAPA	potassium aminopropylamide
KHMDS	potassium hexamethyldisilazide
LiHMDS	lithium hexamethlydisilazide
Me	methyl
mg	milligram
NMO	*N*-methylmorpholine-*N*-oxide
nOe	nuclear Overhauser effect
Ph	phenyl
Pv	pivaloyl
*p*TSA	*p*-toluene sulfonic acid
RCM	ring closing metathesis

t-Bu	*tert*-butyl
TBS	*tert*-butyl dimethylsilyl
TBAF	tetrabutylammonium fluoride
Tol	tolyl
TMS	trimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TPAP	tetrapropyl ammonium perruthenate

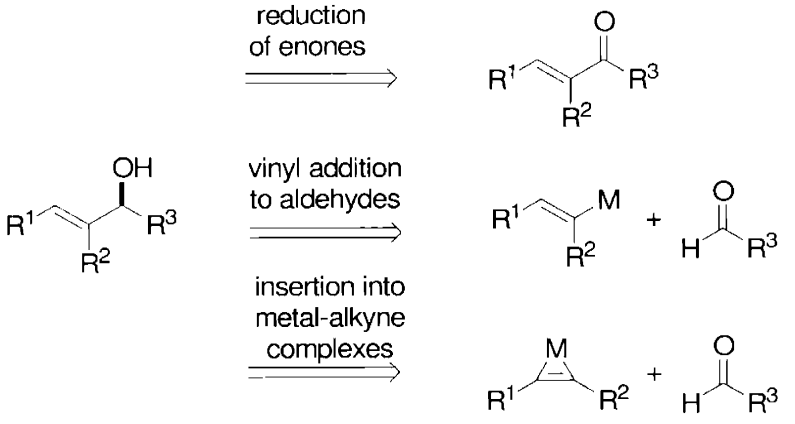
Chapter 1

Nickel Catalyzed Intermolecular Reductive Couplings of Alkynes and Aldehydes

Introduction

The *(E)*-allylic alcohol moiety is a versatile synthetic intermediate[1] found in a large number of natural products. A well-studied approach toward the synthesis of this motif involves the addition of dihydrogen across α,β-unsaturated carbonyls.[2] Though effective, this approach is not feasible for the coupling of complex fragments since formation of allylic alcohols in this manner does not involve C-C bond formation.

Figure 1. Common approaches toward the synthesis of allylic alcohols



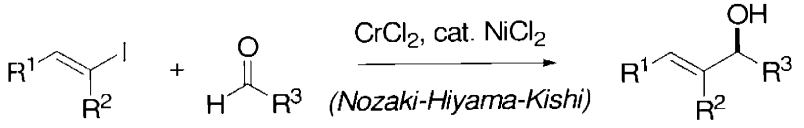
An alternate tactic that involves C-C bond formation consists of adding alkenyl nucleophiles to carbonyl compounds using stoichiometric amounts of metal catalysts.[2] Within this area, several groups have made notable contributions using this strategy. For instance, the Nozaki-Hiyama-Kishi reaction (Scheme 1) describes the coupling of an alkenyl halide to an aldehyde in the presence of excess chromium and a catalytic amount

[1] Reviews: Sigmatropic rearrangements: (a) [2,3]: Brükner, R. In *Comprehensive Organic Synthesis*: Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 6, Chapter 4.6. (b) Hill, R. K. In *Comprehensive Organic Synthesis*: Trost, B. M., Ed.: Pergamon: New York, 1991; Vol. 5, Chapter 7.1. (c) [3,3]: Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 7.2. (d) Directed reactions: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

[2] *Comprehensive Organic Transformations 2nd Ed.*; Larock, R. C.; Wiley VCH: New York, 1999.

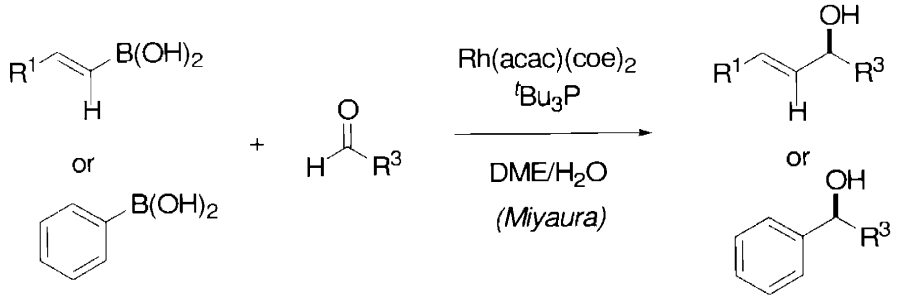
of nickel.[3] This method is limited by the fact that most alkenyl halides are not commercially available and must be synthesized.

Scheme 1. Nozaki-Hiyama-Kishi reaction



Another well studied approach is the rhodium-catalyzed addition of 1-alkenyl or phenyl boronic acids to aldehydes.[4] Pioneered by Miyaura, treatment of the organoboronic acids with a combination of $Rh(acac)(coe)_2$ and $^tBu_3P$ effects nucleophilic addition to a variety of aldehydes in excellent yield (Scheme 2).[5] Batey and co-workers have improved the scope of these reactions by employing potassium alkenyl- and aryltrifluoroborates in place of boronic acids. In addition to their greater stability to air and water, the trifluoroborate salts are thought be more reactive than the corresponding boronic acids under the reaction conditions.[6]

Scheme 2. Rhodium-catalyzed additions of alkenyl- and arylboronic acids to aldehydes



[3] (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (d) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. (e) Fürstner A.; Shi, N. *J. Am. Chem. Soc.* **1996,** *118*, 12349.

[4] Furstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *4*, 343. For rhodium-catalyzed aryl stannane additions to aldehydes: Oi, S.; Moro, M.; Inoue, Y. *Chem. Commun.* **1997**, 1621.

[5] (a) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 3279. (b) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450.

[6] Batey, R.; Thadani, A. N.; Smil, D. A. *Org. Lett.* **1999**, *1*, 1683.

Although there are many methods of generating either alkenyl halides or boronic acids from alkynes, a more efficient approach would make use of the many commercially available alkynes themselves as starting materials for the coupling (Scheme 3). In 1992, Suzuki reported the hydrozirconation of terminal alkynes to generate alkenylzinconocenes that add to aldehydes under $AgClO_4$ catalysis to afford allylic alcohols in excellent yields.[7] At about the same time, Oppolzer[8] reported the hydroboration of terminal alkynes with dicyclohexyl borane, followed by transmetalation with an alkyl zinc species. The alkyl zinc intermediate can then be added to a variety of aldehydes to furnish allylic alcohols. Wipf[9] has utilized an analogous approach involving Schwartz's reagent, Cp_2ZrHCl, as the hydrometalation reagent. While all three protocols begin with readily accessible alkynes, a drawback of the Wipf and Suzuki method is the requirement that the generation of the alkenyl metal species be performed prior to addition of aldehyde. In the case of Oppolzer's method, only terminal alkynes are compatible.

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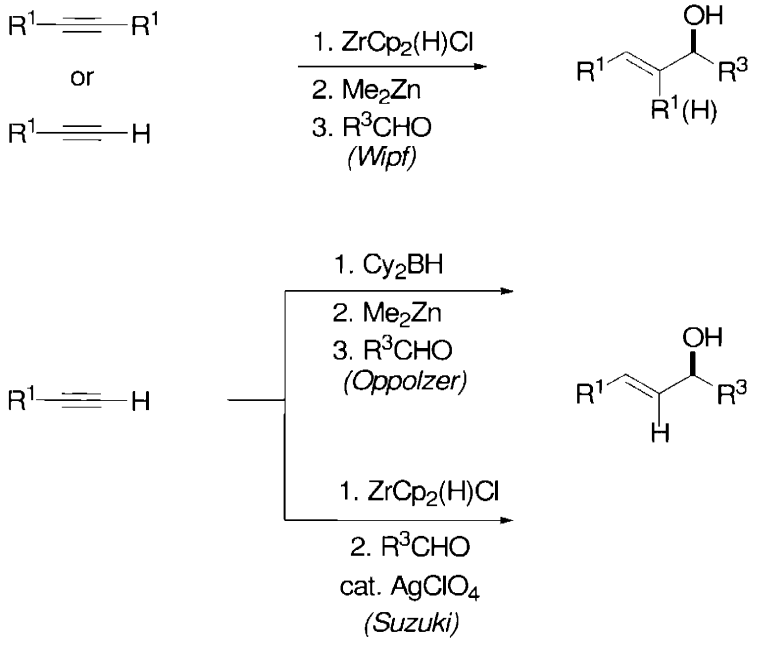
[7] Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965.

[8] (a) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta*, **1992**, *75*, 170. (b) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593. (c) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766.

[9] (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.

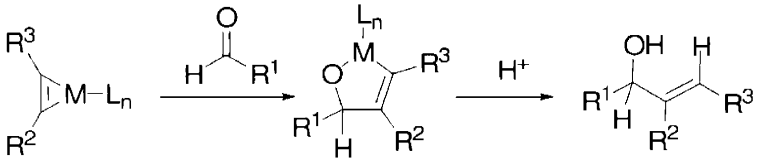
Scheme 3. Synthesis of (*E*)-allylic alcohols by Suzuki, Oppolzer and Wipf



Methods incorporating aldehyde insertions into alkyne-metal complexes have been well studied.[10] In these protocols, alkynes are pretreated with a *stoichiometric* amount of an early transition metal complex to generate an alkyne-metal complex which upon addition of aldehyde, inserts to form an oxametallacycle (Scheme 4). The *(E)*-allylic alcohol would then be liberated following protonolysis.

[10] (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544. (b) Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1989**, *30*, 3495. (c) Takai, K.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1990**, *55*, 1707. (d) Takagi, K.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 1440. (e) Kataoka, Y.; Miyai, J.; Oshima, K.; Takai, K. Utimoto, K. *J. Org. Chem.* **1992**, *57*, 1973. (f) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787. (g) Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1996**, 1725.

Scheme 4.

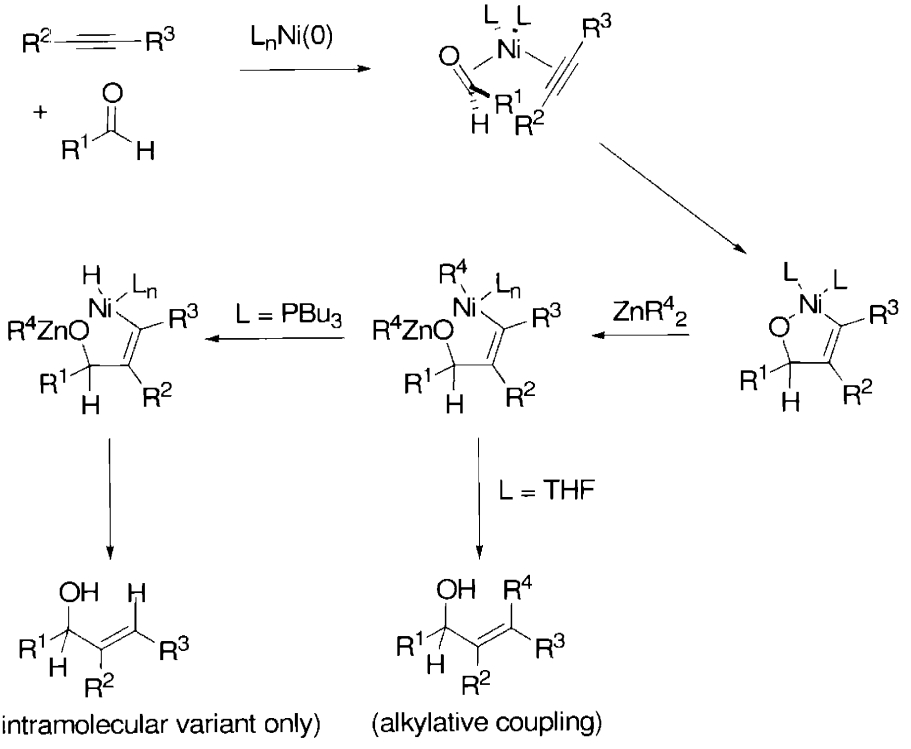


M = Zr (Buchwald, Livinghouse, Negishi)
Ti (Buchwald, Sato, Crowe)
Ta (Takai, Utimoto)
Nb (Takai, Utimoto)

In contrast, the preparation of (*E*)-allylic alcohols via a single-pot reductive coupling using a *catalytic* amount of metal was first reported in 1997 by Montgomery.[11] This initial work described the reductive coupling of alkynes and aldehydes using a combination of $Ni(cod)_2$, PBu_3 and diethylzinc. The proposed mechanism involves the formation of an oxanickellacycle that undergoes σ-bond metathesis with an alkyl zinc. Following β-hydride elimination and reductive elimination, allylic alcohols are obtained. However, this reaction is limited to intramolecular couplings (Scheme 5).

[11] (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) For a review see: Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467.

Scheme 5. Montgomery's Proposed Mechanism for Ynal Cyclizations and Three-Component Couplings.



As part of our interest in catalytic fragment coupling reactions, we were very much interested in the development of a metal-catalyzed *intermolecular* reductive coupling of alkynes and aldehydes. In this chapter, we describe the first reaction of this kind to furnish (*E*)-allylic alcohols with high selectivity. A brief mechanistic discussion will also be presented in light of very recent work by Montgomery[12] which describes an extension of our reductive coupling reaction.

Results and Discussion

At the outset of this work, there were no reports of *intermolecular* reductive couplings of alkynes and aldehydes using a *catalytic* amount of metal.[13] In order to achieve this goal, various technical challenges had to be overcome. The starting

[12] Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698.

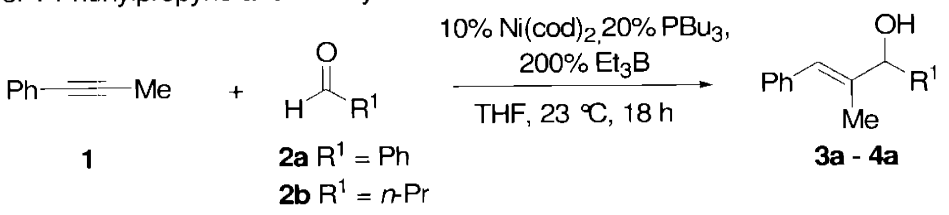
[13] Since this work, Krische has reported the intermolecular cationic rhodium-catalyzed reductive coupling of α-keto aldehydes and 1,3 diynes and 1,3 enynes: (a) Huddleston, R. R.; Jang, H. –Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488. (b) Jang, H. –Y., Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664.

materials were all subject to reduction, and in the case of alkynes, undesired oligomerization was a viable pathway. Depending on the requirement of aldehyde activation, aldol self condensation products may also form as potential unwanted byproducts.

Initial approaches toward the method involved the screening of many combinations of transition metal salts, reducing agents, and additives to find that indeed alkyne polymerization, and simple reduction of both alkyne and aldehyde to be the most common side products.[14] Exclusive however, was the use of 10% $Ni(cod)_2$, 20% PCy_3, and 200% BEt_3, which afforded the desired allylic alcohol in good yield, and high stereoselectivity but with moderate regioselectivity. Further screening disclosed that no bidentate phosphines effected the desired transformation. Of all monodentate phosphines screened, PBu_3 led to the most favorable regioselectivites[15] (Table 1). The solvent choice was critical resulting in the selection of THF and toluene that gave the highest chemical yields. Additionally, the geometric selectivity about the allylic alcohol arose from an exclusive cis addition to the alkyne regardless of solvent screened.[16]

[14] Reactions conducted by Dr. Wei-Sheng Huang.
[15] Ligand investigation conducted by Dr. Wei-Sheng Huang
[16] Other solvents screened include DMF, acetonitrile, CH_2Cl_2, and Et_2O.

Table 1. Effect of Phosphine on Intermolecular Reductive Coupling of 1-Phenylpropyne and Aldehydes



1 **2a** R^1 = Ph; **2b** R^1 = *n*-Pr **3a - 4a**

entry	aldehyde	phosphine	major product	yield,[a] (regioselectivity)[b]
1	**2a**	Cy_3P	**3a**	76% (77:23)
2		Et_3P	**3a**	46% (91:9)
3		$(n\text{-Bu})_3P$	**3a**	77% (92:8)
4	**2b**	$(n\text{-Bu})_3P$	**4a**	49% (95:5)
5[c]		$(n\text{-Bu})_3P$	**4a**	86% (90:10)
6[d]		$(n\text{-Bu})_3P$	**4a**	85% (92:8)
7[c,d]		$(n\text{-Bu})_3P$	**4a**	88% (92:8)

[a]Combined isolated yield of regioisomers. [b]Minor regioisomers (**3b-4b**) not shown. Regioselectivity (**a:b**) was determined either by separation of regioisomers (silica gel chromatography) or with a ^{1}H NMR spectrum of the product mixture. [c]Toluene used as solvent. [d]Reaction conducted at 40 °C.

The efficiency, scope, and high selectivity of this transformation are summarized in Table 2. In most cases, only 100 mol% of alkyne and 100 mol% of aldehyde were necessary for good yield. The aryl-alkyl and alkyl-alkyl alkynes reacted with high efficiency with both aromatic as well as aliphatic aldehydes. The most challenging alkyne substrates were the terminal alkynes, particularly phenyl acetylene, which tended to polymerize under the reaction conditions. Yields were improved with terminal alkyne couplings by conducting the reaction at 0 °C with 200 mol% of alkyne. Alkynes with electron withdrawing groups, such as but-2-ynoic acid ethyl ester, led to exclusive trimerization of the alkyne with no trace of desired product.

The coupling of alkynyltrimethylsilanes led to the formation of allylic alcohols in >98:2 regioselectivity. Both yields and general reactivity, however, were diminished. It was postulated that a combination of the increased steric bulk and the electronics of the

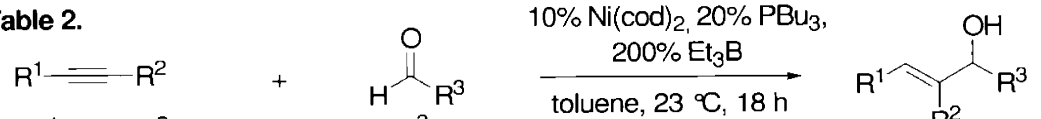
trimethylsilyl group acted to reduce the rate of the reaction.[17] In the case of 1-trimethylsilyl-1-phenylpropyne and benzaldehyde, increasing the temperature was required for adequate conversion. Unbranched aldeydes reacted generally well, however, increasing the sterics about the aldehyde through α-branching reduced the rate significantly (Table 2, Entry 6). The diastereoselectivity observed was consistent with Felkin-Ahn selectivity, as illustrated by the 2:1 mixture favoring the syn diastereomer obtained in entry 8. Conducting the same reaction using Wipf's conditions resulted in the formation of *E/Z isomers* (as well as diastereomers), highlighting a key limitation of the hydrozirconation/transmetalation approach with internal alkynes. Reactions of highly branched aldehydes such as with the coupling of pivoyl aldehyde or 2,6 dimethylbenzaldehyde and 1-phenyl propyne, yielded <5% of the desired allylic alcohol.

As a 1:1 ratio of alkyne to aldehyde was sufficient for high yields of secondary allylic alcohols in most cases, this reaction may find use in joining late-stage intermediates in complex molecule synthesis.[18] Furthermore, reactions of alkynes with ketones such as 3-pentanone or acetophenone did not afford any product suggesting the possibility of applying this method in site-selective fragment couplings.

[17] Coupling of Ph-≡-*i*-Pr occurs smoothly while sterically similar Ph-≡-$SiMe_3$ is unreactive in the coupling with isobutyraldehyde. These reactions were conducted subsequent to our work in this chapter by Mr. Chudi O. Ndubaku.

[18] For asymmetric versions: (a) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156. (b) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, 3442.

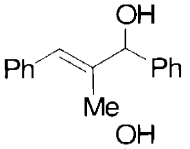
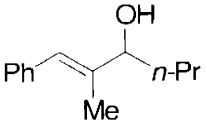
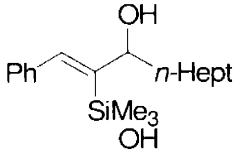
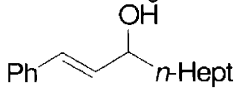
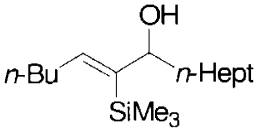
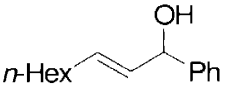
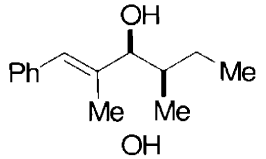
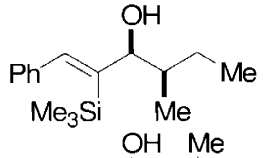
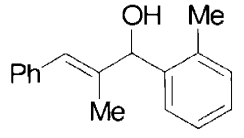
Table 2.



5a R^1 = Ph, R^2 = Me
5b R^1 = Ph, R^2 = $SiMe_3$
5c R^1 = Ph, R^2 = H
5d R^1 = *n*-Bu, R^2 = $SiMe_3$
5e R^1 = *n*-Hex, R^2 = H

6a R^3 = Ph
6b R^3 = *n*-Pr
6c R^3 = *n*-Hept
6d R^3 = *s*-Bu
6e R^3 = *o*-Tol

7a - 16a

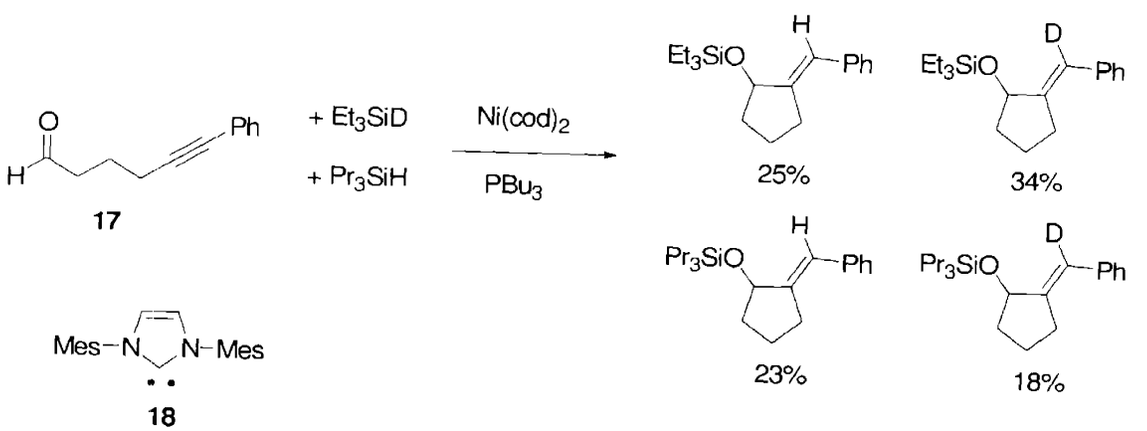
entry	alkyne	aldehyde	major product		yield,[b] (regioselectivity)[c]
1[d]	**5a**	**6a**		**7a**	77% (92:8)
2	**5a**	**6b**[e]		**8a**	85% (92:8)
3[d,f]	**5b**[e]	**6a**		**9a**	49% (>98:2)
4	**5c**	**6c**		**10a**	89% (>98:2)
5[g]	**5c**[e]	**6c**		**11a**	45% (>98:2)
6	**5d**	**6c**		**12a**	58% (>98:2)
7[d]	**5e**[e]	**6a**		**13a**	76% (96:4)
8[f]	**5a**	**6d**		**14a**	41% (94:6) (66:34 dr)
9[f]	**5b**	**6d**		**15a**	31% (>98:2) (58:42 dr)
10	**5a**	**6e**		**16a**	83% (93:7)

[a]Except where noted, all reactions were conducted using 1 mmol of alkyne, 1 mmol of aldehyde, toluene, Ar atmosphere. [b]Combined isolated yield of regioisomers. [c]Minor regioisomers (**7b-16b**) not shown. Regioselectivity (**a:b**) was determined either by separation of regioisomers (silica gel chromatography) or with a ^{1}H NMR spectrum of the product mixture. [d]THF used as solvent. [e]200 mol% used. [f]Reaction conducted under reflux. [g]Reaction conducted at 0 °C.

Mechanistic Considerations

Recently, Montgomery had also developed an intermolecular reductive coupling of alkynes and aldehydes using $Ni(cod)_2$, imidazolium carbene **18**, and Et_3SiH.[12] Included in their studies were crossover experiments involving alkynal **17** with an equimolar mixture Et_3SiD and Pr_3SiH in the presence of PBu_3 or **18**. The experiments showed that significant crossover was observed when PBu_3 was used as a ligand (Scheme 6). However, no crossover was observed when imidazolium carbene **18** was used in place of PBu_3, suggesting that the two reaction mechanisms fundamentally differ.

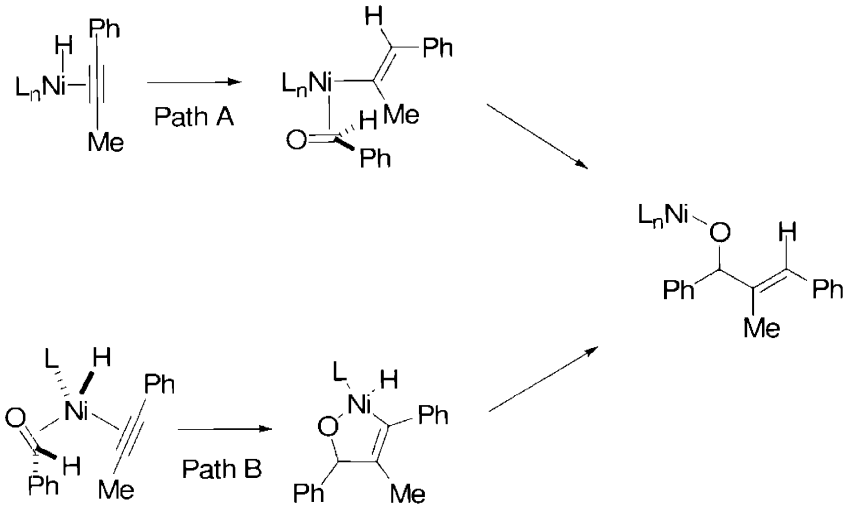
Scheme 6. Montgomery's Cross-over Experiment



No cross-over was observed when **18** *was used in place of* PBu_3.

Montgomery concluded that the mechanism involving PBu_3 likely involved a catalyst possessing a nickel hydride species. Therefore, he suggested two possible pathways to allylic alcohols (Scheme 7). Path A undergoes a hydrometallation of the alkyne followed by addition to aldehyde. Path B proceeds via an oxanickellacycle that is generated through the insertion of aldehyde to a nickel-alkyne complex, a mechanism very similar to that proposed in their original work.

Scheme 7. Montgomery's Proposed Mechanism for the Reductive Coupling of Alkynes and Aldehydes



The data presented by Montgomery is consistent with the results that we obtained in our preliminary mechanistic investigations of the reaction.[19] Omission of Et_3B in the coupling of **5a** and **6a** did not afford any allylic alcohol **7a**. This observation is consistent with either path A or B since a Ni-H species must be preformed in order to initiate the catalytic cycle. A second experiment was conducted where we removed the aldehyde from the reaction. In this case, alkyne **5a** was recovered in 86% yield with *no trace of products resulting from reduction.* This result would rule out path A unless irreversible hydrometalation of the alkyne is dependent on the presence of aldehyde.

Assuming a similar cross-over in our phosphine-based system, it appears likely that the role of Et_3B may be to initiate the catalytic cycle through the formation of a nickel(I)-hydride intermediate. A plausible mechanism by which this may occur could be through a single electron process where both nickel (0) complexes and Et_3B are known to participate.[20]

[19] Mechanistic experiments conducted by Dr. Wei-Sheng Huang
[20] Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415.

Conclusion

The first nickel catalyzed intermolecular reductive coupling of alkynes and aldehydes to form allylic alcohols has been developed. A ligand screen revealed that only monodentate phosphines effected the desired transformation with PBu_3 giving the best combination of yield and selectivity. Reactions of aryl-alkyl or dialkyl alkynes with unbranched aliphatic or aromatic aldehydes worked efficiently. Notably, alkynyltrimethylsilanes coupled with remarkably high regioselectivities; however, reaction rates were diminished. A similar reduction in rate was observed in the coupling of α-branched aldehydes. Under the reaction conditions, 3-pentanone or acetophenone do not undergo coupling suggesting the possibility of applying this method in site selective fragment couplings.

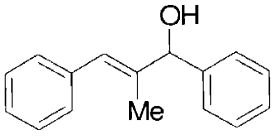
Experimental Section

General Information. $Ni(cod)_2$ was purchased from Strem Chemicals Inc. and used without further purification. Tributylphosphine (97%) and triethylborane (1.0 M solution in hexanes) were purchased from Aldrich Chemical Co. and used without further purification. All alkynes and aldehydes were purchased from Aldrich Chemical Co. or Alfa Aesar and used without further purification. Toluene and tetrahydrofuran were distilled from a deep blue solution of sodium benzophenone ketyl under an atmosphere of N_2 or Ar immediately prior to use.

Standard Experimental Procedure for Intermolecular Reductive Coupling of Alkynes and Aldehydes

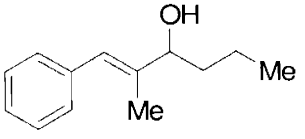
3ew

In a glovebox, $Ni(cod)_2$ (28 mg, 0.1 mmol) was placed into an oven-dried, one-necked Schlenk flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, and toluene (2 mL, degassed with Ar or N_2 by three freeze-pump-thaw cycles) was added via syringe. To this yellow solution, Bu_3P (0.050 mL, 0.2 mmol) was added via syringe; the resultant solution was stirred 5 min at ambient temperature. Et_3B (2.0 mL, 1.0 M in hexanes, 2.0 mmol) was added via syringe, and the resultant mixture was stirred 10-15 min. A solution of the alkyne (1.0 mmol) and aldehyde (1.0 mmol) in toluene (2 mL, degassed with Ar or N_2 by three freeze-pump-thaw cycles) was added dropwise via syringe over 1 min. The resulting solution turned brown in 5-10 min and was stirred at ambient temperature 18 h unless otherwise indicated. Saturated aqueous NH_4Cl (4 mL) and 1 M HCl (1 mL) were added, and the resulting mixture was diluted with water (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic solutions were washed with saturated aqueous NaCl and then dried over $MgSO_4$. After filtration and removal of the solvent *in vacuo*, the allylic alcohol was purified by silica gel chromatography (hexanes:ethyl acetate 15:1 to 5:1).



***(E)*-1,3-diphenyl-2-methyl-2-propen-1-ol (7a)**: In the reductive coupling of 1-phenylpropyne (**5a**, 1.0 mmol, 0.13 mL) and benzaldehyde (**6a**, 1.0 mmol, 0.10 mL), the standard procedure was used. Silica gel chromatography (5:1 hexanes:ethyl acetate) afforded allylic alcohols **7a**, and **7b** as a colorless oil (173 mg, 77%).[21] R_f (5:1 hexanes:ethyl acetate): 0.41.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.19 (m, 10 H), 6.72 (s, 1H), 5.85 (q, J = 6.9 Hz, 0.09H, minor regioisomer), 5.22 (s, 1H), 1.94 (s, 1H), 1.67 (d, J = 1.5 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): δ 142.2, 139.7, 137.6, 129.2, 128.6, 128.3, 127.8, 126.7, 126.6, 126.1, 79.7, 14.2



***(E)*-2-methyl-1-phenyl-1-hexen-3-ol (8a):** In the reductive coupling of 1-phenylpropyne (**5a**, 1.0 mmol, 0.13 mL) and butyraldehyde (**6b**, 2.0 mmol, 0.18 mL), the standard procedure was used except that 200 mol% butyraldehyde was used. Silica gel chromatography (5:1 hexanes:ethyl acetate) afforded allylic alcohols **8a**, and **8b** as a colorless oil (162 mg, 85%). R_f (5:1 hexanes:ethyl acetate): 0.46.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.08 (m, 5H), 6.38 (s, 1H), 5.69 (qd, J^1 = 0.9 Hz, J^2 = 6.9 Hz, 0.08 H, minor regioisomer), 4.20 (m, 0.08 H, minor regioisomer), 4.07 (t, J = 6.3 Hz, 1H), 1.88 (s, 1H), 1.77 (d, J = 1.2 Hz, 3H), 1.54 (dt, J^1 = 6.9 Hz, J^2 = 7.2 Hz, 2H), 1.19-1.44 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): δ 140.6, 137.8, 129.1, 128.3, 126.6, 125.9, 78.1, 37.4, 19.2, 14.2, 13.3.

IR (thin film/NaCl): 3401, 2967, 2869, 1700, 1658, 1491, 1449, 990 cm^{-1}

LRMS (EI) m/e calcd (M^+): 190, found 190.

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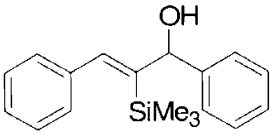
[21] Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411.

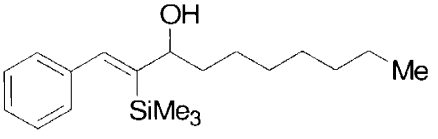


***(Z)*-1,3-diphenyl-2-(trimethylsilyl)-2-propen-1-ol (9a):** In the reductive coupling of 1-phenyl-2-(trimethylsilyl)acetylene (**5b**, 1.0 mmol, 0.20 mL) and benzaldehyde (**6a**, 1.0 mmol, 0.18 mL), the standard procedure was used. Silica gel chromatography (5:1 hexanes:ethyl acetate) afforded allylic alcohols **9a**, and **9b** as a colorless oil (138 mg, 49%). R_f (5:1 hexanes:ethyl acetate): 0.52.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.26-7.47 (m, 10H), 5.51 (s, 1H), 2.15 (s, 1H), -0.14 (s, 9H); ^{13}C (75 MHz, $CDCl_3$): δ 145.7, 143.0, 141.5, 140.2, 128.7, 128.6, 128.0, 127.9, 127.8, 127.2, 78.1, 0.9

IR (thin film/NaCl): 3397, 3059, 2953, 2896, 1594, 1491, 1454, 1248, 1064, 840 cm^{-1}

LRMS (EI) m/e calcd (M^+): 282, found 282.



***(Z)*-1-phenyl-2-(trimethylsilyl)-1-decen-3-ol (10a):** In the reductive coupling of 1-phenyl-2-(trimethylsilyl)acetylene (**5c**, 1.0 mmol, 0.20 mL) and octanal (**6c**, 1.0 mmol, 0.16 mL), the standard procedure was used. Silica gel chromatography (5:1 hexanes:ethyl acetate) afforded allylic alcohols **10a** and **10b** as a colorless oil (270 mg, 89%).[22] R_f (5:1 hexanes:ethyl acetate): 0.63.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.17-7.32 (m, 5H), 4.40 (ddd, J^1 = 1.5 Hz, J^2 = 7.2 Hz, J^3 = 7.5 Hz, 1H), 1.48-1.75 (m, 3H), 1.31 (m, 10H), 0.90 (t, J = 6.9 Hz, 3H), -0.02 (s, 9H); ^{13}C (75 MHz, $CDCl_3$): δ 147.5, 140.4, 128.7, 128.0, 127.1, 76.1, 38.2, 32.1, 29.8, 29.6, 26.3, 22.9, 14.3, 1.1

IR (thin film/NaCl): 3362, 2954, 2927, 1593, 1466, 1249, 876 cm^{-1}

LRMS (EI) m/e calcd (M^+): 304, found 304.

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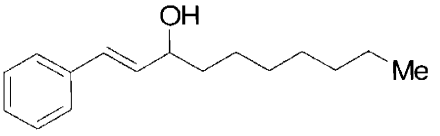
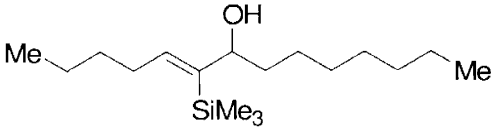
[22] The assignment of olefin geometry was based on comparison of the ^{1}H NMR data with those of similar compounds, with the diagnostic evidence being the chemical shift of the alkene proton. (a) Mitchell, T. N.; Wickenkamp, R.; Amamria, A.; Dicke, R.; Schneider, U. *J. Org. Chem.* **1987**, *52*, 4868. (b) Chatani, N.; Takeyashu, T.; Hanafusa, T. *Tetrahedron Lett.* **1986**, *27*, 1841. (c) Shipman, M.; Thorpe, H. R.; Clemens, I. R. *Tetrahedron* **1998**, *54*, 14265.



***(E)*-1-phenyl-1-decen-3-ol (11a):** In the reductive coupling of phenylacetylene (**5c**, 2.0 mmol, 0.22 mL) and octanal (**6c**, 1.0 mmol, 0.16 mL), the standard procedure was used, except that 200 mol% of phenylacetylene was used. Silica gel chromatography (5:1 hexanes:ethyl acetate) afforded allylic alcohol **11a** as a colorless oil (114 mg, 49%).[23] R_f (5:1 hexanes:ethyl acetate): 0.5.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13-7.32 (m, 5H), 6.48 (d, J = 15.9 Hz, 1H), 6.14 (dd, J^1 = 6.6 Hz, J^2 = 15.9 Hz, 1H), 4.19 (dt, J^1= 6.3 Hz, J^2 = 6.6 Hz, 1H), 1.67 (s, 1H), 1.55 (dt, J^1 = 6.3 Hz, J^2 = 6.9 Hz, 2H), 1.20 (m, 10H), 0.80 (t, J = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): δ 137.0, 132.8, 130.5, 128.8, 127.8, 126.7, 73.4, 37.6, 32.1, 29.8, 29.5, 25.7, 22.9, 14.4.



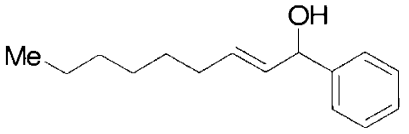
***(Z)*-6-(trimethylsilyl)-5-tetradecen-7-ol (12a):** In the reductive coupling of 1-trimethylsilyl-1-hexyne (**5d**, 2.0 mmol, 0.40 mL) and octanal (**6c**, 2.0 mmol, 0.30 mL), the standard procedure was used with the exception that the scale was doubled. Silica gel chromatography (19:1 hexanes:ethyl acetate), afforded **12a** a colorless oil (327 mg, 58%). R_f (90:10 hexanes:ethyl acetate): 0.53.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.19 (dt, J = 1.1, 7.4 Hz, 1H), 4.14 (t, J = 6.0 Hz, 1H), 2.14 (m, 2H), 1.37 (m, 17H), 0.90 (m, 6H), 0.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.6, 142.1, 77.1, 38.2, 32.4, 32.1, 31.7, 29.8, 29.6, 26.5, 23.0, 22.8, 14.4, 14.4, 1.1.

IR (thin film NaCl): 3450, 2928, 1611, 1458, 1320, 1248, 836, 759 cm^{-1}.

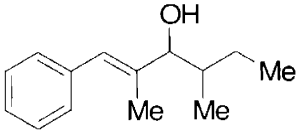
LRMS (CI) m/e calcd (M^+): 284, found 285 [(MH^+)]

[23] Chandrasekhar, S.; Takhi, M.; Yadar, J. S. *Tetrahedron Lett.* **1995**, *36*, 307.



***(E)*-1-phenyl-2-nonen-1-ol (13a):** In the reductive coupling of 1-octyne (**5e**, 2.0 mmol, 0.30 mL) and benzaldehyde (**6a**, 1.0 mmol, 0.10 mL), the standard procedure was used, except that 200 mol% of 1-octyne was used. Silica gel chromatography (5:1 hexanes:ethyl acetate) afforded allylic alcohol **13a** as a colorless oil (167 mg, 76%).[24] R_f (5:1 hexanes:ethyl acetate): 0.51.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.31 (m, 5H), 5.68 (dt, J^1= 6.3 Hz, J^2 = 15.3 Hz, 1H), 5.58 (ddt, J^1= 1.2 Hz, J^2 = 6.3, J^3 = 15.5 Hz, 1H), 5.08 (d, J = 6.0 Hz, 1H), 1.98 (dt, J^1= 6.6 Hz, J^2 = 6.9 Hz, 1H), 1.84 (s, 1H), 1.12-1.33 (m, 8H), 0.80 (t, J = 6.9 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): δ 143.6, 133.0, 132.4, 128.6, 127.6, 126.3, 75.4, 32.4, 31.9, 29.2, 29.1, 22.8, 14.3.



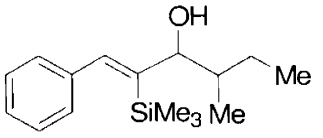
***(Z)*-2,4-dimethyl-1-phenyl-1-hexen-3-ol (14a):** In the reductive coupling of 1-phenylpropyne (**5a**, 2.0 mmol, 0.26 mL) and 2-methylbutyraldehyde (**6d**, 2.0 mmol, 0.22 mL), the standard procedure was used with the exception that the reaction was conducted at 110 °C and the scale was doubled. Silica gel chromatography (9:1 hexanes:ethyl acetate) afforded allylic alcohol **14a** as a pale yellow oil (167 mg, 41%). Diastereomeric ratio (66:34). R_f (4:1 hexanes:ethyl acetate): 0.50

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.39 (m, 5H), 6.49 (s, 1H, major), 6.45 (s, 1H, minor), 3.96 (d, J = 6.6 Hz, 1H, major), 3.87 (d, J = 8.2 Hz, 1H, minor), 0.76-2.28 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.8, 137.8, 137.6, 129.1, 127.2, 126.5, 126.4, 126.3, 83.1, 81.7, 37.9, 26.6, 25.0, 15.9, 14.4, 14.2, 13.4, 12.0, 11.5.

IR (thin film/NaCl): 3405, 2926, 1599, 1448, 1379, 1007, 749, 699 cm^{-1}

EI *m/z* calc'd for $C_{14}H_{20}O$: 204.1513, found [M^+]: 204.1506

[24] Maier, M. E.; Oost, T. *J. Organomet. Chem.* **1995**, *505*, 95.

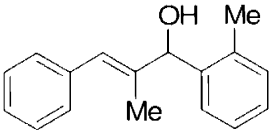


***(Z)*-4-methyl-1-phenyl-2-(trimethylsilyl)-1-hexen-3-ol (15a):** In the reductive coupling of 1-phenyl-2-(trimethylsilyl)-acetylene (**5e**, 2.0 mmol, 0.40 mL) and 2-methyl butyraldehyde (**6e**, 2.0 mmol, 0.22 mL), the general procedure was used with the exception that the scale was doubled. Silica gel column chromatography (19:1 hexanes:ethyl acetate) afforded **15a** as a pale yellowish oil (162 mg, 31%). Diastereomeric ratio (58:42). R_f (9:1 hexanes:ethyl acetate): 0.41

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, J = 7.7 Hz, 1H), 7.17 (m, 5H), 4.31 (s, 1H, major), 4.11 (d, J = 4.7 Hz, 1H), 1.58 (m, 3H), 1.28 (m, 1H), 0.91 (m, 8H), -0.12 (s, 9H, minor), -0.13 (s, 9H, major); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.2, 146.0, 141.3, 140.5, 140.3, 128.6, 128.6, 127.9, 127.0, 127.0, 80.9, 77.6, 76.8, 39.6, 39.3, 27.7, 22.8, 17.1, 12.5, 12.4, 12.0, 1.2, 1.0.

IR (thin film, NaCl): 3395, 2961, 1593, 1491, 1461, 1248, 1134, 1029, 838, 735 cm^{-1}.

HRMS (EI) m/e calcd (M+): 262.175294, found 262.1748



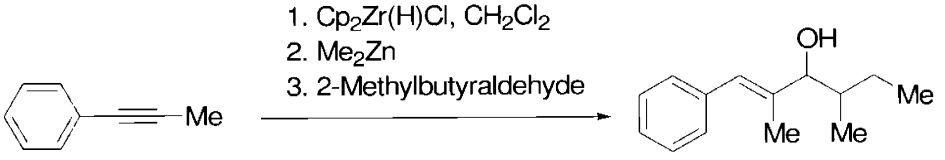
***(E)*-2-methyl-1-(2'-methylphenyl)-3-phenyl-2-propen-1-ol (16a):** In the reductive coupling of 1-phenyl propyne (**5b,** 2.0 mmol, 0.26 mL) and *o*-tolualdehyde (**6e**, 2.0 mmol, 0.23 mL), the general procedure was used with the exception that the scale was doubled. Silica gel column chromatography (9:1 hexanes:ethyl acetate), afforded **16a** and **16b** as a white solid (391 mg, 83%), m.p. 83-85 °C. R_f (4:1 hexanes:ethyl acetate): 0.58

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 2.1 Hz, 1H), 7.35-7.19 (m, 8H), 6.73 (s, 1H), 5.77 (q, 1H, J = 6.9Hz, minor regioisomer), 5.46 (d, J = 3.1 Hz, 1H), 2.40 (s, 3H), 2.26 (s, 3H, minor regioisomer), 1.97 (s, 3H, minor regioisomer), 1.77 (d, J=1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.9, 140.1, 139.9, 138.6, 137.8, 135.3, 130.5, 130.1, 129.0,

128.1, 128.0, 127.5, 127.2, 126.9, 126.5, 126.4, 126.3, 126.1, 125.9, 124.0, 76.0, 74.8, 19.6, 19.4, 14.8, 14.7.

IR (thin film, NaCl): 3333, 3053, 3022, 2915, 1599, 1488, 1442 cm^{-1}.

HRMS (EI) m/e calcd (M+): 238.135765, found 238.1363



To a Schlenck flask under argon was added 1-phenyl propyne (0.28 mL, 2.2 mmol) and 7 mL of dichloromethane (0.3M). Bis(cyclopentadienyl)zirconium chloride hydride (0.57 g, 2.2 mmol) was quickly weighed out and added to the flask under a positive flow of argon. When the solution became homogenous, the reaction mixture was cooled to –61 °C (chloroform-dry ice) and diethyl zinc (2.2 mL of a 1.0 M solution in hexanes, 2.2 mmol) was added dropwise via syringe. Warming to 0 °C, 2-methyl butyraldehyde (0.21 mL, 2.0 mmol) was added and stirring continued for 1.5 hours at 0 C before warming to room temperature for 6 hours. The reaction was quenched with a saturated solution of NH_4Cl (25 mL) and subsequently extracted with ether (3 x 60 mL). Concentration *in vacuo* followed by silica gel column chromatography (9:1 hexanes:ethyl acetate) afforded a yellow oil (160 mg, 39%). R_f (9:1 hexane:ethyl acetate) = 0.53.

^1H NMR (300 MHz, $CDCl_3$): δ 7.18-7.39 (m, 5H), 6.49 (s, 1H, major), 6.45 (s, 1H, minor), 5.78 (m, 1H, regioisomers), 3.96 (d, J = 6.6 Hz, 1H, major), 3.87 (d, J = 8.2, 1H, minor), 0.76-2.28 (m, 12H).

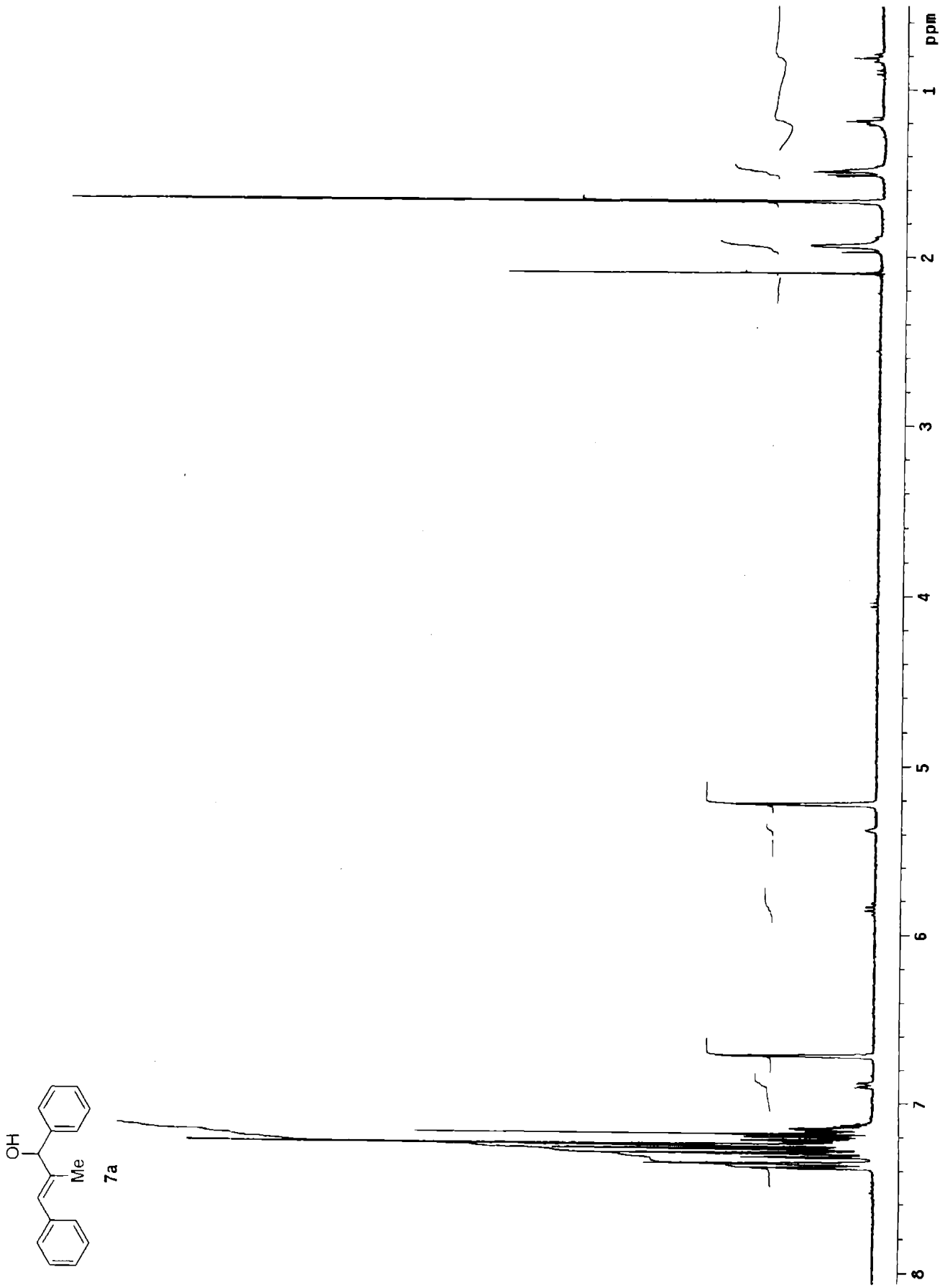
Preliminary Mechanistic Investigations

(a) Omission of aldehyde: Treatment of alkyne **5a** (0.25 mmol) with Et_3B (0.5 mmol), $Ni(cod)_2$ (0.25 mmol), and Bu_3P (0.50 mmol) for 16 h in toluene followed by treatment of the reaction with aqueous HCl provided recovered alkyne (86%) and no trace of allylic alcohol **7a** or products of reduction or oligomerization. In a parallel experiment, treatment of an equivalent reaction mixture after 16 h with additional portions of Et_3B (4.5 mmol) and alkyne **5a** (2.5 mmol), along with aldehyde **6a** (2.25 mmol), afforded a 77% yield of allylic alcohol **7a**. From these

experiments it was concluded that an irreversible hydrometallation of the alkyne does not occur under the reaction conditions, unless this process is dependent on the presence of the aldehyde.

(b) Omission of Et_3B: A solution of $Ni(cod)_2$ (0.25 mmol), Bu_3P (0.50 mmol), alkyne **5a** (2.5 mmol), and aldehyde **6a** (2.25 mmol) in toluene was stirred 16 h at ambient temperature. Treatment of the reaction mixture with aqueous HCl provided recovered alkyne **5a** (92%) and no trace of allylic alcohol **7a** or products of reduction or oligomerization of the alkyne. In a parallel experiment, treatment of an equivalent reaction mixture after 16 h with additional portions of alkyne **5a** (2.5 mmol) and aldehyde **6a** (2.25 mmol), along with Et_3B (5.0 mmol), afforded an 81% yield of allylic alcohol **7a**. From these results it was concluded that the reaction does not proceed via and oxy-metallocycle unless Et_3B is required for its formation.

Chapter 1: Spectra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7a
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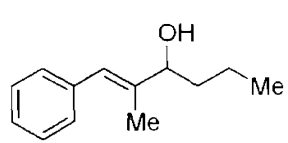
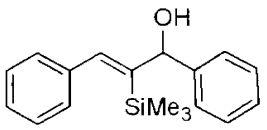
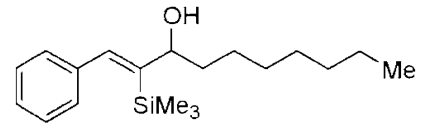
ppm



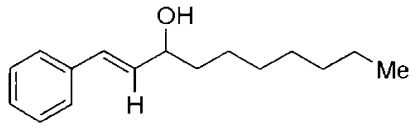
8a



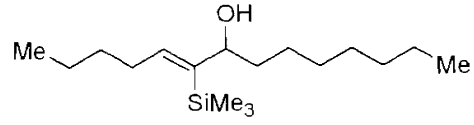
9a



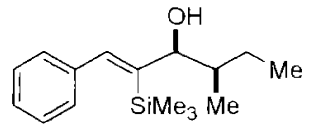
10a



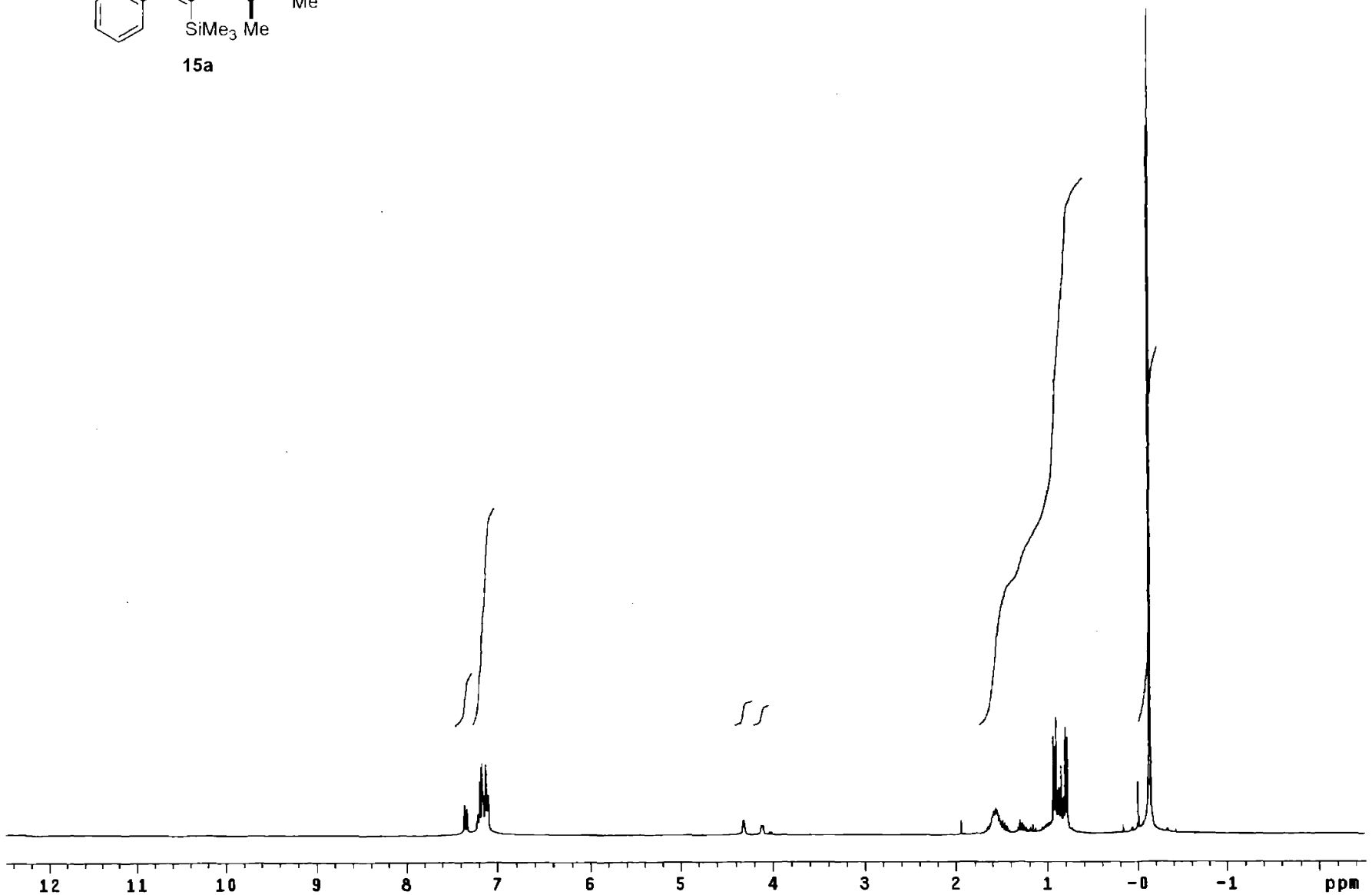
11a

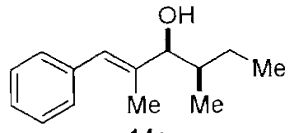


12a

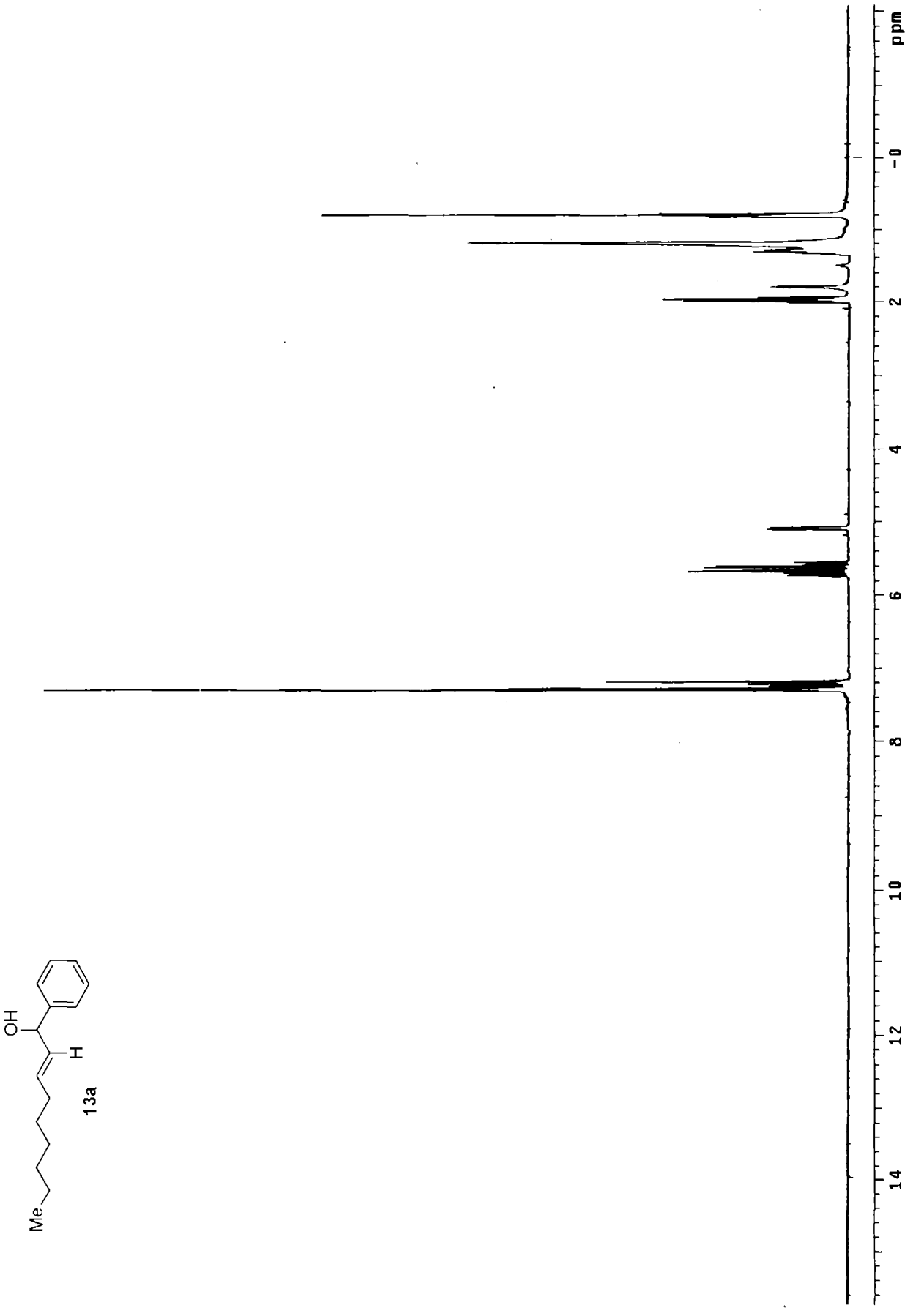


15a





14a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H
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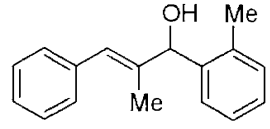
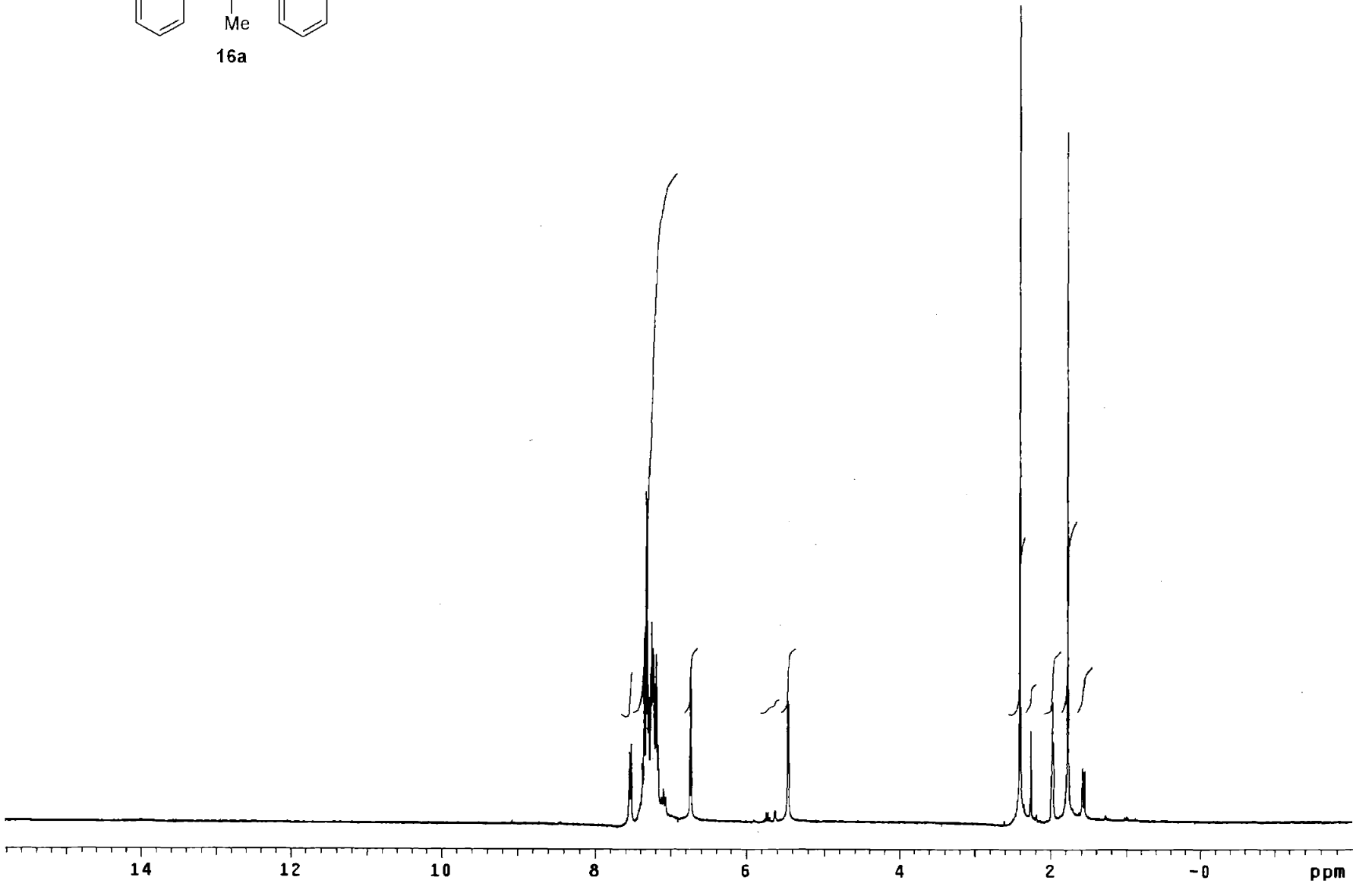


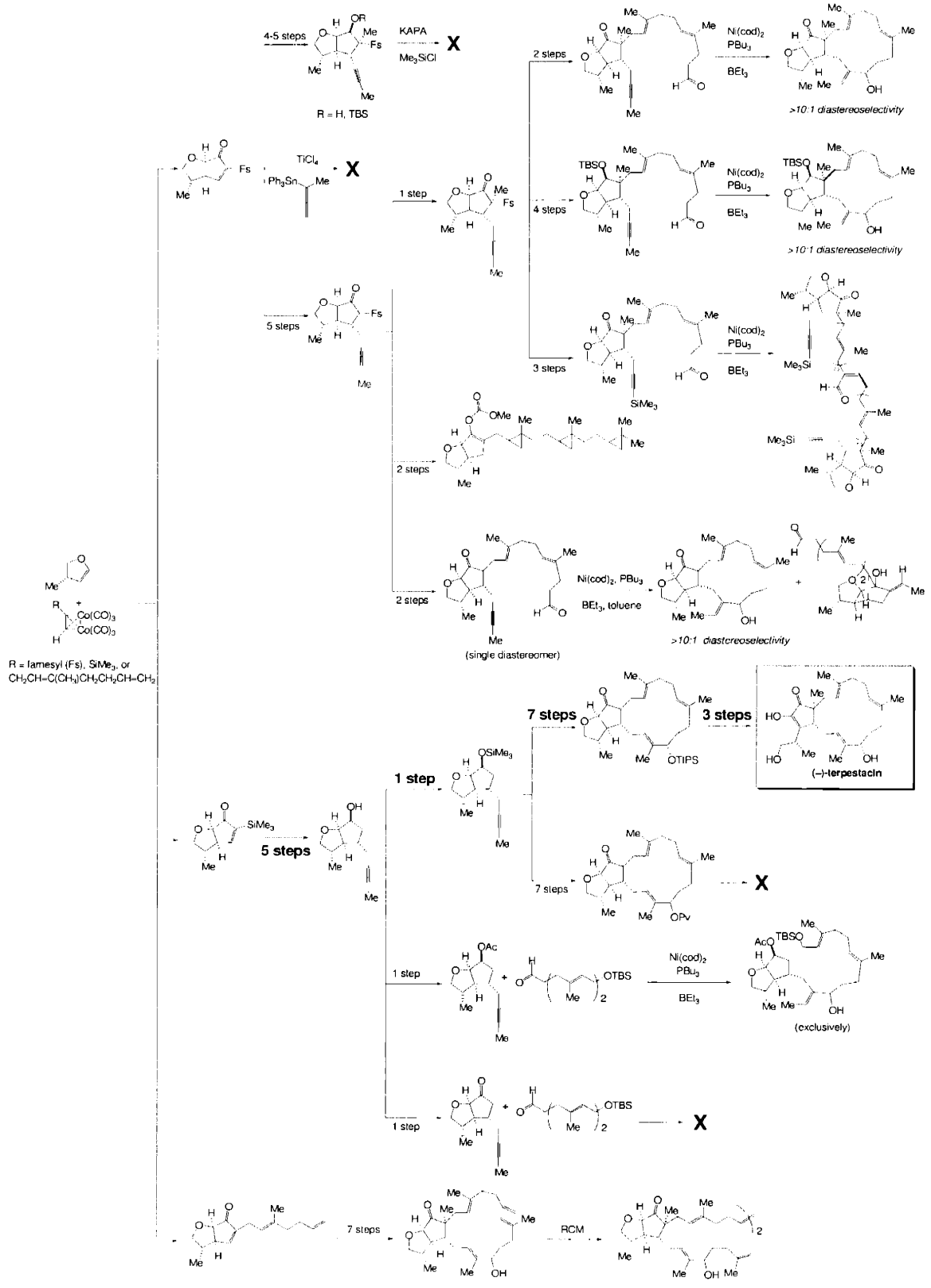
16a



Chapter 2

Enantioselective Synthesis of (–)-Terpestacin and Structural Revision of Siccanol Using Catalytic Stereoselective Fragment Couplings and Macrocyclizations

Summary of the Total Synthesis of (–)-Terpestacin and Related Synthetic Approaches



Introduction

Over the past ten years, several scientific communities have been drawn to the sesterterpene terpestacin (**1**) and structurally related compounds (**2**, **3**) due to both their unique structure and biological activities. Originally isolated by Oka from the fungal strain *Arthrinium* sp. as part of the Bristol-Myers Squibb company interested in anti-HIV agents, terpestacin was found to inhibit the formation of syncytia, giant-multinucleated cells that arise from expression of gp-120 on cell surfaces in the course of HIV infection.[1] Recently, a study of the effects of terpestacin (**1**) on bovine aortic endothelial cells (BAECs) and chorioallantoic membrane (CAM) from growing chick embryos has determined that this natural product also inhibits angiogenesis.[2]

A structurally related compound, proliferin, was discovered shortly thereafter and was renamed fusaproliferin (**3**) since the name "proliferin" was previously used to describe a prolactin-related protein.[3] In a subsequent report, the absolute configuration of fusaproliferin was determined by way of comparing R and Rw values of enantiomorphs derived from X-ray data. Based on a statistically significant difference in R and Rw values between two enantiomorphs, the authors concluded that fusaproliferin was the enantiomer of 23-epi-**3** (terpestacin numbering).[4]

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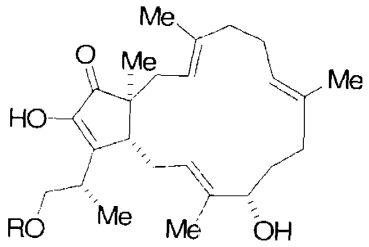
[1] (a) Oka, M.; Iimura, S.; Tenmyo, O.; Sawada, Y.; Sugawara, M.; Ohkusa, N.; Yamamoto, H.; Kawano, K.; Hu, S.-L.; Fukagawa, Y.; Oki, T. *J. Antibiotics* **1993**, *46*, 367. (b) Jung, H. J.; Lee, H. B.; Kim, C. J.; Rho, J.-R.; Shin, J.; Kwon, H. J. *J. Antibiotics* **2003**, *56*, 492.

[2] Jung, H. J.; Lee, H. B.; Kim, C. J.; Rho, J. –R.; Shin, J.; Kwon, H. J. *J. Antibiotics* **2003**, *56*, 492.

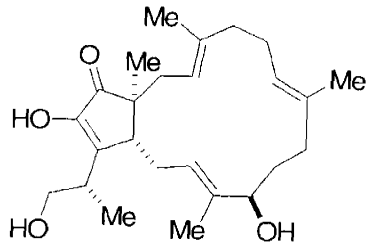
[3] Lee, S. J.; Nathans, D. *J. Biol. Chem.* **1988**, *263(7)*, 3521.

[4] (a) Randazzo, G.; Fogliano, V.; Ritieni, A.; Mannina, L.; Rossi, E.; Scarallo, A.; Segre, A. L. *Tetrahedron* **1993**, *49*, 10883. (b) Manetti, C.; Fogliano, V.; Ritieni, A.; Santini, A.; Randazzo, G.; Logrieco, A.; Mannina, L.; Segre, A. L. *Struct. Chem.* **1995**, *6*, 183. (c) Santini, A.; Ritieni, A.; Fogliano, V.; Randazzo, G.; Mannina, L.; Logrieco, A.; Benedetti, E. *J. Nat. Prod.* **1996**, *59*, 109.

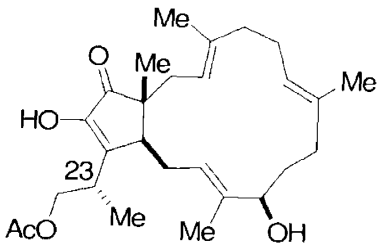
Figure 1.



1 (R = OH; terpestacin)
3 (R = Ac; fusaproliferin)



2
11-*epi*-terpestacin ("siccanol")



***ent*-23-*epi*-3**

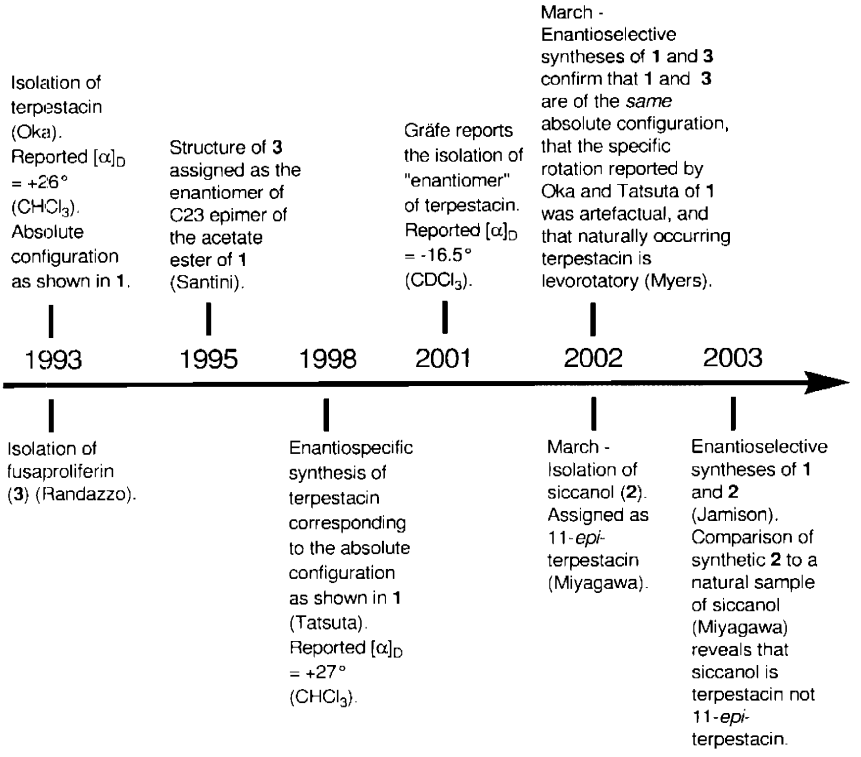
Both terpestacin and fusaproliferin have been prepared by total synthesis[5] with Tatsuta being the first to make terpestacin in 1998 (racemic). Later that same year, they completed an enantiospecific, 38-step synthesis beginning with tri-*O*-acetyl-D-galactal (**4**) that took advantage of a highly selective Horner–Wadsworth–Emmons reaction of **6** to form the critical 15-membered carbocycle. The specific rotation measured for terpestacin ($[\alpha]_D$ = +27, *c* 0.22, $CHCl_3$) was consistent with that obtained by Oka ($[\alpha]_D$ = +26, *c* 0.5, $CHCl_3$) and so it appeared that the absolute configuration of terpestacin had been confirmed by means of chemical synthesis.[6]

---

[5] Approaches toward the synthesis of terpestacin: (a) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1995,** 249. (b) Mermet-Mouttet, M. P.; Gabriel, K.; Heissler, D. *Tetrahedron Lett.* **1999,** *40*, 843.

[6] Tatsuta, K.; Masuda, N. *J. Antibiotics* **1998**, *51*, 602.

Scheme 1. Structural assignment timeline of **1**, **2**, **3**.



However, this conclusion was brought into question as a result of an unusual chain of events. In 2001, Gräfe and co-workers isolated a product from *Ulocladium* sp. that was believed to be the enantiomer of terpestacin[7], since it was spectroscopically identical to Oka's material but differed only in the sign of specific rotation. Interestingly, both "(+)-terpestacin" (Oka) and "(–)-terpestacin" (Gräfe) inhibited syncytium formation. In March 2002, Myers reported enantioselective syntheses of terpestacin (**1**) and fusaproliferin (**3**) beginning with an amide derived from pseudoephedrine (**5**) which should have led to (+)-terpestacin, as reported by Oka and corroborated by Tatsuta. However, having obtained (–)-terpestacin at the end of the synthesis, Myers initiated a thorough series of investigations that ultimately revealed that exposure of (–)-terpestacin to chloroform stored over potassium carbonate gave rise to a chloroetherification product possessing the same sense of specific rotation as that seen by Oka (natural) and Tatsuta (synthetic). Taken together, the results led to the reassignment of the specific rotation of

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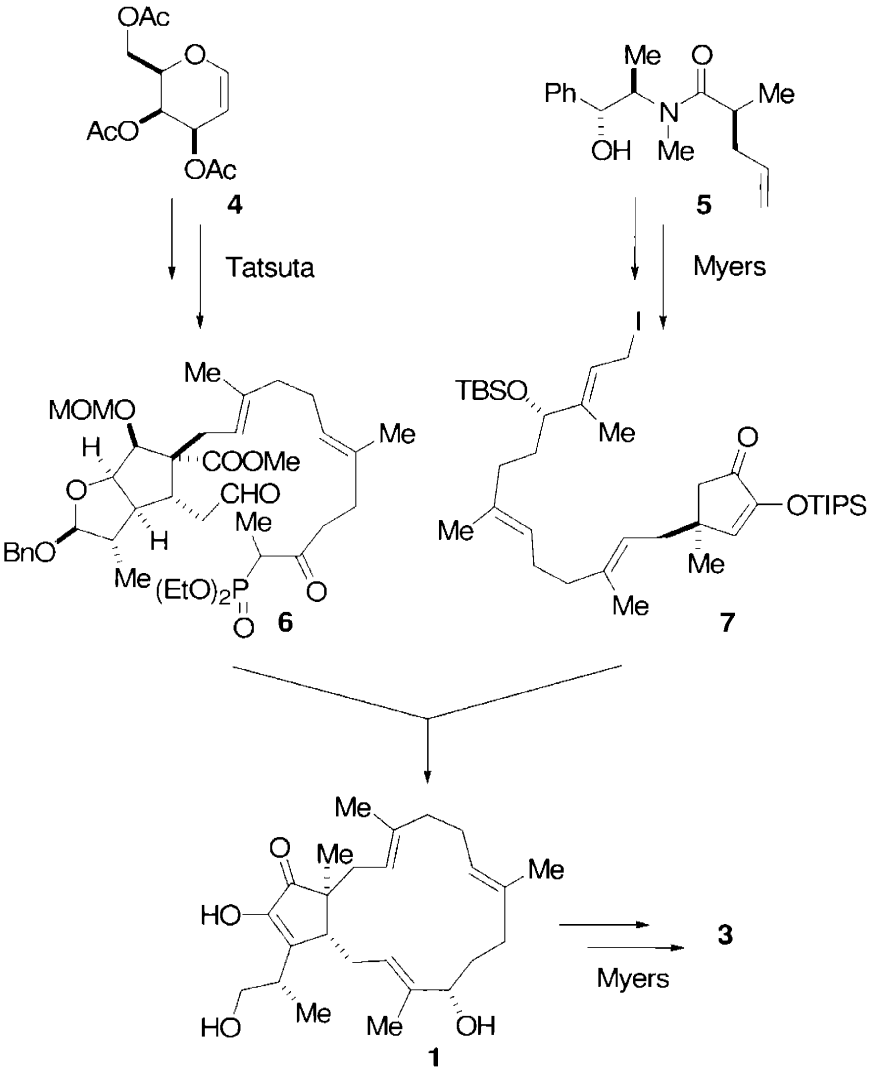
[7] Schlegel, B.; Schmidtke, M.; Dörfelt, H.; Kleinwächter, P.; Gräfe, U. *J. Basic Microbiol.* **2001**, *41*, 179.

naturally-occurring terpestacin as levorotatory.[8] In retrospect, the results of the Myers study suggested that the specific rotation measured by Gräfe and co-workers, on a sample earlier referred to as the "enantiomer" of terpestacin, was in fact of the same absolute configuration as that originally isolated by Oka. By acetylating (–)-**1** to obtain (–)-**3**, Myers discovered that naturally occurring terpestacin (**1**) and fusaproliferin (**3**) formed a homochiral structural series. In other words, natural fusaproliferin was simply an acetate ester of natural terpestacin, not the enantiomeric C23 epimer as was originally reported by Santini.

[8] Myers, A. G.; Siu, M.; Ren, F. *J. Am. Chem. Soc.* **2002**, *124*, 4230.

Scheme 2. Previous enantioselective syntheses of (–)-terpestacin.



Nearly coincident with the Myers syntheses of terpestacin and fusaproliferin, Miyagawa reported the isolation of another natural product, siccanol (**2**) from *Bipolaris sorokiniana,* a fungal strain commonly found in decayed ryegrass leaves. Their structural determination led them to conclude that siccanol was diastereomeric to terpestacin at the allylic carbinol in the fifteen-membered ring (C11), i.e. 11-*epi*-terpestacin.[9] Differing merely by the configuration about the C11 allylic carbinol, **1** and **2** provided an attractive context to pursue our ongoing interest in the stereoselective formation of allylic

[9] Nihashi, Y.; Lim, C.-H.; Tanaka, C.; Miyagawa, H.; Ueno, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 685.

alcohols.[10] This chapter details our account of the syntheses of (–)-terpestacin and (+)-11-*epi*-terpestacin that utilizes our recently developed intermolecular, stereoselective reductive coupling of alkynes and aldehyes to reveal that "siccanol" is *not* 11-*epi*-terpestacin, but in fact is (–)-terpestacin itself.

Retrosynthetic Analysis

A central component of our synthetic strategy for **1** and **2** was the disconnection at the C11-C12 allylic alcohol, in order to examine the feasibility of a catalytic reductive coupling reaction of alkyne and aldehyde, related to methodology developed in our laboratory and by Montgomery.[11] Two basic approaches using this method were devised (Scheme 3). The first utilized an *intramolecular* reductive coupling of alkyne and aldehyde to install the C11 carbinol stereocenter, construct the 15-membered carbocyclic ring, and establish the (*E*)-geometry at one of the three alkenes of this macrocycle. An alternate approach planned on controlling the C11 configuration via an *intermolecular* alkyne-aldehyde reductive coupling of **9** and **10**, with subsequent formation of the macrocycle using an intramolecular allylation of a ketone enolate.

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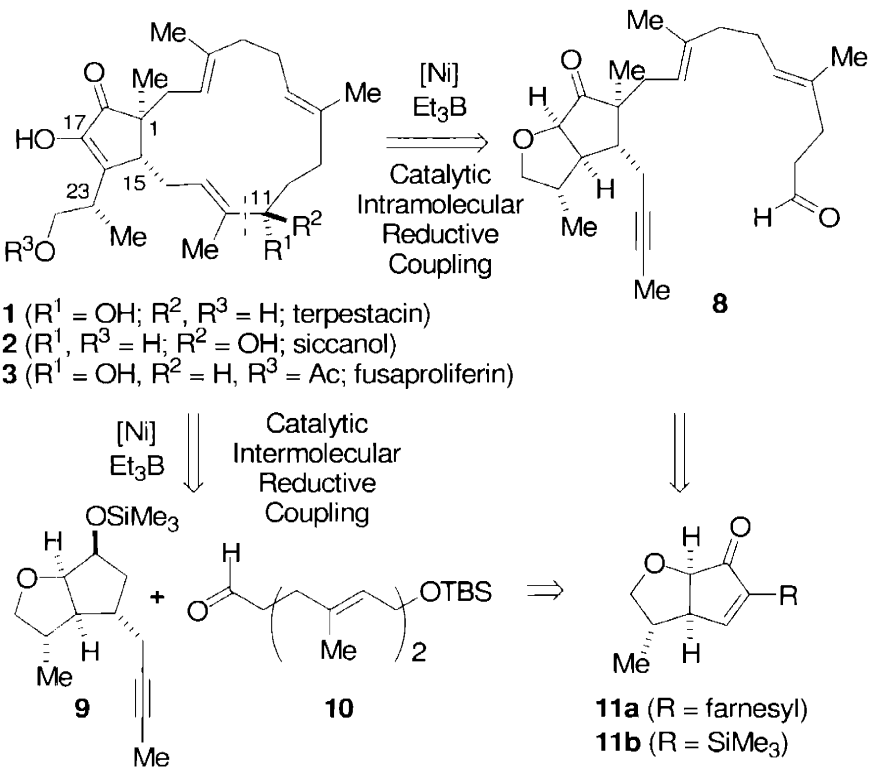
[10] (a) Chan, J.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 11514. (b) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156. (c) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442. (d) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221.

[11] Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467.

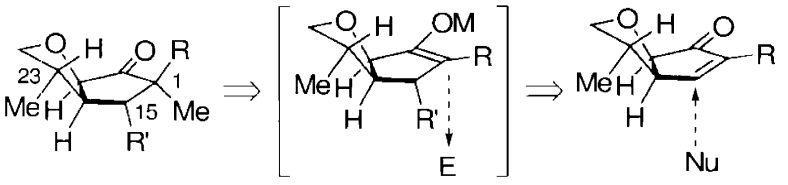
Scheme 3. Nickel-Catalyzed Alkyne-Aldehyde Coupling Strategies



In both approaches, the synthesis of the reductive coupling educts required the protection of two otherwise interfering functional groups, a latent 1,2-diketone located at (C17-C18) and the primary hydroxyl group at C24. We envisioned accomplishing both tasks by effectively lowering the oxidation state of C17 and attaching it to the C24 oxygen, thus forming a tetrahydrofuran, which we planned to unravel at a late stage in the synthesis through an enolate hydroxylation reaction.

The tetrahydrofuran also addressed challenges common to both strategies, namely, establishing the remaining three stereogenic centers (Figure 2). The configuration of C23 would be relayed by way of a conjugate addition to oxabicyclo[3.3.0]octenone **11a** or **11b** to both the quaternary carbon center (C1) and its neighbor (C15) that together also comprise the junction of the five- and fifteen-membered rings. This process was expected to occur on the convex face, but prediction of the major diastereomer in a subsequent enolate alkylation was less clear (desired approach shown: E = MeI) since a substituent on this face, adjacent to the site of alkylation, might strongly influence the stereochemical course of the reaction.

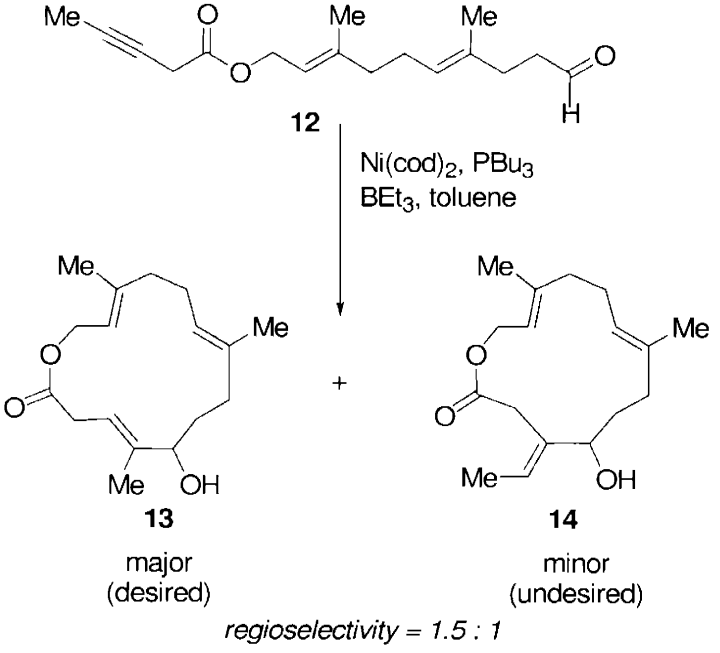
Figure 2. Proposed basis of stereoselectivity in conjugate additions to and alkylations of **11a** and **11b**.



11a R = farnesyl
11b R = $SiMe_3$

Also unclear in both approaches *a priori*, was the degree of influence of the existing stereocenters in determining the selectivity in the formation of the carbinol center at C11 using a nickel-catalyzed alkyne-aldehyde reductive coupling. In both cases, the nearest stereocenter would reside at C15, two bonds away from the site of asymmetric induction. An additional uncertainty particular to the intramolecular reductive coupling approach was the effect of the conformation of the nascent 15-membered ring not only on diastereoselectivity, but also on regioselectivity (15-membered ring vs. 14-membered ring).

Scheme 4.



regioselectivity = 1.5 : 1

Accordingly, a model substrate (**12**) was synthesized[12] and subjected to Et_3B and catalytic amounts of $Ni(cod)_2$ and PBu_3 in order to investigate the feasibility of the macrocylization strategy (Scheme 4). Although the model lacked several features, namely, the *cis*-fused 5,5 ring system and its corresponding functional groups, a 1.5:1 ratio was obtained favoring the formation of the desired regioisomer (**13**), demonstrating the possibility of forming a 15-membered macrocycle with three (*E*)-trisubstituted double bonds by this approach (Scheme 4).

Results and Discussion

Intramolecular Alkyne-Aldehyde Reductive Coupling Approach

Beginning with commercially available β-methallyl alcohol, mole-scale rhodium-catalyzed hydroformylation followed by dehydration under acidic conditions, afforded in 72% yield multi-hundred gram quantities of dihydrofuran **15**.[13] Resolution of **15** was achieved using (+)-$(Ipc)_2BH$ which furnished enantiopure material (>95% ee) at 55% conversion.[14] Initial attempts to promote the intermolecular Pauson-Khand reaction between **15** and cobalt cluster **16** involved the use of heating exclusively or in combination with NMO,[15] cyclohexylamine,[16] or a phosphine sulfide.[17] The greatest success was achieved using a sulfide-promoted intermolecular Pauson-Khand reaction[18] furnishing the desired oxabicyclo[3.3.0]octenone (**11a**) in 40-60% yield. Notably, no

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[12] Model substrate **12** was synthesized through the DCC coupling of **40a** and pent-3-ynoic acid.

[13] Botteghi, C.; Consiglio, G.; Ceccarelli, G.; Stefani, A. *J. Org. Chem.* **1972**, *37*, 1835.

[14] Brown, H. C.; Prasad, J. V. N. Vara *J. Am. Chem. Soc.* **1986**, *108*, 2049.

[15] Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289.

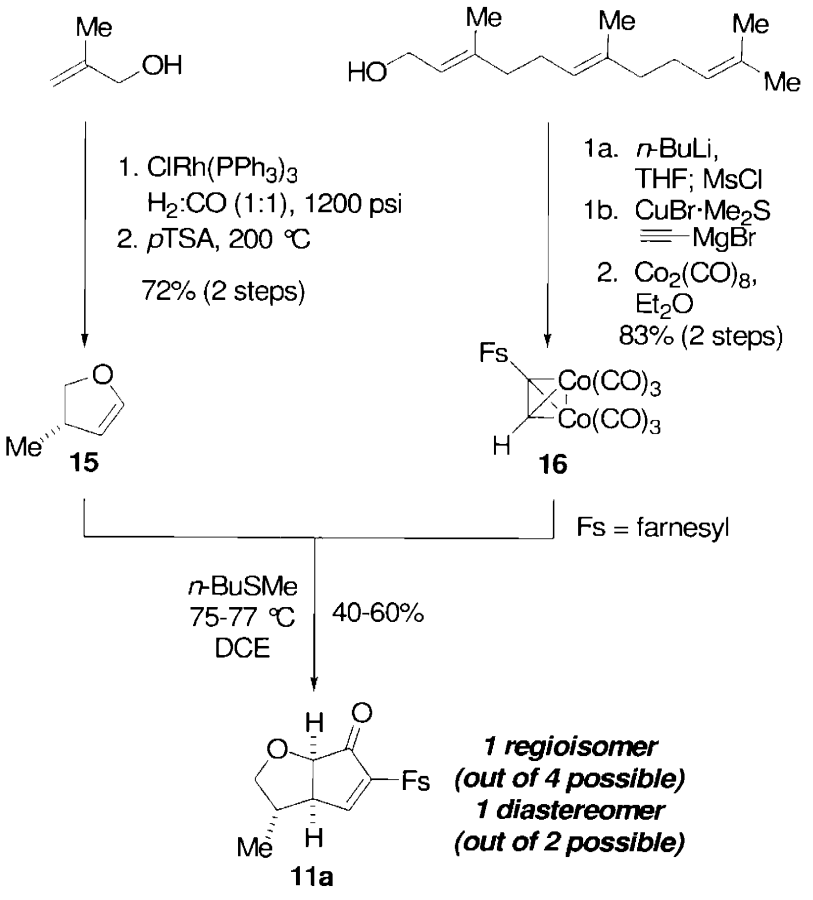
[16] Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem. Int. Ed.* **1997**, *36*, 2801.

[17] Hayashi, M.; Hashimoto, Y.; Yamamoto, Y.; Usuki, J.; Saigo, Kazuhiko *Angew. Chem. Int. Ed.* **2000**, *39*, 631.

[18] Sugihara, T.; Yamada, M.; Yamguchi, M.; Nishizawa, M. *Synlett* **1999**, *6*, 771.

other diastereomers or any of the three other possible regioisomers could be detected (^{1}H NMR).[19]

Scheme 5.



In 1990, Haruta and co-workers demonstrated that allenyltriphenylstannanes participate in $TiCl_4$-mediated conjugate additions to a variety of cyclic enones to afford 1,5-ynones.[20] Attempts at the direct installation of the 2-butynyl moiety at C15 (terpestacin numbering) using the corresponding allenyl stannane (**17**) were unsuccessful. In our studies, we observed that enone **11a** either underwent decomposition readily or no reaction despite the evaluation of several Lewis acids of varying nature and strength ($TiCl_4$, BF_3•OEt_2, $SnCl_4$, Et_2AlCl, $MgBr_2$, Me_3SiCl, $ZnCl_2$, $Ti(OiPr)_4$, $Ti(OiPr)_3Cl$, and $Yb(OTf)_3$).

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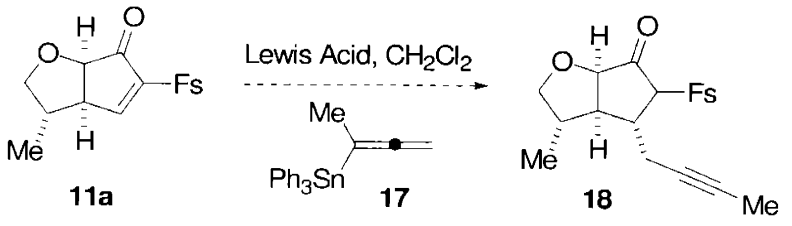
[19] Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *J. Organomet. Chem.* **2001**, *630*, 104.

[20] Haruta, J.; Nishi, K.; Matsuda, S.; Akai, S.; Tamura, Y.; Kita, Y. *J. Org. Chem.* **1990**, *55*, 4853.

Scheme 6.



Consequently, an alternate route was devised that began with a highly diastereoselective conjugate addition of a lithium cuprate (**19**) to **11a** provided **20** in 72% yield and >95:5 diastereoselctivity. Notably, attempts at the use of a trimethylsilyl group in place of triisopropylsilyl in the conjugate addition step gave rise to lower yields possibly due to unimolecular or bimolecular decomposition of the nucleophile.[21] Following reduction, deprotection, isomerization of the terminal alkyne with KO^{t}Bu in DMSO,[22] and a TPAP/NMO oxidation, **18** was delivered in 57% yield over 4-steps. The reduction/oxidation tandem (steps 1 and 4) was necessary since ketones such as **18** were not compatible with KO^{t}Bu in DMSO solutions.

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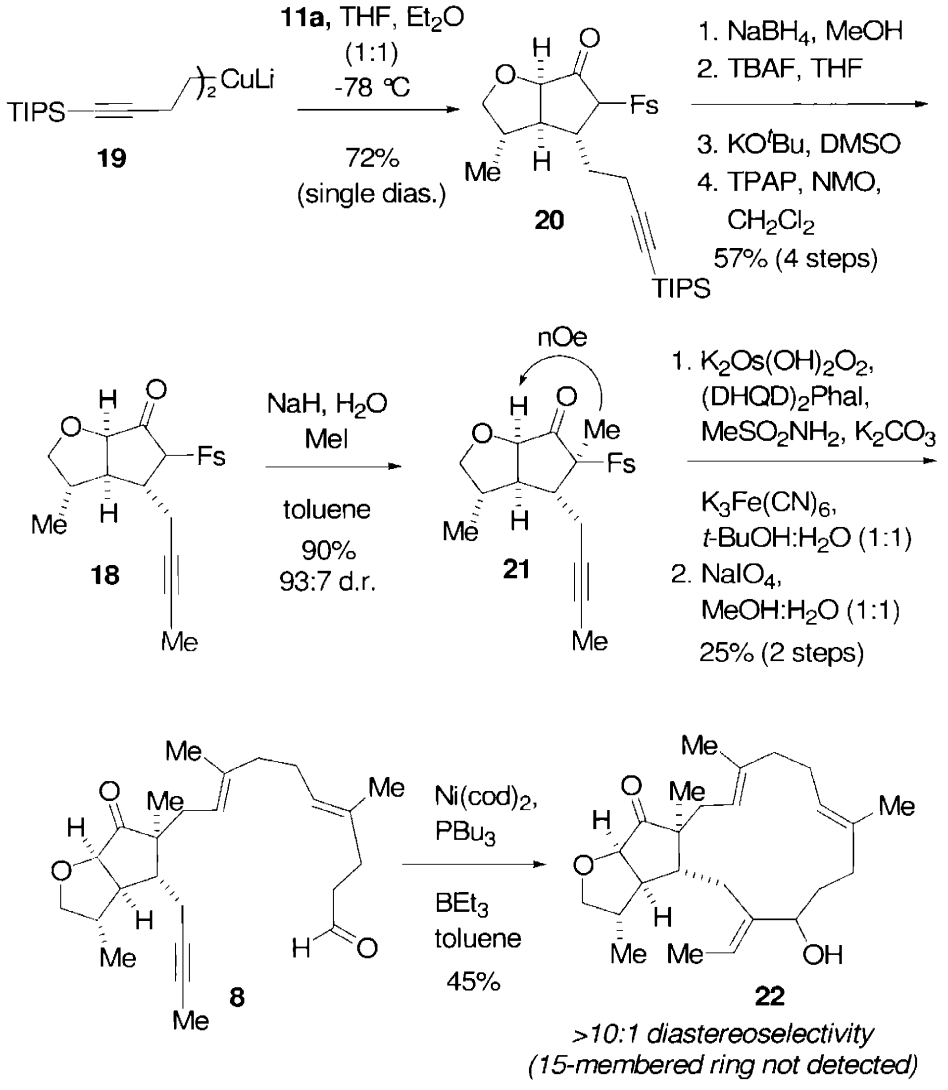
[21] Crude ^{1}H spectra reveals a large number of signals in the vinyl region when the trimethyl silyl protecting group was used in place of triisopropyl silyl.

[22] (a) Takano, S.; Sekiguchi, Y.; Sato, N.; Ogasawara, K. *Synthesis* **1987**, 139. (b) Recent application in total synthesis: Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482.

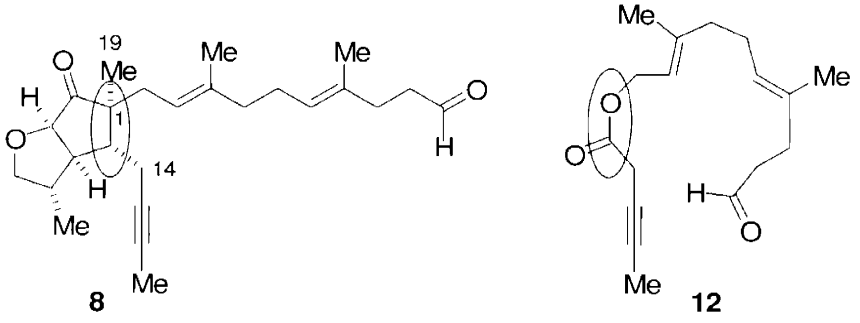
Scheme 7.



Efforts toward the methylation of an enolate derived from ketone **18** involved the investigation of a variety bases and conditions that resulted in either decomposition of the starting material or the formation of an *O*-methyl vinyl ether as the primary product. Exclusively successful was the use of sodium hydride in benzene, effecting a reaction that proceeded with good conversion and site selectivity on small scale (<10 mg). However, upon increasing the scale of the reaction (100 mg), slow decomposition of **10** was observed with no conversion to the desired product. We reasoned that adventitious water might be present in the small scale reaction implying that finely dispersed sodium hydroxide was acting as the operative base. Indeed, the addition of 100 mol% water to a mixture of sodium hydride, ketone, and methyl iodide in toluene resulted in the formation

of **21** in 90% yield with a diastereoselectivity of 93:7 in favor of the desired isomer. The assignment of the newly formed quaternary center was based on an nOe experiment and the finding that the ^{1}H NMR resonance corresponding to the quaternary methyl group in the major product resided upfield relative to the undesired diastereomer (δ 0.92 vs. δ 1.06), likely due to magnetic anisotropy of the triple bond. Selective cleavage of the terminal isopropylidene unit was effected in a two-step sequence that involved a catalytic dihydroxylation using Sharpless' $(DHQD)_2PHAL$ ligand[23] and sodium periodate cleavage of the resulting diol, affording **8** in 25% yield for the two steps.

Figure 3. Comparison of **8** to model substrate **12**



Intramolecular, nickel-catalyzed reductive cyclization of **8** afforded, unfortunately, the undesired 14-membered ring regioisomer (**22**) in 45% yield with no detectable trace of the desired regioisomer (15-membered ring). Formation of the undesired regioisomer was surprising given our results with the model system **12** and raised the possibility, at that time, that the 5,15 ring junction and the stereogenic centers in **8** were critical structural features (Figure 3). Since changing the C15 stereocenter would require major modifications of the existing route, we first focused on altering the nature of C1 through removal of the C19 quaternary methyl group in order to satisfy two ends: First, the elimination of C19 would remove steric interactions with the 2-butynyl group. By this approach, more conformations of the alkyne may be accessible, conceivably effecting the macrocyclization regioselectivity to favor the 15-membered ring. Second, the absence of steric bulk caused by the C19 quaternary methyl group

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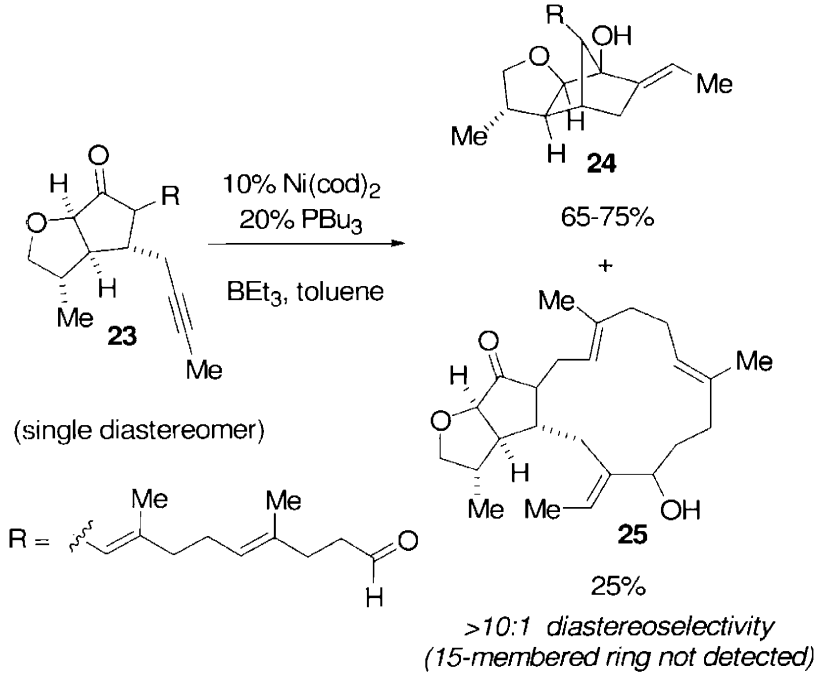
[23] (a) Crispino, G. A.; Sharpless, K. B. *Tetrahedron Lett.* **1992,** *33*, 4273. (b) Crispino, G. A.; Ho, P. T.; Sharpless, K. B. *Science* **1993,** *259*, 64. (c) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995,** *36*, 8741. (d) Corey, E. J.; Zhang, J. *Org. Lett.* **2001,** *3*, 3211.

might perturb the geometry of the sidechain containing the aldehyde, possibly reducing strain in the transition state.

Intramolecular Alkyne and Aldehyde Approach: Cyclization in the Absence of C19

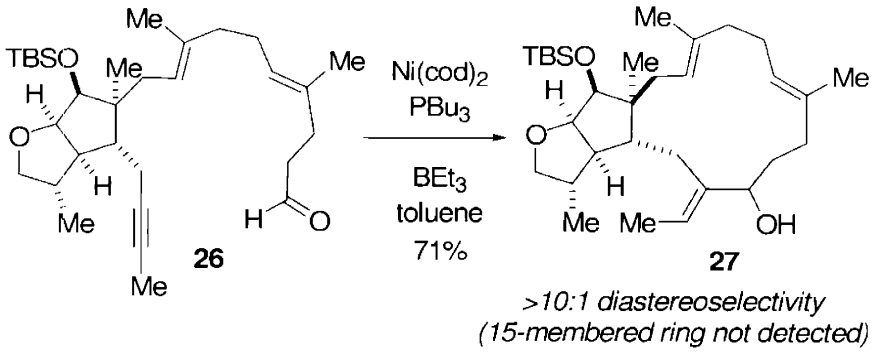
In order to test these hypotheses, alkynal **23** was synthesized in an analogous fashion to the synthesis of **8**. Treatment with $Ni(cod)_2$, PBu_3, and BEt_3 in toluene afforded the undesired regioisomer (**25**) as well as **24**, a product derived from the intramolecular reductive coupling of the alkyne and the ketone. Despite the fact that acetone can be used as a solvent in intermolecular nickel-catalyzed reductive couplings without any trace of alkyne-acetone coupling products, the proximity of the alkyne to the ketone may explain why **24** was formed.

Scheme 8.



The results obtained from these experiments suggested that the ketone might participate in the catalytic reaction, possibly through interaction with nickel. Accordingly, the next logical course of action was to alter the ketone functionality. Reduction with $NaBH_4$ and protection as its *tert*-butyldimethylsilyl ether accomplished this task, but unfortunately, cyclization of **26** also afforded exclusively the 14-membered ring (**27**) in 71% yield (Scheme 9).

Scheme 9.



Intramolecular Alkyne-Aldehyde Approach: Cyclization of an Alkynylsilane.

Having not observed a change in regioselectivity by varying nearby functional groups, we next investigated the effects of altering the nature of alkyne. In general, catalytic additions to internal acetylenes of the type RCH_2–C≡C–Me, i.e., with substitutents nearly identical in electronic nature and steric demand, are typically non-regioselective.[24] In contrast, acetylenes of the type R–C≡C–$SiMe_3$ couple with a high degree of regioselectivity.[25] Therefore, we targeted the alkynylsilane **35** in hopes of observing regioselectivity in the catalytic macrocyclization similar to that seen in intermolecular cases.

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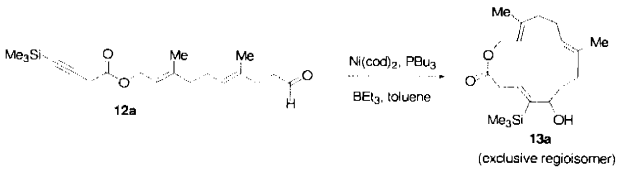
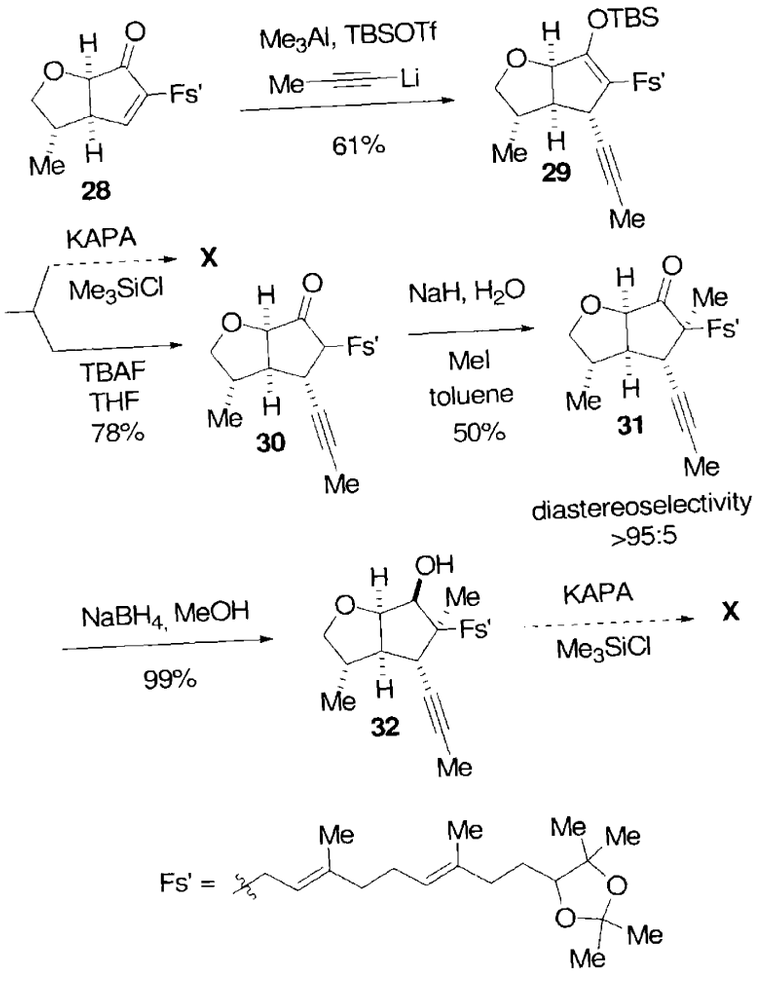
[24] Notable exceptions: (a) Et vs. Me (2:1): Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) *i*-Bu vs. Me (7.3:1): Molander, G. A.; Retsch, W. H. *Organometallics* **1995**, *14*, 4570. (c) *n*-undecyl vs. Me (2.4:1): Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726.

[25] Cyclization of model **12a** gave exclusively **13a** in a model study



Scheme 10.



An approach making use of a KAPA-mediated isomerization[26] (KAPA = potassium 3-aminopropylamide) was undertaken (Scheme 10). Beginning with **28**, the 1,4 addition of 1-lithio-1-propyne-$AlMe_3$ "ate" complex[27] afforded **29**. Following deprotection with TBAF, alkylation of **30** proceeded in greater than 95:5 diastereoselectivity to afford **31** presumably due to the low steric demand of the propynyl group residing on the convex face of the bicyclic system.[28] Reduction by $NaBH_4$

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[26] (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Midland, M. M.; Halterman, R. L. *Tetrahedron Lett.* **1981**, *42*, 4171.

[27] Kim, S.; Park, J. K. *Synlett* **1995**, 163.

[28] We have observed that the diastereoselectivity of quaternary methylation reaction increases as the size of the β-substituent decreases.

furnished the desired substrate **29**. Unfortunately, endeavors to utilize KAPA-mediated isomerizations on either **29** or **32** followed by a trimethylsilyl chloride quench were unsuccessful. Fortunately, a remarkably functional group tolerant alkyne cross metathesis[29] of **33**, using a catalyst developed by Cummins,[30] afforded the desired product (**34**) in 36% yield with 39% identified as recovered **33**. Following removal of the acetonide, and periodate cleavage of the resulting diol to **35**, attempts at nickel-catalyzed reductive cyclization even under forcing conditions (refluxing toluene) afforded only an aldol self-condensation product (**36**) and starting material (Scheme 11).

This observation can be attributed to both the steric and electronic nature of the alkyne. We have observed in our investigations of alkyne scope in intermolecular couplings that alkynylsilanes generally exhibited reduced reactivity relative to other internal acetylenes. In general, as the steric demand of the alkyne increases, as in the case of R**CH$_2$**–≡–Me versus ***t*-Bu**–≡–Me, reactivity decreases.[31] Likewise, the electronics of the trimethylsilyl group affects reactivity as well. For instance, (3-methyl-but-1-ynyl)benzene (Ph–≡–***i*-Pr**) has been found to couple readily[32] whereas sterically similar trimethyl-phenylethynylsilane (Ph–≡–**SiMe$_3$**) exhibited markedly lower reactivities with various aldehydes.

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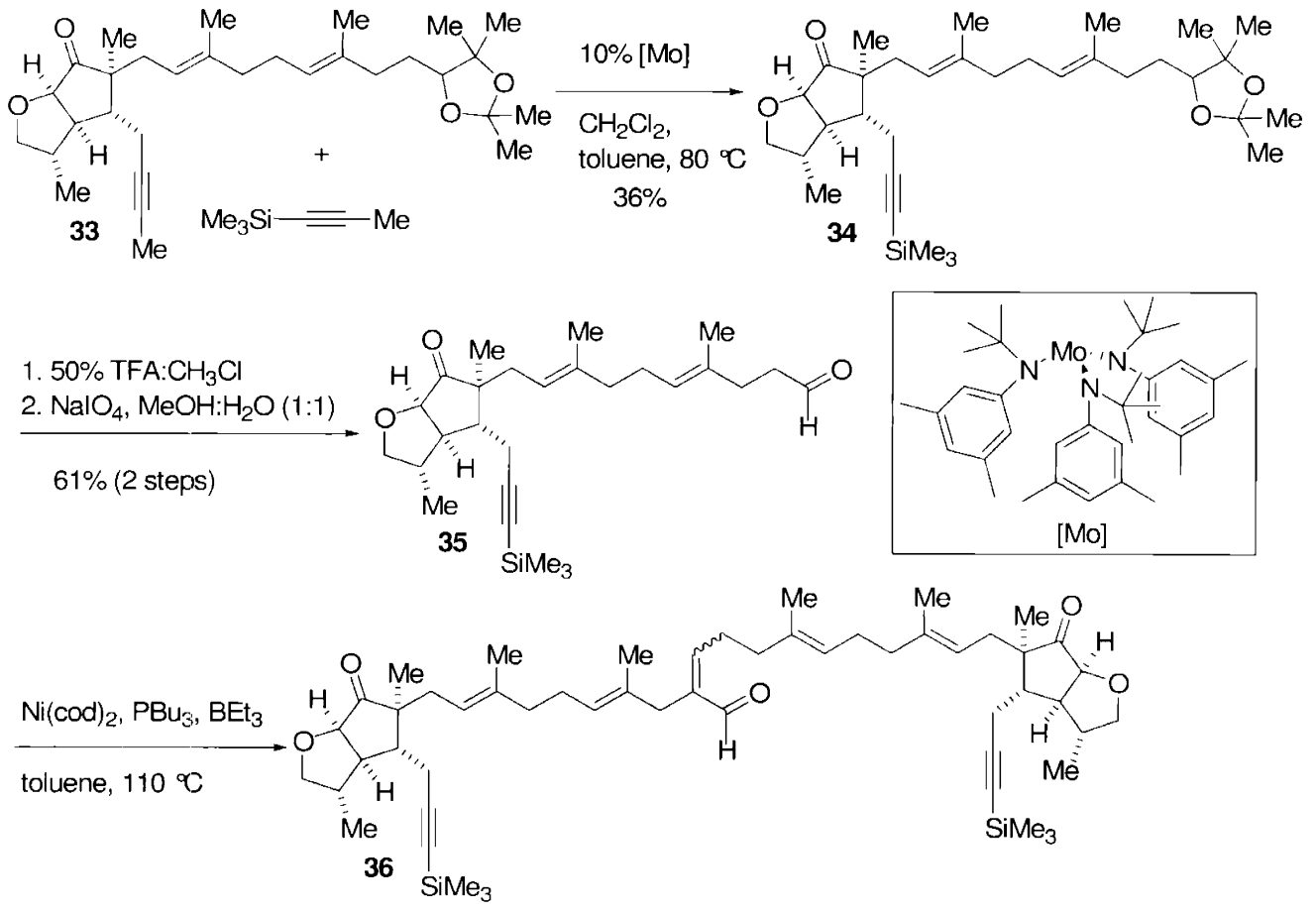
[29] Furstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453. (b) Furstner, A.; Mathes, C. *Org. Lett.* **2001**, *3*, 221.

[30] (a) Laplaza, C. E.; Cummins, C. C. *Science* **1995**, *268*, 861. (b) Laplaza, C. E.; Odom, A. L.; Davis, W. M.; Cummins, C. C. *J. Am. Chem. Soc.* **1995**, *117*, 4999. (c) Laplaza, C. E.; Johnson, A. R.; Cummins, C. C. *J. Am. Chem. Soc.* **1996**, *118*, 709. (d) Laplaza, C. E.; Johnson, M. J. A.; Peters, J. C.; Odom, A. L.; Kim, E.; Cummins, C. C.; George, G. N.; Pickering, I. J. *J. Am. Chem. Soc.* **1996**, *118*, 8623.

[31] Reaction conducted by Mr. Robert A. Jackson

[32] Reaction conducted by Mr. Chudi O. Ndubaku

Scheme 11.



From the previous cyclization experiments, it appears that the unusual regioselectivities observed may be rationalized through mechanistic considerations.[33] A recent report by Montgomery[34] had suggested that the $Ni(cod)_2/PBu_3$ catalyst system can proceed through either an oxametallacyclopentene or through a alkenyl nickel intermediate (Figure 4). Taking into account these two contrasting mechanisms, four different transition states leading to the two macrocycles would be possible as illustrated by intermediates **A-D**. Intermediates **A/B** lead to the 14-membered ring, while **C/D** lead to the desired 15-membered ring. Regioisomeric intermediates **A/C** proceed through an oxametallacycle pathway thought to form from an aldehyde insertion to a nickel-alkyne

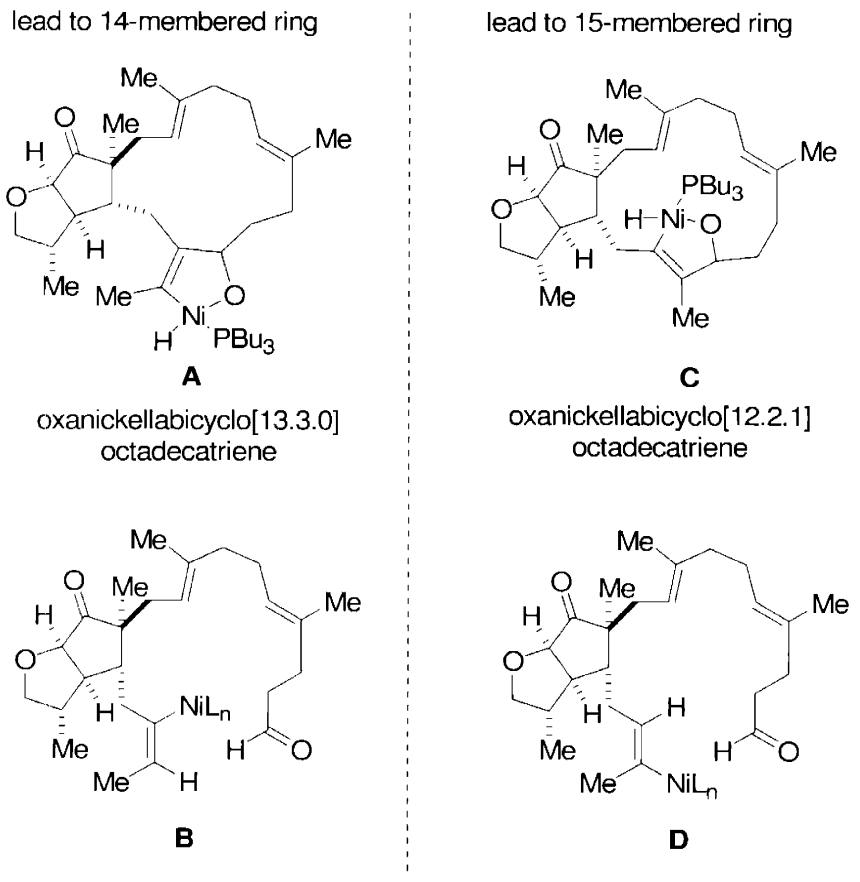
[33] Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.

[34] Mahandriu, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698.

complex. Regioisomeric intermediates **B/D** may form as a result of hydrometallation across the alkyne to form two possible vinyl nickel intermediates.

Our experiments would suggest that putative intermediates **C/D** leading to the 15-membered ring were highly disfavored relative to **A/B**. This bias toward **A/B** was originally postulated to have been caused by either the steric congestion of the C19 quaternary methyl group and/or the trans relationship of the C1/C15 stereocenters at the 5,15 ring junction. However, with no detectable formation of the 15-membered ring upon cyclization in the absence of C19, it appears more likely that the high barrier to **C/D** formation may be linked to the latter which was not a factor included in model substrate **12**. If the cyclization proceeds via an oxametallacyclopentene (**A** vs. **C**), the bicyclo[12.2.1] system in intermediate **C**, possessing a bridgehead olefin, may not form as readily as the bicyclo[13.3.0] system in **A**. Likewise, under the hydrometallation pathway (**B** vs. **D**), incorporation of an extra (*E*)-double bond in **D** may be disfavored over **B** (exocyclic olefin) upon macrocycle formation. Moreover, the added strain created by the trans relationship of C1/C15 stereocenters may also bias the reaction to exclusive 14-membered ring formation. Unfortunately, this hypothesis could not be tested directly as attempts to synthesize substrates with a cis relationship of the C1/C15 stereocenters led to epimerization to the thermodynamic trans product under all conditions attempted.

Figure 4. Putative intermediates in the formation of 14 and 15 membered rings.

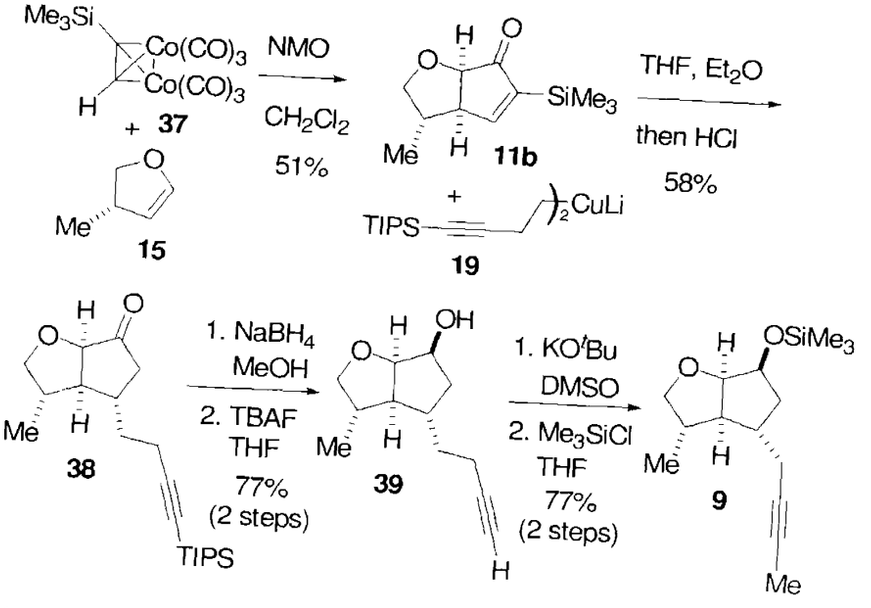


Intermolecular Alkyne-Aldehyde Reductive Coupling Approach

Since the intramolecular approach consistently afforded 14-membered ring products, we aimed to overcome this regioselectivity problem through the assembly of the allylic alcohol by way of an *intermolecular* reductive coupling using methods related to those we had developed in our laboratory.[10] The synthesis of the alkyne fragment began with an NMO-promoted, intermolecular Pauson-Khand reaction between dihydrofuran **15** and the hexacarbonyldicobalt complex of trimethylsilylacetylene (**37**) to afford oxabicyclo[3.3.0]octenone (**11b**) in 51% yield (Scheme 12). As observed in the Pauson-Khand reaction involving the farnesyl derived alkyne hexacobaltdicarbonyl complex (**16**), (Scheme 5), no other diastereomers nor any of three other possible regioisomers could be detected (^{1}H NMR). Conjugate addition of a lithium dialkyl cuprate (**19**) to afford **38** occurred with complete diastereoselectivity as observed before.

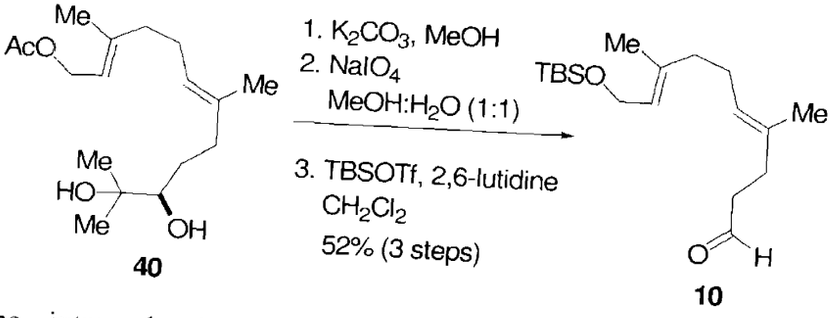
In order to place the triple bond in the proper position required for the catalytic reductive coupling, terminal acetylene (**39**) was isomerized with KO*t*-Bu in DMSO and the secondary alcohol was protected as the trimethylsilyl ether **9** in 77% yield over 2 steps.

Scheme 12.



Synthesis of the aldehyde coupling partner (**10**) commenced with diol **40**, obtained from site selective catalytic dihydroxylation of farnesyl acetate.[23] The acetate ester was cleaved quantitatively under basic conditions, and a sodium periodate cleavage of the unpurified triol afforded the resultant aldehyde that was protected as its TBS ether (**10**) in 52% yield over the two steps (Scheme 13).

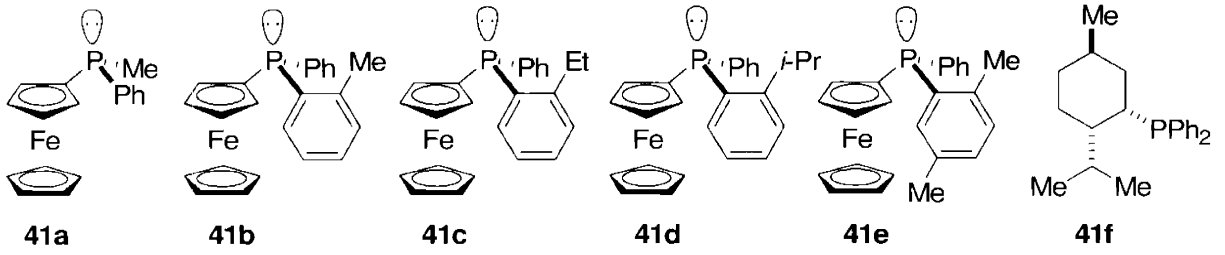
Scheme 13.



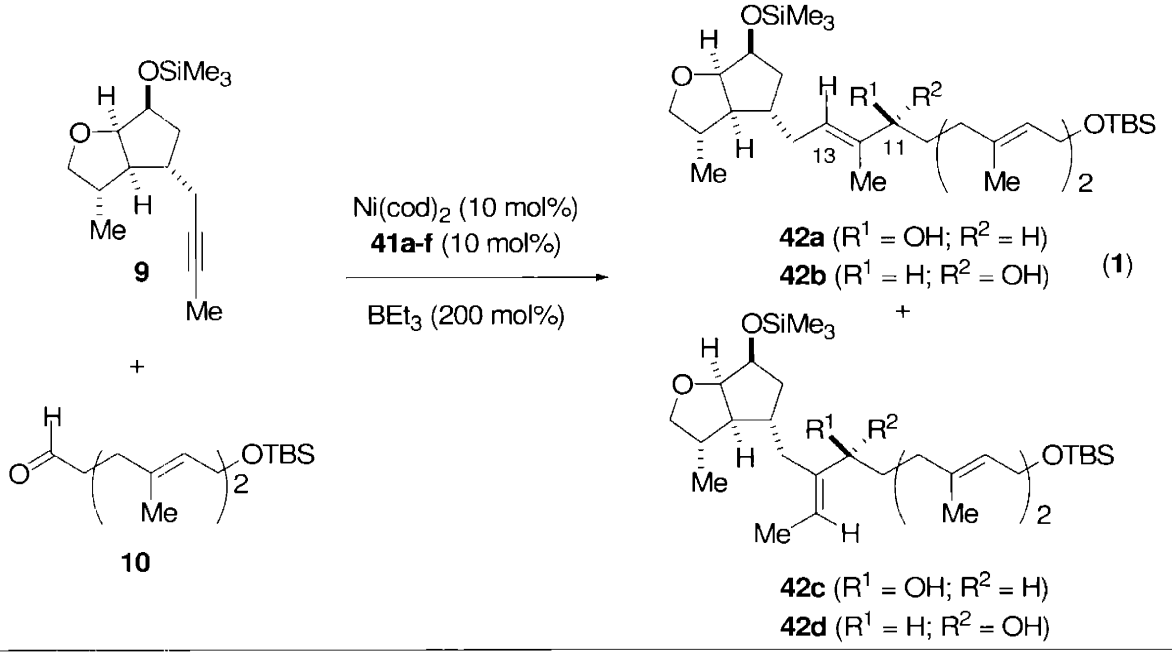
In the intramolecular reductive coupling approach, we had hoped for diastereocontrol of the C11 carbinol through a conformational bias during ring formation and/or ligand control. The absence of such a conformational bias in the intermolecular

fragment coupling, however, predicted that diastereocontrol would be low since the closest stereocenter would be two carbons removed from the site of reaction. In addition, little regiocontrol would also be expected as the catalytic process would have to differentiate between methyl vs. *i*-Bu on the alkyne (CH_3 vs $CH(R)(R')CH_2$). As expected, the use of PBu_3 offered no level of diastereocontrol (1:1). We were pleased, however, to discover that our recently developed ferrocenyl-*P*-chiral phosphine ligands[10] afforded a good level of control at the C11 stereocenter (Table 1). After evaluating a variety of these ligands, we found that a catalyst incorporating *(R)*–**41e** favored the diastereomer (2:1) and regioisomer (2.6:1) corresponding to (–)-terpestacin in a combined yield of 85% (Table 1, **42a**-**42d**). Therefore, the desired allylic alcohol **42a** was obtained in an overall yield of 41% (85% x 2/3 x 2.6/3.6). The diastereomer corresponding to 11-*epi*-terpestacin (**42b**), (terpestacin numbering) was obtained with *equal* regioselectivity and *equal and opposite* diastereoselectivity simply by using *(S)*–**41e**, the enantiomer of the ligand used in the terpestacin-series coupling. Notably, the use of **41a** provided the best diastereoselectivity (3:1) of all ligands examined. However, **41a** also gave reduced regiocontrol (2:1) and chemical yield (70%), corresponding to an overall 35% (70% x 3/4 x 2/3) yield of desired **42a**.

Table 1



41a **41b** **41c** **41d** **41e** **41f**

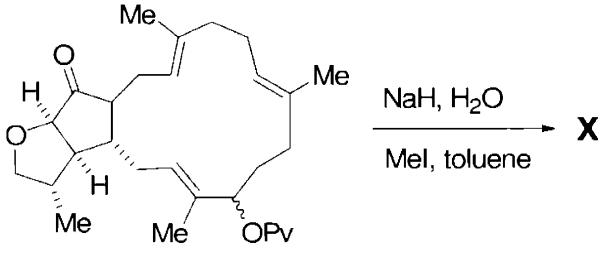


Entry	Ligand	Solvent	Temp (°C)	Yield (%) [a]	Regioselectivity [b]	Diastereoselectivity [c] (C11)
1	Bu_3P	toluene	23	70	1.5:1	1:1
2	**41f**	EtOAc	23	68	1:1.5	2:1
3	**41f**	EtOAc:DMI (1:1)	23	77 [d]	n/a	---
4	**41a**	EtOAc	23	81	2:1	2.5:1
5	**41a**	EtOAc	0	70	2:1	3:1
6	**41a**	EtOAc:DMI (1:1)	0	18	2:1	2:1
7	**41a**	THF	0	46	1.8:1	3:1
8	**41a**	toluene	0	35	2:1	3:1
9	**41a**	acetone	0	65	2:1	3:1
10	**41b**	EtOAc	0	65	2:1	2:1
11	**41c**	EtOAc	0	75	2:1	2:1
12	**41d**	EtOAc	0	83	2.5:1	2:1
13	**41e**	EtOAc	0	85	2.6:1	2:1
14	**41e**	EtOAc	-12	52	2.9:1	3:1
15	**41d**	EtOAc	-12	57	3:1	3:1

[a] Combined yield of all allylic alcohol products (**42a-42d**). [b] Regioselectivity (**42a** + **42b**/**42c** + **42d**) determined by ^{1}H NMR. [c] Estimated diastereoselectivity by ^{1}H NMR. [d] "Alkylative coupling" (Et at C13 instead of H).

The choice of protecting group on the newly formed allylic alcohol would prove crucial into the completion of the synthesis. The main factors considered were balancing functional group compatibility with ease of removal following the late stage alkylation (installation of C19). While protecting the secondary allylic alcohol as a pivaloyl ester may appear to be an attractive choice because of its ease in introduction and removal, we found that this protective group was not compatible under our alkylation conditions (Scheme 14). Attempted methylation of the pivaloyl-ester **Pv-45** resulted in the isolation of multiple unidentifiable products.[35]

Scheme 14.

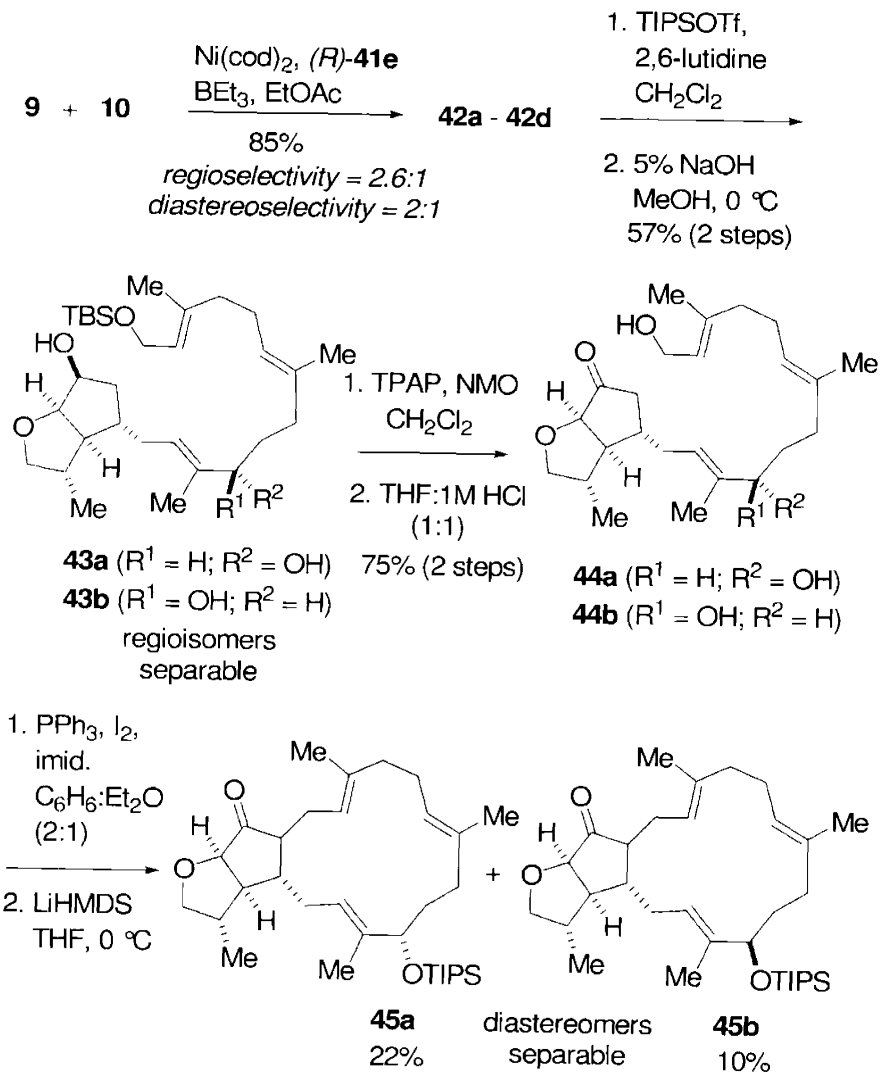


Pv-45

Therefore, the triisopropylsilyl ethers of **42a-42d** were prepared, and the trimethylsilyl groups were removed using 5% sodium hydroxide to give **43a-43d** in methanol in 80% for the two steps. At this stage, the regioisomers formed in the fragment coupling reaction were separated and the desired regioisomers (**43a-43b**) were oxidized under Ley's conditions to afford the desired ketones in 89% yield. After removal of the primary TBS groups (1:1 1M HCl:THF) in 84% yield, **44a** and **44b** were converted to the allylic iodides and treated with LiHMDS to afford a separable mixture of macrocycles **45a** and **45b** via a ketone enolate alkylation in an overall two-step yield of 32% (Scheme 15).

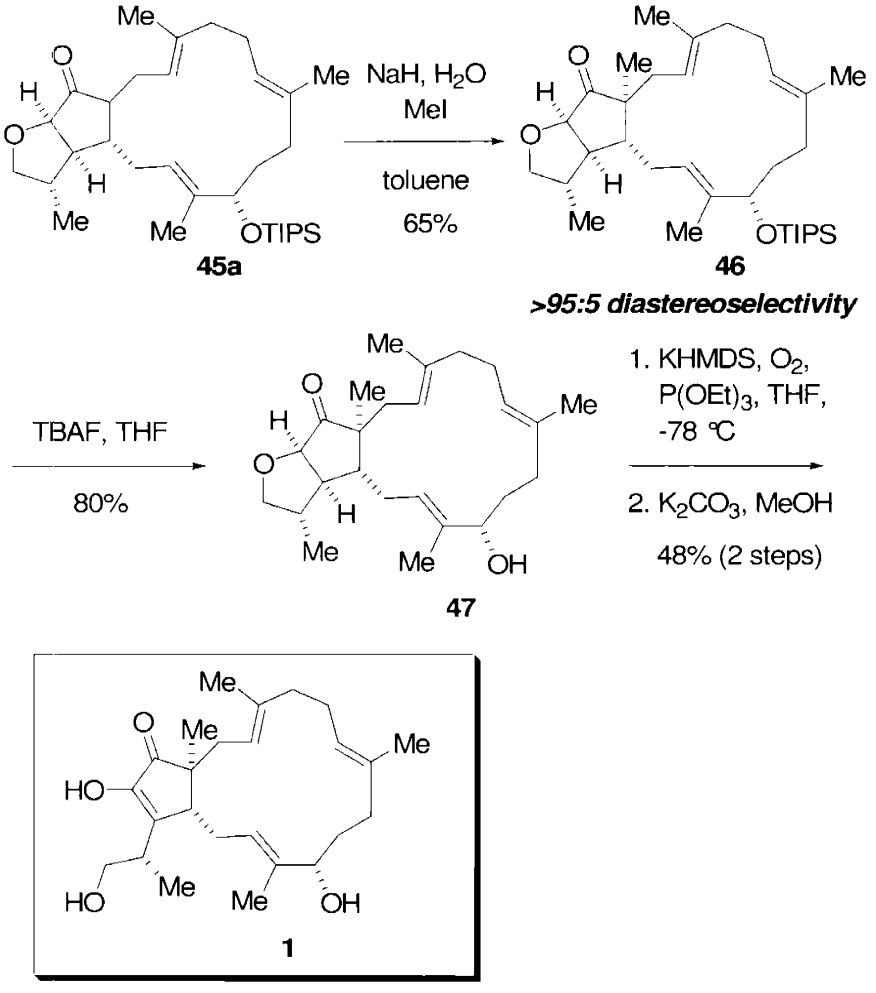
[35] From the crude ^{1}H NMR, it appeared that the pivaloyl-ester was cleaved.

Scheme 15.



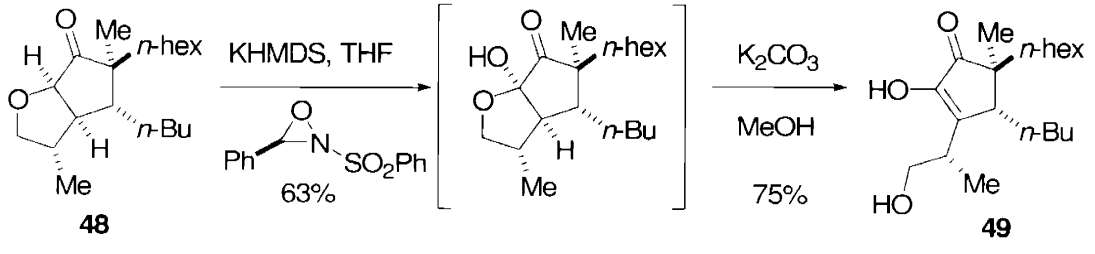
As we observed in the intramolecular reductive coupling approach, installation of the critical quaternary methyl group (C19) at C1 was best accomplished using methyl iodide, and sodium hydroxide generated from sodium hydride (300%) and H_2O (200 mol% relative to **45a**) affording the desired product **46** in >95:5 diastereoselectivity (nOe), with no trace of methylation at the 5,5-ring junction (Scheme 16).

Scheme 16.



Completion of the synthesis of (–)-terpestacin required three further transformations. The TIPS protective group was smoothly removed with TBAF to afford the desired secondary alcohol (**47**). Despite success with Davis' oxaziridine on related model **48**, to afford **49**, utilizing those analogous conditions on **47** did not result in the desired transformation (Scheme 17).

Scheme 17.

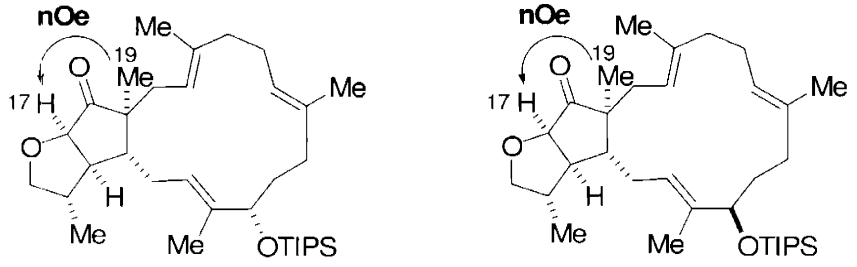


Fortunately, treatment of **47** with 300 mol% of potassium hexamethyldisilazane and $P(OEt)_3$ under an atmosphere of O_2 effected an enolate hydroxylation [36] of the tetrahydrofuran that underwent ring opening with potassium carbonate in methanol to furnish **1**. Synthesis of **2** was prepared utilizing the analogous method. Overall, preparation of **1** and **2** each required 19 steps from β-methallyl alcohol (longest linear sequence).

Comparison of 1 and 2 to Natural Samples of Terpestacin and Siccanol.

The spectroscopic data we obtained for our synthetic (–)-terpestacin were identical in all respects to those previously reported for natural and synthetic material. In comparing of (–)-terpestacin to 11-*epi*-terpestacin, we observed that the chemical shifts, particularly at protons 3, 13, 15 and 19 were significantly different from each other as illustrated in Table 2. Remarkably, the proton chemical shift at C11 is identical for 11-*epi*-terpestacin and (–)-terpestacin while the biggest difference lies between C19 (δ 0.99 vs δ 1.13) suggesting that the C19 diastereomer might have been obtained in the alkylation of ketone **45b**. To eliminate this possibility, separate NMR experiments conducted with **46** and 11-*epi*-**46** showed an nOe between H17 and H19 in both cases, consistent with the conclusion that both compounds have the same relative configurations about C19.

Figure 5. Both 46 and 11-*epi*-46 exhibit nOe between H19 and H17.

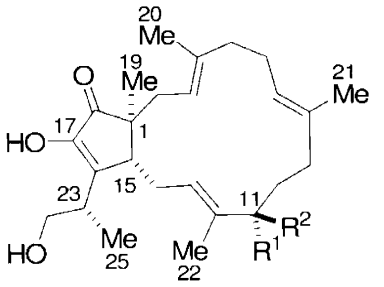


46 11-*epi*-**46**

[36] (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968,** *33*, 3294. (b) Harwig, W.; Born, L. *J. Org. Chem.* **1987,** *52*, 4352. (c) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1988,** *53*, 4724.

Having established that 11-*epi*-**46** leads to 11-*epi*-terpestacin, a comparison of siccanol provided to us from Prof. Miyagawa did not agree with our data for synthetic 11-*epi*-terpestacin and to our surprise, was *indistinguishable* from (–)-*terpestacin*, confirming a structural reassignment – "siccanol" is (–)-terpestacin, not 11-*epi*-terpestacin (Table 2).

Table 2. Selected ^{1}H NMR data for terpestacin, 11-*epi*-terpestacin, and siccanol



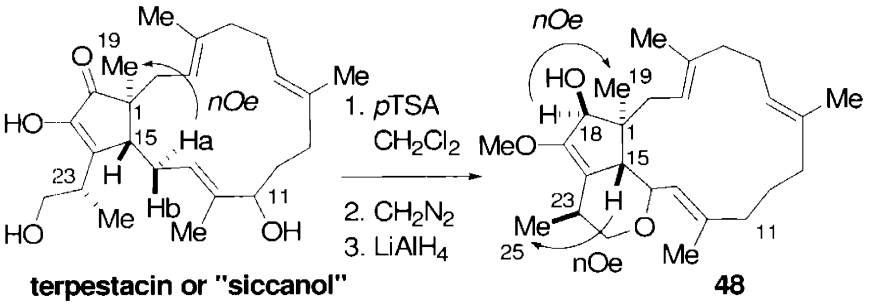
1 (R^1 = OH; R^2 = H; terpestacin)
2 (R^1 = H; R^2 = OH; 11-*epi*-terpestacin)

Carbon	terpestacin (Oka, Myers, Jamison)	11-*epi*-terpestacin (Jamison)	siccanol (from Miyagawa)
2	1.68-1.80, 2.40	2.05-2.27	1.75, 2.36
3	**5.25**	**5.34**	**5.25**
5	1.90-2.04, 2.22-2.30	1.98, 2.05-2.27	2.01, 2.24
6	2.09-2.12, 2.22-2.30	2.05-2.27	2.11, 2.26
7	5.14	5.13	5.13
9	1.68-1.80, 2.09-2.12	1.70-1.88, 2.05-2.27	1.78, 2.18
10	1.68-1.80	1.70-1.88	1.70, 1.75
11	4.06	4.06	4.07
13	**5.41**	**5.50**	**5.38**
14	1.90-2.04, 2.45	1.70-1.88, 2.50	1.92, 2.44
15	**2.72**	**2.57**	**2.72**
19	**1.01**	**1.13**	**0.99**
23	2.68	2.7	2.66
24	3.83, 3.90	3.83, 3.89	3.80, 3.85
25	1.29	1.30	1.29

The sequence of events that led Miyagawa to his original assignment of "siccanol" as 11-*epi*-terpestacin can be explained by his original structural elucidation studies and an unusual chain of events dating back to Oka's discovery of terpestacin nearly ten years before. Paralleling the work of Oka, Miyagawa's structural

determination of "siccanol" began with differentiating the protons on C14 (Ha and Hb) by way of coupling to H15 (Scheme 18). An nOe between Ha and H19 indicated the trans relationship between H15 and H19. Following acid–catalyzed elimination, methylation of the enol with diazomethane, and reduction to afford **50**, an nOe between H15 and H25 established the *relative* relationships of stereocenters C1, C15 and C23. The *absolute* configuration of C18 was determined through the chiral exciton method after benzoylation of **50** and from the presence of an nOe between H18 and H19, the *absolute* configurations of the remaining stereocenters were deduced, except for C11. A Mosher ester analysis led to the assignment of the C11 stereocenter as (*R*), consistent with 11-*epi*-terpestacin, whereas Oka assigned the C11 stereocenter as (*S*), also based on a Mosher analysis. Oka then proceeded further to obtain an X-ray crystal structure of terpestacin to confirm all relative stereocenters but Miyagawa did not characterize "siccanol" crystallographically.

Scheme 18. Structural elucidation of terpestacin (Oka) and siccanol (Miyagawa)



terpestacin or "siccanol" **48**

Experiment	Conclusion
- Examination of coupling constants of Ha and Hb to H15.	- Differentiates of Ha and Hb
- nOe between Ha and H19	- establishes trans relationship of H15 and H19
- nOe between H15 and H25 observed in **48**	- establishes relative relationships of C1, C15, and C23
- nOe between H18 and H19	- relative configuration of C18 and C19 established
- chiral exciton analysis of benzylester of **48**	- absolute configuration of C1, C15, and C23 assigned

Since the specific rotation Miyagawa obtained for "siccanol" did not match the literature value as reported by Oka or Tatsuta, it appears plausible that the authors concluded that they had isolated either the enantiomer or a diastereomer of terpestacin. However, isolation of the enantiomer could be quickly ruled out since the compound possessed the same absolute configurations at C1, C15 and C23 as determined by chiral exciton.

Since Myers' investigations were published at about the same time (March, 2002, J. Am. Chem. Soc. ASAP) as Miyagawa's original report of siccanol, neither Myers nor Miyagawa would be aware of each other's findings except by means other than the chemical literature. Given that the only additional information known at the time was Gräfe's report on the isolation of "terpestacin's enantiomer", Miyagawa made the only obvious conclusion that would account for the all the available data at the time: The

unknown in their possession was 11-*epi*-terpestacin. Obtaining an X-ray crystal structure (as with Myers or Oka) to confirm their Mosher ester analysis would have likely led to further investigations since these two pieces of data would have disagreed. Unfortunately, a crystal structure was not obtained, thereby relying on the incorrectly evaluated Mosher ester analysis as the only source of C11 assignment.

Based on the following excerpt from their report, a plausible explanation for the misassignment could be that the authors had not correctly assigned the absolute configuration of the Mosher ester after treatment with the acid chloride.

> "After the hydroxyl group at C-24 had been protected by converting the pivaloyl ester **8**, a set of (*R*)- and (*S*)-MTPA esters was prepared by reacting **8** with the *respective* MTPA chlorides in pyridine."

Hence, our hypothesis is that the artefactual specific rotation value reported by Oka and Tatsuta (chloroetherification by K_2CO_3 in $CHCl_3$), steered the authors away from the correct C11 assignment and the Mosher ester analysis is the ultimate cause of the discrepancy between the assignments of siccanol by Miyagawa as 11-*epi*-terpestacin and our finding that siccanol is actually terpestacin itself.

Conclusion

We have described the enantioselective synthesis of terpestacin and 11-*epi*-terpestacin to revise the structural assignment of siccanol. Highlights in this route include a highly regio- and diastereoselective Pauson-Khand reaction which proved critical in setting the C23 stereocenter as well as generating terpestacin's diketone. A water-mediated, late stage, highly diastereoselective alkylation was instrumental to installing the quaternary C19 methyl group. Finally, a ligand controlled nickel-catalyzed reductive coupling of alkyne **9** and aldehyde **10** allowed for the formation of C11 stereoselectively. These key steps led to the generation of both terpestacin and 11-*epi*-terpestacin utilizing our reductive coupling of alkynes and aldehydes, a strategy which was instrumental in confirming that siccanol is not 11-*epi*-terpestacin but in fact, terpestacin itself.

Experimental Section

General Information. Unless otherwise noted, all reactions in exclusively organic solvents were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran and diethyl ether were distilled from a blue solution of sodium benzophenone ketyl. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid, potassium permanganate ($KMnO_4$), or ceriumammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh).[37] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Inova 500 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm), or C_6D_6 (128.39 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Tesla Fourier Transform Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical Rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm.

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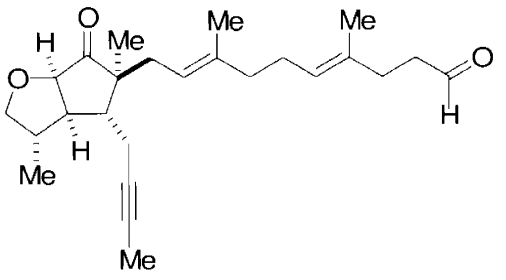
[37] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

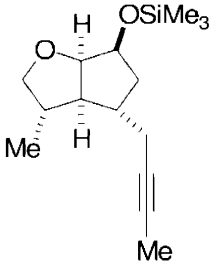


10-(4-But-2-ynyl-3,5-dimethyl-6-oxo-hexahydro-cyclopenta[*b*]furan-5-yl)-4,8-dimethyl-deca-4,8-dienal (8): To a solution of triene (**21**) (25 mg, 0.06 mmol) in 1:1 *tert*-butanol/water (1 mL) at 0 °C was added $(DHQD)_2Phal$ (1 mg, 0.012 mmol), methanesulfonamide (6 mg, 0.06 mmol), potassium carbonate (25 mg, 0.18 mmol), potassium ferricyanide (III) (60 mg, 0.18 mmol) and stirred for 5 minutes. Osmium tetroxide (15 mg, 2%wt in *t*-BuOH, 0.012 mmol) was introduced and the reaction mixture was stirred for 24 h and quenched with saturated sodium metabisulfate (3 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organics dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude yellow oil was purified by silica gel chromatography (60:40 hexanes:ethyl acetate) to afford diol. The diol (7 mg, 0.016 mmol) was taken up in methanol (0.5 mL) and cooled to 0 °C. Sodium periodate (24 mg, 0.11 mmol) was dissolved in water (0.5 mL) and added to the reaction mixture *slowly*. After completion of the reaction was ascertained by TLC, water (2 mL) was added and extracted with diethyl ether (3 x 3 mL). The organics were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (90:10 hexane:ethyl acetate) to afford **8** (6 mg, 25% over 2 steps). R_f (85:15 hexane:ethyl acetate): 0.16.

^1H NMR (500 MHz, CD_6D_6): δ 9.37 (t, J = 1.5 Hz, 1H), 5.31 (t, J = 6.1 Hz, 1H), 5.05 (t, J = 6.7 Hz, 1H), 4.12 (d, J = 7.6 Hz, 1H), 3.70 (dd, J^1 = 5.5 Hz, J^2 = 8.5 Hz, 1H), 3.40 (dd, J^1 = 2.4 Hz, J^2 = 8.5 Hz, 1H), 2.47 (dd, J^1 = 5.8 Hz, J^2 = 8.5 Hz, 1H), 2.29 (dd, J^1 = 9.1 Hz, J^2 = 14.6 Hz, 1H), 2.05 (m, 12 H), 1.68 (m, 1H), 1.60 (s, 3H), 1.53 (t, J = 2.7 Hz, 3H), 1.40 (s, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.69 (s, 3H); ^{13}C NMR (125 MHz, CD_6D_6): δ 217.3, 201.0, 138.0, 134, 125.6, 121.3, 81.6, 78.2, 75.3, 53.4, 52.0, 45.4, 42.6, 41.5, 40.4, 35.1, 32.4, 30.6, 27.2, 20.4, 19.8, 19.1, 16.7, 16.3, 3.7

IR (thin film/NaCl): 2921, 2851, 1747, 1724, 1456, 1377, 1098 cm^{-1}

EI *m/z* calc'd for $C_{25}H_{36}O_3Na$: 407.2557, found: 407.2549.



(4-But-2-ynyl-3-methyl-hexahydro-cyclopenta[*b*]furan-6-yloxy)-trimethyl-silane (9):

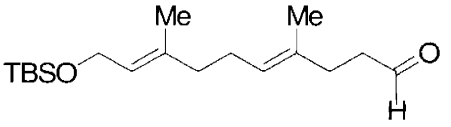
To a solution of **(–)-39a** (1.39g, 7.2 mmol) in THF (50 mL) was added triethylamine (2.0 mL, 14.3 mmol) and chlorotrimethylsilane (1.4 mL, 10.7 mmol). The reaction mixture was stirred at room temperature for 1 h, quenched with water (80 mL) and extracted with diethyl ether (3 x 75 mL). The organics were combined, dried with $MgSO_4$, filtered and concentrated *in vacuo* to afford a yellow oil. The crude product was purified by silica gel chromatography 95:5 (hexane:ethyl acetate) to afford **(–)-9** as a clear colorless oil (1.63 g, 86%). R_f (95:5 hexane:ethyl acetate): 0.38

^1H NMR (500 MHz, $CDCl_3$): δ 4.21 (dd, J^1 = 4.6 Hz, J^2 = 6.1 Hz, 1H), 4.12 (m, 1H), 3.96 (dd, J^1 = 6.1 Hz, J^2 = 8.2 Hz, 1H), 3.37 (dd, J^1 = 5.5 Hz, J^2 = 8.5 Hz, 1H), 2.09 (m, 2H), 2.0 (m, 1H), 1.85 (m, 3H), 1.74 (t, J = 2.7 Hz, 3H), 1.52 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.8, 77.9, 76.3, 76.3, 74.2, 55.2, 42.0, 41.4, 38.0, 25.3, 18.4, 3.5, 0.2.

IR (thin film/NaCl): 2956, 2921, 1456.1438, 1370, 1249, 1101, 841, 749 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{15}H_{26}O_2SiNa$: 289.1594, found: 289.1592.

$[\alpha]_D$ = –35 (*c* 1.0, EtOH)

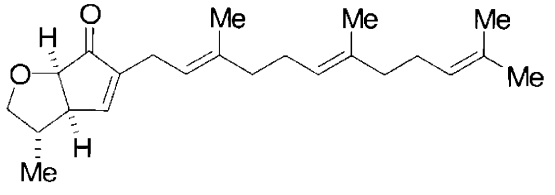


10-(*tert*-Butyl-dimethyl-silanyloxy)-4,8-dimethyl-deca-4,8-dienal (10): To a solution of **40a** (6.2 g, 32 mmol) in dichloromethane (150 mL) was added 2,6-lutidine (11.0 mL, 95 mmol) and cooled to -78 °C. After 10 min, *tert*-butyldimethylsilyltrifluoromethanesulfonate (10.9 mL, 48 mmol) was slowly added and stirred at -78 °C for 2 h. The reaction mixture was diluted with water (200 mL) and the organic layer was collected. The aqueous layer was extracted with dichloromethane (2 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (70:30 hexane:ethyl acetate) afforded **10** (7.5 g, 76%). R_f (95:5 hexane:ethyl acetate): 0.34

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.76 (t, J = 1.8 Hz, 1H), 5.30 (t, J = 6.4 Hz, 1H), 5.15 (t, J = 6.7 Hz, 1H), 4.20 (d, J = 6.4 Hz, 2H), 2.52 (m, 2H), 2.32 (t, J = 7.3 Hz, 2H), 2.10 (m, 2H), 2.03 (m, 2H), 1.62 (s, 6H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.8, 136.7, 133.3, 125.3, 124.8, 60.5, 42.3, 39.5, 32.0, 26.4, 26.2, 25.9, 18.6, 16.5, 16.3, –4.8.

IR (thin film/NaCl): 2955, 2929, 1728, 1670, 1472, 1255, 1066, 836, 776 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{18}H_{34}O_2SiNa$: 333.2220, found: 333.2223.



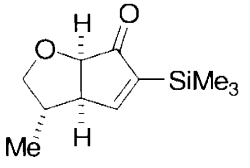
3-Methyl-5-(3,7,11-trimethyl-dodeca-2,6,10-trienyl)-2,3,3a,6a-tetrahydro-cyclopenta[*b*]furan-6-one (11a): To a mixture of cobalt complex (**16**) (4.13 g, 8.0 mmol) and dihydrofuran (**15**) (3.5 mL, 40 mmol) in 1,2-dichloroethane (80 mL) was added *n*-butylmethyl sulfide (4.9 mL, 40 mmol) and heated to 75-77 °C for 96 h. The

mixture was concentrated *in vacuo*, diluted with hexanes (100 mL) and filtered through a plug of silica gel. Ethyl acetate (100 mL) was then added to the filtrate and filtered into a separate flask to collect the desired product. The crude material was concentrated *in vacuo* and purification by silica gel chromatography (92:8 hexanes:ethyl acetate) afforded **11a** (1.44 g, 53%). R_f (80:20 hexane:ethyl acetate): 0.4

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (m, 1H), 5.20 (m, 1H), 5.09 (m, 2H), 4.37 (d, J = 5.5 Hz, 1H), 3.68 (dd, J^1 = 4.9 Hz, J^2 = 8.8 Hz, 1H), 3.59 (dd, J^1 = 2.4 Hz, J^2 = 8.8 Hz, 1H), 2.95 (m, 1H), 2.85 (d, J = 7.0 Hz, 2H), 2.06 (m, 12H), 1.68 (s, 3H), 1.60 (s, 6H), 1.12 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.4, 157.2, 145.9, 138.2, 135.4, 131.6, 124.4, 119.4, 80.5, 74.2, 51.0, 40.0, 39.8, 38.2, 26.9, 26.6, 25.9, 23.7, 19.0, 17.9, 16.2

IR (thin film/NaCl): 2926, 1715, 1625, 1452, 1378, 1344, 1231, 1086, 921 cm^{-1}

EI *m/z* calc'd for $C_{23}H_{34}O_2$: 342.2559, found [M+H]: 343.2636.



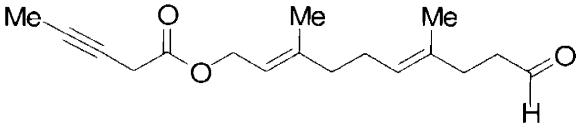
3-Methyl-5-trimethylsilanyl-2,3,3a,6a-tetrahydro-cyclopenta[*b*]furan-6-one (11b): To a solution of **15** (6.8 g, 80 mmol) in dichloromethane (250 mL) was added the dicobalthexacarbonyl complex of trimethyl acetylene (6.1 g, 16 mmol), cooled to 0 °C, and added NMO (12.1 g, 100 mmol) in a single portion. The reaction mixture was allowed to warm to room temperature, stirred 16 h and quenched with 10% HCl (200 mL). The aqueous layer was extracted with dichloromethane (2 x 200 mL) and organic layers combined. This was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to afford a brown oil. The crude product was purified by silica gel chromatography (85:15 hexanes:ethyl acetate) to afford **(–)-11b** (1.71 g, 51%) in >95% ee. The enantiomeric excess was determined by HPLC (chiracel-OD : 0.5% *i*PrOH/hexanes) t_R (minor) 30.1 min, t_R (major) 32.2 min. R_f (80:20 hexane:ethyl acetate): 0.36

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 2.7 Hz, 1H), 4.25 (d, J = 5.5 Hz, 1H), 3.58 (dd, J^1 = 5.2 Hz, J^2 = 8.8 Hz, 1H), 3.52 (dd, J^1 = 2.4 Hz, J^2 = 8.8 Hz, 1H), 2.98 (m, 1H), 2.11 (m, 1H), 1.97 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.0, 171.2, 147.4, 80.6, 73.8, 54.1, 38.0, 19.0, -1.9.

IR (thin film/NaCl): 2960, 2865, 1697, 1573, 1454, 1287, 1243, 1079, 936, 836 cm^{-1}

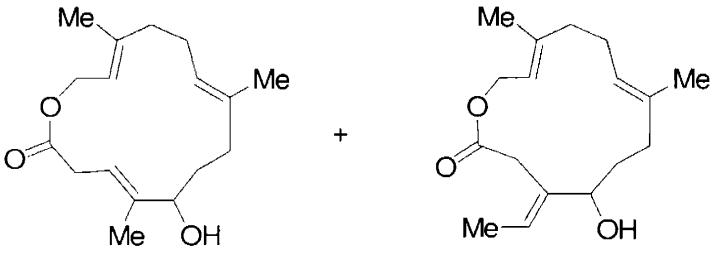
HRMS-ESI(NaI) *m/z* calc'd for $C_{11}H_{18}O_2SiNa$: 233.0968, found: 233.0966.

$[\alpha]_D$ = –56.7 (*c* 1.0, EtOH)



Pent-3-ynoic acid 3,7-dimethyl-10-oxo-deca-2,6-dienyl ester (12): To a solution of alcohol (**40a**) (0.22 g, 1.1 mmol) in dichloromethane (20 mL) at 0 °C was added DMAP (13 mg, 0.11 mmol) followed by a solution of pent-3-ynoic acid (0.13 g, 1.3 mmol) in dichloromethane (5 mL). After 5 minutes, DCC (0.29 g, 1.4 mmol) was added and the reaction mixture was stirred for 1 h. The ice bath was removed after TLC revealed that the reaction was incomplete and the solution was stirred for another 6 h at room temperature. The reaction was diluted with dichloromethane (50 mL), filtered through a plug of silica gel, and concentrated *in vacuo*. Purification of the crude mixture by silica gel chromatography (90:10 hexane:ethylacetate) afforded **12** (113 mg, 37%) as a clear colorless oil. R_f (90:10 hexane:ethyl acetate): 0.2.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (t, J = 1.8 Hz, 1H), 5.27 (dt, J^1 = 1.2 Hz, J^2 = 7.0 Hz, 1H), 5.07 (dt, J^1 = 1.2 Hz, J^2 = 7.0 Hz, 1H), 4.58 (d, J = 7.3, 2H), 3.18 (dd, J^1 = 2.7 Hz, J^2 = 5.2 Hz, 2H), 2.46 (dt, J^1 = 2.1 Hz, J^2 = 7.6 Hz, 2H), 2.26 (t, J = 7.3 Hz, 2H), 2.06 (m, 2H), 2.0 (m, 2H), 1.77 (t, J = 2.7 Hz, 3H), 1.65 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.6, 169.0, 142.4, 133.6, 124.7, 118.2, 79.2, 70.7, 62.3, 42.1, 39.3, 31.8, 26.0, 16.5, 16.2, 3.7.



13 **14**

6-Hydroxy-5,9,13-trimethyl-oxacyclopentadeca-4,9,13-trien-2-one (13) and 4-Ethylidene-5-hydroxy-8,12-dimethyl-oxacyclotetradeca-8,12-dien-2-one (14): To a solution of $Ni(cod)_2$ (11 mg, 0.040 mmol), tributylphosphine (20 μL, 0.080 mmol), and triethylborane (0.40 mL, 2.0 M toluene, 0.80 mmol) in toluene (19.6 mL) was added a solution of the alkyne (**12**) (113 mg, 0.40 mmol) and stirred 12 h. The reaction mixture was quenched with saturated ammonium chloride (50 mL) and the aqueous layer extracted with ethyl acetate (3 x 70 mL). The organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (90:10 hexanes:ethyl acetate) to afford two regioisomers **13** (14 mg, 12 %) R_f (80:20 hexane:ethyl acetate): 0.25, and **14** (10 mg, 8 %) R_f (85:15 hexane:ethyl acetate): 0.4

For compound (**13**): (15 membered ring) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (t, J = 7.0 Hz, 1H), 5.37 (t, J = 3.3 Hz, 1H), 4.93 (s, 1H), 4.68 (dd, J^1 = 7.3 Hz, J^2 = 11.3 Hz, 1H), 4.50 (dd, J^1 = 7.6 Hz, J^2 = 11.3 Hz, 1H), 3.12 (dd, J^1 = 9.5 Hz, J^2 = 13.4 Hz, 1H), 2.99 (m, 1H), 2.00-2.18 (m, 6H), 1.75-1.85 (m, 3H), 1.72 (s, 3H), 1.66-1.70 (m, 2H), 1.65 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.5, 144.1, 139.1, 134.3, 124.0, 121.0, 120.9, 77.0, 60.5, 38.4, 35.5, 34.5, 30.2, 23.7, 15.8, 15.6, 11.1

IR (thin film/NaCl): 3417, 2933, 1733, 1443, 1374, 1247, 1137, 994, 839, 734 cm^{-1}

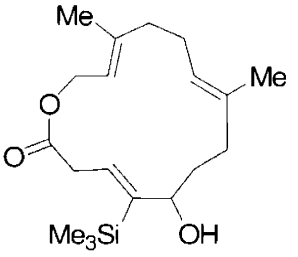
ESI *m/z* calc'd for $C_{17}H_{26}O_3Na$: 301.1774, found: 301.1777

For compound (**14**): (14 membered ring) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (dq, J^1 = 0.9 Hz, J^2 = 7.0 Hz, 1H), 5.25 (t, J = 6.4, 1H), 4.96 (m, 1H), 4.61 (dd, J^1 = 2.7 Hz, J^2 = 7.6 Hz, 1H), 3.95 (dd, J^1 = 4.3 Hz, J^2 = 8.5 Hz, 1H), 3.15 (m, 2H), 2.00-2.30 (m, 7H), 1.71 (d, J = 6.7 Hz, 3H), 1.70 (s, 3H), 1.60-1.66 (m, 2H), 1.58 (s, 3H), 1.51 (m, 1H); ^{13}C

NMR (125 MHz, $CDCl_3$): δ 171.6, 142.2, 134.9, 124.6, 123.4, 120.0, 83.5, 72.6, 61.2, 39.2, 35.3, 33.5, 33.0, 24.5, 16.3, 15.6, 13.7

IR (thin film/NaCl): 3491, 2931, 1735, 1651, 1112, 729 cm^{-1}

EI *m/z* calc'd for $C_{17}H_{26}O_3Na$: 301.1774, found: 301.1780.

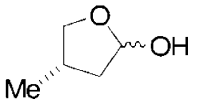


6-Hydroxy-9,13-dimethyl-5-trimethylsilanyl-oxacyclopentadeca-4,8,13-trien-2-one (14a): To a solution of $Ni(cod)_2$ (6.6 mg, 0.024 mmol), tributylphosphine (12 μL, 0.048 mmol), and triethylborane (1.2 mL, 2.0 M toluene, 2.4 mmol) in toluene (8 mL) was added a solution of the trimethylsilyl alkyne (**14b**) (82 mg, 0.24 mmol) and stirred 16 h. The reaction mixture was quenched with saturated ammonium chloride (30 mL) and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (90:10 hexanes:ethyl acetate) to afford **14a** (22 mg, 27%). R_f (85:15 hexane:ethyl acetate): 0.28.

^1H NMR (500 MHz, $CDCl_3$): δ 6.17 (dt, J^1 = 0.9 Hz, J^2 = 7.3 Hz, 1H), 5.50 (dt, J^1 = 1.2 Hz, J^2 = 7.3 Hz, 1H), 4.95 (m, 1H), 4.62 (m, 2H), 4.16 (dd, J^1 = 3.7 Hz, J^2 = 8.8 Hz, 1H), 3.19 (d, J = 7.3 Hz, 2H), 1.72-2.17 (m, 8H), 1.70 (d, J = 1.5 Hz, 3H), 1.67 (bs, 1H), 1.60 (d, J = 0.9 Hz, 3H), 0.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 145.8, 143.5, 135.5, 135.3, 123.7, 120.9, 77.3, 60.8, 38.9, 38.6, 34.7, 34.0, 23.7, 15.8, 15.5, 1.0

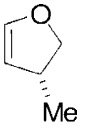
IR (thin film/NaCl): 3445, 2934, 1732, 1663, 1606, 1445, 1251, 1005, 841, 762, 689 cm^{-1}

ESI *m/z* calc'd for $C_{19}H_{32}O_3SiNa$: 359.2013, found: 359.2027.



4-Methyl-tetrahydrofuran-2-ol: A 100 mL round bottom flask charged with β-methallyl alcohol (16.9 mL, 200 mmol), benzene (20 mL), triethylamine (22 mL, 160 mmol), $Rh(Cl)(PPh_3)_3$ (0.10 g, 0.11 mmol) and placed in a steel bomb, which was then pressurized to 1200 psi of 1:1 H_2:CO (synthesis gas) at 80 °C. After stirring 20 h, the reaction mixture was allowed to cool, and the pressure carefully released. After concentration of the solution *in vacuo*, the product was purified by vacuum distillation (80 °C, 50 mmHg) to a clear, colorless oil (16.33 g, 81%).[38]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.51 (t, J = 3.7 Hz, 1H), 4.15 (t, J = 13.3 Hz, 0.6H), 3.92 (t, J = 12.8 Hz, 0.4H), 3.56 (t, J = 13.7Hz, 0.4H), 3.37 (t, J = 12.8Hz, 0.6H), 2.57 (m, 0.4H), 2.29 (m, 0.6H), 2.02 (m, 0.6H), 1.58 (m, 0.6H), 1.46 (m, 0.4H), 1.10 (d, J = 11.0 Hz, 0.4H), 1.04 (d, J = 11.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$):δ 99.4, 98.9, 74.4, 73.6, 41.9, 41.8, 33.4, 31.5, 17.9, 17.3.



3-Methyl-2,3-dihydro-furan (15): To 4-methyl-tetrahydrofuran-2-ol (8.59 g, 85 mmol) was added a catalytic amount of *p*-toluenesulfonic acid and distilled over between 175-200 °C. Water was removed from the biphasic mixture and the organic layer dried with Na_2SO_4. This was filtered through a plug of cotton to provide the title compound (**15**) (8.06 g, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.29 (t, J = 2.4 Hz, 1H), 4.93 (t, J = 2.6 Hz, 1H), 4.37 (t, J = 8.7 Hz, 1H), 3.84 (dd, J^1 = 6.7 Hz, J^2 = 8.7 Hz, 1H), 3.01 (m, 1H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.3, 106.6, 76.9, 36.7, 20.8.

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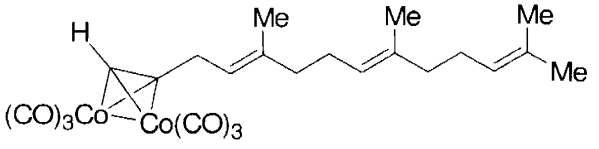
[38] Botteghi, C.; Consiglio, G.; Ceccarelli, G.; Stefani, A. *J. Org. Chem.* **1972**, *37*, 1835.

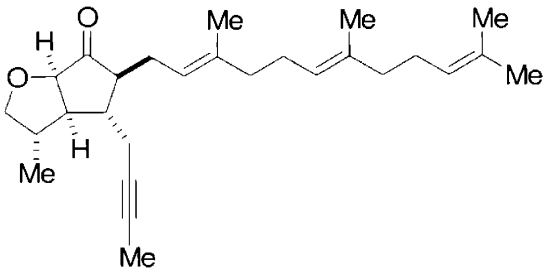
Resolution of (±)-15: To (*1R*)-(+)- -pinene (36.6 mL, 230 mmol) was added borane dimethylsulfide (10 mL, 100 mmol) and the mixture was stirred 1 h. The white precipitate that had formed was diluted with THF (100 mL) and stirred an additional 3 h to ensure full hydroboration. The solvent was removed by vacuum (to remove DMS) and rediluted with THF (100 mL). After cooling to -78 °C, **(±)-15** (15.1 g, 180 mmol) was added and immediately warmed to -25 °C. The white slurry was stirred 16 h and then warmed to 0 °C. At this time a 4:1 solution of 3M NaOH: 30% H_2O_2 was added *slowly* and stirred 2 h. The mixture was extracted with dichloromethane (3 x 100 mL), dried with Na_2SO_4, and filtered. Distillation afforded a solution of enriched **15** that was carried directly onto the next step.



Dicobalthexacarbonyl complex of 5,9,13-Trimethyl-tetradeca-4,8,12-trien-1-yne (16):

To a solution of the alkyne (4.4 g, 19 mmol) in 95 mL of diethyl ether was added dicobalt octacarbonyl (7.15 g, 21 mmol) under an atmosphere of argon. The reaction mixture was stirred at room temperature for 4 h and concentrated *in vacuo*. Silica gel chromatography 99:1 (hexane:ethylacetate) afforded **16** (9.68 g, 99%) as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02 (s, 1H), 5.34 (t, *J* = 7.0 Hz, 1H), 5.12 (d, *J* = 5.8 Hz, 2H), 3.54 (d, *J* = 7.3 Hz, 2H), 2.05 (m, 8H), 1.70 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.0 (m), 137.7, 135.5, 131.4, 124.5, 124.1, 122.3, 97.6, 72.9, 40.0, 39.7, 32.53, 27.0, 26.4, 26.0, 18.0, 16.6, 16.2.

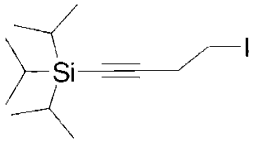


4-But-2-ynyl-3-methyl-5-(3,7,11-trimethyl-dodeca-2,6,10-trienyl)-hexahydro-cyclopenta[*b*]furan-6-one (18): To a mixture of 4 Å molecular sieves in freshly distilled dichloromethane (3 mL) was added *N*-methyl morpholine *N*-oxide (24 mg, 0.2 mmol) and TPAP (2.4 mg, 6.9 μmol) at 0 °C. After stirring for 5 minutes, **20b** (55 mg, 0.14 mmol) in 0.5 mL of dichloromethane was added. The reaction mixture was warmed to room temperature, stirred 4 h and filtered through a pad of silica gel. After eluting with ethyl acetate (3 x 10 mL), the solution was concentrated *in vacuo*. Silica gel chromatography (80:20 hexanes:ethyl acetate) afforded **18** (44 mg, 79%). R_f (85:15 hexane:ethyl acetate): 0.34.

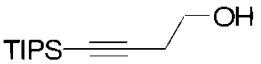
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.11 (m, 3H), 4.41 (d, J = 8.2 Hz, 1H), 3.81 (dd, J^1 = 5.5 Hz, J^2 = 8.5 Hz, 1H), 3.55 (dd, J^1 = 4.0 Hz, J^2 = 8.5 Hz, 1H), 2.31-2.50 (m, 5H), 1.95-2.23 (m, 11H), 1.81 (t, J = 2.7 Hz, 3H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 1.08 (d, J = 7.0Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.0, 137.5, 135.3, 131.5, 124.5, 124.2, 120.8, 78.5, 75.8, 75.4, 52.4, 50.7, 42.9, 40.6, 39.9, 26.9, 26.8, 25.9, 25.9, 23.3, 18.5, 17.9, 16.4, 16.1, 3.7

IR (thin film/NaCl): 2919, 1750, 1667, 1452, 1378, 1110, 1072 cm^{-1}

EI *m/z* calc'd for $C_{27}H_{40}O_2$: 396.3028, found [M+H]: 397.3113.

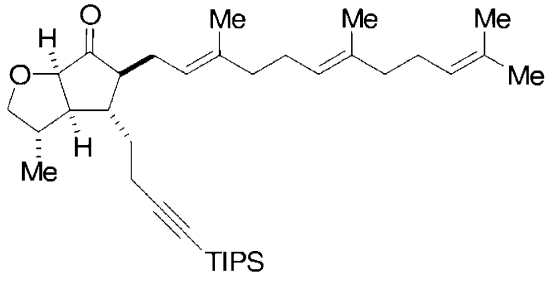


(4-iodo-but-1-ynyl)-triisopropyl-silane (19a): To a solution of triphenylphosphine (11.4 g, 43 mmol) in 3:1 diethyl ether (150 mL): acetonitrile (50 mL) was added iodine (11.0 g, 43 mmol) and stirred for 0.5 h. After the orange precipitate had stopped forming, imidazole (3.0 g, 43 mmol) was added and the reaction mixture was stirred for an additional 5 min before addition of alcohol (**19b**) (6.56 g, 29 mmol). After stirring 1 h, the stir bar was removed and the mixture was concentrated *in vacuo*. The residue was taken up in hexanes (3 x 200 mL) and then filtered through a plug of silica gel. The filtrate was concentrated *in vacuo* to afford **19a** (7.0 g, 72 %).[39] R_f (hexane): 0.6.



19b

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.25 (t, *J* = 7.3 Hz, 2H), 2.84 (t, *J* = 7.3 Hz, 2H), 1.08 (m, 21H)



3-Methyl-4-(4-triisopropylsilanyl-but-3-ynyl)-5-(3,7,11-trimethyl-dodeca-2,6,10-trienyl)-hexahydro-cyclopenta[*b*]furan-6-one (20): To a solution of iodide (**19a**) (1.41 g, 4.2 mmol) in ether (8 mL) at –78 °C was added *tert*-butyllithium (5.6 mL, 1.7M, 8.4

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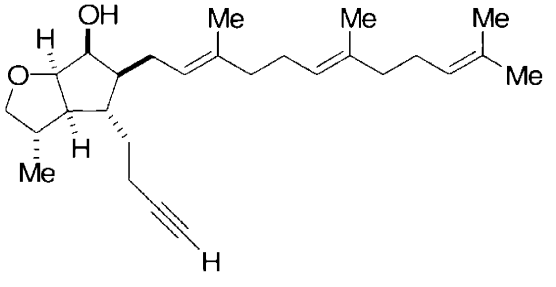
[39] Overman, L. E.; Brown, M. J.; McCann, S. F. *Org. Synth.* **1990,** *68*, 182.

mmol) and stirred 0.25 h. The reaction mixture was warmed to room temperature and allowed to stir 0.5 h. Meanwhile, dimethylsulfide (2.3mL, 53 mmol) was added to a solution of CuI (400 mg, 2.1 mmol) in THF (8mL). After all the CuI had dissolved, the solution was cooled to –78 °C and the generated organolithium solution was added *via cannula* to afford a black slurry. The reaction mixture was warmed to –42 °C for 0.25 h and then recooled to –78 °C. The enone (**11a**) (400 mg, 1.2 mmol) was added and the mixture was allowed to stir for 3.5 h, quenched with a saturated solution of ammonium chloride (30 mL). The biphasic mixture was extracted with ether (3 x 30 mL), washed with brine, dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (90:10 hexanes:ethyl acetate) to afford **20** (421 mg, 65%). R_f (85:15 hexane:ethyl acetate): 0.44.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.13 (t, J = 7.3 Hz, 1H), 5.08 (t, J = 6.1 Hz, 2H), 4.39 (d, J = 8.8 Hz, 1H), 3.74 (dd, J^1 = 5.5 Hz, J^2 = 8.5 Hz, 1H), 3.53 (dd, J^1 = 3.7 Hz, J^2 = 8.5 Hz, 1H), 1.83-2.48 (m, 15H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.58 (s, 3H), 1.04 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.9, 137.3, 135.2, 131.4, 124.5, 124.2, 121.1, 107.8, 82.3, 81.8, 75.1, 54.0, 51.6, 42.7, 41.0, 40.0, 39.9, 35.3, 26.9, 26.8, 26.5, 25.9, 18.8, 18.4, 18.1, 17.8, 16.4, 16.1, 11.4

IR (thin film/NaCl): 2950, 2864, 2170, 1750, 1462, 1381, 1242, 1016, 883, 677 cm^{-1}



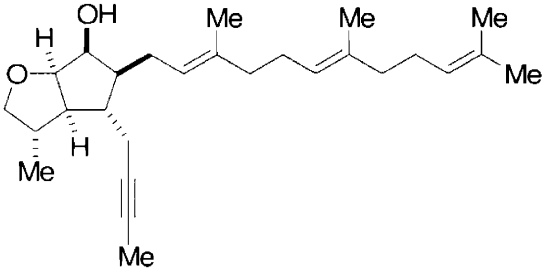
4-But-3-ynyl-3-methyl-5-(3,7,11-trimethyl-dodeca-2,6,10-trienyl)-hexahydro-cyclopenta[*b*]furan-6-ol (20a): To a solution of ketone (**20**) (900 mg, 1.7 mmol) in methanol (17 mL) at 0 °C was added sodium borohydride (32 mg, 0.85 mmol) and stirred 3 h. The reaction mixture was quenched with 50 mL of 1M HCl and diluted with ethyl

acetate (50 mL). After removal of the organic layer, the aqueous layer was extracted with ethyl acetate (2 x 75 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude oil was taken up in THF (15 mL) and cooled to –78 °C. TBAF (2.0 mL, 1.0M THF, 2.0 mmol) was added and the reaction mixture was allowed to warm to room temperature over 16 h. Water (25 μL, 1.4 mmol) was added and the mixture was concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (92:8 hexanes:ethyl acetate) to afford **20a** (503 mg, 66% over 2 steps). R_f (85:15 hexane:ethyl acetate): 0.38

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.21 (t, J = 7.0 Hz, 1H), 5.09 (m, 2H), 4.44 (dd, J^1 = 1.2 Hz, J^2 = 6.5 Hz, 1H), 4.06 (dt, J^1 = 1.5 Hz, J^2 = 6.5 Hz, 1H), 3.92 (t, J = 3.3 Hz, 1H), 3.52 (dt, J^1 = 1.5 Hz, J^2 = 6.7 Hz, 1H), 2.47 (s, 1H), 1.69-2.36 (m, 15H), 1.68 (s, 3H), 1.64 (s, 3H), 1.59 (s, 6H), 1.40 (m, 2H), 1.02 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.9, 135.0, 131.4, 124.5, 124.4, 123.0, 85.1, 84.4, 78.1, 72.5, 69.0, 56.8, 51.9, 45.9, 40.7, 40.0, 39.9, 33.3, 26.9, 26.8, 26.0, 25.9, 17.9, 17.6, 17.5, 16.2

IR (thin film/NaCl): 3464, 3310, 2822, 2118, 1667, 1451, 1380, 1122, 839

EI *m/z* calc'd for $C_{27}H_{40}O_2$: 398.3185, found [M+H]: 399.3247.



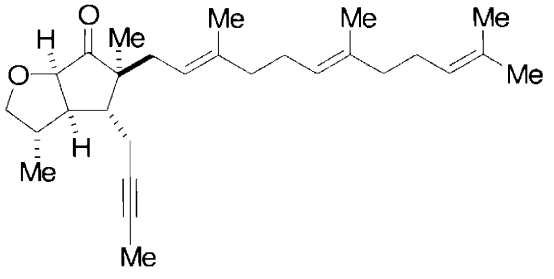
4-But-2-ynyl-3-methyl-5-(3,7,11-trimethyl-dodeca-2,6,10-trienyl)-hexahydro-cyclopenta[*b*]furan-6-ol (20b): To a degassed solution of potassium *tert*-butoxide (0.12 g, 1.1 mmol) in DMSO (5 mL), was added **20a** (140 mg, 0.37 mmol) and stirred 15 minutes. The reaction mixture was quenched with water (15 mL) and 1 M HCl (15 mL). Ether (50 mL) was added, the organic layer was separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were dried ($MgSO_4$),

filtered, and concentrated *in vacuo*. Silica gel chromatography of the crude oil (90:10 hexanes:ethyl acetate) afforded **20b** (121 mg, 83%). R_f (85:15 hexane:ethyl acetate): 0.34.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.24 (t, J = 7.0 Hz, 1H), 5.10 (m, 2H), 4.43 (dd, J^1 = 4.6 Hz, J^2 = 8.2 Hz, 1H), 4.05 (dd, J^1 = 5.5 Hz, J^2 = 8.2 Hz, 1H), 3.94 (t, J = 4.0 Hz, 1H), 3.52 (t, J = 7.6 Hz, 1H), 2.53 (s, 1H), 2.39 (m, 1H), 1.95-2.24 (m, 15H), 1.78 (t, J = 2.4 Hz, 3H), 1.68 (s, 3H), 1.64 (s, 3H), 1.59 (s, 6H), 1.04 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.9, 135.1, 131.4, 124.6, 124.4, 123.0, 84.6, 78.1, 77.3, 77.1, 72.5, 55.8, 50.4, 46.2, 40.8, 40.0, 39.9, 26.9, 26.8, 25.9, 25.7, 21.9, 17.9, 17.6, 16.2, 16.1, 3.7

IR (thin film/NaCl): 3462, 2918, 2360, 1668, 1452, 1379, 1331, 1121, 1046 cm^{-1}

EI *m/z* calc'd for $C_{27}H_{40}O_2$: 398.3185, found [M+H]: 399.3250.



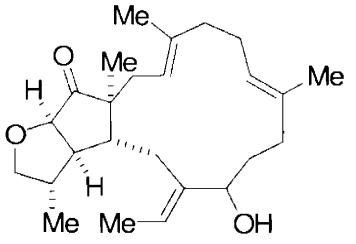
4-But-2-ynyl-3,5-dimethyl-5-(3,7,11-trimethyl-dodeca-2,6,10-trienyl)-hexahydro-cyclopenta[*b*]furan-6-one (21): To a slurry of NaH (15 mg, 60% dispersion in mineral oil, 0.38 mmol) in toluene (0.25 mL) at 0 °C was added a solution of the ketone (**18**) (102 mg, 0.25 mmol) in toluene (0.25 mL). After stirring for 0.5 h, MeI (0.16 mL, 2.5 mmol) and water (2 μL, 0.11 mmol) was added and the reaction mixture was warmed to room temperature. After 5 h, the mixture was filtered through a plug of silica gel. Silica gel chromatography (90:10 hexanes:ethyl acetate) afforded **21** (95 mg, 90%). R_f (85:15 hexane:ethyl acetate): 0.46.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.08 (t, J = 6.7 Hz, 2H), 5.03 (t, J = 7.3 Hz, 1H), 4.40 (d, J = 8.2 Hz, 1H), 3.72 (dd, J^1 = 5.2 Hz, J^2 = 8.5 Hz, 1H), 3.57 (dd, J^1 = 2.4 Hz, J^2 = 8.5

Hz, 1H), 1.90-2.40 (m, 14H), 1.78 (t, J = 2.4 Hz, 3H), 1.67 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.10 (d, J = 5.5 Hz, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 219.2, 138.5, 135.3, 131.5, 124.5, 124.2, 119.8, 81.3, 77.4, 77.4, 75.2, 53.1, 51.2, 45.0, 41.4, 40.2, 39.9, 34.1, 26.9, 26.9, 26.0, 20.0, 19.4, 18.9, 17.9, 16.4, 16.1, 3.6

IR (thin film/NaCl): 2920, 2367, 1750, 1454, 1376, 1098, 1006, 910 cm^{-1}

EI *m/z* calc'd for $C_{28}H_{42}O_2$: 410.3185, found: 410.3133.

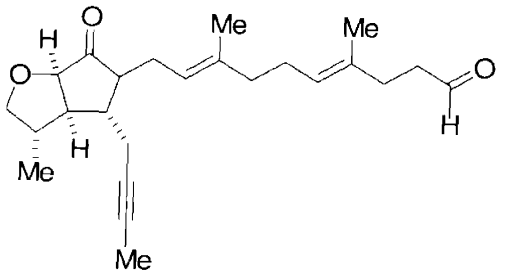


12-Ethylidene-11-hydroxy-1,4,8,16-tetramethyl-18-oxa-tricyclo[12.6.0.0^{15,19}]icosa-3,7-dien-20-one (22): To a solution of $Ni(cod)_2$ (2.8 mg, 0.01 mmol), tributylphosphine (5 μL, 0.02 mmol), and BEt_3 (20 μL, 1.0M in hexanes, 0.02 mmol) in toluene (0.75 mL) was added and stirred 20 minutes. A solution of **8** (4 mg, 0.01 mmol) in toluene (0.25 mL) was introduced and the reaction mixture was stirred 16 h. The reaction was quenched with saturated ammonium chloride (2 mL) and extracted with ether (3 x 4 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (85:15 hexane:ethyl acetate) to afford **22** (1.4 mg, 45%). R_f (70:30 hexane:ethyl acetate): 0.38.

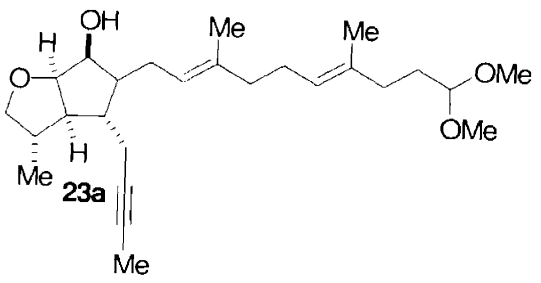
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (q, J = 6.7 Hz, 1H), 4.98 (t, J = 6.1 Hz, 1H), 4.91 (t, J = 5.8 Hz, 1H), 4.52 (d, J = 8.2 Hz, 1H), 3.92 (t, J = 4.0 Hz, 1H), 3.71 (dd, J^1 = 5.2 Hz, J^2 = 8.8 Hz, 1H), 3.57 (dd, J^1 = 1.8 Hz, J^2 = 8.5 Hz, 1H), 2.46 (dd, J^1 = 10.7 Hz, J^2 = 13.1 Hz, 1H), 1.83-2.37 (m, 15 H), 1.79 (d, J = 6.7 Hz, 3H), 1.60 (s, 6H), 1.00 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 291.1, 144.0, 136.7, 134.3, 125.2, 120.3, 119.8, 81.5, 75.0, 70.5, 52.3, 51.0, 43.6, 40.8, 39.2, 35.6, 35.0, 33.5, 29.8, 25.1, 19.8, 18.6, 16.8, 15.6, 13.9.

IR (thin film/NaCl): 3383, 2926, 2855, 1748, 1457, 1379, 1261, 1102, 802 cm^{-1}

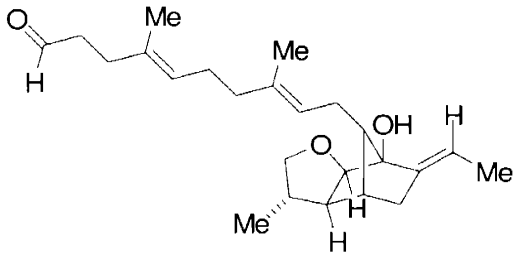
EI *m/z* calc'd for $C_{25}H_{38}O_3Na$: 409.2713, found: 409.2715.



10-(4-But-2-ynyl-3-methyl-6-oxo-hexahydro-cyclopenta[*b*]furan-5-yl)-4,8-dimethyl-deca-4,8-dienal (23): To a solution of alcohol (**23a**) (25 mg, 0.06 mmol) in dichloromethane (0.6 mL), was added 4 Å molecular sieves, NMO (14 mg, 0.12 mmol) and TPAP (2.1 mg, 6 μmol). The reaction mixture was allowed to stir for 3 h at room temperature. When completion of the reaction was ascertained by TLC, the solution was filtered through a plug of silica gel, washed with EtOAc (20 mL), and concentrate *in vacuo* to afford a yellow oil (ketone). The crude material was taken up in chloroform (2 mL) and cooled to 0 °C. A solution of TFA (1 mL, 50% aq.) was added. Immediately after addition, the ice bath was removed and the reaction was allowed to stir for 3 h at room temperature. The solution was then quenched with aqueous $NaHCO_3$ (20 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography to give (**23**) (17 mg, 77% over two steps). R_f (80:20 hexane:ethyl acetate): 0.28.



^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (t, J = 1.8 Hz, 1H), 5.12 (m, 2H), 4.40 (d, J = 7.6 Hz, 1H), 3.80 (dd, J^1 = 5.5 Hz, J^2 = 8.5 Hz, 1H), 3.56 (dd, J^1 = 4.0 Hz, J^2 = 8.5 Hz, 1H), 1.96-2.65 (m, 16 H), 1.80 (t, J = 2.4 Hz, 3H), 1.61 (s, 6H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.9, 203.0, 137.1, 133.3, 125.3, 121.1, 82.4, 78.5, 75.8, 75.4, 52.4, 50.7, 43.0, 42.3, 40.7, 39.7, 32.0, 26.6, 25.9, 23.3, 18.6, 16.4, 16.3, 3.7.

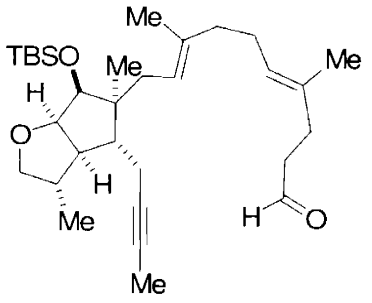


10-(9-Ethylidene-1-hydroxy-5-methyl-3-oxa-tricyclo[5.2.1.0^{2,6}]dec-10-yl)-4,8-dimethyl-deca-4,8-dienal (24): To a solution of Ni(cod)$_2$ (6.3 mg, 2.3 μmol) in toluene (2.8 mL) was added tributylphosphine (11 μL, 4.6 μmol), and triethylborane (0.15 mL of a 3.0 M toluene, 0.046 mmol). Of this solution, 0.28 mL was transferred to a separate flask. Ketone (**23**) (8.5 mg, 0.023 mmol) in toluene (0.1 mL) was added and the reaction mixture was stirred for 16 h at room temperature. The septum was removed from the flask and the mixture was allowed to stir under open air for 10 minutes before diluting in ethyl acetate (2-3 mL) and filtering through a plug of silica gel. The combined organics were concentrated *in vacuo* and purified by silica gel chromatography (70:30 hexane:ethyl acetate) to afford **24** (6 mg, 75%) and **25** (2 mg, 25%). R_f (70:30 hexane:ethyl acetate): 0.36

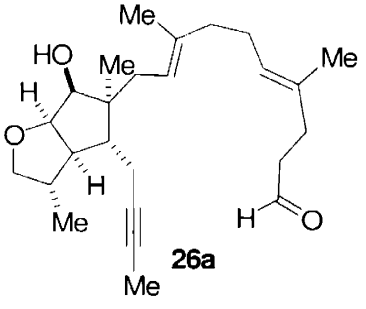
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (t, J = 1.8 Hz, 1H), 5.55 (m, 1H), 5.14 (t, J = 5.8 Hz, 1H), 4.10 (t, J = 8.2 Hz, 1H), 3.75 (d, J = 7.3 Hz, 1Hz), 3.16 (dd, J^1 = 8.8 Hz, J^2 = 10.3 Hz, 1H), 2.51 (m, 3H), 2.33 (m, 4H), 2.19 (m, 2H), 2.08 (m, 2H), 1.85 (m, 2H), 1.60 (m, 11H), 1.04 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.1, 140.9, 135.2, 133.3, 125.4, 124.4, 114.2, 87.0, 85.8, 76.0, 56.8, 53.6, 42.3, 39.8, 39.6, 38.1, 36.3, 32.0, 26.6, 25.1, 17.9, 16.4, 16.2, 13.6.

IR (thin film/NaCl): 3436, 2956, 2917, 2852, 2724, 1724, 1441, 1379, 1341, 1279, 1206, 1143, 1104, 1049, 1019, 984, 892, 852, 825, 682 cm^{-1}

ESI(NaI) *m/z* calc'd for $C_{24}H_{36}ONa$: 395.2557, found: 395.2568.

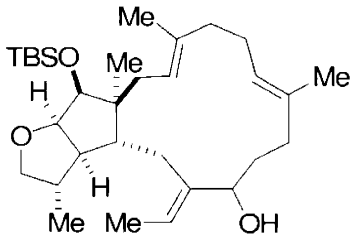


10-[6-(*tert*-Butyl-dimethyl-silanyloxy-4-but-2-ynyl-3,5-dimthyl-hexahydro-cyclopenta[*b*]furan-5-yl)-4,8-dimethyl-deca-4,8-dienal (26): To a solution of **26a** (28 mg, 0.07 mmol) in dichloromethane (1 mL) was added 2,6-lutidine (20 μL, 0.17 mmol) and cooled to –78 °C. To this mixture was added *tert*-butyldimethyltrifluoromethanesulfonate (40 μL, 0.17 mmol), stirred for 0.5 hour, and allowed to warm to 0 °C. After 0.5 h, the reaction was quenched with water(10 mL), and extracted with dichloromethane (3 x 10 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography to give **26** as a clear, colorless oil (14 mg, 39%). R_f (85:15 hexane:ethyl acetate): 0.54.



26a

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.76 (t, J = 2.0 Hz, 1H), 5.15 (m, 2H), 4.50 (dd, J^1 = 4.7 Hz, J^2 = 9.0 Hz, 1H), 4.01 (dd, J^1 = 6.1 Hz, J^2 = 8.0 Hz, 1H), 3.68 (d, J = 4.7 Hz, 1H), 3.43 (dd, J^1 = 5.2 Hz, J^2 = 8.0 Hz, 1H), 2.51 (dt, J^1 = 2.0 Hz, J^2 = 7.5 Hz, 1H), 1.81-2.33 (m, 14 H), 1.79 (t, J = 2.4 Hz, 3H), 1.62 (s, 3H), 1.58 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.67 (s, 3H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.9, 135.9, 133.1, 125.6, 121.9, 84.0, 81.0, 79.3, 77.5, 76.5, 56.6, 50.9, 49.6, 42.4, 40.7, 40.0, 33.5, 32.0, 26.7, 26.4, 19.9, 18.7, 18.6, 18.1, 16.4, 16.3, 3.7, –3.4, –4.9.

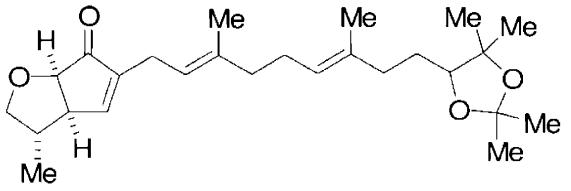


20-(*tert*-Butyl-dimethyl-silanyloxy)-12-ethylidene-1,4,8,16-tetramethyl-18-oxa-tricyclo[12.6.0.0^{15,19}]icosa-3,7-dien-11-ol (27): To a solution of $Ni(cod)_2$ (20 mg, 0.072 mmol) in toluene (6 mL) was added tributylphosphine (35 μL, 0.14 mmol), and triethylborane (0.5 mL of a 3.0 M toluene, 1.4 mmol). Of this solution, 0.12 mL was transferred to a separate flask. Aldehyde (**26**) (7 mg, 0.014 mmol) in toluene (0.1 mL) was added and the reaction mixture was stirred for 12 h at room temperature. The septum was removed from the flask and the mixture was allowed to stir under open air for 10 minutes before diluting in ethyl acetate (2-3 mL) and filtering through a plug of silica gel. The combined organics were concentrated *in vacuo* and purified by silica gel chromatography (85:15 hexane:ethyl acetate) to afford **27** (5 mg, 71%). R_f (80:20 hexane:ethyl acetate): 0.41

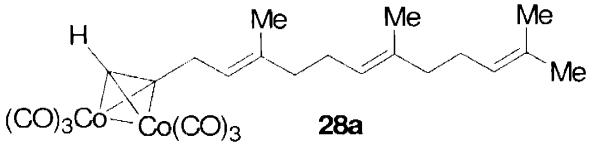
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.69 (q, *J*=6.7 Hz, 1H), 5.39 (t, *J*=5.8 Hz, 1H), 5.00 (t, *J*=5.2 Hz, 1H), 4.49 (dd, J^1=5.5 Hz, J^2=7.6 Hz, 1H), 3.90 (m, 2H), 3.63 (d, *J*=5.2, 1H), 3.41 (m, 1H), 1.88-2.47 (m, 15H), 1.74 (d, *J*=6.4 Hz, 3H), 1.59 (s, 3H), 1.54 (s, 3H), 0.09 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.0, 133.9, 133.4, 125.0, 123.4, 118.5, 84.2, 83.3, 76.3, 70.6, 56.5, 48.9, 45.5, 40.3, 39.6, 35.8, 35.6, 35.1, 30.7, 29.9, 26.4, 25.2, 20.9, 19.9, 16.6, 15.4, 14.0, –4.2, –4.8.

IR (thin film/NaCl): 3468, 2927, 2855, 1461, 1379, 1252, 1131, 1109, 1058, 992, 933, 890, 835, 775, 668 cm^{-1}

ESI(NaI) *m/z* calc'd for $C_{31}H_{54}O_3SiNa$: 525.3734, found: 525.3727.



5-[3,7-Dimethyl-9-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-nona-2,6-dienyl]-3-methyl-2,3,3a,6a-tetrahydro-cyclopenta[*b*]furan-6-one (28): To a solution of cobalt complex (**28a**) (2.0 g, 3.4 mmol), **15** (1.5 mL, 17 mmol) and *n*-butylmethylsulfide (2.1 mL, 17 mmol) in DCE (30 mL) was heated to 75-80 °C. TLC analysis of the reaction mixture after 24h revealed poor conversion. Therefore, **15** (1.5 mL, 17 mmol) was added. After 48 h, the reaction mixture was concentrated *in vacuo*, filtered through a plug of silica gel and concentrated *in vacuo*. Silica gel chromatography (80:20 hexane:ethylacetate) of the crude oil afforded **28** (600 mg, 42%). R_f (80:20 hexane:ethylacetate): 0.5

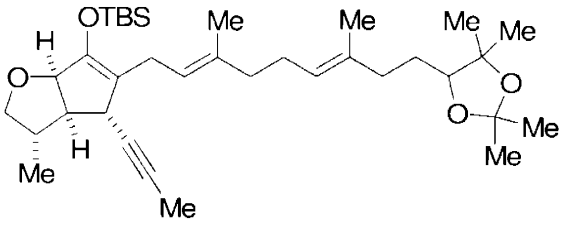


28a

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, J = 1.2 Hz, 1H), 5.20 (t, J = 6.4 Hz, 1H), 5.16 (t, J = 6.4 Hz, 1H), 4.38 (d, J = 5.5 Hz, 1H), 3.66 (m, 2H), 3.59 (dd, J^1 = 2.4 Hz, J^2 = 9.1 Hz, 1H), 2.95 (bs, 1H), 2.85 (d, J = 7.0, 2H), 1.99-2.23 (m, 8H), 1.62 (s, 3H), 1.61 (s, 3H), 1.48 (m, 1H), 1.42 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 206.4, 157.1, 145.8, 138.1, 134.7, 124.7, 124.6, 119.4, 106.6, 83.0, 80.5, 80.3, 74.2, 51.0, 39.8, 38.2, 36.9, 28.8, 27.9, 27.0, 26.7, 26.2, 23.7, 23.1, 19.0, 16.3, 16.24, 16.22.

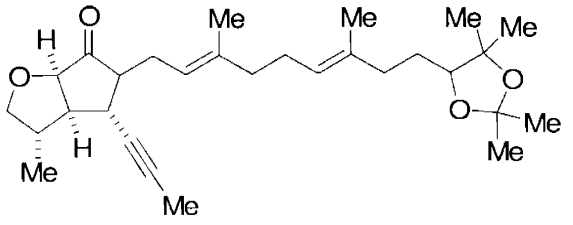
IR (thin film/NaCl): 2976, 2933, 2858, 1716, 1625, 1455, 1369, 1216, 1112, 917 cm^{-1}

ESI *m/z* calc'd for $C_{26}H_{40}O_4Na$: 439.2819, found: 439.2820.



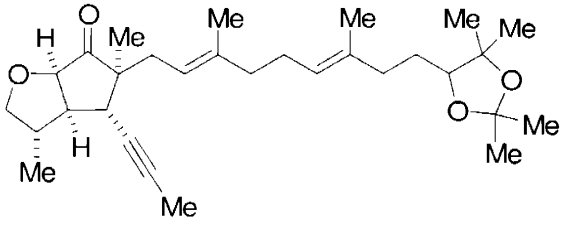
***tert*-Butyl-{5-[3,7-dimethyl-9-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-nona-2,6-dienyl]-3-methyl-4-prop-1-ynyl-dimethyl-silane (29):** To a solution of propynyl lithium (0.1 g, 2.2 mmol) in THF (4 mL) at –78 °C was added trimethylaluminum (1.1 mL, 2.0 M toluene, 2.2 mmol) and stirred 1h. A solution of **28** (0.3 g, 0.72 mmol) in THF (1 mL) and *tert*-butyldimethyltrifluoromethanesulfonate (0.5 mL, 2.2 mmol) was added. The reaction mixture was warmed to –40 °C for 2 h and quenched with a saturated solution of Rochelle's salt (20 mL). After stirring for 1h, the solution was extracted with diethyl ether (3 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Silica gel chromatography (95:5 hexane:ethylacetate) afforded **29** (0.25 g, 61%) as a clear colorless oil. R_f (95:5 hexane:ethylacetate): 0.4.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (t, J = 6.4 Hz, 1H), 5.06 (t, J = 7.3 Hz, 1H), 4.80 (d, J = 7.3 Hz, 1H), 3.62 (dt, J^1 = 3.4 Hz, J^2 = 8.8 Hz, 2H), 3.38 (dd, J^1 = 4.2 Hz, J^2 = 8.5 Hz, 1H), 2.97 (bs, 1H), 2.91 (dd, J^1 = 6.1 Hz, J^2 = 14.6 Hz, 1H), 2.65 (dd, J^1 = 8.5 Hz, J^2 = 14.6 Hz, 1H), 2.30 (m, 1H), 2.17 (m, 1H), 1.89-2.09 (m, 8H), 1.76 (d, J = 2.1 Hz, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.07 (s, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.6, 136.5, 134.4, 124.8, 120.9, 120.4, 106.5, 85.3, 83.0, 81.5, 80.2, 76.6, 72.5, 53.6, 41.7, 39.8, 39.3, 36.9, 28.7, 27.9, 27.0, 26.8, 26.7, 26.2, 26.0, 23.9, 23.1, 18.6, 18.4, 16.3, 16.2, 16.1, 3.8, –3.7, –4.3.



5-[3,7-Dimethyl-9-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-nona-2,6-dienyl]-3-methyl-4-prop-1-ynyl-hexahydro-cyclopenta[*b*]furan-6-one (30): To a solution of **29** (0.5 g, 0.87 mmol) in THF (20 mL) at –78 °C was added TBAF (1.1 mL, 1.1 mmol). The reaction mixture was warmed to 0 °C, stirred 15 minutes, and quenched with water (1 mL). The solution was concentrated *in vacuo*. Silica gel chromatography (80:20 hexane:ethylacetate) of the crude mixture afforded **30** (0.31 g, 78%) as a 2:1 mixture of diastereomers. R_f (80:20 hexane:ethylacetate): 0.6.

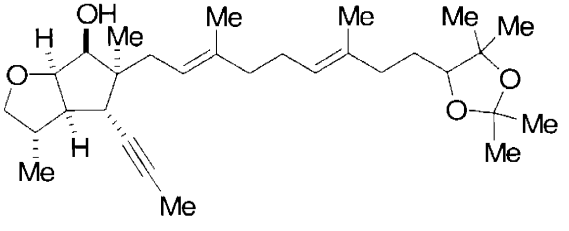
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.12 (m, 2H), 4.27 (d, J = 7.3 Hz, 1H, major dias.), 4.20 (d, J = 7.9 Hz, 0.5H, minor dias.), 4.08 (m, 0.5H, minor dias.), 3.97 (t, J = 6.7 Hz, 0.5 H, minor dias.), 3.76 (t, J = 6.7 Hz, 1H, major dias.), 3.63 (m, 1H, major dias.), 3.55 (m, 1H, major dias.), 3.41 (m, 0.5H, minor dias.), 2.93 (m, 0.5H, minor dias.), 1.86-2.60 (m, 13H), 1.82 (t, J = 1.8 Hz, 3H, major dias.), 1.75 (s, 1.5H, minor dias.), 1.62 (s, 3H), 1.58 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.07 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.6, 213.9, 138.2, 134.7, 125.0, 121.5, 120.3, 106.8, 83.2, 82.3, 81.4, 81.0, 80.5, 80.1, 78.7, 78.6, 77.0, 75.5, 60.8, 55.9, 54.2, 53.9, 50.0, 40.6, 40.2, 40.1, 37.1, 37.0, 36.1, 32.5, 29.0, 28.1, 28.0, 27.2, 27.1, 26.9, 26.4, 26.1, 25.5, 25.2, 23.3, 19.6, 16.8, 16.6, 16.4, 16.3, 14.6, 4.1, 4.0.



5-[3,7-Dimethyl-9-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-nona-2,6-dienyl]-3,5-methyl-4-prop-1-ynyl-hexahydro-cyclopenta[*b*]furan-6-one (31): To a slurry of NaH

(41 mg, 60% dispersion in mineral oil, 1.0 mmol) in toluene (4 mL) at 0 °C was added a solution of the ketone (**30**) (0.31 g, 0.68 mmol) in toluene (2 mL). After stirring for 0.5 h, MeI (0.42 mL, 6.8 mmol) and water (13 μL, 0.68 mmol) was added and the reaction mixture was warmed to room temperature. After 5 h, the mixture was filtered through a plug of silica gel. Silica gel chromatography (90:10 hexanes:ethyl acetate) afforded **31** (160 mg, 50 %). R_f (90:10 hexane:ethyl acetate): 0.2.

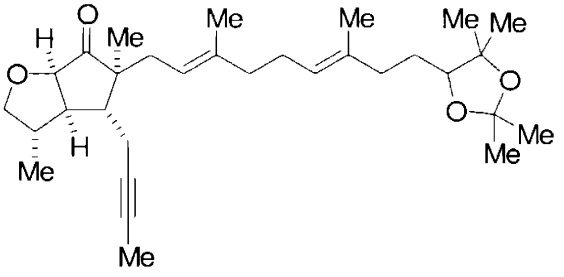
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.08 (t, J = 6.1 Hz, 1H), 5.00 (t, J = 7.6 Hz, 1H), 4.28 (d, J = 7.3 Hz, 1H), 3.69 (dd, J^1 = 5.5 Hz, J^2 = 8.5 Hz, 1H), 3.60 (dd, J^1 = 2.4 Hz, J^2 = 9.5 Hz, 1H), 3.54 (dd, J^1 = 1.2 Hz, J^2 = 8.5 Hz, 1H), 2.50 (d, J = 10.0 Hz, 1H), 2.41 (t, J = 7.6 Hz, 1H), 2.28 (t, J = 6.1 Hz, 1H), 1.91-2.18 (m, 9H), 1.81 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H), 1.41 (m, 1H), 1.37 (s, 3H), 1.27 (s, 3H), 1.19 (s, 3H), 1.05 (m, 6H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.9, 138.9, 134.43, 134.40, 124.6, 119.3, 106.5, 82.8, 80.4, 80.1, 79.7, 77.1, 75.0, 54.2, 51.8, 39.9, 39.8, 39.3, 36.8, 33.1, 28.6, 27.7, 26.9, 26.8, 26.1, 23.0, 20.1, 19.7, 16.3, 16.0, 3.8.



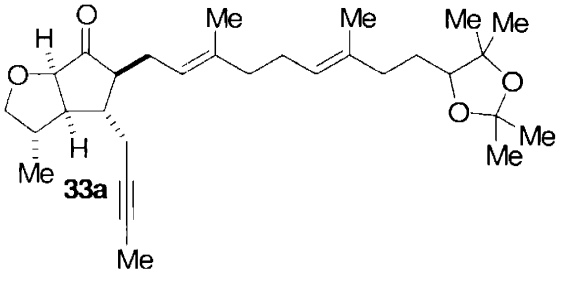
5-[3,7-Dimethyl-9-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-nona-2,6-dienyl]-3,5-methyl-4-prop-1-ynyl-hexahydro-cyclopenta[*b*]furan-6-ol (32): To a solution of ketone (**31**) (0.16g, 0.34 mmol) in methanol (10 mL) at 0 °C was added sodium borohydride (7 mg, 0.17 mmol) and stirred 6 h. The reaction mixture was quenched with water (40 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford **32** (160 mg, 99 %) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.28 (t, J = 7.3 Hz, 1H), 5.15 (t, J = 6.1 Hz, 1H), 4.52 (dd, J^1 = 4.9 Hz, J^2 = 8.5 Hz, 1H), 4.01 (dd, J^1 = 5.8 Hz, J^2 = 8.2 Hz, 1H), 3.63 (m, 2H),

3.53 (dd, J^1 = 5.8 Hz, J^2 = 8.2 Hz, 1H), 2.44 (dd, J^1 = 2.1 Hz, J^2 = 9.5 Hz, 1H), 2.30 (dt, J^1 = 4.3 Hz, J^2 = 8.8 Hz, 1H), 1.96-2.23 (m, 11H), 1.81 (d, J = 2.1 Hz, 3H), 1.60 (m, 6H), 1.45 (m, 1H), 1.40 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H), 1.08 (m, 6H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.3, 125.0, 121.2, 106.6, 83.5, 83.0, 80.3, 79.1, 78.4, 77.8, 75.9, 56.7, 52.2, 44.0, 40.4, 40.1, 36.9, 36.8, 33.5, 28.7, 27.8, 27.0, 26.8, 26.2, 23.1, 18.3, 18.0, 16.4, 16.2, 3.9.



4-But-2-ynyl-5-[3,7-dimethyl-9-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-nona-2,6-dienyl]-3,5-dimethyl-hexahydro-cyclopenta[*b*]furan-6-one (33): To a slurry of NaH (20 mg, 60% dispersion in mineral oil, 0.49 mmol) at 0 °C was added **33a** (115 mg, 0.24 mmol) and stirred for 2 min. Methyl iodide (0.15 mL, 2.4 mmol) was added followed by water (6.5 μL, 0.36 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. TLC revealed that reaction was incomplete. Sodium hydride (10 mg, 60% dispersion in mineral oil, 0.24 mmol) and water (3.3 μL, 0.18 mmol) were added and the reaction mixture stirred for a further 8 h. The mixture was filtered through a pad of silica gel and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (85:15 hexanes:ethyl acetate) to afford **33** (84 mg, 71%). R_f (80:20 hexane:ethyl acetate): 0.35.

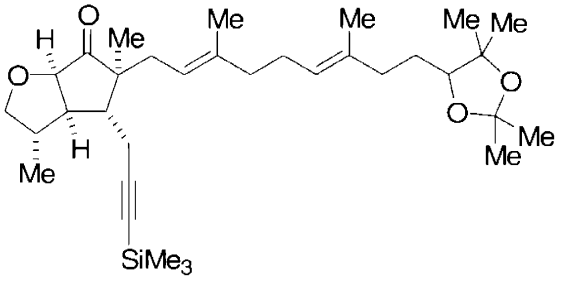


^{1}H NMR (500 MHz, $CDCl_3$): δ 5.12 (t, J = 6.4 Hz, 1H), 5.01 (t, J = 7.0 Hz, 1H), 4.37 (d, J = 8.2 Hz, 1H), 3.70 (dd, J^1 = 5.2 Hz, J^2 = 8.5 Hz, 1H), 3.63 (dd, J^1 = 3.4 Hz, J^2 = 9.5 Hz, 1H), 3.55 (d, J = 8.5 Hz, 1H), 1.86-2.39 (m, 15 H), 1.77 (t, J = 2.1 Hz, 3H), 1.60 (s,

3H), 1.58 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.08 (m, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 219.1, 138.4, 134.6, 124.7, 120.0, 106.5, 83.3, 81.3, 80.2, 77.4, 77.3, 75.1, 53.1, 51.1, 44.9, 41.3, 40.1, 36.9, 34.0, 29.8, 28.7, 27.9, 27.0, 26.9, 26.2, 23.1, 20.0, 19.4, 18.8, 16.4, 16.1, 3.6.

IR (thin film/NaCl): 2970, 2928, 2855, 2360, 1750, 1456, 1369, 1216, 1113, 1003, 912, 856 cm^{-1}

ESI *m/z* calc'd for $C_{31}H_{48}O_4Na$: 502.3445, found: 502.3434.



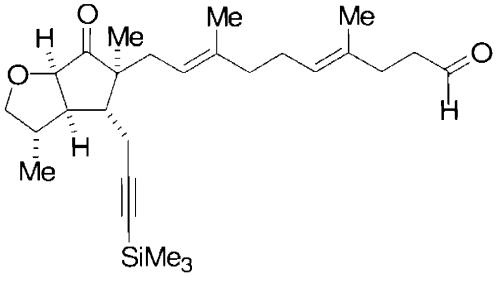
5-[3,7-Dimethyl-9-(2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)-nona-2,6-dienyl]-3,5-dienyl]-3,5-dimethyl-4-(3-trimethylsilanyl-prop-2-ynyl)-hexahydro-cyclopenta[*b*]furan-6-one (34): To a solution of molybdenum catalyst (**Mo**) (4.5 mg, 0.0076 mmol) in toluene (0.75 mL) was added a solution of methyl alkyne (**33**) (37 mg, 0.076 mmol) in toluene (0.25 mL) and 1-trimethylsilyl-1-propyne (88 mg, 0.76 mmol). After stirring 10 minutes, dichloromethane (12 μL, 0.19 mmol) was added and the reaction warmed to 80 °C for 8.5 h. The mixture was diluted with ethyl acetate (5 mL) and the organic layer washed with 1M HCl (3 x 5mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Silica gel chromatography (90:10 hexane:ethyl acetate) afforded **34** (14.5 mg, 36%) and recovered starting material (15 mg, 39%). R_f (80:20 hexane:ethyl acetate): 0.35

^1H NMR (500 MHz, $CDCl_3$): δ 5.14 (t, J = 6.7 Hz, 1H), 5.05 (t, J = 7.6 Hz, 1H), 4.41 (d, J = 8.2 Hz, 1H), 3.70 (dd, J^1 = 5.2 Hz, J^2 = 8.8 Hz, 1H), 3.65 (dd, J^1 = 3.3 Hz, J^2 = 9.4 Hz, 1H), 3.59 (m, 1H), 1.92-2.50 (m, 14H), 1.63 (s, 3H), 1.61 (s, 3H), 1.45 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.10 (m, 6H), 0.92 (s, 3H), 0.16 (s, 9H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 218.9, 138.7, 134.7, 124.7, 119.6, 106.6, 105.1, 86.8, 83.0, 81.2, 80.3, 75.0, 53.1, 51.1, 44.7, 41.4, 40.2, 36.9, 33.9, 28.8, 27.9, 27.1, 27.0, 26.2, 23.1, 21.2, 19.5, 18.8, 16.6, 16.5, 16.2, 0.1

IR (thin film/NaCl): 2962, 2175, 1750, 1456, 1368, 1250, 1216, 1113, 1003, 843 cm^{-1}

ESI *m/z* calc'd for $C_{33}H_{54}O_4SiNa$: 565.3684, found: 565.3670.

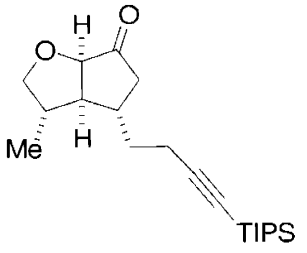


10-[3,5-Diemethyl-6-oxo-4-(3-trimethylsilanyl-prop-2-ynyl)-hexahydro-cyclopenta[*b*]furan-5-yl]-4,8-dimethyl-deca-4,8-dienal (35): To a solution of acetonide (**34**) (40 mg, 74 μmol) in MeOH (2 mL) was added *p*-toluenesulfonic acid (1.3 mg, 7.4 μmol) and stirred for 8 h. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude diol was taken up in MeOH (1 mL) and cooled to 0 °C. A solution of sodium periodate (79 mg, 0.37 mmol) in water (1 mL) was added and the reaction was stirred for 2 h. Water (10 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Silica gel chromatography (80:20 hexane:ethylacetate) of the crude mixture afforded **35** (20 mg, 61% over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.75 (t, J = 1.8 Hz, 1H), 5.11 (dt, J^1 = 1.2 Hz, J^2 = 7.0 Hz, 1H), 5.04 (dt, J^1 = 1.2 Hz, J^2 = 7.6 Hz, 1H), 4.41 (d, J = 7.9 Hz, 1H), 3.70 (dd, J^1 = 5.2 Hz, J^2 = 8.5 Hz, 1H), 3.59 (dd, J^1 = 2.1 Hz, J^2 = 8.5 Hz, 1H), 2.51 (dt, J^1 = 1.8 Hz, J^2 = 7.3 Hz, 2H), 2.43 (dd, J^1 = 5.5 Hz, J^2 = 16.8 Hz, 2H), 1.91-2.34 (m, 13H), 1.62 (s, 3H), 1.60 (s, 3H), 1.10 (d, J = 7.0 Hz, 3H), 0.92 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 218.8, 202.9, 138.4, 133.3, 125.3, 119.7, 105.2, 86.9, 81.2, 75.0, 53.1, 51.1, 44.7, 42.3, 41.4, 39.9, 33.9, 32.0, 26.8, 21.1, 19.5, 18.7, 16.5, 16.3, 0.1.

ESI *m/z* calc'd for $C_{27}H_{42}O_3SiNa$: 465.2903, found: 465.2796.



3-Methyl-5-trimethylsilanyl-2,3,3a,6a-tetrahydro-cyclopenta[*b*]furan-6-one (38):

To a 250 mL round bottom flask equipped with CuI (0.86 g, 4.5 mmol) was added freshly distilled THF (30 mL), and dimethyl sulfide (2.2 mL, 50 mmol). After CuI had dissolved, the solution was cooled to –78 °C. In a separate flask, a solution of **19a** (3.0 g, 9 mmol) in diethyl ether (30 mL) was cooled to –78 °C and added *t*-butyllithium (10.6 mL, 1.7M in hexanes, 18 mmol). The resulting solution was allowed to warm to room temperature after 0.5 h. At this time, the mixture was transferred slowly to the CuI solution *via cannula* to afford a black slurry. A solution **(–)-11b** (0.53 g, 2.5 mmol) in THF (2 mL) was added to the black slurry and stirred at –40 °C for 6 h. The reaction mixture was quenched with 3M HCl and the biphasic mixture was allowed to stir 16 h. After the addition of diethyl ether (50 mL), the mixture was separated into two layers, and the aqueous layer was extracted twice with diethyl ether (2 x 50 mL). The organic layers were combined, washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (85:15 hexanes:ethyl acetate) to afford **(–)-38** (1.92 g, 54%). R_f (80:20 hexane:ethyl acetate): 0.41

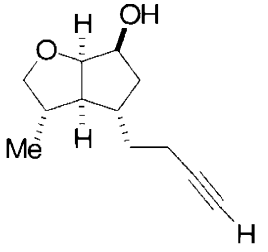
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (d, *J*=5.8 Hz, 1H), 3.89 (m, 1H), 3.51 (m, 1H), 2.55 (dd, J^1 = 5.5Hz, J^2 = 16.2 Hz,1H), 2.35 (m, 2H), 2.17 (m, 3H), 2.04 (dd, J^1 = 1.2Hz, J^2 = 7.9Hz, 1H), 1.75 (m, 1H), 1.63 (m, 1H), 1.07 (d, *J* = 6.7 Hz), 1.03 (s, 18H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 215.3, 107.5, 82.3, 81.6, 75.8, 53.9, 42.9, 40.5, 37.0, 35.5, 18.8, 18.4, 18.0, 11.4

IR (thin film/NaCl): 2941, 2865, 2170, 1754, 1463, 1381, 1062, 995, 883, 676, 661 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{21}H_{36}O_2SiNa$: 371.2377, found: 371.2375.

$[\alpha]_D$ = –8.0, (*c* 1.0, EtOH)



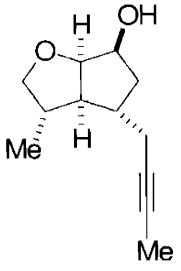
4-But-3-ynyl-3-methyl-hexahydro-cyclopenta[*b*]furan-6-ol (39): To a solution of **(–)-38** (4.0 g, 11.5 mmol) in 75 mL of methanol at 0 °C was added sodium borohydride (0.44 g, 11.5 mmol) and stirred 3 h. The reaction mixture was quenched with 1M HCl (80 mL) and diluted with ethyl acetate (150 mL). After removal of the organic layer, the aqueous layer was extracted with ethyl acetate (2 x 80 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was taken up in THF (75 mL) and cooled to –78 °C. TBAF (17.2 mL, 17.2 mmol, 1.0 M THF) was added and the reaction mixture was allowed to warm to room temperature over 16 h. Water (200 mL) was added and the reaction mixture was extracted with diethyl ether (3 x 150 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (75:25 hexanes:ethyl acetate) to afford **(–)-39** (1.69 g, 76% over 2 steps). R_f (80:20 hexane:ethyl acetate): 0.19

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.45 (dd, J^1 = 5.2 Hz, J^2 = 8.2 Hz, 1H), 4.09 (m, 1H), 4.02 (dd, J^1 = 6.1 Hz, J^2 = 8.5 Hz, 1H), 3.53 (dd, J^1 = 6.1 Hz, J^2 = 8.5 Hz, 1H), 2.63 (dd, J^1 = 0.92 Hz, J^2 = 3.4 Hz, 1H), 2.22 (dt, J^1 = 2.4 Hz, J^2 = 7.3 Hz, 2H), 1.95-2.10 (m, 3H), 1.85 (m, 1H), 1.64 (m, 1H), 1.56 (m, 1H), 1.40 (m, 1H), 1.05 (d, *J* = 4.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.6, 84.0, 77.0, 72.1, 68.7, 56.6, 41.0, 40.1, 39.8, 34.6, 17.9, 17.3

IR (thin film/NaCl): 3451, 3294, 2927, 2116, 1452, 1378, 1341, 1184, 1089, 1054, 1018, 829 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{12}H_{18}O_2Na$: 217.1199, found: 217.1198.

$[\alpha]_D = -38$ (*c* 1.0, EtOH)



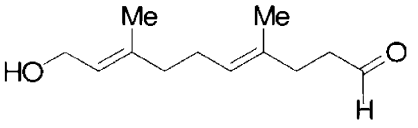
4-But-2-ynyl-3-methyl-hexahydro-cyclopenta[*b*]furan-6-ol (39a): To a degassed solution of potassium *tert*-butoxide (1.12 g, 10 mmol) in DMSO (15 mL), was added **(–)-39** (0.69 g, 3.5 mmol) and stirred 15 min. The reaction mixture was quenched with water (15 mL) and 1 M HCl (15 mL). Diethyl ether (50 mL) was added, the organic layer was separated and the aqueous layer was extracted with ether (2 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude oil was loaded on a plug of silica gel and vacuum filtered using 60:40 hexanes:ethyl acetate as an eluent. The filtered solution was concentrated *in vacuo* to afford **(–)-39a** (0.65 g, 94%). R_f (80:20 hexane:ethyl acetate): 0.28

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.31 (dd, J^1 = 5.2 Hz, J^2 = 7.6 Hz, 1H), 3.98 (m, 1H), 3.89 (dd, J^1 = 6.1 Hz, J^2 = 8.2 Hz, 1H), 3.40 (dd, J^1 = 5.8 Hz, J^2 = 8.2Hz, 1H), 2.80 (d, J = 3.4 Hz, 1H), 1.77-2.10 (m, 6H), 1.66 (t, J = 2.7 Hz, 3H), 1.46 (m, 1H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.8, 77.4, 77.0, 76.5, 72.2, 55.6, 41.4, 41.0, 39.4, 24.1, 17.6, 3.3

IR (thin film/NaCl): 3447, 2920, 2360, 2341, 1653, 1558, 1456, 1088, 1014, 668 cm^{-1}

HRMS-EI *m/z* calc'd for $C_{12}H_{18}O_2$: 193.1223, found: 195.1388.

$[\alpha]_D = -16$ (*c* 1.0, EtOH)

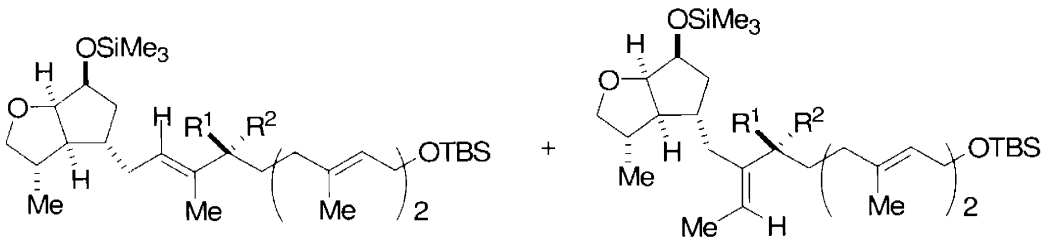


10-Hydroxy-4,8-dimethyl-deca-4,8-dienal (40a): To a solution of acetate (**40**) (2.82 g, 9.4 mmol) in methanol (40 mL) at 0 °C was added potassium carbonate (2.61 g, 19 mmol) and allowed to warm to room temperature. The reaction mixture was stirred for 1 h and then diluted with water (80 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 80 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford the crude triol. The triol was taken up in methanol (40 mL) and cooled to 0 °C. An aqueous solution (40 mL) of sodium periodinate (4.0 g, 19 mmol) was added *slowly*. When disappearance of the starting material was ascertained by TLC analysis, the reaction mixture was diluted with 1M HCl (20 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 80 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (70:30 hexane:ethyl acetate) afforded **40a** (1.34 g, 70% over 2 steps). R_f (70:30 hexane:ethyl acetate): 0.19

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.70 (s, 1H), 5.36 (t, J = 7.0 Hz, 1H), 5.10 (m, 1H), 4.12 (d, J = 6.7 Hz, 2H), 2.49 (t, J = 5.8 Hz, 2H), 2.31 (t, J = 7.3 Hz, 2H), 2.00-2.12 (m, 5H), 1.63 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 138.9, 133.3, 125.1, 124.0, 59.4, 42.0, 39.4, 32.0, 26.0, 16.3, 16.2.

IR (thin film/NaCl): 3382, 2920, 1723, 1668, 1444, 1112, 1013 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{12}H_{20}O_2Na$: 219.1356, found: 219.1361.



42a (R^1 = OH; R^2 = H)
42b (R^1 = H; R^2 = OH)

42c (R^1 = OH; R^2 = H)
42d (R^1 = H; R^2 = OH)

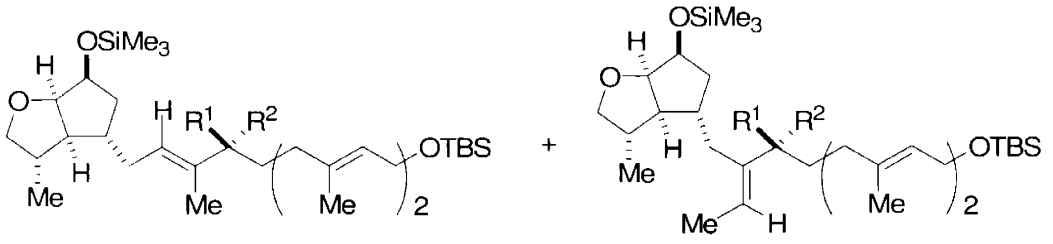
13-(*tert*-Butyl-dimethyl-silanyloxy)-3,7,11-trimethyl-1-(3-methyl-6-trimethylsilanyloxy-hexahydro-cyclopenta[*b*]furan-4-yl)-trien-4-ol (42a-42d):

To a solution of $Ni(cod)_2$ (5.5 mg, 0.02 mmol), (*R*)-*P*-ferrocenyl-*P*-(*p*-*xylyl*)-phenylphosphine (**41e**) (8.5 mg, 0.02 mmol) in ethyl acetate (1 mL) was added triethylborane (58 μL, 0.4 mmol) and stirred 5 min and cooled to 0 °C. A mixture of alkyne (–)- (**9**) (53 mg, 0.2 mmol) and aldehyde (**10**) (125 mg, 0.4 mmol) was added to this mixture and stirred 16 h. The reaction was opened to air and then filtered through a plug of silica gel and concentrated *in vacuo*. Silica gel chromatography (92:8 hexanes:ethyl acetate) afforded the reductive coupled products **42a-42d** (98 mg, 2.6:1 mixture of regioisomers, 2.1:1* mixture of diastereomers, 85%). R_f (80:20 hexane:ethyl acetate): 0.5. * This was determined by NMR integration after the cyclization to compound (–)-(**45**).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.61 (q, *J* = 6.7 Hz, 0.3H minor regioisomer), 5.35 (t, *J* = 7.0 Hz, 0.7H major regioisomer), 5.29 (m, 1H), 5.13 (m, 1H), 4.25 (m, 1H), 4.18 (d, *J* = 6.1 Hz, 2H), 4.10 (m, 1H), 3.97 (m, 2H), 3.38 (m, 1H), 1.94-2.18 (m, 10H), 1.77-1.84 (m, 3H), 1.60-1.69 (m, 11H), 1.45 (m, 1H), 1.01 (m, 3H), 0.89 (s, 9H), 0.13 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 138.5, 136.91, 136.89, 135.0, 134.9, 125.1, 125.0, 124.7, 124.6, 121.5, 84.7, 84.54, 84.52, 77.59, 77.55, 76.30, 76.28, 76.2, 75.4, 74.33, 74.32, 60.5, 56.2, 55.89, 55.85, 42.2, 42.14, 42.10, 42.06, 41.1, 39.7, 38.2, 38.0, 36.3, 36.12, 36.11, 34.3, 34.3, 34.2, 34.1, 33.33, 33.26, 26.41, 26.37, 26.36, 26.2, 18.6, 18.53, 18.51, 16.53, 16.50, 16.2, 16.1, 13.9, 11.9, 11.8, 0.33, 0.31, –4.86, –4.87.

IR (thin film/NaCl): 3451, 2956, 1668, 1472, 1381, 1250, 1065, 838, 776 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{33}H_{62}O_4Si_2Na$: 601.4079, found: 601.4073



42a' (R^1 = OTIPS; R^2 = H)
42b' (R^1 = H; R^2 = OTIPS)

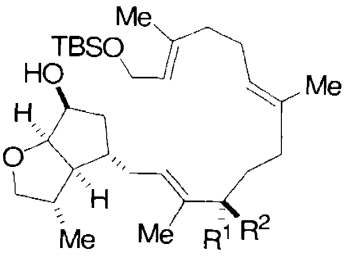
42c' (R^1 = OTIPS; R^2 = H)
42d' (R^1 = H; R^2 = OTIPS)

4-[13-(*tert*-Butyl-dimethyl-silanyloxy)-3,7,11-trimethyl-4-triisopropylsilanyloxy-trideca-2,7,11-trienyl]-3-methyl-6-trimethylsilanyloxy-hexahydro-cyclopenta[*b*]furan (42a'-42d'): To a solution of allylic alcohols **42a-42d** (1.6 g, 2.8 mmol) in dichloromethane (20 mL) was added 2,6-lutidine (1 mL, 8.3 mmol) and cooled to -78 °C. After 10 min, triisopropylsilyltrifluoromethanesulfonate (1.1 mL, 4.1 mmol) was added slowly and stirred 2 h. The reaction mixture was quenched with water (80 mL) and diluted with dichloromethane (80 mL). The organic layer was collected and the aqueous layer was extracted further with dichloromethane (2 x 80 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (95:5 hexane:ethyl acetate) afforded **42a'-42d'** (1.92 g, 97%). R_f (95:5 hexane:ethyl acetate): 0.28

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.30 (t, J = 5.5 Hz, 1H), 5.24 (m, 1H), 5.07 (t, J = 6.4 Hz, 1H), 4.24 (m, 1H), 4.17 (d, J = 6.1 Hz, 2H), 4.07 (m, 2H), 3.96 (m, 1H), 3.40 (m, 1H), 1.70-2.10 (m, 13H), 1.60 (m, 11H), 1.03 (m, 24H), 0.89 (s, 9H), 0.12 (m, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 138.2, 137.0, 135.2, 124.64, 124.59, 124.4, 123.9, 123.8, 84.61, 84.55, 84.4, 78.6, 78.4, 76.2, 74.4, 74.3, 60.5, 55.9, 55.7, 42.2, 42.1, 42.0, 41.3, 41.2, 39.7, 38.0, 37.7, 35.7, 35.6, 34.7, 34.6, 34.3, 34.2, 26.49, 26.46, 26.2, 25.9, 18.7, 18.61, 18.57, 18.5, 18.4, 18.31, 18.28, 18.25, 18.2, 16.5, 16.29, 16.27, 13.9, 12.61, 12.58, 12.5, 11.4, 11.3, 0.3, -4.9

IR (thin film/NaCl): 2957, 2866, 1669, 1464, 1249, 1065, 838, 775, 680 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{42}H_{82}O_4Si_3Na$: 757.5414, found: 757.5418



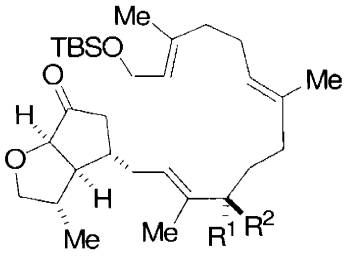
43a (R^1 = OTIPS; R^2 = H)
43b (R^1 = H; R^2 = OTIPS)

4-[13-(*tert*-Butyl-dimethyl-silanyloxy)-3,7,11-trimethyl-4-triisopropylsilanyloxy-trideca-2,7,11-trienyl]-3-methyl-hexahydro-cyclopenta[*b*]furan-6-ol (43a-43b): To a solution of **42a'-42d'** (1.9 g, 2.7 mmol) in methanol (10 mL) at 0 °C was added sodium hydroxide (0.1 g) in methanol (10 mL) and stirred 10 min. The reaction mixture was diluted in water (100 mL), extracted with ethyl acetate (3 x 75 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Silica gel chromatography (92:8 hexanes:ethyl acetate) on the crude oil afforded **43a-43b** (1.05 g, 59%) and its regioisomer **43c-43d** (410 mg, 23%). R_f (85:15 hexane:ethyl acetate): 0.37 (desired) R_f (85:15 hexane:ethyl acetate): 0.39 (undesired).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.29 (t, J = 5.8 Hz, 1H), 5.25 (t, J = 7.0 Hz, 1H), 5.07 (t, J = 6.7 Hz, 1H), 4.41 (m, 1H), 4.17 (d, J = 6.1 Hz, 2H), 4.04 (m, 2H), 3.97 (dt, J^1 = 6.1 Hz, J^2 = 2.1 Hz, 1H), 3.49 (m, 1H), 2.68 (s, 1H), 1.75-2.16 (m, 13H), 1.60 (m, 11H), 1.03 (m, 24H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 138.4, 137.1, 137.0, 135.3, 124.48, 124.47, 124.2, 124.1, 123.9, 84.6, 84.5, 78.6, 78.5, 76.97, 77.00, 72.4, 60.5, 56.5, 56.4, 42.2, 41.3, 41.2, 39.9, 39.7, 35.7, 35.6, 34.74, 34.66, 33.2, 26.5, 26.2, 18.6, 18.4, 18.37, 18.33, 18.28, 18.2, 18.1, 16.5, 16.3, 12.9, 12.6, 12.5, 11.32, 11.30, –4.9

IR (thin film/NaCl): 3473, 2929, 1669, 1464, 1255, 1065, 836, 775, 680 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{39}H_{74}O_4Si_2Na$: 685.5018, found: 685.5000



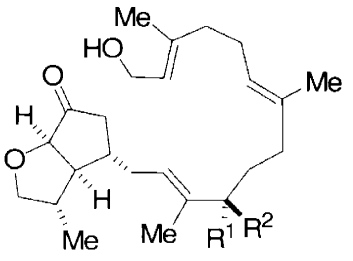
43a' (R^1 = OTIPS; R^2 = H)
43b' (R^1 = H; R^2 = OTIPS)

4-[13-(*tert*-Butyl-dimethyl-silanyloxy)-3,7,11-trimethyl-4-triisopropylsilanyloxy-trideca-2,7,11-trienyl]-3-methyl-hexahydro-cyclopenta[*b*]furan-6-one (43a'-43b'): To a solution of TPAP (56 mg, 0.16 mmol) and NMO (380 mg, 3.2 mmol) in dichloromethane (16 mL) at 0 °C was added **43a-43b** (1.05 g, 1.6 mmol) and stirred for 2.5 h. The reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of silica gel and washed with an additional ethyl acetate (400 mL). The solution was concentrated *in vacuo* and silica gel chromatography of the crude mixture (90:10 hexane:ethyl acetate) afforded **43a'-43b'** (0.93 g, 89%) as a clear colorless oil. R_f (85:15 hexane:ethyl acetate): 0.49

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.28 (m, 2H), 5.06 (m, 1H), 4.22 (d, J = 7.6 Hz, 1H), 4.17 (d, J = 6.1 Hz, 2H), 4.07 (t, J = 7.0 Hz, 1H), 3.92 (m, 1H), 3.48 (m, 1H), 2.50 (m, 1H), 1.78-2.23 (m, 12H), 1.60 (m, 11H), 1.07 (m, 3H), 1.02 (m, 21H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.7, 139.98, 139.89, 137.00, 136.99, 135.15, 135.14, 124.5, 124.0, 122.5, 122.4, 82.34, 82.32, 78.3, 78.2, 76.03, 75.96, 60.4, 53.6, 53.5, 42.5, 42.3, 40.44, 40.42, 39.7, 37.9, 37.8, 35.5, 35.4, 34.7, 34.6, 34.1, 34.0, 26.5, 26.2, 18.6, 18.32, 18.25, 18.2, 17.62, 17.58, 17.4, 16.5, 16.3, 13.0, 12.6, 12.5, 11.6, 11.5, –4.9

IR (thin film/NaCl): 2941, 1754, 1669, 1464, 1255, 1065, 836, 776, 680 cm^{-1}

(ESI/NaI) *m/z* calc'd for $C_{39}H_{72}O_4Si_2Na$: 683.4861, found: 683.4854



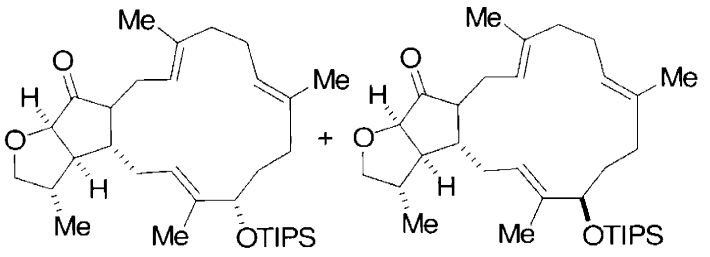
44a (R^1 = OTIPS; R^2 = H)
44b (R^1 = H; R^2 = OTIPS)

4-(13-Hydroxy-3,7,11-trimethyl-4-triisopropylsilanoxy-trideca-2,7,11-trienyl)-3-methyl-hexahydro-cyclopenta[*b*]furan-6-one (44a-44b): To a solution of **43a'-43b'** (0.93, 1.4 mmol) in THF (20 mL) was added 1 M HCl (20 mL) and stirred 8 h. The reaction mixture was diluted with ethyl acetate (60 mL) and water (60 mL). The organic layer was collected while the aqueous layer was washed with ethyl acetate (2x 60 mL). The organics were combined, washed with brine and dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (70:30 hexane:ethyl acetate) afforded **44a-44b** (650 mg, 84%). R_f (70:30 hexane:ethyl acetate): 0.27

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.41 (t, *J* = 7.0 Hz, 1H), 5.28 (t, *J* = 7.0, 1H), 5.07 (m, 1H), 4.24 (d, *J* = 7.9 Hz, 1H), 4.15 (d, *J* = 6.7 Hz, 2H), 4.08 (t, *J* = 6.4 Hz, 1H), 3.95 (m, 1H), 3.50 (m, 1H), 2.50 (m, 1H), 2.01-2.25 (m, 11H), 1.80 (m, 2H), 1.67 (s, 3H), 1.62 (m, 2H), 1.58 (s, 6H), 1.08 (m, 3H), 1.03 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.1, 216.0, 140.0, 139.9, 139.7, 135.4, 124.4, 124.0, 123.84, 123.83, 123.6, 123.5, 122.5, 122.4, 82.41, 82.38, 82.3, 78.7, 78.3, 78.2, 76.1, 76.0, 59.5, 54.6, 53.6, 53.5, 42.9, 42.5, 42.4, 40.5, 40.4, 40.2, 39.7, 37.9, 37.8, 37.4, 35.6, 35.5, 35.3, 34.8, 34.7, 34.6, 34.1, 34.0, 33.2, 26.5, 26.4,3 26.42, 26.2, 18.4, 18.30, 18.27, 17.7, 17.6, 17.5, 16.5, 16.40, 16.36, 16.3, 13.9, 12.62, 12.55, 12.6, 12.3, 11.7, 11.6

IR (thin film/NaCl): 3438, 2942, 1751, 1668, 1464, 1382, 1064, 883, 681 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{33}H_{58}O_4SiNa$: 569.3997, found: 569.3988



45a **45b**

4,8,12,17-Tetramethyl-11-triisopropylsilanyloxy-19-oxa-tricyclo[13.6.0.0]henicosa-3,7,12-trien-21-one (45a): To a solution of triphenylphosphine (77 mg, 0.3 mmol) in 6 mL of a 1:1 mixture of benzene:diethyl ether was added iodine (70 mg, 0.28 mmol) and imidazole (19 mg, 0.28 mmol) and stirred 5 min. A solution of **44a-44b** (100 mg, 0.18 mmol) in benzene (1 mL) was added and the reaction mixture was stirred for 40 min. At this stage, benzene (3 mL) was added and after 15 min, the reaction was complete by TLC. The crude mixture was poured into saturated sodium thiosulfate (40 mL), and diluted with hexane (40 mL). The organic layer was collected and the aqueous layer was extracted further with hexanes (2 x 40 mL). After combining the organic layers, this was washed with brine, dried by $MgSO_4$ and filtered into a round bottom wrapped in foil. The solution was concentrated *in vacuo* to crude iodide and carried onto the next step without further purification.

To the crude iodide was diluted in THF (26 mL), cooled to 0 °C and added LiHMDS (64 mg, 0.38 mmol, 4 mL THF) over 1.5 h. After addition, TLC reveals full conversion. The reaction mixture was diluted with water (50 mL) and extracted with diethyl ether (3 x 40 mL). The organics were combined, washed with brine (40 mL) and dried with $MgSO_4$. The solution was filtered and concentrated *in vacuo* to afford a yellow oil that was purified with silica gel chromatography (90:10 hexane:ethyl acetate) to afford a 2.1:1 mixture of diastereomers (**45a, 45b**) (32 mg, 32% over 2 steps). The desired diastereomer was then separated by silica gel chromatography (95:5 hexane:ethyl acetate). R_f (90:10 hexane:ethyl acetate): 0.31 (desired diastereomer, **(–)-45a**) R_f (90:10) hexane:ethyl acetate): 0.33 (undesired diastereomer **45b**).

^{1}H NMR (500 MHz, C_6D_6): δ 5.48 (m, 1H), 5.16 (t, J = 6.4 Hz, 1H), 5.04 (m, 1H), 4.18 (d, J = 7.6 Hz, 1H), 4.13 (dd, J^1 = 4.2 Hz, J^2 = 10.7 Hz, 1H), 3.71 (dd, J^1 = 5.8 Hz, J^2 =

8.5 Hz, 1H), 3.34 (dd, J^1 = 3.7 Hz, J^2 = 8.5 Hz, 1H), 3.02 (m, 1H), 1.65-2.28 (m, 15 H), 1.64 (s, 3H), 1.58, (s, 3H), 1.49 (s, 3H), 1.13 (m, 21H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 213.8, 136.6, 135.8, 133.8, 126.7, 126.1, 125.7, 82.3, 78.2, 75.2, 56.4, 53.7, 47.2, 40.5, 39.7, 35.7, 34.4, 32.1, 29.9, 24.8, 18.9, 15.9, 15.4, 13.8, 13.1, 10.8

IR (thin film/NaCl): 2939, 2865, 1751, 1457, 1061, 883 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{33}H_{56}O_3SiNa$: 551.3891, found: 551.3909

$[\alpha]_D$ = –8.4 (*c* 1.9, EtOH)

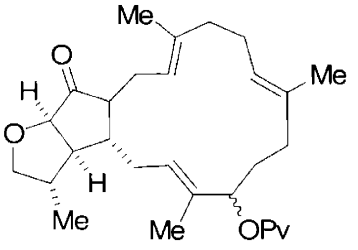
For compound **45b**:

^{1}H NMR (500 MHz, C_6D_6): δ 5.35 (t, J = 6.7 Hz, 1H), 5.22 (t, J = 6.7 Hz, 1H), 4.95 (m, 1H), 4.27 (d, J = 7.9 Hz, 1H), 4.12 (dd, J^1 = 2.7 Hz, J^2 = 11 Hz, 1H), 3.66 (dd, J^1 = 5.8 Hz, J^2 = 8.9 Hz, 1H), 3.36 (dd, J^1 = 3.4 Hz, J^2 = 8.9 Hz, 1H), 2.90 (dd, J^1 = 5.5 Hz, J^2 = 13.1 Hz, 1H), 1.67-2.20 (m, 15H), 1.66 (s, 3H), 1.57 (s, 3H), 1.46 (s, 3H), 1.10 (m, 21H), 0.83 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 213.9, 138.0, 136.5, 133.4, 127.1, 124.4, 123.8, 82.2, 78.1, 75.3, 52.7, 51.6, 45.2, 40.1, 39.9, 36.1, 31.8, 30.1, 27.8, 24.8, 19.5, 18.7, 15.3, 15.1, 13.8, 13.0, 10.5

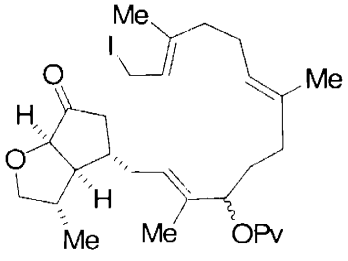
IR (thin film/NaCl): 2940, 1750, 1457, 1064, 883 cm^{-1}

(ESI/NaI) *m/z* calc'd for $C_{33}H_{56}O_3SiNa$: 551.3891, found: 551.3895

$[\alpha]_D$ = –11.4 (*c* 1.9, EtOH)



2,2-Dimethyl-propionic-acid-4,8,12,17-tetramethyl-21-oxo-19-oxa-tricyclo[13.6.0.0^{16,20}]henicosa-3,7,12-trien-11-yl ester (Pv-45): A solution of crude iodide (**PvI-44**) (10 mg, 0.017 mmol) in THF (6.5 mL) at 0 °C was added *via* slow addition (2mL/h) lithium bis(trimethylsilyl) amide (2 mL in THF). After addition, the reaction mixture was allowed to warm to room temperature and stir for 16 h. Saturated sodium thiosulfate (6 mL) was added and the solution was extracted with ether (3 x 7 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography to give **Pv-45** (5.3 mg, 55%). R_f (80:20 hexane:ethyl acetate): 0.32

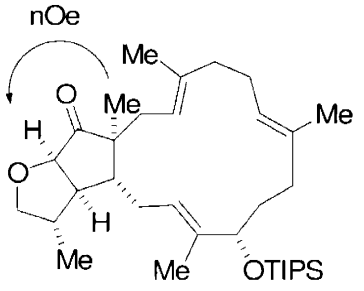


PvI-44

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.40-5.55 (m, 1H), 5.18 (m, 1H), 5.08 (m, 1H), 4.96 (m, 1H), 4.38 (m, 1H), 3.88 (m, 1H), 3.55 (m, 1H), 2.71 (m, 1H), 1.70-2.40 (m, 17H), 1.64 (s, 1.5H), 1.60 (m, 7.5H), 1.18 (s, 9H), 1.08 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 216.0, 177.7, 136.9, 136.1, 133.7, 133.6, 133.1, 132.8, 127.3, 126.9, 126.7, 124.6, 123.5, 122.5, 82.7, 82.2, 79.0, 78.6, 75.7, 75.5, 54.0, 53.0, 52.5, 51.3, 44.2, 43.9, 40.4, 39.7, 39.4, 39.2, 39.1, 35.1, 34.4, 34.0, 30.4, 29.0, 28.4, 27.4, 27.4, 27.3, 26.9, 24.3, 24.2, 18.8, 17.8, 16.2, 15.5, 15.4, 15.0, 11.8, 10.6.

IR (thin film/NaCl): 2927, 2930, 1749, 1724, 1480, 1455, 1396, 1280, 1159, 1031, 957 cm^{-1}

(ESI/NaI) *m/z* calc'd for $C_{29}H_{44}O_4Na$: 479.3132, found: 479.3152.



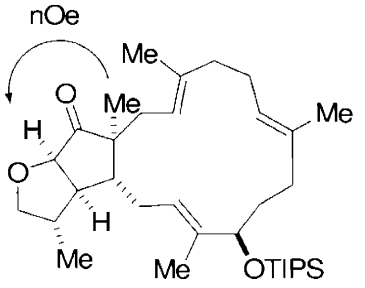
1,4,8,12,17-Pentamethyl-11-triisopropylsilanyloxy-19-oxa-tricyclo[13.6.0.0$^{16.20}$]henicosa-3,7,12-trien-21-one (46): To a solution of **(–)-45a** (19 mg, 0.036 mmol) in toluene (0.5 mL) was added NaH (4.3 mg, 0.11 mmol) and methyl iodide (22 μL, 0.36 mmol) and stirred for 5 min before the addition of water (1.3 μL, 0.072 mmol). The reaction mixture was stirred for 15 h and filtered through a plug of silica gel (40 mL of ethyl acetate). The reaction mixture was concentrated *in vacuo* to afford a yellow oil. Purification by silica gel chromatography (95:5 hexane:ethyl acetate) afforded **(+)-46** (12.1 mg, 62%) and the vinyl-methyl ether (**46a**) (2 mg, 10%). R_f (90:10 hexane:ethyl acetate): 0.34

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (t, J = 6.7 Hz, 1H), 5.02 (t, J = 7.0 Hz, 1H), 4.83 (m, 1H), 4.51 (d, J = 7.9 Hz, 1H), 3.96 (dd, J^1 = 4.0 Hz, J^2 = 10.4 Hz, 1H), 3.74 (dd, J^1 = 5.2 Hz, J^2 = 8.8 Hz, 1H), 3.60 (dd, J^1 = 2.4 Hz, J^2 = 8.8 Hz, 1H), 1.65-2.35 (m, 15H), 1.57 (s, 3H), 1.55 (s, 3H), 1.53 (s, 3H), 1.11 (d, J = 7.0 Hz, 3H), 1.04 (m, 21H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 217.4, 136.6, 136.2, 134.9, 127.5, 125.0, 122.8, 82.1, 79.7, 75.1, 53.2, 53.1, 48.2, 41.8, 39.8, 35.6, 35.5, 32.6, 29.9, 24.4, 19.9, 18.8, 18.1, 16.0, 15.3, 13.1, 10.9

IR (thin film/NaCl): 2932, 2866, 1750, 1462, 1382, 1061, 883 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{33}H_{58}O_3SiNa$: 565.4047, found: 565.4047.

$[\alpha]_D$ = +5.0, (*c* 0.8, EtOH).



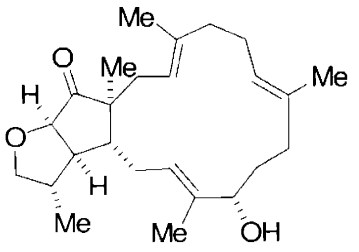
1,4,8,12,17-Pentamethyl-11-triisopropylsilanyloxy-19-oxa-tricyclo[13.6.0.0$^{16.20}$]henicosa-3,7,12-trien-21-one (11-*epi*-46): To a solution of **45b** (40 mg, 0.076 mmol) in toluene (1 mL) was added NaH (9.0 mg, 0.23 mmol) and methyl iodide (50 μL, 0.76 mmol) and stirred for 5 min before the addition of water (3 μL, 0.15 mmol). The reaction mixture was stirred for 6 h and filtered through a plug of silica gel (80 mL of ethyl acetate). The reaction mixture was concentrated *in vacuo* to afford a yellow oil. Purification by silica gel chromatography (95:5 hexane:ethyl acetate) afforded **(+)-11-*epi*-46** (15.1 mg, 37%). R_f (90:10 hexane:ethyl acetate): 0.34

^{1}H NMR (500 MHz, C_6D_6): δ 5.35 (t, J = 6.7 Hz, 1H), 5.22 (t, J = 6.7 Hz, 1H), 4.95 (m, 1H), 4.27 (d, J = 7.9 Hz, 1H), 4.12 (dd, J^1 = 2.7 Hz, J^2 = 11 Hz, 1H), 3.66 (dd, J^1 = 5.8 Hz, J^2 = 8.9 Hz, 1H), 3.36 (dd, J^1 = 3.4 Hz, J^2 = 8.9 Hz, 1H), 2.90 (dd, J^1 = 5.5 Hz, J^2 = 13.1 Hz, 1H), 1.67-2.20 (m, 15H), 1.66 (s, 3H), 1.57 (s, 3H), 1.46 (s, 3H), 1.10 (m, 21H), 0.83 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 213.9, 138.0, 136.5, 133.4, 127.1, 124.4, 123.8, 82.2, 78.1, 75.3, 52.7, 51.6, 45.2, 40.1, 39.9, 36.1, 31.8, 30.1, 27.8, 24.8, 19.5, 18.7, 15.3, 15.1, 13.8, 13.0, 10.5

IR (thin film/NaCl): 2940, 1750, 1457, 1064, 883 cm^{-1}

(ESI/NaI) *m/z* calc'd for $C_{33}H_{56}O_3SiNa$: 551.3891, found: 551.3895

$[\alpha]_D$ = +72.8, (*c* 1.5, EtOH)



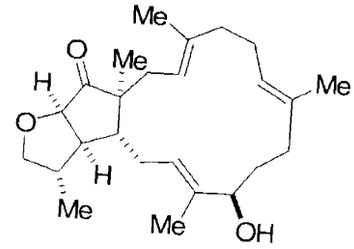
11-Hydroxy-1,4,8,12,17-pentamethyl-19-oxa-tricyclo[13.6.0.0^{16,20}]henicosa-3,7,12-trien-21-one (47): To a solution of **(+)-46** (10 mg, 0.0184 mmol) in THF (0.2 mL) was added TBAF (32 μL, 1.0 M THF) and stirred 3 h. The reaction mixture was diluted with water (2 mL) and extracted with diethyl ether (3 x 3 mL). The organics were combined, dried with $MgSO_4$, filtered through a plug of silica gel, and concentrated *in vacuo* to afford a clear and colorless oil. Purification by silica gel chromatography (85:15 hexane:ethyl acetate) afforded **(+)-47** (5 mg, 72%) as a clear colorless oil. R_f (70:30 hexane:ethyl acetate): 0.19

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.46 (t, J = 7.0 Hz, 1H), 4.92 (t, J = 4.9 Hz, 2H), 4.50 (d, J = 7.9 Hz, 1H), 4.01 (dd, J^1 = 4.0 Hz, J^2 = 8.8 Hz, 1H), 3.79 (dd, J^1 = 5.5 Hz, J^2 = 8.5 Hz, 1H), 3.62 (dd, J^1 = 2.4 Hz, J^2 = 8.5 Hz, 1H), 1.65-2.42 (m, 16 H), 1.62 (s, 3H), 1.57 (s, 3H), 1.54 (s, 3H), 1.14 (d, J = 7.0 Hz, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 219.3, 136.4, 136.2, 135.8, 126.3, 124.6, 122.3, 81.6, 78.3, 75.3, 53.2, 52.4, 46.1, 41.3, 39.0, 34.5, 34.1, 30.0, 29.1, 23.8, 19.8, 18.7, 15.8, 15.0, 12.0.

IR (thin film/NaCl): 3461, 2930, 1748, 1663, 1456, 1381, 1096, 1005, 914, 735 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{25}H_{38}O_3Na$: 409.2713, found: 409.2721.

$[\alpha]_D$ = +27.7, (*c* 0.83, EtOH)



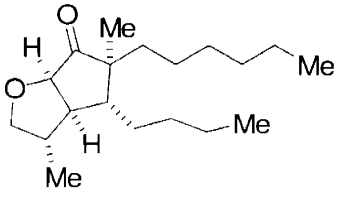
11-Hydroxy-1,4,8,12,17-pentamethyl-19-oxa-tricyclo[13.6.0.0^{16,20}]henicosa-3,7,12-trien-21-one (11-*epi*-47): To a solution of **11-*epi*-46** (15 mg, 28 μmol) in THF (0.4 mL) was added TBAF (42 μL, 1.0 M THF) at room temperature and stirred 16 h. The reaction mixture was quenched with water (8 mL) and extracted with diethyl ether (3 x 8 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (80:20 hexane:ethyl acetate) to afford **11-*epi*-47** (5 mg, 47%) .

^{1}H NMR (500 MHz, C_6D_6): δ 5.23 (m, 1H), 5.11 (dd, J^1 = 1.5 Hz, J^2 = 8.8 Hz, 1H), 4.95 (m, 1H), 4.19 (d, J = 7.3 Hz, 1H), 3.83 (dd, J^1 = 3.7 Hz, J^2 = 11.0 Hz, 1H), 3.76 (dd, J^1 = 5.2 Hz, J^2 = 8.5 Hz, 1H), 3.40 (dd, J^1 = 2.1 Hz, J^2 = 8.8 Hz, 1H), 2.72 (dd, J^1 = 1.5 Hz, J^2 = 12.5 Hz, 1H), 1.68-2.15 (m, 15 H), 1.56 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H), 0.81 (d, J = 7.0 Hz, 3H), 0.66 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 216.8, 136.0, 135.9, 133.9, 127.9, 127.4, 125.8, 123.8, 103.4, 81.4, 76.6, 75.3, 53.8, 53.1, 45.2, 40.4, 38.9, 35.6, 34.3, 30.8, 27.9, 24.2, 20.4, 19.3, 18.5, 15.3, 14.8, 10.4.

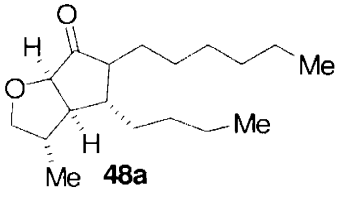
IR (thin film/NaCl): 3446, 2930, 1748, 1662, 1455, 1379, 1091, 810 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{25}H_{38}O_3Na$: 409.2713, found: 409.2721.

$[\alpha]_D$ = +113.3, (*c* 0.75, EtOH)



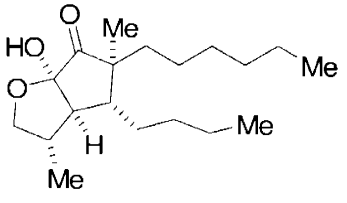
4-Butyl-5-hexyl-3,5-dimethyl-hexahydro-cyclopenta[*b*]furan-6-one (48): To a slurry of NaH (240 mg, 6 mmol, 60 % dispersion in mineral oil) in toluene (2 mL) was added **48a** (480 mg, 2 mmol). After having stirred 5 min, methyl iodide (1.26 mL, 20 mmol) and water (72 μL, 4 mmol) was added. The reaction mixture was stirred 7 h, filtered through a plug of silica gel, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (90:10 hexane:ethyl acetate) to afford **48** (350 mg, 69 %) in 20:1 diastereoselectivity.


48a

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.43 (d, J = 8.2 Hz), 3.68 (dd, J^1 = 5.5 Hz, J^2 = 8.8 Hz, 1H), 3.58 (d, J = 8.5 Hz, 1H), 2.17 (m, 1H), 2.09 (t, J = 8.8 Hz, 1H), 1.15-1.68 (m, 19H), 1.09 (d, J = 7.0 Hz, 3H), 0.94 (t, J = 6.7 Hz, 3H), 0.88 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 219.8, 81.6, 74.9, 52.9, 51.3, 45.3, 41.5, 35.1, 31.9, 30.7, 30.1, 24.6, 23.5, 22.8, 19.8, 19.4, 14.3.

IR (thin film/NaCl): 2958, 1749, 1457, 1378, 1113, 1002, 917, 729 cm^{-1}

(ESI/NaI) *m/z* calc'd for $C_{19}H_{34}O_2$: 295.2632, found: 295.2642



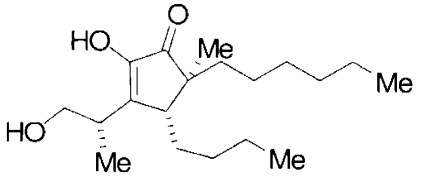
4-Butyl-5-hexyl-6a-hydroxy-3,5-dimethyl-hexahydro-cyclopenta[b]furan-6-one (48b): To a solution of potassium hexamethyl disilazane (35 mg, 0.18 mmol) in THF (0.7 mL) at –78 °C was added **48** (40 mg, 0.14 mmol, in 0.3 mL THF). After stirring 1 h, Davis' oxaziridine (46 mg, 0.18 mmol, in 0.5 mL THF) was added. The reaction mixture

was stirred 0.5 h, quenched with aqueous NH_4Cl_4 (3 mL), and extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (92:8 hexane:ethyl acetate) to afford **48b** (28 mg, 66 %).

^{1}H NMR (500 MHz, C_6D_6): δ 4.02 (t, *J* = 7.9 Hz, 1H), 3.77 (m, 1H), 3.70 (m, 1H), 2.05 (m, 1H), 1.91 (d, *J* = 10.1 Hz, 1H), 1.79 (m, 1H), 1.65 (m, 1H), 1.15-1.38 (m, 11H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.88 (m, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ 215.3, 107.2, 76.9, 58.8, 52.5, 43.6, 39.9, 37.7, 32.3, 31.4, 30.6, 30.5, 25.4, 24.0, 23.4, 20.6, 20.5, 14.7, 14.6.

IR (thin film/NaCl): 3419, 2958, 1753, 1459, 1379, 1077, 1007, 924, 833 cm^{-1}

(ESI/NaI) *m/z* calc'd for $C_{19}H_{34}O_3Na$: 333.2400, found: 333.2392

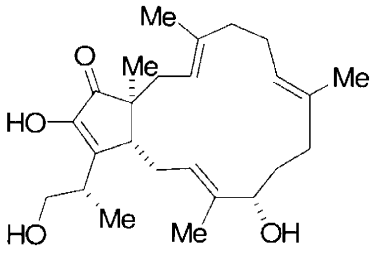


4-Butyl-5-hexyl-2-hydroxy-3-(2-hydroxy-1-methyl-ethyl)-5-methyl-cyclopent-2-enone (49): To a solution of **48b** (28 mg, 0.09 mmol) in MeOH (0.9 mL) was added potassium carbonate (62 mg, 0.45 mmol) and stirred at room temperature for 4 h. The reaction mixture was quenched with saturated ammonium chloride (4 mL) and extracted with ethyl acetate (3 x 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (92:8 hexane:ethyl acetate) to afford **49** (21 mg, 75%) .

^{1}H NMR (500 MHz, C_6D_6): δ 7.35 (s (br), 1H), 3.81 (m, 1H), 3.65 (m, 1H), 2.45 (m, 1H), 2.35 (t, *J* = 6.7 Hz, 1H), 1.1-1.62 (m, 20H), 1.06 (s, 3H), 0.88 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6): δ 208.3, 150.3, 148.3, 66.2, 49.1, 48.9, 41.5, 37.7, 32.4, 32.0, 30.6, 29.8, 25.1, 23.8, 23.4, 19.7, 14.9, 14.7, 14.5.

IR (thin film/NaCl): 3343, 2957, 1694, 1651, 1461, 1406, 1378, 1326, 1117, 1029 cm^{-1}

(ESI/NaI) *m/z* calc'd for $C_{19}H_{34}O_3Na$: 333.2400, found: 333.2402.



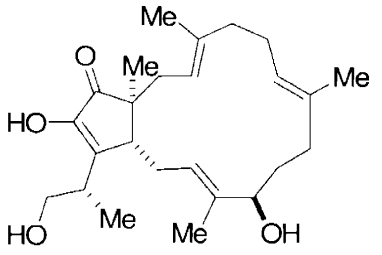
(–)-Terpestacin (1): To a solution of potassium bis(trimethylsilyl)amide (8 mg, 0.039 mmol dissolved in 0.25 mL THF) at -78 °C was added **(+)-47** (5 mg, 0.013 mmol in 0.15 mL THF) and stirred for 1 h. During the addition, the solution progressively turned orange. Triethylphosphite (4 μL, 0.023 mmol) was then added and oxygen was bubbled through the reaction mixture for 45 min whereby the solution becomes colorless. To this colorless solution was added water (4 mL) and extracted with ethyl acetate (3 x 4 mL). The organics were combined, dried with $NaSO_4$, filtered through celite, and concentrated *in vacuo* to afford a clear and colorless oil. The crude hemi-ketal was taken up in MeOH (1 mL), added potassium carbonate (9 mg, 0.065 mmol) and stirred at room temperature for 2 h. The reaction mixture was transferred to water (4 mL) and extracted with ethyl acetate (3 x 4 mL). The organics were combined dried with $NaSO_4$, filtered through celite, and concentrated *in vacuo* to afford a clear and colorless oil. Preparative silica gel chromatography (1:2 ethyl acetate:hexane, 0.5% HOAc) afforded **(–)-1** (2.5 mg, 48% over 2 steps). R_f (1:2 hexane:ethyl acetate, 0.5% HOAc): 0.28

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (s, 1H), 5.41 (m, 1H), 5.25 (dd, J^1 = 5.2 Hz, J^2 = 10.1 Hz, 1H), 5.14 (m, 1H), 4.07 (dd, J^1 = 4.0 Hz, J^2 = 10.1 Hz, 1H), 3.90 (dd, J^1 = 7.0 Hz, J^2 = 10.4 Hz, 1H), 3.83 (dd, J^1 = 5.5 Hz, J^2 = 10.4 Hz, 1H), 2.72 (dd, J^1 = 2.1 Hz, J^2 = 11.3 Hz, 1H), 2.68 (m, 1H), 2.45 (d, J = 17.4 Hz, 1H), 2.40 (dd, , J^1 = 10.4 Hz, J^2 = 13.7 Hz, 1H), 2.22-2.30 (m, 2H), 2.09-2.12 (m, 2H), 1.90-2.04 (m, 2H), 1.68-1.80 (m, 3H), 1.65 (s, 3H), 1.64 (s, 3H), 1.58 (s, 3H), 1.30 (d, J = 7.3 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.0, 149.0, 146.8, 138.3, 136.7, 133.1, 129.1, 124.5, 121.7, 76.7, 66.3, 49.8, 49.1, 40.5, 39.5, 37.3, 35.1, 30.0, 29.0, 24.0, 16.4, 15.8, 15.5, 14.6, 10.7.

IR (thin film/NaCl): 3366, 2925, 1699, 1653 cm^{-1}

HRMS-ESI(NaI) *m/z* calc'd for $C_{25}H_{38}O_4Na$: 425.2662, found: 425.2682

$[\alpha]_D = -18$, (*c* 0.1, MeOH)



(+)-11-*epi*-terpestacin (2): To a solution of potassium bis(trimethylsilyl)amide (8 mg, 0.039 mmol dissolved in 0.25 mL THF) at -78 °C was added C11-***epi*-(+)-47** (5 mg, 0.013 mmol in 0.15 mL THF) and stirred for 1.5 h. During the addition, the solution progressively turns orange. Triethyl phosphite (4 μL, 0.023 mmol) was then added and oxygen was bubbled through the reaction mixture for 30 min whereby the solution becomes colorless. To this colorless solution was added water (4 mL) and extracted with diethyl ether (2 x 8 mL). The organic layers were combined and washed with water (2 x 8 mL), dried with $NaSO_4$, filtered through celite, and concentrated *in vacuo* to afford a clear and colorless oil.

The crude hemi-ketal was taken up in MeOH (1 mL), added potassium carbonate (9 mg, 0.065 mmol) and stirred at room temperature 2.5 h. The reaction mixture was transferred to water (4 mL), extracted with diethyl ether (2 x 8 mL) and washed with water (5 x 8 mL). The organic layers were combined, dried with $NaSO_4$, and concentrated *in vacuo*. Silica gel chromatography (2:1 hexane:ethyl acetate, 0.25% HOAc) afforded (+)-11-*epi*-terpestacin (3.0 mg, 58 %). R_f (1:2 hexane:ethyl acetate, 0.5% HOAc): 0.6.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (dt, J^1 = 0.9 Hz, J^2 = 4.9 Hz, 1H), 5.34 (t, J = 7.3 Hz, 1H), 5.13 (m, 1H), 4.06 (dd, J^1 = 3.7 Hz, J^2 = 9.2 Hz, 1H), 3.89 (dd, J^1 = 6.7 Hz, J^2 = 10.4 Hz, 1H), 3.83 (dd, J^1 = 5.5 Hz, J^2 = 10.4 Hz, 1H), 2.71 (m, 1H), 2.57 (dd, J^1 = 2.1

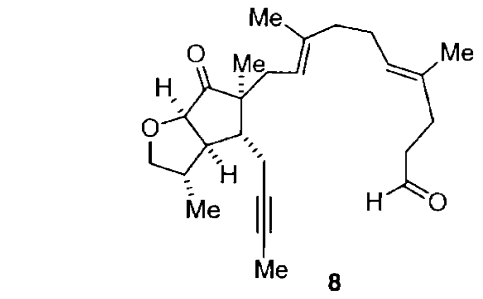
Hz, J^2 = 11.9 Hz, 1H), 2.50 (dd, J^1 = 6.1 Hz, J^2 = 17.4 Hz, 1H), 2.05-2.27 (m, 6H), 1.98 (dd, J^1 = 9.1 Hz, J^2 = 14.0 Hz, 1H), 1.70-1.88 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H), 1.30 (d, J = 7.3 Hz, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.6, 148.9, 146.4, 137.7, 135.9, 134.4, 127.0, 125.6, 121.9, 76.7, 66.4, 48.8, 48.7, 40.3, 38.9, 37.2, 35.5, 29.5, 28.6, 24.3, 16.7, 15.3, 15.2, 14.5, 11.4.

IR (thin film/NaCl): 3344, 2932, 1649, 1651 cm^{-1}

HRMS-ESI *m/z* calc'd for $C_{25}H_{39}O_4$: 403.2843, found: 403.2845

$[\alpha]_D$ = +36, (*c* 0.50, MeOH)

Chapter 2: Spectra



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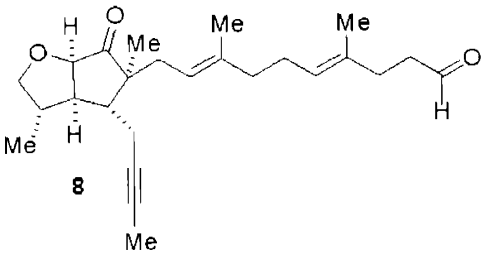
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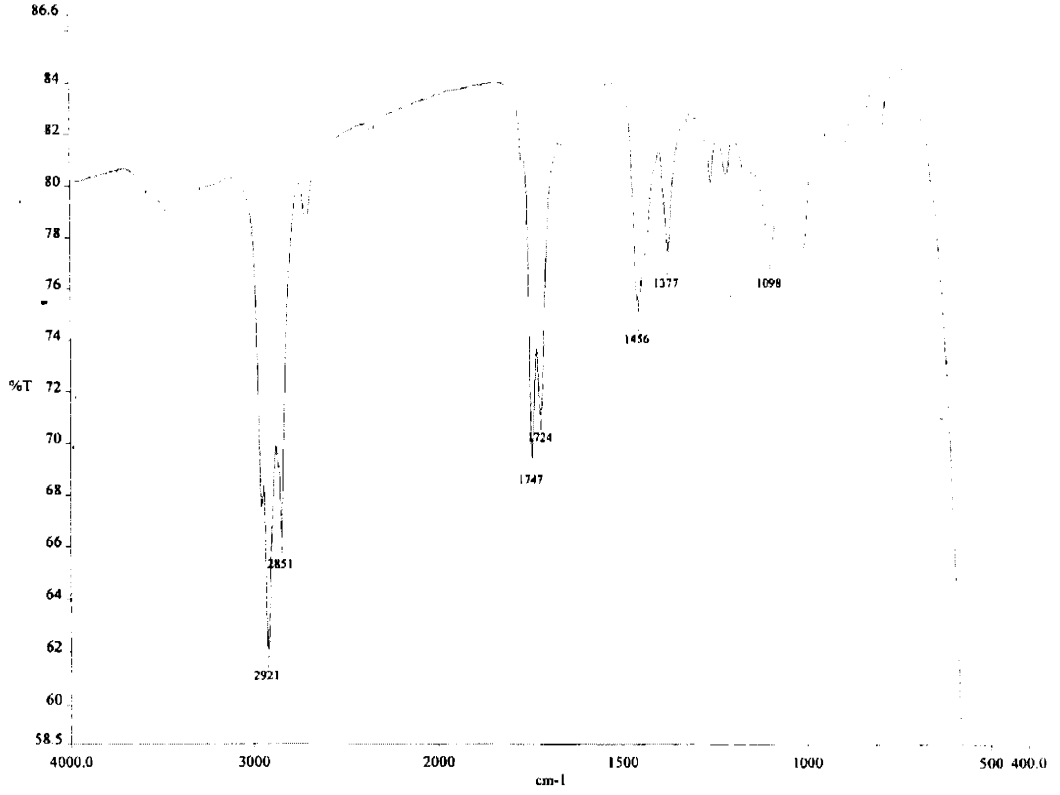
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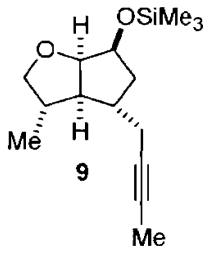

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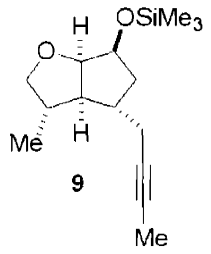
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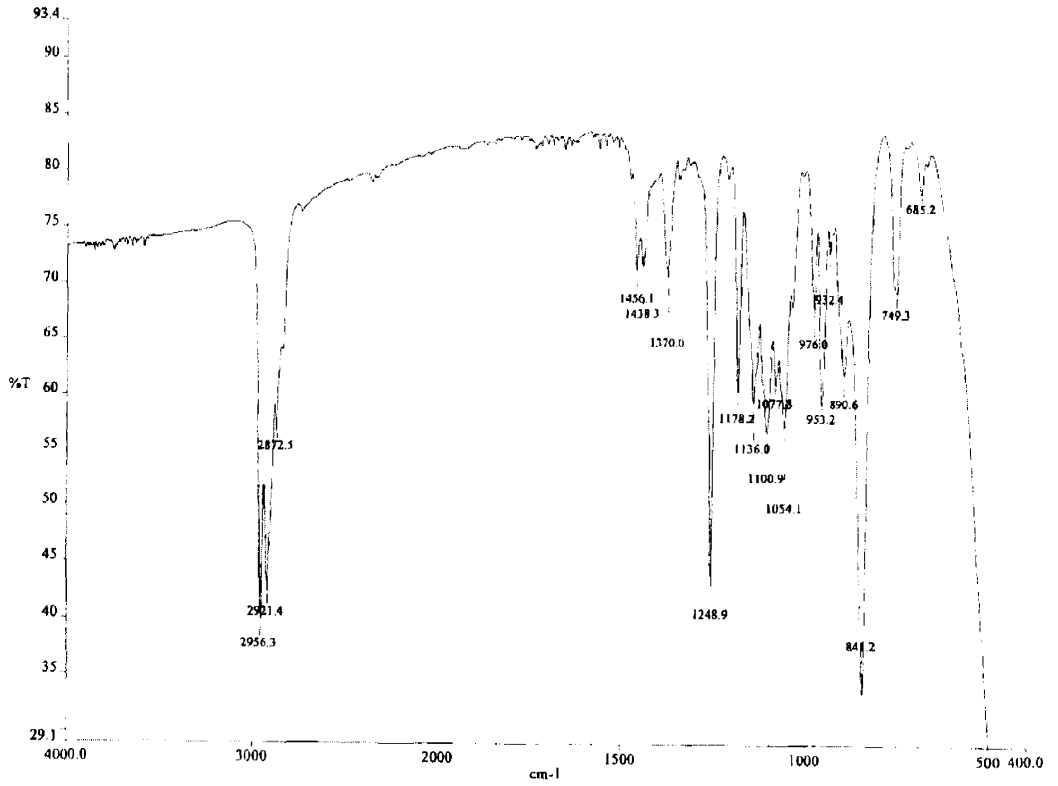
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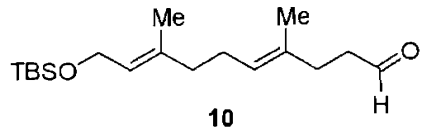

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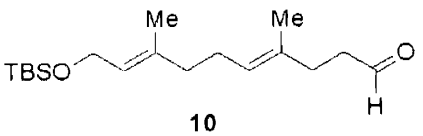
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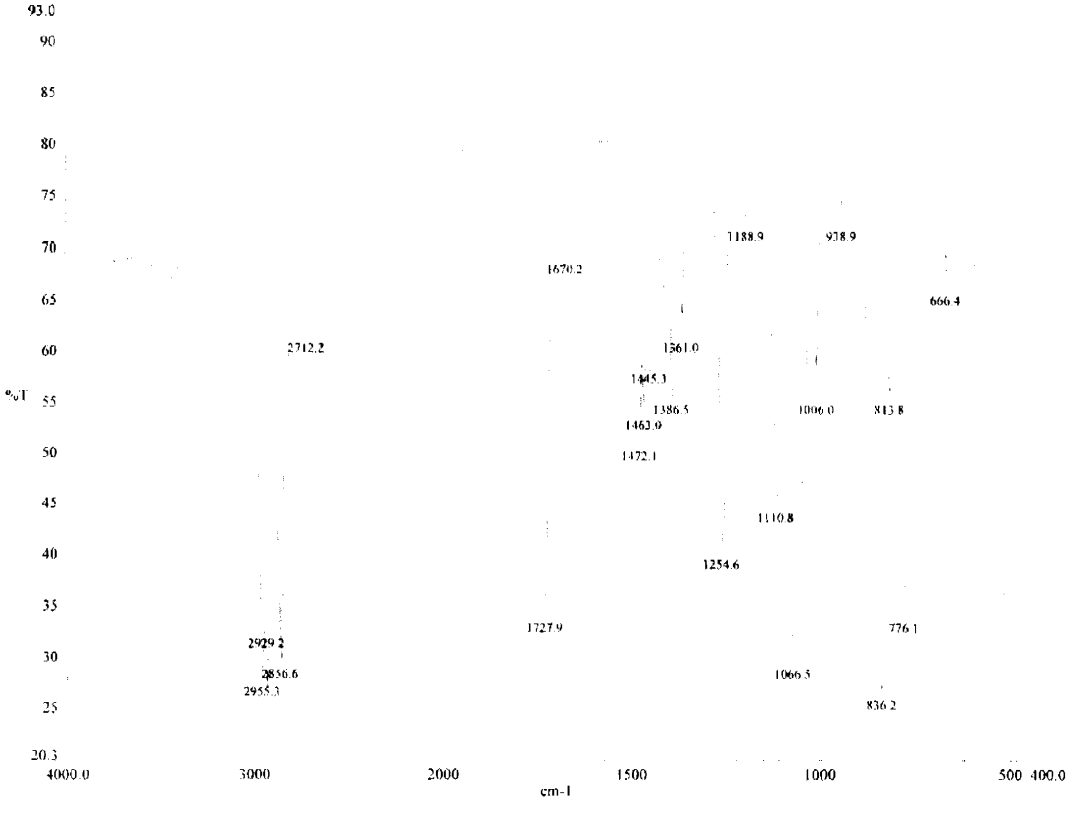
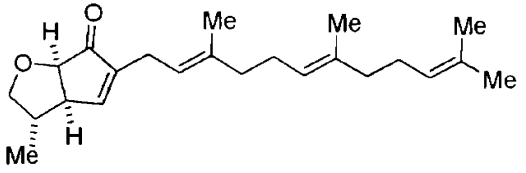
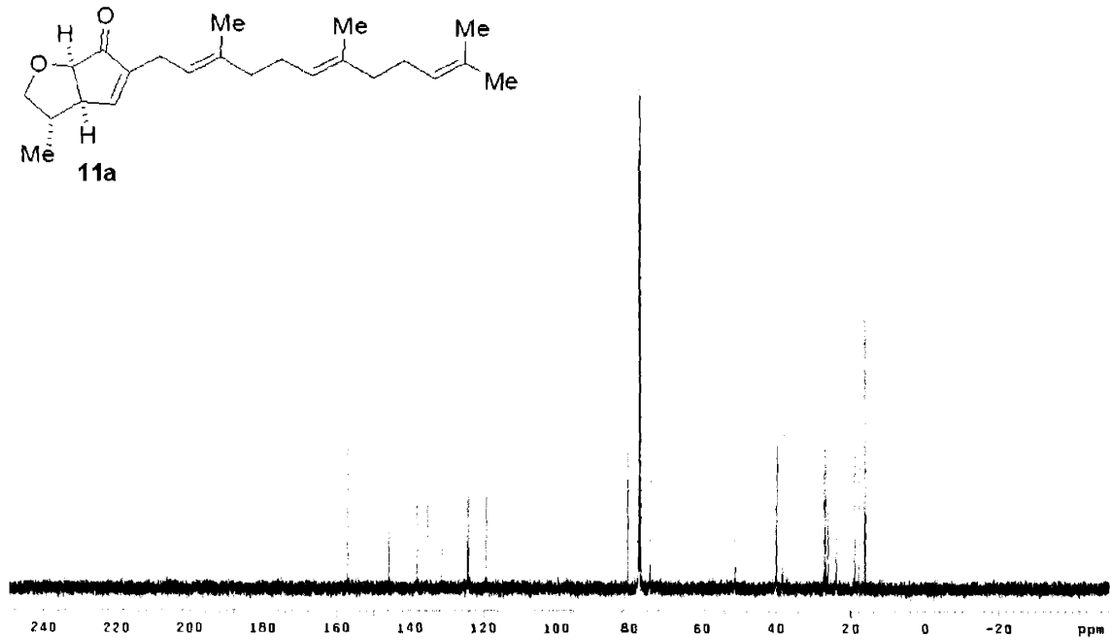
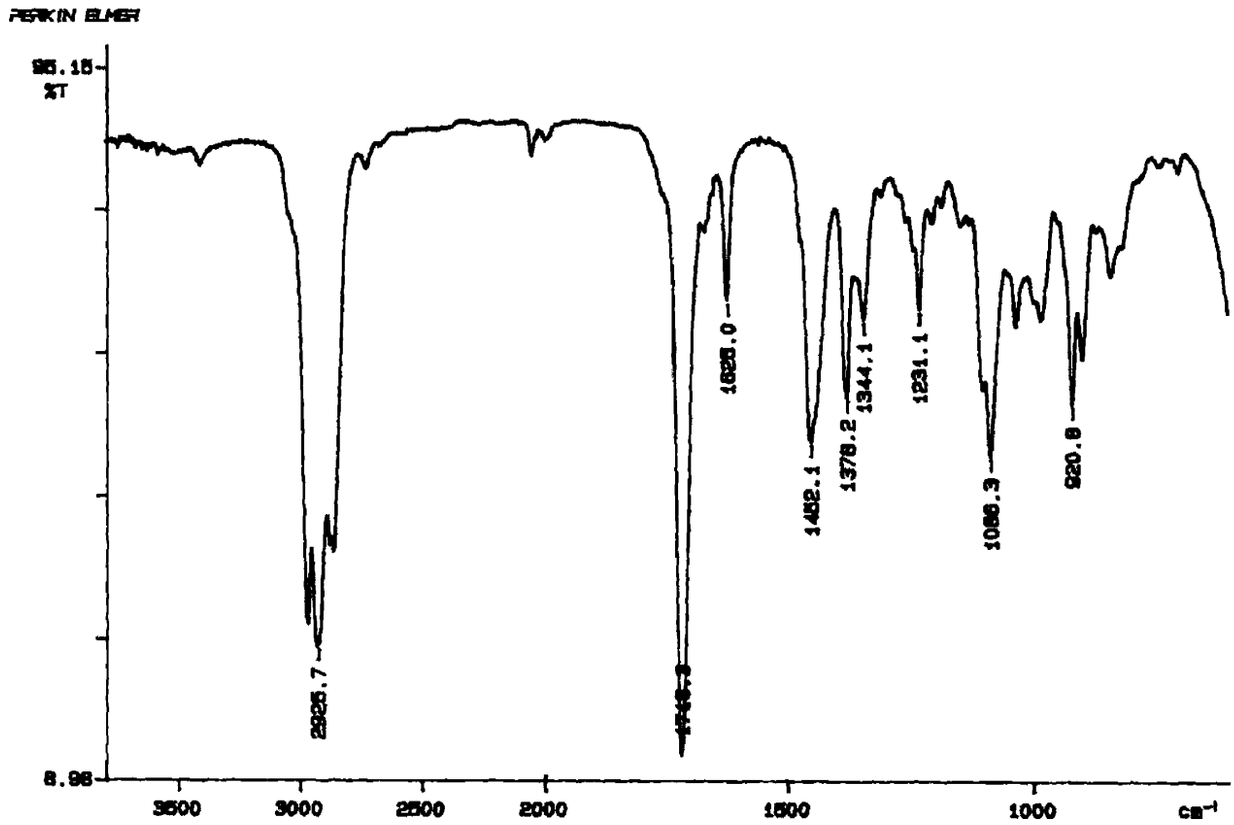
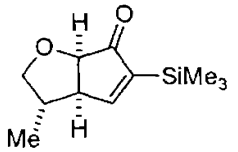

%T
93.0
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20.3
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2955.3
2929.2
2856.6
2712.2
1727.9
1670.2
1472.1
1463.0
1445.3
1386.5
1361.0
1254.6
1188.9
1110.8
1066.5
1006.0
938.9
836.2
813.8
776.1
666.4



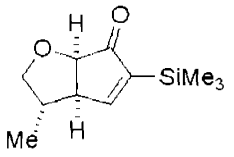
11a


H
O
O
Me
Me
Me
Me
H
Me
11a
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


PERKIN ELMER
95.15
%T
8.98
2925.7
1626.0
1452.1
1378.2
1344.1
1231.1
1066.3
920.8
3500
3000
2500
2000
1500
1000
cm-1

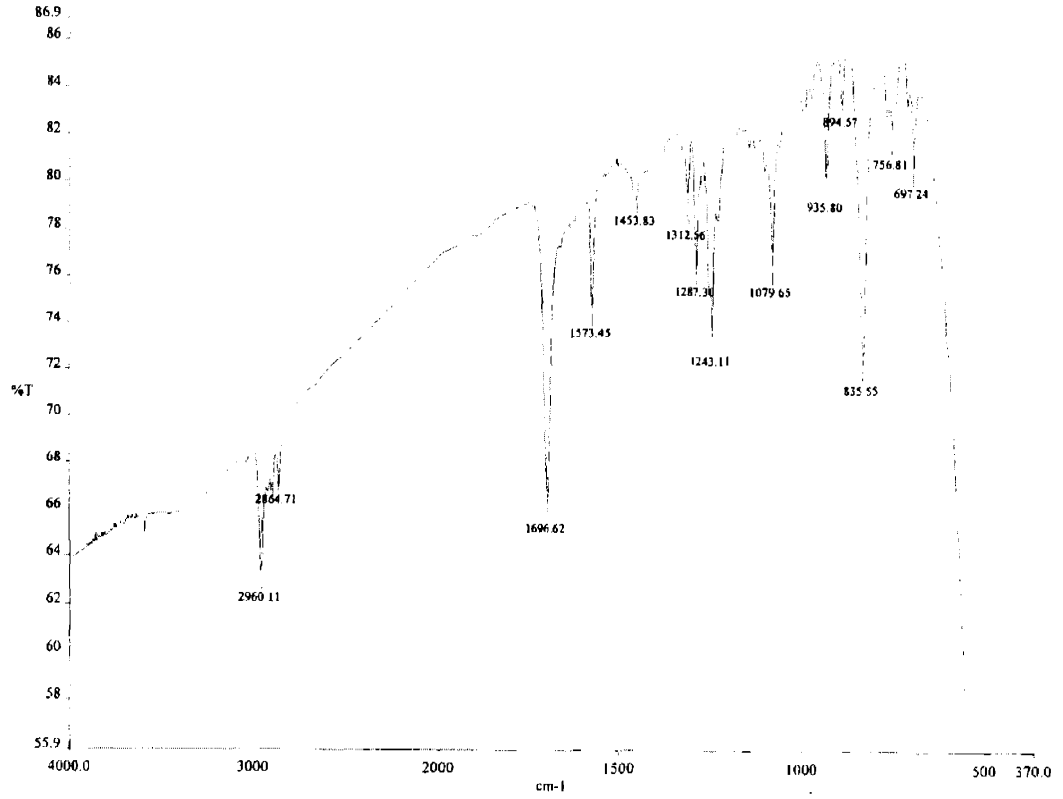


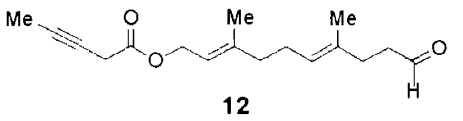
11b


H
O
O
SiMe3
Me
H

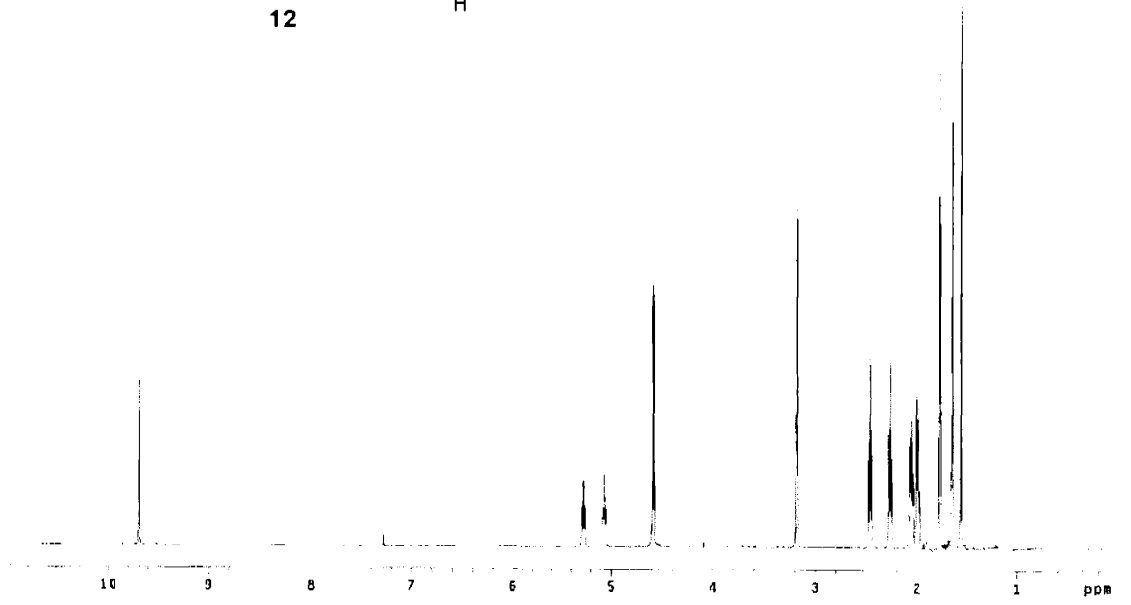
11b

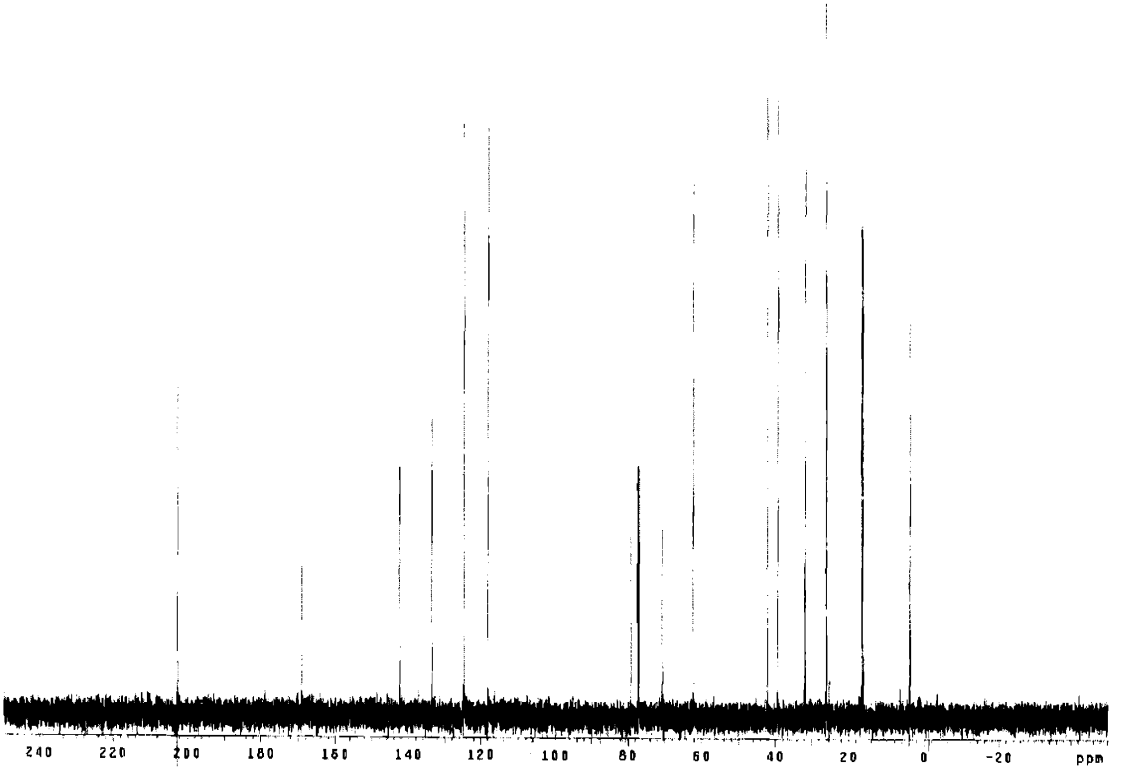
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

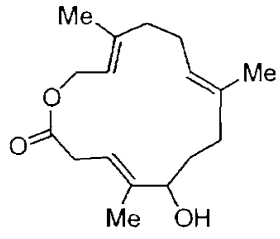

%T
86.9
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
55.9
2864.71
2960.11
1696.62
1573.45
1453.83
1312.56
1287.30
1243.11
1079.65
935.80
894.57
835.55
756.81
697.24
4000.0
3000
2000
1500
1000
500
370.0
cm-1


Me
O
Me
Me
O
O
H

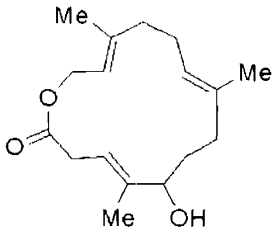
12


10
9
8
7
6
5
4
3
2
1
ppm


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

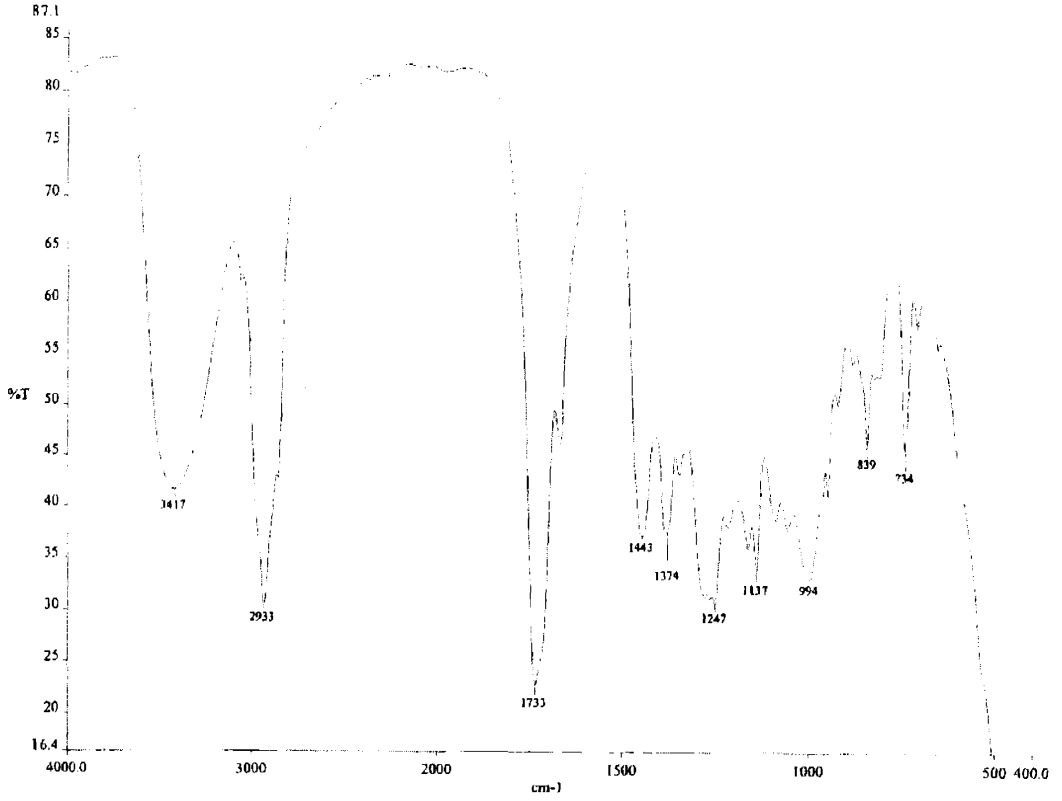


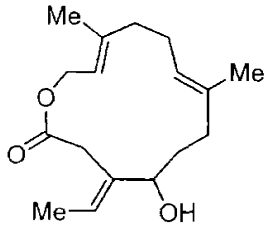
13


Me
Me
O
O
Me
OH

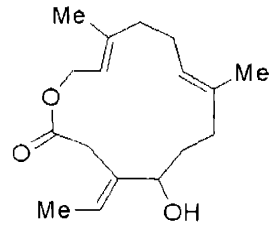
13

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


87.1
85
80
75
70
65
60
55
%T
50
45
40
35
30
25
20
16.4
3417
2933
1733
1443
1374
1247
1137
994
839
734
4000.0
3000
2000
1500
1000
500 400.0
cm-1

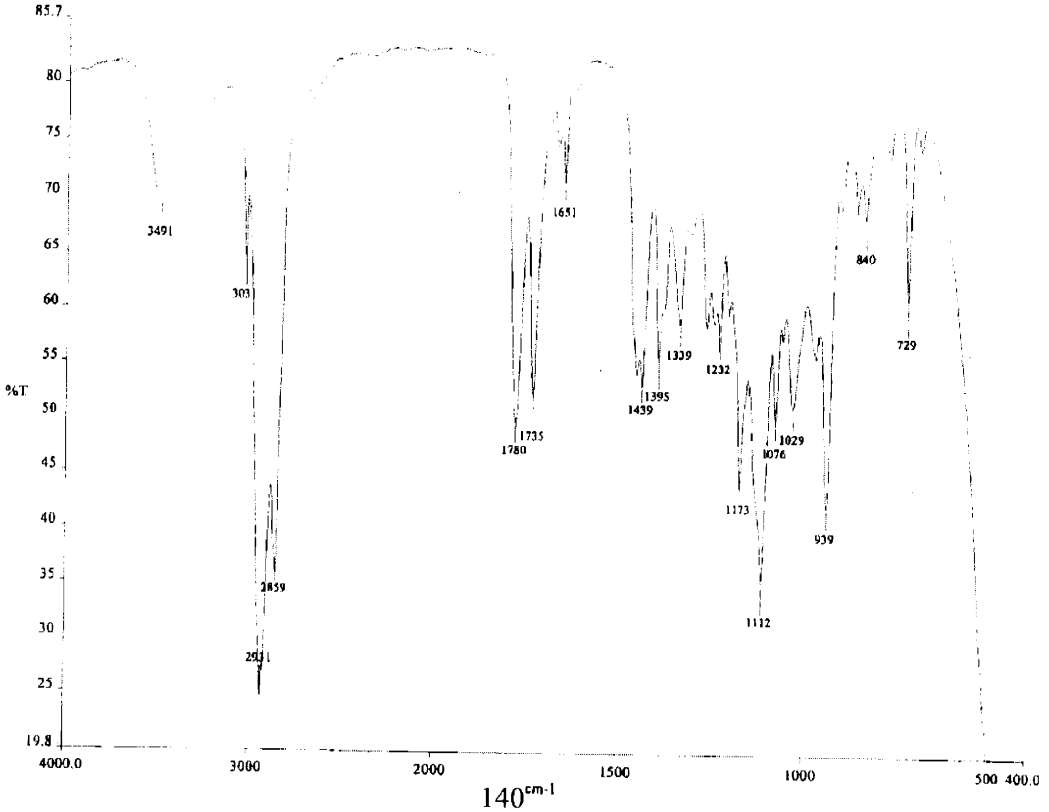


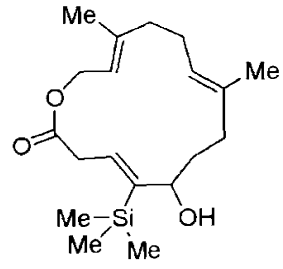
14


Me
Me
O
O
Me
OH

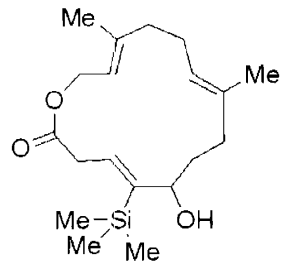
14

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
85.7
80
75
70
65
60
55
50
45
40
35
30
25
19.8
3491
3031
2959
2931
1780
1735
1651
1439
1395
1339
1232
1173
1112
1076
1029
939
840
729
4000.0
3000
2000
1500
1000
500 400.0
cm-1

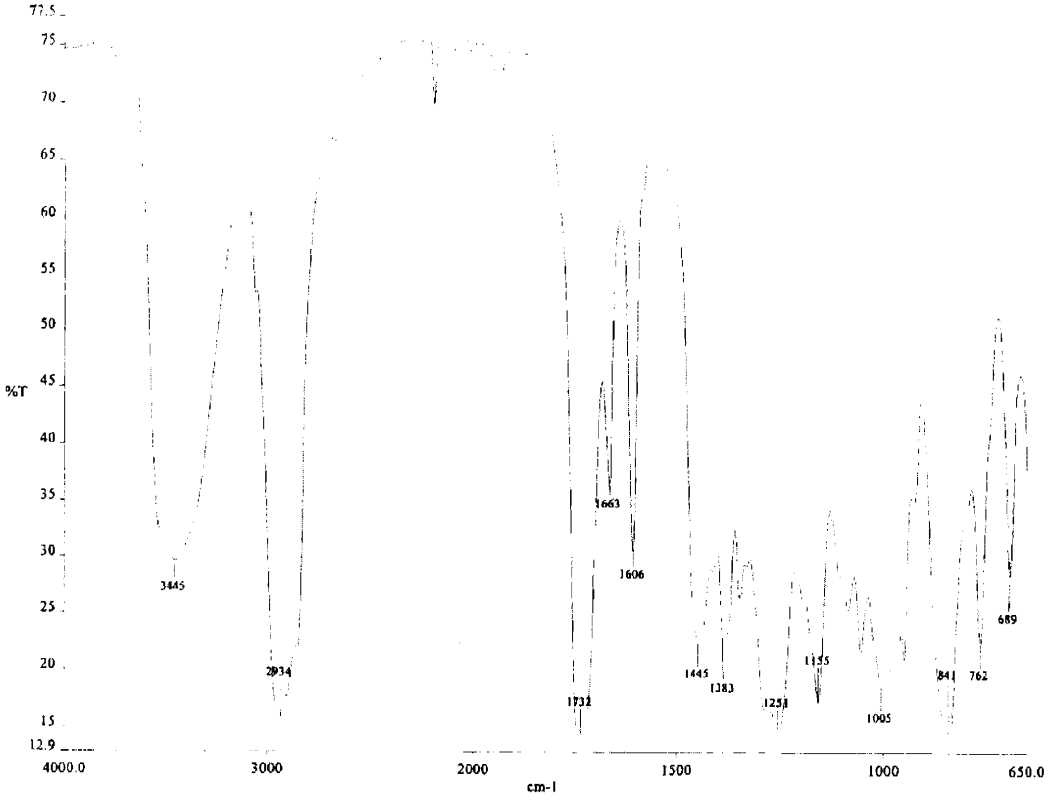


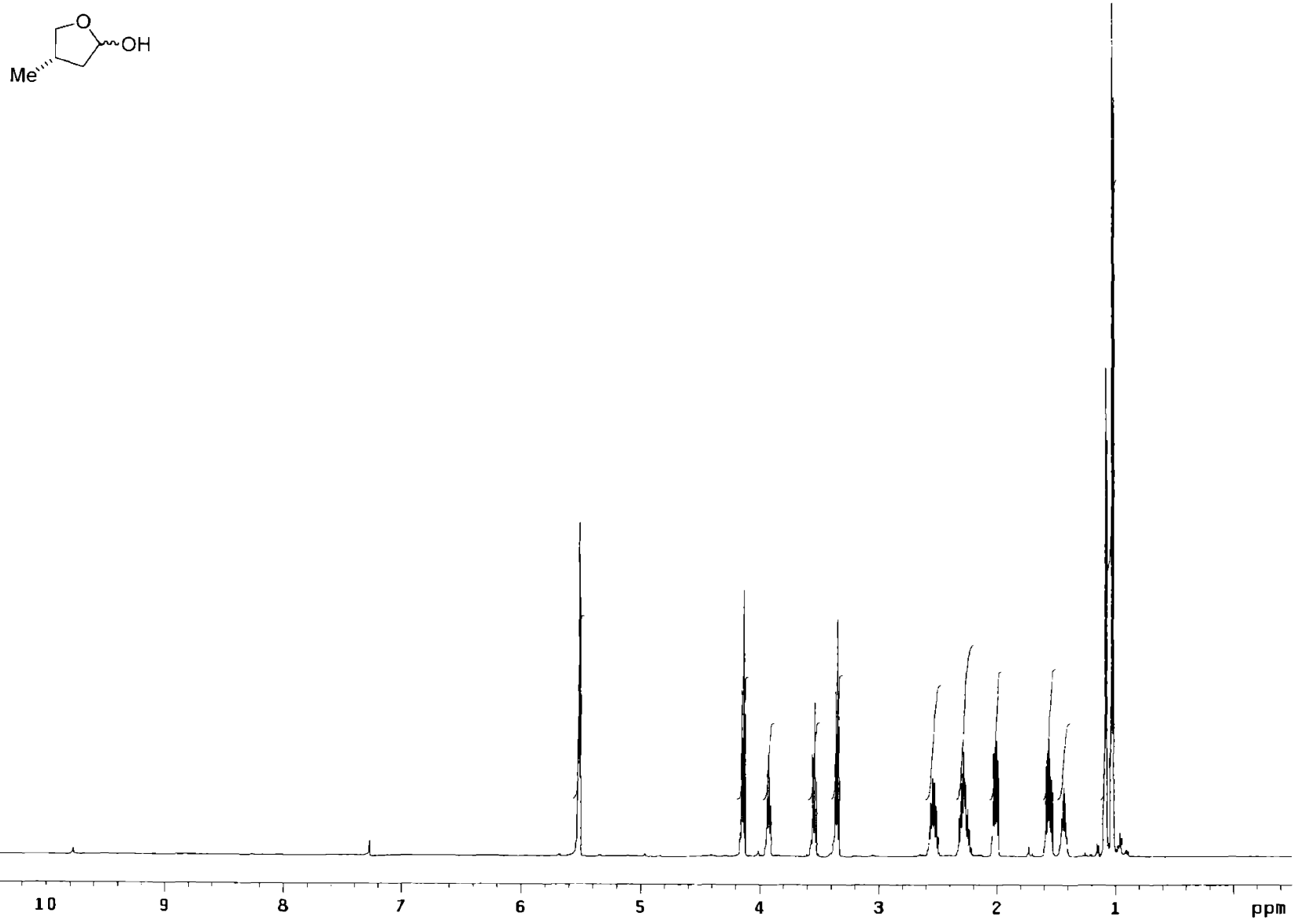
14a

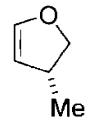

Me
Me
O
O
Me–Si
Me
Me
OH

14a

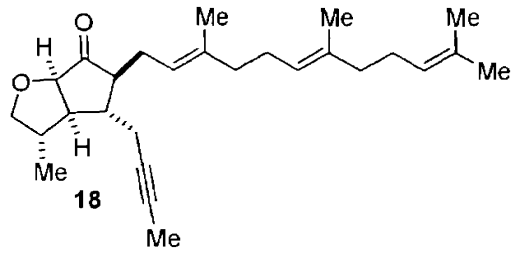
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
3445
2934
1732
1663
1606
1445
1383
1251
1155
1095
841
762
689
4000.0
3000
2000
1500
1000
650.0
cm-1

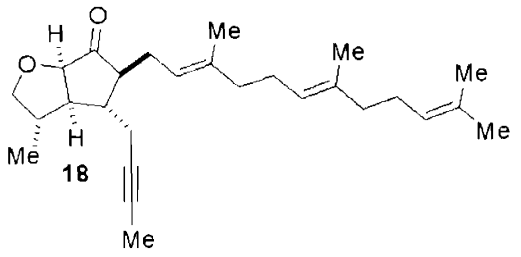

O
OH
Me
11
10
9
8
7
6
5
4
3
2
1
ppm

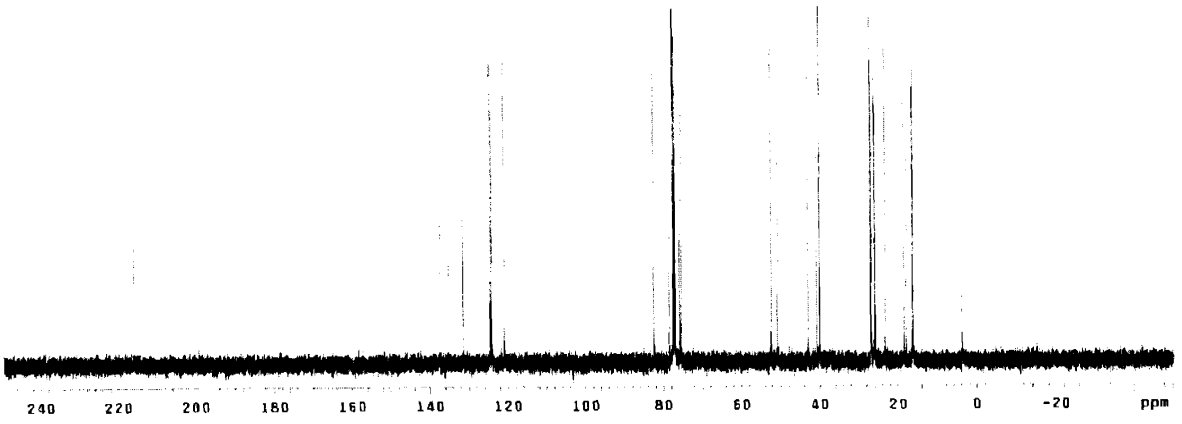


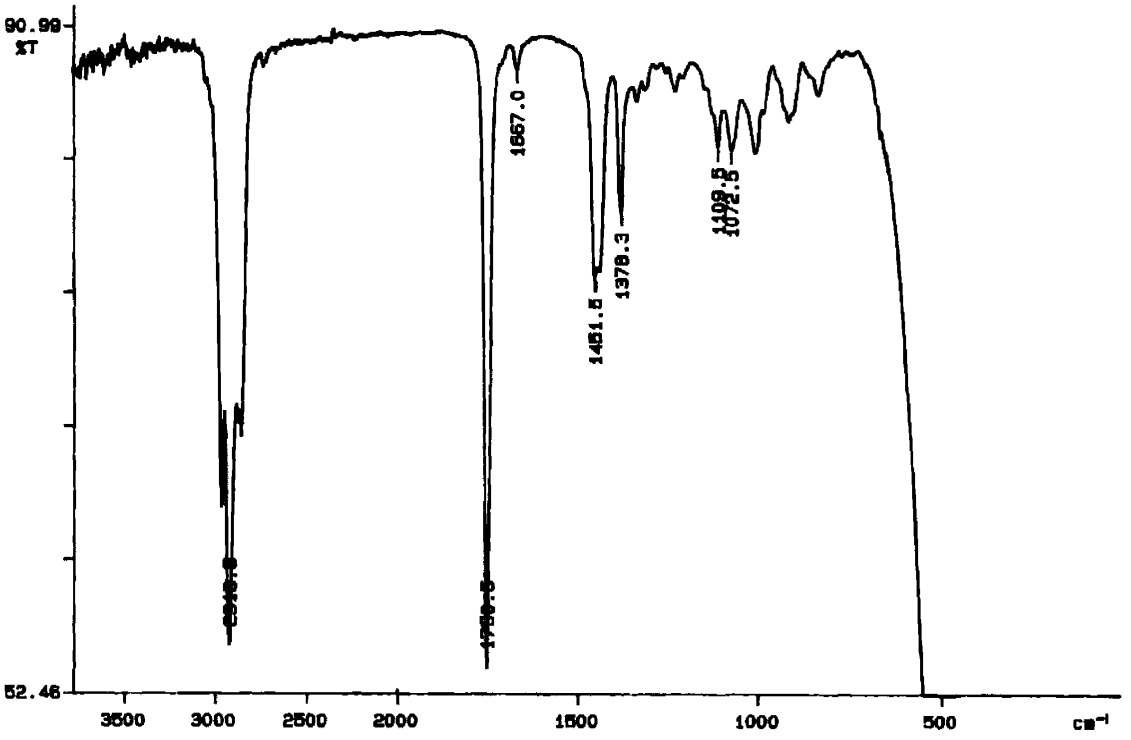
15

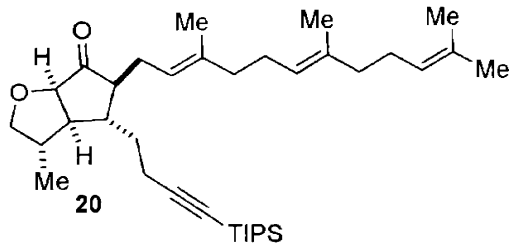

O
H
O
H
Me
Me
Me
Me
Me
18
Me

10
9
8
7
6
5
4
3
2
1
ppm

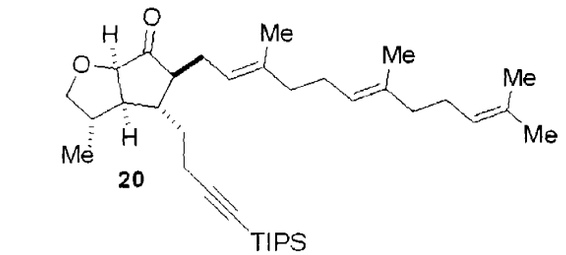

H
O
O
Me
Me
Me
Me
H
Me
18
Me


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


90.99
%T
52.46
1667.0
1451.5
1378.3
3500
3000
2500
2000
1500
1000
500
cm-1

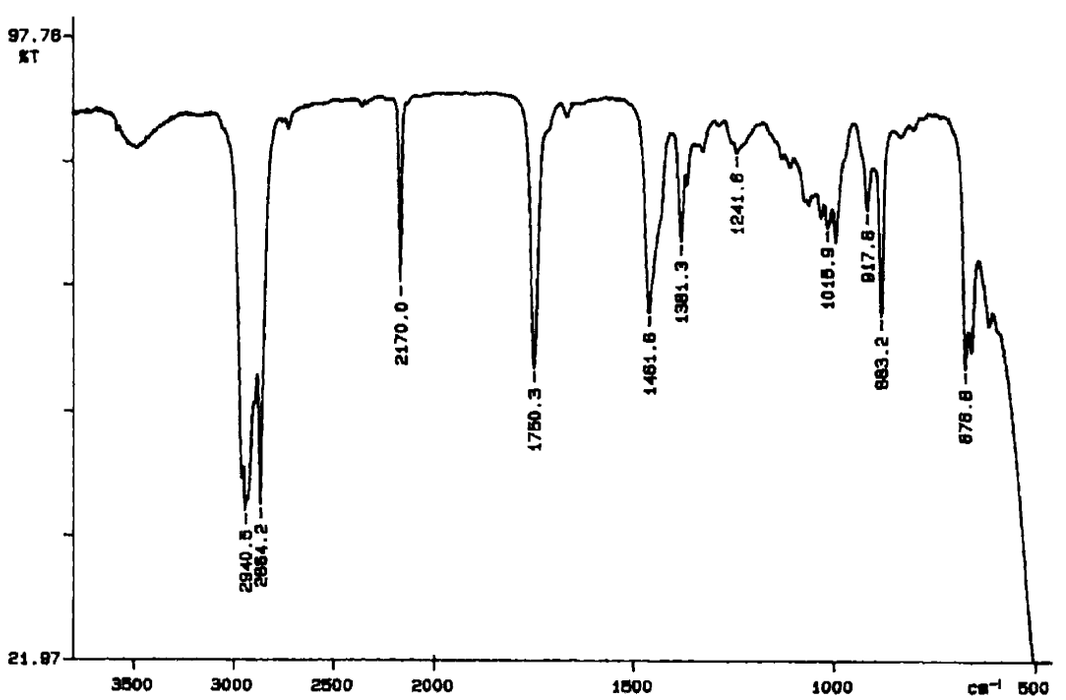


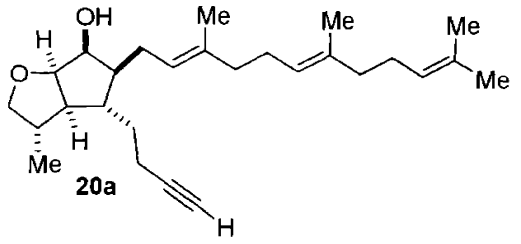
20


H
O
O
Me
Me
Me
Me
H
Me
TIPS

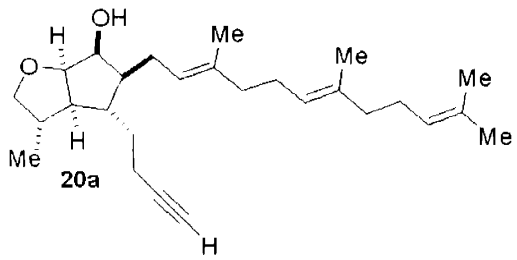
20

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

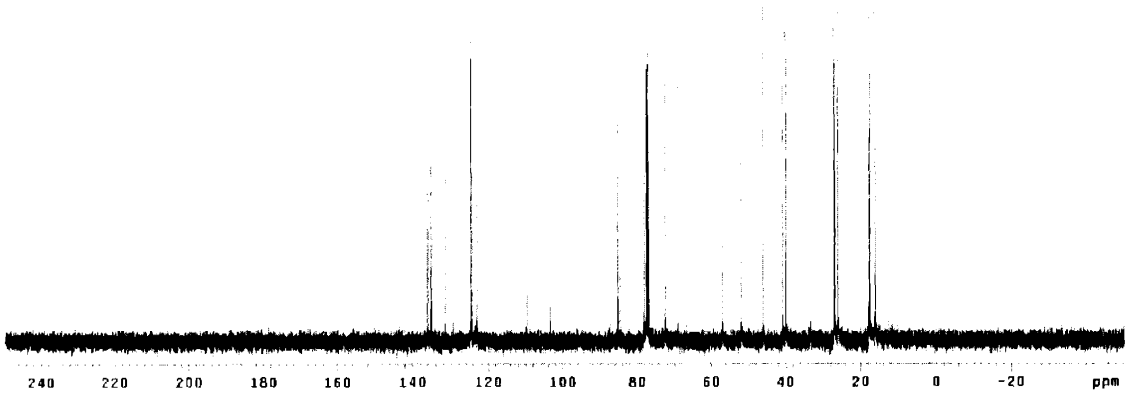

97.76
%T
21.97
2940.5
2864.2
2170.0
1750.3
1461.6
1381.3
1241.6
1015.9
917.6
883.2
678.8
3500
3000
2500
2000
1500
1000
cm-1
500

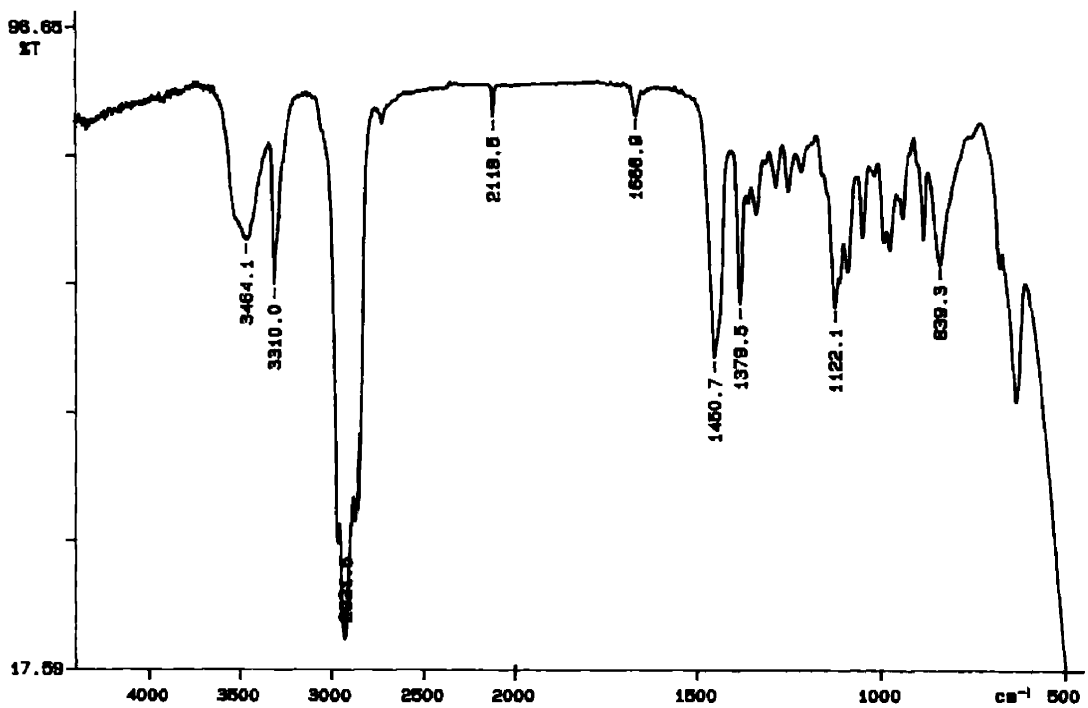


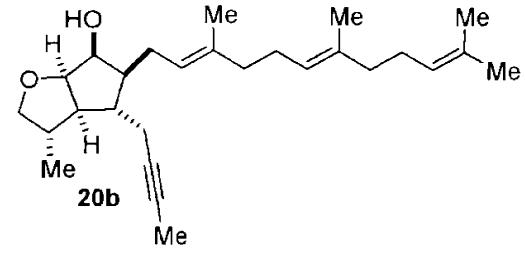
20a


H
OH
Me
Me
Me
O
H
Me
Me
H

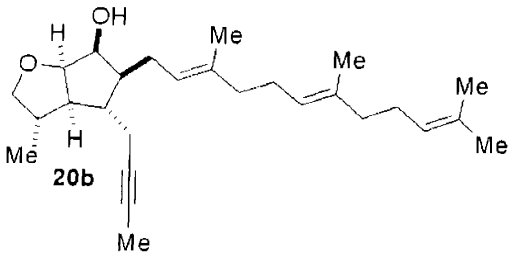
20a


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

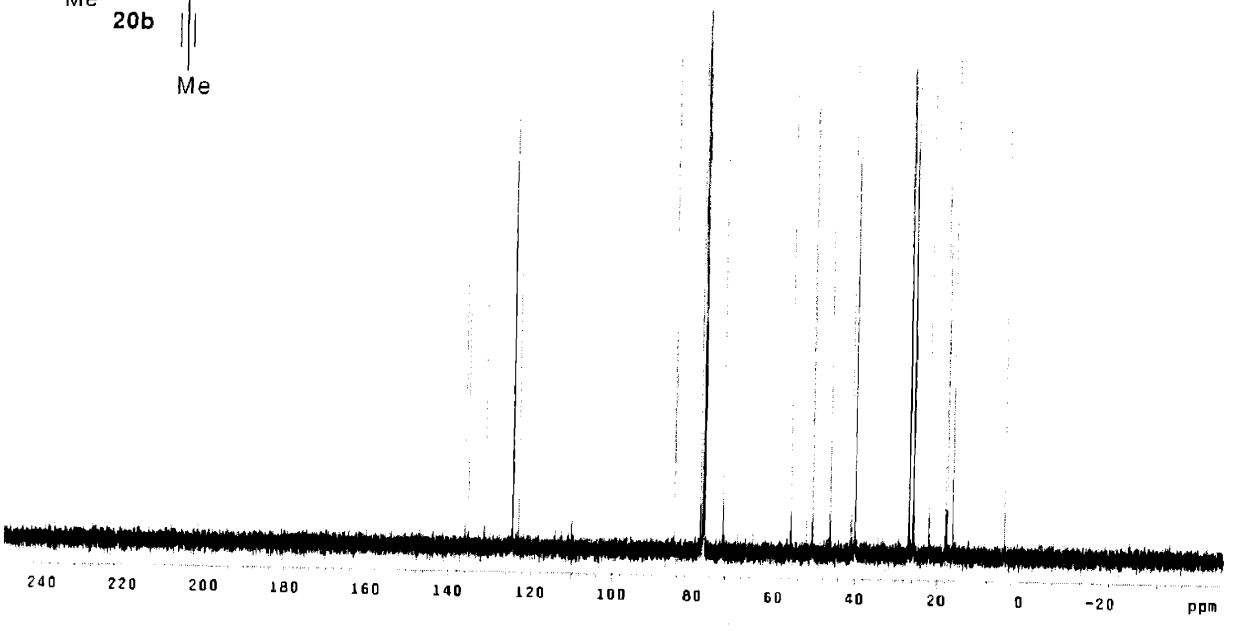

96.68
%T
17.69
3464.1
3310.0
2118.5
1656.9
1450.7
1379.5
1122.1
839.3
4000
3500
3000
2500
2000
1500
1000
cm-1
500

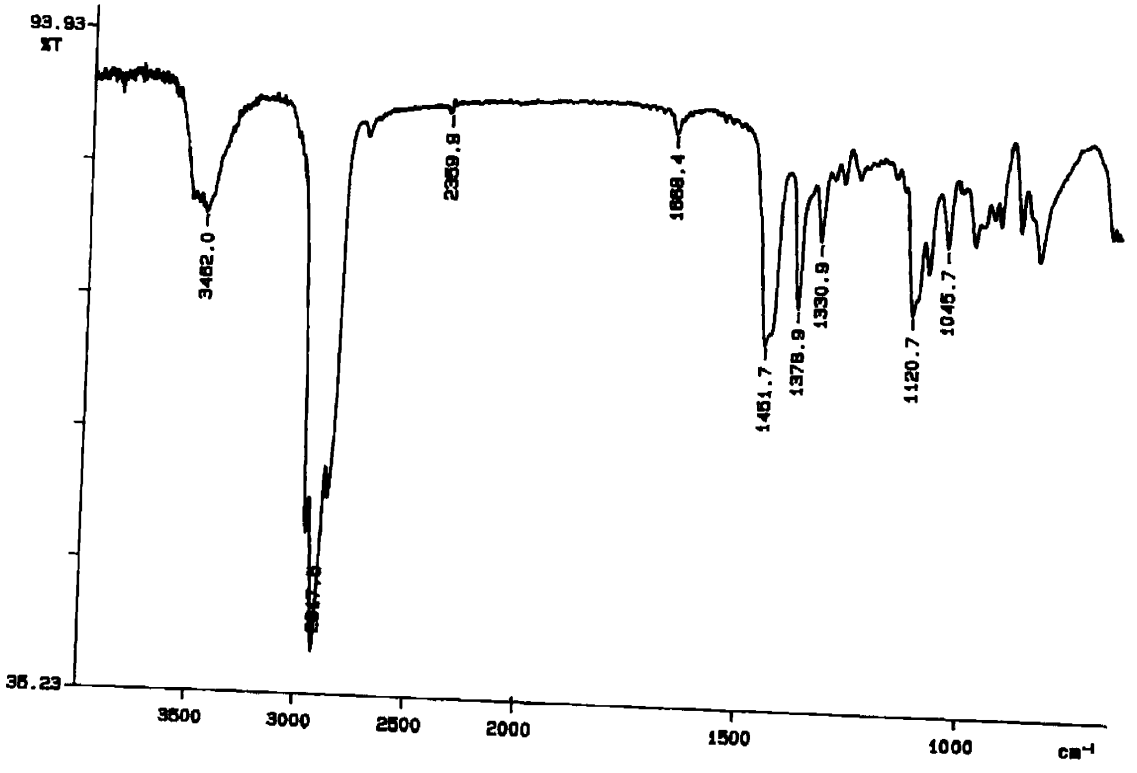

HO
H
O
H
Me
Me
Me
Me
Me
20b
Me

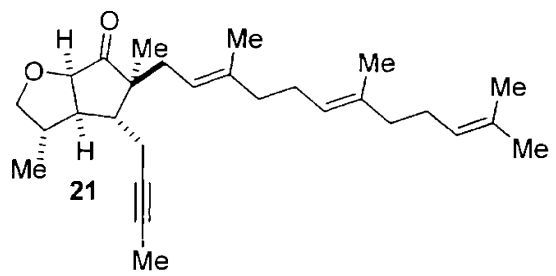
10
9
8
7
6
5
4
3
2
1
ppm


OH
H
O
Me
Me
Me
Me
H
Me
Me

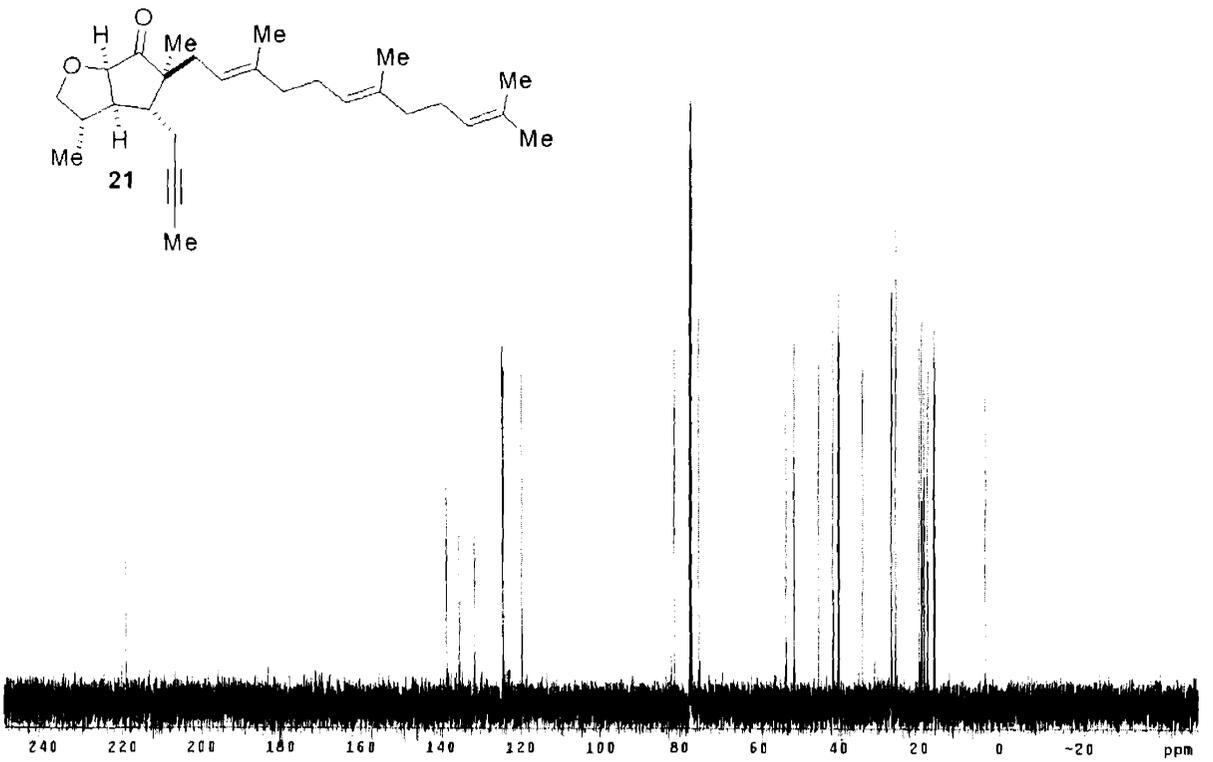
20b

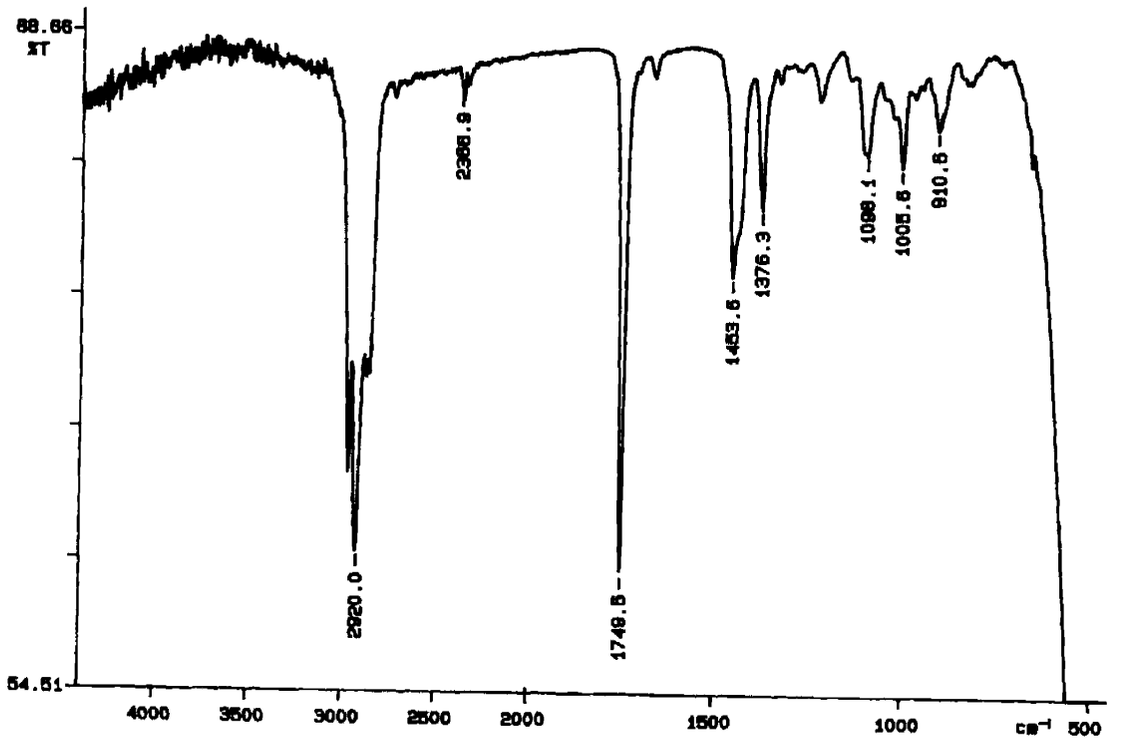

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

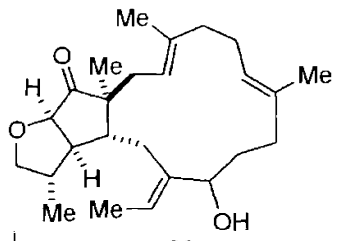

93.93
%T
3482.0
2359.8
1668.4
1451.7
1378.9
1330.9
1120.7
1045.7
36.23
3500
3000
2500
2000
1500
1000
cm-1


H
O
Me
Me
Me
Me
Me
O
H
Me
21
Me

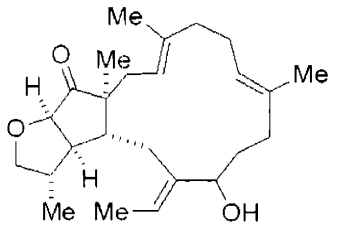
16
14
12
10
8
6
4
2
-0
ppm


H
O
Me
Me
Me
Me
O
H
Me
Me
21
Me
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

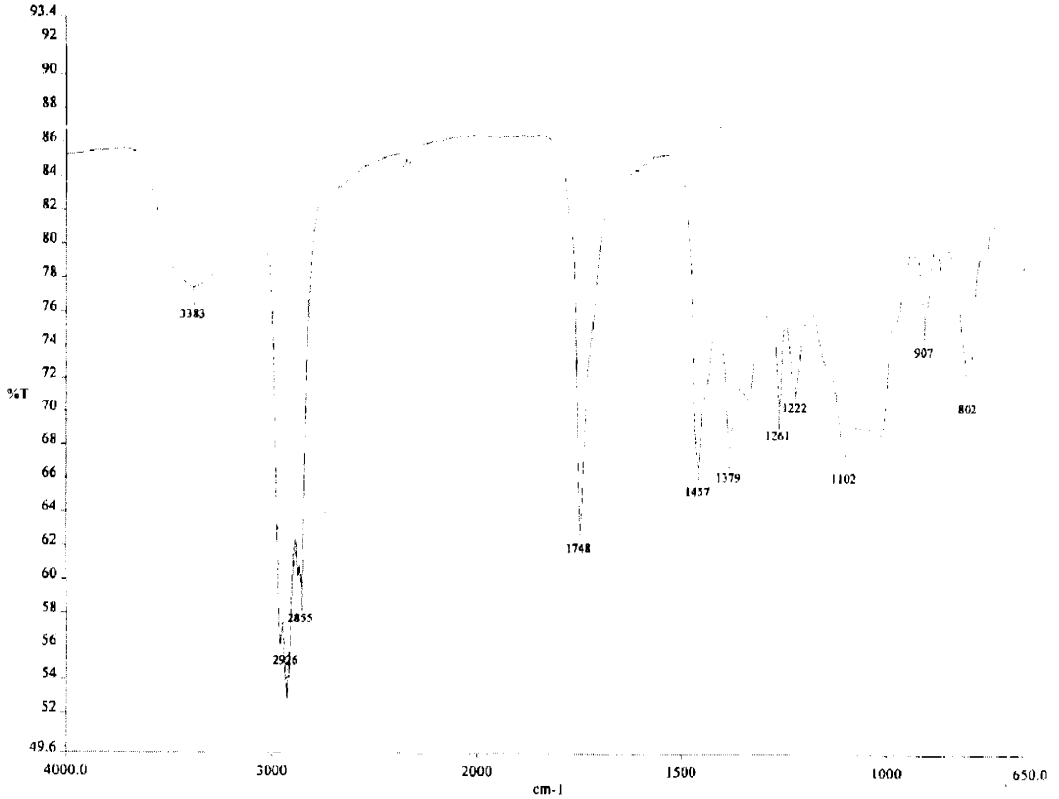

88.66
%T
54.51
2920.0
2366.9
1749.5
1453.6
1376.3
1099.1
1005.6
910.6
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

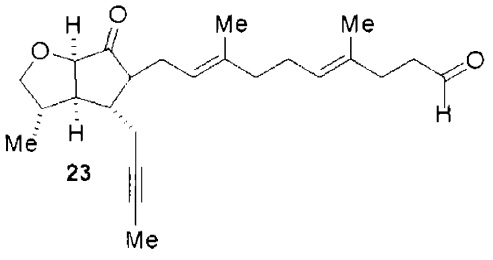


22


Me
O
Me
Me
H
O
H
Me
Me
OH

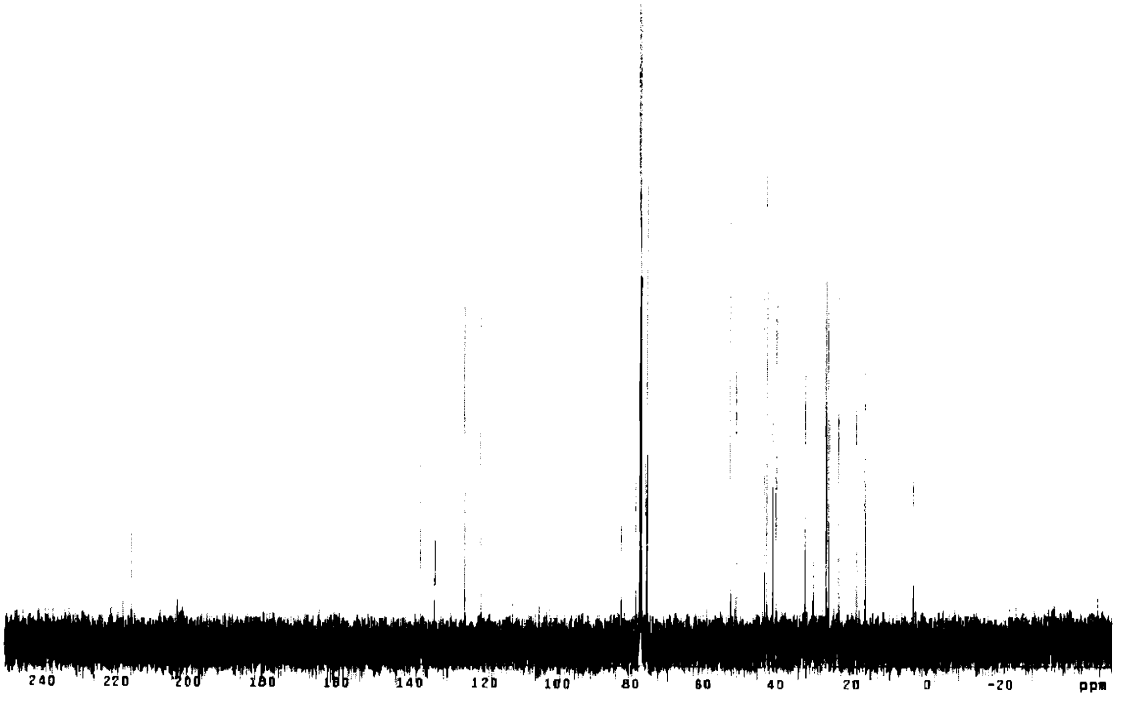
22

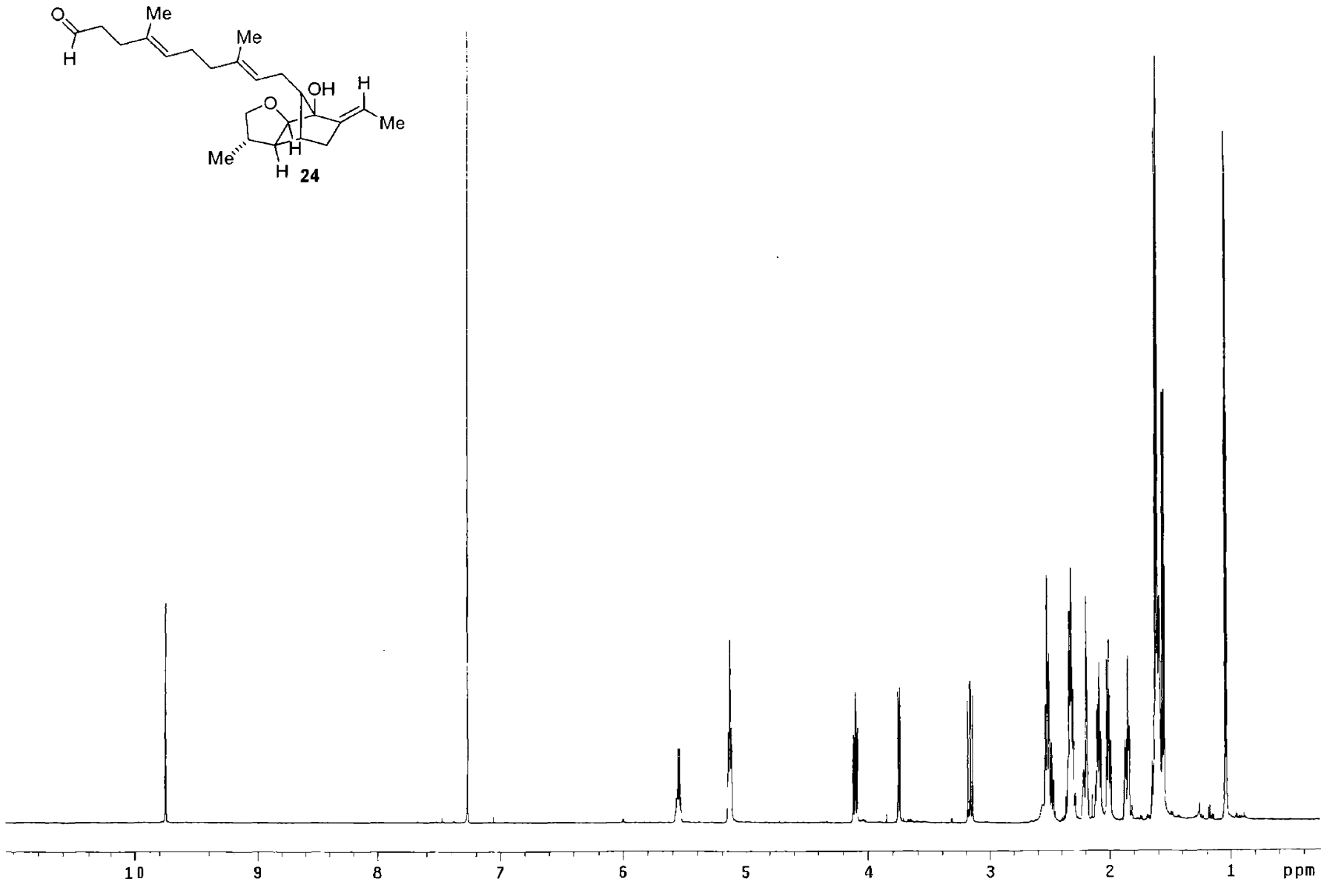

93.4
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
49.6
%T
3383
2926
2855
1748
1457
1379
1261
1222
1102
907
802
4000.0
3000
2000
1500
1000
650.0
cm-1

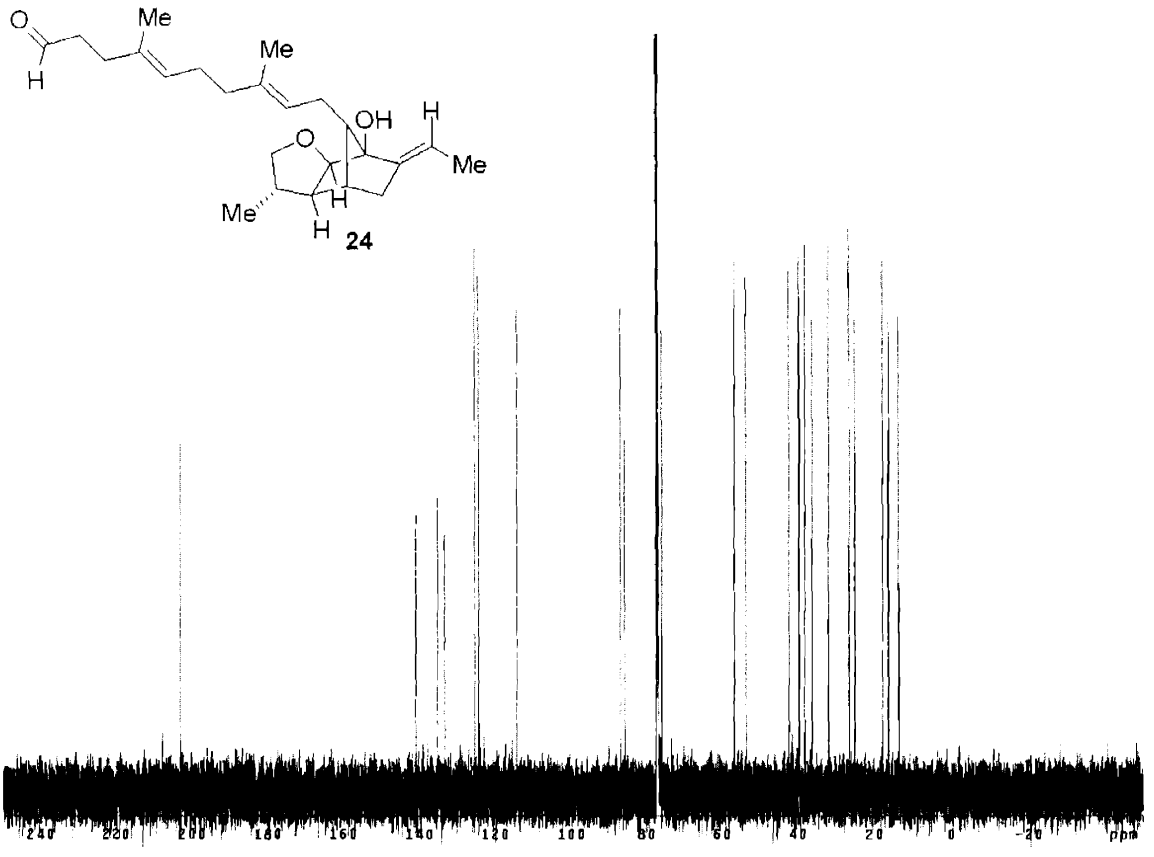

H
O
Me
Me
O
H
Me
H
Me

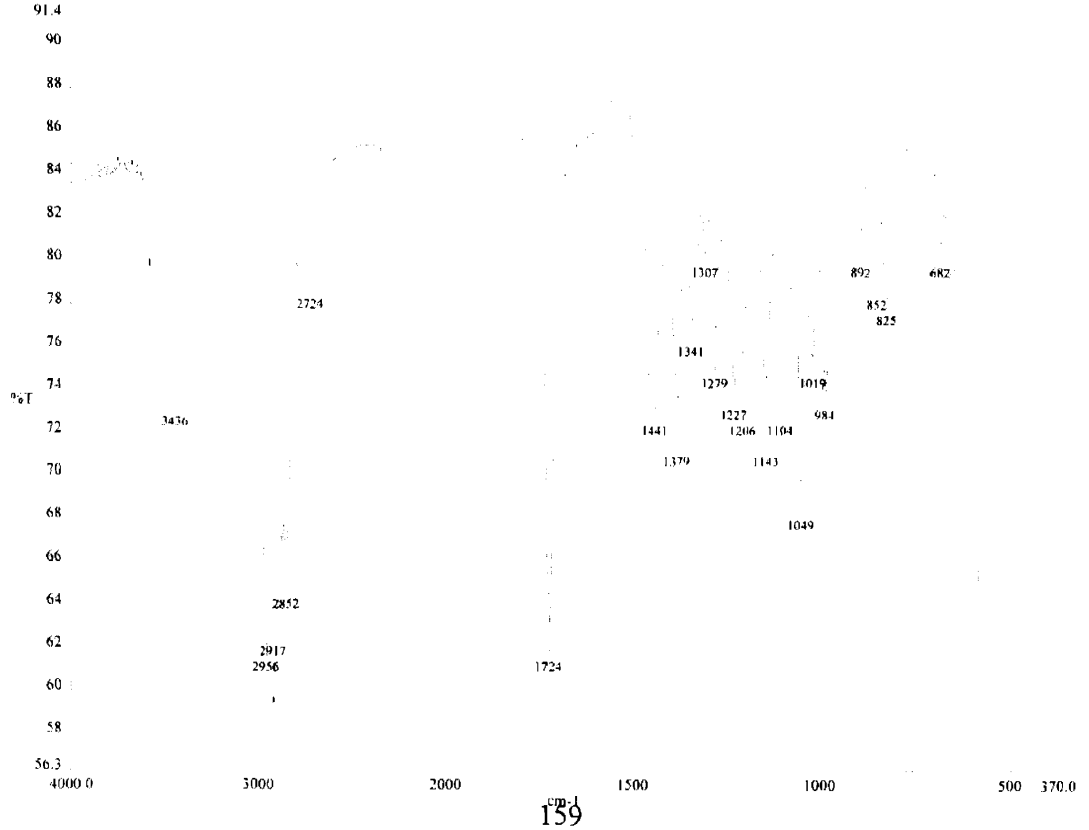
23

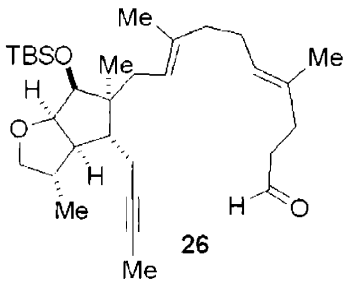
10
9
8
7
6
5
4
3
2
1
ppm


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


O
H
Me
Me
OH
H
O
Me
Me
H
H
24
10
9
8
7
6
5
4
3
2
1
ppm

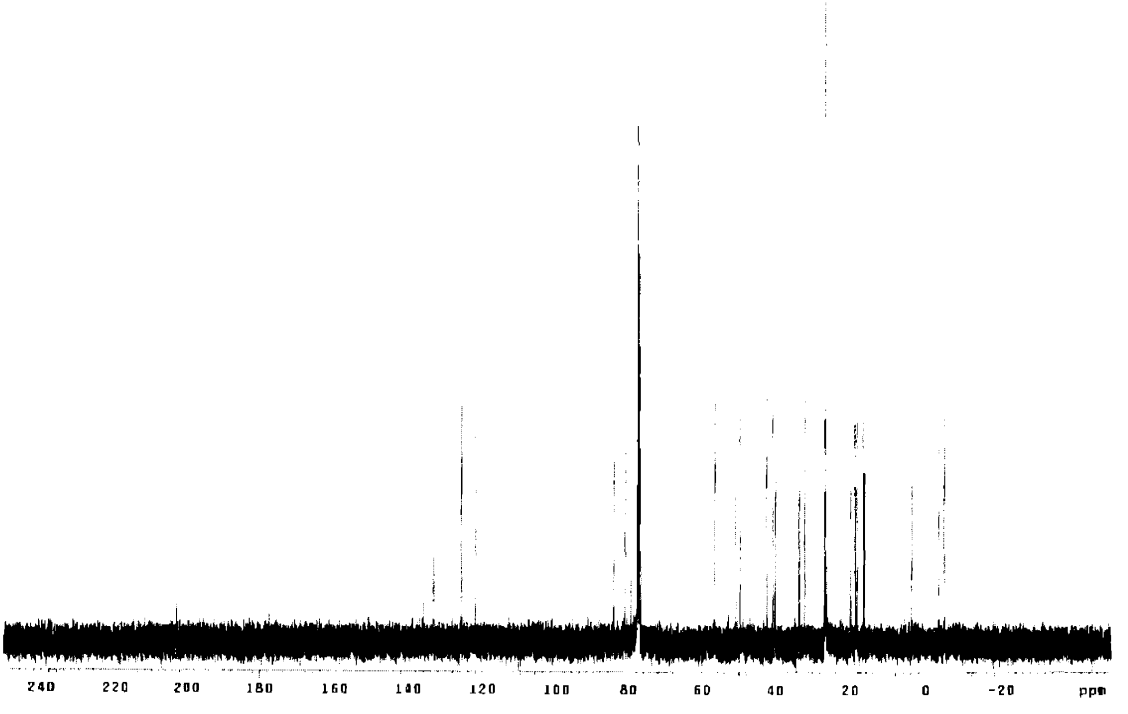

O
H
Me
Me
OH
H
O
Me
Me
H
H
24
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

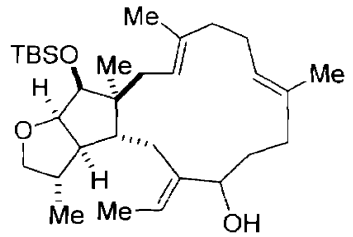

%T
91.4
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56.3
4000.0
3000
2000
1500
1000
500
370.0
cm-1
3436
2956
2917
2852
2724
1724
1441
1379
1341
1307
1279
1227
1206
1143
1104
1049
1019
984
892
852
825
682


Me
TBSO
Me
Me
H
O
H
Me
H
O
Me

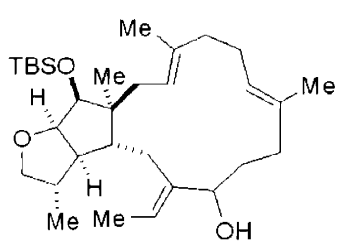
26

10
9
8
7
6
5
4
3
2
1
ppm


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

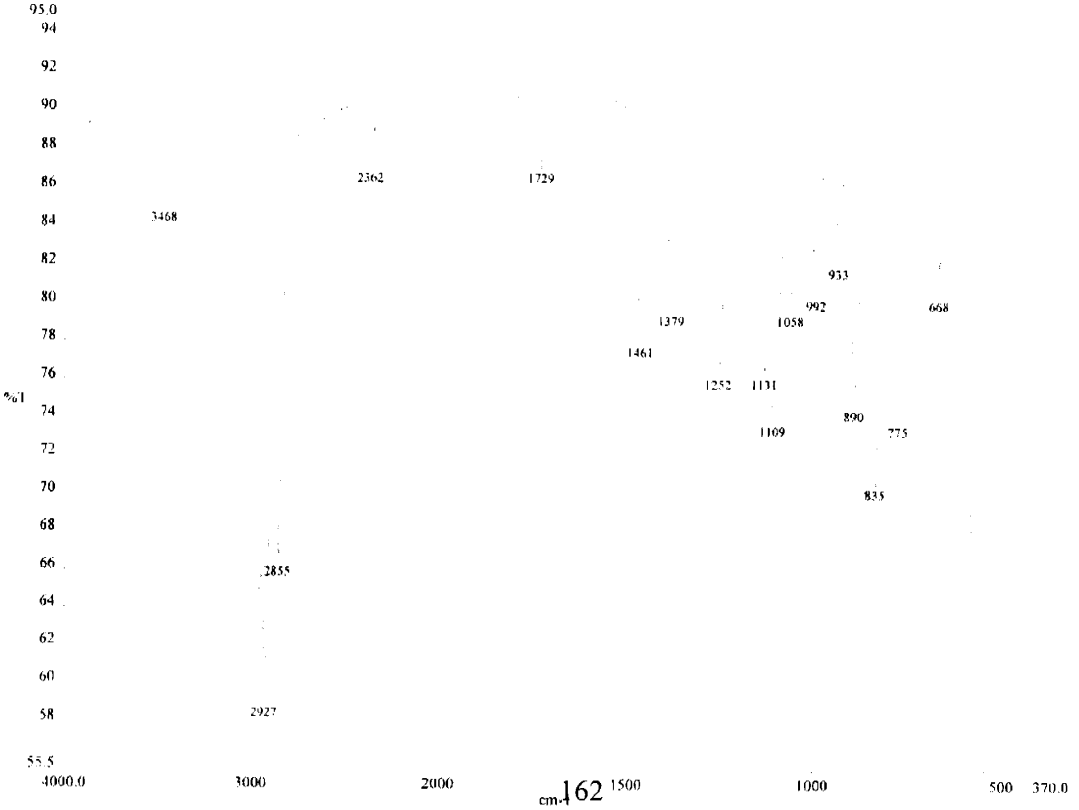


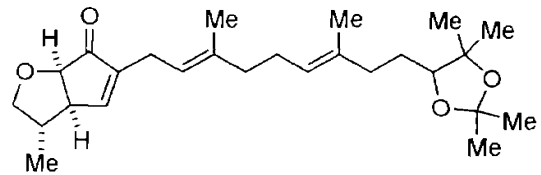
27


Me
TBSO
Me
Me
H
O
H
Me
Me
OH

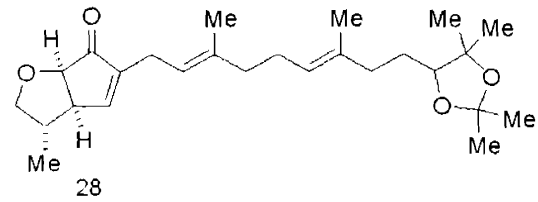
27

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


95.0
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
55.5
%T
4000.0
3000
2000
1500
1000
500
370.0
cm-1
3468
2927
2855
2362
1729
1461
1379
1252
1131
1109
1058
992
933
890
835
775
668

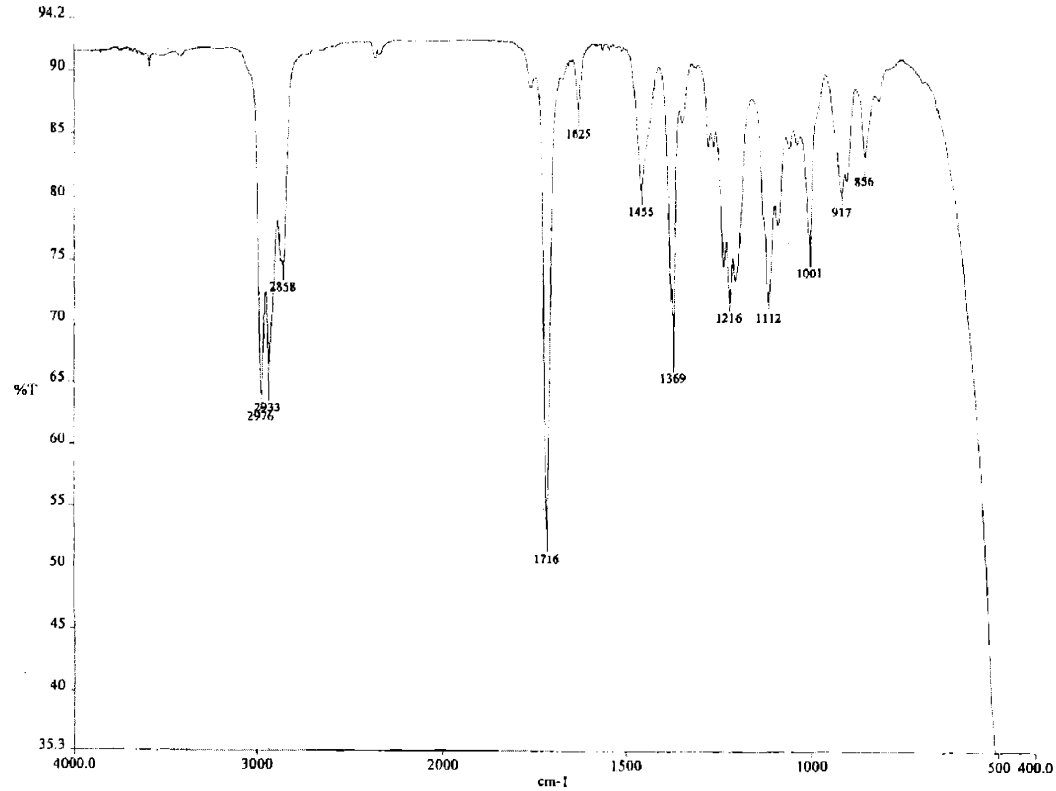


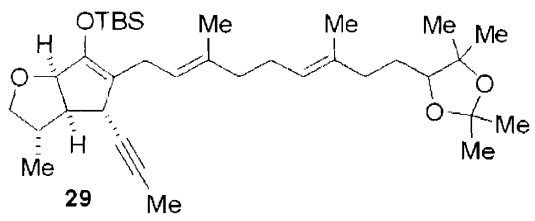
28


O
H
O
Me
Me
Me
Me
Me
O
O
Me
Me
H
Me

28

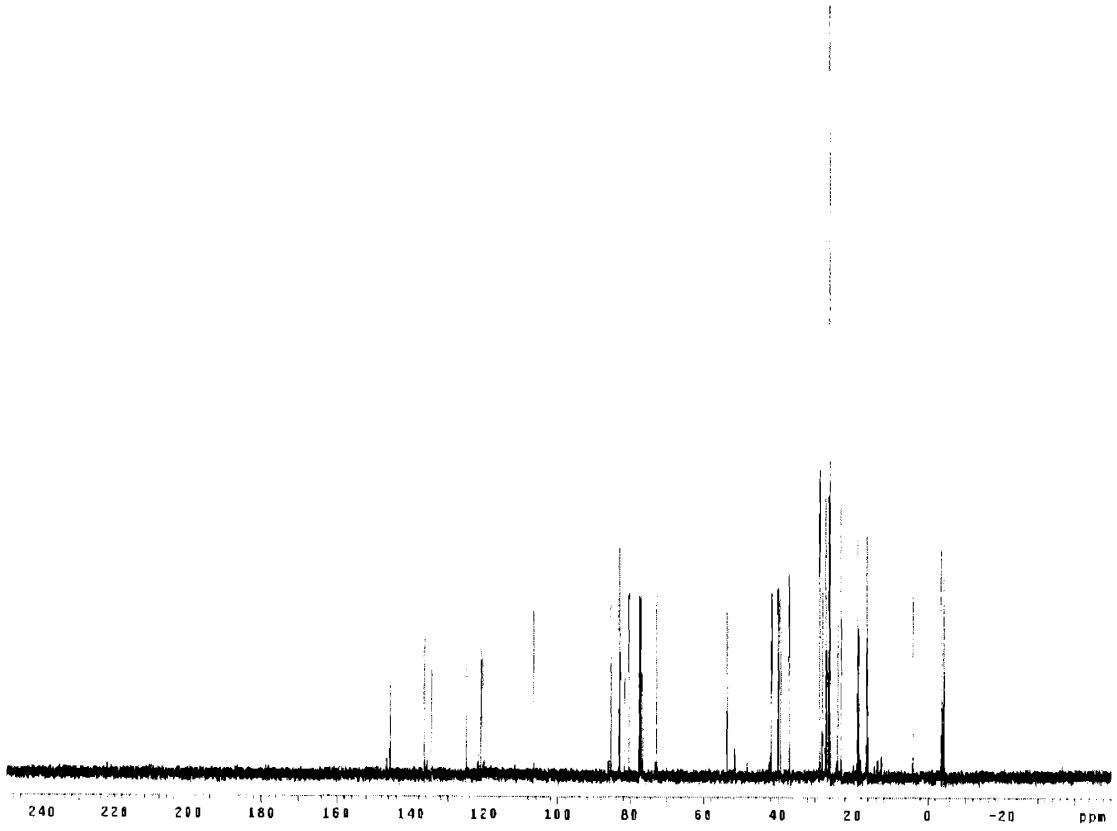
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

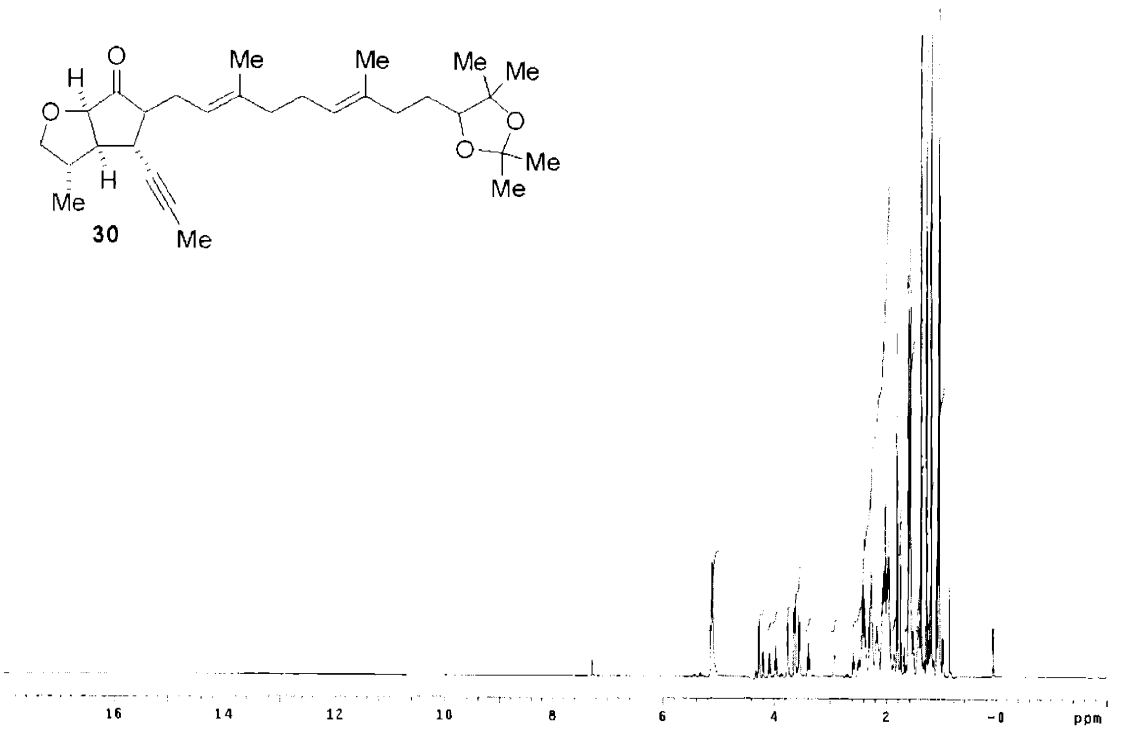

94.2
90
85
80
75
70
65
60
55
50
45
40
35.3
%T
2933
2956
2858
1716
1625
1455
1369
1216
1112
1001
917
856
4000.0
3000
2000
1500
1000
500 400.0
cm-1

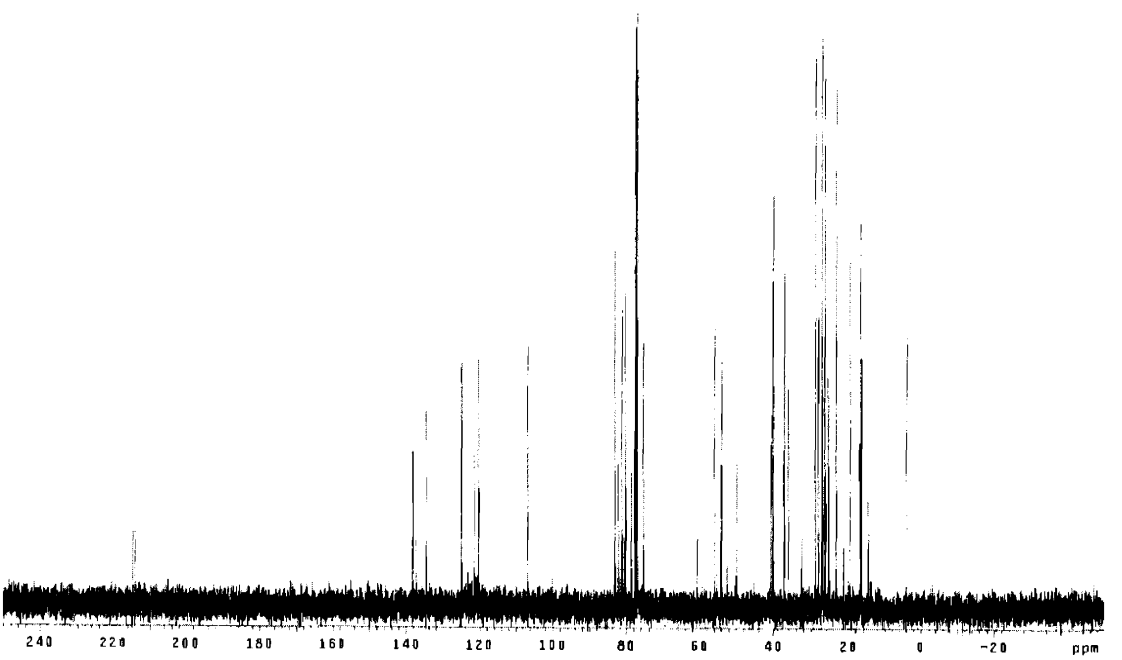

OTBS
Me
Me
Me
Me
H
O
O
O
Me
Me
H
Me
Me

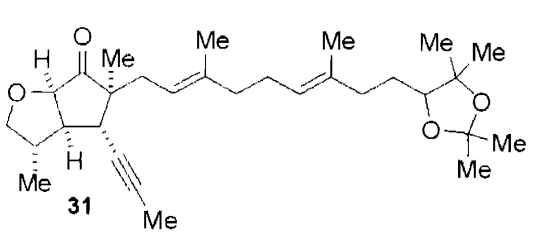
29

16
14
12
10
8
6
4
2
-0
ppm


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

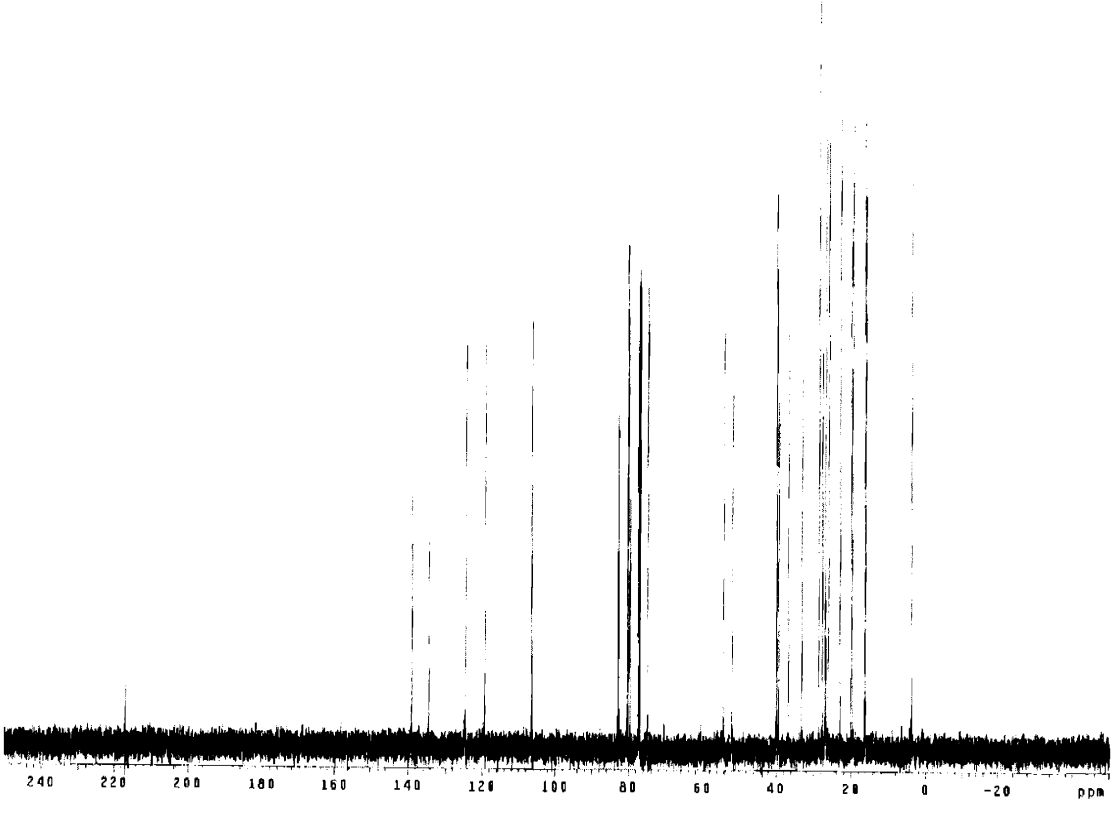

O
H
O
Me
Me
Me
Me
O
O
Me
Me
H
Me
30
Me
16
14
12
10
8
6
4
2
-0
ppm

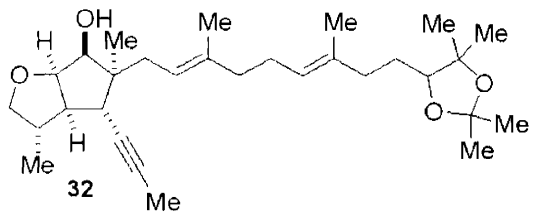

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


O
H
Me
Me
Me
Me
Me
O
O
O
Me
Me
H
Me
Me

31

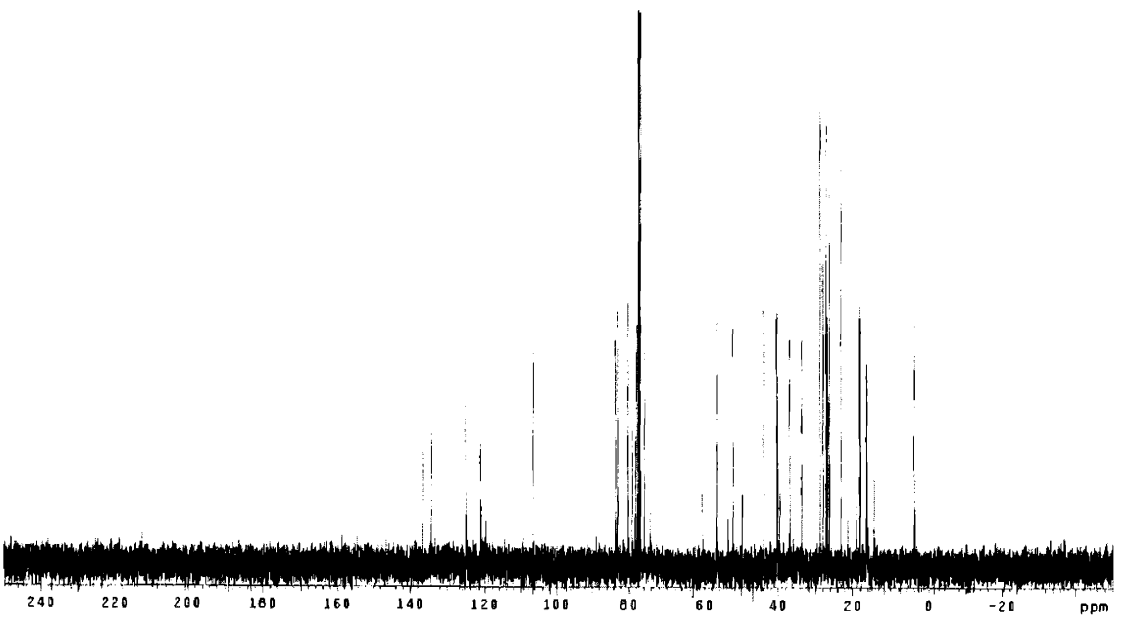
16
14
12
10
8
6
4
2
-0
ppm

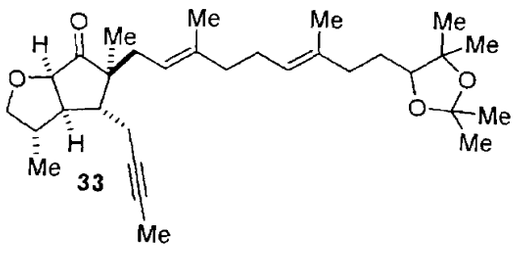

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


OH
H
Me
Me
Me
Me
Me
Me
O
O
O
Me
Me
H
Me
Me

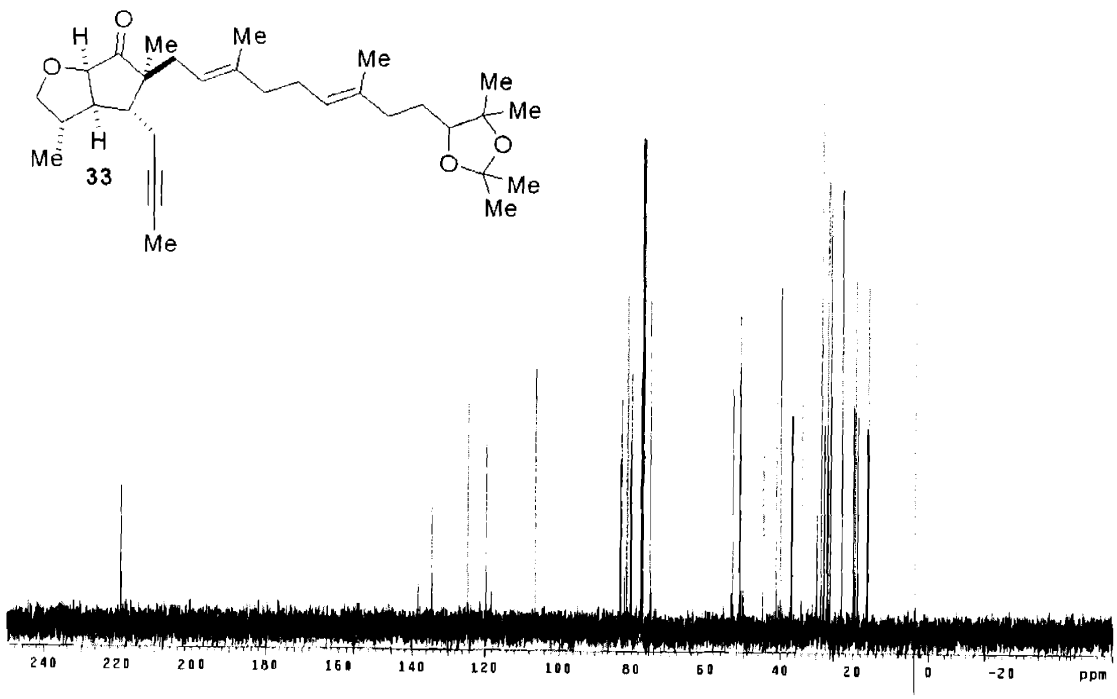
32

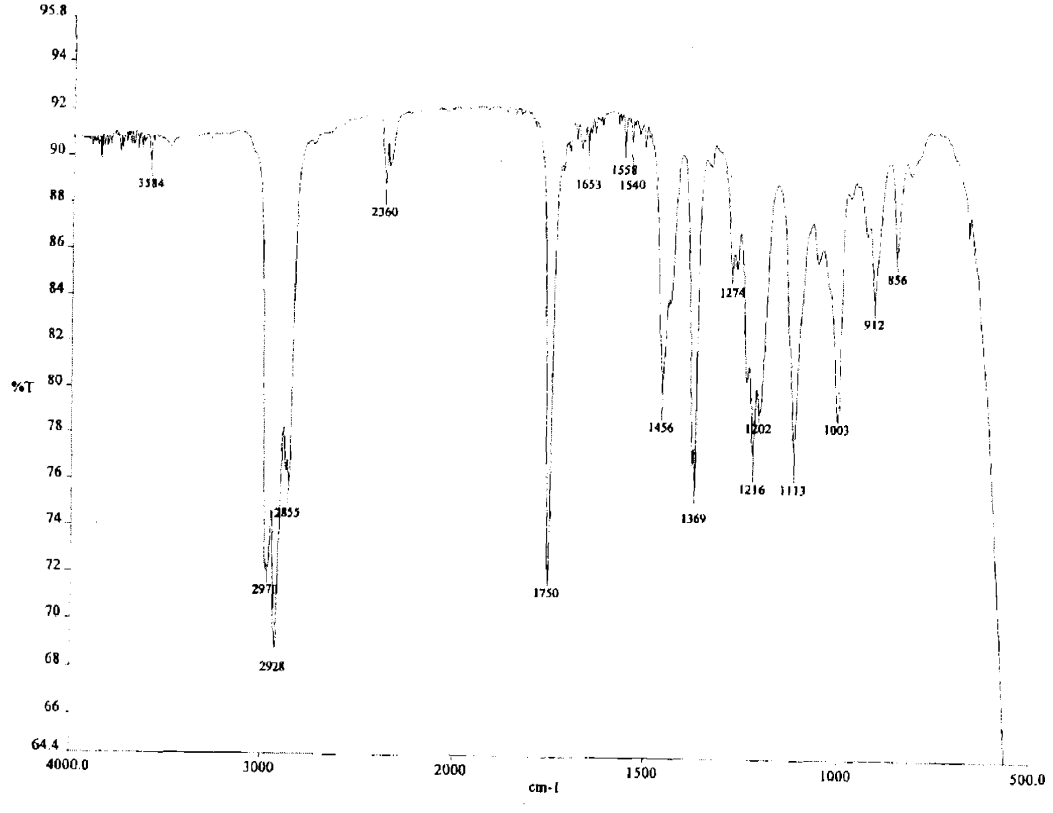
16
14
12
10
8
6
4
2
-0
ppm

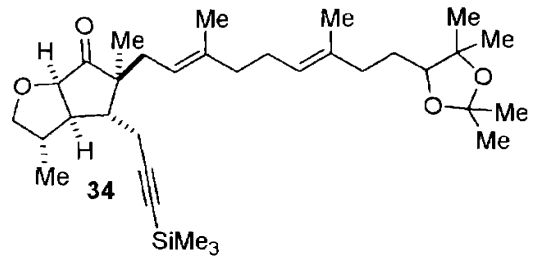

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


O
H
Me
Me
Me
Me
Me
Me
O
O
Me
Me
H
Me
33
Me

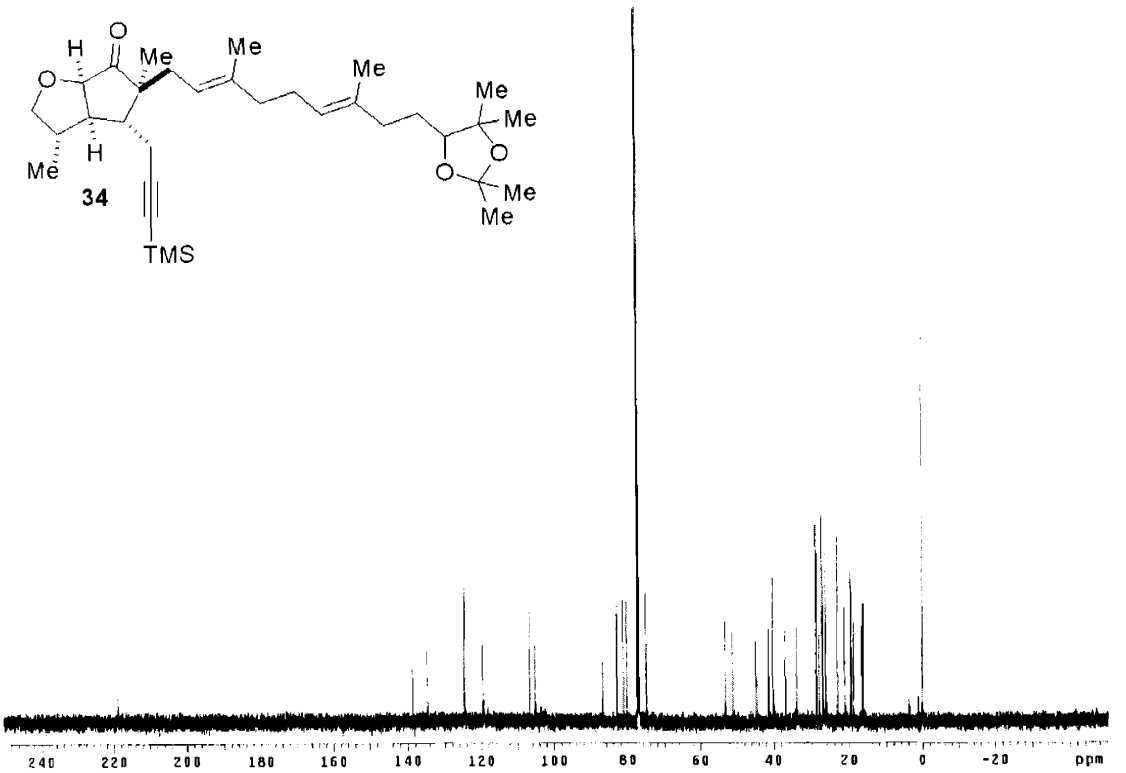
10
9
8
7
6
5
4
3
2
1
ppm

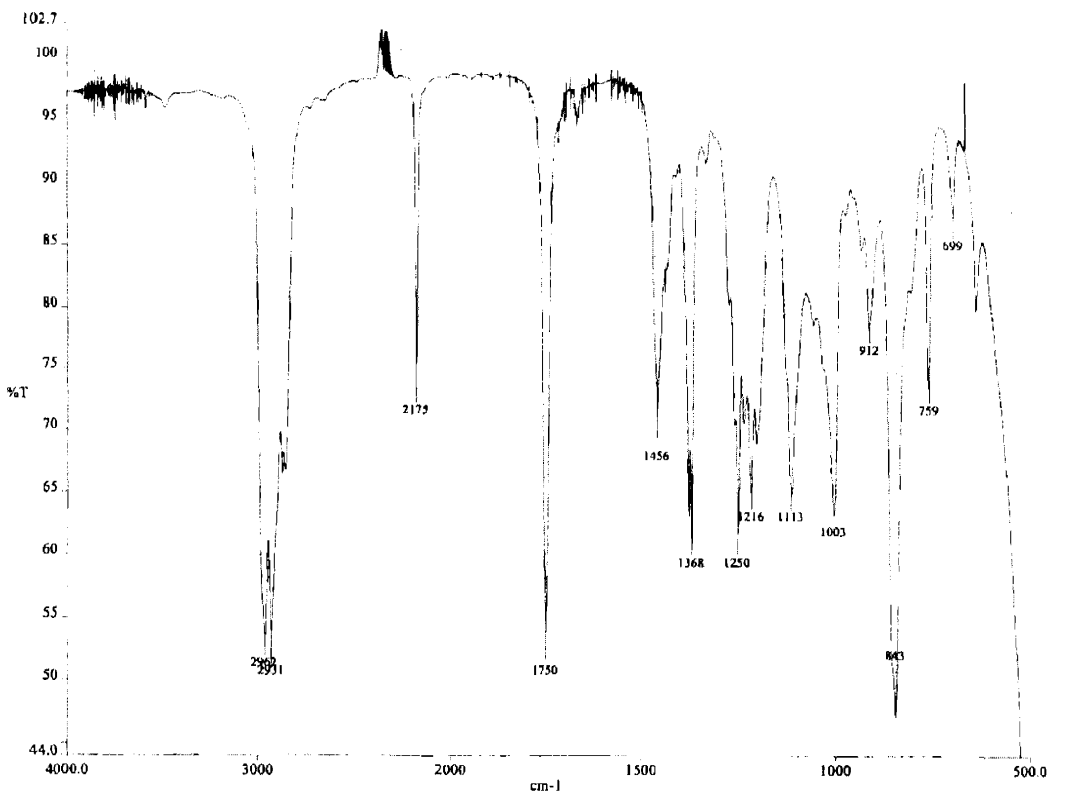

H
O
Me
Me
Me
Me
Me
Me
O
O
Me
Me
H
Me
33
Me
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

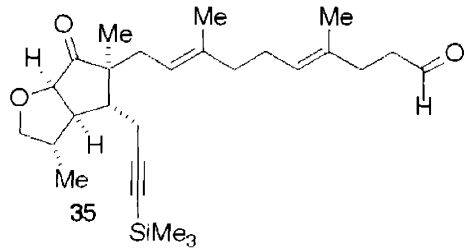

95.8
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64.4
%T
3384
2971
2928
2855
2360
1750
1653
1558
1540
1456
1369
1274
1216
1202
1113
1003
912
856
4000.0
3000
2000
1500
1000
500.0
cm-1


O
H
Me
Me
Me
Me
Me
Me
O
O
Me
Me
H
Me
34
SiMe3

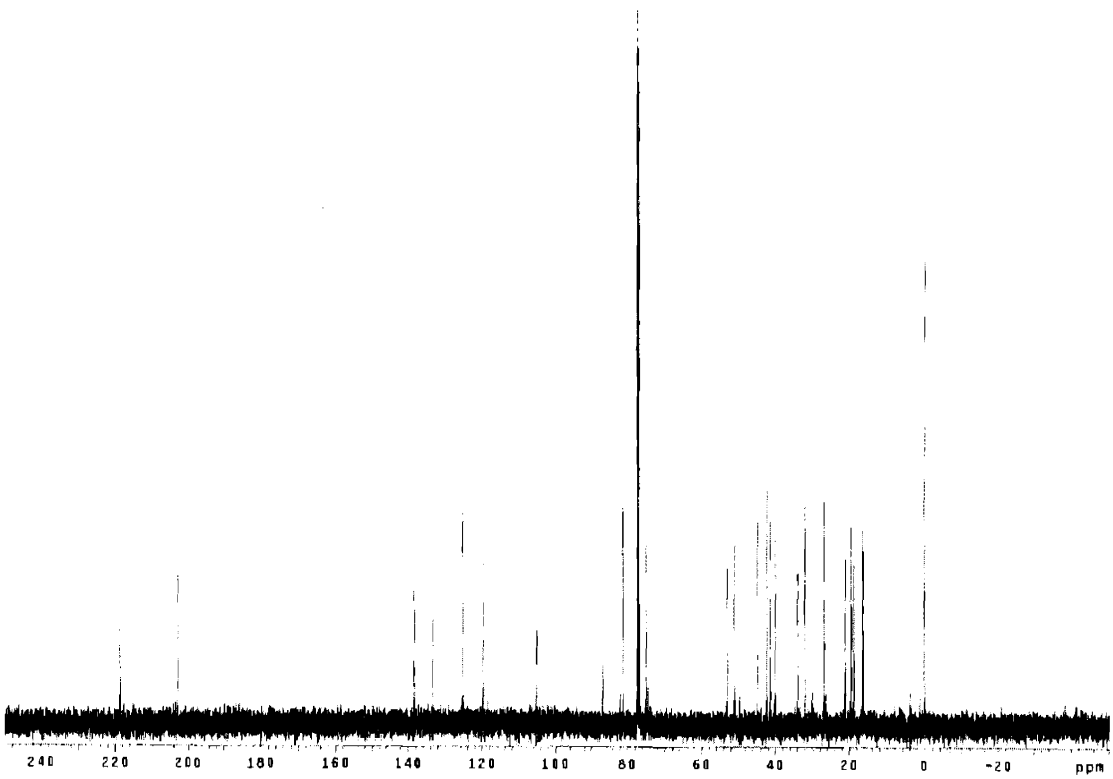
10
9
8
7
6
5
4
3
2
1
ppm

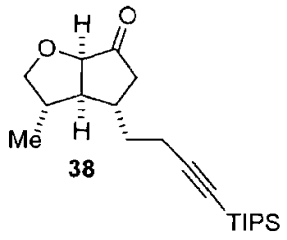

H
O
Me
Me
Me
Me
Me
Me
O
O
Me
Me
H
Me
34
TMS
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


102.7
100
95
90
85
80
75
%T
70
65
60
55
50
44.0
2179
1750
1456
1368
1250
1216
1113
1003
912
759
699
4000.0
3000
2000
1500
1000
500.0
cm-1

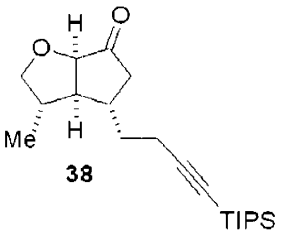

O
Me
Me
Me
H
O
O
H
H
Me
35
SiMe3

10
9
8
7
6
5
4
3
2
1
ppm


240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

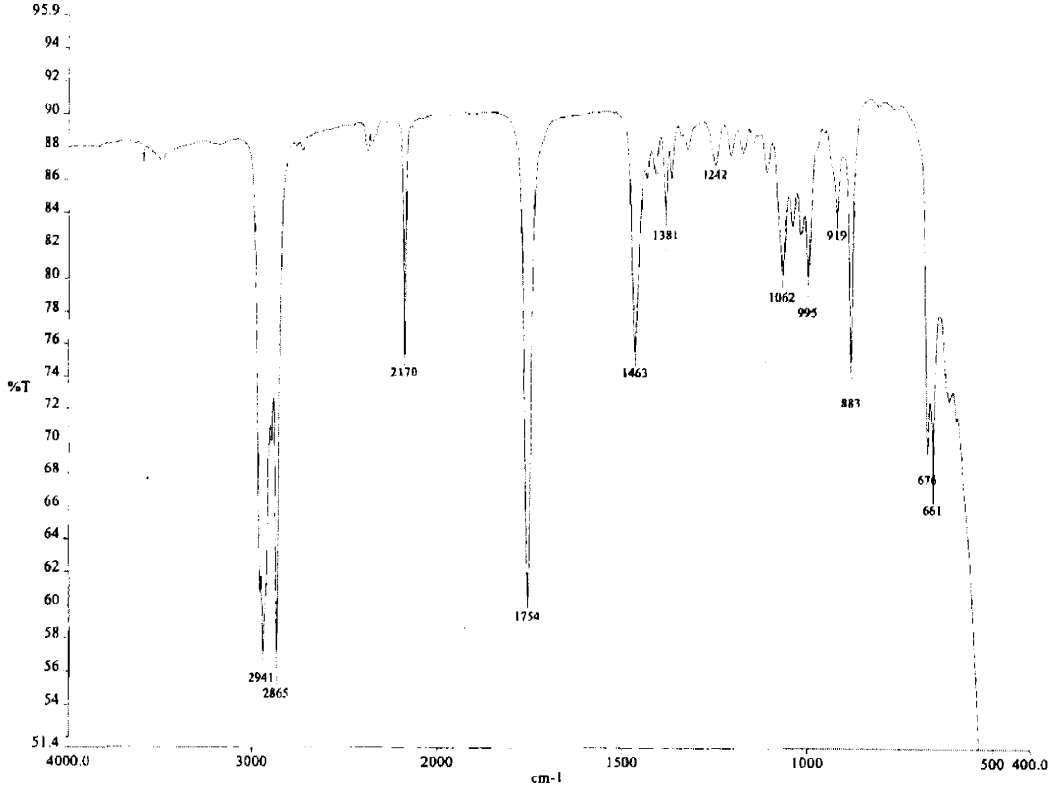


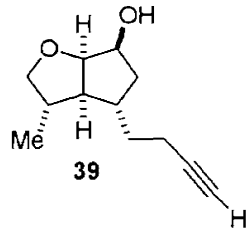
38


H
O
O
Me
H
TIPS

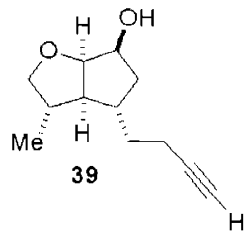
38

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
95.9
94
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
51.4
2941
2865
2170
1754
1463
1381
1242
1062
995
919
883
676
661
4000.0
3000
2000
1500
1000
500 400.0
cm-1

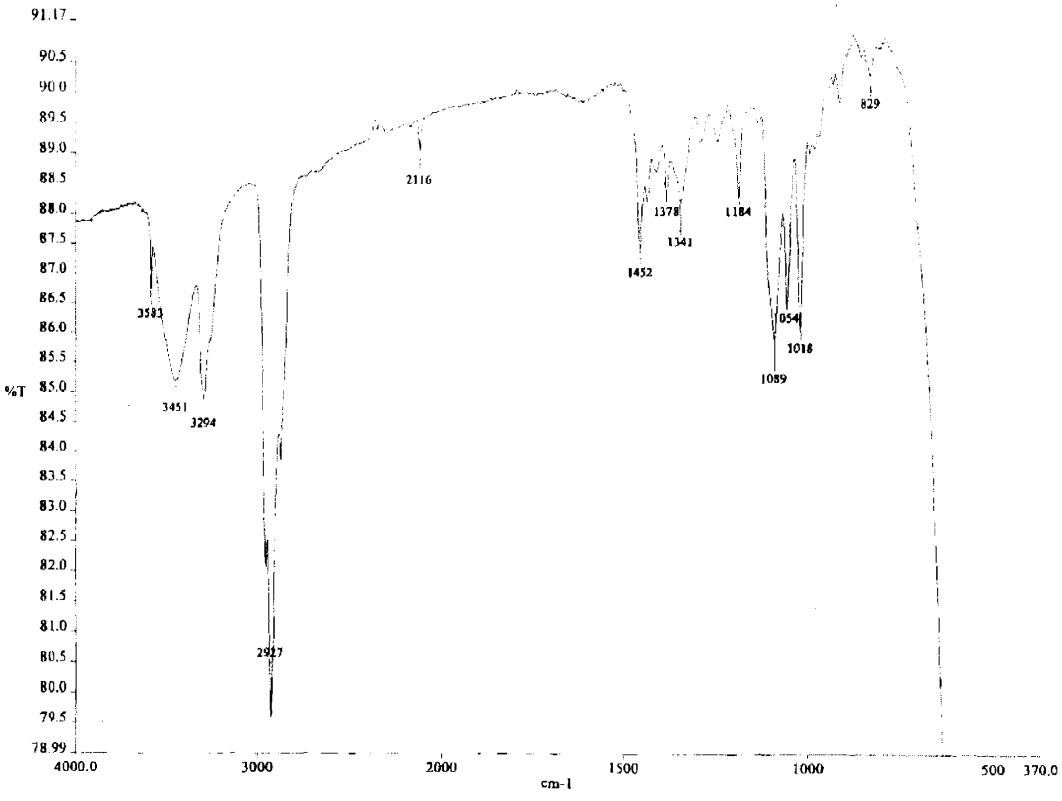


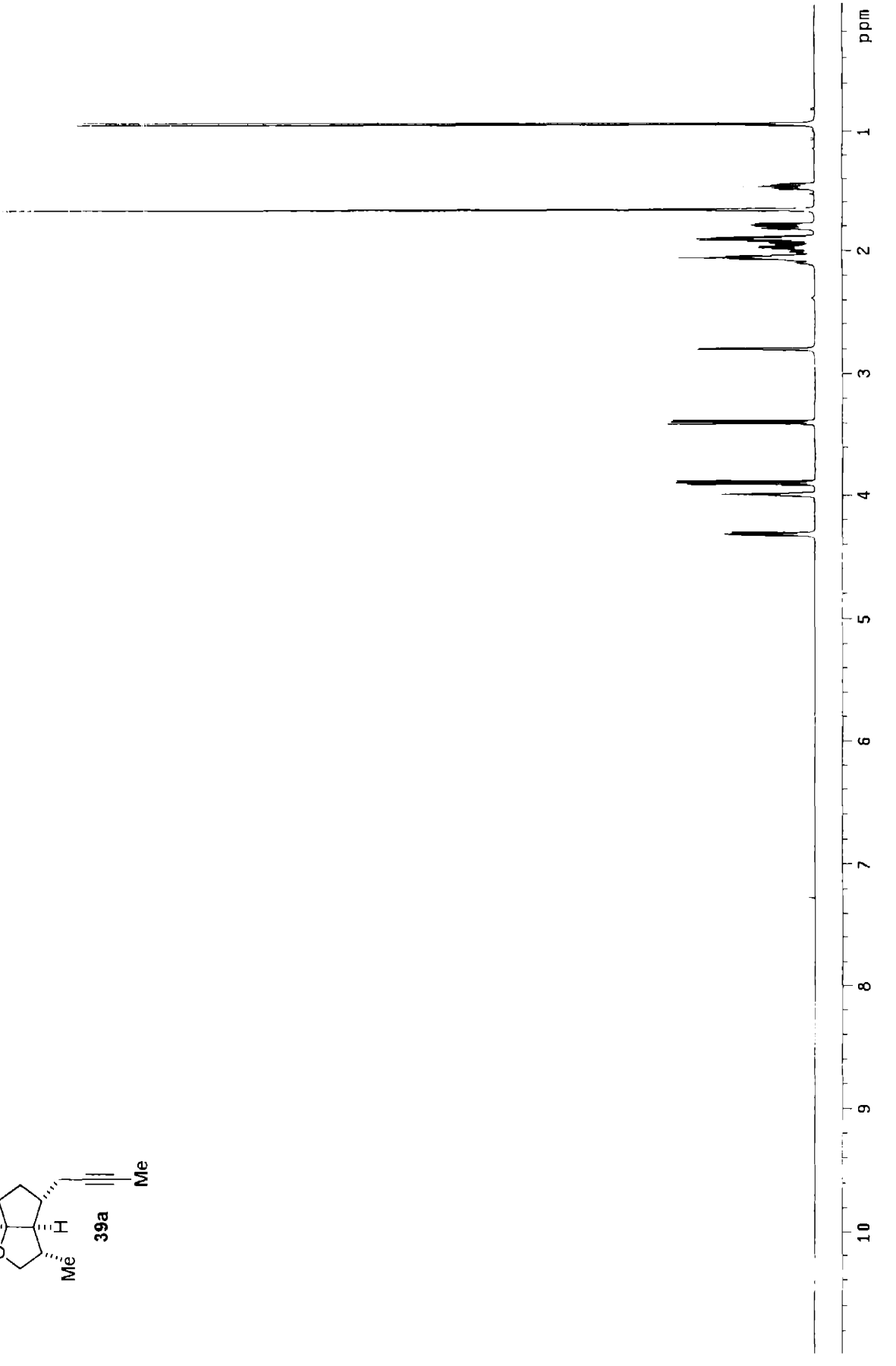
39


H
OH
O
Me
H
H

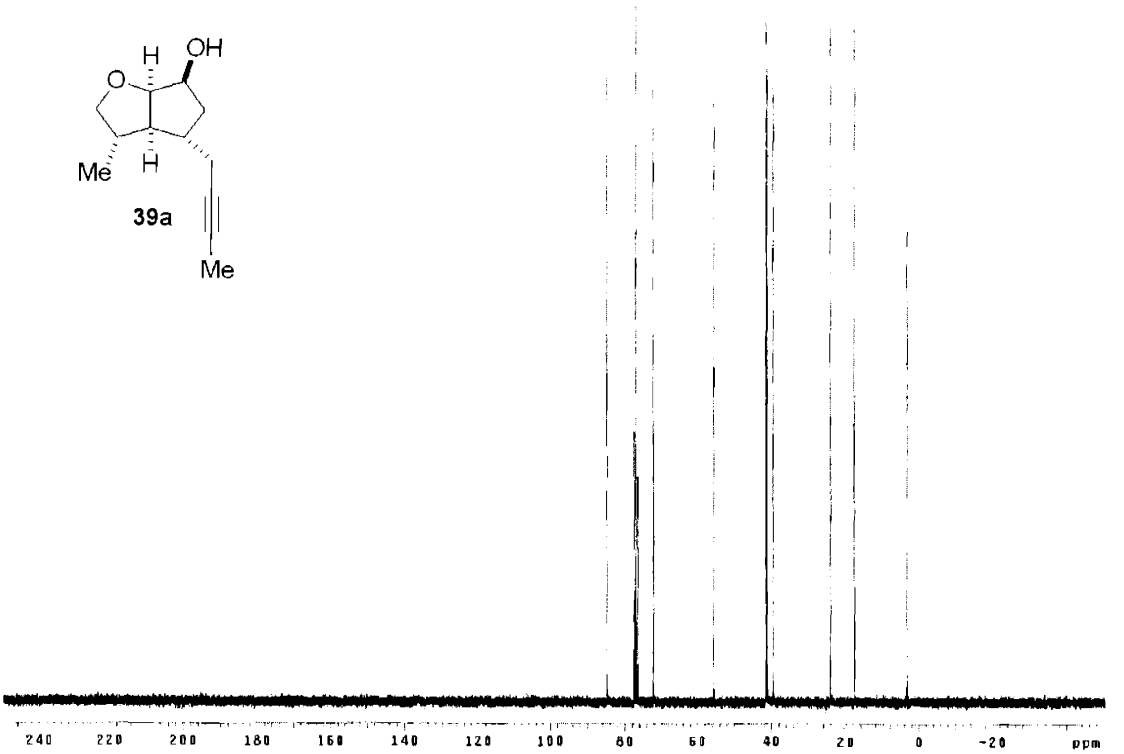
39

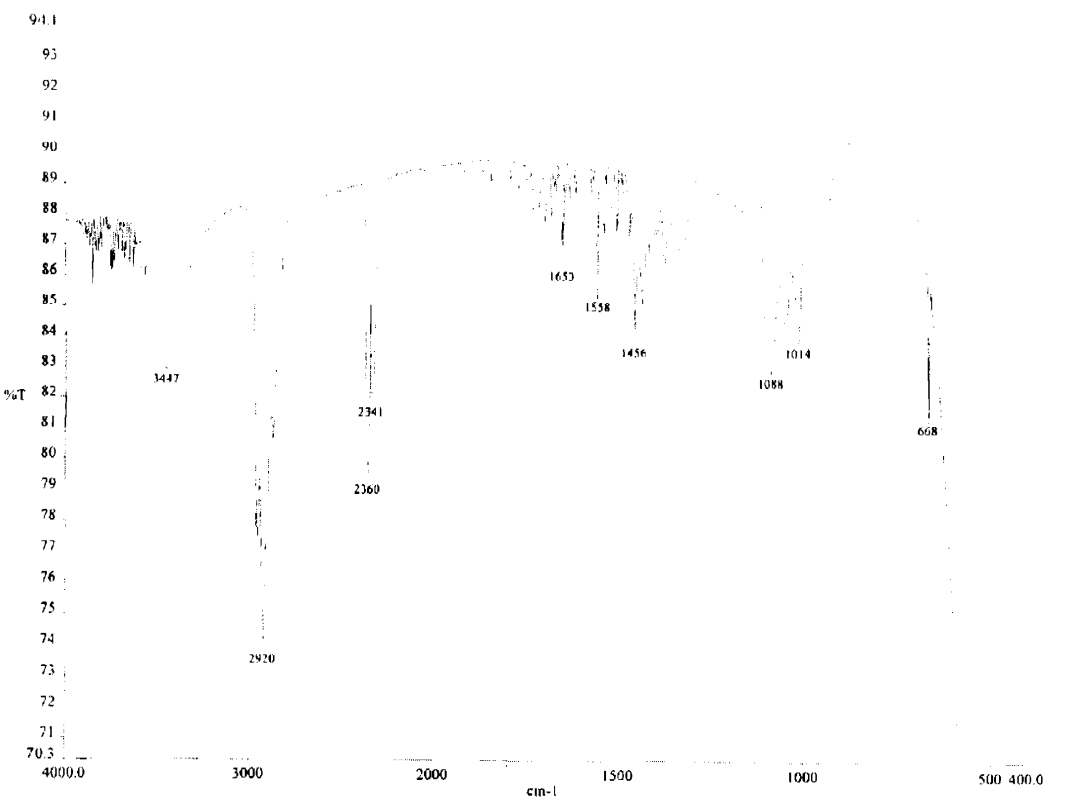
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

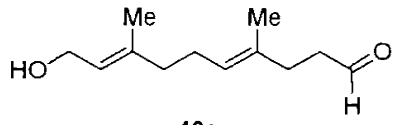

%T
91.17
90.5
90.0
89.5
89.0
88.5
88.0
87.5
87.0
86.5
86.0
85.5
85.0
84.5
84.0
83.5
83.0
82.5
82.0
81.5
81.0
80.5
80.0
79.5
78.99
3583
3451
3294
2927
2116
1452
1378
1341
1184
1089
1054
1018
829
4000.0
3000
2000
1500
1000
500
370.0
cm-1



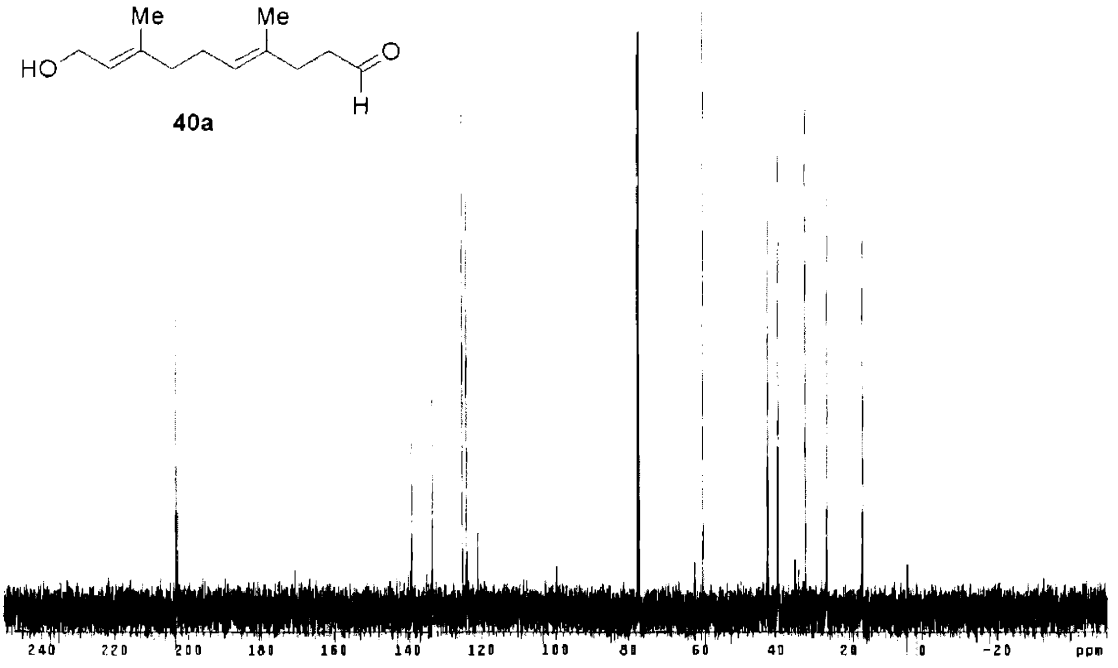
39a

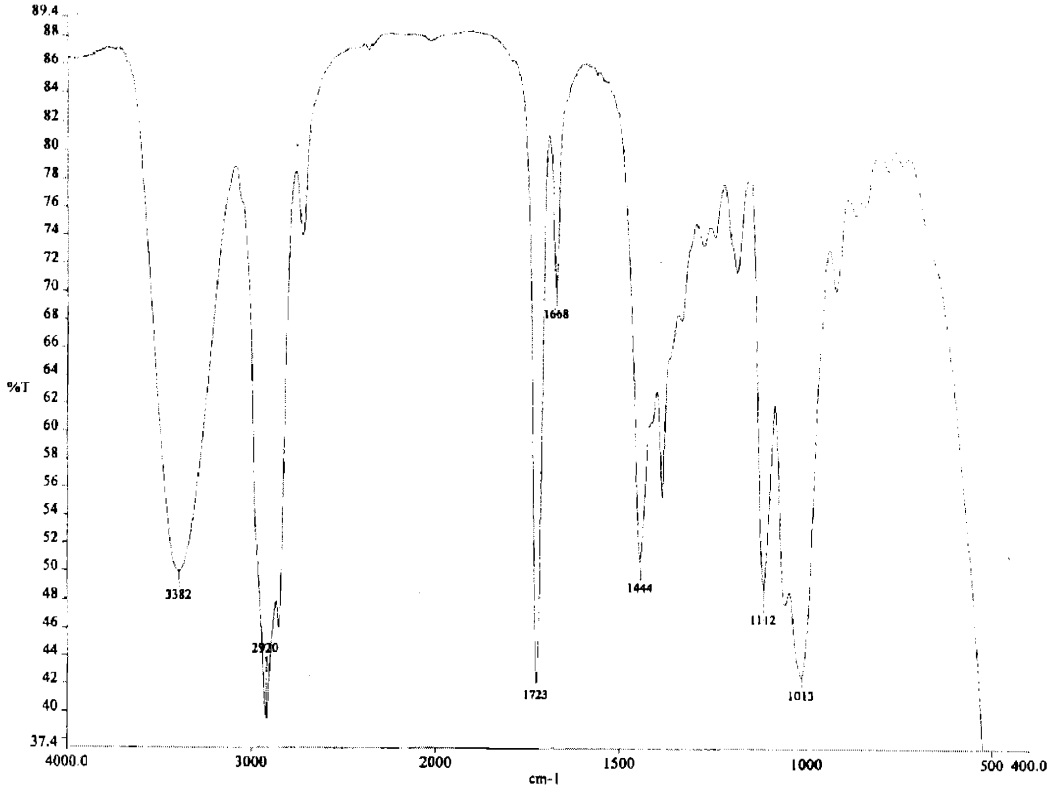

H
OH
O
Me
H
39a
Me
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

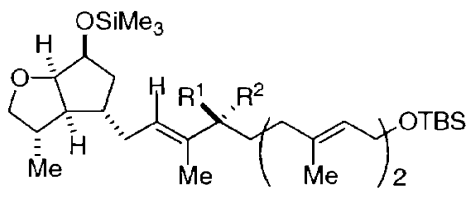

%T
3447
2920
2341
2360
1653
1558
1456
1088
1014
668
4000.0
3000
2000
1500
1000
500
400.0
cm-1



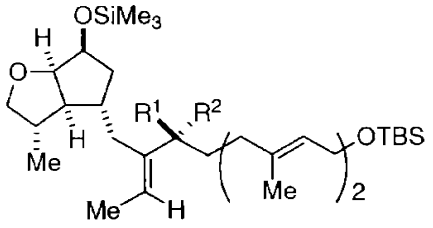
40a


Me
Me
HO
O
H
40a
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
89.4
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
40
37.4
3382
2920
1723
1668
1444
1112
1013
4000.0
3000
2000
1500
1000
500
400.0
cm-1

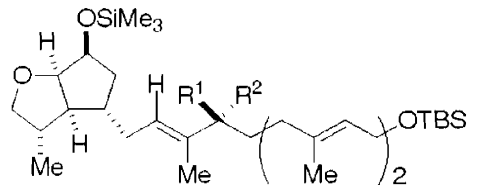


+



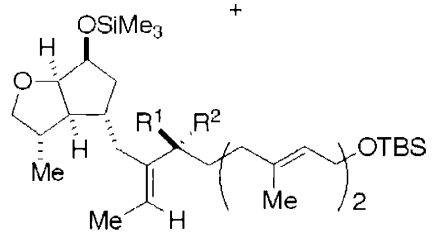
42a (R^1 = OH; R^2 = H)
42b (R^1 = H; R^2 = OH)

42c (R^1 = OH; R^2 = H)
42d (R^1 = H; R^2 = OH)

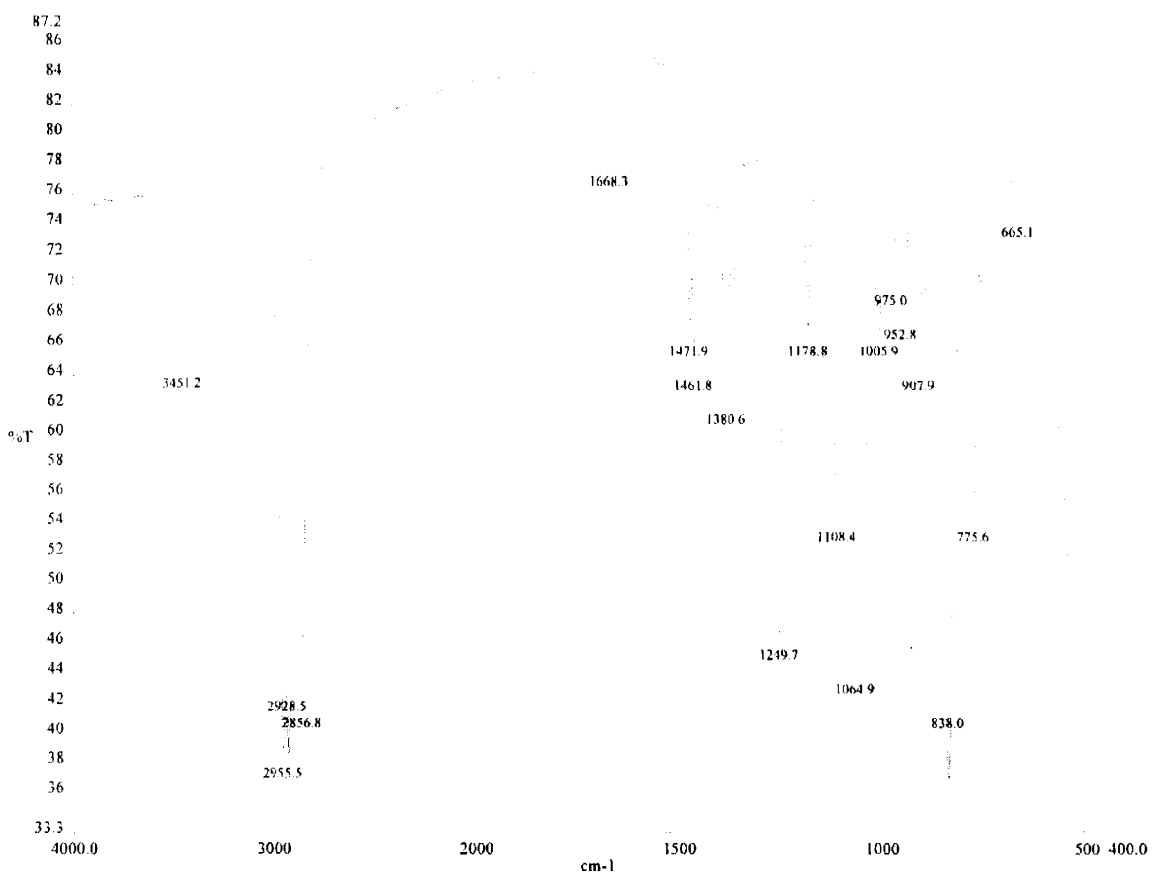


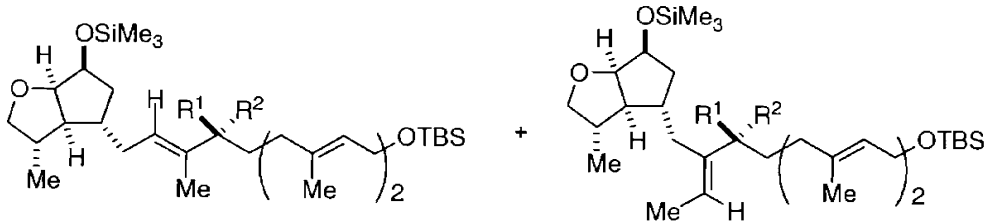
42a (R^1 = OH; R^2 = H)
42b (R^1 = H; R^2 = OH)

+



42c (R^1 = OH; R^2 = H)
42d (R^1 = H; R^2 = OH)

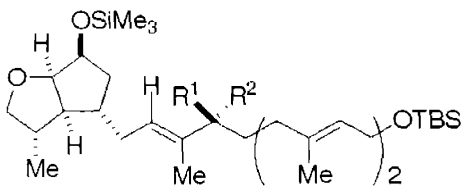




+

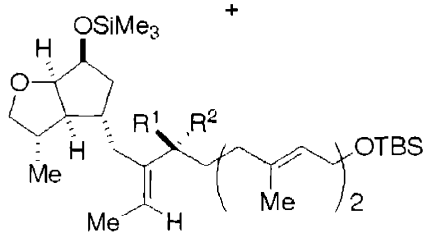
42a' (R^1 = OTIPS; R^2 = H)
42b' (R^1 = H; R^2 = OTIPS)

42c' (R^1 = OTIPS; R^2 = H)
42d' (R^1 = H; R^2 = OTIPS)

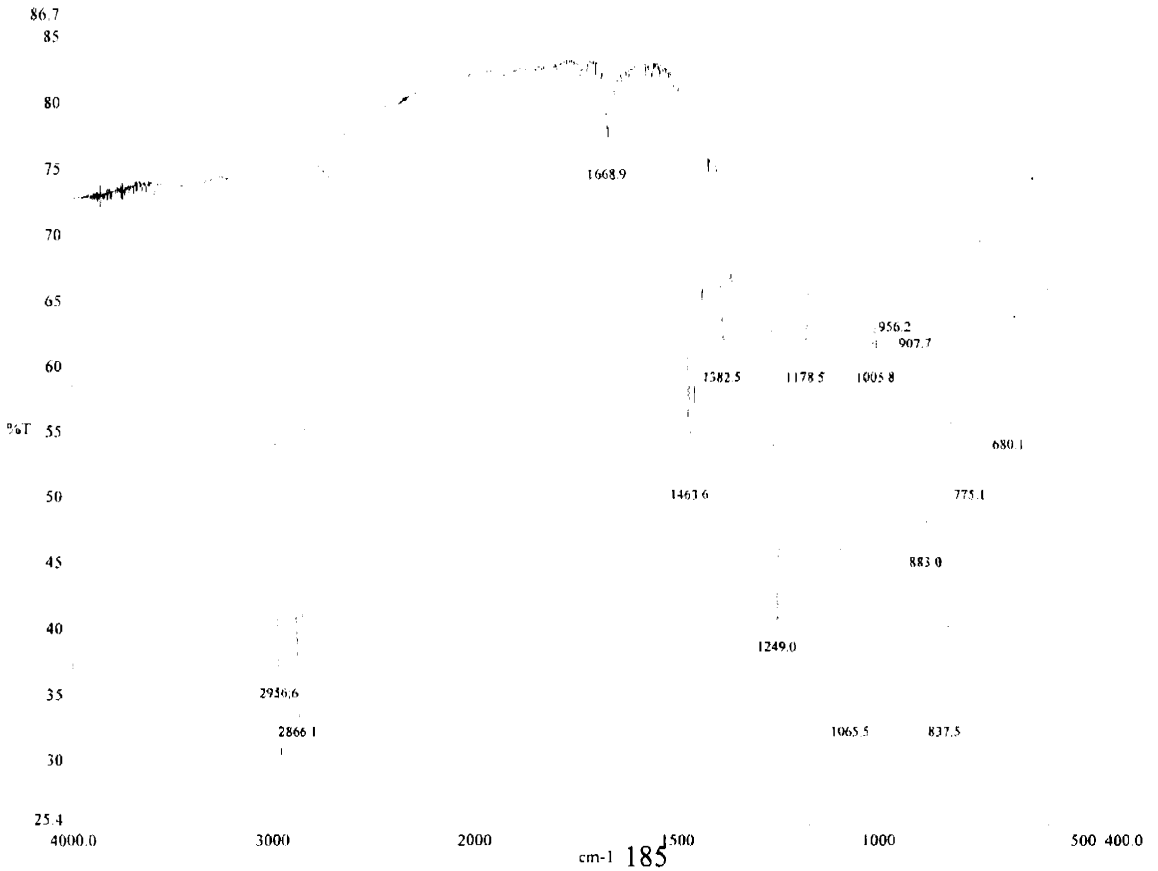


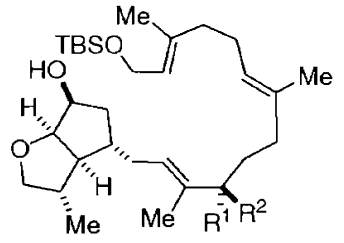
42a' (R^1 = OTIPS: R^2 = H)
42b' (R^1 = H: R^2 = OTIPS)

+

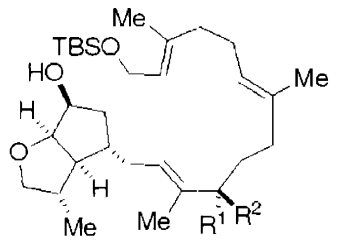


42c' (R^1 = OTIPS: R^2 = H)
42d' (R^1 = H: R^2 = OTIPS)

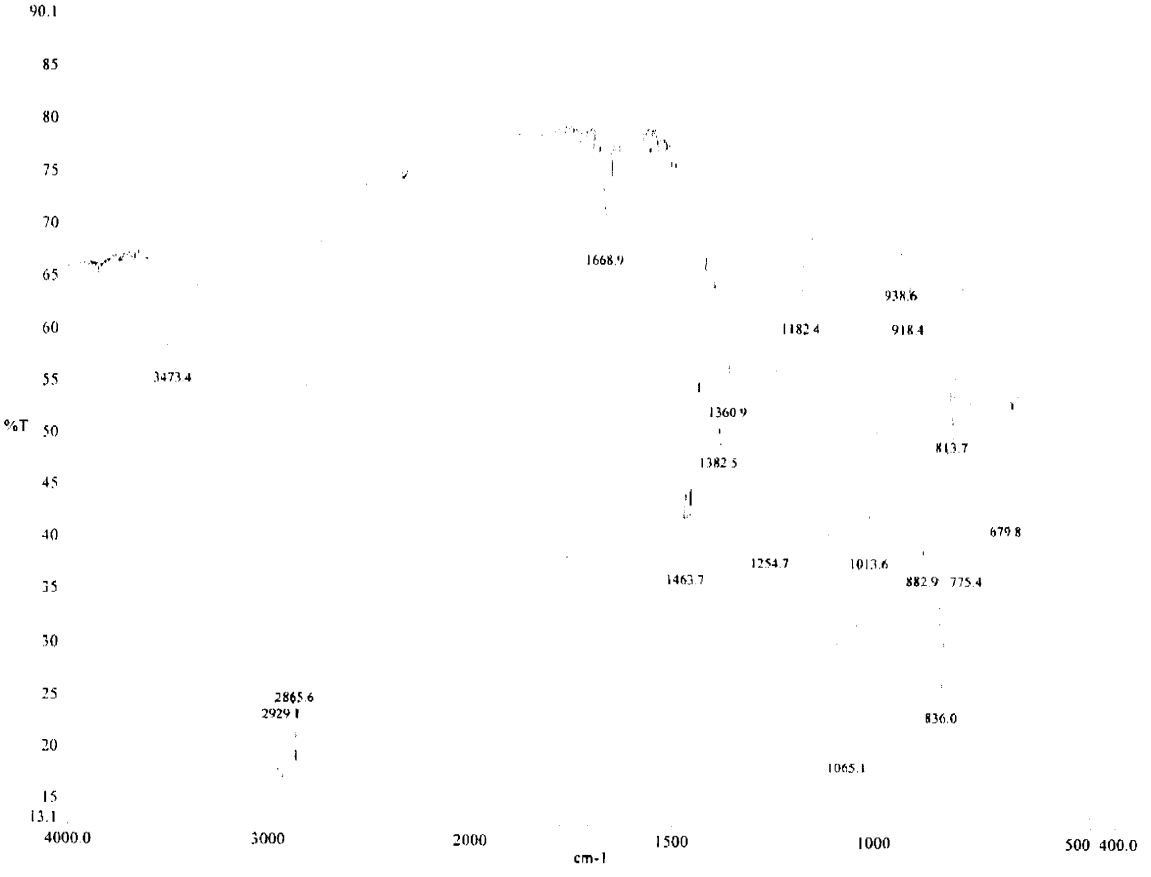


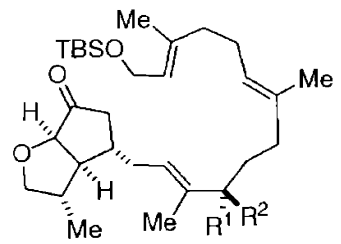


43a (R^1 = OTIPS; R^2 = H)
43b (R^1 = H; R^2 = OTIPS)

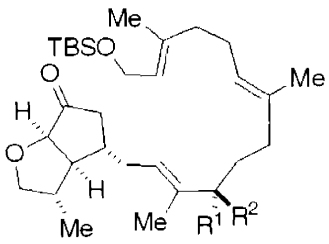


43a (R^1 = OTIPS; R^2 = H)
43b (R^1 = H; R^2 = OTIPS)

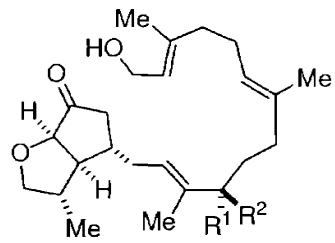




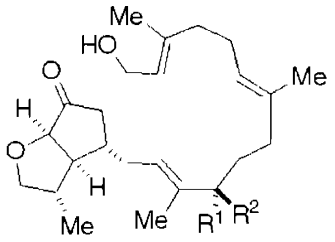
43a' (R^1 = OTIPS; R^2 = H)
43b' (R^1 = H; R^2 = OTIPS)



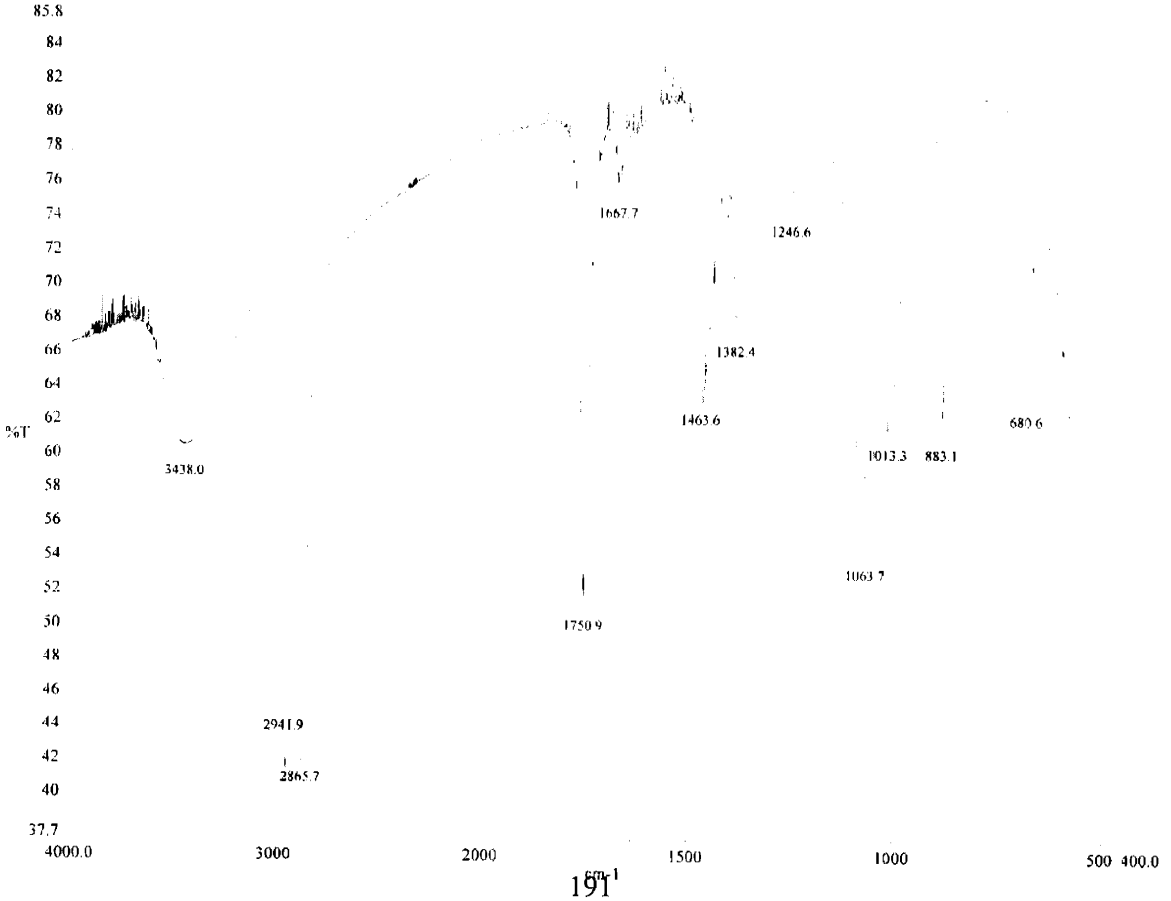
43a' (R^1 = OTIPS; R^2 = H)
43b' (R^1 = H; R^2 = OTIPS)

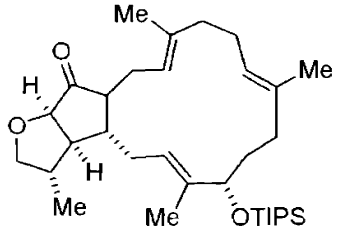


44a (R^1 = OTIPS; R^2 = H)
44b (R^1 = H; R^2 = OTIPS)

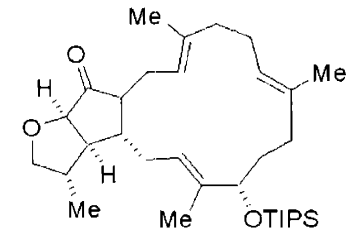


44a (R^1 = OTIPS; R^2 = H)
44b (R^1 = H; R^2 = OTIPS)



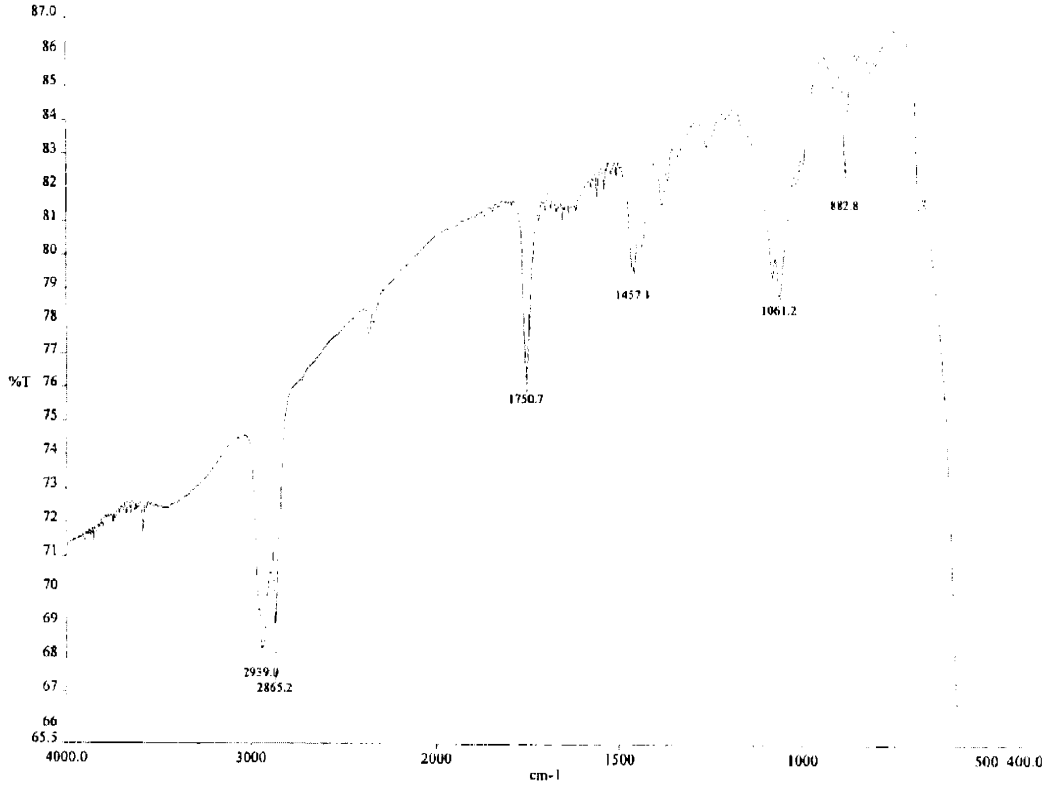


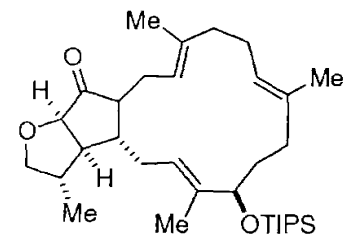
45a


Me
O
H
Me
O
H
Me
Me
OTIPS

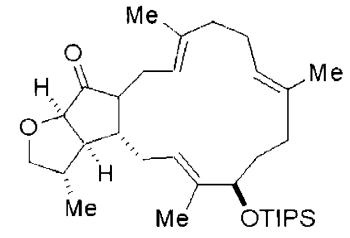
45a

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
2939.0
2865.2
1750.7
1457.1
1061.2
882.8
cm-1
4000.0
3000
2000
1500
1000
500
400.0



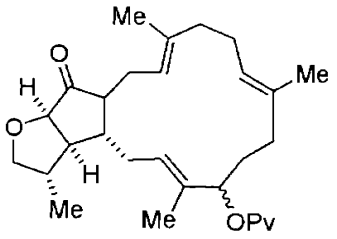
45b


Me
O
H
Me
O
H
Me
Me
OTIPS

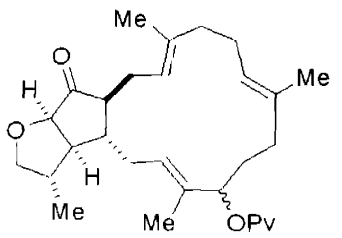
45b

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


88.7
%T
882.7
1457.1
1063.9
1750.1
2939.6
4000.0
3000
2000
1500
1000
500 400.0
cm-1



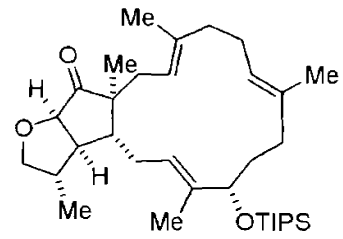
Pv-45


Me
O
H
Me
O
H
Me
Me
OPv

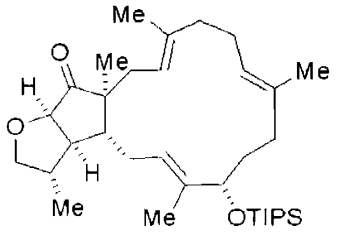
Pv-45

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


87.7
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58.9
%T
733.6
956.6
1395.7
1031.0
1479.7
1280.6
1455.1
1158.9
1749.9
1724.1
2929.7
4000.0
3000
2000
1500
1000
500
400.0
cm-1

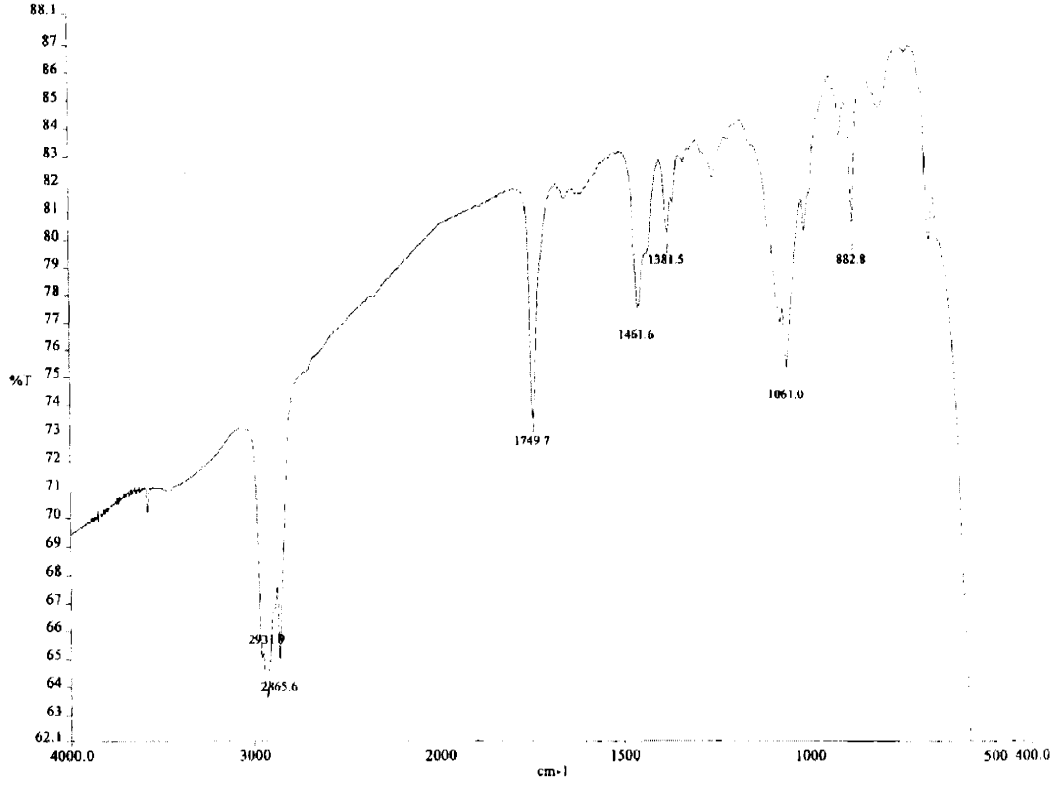


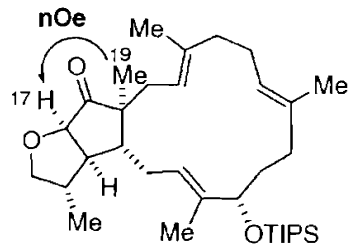
46


Me
O
Me
Me
H
O
H
Me
Me
OTIPS

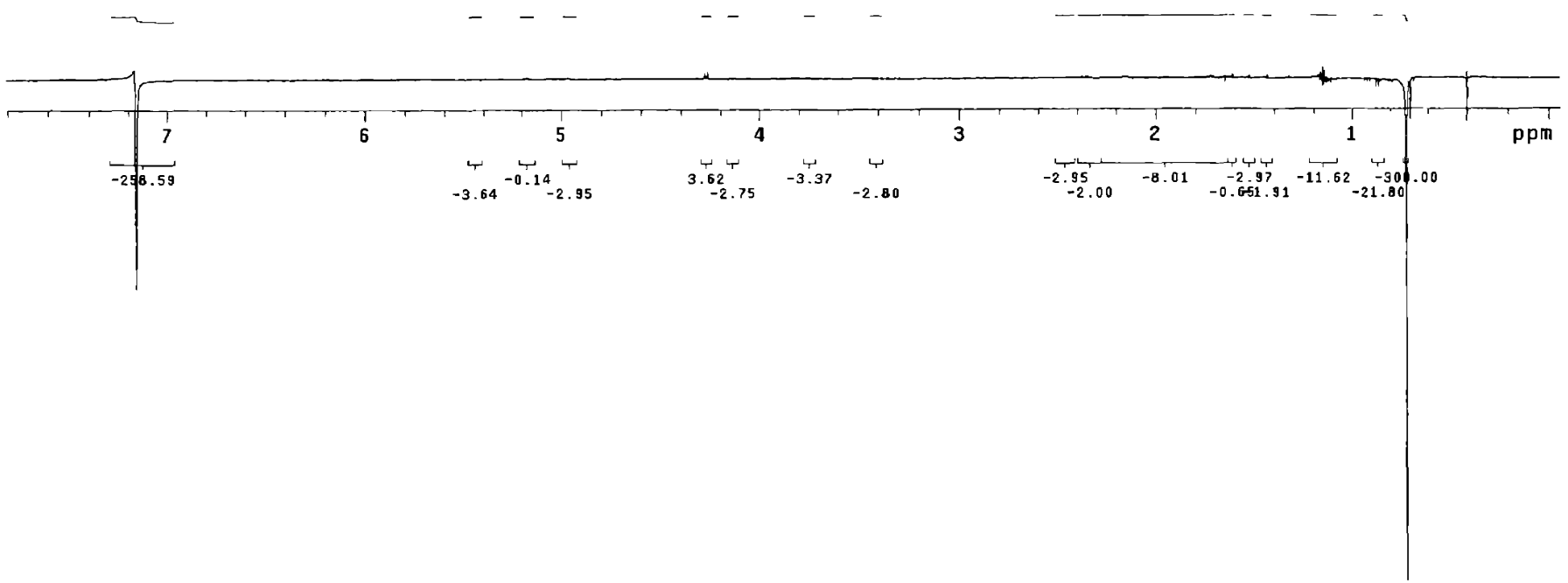
46

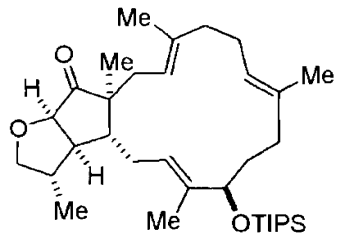
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
1749.7
1461.6
1381.5
1061.0
882.8
2865.6
4000.0
3000
2000
1500
1000
500
cm-1

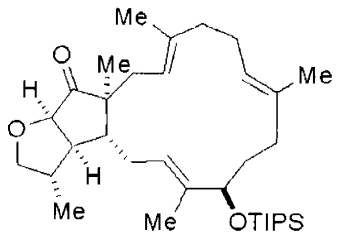

nOe
Me
19
Me
O
17 H
Me
O
H
Me
Me
OTIPS

46


200
7
6
5
4
3
2
1
ppm
-256.59
-3.64
-0.14
-2.95
3.62
-2.75
-3.37
-2.80
-2.95
-2.00
-8.01
-2.97
-0.65
51.91
-11.62
-21.80
-300.00

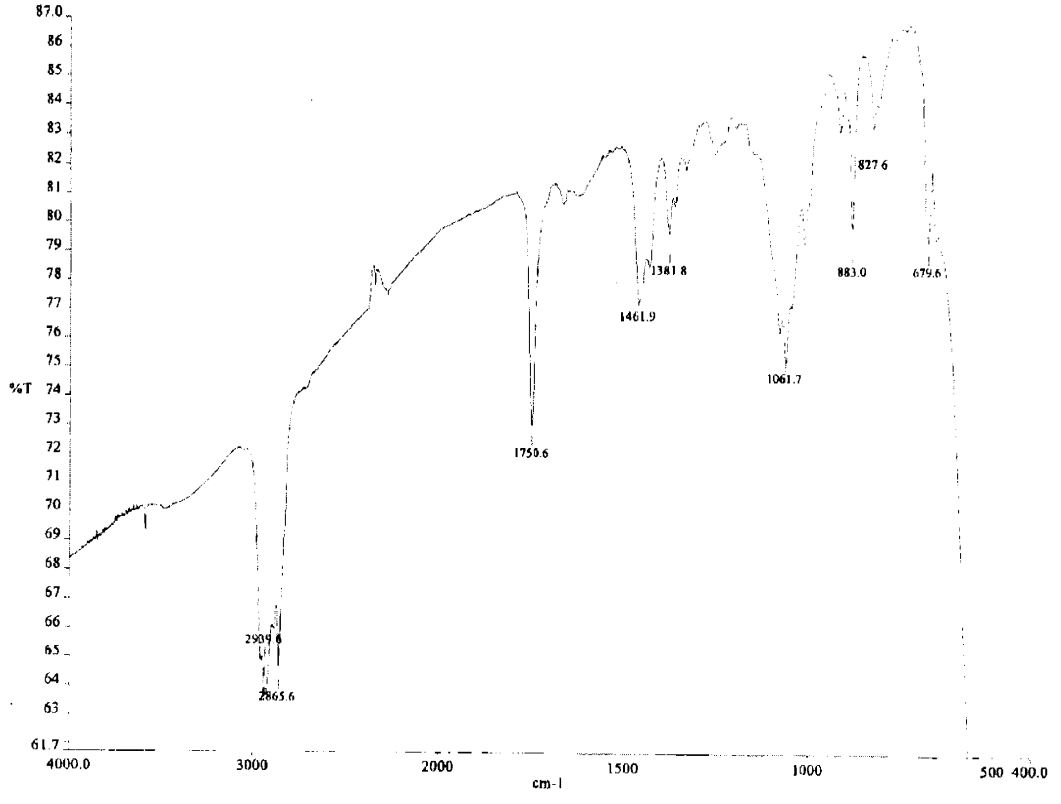


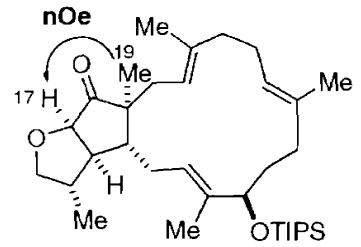
11-*epi*-46


Me
O
Me
Me
H
O
H
Me
Me
OTIPS

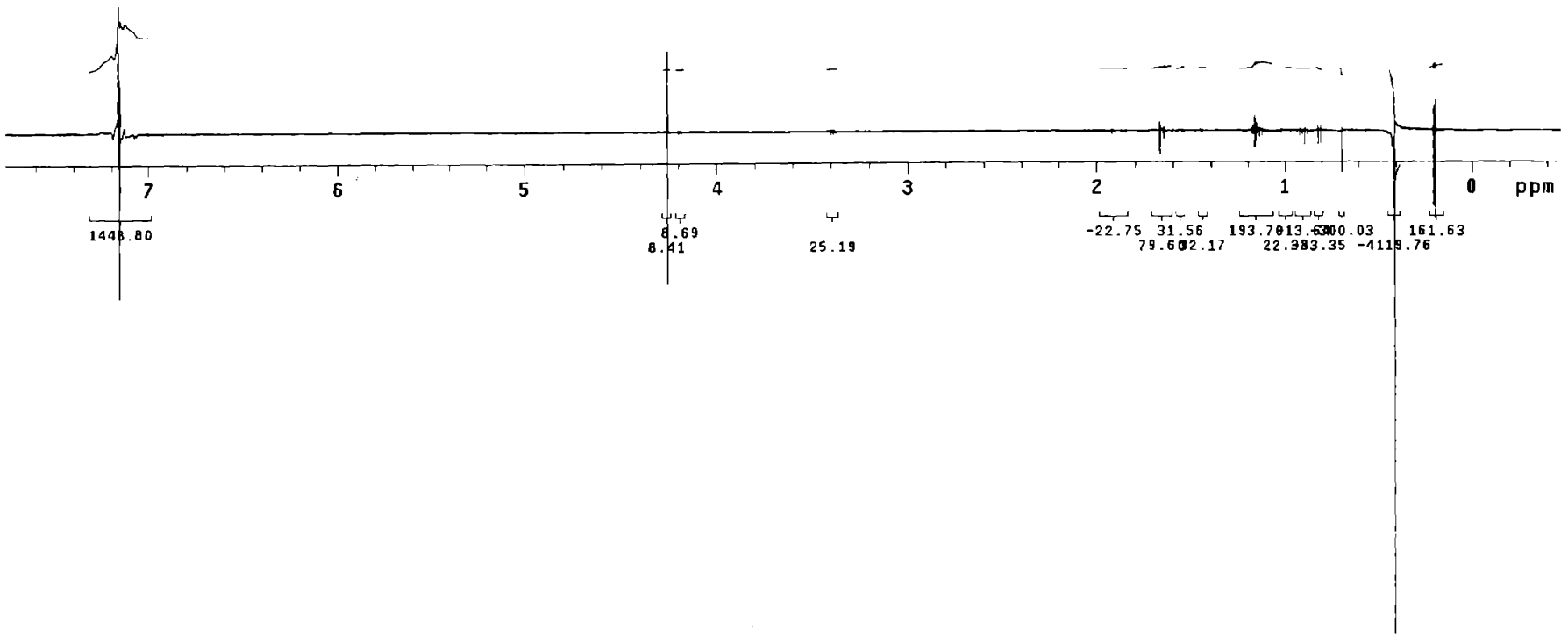
11-*epi*-46

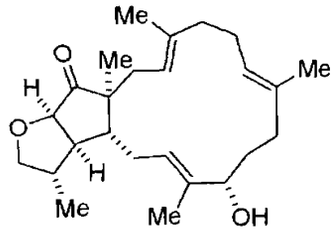
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
87.0
86
85
84
83
82
81
80
79
78
77
76
75
74
73
72
71
70
69
68
67
66
65
64
63
61.7
2909.6
2865.6
1750.6
1461.9
1381.8
1061.7
883.0
827.6
679.6
4000.0
3000
2000
1500
1000
500 400.0
cm-1

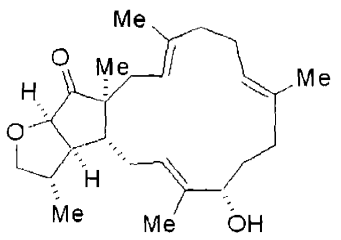

nOe
Me
19
O
Me
17 H
Me
O
H
Me
Me
OTIPS

11-*epi*-46


7
6
5
4
3
2
1
0
ppm
1448.80
8.69
8.41
25.19
-22.75
31.56
79.60
82.17
193.70
13.63
22.98
83.35
00.03
-4118.76
161.63

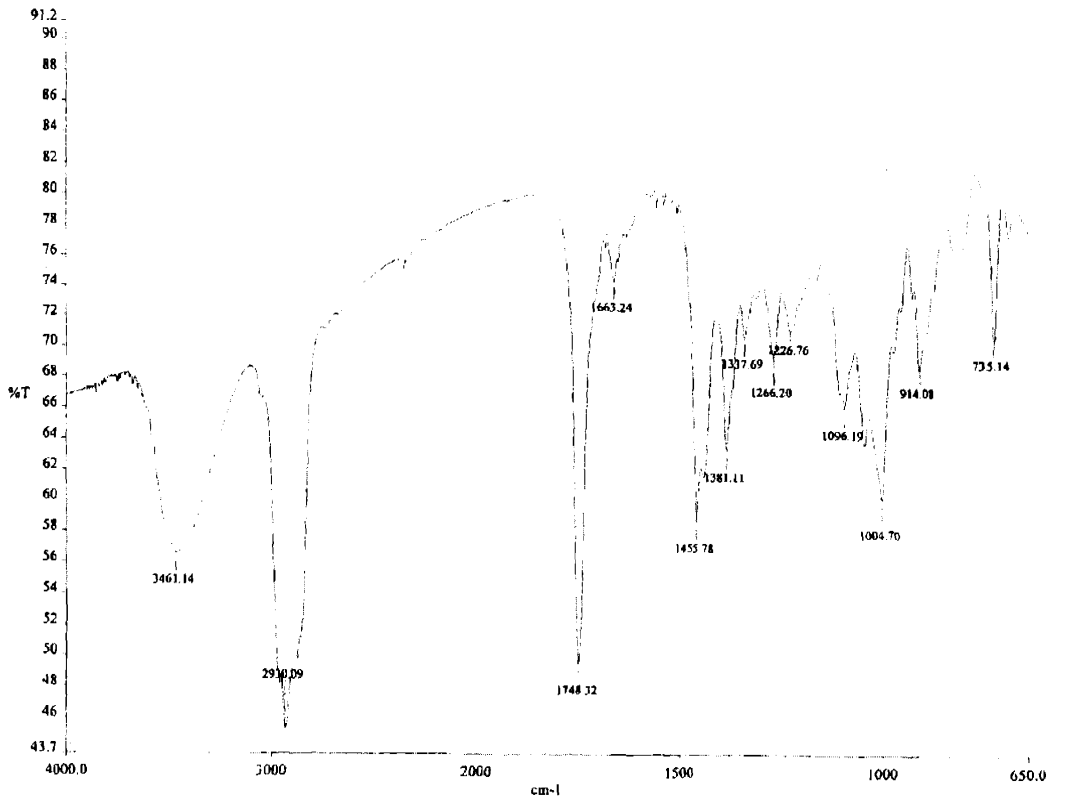


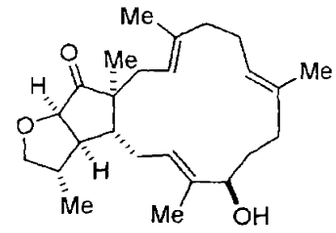
47


Me
O
Me
Me
H
O
H
Me
Me
OH

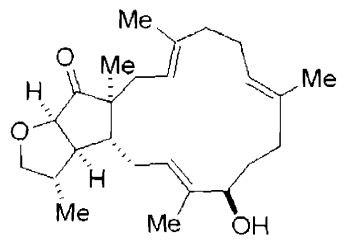
47

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
cm-1
4000.0
3000
2000
1500
1000
650.0
3461.14
2930.09
1748.32
1663.24
1455.78
1381.11
1337.69
1266.20
1226.76
1096.19
1004.70
914.08
735.14

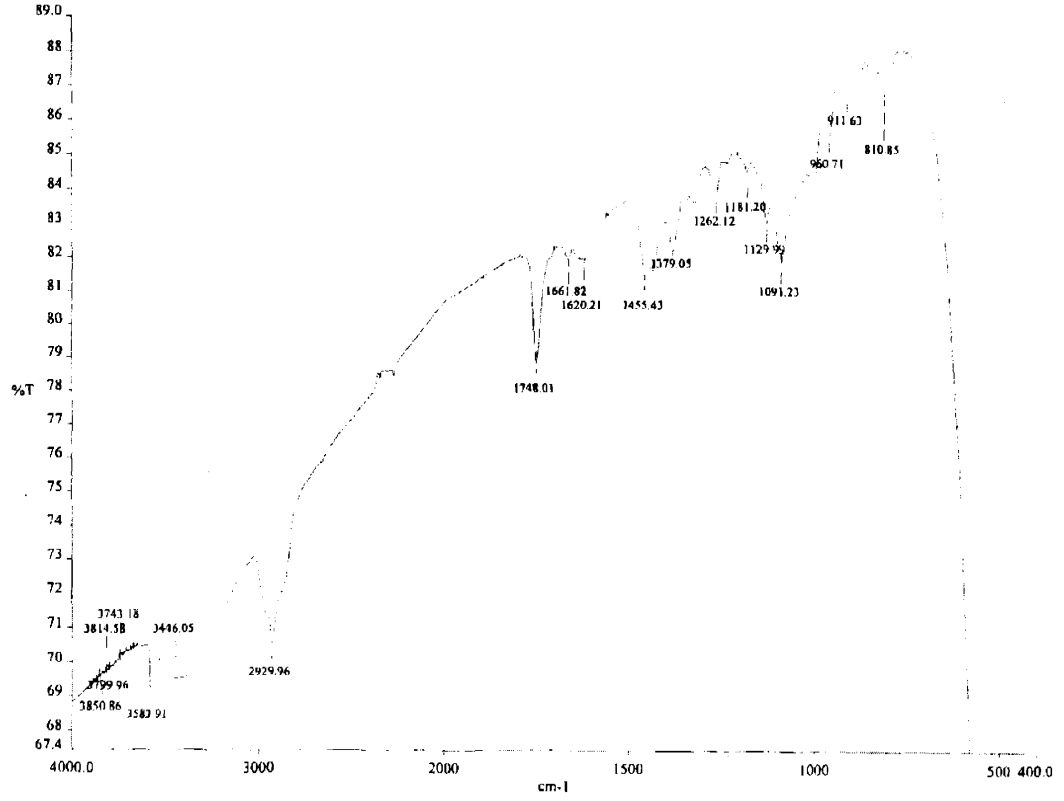


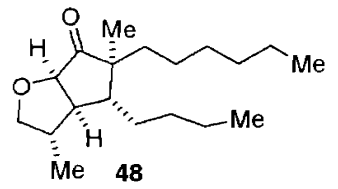
11-*epi*-47


Me
O
Me
Me
H
O
H
Me
Me
OH

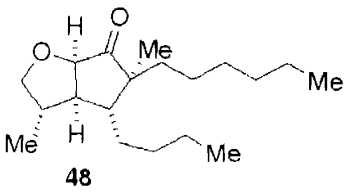
11-*epi*-47

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

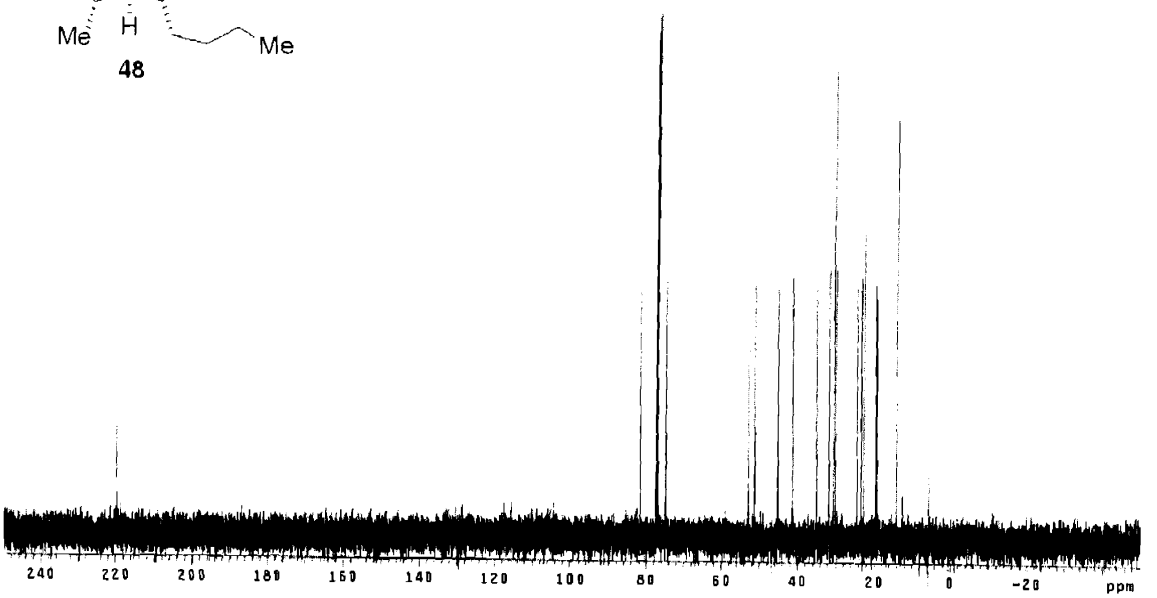

%T
89.0
88
87
86
85
84
83
82
81
80
79
78
77
76
75
74
73
72
71
70
69
68
67.4
3743.18
3814.58
3446.05
3799.96
3850.86
3582.91
2929.96
1748.01
1661.82
1620.21
1455.43
1379.05
1262.12
1181.20
1129.99
1091.23
980.71
911.63
810.85
4000.0
3000
2000
1500
1000
500 400.0
cm-1



48


H
O
O
Me
Me
Me
H
Me

48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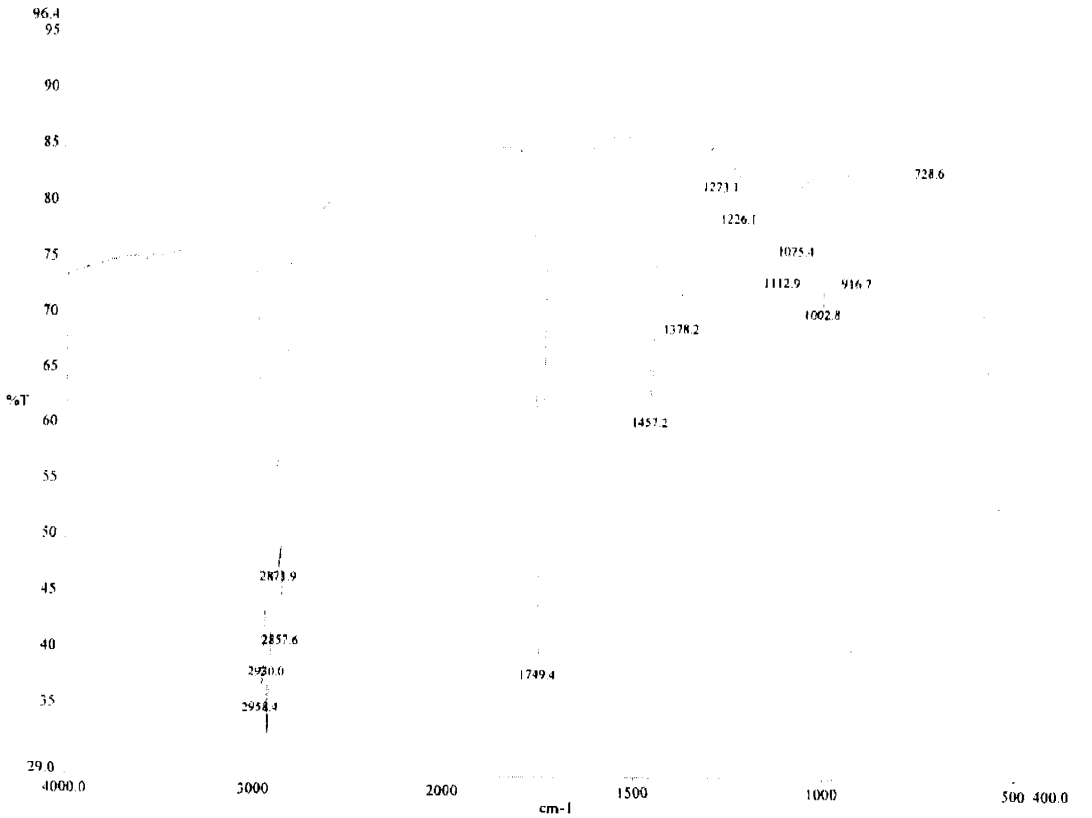
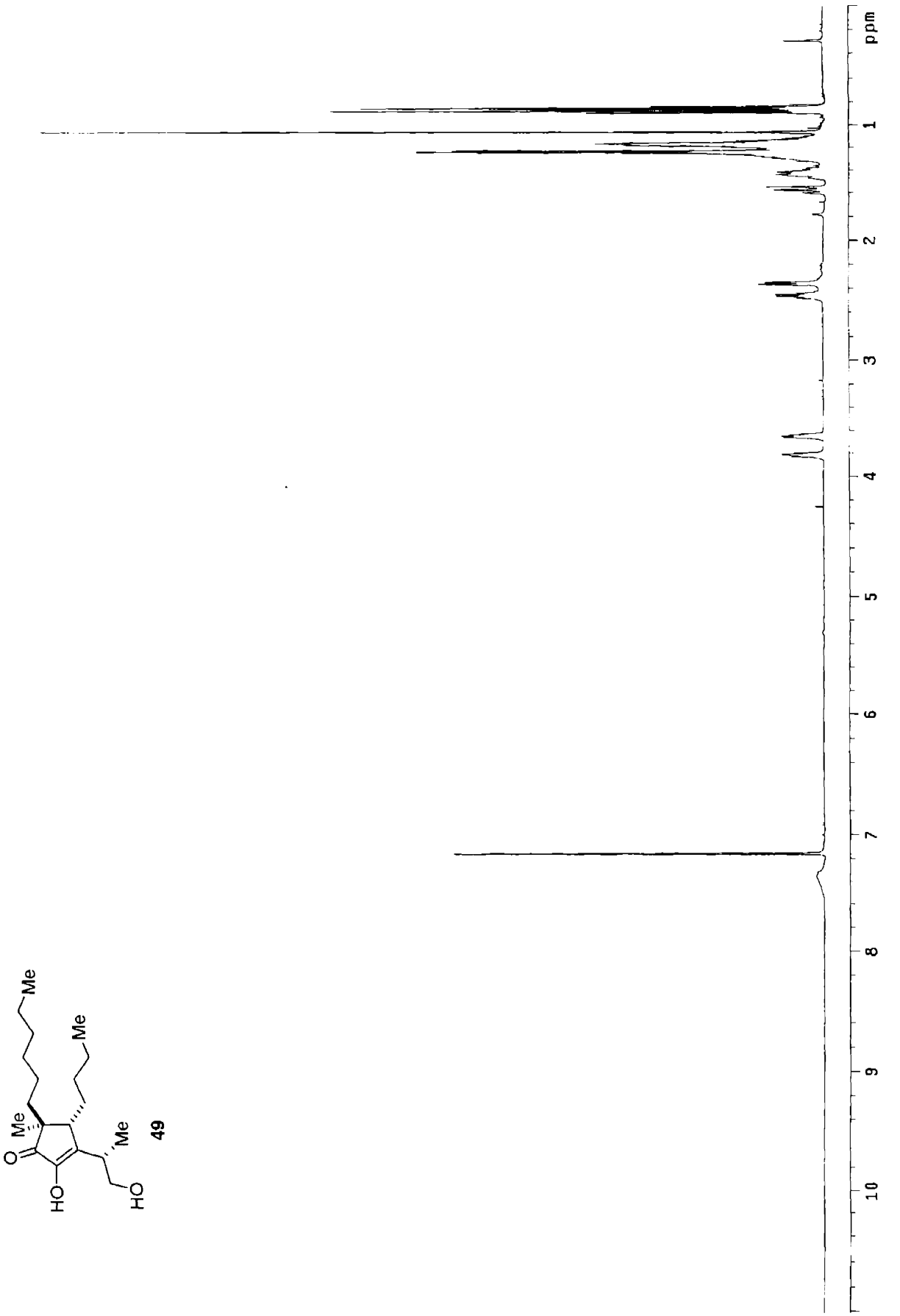
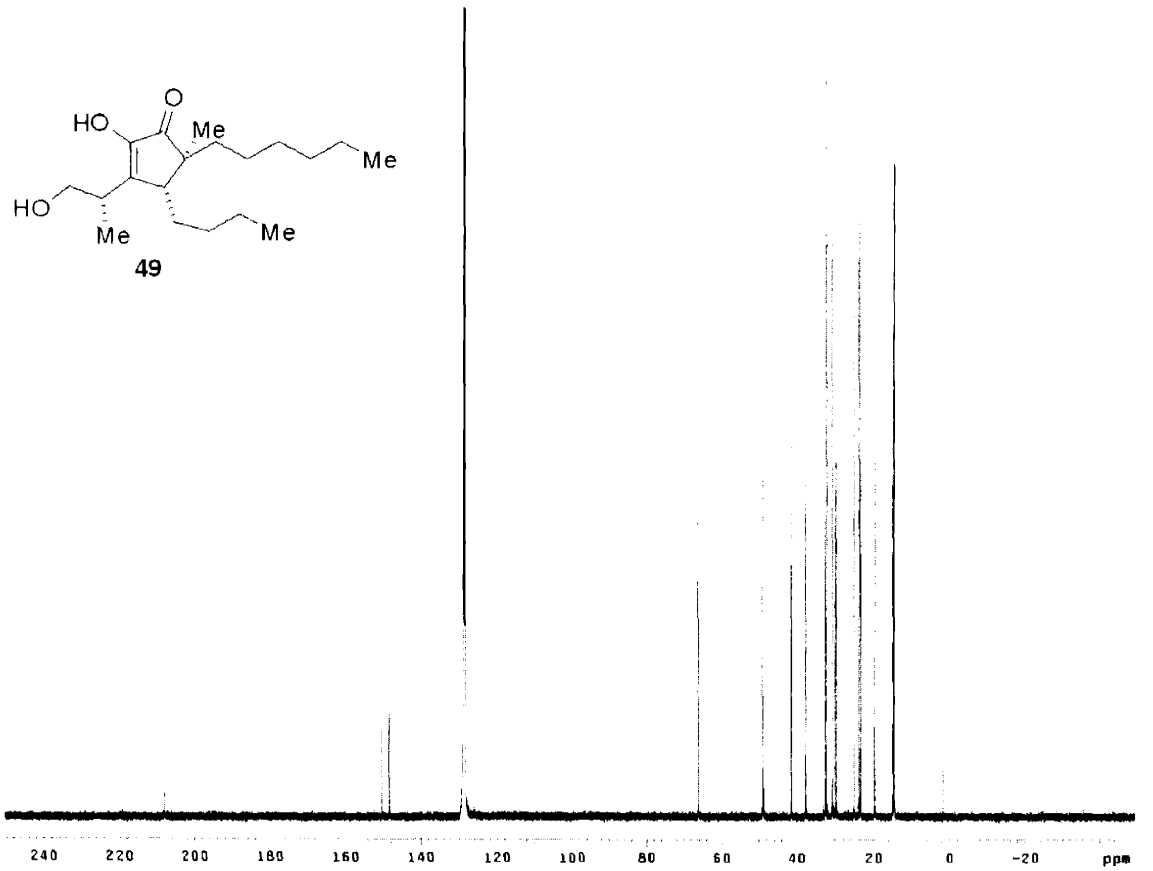
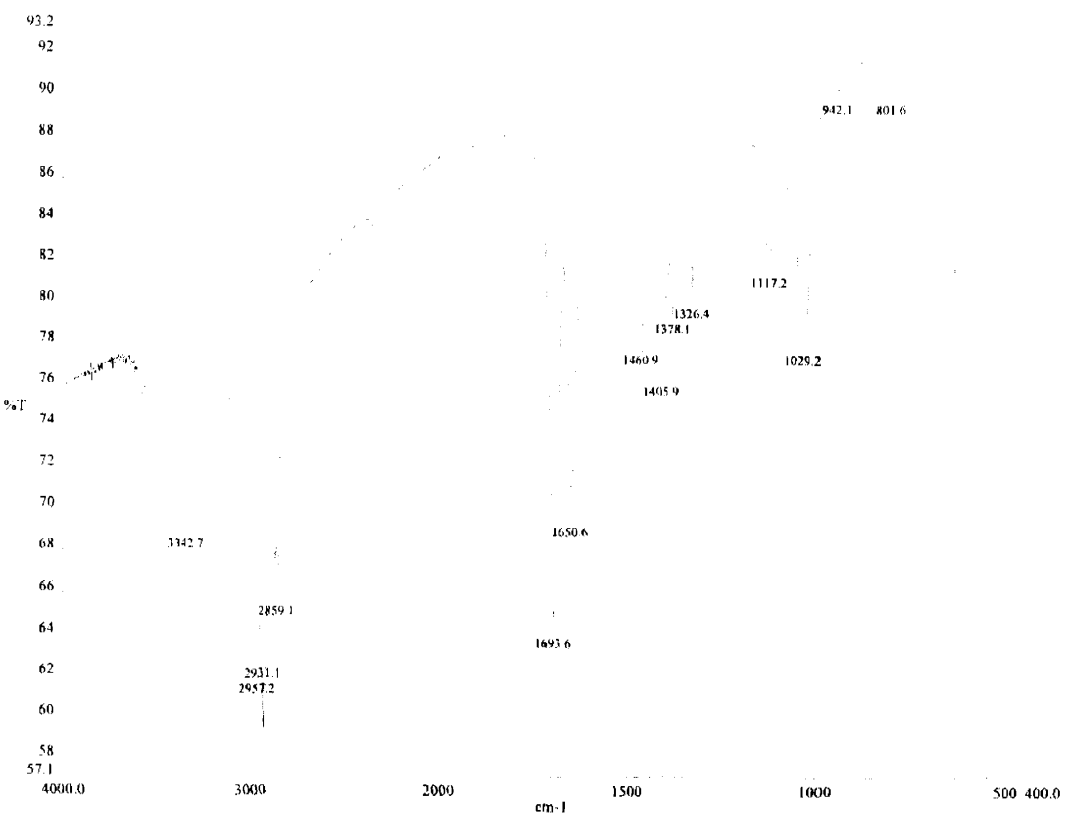
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


96.4
95
90
85
80
75
70
65
%T
60
55
50
45
40
35
29.0
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2871.9
2857.6
2930.0
2958.9
1749.4
1457.2
1378.2
1273.1
1226.1
1075.4
1112.9
1002.8
916.7
728.6



49


HO
O
Me
Me
HO
Me
Me
49
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


%T
942.1
801.6
1117.2
1326.4
1378.1
1460.9
1029.2
1405.9
3342.7
1650.6
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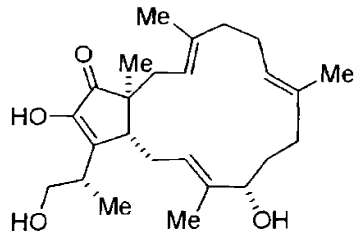
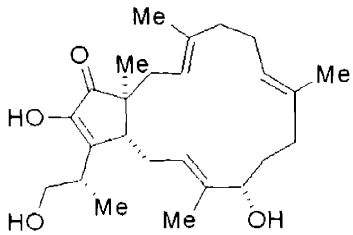
1693.6
2931.1
2957.2
4000.0
3000
2000
1500
1000
500
400.0
cm-1

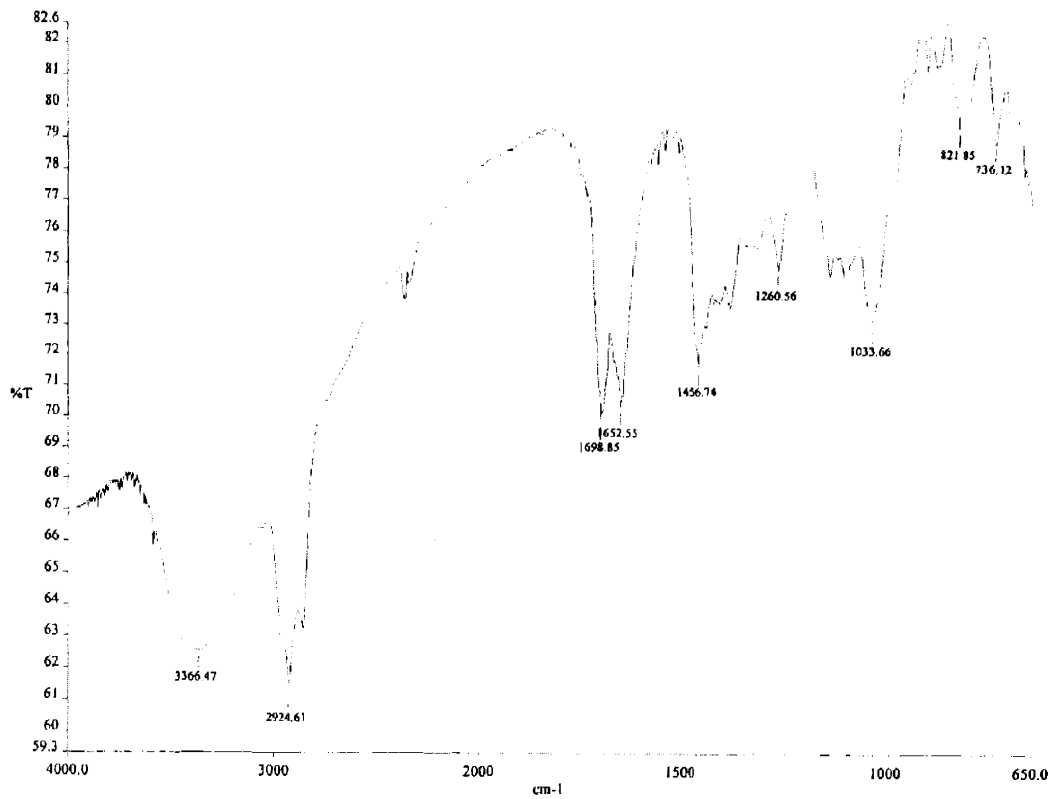


1


Me
O
Me
Me
HO
HO
Me
Me
OH

1

200
180
160
140
120
100
80
60
40
20
ppm


%T
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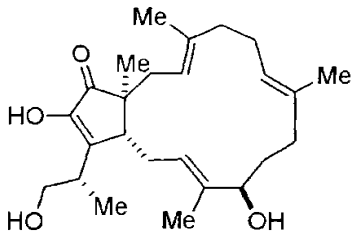
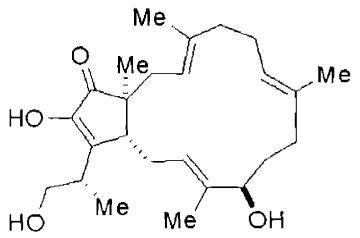
2924.61
1698.85
1652.53
1456.74
1260.56
1033.66
821.85
736.12
4000.0
3000
2000
1500
1000
650.0
cm-1

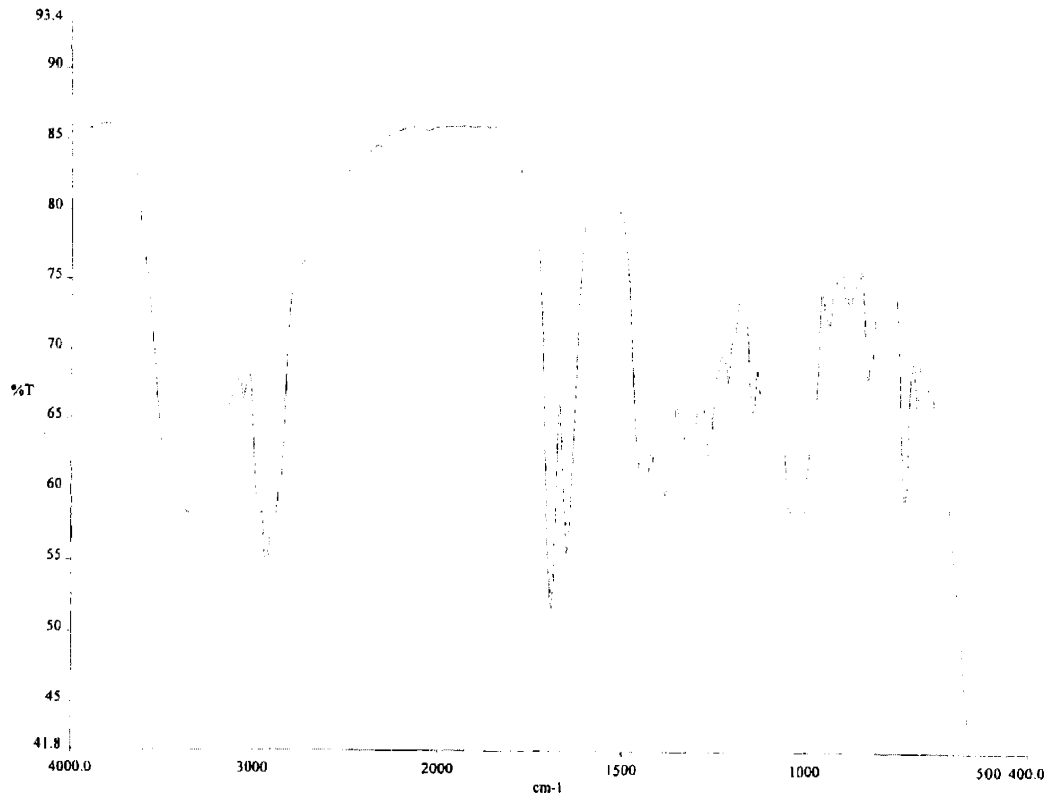


2


Me
O
Me
Me
HO
Me
HO
Me
OH

2

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


93.4
90
85
80
75
70
%T
65
60
55
50
45
41.8
4000.0
3000
2000
1500
1000
500 400.0
cm-1

Curriculum Vitae

Education

PhD. Org. Chemistry Massachusetts Institute of Technology (May 2004)
Thesis Title: "Nickel Catalyzed Intermolecular Reductive Coupling of Alkynes and Aldehydes. Enantioselective Synthesis of (–)-Terpestacin and Structural Revision of Siccanol Using Catalytic Fragment Couplings and Macrocyclizations"
Thesis Advisor: Dr. Timothy F. Jamison

Hons. BSc. Chemistry University of Toronto (May 1999)
Thesis Title: Fluorination of Pyrrolines Using Selectfluor™ and Novel Iodocyclocarbamations
Undergraduate Thesis Advisor: Dr. Robert A. Batey

Research and Teaching Experience

Massachusetts Institute of Technology September 1999- May 2004
Graduate Research Assistant

Massachusetts Institute of Technology September 1999-May 2000
Recitation Instructor
Instructor for Introductory General Chemistry (Course 5.11)
Instructor for Advanced Organic Chemistry (Course 5.13)

University of Toronto May 1998-September 1998
Undergraduate Researcher

University of Toronto May 1998-August 1998
Laboratory Instructor
Instructor for Course CHM240Y (Introductory Organic Chemistry)

Publications and Presentations

Jamison, T. F., **Chan, J.** "The Total Synthesis of (–)-Terpestacin and Structural Revision of Siccanol" 227th ACS National Meeting, Anaheim, CA, March, 2004.

Jamison, T. F., **Chan, J.** "Synthesis of (–)-Terpestacin via Catalytic, Stereoselective Fragment Coupling: Siccanol is Terpestacin, not 11-*epi*-Terpestacin," *J. Am. Chem. Soc.* **2003**, *125*, 11514.

Jamison, T. F., **Chan, J.** "The Total Synthesis of (±)-Terpestacin" Massachusetts Institute of Technology Graduate Symposium, Cambridge, MA, May, 2003.

Jamison, T. F., **Chan, J.** "The Total Synthesis of (±)-Terpestacin" Bristol Myers Squibb Fellowship Symposium, Wallingford, CT, May, 2003.

Jamison, T. F., **Chan, J.** "Nickel-Catalyzed Reductive Couplings between Alkynes and Aldehydes Directed Towards the Synthesis of Terpestacin" 6th Annual Boehringer Ingelheim Pharmaceuticals, Inc. Fellowship Symposium, Danbury, CT, October, 2002.

Jamison, T. F., **Chan, J.** "Nickel-Catalyzed Reductive Couplings between Alkynes and Aldehydes Directed Towards the Synthesis of Terpestacin" 224th ACS National Meeting, Boston, MA, August, 2002.

Chan, J.; Jamison, T. F. "Nickel-Catalyzed Reductive Couplings of Alkynes and Aldehydes Directed Towards the Synthesis of Terpestacin" 84th Canadian Society of Chemistry Conference & Exhibition, Montreal, May, 2001.

Huang, W.-S.; **Chan, J.**; Jamison, T. F. "Nickel-Catalyzed Reductive Couplings of Alkynes and Aldehydes", *Org. Lett.* **2000,** *2*, 4221.

MacKay, Bruce; **Chan, Johann**; Santhakumar, V.; Batey, R.A., "New Approaches Toward Pyrrolidine and Indolizidine Synthesis", Heterocycles Gordon Conference, Rhode Island, July 1998.

Awards Received

(1) Wyeth Travel Award for Oral Presentation: Jamison, T. F., **Chan, J.** "The Total Synthesis of (±)-Terpestacin" Massachusetts Institute of Technology Graduate Symposium, Cambridge, MA – 2003.

(2) Bristol-Myers Squibb Graduate Fellowship in Synthetic Organic Chemistry – 2002.

(3) Boehringer-Ingelheim Research Fellowship – 2002.

(4) Oral Presentation Award: **Chan, J.**; Jamison, T.F. "Nickel-Catalyzed Reductive Couplings of Alkynes and Aldehydes Directed Towards the Synthesis of Terpestacin" 84th Canadian Society of Chemistry Conference & Exhibition. Montreal – 2001.

(5) University of Toronto St. Michael's College Chemistry Medal – 1999.

(6) University of Toronto St. Michael's College In-course Scholarship – 1998.

(7) Ivan Szak Scholarship in Chemistry – 1998.

(8) Frank B. Kenrick Scholarship in Chemistry – 1998.

(9) University of Toronto St. Michael's College In-course Scholarship – 1997.