Diastereoselective Ring Closing Metathesis as an Approach to Cycloalkenes and Symmetrical Bicyclodienes and their Functionalization through Desymmetrization Reactions

by

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A thesis submitted in conformity with the requirements

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Graduate Department of Chemistry

University of Toronto

Objective

The objective of this thesis was twofold: An exploratory endeavor into the effect of bridgehead substituents on the efficiency and diastereoselectivity of the diastereoselective double ring closing olefin metathesis (DSRCM) reaction; and the functionalization of decalin and diquinanes synthesized by the DSRCM strategy through desymmetrization reactions.

Initial attempts at desymmetrization focused on atom transfer reactions. Success at desymmetrization of the decalin and diquinane substrates was achieved through an intramolecular asymmetric Heck reaction, which provides access to polycyclic substrates in good to excellent yields and with enantiomeric excesses as high as 99%.

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Abstract

Cycloalkenes bearing a quaternary carbon center were synthesized using a diastereoselective ring closing metathesis approach. Diastereoselectivities observed in cycloalkene formation were modest (<4.5:1) and thus extension to the synthesis of the analogous bicyclodienes was not pursued.

Application of the intramolecular asymmetric Heck reaction in the desymmetrization of symmetrical bicyclodienes was achieved with good yields and excellent enantioselectivities. In the desymmetrization of bicyclo-[3.3.0]octadienes, polycyles were synthesized in yields as high as 80% and enantioselectivities as high as 99%. Polycycles derived from bicyclo-[4.4.0]decadienes were obtained in modest yields(<60%), and good enantioselectivities (≤82%).

Acknowledgements

I would like to extend my appreciation to my supervisor, Professor Mark Lautens, for his guidance and support throughout the course of my study. NSERC Canada is acknowledged for financial support in the form of a PGS A scholarship.

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List of Abbreviations

Ac – acetyl

acac – acetylacetonate

AHR – Asymmetric Heck Reaction

BINAP – $2,2^1$- bis(diphenylphosphino)-$1,1^1$-binapthyl

Bn – benzyl

Bu – butyl

Bz – benzoyl

cacld – calculated

cat. – catalyst

Cy – cyclohexyl

dba – dibenzylidene acetone

DIPEA – diisopropyl ethylamine

DMA – dimethylacetamide

DMF – dimethylformamide

DSRCM – diastereoselective ring closing metathesis

ee – enantiomeric excess

equiv – equivalent

Et – ethyl

Grubbs' catalyst – bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride

HRMS – high resolution mass spectrum

IMES – 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene

IR – infrared

LDA – lithium diisopropyl amide

NMR – nuclear magnetic resonance

Pd – palladium

Ph – phenyl

PHOX – phosphinooxazoline

PMB – para-methoxybenzyl

R – generic alkyl group

RCM – ring closing metathesis

rt – room temperature

Schrock's catalyst – 2,6-diisopropylphenylimidoneophylidene molybdenum (VI) bis(hexafluoro-*t*-butoxide

TBAF – tetra-*n*-butylammonium fluoride

Tf – trifluoromethanesulfonate

THF – tetrahydrofuran

TLC – thin layer chromatography

TMS – trimethylsilyl

TBDMS – *tert*-butyldimethylsilyl

TBDPS – *tert*-butyldiphenylsilyl

p-tol-BINAP – 2,2^1- bis(di-*o*-tolylphosphino)-1,1^1-binapthyl

Table of Contents

1. General introduction- Olefin Metathesis in Organic Synthesis

The alkene metathesis reaction is the (apparent) interchange of carbon atoms between a pair of double bonds. The reaction is generally catalyzed by a variety of high oxidation state, early transition metal species.[1] Olefin metathesis has been applied to such transformations such as acyclic diene cross-metathesis (ADMET), ring closing metathesis (RCM), and ring-opening metathesis polymerization (ROMP).

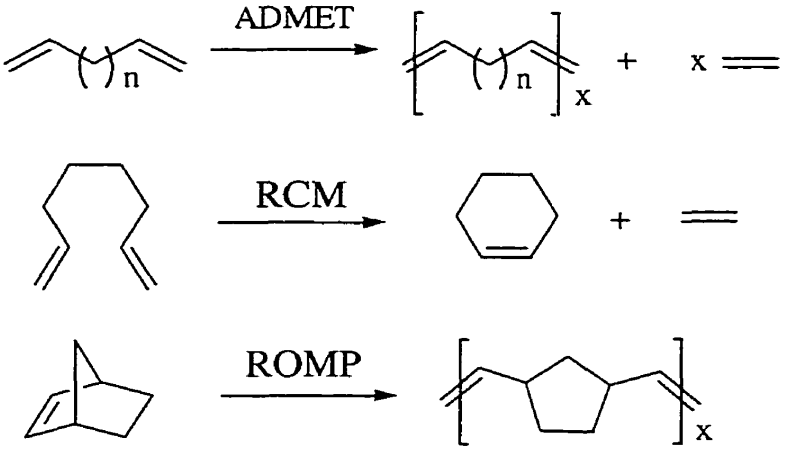


Figure 1. Applications of olefin metathesis in organic synthesis.

The reactions are generally reversible and under thermodynamic control. In accord with the Chauvin mechanism[1], the key step in olefin metathesis is a reaction between and olefin and a transition metal alkylidene complex, in a [2+2] fashion to give an unstable intermediate metalla-cyclobutane ring. The metalla-cyclobutane ring then collapses yielding the transition metal alkylidene and the olefin product.

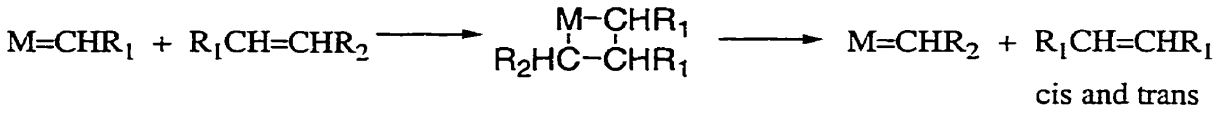


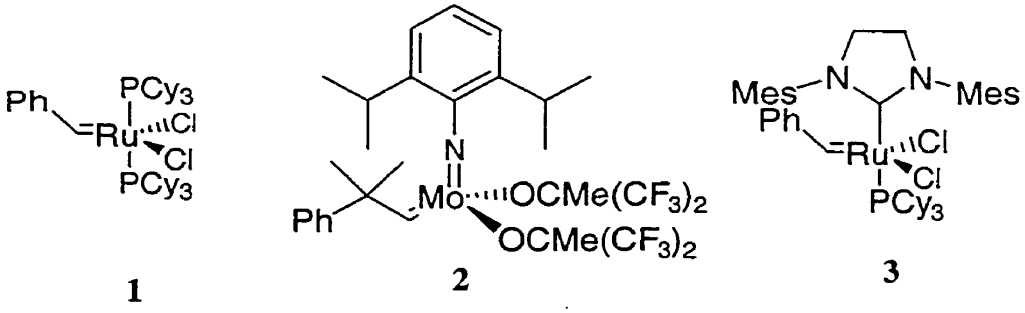
Figure 2. Chauvin mechanism for olefin metathesis.

The interest in olefin metathesis is due to the fact that the strong bond in the alkene, the C=C bond, which has a bond dissociation energy of ~682kJ/mol[2], is broken and reformed during the process. The facile preparation of a variety of olefins is thus made possible using this reaction. Early examples of the use of this chemistry were in polymerization chemistry and cross-metathesis chemistry, the latter being used in pheromone synthesis.

The preparation of well-defined alkylidene (pre)catalysts allows the reactivity of such species towards olefins to be "tuned" for a given class of reactions. The advantage of starting a metathesis reaction with a known amount of well defined initiator that is 100% active is a significant advantage compared to "classical" metathesis recipes where the amount, the identity, and the stability of the actual catalyst is not known. Therefore low yields, irreproducibility, intolerance of functionalities were common when classical catalyst systems were employed. With the advent of well-defined Mo and Ru catalysts, yields have improved and many functionalities are now tolerated.[1] These catalysts allow closer control and better understanding of the mechanism of olefin metathesis reactions. Although the reactions effected by two complexes are essentially the same, the requirements for stable (pre)catalysts and propagating species are quite different in the two. Molybdenum is an early transition metal, in a high oxidation state, analogous to classical metathesis systems while ruthenium is a late transition

metal in a lower oxidation state. The common feature in both systems is that the metal complexes contain less than 18 electrons, and have a vacant coordinate site to accommodate an olefin-binding site. It has become quite evident that the reactivity of the d^0 complexes of molybdenum(VI) (counting the alkylidene ligands as ionic) is increased when the ligands on the metal are made more electron attracting, creating a more electrophilic metal center. In contrast the d^6 ruthenium(II) complexes (counting the alkylidene as a neutral), the reactivity increases with increasing electron richness of the ligands. As a result the molybdenum complexes must be handled in an inert atmosphere whereas the ruthenium complexes can be used in the presence of air and water. However, the ruthenium complexes are less reactive than the molybdenum complexes but show a greater functional group tolerance.

Ring closing olefin metathesis chemistry has been the subject of much attention in recent years due to the development of well defined transition metal alkylidenes such as $[Cl_2(Cy_3P)_2Ru{=}CHPh]$ (**1**), $[PhMe_2CCH{=}Mo{=}N\{2,6\text{-}(iPr)CH\}\{OCMe(CF)_2\}]$ (**2**), and (4,5-DihydroIMES)$(PCy_3)Cl_2Ru{=}CHPh$ (**3**) which display tolerance to a wide range of functional groups.



1 **2** **3**

Figure 3. Olefin Metathesis Catalysts used in organic syntheses.

Molybdenum based catalyst **2** has generally been preferred for substrates requiring a highly active catalyst, e.g. in the synthesis of tetrasubstituted olefins. The advent of the highly active catalyst **3**[3], which displays the high activity of **2** yet retains the air/water stability of **1**, applications by **2** have generally been replaced by the more robust **3**. The electron richness of the imidazolin-2-ylidene ligand[4] coordinated to the ruthenium center is responsible for the favourable properties of **3**.

The synthesis and functionalization of cycloalkenes in a stereocontrolled manner remains a challenge to the synthetic chemist.[5] In this manner, ring-closing olefin metathesis (RCM) has emerged as a powerful and useful transformation among the reaction types available. The olefin products from RCM reactions can then be modified in subsequent transformations to yield highly functionalized products.

Compared to the number of reports on olefin metathesis in general, very few contributions have addressed stereoselective variants. Enantioselective ring-closing metathesis reactions using chirally modified catalysts have been reported.[6] A stereoselective synthesis of 2,5-disubstituted five membered azacycles represents the first diastereoselective ring-closing metathesis reaction.[7] Lautens and Hughes have reported the formation of *cis*- and *trans*-decalin systems as well as *cis*-diquinanes via a diastereoselective double ring closing olefin metathesis reaction (DSRCM)[8], (see **Figure 4.**). These symmetrical bicyclodienes are ideal substrates in the area of alkene differentiation reactions. Desymmetrization of a

symmetrical molecule to yield an enantiomerically enriched product is certainly a topic of current interest.

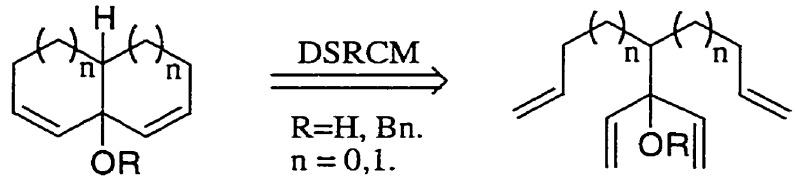
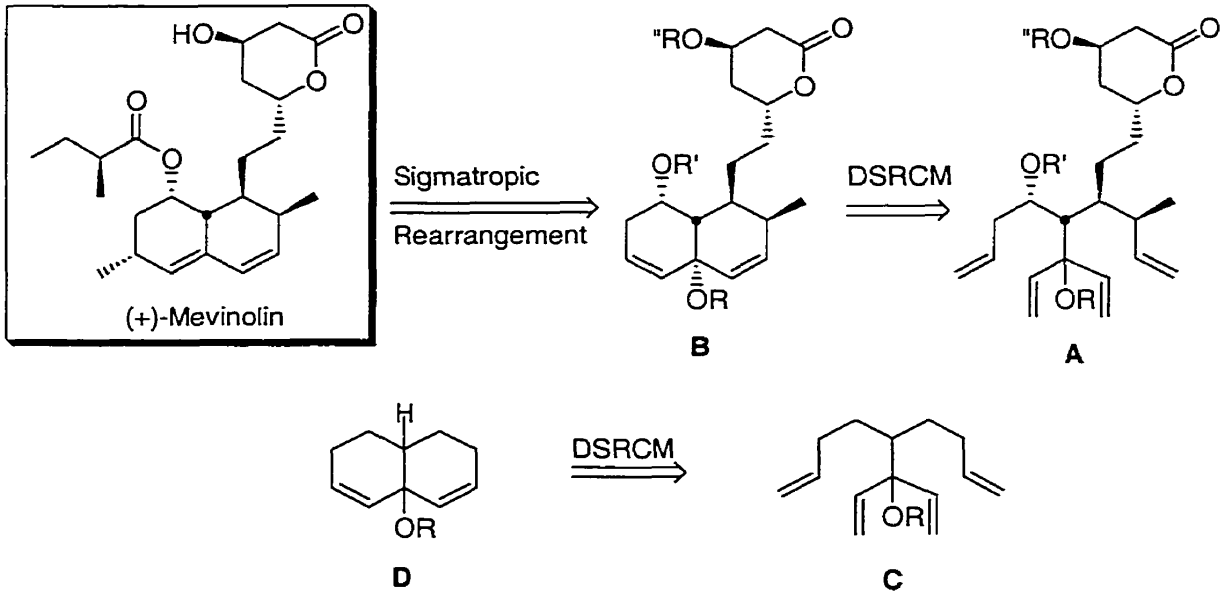


Figure 4. DSRCM as an approach to symmetrical bicyclodienes.

Outlined in this thesis are efforts directed towards extending the DSRCM methodology to the synthesis of bridgehead substituted bicyclic systems. The remainder of the thesis is devoted to attempts to desymmetrize the bicyclodienes synthesized by the DSRCM approach followed by a detailed report on the application of the Asymmetric Heck Reaction (AHR) in the synthesis of enantiomerically enriched polycyclic molecules.

2. Diastereoselective Ring closing Metathesis as an Approach to Symmetrical Bicyclodienes - Background

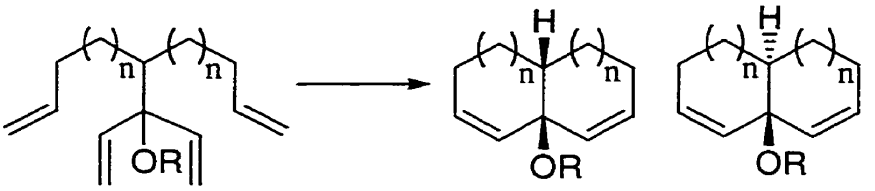
Applications of RCM to organic chemistry and in particular its use as a key step in the synthesis of natural products has been rapidly increasing.[1,5] Studies in the Lautens research group on the synthesis of the HMG CoA reductase inhibitor (+)-mevinolin, revealed that the tetrahydronapthalene skeleton of the natural product could possibly be synthesized via a double ring closing metathesis reaction. To test this approach, unsubstituted tetraenes **C** were synthesized.



Scheme 1. Potential retrosynthetic approach to (+)- Mevinolin proposed by Lautens and Hughes.

Fortuitously, the double ring closing metathesis approach to bicyclodienes was feasible and led to synthesis of diastereomeric bicyclic products. The diastereoselectivity of the process was examined with the two metal alkylidenes available at the time, **1** and **2**, and partial results are presented in **Table 1**.

Table 1. RCM reactions of tetraene substrates.



R=PMB, n=1 **4**
R=H, n=1 **5**
R=Bn, n=0 **6**

cis-**7** R=PMB, n=1
cis-**8** R=H, n=1
cis-**9** R=Bn, n=0

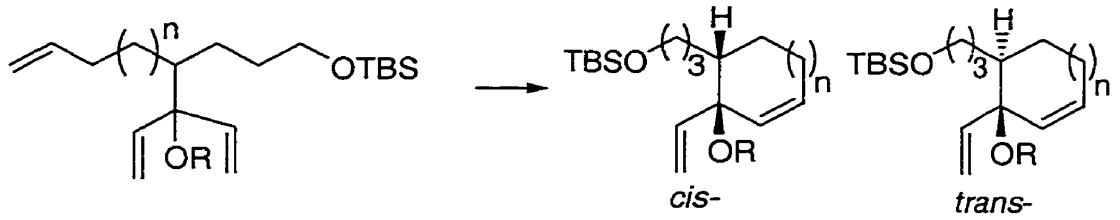
trans-**7** R=PMB, n=1
trans-**8** R=H, n=1
trans-**9** R=Bn, n=0

Entry	Starting material	Product	Conditions[a] [mol %, h]	*Cis*:*trans*	Yield [%]
1	**4**	**7**	A[b] (12, 20)	8:1	80
2	**4**	**7**	B (12, 20)	8:1	82
3	**5**	**8**	A (10, 2.5)	1:2.8	84
4	**6**	**9**	A[b] (4, 20)	[c]	81
5	**6**	**9**	B (4,2)	[c]	66

[a] Reaction conditions: A: 0.1 M in CH_2Cl_2, cat.=**1**, 23°C; B:0.1M in C_6H_6, cat.=**2**, 23°C; [b] Under an ethylene atmosphere. [c] Only the *cis* bicyclic product was observed.

In order to examine the diastereoselectivity in the first step of the cyclization and its reversibility, trienes **10**, **11**, **12**, and **13** were prepared. Subjection of the trienes to **1** and **2** afforded cyclohexenes and cyclopentenes as illustrated in **Table 2**.

Table 2. DSRCM from monocycloalkene formation.



R=H, n=1 **10**
R=PMB, n=1 **11**
R=H, n=0 **12**
R=Bn, n=0 **13**

R=H, n=1 **14**
R=PMB, n=1 **15**
R=H, n=0 **16**
R=Bn, n=0 **17**

Entry	Starting Material	Product	Catalyst	Mol%/ Time(h)	Yield (%)	*cis:trans* CH_2=CH↔$(CH_2)_3$OP
1	**10**	**14**	**1**	12/ 5	80	1:2.8
2	**11**	**15**	**1**	3/ 3	96	6.1:1
3	**11**	**15**	**2**	6/ 1.5	86	7.8:1
4	**12**	**16**	**1**	6/ 1.5	65	1:1
5	**13**	**17**	**1**	3/ 1	99	8.0:1
6	**13**	**17**	**2**	6/ 0.5	94	1.7:1

Treating **10** with **1** gave a 1:2.8 mixture of diastereomers favoring *trans*-**14** (CH_2=CH ↔ $(CH_2)_3OSiR_3$) (entry 1), whereas treating **11** with **1** gave a 6.1:1 mixture of diastereomers favoring the *cis* (CH_2=CH↔$(CH_2)_3OSiR_3$) isomer (entry 2), and switching to **2** gave slightly higher levels of stereoselectivity (7.8:1, entry 3). Cyclopentenol **12** was formed as a 1:1 mixture of diastereomers upon treatment with **1** (entry 4), whereas the benzyl ether **13** gave rise to cyclopentene **17** in a 8.0:1 mixture of diastereomers, favoring *cis*-**17** (entry 5). The use of **2** gave the same sense of selectivity in forming **17**, but with significantly lower levels of stereoselectivity (1.7:1, entry 6).

Lautens and Hughes had thus established that symmetrical bicyclodienes could be efficiently prepared using a diastereoselective double ring closing

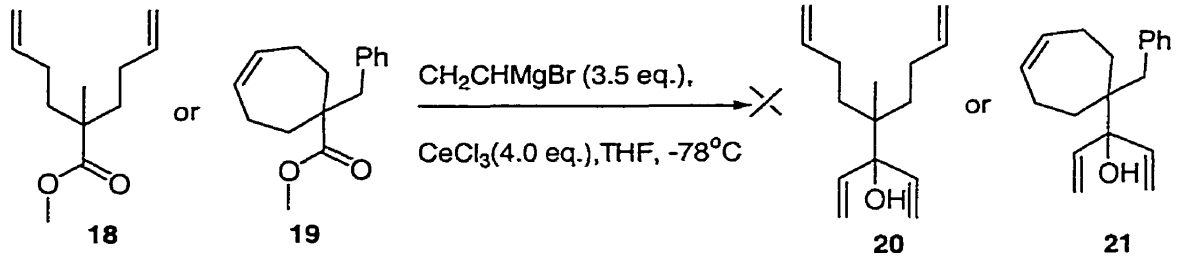
metathesis strategy. Of particular interest is the fact that the results in monocycle formation parallel the observations made in bicycle formation suggesting that although RCM transformations are potentially reversible, that process was not observed in this series. In fact, submitting the minor isomers isolated from the reaction mixtures to the original reaction conditions failed to show any equilibration. This suggests that the formation of the first carbocycle in the bicyclodienes is formed under kinetic control but steric effects prevent the reverse reaction.

2.1 Effect of Bridgehead Substituents on the Efficiency and Diastereoselectivity of the DSRCM

In order to extend the DSRCM strategy in the synthesis of carbocycles, the efficiency and diastereoselectivity of the reaction was investigated with substrates that would be substituted at both bridgehead positions.

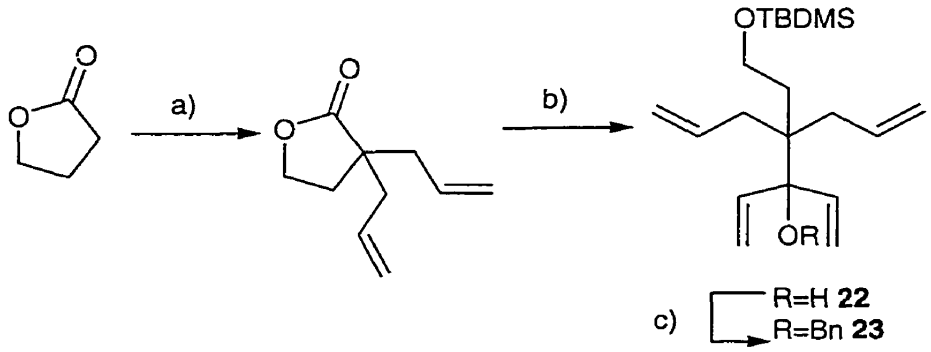
Prior efforts have revealed that bicyclic and monocyclic substrates can be prepared in a diastereoselective fashion using RCM on suitable trienes or tetraenes bearing diastereotopic olefins. However, the scope of the substrates tested was limited to cases where bridgehead substituents were a hydroxyl/ether and hydrogen. Clearly from the results obtained by Lautens and Hughes (see **table 1** and **table 2**), the steric bulk of the hydroxyl/ether group had a pronounced effect on the diastereoselectivity of the RCM reactions. Increasing the steric bulk at the bridgehead position by substituting the hydrogen atom to an alkyl group would provide useful information in terms of the efficiency and diastereoselectivity of the DSRCM reaction.

The synthesis of the requisite substrates proved troublesome, since exposure of the methyl esters **18** and **19** to vinyl cerium[9] failed to provide any of the desired tertiary diallylic substrates (**scheme 2**). Steric effects at the alpha position may be responsible. The use of vinyl cerium was crucial to the success in the synthesis of tertiary diallylic substrates[8], since the use of other vinyl metallic species led to major amounts of butenone products resulting from a 1,4-addition of the second vinyl metallic reagent.



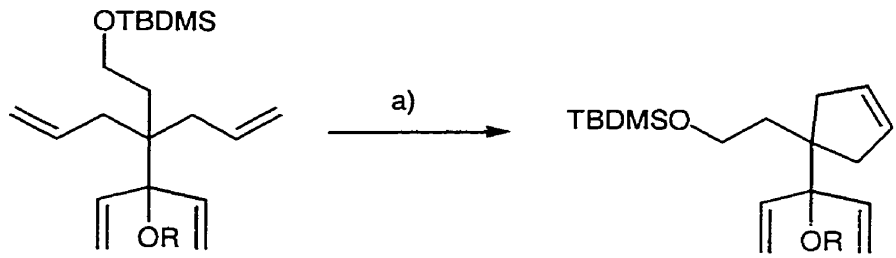
Scheme 2. Failure of esters having an α tertiary center to undergo reaction with vinyl cerium.

The problem of lack of reactivity of esters bearing an α-tertiary center to vinyl cerium was overcome by the use of lactones, where the third substituent is incorporated into the ring. Double alkylation of butyrolactone with allyl bromide, followed by reaction with vinyl cerium gave modest to good yields of the tertiary alcohols as shown in **Scheme 3**. Selective protection of the primary alcohol followed by benzylation provided the ether.



Scheme 3. Synthesis of 3° alcohols and ethers from α,α-disubstituted lactones: a) NaH(4eq.), allyl bromide, DMF, 0 °C → r.t., 80%; b) i. CH_2=CHMgBr (3.5 eq.), $CeCl_3$ (4.0 eq., anhydrous), THF, -78°C, ii. TBSCl (1.05 eq.), imidazole (1.5 eq.), DMF, 23°C, 57% (**22**). c) KH (3.0 eq.), BnBr (1.5 eq.), THF, 23°C, 12hrs, 85% (**23**).

Subjection of alcohol **21** or ether **22** to alkylidene **1** or **2** under a variety of conditions failed to provide any diquinane products. Cyclization of the less hindered olefins was only observed.

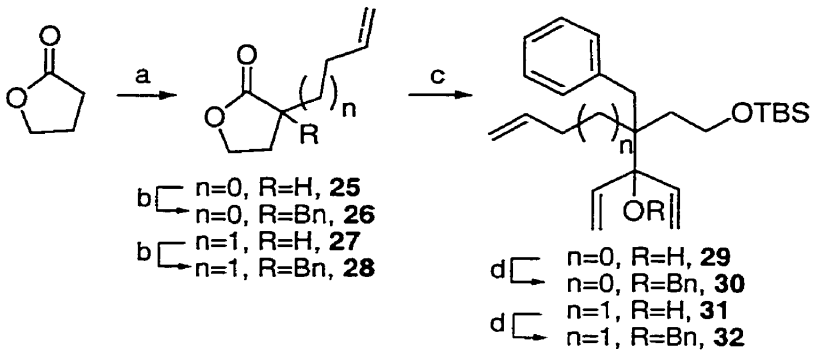


R=H **21**
R=Bn **22**

R=H **23**
R=Bn **24**

Scheme 4. Reactivity pattern of tetraenes bearing contiguous quaternary centers. a) Reaction conditions: 0.1 M in CH_2Cl_2, cat.=**1**, 23°C or reflux; or 0.1M in C_6H_6, cat.=**2**, 23°C; Under an ethylene or Argon atmosphere.

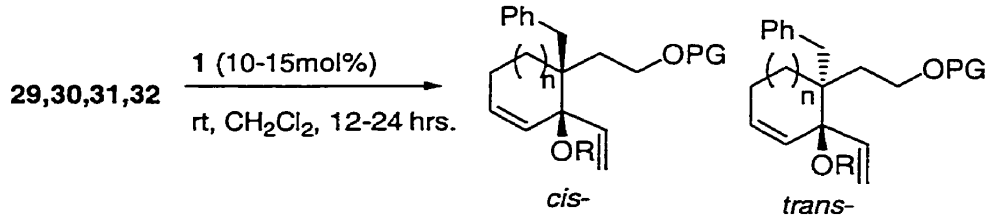
Prior efforts in the group have shown that the substitution of one of the less hindered olefins by a non-reacting alkyl group provides useful information in terms of the diastereoselectivity of the DSRCM reaction, since the diastereoselectivity originates in the first RCM event. This substitution of one of the olefins by an alkyl group also simplifies RCM since cyclization of the less hindered olefins to produce an unwanted cycloalkene generally occurs first. The ring-opening of the undesired cycloalkene may sometimes compete with the decomposition of the catalyst, thus preventing formation of the desired cycloalkenes and ultimately the bicyclodienes. To examine this question in detail, substrates **29-32** were prepared as shown in **Scheme 5.**



Scheme 5. Preparation of 3° alcohols from α,α disubstituted lactones: a) n=0: LDA, allyl bromide, THF, -78°C, 80%; n=1: i) LDA, 1,4-dichlorobut-2-ene, THF/ HMPA (7:1), -78°C. ii) HCO_2NH_4, Pd_2dba_3, nBu_3P, toluene, 100°C, 3 hrs, 45%(2 steps). b) LDA, BnBr, THF, 77% (**26**), 74% (**28**). c) i.. CH_2=CHMgBr (3.5 eq.), $CeCl_3$ (4.0 eq., anhydrous), THF, -78°C, ii. TBSCl (1.05 eq.), imidazole (1.5 eq.), DMF, 23°C, 57% (**29**), 48% (**31**). d) KH (3.0 eq.), BnBr (1.5 eq.), THF, 23°C, 12hrs, 85% (**30**), 90% (**32**).

The butenylation of butyrolactone with conventional methodologies, e.g. use of 4-bromo-1-butene or 4-tosyl-1-butene as the electrophiles, gave only low yields of **27** (<10%) despite literature precedence[10] for effecting this exact transformation. However, utlizing a two step procedure proved to be more successful.[11] Therefore, alkylation of butyrolactone with 1,4-dichlorobutene, followed by palladium catalyzed formate reduction of the resulting allyl chloride, furnished **27** in 45% yield over two steps.

Table 3. DSRCM for 3° diallylic systems having an α quaternary center.



R=H, n=0 **33**
R=Bn, n=0 **34**
R=H, n=1 **35**
R=Bn, n=1 **36**

Entry	Starting Material	Product	Mol%/ Time (h)	Yield(%)	*cis*:*trans* CH_2=CH↔$(CH_2)_3$OP
1	**29**	**33**	15/24	60[a]	<1:>20
2	**30**	**34**	15/24	100[b]	2:1
3	**31**	**35**	8/12	100[b]	1:1
4	**32**	**36**	8/12	100[b]	4.5:1

a. Isolated yield. b. Based on 100% conversion by ^{1}H NMR (400MHz) analysis

The results from treating these trienes with Grubbs' catalyst are summarized in **Table 3**. Reaction of **29** with **1** (24-hour portion wise addition) gave cyclopentene **33** as essentially a single diastereomer in 60% isolated yield. This diastereomer was shown to be *trans* by ROESY[12] experiments, based on the relationship of the CH_2=CH↔$(CH_2)_3$OP substituents (see experimental section). Treatment of **30** with the same catalyst gave a 2:1 mixture of diastereomers, with the *cis* diastereomer now being favoured.

Cyclohexenes having a bridgehead substituent were also formed in good yields. Treatment of the free alcohol **31** with **1** provided **35** as a 1:1 mixture of diastereomers. The stereochemistry of the diastereomers was elucidated through ROESY experiments. The analogous benzyl protected ethers were formed in a 4.5:1 mixture of diastereomers, favouring the *cis* diastereomer.

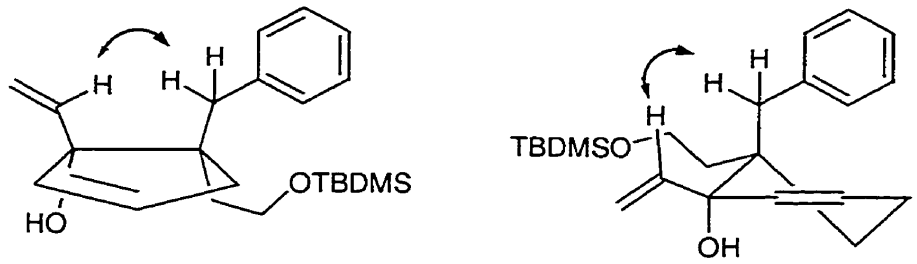


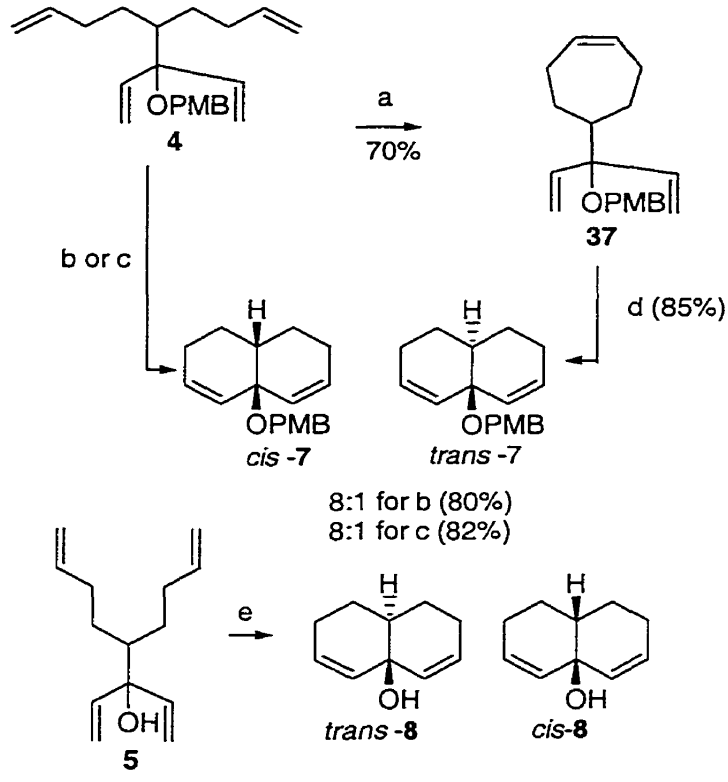
Figure 5. Structure determination through ROESY experiments (NOEs of interest are indicated with arrows).

This study into the efficiency and diastereoselectivity of the DSRCM revealed that cyclopentenes can be prepared in a highly diastereoselective fashion, i.e. the diastereoselective formation of **33**. Optimizing diastereomeric ratios for the cyclohexene series requires an in depth study of other substituents at the bridgehead position. The knowledge from such an exploration should allow for the synthesis of suitable fused bicyclic substrates substituted at both bridgehead positions.

3. Insights into the Mechanism of the DSRCM

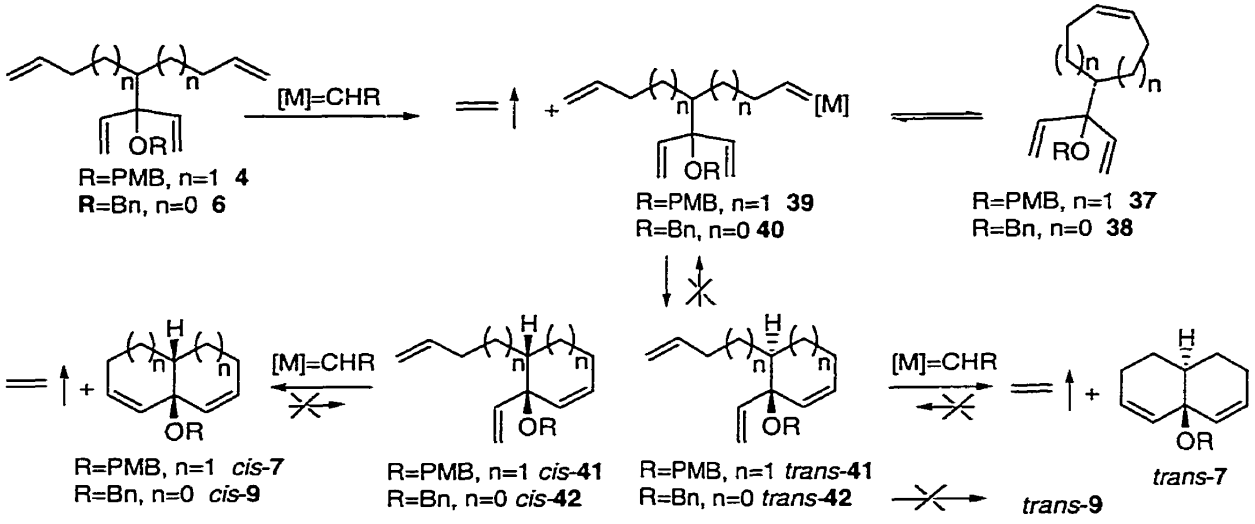
During the course of our investigations in the desymmetrization of the bicyclodienes under study, we came across certain reactivity patterns of the olefin substrates with Grubbs' catalyst, **1**. These findings may help to explain the reactivity pattern of certain substrates and in particular shed some light in the origin of the diastereoselectivity in the synthesis of decalin systems bearing an alcohol functional group. In the free alcohol series the formation of the trans bicyclodienes is favoured, whereas with the ether series the trend is reversed.

The synthesis of the required bicyclodienes in my studies started from tetraenes **4** and **5** as described by Hughes.[8a] This allowed access to bicyclodienes bearing an alcohol functionality or its protected analogues. Access to the decalin series, bearing ether substituents, was possible starting from either tetraene **4** or cycloheptene **37**.

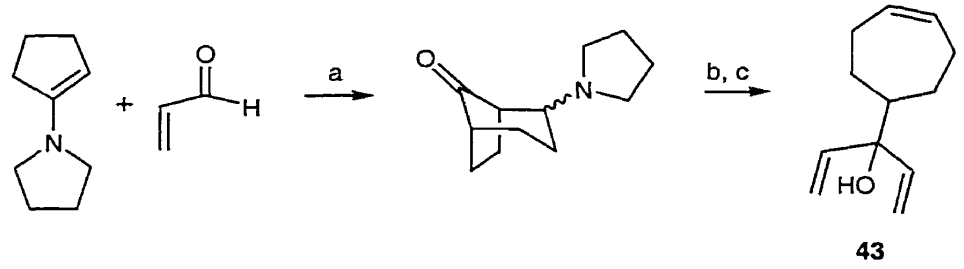


Scheme 6. The DSRCM approach to *cis*- and *trans*-fused decalin systems developed by Lautens and Hughes[8]. a) $(PCy)_2Cl_2Ru$=CHPh (3mol%), CH_2Cl_2, 3 hours. b) $(PCy_3)_2Cl_2Ru$=CHPh (12 mol%), CH_2Cl_2, ethylene atm, 18 hours. c) $((CF_3)_2CH_3CO)_2Mo$(=NAr)(=CHC$(CH_3)_2$Ph) (Ar=2,6 diisopropylphenyl) (12 mol%), C_6H_6, 30min. d) $(PCy_3)_2Cl_2Ru$=CHPh (10 mol%), CH_2Cl_2, ethylene atm, 18 hours. e) $(PCy_3)_2Cl_2Ru$=CHPh (10 mol%), CH_2Cl_2, closed system, 30 min.

Based on these observations and previous work outlining the reactivity patterns of various olefins[13], Lautens and Hughes have proposed the following mechanism in the DSRCM of ether-substituted analogues. The fact that tetraene **39** and triene **37** are in equilibrium, allows for entry into the catalytic cycle from the triene substrate. This substrate[14] was synthesized in fewer steps than tetraene **4** and thus was the starting material of choice in most of the investigations presented in this thesis.



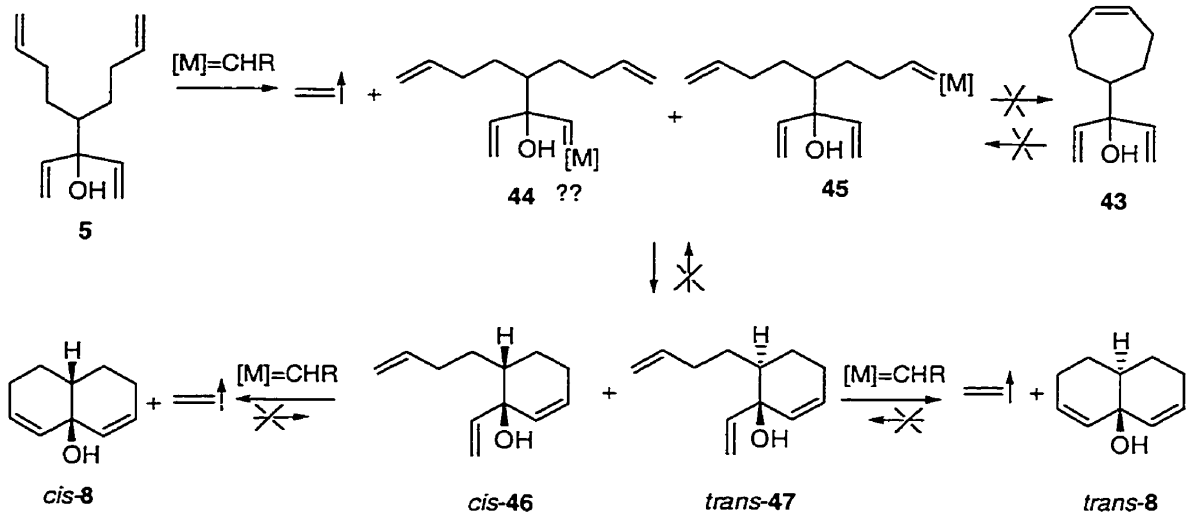
Scheme 7. Reaction pathway of decalin and diquinane formation proposed by Lautens and Hughes.



Scheme 8. Synthesis of cycloheptene tertiary diallylic substrates using a Stork ring expansion[14] procedure. a) Et_2O, 0°C to r.t., 16hrs. b) i. MeI, MeOH, reflux. ii. NaOH, H_2O, relfux, 6hrs. iii. H_2SO_4 (cat.), MeOH, reflux, 24hrs. c) CH_2=CHMgBr (3.5 eq.), $CeCl_3$ (4.0 eq., anhydrous), THF, -78°C.

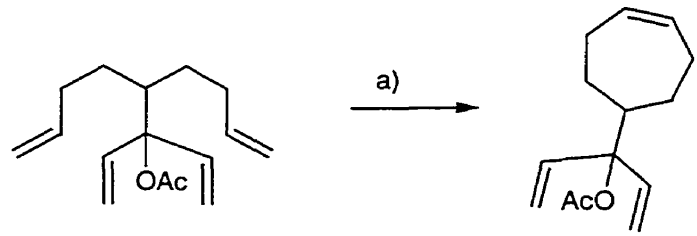
When the alcohol **5** was protected as an ether in the triene, DSRCM proceeds smoothly. In contrast to the tetraene bearing a free alcohol, the cycloheptene triene **43** bearing the free alcohol failed to provide any decalin product under a variety of conditions (e.g. reflux, under an atmosphere of ethylene). Even the highly active ruthenium-based metathesis catalyst (**3**)[3] bearing an imidizoylidene ligand, which prevents unfavourable and unproductive metal chelate complexes with functional groups, failed to provide any decalin products. Starting material was always recovered from the reaction mixture. This result clearly indicates that with the free alcohol, no cycloheptene intermediate is

possible in the formation of decalin substrates. As others have noted, free alcohols appear to cyclize at accelerated rates relative to the analogous ethers.[15] Whereas benzyl ether **4** reacts faster to give the cycloheptene **37** than to form a cyclohexene **41**, no cycloheptene formation was observed when free alcohol **5** was used as the starting material. These results imply that alkylidene formation may be taking place at the more hindered olefin.



Scheme 9. DSRCM reactions involving free alcohols.

Supporting this notion of alkylidene formation at the more hindered allylic olefin comes from the reaction pattern of the analogous acetate substrate. Exposure of the acetate **48** to alkylidenes **1** or **2**, provided cycloheptene **49** in quantitative yield. Resubjection of cycloheptene **49** to standard olefin metathesis conditions resulted in no observable reaction taking place as judged by TLC and ^{1}H NMR analysis.



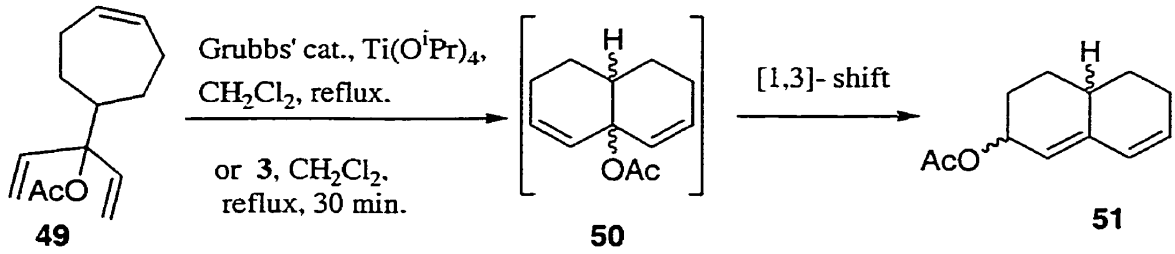
48 **49**

Scheme 10. Reactivity pattern of tetraenes bearing a diallylic acetate group with metal alkylidenes **1** and **2**. a) Reaction conditions: 0.1 M in CH_2Cl_2, cat.=**1**, 23°C or reflux; or 0.1M in C_6H_6, cat.=**2**, 23°C; Under an ethylene or Argon atmosphere.

However, the use of Grubbs' catalyst in the presence of $Ti(O^iPr)_4$ resulted in the formation of a bicyclodiene product, **51**.[16] It is known that the Lewis acid $Ti(O^iPr)_4$ will coordinate to the acetate thus preventing unfavaurable ruthenium based metal chelates from forming. The coordination of titanium to the acetate will invariably provide more steric bulk at the allylic olefins thereby facilitating the reaction of **1** with the internal double bond.[13] The same reaction was observed with (4,5-DihydroIMES)$(PCy_3)Cl_2Ru$=CHPh[3], **3**, recently introduced as a more active metathesis catalyst and which is known not to produce unfavourable metal chelates.

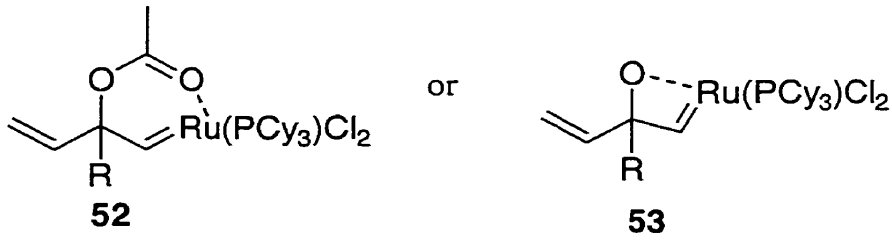
The expected tertiary diallylic bicyclic product **50** is so reactive so as to allow a facile 1,3-acetate shift. The only product ever observed or isolated was the secondary acetate **51**. Such allylic transpositions[17] usually occur at elevated temperatures, yet here the transformation occurs at temperatures <40°C (see later for more details). The fact that with acetate **48** no reaction takes place with Grubbs' catalyst alone provides strong evidence for alkylidene formation at the more hindered olefin. Apparently, this reaction pattern was only observed with substrates capable of forming metal chelates at terminal olefins, i.e. allyic

alcohols, acetates, benzoates, and carbonates, rather than reacting with an internal olefin.



Scheme 11. RCM of acetate **49**.

It has been postulated[16] that Grubbs' catalyst will interact with allylic alcohols and acetates to produce metal chelated complexes that are depicted in **figure 6**. The formation of chelates in the systems under study are reasonable since the catalyst has a choice of forming a stable chelate at a terminal olefin, albeit at a more hindered position, or reacting with an internal olefin, which are known to be less reactive with Grubbs' catalyst **1**.[13]



52 **53**

Figure 6. Possible reaction modes for sequestering Ruthenium in RCM reactions of allylic alcohols[15] and Acetates[16].

If a second olefin cannot approach the metal complex in **52** or **53** for olefin metathesis to occur, e.g. R=cycloheptene, then clearly the metal has been sequestered in an unproductive form.

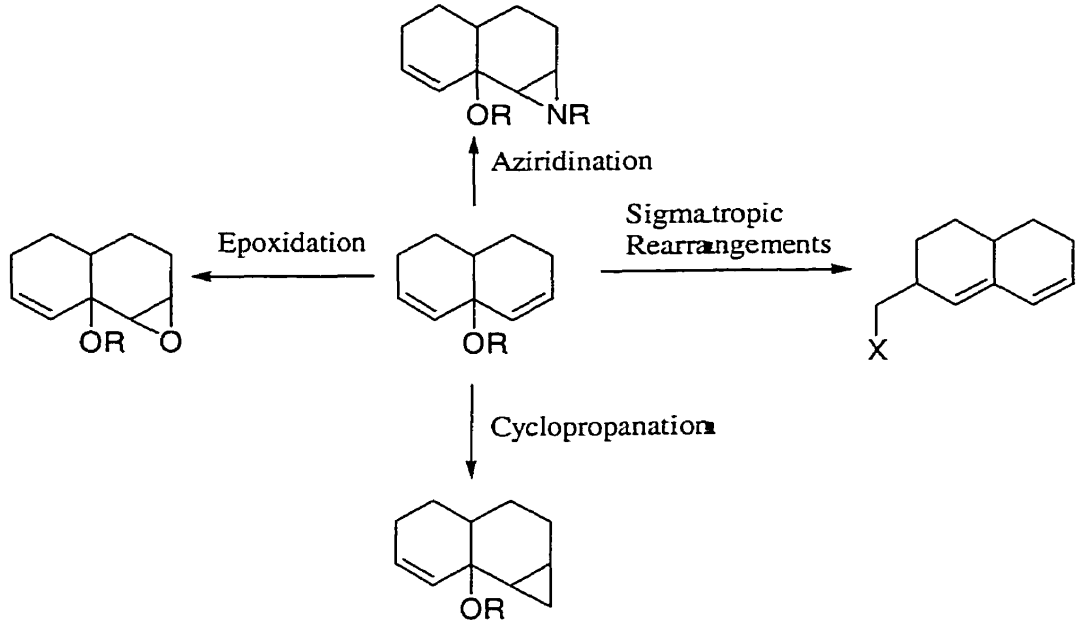
4. Initial Attempts at Enantioselective Alkene Differentiation Reactions

When a plane of symmetry is present in a bifunctional molecule the two halves are in most cases enantiotopic and can therefore be differentiated by reagents capable of chiral recognition. An enantioselective reaction will convert such a molecule into either of two enantiomeric products. Since very few natural products are symmetric, desymmetrization of meso or achiral bifunctional compounds provides a convenient method for the preparation of chiral building blocks in the synthesis of natural products.[18] Such a strategy has been applied to acyclic divinyl carbinols in the so-called "Two-directional synthesis" approach described by S.L. Schreiber.[19] This strategy involves the homologation of an acyclic chain at both ends at the same time and then desymmetrizing the ends. When applied to appropriate target molecules, namely those with a significant element of symmetry, this strategy offers a highly efficient route to stereochemically pure products in relatively few steps compared to one directional linear synthesis and convergent synthesis.

While the ability of enzymes to differentiate between enantiotopically related functional groups is well known, the utility of non-enzymatic methods to achieve the same result is less well known. It must be pointed out that enantioselective differentiation of prochiral functional groups in a symmetrical bifunctional molecule provides an efficient method for creating new chiral centers, since more than chiral center is fixed (created) in the process.

4.1 Atom Transfer Reactions

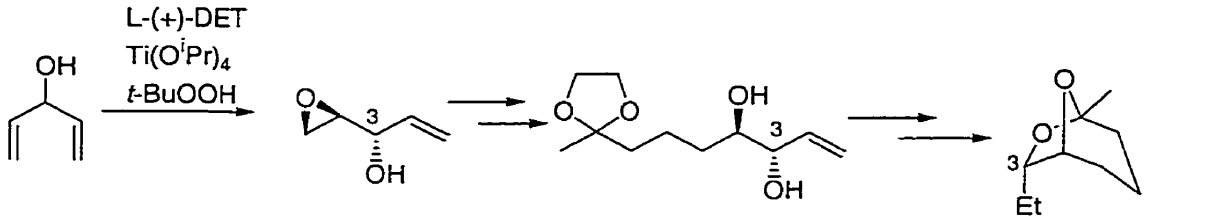
By far the greatest number of enantioselective desymmetrizations of meso or achiral bifunctional compounds involves the formation of a carbon-heteroatom bond.[18] Therefore, at the outset of the investigations in transforming the symmetrical bicyclodienes into enantiomerically enriched products, efforts were directed towards atom transfer processes.



Scheme 12. Initial Strategy for the desymmetrization of symmetrical bicyclodienes.

4.2 Epoxidation Attempts

In 1987 Schreiber published a detailed report on the asymmetric epoxidation of acyclic divinyl carbinols using Sharpless asymmetric epoxidation conditions ($Ti(O^iPr)_4$, (+)-tartrate, *t*-BuOOH). The product epoxides were obtained with high enantiomeric excesses, generally >95%. The utility of such enantiomerically enriched epoxides was shown in many total syntheses including riboflavin, (+)-KDO, (+)-*endo*-brevicomin, and FK-506.[19] Such an approach has been termed "Two-Directional Synthesis by sequential homologation". This strategy has comparable efficiency to one directional linear synthesis but highlights an attractive approach to the synthesis of stereochemically pure building blocks and natural products.



(+)-*endo*-brevicomin

Scheme 13. Synthesis of (+)-*endo*-brevicomin based on the desymmetrization of divinyl carbinol.

Although such examples are impressive, all related reports to date deal with acyclic divinyl carbinols. It would be interesting to investigate whether such a process could be applied to the bicyclic divinyl carbinols under investigation in this thesis. The product epoxides would clearly find many uses as intermediates in total syntheses.

All attempts to epoxidize the bicyclodienes were met with difficulty and little success. Application of Sharpless Asymmetric Epoxidation conditions ($Ti(O^iPr)_4$, (+)-tartrate, *t*-BuOOH) to the bicyclodienes were met with difficulty. In the most optimized conditions, sluggish reactions led to low yields of the racemic bicyclic epoxide.

4.3 Limitations in the Desymmetrization of the Bicyclodienes

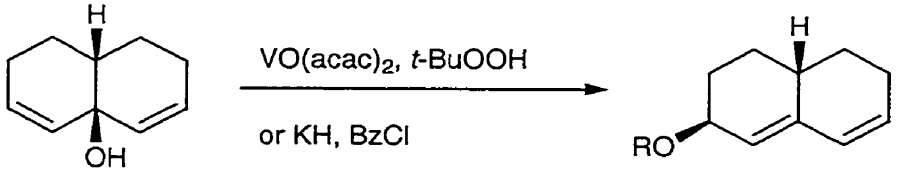
Although little success was realized in trying to desymmetrize the bicyclodienes using asymmetric atom transfer reactions, the results clearly revealed the delicate nature and sensitivity of the substrates under investigation. Some of these attributes have been mentioned previously.[8b] The sensitivity of the bicyclodienes to Lewis acids, especially to ionization is the reason for such problems. It must be pointed out that the purification of the bicyclodienes required the neutralization of silica gel with triethyl amine, otherwise the desired products decomposed on the chromatography column.

Many of the successful catalytic asymmetric atom transfer reactions that have been developed thus far were clearly not mild enough conditions/reagents for the bicyclic, tertiary, diallylic ethers and alcohols. Rearrangements, isomerizations, and degradations were most often observed when attempting cyclopropanations[20], aziridinations[21], epoxidations[22], and carbonyl-ene[23] reactions under a variety of reaction conditions. The Lewis acidic nature of the catalysts employed is most likely the source of the problems.

4.4 [1,3]- Allylic Shifts

Having screened a variety of reaction conditions to effect the desired atom transfer reactions, a series of unexpected and unwanted rearrangements were observed under a variety of reaction conditions. Although these rearrangements were undesired and unexpected, the products obtained might prove to be useful in organic synthesis.

During attempts to epoxidize the decalin substrates, degradation was most often observed under a variety of reaction conditions. Yet utilizing $VO(acac)_2$, *t*-BuOOH the only isolated product was the secondary alcohol **56**. This is somewhat surprising since $VO(acac)_2$ is a transition metal complex which is capable of isomerizing secondary alcohols into tertiary ones.[17] Such allylic rearrangements of allyloxo metal oxo complexes are not uncommon and seem to be quite facile processes with the decalin substrates under study. Analogous transformations were also observed when attempts were made to esterify the free alcohols with acetyl chloride or benzoyl chloride.

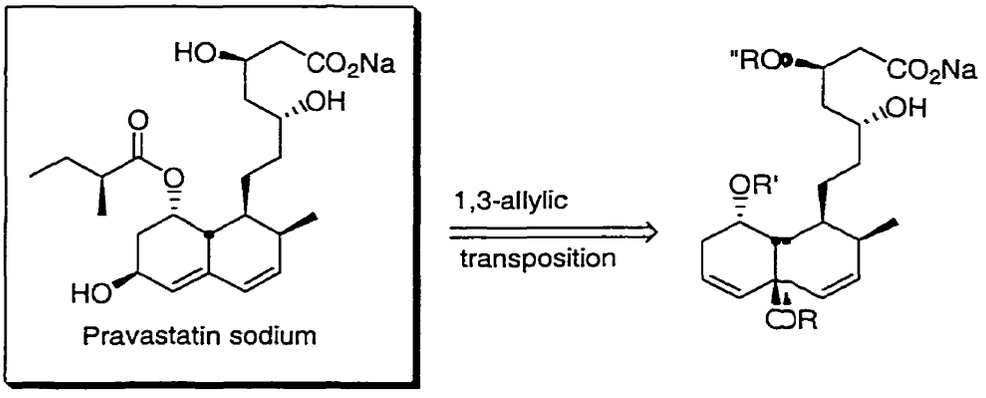


8

R=H **56.**
R=Bz **57.**

Scheme 14. Allylic transposition reactions of decalin substrates

The isomerizations proceed in a suprafacial manner and thus represent an interesting transformation that possibly could be applied to the total synthesis of the HMG CoA reductase pravastatin sodium. The reactions were not explored further in order to determine whether the transformation could be adapted to an enantioselective variant.

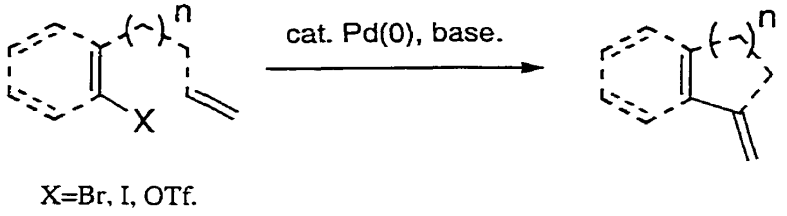


Scheme 15. Potential retrosynthetic approach to Pravastatin sodium.

5. Asymmetric Heck Reactions

5.1 General introduction

The palladium mediated coupling of aryl or vinyl iodides, bromides or triflates with alkenes in the presence of base is generally referred to as the Heck reaction.[24,25] Such carbopalladations are a powerful tool for the controlled construction of carbon-carbon bonds. The Heck reaction can be successfully applied in an intermolecular fashion, or in an intramolecular fashion leading to the facile synthesis of polycyclic compounds.



X=Br, I, OTf.

Figure 7. The palladium catalyzed arylation or vinylation of alkenes.

The intramolecular Heck reaction has been widely applied in the synthesis of common (five- through seven membered) sized rings. The reaction is readily adaptable to the formation of fused, spiro-fused, and bridged bicyclic and polycyclic ring systems. The synthesis of spiro-fused compounds presents the possibility of forming quaternary carbon centers. Yet one distinct shortcoming of the intramolecular Heck reaction is that the reaction often yields a mixture of alkene regioisomers. If the substrate undergoing the Heck reaction has no regiocontrol in alkene formation, the use of Ag or Tl salts can sometimes aid in this process. This attribute can then be coupled to asymmetric variants of the reaction.

The enantioselective variant[26] of the Heck reaction has been successfully developed to the point where both tertiary and quaternary centers can be generated in excellent enantioselectivity and in good to excellent yields. If the reaction is applied intramolecularly, this provides a convenient and efficient method for the synthesis of fused, bridged, or spirocyclic compounds in an enantioselective fashion.

The intramolecular Heck reaction has been extensively used in the construction of polycyclic compounds and in the synthesis of natural products. Shibasaki *et al.* have reported asymmetric Heck reactions of conjugated dienyl-substituted vinylic triflates (eq 1)[27] and 2,5-cyclohexadienyl-substituted vinylic triflates and iodides (eq 2)[28]. This methodology has proven to be a powerful tool for the rapid construction of polycyclic compounds.

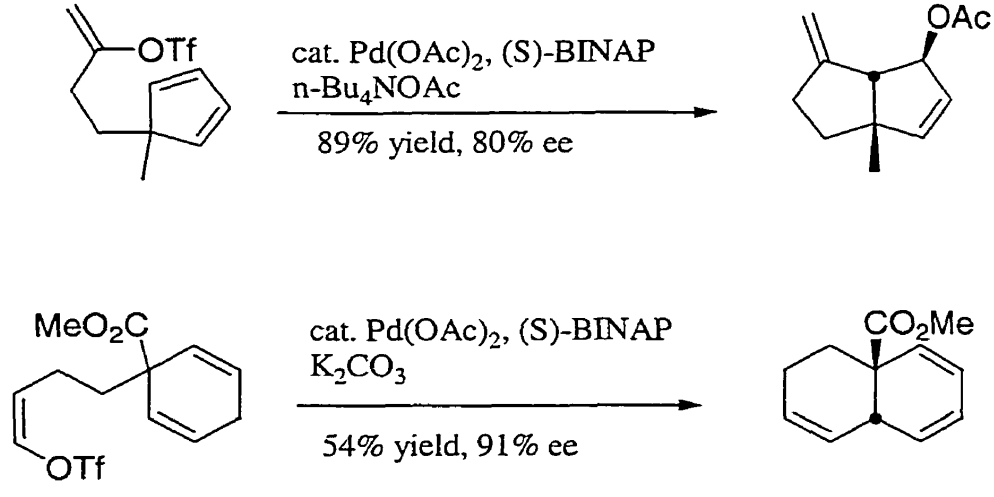
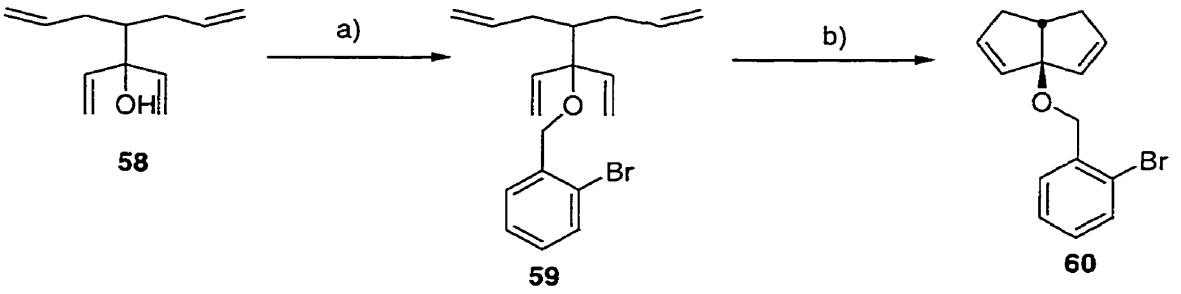


Figure 8. The use of asymmetric Heck reactions in the synthesis of fused bicyclic compounds.

5.2 Enantioselective Synthesis of Polycycles from Bicyclo-[3.3.0]octadienes

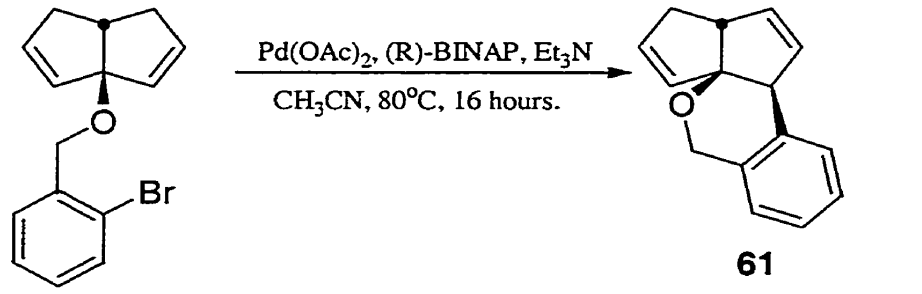
The intramolecular, asymmetric-Heck reaction was applied to the bicyclodienes generated through the DSREDCM methodology presented in this thesis. Substrates were conveniently prepared by appending appropriate aryl-halide tethers to the tertiary diallylic alcohols. Thus, reaction of the tertiary alcohol **58** with potassium hydride and 2-bromo-benzyl bromide under standard conditions provided the coupled product **59** in 87% yield. Ring closing metathesis of the tetraene with **1** provided the diquinane product **60** in good overall yield.



58 **59** **60**

Scheme 16. Synthesis of a bicyclo-[3.3.0]octadiene bearing a tethered aryl bromide for an intamolecular Heck reaction. Conditions: a) KH(2 eq.), 2-bromobenzyl bromide, THF, 23°C, 12 hrs., 87%. b) **1** (6 mol%), CH_2Cl_2, 23°C, 20hrs, 70%.

Subjection of the bromo compound **60** to asymmetric Heck conditions provided the tetracyclic product **61** in modest yield and excellent enantioselectivity.

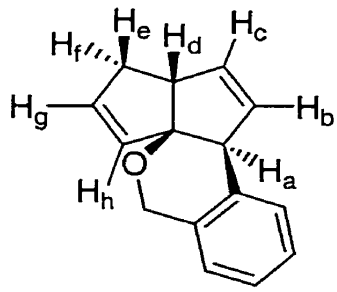


60 **61**

43% yield, 93% e.e.

Scheme 17. Asymmetric Heck Reaction on symmetrical bicyclo-[3.3.0]-octadienes.

The relative stereochemistry of **61** was proven by careful analysis of various 2D NMR experiments (COSY, ROESY, HMQC). NOEs were observed in the ROESY experiment between $H_a \leftrightarrow H_f$ but not between $H_a \leftrightarrow H_d$. Based on this observation, the ring formed in the Heck reaction is a *cis* ring junction.

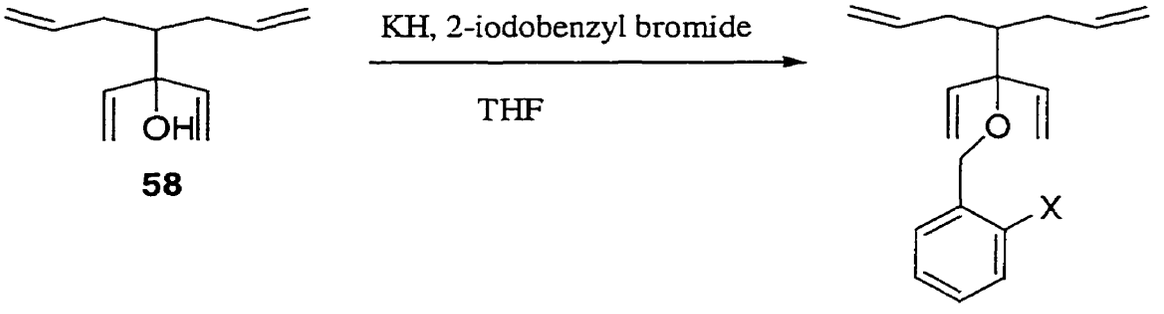


NOEs observed:
$H_a \leftrightarrow H_b$
$H_a \leftrightarrow H_h$
$H_a \leftrightarrow H_f$
$H_d \leftrightarrow H_e$
$H_d \leftrightarrow H_c$

Figure 9. Relative stereochemistry determination of **61** through a ROESY experiment.

Following this lead, optimization of the reaction conditions was sought. Since oxidative addition with aryl iodides proceeds much more facile than the analogous bromides[24], subsequent investigations were carried out with the analogous iodo-compounds. To this end, the iodo analogues were synthesized starting from 2-iodo-benzyl bromide. Another limitation of these tertiary diallylic substrates was evident from this rather simple transformation. Bases other than

potassium hydride generally led to no observable reaction taking place. This fact negates the use of mild reaction conditions in the synthesis of appropriate tethered substrates for the Heck reaction. Reactions at room temperature took place without event. However, by increasing the reaction temperature, very little of the iodo-benzyl product was obtained at the expense of the deiodo-benzyl product. This is not so surprising since one is in essence trying to alkylate an organic substrate that resembles potassium *tert*-butoxide. Under such reaction conditions, the generation of benzyne[29] intermediates would not be surprising. Although this observation may seem trivial, it helps to explain the difficulty in trying to expand the scope of tethered aryl/vinyl halides (see below).

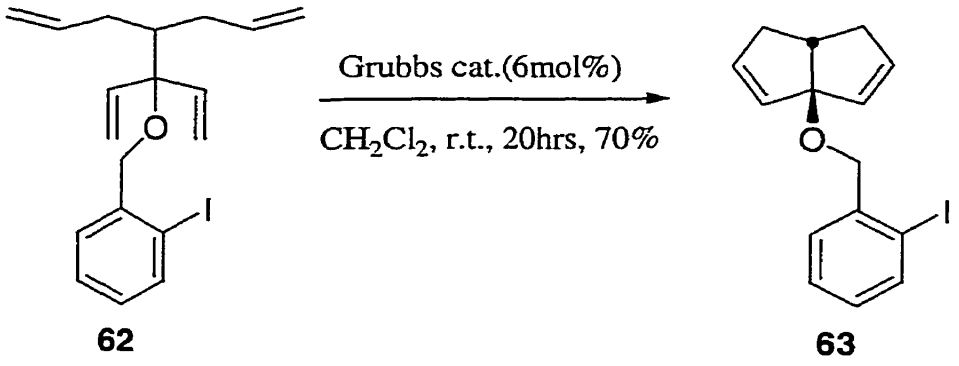


58

Reaction conditions and yield
23°C, 12hrs, 83%. X=I, **62**
80°C, 4hrs, 88%. X=H, **6**

Scheme 18. Inherent sensitivity in the synthesis of tethered aryl iodide for the Heck reaction.

Ring closing metathesis of the iodoaryl tetraene with Grubbs catalyst **1** provided the desired bicyclo-[3.3.0]-octadienes in good overall yields.

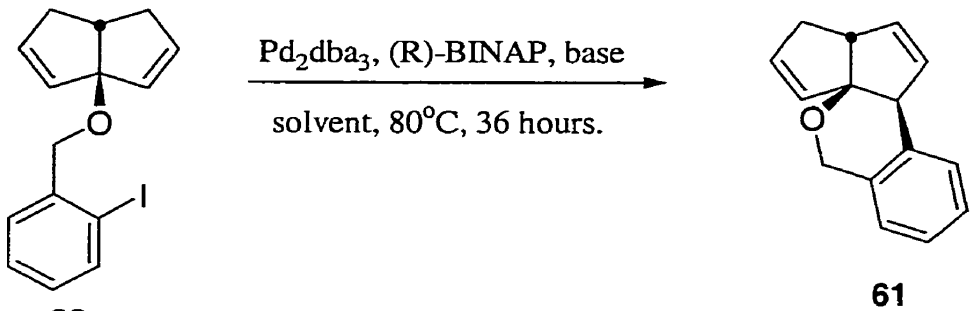


62 **63**

Scheme 19. DSRCM in the synthesis of Heck reaction precursors.

With a reliable and efficient route to the desired bicyclo-[3.3.0]octadienes **63**, a detailed investigation into the asymmetric Heck reaction was then carried out. Pd_2dba_3 was used as the palladium(0) source due to its ease of handling and its reported role in enabling reproducible results[30] in asymmetric Heck reactions. Due to its ubiquitous success in asymmetric Heck reactions called for the use of BINAP as the chiral ligand. The results from screening a variety of bases and solvents are shown in **Table 4**.

Table 4. Effects of Solvents and bases on the asymmetric synthesis of **61**.



63 **61**

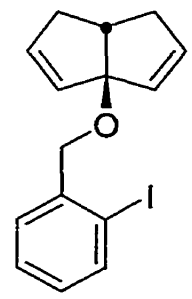
Entry	Solvent	Base (2eq.)	Yield (%)	Enantiomeric excess (e.e.)
1	CH_3CN	Et_3N	52	98.5
2	CH_3CN	K_2CO_3	60	83
3	CH_3CN	Ag_2CO_3	80	97
4	CH_3CN	Ag_3PO_4	37	97
5	THF	Ag_3PO_4	73	94
6	**toluene**	**Ag_3PO_4**	**77**	**99**
7	DMA	Ag_3PO_4	57	91
8	NMP	Ag_3PO_4	60	63

The results presented in **Table 4** show that a variety of conditions can be used successfully in the asymmetric synthesis of **61**. It is generally accepted that cationic conditions, e.g. use of silver(I) salts to sequester a halide from palladium after the oxidative addition of the aryl halide, will generally lead to chiral products with higher enantiomeric ratios than that realized under neutral conditions. Yet under neutral conditions and in the presence of a tertiary amine base, similar levels of enantioselectivity are realized as that seen under cationic conditions.

Overman[31], in his studies in the use of asymmetric Heck reactions in the synthesis of chiral oxindoles noted a similar phenomenon. No conclusive argument was put forth in his studies and results in our own studies do not help to explain the highly effective role of tertiary amine bases in asymmetric Heck reactions.

Although Pd catalysts derived from BINAP, which has clearly been shown in the past to be the best ligand for enantioselective Heck reactions, are used most often, recent advances have shown a variety of other ligands to mediate the reaction with equal levels of efficiency. A small survey of available ligands was carried out in the asymmetric synthesis of **61** and is presented in **Table 5**.

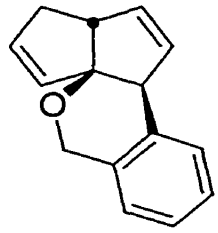
Table 5. Effects of ligands in the asymmetric synthesis of **61**.



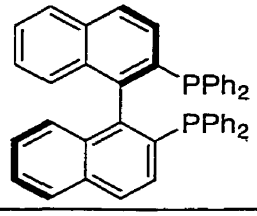
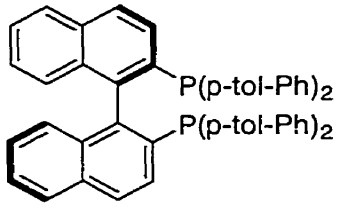
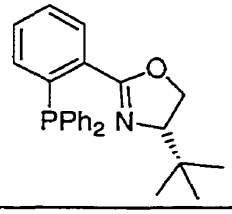
63

Pd_2dba_3, chiral ligand, Ag_3PO_4

DMA, 80°C, 36 hours.



61

Ligand	Yield	e.e.
	57	91
	**87**	**99**
	18	29

Particularly noteworthy from **Table 5**, is the fact that chiral phosphinooxazolines[32] do not efficiently mediate the asymmetric Heck reaction in this case. However, the use of *tol*-BINAP as ligand provides **61** with similar levels of enantioselectivity but in higher yield. Clearly the ligand structure of the binapthyl ligands is crucial to the success of the reaction. The use of cationic conditions with a more electron rich bisphosphine will ensure a tighter binding of the bisphosphine throughout the catalytic cycle of the reaction.

5.3 Cationic and Neutral Pathways in the AHR

A detailed outline of the mechanism of the Heck reaction involving oxidative addition, coordination of the alkene, insertion, and β-hydride elimination was proposed in the 1970s and subsequent studies have provided additional information as discussed in numerous reviews.[24] As in any asymmetric reaction, the first irreversible enantiodifferentiating step would determine the asymmetric induction.[33] The Individual steps of the Heck reaction have been subject to increasing scrutiny over the past several years, especially with the advent of asymmetric variants of the reaction. The fact that two different oxidative addition products can be formed has led to general acceptance of two reaction manifolds[26,31] for Heck reactions: cationic and neutral palladium complexes. These two manifolds are depicted in **figure 10**.

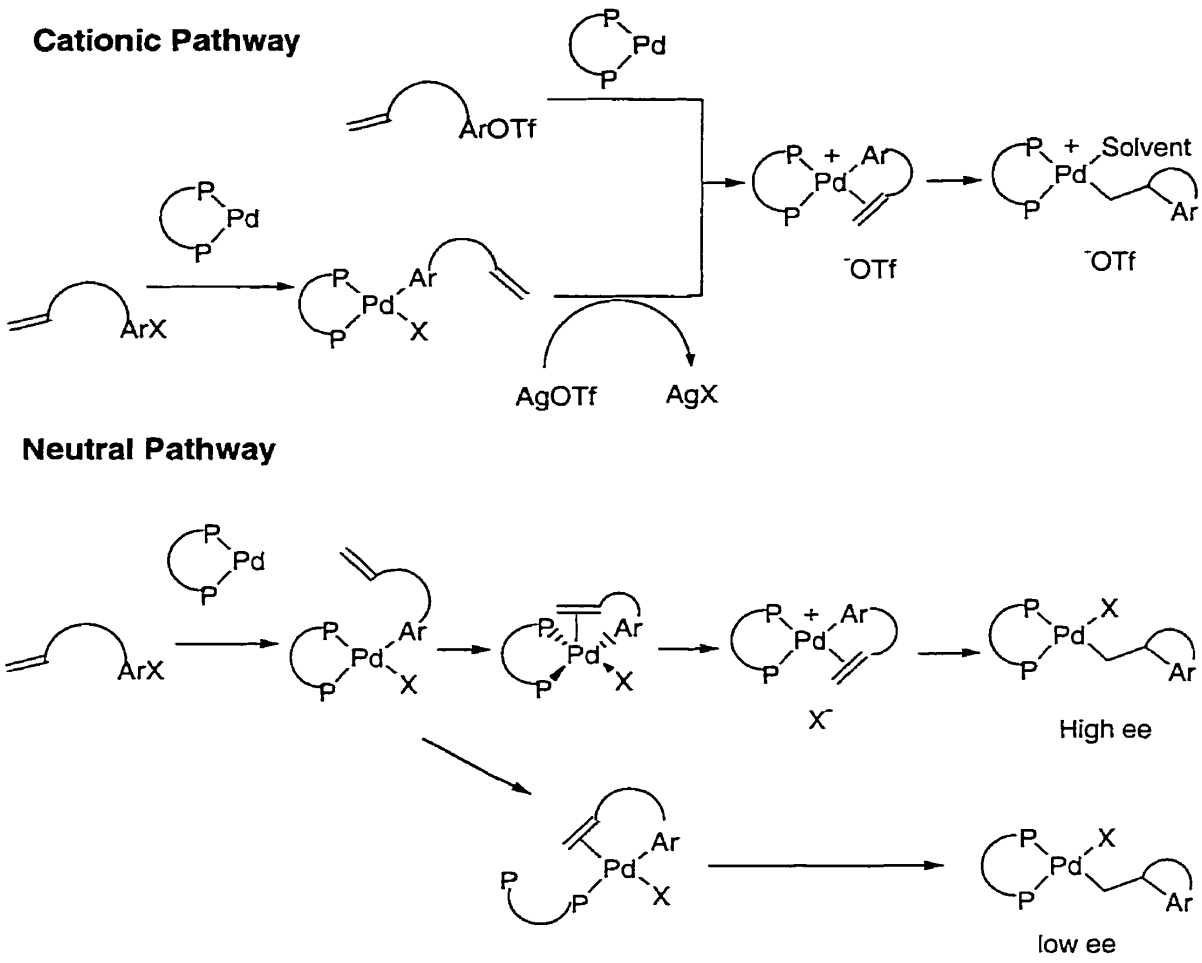


Figure 10. Cationic and neutral Heck reaction manifolds proposed by Overman *et al*[31].

The Heck reaction begins with a bisphosphine palladium(0) species which oxidatively adds into a vinyl/aryl halide bond to produce a square planar palladium (II) species. The alkene substrate then associates with the palladium complex and inserts into the palladium vinyl/aryl σ-bond. β-Hydride elimination from this σ-alkylpalladium species then produces the coordinated alkenyl- or aryl-substituted alkene product and a "HPdI" species. Decomplexation of the product alkene is followed by reaction of the palladium hydride with a base to regenerate the palladium(0) species that re-enters the catalytic cycle.

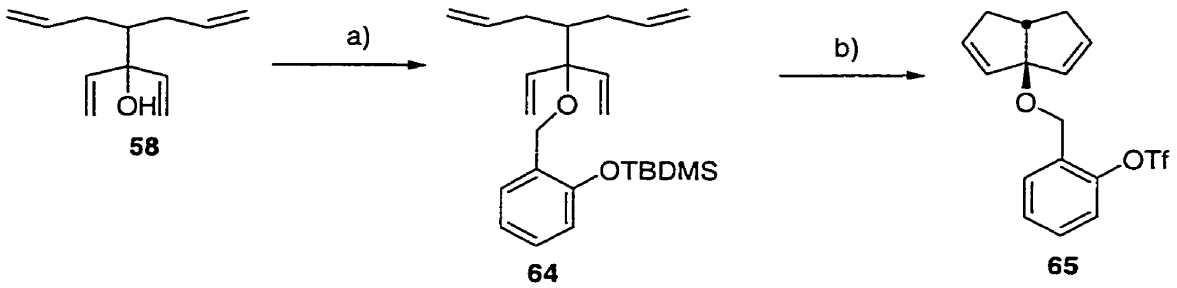
The cationic pathway begins with the dissociation of X from the palladium complex to generate the tri-coordinate 14-electron cationic complex, with a weakly bonding counter-ion. Complexation of the alkene into the vacant site then gives a 16-electron species where both phosphine atoms are bound to palladium in the enantioselective carbopalladation step. In the neutral pathway, there are not enough vacant sites on palladium to accommodate the complexation of the alkene. Thus, either a phosphine must dissociate, which will invariably lead to products of lower enantiomeric excess, or the coordinated alkene will displace the halide from the palladium coordination sphere. This latter speculation has been used to explain the high enantiomeric ratios obtained under favourable neutral conditions.

A variety of conditions were found to produce the polycyclic compounds in high yields and excellent levels of enantioselectivity. It is assumed that the use of silver salts would act to scavenge iodide from palladium, thus freeing a coordination site on the metal and allowing a tighter binding of the chiral bisphosphine in the enantioselective carbopalladation step of the catalytic cycle.

Detailed investigations into the asymmetric Heck reactions by Overman[30,31] have shown that silver salts are not always required to ensure high levels of enantioselectivity. It is generally accepted, that sequestering the halide from the palladium will allow for a tight binding of the bis-phosphine in the enantioselective determining step of the catalytic reaction. This will then ensure that the chiral information in the ligand will transferred to the organic substrate. Yet, as can be

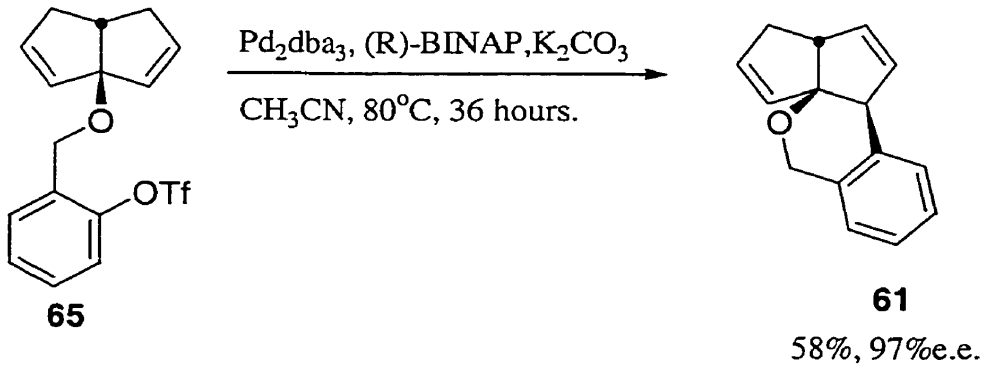
seen in **Table 4**, entry 1, a tertiary organic base is just as capable as a silver salt at effecting the transformation in high levels of enantioselectivity.

In order to further probe the necessity of a 16-electron cationic palladium intermediate in these asymmetric Heck reactions, the analogous aryl triflate was synthesized. The triflate was synthesized by the multi-step sequence shown in **Scheme 20**.



Scheme 20. Synthesis of an aryl triflate tethered to the bicyclo-[3.3.0]octadiene. Conditions: a) KH, *o*-(OTBDMS)benzyl bromide, THF, 23°C, 12 hrs., 85%. b) i) TBAF, THF, 23°C, 30min., 100%. ii) Tf_2O, Et_3N, CH_2Cl_2, -78°C, 15min., 81%. iii) **1** (6mol%), CH_2Cl_2, 23°C, 12hrs, 75%.

Attempts to shorten the synthetic route by coupling 2-trifluorosulfanate-benzyl bromide with the tertiary alcohol proved troublesome, since the triflate substrate underwent degradation. The generation of benzyne[29] intermediates under the reaction conditions is assumed to be responsible for the complex product mixtures obsevered in this case.

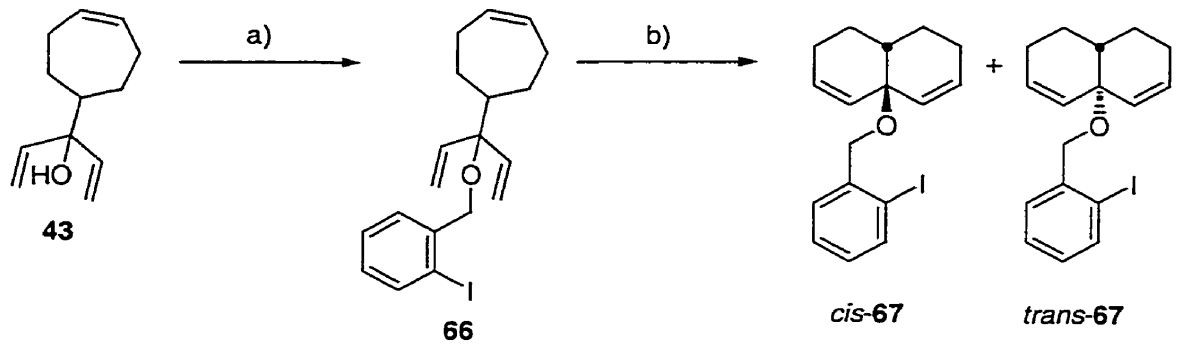


Scheme 21. Asymmetric synthesis of **61** under cationic conditions.

Oxidative addition of arene **65** would result in an 16-electron cationic palladium intermediate, since the triflate anion is weakly coordinating. The high enantiomeric excess obtained with the triflate substrate is the same as when an aryl iodide is used in the presence of a silver salt (**Table 4**, entry 4) and higher than neutral reaction conditions, **Table 4**, entry 2. Clearly the formation of a cationic palladium intermediate results in products with high levels of enantiomeric excesses. This result means that the triflate substrates can be used in lieu of the halide substrates with expensive silver salts.

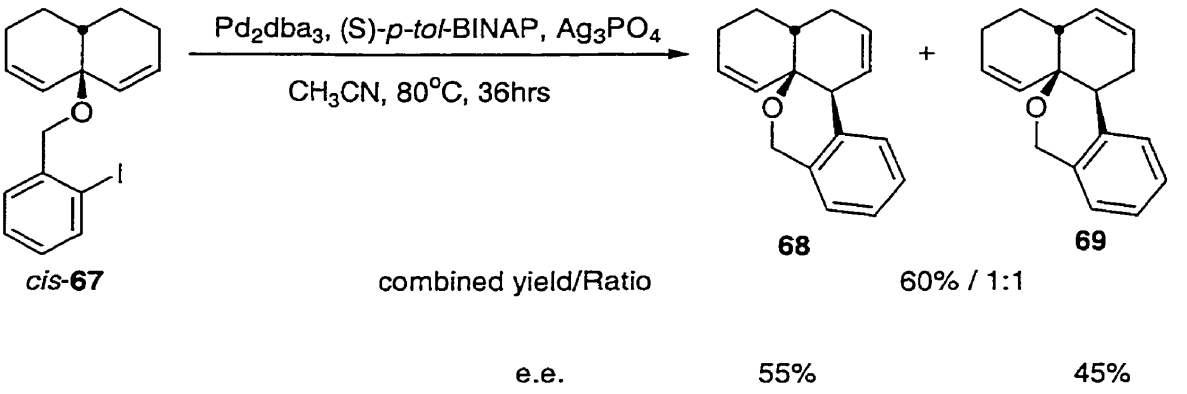
5.4 Desymmetrization of Bicyclo-[4.4.0]decadienes

Having explored the intramolecular asymmetric Heck reaction in the desymmetrization of bicyclo-[3.3.0]octadienes, efforts were directed towards applying the same transformation to the desymmetrization of bicyclo-[4.4.0]decadienes. The synthesis of the required aryl halide tethered substrates was carried out in a similar manner to that discussed above for the preparation of diquinane substrates. The DSRCM event, although possible with **1** and **2**, was carried out in a highly efficient manner with catalyst **3**. The reaction required catalyst loadings as low as 2 mol% (cf. 12mol% of either **1** or **2**)[8] and was complete in 30 minutes in refluxing dichloromethane. A 4.5:1 mixture of diastereomeric bicyclo[4.4.0]decadienes was obtained, favouring the *cis*-fused decalin. The minor diastereomer was removed by stirring the reaction mixture with silica gel for ~15 minutes at room temperature followed by flash chromatography on silica gel not neutralized with triethyl amine. Generally, the isolation of the bicyclodienes mentioned in this thesis required triethyl amine neutralized silica gel in the purification step.



Scheme 22. Synthesis of bicyclo[4.4.0]decadienes for intramolecular Heck reations. Conditions: a) KH, 2-iodobenzyl bromide, THF, 23°C, 12 hrs., 85%. b) cat. **3** (2mol%), CH_2Cl_2, reflux, 30 minutes, 4.5:1 (*cis*-**67**:*trans*-**67**), 100%.

Application of the asymmetric Heck reaction to aryl iodide *cis*-**67** provided regioisomeric alkene products in a 1:1 ratio and a combined 60% yield. Clearly this system is more complex since one now has an additional factor to try to control, namely the olefin isomerization step. Interestingly, the two regioisomeric products have different ee values, indicating that a kinetic resolution[34] is occurring in the β-hydride addition/elimination step.



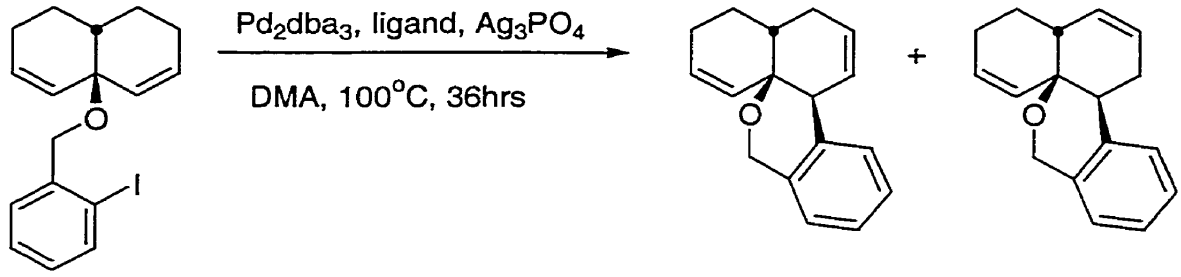
Scheme 23. Application of the asymmetric Heck reaction to the desymmetrization of bicyclo-[4.4.0]decadienes.

The relative stereochemistry of **68** and **69** are assumed as depicted. 2D-NMR experiments were successful at assigning proton-proton correlations (COSY)

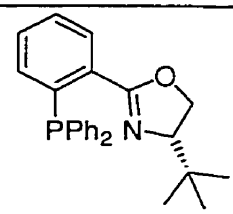
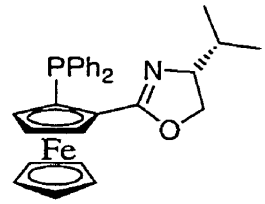
and proton-carbon correlations (HMQC) yet ROESY experiments did not provide any NOEs of interest which would allow relative stereochemistry assignment. Based on the information obtained on the asymmetric Heck reaction of the bicyclo-[3.3.0]octadiene, it is assumed that the ring formed in the bicyclo-[4.4.0]decadiene series, i.e. **68** and **69**, is also a *cis* ring juncture.

Studies on the bicyclo-[3.3.0]octadiene series revealed *p*-tol-BINAP to be the ligand which delivered product with highest enantiomeric excess. Having obtained aryl-substituted alkenes **68** and **69** in modest enantioselectivity, a brief study of chiral ligands was carried out in order to determine whether the alkene isomerization process could be controlled. The results from the chiral ligand study in the desymmetrization of the bicyclo-[4.4.0]decadiene series is presented in **Table 6**.

Table 6. Effect of Ligands in the asymmetric synthesis of **68** and **69**.



cis-**67** **68** **69**

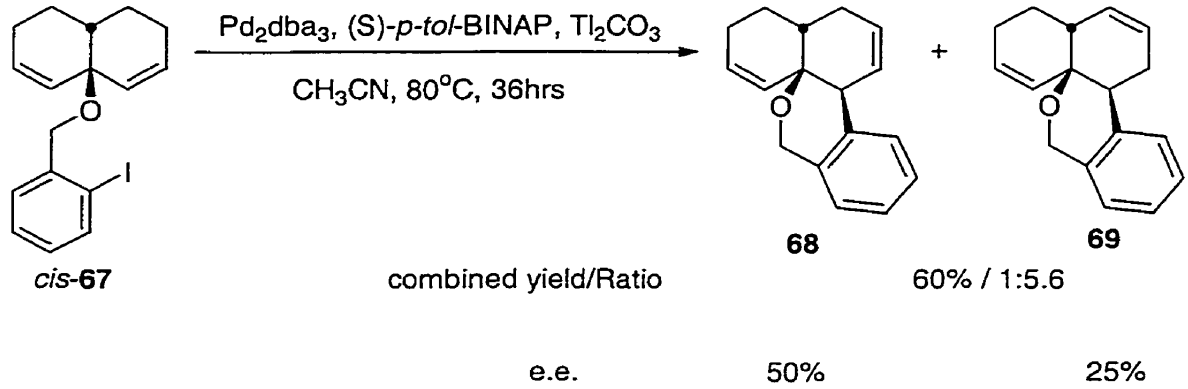
Ligand	**68** : **69**[a)]	**68** ee (%)	**69** ee (%)	Combined yield (%)[b)]
(R)- BINAP	1:1.1	11	30	50
(S)-*p*-*tol*-BINAP	1:1.49	50	35	55
	~1:2	37	c)	40
	1:2.42	19	1.6	53

a) Ratio was determined by integration of the singlet at 3.30ppm and the triplet at 2.83ppm respectively. b) combined isolated yield. c) undetermined

Enantiomeric excesses in this series are lower due to the slightly elevated temperature used here, 100°C versus 80°C. The higher temperatures were required due to the sluggish nature of the Pd-PHOX catalysts in this series. *p*-tol-BINAP is clearly the ligand which affords products with high enantiomeric ratios. Unlike palladium catalysts derived from BINAP, virtually no C-C double bond migration has been reported for Pd-PHOX catalysts. Yet, in the present system,

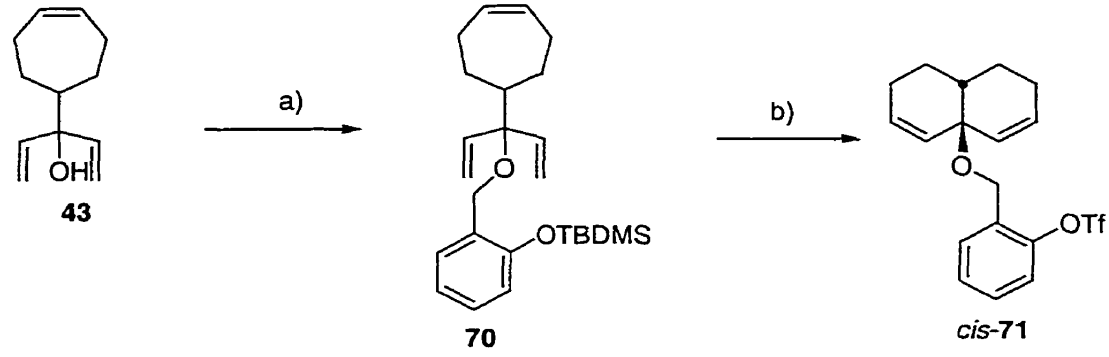
the use of such a catalyst only resulted in a 1:2.4 ratio of the regioisomers **68** and **69** respectively but with lower ees than seen with BINAP catalysts.

The use of silver salts in the present asymmetric Heck reactions did not seem to provide any bias in the formation of the regioisomeric alkene products. However, the utilization of Tl_2CO_3 as base provided alkene products with similar yields and levels of enantiomeric excesses as that seen with silver salts. The ratio of alkene regioisomers was altered, with an observed 1:5.6 ratio of regioisomers being observed favouring the olefin isomerized product **69**. Alkene regiocontrol better than this ratio was never achieved under a variety of conditions tested.



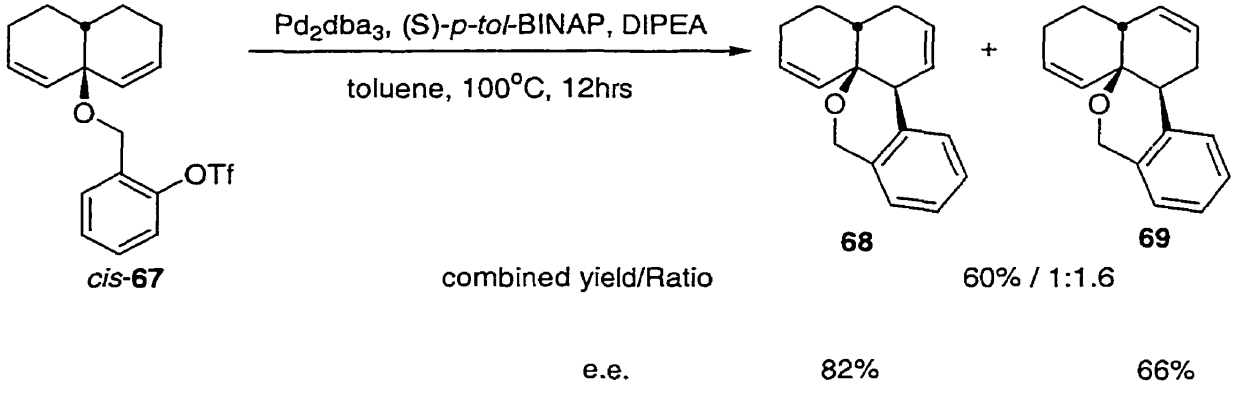
Scheme 24. Regiocontrol in the Asymmetric Heck reaction using Tl salts.

The exploration of the analogous aryl triflate substrates tethered to the bicyclo-[4.4.0]decadienes was next explored in attempts to increase the enantiomeric excesses of the polycyclic products. The synthesis of the required tiflate substrate required the same strategy as described earlier for the synthesis of **65**.



Scheme 25. Synthesis of an aryl triflate tethered to the bicyclo-[4.4.0]decadiene. Conditions: a) KH, *o*-(OTBDMS)benzyl bromide, THF, 23°C, 12 hrs., 85%. b) i) TBAF, THF, 23°C, 30min., 100%. ii) Tf_2O, Et_3N, CH_2Cl_2, -78°C, 15min., 81%. iii) 3 (2mol%), CH_2Cl_2, 45°C, 1hr then SiO_2, 23°C, 15 minutes, 65%.

Subjection of triflate *cis*-**71** under standard asymmetric Heck reactions provided the polycyclic products in ~1:1 ratio but with significantly higher levels of asymmetric induction (**scheme 26**). Attempts to improve upon these results did not lead to higher levels of enantiomeric excesses or alkene product ratios. Thus in the desymmetrization of bicyclo-[4.4.0]decadienes using asymmetric Heck reactions, the use of aryl triflates has a marked affect on the enantiomeric excesses realized as that seen in the analogous aryl iodide/silver base series.



Scheme 26. Asymmetric synthesis of **68** and **69** under cationic conditions.

5.5 Attempts to Extend the Scope of the Asymmetric Heck Reaction

The intramolecular asymmetric Heck reaction is a valuable and versatile method for construction of enantioenriched polycyclic compounds. In order to extend the scope of substrates which could be synthesized utilizing this chemistry, attempts were directed at preparing novel substrates for the intramolecular asymmetric Heck reaction. However, all of the attempts were unsuccessful.

Reaction of the tertiary diallylic alcohols with 2,3-dibromopropene yielded only the propargyl ether in 30% yield. Perhaps this is not surprising since vinyl halides[29] will readily undergo elimination reactions with strong bases. The tertiary allylic alcohols only undergo reaction under forcing conditions. Bases weaker than KH generally do not provide any reaction, either in coupling reactions or in a simple deprotonation. Thus, having prepared the vinyl halides presented in **Figure 11**, no success was obtained in the coupling reactions with the tertiary diallylic alcohols to provide the requisite ethers.

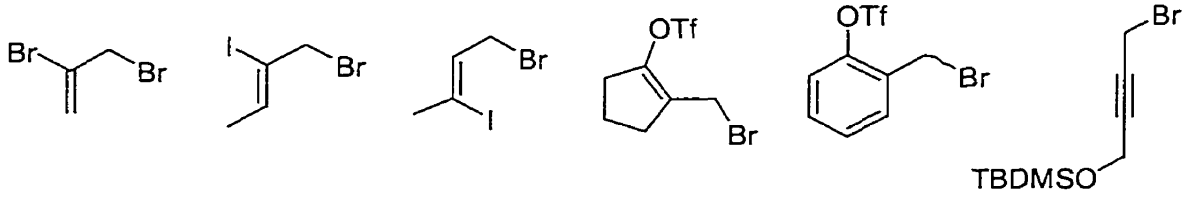


Figure 11. Electrophiles not successful in the preparation of tethered substrates.

6. Summary

The extension of the diastereoselective ring closing metathesis to substrates substituted at the bridgehead position was investigated. Cyclopentenes were synthesized with moderate to excellent levels of diastereoselectivity while the same substitution pattern provided cyclohexenes with poor to moderate diastereoselectivities.

Application of the asymmetric Heck reaction to the bicyclodienes synthesized by the DSRCM reaction resulted in the synthesis of enantio-enriched polycycles in good yields and enantioselectivities as high as 99%.

It must be pointed out that the success in the desymmetrization of the bicyclo-[4.40]decadienes using a nucleophilic palladium catalyst should be contrasted to the little success alluded to earlier in desymmetrization attempts using electrophilic, Lewis acid catalysts. Future success in desymmetrization reactions should be obtained under similar conditions, i.e. avoidance of electrophilic metal catalysts or Lewis acids.

Experimental

The following experimental details apply to all subsequent experiments.

All reactions were carried out under an atmosphere of dry Argon or nitrogen in oven (overnight at 90°C and then cooled under a stream of Ar or N_2) or flamed-dried glassware. Solvents and solutions were transferred with syringes and cannulae using standard inert atmosphere techniques.

^1H NMR spectra were recorded at 400 MHz using a Varian XL400 spectrometer with $CDCl_3$ and TMS as reference standard (δ=0.00ppm or 7.26ppm). Spectral features are tabulated in the following order: chemical shift (δ, ppm); multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-complex multiplet, br-broad); coupling constant (J, Hz); number of protons. ^{13}C NMR were recorded at 100 MHz using the same spectrometer with $CDCl_3$ as reference standard (δ=77.16ppm).

IR spectra were obtained using a Nicolet DX FT-IR spectrometer as a neat film between KBr plates; intensity is described as s-strong, m-medium, w-weak. High resolution mass spectra were obtained from a VG 70-250S (double focusing) mass spectrometer at 70 eV.

High performance liquid chromatography (HPLC) was performed on a Hewlett Packard HPLC using a CHIRACEL OD column. Column chromatography was performed as "Flash Chromatography" as reported by Still[35] using (200-400 mesh) Merck grade silica gel.

Toluene and THF were distilled from sodium/ benzophenone. DMF was dried by prolonged standing over molecular sieves. HMPA was distilled under reduced pressure from CaH_2. CH_2Cl_2 was distilled from CaH_2.

Grubbs' catalyst (**1**) was prepared according to a literature procedure[36] and triturated for 12-18 hours in a 1:1 mixture of acetone and methanol. The absence of free tricyclohexyl phosphine and tricyclohexyl phosphine oxide was confirmed by ^{31}P NMR, and was crucial in order for the double metathesis reactions to proceed. Schrock's catalyst (**2**) was used as received from Strem. (4,5-DihydroIMES)(PCy_3)Cl_2Ru=CHPh (**3**) was prepared according to a literature procedure.[3] The following compounds were prepared as reported in the literature: dihydro-3-(2-propenyl)furan-2(3H)-one (**25**)[37], 2-But-3-enyl-1-vinyl-octa-1,7-dien-3-ol (**5**)[8], *cis*-2,7,8,8a-tetrahydronaphthalen-4-ol (**8**)[8], 4-Allyl-3-vinyl-hepta-1,5-dien-3-ol (**58**)[8] and 2-(*tert*-butyldimethylsilyloxy)benzyl bromide[38].

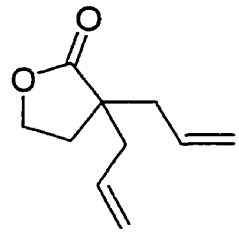
General Procedure for the Conversion of Methyl Esters to Diallylic Tertiary Alcohols:

$CeCl_3 \cdot 7H_20$ (4.0 equivalents) was ground with a mortar and pestle, placed under vacuum (<0.1 mmHg) and warmed to 140°C for 2 hours. A stir bar was added and heating under vacuum continued for a further 4-10 hours. The resulting powder was cooled to 0°C and THF (3 mL/ mmol of $CeCl_3$) was added via cannula under vacuum. The remaining vacuum was displaced with N_2 and the resulting suspension stirred for 24 hours, then cooled to –78°C. Vinylmagnesium bromide (~1 M in THF, 3.5 equivalents) was added via syringe at a rate such that the

internal temperature was kept below –65°C. After 1 hour a solution of ester (1.0 equivalent) in THF (~1 M) was added via cannula at a rate such that the internal temperature did not exceed –65°C. After 30 minutes, the mixture was diluted with ethyl acetate and water was added. The organic layer was decanted off and the aqueous slurry extracted 3 times with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo and purified by flash chromatography on triethyl amine washed silica gel.

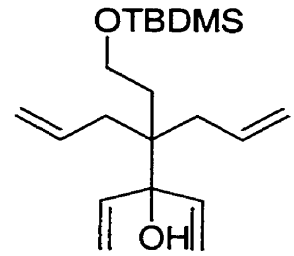
General Procedure for the Benzylation of Tertiary Diallylic Alcohols:

Potassium hydride (35% suspension in oil, 1.5 equivalents) was washed three times with pentane, dried under a stream of argon, and suspended in THF (half of the total reaction volume). A solution of alcohol in THF (half of reaction volume, reaction concentration of 0.2 M) was added via cannula. The resulting suspension was warmed to 60°C and after 10 minutes benzyl bromide (1.5 equivalents) was added via syringe and the resulting mixture was stirred for an hour, cooled to 23°C, diluted with ether and quenched carefully by drop-wise addition of water. The aqueous layer was extracted two times with ether; the organic layers were combined, washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography on triethyl amine washed silica gel.



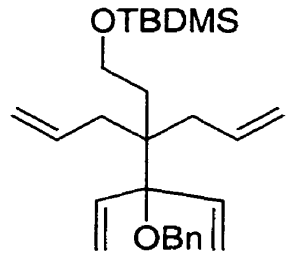
Dihydro-3,3-bis(2-propenyl)furan-2(3*H*)-one

NaH (95% dispersion in mineral oil, 0.69g, 29mmol) is suspended in 15ml of DMF. To this is added γ-butyrolactone (0.5g, 5.5mmol) via syringe. The solution is stirred for 15 minutes at room temperature and then allyl bromide (2.5ml, 29mmol) is added via syringe. The solution is stirred at room temperature for 24 hours at which time the reaction is quenched by the careful addition of water. The reaction mixture is then diluted with water (40ml) and the mixture is extracted with 10% CH_2Cl_2/hexanes (three times). The combined organic extracts are dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (8% EtOAc/hexanes) provides the title compound[37] as a colorless oil. Yield = 593mg (65%). ^1H NMR(400MHz, $CDCl_3$) δ 2.17(t, *J*=7.2Hz, 2H), 2.27-2.32(m, 2H), 2.37-2.42(m, 2H), 4.21(t, *J*=7.2Hz, 2H), 5.13-5.18(m, 4H), 5.70(m, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 30.52, 40.93, 46.14, 65.41, 119.70, 132.67, 180.55. ; IR(neat) 3076(s), 2984(m), 2908(m), 1763(s), 1638(m), 1440(m), 1291(w), 1180(s), 1120(s), 1032(s), 990(s), 921(s), 662(m), 624(m). ; HRMS M+ calculated=166.0993, found=166.0987.



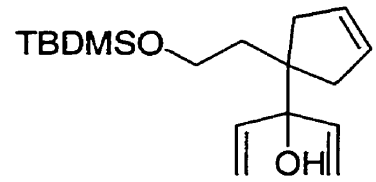
4-Allyl-4-[2-(*t*-butyldimethyl siloxy)]-ethyl-hepta-1,6-dien-3-ol (21)

Dihydro-3,3-bis(2-propenyl)furan-2(3*H*)-one (0.81g, 4.89mmol) was reacted under the standard conditions for the conversion of methyl esters to diallylic tertiary alcohols. The crude product was dissolved in DMF (40ml) and imidazole (0.469g, 6.9mmol) and *t*-butyldimethylsilyl chloride (0.69g, 4.6mmol) were added. The solution is stirred at room temperature for 12 hours. The reaction volume is doubled with water and extracted with ether (three times). The organic layers are washed with water, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (5% Et_2O/hexanes) provided the title compound as a colorless oil (57% over two steps). ^1H NMR(400MHz, $CDCl_3$) δ 0.08(s, 6H), 0.91(s, 9H), 1.71(t, *J*=6Hz, 2H), 2.23-2.36(m, 4H), 3.76(t, *J*=6Hz, 2H), 4.16(s, 1H), 5.01-5.06(m, 4H), 5.16(dd, *J*=10.8Hz, 2Hz, 2H), 5.32(dd, *J*=17.2Hz, 1.6Hz, 2H), 5.83-5.94(m, 2H), 6.16(dd, *J*=17.2Hz, 10.8Hz, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ -5.25, 18.57, 26.15, 36.70, 39.15, 46.32, 60.19, 79.98, 114.33, 117.21, 136.42, 140.72. ; IR(neat) 3366(s), 2931(s), 1840(w), 1634(m), 1436(m), 1253(s), 1085(s), 1001(s), 918(s), 834(s), 731(s), 662(w). ; HRMS (M-C_4H_9)+ calculated= 279.1780, found= 279.1774.



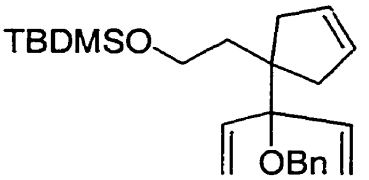
***tert*-Butyl-(3,3-diallyl-4-benzyloxy-4-vinyl-hex-5-enyloxy)-dimethyl-silane (22)**

Alcohol **21** (650mg, 0.44mmol) is reacted according to the general benzylation procedure to yield the title compound as a colorless oil (120mg, 63%) after flash chromatography (100% hexanes) on triethyl amine treated silica gel. ^{1}H NMR(400MHz, $CDCl_3$) δ 0.05(s, 6H), 0.90(s, 9H), 1.75-1.79(m, 2H), 2.34(qd, *J*=18.8Hz, 7.2Hz, 4H), 3.82-3.87(m, 2H), 4.32(s, 2H), 5.02-5.08(m, 4H), 5.32(dd, *J*=17.6Hz, 1.6Hz, 2H), 5.46(dd, *J*=11.2Hz, 1.6Hz, 2H), 5.95-6.06(m, 2H), 6.10(dd, *J*=17.6Hz, 11.2Hz, 2H), 7.23-7.38(m 5H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ -5.01, 18.54, 26.21, 38.09, 39.25, 46.62, 60.72, 65.61, 86.31, 116.52, 118.26, 126.05, 127.03, 127.16, 128.33, 128.48, 128.59, 136.53, 136.53, 136.75, 139.70. ; IR(neat) 3076(m), 1874(w), 1866(w), 1626(w), 1455(m), 1249(m), 1074(m), 906(m), 834(m), 773(m), 727(m). ; HRMS (M-C_4H_9)+ calculated= 369.2249, found= 369.2246.



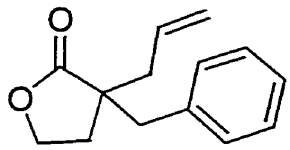
3-{1-[2-(*tert*-Butyl-dimethyl-siloxy)-ethyl]-cyclopent-3-enyl}-penta-1,4-dien-3-ol (23)

Alcohol **21** (20mg, 0.06mmol) is dissolved in 1ml CH_2Cl_2 under nitrogen. Grubbs catalyst **1** (4mg, 0.004mmol) is added and the solution is capped, i.e. no inlets or outlets. After stirring at room temperature for 20 hours, solvent is removed in *vacuo*. ^1H NMR (400MHz) analysis shows a 100% conversion to the cyclopentene product. ^1H NMR(400MHz, $CDCl_3$) δ 0.06(s, 6H), 0.89(s, 9H), 1.74(t, *J*=6.4Hz, 2H), 2.05(d, *J*=14Hz, 2H), 2.63(d, *J*=14Hz, 2H), 3.30(br s, 1H), 3.65(d, *J*=6.4Hz, 2H), 5.19(dd, *J*=10.8Hz, 1.6Hz, 2H), 5.35(dd, *J*=17.2Hz, 1.6Hz, 2H), 5.56(s, 2H), 6.06(dd, *J*=17.2Hz, 10.8Hz, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ -5.19, 18.56, 26.15, 40.62, 41.13, 51.10, 60.64, 79.50, 114.91, 129.30, 140.78. ; IR(neat) 3367(br s), 3044(w), 2926(s), 1729(m), 1253(s), 1081(s), 997(m), 920(m), 836(s), 734(s), 660(m). ; HRMS $(M-C_4H_9)+$ calculated= 251.1467, found= 251.1470.



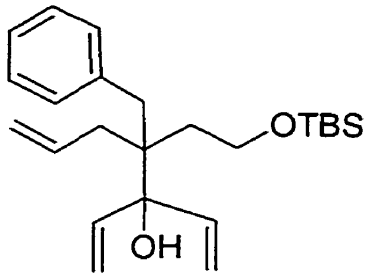
{2-{1-(1-Benzyloxy-1-vinyl-allyl)-cyclopent-3-enyl]-ethoxy}-*tert*-butyl-dimethyl silane (24)

Benzyl ether **22** (17mg, 0.04mmol) is dissolved in 1ml CH_2Cl_2. Grubbs catalyst **1** (4mg, 0.004mmol) is added and the reaction is stirred under an ethylene atmosphere (via a balloon) for 24 hours. Solvent is removed *in vacuo* and the residue is analyzed by ^1H NMR (400 MHz) and shows a 100% conversion to the cyclopentene product. Repeating the reaction with Schrock's catalyst **2** did not alter the outcome of the reaction. ^1H NMR(400MHz, $CDCl_3$) δ 0.01(s, 6H), 0.86(s, 9H), 1.72(m, 2H), 1.97-2.01(m, 2H), 2.77-2.81(m, 2H), 3.55(t, *J*=7.6Hz, 2H), 4.37(s, 2H), 5.30(dd, *J*=17.8Hz, 1.6Hz, 2H), 5.38(dd, *J*=11Hz, 1.6Hz, 2H), 5.55(s, 2H), 5.92(dd, *J*=17.8Hz, 11.2Hz, 2H), 7.17-7.31(m, 5H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ -5.02, 18.52, 26.18, 38.09, 39.95, 42.01, 61.01, 65.79, 118.39, 126.05, 126.69, 126.86, 128.27, 128.48, 128.59, 129.34, 136.90, 140.23. ; IR(neat) 3044(m), 2926(s), 2860(s), 1941(w), 1864(w), 1798(w), 1623(w), 1469(m), 1403(m), 1253(s), 1078(s), 931(s), 909(s), 836(s), 778(m), 730(s). ; HRMS (M-C_4H_9)+ calculated= 341.1936, found= 341.1932.



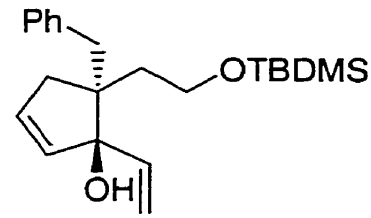
3-Allyl-3-benzyl-dihydro-furan-2-one (26)

Diisopropylamine (10.98mmol, 1.32ml) is added to THF (13ml) and the resulting solution is cooled to -78°C. n-BuLi (10.98mmol, 2.5M in hexanes, 4.39ml) is then added dropwise. The solution is stirred for an additional 30 minutes at –78°C at which time 3-allyl-dihydro-furan-2-one[20] in THF (13ml) is introduced dropwise by cannula addition. The solution is stirred for an additional 30 minutes at –78°C followed by dropwise addition of benzyl bromide (11.98mmol, 1.42ml) in HMPA (2.2ml). The solution is stirred for an additional 3 hours at –78 °C. The reaction is quenched with saturated aqueous ammonium chloride solution and the mixture is diluted with ether. The layers are separated and the aqueous layer is extracted with ether (three times). The combined organic layers are dried over $MgSO_4$, filtered, and concentrated. The crude product is purified by flash chromatography (20%Et_2O/hexanes) to yield the title compound as a colorless oil (1.39 g, 77%). ^1H NMR (400MHz, $CDCl_3$) δ 2.15 (t, *J*=8Hz, 2H), 2.33 (dd, *J*=13.8Hz, 8Hz, 1H), 2.51 (dd, *J*= 14Hz, 6.4Hz, 1H), 2.74 (d, *J*=13.2Hz, 1H), 3.07 (d, *J*=13.2Hz, 1H), 3.46 (q, *J*=8.8Hz, 1H), 4.02 (q, *J*=6.4Hz, 1H), 5.17 (dd, *J*=9.2Hz, 1.2Hz, 1H), 5.21 (s, 1H), 5.79 (qt, *J*=8.4Hz, 2Hz, 1H), 7.19-7.32(m, 5H); ^{13}C NMR (100MHz, $CDCl_3$) δ 29.87, 42.15, 42.88, 48.07, 65.43, 119.98, 127.23, 128.68, 130.08, 132.80, 136.63, 180.96. IR(neat) 2915(m), 1757(s), 1212(w), 1166(s), 1029(s), 920(m), 702(m). HRMS M+ calculated=216.1150, found=216.1152



4-Benzyl-4-(2-*t*-butyldimethylsiloxy- ethyl)-3-vinyl-hepta-1,6-diene-3-ol (29)

3-Allyl-3-benzyl-dihydro-furan-2-one (1.0g, 4.6mmol) was reacted under standard conditions for the conversion of methyl esters to diallylic tertiary alcohols. The crude product was dissolved in DMF (40ml) and imidazole (0.469g, 6.9mmol) and *t*-butyldimethylsilyl chloride (0.69g, 4.6mmol) were added. The solution is stirred at room temperature for 12 hours. The reaction volume is doubled with water and extracted with ether (three times). The organic layers are combined, washed with water, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (5%Et_2O/hexanes) provided the title compound as a colourless oil (1.0g, 57% over two steps). ^1H NMR(400MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.72 (t, *J*=6Hz, 2H), 2.20 (dd, *J*=15Hz, 6.4Hz, 1H), 2.41 (dd, *J*=15Hz, 6.4Hz, 1H), 2.80(d, *J*=14Hz, 1H), 2.88(d, J=14Hz, 1H), 3.77(t, *J*=6Hz, 2H), 4.10(brs, 1H), 4.93-5.01(m, 2H), 5.19(ddd, *J*=10.8Hz, 4.8Hz, 1.6Hz, 2H), 5.35(ddd, *J*=18.5Hz, 3Hz, 1.6hz, 2H), 5.59-5.70 (m, 1H), 6.15(dd, *J*=14.8Hz, 10.8Hz, 1H), 6.20(dd, 14.8Hz, 10.8Hz, 1H), 7.16-2.27(m, 5H); ^{13}C NMR (100MHz, $CDCl_3$) δ-5.23, -5.18, 18.57, 26.17, 36.33, 38.99, 40.49, 47.62, 60.35, 80.24, 114.73, 114.76, 116.98, 126.23, 128.11, 131.21, 1136.70, 139.36, 140.55, 140.58; IR(neat) 3359 (s), 2936 (s), 2838 (w), 2309 (w), 1254 (m), 1081 (s), 997 (m), 916 (m), 839 (m), 772 (w); HRMS (M-CH_3)+ calculated=371.2406, found=371.2414.

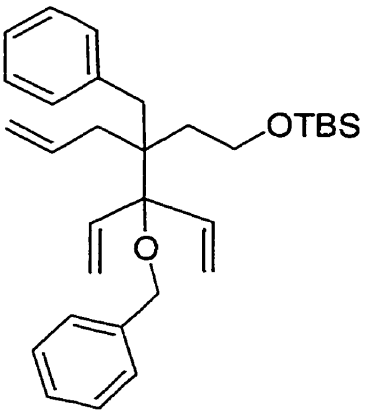


trans-

Trans-5-Benzyl-5-(2-*t*-butyldimethylsiloxy-ethyl)-1-vinyl-cyclopent-2-enol (33)

To a solution of triene **29** (240mg, 0.6217mmol) in dichloromethane (25ml) at 23°C was added **1** (25.5mg, 0.03mmol). The solution is stirred for 6 hours at room temperature at which time **1** (25.5mg, 0.03mmol) is again added. The solution is stirred for an additional 12 hours at room temperature, when **1** (25.5mg, 0.03mmol) is added for the final time. After stirring at room temperature for an additional 6 hours, the reaction is opened to air and the solvent is removed *in vacuo*. Flash chromatography (5%Et_2O/ hexanes) provides the title compound (134mg, 60%) as a single diastereomer, as a colourless oil. R_f=0.10 (5%Et_2O/ hexanes). The stereochemistry was determined by ROESY experiment. ^1H NMR(400MHz, $CDCl_3$) δ 0.55(s, 6H), 0.90(s, 9H), 1.26(m, 2H), 1.86(ddd, *J*=15.2Hz, 10.4Hz, 2.4Hz, 1H), 1.20(dd, *J*=16.2Hz, 1.6Hz, 1H), 2.55(d, *J*=16.4Hz, 1H), 2.64(d, *J*=13.6Hz, 1H), 2.80(d, *J*=13.6Hz, 1H), 3.54(td, *J*=10.4Hz, 1.2Hz, 1H), 3.65(ddd, *J*=10.5Hz, 5.8Hz, 2.8Hz, 1H), 5.16(dd, *J*=10.6Hz, 2Hz, 1H), 5.21(s, 1H), 5.25 (dd, *J*=17.4Hz, 2Hz, 1H), 5.64-5.66 (m, 1H), 5.84-5.87(m, 1H), 5.97(dd, *J*=17.4Hz, 10.8Hz, 1H), 7.11-7.26(m, 5H); ^{13}C NMR(100MHz, $CDCl_3$) -5.57, -5.38, 18.38, 26.05, 37.81, 41.81, 43.20, 52.59, 59.92, 87.75, 112.91, 126.03, 128.06, 129.32, 130.46, 138.24, 140.22, 140.72; IR(neat) 3397 (s), 2928 (s), 1495 (m),

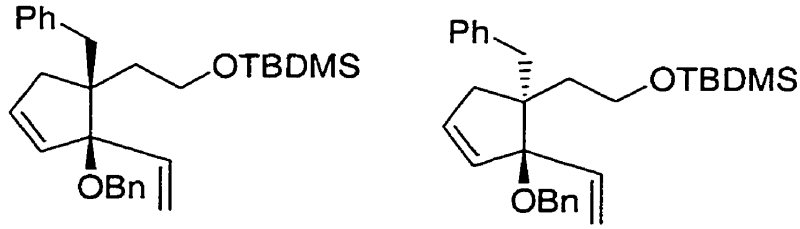
1257(s), 1079 (s), 1023 (m), 836 (m), 720 (m); HRMS M-C_4H_9 calculated=301.1623, found=301.1618.



[2-Allyl-3-benzyloxy-2-(2-*t*-butyldimethylsiloxy-ethyl)-3-vinyl-pent-4-enyl]-benzene (30)

4-Benzyl-4-(2-*t*-butyldimethylsiloxy-ethyl)-3-vinyl-hepta-1,6-diene-3-ol (300mg, 0.77mmol) was reacted according to the general benzylation procedure to yield the title compound as a colorless oil (314mg, 85%) after flash chromatography(100% hexanes). R_f=0.6(5%Et_2O/ hexanes). ^1H NMR(400MHz, $CDCl_3$) δ 0.01(s, 6H), 0.87(s, 9H), 1.745(m, 2H), 2.21(dd, *J*=14.8Hz, 6.8Hz, 1H), 2.37(dd, *J*=14.8Hz, 7.6Hz, 1H), 2.87(d, *J*=13.6Hz, 1H), 2.97(d, *J*=13.6Hz, 1H), 3.68 (m, 1H), 3.87(m, 1H), 4.32(s, 2H), 4.92(dd, *J*=10Hz, 2Hz, 1H), 4.95(dd, *J*=17.2Hz, 2Hz, 1H), 5.30(dd, *J*=4Hz, 1.6Hz, 1H), 5.35(dd, *J*=4Hz, 1.6Hz, 1H), 5.44(dd, *J*=8Hz, 1.6Hz, 1H), 5.47(dd, *J*=6.8Hz, 1.6Hz, 1H), 5.794(m, 1H), 6.04(dd, *J*=16Hz, 11.2Hz, 1H), 6.09(dd, *J*=16Hz, 11.2Hz, 1H), 7.21-7.37(m, 10H); ^{13}C NMR(100MHz, $CDCl_3$) δ -5.01, 18.50, 26.18, 27.06, 37.81, 39.39, 47.79, 60.71, 65.67, 86.48, 116.00, 118.42, 118.60, 126.06, 127.05, 127.12, 127.94, 128.35,

131.36, 136.26, 136.52, 136.89, 139.56, 139.66; IR(neat) 2950(s), 2852(m), 1634(w), 1461(w), 1254(m), 1085(s), 1064(s), 930(m), 835(m), 772(w).; HRMS M-C_4H_9 calculated=419.2406, found=419.2392.



cis- *trans-*

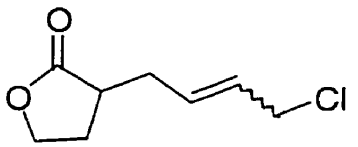
[2-Benzyloxy-1-(2-*t*-butyldimethylsiloxy-ethyl)-2-vinyl-cyclopent-3-enylmethyl]-benzene (34)

To a solution of triene **30** (30mg, 0.063mmol) in dichloromethane (1ml) at 23C was added **1** (5.168mg, 0.0063mmol). After 12 hours at room temperature, the reaction is opened to air and the solvent is removed in vacuo. A crude ^{1}H NMR showed a 2:1 mixture of diastereomers, favouring the *cis-* diastereomer. The two diastereomers were inseparable by flash chromatography. To confirm the stereochemistry of the diastereomers, alcohol, *trans*-**33** (30mg, 0.083mmol) was reacted under the general benzylation procedure to yield *trans*-**34** (35mg, 95%) as a colourless oil after flash chromatography(100% hexanes). *Trans-* ^{1}H NMR(400MHz, $CDCl_3$) δ -0.04(s, 3H), -0.03(s, 3H), 0.84(s, 9H), 1.86(t, 7.6Hz, 2H), 2.10(dt, J=16.8Hz, 2Hz, 1H), 2.33(ddd, *J*=16.6Hz, 2.8Hz, 1.6Hz, 1H), 2.45(d, *J*=13.6Hz, 1H), 2.69(d, *J*=13.6Hz, 1H), 3.69-3.76(m, 1H), 3.84-3.91(m, 1H), 4.39(d, *J*=11.6Hz, 1H), 4.50(d, *J*=11.6Hz, 1H), 5.26(dd, *J*=17.6Hz, 1.6Hz, 1H), 5.34(dd, *J*=10.8Hz, 1.6Hz, 1H), 5.94(dd, *J*=17.6Hz, 10.8Hz, 1H), 5.99(dt, *J*=6Hz,

1.6Hz, 1H), 6.08(dt, *J*=6Hz, 2.4Hz, 1H), 7.15-7.39(m, 10H); IR(neat) 2950(m), 2852(m), 1602(w), 1451(m), 1254(m), 1081(s), 906(m), 737(s), 691(s); HRMS M+ calculated=448.2797, found=448.2802.

Cis-: ^{1}H NMR(400MHz, $CDCl_3$) δ -0.02(s, 3H), -0.01(s, 3H), 0.84(s, 9H), 1.53(t, *J*=7.6Hz, 2H), 2.08(d, *J*=16.4Hz, 1H), 2.58(d, *J*=16.4Hz, 1H), 2.97(d, *J*=13.6Hz, 1H), 3.06(d, *J*=13.6Hz, 1H), 3.38-3.45(m, 1H), 3.55-3.61(m, 1H), 4.37(d, *J*=11.6Hz, 1H), 4.47(d, *J*=11.6Hz, 1H), 5.25(s, 1H), 5.28(dd, *J*=5.2Hz, 1.6Hz, 1H), 5.79(dd, *J*=18Hz, 10.4Hz, 1H), 6.04(s, 2H), 7.15-7.34(m, 10H); IR(neat) 2950(m), 2852(m), 1602(w), 1451(m), 1254(m), 1081(s), 906(m), 737(s), 691(s); HRMS M+ calculated=448.2797, found=448.2802

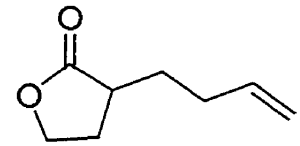
^{13}C NMR(100MHz, $CDCl_3$) mixture of diastereomers: δ -5.10, -5.06, 18.41, 26.12, 33.68, 36.57, 41.00, 41.72, 52.65, 61.41, 65.84, 93.07, 117.10, 125.99, 127.04, 127.10, 127.88, 128.25, 128.54, 128.92, 129.15, 130.98, 131.44, 135.52, 137.92, 139.09, 139.81, 140.07.



2-(4-Chlorobut-2-enyl)-γ-butyrolactone

n-BuLi (7.6ml, 2.3M solution in hexanes) was added to a –78°C solution of diisopropylamine (2.8ml) in 50 ml of THF. After 30 minutes, γ-butyrolactone (1.1ml, 14.36mmol) was added via syringe. After 2 hours , a solution of 1,4-dichlorobut-2-ene (6.00ml, 57.4mmol) in HMPA(20ml) was added via cannula to give a deep red solution. After 2hrours at –78°C, the reaction mixture was slowly

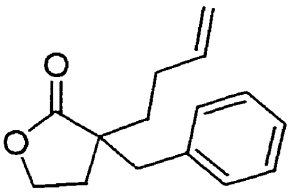
warmed to room temperature and allowed to stir overnight. The mixture was diluted with 50% saturated ammonium chloride solution and the mixture is diluted with ether. The layers are separated and the aqueous layer is extracted with ether(three times). The combined organic layers are dried over $MgSO_4$, filtered, and concentrated. The crude product is purified by flash chromatography(10%→15%→20% EtOAC/hexanes) to give 1.23g (52%) of the desired allyl chloride[11] as an oil. ^1H NMR(400MHz, $CDCl_3$) δ 1.94-2.07(m, 1H), 2.26-2.46(m, 2H), 2.58-2.73(m, 2H), 4.04(d, *J*=5.5Hz, 2/3H), 4.11 (d, *J*=12Hz, 1 1/3H), 4.18-4.25 (m, 1H), 4.32-4.39 (m, 1H), 5.59-5.67(m, 2/3H), 5.70-5.85(m, 1 1/3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 27.32, 27.74, 27.81, 32.46, 38.73, 38.82, 44.53, 66.47, 128.03, 129.10, 130.38, 131.04, 178.34.; IR (neat) 2920, 1771, 1445, 1380, 1256, 1210, 1170.



2-(But-3-enyl) γ-butyrolactone (27)

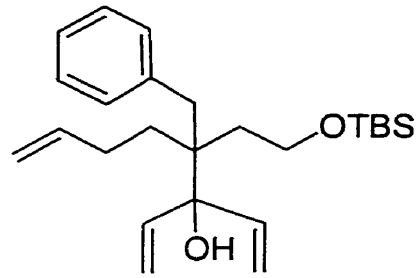
To a 23°C suspension of HCO_2NH_4 (1.02g, 16.24mmol) in toluene (6ml) was added Pd_2dba_3 (67.59mg,0.07mmol) and n-Bu_3P (117μl, 0.62mmol). The dark purple solution turned orange over the course of 10 minutes at which time a solution of 2-(4-Chlorobut-2-enyl)-γ-butyrolactone (1.3g, 7.38mmol) in toluene (10ml) was added via cannula. The resulting lime green solution was placed in an oil bath and heated to 100°C until the solution turned from green back to orange (~3 hours). TLC analysis shows a complete conversion of the allyl chloride to the

product alkene. The solution is cooled to room temperature and diluted with water and ether. The layers are separated and the organic layer is extracted with ether (three times). The combined organic layers are dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (12% EtOAc/hexanes) provides the title compound as a colourless oil (868mg, 84%). The spectral data are in agreement with that reported in the literature[10].



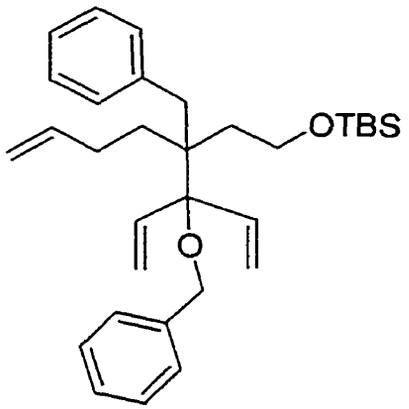
3-Benzyl-3-but-3-enyl-dihydro-furan-2-one (28)

3-But-3-enyl-hihydrofuran-2-one **27** (1.1g, 7.857mmol) was reacted according to the same procedure for the synthesis of 3-allyl-3-benzyl-dihydro-furan-2-one (**26**). Flash chromatography (20%Et_2O/hexanes) provides 1.32g (74%) of the title compound as a colourless oil. R_f=0.5(50%Et_2O/hexanes); ^1H NMR(400MHz, $CDCl_3$) δ 1.68-1.81(m, 2H), 2.06-2.25(m, 4H), 2.75(d, *J*=13.6Hz, 1H), 3.05(d, *J*=13.6Hz), 3.45-3.51(m, 1H), 4.00-4.06(m, 1H), 4.98(d, *J*=10.4Hz, 1H), 5.05(dt, *J*=17.2Hz, 1.6Hz, 1H), 5.75-5.85(m, 1H), 7.18-7.30(m, 5H); ^{13}C NMR(100MHz, $CDCl_3$) δ 28.82, 30.60, 36.74, 42.76, 47.91, 65.26, 115.41, 127.22, 128.67, 130.06, 136.65, 137.52, 181.07; IR(neat) 2910(m), 1760(s), 1634(w), 1447(m), 1173(s), 1029(s), 913(m); HRMS M+ calculated=230.1306, found=230.1259



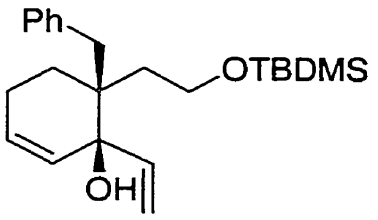
4-Benzyloxy-4-(2-*t*-butyldimethylsiloxy-ethyl)-3-vinyl-octa-1,7-dien-3-ol (31)

3-Benzyl-3-but-3-enyl-dihydro-furan-2-one **38** (1.0g, 4.37mmol) was reacted under standard conditions for the conversion of methyl esters to tertiary diallylic alcohols. The crude product was dissolved in DMF (50ml) and imidazole (0.469g, 6.9mmol) and *t*-butyldimethylsilyl chloride (0.69g, 4.6mmol) were added. After stirring at room temperature for 12 hours, water (50ml) is added. Extract with ether (three times) and wash with water. Dry over Na_2SO_4, filter, and concentrate. Flash chromatography (5%Et_2O/hexanes) provides 0.825g (48% over two steps) of the title compound as a colourless oil. R_f=0.3 (5%Et_2O/hexanes); ^1H NMR (400MHz, $CDCl_3$) δ 0.12(s, 6H), 0.94(s, 9H), 1.50-1.96(m, 6H), 2.81(d, *J*=14Hz, 1H), 2.86(d, *J*=14Hz, 1H), 3.76-3.84(m, 2H), 3.98(br s, 1H), 4.88(s, 1H), 4.91(d, *J*=6.8Hz, 1H), 5.20(dd, *J*=12Hz, 1.6Hz, 1H), 5.23(dd, *J*=12Hz, 1.6Hz, 1H), 5.38(dd, *J*=17.2Hz, 2Hz, 1H), 5.39(dd, *J*=17.2Hz, 2Hz, 1H), 5.66-5.76(m, 1H), 6.20(dd, *J*=17.2Hz, 10.8Hz, 1H), 6.20(dd, *J*=17.2Hz, 10.8Hz, 1H), 7.17-7.29(m, 5H); ^{13}C NMR(100MHz, $CDCl_3$) δ -5.21, -5.17, 18.55, 26.16, 29.30, 33.00, 36.30, 40.78, 47.17, 60.39, 80.19, 114.02, 114.02, 114.73, 114.84, 126.20, 128.11, 130.97, 139.40, 139.54, 140.59, 140.76; IR(neat) 3371(s), 2929(s), 1639(w), 1471(m), 1255(m), 1079(s), 910(s), 836(m), 733(m); HRMS M-C_4H_9 calculated=343.0183, found=343.0187.

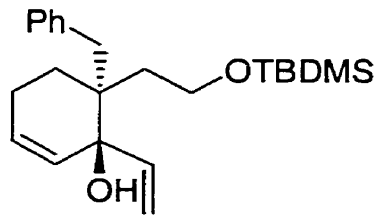


[2-(1-Benzyloxy-1-vinyl-allyl)-2-(2-*t*-butyldimethylsiloxy-ethyl)-hex-5-enyl]-benzene (32)

Alcohol **31** (150mg, 0.375mmol) was reacted according to the general benzylation procedure to yield the title compound as a colourless oil (165mg, 90%) after flash chromatography (100% hexanes). R_f=0.7(5%Et_2O/hexanes); ^1H NMR(400MHz, $CDCl_3$) δ 0.01(s, 6H), 0.87(s, 9H), 1.42-2.11(m, 6H), 2.86(d, *J*=14Hz, 1H), 2.92(d, *J*=13.6Hz, 1H), 3.60-3.67(m, 1H), 3.82-3.88(m, 1H), 4.33(s, 2H), 4.87(s, 1H), 4.90(d, *J*=7.8Hz, 1H), 5.34(dd, *J*=19.4Hz, 2Hz, 1H), 5.34(dd, *J*=17.6Hz, 1.6Hz, 1H), 5.46(dd, *J*=11Hz, 2Hz, 1H), 5.46(dd, *J*=11.2Hz, 1.2Hz, 1H)5.65-5.75(m, 1H), 6.02(dd, *J*=17.8Hz, 11Hz, 1H), 6.07(dd, *J*=17.8Hz, 11Hz, 1H), 7.19-7.36(m, 10H); ^{13}C NMR(100MHz, $CDCl_3$) δ -5.00, 18.49, 26.19, 29.45, 33.58, 37.54, 40.03, 47.45, 60.83, 65.77, 86.63, 113.85, 118.47, 118.70, 126.06, 127.07, 127.10, 128.00, 128.37, 131.11, 136.16, 136.52, 139.65, 139.76, 139.81; IR(neat) 2950(m), 2859(m), 1641(m), 1451(m), 1254(m), 1081(s), 930(m), 835(s); HRMS M-C_4H_9 calculated=433.2562, found=433.2576



cis-

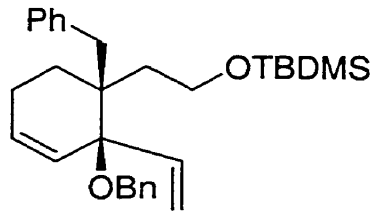


trans-

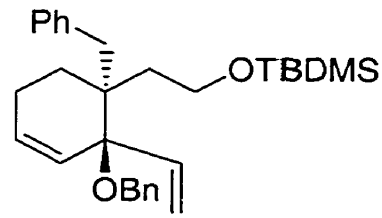
6-Benzyl-6-(2-*t*-butyldimethylsiloxy-ethyl)-1-vinyl-cyclohex-2-en-1-ol (35)

To a solution of triene **31** (100mg, 0.25mmol) in dichloromethane (20ml) is added **1** (24mg, 0.03mmol). The solution is stirred for 12hours at room temperature at which time the reaction is opened to air and the solvent is removed in vacuo. A crude ^{1}H NMR showed a 1:1 mixture of diastereomers at 100% conversion. The residue is purified by flash chromatography (5%Et_2O/hexanes) to provide the R*S* diastereomer (37.6mg, 40%) and the R*R* diastereomer (30mg, 32%) as colourless oils. The stereochemistry of the R*S* diastereomer was proven by ROESY experiment; *Trans-*: ^{1}H NMR(400MHz, $CDCl_3$) δ 0.08(s, 6H), 0.91(s, 9H), 1.43-1.53(m, 2H), 1.58-1.66(m, 1H), 1.73(ddd, *J*=17.6Hz, 8.4Hz, 2.4Hz, 1H), 1.93-2.13(m, 2H), 2.59(d, *J*=13.6Hz, 1H), 3.04(d, *J*=13.6Hz, 1H), 3.68-3.73(m, 1H), 4.01(ddd, *J*=11Hz, 8.8Hz, 2.4Hz, 1H), 4.89(s, 1H), 5.22(dd, *J*=10.8Hz, 2Hz, 1H), 5.29(dd, *J*=17.4Hz, 2Hz, 1H), 5.48(dt, *J*=10Hz, 2.4Hz, 1H), 5.69(dt, *J*=10Hz, 2.4Hz, 1H), 6.10(ddd, *J*=17.2Hz, 10.8Hz, 0.8Hz, 1H), 7.07-7.27(m, 5H); ^{13}C NMR(100MHz, $CDCl_3$) δ -5.29, -5.18, 18.33, 22.69, 26.00, 26.21, 29.10, 35.18, 39.38, 43.31, 60.20, 76.49, 114.46, 125.98, 126.13, 127.98, 131.23, 134.02, 139.08, 142.19; IR(neat) 3388(s), 2929(m), 1471(w), 1255(m), 1078(s), 1003(m), 836(s), 777(m), 702(w); HRMS M+ calculated=372.2482, found=372.2483

Cis-: ^{1}H NMR($CDCl_3$) δ 0.13(d, *J*=0.8Hz, 6H), 0.94(s, 9H), 1.23-1.49(m, 3H), 1.62-1.69(m, 1H), 2.20-2.30(m, 1H), 2.79(d, *J*=14.8Hz, 1H), 3.19(d, *J*=14.8Hz, 1H), 3.48(dt, *J*=11.2Hz, 4.4Hz, 1H), 4.11(td, *J*=10.88Hz, 3.2Hz, 1H), 4.31(br s, 1H), 5.12(dd, *J*=10.6Hz, 1.6Hz, 1H), 5.19, (*J*=16Hz, 2Hz, 1H), 5.43(dt, *J*=9.6Hz, 2.4Hz, 1H), 5.81(dt, *J*=10Hz, 3.6Hz, 1H), 6.14(dd, *J*=17.2Hz, 10.4Hz, 1H), 7.16-7.28(m, 5H); ^{13}C NMR δ -0.53, -5.15, 0.14, 22.92, 26.22, 28.90, 37.39, 43.38, 60.60, 95.61, 114.31, 125.96, 128.12, 130.77, 131.99, 142.65; IR(neat) 3388(s), 2929(m), 1471(w), 1255(m), 1078(s), 1003(m), 836(s), 777(m), 702(w); HRMS M+ calculated=372.2482, found=372.2483



cis-

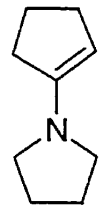


trans-

[2-Benzyloxy-1-(2-*t*-butyldimethylsiloxy-ethyl)-2-vinyl-cyclohex-3-enylmethyl]-benzene (36)

A solution of triene **32** (100mg, 0,204mmol) in dichloromethane (10ml) is added **1** (16mg, 0.02mmol). The solution is stirred for 12hours at room temperature at which time the reaction is opened to air and the solvent removed in vacuo. A crude ^{1}H NMR showed a 4.5:1 mixture of diastereomers, favouring the *cis*-diastereomer. Unable to separate the diastereomers by flash chromatography, the diastereomeric alcohols **35** were reacted under the general benzylation procedure to yield the title compounds as colourless oils.

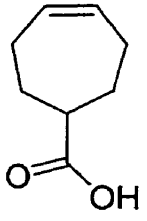
cis- and *trans*- mixture: IR(neat) 2927(m), 1495(w), 1254(m), 1067(s), 929(w), 835(m), 774(w), 731(w), 701(m). ^{1}H NMR(400 MHz, $CDCl_3$) δ -0.11(s, 6H), 0.77(s, 9H), 1.32-1.45(m, 2H), 1.75-1.85(m, 3H), 2.08-2.23(m, 2H), 2.54(d, *J*=13.6Hz, 1H), 2.71(d, *J*=13.6Hz, 1H), 3.35-3.46(m, 1H), 3.62-3.69(m, 1H), 4.38(d, *J*=11.6Hz, 1H), 4.46(d, *J*=11.6Hz, 1H), 5.23(dd, *J*=17.6Hz, 1.6Hz, 1H), 5.79(dt, *J*=10.4Hz, 2Hz, 1H), 6.00(dt, *J*=10.4Hz, 3.6Hz, 1H), 6.05(dd, *J*=17.8Hz, 11.2Hz, 1H), 7.14-7.28(m, 10H). ^{13}C NMR(100MHz, $CDCl_3$) δ -5.08, 18.43, 23.47, 25.47, 26.15, 36.98, 40.12, 43.53, 61.19, 64.88, 118.69, 125.99, 126.95, 126.99, 127.18, 127.98, 128.24, 131.09, 131.18, 139.41, 140.21, 140.79.



1-N-pyrrolidylcyclopentene

In a 500ml flask equipped with a Dean Stark water separator is added cyclopentanone (52.57ml, 0.59mol), pyrrolidine (69.24ml, 0.83mol), benzene (200ml), and *p*-toluenesulfonic acid (200mg). The mixture is refluxed under argon for 3hrs at which point the calculated amount of water (10ml) has been removed from the reaction flask. Benzene and excess pyrrolidine are distilled off at atmospheric pressure. Distillation at reduced pressure (0.5mmHg/35°C) provides 1-N-pyrrolidylcyclopentene (62g, 76%) as an oil. ^{1}H NMR and ^{13}C NMR are in agreement with literature[14]. ^{1}H NMR(400MHz, $CDCl_3$) δ 1.83-190(m, 6H), 2.36-

2.44(m, 4H), 3.05-3.08(m, 4H), 4.05(s, 1H).; ^{13}C NMR(100MHz, $CDCl_3$) δ 23.06, 25.13, 30.70, 32.89, 48.86, 92.07.

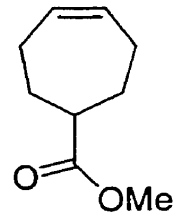


Cyclohept-4-ene carboxylic acid

1-(1-Cyclopenten-1-yl) pyrrolidine (62g, 0.45mol) is dissolved in 120ml of anhydrous Et_2O, cooled to 0°C, and freshly distilled acrolein (30ml, 0.5mol) was added dropwise over 1 hour. The resulting colorless solution was allowed to warm to room temperature and was stirred at room temperature for 36 hours. Evaporation of the solvent at reduced pressure provided a viscous yellow oil. Distillation (0.8mmHg/120-125°C) afforded 46.16g (54%) of the known ketone 2-pyrrolidin-1-yl-bicyclo[3.2.1]octan-8-one[14] as a yellow oil. ^1H NMR(400MHz, $CDCl_3$) δ 1.73-2.50(m, 17H).

The ketone is then dissolved in 200ml of MeOH and methyl iodide (18ml, 0.28mol) is added dropwise under argon. After the addition was complete the reaction mixture was refluxed for 45 minutes and allowed to stir at room temperature overnight. The methanol and excess methyl iodide are evaporated at reduced pressure. 60ml of a 40% aqueous sodium hydroxide solution are added to the residue and the solution is refluxed for 5hrs. The solution is cooled, diluted with water (30ml), washed with ether (60ml), cooled to 0°C, and then acidified with concentrated hydrochloric acid (45ml). The acidified mixture was extracted with

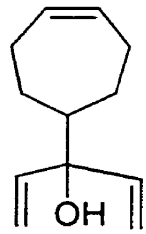
ether (3x60ml). The combined ether extracts were dried over $MgSO_4$, filtered, and concentrated to provide 4-cycloheptene carboxylic acid[14] (24g, 70%) as a yellow/brown solid. ^1H NMR(400MHz, $CDCl_3$) δ 1.62-1.71(m, 2H), 1.97-2.03(m, 2H), 2.06-2.13(m, 2H), 2.27-2.34(m, 2H), 2.57-2.64(m, 1H), 5.76-5.78(m, 2H), 11.16(br s, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 26.73, 29.18, 47.17, 131.78, 182.97.



Cyclohept-4-ene carboxylic acid methyl ester.

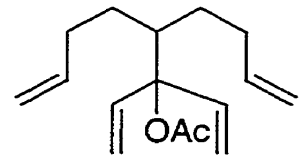
Cyclohept-4-ene carboxylic acid (24g, 0.17mol) is placed in a 200ml round bottom flask and 100ml of MeOH are added. 2ml of concentrated H_2SO_4 are added and the mixture is refluxed for 24 hours. MeOH is then removed by distillation at atmospheric pressure. The residue is then taken up in 200ml Et_2O and washed with $NaHCO_3$ (saturated) solution. The organic layer is then dried over $MgSO_4$, filtered and concentrated. Distillation (4.8mmHg, 84°C) affords methyl 4-cyclohepetene carboxylate (24g, 94%) as a colourless oil. ^1H NMR(400MHz, $CDCl_3$) δ 1.59-1.68(m, 2H), 1.92-1.99(m, 2H), 2.05-2.12(m, 2H), 2.25-2.32(m, 2H), 2.54-2.61(m, 1H), 3.67(s, 3H), 5.75-5.78(m, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 26.82, 29.43, 47.38, 51.62, 131.80, 176.69. ; IR(neat) 3022(s), 2938(s), 1733(s),

1375(m), 1306(m), 1207(s), 1169(s), 1001(m), 948(m), 887(w), 693(m). ; HRMS M+ calculated= 154.0993, found= 154.0994.



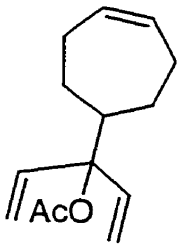
3-Cyclohept-4-enyl-penta-1,4-dien-3-ol (43)

Methyl 4-cycloheptene carboxylate (5.16g, 33.50mmol) was reacted according to the general procedure for the formation of a tertiary diallylic alcohol. Purification by flash chromatography (5%Et_2O/hexanes) on triethyl amine washed silica gel yields the title compound as a colourless oil (5.3g, 90%). ^1H NMR(400MHz, $CDCl_3$) δ 1.05-1.15(m, 2H), 1.57-1.65(m, 2H), 1.89-2.01(m, 4H), 2.24-2.31(m, 2H), 5.16(dd, *J*=10.6Hz, 1.2Hz, 2H), 5.26(dd, *J*=17.4Hz, 1.2Hz, 2H), 5.74-5.77(m, 2H), 5.96(dd, *J*=17.4Hz, 10.4Hz, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 27.79, 27.93, 51.70, 78.94, 113.76, 131.87, 142.13. ; IR(neat) 3470(s), 3022(s), 2926(s), 1850(w), 1700(m), 1634(m), 1443(m), 1407(m), 1319(w), 1103(w), 997(s), 920(s), 847(w), 690(s). ; HRMS M+ calculated=178.1357, found=178.1353.



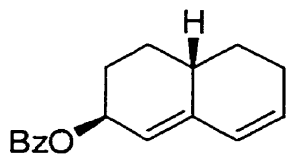
Acetic acid 2-but-3-enyl-1,1-divinyl-hex-5-enyl ester (48)

KH (35% dispersion in mineral oil) is washed three times with pentane and dried under a flow of argon. The hydride is then suspended in 5ml of THF and a solution of 2-buten-3-enyl-1-vinyl-octa-1,7-dien-3-ol[8] (500mg, 2.42mmol) in 10ml THF is slowly added via cannula. The reaction is stirred for 10 minutes at room temperature until all bubbling has subsided. Acetic anhydride (500µl, 5.00mmol) is then added via syringe. The solution is stirred at room temperature for 12 hours. The reaction is diluted with water (20ml), and extracted with ether (three times). The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated to provide a dark red oil. Flash chromatography on triethyl amine treated silica gel (5% Et_2O/hexanes) yields 360mg (60%) of the acetate as a colourless oil. ^1H NMR(400MHz, $CDCl_3$) δ 1.16-1.25(m, 3H), 1.55-1.64(m, 2H), 2.01-2.15(m, 4H), 2.03(s, 3H), 4.93-4.98(m, 4H), 5.01-5.03(m, 4H), 5.24(dd, *J*=16Hz, 1.2Hz, 2H), 5.27(dd, *J*=9.8Hz, 1.2Hz, 2H), 5.73-5.83(m, 2H), 6.07(dd, *J*=17.4Hz, 10.8Hz, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 22.21, 30.23, 33.17, 44.60, 87.13, 114.71, 116.34, 137.80, 138.88, 169.25. ; IR(neat) 3069(m), 2930(s), 2367(s), 2341(s), 1738(s), 1638(s), 1364(s), 1244(s), 1087(m), 1002(s), 914(s), 732(m).



Acetic acid 1-cyclohept-4-enyl-1-vinyl-allyl ester (49)

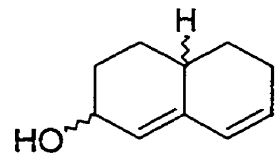
To a solution of acetate **48** (100mg, 0.40mmol) in 10ml of dichloromethane is added Grubbs catalyst **1**. The solution is stirred under an atmosphere of ethylene (attach a balloon of ethylene to the flask) for 24 hours at room temperature. A quantitative conversion to the cycloheptene product is the result. The same result is obtained under reflux, under an argon atmosphere, or utilizing **2** as the catalyst. ^{1}H NMR(400MHz, $CDCl_3$) δ 1.04-1.13(m, 2H), 1.81-1.86(m, 2H), 1.96-2.05(m, 2H), 2.04(s, 3H), 2.22-2.34(m, 3H), 5.23(dd, *J*=13.6Hz, 1.2Hz, 2H), 5.27(dd, *J*=7.2Hz, 1.2Hz, 2H), 5.74-5.76(m, 2H), 6.08(dd, *J*=17.6Hz, 11.2Hz, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 22.14, 27.88, 27.97, 49.85, 86.93, 116.25, 131.81, 137.84, 169.31. ; IR(neat) 3091(m), 2923(s), 1733(s), 1638(m), 1436(m), 1363(s), 1245(s), 1001(s), 918(s), 845(w), 735(m), 693(m), 620(w). ; HRMS M+ calculated= 220.1463, found= 220.1455.



Benzoic acid 2,3,4,4a,5,6-hexahydro-napthalen-2-yl ester (57)

KH (35% dispersion in mineral oil, 226mg, 1.98mmol) is washed three times with pentane and dried under a flow of argon. The hydride is then suspended in 5ml of

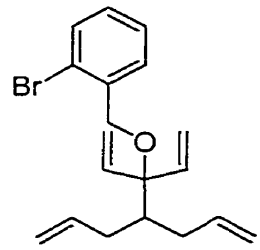
THF and a solution of *cis*-2,7,8,8a-tetrahydro-*1H*-naphthalen-4-ol[8] (100mg, 0.66mmol) in 5ml THF is slowly added via cannula. The reaction is stirred for 10 minutes at room temperature until all bubbling has subsided. Benzoyl chloride (120µl, 0.99mmol) is then added via syringe. The solution is stirred at room temperature for 12 hours. The reaction is diluted with water (20ml), and extracted with ether (three times). The combined organic extracts are dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on triethyl amine treated silica gel (5% Et_2O/hexanes) yields 134mg (80%) of the benzoate as a colourless oil. The stereochemistry of the compound was determined by hydrolysis and comparison of the spectral data to known secondary alcohol.[39] ^{1}H NMR (400MHz, $CDCl_3$) δ 1.26-1.48(m, 2H), 1.68-1.95(m, 3H), 2.14-2.32(m, 4H), 5.48(s, 1H), 5.70(m, 1H), 5.85-5.86(m, 1H), 6.04(d, *J*=10Hz, 1H), 7.43(t, *J*=7.6Hz, 2H), 7.54(m, 1H), 8.04-8.06(m, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 26.14, 28.19, 29.09, 30.23, 35.50, 71.96, 122.09, 128.40, 128.51, 129.72, 130.79, 130.83, 132.92, 141.27, 166.56. ; IR(neat) 3503(w), 2938(s), 1965(w), 1908(w), 1714(s), 1600(w), 1447(m), 1258(s), 1104(s), 952(w), 708(s), 739(s). ; HRMS M+ calculated= 254.1306 , found= 254.1304.



2,3,4,4a,5,6-hexahydro-napthalen-2-ol (56)

In a 25 ml round bottom flask, equipped with a stir bar and condenser, is added acetate **49** and dichloromethane (100ml). To the solution is added catalyst **3** and

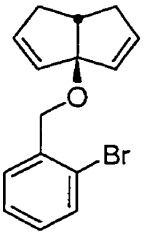
the solution is refluxed for two hours. Complete consumption of the starting material is observed by TLC analysis. The solvent is removed on the rotovap. And the residue is redissolved in 1M KOH in MeOH (10ml). The solution is stirred at room temperature for 12 hours and then diluted with water and extracted with CH_2Cl_2 (three times). The organic layers are dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (30% Et_2O/hexanes) provides a 1:1.6 mixture of the known diastereomeric secondary alocohols.[39] The same result is observed when catalyst **1** is used in the presence of 1 equivalent of $Ti(O^iPr)_4$ at reflux in dichloromethane: Acetate **49** (40mg, 0.16mmol) and $Ti(O^iPr)_4$ (47 µl, 0.16mmol) are dissolved in CH_2Cl_2 (10ml). The mixture is refluxed for 1 hour. Grubbs catalyst **1** (13mg, 0.02mmol) is added and the solution is then refluxed for an additional 20 hours. The solution is then cooled to room temperature, the solvent is removed and the mixture is hydrolyzed to the known diastereomeric alcohols.[39]



1-(2-Allyl-1,1-divinyl-pent-4-enyloxymethyl)-2-bromo-benzene (59)

KH (35% dispersion in mineral oil, 1g, 4eq.) was washed three times with pentane, dried under a stream of argon, and suspended in THF (10ml). A solution of alcohol **58** in THF (5ml) was added dropwise via cannula. After 15 minutes at

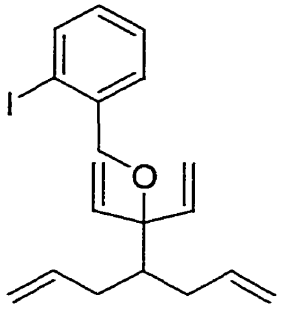
room temperature, 2-bromobenzyl bromide is added all at once and the resulting solution is stirred at room temperature for 2 hrs. The mixture was quenched by drop-wise addition of water (25ml) and then extracted with ether (3x30ml). The organic layers are dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (100% hexanes) on triethyl amine washed silica gel provides the product as a colourless oil (740mg, 95%). ^{1}H NMR(400MHz, $CDCl_3$) δ 1.84-1.90(m, 1H), 1.94-2.02(m, 2H), 2.42-2.48(m, 2H), 4.40(s, 2H), 4.93-5.01(m, 4H), 5.31(dd, *J*=17.6Hz, 0.8Hz, 2H), 5.38(dd, J=11.2Hz, 0.8Hz, 2H), 5.80-5.88(m, 2H), 5.86-5.93(m, 2H), 7.08-7.12(m, 1H), 7.31(t, *J*=7.6Hz, 1H), 7.48(d, *J*=8Hz, 1H), 7.62(d, *J*=8Hz, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 34.56, 48.28, 64.97, 83.98, 115.41, 118.04, 121.89, 127.39, 128.27, 128.44, 132.22, 137.67, 138.78, 139.22. ; IR(neat) 3074(m), 2978(m), 2922(m), 1914(w), 1869(w), 1831(w), 1638(m), 1439(m), 1269(w), 1091(s), 931(s), 910(s), 748(s), 667(w).



3a-(2-Bromo-benzyloxy)-1,3a,6,6a-tetrahydro-pentalene (60)

To a solution of **59** (930mg, 2.67mmol) in 50ml of dichloromethane is added Grubbs catalayst **1** all at once. The reaction is stirred under a closed system for 20 hrs at room temperature. The solvent is removed in *vacuo* and the residue is purified by flash chromatography (100% hexanes→ 5%Et_2O/hexanes) on triethyl

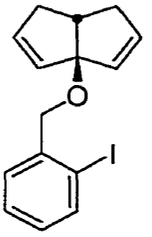
amine washed silica gel to provide the product (530mg, 70%) as a colourless oil. ^{1}H NMR(400MHz, $CDCl_3$) δ 2.08-2.14(m, 2H), 2.84-2.90(m, 3H), 4.46(s, 2H), 5.82-5.84(m, 2H), 5.91-5.94(m, 2H), 7.07-7.11(m, 1H), 7.24-7.30(m, 1H), 7.47-7.53(m, 2H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 40.79, 43.10, 65.13, 106.00, 122.52, 127.43, 128.58, 129.28, 132.35, 132.38, 134.67, 138.97. ; IR(neat) 3047(s), 2918(s), 2851(s), 1619(w), 1467(m), 1350(s), 1218(m), 1097(m), 1070(m), 989(m), 750(s) ; HRMS M+ calculated= 290.0306, found= 290.0301 .



1-(2-Allyl-1,1-divinyl-pent-4-enyloxymethyl)-2-iodo-benzene (62)

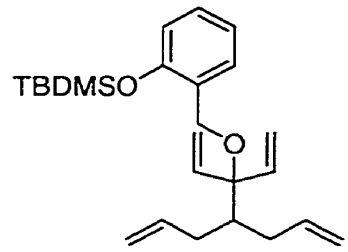
Following the general procedure for the benzylation of tertiary diallylic alcohols, alcohol **58** (1.15g, 6.4mmol) is reacted with 2-iodobenzyl bromide (2.09g, 7.06mmol) to yield the product (2.08g, 83%) as a colourless oil. ^{1}H NMR(400MHz, $CDCl_3$) δ 1.84-1.90(m, 1H), 1.94-2.02(m, 2H), 2.43-2.49(m, 2H), 4.29(s, 2H), 4.94-5.02(m, 4H), 5.31(dd, *J*=17.6Hz, 1.6Hz, 2H), 5.39(dd, *J*=11.2Hz, 1.6Hz, 2H), 5.80-5.89(m, 2H), 5.90(dd, *J*=17.6Hz, 10.8Hz, 2H), 6.96(t, *J*=8Hz, 1H), 7.36(t, *J*=8Hz, 1H), 7.57(d, *J*=7.6Hz, 1H), 7.77(d, *J*=7.6Hz, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 34.56, 48.26, 69.69, 83.99, 96.91, 115.43, 118.08, 128.23, 128.61, 137.63, 138.78, 138.84, 141.95. ; IR(neat) 3073(m), 2911(m), 1952(w), 1908(w),

1864(w), 1627(s), 1440(s), 1085(s), 1012(s), 906(s), 752(s). ; HRMS M+ calculated= 393.0715, found= 393.0703.



3a-(2-Iodo-benzyloxy)-1,3a,6,6a-tetrahydro-pentalene (63)

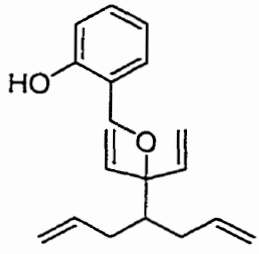
Following the procedure for RCM of tetraene **59**, iodobenzyl ether **62** (2.00g, 5.08mmol) was reacted with Grubbs catalyst **1** (250mg, 6mol%) to provide the product (1.18g, 70%) as a colourless oil after flash chromatography (5%Et_2O/hexanes) on triethyl amine washed silica gel. ^1H NMR(400MHz, $CDCl_3$) δ 2.07-2.15(m, 2H), 2.84-2.91(m, 3H), 4.38(s, 2H), 5.84(dt, *J*=6Hz, 1.6Hz, 2H), 5.92-5.94(m, 2H), 6.92-6.96(m, 1H), 7.30-7.34(m, 1H), 7.47-7.49(m, 1H), 7.76-7.87(m, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 40.80, 43.21, 69.81, 97.70, 106.00, 128.30, 128.90, 128.99, 132.41, 134.71, 139.01, 141.80. ; IR(neat) 3060(s), 2912(s), 1444(m), 1350(s), 1215(m), 1097(m), 1077(s), 1009(s), 942(w), 747(s). ; HRMS M+ calculated=338.0149, found=338.0167.



1-(2-Allyl-1,1-divinyl-pent-4-enyloxymethyl)-2-(*t*-butyldimethylsiloxy)-benzene (64)

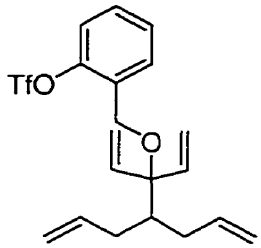
KH (35% dispersion in mineral oil, 1g, 3eq.) is washed three times with pentane, dried under a stream of argon, and suspended in 10ml of THF. Alcohol **58** in 5ml of THF is added via cannula. The solution is heated to reflux for 10 min., cooled to room temperature, and a solution of 2-(*tert*-butyldimethylsilyloxy)benzyl bromide[38] in 5ml of THF is added via cannula. The solution is stirred at reflux for 3 hrs. , cooled to room temperature, quenched by drop-wise addition of water (25ml), extracted with ether (3x30ml), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (100% hexanes) on triethyl amine washed silica gel provides the product (939mg, 85%) as a colourless oil. ^{1}H NMR(400MHz, $CDCl_3$) δ 0.18(s, 6H), 0.97(s, 9H), 1.93-2.01(m 2H), 2.44-2.51(m, 2H), 4.40(s, 2H), 4.94-5.02(m, 4H), 5.29(dd, *J*=17.8Hz, 1.6Hz, 2H), 5.35(dd, *J*=10.8Hz, 1.6Hz, 2H), 5.82-5.92(m, 4H), 6.74(dd, *J*=8Hz, 0.8Hz, 1H), 6.98(td, *J*=7.6Hz, 0.8Hz, 1H), 7.11(td, *J*=7.6Hz, 0.8Hz, 1H), 7.55-7.57(m, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ -4.11, 18.30, 34.57, 48.21, 61.07, 83.69, 115.287, 117.72, 118.03, 121.20, 127.25, 127.46, 131.46, 131.09, 137.91, 138.96, 152.21. ; IR(neat) 3088(s), 2919(s), 2855(s), 1634(m), 1579(m), 1491(s), 1250(s),

1070(m), 913(s), 832(s), 730(m). ; HRMS $(M-C_4H_9)+$ calculated=341.1936, found= 341.1934.



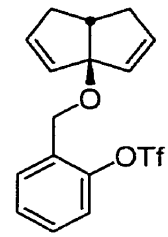
2-(2-Allyl-1,1-divinyl-pent-4-enyloxymethyl)-phenol

In a 10ml round bottom flask is added **64** (300mg, 0.75mmol) and 3ml of THF. To this solution is added TBAF all at once at room temperature and the reaction mixture is stirred at room temperature for 30 minutes. The reaction is diluted with water (10ml) and extracted with ether (3x10ml). The combined organic layers are dried over Na_2SO_4, filtered, and concentrated. The residue is then used in the next reaction without further purification. ^1H NMR(400MHz, $CDCl_3$) δ 1.82-1.87(m, 1H), 1.91-1.99(m, 2H), 2.32-2.39(m, 2H), 4.55(s, 2H), 4.95-5.02(m, 4H), 5.31-5.44(m, 4H), 5.75-5.91(m, 4H), 6.78-6.93(m, 3H), 7.14-7.18(m, 1H), 7.75(br s, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 34.42, 47.79, 65.69, 85.33, 115.92, 116.68, 118.77, 119.82, 123.56, 127.70, 128.98, 136.83, 138.01, 156.33 ; IR(neat) 3386(s), 3075(m), 2923(m), 1826(w), 1638(m), 1491(m), 1241(s), 1026(m), 912(s), 753(s) ; HRMS M+ calculated= 284.1776, found= 284.1780.



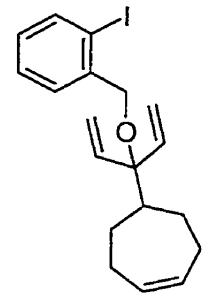
Trifluoro-methansulfonic acid 2-(2-allyl-1,1-divinyl-pent-4-enyloxy methyl)-phenyl ester

In a 10ml round bottom flask is added 2-(2-allyl-1,1-divinyl-pent-4-enyloxymethyl)-phenol (215mg, 0.75mmol) , CH_2Cl_2 (5ml), and Et_3N (440µl, 4 eq.). The solution is then cooled to –78°C and Tf_2O (254µl, 2 eq.) is added drop-wise via syringe. The reaction mixture is stirred at –78°C for 15 minutes at which point water (5ml) is added. The flask is warmed to room temperature, extracted with ether (3x15ml), the organic extracts are dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (2%Et_2O/hexanes) on treithyl amine washed silica gel provides the product as a colourless oil (240mg, 81%). ^1H NMR(400MHz, $CDCl_3$) δ 1.83-189(m, 1H), 1.92-1.99(m, 2H), 2.39-2.45(m, 2H), 4.46(s, 2H), 4.93-5.00(m, 4H), 5.3(dd, *J*=17.6Hz, 1.6Hz, 2H), 5.40(dd, *J*=11.2Hz, 1.2Hz, 2H), 5.78-5.86(m, 2H), 5.87(dd, *J*=17.6Hz, 11.2Hz, 2H), 7.23-7.25(m, 1H), 7.32(td, *J*=8.2Hz, 2Hz, 1H), 7.38(td, *J*=7.6Hz, 1.2Hz, 1H), 7.68(dd, *J*=7.6Hz, 0.8Hz, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 34.48, 48.24, 59.77, 84.27, 115.43, 118.33, 118.72(q, J=319.2Hz), 120.31, 121.00, 128.47, 128.70, 129.77, 132.97, 137.32, 138.66, 146.89. ; IR(neat) 3074(s), 2903(m), 1918(w), 1863(w), 1634(m), 1487(m), 1413(s), 1210(s), 1099(s), 1066(s), 996(s), 896(s), 764(s), 605(m). ; HRMS (M-C_2H_3)+ calculated= 389.1023, found= 389.1034.



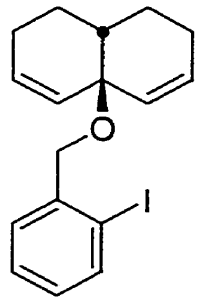
Trifluoro-methanesulfonic acid 2-(6,6a-dihydro-1H-pentalen-3a-yloxymethyl)-phenyl ester (65)

In a 25ml round bottom flask is added Trifluoro-methansulfonic acid 2-(2-allyl-1,1-divinyl-pent-4-enyloxy methyl)-phenyl ester (230mg, 0.58mmol) and 10ml of CH_2Cl_2. To this is added catalyst **3** (24mg, 5mol.%). The solution is stirred under a closed atmosphere at room temperature for 12 hrs. The solvent is removed on the rotary evaporator to provide the crude product which was purified by flash chromatography(100%hexanes→5% Et_2O/hexanes) on triethyl amine washed silica gel. The yield of the product is 150 mg (75%). ^1H NMR(400MHz, $CDCl_3$) δ 1.83-1.89(m, 1H), 1.92-1.99(m, 2H), 2.39-2.45(m, 2H), 4.46(s, 2H), 4.93-5.00(m, 4H), 5.30(dd, *J*=17.6Hz, 1.6Hz, 2H), 5.40(dd, *J*=11.2Hz, 1.2Hz, 2H), 5.78-5.86(m, 2H), 5.87(dd, *J*=17.6Hz, 11.2Hz, 2H), 7.23-7.25(m, 1H), 7.32(td, *J*=8.2Hz, 2Hz, 1H), 7.38(td, *J*=7.6Hz, 1.2Hz, 1H), 7.68(dd, *J*=7.6Hz, 0.8Hz, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 34.48, 48.24, 59.77, 84.27, 115.43, 118.33, 118.72(q, J=319.2Hz), 120.47, 128.70, 129.77, 132.97, 137.32, 138.66, 146.89. ; IR(neat) 3053(m), 2923(m), 2849(m), 1968(w), 1487(m), 1419(s), 1350(m), 1214(s), 1142(s), 1059(m), 992(m), 895(s), 764(m), 707(m), 597(m).



5-[1-(2-Iodo-benzyloxy)-1-vinyl-allyl]-cycloheptene (66)

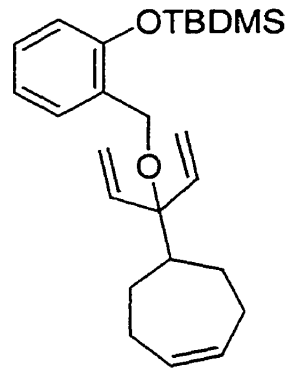
Following the procedure for the general procedure for the benzylation of tertiary diallylic alcohols, alcohol **43** (1.15g, 6.4mmol) is reacted with 2-iodobenzyl bromide (2.09g, 7.06mmol) to yield the product (2.08g, 83%) as a colourless oil. ^{1}H NMR(400MHz, $CDCl_3$) δ 1.04-1.71(m, 2H), 1.82(tt, J=10.8Hz, 2.4Hz, 1H), 1.98-2.07(m, 4H), 2.25-2.32(m, 2H), 4.29(s, 2H), 5.82(dd, *J*=17.8Hz, 1.6Hz, 2H), 5.36(dd, *J*=11.2Hz, 1.6Hz, 2H), 5.77-5.79(m, 2H), 5.87(dd, *J*=17.6Hz, 11.2Hz, 2H), 6.93-6.97(m, 1H), 7.32-7.38(m, 1H), 7.56-7.58(m, 1H), 7.76-7.78(m, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 28.15, 28.18, 69.56, 83.95, 96.97, 117.74, 128.18, 128.23, 128.59, 132.04, 137.88, 138.83, 142.09. ; IR(neat) 3014(m), 2919(s), 1948(w), 1912(w), 1864(w), 1791(w), 1641(w), 1436(s), 1202(m), 1107(s), 928(s), 748(s), 748(s), 690(s). ; HRMS M+ calculated= 394.0792 , found= 394.0793 .



4a-(2-Iodo-benzyloxy)-1,2,4a,7,8,8a-hexahydro-napthalene (67)

In a 100ml round bottom flask is added 5-[1-(2-Iodo-benzyloxy)-1-vinyl-allyl]-cycloheptene (850mg, 2.15mmol) and 50ml of CH_2Cl_2 under nitrogen. To this solution is added ruthenium catalyst **3** (35mg, 0.04mmol) and the solution is refluxed for 1hour at which time all of the starting material has been consumed. ^1H NMR analysis shows a 4.5:1 mixture of diastereomers [integration of signals at 5.89ppm (multiplet corresponding to all of the olefinic protons of the trans decalin plus half of the olefin protons of the cis decalin product) and 5.63ppm(half of the olefin protons of the cis decalin)]. Silica gel (~200mg) is added to the CH_2Cl_2 solution and stirred at room temperature for 15 minutes. The solution is filtered and the silica gel is washed with a copious amount of CH_2Cl_2. The solvent is removed *in vacuo* and the residue is purified by flash chromatography (2% Et_2O/hexanes) to provide 520mg (65%) of the *cis*-bicyclo-[4.4.0]decadiene as a clear oil. ^1H NMR(400MHz, $CDCl_3$) δ 1.51-1.59(m, 2H), 1.83-1.90(m, 2H), 2.01-2.14(m, 4H), 2.17-2.23(m, 1H), 4.42(s, 2H), 5.63(dt, *J*=9.9Hz, 2.1Hz, 2H), 5.89(dt, *J*=9,9Hz, 3.6Hz, 2H), 6.93(t, *J*=7.6Hz, 1H), 7.32(t, *J*=7.6Hz, 1H), 7.52(d, *J*=8Hz, 1H), 7.76(d, *J*=8Hz, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 23.46, 24.51, 34.58, 68.79, 74.68, 97.70, 128.31, 128.81, 129.07, 129.93, 130.29, 138.92, 142.09. ; IR(neat) 3011(m), 2922(s), 1952(w), 1911(w), 1826(w), 1871(w), 1650(w),

1562(m), 1434(s), 1371(m), 1265(m), 1202(m), 1110(m), 1066(s), 945(m), 747(s), 647(m). ; HRMS M+ calculated=366.0480, found=366.0483.

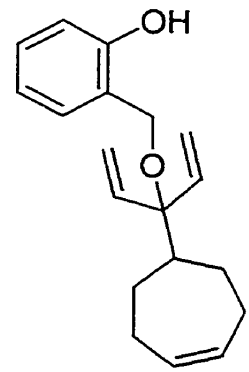


***tert*-Butyl-[2-(1-cyclohept-4-enyl-1-vinyl-allyloxymethyl)-phenoxy]-dimethyl-silane (70)**

KH (35% dispersion in mineral oil, 1g, 3eq.) is washed three times with pentane, dried under a stream of argon, and suspended in 10ml of THF. Alcohol **43** in 5ml of THF is added via cannula. The solution is heated to reflux for 10 min., cooled to room temperature, and a solution of 2-(*tert*-butyldimethylsilyloxy)benzyl bromide[40] in 5ml of THF is added via cannula. The solution is stirred at reflux for 3 hrs. , cooled to room temperature, quenched by drop-wise addition of water (25ml), extracted with ether (3x30ml), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (100% hexanes) on triethyl amine washed silica gel provides the product (939mg, 85%) as a colourless oil.

^{1}H NMR(400MHz, $CDCl_3$) δ 0.18(s, 6H), 0.97(s, 9H), 1.04-1.12(m, 2H), 1.80(tt, *J*=10.8Hz, 2.4Hz, 1H), 1.97-2.08(m, 4H), 2.27-2.32(m, 2H), 4.39(s, 2H), 5.26(dd, *J*=17.6Hz, 1.6Hz, 2H), 5.33(dd, *J*=10.8Hz, 1.6Hz, 2H), 5.77-5.79(m, 2H), 5.84(dd, *J*=17.6Hz, 11.2Hz, 2H), 6.73-6.75(m, 1H), 6.96-7.00(m, 1H), 7.09-7.13(m, 1H),

7.54-7.56(m, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ -4.10, 18.31, 25.85, 28.19, 52.99, 60.92, 83.65, 117.41, 118.09, 121.23, 127.27, 127.48, 131.23, 132.12, 138.18, 152.29. ; IR(neat) 2929(s), 1858(w), 1602(m), 1584(m), 1489(s), 1378(m), 1252(s), 1114(m), 924(s), 838(s), 758(m), 692(m).

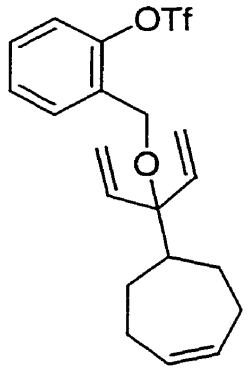


2-(1-Cyclohept-4-enyl-1-vinyl-allyloxymethyl)-phenol

In a 10ml round bottom flask is added **70** (300mg, 0.75mmol) and 3ml of THF. To this solution is added TBAF all at once at room temperature and the reaction mixture is stirred at room temperature for 10 minutes. The reaction is diluted with water (10ml) and extracted with ether (3x10ml). The combined organic layers are dried over Na_2SO_4, filtered, and concentrated. The residue is then used in the next reaction without further purification.

^1H NMR(400MHz, $CDCl_3$) δ 1.06-1.15(m, 2H), 1.82(tt, *J*=10.4Hz, 2.4Hz, 1H), 1.92-2.03(m, 4H), 2.26-2.32(m, 2H), 4.59(s, 2H), 5.32(d, *J*=17.6Hz, 2H), 5.42(d, *J*=10.8Hz, 2H), 5.75-5.77(m, 2H), 5.85(dd, *J*=17.8Hz, 11.2Hz, 2H), 6.80-6.95(m, 3H), 7.16-7.20(m, 1H), 8.01(br s, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 27.98, 28.07, 52.11, 65.74, 85.16, 116.64, 118.60, 119.80, 123.37, 127.60, 128.92, 131.74, 136.92, 156.37. ; IR(neat) 3362(s), 3017(m), 2930(m), 1930(w), 1861(w),

1590(m), 1244(s), 1024(s), 845(w), 754(s), 692(w). ; HRMS M+ calculated= 284.1776, found= 284.1778.

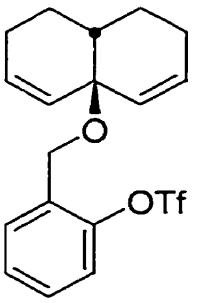


Triflouro-methanesulfonic acid 2-(1-cyclohept-4-enyl-1-vinyl-allyloxymethyl)-phenyl ester

In a 10ml round bottom flask is added 2-(1-cyclohept-4-enyl-1-vinyl-allyloxymethyl)-phenol (215mg, 0.75mmol) , CH_2Cl_2 (5ml), and Et_3N (440µl, 4 eq.). The solution is then cooled to –78°C and Tf_2O (254µl, 2 eq.) is added drop-wise via syringe. The reaction mixture is stirred at –78°C for 15 minutes at which point water (5ml) is added. The flask is warmed to room temperature, extracted with ether (3x15ml), the organic extracts are dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (2%Et_2O/hexanes) on treithyl amine washed silica gel provides the product as a colourless oil (240mg, 81%).

^{1}H NMR(400MHz, $CDCl_3$) δ 1.02-1.10(m, 2H), 1.77-1.83(m, 1H), 1.96-2.03(m, 4H), 2.23-2.30(m, 2H), 4.46(s, 2H), 5.24-5.29(m, 2H), 5.36-5.39(m, 2H), 5.75-5.87(m, 2H), 5.83(dd, *J*=17.8Hz, 10.8Hz, 2H), 7.22-7.24(m, 1H), 7.29-7.33(m, 1H), 7.36-7.39(m, 1H), 7.66-7.68(m, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 28.11, 52.86, 59.71, 84.22, 117.96, 118.72(q, J=319.2Hz), 120.99, 128.47, 128.69, 129.78, 131.98,

131.98, 133.10, 137.60, 147.00. ; IR(neat) 3018(w), 2928(w), 1866(w), 1422(s), 1214(s), 1143(s), 1093(m), 1003(w), 894(m), 767(m), 628(w). ; HRMS M+ calculated= 416.1269, found= 416.1280.



Triflouro-methanesulfonic acid 2-(1,7,8,8a-tetrahydro-2*H*-naphthalen-4a-yloxymethyl)-phenol ester (71)

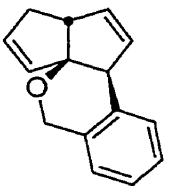
In a 100ml round bottom flask is added triflouro-methanesulfonic acid 2-(1-cyclohept-4-enyl-1-vinyl-allyloxymethyl)-phenyl ester (850mg, 2.15mmol) and 50ml of CH_2Cl_2 under nitrogen. To this solution is added ruthenium catalyst **3** (35mg, 0.04mmol) and the solution is refluxed for 1hour at which time all of the starting material has been consumed. ^1H NMR analysis shows a 4.5:1 mixture of diastereomers [integration of signals at 5.90ppm (multiplet corresponding to all of the olefinic protons of the trans decalin plus half of the olefin protons of the cis decalin product) and 5.59ppm (half of the olefin protons of the cis decalin)]. Silica gel (~200mg) is added to the CH_2Cl_2 solution and stirred at room temperature for 15minutes. The solution is filtered and the silica gel is washed with a copious amount of CH_2Cl_2. The solvent is removed *in vacuo* and the residue is purified by flash chromatography (2% Et_2O/hexanes) to provide 520mg(65%) of the *cis*-bicyclo-[4.4.0]decadiene as a clear oil.

^{1}H NMR(400MHz, $CDCl_3$) δ 1.50-1.59(m, 2H), 1.79-1.87(m, 2H), 2.00-2.20(m, 5H), 4.56(s, 2H), 5.59(dt, *J*=9.6Hz, 2Hz, 2H), 5.90(dt, *J*=10.4Hz, 3.6Hz, 2H), 7.22-7.37(m, 3H), 7.63-7.65(m, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 23.40, 24.39, 34.44, 58.62, 74.97, 118.72(q, J=319.2Hz), 120.95, 128.48, 128.86, 129.59, 130.50, 130.60, 133.09, 147.13. ; IR(neat) 3029(m), 2941(s), 1487(m), 1454(m), 1418(s), 1330(w), 1209(s), 1143(s), 1056(m), 895(s), 763(m), 734(m), 602(m). ; HRMS M+ calculated= 388.0956, found= 388.0962.

General procedure for the asymmetric Heck Reaction using $Pd(OAc)_2$: In a 10ml round bottom flask equipped with a stir bar and reflux condenser is added $Pd(OAc)_2$ (11.5mg, 0.0513mmol), (R) -BINAP (63.88mg, 0.1025mmol), Et_3N (74μl, 0.513mmol), and 2ml of CH_3CN under an argon flush. The mixture is heated to 70°C for 3 hrs and then the aryl halide (0.342mmol) in 1ml of CH_3CN is added via cannula. The reaction is stirred at 70°C for 16hrs. The reaction is cooled to room temperature, diluted with water (5ml) and extracted with ether (3x10ml). The organic layers are combined, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (2.5% Et_2O/hexanes → 5% Et_2O/hexanes) provides the product as an oil.

General procedure for the asymmetric Heck Reaction using Pd_2dba_3: In a 10ml round bottom flask equipped with a stir bar and reflux condenser is added Pd_2dba_3 (8.15mg, 0.0089mmol), (R) –BINAP (12.19mg, 0.01958mmol), and base (0.356mmol) in solvent (1ml) under an argon atmosphere. The solution is stirred

at room temperature for 40 minutes and then a solution of the ary halide (0.178mmol) in 1.5ml of solvent is added via cannula under argon. The reaction is heated to 80°C and stirred at this temperature for 36hrs. The flask is cooled to room temperature, diluted with ether (20ml) and washed with saturated aqueous $NaHCO_3$ (7ml). The aqueous layer was further extracted with Et_2O (2x10ml), and the combined organic extracts were washed with brine (7ml) and dried over Na_2SO_4. Removal of the organic solvent followed by flash chromatography (5-10%Et_2O/hexanes) provides the product as a colourless oil.

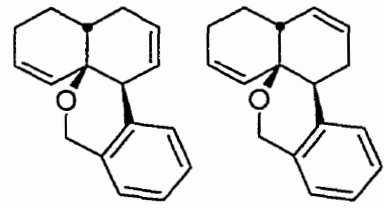


4b,6a,7,11-Tetrahydro-10-oxa-pentaleno[1,6a -a]naphthalene (61)

Following the general procedure for the asymmetric Heck reaction the title compound is obtained as a colorless oil which darkens upon storage at room temperature for prolonged time. Enantiomeric excess of the cyclized product was determined by HPLC analysis : CHIRACEL OD, 10% ^{i}PrOH/hexanes, retention times for the enantiomers=10.9 min., 11.5 min. (V_O= 0.5ml/min, 23°C, UV monitor : 254 nm).

^{1}H NMR(400MHz, $CDCl_3$) δ 2.16(dd, *J*=17.2Hz, 2Hz, 1H), 2.83(ddt, *J*=17.2Hz, 8.8Hz, 2Hz, 1H), 3.48(dt, *J*=8.8Hz, 2Hz, 1H), 3.83(d, *J*=2Hz, 1H), 4.60(d, J=14Hz, 1H), 4.70(d, *J*=14Hz, 1H), 5.66(dt, *J*=6Hz, 1.6Hz, 1H), 5.72(dt, *J*=6.4Hz, 2Hz, 1H), 5.83(dt, *J*=5.6Hz, 2.8Hz, 1H), 5.96(dt, *J*=5.6Hz, 2Hz, 1H), 7.08(d, *J*=7.2Hz, 1H),

7.13(d, *J*=7.2Hz, 1H), 7.18(d, *J*=7.2Hz, 1H), 7.23(d, *J*=7.2Hz, 1H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 36.99, 50.31, 50.46, 64.18, 97.42, 125.13, 125.77, 127.58, 128.06, 132.65, 133.50, 134.14, 134.36, 135.13, 136.10. ; HRMS M+ calculated=210.1042, found= 210.1044.



(68 + 69)

Following the general procedure for the asymmetric Heck reaction the title compounds are obtained as a colorless oils after flash chromatography (2%Et_2O/hexanes → 5% Et_2O/hexanes). Enantiomeric excess of the cyclized products were determined by HPLC analysis : CHIRACEL OD, 10% ^{i}PrOH/hexanes, retention times for the enantiomers: **68**=4.02 min., 4.55 min.; **69**= 4.43 min., 5.60 min. (V_O= 1ml/min, 23°C, UV monitor : 220 nm).

(68) : ^1H NMR(400MHz, $CDCl_3$) δ 1.64-1.87(m, 3H), 2.08-2.65(m, 3H), 2.56-2.63(m, 1H), 3.30(s, 1H), 4.83(d, *J*=15.6Hz, 1H), 4.98(d, *J*=15.6Hz, 1H), 5.50-5.54(m, 1H), 5.66-5.70(m, 2H), 5.90-5.93(m, 1H), 7.01(d, *J*=7.6Hz, 1H), 7.15-7.22(m, 3H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 25.48, 26.16, 28.59, 36.59, 42.07, 62.37, 72.09, 124.12, 124.63, 126.16, 127.02, 127.48, 128.92, 129.18, 129.18, 129.42, 133.9, 136.01. ; HRMS M+ calculated= 238.1357, found= 238.1359.

(69) : ^1H NMR(400MHz, $CDCl_3$) δ 1.41-1.51(m, 1H), 1.89-1.96(m, 1H), 2.03-2.10(m, 2H0, 2.26-2.41(m, 3H), 2.83(t, *J*=6.4Hz, 1H), 5.00(s, 1H), 5.52-5.55(m,

1H), 5.65-5.70(m, 2H), 5.85(dt, *J*=10.4Hz, 3.6Hz, 1H), 7.02-7.04(m, 1H), 7.13-7.21(m, 3H). ; ^{13}C NMR(100MHz, $CDCl_3$) δ 24.48, 27.41, 30.78, 38.92, 39.15, 63.93, 71.89, 124.20, 124.40, 126.20, 126.60, 127.33, 128.63, 129.64, 131.28, 133.91, 138.00. ; HRMS M+ calculated= 238.1357, found= 238.1359.

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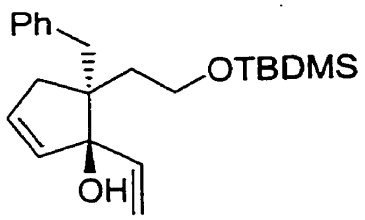
Selected Spectra of Representative Compounds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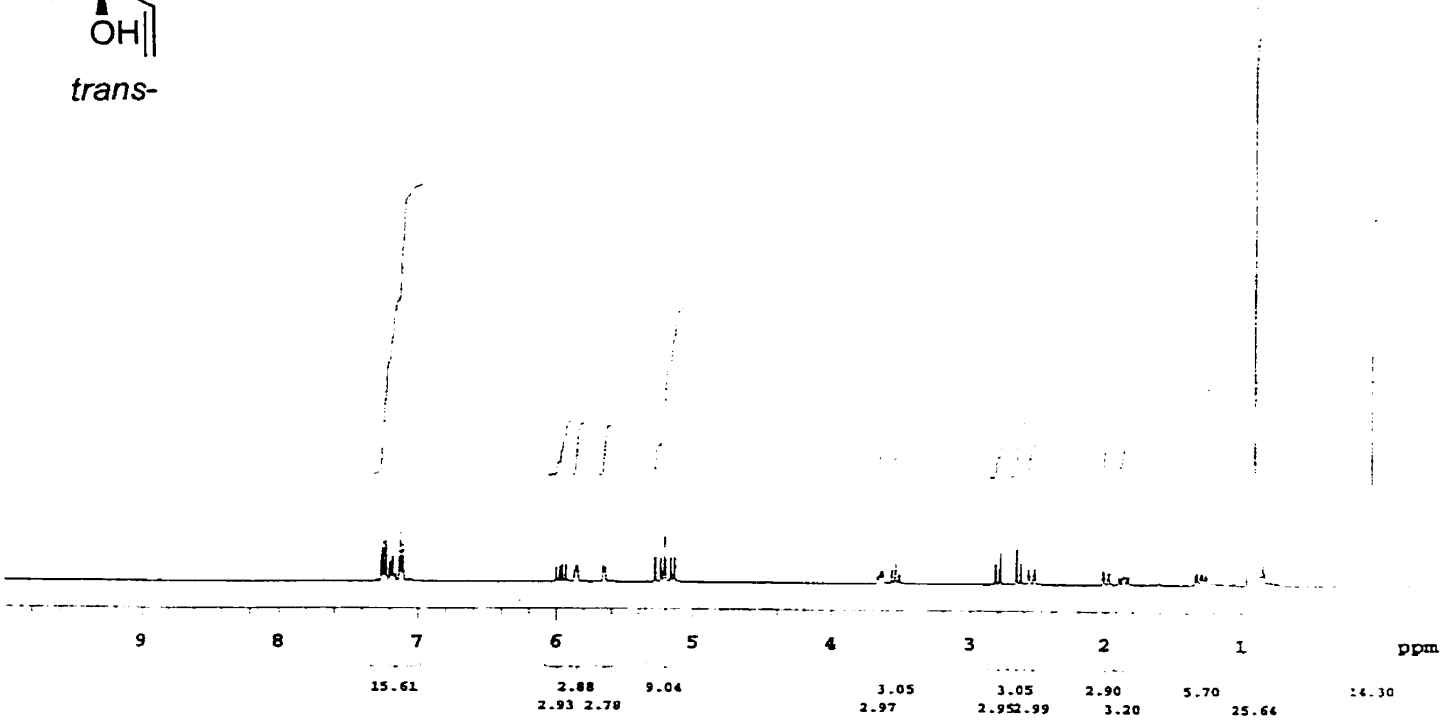
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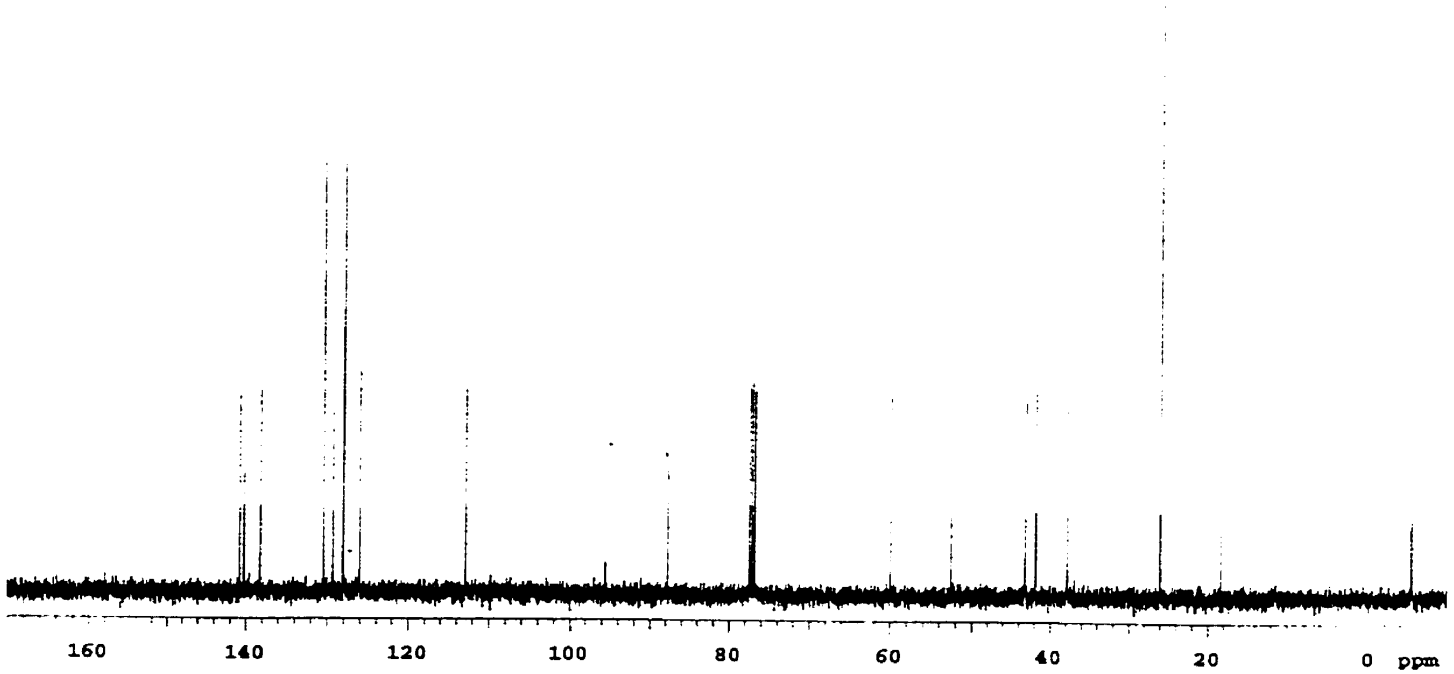
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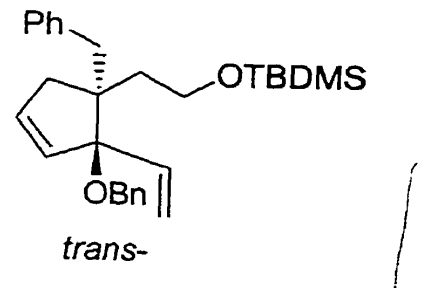
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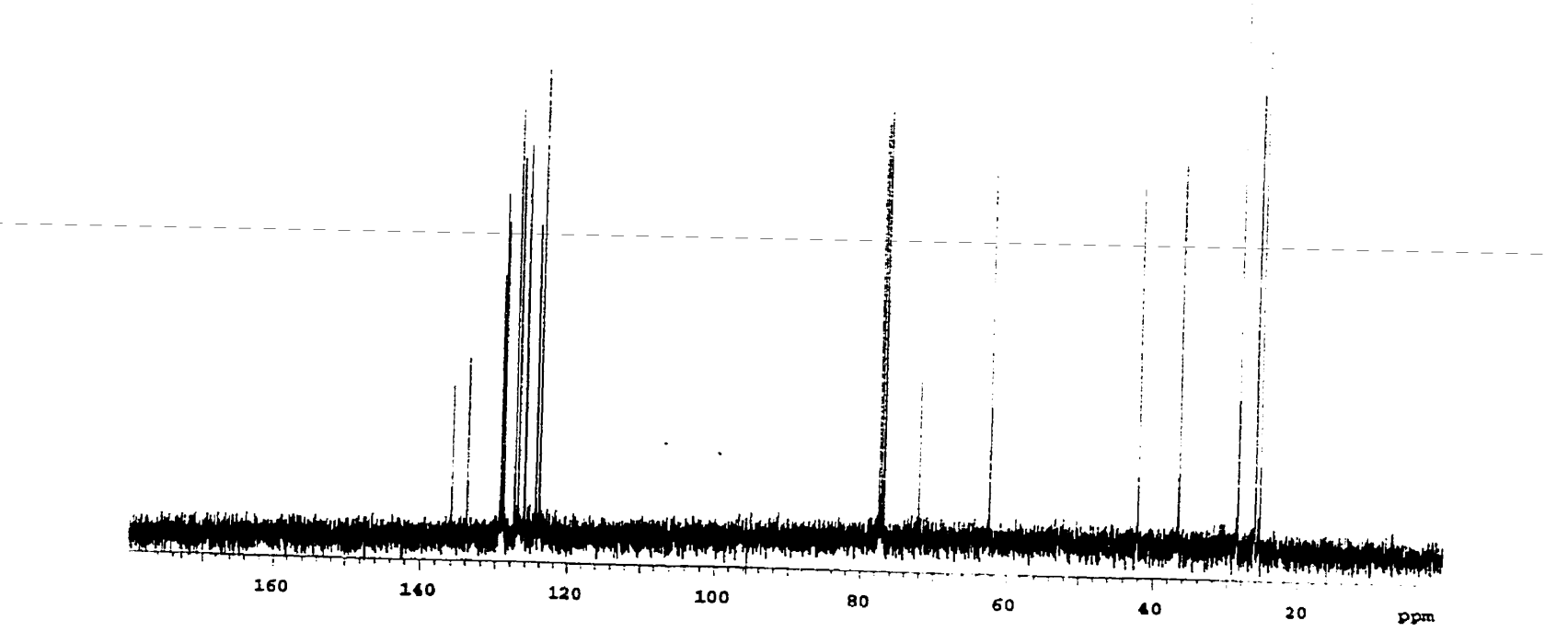
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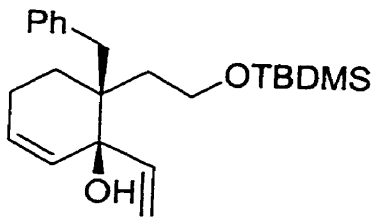
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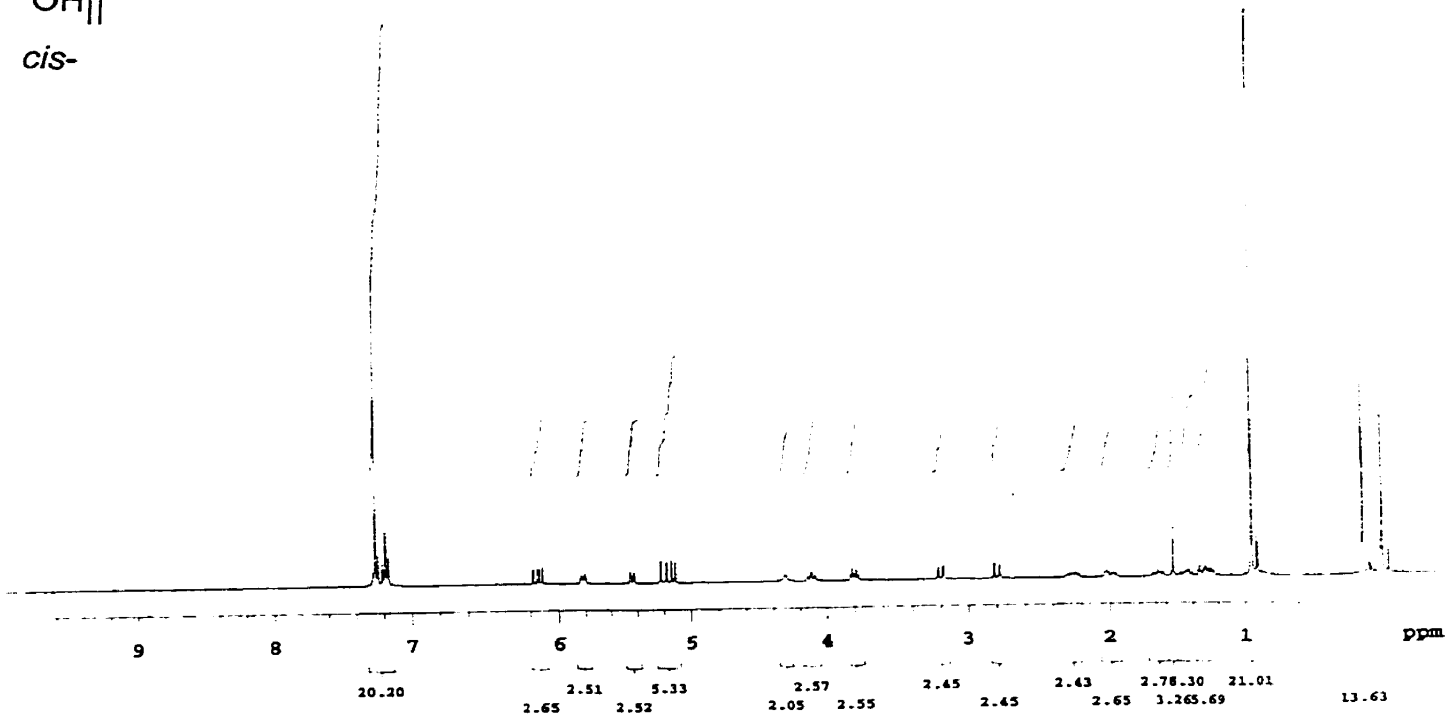
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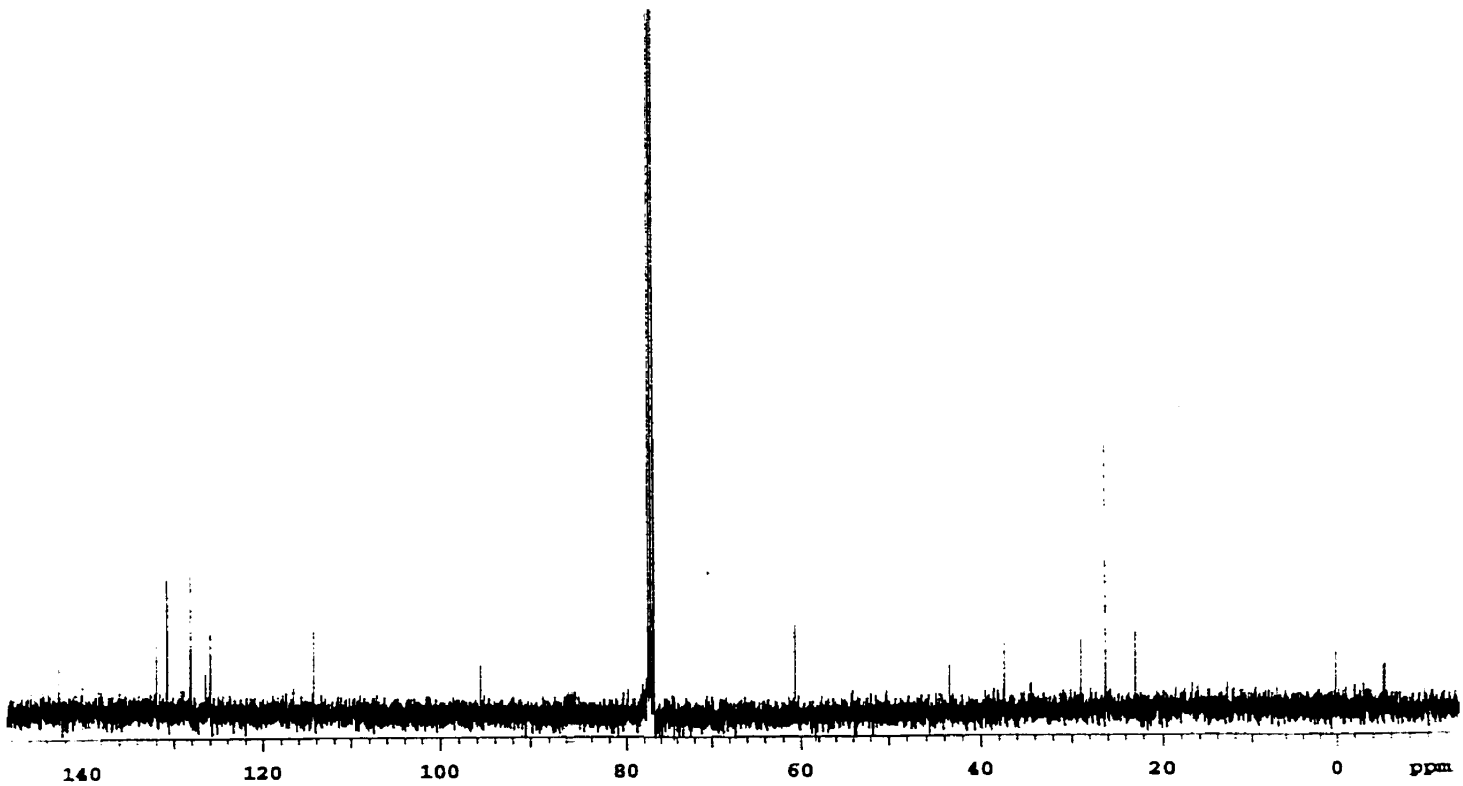
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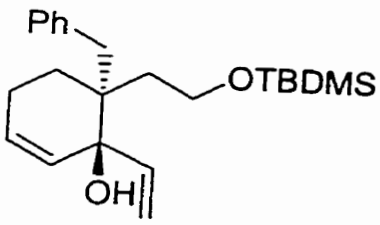
Ph
OTBDMS
OH

trans-

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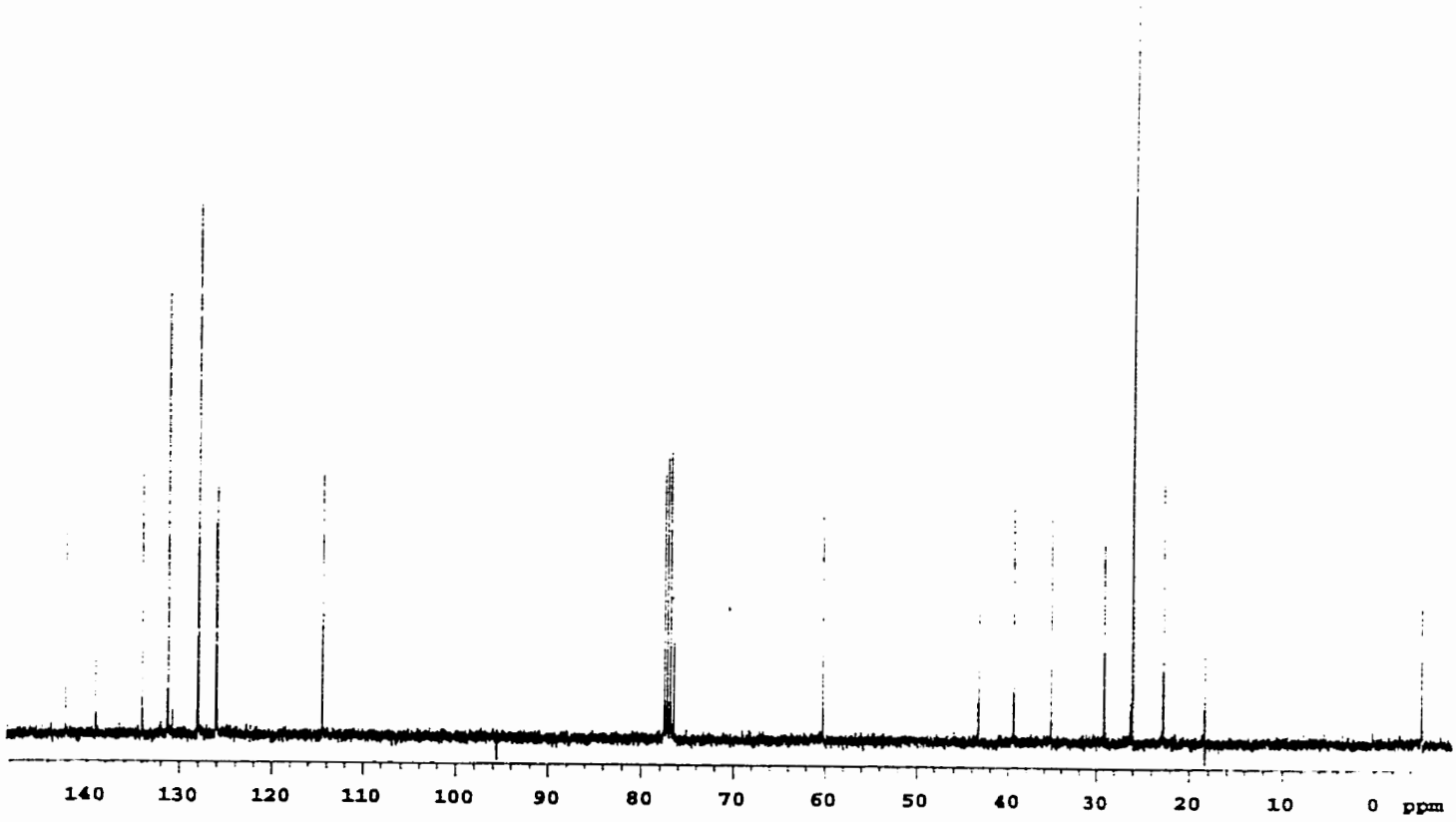
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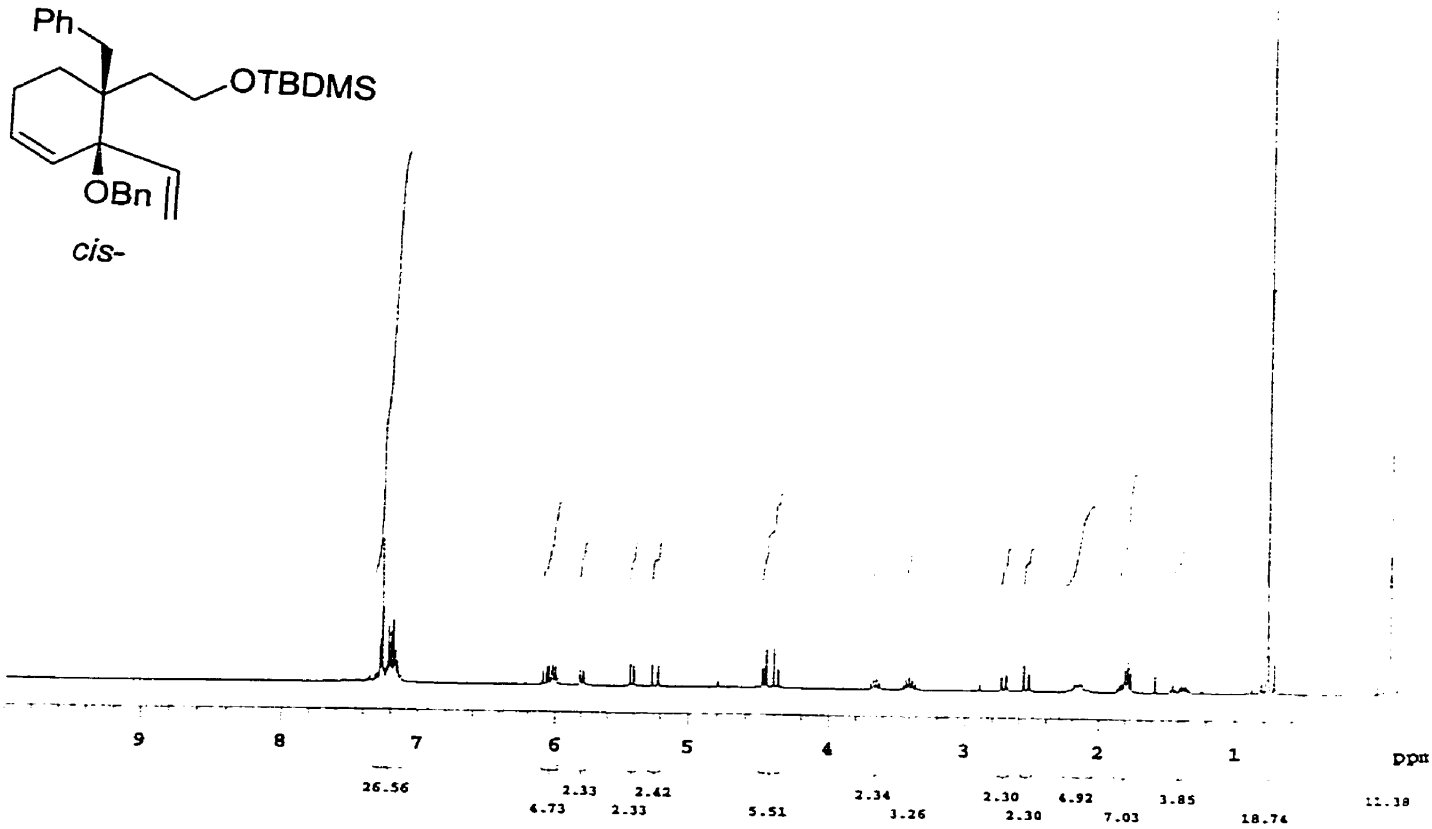
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OTBDMS
OBn
cis-
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5
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6.92
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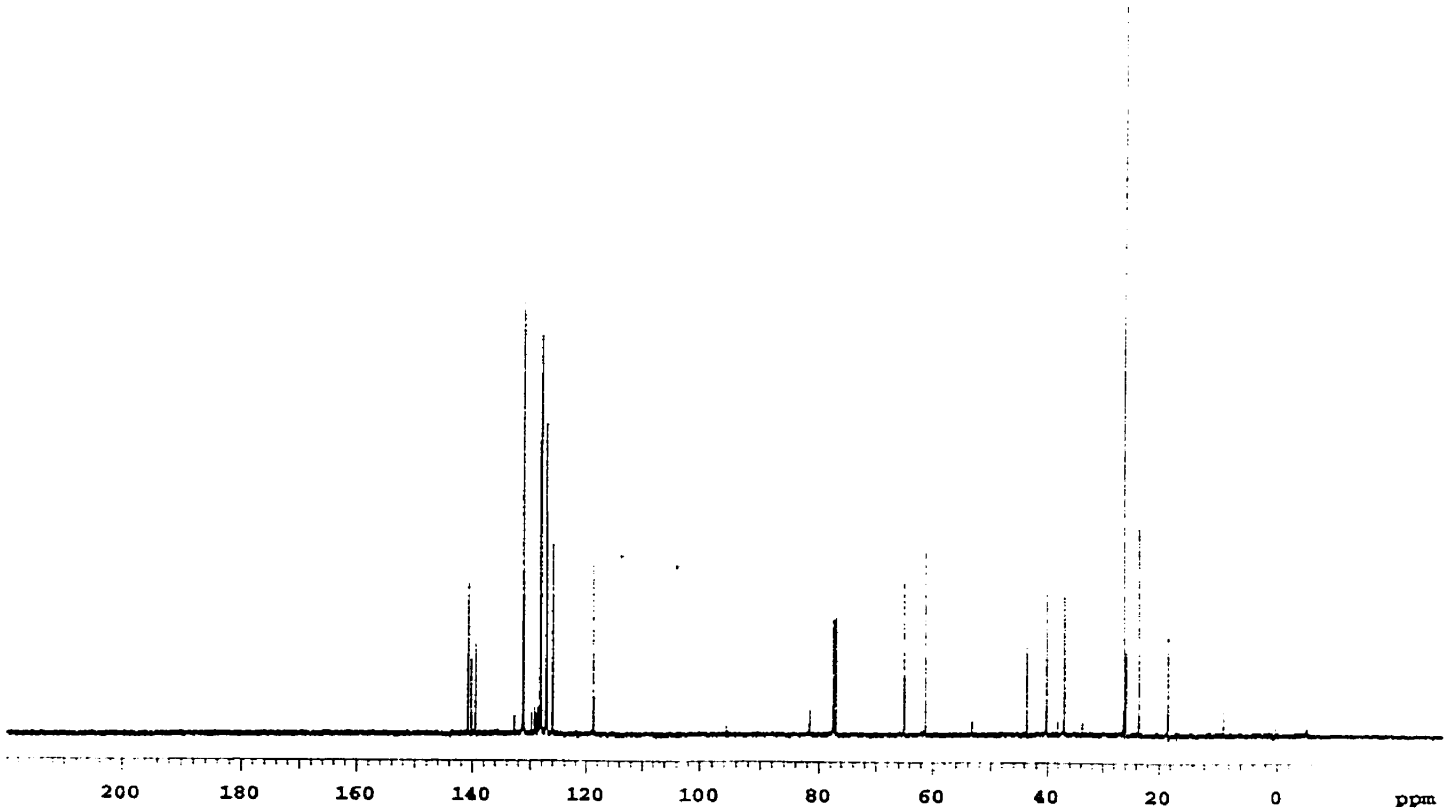
11.18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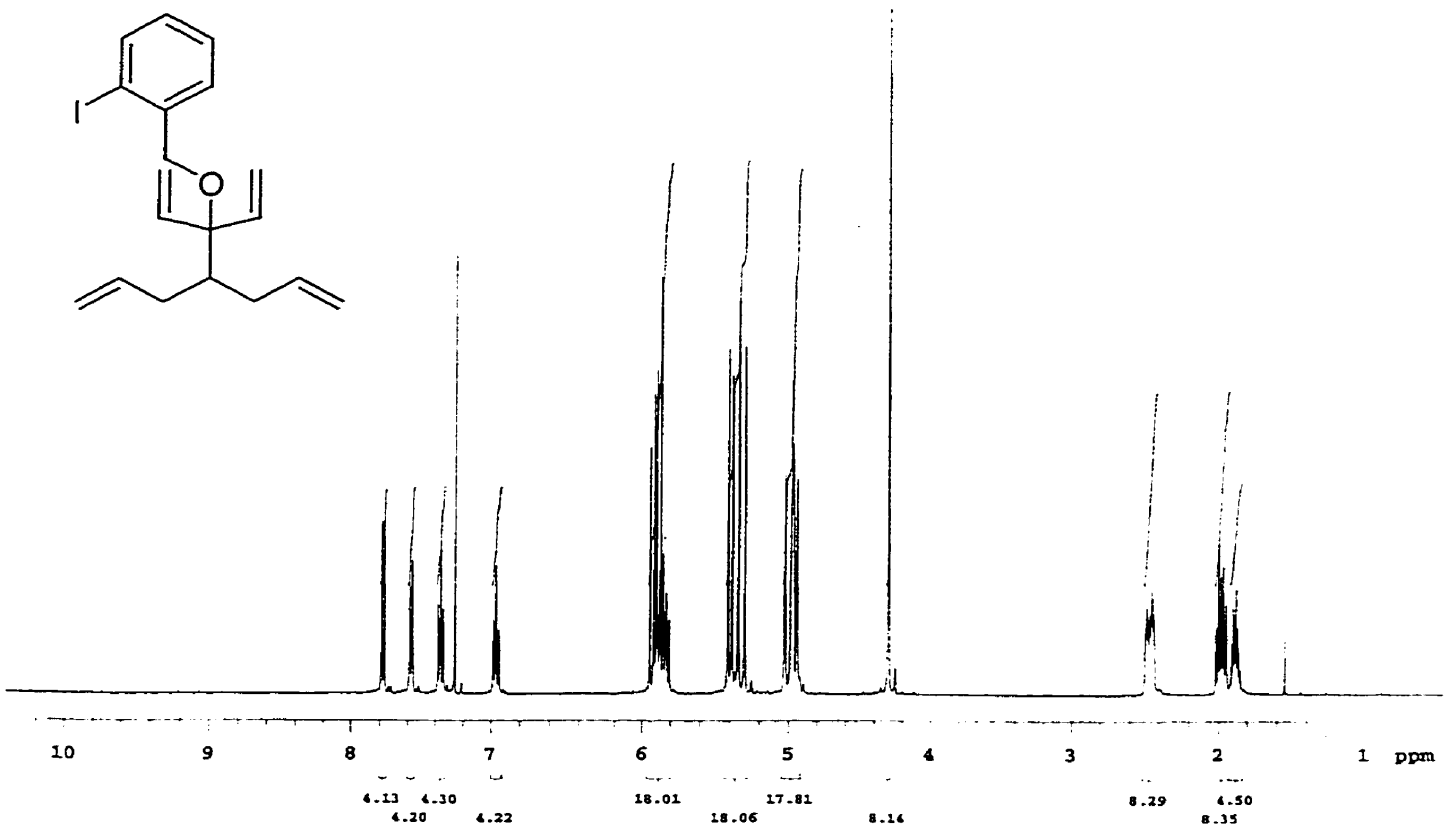
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4
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17.81
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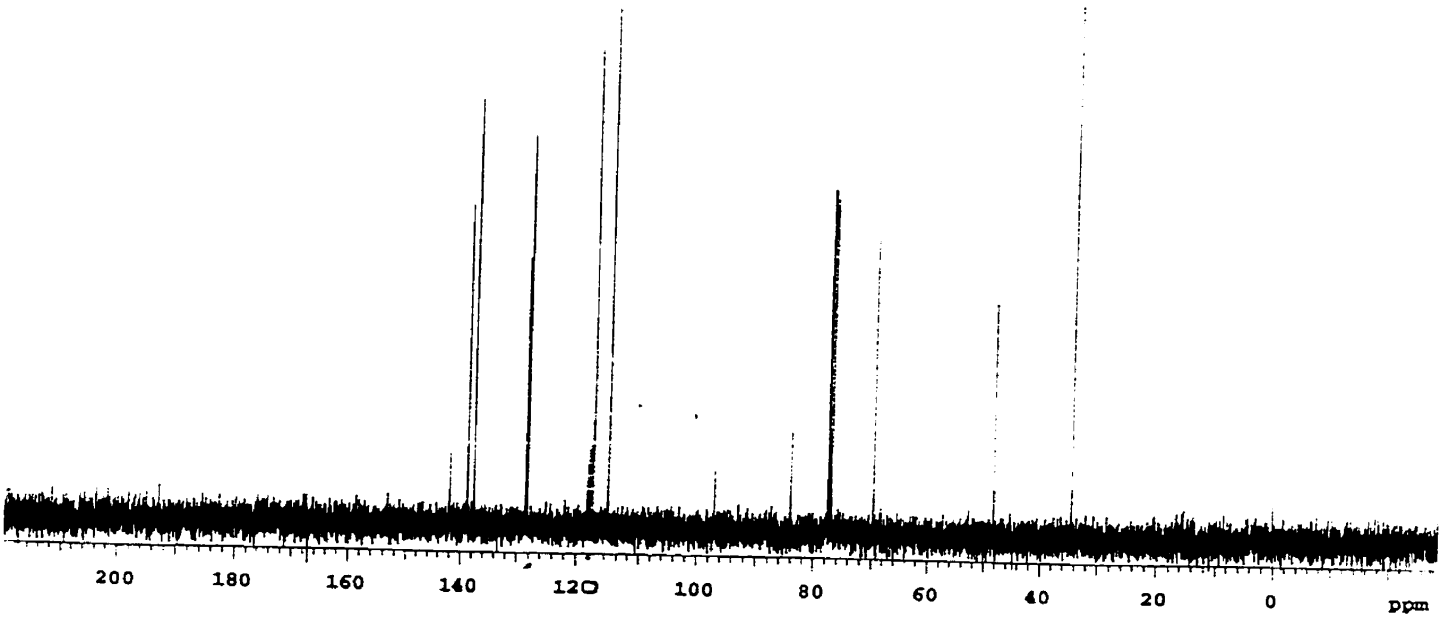
4.50
8.35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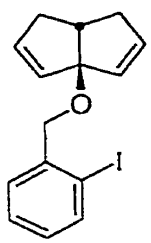
O
I

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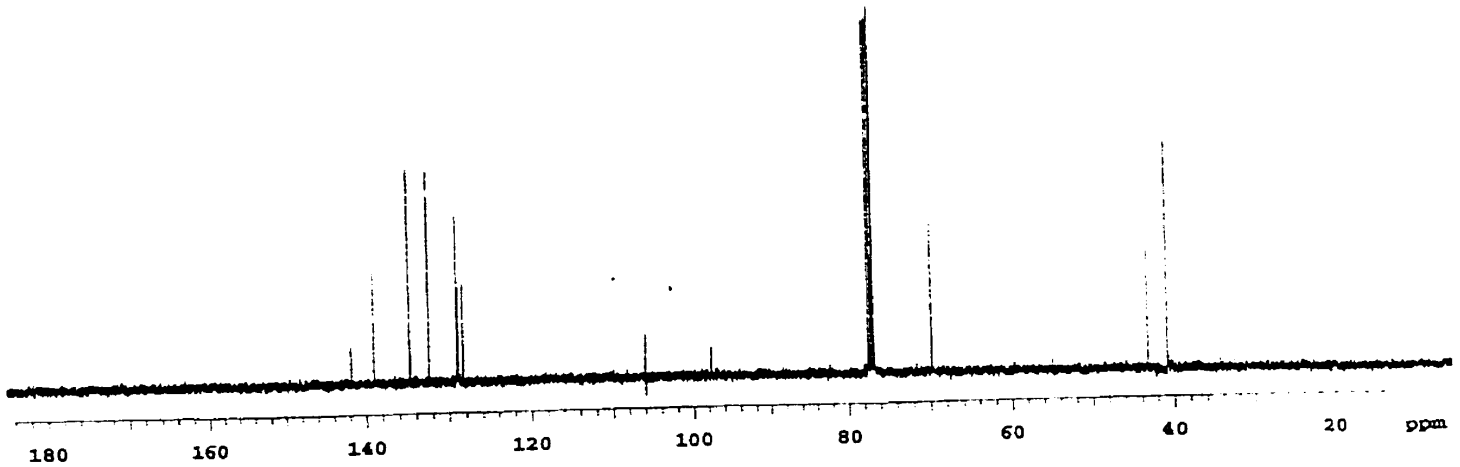
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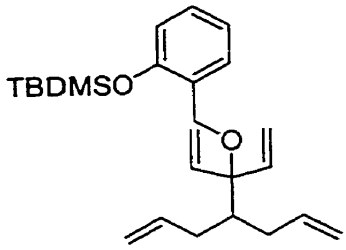
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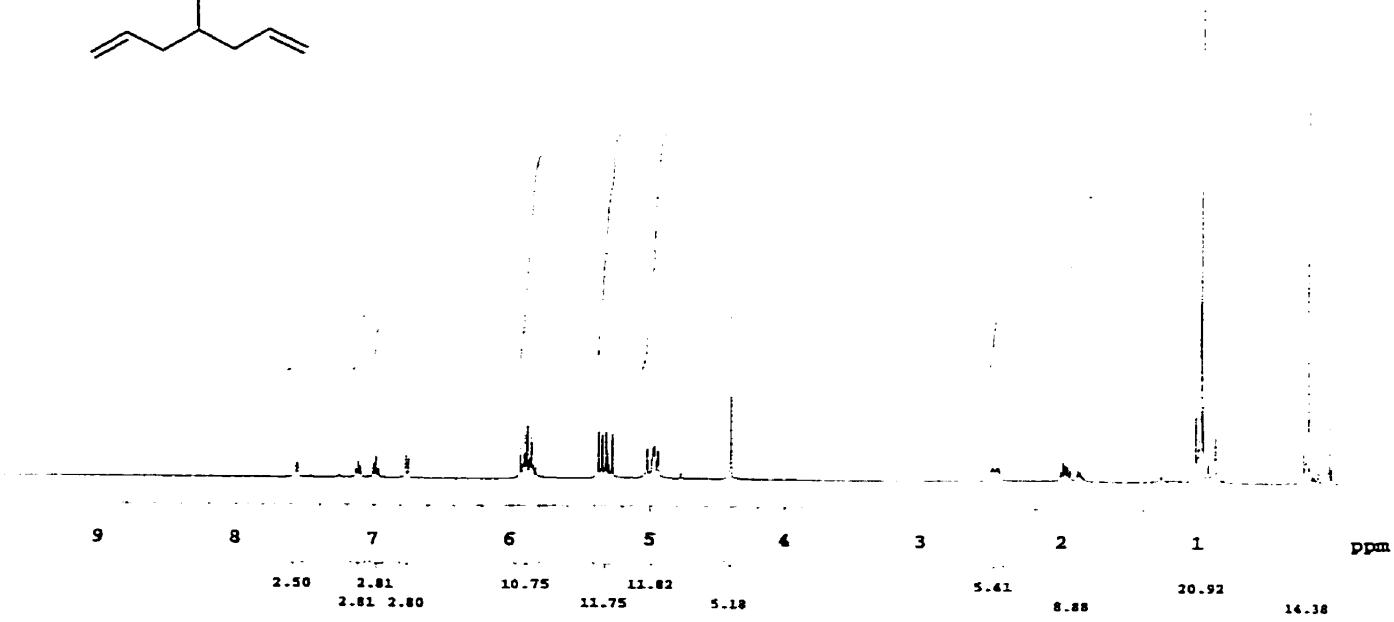
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5
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3
2
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ppm
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2.81 2.80
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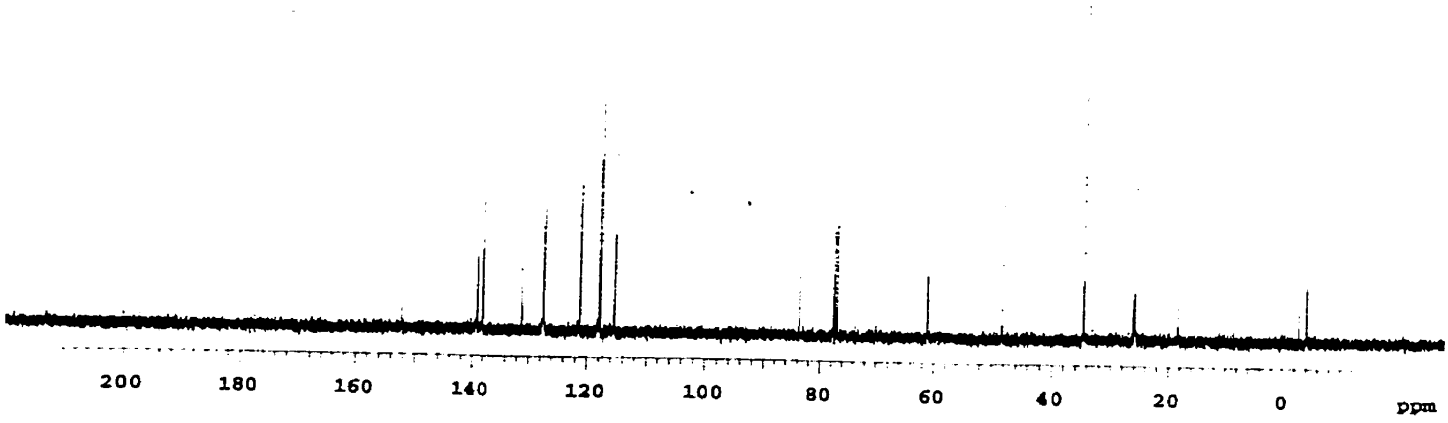
8.88
20.92
14.38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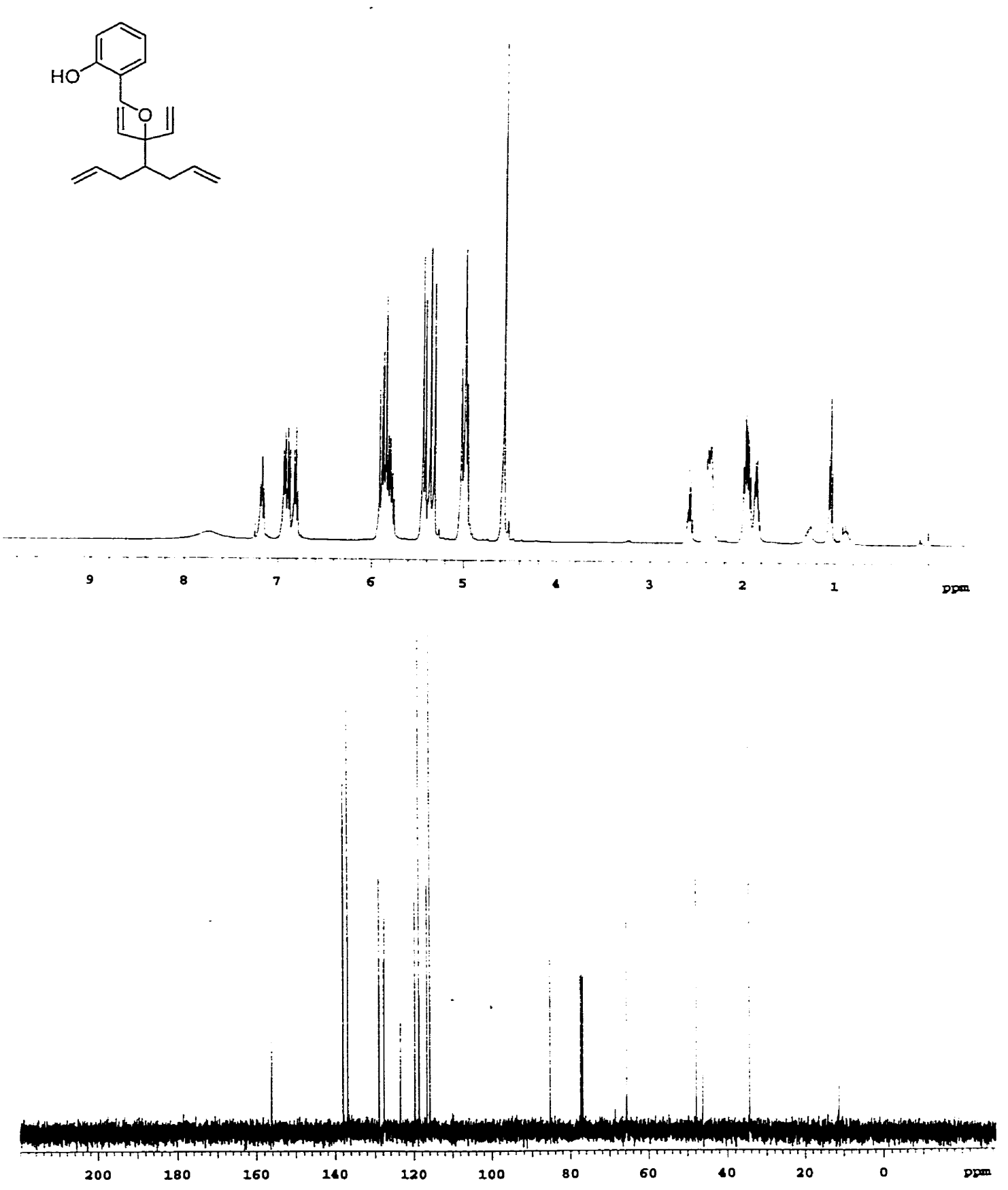
HO
O
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6
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3
2
1
ppm
200
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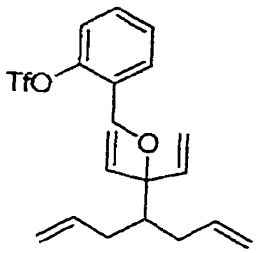
ppm


TfO
O

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8
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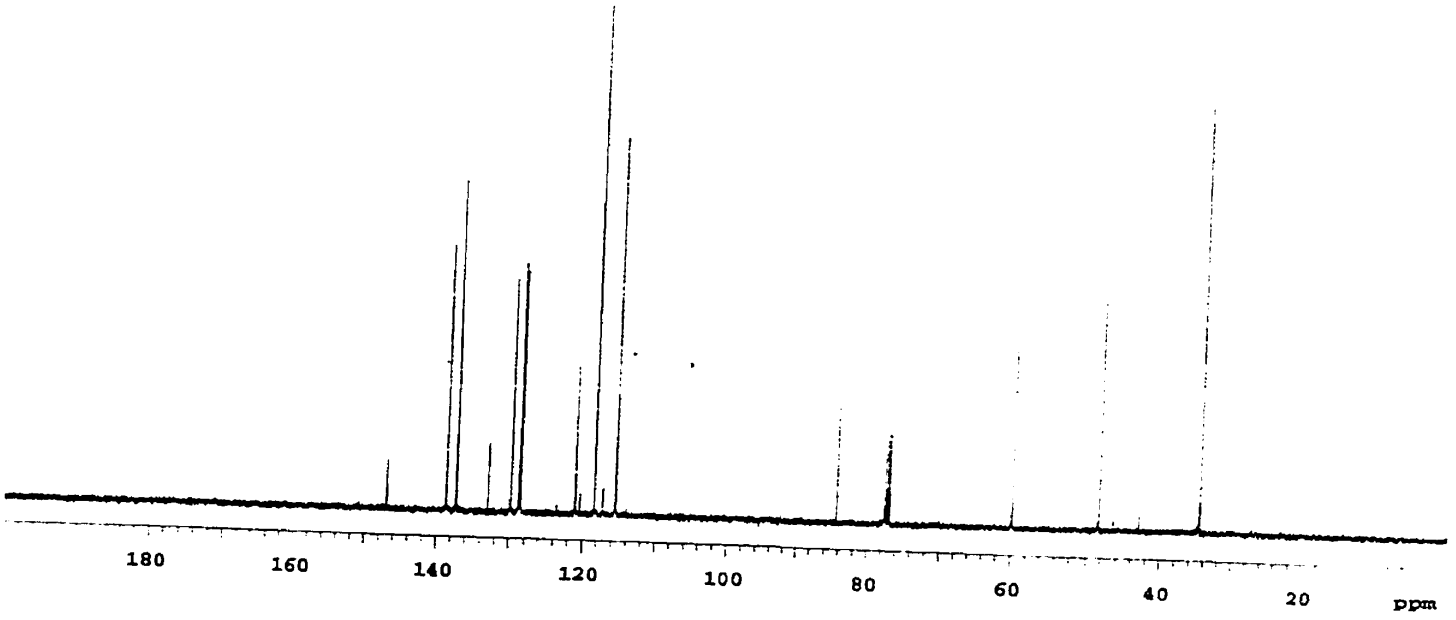
8.63
8.69
13.50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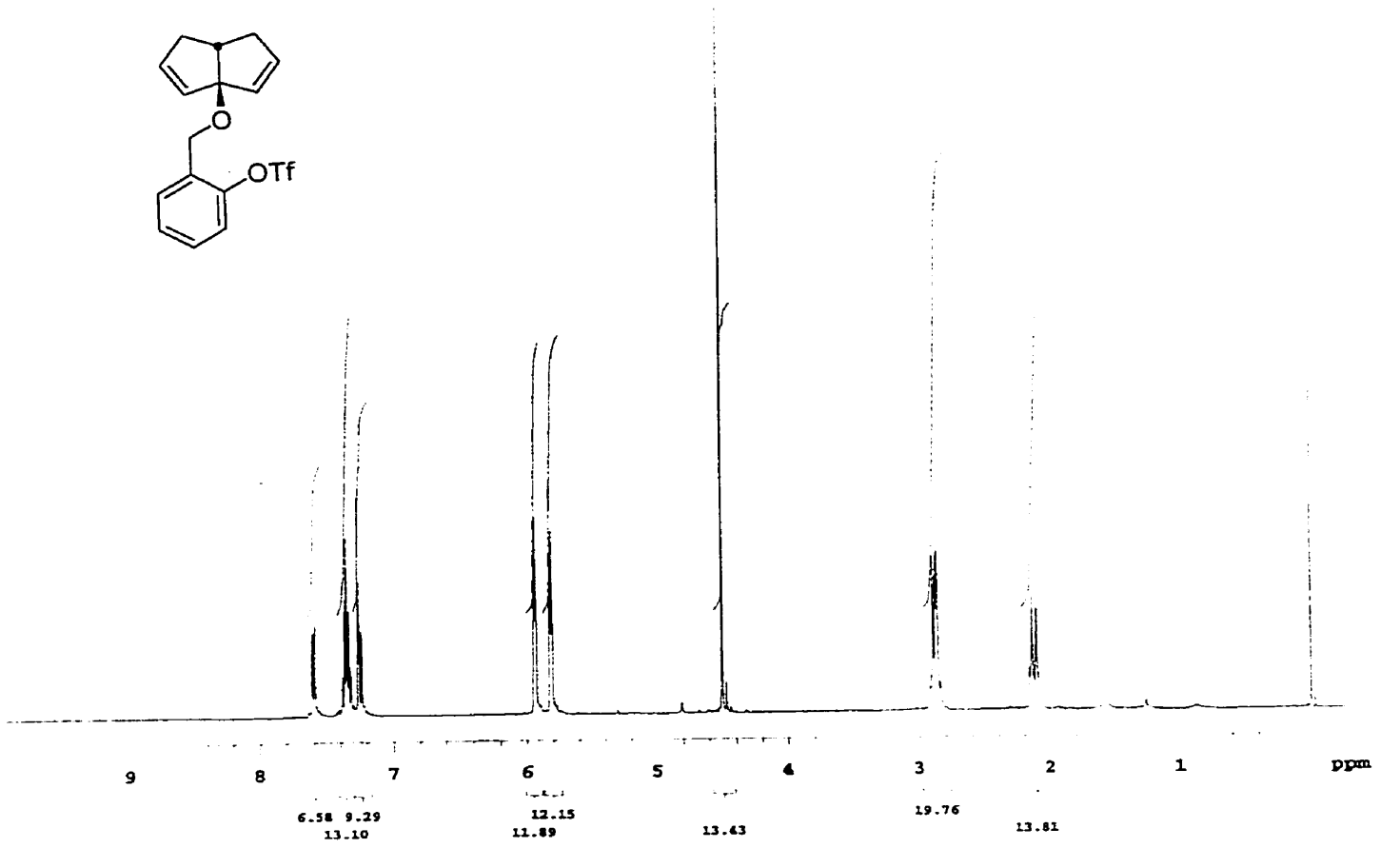
O
OTf
9
8
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6
5
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3
2
1
ppm
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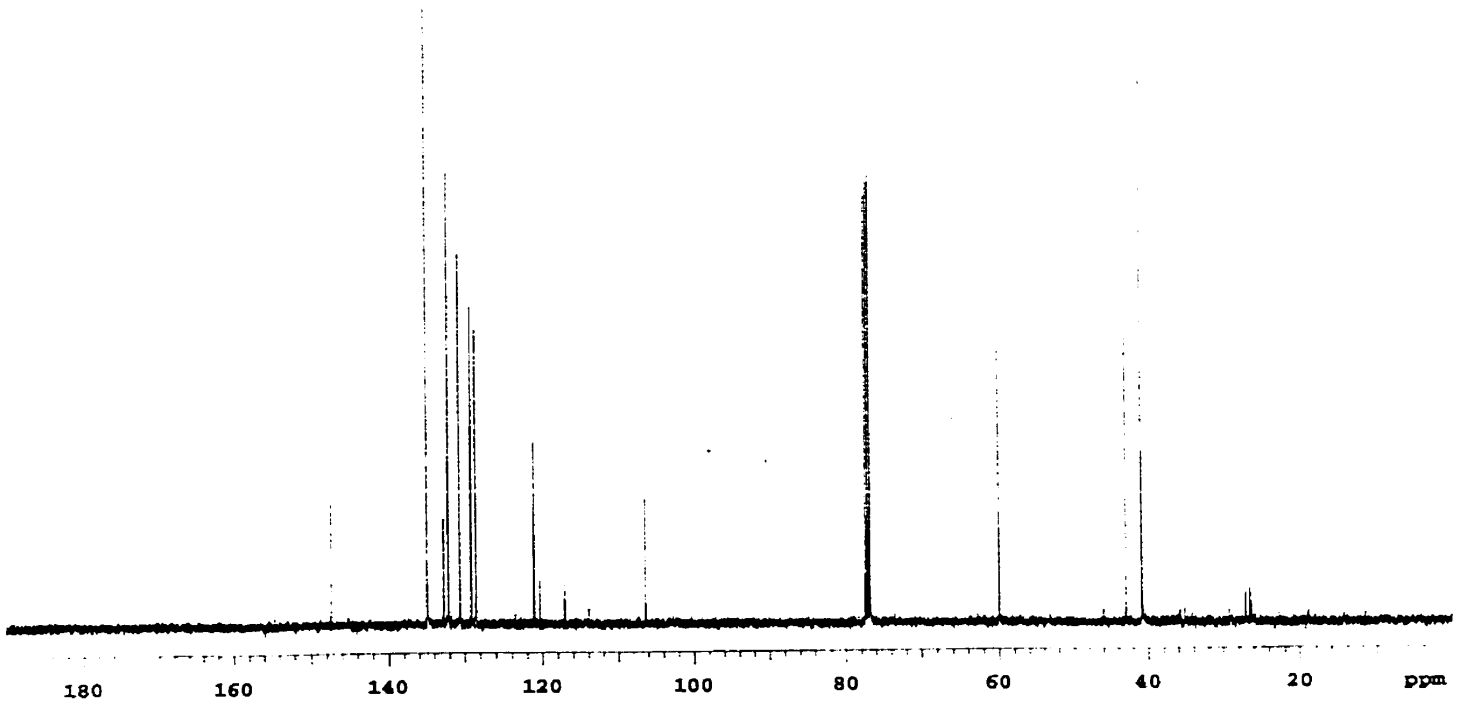
13.10
12.15
11.89
13.43
19.76
13.81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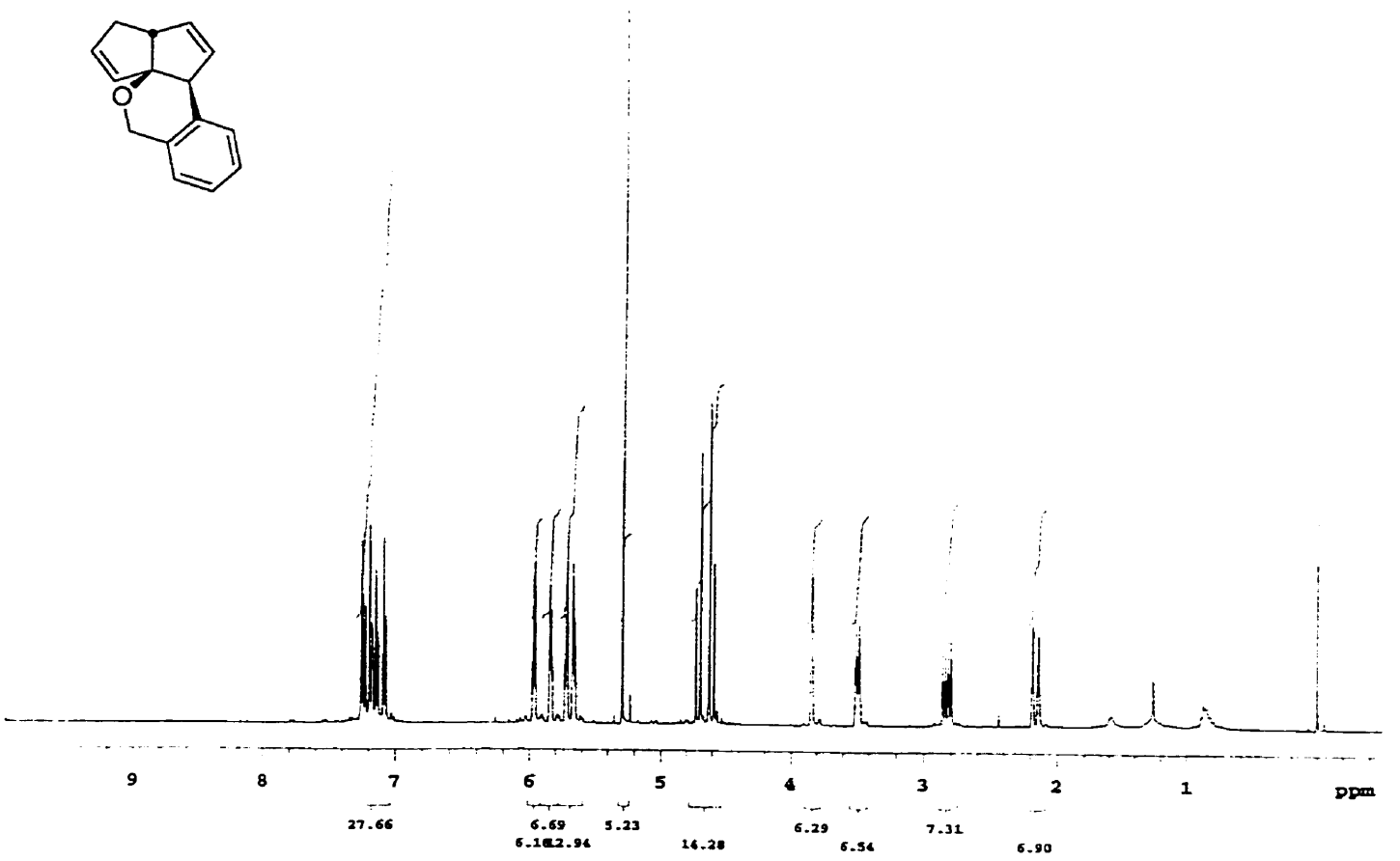
80
60
40
20
ppm


9
8
7
6
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4
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ppm
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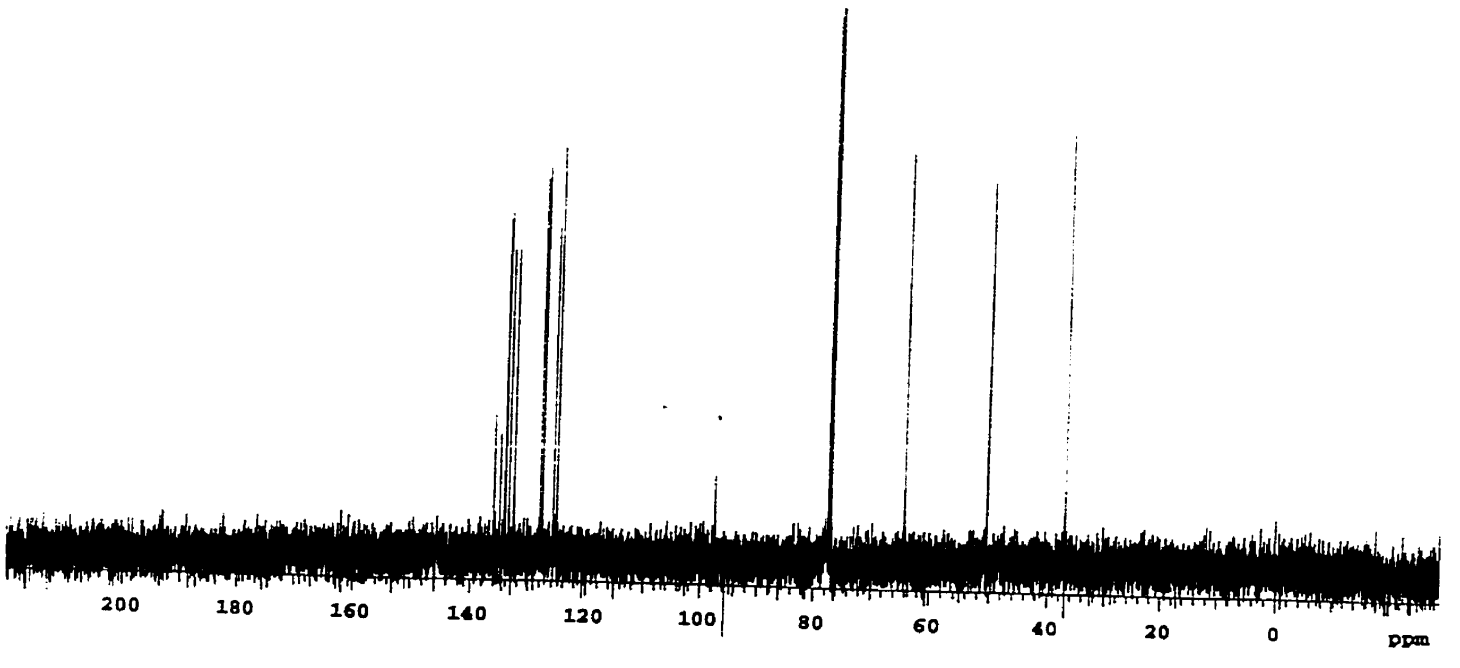
6.69
5.23
16.28
6.29
6.54
7.31
6.90


200
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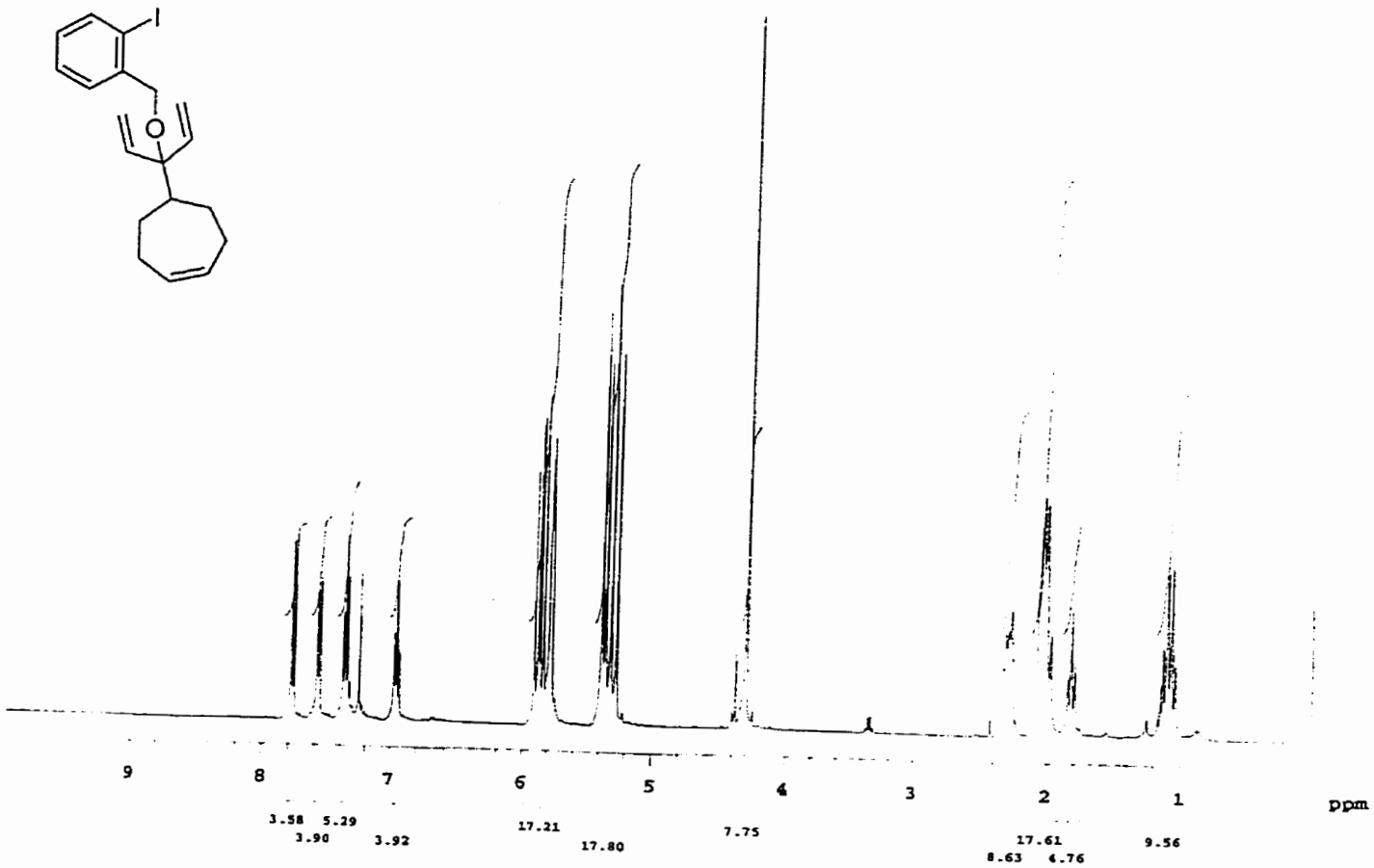
I
O
9
8
7
6
5
4
3
2
1
ppm
3.58
5.29
3.90
3.92
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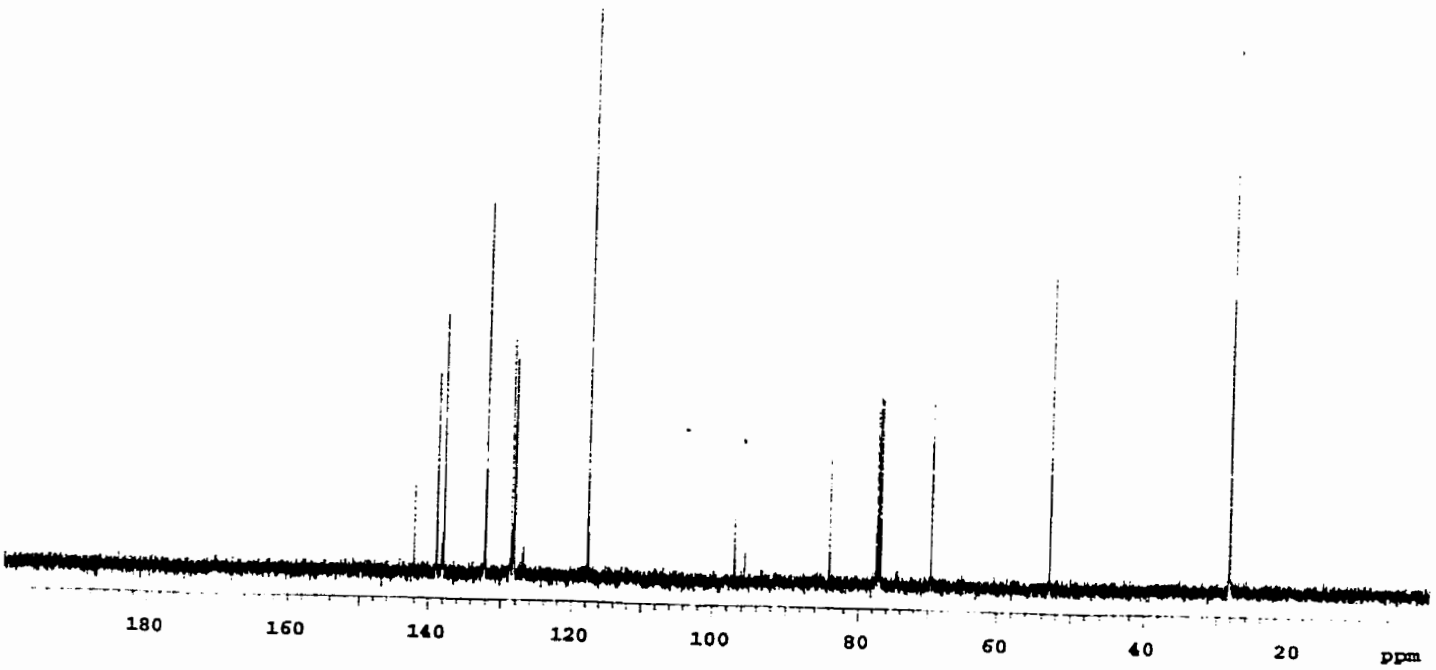
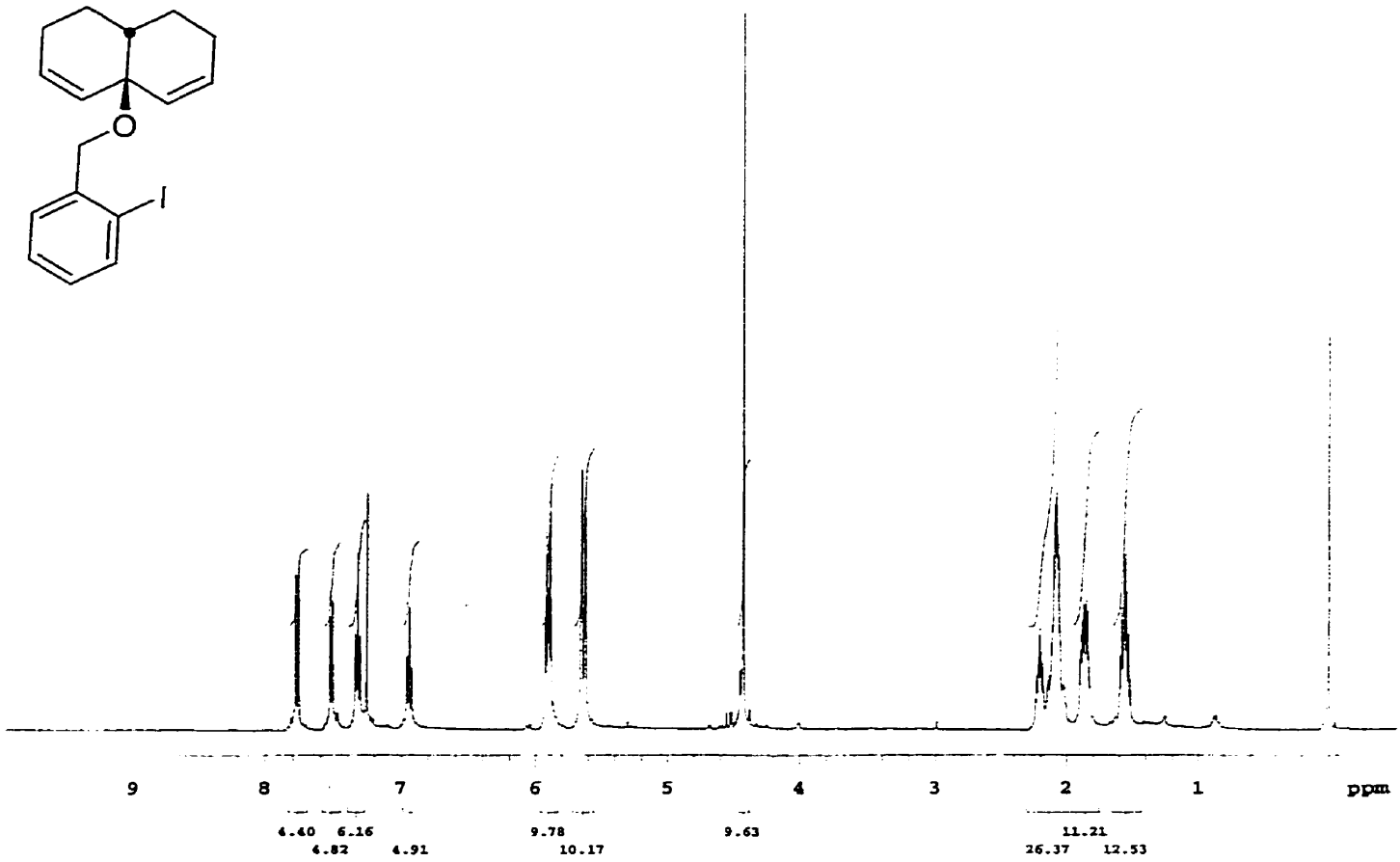
17.80
7.75
17.61
8.63
4.76
9.56


180
160
140
120
100
80
60
40
20
ppm


O
I
9
8
7
6
5
4
3
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1
ppm
4.40
6.16
4.82
4.91
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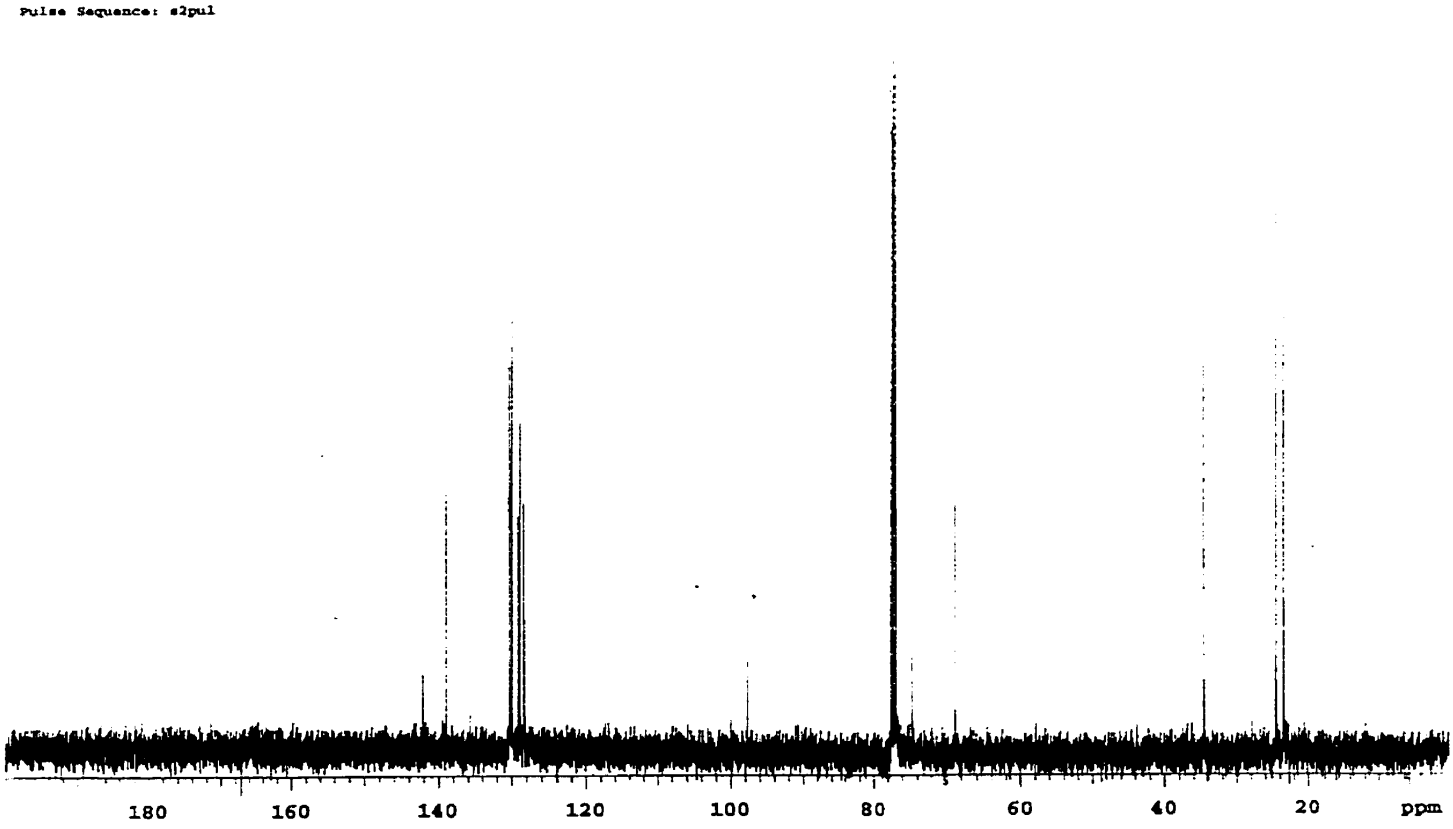
10.17
9.63
11.21
26.37
12.53


Pulse Sequence: s2pul
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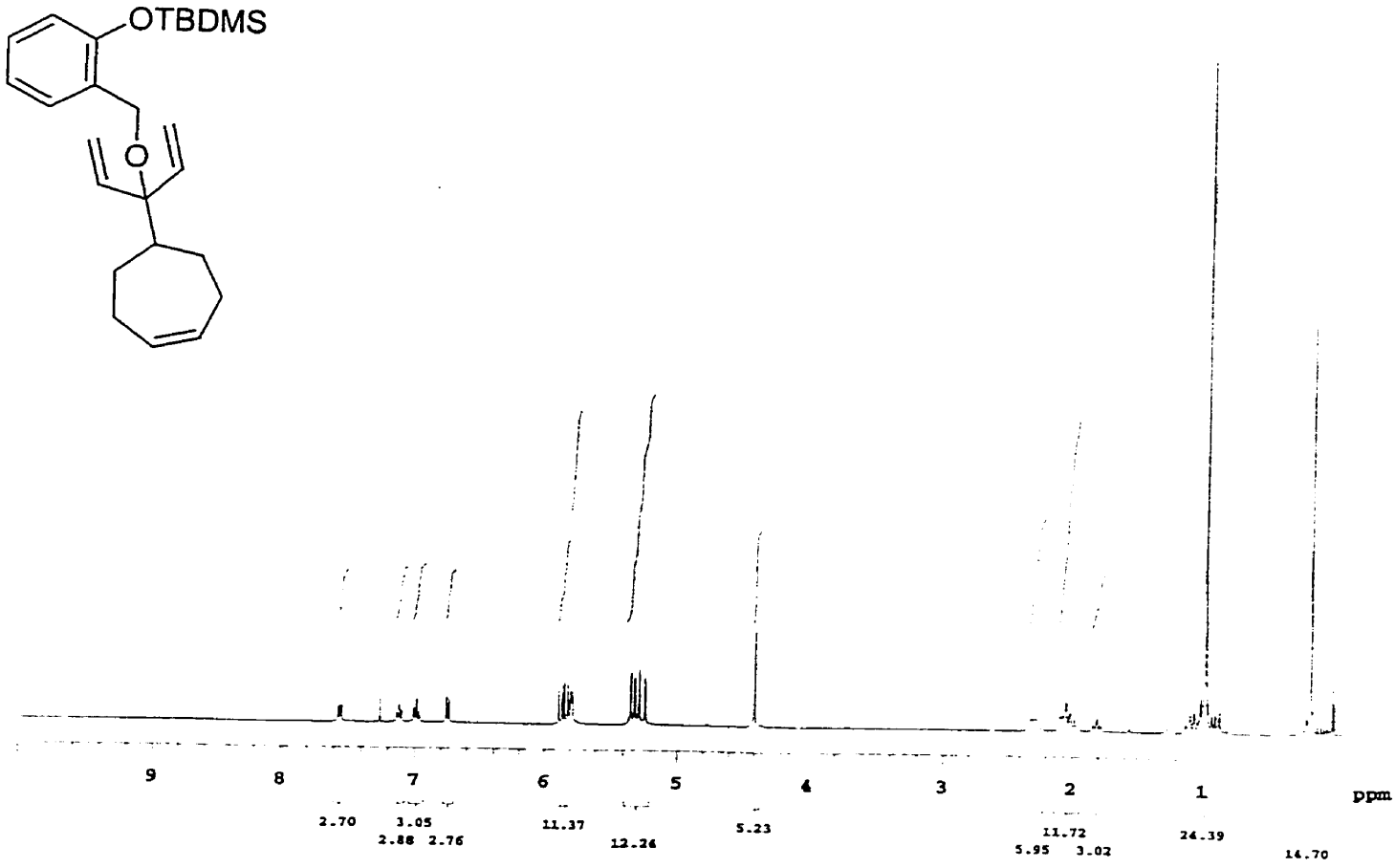
60
40
20
ppm


OTBDMS
O
9
8
7
6
5
4
3
2
1
ppm
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2.76
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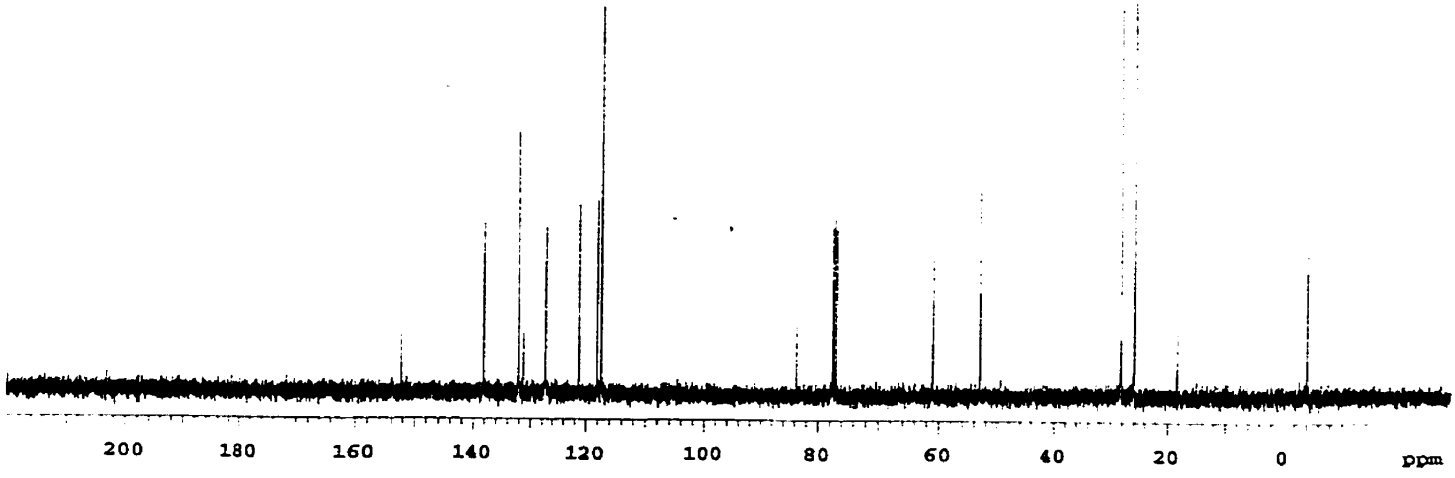
5.23
11.72
5.95
3.02
24.39
14.70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100
80
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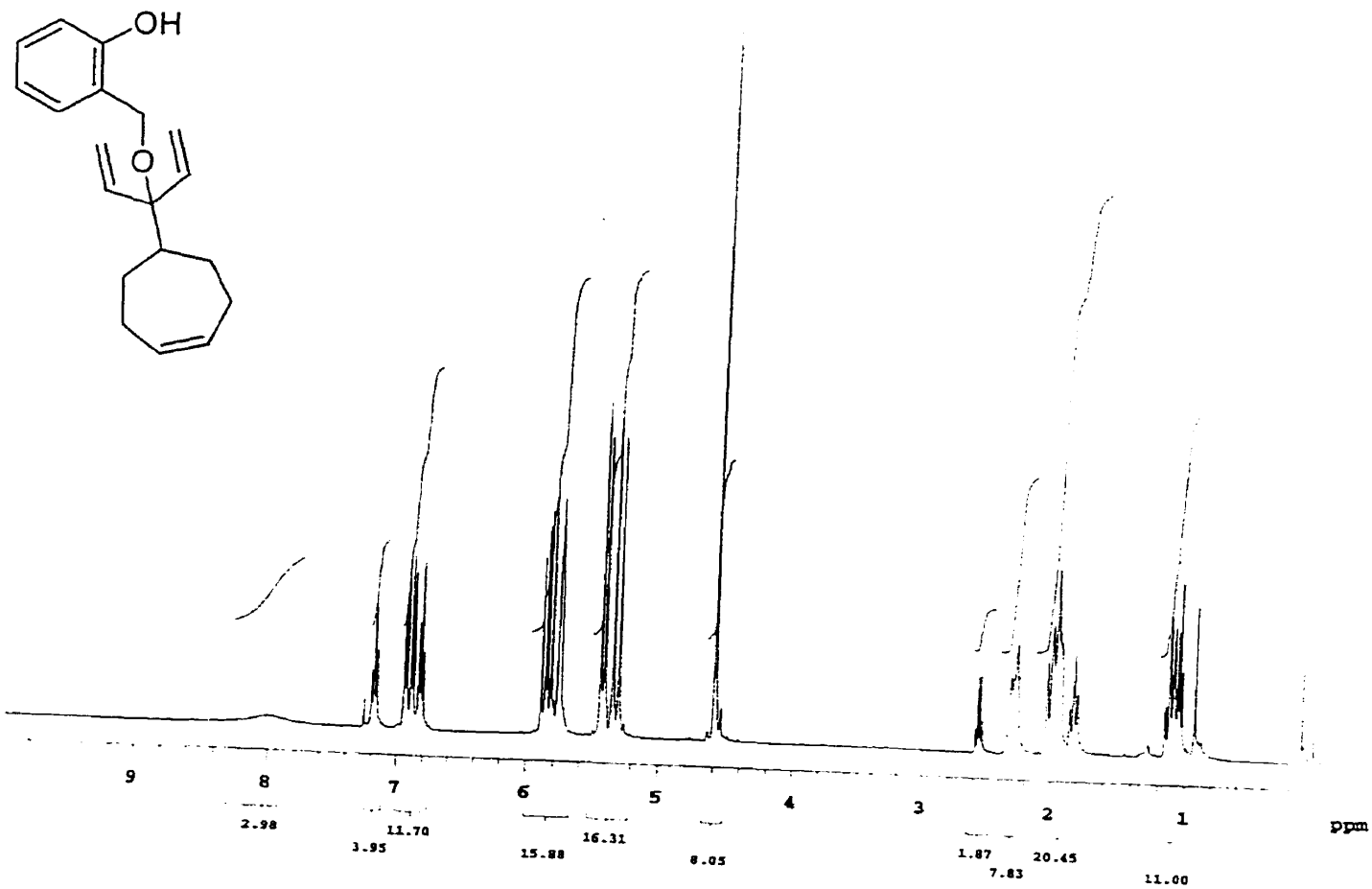
0
ppm


OH
O
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8
7
6
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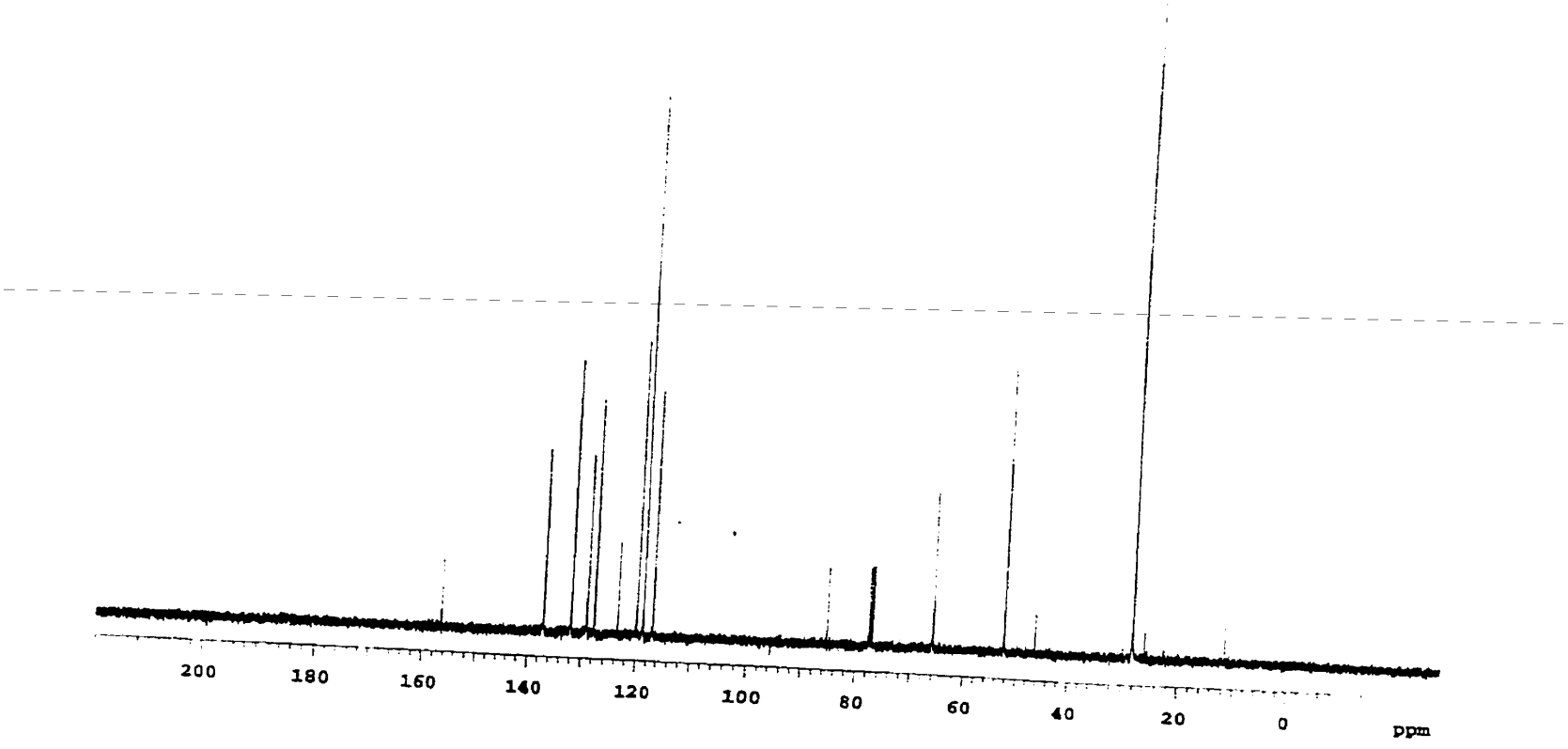
20.45
11.00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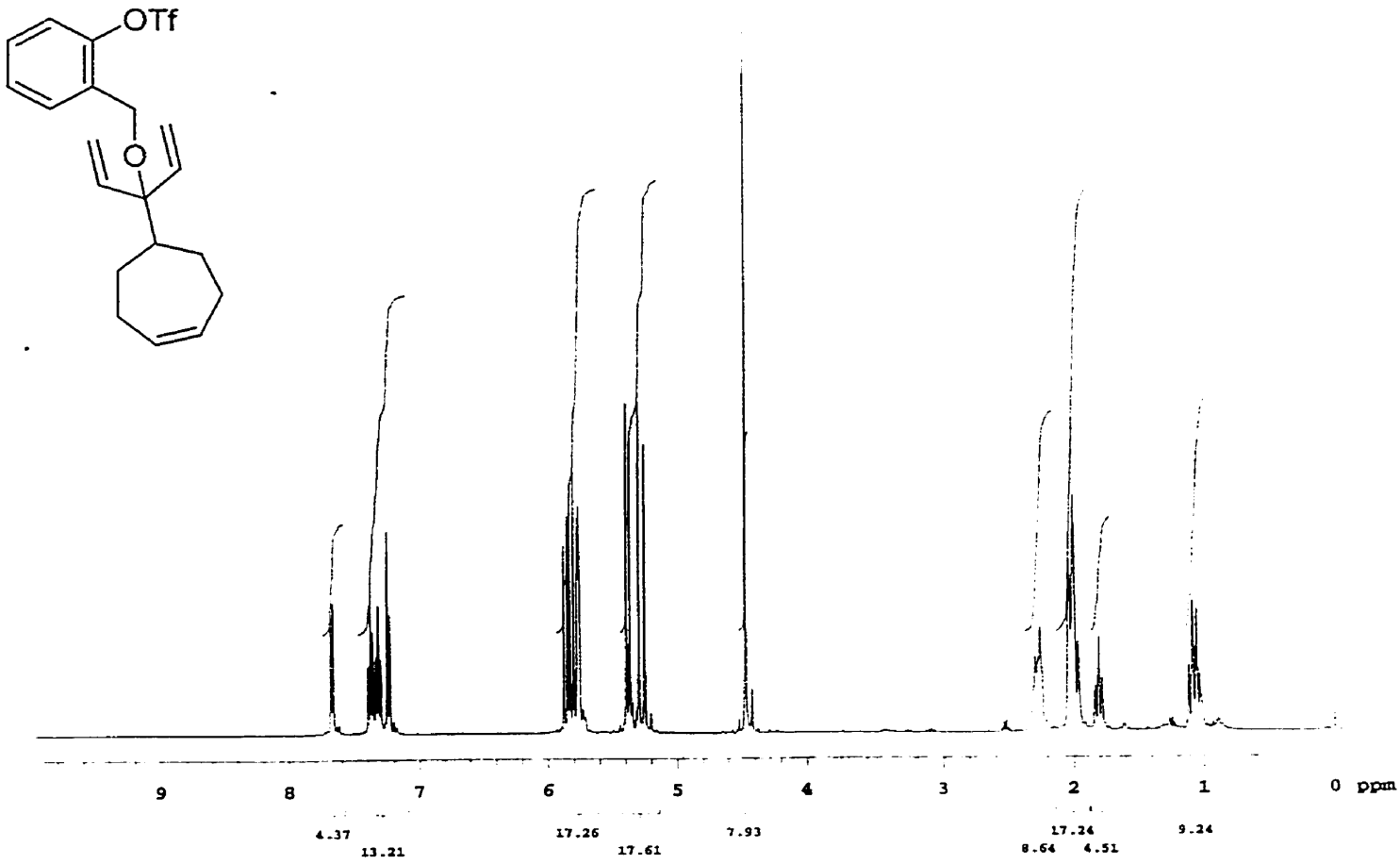
OTf
9
8
7
6
5
4
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0 ppm
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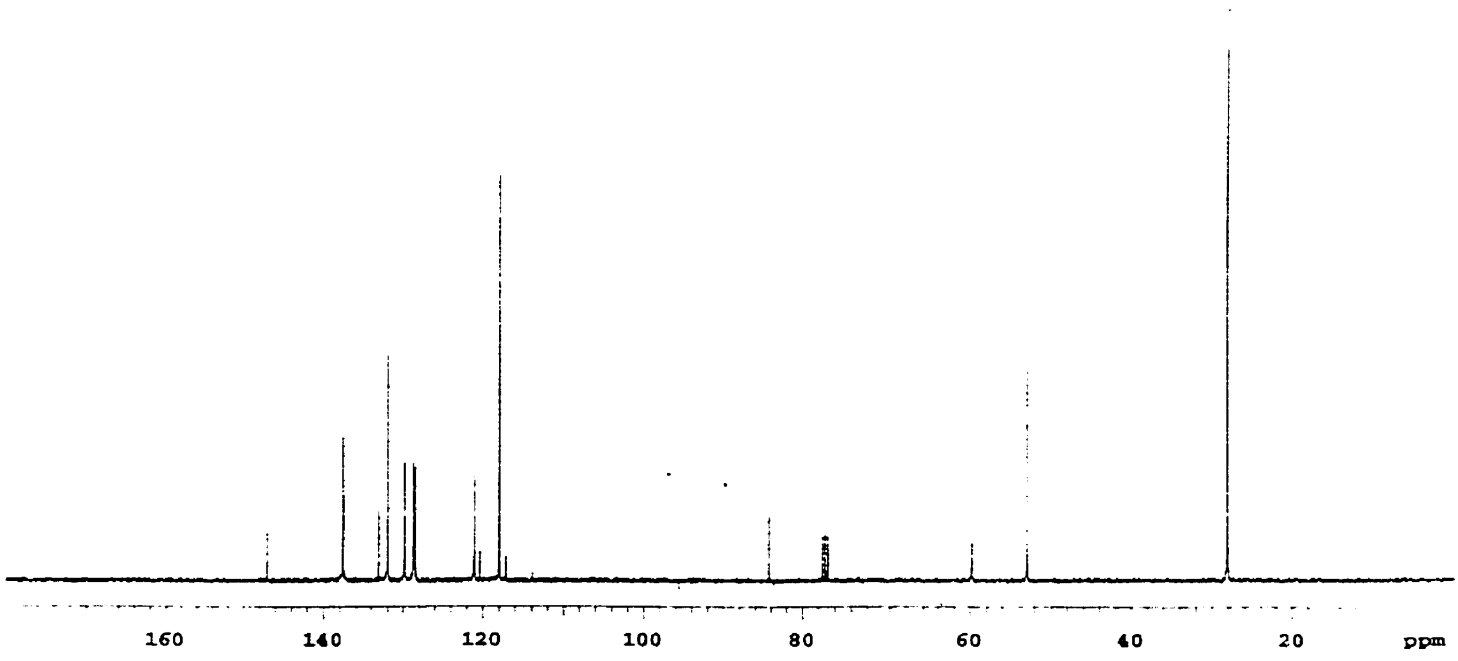
13.21
17.26
17.61
7.93
17.24
8.64
4.51
9.24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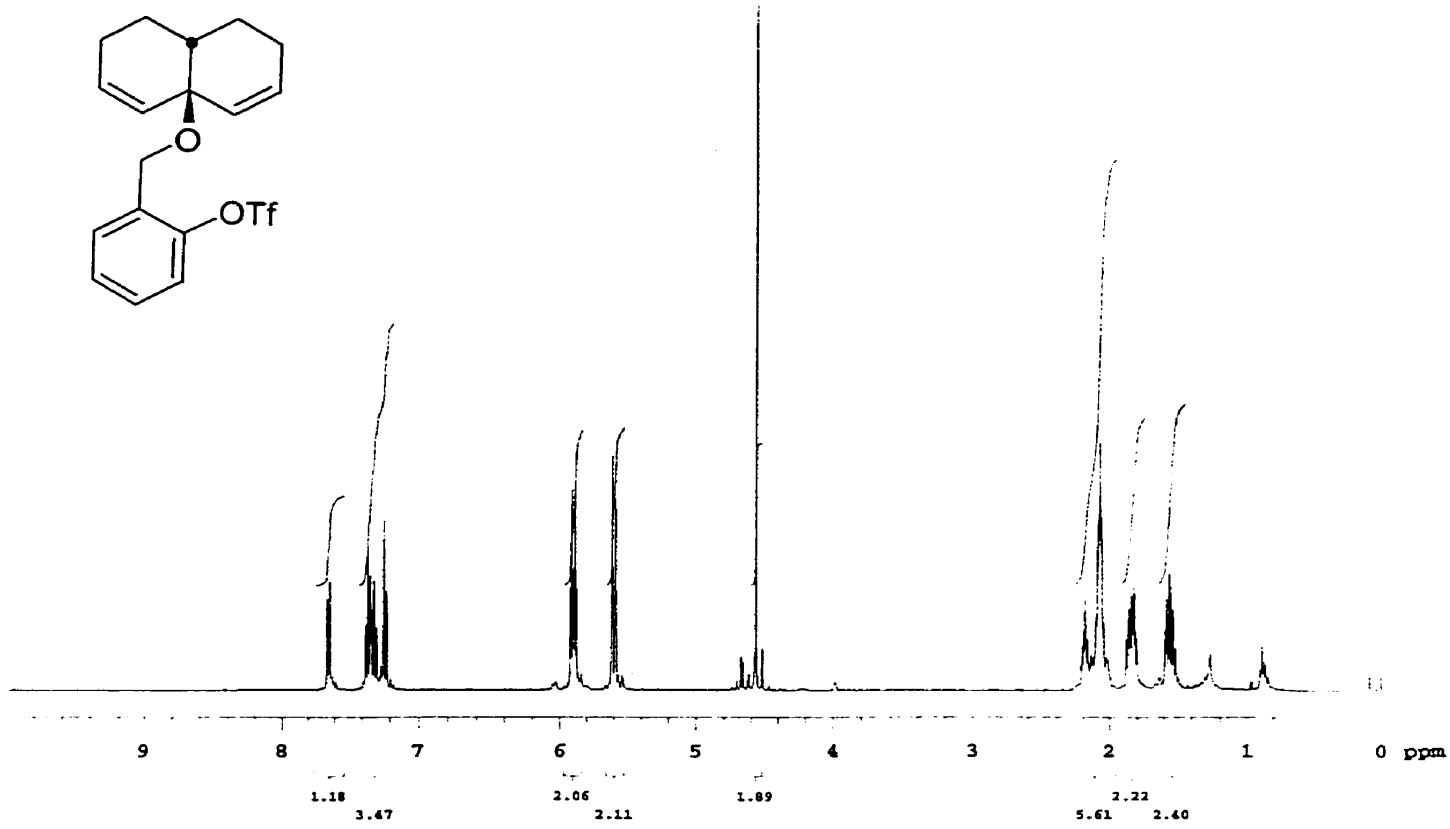
O
OTf
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7
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4
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0 ppm
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2.11
1.89
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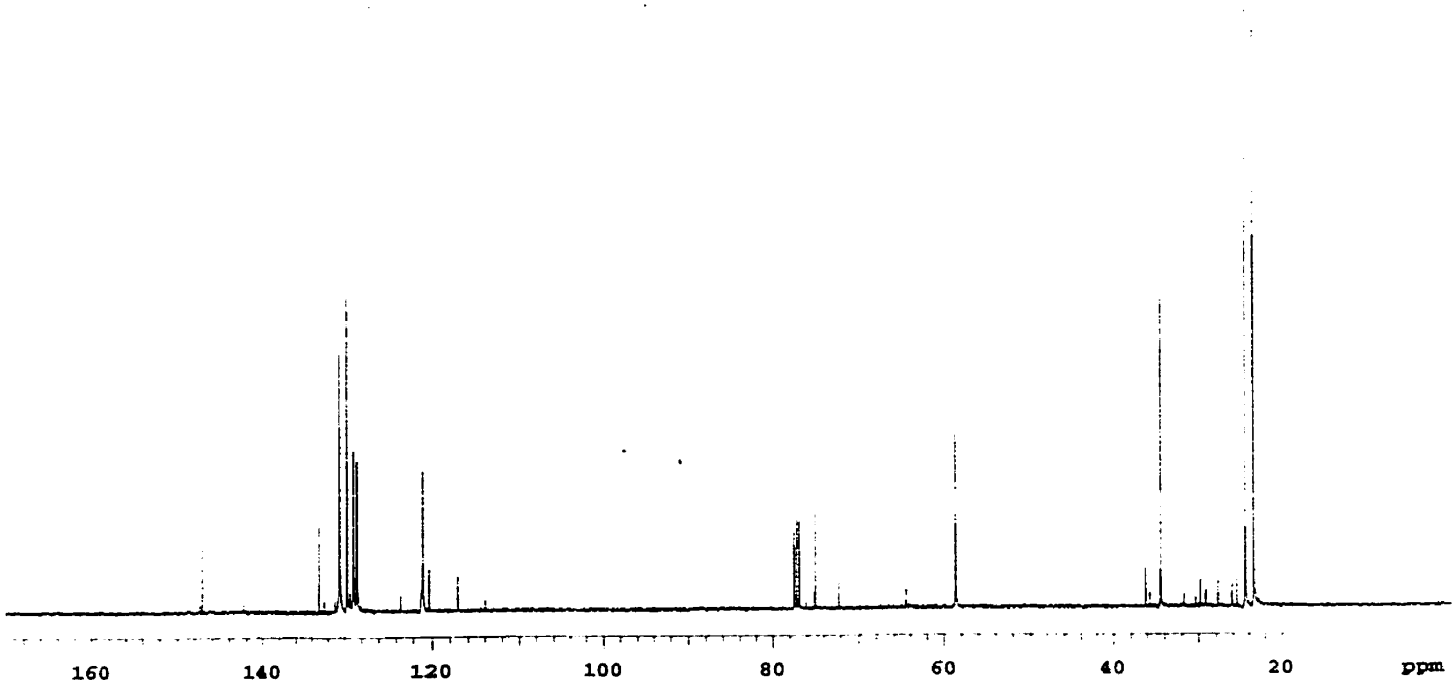
5.61
2.40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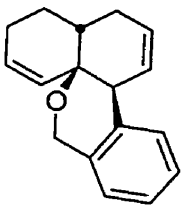

9
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5
4
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5.73
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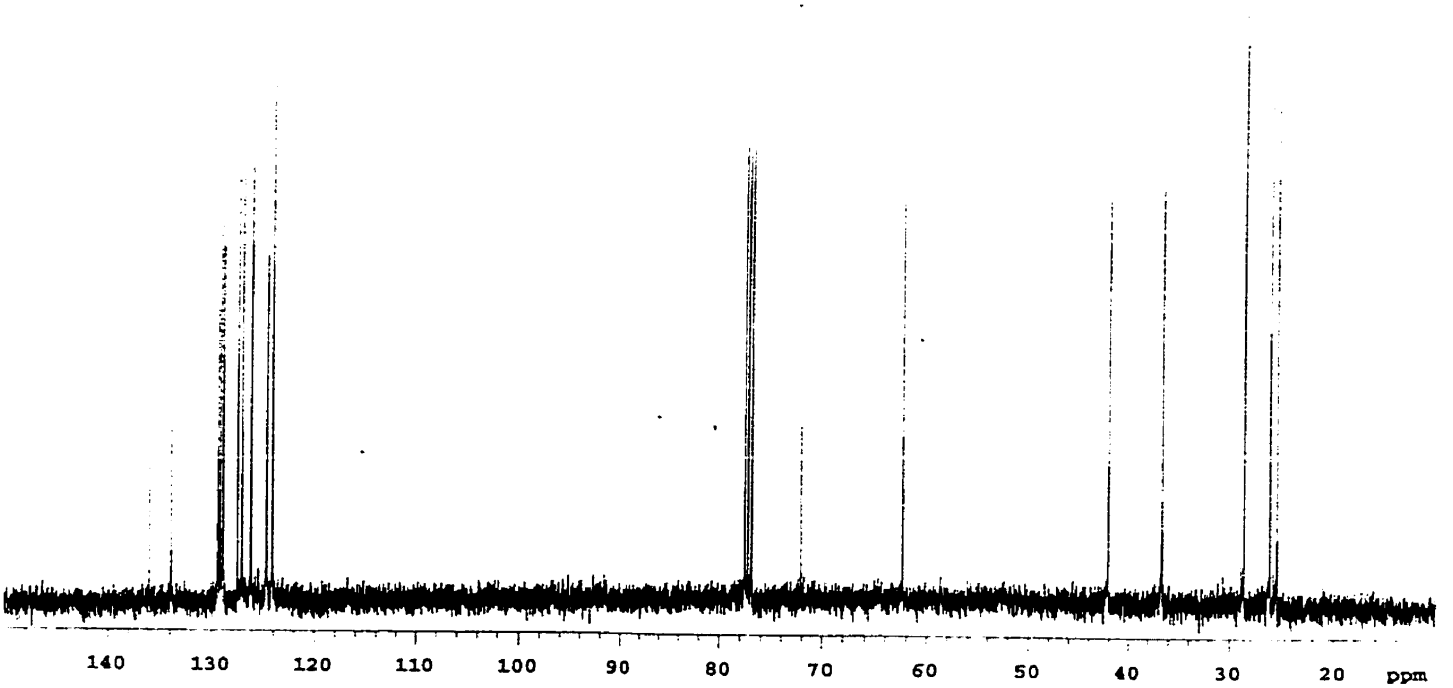
17.04
17.63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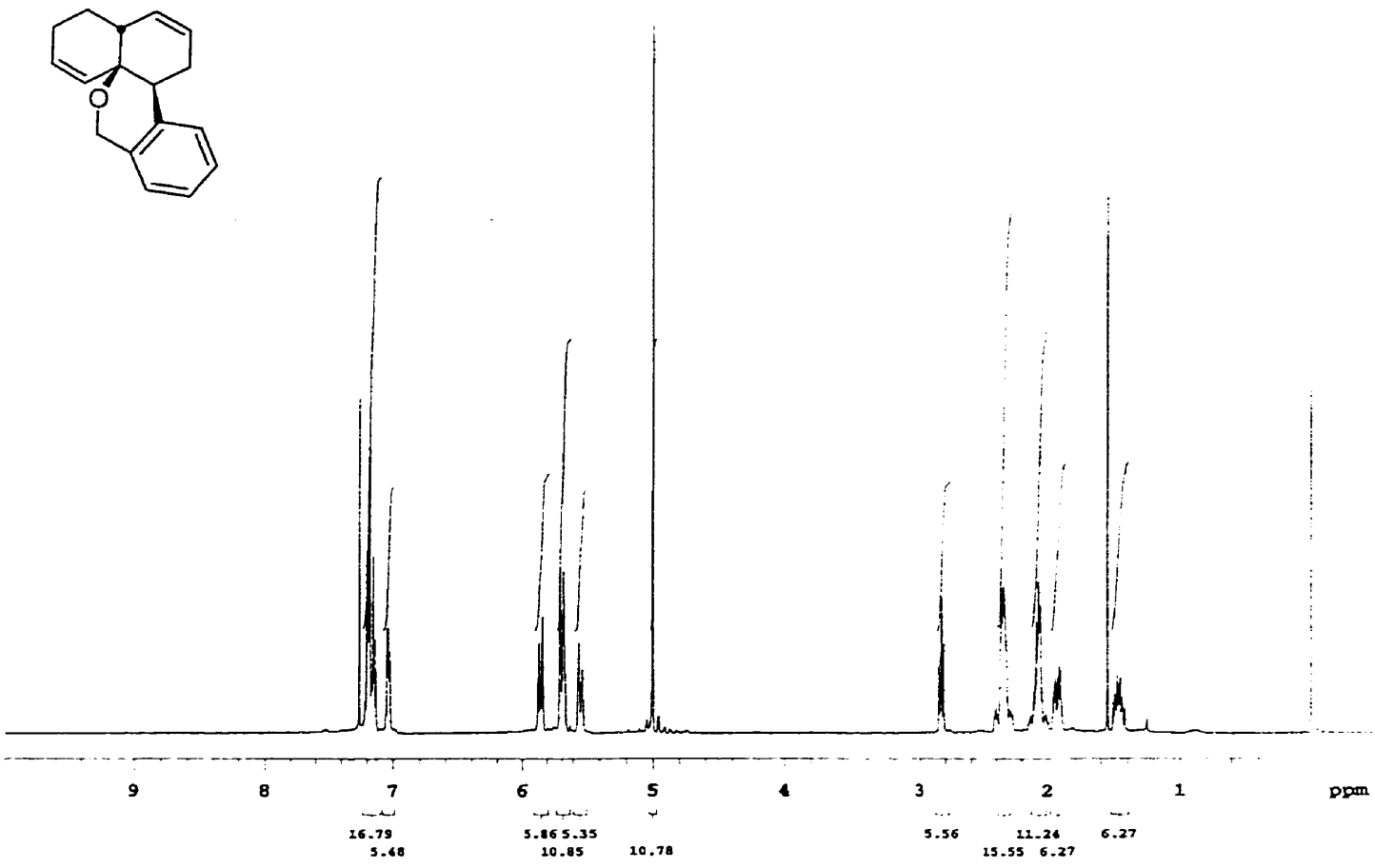
ppm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6
5
4
3
2
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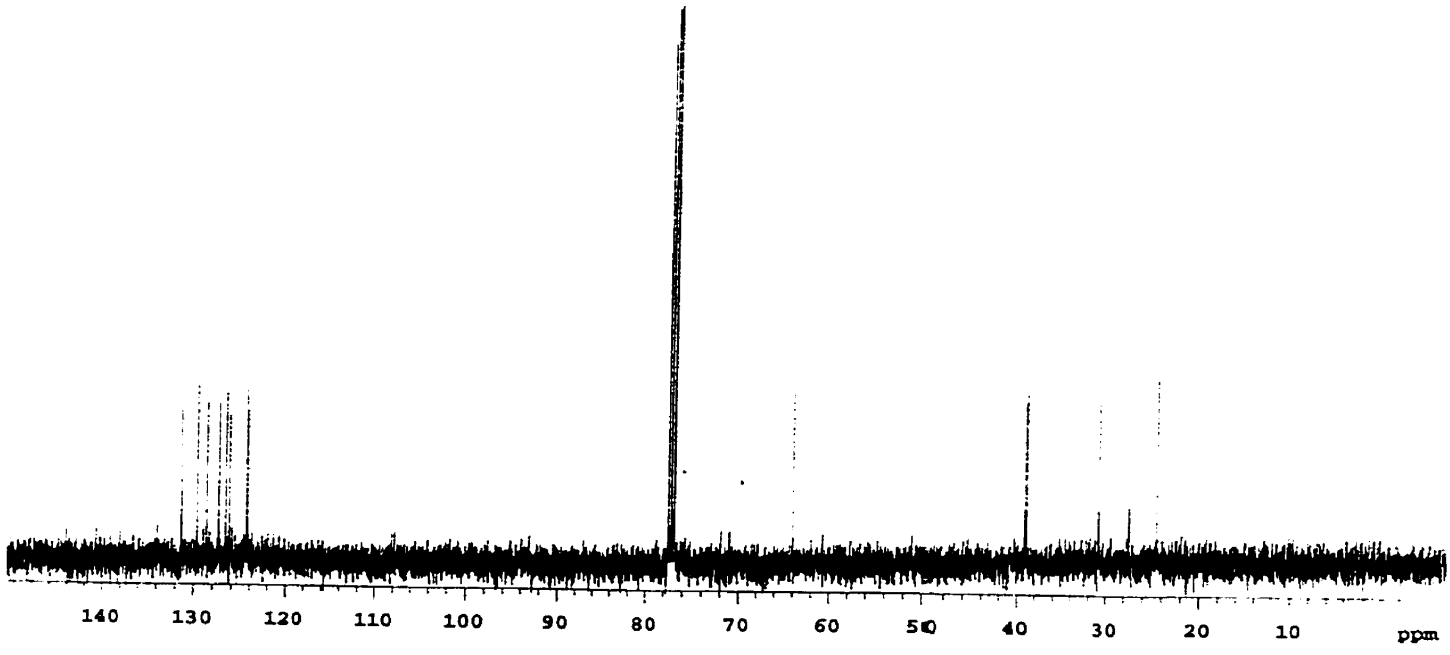
6.27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20
10
ppm