

Palladium-Catalyzed Oligocyclizations of Some 2-Bromotetradec-1-ene-7,13-diynes Under Heck Reaction Conditions

Dissertation

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To my parents

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A. Introduction

Reactions involving the formation of a carbon-carbon bond are considered the most valuable reactions in organic chemistry. Organometallic reagents, such as grignard reagents and organolithium reagent, were among the earliest tools in this regard. Until the sixties of the last century, the synthetic utility of these reagents had, however, been so constrained due to their poor chemoselectivity and to their limited use to form only a sp^3 - sp^3 carbon-carbon bond. The plethora in organometallic chemistry and organotransition metal chemistry had culminated in developing new reagents and catalysts which opened the door for new precious transformations and reactions which had been considered as impossible or difficult to obtain. They have also expanded the utility of the old organometallic reagents by improving their selectivity and the scope of their use.^[1] In this introduction, four processes of these transition-metal catalyzed processes are going to be mentioned; these are cross-coupling reaction of organometallic compounds with organic halides, cycloisomerization reactions, Heck reaction and cascade reactions. Our major concern would be on the last two because they are the subjects of this study.

1. Cross-Coupling Reactions

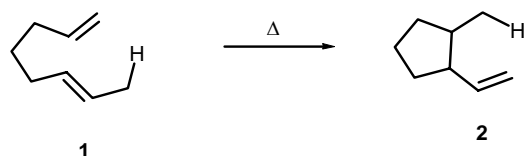
Cross coupling reactions of organometallic compounds with organic halides were among the most extensively studied reactions. Thus by the advent of the new transition metal catalysts, cross-coupling reactions involving the formation of sp^2 - sp^2 or sp^2 - sp carbon-carbon bonds have become widely used reactions. Reactions such as Stille coupling,^[2] Sonogashira reaction^[3] and Suzuki coupling^[4] have now become essential and prominent reactions in organic chemistry, (Scheme 1.).



Scheme 1.

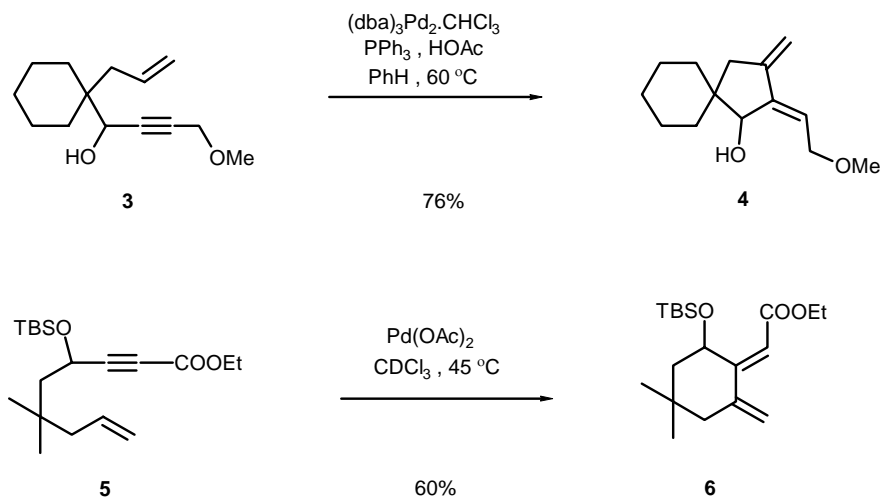
2. Cyclisomerization

Alder-ene reaction,^[5] (Scheme 2), is just another impressive example wherein the transition-metal catalysts played a very important role. Although of its great importance, this reaction had found a limited use due to the high temperatures required to induce this transformation. However, by using catalytic amounts of Lewis acids^[6] or transition-metal compounds, this transformation can smoothly be performed at room temperature. Thus 1,n-diene, 1,n-enyne and 1,n-diyne cycloisomerizations have become easily accessible and feasible processes and they emerged as an extremely efficient way in constructing cyclic compounds which are difficult to obtain by the traditional methods.



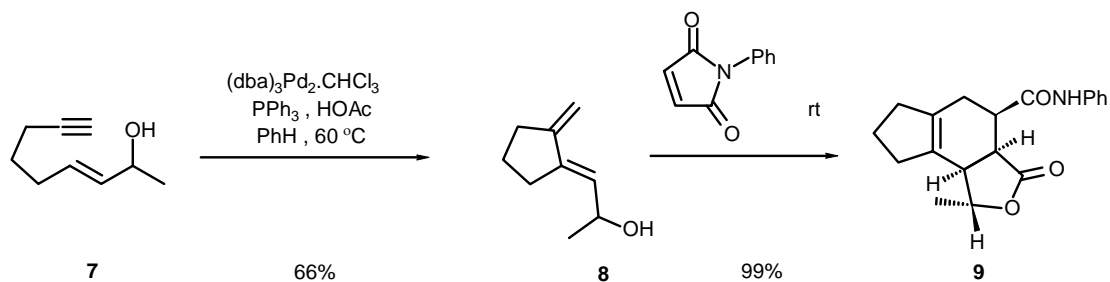
Scheme 2.

Scheme 3 illustrates two examples of 1,6^[7]- and 1,7^[8]- enyne palladium-catalyzed cycloisomerization to afford the five- and six-membered ring systems with 1,3-diene moieties **4,6**.



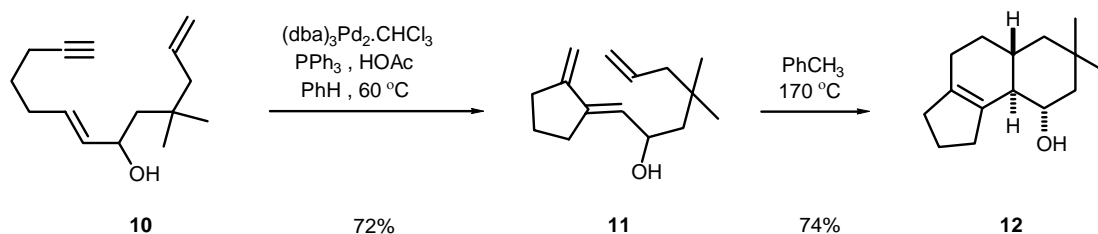
Scheme 3.

Consequently, the formation of 1,3-diene systems opens the door for Diels-Alder reaction as a suitable subsequent reaction,^[9](Scheme 4).



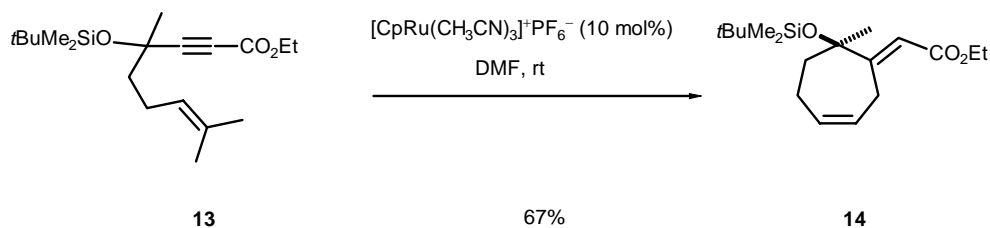
Scheme 4.

More interestingly, a sequence of 1,6-enyne palladium-catalyzed cycloisomerization and Diels-Alder reaction can take place in an intra-intra molecular fashion to produce a tricyclic system from an open chain precursor in a single step,^[9] (Scheme 5).



Scheme 5.

Albeit palladium-catalyzed 1,7-enyne cycloisomerizations to form six-membered systems are feasible processes, they are less efficient than the palladium-catalyzed 1,6-enyne cycloisomerizations which lead to the formation of five-membered ring systems.^[10] Nevertheless, such processes can be induced more efficiently by using Ni-Cr catalyst^[11]. Even though palladium has been the most extensively studied and used metal to induce such transformations, other metals such as Fe,^[12] Ti (Zr),^[13] Pt,^[14] Rh,^[15] Co,^[16] Ir^[17] and Ru^[18] can be used as well. Scheme 6^[19] illustrates an interesting example wherein a Ru complex is used as a catalyst to give a seven-membered ring compound **14**.



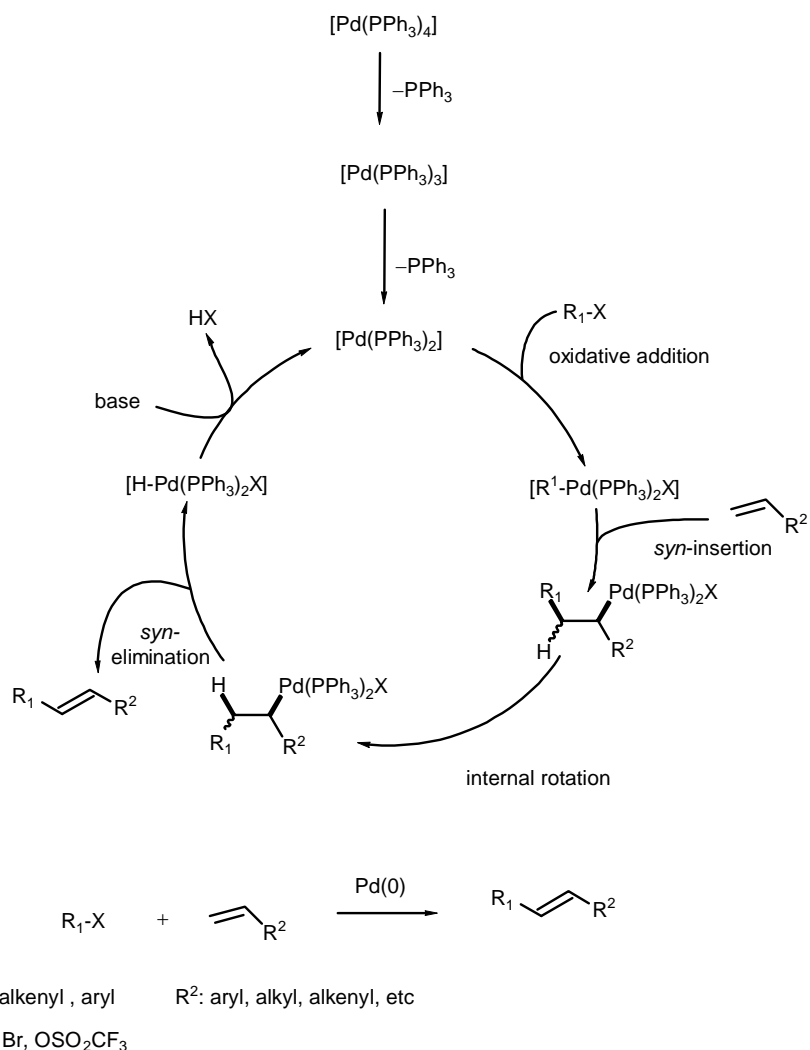
Scheme 6.

Despite the diversity of the metals, which are capable of activating such cycloisomerizations, there are only few general mechanisms via which these metals can induce this cycloisomerization.^[20]

3. Heck Reaction

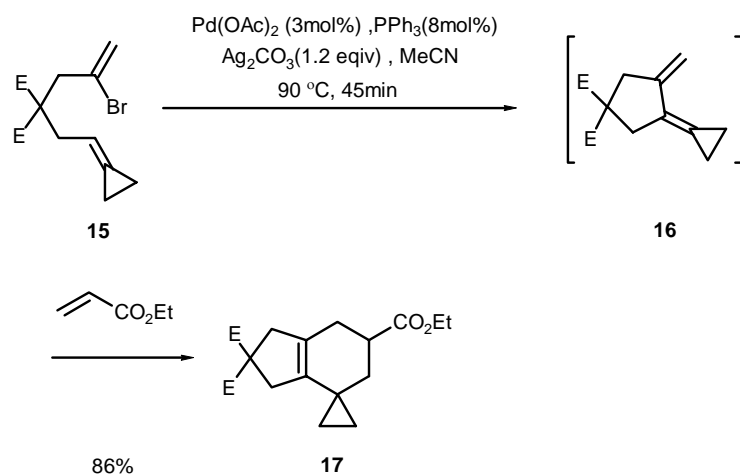
The Heck reaction is another spectacular application for transition metals, specifically for palladium-catalyzed processes, whereby arylation and alkenylation of a vinylic halide or triflate can take place. During the last two decades, the Heck reaction has become one of the most widely used reactions in organic synthesis.^[21]

Scheme 7 illustrates general proposed mechanism for the Heck reaction that suggests formation of a neutral coordinatively unsaturated 14-electron palladium(0) species which is considered the catalytically active complex.^[21] However, studies by Amatore assume that the Heck reaction proceeds via anionic species.^[22]



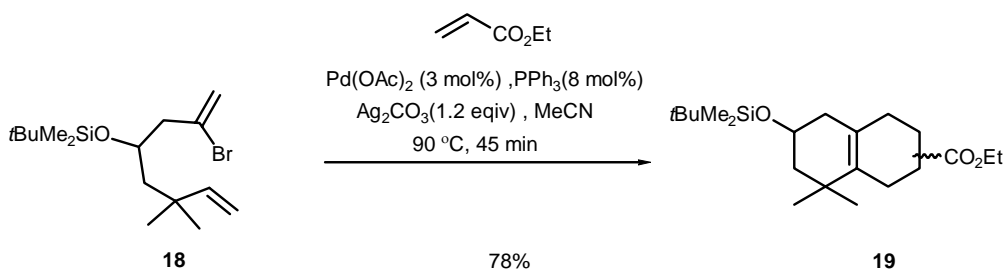
Scheme 7.

In a close analogy to the cycloisomerization reaction, the Heck reaction can be used to construct polycyclic systems in one-pot reactions. Thus, when the 2-bromo-1,6-diene is treated under standard Heck reaction conditions (palladium-acetate (3%), triphenyl phosphine (8%), silver carbonate (1.2 equiv), acetonitrile, 90 C), the cyclic 1,3-diene **16** will evolve which upon treating with a dienophile gives **17**, (Scheme 8.).^[23]



Scheme 8. E = CO_2CH_3 .

In contrast to palladium-catalyzed cycloisomerizations, the formation of six-membered rings and the subsequent reactions can be achieved more efficiently. (Scheme 9).^[23]

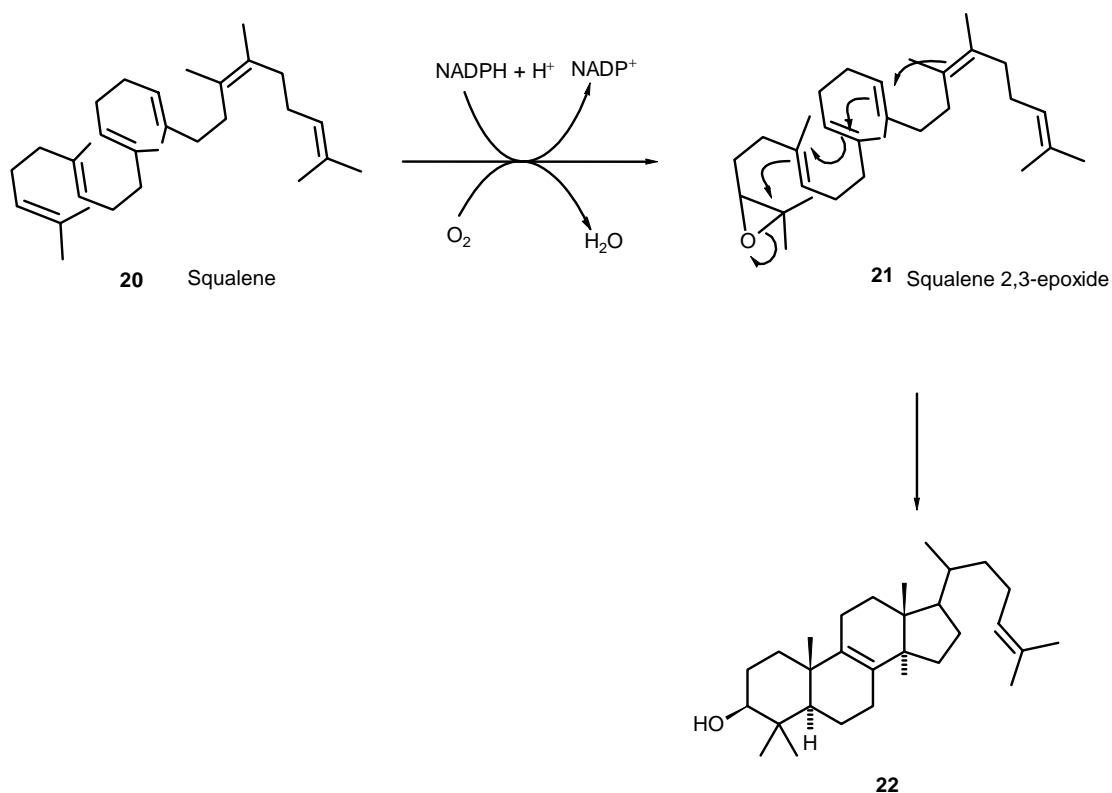


Scheme 9.

The Heck reaction was widely used in the synthesis of various natural products compounds.^[24]

4. Cascade Reactions

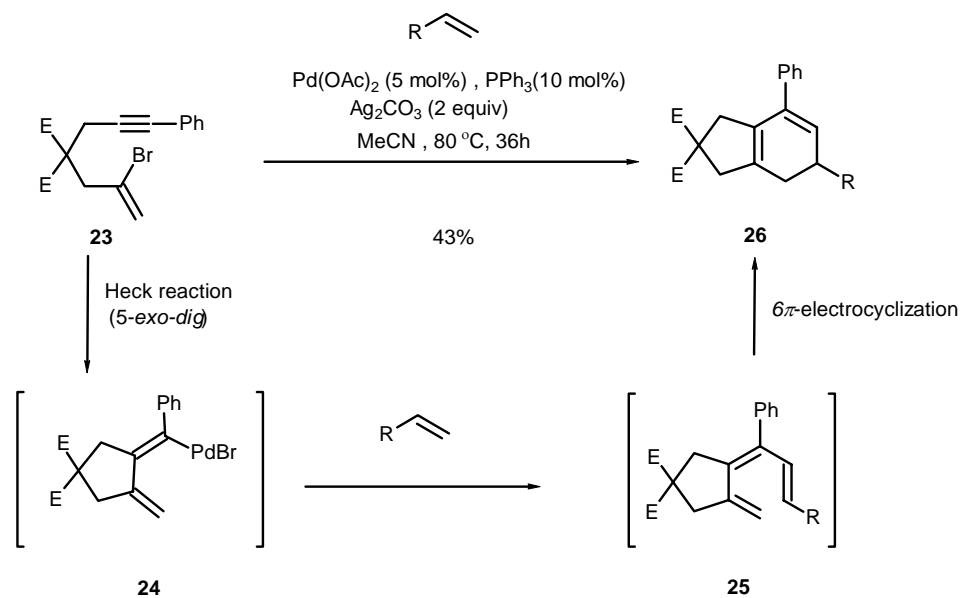
Cascade reactions can be described as sequential reactions with several steps of the same mechanistic type but with a changing substrate^[25] or sequential reactions with several steps of two or more different reaction type.^[26] The subtlest example of this type of the reactions is the one whereby the living cells are synthesizing steroids from Squalene **20** via a series of regio- and stereospecific cationic reactions and rearrangements, (Scheme 10).^[27] Once again we find God's creation in nature is overwhelmingly far ahead of us.



Scheme 10.

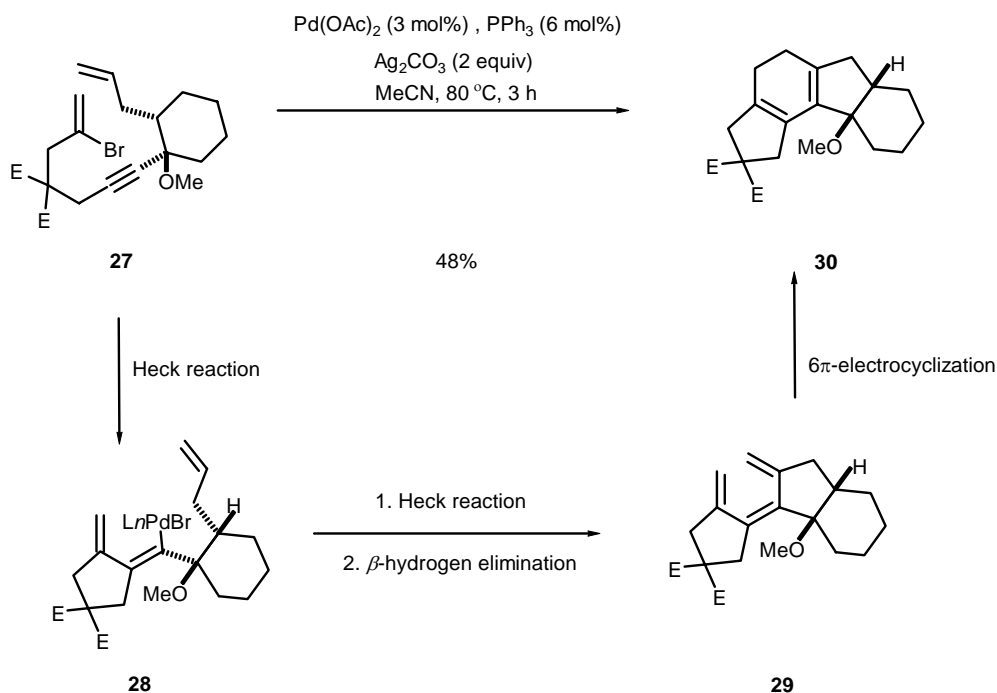
The previous two sections demonstrate two examples of cascade reactions wherein palladium catalyzed cycloisomerization or Heck reaction was followed by either an inter or an intramolecular Diels-Alder reaction.

Furthermore, when 2-halo-1,6-enynes, for example **23**, are used, the resulting intermediates (eg. **24**) will have the potential to undergo a further carbometallation to afford trienes **25** which by 6π -electrocyclization give tricyclic systems as **26**, (Scheme 11.).^[28]



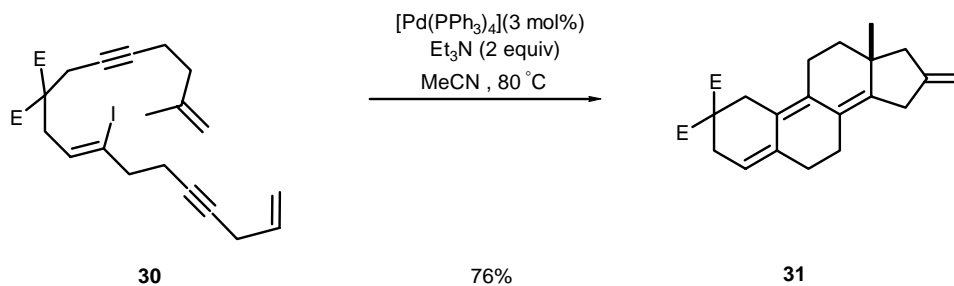
Scheme 11. E = CO₂Et, R = OEt

This type of cascade reaction can be extended in an intramolecular fashion to construct complicated polycyclic systems in a single step. The feasibility of such processes stems from the low reactivity of the vinylmetal intermediate towards β -hydrogen elimination.^[29] Scheme 12 illustrates one example of this process.^[30]



Scheme 12. E = CO₂Et.

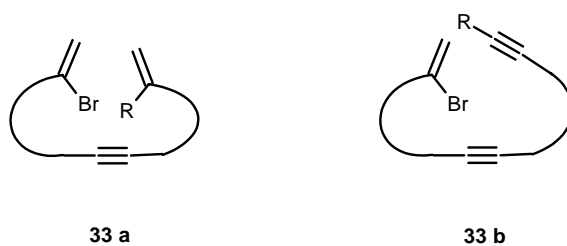
Negishi et al used such cascade reactions, triggered by Heck reaction, to construct steroid skeletons in an elegant way, (Scheme 13.).^[31]



Scheme 13.

Similar cascade reactions can be initiated by palladium cycloisomerization reaction.^[32]

Constructing polycyclic systems with different ring sizes by using cascade reactions of the bromodienyne precursors **33a** was explored.^[33] Cascade reactions which might lead to three fused six-membered rings, using bromodienyne systems **33b**, were not thoroughly investigated.



A recent study by Schweizer et al showed that the outcome of such precursors depends on the substitution at the terminal triple bond to give either aromatic or fulvene systems.^[34]

Therefore this study is aiming at:

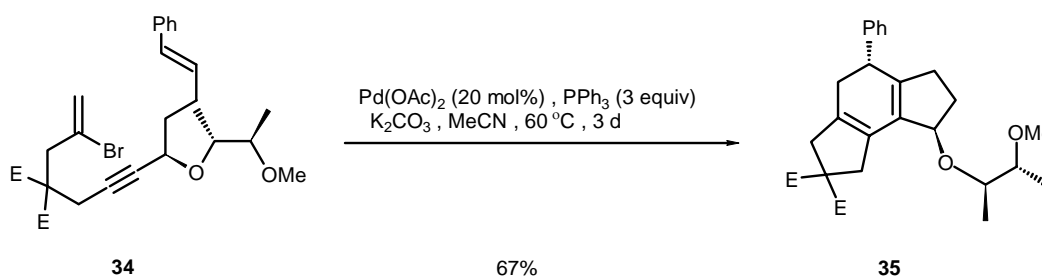
- Synthesis of some bromoendiyne precursors which might lead to the formation of three fused six-membered ring systems.
- Exploring the feasibility of their palladium catalyzed cyclizations.
- Studying the effect of the geminal substitution at the tether linking the vinylbromide moiety and the internal triple bond on the course of the reaction.
- Studying the effect of the substitution at the terminal alkyne.
- Trying to propose mechanisms to explain the outcomes of these cyclizations.

B. Main Part

1. Palladium-catalyzed oligocyclization of 2-bromo-14-phenyl-tetradec-1-ene-7,13-dynes

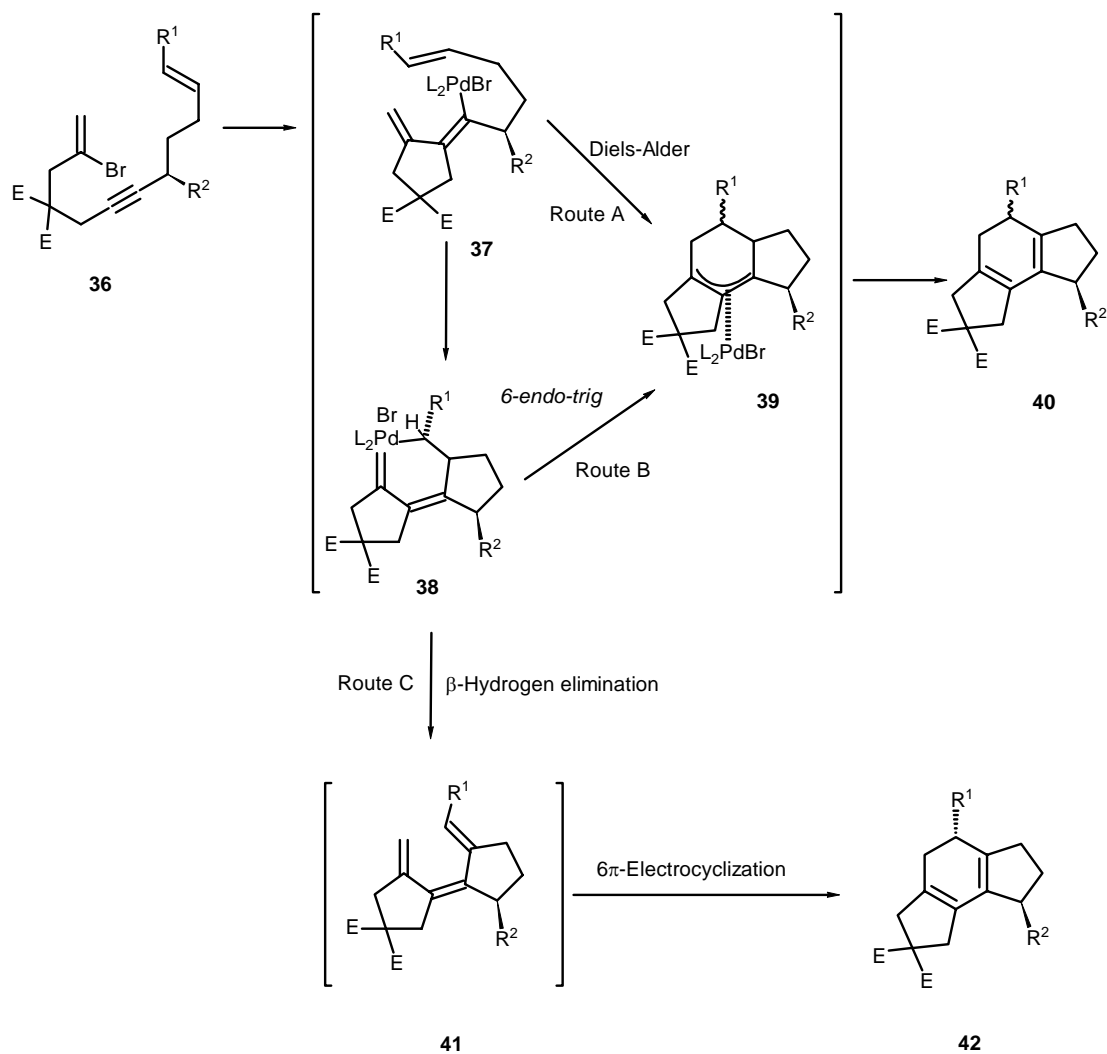
1.1. Prologue

The Palladium-catalyzed oligocyclization of 2-bromo-12-phenyldodeca-1,11-diene-6-yne to afford a tricyclic system with two five-membered rings fused to a six-membered central core was reported (Scheme 14.).^[35]



Scheme 14.

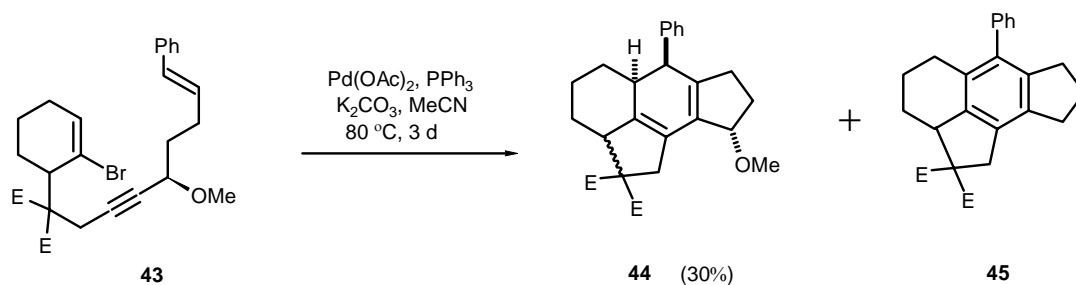
Although there are several mechanistic routes via which such cascade can take place, the fact that only one stereo and regio isomer was formed suggests that the cascade proceeds via a two-fold intramolecular Heck reaction followed by a disrotatory 6π -electrocyclization after β -hydride elimination, (Scheme 15, route C),



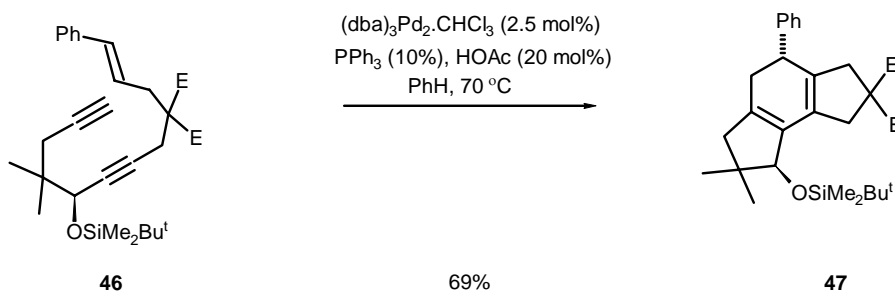
Scheme 15. $R^1 = \text{H, OMe}$, $R^2 = \text{Ph, CO}_2\text{Me}$, $\text{E} = \text{CO}_2\text{Et}$

However, when changing the substituents or the substituent pattern at the non-brominated double bond, the cascade proceeds through one of the other two routes. This means that the pathway which the cascade will adapt depends on the substituents and the substituent pattern of the non-brominated alkene.

Trying to explore the scope of the cascade using different vinyl bromide systems which might lead to more complicated polycyclic systems, resulted in the same pattern of the cyclisation, (Scheme 16.).^[30]

Scheme 16. E = CO₂Et.

Furthermore, when the cascade was initiated by hydropalladation instead of Heck reaction, similar results were obtained (Scheme 17).^[32]

Scheme 17. E = CO₂Et.

When the double bond bearing the phenyl moiety is replaced with a triple bond, the possibility for β -hydrogen elimination and tandem disrotatory 6π -electrocyclization or for Diels-Alder reactions (routes A&C, Scheme 15) will be eliminated.

It is, therefore, of interest to examine the feasibility of the cascade reactions when the phenyl substituted alkene is replaced by phenyl substituted alkyne and to explore the scope of the cascade in constructing new polycyclic systems bearing three fused six-membered rings. Thus, the synthesis and palladium-catalyzed oligocyclisation of precursors such as **48** and **49** will be investigated

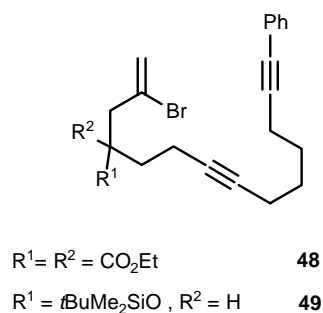
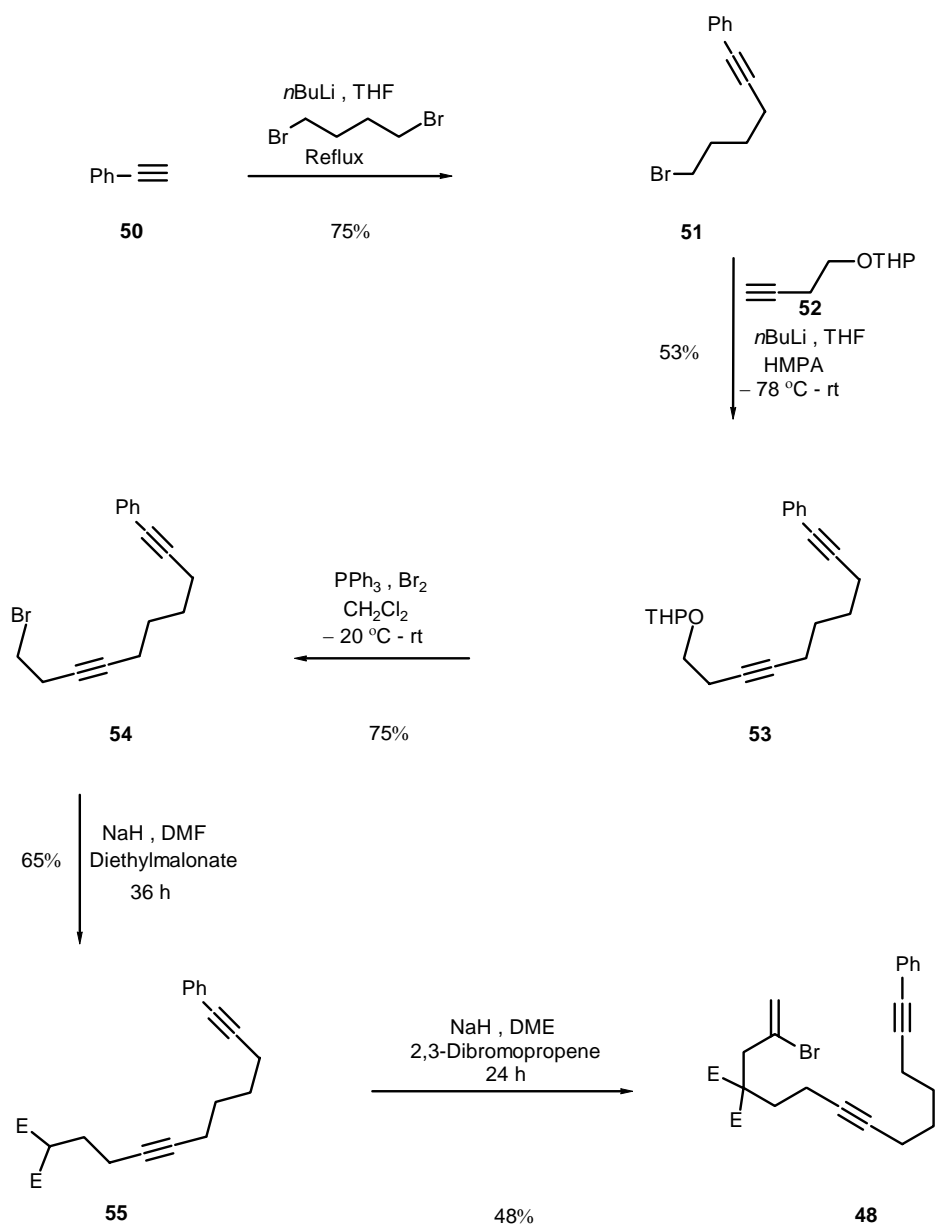


Fig 1

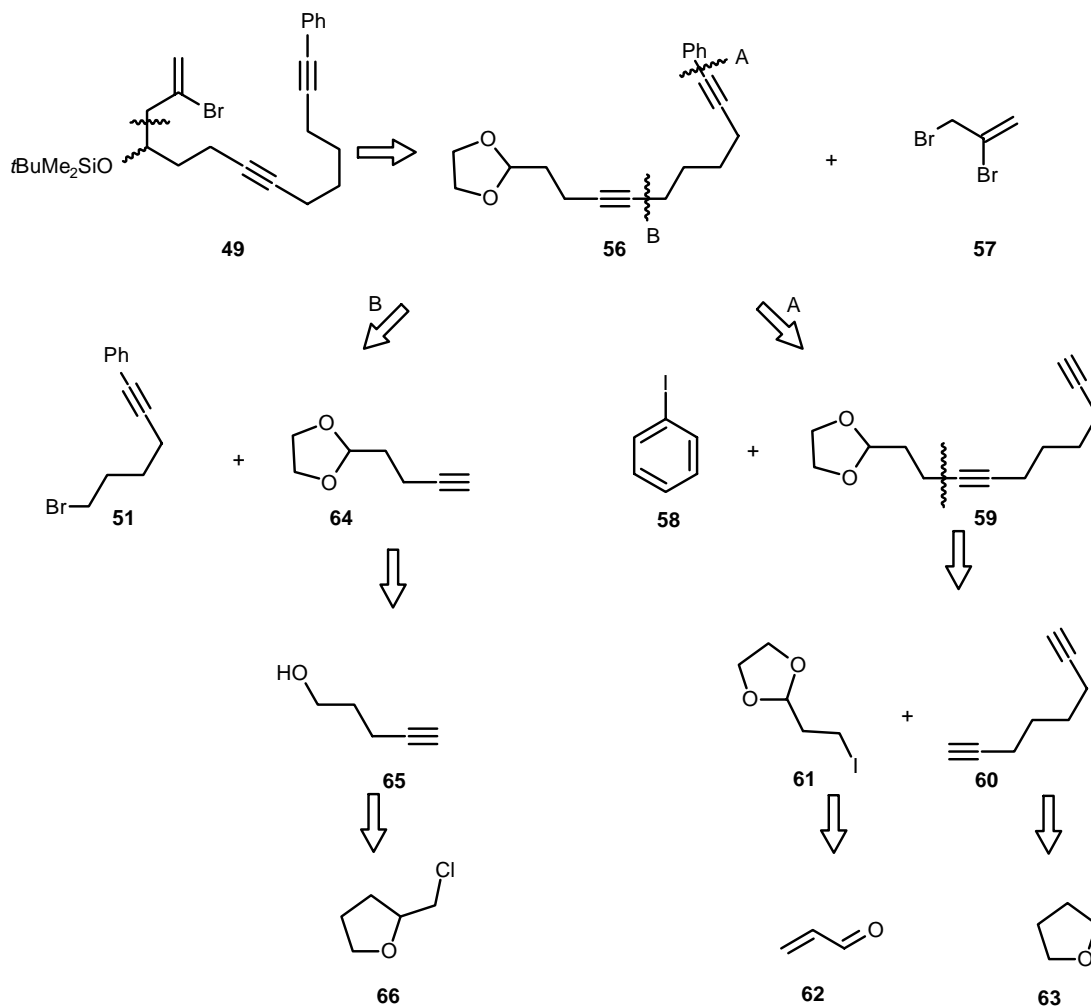
1.2. Synthesis of phenyl substituted precursors

The synthesis of **48** can be achieved by a series of carbon-carbon coupling steps, (Scheme18.). Consequently, treating phenyl acetylene with *n*-butyl lithium and further coupling with 1,4-dibromobutane, following a general protocol described by J.K. Crandall et al,^[36] gives 6-bromo-1-phenyl-1-hexyne (**51**) in a 77% yield . The reaction is highly sensitive to the quantity of *n*-butyl lithium used , since excessive use of *n*-butyl lithium would lead to the undesired free radical cyclization of the product and hence lowering the yield.^[37] The produced compound **51** is then coupled, at $-78\text{ }^\circ\text{C}$, with lithiated 2-(3-butynyloxy)tetrahydro-2H-pyran **52**, prepared from PPTS-catalyzed reaction of 2,3-dihydropyran with 3-butyne-1-ol which was obtained from acetylene and ethylene oxide,^[38] in THF and HMPA to give **53** in a 48% yield. Subsequently, the OTHP group of **53** is converted into its corresponding bromide^[39] **54** which is then attached to sodium malonate, generated by treating diethyl malonate with sodium hydride, to furnish **55** in a 63% yield. The produced diethyl 2-(10'-phenyl-3',9'-decadiynyl)malonate **55** is then treated with sodium hydride in DME and coupled with 2,3-dibromopropene to afford the target precursor **48** in a 44% yield. As the last step is a solvent sensitive $\text{S}_{\text{N}}2$ nucleophilic substitution,^[40] it will be shown latter that altering the solvent polarity will highly affect the yield.

Scheme 18. E = CO₂Et.

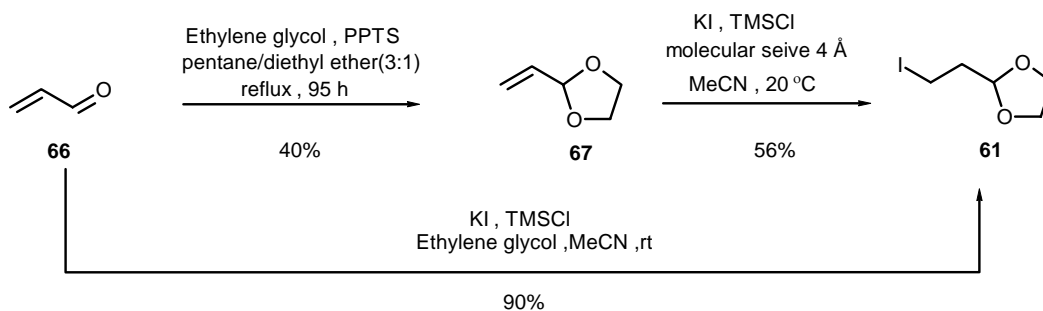
The retro synthesis of **49** reveals two approaches for preparing it, (Scheme 19.). The first step in both approaches involves disconnecting the bond between the carbon bearing the silyloxy group and the allyl bromide moiety. The second step in the first approach involves breaking the C-C bond which links the internal acetylene with 1-phenyl-1-hexyne moiety to afford the synthons **51** And **64**, (route B). However, the second step in the second approach involves disconnecting the phenyl moiety followed by breaking the

C-C bond from the left side of the internal acetylene moiety to afford **60** And **61**, (route A).



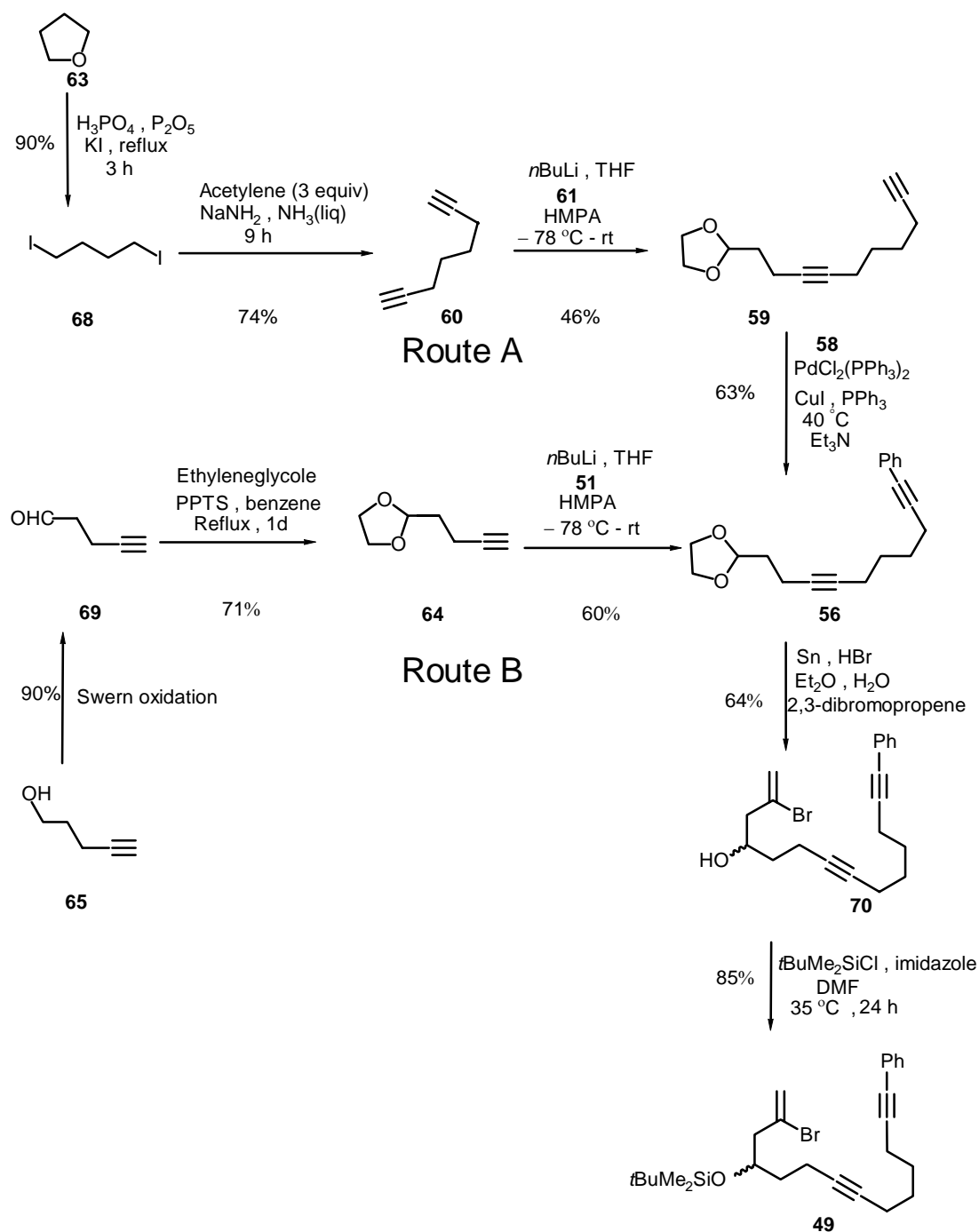
Scheme 19.

Compound **61** can be synthesised from acroleine **66** by either one^[41] or two step synthesis (Scheme 20.).^[42] 1,7-octadiyne **60** can be obtained from tetrahydrofuran as shown in Scheme 21.



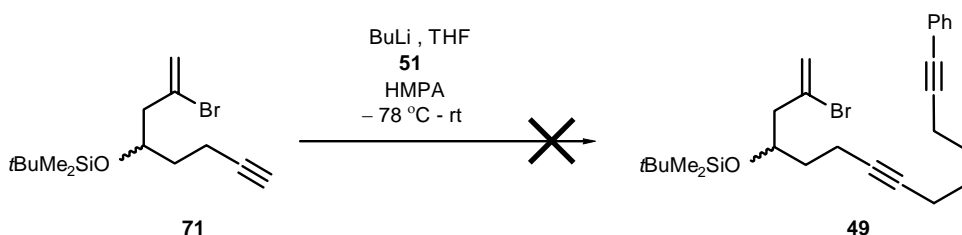
Scheme 20.

Scheme 21 illustrates the synthesis of **49** using the two approaches. Thus Swern oxidation of pentyn-1-ol,^[43] prepared by treating of chloromethyltetrahydrofuran with sodium amide in liquid ammonia,^[44] gives the unstable aldehyde **69** in a 90% yield which is then refluxed with ethylene glycol and PPTS in benzene to give the corresponding acetal **64**. Treating the acetal with *n*-butyl lithium and then coupling with 6-bromo-1-phenyl-1-hexyne (**51**) produces **56** in a 60% yield. Alternatively, the acetal **56** can be obtained by rout B. Thus treating tetrahydrofuran with phosphorous pentoxide and potassium iodide affords 1,4-diiodobutane (**68**)^[45] which is then treated with the acetylenic anion in liquid ammonia to give 1,7-octadiyne (**60**)^[46] in a 73% yield. **60** is then treated with *n*-butyl lithium and coupled with 2-(1,3-dioxolan-2-yl)ethyl iodide **61** to produce **59** in a 46% yield. The low yield might be attributed to the chemoselectivity problem of the 1,7-octadiyne and the subsequent side reactions that might take place. Nonetheless, about 40% of 1,7-octadiyne can be recovered. Despite the possible side reactions, using Sonogashira^[3] coupling to attach the phenyl group to the terminal alkyne of **59** succeeds in a reasonable yield. Consequently, when **59** is treated with iodobenzene (**58**) in the presence of (0.5 mol %) PdCl₂(PPh₃)₂ and (2 mol %) CuI in triethylamine, it affords **56** in a 63% yield. The produced phenyl-substituted acetal **56**, from both routes A & B, is then coupled with 2,3-dibromopropene in the presence of powdered tin, by modifying the procedure described by Otera et al,^[47] to afford the alcohol **70**. Because the reaction is time-dependant, stirring the reaction for longer periods, 4-5 days, will improve the yield significantly. The alcohol is then protected by *tert*-butyldimethylsilyl chloride using imidazole in DMF to give the target precursor **49** in an 82% yield.



Scheme 21.

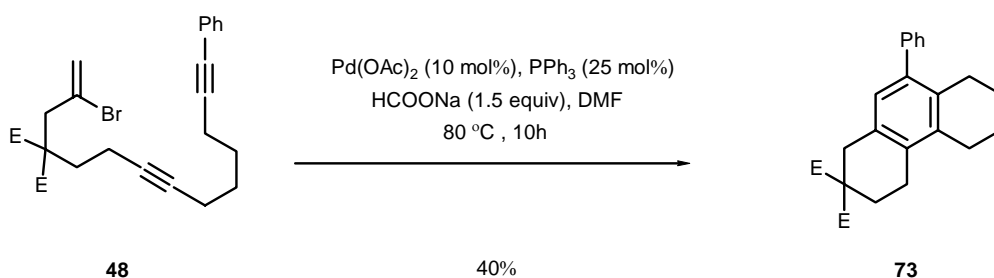
It is noteworthy that trying to synthesize **49** by direct coupling of **71**^[48] with 6-bromo-1-phenyl-1-hexyne **51** was unsuccessful, (Scheme 22.).



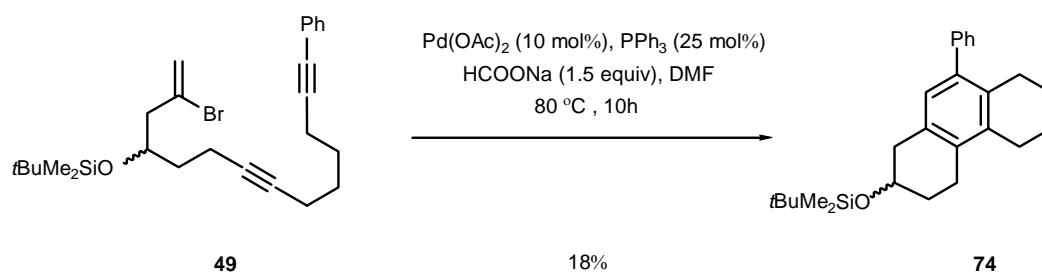
Scheme 22.

1.3. Palladium-catalyzed oligocyclizations of phenyl substituted precursors

When **48** had been heated at 80 °C in DMF in the presence of palladium acetate (10 mol%), triphenyl phosphine (25 mol%) and sodium formate, compound **73** was formed in a 40% yield, (Scheme 23.). Apparently, a palladium-catalyzed oligocyclization had taken place to give **73**. The structure of **73** was established by one- and two-dimensional NMR techniques. Mass spectroscopy proved the loss of HBr while the appearance of new six olefinic signals in ^{13}C -NMR spectrum indicates the formation of a tricyclic system with a two tetrasubstituted double bonds and one trisubstituted double bond. The presence of new olefinic singlet at 6.90 ppm in the ^1H -NMR spectrum confirms this conclusion. H/H COSY and gHSQC are in agreement with the proposed structure.

Scheme 23. E = CO₂Et

Subjecting **49** to the standard Heck reaction conditions, palladium acetate, triphenyl phosphine and potassium carbonate in acetonitrile, had failed to induce the desired cascade and only the starting material was recovered. Nevertheless, when **49** had been heated at 80 °C in DMF and in the presence of palladium acetate (10 mol%), triphenyl phosphine (25 mol%) and sodium formate, compound **74** was formed in a 15% yield, (Scheme 24.). Compound **74** was characterized by one- and two-dimensional NMR and it showed nearly similar spectral patterns as those for **73**.



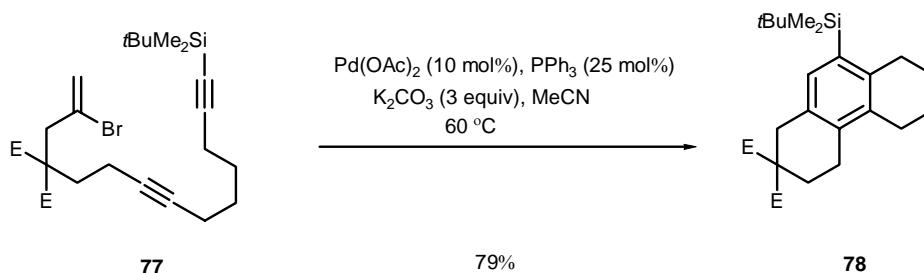
Scheme 24.

It is clear from schemes 23 and 24 that the presence of the malonate group has an influence on the yield of the cascade but not the outcome of the cascade.

2. Palladium-catalyzed oligocyclization of 2-bromo-14-*tert*-butyldimethylsilyl tetradec-1-ene-7,13-dynes

2.1. Prologue

Palladium-catalyzed oligocyclization of *tert*-butyldimethylsilyl substituted of 2-bromo-tetradec-1-ene-7,13-diyne such as **77** was reported, (Scheme 25.)^[34]



Scheme 25.

Nevertheless, in the last section it was observed that the geminal substitution at the tether which links the vinyl bromide moiety with internal alkyne of such precursors has an influence on the yield of the cascade. Thus, when the malonate was replaced by the bulky *tert*-butyldimethylsilyloxy group, the cascade's yield sharply decreased. The reason behind this is not clear yet. It might be attributed to sterical factors imposed by the malonate group or any similar group on the carbon chain that make it into more suitable conformation for such cyclizations or to instability of the final outcomes of the cascade. It is, therefore, of interest to investigate the feasibility of such cyclizations when the malonate is replaced with *tert*-butyldimethylsilyloxy group such as **80** or with substituents devoid steric hindrance such as **79**

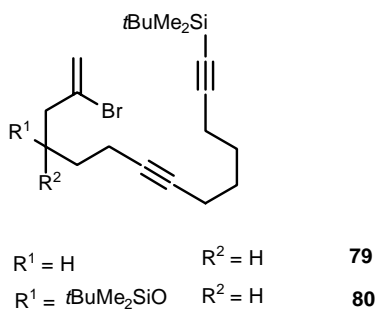
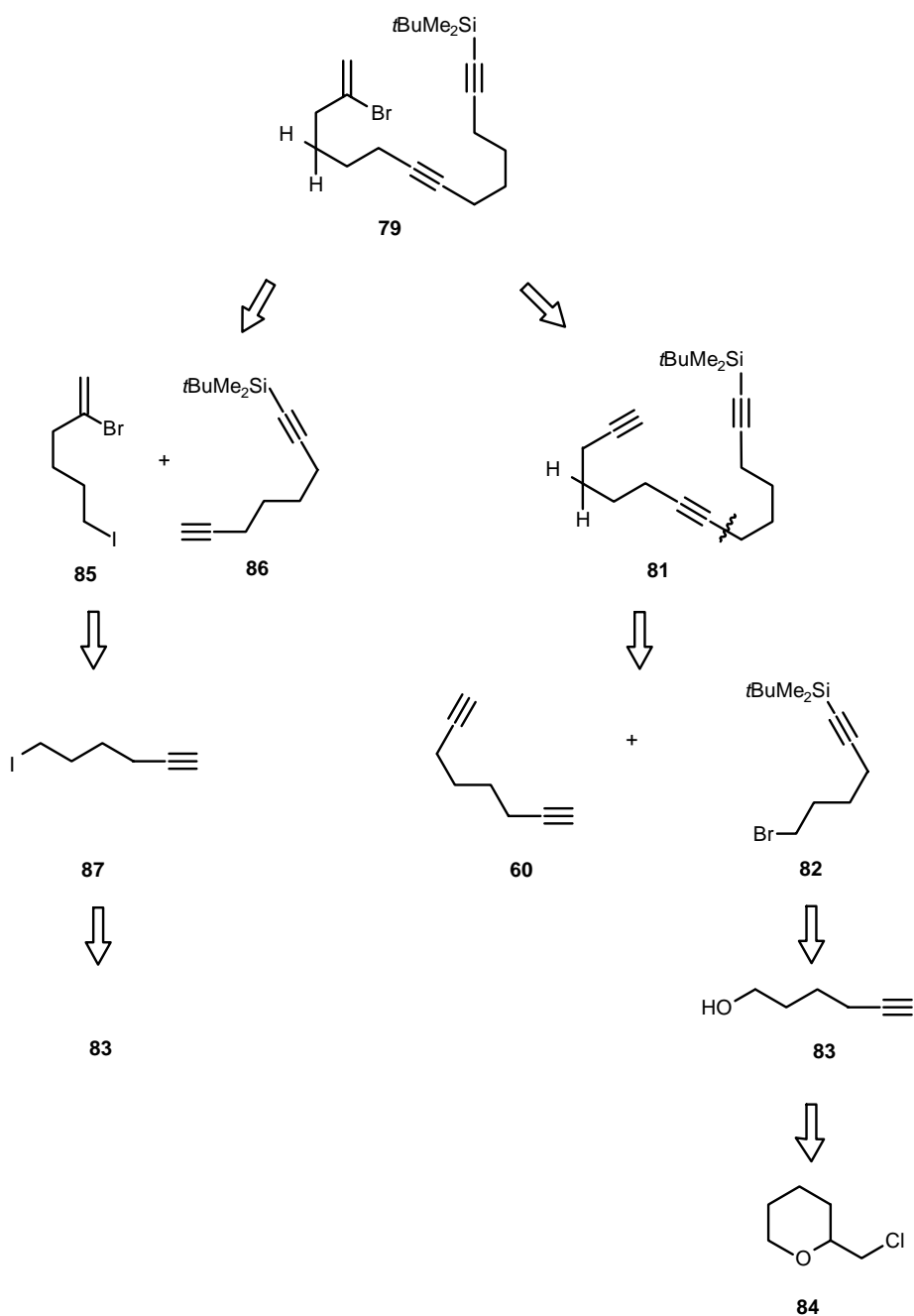


Fig 2.

2.2. Synthesis of *tert*-butyldimethylsilyl substituted precursors

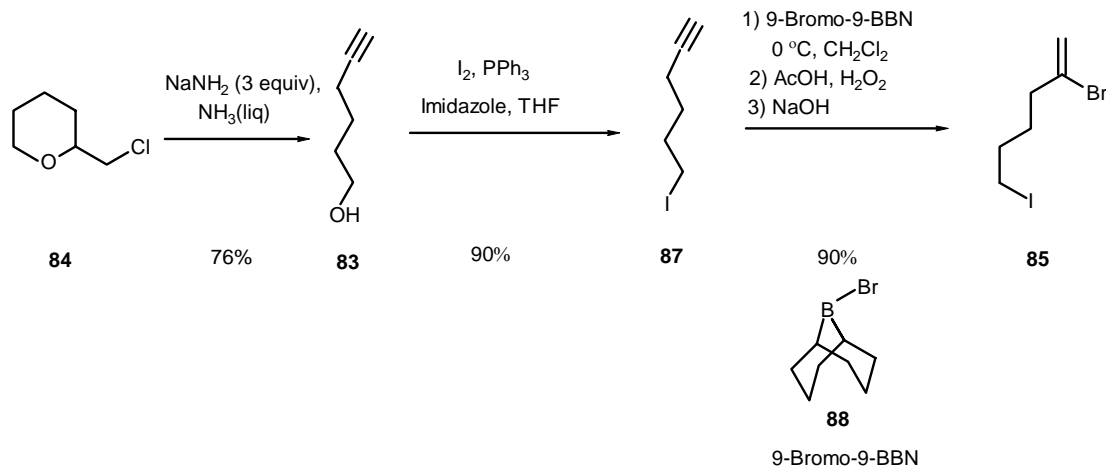
The retrosynthesis of **79** reveals two routes for preparing **79** (Scheme 26). The first route starts with dehydrohalogenation of the vinyl bromide to afford a triyne system **81**. Further fragmentation of the later by breaking the C-C bond from the right side of the internal alkyne would produce **60** and **82** which can be easily prepared from 5-hexyn-1-ol **83**. The second approach involves breaking the C-C bond from the left side of the internal alkyne to afford **86** and **85** which can also be prepared from 5-hexyn-1-ol (**83**).



Scheme 26.

Before describing the synthesis of **79**, compound **85** can be prepared by converting 5-hexyn-1-ol (**83**), which can be obtained from treating 2-chloromethyl-tetrahydro-2H-pyran (**84**) with sodium amide in liquid ammonia,^[49] into the corresponding iodide **87** and then hydrobromination the terminal alkyne with B-bromo-9-

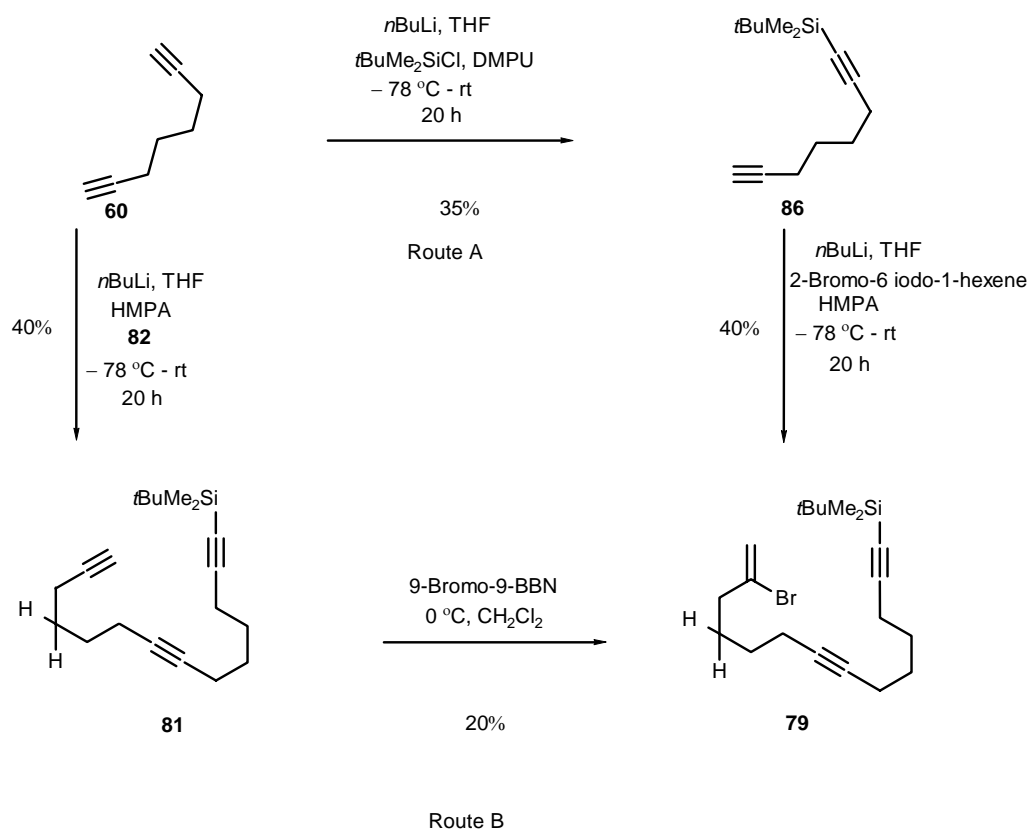
borabicyclo[3.3.1]nonane (9-bromo-9-BBN) (**88**), a protocol described by W.F.Baily et al.^[37], (Scheme 27.).



Scheme 27.

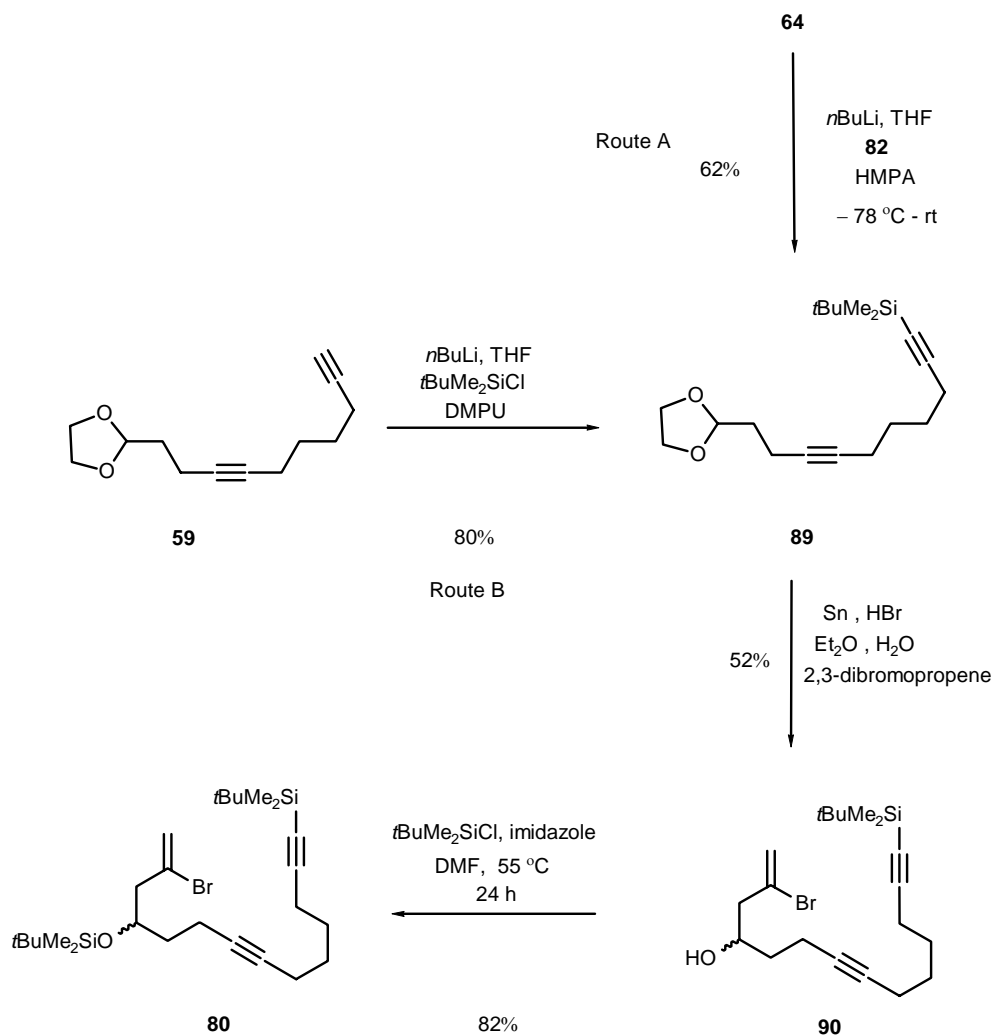
Compound **82** can also be synthesized from hexyn-1-ol (**83**) according to a described procedure.^[33]

Compound **79** can be synthesized by two routes, (Scheme 28.). In Route A, 1,7-octadiyne (**60**) is treated with *n*-butyl lithium and HMPA in THF and coupled with 6-bromo-1-*tert*-butyldimethylsilyl hex-1-yn **82** to give the triyne system **81**. Treatment the resulting triyne with 9-bromo-9-BBN **88** in dichloromethane and subsequent protonolysis gives the desired precursor **79** in a 20% yield. Despite the high chemo-, regio- and stereoselectivity of the 9-bromo-9-BBN^[50] (the haloboration can take place only at the terminal mono substituted alkynes and not at the internal disubstituted alkynes) the yield of the last step is not very high. This is maybe due to the polymerization of **81** or side reactions that might take place. Because of the low yield of Route A, Route B becomes an alternative approach. In Route B, the lithiated 1,7-octadiyne is attached to *tert*-butyldimethylsilyl chloride^[51] followed by coupling with **85** to give the precursor **79** in a 40% yield. Unfortunately Route B does not offer a good substitute for Route A this due to the low yield of its two steps.



Scheme 28.

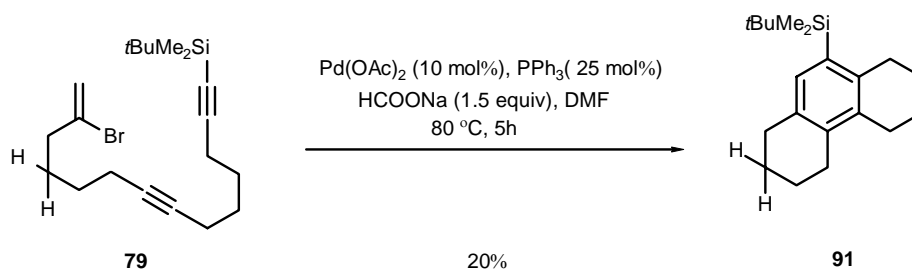
Compound **80** is prepared in a similar manner like **49**. Thus compound **89** can be prepared following the same two routes for preparing **49**, (Scheme 29.). In Route A, compound **89** is generated from linking the lithiated acetal **64** with 6-bromo-1-*tert*-butyldimethylsilyl hex-1-yn (**82**). However, in Route B, it is produced by alkylating the lithiated 1,7-octadiyne with **61** to produce **59**, (Scheme 21, Route A), and Silylation of the terminal triple bond of the later with *tert*-butyldimethylsilyl chloride. Treatment **89** with 2,3-dibromopropene in the presence of tin powder produces the alcohol **90** which is then protected by *tert*-butyldimethylsilyl chloride to give **80**.



Scheme 29.

2.3. Palladium-catalyzed oligocyclizations of tert-butyldimethylsilyl substituted precursors

Table 1 shows different variations of conditions to cyclize **79**. In most cases the starting material was recovered and the cyclization had not taken place. However, only when **79** had been treated at $80\text{ }^\circ\text{C}$ with palladium acetate (10 mol%) and sodium formate in DMF, did the cyclization take place to afford the bisannulated benzene derivative **91**, (Scheme 30.)



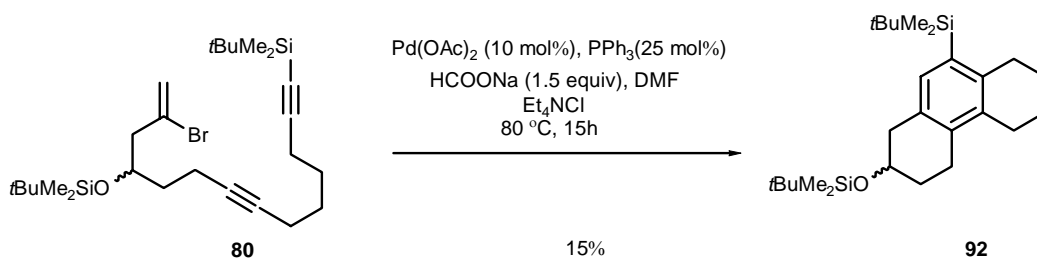
Scheme 30. (Conditions, see Table1)

Table 1

Entry	Reaction Conditions and Reagents	Product
1	Pd(OAc)_2 , PPh_3 , K_2CO_3 , CH_3CN , $60\text{ }^\circ\text{C}$, 20 h	starting material
2	Pd(OAc)_2 , PPh_3 , Ag_2CO_3 , THF, $60\text{ }^\circ\text{C}$, 20 h	starting material
3	Pd(OAc)_2 , PPh_3 , Ag_2CO_3 , DMF, $80\text{ }^\circ\text{C}$, 20 h	starting material
4	Pd(OAc)_2 , PPh_3 , Et_3N , DMF, $80\text{ }^\circ\text{C}$, 20 h	starting material
5	Pd(OAc)_2 , PPh_3 , HCOONa , DMF, $80\text{ }^\circ\text{C}$, 20 h	91

Again the disappearance of the acetylenic carbon signals and the appearance of new six olefinic carbons in the ^{13}C -NMR indicate the formation of three double bonds. Mass spectroscopy confirms the loss of HBr and the ^1H -NMR shows the appearance of a new singlet at 7.05 ppm which supports the formation of a tricyclic system with two tetrasubstituted double bonds and one trisubstituted double bond. H/H COSY and gHSQC are in agreement with this conclusion.

Similarly, trying to subject precursor **80** to different reaction conditions, failed to induce the desired oligocyclization, (Table2). Nonetheless, the cyclization did take place when **80** had been treated at $80\text{ }^\circ\text{C}$ with tetraethyl ammonium chloride, palladium acetate and sodium formate in DMF to give also an aromatic system **92**, (Scheme 31.).



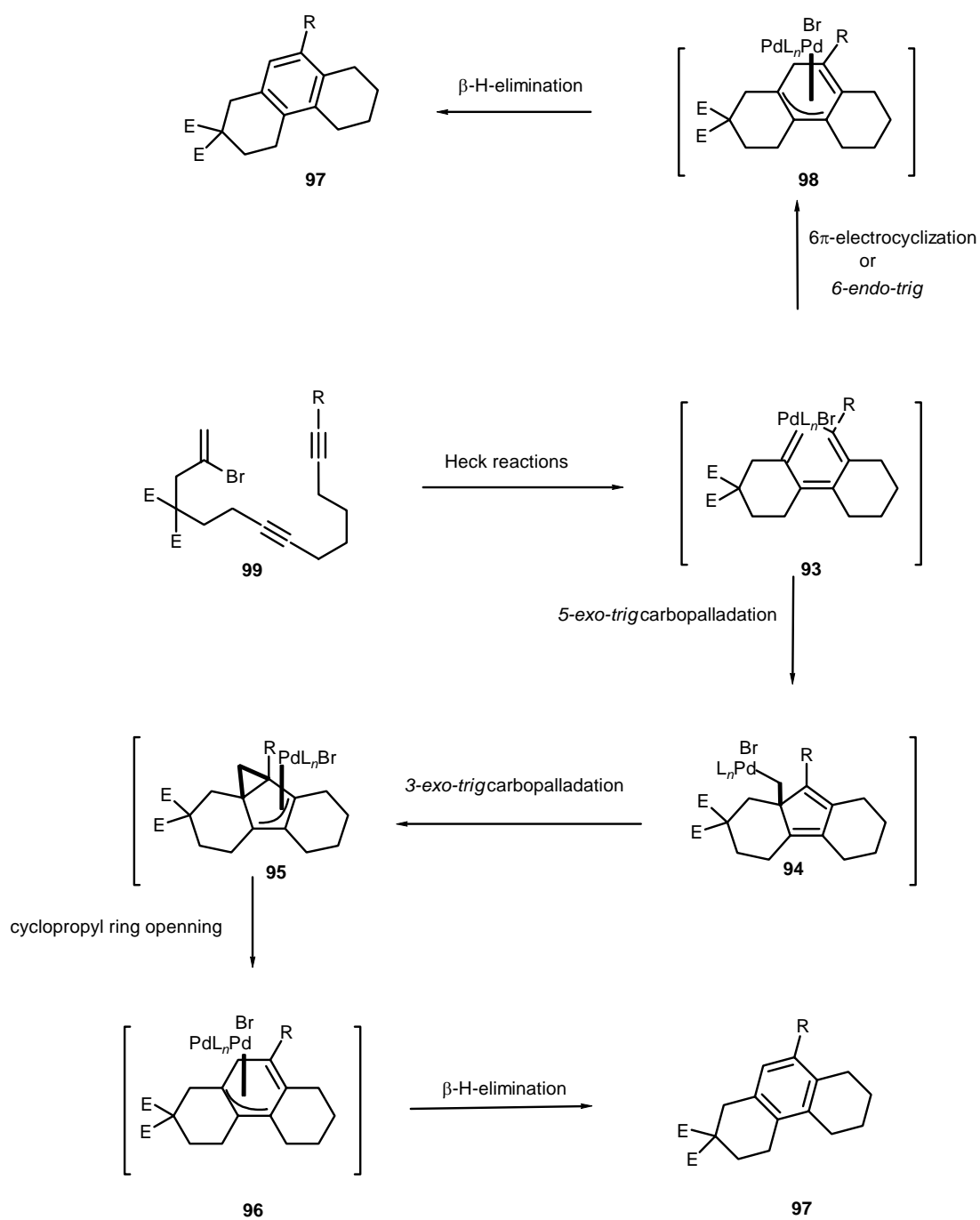
Scheme 31.

Table 2

Entry	Reaction Conditions and Reagents	Product
1	Pd(OAc)_2 , PPh_3 , K_2CO_3 , CH_3CN , $60\text{ }^\circ\text{C}$, 20 h	starting material
2	Pd(OAc)_2 , PPh_3 , Ag_2CO_3 , CH_3CN , $60\text{ }^\circ\text{C}$, 20h	starting material
3	Pd(OAc)_2 , PPh_3 , Ag_2CO_3 , DMF, $80\text{ }^\circ\text{C}$, 20 h	starting material
4	Pd(OAc)_2 , PPh_3 , Et_3N , DMF, $80\text{ }^\circ\text{C}$, 20 h	starting material
5	Pd(OAc)_2 , PPh_3 , AcONa , DMF, $80\text{ }^\circ\text{C}$, 20 h	starting material
6	Pd(OAc)_2 , PPh_3 , HCOONa , DMF, $80\text{ }^\circ\text{C}$, 20 h	mixture of products

The structure of **92** was characterised by using one- and two-dimensional NMR techniques. The spectra of **92** show the same spectral patterns as the analogous aromatic system of **74**.

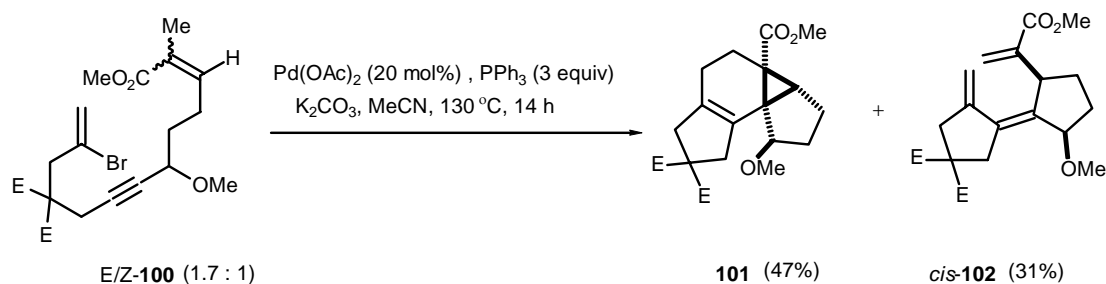
In general the formation of **73**, **74**, **91** and **92** can be rationalized by several possible mechanistic pathways, (Scheme 32.). In the first pathway, the cascade might go throughout a twofold Heck reaction followed by either 6π -electrocyclization or *6-endo-trig* carbopalladation and then β -hydrogen elimination to form three fused six-membered rings or bisannelated benzene derivative **97**. The other possibility is that instead of the 6π -electrocyclization or the *6-endo-trig* carbopalladation, a *5-exo-trig* carbopalladation will take place and neopentyl-like system **94** will be formed. Farther *3-exo-trig* carbopalladation will yield **95** which will undergo ring opening to give **96** followed by β -hydrogen elimination to produce **97**. In the event that 6π -electrocyclization or *6-endo-trig* carbopalladation occurred, the outcome of the cascade reaction, would always be three fused six-membered rings or bisannelated benzene regardless the substituent type at the terminal alkyne (R) of **99**. However, this will not be the case when different substituents other than phenyl or *tert*-butyldimethylsilyl group at the terminal alkyne are used. It will be shown in the next sections that the cascade reaction of **99** offers different types of polycyclic systems depending on the nature of the substituent at the terminal triple bond and this, in fact, makes the *5-exo-trig* carbopalladation route more convenient to explain the formation of **73**, **74**, **91** and **92**.

Scheme 32. E = CO₂Et, R = Ph, *t*BuMe₂Si

3. Palladium-catalyzed oligocyclization of terminally alkoxy carbonyl-Substituted 2-bromo-14-tetradec-1-ene-7,13-dyne

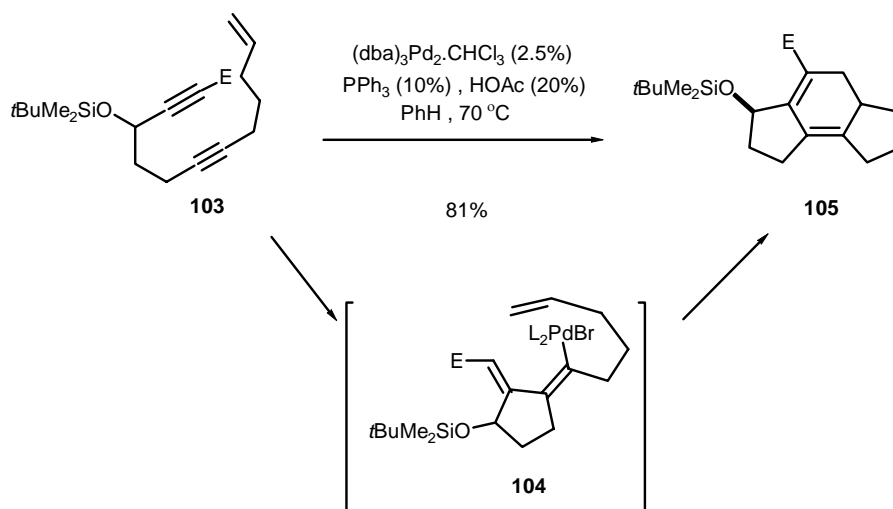
3.2. Prologue

It was mentioned earlier that the nature of the substituents and the substitution pattern at the non-brominated terminal alkene of 2-bromo-12-dodec-1,11-diene-6-yne would determine the cascade's pathway. Thus, replacing the phenyl with an ester group would convert the terminal alkene into an activated dienophile and consequently a pathway involving intramolecular Diels-Alder reaction would become another possible pathway for such cascade. This indeed was the case when **100** had been treated at 130 °C with palladium acetate and potassium carbonate in acetonitrile to afford the Diels-Alder product **101** and the triene system **102**, (Scheme 33.).^[30]

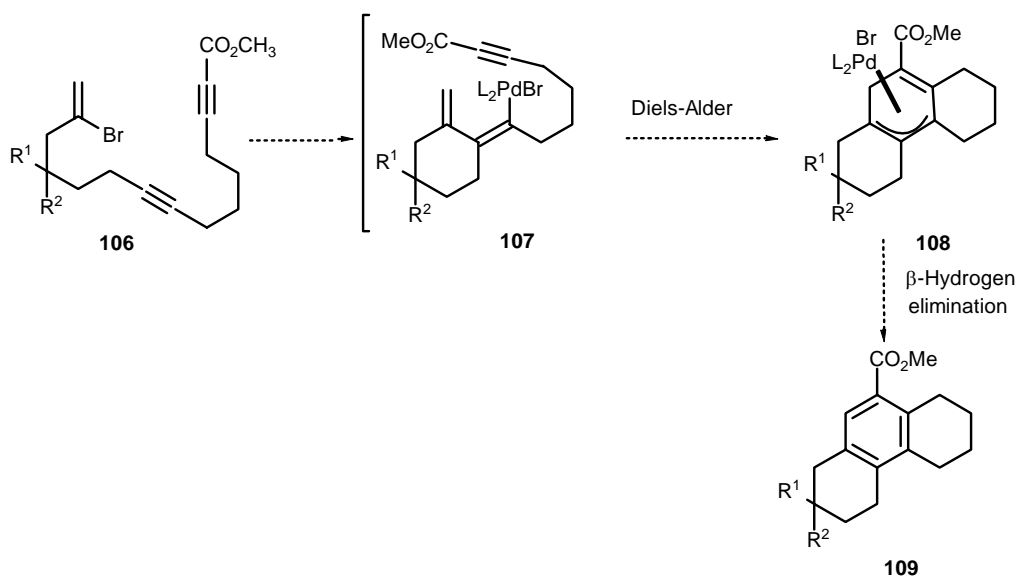


Scheme 33. E = CO₂Et

Similar observations were obtained by Trost et al. However, in this case it was presumed that the Diels-Alder would be induced by the steric strain of the activated diene **104** (Scheme 34.).^[32]

Scheme 34. E = CO₂Me

Although it might be slowed down by increasing the length of the tether linking the diene with dienophile, it would be anticipated, based on the above results, that the cascade reaction of **106**, wherein the terminal triple bond is substituted with an alkoxycarbonyl group, may go through a one Heck reaction followed by an intramolecular Diels-Alder reaction of **107** to give **108** and finally β -hydrogen elimination to produce three fused six-membered rings or a bisannulated methyl benzoate system **109**, (Scheme 35.).

Scheme 35. R¹ = R² = CO₂Me

To probe this hypothesis and to examine the effect of replacing an electron donating group with an electron withdrawing group at the terminal triple bond, compounds such as **110** & **111** are needed to be synthesized and cyclized.

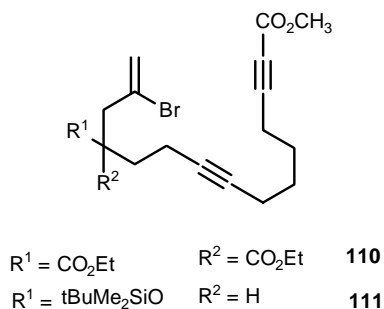
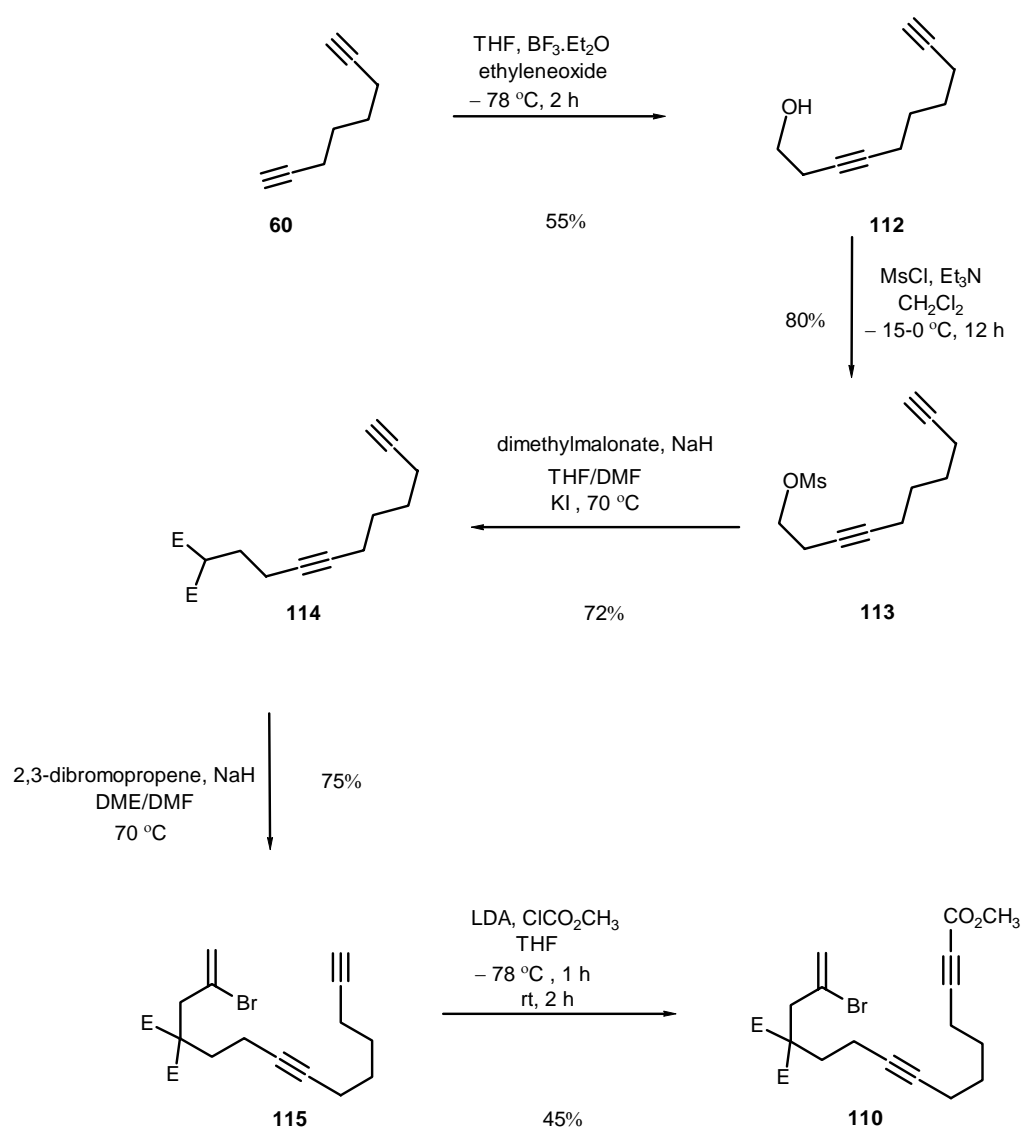


Fig 3.

3.2. Synthesis of the alkoxy carbonyl-substituted precursors

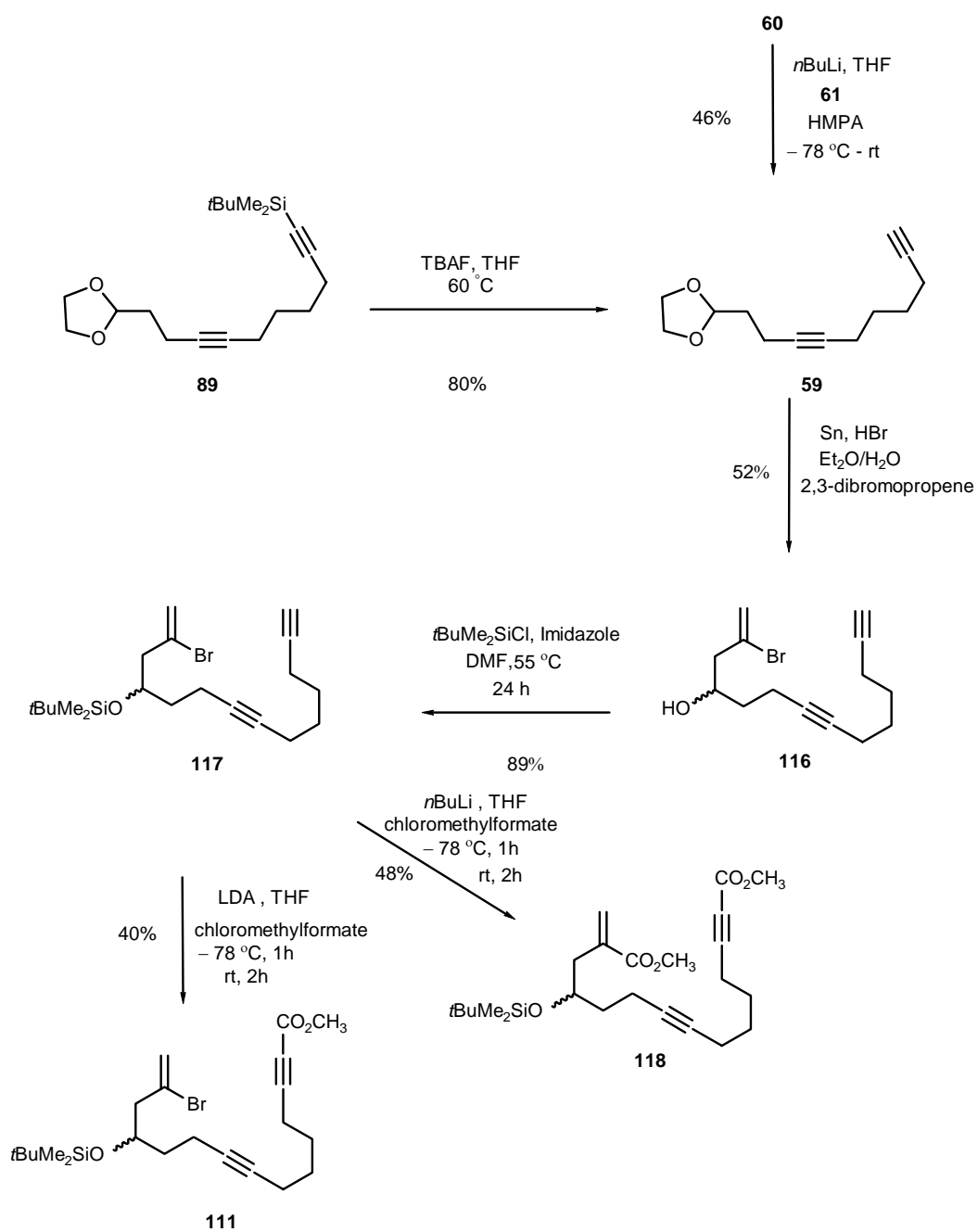
Again the synthesis of **110** can be achieved starting from 1,7-octadiyne, (Scheme 36.). Thus, treating the lithiated 1,7-octadiyne with ethylene oxide in the presence of ethereal solution of boron trifluoride at $-78\text{ }^\circ\text{C}$ in THF, gives the alcohol **112** in a 60% yield. It should be noted that the reaction should be quenched at $-78\text{ }^\circ\text{C}$ because leaving the reaction to warm up to room temperature will lead to polymerization products instead of the desired product. The alcohol **112** is then converted into the mesylate and coupled with sodium malonate to afford the substituted malonate **114**. **114** is then treated at $70\text{ }^\circ\text{C}$ with sodium hydride and 2,3-dibromopropene to afford **115** in a rather poor yield. As it was mentioned before, the nucleophilic substitution at the allylic bromide proceeds via $\text{S}_{\text{N}}2$ type mechanism which is proved to be highly sensitive to the solvent polarity. Therefore, it was found that modifying the solvent polarity by adding a small portion (10-15% by volume) of DMF to DME, improves the yield of such substitution significantly and **115** can be obtained in a 72% yield. The final step involves the attachment of the ester group at the terminal alkyne. Conducting this step, which requires using a strong base to abstract the acetylenic hydrogen, in the presence of both the base-sensitive malonate unit and the vinyl bromide makes this step very difficult to be achieved. However, carrying out this reaction at $-78\text{ }^\circ\text{C}$ using LDA (lithium diisopropyl amide) will offer the desired precursor **110** in a 44% yield. Trying to use *n*-butyl lithium instead

of LDA will decrease the yield and results in a complicated mixture to separate.



Scheme 36. E = CO₂Me

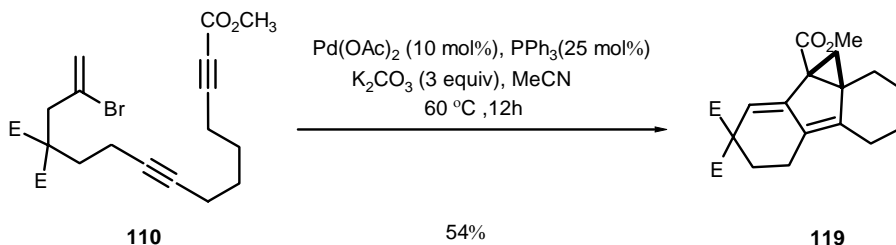
In a similar manner like **49** and **80**, synthesis of **111** was achieved by two routes, (Scheme 37.). In Route A compound **59** can be prepared by linking the acetal **64** to 1-*tert*-butyldimethylsilyl hex-1-yn (**82**), (Scheme 29.), and then removing the silyl group from the terminal alkyne of the produced diyne **89** by tetrabutylammonium fluoride,^[52] while in Route B compound **59** can be prepared by coupling the lithiated 1,7-octadiyne with **61**. Treating **59** with 2,3-dibromopropene in the presence of powder tin will offer the alcohol **116** which is then protected by *tert*-butyldimethylsilyl chloride to produce **117**. When **117** is treated with *n*-butyl lithium, the abstraction of the acetylenic proton is accompanied by transmetallation at the vinylic bromide which leads to the formation of **118** instead of **111**. To overcome this difficulty, LDA is used as a base to furnish **111** in a 48% yield.



Scheme 37.

3.3. Palladium-catalyzed oligocyclizations of alkoxy carbonyl-substituted precursors

Unexpectedly, when **110** is treated at 60 °C with palladium acetate (10 mol %) in the presence of sodium carbonate and triphenyl phosphine in acetonitrile, the tetracyclic system **119** is formed, (Scheme 38.).



Scheme 38. E = CO₂Me

Examining the ¹³C-NMR spectrum of **119** shows only four olefinic carbons at $\delta = 144.58$, 143.23, 126.21 & 116.21 ppm which indicate that there are only two C-C double bonds and a tetracyclic system. All the carbonyl carbons' chemical shifts are down field shifted, i.e. they have values higher than 170 ppm, which indicates that the three carboxylate groups are situated on saturated carbons. This is also reinforced by the IR spectrum which shows only a broad band at 1730 cm⁻¹ while there are no bands between 1690-1700 cm⁻¹ which are characteristic for carboxylates at unsaturated carbons. DEPT elucidates the formation of two quartet carbons at $\delta = 36.72$ & 45.87 ppm and a methylene group (CH₂) at $\delta = 39.13$ ppm corresponding to the bridge head carbons and the bridging carbon (cyclopropyls' carbon) respectively. Furthermore, it shows that there is only one olefinic (CH) carbon and three olefinic quartet carbons which indicates the presence of one trisubstituted double bond and one tetrasubstituted double bond. gHSQC establishes a direct correlation between the methylene group carbon signal at $\delta = 39.13$ ppm and two doublets in ¹H-NMR spectrum at $\delta = 1.94$, ²J = 3.0 Hz and 1.06, ²J = 3.0 Hz corresponding to two geminal protons located on this carbon. The big difference in the chemical-shift value between these two protons can be attributed to the anisotropic effect of one of the double bonds on one of these protons. H/H COSY shows that these two protons are coupled to each other. It also shows that the olefinic proton, which appears as a singlet at $\delta = 6.03$ ppm, and the bridging protons are not coupled with any other proton in the compound. This is in agreement with the proposed regioisomer. The

correlation between the methyl ester protons and the bridge head carbon at $\delta = 36.72$ in HMBC (long range C/H correlation) affirms that the methyl ester group is located on this carbon. The fact that the olefinic proton has only two correlations, one with one of the olefinic carbons and the other with ester substituted bridge head carbon $\delta = 36.72$ excludes any possibility for the formation of any other tetracyclic systems such as **120** (Fig 5.). Fig 4 illustrates a summary of HMBC correlations.

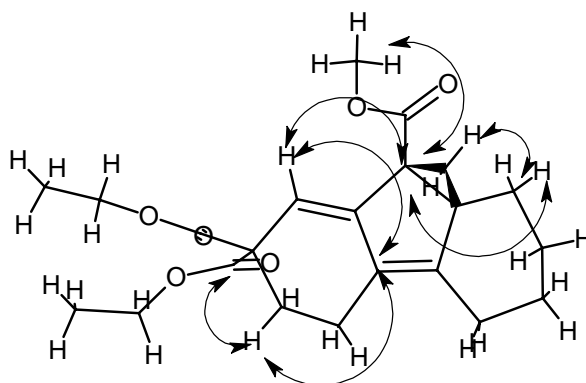


Fig 4: Summary of HMBC Correlations of **119**

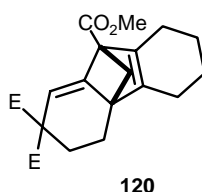


Fig 5.

Apparently, the ester group has a drastic effect on the NMR properties of the cyclopropyl moiety of such systems. While in unsubstituted fused cyclopropyl systems, such as **121**,^[33] the cyclopropyl's carbon and the protons attached to it appear up field at around 25 ppm and 0.0-1.5 ppm respectively, the cyclopropyl's carbon and the protons attached to it in **119** are deshielded and appear down field at 39.13 ppm and 1.0-2.0 ppm respectively. However, the α -carbon to the ester group is shielded and it appears up-field at $\delta = 36.72$. Clearly the ester group in such system has β -deshielding effect while it has α -shielding effect.

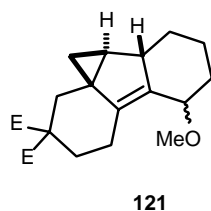
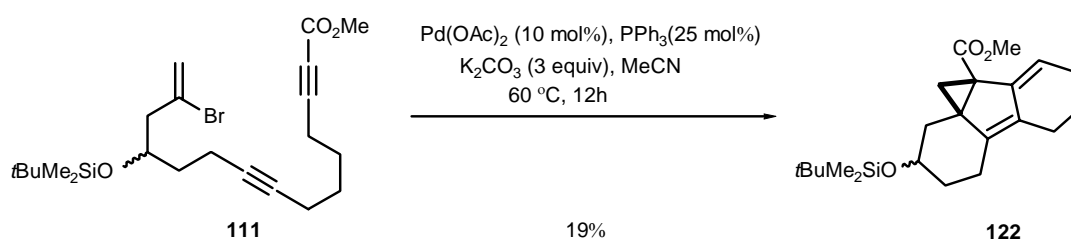


Fig 6.

Similarly, when **111** is treated with palladium acetate in the presence of potassium carbonate and triphenyl phosphine in acetonitrile, **122** is formed in a 19% as a 2:1 diastereomeric mixture, Scheme 39.



Scheme 39.

Compound **122** shows the same spectral properties as **119**. However, the olefinic proton appears as a triplet at 5.89 ppm which gives rise to further two possible compounds, **123** and **124**. H/H COSY shows no correlation between this olefinic proton and the α -proton to the silyloxy group which excludes the formation of **123**. Moreover, HMBC shows a strong correlation between this proton and the carbon bearing the ester group which excludes the formation of **124** Fig (7.).

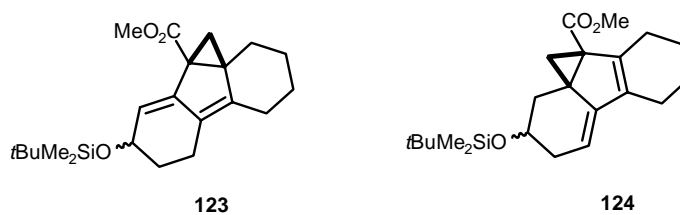
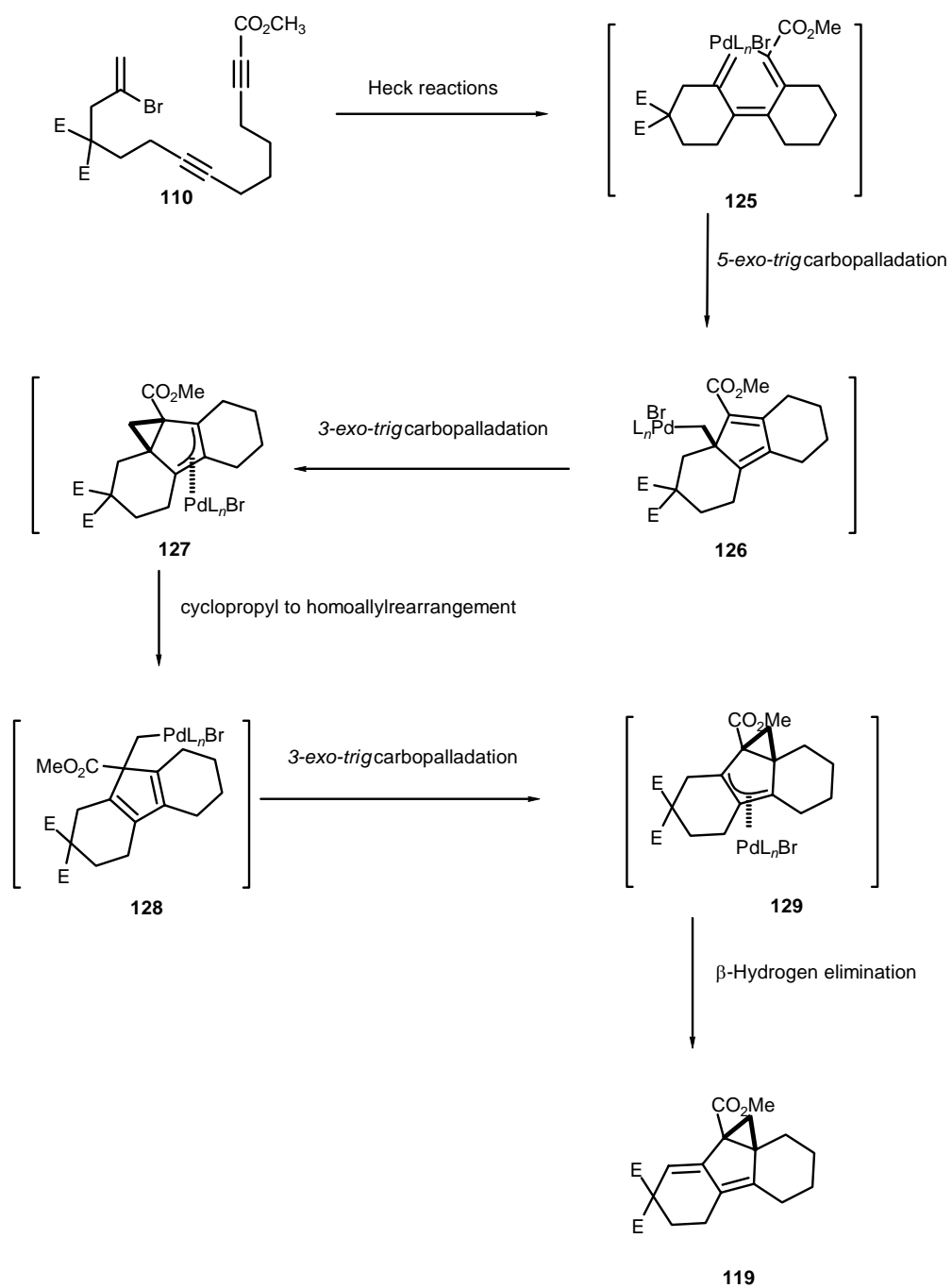


Fig 7.

3.4. The mechanism of palladium-catalyzed oligocyclization of the alkoxy-carbonyl-substituted precursors

Clearly the formation of **119** & **122** discards the intramolecular Diels-Alder reaction as well as a possible 6π -electrocyclization. The mechanism leading to the formation **119** & **122** is illustrated in Scheme 40. After the two-fold Heck reaction, a further carbapalladation takes place in a *5-exo-trig* fashion to form the neopentyl-like system **126** which further undergoes a *3-exo-trig* carbapalladation to give the cyclopropyl intermediate **127**. Cyclopropyl-to-homoallyl rearrangement will yield the diene system **128** which undergoes a *3-exo-trig* carbapalladation to give **129** followed by β -hydrogen elimination to produce **119**.

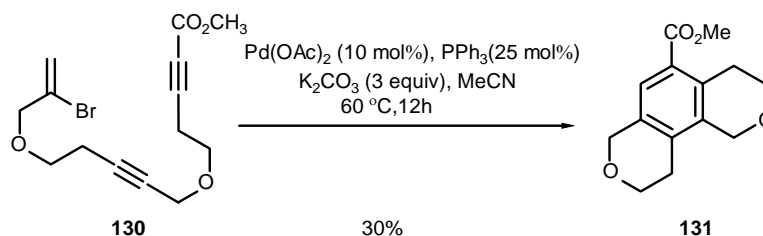
Scheme 40. E = CO_2Me

4. Palladium-catalyzed oligocyclization of terminally alkoxy-carbonyl-substituted 10-(2-bromoallyloxy)-1,7-decadiyne

4.1. Prologue

In the previous section, it was mentioned that introducing an ester group into the terminal triple bond would result in tetracyclic systems such as **119** and **122**. The formation of such systems eliminates the possibility that the cascade proceeds via $\beta\pi$ -electrocyclization or Diels-Alder reaction.

Nonetheless, when the carbon skeleton bears two oxygen atoms (two methylene groups are replaced by two oxygen atoms) compound **130**, only can the aromatic compound **131** be isolated, (Scheme 40).^[53] Obviously, the mechanism of formation of **131** is similar to that of **73** & **71**, which includes *5-exo-trig* step, (Scheme 32.).



Scheme 41.

It is interesting to study the effect when only one methylene group is replaced by one oxygen atom or when the carbon skeleton bears one oxygen atom, e.g. compound **132**.

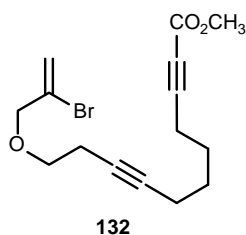
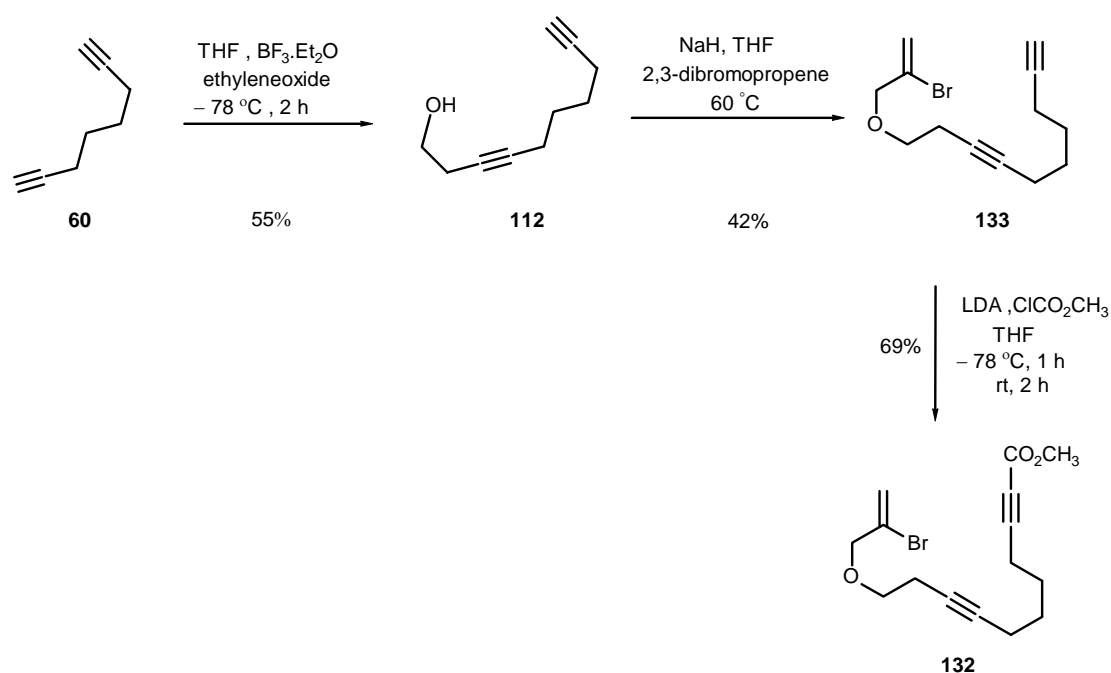


Fig 8.

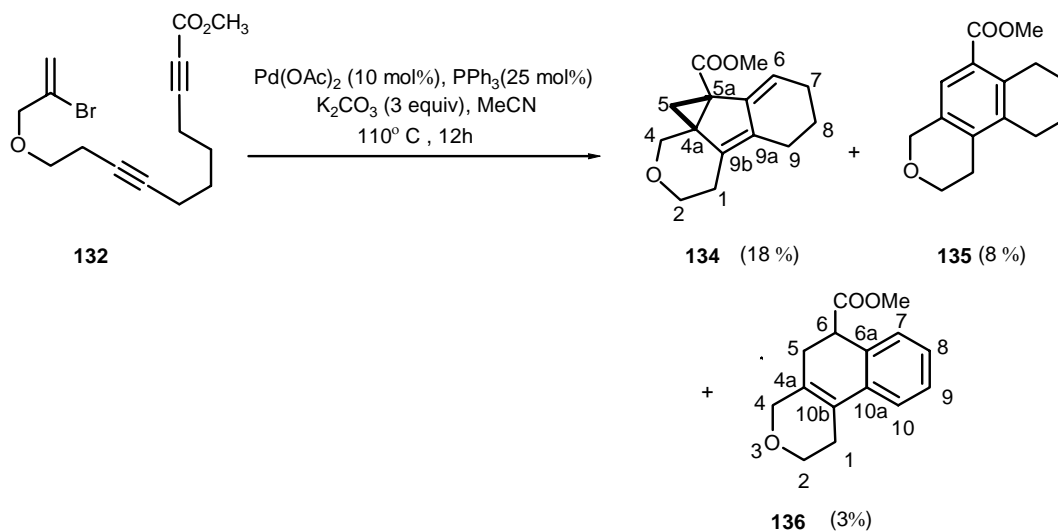
4.2. *Synthesis and oligocyclization of the alkoxy carbonyl-substituted heteroatom-tethered precursor.*

The synthesis of **132** can be achieved starting from 1,7-octadiyne, (Scheme 42.). Thus, treating the lithiated 1,7-octadiyne with ethylene oxide in the presence of borontrifluoride ether complex affords the alcohol **112** which is attached to 2,3-dibromopropene by regular Williamson reaction to give the ether **133** in a 42% yield. Treating **133** with LDA and chloromethylformate at $-78\text{ }^{\circ}\text{C}$ gives **132** in a 69% yield.



Scheme 42.

When **132** is treated at $110\text{ }^{\circ}\text{C}$ with palladium acetate (10 mol%), triphenylphosphine (25 mol%) and sodium carbonate in acetonitrile, compounds **134**, **135** and **136** are formed in 18%, 8% and 3% yield respectively, (Scheme 43.).



Scheme 43.

Fortunately, compound **134** affords unambiguous spectra which confirms the structure of **134** and allows us to conduct further NMR experiments to exclude any alternative structure. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra show similar patterns as those for **119**. The bridging carbon (cyclopropyl's carbon) also appears at $\delta = 37.29$ ppm and the two protons connected to it also appear as two doublets at $\delta = 1.10$ & 2.05 ppm. The position of the cyclopropyl ring with respect to the heterocyclic ring enables us to assign the structure clearly from HMBC spectrum. A strong coupling can be observed between C-4 protons (H-4) (adjacent to the oxygen atom) and the bridging methylene carbon (cyclopropyl's carbon) C-5 and *vice versa*, *i.e.* between the C-5 protons (H-5) and the C-4 carbon. The size of the coupling, and hence the intensity of the correlation, can be determined by the dihedral angles (Karplus relation) and the number of bonds separating the two coupled proton and carbon.^[54] Providing that, for instance, **137** were the correct structure, the coupling between the bridging methylene carbon (C-14) and C-6 protons (H-6) would take place through four bonds and, consequently, the resulting coupling constant ($^4J_{\text{C-H}} \leq 1\text{hz}$) would be so small so that the correlation can not be detected. Moreover, the HMBC spectrum of **134** shows a strong correlation between C-4 protons (H-4) and the bridge head carbon C-4a $\delta = 42.87$ ppm. Such correlation would not appear were the structure **137** the right compound. The HMBC proves that **134** is the right structure for these tetracyclic systems and it indicates that any other structure, such as **137**, can not be right. (Fig. 9.) summarizes the HMBC correlations of **134**.

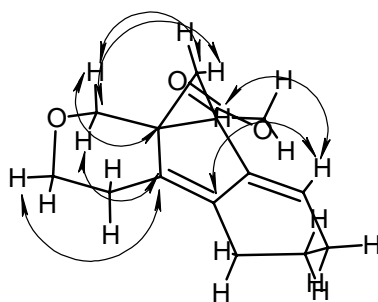


Fig 9: Summary of HMBC Correlations of **134**

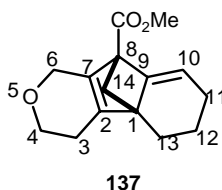


Fig 10.

The presence of the cyclopropyl moiety can be further proved by NOE experiments. Fig 11 shows a short distance between the *exo*-bridging methylene proton (*exo*-H-5) and the C-4 equatorial proton Heq-4, whereas such distance is quite large in the case of **137**. Therefore, upon irradiating *exo*-H-5, we would expect NOE on the Heq-4 and the same thing would be observed for *exo*-H-5 upon irradiating Heq-4. From Fig 11 it can be seen that there would be insignificant NOEs between the *endo*-H-5 and both the Heq-4 and the Hax-4 (the axial proton of C-4) or between the Hax-4 and the two protons of C-5 because these protons are too far away to be involved in such NOEs. Thus, when the *exo*-H-5 is irradiated, a strong enhancement on the Heq-4 is observed and *vice versa*. Only very small NOEs are observed on the Heq-4 and the olefinic proton (H-6) when the *endo*-H-5 is irradiated. NOE is observed on the Hax-2 when Hax-4 is irradiated. These NOE-difference experiments, illustrated in Fig 11, provide a sharp confirmation for the presence of the cyclopropyl moiety and the structure **134**. At the same time they exclude any other structure.

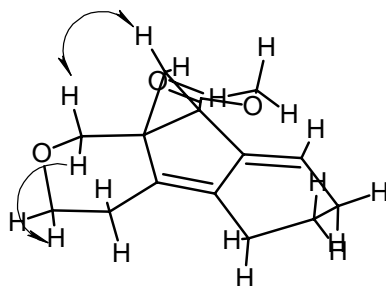


Fig 11: NOE Correlations of **134**

The structure of **136** is determined by one- and two-dimensional NMR spectra. The ^{13}C -NMR spectrum shows eight signals in the olefinic region which indicates that there are four double bonds. Four of these signals are corresponding to four CH carbons, while the other four are corresponding to four quartet carbons. The presence of the carbonyl carbon at $\delta = 173.68$ ppm indicates that the methyl carboxylate group is situated on a saturated carbon. ^{13}C -NMR also shows one CH at $\delta = 43.34$ ppm, corresponds to the ester-substituted carbon, two methylene groups in the aliphatic region at (δ 24.52 & 26.49 ppm) and two methylene groups at $\delta = 64.71$ & 67.93 ppm, which are obviously corresponding to the oxygen bonded methylenes. ^1H -NMR shows the appearance of a multiplet in the aromatic region, which corresponds to the four aromatic protons, and a triplet at $\delta = 3.71$ ppm, $^3J = 6.5$ Hz, which corresponds to the single proton of the ester substituted CH group. Mass spectroscopy confirms the loss of one hydrogen molecule (H_2) and one hydrobromide molecule (HBr) which gives rise to a tricyclic system with four double bonds. H/H COSY establishes a correlation between the proton at $\delta = 3.71$ ppm and the two protons at $\delta = 2.32$ & 2.43 ppm of one of the two methylene groups, while the protons of the other methylene group establishes a correlation with protons of one of the oxygen-bonded methylenes. This clearly indicates that one of the methylene groups is adjacent to the ester substituted carbon while the other is a part of the heterocyclic moiety. The final evidence for the structure of **136** is derived from the HMBC spectrum. The proton at $\delta = 3.71$ ppm shows a strong correlation with the ester carbonyl carbon, which affirms that the ester group is situated on this carbon, and another correlation with one of the methylene carbons at $\delta = 26.49$ ppm. It also shows strong correlations with two quartet olefinic carbons and one olefinic or aromatic CH. Furthermore, HMBC shows a correlation between the protons of one of the oxygen-

bonded methylene groups (H-2) and one of the olefinic quartet carbons at $\delta = 124.41$ ppm, while the protons of the other oxygen-bonded methylene group show a correlation with this carbon and with another olefinic quartet carbon at $\delta = 130.32$ ppm. These later correlations confirm the position of the tetrasubstituted double bond. Fig 12 shows a summary of HMBC correlations which are in total agreement with the structure of **136**.

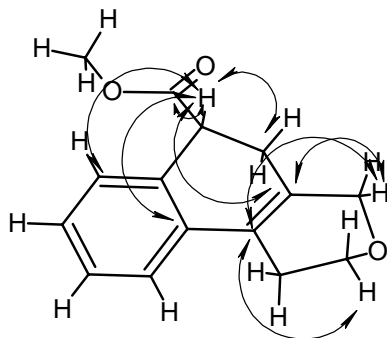
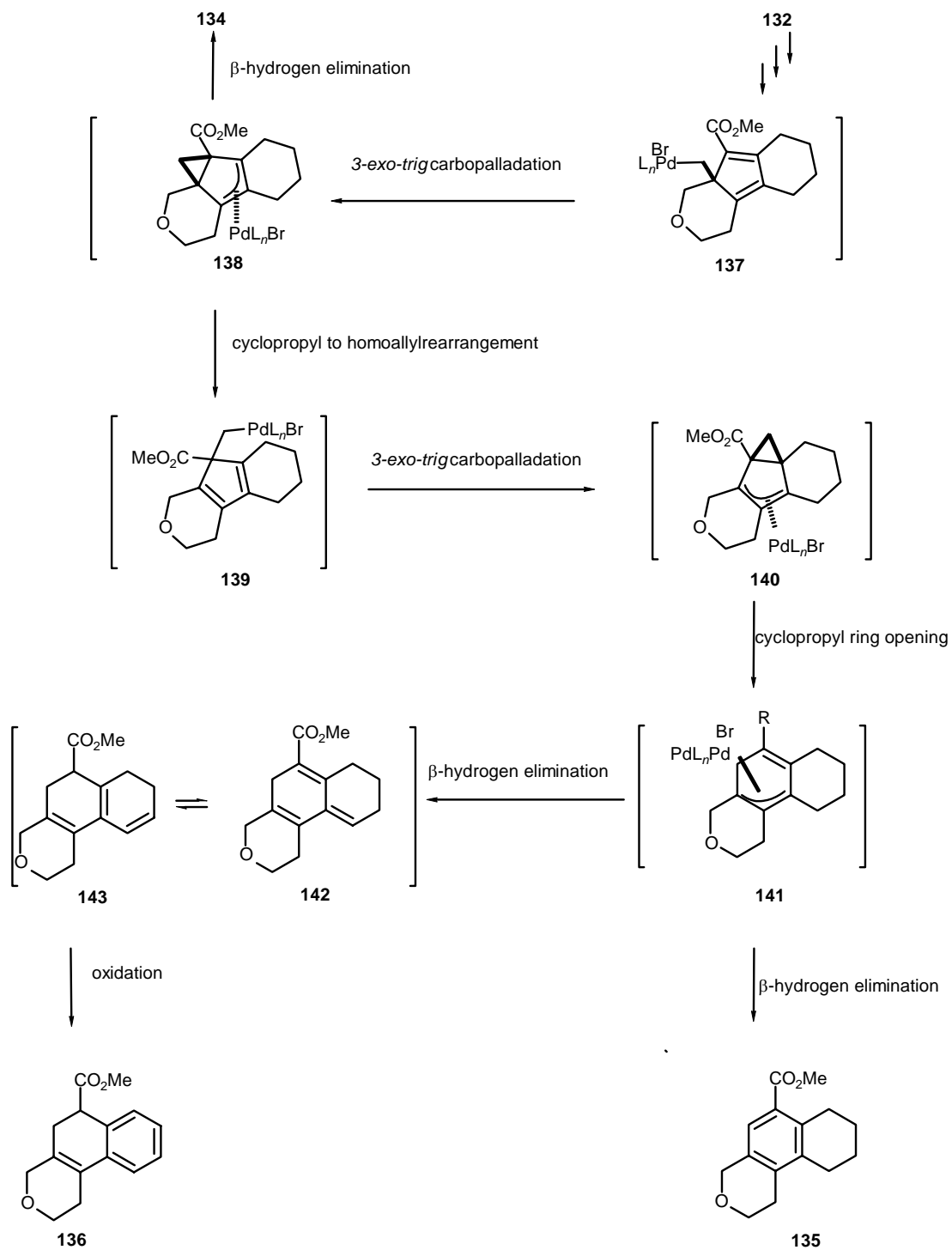


Fig 12: Summary of HMBC Correlations of **136**

4.3. The mechanism of the palladium –catalyzed oligocyclization of the hetero-atom tethered precursor.

Compound **135** shows the same spectral patterns as **91** and **92**.

The mechanism of formation of **134** & **135** is similar to that of **119** & **91**, (Scheme 44.) Thus, *3-exo-trig* carbopalladation of the neopentyl-like system **137** yields the cyclopropyl intermediate complex **138** which might undergo either a β -hydrogen elimination to give **134** or cyclopropyl ring-opening to form the diene system **139**. The later undergoes a further *3-exo-trig* carbopalladation and cyclopropyl ring opening to offer **141** which undergoes β -hydrogen elimination either from the methylene group adjacent to the ester group to afford the aromatic compound **135** or from the methylene group of the annelated cyclohexyl moiety to afford the highly unstable intermediate **142** that undergoes a further double bond migration to produce the cyclohexadiene system **143**. Oxidation of the later will afford the aromatic system **136**. The last oxidation step might be invoked by the presence of palladium. Such palladium-induced oxidations of cyclohexadiene systems into aromatic system are frequently reported in the literature.^[55]



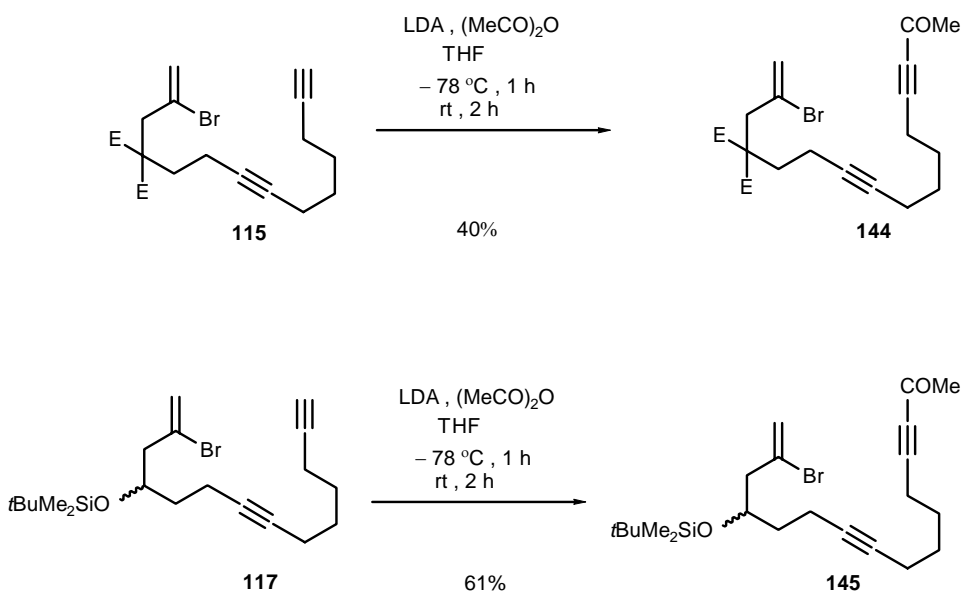
Scheme 44.

5. Palladium-catalyzed oligocyclization of terminally acetyl-Substituted 2-bromo-14-tetradec-1-ene-7,13-dyne

5.1. Synthesis of acetyl-substituted precursors

Spurred by the results of the ester substituted terminal alkyne precursors **110** & **111**, it would be interesting to try other electron withdrawing groups such as the acetyl group. Therefore, precursors such as **144** and **145**, (Scheme 45.), were to be synthesized and cyclized.

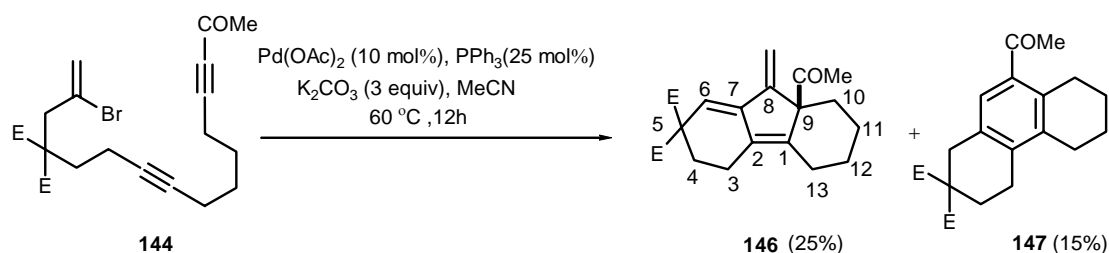
The synthesis of such precursors can be achieved in a similar way to that of their ester analogues. Thus, when **115** & **117** are treated at $-78\text{ }^{\circ}\text{C}$ with LDA and acetic anhydride in THF, **144** and **145** are formed in 40% and 61% yield respectively, (Scheme 45.).



Scheme 45. E = CO₂Me

5.2. Palladium-catalyzed oligocyclizations of acetyl-substituted precursors and their mechanism

Stunningly, when **144** is treated, at 65°C, with palladium acetate (10 mol%) in the presence of triphenyl phosphine (25 mol%) and potassium carbonate in acetonitrile, compounds **146** and **147** are formed in a 25% and 15% yield respectively, (Scheme 46.).



Scheme 46. E = CO₂Me

The structure of **146** can easily be verified by NMR techniques, especially HMBC and H/H-NOESY. ¹H-NMR spectrum shows three olefinic singlets at $\delta = 6.00$, 5.51 and 4.90 ppm corresponding to three olefinic protons. ¹³C-NMR spectrum shows six olefinic carbons, four quartets at $\delta = 148.44$, 143.27, 143.22 & 132.56 ppm, one CH₂ at $\delta = 107.19$ ppm and one CH at $\delta = 110.25$ ppm. ¹³C-NMR spectrum also shows a quartet at $\delta = 67.24$ ppm. gHSQC indicates that the two olefinic protons at $\delta = 5.51$ and 4.90 ppm are attached to the methylene carbon at $\delta = 107.19$ ppm and they have zero geminal coupling constant. Such pattern, was observed for similar cyclic systems.^[56] HMBC confirms the elucidated structure. The quartet carbon at $\delta = 67.24$ ppm has a correlation with the protons of the acetyl group which indicates that the acetyl group is bonded to this carbon. It also shows a strong correlation with the protons of the *exo*-methylene group. This strong correlation can be attributed to the large coupling between such allylic protons and their corresponding allylic γ -carbon in such allylic systems ($^3J_{\text{H-C-C-C}} \sim 15$ Hz),^[54] (of course the *trans* proton has a larger coupling constant, and hence a stronger correlation, to the quartet carbon than the *cis*-proton. The same situation applies when we consider the correlation between these protons and the quartet carbon of the trisubstituted double bond (C-7)). These correlations specify exactly the position and the substitution of this quartet carbon. The strength and the pattern of the other correlations in the HMBC spectrum are in consistence of the deduced structure **146**. Fig 13 shows a summary these

HMBC correlations.

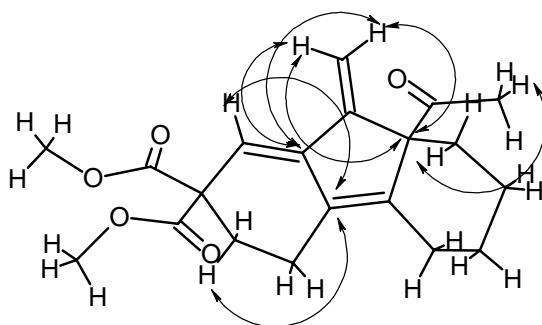


Fig 13: Summary of HMBC Correlations of **146**

Further evidence which proves the structure **146** can be obtained from H/H.NOESY of **146**. It reveals a strong correlation between the olefinic proton of the trisubstituted double bond and the *exo*-methylene protons. It also shows a correlation between the two geminal protons of the *exo*-methylene group. Fig 14 illustrates these space interactions.

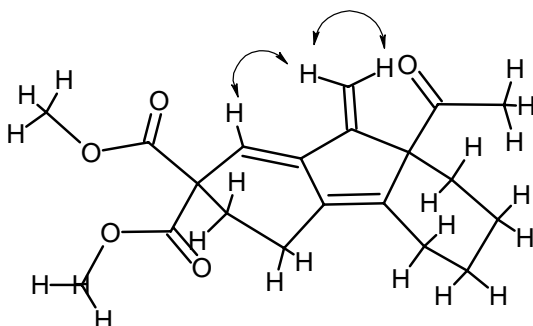
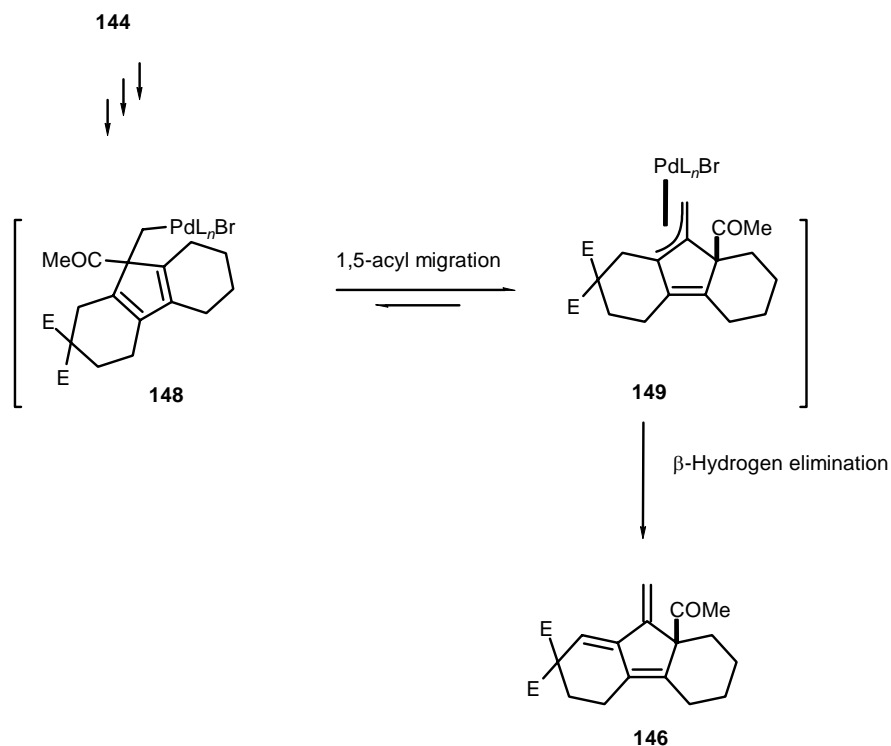


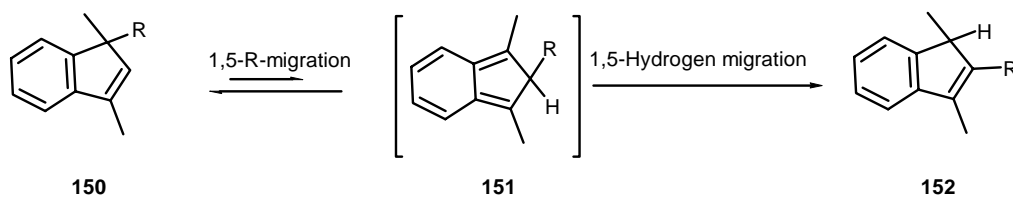
Fig 14: NOESY Correlations of **146**

It is clear from the structure of **146** that the acetyl group has undergone a sort of migration. There are two possible mechanisms by which the formation of **146** can be explained. The first mechanism presumes that the diene system of **148**, which is formed by the same sequence of steps illustrated in Scheme 40, undergoes a thermal 1,5-acyl migration to form **149**. Apparently the equilibrium is shifted to the right by the fast formation of the stable palladium complex **149**, i.e. the complexation step will overcome the reverse 1,5-acyl migration. Subsequent β -hydrogen elimination will furnish compound **146**, (Scheme 47.).

Scheme 47. E = CO₂Me

There are a few reports in the literature which describe the thermal 1,5-acyl migration.^[57] However, such migration is usually induced photochemically.^[58]

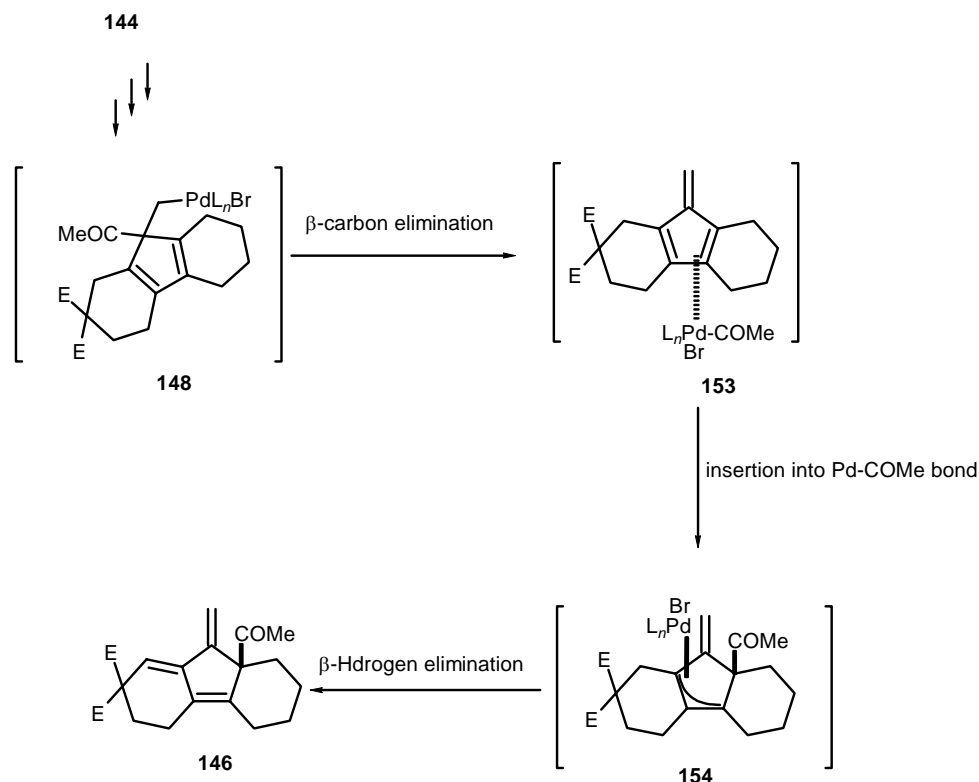
In an investigation about the thermal 1,5 migratory aptitude using indene, Scheme 48, it was found that the 1,5 migratory aptitude decreases in the following order: HCO > Bz ~ Ac > H > vinyl > CONHMe > CO₂Ph > CO₂Me > CN ~ C≡C > alkyl.^[59] The low migratory aptitude of the methyl ester might explain why such migrations are not observed in the case of ester-substituted precursors.



Scheme 48.

The second mechanism is based on recent findings by S. Uemura et al, which includes β-carbon elimination from cyclobutane systems to afford ketones or nitriles.^[60] Thus according to these results, the diene intermediate **148** would undergo β-carbon

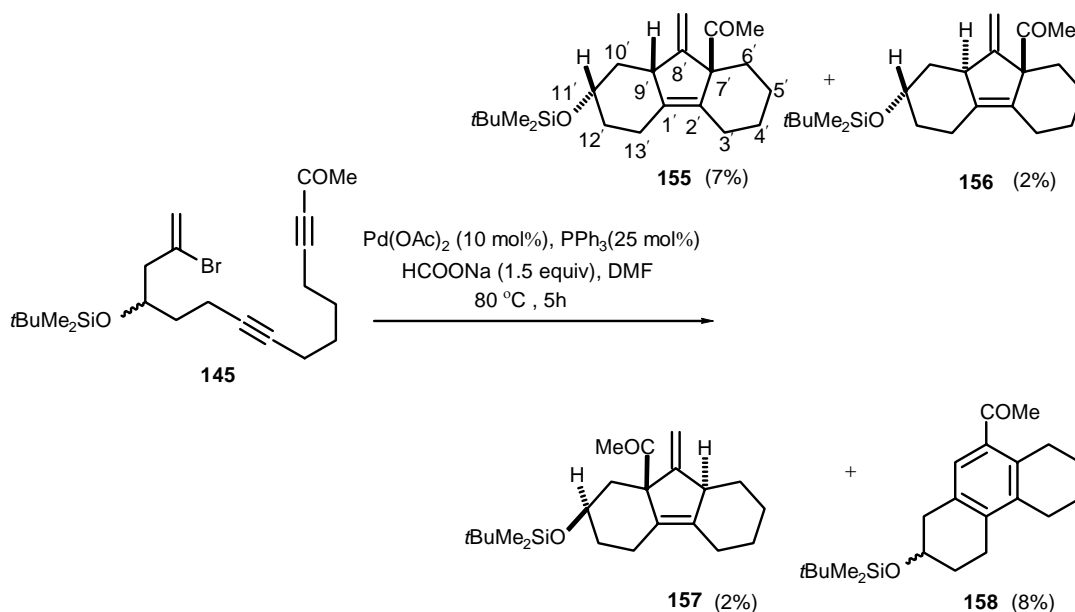
elimination to produce the fulvene system **153**. Subsequently, one of the endo-fulvene's double bonds would undergo an insertion into the palladium-acetyl bond to form the complex **154**, which by β -hydrogen elimination would afford **146**, (Scheme 49.). Alkene insertion into palladium-acetyl bond was reported in literature.^[61]



Scheme 49. E = CO₂Me

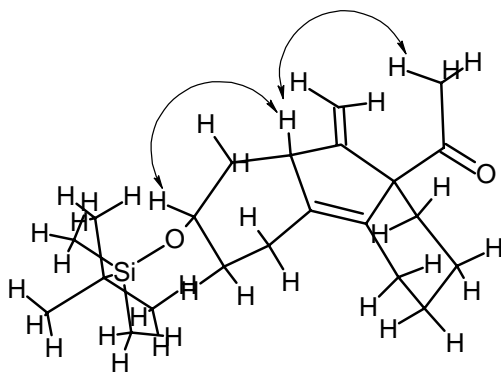
Whether the cascade would follow the first or the second mechanism depends on the rate of the competing reactions for these mechanisms.

Upon treating **145** with palladium acetate in the presence of triphenylphosphine and potassium carbonate in acetonitrile, no reaction is observed and all the starting materials are recovered. However, when **145** is treated with palladium acetate (10 mol%) in the presence of triphenylphosphine (25 mol%) and sodium formate in DMF, a complicated mixture of diastereomers is formed. Nonetheless, compounds **155**, **158**, and an inseparable mixture of **156** & **157** were isolated and identified, (Scheme 50.).



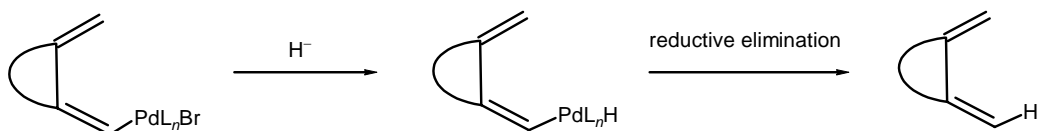
Scheme 50.

Compound **155** can be identified by one- and two-dimensional NMR techniques in addition to mass spectroscopy. Thus the structure of **155** is accurately elucidated by ^1H -NMR, ^{13}C -NMR, gHSQC, H/H COSY and HMBC. The stereochemistry of **155** is determined by a series of NOE experiments. Thus, upon irradiating the angular proton (H-9'), NOE enhancements are observed on the acetyl group protons' signal and on the signal of the α -proton of the silyloxy group (H-11'). Similarly, when the protons of the acetyl group or the α -proton of the silyloxy group is irradiated, a NOE enhancement is observed on the signal of the angular proton. Fig 15 illustrates these NOE correlations.

Fig 15:NOE correlations of **155**

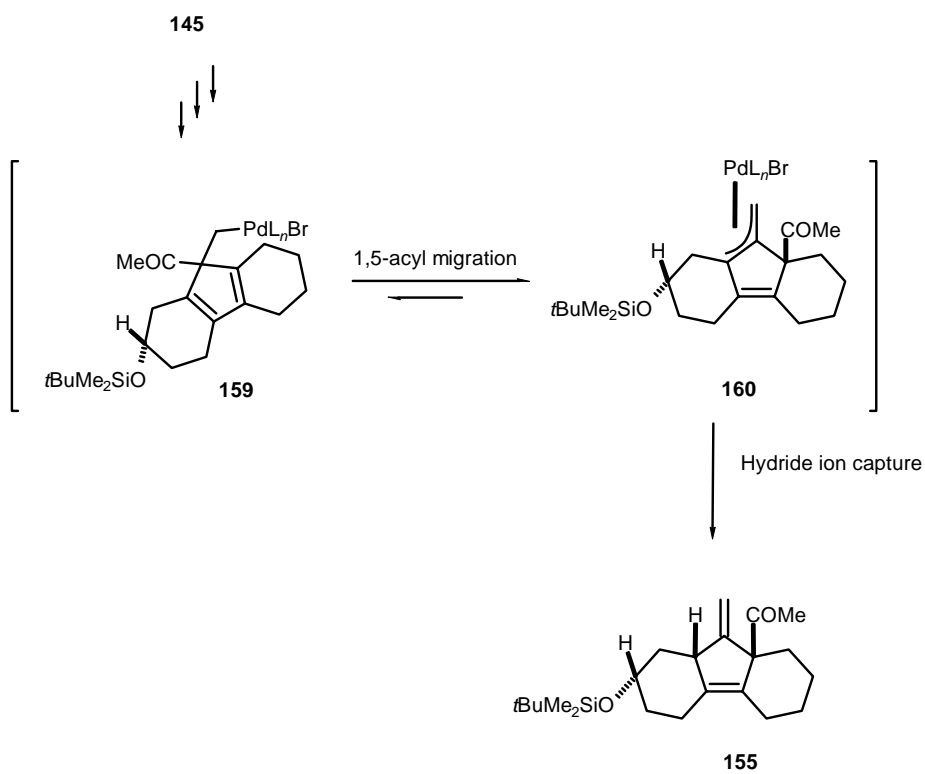
Similarly the structures of **156**, **157** and **158** can be assigned.

The formation of **155**, **156** and **157** can be explained by the same mechanisms used to explain the formation of **146**. However, the last step in the formation of these compounds includes hydride ion capture. This process arises when the possibility for β -hydrogen elimination is eliminated or it becomes very difficult. The process incorporates an exchange of the halide ion with hydride, which is generated from sodium formate, at the palladium centre followed by reductive elimination, (Scheme 51.). This process had firstly been observed by R. Grigg et al and the term “hydride ion capture” was proposed to avoid using “cross coupling”.^[62]



Scheme 51

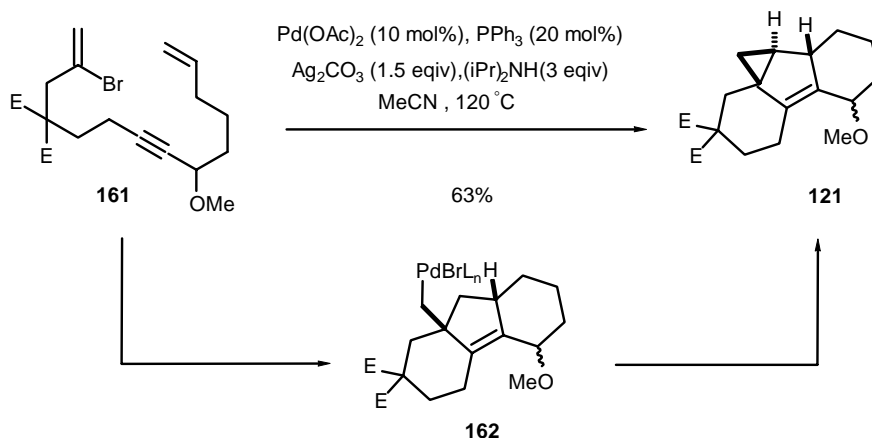
Scheme 52 illustrates the formation of **155** by the first mechanism. Consequently, 1,5-acyl migration yields the complex **160**. The complex **160** clearly has a weak possibility to undergo β -hydrogen elimination and, therefore, it undergoes hydride ion capture process to afford the reduced compound **155**



Scheme 52.

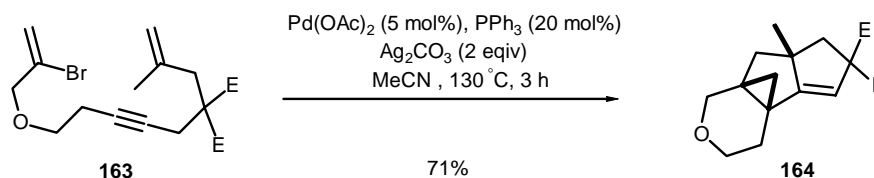
6. Palladium-catalyzed oligocyclization of 2-bromo-14-tetradec-1-ene-7,13-diyne

It was mentioned earlier that palladium-catalyzed oligocyclizations of substituted terminal alkenes follow different routes depending on the nature and the pattern of the substituents on these alkenes. Scheme 14 and Scheme 33 illustrate that the cascade reaction of such precursors can occur via a sequence of either Heck-Heck-6 π -electrocyclization, (Scheme 14.), or Heck-Heck-Diels-Alder reaction, (Scheme 33.), to afford in both cases tricyclic systems. However, when unsubstituted terminal alkene precursors, which might lead to three fused six-membered ring systems, such as **161**, had been used, the cascade took place through a sequence of Heck reactions followed by 5-*exo-trig* carbopalladation (Heck-Heck-5-*exo-trig* sequence) to afford the neopentyl like system **162** which might undergo γ -hydrogen elimination, to afford **121**, (Scheme 53.).^[63]



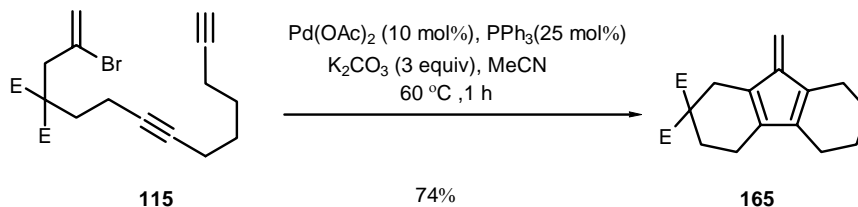
Scheme 53. E = CO₂Me

A similar sequence was also observed when the β -hydrogen elimination step had been blocked by introducing a substituent R (Me) adjacent to the terminal methylene group, (Scheme 54.).^[64]



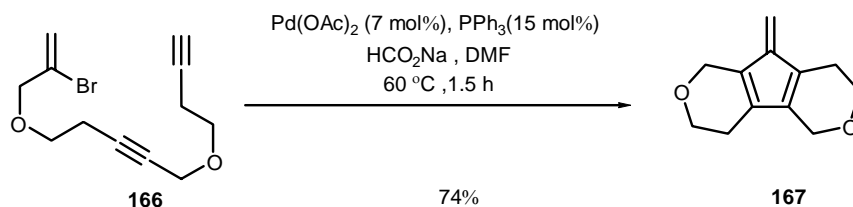
Scheme 54.

When unsubstituted terminal alkyne precursors which might lead to three fused six-membered rings system, such as **115**, had been cyclized, fulvene systems **165** were produced, (Scheme 55).^[34]



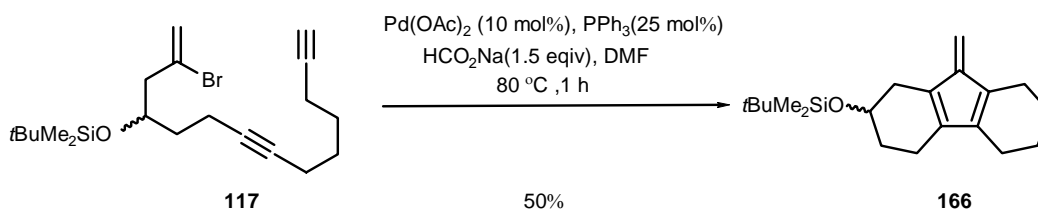
Scheme 55.

Even upon using carbon skeletons bearing heteroatoms, such as oxygen, the same result was obtained, (Scheme 56).^[34]



Scheme 56.

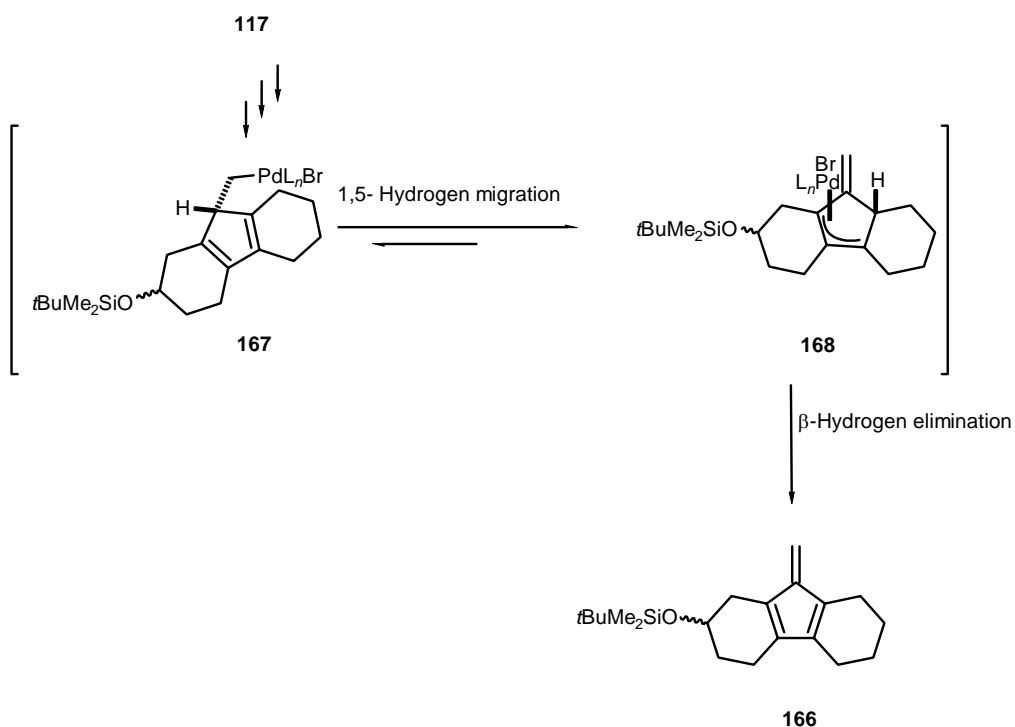
It has also been mentioned that when the geminal substitution (diethyl malonate group or similar groups) at the tether linking the vinylbromide with internal alkyne had been replaced by a silyloxy group, the yield of the cascade was decreased significantly. Therefore, it is interesting to examine this in the case of unsubstituted terminal alkyne. Thus, when **117** had been subjected to palladium acetate (10 mol%) in the presence of potassium carbonate and triphenyl phosphine (25 mol%) in acetonitrile at $60\text{ }^\circ\text{C}$, the starting material was recovered and the reaction did not take place. However, when **117** is treated at $80\text{ }^\circ\text{C}$ with palladium acetate (10 mol%) in the presence of triphenyl phosphine (25 mol%) and sodium formate in DMF, the fulvene system **166** is formed in a 50% yield, (Scheme 57).



Scheme 57.

Surprisingly, the fulvene can be isolated in a good yield, and the sharp decrease in the yield due to the removal of the geminal substitution is not as severe as in the previous examples.

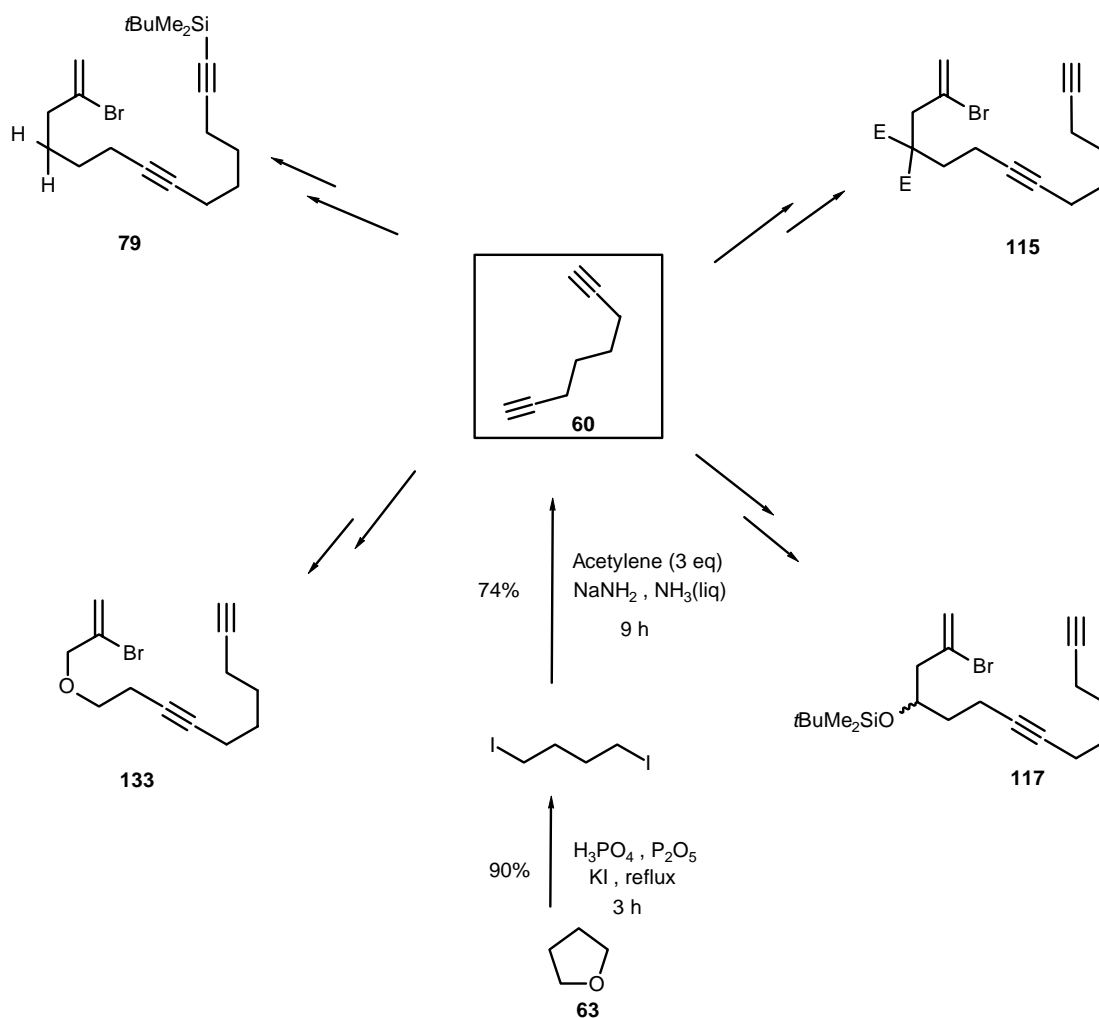
In the light of the previous section, one mechanism involving 1,5-hydrogen migration appears as a feasible pathway for the formation of the fulvene system. Thus, after the formation of the diene system **167**, 1,5-hydrogen migration will take place to form the complex **168** which undergoes a further β -hydrogen elimination to give the fulvene **166**, (Scheme 58.). A mechanism involves β -hydrogen elimination from the diene system **167** was also used to describe the formation of the fulvene system.^[34]



Scheme 58.

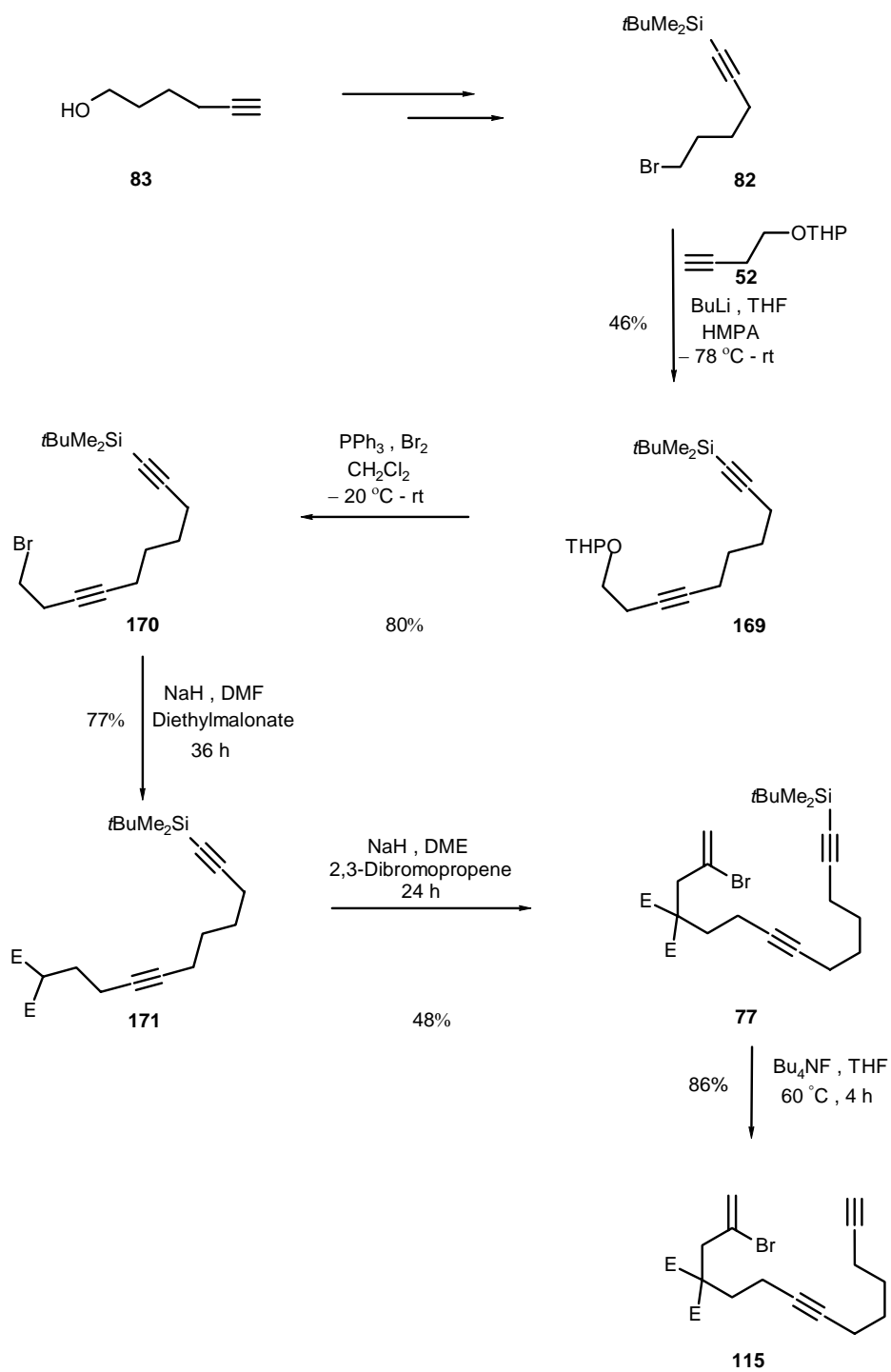
7. Summary for the Synthesis of the Precursors

The viability of these cyclizations, and therefore their applications, depends on cost and on how easy the precursors needed for such cyclizations can be prepared. In this study, and maybe in other studies which require similar precursors, 1,7-octadiyne (**60**) offers a cheap, easy and general starting material for preparing such precursors. As it can be obtained from THF, (Scheme 21.), it can be considered a cheap starting material. As soon as 1,7-octadiyne is prepared, all the desired precursors can be built by a few steps which saves time and effort and makes it a general starting material for preparing these precursors, (Scheme 59.).



Scheme 59.

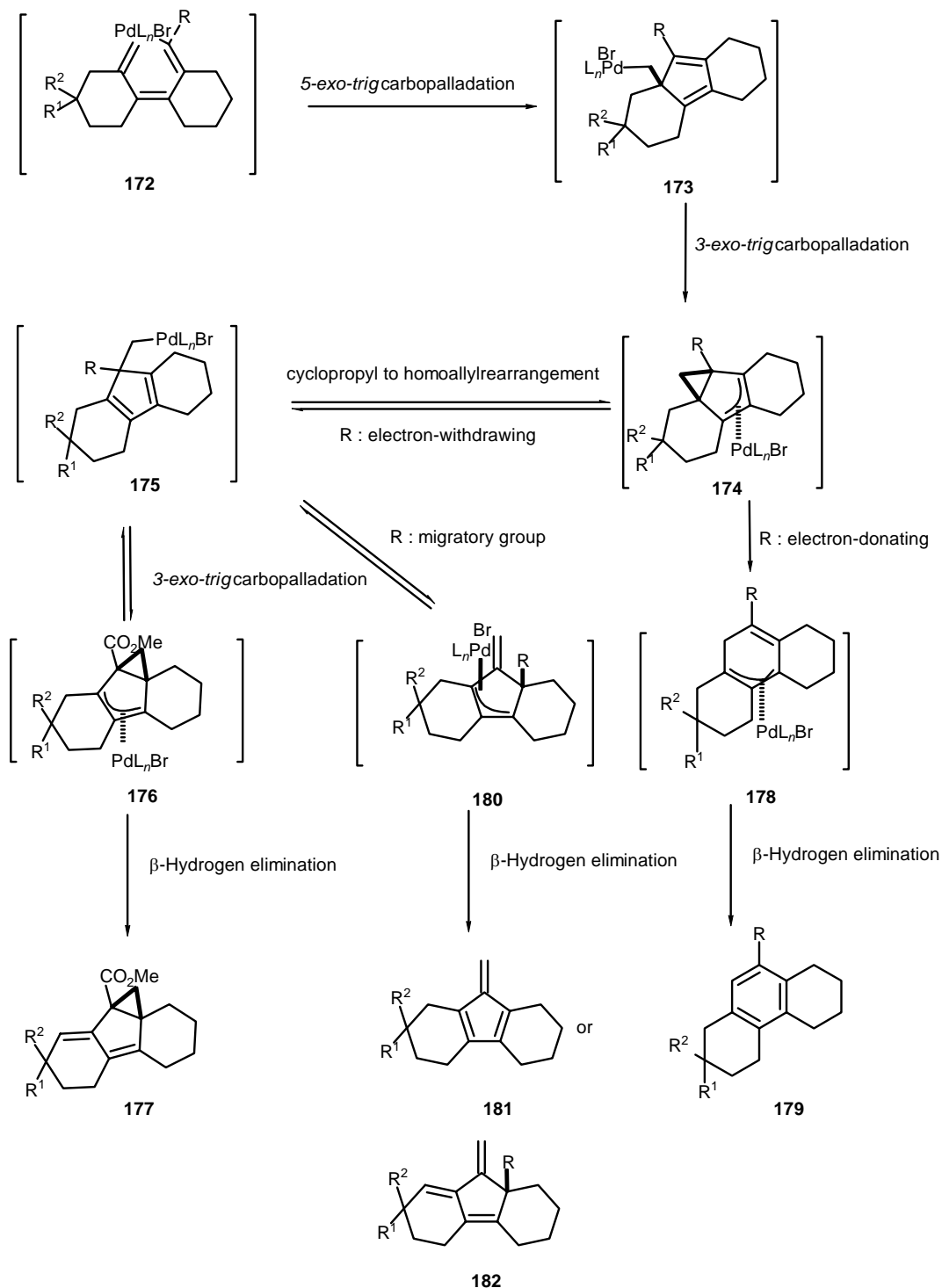
Alternative approaches which start from different starting material are not as efficient as the approaches which start from 1,7-octadiyne. Thus, for example, synthesis of **115** starting from other starting materials, requires extra steps in protecting and de-protecting and it also requires starting materials which are either laborious to synthesize or expensive to buy, (Scheme 60).^[33] Other examples were shown in the previous sections which makes 1,7-octadiyne a good choice for synthesizing these precursors.

Scheme 60. E = CO₂Me

8. Summary of the mechanistic aspects.

As mentioned earlier, there are several mechanistic pathways via which palladium catalyzed oligocyclization of terminal alkene precursors can take place. The route that the cascade may follow can be determined by the type and the pattern of the substitution at the terminal alkenes of these precursors. However, in the case of the terminal alkyne precursors which might lead to formation of three fused six-membered rings, there is only one mechanistic pathway via which the oligocyclization might take place. This pathway involves two Heck reactions followed by a *5-exo-trig* carbapalladation (Heck-Heck-*5-exo-trig* sequence). This stems from the fact that cascade's outcome of such precursors depends on the substituent type at the terminal alkyne and this route provides the only pathway by which the role of these substituents can be rationalized. Thus after two Heck reactions the cascade will undergo *5-exo-trig* carbapalladation to afford the neopentyl-like system **173**, Scheme 61. Providing that 6π -electrocyclization took place, the reaction outcome would always be a tricyclic system with three fused six-membered rings. In fact, this will not be the case when the terminal triple bond bears an electron-withdrawing group such as an ester group is cyclized. Furthermore, the formation of the tetracyclic system **177**, which clearly formed via *5-exo-trig* carbametallation, in the later case will, in fact, eliminate any possibility for *6-endo-trig* carbapalladation because there is no reasonable reason why the cascade would follow *6-endo-trig* mode in one case while it would follow *5-exo-trig* mode in another, bearing in mind that the determining factor for either mode is the geometry of the intermediate triene **172**. Thus, after a *5-exo-trig* carbapalladation, a further *3-exo-trig* carbapalladation will take place to offer the complex **174**. At this stage there are two possibilities, depending on the substituent R, via which the cascade might continue its way. Thus, when R is an electron-donating group, it will undergo cyclopropyl ring opening to form the three fused six-membered ring system **178** which undergoes β -hydrogen elimination to afford the thermodynamically stable bisannelated benzene **179**. When R is an electron-withdrawing group, such as an ester, cyclopropylhomoallyl rearrangement will take place to offer the diene system **175**, which undergoes a further *3-exo-trig* carbapalladation followed by β -hydrogen elimination to afford the tetracyclic system **179**. On the other hand, in the later case, when R is a group which is capable of migration or elimination such as acetyl or hydrogen, the R group at

diene system **175** might undergo 1,5-migration or β -carbon elimination to offer fulvene **181** systems or fulvene-like **182** systems. Scheme 61 illustrates these considerations.



Scheme 61.

C. Experimental Part

1. General Notes

The synthesized compounds were characterized by the following conditions and instruments.-IR: Bruker IFS 66, Perkin-Elmer 298.-¹H-NMR: Bruker AM 250 (250 MHz), Varian INOVA-500 (500 MHz), Varian INOVA-600 (600 MHz), δ (ppm) = 0 for tetramethylsilane, 7.26 for chloroform. The signals were characterized : s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, ddd = double of doublet, dt = double of triplet, tt = triple of triplet, dq = double of quartet, tq = triple of quartet, m = multiplet, *J*_{ax-ax} = *J*_{axial-axial}, *J*_{ax-eq} = *J*_{axial-equatorial}, *J*_{eq-eq} = *J*_{equatorial-equatorial}, THP-H = tetrahydropyranyl proton, TBDMS-H = *tert*-butyldimethylsilyl proton. ¹³C-NMR Bruker AM 250 (62.5 MHz), Varian INOVA-500 (125.7 MHz), Varian INOVA-600 (150.8 MHz), δ (ppm) = 0 for tetramethylsilane, 77.0 for chloroform-d. * = assignment is interchangeable. The multiplicities of ¹³C-NMR signals were determined with help of either DEPT-(Distortionless Enhancement by Polarization Transfer) or APT-(Attached Proton Test) and are designated as follows: CH₃, CH = (+) (DEPT and APT), CH₂ = (-), (DEPT and APT), quaternary C = (-) (APT), C_{quart} (DEPT), TBDMS-C = *tert*-butyldimethylsilyl carbon THP-C = tetrahydropyranyl carbon, rot = rotomer.-MS: Varian MAT CH 7, MAT 731.-HRMS: Varian MAT 311 A.-Microanalysis: Mikroanalytisches Laboratorium des Instituts für Organische Chemie der Georg-August-Universität Göttingen.-Column chromatography was performed on Merck Silica gel 60 (0.063-0.200 mm).- Thin layer chromatography : Macherey-Nagel Alugram G/UV₂₅₄ 0.25 mm silica gel with fluorescent indicator.- Developer: molybdenum phosphoric acid solution (10% in ethanol).-All operations were performed under Nitrogen or Argon atmosphere.-Solvents were purified and dried according to the conventional methods. The following abbreviations have been used: DME = 1,2-dimethoxyethane, DMPU = 1,3-dimethyltetrahydro-2(1H)-pyrimidinon, HMPA = hexamethylphosphoramide, DMF = dimethylformamide.

2. General procedures

General Procedure for Alkylation of Alkyne with Alkylbromide (GP1)

To a solution of n- butyllithium (hexane solution) in 20 ml of dry THF is added at -78 °C, slowly, the alkyne (10 mmol). After stirring for 15 min, HMPA and a solution of alkylbromide (1.2 mmol) in 5 ml THF are added to the alkyne mixture and stirring is continued for 1 h at -78 °C and 24 h at room temperature. The reaction mixture is then quenched with saturated solution of ammonium chloride and extracted with diethyl ether (3×20 ml). After drying over magnesium sulfate, the ether is evaporated and the residue is eluted with pentane-ether over silica gel using column chromatography.

General Procedure for Brominating of Tetrahydropyranyl Ether (GP2).

Bromine (40 mmol) is added, dropwise, into a solution of triphenylphosphine (42 mmol) in dichloromethane at -20 °C. After stirring for 30 min, tetrahydropyranylether (12 mmol) is added to the resulting white suspension. The reaction mixture is allowed to warm to room temperature and stirring is continued for additional 12 h. The reaction mixture is then concentrated and the residue is treated with pentane (3000 ml). The precipitating triphenylphosphine oxide is filtered and the pentane is evaporated. The residue is purified using column chromatography (silica gel, pentane-diethyl ether as eluent).

General Procedure for Dialkyl malonate Coupling with Alkyl halide and Mesylate (GP3).

A. Coupling with alkyl halides

Dialkyl malonate (10 mmol) is added, dropwise, to a suspension of sodium hydride (0.4 g 60% oil suspension, 10 mmol) in dimethylformamide DMF 20 ml. After the addition, the mixture is warmed gently (at ~ 50 °C) till it becomes a clear solution and all the suspension dissolves. The alkyl halide is added to the resulting clear solution and stirring is continued for 36 h at room temperature. The reaction mixture was then poured into 70 ml of water and extracted with (3×70 ml) diethyl ether. The combined ether layers are washed with brine, dried over MgSO_4 and concentrated. The residue is purified using column chromatography (silica gel, pentane-diethyl ether as eluent).

B. Coupling with Mesylate^[65]

Dialkyl malonate (15 mmol) is added at 50 °C, dropwise, into a suspension of sodium hydride (0.6 g 60% oil suspension, 15 mmol) in DMF (50 ml). The resulting clear solution, is added to a solution of mesylate (6.11 mmol), potassium iodide (KI) (6.11 mmol), in THF and the reaction mixture was refluxed at 70 °C for 24 h. After cooling, the mixture is treated with saturated solution of ammonium chloride and extracted with (4×70 ml) diethyl ether. The combined ether layers are washed with brine, dried over MgSO₄ and concentrated. The residue is distilled using kugelrohr distillation and further purified by column chromatography (silica gel and pentane-diethyl ether as eluent).

General Procedure for Tin Catalyzed Coupling of Acetals with Allylic Bromide (GP4)

To a suspension of tin powder in diethyl ether /water mixture (5:2 v/v) is added, successively, 2,3-dibromopropene (**57**), 40 drops of 48% HBr and the acetal. The mixture is vigorously stirred for 5-6 days at room temperature. The reaction mixture is then diluted with 150 ml of water and 150 ml of diethyl ether and extracted thoroughly with (10×100 ml) of diethyl ether. The combined ether layers are dried over MgSO₄, and concentrated. The produced alcohol is immediately purified using column chromatography (silica gel and pentane-diethyl ether as eluent).

General Procedure for Protecting of Alcohols with tert-Butyldimethylsilyl chloride (GP5)

tert-butyldimethylsilyl chloride (8 mmol) is added to a solution of the alcohol (5.6 mmol) and imidazole (20 mmol) in DMF (20 ml) at 55 °C. After stirring at 55 °C for 12 h, the reaction mixture is poured into 70 ml of water and extracted with (3×40 ml) of diethyl ether. The combined ether layers are dried over MgSO₄, and concentrated. The residue is purified using column chromatography (silica gel and pentane-diethyl ether as eluent).

General Procedure for Terminal Alkyne Coupling with Anhydride or Methylchloroformate (GP6).

A solution of LDA (4.2 mmol) (lithium diisopropyl amine) in THF (10 ml) is added -78 °C, dropwise, to a solution of the terminal alkyne (3.8 mmol) in THF (10 ml) at -78 °C. After stirring for 30 min, HMPA and acetyl anhydride or chloromethylformate are added to the reaction mixture and stirring is continued for 1 h at -78 °C and 2 h at room temperature. The resulting reaction mixture is then quenched with saturated solution of ammonium chloride and extracted with (3×50 ml) diethyl ether. The combined ether layers are dried (MgSO_4), concentrated, and the residue is purified by using column chromatography (silica gel and pentane-diethyl ether as eluent).

General Procedure for Brominating a Terminal Alkyne with B-Bromo-9-borabicyclo[3.3.1]nonane (B-Br-9-BBN)(GP7)

The alkyne (3.3 mmol) is added to a solution of B-Br-9-BBN (7.3 mmol) in a 25 ml dichloromethane (prepared by adding a 7.3 ml of 1M commercially available solution of B-Br-9-BBN in dichloromethane to a 17.7 ml dichloromethane) under argon atmosphere and at 0 °C. After stirring for 3 h at 0 °C, 2 ml of glacial acetic acid is added and stirring is continued for additional 1 h before adding 30 ml of 3 M aqueous sodium hydroxide followed by dropwise addition of 6 ml of 30% hydrogen peroxide. The reaction mixture is stirred for further 1 h and the resulting two layers are separated. The aqueous layer is extracted with (3×40 ml) dichloromethane and the combined organic layers are washed sequentially with 100 ml of water, 100 ml of saturated solution of sodium bicarbonate, and 100 ml of water. The combined organic layers are then dried (MgSO_4), concentrated, and the residue is eluted with pentane from a column of silica gel.

General Procedure for Palladium Oligocyclizations (Heck reaction) (GP8).

The palladium catalyzed oligocyclization is induced by different reaction conditions which are illustrated by the following methods:

Method A:

palladium acetate (0.1 equiv) is added at 60 °C to a degassed mixture, place in a Pyrex[®] crucible, of triphenylphosphine (0.25 equiv), potassium carbonate (2.5 equiv), and 2-

bromoalk-1-eneyene precursor (1 equiv) in acetonitrile. After stirring for 1 to 12 h at 60 °C, the reaction mixture is allowed to cool to room temperature, filtered over two layers of celita and charcoal and concentrated. The residue is purified by thick layer chromatography (TLC) using 20×20 cm plates coated with silica gel 60 PF₂₅₄ containing 2.5% CaSO₄ .

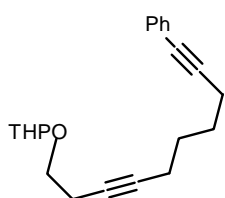
Method B:

Palladium acetate (0.1 equiv) is added at 80 °C to a degassed mixture, placed in a Pyrex[®] crucible, of triphenylphosphine (0.25 equiv), sodium formate (1.2 equiv), and the 2-bromoalk-1-eneyene precursor (1 equiv) in DMF. After stirring from 1 to 12 h at 80 °C, the reaction mixture is poured into 30 ml of water and extracted (3×20 ml) with diethyl ether. The combined ether layers are dried (MgSO₄), concentrated and the residue is purified by thick layer chromatography (TLC) using 20×20cm plates coated with silica gel 60 PF₂₅₄ containing 2.5% CaSO₄ .

3. Synthesis of the precursors

1-phenyl-10-tetrahydro-2H-pyran-1,7-decadiyne (53)

According to GP1, 1.4 g (10 mmol) of 2-(3-butynyloxy)tetrahydro-2H-pyran (**52**) in 5 ml THF was added at $-78\text{ }^{\circ}\text{C}$ to a solution of 5 ml (11 mmol) of n-butyl lithium (2.3 M in

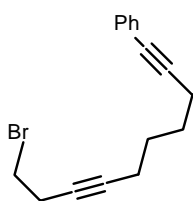


hexane) in 20 ml dry THF. After stirring for 15 min, 1.8 ml (10 mmol) of HMPA and 2.6 g (11 mmol) of 6-bromo-1-phenyl hex-1-yne **51** were added sequentially to the reaction mixture. After stirring for 1 h at $-78\text{ }^{\circ}\text{C}$ and 24 h at room temperature, the reaction

mixture was quenched with 40 ml of saturated solution of ammonium chloride, the organic layer was separated, and the aqueous layer was extracted with (3×30 ml) of diethyl ether. The combined organic layers were dried (MgSO_4), concentrated and the residue was purified by column chromatograph (60g silica gel and 20:1 pentane/diethyl ether) to afford a colorless liquid 1.5 g (48%). ($R_f = 0.13$, 20:1 pentane/diethyl ether). -IR (Film) : $\nu = 3057\text{ cm}^{-1}$, 2945, 2231, 1739, 1598, 1490, 1439, 1382, 1326, 1120, 1033, 758, 693. - $^1\text{H-NMR}$ (250 MHz, CDCl_3) : $\delta = 1.50 - 1.80$ (m, 10 H, 6 H, THP-H, 4 H, 4(5)-H), 2.18 - 2.24 (m, 2 H, 3-H), 2.39 - 2.50 (m, 4 H, 2-H, 6-H), 3.47 - 3.57 (m, 2H, THP-H), 3.75-3.85 (m, 2 H, 10-H), 4.64 (m, 1 H, THP-H), 7.19 - 7.40 (m, 5 H, phenyl-H). - $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT) : $\delta = 18.31$ (-, C-6), 18.96 (-, C-5), 19.40 (-, C-9), 20.20 (-, THP-C), 25.40 (-, THP-C), 27.76 (-, C-4*), 28.05 (-, C-5*), 30.54 (-, THP-C), 62.16 (-, THP-C), 66.16 (-, C-10), 77.00 (C_{quart} , C-8), 79.17 (C_{quart} , C-2), 80.76 (C_{quart} , C-7), 89.86 (C_{quart} , C-1), 98.69 (+, THP-C), 123.90 (C_{quart} , phenyl-C), 127.44 (+, *o*-phenyl-C), 128.15 (+, *m*-phenyl-C), 131.50 (+, *p*-phenyl-C). - MS (EI, 70 eV), m/z (%) : 310 (6) [M^+], 208 (16) [$\text{M}^+ - \text{OTHP}$], 167 (20), 141 (10), 128 (19), 115 (41) [C_9H_7^+], 85 (100) [$\text{C}_5\text{H}_9\text{O}^+$], 57 (16), 41 (24). - $\text{C}_{21}\text{H}_{26}\text{O}_2$ (310.2)

1-(10'-bromo-1',7'-decadiynyl)benzene (54)

According to GP2, 4g (13 mmol) of 1-phenyl-10-tetrahydro-2H-pyranyloxy-1,7-decadiyne(**53**) was added at $-20\text{ }^{\circ}\text{C}$ to a white suspension of triphenylphosphine



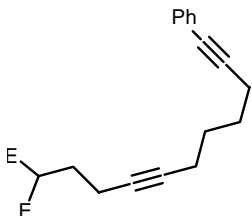
dibromide, which had been prepared by dropwise addition of 6.4 g (40 mmol) of bromine to a solution of 9.3 g (35.5 mmol) triphenylphosphine in dichloromethane at $-20\text{ }^{\circ}\text{C}$ and stirring for 30 min, and stirring was continued for 20 h at room temperature. After

working up, as described in GP2, the resulting residue was purified using column chromatography (50 g of silica gel, 20:1 pentane/diethyl ether) to afford 2.8 g (75%) of a yellow oil. ($R_f = 0.63$, 20:1 pentane/diethyl ether). -IR (Film): $\nu = 3055\text{cm}^{-1}$, 2925, 2361,

2338, 1734, 1598, 1490, 1439, 1271, 1212, 757, 692. - $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.63 - 1.75$ (m, 4 H, 4' (5')-H), 2.22 (m, 2 H, 3'-H), 2.44 (t, $^3J = 6.6$ Hz, 6'-H), 2.72 (dt, $^3J = 7.3$, $^2J = 2.3$ Hz, 2 H, 9'-H), 3.44 (t, $^3J = 6.6$ Hz, 2 H, 10'-H), 7.26 - 7.41 (m, 5 H, phenyl-H). - $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 18.27$ (-, C-6'), 18.94 (-, C-3'), 23.32 (-, C-9'), 27.74 (-, C-4'*), 27.87 (-, C-5'*), 30.27 (-, C-10'), 77.29 (C_{quart} , C-8'), 80.85 (C_{quart} , C-7'), 82.11 (C_{quart} , C-2'), 89.81 (C_{quart} , C-1'), 123.90 (C_{quart} , phenyl-C), 127.53 (+, *o*-phenyl-C), 128.18 (+, *m*-phenyl-C), 131.51 (+, *p*-phenyl-C). - MS (EI, 70 eV) m/z (%): 288/290 (3/3) [M^+], 195 (28), 167 (14), 141 (9), 129 (10) [$\text{C}_{10}\text{H}_9^+$], 123 (100), 115 (48) [C_9H_7^+], 91 (25) [C_7H_7^+], 67 (17), 41 (14). - $\text{C}_{16}\text{H}_{17}\text{Br}$ (289.06)

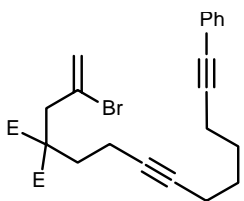
Diethyl-(10'-phenyl-3',9'-decadiynyl)malonate (55)

According to GP3A, 1.6 g (10 mmol) of diethyl malonate was added, dropwise, to a suspension of 0.4 g(10 mmol) of sodium hydride (60% oil suspension) in 20 ml of dry DM. After the suspension had dissolved (warming to $\sim 50\text{ }^{\circ}\text{C}$ if necessary), 2.5 g (8.6 mmol) of 1-(10'-bromo-1',7'-decadiynyl)benzene (**54**) was added and stirring was continued for 36 h at room temperature. The resulting residue, after working up as described in GP3, was purified by column chromatography (100 g of



silica gel , 1:10 pentane/diethyl ether) to afford 2g of a colorless oil. ($R_f = 0.28$, 10:1 pentane/diethyl ether).-IR (Film) : $\nu = 3059 \text{ cm}^{-1}$, 2983, 2862, 2839, 1753, 1730, 1599, 1491, 1442, 1246, 1151, 1049, 1025, 758, 693.- $^1\text{H-NMR}$ (250 MHz , CDCl_3): $\delta = 1.25$ (t, $^3J = 7 \text{ Hz}$, 6 H, $\text{COOCH}_2\text{CH}_3$), 1.65 – 1.70 (m, 4 H, 6', 7'-H), 2.05 (m, 2 H, 1'-H), 2.18 – 2.24 (m, 4 H, 2' (5')-H), 2.42 (t, $^3J = 6.5 \text{ Hz}$, 2 H, 8'-H), 3.55 (t, $^3J = 6 \text{ Hz}$, 1 H, 2-H), 4.18 (q, $^3J = 6 \text{ Hz}$, 4 H, $\text{COOCH}_2\text{CH}_3$), 7.24 – 7.40 (m, 5 H, phenyl-H).- $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 14.04$ (+, $\text{COOCH}_2\text{CH}_3$), 16.74 (–, C-2'), 18.28 (–, C-5'), 18.96 (–, C-8'), 27.37 (–, C-1'), 27.97 (–, C-6'*), 28.06 (–, C-7'*), 50.58 (+, C-2), 61.39 (–, $\text{COOCH}_2\text{CH}_3$), 78.33 (C_{quart} , C-3'), 80.79 (C_{quart} , C-4'), 81.22 (C_{quat} , C-9'), 89.83 (C_{quart} , C-10'), 123.90 (C_{quart} , phenyl-c), 127.49 (+, *o*-phenyl-C), 128.14 (+, *m*-phenyl-C), 131.50 (+, *p*-phenyl-C), 169.2 (C_{quart} , $\text{COOCH}_2\text{CH}_3$) . -MS (DCI, NH_3 , 70eV) m/z (%): 754 (2) [$2\text{M}+\text{NH}_4^+$], 386 [$\text{M}+\text{NH}_4^+$]. – $\text{C}_{23}\text{H}_{28}\text{O}_4$ (368)

Diethyl-2-(2''-bromoallyl)-2-(10'-phenyl-3',9'-decadiynyl)malonate (48)



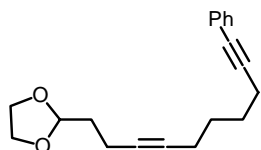
To a suspension of 0.32 g (8 mmol) of sodium hydride (60% oil suspension) in 15 ml of DME (1,2-dimethoxyethane) was added, dropwisely, a solution of 2.2 g (5.9mmol) of diethyl 2-(10'-phenyl-3',9'-decadiynyl)malonate (**55**) in 5 ml of DME. After warming for 30 min at $\sim 50 \text{ }^\circ\text{C}$, 2.1 g (10.5 mmol) of 2,3-dibromopropene was added and the reaction was stirred for 30 h at room temperature. The reaction mixture was then poured into 50 ml of water, the two layers were separated, and the aqueous layer was extracted with (3 \times 50 ml) diethyl ethyl ether. the combined ether layers were dried (MgSO_4), concentrated and the residue was purified by column chromatography (100 g silica gel , 20:1 pentane/diethyl ether) to afford 1.3 g (44%) of a colorless oil . ($R_f = 0.12$, 20:1 pentane/diethyl ether).-IR (Film) : $\nu = 3056 \text{ cm}^{-1}$, 2982, 2943, 2839, 2230, 1725, 1625, 1491, 1445, 1367, 1270, 1242, 1186, 1024, 898, 759, 737, 693.- $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.25$ (t, $^3J = 7 \text{ Hz}$, 6 H, $\text{COOCH}_2\text{CH}_3$), 1.65 (m, 4H, 6'(7')-H), 2.12 – 2.25 (m, 6 H, 1' (5' 8') – H), 2.42 (t, $^3J = 6.6 \text{ Hz}$, 2 H, 2' – H), 3.16 (s , 2 H, 1'' – H), 4.19

(q, $^3J = 7$ Hz, 4 H, COOCH₂CH₃), 5.58 (d, $^2J = 1.7$ Hz, 1H, 3'' – H), 5.67 (m, 1 H, 3'' – H), 7.25 – 7.40 (m, 5 H, phenyl-H).-¹³C-NMR (62.5MHz, CDCl₃, DEPT): $\delta = 13.94$ (+, COOCH₂ CH₃), 14.23 (–, C- 2'), 18.33 (–, C- 5'), 18.95 (–, C-8'), 27.81 (–, C-6^{*}), 28.02 (–, C-7^{*}), 42.98 (–, C-1''), 56.47 (C_{quart}, C-2), 61.65 (–, COOCH₂ CH₃), 78.79 (C_{quart}, C- 3'), 80.41 (C_{quart}, C-4'), 80.79 (C_{quart}, C- 9'), 89.85 (C_{quart}, C-10'), 121.89 (–, C-3''), 123.90 (C_{quart}, phenyl-C), 127.02 (C_{quart}, C-2''), 127.49 (+, *o*-phenyl-C), 128.15 (+, *m*-phenyl-C), 131.51 (+, *p*-phenyl-C), 170.12(C_{quart}, COOCH₂ CH₃).-MS (DCI, NH₃, 70eV) *m/z* (%): 506 (100) [M+NH₄⁺].- C₂₆H₃₁O₄Br(487.1)

10-(1',3'-dioxolan-2'-yl)-1-phenyl-1,7-decadiyne (56)

Method A:

By adapting GP1, 1.8 g (14.8 mmol) of 2-(3-butynyl)-1,3-dioxolane(**64**) was added at –78 °C to a solution of 9.5 ml (14.8 mmol) of n-butyl lithium (1.56M in hexane) in 30 ml of THF. After stirring for 15 min, 2.6 ml (14.4 mmol) of HMPA and 3.5 g (14.8 mmol) of 6-bromo-1-phenyl hex-1-yne (**51**) were added sequentially to the reaction mixture. After stirring at –78 °C for 1 h, the reaction mixture was allowed to warm to room temperature and stirring was continued for additional 24 h. Working up, as described in GP1, and purifying by column chromatography (80 g silica gel, 20:1 pentane/diethyl ether) afforded 2.5 g (60%) of a colorless liquid. (*R_f* = 0.28, 10:1 pentane/diethyl ether).



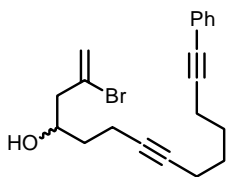
Method B: Using Sonogashira Reaction

1.5 g (7.28 mmol) of 2-(3',9'-decadiynyl)-1,3-dioxoline(**59**) was added to a mixture of 30 mg(0.042 mmol) of dichlorobis(triphenylphosphine)palladium [PdCl₂(PPh₃)₂], 20 mg (0.1 mmol) of cuprous iodide (CuI), 40 mg (0.15 mmol) of triphenylphosphine, 1.5 g (7.30 mmol) of iodobenzene and 50 ml of triethylamine (Et₃N). The reaction was stirred at 40 °C for 14 h during which a substantial amount of white solid was formed. The reaction mixture was then quenched with a saturated solution of ammonium chloride and

extracted with (5×50 ml) diethyl ether. The combined ether layers were evaporated and the residue was purified by column chromatography (70 g silica gel , 20:1 pentane/diethyl ether) to afford 1.3 g (63%) of a colorless liquid.-IR (Film): $\nu = 3056 \text{ cm}^{-1}$, 2942, 2861, 2837, 2230, 1951, 1877, 1598, 1490, 1441, 1330, 1146, 1128, 1072, 1046, 943, 896, 758, 693, 525.- $^1\text{H-NMR}$ (250 MHz , CDCl_3): $\delta = 1.61 - 1.73$ (m, 4 H, 4(5)-H), 1.84 (dt, $^3J = 4.8 \text{ Hz}$ $^3J = 7.4 \text{ Hz}$, 2 H, 10-H), 2.17 – 2.33 (m, 4 H, 3(6)-H), 2.42 (t, $^3J = 6.7 \text{ Hz}$, 2 H, 9-H), 3.88 – 3.96 (m, 4 H, O- CH_2CH_2 -O), 4.95 (t, $^3J = 4.7 \text{ Hz}$, 1 H, 2'-H), 7.24 – 7.41 (m, 5 H, phenyl-H). – $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 13.72$ (–, C-9) , 18.30 (–, C-6), 18.95 (–, C-3), 27.79 (–, C-5*), 28.11 (–, C-4*), 33.32 (–, C-10), 64.89 (–, O- CH_2CH_2 -O), 79.29 (C_{quart} , C-8), 80.00 (C_{quart} , C-7), 80.76 (C_{quart} , C-2), 89.90 (C_{quart} , C-1), 103.33 (+, C-2'), 123.92 (C_{quart} , phenyl-C), 127.48 (+, *o*-phenyl-C), 128.14 (+, *m*-phenyl-C), 131.50 (+, *p*-phenyl-C). – MS (DCI, NH_3 , 70eV) m/z (%): 582 (2) [$2\text{M}+\text{NH}_4^+$], 300 (100) [$\text{M}+\text{NH}_4^+$], 283 (6) [$\text{M}+\text{H}^+$].- $\text{C}_{19}\text{H}_{22}\text{O}_2$ (282.2) calcd for: C 80.82, H 7.85; found: C 80.56, H 7.62

2-bromo-14-phenyl-1-tetradecen-7,13-diyn-4-ol (70)

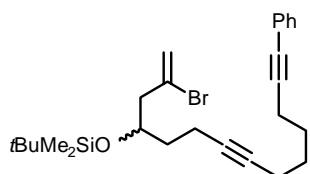
According GP4, to a suspension of 0.73 g (6.1 mmol) of powder tin in diethyl ether(8.7 ml) /water(3.5ml) mixture (5:2 v/v) was added, successively, 1.2 g(6.1mmol) of 2,3-dibromopropene, 40 drops of 48% HBr and 1.1 g(3.9 mmol) of 10-(1',3'-dioxolan-2'-yl)-1-phenyl-1,7-decadiyne (**56**). The mixture was vigorously stirred for 5days at room temperature .The reaction mixture was then diluted with 150 ml of water and 150 ml of diethyl ether and extracted thoroughly with (10×100 ml) of diethyl ether. The combined ether layers were dried over MgSO_4 , and concentrated. The produced alcohol was immediately eluted from a column of silica gel (50 g), using (10:1) pentane/diethyl ether till the starting material was removed and then raising the polarity to (20:3) to remove the product, to afford 1 g (70%) of a colorless oil. ($R_f = 0.18$, 20:3 pentane/diethyl ether).-IR (Film): $\nu = 3500 \text{ cm}^{-1}$, 3079, 3056, 2948, 2901, 2838, 2228, 1949, 1876, 1631, 1490, 1439, 1331, 1121, 1068, 913, 891, 758, 693.- $^1\text{H-NMR}$ (250



MHz, CDCl_3): $\delta = 1.62 - 1.72$ (m, 6 H, 5 (10, 11)-H), 2.08 (s, 1H, OH), 2.22 (m, 2 H, 12-H), 2.33 (m, 2 H, 9-H), 2.43 (m, 2 H, 6-H), 2.55 (d, $^2J = 6.25$ Hz, 2 H, 3-H), 4.10 (m, 1 H, 4-H), 5.53 (d, $^2J = 1.5$ Hz, 1 H, 1-H), 5.69 (d, $^2J = .85$ Hz, 1 H, 1-H), 7.24 – 7.41 (m, 5 H, phenyl-H).- ^{13}C -NMR (62.5 MHz, CDCl_3 , DEPT): $\delta = 15.37$ (-, C-6), 18.30 (-, C-9), 18.97 (-, C-12), 27.81 (-, C-10*), 28.09 (-, C-11*), 35.09 (-, C-5), 49.11 (-, C-3), 68.38 (+, C-4), 79.55 (C_{quart} , C-7), 80.84 (C_{quart} , C-8), 89.85 (C_{quart} , C-14), 119.64 (-, C-1), 123.90 (C_{quart} , phenyl-C), 127.50 (+, *o*-phenyl-C), 128.15 (+, *m*-phenyl-C), 130.42 (C_{quart} , C-2), 131.51 (+, *p*-phenyl-C). – MS (DCI, NH_3 , 70 eV) m/z (%): 736 (1) [$2\text{M} + \text{NH}_4^+$], 376/378 (100/98) [$\text{M} + \text{NH}_4^+$], 298 (11) [$(\text{M} - \text{Br}) + \text{NH}_4^+$]. – $\text{C}_{20}\text{H}_{23}\text{BrO}$ (358.2)

1-(13'-bromo-11'-(tert-butyldimethylsilyloxy)-13'-tetradecen-1',7'-diynyl)benzene (49)

According to GP5, 0.5 g(3.33mmol) of *tert*-butyldimethylsilyl chloride was added at 55



$^{\circ}\text{C}$ to a solution of 1 g(2.77mmol) of 2-bromo-14-phenyl-1-tetradecen-7,13-diyn-4-ol (**70**) and 0.65 g(9.8 mmol) of imidazole in 10 ml DMF. After stirring at 55 $^{\circ}\text{C}$ for 12 h, the reaction mixture was poured into 70ml of water and

extracted with (3 \times 40 ml) of diethyl ether. The combined ether layers were dried over MgSO_4 , and concentrated. The residue was purified by column chromatography (50 g silica gel and 80:1 pentane/diethyl ether) to afford 1.1 g (82%) of a colorless oil. ($R_f = 0.63$, 80:1 pentane/diethyl ether).-IR (Film) : $\nu = 3081$ cm^{-1} , 3053, 2957, 2928, 2856, 2232, 1631, 1490, 1434, 1362, 1255, 1075, 1005, 890, 836, 777, 755, 692.- ^1H -NMR (250 MHz, CDCl_3) : $\delta = 0.095$ (s, 6 H, TBDMS-H), 0.88 (s, 9 H, TBDMS-H), 1.67 – 1.72 (m, 6 H, 4' (5',10')-H), 2.22 (m, 4 H, 3 (6')-H), 2.40 – 2.47 (m, 2 H, 9'-H), 2.51 – 2.57 (dd, $^2J = 6.4$ Hz, $^2J = 4$ Hz, 2 H, 12'-H), 4.10 (m, 1H, 11'-H), 5.43 (d, $^2J = 1.3$ Hz, 1 H, 14'-H), 5.61 (d, $^2J = 1.3$ Hz, 1 H, 14'-H), 7.24 – 7.41 (m, 5 H, phenyl -H).- ^{13}C -NMR (62.5 MHz, CDCl_3 , DEPT) : $\delta = -4.60$ (+, TBDMS-C), -4.40 (+, TBDMS-C), 14.74 (-, C-9'), 18.022 (C_{quart} , TBDMS-C), 18.32 (-, C-6'), 18.99 (-, C-3'), 25.84 (+, TBDMS-C), 27.83 (-, C-5'*), 28.18 (-, C-4'*), 35.78 (-, C-10'), 49.34 (-, C-12'), 68.83 (-, C-10'),

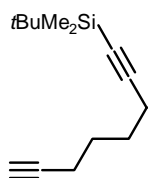
79.92 (C_{quart}, C-8'), 80.13 (C_{quart}, C-7'), 80.78 (C_{quart}, C-2'), 89.88 (C_{quart}, C-1'), 119.12 (–, C-14'), 123.94 (C_{quart}, phenyl-C), 127.48 (+, *o*-phenyl-C), 128.14 (+, *m*-phenyl-C), 130.83 (C_{quart}, C-13'), 131.51 (+, *p*-phenyl-C).– MS (DCI, NH₃, 70 eV) *m/z* (%): 490/492 (88/100) [M+NH₄⁺], 412 (20) [(M–Br)+NH₄⁺] .– C₂₆H₃₇BrOSi(473.2)

1-(tert – butyldimethylsilyl) 1,8–octadiyne (86)

The synthesis of this compound was reported using ethyl magnesium bromide as a base.^[51]

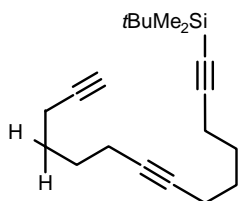
3.13 ml (4.8 mmol) of *n*-butyl lithium was added at –78 °C to a solution of 0.5 g (4.7 mmol) of 1,7-octadiyne in 15 ml of THF and stirring was continued for 30 min. To the resulting white suspension were added 0.82 ml (4.7 mmol) of HMPA, 0.55 ml (4.6 mmol) of DMPU and 0.7 g (4.7 mol) of *tert*-butyldimethylsilyl chloride and the reaction mixture was allowed to warm to room temperature. After stirring for 20 h at room temperature, the reaction mixture was treated with 100 ml diethyl ether and 30 ml of a saturated solution of ammonium chloride. The aqueous layer was extracted with (3×50 ml) of diethyl ether and the combined organic phases were dried (MgSO₄) and concentrated. The resulting residue was purified by column chromatography (40 g silica gel, pentane) to afford 0.36 g (35%) of **86** and 0.3g (20%) of the disubstituted derivative.

¹H-NMR (250 MHz, CDCl₃): δ = 0.072 (s, 6 H, TBDMS-H), 0.91 (s, 9 H, TBDMS- H), 1.60 – 1.66 (m, 4 H, 4, 5-H), 1.94 (t, ⁴*J* = 2.62 Hz, 1 H, 8-H), 2.19 – 2.26 (m, 4H, 3, 6-H).- ¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = – 4.48 (+, TBDMS-C), 16.48 (C_{quart}, TBDMS-C), 17.87 (–, C-6), 19.29 (–, C-3), 26.04 (+, TBDMS-C), 27.38 (–, C-4*), 27.53 (–, C-5*), 68.40 (+, C-8), 82.10 (C_{quart}, C-7), 84.10 (C_{quart}, C-2), 107.35 (C_{quart}, C-1).



1-(tert-butyldimethylsilyl)-1,7,13-tetradecatriyne (81)

By adapting GP1, 6 ml (9.3 mmol) of *n*-butyl lithium (1.5M in hexane) was added, at -78 °C, dropwise to a solution of 0.96 g (9.1 mmol) of 1,7-octadiyne in 40 ml of THF. After addition, the reaction was stirred for 30 min and to the resulting white suspension was added, sequentially, 1.6 ml (9.1 mmol) of HMPA and 2.5 g (9.1 mmol) of 6-bromo-1-(*tert*-butyldimethylsilyl) hex-1-yne (**82**). Stirring

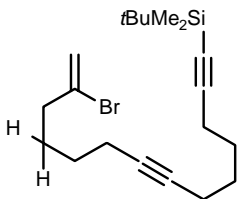


was continued for 2 h at -78 °C and 14 h at room temperature. The reaction mixture was diluted with 150 ml of water, the two layers were separated, and the aqueous layer was extracted with (5×50 ml) of diethyl ether. The combined organic layers were dried (MgSO_4), concentrated, and the residue was purified by column chromatography (60g silica gel, pentane) to afford 1.2 g (45%) of a colorless liquid. ($R_f = 0.4$, pentane).-IR (Film) : $\nu = 3313 \text{ cm}^{-1}$, 2955, 2928, 2857, 2173, 1680, 1467, 1252, 1109, 1009, 840, 776, 679.- $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 0.072$ (s, 6 H, TBDMS-H), 0.92 (s, 9 H, TBDMS-H), 1.59 (m, 8 H, 4 (5,10,11)-H), 1.94 (t, $^4J = 2.64$ Hz, 1 H, 14-H), 2.16 – 2.27 (m, 8 H, 3(6,9,12)-H).- $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = -4.46$ (+, TBDMS-C), 16.49 (C_{quart} , TBDMS-C), 17.93 (–, C-9), 18.17 (–, C-3*), 18.21 (–, C-12*), 19.35 (–, C-6), 26.04 (+, TBDMS-C), 27.47 (–, C-10**), 27.71 (–, C-11**), 27.97 (–, C-5***), 28.04 (–, C-4***), 68.34 (+, C-14), 79.85 (C_{quart} , C-13****), 80.03 (C_{quart} , C-8****), 82.62 (C_{quart} , C-7), 84.24 (C_{quart} , C-2), 107.65 (C_{quart} , C-1).- MS (DCI, NH_3 , 70 eV) m/z (%): 318 (100) [$\text{M}+\text{NH}_4^+$], 300 (18) [M^+], 178 (15), 161 (62), 154 (10). – $\text{C}_{20}\text{H}_{32}\text{Si}$ (300.5)

2-bromo-14-(tert-butyldimethylsilyl)-1-tetradecen-7,13,-diyne (79)

Method A: by brominating 1-(tert-butyldimethylsilyl)-1,7,13-tetradecatriyne with B-Bromo-9-borabicyclo[3.3.1]nonane (B-Br-9-BBN)

According to GP7, 1 g (3.3mmol) of 1-(tert-butyldimethylsilyl)-1,7,13-tetradecatriyne(**81**) was added, at 0 °C, and under argon atmosphere, to a solution of (7.3mmol) of B-Br-9-BBN(**88**) in 25 ml dichloromethane (prepared by adding 7.3 ml of 1M of a commercially available solution of B-Br-9-BBN in dichloromethane to 17.7 ml dichloromethane) . After stirring for 3 h



at 0 °C, 2 ml of glacial acetic acid was added and stirring was continued for additional 1 h before adding 30 ml of 3 M aqueous sodium hydroxide followed by dropwise addition of 6 ml of 30% hydrogen peroxide. The reaction mixture was stirred for further 1 h and the resulting two layers were separated. The aqueous layer was extracted with (3×40 ml) dichloromethane and the combined organic layers were washed sequentially with 50 ml of water, 50 ml of saturated solution of sodium bicarbonate and 50 ml of water. The combined organic layers were then dried (MgSO₄), concentrated, and the residue was eluted with pentane from a column of silica gel (50 g) to afford 0.2 g (16%) of a colorless oil.

Method B: by coupling with 1-(tert – butyldimethylsilyl) 1,8–octadiyne

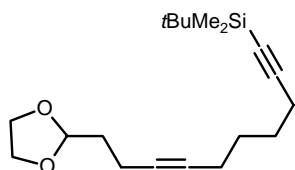
1.8 ml (2.8 mmol) of n-butyl lithium (1.5M in hexane) was added at –78 °C, dropwise, to a solution of 0.6 g (2.71 mmol) of 1-(tert – butyldimethylsilyl) 1,8–octadiyne in 15 ml of THF. After addition, the reaction was stirred for 30 min and to the resulting white suspension was added, sequentially, 0.48 ml (2.73 mmol) of HMPA and 0.78 g (2.71 mmol) of 2-bromo-6-iodohex-1-ene (**85**). Stirring was continued for 2 h at –78 °C and 14 h at room temperature. The reaction mixture was diluted with 50 ml of water, the two layers were separated, and the aqueous layer was extracted with (5×30 ml) of diethyl ether. The combined organic layers were dried (MgSO₄), concentrated, and the residue was purified by column chromatography (30 g silica gel, pentane) to afford 0.3 g (28%) of a colorless oil. (R_f = 0.32, pentane).-IR (Film): $\nu = 2956\text{ cm}^{-1}$, 2928, 2857, 2173, 1630, 1602, 1467, 1362, 1251, 1175, 1083, 1007, 886, 842, 828, 572.- ¹H-NMR (250 MHz,

CDCl₃): δ = 0.075 (s, 6 H, TBDMS-H), 0.92 (s, 9 H, TBDMS-H), 1.45 – 1.77 (m, 8 H, 4, 5, 10, 11-H), 2.15 – 2.27 (m, 6 H, 6, 9, 12-H), 2.43 (t, 3J = 6.88 Hz, 2 H, 3-H), 5.39 (d, 2J = 1.52 Hz, 1 H, 1-H), 5.56 (dd, 2J = 1.46 Hz, 4J = 0.78 Hz, 1 H, 1-H). ¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = – 4.46 (+, TBDMS- C), 16.49 (C_{quart}, TBDMS-C), 18.20 (–, C-12), 18.43 (–, C-9*), 19.37 (–, C-6*), 26.05 (+, TBDMS-C), 26.93 (–, C-5), 27.69 (–, C-10**), 27.72 (–, C-11**), 28.04 (–, C-4), 40.85 (–, C-3), 79.90 (C_{quart}, C-7***), 79.97 (C_{quart}, C-8***), 80.06 (C_{quart}, C-13), 107.94 (C_{quart}, C-14), 116.53 (–, C-1), 134.40 (C_{quart}, C-2). – MS (DCI, NH₃, 70 eV) *m/z* (%): 398/400 (94/100) [M+NH₄⁺], 381/383 (16/18) [M⁺]. – C₂₀H₃₃BrSi (381.5)

10-(1',3'-dioxolan-2'-yl)-1-(tert-butyldimethylsilyl)-1,7-decadiyne (89)

Method A

According to GP1, 1.37 g (10.9 mmol) of 2-(3-butynyl)-1,3-dioxolane (**59**) was added at –78 °C to a solution of 7.0 ml (10.9 mmol) of n-butyl lithium (1.56M in hexane) in 30 ml of THF. After stirring for 15 min, 1.91 ml (10.9 mmol) of HMPA and 3 g (10.9 mmol) of 6-bromo-1-(tert-butyldimethylsilyl) hex-1-yne (**82**) were added sequentially to the reaction mixture. After stirring at –78 °C for 1 h, the reaction mixture was allowed to warm to room temperature and stirring was continued for additional 24 h. Working up, as described in GP1, and purifying by column chromatography (100g silica gel, 20:1 pentane/diethyl ether) afforded 2.2 g (62%) of a colorless liquid. (*R*_f = 0.37, 10:1 pentane/diethyl ether).

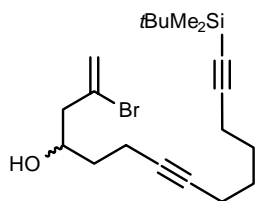


Method B

1.5 g (7.27 mmol) of 2-(3',9'-decadiynyl)-1,3-dioxoline (**59**) was added at –78 °C to a solution of 3.6 ml (7.2 mmol) of n-butyl lithium (2M in hexane) in 30 ml of THF. After stirring for 15 min, 0.84 ml (7 mmol) of DMPU and 1.2 g (8 mmol) of tert-butyldimethylsilyl chloride in 5 ml THF were added sequentially to the reaction mixture. After stirring at –78 °C for 1 h, the reaction mixture was allowed to warm to room temperature and stirring was continued for additional 24 h. The reaction was quenched

with 5ml water, the two layers were separated, and the aqueous layer was extracted with (3×40 ml) of diethyl ether. The combined organic layers were dried (MgSO₄), concentrated, and purified by column chromatography (100 g silica gel, 20:1 pentane/diethyl ether) to afford 2 g (85%) of colorless liquid.-IR (Film): $\nu = 2957 \text{ cm}^{-1}$, 2929, 2855, 2172, 1469, 1434, 1411, 1362, 1252, 1146, 1072, 897, 840, 775, 681.-¹H-NMR (250 MHz, CDCl₃): $\delta = 0.072$ (s, 6 H, TBDMS-H), 0.91 (s, 9 H, TBDMS-H), 1.59 (m, 4 H, 4(5)-H), 1.83 (dt, ³J = 7.3 Hz, ²J = 4.7 Hz, 2 H, 10-H), 2.15 – 2.31 (m, 6 H, 3(6,9)-H), 3.85 – 3.99 (m, 4 H, O-CH₂CH₂-O), 4.96 (t, ³J = 4.7 Hz, 1 H, 2'-H).-¹³C-NMR (62.5 MHz, CDCl₃, DEPT): $\delta = -4.62$ (+, TBDMS-C), 13.69 (-, C-9), 16.49 (C_{quart}, TBDMS-C), 18.20 (-, C-6), 19.35 (-, C-3), 26.05 (+, TBDMS-C), 27.69 (-, C-5*), 27.97 (-, C-4*), 33.22 (-, C-10), 64.90 (-, O-CH₂CH₂-O), 79.21 (C_{quart}, C-8), 79.97 (C_{quart}, C-7), 82.61 (C_{quart}, C-2), 103.33 (+, C-2'), 107.63 (C_{quart}, C-1).-MS (DCI, NH₃, 70 eV) *m/z* (%): 658 (0.1) [2M+NH₄⁺], 338 (100) [M+NH₄⁺].-C₁₉H₃₂O₂Si(320.2) calcd for: C 71.19, H 10.06; found: C 71.36, H 10.00

2-bromo-14-(tert-butyldimethylsilyl)-1-tetradecen-7,13-diyne-4-ol (90)

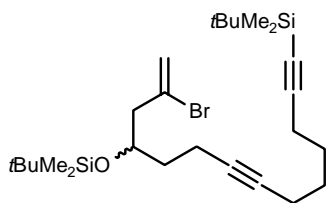


According GP4, to a suspension of 1.3 g (11.24 mmol) of powder tin in diethyl ether(8.7 ml) /water(3.5ml) mixture (5:2 v/v) was added, successively, 2.1 g(11.24mmol) of 2,3- dibromopropene, 40 drops of 48%HBr and 1.8 g(5.64 mmol) of 10-(1',3'-dioxolan-2'-yl)-1- (tert-butyldimethylsilyl)-1,7-decadiyne(**89**).The mixture was vigorously stirred for 5 days at room temperature. The reaction mixture was then diluted with 200 ml of water and 200 ml of diethyl ether and extracted thoroughly with (12×100 ml) of diethyl ether. The combined ether layers were dried over MgSO₄, and concentrated. The produced alcohol was immediately purified by column chromatography (70 g silica gel, and 10:1 pentane/diethyl ether) to afford 1.6 g (71%) of a colorless oil. (R_f = 0.22, 10:1 pentane/diethyl ether).-IR (Film): $\nu = 3500 \text{ cm}^{-1}$, 2954, 2928, 2856, 2173, 1631, 1468, 1363, 1251, 1121, 1065, 891, 840, 808, 775, 680, 597.-¹H-

NMR (250 MHz, CDCl₃): δ = 0.075 (s, 6 H, TBDMS-H), 0.92 (s, 9 H, TBDMS-H), 1.59 – 1.69 (m, 6 H, 5 (10,11)-H), 2.05 (bs, 1 H, OH), 2.15 – 2.33 (m, 6 H, 6(9,12)-H), 2.55 (d, 3J = 6.35 Hz, 2 H, 3-H), 4.08 (m, 1 H, 4-H), 5.31 (d, 2J = 2.1 Hz, 1 H, 1-H), 5.54 (d, 2J = 1.8 Hz, 1 H, 1-H).-¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = - 4.45 (+, TBDMS-C), 15.37 (-, C-6), 16.49 (C_{quart}, TBDMS-C), 18.19 (-, C-9), 19.36 (-, C-12), 26.06 (+, TBDMS-C), 27.72 (-, C-10*), 27.94 (-, C-11*), 35.10 (-, C-5), 49.13 (-, C-3), 68.37 (+, C-4), 79.48 (C_{quart}, C-7), 80.81 (C_{quart}, C-8), 82.67 (C_{quart}, C-13), 107.58 (C_{quart}, C-14), 119.65 (-, C-1), 130.42 (C_{quart}, C-2).- MS (DCI, NH₃, 70 eV) *m/z* (%): 812 (8) [2M+NH₄⁺], 414/416 (91/100) [M+NH₄⁺], 336 (8) [(M-Br)+NH₄⁺].
-C₂₀H₃₃BrOSi(397.2)

2-bromo-4-(tert-butyldimethylsilyloxy)-14-(tert-butyldimethylsilyl)-1-tetradecen-7,13-diyne (80)

According to GP5, 0.38 g(2.58mmol) of *tert*-butyldimethylsilyl chloride was added at 55 °C to a solution of 0.85 g(2.14mmol) of 2-bromo-14-(*tert*-butyldimethylsilyl)-1-tetradecen-7,13-diyn-4-ol (**90**) and 0.5 g(7.5 mmol) of imidazole in 10 ml DMF. After stirring at 55 °C for 12 h, the reaction mixture was poured into 70 ml of water and extracted with (3×40 ml) of diethyl ether. The

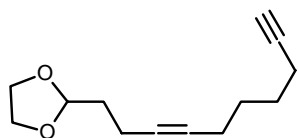


combined ether layers were dried over MgSO₄, and concentrated. The residue was purified by column chromatography (30 g silica gel and 80:1 pentane/diethyl ether) to afford 0.9 g(82%) of a colorless oil. (R_f = 0.79, 80:1 pentane/diethyl ether).-IR (Film): ν = 3314 cm⁻¹, 2959, 2928, 2855, 2173, 1631, 1469, 1362, 1254, 1101, 1077, 1006, 840, 774, 681.-¹H-NMR (250 MHz, CDCl₃): δ = 0.072 (s, 3 H, C-TBDMS-H), 0.076 (s, 3 H, O-TBDMS-H), 0.88 (s, 9 H, C-TBDMS-H), 0.92 (s, 9 H, O-TBDMS-H), 1.52 – 1.72 (m, 6 H, 5 (10,11)-H), 2.17 – 2.27 (m, 6 H, 6 (9,12)-H), 2.48 (dd, 2J = 6.4 Hz, 3J = 14.1 Hz, 1 H, 3-H), 2.58 (dd, 2J = 6.1 Hz, 3J = 14.1 Hz, 1 H, 3-H), 4.07 (m, 1 H, 4-H), 5.43 (s, 1 H, 1-H), 5.61 (s, 1 H, 1-H).-¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = - 4.61 (+, C-TBDMS-C), - 4.40 (+, O-TBDMS-C), 14.71 (-, C-6), 16.49 (C_{quart}, C-TBDMS-C),

18.01 (C_{quart}, O-TBDMS-C), 18.21 (–, C-9), 19.38 (–, C-12), 25.83(+, O- TBDMS-C), 26.06 (+, C-TBDMS-C), 27.75 (–, C-10*), 28.08 (–, C-11*), 35.77 (–, C- 5), 49.32 (–, C-3), 68.83 (+, C-4), 77.49 (C_{quart}, C-7), 79.85 (C_{quart}, C-8), 80.09(C_{quart}, C-13), 107.62 (C_{quart}, C-14), 119.12 (–, C-1), 130.82 (C_{quart}, C-2). – MS (DCI, NH₃, 70 eV) *m/z* (%): 528/530 (88/100) [M+NH₄⁺], 513 [M+H⁺], 450 (4) [(M–Br)+NH₄⁺]. –C₂₆H₄₇BrOSi₂(511.3)

2-(3',9'-decadiynyl)-1,3-dioxoline (**59**)

Method A: by using tetrabutylammonium fluoride



4.5 g (14 mmol) of 10-(1',3'-dioxolan-2'-yl)-1-(tert-butyltrimethylsilyl)-1,7-decadiyne(**89**) was added at 60 °C to a mixture of 17.7 g(56 mmol) of tetrabutylammonium fluoride

in 270 ml THF and 2.2 ml of water. After stirring for 12 h at 60 °C, 200 ml of water was added, the two layers were separated, and the aqueous layer was extracted with (3×150 ml) of diethyl ether. The combined organic layers were dried (MgSO₄), concentrated, and the residue was purified by column chromatography (70 g silica gel, 20:1 pentane/diethyl ether) to afford 2.3 g (80%) of a colorless liquid. (R_f = 0.30, 10:1 pentane/diethyl ether).

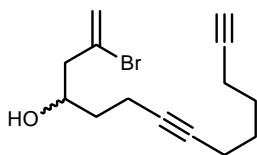
Method B: coupling of 1,7-octadiyne with 2-(1,3-dioxolan-2-yl)ethyl iodide

12.5 ml (18.7 mmol) of butyl lithium (1.5M in hexane) was added at –78 °C, dropwise, to a solution of 2 g (18.8 mmol) of 1,7-octadiyne in 40 ml of THF. After addition, the reaction was stirred for 30 min and to the resulting white suspension was added, sequentially, 3.3 ml (18.8 mmol) of HMPA and 4.5 g (19.7 mmol) of 2-(1,3-dioxolan-2-yl)ethyl iodide(**61**). Stirring was continued for 2 h at –78 °C and 14 h at room temperature. The reaction mixture was diluted with 150 ml of water, the two layers were separated, and the aqueous layer was extracted with (5×50 ml) of diethyl ether. The combined organic layers were dried (MgSO₄), concentrated, and the residue was purified by column chromatography (70 g silica gel, 40:1 pentane/diethyl ether) to afford 1.8g(46%) of a colorless liquid. (R_f = 0.16, 40:1 pentane/diethyl ether).-IR (Film): ν = 3287 cm⁻¹, 2944, 2863, 2712, 2657, 2116, 1434, 1412, 1330, 1147, 1127, 1072, 1045,

943, 898, 626. $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.55 - 1.68$ (m, 4 H, 6'(7')-H), 1.82 (dt, $^3J = 4.8$ Hz, $^3J = 7.4$ Hz, 2 H, 1'-H), 1.93 (t, $^4J = 2.6$ Hz, 1 H, 10'-H), 3.81 - 3.91 (m, 4 H, O- $\text{CH}_2\text{CH}_2\text{-O}$), 4.95 (t, $^3J = 4.8$ Hz, 1 H, 2-H). $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 13.68$ (-, C-2'), 17.92 (-, C-5**), 18.20 (-, C-8**), 27.46 (-, C-6**), 27.88 (-, C-7**), 33.30 (-, C-1'), 64.88 (-, O- $\text{CH}_2\text{CH}_2\text{-O}$), 68.34 (+, C-10'), 79.30 (C_{quart} , C-3'), 79.84 (C_{quart} , C-5'), 84.21 (C_{quart} , C-9'), 103.31 (+, C-2). - MS (DCI, NH_3 , 70 eV) m/z (%): 430 (11) [$2\text{M}+\text{NH}_4^+$], 224 (100) [$\text{M}+\text{NH}_4^+$], 207 (6) [$\text{M}+\text{H}^+$]. $-\text{C}_{13}\text{H}_{18}\text{O}_2$ (206.1) calcd for: C 75.69, H 8.75; found: C 75.61, H 8.60

2-bromo-1-tetradecen-7,13-diyn-4-ol (**116**)

According GP4, to a suspension of 2 g (17.2 mmol) of powder tin in diethyl ether(16.6 ml) /water(6.5ml) mixture (5:2 v/v) was added, successively, 3.3 g (16.6mmol) of 2,3- dibromopropene, 40 drops of 48% HBr and 2.5 g (12.2 mmol) of 2-(3',9'-decadiynyl)-1,3-dioxoline(**59**). The mixture was vigorously stirred for 5 days at room temperature.

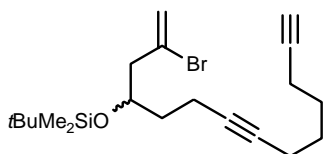


The reaction mixture was then diluted with 200 ml of water and 200 ml of diethyl ether and extracted thoroughly with (12×100 ml) of diethyl ether. The combined ether layers were dried over MgSO_4 , and concentrated. The produced alcohol was immediately eluted from a column of silica gel (70 g) using a polarity gradient from (10:1) pentane/diethyl ether to (20:3) pentane/diethyl ether after removing the starting material to afford 1.8 g(52%) of a colorless oil. ($R_f = 0.20$, 10:3 pentane/diethyl ether).-IR (Film): $\nu = 3500$ cm^{-1} , 3305, 2948, 2862, 2173, 2116, 1719, 1631, 1432, 1330, 1120, 1070, 893, 842, 634. $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.59 - 1.69$ (m, 4 H, 10(11)-H), 1.94 (t, $^4J = 2.5$ Hz, 1 H, 14-H), 2.07 (bs, 1 H, OH), 2.15 - 2.24 (m, 4 H, 9 (12)-H), 2.27 - 2.37 (m, 2H, 6-H), 2.55 (d, $^3J = 6.30$ Hz, 2 H, 3-H), 4.09 (m, 1 H, 4-H), 5.53 (d, $^2J = 1.5$ Hz, 1 H, 1-H), 5.69 (d, $^2J = 0.87$ Hz, 1 H, 1-H). $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 15.33$ (-, C-6), 17.94 (-, C-9), 18.21 (-, C-12), 27.49 (-, C-10*), 27.87 (-, C-11*), 35.11 (-, C-5), 49.12 (-, C-3), 68.31 (+, C-4), 68.41 (C_{quart} , C-14), 79.56 (C_{quart} , C-7), 80.67 (C_{quart} ,

C-8), 84.19 (C_{quart}, C-13), 119.60 (–, C-1), 130.44(C_{quart}, C-2).– MS (DCI, NH₃, 70 eV) *m/z* (%): 584 (6) [2M+NH₄⁺], 301 (100) [M+NH₄⁺].
–C₁₄H₁₉BrO(283.0)

2-bromo-4-(tert-butyltrimethylsilyloxy)-1-tetradecen-7,13-diyne (117)

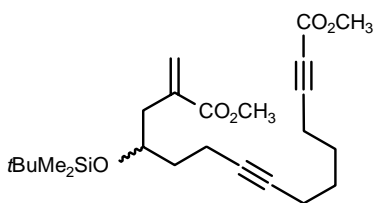
According to GP5, 1.2 g (8 mmol) of *tert*-butyldimethylsilyl chloride was added at 55 °C to a solution of 1.6 g (5.67 mmol) of 2-bromo-1-tetradecen-7,13-diyne-4-ol (**116**) and 1.3 g (19.84 mmol) of imidazole in 20 ml DMF. After stirring at 55 °C for 12 h, the reaction mixture was poured into 100 ml of water and extracted with (3×50 ml) of diethyl ether. The combined ether layers were dried over MgSO₄,



and concentrated. The residue was purified by column chromatography (50 g silica gel and 80:1 pentane/diethyl ether) to afford 2 g (89%) of a colorless oil. (*R_f* = 0.71, 80:1 pentane/diethyl ether).-IR (Film): $\nu = 3311 \text{ cm}^{-1}$, 2959, 2928, 2857, 1631, 1469, 1432, 1255, 1101, 1077, 1005, 836, 776, 628.- ¹H-NMR (250 MHz, CDCl₃): $\delta = 0.087$ (s, 6 H, TBDMS-H), 0.91 (s, 9 H, TBDMS -H), 1.52 – 1.74 (m, 6 H, 5, 10, 11-H), 1.93 (t, ⁴*J* = 2.6 Hz, 1 H, 14-H), 2.15 – 2.23 (m, 6 H, 6, 9, 12-H), 2.44 – 2.62 (m, 2 H, 3-H), 4.08 (m, 1 H, 4-H), 5.43 (d, ²*J*=1.47 hz, 1 H, 1-H), 5.60 (bs, 1 H, 1-H).- ¹³C-NMR (62.5 MHz, CDCl₃, DEPT): $\delta = -4.62$ (+, TBDMS-C), -4.40 (+, TBDMS-C), 14.71 (–, C-6), 17.96 (–, C-9), 18.01 (C_{quart}, TBDMS-C), 18.22 (–, C-12), 25.74 (+, TBDMS-C), 27.51 (–, C-10*), 27.95 (–, C-11*), 35.76 (–, C-5), 49.32 (–, C-3), 68.35 (C_{quart}, C-14), 68.82 (+, C-4), 79.93 (C_{quart}, C-7), 80.00 (C_{quart}, C-8), 84.21(C_{quart}, C-13), 119.11 (–, C-1),130.82 (C_{quart}, C-2) .– MS (DCI, NH₃, 70 eV) *m/z* (%): 416 (100) [M+NH₄⁺], 399 (2) [M+H⁺], 336 (1) [(M–Br)+NH₄⁺]. –C₂₀H₃₃BrOSi(397.2) calcd for: C 60.44, H 8.37; found: C 60.27, H 8.11

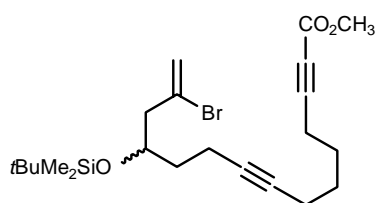
Dimethyl 14-methylene-12-(tert-butyldimethylsilyloxy)-2,8-pentadecadienedioate (118)

To a solution of 0.9 g (2.27 mmol) of 2-bromo-4-(tert-butyldimethylsilyloxy)-1-



tetradecen-7,13-diyne(**117**) in 5 ml THF was added at $-78\text{ }^{\circ}\text{C}$, dropwise, 1.6 ml (2.5 mmol) of n-butyl lithium (1.56M in hexane) and the stirring was continued for further 30 min. The solution was then transferred into a actone-dry-ice cooled dropping funnel and it was

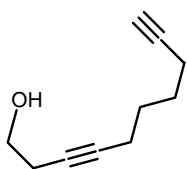
added at $-78\text{ }^{\circ}\text{C}$, over two hours, into a solution of 0.46 g (4.7 mmol) of chloromethylformate in 20 ml THF. The stirring was continued for 1 h at $-78\text{ }^{\circ}\text{C}$ and 2 h at room temperature. The reaction was then treated with 30 ml of a saturated solution of NaHCO_3 and extracted with (3×40 ml) of diethyl ether. The combined ether fractions were dried (MgSO_4) and concentrated. The resulting residue was purified by column chromatography (30 g silica gel, 10:1pentane/diethyl ether) to afford 0.48 g (48%) of a colorless oil. ($R_f = 0.32$, 10:1pentane/diethyl ether).- $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 0.092$ (s, 6 H, TBDMS-H), 0.86 (s, 9 H, TBDMS-H), 1.54 - 1.84 (m, 6 H, 5(6,11)-H), 2.14 - 2.29 (m, 4 H, 7(10)-H), 2.35 (t, $^3J = 6.9$ Hz, 2 H, 4-H), 2.50 (dd, $^2J = 7.5$ Hz, $^3J = 14.2$ Hz, 2 H, 14-H), 3.74 (s, 3 H, COOCH_3), 3.75 (s, 3 H, COOCH_3), 4.94 (m, 1 H, 12-H), 5.43 (d, $^2J = 2.4$ Hz, 1 H, $=\text{CH}_2$), 5.73 (d, $^2J = 2.5$ Hz, 1 H, $=\text{CH}_2$).- $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = -6.13$ (+, TBDMS-C), -5.95 (+, TBDMS-C), 15.04 (-, C-10), 16.94 (C_{quart} , TBDMS-C), 18.12 (-, C-7*), 18.20 (-, C-4*), 26.50 (-, C-6**), 26.70 (+, TBDMS-C), 27.84 (-, C-5**), 33.23 (-, C-11), 41.30 (-, C-13), 52.53 (+, COOCH_3), 54.54 (+, COOCH_3), 72.98 (C_{quart} , C-2), 77.50 (+, C-12), 79.35 (C_{quart} , C-9), 79.89 (C_{quart} , C-8), 89.38 (C_{quart} , C-3), 129.44 (-, $=\text{CH}_2$), 144.75 (C_{quart} , C-14), 155.40 (C_{quart} , COOCH_3), 162.0 (C_{quart} , COOCH_3). - MS (DCI, NH_3 , 70 eV) m/z (%): 886 (4) [$2\text{M} + \text{NH}_4^+$], 452 (100) [$\text{M} + \text{H}^+$].- $\text{C}_{24}\text{H}_{38}\text{O}_5\text{Si}$ (434.6)

Methyl-14-bromo-12-(tert-butyldimethylsilyloxy)-14-pentadecene-2,8-diynoate (111)

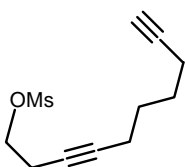
By adapting GP6, a solution of LDA (4.2 mmol) in 10 ml THF (prepared by dropwise addition, at $-78\text{ }^{\circ}\text{C}$, of 0.42 g (4.2 mmol) of diisopropylamine to a solution of 2.8 ml (4.2 mmol) of butyl lithium (1.56M in hexane) in 10 ml THF and stirring for 30 min) was added dropwise, at $-78\text{ }^{\circ}\text{C}$, to a solution of 1.5 g (3.8 mmol) of 2-bromo-4-(*tert*-butyldimethylsilyloxy)-1-tetradecen-7,13-diyne (**117**) in 10 ml THF. After stirring for 30 min, 0.7 ml (3.9 mmol) of HMPA and 2.9 ml (37mmol) of chloromethylformate were added and stirring was continued for 1 h at $-78\text{ }^{\circ}\text{C}$ and 2 h at room temperature. After working up, as described in GP6, the resulting residue was purified by column chromatography (60 g silica gel and 40:1 pentane/diethyl ether) to afford 0.7 g (40%) of colorless oil. (R_f =0.33, 20:1 pentane/diethyl ether).-IR (Film): $\nu = 2950\text{ cm}^{-1}$, 2928, 2843, 2173, 1750, 1250, 1073, 941, 823, 764.- $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 0.09$ (s, 6 H, TBDMS-H), 0.87 (s, 9 H, TBDMS-H), 1.52 – 1.73 (m, 6 H, 5(6,11)-H), 2.15 – 2.23 (m, 4 H, 7(10)-H), 2.35 (t, $^3J = 6.8\text{ Hz}$, 2 H, 4-H), 2.47 – 2.57 (m, 2 H, 13-H), 3.75 (s, 3 H, COOCH_3), 4.06 (m, 1 H, 12-H), 5.43 (d, $^2J = 1.5\text{ Hz}$, 1 H, 15-H), 5.60 (d, $^2J = 1.13\text{ Hz}$, 1 H, 15-H).- $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = -4.62$ (+, TBDMS-C), -4.40 (+, TBDMS-C), 14.69(–, C -10), 18.01 (C_{quart} , TBDMS-C), 18.15 (–, C-7), 18.23 (–, C-4), 25.82 (+, TBDMS-C), 26.54 (–, C-6), 27.92 (–, C-5), 35.73 (–, C-11), 49.32 (–, C-13), 52.55 (+, COOCH_3), 68.82 (+, C-12), 77.19 (C_{quart} , C-9), 79.61 (C_{quart} , C-8), 80.24 (C_{quart} , C-3), 89.35 (C_{quart} , C-2), 119.16 (–, C-15), 130.79 (C_{quart} , C-14), 154 (C_{quart} , COOCH_3). – MS (DCI, NH_3 , 70 eV) m/z (%): 472/474 (90/100) [$\text{M}+\text{NH}_4^+$], 457 (18) [$\text{M}+\text{H}^+$], 394 (18) [($\text{M}-\text{Br}$)+ NH_4^+]. $-\text{C}_{22}\text{H}_{35}\text{BrO}_3\text{Si}$ (455.5)

3,9-decadiyn-1-ol (112)

17.6 ml (27.4 mmol) of n-butyl lithium (1.56M in hexane) was added at -78°C , dropwise, to a solution of 3 g (28.3 mmol) of 1,7-octadiyne in 175 ml of THF. After stirring for 30 min, 3.5 ml (27.8 mmol) of boron trifluoride ether complex ($\text{BF}_3\cdot\text{Et}_2\text{O}$) was added to the resulting white suspension. The reaction mixture was stirred for further 15 min followed by addition of 14.11 ml (283 mmol) of ethylene oxide. After stirring for 2 h, the reaction mixture was quenched at -78°C with 120 ml of saturated solution of ammonium chloride and extracted with (4×100 ml) of diethyl ether. The combined ether fractions were dried (MgSO_4), concentrated, and the residue was purified by column chromatography (60 g of silica gel and 2:1 pentane/diethyl ether) to afford 2.5 g (60%) of a colorless liquid. ($R_f = 0.6$, 1:1 pentane/diethyl ether). IR (Film): $\nu = 3303\text{ cm}^{-1}$, 2950, 2863, 2116, 1431, 1330, 1272, 1186, 1038, 849, 621. - $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.60$ (m, 4 H, 6, 7-H), 1.80 (bs, 1 H, OH), 1.94 (t, $^4J = 2.65\text{ Hz}$, 1 H, 10-H), 2.15 – 2.23 (m, 4 H, 5, 8-H), 2.41 (m, 2 H, 2-H), 3.66 (t, $^3J = 6.0\text{ Hz}$, 2 H, 1-H). - $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 17.88$ (–, C-5), 18.23 (–, C-8), 23.11 (–, C-2), 27.30 (–, C-6*), 27.48 (–, C-7*), 61.31 (–, C-1), 68.45 (–, C-10), 76.74 (C_{quart} , C-3), 81.97 (C_{quart} , C-4), 84.14 (C_{quart} , C-9). – MS (DCI, NH_3 , 70 eV) m/z (%): 185 (93) [$\text{M}+\text{N}_2\text{H}_7^+$], 168 (100) [$\text{M}+\text{NH}_4^+$]. – $\text{C}_{10}\text{H}_{14}\text{O}$ (150.1) calcd for: C 79.96, H 9.39; found: C 79.71, H 9.14

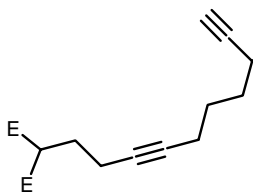
*3,9-decadiynyl methansulfonate (113)*

4.2 ml (54 mmol) of methyl sulfonyl chloride was added at -10°C to mixture of 5.4 g (36 mmol) of 3,9-decadiyn-1-ol (**112**), 10 ml (72 mmol) of triethyl amine (Et_3N) and 120 ml of dichloromethane. After stirring for 12 h at -10°C , the reaction mixture was poured into 120 ml of water, the two layers were separated, and the aqueous layer was extracted with (30×3 ml) of dichloromethane. The combined organic phases were dried (MgSO_4), concentrated and the residue was purified by column chromatography (120 g silica gel, 2:1 pentane/diethyl ether) to afford 7 g (85%) of a yellowish liquid. ($R_f = 0.6$, 1:1



pentane/diethyl ether).-IR (Film): $\nu = 3289 \text{ cm}^{-1}$, 3026, 2940, 2856, 2115, 1734, 1356, 1175, 964, 904, 801, 649.- $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.54 - 1.67$ (m, 4 H, 6, 7-H), 1.94 (t, $^4J = 2.7 \text{ Hz}$, 1 H, 10-H), 2.13 – 2.23 (m, 4 H, 5, 8-H), 2.6 (m, 2 H, 2-H), 3.03 (s, 3 H, CH_3SO_3), 4.25 (t, $^3J = 6.78 \text{ Hz}$, 2 H, 1-H).- $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT) : $\delta = 17.90$ (–, C-2), 18.12 (–, C-5), 20.00 (–, C-8), 27.41 (–, C-6*), 27.58 (–, C-7*), 37.61 (+, CH_3SO_3), 67.85 (–, C-1), 68.51 (C_{quart} , C-10), 74.50 (C_{quart} , C-3), 82.43 (C_{quart} , C-4), 84.07 (C_{quart} , C-9). – MS (DCI, NH_3 , 70 eV) m/z (%): 474 (64) [$2\text{M}+\text{NH}_4^+$], 246.1 (100) [$\text{M}+\text{NH}_4^+$]. – $\text{C}_{11}\text{H}_{16}\text{O}_3\text{S}$ (228.1) calcd for: C 57.87, H 7.06; found: C 57.97, H 6.91

Dimethyl 2-(3',9'-decadiynyl)malonate (114-COOMe) (E = COOMe)



By adapting GP3B, 8.1 g (61 mmol) of dimethyl malonate was added at 50 °C, dropwise, to a suspension of 2.45 g (61 mmol) of sodium hydride (60% oil suspension) in 200 ml of DMF. The resulting clear solution had been transferred into a mixture of 7 g (30 mmol) of 3,9-decadiynyl methansulfonate, 5.1 g of potassium iodide (30 mmol) and 200 ml of THF and the resulting reaction mixture was refluxed at 70 °C for 18 h. The reaction mixture was then treated with 200 ml of saturated solution of ammonium chloride (NH_4Cl), the two layers were separated and the aqueous layer was extracted with (3×100 ml) of diethyl ether. The combined organic phases were dried (MgSO_4), concentrated, and the resulting residue was purified by azeotropic kugelrohr distillation (at 170 °C, 0.1 mm) after adding 3 drops of methylal to produce 6.7 g (83%) of a colorless oil. An analytical sample was further purified by column chromatography (silica gel, 5:1 pentane/diethyl ether). (R_f=0.16, 5:1 pentane/diethyl ether).-IR (Film): $\nu = 3304 \text{ cm}^{-1}$, 3004, 2955, 2865, 2843, 2116, 1762, 1728, 1433, 1360, 1250, 1150, 1050, 632.- $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.61$ (m, 4 H, 6'(7')-H), 1.94 (t, $^4J = 2.7 \text{ Hz}$, 1 H, 10'-H), 2.08 (q, $^3J = 6.4 \text{ Hz}$, 2 H, 1'-H), 2.15 – 2.23 (m, 6 H, 2'(5',8')-H), 3.61 (t, $^3J = 7.2 \text{ Hz}$, 1 H, 2-H), 3.74 (s, 3 H, COOCH_3).- $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 16.72$ (–, C-2'), 17.94 (–, C-5'), 18.20 (–, C-8'), 27.44 (–, C-1'), 27.83 (–, C-6'*), 28.02 (–, C-7' *), 50.27 (+, C-2), 52.58 (+, COOCH_3), 68.39 (+, C-10'), 78.19 (C_{quart} , C-3'),

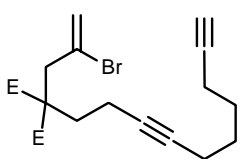
81.26 (C_{quart}, C-4'), 83.30 (C_{quart}, C-9'), 169.59 (C_{quart}, COOCH₃).- MS (DCI, NH₃, 70 eV) *m/z* (%): 282 (100) [M+NH₄⁺], 236 (2), 206 (4), 167 (8), 150 (8).-C₁₅H₂₀O₄ (264.3) calcd for: C 68.16, H 7.63; found: C 68.15, H 7.43

Diethyl 2-(3',9'-decadiynyl)malonate (114-COOEt) (E = COOEt)

By following the same procedure for preparing the dimethyl derivative, afforded (75%) of colorless oil. (R_f = 0.15, 5:1 pentane/diethyl ether). ¹H-NMR (250 MHz, CDCl₃): δ = 1.26 (t, ³J = 7.1 Hz, 6 H, COOCH₂CH₃), 1.60 (m, 4 H, 6'(7')-H), 1.94 (t, ⁴J = 2.7 Hz, 1 H, 10'-H), 2.07 (m, 2 H, 1'-H), 2.17 – 2.24 (m, 6 H, 2'(5',8')-H), 3.55 (t, ³J = 7.3 Hz, 1 H, 2-H), 4.18 (q, ³J = 7.1 Hz, 4 H, COOCH₂CH₃).-¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = 14.07 (+, COOCH₂CH₃), 16.71 (-, C-2'), 17.92 (-, C-5'), 18.19 (-, C-8'), 27.44 (-, C-1'), 27.83 (-, C-6'*), 27.95 (-, C-7' *), 50.67 (+, C-2), 61.39 (-, COOCH₂CH₃), 68.38 (+, C-10'), 78.34 (C_{quart}, C-3'), 81.00 (C_{quart}, C-4'), 84.17 (C_{quart}, C-9'), 169.19 (C_{quart}, COOCH₂CH₃).- MS (DCI, NH₃, 70 eV) *m/z* (%): 602 (17) [2M+NH₄⁺], 310 (100) [M+NH₄⁺], 293 (7) [M+H⁺]. -C₁₇H₂₄O₄ (292.1)

Dimethyl 2-(2''-bromoallyl)-2-(3',9'-decadiynyl)malonate (115-COOMe) (E = COOMe)

6.4 g (23.79 mmol) of Dimethyl 2-(3',9'-decadiynyl)malonate (**114**) was added at 50 °C,



dropwise, to a suspension of 0.95 g (23.79 mmol) of sodium hydride in 90 ml of 1,2-dimethoxyethane (DME). To the resulting mixture were added 7.13 g (35.68 mmol) of 2,3-dibromopropene and 10 ml of DMF. After refluxing at 70 °C for 20 h, the reaction mixture was allowed to cool, treated with 120 ml of water, and extracted with (5×50 ml) of diethyl ether. The combined organic phases were dried (MgSO₄), concentrated, and the produced crude material was purified by column chromatography (200 g silica gel, 5:4 pentane/dichloromethane) to afford 7.8 g (85%) of a colorless oil. (R_f = 0.72, 5:4 pentane/dichloromethane).-IR (Film) : ν = 3311 cm⁻¹, 2928, 2845, 2116, 1740, 1624, 1464, 1378, 1273, 1200, 1153, 898, 741.- ¹H-NMR (250 MHz, CDCl₃): δ = 1.59 (m, 4 H, 6' (7')-H), 1.94 (t, ⁴J = 1.96 Hz, 1 H, 10'-H), 2.08 – 2.26 (m, 8 H, 1'(2',5',8')-H), 3.16

(s, 2 H, 1''-H), 3.73 (s, 6 H, COOCH₃), 5.59 (d, ²J = 1.78 Hz, 1 H, 3''-H), 5.67 (d, ²J = 1.67 Hz, 1 H, 3''-H).- ¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = 14.26 (-, C-2'), 17.94 (-, C-5'), 18.26 (-, C-8'), 27.48 (-, C-6'*), 27.79 (-, C-7'*), 31.15 (-, C-1'), 43.19 (-, C-1''), 52.74 (+, COOCH₃), 56.45 (C_{quart}, C-2), 68.40 (C_{quart}, C-10'), 78.65 (C_{quart}, C-3'), 80.41 (C_{quart}, C-4'), 84.20 (C_{quart}, C-9'), 122.08 (-, C-3''), 126.83 (C_{quart}, C-2''), 170.54 (C_{quart}, COOCH₃). - MS (DCI, NH₃, 70 eV) *m/z* (%): 784 (45) [2M+NH₄⁺], 400/402 (100/98) [(M-H)+NH₄⁺], 383/385 (9/9) [M⁺+H], 303 (8) [M⁺-Br].- C₁₈H₂₃BrO₄ (383.2) calcd for: C 56.41, H 6.05; found: C 56.70, H 5.82

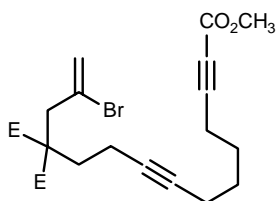
Diethyl 2-(2''-bromoallyl)-2-(3',9'-decadiynyl)malonate (115-COOEt) (E = COOEt)

The same procedure for preparing the dimethyl derivative was followed to afford (77%) of a colorless oil. (R_f=0.72, 5:4 pentane/dichloromethane).¹H-NMR (250 MHz, CDCl₃): δ = 1.25 (t, ³J = 6.5 Hz, 6 H, COOCH₂CH₃), 1.59 (m, 4 H, 6' (7')-H), 1.94 (t, ⁴J = 1.96 Hz, 1 H, 10'-H), 2.10 – 2.22 (m, 8 H, 1'(2',5',8')-H), 3.15 (s, 2 H, 1''-H), 4.18 (q, ³J = 6.55 Hz, 4 H, COOCH₂CH₃), 5.58 (d, ²J = 1.75 Hz, 1 H, 3''-H), 5.67 (d, ²J = 1 Hz, 1 H, 3''-H).- ¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = 13.94 (+, COOCH₂CH₃), 14.21 (-, C-2'), 17.94 (-, C-5'), 18.25 (-, C-8'), 27.48 (-, C-6'*), 27.80 (-, C-7'*), 31.02 (-, C-1'), 42.96 (-, C-1''), 56.46 (C_{quart}, C-2), 61.65 (-, COOCH₂CH₃), 68.38 (C_{quart}, C-10'), 78.81 (C_{quart}, C-3'), 80.28 (C_{quart}, C-4'), 84.20 (C_{quart}, C-9'), 121.89 (-, C-3''), 127.06 (C_{quart}, C-2''), 170.11 (C_{quart}, COOCH₂CH₃). - MS (DCI, NH₃, 70 eV) *m/z* (%): 840 (58) [2M+NH₄⁺], 428/430 (100/98) [(M-H)+NH₄⁺], 411/413 (9/9) [M⁺], 350 (2) [(M-Br)+NH₄⁺], 331 (8) [(M-H)⁺-Br].- C₂₀H₂₇BrO₄ (411.1)

11,11-dimethyl-1-methyl 13-bromo-13-tetradecen-1,7-diyne-1,11,11-tricarboxylate (110-COOMe)(E = COOMe)

By using LDA.

By adapting GP6, a solution of LDA (14.8 mmol) in 25 ml THF (prepared by dropwise addition, at $-78\text{ }^{\circ}\text{C}$, of 1.5 g of diisopropylamine to a solution of 10 ml (15.6 mmol) of *n*-butyl lithium (1.56M in hexane) in 25 ml THF and stirring for 30 min) was added dropwise, at $-78\text{ }^{\circ}\text{C}$, to a solution of 5.4 g (14.2 mmol) of dimethyl 2-(2''-bromoallyl)-2-(3',9'-decadiynyl)malonate in 25 ml THF. After stirring for 30 min, 2.48 ml (13.7 mmol) of HMPA and 10.8 ml (142mmol) of chloromethylformate were added and stirring was continued for 1 h at $-78\text{ }^{\circ}\text{C}$ and 2 h at room temperature. After working up, as described in GP6, the resulting residue was purified by column chromatography (100 g silica gel and using a polarity gradient starting with 8:1 pentane/diethyl ether till the starting materials were removed; then with 6:1 pentane/diethyl ether and finally with 4:1 pentane/diethyl ether to elute the product) to afford 2.8 g (44%) of a colorless oil. ($R_f = 0.36$, 4:1 pentane/diethyl ether).



By using n-butyl lithium

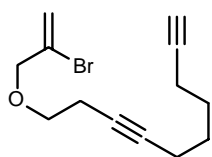
The above procedure was followed, but instead of using LDA, *n*-butyl lithium was used. The compound was separated from a complicated mixture of byproducts by using column chromatography (silica gel, 8:1 pentane/diethyl ether) in a 20% yield. -IR (Film): $\nu = 3002\text{ cm}^{-1}$, 2953, 2865, 2236, 1736, 1708, 1625, 1433, 1274, 1179, 1152, 1080, 902, 753, 591. - $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.53 - 1.72$ (m, 4 H, 4(5)-H), 2.01 - 2.24 (m, 6 H, 6(9,10)-H), 2.34 (t, $^3J = 6.80\text{ Hz}$, 2 H, 3-H), 3.15 (s, 2 H, 12-H), 3.72 (s, 3 H, COOCH_3), 3.74 (s, 3 H, COOCH_3), 5.58 (d, $^2J = 1.78\text{ Hz}$, 1 H, 14-H), 5.66 (d, $^2J = 1.62\text{ Hz}$, 1H, 14-H). - $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 14.24$ (-, C-9), 18.20 (-, C-6), 18.21 (-, C-3), 26.50 (-, C-5), 27.75 (-, C-4), 31.12 (-, C-10), 43.19 (-, C-12), 52.57 (+, COOCH_3), 52.74 (+, COOCH_3), 56.43 (C_{quart} , C-11), 73.02 (C_{quart} , C-1), 78.93 (C_{quart} , C-8), 80.03 (C_{quart} , C-7), 89.30 (C_{quart} , C-2), 122.09 (-, C-14), 126.79 (C_{quart} , C-13), 154.18 (C_{quart} , COOCH_3), 170.52 (C_{quart} , COOCH_3). - MS (DCI, NH_3 , 70 eV) m/z (%):

460/458 (100/96) [(M-H)+NH₄⁺], 340 (4), 208 (4). – C₂₀H₂₅BrO₆ (441.3) calcd for: C 54.43, H 5.71; found: C 54.43, H 5.41

11,11-diethyl-1-methyl 13-bromo-13-tetradecen-1,7-diyne-1,11,11-tricarboxylate (110-COOEt) (E = COOEt)

The same procedure for preparing the dimethyl derivative was followed to afford (41%) of a colorless oil. (R_f = 0.34, 4:1 pentane/diethyl ether). ¹H-NMR (250 MHz, CDCl₃): δ = 1.25 (t, ³J = 7.10 Hz, 6 H, COOCH₂CH₃), 1.56 – 1.69 (m, 4 H, 4(5)-H), 2.11 – 2.24 (m, 6 H, 6(9,10)-H), 2.35 (t, ³J = 6.80 Hz, 2 H, 3-H), 3.15 (s, 2 H, 12-H), 3.74 (s, 3 H, COOCH₃), 4.18 (q, ³J = 7.11 Hz, 4 H, COOCH₂CH₃), 5.58 (d, ²J = 1.78 Hz, 1 H, 14-H), 5.67 (d, ²J = 1.62 Hz, 1 H, 14-H). ¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = 13.94 (+, COOCH₂CH₃), 14.20 (–, C-9), 18.18 (–, C-6), 18.21 (–, C-3), 26.51 (–, C-5), 27.76 (–, C-4), 31.00 (–, C-10), 42.97 (–, C-12), 52.57 (+, COOCH₃), 56.45 (C_{quart}, C-11), 61.66 (–, COOCH₂CH₃), 73.02 (C_{quart}, C-1), 79.09 (C_{quart}, C-8), 79.90 (C_{quart}, C-7), 89.33 (C_{quart}, C-2), 121.91 (–, C-14), 127.04 (C_{quart}, C-13), 154.20 (C_{quart}, COOCH₃), 170.09 (C_{quart}, COOCH₂CH₃). – MS (DCI, NH₃, 70 eV) m/z (%): 956 (0.1) [2M+NH₄⁺], 486/488 (97/100) [M+NH₄⁺], 408 (25) [(M-Br)+NH₄⁺]. – C₂₂H₂₉BrO₆ (469.0)

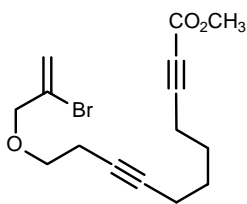
2'-bromoallyl 3,9-decadiynyl ether (**133**)



3.8 g (25.25 mmol) of 3,9-decadiyn-1-ol (**112**) was added at 70 °C, dropwise, to a suspension of 1.5 g (38 mmol) of sodium hydride (60% oil suspension) in 60 ml of THF. To the resulting mixture was added 7.6 g (38 mmol) of 2,3-dibromopropene and refluxed at 70 °C for 12 h. After cooling, the reaction mixture was quenched with 80 ml of a saturated solution of ammonium chloride and extracted with (4×40 ml) of diethyl ether. The combined ether layers were dried (MgSO₄) and concentrated. The resulting residue was purified by column chromatography (100 g silica gel and 20:1 pentane/diethyl ether) to afford 2.9 g (42%) of a colorless oil. (R_f = 0.40, 10:1 pentane/diethyl ether).-IR (Film): ν = 3304 cm⁻¹, 2948, 2907, 2864, 2116, 1735, 1640, 1434, 1333, 1110, 895, 638. ¹H-NMR (250 MHz, CDCl₃): δ = 1.57 – 1.65 (m, 4 H, 6 (7)-H), 1.94 (t, ⁴J = 2.69 Hz, 1 H,

10-H), 2.15 – 2.23 (m, 4 H, 5(8)-H), 2.43 – 2.49 (m, 2 H, 2-H), 3.56 (t, $^3J = 7.00$ Hz, 2 H, 1-H), 4.12 (s, 2 H, 1'-H), 5.61 (dd, $^2J = 1.75$ Hz, $^4J = 0.64$ Hz, 1 H, 3'-H), 5.95 (d, $^2J = 1.36$ Hz, 1 H, 3'-H).- ^{13}C -NMR (62.5 MHz, CDCl_3 , DEPT): $\delta = 17.93$ (-, C-5*), 18.02 (-, C-8*), 20.10 (-, C-2), 27.47 (-, C-6**), 27.79 (-, C-7**), 68.36 (+, C-10), 69.07 (-, C-1), 74.83 (-, C-1'), 76.76 (C_{quart} , C-3), 80.97 (C_{quart} , C-4), 84.17 (C_{quart} , C-9), 117.34 (-, C-3'), 129.33 (C_{quart} , C-2').- MS (DCI, NH_3 , 70 eV): 286/288 (100/98) $[\text{M}+\text{NH}_4^+]$. - $\text{C}_{13}\text{H}_{17}\text{BrO}$ (269.2) calcd for: C 58.01, H 6.37; found: C 58.32, H 6.25

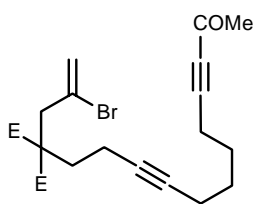
Methyl 11-(2'-bromoallyloxy)-2,8-undecadiynoate (132)



By adapting GP6, a solution of LDA (9.1 mmol) in 15 ml THF (prepared by dropwise addition, at -78 °C, of 0.92 g of diisopropylamine to a solution of 4.5 ml (9 mmol) of n-butyl lithium (2 M in hexane) in 15 ml THF and stirring for 30 min) was added, dropwise, at -78 °C to a solution of 2.3 g (8.5 mmol) of 2'-bromoallyl 3,9-decadiynyl ether (**133**) in 15 ml THF. After stirring for 30 min, 1.5 ml (8.2 mmol) of HMPA and 6.4 ml (81.6 mmol) of chloromethylformate were added and stirring was continued for 1 h at -78 °C and 2 h at room temperature. After working up, as described in GP6, the resulting residue was purified by column chromatography (80g silica gel and 10:1 pentane/diethyl ether) to afford 1.9 g (68%) of a colorless oil. ($R_f = 0.12$, 20:1 pentane/diethyl ether).-IR (Film): $\nu = 3409$ cm^{-1} , 3305, 2954, 2866, 2235, 1719, 1639, 1434, 1251, 1109, 1078, 894, 752, 670.- ^1H -NMR (250 MHz, CDCl_3): $\delta = 1.56 - 1.72$ (m, 4 H, 5(6)-H), 2.15 – 2.21 (m, 2H, 7 H), 2.35 (t, $^3J = 6.83$ Hz, 2 H, 4-H), 2.41 – 2.49 (m, 2 H, 10-H), 3.55 (t, $^3J = 6.91$ Hz, 11-H), 3.75 (s, 3 H, COOCH_3), 4.12 (dd, $^2J = 2.26$ Hz, $^4J = 1.05$ Hz, 2 H, 1'-H), 5.61 (dd, $^2J = 1.75$ Hz, $^4J = 0.95$ Hz, 1 H, 3'-H), 5.94 (dd, $^2J = 2.69$ Hz, $^4J = 1.28$ Hz, 1 H, 3'-H).- ^{13}C -NMR (62.5 MHz, CDCl_3 , DEPT): $\delta = 18.16$ (-, C-7*), 18.21 (-, C-4*), 20.09 (-, C-10), 26.52 (-, C-6), 27.76 (-, C-5), 52.52 (+, COOCH_3), 69.02 (-, C-11), 74.84 (-, C-1'), 77.08 (C_{quart} , C-2**), 77.17 (C_{quart} , C-9**), 80.58 (C_{quart} , C-8), 89.28 (C_{quart} , C-3), 117.37 (-, C-3'), 129.33 (C_{quart} , C-

2'), 159.94 (C_{quart} , COOCH_3). – MS (DCI, NH_3 , 70 eV): 344/346 (98/100) [(M-H)+ NH_4^+]. – $\text{C}_{13}\text{H}_{17}\text{BrO}$ (327.2).

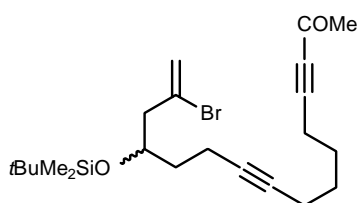
Dimethyl 2-(2''-bromoallyl)-2-(11'-oxo-3',9'-dodecadiynyl)malonate (144)



By adapting GP6, a solution of LDA (16.8 mmol) in 30 ml THF (prepared by dropwise addition, at $-78\text{ }^\circ\text{C}$, of 1.7 g of diisopropylamine to a solution of 7.8 ml (17.9 mmol) of n-butyl lithium (2.3M in hexane) in 30 ml THF and stirring for 30 min) was added, dropwise, at $-78\text{ }^\circ\text{C}$ to a solution of 6 g (15.7 mmol) of dimethyl 2-(2''-bromoallyl)-2-(3',9'-decadiynyl)malonate(**115**) in 30 ml THF. After stirring for 30 min, 2.74 ml (15.1 mmol) of HMPA and 14.8 ml (157 mmol) of acetic anhydride were added and stirring was continued for 1 h at $-78\text{ }^\circ\text{C}$ and 2 h at room temperature. The reaction mixture was treated 100 ml water, 50 ml saturated solution of ammonium chloride and extracted with (4×50 ml) of diethyl ether. The combined ether layers were further washed with 50 ml of 0.1 M of potassium hydroxide, 50 ml of water, dried (MgSO_4) and concentrated. The resulting residue was purified by column chromatography (100 g silica gel and using polarity gradient starting with 8:1 pentane/diethyl ether till the starting materials were removed, then with 6:1 pentane/diethyl ether and finally with 4:1 pentane/diethyl ether to elute the product) to afford 2.6 g (40%) of a colorless oil. (R_f =0.36, 4:1 pentane/diethyl ether).-IR (Film): $\nu = 3329\text{ cm}^{-1}$, 3003, 2953, 2841, 2211, 1725, 1677, 1625, 1434, 1360, 1276, 1247, 1178, 1152, 1082, 902, 738, 559.- H-NMR (250 MHz, CDCl_3): $\delta = 1.54 - 1.69$ (m, 4 H, 6'(7')-H), 2.08 – 2.25 (m, 6H, 2'(5',8')-H), 2.31 (s, 3 H, COCH_3), 2.37 (t, $^3J = 6.82\text{ Hz}$, 2 H, 1'-H), 3.16 (d, $^2J = 0.7\text{ Hz}$, 2 H, 1''-H), 3.73 (s, 3 H, COOCH_3), 5.58 (d, $^2J = 1.8\text{ Hz}$, 1 H, 3''-H), 5.67 (d, $^2J = 1.73\text{ Hz}$, 1 H, 3'''-H).- ^{13}C -NMR (62.5 MHz, CDCl_3 , DEPT): $\delta = 14.25$ (–, C-8'), 18.20 (–, C-2''), 18.48 (–, C-5''), 26.68 (–, C-6'), 27.82 (–, C-7'), 31.14 (–, C-1'), 32.77 (+, COCH_3), 43.17 (–, C-1''), 52.75 (+, COOCH_3), 56.45 (C_{quart} , C-2), 78.93(C_{quart} , C-10'), 80.05 (C_{quart} , C-3'), 81.52 (C_{quart} , C-4'), 93.47 (C_{quart} , C-9'), 122.08

(-, C-3''), 126.80 (C_{quart}, C-2''), 170.52 (C_{quart}, COOCH₃), 184.93 (C_{quart}, COCH₃).- MS (DCI, NH₃, 70 eV) *m/z* (%): 868 (0.1) [2M+NH₄⁺], 442/444 (93/100) [(M-H)+NH₄⁺], 364 (52) [(M-Br)+NH₄⁺], 324 (36) [(M-2COOMe)+NH₄⁺], 282 (12).- C₂₀H₂₅BrO₅ (425.3)

15-bromo-13-(tert-butyldimethylsilyloxy)-15-hexadecen-3,9-diyne-2-one (145)

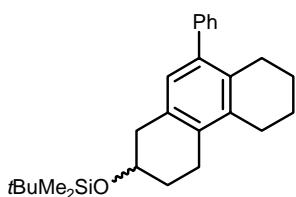


By adapting GP6, a solution of LDA (7 mmol) in 20 ml THF (prepared by dropwise addition, at $-78\text{ }^{\circ}\text{C}$, of 0.7 g of diisopropylamine to a solution of 3.5 ml (7 mmol) of *n*-butyl lithium (2M in hexane) in 20 ml THF and stirring for 30 min) was added, dropwise, at $-78\text{ }^{\circ}\text{C}$ to a solution of 2.5 g (6.3 mmol) of 2-bromo-4-(tert-butyldimethylsilyloxy)-1-tetradecen-7,13-diyne(**117**) in 20 ml THF. After stirring for 30 min, 1.1 ml (6 mmol) of HMPA and 6 ml (63 mmol) of acetic anhydride were added and stirring was continued for 1 h at $-78\text{ }^{\circ}\text{C}$ and 2 h at room temperature. The reaction mixture was treated 100 ml water, 50 ml saturated solution of ammonium chloride and extracted with (4×50 ml) of diethyl ether. The combined ether layers were dried (MgSO₄), concentrated, and the resulting residue was purified by column chromatography (70 g silica gel and 20:1 pentane/diethyl ether) to afford 1.7 g (61%) of a colorless oil. (*R_f* = 0.20, 20:1 pentane/diethyl ether).-IR (Film): $\nu = 3336\text{ cm}^{-1}$, 2956, 2929, 2856, 2211, 1678, 1631, 1471, 1433, 1358, 1227, 1077, 1004, 837, 776, 661.-¹H-NMR (250 MHz, CDCl₃): $\delta = 0.086$ (s, 3 H, TBDMS-H), 0.091 (s, 3 H, TBDMS-H), 0.87 (s, 9 H, TBDMS-H), 1.52-1.75 (m, 6 H, 6(7,12)-H), 2.18 - 2.24 (m, 4 H, 8(11)-H), 2.31 (s, 3 H, COCH₃), 2.37 (t, ³*J* = 6.8 Hz, 2 H, 5-H), 2.51 (d, ³*J* = 6.4 Hz, 1 H, 14-H), 2.55 (d, ³*J* = 6.9 Hz, 1 H, 14-H), 4.07 (m, 1 H, 13-H), 5.43 (d, ²*J* = 1.5 Hz, 1 H, 16-H), 5.60 (bs, 1 H, 16-H).-¹³C-NMR (62.5 MHz, CDCl₃, DEPT): $\delta = -4.62$ (+, TBDMS-C), -4.39 (+, TBDMS-C), 14.69 (-, C-5), 18.01 (C_{quart}, TBDMS-C), 18.17 (-, C-11*), 18.50 (-, C-8*), 25.82 (+, TBDMS-C), 26.71 (-, C-7**), 27.99 (-, C-6**), 32.74 (+, COCH₃), 35.73 (-, C-12), 49.32 (-, C-14), 68.81 (+, C-13), 79.63 (C_{quart}, C-4), 80.22 (C_{quart}, C-10), 81.51 (C_{quart}, C-9), 93.50 (C_{quart},

C- 3), 119.16 (–, C-16), 130.79 (C_{quart}, C-15), 210.07 (C_{quart}, COCH₃). (DCI, NH₃, 70 eV)
m/z (%): 896 (0.1) [2M+NH₄⁺], 458/456 (100/96) [(M–H)+NH₄⁺], 441/439 (20/19) [M⁺],
 378 (35) [(M–Br)+NH₄⁺], 319 (15). – C₂₂H₃₅BrO₂Si (439.5).

4. Palladium-catalyzed Oligocyclizations

5-(*tert*-butyldimethylsilyloxy)-9-phenyltricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene (**74**)

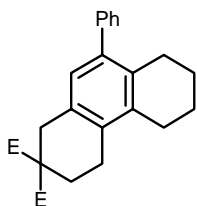


By adapting GP8 method B, 9.48 mg (0.042 mmol) of palladium acetate was added at 80 °C to a degassed mixture of 28 mg (0.10 mmol) of triphenylphosphine, 34.4 mg (0.50 mmol) of sodium formate, and 200 mg (0.42 mmol) of 1-(13'-bromo-11'-(*tert*-butyldimethylsilyloxy)-13'-tetradecen-1',7'-diynyl)benzene(**49**) in 5 ml DMF. After stirring from 5 h at 80 °C, the reaction mixture was poured into 30 ml of water and extracted (3×20 ml) with diethyl ether. The combined ether layers were dried (MgSO₄), concentrated and the residue was eluted from 20×20 cm plates coated with thick layer of silica gel (Silica gel 60 PF₂₅₄ containing CaSO₄) with 2:1 pentane/dichloromethane. The third fraction (R_f =0.55, 2:1 pentane/dichloromethane) from the plates' top afforded 25 mg (15%) of the title compound as a yellow oil.-IR (Film): $\nu = 3057\text{ cm}^{-1}$, 2927, 2856, 1462, 1251, 1095, 882, 773.- ¹H-NMR (250 MHz, CDCl₃): $\delta = 0.11$ (s, 6 H, TBDMS-H), 0.92 (s, 9 H, TBDMS-H), 1.60 – 1.89 (m, 5 H, 3(11,14)-H), 2.07 (m, 1 H, 14-H), 2.58 (t, ³J = 6.35 Hz, 2 H, 4-H), 2.63 – 2.93 (m, 6 H, 6(12,13)-H), 4.10 (m, 1 H, 5 H), 6.84 (s, 1 H, 8-H), 7.25 - 7.41 (m, 5 H, Aromatic-H).- ¹H-NMR (500 MHz, CDCl₃): $\delta = 0.12$ (s, 6 H,TBDMS-H), 0.94 (s, 9 H, TBDMS-H), 1.60 - 1.72 (m, 2 H, 3 H), 1.76 –1.92 (m, 3H, 11(14)-H), 2.10 (m, 1 H, 14 H), 2.56 (t, ³J = 10 Hz, 2 H, 4-H), 2.58 – 2.74 (m, 2H, 13-H), 2.74 – 2.88 (m, 3 H, 6(12)-H), 2.96 (dd, ²J = 4 Hz, ³J = 15 Hz, 1 H, 6-H), 4.08 (m, 1 H, 5-H), 6.84 (s, 1 H, 8-H), 7.25 – 7.40 (m, 5 H, Aromatic-H).- ¹³C-NMR (150.82 MHz, CDCl₃, APT): $\delta = -4.62$ (+, TBDMS-C), – 4.59 (+, TBDMS-C), 18.30 (–, TBDMS-C), 22.90 (–, C-3), 23.15 (–, C-11), 25.87 (–, C-12), 25.95 (+, TBDMS-C), 27.02 (–, C-13), 28.83 (–, C-4), 32.60 (–, C-14), 39.55 (–, C-6), 68.13 (+, C- 5), 126.53 (+, Aromatic-C, rot), 127.91 (+,

Aromatic-C, rot), 128.12 (+, Aromatic-C, rot), 128.44 (+, Aromatic-C, rot), 128.49 (+, Aromatic-C, rot), 128.52 (+, Aromatic-C, rot), 128.73 (+, Aromatic-C, rot), 129.27 (+, Aromatic-C, rot), 132.22 (-, Aromatic-C), 132.37 (-, Aromatic-C), 133.53 (-, Aromatic-C), 133.66 (+, Aromatic-C, rot), 133.78 (+, Aromatic-C, rot), 135.22 (-, Aromatic-C), 139.95 (-, Aromatic-C), 142.06 (-, Aromatic-C). - MS (DCI, NH₃, 70 eV) *m/z* (%): 410 (100) [M+NH₄⁺], 495 (26) [(M-CH₃)+NH₄⁺], 352 (7) [(M+H)-C(CH₃)₃+NH₄⁺], 296 (12) [(M-t-BuMe₂Si)+NH₄⁺], 279 (16) [(M-H)-t-BuMe₂SiO+NH₄⁺], 263 (27). - C₂₆H₃₆OSi (392.6) calcd for: C 79.53, H 9.24; found: C 79.41, H 9.08

Diethyl 9-phenyltricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene-5,5-dicarboxylate (73)

By adapting GP8 method B, 11.25 mg (0.050 mmol) of palladium acetate was added at 80 °C to a degassed mixture of 33 mg (0.125 mmol) of triphenylphosphine, 40.9 mg (0.60 mmol) of sodium formate, and 244 mg (0.50 mmol) of Diethyl2-(2''-

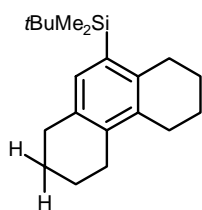


bromoallyl)-2-(10'-phenyl-3',9'-decadiynyl)malonate(48) in 5ml DMF. After stirring from 5 h at 80 °C, the reaction mixture was poured into 30 ml of water and extracted (3×20 ml) with diethyl ether. The combined ether layers were dried (MgSO₄), concentrated

and the residue was eluted from 20×20cm plates coated with thick layer of silica gel (Silica gel 60 PF₂₅₄ containing CaSO₄) with 5:1 pentane/diethyl ether. The third fraction (R_f=0.34, 5:1 pentane/diethyl ether) from the plates' top afforded 64 mg (40%) of the title compound as an orange oil. -IR (Film): $\nu = 3057 \text{ cm}^{-1}$, 2983, 2929, 2854, 1732, 1440, 1252, 1180, 1097, 1081, 711, 704. -¹H-NMR (250 MHz, CDCl₃): $\delta = 1.21$ (t, ³J = 7.15 Hz, 6 H, COOCH₂CH₃), 1.61 – 1.67 (m, 2 H, 12-H), 1.80 (m, 2 H, 13-H), 2.36 (t, ³J = 6.80 Hz, 2 H, 4-H), 2.57 (m, 4 H, 11(14)-H), 2.68 (t, ³J = 6.58 Hz, 2 H, 3-H), 3.26 (s, 2 H, 6-H), 4.20 (q, ³J = 7 Hz, 4H, COOCH₂CH₃), 6.86 (s, 1 H, 8-H), 7.20-7.40 (m, 5 H, Aromatic-H). -¹H-NMR (500 MHz, CDCl₃): $\delta = 1.21$ (t, ³J = 7.5 Hz, 6 H, COOCH₂CH₃), 1.64 (m, 2 H, 12-H), 1.80 (m, 2 H, 13-H), 2.36 (t, ³J = 7.5 Hz, 2 H, 4-H), 2.55 (t, ³J = 5 Hz, 2 H, 14-H), 2.60 (t, ³J = 5.5 Hz, 2 H, 11-H), 2.68 (t, ³J = 6 Hz, 2 H, 3-H), 3.26 (s, 2 H, 6-H), 4.18 (q, ³J = 6 Hz, 4 H, COOCH₂CH₃), 6.86 (s, 1 H, 8-H), 7.20 –

7.40 (m, 5 H, Aromatic-H) .- ^{13}C -NMR (150.82 MHz, CDCl_3 , APT) : δ = 14.01 (+, $\text{COOCH}_2\text{CH}_3$) , 22.82 (-, C-3), 23.00 (-, C-13*), 23.30 (-, C-12*), 26.82 (-, C-4), 28.19 (-, C-14**), 28.80 (-, C-11**), 34.91 (-, C-6), 53.08 (-, C-5), 61.34 (-, $\text{COOCH}_2\text{CH}_3$), 126.49 (+, Aromatic-C) 127.50, (+, Aromatic-C), 127.86 (+, C-8), 128.00 (+, Aromatic-C), 129.26 (+, Aromatic-C), 132.06 (-, Aromatic-C), 132.58 (-, Aromatic-C), 135.14 (-, Aromatic-C), 139.89 (-, Aromatic-C), 142.06 (-, Aromatic-C), 171.38 (-, $\text{COOCH}_2\text{CH}_3$).- MS (DCI, NH_3 , 70 eV) m/z (%): 830 (4) [$2\text{M}+\text{NH}_4^+$], 424 (100) [$\text{M}+\text{NH}_4^+$], 352 (4) [$(\text{M}-\text{COOCH}_2\text{CH}_3)+\text{NH}_4^+$].- $\text{C}_{26}\text{H}_{30}\text{O}_4$ (406.5).

8-(*tert*-butyldimethylsilyl)-tricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene (**91**)

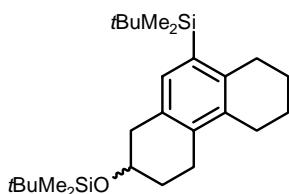


By adapting GP8 method B, 11.8 mg (0.052 mmol) of palladium acetate was added at 80 °C to a degassed mixture of 33 mg (0.125 mmol) of triphenylphosphine, 42 mg (0.62 mmol) of sodium formate and 200 mg (0.52 mmol) of 2-bromo-14-(*tert*-butyldimethylsilyl)-1-tetradecen-7,13,-diyne(**79**) in 5 ml DMF.

After stirring from 3 h at 80 °C, the reaction mixture was poured into 30 ml of water and extracted (3×20 ml) with diethyl ether. The combined ether layers were dried (MgSO_4), concentrated and the residue was eluted from a column of silica gel (7 g) with pentane to afford two fractions. The first fraction was composed of polymers. The second fraction afforded 30 mg (20%) of **91** as orange oil. ($R_f=0.80$, pentane).-IR (Film): ν = 3053 cm^{-1} , 2957, 2926, 2854, 1667, 1571, 1469, 1391, 1252, 1075, 1008, 838, 775, 739, 676.- ^1H -NMR (250 MHz, CDCl_3): δ = 0.31 (s, 6 H, TBDMS-H), 0.90 (s, 9 H, TBDMS-H), 1.66 – 1.88 (m, 8 H, 4(5,12,13)-H), 2.53 – 2.60 (m, 4 H, 3(11)-H), 2.73 (t, $^3J=5.91$ Hz, 2 H, 6-H), 2.81 (t, $^3J=5.95$ Hz, 2 H, 14-H), 7.04 (s, 1 H, 9-H) .- ^1H -NMR (500 MHz, CDCl_3) : δ = 0.28 (s, 6 H, TBDMS-H), 0.88 (s, 9 H, TBDMS-H), 1.67 – 1.84 (m, 8 H, 4(5,12,13)-H), 2.52 – 2.59 (q, $^3J=5.5$ Hz, 4 H, 3(11)-H), 2.72 (t, $^3J=5.5$ Hz, 2 H, 6-H), 2.80 (t, $^3J=5.5$ Hz, 2 H, 14-H), 7.05 (s, 1 H, 9-H).- ^{13}C -NMR (125.705 MHz, CDCl_3): δ = - 2.48 (TBDMS-C), 18.03 (TBDMS-C), 22.84 (C- 12*), 23.08 (C-13*), 23.16 (C-4*), 23.52 (C-5), 26.43 (C-11**), 26.73 (C-3**), 27.14 (TBDMS-C), 30.14 (C-6), 32.21 (C-

14), 132.92 (Aromatic-C), 133.13 (Aromatic-C), 134.81 (Aromatic-C), 135.04 (C-9), 136.61 (Aromatic-C), 140.55 (Aromatic-C).– MS (EI, 70 eV), m/z (%): 300 (8) [M^+], 243 (100) [$M^+ - C(CH_3)_3$].– $C_{20}H_{32}Si$ (300.5): found 300.2273 (HRMS correct)

5-(tert-butyltrimethylsilyloxy)-9-(tertbutyltrimethylsilyl)tricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene (92)

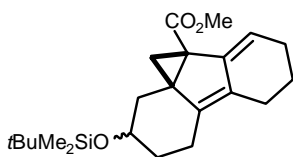


By adapting GP8 method B, 8.8 mg (0.039 mmol) of palladium acetate was added at 80 °C to a degassed mixture of 25.68 mg (0.098 mmol) of triphenylphosphine, 53.2 mg (0.78 mmol) of sodium formate, 129.4 mg (0.78 mmol) of tetraethylammonium chloride, and 200 mg (0.39 mmol) of 2-bromo-4-(*tert*-butyltrimethylsilyloxy)-14-(*tert*-butyltrimethylsilyl)-1-tetradecen-7,13-diyne(**80**) in 5ml DMF. After stirring from 4 h at 80 °C, the reaction mixture was poured into 30 ml of water and extracted (3×20 ml) with diethyl ether. The combined ether layers were dried (MgSO₄), concentrated and the residue was eluted from 20×20 cm plates coated with thick layer of silica gel (Silica gel 60 PF₂₅₄ containing CaSO₄) with 100:1 pentane/diethyl ether. The fourth fraction ($R_f = 0.8$, 80:1 pentane/ diethyl ether) from the plates' top afforded 28 mg (16%) of the title compound as a pale yellow solid. –IR (KBr): $\nu = 2855\text{ cm}^{-1}$, 1468, 1292, 1092, 837, 774, 685. –¹H-NMR (250 MHz, CDCl₃): $\delta = 0.10$ (s, 6 H, O -TBDMS-H), 0.32 (s, 6 H, C- TBDMS-H), 0.91 (s, 9 H, C-TBDMS-H), 0.92 (s, 9 H, O -TBDMS-H), 1.68 – 1.87 (m, 5 H, 4(12,13)-H), 2.03 (m, 1 H, 4 H), 2.50 – 2.63 (m, 4 H, 3(11)-H), 2.70 – 2.95 (m, 4 H, 6(14)-H), 4.03 (m, 1 H, 5-H), 7.03 (s, 1 H, 8-H). –¹³C-NMR (125.705 MHz, CDCl₃): $\delta = -4.59$ (O -TBDMS-C), -4.56 (O -TBDMS-C), -2.56 (C-TBDMS-C), -2.42 (C-TBDMS-C), 18.03 (C-TBDMS-C), 18.27 (O -TBDMS-C), 23.05 (C- 13*), 23.13 (C-12*), 25.71 (C-3**), 25.95 (O -TBDMS-C), 26.92 (C-11**), 27.13 (C- TBDMS-C), 32.16 (C-14), 32.65 (C-4), 39.81 (C-6), 68.24 (C-5), 131.33(Aromatic- C), 133.60 (Aromatic-C), 134.43 (Aromatic-C), 135.18 (C-8), 135.49 (Aromatic-C), 140.95 (Aromatic-C).– MS (DCI, NH₃, 70 eV) m/z (%): 878 (0.1) [$2M+NH_4^+$], 449 (32) [($M+H$)+NH₄⁺], 448 (94) [$M+NH_4^+$], 431 (100) [$M+H^+$], 390 (17)

[(M+H)-C(CH₃)₃+NH₄⁺], 334 (16) [(M-t-BuMe₂Si)+NH₄⁺], 299 (17), 185 (10), 132 (4).- C₂₆H₄₆O₂Si₂(430.8).

Methyl 13-(tert-butyldimethylsilyloxy)tetracyclo[8.4.0.0^{1,3}.0^{4,9}]tetradeca-4,9-dien-3-carboxylate (122)

By adapting GP8 method A, 9.8 mg (0.050 mmol) of palladium acetate was added at 60 °C to a degassed mixture, placed in a Pyrex[®] crucible, of 29 mg (0.11 mmol) of triphenylphosphine, 182.6 mg (1.3 mmol) of potassium carbonate, and 200 mg (0.44 mmol) of Methyl-14-bromo-12-(*tert*-butyldimethylsilyloxy)-14-pentadecene-2,8-diynoate in 5 ml acetonitrile . The reaction mixture was stirred at 60 °C

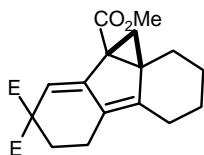


for 18 h and worked up as described in GP8 method A. The residue was purified by thick layer chromatography using 20×20 cm plates coated with thick layer of silica gel (Silica gel 60 PF₂₅₄ containing CaSO₄). The plates were developed twice, once by using 2:1 pentane/dichloromethane and another by 10:1 pentane/diethyl ether. The first fraction (R_f = 0.12, 5:1 pentane/diethyl ether) from the plates' top afforded 32 mg (19%) of 2:1 of a diastomeric mixture of the title compound as a colorless oil .-IR (Film): ν = 2957 cm⁻¹, 2854, 2240, 1734, 1437, 1255, 1202, 835, 777, 736.- ¹H-NMR (250 MHz , CDCl₃): δ = 0.064 (s, 6 H, TBDMS-H), 0.90 (s, 9 H, TBDMS- H), 1.05 (d, ²J = 3.20 Hz, 1 H, 2-H), 1.42 (m, 1 H, 4-H), 1.64 - 1.74 (m, 2 H, 7(8)-H), 1.82 (m, 3 H, 12(14)-H), 1.90 (d, ²J = 3.11 Hz, 1 H, 2-H), 2.02 - 2.18 (m, 2 H, 6(8)-H), 2.23 - 2.34 (m, 3 H, 6(7,11)-H), 2.51 (d, ³J = 5.6 Hz, 11-H), 3.71 (s, 3 H, COOCH₃), 4.25 (s, 1 H, 13-H), 5.89 (t, ³J = 4.3 Hz, 1 H, 5-H).- ¹H-NMR (500 MHz, CDCl₃): δ = 0.04 (s, 6 H, TBDMS-H), 0.88 (s, 9 H, TBDMS-H), 1.03 (d, ²J = 3.1 Hz, 1 H, 2-H), 1.40 (m, 1 H, 14-H), 1.54 - 1.72 (m, 1 H, 7-H), 1.74 (t, ³J = 4Hz, 1 H, 8-H), 1.80 (m, 3 H, 10(14)-H), 1.90 (d, ²J = 3.15 Hz , 1 H , 2-H), 2.00 (m, 1 H, 8-H), 2.10 (m, 1 H, 6-H), 2.20 - 2.34 (m, 3 H, 6(7,11)-H), 2.50 (d, ³J = 5 Hz, 1 H, 11-H), 3.70 (s, 3 H, COOCH₃), 4.24 (bs, 1 H, 13-H), 5.88 (t, ³J = 5.5 Hz, 1 H ,5-H).- ¹³C-NMR (125.705 MHz, CDCl₃, APT): δ = - 4.88 (+, TBDMS-C), 17.99 (-, TBDMS-C), 19.10 (-, C-11), 22.46 (-, C-7), 22.65 (-, C-8), 25.43 (-, C-6), 25.75 (+, TBDMS-C), 31.68 (-, C-14), 34.82 (-, C-12), 35.53 (-, C-3), 38.77 (-, C-2), 43.37 (-,

C-1), 51.63 (+, COOCH₃), 66.77 (+, C-13), 120.52 (+, C-5), 128.21 (–, C-9), 139.45 (–, C-10), 142.12 (–, C-4), 171.92 (–, COOCH₃).– MS (DCI, NH₃, 70 eV) *m/z* (%): 392 (100) [M+NH₄⁺], 375 (70) [M+H⁺], 260 (8) [M⁺– t-BuMe₂Si].– C₂₂H₃₄O₃Si (374.6) calcd for: C 70.54, H 9.15; found: C 70.42, H 9.03

6,6-dimethyl 3-methyl tetracyclo[8.4.0.0^{1,3}.0^{4,9}]tetradeca-4,9-diene-3,6,6-tricarboxylate (119-COOMe) (E = COOMe)

By adapting GP8 method A, 150 mg (0.66 mmol) of palladium acetate was added at 60 °C to a degassed mixture, placed in a Pyrex[®] crucible, of 430 mg (1.64 mmol) of triphenylphosphine, 2.72 g (19.7 mmol) of potassium carbonate, and 2.9 g (6.59 mmol) of 11,11-dimethyl-1-methyl 13-bromo-13-tetradecen-1,7-diyne-1,11,11-tricarboxylate in 100ml acetonitrile.



After stirring at 60 °C for 20 h, the reaction mixture was cooled and filtered over two layers of Celite[®] and silica gel. The resulting filtrate was treated with 200 ml of water and extracted with (4×50 ml) of diethyl ether. The combined organic phases were dried (MgSO₄), concentrated, and the residue was purified by column chromatography (60 g silica gel and 4:1 pentane/diethyl ether) to afford 1.3 g (54%) of an orange oil. (*R_f* = 0.17, 4:1 pentane/diethyl ether).-IR (Film): $\nu = 2996 \text{ cm}^{-1}$, 2954, 2855, 1755, 1715, 1433, 1302, 1226, 1197, 1154, 1076, 1062, 851, 833, 735, 702.-¹H-NMR (250 MHz, CDCl₃): $\delta = 1.07$ (d, ²*J* = 2.9 Hz, 1 H, 2-H), 1.24 (m, 1 H, 12- H), 1.46 - 1.56 (m, 1 H, 12-H), 2.68 (dt, ²*J* = 2.8 Hz, ³*J* = 15 Hz, 1 H, 14-H), 1.8 - 1.89 (m, 2 H, 11(14)-H), 1.95 (d, ²*J* = 3.0 Hz, 1 H, 2-H), 2.00 - 2.37 (m, 4 H, 7 (8,13)-H), 2.40 - 2.61 (m, 3 H, 8(11,13)-H), 3.70 (s, 3 H, COOCH₃), 3.72 (s, 3 H, COOCH₃), 3.75 (s, 3 H, COOCH₃), 6.09 (s, 1 H, 5-H).-¹³C-NMR (62.5 MHz, CDCl₃, DEPT): $\delta = 19.15$ (–, C-8), 24.82 (–, C-12), 24.93 (–, C-11), 25.36 (–, C-13), 27.98 (–, C-14), 28.70 (–, C-7), 36.65 (C_{quart}, C-3), 39.29 (–, C-2), 45.88 (C_{quart}, C-1), 51.80 (+, COOCH₃), 52.68 (+, COOCH₃), 52.82 (+, COOCH₃), 55.28 (C_{quart}, C-6), 115.88 (+, C-5), 126.03 (C_{quart}, C-9), 143.53 (C_{quat}, C-4), 144.75 (C_{quart}, C-10), 170.96 (C_{quart}, COOCH₃), 171.35 (C_{quart}, COOCH₃), 171.72 (C_{quart}, COOCH₃).– MS (EI, 70 eV), *m/z* (%): 360 (10) [M⁺], 328 (24) [M⁺–CH₃OH],

301 (30) [M^+ -COOCH₃], 269 (46) [M^+ -CH₃OH-COOCH₃], 241 (39), 209 (20), 159 (30), 115 (72), 74 (79), 59 (100), 45 (64), 43 (27).- C₂₀H₂₄O₆(360.4) calcd for: C 66.65, H 6.43; found: C 66.76, H 6.43.

6,6-diethyl 3-methyl tetracyclo[8.4.0.0^{1,3}.0^{4,9}]tetradeca-4,9-diene-3,6,6-tricarboxylate (119-COOEt) (E = COOEt)

Similar procedure for preparing the dimethyl derivative was followed. However, the compound was purified by thick layer chromatography 20×20 cm plates coated with thick layer of silica gel (Silica gel 60 PF₂₅₄ containing CaSO₄). After elution with 4:1 pentane/diethyl ether, the first fraction (R_f = 0.43, 4:1 pentane/diethyl ether), from the plates' top, offered the title compound in a 52% yield as an orange oil.-IR (Film): ν = 2932 cm⁻¹, 1732, 1438, 1235, 1063.-¹H-NMR (250 MHz, CDCl₃): δ = 1.07 (d, ²J = 3.0 Hz, 1 H, 2-H), 1.16 - 1.41 (m, 7 H, 12-H, COOCH₂CH₃), 1.46 - 1.65 (m, 2 H, 12(14)-H), 1.79 - 1.89 (m, 2 H, 11(14)-H), 1.94 (d, ²J = 3.0 Hz, 1 H, 2-H), 1.99 - 2.38 (m, 4 H, 7(8,13)-H), 2.40 - 2.54 (m, 3H, 8(11,13)-H), 3.72 (s, 3 H, COOCH₃), 4.13 - 4.25 (m, 4 H, COOCH₂CH₃), 6.03 (s, 1H, 5-H).-¹H-NMR (500 MHz, CDCl₃): δ = 1.04 (d, ²J = 3.0 Hz, 1 H, 2-H), 1.14 - 1.30 (m, 7 H, 12-H, COOCH₂CH₃), 1.46 (m, 1 H, 12-H), 1.62 (dt, ²J = ³J_{ax-ax} = 10 Hz, ³J_{ax-eq} = 3 Hz, 1 H, 14-H), 1.78 (m, 1 H, 14-H), 1.83 (m, 1 H, 11-H), 1.92 (d, ²J = 3 Hz, 1 H, 2-H), 1.96 (m, 1 H, 13-H), 2.00- 2.08 (m, 1 H, 7-H), 2.22 - 2.28 (m, 1 H, 8-H), 2.38 - 2.54 (m, 3 H, 8(11,13)-H), 3.70 (s, 3 H, COOCH₃), 4.08 - 4.22 (m, 4 H, COOCH₂CH₃), 6.02 (s, 1 H, 5-H).-¹³C-NMR (62.5 MHz, CDCl₃, DEPT): δ = 14.04 (+, COOCH₂CH₃), 19.14 (-, C-8), 24.84 (-, C-12), 24.93 (-, C-11), 25.36 (-, C-13), 27.98 (-, C-14), 28.55 (-, C-7), 36.72 (C_{quart}, C-3), 39.13 (-, C-2), 45.87 (C_{quart}, C-1), 51.77 (+, COOCH₃), 55.28 (C_{quart}, C-6), 65.83 (-, COOCH₂CH₃), 116.22 (+, C-5), 126.21 (C_{quart}, C-9), 143.23 (C_{quart}, C-4), 144.58 (C_{quart}, C-10), 170.92 (C_{quart}, COOCH₂CH₃), 170.97 (C_{quart}, COOCH₂CH₃), 171.17 (C_{quart}, COOCH₃).- MS (EI, 70 eV), *m/z* (%): 388 (78) [M^+], 357 (30) [M^+ -OCH₃], 356 (100) [M^+ -CH₃OH], 329 (68) [M^+ -COOCH₃], 315 (24) [M^+ -COOCH₂CH₃], 314 (34), 283 (97) [M^+ -CH₃OH-COOCH₂CH₃], 255 (60) [M^+ -COOCH₂CH₃-COOCH₂CH₃], 211 (34), 183 (38), 155 (12), 141 (21).- C₂₂H₂₈O₆ (388.4): found 388.1885 (HRMS correct)

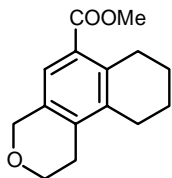
Palladium catalysed oligocyclization of Methyl 11-(2'-bromoallyloxy)-2,8-undecadiynoate (132)

By adapting GP8 method A, 34 mg (0.15 mmol) of palladium acetate was added to a mixture, placed in a Pyrex[®] crucible, of 99.8 mg (0.38 mmol) of triphenylphosphine 630 mg (4.5 mmol) of potassium carbonate, and 500 mg (1.5 mmol) of methyl 11-(2'-bromoallyloxy)-2,8-undecadiynoate (**132**) in 30 ml acetonitrile. The reaction mixture was stirred at 106 °C for 18 h and worked up as described in GP8 method A. The residue was purified by thick layer chromatography using 20×20 cm plates coated with thick layer of silica gel (Silica gel 60 PF₂₅₄ containing CaSO₄). The plates were eluted twice with 5:1 pentane/dichloromethane and once with 10:1 pentane/diethyl ether to afford the following fractions:

Fraction I

Methyl 1,4,7,8,9,10-hexahydro-2H-benzof[f]isochromene-6-carboxylate (135)

The first fraction ($R_f = 0.23$, 5:1 pentane/diethyl ether) from the plates' top afforded 35 mg (10%) of the title compound as a white solid.



-IR (KBr): $\nu = 2938$ cm^{-1} , 1719, 1430, 1292, 1202, 1184, 1155, 1017, 925, 778. ¹H-NMR (250 MHz, CDCl₃): $\delta = 1.71 - 1.83$ (m, 4 H, 8(9)-H), 2.59 (t, ³J = 6 Hz, 2 H, 10-H), 2.66 (t, ³J = 5.7 Hz, 2 H, 1-H), 3.03 (t, ³J = 5.9 Hz, 2 H, 7-H), 3.85 (s, 3H, COOCH₃), 3.99 (t, ³J = 5.8 Hz, 2 H, 2-H), 4.74 (s, 2 H,

4-H), 7.35 (s, 1 H, 5-H). ¹H-NMR (500 MHz, CDCl₃): $\delta = 1.68 - 1.77$ (m, 2 H, 8-H), 1.78 - 1.84 (m, 2H, 9-H), 2.57 (t, ³J = 5.5 Hz, 2 H, 10-H), 2.64 (t, ³J = 5.6 Hz, 2 H, 1-H), 3.01 (t, ³J = 6 Hz, 2 H, 7-H), 3.82 (s, 3 H, COOCH₃), 4.00 (t, ³J = 6.1 Hz, 2 H, 2-H), 4.71 (s, 2H, 4-H), 7.34 (s, 1 H, 5-H). ¹³C-NMR (62.5 MHz, CDCl₃, DEPT): $\delta = 22.37$ (-, C-9), 22.61 (-, C-8), 26.08 (-, C-1), 26.55 (-, C-10), 28.19 (-, C-7), 51.77 (+, COOCH₃), 65.21 (-, C-2), 67.97 (-, C-4), 123.86 (+, C-5), 127.77 (C_{quart}, Aromatic-C), 131.59 (C_{quart}, Aromatic-C), 136.00 (C_{quart}, Aromatic-C), 136.50 (C_{quart}, Aromatic-C), 136.60 (C_{quart}, Aromatic-C), 168.42 (C_{quart}, COOCH₃). - MS (EI, 70 eV), m/z (%): 246 (100) [M⁺], 231 (21) [M⁺-CH₃], 214 (88) [M⁺-OCH₃], 187 (77) [M⁺-COOCH₃], 159 (36), 157 (19) [M⁺-COOCH₃-H₂C=O], 141 (17), 129 (25), 115 (23), 91 (16). - C₁₅H₁₈O₃

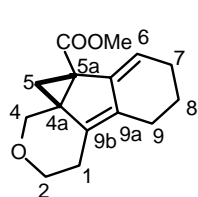
(246.3): found 246.1256 (HRMS correct)

Fraction II

Methyl 1,5,5a,7,8,9-hexahydro-2H-cyclopropa[2,3]indeno[2,1-c]pyran-5a-carboxylate

(134)

The second fraction ($R_f = 0.18$, 5:1 pentane/diethyl ether) from the plates' top afforded 80 mg (21%) of the title compound as a colorless oil. IR (Film): $\nu = 2992\text{ cm}^{-1}$, 2926,



2857, 2827, 1715, 1436, 1382, 1363, 1298, 1247, 1221, 1199, 1163,

1082, 1050, 971, 855, 731, 666, 611. $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta =$

1.10 (d, $^2J = 3.2\text{ Hz}$, 1 H, 5-H), 1.65 (m, 2 H, 8-H), 2.04 (d, $^2J = 2.08\text{ Hz}$, 1 H, 5-H), 2.07 - 2.39 (m, 6 H, 1(7,9)-H), 3.23 - 3.34 (m, 1 H, 2-

H), 3.69 (s, 3 H, COOCH_3), 3.75 (d, $^2J = 11.4\text{ Hz}$, 1 H, 4-H), 4.0 (d, $^2J = 11.4\text{ Hz}$, 1 H, 4-H), 4.10 (dd, $^2J = 9.4\text{ Hz}$, $^3J = 4.2\text{ Hz}$, 1 H, 2-H), 6.04 (t, $^3J = 4.2\text{ Hz}$, 1 H, 6-H). $^1\text{H-NMR}$

(600 MHz, CDCl_3): $\delta = 1.08$ (d, $^2J = 3.1\text{ Hz}$, 1 H, 5-H), 1.63 (m, 2 H, 8-H), 2.02 (d, $^2J = 3\text{ Hz}$, 5-H), 2.05 - 2.15 (m, 2 H, 7(9)-H), 2.23 (m, 1 H, 7-H), 2.30 (m, 1 H, 9-H),

2.37 (dt, $^3J_{\text{ax-ax}} = ^2J = 10\text{ Hz}$, $^3J_{\text{ax-eq}} = 5\text{ Hz}$, 1 H, 2-H), 3.67 (s, 3 H, COOCH_3), 3.74

(d, $^2J = 12\text{ Hz}$, 1 H, 4-H), 3.99 (d, $^2J = 12\text{ Hz}$, 1 H, 4-H), 4.10 (ddd, $^2J = 11\text{ Hz}$, $^3J_{\text{eq-eq}} = 5.5\text{ Hz}$, $^3J_{\text{eq-ax}} = 2\text{ Hz}$, 1H, 2-H), 6.0 (t, $^3J = 4\text{ Hz}$, 1 H, 6-H). $^{13}\text{C-NMR}$ (150.82 MHz,

CDCl_3 , DEPT): $\delta = 22.19$ (-, C-8), 22.52 (-, C-9), 25.34 (-, C-7), 26.23 (-, C-1), 35.52 (C_{quart} , C-5a), 37.30 (-, C-5), 42.87 (C_{quart} , C-4a), 51.71 (+, COOCH_3), 66.86 (-, C-2),

70.03 (-, C-4), 121.78 (+, C-6), 130.30 (C_{quart} , C-9a), 134.77 (C_{quart} , C-9b), 141.08 (C_{quart} , C-5b), 171.30 (C_{quart} , COOCH_3). MS (EI, 70 eV), m/z (%): 246 (23) [M^+], 215 (6)

[$\text{M}^+ - \text{OCH}_3$], 187 (100) [$\text{M}^+ - \text{COOCH}_3$], 157 (43) [$\text{M}^+ - \text{COOCH}_3 - \text{H}_2\text{C}=\text{O}$], 141 (14), 129 (25), 115 (12). $\text{C}_{15}\text{H}_{18}\text{O}_3$ (246.3): found 246.1256 (HRMS correct)

Fraction IV

Methyl 1,4,5,6-tetrahydro-2H-benzo[f]isochromene-6-carboxylate (136)

The fourth fraction ($R_f = 0.11$, 5:1 pentane/diethyl ether) from the plates' top afforded 10 mg (3%) of the title compound as a colorless oil.-IR (Film): $\nu = 3029 \text{ cm}^{-1}$, 2954, 2926,

2252, 1740, 1490, 1435, 1270, 1214, 1158, 910, 765, 732.- $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 2.27$ (m, 2 H, 2, 1-H), 2.48 - 2.57 (m, 2 H, 1(5)-H), 3.66 (s, 3 H, COOCH_3), 3.77 (t, $^3J = 5.2 \text{ Hz}$, 1 H, 6-H), 3.83 - 3.98 (m, 1 H, 2-H), 4.00 - 4.08 (m, 1 H, 2-H), 4.14 (d, $^2J = 15 \text{ Hz}$, 1 H, 4-H), 4.25 (d, $^2J = 16 \text{ Hz}$, 1H, 4-H), 7.16 - 7.31 (m, 4 H, Aromatic-H).

$^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 2.26$ (m, 1 H, 5-H), 2.32 (ddd, $^2J = 2 \text{ Hz}$, $^3J_{\text{ax-eq}} = 3.5 \text{ Hz}$, $^3J_{\text{ax-ax}} = 7 \text{ Hz}$, 1 H, 1-H), 2.43 (dt, $^2J = ^3J_{\text{eq-ax}} = 1 \text{ Hz}$, $^3J_{\text{eq-eq}} = 4.5 \text{ Hz}$, 1 H, 1-H), 2.47 - 2.53 (m, 1 H, 5-H), 3.60 (s, 3 H, COOCH_3), 3.71 (t, $^3J = 6.5 \text{ Hz}$, 1 H, 6-H), 3.81 (ddd, $^2J = 11 \text{ Hz}$, $^3J_{\text{ax-ax}} = 7 \text{ Hz}$, $^3J_{\text{ax-eq}} = 4.5 \text{ Hz}$, 1 H, 2-H), 3.95 (dt, $^2J = 11.5 \text{ Hz}$, $^3J_{\text{eq-eq}} = ^3J_{\text{eq-ax}} = 6 \text{ Hz}$, 1 H, 2-H), 4.08 (d, $^2J = 17 \text{ Hz}$, 1 H, 4-H), 4.17 (d, $^2J = 17 \text{ Hz}$, 4-H), 7.08 - 7.22 (m, 4 H, Aromatic-H).- $^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3 , DEPT): $\delta = 24.52$ (-, C-5), 26.49 (-, C-1), 43.34 (+, C-6), 52.21 (+, COOCH_3), 64.71 (-, C-2), 67.93 (-, C-4), 121.69 (+, Aromatic-C), 124.41 (C_{quart} , Aromatic-C), 126.68 (+, Aromatic-C), 127.78 (+, Aromatic-C), 128.47 (+, Aromatic-C), 130.32 (C_{quart} , Aromatic-C), 131.32 (C_{quart} , C-10b*), 134.42 (C_{quart} , C-4a*), 173.68 (C_{quart} , COOCH_3). - MS (EI, 70 eV), m/z (%): 244 (54) [M^+], 184 (100) [($\text{M}^+ - \text{H}$) - COOCH_3], 155 (69) [$\text{M}^+ - \text{COOCH}_3 - \text{H}_2\text{C}=\text{O}$], 129 (14); (DCI, NH_3 , 70 eV) m/z (%): 506 (13) [$2\text{M} + \text{NH}_4^+$], 279 (16) [$\text{M} + \text{N}_2\text{H}_7^+$], 262 (100) [$\text{M} + \text{NH}_4^+$]. - $\text{C}_{15}\text{H}_{16}\text{O}_3$ (244.3)

Palladium catalysed oligocyclization of Dimethyl 2-(2''-bromoallyl)-2-(11'-oxo-3',9'-dodecadiynyl)malonate (144)

By adapting GP8 method A, 120 mg (0.55 mmol) of palladium acetate was added at 60 °C to a degassed mixture, placed in a Pyrex[®] crucible, of 350 mg (1.35 mmol) of triphenylphosphine, 2.24 g (16.2 mmol) of potassium carbonate, and 2.3 g (5.42 mmol) of dimethyl 2-(2''-bromoallyl)-2-(11'-oxo-3',9'-dodecadiynyl)malonate(**144**) in 80ml

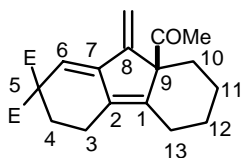
acetonitrile. After stirring at 60 °C for 12 h, the reaction mixture was cooled and filtered over two layers of Celite[®] and silica gel. The resulting filtrate was concentrated and the residue was purified by column chromatography (50g silica gel and 2:1 pentane/diethyl ether) to afford the following two fractions:

Fraction II

Dimethyl 9-acetyl-8-methylenetricyclo[7.4.0.0^{2,7}]trideca-1,6-diene-5,5-dicarboxylate
(146)

The second fraction ($R_f = 0.14$, 5:1 pentane/diethyl ether) from the plates' top afforded 430 mg (23%) of the title compound as a gummy yellowish material .-

IR (KBr): $\nu = 2937 \text{ cm}^{-1}$, 1729, 1703, 1434, 1357, 1263, 1068, 906, 835. - ¹H-NMR (250 MHz, CDCl₃): $\delta = 1.10$ (dt, ² $J =$ ³ $J_{ax-ax} = 13.1$ Hz, ³ $J_{ax-eq} = 4$ Hz, 1 H, 10-H), 1.18 - 1.23 (m, 1 H, 12-H), 1.24 - 1.49 (m, 1 H, 11-H), 1.61 - 1.67 (m, 1 H, 11-H), 1.70 - 1.87 (m, 2 H, 12(13)-H), 1.88 (s, 3 H, COCH₃), 2.03 - 2.14 (m, 1 H, 4-H), 2.24 - 2.32 (m, 1 H, 4-H), 2.54 - 2.62 (m, 4 H, 3(10,13)-H), 3.74 (s, 3 H, COOCH₃), 3.75 (s, 3 H, COOCH₃), 4.90 (s, 1 H, =CH₂), 5.59 (s, 1 H, =CH₂), 6.0 (s, 1 H, 6-H). - ¹H-NMR (500 MHz, CDCl₃): $\delta = 1.08$ (dt, ² $J =$ ³ $J_{ax-ax} = 13.5$ Hz, ³ $J_{ax-eq} = 4$ Hz, 1 H, 10-H), 1.14 (dt, ³ $J_{ax-ax} =$ ³ $J_{ax-eq} = 4$ Hz, ² $J = 13.5$ Hz, 1 H, 12-H), 1.37 (tq, ² $J = 3$ Hz, ³ $J = 13.5$ Hz, 1 H, 11-H), 1.60 - 1.65 (m, 1 H, 11-H), 1.70 - 1.80 (m, 2 H, 12(13)-H), 1.87 (s, 3 H, COCH₃), 2.01 - 2.11 (m, 1 H, 4-H), 2.23 - 2.29 (m, 1 H, 4-H), 2.51 - 2.60 (m, 4 H, 3(10,13)-H), 3.74 (s, 3 H, COOCH₃), 3.75 (s, 3 H, COOCH₃), 4.90 (s, 1 H, =CH₂), 5.50 (s, 1 H, =CH₂), 6.0 (s, 1 H, 6-H). - ¹³C-NMR (125.707 MHz, CDCl₃, APT): $\delta = 19.54$ (-, C-3), 23.56 (-, C-11), 25.72 (-, C-13), 25.79 (+, COCH₃), 26.64 (-, C-12), 28.57 (-, C-4), 33.52 (-, C-10), 52.84 (+, COOCH₃), 52.85 (+, COOCH₃), 55.14 (-, C-5), 67.26 (-, C-9), 107.19 (-, =CH₂), 110.28 (+, C-6), 132.58 (-, C-2), 143.23 (-, C-7*), 143.29 (-, C-1*), 148.47 (-, C-8), 171.11 (-, COOCH₃), 171.44 (-, COOCH₃), 207.04 (-, COCH₃). - MS (EI, 70 eV), m/z (%): 344 (12) [M⁺], 301 (100) [M⁺-COCH₃], 242 (8) [M⁺-COOCH₃-COCH₃], 241 (32) [(M⁺-H)-COOCH₃-COCH₃], 209 (6), 183 (4), 155 (6), 43 (0.7) [C₂H₃O⁺]. - C₂₀H₂₄O₅ (344.4): found 344.1624 (HRMS correct).

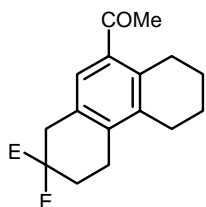


Fraction III

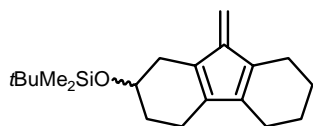
Dimethyl 9-acetyltricyclo[8.4.0.0^{2,7}]tetradeca-1(10),2(7),8-triene-5,5-dicarboxylat (147)

The second fraction ($R_f = 0.08$, 5:1 pentane/diethyl ether) from the plates' top afforded 213 mg (11%) of the title compound as a white solid. -IR (KBr): $\nu = 2956 \text{ cm}^{-1}$, 1752,

1731, 1677, 1433, 1278, 1079. -¹H-NMR (250 MHz, CDCl₃): $\delta = 1.66 - 1.82$ (m, 4 H, 12(13)-H), 2.34 (t, ³ $J = 6.7$ Hz, 2 H, 4-H), 2.53 (m, 5 H, 14-H, COCH₃), 2.62 (t, ³ $J = 6.7$ Hz, 2 H, 3-H), 2.90 (t, ³ $J = 6.2$ Hz, 2 h, 11-H), 3.28 (s, 2 H, 6-H), 3.72 (s, 6 H, COOCH₃), 7.24 (s, 1 H, 8-H). -¹H-NMR (500 MHz, CDCl₃): $\delta = 1.68$ (m, 2 H, 12-H), 1.79 (m, 2 H, 13-H), 2.34 (t, ³ $J = 6$ Hz, 2 H, 4-H), 2.53 (s, 3 H, COCH₃), 2.56 (t, ³ $J = 6.2$ Hz, 2 H, 14-H), 2.60 (t, ³ $J = 6.5$ Hz, 2 H, 3-H), 2.95 (t, ³ $J = 6$ Hz, 2 H, 11-H), 3.28 (s, 2 H, 6-H), 3.72 (s, 6 H, COOCH₃), 7.24 (s, 1 H, 8-H). -¹³C-NMR (125.707 MHz, CDCl₃, DEPT, 62.5 MHz): $\delta = 22.51$ (-, C-13*), 22.51 (-, C-12*), 23.75 (-, C-3), 26.93 (-, C-14), 28.08 (-, C-4), 28.26 (-, C-11), 30.12 (+, COCH₃), 35.04 (-, C-6), 52.68 (+, COOCH₃), 52.81 (+, COOCH₃), 52.93 (C_{quart}, C-5), 126 (+, C-8), 129.97 (C_{quart}, Aromatic-C), 134.72 (C_{quart}, Aromatic-C), 136.50 (C_{quart}, Aromatic-C), 136.56 (C_{quart}, Aromatic-C), 136.79 (C_{quart}, Aromatic-C), 171.59 (C_{quart}, COOCH₃), 202.74 (C_{quart}, COCH₃). - MS (EI, 70 eV), m/z (%): 344 (100) [M⁺], 329 (17) [M⁺-CH₃], 301 (3) [M⁺-COCH₃], 285 (23) [M⁺-COOCH₃], 284 (58) [(M⁺-H)-COOCH₃], 269 (19) [(M⁺-H)-COOCH₃-CH₃], 241 (11) [(M⁺-H)-COOCH₃-COCH₃], 225 (13) [(M⁺-H)-2COOCH₃], 209 (6), 181 (15), 43 (18) [C₂H₃O⁺]. - C₂₀H₂₄O₅ (344.4): found 344.1624 (HRMS correct).



5-(tert-butyl dimethylsilyloxy)-8-methylenetricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-diene (166)



By adapting GP8 method B, 16.82 mg (0.072 mmol) of palladium acetate was added at 80 °C to a degassed mixture of 49.6 mg (0.18 mmol) of triphenylphosphine, 60 mg (0.90 mmol) of sodium formate, and 300 mg (0.72 mmol) of 2-bromo-4-(tert-butyl dimethylsilyloxy)-1-tetradecen-7,13-diyne (**117**) in 10 ml DMF. After stirring for 2

h at 80 °C, the reaction mixture was poured into 100 ml of ammonium chloride solution and extracted (3×50 ml) with diethyl ether. The combined ether layers were dried (MgSO₄), concentrated and the residue was purified by column chromatography (25 g of flash silica gel and 100:2 pentane/diethyl ether) to afford 127 mg (53%) of an orange oil. (*R*_f = 0.60, 100:2 pentane/diethyl ether).-IR (Film): $\nu = 3079 \text{ cm}^{-1}$, 2928, 1635, 1472, 1251, 1096, 904, 835, 774, 669.-¹H-NMR (250 MHz, CDCl₃): $\delta = 0.08$ (s, 6 H, TBDMS-H), 0.90 (s, 9 H, TBDMS-H), 1.71 (m, 5 H, 4(11,12)-H), 1.88 (m, 1 H, 4-H), 2.19-2.38 (m, 7 H, 3(6,10)-H), 2.58 (m, 1 H, 6-H), 3.97 (m, 1 H, 5-H), 5.44 (m, 2 H, =CH₂).-¹H-NMR (600 MHz, CDCl₃): $\delta = 0.09$ (s, 6 H, TBDMS-H), 0.90 (s, 9 H, TBDMS-H), 1.70 (m, 5 H, 4(11,12)-H), 1.90 (m, 1 H, 4-H), 2.19 (m, 2 H, 10-H), 2.22 (m, 1 H, 6-H), 2.25 (m, 1 H, 3-H), 2.31 (m, 3 H, 3(13)-H), 2.61 (dd, 1 H, ²*J* = 6 Hz, ³*J* = 18 Hz, 6-H), 3.98(m, 1 H, 5-H), 5.44 (d, ²*J* = 0.5 Hz, 1 H, =CH₂), 5.45 (d, ²*J* = 0.5 Hz, 1 H, =CH₂).-¹³C-NMR (150.82 MHz, CDCl₃, DEPT, 62.5 MHz): $\delta = -4.68$ (+, TBDMS-C), -4.62(+, TBDMS-C), 18.26 (C_{quart}, TBDMS-C), 21.17 (-, C-3), 21.46 (-, C-13), 22.47 (-, C-10), 22.73 (-, C-11*), 22.89 (-, C-12*), 25.92 (+, TBDMS-C), 31.41 (-, C-6), 32.35 (-, C-4), 69.27 (+, C-5), 111.09 (-, =CH₂), 125.47 (C_{quart}, C-9), 128.30 (C_{quart}, C-7), 140.67 (C_{quart}, C-1*), 140.78 (C_{quart}, C-2*), 151.46 (C_{quart}, C-8).- MS (EI, 70 eV), *m/z* (%): 316 (20) [M⁺], 259 (13) [M⁺-C(CH₃)₃], 186 (8) [M⁺-t-BuMe₂SiO], 185 (10) [(M⁺-H)-t-BuMe₂SiO], 158 (100) [(M⁺-H)-t-BuMe₂SiO-C₂H₄], 143 (4).- C₂₀H₃₂OSi (316.5) found: 316.2222 (HRMS correct).

Palladium catalysed oligocyclization of 15-bromo-13-(tert-butyldimethylsilyloxy)-15-hexadecen-3,9-diyne-2-one (145)

By adapting GP8 method B, 15.3 mg (0.068 mmol) of palladium acetate was added at 80 °C to a degassed mixture of 44.7 mg (0.17 mmol) of triphenylphosphine, 70 mg (1 mmol) of sodium formate, and 300 mg (0.68 mmol) of 15-bromo-13-(tert-butyldimethylsilyloxy)-15-hexadecen-3,9-diyne-2-one(145) in 8ml DMF. After stirring from 3 h at 80 °C, the reaction mixture was poured into 30 ml of water and extracted (3×20 ml) with diethyl ether. The combined ether layers were dried (MgSO₄),

concentrated and the residue, which was composed of a complicated mixture of diastereomers, was eluted three times from 20×20 cm plates coated with thick layer of silica gel (Silica gel 60 PF₂₅₄ containing CaSO₄) with 20:1 pentane/diethyl ether. The following fractions were separated and identified:

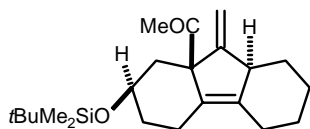
Fraction I

Fraction I from plates' top ($R_f=0.64$, 20:1 pentane/diethyl ether) provided 12 mg (5%) of an inseparable 1:1 mixture **156** and **157** as a colorless oil.

1-[(7'R,9'R,11'S)-8'-methylene-11'-(tert-

butyldimethylsilyloxy)tricyclo[7.4.0.0^{2,7'}]tridec-1'-en-7'-yl]-1-ethanone (157)

¹H-NMR (600MHz, CDCl₃): δ = 0.06 (s, 3 H, TBDMS-H), 0.08 (s, 3 H, TBDMS-H), 0.86 (s, 9 H, TBDMS-H), 1.12 (t, ³*J* = 11.5 Hz, 1 H, 10'-H),

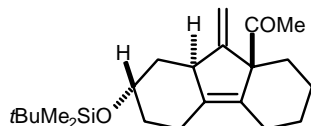


1.18 (m, 1 H, 12'-H), 1.20 (m, 1 H, 6'-H), 1.42 (t, ³*J* = 3 Hz, 1 H, 3'-H), 1.6 (m, 1 H, 13'-H), 1.85 (m, 5 H, 3'(4',5',12')-H), 1.98 (s, 3 H, COCH₃), 2.06 (m, 1 H, 6'-H), 2.45 (dq, ²*J* = 3 Hz, ³*J* = 13.5 Hz, 1 H, 13'-H), 2.50 - 2.60 (m, 1 H, 10'-H), 2.85 (m, 1 H, 9'-H), 4.98 (d, ²*J* = 2 Hz, 1 H, =CH₂), 5.07 (d, ²*J* = 2.1 Hz, 1 H, =CH₂).

¹³C-NMR (125.7 MHz, CDCl₃, DEPT, 62.5 MHz): δ = - 4.83 (+, TBDMS-C), - 4.58 (+, TBDMS-C), 18.18 (C_{quart}, TBDMS-C), 22.34 (-, C-13'), 25.55 (+, COCH₃), 25.87 (+, TBDMS-C), 26.06 (-, C-4'), 26.20 (-, C-3'), 27.15 (-, C-5'), 33.93 (-, C-6'), 36.39 (-, C-12'), 43.53 (-, C-10'), 50.92 (+, C-9'), 65.14 (C_{quart}, C-7'), 68.63 (+, C-11'), 108.82 (+, =CH₂), 131.65 (C_{quart}, C-2'), 138.43 (C_{quart}, C-1'), 156.93 (C_{quart}, C-8'), 208.26 (C_{quart}, COCH₃). - MS (EI, 70 eV), *m/z* (%): 360 (2) [M⁺], 317 (100) [M⁺-COCH₃], 303 (4) [M⁺-C(CH₃)₃], 185 (100), 73 (6), 43 (3) [C₂H₃O⁺]. - C₂₂H₃₆O₂Si (360.6): found 360.2485 (HRMS correct).

1-[(5'R,7'S,9'S)-8'-methylene-5'-(tert-butyl dimethylsilyloxy)tricyclo[7.4.0.0^{2,7'}]tridec-1'-en-7'-yl]-1-ethanone (156)

¹H-NMR (600 MHz, CDCl₃): δ = 0.02 (s, 3 H, TBDMS-H), 0.04 (s, 3 H, TBDMS-H), 0.84 (s, 9 H, TBDMS-H), 1.06 (dt, ³J_{ax-ax} = 12.5 Hz, ³J_{ax-eq} = ²J = 4 Hz, 1 H, 10'-H), 1.22 (m, 2 H, 11'-H), 1.28 (m,



1 H, 4'-H), 1.36 (dd, ³J = 13.5 Hz, ²J = 2.5 Hz, 1 H, 6'-H), 1.40 (m, 2 H, 12'-H), 1.75 (m, 1 H, 4'-H), 1.85 (m, 3 H,

10'(13')-H), 2.09 (s, 3 H, COCH₃), 2.31 - 2.34 (m, 2 H, 3'-H), 2.78 (dq, ²J = 2 Hz, ³J =

13.5 Hz, 1 H, 6'-H), 2.85 (m, 1 H, 9'-H), 4.00 (m, 1 H, 5'-H), 4.81 (d, ²J = 2.6 Hz, 1 H,

=CH₂), 4.96 (d, ²J = 2.6 Hz, 1 H, =CH₂).-¹³C-NMR (125.7 MHz, CDCl₃, DEPT, 62.5

MHz): δ = - 5.28 (+, TBDMS-C), - 5.05 (+, TBDMS-C), 18.10 (C_{quart}, TBDMS-C),

19.49 (-, C-3'), 25.63 (+, COCH₃), 25.81 (-, C-13'), 25.84 (+, TBDMS-C), 25.93 (-, C-

12'), 26.66 (-, C-11'), 34.53 (-, C-4'), 34.84 (-, C-10'), 43.32 (-, C-6'), 50.64 (+, C-9'),

67.40 (+, C-5'), 68.91 (C_{quart}, C-7'), 108.19 (-, =CH₂), 131.33 (C_{quart}, C-2'), 137.42 (C_{quart},

C-1'), 156.28 (C_{quart}, C-8'), 208.68 (C_{quart}, COCH₃). - MS (EI, 70 eV), *m/z* (%): 360 (2)

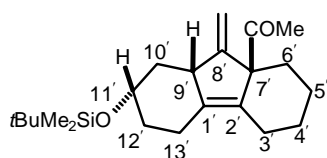
[M⁺], 317 (100) [M⁺-COCH₃], 303 (4) [M⁺-C(CH₃)₃], 185 (100), 73 (6), 43 (3)

[C₂H₃O⁺].- C₂₂H₃₆O₂Si (360.6): found 360.2485 (HRMS correct).

Fraction IV

1-[(7'R,9'S,11'S)-8'-methylene-11'-(tert-butyltrimethylsilyloxy)tricyclo[7.4.0.0^{2,7'}]tridec-1'-en-7'-yl]-1-ethanone (155)

The fourth fraction ($R_f=0.60$, 20:1 pentane/diethyl ether) from the plates' top afforded 20



mg (8%) of the title compound as a colorless oil.-IR

(Film): $\nu = 2956 \text{ cm}^{-1}$, 2930, 2857, 1707, 1470, 1443,

1353, 1254, 1100, 1068, 836, 775.-¹H-NMR (250 MHz,

CDCl_3): $\delta = 0.086$ (s, 6 H, TBDMS-H), 0.89 (s, 9 H,

TBDMS- H), 1.00 - 1.44 (m, 5 H, 4'(5',10',12')-H), 1.59 - 1.77 (m, 3 H, 3'(4',5')-H), 1.95

(m, 1 H, 13'-H), 1.96 (s, 3 H, COCH_3), 1.96 - 2.02 (m, 1 H, 12'-H), 2.16-2.26 (m, 1 H,

10'-H), 2.47 - 2.64 (m, 3 H, 3'(6',13')-H), 3.15 - 3.20 (m, 1 H, 9'-H), 3.77 (m, 1 H, 11'-H),

4.87 (d, $^2J = 2.6$ Hz, 1 H, $=\text{CH}_2$), 4.97 (d, $^2J = 2$ Hz, 1 H, $=\text{CH}_2$). -¹H-NMR (600 MHz,

CDCl_3): $\delta = 0.077$ (s, 6 H, TBDMS-H), 0.87 (s, 9 H, TBDMS-H), 1.04 (dt, $^2J = ^3J_{\text{ax-ax}} =$

13.5 Hz, $^3J_{\text{ax-eq}} = 4$ Hz, 1 H, 6'-H), 1.08 (m, 1 H, 4'-H), 1.14 (q, $^3J = ^2J = 12$ Hz, 1 H,

10'-H), 1.23 (m, 1 H, 12'-H), 1.35 (tq, $^2J = ^3J_{\text{ax-ax}} = 14$ Hz, $^3J_{\text{ax-eq}}=3.5$ Hz, 1 H, 5'-H),

1.56 - 1.64 (m, 2 H, 3'(5')-H), 1.72 (m, 1 H, 4'-H), 1.84 -1.92 (m, 1 H, 13'-H), 1.95 (s, 3

H, COCH_3), 1.93 - 1.98 (m, 1 H, 12'-H), 2.19 (m, 1H, 10'-H), 2.48 (m, 1 H, 3'-H), 2.52 -

2.60 (m, 2 H, 6'(13')-H), 3.17 (m, 1 H, 9'-H), 3.76 (tt, $^3J_{\text{ax-ax}} = 12$ Hz, $^3J_{\text{ax-eq}} = 4$ Hz, 1

H, 11'-H), 4.85 (d, $^2J = 2$ Hz, 1 H, $=\text{CH}_2$), 4.96 (d, $^2J = 1.5$ Hz, 1 H, $=\text{CH}_2$).-¹³C-NMR

(150.82 MHz, CDCl_3 , APT): $\delta = -4.60$ (+, TBDMS- C), 18.16 (-, TBDMS-C), 22.87

(-, C-13'), 23.91 (-, C-4'*), 25.23 (-, C-3'), 25.85 (+, TBDMS-C), 25.85 (+, COCH_3),

27.15 (-, C-5'*), 35.60 (-, C-6'), 35.86 (-, C-12'), 43.64 (-, C-10'), 48.38 (+, C-9'), 68.85

(-, C-7'), 70.80 (+, C-11'), 108.08 (-, $=\text{CH}_2$), 134.42 (-, C-2'), 135.62 (-, C-1'), 156.39

(-, C-8'), 208.43 (-, COCH_3).- MS (EI, 70 eV), m/z (%): 360 (2) [M^+], 317 (32)

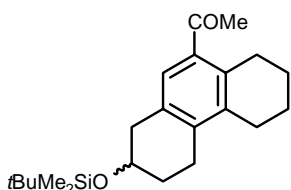
[$\text{M}^+ - \text{COCH}_3$], 303 (4) [$\text{M}^+ - \text{C}(\text{CH}_3)_3$], 228 (4), 211 (3), 185 (100), 159 (4), 143 (7), 129

(5), 73 (6), 43 (3) [$\text{C}_2\text{H}_3\text{O}^+$].- $\text{C}_{22}\text{H}_{36}\text{O}_2\text{Si}$ (360.6): found 360.2485 (HRMS correct).

Fraction VI

1-[12'-(tert-butyl dimethylsilyloxy)tricyclo[8.4.0.0^{2,7'}]]tetradeca-1'(10'),2'(7'),8'-trien-8'-yl]-1-ethanone (158)

The sixth fraction ($R_f=0.35$, 20:1 pentane/diethyl ether) from the plates' top afforded 20 mg (8%) of the title compound as a colorless liquid.-IR



(Film): $\nu = 2958 \text{ cm}^{-1}$, 2927, 2855, 1709, 1681, 1564, 1467, 1431, 1355, 1275, 1252, 1100, 884, 836, 776, 627.- $^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 0.096$ (s, 3 H, TBDMS-H), 0.099 (s, 3 H, TBDMS-H), 0.90 (s, 9 H, TBDMS-H), 1.64 - 1.83 (m, 5 H, 4'(5',13')-H), 2.02 (m, 1 H, 13'-H), 2.53 (s, 3 H, COCH_3), 2.54 - 2.59 (m, 3 H, 3'(14')-H), 2.78 - 2.92 (m, 5 H, 6'(11',14')-H), 4.03 (m, 1 H, 12'-H), 7.19 (s, 1 H, 9'-H).- $^1\text{H-NMR}$ (600 MHz, CDCl_3): $\delta = 0.060$ (s, 3 H, TBDMS-H), 0.069 (s, 3 H, TBDMS-H), 0.88 (s, 9 H, TBDMS-H), 1.64 - 1.70 (m, 2 H, 4'(5')-H), 1.72 - 1.82 (m, 3 H, 4'(5',13')-H), 2.00 (m, 1 H, 13'-H), 2.51 (s, 3 H, COCH_3), 2.52 - 2.62 (m, 3 H, 3'(14')-H), 2.71 - 2.80 (m, 2 H, 11' (14')-H), 2.87 - 2.95 (m, 3 H, 6'(11')-H), 4.03 (m, 1 H, 12'-H), 7.17 (s, 1 H, 9'-H).- $^{13}\text{C-NMR}$ (150.82 MHz, CDCl_3 , APT): $\delta = -4.65$ (+, TBDMS-C), -4.61 (+, TBDMS-C), 18.21 (-, TBDMS-C), 22.67 (-, C-4'), 22.67 (-, C-5'), 25.32 (-, C-14'), 25.87 (+, TBDMS-C), 27.11 (-, C-3'), 28.27 (-, C-6'), 30.11 (+, COCH_3), 32.03 (-, C-13'), 39.40 (-, C-11'), 67.44 (-, C-12'), 127.51 (+, C-9'), 131.88 (-, Aromatic-C), 134.23 (-, Aromatic-C), 136.31 (-, Aromatic-C*), 136.41 (-, C-8*), 138.43 (-, Aromatic-C), 202.74 (-, COCH_3).- MS (EI, 70 eV), m/z (%): 358 (1) [M^+], 301 (100) [$\text{M}^+ - \text{C}(\text{CH}_3)_3$], 285 (7), 227 (7), 185 (15), 75 (13), 43 (8) [$\text{C}_2\text{H}_3\text{O}^+$].- $\text{C}_{22}\text{H}_{34}\text{O}_2\text{Si}$ (358.6): found 358.2328 (HRMS correct).

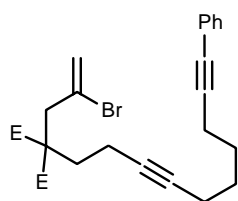
D. Conclusion and abstract

Synthesis of different substituted 2-bromotetradeca-1-ene-7,13-diyne precursors can be easily achieved by using 1,7-octadiyne (**60**).

The cyclization outcome of these precursors depends on the type of substituent at the terminal triple bond. Thus, when the terminal triple bond bears an electron-withdrawing group, such as a methoxycarbonyl group in **110**, a tetracyclic system with an annelated cyclopropane ring, such as **119**, will be formed. However, when the triple bond bears an electron releasing trialkylsilyl or phenyl group, such as in **48**, the thermodynamically most stable aromatic compound, of type **73**, will be formed. When the terminal triple bond bears a proton (unsubstituted) **117** or a group with an aptitude for migration, such as **144**, fulvene systems **166** and tricyclic systems with an *exo*-double bond **146** are being formed, respectively.

The cyclization mechanism of these precursors can go via twofold Heck reactions followed by *5-exo-trig* carbopalladation (Heck-Heck-*5-exo-trig* sequence). The variation in the outcome of these precursors excludes the other possibilities, such as intramolecular Diels-Alder, 6π -electrocyclization and *6-endo-trig* carbopalladation. These mechanistic considerations are illustrated in section 8, page 64, and in the Scheme 61 therein.

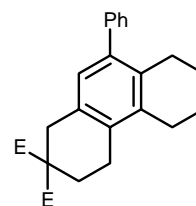
The geminal substitution at the tether linking the vinyl bromide moiety would affect the yield of such precursors (2-bromotetradeca-1-ene-7,13-diyne), but it has no effect on the outcome of the palladium-catalyzed transformations of these precursors.



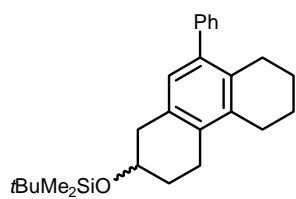
48



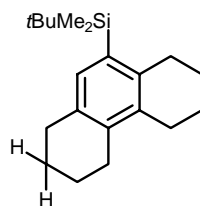
60



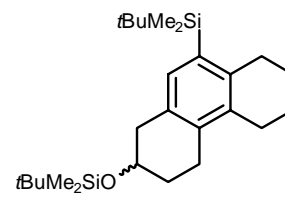
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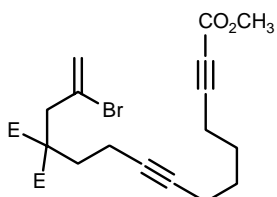
74



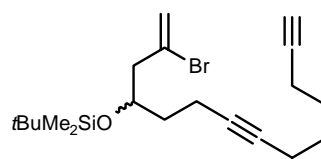
91



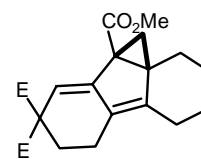
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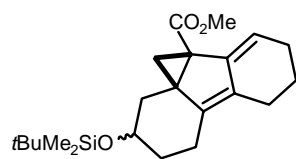
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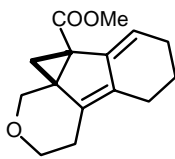
117



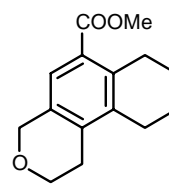
119



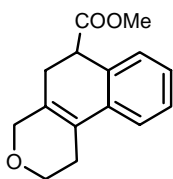
122



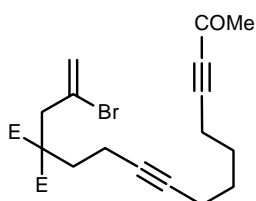
134



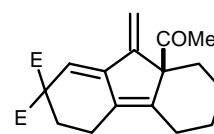
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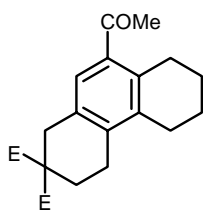
136



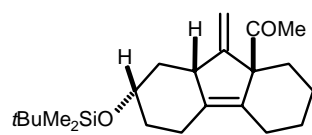
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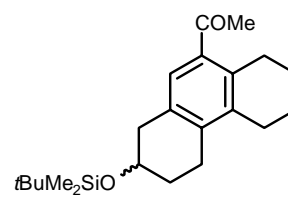
146



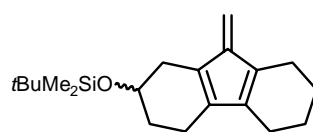
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158



166

E. References and Literature

- [1] E. Negishi; F. Liu in *Metal-Catalyzed Cross-Coupling Reactions* (Eds: F. Diederich; P. J. Stang) WILEY-VCH, Weinheim **1998**, pp. 1-47.
- [2] J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508-524; T. N. Mitchell in *Metal-Catalyzed Cross-Coupling Reactions* (Eds: F. Diederich; P. J. Stang) WILEY-VCH, Weinheim, **1998**, pp. 167-202.
- [3] K. Sonogashira in *Metal-Catalyzed Cross-Coupling Reactions* (Eds: F. Diederich; P. J. Stang) WILEY-VCH, Weinheim, **1998**, pp. 203-229.
- [4] A. Suzuki in *Metal-Catalyzed Cross-Coupling Reactions* (Eds: F. Diederich; P. J. Stang) WILEY-VCH, Weinheim, **1998**, pp. 49-91.
- [5] K. Alder; F. Pascher; A. Schmitz, *Chem. Ber.* **1943**, *76*, 27.
- [6] L. F. Tietze; V. Beifuss; M. Ruther, *J. Org. Chem.* **1989**, *54*, 3120.
- [7] B. M. Trost; D. C. Lee; F. Rise, *Tetrahedron Lett.* **1989**, *30*, 651.
- [8] B. M. Trost; O. J. Gelling, *Tetrahedron Lett.* **1993**, *34*, 8233-8236.
- [9] B. M. Trost; D. C. Lee, *J. Org. Chem.* **1989**, *54*, 2271.
- [10] B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34-42.
- [11] B. M. Trost; J. M. Tour, *J. Am. Chem. Soc.* **1987**, *109*, 5268-5270.
- [12] J. M. Takacs; J. J. Wiedner; B. E. Takacs, *Tetrahedron Lett.* **1990**, *31*, 2865-2868; J. M. Takacs; J. J. Wiedner; B. E. Takacs, *Tetrahedron Lett.* **1993**, *34*, 6219-6222; J. M. Takacs; Y.C. Myoung; L.G. Anderson, *J. Org. Chem.* **1994**, *59*, 6928-6942.
- [13] F. Sato; H. Urabe, in *Titanium and Zirconium in Organic Synthesis* (Ed: I. Marek) WILEY-VCH, Weinheim, **2002**, pp. 319-354.; S. J. Sturla; N. M. Kablaoui; S. L. Bächwald, *J. Am. Chem. Soc.* **1999**, *121*, 1976-1977; for Zirconium see: E. Negishi; S. Huo, in *Titanium and Zirconium in Organic Synthesis* (Ed: I. Marek) WILEY-VCH, Weinheim, **2002**, pp. 1-49.; S. Dixon; R. J. Whitby, in *Titanium and Zirconium in Organic Synthesis* (Ed: I. Marek) WILEY-VCH, Weinheim, **2002**, pp.86-109.
- [14] N. Chanti; N. Furukawa; H. Sakurai; S. Murai, *Organometallics*, **1996**, *15*, 901-903; C. Fernandez-Riva; M. Mendez; A. M. Echavarran, *J. Am. Chem. Soc.* **2000**, *122*,

1221-1222.

- [15] P. Cao,; X. Zhang, *J. Am. Chem. Soc.* **2000**, *122*, 6490-6491.
- [16] K. M. Brummond; J. L. Kent, *Tetrahedron* **2000**, *56*, 3263-3283.
- [17] N. Chanti; H. Inoue; T. Morimoto; T. Muto; S. Nuri, *J. Org. Chem.* **2001**, *66*, 4433-4436.
- [18] B. M. Trost; F. D. Toste; A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067-2096.
- [19] B. M. Trost; F. D. Toste, *J. Am. Chem. Soc.* **2002**, *124*, 5025-5036.
- [20] C. Aubert; O. Buisine; M. Malacria, *Chem. Rev.* **2002**, *102*, 813-834.
- [21] A. de Meijere; F. E. Meyer, *Angew. Chem. Int. Ed.* **1994**, *33*, 2379-2411.
- [22] C. Amatore; A. Justand, *Acc. Chem. Res.* **2000**, *33*, 314-321.
- [23] K. H. Ang; S. Bräse; A. G. Steinig; F. E. Meyer; A. Llebaria,; K. Voigt,; A. de Meijere, *Tetrahedron* **1996**, *52*, 11503-11528.
- [24] J. T. Link; L. E. Overman in *Metal-Catalyzed Cross-Coupling Reactions* (Eds: F. Diederich, P. J. Stang) WILEY-VCH, Weinheim, **1998**, pp. 231-269.
- [25] L. F. Tietze; U. Beifuss, *Angew. Chem. Int. Ed.* **1993**, *32*, 131-163.
- [26] S. E. Denmark; A. Thoraensen, *Chem. Rev.* **1996**, *96*, 137-165.
- [27] D. Nelson; M. M. Cox, *Lehninger Principles of Biochemistry*, third edition, Worth Publishers. New York. **2000**.
- [28] H. Henniges, Dissertation, Universität Goettingen, **1994**.
- [29] J. P. Collman; L. S. Hegedus; J. R. Norton; R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Vally, **1987**, Chapters 3 and 6.
- [30] H. Henniges; F. E. Meyer; U. Schick; F. Funke; P. Parsons; A. de Meijere, *Tetrahedron* **1996**, *52*, 11545-11578.
- [31] Y. Zahang; G. Wu; Angel, G.; E-I. Negishi, *J. Am. Chem. Soc.* **1990**, *112*, 8590-8592.
- [32] B. M. Trost; Y. Shi; *J. Am. Chem. Soc.* **1993**, *115*, 12491-12509.
- [33] S. Schweizer, Dissertation, Universität Goettingen, **1998**.
- [34] S. Schweizer; M. Schelper; C. Thies; P. J. Parsons; M. Noltmeyer; A. de Meijere,; *Synnlett.* **2001**, 920-922.
- [35] F. E. Meyer; H. Henniges; A. de Meijere, *Tetrahedron Lett.* **1992**, *33*, 8039-8042

- [36] J. K. Crandall; W. J. Michaely, *J. Org. Chem.* **1984**, *49*, 4244-4248.
- [37] W. F. Baily, N. M. Wachter-Jurcsak; M. R. Pineau; T. V. Ovaska; R. R. Warren; C. E. Lewis, *J. Org. Chem.* **1996**, *61*, 8216-8228.
- [38] L. Brandsama, *Preparative Acetylenic Chemistry*, Elsevier Verlag, Amestrdam, **1988**
- [39] P. E. Sonnet, *Synthetic Communications*, **1976**, *6(1)*, 21-26.
- [40] J. Clayden; N. Greeves; S. Warren; P. Wothers; *Organic Chemistry*, Oxford University Press, New York, **2001**.
- [41] G. L. Larson; R. J. Klesse, *Org. Chem.* **1985**, *50*, 3627.
- [42] R. M. Coates; S. J. Hobbs, *J. Org. Chem.* **1984**, *49*, 140-152; B. Feringa, *Synthetic Communication*, **1985**, *15(2)*, 87-89.
- [43] A. J. Mancuso; D. Swern; *Synthesis*, **1981**, 165
- [44] E. R. H. Jones; G. Eglinton; M. C. Whiting, *Org. Synthesis*. coll. vol IV. Wiley, New York, **1963**, 755.
- [45] B. S. Furiness; A. J. Hannaford; P. W. G. Smith; A. R. Tatchell, *Vogel's Textbook of Organic Chemistry*. fifth edition, Longman Group, U.K., **1989**.
- [46] F. D. Gunstone; P. J. Sykes, *J. Chem. Soc.* **1962**, 3055-3058.
- [47] T. Mandai; J. Nokami; T. Yano; Y. Yoshinaga; J. Otera; *J. Org. Chem.* **1984**, *49*, 172-174.
- [48] A. Llebaria; Research Report; University of Goettingen. **1993**.
- [49] J. J. Tafariello; E. Trybulski; *J. Org. Chem.* **1974**, *39*, 3378-3384.
- [50] S. Hara; H. Dojo; S. Takinami; A. Suzuki, *Tetrahedron Lett.* **1983**, *24*, 731-734.
- [51] Y. Makioka; Y. Taniguchi; T. Kitamura; Y. Fujiwara; A. Saiki; K. Takaki, *Bull. Soc. Chim. Fr.* **1997**, *134*, 349-355.
- [52] E. J. Corey; A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190.
- [53] C. Thies, Dissertation, Universität Goettingen, **1999**.
- [54] T. D. W. Claridge; *High-Resolution NMR Techniques in Organic Chemistry*. Pergamon, An imprint of Elsevier Science, Amsterdam, **1999**.
- [55] J-E. Bäckvall; R. B. Hopkins; H. Grennberg; M. M. Mader; A. K. Awasthi, *J. Am. Chem. Soc.* **1990**, *112*, 5160-5166.
- [56] R. Grigg, M. Korbes, *Eur. J. Org. Chem.* **2001**, 707-712.
- [57] S. Copper; P. G. Sammes; *J. Chem. Soc. Perkin I.* **1984**, 2407-2413; P. Schiess; P.

Funfschilling, *Tetrahedron Lett.* **1972**, 5195-5198.

[58] See for example : I. W. J. Still; T. Sang; *Tetrahedron Lett.* **1979**, 3613-3614; P. A. Knott; J. M. Mellor, *J. Chem. Soc. Perkin Trans I.* **1972**, 8, 1030-1033.

[59] D. J. Field; D. W. Jones; G. Keen, *J. Chem. Soc. Perkin I.* **1978**, 1050-1058.

[60] T. Nishimura; S. Matsumura; Y. Maeda; S. Uemura, *Tetrahedron Lett.* **2002**, 43, 3037-3039; T. Nishimura; S. Matsumura; Y. Maeda; S. Uemura, *Chem. Commun.* **2002**, 50-51; T. Nishimura; S. Uemura, *J. Am. Chem. Soc.* **2000**, 122, 12049-12050.

[61] M. J. Green; J. P. Britovesk; K. Cavell; B. Skelton; A. White, *Chem. Commun.* **1996**, 1563-1564.

[62] B. Burns; R. Grigg; V. Sridharan; T. Worakun, *Tetrahedron Lett.* **1988**, 29, 4325-4328.

[63] S. Schweizer; Z-Z. Song; F. E. Meyer; P. J. Parsons; A. de Meijere, *Angew. Chem. Int. Ed.* **1999**, 38, 1452-1454.

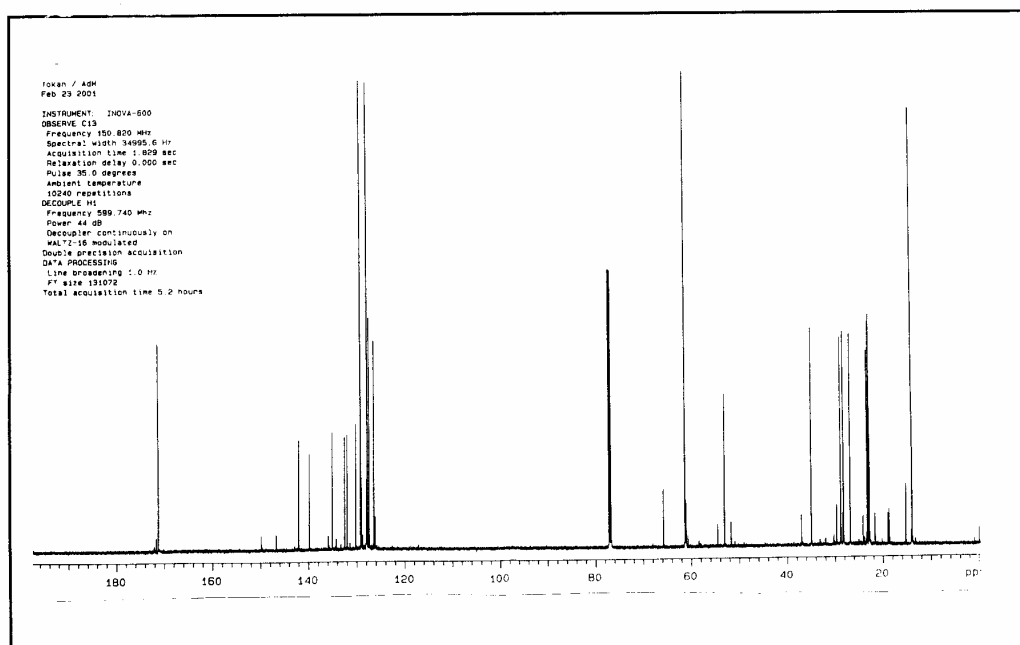
[64] F. E. Meyer; P. J. Parsons; A. de Meijere, *J. Org. Chem.* **1991**, 56, 6487-6488.

[65] S. Girard; P. Deslongchamps, *Can. J. Chem.* **1992**, 70, 1256-1273.

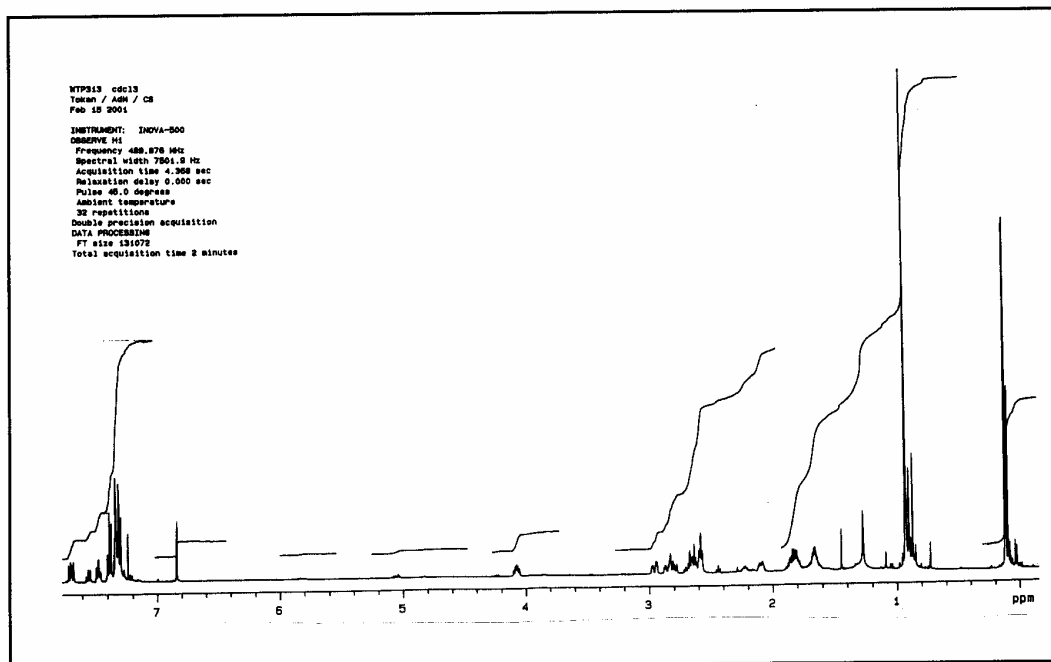
F-Spectral Data



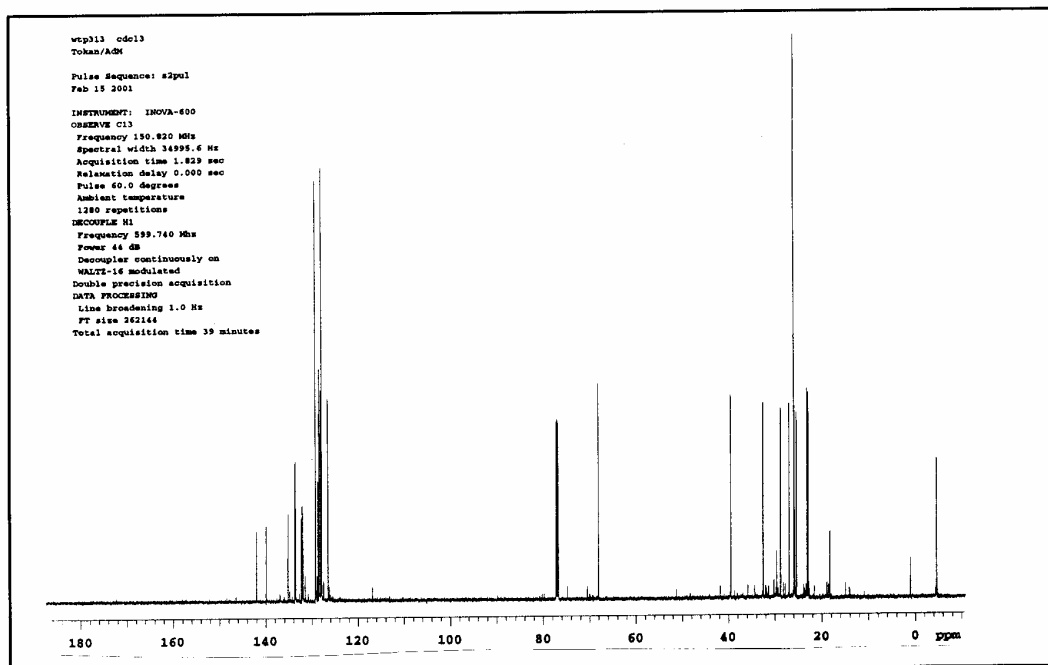
$^1\text{H-NMR}$ spectrum of diethyl 9-phenyltricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene-5,5-dicarboxylate (**73**)



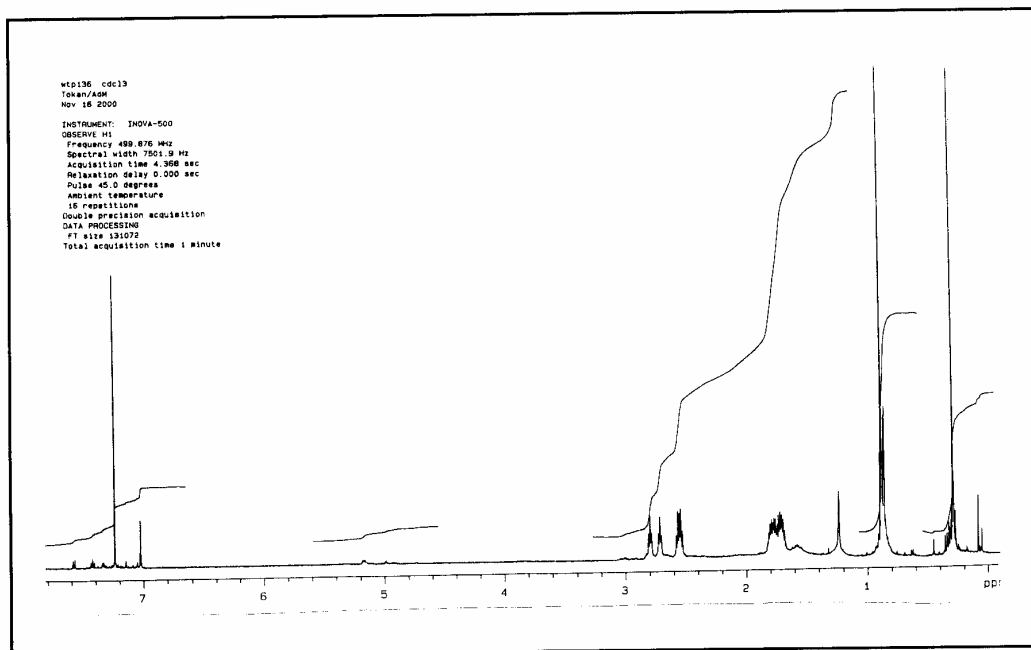
$^{13}\text{C-NMR}$ spectrum of diethyl 9-phenyltricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene-5,5-dicarboxylate (**73**)



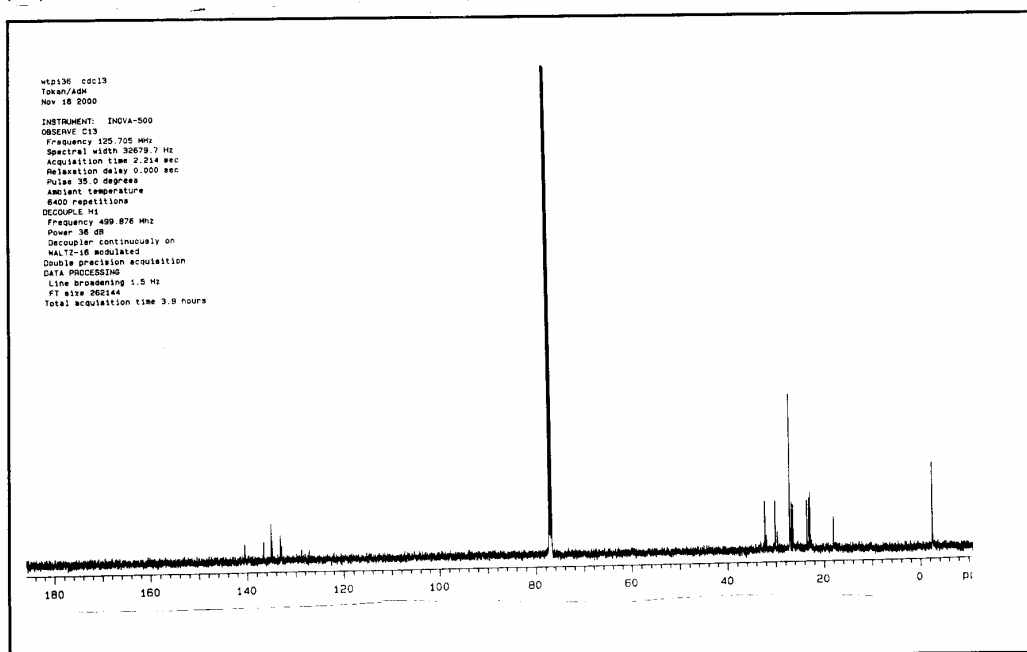
¹H-NMR spectrum of 5-(tert-butyltrimethylsilyloxy)-9-phenyltricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene (74)



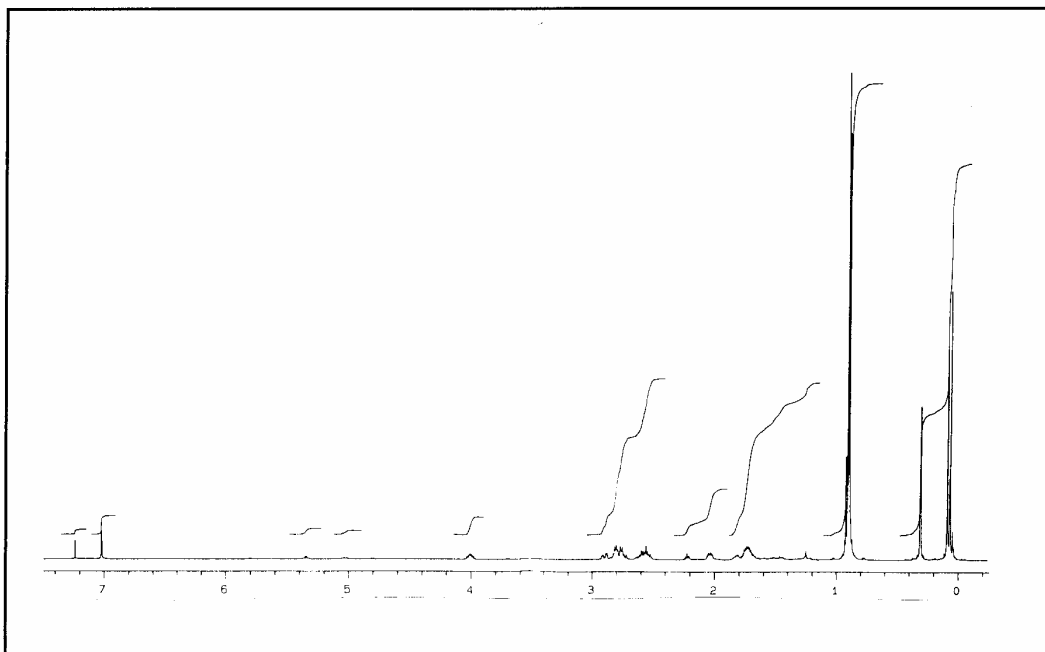
¹³C-NMR spectrum of 5-(tert-butyltrimethylsilyloxy)-9-phenyltricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene(74)



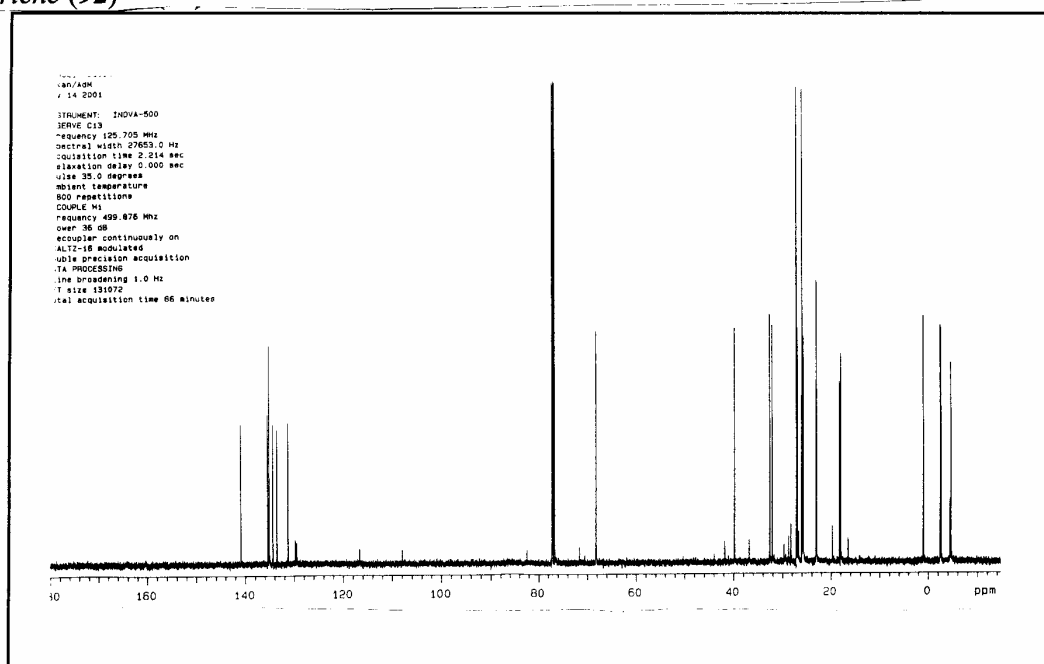
¹H-NMR spectrum of 8-(tert-butyltrimethylsilyl)-tricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene (91)



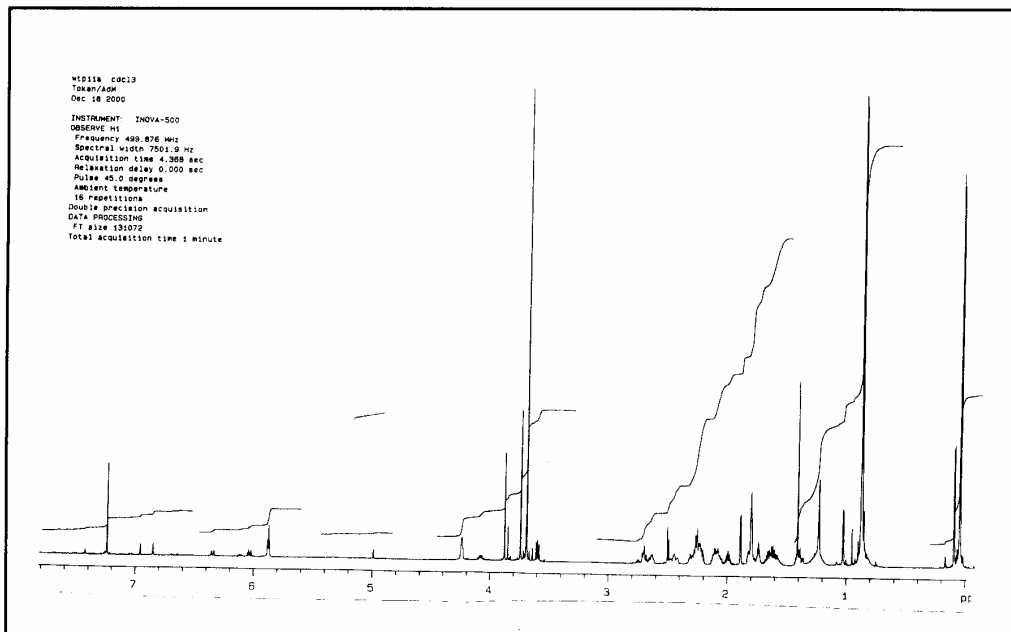
¹³C-NMR spectrum of 8-(tert-butyltrimethylsilyl)-tricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene (91)



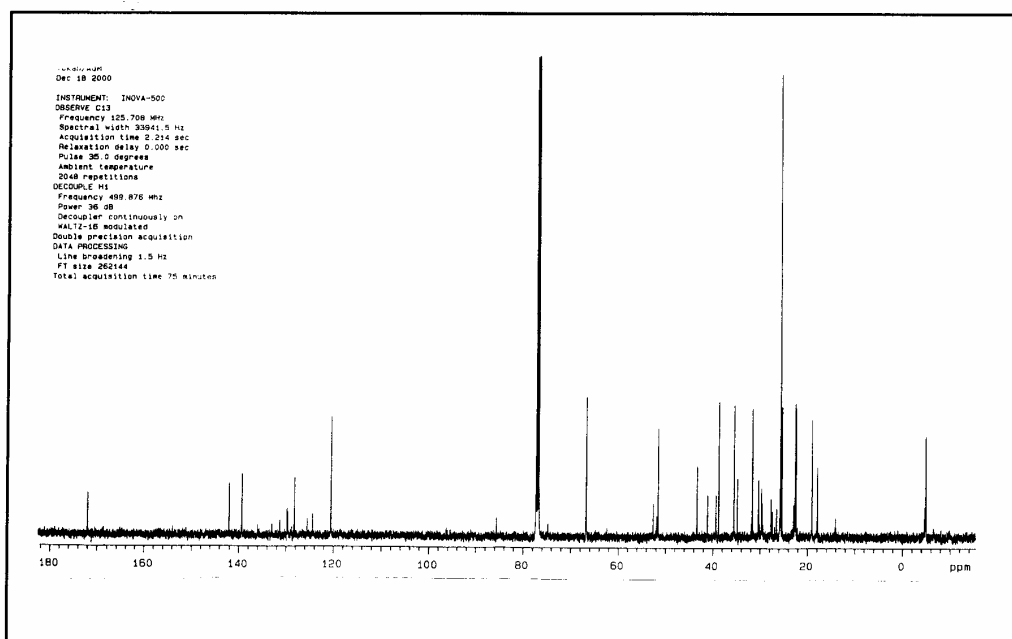
¹H-NMR spectrum of
5-(tert-butyl dimethylsilyloxy)-9-(tertbutyldimethylsilyl)tricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene (92)



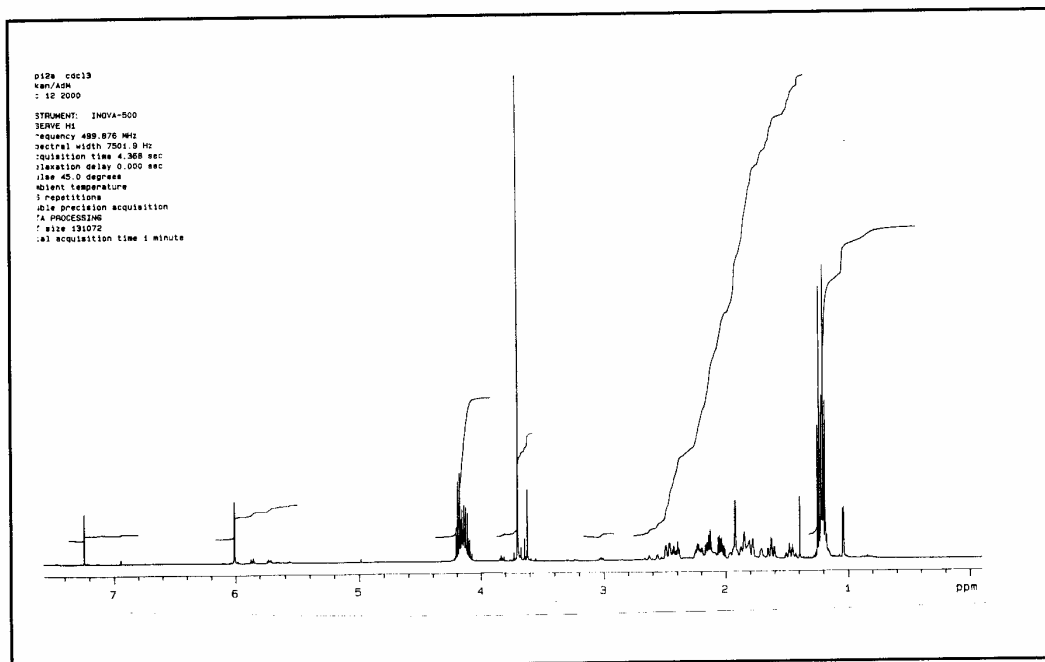
¹³C-NMR spectrum of
5-(tert-butyl dimethylsilyloxy)-9-(tertbutyldimethylsilyl)tricyclo[8.4.0.0^{2,7}]tetradeca-1,7,9-triene (92)



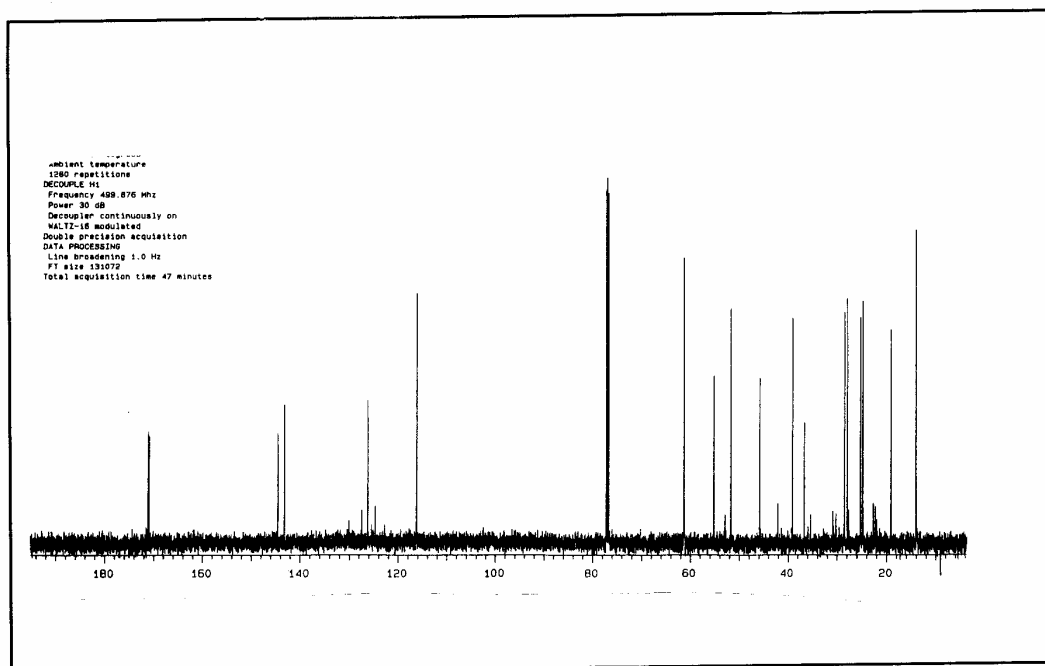
¹H-NMR spectrum of
 methyl 13-(tert-butyl dimethylsilyloxy)tetracyclo[8.4.0.0^{1,3}.0^{4,9}]tetradeca-4,9-dien-3-
 carboxyl-ate (122)



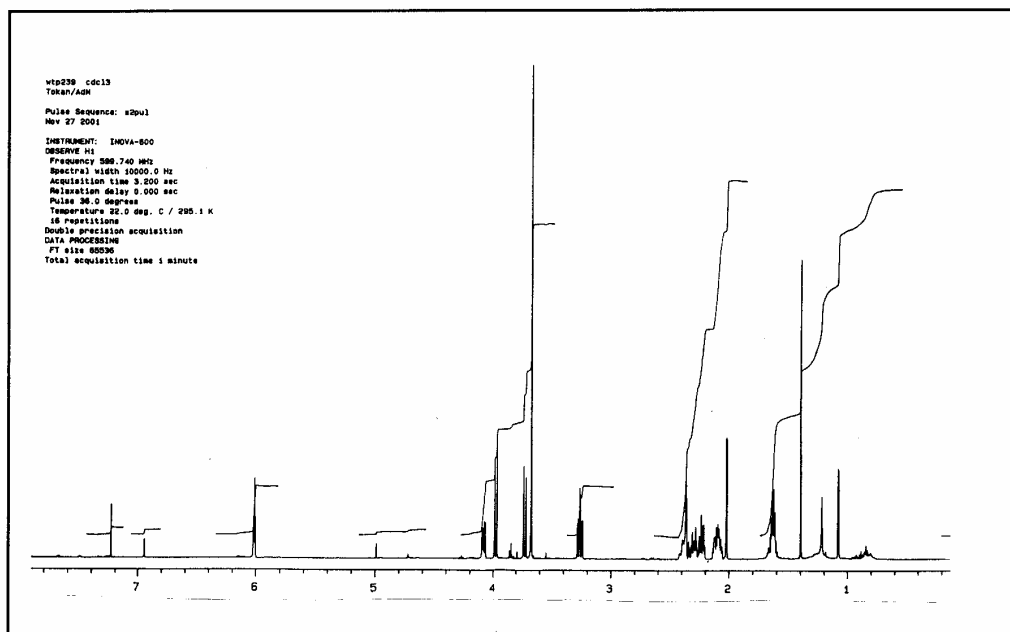
¹³C-NMR spectrum of
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 carboxyl-ate (122)



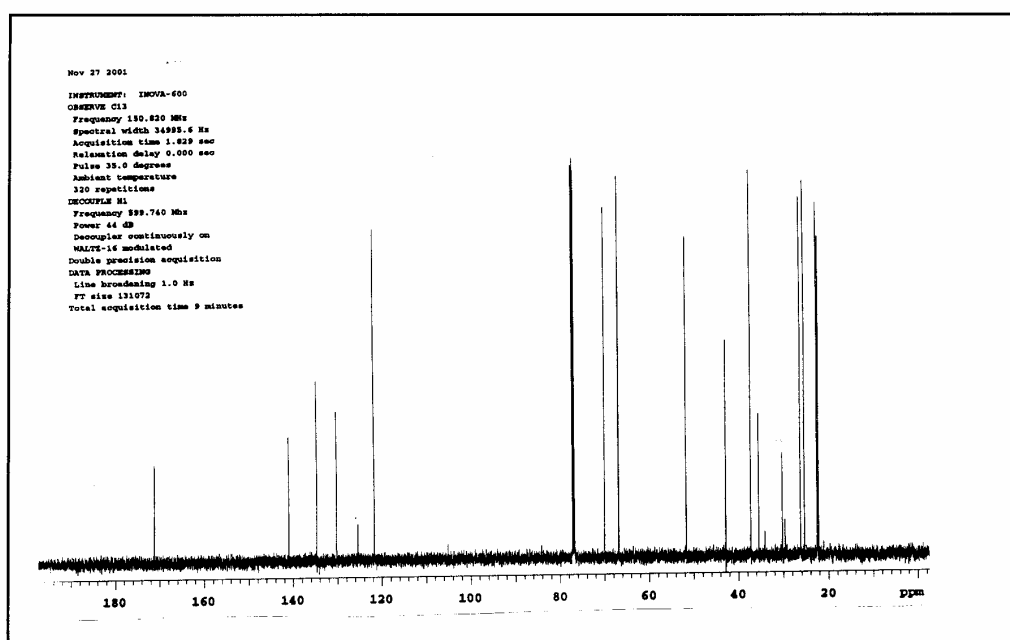
¹H-NMR spectrum of 6,6-diethyl 3-methyl tetracyclo[8.4.0.0^{1,3}.0^{4,9}]tetradeca-4,9-diene-3,6,6-tricarboxylate (119-COOEt)



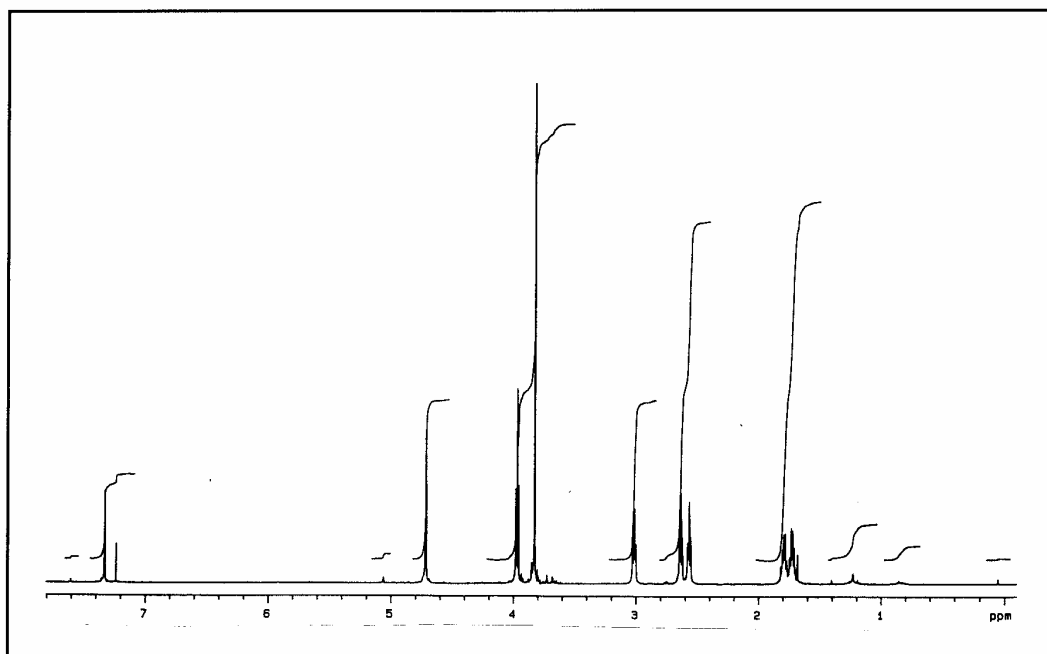
¹³C-NMR spectrum of 6,6-diethyl 3-methyl tetracyclo[8.4.0.0^{1,3}.0^{4,9}]tetradeca-4,9-diene-3,6,6-tricarboxylate (119-COOEt)



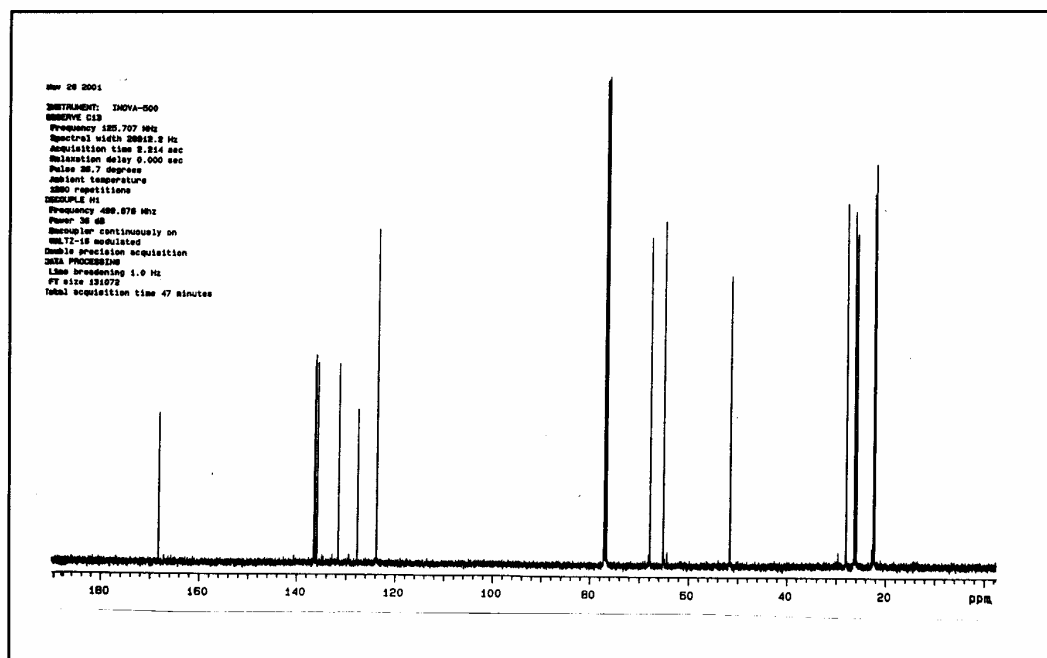
$^1\text{H-NMR}$ spectrum of methyl 1,5,5a,7,8,9-hexahydro-2H-cyclopropa[2,3]indeno[2,1-c]pyran-5a-carboxylate (**134**)



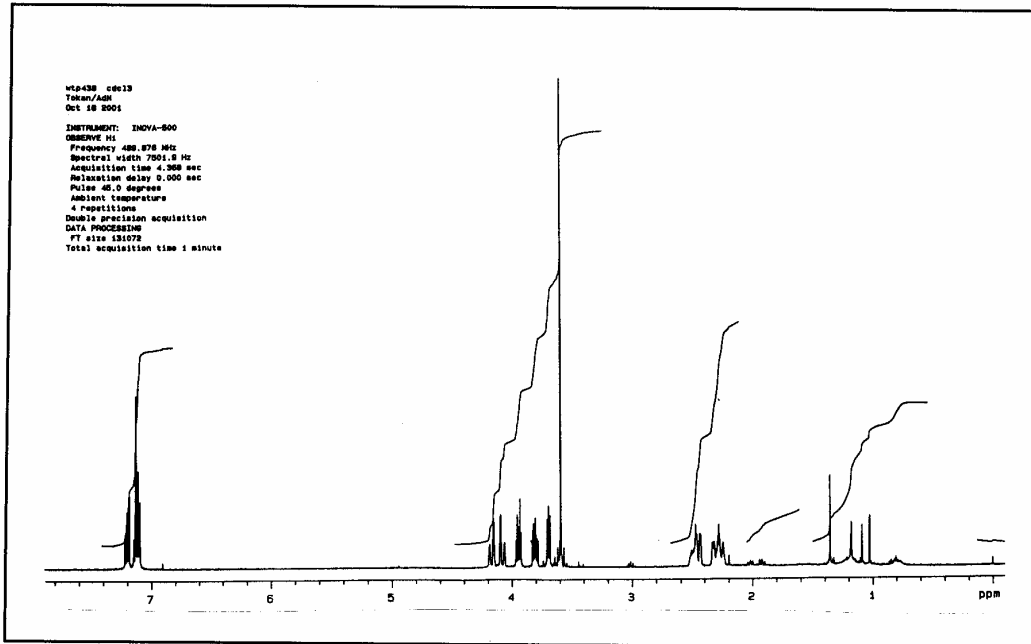
$^{13}\text{C-NMR}$ spectrum of methyl 1,5,5a,7,8,9-hexahydro-2H-cyclopropa[2,3]indeno[2,1-c]pyran-5a-carboxylate (**134**)



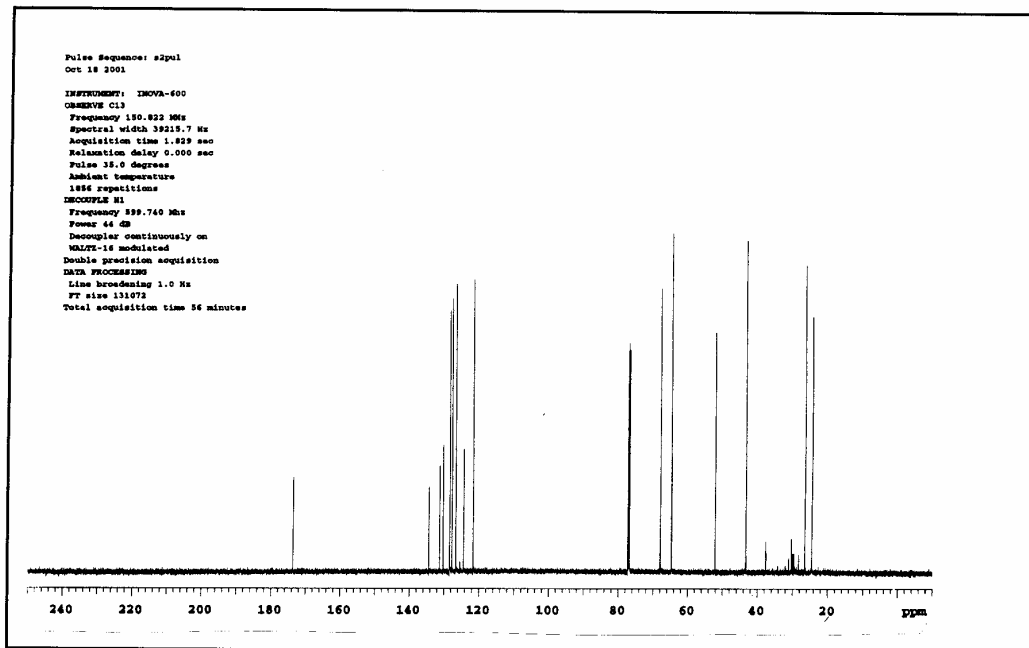
$^1\text{H-NMR}$ spectrum of methyl 1,4,7,8,9,10-hexahydro-2H-benzo[f]isochromene-6-carboxylate (135)



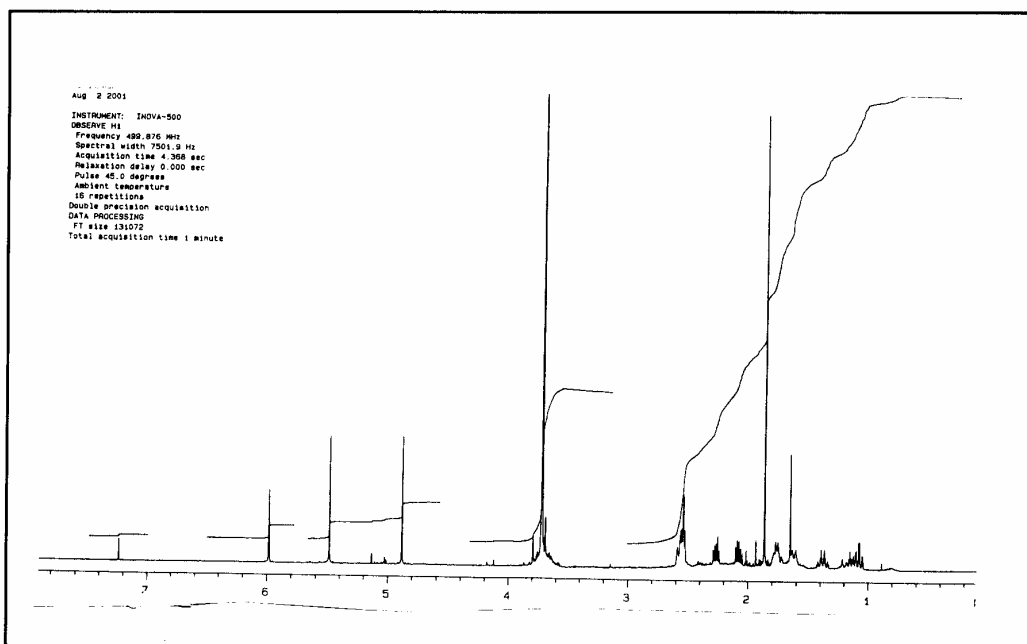
$^{13}\text{C-NMR}$ spectrum of Methyl 1,4,7,8,9,10-hexahydro-2H-benzo[f]isochromene-6-carboxylate (135)



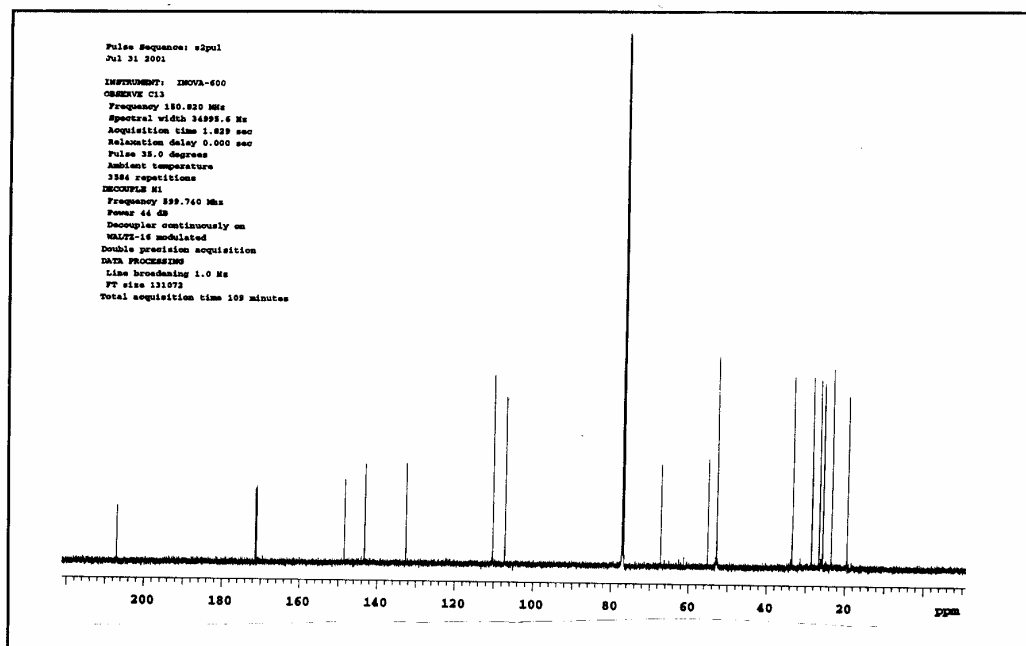
¹H-NMR spectrum of methyl 1,4,5,6-tetrahydro-2H-benzo[ff]isochromene-6-carboxylate (136)



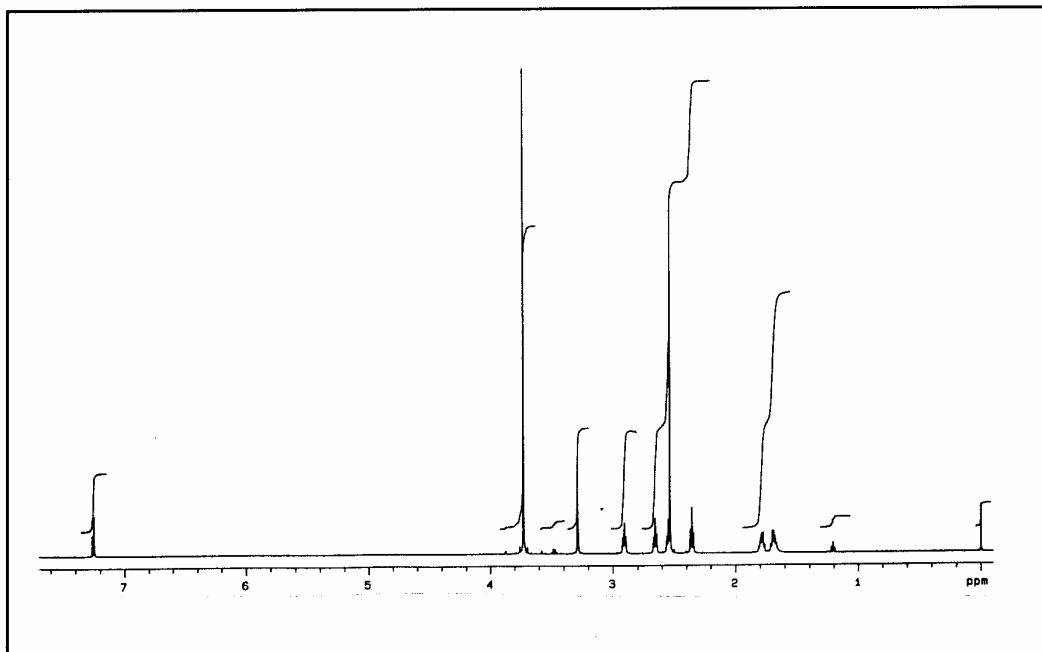
¹³C-NMR spectrum of methyl 1,4,5,6-tetrahydro-2H-benzo[ff]isochromene-6-carboxylate(136)



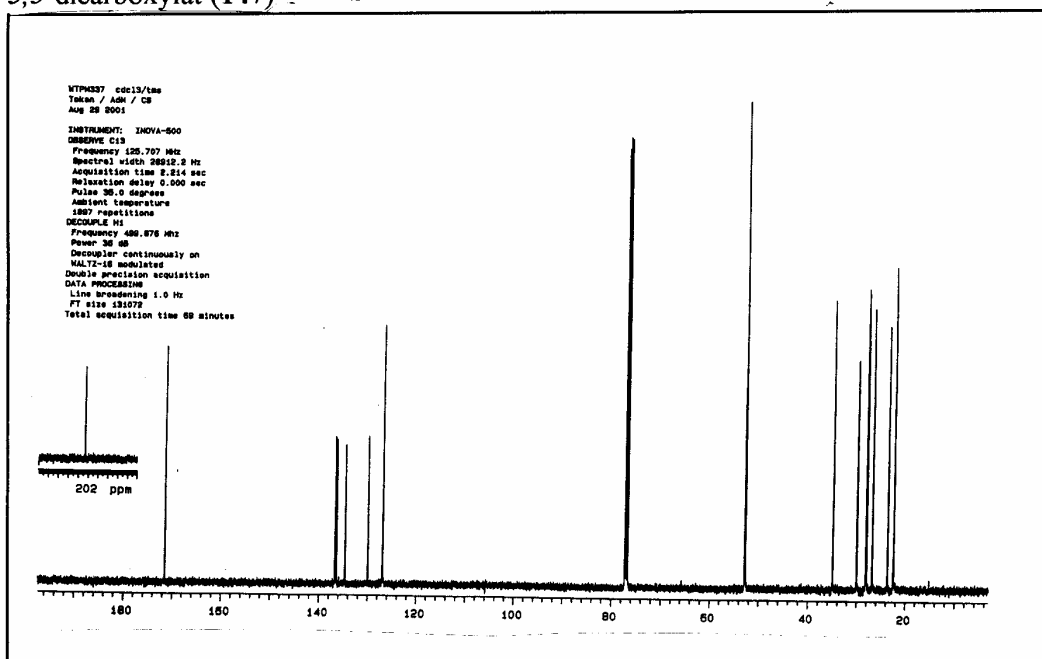
$^1\text{H-NMR}$ spectrum of dimethyl 9-acetyl-8-methylenetricyclo[7.4.0.0^{2,7}]trideca-1,6-diene-5,5-dicarboxylate (146)



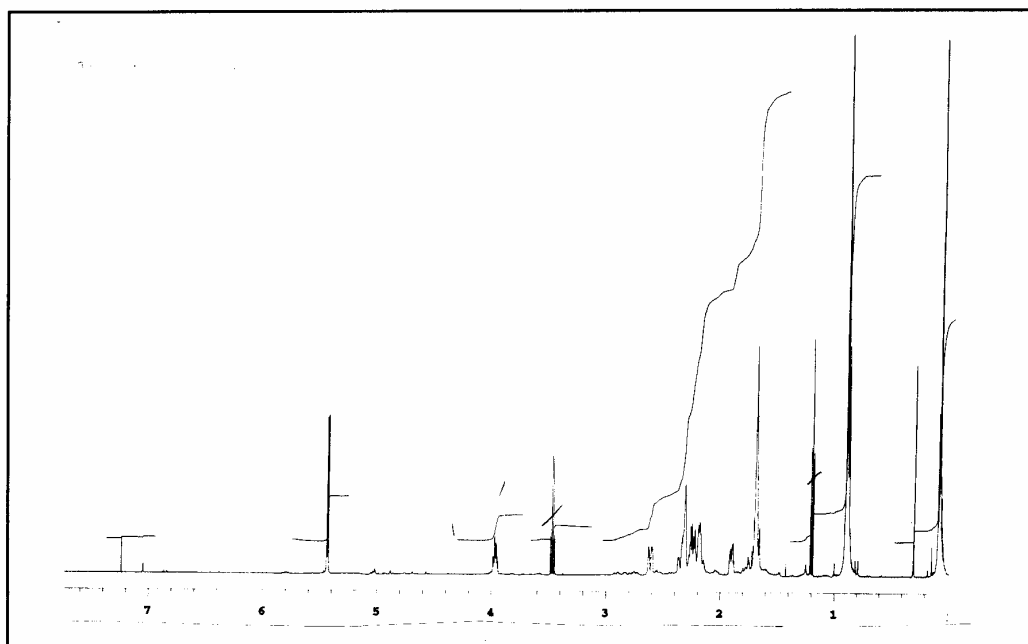
$^{13}\text{C-NMR}$ spectrum of dimethyl 9-acetyl-8-methylenetricyclo[7.4.0.0^{2,7}]trideca-1,6-diene-5,5-dicarboxylate (146)



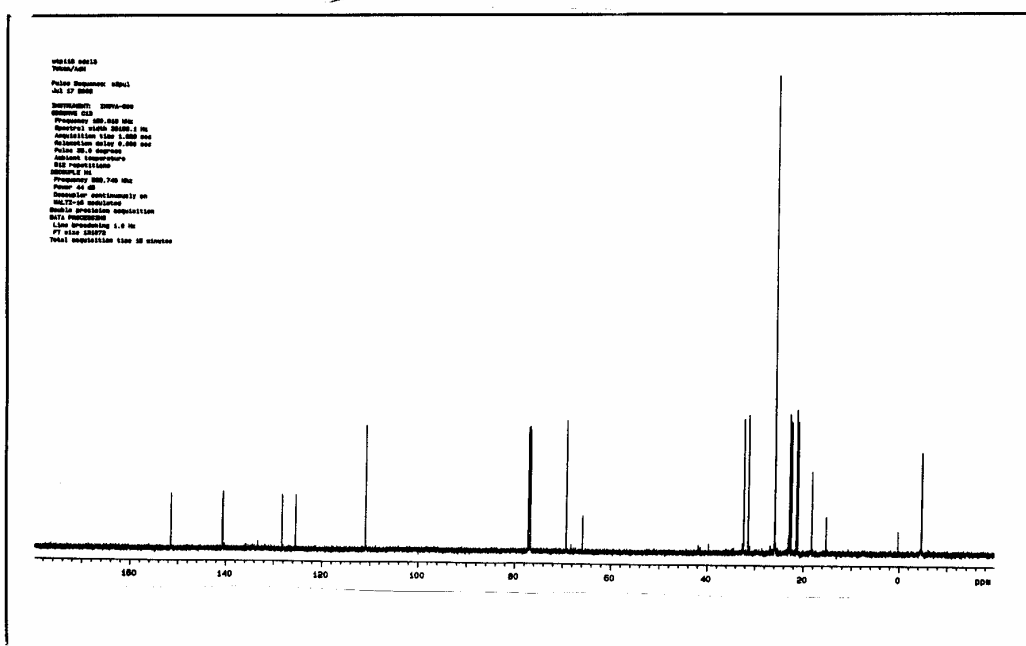
$^1\text{H-NMR}$ spectrum of dimethyl 9-acetyltricyclo[8.4.0.0^{2,7}]tetradeca-1(10),2(7),8-triene-5,5-dicarboxylat (147)



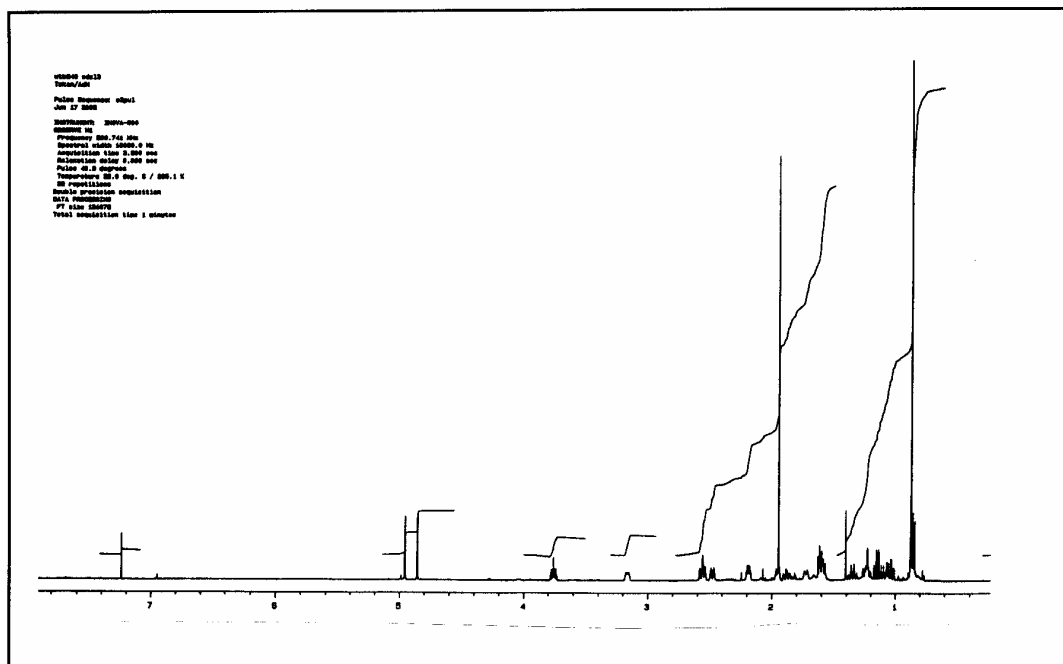
$^{13}\text{C-NMR}$ spectrum of dimethyl 9-acetyltricyclo[8.4.0.0^{2,7}]tetradeca-1(10),2(7),8-triene-5,5-dicarboxylat (147)



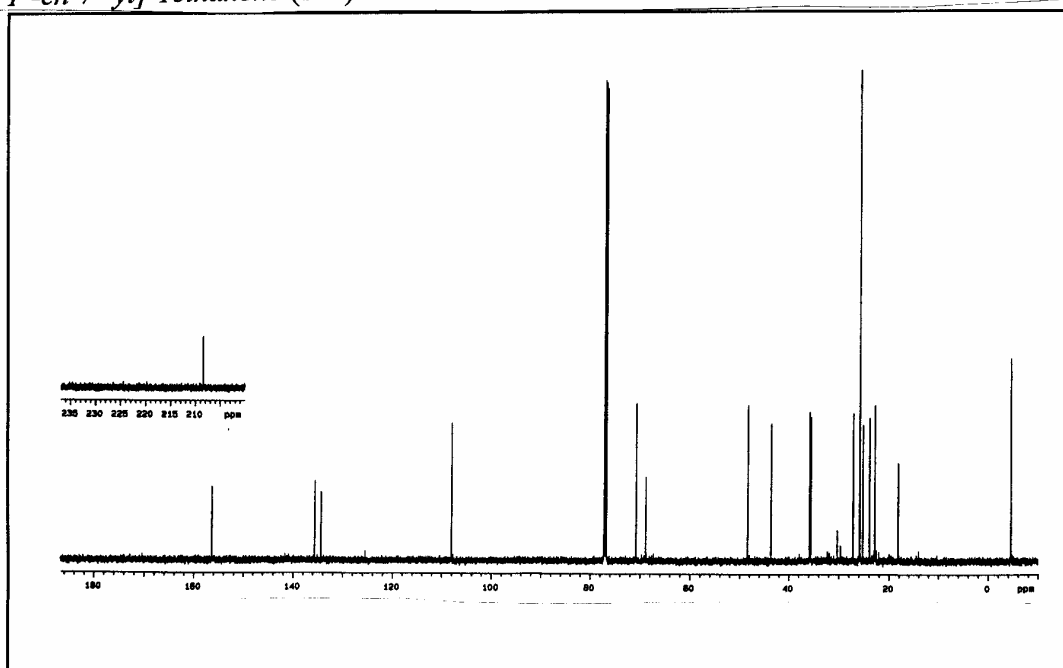
$^1\text{H-NMR}$ spectrum of
5-(*tert*-butyldimethylsilyloxy)-8-methylenetricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-diene(166)



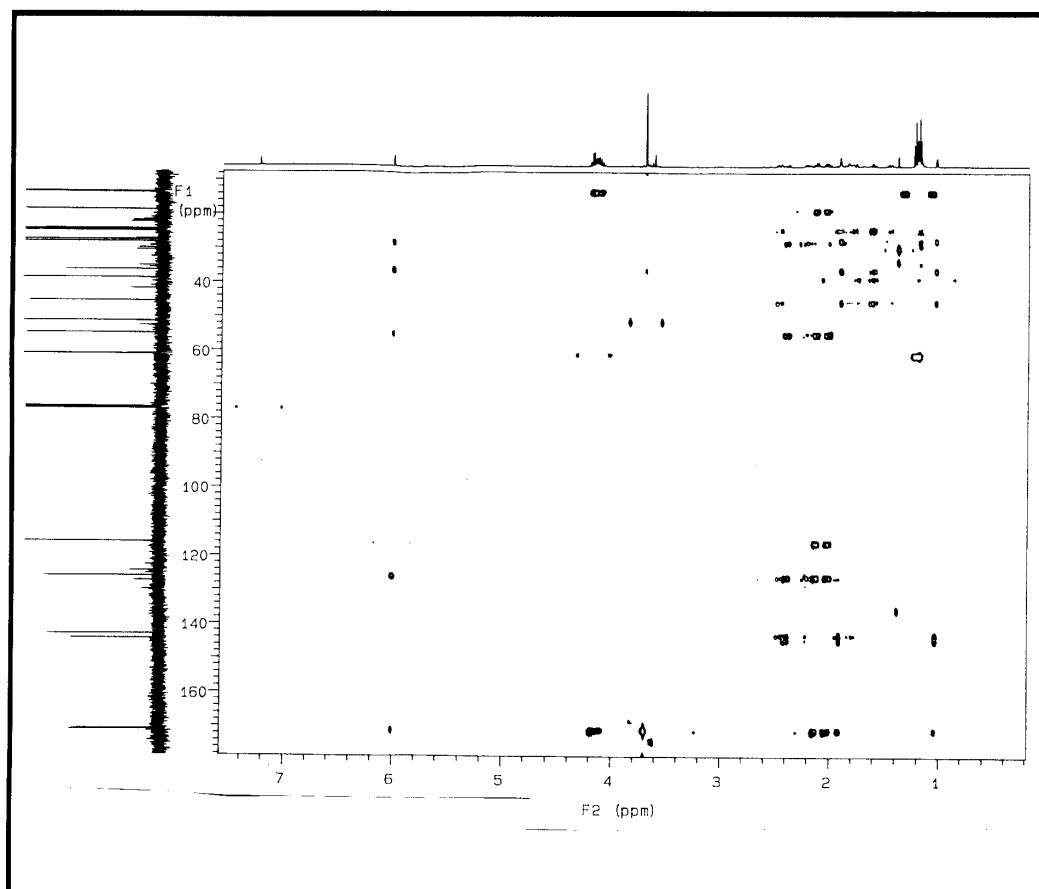
$^{13}\text{C-NMR}$ spectrum of
5-(*tert*-butyldimethylsilyloxy)-8-methylenetricyclo[7.4.0.0^{2,7}]trideca-1(9),2(7)-diene(166)



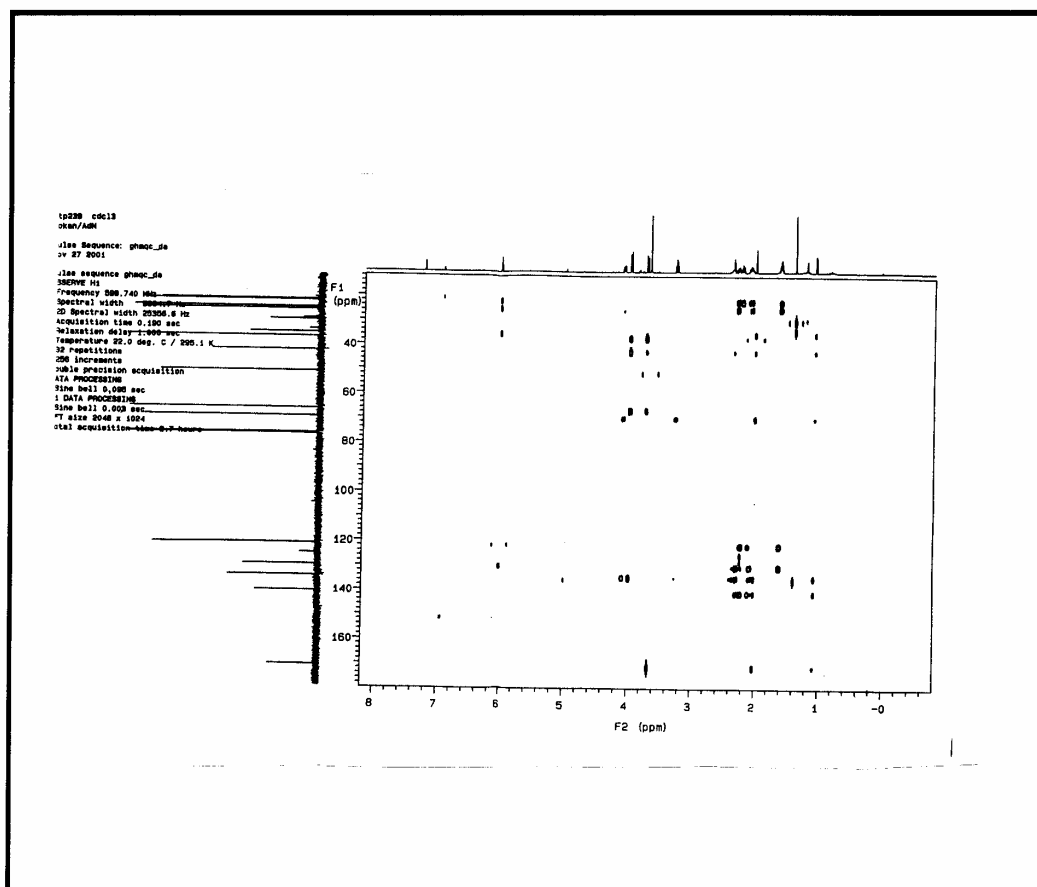
¹H-NMR spectrum of
1-[(7'R,9'S,11'S)-8'-methylene-11'-(tert-butyl dimethylsilyloxy)tricyclo[7.4.0.0^{2;7'}]tridec-1'-en-7'-yl]-1-ethanone (155)



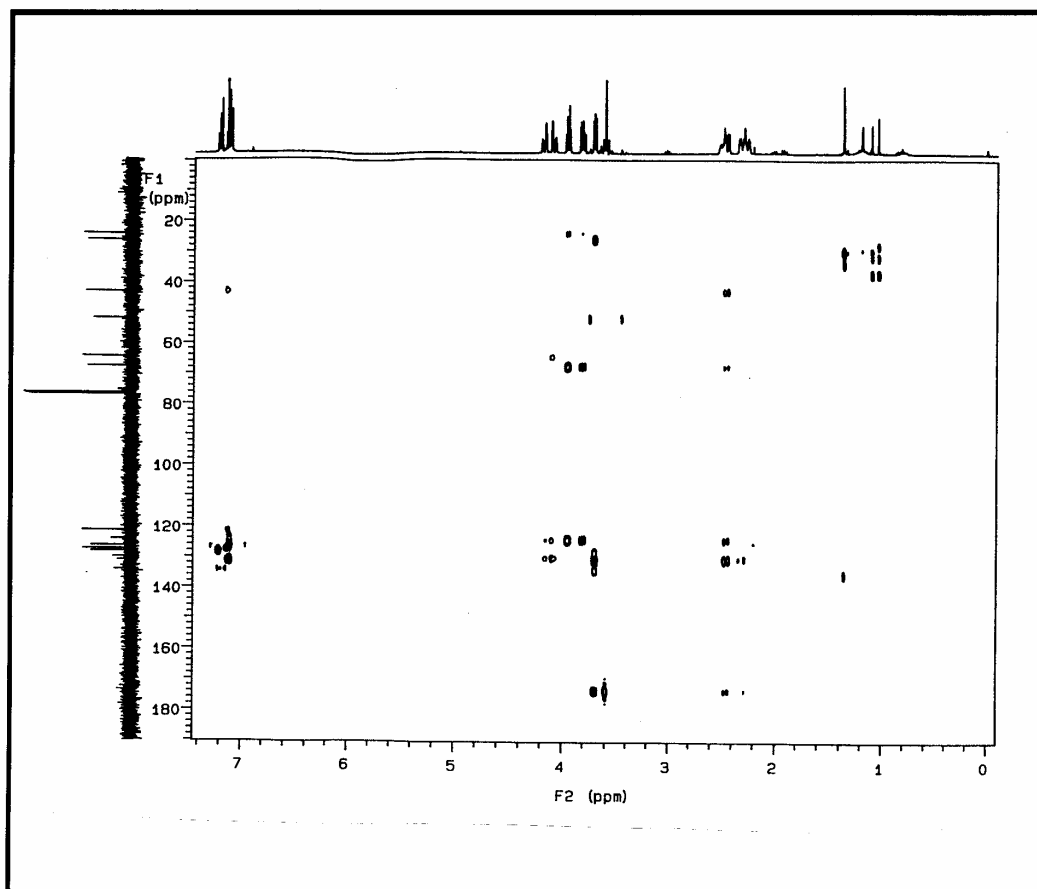
¹³C-NMR spectrum of
1-[(7'R,9'S,11'S)-8'-methylene-11'-(tert-butyl dimethylsilyloxy)tricyclo[7.4.0.0^{2;7'}]tridec-1'-en-7'-yl]-1-ethanone (155)



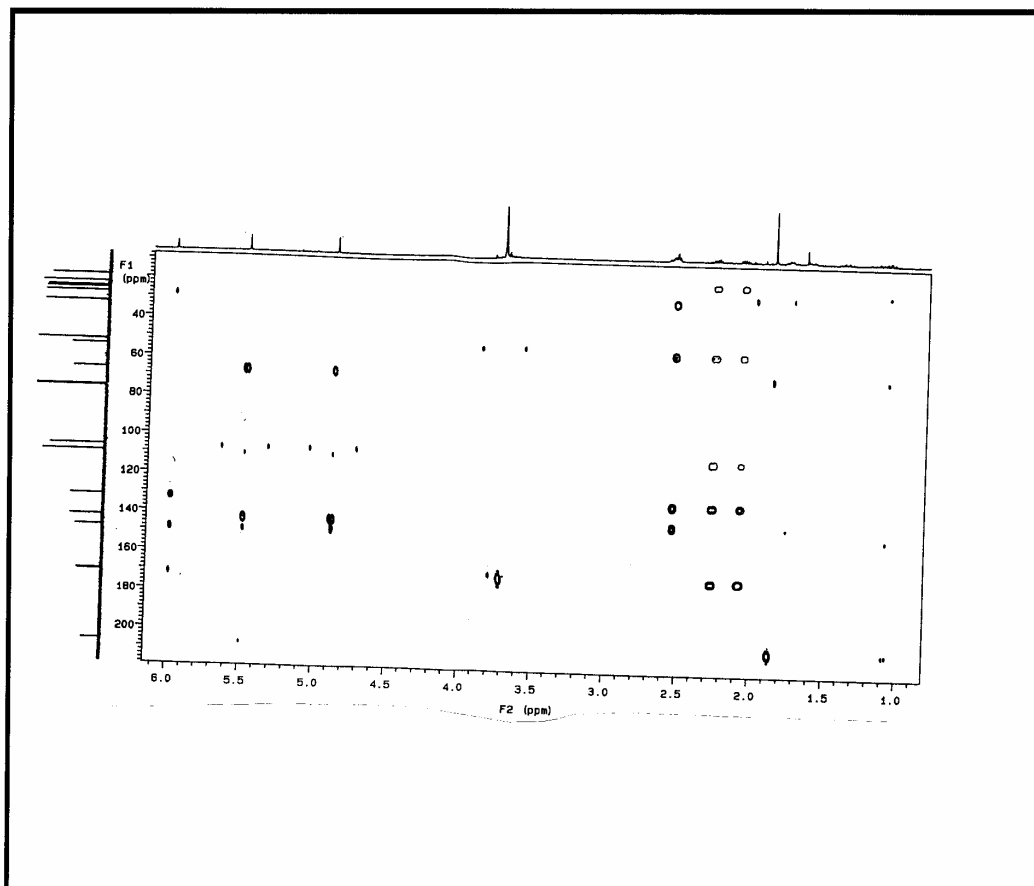
HMBC spectrum of 6,6-diethyl 3-methyl tetracyclo[8.4.0.0^{1,3}.0^{4,9}]tetradeca-4,9-diene-3,6,6-tricarboxylate (119-COOEt)



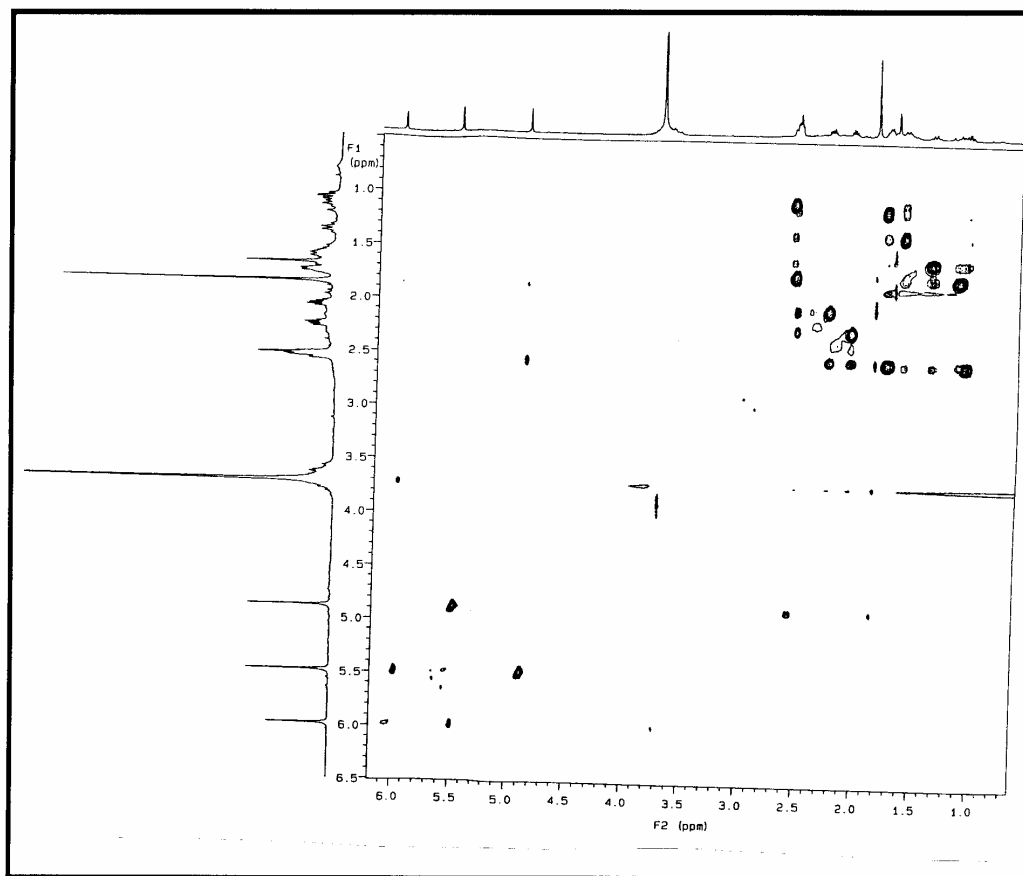
HMBC spectrum of methyl 1,5,5a,7,8,9-hexahydro-2H-cyclopropa[2,3]indeno[2,1-c]pyran-5a-carboxylate (134)



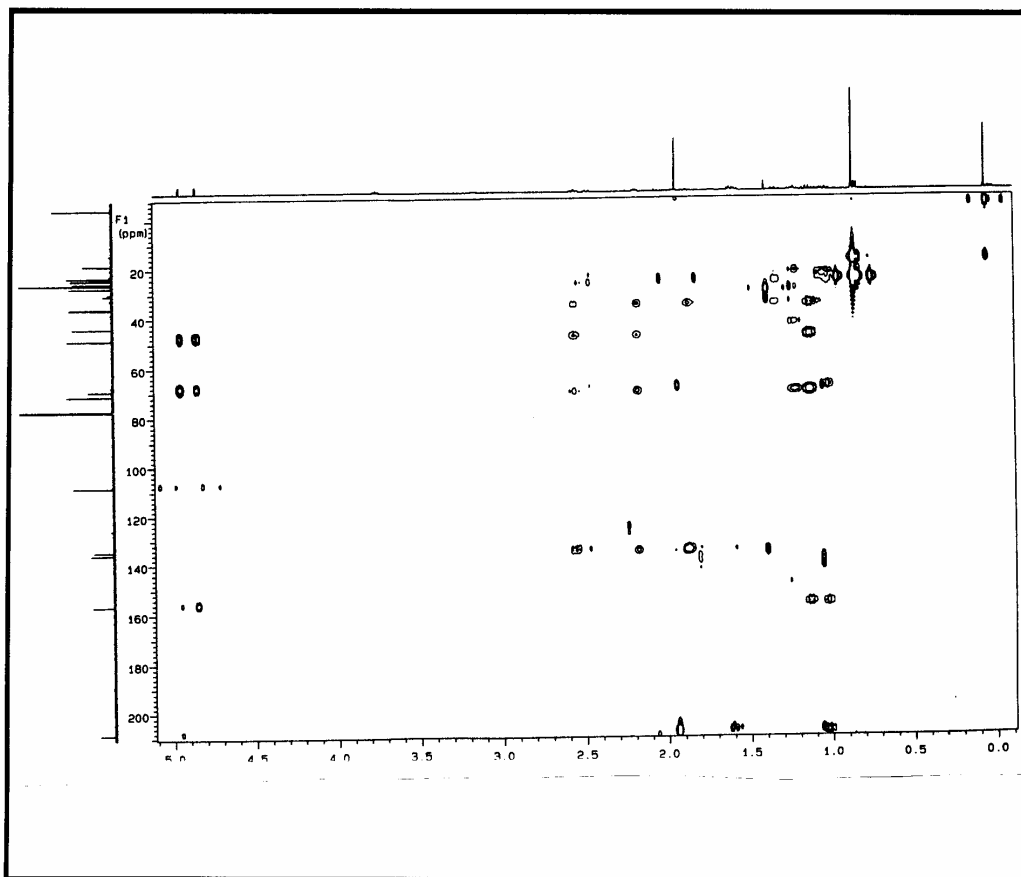
HMBC spectrum of methyl 1,4,5,6-tetrahydro-2H-benzo[f]isochromene-6-carboxylate (136)



HMBC spectrum of dimethyl 9-acetyl-8-methylenetricyclo[7.4.0.0^{2,7}]trideca-1,6-diene-5,5-dicarboxylate (146)



H/H NOESY spectrum of dimethyl 9-acetyl-8-methylenetricyclo[7.4.0.0^{2,7}]trideca-1,6-diene-5,5-dicarboxylate (146)



HMBC spectrum of
1-[(7'R,9'S,11'S)-8'-methylene-11'-(tert-butyl dimethylsilyloxy)tricyclo[7.4.0.0^{2,7'}]tridec-1'-en-7'-yl]-1-ethanone (155)

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Lebenslauf

Ich wurde am 16.9.1968 als Sohn von Mohammad Tokan und seiner Frau Wijdan Mohyar in Amman in Jordanien geboren. Von 1972 bis 1985 besuchte ich das „Islamic Scientific College“ in Amman. Im Anschluss daran besuchte ich die Yarmouk University in Irbid welche ich mit dem Titel B.Sc abschloss. Im Jahr 1990 wechselte ich zur University of Jordan in Amman, wo mir 1995 der Titel M.Sc. in Chemie verliehen wurde. Von 1995 bis Ende 1998 war ich als „faculty member“ des Medical Science Fachbereichs der Al Isra University in Amman angestellt. Seit Februar 1999 fertige ich unter der Leitung von Herrn Prof. Dr. Armin de Meijere meine Doktorarbeit an.