CARBON-CARBON BOND FORMATION. REACTIONS OF ALKENYLTRIMETHYLSTANNANES MEDIATED BY COPPER(I) SALTS

BY

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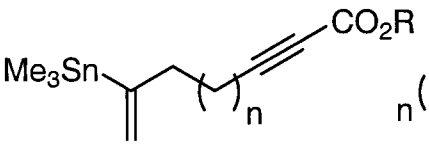
ABSTRACT

The work in this thesis is described in two sections. In the first section, the conjugate addition of alkenyltrimethylstannane functions to α,β-alkynic esters mediated by copper(I) chloride are discussed. An experimental protocol employing copper(I) chloride and acetic acid in *N,N*-dimethylformamide was developed to effect the stereoselective conversion of the precursors **80** and **178-185** into the monocyclic compounds **81** and bicyclic compounds **186-193**, respectively. The intramolecular copper(I)-mediated conjugate addition of aryltrimethyl stannane functions to α,β-alkynic esters was also explored. A variety of bicyclic compounds of general structure **89** that each incorporate an aromatic ring were prepared by this method. α,β-Alkynic aldehydes and α,β-alkynic ketones were shown to function as viable Michael acceptors in the conversion of **233** and **235** into **236-237** and **238-239**, respectively. The catalytic nature of the copper(I) chloride in the reaction was also demonstrated.

In the second part of this thesis, the copper(I) chloride-mediated oxidative coupling of alkenyltrimethylstannane and aryltrimethylstannane functions is discussed. The intermolecular homocoupling of β-trimethylstannyl-α,β-unsaturated ketones **100** produced the structurally unusual diketones **101** upon the treatment of the precursors with copper(I) chloride. The synthesis of the 5-, 6-, and 7-membered ring compounds **105**, **107**, **109**, **111**, and **113** from the precursors **104**, **106**, **108**, **110**, and **112,** respectively, was accomplished by use of the intramolecular variant of the coupling reaction. The scope of the methodology was extended to include the formation of 9-membered and 10-membered ring compounds of general structure **115**.



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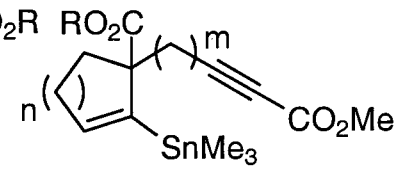
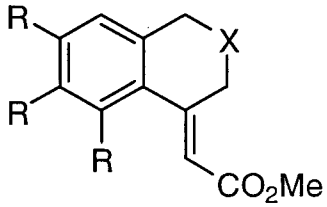
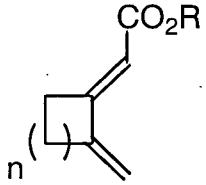


178-185



R = H, Me, or OMe
X = O or $C(CO_2Et)_2$

89



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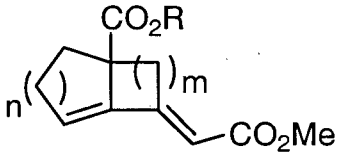

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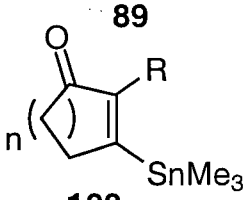

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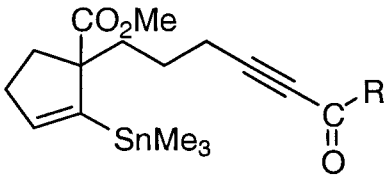

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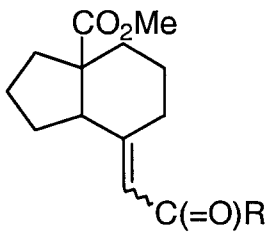
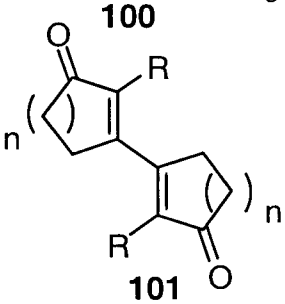
235 R = Me



236,237 R = H
238,239 R = Me



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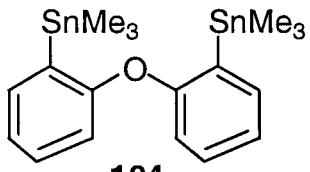

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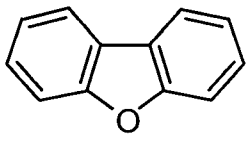

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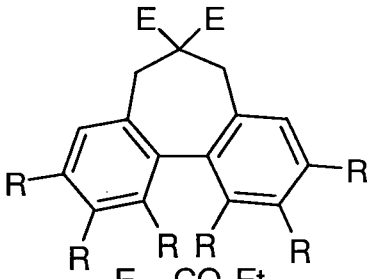
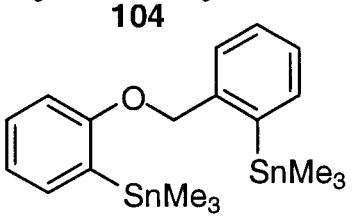


E = CO_2Et

111



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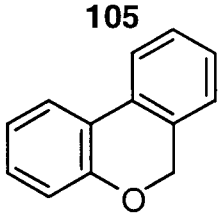

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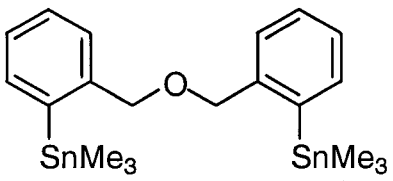

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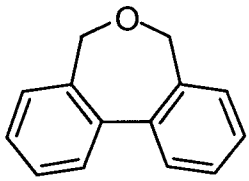

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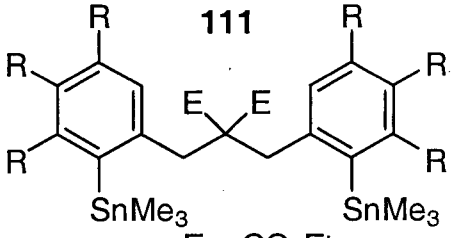
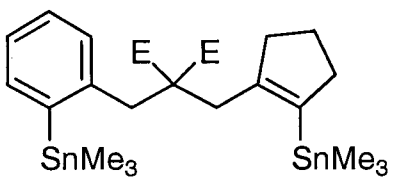


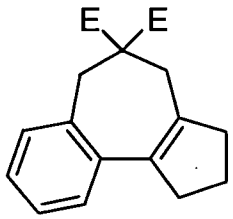
E = CO_2Et

110



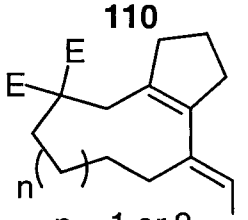
E = CO_2Et

112



E = CO_2Et

113



n = 1 or 2
E = CO_2Et

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LIST OF GENERAL PROCEDURES

LIST OF ABBREVIATIONS

α	-	1,2 relative position
Ac	-	acetyl
anal.	-	analysis
APT	-	attached proton test
β	-	1,3 relative position
Bn	-	benzyl
bp	-	boiling point
br	-	broad
Bu	-	butyl
°C	-	degrees Celsius
calcd.	-	calculated
cm	-	centimeter
COSY	-	(^{1}H-^{1}H) - homonuclear correlation spectroscopy
C-x	-	carbon number x
d	-	doublet
δ	-	chemical shift in parts per million from tetramethylsilane
Δ	-	heat
DIBAL	-	diisobutylaluminum hydride
DMF	-	*N,N*-dimethylformamide
DMI	-	1,3-dimethyl-2-imidazolidinone
DMPU	-	*N,N'*-dimethylpropyleneurea
DMS	-	dimethyl sulfide
DMSO	-	dimethyl sulfoxide
E	-	entgegen (configuration)
ed.	-	edition
Ed.	-	editor
e.g.	-	*exempli gratia* (for example)

equiv - equivalent(s)
Et - ethyl
g - gram
gc - gas-liquid chromatography
h - hour(s)
HMPA - hexamethylphosphoramide
H-x - hydrogen number x
Hz - Hertz
IR - infrared
J - coupling constant in hertz
$^{n}J_{Sn-H}$ - n bond coupling for tin and proton nuclei in Hertz
LDA - lithium diisopropylamide
m - multiplet
m - meta
M - molar
Me - methyl
mg - milligram(s)
MHz - megahertz
min - minute(s)
mL - milliliter(s)
μL - microliter(s)
mm - millimeter(s)
mmol - millimole(s)
mol. - molecular
mp - melting point
NMP - *N*-methylpyrrolidone
nmr - nuclear magnetic resonance
noed - nuclear Overhauser effect difference
o - ortho
pg - page(s)
p - para

PCC	-	pyridinium chlorochromate
Ph	-	phenyl
ppm	-	parts per million
PPTS	-	pyridinium *p*-toluenesulfonate
Pr	-	propyl
q	-	quartet
rt	-	room temperature
s	-	singlet
t	-	triplet
t	-	tertiary
TBAF	-	tetrabutylammonium fluoride
TBS	-	*tert*-butyldimethylsilyl
tert	-	tertiary
THF	-	tetrahydrofuran
tlc	-	thin layer chromatography
TMEDA	-	*N,N,N',N'*-tetramethyleneethylenediamine
-ve	-	negative
Z	-	zusammen (configuration)
•	-	coordination or complex

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank my graduate research supervisor Dr. Edward Piers for his guidance and for the opportunity to join his research group. The contribution of all members of the Piers research group, who have made my stay a pleasurable and exciting experience, is gratefully acknowledged. For listening to me chatter incessantly and inanely over many years, the patience of Al Kaller, Serge Boulet, Rob Britton, Shawn Walker, Elizabeth Cheu, Alex Wong, Gay Yuyitung, and Krystyna Skupinska is particularly noted. The assistance of the support staff at the UBC chemistry department is acknowledged.

A special thanks goes to Patricia Gladstone who was not only a mentor and a labmate but also a best friend.

The extraordinary support and encouragement from Ipi Yuyitung is also immensely appreciated.

Lastly, this thesis is dedicated to my parents for always being there.

I. INTRODUCTION

1. General

Research in the area of synthetic organic chemistry can be generally divided into two central themes. In the first theme, the research is target-based and a particular substance is synthesized from simple, commercially available starting materials. By performing a sequence of transformations that modify or combine various existing fragments, more complex structures are obtained until the desired final product or target is made. The targets chosen for synthesis may be of industrial value, such as monomers or plant growth hormones, of medicinal value, or simply chosen for esthetic reasons. The final products of the synthesis may also serve to confirm constitutional and stereochemical assignments. For products that exhibit interesting pharmacological or biological activity, the process often culminates in the total synthesis of a natural product or an analog thereof. This involves the construction of molecules that exist in nature from terrestrial or marine origin.

In order to construct a structurally complex substance, a series of reactions, each employing a substrate and a reagent to perform the desired conversion, must be employed. Consequently, the second major theme of synthetic organic chemistry is concerned with discovering and developing new reagents and methods for synthesis. Such methodological studies, leading to new protocols for the construction and manipulation of the bonds between carbon and other elements, are of major interest to the practicing organic chemist.

A desirable chemical transformation is a reaction that is high yielding, occurs under mild reaction conditions, and employs cheap, non-hazardous starting materials and reagents. For certain reactions, a high degree of chemoselectivity, regioselectivity, enantioselectivity, or diastereoselectivity may be required. Many transformations that presently exist or that synthetic organic chemists may desire to carry out are inefficient or

simply not possible with known procedures. A great deal of effort is spent on developing new reagents and synthetic methods to satisfy some of these goals.

As new protocols and reactions are developed, unique or more efficient access to potentially valuable compounds becomes possible. In particular, an important application of newly developed reactions is the synthesis of natural products or analogs, in the hopes of discovering new or more effective therapeutic agents. Another use of new processes is the application of the methodology to large-scale industrial chemical preparations. Also important, in this era of environmental responsibility, is the search for environmentally safer alternatives to known reactions and industrial procedures that employ toxic reagents and produce unwanted byproducts or hazardous effluent. An enormous amount of time and resources is spent finding viable and better alternatives to existing processes.

Alongside the discovery and use of a reaction is the mechanistic understanding that underlies the transformation. Methodological studies provide the scope and limitations of a reaction, with respect to both the substrate and the reagent, and, in some instances, may give insight into the mechanistic pathway that may be involved. Indeed, a greater understanding of how a reaction occurs can often lead to proposing and developing reaction conditions that improve and expand the usefulness of the process. Thus, the practicing organic chemist is supplied with a rationale to attempt alternative conditions in the laboratory to achieve a more desirable outcome.

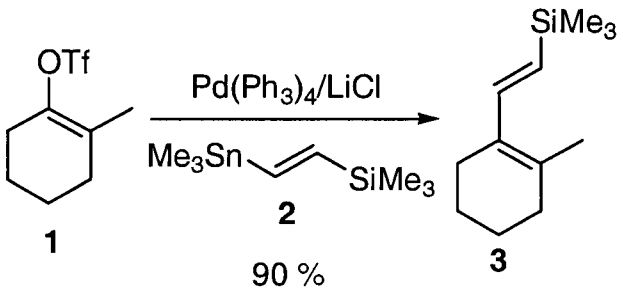
2. Background

2.1 General Background

One of the most well known transition metal-mediated organic transformations is the Stille coupling reaction.[1] Formulated in general terms as shown in equation 1, the reaction cross-couples a tetraorganostananne ($RSnR'_3$) with an appropriate electrophile (R"-X) and is catalyzed by a palladium(0) complex. The structure of the organostananne partner that participates in the reaction can be quite varied and may incorporate alkenyl, alkynyl, allyl, aryl, and benzyl groups. Alkyl groups transfer at the slowest rate and

hence act as the nontransferable or dummy ligands (R') when a ligand (R) that participates at a faster rate is present.[2] The electrophile is often an alkenyl halide or alkenyl triflate but acid chlorides, allyl halides, aryl halides, benzyl halides, and aryl triflates have been used as well. An illustrative example is given in equation 2.[1a]

$$RSnR'_3 + R''\text{-}X \xrightarrow{Pd(0)} R\text{-}R'' + XSnR'_3 \quad (1)$$



(2)

The Stille reaction is thought to proceed via a pathway displayed in a general manner in Figure 1.[1a] The reaction is believed to be initiated by the (reversible) loss of a pair of ligands from the tetracoordinate palladium(0) species (PdL_4) to form a coordinatively unsaturated species (PdL_2). In the presence of the appropriate electrophile

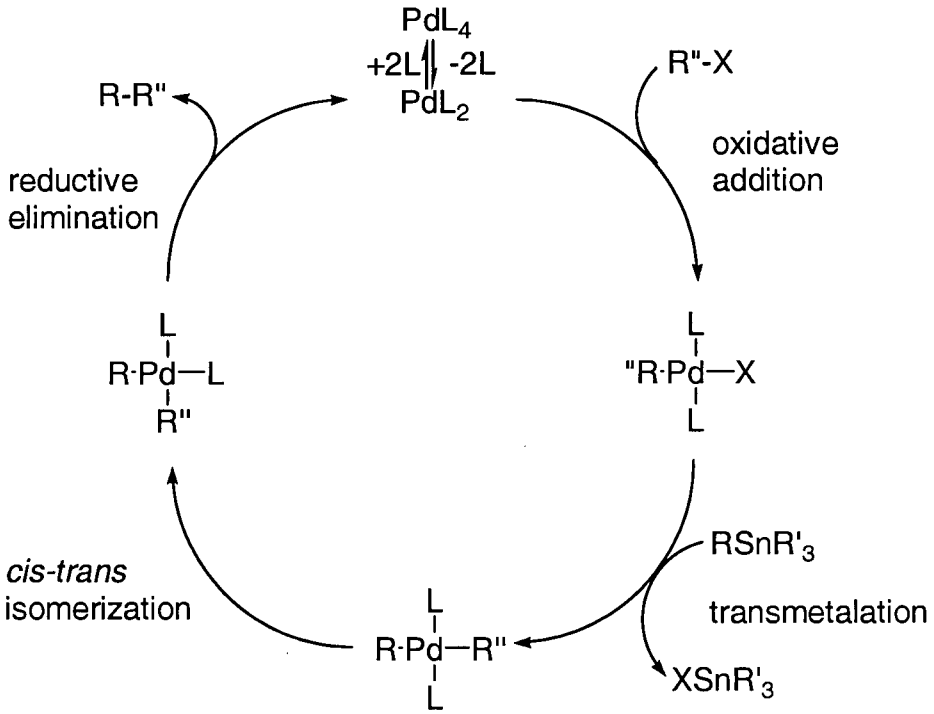


Figure 1. Catalytic cycle of the Stille coupling reaction

(R"-X), an oxidative addition of the PdL_2 to the C-X bond produces a palladium(II) complex. The palladium(II) species undergoes a transmetalation with the tetraorganostannane ($RSnR'_3$) to form the bis(organo)palladium(II) species (R-Pd(L_2)-R") and a triorganostannyl-X side-product. This transmetalation step is considered to be the rate limiting step in the catalytic cycle of the Stille reaction. A *cis-trans* isomerization, followed by a rapid reductive elimination, yields the cross-coupled product (R-R") and results in the regeneration of the coordinatively unsaturated palladium(0) catalyst to participate further in the catalytic cycle.

An important advance in Stille coupling chemistry was the discovery that copper(I) salts (CuCl, CuBr, CuI) accelerate the reaction rate of the coupling process, often by a thousand fold or more.[3] The copper(I) salt is thought to have two major influences. The first is that the copper(I) salt acts as a ligand scavenger to help form the coordinatively unsaturated palladium(0) species (PdL_2). In addition, in highly polar solvents such as *N,N*-dimethylformamide (DMF) and *N*-methylpyrrolidone (NMP), a reversible tin-copper transmetalation occurs which produces an organocopper(I) derivative (*vide infra*). The organocopper(I) species (RCu) transmetalates with the palladium(II) species (R"-Pd(L_2)-X) to form the bis(organo)palladium complex

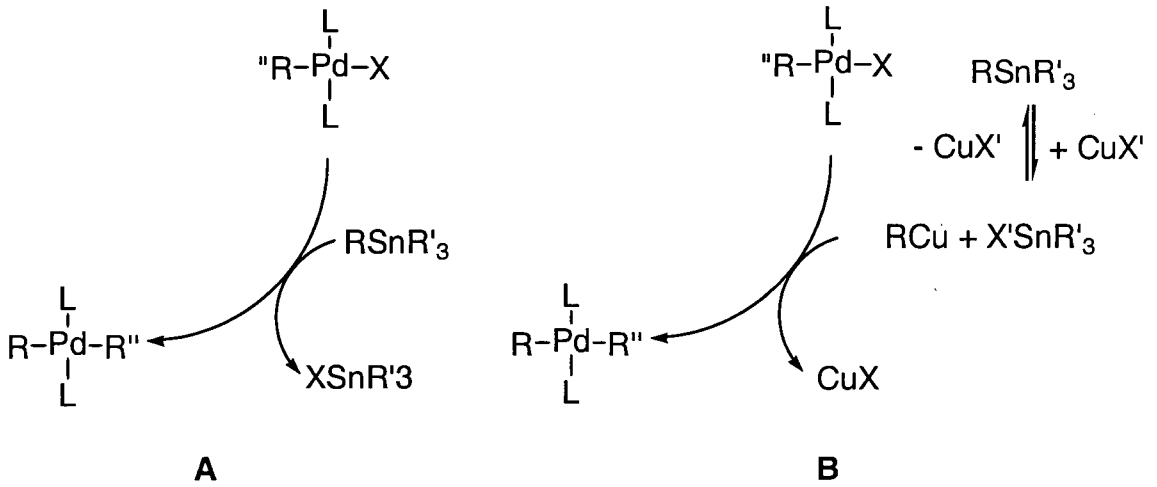
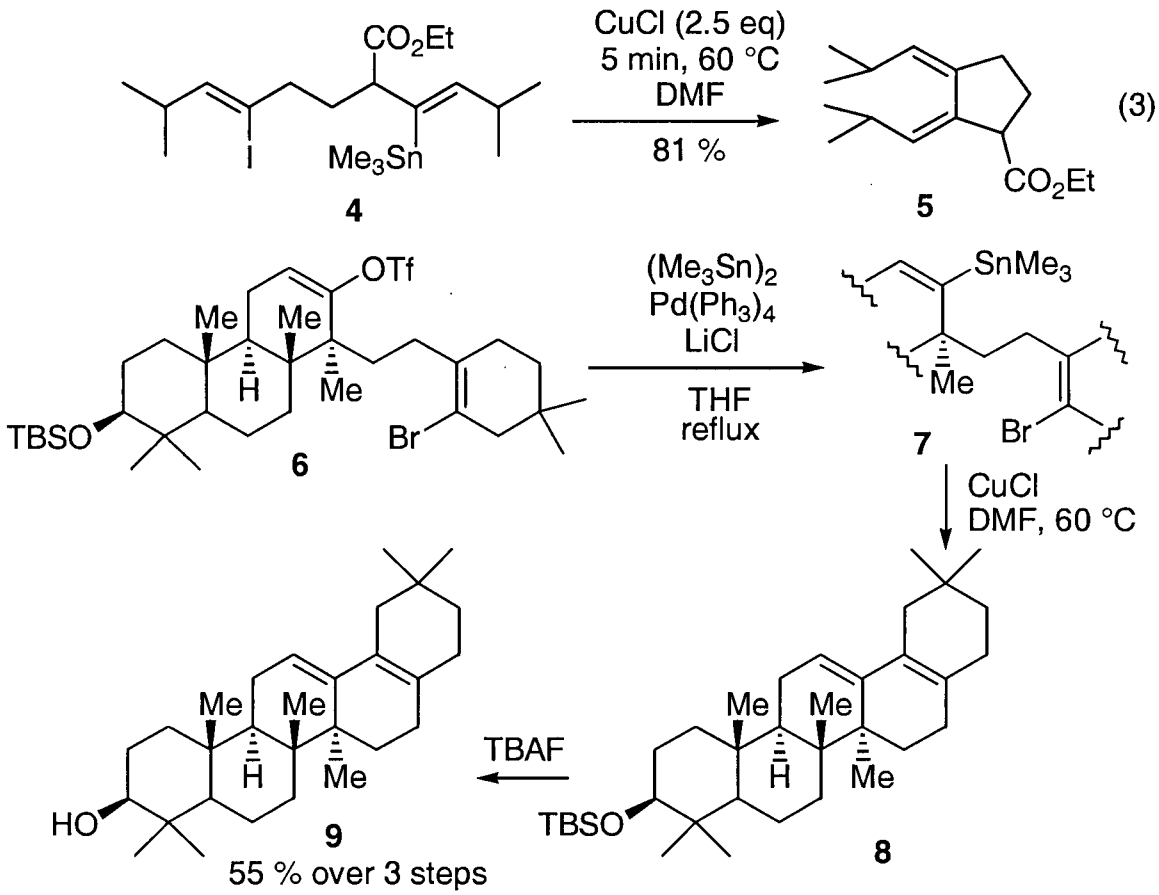


Figure 2. Effect of copper(I) salts in the Stille reaction

(R-PdL_2-R") (pathway B in Figure 2) at a rate faster than the palladium-tin transmetalation (pathway A in Figure 2). The end result is that the two step process

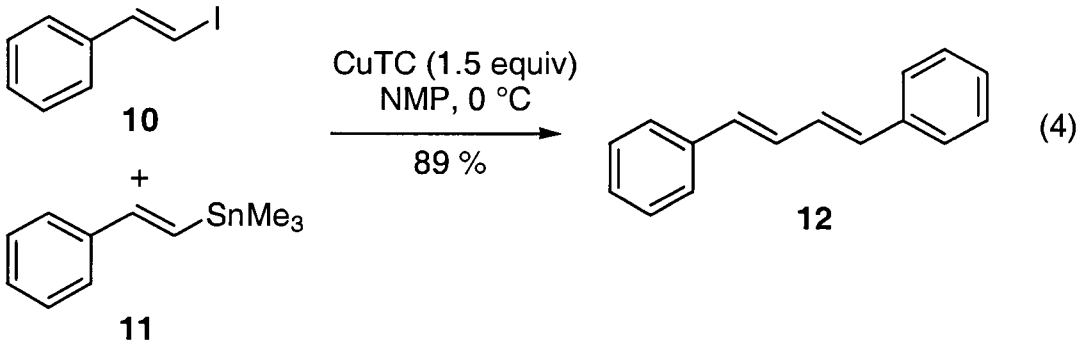
(pathway B) occurs at a rate faster than the one step transmetalation of the palladium(II) complex (R-PdL_2-X) and the tetraorganostannane ($RSnR'_3$) (pathway A).

In studies involving the use of the intramolecular variant of the Stille reaction[4] for the synthesis of substituted bis(alkylidene)cyclopentanes utilizing copper(I) salts as a co-catalyst, Piers and Wong[5] made a valuable discovery: the cyclization was found to proceed rapidly and smoothly *in the absence of any palladium catalyst.* For example, in the conversion of **4** into **5** (equation 3), the yield of the transformation improved remarkably from 52% under "standard" Stille reaction conditions ($Pd(Ph_3P)_4$ (5 mol %), LiCl (2 equiv), 105 °C, 1.5 h, DMF) to 81% when copper(I) chloride was employed alone (equation 3).[5b] This method was recently exploited by Corey in the total synthesis of aegiceradienol[6] (**9**). In this case, the internal Stille coupling of the alkenylstannane-alkenylbromide **7** failed under traditional palladium catalysis but successfully gave **8** when treated with copper(I) chloride. The key steps in the synthesis are shown below in Scheme 1.



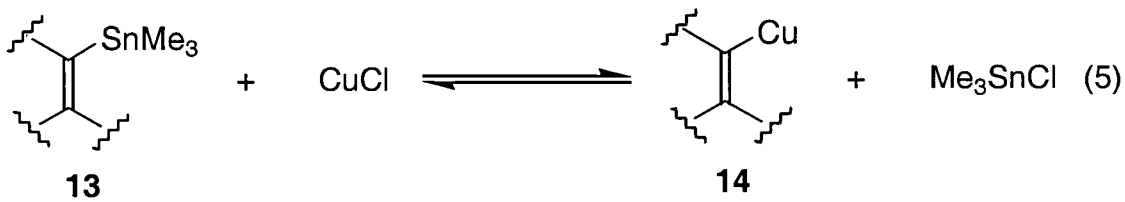
Scheme 1.

Since the initial report by Piers, several instances of copper(I) salt mediated couplings have appeared in the literature. An important advance was reported by Allred and Liebeskind,[7] who showed that copper(I) thiophene-2-carboxylate (CuTC) effectively carries out intermolecular cross couplings of alkenyl- and aryl iodides with alkenyl- and aryltributylstannanes in NMP. An example of this process is shown below in equation 4.



(4)

More detailed investigations, by Liebeskind, Piers, and others, into the mechanism of the copper(I) halide co-catalyst effect in the Stille cross-coupling reaction and of the copper(I) chloride mediated cross-coupling processes, led to the suggestion that these reactions proceed via a common initial intermediate. Liebeskind and coworkers,[3a] by employing ^{119}Sn nmr spectroscopy, showed that, in polar solvents, copper(I) iodide reacts with phenyltributyltin to produce tributyltin iodide and, presumably, a phenylcopper(I) species. Furthermore, in studies related to the copper(I) effect in Stille reactions, it was shown that the rate of the coupling was retarded by the addition of Bu_3SnCl to the reaction mixture.[7] These two observations, as well as similar evidence provided by other research groups,[3] led to the conclusion that the copper(I) halide participates in the *reversible* transmetalation with the alkenyl- or aryltrialkylstannane to produce, in each case, an organocopper(I) species and a triorganohalide as the co-product (equations 5 and 6). This would be consistent with the shift of the equilibrium (left) toward the stannane with added Bu_3SnCl and, as a result, the beneficial effect of the added copper(I) salt would be lessened or annulled.



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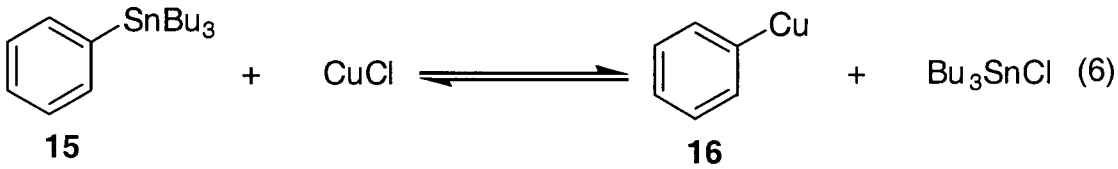
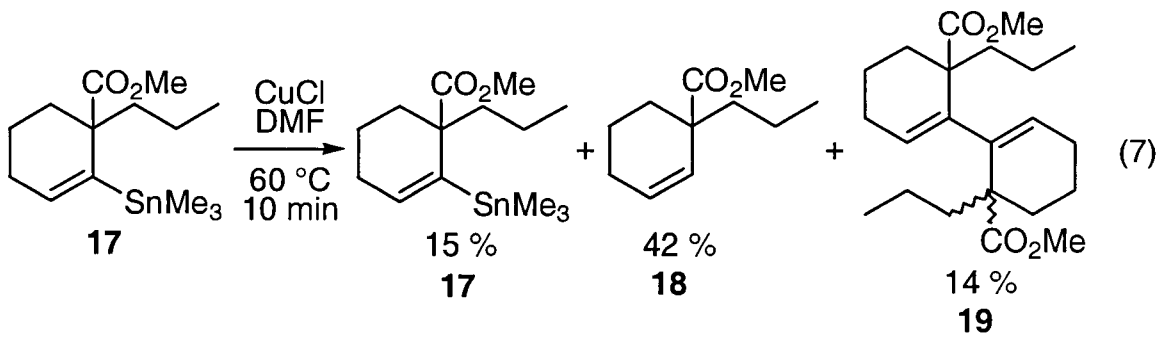


Aside from the rate enhancing effects observed in the Stille cross-coupling reaction, the organocopper(I) species derived from reaction of alkenylstannanes with copper(I) salts has been found in the Piers laboratory, under certain conditions, to react in two other synthetic operations: the oxidative homocoupling of bisalkenylstannanes and the intramolecular conjugate addition of alkenyltrialkylstannanes to Michael acceptors, each mediated by copper(I) salts.

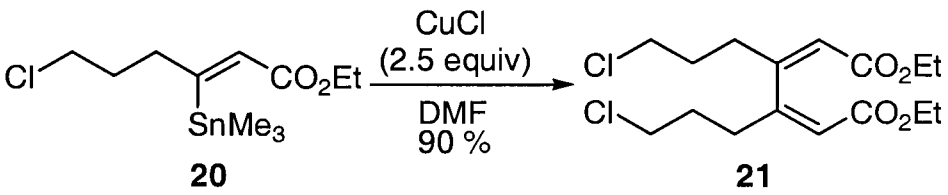
2.2 Oxidative Homocoupling of Alkenyltrimethylstannanes

An important observation made by Piers and Wong during mechanistic investigations related to the copper(I) chloride-mediated intramolecular coupling of alkenylstannane and alkenyl halide functions was that minor amounts of a dimerized product, resulting from the homocoupling of two alkenyltrimethylstannane moieties, were produced. For example, in a control experiment (equation 7),[5b] in which the stannane **17** was treated with 2.1 equiv of CuCl in warm DMF, a low yield (14%) of the homocoupled product **19** was obtained. The remainder of the isolated material was recovered starting material **17** (15%) and the protiodestannylated product **18** (42%).



This key observation was investigated further by Piers and coworkers,[8] with the aim of determining the generality of this new homocoupling protocol. It was found that a wide variety of alkenyltrimethylstannanes bearing allylic alcohol, α,β-unsaturated ester and α,β-unsaturated aldehyde functions are amenable to this copper(I) mediated process (equations 8, 9, 10, and 12). In the case of α,β-unsaturated esters, the coupling reactions

were shown to be stereospecific, since the configurational integrity of the double bond remained intact. Examples are shown in the conversions of the esters **20** and **22** into the dienes **21** and **23**, respectively (equations 8 and 9). In general, it was found that superior yields are obtained from substrates that possess the alkenyltrimethylstannane function on the β carbon of α,β-unsaturated aldehydes or esters. Alkenyltributylstannanes also undergo this transformation as shown by the conversion of the stannane **26** into the diene **25** in a moderate yield (51%) (equation 11).



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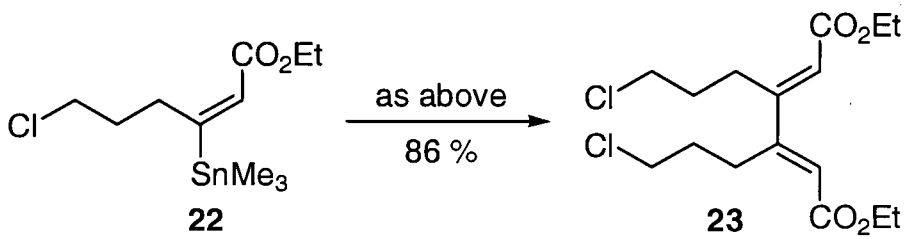

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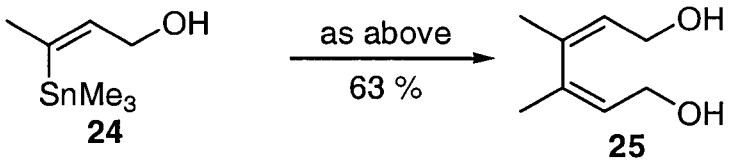

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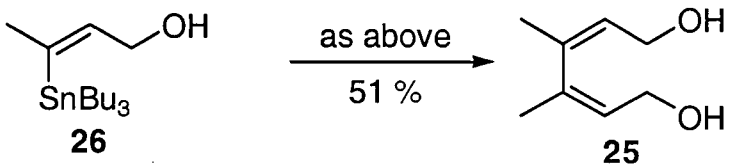
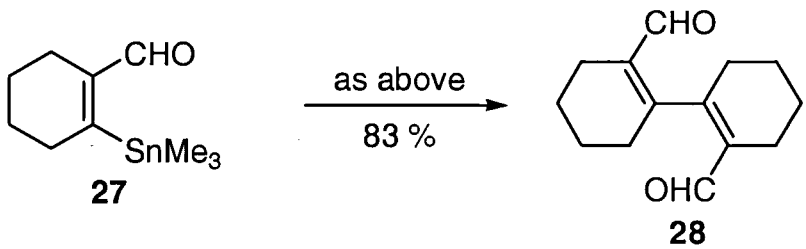


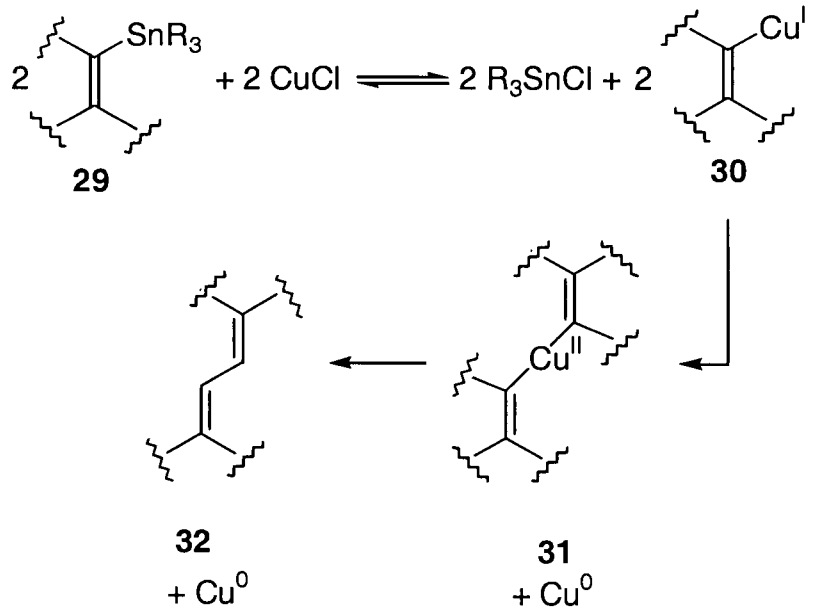
(11)



(12)

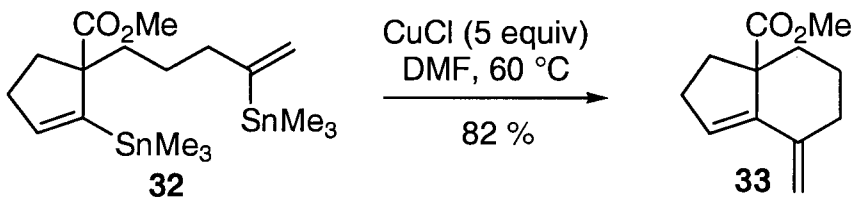
The mechanistic details of the copper(I) chloride-mediated oxidative coupling of alkenyltrialkylstannanes remain elusive. From quantitative determinations of the copper metal produced in the reaction, it was found that 2 mols of copper metal are produced for each mol of diene that is produced in the reaction.[8b] A reasonable mechanistic pathway

would involve transmetalation of the organotrialkylstananne moiety in **29** (*vide supra*) to produce the corresponding organocopper(I) species **30** and the triorganostannyl halide (R_3SnX). Disproportionation of **30** would produce the copper(II) intermediate **31** and one equivalent of Cu(0). A subsequent reductive elimination of Cu(0) from **31** would yield the coupled product **32** (Scheme 2).

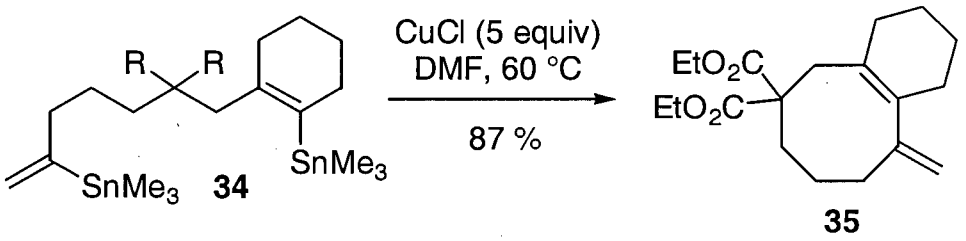


Scheme 2.

This coupling method has been expanded by Piers and Romero to include the *intra*molecular coupling of bisalkenyltrimethylstanannes.[9] This powerful cyclization method was demonstrated to form an impressive array of 4- to 8-membered rings. For example, the distannanes **32** and **34** were converted into the 6- and 8-membered ring bicycles **33** and **35**, respectively, in excellent yields when the substrates were treated with 5 equiv of copper(I) chloride in warm DMF (equations 13 and 14).

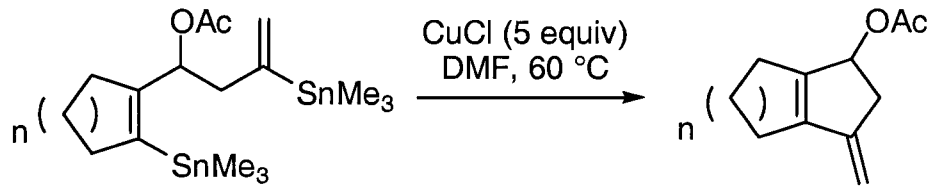


(13)



(14)

Piers and Kaller investigated the possibility of using the oxidative homocoupling of alkenyltrimethylstannanes in a methylenecyclopentene annulation sequence.[10] In this study, a series of cyclopentene derivatives was formed in moderate to good yields. A highlight of the method developed is the formation of the bicyclic systems **39-41** from the monocyclic precursors **36-38**, respectively (equation 15).

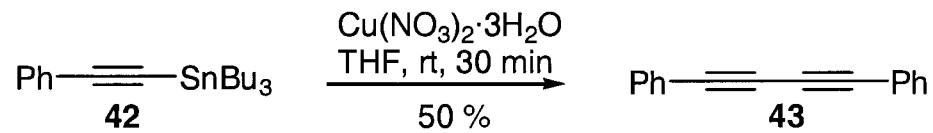


36 n = 1
37 n = 2
38 n = 3

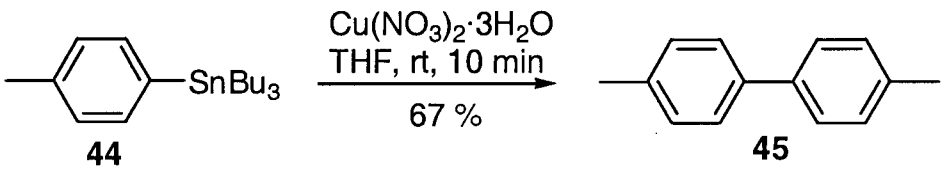
39 n = 1, 67 %
40 n = 2, 82 %
41 n = 3, 42 %

(15)

It should be noted that other protocols have been developed to accomplish the homocoupling of organotrialkylstannanes. The most noteworthy is the copper(II) nitrate-mediated coupling of organostannanes. Kyler and coworkers, for example, employed copper(II) nitrate to oxidatively homocouple aryl-, alkynyl-, and alkenylstannanes to produce an assortment of unsaturated systems (equation 16 and 17).[11] The exact mechanistic details of this process are unclear.



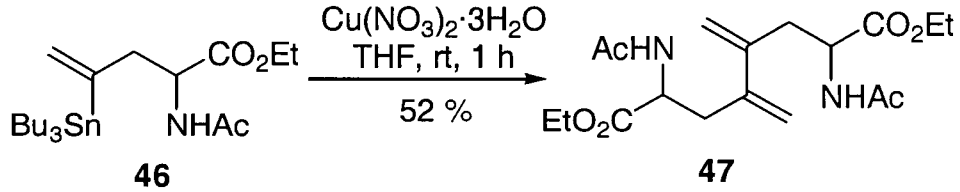
(16)



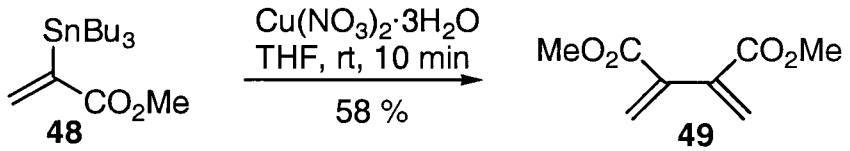
(17)

Since this initial report, Crisp and Glink reported the dimerization of certain alkenylstannanes facilitated by copper(II) nitrate (equation 18) in THF.[12] Zhang and coworkers reported the single example of a copper(II)-mediated coupling of an α-tributylstannyl α,β-unsaturated ester (equation 19).[13] Finally, a series of

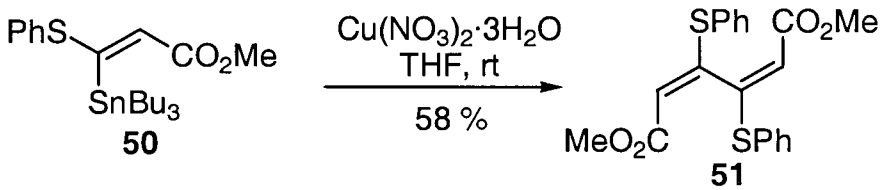
β-trimethylstannyl α,β-unsaturated ketones and esters were reported to undergo copper(II) nitrate-mediated couplings by Quayle and coworkers.[14] One example reported is given in equation 20 where the conversion of the alkenyltributylstannane **50** proceeded to give the corresponding dimerized product **51** in a moderate yield (58%).



46 **47** (18)

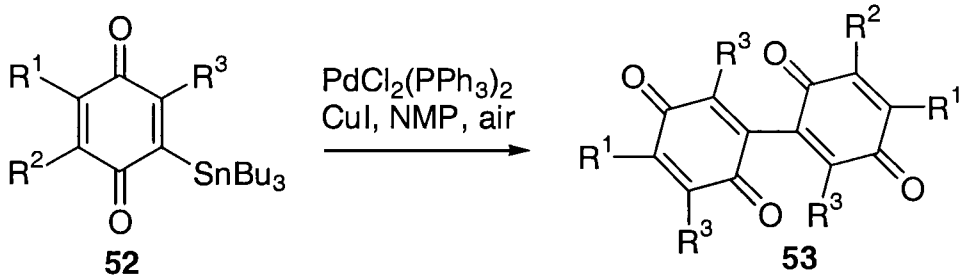


48 **49** (19)



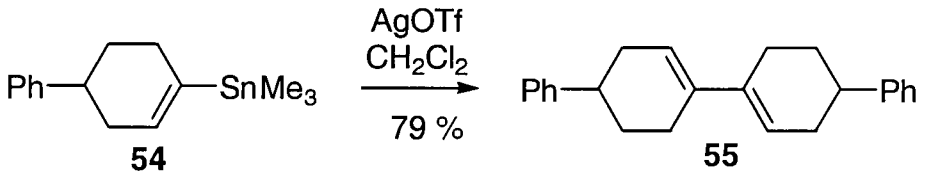
50 **51** (20)

Palladium salts have recently been reported by Liebeskind and Riesinger to mediate the coupling process.[15,16] Stannylquinones of general structure **52** were found to dimerize to give the corresponding 2,2'-bisquinones **53** in moderate to good yields (65-80%) when treated with $PdCl_2(PPh_3)_2$ and copper(I) iodide in the presence of air.



52 **53** (21)

Lastly, silver salts, in particular silver(I) triflate, have been reported by Tius and Kawakami to mediate the coupling of two alkenyltrimethylstannane functions.[17] The alkenylstannane **54** upon treatment with 1.1 equiv of silver(I) triflate in CH_2Cl_2 resulted in the formation of the dimer **55** in good yield (79%) (equation 22).

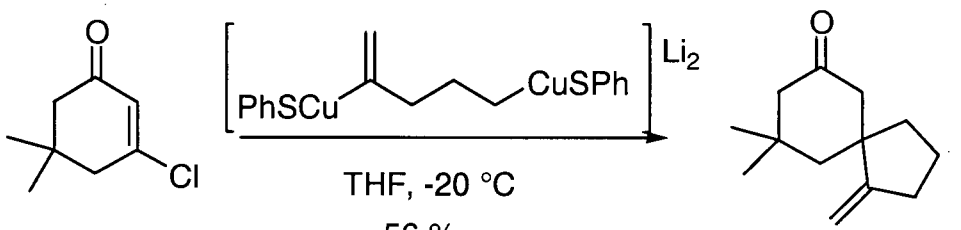


54 **55** (22)

2.3 Intramolecular Conjugate Addition

The synthetic usefulness of organocopper(I) derivatives, formed from the transmetalation of organostannanes with copper(I) salts, has been further demonstrated in their ability to participate in intramolecular conjugate additions. Although the ability of organocopper(I) reagents to add *inter*molecularly, in a conjugate sense, to α,β-unsaturated carbonyl systems is well known,[18] reports on the *intra*molecular conjugate addition of unstabilized carbanions[19] to Michael acceptors is a rarity in the published literature. The primary reason for this scarcity is the inherent difficulty in forming a reactive carbanion-like centre in the presence of an electron deficient π system, such as a carbonyl functionality or a Michael acceptor, where competing 1,2 and 1,4 modes of addition may operate. A few reports have emerged regarding intramolecular conjugate additions of non-stabilized carbanions and several deserve mention here.[20]

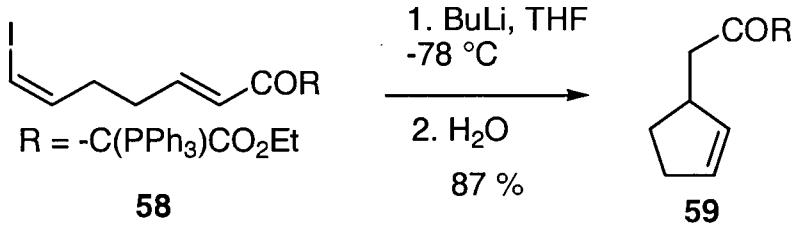
By employing a bis(cuprate) addition-spiroannulation strategy, Wender and White produced the spiro system **57** from the β-chloro enone **56** in a moderate (56%) yield (equation 23).[21] In this case, the order of addition of the alkenyl (sp^2) centre and the primary (sp^3) centre of the bis(cuprate) to the unsaturated enone is not known. This type of reaction was applied to form a variety of spiro compounds in moderate to excellent yields (39-94%).



56 **57** (23)

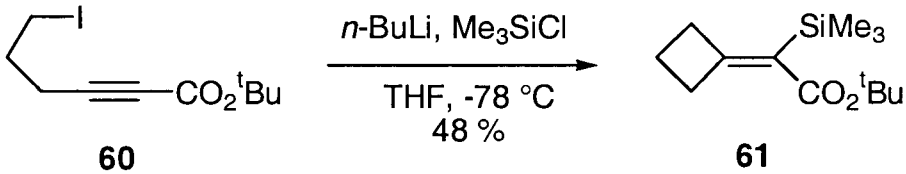
In studies by Cooke and Widener,[22] the intramolecular conjugate additions of alkenyl centres to unsaturated acylphosphoranes, mediated by BuLi, were performed. Treatment of the terminal alkenyl iodide **58** with BuLi, to effect a halogen-metal

exchange, followed by quenching the addition product with water, resulted in an excellent yield (87%) of the cyclized product **59** (equation 24).



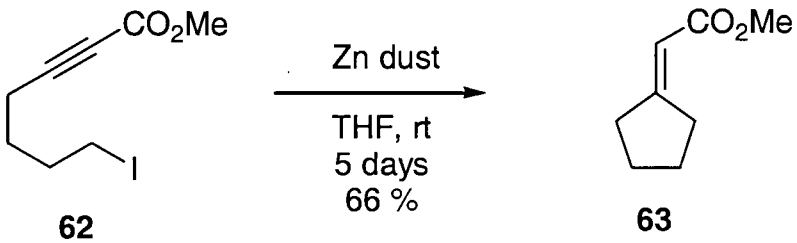
(24)

In another report by Cooke,[23] the conjugate addition of unstabilized primary carbanion functions to α,β-alkynic esters were reported. In a specific example, the primary iodide **60** was treated with BuLi and trimethylsilyl chloride (TMSCl) to provide the cyclobutane derivative **61** in a moderate yield (equation 25). The presence of the TMSCl as a trap for the intermediate allenoate was found to be essential, as the yield of the cyclization was very poor (11%) in its absence.



(25)

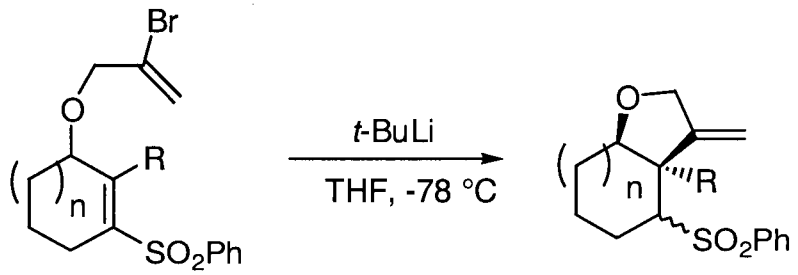
In a study by Danheiser and coworkers,[24] the conjugate addition of primary carbanionic species, formed from the reaction of primary iodides with activated zinc dust, to a variety of Michael acceptors (α,β-unsaturated esters, enones, and alkynoates) were achieved. In one example, involving treatment of the α,β-alkynic ester **62** with zinc dust in THF, the α,β-unsaturated ester **63** was obtained in a moderate yield (66%) (equation 26).



(26)

Finally, the conjugate addition of alkenyl systems to α,β-unsaturated sulfones in the synthesis of a series of *cis*-fused bicyclic ethers was reported by Fuchs and Lee.[25] In this study, halogen-metal exchange of the alkenyl bromides of general structure **64** with

t-BuLi resulted in the formation of the cyclic ethers **65** in moderate to good yields as mixtures of diastereomers (equation 27).

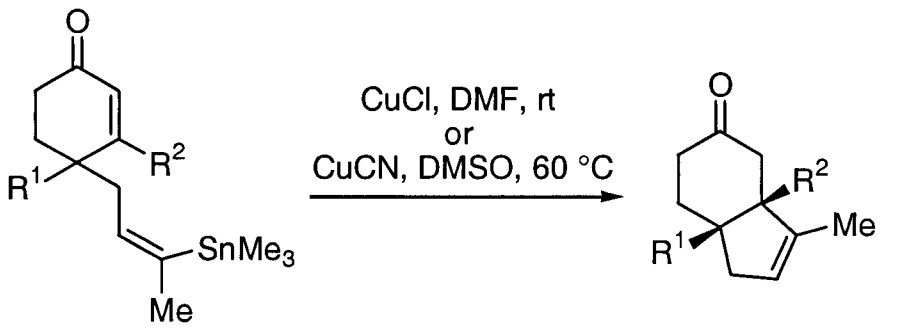


(27)

64a n = 1, R = H
64b n = 1, R = Me
64c n = 0, R = H

65a 86 %
65b 75 %
65c 45 %

Piers and coworkers have used organocopper(I) intermediates to effect intramolecular conjugate additions of alkenyl functions to α,β-unsaturated ketones (enones).[26] A series of *cis*-fused bicyclo[4.3.0]nonenones **67** can be prepared efficiently via this method by the formation of the five membered rings under mild conditions (equation 28). In this work, copper(I) chloride in DMF or copper(I) cyanide in warm (60 °C) dimethyl sulfoxide (DMSO) were found to be effective protocols for accomplishing these reactions (Table 1). In some instances in which the β-positions of the enones were sterically hindered (R^2 = Et, *i*-Pr, or $CH{=}CH_2$), the use of copper(I) cyanide was found to give results superior to those derived from the use of copper(I) chloride. For example, when R^1 = H and R^2 = *i*-Pr, the application of the reaction protocol employing copper(I) cyanide gave a good yield (73%) (entry 6) of the cyclized adduct. The same conversion proved to be inefficient under the conditions employing copper(I) chloride in DMF (entry 5).



(28)

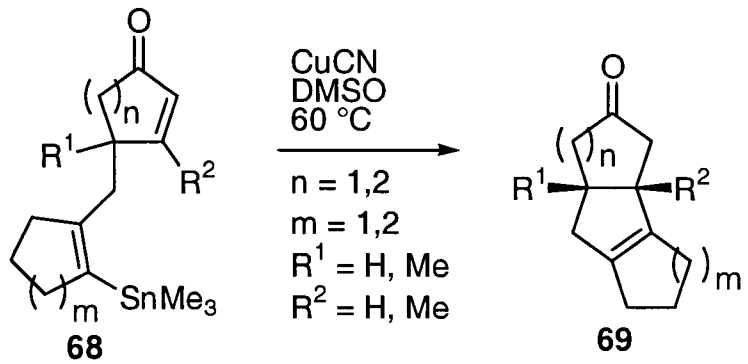
66 **67**

Table 1. Synthesis of the bicycles **67**

Entry	R^1	R^2	Copper Source[a]	% Yield[b]
1	H	H	CuCl	96
2	H	Me	CuCl	81
3	H	Et	CuCl	48
4	H	Et	CuCN	91
5	H	*i*-Pr	CuCl	15[c]
6	H	*i*-Pr	CuCN	73
7	H	$CH=CH_2$	CuCl	6[c]
8	H	$CH=CH_2$	CuCN	60
9	Me	H	CuCl	85
10	Me	Me	CuCl	90

[a] Reaction conditions: CuCl (2.5 equiv), DMF, rt, or CuCN (2.5 equiv), DMSO, 60 °C.
[b] Unless otherwise stated, isolated yield of the purified product.
[c] Glc yields of desired product in crude reaction mixtures.

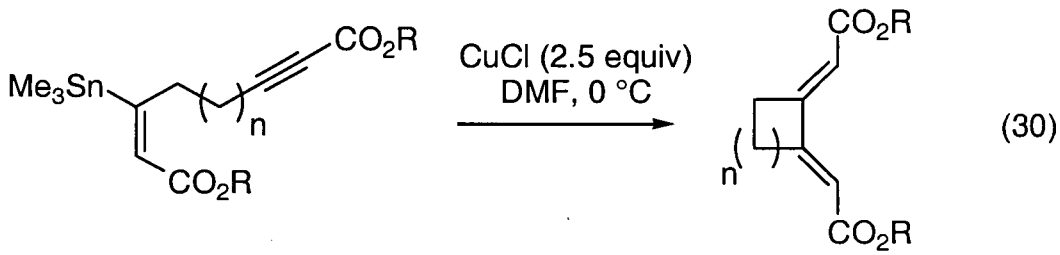
In manner similar to that described above, the syntheses of tricyclic compounds of general structure **69** were reported by Piers and coworkers.[27] The intramolecular conjugate addition of cyclic alkenyltrimethylstannane functions to α,β-unsaturated ketones utilizing copper(I) cyanide in warm DMSO was described (equation 29). By the formation of the central five-membered ring, the functionalized tricyclic ketones **69** were synthesized in excellent yields (80-94%).



68 69 (29)

Finally, intramolecular conjugate additions of alkenyltrimethylstannane functions to α,β-alkynic esters mediated by copper(I) chloride were achieved by Eva Boehringer in Dr. Piers' laboratory.[28] In this work, 2.5 equiv of copper(I) chloride in DMF was utilized

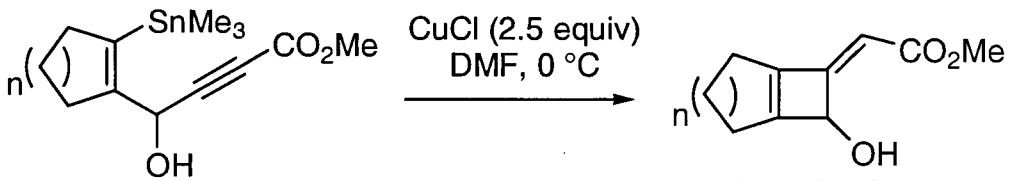
in the formation of symmetrical 4-6 membered monocycles with good to excellent yields (74-95%) (equation 30). Bicyclo[4.2.0]octane and bicyclo[3.2.0]heptane structures, arising from the formation of a four membered ring, were also synthesized in good yields (equation 31). The reader is refered to Introduction section 3.4.1 for a discussion on the proposed mechanism of this transformation.



(30)

70 n = 1, R = Me
71 n = 2, R = Et
72 n = 3, R = Me

73 n = 1, 95 %
74 n = 2, 94 %
75 n = 3, 74 %



(31)

76 n = 1
77 n = 2

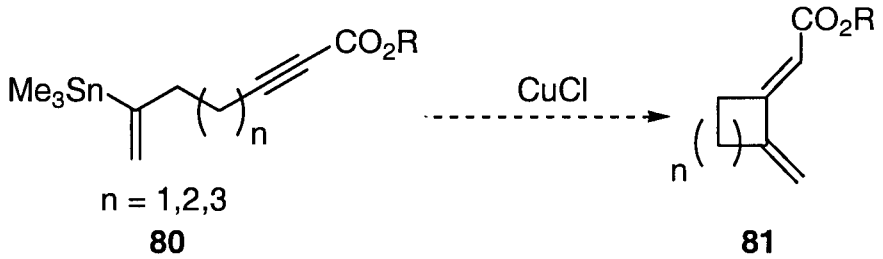
78 n = 1, 73 %
79 n = 2, 75 %

3. Proposals

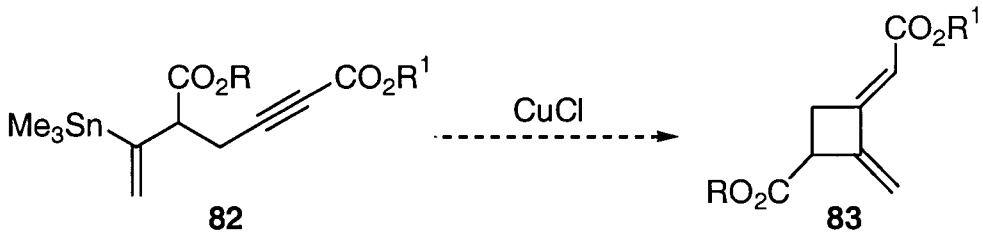
3.1 Intramolecular conjugate addition of alkenyltrimethylstannane functions to α,β-alkynic esters to form monocycles

The scope and utility of the copper(I)-mediated cyclization protocol broadened significantly with the discovery of the intramolecular conjugate addition reaction of alkenyltrimethylstannane functions to α,β-alkynic esters by Piers and Boehringer (see previous section). However, only four successful examples of the formation of monocyclic ring structures were presented and, of these, three of the carbocycles synthesized were symmetrical in nature (equation 30). To explore further the generality of the reaction, a series of cyclization precursors **80** and **82**, incorporating

alkenyltrimethylstannane and α,β-alkynic ester moieties in the same molecular construct, would be prepared and subjected to the intramolecular conjugate addition protocol (equations 32 and 33). In this manner, the flexibility of the reaction to form unsymmetrical 4- to 6-membered monocycles could be explored. For a discussion on the proposed mechanistic pathway of the reaction, the reader is referred to Introduction section 3.4.1.



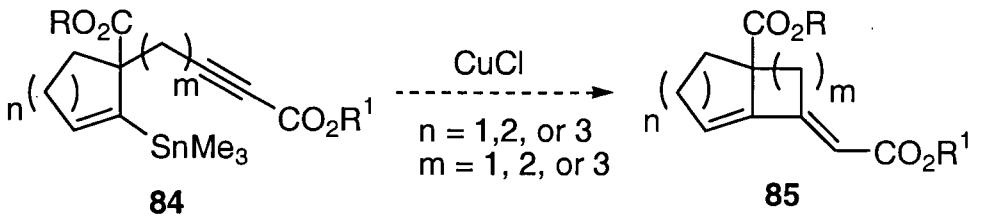
(32)



(33)

3.2 Intramolecular conjugate addition of alkenyltrimethylstannane functions to α,β-alkynic esters to form bicycles

In the previous study by Piers and coworkers describing the synthesis of bicyclic systems via the copper(I)-initiated internal conjugate addition of alkenyl functions to α,β-alkynic esters,[28a] two successful examples were presented in which good yields were reported (equation 31). It was proposed to undertake a study to determine whether the reaction could be extended to include the synthesis of bicyclic ring systems of general structure **85** (equation 34). To accomplish this, the cyclizations of a series of precursors **84** were envisaged in which the chain length of the appendage, terminating with an α,β-alkynic ester moiety, and the size of the preexisting ring structure in the cyclization precursors could be varied. The result, should the copper(I)-mediated transformations of

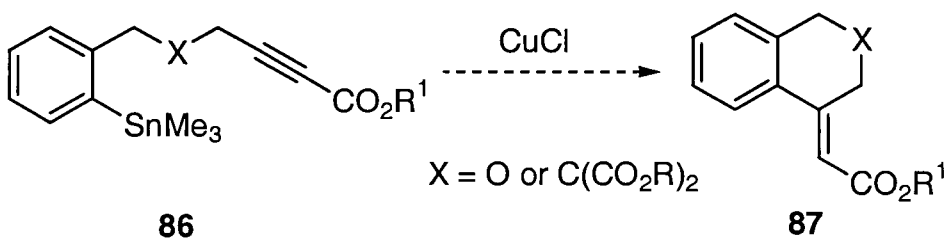


84 **85** (34)

84 into **85** prove to be successful, would be the synthesis of a series of bicyclic structures which incorporate 4- to 7-membered rings and various functionality to serve as a handle in future synthetic manipulations. The configuration associated with the exocyclic double bond in the bicycles is predicted to be *trans* by analogy with the previous examples of bicycle and monocycle formation (see Introduction section 3.4.1, pg. 19).

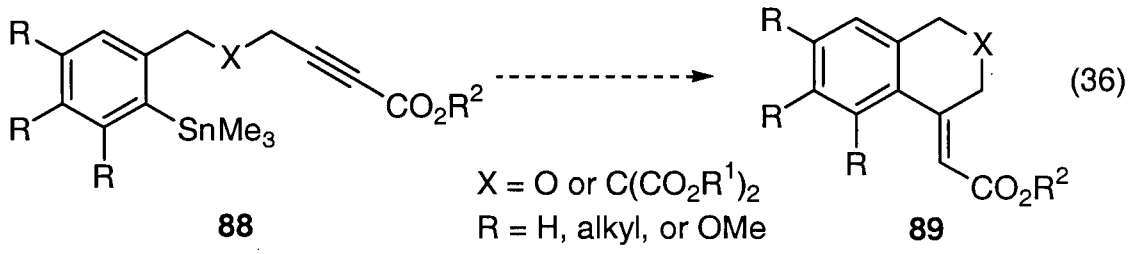
3.3 Intramolecular conjugate addition of aryltrimethylstannane functions to α,β-alkynic esters to form bicycles incorporating an aromatic ring

As a result of the mechanistic investigations into the "copper effect" in the Stille and related coupling protocols, it was determined that it was possible for aryltrialkylstannanes to undergo a reversible transmetalation with copper(I) salts (Introduction section 2.1, pg. 6). Analogous to the conjugate addition reaction of alkenyltrimethylstannane functions to α,β-alkynic esters mediated by copper(I) chloride discussed previously, it was hypothesized that aryltrimethylstannanes should behave in a similar manner (i.e. copper-tin transmetalation followed by internal conjugate addition, see Introduction section 3.4.1). To test this premise, two model systems of general structure **86**, which contain an ether linkage (X = O) or a malonate unit (X = $C(CO_2R)_2$), would be prepared and the intramolecular conjugate additions mediated by copper(I) chloride would be investigated (equation 35).



86 **87** (35)

Should the initial test cases to form the aromatic bicyclic compounds **87** prove to be successful, a series of cyclization precursors **88** would be tested to expand the generality and scope of the reaction (equation 36).



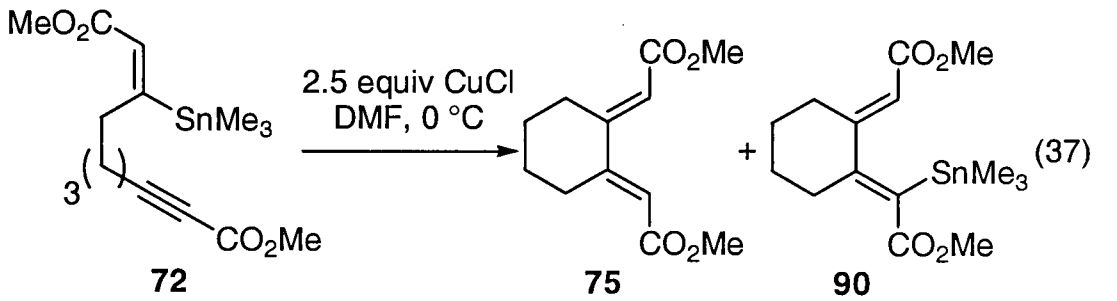
88 **89** (36)

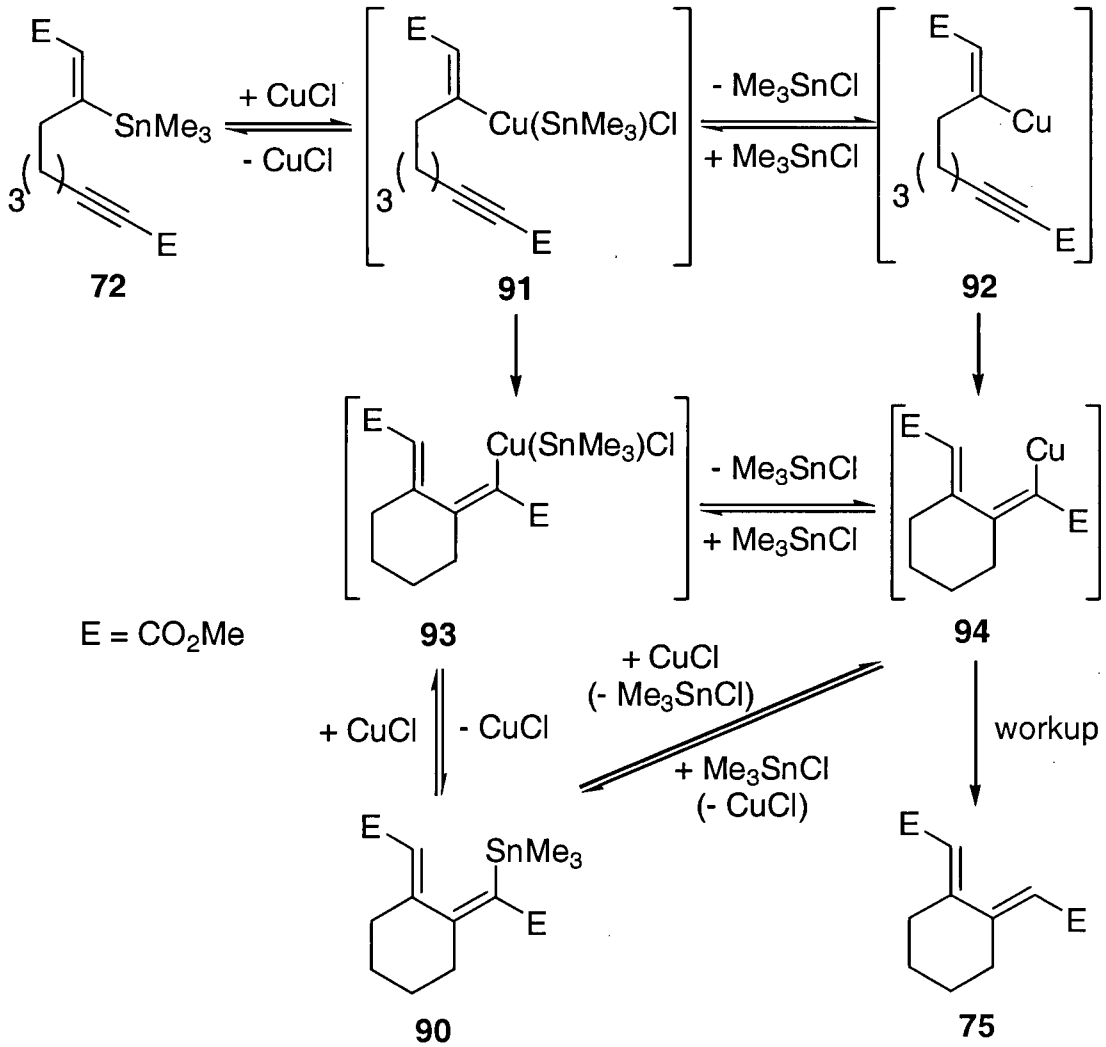
3.4 Limitations, extensions and mechanistic considerations

3.4.1 Mechanistic considerations

The proposed mechanistic pathway for the conjugate addition reaction of alkenyltrimethylstannane functions to α,β-alkynic esters was first postulated in work by Piers and Boehringer (Scheme 3).[28b] In this proposal, using the conversion of the stannane **72** to the diene **75** as an illustrative example, an initial copper-tin transmetalation of the alkenyltrimethylstannane **72** with copper(I) chloride results in the formation of the copper(III) intermediate **91**. The intermediate **91** can proceed to form, via the elimination of Me_3SnCl, the expected copper(I) intermediate **92**. This hypothesis differs slightly from the "simple" copper-tin transmetalation postulated in previous studies (see equation 5, pg. 6).

Support for the formation of the copper(III) intermediate[29] **91** was supplied by the observation that, if the cyclization reaction was allowed to proceed for a relatively short period of time (7 min), a mixture (ratio ~2:1, respectively, by gas-liquid chromatography) of the diene **75** and the α-trimethylstannane **90** was obtained after aqueous workup (equation 37). When the reaction time was extended to 60 min, the diene **75** was produced exclusively. This would suggest that two competing intramolecular conjugate additions in a *cis* manner[30] across the triple bond of the α,β-alkynic ester in the intermediates **91** and **92** was taking place to form the cyclized adducts **93** and **94**,



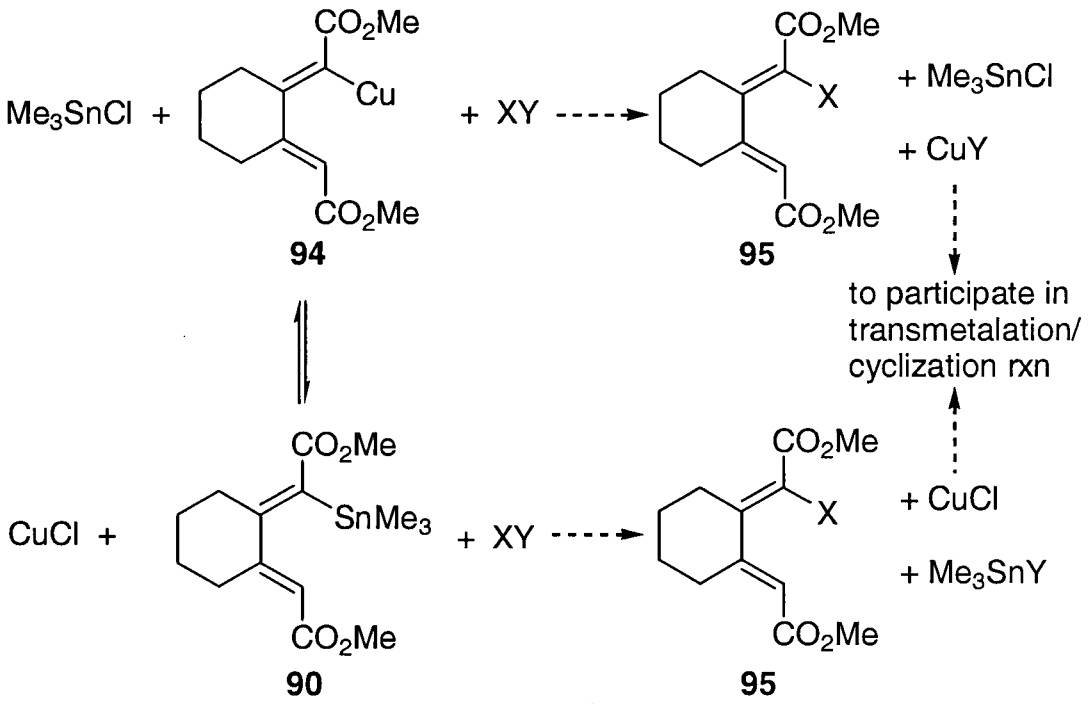


Scheme 3.

respectively (Scheme 3). A subsequent reductive elimination of CuCl from the intermediate **93** allows for the formation of the α-trimethylstannyl ester **90**. It is then

reasonable to suggest that a second copper-tin transmetalation between **90** and **94** would take place which, based on the disappearance of the stannane **90** upon prolonged reaction times, would lie largely toward the alkenylcopper(I) species **94**. Eventually, the α-copper(I) adduct **94** is formed from both cyclization pathways and, lastly, protonation of **94** upon aqueous workup provides the conjugated (*E,E*)-diene **75**. A premature quench of the reaction mixture would result in the isolation of the observed α-trimethylstannyl ester **87**.

Upon further examination of the proposed mechanism, it may be noted that copper(I) chloride is regenerated in the sequence of events leading to the formation of the α-stannyl ester **90**. This led to the speculation that, under the appropriate conditions, the copper(I) chloride (or another copper(I) salt derived therefrom) may be used under catalytic conditions. For this requirement to be satisfied, the alkenylcopper(I) species **94**



Scheme 4.

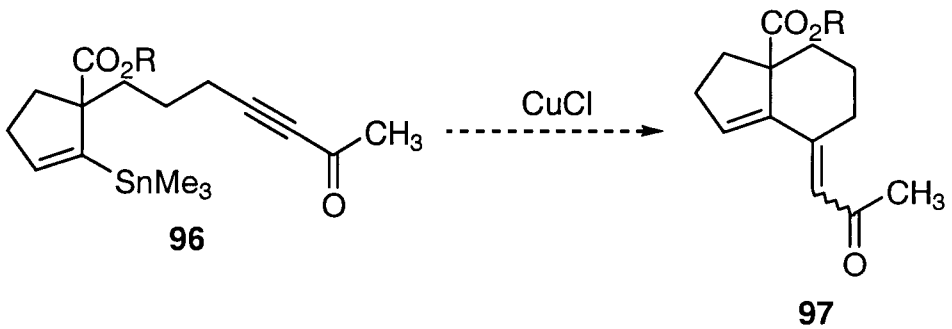
and/or the α-stannyl ester **90** must be intercepted with a suitable *in situ* quench and, in doing so, regenerate a copper(I) salt that would be capable of participating in the transmetalation and cyclization events (Scheme 4). In addition, for this concept to be viable, the intramolecular cyclization process must obviously transpire at a rate faster

than that of the intermolecular quench. Otherwise, an undesired acyclic product arising from the premature quenching of the alkenylcopper species **91** or **92** would be produced.

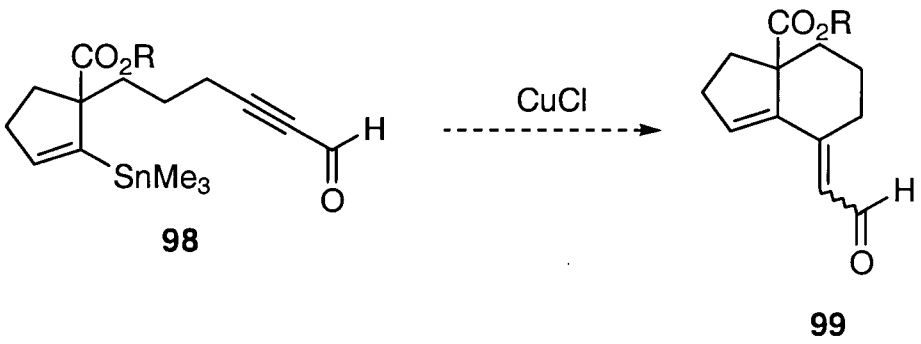
To examine this intriguing possibility of employing the copper(I) salt in a catalytic fashion, a variety of additives (XY, e.g. acetic acid) that may perform the two-fold function of quenching the alkenylcopper(I) species **94** and regenerating a copper(I) salt (CuY) would be investigated (Scheme 4).

3.4.2 Intramolecular conjugate addition of alkenyltrimethylstannane functions to α,β-alkynic aldehydes and α,β-alkynic ketones

Up to the present, α,β-unsaturated ketones and α,β-alkynic esters have been the only Michael acceptors that have been examined in the Piers laboratory with respect to the intramolecular conjugate addition of alkenyltrimethylstannane functions mediated by copper(I) salts. It was of interest to ascertain whether or not other Michael acceptors that contain the carbon-carbon triple bond subunit are amenable to the cyclization protocols developed. To explore this possibility, it was proposed that two test substrates, the α,β-alkynic ketone **96** and the α,β-alkynic aldehyde **98** would be synthesized and subjected to the copper(I) salt mediated process to form the bicycles **97** and **99**, respectively. The stereochemical outcome of the conjugate addition with respect to the newly formed double bond is uncertain. However, by analogy to previous studies with α,β-alkynic esters, the *E* configuration of the double bond would be expected (see previous section).



96 **97** (38)

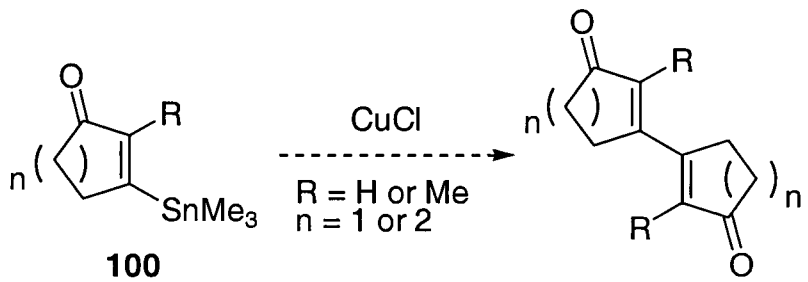


98 **99** (39)

3.5 Intermolecular oxidative homocoupling of β-trimethylstannyl α,β-unsaturated ketones mediated by copper(I) chloride

Although a considerable number of examples of alkenyltrialkylstannane intermolecular couplings have been reported recently, there still remains some uncertainty as to which functional groups are tolerated by the copper(I) chloride-mediated protocol. It has been shown that a variety of β-trimethylstannyl α,β-unsaturated ester and β-trimethylstannyl α,β-unsaturated aldehyde precursors undergo the copper(I)-induced coupling process (see Introduction section 2.2, pg. 7). However, β-trimethylstannyl α,β-unsaturated ketones had not been shown to react with copper(I) chloride to produce the corresponding homocoupled product and a short study to further explore this aspect of the reaction was to be undertaken.

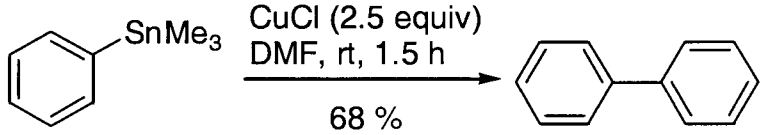
A series of β-trimethylstannyl α,β-unsaturated ketones of general structure **100** would be prepared and subjected to the copper(I) chloride-mediated process to produce, if successful, the corresponding highly conjugated diketones **101** (equation 40).



100 **101** (40)

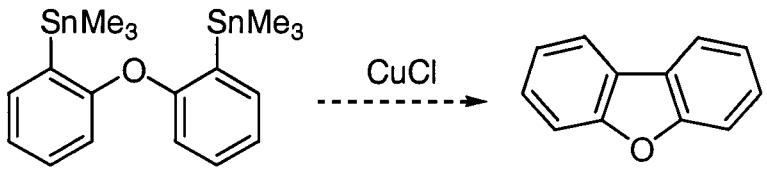
3.6 Oxidative intramolecular couplings of bisaryltrimethylstannanes mediated by copper(I) chloride

Since several reports of the oxidative homocoupling reactions of alkenyltrialkylstannanes had appeared in the literature (see Introduction section 2.2, pg. 7), it was proposed that arylstannanes, since they should possess properties similar to those of alkenylstannanes, should undergo similar homocoupling processes mediated by copper(I) chloride. Indeed, concurrent with this work, the *inter*molecular oxidative coupling of aryltrimethylstannanes was discovered.[31] In one example of this process, it was found that treatment of trimethylstannylbenzene (**102**) with 2.5 equiv of copper(I) chloride in DMF resulted in the isolation of biphenyl (**103**) in good yield (68%).

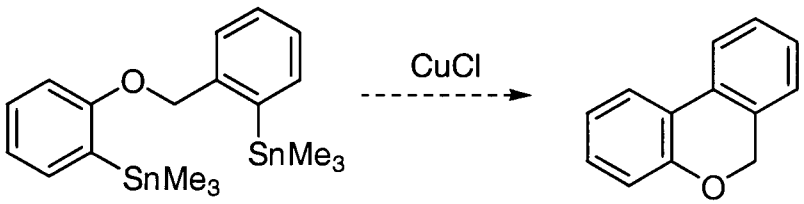


102 **103** (41)

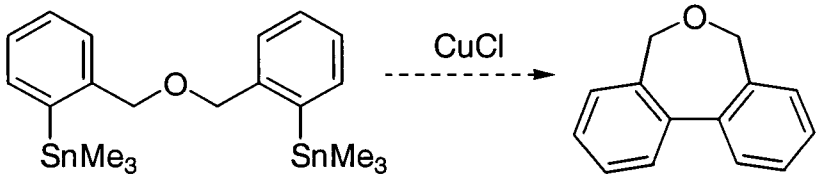
It was proposed in collaboration with Dr. Patricia Gladstone, a postdoctoral research fellow in Dr. Piers' laboratory, that the copper(I)-mediated intramolecular coupling of bisaryltrimethylstannane functions may offer a viable synthetic route to 5-, 6-, and 7-membered ring compounds. To test the proposed methodology, a series of bisaryltrimethylstannanes **104**, **106**, and **108**, in which each of the two aryltrimethylstannane functions in the precursors are connected together via an ether linkage, would be subjected to the oxidative copper(I) chloride-mediated coupling protocol (equations 42, 43, and 44).



104 **105** (42)

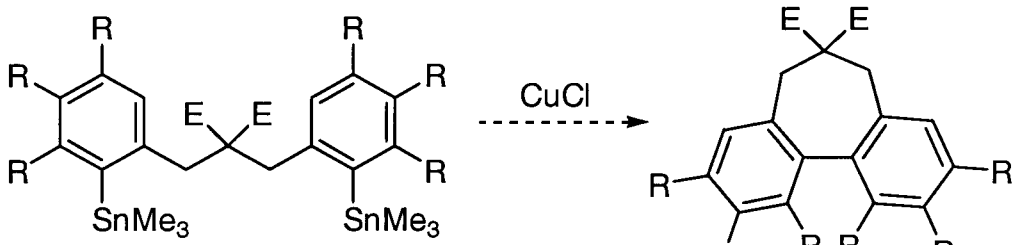


106 107 (43)



108 109 (44)

If the synthesis of the seven membered ring **109** proved to be successful, it was proposed that the methodology would then be extended to encompass the synthesis of the carbocyclic ring structures of general structure **111** (equation 45). The scope of the reaction would be explored by the addition of substituents (alkyl or methoxy) located on each of the aromatic rings.

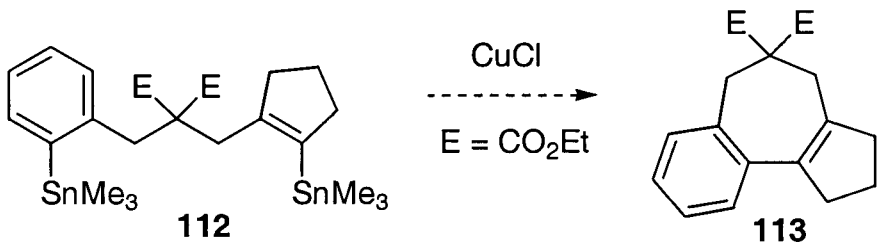


110 (45)

E = CO_2Et
R = H, Alkyl, or OMe

111

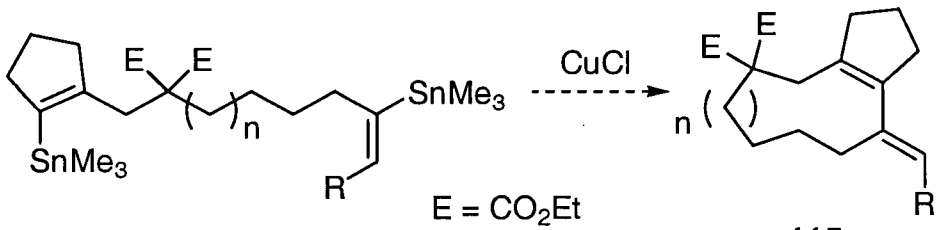
Lastly, an example involving a "mixed" aryltrimethylstannane and alkenyltrimethylstannane coupling would be attempted. It was envisaged that the distannane **112** would be transformed into the tricycle **113** upon treatment with copper(I) chloride (equation 46).



112 (46) 113

3.7 Intramolecular oxidative coupling of bisalkenyltrimethylstannanes to produce 9- and 10-membered rings

With the successful development of the intramolecular oxidative coupling protocol of bisalkenyltrialkylstannane functions to form 4- to 8-membered rings,[9] it seemed only logical to extend the scope of the copper(I)-mediated reaction to include the formation of 9- and 10-membered carbocycles. With this in mind, the substrates of general structure **114**, which incorporate two alkenyltrimethylstannane moieties, would be subjected to the copper(I)-mediated coupling process to form the medium ring bicycles **115** (equation 47). The configuration of the exocyclic diene in the final products **115** is likely to be *E* based on the analogous stereospecific intermolecular coupling of alkenyltrialkylstannanes (see Introduction section 2.2, pg. 7).



114 **115**

E = CO_2Et
R = H, CO_2Me, or CH_2O-Alkyl
n = 1 or 2

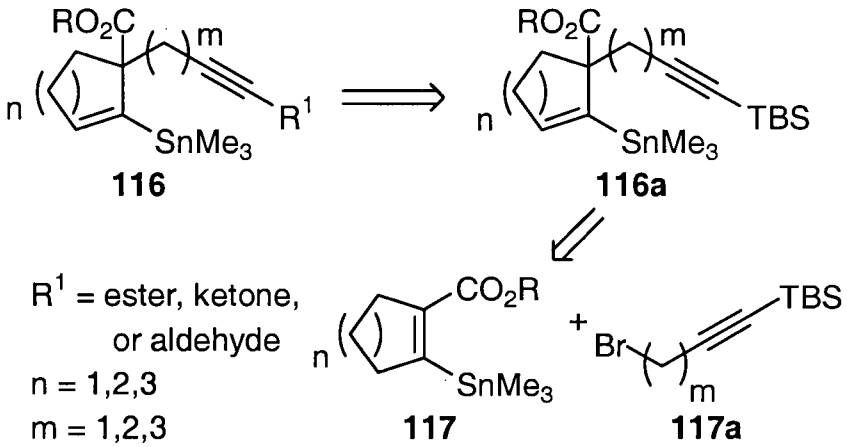
(47)

II. RESULTS AND DISCUSSION

1. Intramolecular conjugate additions of alkenyl- and aryltrimethylstannane functions to α,β-alkynic Michael acceptors mediated by copper(I) salts

1.1 Introductory remarks

In this study, we desired a synthetic pathway to the substrates necessary for the cyclization studies that was easily adaptable to future changes. With this in mind, it was envisaged that the α,β-alkynic ester functionality would be installed, in each case, at the end of the synthesis. In this manner, we could take advantage of the ability to easily change the pendant Michael acceptor and assess its potential in the methodology. For example, in the synthesis of the substrates of general structure **116**, a deconjugation-alkylation[32] strategy involving cyclic β-trimethylstannyl α,β-unsaturated esters would be employed and is shown in the brief retrosynthesis in Scheme 5. With access to esters **117** with different ring sizes and acyclic alkylating agents **117a**, the capacity to rapidly

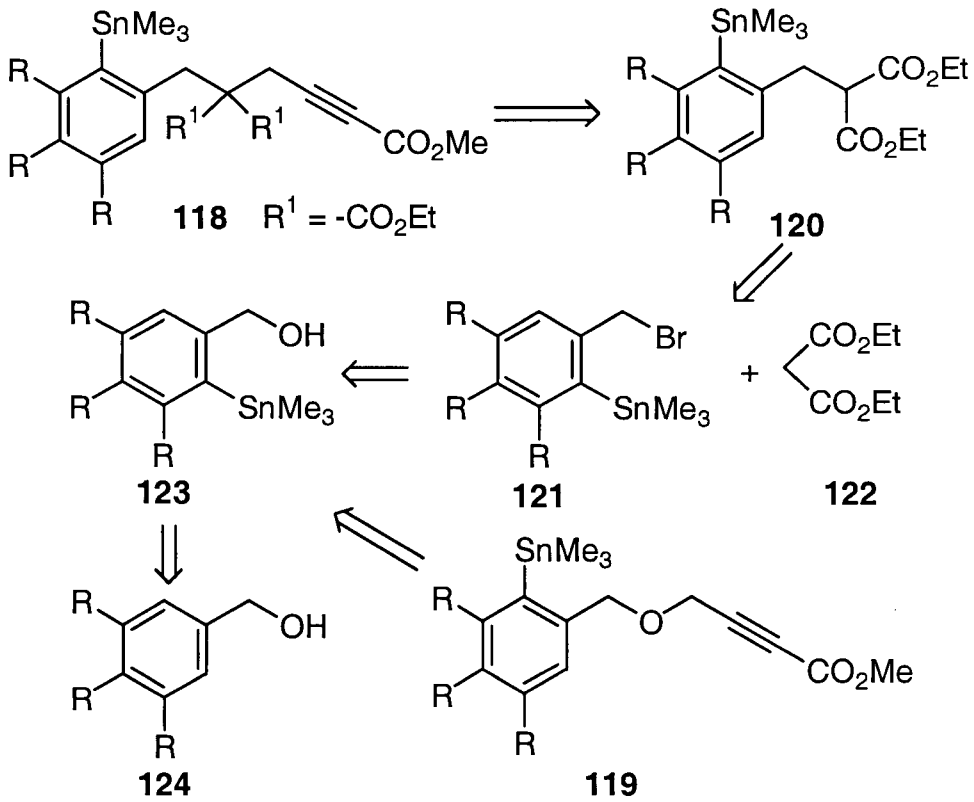


Scheme 5.

synthesize an assortment of alkenyltrimethylstannane precursors **117** and to assess the flexibility of the cyclization methodology is readily apparent. Through various functional

group manipulations, the alkyne termini contained in **116a** can be altered to synthesize not only α,β-alkynic esters but also α,β-alkynic ketones and α,β-alkynic aldehydes for investigations into the limitations and extensions of the copper(I)-mediated methodology.

Concise syntheses of the aryltrimethylstananne precursors **118** and **119** employing malonate alkylations and Williamson etherifications were planned as shown in the retrosynthetic pathways summarized in Scheme 6. The series of substituted *o*-trimethylstannylbenzyl alcohols **123** and, by a suitable functional group interconversion, the *o*-trimethylstannylbenzyl bromides **121** can be accessed by use of directed ortho-metalation[33] (DoM) of the benzyl alcohols **124**. The malonate dialkylation, ether formation, and DoM reactions together impart to the overall synthetic pathway a great deal of flexibility.

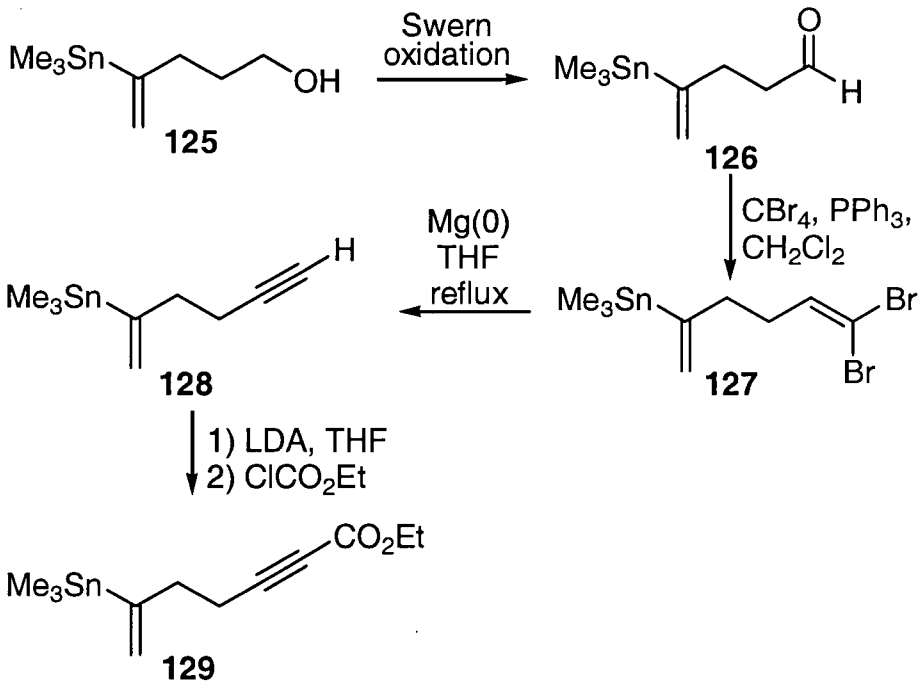


Scheme 6.

1.2 Intramolecular conjugate additions to form monocycles

1.2.1 Preparation of acyclic cyclization precursors

The synthesis of the cyclization precursor **129** (Scheme 7) began with the Swern oxidation[34] of 4-trimethylstannylpent-4-en-1-ol[35] (**125**) to the corresponding aldehyde **126** with oxalyl chloride, DMSO, and triethylamine in methylene chloride. Because the acquired aldehyde **126** was found to be quite unstable (significant decomposition of the material was observed after several hours at room temperature), the crude product of the oxidation reaction was immediately subjected to the two-step one-carbon homologation protocol developed by Corey and Fuchs.[36] Thus, treatment of the crude aldehyde **125** with carbon tetrabromide and triphenylphosphine in methylene chloride afforded the dibromoolefin **127** in excellent overall yield (90%) from the alcohol **125**.



Scheme 7.

The proposed structure of the dibromoolefin **127** was confirmed by the spectroscopic data. For example, the IR spectrum of **127** showed a tin-methyl rocking absorption at 770 cm^{-1}. The ^1H nmr spectrum indicated the presence of a

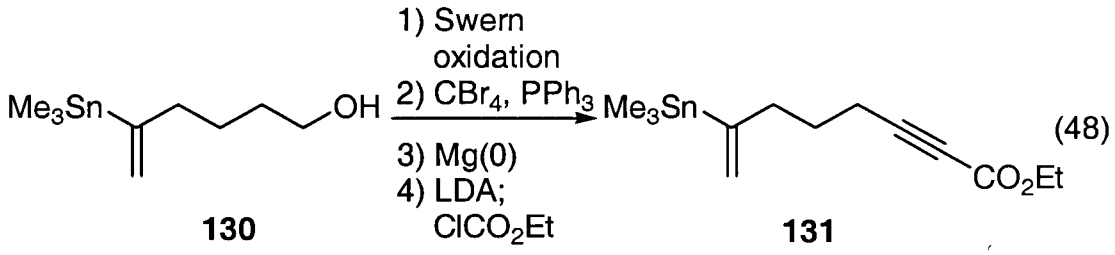
trimethylstannyl function as a 9 proton singlet located at δ 0.14, with satellite peaks (J = 52.0 Hz) arising from tin-proton coupling, three alkenyl protons (a one proton singlet at δ 5.19, $^3J_{Sn\text{-}H}$ = 69.4 Hz, a one proton singlet at δ 5.67, $^3J_{Sn\text{-}H}$ = 148.0 Hz, and a one proton triplet at δ 6.45, J = 7.0 Hz), and two methylene groups (a 2 proton multiplet at δ 2.12-2.20 and a 2 proton triplet at δ 2.35, J = 7.6 Hz, $^3J_{Sn\text{-}H}$ = 69.4 Hz). The ^{13}C nmr spectrum contained the expected 7 signals. A high resolution mass spectrometric measurement on the (M^+-Me) fragment confirmed the molecular formula of **127**.

Conversion of the dibromoalkene **127** to the alkyne **128** was accomplished by the treatment of **127** with crushed magnesium metal in refluxing THF, a protocol developed by Hijfte and coworkers.[37] Because the resultant alkyne **128** was found to be volatile and also produced an extremely sharp noxious odour, it was decided that the product, after purification by flash column chromatography on silica gel, would be immediately converted to the alkynoate **129** without characterization. A modified literature acylation procedure,[38] employing lithium diisopropylamide (LDA) and ethyl chloroformate, served to convert **128** to ethyl 6-trimethylstannylhept-6-en-2-ynoate (**129**). The overall yield of the two-step process was 79% from the dibromoalkene **127**.

The structure of ethyl 6-trimethylstannylhept-6-en-2-ynoate (**129**) was confirmed by an analysis of the spectroscopic (^{1}H nmr, ^{13}C nmr, and IR) data. The ^{1}H nmr spectrum indicated the presence of a Me_3Sn function as a 9 proton singlet located at δ 0.14 with satellite peaks (J = 53.1 Hz), two methylene groups (a 2 proton triplet at δ 2.40, J = 7.5 Hz, and a 2 proton triplet at δ 2.52, J = 7.5 Hz, $^3J_{Sn\text{-}H}$ = 50.7 Hz), and the ethyl ester function (a 3 proton triplet at δ 1.28, J = 7.2 Hz, and a 2 proton quartet at δ 4.20, J = 7.2 Hz). The ^{13}C nmr spectrum contained the expected 10 signals. In the IR spectrum, the presence of the alkyne function was indicated by the absorption at 2236 cm^{-1} and the carbonyl function was shown by the absorption at 1713 cm^{-1}. In addition, the molecular formula of **129** was confirmed by a high resolution mass spectrometric measurement on the (M^+-Me) fragment.

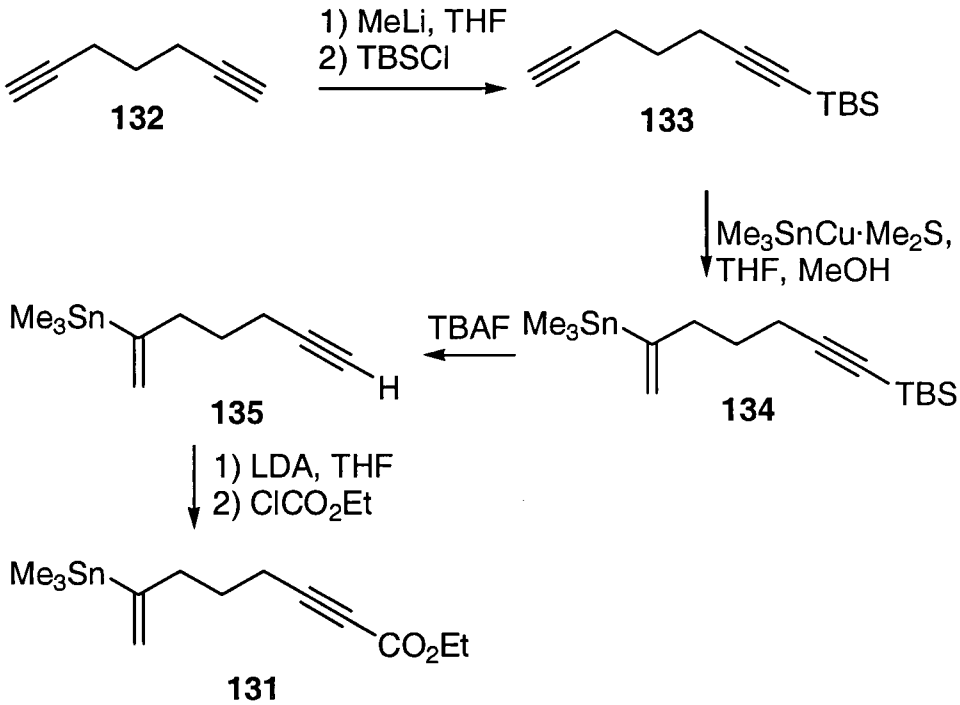
In a reaction sequence analogous to that employed to synthesize the stannane **129**, as described above, the cyclization precursor **131** was synthesized in four steps from 5-trimethylstannylhex-5-en-1-ol[35] (**130**) in an overall yield of 72% (equation 48). The structure of **129** was confirmed by analyses of the ^{1}H nmr, ^{13}C nmr, and IR spectra.

Notable in the ^{1}H nmr spectrum were the signals due to the Me_3Sn function (a 9 proton singlet at δ 0.12, $^2J_{Sn\text{-}H}$ = 52.6 Hz), three methylene groups (a 2 proton multiplet centred at δ 1.65, a 2 proton triplet at δ 2.28, J = 7.1 Hz, and a 2 proton triplet at δ 2.35, J = 7.6 Hz, $^3J_{Sn\text{-}H}$ = 63.9 Hz), and two alkenyl protons (a 1 proton multiplet at δ 5.15-5.20, $^3J_{Sn\text{-}H}$ = 70.4 Hz, and a 1 proton multiplet at δ 5.65-5.70, $^3J_{Sn\text{-}H}$ = 150.0 Hz). In addition, the ^{13}C nmr spectrum displayed the expected 11 signals. The molecular formula of **131** was confirmed by a high resolution mass spectrometric measurement on the (M^+-Me) fragment.



(48)

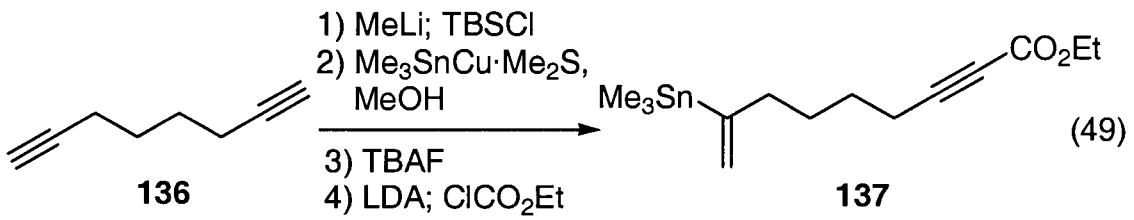
An alternative synthetic route to prepare the stannane **131** is illustrated in Scheme 8. Monosilylation of commercially available 1,6-heptadiyne (**132**) was achieved by treatment of this material with methyllithium (MeLi) in THF at -20 °C, followed by quenching the resultant lithium acetylide with *t*-butyldimethylsilyl chloride (TBSCl).



Scheme 8.

The acquired TBS-capped acetylene **133**[10] was converted to the alkenyltrimethylstannane **134** by the treatment of **133** with the organocopper reagent $Me_3SnCu{\cdot}Me_2S$[35] in THF in the presence of methanol. As a result of the extreme difficulty in separating the starting material **133** from the stannane **134** by column chromatography, the mixture of **133** and **134**, obtained after flash column chromatography of the crude product on silica gel, was treated with with tetrabutylammonium fluoride[39] (TBAF) in THF. The resultant mixture of **132** and **135** could be separated by chromatography on silica gel. To complete the synthetic sequence, acylation[38] of the terminal alkyne function of **135** by sequential treatment with LDA and ethyl chloroformate provided **131** in a four-step overall yield of 20% from the diyne **132**. The material obtained by this synthetic route was found to be spectroscopically identical with the material synthesized previously (*vide supra*).

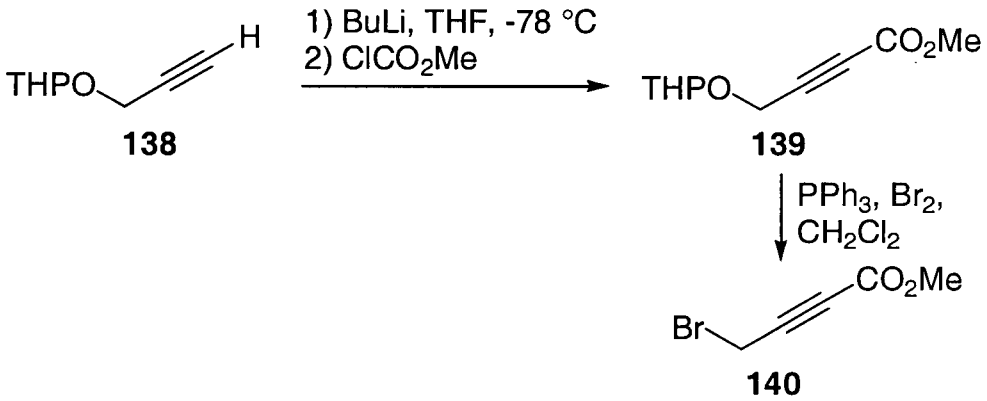
A route essentially identical with that shown in Scheme 8 was employed to synthesize the six-membered ring cyclization precursor **137** in four steps from commercially available octa-1,7-diyne (**136**) with an overall yield of 28% (equation 49). The proposed structure of ethyl 8-trimethylstannnylnon-8-en-2-ynoate (**137**) was supported by spectroscopic data. For example, the ^1H nmr spectrum of **137** showed resonances corresponding to the Me_3Sn function, four methylene groups, two alkenyl protons, and the ethyl ester moiety. The ^{13}C nmr spectrum displayed the expected 12 signals and a high resolution mass spectrometric measurement on the (M^+-Me) fragment confirmed the molecular formula of $C_{14}H_{24}O_2Sn$.



(49)

Methyl 4-bromobut-2-ynoate (**140**) was required for the projected synthesis of the cyclization precursor **143** (Scheme 10). The former substance was prepared in two steps from commercially available tetrahydro-2-(2-propynyloxy)-2*H*-pyran (**138**) (Scheme 9). Sequential treatment of **138** with BuLi and methyl chloroformate[38] in THF at -78 °C provided the α,β-alkynic ester **139** in an excellent yield (99%). Following a modified literature procedure,[40] the tetrahydropyranyl ether function in **139** was converted directly to the bromide by treatment of this material with triphenylphosphine dibromide in

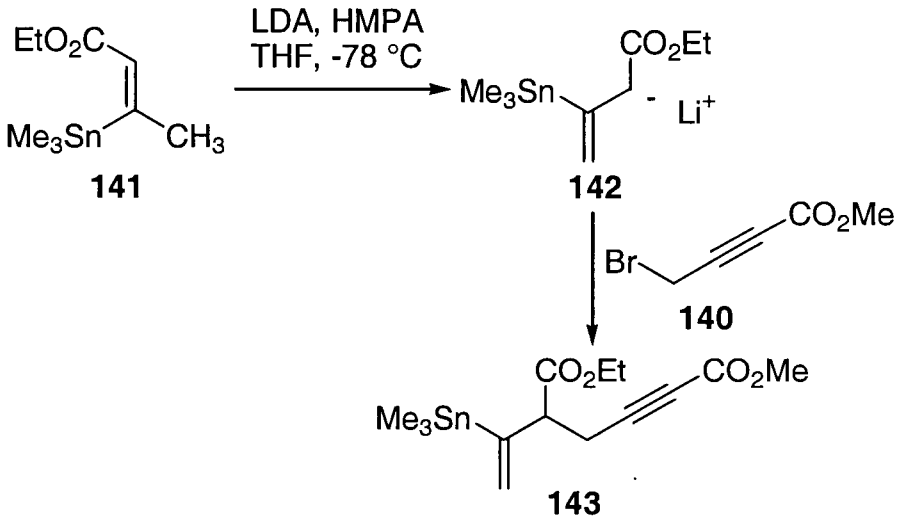
methylene chloride. The required alkylating agent **140** was obtained in very good yield (87%).



Scheme 9.

The identity of the bromide **140** was confirmed by an analysis of the spectroscopic data. The presence of the alkyne moiety was indicated by the C-C triple bond stretch in the IR spectrum at 2245 cm^{-1}, the bromide function by the C-Br stretching absorption located at 625 cm^{-1}, and the carbonyl group was shown by the absorption at 1718 cm^{-1}. In the ^{1}H nmr spectrum, signals for the methylene group (a 2 proton singlet at δ 3.93), and the methyl ester function (a 3 proton singlet at δ 3.77) were present. In addition, the expected 5 signals were present in the ^{13}C nmr spectrum. Lastly, the molecular formula of $C_5H_5O_2Br$ was confirmed by a high resolution mass measurement on the molecular ion.

With the bromide **140** in hand, the cyclization precursor **143** could readily be prepared from ethyl (*Z*)-3-trimethylstannylbut-2-enoate (**141**).[41] The latter material was prepared by reaction of ethyl but-2-ynoate with lithium trimethylstannyl(cyano)cuprate according to a literature procedure.[38] Treatment[32] of **141** with LDA and hexamethylphosphoramide (HMPA) in THF, followed by quenching the resulting enolate anion **142** with the bromide **140**, afforded, after an aqueous work-up, a mixture of **143** and a substantial amount of a brown, intractable material. Flash chromatography of this material afforded **143** in moderate yield (58%). Nevertheless, sufficient quantities for use in this study were prepared in this fashion.



Scheme 10.

The proposed structure of methyl 5-ethoxycarbonyl-6-trimethylstannylhept-6-en-2-ynoate (**143**) formed from the deconjugation-alkylation reaction was confirmed by the spectroscopic (^{1}H nmr, ^{13}C nmr, and IR) data. For instance, in the IR spectrum, the presence of the alkyne moiety was indicated by the C-C triple bond absorption located at 2241 cm^{-1}, the carbonyl functions by the strong absorption band located at 1718 cm^{-1}, and the Me_3Sn moiety by the absorption at 773 cm^{-1}. Notable in the ^{1}H nmr spectrum were the resonances ascribed to the Me_3Sn function (a 9 proton singlet at δ 0.11, $^2J_{Sn\text{-}H}$ = 52.9 Hz), the methine proton (a 1 proton triplet at δ 3.43, J = 7.5 Hz, $^3J_{Sn\text{-}H}$ = 58.2 Hz), a set of diastereotopic methylene protons (a 1 proton doublet of doublets at δ 2.51, J = 7.5, 17.2 Hz, mutually coupled to a 1 proton doublet of doublets at δ 2.88, J = 7.5, 17.2 Hz), and two vinylic protons (two 1 proton multiplets centred at δ 5.40 and δ 5.83). The ^{13}C nmr spectrum contained the 12 resonances expected for **143**. Lastly, a high resolution mass measurement on the (M^+-Me) fragment confirmed the molecular formula of the stannane **143**.

Having completed the syntheses of the desired cyclization precursors **129**, **131**, **137**, and **143**, we could now investigate the copper(I)-mediated conjugate addition processes.

1.2.2 Copper(I) chloride-mediated cyclizations

To begin the study, ethyl 6-trimethylstannylhept-6-en-2-ynoate (**129**) was subjected to a reaction protocol developed previously for the copper(I)-mediated cyclization of alkenyltrimethylstannane functions to α,β-alkynic esters[28] (Table 2, entry 1). After treatment of **129** with 2.5 equiv of copper(I) chloride in dry DMF at 0 °C for 15 min, quenching the dark red reaction mixture with aqueous ammonium chloride-ammonia, and subsequent purification of the crude product by flash column chromatography, the cyclobutane derivative **144** was obtained in a modest yield (64%). Not unexpectedly (see Introduction section 3.4.2, pg. 22), the major side product in the reaction was determined to be the α-trimethylstannyl ester **145** in an isolated yield of 18%. In addition, by thin layer chromatographic (tlc) analysis, uncharacterized polar material was detected in the crude reaction mixture.

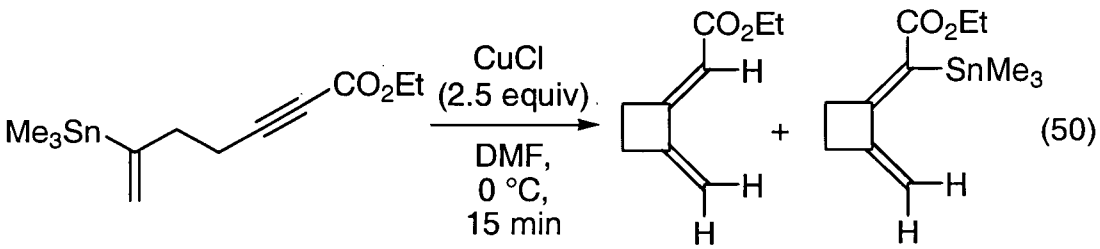


Table 2. Synthesis of the dienes **144** and **145**

Entry	Reaction Conditions[a]	% Yield[b] **144**	% Yield[b] **145**
1	CuCl (2.5 equiv), DMF, 0 °C, 15 min	64	18
2	CuCl (2.5 equiv), DMF, 0 °C, 1 h	60	6
3	CuCl (2.5 equiv), DMF, 0 °C, 15 min, then 1 M HCl	77	0
4	CuCl (2.5 equiv), AcOH (5 equiv), DMF, 0 °C, 15 min	85	0

[a] NH_4Cl-NH_3 (pH 8) was used in the workup in each case.
[b] Isolated yield of purified products.

The proposed structure of the diene **144** was confirmed by the spectral (^1H nmr, ^{13}C nmr, and IR) data. In the IR spectrum of **144**, the carbonyl function was indicated by the absorption located at 1713 cm^{-1}. In the ^1H nmr spectrum, resonances due to two methylene groups (a 2 proton multiplet centred at δ 2.73 and a 2 proton triplet of doublets

at δ 3.02, J = 8.0, 2.5 Hz), three alkenyl proton signals (a 1 proton singlet at δ 4.94, a 1 proton multiplet centred at δ 5.38, and a 1 proton multiplet centred at δ 5.87), and the ethyl ester function (a 3 proton triplet at δ 1.26, J = 7.1 Hz, and a 2 proton quartet at δ 4.15, J = 7.1 Hz) were present. In addition, the (*E*)-configuration of the newly formed α,β-unsaturated ester function in **144** was confirmed by suitable nuclear Overhauser enhancement difference (nOed) experiments.[42] Thus, irradiation of the resonance attributable to the olefinic methine proton, located at δ 5.87, resulted in an enhancement in the resonance due to the proximal vinylic proton at δ 5.38. Confirming the results from the first nOed experiment, the reverse nOe enhancement was also observed. The remainder of the nOed experiments carried out on **144** are summarized in Figure 3. In the ^{13}C nmr spectrum, the expected 13 resonances were shown and, in an APT experiment, two negative signals at δ 14.3 and 108.3 could be attributed to the trimethylstannyl group and the lone sp^2 methine carbon, respectively. The molecular formula of **144** was confirmed with a HRMS measurement on the molecular ion.

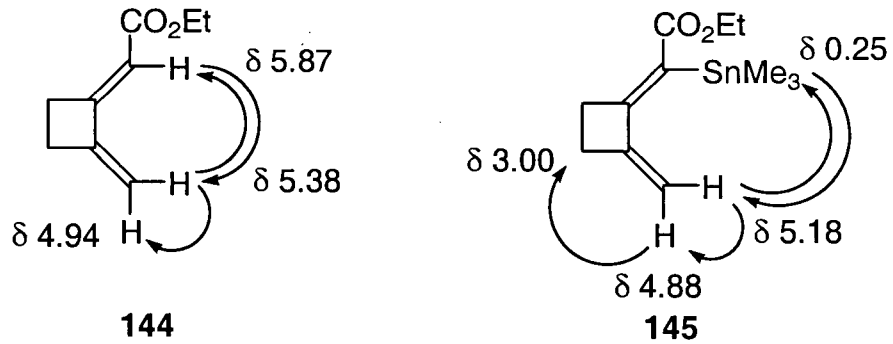


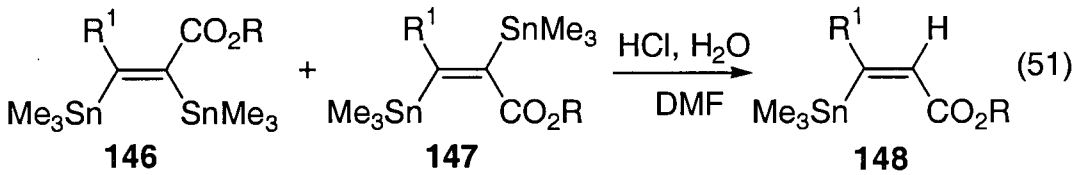
Figure 3. NOed experiments on **144** and **145**

The constitution and configuration of the minor product **145** was determined with various spectroscopic aids. In the IR spectrum, the carbonyl function was shown by the absorption at 1699 cm^{-1} and the presence of the trimethylstannyl function was indicated by the tin-methyl rocking absorption located at 772 cm^{-1}. The ^1H nmr spectrum exhibited signals due to the presence of the Me_3Sn moiety (a 9 proton singlet at δ 0.25, $^3J_{Sn\text{-}H}$ = 56.2 Hz), two methylene groups (a 2 proton multiplet centred at δ 2.62 and a 2 proton multiplet centred at δ 2.95), two alkenyl protons (a 1 proton singlet at δ 4.88 and a 1 proton triplet at δ 5.18, J = 2.7 Hz), and the ethyl ester function (a 3 proton triplet at

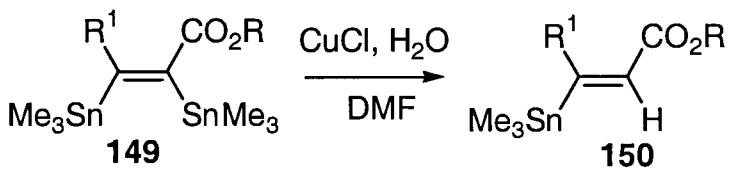
δ 1.26, J = 7.1 Hz and a 2 proton quartet at δ 4.14, J = 7.1 Hz). A nOed experiment, in which irradiation of the signal located at δ 5.18 enhanced the resonances attributable to the geminal proton at δ 4.88 and the Me_3Sn group, determined the (*Z*)-configuration of the exocyclic tetrasubstituted double bond. The corresponding reverse nOed effects were also observed (Figure 3). Lastly, a HRMS measurement on the (M^+-Me) fragment confirmed the molecular formula of **145**.

It was found that increasing the duration of the reaction from 15 min to 1 h (Table 2, entry 2), a modification shown in previous studies to eliminate related α-stannylated side products,[28b] successfully reduced the production of the α-trimethylstannyl ester **145** to 6% but, unfortunately, simutaneously diminished the yield of the desired cyclized product **144** to 60%. In addition, tlc analyses showed that a considerable amount of polar material was present in the crude product. It appeared that by allowing the reaction to proceed for extended periods of time, competitive decomposition of reaction intermediates and/or reaction products was occurring in the reaction mixture. This poor outcome forced us to abandon this strategy.

It was surmised that a successful reaction protocol would require a suitable quenching agent and, furthermore, it was our belief that a proton source more acidic than the aqueous ammonium chloride-ammonia (pH 8) employed in the workup would be required to protiodestannylate the α-trimethylstannyl ester **145** formed in the reaction pathway (Scheme 11). This notion was supported by related work in our laboratory which had shown that the α-trimethylstannyl function of alkyl (*Z*)- and (*E*)-2,3-bis(trimethylstannyl)-2-alkenoates **146**, **147**, and **149** can be selectively removed by hydrochloric acid-mediated and copper(I) chloride-catalyzed protiodestannylations (equations 51 and 52, respectively).[43]

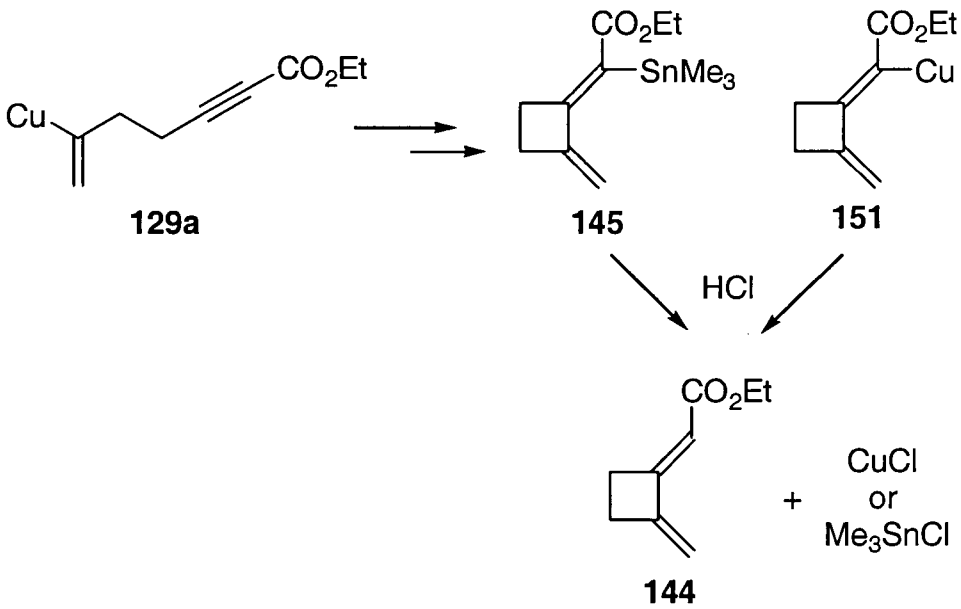


(51)



(52)

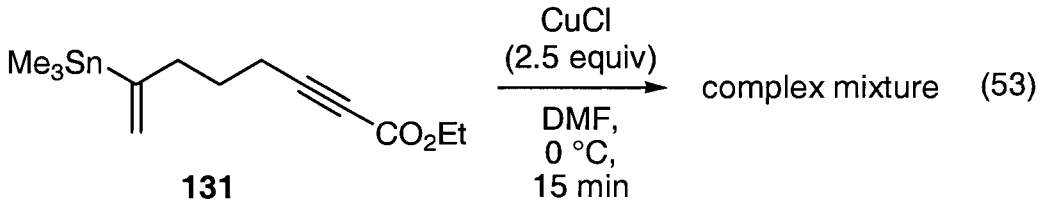
Indeed, the presence of the undesired stannane **145** was completely curtailed with a simultaneous increase in the isolated yield of **144** to a satisfactory 77% when aqueous 1 M HCl was added after the reaction had been allowed to proceed for 15 min (Table 2, entry 3). The hydrochloric acid appeared to serve well in the capacity to protiodestannylate the α-trimethylstannyl ester **145** and to quench the α-copper(I) intermediate **151** (Scheme 11). This alternative protiodestannylation/quenching strategy led to the development of an experimental protocol employing the use of an *in situ* proton source (acetic acid) in the reaction pot (see Discussion section 1.5.1, pg. 64, for additional details).



Scheme 11.

An excellent yield (85%) of (*E*)-1-ethoxycarbonylmethylidene-2-methylidene cyclobutane (**144**) was obtained when the alkenyltrimethylstannane **129** was treated with 2.5 equiv of CuCl and 5 equiv of acetic acid at 0 °C in dry DMF for 15 min (Table 2, entry 4). More satisfyingly, no other detectable products, including the geometric isomer of **144**, were seen by tlc or ^{1}H nmr analysis of the crude reaction mixtures. It is clear from this result that the intramolecular cyclization process is faster than the intermolecular quench of the acyclic species **129a** by acetic acid. Motivated by these key observations and by having prepared the cyclobutane derivative **144** in a very satisfactory yield, it was decided to test the next cyclization precursor in the study.

Surprisingly, when the 5 membered ring precursor **131** was subjected to the initially employed reaction conditions (Table 2, entry 1), the reaction failed. Tlc analyses of the crude product after aqueous workup showed the presence of only minor amounts of the product **153** (Scheme 12) and a great deal of colored polar material (equation 53).



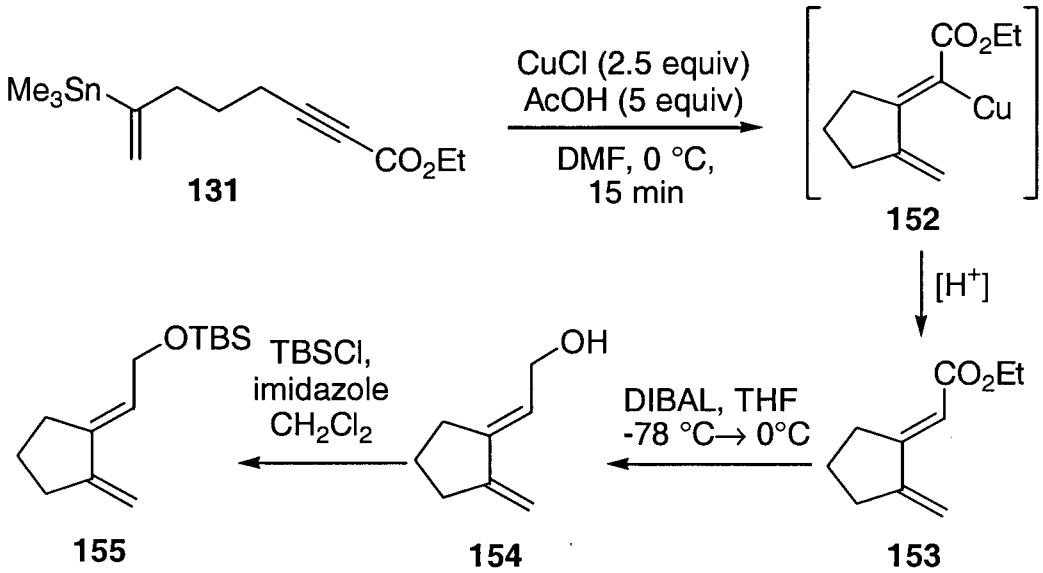
131

The polar material, containing several compounds by tlc analysis, was isolated as one fraction after flash column chromatography of the crude product. However, a ^{1}H nmr spectrum of the acquired mixture did not provide any useful information to identify the products formed. To further complicate matters, the isolated traces of the desired product **153** proved to be unstable and polymerized upon standing in a freeezer over a period of a couple of days. However, the slow rate at which the product **153** decomposed/polymerized did not account for the low yield of **153** nor for the formation of large amounts of yellow polar material during the relatively short reaction times (15 min). The attempted conversion of **131** into **153** under these reaction conditions was not investigated further.

Gratifyingly, when the modified reaction conditions (Table 2, entry 4) with acetic acid present in the reaction mixture were employed, the desired cyclized product **153** was formed in ~80% yield (Scheme 12). Apparently, the increase in the efficiency of the transformation was due to the relatively rapid protonation of the intermediate copper(I) species **152** by the acetic acid, thus precluding extensive decomposition of this intermediate. However, as mentioned previously, the diene **153** was prone to polymerization/decomposition and a suitable analytical sample could not be obtained.

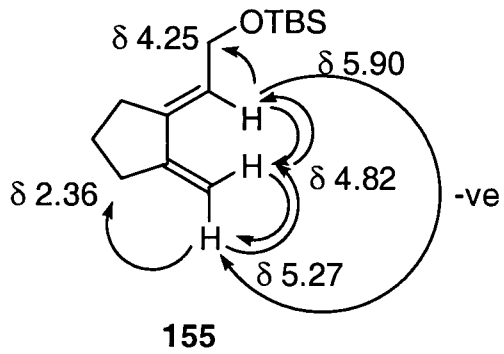
In the hopes of obtaining a stable derivative for characterization purposes, it was decided to reduce **153** to the corresponding alcohol. Treatment of the crude product of the cyclization process with diisobutylaluminum hydride[44] (DIBAL) in THF yielded the allylic alcohol **154**. Disappointingly, this product also proved to be unstable and polymerized over several days to give a hard, plastic-like substance. Not to be discouraged, a stable derivative which could be stored for extended periods of time was

obtained by conversion of the alcohol **154** into the TBS ether **155**. Thus, treatment of **154** with TBSCl[39] in the presence of imidazole formed the ether **155** in excellent overall yield (84%) from the stannane **131** (Scheme 12).



Scheme 12.

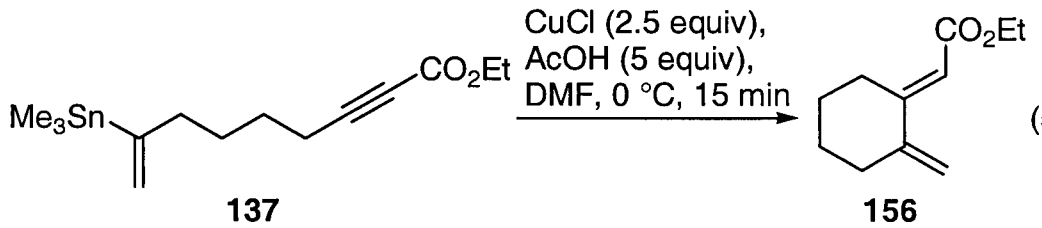
The structure of the TBS ether **155** was confirmed by an analysis of spectrometric data. Notable in the IR spectrum was the presence of a C-C double bond stretching absorption at 1628 cm^{-1}. In the ^1H nmr spectrum, resonances due to four methylene groups (a 2 proton multiplet at δ 1.60-1.75, a 4 proton multiplet at δ 2.30-2.42, and a 2 proton doublet at δ 4.25, J = 6.2 Hz), three alkenyl protons (two 1 proton singlets at δ 4.82 and 5.27 and a 1 proton multiplet centred at δ 5.90), and the *t*-butyldimethylsilyl ether moiety (a 6 proton singlet at δ 0.06 and a 9 proton singlet at δ 0.89) were seen. In addition, the ^{13}C nmr spectrum of **155** displayed the expected 11 signals and the molecular formula of $C_{14}H_{26}OSi$ was confirmed by a high resolution mass spectrometric measurement on the molecular ion. The (*E*)-configuration of the exocyclic double bond was confirmed by a series of nOed experiments which are summarized in Figure 4. Serving as additional confirmation to the nOe effects already gathered, a negative or "relay" nOe[45] was also observed as illustrated below.



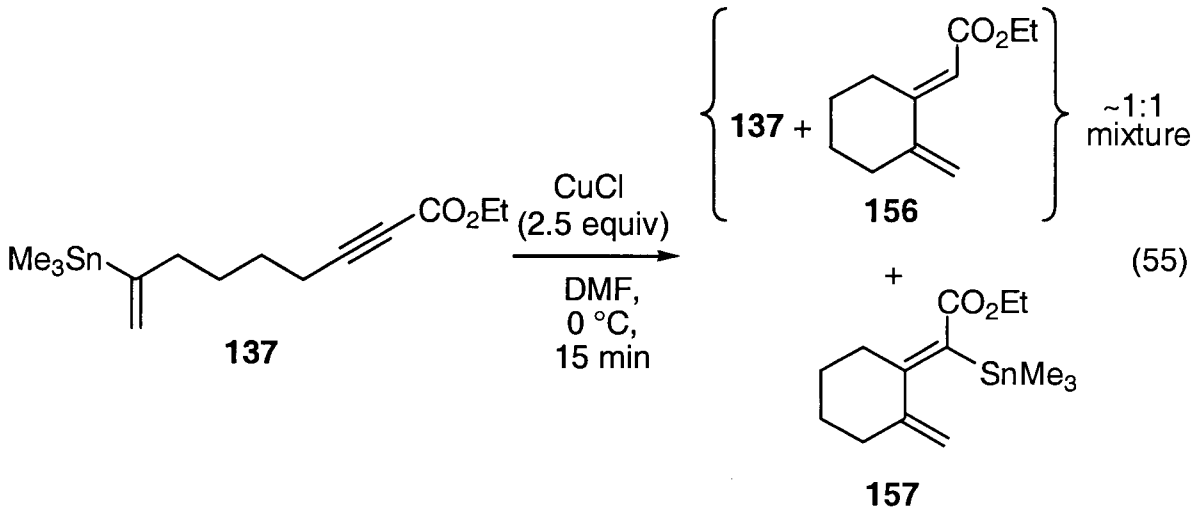
155

Figure 4. NOed experiments on **155**

The superiority of the modified cyclization procedure, employing acetic acid, to form a 6-membered ring was exemplified in the conversion of the precursor **137** to the cyclic diene **156** (equation 54). It was found that treatment of the stannane **137** under "standard" conditions (2.5 equiv CuCl, 5 equiv AcOH, DMF, 0 °C, 15 min) resulted in



137 **156** (54)



137 **156** **157** (55)

the formation of **156** in an excellent isolated yield (87%). In stark contrast, subjection of **137** to the experimental conditions that did not employ acetic acid in the reaction pot resulted in a 48% isolated yield of the α-trimethylstannyl ester **157** and an inseparable

mixture of the cyclized product **156** and the starting material **137** in a ~1:1 ratio (equation 55).

The structural assignment for **156** was fully supported by the spectroscopic data collected. For example, the IR spectrum clearly showed the C=C bond stretch due to the exocyclic methylene at 1636 cm^{-1} and the carbonyl absorption at 1714 cm^{-1}. Notable in the ^1H nmr spectrum were the signals for three alkenyl protons (three 1 proton multiplets centred at δ 4.70, 5.03, and 5.83), and four methylene groups (a 4 proton multiplet at δ 1.60-1.75, and two 2 proton broad unresolved multiplets at δ 2.30 and 2.60). The molecular formula of **156** was confirmed by a high resolution mass measurement on the molecular ion. Finally, the (*E*)-configuration of the trisubstituted olefin bearing the ethyl ester function was confirmed by a series of nOed experiments summarized in Figure 5.

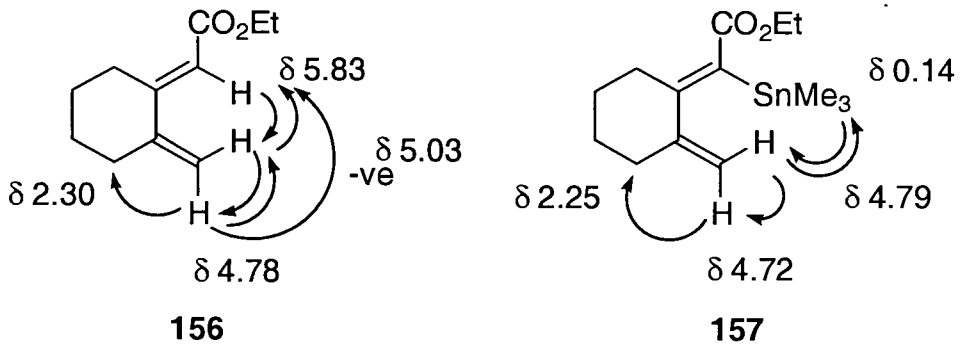
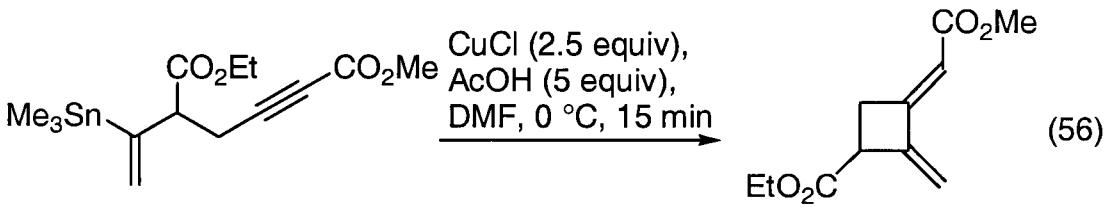


Figure 5. NOed experiments on **156** and **157**

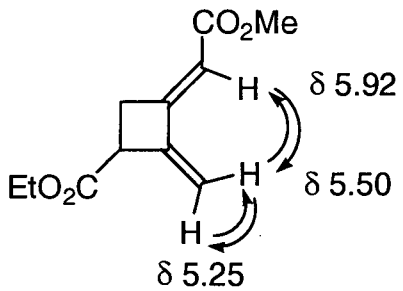
The constitution and configuration of the minor product **157** was confirmed by the spectrometric data (^1H nmr and IR). The IR spectrum showed the presence of the trimethylstannyl function by the absorption at 774 cm^{-1} and the alkenyl functions by the stretching absorptions at 1604 and 1635 cm^{-1}. The ^1H nmr spectrum displayed resonances due to the trimethylstannyl function (a 9 proton singlet at δ 0.14, $^2J_{Sn\text{-}H}$ = 53.1 Hz), four methylene groups (two 2 proton multiplets centred at δ 2.41 and 2.25 and a four proton multiplet centred at δ 1.67), and two alkenyl signals (two 1 proton multiplets centred at δ 4.79 and 4.72). The molecular formula of **157** was confirmed by a HRMS measurement on the (M^+-Me) fragment. The (*Z*)-configuration of the double bond was confirmed by a series of nOed experiments summarized in Figure 5.

Lastly, the acyclic precursor **143** was subjected to the copper(I)-mediated cyclization protocol without the addition of the acetic acid. Disappointingly, after purification of the crude product by flash column chromatography on silica gel, a moderate yield (52%) of **158** was obtained. However, upon switching to the modified reaction conditions employing 5 equiv of acetic acid (equation 56), the yield of **158** improved to 85%. Also isolated was a very minor amount (~5%) of unidentifed protiodestannylated starting material.



143 **158** (56)

The spectroscopic data collected fully support the proposed structure of **158**. In the IR spectrum, the carbonyl stretching absorption band at 1734 cm^{-1} and the C=C double bond stretch at 1665 cm^{-1} could be seen clearly. The ^1H nmr spectrum showed signals due to the methylene protons (a 1 proton doublet of doublets at δ 3.22, J = 2.5, 18.1 Hz, mutually coupled to a 1 proton doublet of doublets at δ 3.38, J = 2.8, 18.1 Hz), the cyclobutane methine proton (a 1 proton multiplet centred at δ 3.80), and the three alkenyl protons (a 1 proton singlet at δ 5.25, a 1 proton doublet at δ 5.50, J = 2.5 Hz, and a 1 proton doublet of doublets at δ 5.92, J = 2.5, 2.5 Hz). By a series of nOed experiments summarized in Figure 6, the trisubstituted double bond in the diester **158** was determined to possess an (*E*)-configuration.



158

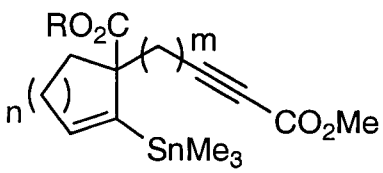
Figure 6. NOed experiments on **158**

The positive impact of the new protocol developed for the cyclization of alkenyltrimethylstannane functions to α,β-alkynic esters can be seen clearly in the increased efficiency of the transformations, especially in the conversion of **143** to **158** and **137** to **156**. These impressive results to form the stereodefined 4-, 5-, and 6-membered ring compounds **144** and **158**, **153**, and **156**, respectively, prompted us to apply this vastly improved protocol (2.5 equiv CuCl, 5 equiv AcOH, DMF, 0 °C, 15 min) in future studies relating to the intramolecular conjugate addition of alkenyl- and aryltrimethylstannane functions to α,β-alkynic esters. A discussion of a mechanistic pathway somewhat modified from that proposed previously[28] can be found in Discussion section 1.5.1.

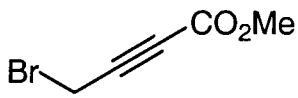
1.3 Intramolecular cyclizations to form bicyclic compounds

1.3.1 Preparation of cyclization precursors

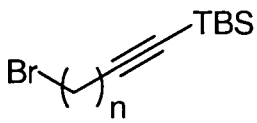
In order to prepare a series of bicyclic cyclization precursors of general structure **116b**, we required the alkylating agents **140**, **159**, and **160-162** and the cyclic β-trimethylstannyl α,β-unsaturated esters **163-165**. Collectively, these substances could



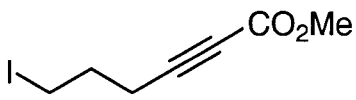
116b



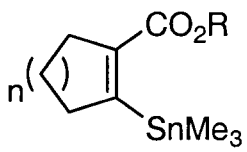
140



160 n = 1
161 n = 2
162 n = 3



159

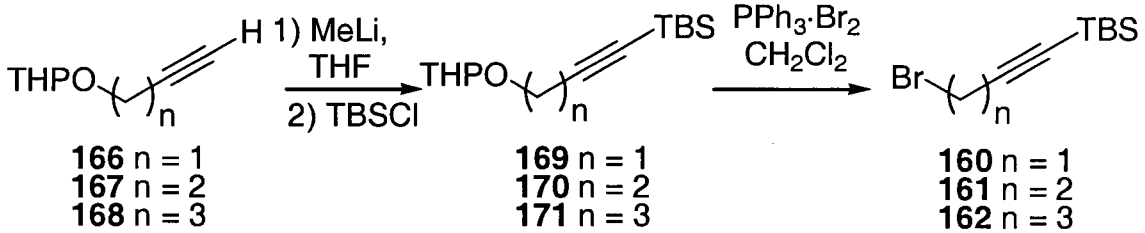


163 n = 1, R = Me
164 n = 2, R = Et
165 n = 3, R = Me

Chart 1.

be employed in a number of deconjugation-alkylation reactions. Of the electrophiles shown in Chart 1, the preparation of the propargylic bromide **140** was described in section 1.2.1. The remaining compounds were prepared as described below.

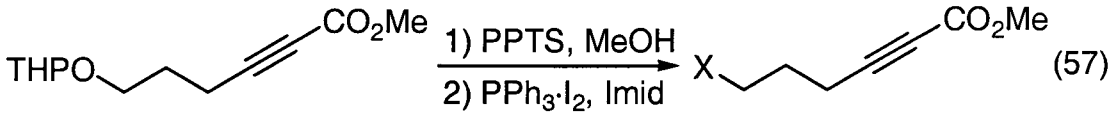
Each of the bromides **160-162** were synthesized as illustrated in Scheme 13. Silylation of the terminal alkynes **166-168**[46] was, in each case, achieved by reaction of the substrate with MeLi in THF, followed by quenching the resultant lithium acetylide with TBSCl.[10] Reaction of each of the resultant products **169-171** with triphenylphosphine dibromide in methylene chloride as described by Sonnet,[40] effected the conversion of the THPO function into the corresponding bromide. Thus, the bromides **160-162** were formed in two step yields of 70%, 55%, and 53% from the alkynes **166-168**, respectively. The spectral data (^{1}H nmr, ^{13}C nmr, and IR) obtained from the silyl ethers **169-171** and the bromides **160-162** were fully consistent with their assigned structures and their molecular formulae were confirmed by suitable HRMS measurements.



166 n = 1 **167** n = 2 **168** n = 3 | **169** n = 1 **170** n = 2 **171** n = 3 | **160** n = 1 **161** n = 2 **162** n = 3

Scheme 13.

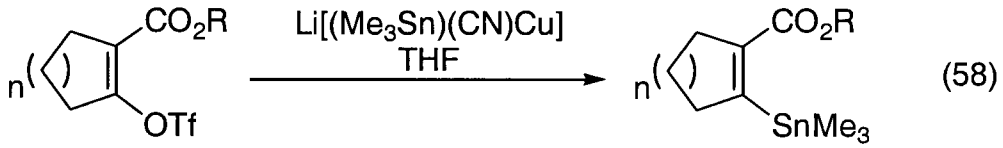
The iodide **159** was prepared from the known alkynoate **172**[47] by a standard removal of the THP group with pyridinium *p*-toluenesufonate (PPTS) in methanol,[46] followed by treatment of the resultant alcohol with triphenylphosphine diiodide and imidazole.[48] The overall yield of **159** was 79%. The iodide **159** exhibited spectral characteristics identical with those reported previously.[47]



172 | **173** X = OH **159** X = I (57)

Reaction of each of the enol triflates **174**,[28b] **175**,[28b] and **176**[10] with lithium (trimethylstannyl)(cyano)cuprate[38] in THF provided the known cyclic

alkenyltrimethylstannanes **163-165** in isolated yields of 92%, 93%, and 76%,[49] respectively (equation 58). The spectroscopic data derived from the esters **163-164**[28b] and **165**[10] were in full accord with those previously reported.

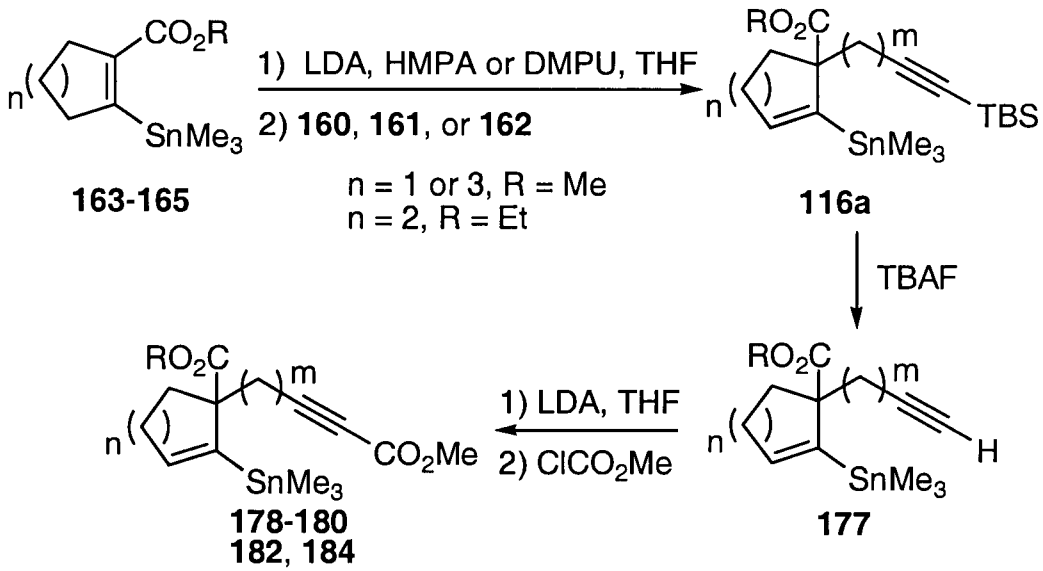


(58)

174 n = 1, R = Me
175 n = 2, R = Et
176 n = 3, R = Me

163 n = 1, R = Me
164 n = 2, R = Et
165 n = 3, R = Me

The cyclization precursors **178-180**, **182**, and **184** were prepared as shown in Scheme 14 and in Table 3, entries 1-3, 5, and 7. The deconjugation-alkylation[32] of the esters **163-165** with LDA and HMPA (or DMPU) in THF, followed by quenching the derived enolate with the appropriate bromide **160**, **161**, or **162**, provided the alkylated substances **115**. The silyl functions in **116a** were removed with TBAF in THF to give the terminal alkynes **177** and, lastly, the terminal ester function was installed by the sequential treatment of the alkynes **177** with LDA and methyl chloroformate to provide the cyclization precursors **178-180**, **182**, and **184**. The moderate three step overall

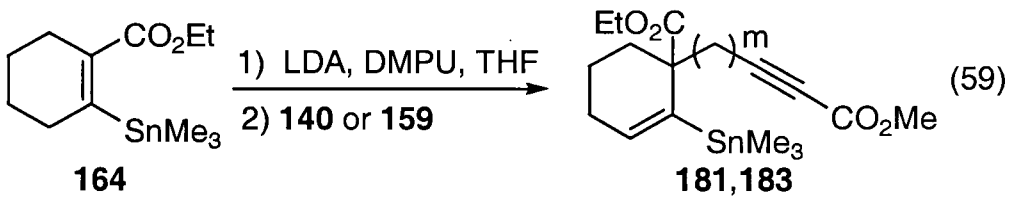


Scheme 14.

yields (33%, 35%) of **179** and **182** (Table 3, entries 2 and 5) were mainly due to difficulties arising from the elimination of HBr from the homopropargylic bromide **161** in

the deconjugation-alkylation step. On the other hand, for reasons which are not readily apparent, alkylation of the alkenylstannane **165** with the bromide **162** was also an inefficient process (~35%, see Experimental pg. 160) and, as a result, the overall yield of **184** from **165** was only 22% (Table 3, entry 7). Despite these problems, sufficient quantities of the cyclization precursors to test the proposed methodology were prepared in this manner.

Lastly, treatment of ethyl 2-trimethylstannylcyclohex-1-enecarboxylate (**164**) with LDA and DMPU, followed by the addition of the propargylic bromide **140** or the primary alkyl iodide **159,** supplied the expected alkylated substances **181** and **183**, respectively (equation 59 and Table 3, entries 4 and 6).



164 **181,183** (59)

Table 3. Synthesis of the cyclization precursors **178-184**

Entry	Substrate	n	m	Product	Procedure[a]	% Yield[b]
1	**163**	1	1	**178**	A	55
2	**163**	1	2	**179**	A	33[c]
3	**163**	1	3	**180**	A	65
4	**164**	2	1	**181**	B	51
5	**164**	2	2	**182**	A	35[c]
6	**164**	2	3	**183**	B	58
7	**165**	3	3	**184**	A	22

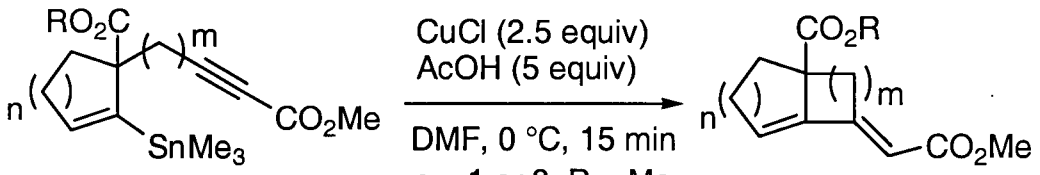
[a] Procedure A - following the reaction sequence illustrated in Scheme 14.
Procedure B - following the reaction sequence illustrated in equation 59.
[b] Isolated (overall) yields of purified products from the substrates **163-165**.
[c] Elimination of the homopropargylic bromide alkylating agents was a major side reaction in the deconjugation-alkylation step.

In each case, the spectral data collected for the diesters **178-184** were in full accord with their assigned structures. Using methyl 5-(1-methoxycarbonyl-2-trimethyl stannylcyclopent-2-en-1-yl)pent-2-ynoate (**179**) as an example, the IR spectrum indicated the presence of the alkynic function by the C-C triple bond stretching absorption at

2239 cm^{-1}, the carbonyl functions by the strong C=O stretching absorption band centred at 1718 cm^{-1}, and the Me_3Sn function by the tin-methyl rocking absorption at 770 cm^{-1}. In the ^1H nmr spectrum, resonances due to the Me_3Sn moiety (a 9 proton singlet at δ 0.13, $^2J_{Sn-H}$ = 54.3 Hz), four methylene groups (8 protons displayed as a 2 proton multiplet at δ 1.68-1.78, a 3 proton multiplet at δ 2.15-2.30, a 2 proton multiplet at δ 2.36-2.45, and a 1 proton multiplet at δ 2.47-2.56), the two methyl ester functions (two 3 proton singlets at δ 3.64 and 3.72), and one alkenyl proton (a 1 proton doublet of doublets at δ 5.98, J = 2.1, 2.1 Hz) could be identified. The ^{13}C nmr spectrum displayed the appropriate number of signals, 14, and four negative signals that appeared in an APT experiment (δ -8.6, 52.0, 52.5, and 144.3) were attributed to the Me_3Sn function, the two methyl signals from the methyl ester functions, and the olefinic methine carbon, respectively. A high resolution mass spectrometric measurement on the (M^+-Me) fragment confirmed the molecular formula of **179**. A similar analysis of the spectroscopic data (^1H nmr, ^{13}C nmr, and IR) and the HRMS measurements acquired from the remainder of the alkenyltrimethylstannanes **178** and **180-184** provided suitable confirmation of their structural identities. With the desired cyclization precursors in hand, we could now examine the copper(I) chloride-mediated methodology.

1.3.2 Copper(I) mediated cyclizations

The results derived from treatment of the cyclization precursors **178-185** with 2.5 equiv of coppper(I) chloride and 5 equiv of acetic acid in dry DMF at 0 °C for 15 min to yield the bicyclic dienes **186-193** are summarized in Table 4.



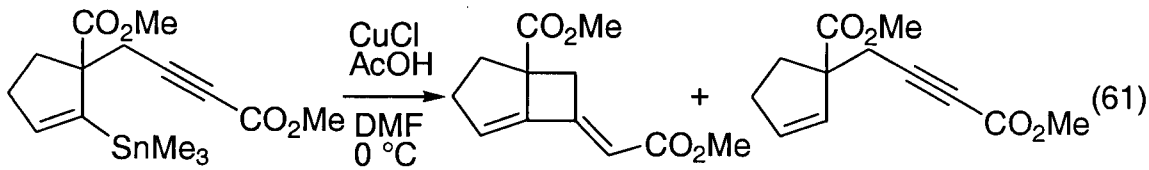
178-185 **186-193** (60)

Table 4. Synthesis of the bicycles **186-193**

Entry	Substrate	n	m	Product	% Yield[a]
1	**178**	1	1	**186**	0[b]
2	**179**	1	2	**187**	93
3	**180**	1	3	**188**	99
4	**181**	2	1	**189**	94
5	**182**	2	2	**190**	98
6	**183**	2	3	**191**	92[d]
7	**184**	3	3	**192**	94
8[c]	**185**	3	1	**193**	82

[a] Isolated yields of purified products.
[b] A complex mixture that included the cyclized product and protiodestannylated material was obtained.
[c] This example was performed by Dr. Patricia Gladstone.[31]
[d] The reaction in this case required 1 h to go to completion.

Disappointingly, when the cyclization substrate **178** was treated under standard conditions (equation 61), a complex mixture of compounds (>5 components) and colored polar baseline material was identified by tlc analysis after aqueous workup. ^{1}H nmr spectroscopic analysis of the crude product indicated the presence of two main components, the desired compound **186** and the protiodestannylated product **194**, in a ratio of ~1:1.



178 **186** **194**

Curiously, upon flash column chromatography of the crude product on silica gel, only trace amounts of the compounds that were present in the crude mixture, as indicated by the ^{1}H nmr spectrum, were obtained from the collected column fractions. Upon some investigation, it was found that the crude product mixture was very unstable and was transformed into an intractable material within minutes when concentrated. Certainly the

instability of **186** would not be unexpected, since the bicyclo[3.2.0]heptene skeleton present in this substance is extremely strained.

The presence of a significant amount of protiodestannylated product, a result unlike that observed in the remainder of the cyclization reactions of the substrates **179-185**, indicated that the intramolecular conjugate addition process for **178** was more difficult and that the rate of the cyclization process of the (proposed) organocopper intermediates **195** to the α-copper adducts **196**, in this case, was comparable to the intermolecular protonation of **195** by the acetic acid. This result is not unexpected, since the highly strained nature of the α-copper adduct **196** would infer that the transition state leading from **195** to **196** is high in energy and, as a result, the cyclization event would be disfavored. Consequently, the undesirable protiodestannylation event (**195** to **194**) might be expected to become a major pathway in this case.

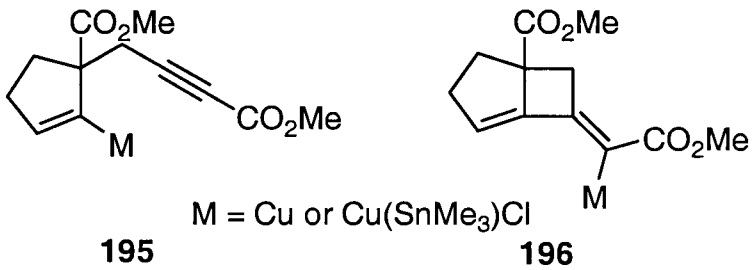


Chart 2.

In view of the failures outlined above, it was decided to treat the substrate **178** under cyclization conditions without acetic acid (i.e. 2.5 equiv CuCl, DMF, 15 min, 0 °C or 2.5 equiv CuCl, DMF, 15 min, 0 °C, then 1M HCl), in the hope that the cyclization would proceed without the premature protonatation of the uncyclized copper intermediate **195**. Unfortunately, in each case, only the presence of relatively minor amounts of the protiodestannylated product **194** was seen in the ^{1}H nmr spectrum of the crude material. No product that might correspond to the bicycle **186** could be detected. The increased presence of unidentified polar materials was indicated by tlc analysis and components of unknown structure were also seen in the ^{1}H nmr spectrum. To further exacerbate the problem, rapid product decomposition remained a major impediment in identifying and characterizing the various components in the reaction mixtures. Brief attempts to derivatize the crude product after an aqueous workup failed utterly.

Reduction/protection of the ester function in a reaction sequence similar to that used to synthesize the *t*-butyldimethylsilyl protected allylic alcohol **155** (see Discussion section 1.2.2, pg. 40) or a hydrogenation of the diene unit with H_2/Pd/C or H_2/Pt failed to provide identifiable compounds. It was at this point it was decided to abandon this particular example and to focus on testing the remaining substrates.

Greater success of the cyclization protocol was observed in the stereoselective conversion of the substrate **179** to the diene **187** (equation 60 and Table 4, entry 2, pg. 49). An excellent yield (93%) of 1-methoxycarbonyl-(*E*)-6-methoxycarbonyl methylidenebicyclo[3.3.0]oct-4-ene (**187**) was obtained after purification of the crude product by flash column chromatography on silica gel. This product was also somewhat unstable and completely polymerized over a period of a few weeks when stored under argon in a freezer. Nevertheless, the diester **187** could be characterized and the spectral data collected were in full accord with the proposed structure. In the IR spectrum, the presence of the carbonyl functions was shown by a strong absorption at 1725 cm^{-1} and a C-C double bond stretching absorption appeared at 1636 cm^{-1}. In the ^1H nmr spectrum, the resonances due to four methylene groups (see experimental section for assignments), two CO_2Me functions, and two alkenyl protons were clearly visible. With the aid of a ^1H-^1H correlated spectroscopy (COSY) spectrum, the assignment of the proton resonances in the ^1H nmr spectrum of **187** could be made and the (*E*)-configuration of the exocyclic double bond was confirmed by several ^1H nmr nOed experiments, which are illustrated in Figure 7. In the ^{13}C nmr spectrum of **187**, the expected 13 signals were observed. A high resolution mass spectrometric measurement on the molecular ion confirmed the molecular formula of $C_{13}H_{16}O_4$. In addition, a successful elemental analysis was obtained.

Results similar to that described for the conversion of **179** into **187** were obtained from the intramolecular conjugate addition of the substrates **180-185** (equation 60 and Table 4, entries 3-8, pg. 49). The corresponding bicyclic structures **188-193** were produced in excellent isolated yields (82-99%). In the case of the conversion of **183** into

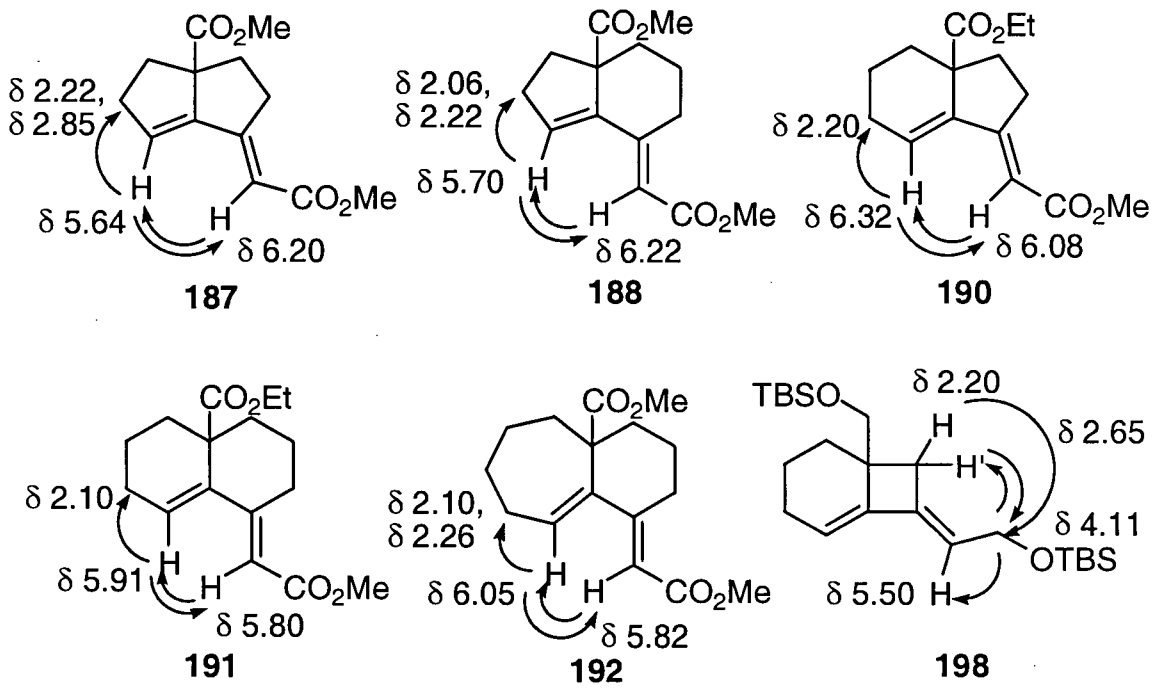


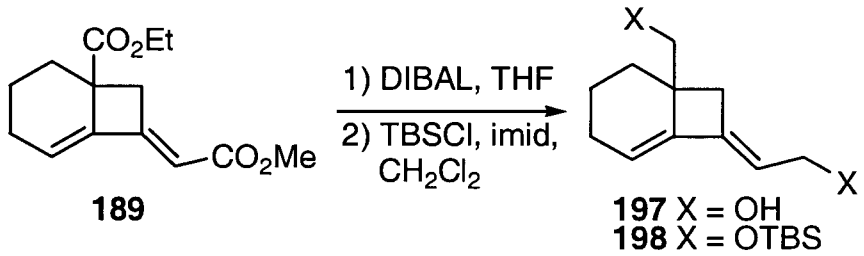
Figure 7. NOed experiments on **187**, **188**, **190-192**, and **198**

191 (Table 4, entry 6, pg. 49), the reaction required 1 h to reach completion, rather than being finished within 15 min. The reasons for this slight anomaly are not clear. Regardless, 1-ethoxycarbonyl-(*E*)-7-methoxycarbonylmethylidenebicyclo[4.4.0]oct-5-ene (**191**) was obtained from the stannane **183** in excellent yield (92%).

The spectral data (^{1}H nmr, ^{13}C nmr, and IR) and HRMS molecular mass determinations derived from the compounds **188-193** were in full accord with the assigned structures. Also, the configuration of the trisubstituted exocyclic double bond was rigorously determined for each of the compounds **188-192** through a series of ^{1}H nmr nOed experiments which are summarized in Figure 7. The (*E*) stereochemical assignment of the bicyclo[5.2.0]nonene derivative **193** was designated by analogy with the (*E*)-olefin in the bicyclo[4.2.0]octene derivative **189** and with the previous examples of four membered ring formation via this methodology (see Discussion section 1.2.2).

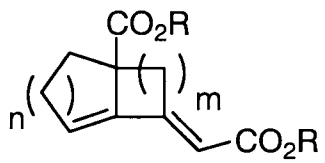
1-Ethoxycarbonyl-(*E*)-7-methoxycarbonylmethylidenebicyclo[4.2.0]oct-5-ene (**189**) although more stable than its more strained lower homolog counterpart **186**, was observed to polymerize over a period of approximately one month. For the purposes of characterization and long term storage of the material, the diester **189** was reduced with 6

equiv of DIBAL[44] in THF and the resultant diol **197**, which also proved to be prone to polymerization, was allowed to react with TBSCl and imidazole in CH_2Cl_2 to give the disilyl ether **198** (equation 62). ^1H nmr nOed experiments (Figure 7) performed on the disilyl ether **198** provided clear evidence for the (*E*)-stereochemical assignment of the trisubstituted exocyclic alkene function in **198** and, by analogy, in the α,β-unsaturated ester function of the bicycle **189**.



(62)

Collectively, the acquisition of the bicyclic cyclization products **186-193** illustrates the flexibility and versatility of the copper(I) chloride-mediated cyclization methodology to stereoselectively produce bicyclic systems of general structure **85** (Chart 3). As a testament to the scope and generality of the cyclization methodology, it is interesting to note that strained bicycles incorporating unsaturated four membered rings can also be synthesized. With the lone exception involving the conversion of the cyclization precursor **178** into the bicycle **186**, the intramolecular conjugate additions of alkenyltrimethylstannane functions to α,β-alkynic esters are not only very clean and efficient, but, experimentally, the reactions occur under mild conditions and are very facile to perform. For a discussion of the proposed mechanistic pathway of this transformation, see Discussion section 1.5.1, pg. 64).



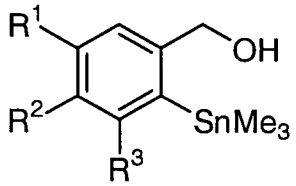
85

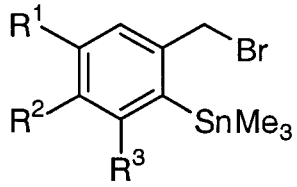
Chart 3.

1.4 Copper (I)-mediated intramolecular cyclizations of aryltrimethylstannane functions to α,β-alkynic esters

1.4.1 Preparation of cyclization precursors

The starting materials required for use in this study were the trimethylstannylbenzyl alcohols **199-201** and the corresponding benzyl bromides **202-204** (Chart 4). The preparation of these substances is described below.





199 $R^1 = R^2 = R^3 = H$
200 $R^1 = R^3 = H$, $R^2 = Me$
201 $R^1 = R^2 = R^3 = OMe$

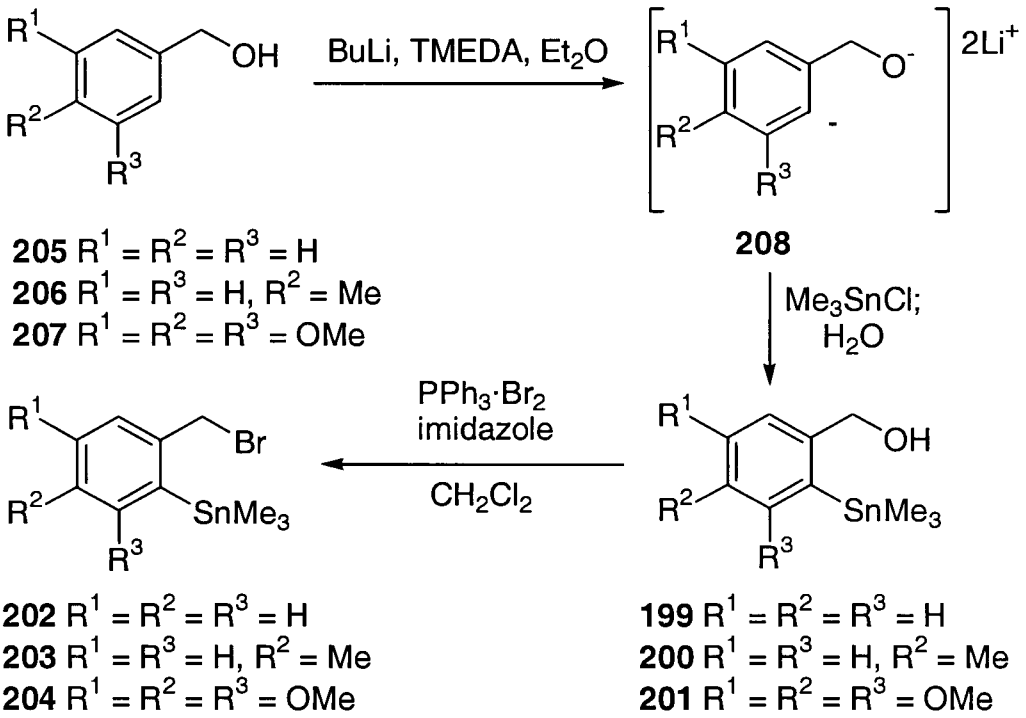
202 $R^1 = R^2 = R^3 = H$
203 $R^1 = R^3 = H$, $R^2 = Me$
204 $R^1 = R^2 = R^3 = OMe$

Chart 4.

Following a modified literature procedure for the directed orthometalation of benzyl alcohols,[50] each of the commerically available benzyl alcohols **205-207** were treated with 2.5 equiv of BuLi and TMEDA in Et_2O (Scheme 15). The dianions **208** formed from this deprotonation process[33] were quenched with 1.5 equiv of Me_3SnCl. Workup involving the addition of excess water furnished the *o*-trimethylstannylbenzyl alcohol derivatives **199-201** in moderate yields (54-64%).

Of the alcohols **199-201**, the benzyl alcohol **199** had been prepared previously and the spectral data was in full accord with that reported in the literature.[50] The spectral data (^1H nmr, ^{13}C nmr, and IR) obtained from the alcohols **200** and **201** were also in total agreement with their assigned structures. Using 3,4,5-trimethoxy-2-trimethylstannyl benzyl alcohol (**201**) as an example, the IR spectrum showed a broad OH absorption at 3432 cm^{-1} and the tin-methyl rocking absorption at 774 cm^{-1}. In the ^1H nmr spectrum, signals due to the Me_3Sn function (a 9 proton singlet at δ 0.30, $^2J_{Sn-H}$ = 54.5 Hz), three methoxy groups (three 3 proton singlets at δ 3.81, 3.84, and 3.85), the benzylic methylene group (a 2 proton doublet at δ 4.54, J = 5.7 Hz), the aromatic proton (a 1 proton singlet at

δ 6.78, $^4J_{Sn\text{-}H}$ = 15.6 Hz), and the alcoholic proton resonance (a 1 proton triplet at δ 1.53, J = 5.7 Hz, disappears when shaken with D_2O) were clearly visible. The ^{13}C nmr spectrum revealed the expected 11 signals and a high resolution mass measurement on the (M^+-Me) fragment confirmed the molecular formula of **201**.



205 $R^1 = R^2 = R^3 = H$
206 $R^1 = R^3 = H$, $R^2 = Me$
207 $R^1 = R^2 = R^3 = OMe$

208

202 $R^1 = R^2 = R^3 = H$
203 $R^1 = R^3 = H$, $R^2 = Me$
204 $R^1 = R^2 = R^3 = OMe$

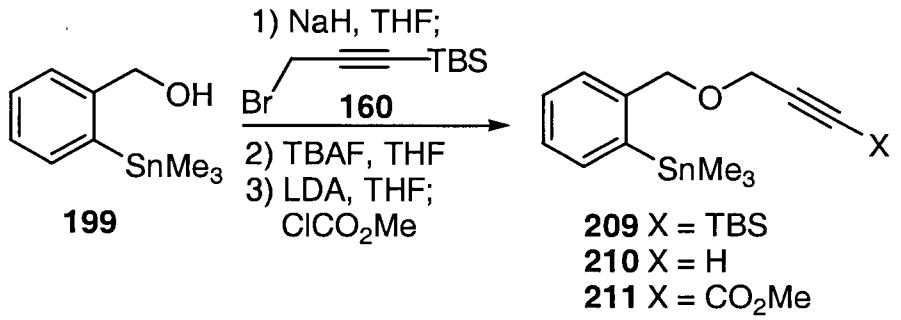
199 $R^1 = R^2 = R^3 = H$
200 $R^1 = R^3 = H$, $R^2 = Me$
201 $R^1 = R^2 = R^3 = OMe$

Scheme 15.

Treatment of each of the benzyl alcohols **199-201** with triphenylphosphine dibromide[51] and imidazole in methylene chloride provided the corresponding trimethylstannylbenzyl bromides **202-204** in moderate to good yields (65-88%) (Scheme 15). Again, the proposed structures of the stannanes **202-204** were fully supported by the spectral data. For instance, in the IR spectrum of **204**, the presence of the Me_3Sn function was confirmed by the absorption at 773 cm^{-1}. The ^1H nmr spectrum of **204** showed resonances due to the trimethylstannyl moiety (a 9 proton singlet at δ 0.36, $^2J_{Sn\text{-}H}$ = 54.8 Hz), three methoxy groups (three 3 proton singlets at δ 3.82, 3.84, and 3.86), the benzylic methylene protons (a 2 proton singlet at δ 4.66), and the lone aromatic proton (a 1 proton singlet at δ 6.72, $^4J_{Sn\text{-}H}$ = 16.1 Hz). The ^{13}C nmr spectrum also contained the expected 11 signals. A HRMS measurement on the (M^+-Me) fragment

confirmed the molecular formula of **204**. In a manner analogous to that described above, the structures of the remaining two arylstannanes **202** and **203** were confirmed.

With the alcohol **199** in hand, the cyclization precursor **211** was prepared via a three-step reaction sequence (equation 63). Thus, treatment of **199** with sodium hydride in THF[52] and quenching the resultant alkoxide with the previously prepared bromide **160** (see Discussion section 1.3.1, pg. 45) yielded the silyl capped intermediate **209** in excellent yield (94%). Removal of the TBS function with TBAF[39] in THF provided the alkyne **210** as a volatile oil. The alkyne **210** was immediately sequentially treated with LDA in THF and methyl chloroformate[41] to give the ester **211** in excellent yield (90% over 2 steps from **282**).

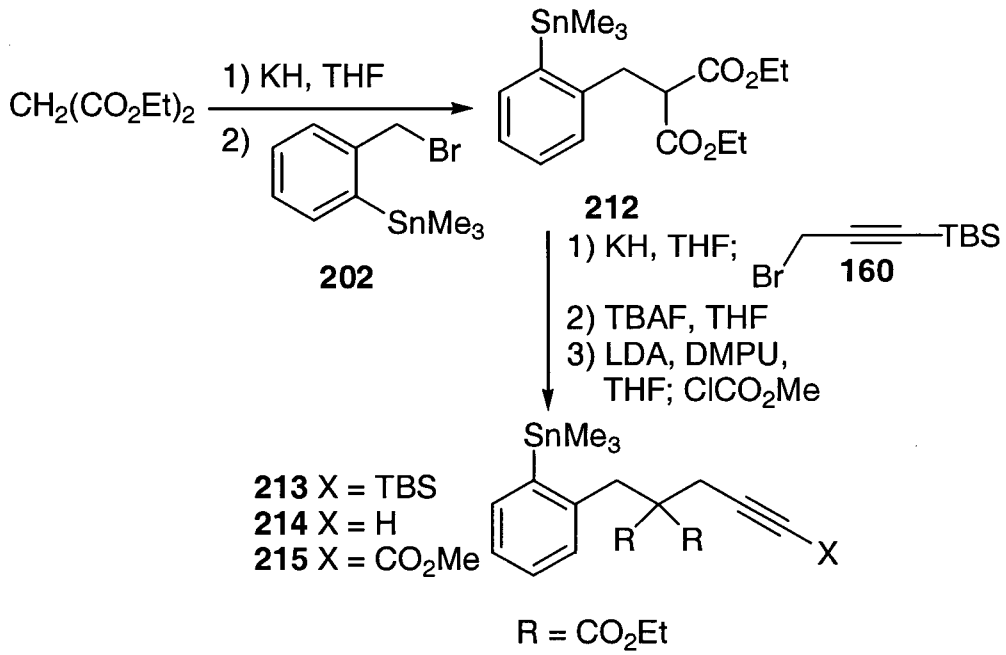


(63)

The spectral data (^{1}H nmr, ^{13}C nmr, and IR) acquired from the stannane **211** was fully consistent with the assigned structure. In the IR spectrum, the C-C triple bond stretching absorption at 2239 cm^{-1}, the carbonyl stretching band at 1718 cm^{-1}, and the tin-methyl rocking absorption at 751 cm^{-1} were present. In the ^{1}H nmr spectrum, the resonances due to the Me_3Sn moiety (a 9 proton singlet at δ 0.28, $^2J_{Sn\text{-}H}$ = 53.8 Hz), the methyl ester function (a 3 proton singlet at δ 3.78), the propargylic methylene group (a 2 proton singlet at δ 4.23), the benzylic methylene group (a 2 proton singlet at δ 4.59), and four aromatic protons (a 3 proton multiplet at δ 7.25-7.35, and a 1 proton doublet of multiplets at δ 7.51, J = 5.3 Hz, $^3J_{Sn\text{-}H}$ = 48.9 Hz) were present. The ^{13}C nmr spectrum exhibited the expected 13 signals and a high resolution mass spectrometric measurement on the (M^+-Me) fragment confirmed the molecular formula of **211**.

The carbocyclic cyclization precursor **215** was prepared by successive diethyl malonate alkylations[9] with potassium hydride and the bromides **202** and **160** to provide the dialkylated product **212** (Scheme 16). Removal of the TBS function of **212** with TBAF[39] in THF and acylation[41] (LDA, DMPU, THF; $ClCO_2Me$) of the resultant terminal

alkynic function of **214** provided the alkynoate **215** in good overall yield (74% over 4 steps).

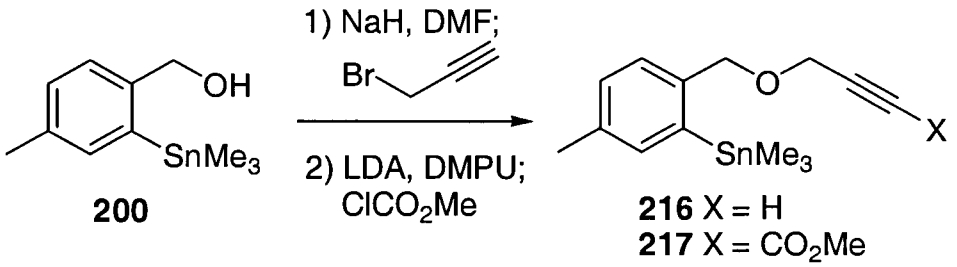


Scheme 16.

The spectral data obtained from **215** confirmed the proposed structure. In the IR spectrum, the absorptions attributable to the C-C triple bond at 2242 cm^{-1} and the trimethylstannyl group at 770 cm^{-1} were visible. In the ^1H nmr spectrum of **215**, the resonances ascribed to the trimethylstannyl function (a 9 proton singlet at δ 0.34, $^2J_{Sn\text{-}H}$ = 53.3 Hz), two methylene groups (a 2 proton singlet at δ 2.93 and a 2 proton singlet at δ 3.49), two ethyl ester functions (a 6 proton triplet at δ 1.19, J = 7.3 Hz and a 4 proton multiplet centred at δ 4.17), the methyl ester function (a 3 proton singlet at δ 3.71), and four aromatic protons (a one proton multiplet centred at δ 7.08, a 2 proton multiplet centred at δ 7.18, and a 1 proton doublet of multiplets at δ 7.39, J = 6.3 Hz, $^3J_{Sn\text{-}H}$ = 47.4 Hz) were present. The ^{13}C nmr spectrum showed the expected 17 signals and a HRMS measurement on the (M^+-Me) fragment confirmed the molecular formula of **215**.

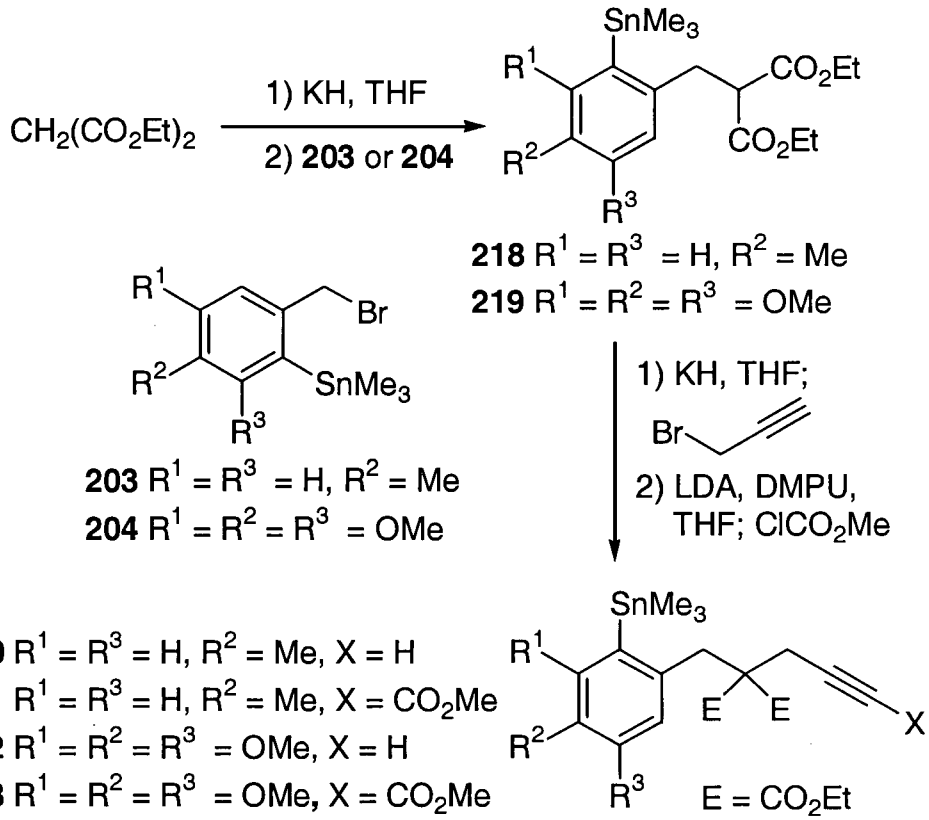
A second cyclization precursor incorporating an oxygen ether linkage was synthesized in two steps from the stannane **200** (equation 64). Thus, treatment of the alcohol **200** with sodium hydride[52] in dry DMF, followed by the addition of propargyl bromide, gave the stannane **216** as an oil that exhibited an extremely noxious odour. The

terminal alkyne **216** was treated with LDA and methyl chloroformate[41] to furnish the α,β-alkynic ester **217** in excellent yield (87% over 2 steps). The structural assignment of compound **217** was fully supported by the spectrometric data (IR, ^{1}H nmr, ^{13}C nmr, and HRMS).



200 **216** X = H; **217** X = CO_2Me (64)

Finally, alkylation[9] of diethyl malonate with each of the benzyl bromides **203** or **204**, followed by alkylation of the derived products **218** and **219** with propargyl bromide, yielded the stannanes **220** and **222** in yields of 85% and 94%, respectively (Scheme 17).



Scheme 17.

Reaction of the terminal alkyne functions of **220** and **222** with LDA and DMPU in THF and treatment of the resultant lithium acetylides with methyl chloroformate[41] provided the cyclization precursors **221** and **223** in 63% and 80% yields, respectively.

The spectral data (^{1}H nmr, ^{13}C nmr, and IR) and HRMS mass determinations obtained from the compounds **221** and **223** were in full accord with their assigned structures. For instance, in the ^{1}H nmr spectrum of **223**, two singlets at δ 3.71 and 3.84, and two overlapping resonances appearing as a singlet at δ 3.78, attributable to the three methoxy groups and the methyl ester function, were clearly visible. The resonances belonging to the trimethylstannyl groups were present in the ^{1}H nmr spectra of both **221** and **223** (as a 9 proton singlet at δ ~0.30). The ^{13}C nmr spectrum of **221** and **223** displayed the expected 17 and 20 signals, respectively. Lastly, the IR spectrum of each of these substances showed a carbonyl absorption at ~1720 cm^{-1} and tin-methyl rocking absorption at ~770 cm^{-1}.

With the synthesis of the precursors incorporating aryltrimethylstannane and alkynoate functions completed, investigations into the internal conjugate addition reaction of arylcopper(I) species, derived from aryltrimethylstannanes, to α,β-alkynic ester functions could be carried out.

1.4.2 Copper(I)-mediated cyclizations of aryltrimethylstannane functions to α,β-alkynic esters

The experimental results arising from the treatment of the cyclization precursors **211**, **217**, **215**, **221**, and **223** with 2.5 equiv of copper(I) chloride and 5 equiv of acetic acid in dry DMF at 0 °C for 15 minutes (equation 65) to provide the bicycles **224-228** are summarized in Table 5.

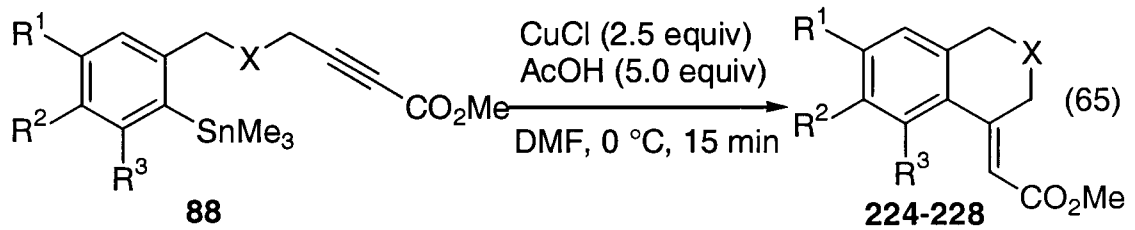


Table 5. Synthesis of the bicycles **224-228**

Entry	Substrate	R^1	R^2	R^3	X	Product	% Yield[a]
1	**211**	H	H	H	-O-	**224**	92
2	**217**	H	Me	H	-O-	**225**	97
3	**215**	H	H	H	$-C(CO_2Et)_2-$	**226**	98
4	**221**	H	Me	H	$-C(CO_2Et)_2-$	**227**	92
5	**223**	OMe	OMe	OMe	$-C(CO_2Et)_2-$	**228**	97

[a] Isolated yield of purified products

Gratifyingly, the ethers **211** and **217** were efficiently transformed into the bicycles **224** and **225** (Table 5, entries 1 and 2) upon subjection to the standard cyclization protocol (equation 65), followed by purification of the crude product by flash column chromatography on silica gel (92% and 97%, respectively).

The spectral data (^{1}H nmr, ^{13}C nmr, and IR) derived from **225** were in full accord with the assigned structure. For example, the IR spectrum of (*Z*)-4-(methoxy carbonylmethylidene)-6-methylisochromane (**225**) showed the methyl ester function by the strong C=O absorption located at 1704 cm^{-1}. In the ^{1}H nmr spectrum of **225**, the signals due to the methyl group (a 3 proton singlet at δ 2.34), the methyl ester function (a 3 proton singlet at δ 3.73), the benzylic methylene group (a 2 proton singlet at δ 4.64), the allylic methylene group (a 2 proton doublet at δ 5.09, J = 2.0 Hz), the lone olefinic proton (a 1 proton triplet at δ 6.35, J = 2.0 Hz), two mutually coupled aromatic ortho protons (two 1 proton doublets at δ 6.98 and 7.15 each having J = 7.6 Hz), and the isolated aromatic proton (a 1 proton singlet at δ 7.52) could be identified. The ^{13}C nmr spectrum of **225** revealed the expected 13 resonances. In an APT experiment, six negative signals (δ 21.3, 51.4, 110.0, 124.3, 125.1, and 131.0) were attributed to the aromatic methyl group, the methyl carbon of the ester function, and four sp^2 methine carbons, respectively. A high resolution mass spectrometric measurement on the molecular ion confirmed the molecular formula of $C_{13}H_{14}O_3$. In addition, ^{1}H nmr nOed experiments confirmed the (*Z*)-configuration of the alkenic function in **225** (Figure 8). Likewise, the spectral data (IR, ^{1}H nmr, and ^{13}C nmr) confirmed the proposed structure of

the bicycle **224** and ^{1}H nmr nOed experiments determined the (*Z*)-orientation of the exocyclic double bond (Figure 8).

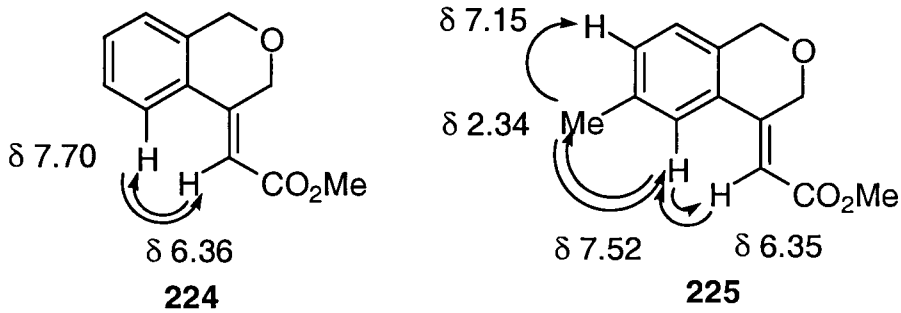
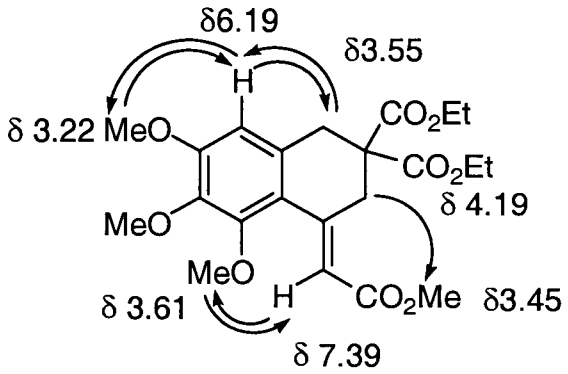


Figure 8. NOed experiments on **224** and **225**

When the copper(I) chloride/acetic acid cyclization protocol (equation 65, pg. 59) was applied to the substrates **215**, **221**, and **223** and the crude products were purified by flash column chromatography on silica gel, the carbobicycles **226-228** were produced cleanly and efficiently (yields >90 %, Table 5, entries 3-5, pg. 60).

The spectral data acquired from the bicycles **226-228** were fully consistent with their assigned structures. For instance, the IR spectrum of the trimethoxy substituted bicycle **228** showed the three carbonyl functions as one broad absorption at 1734 cm^{-1}. Notable in the ^{1}H nmr spectrum were the resonances ascribed to the benzylic methylene group (a 2 proton singlet at δ 3.35), three methoxy groups (three 3 proton singlets at δ 3.22, 3.61, and 3.66), one aromatic proton (a 1 proton singlet at δ 6.19), and one alkenyl proton (a 1 proton broad triplet at δ 7.39, J = 1.8 Hz) mutually coupled to the allylic methylene protons (a 2 proton doublet at δ 4.19, J = 1.8 Hz). The presence of four CH_3 singlets that each integrated to three protons proved to be problematic in the assignment of the proton nmr spectrum. However, with the assistance of Heteronuclear Mutiple Bond Correlation (HMBC) and Heteronuclear Multiple Quantum Coherence (HMQC) spectra, the complete assignment of the proton and carbon nmr spectra could be made (see Experimental, pg. 201 and 202). With the assignment of the proton nmr spectrum in hand, a series of ^{1}H nmr nOed experiments determined that the exocyclic double bond in **228** possessed an (*E*)-configuration. The complete results of the ^{1}H nmr nOed experiments derived from **228** are summarized in Figure 9. Fortunately, analyses of the simpler spectral data (^{1}H nmr, ^{13}C nmr, and IR) recorded for the compounds **226**

and **227** provided suitable confirmation of their structures. In addition, the (*E*)-configuration of the trisubstituted double bonds in **226** and **227** were rigorously determined with ^{1}H nmr nOed experiments (see Experimental, pg. 198 and 199).

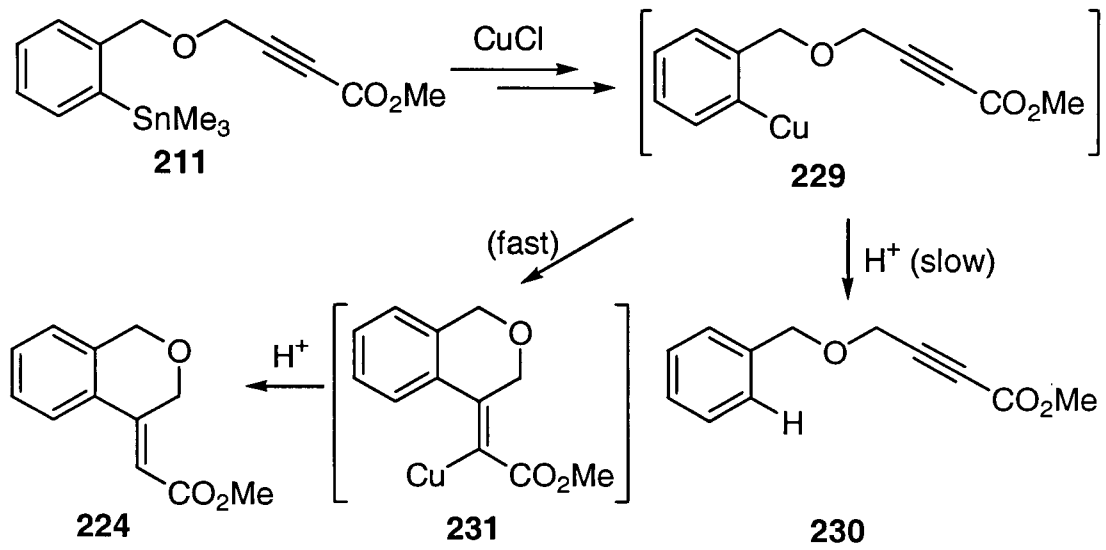


228

Figure 9. NOed experiments on **228**

The mechanism of the conjugate addition likely follows a pattern similar to that proposed for the addition of alkenylstannane functions to α,β-alkynic esters (see Introduction section 3.4.1, pg. 19 and Discussion section 1.5.1, pg. 64). As has been noted for the analogous additions of alkenyltrimethylstannane functions to α,β-alkynic esters, the internal cyclization process is faster than the intermolecular quench by the acetic acid. For example, the protonation of the arylcopper(I) intermediate **229** to produce the protiodestannylated product **230** is slower than the conjugate addition to form the adduct **231** (Scheme 18).

It should be emphasized that the bicycles **224-228** (Table 5, pg. 60) were produced in excellent yields and no trace of the configurational isomers were detected by tlc analyses of the reaction mixtures or by ^{1}H nmr analyses of the crude products. The high efficiency of the conversion of **223** into **228** (Table 5, entry 5) implies that the overall reaction is somewhat insensitive to the steric hinderance supplied by the two *ortho* substituents that surround the trimethylstannane function in compound **223**. A determination of whether or not substrates in which the MeO groups of **223** are replaced by alkyl groups would also be efficiently transformed in the corresponding bicyclic products will require additional experimentation.



Scheme 18.

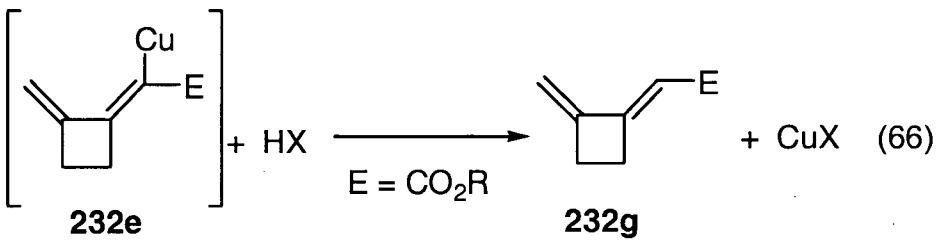
In summary, the intramolecular conjugate addition of arylcopper species, formed from the reversible copper-tin transmetalation of aryltrimethylstannane functions with copper(I) chloride, to α,β-alkynic esters are highly efficient and the results show clearly that the cyclization reaction represents a viable synthetic process.

1.5 Limitations, extensions, and mechanistic considerations

1.5.1 Effect of varying solvents and additives

1.5.1.1 Development of the use of an *in situ* proton source

Throughout this section (1.5.1), the reader is referred to the proposed reaction pathway of the copper(I) mediated conjugate additions found in Scheme 19 (see next page). Using the stannane **232a** as an example, the reaction is believed to be initiated by the oxidative addition of CuCl to the organostannane **232a** to provide the copper(III) intermediate **232b** (Introduction section 3.4.1, pg. 19). The intermediate **232b** can then undergo two different reaction pathways. By the reductive loss of Me_3SnCl from the intermediate **232b**, the alkenylcopper(I) species **232c** is formed. Alternatively, the intramolecular cyclization of the intermediate **232b** and subsequent reductive elimination of CuCl yields the α-stannyl ester **232f**. The alkenylcopper(I) function in **232c** can cyclize onto the α,β-alkynic ester to give the copper(I) adduct **232e**. The work described in this section focused on the search for an appropriate proton source (HX) that would react with the intermediates **232d** and/or **232e** *in situ* to yield the diene **232g** (equations 66 and 67).



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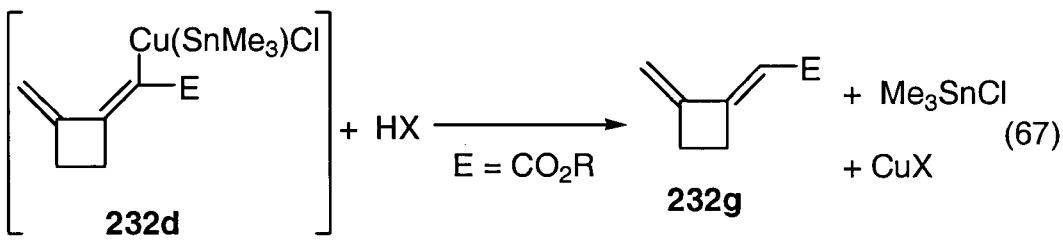

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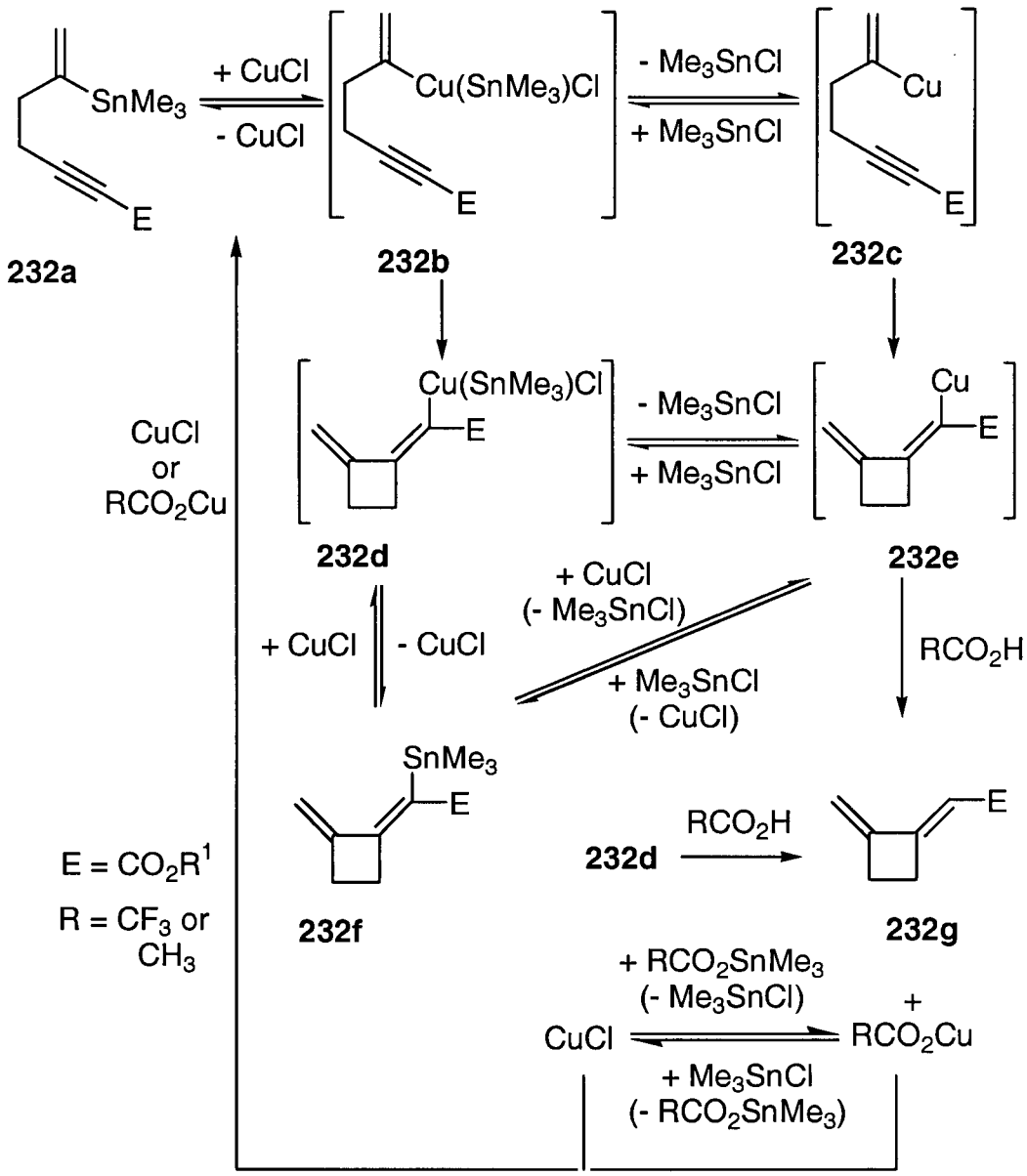
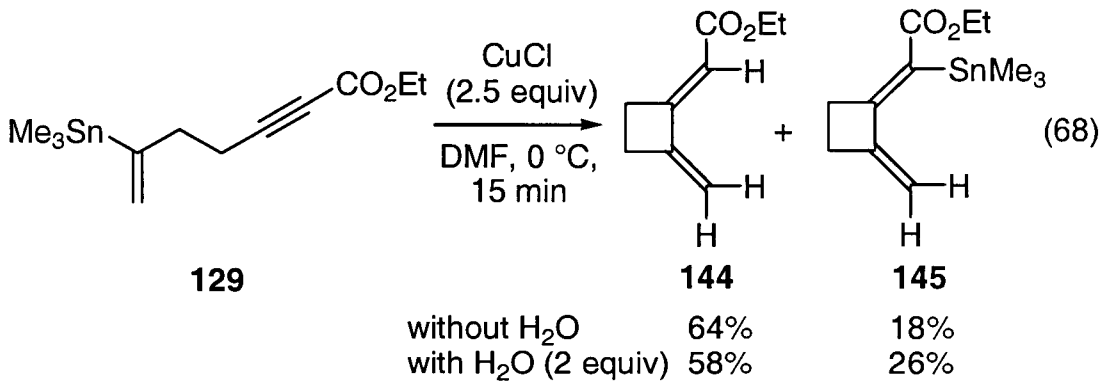
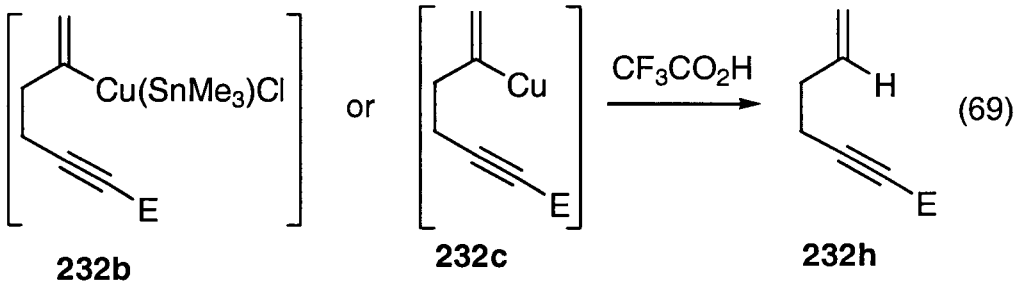


Scheme 19.

The transformation of **129** into **144** (and **145**) was found to be proceed in the presence of 2 equiv of water (equation 68) without much change in the isolated yields. This result indicated that the intermediates **232d** and **232e** (Scheme 19) are not sufficiently basic to react with water to any great extent. From this result, it was surmised that a more acidic proton source could be employed in the reaction mixture.



Satisfyingly, in the conversion of precursor **143** into the monocycle **158**, the addition of trifluoroacetic acid (5.0 equiv) to the reaction mixture improved the yield obtained to 74% from 52% (Table 6, entries 1 and 2). A mixture of unidentified destannylated material was also isolated (~15%) after purification of the crude product by flash column chromatography on silica gel. This result revealed a vital aspect of the reaction: the intramolecular cyclization of the intermediates **232b** and/or **232c** into the adducts **232d** and/or **232e**, respectively, is faster than the intermolecular quench of **232b** and/or **232c** by the trifluoroacetic acid (Scheme 19 and equation 69). For an exception to



this generality, the reader is referred to Discussion section 1.3.2, pg. 49. The presence of the unidentified side products may be due to homocoupling[8] or protiodestannylation[43] of the starting material or to some other unknown reactions.

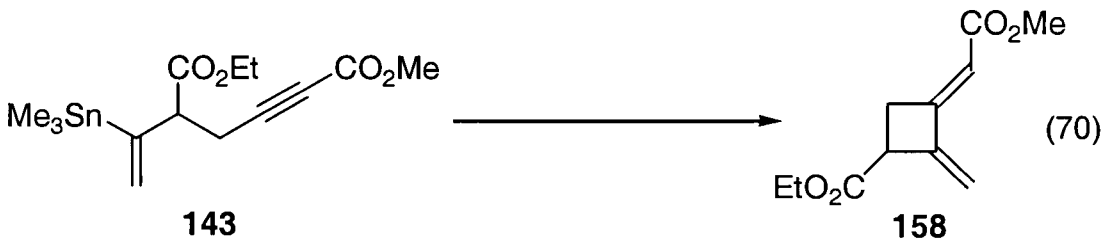


Table 6. Synthesis of the diene **158**

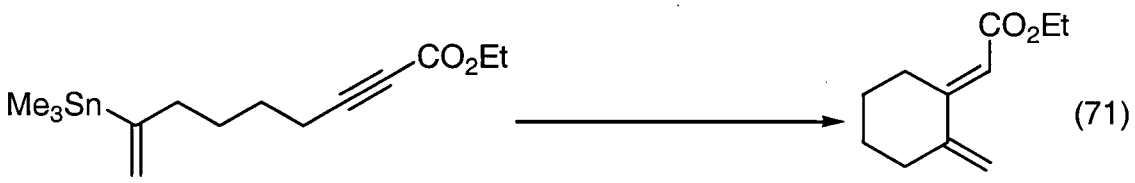
Entry	Reaction Conditions	% Yield[a]
1	2.5 equiv CuCl, 0 °C, DMF, 15 min	52
2	2.5 equiv CuCl, 5.0 equiv CF_3CO_2H, 0 °C, DMF, 15 min	74
3	2.5 equiv CuCl, 5.0 equiv CH_3CO_2H, 0 °C, DMF, 15 min	85

[a] Isolated yield of purified product.

The appropriate choice of the proton source appeared to depend upon a delicate balance between the ability of the acid to selectively protonate the intermediates **232d** and **232e** in the presence of the intermediates **232b** and **232c**. Also, protiodestannylation of the alkenyltrimethylstannyl function in the starting material **232a** had to be avoided (Scheme 19, pg. 65). To our delight, the use of acetic acid served these purposes adequately (Table 6, entry 3). Upon changing the reaction conditions to include the addition of 5.0 equiv of acetic acid, the yield of **158** was excellent (85%) with the concomitant production of only minor amounts of unidentified destannylated material (~5%). Gratifyingly, these reaction conditions were found to be successful across a number of examples (see Discussion sections 1.2.2, 1.3.2, and 1.4.2).

1.5.1.2 Use of catalytic amounts of CuCl in the conjugate addition reaction

As an examination of the proposed reaction pathway using acetic acid revealed the plausible generation of CuOAc (Scheme 19 and equation 66, where HX = HOAc), it was of interest to ascertain the efficacy of copper(I) acetate in the reaction. In one control experiment, treatment of the stannane **136** with 2.5 equiv of copper(I) acetate in dry DMF provided a good yield (78%) of the cyclized product **156** (Table 7, entry 3). Therefore, copper(I) acetate is a suitable agent to mediate the conjugate addition reaction.



(71)

136 **156**

Table 7. Synthesis of the diene **156**

Entry	Reaction Conditions[a]	% Yield[b]
1	2.5 equiv CuCl, 0 °C, DMF, 1 h	-[c]
2	2.5 equiv CuCl, 5.0 equiv CH_3CO_2H, 0 °C, DMF, 15 min	87
3	2.5 equiv CuOAc, 5.0 equiv CH_3CO_2H, 0 °C, DMF, 15 min	78
4	2.5 equiv CuCl, 5.0 equiv CH_3CO_2H, 0 °C, DMI, 15 min	83
5	0.1 equiv CuCl, 5.0 equiv CH_3CO_2H, 0 °C, DMF, 1 h	0[e,f]
6	0.5 equiv CuCl, 2.0 equiv CH_3CO_2H, 0 °C, DMF, 45 min[d]	89
7	0.1 equiv CuCl, 2.0 equiv CH_3CO_2H, 0 °C, DMF, 4 h 15 min[d]	76
8	2.5 equiv $CuCl_2$, 5.0 equiv CH_3CO_2H, 0 °C, DMF, 15 min	0[e]
9	2.5 equiv $Cu(OAc)_2$, 5.0 equiv CH_3CO_2H, 0 °C, DMF, 15 min	0[e]

[a] Unless otherwise stated, [CuCl] ~ 0.25 M.
[b] Isolated yield of purified products.
[c] A ~1:1 mixture of cyclized material **156** and starting material **136** was obtained (see Discussion section 1.2.2).
[d] The substrate was added via a syringe pump over the first 15 min.
[e] Only starting material was identified in the ^1H nmr spectrum of the crude product.
[f] [CuCl] ~ 0.01 M.

Given the latter result, it was conceivable that copper(I) chloride might be used catalytically in the presence of acetic acid. However, it was found that no reaction took place upon the treatment of the stannane **136** with 0.1 equiv of copper(I) choride and 5 equiv of acetic acid in dry DMF (Table 7, entry 5). The lack of any reaction was attributed to the low concentration of the copper(I) chloride ([CuCl] ~0.01 M) employed in this experiment. Thus, under these conditions, the equilibrium of the copper-tin transmetalation reaction lies heavily toward starting material **232a** (Scheme 19, pg. 65) and the overall cyclization process is inhibited. In contrast, application of the standard

reaction protocol where the concentration of copper(I) chloride is ~0.25 M provided an excellent yield of **156** (Table 7, entry 2).

Equipped with this information, reaction conditions employing catalytic amounts of CuCl (0.5 equiv) were successfully developed (Table 7, entry 6). Vital to the success of this reaction was the use of CuCl at the same concentration in the standard cyclization protocol (~0.25 M, Table 7, entry 2). To maintain the concentration of CuCl at ~0.25 M while simutaneously decreasing the quantity of CuCl from 2.5 to 0.5 equiv, a proportionate 5-fold reduction in the amount of solvent (DMF) relative to the standard reaction protocol was necessary. Under these altered conditions, the slow addition of a DMF solution of the stannane **137** over a 15 min period to 0.5 equiv of CuCl and acetic acid (2 equiv) in dry DMF at 0 °C provided an excellent yield (89%) of the cyclized product **156** (Table 7, entry 6). Under these new conditions where the [CuCl] ~0.25 M, the yield was virtually identical to the conditions employing 2.5 equiv of copper(I) chloride (87%, Table 7, entry 2).

A successful protocol employing 0.1 equiv of copper(I) chloride was also developed (Table 7, entry 7). In this case, a 25-fold decrease in the amount of DMF used compared to the standard cyclization conditions (Table 7, entry 2) was the key difference between these two protocols. As a result, the concentration of CuCl in this experiment was also kept at ~0.25 M. Thus, treatment of CuCl (0.1 equiv) in DMF with the stannane **137** provided the desired product **156** in good yield (76%), although somewhat less efficiently than that observed in the previously discussed experiment (Table 7, entry 6). A contributing factor to the reduced yield in this experiment could arise from the increase in the concentrations of acetic acid and the organostannane precursor **137** compared to those employed in the standard cyclization protocol (Table 7, entry 2). This heightens the propensity of the organostannane starting material to participate in intermolecular protiodestannylation[43] or oxidative homocoupling pathways.[8] In addition, the relatively large volumes of acetic acid and cyclization precursor in the reaction pot may have a deleterious effect by altering the characteristics of the solvent (e.g. solubility properties).

To summarize the key events of catalytic cycle using acetic acid (Scheme 19, pg. 65, R = CH_3), the copper-tin transmetalation and internal conjugate addition leading to the formation of the intermediates **232d** and **232e** are analogous to those discussed

previously (See Introduction section 3.4.1, pg. 19). The *in situ* quench of the copper(I) adduct **232e** by acetic acid provides the desired diene **232g** and copper(I) acetate (equation 66, pg. 64). Reaction of the intermediate **232d** with acetic acid would provide copper(I) acetate and Me_3SnCl (equation 67). A mechanism by which CuCl is regenerated can be proposed and is illustrated at the bottom of Scheme 19. It is plausible that CuOAc and Me_3SnCl can react (reversibly) to form Me_3SnOAc and regenerated CuCl. Copper(I) chloride is also formed during the reductive elimination process of the intermediate **232d** to form the stannane **232f**. The catalytic cycle is then completed by the participation of the copper(I) salt (CuCl or CuOAc) in the initial equilibrium between **232a** and **232b**. The transformation is assisted by driving the transmetalation equilibrium towards the intermediates **232b** and **232c** in the presence of elevated concentrations of CuCl. In addition, any possible decomposition of the intermediates **232d** and **232e** is minimized by the facile protonation of these intermediates by the acetic acid.

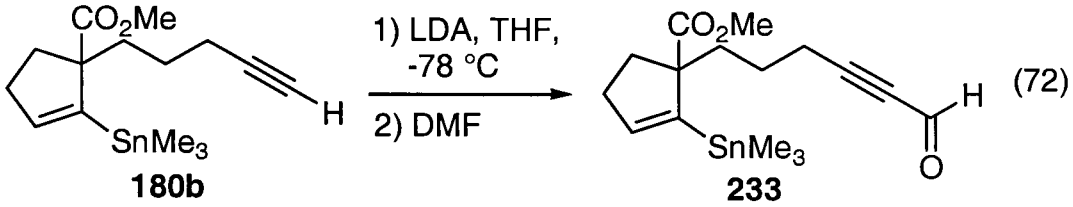
As a side note, it is clear from previous studies[3,5,53] that polar aprotic solvents, such as DMF or DMSO, promote the transmetalation of alkenylstannanes with copper(I) salts. This has been attributed to the belief that the transmetalation is facilitated by the relatively high solublity of copper(I) salts and the high dielectric constant of these solvents. A high dielectric constant enhances charge separation and may increase the reactivity of the dissolved ions.[53] Continuing the investigation for compatible solvent systems for use in the cyclization, it has been shown recently that trimethylsilylacetylenes undergo copper/silicon transmetalation with CuCl in DMF or 1,3-dimethyl-2-imidazolidinone (DMI).[54] Thus, it seemed reasonable that DMI might serve as a suitable reaction medium in our work. This hypothesis proved to be correct as the cyclization reaction employing DMI, since the use of this solvent provided a good yield (83%) of **156,** after purification of the crude material on silica gel (Table 7, entry 4, pg. 68).

Lastly, additional control experiments confirmed the fact that both copper(II) acetate and copper(II) chloride were unable to effect the transmetalation/cyclization reaction. It was found that treatment of **137** with 2.5 equiv of $CuCl_2$ or $Cu(OAc)_2$ in dry DMF resulted in the recovery of intact starting material (Table 7, entries 8 and 9, respectively). Unfortunately, due to time constraints, further experiments to explore the

limitations and generality of the copper(I) catalyzed protocol and the nature of the reaction pathway were discontinued.

1.5.2 Preparation of α,β-alkynic ketone and aldehyde precursors

The preparation of the substrates for use in this study required the alkyne **180b**, whose synthesis was described in Discussion section 1.3.1, pg 46 and Experimental pg. 150. Following a modified literature procedure describing the one-step formation of alkynals from alkynes,[55] treatment of the alkyne **180b** with LDA in THF and reaction of the resultant acetylide with DMF provided the alkynal **233** after workup with aqueous potassium dihydrogen phosphate (equation 72). The yield of the conversion after flash column chromatography of the crude product on silica gel was moderate (66%).

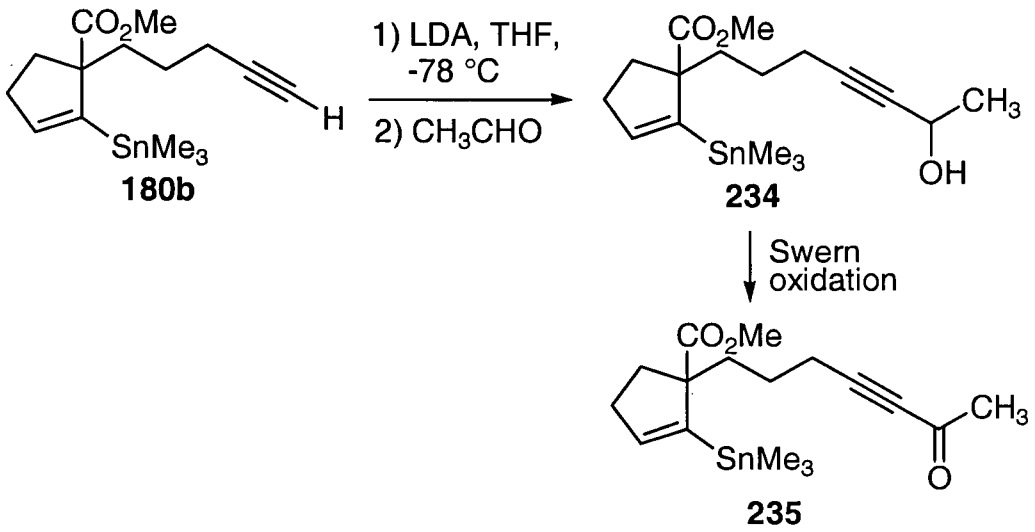


(72)

The spectral data acquired from the aldehyde **233** was fully consistent with the assigned structure. For example, in the IR spectrum, the alkyne function was indicated by the C-C triple bond stretch at 2201 cm^{-1}, the carbonyl function by the absorption located at 1733 cm^{-1}, and the Me_3Sn function by the absorption at 772 cm^{-1}. Significant resonances in the ^1H nmr spectrum could be ascribed to the Me_3Sn group (a 9 proton singlet at δ 0.12, $^2J_{Sn\text{-}H}$ = 54.3 Hz), the methyl ester moiety (a 3 proton singlet at δ 3.63), the olefinic proton (a 1 proton doublet of doublets at δ 5.96, J = 2.1, 2.1 Hz, $^3J_{Sn\text{-}H}$ = 37.9 Hz), and the aldehyde proton (a 1 proton singlet at δ 9.14). The ^{13}C nmr spectrum displayed the expected 14 signals and a HRMS measurement on the (M^+-Me) fragment confirmed the molecular formula of **233**.

7-(1-Methoxycarbonyl-2-trimethylstannylcyclopent-2-en-1-yl)hept-3-yn-2-one (**235**) was prepared in two straightforward transformations from the alkyne **180b** (Scheme 20). Thus, treatment of **180b** with LDA followed by the addition of ethanal[56] yielded the propargylic alcohol **234**, presumably as a mixture of diastereomers. The

secondary alcohol was then converted to the corresponding ketone **235** via a Swern oxidation.[34] The overall yield of the two-step process was 70% from the alkyne **180b**.



Scheme 20.

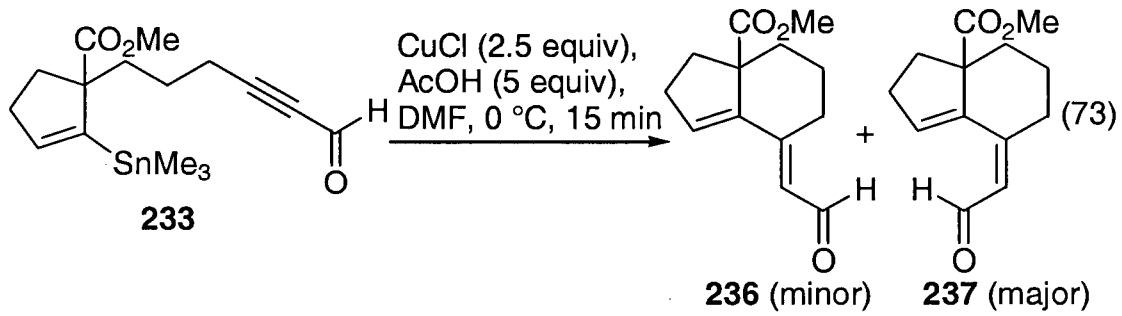
The spectral data collected support the proposed structure of the alkynone **235**. For instance, the IR spectrum displayed the alkyne triple bond stretch at 2211 cm^{-1} and the carbonyl functions at 1729 cm^{-1}. The ^1H nmr spectrum showed key signals corresponding to the Me_3Sn function (a 9 proton singlet at δ 0.13, $^2J_{Sn\text{-}H}$ = 54.3 Hz), the methyl ketone function (a 3 proton singlet at δ 2.28), the methyl ester moiety (a 3 proton singlet at δ 3.63), and the olefinic proton (a 1 proton doublet of doublets at δ 5.96, J = 2.1, 2.1 Hz, $^3J_{Sn\text{-}H}$ = 38.0 Hz). The ^{13}C nmr spectrum exhibited the expected 15 signals. Lastly, a high resolution mass spectrometric measurement on the (M^+-Me) fragment confirmed the molecular formula of $C_{17}H_{26}O_3Sn$.

With the α,β-alkynic aldehyde **233** and ketone **235** in hand, the copper(I) chloride-mediated cyclization processes could then be examined.

1.5.3 Cyclization of acetylenic ketone and aldehyde precursors

It was found that treatment of the stannane **233** under standard cyclization conditions (equation 73) resulted in the clean formation of two isomeric aldehydes **236** and **237**. These substances were not separable by flash column chromatography on silica

gel. The combined yield of the configurational isomers **236** and **237** was 89%. The ratio of these materials, as determined by integration of the aldehyde resonances in the ^{1}H nmr spectrum of the crude product, was ~1:4 ratio, respectively.



The spectral data derived from the mixture support the proposed structures of **236** and **237**. In the IR spectrum of the mixture, absorptions belonging to the ester function at 1728 cm^{-1} and the α,β-unsaturated aldehyde at 1672 cm^{-1} were visible. A high resolution mass measurement of the mixture confirmed the molecular formula of $C_{13}H_{16}O_3$. Two sets of signals in the ^{1}H and ^{13}C nmr spectra were attributed to the presence of the isomers **236** and **237**.

In the ^{1}H nmr spectrum of the mixture of the two compounds, the signals ascribed to the major isomer **237** were the methyl ester function (a 3 proton singlet at δ 3.19), two olefinic protons (two 1 proton doublet of doublets at δ 5.44, J = 2.1, 2.1 Hz, and at δ 5.91, J = 2.0, 7.9 Hz), and the aldehyde proton (a 1 proton doublet at δ 10.12, J = 7.9 Hz). In the ^{13}C nmr spectrum of the mixture, the expected 13 resonances belonging to the substance **237** could be identified. In an APT experiment, four negative signals at δ 52.1, 127.5, 135.5, and 193.1 were attributed to the methoxy carbon, two methine olefin carbons, and the aldehyde function, respectively.

The minor compound **236** displayed the methyl ester function (a 3 proton singlet at δ 3.23), two olefinic protons (two 1 protons doublet of doublets at δ 5.62, J = 2.5, 2.5 Hz, and δ 6.22, J = 2.1, 8.0 Hz), and the aldehyde resonance (a 1 proton doublet at δ 9.92, J = 8.0 Hz) in the ^{1}H nmr spectrum of the mixture. In the ^{13}C nmr spectrum, the expected 13 carbon resonances arising from the presence of **236** were found. In the APT experiment, the four negative signals at δ 52.1, 124.0, 132.5, and 190.6 could be attributed to the methoxy carbon, two olefinic carbons, and the aldehyde carbon, respectively.

The configuration of the double bonds in **236** and **237** were indicated by the relative chemical shifts of the alkenyl and aldehyde protons in the ^{1}H nmr spectrum. The aldehyde resonance attributed to the major compound **237** was located at δ 10.22 whereas the minor compound **236** resonated at δ 9.92. The downfield shift of the aldehyde signal in the major isomer **237** is the likely result of the deshielding effects of the proximate double bond. Likewise, the relative downfield resonance of the exocyclic methine proton in the minor product **236** (δ 6.22) compared to the major product **237** (δ 5.91) also provided strong diagnostic evidence to assign the configuration of the trisubstituted olefins. More definitive evidence was supplied by a series of nOed experiments (Figure 10) which conclusively assigned the (*Z*)-configuration to the major compound **237** and the (*E*)-configuration to the minor compound **236**.

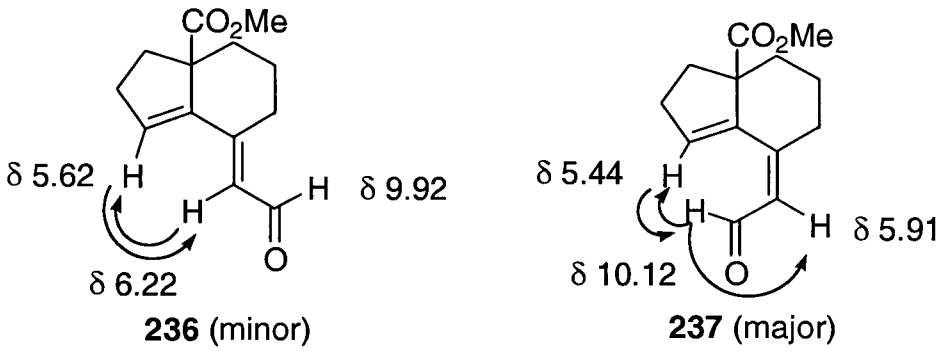
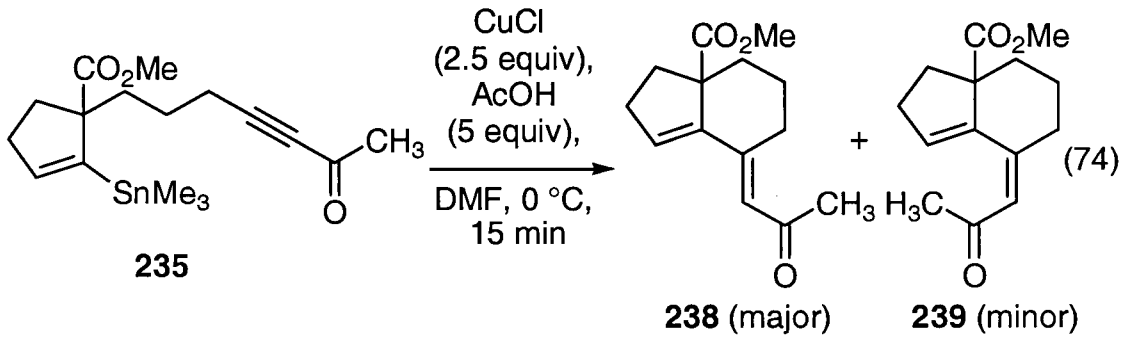


Figure 10. NOed experiments on **236** and **237**

This lack of stereoselectivity was also seen in the conversion of the stannane **235** into a mixture of the ketones **238** (major) and **239** (minor) in a ratio of ~4:1, as indicated by integration of the olefinic protons in the ^{1}H nmr spectrum of the crude product (equation 74). The minor compound **239** proved to be unstable and was found to decompose when subjected to flash column chromatography on silica gel. Consequently, it was not possible to obtain an analytically pure sample of this material. However, a moderate yield (55%) of the major compound **238** could be isolated as a colorless solid (mp 40-44 °C).



The spectral data fully support the proposed structure of the ketone **238**. In the IR spectrum, the carbonyl functions were indicated by the C=O stretching frequencies located at 1728 cm^{-1} and 1681 cm^{-1}. Notable in the ^1H nmr spectrum were the presence of the signals due to ten methylene protons, the methyl ester group (a 3 proton singlet at δ 3.63), the methyl ketone (a 3 proton singlet at δ 2.19), and two alkenyl protons (a 1 proton broad singlet at δ 6.04 and a 1 proton doublet at δ 6.34, J = 2.4 Hz). The ^{13}C nmr spectrum showed the expected 14 carbon resonances and a high resolution mass spectrometric measurement on the (M^+) fragment confirmed the molecular formula of **238**. The configuration of the double bond was determined to be *E* as determined by a ^1H nmr nOed experiment, the results of which are illustrated in Figure 11.

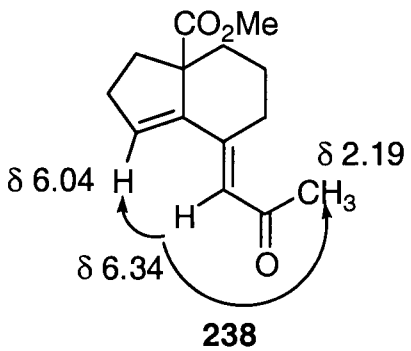
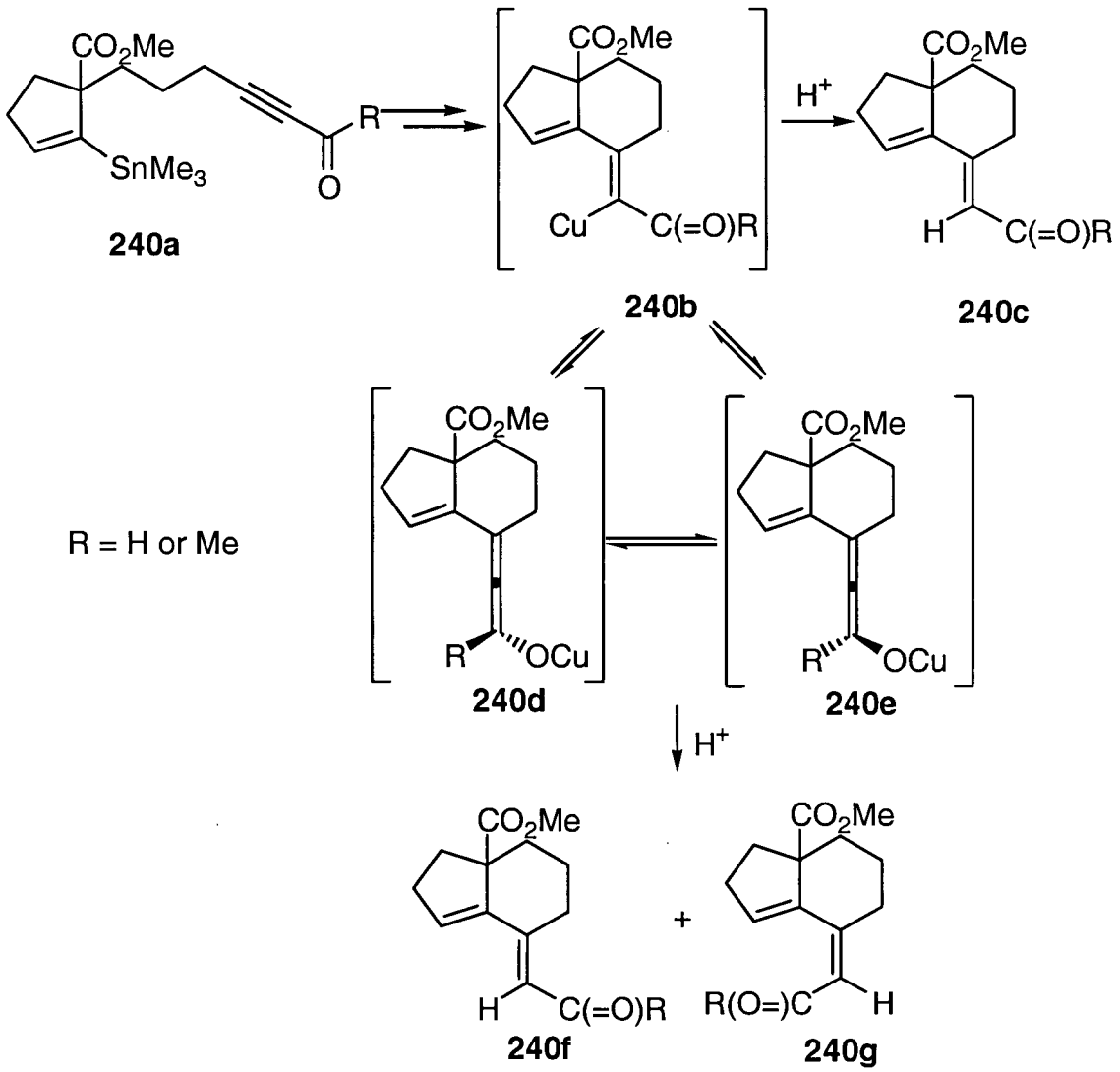


Figure 11. NOed experiments on **238**

The formation of isomeric mixtures of aldehydes and ketones in these instances can be explained by a modified reaction pathway illustrated in Scheme 21. Following transmetallation and cyclization (see Discussion section 1.5.1, pg. 64), it may be proposed that the intermediates **240b** can undergo isomerization to the corresponding copper(I) allenoates **240d** and **240e**. The allenoates **240d** and **240e** are then protonated

by the acetic acid from either face of the allenoate function to provide the configurational isomers **240f** and **240g**. In the case of the aldehydes **236** and **237**, it is interesting to note that the major compound formed possesses the configuration opposite to that obtained exclusively in the cyclization of alkenyltrimethylstannanes to α,β-alkynic esters. This suggests that under the reaction conditions, isomerization of the unsaturated aldehyde **240b** (where R = H) is fast and that protonation occurs from the least hindered face of the allenoate (opposite to the five membered ring). The isomerization of α-copper(I)-α,β-unsaturated aldehydes and ketones to allenoate species is not unprecedented, since allenoates derived from the conjugate addition of organocopper reagents to both alkynones and alkynoates have been postulated in the literature.[57]

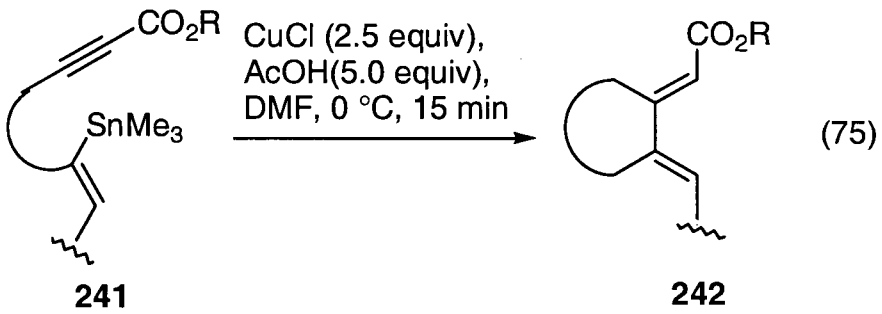


Scheme 21.

Since only two substrates were employed to probe the reaction, it is difficult without exploration of the reaction conditions and substrate structure to comment in detail on the conjugate addition of alkenyltrimethylstannane functions to α,β-alkynals and α,β-alkynones. However, this work supplies promising preliminary results on which to base further studies. Additional work may include examination of other systems (formation of monocyclic products for example) or a study of altering the experimental conditions with the goal of optimizing the ratio of geometric isomers to favor production of (Z)-olefins. This may provide a future stereoselective route to (Z)-substituted bicyclic dienes and would complement the conjugate addition methodology employing α,β-alkynic esters.

1.6 Summary

In summary, a series of cyclization precursors of general structure **241** that incorporate α,β-alkynic ester and alkenyl- or aryltrimethylstannane moieties were synthesized. When these substances were treated as shown in equation 75, the carbon centre bearing the trimethylstannane function was shown to add successfully in a conjugate (1,4) sense to the unsaturated ester function to produce **242**. In most cases, subjection of the cyclization precursors to the protocol developed (2.5 equiv CuCl, 5 equiv AcOH, 0 °C, DMF, 15 min) provided configurationally defined monocyclic and bicyclic systems very efficiently (Chart 5). A brief investigation demonstrated the adaptation of the methodology to include α,β-alkynic ketone and α,β-alkynic aldehyde functions as potential Michael acceptors (equation 76). The use of a catalytic amount of copper(I) chloride was also successfully demonstrated (equation 77).



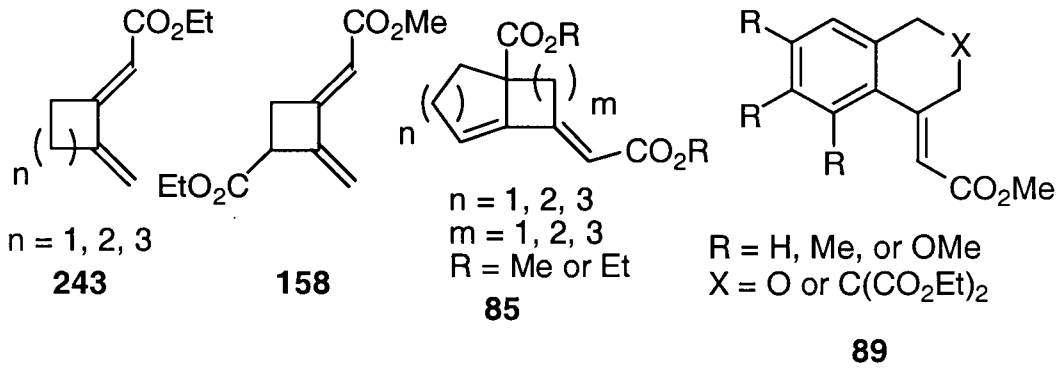
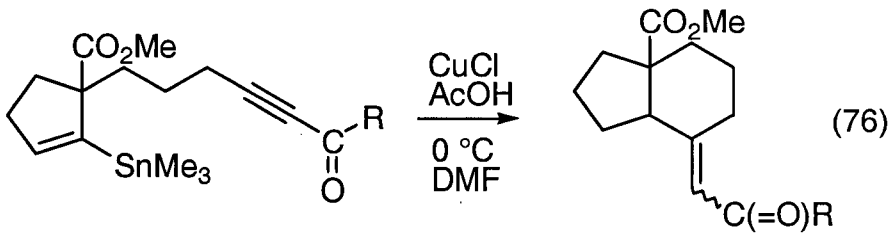
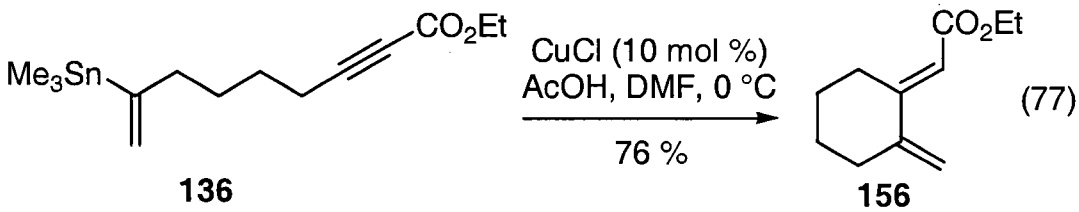


Chart 5. Compounds **243**, **158**, **85**, and **89**.

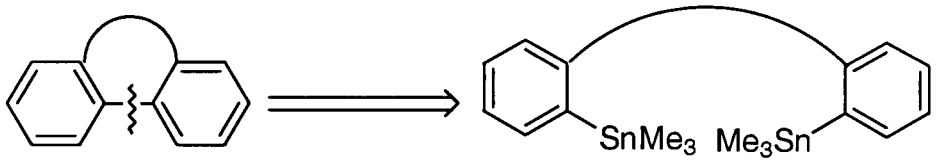




2. Intermolecular and intramolecular oxidative coupling of alkenyl- and aryltrimethylstannanes mediated by copper(I) chloride

2.1 Introductory remarks

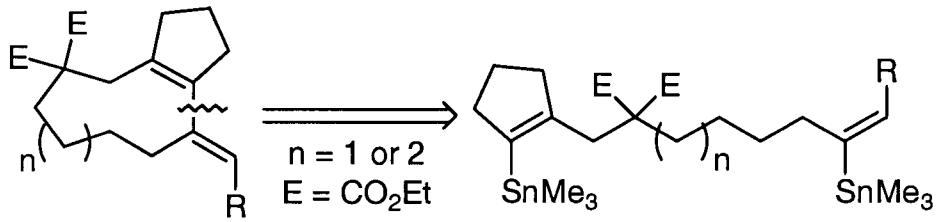
Previous studies[8] have described the copper(I) mediated intermolecular homocoupling of alkenylstannanes. This part of the thesis is mainly focused on the intramolecular variant of the transformation.[9,10] In particular, it was envisaged that tricyclic systems of general structure **243** could be produced by the copper(I)-mediated oxidative coupling of two aryltrimethylstannane functions. A generalized retrosynthetic disconnection is shown below (equation 78).



(78)

243 **244**

At this point, another potential useful application of the copper(I) mediated intramolecular homocoupling had yet to be explored fully (see retrosynthetic scheme in equation 79). The synthesis of medium-sized rings (8-11 membered) has often proved to be very difficult to accomplish.[58] The reason for this has been attributed to a variety of unfavorable entropic and enthalpic factors in the cyclization.[59] To test the limits of the coupling methodology, a brief study into the formation of 9- and 10-membered rings of general structure **115** was undertaken (equation 79).



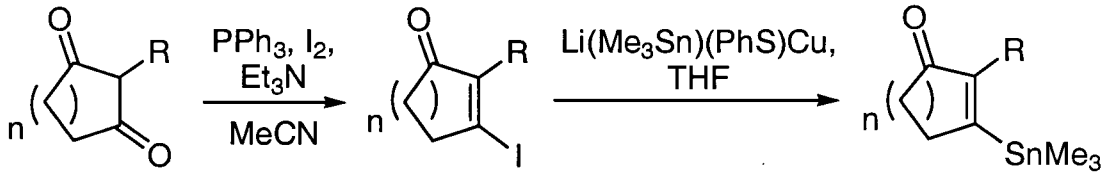
(79)

115 **114**

2.2 Intermolecular coupling of β-trimethylstannyl-α,β-unsaturated ketones mediated by copper(I) chloride

2.2.1 Preparation of β-trimethylstannyl-α,β-unsaturated ketones

The coupling precursors required for this study were prepared via published literature procedures. Conversion of the cyclic diketones of general structure **245** (n = 1 or 2 and R = H or Me) to the β-iodoenones **246** was accomplished by treatment of the diketones **245** with triphenylphosphine, iodine, and triethylamine in acetonitrile (Table 8).[60] The β-trimethylstannyl-α,β-unsaturated ketones of general structure **247-250** were prepared by following the procedure devised by Piers, Morton, and Chong[61] which involved the addition of lithium (trimethylstannyl)(phenylthio)cuprate to the β-iodoenones **246**. The spectral data derived for the compounds **246a-246d** and **247-250** were in full accord with the values published in the literature.[60,61]



245 **246** **247-250**

Scheme 22.

Table 8. Synthesis of the iodides **246a-246d** and stannanes **247-250**

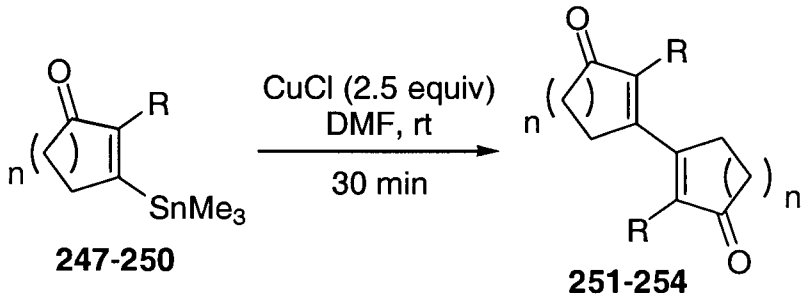
Entry	n	R	Product	% Yield[a]	Product	% Yield[b]
1	1	H	**246a**	79	**247**	38
2	1	Me	**246b**	92	**248**	74
3	2	H	**246c**	83	**249**	34
4	2	Me	**246d**	91	**250**	56

[a] Isolated yield from the diketones **245**.

[b] Isolated yield from the β-iodoketones **246**.

2.2.2 Copper(I) salt mediated coupling

The results of the copper(I)-mediated homocoupling experiments, in which the β-trimethylstannyl enones **247-250** were treated with 2.5 equiv of CuCl in dry DMF for 30 minutes at room temperature, are summarized in Table 9. In each instance (entries 1-4, Table 9), the structurally unusual, crystalline bis-enones **251-254** were produced, after aqueous workup and purification of the crude product by flash column chromatography on silica gel, in excellent yields (81-94%).



247-250 **251-254** (80)

Table 9. Synthesis of the diketones **251-254**

Entry	Substrate	n	R	Product	% Yield[a]
1	**247**	1	H	**251**	81
2	**248**	1	Me	**252**	91
3	**249**	2	H	**253**	94
4	**250**	2	Me	**254**	91

[a] Isolated yield of purified products.

The proposed structures of the homocoupled products **251-254** were confirmed by an analysis of the spectrometric (^{1}H nmr, ^{13}C nmr, IR, and HRMS) data. For example, the IR spectrum of **251** (n = 1, R = H) showed the C=O absorption at 1698 cm^{-1}. The ^{1}H nmr spectrum showed resonances attributable to the four methylene groups (two 4 proton multiplets centred at δ 2.55 and 2.88), and the two alkenyl protons (a 2 proton triplet at δ 6.43, J = 1.5 Hz). The symmetrical nature of the product was clearly shown by the simplicity of the ^{13}C nmr spectrum, which displays resonances that correspond to the four methylene carbons (δ 28.2 and 35.1), four alkenyl carbons (δ 132.6 and 166.9), and the two carbonyl carbons (δ 208.7). The molecular formula of 3-(3-oxocyclopent-1-en-1-

yl)cyclopent-2-en-1-one (**251**) was confirmed by a HRMS measurement on the molecular ion.

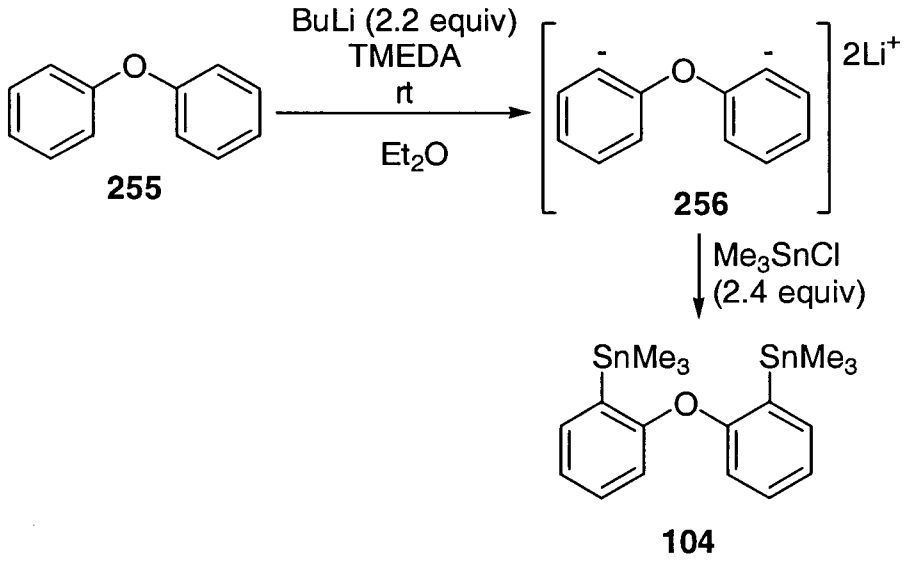
The structures of the remaining homocoupled products **252-254** were assigned by similar analyses of their ^{1}H nmr, ^{13}C nmr, and IR spectra and their molecular masses were confirmed by high resolution mass spectrometric measurements. Of particular interest in the ^{1}H nmr spectra of the compounds **252** and **254** are the resonances due to the methyl groups which each exhibit long range coupling to a set of methylene protons and appear as triplets (δ 1.67, J = 2.1 Hz and δ 1.61, J = 1.9 Hz for the diketones **252** and **254**, respectively). The element of symmetry that the products **252-254** possess was highlighted in the ^{13}C nmr spectra by the appearance of 6, 6, and 7 carbon resonances, respectively.

The examples presented clearly show that β-trimethylstannyl-α,β-unsaturated ketone functions are amenable to the copper(I) chloride-mediated homocoupling protocol. Future work in this area may include investigations into the stereospecific nature of the reaction, since the substrates in this study incorporated an endocyclic double bond and, as a result, stereospecificity was not an issue. The mechanism of the homocoupling reaction of alkenyltrimethylstannanes has been discussed previously (see Introduction section 2.2, pg. 8).

2.3 Intramolecular copper(I)-mediated coupling of aryltrimethylstannane functions to aryltrimethylstannane and alkenyltrimethylstannane functions

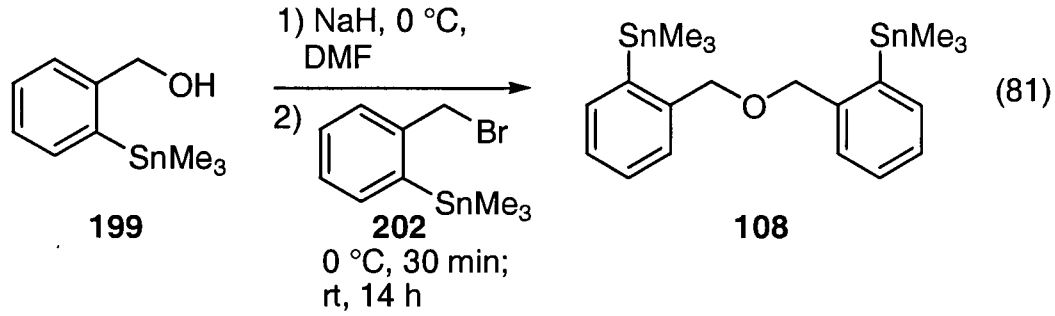
2.3.1 Preparation of cyclization precursors

The coupling substrates utilized in this study were prepared using the following protocols. Treatment of commercially available diphenyl ether (**255**) with 2.2 equiv of BuLi[33] and TMEDA in Et_2O for 3 h at room temperature and quenching the resultant ortho-lithiated dianion **256** with 2.4 equiv of trimethylstannyl chloride provided, as a crystalline solid (mp 67-69 °C), bis(trimethylstannylphenyl) ether (**104**) in a good yield (74%) (Scheme 23).



Scheme 23.

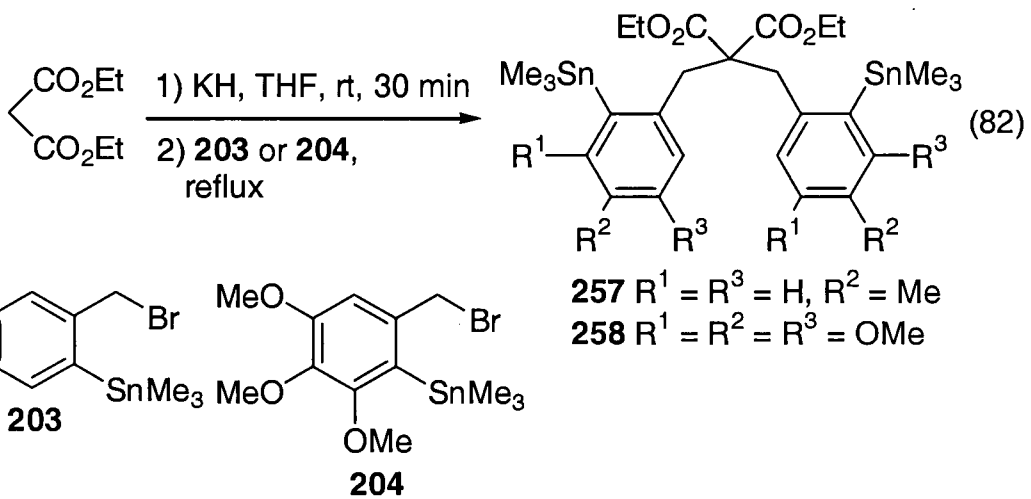
The seven-membered ring coupling precursor **108** was synthesized from the previously prepared *o*-trimethylstannylbenzyl alcohol (**199**) and *o*-trimethylstannylbenzyl bromide (**202**) (see Discussion section 1.4.1, pg. 55). Reaction of the alkoxide of **199**, formed from the treatment of the benzyl alcohol **199** with sodium hydride in dry DMF,[52] with the bromide **202** provided the symmetrical ether **108** in excellent yield (98%) (equation 81).



(81)

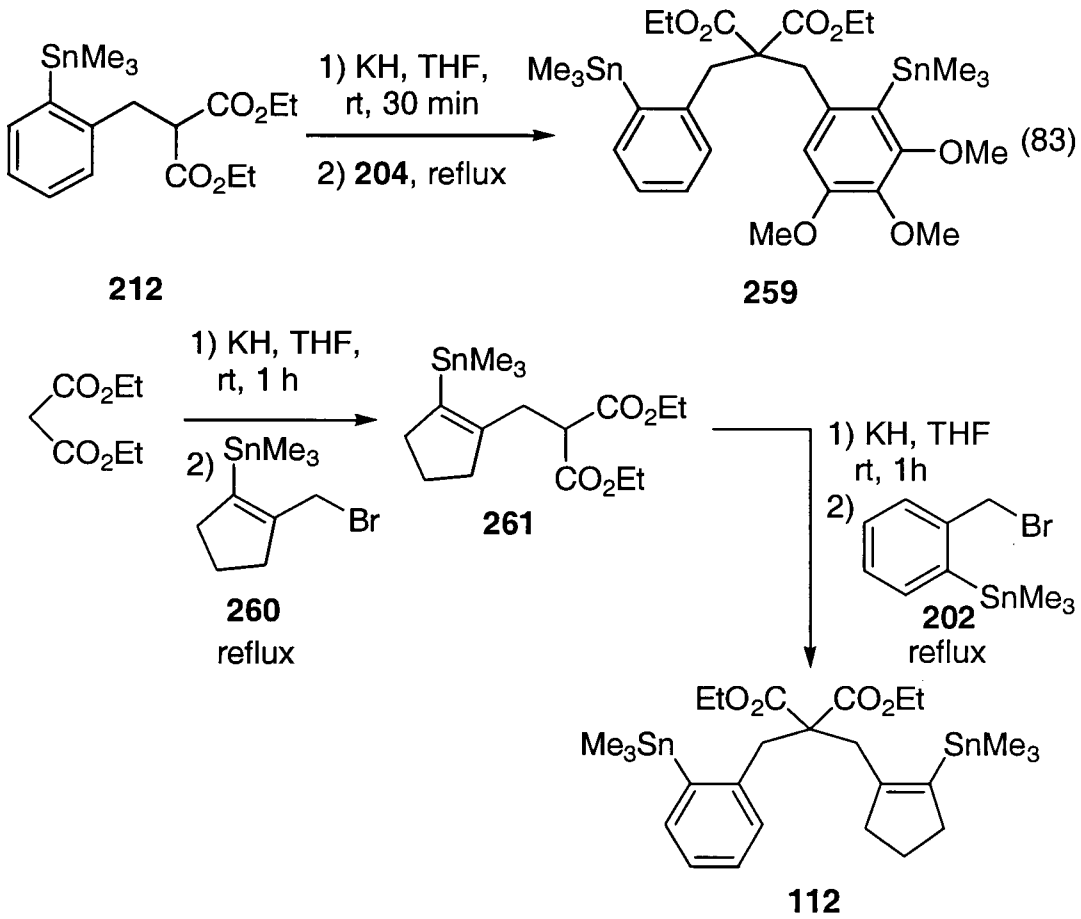
The proposed structures of the symmetrical ethers **104** and **108** were fully consistent with the spectral data. Using the distannane **108** as an example, the IR spectrum showed the tin-methyl rocking absorption at 755 cm^{-1}. The ^1H nmr spectrum contained resonances corresponding to the Me_3Sn groups (an 18 proton singlet at δ 0.26, $^2J_{Sn\text{-}H}$ = 54.9 Hz), the methylene groups (a 4 proton singlet at δ 4.43), and eight aromatic protons (a 6 proton multiplet at δ 7.20-7.33 and a 2 proton multiplet at δ 7.45-7.58). The ^{13}C nmr spectrum of **108** showed the expected 8 resonances. The molecular formula of **108** was confirmed by a HRMS measurement on the (M^+-Me) fragment.

A series of intramolecular coupling precursors was synthesized by successive alkylations of diethyl malonate. Dialkylation[9] of diethyl malonate by treatment with excess potassium hydride (2.5 equiv) in THF followed by the addition of 2 equiv of the benzyl bromides **203** or **204** (see Discussion section 1.4.1, pg. 55) provided the symmetrical substrates **257** and **258** in 95% and 62% yields, respectively (equation 82). Treatment of the monoalkylated malonate **212** (pg. 57) with potassium hydride[9] in THF,



(82)

followed by addition of the bromide **204,** provided the "mixed" bisaryltrimethylstannane **259** in good yield (78%) (equation 83). Lastly, sequential alkylation[9] of diethyl malonate with the bromides **260**[27] and **202** provided the distannane **113** (Scheme 24).



Scheme 24.

The spectral data derived from the dialkylated malonate esters **257-259**, and **112** were fully consistent with their assigned structures. For example, in the spectrometric data acquired from the diester **257**, the IR spectrum showed the C=O absorption at 1726 cm^{-1} and the tin-methyl rocking absorption at 776 cm^{-1}. The ^1H nmr spectrum displayed resonances due to the Me_3Sn groups (an 18 proton singlet at δ 0.24, $^2J_{Sn\text{-}H}$ = 53.1 Hz), the benzylic methylene groups (a 4 proton singlet at δ 3.38), two aromatic methyl groups (a 6 proton singlet at δ 2.25), the ethyl ester functions (a 6 proton triplet at δ 1.03, J = 7.1 Hz, mutually coupled to a 4 proton quartet at δ 4.01, J = 7.1 Hz), and six aromatic protons (a 4 proton multiplet centred at δ 7.00 and a 2 proton singlet at δ 7.16,

$^3J_{Sn-H}$ = 50.6 Hz). The symmetrical nature of the diester **257** was illustrated by the appearance of 13 resonances in the ^{13}C nmr spectrum. The six negative resonances seen in an APT experiment (δ -7.4, 13.8, 20.1, 127.8, 129.0, and 137.2) could be attributed to the trimethylstannyl functions, the methyl groups, the methyl carbon of the ester moieties, and the six sp^2 methine carbons. The molecular formula of **257** was confirmed by a HRMS measurement on the (M^+-Me) fragment. Analyses of the spectral data (^1H nmr, ^{13}C nmr, and IR) confirmed the assigned structures of the remaining distannanes **258-259** and **112** and their molecular masses were also confirmed by HRMS measurements on their respective (M^+-Me) fragments.

The coupling substrates **104, 108, 112,** and **257-259** collectively provide a diverse series of distannanes with which to examine the scope and limitations of the proposed copper(I)-mediated methodology.

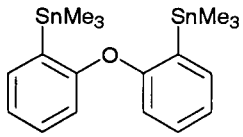
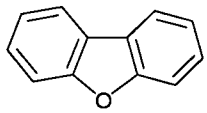
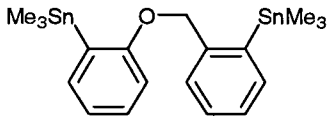
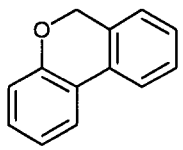
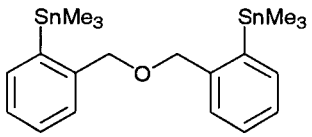
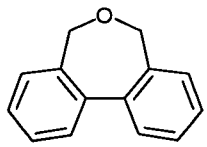
2.3.2 Copper(I) chloride-mediated cyclizations

The results of the copper(I) chloride-mediated ring closures of the substrates **104**, **106**, and **108** to form the 5-, 6-, and 7-membered cyclic ethers **105**, **107**, and **109** are summarized in Table 10. Treatment of a dry DMF solution of the distannane **104** with 5 equiv of CuCl, followed by stirring of the resultant mixture for 30 min at room temperature (referred to as procedure A), resulted in the clean formation of dibenzofuran (**105**) (98%, Table 10, entry 1). Application of this procedure to the conversion of **106** into the tricyclic ether **107**, by the formation of a six-membered ring, was also very efficient (91%, Table 10, entry 2).

However, upon application of the protocol (procedure A) developed to the symmetrical ether **108**, the yield of the transformation to synthesize **109** was slightly lower (75%, Table 10, entry 3). Tlc analyses of the crude reaction mixtures suggested that, in addition to **109**, polar polymeric material, perhaps due to competing intermolecular oxidative coupling processes, was being produced. Fortunately, this situation could be ameliorated to a large degree by the use of a modified protocol (referred to as procedure B) in which a DMF solution of the substrate was added slowly over a period of 30 min to a stirred solution-suspension of 5 equiv of copper(I) chloride

in dry DMF. Under these new conditions, the yield of the conversion of **108** to **109** was excellent (91%). Each of the compounds **105**, **107**, and **109** have been prepared previously and the spectral data of **107**[62] and **109**[63] were in full agreement with those reported in the literature. The synthetic sample of **105** was spectroscopically identical to a commericailly available sample of dibenzofuran (**105**) and the melting points of the two samples were identical.

Table 10. Synthesis of the tricycles **105**, **107**, and **109**

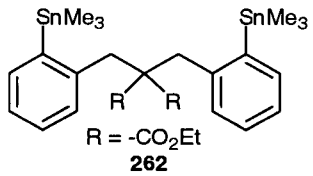
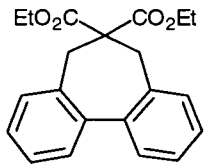
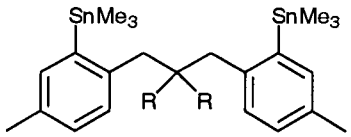
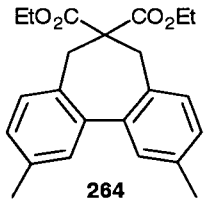
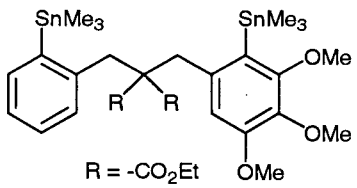
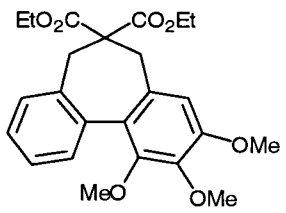
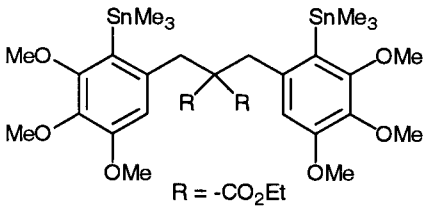
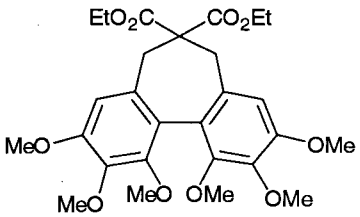
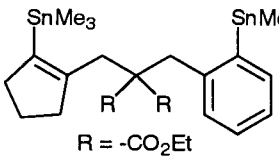
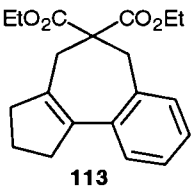
Entry	Starting Material	Product	% Yield[a]
1	 **104**	 **105**	98[b]
2	 **106**	 **107**	91[c,d]
3	 **108**	 **109**	75[b] 91[c]

[a] Isolated yield of purified products.
[b] Procedure A employed - 5 equiv CuCl, DMF, rt, 30 min.
[c] Procedure B employed - 5 equiv CuCl, DMF, rt, add substrate over 30 min, stir for an additional 30 min
[d] This experimental procedure was performed by Dr. Patricia Gladstone.[31]

Examples of the formation of seven-membered carbocycles via CuCl-mediated coupling of two aryltrimethylstannane moieties are summarized in Table 11. Treatment of substrate **262** with 5 equiv of CuCl in dry DMF for 30 min (procedure A) provided a satisfactory yield (78%) of the tricycle **263** (Table 11, entry 1). However, increased yields were obtained when procedure B was applied to the remaining examples. For instance, slow addition of a dry DMF solution of the distannane **257** to a solution-suspension of 5 equiv of CuCl in dry DMF proceeded to give the tricycle **264** in excellent

yield (95%, Table 11, entry 2). Although, not unexpectedly, ring closure of the highly substituted hexamethoxy compound **258** to provide the sterically congested substance **266** was somewhat less facile, the yield (62%) was still quite good (Table 11, entry 4). On the other hand, the transformation of **259** into the unsymmetrical trimethoxy tricycle

Table 11. Synthesis of the tricycles **113** and **263-266**

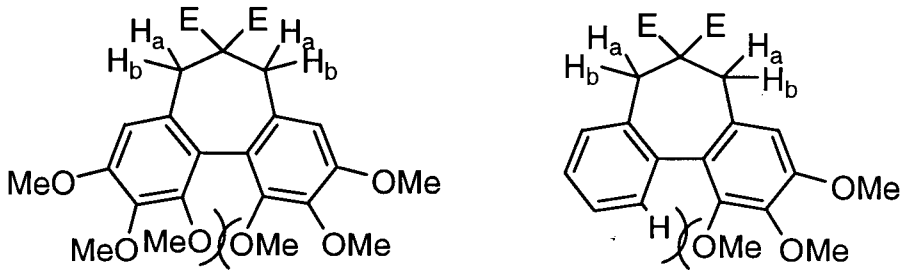
Entry	Starting Material	Product	Yield[a]
1	 **262**	 **263**	78[b,d]
2	 **257**	 **264**	95[c]
3	 **259**	 **265**	92[c]
4	 **258**	 **266**	62[c]
5	 **112**	 **113**	94[c]

[a] Isolated yield of purified products.
[b] Procedure A employed - 5 equiv CuCl, DMF, rt, 30 min.
[c] Procedure B employed - 5 equiv CuCl, DMF, rt, add substrate over 30 min, stir for an additional 30 min.
[d] This example was performed by Dr. Patricia Gladstone.[31]

265 was highly efficient (92%, Table 11, entry 3). The last example (Table 11, entry 5) illustrates a "mixed" intramolecular coupling of alkenyl- and arlytrimethylstannane functions to form a seven-membered ring. Thus, subjection of the distannane **112** to procedure B afforded the structurally novel tricycle **113** in high yield (94%).

Of the seven-membered carbocyclic compounds **263-266** listed in Table 11, the compound **263** had been reported previously and the spectral data were in accordance with the reported literature values.[63] The previously unreported tricycles **264-266** (Table 11, entries 2-5) exhibited spectral data (^{1}H nmr, ^{13}C nmr, and IR) and HRMS measurements in full agreement with their assigned structures. For example, the IR spectrum of **266** showed the carbonyl absorption band at 1726 cm^{-1}. The ^{1}H nmr spectrum of **266** showed the presence of the ethyl ester functions (a 6 proton triplet at δ 1.26, J = 7.1 Hz, and a 4 proton multiplet centred at δ 4.18), six methoxy groups (three 6 proton singlets at δ 3.64, 3.84, and 3.87), and the isolated aromatic protons (a 2 proton singlet at δ 6.56). It is interesting to note that compound **266** exhibits a ^{1}H nmr spectrum in which the benzylic methylene protons exhibit geminal coupling (two 2 proton doublets at δ 2.73 and 3.08, J = 14.0 Hz). A similar pattern is exhibited by the ^{1}H nmr spectrum of **265**. This behavior can be explained by noncoplanarity of the aromatic rings which is assisted by hindered rotation about the newly formed carbon-carbon bond. From an examination of molecular models, these tricycles incur severe steric interaction between the two proximal substituents (methoxy-methoxy or methoxy-hydrogen, Figure 12). As a result, free rotation about the sigma bond linking the two aryl groups is restricted. This form of atropisomerism[64] causes the supposedly enantiotopic methylene protons (H_a, H_b) to become diastereotopic and, consequently, the protons appear as two doublets in the ^{1}H nmr spectrum. The ^{13}C nmr spectrum of **266** displays only 14 signals, which is not surprising given the symmetrical nature of the product. In an APT experiment, five negative signals (δ 14.2, 55.9, 60.7, 60.9, and 108.4) could be attributed to the methyl carbons of the ethyl ester functions, three pairs of methoxy groups, and the aryl methine carbons, respectively. The molecular formula of **266** was confirmed by a HRMS measurement on the molecular ion. An examination of the spectrometric data (^{1}H nmr,

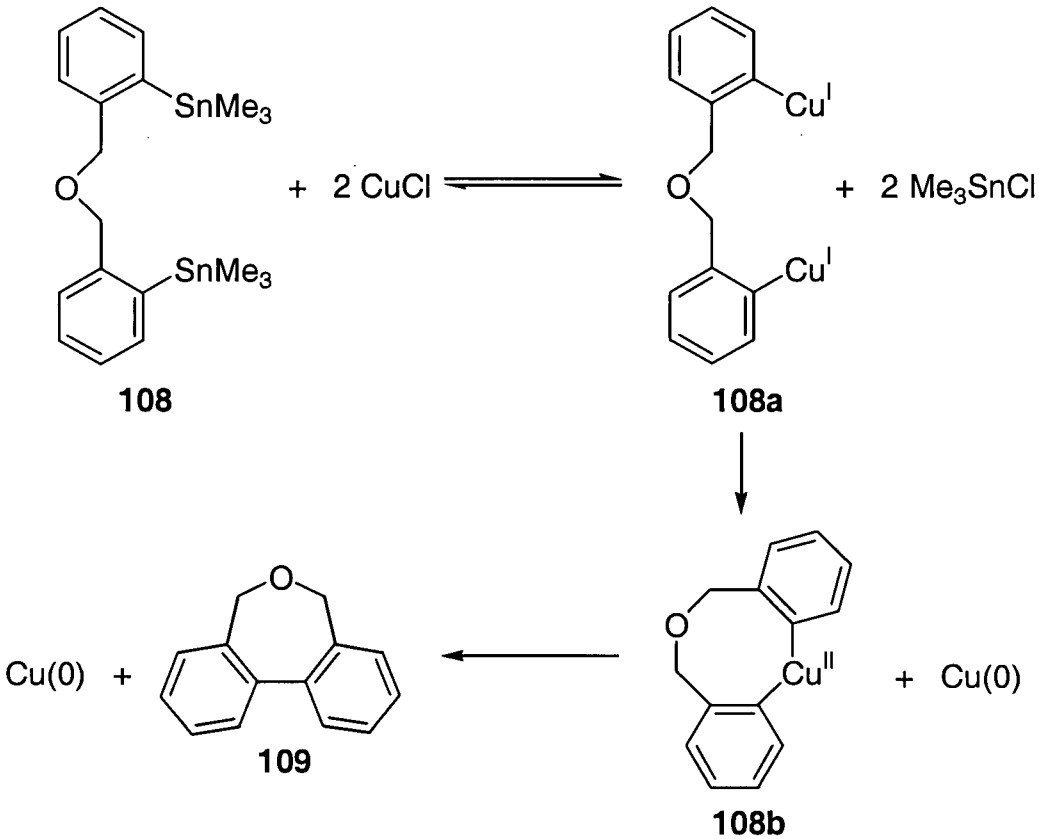
^{13}C nmr, HRMS, and IR) acquired from the substances **264**, **265**, and **113** also confirmed their respective proposed structures.



266 E = CO_2Et **265**

Figure 12. Steric interactions in **265** and **266**

A plausible mechanistic pathway for the intramolecular coupling reaction of aryltrimethylstannanes is shown in Scheme 25 and is analogous to that previously proposed for the copper(I) chloride-mediated homocoupling of alkenyltrimethyl stannanes (see Introduction section 2.2, pg. 8). Briefly, using conversion of **108** into **109** as an illustrative example, a reversible copper-tin transmetalation[3] of both trimethyl-



108 **108a** **109** **108b**

Scheme 25.

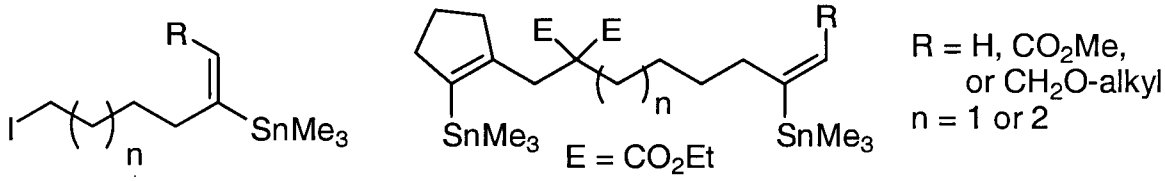
stannane moieties in **108** with 2 equiv of CuCl would result in the bisarylcopper(I) species **108a** and 2 equiv of Me_3SnCl. A disproportionation[8] of **108a** would form Cu(0) and the copper(II) intermediate **108b**, which upon a reductive elimination of a second equivalent of Cu(0) would result in the formation of the observed product **109**. The use of 5 equiv of CuCl, as described in the general reaction procedure (see Experimental, pg. 229), would facilitate the coupling process by forcing the transmetalation equilibrium (right) toward the bisarylcopper(I) species **108a**.

The examples presented collectively in Tables 9 and 10 (pg. 87 and 88, respectively) demonstrate the efficacy of copper(I) chloride to promote the intramolecular coupling of aryltrimethylstannane functions to form 5-, 6-, and 7-membered rings. Especially impressive is the formation of the highly substituted hexamethoxy derivative **266** albeit with reduced yield (62%). An exploration of the electronic effects from aryl substituents on the efficiency of the transformation will have to await furthur experimentation.[65] Lastly, it is also interesting to note that "mixed" intramolecular cross-coupling of alkenyl- and aryltrimethylstannanes can be very efficient processes (Table 11, entry 5), which expands the synthetic utility of the reaction.

2.4 Intramolecular oxidative coupling of bisalkenyltrimethylstannanes to form bicyclo[7.3.0]dodecane and bicyclo[8.3.0]tridecane derivatives

2.4.1 Preparation of cyclization precursors

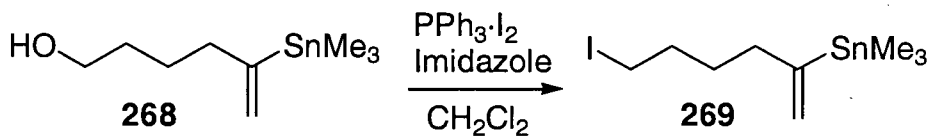
A series of alkylating agents of general structure **267** (Chart 6) were required for use in the synthesis of the distannanes **79** and their preparation is described below.



267 **79**

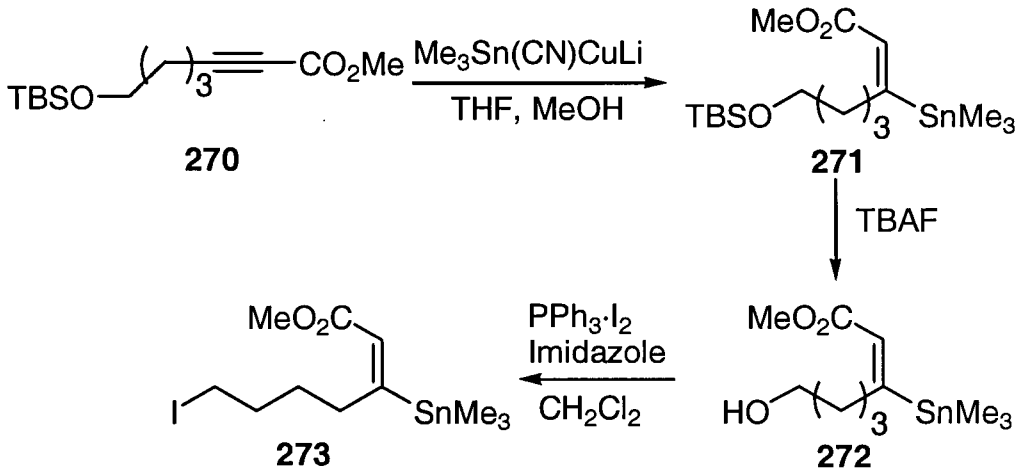
Chart 6.

Treatment of the known alcohol **268**[47] with triphenylphosphine diiodide and imidazole[48] in CH_2Cl_2 provided the iodide **269** in excellent yield (93%). The spectral data derived from **269** were in full agreement with those previously reported.[47]



268 **269** (84)

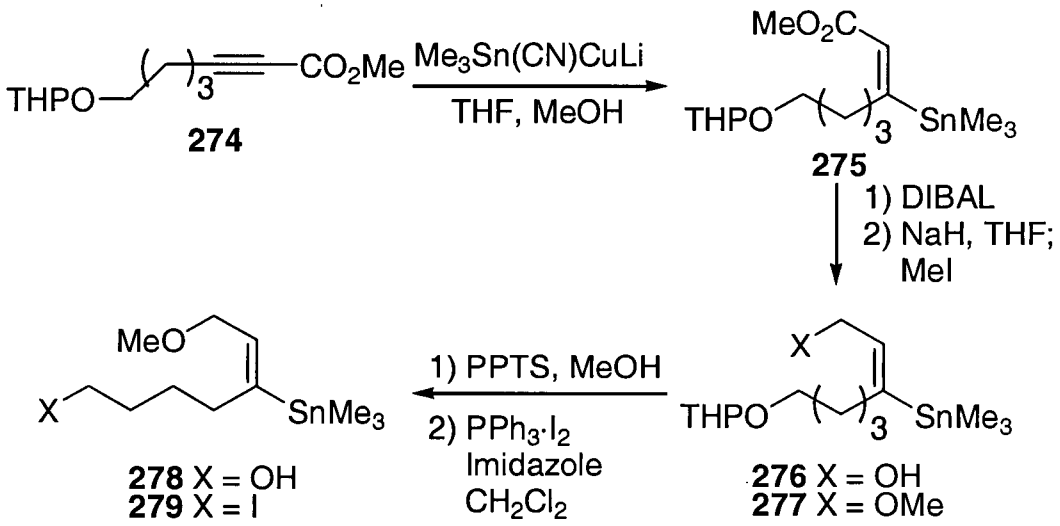
Reaction of alkynoate **270**[66] with lithium trimethylstannyl(cyano)cuprate[38] and methanol in THF, followed by purification of the crude material by flash column chromatography, afforded the ester **271** as a colorless oil. This material was converted to the alkyl iodide **273** with a standard deprotection-iodination sequence. Thus, treatment of the stannane **271** with TBAF[39] in THF followed by treatment of the resultant alcohol with triphenylphosphine diiodide and imidazole[48] in methylene chloride provided the alkylating agent **273** (Scheme 26). The overall yield of the three-step sequence was 65%.



Scheme 26.

The spectral data support the proposed structure of the iodide **273**. For instance, the ^{1}H nmr spectrum showed diagnostic resonances corresponding to the trimethylstannyl function (a 9 proton singlet at δ 0.20, $^2J_{Sn\text{-}H}$ = 54.6 Hz) and the methyl ester function (a 3 proton singlet at δ 3.67). The (*E*)-configuration of the double bond was determined by the tin-proton coupling constant of the olefinic proton (a 1 proton triplet at δ 5.97, J = 1.2 Hz, $^3J_{Sn\text{-}H}$ = 72.5 Hz). It is well established that the coupling constant of a vicinal proton on a double bond *cis* to a trimethylstannyl function are of lower magnitude (~70 Hz) than those in which the Me_3Sn group and the hydrogen are *trans* to one another (~120 Hz).[67] The ^{13}C nmr spectrum displayed the expected 9 signals. Finally, the molecular formula of **273** was confirmed by a HRMS measurement on the (M^+-Me) fragment.

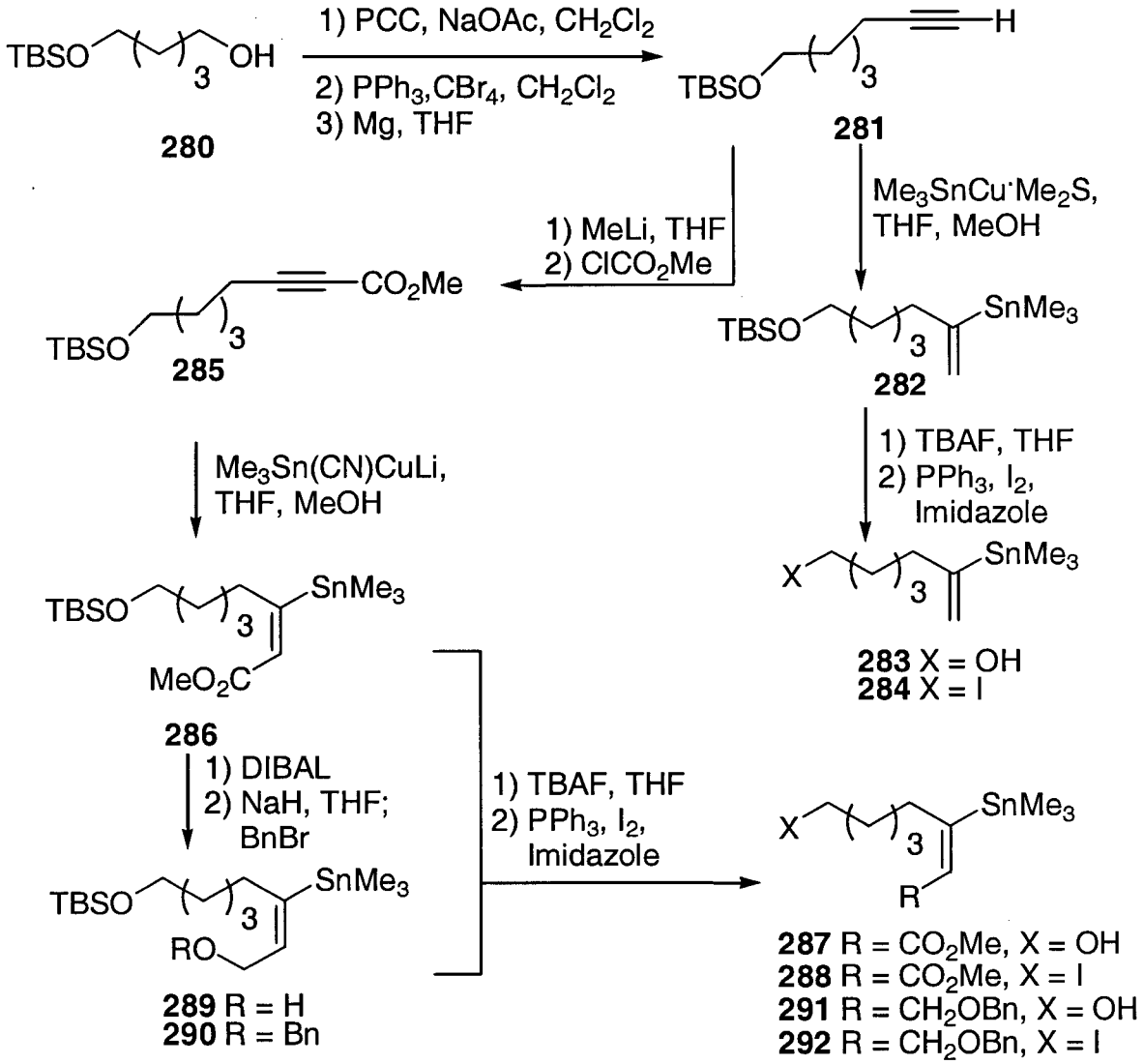
The methyl ether **279** was prepared in five steps from the tetrahydropyranyl protected alcohol **274**[41] (Scheme 27). Treatment of the latter material with lithium trimethylstannyl(cyano)cuprate[38] and MeOH in THF yielded the alkenylstannane **275**. Reduction of ester **275** with DIBAL[44] followed by treatment of the resultant allylic alcohol **276** with sodium hydride and methyl iodide[52] in THF provided the alkenylstannane **277**. The iodide **279** was obtained by the removal of the tetrahydropyranyl group with PPTS in methanol[46] and subsequent conversion of the acquired primary alcohol to the iodide.[48] The four-step overall yield was 35% from the alkynoate **274**.



Scheme 27.

The spectral data was in full accord with the proposed structure of **279**. The ^{1}H nmr spectrum showed key resonances corresponding to the trimethylstannyl group (a 9 proton singlet at δ 0.12, $^{2}J_{Sn\text{-}H}$ = 52.5 Hz), the methyl ether moiety (a 3 proton singlet at δ 3.33), and the lone olefinic proton (a 1 proton triplet of triplets, J = 1.2, 6.0 Hz, $^{3}J_{Sn\text{-}H}$ = 77.2 Hz). The (*E*)-configuration of the trisubstituted olefin was confirmed by the magnitude of the tin-proton coupling constant.[67] The ^{13}C nmr spectrum showed the expected 9 resonances. The molecular formula of **279** was confirmed by a HRMS measurement on the (M^{+}-Me) fragment.

The alkylating agents **284**, **288**, and **292** were prepared according to the reaction sequences outlined in Scheme 28. Oxidation of the alcohol **280**[68] with pyridinium chlorochromate in methylene chloride,[69] provided the corresponding crude aldehyde. The use of a modified Corey-Fuch one carbon homologation protocol[36,37] employed previously (see Discussion section 1.2.1, pg. 29) provided 7-*tert*-butyldimethylsilylhept-1-yne (**281**) in 43% overall yield.



Scheme 28.

The spectral data was consistent with the proposed structure of **281**. For example, in the IR spectrum, the alkynic function was clearly shown by C-H stretching absorption at 3314 cm^{-1} and the C-C triple bond stretch at 2120 cm^{-1}. The ^{1}H nmr spectrum showed key signals ascribed to the silyl ether moiety (a 6 proton singlet at δ 0.02 and a 9 proton singlet at δ 0.87) and the alkyne proton (a 1 proton triplet at δ 1.90, J = 2.6 Hz). The ^{13}C nmr spectrum displayed the correct number of signals, 10, and the molecular formula was confirmed by a HRMS measurement on the (M^{+}-Me) fragment.

Treatment of the terminal alkyne **281** with $Me_3SnCu{\cdot}Me_2S$[41] and methanol in THF and purification of the crude material by flash column chromatography on silica gel served to provide the alkenylstannane **282** (Scheme 28) in good yield (73%). Subjection of **282** to a two-step deprotection-iodination sequence provided the iodide **284**. Thus, removal of the TBS group with TBAF[39] in THF yielded the alcohol **283**. The stannane **283** was found to protiodestannylate during purfication by flash column chromatography on silica gel. However, treatment of crude **283** with triphenylphosphine diiodide and imidazole[48] gave the iodide **284** in excellent yield (84%) from the stannane **282**.

The spectroscopic data acquired fully support the proposed structure of the iodide **284**. For instance, the ^1H nmr spectrum showed the trimethylstannyl function (a 9 proton singlet at δ 0.10, $^2J_{Sn\text{-}H}$ = 52.8 Hz), the TBS group (a 6 proton singlet at δ 0.02 and a 9 proton singlet at δ 0.82), and two olefinic protons (two 1 proton multiplets centred at δ 5.10 and 5.62). The ^{13}C nmr spectrum showed the expected 11 carbon resonances and a HRMS mass measurement confirmed the molecular formula of **284**.

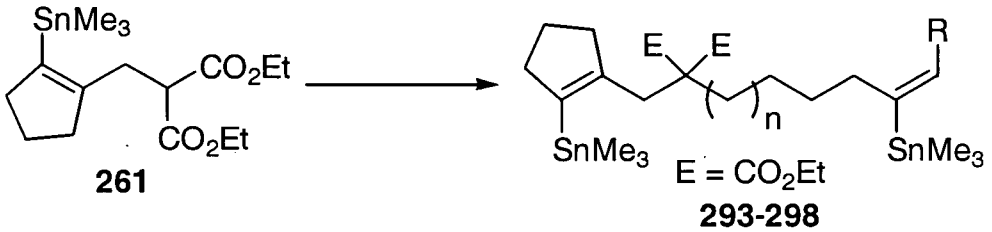
Preparation of the iodide **288** commenced with acylation of the terminal alkyne **281** by sequential treatment with MeLi and methylchloroformate[38] to provide the α,β-alkynic ester **285**. Reaction of the alkynoate **285** with lithium trimethylstannyl (cyano)cuprate[38] and MeOH in THF afforded the alkenylstannane **286** in 78% yield (Scheme 28). In a two step deprotection-iodination sequence as described above, the alkenylstannane **286** was converted to the electrophile **288** in excellent yield (97%).

The proposed structure of **288** was confirmed by the spectral data (^1H nmr, ^{13}C nmr, and IR). In particular, the (*E*)-configuration of the double bond was confirmed by the tin-proton coupling constant of the lone olefinic proton ($^3J_{Sn\text{-}H}$ = 64.6 Hz).[67] The ^{13}C nmr spectrum showed the presence of the expected 10 carbon resonances. The molecular formula of $C_{12}H_{23}O_2SnI$ was confirmed by a HRMS measurement on the (M^+-Me) fragment.

Lastly, reduction of the ester **286** with DIBAL[44] and reaction of the resultant allylic alcohol **289** with NaH and BnBr[52] provided the benzyl ether **290** (Scheme 28). Treatment of the latter substance with TBAF in THF,[39] and subjection of the acquired primary alcohol **291** to triphenylphosphine diiodide and imidazole[48] afforded the iodide **292**. The four-step overall yield was 68% from the stannane **286**.

The proposed structure of **292** was fully consistent with the spectroscopic data. For instance, the ^{1}H nmr spectrum of **292** displayed the trimethylstannyl group (a 9 proton singlet at δ 0.11), the benzyl group (a 5 proton multiplet centred at δ 7.30), the olefinic proton (a 1 proton triplet of triplets, J = 1.2, 6.0 Hz, $^3J_{Sn\text{-}H}$ = 77.9 Hz), and six methylene groups. The ^{13}C nmr spectrum showed the expected 14 carbons. The molecular formula of **292** was confirmed by a HRMS measurement on the (M^+-Me) fragment.

Straightforward alkylations[9] of the malonate **261** (whose preparation was described in Discussion section 2.3.1, pg. 85), by treatment of this material with LDA or KH in THF, followed by quenching the resultant enolate anion formed with each of the iodides **269**, **273**, **279**, **284**, **288**, and **292**, provided the crude distannanes **293-298**, respectively. Purification of the crude materials by flash column chromatography on silica gel afforded good to excellent yields of **293-298** (73-96%, Table 12).



(85)

Table 12. Synthesis of the distannanes **293-298**

Entry	n	R	Reaction conditions	Product	% Yield[a]
1	1	-H	LDA, THF, 0 °C; **269**, reflux	**293**	78
2	1	-CO_2Me	LDA, THF, 0 °C; **273**, reflux	**294**	86
3	1	-CH_2OMe	KH, THF, rt; **279**, reflux	**295**	92
4	2	-H	KH, THF, rt; **284**, reflux	**296**	96
5	2	-CO_2Me	KH, THF, rt; **288**, reflux	**297**	82
6	2	-CH_2OBn	KH, THF, rt; **292**, reflux	**298**	73

[a] Isolated yield of purified products.

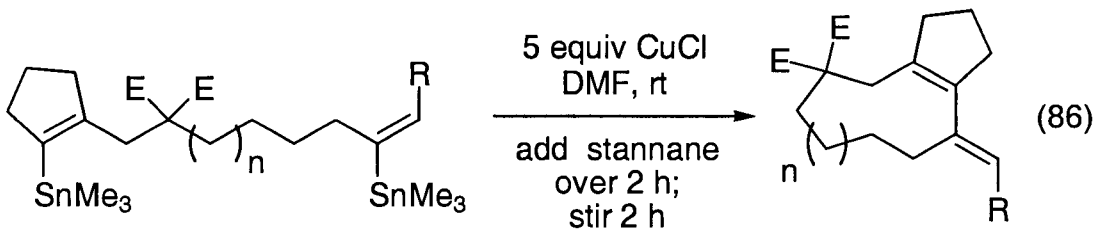
The structures of the dialkylated materials **293-298** were fully supported by their respective ^{1}H nmr, ^{13}C nmr, and IR spectra. For instance, the C=O functions in **294** were indicated by the broad absorption at 1729 cm^{-1}. The ^{1}H nmr spectrum of **294** showed the

presence of two alkenyltrimethylstannane functions, nine methylene groups, two ethyl ester functions, the methyl ester moiety, and the lone olefinic proton (see Experimental pg. 256 for assignments). In addition, the *trans* configuration of the α,β-unsaturated ester function was confirmed by the magnitude of the tin-proton coupling constant[67] of the alkenyl proton ($^3J_{Sn\text{-}H}$ = 73.7 Hz). The ^{13}C nmr spectrum showed the expected 21 signals. Also, the molecular formula of $C_{28}H_{50}O_6Sn_2$ was confirmed by a HRMS measurement on the (M^+-Me) fragment. The structures of the remaining distannanes **293** and **295-298** were confirmed by analyses of their spectrometric data (^1H nmr, ^{13}C nmr, IR, and HRMS).

Collectively, the cyclization substrates **293-298** display a variety of alkenyltrimethylstannane partners with which to test the copper(I) chloride-mediated oxidative coupling process to form 9- and 10-membered rings.

2.4.2 Copper(I) mediated cyclizations

Individual solution-suspensions of CuCl (5 equiv) in dry DMF were treated with a DMF solution of each of the distannanes **293-298** (1 equiv), added over a period of 2 h, followed by stirring the reaction mixture for an additional 2 h. The results derived from these experiments are summarized in Table 13.



(86)

E = CO_2Et
293-298

E = CO_2Et
299-304

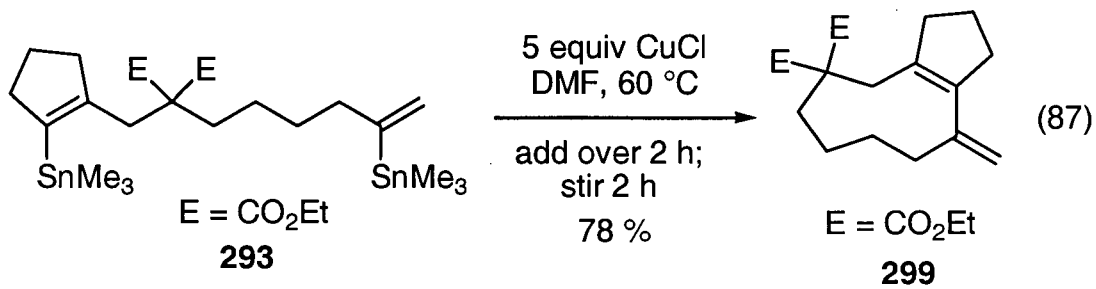
Table 13. Synthesis of the bicyclic dienes **299-304**

Entry	Starting Material	n	R	Product	Yield[a]
1	**293**	1	H	**299**	93
2	**294**	1	$-CO_2Me$	**300**	72
3	**295**	1	$-CH_2OMe$	**301**	91
4	**296**	2	H	**302**	-[b]
5	**297**	2	$-CO_2Me$	**303**	45
6	**298**	2	$-CH_2OBn$	**304**	-[c]

[a] Yield of purified products.
[b] A mixture of product **302**, protiodestannylated, dichlorodestannylated, and chlorodestannylated material was obtained.
[c] A mixture of product **304**, protiodestannylated and chlorodestannylated material was obtained.

Under the cyclization conditions described above (equation 86), the distannanes **293-295** were transformed into the 9-membered carbocycles **299-301**, respectively, in good to excellent yields (71-93%).

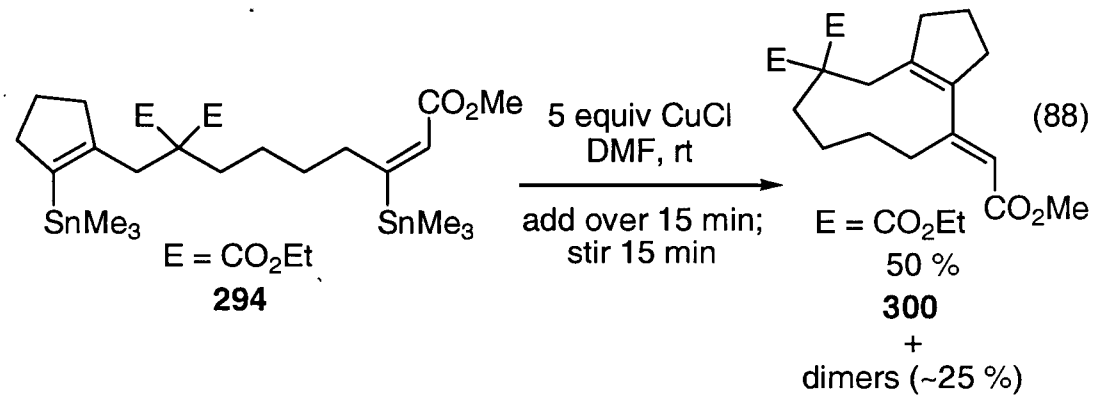
The experimental conditions employed in this study differed somewhat from that developed previously (5 equiv CuCl, DMF, 60 °C, addition of the substrate over 15 min followed by stirring the mixture for an additional 15 min).[9] In particular, it was found that elevated reaction temperatures (60 °C) diminished the efficiency of the conversion of **293** into **299** to 78% (cf. 93%, Table 13, entry 1) after workup and flash column chromatography on silica gel (equation 87).



(87)

A faster rate of addition was also detrimental to the yield of the reaction. By the addition of the cyclization substrate **294** to the CuCl over a period of 15 min, the yield of the transformation to form **300** was reduced from 72% (Table 13, entry 2) to 50%

(equation 88). The reduction in the yield was due to competing intermolecular homocoupling[8] processes.

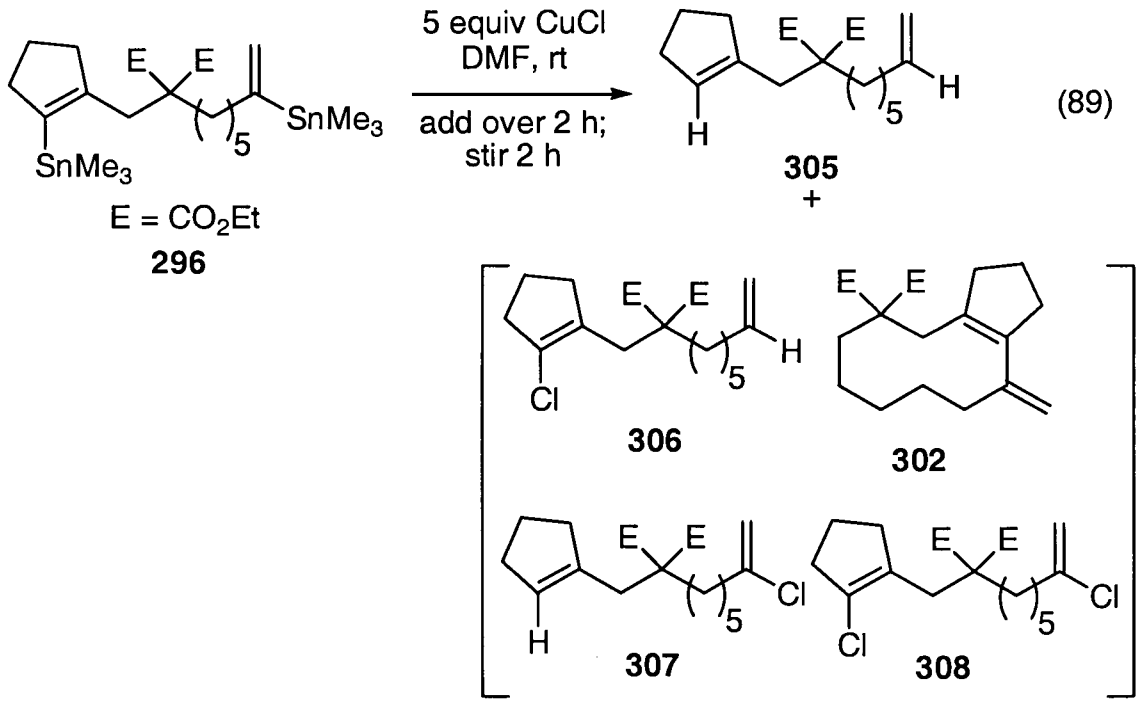


(88)

The structures of the carbocycles **299-301** were confirmed by an analysis of the spectroscopic data. For instance, in the IR spectrum of **299**, the carbonyl stretch was present at 1729 cm^{-1} and a C=C bond stretch at 1626 cm^{-1}. In the ^1H nmr spectrum, aside from the ethyl ester functions (a 6 proton triplet at δ 1.21, J = 7.1 Hz, and a 4 proton multiplet centred at δ 4.16) and eight methylene groups, the key indication that the cyclization successfully formed **299** was the appearance of the resonances corresponding to only two alkenyl protons (a 1 proton doublet at δ 4.90, J = 2.0 Hz, and a 1 proton broad singlet at δ 4.94). The ^{13}C nmr spectrum contained the expected 16 signals and, in an APT experiment, the presence of only one negative resonance at δ 14.0 was attributed to the methyl group of the ester functions. Lastly, the molecular formula of **299** was confirmed by a high resolution mass spectrometric measurement on the molecular ion.

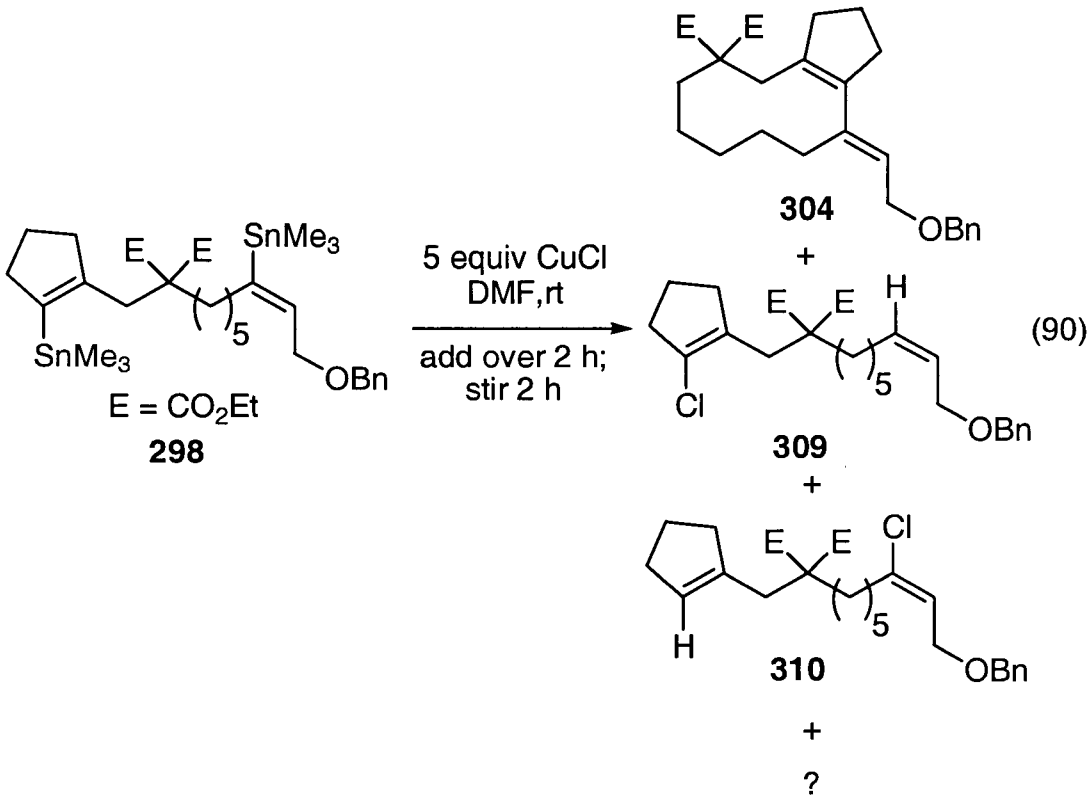
The structures of the remaining 9-membered ring compounds **300** and **301** were assigned by analyses of their respective ^1H nmr, ^{13}C nmr, and IR spectra. For instance, the key resonances in the ^1H nmr spectrum of **300** and **301** was the presence of only one alkenyl proton (a 1 proton singlet at δ 5.67 and a 1 proton triplet at 5.41, J = 6.4 Hz, respectively). The ^{13}C nmr spectra of each compound contained the expected 18 resonances. The molecular formulae of **300** and **301** were confirmed by suitable HRMS measurements on their molecular ions. Lastly, the (*E*)-configuration of the trisubstituted double bond in **300** and **301** was determined by a series of ^1H nmr nOed experiments (see Experimental, pg. 267 and 269).

In contrast to the cyclizations to form the 9-membered ring compounds **299-301**, application of the methodology to form the 10-membered ring compounds **302-304** was notably less successful (Table 13, entries 4-6, pg. 99). For example, upon treatment of the distannane **296** with 5 equiv of copper(I) chloride in dry DMF (equation 89), a complex mixture was isolated after aqueous workup (Table 13, entry 4). The major products isolated from a flash chromatographic column were protiodestannylated material **305** (~30%) and an inseparable mixture (>6 compounds, ~50%) consisting primarily of cyclized adduct **302** (m/z = 334), chloroprotiodestannylated materials **306** and **307** (m/z = 370), and dichlorodestannylated material **308** (m/z = 404) in an ~6:2:1 ratio, respectively, as determined by GC and GC-MS analysis.



(89)

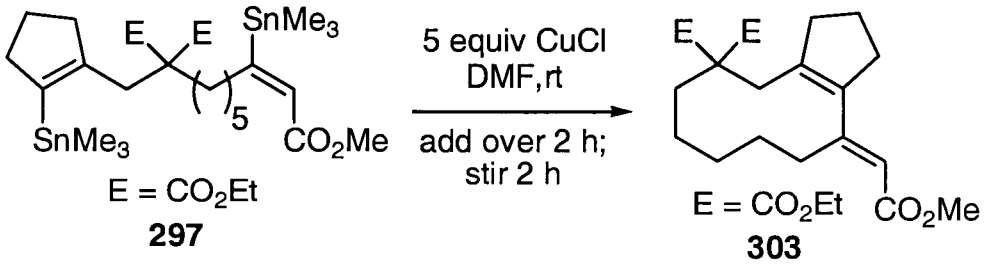
Disappointingly, a similar result was obtained in the attempted conversion of **298** into **304** (Table 13, entry 6). After aqueous workup, an inseparable mixture of compounds was obtained by a flash chromatography of the crude material on silica gel. The mass balance was moderate (~70%). The purified material consisted of the cyclized adduct **304** (m/z = 454), chloroprotiodestannylated compounds **309** and **310** (m/z = 490), and unidentifiable material in a ratio of ~5:3:2, respectively, as determined by GC and GC-MS analysis (equation 90).



(90)

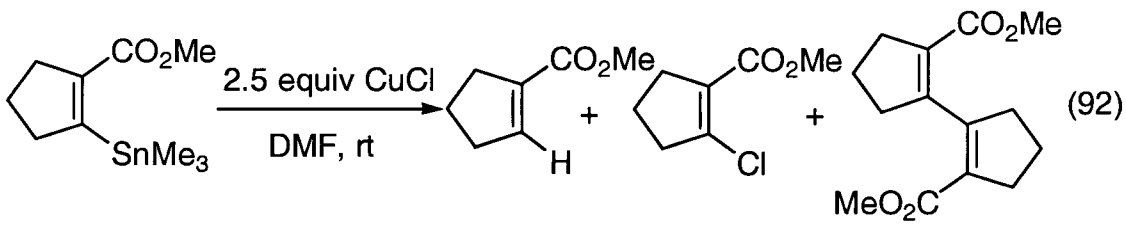
On the other hand, treatment of the distannane **297** with 5 equiv of copper(I) chloride successfully produced the cyclized adduct **303** in moderate yield (45%, Table 13, entry 5, pg. 99). The reaction was not clean. Tlc analyses of the crude reaction mixtures indicated that, in addition to **303**, a polar unidentified mixture was present (>5 compounds). In this case, the structural assignment related to **303** as derived from the spectral data (^{1}H nmr) was difficult. This difficulty was due to the numerous possible conformations of the carbocycle **303** as indicated by molecular models. The ^{1}H nmr spectra was riddled with broad unresolved multiplets but, fortunately, the vinylic region of the spectrum contained one clear singlet at δ 5.59 which corresponded to the lone olefinic proton in **303**. The ^{13}C nmr spectrum showed the expected 19 resonances and three negative resonances (δ 14.1, 50.9, and 115.0) in an APT experiment could be ascribed to the methyl carbons of the ethyl ester functions, the methyl ester, and the lone sp^2 olefinic C-H, respectively. The IR spectrum showed a carbonyl absorption at 1730 cm^{-1} and a C-C double bond stretching absorption at 1620 cm^{-1}. Lastly, the molecular formula of **303** was confirmed by a HRMS measurement on the molecular ion. The configuration of the exocyclic double bond in **303** could not be directly confirmed by

suitable nOed experiments nor did recrystallization attempts provide crystals suitable for X-ray analysis. As a result, the (*E*)-configuration of the olefin could only be designated by analogy with the 9-membered homolog **300**.



(91)

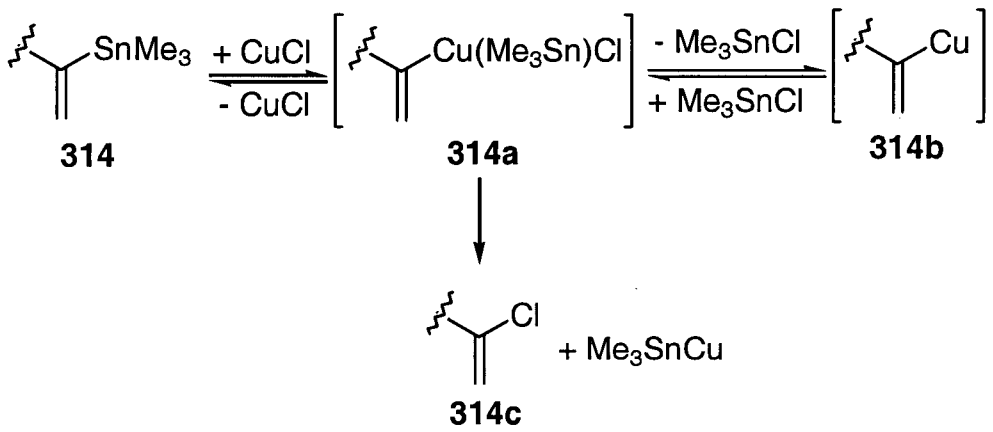
The presence of chlorodestannylated material **306-308** (equation 89) and **309-310** (equation 90) in the cyclization reactions is not unprecedented. Previous work in our laboratory had shown that, in the presence of elevated amounts of Me_3SnCl (5 equiv), the intermolecular homocoupling reaction of **163** is retarded and increased amounts of chlorodestannylated material **312** is formed (equation 92).[53]



(92)

163	**311**		**312**		**313**	
0 equiv Me_3SnCl, 1 h	2	:	10	:	87	
5 equiv Me_3SnCl, 48 h	0	:	92	:	8	glc ratio

It has been proposed[53] that the formation of chlorodestannylated material may be rationalized by invoking a pathway involving the copper(III) intermediate **314a** formed from the oxidative addition of CuCl with the alkenylstannane **314** (Scheme 29). The copper(III) intermediate **314a** may undergo a reductive elimination of Me_3SnCu to provide the chlorodestannylated product **314c**. Alternatively, **314a** may reductively eliminate Me_3SnCl to give the copper(I) intermediate **314b**. The intermediate **314b** can then undergo the oxidative coupling process (see Introduction section 2.2, pg. 8). However, the presence of Me_3SnCl would shift the equilibrium between **314a** and **314b** toward the copper(III) species **314a** (left) and, consequently, retard the coupling reaction and promote the formation of the alkenyl chloride **314c**.



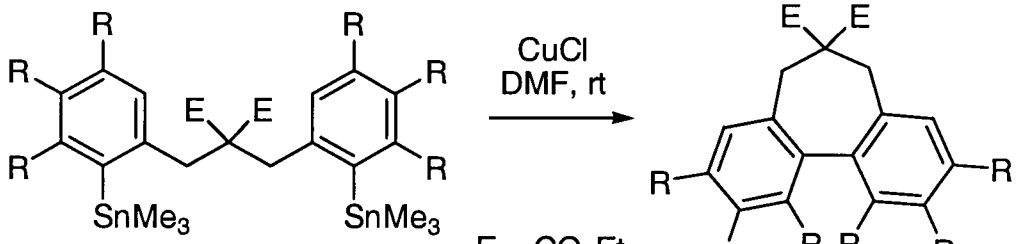
Scheme 29.

This rationale is consistent with the speculation that the reaction, as expected, provide, during the initial stages of the processes, the desired cyclized products. With continued slow addition of the cyclization substrates, the copper(I) chloride is consumed while the coproduct, Me_3SnCl, remains in the reaction pot. In cases where the intramolecular cyclizations are not favored (Table 13, entries 4-6, pg. 99), the organocopper(III) intermediates (**314a**) persist in the reaction mixture for longer periods of time. The combination of slow rates of cyclization and higher concentrations of Me_3SnCl results in the formation of chlorodestannylated material in the latter stages of the reaction. Future work in this area may include the addition of reagents, such as CsF,[7] whose purpose is to sequester Me_3SnCl and avert the formation of such side products.

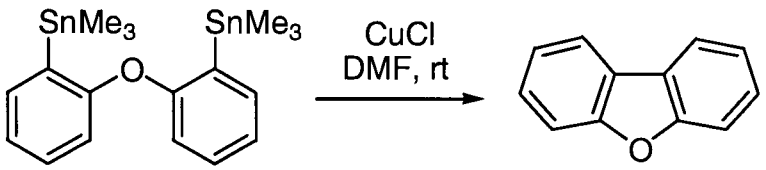
The results of this study indicate that the intramolecular copper(I) chloride-mediated coupling of alkenylstannane functions to form 9-membered rings is a feasible synthetic process. The use of alkenylstannane substrates that contain ester and alkyl ether functions shows that these functional groups are tolerated in the cyclization methodology. However, the less facile formation of 10-membered rings and competing side reactions shows a possible limitation of the copper(I)-mediated methodology.

2.5 Summary

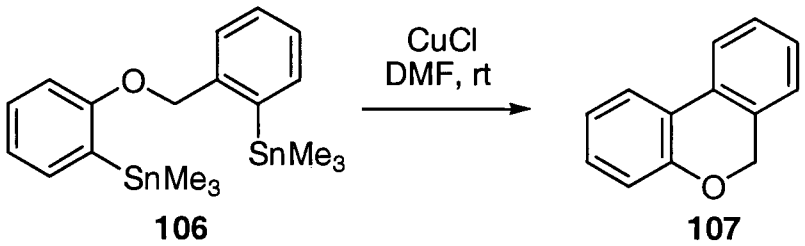
In the work described in this section, a variety of aryl- and alkenyltrimethylstannane precursors were prepared by via a series of known synthetic transformations. These precursors were then subjected to treatment with copper(I) chloride to effect bond formation between the carbon centres bearing the trimethylstannane functions. For instance, the intermolecular oxidative homocoupling of β-trimethylstannyl α,β-unsaturated ketones **247-250** was shown to give the corresponding products **251-254** in excellent yields (equation 80, pg. 81). In another study, the intramolecular coupling of two aryltrimethylstannane functions produced 5-, 6-, and 7-membered tricycles in good yields (equations 93-96). An extension to this methodology is illustrated by the successful mixed coupling of alkenyl- and aryltrimethylstannane functions (equation 97). Lastly, a brief investigation relating to the intramolecular coupling of bisalkenyltrimethylstannanes was undertaken. By the use a modified experimental procedure, a series of bicyclic systems **115** were synthesized by the closure of several 9-membered rings and one 10-membered ring (equation 98).



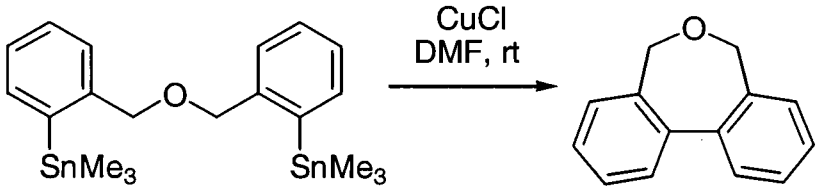
110 **111** (93)



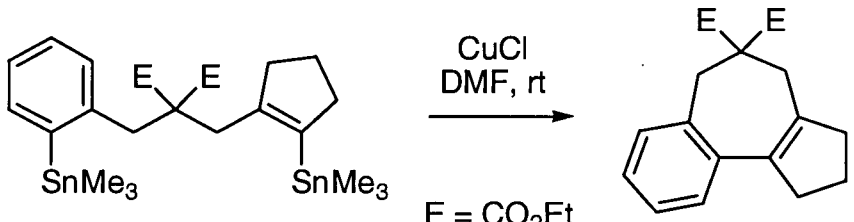
104 **105** (94)



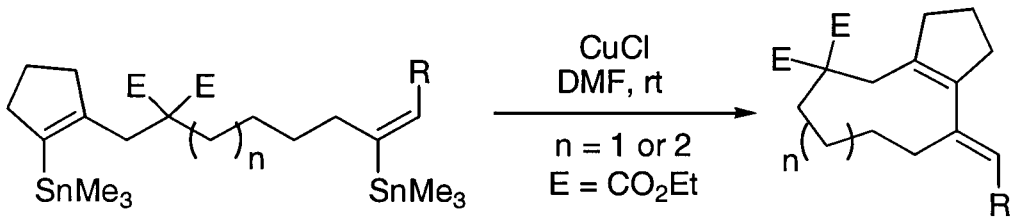
106 107 (95)



108 109 (96)



112 113 (97)



114 115 (98)

III. EXPERIMENTAL

1. General

1.1 Data acquisition, presentation, and techniques

Proton nuclear magnetic resonance (^{1}H nmr) spectra were obtained on a Bruker model WH-400 (400 MHz) or AMX-500 (500.2 MHz) spectrometer utilizing deuteriochloroform ($CDCl_3$) or hexadeuteriobenzene (C_6D_6) as the solvent. Signal positions (δ) were recorded in parts per million (ppm) from tetramethylsilane (δ 0) and were measured relative to the residual proton signal of chloroform (δ 7.24) or benzene (δ 7.15). Coupling constants (*J* values) are given in Hertz and are reported to the nearest 0.1 Hz). Tin-proton coupling constants (J_{Sn-H}) are given as an average of the ^{117}Sn and ^{119}Sn values. The multiplicity, number of protons, coupling constants, and assignments (where possible) are given in parentheses following the chemical shift. Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. In the ^{1}H nmr spectra data, H-x and H-x' have been used to designate protons on the same carbon, with H-x' being the proton resonating downfield to H-x. In some cases, the proton assignments were supported by two-dimensional (^{1}H-^{1}H) - homonuclear correlation spectroscopy (COSY), which was carried out using a Bruker AC-200E or WH-400 spectrometer.

Carbon nuclear magnetic resonance (^{13}C nmr) spectra were obtained on a Varian model XL-300 (75.5 MHz) or on Bruker models AC-200E (50.3 MHz) or AMX-500 (125.8 MHz) spectrometers using deuteriochloroform ($CDCl_3$) or hexadeuteriobenzene (C_6D_6) as the solvent. Signal positions (δ) were given in parts per million from tetramethylsilane and were measure relative to the signal of deuteriochloroform (δ 77.0) or hexadeuteriobenzene (δ 128.0). Attached proton tests (APTs), used to differentiate methyl and methine (negative phase signals) from methylene and quaternary carbons

(positive phase signals), were recorded on a Varian XL-300 or Bruker AC-200E spectrometers. Where APT data is given, signals with negative phases are so indicated in brackets (-ve) following the ^{13}C nmr chemical shifts. In some cases, the proton and carbon assignments were supported by two-dimensional (^{1}H,^{13}C) - heteronuclear multiple quantum coherence experiments (HMQC) and heteronuclear multiple bond correlation experiments (HMBC), which were carried out using a Bruker AMX-500 spectrometer.

Infrared (IR) spectra were recorded on a Perkin Elmer 1710 Fourier transform spectrophotometer with internal calibration between sodium chloride plates (liquid samples) or as potassium bromide pellets (solid samples). In each case, only selected characteristic absorption data are given for each compound.

Low and high resolution mass spectra were recorded on a Kratos MS 80 or on a Kratos Concept II HQ mass spectrometer using an electron impact source. The molecular ion (M^+) masses are given unless otherwise noted. For some of the compounds containing the trimethylstannyl (Me_3Sn) or the *tert*-butyldimethylsilyl (*t*-$BuMe_2Si$) moiety, the high resolution mass spectrometry molecular mass determinations were based on the (M^+-Me) peak. All compounds subjected to high resolution mass measurements were homogeneous by GLC and/or TLC analyses. Gas-liquid chromatography-mass spectrometry (GLCMS) was performed on a Carlo Erba model 4160 capillary gas chromatograph (15 m x 0.25 mm fused silca column coated with DB-5) and a Kratos/RFA MS 80 mass spectrometer. All compounds subjected to high resolution mass measurements were homogeneous by GLC and /or TLC analyses.

Elemental analyses were performed on a Carlo Erba CHN model 1106 or on a Fisons EA model 1108 elemental analyzer, by the UBC Microanalytical Laboratory.

Melting points (mp) were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperature (air baths), which refer to bulb-to-bulb (Kugelrorh) distillations, are uncorrected.

Unless otherwise noted, all reactions were carried out under an atmosphere of dry argon using glassware that had been oven (~140 °C) dried and/or flame dried. Glass syringes, stainless steel needles, and Teflon cannulae used to handle various anhydrous solvents and reagents were oven dried and flushed with argon prior to use. Plastic syringes were flushed with argon prior to use. The small and large bore Teflon cannulae

has an inner diameter of 0.38 mm and a wall thickness of 0.23 mm; the large cannulae has an inner diameter of 0.97 mm and a wall thickness of 0.30 mm.

Thin layer chromatography (TLC) was perfomed using commercial aluminum backed silica gel 60 F_{254} plates (E. Merck, type 5554, thickness 0.2 mm). Visualization of the chromatograms was accomplished using ultraviolet light (254 nm) and/or iodine (iodine which had been adsorbed onto unbound silca gel) followed by heating the plate after staining with one of the following solutions: (a) vanillin in a sulfuric acid-EtOH mixture (6% vanillin w/v, 4% sulfuric acid v/v, and 10% water v/v in EtOH), (b) phosphomolybdic acid in EtOH (20% phosphomolybdic acid w/v, Aldrich), (c) anisaldehyde in a sulfuric acid-EtOH mixture (5% anisaldehyde v/v and 5% sulfuric acid v/v in EtOH). Flash chromatography[70] was performed using 230-400 mesh silica gel (E. Merck, Silica Gel 60), followed the technique described by Still.

Gas liquid chromatography (GLC) was perfomed on a Hewlett-Packard model 5890 gas chromatograph equipped with flame ionization detectors and fused silica columns (Hewlett-Packard HP-5), 25 m x 0.20 mm coated with 5% phenylmethylsilicone.

Concentration, evaporation, removal of solvent *in vacuo*, or removal of solvent under reduced pressure (water aspirator) refers to solvent removal via a Büchi rotary evaporator at ~15 torr.

Cold temperatures were maintained by the use of the following baths: 0 °C, ice-water; -20 °C, -35 °C, -48 °C, aqueous calcium chloride-dry ice (27, 39, and 47 g $CaCl_2$/100 mL H_2O, respectively); -78 °C, acetone-dry ice.

1.2 Solvents and reagents

All solvents and reagents were purified, dried, and/or distilled using standard procedures.[71] Benzene and dichloromethane were distilled from calcium hydride. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. The four aforementioned solvents were distilled under an atmosphere of dry argon and used immediately.

Triethylamine, diisopropylamine, and hexamethylphosphoroamide (HMPA) were distilled from calcium hydride. Magnesium was added to methanol and, after refluxing the mixture, the methanol was distilled from the resulting solution of magnesium methoxide. *N,N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were sequentially dried over 3 Å molecular sieves.[72] The aforementioned reagents were stored under an atmosphere of argon in bottles sealed with a Sure/Seal (Aldrich Chemical Co., Inc.).

Petroleum ether refers to a hydrocarbon mixture with a boiling range of 35-60 °C.

Solutions of methyllithium in diethyl ether and *n*-butyllithium in hexanes were obtained from Aldrich Chemical Co., Inc. and Acros and standardized using the procedure of Kofron and Baclawski.[73]

Copper(I) bromide-dimethyl sulfide complex was prepared by the method described by Wuts[74] (by René Lemieux of Dr. Piers' research group at UBC) and was stored in a desiccator under an atmosphere of dry argon. Copper(I) chloride (99.995% or 99%+), copper(I) cyanide, and phenylthiocopper(I) were purchased from Aldrich Chemical Co., Inc., and were used without further purification.

Hexamethylditin and trimethyltin chloride were obtained from Organometallics Inc. and Aldrich Chemical Co., Inc., respectively, and were used without further purification.

Lithium diisopropylamide (LDA) was prepared by the addition of a solution of *n*-butyllithium (1 equiv) in hexanes to a solution of dry diisopropylamine (1.1 equiv) in dry tetrahydrofuran at 0 °C. The resulting colorless solution was stirred at 0 °C for 15 minutes prior to use.

Potassium hydride was obtained as a 35% suspension in mineral oil and sodium hydride as a 60% dispersion in mineral oil from Aldrich Chemical Co., Inc., and were rinsed free of oil with dry diethyl ether or pentane under a stream of dry argon prior to use.

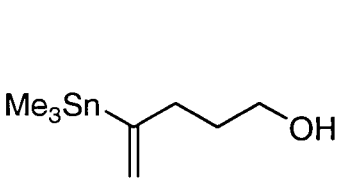
All other reagents were commercially available and were used without further purification.

Aqueous ammonium chloride-ammonia (NH_4Cl-NH_3-H_2O) (pH 8) was prepared by the addition of ~50 mL of concentrated aqueous ammonia to 950 mL of a saturated aqueous ammonium chloride solution.

2. Intramolecular conjugate additions to form monocycles

2.1 Preparation of cyclization precursors

Preparation of 2-(trimethylstannyl)-6,6-dibromohexa-1,5-diene (**127**)



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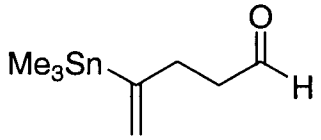
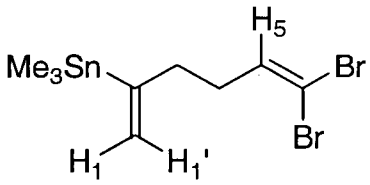


126



127

To a cold (-78 °C), stirred solution of oxalyl chloride (1.10 mL, 12.6 mmol) in dry CH_2Cl_2 (40 mL) was added dimethyl sulfoxide (2.00 mL, 23.5 mmol) dropwise via a syringe. The solution was stirred for a period of 15 min. 4-Trimethylstannylpent-4-en-1-ol (**125**)[35] was added over 3 min as a solution in dry CH_2Cl_2 (5 mL). The cloudy white suspension was stirred for an additional 15 min. Triethylamine (8.00 mL, 57.0 mmol) was added dropwise via a syringe and the mixture was stirred for 20 min. The reaction mixture was warmed to room temperature and water (20 mL) was added. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (30 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to provide the aldehyde **126** as a crude oil.

To a cool (0 °C), stirred solution of carbon tetrabromide (1.96 g, 5.90 mmol) in dry CH_2Cl_2 (80 mL) was added triphenylphosphine (8.55 g, 32.3 mmol) in one portion. The mixture was stirred for 10 min. A solution of the crude oil (obtained as described above) in dry CH_2Cl_2 (5 mL) was added via a cannula. The reaction mixture turned from a bright orange-yellow suspension into a brown suspension. The mixture was stirred for 40 min. Pentane (200 mL) was added and the mixture was filtered through silica gel (~20 g) and the cake was eluted with pentane (200 mL). The combined filtrate was concentrated under reduced pressure. Flash column chromatography (75 g of silica gel, petroleum ether) of the crude product and removal of trace amounts of solvent (vacuum

pump) from the acquired material yielded 2.08 g (90% over two steps) of the dibromoalkene **127** as a colorless clear oil.

IR (neat): 3035, 1602, 1276, 920, 770, 528 cm^{-1}.

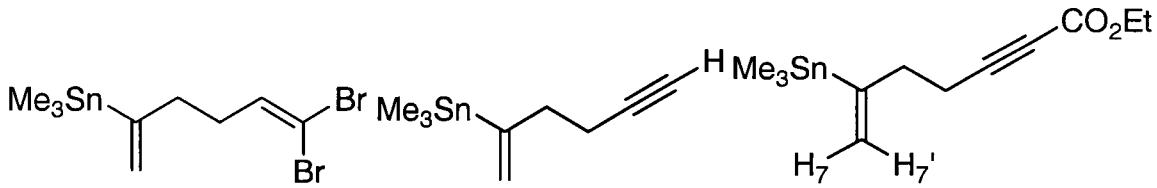
^1H nmr (400 MHz, $CDCl_3$) δ: 0.14 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 52.0 Hz), 2.12-2.20 (m, 2H, H_4), 2.35 (t, 2H, H_3, J = 7.6 Hz, $^3J_{Sn\text{-}H}$ = 47.5 Hz), 5.19 (s, 1H, H_1, $^3J_{Sn\text{-}H}$ = 69.4 Hz), 5.67 (s, 1H, H_1', $^3J_{Sn\text{-}H}$ = 148.0 Hz), 6.45 (t, 1H, H_5, J = 7.0 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -9.4, 33.0, 38.3, 88.9, 125.7, 137.9, 153.8.

HRMS calcd for $C_8H_{13}{}^{120}Sn^{79}Br^{81}Br$ (M^+-Me): 388.8386; found: 388.8386.

Anal. calcd for $C_9H_{16}Br_2Sn$: C 26.84, H 4.00; found: C 27.12, H 4.00.

<u>Preparation of ethyl 6-trimethylstannylhept-6-en-2-ynoate (**129**)</u>



127 **128** **129**

To a stirred suspension of crushed magnesium metal (189 mg, 7.75 mmol) in dry THF (15 mL) was added a few crystals of iodine and the mixture was refluxed for 1 h. [**Note**: The magnesium metal must be freshly crushed and the particles small otherwise no reaction occurs.] The dibromoalkene **127** (2.08 g, 5.16 mmol) dissolved in dry THF (5 mL) was added and the mixture was stirred at reflux for 1 h. The mixture was cooled to room temperature and pentane (20 mL) was added. The white suspension was filtered through silica gel (~5 g) and the cake was eluted with pentane (50 mL). The combined filtrate was concentrated under reduced pressure to yield the alkyne **128** as a slightly

yellow tinged oil. This oil proved to be volatile and was immediately used in the next reaction.

To a cold (-78 °C), stirred solution of LDA (5.44 mmol) in dry THF (40 mL) was added a solution of the crude oil (obtained as described above) in dry THF (3 mL). The solution was stirred at -78 °C for 25 min. Ethyl chloroformate (0.72 ml, 7.5 mmol) was added and the solution was stirred for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (30 mL) was added and the aqueous layer was extracted with Et_2O (3 x 20 mL). The organic extracts were combined, washed with brine (60 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (125 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude oil and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.29 g (79% over two steps) of the ester **129** as a clear oil.

IR (neat): 2236, 1713, 1447, 1251, 1073, 770, 467 cm^{-1}.

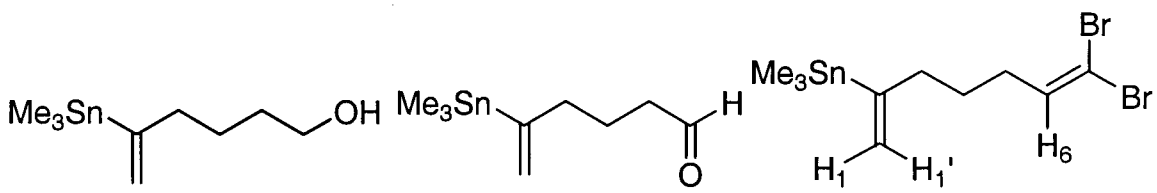
^1H nmr (400 MHz, $CDCl_3$) δ: 0.14 (s, 9H, -Sn$\underline{Me}_3$ $^2J_{Sn\text{-}H}$ = 53.1 Hz), 1.28 (t, 3H, -$CO_2CH_2C\underline{H}_3$, J = 7.2 Hz), 2.40 (t, 2H, H_4, J = 7.5 Hz), 2.52 (t, 2H, H_5, J = 7.5 Hz, $^3J_{Sn\text{-}H}$= 50.7 Hz), 4.20 (q, 2H, -$CO_2C\underline{H}_2CH_3$, J = 7.2 Hz), 5.22 (s, 1H, H_7, $^3J_{Sn\text{-}H}$ = 68.7 Hz), 5.79 (s, 1H, H_7', $^3J_{Sn\text{-}H}$= 146.8 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -9.5, 14.0, 18.7, 37.9, 61.7, 73.6, 88.6, 126.0, 152.5, 153.7.

HRMS calcd for $C_{11}H_{17}O_2{}^{120}Sn$ (M^+-Me): 301.0251; found: 301.0257.

Anal. calcd for $C_{12}H_{20}O_2Sn$: C 45.76, H 6.40; found: C 45.82, H 6.46.

Preparation of 2-(trimethylstannyl)-7,7-dibromohepta-1,6-diene (**130b**)



130 **130a** **130b**

To a cold (-78 °C), stirred solution of oxalyl chloride (1.10 mL, 12.6 mmol) in dry CH_2Cl_2 (40 mL) was added dimethyl sulfoxide (1.70 mL, 24.0 mmol) dropwise via a syringe. The solution was stirred for a period of 15 min. 5-Trimethylstannylhex-5-en-1-ol (**130**)[35] (1.50 g, 5.72 mmol) was added over 3 min as a solution in dry CH_2Cl_2 (5 mL). The cloudy white suspension was stirred for an additional 15 min. Triethylamine (6.50 mL, 46.6 mmol) was added dropwise via a syringe and the mixture was stirred for 20 min. The reaction mixture was warmed to room temperature and water (20 mL) was added. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to provide the aldehyde **130a** as a crude oil.

To a cool (0 °C), stirred solution of carbon tetrabromide (5.85 g, 17.6 mmol) in dry CH_2Cl_2 (100 mL) was added triphenylphosphine (9.36 g, 35.7 mmol) in one portion. The mixture was stirred for 10 min. A solution of the aldehyde **130a** (obtained as described above) in dry CH_2Cl_2 (5 mL) was added via a cannula. The reaction mixture turned from a bright orange-yellow suspension into a brown suspension. The mixture was stirred for 40 min. Pentane (200 mL) was added and the mixture was filtered through a pad of silica gel (~20 g) and the cake was eluted with pentane (200 mL). The combined filtrate was concentrated under reduced pressure. Flash column chromatography (75 g of silica gel, petroleum ether) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 2.16 g (91% over two steps) of the dibromoalkene **130b** as a colorless clear oil.

IR (neat): 2361, 1837, 1718, 1621, 1437, 1189, 917, 867, 769, 575 cm^{-1}.

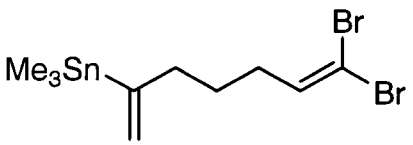
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.12 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 52.9 Hz), 1.40-1.60 (m, 2H, H_4), 2.00-2.15 (m, 2H, H_5), 2.28 (t, 2H, H_3, J = 6.5, $^3J_{Sn\text{-}H}$ = 50.9 Hz), 5.15-5.19 (m, 1H, H_1, $^3J_{Sn\text{-}H}$ = 70.6 Hz), 5.63-5.65 (m, 1H, H_1', $^3J_{Sn\text{-}H}$ = 171.9 Hz), 6.37 (t, 1H, H_6, J = 7.2 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.4 (-ve), 27.6, 32.5, 40.0, 88.9, 125.2, 138.4 (-ve), 154.7.

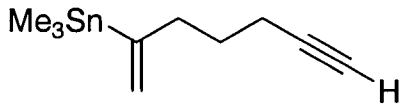
HRMS calcd for $C_9H_{15}{}^{118}Sn^{79}Br^{81}Br$ (M^+-Me): 400.8536; found: 400.8530.

Anal. calcd for $C_{10}H_{18}Br_2Sn$: C 28.82, H 4.35; found: C 28.61, H 4.35.

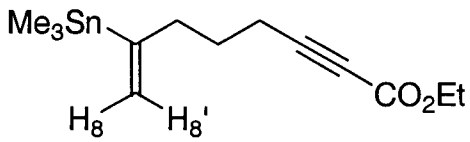
<u>Preparation of ethyl 7-trimethylstannyloct-7-en-2-ynoate (**131**)</u>



130b



135



131

To a stirred suspension of freshly crushed magnesium metal (201 mg, 8.26 mmol) in dry THF (15 mL) was added a few crystals of iodine and the mixture was refluxed for 1 h. A solution of the dibromoalkene **130b** (1.68 g, 4.05 mmol) in dry THF (5 mL) was added and the mixture was stirred at reflux for 1 h. [**Note**: The magnesium metal must be freshly crushed and the particles small otherwise no reaction occurs.] The mixture was cooled to room temperature and pentane (20 mL) was added. The white suspension was filtered through a pad of silica gel (~10 g) and the cake was eluted with pentane (150 mL). The combined filtrate was concentrated under reduced pressure to yield the

alkyne **135** as a yellow crude oil. This oil proved to be volatile and was immediately used in the next reaction.

To a cold (-78 °C), stirred solution of LDA (4.96 mmol) in dry THF (30 mL) was added a solution of the alkyne **135** (obtained as described above) in dry THF (2 mL). The solution was stirred at -78 °C for 30 min. Ethyl chloroformate (0.80 mL, 8.4 mmol) was added and the solution was stirred for 1 h at -78 °C and 1.5 h at room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added and the aqueous layer was extracted with Et_2O (3 x 20 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (125 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.04 g (79 % over two steps) of the ester **131** as a clear oil.

IR (neat): 2237, 1714, 1456, 1250, 1073, 919, 753, 526 cm^{-1}.

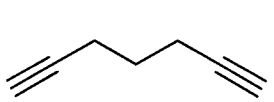
^1H nmr (400 MHz, $CDCl_3$) δ: 0.12 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 52.6 Hz), 1.28 (t, 3H, -$CO_2CH_2C\underline{H}_3$, J = 7.2 Hz), 1.60-1.70 (m, 2H, H_5), 2.28 (t, 2H, H_4, J = 7.1 Hz), 2.35 (t, 2H, H_6, J = 7.6 Hz, $^3J_{Sn-H}$ = 63.9 Hz), 4.16 (q, 2H, -$CO_2C\underline{H}_2CH_3$, J = 7.2 Hz), 5.15-5.20 (m, 1H, H_8, $^3J_{Sn-H}$ = 70.4 Hz), 5.65-5.70 (m, 1H, H_8', $^3J_{Sn-H}$ = 150.0 Hz).

^{13}C nmr (75.5 MHz) δ: -9.6 (-ve), 14.0 (-ve), 17.9, 27.1, 39.4, 61.6, 73.4, 88.8, 125.8, 153.7, 153.9.

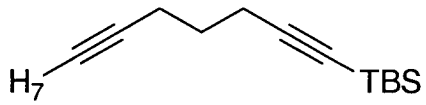
HRMS calcd for $C_{12}H_{19}O_2{}^{120}Sn$ (M^+-Me): 315.0407; found: 315.0409.

Anal. calcd for $C_{13}H_{22}O_2Sn$: C 47.46, H 6.74; found: C 47.65, H 6.90.

Preparation of 1-(*tert*-butyldimethylsilyl)hepta-1,6-diyne (**133**)



132



133

To a cold (-78 °C), stirred solution of hepta-1,6-diyne (**132**) (2.70 mL, 23.6 mmol) in dry THF (100 mL) was added MeLi (20.0 mL, 1.56 M in Et_2O, 31.2 mmol). After 10 min, the reaction mixture was warmed to -20 °C and stirred for an additional 60 min. *tert*-Butyldimethylsilyl chloride (4.95 g, 32.8 mmol) was added in one portion and the solution was stirred at -20 °C for 15 min and then warmed to room temperature for 60 min. Saturated aqueous sodium bicarbonate (50 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed once with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the crude material by flash column chromatography (150 g of silica gel, petroleum ether), followed by bulb-to-bulb distillation (50-60 °C/0.1 torr) of the acquired liquid, provided 4.07 g (83 %) of the alkyne **133** as a colorless oil.

IR (neat): 3313, 2175, 1251, 839, 776 cm^{-1}.

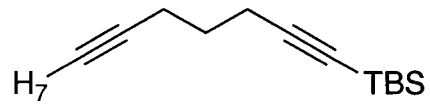
^1H nmr (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H, -Si$\underline{Me_2}$-), 0.90 (s, 9H, -Si$^t\underline{Bu}$-), 1.69-1.76 (m, 2H, H_4), 1.93 (t, 1H, H_7, J = 2.5 Hz), 2.29 (td, 2H, H_5, J = 7, 2.5 Hz), 2.34 (t, 2H, H_3, J = 7 Hz).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: -4.5, 16.5, 17.5, 18.9, 26.1, 27.7, 68.7, 83.4, 83.5, 106.6.

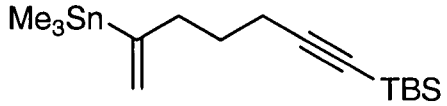
HRMS calcd for $C_{13}H_{22}Si$: 206.1491; found: 206.1495.

Anal. calcd for $C_{13}H_{22}Si$: C 75.65, H 10.74; found: C 75.58, H 10.71.

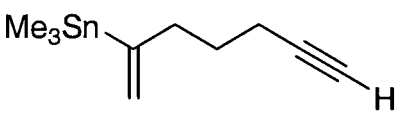
Alternative preparation of ethyl 7-trimethylstannyloct-7-en-2-ynoate (**131**)



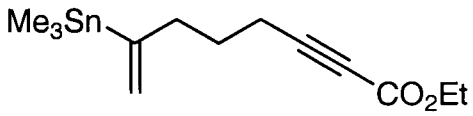
133



134



135



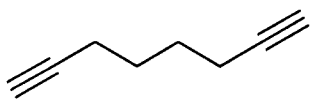
131

To a cold (-78 °C), stirred solution of hexamethylditin (7.98 g, 24.4 mmol) in dry THF (150 mL) was added a solution of MeLi (17.2 mL, 1.41 M in Et_2O, 24.3 mmol) via a syringe and the solution was stirred for 30 min. The solution was cooled to -78 °C and copper bromide–dimethyl sulfide complex (4.89 g, 23.8 mmol) was added in one portion. The red-brown suspension was stirred for 30 min. 1-(*tert*-Butyldimethylsilyl)hepta-1,6-diyne (**133**) (4.30 g, 20.9 mmol) was added neat via a cannula with dry THF (3 mL) as a rinse. Dry methanol (40.0 mL, 987 mmol) was added dropwise over 2 min via a syringe. The reaction mixture was stirred at -78 °C for 3 h , -30 °C for 3 h, and at 0 °C for 1 h. The mixture was opened to the air and aqueous ammonium chloride-ammonia (pH 8) (150 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 x 150 mL). The organic layers were combined, washed with brine (350 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash column chromatography (150 g of silica gel, petroleum ether) yielded 3.00 g of the stannane **134** as a clear oil which was contaminated with a trace amount of the starting material **133**.

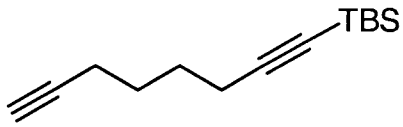
The stannane **134** thus obtained was dissolved in dry THF (80 mL) and a solution of tetrabutylammonium fluoride (16.1 mL, 1.0 M in THF, 16.1 mmol) was added. The solution was stirred at room temperature for 1.5 h. Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The organic extracts were combined, washed with brine (200 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield the alkyne **135** as a crude oil. This oil proved to be volatile and was immediately used in the next reaction.

To a cold (-78 °C), stirred solution of LDA (15.9 mmol) in dry THF (100 mL) was added a solution of the alkyne **135** (obtained as described above) in dry THF (2 mL). The solution was stirred for 30 min. Ethyl chloroformate (1.60 mL, 16.7 mmol) was added and the solution was stirred at -78 °C for 1 h and at room temperature for 1.5 h. Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by flash column chromatography (200 g of silica gel, 96:4 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.76 g (24 % over 3 steps) of the ester **131** as a clear oil. The material exhibited spectral characteristics (^1H nmr) identical with those previously mentioned for this compound.

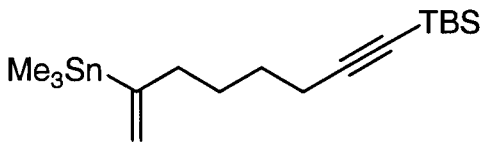
Preparation of ethyl 8-trimethylstannylnon-8-en-2-ynoate (**137**)



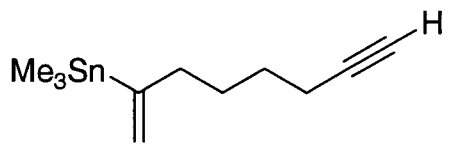
136



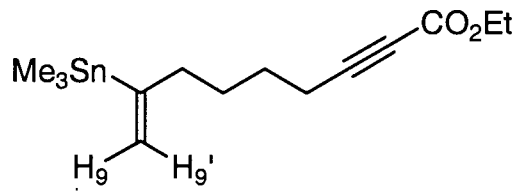
136a



136b



136c



137

To a cold (-78 °C) solution of octa-1,6-diyne (**136**) (2.70 mL, 23.6 mmol) in dry THF (100 mL) was added a solution of MeLi (20.0 mL, 1.56 M in Et_2O, 31.2 mmol). After 10 min, the reaction mixture was warmed to -20 °C and stirred for 1 h. *tert-*

Butyldimethylsilyl chloride (4.95 g, 32.8 mmol) was added in one portion and the solution was stirred at -20 °C for 15 min and then warmed to room temperature for 1 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed once with brine (50 mL), dried ($MgSO_4$), and concentrated. Purification of the crude material by flash column chromatography (150 g of silica gel, petroleum ether), followed by bulb-to-bulb distillation (50-60 °C/0.1 torr) of the acquired liquid, provided 4.07 g of alkyne **136a** as a colorless oil which was contaminated with a small amount of starting material **136**.

To a cold (-20 °C), stirred solution of hexamethylditin (10.3 g, 31.5 mmol) in dry THF (150 mL) was added MeLi (22.2 mL, 1.42 M in Et_2O, 31.5 mmol) via a syringe and the solution stirred for 30 min. The solution was cooled to -78 °C and copper bromide–dimethyl sulfide complex (6.48 g, 31.5 mmol) was added in one portion. The red-brown suspension was stirred for 30 min. 1-(*tert*-Butyldimethylsilyl)octa-1,6-diyne (**136a**) (obtained as described above) was added neat via a cannula with dry THF (3 mL) as a rinse. Dry methanol (50.0 mL, 1.23 mol) was added dropwise over 2 min via a syringe. The reaction mixture was stirred at -78 °C for 3.5 h, at -48 °C for 3.5 h, and at room temperature for 20 min. The mixture was opened to the air and aqueous ammonium chloride-ammonia (pH 8) (150 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the organic layer was extracted with Et_2O (3 x 150 mL). The organic layers were combined, washed with brine (400 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo*. Flash column chromatography (200 g of silica gel, petroleum ether) of the crude product yielded 4.55 g of the stannane **136b** which was contaminated with a minor amount of the starting material **136a**.

The oil thus obtained was dissolved in dry THF (80 mL) and a solution of tetrabutylammonium fluoride (26.0 mL, 1.0 M in THF, 26.0 mmol) was added. The solution was stirred for 2.5 h at room temperature. Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL).

The organic extracts were combined, washed with brine (200 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield 4.27 g of a crude oil. The crude product proved to be volatile and was used immediately in the next step.

To a cold (-78 °C), stirred solution of LDA (32.0 mmol) in dry THF (100 mL) was added the crude oil as a solution in dry THF (2 mL). The solution was stirred for 30 min. Ethyl chloroformate (3.20 mL, 33.4 mmol) was added and the solution stirred at -78 °C for 1 h and at room temperature for 1.5 h. Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification of the residual material by flash column chromatography (200 g of silica gel, 96:4 petroleum ether-Et_2O), followed by bulb-to-bulb distillation (155-180 °C/0.3 torr), yielded 2.38 g (28 % over 4 steps) of the stannane **137** as a clear oil.

IR (neat): 2237, 1713, 1250, 1077, 916, 753 cm^{-1}.

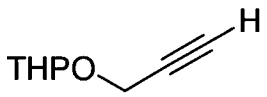
^1H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 52.9 Hz), 1.27 (t, 3H, -$CO_2CH_2C\underline{H}_3$, J = 7.2 Hz), 1.40-1.60 (m, 4H), 2.10-2.40 (m, 4H), 4.19 (q, 2H, -$CO_2C\underline{H}_2CH_3$, J = 7.2 Hz), 5.10-5.15 (m, 1H, H_9, $^3J_{Sn-H}$ = 70.8 Hz), 5.60-5.65 (m, 1H, H_9', $^3J_{Sn-H}$ = 151.4 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.6 (-ve), 14.0 (-ve), 18.4, 26.8, 28.4, 40.0, 61.7, 73.3, 89.0, 124.9, 153.7, 155.0.

HRMS calcd for $C_{13}H_{21}O_2{}^{120}Sn$ (M^+-Me): 329.0564; found: 329.0563.

Anal. calcd for $C_{14}H_{24}O_2Sn$: C 49.02, H 7.05; found: C 49.02, H 7.09.

Preparation of methyl 4-(tetrahydro-2*H*-pyranyloxy)-but-2-ynoate (**139**)



138

139

To a cold (-78 °C), stirred solution of commercially available ether **138** (10.0 mL, 71.4 mmol) in dry THF (40 mL) was added a solution of *n*-butyllithium (55.0 mL, 1.55 M in hexanes, 85.0 mmol). The solution was stirred at -78 °C for 30 min. Methyl chloroformate (6.60 mL, 85.0 mmol) was added and the solution was stirred for 2 h at -78 °C and 2 h at room temperature. Saturated aqueous sodium bicarbonate (200 mL) was added and the aqueous layer was extracted with Et_2O (3 x 100 mL). The organic extracts were combined, washed with brine (200 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and bulb-to-bulb distillation (120-140 °C/0.1 torr) of the crude material yielded 14.0 g (99%) of the ester **139** as a clear oil.

IR (neat): 2241, 1718, 1436, 1256, 1203, 1123, 1029, 943, 903, 752 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 1.50-1.90 (m, 6H), 2.50-2.60 (m, 1H), 3.70-3.90 (m, 4H, includes 3H -CO_2Me singlet at 3.76), 4.36 (s, 2H), 4.78 (m, 1H).

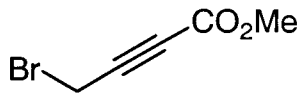
^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 18.5, 25.0, 29.8, 52.5, 53.3, 61.6, 77.0, 83.7, 96.9, 153.3.

HRMS calcd for $C_{10}H_{14}O_4$: 197.0813; found: 197.0806.

Anal. calcd for $C_{10}H_{14}O_4$: C 60.59, H 7.12; found: C 60.58, H 7.24.

Preparation of methyl 4-bromobut-2-ynoate (**140**)

139



140

To a cool (0 °C) solution of triphenylphosphine (8.97 g, 34.1 mmol) in dry CH_2Cl_2 (200 mL) was added bromine (~2.0 mL) dropwise until a yellow color persisted. A few crystals of triphenylphosphine were added until the solution was colorless. The reaction mixture was stirred for 20 min and a white precipitate appeared. The mixture was warmed to room temperature and the ester **139** (5.70 g, 30.0 mmol) was added neat via a cannula with CH_2Cl_2 (5 mL) as a rinse. The mixture was stirred for 1 h and the white precipitate disappeared. Pentane (200 mL) was added and the mixture was filtered through a cake of silica gel (~30 g) and the silica gel was eluted with Et_2O (300 mL). The combined filtrate was concentrated *in vacuo*. Flash column chromatography (300 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 4.48 g of the bromide **140** (87 %) as a colorless oil. Updated characterization data is given below.[75]

IR (neat): 2358, 2245, 1718, 1436, 1269, 1083, 945, 751, 625 cm^{-1}.

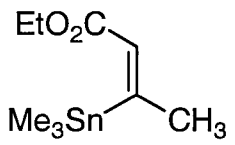
^1H nmr (400 MHz, $CDCl_3$) δ: 3.77 (s, 3H, -$CO_2\underline{Me}$), 3.93 (s, 2H, Br-$C\underline{H_2}$-).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 11.6, 52.8 (-ve), 76.6, 81.6, 152.9.

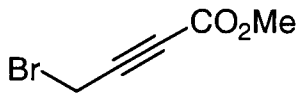
HRMS calcd for $C_5H_5O_2{}^{81}Br$: 177.9453; found: 177.9449.

Anal. calcd for $C_5H_5O_2Br$: C 33.93, H 2.84; found: C 34.17, H 2.91.

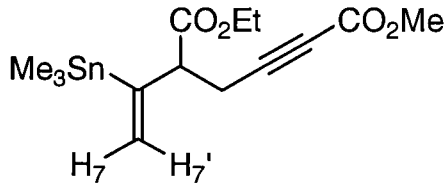
Preparation of methyl 5-ethoxycarbonyl-6-trimethylstannylhept-6-en-2-ynoate (**143**)



141



140



143

To a cold (-78 °C), stirred solution of LDA (12.4 mmol) in dry THF (110 mL) was added HMPA (2.20 mL, 12.4 mmol). A solution of ethyl (*Z*)-3-trimethylstannylbut-2-enoate (**141**)[41] (2.87 g, 10.4 mmol) in dry THF (5 mL) was added to the reaction mixture. The mixture was stirred at -78 °C for 30 min and at 0 °C for 30 min. The orange suspension was cooled to -78 °C and methyl 4-bromobut-2-ynoate (**140**) (2.22 g, 12.5 mmol) dissolved in dry THF (5 mL) was added to the reaction mixture. After 15 min, the reaction mixture turned dark brown and saturated aqueous sodium bicarbonate (110 mL) was added. The mixture was warmed to room temperature and the black suspension was extracted with Et_2O (3 x 150 mL). The organic extracts were combined, washed with brine (2 x 300 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (200 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude oil and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 2.24 g (58%) of the ester **143** as a clear oil.

IR (neat): 2241, 1718, 1259, 1176, 1079, 773, 529 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.16 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 53.9 Hz), 1.25 (t, 3H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 2.51 (dd, 1H, H_4, J = 7.5, 17.2 Hz), 2.80 (dd, 1H, H_4', J = 7.5, 17.2 Hz), 3.43 (t, 1H, H_5, J = 7.5 Hz, $^3J_{Sn\text{-}H}$ = 58.2 Hz), 3.72 (s, 3H, -$CO_2C\underline{H}_3$), 4.10-4.20 (m, 2H, -$CO_2C\underline{H}_2CH_3$), 5.37-5.42 (m, 1H, H_7, $^3J_{Sn\text{-}H}$ = 63.6 Hz), 5.80-5.85 (m, 1H, H_7', $^3J_{Sn\text{-}H}$ = 133.6 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.5 (-ve), 13.9 (-ve), 22.1, 52.3 (-ve), 53.8 (-ve), 61.0, 74.0, 86.1, 129.1, 150.7, 153.6, 172.2.

HRMS calcd for $C_{13}H_{19}O_4{}^{120}Sn$ (M^+-Me): 359.0306; found: 359.0311.

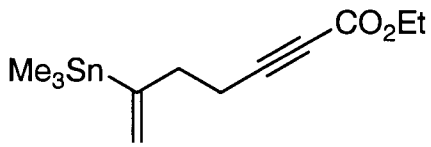
Anal. calcd for $C_{14}H_{22}O_4Sn$: C 45.08, H 5.94; found: C 44.99, H 6.03.

2.2 Copper(I) mediated cyclizations

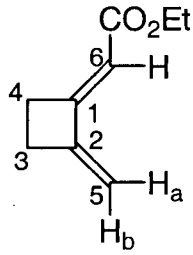
General Procedure 1: CuCl-mediated intramolecular conjugate addition of alkenyltrimethylstannanes to alkynic esters

To a cool (0 °C), stirred solution-suspension of CuCl (~2.5 equiv) in dry DMF (2 mL/mmol CuCl) was added glacial acetic acid (5.0 equiv). The mixture was stirred for 5 min and changed from a yellow to a gray-blue suspension. A solution of the ester (1 equiv) in dry DMF (5 mL/mmol of ester) was added dropwise via a cannula. After 15 min, the mixture became bright green. The mixture was opened to the air, was treated with aqueous ammonium chloride-ammonia (pH 8) (~10 mL/mmol of ester), and was stirred until the aqueous phase became deep blue. The mixture was diluted with water (~10 mL/mmol of ester) and then was extracted with Et_2O (3 x ~10 mL/mmol of ester). The combined organic phases were washed with brine (3 x ~20 mL/mmol of ester), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

Preparation of (*E*)-1-ethoxycarbonylmethylidene-2-methylidenecyclobutane (**144**)



129



144

Following general procedure 1, the cyclobutane derivative **144** was prepared by the addition of the ester **129** (102 mg, 0.322 mmol), as a solution in dry DMF (1.6 mL), to a cool (0 °C), stirred solution-suspension of CuCl (77 mg, 0.78 mmol) and glacial acetic acid (90 μL, 1.6 mmol) in dry DMF (1.5 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 94:6 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 42 mg (85 %) of the cyclization product **144** as a colorless oil.

IR (neat): 1713, 1654, 1368, 1266, 1186, 1054, 857 cm^{-1}.

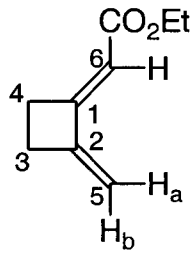
^1H nmr (400 MHz, $CDCl_3$) δ: 1.26 (t, 3H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 2.65-2.80 (m, 2H, H-3), 3.02 (td, 2H, H-4, J = 8.0, 2.5 Hz), 4.15 (q, 2H, $-CO_2C\underline{H}_2CH_3$, J = 7.1 Hz), 4.94 (br s, 1H, H-5b), 5.35-5.40 (m, 1H, H-5a), 5.84-5.90 (m, 1H, H-6).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 14.3 (-ve), 28.6, 29.9, 59.8, 108.3 (-ve), 108.6, 147.9, 161.2, 166.9.

HRMS calcd for $C_9H_{12}O_2$: 152.0837; found: 152.0842.

Anal. calcd for $C_9H_{12}O_2$: C 71.03, H 7.95; found: C 70.99, H 7.89.

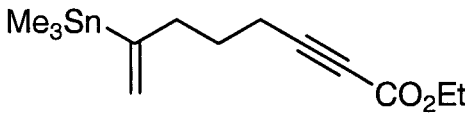
Table 14. ^{1}H nmr (400 MHz, $CDCl_3$) data for the ester **144**: COSY (200 MHz) and NOED experiments



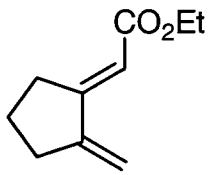
144

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	COSY Correlations	NOED Correlations
H-3	2.65-2.80 (m)	H-4	
H-4	3.02 (td, *J* = 2.5, 8.0)	H-3, H-6	
H-5a	5.35-5.40 (m)	H-5b	H-5b, H-6
H-5b	4.94 (br s)	H-5a	H-3, H-5a
H-6	5.84-5.90 (m)	H-4	H-5a
$-CO_2C\underline{H}_2CH_3$	4.15 (q, *J* = 7.1)	$-CO_2CH_2C\underline{H}_3$	
$-CO_2CH_2C\underline{H}_3$	1.26 (t, *J* = 7.1)	$-CO_2C\underline{H}_2CH_3$	

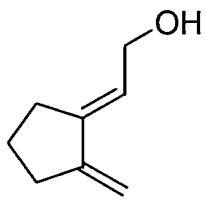
Preparation of (*E*)-1-hydroxymethylmethylidene-2-methylidenecyclopentane (**154**)



131



153



154

Following general procedure 1, the cyclopentane derivative **153** was prepared by the addition of the ester **131** (333 mg, 1.01 mmol), as a solution in dry DMF (5 mL), to a cool (0 °C), stirred solution-suspension of CuCl (262 mg, 2.65 mmol) and glacial acetic acid (289 μL, 5.05 mmol) in dry DMF (5 mL). Following the workup as described in the

general procedure, the crude oil containing the ester **153** was used in the next step without purification because this material is prone to polymerization when concentrated.

To a cold (-78 °C), stirred solution of the ester **153** (obtained as described above) in dry THF (10 mL) was added a solution of DIBAL (4.00 mL, 1.0 M in hexanes, 4 equiv) and the mixture was stirred for 45 min. The solution was warmed to room temperature and stirring was continued for 45 min. Saturated aqueous ammonium chloride (2 mL) was added to the solution and the mixture was stirred for 30 min. $MgSO_4$ (~100 mg) was added and the white suspension was stirred for an additional 30 min. The mixture was diluted with Et_2O (20 mL) and then was filtered through Florisil (~5 g) and the cake was eluted with Et_2O (150 mL). The combined filtrate was concentrated under reduced pressure. Flash column chromatography (20 g of silica gel, 13:7 petroleum ether-Et_2O) of the crude oil and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 116 mg (92 % over two steps) of the allylic alcohol **154** as a clear oil. This compound proved to be unstable when stored under argon for extended periods of time in a freezer.

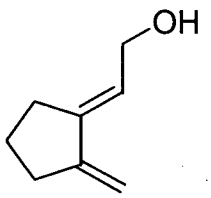
IR (neat): 3305, 1627, 1430, 1045, 995, 878 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 1.34 (br s, 1H, -O<u>H</u>, exchanges with D_2O), 1.60-1.73 (m, 2H, -CH_2-C<u>H_2</u>-CH_2-), 2.35-2.45 (m, 4H, -C<u>H_2</u>-CH_2-C<u>H_2</u>-), 4.22 (d, 2H, -O-C<u>H_2</u>-, J = 6.9 Hz), 4.86 (br s, 1H), 5.30 (br s, 1H), 5.95-6.05 (m, 1H, =C<u>H</u>-CH_2-O-).

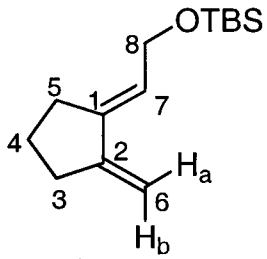
^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 24.0, 30.0, 34.0, 61.1, 103.2, 118.2 (-ve), 142.9, 149.0.

HRMS calcd for $C_8H_{12}O$: 124.0888; found: 124.0889.

Preparation of (*E*)-1-(*tert*-butyldimethylsiloxymethylmethylidene)-2-methylidenecyclopentane (**155**)



154



155

To a stirred solution of the diene **154** (116 mg, 0.933 mmol) in dry CH_2Cl_2 (4 mL) at room temperature was added *tert*-butyldimethylsilyl chloride (305 mg, 2.02 mmol) in one portion, followed immediately by imidazole (289 mg, 4.14 mmol). The white suspension was stirred for 1 h. The solvent was removed under reduced pressure. Flash column chromatography (20 g of silica gel, 400:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 202 mg (91 %) of the silyl ether **155** as a colorless clear oil.

IR (neat): 1628, 1463, 1375, 1255, 1181, 837, 777 cm^{-1}.

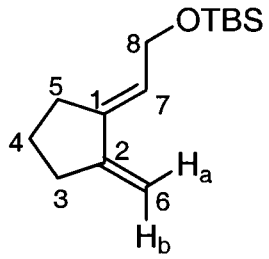
^1H nmr (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H, -Si<u>Me</u>$_2$-), 0.89 (s, 9H, -Si^t<u>Bu</u>-), 1.60-1.75 (m, 2H, H-4), 2.30-2.42 (m, 4H, H-3 and H-5), 4.25 (d, 2H, H-8, J = 6.2 Hz), 4.82 (br s, 1H, H-6b), 5.27 (br s, 1H, H-6a), 5.85-5.95 (m, 1H, H-7).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -5.1 (-ve), 18.4, 24.0, 26.0 (-ve), 30.0, 34.0, 61.8, 102.5, 119.5 (-ve), 140.5, 149.1.

HRMS calcd for $C_{14}H_{26}OSi$: 238.1753; found: 238.1751.

Anal. calcd for $C_{14}H_{26}OSi$: C 70.52, H 10.99; found: C 70.31, H 11.03.

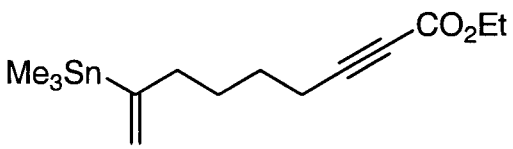
Table 15. ^{1}H nmr (400 MHz, $CDCl_3$) data for the silyl ether **155**: NOED experiments



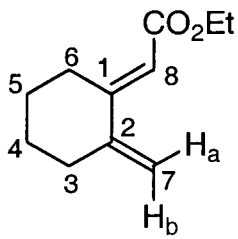
155

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-6a	4.82 (br s)	H-6b, H-7
H-6b	5.27 (br s)	H-6a, H-7 (-ve), H-3
H-7	5.85-5.95 (m)	H-6a, H-6b (-ve), H-8

Preparation of (*E*)-1-ethoxycarbonylmethylidene-2-methylidenecyclohexane (**156**)



137



156

Following general procedure 1, the cyclohexane derivative **156** was prepared by the addition of the ester **137** (100 mg, 0.290 mmol), as a solution in dry DMF (1.5 mL), to a cool (0 °C), stirred solution-suspension of CuCl (75 mg, 0.76 mmol) and glacial acetic acid (83 μL, 1.5 mmol) in dry DMF (1.4 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 97:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 45 mg (87 %) of the cyclization product **156** as a colorless oil.

IR (neat): 1714, 1636, 1444, 1370, 1295, 1184, 1158, 1039, 901 cm^{-1}.

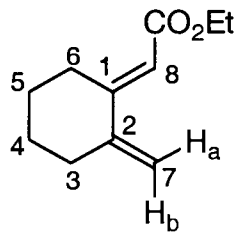
^1H nmr (400 MHz, $CDCl_3$) δ: 1.26 (t, 3H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 1.60-1.75 (m, 4H, H-4 and H-5), 2.30 (br s, 2H, H-3), 2.90 (br s, 2H, H-6), 4.14 (q, 2H, $-CO_2C\underline{H}_2CH_3$, J = 7.1 Hz), 4.75-4.80 (m, 1H, H-7b), 5.00-5.05 (m, 1H, H-7a), 5.80-5.85 (m, 1H, H-8).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.3 (-ve), 25.9, 26.5, 29.7, 35.3, 59.7, 110.7, 112.9 (-ve), 149.6, 161.0, 166.9.

HRMS calcd for $C_{11}H_{16}O_2$: 180.1151; found: 180.1154.

Anal. calcd for $C_{11}H_{16}O_2$: C 73.30, H 8.95; found: C 73.00, H 9.05.

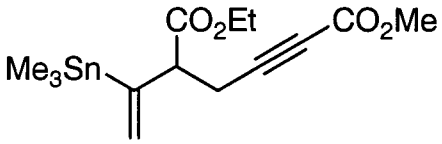
Table 16. ^1H nmr (400 MHz, $CDCl_3$) data for the ester **156**: NOED experiments



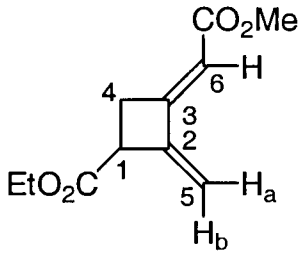
156

Assignment H-x	^1H nmr (400 MHz) δ (multiplicity, J (Hz))	NOED Correlations
H-7a	5.00-5.05 (m)	H-7b, H-8
H-7b	4.75-4.80 (m)	H-3, H-7a, H-8 (-ve)
H-8	5.80-5.85 (m)	H-7a

Preparation of Ethyl (*E*)-3-methoxycarbonylmethylidene-2-methylidenecyclobutane-1-carboxylate (**158**)



143



158

Following general procedure 1, the cyclobutane derivative **158** was prepared by the addition of the diester **143** (146 mg, 0.392 mmol), as a solution in dry DMF (2 mL), to a cool (0 °C), stirred solution-suspension of CuCl (102 mg, 1.03 mmol) and glacial acetic acid (120 μL, 2.10 mmol) in dry DMF (2 mL). Purification of the crude product by flash column chromatography (12 g of silica gel, 9:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 70 mg (85 %) of the cyclization product **158** as a colorless oil.

IR (neat): 1734, 1665, 1542, 1436, 1321, 1269, 1171, 1020 cm^{-1}.

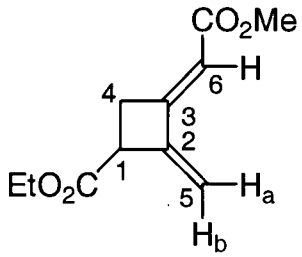
^1H nmr (400 MHz, $CDCl_3$) δ: 1.26 (t, 3H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 3.22 (dd, 1H, H-4, J = 2.5, 18.1 Hz), 3.38 (dd, 1H, H-4', J = 2.8, 18.1 Hz), 3.70 (s, 3H, $-CO_2\underline{Me}$), 3.75-3.85 (m, 1H, H-1), 4.10-4.25 (m, 2H, $-CO_2C\underline{H}_2CH_3$), 5.25 (br s, 1H, H-5b), 5.50 (d, 1H, H-5a, J = 2.5 Hz), 5.92 (dd, 1H, H-6, J = 2.5, 2.5 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.0 (-ve), 33.2, 44.4 (-ve), 51.0 (-ve), 60.8, 109.3 (-ve), 110.5, 145.1, 157.2, 166.6, 171.2.

HRMS calcd for $C_{11}H_{14}O_4$: 210.0892; found: 210.0896.

Anal. calcd for $C_{11}H_{14}O_4$: C 62.85, H 6.71; found: C 62.79, H 6.81.

Table 17. ^{1}H nmr (400 MHz, $CDCl_3$) data for the diester **158**: NOED experiments



158

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-5a	5.50 (d, *J* = 2.5)	H-5b, H-6
H-5b	5.25 (br s)	H-5a
H-6	5.92 (dd, *J* = 2.5, 2.5)	H-5a

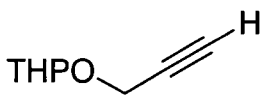
3. Intramolecular conjugate additions to form bicyclic compounds

3.1 Preparation of cyclization precursors

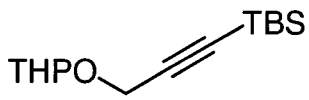
General Procedure 2: Protection of terminal alkynes with *tert*-butyldimethylsilyl chloride

To a cold (-78 °C), stirred solution of the appropriate terminal alkyne (1 equiv) in dry THF (~5 mL/mmol of alkyne) was added a solution of MeLi (1.2-1.4 equiv) in Et_2O and the solution was stirred for 10 min. The mixture was warmed to -20 °C and was stirred for 1 h. *tert*-Butyldimethylsilyl chloride (1.3-1.5 equiv) was added in one solid portion and the mixture was stirred for 1 h at -20 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (~1 mL/mL of THF) was added and the mixture was extracted with Et_2O (3 x ~1 mL/mL of THF). The combined organic extracts were washed with brine (~3 mL/mL of THF), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification of the crude product was accomplished with flash column chromatography on silica gel.

Preparation of 1-(*tert*-butyldimethylsilyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)propyne (**169**)



166



169

Following general procedure 2, the commercially available alkyne **166** (5.00 g, 35.7 mmol) in dry THF (200 mL) was converted into the title compound **169** with MeLi (27 mL, 1.6 M in Et_2O, 43 mmol) and *tert*-butyldimethylsilyl chloride (7.00 g, 46.5 mmol). Purification of the crude product by flash column chromatography (250 g of silica gel, 19:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 6.90 g (72 %) of the alkyne **169** as a colorless oil.

IR (neat): 2175, 1472, 1251, 1122, 1030, 826 cm^{-1}.

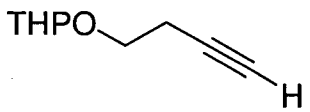
^1H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 6H, -Si<u>Me_2</u>-), 0.91 (s, 9H, -Si<u>^tBu</u>-), 1.50-1.64 (m, 4H), 1.65-1.75 (m, 2H), 3.46-3.52 (m, 1H), 3.79-3.85 (m, 1H), 4.25 (s, 2H, -O-C<u>H_2</u>-), 4.82 (t, 1H, J = 3.3 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -4.8, 16.2, 18.5, 25.3, 25.9, 30.1, 54.4, 61.6, 88.7, 96.2, 102.2.

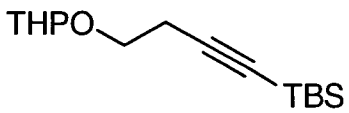
DCI-HRMS calcd for $C_{14}H_{27}O_2Si$ (M^++H): 255.1780; found: 255.1779.

Anal. calcd for $C_{14}H_{26}O_2Si$: C 66.04, H 10.30; found: C 66.14, H 10.20.

<u>Preparation of 1-(*tert*-butyldimethylsilyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)but-1-yne (**170**)</u>



167



170

Following general procedure 2, the alkyne **167**[46] (3.62 g, 23.5 mmol) in dry THF (125 mL) was converted into the title compound **170** with MeLi (17.6 mL, 1.6 M in Et_2O, 28.2 mmol) and *tert*-butyldimethylsilyl chloride (5.10 g, 33.8 mmol). Purification of the crude product by flash column chromatography (150 g of silica gel, 37:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 3.58 g (57 %) of the ether **170** as a colorless oil.

IR (neat): 2177, 1471, 1251, 1124, 1035, 838 cm^{-1}.

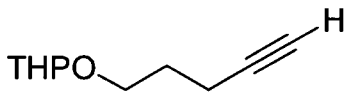
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 6H, -Si<u>Me</u>$_2$-), 0.91 (s, 9H, -Si^t<u>Bu</u>-), 1.48-1.58 (m, 4H), 1.65-1.72 (m, 1H), 1.78-1.85 (m, 1H), 2.51 (t, 2H, -C<u>H</u>$_2$-CH$_2$-), 3.49-3.56 (m, 2H), 3.77-3.90 (m, 2H), 4.64 (t, 1H, J = 3.3 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -4.6, 16.4, 19.1, 21.3, 25.4, 26.0, 30.4, 61.8, 65.6, 83.5, 98.5, 104.5.

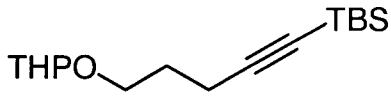
HRMS calcd for $C_{11}H_{19}O_2Si$ (M^+-^{t}Bu): 211.1154; found: 211.1147.

Anal. calcd for $C_{15}H_{28}O_2Si$: C 67.11, H 10.51; found: C 67.31, H 10.53.

<u>Preparation of 1-(*tert*-butyldimethylsilyl)-3-(tetrahydro-2*H*-pyran-2-yloxy)pent-1-yne (**171**)</u>



168



171

Following general procedure 2, the alkyne **168**[46] (2.25 g, 13.4 mmol) in dry THF (125 mL) was converted into the title compound **171** with MeLi (13.4 mL, 1.4 M in Et_2O, 18.8 mmol) and *tert*-butyldimethylsilyl chloride (3.15 g, 20.8 mmol). Purification of the crude product by flash column chromatography (100 g of silica gel, 37:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 2.16 g (57 %) of the alkyne **171** as a colorless oil.

IR (neat): 2174, 1466, 1253, 1129, 1037, 826 cm^{-1}.

^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 6H, -Si<u>Me</u>$_2$-), 0.91 (s, 9H, -Si^t<u>Bu</u>-), 1.48-1.90 (m, 8H), 2.33 (t, 2H, J = 7.0 Hz), 3.42-3.49 (m, 2H), 3.78-3.87 (m, 2H), 4.57 (t, 1H, J = 2.7 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -4.6 (-ve), 16.4, 16.6, 19.3, 25.4, 25.9 (-ve), 28.8, 30.5, 61.8, 65.6, 82.6, 98.5 (-ve), 107.2.

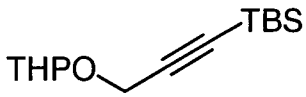
HRMS calcd for $C_{16}H_{29}O_2Si$ (M^+-H): 281.1937; found: 281.1929.

Anal. calcd for $C_{16}H_{30}O_2Si$: C 68.03, H 10.70; found: C 67.76, H 10.81.

General Procedure 3: Conversion of THP ethers into alkyl bromides

To a cool (0 °C), stirred solution of triphenylphosphine (~1.3 equiv) in dry CH_2Cl_2 (10 mL/mmol of THP ether) was added bromine (~1.3 equiv) dropwise until a yellow color persisted. A few crystals of triphenylphosphine were added until the color disappeared. The solution was stirred for a period of 20 min. The appropriate THP ether (1 equiv) was added neat and the solution was stirred at 0 °C for 20 min and at room temperature for 1 h. Pentane was added (~1 mL/mL of CH_2Cl_2) and the white suspension was filtered through a cake of silica gel (~10 g/g of triphenylphosphine) and the silica gel was eluted with Et_2O (~2 mL/mL of CH_2Cl_2). After concentration of the combined filtrate under reduced pressure, the crude product was purified by flash column chromatography on silica gel.

Preparation of 3-bromo-1-(*tert*-butyldimethylsilyl)propyne (**160**)



169

160

Following general procedure 3, the alkyne **169** was converted into the bromide **160** with the following amounts of solvent and reagents: alkyne **169** (6.90 g, 25.7 mmol), bromine (~1.7 mL), triphenylphosphine (8.77 g, 33.3 mmol), and CH_2Cl_2 (250 mL). The crude product was purified by flash column chromatography (200 g of silica gel, petroleum

ether) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 6.16 g (97 %) of the bromide **160** as a colorless oil.

IR (neat): 2179, 1472, 1253, 1039, 840 cm^{-1}.

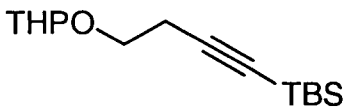
^1H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 6H, -Si<u>Me</u>$_2$-), 0.90 (s, 9H, -Si<u>^{t}Bu</u>-), 3.90 (s, 2H, Br-C<u>H</u>$_2$-).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -4.8, 14.7, 16.5, 26.0, 90.8, 113.3.

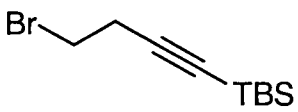
HRMS calcd for $C_9H_{17}Si^{81}Br$: 234.0263; found: 234.0265.

Anal. calcd for $C_9H_{17}SiBr$: C 46.35, H 7.35; found: C 46.67, H 7.38.

<u>Preparation of 4-bromo-1-(*tert*-butyldimethylsilyl)but-1-yne (**161**)</u>



170



161

Following general procedure 3, the alkyne **170** was converted into the bromide **161** with the following amounts of solvent and reagents: alkyne **170** (5.22 g, 19.5 mmol), bromine (~1.2 mL), triphenylphosphine (6.27 g, 24.0 mmol), and CH_2Cl_2 (200 mL). The crude material was purified by flash column chromatography (100 g of silica gel, 200:3 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 4.60 g (96 %) of the bromide **161** as a colorless oil.

IR (neat): 2177, 1472, 1251, 839 cm^{-1}.

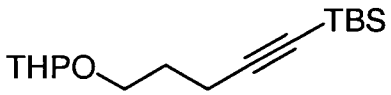
^1H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 6H, -Si<u>Me</u>$_2$-), 0.90 (s, 9H, -Si<u>^{t}Bu</u>-), 2.76 (t, 2H, -C<u>H</u>$_2$-CH$_2$-Br, J = 7.4 Hz), 3.41 (t, 2H, -CH$_2$-C<u>H</u>$_2$-Br, J = 7.4 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -4.7, 16.4, 24.3, 26.0, 29.3, 85.1, 106.6.

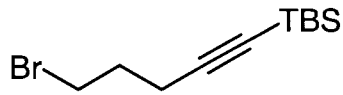
HRMS calcd for $C_{10}H_{19}Si^{81}Br$: 248.0419; found: 248.0423.

Anal. calcd for $C_{10}H_{19}SiBr$: C 48.58, H 7.75; found: C 48.87, H 7.48.

Preparation of 5-bromo-1-(*tert*-butyldimethylsilyl)pent-1-yne (**162**)



171



162

Following general procedure 3, the alkyne **171** was converted into the bromide **162** with the following amounts of solvent and reagents: alkyne **171** (924 mg, 3.27 mmol), bromine (~0.20 mL), triphenylphosphine (1.02 g, 3.90 mmol), and CH_2Cl_2 (35 mL). The crude product was purified by flash column chromatography (60 g of silica gel, 200:3 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 797 mg (93 %) of the bromide **162** as a colorless oil.

IR (neat): 2174, 1431, 1250, 827 cm^{-1}.

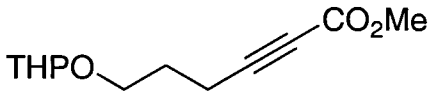
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 6H, -Si$\underline{Me_2}$-), 0.90 (s, 9H, -Si$^t\underline{Bu}$-), 2.00-2.10 (m, 2H, -CH_2-C$\underline{H_2}$-CH_2-), 2.41 (t, 2H, Br-CH_2-CH_2-C$\underline{H_2}$-, J = 6.8 Hz), 3.50 (t, 2H, Br-C$\underline{H_2}$-, J = 6.6 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -4.5 (-ve), 16.4, 18.5, 26.0 (-ve), 31.4, 32.0, 83.8, 105.4.

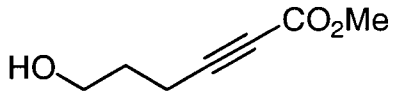
HRMS calcd for $C_{11}H_{21}Si^{81}Br$: 262.0575; found: 262.0580.

Anal. calcd for $C_{11}H_{21}SiBr$: C 50.57, H 8.10; found: C 50.87, H 8.17.

Preparation of methyl 6-iodohex-2-ynoate (**159**)



172



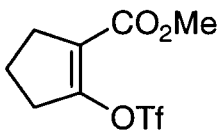
173

159

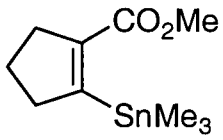
To a cool (0 °C), stirred solution of the ester **172**[47] (4.22 g, 18.7 mmol) in dry MeOH (50 mL) was added PPTS (463 mg, 1.87 mmol). The mixture was warmed to reflux for 21 h and then the solvent was removed *in vacuo*. Flash column chromatography (100 g of silica gel, 1:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 2.29 g of the alcohol **173** as a colorless oil.

To a cool (0 °C), stirred solution of iodine (5.26 g, 20.9 mmol) in dry CH_2Cl_2 (125 mL) was added triphenylphosphine (5.43 g, 16.1 mmol) in one solid portion. The mixture was stirred for 30 min and then imidazole (1.65 g, 24.2 mmol) was added. A solution of the alcohol **173** (obtained as described above) in dry CH_2Cl_2 (5 mL) was added via a cannula and the reaction mixture was stirred for 30 min at 0 °C. Pentane (125 mL) was added to the mixture. The white suspension was filtered through silica gel (~30 g) and the cake was eluted with Et_2O (~400 mL). The combined filtrate was concentrated under reduced pressure. Flash column chromatography (100 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 3.23 g (79 %) of the ester **159** as a colorless oil. This material exhibited spectral data (^1H nmr) identical with those previously reported.[47]

Preparation of methyl 2-trimethylstannylcyclopent-1-enecarboxylate (**163**)



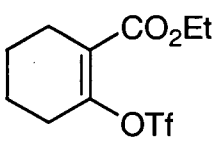
174



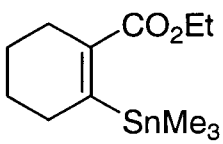
163

To a cold (-48 °C), stirred solution of hexamethylditin (23.9 g, 73.1 mmol) in dry THF (500 mL) was added MeLi (46.0 mL, 1.60 M in Et_2O, 73.6 mmol) via a syringe and the solution was stirred for 30 min. Copper(I) cyanide (2.99 g, 75.2 mmol) was added to the solution in one solid portion and stirring was continued for 30 min. A solution of the enol triflate **174**[28b] (15.4 g, 56.1 mmol) in dry THF (5 mL) was added via a cannula to the mixture and stirring was continued for 1 h at -48 °C and for 1 h at 0 °C. The mixture was opened to the air and aqueous ammonium chloride-ammonia (pH 8) (250 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 150 mL). The organic layers were combined, washed with brine (500 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash column chromatography (400 g of silica gel, 39:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 14.9 g (92 %) of the stannane **163**[28b] as a colorless clear oil.

Preparation of ethyl 2-trimethylstannylcyclohex-1-enecarboxylate (**164**)



175

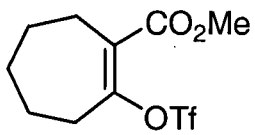


164

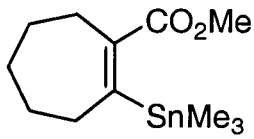
To a cold (-48 °C), stirred solution of hexamethylditin (5.33 g, 16.2 mmol) in dry THF (80 mL) was added MeLi (12.0 mL, 1.40 M in Et_2O, 16.8 mmol) via a syringe and the solution was stirred for 30 min. Copper(I) cyanide (1.76 g, 19.6 mmol) was added to the solution in one solid portion and stirring was continued for 30 min. A solution of the enol triflate **175**[28b] (3.32 g, 11.0 mmol) in dry THF (10 mL) was added via a cannula to the mixture and stirring was continued for 1 h at -48 °C and for 1 h at 0 °C. The mixture

was opened to the air and aqueous ammonium chloride-ammonia (pH 8) (150 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 200 mL). The organic layers were combined, washed with brine (500 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash column chromatography (200 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 3.24 g (93 %) of the stannane **164**[28b] as a colorless clear oil.

Preparation of methyl 2-trimethylstannylcyclohept-1-enecarboxylate (**165**)



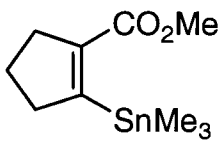
176



165

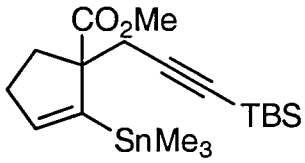
To a cold (-48 °C), stirred solution of hexamethylditin (7.56 g, 23.1 mmol) in dry THF (100 mL) was added MeLi (14.8 mL, 1.53 M in Et_2O, 22.6 mmol) via a syringe and the solution was stirred for 30 min. Copper(I) cyanide (2.10 g, 23.5 mmol) was added to the solution in one solid portion and stirring was continued for 30 min. A solution of the enol triflate **176**[10] (5.27 g, 17.4 mmol) in dry THF (12 mL) was added via a cannula to the mixture and stirring was continued for 1 h at -48 °C and for 1 h at 0 °C. The mixture was opened to the air and aqueous ammonium chloride-ammonia (pH 8) (30 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the organic phase was washed with water (2 x 40 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash column chromatography (60 g of silica gel, 19:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 4.19 g (76 %) of the stannane **165**[10] as a colorless clear oil.

Preparation of methyl 1-(3-*tert*-butyldimethylsilylprop-2-yn-1-yl)-2-trimethylstannyl cyclopent-2-ene-1-carboxylate (**178a**)



163

160



178a

To a cold (-48 °C), stirred solution of LDA (8.06 mmol) in dry THF (60 mL) was added HMPA (1.4 mL, 8.1 mmol) and stirring was continued for 10 min. A solution of the ester **163** (1.94 g, 6.72 mmol) in dry THF (2 mL) was added via a cannula and the mixture was stirred for 40 min. The solution was cooled to -78 °C and the bromide **160** (2.55 g, 11.0 mmol) was added as a solution in dry THF (2 mL). The mixture was stirred at -48 °C for 40 min and then was warmed to room temperature. Saturated aqueous sodium bicarbonate (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (3 x 60 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (100 g of silica gel, 200:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 2.30 g (78 %) of the stannane **178a** as a colorless oil.

IR (neat): 2176, 1727, 1250, 775 cm^{-1}.

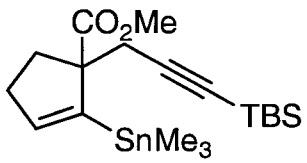
^1H nmr (400 MHz, $CDCl_3$) δ: 0.03 (s, 6H, -SiMe$_2$-), 0.12 (s, 9H, -SnMe$_3$, $^2J_{Sn\text{-}H}$ = 54.4 Hz), 0.88 (s, 9H, -Si^{t}Bu-), 1.98-2.05 (m, 1H), 2.40-2.52 (m, 4H), 2.71 (d, 1H, J = 6.7 Hz), 3.64 (s, 3H, -CO_2Me), 6.00 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn\text{-}H}$ = 36.6 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.5, -4.6, 16.4, 26.0, 29.3, 32.4, 34.3, 52.0, 65.2, 84.4, 104.3, 113.2, 144.8, 175.7.

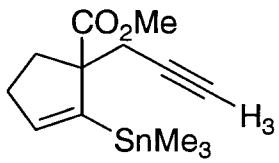
HRMS calcd for $C_{18}H_{31}O_2Si^{120}Sn$ (M^+-Me): 428.1138; found: 428.1145.

Anal. calcd for $C_{19}H_{34}O_2SiSn$: C 51.72, H 7.77; found: C 51.94, H 7.84.

Preparation of methyl 1-(prop-2-yn-1-yl)-2-trimethylstannylcyclopent-2-ene-1-carboxylate (**178b**)



178a



178b

To a stirred solution of the stannane **178a** (848 mg, 1.92 mmol) in dry THF (20 mL) at room temperature was added a solution of tetrabutylammonium fluoride (2.5 mL, 1 M in THF, 2.5 mmol) and the solution was stirred for 1 h. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude oil. Flash column chromatography (50 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 609 mg (97 %) of the ester **178b** as a colorless clear oil.

IR (neat): 1729, 1435, 1200, 772 cm^{-1}.

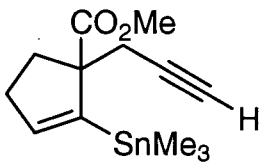
^1H nmr (400 MHz, $CDCl_3$) δ: 0.13 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.6 Hz), 1.90 (t, 1H, H_3, J = 2.6 Hz), 1.96-2.02 (m, 1H), 2.35-2.53 (m, 4H), 2.67 (dd, 1H, J = 2.6, 6.6 Hz), 3.67 (s, 3H, -CO_2<u>Me</u>), 6.02 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn\text{-}H}$ = 36.6 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.8, 27.7, 32.6, 34.1, 52.0, 64.7, 69.8, 81.2, 144.8, 175.5, 219.4.

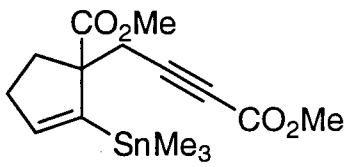
HRMS calcd for $C_{12}H_{17}O_2{}^{120}Sn$ (M^+-Me): 313.0251; found: 313.0248.

Anal. calcd for $C_{13}H_{20}O_2Sn$: C 47.75, H 6.16; found: C 47.83, H 6.04.

Preparation of methyl 4-(1-methoxycarbonyl-2-trimethylstannylcyclopent-2-en-1-yl) but-2-ynoate (**178**)



178b



178

To a cold (-78 °C), stirred solution of LDA (2.38 mmol) in dry THF (12 mL) was added a solution of the alkyne **178b** (602 mg, 1.84 mmol) in dry THF (2 mL) via a cannula. The reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (220 μL, 2.75 mmol) was added via a syringe and stirring was continued for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (50 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 510 mg (73 %) of the ester **178** as a colorless clear oil.

IR (neat): 2238, 1718 (br), 1580, 1435, 1251, 773 cm^{-1}.

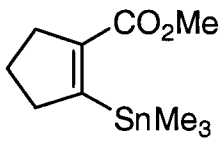
^1H nmr (400 MHz, $CDCl_3$) δ: 0.14 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 54.6 Hz), 1.93-2.01 (m, 1H), 2.41-2.56 (m, 4H), 2.81 (d, 1H, J = 7.1 Hz), 3.67 (s, 3H, -CO_2<u>Me</u>), 3.71 (s, 3H, -CO_2<u>Me</u>), 6.06 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn-H}$ = 35.8 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.9 (-ve), 27.8, 32.9, 34.2, 52.2 (-ve), 52.4 (-ve), 64.2, 73.9, 86.3, 145.3 (-ve), 146.2, 153.8, 175.1.

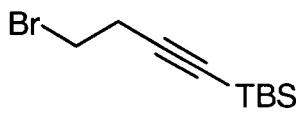
HRMS calcd for $C_{14}H_{19}O_4{}^{120}Sn$ (M^+-Me): 371.0306; found: 371.0314.

Anal. calcd for $C_{15}H_{22}O_4Sn$: C 46.79, H 5.76; found: C 47.09, H 5.87.

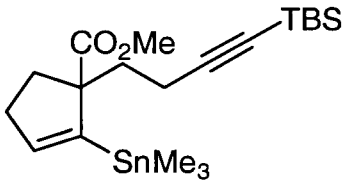
Preparation of methyl 1-(but-3-yn-1-yl)-2-trimethylstannylcyclopent-2-ene-1-carboxylate **(179b)**



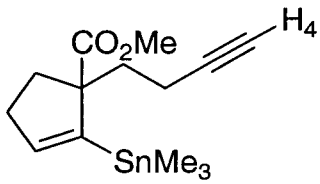
163



161



179a



179b

To a cold (-48 °C), stirred solution of LDA (4.14 mmol) in dry THF (32 mL) was added HMPA (740 μL, 4.49 mmol) and stirring was continued for 10 min. A solution of the ester **163** (998 mg, 3.45 mmol) in dry THF (2 mL) was added via a cannula and the mixture was stirred for 40 min. The solution was cooled to -78 °C and the bromide **161** (1.03 g, 4.16 mmol) was added as a solution in dry THF (2 mL) via a cannula. The reaction mixture was stirred at -78 °C for 1 h and at room temperature for 1 h. Saturated aqueous sodium bicarbonate (30 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were extracted with brine (3 x 30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (50 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude product yielded the deconjugated-alkylated product **179a** as a colorless clear oil which was contaminated with the stannane **163**.

To a stirred solution of the stannane **179a** (obtained as described above) in dry THF (12 mL) at room temperature was added a solution of tetrabutylammonium fluoride (7.0 mL, 1 M in THF, 7.0 mmol). The solution was stirred for 1 h. Saturated aqueous sodium bicarbonate (30 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude oil. Flash column chromatography (50 g silica gel, 98:2 petroleum ether-Et_2O) of the crude product and removal of trace

amounts of solvent (vacuum pump) from the acquired material yielded 541 mg (46 %) of the alkyne **179b** as a colorless clear oil.

IR (neat): 3308, 2120, 1733, 1580, 1435, 1167, 770 cm^{-1}.

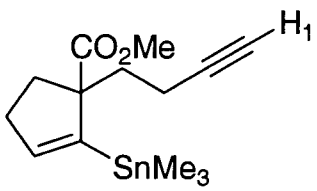
^1H nmr (400 MHz, $CDCl_3$) δ: 0.14 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 54.3 Hz), 1.64-1.80 (m, 2H), 1.91 (t, 1H, H_4, J = 2.6 Hz), 2.00-2.20 (m, 3H), 2.36-2.55 (m, 3H), 3.64 (s, 3H, -CO_2<u>Me</u>), 5.91 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn-H}$ = 35.4 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -8.6, 14.5, 31.6, 34.2, 37.1, 51.9, 65.4, 68.4, 84.0, 144.0, 148.1, 176.2.

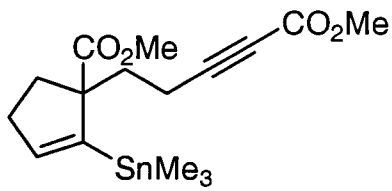
HRMS calcd for $C_{13}H_{19}O_2{}^{120}Sn$ (M^+-Me): 327.0407; found 327.0404.

Anal. calcd for $C_{14}H_{22}O_2Sn$: C 49.31, H 6.50; found: C 49.55, H 6.65.

<u>Preparation of methyl 5-(1-methoxycarbonyl-2-trimethylstannylcyclopent-2-en-1-yl) pent-2-ynoate (**179**)</u>



179b



179

To a cold (-78 °C), stirred solution of LDA (1.55 mmol) in dry THF (11 mL) was added a solution of the alkyne **179b** (405 mg, 1.19 mmol) in dry THF (1 mL) via a cannula. The reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (140 μL, 1.81 mmol) was added via a syringe and stirring was continued for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced

pressure. Flash column chromatography (50 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product, followed by bulb-to-bulb distillation (160-185 °C/0.3 torr) of the acquired material, yielded 338 mg (71 %) of the diester **179** as a colorless clear oil.

IR (neat) 2239, 1718 (br), 1435, 1256, 770 cm^{-1}.

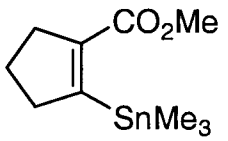
^1H nmr (400 MHz, $CDCl_3$) δ: 0.13 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 54.3 Hz), 1.68-1.78 (m, 2H), 2.15-2.30 (m, 3H), 2.36-2.45 (m, 2H), 2.47-2.56 (m, 1H), 3.64 (s, 3H, -CO_2<u>Me</u>), 3.72 (s, 3H, -CO_2<u>Me</u>), 5.98 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn-H}$ = 36.1 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.6 (-ve), 14.8, 31.7, 34.1, 35.8, 52.0 (-ve), 52.5 (-ve), 64.9, 72.9, 89.0, 144.3 (-ve), 147.7, 154.1, 175.9.

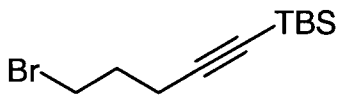
HRMS calcd for $C_{15}H_{21}O_4{}^{120}Sn$ (M^+-Me): 385.0462; found: 385.0461.

Anal. calcd for $C_{16}H_{24}O_4Sn$: C 48.16; H 6.06. found C 48.34; H 6.16.

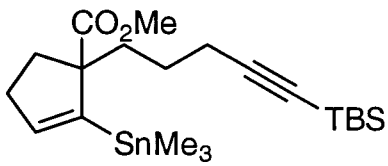
<u>Preparation of methyl 1-(5-*tert*-butyldimethylsilylpent-4-yn-1-yl)-2-trimethylstannyl cyclopent-2-ene-1-carboxylate (**180a**)</u>



163



162



180a

To a cold (-48 °C), stirred solution of LDA (7.68 mmol) in dry THF (60 mL) was added HMPA (1.33 mL, 7.68 mmol) and stirring was continued for 10 min. The ester **163** (1.85 g, 6.40 mmol) was added as a solution in dry THF (4 mL) via a cannula and the mixture was stirred for 40 min. The solution was cooled to -78 °C and a solution of the bromide **162** (2.09 g, 8.00 mmol) in dry THF (2 mL) was added via a cannula. The reaction mixture was stirred at -48 °C for 40 min and then the mixture was warmed to room temperature. Saturated aqueous sodium bicarbonate (50 mL) was added and the

mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (3 x 60 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (100 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 2.50 g (83 %) of the stannane **180a** as a colorless clear oil.

IR (neat): 2174, 1733, 1251, 775 cm^{-1}.

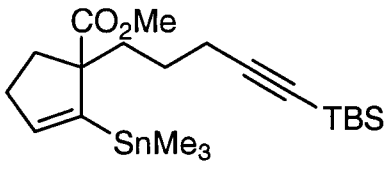
^1H nmr (400 MHz, $CDCl_3$) δ: 0.05 (s, 6H, -Si$\underline{Me_2}$-), 0.12 (s, 9H, -Sn$\underline{Me_3}$, $^2J_{Sn\text{-}H}$ = 54.2 Hz), 0.91 (s, 9H, -Si$^t\underline{Bu}$-), 1.29-1.53 (m, 3H), 1.69-1.76 (m, 1H), 1.97 (td, 1H, J = 4.2, 12.6 Hz), 2.20 (t, 2H, J = 6.8 Hz), 2.35-2.51 (m, 3H), 3.63 (s, 3H, -CO_2Me), 5.94 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn\text{-}H}$ = 37.7 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.5 (-ve), -4.5 (-ve), 16.4, 20.1, 24.4, 26.0 (-ve), 32.0, 33.9, 37.8, 51.6 (-ve), 65.2, 82.6, 107.3, 143.1 (-ve), 148.6, 176.5.

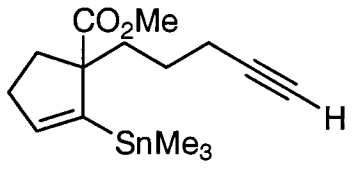
HRMS calcd for $C_{20}H_{35}O_2Si^{120}Sn$ (M^+-Me): 455.1428; found: 455.1431.

Anal. calcd for $C_{21}H_{38}O_2SiSn$: C 53.75, H 6.18; found: C 54.03, H 8.04.

Preparation of methyl 1-(pent-4-yn-1-yl)-2-trimethylstannylcyclopent-2-ene-1-carboxylate (**180b**)



180a



180b

To a stirred solution of the stannane **180a** (1.23 g, 2.62 mmol) in dry THF (26 mL) at room temperature was added a solution of tetrabutylammonium fluoride (3.4 mL, 1 M in THF, 3.4 mmol) and the solution was stirred for 1 h. Saturated aqueous sodium

bicarbonate (25 mL) was added and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude oil. Flash column chromatography (100 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 900 mg (97 %) of the alkyne **180b** as a colorless clear oil.

IR (neat): 3310, 1733, 1166, 771 cm^{-1}.

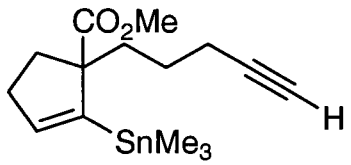
^1H nmr (400 MHz, $CDCl_3$) δ: 0.13 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 54.2 Hz), 1.30-1.54 (m, 4H), 1.70-1.78 (m, 1H), 1.91-2.00 (m, 2H), 2.15 (tdd, 1H, J = 7.0, 1.0, 1.5 Hz), 2.35-2.53 (m, 3H), 3.64 (s, 3H), 5.95 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn-H}$ = 38.0 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.6, 18.7, 24.0, 31.8, 34.1, 37.5, 51.7, 65.1, 68.6, 83.9, 143.2, 148.5, 176.6.

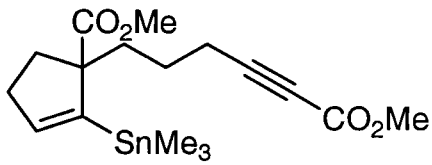
HRMS calcd for $C_{14}H_{21}O_2{}^{120}Sn$ (M^+-Me): 341.0564; found: 341.0564.

Anal. calcd for $C_{15}H_{24}O_2Sn$: C 50.74, H 6.81; found: C 50.94, H 6.94.

<u>Preparation of methyl 6-(1-methoxycarbonyl-2-trimethylstannylcyclopent-2-en-1-yl) hex-2-ynoate (**180**)</u>



180b



180

To a cold (-78 °C), stirred solution of LDA (2.43 mmol) in dry THF (18 mL) was added a solution of the alkyne **180b** (663 mg, 1.87 mmol) in dry THF (1 mL) via a cannula and the reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (200 μL, 2.62 mmol) was added via a syringe and stirring was continued for 1 h at -78 °C and 1 h

at room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (20 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product, followed by bulb-to-bulb distillation (170-190 °C/0.3 torr) of the acquired liquid, yielded 627 mg (81 %) of the diester **180** as a colorless clear oil.

IR (neat): 2238, 1718 (br), 1257, 772 cm^{-1}.

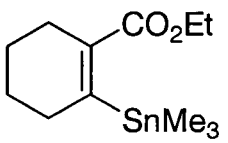
^1H nmr (400 MHz, $CDCl_3$) δ: 0.12 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.2 Hz), 1.40-1.54 (m, 3H), 1.70-1.76 (m, 1H), 1.92-1.98 (m, 1H), 2.28-2.31 (m, 2H), 2.35-2.53 (m, 3H), 3.64 (s, 3H, -CO_2<u>Me</u>), 3.73 (s, 3H, -CO_2<u>Me</u>), 5.90 (dd, 1H, olefinic proton, J = 2.0, 2.0 Hz, $^3J_{Sn\text{-}H}$ = 37.4 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.6 (-ve), 18.9, 23.2, 31.8, 34.1, 37.5, 51.7 (-ve), 52.4 (-ve), 65.1, 73.1, 88.8, 143.4 (-ve), 148.3, 153.9, 176.4.

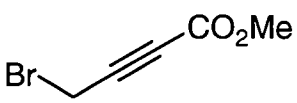
HRMS calcd for $C_{16}H_{23}O_4{}^{120}Sn$ (M^+-Me): 399.0618; found: 399.0619.

Anal. calcd for $C_{17}H_{26}O_4Sn$: 49.43, H 6.34; found: C 49.79, H 6.38.

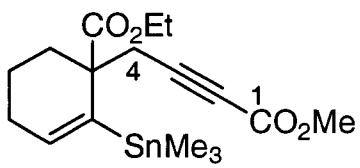
<u>Preparation of methyl 4-(1-ethoxycarbonyl-2-trimethylstannylcyclohex-2-en-1-yl) but-2-ynoate (**181**)</u>



164



140



181

To a cold (-78 °C), stirred solution of LDA (1.79 mmol) in dry THF (7 mL) was added DMPU (230 μL, 1.90 mmol) and stirring was continued for 5 min. A solution of the ester **164** (434 mg, 1.37 mmol) in dry THF (1 mL) was added via a cannula to the

reaction mixture. The mixture was stirred at -78 °C for 30 min and at 0 °C for 50 min. The orange suspension was cooled to -78 °C and methyl 4-bromobut-2-ynoate (**140**) (340 mg, 1.90 mmol), dissolved in dry THF (1 mL), was added via a cannula to the reaction mixture. After 10 min, the reaction mixture turned dark brown and saturated aqueous sodium bicarbonate (30 mL) was added at -78 °C. The mixture was then warmed to room temperature. The black suspension was extracted with Et_2O (3 x 25 mL). The organic extracts were combined, washed with brine (2 x 25 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (40 g of silica gel, 95:5 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 290 mg (51 %) of the ester **181** as a clear oil.

IR (neat): 2237, 1718 (br), 1603, 1435, 1256, 1074, 769 cm^{-1}.

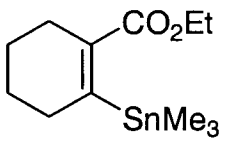
^1H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 52.8 Hz), 1.25 (t, 3H, -CO_2CH_2C<u>H</u>$_3$, J = 7.2 Hz), 1.60-1.78 (m, 2H), 1.80-1.90 (m, 1H), 2.00-2.15 (m, 3H), 2.55 (d, 1H, H-4, J = 17.2 Hz), 2.81 (d, 1H, H-4', J = 17.2 Hz), 3.72 (s, 3H, -CO_2<u>Me</u>), 4.07-4.20 (m, 2H, -CO_2C<u>H</u>$_2CH_3$), 6.03 (dd, 1H, olefinic proton, J = 3.7, 3.7 Hz, $^3J_{Sn\text{-}H}$ = 71.2 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -7.7 (-ve), 13.9 (-ve), 18.4, 26.7, 29.1, 30.8, 50.4, 52.3 (-ve), 61.1, 74.7, 85.8, 141.1 (-ve), 142.1, 153.6, 174.6.

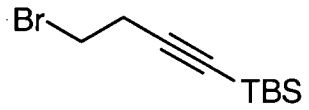
HRMS calcd for $C_{16}H_{23}O_4{}^{120}Sn$ (M^+-Me): 399.0618; found: 399.0618.

Anal. calcd for $C_{17}H_{26}O_4Sn$: C 49.43, H 6.34; found: C 49.68, H 6.28.

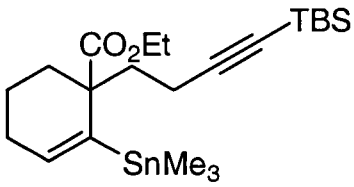
Preparation of ethyl 1-(but-3-yn-1-yl)-2-trimethylstannylcyclohex-2-ene-1-carboxylate (**182b**)



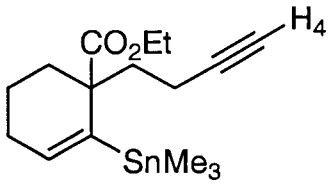
164



161



182a



182b

To a cold (-48 °C), stirred solution of LDA (8.60 mmol) in dry THF (60 mL) was added HMPA (1.50 mL, 8.6 mmol) and stirring was continued for 10 min. A solution of the ester **164** (2.05 g, 6.46 mmol) in dry THF (2 mL) was added via a cannula and the mixture was stirred for 40 min. The solution was cooled to -78 °C and the bromide **161** (2.19 g, 8.87 mmol) was added as a solution in dry THF (2 mL) via a cannula. The reaction mixture was stirred at -78 °C for 3 h and then warmed to room temperature. Saturated aqueous sodium bicarbonate (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (3 x 60 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (100 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude product resulted in the isolation of 248 mg of the stannane **164** and 1.56 g of a colorless clear oil containing a mixture of the alkylated product **182a** and the starting material **164**.

To a stirred solution of the stannane **182a** (obtained as described above) in dry THF (30 mL) at room temperature was added a solution of tetrabutylammonium fluoride (6.5 mL, 1 M in THF, 6.5 mmol) and stirring was continued for 1 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude oil. Flash column chromatography (100 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude product and

removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 635 mg of the ester **164** and 623 mg (46 % over 2 steps based on the total amount (883 mg) of recovered starting material **164**) of the alkyne **182b** as a colorless clear oil.

IR (neat): 3310, 2120, 1719, 1180, 769 cm^{-1}.

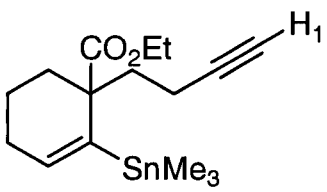
^1H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, $-SnMe_3$, $^2J_{Sn-H}$ = 52.3 Hz), 1.25 (t, 3H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 1.50-1.64 (m, 3H), 1.70-1.81 (m, 1H), 1.92 (t, 1H, H_4, J = 2.4 Hz), 2.00-2.15 (m, 6H), 4.00-4.20 (m, 2H, $-CO_2C\underline{H}_2CH_3$), 5.97 (dd, 1H, olefinic proton, J = 3.6, 3.6 Hz, $^3J_{Sn-H}$ = 75.0 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -7.1, 14.0, 14.2, 19.0, 27.2, 29.9, 38.3, 50.5, 60.8, 68.4, 84.0, 140.2, 144.8, 176.0.

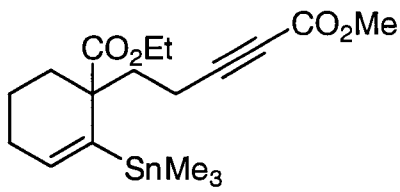
HRMS calcd for $C_{15}H_{23}O_2{}^{120}Sn$ (M^+-Me): 355.0720; found: 355.0725.

Anal. calcd for $C_{16}H_{26}O_2Sn$: C 52.07, H 7.10; found: C 52.30, H 7.19.

Preparation of methyl 5-(1-ethoxycarbonyl-2-trimethylstannylcyclohex-2-en-1-yl) pent-2-ynoate (**182**)



182b



182

To a cold (-78 °C), stirred solution of LDA (1.72 mmol) in dry THF (12 mL) was added a solution of the alkyne **182b** (486 mg, 1.32 mmol) in dry THF (1 mL) via a cannula and stirring was contiuned for 1 h. Methyl chloroformate (153 μL, 1.98 mmol) was added via a syringe and the mixture was stirred for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted

with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (20 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product, followed by bulb-to-bulb distillation (160-190 °C/0.3 torr) of the acquired oil, yielded 431 mg (77 %) of the diester **182** as a colorless clear oil.

IR (neat): 2239, 1719 (br), 1435, 1256, 769 cm^{-1}.

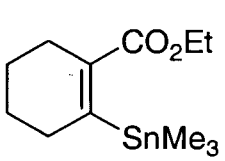
^1H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 52.4 Hz), 1.24 (t, 3H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 1.50-1.65 (m, 3H), 1.73-1.81 (m, 1H), 1.95-2.14 (m, 4H), 2.27 (t, 2H, J = 8.1 Hz), 3.73 (s, 3H, -$CO_2\underline{Me}$), 4.05-4.19 (m, 2H, -$CO_2\underline{CH}_2CH_3$), 5.90 (dd, 1H, olefinic proton, J = 3.6, 3.6 Hz, $^3J_{Sn\text{-}H}$ = 70.1 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -7.2 (-ve), 14.1 (-ve), 14.3, 18.9, 27.1, 30.0, 36.9, 50.3, 52.6 (-ve), 60.9, 72.9, 89.2, 140.6 (-ve), 144.3, 154.1, 175.8.

HRMS calcd for $C_{17}H_{25}O_4{}^{120}Sn$ (M^+-Me): 413.0775, found: 413.0783.

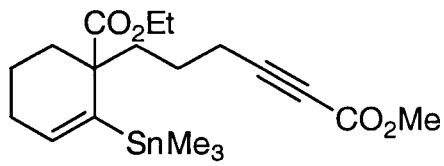
Anal. calcd for $C_{18}H_{28}O_4Sn$: C 50.62, H 6.61; found: C 50.77, H 6.61.

Preparation of methyl 6-(1-ethoxycarbonyl-2-trimethylstannylcyclohex-2-en-1-yl) hex-2-ynoate (**183**)



164

159



183

To a cold (-78 °C), stirred solution of LDA (5.50 mmol) in dry THF (30 mL) was added DMPU (660 μL, 5.50 mmol) and stirring was continued for 10 min. The mixture was warmed to -40 °C and a solution of the ester **164** (1.33 g, 4.20 mmol) in dry THF (3 mL) was added via a cannula. The reaction mixture was then stirred for 40 min. Methyl

6-iodohex-2-ynoate (**159**) (1.43 g, 5.70 mmol) was added as a solution in dry THF (3 mL) via a cannula. The reaction mixture was stirred at -40 °C for 40 min and then was allowed to warm to room temperature. Saturated aqueous sodium bicarbonate (25 mL) was added and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (100 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product, followed by bulb-to-bulb distillation (150-200 °C/0.3 torr) of the acquired oil, yielded 1.07 g (58 %) of the stannane **183** as a colorless clear oil.

IR (neat): 2238, 1713 (br), 1435, 1256, 769 cm^{-1}.

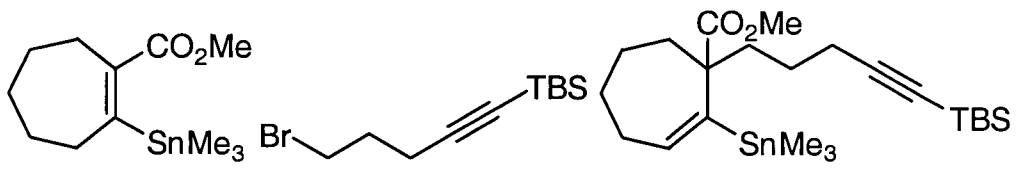
^1H nmr (400 MHz, $CDCl_3$) δ: 0.10 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 52.3 Hz), 1.25 (t, 3H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 1.40-1.64 (m, 7H), 1.86-1.94 (m, 1H), 2.00-2.12 (m, 2H), 2.28 (t, 2H, J = 6.7 Hz), 3.73 (s, 3H, -$CO_2\underline{Me}$), 4.00-4.21 (m, 2H, -$CO_2C\underline{H}_2CH_3$), 5.94 (dd, 1H, olefinic proton, J = 3.7, 3.7 Hz, $^3J_{Sn-H}$ = 75.7 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -7.1 (-ve), 14.2 (-ve), 19.0 (2C), 22.8, 27.2, 30.2, 39.0, 50.6, 52.5 (-ve), 60.7, 73.1, 89.0, 139.7 (-ve), 145.4, 154.1, 176.2.

HRMS calcd for $C_{18}H_{27}O_4{}^{120}Sn$ (M^+-Me): 427.0931; found: 427.0939.

Anal. calcd for $C_{19}H_{30}O_4Sn$: C 51.73, H 6.85; found: C 51.86, H 6.78.

Preparation of methyl 1-(5-*tert*-butyldimethylsilylpent-4-yn-1-yl)-2-trimethylstannyl cyclohept-2-ene-1-carboxylate (**184a**)



165 **162** **184a**

To a cold (-78 °C), stirred solution of LDA (0.504 mmol) in dry THF (3 mL) was added DMPU (61 μL, 2.2 mmol) and stirring was continued for 10 min. The ester **165** (123 mg, 0.388 mmol) was added as a solution in dry THF (2 mL) via a cannula and the mixture was stirred at -48 °C for 40 min. The bromide **162** (1.03 g, 4.16 mmol) was added as a solution in dry THF (2 mL) via a cannula. The reaction mixture was stirred at -48 °C for 40 min and then the mixture was warmed to room temperature. Saturated aqueous sodium bicarbonate (5 mL) was added and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (50 g of silica gel, 197:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired oils resulted in the isolation of 23 mg of the stannane **165** and 68 mg (35 %, 43 % based on the recovered starting material **165**) of the alkylated product **184a** as a colorless clear oil.

IR (neat): 2173, 1723, 1596, 1251, 775 cm^{-1}.

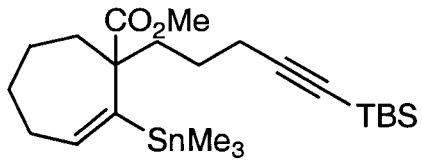
^1H nmr (400 MHz, $CDCl_3$) δ: 0.05 (s, 15H, includes 6H -Si$\underline{Me}_2$- and 9H -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 51.6 Hz), 0.72 (s, 9H, -Si$^t\underline{Bu}$-), 1.36-1.48 (m, 3H), 1.60-1.67 (m, 1H), 1.70-1.81 (m, 3H), 1.82-1.87 (m, 2H), 1.91-1.99 (m, 1H), 2.17-2.23 (m, 4H), 3.65 (s, 3H, -$CO_2\underline{Me}$), 5.99 (dd, 1H, olefinic proton, J = 5.2, 7.2 Hz, $^3J_{Sn\text{-}H}$ = 84.9 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -6.5, -4.2, 16.5, 20.4, 24.6, 26.1 (2C), 26.7, 29.8, 34.3, 36.4, 51.9, 56.8, 82.7, 107.6, 141.7, 150.5, 178.3.

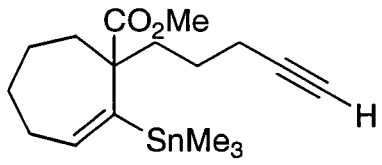
HRMS calcd for $C_{22}H_{42}O_2SiSn$ (M^+-Me): 483.1741; found: 483.1745.

Anal. calcd for $C_{23}H_{42}O_2SiSn$: C 55.54, H 8.51; found: C 55.64, H 8.49.

Preparation of methyl 1-(pent-4-yn-1-yl)-2-trimethylstannylcyclohept-2-ene-1-carboxylate (**184b**)



184a



184b

To a stirred solution of the stannane **184a** (139 mg, 0.278 mmol) in dry THF (3 mL) at room temperature was added a solution of tetrabutylammonium fluoride (0.42 mL, 1 M in THF, 0.42 mmol) and the solution was stirred for 1 h. Saturated aqueous sodium bicarbonate (5 mL) was added and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude oil. Flash column chromatography (12 g silica gel, 98:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 93 mg (87 %) of the alkyne **184b** as a colorless clear oil.

IR (neat): 3309, 1719, 1596, 1214, 768 cm^{-1}.

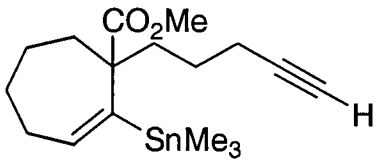
^1H nmr (400 MHz, $CDCl_3$) δ: 0.06 (s, 9H, -$SnMe_3$, $^2J_{Sn-H}$ = 51.6 Hz), 1.40-1.51 (m, 3H), 1.60-1.80 (m, 4H), 1.87 (t, 2H, J = 5.9 Hz), 1.91-2.00 (m, 2H), 2.13-2.27 (m, 4H), 3.65 (s, 3H, -CO_2Me), 6.00 (dd, 1H, olefinic proton, J = 5.2, 7.2 Hz, $^3J_{Sn-H}$ = 84.9 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -6.6, 18.9, 24.2, 24.4, 26.5, 29.5, 33.9, 36.6, 51.8, 56.8, 68.5, 84.0, 141.7, 150.3, 178.0.

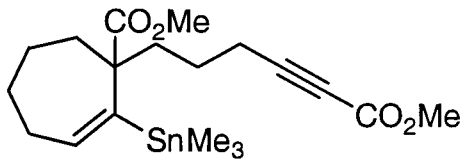
HRMS calc for $C_{16}H_{25}O_2{}^{120}Sn$ (M^+-Me): 369.0877; found: 369.0872.

Anal. calcd for $C_{17}H_{28}O_2Sn$: C 53.30, H 7.37; found: C 53.32, H 7.51.

Preparation of methyl 6-(1-methoxycarbonyl-2-trimethylstannylcyclohept-2-en-1-yl)-hex-2-ynoate (**184**)



184b



184

To a cold (-78 °C), stirred solution of LDA (0.808 mmol) in dry THF (5 mL) was added a solution of the alkyne **184b** (238 mg, 0.622 mmol) in dry THF (1 mL) via a cannula and the reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (72 μL, 0.93 mmol) was added via a syringe and stirring was continued for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (20 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product, followed by bulb-to-bulb distillation (170-190 °C/0.3 torr) of the acquired material, yielded 249 mg (91 %) of the diester **184** as a colorless clear oil.

IR (neat): 2238, 1718 (br), 1435, 1257, 753 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.13 (s, 9H, $^2J_{Sn-H}$ = 51.6 Hz), 1.41-1.56 (m, 3H), 1.60-1.80 (m, 4H), 1.85-1.89 (m, 2H), 1.91-1.99 (m, 1H), 2.17-2.23 (m, 2H), 2.30 (t, 2H, J = 7.0 Hz), 3.65 (s, 3H, -CO_2Me), 3.73 (s, 3H, -CO_2Me), 6.00 (dd, 1H, olefinic proton, J = 5.4, 7.0 Hz, $^3J_{Sn-H}$ = 85.2 Hz)

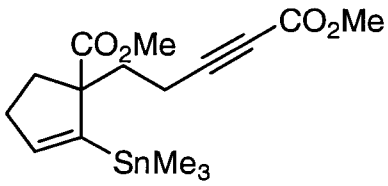
^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -6.5 (-ve), 19.3, 23.5, 24.5, 26.6, 29.6, 34.0, 36.4, 52.1 (-ve), 52.6 (-ve), 56.9, 73.2, 89.3, 142.1 (-ve), 150.0, 154.2, 178.0.

HRMS calcd for $C_{18}H_{27}O_4{}^{120}Sn$ (M^+-Me): 427.0931; found: 427.0941.

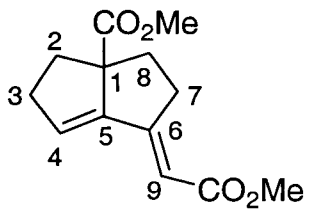
Anal calcd. for $C_{19}H_{30}O_4Sn$: C 51.73, H 6.85; found: C 51.99, H 6.88.

3.2 Copper(I) mediated conjugate additions

Preparation of 1-methoxycarbonyl-(*E*)-6-methoxycarbonylmethylidenebicyclo[3.3.0]oct-4-ene (**187**)



179



187

Following general procedure 1 (see pg. 126), the bicyclic diester **187** was prepared by the addition of the diester **179** (92 mg, 0.23 mmol), as a solution in dry DMF (1.2 mL), to a cool (0 °C), stirred solution-suspension of CuCl (60 mg, 0.61 mmol) and glacial acetic acid (65 μL, 1.1 mmol) in dry DMF (1.1 mL). Purification of the crude product by flash column chromatography (12 g of silica gel, 4:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 50 mg (93 %) of the bicyclic compound **187** as a colorless clear oil. This compound proved to be unstable when stored under argon for extended periods of time in a freezer.

IR (neat): 1725 (br), 1636, 1434, 1353, 1161 cm^{-1}.

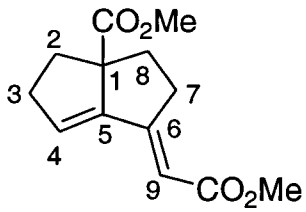
^1H nmr (400 MHz, C_6D_6) δ 1.11-1.19 (m, 1H, H-8), 1.45-1.53 (m, 1H, H-2), 2.22 (ddd, 1H, H-3, J = 3.8, 8.6, 17.1 Hz), 2.33 (br dd, 1H, H-8', J = 8.0, 12.3 Hz), 2.42 (br dd, 1H, H-2', J = 6.5, 12.5 Hz), 2.78-2.87 (m, 1H, H-3'), 3.20 (s, 3H, -CO_2Me), 3.30-3.46 (m, 4H, includes 3H -CO_2Me singlet at 3.42, H-7), 3.51 (dddd, 1H, H-7', J = 1.0, 1.9, 8.0, 19.4 Hz), 5.64 (dd, 1H, H-4, J = 3.8, 2.3 Hz), 6.20 (br s, 1H, H-9).

^{13}C nmr (75.5 MHz, C_6D_6) δ: 35.2, 37.0, 37.9, 38.6, 50.7, 51.5, 64.4, 110.9, 128.1, 152.0, 153.7, 167.0, 175.0.

HRMS calcd for $C_{13}H_{16}O_4$: 236.1049; found: 236.1047.

Anal. calcd for $C_{13}H_{16}O_4$: C 66.09, H 6.83; found: C 66.14, H 6.97.

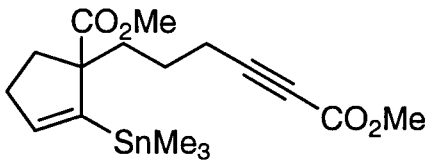
Table 18. ^1H nmr (400 MHz, $CDCl_3$) data for the diester **187**: COSY (200 MHz) and NOED experiments



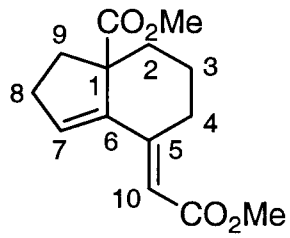
187

Assignment H-x	^1H nmr (400 MHz) δ (multiplicity, *J* (Hz))	COSY Correlation	NOED Correlation
H-2	1.45-1.53 (m)	H-2', H-3, H-3'	
H-2'	2.42 (br dd, *J* = 6.5, 12.5)	H-2, H-3'	
H-3	2.22 (ddd, *J* = 3.8, 8.6, 17.1)	H-2, H-3', H-4	
H-3'	2.78-2.87 (m)	H-2, H-2', H-3, H-4	
H-4	5.64 (dd, 1H, *J* = 3.8, 2.3)	H-3, H-3'	H-3, H-3', H-9
H-7	Part of 3.30-3.46 (m)	H-7', H-8, H-8', H-9	
H-7'	3.51 (dddd, *J* = 1.0, 1.9, 8.0, 19.4)	H-7, H-8, H-8', H-9	
H-8	1.11-1.19 (m)	H-7, H-7', H-8'	
H-8'	2.33 (br dd, *J* = 8.0, 12.3)	H-7, H-7', H-8	
H-9	6.20 (br s)	H-7, H-7'	H-4
-CO_2Me	3.20 (s)		
-CO_2Me	Part of 3.30-3.46 (m)		

Preparation of 1-methoxycarbonyl-(*E*)-5-methoxycarbonylmethylidenebicyclo[4.3.0]non-6-ene (**188**)



180



188

Following general procedure 1 (see pg. 126), the bicyclic diester **188** was prepared by the addition of the diester **180** (122 mg, 0.296 mmol), as a solution in dry DMF (1.5 mL), to a cool (0 °C), stirred solution-suspension of CuCl (75 mg, 0.74 mmol) and glacial acetic acid (85 μL, 1.5 mmol) in dry DMF (1.5 mL). Purification of the crude oil by flash column chromatography (12 g of silica gel, 4:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 73 mg (99 %) of the diester **188** as a colorless clear oil.

IR (neat): 1713 (br), 1626, 1435, 1158 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 1.38-1.54 (m, 2H), 1.75-1.92 (m, 2H), 2.00-2.09 (m, 1H), 2.31-2.45 (m, 4H), 3.62-3.70 (m, 7H, includes two 3H -CO_2Me singlets at 3.63 and 3.68), 5.95 (d, 1H, J = 2.3 Hz), 5.99 (br s, 1H).

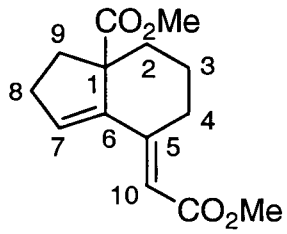
^1H nmr (400 MHz, C_6D_6) δ: 1.12 (td, 1H, J = 4.3, 12.7 Hz), 1.49-1.64 (m, 3H), 1.94-2.01 (ddd, 1H, J = 3.0, 8.8, 16.5 Hz), 2.01-2.12 (m, 1H, H-8), 2.17-2.27 (m, 1H, H-8'), 2.31 (dd, 1H, J = 8, 12.5 Hz), 2.41 (dm, 1H, J = 13.5 Hz), 3.25 (s, 3H, -CO_2Me), 3.41 (s, 3H, -CO_2Me), 4.09 (dm, 1H, J = 13.5 Hz), 5.70 (dd, 1H, H-7, J = 2.4, 2.4 Hz), 6.22 (d, 1H, H-10, J = 2.2 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 23.1, 28.5, 30.5, 36.4, 38.6, 50.8 (-ve), 52.0 (-ve), 58.2, 112.8 (-ve), 130.4 (-ve), 144.1, 151.5, 167.1, 176.3.

HRMS calcd for $C_{14}H_{18}O_4$: 250.1205; found: 250.1213.

Anal calcd for $C_{14}H_{18}O_4$: C 67.18, H 7.25; found: C 67.32, H 7.24.

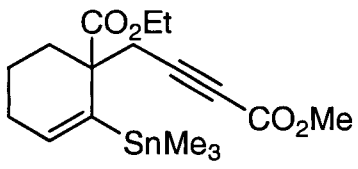
Table 19. ^{1}H nmr (400 MHz, C_6D_6) data for the diester **188**: NOED experiments



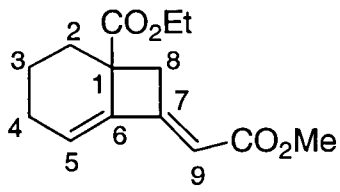
188

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlation
H-7	5.70 (dd, *J* = 2.4, 2.4)	H-8, H-8', H-10
H-10	6.22 (d, *J* = 2.2)	H-7

Preparation of 1-ethoxycarbonyl-(*E*)-7-methoxycarbonylmethylidenebicyclo[4.2.0]oct-5-ene (**189**)



181



189

Following general procedure 1 (see pg. 126), the diene **189** was prepared by the addition of the diester **181** (90 mg, 0.22 mmol), as a solution in dry DMF (1 mL), to a cool (0 °C), stirred solution-suspension of CuCl (57 mg, 0.58 mmol) and glacial acetic acid (60 μL, 1.1 mmol) in dry DMF (1 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 4:1 petroleum ether-Et_2O) and removal of trace

amounts of solvent (vacuum pump) from the acquired material yielded 52 mg (94 %) of the bicyclic compound **189** as a colorless oil.

IR (neat): 1723 (br), 1673, 1436, 1338, 1282, 1203, 1152, 1026 cm^{-1}.

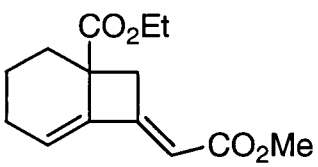
^1H nmr (400 MHz, $CDCl_3$) δ: 1.2-1.4 (m, 4H, includes 3H $-CO_2CH_2C\underline{H}_3$ triplet at 1.23 with J = 7 Hz), 1.50-1.65 (m, 2H), 1.65-1.85 (m, 1H), 2.1-2.35 (m, 2H), 2.39 (dt, 1H, J = 3.4, 12.3 Hz), 2.95 (dd, 1H, H-8, J = 2.6, 16.5 Hz), 3.38 (dd, 1H, H-8', J = 1.9, 16.5 Hz), 3.68 (s, 3H, $-CO_2\underline{Me}$), 4.10-4.20 (m, 2H, $-CO_2C\underline{H}_2CH_3$), 5.80 (s, 1H, olefinic proton), 5.90-6.00 (m, 1H, olefinic proton).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.1 (-ve), 19.5, 24.6, 29.6, 44.1, 51.0 (-ve), 51.3, 66.8, 106.5 (-ve), 123.2 (-ve), 140.8, 159.8, 167.3, 174.5.

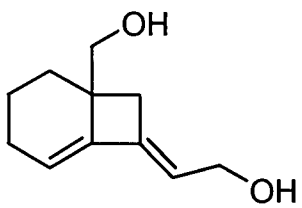
HRMS calcd for $C_{14}H_{18}O_4$: 250.1205; found: 250.1197.

Anal. calcd for $C_{14}H_{18}O_4$: C 67.18, H 7.25; found: C 67.02, H 7.11.

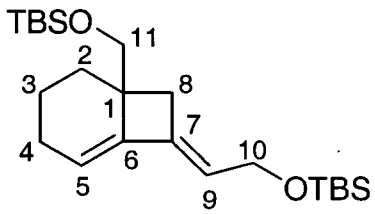
Preparation of 1-(*tert*-butyldimethylsiloxymethyl)-(*E*)-7-(*tert*-butyldimethylsiloxymethyl methylidene)bicyclo[4.2.0]oct-5-ene (**198**)



189



197



198

To a cold (-78 °C), stirred solution of the diester **189** (161 mg, 0.642 mmol) in dry THF (6.5 mL) was added a solution of DIBAL (3.90 mL, 1.0 M in hexanes, 6 equiv) and stirring was continued for 45 min. The solution was warmed to room temperature and stirred for 45 min. Saturated aqueous ammonium chloride (2 mL) was added and the solution was stirred for 30 min. $MgSO_4$ (~100 mg) was added and the white suspension was stirred for an additional 30 min. The mixture was diluted with Et_2O (10 mL). The

mixture was then filtered through Florisil (~10 g) and the cake was eluted with Et_2O (50 mL) and MeOH (25 mL). The combined filtrate was concentrated under reduced pressure. Flash column chromatography (12 g of silica gel, 98:2 Et_2O-MeOH) of the crude product yielded the diol **197** as a clear oil. This material proved to be unstable in previous experiments and the purified material was immediately used in the next step.

The oil thus obtained was dissolved in dry CH_2Cl_2 (5 mL). With stirring, *tert*-butyldimethylsilyl chloride (265 mg, 1.76 mmol) was added in one portion, followed by imidazole (259 mg, 3.80 mmol) in one portion. The white suspension was stirred for 1 h. The solvent was removed under reduced pressure. Flash column chromatography (12 g of silica gel, 98:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 194 mg (74 % over 2 steps) of the disilyl ether **198** as a colorless clear oil.

IR (neat): 1472, 1375, 1255, 1084, 837, 775 cm^{-1}.

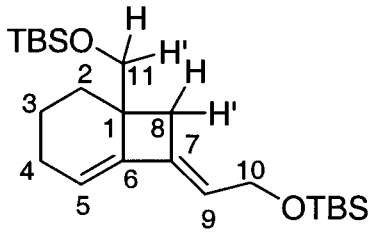
^1H nmr (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H, -Si<u>Me</u>$_2$-), 0.05 (s, 6H, -Si<u>Me</u>$_2$-), 0.87 (s, 9H, -Si^t<u>Bu</u>-), 0.88 (s, 9H, -Si^t<u>Bu</u>-), 1.11 (td, 1H, J = 4.4, 12.4 Hz), 1.55-1.70 (m, 2H), 1.97 (dt, 1H, J = 3.4, 12.4 Hz), 2.05-2.15 (m, 2H), 2.20 (d, 1H, H-8, J = 13 Hz), 2.65 (d, 1H, H-8', J = 13 Hz), 3.50 (dd, 1H, H-11, J = 0.9, 10 Hz), 3.65 (dd, 1H, H-11', J = 1.8, 10 Hz), 4.11 (d, 2H, H-10, J = 6.5 Hz), 5.45-5.55 (m, 1H, H-9). 5.57 (br t, 1H, H-5, J = 3.8 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$) δ: -5.39, -5.34, -5.06, -5.02, 18.5 (2C), 24.3, 26.0 (7C) (-ve), 27.6, 38.8, 46.8, 60.9, 65.7, 116.7 (-ve), 116.9 (-ve), 142.5, 143.2.

HRMS calcd for $C_{23}H_{44}O_2Si_2$: 408.2880; found: 408.2877.

Anal. calcd for $C_{23}H_{44}O_2Si_2$: C 67.58, H 10.85: found: C 67.42, H 10.80.

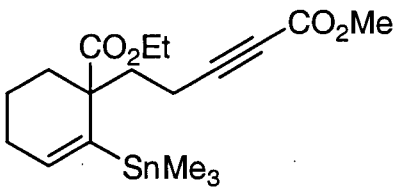
Table 20. ^{1}H nmr (400 MHz, $CDCl_3$) data for the diester **198**: NOED experiments



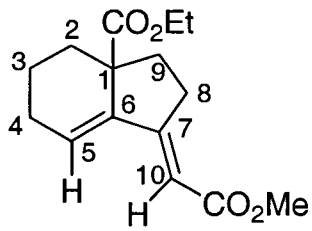
198

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-8	2.20 (d, *J* = 13)	H-8', H-10
H-8'	2.65 (d, *J* = 13)	H-8, H-10, H-11, H-11'
H-10	4.11 (d, *J* = 6.5)	H-8', H-9
H-11	3.50 (dd, *J* = 0.9, 10)	H-8, H-11'
H-11'	3.65 (dd, *J* = 1.8, 10)	H-11

Preparation of 1-ethoxycarbonyl-(*E*)-7-methoxycarbonylmethylidenebicyclo[4.3.0]non-5-ene (**190**)



182



190

Following general procedure 1 (see pg. 126), the bicyclic diester **190** was prepared by the addition of the diester **182** (84 mg, 0.20 mmol), as a solution in dry DMF (1 mL), to a cool (0 °C), stirred solution-suspension of CuCl (51 mg, 0.52 mmol) and glacial acetic acid (56 μL, 0.98 mmol) in dry DMF (1 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 4:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 51 mg (98 %) of

the diene **190** as a white solid (mp 55-57 °C).

IR (KBr): 1718 (br), 1631, 1435, 1159, 733 cm^{-1}.

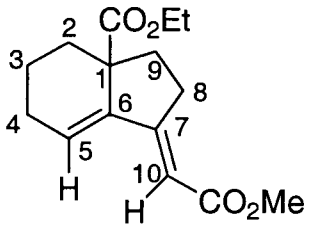
^1H nmr (400 MHz, $CDCl_3$) δ: 1.14-1.23 (m, 4H, H-2 and 3H $-CO_2CH_2C\underline{H}_3$ triplet at 1.18 with J = 7.2 Hz), 1.41-1.54 (m, 2H, H-3 and H-9), 1.70-1.80 (m, 1H, H-3'), 2.10-2.30 (m, 2H, H-4 and H-4'), 2.35 (dd, 1H, H-9', J = 8.1, 12.8 Hz), 2.48 (dt, 1H, H-2', J = 3.3, 12.8 Hz), 2.58-2.69 (m, 1H, H-8), 3.08 (ddd, 1H, H-8', J = 1.5, 8.5, 19.4 Hz), 3.68 (s, 3H, $-CO_2\underline{Me}$), 4.03-4.15 (m, 2H, $-CO_2C\underline{H}_2CH_3$), 6.08 (br s, 1H, H-10), 6.32 (dd, 1H, H-5, J = 3.9, 3.9 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.1 (-ve), 19.4, 25.3, 30.2, 32.2, 36.6, 50.9 (-ve), 52.9, 60.8, 106.9 (-ve), 125.5, 141.6, 160.5, 167.7, 175.4.

HRMS calcd for $C_{15}H_{20}O_4$: 264.1362; found: 264.1362.

Anal. calcd for $C_{15}H_{20}O_4$: C 68.16, H 7.63; found: C 67.86, H 7.68.

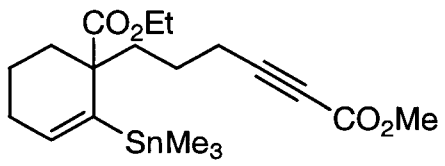
Table 21. ^{1}H nmr (400 MHz, $CDCl_3$) data for the diester **190**: COSY and NOED experiments



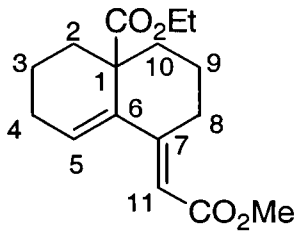
190

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	COSY Correlations	NOED Correlations
H-2	Part of 1.14-1.23 (m)	H-2', H-3, H-3'	
H-2'	2.48 (dt, *J* = 3.3, 12.8)	H-2, H-3'	
H-3	Part of 1.41-1.54 (m, 2H)	H-2, H-2', H-3', H-4, H-4'	
H-3'	1.70-1.80 (m)	H-2, H-2', H-3, H-4, H-4'	
H-4	Part of 2.10-2.30 (m, 2H)	H-3, H-3', H-5	
H-4'	Part of 2.10-2.30 (m, 2H)	H-3, H-5	
H-5	6.32 (dd, *J* = 3.9, 3.9)	H-4, H-4'	H-4, H-4', H-10
H-8	2.58-2.69 (m)	H-8', H-9, H-9'	
H-8'	3.08 (ddd, *J* = 1.5, 8.1, 19.4)	H-8, H-9, H-9'	
H-9	Part of 1.41-1.54 (m, 2H)	H-8, H-8'	
H-9'	2.35 (dd, *J* = 8.1, 12.8)	H-8, H-8'	
H-10	6.08 (br s)		H-5
-CO_2Me	3.68 (s)		
-$CO_2CH_2CH_3$	4.03-4.15 (m)	-$CO_2CH_2CH_3$	
-$CO_2CH_2CH_3$	Part of 1.14-1.23 (m, *J* = 7.2)	-$CO_2CH_2CH_3$	

Preparation of 1-ethoxycarbonyl-(*E*)-7-methoxycarbonylmethylidenebicyclo[4.4.0] non-5-ene (**191**)



183



191

Following general procedure 1 (see pg. 126), the bicyclic diester **191** was prepared by the addition of the diester **183** (124 mg, 0.281 mmol), as a solution in dry DMF (1.4 mL), to a cool (0 °C), stirred solution-suspension of CuCl (73 mg, 0.74 mmol) and glacial acetic acid (81 μL, 1.4 mmol) in dry DMF (1.4 mL). In this case, the reaction required 1 h to go to completion. Purification of the crude product by flash column chromatography (12 g of silica gel, 17:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 72 mg (92 %) of the bicyclic compound **191** as a colorless clear oil.

IR (neat): 1718 (br), 1619, 1450, 1159 cm^{-1}.

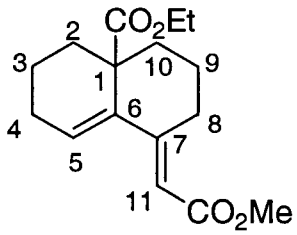
^1H nmr (400 MHz, $CDCl_3$) δ: 1.17 (t, 3H, $-CO_2CH_2C\underline{H}_3$, J = 7.3 Hz), 1.33-1.44 (m, 3H), 1.58-1.64 (m, 1H), 1.69-1.74 (m, 1H), 1.91-2.00 (m, 1H), 2.08-2.11 (m, 3H), 2.14-2.18 (dd, 1H, J = 4.5, 10.2 Hz), 2.24-2.28 (m, 1H), 3.64 (s, 3H, $-CO_2\underline{Me}$), 3.79 (dm, 1H, J = 16.4 Hz), 4.01-4.15 (m, 2H, $-CO_2C\underline{H}_2CH_3$), 5.80 (d, 1H, H-11, J = 2.5 Hz), 5.91 (dd, 1H, H-5, J = 3.8, 3.8 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.2 (-ve), 19.0, 22.3, 26.2, 29.3, 35.4, 37.2, 49.2, 50.8 (-ve), 60.7, 113.3 (-ve), 127.5 (-ve), 140.1, 160.8, 167.5, 175.7.

HRMS calcd for $C_{16}H_{22}O_4$: 278.1518; found: 278.1522.

Anal. calcd for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 69.17, H 7.97.

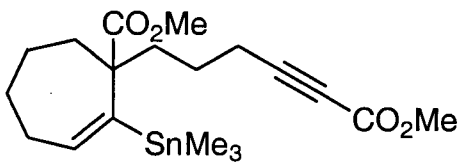
Table 22. ^{1}H nmr (400 MHz, $CDCl_3$) data for the diester **191**: selected COSY and NOED experiments



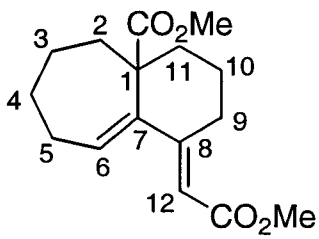
191

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	COSY Correlations	NOED Correlations
H-5	5.91 (dd, *J* = 3.8, 3.8)	Part of m at 2.08-2.11	H-11, Part of m at 2.08-2.11
H-11	5.80 (d, *J* = 2.5)	1.91-2.00 (m, H-8)	H-5

Preparation of 1-methoxycarbonyl-(*E*)-8-methoxycarbonylmethylidenebicyclo[5.4.0] undec-6-ene (**192**)



184



192

Following general procedure 1 (see pg. 126), the bicyclic diester **192** was prepared by the addition of the diester **184** (68 mg, 0.15 mmol), as a solution in dry DMF (0.75 mL), to a cool (0 °C), stirred solution-suspension of CuCl (42 mg, 0.30 mmol) and glacial acetic acid (44 μL, 0.77 mmol) in dry DMF (0.75 mL). Purification of the crude product by flash column chromatography (10 g of silica gel, 4:1 petroleum ether-Et_2O) and removal

of trace amounts of solvent (vacuum pump) from the acquired material yielded 40 mg (94 %) of the diester **192** as a colorless, viscous oil.

IR (neat): 1718 (br), 1610, 1434, 1158 cm^{-1}.

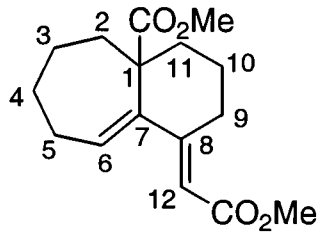
^1H nmr (400 MHz, $CDCl_3$) δ: 1.35-1.75 (m, 7H), 1.84-1.93 (m, 2H), 2.01 (dm, 1H, J = 13.1 Hz), 2.05-2.14 (m, 1H, H-5), 2.18-2.34 (m, 2H, H-5' and one of H-9), 3.45 (dm, 1H, J = 15.2 Hz), 3.65 (s, 3H, -CO_2Me), 3.66 (s, 3H, -CO_2Me), 5.82 (br s, 1H, H-12), 6.05 (dd, 1H, H-6, J = 5.4, 7.2 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 21.8, 25.1, 25.2, 26.9, 28.4, 37.2, 38.7, 50.8 (-ve), 51.8 (-ve), 54.0, 114.5 (-ve), 132.7 (-ve), 144.4, 163.0, 167.4, 175.7.

HRMS calcd for $C_{16}H_{22}O_4$: 278.1518; found: 278.1521.

Anal calcd for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.86, H 7.87.

Table 23. ^1H nmr (400 MHz, $CDCl_3$) data for the diester **192**: selected COSY and NOED experiments



192

Assignment H-x	^1H nmr (400 MHz) δ (multiplicity, J (Hz))	COSY Correlations	NOED Correlations
H-6	6.05 (dd, J = 5.4, 7.2)	2.05-2.14 (m, H-5), upfield part of 2.18-2.34 (m, H-5')	H-12, 2.05-2.14 (m, H-5), upfield part of 2.18-2.34 (m, H-5')
H-12	5.82 (br s)	downfield part of 2.18-2.34 (m)	H-6

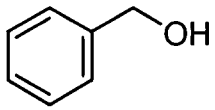
4. Copper(I) mediated intramolecular conjugate additions of aromatic stannanes to α,β-alkynic ester functions

4.1 Preparation of precursors

General Procedure 4: Preparation of 2-trimethylstannylbenzyl alcohol derivatives

To a cold (-78 °C), stirred solution of *n*-BuLi (2.5 equiv) in dry Et_2O (~10 mL/mmol of alcohol) was added TMEDA (2.5 equiv) via a syringe and stirring was continued for 5 min. The appropriately substituted benzyl alcohol (1 equiv) was added neat via a syringe and the solution was warmed to room temperature. After 3 h, the solution turned a dark red color. The solution was cooled to -78 °C and trimethyltin chloride (~1.5 equiv) was added in one solid portion. The reaction mixture was warmed to room temperature and stirred for 2 h whereupon the solution became turbid. Water was added (~10 mL/mmol of alcohol) and the mixture was extracted with Et_2O (3 x ~10 mL/mmol of alcohol). The combined organic extracts were washed with brine (~20 mL/mmol of alcohol), dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude material was accomplished by flash column chromatography on silica gel.

Preparation of 2-trimethylstannylbenzyl alcohol (**199**)



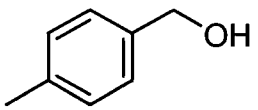
205

199

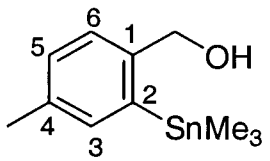
Following general procedure 4, the stannane **199** was prepared with the following amounts of solvent and reagents: *n*-BuLi (30.1 mL, 1.6 M in hexanes, 48 mmol), TMEDA (7.39 mL, 50.0 mmol), Et_2O (200 mL), benzyl alcohol (**205**) (2.11 mL, 20.0 mmol), and trimethyltin chloride (6.00 g, 30.2 mmol). Flash column chromatography (200 g of silica gel, 4:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded

3.50 g (64 %) of the alcohol **199** as a colorless oil. This oil exhibited spectral properties (^{1}H nmr) identical with those previously reported.[50]

Preparation of 4-methyl-2-trimethylstannylbenzyl alcohol (**200**)



206



200

Following general procedure 4, the stannane **200** was prepared with the following amounts of solvent and reagents: *n*-BuLi (45.0 mL, 1.6 M in hexanes, 74 mmol), TMEDA (11.0 mL, 72.9 mmol), Et_2O (250 mL), 4-methylbenzyl alcohol (**206**) (3.60 g, 29.5 mmol), and trimethyltin chloride (9.11 g, 45.7 mmol). Flash column chromatography (250 g of silica gel, 7:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 5.08 g (60 %) of the alcohol **200** as a colorless solid (mp 48-49 °C).

IR (KBr): 3379, 2357, 1471, 1012, 818, 764 cm^{-1}.

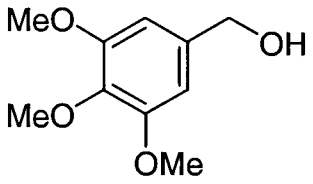
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.30 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.5 Hz), 1.65 (br s, 1H, -OH, exchanges with D_2O), 2.34 (s, 3H, -<u>Me</u>), 4.62 (d, 2H, -C<u>H</u>$_2$-OH, J = 5.6 Hz), 7.11 (d, 1H, J = 7 Hz), 7.20 (d, 1H, J = 7 Hz), 7.33 (s, 1H, H-3, $^3J_{Sn\text{-}H}$ = 50.4 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.0 (-ve), 21.1 (-ve), 67.0, 127.2 (-ve), 129.1 (-ve), 136.6, 137.3 (-ve), 141.3, 144.1.

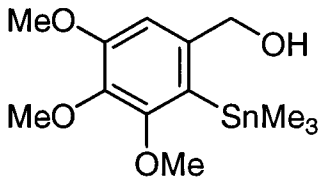
HRMS calcd for $C_{10}H_{15}O^{120}Sn$ (M^+-Me): 271.0145; found: 271.0138.

Anal. calcd for $C_{11}H_{18}OSn$: C 46.37, H 6.37; found: C 46.59; H 6.55.

Preparation of 3,4,5-trimethoxy-2-trimethylstannylbenzyl alcohol (**201**)



207



201

Following general procedure 4, the stannane **201** was prepared with the following amounts of solvent and reagents: *n*-BuLi (8.0 mL, 1.6 mol/L, 12.8 mmol), TMEDA (1.85 mL, 12.5 mmol), Et_2O (250 mL), 3,4,5-trimethoxybenzyl alcohol (**207**) (0.81 mL, 5.0 mmol), and trimethyltin chloride (1.55 g, 7.82 mmol). Flash column chromatography (250 g of silica gel, 7:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 986 mg (54 %) of the alcohol **201** as a colorless viscous oil.

IR (neat): 3432, 1583, 1478, 1316, 1015, 774, 525 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.30 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.5 Hz), 1.53 (br t, 1H, -OH, exchanges with D_2O, J = 5.7 Hz), 3.81 (s, 3H, -O<u>Me</u>), 3.84 (s, 3H, -O<u>Me</u>), 3.85 (s, 3H, -O<u>Me</u>), 4.54 (d, 2H, -C<u>H</u>$_2$-OH, J = 5.7 Hz), 6.78 (s, 1H, aromatic proton, $^4J_{Sn\text{-}H}$ = 15.6 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -6.3 (-ve), 55.9 (-ve), 60.5 (-ve), 60.8 (-ve), 66.4, 107.8, 125.2 (-ve), 140.1, 143.2, 154.2, 157.9.

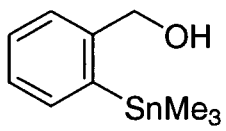
HRMS calcd for $C_{12}H_{19}O_4{}^{120}Sn$ (M^+-Me): 347.0306; found: 347.0313.

Anal. calcd for $C_{13}H_{22}O_4Sn$: C 43.25, H 6.14; found: C 43.64, H 5.93.

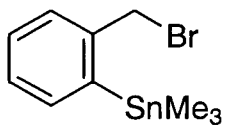
General Procedure 5: Conversion of benzyl alcohol derivatives into benzyl bromides

To a cool (0 °C), stirred solution of triphenylphosphine (~1.3 equiv) in dry CH_2Cl_2 (10 mL/mmol of alcohol) was added bromine (~1.3 equiv) dropwise until a yellow color persisted. A few crystals of triphenylphosphine were added until the color disappeared. The solution was stirred for a period of 20 min. Imidazole was added (~1.4 equiv) to the mixture in one solid portion and stirring was continued for 20 minutes. The appropriate alcohol (1 equiv) was added as a solution in CH_2Cl_2 and the solution was stirred at 0 °C for 20 min and at room temperature for 1 h. Pentane (~1 mL/mL of CH_2Cl_2) was added and the white suspension was filtered through a cake of silica gel (~10 g/g of triphenylphosphine) and the silica gel was eluted with Et_2O (~2 mL/mL of CH_2Cl_2). After concentration of the combined filtrate under reduced pressure, the crude product was purified by flash column chromatography on silica gel.

Preparation of 2-trimethylstannylbenzyl bromide (**202**)



199



202

Following general procedure 5, the benzyl bromide **202** was prepared with the following amounts of solvent and reagents: triphenylphosphine (3.41 g, 13.0 mmol), bromine (~0.7 mL), imidazole (963 mg, 14.1 mmol), CH_2Cl_2 (100 mL), and 2-trimethyl stannylbenzyl alcohol (**199**) (2.66 g, 9.85 mmol). The crude product was purified by flash column chromatography (75 g of silica gel, 193:7 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 2.88 g (88 %) of the bromide **202** as a colorless clear oil.

IR (neat): 1471, 1220, 764, 609, 529 cm^{-1}.

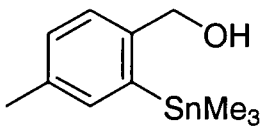
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.39 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.8 Hz), 4.51 (s, 2H, -C<u>H</u>$_2$-Br, J = 5.7 Hz), 7.24 (dt, 1H, J = 1.2, 7.4 Hz), 7.30 (dt, 1H, J = 1.5, 7.5 Hz), 7.38-7.54 (m, 2H).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -7.8, 36.9, 127.8, 129.0, 129.9, 136.8, 143.5, 144.5.

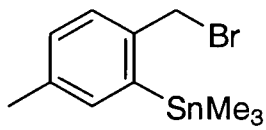
HRMS calcd for $C_9H_{12}{}^{79}Br^{120}Sn$ (M^+-Me): 318.9144; found: 318.9144.

Anal. calcd for $C_{10}H_{15}BrSn$: C 35.98, H 4.53; found: C 36.28, H 4.49.

<u>Preparation of 4-methyl-2-trimethylstannylbenzyl bromide (**203**)[76]</u>



200



203

Following general procedure 5, the benzyl bromide **203** was prepared with the following amounts of solvent and reagents: triphenylphosphine (5.06 g, 19.3 mmol), bromine (~1 mL), imidazole (1.4 g, 21 mmol), CH_2Cl_2 (70 mL), and 4-methyl-2-trimethylstannylbenzyl alcohol (**200**) (2.20 g, 7.72 mmol). The crude product was purified by flash column chromatography (75 g of silica gel, 193:7 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 2.19 g (87 %) of the bromide **203** as a colorless clear oil.

IR (neat): 1594, 1443, 1480, 1210 cm^{-1}.

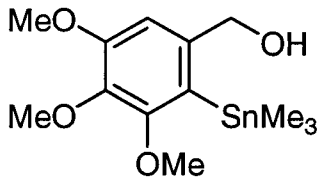
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.32 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 50.0 Hz), 2.31 (s, 3H, -<u>Me</u>), 4.50 (s, 2H, -C<u>H</u>$_2$-Br), 7.05-7.10 (m, 1H), 7.20-7.45 (m, 2H).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -7.9, 21.2, 37.0, 128.9, 129.7 (2C), 137.5, 141.5, 143.2.

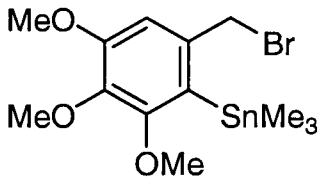
HRMS calcd for $C_{10}H_{14}{}^{79}Br^{120}Sn$ (M^+-Me): 322.9301; found: 322.9301.

Anal. calcd for $C_{11}H_{17}BrSn$: C 37.98, H 4.93; found: C 38.13, H 4.89.

Preparation of 3,4,5-trimethoxy-2-trimethylstannylbenzyl bromide (**204**)



201



204

Following general procedure 5, the benzyl bromide **204** was prepared with the following amounts of solvents and reagents: triphenylphosphine (928 mg, 3.54 mmol), bromine (~0.2 mL), imidazole (252 mg, 3.70 mmol), CH_2Cl_2 (28 mL), and the stannane **201** (986 mg, 2.74 mmol). The crude product was purified by flash column chromatography (30 g of silica gel, 22:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 754 mg (65 %) of the bromide **204** as a colorless clear oil. [**Note**: Perform all procedures in the fumehood as this oil is extremely volatile.]

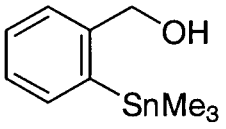
IR (neat): 1581, 1481, 1323, 1099, 773 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.36 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.8 Hz), 3.82 (s, 3H, -O<u>Me</u>), 3.84 (s, 3H, -O<u>Me</u>), 3.86 (s, 3H, -O<u>Me</u>), 4.46 (s, 2H, -C<u>H</u>$_2$-Br), 6.72 (s, 1H, aromatic proton, $^4J_{Sn\text{-}H}$ = 16.1 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -6.2 (-ve), 37.1, 56.0 (-ve), 60.5 (-ve), 60.8 (-ve), 109.9 (-ve), 128.0, 139.7, 140.8, 154.2, 157.6.

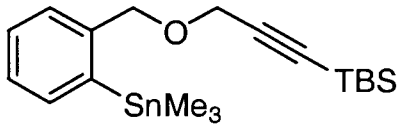
HRMS calcd for $C_{12}H_{18}{}^{79}Br^{120}Sn$ (M^+-Me): 408.9461; found: 408.9467.

Preparation of 1-(*tert*-butyldimethylsilyl)-4-oxa-5-(2-trimethylstannylphenyl)pent-1-yne (**209**)



199

160



209

To a cool (0 °C), stirred suspension of sodium hydride (30 mg, 1.3 mmol, washed with pentane) in dry DMF (6 mL) was added 2-trimethylstannylbenzyl alcohol (**199**) (252 mg, 0.933 mmol) as a solution in dry DMF (2 mL) via a cannula. The reaction mixture was stirred for 30 min. The bromide **160** (519 mg, 2.23 mmol) was added as a neat liquid via a syringe and the mixture was stirred at 0 °C for 30 min and at room temperature for 18 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (15 g of silica gel, 94:6 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent from the acquired material yielded 369 mg (94 %) of the ether **209** as a colorless clear oil.

IR (neat): 2174, 1471, 1251, 1088, 826, 776 cm^{-1}.

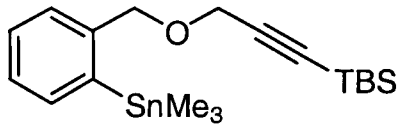
^1H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 6H, -Si$\underline{Me_2}$-), 0.28 (s, 9H, -Sn$\underline{Me_3}$, $^2J_{Sn\text{-}H}$ = 53.5 Hz), 0.94 (s, 9H, -Si$^t\underline{Bu}$-), 4.14 (s, 2H, -C$\underline{H_2}$-), 4.59 (s, 2H, -C$\underline{H_2}$-), 7.20-7.30 (m, 3H), 7.50 (dm, 1H, aromatic proton α to -$SnMe_3$, J = 6.1 Hz, $^3J_{Sn\text{-}H}$ = 50.4 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.0, -4.6, 16.5, 26.1, 57.8, 73.1, 90.2, 101.8, 127.3, 128.21, 128.25, 136.6, 141.8, 143.9.

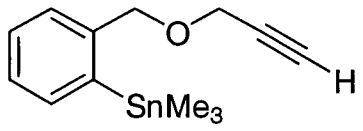
HRMS calcd for $C_{18}H_{29}OSi^{120}Sn$ (M^+-Me): 409.1010; found: 409.1005.

Anal. calcd for $C_{19}H_{32}OSiSn$: C 53.92, H 7.62; found: C 54.22, H 7.45.

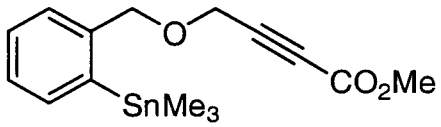
Preparation of methyl 5-oxa-6-(2-trimethylstannylphenyl)hex-1-ynoate (**211**)



209



210



211

To a stirred solution of the stannane **209** (353 mg, 0.800 mmol) in dry THF (10 mL) at room temperature was added a solution of tetrabutylammonium fluoride (1.25 mL, 1 M in THF, 1.25 mmol) and stirring was continued for 1 h. Saturated aqueous sodium bicarbonate was added (15 mL) and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (20 g of silica gel, 99:1 petroleum ether-Et_2O) of the crude product yielded 243 mg (99 %) of the compound **210** a clear oil. [**Note:** This oil exhibited an **extremely** noxious odour and was immediately used in the next step.]

To a cold (-78 °C), stirred solution of LDA (1.02 mmol) in dry THF (5 mL) was added DMPU (123 μL, 1.02 mmol) and stirring was continued for 5 min. A solution of the stannane **210** (obtained as described above) in dry THF (2 mL) was added via a cannula and the reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (91 μL, 1.2 mmol) was added via a syringe and stirring was continued for 1 h at -78 °C and for 1 h at room temperature. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. Flash column chromatography (30 g of silica gel, 95:5 petroleum ether-Et_2O) and removal of trace amounts of solvent from the acquired liquid (vacuum pump) yielded 268 mg (90 % over 2 steps) of the alkynic ester **211** as a colorless clear oil.

IR (neat): 2239, 1718, 1435, 1251, 1094, 751 cm^{-1}.

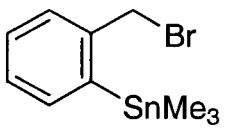
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.28 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.8 Hz), 3.78 (s, 3H, -CO_2<u>Me</u>), 4.23 (s, 2H, -C<u>H</u>$_2$-), 4.59 (s, 2H, -C<u>H</u>$_2$-), 7.25-7.32 (m, 3H), 7.51 (dm, 1H, aromatic proton α to -$SnMe_3$, J = 5.3 Hz, $^3J_{Sn\text{-}H}$ = 48.9 Hz).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: -8.1 (-ve), 52.7 (-ve), 56.5, 73.8, 78.2, 83.2, 127.5 (-ve), 128.3 (-ve), 128.5 (-ve), 136.6 (-ve), 142.2, 143.0, 153.4.

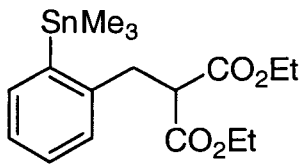
HRMS calcd for $C_{14}H_{17}O_3{}^{120}Sn$ (M^+-Me): 353.0200; found: 353.0194.

Anal. calcd for $C_{15}H_{20}O_3Sn$: C 49.09, H 5.49; found: C 49.14, H 5.45.

<u>Preparation of diethyl 2-(2-trimethylstannylbenzyl)malonate (**212**)</u>



202



212

To a stirred suspension of potassium hydride (543 mg, 13.5 mmol, washed with pentane) in dry THF (130 mL) at room temperature was added diethyl malonate (2.3 mL, 15 mmol) via a syringe. Evolution of hydrogen gas was observed and the reaction mixture was stirred for 1 h. A solution of the bromide **199** (1.47 g, 4.39 mmol) in dry THF (10 mL) was added and the mixture was warmed to reflux for 1.5 h. The reaction mixture was cooled to room temperature and water (50 mL) was added. The mixture was then extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (100 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.74 g (96 %) of the stannane **212** as a colorless clear oil.

IR (neat): 1731, 1200, 1036, 770 cm^{-1}.

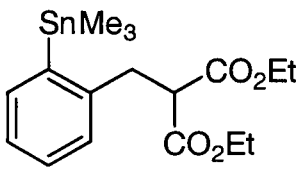
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.34 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.2 Hz), 1.11 (t, 6H, -$CO_2CH_2C\underline{H}_3$, J = 7.2 Hz), 3.25 (d, 2H, -C<u>H</u>$_2$-CH-, J = 7.8 Hz), 3.60 (t, 1H, -CH_2-C<u>H</u>-, J = 7.8 Hz), 4.10-4.20 (m, 4H, -$CO_2C\underline{H}_2CH_3$), 7.12-7.25 (m, 3H), 7.40 (m, 1H, aromatic proton α to -$SnMe_3$, $^3J_{Sn\text{-}H}$ = 49.8 Hz).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: -8.3 (-ve), 13.8 (-ve), 37.1, 53.6 (-ve), 61.2, 126.1 (-ve), 128.1 (-ve), 128.4 (-ve), 136.4 (-ve), 142.3, 144.4, 168.5.

HRMS calcd for $C_{16}H_{23}O_4{}^{120}Sn$ (M^+-Me): 399.0618; found: 399.0624.

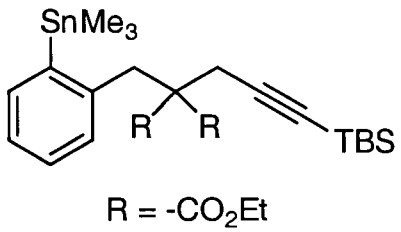
Anal. calcd for $C_{17}H_{26}O_4Sn$: C 49.43, H 6.34; found: C 49.78, H 6.38.

<u>Preparation of 1-(*tert*-butyldimethylsilyl)-4,4-bis(ethoxycarbonyl)-5-(2-trimethylstannyl phenyl)pent-1-yne (**213**)</u>



212

160



213

To a stirred suspension of potassium hydride (100 mg, 2.50 mmol, washed with pentane) in dry THF (12 mL) at room temperature was added a solution of the diester **212** (721 mg, 1.75 mmol) in dry THF (1 mL). The reaction mixture was stirred for 1 h. The bromide **160** (775 mg, 3.33 mmol) was added neat via a syringe and the mixture was warmed to reflux for 1.5 h. The reaction mixture was cooled to room temperature and water (20 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (40 g of silica gel, 96:4 petroleum ether-Et_2O) of the crude product and removal of trace amounts

of solvent (vacuum pump) from the acquired material yielded 986 mg (98 %) of the stannane **213** as a colorless clear oil.

IR (neat): 2179, 1752, 1584, 1201, 1030, 775 cm^{-1}.

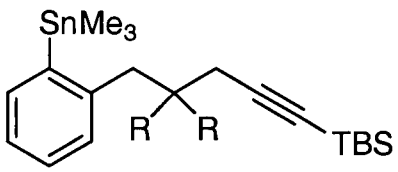
^1H nmr (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H, -Si<u>Me</u>$_2$-), 0.34 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 55.4 Hz), 0.90 (s, 9H, -Si<u>^{t}Bu</u>-), 1.11 (t, 6H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 2.95 (s, 2H, -C<u>H</u>$_2$-), 3.49 (s, 2H, -C<u>H</u>$_2$-), 4.00-4.12 (m, 4H, -$CO_2C\underline{H}_2CH_3$), 7.13-7.26 (m, 3H), 7.34 (d, 1H, aromatic proton α to -$SnMe_3$, J = 7.0 Hz, $^3J_{Sn\text{-}H}$ = 48.5 Hz).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: -7.2 (-ve), -4.6 (-ve), 13.8 (-ve), 16.4, 25.3, 26.0 (-ve), 40.3, 58.5, 61.4, 86.5, 102.3, 126.2 (-ve), 128.0 (-ve), 128.4 (-ve), 136.6 (-ve), 142.9, 144.9, 169.8.

HRMS calcd for $C_{25}H_{39}O_4Si^{120}Sn$ (M^+-Me): 551.1639; found: 551.1640.

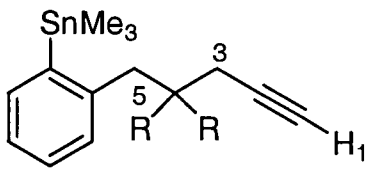
Anal. calcd for $C_{26}H_{42}O_4SiSn$: C 55.23, H 7.49; found: C 55.58, H 7.40.

<u>Preparation of 4,4-bis(ethoxycarbonyl)-5-(2-trimethylstannylphenyl)pent-1-yne (**214**)</u>



R = -CO_2Et

213



R = -CO_2Et

214

To a stirred solution of the stannane **213** (511 mg, 0.923 mmol) in dry THF (10 mL) at room temperature was added a solution of tetrabutylammonium fluoride (1.40 mL, 1 M in THF, 1.40 mmol) and stirring was continued for 1 h. Saturated aqueous sodium bicarbonate was added (15 mL) and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the

solvent was removed under reduced pressure. Flash column chromatography (20 g of silica gel, 95:5 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 398 mg (98 %) of the alkyne **214** as a clear oil.

IR (neat): 3290, 1736, 1440, 1192, 774 cm^{-1}.

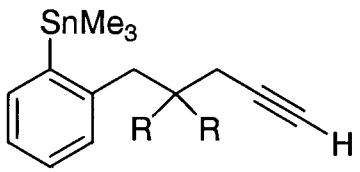
^1H nmr (400 MHz, $CDCl_3$) δ: 0.34 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.4 Hz), 1.17 (t, 6H, -CO_2CH_2C<u>H_3</u>, J = 7.2 Hz), 2.00 (t, 1H, H-1, J = 2.7 Hz), 2.84 (d, 2H, H-3, J = 2.7 Hz), 3.51 (s, 2H, H-5), 4.00-4.21 (m, 4H, -CO_2<u>CH_2</u>CH_3), 7.10-7.21 (m, 3H), 7.38 (dm, 1H, aromatic proton α to -$SnMe_3$, J = 6.6 Hz, $^3J_{Sn\text{-}H}$ = 48.0 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -7.2, 13.9, 23.3, 40.2, 57.9, 61.7, 71.7, 79.4, 126.3, 127.8, 128.2, 136.8, 142.6, 145.0, 170.1.

HRMS calcd for $C_{19}H_{25}O_4{}^{120}Sn$ (M^+-Me): 437.0775; found: 437.0778.

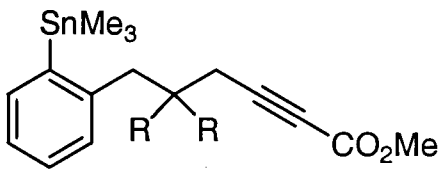
Anal. calcd for $C_{20}H_{28}O_4Sn$: C 53.25, H 6.26; found: C 53.11, H 6.13.

<u>Preparation of methyl 5,5-bis(ethoxycarbonyl)-6-(2-trimethylstannylphenyl)hex-2-ynoate (**215**)</u>



R = -CO_2Et

214



R = -CO_2Et

215

To a cold (-78 °C), stirred solution of LDA (1.15 mmol) in dry THF (6 mL) was added DMPU (139 μL, 1.15 mmol) and stirring was continued for 5 min. A solution of the acetylene **214** (398 mg, 0.843 mmol) in dry THF (2 mL) was added via a cannula and the

reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (103 μL, 1.33 mmol) was added via a syringe. The mixture was stirred for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (30 g of silica gel, 85:15 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 357 mg (80 %) of the alkynic triester **215** as a colorless clear oil.

IR (neat): 2242, 1719 (br), 1438, 1259, 1079, 770 cm^{-1}.

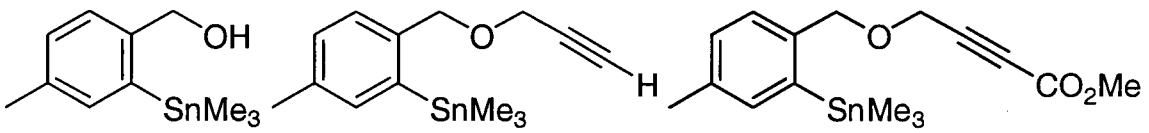
^1H nmr (400 MHz, $CDCl_3$) δ: 0.34 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.3 Hz), 1.19 (t, 6H, -CO_2CH_2C<u>H</u>$_3$, J = 7.3 Hz), 2.93 (s, 2H, -C<u>H</u>$_2$-), 3.49 (s, 2H, -C<u>H</u>$_2$-), 3.71 (s, 3H, -CO_2<u>Me</u>), 4.10-4.25 (m, 4H, -CO_2C<u>H</u>$_2CH_3$), 7.05-7.11 (m, 1H), 7.15-7.21 (m, 2H), 7.39 (dm, 1H, aromatic proton α to -$SnMe_3$, J = 6.3 Hz, $^3J_{Sn-H}$ = 47.4 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -7.4 (-ve), 13.8 (-ve), 23.5, 40.6, 52.5 (-ve), 57.6, 62.0, 75.3, 84.2, 126.4 (-ve), 127.7 (-ve), 128.3 (-ve), 136.8 (-ve), 141.9, 144.9, 153.5, 169.5.

HRMS calcd for $C_{21}H_{27}O_6{}^{120}Sn$ (M^+-Me): 495.0830; found: 495.0831.

Anal. calcd for $C_{22}H_{30}O_6Sn$: C 51.90, H 5.94; found: C 52.11, H 5.84.

Preparation of methyl 5-oxa-6-(4-methyl-2-trimethylstannylphenyl)hex-2-ynoate (**217**)



200 **216** **217**

To a cool (0 °C), stirred suspension of sodium hydride (46 mg, 1.9 mmol, washed with pentane) in dry DMF (8 mL) was added 2-trimethylstannylbenzyl alcohol (**200**) (467 mg, 1.63 mmol) as a solution in dry DMF (2 mL) via a cannula. The reaction mixture was stirred for 30 min. A solution of propargyl bromide (484 mg, 80 wt % in toluene, 3.26 mmol) was added via a syringe and the mixture was stirred at 0 °C for 30 min and at room temperature for 18 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (25 g of silica gel, 200:3 petroleum ether-Et_2O) of the crude oil yielded 529 mg of the alkyne **216** as a colorless clear oil. [**Note:** This oil exhibited an **extremely** noxious odour and was immediately used in the next step.]

To a cold (-78 °C), stirred solution of LDA (2.27 mmol) in dry THF (16 mL) was added DMPU (258 μL, 2.13 mmol) and stirring was continued for 5 min. A solution of the stannane **216** (obtained as described above) in dry THF (2 mL) was added via a cannula and the reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (211 μL, 2.72 mmol) was added via a syringe and stirring was continued for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. Flash column chromatography (30 g of silica gel, 92:8 petroleum ether-Et_2O) and removal of trace amounts of solvent from the acquired liquid (vacuum pump) yielded 542 mg (87 % over 2 steps) of the alkynic ester **217** as a colorless clear oil.

IR (neat): 2238, 1719, 1435, 1251, 1060, 751 cm^{-1}.

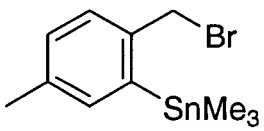
^1H nmr (400 MHz, $CDCl_3$) δ: 0.27 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.6 Hz), 2.31 (s, 3H, -<u>Me</u>), 3.78 (s, 3H, -CO_2<u>Me</u>), 4.20 (s, 2H, -C<u>H</u>$_2$-), 4.56 (s, 2H, -C<u>H</u>$_2$-), 7.09 (dd, 1H, J = 1.2, 7.6 Hz), 7.15-7.21 (m, 1H), 7.31 (br s, 1H, aromatic proton α to -$SnMe_3$, $^3J_{Sn-H}$ = 23.9 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.0 (-ve), 21.2 (-ve), 52.7 (-ve), 56.3, 73.6, 78.1, 83.4, 128.7 (-ve), 129.0 (-ve), 137.1, 137.5 (-ve), 140.0, 142.1, 152.8.

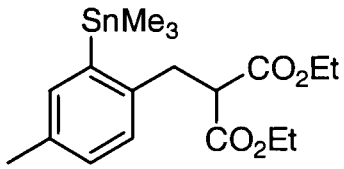
HRMS calcd for $C_{15}H_{19}O_3{}^{120}Sn$ (M^+-Me): 367.0356; found: 367.0352.

Anal. calcd for $C_{16}H_{22}O_3Sn$: C 50.43, H 5.82; found: C 50.61, H 5.75.

<u>Preparation of diethyl 2-(4-methyl-2-trimethylstannylbenzyl)malonate (**218**)</u>



203



218

To a stirred suspension of potassium hydride (144 mg, 3.60 mmol, washed with pentane) in dry THF (35 mL) at room temperature was added diethyl malonate (575 μL, 3.80 mmol) via a syringe. Evolution of hydrogen gas was observed and the reaction mixture was stirred for 1 h. The bromide **203** (391 mg, 1.13 mmol) was added neat via a syringe and the mixture was warmed to reflux for 1.5 h. The reaction mixture was cooled to room temperature and water (15 mL) was added. The mixture was then extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography (30 g of silica gel, 91:9 petroleum

ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 415 mg (86 %) of the diester **218** as a colorless oil.

IR (neat): 1735, 1152, 858, 771 cm^{-1}.

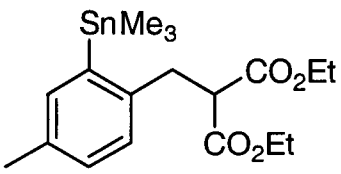
^1H nmr (400 MHz, $CDCl_3$) δ: 0.32 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.0 Hz), 1.20 (t, 6H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 2.27 (s, 3H, -<u>Me</u>), 3.21 (d, 2H, -$C\underline{H}_2$-CH-, J = 7.8 Hz), 3.57 (t, 1H, -CH_2-C<u>H</u>-, J = 7.8 Hz), 4.11-4.21 (m, 4H, -$CO_2C\underline{H}_2CH_3$), 7.01-7.10 (m, 2H), 7.21 (br s, 1H, aromatic proton α to -$SnMe_3$, $^3J_{Sn\text{-}H}$ = 50.0 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.1 (-ve), 14.0 (-ve), 21.0 (-ve), 36.7, 53.9 (-ve), 61.5, 128.1 (-ve), 129.3 (-ve), 135.5, 137.3 (-ve), 141.4, 142.2, 168.9.

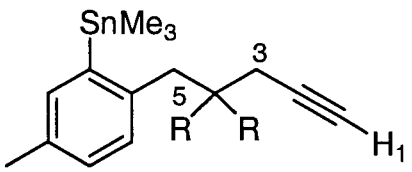
HRMS calcd for $C_{17}H_{25}O_4{}^{120}Sn$ (M^+-Me): 413.0775; found: 413.0781.

Anal. calcd for $C_{18}H_{28}O_4Sn$: C 50.62, H 6.61; found: C 50.51, H 6.65.

<u>Preparation of 4,4-bis(ethoxycarbonyl)-5-(4-methyl-2-trimethylstannylphenyl)pent-1-yne (**220**)</u>



218



R = -CO_2Et

220

To a stirred suspension of potassium hydride (34 mg, 0.85 mmol, washed with pentane) in dry THF (8 mL) at room temperature was added a solution of the stannane **218** (343 mg, 0.80 mmol) in dry THF (1 mL) via a cannula. The reaction mixture was stirred for 1 h. A solution of propargyl bromide (309 mg, 80 wt % in toluene, 2.08 mmol) was added via a syringe and the reaction mixture was warmed to reflux for 1.5 h. The

mixture was cooled to room temperature and water (10 mL) was added. The mixture was then extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography (20 g of silica gel, 50:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 373 mg (99 %) of the diester **220** as a colorless oil.

IR (neat): 3285, 1734, 1480, 1190, 772 cm^{-1}.

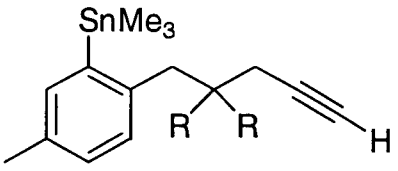
^1H nmr (400 MHz, $CDCl_3$) δ: 0.34 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 56.1 Hz), 1.19 (t, 6H, -CO_2CH_2C<u>H_3</u>, J = 7.1 Hz), 1.99 (t, 1H, H-1, J = 2.6 Hz), 2.27 (s, 3H, -<u>Me</u>), 2.82 (d, 2H, H-3, J = 2.6 Hz), 3.48 (s, 2H, H-5), 4.09-4.23 (m, 4H, -CO_2C<u>H_2</u>CH_3), 6.99-7.94 (m, 2H), 7.19 (br s, 1H, aromatic proton α to -$SnMe_3$, $^3J_{Sn\text{-}H}$ = 49.3 Hz).

^{13}C nmr (128.5 MHz, $CDCl_3$) δ: -7.2, 13.9, 20.6, 23.3, 39.6, 58.0, 61.7, 71.6, 79.6, 127.6, 129.0, 135.5, 137.4, 139.4, 144.7, 170.1.

HRMS calcd for $C_{20}H_{27}O_4{}^{120}Sn$ (M^+-Me): 451.0931; found: 451.0928.

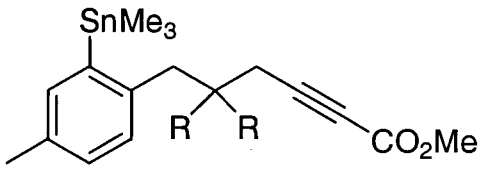
Anal. calcd for $C_{21}H_{30}O_4Sn$: C 54.22, H 6.50; found: C 54.50, H 6.49.

<u>Preparation of methyl 5,5-bis(ethoxycarbonyl)-6-(2-trimethylstannylphenyl)hex-2-ynoate (**221**)</u>



R = -CO_2Et

220



R = -CO_2Et

221

To a cold (-78 °C), stirred solution of LDA (0.85 mmol) in dry THF (6 mL) was added

DMPU (102 μL, 0.85 mmol) and stirring was continued for 5 min. A solution of the acetylene **220** (304 mg, 0.653 mmol) in dry THF (2 mL) was added via a cannula and the reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (76 μL, 0.98 mmol) was added via a syringe. The mixture was stirred for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (5 mL) was added and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (30 g of silica gel, 85:15 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 79 mg of the stannane **220** and 217 mg (63 %, 86 % based on recovered starting material) of the cyclization precursor **221** as a colorless clear oil.

IR (neat): 2241, 1719 (br), 1436, 1258, 1079, 772 cm^{-1}.

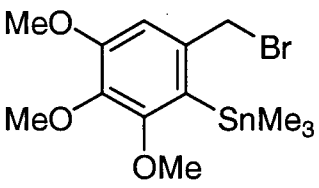
^1H nmr (400 MHz, $CDCl_3$) δ: 0.33 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.2 Hz), 1.20 (t, 6H, -CO_2CH_2C<u>H</u>$_3$, J = 7.1 Hz), 2.26 (s, 3H, -<u>Me</u>), 2.90 (s, 2H, -C<u>H</u>$_2$-), 3.45 (s, 2H, -C<u>H</u>$_2$-), 3.70 (s, 3H, -CO_2<u>Me</u>), 4.12-4.23 (m, 4H, -CO_2C<u>H</u>$_2CH_3$), 6.92-7.04 (m, 2H), 7.17 (br s, 1H, aromatic proton α to -$SnMe_3$, $^3J_{Sn\text{-}H}$ = 49.9 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -7.4 (-ve), 13.9 (-ve), 20.9 (-ve), 23.4, 40.2, 52.5 (-ve), 57.7, 62.0, 75.2, 84.4, 127.5 (-ve), 129.1 (-ve), 135.8, 137.5 (-ve), 138.7, 144.7, 153.6, 169.7.

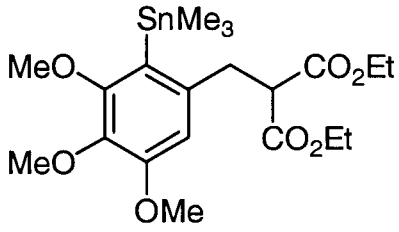
HRMS calcd for $C_{22}H_{29}O_6{}^{120}Sn$ (M^+-Me): 509.0986; found: 509.0979.

Anal. calcd for $C_{23}H_{32}O_6Sn$: C 52.80, H 6.16; found: C 52.69, H 6.14.

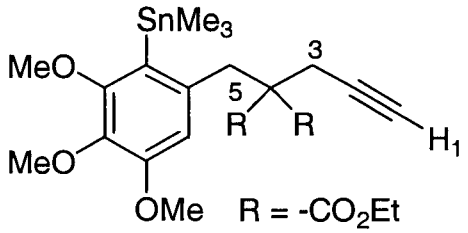
Preparation of 4,4-bis(ethoxycarbonyl)-5-(3,4,5-trimethoxy-2-trimethylstannyl phenyl)pent-1-yne (**222**)



204



219



222

To a stirred suspension of potassium hydride (213 mg, 5.35 mmol, washed with pentane) in dry THF (15 mL) at room temperature was added diethyl malonate (945 μL, 6.23 mmol). The reaction mixture was stirred for 1 h. A solution of the bromide **204** (754 mg, 1.78 mmol) in dry THF (2 mL) was added via a cannula and the mixture was warmed to reflux for 1.5 h. The reaction mixture was cooled to room temperature and water (15 mL) was added. The mixture was then extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography (30 g of silica gel, 7:3 petroleum ether-Et_2O) yielded 839 mg of a mixture of diethyl malonate and the diester **219** as a colorless oil.

To a stirred suspension of potassium hydride (200 mg, 5.00 mmol, washed with pentane) in dry THF (17 mL) at room temperature was added a solution of diethyl malonate and the stannane **219** (obtained as described above) in dry THF (2 mL) via a cannula. The reaction mixture was stirred for 1 h. A solution of propargyl bromide (668 mg, 80 wt % in toluene, 4.49 mmol) was added via a syringe and the mixture was warmed to reflux for 1.5 h. The reaction mixture was cooled to room temperature and water (17 mL) was added. The mixture was then extracted with Et_2O (3 x 10 mL). The combined organic

extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography (30 g of silica gel, 7:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the purified material yielded 903 mg (94 % over 2 steps) of the alkyne **222** as a colorless oil.

IR (neat): 3280, 1734 (br), 1585, 1102, 774 cm^{-1}.

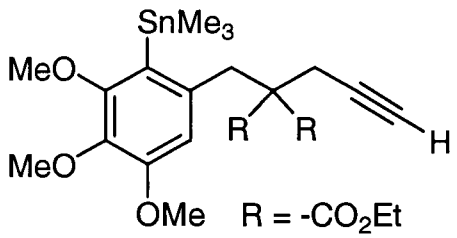
^1H nmr (400 MHz, $CDCl_3$) δ: 0.31 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.3 Hz), 1.17 (t, 6H, -$CO_2CH_2C\underline{H}_3$, J = 7.2 Hz), 2.02 (t, 1H, H-1, J = 2.6 Hz), 2.77 (d, 2H, H-3, J = 2.6 Hz), 3.40 (s, 2H, H-5), 3.78 (s, 6H, includes 2 3H -O<u>Me</u> singlets), 3.83 (s, 3H, -O<u>Me</u>), 4.06-4.19 (m, 4H, -$CO_2C\underline{H}_2CH_3$), 6.59 (s, 1H, aromatic proton, $^4J_{Sn\text{-}H}$ = 17.4 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -5.4, 13.9, 23.1, 38.6, 55.8, 58.5, 60.4, 60.9, 61.6, 71.9, 79.5, 108.6, 129.2, 138.3, 139.5, 153.8, 157.2, 170.0.

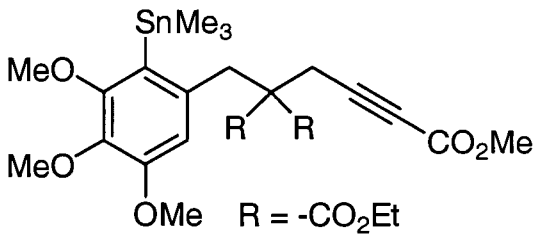
HRMS calcd for $C_{22}H_{31}O_7{}^{120}Sn$ (M^+-Me): 527.1092; found: 527.1081.

Anal. calcd for $C_{23}H_{34}O_7Sn$: C 51.04, H 6.33; found: C 51.04, H 6.19.

<u>Preparation of methyl 5,5-bis(ethoxycarbonyl)-6-(3,4,5-trimethoxy-2-trimethylstannyl phenyl)hex-2-ynoate (**223**)</u>



222



223

To a cold (-78 °C), stirred solution of LDA (3.36 mmol) in dry THF (15 mL) was added DMPU (406 μL, 3.36 mmol) and stirring was continued for 5 min. A solution of the

acetylene **222** (903 mg, 1.67 mmol) in dry THF (2 mL) was added via a cannula and the reaction mixture was stirred for 1 h at -78 °C. Methyl chloroformate (390 μL, 5.00 mmol) was added to the reaction mixture via a syringe. The mixture was stirred for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (15 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (50 g of silica gel, 7:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 805 mg (80 %) of the alkynic triester **223** as a colorless clear oil.

IR (neat): 2241, 1719 (br), 1585, 1558, 1261, 1099, 775 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.30 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 54.3 Hz), 1.20 (t, 6H, -CO_2CH_2C<u>H</u>$_3$, J = 7.1 Hz), 2.88 (s, 2H, -C<u>H</u>$_2$-), 3.39 (s, 2H, -C<u>H</u>$_2$-), 3.71 (s, 3H, -O<u>Me</u>), 3.78 (s, 6H, includes 2 3H -O<u>Me</u> singlets), 3.84 (s, 3H, -O<u>Me</u>), 4.10-4.24 (m, 4H, -CO_2C<u>H</u>$_2CH_3$), 6.54 (s, 1H, aromatic proton, $^4J_{Sn-H}$ = 17.3 Hz).

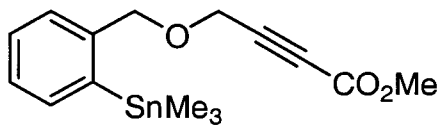
^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -6.2 (-ve), 13.9 (-ve), 23.5, 39.2, 52.6 (-ve), 55.8 (-ve), 58.2, 60.4 (-ve), 60.9 (-ve), 62.0, 75.5, 84.3, 109.0 (-ve), 129.3, 137.8, 139.7, 153.6, 154.0, 157.3, 169.6.

HRMS calcd for $C_{24}H_{33}O_9{}^{120}Sn$ (M^+-Me): 585.1147; found: 585.1151.

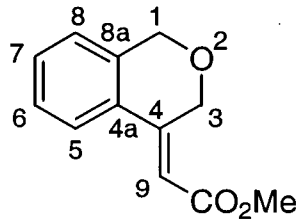
Anal. calcd for $C_{25}H_{36}O_9Sn$: C 50.11, H 6.06; found: C 50.35, H 5.99.

4.2 Copper(I) mediated conjugate additions

Preparation of (Z)-4-(methoxycarbonylmethylidene)isochromane (**224**)



211



224

Following general procedure 1 (pg. 126), the ester **224** was prepared by the addition of the stannane **211** (85 mg, 0.23 mmol), as a solution in dry DMF (1 mL), to a cool (0 °C), stirred solution-suspension of CuCl (57 mg, 0.58 mmol) and glacial acetic acid (61 μL, 1.1 mmol) in dry DMF (1.1 mL). Purification by flash column chromatography (10 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 40 mg (92 %) of the isochromane derivative **224** as a white solid (mp 62-63 °C).

IR (KBr): 1708, 1622, 1174, 1110 cm^{-1}.

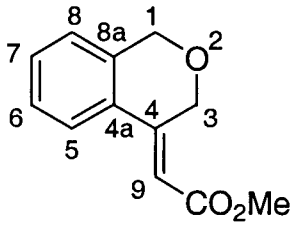
^1H nmr (400 MHz, $CDCl_3$) δ: 3.73 (s, 3H, -CO_2Me), 4.67 (s, 2H, H-1), 5.11 (d, 2H, H-3, J = 2.1 Hz), 6.36 (t, 1H, H-9, J = 2.1 Hz), 7.09 (d, 1H, J = 7.4 Hz), 7.25-7.35 (m, 2H), 7.70 (d, 1H, H-5, J = 7.7 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 51.3 (-ve), 68.0 (2C), 110.3 (-ve), 123.9 (-ve), 125.1 (-ve), 127.6 (-ve), 129.9, 130.0 (-ve), 137.2, 149.6, 166.7.

HRMS calcd for $C_{12}H_{12}O_3$: 204.0786; found: 204.0782.

Anal. calcd for $C_{12}H_{12}O_3$: C 70.59, H 5.92; found: C 70.49, H 5.85.

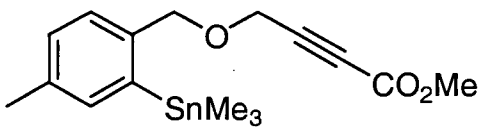
Table 24. ^{1}H nmr (400 MHz, $CDCl_3$) data for the ester **224**: NOED experiments



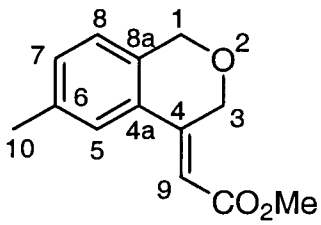
224

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-5	7.70 (d, *J* = 7.7)	H-9, Part of m at 7.25-7.35
H-9	6.36 (t, *J* = 2.1)	H-5

Preparation of (Z)-4-(methoxycarbonylmethylidene)-6-methylisochromane (**225**)



206



225

Following general procedure 1 (see pg. 126), the ester **225** was prepared by the addition of the stannane **206** (78 mg, 0.20 mmol), as a solution in dry DMF (1 mL), to a cool (0 °C), stirred solution-suspension of CuCl (54 mg, 0.55 mmol) and glacial acetic acid (58 μL, 1.1 mmol) in dry DMF (1 mL). Purification by flash column chromatography (10 g of silica gel, 3:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 43 mg (97 %) of the isochromane derivative **225** as a white solid (mp 94-94.5 °C).

IR (KBr): 1704, 1604, 1170, 1105 cm^{-1}.

^{1}H nmr (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H, -Me), 3.73 (s, 3H, -CO_2Me), 4.64 (s, 2H, H-1),

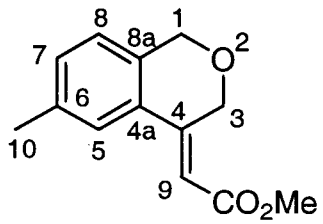
5.09 (d, 2H, H-3, J = 2.0 Hz), 6.35 (t, 1H, H-9, J = 2.0 Hz), 6.98 (d, 1H, H-8, J = 7.6 Hz), 7.15 (d, 1H, H-7, J = 7.6 Hz), 7.52 (s, 1H, H-5).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 21.3 (-ve), 51.4 (-ve), 67.9, 68.0, 110.0 (-ve), 124.3 (-ve), 125.1 (-ve), 129.7, 131.0 (-ve), 134.4, 137.1, 149.9, 166.8.

HRMS calcd for $C_{13}H_{14}O_3$: 218.0943; found: 218.0939.

Anal. calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47; found: C 71.74, H 6.58.

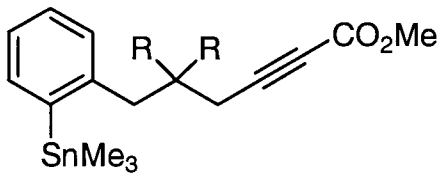
Table 25. ^{1}H nmr (400 MHz, $CDCl_3$) data for the ester **225**: NOED experiments



225

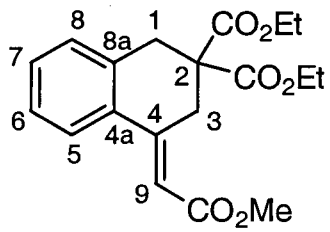
Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, J (Hz))	NOED Correlations
H-5	7.52 (s)	H-9, H-10
H-9	6.35 (t, J = 2.0)	H-5
H-10	2.34 (s)	H-5, H-7

Preparation of 2,2-bis(ethoxycarbonyl)-(*E*)-4-methoxycarbonylmethylidene-1,2,3,4-tetra hydronapthalene (**226**)



R = -CO_2Et

215



226

Following general procedure 1 (see pg. 126), the triester **226** was prepared by the addition of the stannane **215** (84 mg, 0.17 mmol), as a solution in dry DMF (0.9 mL), to a cool (0 °C), stirred solution-suspension of CuCl (44 mg, 0.45 mmol) and glacial acetic acid (47 μL, 0.82 mmol) in dry DMF (0.8 mL). Purification of the crude product by flash column chromatography (10 g of silica gel, 7:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 57 mg (98 %) of the triester **226** as a colorless viscous oil.

IR (neat): 1734 (br), 1620, 1435, 1230, 1046 cm^{-1}.

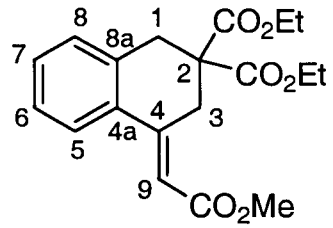
^1H nmr (400 MHz, $CDCl_3$) δ: 1.13 (t, 6H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 3.30 (s, 2H, H-1), 3.69 (d, 2H, H-3, J = 1.8 Hz), 3.74 (s, 3H, -$CO_2\underline{Me}$), 4.10 (q, 4H, -$CO_2C\underline{H}_2CH_3$, J = 7.1 Hz), 6.38 (br t, 1H, H-9, J = 1.8 Hz), 7.15-7.30 (m, 3H), 7.60 (d, 1H, H-5, J = 7.8 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 13.8 (-ve), 33.6, 35.3, 51.1 (-ve), 53.9, 61.6, 113.8 (-ve), 124.4 (-ve), 127.1 (-ve), 129.3 (-ve), 130.1 (-ve), 133.0, 135.6, 150.4, 166.8, 170.4.

HRMS calcd for $C_{19}H_{22}O_6$: 346.1416; found: 346.1420.

Anal. calcd for $C_{19}H_{22}O_6$: C 65.88, H 6.40; found: C 66.08, H 6.31.

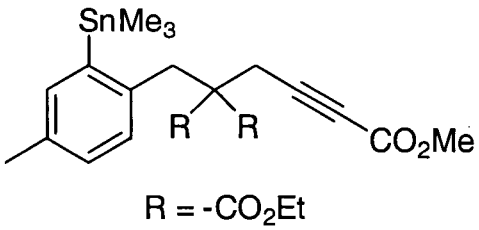
Table 26. ^{1}H nmr (400 MHz, $CDCl_3$) data for the triester **226**: NOED experiments



226

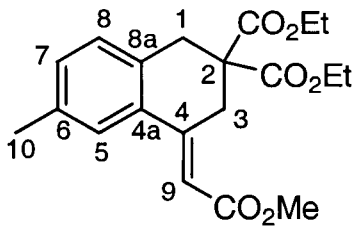
Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-5	7.60 (d, *J* = 7.8)	H-9, Part of m at 7.15-7.30
H-9	6.38 (br t, *J* = 1.8)	H-5

Preparation of 2,2-bis(ethoxycarbonyl)-(*E*)-4-methoxycarbonylmethylidene-6-methyl-1,2,3,4-tetrahydronapthalene (**227**)



R = -CO_2Et

221



227

Following general procedure 1 (see pg. 126), the triester **227** was prepared by the addition of the stannane **221** (52 mg, 0.10 mmol), as a solution in dry DMF (0.5 mL), to a cool (0 °C), stirred solution-suspension of CuCl (24 mg, 0.24 mmol) and glacial acetic acid (28 μL, 0.50 mmol) in dry DMF (0.5 mL). Purification by flash column chromatography (10 g of silica gel, 7:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 34 mg (92 %) of the triester **227** as a white solid (mp 91-92 °C).

IR (KBr): 1733 (br), 1606, 1435, 1263, 1047 cm^{-1}.

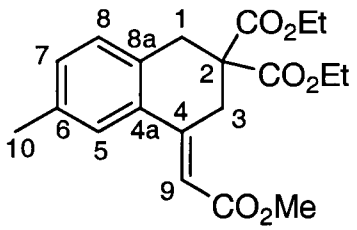
^{1}H nmr (400 MHz, $CDCl_3$) δ: 1.14 (t, 6H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 2.30 (s, 3H, -$\underline{Me}$), 3.25 (s, 2H, H-1), 3.67 (d, 2H, H-3, J = 1.9 Hz), 3.73 (s, 3H, -$CO_2\underline{Me}$), 4.10 (q, 4H, -$CO_2C\underline{H}_2CH_3$, J = 7.1 Hz), 6.37 (br t, 1H, H-9, J = 1.9 Hz), 7.04 (d, 1H, H-8, J = 7.7 Hz), 7.10 (dd, 1H, H-7, J = 1.0, 7.7 Hz), 7.40 (br s, 1H, H-5).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: 13.9 (-ve), 21.1 (-ve), 33.6, 35.2, 51.1 (-ve), 54.0, 61.5, 113.6 (-ve), 124.9 (-ve), 129.2 (-ve), 131.1 (-ve), 132.7, 132.8, 136.6, 150.6, 166.9, 170.5.

HRMS calcd for $C_{20}H_{24}O_6$: 360.1573; found: 360.1564.

Anal. calcd for $C_{20}H_{24}O_6$: C 66.65, H 6.71; found: C 66.57, H 6.80.

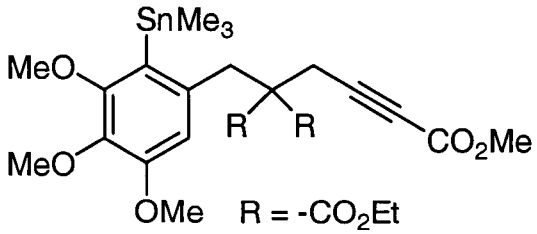
Table 27. ^{1}H nmr (400 MHz, $CDCl_3$) data for the triester **227**: NOED experiments



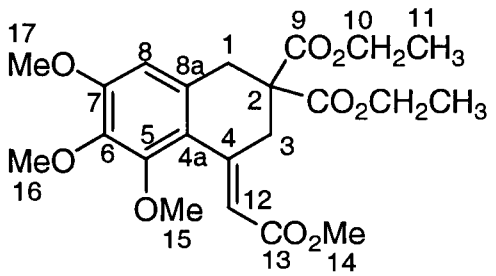
227

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, J (Hz))	NOED Correlations
H-1	3.25 (s)	H-8
H-5	7.40 (br s)	H-9, H-10
H-9	6.37 (br t, J = 1.9)	H-5
H-10	2.30 (s)	H-5, H-7

Preparation of 2,2-bis(ethoxycarbonyl)-(*E*)-4-methoxycarbonylmethylidene-5,6,7-trimethoxy-1,2,3,4-tetrahydronapthalene (**228**)



223



228

Following general procedure 1 (see pg. 126), the triester **228** was prepared by the addition of the stannane **223** (96 mg, 0.16 mmol), as a solution in dry DMF (0.8 mL), to a cool (0 °C), stirred solution-suspension of CuCl (43 mg, 0.44 mmol) and glacial acetic acid (46 μL, 0.80 mmol) in dry DMF (0.8 mL). Purification by flash column chromatography (10 g of silica gel, 1:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 68 mg (97 %) of the triester **228** as a colorless, viscous oil.

IR (neat): 1734 (br), 1591, 1489, 1250, 915, 733 cm^{-1}.

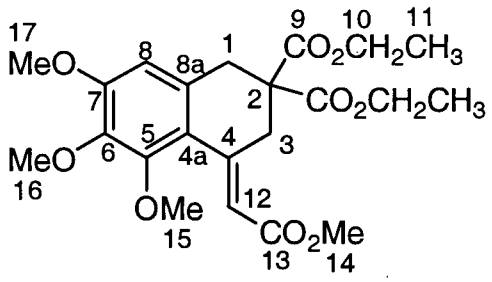
^1H nmr (500.2 MHz, C_6D_6) δ: 0.83 (t, 6H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 3.22 (s, 3H, H-17), 3.35 (s, 2H, H-1), 3.45 (s, 3H, $-CO_2\underline{Me}$), 3.61 (s, 3H, H-15), 3.66 (s, 3H, H-16), 3.88 (q, 4H, $-CO_2C\underline{H}_2CH_3$, J = 7.1 Hz), 4.19 (d, 2H, H-3, J = 1.8 Hz), 6.19 (s, 1H, H-8), 7.39 (br t, 1H, H-12, J = 1.8 Hz).

^{13}C nmr (125.8 MHz, C_6D_6) δ: 13.9, 34.9, 36.8, 50.6, 54.4, 55.3, 60.4, 60.6, 61.5, 108.2, 117.8, 121.3, 133.1, 142.6, 147.3, 153.6, 154.8, 167.7, 170.7.

HRMS calcd for $C_{22}H_{28}O_9$: 436.1733; found: 436.1729.

Anal. calcd for $C_{22}H_{28}O_9$: C 60.54, H 6.47; found: C 60.22, H 6.67.

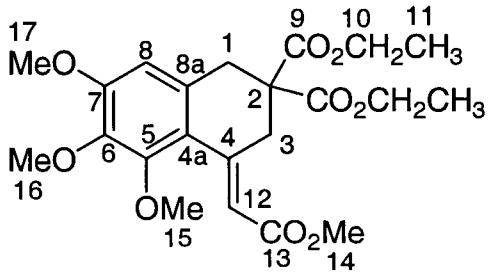
Table 28. ^{1}H nmr (400 MHz, C_6D_6) data for the triester **228**: NOED experiments



228

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-1	3.35 (s)	H-8
H-3	4.19 (d, *J* = 1.8)	H-14
H-8	6.19 (s)	H-1, H-17
H-10, -$CO_2C\underline{H}_2CH_3$	3.88 (q, *J* = 7.1)	
H-11, -$CO_2CH_2C\underline{H}_3$	0.83 (t, *J* = 7.1)	
H-12	7.39 (br t, *J* = 1.8)	H-15
H-14, -$CO_2\underline{Me}$	3.45 (s)	H-3
H-15	3.61 (s)	H-12
H-16	3.66 (s)	
H-17	3.22 (s)	H-8

Table 29. ^{13}C nmr (128.5 MHz, C_6D_6) data for the triester **228**: HMBC and HMQC experiments



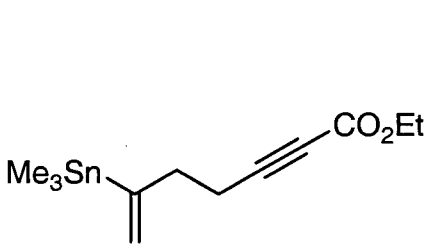
228

Assignment C-x	^{13}C nmr (125.8 MHz) δ	HMQC Correlations	HMBC Correlations
C-1	36.8	H-1	
C-2	54.4		H-1
C-3	34.9	H-3	H-1, H-12
C-4	147.3		H-3
C-4a	133.1		H-1
C-5	153.6		H-15
C-6	142.6		H-9, H-16
C-7	154.8		H-9, H-17
C-8	108.2	H-8	H-1
C-8a	121.3		H-1, H-3, H-8, H-12
C-9	170.7		H-3, H-10
C-10	61.5	H-10	H-11
C-11	13.9	H-11	H-10
C-12	117.8	H-12	H-3
C-13	167.7		H-14
C-14	50.6	H-14	
C-15	60.3	H-15	
C-16	60.6	H-16	
C-17	55.3	H-17	

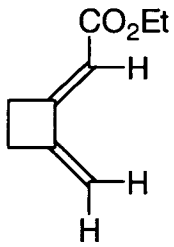
5. Extensions and limitations

5.1 Effect of solvent and additives

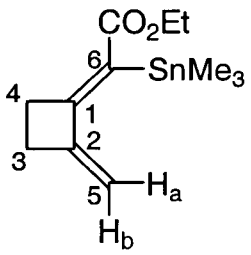
Conjugate addition in the absence of a proton source



129



144



145

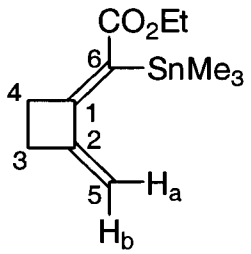
To a cool (0 °C), stirred solution of the stannane **B3** (142 mg, 0.43 mmol) in dry DMF (4.3 mL) was added copper(I) chloride (111 mg, 1.12 mmol) in one solid portion. The resulting red suspension was stirred for 15 min. Aqueous ammonium chloride-ammonia (pH 8) (4 mL) was added and stirred until the mixture was a deep blue. The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with brine (3 x 20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification of the crude product by flash column chromatography (12 g of silica gel, 24:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 42 mg (64 %) of the diene **144** and 26 mg (18 %) of the stannane **146**, both as colorless oils. The diene **144** exhibited spectral characteristics (^{1}H nmr) identical with those previously mentioned (pg. 127). In a separate experiment, when the reaction time was increased to a period of 1 h, the diene **144** and the stannane **145** were obtained in 60 % and 6 % yields, respectively. Characterization data for the stananne **145** is given below.

IR (neat): 1699, 1600, 1207, 772 cm^{-1}.

^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.25 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 56.2 Hz), 1.26 (t, 3H, -CO_2CH_2C<u>H</u>$_3$, J = 7.1 Hz), 2.56-2.70 (m, 2H, H-4), 2.88-3.02 (m, 2H, H-3), 4.14 (q, 2H, -CO_2C<u>H</u>$_2CH_3$, J = 7.1 Hz), 4.88 (br s, 1H, H-5b), 5.18 (br t, 1H, H-5a, J = 2.7 Hz).

HRMS calcd for $C_{11}H_{17}O_2Sn$ (M^+-Me): 301.0251; found: 301.0253.

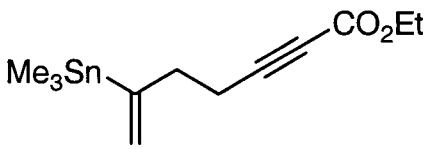
Table 30. ^1H nmr (200 MHz, $CDCl_3$) data for the ester **145**: NOED experiments



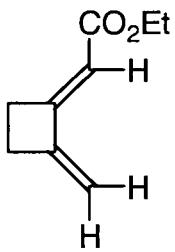
145

Assignment H-x	^1H nmr (200 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
-$SnMe_3$	0.25 (s)	H-5a
H-5a	5.18 (br t, *J* = 2.7)	H-5b, -$SnMe_3$
H-5b	4.88 (br s)	H-3, H-5a

Conjugate addition utilizing an aqueous HCl work up



129

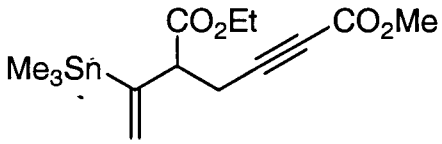


144

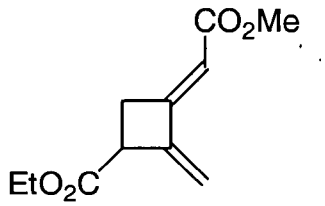
To a cool (0 °C), stirred solution of the stannane **129** (142 mg, 0.43 mmol) in dry DMF (4.3 mL) was added copper(I) chloride (111 mg, 1.12 mmol) in one solid portion. The resulting red suspension was stirred for 15 min. To the mixture was added aqueous 1 M HCl (2 mL, 2 mmol) and stirring was continued for 5 min. Aqueous ammonium chloride-ammonia (pH 8) (4 mL) was added and stirred until the mixture was a deep blue. The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic extracts

were washed with brine (3 x 20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification of the crude product by flash column chromatography (12 g of silica gel, 24:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 39 mg (77 %) of the diene **144** as a colorless oil. The diene **144** exhibited spectral characteristics (^1H nmr) identical with those previously mentioned (pg. 127).

Conjugate addition in the presence of CF_3CO_2H



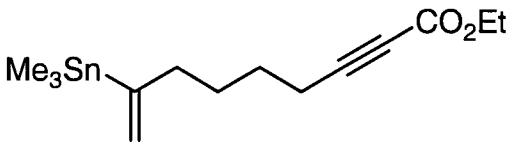
143



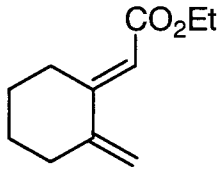
158

Following general procedure 1 (see pg. 126), the cyclobutane derivative **158** was prepared by the addition of the ester **143** (161 mg, 0.433 mmol), as a solution in dry DMF (2 mL), to a cool (0 °C), stirred solution-suspension of CuCl (115 mg, 1.16 mmol) and trifluoroacetic acid (166 μL, 2.17 mmol) in dry DMF (2 mL). Purification of the crude product by flash column chromatography (12 g of silica gel, 9:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 67 mg (74 %) of the cyclization product **158** as a colorless oil. The product obtained exhibited spectral characteristics (^1H nmr) identical with those previously mentioned (pg. 133). In addition, 18 mg of an uncharacterized mixture of unidentified destannylated material was obtained.

Conjugate addition utilizing copper(I) acetate as the copper(I) source



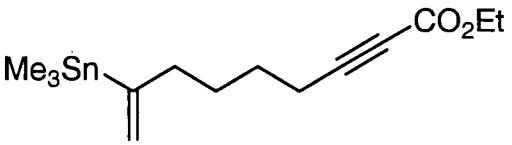
136



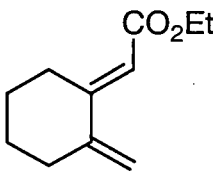
156

Following general procedure 1 (see pg. 126), the cyclohexane derivative **156** was prepared by the addition of the ester **136** (105 mg, 0.306 mmol), as a solution in dry DMF (1.7 mL), to a cool (0 °C), stirred solution-suspension of CuOAc (95 mg, 0.77 mmol) and glacial acetic acid (91 μL, 1.53 mmol) in dry DMF (1.7 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 96:4 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 43 mg (78 %) of the cyclization product **156** as a colorless oil. The diene **156** exhibited spectral characteristics (^1H nmr) identical with those previously mentioned (pg. 131).

Conjugate addition in the presence of 0.5 equiv CuCl



136

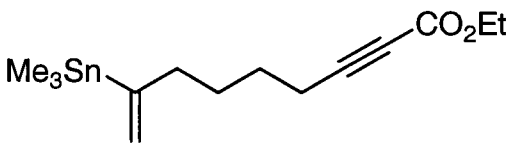


156

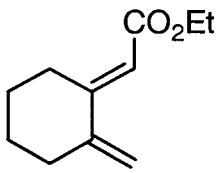
To a cool (0 °C), stirred solution-suspension of CuCl (12.2 mg, 0.12 mmol) in dry DMF (240 μL) was added glacial acetic acid (27 μL, 0.47 mmol) and stirring was continued for 5 minutes. To the grey-blue suspension was added, via a syringe pump over 15 min, the stannane **136** (81 mg, 0.24 mmol) as a solution in dry DMF (240 μL). The mixture was stirred for 30 min, during which time the following color and texture changes were noted: a green suspension to a yellow suspension to an opaque, cloudy green suspension. Workup as described in general procedure 1 (see pg. 126) and purification of the crude material by flash column chromatography (10 g of silica gel, 97:3 petroleum ether-Et_2O)

yielded 38 mg (89 %) of the cyclohexane derivative **156**. The diene **156** exhibited spectral characteristics (^{1}H nmr) identical with those previously mentioned (pg. 131).

Conjugate addition in the presence of 0.1 equiv CuCl



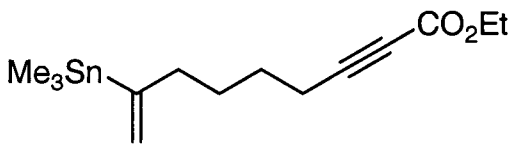
136



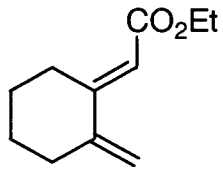
156

To cool (0 °C), test tube (1 mL volume) equipped with a rubber septa and a microstirbar was added CuCl (1.5 mg, 0.015 mmol), dry DMF (18 μL), and glacial acetic acid (17 μL, 0.30 mmol) and the mixture was stirred for 5 minutes. To the clear solution was added, via a syringe pump over 15 min, a solution of the stannane **136** (50 mg, 0.15 mmol) in dry DMF (20 μL) and with dry DMF (20 μL) as a rinse. The mixture was stirred for 4 h, during which time the following color and texture changes were noted: a colorless solution to a cloudy white suspension to a cloudy green/black suspension to a very pasty white slurry. With no work-up, the mixture was subjected directly to flash column chromatography (10 g of silica gel, 97:3 petroleum ether-Et_2O). Removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 20 mg (76 %) of the cyclohexane derivative **156**. In addition, 2 mg of uncharacterized destannylated material was recovered. The diene **156** exhibited spectral characteristics (^{1}H nmr) identical with those previously mentioned (pg. 131).

Conjugate addition utilizing DMI as the solvent



136

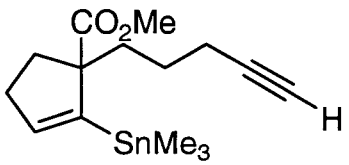


156

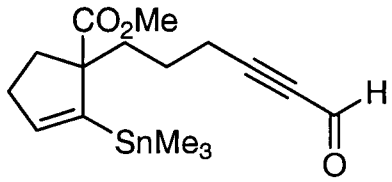
Following general procedure 1 (see pg. 126), the cyclohexane derivative **156** was prepared by the addition of the ester **136** (115 mg, 0.334 mmol), as a solution in dry DMI (1.7 mL), to a cool (0 °C), stirred solution-suspension of CuCl (87 mg, 0.88 mmol) and glacial acetic acid (100 μL, 1.67 mmol) in dry DMI (1.7 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 96:4 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 50 mg (83 %) of the cyclization product **156** as a colorless oil. The diene **156** exhibited spectral characteristics (^1H nmr) identical with those previously mentioned (pg. 131).

5.2 Preparation of α,β-alkynic aldehyde and ketone substrates

Preparation of 6-(1-methoxycarbonyl-2-trimethylstannylcyclopent-2-en-1-yl)hex-2-ynal (**233**)



180b



233

To a cold (-78 °C), stirred solution of LDA (0.45 mmol) in dry THF (2 mL) was added a solution of the stannane **180b** (107 mg, 0.300 mmol) (pg. 150) in dry THF (1 mL) and the solution was warmed to -48 °C. The reaction mixture was stirred for 1 h. To the mixture was added DMF (46 μL, 0.60 mmol) via a syringe and the solution was warmed to room temperature. The mixture was stirred for 30 min. The reaction mixture was transferred via a cannula to a vigorously stirred aqueous solution of 10 % KH_2PO_4 (10 mL) and

stirring was continued for 1 h. The mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (10 g of silica gel, 4:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 76 mg (66 %) of the aldehyde **233** as a colorless clear oil.

IR (neat): 2201, 1733, 1670, 1434, 1166, 772 cm^{-1}.

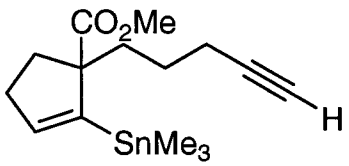
^1H nmr (400 MHz, $CDCl_3$) δ: 0.12 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.3 Hz), 1.40-1.60 (m, 3H), 1.68-1.77 (m, 1H), 1.93-2.00 (m, 1H), 2.36-2.55 (m, 5H), 3.63 (s, 3H, -CO_2<u>Me</u>), 5.96 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn\text{-}H}$ = 37.9 Hz), 9.14 (s, 1H, -C(=O)<u>H</u>).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: -8.6 (-ve), 19.5, 23.3, 32.0, 34.2, 37.7, 51.8 (-ve), 65.2, 81.9, 98.3, 143.6 (-ve), 148.4, 176.6, 176.9 (-ve).

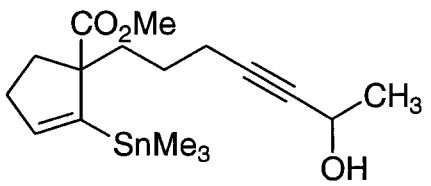
HRMS calcd for $C_{15}H_{21}O_3{}^{120}Sn$ (M^+-Me): 369.0513; found: 369.0505.

Anal. calcd for $C_{16}H_{24}O_3Sn$: C 50.17, H 6.32; found: C 50.40, H 6.47.

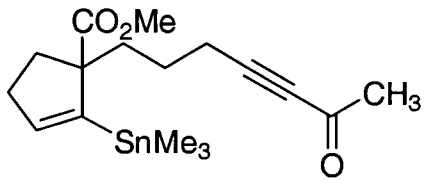
<u>Preparation of 7-(1-methoxycarbonyl-2-trimethylstannylcyclopent-2-en-1-yl)hept-3-yn-2-one (**234**)</u>



180b



234



235

To a cold (-78 °C), stirred solution of LDA (2.48 mmol) in dry THF (15 mL) was added DMPU (300 μL, 2.48 mmol) and stirring was continued for 5 min. A solution of the alkyne **180b** (585 mg, 1.65 mmol) (pg. 150) in dry THF (2 mL) was added via a cannula and the reaction mixture was stirred for 1 h at -78 °C. Ethanal (270 μL, 4.83 mmol) was added neat via a syringe. The mixture was stirred for 1 h at -78 °C and 1 h at room temperature. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (20 g of silica gel, 3:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 486 mg (74 %) of the alcohol **234** as a colorless clear oil.

To a cold (-78 °C), stirred solution of oxalyl chloride (0.92 mL, 2 M in CH_2Cl_2, 1.84 mmol) in dry CH_2Cl_2 (10 mL) was added dimethyl sulfoxide (260 μL, 3.66 mmol) dropwise via a syringe. The solution was stirred for 15 min. The alcohol (**234**) (obtained as described above) was added over 3 min as a solution in dry CH_2Cl_2 (2 mL). The cloudy white suspension was stirred for an additional 15 min. Triethylamine (1.00 mL, 7.17 mmol) was added dropwise via a syringe and the mixture was stirred for 20 min. The reaction mixture was warmed to room temperature and water (10 mL) was added. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (40 g of silica gel, 3:2 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 460 mg (70 % over 2 steps) of the alkynic ketone **235** as a colorless clear oil.

IR (neat): 2211, 1729, 1678, 1433, 1228, 768 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.13 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 54.3 Hz), 1.38-1.56 (m, 3H), 1.68-1.77 (m, 1H), 1.92-2.00 (m, 1H), 2.26-2.52 (m, 8H, includes 3H -C<u>H</u>$_3$ singlet at 2.28), 3.63 (s, 3H, -CO_2<u>Me</u>), 5.96 (dd, 1H, olefinic proton, J = 2.1, 2.1 Hz, $^3J_{Sn-H}$ = 38.0 Hz).

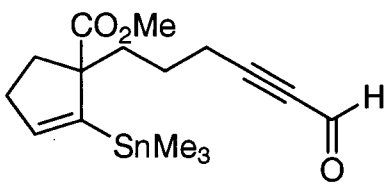
^{13}C nmr (125.8 MHz, $CDCl_3$) δ: -8.6 (-ve), 19.3, 23.5, 31.9, 32.7 (-ve), 34.2, 37.7, 51.7 (-ve), 65.2, 81.6, 93.1, 143.6 (-ve), 148.3, 176.6, 184.7.

HRMS calcd for $C_{16}H_{23}O_3{}^{120}Sn$ (M^+-Me): 383.0669; found: 383.0673.

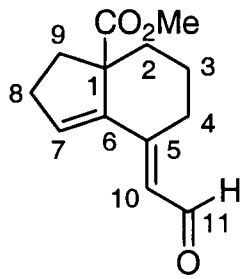
Anal. calcd for $C_{17}H_{26}O_3Sn$: C 51.42, H 6.60; found: C 51.48, H 6.70.

<u>5.3 Copper(I) mediated cyclizations</u>

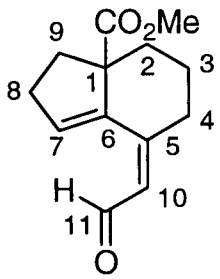
<u>Preparation of 1-methoxycarbonyl-(*E*)-5-formylmethylidenebicyclo[4.3.0]non-6-ene (**236**) and 1-methoxycarbonyl-(*Z*)-5-formylmethylidenebicyclo[4.3.0]non-6-ene (**237**)</u>



233



236 (minor)



237 (major)

Following general procedure 1 (see pg. 126), the aldehydes **236** and **237** was prepared by the addition of the stannane **233** (60 mg, 0.16 mmol), as a solution in dry DMF (0.8 mL), to a cool (0 °C), stirred solution-suspension of CuCl (44 mg, 0.45 mmol) and glacial acetic acid (45 μL, 0.79 mmol) in dry DMF (0.8 mL). Purification of the crude product by flash column chromatography (10 g of silica gel, 3:2 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided

30 mg (89 %) of a mixture of the isomeric aldehydes **236** and **237** as a colorless clear oil. The ratio of these products, as determined by integration of the ^{1}H nmr aldehyde signals, was ~1:4, respectively.

IR (neat): 1728, 1672, 1434, 1241, 1152 cm^{-1}.

Signals attributable to the major isomer **237**:

^{1}H nmr (400 MHz, C_6D_6) δ: 3.19 (s, 3H, -CO_2Me), 5.44 (dd, 1H, H-7, J = 2.1, 2.1 Hz), 5.91 (dd, 1H, H-10, J = 2.0, 7.9 Hz), 10.12 (d, 1H, H-11, J = 7.9 Hz).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: 24.8, 31.4, 36.1, 37.3, 37.6, 52.1 (-ve), 59.2, 127.5 (-ve), 135.3 (-ve), 139.6, 159.7, 175.8, 193.1 (-ve).

Signals attributable to the minor isomer **236**:

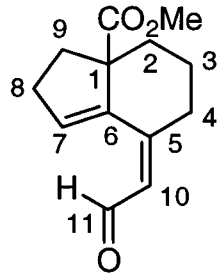
^{1}H nmr (400 MHz, C_6D_6) δ: 2.83 (dm, 1H, H-4, J = 15.4 Hz), 3.23 (s, 3H, -CO_2Me), 5.62 (dd, 1H, H-7, J = 2.5, 2.5 Hz), 6.22 (dd, 1H, H-10, J = 2.1, 8.0 Hz), 9.92 (d, 1H, H-11, J = 8.0 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 23.1, 27.7, 30.8, 36.2, 38.6, 52.1 (-ve), 58.2, 124.0 (-ve), 132.5 (-ve), 143.6, 156.9, 176.0, 190.6 (-ve).

HRMS calcd for $C_{13}H_{16}O_3$: 220.1099; found: 220.1100.

Anal. calcd for $C_{13}H_{16}O_3$: C 70.89, H 7.32; found: C 70.96, H 7.20.

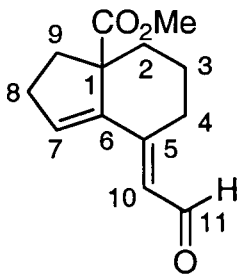
Table 31. ^{1}H nmr (400 MHz, $CDCl_3$) data for the aldehdye **237**: NOED experiments



237

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-7	5.44 (dd, *J* = 2.1, 2.1)	H-11
H-10	5.91 (dd, *J* = 2.0, 7.9)	
H-11	10.12 (d, *J* = 7.9)	H-7, H-10

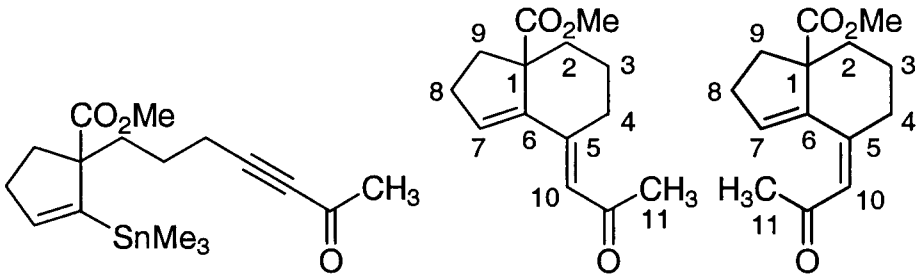
Table 32. ^{1}H nmr (400 MHz, $CDCl_3$) data for the aldehyde **236**: NOED experiments



236

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-7	5.62 (dd, *J* = 2.5, 2.5)	H-10
H-10	6.22 (dd, *J* = 2.1, 8.0)	H-7
H-11	9.92 (d, *J* = 8.0)	One of H-4

Preparation of 1-methoxycarbonyl-(*E*)-5-acetylmethylidenebicyclo[4.3.0]non-6-ene (**238**)



235 **238** (major) **239** (minor)

Following general procedure 1 (see pg. 126), the ester **238** was prepared by the addition of the stannane **235** (83 mg, 0.21 mmol), as a solution in dry DMF (1 mL), to a cool (0 °C), stirred solution-suspension of CuCl (54 mg, 0.55 mmol) and glacial acetic acid (60 μL, 1.1 mmol) in dry DMF (1 mL). Purification by flash column chromatography (12 g of silica gel, 13:7 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 27 mg (55 %) of the ketone **238** as a colorless solid (mp 40-44 °C) and 7.6 mg of a mixture of the two geometric isomers **238** and **239**. The minor isomer **239** proved to be extremely unstable and the mixture containing both compounds decomposed readily. The major isomer **238** decomposed to a small degree over long ^{13}C nmr acquisition times in $CDCl_3$; however a clean ^1H nmr spectrum was obtained. Integration of the olefinic protons, in the ^1H nmr spectrum of the crude product after workup, provided a ratio of ~4:1 of the methyl ketones **238** and **239**, respectively. Characterization data for the ketone **238** is given below.

IR (KBr): 1728, 1681, 1433, 1357, 1165 cm^{-1}.

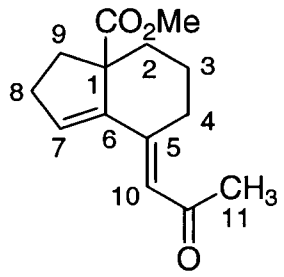
^1H nmr (400 MHz, $CDCl_3$) δ: 1.37-1.51 (m, 2H), 1.70-1.76 (m, 1H), 1.82-1.92 (m, 1H), 2.00-2.10 (m, 1H), 2.19 (s, 3H, -C(=O)C<u>H</u>$_3$), 2.33-2.47 (m, 4H), 3.57-3.65 (m, 4H, includes 3H -CO_2<u>Me</u> singlet at 3.63), 6.04 (br s, 1H, H-7), 6.34 (d, 1H, H-10, J = 2.4 Hz).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: 23.0, 28.8, 30.5, 32.1 (-ve), 36.3, 38.7, 52.1 (-ve), 58.2, 120.6 (-ve), 130.7 (-ve), 144.4, 152.6, 176.4, 199.0.

HRMS calcd for $C_{14}H_{18}O_3$: 234.1256; found: 234.1251.

Anal. calcd for $C_{14}H_{18}O_3$: C 71.77, H 7.74; found: C 71.49, H 7.95.

Table 33. ^{1}H nmr (400 MHz, $CDCl_3$) data for the ketone **238**: NOED experiments



238

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	NOED Correlations
H-7	6.04 (br s)	Part of m at 2.33-2.47
H-10	6.34 (d, *J* = 2.4)	H-7, -C(=O)CH_3
-C(=O)CH_3	2.19 (s)	

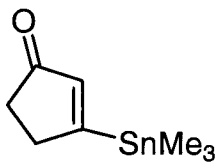
6. Intermolecular coupling of β-trimethylstannyl-α,β-unsaturated ketones mediated by copper(I) chloride

6.1 Intermolecular copper(I) mediated couplings

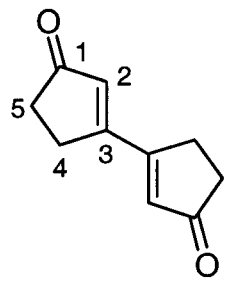
General Procedure 6: Copper(I) chloride mediated intermolecular coupling of β-trimethylstannyl-α,β-unsaturated ketones

To a stirred solution-suspension of CuCl (2.5 equiv) in dry DMF (~4 ml/mmol of substrate) at room temperature was added a solution of the appropriate alkenyltrimethylstannane (1 equiv) in dry DMF (~4 ml/mmol of substrate), and the resulting mixture was stirred for 30 min. Saturated aqueous ammonium chloride (~1 mL/mL of DMF) and water (~1 mL/mL of DMF) were added and the mixture was opened to the atmosphere. The mixture was stirred until the aqueous layer turned bright blue and then was extracted with Et_2O or CH_2Cl_2 (3 x ~1 mL/mL of DMF). The combined organic extracts were washed with water (~2 mL/mL of DMF) and brine (3 x ~2 mL/mL of DMF), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel.

Preparation of 3-(3-oxocyclopent-1-en-1-yl)cyclopent-2-en-1-one (**251**)



247



251

Following general procedure 6, the diketone (**251**) was synthesized from 3-trimethyl stannylcyclopent-2-en-1-one (**247**)[61] (101 mg, 0.414 mmol), copper(I) chloride (104 mg, 1.05 mmol), and dry DMF (4.4 mL). In this case, the crude product was isolated by the extraction of the reaction mixture with CH_2Cl_2. Flash column chromatography of the

crude product (12 g of silica gel, ethyl acetate) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 27 mg (81 %) of the coupled product **251** as a colorless crystalline solid (mp 211-214 °C).

IR (neat): 1698, 1675, 1561, 1243, 1184, 865, 848 cm^{-1}.

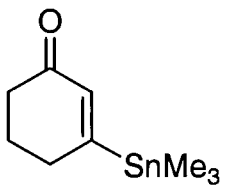
^1H nmr (400 MHz, $CDCl_3$) δ: 2.52-2.57 (m, 4H), 2.85-2.90 (m, 4H), 6.43 (t, 2H, H-2, J = 1.5 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 28.2, 35.1, 132.6, 166.9, 208.7.

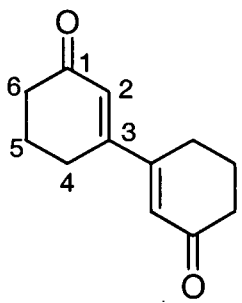
HRMS calcd for $C_{10}H_{10}O_2$: 162.0681; found: 162.0677.

Anal. calcd for $C_{10}H_{10}O_2$: C 74.06, H 6.21; found: C 74.13, H 6.10.

Preparation of 3-(3-oxocyclohex-1-en-1-yl)cyclohex-2-en-1-one (**253**)



249



253

Following general procedure 6, the diene **253** was prepared from 3-trimethylstannylcyclohex-2-en-1-one (**249**)[61] (121 mg, 0.469 mmol), copper(I) chloride (120 mg, 1.21 mmol), and dry DMF (4.6 mL). In this case, the crude product was obtained by the extraction of the reaction mixture with Et_2O. Purification of the crude product by flash column chromatography (7 g of silica gel, Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 40 mg (91 %) of the diene **253** as a colorless crystalline solid (mp 107-108 °C).

IR (neat): 1662, 1575, 1263, 1186, 1144, 901 cm^{-1}.

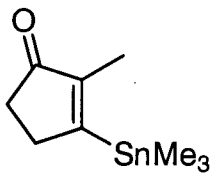
^1H nmr (400 MHz, $CDCl_3$) δ: 2.00-2.15 (m, 4H, H-5), 2.42 (t, 4H, J = 6.7 Hz), 2.50 (t, 4H, J = 6.0 Hz), 6.27 (s, 2H).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 22.2, 25.8, 37.4, 128.0, 156.5, 199.7.

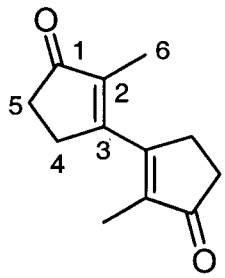
HRMS calcd for $C_{12}H_{14}O_2$: 190.0994; found: 190.0993.

Anal. calcd for $C_{12}H_{14}O_2$: C 75.76, H 7.42; found: C 75.54, H 7.42.

Preparation of 2-methyl-3-(2-methyl-3-oxocyclopent-1-en-1-yl)cyclopent-2-en-1-one (**252**)



248



252

Following general procedure 6, the diketone **252** was synthesized from 2-methyl-3-trimethylstannylcyclopent-2-en-1-one (**248**)[61] (110 mg, 0.43 mmol), copper(I) chloride (110 mg, 1.11 mmol), and dry DMF (4.2 mL). In this case, the crude product was obtained by the extraction of the reaction mixture with CH_2Cl_2. Purification of the crude product by flash column chromatography (20 g of silica gel, ethyl acetate) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 38 mg (94 %) of the coupled product **252** as a colorless crystalline solid (mp 94-94.5 °C).

IR (neat): 1690, 1626, 1292, 995, 947, 781 cm^{-1}.

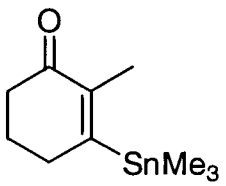
^{1}H nmr (400 MHz, $CDCl_3$) δ: 1.67 (t, 6H, H-6, J = 2.1 Hz), 2.48-2.53 (m, 4H), 2.65-2.72 (m, 4H).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 9.9 (-ve), 28.5, 33.8, 138.7, 163.5, 208.6.

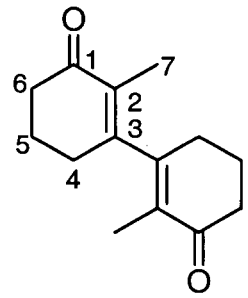
HRMS calcd for $C_{12}H_{14}O_2$: 190.0994; found: 190.0993.

Anal. calcd for $C_{12}H_{14}O_2$: C 75.76, H 7.42; found: C 75.72, H 7.68.

Preparation of 2-methyl-3-(2-methyl-3-oxocyclohex-1-en-1-yl)cyclohex-2-en-1-one (**254**)



250



254

Following general procedure 6, the compound **254** was prepared from 2-methyl-3-trimethylstannylcyclohex-2-en-1-one (**250**)[61] (114 mg, 0.421 mmol), copper(I) chloride (111 mg, 1.12 mmol), and dry DMF (4.2 mL). In this case, the crude material was isolated by the extraction of the reaction mixture with CH_2Cl_2. Flash column chromatography (21 g of silica gel, 1:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 41 mg (91 %) of the diketone **254** as a colorless crystalline solid (mp 121-122 °C).

IR (neat): 1657, 1606, 1299, 1195, 1113, 1035, 900 cm^{-1}.

^{1}H nmr (400 MHz, $CDCl_3$) δ: 1.61 (br t, 6H, H-7, J = 1.9 Hz), 1.95-2.11 (m, 4H), 2.20-2.32 (m, 2H), 2.38-2.52 (m, 6H).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 11.9, 22.9, 28.9, 37.7, 129.8, 155.4, 198.9.

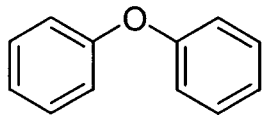
HRMS calcd for $C_{14}H_{18}O_2$: 218.1307; found: 218.1309.

Anal. calcd for $C_{14}H_{18}O_2$: C 77.03, H 8.31; found: C 77.11, H 8.46.

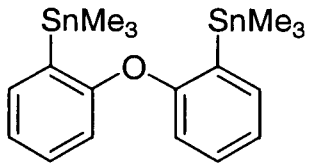
7. Intramolecular coupling of aryltrimethylstannanes mediated by copper(I) chloride

7.1 Preparation of coupling precursors

Preparation of bis(trimethylstannylphenyl) ether (**104**)



255



104

To a cold (-78 °C), stirred solution of *n*-BuLi (2.75 mL, 1.6 M in hexanes, 4.40 mmol) in dry Et_2O (20 mL) was added TMEDA (664 μL, 4.40 mmol) followed by diphenyl ether (**255**) (320 μL, 2.01 mmol) neat via a syringe. The reaction mixture was warmed to room temperature and stirred for 3 h. The dark red solution was cooled to -78 °C and trimethyltin chloride (958 mg, 4.81 mmol) was added as a solid in one portion. The mixture was warmed to room temperature and stirred for 1.5 h. Saturated aqueous sodium bicarbonate (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography of the crude product (30 g of silica gel, pentane) yielded 669 mg of the distannane **104** and further flash column chromatography (20 g of silica gel, pentane) on the impure material yielded 68 mg, giving a total yield of 737 mg (74 %) of the stannane **104** as a crystalline solid (mp 67-69 °C).

IR (KBr): 1578, 1205, 755 cm^{-1}.

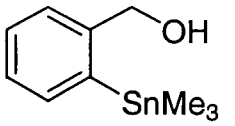
^1H nmr (400 MHz, $CDCl_3$) δ: 0.26 (s, 18H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.9 Hz), 6.62-6.68 (m, 2H), 7.05-7.10 (m, 2H), 7.20-7.24 (m, 2H), 7.46 (dd, 2H, J = 1.6, 7.1 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.6 (-ve), 118.1 (-ve), 123.6 (-ve), 130.5 (-ve), 132.8, 137.0 (-ve), 163.3.

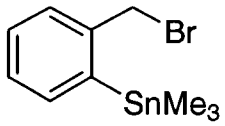
HRMS calcd for $C_{17}H_{23}O^{120}Sn_2$ (M^+-Me): 482.9793; found: 482.9802.

Anal. calcd for $C_{18}H_{26}OSn_2$: C 43.61, H 5.29; found: C 43.93, H 5.30.

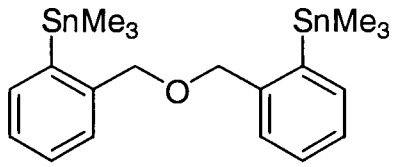
Preparation of bis(2-trimethylstannybenzyl) ether (**108**)



199



202



108

To a cold (0 °C), stirred suspension of sodium hydride (79 mg, 3.3 mmol, washed with pentane) in dry DMF (12 mL) was added a solution of the alcohol **199** (211 mg, 0.779 mmol) in dry DMF (5 mL) via a cannula. After 30 min, a solution of the bromide **202** (443 mg, 1.33 mmol) in dry DMF (4 mL) was added via a cannula and the reaction mixture was stirred for 30 min at 0 °C and at room temperature for 14 h. Et_2O (40 mL) was added and the mixture was washed with water (2 x 20 mL). The organic extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash column chromatography (30 g silica gel, 99:1 petroleum ether-Et_2O with gradual elution to 95:5 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 401 mg (99 %) of the distannane **108** as a colorless oil.

IR (neat): 1069, 1047, 751 cm^{-1}.

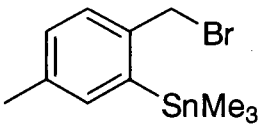
^1H nmr (400 MHz, $CDCl_3$) δ: 0.22 (s, 18H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.5 Hz), 4.43 (s, 4H, -C<u>H</u>$_2$-O-), 7.20-7.33 (m, 6H), 7.45-7.58 (m, 2H).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -8.1 (-ve), 72.8, 127.2 (-ve), 128.2 (-ve), 128.3 (-ve), 136.6 (-ve), 142.1, 144.1.

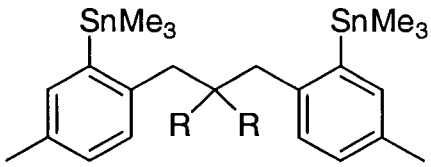
HRMS calcd for $C_{19}H_{27}O^{120}Sn_2$ (M^+-Me): 511.0106; found: 511.0088.

Anal. calcd for $C_{20}H_{30}OSn_2$: C 45.86, H 5.77; found: C 46.02, H 5.88.

Preparation of diethyl 2,2-bis(4-methyl-2-trimethylstannylbenzyl)malonate (**257**)



203



R = -CO_2Et

257

To a stirred suspension of potassium hydride (73 mg, 1.8 mmol, washed with pentane) in dry THF (10 mL) at room temperature was added diethyl malonate (108 μL, 0.715 mmol) via a syringe and the reaction mixture was stirred for 30 min. A solution of the bromide **203** (514 mg, 1.48 mmol) in dry THF (1 mL) was added via a cannula and the mixture was warmed to reflux for 1 h. The reaction mixture was cooled to room temperature and water (10 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (25 g of silica gel, 47:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 486 mg (98 %) of the distannane **257** as a colorless solid (mp 101-103 °C).

IR (KBr): 1726, 1251, 776 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.24 (s, 18H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.1 Hz), 1.03 (t, 6H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 2.25 (s, 6H, -<u>Me</u>), 3.38 (s, 4H, -$C\underline{H}_2$-), 4.01 (q, 4H,

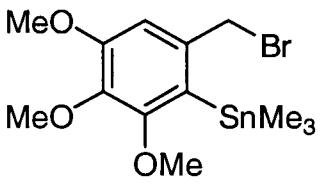
-$CO_2C\underline{H}_2CH_3$, J = 7.1 Hz), 6.97-7.03 (m, 4H), 7.16 (s, 2H, aromatic protons α to -$SnMe_3$, $^3J_{Sn\text{-}H}$ = 50.6 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -7.4 (-ve), 13.8 (-ve), 20.1 (-ve), 42.0, 59.8, 61.3, 127.8 (-ve), 129.0 (-ve), 135.3, 137.2 (-ve), 140.2, 144.6, 171.4.

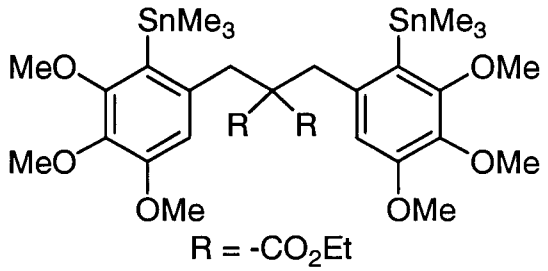
HRMS calcd for $C_{28}H_{41}O_4{}^{120}Sn^{118}Sn$ (M^+-Me): 679.1043; found: 679.1050.

Anal. calcd for $C_{29}H_{44}O_4Sn_2$: C 50.19, H 6.39; found: C 50.50, H 6.57.

Preparation of diethyl 2,2-bis(3,4,5-trimethoxy-2-trimethylstannylbenzyl)malonate (**258**)



204



258

To a stirred suspension of potassium hydride (56 mg, 1.4 mmol, washed with pentane) in dry THF (10 mL) at room temperature was added diethyl malonate (94 μL, 0.62 mmol) and stirring was continued for 30 min. A solution of the bromide **204** (574 mg, 1.32 mmol) in dry THF (1 mL) was added via a cannula and the mixture was warmed to reflux for 1.5 h. The reaction mixture was cooled to room temperature and water (10 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (25 g of silica gel, 7:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 437 mg (84 %) of the distannane **258** as a colorless solid (mp 111-112 °C).

IR (KBr): 1727, 1102, 770 cm^{-1}.

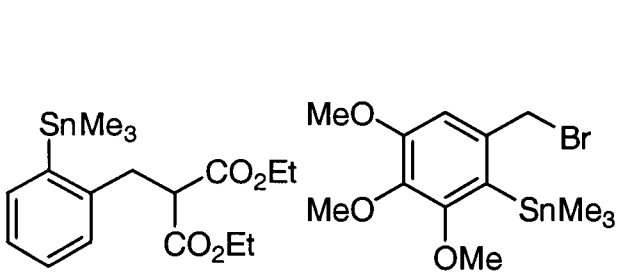
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.25 (s, 18H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.2 Hz), 0.99 (t, 6H, -$CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 3.11 (s, 4H, -C<u>H</u>$_2$-), 3.76 (s, 6H, -O<u>Me</u>), 3.77 (s, 6H, -O<u>Me</u>), 3.83 (s, 6H, -O<u>Me</u>), 3.92 (q, 4H, -$CO_2C\underline{H}_2CH_3$, J = 7.1 Hz), 6.60 (s, 2H, aromatic protons, $^4J_{Sn\text{-}H}$ = 17.5 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -5.3 (-ve), 13.7 (-ve), 41.8, 55.8 (-ve), 60.4 (-ve), 60.8 (-ve), 60.9, 61.3, 109.2 (-ve), 128.7, 139.25, 139.36, 153.7, 157.0, 171.2.

HRMS calcd for $C_{32}H_{49}O_{10}{}^{120}Sn_2$ (M^+-Me): 833.1370; found: 833.1393.

Anal. calcd for $C_{33}H_{52}O_{10}Sn_2$: C 46.84, H 6.19; found: C 47.15, H 6.26.

<u>Preparation of diethyl 2-(3,4,5-trimethoxy-2-trimethylstannylbenzyl)-2-(2-trimethyl stannylbenzyl)malonate (**259**)</u>



212 **204** **259**

To a stirred suspension of potassium hydride (42 mg, 1.05 mmol, washed with pentane) in dry THF (8 mL) at room temperature was added a solution of the stannane **212** (344 mg, 0.832 mmol) in dry THF (1 mL). After 1 h, a solution of the bromide **204** (364 mg, 0.861 mmol) in dry THF (1 mL) was added via a cannula. The reaction mixture was warmed to reflux for 1.5 h and then was cooled to room temperature. Water (10 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (30 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump)

from the acquired material yielded 489 mg (78 %) of the distannane **259** as a white solid (mp 66-71 °C).

IR (KBr): 1727, 1102, 771 cm^{-1}.

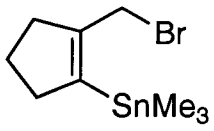
^1H nmr (400 MHz, $CDCl_3$) δ: 0.20 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 53.0 Hz), 0.25 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 54.0 Hz), 1.01 (t, 6H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 3.34 (s, 2H, -C$\underline{H}_2$-), 3.42 (s, 2H, -C$\underline{H}_2$-), 3.74 (s, 3H, -O$\underline{Me}$), 3.78 (s, 3H, -O$\underline{Me}$), 3.84 (s, 3H, -O$\underline{Me}$), 3.99 (q, 4H, $-CO_2C\underline{H}_2CH_3$, J = 7.1 Hz), 6.54 (s, 1H, $^4J_{Sn-H}$ = 17.6 Hz), 7.11-7.24 (m, 3H), 7.34-7.34 (m, 1H).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -7.5 (-ve), -5.4 (-ve), 13.6 (-ve), 41.5, 42.2, 49.2, 55.6 (-ve), 60.3 (-ve), 60.7 (-ve), 61.0, 108.9 (-ve), 125.9 (-ve), 127.9 (-ve), 128.0 (-ve), 128.9, 136.7 (-ve), 138.9, 139.4, 143.4, 144.6, 153.7, 157.0, 171.1.

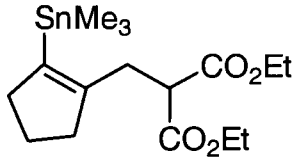
HRMS calcd for $C_{29}H_{43}O_7{}^{120}Sn_2$ (M^+-Me): 743.1053; found: 743.1061.

Anal. calcd for $C_{30}H_{46}O_7Sn_2$: C 47.66, H 6.13; found: C 47.87, H 6.20.

Preparation of diethyl 2-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]malonate (**261**)



260



261

To a stirred suspension of potassium hydride (0.546 g, 13.6 mmol) in dry THF (50 mL) at room temperature was added diethyl malonate (3.00 mL, 17.8 mmol) neat via a syringe. After 1 h, a solution of the bromide **260**[27,76] (1.44 g, 4.39 mmol) in dry THF (5 mL) was added to the mixture via a cannula. The reaction mixture was warmed to reflux for 1 h and then was cooled to room temperature. Water (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with

brine (100 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (100 g of silica gel, 93:7 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.47 g (82 %) of the diester **261** as a colorless clear oil.

IR (neat): 1736, 1615, 1239, 1039, 771 cm^{-1}.

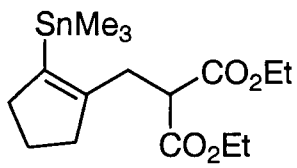
^1H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.8 Hz), 1.19 (t, 6H, -CO_2CH_2C<u>H</u>$_3$, J = 7.1 Hz), 1.70-1.80 (m, 2H, -CH_2-C<u>H</u>$_2$-CH_2-), 2.20-2.30 (br t, 2H, -C<u>H</u>$_2$-CH_2-CH_2- J = 7.4 Hz), 2.30-2.35 (m, 2H, -CH_2-CH_2-C<u>H</u>$_2$-), 2.72 (d, 2H, -C<u>H</u>$_2$-CH-, J = 7.8 Hz), 3.43 (t, 1H, -CH_2-C<u>H</u>-, J = 7.8 Hz), 4.10-4.19 (m, 4H, -CO_2C<u>H</u>$_2CH_3$).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: -9.5 (-ve), 14.0 (-ve), 24.3, 32.3, 35.6, 39.3, 51.2 (-ve), 61.1, 139.8, 148.6, 169.0.

HRMS calcd for $C_{15}H_{25}O_4{}^{120}Sn$: 389.0775; found: 389.0770.

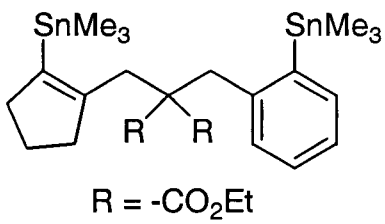
Anal. calcd for $C_{16}H_{28}O_4Sn$: C 47.68, H 7.00; found: C 47.60, H 7.03.

<u>Preparation of diethyl 2-[(2-trimethylstannylcyclopenten-1-yl)methyl]-2-(2-trimethyl stannylbenzyl)malonate (**113**)</u>



260

202



112

To a stirred suspension of potassium hydride (56 mg, 1.4 mmol, washed with pentane) in dry THF (13 mL) at room temperature was added a solution of the stannane **260** (534 mg, 1.32 mmol) in dry THF (1 mL) via a cannula. After 1 h, a solution of the bromide **202** (703 mg, 2.10 mmol) in dry THF (1 mL) was added via a cannula. The reaction mixture

was warmed to reflux for 1.5 h and then was cooled to room temperature. Water (20 mL) was added and the mixture was extracted with Et_2O (3 x 15 mL). The organic extracts were combined, washed with brine (40 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (50 g of silica gel, 24:1 petroleum ether-Et_2O) of the crude product afforded, after removal of trace amounts of solvent (vacuum pump) from the acquired material, 822 mg (94 %) of the distannane **112** as a white solid (mp 67-69 °C).

IR (KBr): 1744, 1722, 1248, 773 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.08 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.6 Hz), 0.30 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.2 Hz), 1.09 (t, 6H, -CO_2CH_2C<u>H</u>$_3$, J = 7.1 Hz), 1.74-1.81 (m, 2H, -CH_2-C<u>H</u>$_2$-CH_2-), 2.24 (br t, 2H, -C<u>H</u>$_2$-CH_2-CH_2-, J = 7.3 Hz), 2.31 (br t, 2H, -CH_2-CH_2-C<u>H</u>$_2$-, J = 7.0 Hz), 2.98 (s, 2H, -C<u>H</u>$_2$-), 3.32 (s, 2H, -C<u>H</u>$_2$-), 4.00-4.07 (m, 4H, -CO_2C<u>H</u>$_2$$CH_3$), 7.11-7.18 (m, 3H), 7.29-7.45 (m, 1H).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -9.2 (-ve), -7.3 (-ve), 13.9 (-ve), 24.7, 36.3, 39.0, 39.2, 42.8, 58.5, 61.1, 126.0 (-ve), 128.0 (-ve), 128.1 (-ve), 136.4 (-ve), 141.8, 143.4, 143.7, 148.3, 171.4.

HRMS calcd for $C_{25}H_{39}O_4{}^{120}Sn_2$ (M^+-Me): 643.0892; found: 643.0895.

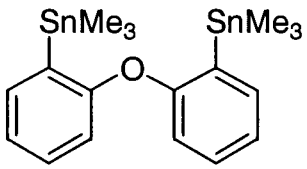
Anal. calcd for $C_{26}H_{42}O_4Sn_2$: C 47.60, H 6.45; found: C 47.89, H 6.36.

7.2 Intramolecular couplings mediated by copper(I) chloride

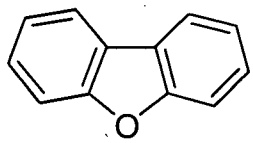
General Procedure 7: Copper(I) chloride mediated intramolecular coupling of aryltrimethylstannanes

To a stirred, solution-suspension of copper(I) chloride (~5 equiv) in dry DMF (~15 mL/mmol of substrate) at room temperature was added, via a syringe pump over 30 min, a solution of the appropriate distannane (1 equiv) in dry DMF (~15 mL/mmol of substrate). The mixture was stirred for an additional 30 min. Aqueous ammonium chloride-ammonia (pH 8) was added (~2 mL/mL of DMF) and the mixture was stirred open to the atmosphere until it was a deep blue. The mixture was extracted with Et_2O (3 x ~2 mL/mL of DMF) and the combined organic extracts were washed with brine (3 x ~2 mL/mL of DMF), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The resulting crude material was purified by flash column chromatography.

Preparation of dibenzofuran (**105**)



104

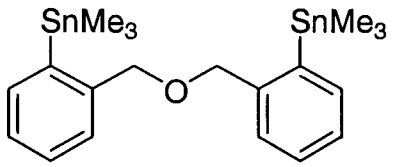


105

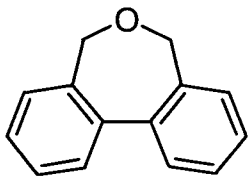
To a stirred solution of the distannane **104** (113 mg, 0.228 mmol) in dry DMF (4.5 mL) at room temperature was added, in one portion, solid CuCl (120 mg, 1.22 mmol). The resulting mixture was stirred for a period of 30 min. Aqueous ammonium chloride-ammonia (pH 8) (5 mL) was added and stirring was continued, open to the atmosphere, until the mixture was a deep blue. The mixture was then extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (10 g of silica gel, 99:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 37 mg (98 %) of dibenzofuran (**105**) as a white solid (mp 81-83 °C). This material

exhibited spectral characteristics (^{1}H nmr) identical with those of an authentic sample and a melting point simliar to that previously reported (mp 83-85 °C).[77]

Preparation of dibenzo[c,e]oxepine (**109**)



108



109

Following general procedure 7, the ether **108** was prepared by the addition of the distannane **108** (92 mg, 0.18 mmol) in dry DMF (2.5 mL) to a stirred solution-suspension of CuCl (97 mg, 0.98 mmol) in dry DMF (1.5 mL). Purification of the crude material by flash column chromatography (7 g of silica gel, 9:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 32 mg (91 %) of the cyclic ether **109**[63] as a colorless oil.

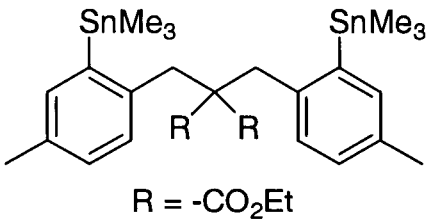
IR (KBr): 1077, 752 cm^{-1}.

^{1}H nmr (400 MHz, $CDCl_3$) δ: 4.35 (s, 4H), 7.55 (d, 2H, J = 7.4 Hz), 7.49 (td, 2H, J = 1.8, 7.5 Hz), 7.40-7.43 (m, 4H).

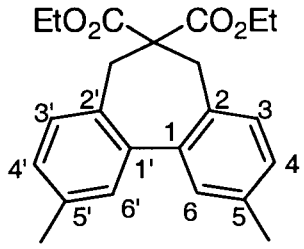
^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 67.5, 127.4, 128.2, 128.9, 129.7, 135.1, 141.2.

HRMS calcd for $C_{14}H_{12}O$: 196.0888; found: 196.0882.

Preparation of 2,2'-(2,2-bis(ethoxycarbonyl)propane-1,3-diyl)-5,5'-dimethylbiphenyl (**264**)



257



264

Following general procedure 7, the diester **264** was prepared by the addition of the distannane **257** (86 mg, 0.12 mmol) in dry DMF (1.9 mL) to a stirred solution-suspension of CuCl (62 mg, 0.63 mmol) in dry DMF (1.9 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 17:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 43 mg (95 %) of the diester **264** as a colorless solid (mp 88-89 °C).

IR (KBr): 1729, 1266, 1197 cm^{-1}.

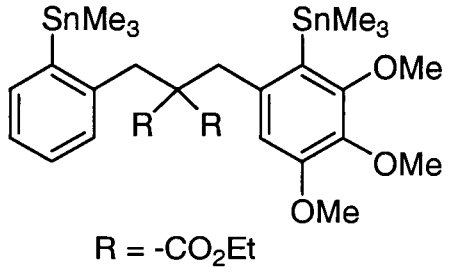
^1H nmr (400 MHz, $CDCl_3$) δ: 1.26 (t, 6H, J = 7.1 Hz), 2.37 (s, 6H, -Me), 2.82 (br s, 2H), 3.14 (br s, 2H), 4.20 (br s, 4H), 7.06 (m, 2H), 7.16 (d, 2H, J = 7.6 Hz), 7.19 (s, 2H).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.1 (-ve), 21.2 (-ve), 36.4, 61.4, 64.6, 128.0 (-ve), 128.8 (-ve), 129.9 (-ve), 132.4, 137.0, 140.5, 170.9.

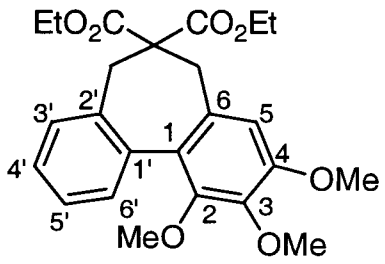
HRMS calcd for $C_{23}H_{26}O_4$: 366.1831; found: 366.1831.

Anal. calcd for $C_{23}H_{26}O_4$: C 75.38, H 7.15; found: C 75.41, H 7.24.

Preparation of 2',6-(2,2-bis(ethoxycarbonyl)propane-1,3-diyl)-2,3,4-trimethoxybiphenyl (**265**)



259



265

Following general procedure 7, the diester **265** was prepared by the addition of the distannane **259** (97 mg, 0.13 mmol) in dry DMF (2 mL) to a stirred solution-suspension of CuCl (63 mg, 0.64 mmol) in dry DMF (2 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 7:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 50 mg (92 %) of the diester **265** as a colorless solid (mp 94-96 °C).

IR (KBr): 1729, 1599 cm^{-1}.

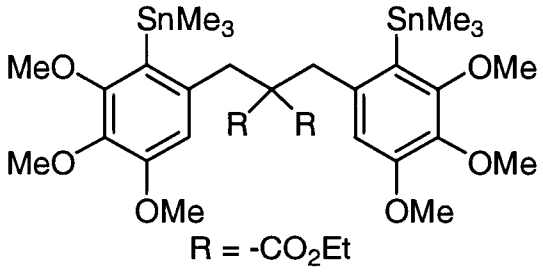
^1H nmr (400 MHz, $CDCl_3$) δ: 1.26 (t, 3H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.72 (d, 1H, J = 13.7 Hz), 2.85 (d, 1H, J = 13.7 Hz), 3.09 (d, 1H, J = 13.7 Hz), 3.18 (d, 1H, J = 13.7 Hz), 3.57 (s, 3H, -O<u>Me</u>), 3.86 (s, 3H, -O<u>Me</u>), 3.89 (s, 3H, -O<u>Me</u>), 4.15-4.27 (m, 4H, $-CO_2C\underline{H}_2CH_3$), 6.61 (s, 1H), 7.19-7.31 (m, 3H), 7.49 (dd, 1H, J = 1.0, 7.5 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.1 (-ve), 14.2 (-ve), 36.7, 37.0, 55.9 (-ve), 60.8 (-ve), 61.0 (-ve), 61.5, 61.6, 64.4, 108.2 (-ve), 125.8, 126.7 (-ve), 127.0 (-ve), 129.8, 130.1 (-ve), 131.5 (-ve), 135.5, 135.9, 141.6, 150.8, 152.3, 170.3, 170.7.

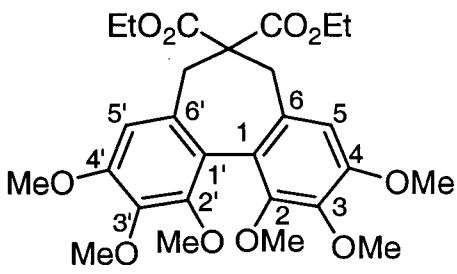
HRMS calcd for $C_{24}H_{28}O_7$: 428.1835; found: 428.1831.

Anal. calcd for $C_{24}H_{28}O_7$: C 67.28, H 6.59; found: C 67.03, H 6.86.

Preparation of 6,6'-(2,2-bis(ethoxycarbonyl)propane-1,3-diyl)-2,2',3,3',4,4'-hexamethoxy biphenyl (**266**)



258



266

Following general procedure 7, the diester **266** was prepared by the addition of the distannane **258** (43 mg, 0.18 mmol) in dry DMF (0.8 mL) to a stirred solution-suspension of CuCl (25 mg, 0.25 mmol) in dry DMF (0.8 mL). Purification of the crude product by flash column chromatography (12 g of silica gel, 13:7 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 16.4 mg (62 %) of the diester **266** as a colorless solid (mp 141-142 °C).

IR (KBr): 1726, 1599, 1111 cm^{-1}.

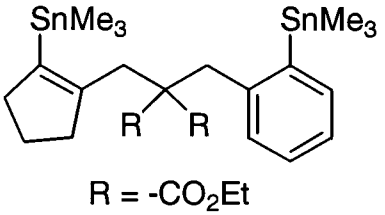
^1H nmr (400 MHz, $CDCl_3$) δ: 1.26 (t, 6H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 2.73 (d, 2H, J = 14.0 Hz), 3.08 (d, 2H, J = 14.0 Hz), 3.64 (s, 6H, -O<u>Me</u>), 3.84 (s, 6H, -O<u>Me</u>), 3.87 (s, 6H, -O<u>Me</u>), 4.11-4.26 (m, 4H, $-CO_2C\underline{H}_2CH_3$), 6.56 (s, 2H).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.2 (-ve), 36.9, 55.9 (-ve), 60.7 (-ve), 60.9 (-ve), 61.5, 63.9, 108.4 (-ve), 122.2, 131.3, 141.2, 151.4, 152.4, 170.5.

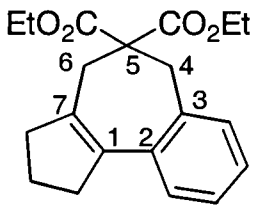
HRMS calcd for $C_{27}H_{34}O_{10}$: 518.2152; found: 518.2150.

Anal. calcd for $C_{27}H_{34}O_{10}$: C 62.54, H 6.61; found: C 62.20, H 6.59.

Preparation of 2,3-benzo-5,5-bis(ethoxycarbonyl)bicyclo[5.3.0]dec-1(7)-ene (**113**)



112



113

Following general procedure 7, the diester **113** was prepared by the addition of the distannane **112** (86 mg, 0.13 mmol) in dry DMF (2 mL) to a stirred solution-suspension of CuCl (68 mg, 0.69 mmol) in dry DMF (2 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 9:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 40 mg (94 %) of the diester **112** as a colorless solid (mp 72-73 °C).

IR (KBr): 1736, 1641, 1251, 762 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 1.14 (t, 6H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 1.89-1.98 (m, 2H), 2.60 (br t, 2H, J = 7.6 Hz), 2.70 (s, 2H), 2.77-2.82 (m, 2H), 3.24 (s, 2H), 4.00-4.11 (m, 4H, $-CO_2C\underline{H}_2CH_3$), 7.01-7.11 (m, 1H), 7.18-7.20 (m, 3H).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: 14.0 (-ve), 22.1, 35.8, 36.8, 39.5, 40.0, 60.7, 61.3, 125.9 (-ve), 126.3 (-ve), 126.8 (-ve), 131.2 (-ve), 134.7, 135.3, 137.1, 137.9, 171.2.

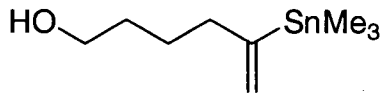
HMRS calcd for $C_{20}H_{24}O_4$: 328.1675; found: 328.1664.

Anal. calcd for $C_{20}H_{24}O_4$: C 73.15, H 7.37; found: C 73.07, H 7.46.

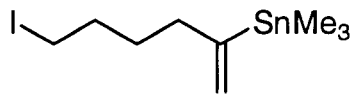
8. Intramolecular oxidative coupling of bisalkenyltrimethylstannanes to form bicyclo[7.3.0]dodecane and bicyclo[8.3.0]tridecane derivatives

8.1 Preparation of precursors

Preparation of 6-iodo-2-trimethylstannylhex-1-ene (**269**)



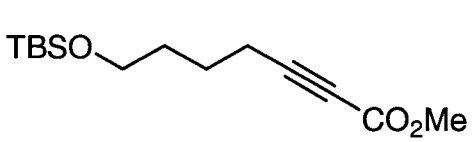
268



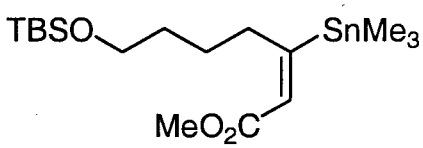
269

To a cool (0 °C), stirred suspension of iodine (3.02 g, 11.8 mmol) in dry CH_2Cl_2 (100 mL) was added triphenylphosphine (3.05 g, 11.6 mmol) in one solid portion. The mixture was stirred for 20 min and a yellow precipitate appeared. Imidazole (1.37 g, 20.1 mmol) was added in one solid portion and the mixture was stirred for an additional 20 min. A solution of the alcohol **268**[47] (2.62 g, 10.0 mmol) in dry CH_2Cl_2 (5 mL) was added via a cannula and the reaction mixture was stirred for 1 h. Pentane (125 mL) was added and the mixture was filtered through a cake of silica gel (~30 g) and the silica gel was eluted with 9:1 petroleum ether-Et_2O (500 mL). The combined filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (100 g of silica gel, 99:1 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 3.46 g (93 %) of the iodide **269** as a colorless clear oil. This material exhibited spectral characteristics (^{1}H nmr) identical to those previously reported.[78]

Preparation of methyl (*E*)-7-*tert*-butyldimethylsiloxy-3-trimethylstannylhept-2-enoate (**271**)



270



271

To a cold (-48 °C), stirred solution of hexamethylditin (10.6 g, 32.4 mmol) in dry THF (200 mL) was added MeLi (21.0 mL, 1.55 M in Et_2O, 32.5 mmol) via a syringe and the solution was stirred for 30 min. Copper(I) cyanide (2.99 g, 33.3 mmol) was added to the solution in one solid portion and stirring was continued for 30 min. The mixture was cooled to -78 °C and dry methanol (1.31 mL, 32.4 mmol) was added via a syringe. The reaction mixture was stirred for 5 min. A solution of the ester **270**[66] (6.06 g, 25.0 mmol) in dry THF (5 mL) was added via a cannula to the mixture and stirring was continued for 4 h. The mixture was warmed to room temperature, opened to the air, and aqueous ammonium chloride-ammonia (pH 8) (150 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 150 mL). The organic layers were combined, washed with brine (350 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash column chromatography (250 g of silica gel, 24:1 petroleum ether-Et_2O with gradual change to 93:7 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 8.57 g (78 %) of the stannane **271** as a colorless clear oil.

IR (neat): 1718, 1596, 1163, 835, 775 cm^{-1}.

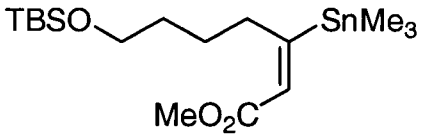
^1H nmr (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H, -Si$\underline{Me_2}$-), 0.18 (s, 9H, -Sn$\underline{Me_3}$, $^2J_{Sn\text{-}H}$ = 53.4 Hz), 0.87 (s, 9H, -Si$^t\underline{Bu}$-), 1.40-1.58 (m, 4H, -C$\underline{H_2}$-C$\underline{H_2}$-), 2.89 (td, 2H, allylic -C$\underline{H_2}$-, J = 7.7, 1.2 Hz, $^3J_{Sn\text{-}H}$ = 61.9 Hz), 3.60 (t, 2H, -O-C$\underline{H_2}$-, J = 6.6 Hz), 3.67 (s, 3H, -$CO_2\underline{Me}$), 5.95 (t, 1H, olefinic proton, J = 1.2 Hz, $^3J_{Sn\text{-}H}$ = 73.6 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -9.1, -6.3, 18.3, 25.95, 26.02, 32.8, 34.4, 50.8, 62.9, 127.0, 164.6, 173.7.

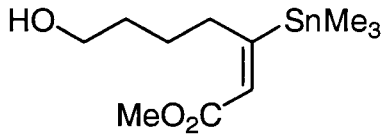
HRMS calcd for $C_{16}H_{33}O_3Si^{120}Sn$ (M^+-Me): 421.1221; found: 421.1230.

Anal. calcd for $C_{17}H_{36}O_3SiSn$: C 46.91, H 8.34; found: C 47.17, H 8.38.

Preparation of methyl (*E*)-7-hydroxy-3-trimethylstannylhept-2-enoate (**272**)



271



272

To a cool (0 °C), stirred solution of the stannane **271** (5.93 g, 13.7 mmol) in dry THF (130 mL) was added a solution of tetrabutylammonium fluoride (20.4 mL, 1 M in THF, 20.4 mmol) and the solution was stirred for 2 h. Saturated aqueous sodium bicarbonate (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude oil. Flash column chromatography (150 g of silica gel, 1:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 4.16 g (95 %) of the stannane **272** as a colorless clear oil.

IR (neat): 1719, 1594, 1161, 770 cm^{-1}.

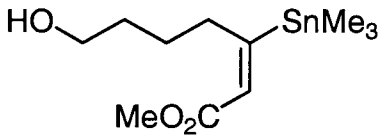
^1H nmr (400 MHz, $CDCl_3$) δ: 0.18 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 53.4 Hz), 1.45-1.76 (m, 5H, -O$\underline{H}$ and -C$\underline{H}_2$-C$\underline{H}_2$-), 2.87 (t, 2H, allylic -C$\underline{H}_2$- J = 7.8 Hz, $^3J_{Sn\text{-}H}$ = 61.4 Hz), 3.64-3.68 (m, 5H, includes 3H -$CO_2\underline{Me}$ singlet at 3.66 and HO-C$\underline{H}_2$-), 5.96 (s, 1H, olefinic proton, $^3J_{Sn\text{-}H}$ = 72.5 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -9.3, 25.4, 32.4, 33.9, 50.8, 61.9, 127.0, 164.6, 173.9.

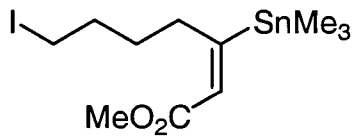
HRMS calcd for $C_{10}H_{19}O_3{}^{120}Sn$ (M^+-Me): 307.0356; found: 307.0363.

Anal. calcd for $C_{11}H_{22}O_3Sn$: C 41.16, H 6.91; found: C 41.43, H 6.98.

Preparation of methyl (*E*)-7-iodo-3-trimethylstannylhept-2-enoate (**273**)



272



273

To a cool (0 °C), stirred suspension of iodine (3.15 g, 12.4 mmol) in dry CH_2Cl_2 (100 mL) was added triphenylphosphine (3.30 g, 12.6 mmol) in one solid portion. The mixture was stirred for 20 min and a yellow precipitate appeared. Imidazole (1.37 g, 20.1 mmol) was added in one solid portion and the mixture was stirred for an additional 20 min. A solution of the alcohol **272** (3.03 g, 9.44 mmol) in dry CH_2Cl_2 (5 mL) was added via a cannula and the reaction mixture was stirred for 1 h. Pentane (150 mL) was added and the mixture was filtered through a cake of silica gel (~30 g) and the silica gel was eluted with Et_2O (250 mL). The combined filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (100 g of silica gel, 19:1 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 3.56 g (88 %) of the iodide **273** as a colorless clear oil.

IR (neat): 1717, 1595, 1173, 773 cm^{-1}.

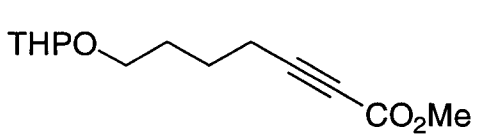
^1H nmr (400 MHz, $CDCl_3$) δ: 0.20 (s, 9H, -Sn<u>Me</u>$_3$, $^3J_{Sn\text{-}H}$ = 54.6 Hz), 1.47-1.55 (m, 2H, -C<u>H</u>$_2$-CH$_2$-), 1.80-1.88 (m, 2H, -CH$_2$-C<u>H</u>$_2$-), 2.89 (td, 2H, allylic proton, J = 7.3, 1.2 Hz, $^3J_{Sn\text{-}H}$ = 70.7 Hz), 3.19 (t, 2H, I-C<u>H</u>$_2$-, J = 6.6 Hz), 3.67 (s, 3H, -CO$_2$<u>Me</u>), 5.97 (t, 1H, olefinic proton, J = 1.2 Hz, $^3J_{Sn\text{-}H}$ = 72.5 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.0, 6.8, 30.4, 33.1, 33.4, 50.9, 127.5, 164.5, 172.7.

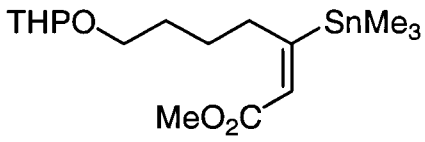
HRMS calcd for $C_{10}H_{18}O_2{}^{120}SnI$ (M^+-Me): 416.9374; found: 416.9371.

Anal. calcd for $C_{11}H_{21}O_2SnI$: C 30.66, H 4.91; found: C 30.82, H 4.96.

Preparation of methyl (*E*)-7-(tetrahydro-2*H*-pyran-2-yloxy)-3-trimethylstannylhept-2-enoate (**275**)



274



275

To a cold (-48 °C), stirred solution of hexamethylditin (10.6 g, 32.4 mmol) in dry THF (200 mL) was added MeLi (20.2 mL, 1.55 M in Et_2O, 32.3 mmol) via a syringe and the solution was stirred for 30 min. Copper(I) cyanide (2.95 g, 33.0 mmol) was added to the solution in one solid portion and stirring was continued for 30 min. The mixture was cooled to -78 °C and dry methanol (1.30 mL, 32.2 mmol) was added via a syringe. The reaction mixture was stirred for 5 min. A solution of the ester **274**[41] (6.00 g, 25.0 mmol) in dry THF (5 mL) was added via a cannula and stirring was continued for 4 h. The mixture was warmed to room temperature, opened to the air, and aqueous ammonium chloride-ammonia (pH 8) (150 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 150 mL). The organic layers were combined, washed with brine (350 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash column chromatography (250 g of silica gel, 17:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 7.11 g (70 %) of the stannane **275** as a colorless clear oil.

IR (neat): 1719, 1595, 1166, 770 cm^{-1}.

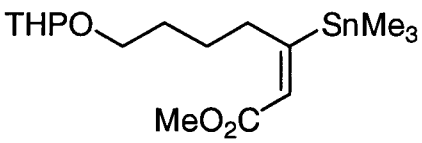
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.18 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.4 Hz), 1.40-1.85 (m, 10H), 2.91 (br t, 2H, allylic -C<u>H</u>$_2$-, J = 7.7 Hz, $^3J_{Sn\text{-}H}$ = 61.2 Hz), 3.34-3.40 (m, 1H), 3.44-3.50 (m, 1H), 3.66 (s, 3H, -CO_2<u>Me</u>), 3.69-3.75 (m, 1H), 3.80-3.83 (m, 1H), 4.56 (t, 1H, J = 3.7 Hz), 5.96 (t, 1H, olefinic proton, J = 1.3 Hz, $^3J_{Sn\text{-}H}$ = 73.4 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -9.1 (-ve), 19.5, 25.5, 26.3, 29.6, 30.7, 34.7, 50.8 (-ve), 62.1, 67.1, 98.7 (-ve), 127.1 (-ve), 164.6, 173.4.

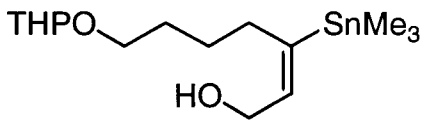
HRMS calcd for $C_{15}H_{27}O_4{}^{120}Sn$ (M^+-Me): 391.0931; found: 391.0932.

Anal. calcd for $C_{16}H_{30}O_4Sn$: C 47.44, H 7.46; found: C 47.69, H 7.55.

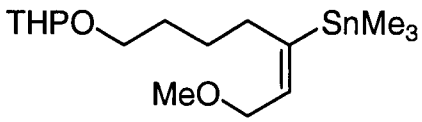
<u>Preparation of (*E*)-7-(tetrahydro-2*H*-pyran-2-yloxy)-1-methoxy-3-trimethylstannylhept-2-ene (**277**)</u>



275



276



277

To a cold (-78 °C), stirred solution of the ester **275** (6.19 g, 15.3 mmol) in dry THF (150 mL) was added a solution of DIBAL (38.5 mL, 1.0 M in hexanes, 38.5 mmol, 2.5 equiv) and the mixture was stirred for 1 h. The solution was warmed to room temperature and stirring was continued for 1 h. Saturated aqueous potassium sodium tartrate (Rochelle salt) (125 mL) was added and, after the mixture had been stirred for 1 h, it was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (200 g of silica gel, 1:1 petroleum ether-Et_2O)

of the crude material yielded 5.25 g (92 %) of the alcohol **276** as a clear oil. This oil was used directly in the next step.

To a cool (0 °C), stirred suspension of sodium hydride (466 mg, 19.4 mmol) in dry THF (140 mL) was added a solution of the alcohol **276** (obtained as described above) in dry THF (5 mL). The mixture was stirred for 1 h. Methyl iodide (2.6 mL, 42 mmol) was added to the suspension neat via a syringe and stirring was continued for 1 hr at 0 °C and for 24 h at room temperature. Water (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. Flash column chromatography (200 g of silica gel, 17:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 5.21 g (96 %, 88 % over 2 steps) of the stannane **277** as a clear oil.

IR (neat): 1454, 1121, 1035, 768 cm^{-1}.

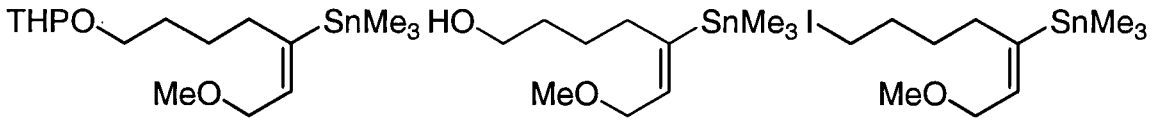
^1H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 52.5 Hz), 1.38-1.84 (m, 10H), 2.31 (t, 2H, J = 7.6 Hz, $^3J_{Sn\text{-}H}$ = 62.4 Hz), 3.32 (s, 3H, -O<u>Me</u>), 3.34-3.39 (m, 1H), 3.45-3.49 (m, 1H), 3.68-3.74 (m, 1H), 3.81-3.87 (m, 1H), 4.00 (d, 2H, Me-O-C<u>H</u>$_2$-, J = 5.9 Hz), 4.54-4.57 (m, 1H), 5.68 (t, 1H, olefinic proton, J = 5.9 Hz, $^3J_{Sn\text{-}H}$ = 78.2 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -9.3 (-ve), 19.5, 25.5, 26.8, 29.4, 30.7, 32.9, 58.1 (-ve), 62.1, 67.1, 68.7, 98.7 (-ve), 136.2 (-ve), 148.7.

HRMS calcd for $C_{15}H_{29}O_3{}^{120}Sn$ (M^+-Me): 377.1139; found: 377.1132.

Anal. calcd for $C_{16}H_{32}O_3Sn$: C 49.14, H 8.25; found: C 49.44, H 8.46.

Preparation of (*E*)-7-iodo-1-methoxy-3-trimethylstannylhept-2-ene (**279**)



277 **278** **279**

To a stirred solution of the stannane **277** (4.84 g, 12.5 mmol) in dry methanol (125 mL) at room temperature was added PPTS (471 mg, 1.87 mmol) in one solid portion. The mixture was warmed to reflux for 2 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure. Purification of the crude product by flash column chromatography (100 g of silica gel, 1:1 petroleum ether-Et_2O with gradual change to Et_2O) yielded 1.68 g (35 %) of the starting material **277** and 2.25 g (59 %, 90 % based on recovered starting material) of the alcohol **278** as a clear oil.

To a cool (0 °C), stirred suspension of iodine (2.51 g, 9.89 mmol) in dry CH_2Cl_2 (75 mL) was added triphenylphosphine (2.67 g, 10.2 mmol) in one solid portion. The mixture was stirred for 20 min and a yellow precipitate appeared. Imidazole (731 mg, 10.7 mmol) was added in one solid portion and the mixture was stirred for an additional 20 min. A solution of the alcohol **278** (obtained as described above) in dry CH_2Cl_2 (5 mL) was added via a cannula and the reaction mixture was stirred for 1 h. Pentane (150 mL) was added and the mixture was filtered through a cake of silica gel (~30 g) and the silica gel was eluted with Et_2O (250 mL). The combined filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (60 g of silica gel, 24:1 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 2.92 g (56 % over two steps) of the iodide **279** as a colorless clear oil.

IR (neat): 1456, 1211, 1115, 763 cm^{-1}.

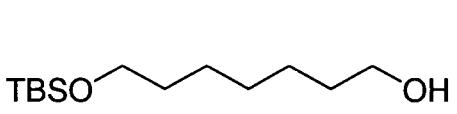
^1H nmr (400 MHz, $CDCl_3$) δ: 0.12 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 52.5 Hz), 1.39-1.46 (m, 2H, -C$\underline{H}_2$-CH_2-), 1.75-1.82 (m, 2H, -CH_2-C$\underline{H}_2$-), 2.30 (br t, 2H, allylic -C$\underline{H}_2$-, J = 7.2 Hz, $^3J_{Sn\text{-}H}$ = 61.1 Hz), 3.17 (t, 2H, I-C$\underline{H}_2$-, J = 6.9 Hz), 3.33 (s, 3H, -O$\underline{Me}$), 3.99 (d, 2H, -O-C$\underline{H}_2$-, J = 6.0 Hz), 5.71 (tt, 1H, olefinic proton, J = 1.2, 6.0 Hz, $^3J_{Sn\text{-}H}$ = 77.2 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.3 (-ve), 6.7, 30.7, 31.9, 32.9, 58.1 (-ve), 68.5, 136.4 (-ve), 148.1.

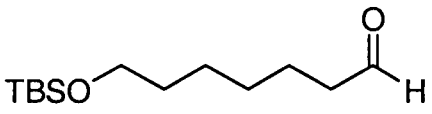
HRMS calcd for $C_{10}H_{20}O^{120}SnI$ (M^+-Me): 402.9581; found: 402.9587.

Anal. calcd for $C_{11}H_{23}OSnI$: C 31.69, H 5.56; found: C 31.86, H 5.65.

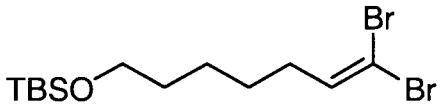
Preparation of 7-*tert*-butyldimethylsiloxyhept-1-yne (**281**)



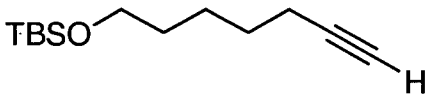
280



280a



280b



281

To a stirred solution of the alcohol **280**[68] (11.8 g, 47.8 mmol) in dry CH_2Cl_2 (475 mL) at room temperature was added sodium acetate (2.88 g, 35.1 mmol) and PCC (20.8 g, 96.5 mmol), each as solids. The reaction mixture was stirred for 2 h. The mixture was diluted with Et_2O (500 mL) and then was filtered through Florisil (~50 g). The cake of Florisil was eluted with Et_2O (1 L) and the combined filtrate was concentrated under reduced pressure. Flash column chromatography (200 g of silica gel, 7:3 petroleum ether-Et_2O) of the crude material yielded 8.62 g (78 %) of the aldehyde **280a** as an oil. This material was used immediately in the next reaction.

To a cool (0 °C), stirred solution of carbon tetrabromide (18.7 g, 56.4 mmol) in dry CH_2Cl_2 (500 mL) was added triphenylphosphine (29.5 g, 112 mmol) in one portion. The mixture was stirred for 10 min. A solution of the aldehyde **280a** (8.62 g, 37.4 mmol) in dry CH_2Cl_2 (20 mL) was added via a cannula. The mixture was stirred for 40 min. Pentane (500 mL) was added and the mixture was filtered through silica gel (~20 g) and

the cake was eluted with pentane (200 mL). The combined filtrate was concentrated under reduced pressure. Flash column chromatography (300 g of silica gel, 200:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 9.63 g (67 %) of the dibromoalkene **280b** as a colorless clear oil. This oil was used directly in the next reaction.

To a stirred suspension of magnesium metal (3.00 g, 123 mmol) in dry THF (100 mL) at room temperature was added a solution of the alkene **280b** (9.63 g, 24.9 mmol) in dry THF (5 mL) via a cannula. The resulting mixture was sonicated for 18 h. Pentane (100 mL) was added and the mixture was filtered through a pad of silica gel (~50 g). The cake of silica gel was eluted with Et_2O (400 mL) and the combined filtrate was concentrated under reduced pressure. Bulb-to-bulb distillation (140-160 °C/15 torr) of the crude product yielded 4.69 g (83 %, 43 % over 3 steps) of the alkyne **281** as a colorless clear oil.

IR (neat): 3314, 1256, 1161, 838, 776 cm^{-1}.

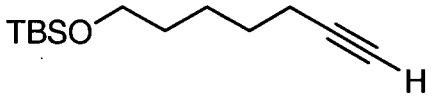
^1H nmr (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H, -Si$\underline{Me_2}$-), 0.87 (s, 9H, -Si$^t\underline{Bu}$-), 1.37-1.57 (m, 6H), 1.90 (t, 1H, acetylenic proton, J = 2.6 Hz), 2.17 (td, 2H, propargylic -C$\underline{H_2}$-, J = 7.0, 2.6 Hz), 3.59 (t, 2H, -O-C$\underline{H_2}$-, J = 6.3 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -5.3, 18.4, 25.0, 25.9 (2C), 28.3, 32.3, 62.9, 68.2, 84.4.

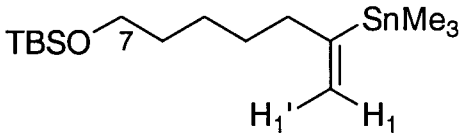
HRMS calcd for $C_{12}H_{23}OSi$ (M^+-Me): 211.1518; found: 211.1517.

Anal. calcd for $C_{13}H_{26}OSi$: C 68.96, H 11.57; found: C 69.01, H 11.51.

Preparation of 7-*tert*-butyldimethylsiloxy-2-trimethylstannylhept-1-ene (**282**)



281



282

To a cold (-48 °C), stirred solution of hexamethylditin (6.80 g, 20.5 mmol) in dry THF (80 mL) was added a solution of MeLi (13.1 mL, 1.6 M in Et_2O, 21.0 mmol) via a syringe and the solution was stirred for 30 min. The solution was cooled to -78 °C and copper bromide–dimethyl sulfide complex (4.70 g, 22.8 mmol) was added in one portion. The red-brown suspension was stirred for 30 min. A solution of the alkyne **281** (2.26 g, 10.0 mmol) in dry THF (20 mL) was added via a cannula to the mixture followed by dry methanol (24.0 mL, 59.2 mmol) dropwise over 2 min via a syringe. The reaction mixture was stirred at -78 °C for 3 h , at -48 °C for 3 h, and at 0 °C for 1 h. The mixture was opened to the air and aqueous ammonium chloride-ammonia (pH 8) (100 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous layer was extracted with Et_2O (3 x 150 mL). The organic layers were combined, washed with brine (200 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash column chromatography (100 g of silica gel, 200:1 petroleum ether-Et_2O) yielded 2.86 g (73 %) of the stannane **282** as a clear oil.

IR (neat): 1472, 1255, 1105, 835, 774 cm^{-1}.

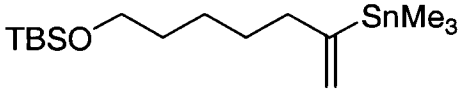
^1H nmr (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H, -Si$\underline{Me_2}$-), 0.10 (s, 9H, -Sn$\underline{Me_3}$, $^2J_{Sn\text{-}H}$ = 52.8 Hz), 0.82 (s, 9H, -Si$^t\underline{Bu}$-), 1.25-1.41 (m, 4H), 1.46-1.53 (m, 2H), 2.25 (t, 2H, H-3, J = 7.4 Hz, $^3J_{Sn\text{-}H}$ = 52.2 Hz), 3.58 (t, 2H, H-7, J = 6.7 Hz), 5.09-5.11 (m, 1H, H-1, $^3J_{Sn\text{-}H}$ = 71.8 Hz), 5.61-5.63 (m, 1H, H-1', $^3J_{Sn\text{-}H}$ = 154.6 Hz).

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: -9.5 (-ve), -5.3 (-ve), 18.4, 25.4, 26.0 (-ve), 29.6, 32.7, 40.8, 63.2, 124.3, 135.8.

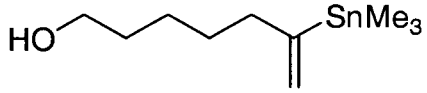
HRMS calcd for $C_{15}H_{33}OSi^{120}Sn$ (M^+-Me): 377.1323; found: 377.1326.

Anal. calcd for $C_{16}H_{36}OSiSn$: C 49.12, H 9.24; found: C 49.35, H 9.22.

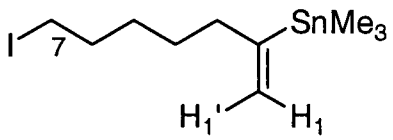
Preparation of 7-iodo-2-trimethylstannylhept-1-ene (**284**)



282



283



284

To a cool (0 °C), stirred solution of the stannane **282** (1.09 g, 2.80 mmol) in dry THF (25 mL) was added a solution of tetrabutylammonium fluoride (4.2 mL, 1 M in THF, 4.2 mmol) and the solution was stirred for 1 h. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to provide a crude oil that was used directly for the next reaction.

To a cool (0 °C), stirred suspension of iodine (1.15 g, 4.48 mmol) in dry CH_2Cl_2 (25 mL) was added triphenylphosphine (1.15 g, 4.38 mmol) in one solid portion. The mixture was stirred for 20 min and a yellow precipitate appeared. Imidazole (0.373 g, 5.47 mmol) was added in one solid portion and the mixture was stirred for an additional 20 min. A solution of the alcohol **283** (obtained as described above) in dry CH_2Cl_2 (2 mL) was added via a cannula and the reaction mixture was stirred for 1 h. Pentane (50 mL) was added and the mixture was filtered through a cake of silica gel (~15 g) and the silica gel was eluted with Et_2O (150 mL). The combined filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (60 g of silica gel, petroleum ether) which, after removal of trace amounts of solvent (vacuum pump)

from the acquired material, yielded 910 mg (84 % over 2 steps) of the iodide **284** as a colorless clear oil.

IR (neat): 1434, 1209, 916, 769 cm^{-1}.

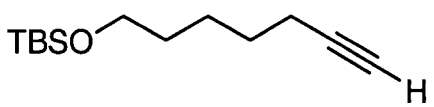
^1H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 52.8 Hz), 1.35-1.39 (m, 4H), 1.77-1.85 (m, 2H), 2.24-2.24 (m, 2H, H-3, $^3J_{Sn-H}$ = 51.7 Hz), 3.16 (t, 2H, H-7, J = 7.0 Hz), 5.12-5.13 (m, 1H, H-1, $^3J_{Sn-H}$ = 52.2 Hz), 5.61-5.63 (m, 1H, H-1', $^3J_{Sn-H}$ = 152.7 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.4, 7.0, 28.4, 30.0, 33.4, 40.5, 124.6, 155.5.

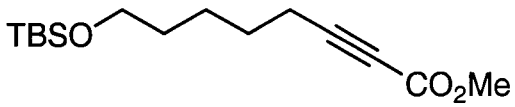
HRMS calcd for $C_9H_{18}{}^{120}SnI$ (M^+-Me): 372.9475; found: 372.9473.

Anal. calcd for $C_{10}H_{21}SnI$: C 31.05, H 5.47; found: C 31.09, H 5.53.

<u>Preparation of methyl 8-*tert*-butyldimethylsiloxyoct-2-ynoate (**285**)</u>



281



285

To a cold (-78 °C), stirred solution of the alkyne **281** (2.87 g, 12.7 mmol) in dry THF (50 mL) was added a solution of methyllithium (11.2 mL, 1.6 M in hexanes, 17.9 mmol). The solution was stirred for 10 min at -78 °C and for 1 h at -20 °C. Methyl chloroformate (1.50 mL, 19.4 mmol) was added neat via a syringe and the mixture was stirred for 1 h at -20 °C and at room temperature for 1 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography (100 g of silica gel, 19:1 petroleum ether-Et_2O) and removal of trace

amounts of solvent (vacuum pump) from the acquired material yielded 3.34 g (93 %) of the ester **285** as a colorless oil.

IR (neat): 2239, 1724, 1435, 1267, 1099, 839, 774 cm^{-1}.

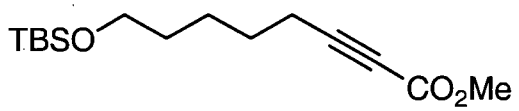
^1H nmr (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H, -Si$\underline{Me_2}$-), 0.87 (s, 9H, -Si$^t\underline{Bu}$-), 1.40-1.60 (m, 6H), 2.32 (t, 2H, propargylic -C$\underline{H_2}$-, J = 7.1 Hz), 3.59 (t, 2H, -O-C$\underline{H_2}$-, J = 6.2 Hz), 3.73 (s, 3H, -$CO_2\underline{Me}$).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -5.4 (-ve), 18.3, 18.6, 25.1, 25.9 (-ve), 27.3, 32.1, 52.4 (-ve), 62.8, 72.9, 89.6, 154.1.

HRMS calcd for $C_{14}H_{25}O_3Si$ (M^+-Me): 269.1573; found: 269.1574.

Anal. calcd for $C_{15}H_{28}O_3Si$: C 63.33, H 9.92; found: C 63.66, H 9.93.

Preparation of methyl (*E*)-8-*tert*-butyldimethylsiloxy-3-trimethylstannyloct-2-enoate (**286**)



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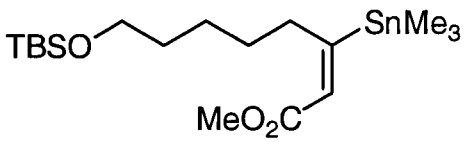


286

To a cold (-48 °C), stirred solution of hexamethylditin (5.31 g, 16.2 mmol) in dry THF (200 mL) was added MeLi (10.1 mL, 1.6 M in Et_2O, 16.2 mmol) via a syringe and the solution was stirred for 30 min. Copper(I) cyanide (1.49 g, 16.2 mmol) was added to the solution in one solid portion and stirring was continued for 30 min. The mixture was cooled to -78 °C and dry methanol (0.60 mL, 16.2 mmol) was added via a syringe. The reaction mixture was stirred for 5 min. A solution of the ester **285** (3.55 g, 12.5 mmol) in dry THF (5 mL) was added via a cannula to the mixture and stirring was continued for 4 h. The mixture was warmed to room temperature, opened to the air, and aqueous

ammonium chloride-ammonia (pH 8) (150 mL) was added. The suspension was stirred until the aqueous phase became a deep blue color. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 x 150 mL). The organic layers were combined, washed with brine (350 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (250 g of silica gel, 40:1 petroleum ether-Et_2O with gradual change to 20:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material provided 8.57 g (78 %) of the stannane **286** as a colorless clear oil.

IR (neat): 1719, 1596, 1164, 837, 775 cm^{-1}.

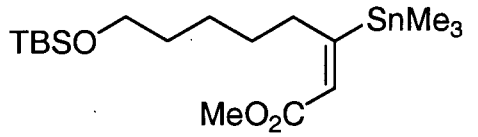
^1H nmr (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H, -Si$\underline{Me}_2$-), 0.17 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 53.2 Hz), 0.87 (s, 9H, -Si$^t\underline{Bu}$-), 1.32-1.53 (m, 6H), 2.87 (tm, 2H, allylic -C$\underline{H}_2$-, J = 7.0 Hz, $^3J_{Sn\text{-}H}$ = 64.6 Hz), 3.58 (t, 2H, -O-C$\underline{H}_2$-, J = 6.5 Hz), 3.60 (s, 3H, -$CO_2\underline{Me}$), 5.94 (t, 1H, olefinic proton, J = 1.2 Hz, $^3J_{Sn\text{-}H}$ = 73.7 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.3 (-ve), -5.3 (-ve), 18.3, 25.8, 26.0 (-ve), 29.5, 32.7, 34.7, 50.8 (-ve), 63.1, 126.9 (-ve), 164.6, 173.8.

HRMS calcd for $C_{17}H_{35}O_3Si^{120}Sn$ (M^+-Me): 435.1377; found: 435.1371.

Anal. calcd for $C_{18}H_{38}O_3SiSn$: C 48.12, H 8.53; found: C 47.88, H 8.58.

Preparation of methyl (*E*)-8-iodo-3-trimethylstannyloct-2-enoate (**288**)



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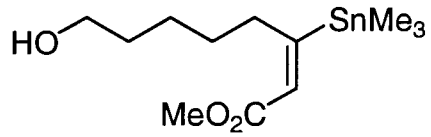

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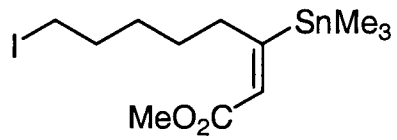


288

To a stirred solution of the stannane **286** (1.38 g, 3.07 mmol) in dry THF (30 mL) at room temperature was added a solution of tetrabutylammonium fluoride (4.6 mL, 1 M in THF, 4.6 mmol) and the solution was stirred for 1 h. Saturated aqueous sodium bicarbonate (20 mL) was added and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a crude oil. Flash column chromatography (12 g silica gel, 98:2 petroleum ether-Et_2O) of the crude product yielded the alcohol **287** as a colorless clear oil that was used directly in the next reaction.

To a cool (0 °C), stirred suspension of iodine (1.15 g, 4.55 mmol) in dry CH_2Cl_2 (30 mL) was added triphenylphosphine (1.19 g, 4.55 mmol) in one solid portion. The mixture was stirred for 20 min and a yellow precipitate appeared. Imidazole (494 mg, 7.25 mmol) was added in one solid portion and the mixture was stirred for an additional 20 min. A solution of the alcohol **287** (obtained as described above) in dry CH_2Cl_2 (5 mL) was added via a cannula and the reaction mixture was stirred for 1 h. Pentane (150 mL) was added and the mixture was filtered through a cake of silica gel (~30 g) and the silica gel was eluted with Et_2O (250 mL). The combined filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (100 g of silica gel, 19:1 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 1.32 g (97 % over 2 steps) of the iodide **288** as a colorless clear oil.

IR (neat): 1718, 1595, 1172, 771 cm^{-1}.

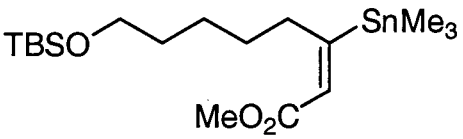
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.17 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 54.4 Hz), 1.38-1.44 (m, 4H), 1.79-1.87 (m, 2H), 2.87 (td, 2H, allylic -C<u>H</u>$_2$-, J = 6.8, 1.3 Hz, $^3J_{Sn\text{-}H}$ = 64.6 Hz), 3.17 (t, 2H, I-C<u>H</u>$_2$-, J = 6.7 Hz), 3.68 (s, 3H, -CO_2<u>Me</u>), 5.96 (t, 1H, olefinic proton, J = 1.3 Hz, $^3J_{Sn\text{-}H}$ = 73.1 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.1 (-ve), 6.9, 28.3, 30.3, 33.1, 34.3, 50.8 (-ve), 127.2 (-ve), 164.5, 173.2.

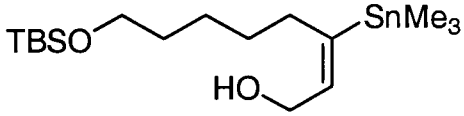
HRMS calcd for $C_{11}H_{20}O_2{}^{120}SnI$ (M^+-Me): 428.9524; found: 428.9525.

Anal. calcd for $C_{12}H_{23}O_2SnI$: C 32.40, H 5.21; found: C 32.29, H 4.99.

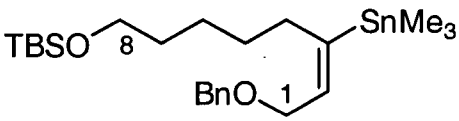
<u>Preparation of (*E*)-1-benzyloxy-8-*tert*-butyldimethylsiloxy-3-trimethylstannyloct-2-ene (**290**)</u>



286



289



290

To a cold (-78 °C), stirred solution of the ester **286** (1.77 g, 3.94 mmol) in dry THF (40 mL) was added a solution of DIBAL (11.8 mL, 1.0 M in hexanes, 11.8 mmol, 3.0 equiv) and the mixture was stirred for 1 h. The solution was warmed to room temperature and stirring was continued for 1 h. Saturated aqueous potassium sodium tartrate (Rochelle salt) (50 mL) was added. After the mixture had been stirred for 1 h, it was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure to provide the alcohol **289** as a crude oil that was used directly in the next reaction.

To a cool (0 °C), stirred suspension of sodium hydride (142 mg, 5.91 mmol) in dry THF (40 mL) was added a solution of the alcohol **289** (obtained as described above) in dry THF (5 mL) via a cannula. The reaction mixture was stirred for 1 h. Benzyl bromide (1.50 mL, 12.6 mmol) was added via a syringe and stirring was continued for 1 hr at 0 °C and for 24 h at room temperature. Water (50 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo*. Flash column chromatography (200 g of silica gel, 9:1 petroleum ether-Et_2O) of the crude oil and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.51 g (75 % over 2 steps) of the stannane **290** as a clear oil.

IR (neat): 1497, 1255, 1099, 836, 775 cm^{-1}.

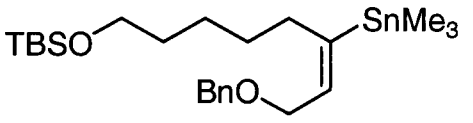
^1H nmr (400 MHz, $CDCl_3$) δ: 0.02 (s, 6H, -SiMe$_2$-), 0.10 (s, 9H, -SnMe$_3$, $^2J_{Sn\text{-}H}$ = 52.5 Hz), 0.87 (s, 9H, -Si^{t}Bu-), 1.28-1.38 (m, 4H), 1.44-1.53 (m, 2H), 2.25 (br t, 2H, H-4, J = 7.0 Hz, $^3J_{Sn\text{-}H}$ = 62.0 Hz), 3.56 (t, 2H, H-8, J = 6.5 Hz), 4.10 (d, 2H, H-1, J = 5.9 Hz), 4.50 (s, 2H, benzylic -CH$_2$-), 5.92-5.78 (m, 1H, H-2, $^3J_{Sn\text{-}H}$ = 77.5 Hz), 7.24-7.35 (m, 5H, aromatic protons).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.2 (-ve), -5.3 (-ve), 18.4, 25.6, 26.0 (-ve), 30.0, 32.7, 33.2, 63.1, 66.3, 72.1, 127.6, 127.8 (-ve), 128.3 (-ve), 136.0 (-ve), 138.3 (-ve), 149.1.

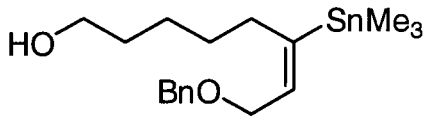
HRMS calcd for $C_{23}H_{41}O_2Si^{120}Sn$ (M^+-Me): 497.1898; found: 497.1884.

Anal. calcd for $C_{24}H_{44}O_2SiSn$: C 56.37, H 8.67; found: C 56.59, H 8.60.

Preparation of (*E*)-1-benzyloxy-8-iodo-3-trimethylstannyloct-2-ene (**292**)



290



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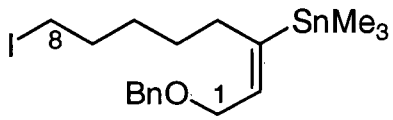


292

To a stirred solution of the stannane **290** (1.51 g, 2.94 mmol) in dry THF (30 mL) at room temperature was added a solution of tetrabutylammonium fluoride (4.5 mL, 1 M in THF, 4.5 mmol) and the solution was stirred for 1 h. Saturated aqueous sodium bicarbonate (30 mL) was added and the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent was removed *in vacuo* to provide the alcohol **291** as a crude oil that was used directly for the next reaction.

To a cool (0 °C), stirred suspension of iodine (1.15 g, 4.55 mmol) in dry CH_2Cl_2 (50 mL) was added triphenylphosphine (1.28 g, 4.87 mmol) in one solid portion. The mixture was stirred for 20 min and a yellow precipitate appeared. Imidazole (420 mg, 6.17 mmol) was added in one solid portion and the mixture was stirred for 20 min. A solution of the alcohol **291** (obtained as described above) in dry CH_2Cl_2 (5 mL) was added via a cannula and the reaction mixture was stirred for 1 h. Pentane (100 mL) was added and the mixture was filtered through a cake of silica gel (~30 g) and the silica gel was eluted with Et_2O (250 mL). The combined filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (75 g of silica gel, 24:1 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 1.34 g (90 % over 2 steps) of the iodide **292** as a colorless clear oil.

IR (neat): 1454, 1358, 1204, 1092, 767 cm^{-1}.

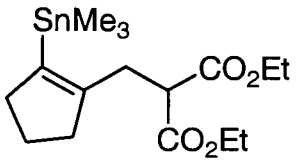
^{1}H nmr (400 MHz, $CDCl_3$) δ: 0.11 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 52.5 Hz), 1.30-1.38 (m, 4H), 1.74-1.81 (m, 2H), 2.25 (br t, 2H, H-4, J = 6.0 Hz, $^3J_{Sn\text{-}H}$ = 61.6 Hz), 3.14 (t, 2H, H-8, J = 7.0 Hz), 4.08 (d, 2H, H-1, J = 6.0 Hz), 4.51 (s, 2H, benzylic -C<u>H</u>$_2$-), 5.77 (tt, 1H, H-2, J = 1.2, 6.0 Hz, $^3J_{Sn\text{-}H}$ = 77.9 Hz), 7.26-7.34 (m, 5H, aromatic protons).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.2 (-ve), 6.9, 29.0, 30.2, 32.9, 33.2, 66.2, 72.4, 127.5 (-ve), 127.8 (-ve), 128.3 (-ve), 136.3 (-ve), 138.2, 148.7.

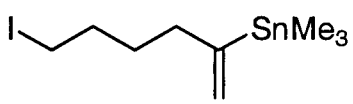
HRMS calcd for $C_{17}H_{26}O^{120}SnI$ (M^+-Me): 493.0050; found: 493.0049.

Anal. calcd for $C_{18}H_{29}OSnI$: C 42.64, H 5.77; found: C 42.83, H 5.83.

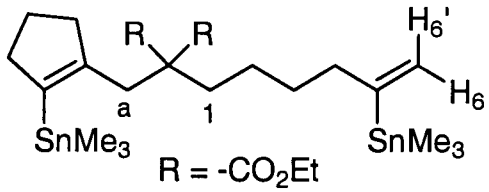
<u>Preparation of diethyl 2-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]-2-(5-trimethylstannylhex-5-en-1-yl)malonate (**293**)</u>



261



269



293

To a cold (-78 °C), stirred solution of LDA (1.80 mmol) in dry THF (18 mL) was added a solution of the stannane **261** (763 mg, 1.89 mmol) in dry THF (1 mL) via a cannula. The mixture was stirred for 1 h at -78 °C and at 0 °C for 15 min. A solution of the iodide **269** (876 mg, 2.35 mmol) in dry THF (1 mL) was added via a cannula and the mixture was warmed to reflux for 21 h. The reaction mixture was cooled to room temperature and saturated aqueous sodium bicarbonate (15 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (50 mL),

dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (100 g of silica gel, 95:5 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 888 mg (72 %) of the distannane **293** as a colorless clear oil.

IR (neat): 1734, 1607, 1240, 770, 471 cm^{-1}.

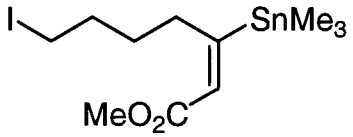
^1H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 52.8 Hz), 0.15 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.2 Hz), 1.15-1.27 (m, 8H, includes 6H -$CO_2CH_2C\underline{H}_3$ triplet at 1.22 with J = 7.1 Hz), 1.30-1.40 (m, 2H), 1.73-1.85 (m, 4H), 2.15-2.35 (m, 6H), 2.86 (br s, 2H, H-a), 4.10-4.20 (m, 4H, -$CO_2C\underline{H}_2CH_3$), 5.07-5.10 (m, 1H, H-6, $^3J_{Sn-H}$ = 70.4 Hz), 5.58-5.60 (m, 1H, H-6', $^3J_{Sn-H}$ = 117.6 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.5 (-ve), -9.2 (-ve), 14.0 (-ve), 24.1, 24.7, 29.8, 33.7, 35.8, 37.5, 38.8, 40.4, 57.1, 61.0, 124.5, 141.3, 148.2, 155.4, 171.8.

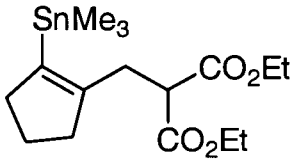
HRMS calcd for $C_{24}H_{43}O_4{}^{118}Sn\,{}^{120}Sn$ (M^+-Me): 633.1199; found: 633.1204.

Anal. calcd for $C_{25}H_{46}O_4Sn_2$: C 46.34, H 7.15; found: C 46.63, H 7.39.

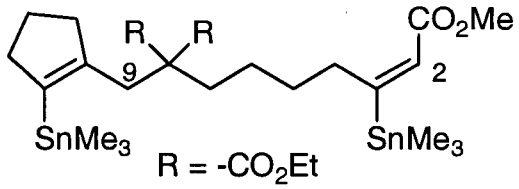
Preparation of methyl (*E*)-8,8-bis(ethoxycarbonyl)-3-trimethylstannyl-9-(2-trimethyl stannylcyclopent-1-en-1-yl)non-2-enoate (**294**)



273



261



294

To a cold (-78 °C), stirred solution of LDA (2.52 mmol) in dry THF (25 mL) was added a solution of the stannane **261** (1.07 g, 2.66 mmol) in dry THF (5 mL). The mixture was stirred for 1 h at -78 °C and at 0 °C for 15 min. A solution of the iodide **273** (1.41 g, 3.30 mmol) in dry THF (5 mL) was added via a cannula and the mixture was warmed to reflux for 21 h. The reaction mixture was cooled to room temperature and saturated aqueous sodium bicarbonate (30 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (100 g of silica gel, 37:3 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 1.54 g (86 %) of the distannane **294** as colorless viscous oil.

IR (neat): 1729, 1597, 1163, 771 cm^{-1}.

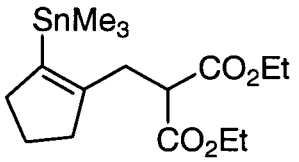
^1H nmr (400 MHz, $CDCl_3$) δ: 0.15 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.4 Hz), 0.16 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 53.3 Hz), 1.20-1.40 (m, 10H, includes 6H -CO_2CH_2C<u>H_3</u> triplet at 1.22 with J = 7.1 Hz), 1.73-1.80 (m, 4H), 2.19 (br t, 2H, J = 7.2 Hz), 2.32 (br t, 2H, J = 7.2 Hz), 2.74-2.94 (m, 4H, H-4 and H-9), 3.66 (s, 3H, -CO_2<u>Me</u>), 4.10-4.20 (m, 4H, -CO_2C<u>H_2</u>CH_3), 5.93 (s, 1H, H-2, $^3J_{Sn\text{-}H}$ = 73.4 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.3 (-ve), -9.2 (-ve), 14.0 (-ve), 24.63, 24.67, 30.0, 33.9, 34.4, 35.8, 37.7, 38.8, 50.7, 57.1, 60.9, 127.1 (-ve), 141.3, 148.2, 164.4, 171.7, 173.0.

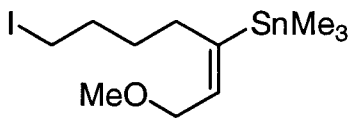
HRMS calcd for $C_{26}H_{45}O_6{}^{120}Sn_2$ (M^+-Me): 693.1260; found: 693.1258.

Anal. calcd for $C_{27}H_{48}O_6Sn_2$: C 45.93, H 6.85; found: C 45.89, H 6.76.

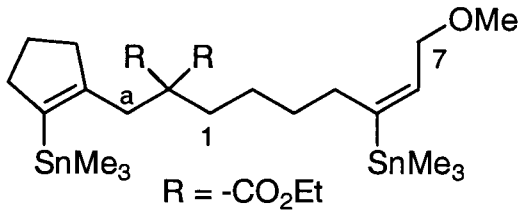
Preparation of diethyl 2-[(*E*)-7-methoxy-5-trimethylstannylhept-5-en-1-yl]-2-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]malonate (**295**)



261



279



295

To a stirred suspension of potassium hydride (143 mg, 3.58 mmol) in dry THF (25 mL) at room temperature was added a solution of the stannane **261** (1.24 g, 3.08 mmol) in dry THF (5 mL) via a cannula. The mixture was stirred for 1 h. A solution of the iodide **279** (876 mg, 2.35 mmol) in dry THF (5 mL) was added via a cannula and the mixture was warmed to reflux for 2 h. The reaction mixture was cooled to room temperature and saturated aqueous sodium bicarbonate (30 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (80 g of silica gel, 92:8 petroleum ether-Et_2O with gradual change to 4:1 petroleum ether-Et_2O) which, after removal of trace amounts of solvent (vacuum pump) from the acquired material, yielded 888 mg (72 %) of the distannane **295** as a colorless clear oil.

IR (neat): 1733, 1607, 1237, 769 cm^{-1}.

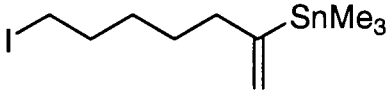
^1H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 52.6 Hz), 0.16 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.3 Hz), 1.18-1.33 (m, 10H, includes 6H -CO_2CH_2C<u>H</u>$_3$ triplet at 1.22 with J = 7.1 Hz), 1.73-1.80 (m, 4H), 2.15-2.19 (m, 2H), 2.25 (br t, 2H, J = 7.3 Hz), 2.30-2.35 (m, 2H), 2.86 (br s, 2H, H-a), 3.32 (s, 3H, -O<u>Me</u>), 3.97 (d, 2H, H-7, J = 6.0 Hz), 4.12-4.18 (m, 4H, -CO_2C<u>H</u>$_2CH_3$), 5.66 (tm, 1H, H-6, J = 6.0 Hz, $^3J_{Sn-H}$ = 78.0 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.3 (-ve), -9.2 (-ve), 14.0 (-ve), 24.6, 24.7, 30.6, 33.1, 33.8, 35.8, 37.6, 38.8, 57.1, 58.1 (-ve), 61.0, 68.6, 136.0 (-ve), 141.1, 148.2, 148.7, 171.8.

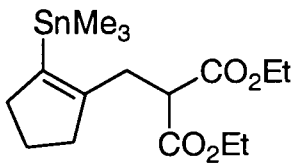
HRMS calcd for $C_{26}H_{47}O_5{}^{120}Sn_2$ (M^+-Me): 679.1467; found: 679.1462.

Anal. calcd for $C_{27}H_{50}O_5Sn_2$: C 46.98, H 7.28; found: C 46.68, H 7.23.

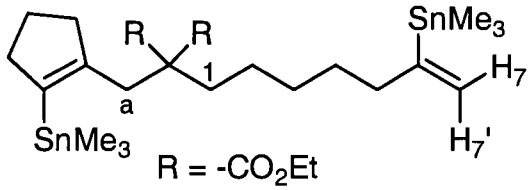
<u>Preparation of diethyl 2-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]-2-(6-trimethylstannylhept-6-en-1-yl)malonate (**296**)</u>



284



261



296

To a stirred suspension of potassium hydride (114 mg, 2.86 mmol) in dry THF (25 mL) at room temperature was added a solution of the diester **261** (1.16 g, 2.89 mmol) in dry THF (5 mL) via a cannula. After 1 h, a solution of the iodide **284** (910 mg, 2.35 mmol) in dry

THF (2 mL) was added to the mixture via a cannula. The reaction mixture was warmed to reflux for 18 h and then cooled to room temperature. Water (20 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (60 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (80 g of silica gel, 24:1 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.50 g (96 %) of the distannane **296** as a colorless, extremely viscous oil.

IR (neat): 1733, 1607, 1234, 769 cm^{-1}.

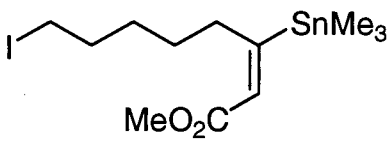
^1H nmr (400 MHz, $CDCl_3$) δ: 0.08 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.6 Hz), 0.15 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 54.6 Hz), 1.16-1.36 (m, 12H, includes 6H -$CO_2CH_2C\underline{H}_3$ triplet at 1.22 with J = 7.2 Hz), 1.70-1.80 (m, 4H), 2.16-2.34 (m, 6H), 2.86 (br s, 2H, H-a), 4.10-4.20 (m, 4H, -$CO_2C\underline{H}_2CH_3$), 5.08-5.10 (m, 1H, H-7, $^3J_{Sn-H}$ = 70.5 Hz), 5.58-5.60 (m, 1H, H-7', $^3J_{Sn-H}$ = 154.0 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.6 (-ve), -9.2 (-ve), 14.0 (-ve), 24.4, 24.6, 29.3, 29.4, 33.7, 35.8, 37.5, 38.8, 40.7, 57.1, 60.9, 124.3, 141.2, 148.2, 155.6, 171.8.

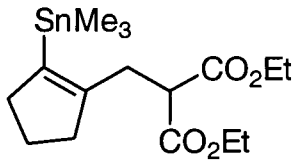
HRMS calcd for $C_{25}H_{45}O_4{}^{120}Sn_2$ (M^+-Me): 649.1362; found: 649.1352.

Anal. calcd for $C_{26}H_{48}O_4Sn_2$: C 47.17, H 7.31; found: C 47.23, H 7.18.

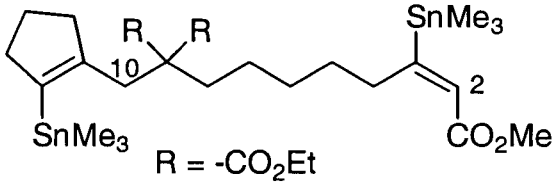
Preparation of methyl (*E*)-9,9-bis(ethoxycarbonyl)-3-trimethylstannyl-10-(2-trimethylstannylcyclopent-1-en-1-yl)dec-2-enoate (**297**)



288



261



297

To a stirred suspension of potassium hydride (88 mg, 2.2 mmol) in dry THF (25 mL) at room temperature was added a solution of the diester **261** (992 mg, 2.46 mmol) in dry THF (2 mL) via a syringe. After 1 h, a solution of the iodide **288** (876 mg, 1.97 mmol) in dry THF (2 mL) was added to the mixture via a cannula. The reaction mixture was warmed to reflux for 1.5 h and then was cooled to room temperature. Water (30 mL) was added and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (75 g of silica gel, 37:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.17 g (82 %) of the distannane **297** as a colorless, extremely viscous oil.

IR (neat): 1729 (br), 1596, 1434, 1171, 770 cm^{-1}.

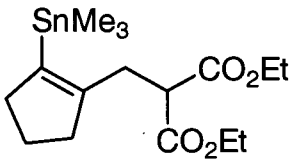
^1H nmr (400 MHz, $CDCl_3$) δ: 0.15 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 52.3 Hz), 0.16 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn\text{-}H}$ = 52.1 Hz), 1.16-1.39 (m, 12H, includes 6H -CO_2CH_2C<u>H</u>$_3$ triplet at 1.24 with J = 7.1 Hz), 1.73-1.80 (m, 4H), 2.18 (br t, 2H, J = 7.3 Hz), 2.31 (br t, 2H, J = 7.1 Hz), 2.82-2.88 (m, 4H, H-4 and H-10), 3.66 (s, 3H, -CO_2<u>Me</u>), 4.10-4.20 (m, 4H, -CO_2C<u>H</u>$_2CH_3$), 5.94 (t, 1H, H-2, J = 2.1 Hz, $^3J_{Sn\text{-}H}$ = 73.7 Hz).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.2 (-ve), -9.1 (-ve), 14.0 (-ve), 24.56, 24.60, 29.5, 30.0, 33.7, 34.6, 35.8, 37.5, 38.8, 50.7 (-ve), 57.1, 60.9, 126.9 (-ve), 141.2, 148.2, 164.5, 171.8, 173.5.

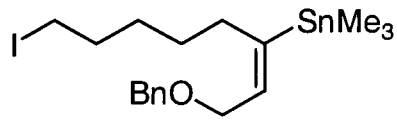
HRMS calcd for $C_{27}H_{47}O_6{}^{118}Sn^{120}Sn$ (M^+-Me): 705.1411; found: 705.1418.

Anal. calcd for $C_{28}H_{50}O_6Sn_2$: C 46.70, H 7.00; found: C 47.02, H 7.03.

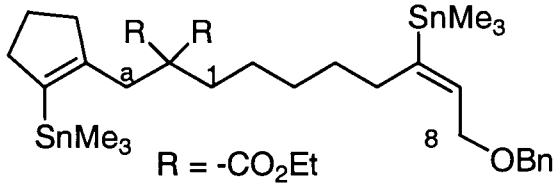
Preparation of diethyl 2-[(*E*)-8-benzyloxy-6-trimethylstannyloct-6-en-1-yl]-2-[(2-trimethylstannylcyclopent-1-en-1-yl)methyl]malonate (**298**)



261



292



298

To a stirred suspension of potassium hydride (93 mg, 2.3 mmol) in dry THF (25 mL) at room temperature was added a solution of the diester **261** (992 mg, 2.46 mmol) in dry THF (2 mL) via a syringe. After 1 h, a solution of the iodide **292** (1.00 g, 1.97 mmol) in dry THF (2 mL) was added to the mixture via a cannula. The reaction mixture was warmed to reflux for 2 h and then was cooled to room temperature. Water (30 mL) was added and the mixture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. Flash column chromatography (75 g of silica gel, 17:3 petroleum ether-Et_2O) of the crude product and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 1.11 g (73 %) of the distannane **298** as a colorless, extremely viscous oil.

IR (neat): 1729, 1607, 1234, 769 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 0.09 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 52.6 Hz), 0.16 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53.0 Hz), 1.17-1.30 (m, 12H, includes 6H -CO_2CH_2C<u>H_3</u> triplet at 1.22 with J = 7.1 Hz), 1.73-1.81 (m, 4H), 2.10-2.35 (m, 6H), 2.85 (br s, 2H, H-a), 4.05-4.20 (m, 6H, includes H-8 and -CO_2C<u>H_2</u>CH_3), 4.50 (s, 2H, benzylic -C<u>H_2</u>-), 5.73 (t, 1H, H-7, J = 6.0 Hz, $^3J_{Sn-H}$ = 74.0 Hz), 7.24-7.35 (m, 5H, aromatic protons).

^{13}C nmr (75.5 MHz, $CDCl_3$) δ: -9.3 (-ve), -9.2 (-ve), 14.0 (-ve), 24.60, 24.64, 29.8, 30.0, 33.2, 33.8, 35.8, 37.6, 38.8, 57.1, 60.9, 66.3, 72.4, 127.5 (-ve), 127.8 (-ve), 128.3 (-ve), 136.1 (-ve), 138.3, 141.3, 148.2, 148.9, 171.8.

HRMS calcd for $C_{33}H_{53}O_5{}^{118}Sn^{120}Sn$ (M^+-Me): 767.1931; found: 767.1929.

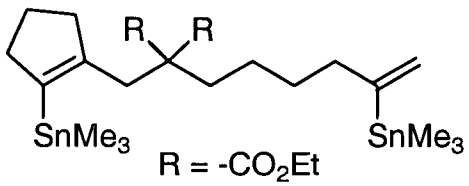
Anal. calcd for $C_{34}H_{56}O_5Sn_2$: C 52.21, H 7.22; found: C 52.07, H 7.27.

8.2 Intramolecular oxidative couplings mediated by copper(I) chloride

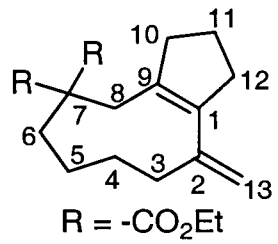
General Procedure 8: CuCl-mediated intramolecular oxidative coupling of bisalkenyltrimethylstannanes

To a stirred solution-suspension of CuCl (~5 equiv) in dry DMF (10 mL/mmol of substrate) at room temperature was added a solution of the bisalkenyltrimethylstannane (1 equiv) in dry DMF (20 mL/mmol of substrate) via a syringe pump over 2 h. After the addition of the stannane was complete, the reaction mixture was stirred for 2 h. The mixture was opened to the atmosphere, aqueous ammonium chloride-ammonia (pH 8) (~5 mL/mmol of substrate) was added, and the mixture was stirred until the aqueous phase became deep blue. The mixture was diluted with water (~5 mL/mmol of substrate) and extracted with Et_2O (3 x ~10 mL/mmol of substrate). The combined organic phases were washed with brine (3 x ~20 mL/mmol of substrate), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

Preparation of 7,7-bis(ethoxycarbonyl)-2-methylidenebicyclo[7.3.0]-dodec-1(9)-ene (**299**)



293



299

Following general procedure 8, the diene **299** was prepared by the addition of the distannane **293** (91 mg, 0.14 mmol), as a solution in dry DMF (2.8 mL), to a stirred solution-suspension of CuCl (71 mg, 0.72 mmol) in dry DMF (1.4 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 19:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 42 mg (93 %) of the diene **299** as a colorless oil.

IR (neat): 1729, 1467, 1446, 1203 cm^{-1}.

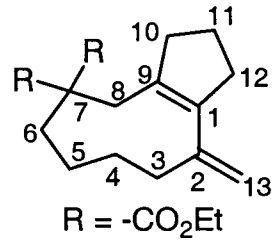
^1H nmr (400 MHz, $CDCl_3$) δ: 1.21 (t, 6H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 1.33-1.39 (m, 2H, H-5), 1.60-1.74 (m, 4H, H-4 and H-11), 1.88 (br t, 2H, H-6, J = 6.2 Hz), 2.18 (br t, 2H, H-10, J = 7.4 Hz), 2.30 (br t, 2H, H-3, J = 7.3 Hz), 2.42 (br t, 2H, H-12, J = 7.2 Hz), 2.92 (br s, 2H, H-8), 4.08-4.20 (m, 4H, $-CO_2C\underline{H}_2CH_3$), 4.90 (d, 1H, H-13, J = 2.0 Hz), 4.94 (unresolved m, 1H, H-13').

^{13}C nmr (50.3 MHz, $CDCl_3$) δ: 14.0 (-ve), 20.3, 22.1, 28.6, 29.6, 31.0, 32.3, 37.6, 38.8, 57.2, 61.0, 114.8, 132.0, 142.6, 147.3, 171.9.

HRMS calcd for $C_{19}H_{28}O_4$: 320.1988; found: 320.1988.

Anal. calcd for $C_{19}H_{28}O_4$: C 71.22, H 8.81; found: C 70.98, H 9.07.

Table 34. ^{1}H nmr (200 MHz, $CDCl_3$) data for the diester **299**: COSY experiment

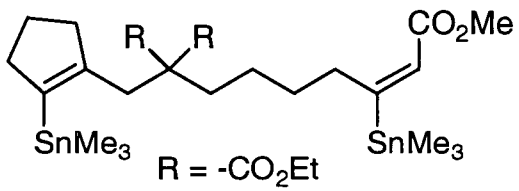


R = -CO_2Et

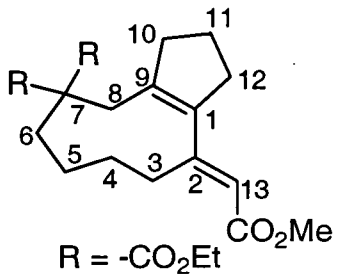
299

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	COSY Correlations
H-3	2.30 (br t, *J* = 7.3)	H-4, H-13
H-4	high-field portion of 1.60-1.74 (m)	H-3, H-5
H-5	1.33-1.39 (m)	H-4, H-6
H-6	1.88 (br t, *J* = 6.2)	H-5
H-8	2.92 (br s)	
H-10	2.18 (br t, *J* = 7.4)	H-11
H-11	low-field portion of 1.60-1.74 (m)	H-10, H-12
H-12	2.42 (br t, *J* = 7.2)	H-11
H-13	4.90 (d, *J* = 2.0)	H-3
H-13'	4.94 (unresolved m)	
-$CO_2C\underline{H}_2CH_3$	4.08-4.20 (m)	-$CO_2CH_2C\underline{H}_3$
-$CO_2CH_2C\underline{H}_3$	1.21 (t, *J* = 7.1)	-$CO_2C\underline{H}_2CH_3$

Preparation of 7,7-bis(ethoxycarbonyl)-2-[(*E*)-methoxycarbonylmethylidene] bicyclo[7.3.0]dodec-1(9)-ene (**300**)



294



300

Following general procedure 8, the triester **300** was prepared by the addition of the distannane **294** (154 mg, 0.218 mmol), as a solution in dry DMF (4.5 mL), to a stirred solution-suspension of CuCl (111 mg, 1.12 mmol) in dry DMF (2.5 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 9:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 60 mg (72 %) of the triester **300** as a colorless oil.

IR (neat): 1730, 1627, 1590, 1432, 1163 cm^{-1}.

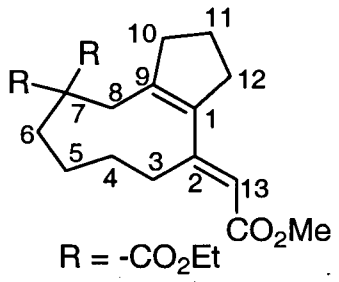
^1H nmr (400 MHz, $CDCl_3$) δ: 1.17-1.29 (m, 8H, includes 6H $-CO_2CH_2C\underline{H}_3$ triplet at 1.19 with J = 7.1 Hz and H-5), 1.70-1.90 (m, 6H, H-4, H-6, H-11), 2.19 (br t, 2H, H-10, J = 7.3 Hz), 2.44 (unresolved m, 2H, H-12), 2.67 (unresolved m, 2H, H-3), 2.87 (br s, 2H, H-8), 3.67 (s, 3H, $-CO_2\underline{Me}$), 3.95-4.20 (m, 4H, $-CO_2\underline{CH}_2CH_3$), 5.67 (s, 1H, H-13).

^{13}C nmr (125.8 MHz, $CDCl_3$) δ: 14.0 (-ve), 19.9, 22.4, 26.5, 27.6, 28.4, 30.7, 37.8, 38.7, 50.9 (-ve), 56.2, 61.2, 117.8, 134.0, 143.9, 160.6, 166.5, 171.6.

HRMS calcd for $C_{21}H_{30}O_6$: 378.2043; found: 378.2043.

Anal. calcd for $C_{21}H_{30}O_6$: C 66.65, H 7.99; found: C 66.47, H 7.96.

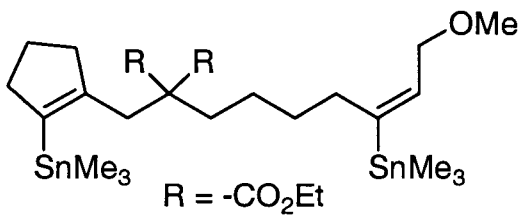
Table 35. ^{1}H nmr (400 MHz, $CDCl_3$) data for the diester **300**: NOED and COSY experiments



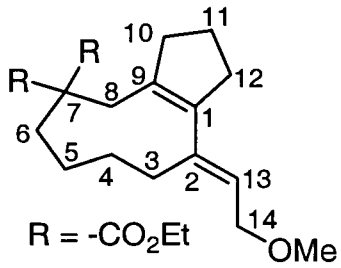
300

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	COSY Correlation	NOED Correlation
H-3	2.67 (unresolved m)	H-4	
H-4 and H-6	low-field portion of 1.70-1.90 (m)	H-3, H-5	
H-5	low-field portion of 1.17-1.29 (m)	H-4, H-6	
H-8	2.87 (br s)		
H-10	2.19 (br t, *J* = 7.3)	H-11, H-12	H-8, H-11, H-12 (-ve), $-CO_2C\underline{H}_2CH_3$
H-11	high-field portion of 1.70-1.90 (m)	H-10, H-12	
H-12	2.44 (unresolved m)	H-10, H-11	H-11, H-13
H-13	5.67 (s)		H-12
$-CO_2C\underline{H}_2CH_3$	3.95-4.20 (m)	$-CO_2CH_2C\underline{H}_3$	
$-CO_2CH_2C\underline{H}_3$	high-field portion of 1.17-1.29 (m)	$-CO_2C\underline{H}_2CH_3$	
$-CO_2\underline{Me}$	3.67 (s)		

Preparation of 7,7-bis(ethoxycarbonyl)-2-[(*E*)-methoxymethylmethylidene]bicyclo[7.3.0] dodec-1(9)-ene (**301**)



295



301

Following general procedure 8, the diester **301** was prepared by the addition of the distannane **295** (115 mg, 0.166 mmol), as a solution in dry DMF (3.4 mL), to a stirred solution-suspension of CuCl (82 mg, 0.83 mmol) in dry DMF (1.7 mL). Purification of the crude product by flash column chromatography (12 g of silica gel, 4:1 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 55 mg (91 %) of the diester **301** as a colorless oil.

IR (neat): 1729, 1466, 1367, 1197 cm^{-1}.

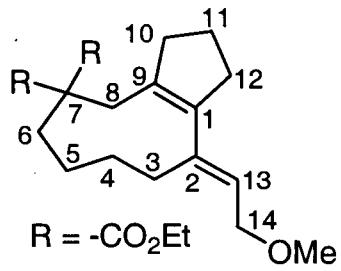
^1H nmr (400 MHz, $CDCl_3$) δ: 1.21 (t, 6H, $-CO_2CH_2C\underline{H}_3$, J = 7.1 Hz), 1.26-1.33 (m, 2H, H-5), 1.55-1.62 (m, 2H, H-4), 1.67-1.75 (m, 2H, H-11), 1.83 (br t, 2H, H-6, J = 6.7 Hz), 2.14 (br t, 2H, H-10, J = 7.5 Hz), 2.28 (br t, 2H, H-3, J = 6.5 Hz), 2.39 (unresolved m, 2H, H-12), 2.85 (br s, 2H, H-8), 3.32 (s, 3H, -O<u>Me</u>), 3.95 (d, 2H, H-14, J = 6.4 Hz), 4.08-4.19 (m, 4H, $-CO_2C\underline{H}_2CH_3$), 5.41 (t, 1H, H-13, J = 6.4 Hz).

^{13}C nmr (75.3 MHz, $CDCl_3$) δ: 14.0 (-ve), 19.1, 22.2, 26.7 (2C), 27.2, 30.3, 37.7, 38.0, 56.0, 58.0 (-ve), 61.0, 69.1, 125.6, 130.7, 140.2, 144.6, 171.7.

HRMS calcd for $C_{21}H_{32}O_5$: 364.2250; found: 364.2253.

Anal. calcd for $C_{21}H_{32}O_5$: C 69.20, H 8.85; found: C 68.98, H 8.87.

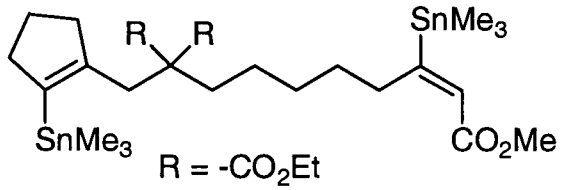
Table 36. ^{1}H nmr (400 MHz, $CDCl_3$) data for the diester **301**: NOED and COSY experiments



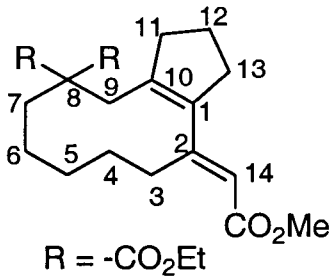
301

Assignment H-x	^{1}H nmr (400 MHz) δ (multiplicity, *J* (Hz))	COSY Correlation	NOED Correlation
H-3	2.28 (br t, *J* = 6.5)	H-4	
H-4	1.55-1.62 (m)	H-3, H-5	
H-5	1.26-1.33 (m)	H-4, H-6	
H-6	1.83 (br t, *J* = 6.7)	H-5	
H-8	2.85 (br s)		
H-10	2.14 (br t, *J* = 7.5)	H-11, H-12	
H-11	1.67-1.75 (m)	H-10, H-12	
H-12	2.39 (unresolved m)	H-10, H-11	H-11, H-13
H-13	5.41 (t, *J* = 6.4)	H-14	H-12, H-14
H-14	3.95 (d, *J* = 6.4)	H-13	H-3, H-13, -O<u>Me</u>
-$CO_2C\underline{H}_2CH_3$	4.08-4.19 (m)	-$CO_2CH_2C\underline{H}_3$	
-$CO_2CH_2C\underline{H}_3$	1.21 (t, *J* = 7.1)	-$CO_2C\underline{H}_2CH_3$	
-O<u>Me</u>	3.32 (s)		

Preparation of 8,8-bis(ethoxycarbonyl)-2-[(*E*)-methoxycarbonylmethylidene] bicyclo[8.3.0]tridec-1(10)-ene (**303**)



297



303

Following general procedure 8, the triester **303** was prepared by the addition of the distannane **297** (96 mg, 0.13 mmol), as a solution in dry DMF (2.6 mL), to a stirred solution-suspension of CuCl (68 mg, 0.69 mmol) in dry DMF (1.3 mL). Purification of the crude product by flash column chromatography (7 g of silica gel, 17:3 petroleum ether-Et_2O) and removal of trace amounts of solvent (vacuum pump) from the acquired material yielded 24 mg (45 %) of the triester **303** as a colorless oil. This material solidified upon prolonged standing in a freezer to give a waxy white solid (mp 88-90 °C).

IR (neat): 1730 (br), 1620, 1435, 1276, 1166 cm^{-1}.

^1H nmr (400 MHz, $CDCl_3$) δ: 1.00-1.90 (br m, 16H, includes 6H $-CO_2CH_2C\underline{H}_3$ br t at 1.22 with J = 6.8 Hz), 1.90-2.80 (br m, 6H), 3.00-3.50 (br s, 2H), 3.68 (s, 3H, $-CO_2\underline{Me}$), 4.11-4.20 (m, 4H, $-CO_2C\underline{H}_2CH_3$), 5.59 (br s, 1H, H-14).

^{13}C nmr (75.3 MHz, $CDCl_3$) δ: 14.1 (-ve), 19.5, 21.5, 22.3, 27.7, 28.4, 29.8 (2C), 36.3, 36.4, 50.9 (-ve), 55.6, 61.3, 111.4, 115.0 (-ve), 135.5, 143.2, 161.8, 167.1.

HRMS calcd for $C_{22}H_{32}O_6$: 392.2199; found: 392.2199.

Anal. calcd for $C_{22}H_{32}O_6$: C 67.32, H 8.22; found: C 67.36, H 8.11.

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