

The use of some bifunctional reagents in organic synthesis

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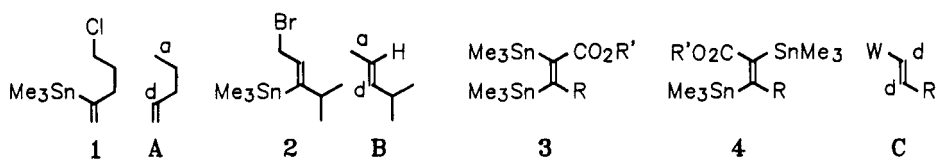
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Abstract: The preparation and synthetic uses of a number of bifunctional reagents (5-chloro-2-trimethylstannyl-2-pentene and related substances, (*Z*)-1-bromo-4-methyl-3-trimethylstannyl-2-pentene, and alkyl (*Z*)- and (*E*)-2,3-bis(trimethylstannyl)-2-alkenoates) are described. In this work a number of useful annulation methods were developed and these annulation sequences played key roles in effecting total syntheses of the sesquiterpenoids (\pm)-axamide-1 and (\pm)-axisonitrile-1, the diterpenoid (\pm)-(14 \underline{S})-dolasta-1(15),7,9-trien-14-ol, and the sesterterpenoid (\pm)-palauolide. A versatile synthesis of functionalized, stereochemically defined tetra-substituted alkenes, starting from α,β -acetylenic esters, has been developed.

INTRODUCTION

Organic reagents that possess two reactive sites (normally nucleophilic and/or electrophilic) and are incorporated into a substrate molecule via sequential or "simultaneous" deployment of the reactive centers have become increasingly important in organic synthesis. A perusal of the recent chemical literature makes it clear that these "bifunctional conjunctive reagents" (ref. 1) are particularly useful for the production of carbocycles via annulation sequences. The utility of the bifunctional reagents lies mainly in the fact that relatively short synthetic sequences are involved in converting structurally rather simple substrates into significantly more complex, usefully functionalized products.

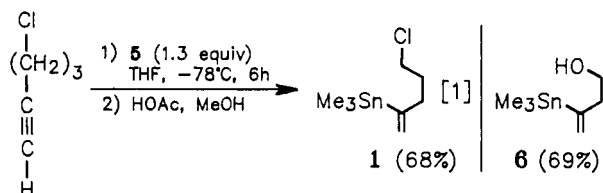
In this paper we describe the preparation of a number of bifunctional reagents and outline some of the uses of these substances in organic synthesis. Specifically, we report on the synthesis and chemistry of (a) 5-chloro-2-trimethylstannyl-1-pentene (**1**) and related substances, (b) (*Z*)-1-bromo-4-methyl-3-trimethylstannyl-2-pentene (**2**), and (c) alkyl (*Z*)-(**3**) and (*E*)-2,3-bis(trimethylstannyl)-2-alkenoates (**4**). In the work described below, compounds **1** and **2** served well as synthetic equivalents to the donor-acceptor synthons (ref. 2) **A** and **B**, respectively, while **3** and **4** performed as synthetic equivalents to the donor-donor synthon (ref. 2) **C** (*W* = functional group derived from CO₂R').



CHEMISTRY OF **1** AND RELATED SUBSTANCES

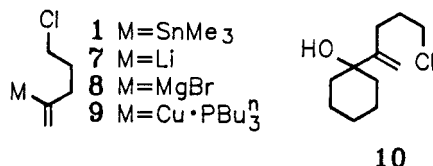
Preparation

2-Trimethylstannyl-1-alkenes can be synthesized readily by reaction (ref. 3), under appropriate conditions, of the corresponding 1-alkyne with Me₃SnCu·Me₂S (**5**), one member of a series of (trimethylstannyl)copper(I) reagents first prepared in our laboratory (ref. 4). Thus, treatment of 5-chloro-1-pentyne with **5** under the conditions shown in Eq. 1 provided compound **1** in 68% yield. In similar fashion, other ω -substituted 2-trimethylstannyl-1-alkenes (e.g. **6**) can be prepared efficiently (ref. 3).

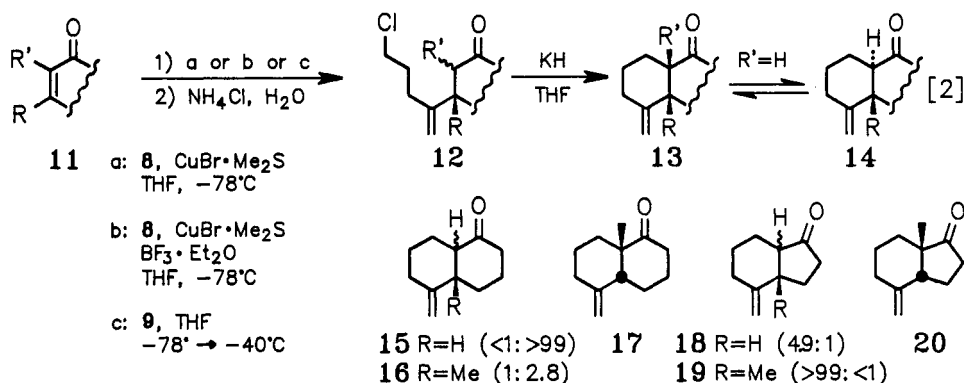


Methylenecyclohexane annulations

Transmetalation [MeLi, tetrahydrofuran (THF), $-78\text{ }^{\circ}\text{C}$] of **1** is a very facile process and produces cleanly the bifunctional reagent 5-chloro-2-lithio-1-pentene (**7**) (ref. 5). The latter species is stable for reasonable time periods at temperatures below approximately $-60\text{ }^{\circ}\text{C}$, but at higher temperatures it "self-destructs", presumably to give methylenecyclobutane. For example, stirring of a THF solution of **7** at $-78\text{ }^{\circ}\text{C}$ for 30 min, followed by addition of cyclohexanone, provided the alcohol **10** in 84% yield. On the other hand, when separate THF solutions of **7** were stirred (30 min) at -63 , -48 , and $-20\text{ }^{\circ}\text{C}$ prior to addition (at $-78\text{ }^{\circ}\text{C}$) of cyclohexanone, compound **10** was obtained in yields of 76, 58, and 0%, respectively.



Addition of MgBr_2 (1.2 equiv) or $\text{CuBr}\cdot\text{Me}_2\text{S}$ (1.1 equiv)- $n\text{-Bu}_3\text{P}$ (2 equiv) (ref. 6) to a THF solution ($-78\text{ }^{\circ}\text{C}$) of **7** readily converted the latter species into reagents **8** and **9**, respectively. Under appropriate conditions, **8** and **9** react with cyclic α,β -unsaturated ketones **11** to afford the conjugate addition products **12** (Eq. 2). Intramolecular alkylation of **12** provides the *cis*-fused bicyclic ketones **13**, which, if $\text{R}' = \text{H}$, can undergo equilibration with the corresponding *trans* isomers **14**. In this manner, starting from the appropriate enone **11**, good to excellent overall yields of the methylenecyclohexane annulation products **15** - **20** were prepared (ref. 5). The numbers given in parentheses (see **15**, **16**, **18**, **19**) represent *cis*:*trans* ratios measured after equilibration (NaOMe , MeOH , reflux) of the initially formed product(s).

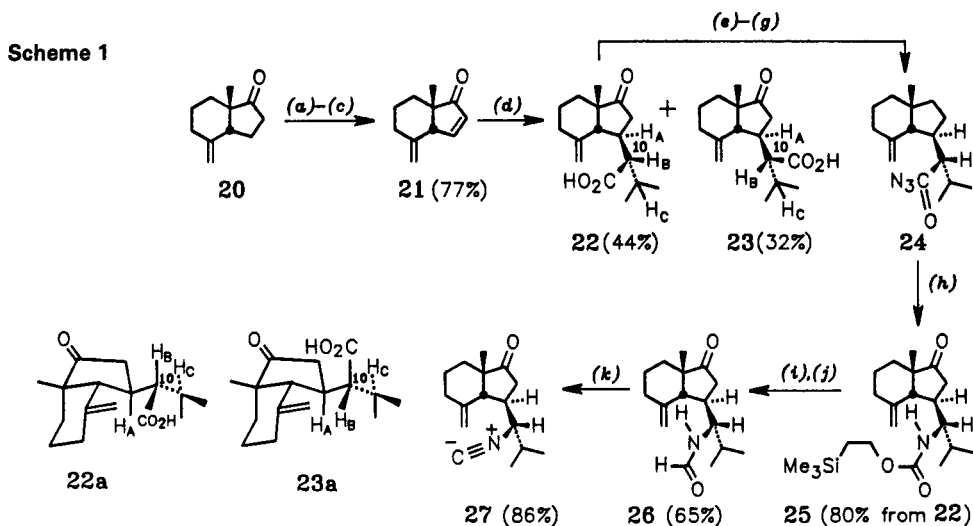


Natural product synthesis: (\pm)-axamide-1, (\pm)-axisonitrile-1

The methylenecyclohexane moiety (see **15** - **20**) is a structural feature of a number of natural products, particularly in the terpenoid family. For example, the structurally unusual axane-type sesquiterpenoids (+)-axamide-1 and (+)-axisonitrile-1, isolated from the marine sponge *Axinella cannabina*, were shown (ref. 7) to possess the constitution and absolute stereochemistry shown in **26** and **27**, respectively. The total synthesis of (\pm)-**26** and (\pm)-**27**, starting from the annulation product **20**, was achieved as shown in Scheme 1 (ref. 8).

Conversion of **20** into the enone **21** was accomplished via straightforward reactions. Importantly, under the conditions employed for the preparation of **21**, the exocyclic double bond showed no inclination to migrate into conjugation with the enone function. Conjugate addition of a nucleophile to the enone **21** would be expected to take place from the sterically more accessible top (convex) face of the molecule. Indeed, TiCl_4 -catalyzed addition (ref. 9) of 3-methyl-1,1-bis(trimethylsiloxy)-1-butene to **21**, followed by aqueous work-up, gave only two products, **22** and **23**, which were separated by a combination of column chromatography and fractional crystallization.

The stereochemistry of **22** and **23** at C-10 (axane numbering) was assigned initially on the basis of ^1H NMR spectroscopy. Examination of the spectra of these substances, along with suitable decoupling experiments, showed that, in **22**, $J_{\text{AB}} = 9.5\text{ Hz}$, while $J_{\text{BC}} = 4.5\text{ Hz}$. The corresponding values in **23** are 3.5 and 9.5 Hz. On the basis of examination of molecular models, it seems likely that the preferred conformations of **22** and **23** are as shown in **22a** and **23a**. If this prediction is correct, the $\text{H}_\text{A}-\text{H}_\text{B}$ and $\text{H}_\text{B}-\text{H}_\text{C}$ dihedral angles in **22a** would be -180° and -60° , respectively, while in **23a** the corresponding angles would be the reverse (-60° and -180° , respectively). Consequently, the observed coupling constants are certainly



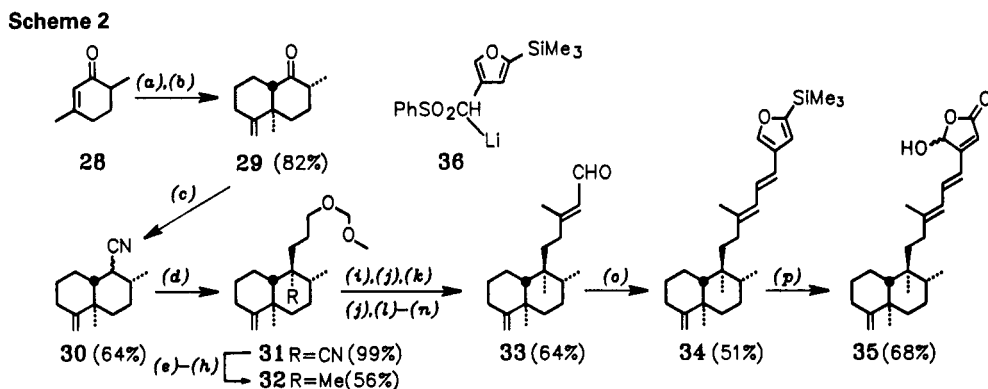
(a) $i\text{-Pr}_2\text{NLi}$, THF, -78°C ; Me_3SiCl ; (b) N -bromosuccinimide, THF, 0°C ; (c) LiBr , Li_2CO_3 , N,N -dimethylformamide, reflux; (d) 3-methyl-1,1-bis(trimethylsiloxy)-1-butene, TiCl_4 , CH_2Cl_2 , -78°C ; H_2O ; (e) N_2H_4 , diethylene glycol, $110 - 190^\circ\text{C}$; cool, add KOH , then heat at 190°C ; H^+ ; (f) $(\text{COCl})_2$, PhCH_3 ; (g) NaN_3 , acetone- H_2O , 0°C ; (h) PhCH_3 , 80°C ; $\text{Me}_3\text{SiCH}_2\text{CH}_2\text{OH}$, PhCH_3 , 80°C ; (i) $n\text{-Bu}_4\text{NF}$, THF, 50°C ; (j) MeCO_2CHO , Et_2O ; (k) p -toluenesulfonyl chloride, pyridine.

plausible and provide reasonable evidence to support the stereochemical assignments. These assignments were subsequently corroborated by a single crystal X-ray analysis of **22** (m.p. $172 - 173^\circ\text{C}$), which showed that, in the crystal, the conformation of this substance is very close to that shown in **22a**.

Wolff-Kishner reduction of **22** gave the corresponding acid, which was converted (ref. 10) efficiently into the crystalline carbamate **25**. The latter material was transformed into (\pm)-axamide-1 (**26**), which was dehydrated (ref. 11) to afford (\pm)-axisonitrile-1 (**27**) (m.p. $45 - 46^\circ\text{C}$).

Natural product synthesis: (\pm)-palauolide

Palauolide, a structurally unique antimicrobial sesterterpenoid isolated from a mixture of sponges collected from Palau, Western Caroline Islands, was shown (ref. 12) to possess structure **35**. The total synthesis of (\pm)-**35** is summarized in Scheme 2 (ref. 13).

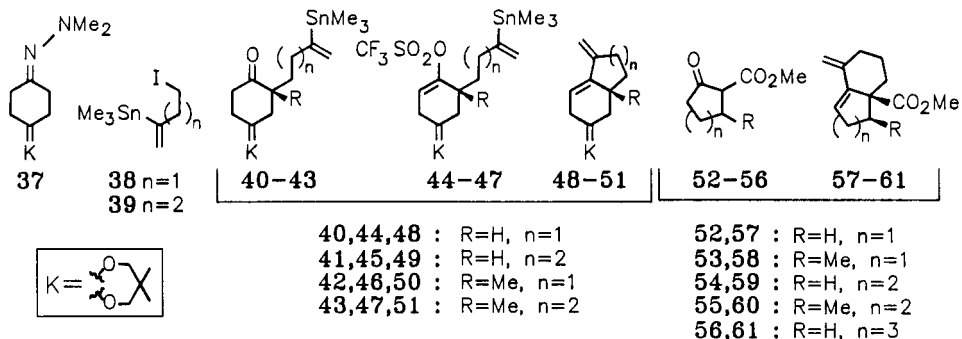


(a) **2**, $\text{CuBr}\cdot\text{Me}_2\text{S}$, $\text{BF}_3\cdot\text{Et}_2\text{O}$, THF, -78°C ; NH_4Cl , H_2O ; (b) Me_3COK , Me_3COH , 30°C ; (c) (p -toluenesulfonyl)methyl isocyanide, Me_3COK , Me_3COH -hexamethylphosphoramide (HMPA), $40 - 55^\circ\text{C}$; (d) $i\text{-Pr}_2\text{NLi}$, THF-HMPA, 0°C ; $\text{I}(\text{CH}_2)_3\text{OCH}_2\text{OMe}$, $0 \rightarrow 22^\circ\text{C}$; (e) $i\text{-Bu}_2\text{AlH}$, 1,2-dimethoxyethane (DME), 60°C ; $\text{HOAc}\cdot\text{H}_2\text{O}$, THF, 22°C ; (f) LiAlH_4 , Et_2O ; (g) $n\text{-BuLi}$, DME- N,N,N',N' -tetramethylethylenediamine; $\text{Cl}_2\text{PONMe}_2$; Me_2NH ; (h) Li , MeNH_2 , -20°C , 10 min; (i) pyridinium p -toluenesulfonate, Me_3COH , reflux; (j) pyridinium chlorochromate, NaOAc , CH_2Cl_2 ; (k) MeLi , Et_2O ; (l) $[\text{EtO}_2\text{CCHPO}(\text{OEt})_2]\text{K}$, THF; (m) $i\text{-Bu}_2\text{AlH}$, Et_2O , $-78 \rightarrow 0^\circ\text{C}$; (n) MnO_2 , hexane; (o) **36**, THF, -78°C ; PhCOCl , $-78 \rightarrow 22^\circ\text{C}$; $\text{Na}(\text{Hg})$, $\text{MeOH}\text{-THF}$, -20°C ; (p) $h\nu$ (tungsten halogen lamp, aqueous NaNO_2 filter), O_2 , Rose Bengal (catalyst), $\text{MeOH}\text{-CH}_2\text{Cl}_2$, -78°C ; 8 min; purge reaction mixture with argon and then allow to stand at 22°C in the dark for 3 h.

When 3,6-dimethyl-2-cyclohexen-1-one (**28**) was subjected to our methylenecyclohexane annulation method (*vide supra*), the bicyclic ketone **29** was obtained in high yield. Conversion (ref. 14) of **29** into the nitriles **30**, followed by alkylation of the latter material with $I(CH_2)_3OCH_2OMe$ gave *exclusively* (steric approach control) the nitrile **31**. Thus, the short, efficient sequence **28** → **31** allows for a high degree of control of the relative stereochemistry of the four chiral centers present in the decalin portion of palauolide. Reductive conversion (refs. 15,16) of the nitrile function of **31** into a methyl group was followed by straightforward transformation of the resultant substance **32** into the aldehyde **33**. A Julia alkene synthesis (ref. 17) involving **33** and reagent **36** gave the furan **34**, which, upon photosensitized oxygenation (ref. 18), provided (\pm)-palauolide (**35**).

Annulation sequences leading to dienes

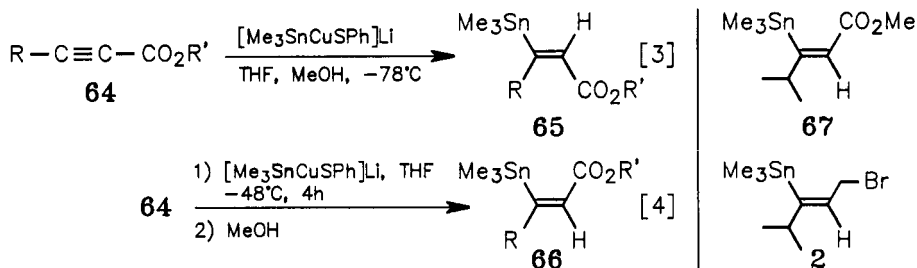
In the annulation sequences described above, the donor center of the donor-acceptor bifunctional reagents involved was, in each case, deployed before the acceptor center. If one reverses this order of deployment, chemistry quite different from that outlined above can be developed (ref. 19). For example, alkylation (*i*-Pr₂NLi, THF) of the dimethylhydrazone **37** with the iodides **38** and **39** (readily prepared from the alcohol **6** and the chloride **1**, respectively) gave, after hydrolysis of the hydrazone function, the ketones **40** and **41**, which could be methylated (KOCMe₃, MeI) to give **42** and **43**, respectively. Ketones **40** - **43** could readily be converted (ref. 20) into the corresponding enol trifluoromethanesulfonates (triflates) **44** - **47**, which, upon treatment with 0.05 equiv of Pd(PPh₃)₄ in THF (ref. 21), afforded the dienes **48** - **51**, respectively, in >80% yields. Similarly, alkylation of the keto esters **52** - **56** with the iodide **39**, conversion of the resultant products into the corresponding enol triflates, and subsequent Pd(0)-catalyzed cyclization gave the diene esters **57** - **61**. The ring closure reactions were clean and efficient (~85% yields). Similar annulations leading to stereochemically homogeneous diene systems of general structures **62** and **63** have also been developed (ref. 22).



CHEMISTRY OF **2**

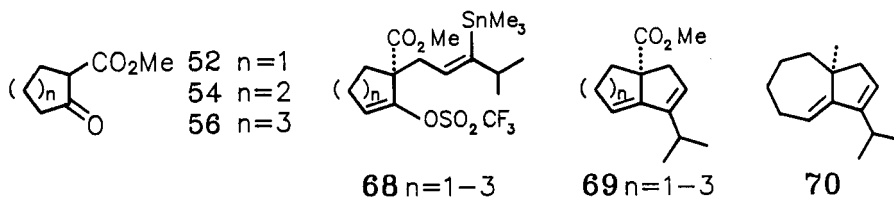
Preparation

We have reported (ref. 23) that the stereochemical outcome of the reaction of α,β -acetylenic esters **64** with the trimethylstannylcuprate reagent $[Me_3SnCuSPh]Li$ (ref. 4) can be controlled experimentally to produce either alkyl (E)-3-trimethylstannyl-2-alkenoates (**65**) (Eq. 3) or the corresponding (Z) isomers **66** (Eq. 4). The latter reaction served well for the synthesis of **2**. Thus, reaction of methyl 4-methyl-2-pentynoate with $[Me_3SnCuSPh]Li$ under conditions similar to those given in Eq. 4 provided (83%) the ester **67**, which was readily converted (*i*-Bu₂AlH, Et₂O; Ph₃PBr₂, CH₂Cl₂, Et₃N; 80%) into the required bromide **2** (ref. 24).



Annulation reactions

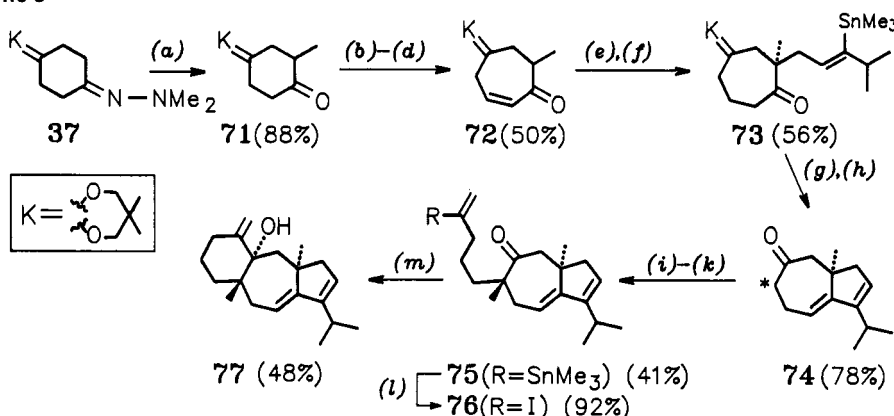
Substance **2** can be employed (ref. 24) as a useful reagent for five-membered ring formation via chemistry similar to that described for the annulative preparation of the dienes **48** - **51** and **57** - **61** (*vide supra*). However, use of **2** and structurally related materials leads to diene systems in which both of the double bonds are endocyclic. Thus, for example, alkylation (KH, THF) of the keto esters **52**, **54** and **56** with the bromide **2** and conversion (ref. 20) of the resultant products into the enol triflates **68** could be accomplished in overall yields of ~70%. Treatment of **68** with Pd(PPh₃)₄ (5 mol %) in refluxing MeCN provided cleanly (81 - 84%) the bicyclic dienes **69**. In similar fashion, alkylation (KOCMe₃, HOCMe₃-THF) of 2-methylcycloheptanone with **2** and subsequent suitable synthetic manipulations (enol triflate formation; Pd(O)-catalyzed ring closure) gave the substituted bicyclo[5.3.0]decadiene **70** (ref. 22(b)). The latter sequence of reactions served as a model for the total synthesis of a dolastane-type diterpenoid (see below).

Natural product synthesis: (\pm)-(14S)-dolasta-1(15),7,9-trien-14-ol

The triene alcohol **77** [14(S)-dolasta-1(15),7,9-trien-14-ol] is a member of the structurally and physiologically interesting dolastane family of marine diterpenoids (ref. 25). The total synthesis of (\pm)-**77** is summarized in Scheme 3 (ref. 24). Methylation-hydrolysis of the dimethylhydrazone **37**, followed by ring expansion (ref. 25) of the resultant product **71**, gave the enone **72**. Hydrogenation of **72** and subsequent alkylation of the resultant ketone with the allylic bromide **2** gave **73**, which was converted efficiently into the bicyclic keto diene **74**.

On the basis of steric and stereoelectronic considerations (molecular models), it appeared that alkylation of **74** at C* would take place preferentially from the side opposite the angular methyl group. Therefore, addition of the necessary appendages to the ketone **74** had to be done in a specific order. In the event, alkylation of the dimethylhydrazone of **74** with reagent **39** provided, after hydrolysis of the hydrazone linkage, a single product that, upon methylation, was converted into the ketone **75**. Reaction of the latter material with iodine in CH₂Cl₂ gave **76**. It is evident (molecular models) that cyclization of **76** should occur in the desired stereochemical sense. Indeed, treatment of **76** with magnesium in refluxing THF gave a single cyclized product, which was spectrally identical with (14S)-dolasta-1(15),7,9-trien-14-ol (**77**).

Scheme 3

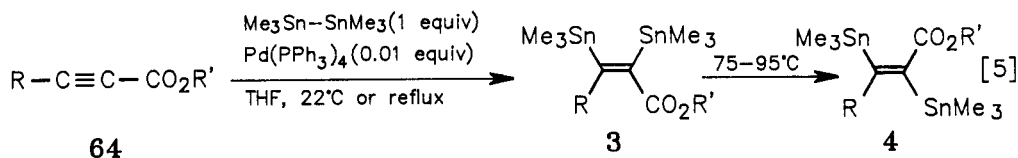


(a) *i*-Pr₂NLi, THF, -78 → 0 °C; MeI, 22 °C; NaIO₄, pH 7 phosphate buffer, THF, 22 °C; (b) *i*-Pr₂NLi, DME, 0 °C; Me₃SiCl, Et₃N, 0 → 22 °C; (c) CH₂I₂, Et₂Zn, PhCH₃, 55 °C; (d) FeCl₃, N,N-dimethylformamide, pyridine, 0 → 22 °C; NaOAc, MeOH, reflux; (e) H₂, Pd-C, hexane; (f) Me₃COK, Me₃COH, DME; **2**, 22 °C; (g) *i*-Pr₂NLi, THF-HMPA, -78 → 0 °C; PhN(SO₂CF₃)₂, 22 °C; catalytic Pd(PPh₃)₄, 22 → 30 °C, 5 min; (h) H₃O⁺, acetone; (i) H₂NNMe₂, MeOH, 4-Å molecular sieves, reflux; (j) *i*-Pr₂NLi, THF, -78 → 0 °C; **39**, 0 → 22 °C; NaIO₄, pH 7 phosphate buffer, THF, 40 °C; (k) Me₃COK, THF-HMPA, 60 °C; MeI, 60 °C; (l) I₂, CH₂Cl₂, 22 °C; (m) Mg, THF, reflux.

CHEMISTRY OF **3** AND **4**

Preparation

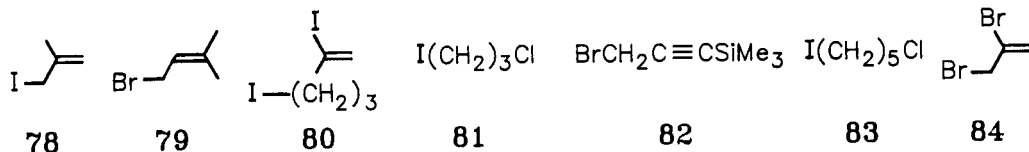
Recently, we reported (ref. 27(a)) that α,β -acetylenic esters **64** react smoothly with hexamethylditin in the presence of $\text{Pd}(\text{PPh}_3)_4$ to provide alkyl (*Z*)-2,3-bis(trimethylstannyl)-2-alkenoates (**3**) (Eq. 5). A wide variety of functional groups can be tolerated in this reaction and the products are formed cleanly and efficiently (66 - 90%). Interestingly, compounds **3** are thermally unstable and, upon heating (neat) to 75 - 95 °C (Eq. 5), rearrange smoothly to the corresponding (*E*) isomers **4** (81 - 98%). Thus, both alkyl (*Z*)- and (*E*)-2,3-bis(trimethylstannyl)-2-alkenoates are readily available via experimentally straightforward reactions.



a, R=Me; **b**, R=Et; **c**, R=*i*-Pr; **d**, R=cyclopropyl; **e**, R=2(2-cyclopentenyl)ethyl;
f, R=*t*-BuMe₂SiOCH₂; **g**, R=Cl(CH₂)₃; **h**, R=Br(CH₂)₃; **i**, R=Br(CH₂)₄; **j**, R=Br(CH₂)₅

Use of **3** and **4** for preparation of stereochemically defined tetrasubstituted alkenes

Although a number of excellent methods for the stereocontrolled formation of di- and trisubstituted alkenes are known, methods useful for the preparation of stereochemically homogeneous tetrasubstituted olefins have been scarce. In our investigations of the chemistry of **3** and **4**, we have found that these substances are valuable precursors for the synthesis of diversely functionalized, stereochemically defined tetrasubstituted alkenes (ref. 27(b)).

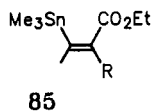


Treatment of **4a** (R' = Et) with MeLi in THF (-98 °C) effected clean transmetalation of the α -Me₃Sn group. Alkylation of the resultant anion with the alkylating agents **78** - **82** gave **85a** - **g**, respectively, as the sole substitution products. Similarly, transmetalation of **4d** (R' = Me) and **4f** (R' = Et) and alkylation (**4d**: MeI, **78**; **4f**: MeI, **78**, **79**) of the resultant anions gave **86a,b** and **87a** - **c**, respectively. In each case, the alkylation product was formed as a single isomer. Furthermore, transmetalation-alkylation of the (*Z*)-2,3-bis(trimethylstannyl)-2-alkenoates **3** provides products with the same stereochemistry as those derived from the (*E*) isomers **4**. For example, successive treatment of THF solutions (-98 °C) of **3b** (R' = Me) and **3c** (R' = Me) with MeLi and 3-iodopropene gave excellent yields of **88** and **89**, respectively.

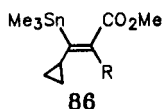
Alkyl 2-trimethylstannyl-1-cycloalkenecarboxylates can also be prepared via this methodology. For example, treatment of **3h** (R' = Me) or **4g** (R' = Me) with MeLi in THF-HMPA (-98 °C, 20 min) gave the cyclic ester **90** (~70%). Similarly, substrates **3i** and **j** (R' = Me) were transformed into **91** and **92**, respectively.

Reduction (*i*-Bu₂AlH, Et₂O) of the esters **88** and **89** gave the corresponding alcohols **93** and **95**, which could be transformed (I₂, CH₂Cl₂) smoothly into the iodo alcohols **94** and **96**, respectively. Treatment of the latter substances with MeOCH₂CH₂OCH₂Cl-*i*-Pr₂NEt in CH₂Cl₂ gave the ethers **97** and **100**, while oxidation (pyridinium chlorochromate, NaOAc, CH₂Cl₂) of **94**, followed by reaction of the resultant aldehyde **98** with Ph₃P=CH₂, provided the triene iodide **99**.

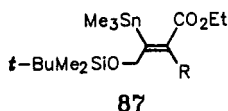
Treatment of the iodides **97**, **99**, and **100** with *n*-BuLi (2.2 equiv) in THF (-78 °C) effected, in each case, lithium-iodine exchange and the resultant vinyllithium species (**101**, **103**, **105**, respectively) could be converted (1 equiv CuBr·Me₂S, -48 °C) into the corresponding vinylcopper(I) reagents **102**, **104**, and **106**. Alkylation of **101** with MeI, *n*-BuI, and reagents **79** and **83** afforded the stereochemically homogeneous tetrasubstituted alkenes **107** - **110**, respectively, while treatment of **103** with *n*-BuI gave **113**. On the other hand, reaction of the vinyllithium **101** with the allylic iodide **78** produced the vinyl iodide **97** via a "reverse" lithium-iodine exchange. This problem could be avoided by using vinylcopper(I) reagents. Thus, reagents **102**, **104**, and **106** reacted smoothly with allylic halides (e.g. **78,84**) to provide the corresponding alkenes (e.g. **111**, **112**, **114** - **116**).



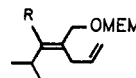
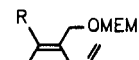
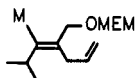
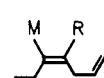
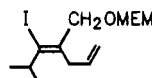
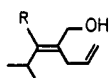
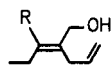
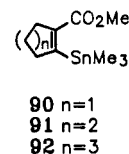
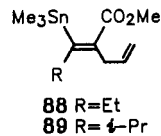
- a R = CH₂CMe
 b R = CH₂CH=CMe₂
 c R = (CH₂)₃Cl
 d R = (CH₂)₃Cl
 e R = CH₂C≡CSiMe₃



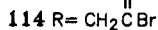
- a R = Me
 b R = CH₂CMe



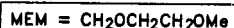
- a R = Me
 b R = CH₂CMe
 c R = CH₂CH=CMe₂



- 111** R = CH₂CMe
112 R = CH₂CBr



- 116** R = CH₂CBr



It is worthwhile to note that in the tetrasubstituted alkenes prepared via the methods summarized above, one pair of trans substituents on the double bond is derived from readily synthesized α,β -acetylenic esters, while the other (trans) groups are introduced by alkylation reactions. Since the ester function can be synthetically manipulated and since it should be possible to use a variety of functionalized alkylating agents in addition to **78** - **84**, it is evident that a versatile, effective synthesis of stereochemically defined tetrasubstituted alkenes has been developed.

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