The use of some bifunctional reagents in organic synthesis

Edward Piers
Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Y6

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 (+)-axamide-1 and (+)-axisonitrile-1, the diterpenoid (+)-(14S)-dolasta-1(15),7,9-trien-14-ol, and the sesterterpenoid (+)-palaudilide. A versatile synthesis of functionalized, stereochemically defined tetrasubstituted 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)- 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 Me₃SnCuMe₂S (2), 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 2 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

Transmetallation [MeLi, tetrahydrofuran (THF), -78 °C] of 1 is a very facile process and produces cleanly the bifunctional reagent 5-chloro-2-lithio-1-pentene (2) (ref. 5). The latter species is stable for reasonable time periods at temperatures below approximately -60 °C, but at higher temperatures it "self-destructs", presumably to give methylenecyclobutane. For example, stirring of a THF solution of 2 at -78 °C for 30 min, followed by addition of cyclohexanone, provided the alcohol 10 in 94% yield. On the other hand, when separate THF solutions of 2 were stirred (30 min) at -63, -48, and -20 °C prior to addition (at -78 °C) of cyclohexanone, compound 10 was obtained in yields of 76, 58, and 0%, respectively.

Addition of MgBr2 (1.2 equiv) or CuBr·Me2S (1.1 equiv)·Bu3P (2 equiv) (ref. 6) to a THF solution (-78 °C) of 2 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 R' = 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: (+)-axamide-1, (+)-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 2 and 27, respectively. The total synthesis of (+)-26 and (+)-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, TICl4-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, JAB = 9.5 Hz, while JBC = 4.5 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 H4-H5 and H6-H7 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
Use of bifunctional reagents in organic synthesis

(a) 1-Pr2NLi, THF, -78 °C; Me3SiCl; (b) N-bromosuccinimide, THF, 0 °C; (c) LiBr, Li2CO3, N,N-dimethylformamide, reflux; (d) 3-methyl-1,1-bis(trimethylsiloxy)-1-butene, TiCl4, CH2Cl2, -78 °C; H2O; (e) N2H4, diethylene glycol, 110 - 190 °C; cool, add KOH, then heat at 190 °C; H2; (f) (COCl)2, PhCH3; (g) NaN3, acetone-H2O, 0 °C; (h) PhCH3, 80 °C; Me3SiCH2CH2ONa, PhCH3, 80 °C; (i) n-Bu4NF, THF, 50 °C; (j) MeCO2CHO, Et2O; (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 °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 (±)-axisonitrile-1 (27) (m.p. 45 - 46 °C).

Natural product synthesis: (±)-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 21. The total synthesis of (±)-33 is summarized in Scheme 2 (ref. 13).

(a) Ag, CuBr·Me2S, BF3·Et2O, THF, -78 °C; NH4Cl, H2O; (b) Me3COK, Me3COH, 30 °C; (c) (p-toluenesulfonylmethyl isocyanide, Me3COK, Me3COH, Hexamethyldisilazane (HMDS), 40 - 55 °C; (d) i-Pr2NLi, THF-HMDS, 0 °C; I(CH2)3CH2OMe, 0-22 °C; (e) i-Bu2AlH, 1,2-dimethoxyethane (DME), 60 °C; HOAc-H2O, THF, 22 °C; (f) LiAlH4, Et2O; (g) n-BuLi, DME-N,N,N,N'-tetramethylethylenediamine; Cl2PONMe2; Me2NH; (h) Li, MeNH2, -20 °C, 10 min; (i) pyridinium p-toluenesulfonate, Me3CONH, reflux; (j) pyridinium chlorochromate, NaOAc, CH2Cl2; (k) MeLi, Et2O; (l) [EtO2CCO(OEt)2]2K, THF; (m) i-Bu2AlH, Et2O, -78 → 0 °C; (n) Mn2O, hexane; (o) 35, THF, -78 °C; PhCOCl, -78 → 22 °C; Na(Hg), MeOH-THF, -20 °C; (p) hv (tungsten halogen lamp, aqueous NaNO2 filter), O2, Rose Bengal (catalyst), MeOH-CH2Cl2, -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 \((\text{CH}_2)_3\text{C}O\text{H}_2\text{Me}\) gave exclusively (steric approach control) the nitrile 31. Thus, the short, efficient sequence 28 \(\rightarrow\) 29 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 \((\text{I}-\text{Pr}_2\text{NLi}, \text{THF})\) 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 \((\text{KOCH}_3, \text{MeI})\) 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\((\text{PH}_3)_4\) in THF (ref. 21), afforded the dienes 48 - 51, respectively, in >80% yields. Similarly, alkylation of the keto esters 52 - 56 with the iodide 32, 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 annihilations 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 \(\alpha,\beta\)-acetylenic esters 64 with the trimethylstannylicalcurate reagent \([\text{Me}_3\text{SnCuSPhLi}\] (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 \([\text{Me}_3\text{SnCuSPhLi}\] under conditions similar to those given in Eq. 4 provided (83%) the ester 67, which was readily converted \((\text{L}-\text{Bu}_2\text{A}H, \text{Et}_2\text{O}; \text{Ph}_3\text{PBr}_2, \text{CH}_2\text{Cl}_2, \text{Et}_3\text{N}; 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 52 - 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(0)-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: (+)-(14S)-dolasta-1(15),7,9 -trien-l<. 01

The triene alcohol 77 [14(S)-dolasta-1(15),7,9-trien-l4-ol] is a member of the structurally and physiologically interesting dolastane family of marine diterpenoids (ref. 25). The total synthesis of (+)-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 C9 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.

Scheme 3

![Chemical diagram of Scheme 3](attachment:image.png)

(a) 1-Pr2NLi, THF, -78 + 0 °C; MeI, 22 °C; NaIO4, pH 7 phosphate buffer, THF, 22 °C; (b) 1-Pr2NLi, DME, 0 °C; Me2SOCl, Et3N, 0 -> 22 °C; (c) CH2I2, Et2Zn, PhHCH3, 55 °C; (d) FeCl3, N,N-dimethylformamide, pyridine, 0 -> 22 °C; NaOAc, MeOH, reflux; (e) H2, Pd-C, hexane; (f) Mg2(CO)3, Mg3(CO)3, DME; 2, 22 °C; (g) 1-Pr2NLi, THF-HMPA, -78 + 0 °C; PH3(SO2CF3)2, 22 °C; catalytic Pd(PPh3)4, 22 -> 30 °C, 5 min; (h) H3O+, acetone; (i) H2NNMe2, MeOH, 4-A molecular sieves, reflux; (j) 1-Pr2NLi, THF, -78 - 0 °C; 32, 0 -> 22 °C; NaIO4, pH 7 phosphate buffer, THF, 40 °C; (k) Mg2(CO)3, 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 Pd(PPh3)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 2 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.

\[
R - C\equiv C - CO_2R' \xrightarrow{\text{MegSn-SnMeg(1 equiv)}} \xrightarrow{\text{Pd(PPh3)4(0.01 equiv)}} R - C\equiv C - CO_2R' \xrightarrow{\text{SnMe3}} 3 \\
\]

64

\[
a, R=\text{Me}; b, R=\text{Et}; c, R=i-\text{Pr}; d, R=\text{cyclopropyl}; e, R=2(2-cyclopentenyl)ethyl; f, R=t-\text{Bu} \xrightarrow{\text{SnOCH2}}; g, R=\text{Cl(CH2)3}; h, R=\text{Br(CH2)3}; i, R=\text{Br(CH2)4}; j, R=\text{Br(CH2)5}
\]

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)).

\[
\text{Br-} - \text{P(}\text{I} - \text{CH2)3Cl} \xrightarrow{\text{BrCH2CFCSiMe3 I(CH2)sCl Br}} 80 \\
78 \quad 79 \quad 80 \quad 81 \quad 82 \quad 83 \quad 84
\]

Treatment of 4a (R'- Et) with MeLi in THF (-98 °C) effected clean transmetallation of the α-Me3Sn group. Alkylation of the resultant anion with the alkylating agents 78 - 82 gave 85a - e, respectively, as the sole substitution products. Similarly, transmetallation of 4d (R'- Me) and 4f (R'- Et) and alkylation (M: 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, transmetallation-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 3h (R'- Me) and 3e (R'- Me) with MeLi and 3-iodopropene gave excellent yields of 88 and 89, respectively.

Alkyl 2-trimethylstannyl-1-cycloalkene carboxylates 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 4i (R'- Me) were transformed into 91 and 92, respectively.

Reduction (Li-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+MegS, -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 111. 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).
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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