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Approaches to the stereoselective total synthesis of biologically active natural products*

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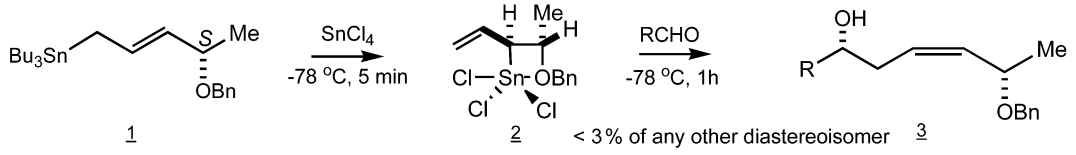
Abstract: Total syntheses of epothilone B and pamamycin 607, which feature reactions between functionalized allylstannanes and aldehydes to introduce a (*Z*)-trisubstituted double-bond and remote stereocenters stereoselectively, are discussed. Recent work concerned with carrying out this chemistry without the use of allylstannanes as starting materials and progress toward a total synthesis of bryostatins are also presented.

INTRODUCTION

One of the themes of this IUPAC conference was the isolation and chemistry of biologically active natural products. Approaches to the total synthesis of some complex natural products will be discussed here, including syntheses that demonstrate the use of functionalized allylstannanes for the stereoselective introduction of trisubstituted double-bonds and for remote stereocontrol. New procedures for carrying out this chemistry without using allylstannanes as starting materials will be presented. Finally, recent progress toward a synthesis of bryostatins will be discussed.

NATURAL PRODUCT SYNTHESIS: STEREOCONTROL USING ALLYLSTANNANES

Allylstannanes are widely used in organic synthesis. Functionalized allylstannanes can undergo stereoselective transmetallation with tin(IV) halides to give allyltin trihalides, which react with aldehydes to give (*Z*)-homoallylic alcohols with useful levels of 1,5-, 1,6-, and 1,7-stereocontrol [1]. For example, stannanes **1** and **4** are transmetallated to give the allyltin trichlorides **2** and **5**, which react with aldehydes with efficient 1,5-stereocontrol to give the (*Z*)-1,5-*syn*- and (*Z*)-1,5-*anti*-alcohols **3** and **6**, respectively, via six-membered, chair-like transition structures. More remote 1,8- and 1,9-stereocontrol can be achieved by sigmatropic rearrangement of these products with migration of one of the stereogenic centers further along the chain [2].



1 2 < 3% of any other diastereoisomer 3

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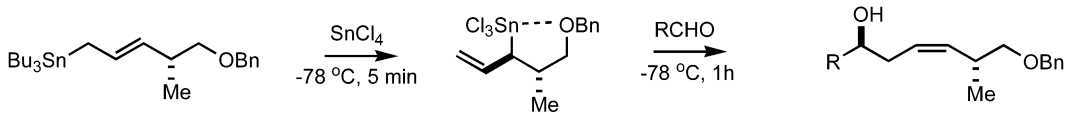
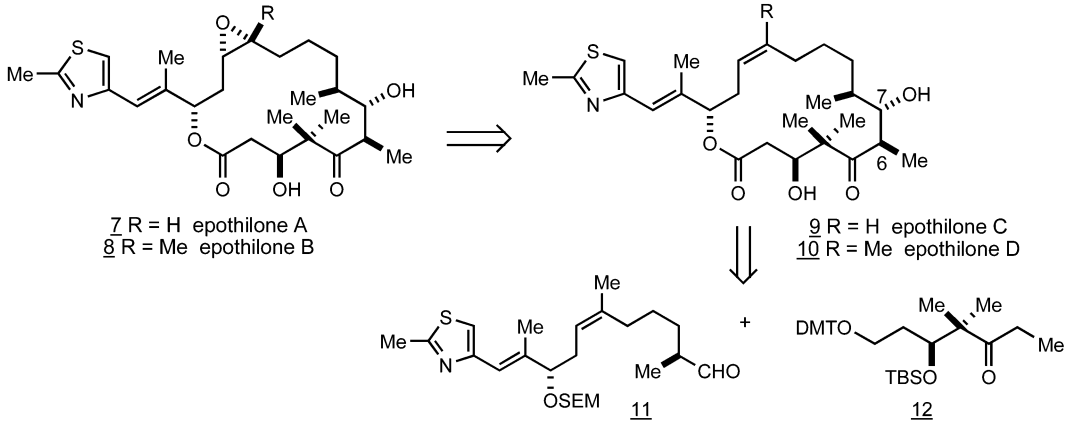


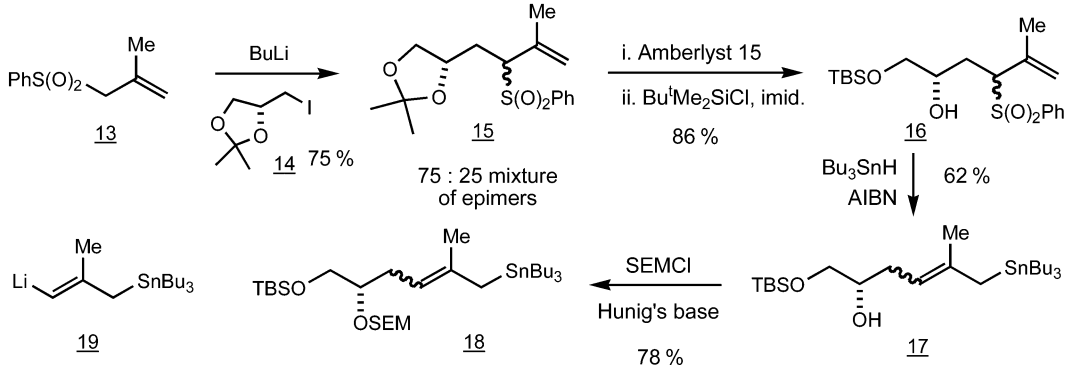
4 5 1,5-*anti* : 1,5-*syn* ≥ 96 : 4 6

The epothilones, e.g., epothilones A–D, **7**–**10**, have attracted considerable interest from synthetic chemists because of their potent anticancer activity. Several total syntheses have been described, and many analogs have been synthesized [3]. A well-studied approach to the epothilones is based on the use of stereoselective aldol reactions to form the 6,7-double-bond followed by macrolactonization and deprotection. Following this protocol, it was expected that epothilone D **10** would be available from the aldehyde **11** and ethyl ketone **12**, and that subsequent regio- and stereoselective epoxidation would give epothilone B **8**.



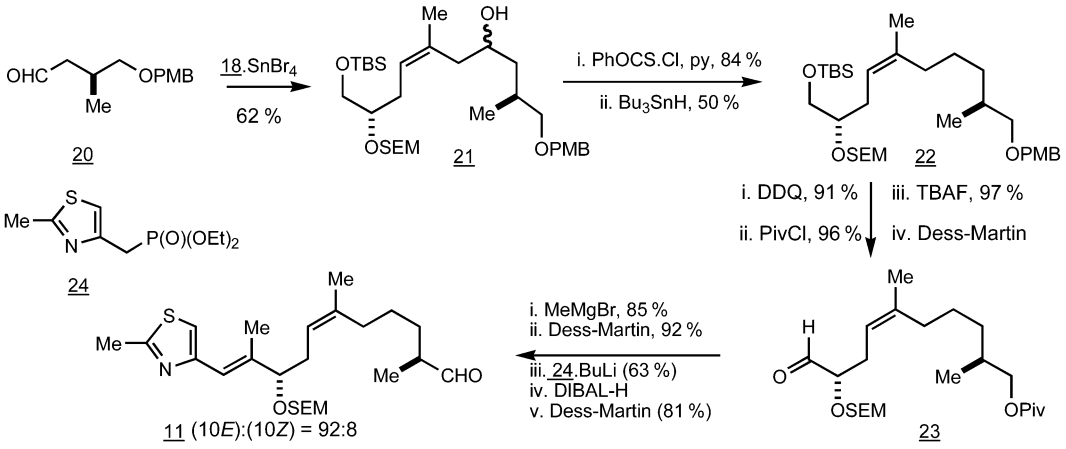
The aldehyde **11** is of interest in the context of remote stereocontrol since it contains two stereogenic centers with a 1,8-relationship. A stereoselective approach to this aldehyde based on 1,6-stereocontrol using an allylstannane followed by an Ireland–Claisen rearrangement has been investigated [4]. However, a more convergent route which employed the coupling of an allylstannane with a chiral aldehyde for the introduction of the trisubstituted 12,13-double-bond (epothilone numbering) regio- and stereoselectively was found to be more effective and led to a total synthesis of the epothilones [4].

The allylstannane **18** used in this synthesis was prepared by alkylation of the lithiated 2-methylprop-2-enyl phenyl sulfone **13** by the (*R*)-alkyl iodide **14** to give a mixture of the epimeric sulfones **15** which were converted into the monoprotected dihydroxysulfone **16** in two steps. Free-radical reaction with tributyltin hydride then gave the allylstannane **17** as a mixture of geometrical isomers which was

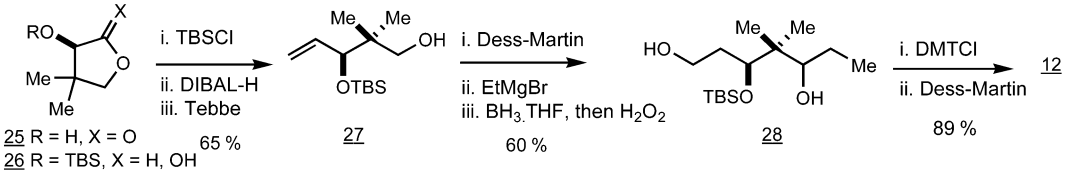


protected as its trimethylsilylethoxymethoxy (SEM) ether **18**. In this synthesis, the lithiated sulfone **13** is being used as the synthetic equivalent of the vinyllithium species **19**.

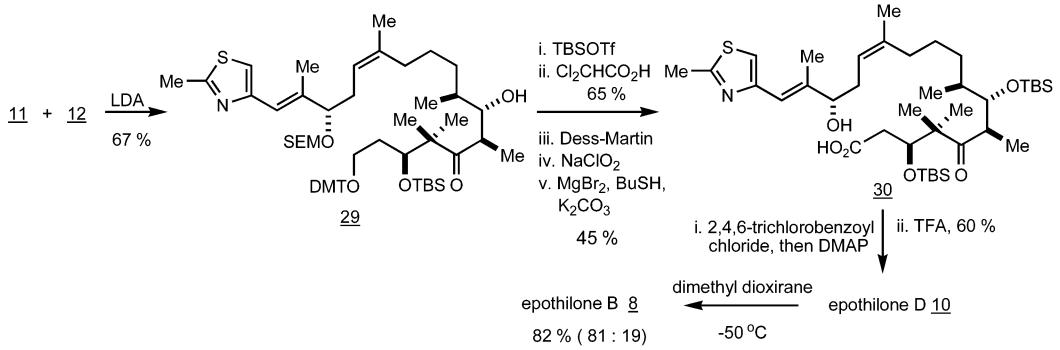
As expected for a bis-protected 5,6-dihydroxyhex-2-enylstannane [1], the tin(IV) bromide-mediated reaction of stannane **18** with (*R*)-4-*p*-methoxybenzyl-3-methylbutanal **20** gave a mixture of epimeric adducts **21**, but both of these had exclusively the required (*Z*)-alkene geometry. Removal of the hydroxyl group using a Barton procedure gave the fully protected trihydroxydec-4-ene **22**, which was taken through to the aldehyde **23** by oxidative removal of the *p*-methoxybenzyl group and reprotection of the primary alcohol as its pivalate ester, followed by fluoride removal of the *tert*-butyldimethylsilyl group and oxidation [5]. Addition of methyl magnesium bromide, oxidation and condensation with the lithiated phosphonate **24** gave the required aldehyde **11** as a 92:8 mixture of (10*E*)- and (10*Z*)-isomers after reductive removal of the pivaloyl group and oxidation.



The C(1)–C(6) fragment **12** was prepared from (*R*)-pantolactone **25** by protection as its *tert*-butyldimethylsilyl ether and reduction to the lactol **26** followed by olefination with the Tebbe reagent to give the alkene **27** [6]. Dess–Martin oxidation and addition of ethyl magnesium bromide followed by hydroboration/oxidation gave the diol **28**. Selective protection of the primary alcohol as its dimethoxytrityl derivative and Dess–Martin oxidation of the secondary alcohol then gave the required ethyl ketone **12**.

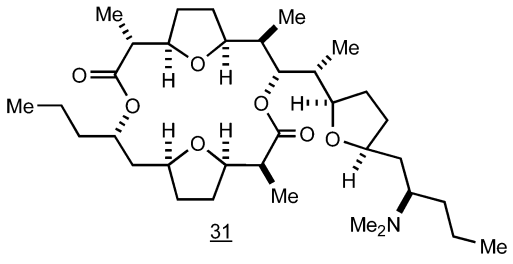


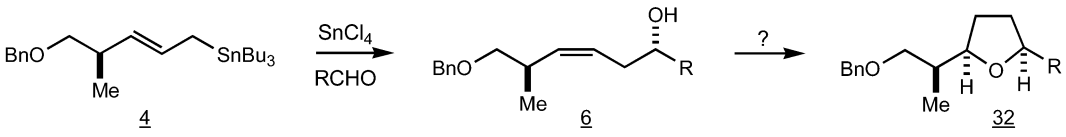
The completion of a synthesis of epothilones D and B then involved a lithium aldol condensation between the ketone **12** and the aldehyde **11**, which was highly selective in favor of the required adduct **29** [7]. Protection of the 7-OH followed by deprotection of the primary alcohol, oxidation and removal of the SEM-group gave the hydroxy-acid **30**. Cyclization using the modified Yamaguchi procedure and deprotection then gave epothilone D **10**. In our hands, epoxidation of epothilone D using dimethyl dioxirane was regioselective, but gave a mixture of epothilone B **8** and its diastereoisomer formed by epoxidation on the other face of the 12,13-double-bond, ratio 81:19 in favor of epothilone B **8** [3,4].



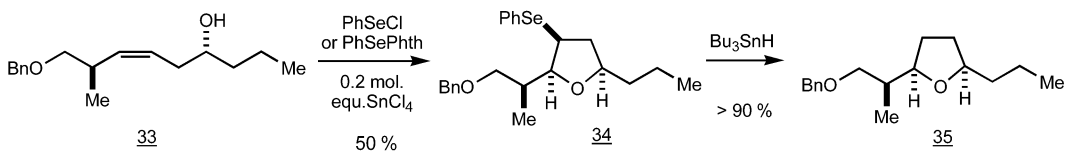
This synthesis of the epothilones uses the reaction between the functionalized allylstannane **18** and the aldehyde **20** to introduce the 12,13-double-bond stereoselectively, but did not exploit the ability of these reactions to proceed with effective remote stereocontrol. In contrast, a synthesis of pamamycin 607 **31** has been completed in which 1,5-stereocontrol involving allylstannanes plays a major role [8].

The pamamycins [9] are a group of macrodiolides which possess antibiotic activity and which have been the focus of considerable attention from synthetic chemists [10,11]. A recurring structural feature of the pamamycins, as represented by pamamycin 607 **31**, is the presence of 2,5-*cis*-difunctionalized tetrahydrofurans with methyl-bearing stereogenic centers adjacent to the tetrahydrofuran rings. It was thought that rapid access to these fragments, i.e., **32**, could be obtained by cyclization of the (*Z*)-1,5-*anti*-products **6** accessible from tin(IV) chloride mediated reactions between the allylstannane **4** and aldehydes.



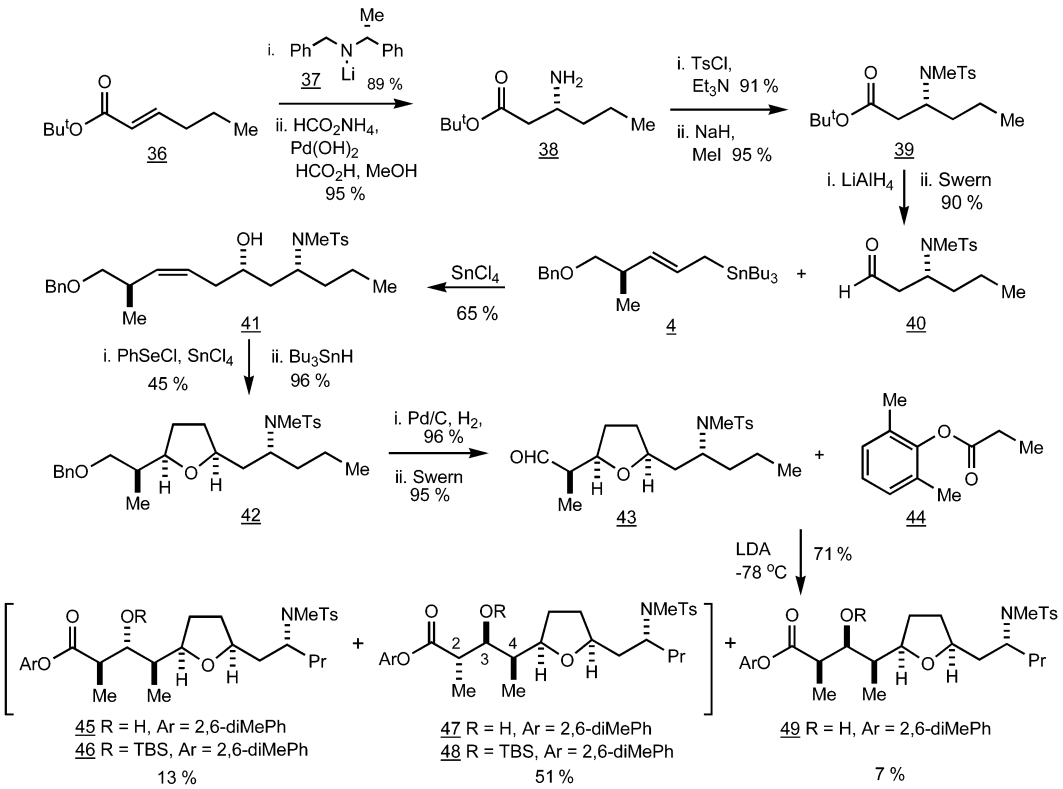


Several procedures have been reported for the stereoselective cyclization of (*Z*)-homoallylic alcohols to 2,5-*cis*-disubstituted tetrahydrofurans [12], but in our hands, cyclization of the model compound **33** (**6**, R = *n*-Pr) using these procedures was not usefully efficient. However, when ca. 20 mole% of a Lewis acid, typically tin(IV) chloride, was added to phenylseleno etherification using either phenyl selenenyl chloride or phthalimide, better yields of the tetrahydrofuran **34** were obtained. Deselenylation was then achieved by free-radical reduction using tributyltin hydride to give the required tetrahydrofuran **35**.



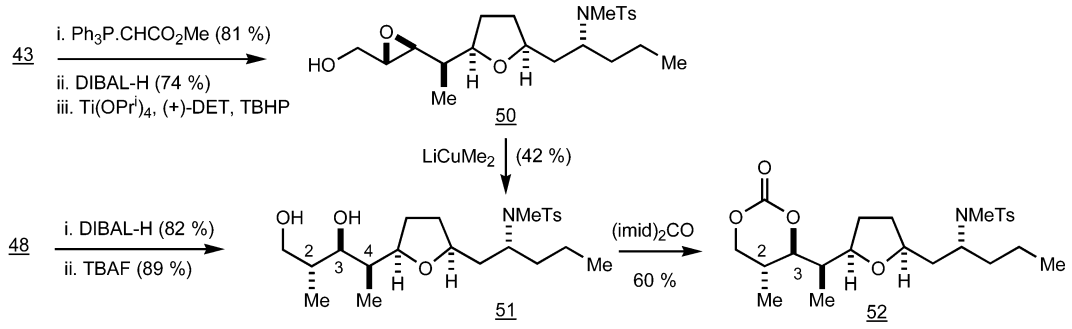
This cyclization was extremely stereoselective. In fact, cyclizations of all of the *anti*-homoallylic alcohols **6** examined to date have given all *cis*-2,3,5-trisubstituted tetrahydrofurans exclusively, whereas the one (*Z*)-*syn*-5-methylalk-3-enol studied to date was slightly less stereoselective although the all *cis*-diastereoisomer was still the major product isolated, vide infra. It would appear that both stereogenic centers in these homoallylic alcohols influence the cyclization stereoselectivity with those in the *anti*-isomers constituting a matched pair.

The synthesis of the C(1)–C(18) fragment **56** of pamamycin 607 **31** started with an asymmetric conjugate addition of the homochiral lithium amide **37** to the α,β-unsaturated ester **36** [13]. Transfer hydrogenolysis then gave the amino-ester **38** estimated to have an ee of ca. 95 %. At this stage, it was necessary to protect the amino-group using an electron-withdrawing group to minimize participation in subsequent phenylseleno etherifications, and so the amine was converted into the corresponding toluene *p*-sulfonamide, which was methylated to give the *N*-methyl derivative **39**. Reduction/oxidation gave the aldehyde **40**, which reacted with the allyltin trihalide generated from the allylstannane **4** to give the 1,5-*anti*-(*Z*)-product **41** with excellent stereoselectivity. Cyclization, using phenyl selenenyl chloride and tin(IV) halide, gave the 2,5-*cis*-disubstituted tetrahydrofuran **42** after reductive removal of the phenylseleno group, and hydrogenolysis followed by oxidation gave the aldehyde **43**. The aldol condensation of this aldehyde with the lithium enolate of 2,6-dimethylphenyl propanoate **44** gave the required 2,3-*anti*-3,4-*syn*-adduct **47** as the major product, although the 2,3-*anti*-3,4-*anti*- and 2,3-*syn*-3,4-*syn*-diastereoisomers **45** and **49** were also formed as minor products. The adduct **49** could be separated directly from this reaction mixture in a yield of 7 %, with the adducts **45** and **47** being separated as their *tert*-butyldimethylsilyl ethers **46** and **48** in overall yields of 13 and 51 %, respectively.



The structure assigned to the major silylated adduct **48** was confirmed by comparison of the diol **51**, and carbonate **52**, prepared from **48** by reduction and desilylation, with samples prepared from the

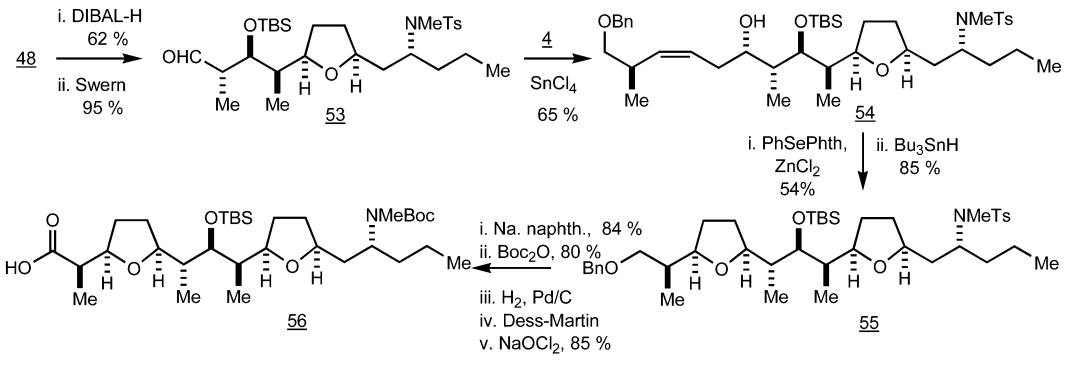
aldehyde **43** by Wittig homologation, reduction, and Sharpless epoxidation using (+)-diethyl tartrate followed by regioselective ring-opening of the epoxide **50** using lithium dimethylcuprate.



The major aldol adduct possessed the required 2,3-*anti*, 3,4-*syn*-configuration. This was as expected since the lithium enolate of ester **44** is known to react with aldehydes to give 2,3-*anti*-adducts via Zimmerman–Traxler transition structures [14], and the 3,4-*syn*-configuration follows from both Felkin–Anh and chelation control by the tetrahydrofuran. Although improved stereoselectivity would probably have been obtained using homochiral *anti*-selective aldol reagents, the achiral ester **44** was retained as the enolate component to minimize the use of chiral reagents in the synthesis.

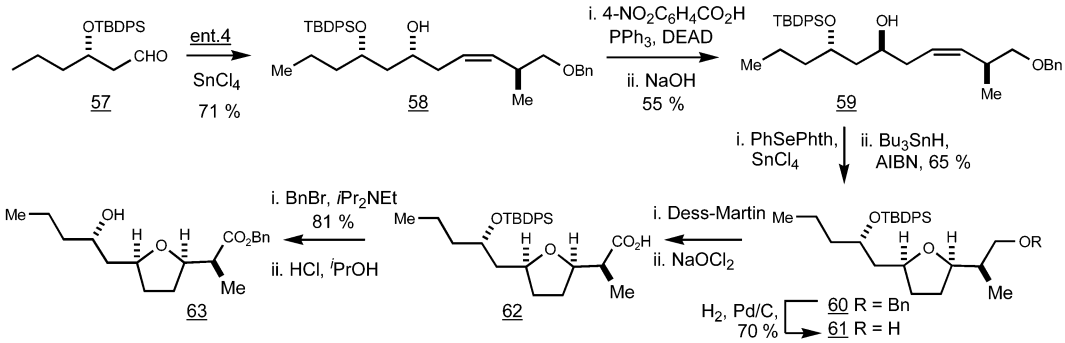
The *O*-silylated major aldol adduct **48** was taken through to the C(1)–C(18)-fragment **56** of pamamycin 607 **31** by conversion into the aldehyde **53** by reduction/oxidation and reaction of the aldehyde with the allyltin trichloride generated from stannane **4** to give the 1,5-*anti*-product **54** with excellent stereocontrol. Cyclization in this case was best carried out using phenylselenenyl phthalimide in the presence of zinc(II) chloride as the Lewis acid and gave the bis-tetrahydrofuran **55** after reductive removal of the phenylselenenyl group. This intermediate has the stereochemistry and carbon framework required for incorporation into pamamycin 607.

Reductive removal of the toluene *p*-sulfonyl group using sodium naphthalenide, *N*-acylation with BOC-anhydride, hydrogenolysis of the *O*-benzyl group, and oxidation of the primary alcohol via a Swern oxidation followed by further oxidation using $NaOCl_2$ then gave the required acid **56**.

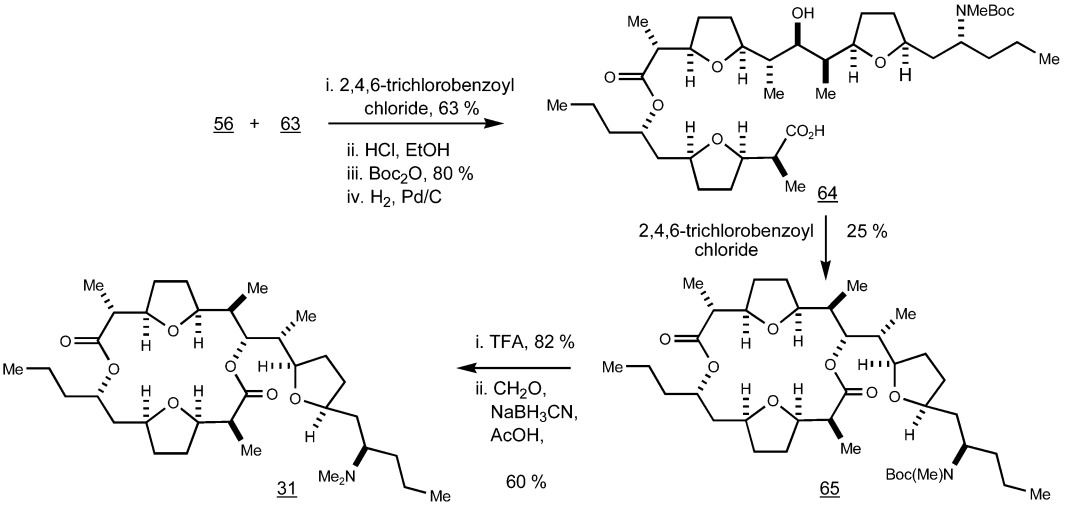


The C(1')–C(11') fragment of pamamycin 607 **63** was prepared from the (*S*)-3-silyloxyhexanal **57** by reaction with the allyltin trichloride generated from the enantiomer of the allylstannane **4**. This gave the 1,5-*anti*-product **58** with excellent stereocontrol, which was taken through to its 1,5-*syn*-diastereoisomer **59** by a Mitsunobu inversion [15] followed by saponification. In this case, cyclization using phenylselenenyl phthalimide was not entirely stereoselective with ca. 10 % of a mixture of minor products being formed as well as the major product **60** on reductive removal of the phenylselenenyl group. These products were best separated after hydrogenolysis, which gave a mixture of products from

which the major component **61** could be isolated pure in a yield of 70 %. Oxidation then gave the carboxylic acid **62**, which was converted into its benzyl ester and removal of the *tert*-butyldiphenylsilyl group using aqueous hydrogen chloride in isopropanol (because desilylation using tetrabutylammonium fluoride was accompanied by deprotonation α to the ester and ring-opening of the tetrahydrofuran ring) gave the alcohol **63**.



The completion of the synthesis of pamamycin 607 **31** then involved esterification of the acid **56** using the alcohol **63**, deprotection of the 8-OH using aqueous hydrogen chloride in methanol, reinstatement of the Boc-protecting group on nitrogen, and hydrogenolysis to give the seco-acid **64**. Cyclization using the modified Yamaguchi procedure gave the macrolide **65**, which was taken through to pamamycin 607 **31** by removal of the *N*-Boc protecting group and reductive methylation to introduce the second methyl group on the nitrogen. The sample of synthetic pamamycin 607 **31** so obtained was identical to an authentic sample kindly provided by Prof. Natsume [8].

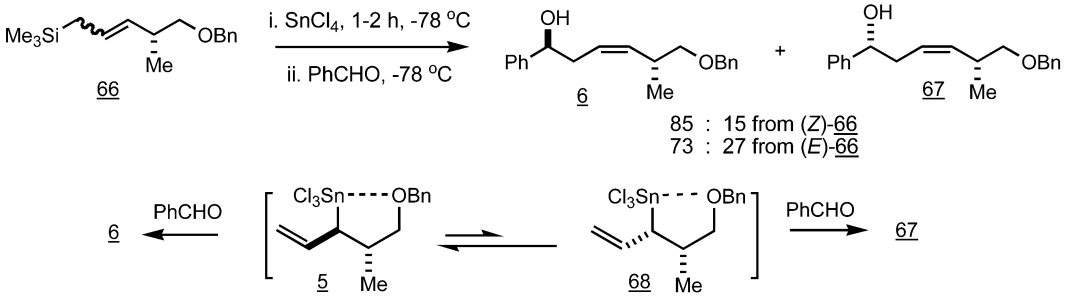


NEW PROCEDURES FOR REMOTE STEREOCONTROL USING ALLYLMETAL REAGENTS

The syntheses of epothilones and pamamycin 607 outlined above illustrate uses of functionalized allylstannanes in synthesis for remote stereocontrol and for the stereoselective introduction of trisubstituted alkenes. However, trialkyltin halides are side-products of the initial transmetallation reactions and have

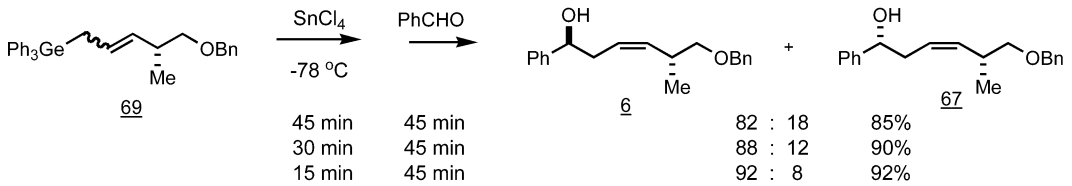
to be separated from the required products. For this reason, and the toxicity of organostannanes, alternative procedures for carrying out these reactions have been investigated.

Allylsilanes are known to be transmetallated by tin(IV) halides at –78 °C to generate allytin trichlorides [16]. However, transmetallation of the (*Z*)- and (*E*)-pent-2-enylsilanes (***Z***)-**66** and (***E***)-**66** by tin(IV) chloride required 1 to 2 h at –78 °C [17] and under these conditions, the kinetically preferred allyltin trichloride **5** is known to equilibrate with its *syn*-diastereoisomer **68** [18]. Therefore, the overall stereoselectivities observed in reactions with aldehydes, e.g., benzaldehyde, were less than those obtained with allylstannane **4** [17].

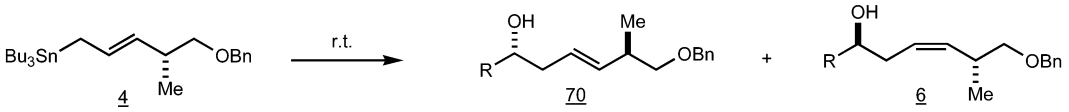


Allylgermanes [19] are more reactive than allylsilanes, but less reactive than allylstannanes. It was, therefore, of interest to investigate the stereoselectivity of their transmetallation using tin(IV) halides and subsequent reaction of the allyltin trihalides so formed with aldehydes.

The preliminary results obtained with a mixture of the (*E*)- and (*Z*)-isomers of the allylgermane **69**, prepared using the Barbier reaction between the corresponding pent-2-enyl chloride and triphenylgermanium bromide, are consistent with longer transmetallation times allowing equilibration of the intermediate allyltin trihalides **5** and **68** so, resulting in lower overall stereoselectivity. Thus, with 45 min allowed for transmetallation using tin(IV) chloride, a mixture of the 1,5-*anti*- and 1,5-*syn*-diastereoisomers **6** and **67**, ratio 82:18, was obtained, whereas this ratio improved to 92:8 if the transmetallation time was reduced to 15 min. Shorter times than this led to further improvement in the stereoselectivity, but only at the expense of side-product formation consistent with incomplete transmetallation before the aldehyde is added [20].



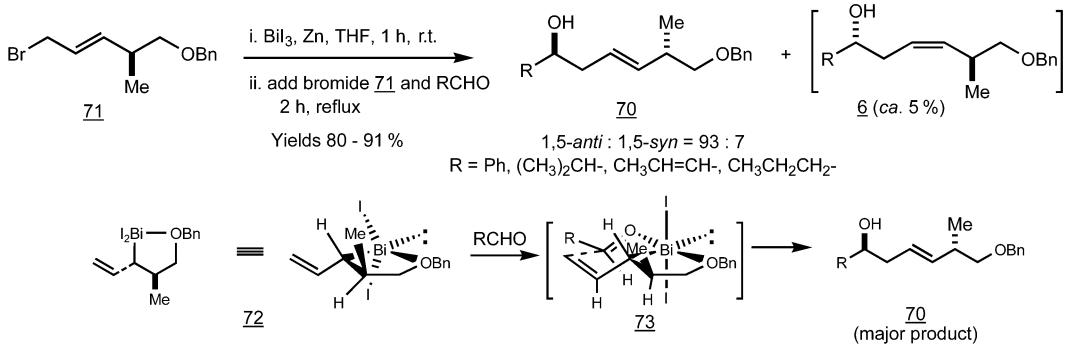
Procedures for remote stereocontrol not involving allyltin trihalides have also been studied. Transmetallation of the allylstannane **4** using indium trihalides followed by reaction of the intermediate allylindium dihalide with benzaldehyde unexpectedly gave predominantly (*E*)-homoallylic alcohols in contrast to the exceptionally high stereoselectivity in favor of the (*Z*)-products on transmetallation using tin(IV) halides. Slightly better stereoselectivity was obtained in favor of the (*E*)-1,5-*anti*-diastereoisomer **70** with increasing bulk of the halide [21]. However, useful levels, typically 93:7, of 1,5-stereocontrol in favor of the (*E*)-1,5-*anti*-diastereoisomer **70** were obtained on transmetallation using bismuth(III) iodide, and this was found to be applicable to a range of aldehydes with better chemical yields being obtained with a mixed solvent system of acetonitrile and dichloromethane [21].



R = Ph $InCl_3$, CH_2Cl_2	*E*, 1,5-*anti* : *syn* = 70 : 30 (72 %)	10 %
R = Ph $InBr_3$, CH_3CN	*E*, 1,5-*anti* : *syn* = 78 : 22 (66 %)	5 %
R = Ph InI_3, CH_3CN	*E*, 1,5-*anti* : *syn* = 80 : 20 (42 %)	5 %
R = Ph BiI_3, CH_3CN	*E*,1,5-*anti* : *syn* = 92 : 8 (51 %)	5 %
R = Ph BiI_3, CH_3CN, CH_2Cl_2	*E*,1,5-*anti* : *syn* = 92 : 8 (80 %)	"
R = *p*-NO_2CH_4 BiI_3, CH_3CN	*E*,1,5-*anti* : *syn* = 92 : 8 (53 %)	"
R = *p*-$MeOC_6H_4$ BiI_3, CH_3CN	*E*,1,5-*anti* : *syn* = 92 : 8 (56 %)	"
R = CH_3CH=CH- BiI_3, CH_3CN	*E*,1,5-*anti* : *syn* = 90 : 10 (45 %)	"
R =$(CH_3)_2CH$- BiI_3, CH_3CN	*E*,1,5-*anti* : *syn* = 93 : 7 (55 %)	"
R =$CH_3CH_2CH_2$ BiI_3, CH_3CN	*E*,1,5-*anti* : *syn* = 93 : 7 (61 %)	"
R =$CH_3CH_2CH_2$ BiI_3, CH_3CN, CH_2Cl_2	*E*,1,5-*anti* : *syn* = 93 : 7 (92 %)	"

As the reactions of the allylstannane **4** mediated by bismuth(III) iodide probably proceed via an intermediate allylbismuth diiodide, it was of interest to see whether such an intermediate could be generated stereoselectively in situ from starting materials other than allylstannanes. In the event, it was found that if the pent-2-enyl bromide **71** and an aldehyde were added to a suspension containing bismuth(0) formed by stirring bismuth(III) iodide and zinc powder in tetrahydrofuran at room temperature [22], and the mixture heated under reflux for a further 2 h, then good yields of homoallylic alcohols with useful stereoselectivity in favor of the (*E*)-1,5-*anti*-isomer **70** were obtained [23].

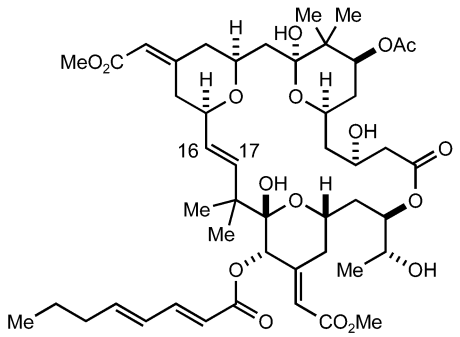
The formation of the (*E*)-1,5-*anti*-products in the reactions of the allylstannane **4** mediated by bismuth(III) iodide and in the reactions of the allyl bromide **71** induced by bismuth(0) is consistent with participation in both reactions of the allylbismuth diiodide **72**, which reacts with aldehydes through the chair-like transition structure **73** in which the group α to bismuth has adopted the equatorial position. However, as bond lengths to tin and bismuth are rather similar, and as the coordination around the bismuth in the allylbismuth diiodide **72** is similar to that in the tin intermediate **4** (allowing for the lone-pair of electrons on the bismuth), it is difficult at this stage to explain why allyltin trihalides, e.g., **4**, give rise to (*Z*)-alkenes **6** with excellent stereoselectivity, whereas (*E*)-alkenes **70** are formed preferentially in reactions of the allylbismuth diiodide [24].



These early observations have shown that remote stereocontrol in alicyclic systems can be effective using allylmetal systems not involving tin [25]. Further development of this chemistry, including mechanistic studies and applications to the synthesis of natural products, can be expected.

AN APPROACH TO THE SYNTHESIS OF BRYOSTATINS

The bryostatins are a group of important marine macrolides with potent anticancer activity which are presently undergoing clinical evaluation, often in conjunction with other chemotherapies, for the treatment of various cancers [26]. Examples include bryostatin 1 **74** and bryostatin 10 **75**, which lacks a 20-acyloxy substituent.



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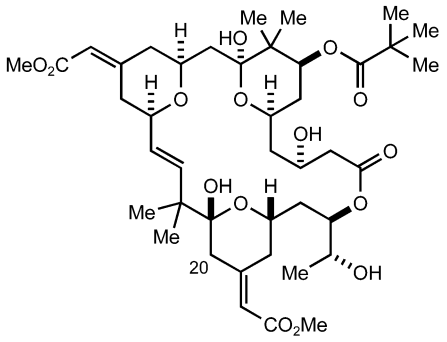
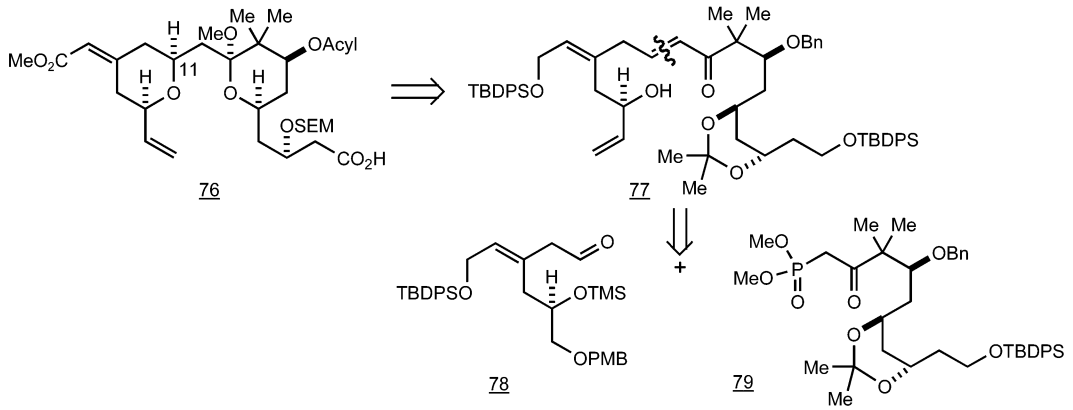


75

Many research groups have been involved in synthetic approaches to bryostatins with three total syntheses completed to date [27]. In addition, important analog work has been carried out with simplified C(1)–C(15) fragments and a cyclic acetal replacing the 4-methoxycarbonylmethylenetetrahydropyran [28]. Despite all this excellent synthetic work, there remains a need for a convergent approach to the synthesis of bryostatins and analogs for further biological evaluation.

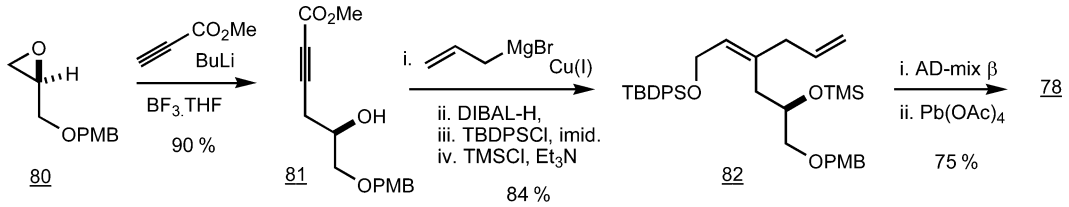
To date, Julia reactions have been used to assemble bryostatins through formation of the 16,17-double-bond followed by lactonization (see **74**) [26,27]. However, it would be of interest to see whether other reactions could be used to assemble the bryostatin nucleus, e.g., alkene metathesis, since this chemistry would be compatible with more highly functionalized intermediates so making the synthesis more convergent. It was, therefore, decided to attempt to develop multi-gramme syntheses of advanced intermediates corresponding to the C(1)–C(16) and C(17)–C(27) fragments which would then be used to assess different assembly strategies to both bryostatins 1 **74** and 10 **75**.

The unsaturated acid **76** corresponds to the C(1)–C(16) fragment required for the metathesis approach. Cyclization of the αβ-unsaturated hydroxyketone **77** via an intramolecular conjugate addition, followed by functional group modification, was identified as an approach to this acid. Indeed, preliminary studies have already shown that the cyclization is likely to be stereoselective and give the required configuration at C(11) [29,30]. The unsaturated ketone **77** was to be assembled by a

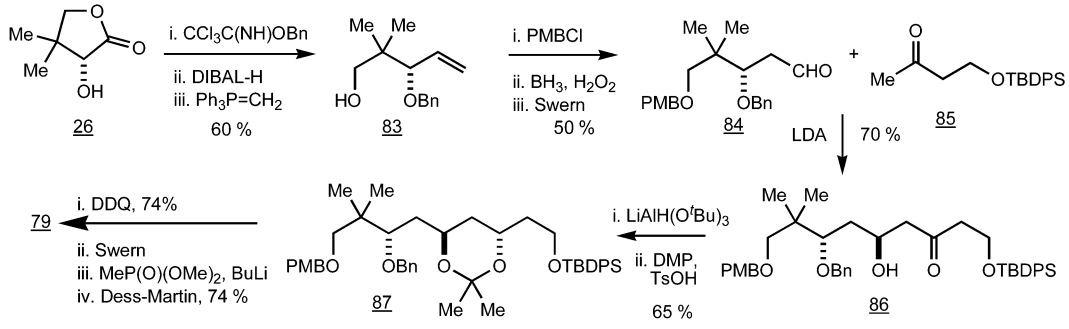


Wadsworth–Emmons–Horner condensation between the aldehyde **78** and the ketophosphonate **79** followed by selective desilylation.

The aldehyde **78** was prepared from the PMB-protected glycidol **80** by epoxide ring-opening using lithiated methyl propiolate in the presence of boron trifluoride tetrahydrofuran complex to give the alkynyl ester **8**1 [31]. Copper-catalyzed conjugate addition of allylmagnesium bromide to this ester was highly stereoselective in favor of the required (*Z*)-alkene and reduction followed by protection, first of the primary alcohol as its *tert*-butyldiphenylsilyl ether then of the secondary alcohol as its trimethylsilyl ether, gave the differentially protected triol **82** in excellent overall yield. Selective oxidation of the terminal double-bond was best achieved using AD-mix β, but cleavage of the vicinal diol so formed to the aldehyde **78** required the use of lead tetra-acetate since oxidative cleavage using sodium periodate resulted in partial loss of the trimethylsilyl group [32].

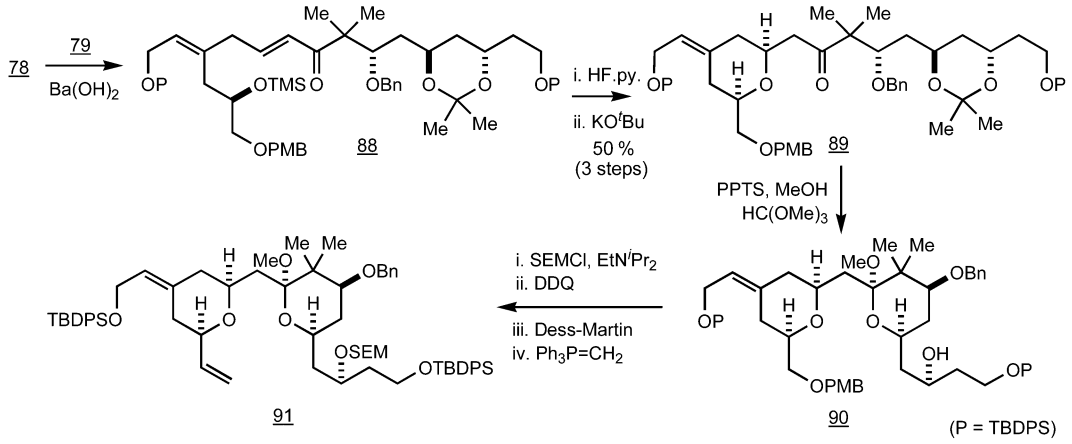


To prepare the phosphonate **79**, (*R*)-pantolactone **26** was protected as its benzyl ether then reduction using DIBAL-H followed by a Wittig reaction [6] gave the alkene **83**. Protection of this alcohol as its *p*-methoxybenzyl ether followed by hydroboration/oxidation and a Swern oxidation of the primary alcohol so obtained gave the aldehyde **84**. Following the literature precedent [33], the lithium aldol condensation between the 4-silyloxybutan-2-one **85** and this aldehyde was highly stereoselective in favor of the *anti*-product **86** due to chelation control, and an *anti*-selective reduction followed by protection of the 1,3-diol gave the acetonide **87**. Oxidative removal of the *p*-methoxybenzyl group and oxidation gave an aldehyde, which was taken through to the required ketophosphonate **79** by addition of lithiated dimethyl methylphosphonate and a Dess–Martin oxidation.



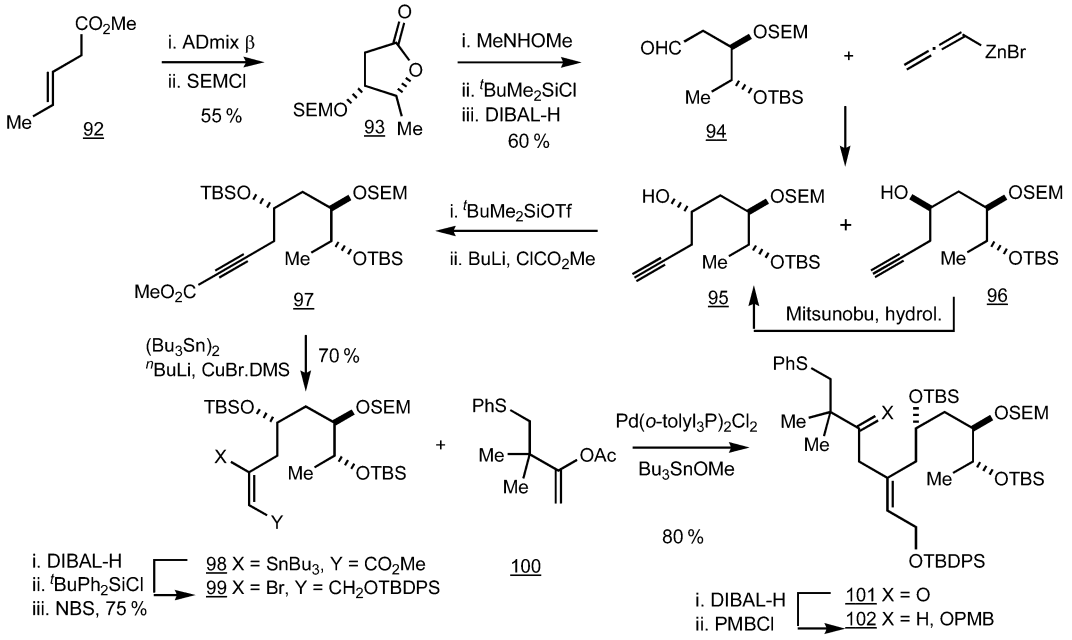
The Wadsworth–Emmons–Horner condensation between the aldehyde **78** and the phosphonate **79** gave the alkene **88** which was converted into the substituted 4-methylenetetrahydropyran **89** by selective removal of the trimethylsilyl group using the hydrogen fluoride.pyridine complex and base-catalyzed cyclization. Treatment of the acetonide **89** with trimethyl orthoformate in methanol in the presence of PPTS resulted in methanolysis of the acetonide and cyclization to give the methoxyacetal **90**, which had the structure and stereochemistry corresponding to the C(1)–C(16) fragment of the bryostatins **76**. To date, this has been taken through to the alkene **91** by protection of the 3-OH as its SEM-ether, oxidative removal of the *p*-methoxybenzyl group, oxidation of the primary alcohol to the corresponding aldehyde, and a Wittig condensation. Present work is concerned with reductive removal

of the benzyl group followed by acylation of the 7-OH and desilylation followed by oxidation of the primary alcohols with mono-esterification to give the ester-acid **76**.



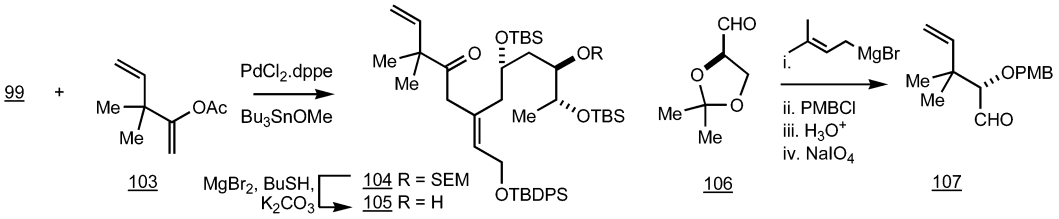
An approach to the C(17)–C(27) fragment of the 20-deoxybryostatin, e.g., **75**, for incorporation via either a Julia condensation or by metathesis has been developed based on the stereospecific synthesis of βγ-unsaturated ketones by the palladium mediated coupling of vinylic bromides with tin enolates generated in situ from enol acetates [34].

Asymmetric hydroxylation of methyl pent-3-enoate **92** using ADmix β was accompanied by lactonization and gave the protected hydroxy-lactone **93** after reaction with SEM-chloride and Hunig's base. This was taken through to the aldehyde **94** by ring-opening using *N*,*O*-dimethylhydroxylamine, *O*-silylation, and reduction of the intermediate Weinreb amide. Unfortunately, the addition of organometallic reagents to this aldehyde was not subject to effective chelation control, and mixtures of diastereoisomers were invariably obtained. For example, addition of allenylzinc bromide to the aldehyde **94**, which was stereoselective in closely related systems in favor of the chelation controlled 1,3-*anti*-product [35], gave an approximately 50:50 mixture of the 1,3-*anti*- and 1,3-*syn*-products **95**



and **96**. However, these could be separated and the *syn*-isomer **96** converted into the required *anti*-isomer **95** via a Mitsunobu inversion which gave the required *anti*-isomer **95** in an overall yield of 70 % based on the aldehyde **94**. After *O*-silylation, methoxycarbonylation of the alkyne gave the ester **97**, which on treatment with a tributyltin cuprate was converted into the (*E*)-vinylstannane **98** [36]. After reduction of the methoxycarbonyl group and silylation of the primary alcohol so obtained, the vinyl stannane was converted into the vinyl bromide **99** by reaction with *N*-bromosuccinimide. This vinyl bromide was then coupled with the enol acetate **100** using Pd(*o*-tolyl$_3$P)$_2$Cl$_2$ in the presence of tributyltin methoxide in toluene heated under reflux to give an excellent yield of the required nonconjugated ketone **101** with retention of the double-bond geometry [35]. This ketone has been taken through to the fully protected polyol **102** in anticipation of a Julia coupling by reduction using DIBAL-H and protection using *p*-methoxybenzyl chloride.

The vinyl bromide **99** has also been coupled with the enol acetate **103** to give the ketone **104**, although in this case Pd(Ph$_2$PCH$_2$CH$_2$PPh$_3$)Cl$_2$ (PdCl$_2$.dppe) was the better catalyst and a small amount, ca. 15 % of the product, of the stereoisomeric alkene was also obtained [37]. The ketone **104** has been deprotected to give the alcohol **105**, which is ready for the metathesis assembly strategy.



Some of the intermediates in this work may also be useful for the synthesis of bryostatin 1 **74** and analogous bryostatins which possess 20-acyloxy substituents. For example, the aldehyde **107** has been prepared from the acetal **106** by chelation-controlled addition of isopropenyl magnesium bromide, *O*-protection, selective acetal hydrolysis, and oxidative cleavage of the diol so obtained. The chelation-controlled addition of vinyl organometallics derived from vinyl bromide **99** and analogous iodides to this aldehyde is currently under investigation [38].

These syntheses of the C(1)–C(16) fragment **91**, the C(17)–C(27) alkene **105** and the C(17)–C(27) sulfide **102** have provided sufficient quantities of these advanced intermediates so that different reaction sequences for the assembly of bryostatins can be evaluated. Present work is concerned with converting the C(1)–C(16) fragment **91** into the acid **76**. Following esterification with the alcohol **105**, ring-closing metathesis will be studied to evaluate this route to the bryostatins. As an alternative, the aldehyde corresponding to **91** may be coupled with the sulfone prepared from the sulfide **102** using a Julia reaction.

This lecture has presented some approaches to natural product synthesis with examples illustrating applications of allylmetal reagents for stereochemical control.

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6. The ease of olefination of lactols derived from pantolactone was found to depend on the *O*-protecting group, compare the synthesis of **27** and **83**. In some cases, the Wittig reagent was fine, but in others less satisfactory results were obtained and so alternative reagents had to be used. This behavior of the different lactols may depend on the rate of equilibration between the lactol and the open-chain hydroxyaldehyde.
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24. A transition state analogous to that shown in **73** but with the group α to the metal in the axial position is consistent with the behavior of allylstannanes (see [1]). The preference for the group α to the metal to adopt either the axial or equatorial position may be determined by the preferred conformation of the intermediate, i.e., the preference for the oxygen ligand of the metal to adopt an apical position. Alternatively, the preference of allylstannanes to give (*Z*)-alkenes exclusively for 1,5-, 1,6 and 1,7-stereocontrol may be indicative of a two-step process for the reaction be-

tween the allyltin trihalide and an aldehyde, the first step being a displacement on the tin of the coordinating oxygen substituent by the aldehyde followed by allyl group transfer in a separate step. Studies into the structures of the intermediates may help to resolve this dichotomy.

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