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Studies toward the Synthesis of (−)-Zampanolide: Preparation of the Macrocyclic Core

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Dedicated to Prof. Chi-Huey Wong on the occasion of his 60th birthday.

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Abstract: Studies towards the synthesis of the macrocyclic core of (−)-zampanolide are reported. The synthetic approach features a one-pot reduction/vinylogous aldol reaction for construction of the C-15–C-20 fragment, an intramolecular silyl-modified Sakurai (ISMS) reaction for construction of the 2,6-*cis*-disubstituted *exo*-methylene pyran subunit, and use of an sp^2-sp^3 Stille reaction for macrocyclization.

Keywords: allylsilanes; macrolide; *exo*-methylene pyrans; sp^2-sp^3 coupling; Stille reaction; zampanolide

Introduction

The intriguing natural product (−)-zampanolide, (Figure 1, **1)** was isolated in 1996 by Tanaka and Higa from the Okinawan sponge, *Fasciospongia rimosa,* collected off of the coast of Okinawa, Japan.[1] Zampanolide is a 20-membered macrolide which contains a high degree of unsaturation, a 2,6-disubstituted *exo*-methylene pyran ring, and a *N*-acyl hemiaminal sidechain. Both the relative stereochemistry at the C-20 stereocenter and the absolute stereochemistry were determined *via* total synthesis in 2001 by Smith's laboratory[2] which was further confirmed by Hoye and Hu's synthesis in 2002.[3,4] The related natural product, (+)-dactylolide (**2)** was isolated in 2001 by Riccio and co-workers from the Vanuatu sponge *Dactylospongia sp.*[59] Interestingly, the absolute configurations of **1** and **2** were found to be opposite, although, as pointed out by Hoye and coworkers,[3] the propensity of the aldehyde of **2** to hydrate may affect the accuracy of optical rotation measurements.[3] Regarding biological activity, (−)-zampanolide displayed cytotoxicity against P388, HT29, A549, and MEL28 cell lines (IC_{50} 1–5 ng/mL). (+)-Dactylolide showed cytotoxicity toward L1210 and SK-OV-3 cell lines (63% and 40% inhibition at 3.2 μg mL^{-1}, respectively).[4]

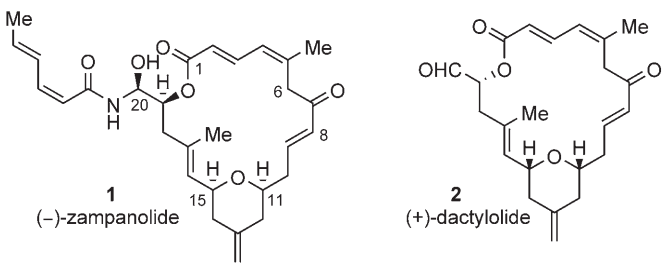


Figure 1. (−)-Zampanolide and (+)-dactylolide.

Since the initial isolation and structure elucidation of (−)-zampanolide in 1996, researchers have been unable to isolate additional amounts of the natural product from the Okinawan sponge or any other source. Interest in this biologically interesting compound, as well as its challenging structural architecture, has sparked a great deal of attention in the synthetic organic community. The first syntheses of zampanolide and dactylolide were published by Smith and co-workers in 2001 and 2002, respectively.[2] These initial reports were followed by Hoye and Hu's syntheses of both molecules in 2003.[3] Other syntheses of dactylolide have been published by Floreancig,[6] Keck,[7] Jennings,[8] and McLeod.[9] Our work in this area was initiated by interest in the *N*-acyl hemiaminal side chain and its apparent stabilization through an intramolecular hydrogen bond network and entailed preparation of a *N*-acyl hemiaminal model system.[10] In this paper, we report our studies towards the synthesis of the macrocyclic core of (−)-zampano-

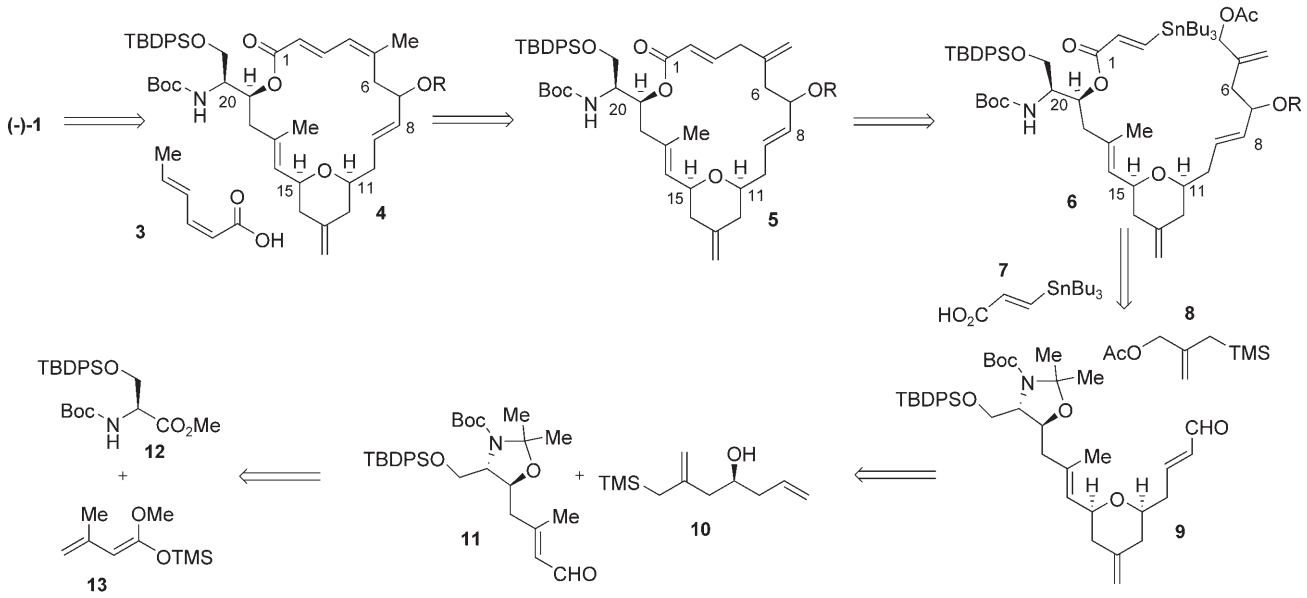


Figure 2. Retrosynthetic analysis.

lide featuring a one-pot reduction/vinylogous aldol reaction, an intramolecular silyl-modified Sakurai reaction (ISMS), and use of an sp^2-sp^3 Stille reaction for construction of the macrocyclic core.

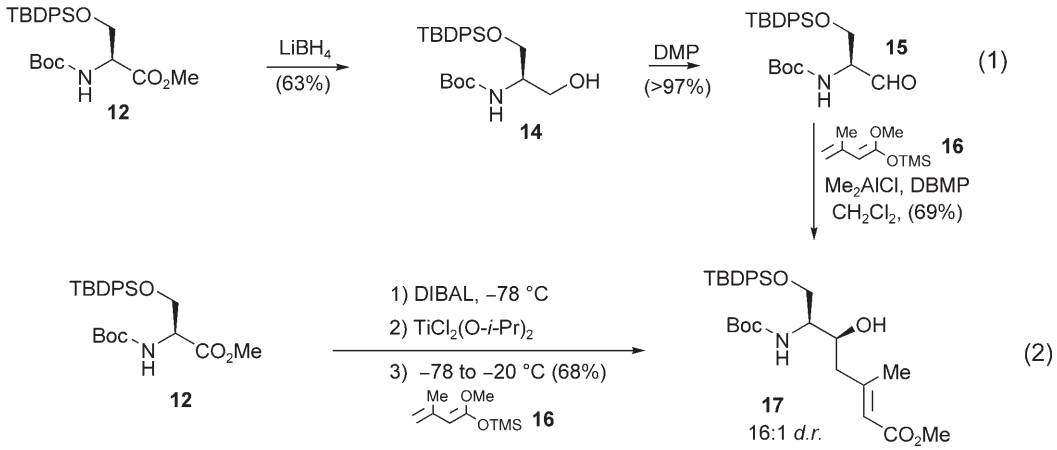
Results and Discussion

Retrosynthetic Analysis

Our retrosynthetic analysis for (−)-zampanolide, (−)-**1** is outlined in Figure 2. The *N*-acyl hemiaminal sidechain may be derived from the protected amino alcohol-bearing macrolide **4** and installed at a late stage using our previously reported oxidative decarboxylation-hydrolysis approach.[9] Further disconnection of the macrolide core affords three major fragments; (1) the C-15–C-20 δ-hydroxy-α,β-unsaturated portion, (2) the 2,6-*cis*-disubstituted *exo*-methylene pyran ring, and (3) the C-1–C-9 triene system. In an effort to install the potentially sensitive 1,3-dienoate portion of the macrolide at a late stage of the synthesis, a less conventional disconnection was investigated. Rather than preparing 1,3-dienoate **4**, we targeted preparation of the 1,4-dienoate **5**. Subsequent isomerization was imagined to occur under macrocyclic control.[11] Installation of the dienoate in a "masked" format would allow for unveiling after construction of the macrolide. Further disconnection of macrolide **5** at the C-3−C-4 bond affords the acyclic precursor **6** *via* intramolecular Stille reaction.[12] Although there are numerous literature examples involving Pd(0)-mediated coupling of vinylstannanes and allylic acetates,[13] use of such sp^2-sp^3 Stille macrocyclizations in complex synthesis has received limited attention.[14] Disconnection at the ester bond gives the β-stannylacrylic acid **7**. Disconnection at the C-6−C-7 bond provides allylic acetate **8** and the pyran fragment **9**. Pyran **9** may be formed using an intramolecular silyl-modified Sakurai (ISMS)[15] reaction between allyl silane **10** and α,β-unsaturated aldehyde **11**. The C-15–C-20 fragment may be constructed using a vinylogous aldol reaction[16] between protected serine derivative **12** and dienol ether **13**.

Synthesis of the C-15–C-20 Fragment

The vinylogous aldol reaction is an efficient method for formation δ-hydroxy-α,β-unsaturated esters which are common motifs in natural products.[17] The vinylogous aldol reaction has the potential to generate three elements of stereogenicity (two carbons and one double bond) in a single transformation.[6,18] Literature examples indicate that the stereoselectivity of this reaction can be dictated by either chelation or Felkin–Anh control as is the case for typical aldol reactions. We employed a vinylogous aldol reaction for construction of amino alcohol C-15–C-20 **17** by condensation of aldehyde **15** and silylketene acetal **16**[19] [Scheme 1, Eq. (1)]. The reaction sequence involves reduction of serine-derived methyl ester **12** and subsequent oxidation to provide aldehyde **15**. A number of conditions to oxidize serine derivative **14** [e.g., Swern, IBX, IBX/Bu_4NI, and Pd(I-*i*-Pr)$_2$(OPiv)$_2$/O_2[20]] were evaluated, but most led to incomplete conversion or epimerization of the stereocenter. Interestingly, Dess–Martin periodinane[21] was the only oxidant found to produce **15** without epimerization of the α-chiral center.[22] However, the latter oxidation generally did

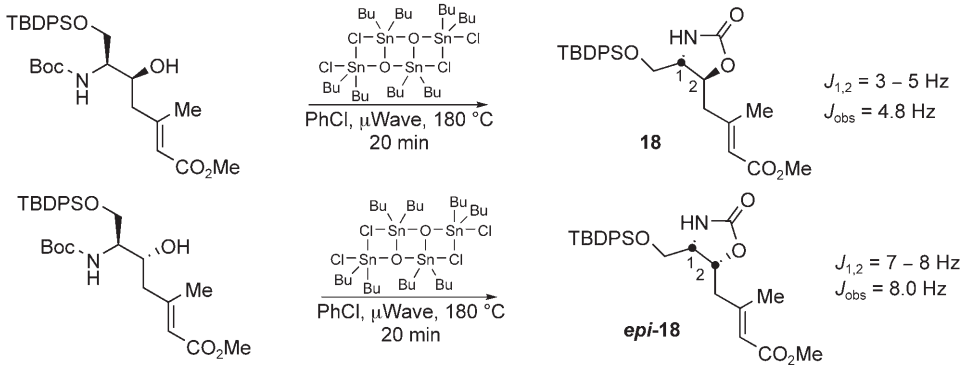


Scheme 1. Vinylogous aldol reaction to access the C-15–C-20 fragment.

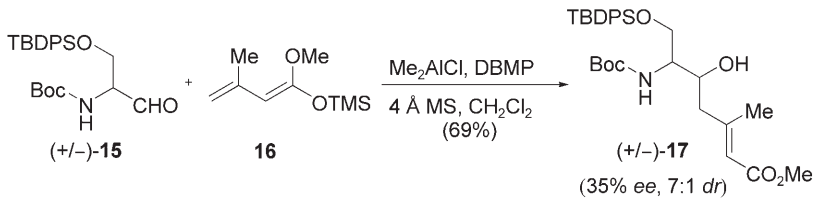
not proceed to completion, in particular on a larger scale, (e.g., 10 g) which required investigation of alternative routes. A number of tactics have been employed[23] to circumvent racemization of the α-chiral stereocenter of α-amino aldehydes.[24] In particular, one-pot reduction/nucleophilic additions of esters involving DIBAL-H have been reported in the literature.[25] Polt and co-workers used this tactic for *in situ* reduction of an ester, followed by addition of a nucleophile (RMgBr, RLi).[20a] In this case, DIBAL-H was used in conjunction with tri-*iso*-butylaluminum (*i*-Bu_3Al) to moderate its reactivity as well as to activate the substrate for the nucleophilic addition.[26] In a related approach, Kiyooka and co-workers found that reduction with DIBAL-H, followed by addition of $TiCl_2(O\text{-}i\text{-}Pr)_2$, also activated the alkoxyaluminum intermediate for nucleophilic addition.[27] Both of these protocols avoided isolation of the aldehyde and are mild enough to be used with a number of different nucleophiles without racemization.

After evaluation and optimization of the DIBAL-H/Me_2AlCl system developed by Polt and co-workers, the highest yield of the desired homoallylic alcohol **17** attained was 36% using 1.5 equiv. of DIBAL-H and 1.5 equiv. of Me_2AlCl. The two-step process developed by Kiyooka[27] using DIBAL-H and $TiCl_2(O\text{-}i\text{-}Pr)_2$ was next investigated. Reaction optimization provided the desired vinylogous aldol product, **17** (*dr* = 16:1) in 68% yield from the methyl ester [(Scheme 1, Eq. (2)]. The three-step, one-pot protocol previously employed resulted in a 44% overall yield of adduct **17** [Eq. (1)] from the methyl ester without epimerization.

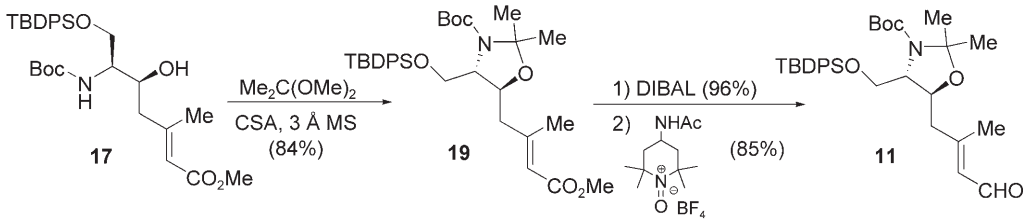
In order to assign stereochemistry of the vinylogous aldol product, substrate **17** was treated with Otera's distannoxane catalyst[28] (1,3-dichlorodistannoxane) and subjected to microwave irradiation to afford cyclic carbamate **18** (Scheme 2).[29] The minor *anti*-diastereomer was also isolated and treated with Otera's catalyst to afford the cyclic carbamate *epi*-**18** (Scheme 3 and Scheme 4). Analysis of coupling constants between H-1 and H-2 showed $J_{1,2} = 4.8$ Hz for **18** and $J_{1,2} = 8.0$ Hz for *epi*-**18**, which are within the same range as similar substrates reported in literature.[30] The stereochemical assignment was further confirmed by NOE experiments. Carbamate **18** showed a 15% NOE between H-1 and the allylic methylene and a 5% NOE between H-2 and the other methylene (no NOE was observed between the



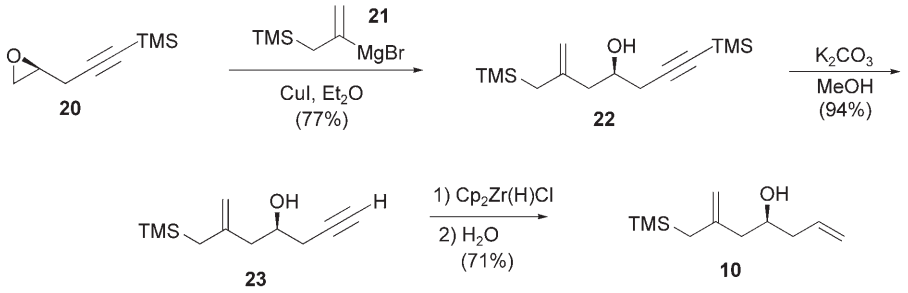
Scheme 2. Stereochemical assignment of the vinylogous aldol products.



Scheme 3. Vinylogous aldol reaction using a highly racemized aldehyde substrate.



Scheme 4. Further advancement of the vinylogous aldol product



Scheme 5. Synthesis of the hydroxyallylsilane reagent.

two methylene groups). Substrate *epi*-**18** showed a 13% NOE between the two methylenes.

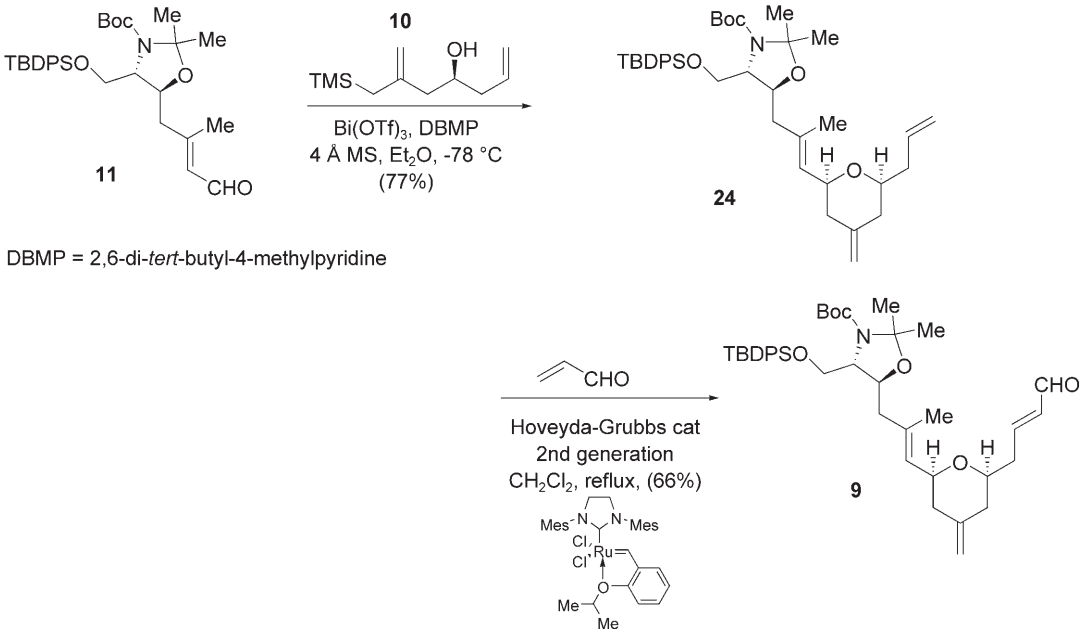
To rule out racemization during the reaction, we conducted a vinylogous aldol reaction using a largely racemized sample of aldehyde **15** to provide a vinylogous aldol product (±)-**17** (35% *ee*. *dr* = 7:1, Scheme 3). Comparison of this product to material obtained using the one-pot DIBAL-H reduction/vinylogous aldol process (Scheme 1) by chiral HPLC, indicated that the latter process proceeded without racemization of the intermediate aldehyde or equivalent to afford adduct **17** in > 99% **ee** and *dr* = 16:1.

Vinylogous aldol substrate **17** was next advanced to the α,β-unsaturated aldehyde, **11** (Scheme 4). Amino alcohol **17** was protected as the *N*,*O*-acetonide **19** which was followed by reduction of the methyl ester with DIBAL-H. Subsequent oxidation with 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (Bobbitt reagent)[3,31] afforded enal **11**. Initially, Dess–Martin reagent was used for this oxidation; however, formation of an unidentified by-product caused lower yields in the subsequent pyran annulation (*vide infra*).

Synthesis of the *exo*-Methylene Pyran Subunit

A number of syntheses of zampanolide and dactylolide[3,7] have utilized the intramolecular silyl-modified Sakurai (ISMS) reaction[15] for construction of the 2,6-disubstituted *exo*-methylene pyran subunit. For our synthetic route, the requisite allylsilane **10** for an ISMS reaction was obtained from Cu(I)-mediated addition[32] of vinyl-Grignard reagent **21**[33] to chiral epoxide **20** (Scheme 5). Compound **20** was prepared by addition of trimethylsilylacetylene anion to (*S*)-epichlorohydrin followed by epoxide formation from the subsequent chlorohydrin.[34] Subsequent desilylation and alkyne reduction to the terminal olefin with $Cp_2Zr(H)Cl$ (Schwartz's reagent[35]) afforded hydroxyallylsilane **10** in good overall yield.

With aldehyde **11** and silane **10** in hand, the ISMS reaction was next explored. After evaluation of a number of Brønsted and Lewis acid catalysts, we found that $Bi(OTf)_3$[36] (1.5 equiv.) in conjunction with 2,6-di-*tert*-butylpyridine as a triflic acid scavenger[37] was found to mediate the desired reaction to cleanly afford pyran **24** as a single diastereomer (68%). The



Scheme 6. ISMS reaction to construct the *exo*-methylene pyran.

relative stereochemistry of *exo*-methylene pyran **24** was determined to be *syn* by NOE studies. Elaboration of the terminal olefin by cross-metathesis[38] using the Grubbs-Hoveyda second generation catalyst[39] provided α,β-unsaturated aldehyde **9** as a single olefin isomer in 66% yield (Scheme 6).

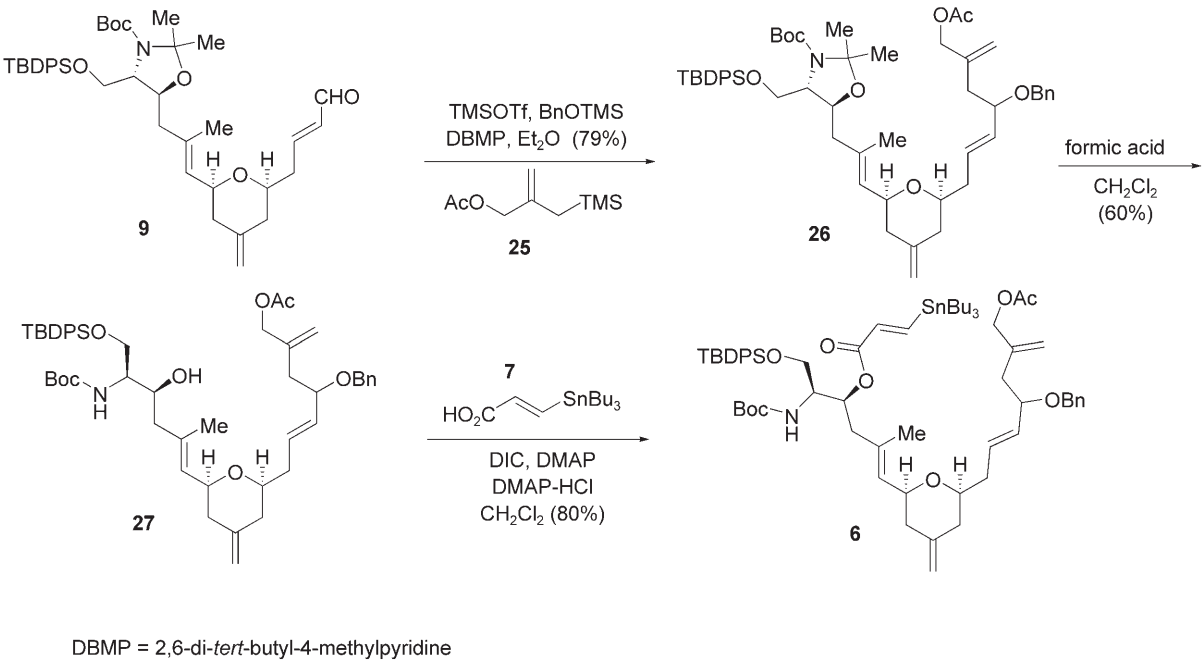
Construction of a Macrolide Precursor

As described in our retrosynthetic analysis (Figure 2), we planned to prepare vinylstannane **6** in order to evaluate sp^2-sp^3 Stille macrocyclization for construction of the macrocyclic core. Construction of the C-6–C-7 bond *via* allylation to install an allylic acetate function was more difficult than anticipated. However, we found that activation of the aldehyde as an oxocarbenium ion with BnOTMS led to good conversion while simultaneously protecting the emerged hydroxy group (Scheme 7). Optimization of reaction conditions led to the identification of TMSOTf as a promoter for allylation of **9** with the Trost trimethylenemethane (TMM) reagent **25**[40] in the presence of BnOTMS which cleanly afforded allylic acetate **26** (83% yield, *dr* = 1:1).

Removal of the acetonide protecting group was next attempted using standard conditions. Traditional methods for acetonide deprotection including AcOH/MeOH,[41] PPTS/MeOH,[42] and TsOH/MeOH[43] led to incomplete conversion, loss of the TBDPS ether, or loss of the allylic acetate functionality. All attempts to remove the acetonide under other conditions [e.g., $CeCl_3/(CO_2H)_2$/MeCN,[44] $BiCl_3$/aqueous MeCN,[45] CBr_4/MeOH[46]] afforded a low yield of the *N*-Boc-amino alcohol product or decomposition of the starting material. Finally, treatment of **26** with 50% formic acid in CH_2Cl_2[47] provided the desired secondary alcohol in 60% yield. Esterification of **27** with **7**[48] provided the macrocylization precursor **6** in 80% yield.

Model Studies for the Stille Macrocyclization

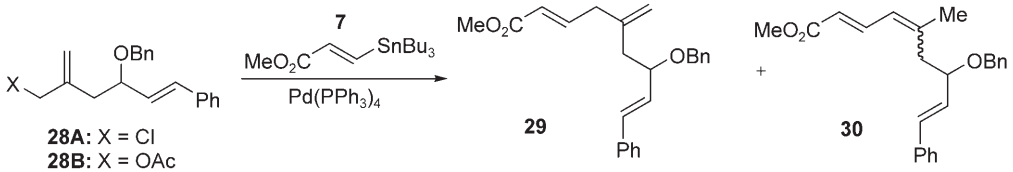
Conditions for the critical sp^2-sp^3 Stille macrocyclization were first examined in an intermolecular fashion employing model system **38** (Table 1). Initial screening of the palladium source [$Pd(PPh_3)_4$, $Pd_2(dba)_3$, $PdCl_2(BnCN)_2$] and ligands [PPh_3, $AsPh_3$, $P(2\text{-furyl})_3$] showed $Pd(PPh_3)_4$ to be the most efficient catalyst for coupling of **28A** and **B** and β-stannyl acrylate **7**.[49] Initial screening with Cu(I) and *N,N*-diisopropylethylamine (DIEA) (entries 1–3) afforded only the 1,4-diene product **29** in low conversion. Replacing the allylic acetate with a chloride was examined using NMP as solvent (entry 4) which afforded 44% of the 1,4-product, **29** along with numerous side products. In an attempt to accelerate the reaction and increase the conversion, use of tetrabutylammonium iodide (TBAI) as an additive[50] was investigated (entries 5–8). Quaternary ammonium salts have been employed to accelerate metal-mediated couplings involving alkynes,[51] alkenes,[52] and alkyl[53] substrates. When TBAI was employed for the coupling of acetate **28** and model vinylstannane **7**, the reaction proceed to completion and provided the 1,3-diene product **30** as the sole product. When Bu_4NCl[54] was used in place



DBMP = 2,6-di-*tert*-butyl-4-methylpyridine

Scheme 7. Synthesis of a macrocyclization substrate.

Table 1. Model Stille reactions.



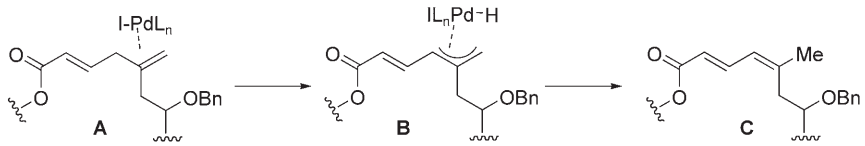
Entry	X	Additive	Solvent/Temperature	Result
1	OAc	CuI	PhMe/reflux	only **29**[a]
2	OAc	DIEA	PhMe/reflux	1:2; **29**:**30**
3	OAc	DIEA, CuI	PhMe/reflux	**29** (trace **30**)[a]
4	Cl	DIEA, CuTC	NMP/60 °C	44% **29**[a,b]
5	OAc	DIEA, CuI, Bu_4NI	PhMe/reflux	57% **30**[b]
6	OAc	DIEA, Bu_4NI	PhMe/reflux	62% **30**[b]
7	Cl	DIEA, Bu_4NI	PhMe/reflux	44% **30**[b]
8	OAc	DIEA, Bu_4NCl	PhMe/reflux	mixture of **29** and **30**

[a] Significant impurity present.
[b] Isolated yields after silica gel chromatography.

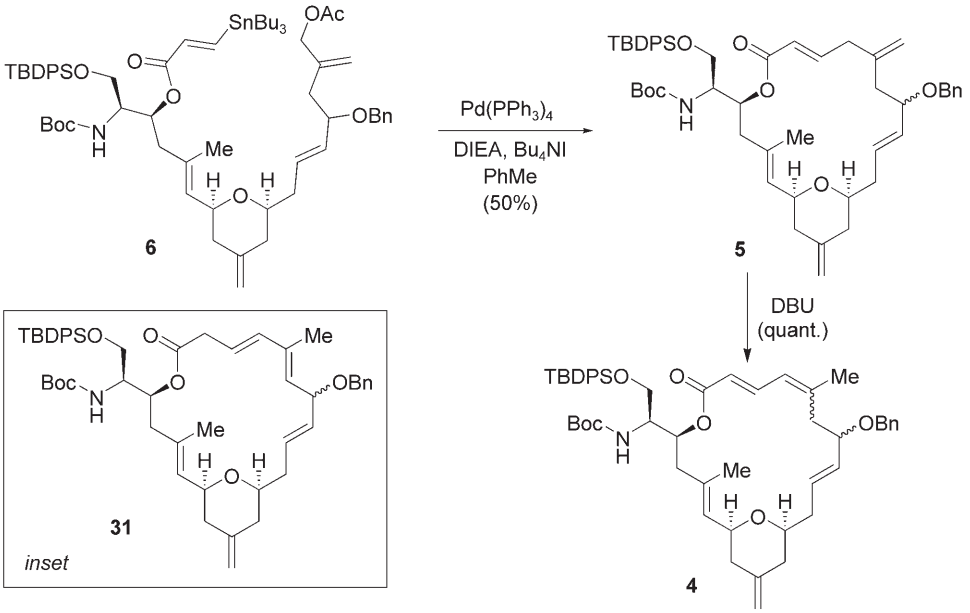
of TBAI, a mixture of 1,4- and 1,3-product was observed. According to a literature precedent, the additive TBAI may form an anionic Pd(0) species which is highly reactive in oxidative addition.[55] One possible pathway for the isomerization is shown in Scheme 8. The initially formed 1,4-diene (**A**) may undergo a β-hydride elimination to form the π-allyl species **B**, followed by reductive elimination, to afford the more stable 1,3-diene **C**.

Macrocyclization *via* sp^2-sp^3 Coupling

Optimized conditions for sp^2-sp^3 coupling derived from the model studies (Table 1) were evaluated for the construction of the zampanolide macrolide core (Scheme 9). After considerable experimentation, we found that macrocyclization of vinylstannane **6** (0.005 M in toluene) could be achieved using 20% Pd-$(PPh_3)_4$, 3.0 equiv. of Bu_4NI, and DIEA (2 equiv.) (48 h, reflux) to afford macrolactone **5** in 50% yield.



Scheme 8. Isomerization to a 1,3-diene.



Scheme 9. Stille macrocyclization.

Interestingly, only 1,4-diene product **5** was observed in these experiments with no evidence of isomerized dienoate products formed. This is likely due to the constraints of the macrolide on olefin isomerization. In the cyclization, the two C-7 diastereomers of **5** were found to be separable though this is inconsequential for the reaction sequence as the secondary alcohol will later be oxidized to a ketone in the final product. Subsequent treatment with DBU in THF at 45 °C afforded the 1,3-diene **4** in quantitative yield as a 1:1 mixture of *E*,*Z* and *E*,*E*-isomers. In an effort to perform the reaction at a lower temperature, NaHMDS was evaluated, but gave no reaction, even with higher equivalents of base. DBU isomerization has been performed in *i*-PrOH[56] which allows for olefin isomerizations at room temperature due to assumed carbonyl activation by the protic solvent. Interestingly, the latter conditions produced the 2,4-diene **31** as the only product (*inset*). Isomerization using a phosphazene base, BEMP[57] was also evaluated, but no reaction was observed in this case. Other reactions may be examined to produce the *E*,*Z*-dienoate, however, access to both olefin isomers is also useful in terms of obtaining the *E*,*E*-dienoate macrolactone core for further studies and to probe the effect of the C-7 stereocenter on the dienoate geometry. Further studies involving oxidative deprotection of the allylic benzyl ether[58] will be evaluated in order to obtain the (−)-zampanolide macrolide core and should provide materials for final oxidative decarboxylation-hydrolysis protocols[10] for the late stage introduction of the sensitive *N*-acylheminal side-chain.

Conclusions

Herein, we have reported the synthesis of the zampanolide macrolide core which features a one-pot reduction/vinylogous aldol reaction, an intramolecular silyl-modified Sakurai (ISMS) reaction to construct the 2,6-disubstituted *exo*-methylene pyran, and sp^2-sp^3 Stille reaction employing a vinylstannane/allylic acetate substrate for macrocyclization. Initial studies have been performed to isomerize the 1,4-diene macrolactone product to the requisite 1,3-diene. Further studies on the completion of the synthesis of (−)-zampanolide are in progress and will be reported in due course.

Experimental Section[59]

Methyl 3-(Diphenyl-*tert*-butylsilyl)oxy-2-*tert*-butoxycarbonylaminopropanoate 12

N-(*tert*-Butoxycarbonyl)-L-serine methyl ester (9.54 g, 43.5 mmol, 1.0 equiv.) was dissolved in 44 mL of DMF. *tert*-Butyldiphenylsilyl chloride (17 mL, 65.2 mmol, 1.5 equiv.) and imidazole (5.92 g, 87 mmol, 2.0 equiv.) were added. The reaction was stirred at room temperature for 5 h. EtOAc was used to dilute the reaction mixture. The organic layer was washed by pH 7 buffer, water, and saturated aqueous NaCl. The combined organic layers were dried over $NaSO_4$, filtered, and concentrated under vacuum. Purification on silica gel (5% ether in hexane was used to remove TBDPSOH, then 20% EtOAc in hexane) provided methyl ester **12** as a colorless viscous oil; yield: 19.5 g (42.6 mmol, 98%).

Silylketene Acetal 16

To a solution of methyl 3,3-dimethylacrylate (5.0 mL, 38.2 mmol, 1.0 equiv.) in 120 mL THF at −78 °C was added NaHMDS (45.0 mL, 45.9 mmol, 1.0 M in THF, 1.0 equiv.) dropwise. The reaction was stirred at −78 °C for 1 h then freshly distilled TMSCl (6.3 mL, 49.7 mmol, 1.3 equiv.) was added. The reaction mixture was brought to room temperature then concentrated under vacuum. The residue was dissolved in dry hexanes, filtered, and concentrated under vacuum. Purification by high vacuum distillation provided silylketene acetal **16**; yield: 4.98 g (26.7 mmol, 70%). Spectral data were found to match data reported in the literature.[19]

Methyl 7-(Diphenyl-*tert*-butylsilyl)oxy-5-hydroxy-3-methyl-6-*tert*-butoxycarbonylaminohept-2-enoate 17

Methyl ester **12** (4.88 g, 10.7 mmol, 1.0 equiv.) was dissolved in 53 mL of CH_2Cl_2 and cooled to −78 °C. A solution of DIBAL-H (1.0 M in hexanes) (16.0 mL, 15.0 mmol, 1.5 equiv.) was added dropwise. After 1 h at −78 °C, a solution of $TiCl_2(O\text{-}i\text{-}Pr)_2$ (freshly prepared, 1:1 mixture of $TiCl_4$ and $Ti(O\text{-}i\text{-}Pr)_4$, 1.0 M in CH_2Cl_2, 20 min 0 °C to room temperataure) was added dropwise at −78 °C. After five minutes, silylketene acetal **16** (6.15 g, 33.0 mmol, 3.1 equiv.) was added. After 2 h, the reaction was slowly warmed from −78 °C to −20 °C over 3 h. The total reaction time was 24 h from addition of the silylketene acetal. The reaction mixture was quenched at −78 °C with Rochelle's salt and brought to room temperature, diluted with EtOAc, and the organic layer washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (10–20% EtOAc in hexane) provided δ-hydroxy-α,β-unsaturated ester **17** as a colorless oil; yield: 3.93 g (7.25 mmol, 68%).

Methyl 4-{4-[(Diphenyl-*tert*-butyl-silyl)oxymethyl]-2-oxooxazolidin-5-yl}-3-methylbut-2-enoate 18

Methyl ester **17** (64.2 mg, 0.119 mmol, 1.0 equiv.) was dissolved in 1.2 mL PhCl. Otera's catalyst (13.1 mg, 1.19×10^{-2} mmol, 0.1 equiv.) was added and the reaction was purged with argon and sealed. Reaction was subjected to microwave irradiation (temperature: 180 °C, 250 W power) for 30 min. The reaction mixture was cooled to room temperature and concentrated under vacuum. Purification on silica gel (10–30% EtOAc in hexane) provided cyclic carbamate **18** as a colorless oil; yield: 40.1 mg (0.86 mmol, 95%).

tert-Butyl 4-[(Diphenyl-*tert*-butyl-silyl)oxymethyl]-5-(3-methoxycarbonyl-2-methylprop-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate 19

Methyl ester **17** (5.70 g, 10.5 mmol, 1.0 equiv.) was dissolved in 53 mL of CH_2Cl_2 (0.2 M). 3 Å Molecular sieves (2.1 g) and 2,2-dimethoxypropane (6.5 mL, 52.6 mmol, 5.0 equiv.), followed by (+/-)-CSA (488.8 mg, 2.10 mmol, 0.2 equiv.). The reaction mixture was stirred at room temperature for 36 h, diluted with EtOAc, and the organic layer washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (10–20% EtOAc in hexane) provided the acetonide **19** as a colorless oil; yield: 5.14 g (8.84 mmol, 84%).

tert-Butyl 4-[(Diphenyl-*tert*-butylsilyloxy)methyl]-5-(4-hydroxy-2-methylbut-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate 31

Methyl ester **19** (1.46 g, 2.52 mmol, 1.0 equiv.) was dissolved in 12.6 mL of CH_2Cl_2 and cooled to −78 °C. A solution of DIBAL-H (1.0 M in hexanes) (7.55 mL, 7.55 mmol, 3.0 equiv.) was added dropwise. After 1 h, the reaction mixture was quenched with saturated aqueous Rochelle's salt and warmed to room temperature. The mixture was stirred for three hours at room temperature. The reaction mixture was diluted with EtOAc and the organic layer washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (20% EtOAc in hexane) provided allylic alcohol **31** as a colorless oil; yield: 1.34 g (2.42 mmol, 96%).

α,β-Unsaturated Aldehyde 11

Allylic alcohol **33** (1.35 g, 2.45 mmol, 1.0 equiv.) was dissolved in 24 mL of CH_2Cl_2. 2.0 g of silica gel (1.5% wt) were added followed by addition of the solid Bobbitt reagent (809.4 mg, 2.69 mmol, 1.1 equiv.) at room temperature. The heterogeneous bright yellow mixture was stirred for 6 h. The reaction mixture was filtered through a silica plug and washed thoroughly with CH_2Cl_2. The filtrate was concentrated under vacuum to provide α,β-unsaturated aldehyde **11** as a viscous oil; yield: 1.14 g (2.08 mmol, 85%).

Chlorohydrin 32

Trimethylsilylacetylene (6.0 mL, 43.4 mmol, 1.5 equiv.) was dissolved in 116 mL hexane. After cooling the reaction mixture to 0 °C, *n*-butyllithium (2.3 M, 12.6 mL, 28.9 mmol, 1.0 equiv.) was added, reaction was stirred for 10 min. Et_2AlCl (28.9 mL, 28.9 mmol, 1.0 M in hexane, 1.0 equiv.) was added, reaction was stirred for 30 min at 0 °C. The (*S*)-epichlorohydrin (2.68 g, 28.9 mmol, 1.0 equiv.) in hexane was transferred into a reaction flask *via* cannula. After 2.5 h at 0 °C, reaction mixture was quenched with 1 N aqueous

HCl and was extracted with ether. Then the organic layers were washed with saturated aqueous NaCl. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to afford of chlorohydrins **34**; yield: 5.16 g (27.0 mmol, 94%). The material was carried on to next step without further purification.

Epoxide 20

Chlorohydrin **34** (5.16 g, 27.0 mmol, 1.0 equiv.) was dissolved in 135 mL of Et_2O, and powdered NaOH (1.6 g, 40.6 mmol, 1.5 equiv.) was added. The reaction was stirred for 24 h at room temperature. The reaction was filtered through Celite, the organic layer was washed with pH 7 buffer, dried over Na_2SO_4, filtered, and concentrated under vacuum. The chiral epoxide (3.33 g, 21.6 mmol, 80%) was used without further purification. Attempts to purify on silica gel caused product decomposition. Spectral data for epoxide **20** matched literature data.[34]

Allylsilane 22

(2-Bromoallyl)trimethylsilane (16.8 g, 87.1 mmol, 1.0 equiv.) was dissolved in 51 mL of ether at −78 °C. *tert*-Butyllithium (1.70 M, 102 mL, 174.2 mmol, 2.0 equiv.) was added and reaction mixture was stirred for 1 h at −78 °C. $MgBr_2{\cdot}Et_2O$ (1 M, 95.8 mL, 1.1 equiv.) was added and stirring was continued for 30 min at −78 °C to afford the Grignard reagent (**21**) *in situ*. In a separate flask, flame-dried CuI (772.0 mg, 4.05 mmol, 0.1 equiv.) was mixed with 203 mL of Et_2O, and the reaction mixture was cooled to −30 °C. The Grignard reagent (184.8 mL, 0.329 M, 1.5 equiv.) described above was transferred into the flask *via* cannula and stirred for 15 min. Then (*S*)-epoxide **20** (6.25 g, 40.5 mmol, 1.0 equiv.) in Et_2O was added, and the reaction mixture was stirred for 24 h at −30 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl at −30 °C and was warmed to room temperature and diluted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (5% ether in hexane) provided allylsilane **22** as a light yellow oil; yield: 8.39 g (31.2 mmol, 77%).

Terminal Alkyne 23

Trimethylsilylalkyne **22** (1.45 g, 5.39 mmol, 1.0 equiv.) was dissolved in 26 mL of MeOH at room temperature. K_2CO_3 (744.2 mg, 5.39 mmol, 1.0 equiv.) was added and reaction mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with pH 7 buffer and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (5% Et_2O in pentane) provided allylsilane **23** as a light yellow oil; yield: 8.39 g (31.2 mmol, 77%).

Terminal Olefin 10

Alkyne **23** (418.1 mg, 2.13 mmol, 1.0 equiv.) was dissolved in 10 mL THF at 0 °C. $Cp_2Zr(H)Cl$ (1.15 g, 4.47 mmol, 2.1 equiv.) was added and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched with H_2O and warmed to room temperature. The reaction mixture was diluted with Et_2O and washed with saturated aqueous NaCl. The organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (5% ether in pentane) provided terminal olefin **10** as a light yellow oil; yield: 300 mg (1.51 mmol, 71%).

2,6-Disubstituted Pyran 24

$Bi(OTf)_3$ (3.10 g, 4.60 mmol, 1.5 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (377.9 mg, 1.84 mmol, 0.6 equiv.), and 4 Å molecular sieves (614.0 mg) were azeotroped under vacuum with toluene. 30.7 mL of Et_2O were added and reaction mixture was cooled to −78 °C. Aldehyde **11** (1.69 g, 3.07 mmol, 1.0 equiv.) and allylsilane **10** (852.0 mg, 4.296 mmol, 1.4 equiv.) were added as a solution in ether and the mixture was stirred at −78 °C for 24 h. The reaction was quenched with *N,N,N′*-trimethylethylenediamine (1.8 mL, 13.8 mmol, 4.5 equiv.) and brought to room temperature. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (0–10% EtOAc in hexane) provided pyran **24** as an oil; yield: 1.56 g (2.37 mmol, 77%).

α,β-Unsaturated Aldehyde 9

Pyran **24** (364.8 mg, 0.55 mmol, 1.0 equiv.) and freshly distilled acrolein (110.8 μL, 1.66 mmol, 3.0 equiv.) were dissolved in 5.5 mL of CH_2Cl_2. Hoveyda-Grubbs 2nd generation catalyst (35.2 mg, 5.53×10^{-2} mmol, 0.1 equiv.) wase added and reaction mixture was refluxed for 12 h. The mixture was cooled to room temperature and concentrated under vacuum. Purification on silica gel (0–10% EtOAc in hexane) provided α,β-unsaturated aldehyde **9** as a light yellow oil; yield: 251 mg (0.367 mmol, 66%).

Allyllic Acetate 26

2,6-Di-*tert*-butyl-4-methylpyridine (2.9 mg, 0.014 mmol, 0.1 equiv.) and 4 Å molecular sieves (28.0 mg) were azeotroped under vacuum with toluene. 1.4 mL of Et_2O were added and the reaction mixture was cooled to −78 °C. Aldehyde **9** (95.7 mg, 0.14 mmol, 1.0 equiv.) and 2-((trimethylsilyl)methyl)-2-propen-1-yl acetate **25** (34.6 μL, 0.167 mmol, 1.2 equiv.) were added as a solution in ether followed by BnOTMS (35.6 μL, 0.18 mmol, 1.2 equiv,) and TMSOTf (5.0 μL, 2.80×10^{-2} mmol, 0.2 equiv.) and the mixture was stirred at −78 °C for 24 h. Purification on silica gel (0–10% EtOAc in hexane) provided allylic acetate **26** as a light yellow oil; yield: 98.3 mg (0.110 mmol, 79%).

Secondary Alcohol 27

To a solution of acetonide **26** (77.3 mg, 8.66×10^{-2} mmol, 1.0 equiv.) in 870 μL CH_2Cl_2 at 0 °C was added 870 μL formic acid and the reaction stirred for 3 h at 0 °C. Reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. Organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (10–20% EtOAc in hexane) provided secondary alcohol **27** as a light yellow oil; yield: 48.0 mg (5.63×10^{-2} mmol, 66%).

Stannyl Ester 6

Alcohol **27** (47.2 mg, 5.54×10^{-2} mmol, 1.0 equiv.), β-stannylacrylic acid **7** (44.0 mg, 0.122 mmol, 2.2 equiv.), DMAP (0.5 mg, 3.9×10^{-3} mmol, 0.07 equiv.), and DMAP·HCl (1.1 mg, 7.2×10^{-3} mmol, 0.13 equiv.) in 1.1 mL CH_2Cl_2 were cooled to 0 °C. DIC (8.7 μL, 0.122 mmol, 2.2 equiv.) was added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (5–20% EtOAc in hexane) provided secondary alcohol **6** as a light yellow oil; yield: 52.3 mg (4.38×10^{-2} mmol, 79%).

1,4-Diene Macrolactone 5

To a flame-dried Schlenk tube was added $Pd(PPh_3)_4$ (7.9 mg, 6.86×10^{-3} mmol, 0.2 equiv.), tetrabutylammonium iodide (38.0 mg, 0.103 mmol, 3.0 equiv.), DIEA (11.9 μL, 6.86×10^{-2} mmol, 2.0 equiv.), cyclization precursor **6** (41.0 mg, 3.43×10^{-2} mmol, 1.0 equiv.), and 6.9 mL of degassed toluene (three cycles of freeze-pump-thaw). The Schlenk tube was purged with argon, sealed with a glass stopper, covered with aluminum foil, and the reaction mixture was refluxed for 48 h. It was then cooled to room temperature, diluted with EtOAc, washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (0–10% EtOAc in hexane) afforded 1,4-diene macrolactone **5** as a oil; yield: 14.4 mg (1.72×10^{-2} mmol, 50%).

1,3-Diene Lactone 4

1,4-Diene lactone **5** (12.9 mg, 1.52×10^{-2} mmol, 1.0 equiv.) was dissolved in 304 μL of THF and DBU (2.3 μL, 1.52×10^{-2} mmol, 1.0 equiv.) was added. The reaction mixture was heated to 45 °C for 12 h. It was then cooled to room temperature and diluted with EtOAc. The organic layers were washed with H_2O, saturated aqueous NaCl, dried over NaCl, dried again over Na_2SO_4, filtered, and concentrated under vacuum. Purification on silica gel (5–10% EtOAc in hexane) provided 1,3-diene **4** as a 1:1 mixture of *E,Z:E,E*-isomers; yield: 12.5 mg (1.48×10^{-2} mmol, 97%).

Supporting Information

Spectral data and HPLC traces are given in the Supporting Information.

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