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Stereoselective synthesis of a fully protected C_{13}–C_{23} fragment of tedanolide

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ABSTRACT

The combination of a high-yielding dienyllithium addition and a highly diastereoselective 1,2-reduction allows the preparation of the completely protected C_{13}–C_{23} fragment **3** of the potent cytotoxic agent tedanolide **1**. A convergent approach was used, namely a late stage coupling of the dienyllithium **16** with the selectively protected aldehyde **5** followed by oxidation–reduction and final epoxidation to give **3**. The dienylstannane **4** was prepared from the dibromide **6** in five steps, the key step being the highly regio- and stereoselective stannylcupration of the alkyne **7**. The commercially available hydroxy ester **10** was converted in 11 steps to the aldehyde **5**. The compound **3** could potentially be a key intermediate for the synthesis of tedanolide **1**.

1. Introduction

Schmitz and co-workers isolated the macrolide tedanolide **1** in 1984 from the Caribbean sponge *Tedania ignis*.[1] This lactone epoxide exhibits very potent cytotoxicity, with ED_{50}s of 250 pg/mL against human nasopharynx carcinoma and 16 pg/mL against in vitro lymphocytic leukemia. Because of its excellent antitumor activity and its intriguing structural features (18-membered macrocyclic lactone with a polypropionate skeleton, an internal trisubstituted *E* olefin, and 13 stereocenters), tedanolide has generated considerable synthetic interest. Three total syntheses[2] have resulted as well as a significant amount of synthetic work.[3]

2. Background

In our attempts to synthesize this molecule, our group has employed over the last few years the non-aldol aldol process, a reaction that we developed for the preparation of aldol natural products.[4,5] Recently we reported two approaches for the preparation of the C_1–C_{12} fragment of tedanolide **2** using an alkenyllithium addition followed by a reductive hydroboration methodology[6a] and the combination of aldol and non-aldol aldol methodology,[6b] respectively. We report herein the efficient preparation of the fully protected C_{13}–C_{23} fragment of tedanolide **3** by a convergent synthetic method that involves a dienyllithium addition and a highly diastereoselective reduction of an enone as the key steps. Our proposed retrosynthesis for tedanolide **1** using these fragments is shown in Fig. 1. We designed the synthetic route for fragment **3** from the dienylstannane **4** via nucleophilic addition of the derived dienyllithium to the selectively protected aldehyde **5**. Although this addition would be expected to give the undesired stereochemistry at C_{17} due to Cram–Felkin–Anh control,[7] the stereochemistry at C_{17} could be easily changed via a simple oxidation–reduction protocol using a bulky hydride agent, again via Cram–Felkin–Anh control.

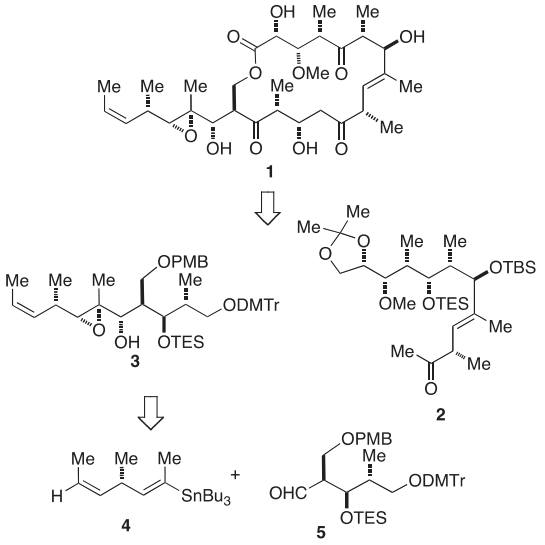

Fig. 1. Retrosynthesis of tedanolide **1**.

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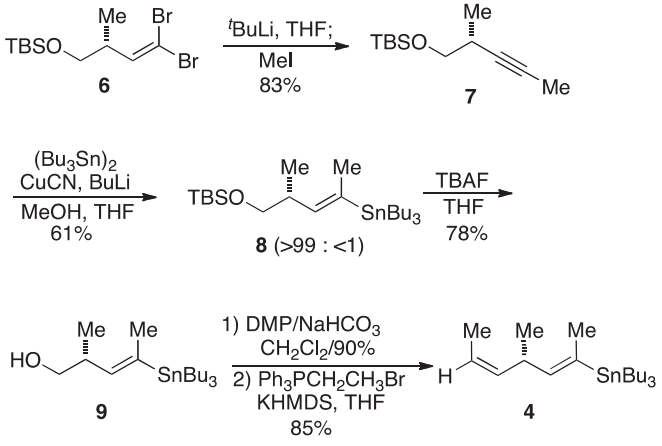
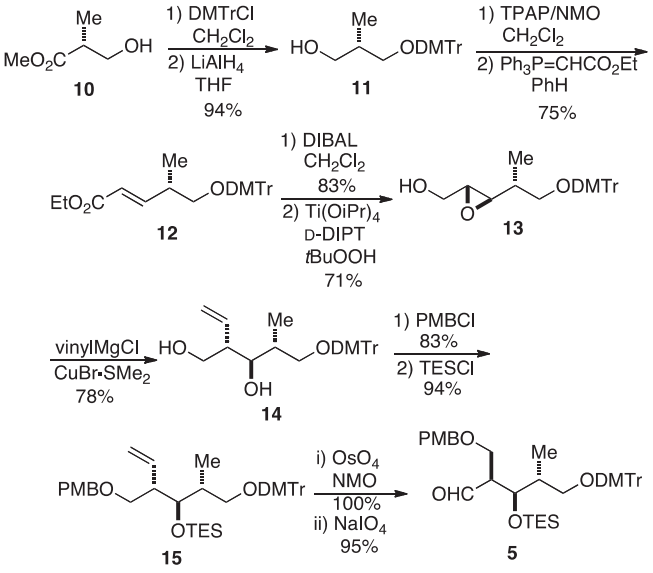
3. Results and discussion

In order to prepare the fully protected C_{13}–C_{23} fragment of tedanolide **3**, efficient syntheses of both the dienylstannane **4** and the protected aldehyde **5** were required. The synthesis of the dienylstannane with high *E*-selectivity was difficult to achieve. Finally we developed a method that utilized a regio- and stereoselective hydrostannylation of a substituted alkyne to prepare the desired vinylstannane, which could then be converted into the dienylstannane without any loss of the tin component. Thus the alkyne **7** was prepared from the dibromoolefin **6**, prepared by a Corey–Fuchs reaction on the known aldehyde, in 83% yield via lithium–halogen exchange followed by trapping with iodomethane (Scheme 1). Initially we explored the palladium-catalyzed hydrostannylation using Yamamoto's procedure.[8] However the desired vinylstannane **8** was obtained in only 13% yield along with a small amount of the undesired regioisomer (6:1 ratio). When a larger amount of the palladium catalyst and tributyltin hydride was used, the yield of the vinylstannane increased while the regioselectivity unfortunately decreased. However, when stannylcupration[9] of the alkyne **7** was carried out, the desired vinylstannane **8** was isolated in good yield and with superb regioselectivity (>99:1). Desilylation of **8** with TBAF gave the primary alcohol **9**. Oxidation of this alcohol using Dess–Martin periodinane (DMP)[10] afforded in 90% yield the somewhat unstable aldehyde, which was immediately subjected to the Wittig olefination with ethyltriphenylphosphonium bromide using potassium hexamethyldisilazide (KHMDS) in THF to afford the desired dienylstannane **4** in 85% yield. All of the vinylstannanes—**4**, **8**, and **9**—are unstable on normal silica gel chromatography. Therefore, either adding triethylamine in the eluent or chromatography on neutral alumina is preferred for purification of these compounds.



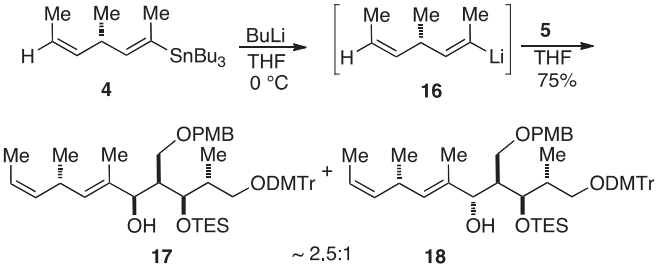
Scheme 1.

The coupling partner for the dienylstannane, the aldehyde **5**, was prepared from the commercially available methyl (*R*)-3-hydroxy-2-methylbutanoate **10** by a short sequence (Scheme 2). Protection of the alcohol as the 4,4′-dimethoxytrityl (DMTr) ether followed by reduction of the ester gave the known[4d] alcohol **11** in 94% yield. Oxidation with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO)[11] afforded the aldehyde, which was immediately subjected to the Wittig reaction with (ethoxycarbonylmethylidene)triphenylphosphorane to give the desired *E*-enoate **12** in 75% yield for the two steps. Reduction of the ester **12** with DIBAL furnished, in 83% yield, the allylic alcohol, which upon Sharpless asymmetric epoxidation[12] afforded the β-epoxy alcohol **13** in 71% yield and >90% ee. The epoxide was opened regio- and stereoselectively by treatment of vinylmagnesium chloride and copper(I) bromide–dimethyl sulfide complex[13] to give the diol **14**. Selective protection of the primary alcohol of this diol as the *p*-methoxybenzyl (PMB) ether proceeded in 83% yield. Final protection of the secondary alcohol as the triethylsilyl (TES) ether afforded the selectively protected alkene **15** in 94% yield. Finally dihydroxylation with catalytic osmium tetroxide/NMO gave in quantitative yield the expected diol mixture, which underwent oxidative cleavage using sodium periodate to afford the desired aldehyde **5**.



Scheme 2.

With both the dienylstannane **4** and the aldehyde **5** in hand, we next explored the coupling reaction (Scheme 3). Lithium–tin exchange of **4** was achieved with *n*-butyllithium at 0 °C within 10 min to give the dienyllithium **16**. Carrying out this exchange reaction at −78 °C resulted in no significant exchange of tin for lithium. Addition of the dienyllithium **16** to the aldehyde **5** afforded an approximately 2.5:1 mixture of the two diastereomeric allylic alcohols **17** (β-OH) and **18** (α-OH) in 75% yield. To confirm the stereochemistry at the newly generated chiral center, the major diastereomer **17** was transformed to the corresponding acetonide **19** by removal of the silyl ether with TBAF and acetonide formation (Fig. 2). The stereochemistry was confirmed via coupling constant (small *J* values) and NOE analysis.



Scheme 3.

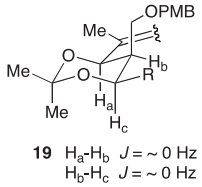
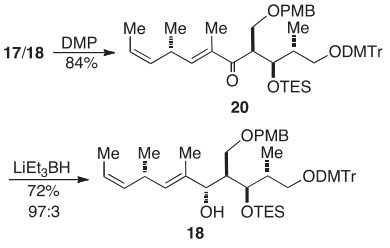


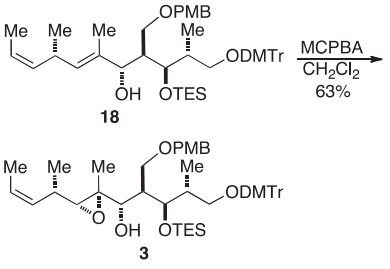
Fig. 2. NMR data of **19** for structure determination of **17**.

The mixture of undesired and desired isomers **17** and **18**, which were difficult to cleanly separate, could be readily converted into only the desired isomer **18** via an oxidation–reduction protocol (Scheme 4). Dess–Martin oxidation[9] of the allylic alcohol afforded the ketone **20** in 84% yield. Several reducing reagents were screened to effect diastereoselective reduction of the enone. Small reducing agents gave a mixture of diastereomers in which **17** predominated, e.g., DIBAL, afforded a 2:1 mixture favoring **17**. However, Super Hydride reduction afforded the desired diastereomer **18** in 72% yield with an excellent diastereomeric ratio (97:3). In an attempt to increase the selectivity, we used the more sterically bulky hydride L-Selectride, but it gave only the product of 1,4-reduction.



Scheme 4.

In order to guarantee the success of the epoxidation of the allylic alcohol moiety in a late intermediate for the synthesis of tedanolide **1**, we tried the reaction on **18** (Scheme 5). Oxidation of **18** with MCPBA in dichloromethane afforded the bottom fragment of tedanolide **3** in 63% yield and with high regio- and stereoselectivity.



Scheme 5.

In summary, we have achieved an efficient, straightforward synthesis of the fully protected C_{13}–C_{23} fragment of tedanolide **3**, which features the addition of the dienyllithium reagent **16**, prepared by lithium–tin exchange of the dienylstannane **4**, to the selectively protected aldehyde **5**. The mixture of the undesired and desired diastereomers **17** and **18** could be transformed nearly exclusively to the desired diastereomer **18** in two steps through an oxidation–reduction protocol. Finally the allylic alcohol of **18** could be readily converted into the desired epoxy alcohol regio- and stereoselectively to give the desired C_{13}–C_{23} fragment of tedanolide **3**. Further progress toward the total synthesis of tedanolide will be reported in due course.

4. Experimental section

4.1. Ethyl (*S*,*E*)-5-(4,4′-dimethoxytrityl)-4-methyl-2-pentenoate 12

Methyl (*R*)(−)-3-hydroxy-2-methylpropionate **10** (0.75 g, 6.35 mmol) was dissolved in dichloromethane (35 mL). Collidine (2.54 mL, 19.2 mmol) was then added to the solution, which was stirred for 2 min at 21 °C. The reaction mixture was then cooled to 0 °C, treated with 4,4′-dimethoxytrityl chloride (2.79 g, 8.25 mmol), and the reaction was allowed to warm to 21 °C with stirring overnight. The reaction was quenched with satd NH_4Cl solution (30 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (50 mL). The organic phase was combined, washed with brine (40 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure yielded crude orange oil, which was used without further purification. A solution of the crude dimethoxytrityl methyl ester in THF (80 mL) was cooled to 0 °C and treated with LAH (0.49 g, 12.7 mmol). The suspension was then allowed to warm to 21 °C and stirred for 1 h. After being cooled to 0 °C, the reaction was quenched by the successive addition of water (0.65 mL), 15% NaOH solution (0.65 mL), and water (1.95 mL) with vigorous stirring. The insoluble materials were filtered off through Celite and the solute was washed with diethyl ether (3×40 mL). The solvents were concentrated under reduced pressure and the residue was purified by flash silica column chromatography (20% ethyl acetate in hexane) to yield 2.34 g (94%) of the alcohol **11** as a viscous yellowish oil. To a stirred solution of the alcohol **11** (2.34 g, 5.96 mmol) and 4 Å molecular sieves in dichloromethane (60 mL) was added NMO (1.05 g, 8.94 mmol) followed by TPAP (0.21 g, 0.60 mmol) at 21 °C. After 1 h, the reaction mixture was passed through Celite, and the filtrate was concentrated. Purification by short column chromatography on silica gel (13% ethyl acetate in hexane) yielded the desired aldehyde. The aldehyde was then dissolved in benzene (80 mL), treated with (ethoxycarbonylmethylidene)triphenylphosphorane (3.12 g, 8.94 mmol) and stirred overnight. After evaporation of the benzene, the residue was purified by flash silica column chromatography (13% ethyl acetate in hexane) to yield 2.06 g (75%) of the conjugated ester **12** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.43 (2H, m), 7.26–7.35 (6H, m), 7.15–7.22 (1H, m), 6.94 (1H, dd, J=15.8, 7.3 Hz), 6.80–6.85 (4H, m), 5.82 (1H, dd, J=15.8, 1.3 Hz), 4.19 (2H, q, J=7.1 Hz), 3.79 (6H, s), 3.07 (1H, dd, J=8.8, 6.7 Hz), 3.01 (1H, dd, J=8.8, 6.4 Hz), 2.60 (1H, b septet, $J\sim$7 Hz), 1.29 (3H, t, J=7.1 Hz), 1.08 (3H, d, J=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 158.4, 151.7, 145.1, 136.27, 136.26, 130.1, 128.2, 127.8, 126.7, 120.9, 113.1, 85.9, 67.1, 60.2, 55.2, 37.3, 16.3, 14.3. IR (neat) ν_{max} 1717 cm^{-1}. HRMS calcd for $C_{29}H_{32}O_5$: 460.2250. Found: 460.2251.

4.2. (*S*,*E*)-5-((4,4′-Dimethoxytrityl)methoxy)-4-methylpent-2-en-1-ol 12a

A solution of **12** (1.55 g, 3.37 mmol) in dichloromethane (30 mL) was treated with a 1 M solution of DIBAL in hexane (8.43 mL, 8.43 mmol) at 21 °C. This reaction was quenched after 30 min by addition of a satd Rochelle's salt solution (70 mL), followed by dilution with diethyl ether (70 mL), and addition of water (30 mL). The reaction was stirred at 21 °C until both phases were clearly separated and the organic layer was clear. After extraction, the separated organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting mixture was purified by flash silica column chromatography (20% ethyl acetate in hexane) to give 1.17 g (83%) of compound **12a** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.47 (2H, m), 7.24–7.35 (6H, m), 7.16–7.21 (1H, m), 6.80–6.83 (4H, m), 5.64–5.66 (2H, m), 4.09 (2H, m), 3.79 (6H, s), 3.01 (1H, dd, J=8.7, 6.4 Hz), 2.92 (1H, dd, J=8.7, 6.8 Hz), 2.48 (1H, b septet, $J\sim$7 Hz), 1.05 (3H, d, J=6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.3, 145.3, 136.5, 136.0, 130.1, 130.0, 129.1, 128.5, 128.3, 127.7, 126.6, 113.0, 85.6, 67.8, 63.9, 55.2, 37.0, 17.1. IR (neat) ν_{max} 3373 cm^{-1}. HRMS calcd for $C_{27}H_{30}O_4$: 418.2144. Found: 418.2142.

4.3. ((2*R*,3*R*)-3-((*R*)-1-((4,4′-Dimethoxytrityl)methoxy) propan-2-yl)oxiran-2-yl)methanol 13

D(−)-Diisopropyl tartrate (99 mg, 0.21 mmol) and 4 Å powdered molecular sieves (84 mg) were suspended in dichloromethane

(2 mL). The suspension was cooled to −20 °C and treated with titanium (IV) isopropoxide (0.12 mL, 0.42 mmol) followed by stirring for 20 min at −20 °C. A 5.8 M solution of *tert*-butyl hydroperoxide in decane (0.41 mL, 2.36 mmol) was then added and the reaction mixture was stirred for a further 20 min at −20 °C. A solution of **12a** (0.47 g, 1.12 mmol) in dichloromethane (3 mL) was then introduced and the reaction temperature kept at −23 °C for 24 h. The reaction was then diluted with diethyl ether (10 mL) and filtered through a mixture of Celite and silica gel. The solvent was then removed under reduced pressure and the resulting mixture was purified by flash silica column chromatography (13% ethyl acetate in hexane) to give 0.35 g (71%) of compound **13** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.45 (2H, m), 7.27–7.35 (6H, m), 7.16–7.22 (1H, m), 6.81–6.84 (4H, m), 3.91 (1H, ddd, J=12.4, 5.6, 2.4 Hz), 3.79 (6H, s), 3.62 (1H, ddd, J=12.4, 7.3, 4.2 Hz), 3.11 (2H, m), 2.98 (2H, m), 1.79 (1H, b septet, $J\sim$7 Hz), 0.99 (3H, d, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4, 145.2, 136.4, 130.1, 128.2, 127.8, 126.7, 113.1, 85.8, 65.4, 62.0, 58.1, 56.9, 55.2, 36.1, 13.3. IR (neat) ν_{max} 3440 cm^{-1}. HRMS calcd for $C_{27}H_{30}O_5$: 434.2093. Found: 434.2097.

4.4. (2*S*,3*R*,4*R*)-5-((4,4′-Dimethoxytrityl)methoxy)-4-methyl-2-ethenylpentane-1,3-diol 14

To a suspension of copper(I) bromide–dimethyl sulfide complex (50 mg, 0.24 mmol) in Et_2O (40 mL) was added a 1.6 M solution of vinylmagnesium chloride in THF (1.51 mL, 2.42 mmol) and then added a solution of epoxy alcohol **13** (0.35 g, 0.81 mmol) in Et_2O (3 mL) at −30 °C. After stirring for 12 h at 0 °C, the reaction was quenched with satd NH_4Cl solution (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash silica column chromatography of the residue (33% ethyl acetate in hexane) yielded 0.29 g (78%) of the desired diol **14**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.45 (2H, m), 7.29–7.34 (6H, m), 7.21–7.25 (1H, m), 6.80–6.86 (4H, m), 5.57 (1H, ddd, J=17.2, 10.3, 9.1 Hz), 5.00 (1H, dd, J=10.3, 1.8 Hz), 4.82 (1H, dd, J=17.2, 1.8 Hz), 3.91 (1H, d, J=6.4 Hz), 3.80 (6H, s), 3.73–3.78 (1H, m), 3.61–3.67 (1H, m), 3.55–3.60 (1H, m), 3.32 (1H, dd, J=9.4, 3.5 Hz), 3.24 (1H, dd, J=9.4, 4.7 Hz), 3.05 (1H, m), 2.05 (1H, m), 1.88 (1H, m), 1.16 (3H, d, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.6, 144.3, 136.6, 135.7, 135.5, 130.0, 129.9, 128.04, 128.00, 126.7, 117.5, 113.3, 87.0, 79.8, 65.9, 65.4, 55.3, 49.5, 35.6, 15.4. IR (neat) ν_{max} 3423 cm^{-1}.

4.5. (2*R*,3*R*,4*S*)-1-((4,4′-Dimethoxytrityl)methoxy)-4-((4-methoxybenzyloxy)methyl)-2-methylhex-5-en-3-ol 14a

To a suspension of 60% sodium hydride dispersion in mineral oil (63 mg, 1.57 mmol) in THF (15 mL) at 21 °C was slowly added diol **14** (0.29 g, 0.63 mmol) in THF (5 mL) via syringe. The resulting heterogeneous mixture was stirred at 21 °C for 0.5 h and freshly prepared *p*-methoxybenzyl chloride (0.11 mL, 0.81 mmol) was added. After stirring at 21 °C for 12 h, the mixture was carefully quenched by addition of 1 mL of water followed by dilution with 50 mL of diethyl ether. The resulting mixture was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. For flash silica column chromatography, starting eluent was 50% diethyl ether in petroleum ether mixtures to remove some less polar material, then solvent polarity was increased to 33% ethyl acetate in hexane to collect 0.30 g (83%) of the desired product **14a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.44 (2H, m), 7.27–7.34 (6H, m), 7.17–7.23 (3H, m), 6.80–6.88 (6H, m), 5.67 (1H, ddd, J=17.2, 10.3, 8.9 Hz), 4.98 (1H, dd, J=10.3, 1.8 Hz), 4.83 (1H, dd, J=17.2, 1.8 Hz), 4.41 (2H, s), 3.79 (3H, s), 3.78 (6H, s), 3.55–3.60 (2H, m), 3.52 (2H, m), 3.20 (1H, dd, J=9.2, 4.9 Hz), 3.19 (1H, dd, J=9.2, 5.2 Hz), 2.24 (1H, m), 1.92 (1H, m), 1.22 (3H, d, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 158.5, 144.9, 137.6, 136.2, 136.1, 130.3, 130.10, 130.07, 129.2, 128.2, 127.8, 126.8, 116.6, 113.8, 113.1, 86.4, 77.3, 72.9, 71.7, 65.3, 55.3, 55.2, 47.7, 36.2, 15.6. IR (neat) ν_{max} 3493 cm^{-1}.

4.6. (3*S*,4*R*,5*R*)-6-((4,4′-Dimethoxytrityl)methoxy)-3-((4-methoxybenzyloxy)methyl)-5-methyl-4-triethylsilyloxyhex-1-ene 15

To **14a** (0.30 g, 0.51 mmol) in dichloromethane (20 mL) cooled to −78 °C was added Hünig's base (0.26 mL, 1.54 mmol) followed by dropwise addition of TESOTf (0.17 mL, 0.77 mmol). After 1 h, the reaction was quenched with satd $NaHCO_3$ solution (50 mL) and extracted with dichloromethane (30 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (13% ethyl acetate in hexane) provided 0.34 g (94%) of **15** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.43 (2H, m), 7.27–7.32 (6H, m), 7.16–7.24 (3H, m), 6.83–6.86 (2H, m), 6.78–6.81 (4H, m), 5.66 (1H, ddd, J=18.2, 9.1, 8.9 Hz), 4.92–4.96 (2H, m), 4.40 (1H, d, J=11.7 Hz), 4.37 (1H, d, J=11.7 Hz), 3.79 (3H, s), 3.78 (6H, s), 3.19 (1H, dd, J=8.8, 5.5 Hz), 2.80 (1H, t, J=8.7 Hz), 2.41 (1H, m), 2.07 (1H, m), 0.99 (3H, d, J=7.0 Hz), 0.84 (9H, t, J=7.9 Hz), 0.46 (6H, q, J=7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 158.2, 145.5, 138.9, 136.8, 136.7, 130.8, 130.2, 130.1, 129.2, 128.3, 127.7, 126.5, 116.3, 113.7, 112.9, 85.7, 75.4, 72.6, 70.8, 64.9, 55.3, 55.2, 48.2, 38.5, 14.9, 7.1, 5.3. IR (neat) ν_{max} 1609 cm^{-1}.

4.7. (2*S*,3*R*,4*R*)-5-((4,4′-Dimethoxytrityl)methoxy)-2-((4-methoxybenzyloxy)methyl)-4-methyl-3-triethylsilyloxypentanal 5

To a solution of **15** (0.13 g, 0.19 mmol) in acetone/water (4:1, 5 mL) at 0 °C, NMO (44 mg, 0.37 mmol) and OsO_4 (7.1 mg, 0.028 mmol) were added and the solution was stirred overnight at 21 °C. The product was extracted with ethyl acetate (30 mL) and satd sodium sulfite solution (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude diol was dissolved in acetone/water (4:1, 5 mL) and $NaIO_4$ (0.12 g, 0.56 mmol) was added. The mixture was kept stirring for 1 h at 21 °C. The product was extracted with Et_2O (30 mL), and satd sodium thiosulfate solution (30 mL). The solvent was removed under reduced pressure and the crude product was purified by flash silica column chromatography (13% ethyl acetate in hexane) to obtain 0.12 g (95%) of the aldehyde **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.66 (1H, d, J=1.8 Hz), 7.40–7.41 (2H, m), 7.16–7.39 (9H, m), 6.84–6.88 (2H, m), 6.79–6.83 (4H, m), 4.41 (1H, d, J=11.7 Hz), 4.39 (1H, d, J=11.7 Hz), 4.20 (1H, dd, J=5.5, 4.6 Hz), 3.82 (1H, t, J=9.7 Hz), 3.80 (3H, s), 3.78 (6H, s), 3.68 (1H, dd, J=9.7, 4.4 Hz), 3.12 (1H, dd, J=9.0, 6.2 Hz), 2.85 (1H, dd, J=9.1, 7.3 Hz), 2.67 (1H, dddd, J=8.9, 4.4, 4.4, 1.7 Hz), 2.04 (1H, b septet, $J\sim$7 Hz), 0.94 (3H, d, J=6.9 Hz), 0.82 (9H, t, J=8.0 Hz), 0.42 (6H, q, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.1, 159.2, 158.4, 145.2, 136.40, 136.38, 130.14, 130.08, 129.3, 128.2, 127.7, 126.7, 116.3, 113.8, 113.0, 86.0, 73.0, 71.6, 65.9, 65.3, 55.28, 55.25, 55.19, 39.4, 14.1, 6.9, 5.0. IR (neat) ν_{max} 1725, 1609 cm^{-1}.

4.8. (*R*,*E*)-Tributyl(4-methyl-5-((2,3,3-trimethylbutan-2-yl)oxy)pent-2-en-2-yl)stannane 8

To a solution of hexabutylditin (2.28 g, 3.94 mmol) in THF (3 mL) was added 2.5 M solution of *n*-butyllithium in hexane (1.58 mL, 3.94 mmol) at −78 °C. The solution was stirred for 30 min at −40 °C. Then the mixture was added via cannula to a suspension of CuCN (0.18 g, 1.97 mmol) in THF (3 mL) at −78 °C. The solution was stirred at −40 °C until obtention of a yellow gold solution and recooled to −78 °C. Anhydrous MeOH (1 mL) was added, then the

yellow solution turned to a red gel. The temperature was allowed to warm to −10 °C for 30 min, until obtention of a red solution. A solution of the alkyne **7** (0.11 g, 0.52 mmol) in THF (1 mL) was added at −78 °C, and the temperature was allowed to warm to −5 °C overnight. The reaction mixture was poured into Et_2O (30 mL) and a satd NH_4Cl/concentrated ammonia (5:1) solution (60 mL). The mixture was extracted with Et_2O (30 mL), and the organic layer was washed with brine (40 mL), dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash silica column chromatography (1% triethylamine, 6% ethyl acetate in hexane) to obtain 0.16 g (61%) of **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.27 (1H, dq, J=8.7, 1.8 Hz), 3.45 (1H, dd, J=9.7, 6.0 Hz), 3.35 (1H, dd, J=9.7, 7.2 Hz), 2.78 (1H, dm), 1.85 (3H, d, J=1.8 Hz), 1.40–1.48 (6H, m), 1.31 (6H, sextet, J=7.2 Hz), 0.94 (3H, d, J=6.6 Hz), 0.83–0.90 (6H, m), 0.89 (9H, s), 0.88 (9H, t, J=7.3 Hz), 0.04 (3H, s), 0.03 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.9, 137.8, 67.9, 35.2, 29.2, 27.4, 25.9, 19.4, 18.3, 17.2, 13.7, 9.1, -5.28, -5.36. IR (neat) ν_{max} 1463 cm^{-1}.

4.9. (*R*,*E*)-2-Methyl-4-(tributylstannyl)pent-3-en-1-ol 9

To a stirred solution of the vinylstannane **8** (0.16 g, 0.32 mmol) in THF (3 mL) at 21 °C was added 1.0 M solution of TBAF in THF (0.95 mL, 0.95 mmol). The reaction mixture was stirred for 1 h and then diluted with hexanes (10 mL). The resulting mixture was filtered and the filtrate was concentrated under reduced pressure. Purification by flash silica column chromatography (1% triethylamine, 19% ethyl acetate in hexane) provided 96 mg (78%) of **9** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.24 (1H, dq, J=9.0, 1.8 Hz), 3.48 (1H, m), 3.32 (1H, dd, J=8.2, 3.4 Hz), 2.88 (1H, m), 1.89 (3H, d, J=1.8 Hz), 1.44–1.53 (6H, m), 1.31 (6H, sextet, J=7.2 Hz), 0.94 (3H, d, J=6.6 Hz), 0.86–0.90 (6H, m), 0.89 (9H, t, J=7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.9, 141.0, 67.6, 35.2, 29.2, 27.3, 19.6, 16.8, 13.7, 9.1. IR (neat) ν_{max} 3345, 1463 cm^{-1}.

4.10. Tributyl((*S*,2*E*,5*Z*)-4-methylhepta-2,5-dien-2-yl) stannane 4

To a stirred solution of alcohol **9** (96 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) at 0 °C were added $NaHCO_3$ (21 mg, 0.25 mmol) and Dess–Martin periodinane (0.16 g, 0.37 mmol). The reaction mixture was stirred for 0.5 h at 0 °C and then quenched with satd $NaHCO_3$ solution (5 mL) and 10% $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with Et_2O (20 mL), and the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash silica column chromatography (1% triethylamine, 19% ethyl acetate in hexane) provided 86 mg (90%) of the desired aldehyde as a colorless oil. To a solution of ethyltriphenylphosphonium bromide (0.41 g, 1.10 mmol) in THF (3 mL) was added 0.5 M solution of KHMDS in toluene (2.10 mL, 1.05 mmol) at 0 °C. The suspension was stirred for 30 min and then recooled to −78 °C. To the reddish slurry was added the aldehyde prepared above in THF (2 mL) at −78 °C. The reaction mixture was warmed up to 0 °C then stirred for 1 h. The reaction was quenched with satd NH_4Cl solution (3 mL) and diluted with Et_2O (30 mL). The organic layer was washed with water (30 mL) and dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (1% triethylamine, 12% ethyl acetate in hexane) to give 75 mg (85%) of the diene **4** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.23–5.29 (3H, m), 3.54 (1H, m), 1.86 (3H, d, J=1.8 Hz), 1.64 (3H, dd, J=6.4, 1.4 Hz), 1.42–1.50 (6H, m), 1.30 (6H, sextet, J=7.3 Hz), 1.00 (3H, d, J=6.8 Hz), 0.88 (9H, t, J=7.4 Hz), 0.83–0.87 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.4, 135.7, 135.3, 121.6, 30.7, 29.1, 27.3, 21.6, 19.1, 13.7, 12.9, 9.1.

4.11. (2*R*,3*R*,4*R*,5*RS*,6*E*,8*S*,9*Z*)-1-((4,4′-Dimethoxytrityl) methoxy)-4-((4-methoxybenzyl-oxy)methyl)-2,6,8-trimethyl-3-triethylsilyloxyundeca-6,9-dien-5-ol 17 and 18

To a stirred solution of a vinylstannane **4** (75 mg, 0.19 mmol) in THF (1 mL) at 0 °C was added 1.6 M solution of butyllithium in hexane (0.14 mL, 0.23 mmol). The reaction mixture was stirred for 10 min and recooled to −78 °C. A solution of aldehyde **5** (98 mg, 0.14 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 30 min at −78 °C and then quenched with satd NH_4Cl solution (3 mL). The resulting mixture was extracted with ethyl acetate (30 mL) and water (30 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash silica column chromatography (13% ethyl acetate in hexane) provided 85 mg (75%) of a mixture of **17** (major isomer) and **18** (minor isomer) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.44 (2H, m), 7.17–7.34 (9H, m), 6.79–6.90 (6H, m), 5.14–5.34 (3H, m), 4.19–4.38 (2H, m), 3.80 (3H, s), 3.78 (6H, s), 3.61 (1H, dd, J=9.3, 4.5 Hz—major dia), 3.55 (1H, dd, J=9.3, 2.5 Hz—minor dia), 3.32–3.43 (2H, m), 3.10–3.19 (2H, m), 2.87 (1H, t, J=9.0 Hz—major dia), 2.78 (1H, t, J=8.8 Hz—minor dia), 2.16–2.22 (1H, m), 1.64 (3H, dd, J=6.6, 1.6 Hz—major dia), 1.61 (3H, dd, J=6.6, 1.6 Hz—minor dia), 1.56 (3H, d, J=1.0 Hz—major dia), 1.37 (3H, d, J=1.0 Hz—minor dia), 1.09 (3H, d, J=6.8 Hz—major dia), 1.05 (3H, d, J=6.8 Hz—minor dia), 0.85 (9H, t, J=8.0 Hz), 0.48 (6H, q, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 158.3, 145.3, 136.6, 135.5, 134.0, 130.1, 129.7, 128.9, 128.3, 127.7, 126.5, 121.5, 113.8, 113.6, 113.0, 85.8, 78.5, 73.8, 73.3, 55.3, 55.2, 43.5, 37.9, 30.4, 21.5, 15.7, 13.0, 12.9, 7.1, 6.9, 5.4, 5.0. IR (neat) ν_{max} 3484, 1610 cm^{-1}.

4.12. (2*R*,3*R*,4*S*,6*E*,8*S*,9*Z*)-1-((4,4′-Dimethoxytrityl)methoxy)-4-((4-methoxybenzyloxy)-methyl)-2,6,8-trimethyl-3-triethylsilyloxyundeca-6,9-dien-5-one 20

To a stirred solution of alcohol **17** and **18** (85 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added $NaHCO_3$ (8.8 mg, 0.11 mmol) and Dess–Martin periodinane (0.13 g, 0.32 mmol). The reaction mixture was stirred for 1 h at 0 °C and then quenched with satd $NaHCO_3$ solution (5 mL) and 10% $Na_2S_2O_3$ solution (5 mL). The aqueous layer was extracted with Et_2O (20 mL), and the organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash silica column chromatography (20% ethyl acetate in hexane) provided 71 mg (84%) of **20** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.45 (2H, m), 7.14–7.29 (9H, m), 6.78–6.85 (6H, m), 6.38 (1H, d, J=9.2 Hz), 5.39 (1H, dqd, J=10.6, 6.8, 1.0 Hz), 5.10 (1H, ddq, J=10.6, 9.8, 1.0 Hz), 4.36 (1H, d, J=11.6 Hz), 4.31 (1H, d, J=11.6 Hz), 3.92 (1H, dd, J=6.6, 4.0 Hz), 3.78 (3H, s), 3.77 (6H, s), 3.69 (2H, m), 3.46 (1H, m), 3.16 (1H, dd, J=9.0, 5.2 Hz), 2.65 (1H, t, J=8.8 Hz), 1.89 (1H, m), 1.68 (3H, d, J=1.0 Hz), 1.59 (3H, dd, J=6.8, 1.7 Hz), 0.98 (3H, d, J=7.0 Hz), 0.96 (3H, d, J=6.8 Hz), 0.84 (9H, t, J=8.0 Hz), 0.44 (6H, q, J=8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.3, 158.3, 146.8, 145.3, 136.7, 136.5, 135.5, 133.0, 130.7, 130.2, 130.1, 129.1, 128.9, 128.3, 127.6, 126.5, 123.8, 113.5, 113.0, 85.9, 75.1, 72.8, 70.4, 65.4, 55.3, 55.2, 49.1, 40.1, 31.9, 20.4, 14.8, 13.1, 11.6, 6.9, 5.1. IR (neat) ν_{max} 1659, 1609 cm^{-1}.

4.13. (2*R*,3*R*,4*R*,5*S*,6*E*,8*S*,9*Z*)-1-((4,4′-Dimethoxytrityl) methoxy)-4-((4-methoxybenzyl-oxy)methyl)-2,6,8-trimethyl-3-triethylsilyloxyundeca-6,9-dien-5-ol 18

A solution of enone **20** (23 mg, 0.028 mmol) in THF (3 mL) was cooled to −78 °C, and 1.0 M solution of $LiEt_3BH$ in THF (0.085 mL, 0.085 mmol) was added via syringe. The solution was warmed to 0 °C and the reaction mixture was cautiously quenched with satd NH_4Cl solution (1 mL). The solution was

diluted with CH_2Cl_2 (20 mL) and extracted with water (10 mL), and the organic phase was washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Flash silica column chromatography (33% of ethyl acetate in hexane) gave 17 mg (72%) of **18** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (2H, br d, $J\sim$8 Hz), 7.31 (4H, br d, J=8.9 Hz), 7.17–7.28 (5H, m), 6.85 (2H, br d, $J\sim$8 Hz), 6.80 (4H, br d, J=8.9 Hz), 5.30 (1H, br dq, J=11.7, 6.7 Hz), 5.17–5.23 (2H, m), 4.31 (1H, d, J=11.5 Hz), 4.24 (1H, d, J=11.5 Hz), 4.04 (1H, dd, J=5.6, 2.4 Hz), 3.98 (1H, dd, J=5.6, 2.4 Hz), 3.79 (3H, s), 3.78 (6H, s), 3.32–3.40 (3H, m), 3.26 (1H, m), 3.13 (1H, dd, J=9.9, 5.7 Hz), 2.77 (1H, t, J=8.8 Hz), 2.19 (1H, m), 2.02 (1H, m), 1.60 (3H, dd, J=6.6, 1.5 Hz), 1.56 (3H, s), 1.04 (3H, d, J=6.8 Hz), 0.99 (3H, d, J=6.7 Hz), 0.85 (9H, t, J=7.9 Hz), 0.48 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0, 158.3, 145.4, 136.7, 135.3, 133.9, 130.7, 103.1, 129.1, 128.9, 128.3, 127.7, 126.6, 121.6, 113.6, 112.9, 85.9, 77.8, 74.5, 72.6, 68.6, 55.3, 55.2, 38.1, 30.4, 25.3, 21.4, 15.1, 13.0, 11.4, 6.9, 5.0. IR (neat) ν_{max} 3476, 1609 cm^{-1}.

4.14. (1*S*,2*R*,3*R*,4*R*)-5-((4,4′-Dimethoxytrityl)methoxy)-2-((4-methoxybenzyloxy)methyl)-4-methyl-1-((2*R*,3*R*)-2-methyl-3-((*S*,*Z*)-pent-3-en-2-yl)oxiran-2-yl)-3-triethylsilyloxy-pentan-1-ol 3

To a solution of allyl alcohol **18** (17 mg, 0.021 mmol) in CH_2Cl_2 (3 mL) was added 70% MCPBA (5.7 mg, 0.023 mmol) at −20 °C. After stirring for 10 h, satd $NaHCO_3$ solution (5 mL) and satd $Na_2S_2O_3$ solution (5 mL) were added. The mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash silica column chromatography (20% ethyl acetate in hexane) to give 11 mg (63%) of epoxy alcohol **3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (2H, br d, $J\sim$8 Hz), 7.16–7.36 (9H, m), 6.86 (2H, br d, $J\sim$8 Hz), 6.79 (4H, br d, J=8.9 Hz), 5.43 (1H, br dq, J=11.0, 6.7 Hz), 5.22 (1H, br dd, J=11.2, 9.4 Hz), 4.39 (1H, d, J=11.6 Hz), 4.26 (1H, d, J=11.6 Hz), 4.01 (1H, dd, J=7.5, 1.6 Hz), 3.78 (9H, s), 3.43 (1H, dd, J=9.8, 7.3 Hz), 3.35 (1H, dd, J=8.6, 4.4 Hz), 3.25 (1H, dd, J=9.8, 8.2 Hz), 3.08 (1H, dd, J=10.4, 2.0 Hz), 2.87 (1H, br s), 2.74 (1H, t, J=8.8 Hz), 2.52 (1H, d, J=9.2 Hz), 2.40–2.47 (1H, m), 2.13–2.20 (1H, m), 2.00–2.09 (1H, m), 1.58 (3H, dd, J=6.8, 1.7 Hz), 1.30 (3H, s), 1.11 (3H, d, J=6.4 Hz), 1.02 (3H, d, J=6.8 Hz), 0.79 (9H, t, J=7.9 Hz), 0.38 (6H, m).

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.10.024.

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