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Stereocontrolled Synthesis of Dehydrodendrolasin: Unstable Polyene Furanosesquiterpenoids

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Abstract: Marine furanosesquiterpenoids, (2*E*,4*E*,6*E*)- and (2*Z*,4*E*,6*E*)-dehydrodendrolasin (**2**) and (**3**), were synthesized in a geometrically controlled fashion. For the synthesis of **2**, stereospecific addition of methyl(tributylstannyl)magnesium to *E*-enyne was employed effectively to afford (2*E*,4*E*)-3-(5-iodo-4-methyl-2,4-pentadienyl)furan (**15**). For the synthesis of **3**, the key geometrical control for Z-enyne intermediate (**7**) was performed by a Pd catalyzed stereospecific hydrogenolysis of 3-(3-furyl)-1,1-dibromopropene (**16**) and successive Sonogashira coupling with trimethylsilylacetylene to give (Z)-3-(5-trimethylsilyl-2-penten-4-ynyl)furan (**18**) in one pot.

Introduction

A great number of organic compounds have been obtained from marine organisms in this decade, which often possess unique structures and specific biological activities.[1] Polyenes and their condensed compounds have been isolated from marine organisms, particularly marine sponges. Polyene natural products containing a furan ring are of interest for stereocontrolled synthesis as well as novel pharmaceutical activities. Furanosesquiterpenoid, dendrolasin (**1**) having a furan ring and two olefin units, was found from various natural sources.[2] Its dehydrated compound is known as dehydrodendrolasin, and shown in Figure 1. In the past, three geometrical isomers, **2**,[3] **3**,[4] and **4**,[5] and one regio isomer **5**,[6] were obtained from marine sponges. These materials, released by the sponges, are considered to be a defensive substance against natural enemies. Among them, dehydrodendrolasin (**2**) was isolated from sponge, *Pleraplysilla spinifera* in 1972[3] and its geometrical isomer **3** was isolated from *Dysidea herbacea* along with **2** in 1982.[4] These structures consist of a consecutive triene and a furan ring connected by a methylene bridge, and are unstable against acids, heat, and also light. In fact, synthesized materials stored in a flask at room temperature decomposed within a few weeks. In this paper, the stereospecific synthesis of **2** and **3** are reported.

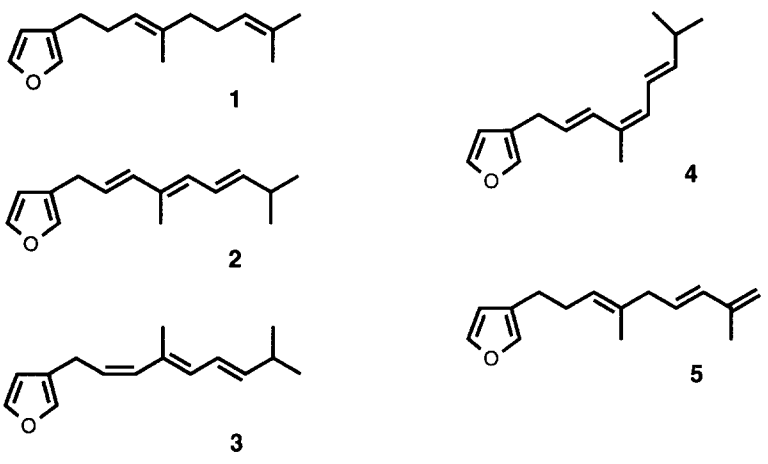


Figure 1

Results and Discussion

The retro synthetic plan for **2** and **3** is outlined below in Figure 2. The important key intermediates for the syntheses are analyzed to be *E*- and *Z*-enynes, **6** and **7**, respectively. Regio and stereo specific introduction of 1,2-*syn* halide and methyl groups to these enynes is performed by stannylmagnesiation or carbometallation to the enynes. Both enynes are derived from 3-furylacetoaldehyde (**8**).

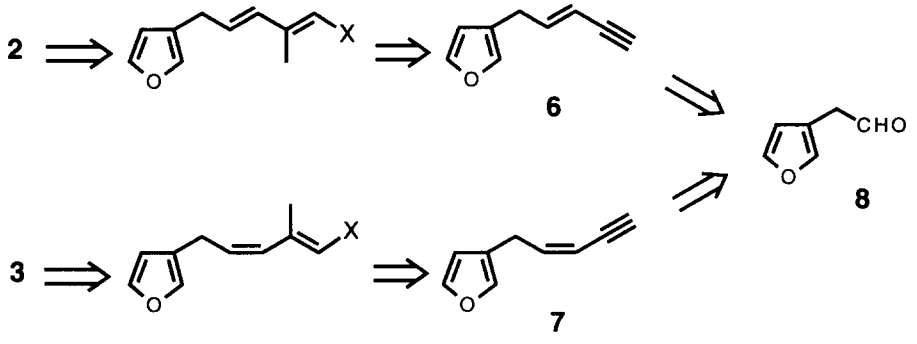
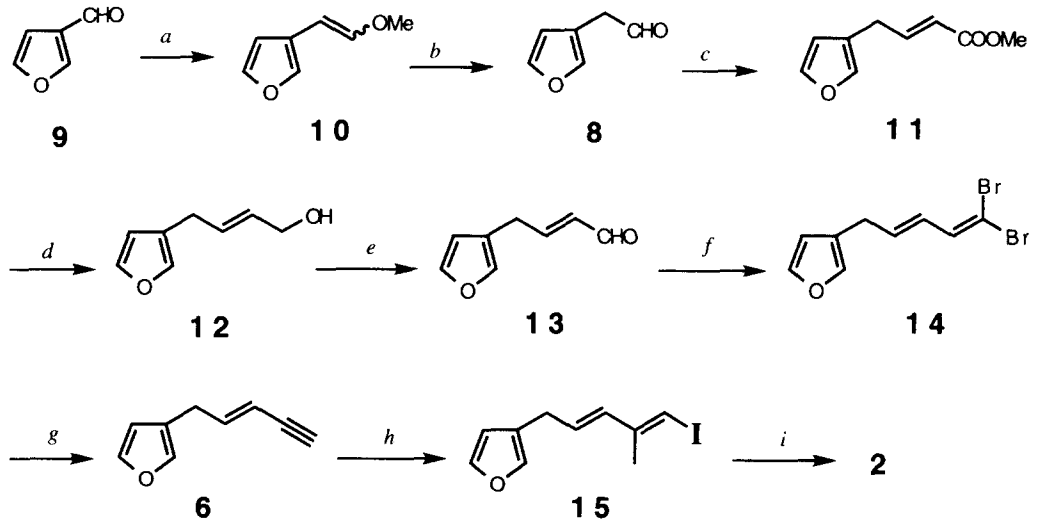


Figure 2

The Wittig reaction of commercially available 3-furfural (**9**) with methoxymethylidenephosphorane gave methoxyvinylfuran **10** in 87% yield as a 2:1 mixture of *E*- and *Z*-isomers. Acid hydrolysis of **10** with diluted

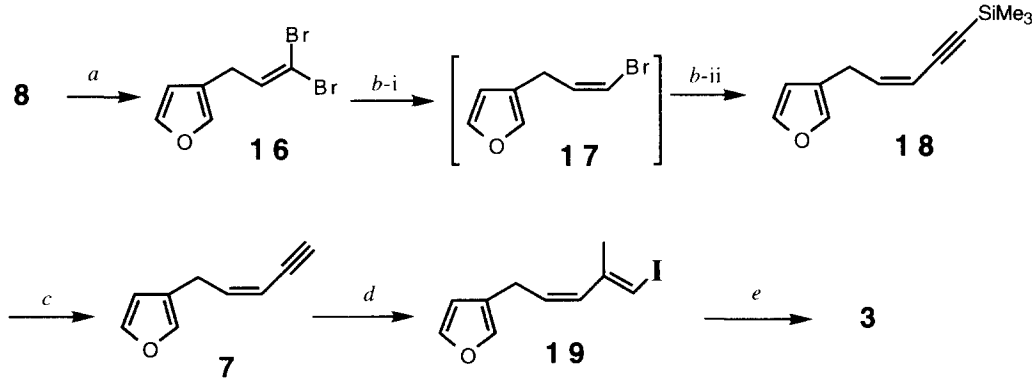
sulfuric acid afforded aldehyde, **8**[7] in 51% yield. An extension of a two carbon unit to the aldehyde with carbomethoxymethylenephosphorane provided *trans* α,β-unsaturated ester **11** in 93% yield along with *cis* isomer in 6% yield. These were separated by column chromatography on silica gel. Reduction of **11** was carried out in methylene chloride with DIBAL-H at -78°C to give **12**, and oxidation of **12** with Dess-Martin reagent[8] afforded α,β-unsaturated aldehyde **13** in 73% in two steps. Manipulation of α,β-unsaturated aldehyde to terminal enyne was performed by the standard procedures. Thus, treatment of **13** with carbon tetrabromide and triphenylphosphine gave 1,1-dibromo-1,3-diene, **14** in 91% yield, which was then treated with an excess of LDA at -78°C to afford terminal enyne, **6** in 94% yield. The stereochemistry of the *E*-enyne structure was identified by proton nmr, in which two *trans* olefinic protons were observed at 5.52 and 6.34 ppm having 15.9 Hz of the coupling constant, and a terminal alkynic proton was observed at 2.82 ppm. Previously, we have reported the stereospecific preparation of 2-substituted 1-iodo-1,3-dienes[9] by the addition of methyl(tributylstannyl)magnesium reagent[10] to terminal enyne. The same method was adopted here to prepare **15**. Thus, the introduction of *syn* methyl and iodide functions to terminal alkyne was carried out in THF by treating **6** with methyl(tributylstannyl)magnesium to give a 1-tributylstannyl-2-methylmagnesium alkene intermediate. Successively, it was quenched with iodomethane giving a 1-tributylstanyl-2-methyl-1,3-diene unit and then substitution of the tributylstannyl group with iodide furnished the desired methyl substituted iododiene, **15** in 72% yield. The stereochemistry of *E*-alkene was completely retained in this reaction. This iododiene was coupled with (*E*)-2-(3-methyl-1-butenyl)-1,3,2-benzodioxaborole under the modified Suzuki conditions.[11] Thus, the reaction carried



Reagents and Conditions; a) $MeOCH_2PPh_3Cl$, Bu^tOK, THF, -78°C; *b)* 0.1 M H_2SO_4 (aq): THF (1:2), reflux; *c)* $Ph_3P{=}CHCO_2Me$, Benzene, r.t.; *d)* DIBAL, CH_2Cl_2, -78°C; *e)* Dess-Martin periodinate, CH_2Cl_2, r.t.; *f)* CBr_4, PPh_3, CH_2Cl_2, 0°C; *g)* LDA, THF, -78-0°C; *h)* i, $MeMgSnBu_3$, cat. CuCN, THF, -20°C, ii, MeI, -20°C, iii, dry hexane extraction, iv, I_2, CH_2Cl_2, 0°C; *i)* (*E*)-2-(3-Methyl-1-butenyl)-1,3,2-benzodioxaborole, cat. $Pd(PPh_3)_4$, Ag_2CO_3, aq. KOH, THF, r.t.

out in THF at room temperature in the presence of silver carbonate and aq. potassium hydroxide for 3.5 hr. The desired product **2** was obtained in 83% yield as a single geometrical isomer. All the spectroscopic data of the synthetic **2** including proton and carbon nmr, and UV spectrum were in accordance with those in the literature.[3]

The other geometrical isomer **3** was synthesized in 6 steps from 3-furylacetoaldehyde (**8**). A *Z*-enyne unit was constructed by the one-pot procedure which we have recently developed.[12] Dibromomethylenation of **8** with carbon tetrabromide and triphenylphosphine in methylene chloride gave **16** in a quantitative yield. Discrimination of one of the two geminal bromides was made by palladium catalyzed hydrogenolysis with tributyltin hydride in which *trans* bromide was stereospecifically replaced by hydrogen. The resulting *Z*-bromoalkene was successively coupled with trimethylsilylacetylene under the Sonogashira reaction conditions.[13] As both reactions proceeded in the presence of a palladium catalyst, they were able to be carried out in one-pot. In fact, enyne **18** was yielded in 80% from **16**. Desilylation of **18** gave enyne **7** in 56% yield by treatment with tetrabutylammonium fluoride. Treatment of **7** with trimethylaluminum in the presence of a catalytic amount of Cp_2ZrCl_2 followed by quenching with iodine afforded (2*Z*,4*E*)-3-(5-iodo-4-methyl-2,4-pentadienyl)furan (**19**) in 44% yield as a single stereoisomer.[14] Stereospecific triene synthesis of **3** was performed by the same coupling procedure described for **2**. In this case, the coupling of **19** with (*E*)-2-(3-methyl-1-butenyl)-1,3,2-benzodioxaborole required 2 days at room temperature to provide **3** in 79% yield. Alkenyl protons of **3** appeared at 5.47 and 5.94 ppm indicating a double triplet and a doublet, respectively, and its *cis* geometry was clearly identified by an 11.7 Hz of the coupling constant. All other spectroscopic data also supported the structure of **3**, in particular, the UV spectrum was consistent with those reported.[4]



Reagents and Conditions; a) CBr_4, PPh_3, CH_2Cl_2, 0°C; *b)* i, cat. Pd $(PPh_3)_4$, Bu_3SnH, Benzene, r.t., ii, TMS-acetylene, cat. CuI, Pr^i_2NH, r.t.; *c)* Bu_4NF, THF, -15°C *d)* i, Me_3Al, cat. Cp_2ZrCl_2, $ClCH_2CH_2Cl$, r.t., ii, I_2, THF, 0°C; *e)* (*E*)-2-(3-Methyl-1-butenyl)-1,3,2-benzodioxaborole, cat. $Pd(PPh_3)_4$, Ag_2CO_3, aq. KOH, THF, r.t.

In conclusion, the total synthesis of two stereoisomers of (2*E*,4*E*,6*E*)- and (2*Z*,4*E*,6*E*)-dehydrodendrolasin (**2**) and (**3**) was achieved stereospecifically. Particularly, consecutive *E*,*E*,*E*- and *Z*,*E*,*E*-trienes were prepared without any isomerization. The current polyene syntheses will be valuable in other synthetic cases for complex and unstable polyene natural products.

Experimental

General. ^1H and ^{13}C NMR spectra were recorded on Bruker AMX-R400, JEOL GSX400 and Varian Gemini 300 spectrometers for ^1H (400 MHz or 300 MHz) and for ^{13}C (100 MHz or 75 MHz). The chemical shifts were shown as δ-values using tetramethylsilane (0 ppm) for proton spectra and $CDCl_3$ (77.0 ppm) for carbon spectra as an internal standard. Infrared spectra (IR) were recorded by the use of a JASCO FT/IR-230 spectrometer and were taken as liquid films. UV spectra were taken on a JASCO V-530 spectrometer. Low and high resolution mass spectra (LRMS and HRMS) were obtained on a JEOL MStation spectrometer at the Analytical Center of Okayama University of Science by the electron impact (EI) method at 70 eV unless otherwise stated. Only significant peaks are described here for IR and MS spectra. Silica gel (Merck 7734, 70-230 mesh) was used for gravity column chromatography and silica gel (Merck 9385, 230-400 mesh) for flash column chromatography. Al_2O_3 (Wako 15-08297, 200 mesh) was used for alumina column chromatography. Precoated silica gel plates (Merck 5715, 60 F_{254}) were used for thin layer chromatography. All air sensitive reactions were conducted in flame dried glass ware under an Ar atmosphere. Solvents used for reactions were dried over sodium benzophenone ketyl for THF, benzene and ether, phosphorus pentoxide for methylene chloride and 1,2-dichloroethane, and calcium hydride for hexane and these solvents were freshly distilled just before use.

3-(2-Methoxyvinyl)furan (10): To an ice cooled suspension of (methoxymethyl)triphenylphosphonium chloride (4.64 g, 13.53 mmol) in THF (10 mL) was added THF (30 mL) solution of potassium *tert*-butoxide (1.52 g, 13.53 mmol) dropwise during 15 min. The mixture was stirred for 1 hr at room temperature to form a deep red solution. This ylide solution was cooled to -78°C and then 3-furfural (1.0 g, 10.4 mmol) in THF was added. Then the bath was removed and the mixture was further stirred for 20 min at room temperature. Pentane (50 mL) was added and the whole mixture was roughly purified by silica gel column chromatography eluted with 10% ether in pentane. The elutions were collected and condensed. The residual oil was distilled to give 3-(2-methoxyvinyl)furan (1.12 g) in 87% yield. A 2:1 mixture of *E* and *Z* isomers. Yellow liquid, bp 34-35°C/2 mmHg. *Rf* = 0.35 (5% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) for *E*-isomer δ 3.64 (3H, s), 5.64 (1H, d, *J* = 13.0 Hz), 6.8 (1H, m), 6.84 (1H, d, *J* = 13.0 Hz), 7.31 (1H, m), 7.32-7.35 (1H, m), and for *Z*-isomer δ 3.76 (3H, s), 5.14 (1H, d, *J* = 6.4 Hz), 6.07 (1H, d, *J* = 6.4 Hz), 6.54 (1H, m), 7.32-7.35 (1H, m), 7.60 (1H, m); LRMS *m/z* (rel. intensity) 124 (M^+, base), 109 (5), 95 (8), 81 (16). HRMS *m/z* calcd for $C_7H_8O_2$ (M^+) 124.0524. Found 124.0511.

3-Furylacetoaldehyde (8): A mixture of 3-(2-methoxyvinyl)furan (1.07 g, 8.62 mmol) in THF (43 mL) and dil. sulfuric acid (0.1 M, 21 mL) was heated under refluxing for 9 h. After cooling, the reaction mixture was extracted with ether (30 mL) and the extract was washed with saturated sodium bicarbonate solution (20 mL), water (1 mL), and brine (1 mL). The aqueous layer was re-extracted with ether (10 mL X2). The extracts were combined and dried over $MgSO_4$, and condensed under vacuo. The residual oil was distilled to give 3-furylacetoaldehyde (486 mg) in 51% yield. Pale yellow liquid, bp 31-32°C/2 mmHg. *Rf* = 0.23 (10% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (2H, m), 6.33 (1H, m), 7.41 (1H, m), 7.44 (1H, t, *J* = 1.7 Hz), 9.73 (1H, t, *J* = 2.0 Hz); MS *m/z* (rel. intensity) 110 (M^+, 91), 81 (base). HRMS *m/z* calcd for $C_6H_6O_2$ (M^+) 110.0368. Found 110.0356.

Methyl (*E*)-4-(3-furyl)-2-butenoate (11): A mixture of aldehyde **8** (513 mg, 4.66 mmol) and (carbomethoxymethylene)triphenylphosphorane (2.23 g, 6.67 mmol) in benzene (20 mL) was stirred for 10 min at room temperature. The mixture was diluted with pentane (100 mL) and the whole mixture was directly purified by column chromatography on silica gel eluted with 2.5% ether in pentane to give *cis* product (43 mg) in 6% yield and eluted with 5% ether in pentane to afford *trans* isomer (720 mg) in 93% yield. Pale yellow oil. *Rf* = 0.37 (10% EtOAc in hexane); IR (neat) 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.34 (2H, br d, *J* = 6.6 Hz), 3.73 (3H, s), 5.86 (1H, dt, *J* = 15.8 and 1.8 Hz), 6.27 (1H, d, *J* = 1.1 Hz), 7.06 (1H, dt, *J* = 15.8 and 6.6 Hz), 7.26 (1H, m), 7.38 (1H, t, *J* = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 51.4, 111.0, 120.8, 121.9, 139.6, 143.2, 146.6, 166.8; MS *m/z* (rel. intensity) 166 (M^+, base), 151 (15), 135 (64), 134 (51), 107 (88), 106 (46), 79 (57), 77 (52). HRMS *m/z* calcd for $C_9H_{10}O_3$ (M^+) 166.0630. Found 166.0642.

(*E*)-4-(3-Furyl)-2-buten-1-ol (12): To a cooled solution of **11** (143 mg, 0.86 mmol) in anhydrous methylene chloride (5 mL) at -78°C was added DIBAL-H (0.95 M in hexane solution, 2.0 mL, 1.89 mmol) during 5 min. The mixture was diluted with ether (50 mL) and the bath was removed . Then, it was quenched with sat. ammonium chloride (10 mL) and the whole was stirred vigorously for 20 min. The formed solid was removed by filtration through a celite pad under vacuum and the organic filtrate was washed with brine (3 mL) and dried over $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica gel eluted with 20% ether in pentane. Alcohol **12** (108 mg) was obtained in 91% yield. Colorless oil. *Rf* = 0.29 (30% EtOAc in hexane); IR (neat) 3340 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (1H, br s), 3.19 (2H, d, *J* = 6.0 Hz), 4.13 (2H, dt, *J* = 5.5 and 1.1 Hz), 5.72 (1H, dtd, *J* = 15.2, 5.5 and 1.1 Hz), 5.81 (1H, dtd, *J* = 15.2, 6.0 and 1.1 Hz), 6.27 (1H, m), 7.23 (1H, m), 7.36 (1H, t, *J* = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 63.4, 111.1, 123.0, 130.2, 130.5, 139.1, 142.9; MS *m/z* (rel. intensity) 138 (M^+, 78), 120 (22), 107 (62), 94 (47), 78 (base). HRMS *m/z* calcd for $C_8H_{10}O_2$ (M^+) 138.0681. Found 138.0696.

(*E*)-4-(3-Furyl)-2-butenal (13): A mixture of **12** (159 mg, 1.15 mmol) and Dess-Martin periodinate (732 mg, 1.73 mmol) was stirred in methylene chloride (15 mL) at room temperature. After 5 min, sat. sodium bicarbonate (30 mL) containing 2.85 g of $Na_2S_2O_3 \cdot 5H_2O$ was added to the mixture and the whole was stirred for 5 min. The mixture was extracted with ether (50 mL) and washed with water (2 mL), and brine (3 mL). The extract was dried over $MgSO_4$ and condensed. The residual oil was purified by silica gel flash chromatography eluted with 5% ether in pentane to give **13** (125 mg) in 80% yield. Yellow oil. *Rf* = 0.30 (15% EtOAc in hexane); IR (neat) 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.48 (2H, d, *J* = 6.4 Hz), 6.15 (1H, ddt, *J* = 15.5, 7.9 and 1.6 Hz), 6.28 (1H, m), 6.92 (1H, dt, *J* = 15.5 and 6.4 Hz), 7.29 (1H, m), 7.41 (1H, t, *J* = 1.7 Hz), 9.56 (1H, d, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 110.9, 120.2, 133.5, 139.8, 143.5, 155.5, 193.7; MS *m/z* (rel. intensity) 136 (M^+, 29), 107 (26), 79 (33), 78 (93), 77 (43), 58 (base). HRMS *m/z* calcd for $C_8H_8O_2$ (M^+) 136.0524. Found 136.0512.

(2*E*)-3-(5,5-Dibromopenta-2,4-dienyl)furan (14): Triphenylphosphine (713 mg, 2.72 mmol) was added to a methylene chloride (5 mL) solution of carbon tetrabromide (338 mg, 1.02 mmol) at 0°C, and the mixture was stirred for 10 min at the same temperature to form a yellow solution. Then, a methylene chloride solution of **13** (93 mg, 0.68 mmol) in 1 mL was added dropwise to the yellow solution and the mixture was diluted with pentane (50 mL). The whole solution was purified by column chromatography on silica gel eluted with pentane to give **14** (181 mg) in 91% yield. Colorless oil. *Rf* = 0.43 (Hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 3.23 (2H, d, *J* = 6.6

Hz), 5.99 (1H, dt, J = 15.4 and 6.6 Hz), 6.17 (1H, ddt, J = 15.4, 9.9 and 1.5 Hz), 6.27 (1H, m), 6.93 (1H, d, J = 9.9 Hz), 7.24 (1H, m), 7.38 (1H, t, J = 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 89.7, 110.9, 122.1, 128.1, 136.3, 136.6, 139.3, 143.1; MS *m/z* (rel. intensity) 294 (M^+, 11), 292 (M^+, 23), 290 (M^+, 12), 213 (57), 211 (61), 132 (base), 131 (91), 104 (84), 103 (68), 77 (45). HRMS *m/z* calcd for $C_9H_8OBr_2$ (M^+) 293.8901, 219.8921 and 289.8942. Found 293.8870, 291.8901 and 289.8930.

(*E*)-3-(2-Penten-4-ynyl)furan (6): To a cooled THF (5 mL) solution of **14** (620 mg, 2.12 mmol) was dropped LDA (0.5 M in THF solution, 13.5 mL, 6.75 mmol) at -78°C. The reaction mixture was kept for 5 min at the same temperature and stirred for an additional 10 min at 0°C. Then, the mixture was quenched with sat. ammonium chloride (10 mL) and extracted with pentane (100 mL). The organic extract was washed with water (2 mL), and brine (3 mL), and dried over $MgSO_4$. After evaporation of the solvent, the residual oil was purified by flash chromatography on silica gel eluted with pentane to give **6** (262 mg) in 94% yield. Pale yellow oil. *Rf* = 0.29 (Hexane); UV (Cyclohexane) λ_{max} 233 (ε 9500), 222 (13400), 215 nm (12400, sh); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82 (1H, dd, J = 2.2 and 0.6 Hz), 3.25 (2H, br d, J = 6.6 Hz), 5.52 (1H, ddt, J = 15.9, 2.2 and 1.8 Hz), 6.26 (1H, m), 6.34 (1H, dtd, J = 15.9, 6.6 and 0.6 Hz), 7.24 (1H, m), 7.37 (1H, t, J = 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 76.6, 82.0, 109.8, 111.0, 121.6, 139.5, 143.1, 143.8; MS *m/z* (rel. intensity) 132 (M^+, base), 131 (25), 104 (22), 103 (18), 78 (14), 77 (12). HRMS *m/z* calcd for C_9H_8O (M^+) 132.0575. Found 132.0552.

(2*E*,4*E*)-3-(5-Iodo-4-methyl-penta-2,4-dienyl)furan (15): To a suspension of anhydrous $SnCl_2$ (864 mg, 4.56 mmol) in THF (5 mL) was added BuLi (1.61 M solution in hexane, 8.4 mL, 13.7 mmol) dropwise at -20°C and stirred for 20 min. To this solution, methylmagnesium bromide (0.94 M solution in THF, 4.8 mL, 4.56 mmol) was dropped during 10 min and stirred for an additional 15 min. Cuprous cyanide (6 mg, 0.06 mmol) was added and **6** (100 mg, 0.76 mmol) in THF (2 mL) was dropped slowly. After stirring for 15 min, iodomethane (0.7 mL, 12.2 mmol) was dropped and stirred for 20 min. To the reaction mixture, anhydrous hexane (40 mL) was added and stirred vigorously for 10 min. Upto this stage, all the reactions were carried out at -20°C. After the mixture separated to two layers, the upper layer was transferred *via* cannula to the ice cooled flask, to which iodine solution* in CH_2Cl_2 was dropped carefully by monitoring on tlc. The ice bath was then removed, and the mixture was diluted with ether (60 mL) and washed with sodium thiosulfate (4 mL), water (2 mL X 2), and brine (2 mL). The organic layer was dried over $MgSO_4$ and condensed. The residual oil was purified by column chromatography on alumina eluted with pet. ether to give **15** (150 mg) in 72% yield. Pale yellow oil. *Rf* = 0.40 (Hexane); UV (Cyclohexane) λ_{max} 253 (ε 24300), 247 (24400), 237 (sh), 216 nm (11100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, d, J = 1.1 Hz), 3.20 (2H, d, J = 6.6 Hz), 5.86 (1H, dt, J = 15.4 and 6.6 Hz), 6.21 (1H, dm, J = 15.4 Hz), 6.24 (1H, s), 6.26 (1H, m), 7.23 (1H, m), 7.37 (1H, t, J = 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 28.1, 82.2, 111.1, 122.8, 128.8, 132.1, 139.2, 143.0, 144.9; MS *m/z* (rel. intensity) 274 (M^+, 71), 147 (base), 129 (40), 119 (40), 117 (26), 91 (62). HRMS calcd for $C_{10}H_{11}OI$ (M^+) 273.9855. Found 273.9835.

* Iodine (2 g) was dissolved in CH_2Cl_2 (20 mL) solution and anhydrous Na_2CO_3 (1 g) was added to the solution.

(2*E*,4*E*,6*E*)-Dehydrodendrolasin (2): To a degassed solution of **15** (60 mg, 0.22 mmol) and (*E*)-2-(3-methyl-1-butenyl)-1,3,2-benzodioxaborole (62 mg, 0.33 mmol) in THF (4 mL), was added silver carbonate (78 mg, 0.28

mmol) and $Pd(PPh_3)_4$ (10 mg, 9 μmol). Then, aqueous potassium hydroxide solution (2 M, 1.25 mL) was added and stirred for 3.5 hr. The mixture was diluted with pentane (30 mL) and washed with water (2 mL), brine (1 mL X3), and dried over $MgSO_4$. After removal of solvent, the residue was chromatographed on silica gel eluted with pentane to give **2** (39 mg) in 83% yield. Colorless oil. *Rf* = 0.36 (Hexane); UV (Cyclohexane) λ_{max} 286 (ε 64600), 274 (83700), 265 (64300), 254 (38400, sh), 210 nm (37600); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (6H, d, *J* = 7.0 Hz), 1.85 (3H, s), 2.38 (1H, octet, *J* = 7.0 Hz), 3.25 (2H, d, *J* = 7.0 Hz), 5.69 (1H, dd, *J* = 15.0 and 7.0 Hz), 5.73 (1H, dt, *J* = 15.4 and 7.0 Hz), 5.97 (1H, d, *J* = 11.4 Hz), 6.15 (1H, d, *J* = 15.4 Hz), 6.27 (1H, d, *J* = 0.7 Hz), 6.32 (1H, dd, *J* = 15.0 and 11.4 Hz), 7.22 (1H, s), 7.36 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 22.5 (2C), 28.4, 31.6, 111.2, 123.7, 123.7, 126.2, 130.2, 132.8, 135.9, 139.1, 142.5, 142.8; MS *m/z* (rel. intensity) 216 (M^+, base), 201 (6), 173 (22), 159 (8), 145 (12), 135 (20), 131 (10), 107 (16), 93 (31), 81 (21), 69 (9), 58 (36). HRMS calcd for $C_{15}H_{20}O$ (M^+) 216.1514. Found 216.1512.

3-(3-Furyl)-1,1-dibromopropene (16): To a mixture of 3-furylacetoaldehyde **8** (383 mg, 3.48 mmol) and carbon tetrabromide (2.31 g, 6.96 mmol) in methylene chloride (20 mL) was added triphenylphosphine (3.65 g, 13.92 mmol) in 8 portions at 0°C. After the addition, the mixture was diluted with hexane (100 mL) and the whole was chromatographed on silica gel. Elution of hexane gave dibromoalkene (916 mg) in 99% yield. Colorless oil. *Rf* = 0.50 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.24 (2H, dd, *J* = 7.3 and 1.1 Hz), 6.30 (1H, d, *J* = 1.8 Hz), 6.53 (1H, t, *J* = 7.3 Hz), 7.27 (1H, m), 7.38 (1H, t, *J* = 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 90.2, 110.7, 120.6, 136.3, 139.3, 143.4; MS *m/z* (rel. intensity) 268, 266, and 264 (M^+, 24, 49 and 24), 187 (99), 185 (base), 159 (32), 157 (32). HRMS calcd for $C_7H_6OBr_2$ (M^+) 267.8745, 265.8765 and 263.8785. Found 267.8860, 265.8771 and 263.8783.

(*Z*)-3-(5-Trimethylsilyl-2-penten-4-ynyl)furan (18): To a mixture of **16** (916 mg, 3.44 mmol) and $Pd(PPh_3)_4$ (159 mg, 4 mol%) in benzene (15 mL) was added Bu_3SnH (1.02 mL, 1.1 g, 3.78 mmol) at room temperature, and the mixture was stirred for 40 min. To this mixture, CuI (197 mg, 1.03 mmol), diisopropylamine (2.71 mL, 20.64 mmol), and trimethylsilylacetylene (0.73mL, 5.16 mmol) were successively added. The whole mixture was stirred for 30 min at room temperature, diluted with hexane, and washed with water (2 mL), and then brine (2 mL). The organic extract was dried over $MgSO_4$ and condensed. The crude product was purified by column chromatography on alumina eluted with hexane to give **18** (562 mg) in 80% yield. Colorless oil. *Rf* = 0.27 (Hexane); UV (Cyclohexane) λ_{max} 247 (ε 12500), 236 (15000), 227 (12500), 216 nm (9960, sh); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (9H, s), 3.46 (2H, d, *J* = 7.3 Hz), 5.59 (1H, dt, *J* = 10.7 and 1.3 Hz), 6.05 (1H, dt, *J* = 10.7 and 7.3 Hz), 6.32 (1H, br s), 7.26 (1H, m), 7.37 (1H, t, *J* = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.04, 25.9, 99.5, 101.5, 110.1, 111.0, 122.6, 139.1, 142.3, 142.9; MS *m/z* (rel. intensity) 204 (M^+, 32), 189 (base), 176 (9), 176 (6), 161 (23). HRMS calcd for $C_{12}H_{16}OSi$ (M^+) 204.0971. Found 204.0977.

Before the addition of trimethylsilylacetylene, the first reaction was stopped and worked up at this stage. Z-bromoalkene, **17**, was obtained in 87% yield. Physical and spectroscopic data were as follows; Colorless oil. *Rf* = 0.48 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (2H, d, *J* = 6.6 Hz), 6.23 (1H, dt, *J* = 7.0 and 6.6 Hz), 6.27 (1H, dd, *J* = 7.0 and 1.1 Hz), 6.30 (1H, m), 7.26 (1H, m), 7.37 (1H, t, *J* = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 108.7, 110.9, 121.7, 132.7, 139.2, 143.0; MS *m/z* (rel. intensity) 188 and 186 (M^+, 28 and 28), 107 (base), 79 (35). HRMS calcd for C_7H_7OBr (M^+) 187.9660 and 185.9680. Found 187.9662 and 185.9686.

(*Z*)-3-(2-Penten-4-ynyl)furan (7): THF solution of tetrabutylammonium fluoride (1.0 M, 0.54 mL, 0.54 mmol) was added dropwise slowly to **18** (100 mg, 0.49 mmol) in THF (4.9 mL) at -15°C. After the addition, the mixture was diluted with pentane (30 mL) and washed with brine (3 mL). The extract was dried over $MgSO_4$ and condensed. The residue was purified by column chromatography on silica gel eluted with pentane to afford **7** (36 mg) in 56% yield. Colorless oil. *Rf* = 0.30 (Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13 (1H, dd, *J* = 2.2 and 0.5 Hz), 3.47 (2H, d, *J* = 7.4 Hz), 5.55 (1H, ddt, *J* = 10.7, 2.2, and 1.5 Hz), 6.11 (1H, dtd, *J* = 10.7, 7.4, and 1.0 Hz), 6.30 (1H, m), 7.25 (1H, m), 7.36 (1H, t, *J* = 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 79.9, 82.0, 109.0, 110.9, 122.4, 139.1, 143.0 (2C); MS *m/z* (rel intensity)132 (M^+, 17), 131 (74), 104 (base), 103 (34).

(2*Z*,4*E*)-3-(5-Iodo-2,4-pentadienyl)furan (19) : To a 1,2-dichloroethane (2.1 mL) solution of Cp_2ZrCl_2 (13.2 mg, 0.045 mmol) was added trimethylaluminum (1.08 M solution in hexane, 0.42 mL, 0.45 mmol) during 1 min at room temperature. The mixture was stirred for 10 min at the same temperature to form a light yellow solution. Enyne **7** (30 mg, 0.225 mmol) dissolved in 1,2-dichloroethane (1.0 mL) was dropped into the yellow solution during 2 min, and stirred for an additional 5 min at room temperature. The reaction mixture was cooled to 0°C and then THF (1.5 mL) solution of iodine (57 mg, 0.225 mmol) was added in one portion. The mixture was quenched with ice water (1 mL) and diluted with hexane (75 mL) to form precipitates, which was filtered through a celite pad. The organic filtrate was washed with water (1 mL X2), brine (2 mL) and dried over $MgSO_4$. The solvent was removed and the residual oil was purified by column chromatography on silica gel eluted with hexane to afford **19** (27 mg) in 44% yield. Colorless oil. *Rf* = 0.40 (Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, d, *J* = 0.6 Hz), 3.30 (2H, d, *J* = 7.5 Hz), 5.58 (1H, dt, *J* = 11.3 and 7.5 Hz), 5.92 (1H, dd, *J* = 11.3 and 1.2 Hz), 6.14 (1H, s), 6.26 (1H, br s), 7.21 (1H, t, *J* = 1.0 Hz), 7.36 (1H, t, *J* = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 24.9, 80.4, 110.8, 123.6, 129.4, 130.5, 138.9, 143.0, 144.0.

(2*Z*,4*E*,6*E*)-Dehydrodendrolasin (3): The coupling reaction of **19** with (*E*)-2-(3-methyl-1-butenyl)-1,3,2-benzodioxaborole was carried out in the same conditions described for synthesis of **2**. The chemical yield was 79% in 30 mg reaction scale. Colorless oil. *Rf* = 0.39 (Hexane); UV (Cyclohexane) λ_{max} 288 (ε 19300, sh), 275 (28900) 265 (26900), 254 (19000, sh), 211 nm (10800); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (6H, d, *J* = 6.7 Hz), 1.93 (3H, s), 2.39 (1H, octet, *J* = 6.7 Hz), 3.41 (2H, d, *J* = 7.6 Hz), 5.47 (1H, dt, *J* = 11.7 and 7.6 Hz), 5.67 (1H, dd, *J* = 15.0 and 7.0 Hz), 5.94 (1H, d, *J* = 11.7 Hz), 5.99 (1H, d, *J* = 11.0 Hz), 6.27 (1H, ddd, *J* = 15.0, 11.0 and 1.0 Hz), 6.28 (1H, d, *J* = 0.8 Hz), 7.22 (1H, br s), 7.35 (1H, t, *J* = 1.5 Hz); ^{13}C NMR (100Hz, $CDCl_3$) δ 17.0, 22.5(2C), 24.7, 31.6, 110.9, 123.4, 124.4, 127.3, 130.4, 132.1, 133.8, 139.0, 142.5, 142.8; MS *m/z* (rel. intensity) 216 (M^+, base), 201 (38), 173 (35), 159 (22), 145 (21), 135 (25), 131 (16), 107 (21), 93 (44), 81 (35). HRMS calcd for $C_{15}H_{20}O$ (M^+) 216.1514. Found 216.1509.

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14, We first tried the above tributylstannylmagnesiation to **7**, however, the desired **19** was obtained as a minor product. A geometric isomer, having 2*Z*,4*E* geometories produced unexpectedly under these conditions.

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