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Concise enantioselective synthesis of furocaulerpin

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Abstract—The first total synthesis of both enantiomers of furocaulerpin was accomplished in good yields with a high control of the stereogenic center by enzymatic resolution, a total control of the configuration of the central double bond and the construction of the dienyne moiety via a Stille cross-coupling.

1. Introduction

Some metabolites from tropical algae have been implicated in chemical defense against grazing fish and invertebrates in herbivore-rich tropical waters[1] and this has been proposed to explain the proliferation of *Caulerpa taxifolia*, a tropical green seaweed, accidentally introduced in the Mediterranean. Compared to other *Caulerpa* species in the tropics, *C. taxifolia* contains large amounts of caulerpenyne (**CYN**), a sesquiterpene isolated from 10 different species of *Caulerpa* and first identified from *Caulerpa prolifera*.[2] Among its biological activities, which are attributed to the diacetoxybutadiene moiety, **CYN** inhibits the proliferation of the fibroblastic cell line BHK 21/C13 from baby hamster kidney and the division of sea urchin eggs.[3] The cytotoxicity was also demonstrated in various tumor cell lines[4] and recently it was demonstrated that **CYN** has an antiproliferative activity on tumor cell line SK-N-SH and modifies the microtubule network.[5] **CYN**, which has got a fragile diacetoxybutadiene moiety, is relatively unstable and, for example, reacts with primary amines to form pyrrole derivatives.[6] Equally, it yields, via hydrolysis and cyclization, a furan metabolite, furocaulerpin **1** ($[\alpha]_D^{20} = -15.0$, *c* 1, $CHCl_3$), which was extracted and identified from *C. prolifera* by De Napoli et al. in 1981.[7]

To provide material for a more extensive biological evaluation of the microtubule network and to confirm the hypothesis that the diacetoxybutadiene moiety is directly implicated in the biological activities of such compounds, along with access to novel analogues, we have undertaken the total synthesis of furocaulerpin **1**.

Herein is a full account of our preliminary communication,[8] which discloses results about racemic and enantioselective syntheses of this secondary metabolite. Other enantioselective approaches are also discussed.

2. Results and discussion

The main structural features of **1** are a dienyne function in which the trisubstituted C6–C7 double bond presents an *E* configuration and a secondary acetate stereocenter at C4. Our strategy for synthesizing furocaulerpin **1** from the commercially available 3-furaldehyde and 3-methylbut-2-enal is outlined in Scheme 1.

Our planned synthesis of **1** was derived from the one we applied in our synthesis of caulerpenyne **A**[9] and called for the initial preparation of two fragments **I** and **II**. Furocaulerpin **1** would be constructed through a Stille reaction between the residual vinyl iodide function (segment **II**) and an alkynyl stannane (segment **I**). The control of the configuration of the trisubstituted double bond of **II** would accomplished via stannylcupration and iododestannylation reactions. The control of the stereogenic center would be realized via an enzymatic resolution.

2.1. Racemic synthesis

The fragment **I** was prepared via the Corey alkynylation reaction.[10] Commercially available 3-methylbut-2-enal

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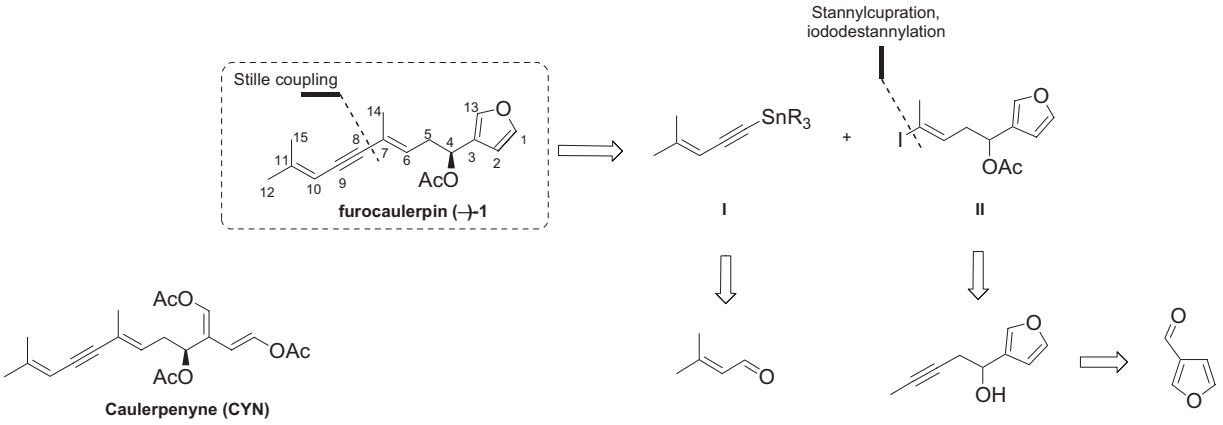
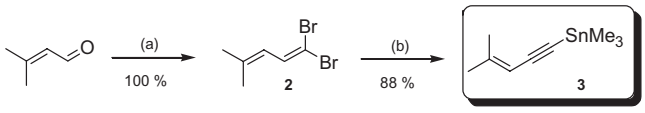


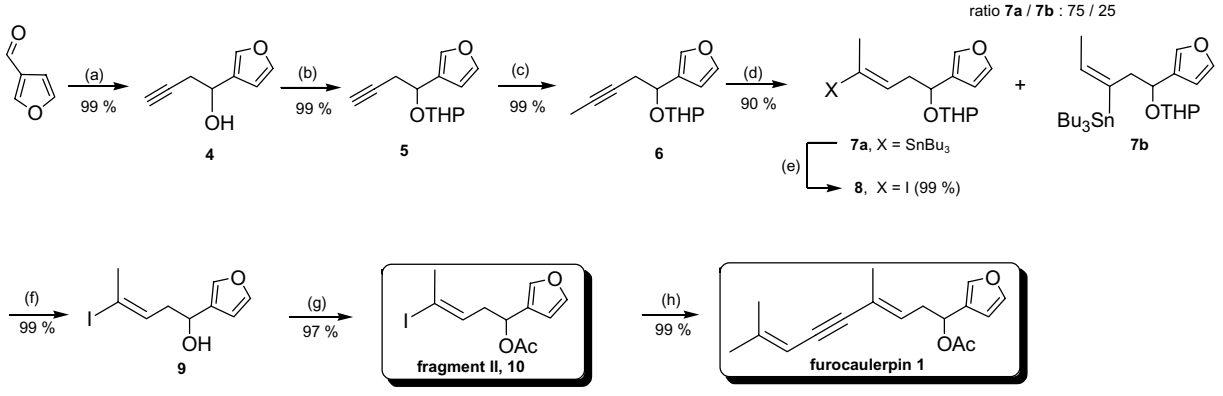
Scheme 1.

was reacted with the reagent prepared from carbon tetrabromide, zinc, and triphenylphosphine to give *gem*-dibromodiene **2**. Treatment of **2** with butyllithium (2 equiv) followed by addition of trialkyltin chloride afforded the stannylenyne **3** in 88% yield. It should be noticed that the best result was obtained with trimethyltin chloride instead of tributyltin chloride. Moreover, the purification step by silica gel chromatography being impossible for both compounds, distillation was found easier for the trimethyl analogue than for the tributyl analogue, which was found unstable at high temperature (Scheme 2).



Scheme 2. Synthesis of **3**. Reagents and conditions: (a) CBr_4, PPh_3, Zn, CH_2Cl_2, rt; (b) (i) *n*-BuLi, THF, −78 °C, (ii) Me_3SnCl, −78 °C to rt.

Synthesis of fragment **II** (Scheme 3) began with condensation of allenyl magnesium bromide to 3-furaldehyde furnishing the crude alcohol **4** in quantitative yield. The next step was methylation of **4**. First attempts were conducted without protection of the hydroxy function using BuLi/THF or $LiNH_2/NH_3$ as metalating agents and methyl iodide and afforded an inseparable mixture of methoxy derivatives of **4** and **12**. To avoid this problem, the hydroxyl function was protected as the tetrahydropyranyl ether with dihydropyrane in the presence of catalytic amount of PPTS. Then the methylation reaction of **5** was performed with (1) $LiNH_2/NH_3$ and (2) MeI to afford **6** in 98% yield over three steps.[11] The achievement of the east fragment and the construction of the central double bond with an *E* configuration was accomplished via the stannylcupration[12] of the triple bond followed by iododestannylation.[13] From **6**, the stannylcupration reaction using the stannyl cuprate $Bu_3Sn(Bu)CuLi$, LiCN (Lipshutz reagent) at −78 °C was found to be dependent on the temperature and on the presence of methanol. In each case, the stannylcupration in the presence or not of methanol was incomplete (68% conversion without MeOH at −78 °C, 90% with MeOH at −40 °C). In the presence of methanol at −40 °C, the stannylcupration reaction yielded a separable 75/25 mixture of two regioisomers **7a** and **7b** (observed by TLC and ^1H NMR). Iododestannylation of **7a** with iodine in ether furnished, in 99% yield the corresponding vinyliodides **8**. Acid deprotection,[14] followed by protection of the hydroxyl group as the acetate using acetic anhydride

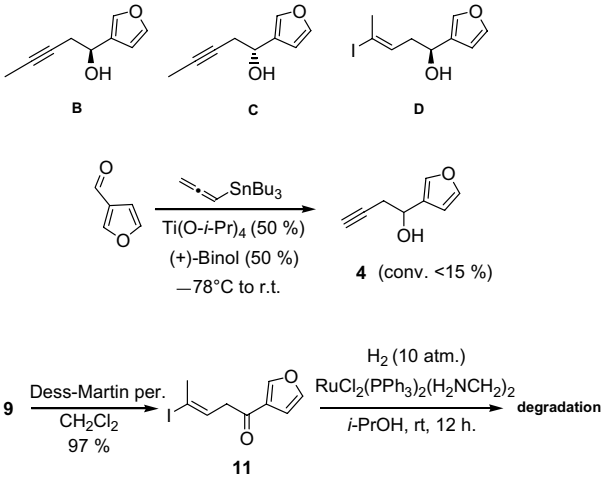


Scheme 3. Synthesis of racemic furocaulerpin **1**. Reagents and conditions: (a) allenyl magnesium bromide, −78–0 °C; (b) DHP, PPTS, CH_2Cl_2; (c) (i) $LiNH_2/NH_3$, (ii) MeI; (d) 3 equiv $Bu_3Sn(Bu)CuLi$, LiCN, MeOH, −40 °C; (e) I_2, ether; (f) $AcOH/H_2O/THF$, 45 °C; (g) pyridine Ac_2O, DMAP; (h) **3**, $PdCl_2(MeCN)_2$, DMF.

and a catalytic amount of DMAP in pyridine gave racemic fragment **II** in 96% yield over two steps. The last step of the synthesis is the coupling reaction[15] between vinyl iodide **10** with stannylenyne **3**, using 5 mol% of bis-acetonitrile palladium chloride, giving furocaulerpin **1** in 99% yield. The data for this synthetic racemic furocaulerpin (500 MHz ^{1}H NMR $CDCl_3$, 50 MHz ^{13}C NMR $CDCl_3$, GC/MS, and TLC mobility) are in agreement with those reported in the literature.

2.2. Enantioselective synthesis

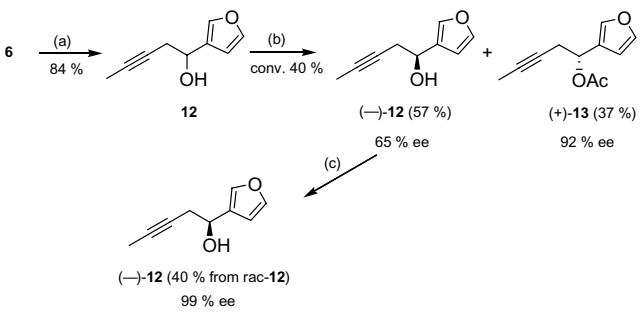
Our initial objective was to develop an enantioselective synthesis of alcohols **B**, **C**, **D**. These alcohols share an identical homoallylic hydroxy function. We planned to prepare **B** or **C** using a chiral Lewis acid promoted asymmetric propargylation of 3-furaldehyde. Keck et al. have reported promising results in this area starting from 2-furaldehyde.[16] Unfortunately, the extension of this reaction gave only poor results and all the attempts we performed, using allenyltributyl stannane in presence of 50 mol% (1/1 mixture) of Ti(O-*i*-Pr)$_4$ and (+)-Binol led to low conversion rates into the desired homopropargylic alcohol **4** (<15%). As a possible explanation, a strong chelation of the furyl oxygen atom with the Lewis acid would lead to the nonactivation of the carbonyl group (Scheme 4).



Scheme 4.

The second way we investigated was the asymmetric hydrogenation of ketone using Noyori's conditions.[17] First of all, the ketone **11** was prepared in 97% yield from **9** using the Dess–Martin periodinane.[18] It should be noticed that the Dess–Martin's conditions cleanly afforded the β,γ-unsatured ketone without any trace of conjugated α,β-unsatured issues. Unfortunately, the first trials on racemic reduction using *trans*-[$RuCl_2$(triphenylphosphine)$_2$(1,2-diamine)] as catalyst gave unsatisfactory results and numerous unidentified degradation products were observed (Scheme 4).

We next thought to explore an enzymatic resolution to prepare **12** in its enantiomerically pure form. Moreover,



Scheme 5. Reagents and conditions: (a) AcOH/H_2O/THF, 45 °C; (b) vinyl acetate, hexane, *Ps. fluorescenes*, 26 h; (c) vinyl acetate, hexane, *Ps. fluorescenes*, 100 h.

it was interesting for us to test the influence of the stereogenic center in biological tests. Acetic acid hydrolysis of **6** furnished **12** in 84% yield. Then, the enzymatic reaction was examined with various lipases using standard conditions (vinyl acetate (3 equiv), lipase 50% by weight, hexane 0.05 M) (Scheme 5). Results are given in Table 1. Best results for conversion rate and enantiomeric excess[19] were obtained with *Pseudomonas fluorescens*. In a study relating to the enzymatic resolution of secondary alcohols by lipases from *Pseudomonas* sp. Burgess has proposed a simple active site model for predicting enantioselectivity.[20] This model predicts that alcohols that are resolved most efficiently have one small and one relatively large group attached to the hydroxymethine functionality. According to this model, we assume that only (*R*)-isomer of **12** was transformed into acetate **13**. After 26 h at room temperature, the active enzyme was recovered for re-use after filtration. Separation by chromatography on silica gel afforded a 57% yield of the alcohol (−)-**12** (65% ee) and a 37% yield of the acetate (+)-**13** {$[\alpha]_D^{24} = +41.4$, (*c* 1, $CHCl_3$), 92% ee}. The remaining alcohol (−)-**12** was resubjected to the same conditions of enzymatic transesterification using the recovered enzyme. The progress of the reaction was monitored by chiral phase analytical GC until one enantiomer of the starting material was completely consumed. After 100 h, (−)-**12** {$[\alpha]_D^{24} = -32.8$, (*c* 1, $CHCl_3$)} was obtained in 40% overall yield and 99% ee.

Table 1

Lipase	Time (h)	Conversion (%)	Ee (%)
Candida antartica	120	42	88
Candida cylindracea	72	12	—
Mucor miehei	96	<5	
Aspergillus niger	72	6	—
Ps. cepacia	12	46	91
Ps. fluorescens	8	45	94
Rhizopus arrhizus	72	<5	
Rhizopus niveus	72	<5	
Hog pancreas	96	<5	

The end of the synthesis was identical to the racemic synthesis. From (+)-**13**, the stannylcupration reaction

using the stannyl cuprate $Bu_3Sn(Bu)CuLi$, LiCN at −78 °C gave unexpected products. A 4:6 mixture of alcohol (+)-**12** and vinylstannane (+)-**14** was obtained using 3 equiv of Lipshutz reagent whereas 6 equiv furnished a 2:8 mixture of the same products. After purification, pure vinylstannane (+)-**14** $\{[\alpha]_D^{24} = +10$, (c 1, $CHCl_3)\}$ was obtained in 58% yield with a surprising total regio- and stereoselectivity (E-configuration). It should be noted that in each attempt we conducted, the acetate function was reactive. This could be explained by the addition of a butyl moiety of the vinylcuprate to the ester carbonyl followed by a retrostannylcupration giving the corresponding alcohol (Scheme 6).

In contrast, clean access of (−)-**14** from (−)-**12** was found, as for **7**, to be dependent on the temperature and on the presence of methanol. In each case and independently of the number of equivalents of the Lipshutz reagent, the stannylcupration in the presence or not of methanol was incomplete (10% of conversion without MeOH at −78 °C, 70% with MeOH at −40 °C and 76% at −10 °C). In the presence of methanol at −40 °C, the stannylcupration reaction yielded a 95:5 mixture of two regioisomers (observed by TLC and ^{1}H NMR). At −10 °C, the regioselectivity was found to be complete in favor of stannane (−)-**14**. After purification, pure vinylstannane (−)-**14** $\{[\alpha]_D^{24} = -11.7$, ($c$ 1, $CHCl_3)\}$ was obtained in 43% yield. Iododestannylation of (+)-**14** and (−)-**14** yielded, respectively, 99% and 96% of the corresponding vinyliodides (+)-**9** $\{[\alpha]_D^{24} = +12.3$, ($c$ 1, $CHCl_3)\}$ and (−)-**9** $\{[\alpha]_D^{24} = -13.0$, ($c$ 1, $CHCl_3)\}$. The hydroxyl group of (+)-**9** and (−)-**9** was protected as the acetate using acetic anhydride and a catalytic amount of DMAP in pyridine providing, respectively, (+)-**10** in 93% yield $\{[\alpha]_D^{24} = +25$, (c 1, $CHCl_3)$, 92% ee$\}$ and (−)-**10** in 87% yield $\{[\alpha]_D^{24} = -26.6$, ($c$ 1, $CHCl_3)$, ee > 99%$\}$. To finish, the coupling reaction between vinyl iodide (+)-**10** and (−)-**10** with stannylenyne **3**, using 5 mol% of bis-acetonitrile palladium chloride, gave (+)-furocaulerpin **1** $\{[\alpha]_D^{24} = +13.8$, ($c$ 1, $CHCl_3)\}$ in 94% yield and (−)-furocaulerpin **1** $\{[\alpha]_D^{24} = -14.6$, ($c$ 1, $CHCl_3)\}$ in 90% yield (Scheme 7).

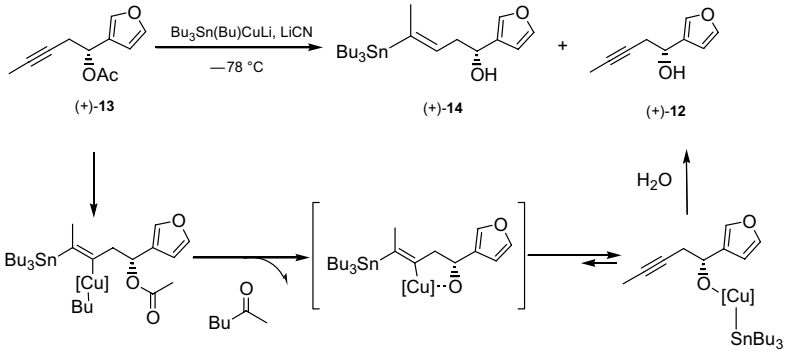
3. Conclusion

In conclusion, the first total synthesis of furocaulerpin has been carried out in good yield. The overall yields were 15% for (+)-**1**, 11% for natural product, and 62% for (±)-**1**.

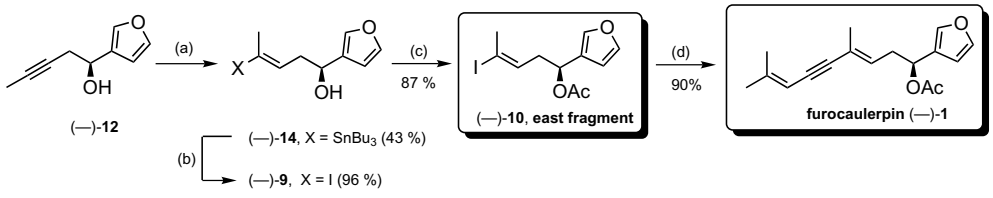
4. Experimental

4.1. General

All reactions sensitive to oxygen and moisture were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker AC200, Bruker AC300, Bruker AM400, or Bruker AC500. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in hertz (Hz). Chemical shifts for ^{13}C NMR were reported in ppm relative to the central line of a triplet at 77.1 ppm for deuteriochloroform. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 Fourier Transform Infrared spectrophotometer and are reported in



Scheme 6.



Scheme 7. Reagents and conditions: (a) 4 equiv, $Bu_3Sn(Bu)CuLi$, LiCN, MeOH, −10 °C; (b) I_2, Et_2O, 0 °C to rt; (c) Ac_2O, DMAP, pyridine; (d) **3**, $PdCl_2(MeCN)_2$, DMF.

wave numbers (cm^{-1}). Mass spectra (MS) were obtained on a Hewlett Packard apparatus (engine 5989A) at 70 eV in the GC/MS mode. Enantiomeric excess (ee) was determined by the ratio of the peak areas obtained by GC separation using a chiral phase (WCOT Fused Silica 25 m × 0.25 mm Coating CP CHIRASIL-DEX CB DF = 0.25). Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F254. Flash column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Reagents and solvents were commercial grades and were used as supplied. Dichloromethane, benzene, and toluene were distilled from calcium hydride and stored over molecular sieves 4 Å. THF and diethyl ether were distilled from sodium benzophenone ketyl prior to use. *N*,*N*-dimethylformamide and hexanes were purchased anhydrous and stored over molecular sieves 4 Å under argon.

4.2. 1,1-Dibromo-4-methylpent-1,3-diene 2

Carbon tetrabromide (24.87 g, 75 mmol), triphenylphosphine (19.67 g, 75 mmol), and zinc dust (4.69 g, 75 mmol) were placed in a dry 500 mL round-bottomed flask under a nitrogen atmosphere. The flask was cooled to 0 °C and CH_2Cl_2 (300 mL) added to the mixture of the solids, giving a green suspension. The reaction mixture was allowed to warm to room temperature and was then stirred for 24 h, after which time it was pink in color. 3-Methylbut-2-enal (2.89 mL, 30 mmol) was then added via syringe and the mixture stirred for a further 2 h. The now purple suspension was transferred to a large conical flask, pentane (400 mL) added, and the resultant solution was filtered. The residue was dissolved in CH_2Cl_2 (200 mL) and then further pentane (500 mL). This was also filtered and the combined filtrates were concentrated to a colorless oil. This was triturated with pentane (20 mL) and filtered through a short pad of silica to remove triphenylphosphine oxide. After removal of solvents in vacuum, *gem*-dibromodiene **2** was obtained as colorless oil in quantitative yield. ν_{max} (film/cm^{-1}) 3010, 1630, 1560, 1250, 850, 770; ^{1}H NMR (400 MHz, $CDCl_3$) 1.74 (s, 3H), 1.78 (s, 3H), 5.83 (m, $J = 10.6$ Hz, 1H), 7.07 (d, $J = 10.6$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 19.4, 26.4, 88.6, 122.3, 133.6, 140.8; m/z (70 eV) 240 ($M^{+\cdot}$, 39), 161 (14), 80 (44), 79 (100), 77 (45), 51 (13).

4.3. 1-Trimethylstannyl-4-methylpent-3-en-1-yne 3

To a solution of 1,1-dibromo-4-methylpent-1,3-diene **2** (1 g, 3.4 mmol) in THF (15 mL) under a nitrogen atmosphere at −78 °C, butyllithium (2.5 M, 2.86 mL, 7.1 mmol) was added dropwise. The clear yellow solution was stirred at −78 °C for 1.5 h and then trimethylstannylchloride (710 mg, 3.57 mmol) was added. After warming to room temperature the mixture was quenched with water (5 mL). The aqueous phase was extracted with diethyl ether. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under vacuum to give 1-trimethylstannyl-4-methylpent-3-en-1-yne **3** in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 0.25 (s, $^2J_{Sn-H} = 59$ Hz, 9H), 1.74 (s, 3H), 1.87 (s, 3H), 5.25 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) −7.7 ($^1J_{Sn-C} = 404$ Hz), 21.1, 24.7, 94.8, 105.7, 107.3, 149.1; ^{119}Sn NMR (149.21 MHz, $CDCl_3$) −67.73; m/z (70 eV) organotin fragments 244 ($M^{+\cdot}$, 18), 229 (100), 199 (32), 120 (10).

4.4. 1-(3-Furyl)but-3-yn-1-ol 4

In a hermetically two-neck flask with a refluxing condenser, were added magnesium (174 mg, 7.2 mmol), Et_2O (1 mL), and $HgCl_2$ (100 mg). The mixture was stirred for 30 min and Et_2O (3 mL) was added. The mixture was cooled with an ice bath then propargyl bromide (50 μL, 0.05 mmol) was added. When the reaction was started, the remainder of propargyl bromide (0.47 mL, 4.3 mmol) was added dropwise then the mixture was stirred at 0 °C for 3 h. To a solution of 3-furaldehyde (0.2 mL, 2.4 mmol) in Et_2O (4 mL) was added, at −78 °C, the Grignard reagent prepared below. The mixture was warmed to 0 °C then hydrolyzed with a saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$ then concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum–Et_2O, 5/5) to give 1-(3-furyl)but-3-yn-1-ol **4** in 99% yield. ν_{max} (film/cm^{-1}) 3400, 3292, 2120, 1598, 1503, 1158, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) 2.07 (t, $J = 2.6$ Hz, 1H), 2.26 (m, 1H), 2.63 (m, 2H), 4.82 (br q, $J = 5.6$ Hz, 1H), 6.43 (br dd, $J = 1.8$, 0.8 Hz, 1H), 7.38 (br t, $J = 1.8$ Hz, 1H), 7.44 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 27.9, 65.1, 71.0, 80.5, 108.4, 127.3, 139.2, 143.1; m/z (70 eV) 136 ($M^{+\cdot}$, 4), 107 (23), 97 (90), 95 (13), 69 (44), 51 (15), 41 (100), 40 (10), 39 (89), 38 (20).

4.5. 1-(3-Furyl)-1-(2-tetrahydropyranyloxy)but-3-yne 5

A mixture of 1-(3-furyl)but-3-yn-1-ol **4** (500 mg, 3.68 mmol), CH_2Cl_2 (10 mL), dihydropyrane (0.67 mL, 7.4 mmol), and PPTS (90 mg, 0.37 mmol) was stirred until the disappearance of the starting material. Then the solution was concentrated under vacuum and the crude product was purified by flash chromatography (light petroleum–Et_2O, 7/3) to give 1-(3-furyl)-1-(2-tetrahydropyranyloxy)but-3-yne **5**, as 1/1 mixture of diastereoisomers, in 99% yield. ν_{max} (film/cm^{-1}) 3295, 3133, 1595, 1502, 1122, 1025, 980; ^{1}H NMR (300 MHz, $CDCl_3$) 1.41–1.91 (m, 12H), 1.96 (t, $J = 2.6$ Hz, 1H), 1.97 (t, $J = 2.6$ Hz, 2H), 2.53–2.78 (m, 4H), 3.39–3.53 (m, 2H), 3.74 (br ddd, $J = 11.3$, 8.7, 3.2 Hz, 1H), 3.98 (br ddd, $J = 11.3$, 8.3, 3.7 Hz, 1H), 4.55 (br t, $J = 3.3$ Hz, 1H), 4.78–4.84 (m, 2H), 4.92 (m, 1H), 6.39 (m, 1H), 6.46 (m, 1H), 7.36 (t, $J = 1.7$ Hz, 1H), 7.37 (t, $J = 1.7$ Hz, 1H), 7.41 (m, 1H), 7.45 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 19.05, 19.13, 25.3, 25.4, 25.6, 26.9, 30.3, 30.4, 61.8, 62.1, 67.6, 69.2, 70.0, 70.2, 80.7, 80.9, 94.9, 97.5, 108.6, 109.1, 124.5, 126.3, 139.5, 140.7, 142.8, 143.3; m/z (70 eV) 136 ($M^{+\cdot}$ −84, 15), 119 (15), 91 (34), 85 (100), 67 (20), 65 (21), 57 (21), 55 (10), 43 (23), 41 (36), 39 (28).

4.6. 1-(3-Furyl)-1-(2-tetrahydropyranyloxy)pent-3-yne 6

To a solution of lithium amide prepared from lithium (52 mg, 7.5 mmol), ferric nitrate (1 mg), and ammonia (35 mL) was added 1-(3-furyl)-1-(2-tetrahydropyranyloxy)but-3-yne **5** (410 mg, 1.88 mmol) at −40 °C. The mixture was stirred at −40 °C for 2 h then methyliodide (1.17 mL, 18.8 mmol) was added. After 12 h the reaction was quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O. The organic layers were dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (light petroleum–Et_2O, 8/2) giving 1-(3-furyl)-1-(2-tetrahydropyranyloxy)pent-3-yne **6**, as an 1/1 mixture of diastereoisomers, in 99% yield. ν_{max} (film/cm^{-1}) 1501, 1120, 1025, 975; ^1H NMR (400 MHz, $CDCl_3$) 1.43–1.92 (m, 18H), 2.47–2.71 (m, 4H), 3.41–3.51 (m, 2H), 3.75 (m, 1H), 3.99 (m, 1H), 4.55 (m, 1H), 4.75 (m, 2H), 4.91 (m, 1H), 6.38 (s, 1H), 6.45 (s, 1H), 7.35 (br s, 1H), 7.36 (br s, 1H), 7.39 (s, 1H), 7.44 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 3.4 (2C), 19.1, 19.3, 25.4, 25.6, 25.9, 27.3, 30.4, 30.6, 61.8, 62.2, 68.3, 69.8, 75.5, 75.7, 77.2, 77.4, 95.0, 97.5, 108.7, 109.3, 125.0, 126.7, 139.5, 140.6, 142.7, 143.2; m/z (70 eV) 150 ($M^{+\cdot}$ −84, 7), 105 (11), 85 (100), 77 (13), 67.05 (21), 57 (24), 55 (11), 53 (10), 43 (26), 41 (36), 39 (20).

4.7. (*E*)-4-Tributylstannyl-1-(3-furyl)-1-(2-tetrahydropyranyloxy)pent-3-ene 7a

CuCN (688 mg, 7.68 mmol) was suspended in freshly distilled THF (21 mL), cooled at −78 °C, and treated with *n*-BuLi in hexane (2.5 M, 6.15 mL, 15.36 mmol). The mixture was allowed to warm slightly to yield a colorless, homogenous solution, which was recooled to −78 °C where Bu_3SnH (4.07 mL, 15.36 mmol) was added dropwise via syringe. Stirring was continued and, over ca. 10 min, the solution yellowed and H_2 gas was liberated. Methanol (11.4 mL, 282 mmol) was then added, and the mixture was allowed to warm to −40 °C and 1-(3-furyl)-1-(2-tetrahydropyranyloxy)pent-3-yne **6** (600 mg, 2.56 mmol) was added and stirred overnight at −40 °C. The mixture was quenched with a saturated aqueous NH_4Cl solution, filtered, and aqueous layer was extracted with Et_2O. The organic layers were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (light petroleum–Et_2O, 95/5 to 9/1) to yield a separable 75/25 mixture of regioisomers **7a** and **7b**. Sixty milligrams of 1-(3-furyl)-1-(2-tetrahydropyranyloxy)pent-3-yne **6** was also recovered. Several purifications lead to the pure vinyl stannane **7a** as a mixture of diastereoisomers. ν_{max} (film/cm^{-1}) 1501, 1118, 1023; ^1H NMR (300 MHz, $CDCl_3$) 0.79–0.88 (m, 30H), 1.24–1.72 (m, 36H), 1.80 (m, $^3J_{Sn-H} = 46$ Hz, 6H), 2.47–2.70 (m, 4H), 3.38–3.51 (m, 2H), 3.76 (m, 1H), 3.90 (m, 1H), 4.54 (br t, $J = 3.2$ Hz, 1H), 4.65 (t, $J = 6.7$ Hz, 2H), 4.81 (br t, $J = 3.5$ Hz), 5.51 (br t, $J = 6.8$ Hz, $^3J_{Sn-H} = 71$ Hz, 1H), 5.56 (bt, $J = 6.8$ Hz, $^3J_{Sn-H} = 71$ Hz, 1H), 6.36 (br s, 1H), 6.41 (br s, 1H), 7.32–7.36 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) 9.1 ($^1J_{Sn-C} = 322$ Hz, 6C), 13.7 (6C), 19.2, 19.3 (2C), 19.5, 25.5, 25.7, 27.5 ($^3J_{Sn-C} = 55$ Hz, 6C), 29.2 ($^2J_{Sn-C} = 18$ Hz, 6C), 30.6, 30.8, 34.2, 35.5, 61.8, 62.3, 68.9, 71.1, 94.5, 97.8, 108.9, 109.5, 125.7, 127.5, 135.9, 136.4, 139.4, 140.4, 140.5, 140.8, 142.7, 143.2; m/z (70 eV) organotin fragments 469 ($M^{+\cdot}$ −57, 20), 367 (27), 335 (30), 235 (13), 179 (19), 177 (19), 121 (10), 120 (10), organic fragments 85 (100), 67 (19), 57 (24), 55 (11), 43 (21), 41 (33).

4.8. (*E*)-1-(3-Furyl)-4-iodo-1-(2-tetrahydropyranyloxy)-pent-3-ene 8

To a solution of (*E*)-4-tributylstannyl-1-(3-furyl)-1-(2-tetrahydropyranyloxy)-pent-3-ene **7a** (450 mg, 0.86 mmol) in Et_2O (5mL), was added dropwise iodine (250 mg, 1.03 mmol) in 5 mL of Et_2O at 0 °C. The mixture was stirred 2 h at room temperature and quenched with 1 M aqueous KF solution (2.5 mL) and acetone (2.5 mL). After stirring 2 h the solution was filtered through a pad of Celite. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with a saturated aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum–Et_2O, 9/1) giving (*E*)-1-(3-furyl)-4-iodo-1-(2-tetrahydropyranyloxy)pent-3-ene **8** in 99% yield as an mixture of diastereoisomers. ν_{max} (film/cm^{-1}) 1501, 1120, 1024, 977, 602; ^1H NMR (300 MHz, $CDCl_3$) 1.42–1.86 (m, 12H), 2.25–2.62 (m, 10H), 3.37–3.52 (m, 2H), 3.72 (m, 1H), 3.87 (m, 1H), 4.51 (br t, $J = 3.3$ Hz, 1H), 4.63–4.68 (m, 2H), 4.76 (br t, $J = 3.2$ Hz, 1H), 6.14 (br t, $J = 7.6$ Hz, 1H), 6.20 (br t, $J = 7.6$ Hz, 1H), 6.33 (br s, 1H), 6.38 (br s, 1H), 7.34–7.37 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) 19.2, 19.3, 25.4, 25.6, 27.8 (2C), 30.5, 30.7, 36.5, 37.8, 62.0, 62.4, 67.9, 70.0, 94.8, 95.9 (2C), 97.7, 108.7, 109.2, 125.1, 126.7, 136.6, 137.1, 139.4, 140.5, 143.0, 143.5.

4.9. (*E*)-1-(3-Furyl)-4-iodopent-3-en-1-ol 9

To a (3/2/2; 10 mL) mixture of acetic acid, THF, and water was added (*E*)-1-(3-furyl)-4-iodo-1-(2-tetrahydropyranyloxy)-pent-3-ene **8** (196 mg, 0.54 mmol). The solution was heating to 45 °C and the reaction was monitored by TLC. After disappearance of the starting material, the mixture was treated with a solution of K_2CO_3 (10 g). The aqueous layer was extracted with Et_2O then the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum–Et_2O, 7/3) giving (*E*)-1-(3-furyl)-4-iodopent-3-en-1-ol **9** in 99% yield. ν_{max} (film/cm^{-1}) 3376, 1501, 1158, 1027, 600; ^1H NMR (300 MHz, $CDCl_3$) 1.81 (d, $J = 4.1$ Hz, 1H), 2.36 (s, 3H), 2.39–2.54 (m, 2H), 4.70 (m, 1H), 6.19 (br t, $J = 7.5$ Hz, 1H), 6.38 (s, 1H), 7.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) 27.9, 39.0, 66.0, 96.6, 108.4, 128.2, 136.4, 139.1, 143.5; m/z (PCI, 70 eV) 279 ($M^{+\cdot}$+1, 10), 152 (18), 151 (76), 135 (15), 134 (100), 133 (85), 123 (21), 109 (21), 97 (71), 95 (10), 83 (12), 69 (16).

4.10. (±)-, (+)-, and (−)-(*E*)-1-(3-Furyl)-4-iodopent-3-en-1-yl acetate 10

A solution of (±), (+), or (−)-(*E*)-1-(3-furyl)-4-iodopent-3-en-1-ol **9** (58 mg, 0.21 mmol), acetic anhydride (0.04 mL, 0.421 mmol), DMAP (1.2 mg, 0.01 mmol), and pyridine (1 mL) was stirred until disappearance of the starting material. The mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether and the organic layers were washed with a saturated aqueous $CuSO_4$ solution, water, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum–Et_2O, 9/1) to give (*E*)-1-(3-furyl)-4-iodopent-3-en-1-yl acetate in 97% yield, (+)-(*E*)-1-(3-furyl)-4-iodopent-3-en-1-yl acetate $\{[\alpha]_D^{24} = +25$, (*c* 1, $CHCl_3$), *ee* = 92%} in 93% yield, or (−)-(*E*)-1-(3-furyl)-4-iodopent-3-en-1-yl acetate $\{[\alpha]_D^{24} = -26.6$, (*c* 1, $CHCl_3$), *ee* > 99%} in 87% yield. ν_{max} (film/cm^{-1}) 1737, 1502, 1235, 1023, 602; ^{1}H NMR (400 MHz, $CDCl_3$) 2.04 (s, 3H), 2.34 (br s, 3H), 2.46 (ddd, *J* = 14.6, 7.4, 6.7 Hz, 1H), 2.59 (ddd, *J* = 14.6, 7.4, 6.7 Hz, 1H), 5.75 (t, *J* = 6.7 Hz, 1H), 6.08 (br t, *J* = 7.4 Hz, 1H), 6.36 (m, 1H), 7.37 (br t, *J* = 1.7 Hz, 1H), 7.40 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 21.2, 27.8, 35.8, 67.2, 96.8, 108.8, 124.1, 135.2, 140.4, 143.4, 170.2.

4.11. (±)-, (+)-, and (−)-(*E*)-1-(3-Furyl)-4,8-dimethylnona-3,7-dien-5-yn-1-yl acetate (±)-, (+)-, and (−)-furocaulerpin 1

In a dry 10-mL Schlenk tube, (±)-, (+)-, or (−)-(*E*)-1-(3-furyl)-4-iodopent-3-en-1-yl acetate **10** (60 mg, 0.187 mmol) in DMF (2 mL) was added $PdCl_2(MeCN)_2$ (2.5 mg, 0.009 mmol). The solution was degassed and 1-trimethylstannyl-4-methylpent-3-en-1-yne **3** (68 mg, 0.3 mmol) was added and the reaction mixture immediately turned black. The reaction progress was monitored by GC. After complete conversion, water was added. The aqueous layer was extracted with Et_2O. The organic layers were washed with water, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum–Et_2O, 9/1) giving (±)-furocaulerpin in 99% yield, (−)-furocaulerpin $\{[\alpha]_D^{24} = -14.6$, (*c* 1, $CHCl_3$)} in 90% yield, and (+)-furocaulerpin $\{[\alpha]_D^{24} = +13.8$, (*c* 1, $CHCl_3$)} in 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$) 1.79 (s, 6H), 1.87 (s, 3H), 2.03 (s, 3H), 2.57 (ddd, *J* = 14.7, 7.3, 6.8 Hz, 1H), 2.68 (ddd, *J* = 14.7, 7.3, 6.8 Hz, 1H), 5.33 (s, 1H), 5.69 (br t, *J* = 7.3 Hz, 1H), 5.77 (t, *J* = 6.8 Hz, 1H), 6.38 (br s, 1H), 7.36 (br t, *J* = 1.7 Hz, 1H), 7.40 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 17.8, 21.0, 21.3, 24.9, 34.0, 67.8, 85.2, 94.2, 105.3, 108.9, 121.4, 124.4, 130.2, 140.5, 143.3, 148.2, 170.3; *m*/*z* (70 eV) 272 (M, 0.3), 212 (21), 133 (21), 105 (15), 97 (46), 91 (20), 77 (16), 43 (100), 41 (22), 39 (16).

4.12. (*E*)-1-(3-Furyl)-4-iodopent-3-en-1-one 11

To a stirred solution of (*E*)-1-(3-furyl)-4-iodopent-3-en-1-ol **9** (250 mg, 0.90 mmol) in CH_2Cl_2 (18 mL) at 0 °C was added Dess–Martin periodinane (765 mg, 1.80 mmol). The reaction mixture was stirred under nitrogen at room temperature and followed by TLC. After disappearance of the starting material, the mixture was poured into a separating funnel containing saturated aqueous $Na_2S_2O_3/NaHCO_3$ solution (8 mL, 1/1) and shaken vigorously for 5 min. The aqueous layer was extracted with diethyl ether and the organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum–Et_2O, 6/4) to give (*E*)-1-(3-furyl)-4-iodopent-3-en-1-one **11** in 97% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 2.39 (s, 3H), 3.44 (d, *J* = 7.1 Hz, 2H), 6.39 (br t, *J* = 7.1 Hz, 1H), 6.72 (br s, 1H), 7.42 (br s, 1H), 8.01 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.1, 41.6, 96.8, 108.7, 127.0, 132.1, 144.4, 147.3, 190.4.

4.13. (3-Furyl)pent-3-yn-1-ol 12

To a (3/2/2; 28 mL) mixture of acetic acid, THF, and water was added 1-(3-furyl)-1-(2-tetrahydropyranyloxy)pent-3-yne **6** (0.346 g, 1.48 mmol). The solution was heating to 45 °C and was monitored by TLC. After disappearance of the starting material, the mixture was hydrolyzed with a solution of K_2CO_3 (28 g). The aqueous layer was extracted with Et_2O then the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum–Et_2O, 7/3) giving 1-(3-furyl)pent-3-yn-1-ol **12** in 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$) 1.79 (t, *J* = 2.6 Hz, 3H), 2.24 (d, *J* = 4.5 Hz, 1H), 2.48–2.65 (m, 2H), 4.75 (m, 1H), 6.41 (br dd, *J* = 1.7, 0.8 Hz, 1H), 7.37 (br t, *J* = 1.7 Hz, 1H), 7.42 (br dd, *J* = 1.7, 0.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 3.5, 28.7, 65.7, 75.0, 78.8, 108.6, 127.7, 139.2, 143.2; *m*/*z* (70 eV) 121 ($M^{+\cdot}-C_3H_4$, 10), 97 (100), 95 (11), 69 (61), 53 (14), 51 (18), 41 (95), 39 (53).

4.14. (+)-1-(3-Furyl)pent-3-yn-1-yl acetate (+)-13, and (−)-1-(3-furyl)pent-3-yn-1-ol (−)-12

To a solution of (±)-1-(3-furyl)pent-3-yn-1-ol **12** (1.00 g, 6.7 mmol) in hexane (100 mL) was added vinyl acetate (1.84 mL, 20 mmol) and *Ps. fluorescens* lipase (0.5 g). The mixture was stirred magnetically in a hermetically stoppered one-neck flask at room temperature. The reaction progress was monitored by capillary GC on chiral column. After 26 h and 40% of conversion rate, the reaction was stopped by filtration. Removal of the solvent, followed by silica gel column chromatography (light petroleum–Et_2O, 7/3), yielded 620 mg (57%) of nonreactive alcohol (−)-1-(3-furyl)pent-3-yn-1-ol (−)-**12** (*ee* = 65%, determined by chiral GC) and 457 mg (37%) of (+)-1-(3-furyl)pent-3-yn-1-yl acetate (+)-**13** $\{[\alpha]_D^{24} = +41.4$, (*c* 1, $CHCl_3$), *ee* = 92%}. ^{1}H NMR (300 MHz, $CDCl_3$) 1.74 (t, *J* = 2.6 Hz, 3H), 2.06 (s, 3H), 2.57–2.74 (m, 2H), 5.83 (t, *J* = 6.6 Hz, 1H), 6.42 (m, 1H), 7.36 (br t, *J* = 1.7 Hz, 1H), 7.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 3.5, 21.2, 25.5, 67.1, 74.2, 78.1, 109.0, 124.0, 140.5, 143.1, 170.2; *m*/*z* (70 eV) 192 (M, 0.2), 150 (12), 139 (17), 132 (10), 97 (39), 43 (100), 39 (15).

The remaining alcohol (−)-1-(3-furyl)pent-3-yn-1-ol (−)-**12** (*ee* = 65%) was resubjected to the same conditions using the recovered active enzyme. The reaction progress was monitored by chiral GC. After 100 h, GC analysis showed that one enantiomer was completely consumed. The reaction was stopped by filtration. Removal of the solvent followed by silica gel column chromatography yielded 400 mg (40% overall yield from (±)-1-(3-furyl)pent-3-yn-1-ol **12)** of (−)-1-(3-furyl)pent-3-yn-1-ol (−)-**12** {$[\alpha]_D^{24} = -32.8$, (*c* 1, $CHCl_3$), *ee* > 99%}.

4.15. (−)-(*E*)-4-Tributylstannyl-1-(3-furyl)pent-3-en-1-ol (−)-14

CuCN (238 mg, 2.7 mmol) was suspended in freshly distilled THF (8 mL), cooled at −78 °C, and treated with *n*-BuLi in hexane (2.5 M, 2.13 mL, 5.3 mmol). The mixture was allowed to warm slightly to yield a colorless, homogenous solution that was recooled to −78 °C where Bu_3SnH (1.41 mL, 5.3 mmol) was added dropwise via syringe. Stirring was continued and, over ca. 10 min, the solution yellowed and H_2 gas was liberated. Methanol (3 mL, 73 mmol) was then added, and the mixture was allowed to warm to −40 °C and (−)-1-(3-furyl)pent-3-yn-1-ol (−)-**12** (100 mg, 0.66 mmol) was added at −78 °C. The reaction was allowed to warm to −10 °C and stirred overnight at −10 °C. The mixture was quenched with a saturated aqueous NH_4Cl solution, filtered, and aqueous layer was extracted with Et_2O. The organic layers were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (light petroleum–Et_2O, 7/3) to give 24% of (−)-1-(3-furyl)pent-3-yn-1-ol (−)-**12** and 43% of (−)-(*E*)-4-tributylstannyl-1-(3-furyl)pent-3-en-1-ol (−)-**14** {$[\alpha]_D^{24} = -11.7$, (*c* 1, $CHCl_3$)}. ^{1}H NMR (200 MHz, $CDCl_3$) 0.81–0.90 (m, 15H), 1.19–1.58 (m, 12H), 1.84 (br s, $^3J_{Sn-H} = 45$ Hz, 3H), 1.86 (br s, 1H), 2.46–2.72 (m, 2H), 4.69 (m, 1H), 5.52 (br t, $J = 6.9$ Hz, $^3J_{Sn-H} = 69$ Hz, 1H), 6.40 (br t, $J = 1.4$ Hz, 1H), 7.35 (br s, 1H), 7.36 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 9.2 ($^1J_{Sn-C} = 330$ Hz, 3C), 13.8 (3C), 19.5, 27.4 ($^3J_{Sn-C} = 55$ Hz, 3C), 29.2 ($^2J_{Sn-C} = 20$ Hz, 3C), 36.8, 66.8, 108.7, 128.8, 135.2, 139.1, 143.0, 143.3; *m*/*z* (70 eV) organotin fragments: 385 ($M^{+\cdot}-57$, 85), 367 (14), 303 (10), 251 (100), 235 (10), 195 (18), 179 (27), 177 (40), 135 (43), 121 (27), 120 (14), MS (70 eV) organic fragments: 105 (28), 97 (28), 95 (14), 79 (19), 77 (12), 69 (22), 55 (14), 43 (12), 41 (53), 39 (25).

4.16. (+)-(*E*)-4-Tributylstannyl-1-(3-furyl)pent-3-en-1-ol (−)-14

CuCN (780 mg, 8.74 mmol) was suspended in freshly distilled THF (12 mL), cooled at −78 °C, and treated with *n*-BuLi in hexane (2.5 M, 7 mL, 17.4 mmol). The mixture was allowed to warm slightly to yield a colorless, homogenous solution, which was recooled to −78 °C where Bu_3SnH (4.63 mL, 17.4 mmol) was added dropwise via syringe. Stirring was continued and, over ca. 10 min, the solution yellowed and H_2 gas was liberated. (+)-1-(3-Furyl)pent-3-yn-1-yl acetate (+)-**13** (0.280 g, 1.47 mmol) was added at −78 °C and stirred overnight at −78 °C. The mixture was quenched with a saturated aqueous NH_4Cl solution, filtered, and aqueous layer was extracted with Et_2O. The organic layers were washed with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (light petroleum–Et_2O, 7/3) to give (+)-(*E*)-4-tributylstannyl-1-(3-furyl)pent-3-en-1-ol (+)-**14** {$[\alpha]_D^{24} = +10.0$, (*c* 1, $CHCl_3$)} in 58% yield. Sixteen percent of (+)-1-(3-furyl)pent-3-yn-1-ol (+)-**12** was also recovered at end of reaction.

4.17. (+) and (−)-(*E*)-1-(3-Furyl)-4-iodopent-3-en-1-ol 9

To a solution of (+) or (−)-(*E*)-4-tributylstannyl-1-(3-furyl)pent-3-en-1-ol **14** (353 mg, 0.83 mmol) in Et_2O (5 mL), was added dropwise iodine (0.25 g, 1 mmol) in 5 mL of Et_2O at 0 °C. The mixture was stirred 2 h at room temperature and quenched with 1 M aqueous KF solution (3 mL) and acetone (3 mL). After stirring 2 h the solution was filtered through a pad of Celite. The aqueous layer was extracted with Et_2O. The organic layers were washed with a saturated aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (light petroleum–Et_2O, 7/3) giving (+)-(*E*)-1-(3-furyl)-4-iodopent-3-en-1-ol **(+)-9** {$[\alpha]_D^{24} = +12.3$, (*c* 1, $CHCl_3$)} in 99% yield or (−)-(*E*)-1-(3-furyl)-4-iodopent-3-en-1-ol **(−)-9** {$[\alpha]_D^{24} = -13.0$, (*c* 1, $CHCl_3$)} in 96% yield.

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References and notes

1. Paul, V. J.; Littler, M. M.; Littler, D. S.; Fenical, W. *J. Chem. Ecol.* **1987**, *13*, 1171–1185.
2. Amico, V.; Oriente, G.; Piatelli, M.; Tringali, C. *Tetrahedron Lett.* **1978**, 3593–3596.
3. Lemée, R.; Pesando, D.; Durand-Clement, M.; Dubreuil, A.; Meinesz, A.; Guerriero, A.; Pietra, F. *J. Appl. Phycol.* **1993**, *5*, 485–493.
4. Fischer, J. L.; Lemee, R.; Formento, P.; Caldani, C.; Moll, J. L.; Pesando, D.; Meinesz, A.; Grelier, P.; Pietra, F.; Guerriero, A.; Milano, G. *Anticancer Res.* **1995**, *15*, 2155–2160.
5. Barbier, P.; Guise, S.; Huitorel, P.; Amade, P.; Pesando, D.; Briand, C.; Peyrot, V. *Life Sci.* **2001**, *70*, 415–429.
6. Guerriero, A.; Dependori, D.; D'Ambrosio, M.; Pietra, F. *Helv. Chim. Acta* **1995**, *78*, 1755–1762.
7. de Napoli, L.; Fattorusso, E.; Magno, S.; Mayol, L. *Experentia* **1981**, *37*, 1132.
8. Commeiras, L.; Santelli, M.; Parrain, J. L. *Synlett* **2002**, *5*, 743–746.

9. Commeiras, L.; Santelli, M.; Parrain, J. L. *Org. Lett.* **2001**, *3*, 1713–1715.
10. (a) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745–1747; (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *14*, 3769–3770; (c) Hollingworth, G. J.; Richecoeur, A. M. E.; Sweeney, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2833–2836.
11. Flahaut, J.; Miginiac, P. *Helv. Chim. Acta* **1978**, *61*, 2275–2285.
12. (a) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065–2068; (b) Beaudet, I.; Parrain, J.-L.; Quintard, J.-P. *Tetrahedron Lett.* **1991**, *32*, 6333–6336; (c) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768–7780.
13. (a) Baekelmans, P.; Gielen, M.; Malfroid, P.; Nasielski, J. *Bull. Soc. Chim. Belg.* **1968**, *77*, 85–88; (b) Fargeas, V.; Le Ménez, P.; Berque, I.; Ardisson, J.; Pancrazi, A. *Tetrahedron* **1996**, *52*, 6613–6634.
14. Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4011–4013.
15. (a) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340–348; (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524; (c) Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.-L. *Synlett* **1999**, 141–143.
16. Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett.* **1994**, *35*, 8323–8324.
17. Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703–1707.
18. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
19. Capillary GC monitored the progress of the reaction. The enantiomers of both alcohol and the acetate were separable.
20. (a) Burgess, K.; Jennings, L. D. *J. Am. Chem. Soc.* **1990**, *112*, 7434–7436; (b) Wong, C. H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Oxford: Pergamon, 1984.