Rapid Synthesis of Taxifolione and Taxifolial D, Two Metabolites from the Marine Alga *Caulerpa taxifolia*

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Abstract: The synthesis of two natural products - Taxifolione and Taxifolial D – isolated from the marine alga *Caulerpa taxifolia* invading the Mediterranean Sea was performed. Coupling reactions allowed for a rapid synthesis. The surprising *Z* configuration of Taxifolial D was confirmed after synthesis and comparison of each synthetic stereoisomer.

Keywords: Terpenoids, enynes, cross-coupling, antitumor agents.

INTRODUCTION

Tropical algae usually living in herbivore-rich tropical waters have set up various defense systems against grazing fishes and invertebrates. One of the most efficient systems is based on the release of repulsive and toxic metabolites [1]. A tropical green seaweed, *Caulerpa taxifolia*, was accidentally introduced in the Mediterranean Sea more than a decade ago [2], and after adaptation [3], this alga started spreading, now covering thousands of sea floor square kilometers, and leading to modifications in the Mediterranean ecosystem with a notable decrease in the biodiversity [4]. Due to its origin, this alga is releasing a cocktail of toxic and repellent metabolites and this has been proposed to explain its rapid proliferation [5]. The major metabolite Caulerpenyne (Fig. **1**) exhibits several biological activities [3, 6], among which are antiproliferative activity and modification of the cell microtubule network [7]. The activities of the other metabolites so far remain unknown.

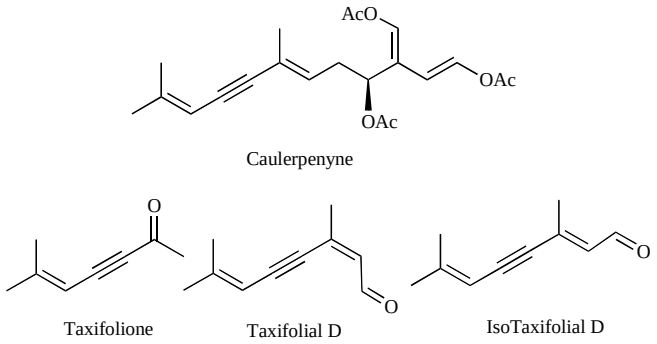


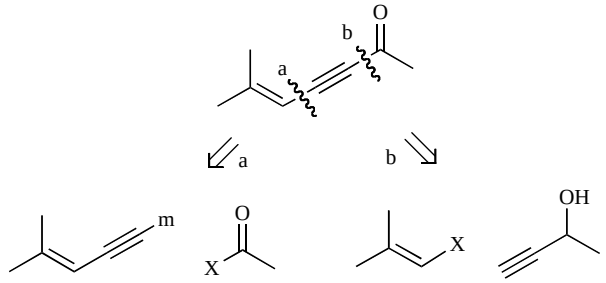
Fig. (1).

In order to learn more on the bioactivity of each metabolites, we embarked on the synthesis of each of them [8], and we reported here the first total synthesis of two of them, i. e. Taxifolione and Taxifolial D (Fig. **1**). These natural products are probably oxidation products derived from the other metabolites or from a common biogenic precursor. Surprisingly, Taxifolial D was reported as a *Z* stereoisomer while all other related metabolites exhibit the *E* stereochemistry for the same double bond (Fig. **1**). This led us to synthesize both isomers in order to check its stereochemistry.

RESULTS AND DISCUSSION

Synthesis of Taxifolione

A rapid and convergent access to Taxifolione can be envisaged through either acylation of 4-methylpent-3-en-1-yne or coupling reaction [9] between 1-bromo-2-methylpropene and but-1-yn-3-ol, both being commercially available, (Scheme **1**, routes ***a*** and ***b*** respectively). Both routes were explored to find the more appropriate on large scale.



Scheme 1.

Indeed, based on the Holmes procedure [10], we were able to exchange the silyl group of 1-trimethylsilyl-4-methylpent-3-en-1-yne **1** by lithium (Scheme **2**). However, the so formed lithium acetylide could not be trapped by conventionnal acetylating agents and only N-methoxy-N-methylacetamide [11] proved to be effective enough, but at room temperature. The starting enyne **1** was obtained from the commercially available 1-bromo-3-trimethylsilylprop-2-yne by phosphonylation and Wadsworth-Emmons condensation with acetone [12].

Alternatively, but-1-yn-3-ol was coupled with 1-bromo-2-methylpropene in the presence of catalytic amounts of bis(triphenylphosphine)palladium dichloride and copper io-

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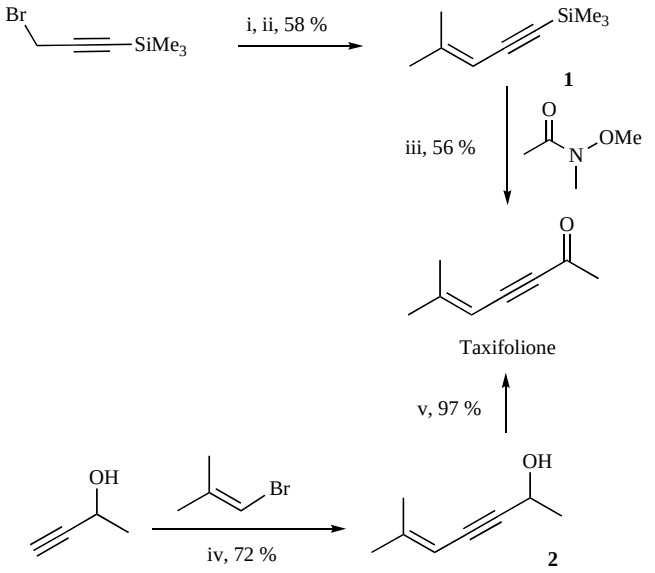
dide in Sonogashira conditions [13] (Scheme **2**). The enynol **2** was isolated in good yields. Although propargylic, this alcohol was best oxidized with pyridinium dichromate in dichloromethane.

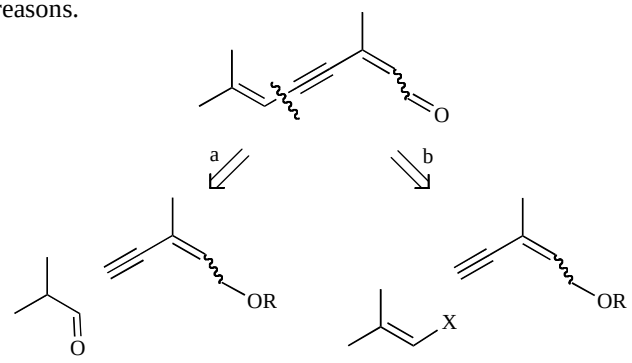


Scheme 2. i) $HP(O)(OEt)_2$, THF, LiHMDS, -78°C; ii) LiHMDS, THF, then Me_2CO, -78°C; iii) MeLi.LiBr, THF, rt; iv) $PdCl_2(PPh_3)_2$ 5 mol%, CuI 10 mol%, $HNEt_2$; v) PDC, CH_2Cl_2, rt.

The enynone so obtained proved identical with the natural compound. Taxifolione was thus obtained in either 2 steps with an excellent overall yield (69%) or in 3 steps but less effectively (31% overall yield). The coupling route was thus the best and more scalable. However, the acetylation route allows introducing labels at various locations into the structure for biological studies.

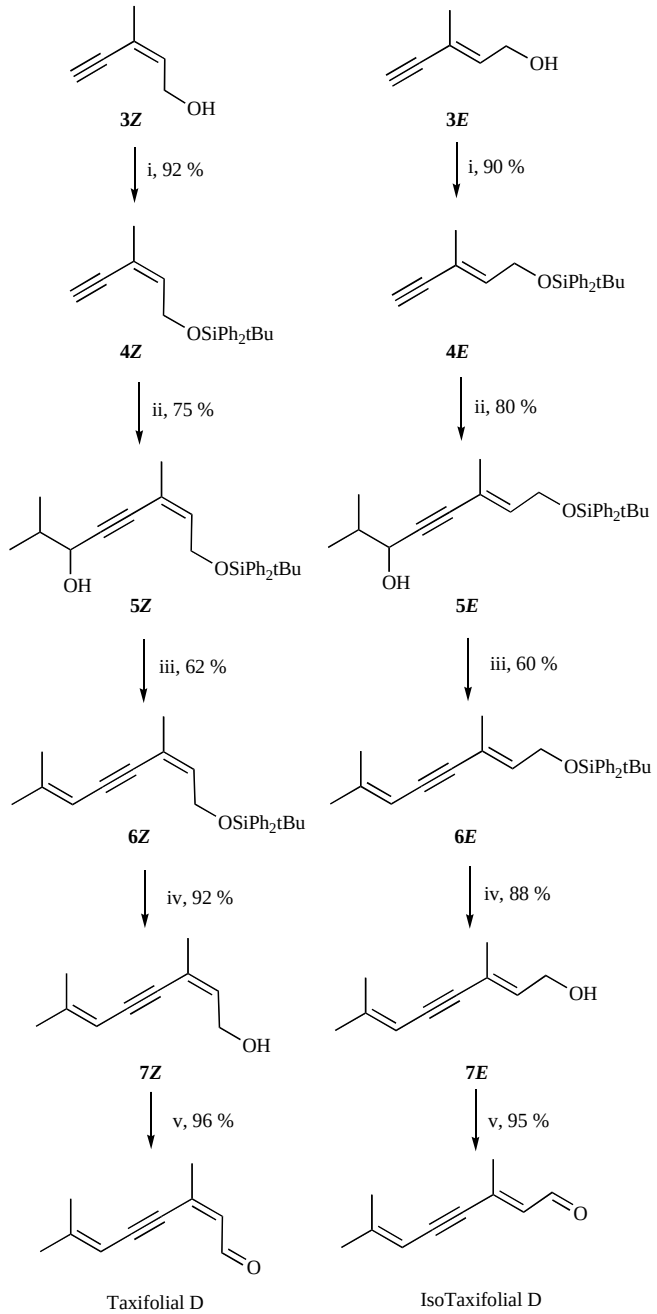
Synthesis of Taxifolial D and Isotaxifolial D

The synthesis of Taxifolial D and its stereoisomer Isotaxifolial D can also be envisaged through either alkylation (Scheme **3**, route a) or coupling reactions (route b) [9], and again, both routes were explored for the same reasons.



Scheme 3.

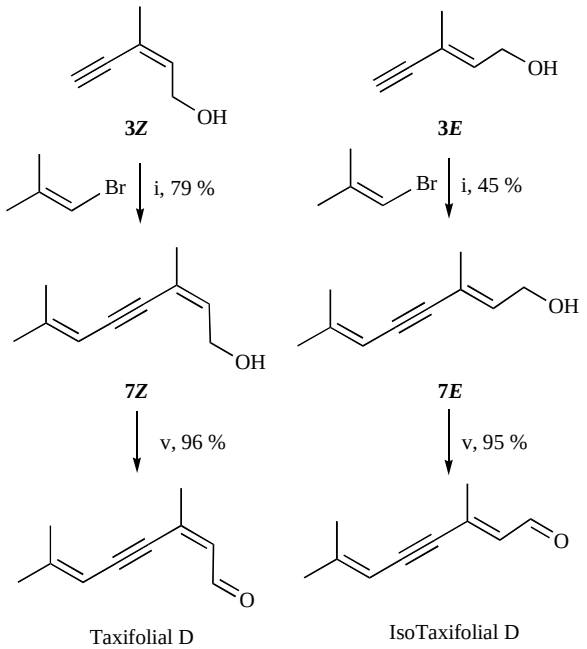
The alkylation route was based on the addition of the anion derived from *Z* or *E* 3-methylpent-2-en-3-yn-1-ol, **3*Z*** or **3*E*** respectively [14, 14c], to isobutyraldehyde, followed by elimination (Scheme **4**). Each alcohol **3*Z*** or **3*E*** was first protected as *tert*-butyldiphenylsilyl ether. These ethers **4*Z*** or **4*E*** were then deprotonated with *n*-BuLi in THF at -78°C, and the corresponding acetylides were trapped by isobutyraldehyde, giving the corresponding alcohols **5*Z*** or **5*E*** in good yields. The elimination step proved to be far from obvious and eventually, we found that treatment with triflic anhydride in the presence of pyridine at low but controlled temperature gave the expected dienynes **6*Z*** or **6*E*** with reasonable yields. Deprotection by tetrabutylammonium fluoride treatment followed by manganese dioxide oxidation provided Taxifolial D and Isotaxifolial D. These compounds were thus obtained in 5 steps with respectively 38 and 36 % overall yields.



Scheme 4. i) $tBuPh_2SiCl$, imidazole, CH_2Cl_2; ii) *n*-BuLi, THF-78°C, then *i*PrCHO; iii) Tf_2O, pyridine, CH_2Cl_2, -30°C; iv) nBu_4NF, CH_2Cl_2, rt; v) MnO_2, CH_2Cl_2, rt.

Pd-catalyzed coupling reactions usually are tolerant to hydroxyl groups. We thus performed these reactions with 1-bromo-2-methylpropene and **3*Z*** or **3*E*** without protecting group (Scheme **5**). Under the original Sonogashira conditions [13], the expected dienynols **7*Z*** or **7*E*** were indeed stereospecificaly obtained. However, the yield was very good for the *Z* isomer (79%) but surprisingly low for the *E* isomer (45%). These dienynols were then independently oxidized with manganese dioxide providing Taxifolial D and Isotaxifolial D in respectively 76 % and 43 % yield over 2 steps.

With no protection-deprotection steps, the coupling route proved to be faster and more efficient than the alkylation route, especially for the *Z* isomer, the natural one (76 vs 38 % overall yield).



Scheme 5. i) $PdCl_2(PPh_3)_2$ 5 mol%, CuI 10 mol%, $HNEt_2$; ii) MnO_2, CH_2Cl_2, rt.

Comparison of ^1H and ^{13}C NMR spectra of synthetic Taxifolial D and Isotaxifolial D revealed some key differences.

For the synthetic *Z* isomer, NMR spectra proved to be identical to those described by Pietra and *al* [5] for the natural Taxifolial D. Surprisingly, the ^1H NMR spectra of the synthetic *E* isomer were very similar to the *Z* isomer. Only the signals corresponding to the vinylic H_2 proton and the methyl group β to the carbonyl group were significantly shifted (from 6.09 ppm in the *Z* to 6.16 ppm in the *E* isomer, and from 2.12 ppm in the *Z* to 2.31 ppm in the *E* isomer, respectively). In contrast, the ^{13}C NMR spectra were quite different with the signals of the enynal system shifted. The most significant shift was observed for the same methyl group (from 25.1 ppm for the *Z* to 18.6 ppm for the *E* isomer). NOE experiments revealed a clear relation between this methyl group and the vinylic H_2 proton for the *Z* isomer and between this methyl group and the aldehyde proton for the *E* isomer. All these data confirmed the surprising stereochemistry of the natural Taxifolial D.

CONCLUSION

In conclusion, two metabolites isolated from the alga *Caulerpa taxifolia* were synthesized with good overall yields and various routes were evaluated. By synthesizing the *Z* and *E* isomers of Taxifolial D, we were able to confirm the stereochemistry of the natural compound. We are currently evaluating the bioactivity of these compounds.

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded on Bruker AC-300 spectrometers. For ^1H NMR, TMS was used as internal standard, for ^{13}C NMR, solvent peak at 77.00 ($CDCl_3$) were used. Column chromatography was performed with Merck silica gel (0.040–0.063 mesh). TLC used MERCK Art 5554 DC Alufolien Kieselgel 60 PF254 with detection by UV-absorption (254 nm) and appropriate staining. All reactions involving air and moisture sensitive materials were conducted under an atmosphere of dry argon. All solvents were freshly distilled by standard procedures.

Taxifolione Synthesis Through Cross-Coupling

6-Methylhept-5-en-3-yn-2-ol (2)

To a solution of 1-bromo-2-methylpropene (1.20 g, 8.89 mmol, 1.1 eq.) in anhydrous and degassed Et_2NH (10 mL) were successively added at 0°C, $PdCl_2(PPh_3)_2$ (0.104 g 0.148 mmol, 0.02 eq.), CuI (0.141 g, 0.740 mmol, 0.10 eq.) and a solution of butyn-3-ol (0.571 g, 8.15 mmol, 1 eq.) in anhydrous and degassed Et_2NH (20 mL). The initially slightly yellow solution gradually darkened. After disappearance of the starting material as judged from TLC (3 to 4 h), a saturated aqueous solution of ammonium chloride was added at 0°C. After extraction with diethyl ether, the combined organic layers were washed with water, dried over Na_2SO_4, filtrated and concentrated. The orange oil was purified by flash-chromatography (cyclohexane/EtOAc: 4/1) to give pure product **2** (0.725 g, 72%).

^1H-NMR (300 MHz) $CDCl_3$: 1.47 (d, 3H, *J* = 6.6 Hz); 1.79 (br d, 3H, *J* = 1.4 Hz); 1.87 (br s, 3H); 2.01 (s, 1H); 4.66 (qd, 1H, *J* = 1.4, 6.5 Hz); 5.23-5.26 (m, 1H). ^{13}C-NMR (75 MHz) $CDCl_3$: 20.9 (CH_3); 24.6 (CH_3); 24.8 (CH_3); 58.9 (CH); 82.0 (Cq); 93.1 (Cq); 104.5 (CH); 149.1 (Cq). MS (EI): *m/z (%)* = 124.1 ($[M]^+$, 50); 109.1 (100); 79.1 (35). IR (NaCl; cm^{-1}): 1055; 1215; 1633; 2206; 2922; 2933; 2991; 3015; 3388.

Taxifolione (= 6-methylhept-5-en-3-yn-2-one)

To a solution of enynol **2** (0.500 g, 4.03 mmol) in anhydrous CH_2Cl_2 (20 mL) was added anhydrous PDC (3.18 g, 8.45 mmol, 2.1 eq.). The mixture was stirred overnight, filtered through a pad of Celite® and rinsed with EtOAc. After evaporation, the yellow-brown oil was purified by flash-chromatography (cyclohexane/EtOAc: 7/3) providing pure Taxifolione (0.477 g, 97%) as slightly yellow oil.

^1H-NMR (300 MHz) $CDCl_3$: 1.90 (br d, 3H, *J* = 1.5 Hz); 1.99 (br s, 3H); 2.36 (s, 3H); 5.39-5.42 (m, 1H). ^{13}C-NMR (75 MHz) $CDCl_3$: 21.8 (CH_3); 25.5 (CH_3); 32.7 (CH_3); 89.7 (Cq); 91.6 (Cq); 103.5 (CH); 158.2 (Cq); 184.7 (Cq). MS

(EI): *m/z (%)* = 122.1 ([M]$^+$, 51); 107.1 (100); 77.1 (43). IR (NaCl; cm^{-1}): 755; 1249; 1360; 1618; 1654; 2913-3016.

1-Trimethylsilyl-4-methylpent-3-en-1-yne (1)

A solution of LiHMDS (13.55 mL, 1.06 M, 14.36 mmol, 1.1 eq.) in THF was slowly added to a solution of diethyl (3-trimethylsilylprop-2-ynyl)phosphonate (3.24 g, 13.05 mmol) in THF (25 mL) at –78 °C. The resulting red solution was stirred for 30 min. at -78°C. At this temperature, acetone (1.44 mL, 9.60 mmol, 1.5 eq.) was then added. The resulting yellow solution was stirred at -78 °C for a further 30 min. and then at room temperature for 18 h. The mixture was then diluted with hexane (100 mL) and water (50 mL). The aqueous layer was decanted and extracted twice with hexane (50 mL). The organic layer was washed twice with brine (100 mL). The combined organic layers were then dried over $MgSO_4$, filtered and evaporated in an ice-bath. The residue was purified by flash-chromatography on silica gel (pentane) and the solvent was evaporated in an ice bath to give **1** as a colourless and volatile liquid (1.43 g, 72%).

^{1}H-NMR (300 MHz) $CDCl_3$: 0.09 (s, 9H); 1.61 (br d, 3H, *J* = 1.9 Hz); 1.72 (br d, 3H, *J* = 1.3 Hz); 5.08-5.11 (m, 1H). ^{13}C-NMR (75 MHz) $CDCl_3$: 0.1 (CH_3); 21.1 (CH_3); 24.7 (CH_3); 95.9 (Cq); 103.4 (Cq); 105.3 (CH); 150.2 (Cq).

Taxifolione Via Weinreb Amide Coupling

To a solution of 1-trimethylsilyl-4-methylpent-3-enyne **1** (105 mg, 0.69 mmol, 1 eq.) in anhydrous THF (4.5 mL) was added at room temperature MeLi-LiBr (0.51 mL, 1.5 M in diethylether; 0.76 mmol, 1.1 eq.). The resulting yellow-orange mixture was stirred 3h at this temperature. At -78°C, a solution of *N*-methoxy-N-methylacetamide (142 mg, 1.38 mmol, 2 eq.) in THF (5 mL) was added. The mixture was stirred for 2h at -78°C and 2h at room temperature. The reaction was then quenched by addition of aqueous saturated NH_4Cl solution. The organic layer was extracted with diethyl ether, washed twice with a saturated solution of NH_4Cl and once with water. The organic layer was dried over $MgSO_4$, filtrated and concentrated to give the slightly yellow liquid Taxifolione (47 mg, 56%).

Taxifolial and Isotaxifolial D Synthesis Through Alkylation

(2Z)-1-tert-Butyldiphenylsilyloxy-3-methylpent-2-en-4-yne (4Z)

To a solution of freshly distilled (*2Z*)-3-methylpent-2-en-4-ynol **3*Z*** (1.83 g, 19.4 mmol) in DMF (15 mL) were added at room temperature *tert*-butyldiphenylchlorosilane (6.5 mL, 25.0 mmol; 1.3 eq.) and imidazole (3.39 g, 49.8 mmol; 2.6 eq.). After overnight stirring, water (20 mL) was added and the resulting mixture was stirred for 30 min. The aqueous layer was extracted with dichloromethane. The organic layers were then combined, dried over Na_2SO_4 and concentrated. A flash-chromatography (cyclohexane/EtOAc: 97/3) gave pure product **4*Z*** (5.97 g, 92%).

^{1}H-NMR (300 MHz) $CDCl_3$: 1.05 (s, 9H); 1.62 (dt, 3H, *J* = 1.1, 2.5 Hz); 2.80 (s, 1H); 4.27 (dq, 2H, *J* = 1.0, 6.2 Hz); 6.12 (tq, 1H, *J* = 1.5, 6.2 Hz); 7.36-7.71 (m, 10H). ^{13}C-NMR (75 MHz) $CDCl_3$: 17.4 (CH_3); 19.2 (Cq); 26.8 (CH_3); 60.7 (CH_2); 74.6 (Cq); 86.2 (CH); 117.8 (Cq); 127.7 (CH); 129.7 (CH); 133.5 (Cq); 135.6 (CH); 138.2 (CH). IR (NaCl; cm^{-1}): 1057; 1115; 1427; 1589-1620; 2188; 3073.

(2E)-1-tert-Butyldiphenylsilyloxy-3-methylpent-2-en-4-yne (4E)

To a solution of freshly distilled (*2E*)-3-methylpent-2-en-4-ynol **3*E*** (1.85 g, 19.2 mmol) in DMF (20 mL) were added at room temperature *tert*-butyldiphenylchlorosilane (6.5 mL, 25.0 mmol; 1.3 eq.) and imidazole (3.39 g, 49.8 mmol; 2.6 eq.). After overnight stirring, 20 mL of H_2O were added and the resulting mixture was stirred for 30 min. The aqueous layer was extracted with dichloromethane. The combined organic layers were then dried over Na_2SO_4, filtered and concentrated. Flash chromatography (cyclohexane/EtOAc: 97/3) gave pure product **4*E*** (5.78 g, 90%).

^{1}H-NMR (300 MHz) $CDCl_3$: 1.14 (s, 9H); 1.91 (q, 3H, *J* = 1.4 Hz); 3.05 (s, 1H); 4.52 (dq, 2H, *J* = 1.4, 6.3 Hz); 6.00 (tq, 1H, *J* = 1.5, 6.3 Hz); 7.41-7.80 (m; 10H). ^{13}C-NMR (75 MHz) $CDCl_3$: 19.3 (Cq); 23.0 (CH_3); 27.0 (CH_3); 63.0 (CH_2); 82.0 (CH and Cq); 117.9 (Cq); 127.8 (CH); 129.7 (CH); 133.8 (Cq); 135.7 (CH); 136.4 (CH). IR (NaCl; cm^{-1}): 1056; 1112; 1427; 1589-1620; 1822-1990; 2188; 2857-2959; 3071.

(2Z)-1-tert-butyldiphenyl-silyloxy-3,7-dimethylocta-2-en-4-yn-6-ol (5Z)

To a solution of (*2Z*)-1-*tert*-butyldiphenylsilyloxy-3-methylpent-2-en-3-yn-1-ol **4*Z*** (1.00 g, 2.99 mmol) in anhydrous THF (20 mL) at -78 °C under argon were added *n*-BuLi (2.40 mL, 1.48 M in hexane; 3.55 mmol, 1.2 eq.). After stirring for 1h at -78 °C, isobutyraldehyde (0.33 mL, 3.62 mmol, 1.2 eq.) was added. The yellow solution was further stirred for a further 2 h at -78°C. The reaction was then quenched by an aqueous saturated NH_4Cl solution. The aqueous layer was extracted with dichloromethane. The combined organic layers were then dried over Na_2SO_4, filtered and concentrated. Flash-chromatography (cyclohexane/EtOAc: 9/1) provided pure product **5*Z*** (0.915 g, 75%) as yellowish viscous oil.

^{1}H-NMR (300 MHz) $CDCl_3$: 0.87 (d, 3H, *J* = 6.8 Hz); 0.87 (d, 3H, *J* = 6.7 Hz); 1.05 (s, 9H); 1.52 (s, 1H); 1.70-1.81 (m, 1H); 1.84 (br d, 3H, *J* = 1.4 Hz); 4.16 (d, 1H, *J* = 5.5 Hz); 4.40 (dq, 2H, *J* = 1.3, 6.3 Hz); 5.87 (tq, 1H, *J* = 1.5, 6.3 Hz); 7.35-7.71 (m, 10H). ^{13}C-NMR (75 MHz) $CDCl_3$: 17.4 (CH_3); 18.1 (CH_3); 19.2 (Cq); 23.0 (CH_3); 26.9 (CH_3); 34.5 (CH); 63.2 (CH_2); 68.3 (CH); 83.9 (Cq); 93.6 (Cq); 118.4 (Cq); 127.7 (CH); 129.6 (CH); 133.8 (Cq); 135.6 (CH); 136.7 (CH). MS (ESI): m/z = 429.22 [M+Na]$^+$. IR (NaCl; cm^{-1}): 705, 774, 1064, 1110, 1381, 1427, 1470, 3074, 3047, 3407.

(2E)-1-tert-butyldiphenyl-silyloxy-3,7-dimethylocta-2-en-4-yn-6-ol (5E)

To a solution of (*2E*)-1-*tert*-butyldiphenylsilyloxy-3-methylpent-2-en-3-yn-1-ol **4*E*** (1.00 g, 2.99 mmol) in anhydrous THF (20 mL) at -78 °C under argon, was added n-BuLi (2.40 mL, 1.48 M in hexane, 3.55 mmol, 1.2 eq.). After stirring for 1h at -78 °C, isobutyraldehyde (0.33 mL, 3.62 mmol, 1.2 eq.) was added. The yellow solution was stirred for a further 2 h at -78°C. The reaction was then quenched by an aqueous saturated NH_4Cl solution. After decantation,

the aqueous layer was extracted with dichloromethane. The combined organic layers were then dried over Na_2SO, filtered and evaporated. Flash-chromatography (cyclohexane/EtOAc: 9/1) provided pure product ***5E*** (0.969 g, 80%)as yellowish viscous oil.

^{1}H-NMR (300 MHz) $CDCl_3$: 1.01 (d, 3H, *J* = 6.7 Hz); 1.03 (d, 3H, *J* = 6.7 Hz); 1.05 (s, 9H); 1.62 (dt, 3H, *J* = 1.0, 1.4 Hz); 1.76 (d, 1H, *J* = 5.6 Hz); 1.90 (m, 1H); 4.27 (dq, 2H, *J* = 1.1, 6.3 Hz); 4.29 (d, 1H, *J* = 5.4 Hz); 6.02 (tq, 1H, *J* = 1.4, 6.2 Hz); 7.37-7.72 (m, 10H). ^{13}C-NMR (75 MHz) $CDCl_3$: 17.6 (CH_3); 17.8 (CH_3); 18.2 (CH_3); 19.2 (Cq); 26.8 (CH_3); 34.7 (CH); 60.8 (CH_2); 68.4 (CH); 86.4 (Cq); 88,1 (Cq); 118.4 (Cq); 127.8 (CH); 129.7 (CH); 133.6 (Cq); 135.6 (CH); 136.7 (CH). MS (ESI): m/z = 429.22 $[M+Na]^+$. IR (NaCl; cm^{-1}): 705, 775, 1064, 1110, 1381, 1427, 1470, 1050, 3407.

(2Z)-1-tert-butyldiphenylsilyloxy-3,7-dimethylocta-2,6-dien-4-yne (6Z)

At -30°C in CH_2Cl_2 (5 mL) were successively added pyridine (35 µL, 0.434 mmol, 1.05 eq.) and triflic anhydride (75 µL, 0.445 mmol, 1.07 eq.). The resulting yellow solution containing a white precipitate was stirred over 30 min. A solution of (*2Z*)-1-*tert*-butyl-diphenylsilyloxy-3,7-dimethyl-octa-2-en-4-yn-6-ol **5*Z*** (169 mg, 0.416 mmol) in CH_2Cl_2 (5 mL) was added. When the solution began to turn brown (5 min.), pyridine (340 µL, 4.21 mmol, 10 eq.) were added. The solution was further stirred for a further 3h at -30°C. The reaction was then hydrolyzed by addition of water. The aqueous layer was extracted with dichloromethane. The combined organic layers were then dried over Na_2SO_4, filtrated and evaporated. A flash-chromatography (cyclohexane/EtOAc: 9/1) gave the product **6*Z*** (101 mg, 62%).

^{1}H-NMR (300 MHz) $CDCl_3$: 1.07 (s, 9H); 1.72 (br s, 3H); 1.79 (br d, 3H, *J* = 1.5 Hz); 1.88 (br d; 3H; *J* = 1.4 Hz); 4.46 (dq, 2H, *J* = 1.3, 6.3 Hz); 5.30-5.32 (m, 1H); 5.81 (tq; 1H; *J* = 1.5, 6.2 Hz); 7.35-7.72 (m; 10H). ^{13}C-NMR (75 MHz) $CDCl_3$: 19.3 (Cq); 20.9 (CH_3); 23.2 (CH_3); 24.9 (CH_3); 26.9 (CH_3) 63.3 (CH_2); 90.0 (Cq); 92.5 (Cq); 105.4 (CH); 119.3 (Cq); 127.6 (CH); 129.5 (CH) 133.9 (Cq); 135.2 (CH); 135.6 (CH); 148.4 (Cq). MS (CI/Isobutane): *m/z (%)* = 389.2 ($[M+H]^+$,18); 331.1 (65); 311 (21); 199.1 (56); 133.2 (100). IR (NaCl; cm^{-1}): 1056; 1112; 1427; 1589-1620; 1822-1990; 2188; 2857-2959; 3071.

(2E)-1-tert-butyldiphenylsilyloxy-3,7-dimethylocta-2,6-dien-4-yne (6E)

At -30°C in CH_2Cl_2 (5 mL) were successively added pyridine (35 µL, 0.434 mmol, 1.05 eq.) and triflic anhydride (75 µL, 0.445 mmol, 1.07 eq.). The resulting yellow solution containing a white precipitate was stirred for 30 min. A solution of (*2E*)-1-*tert*-butyldiphenylsilyloxy-3,7-dimethylocta-2-en-4-yn-6-ol **5*E*** (169 mg, 0.416 mmol) in CH_2Cl_2 (5 mL) was then added. When the solution began to turn brown (5 min.), pyridine (340 µL, 4.37 mmol, 10 eq.) were added. The solution was still stirred for a further 3h at –30 °C. The reaction was then hydrolyzed by addition of water. The aqueous layer was extracted with dichloromethane. The combined organic layers were then dried over Na_2SO_4, filtrated and evaporated. A flash-chromatography (cyclohexane/EtOAc: 9/1) gave the product **6*E*** (98 mg, 60%).

^{1}H-NMR (300 MHz) $CDCl_3$: 1.06 (s, 9H); 1.65 (br d, 3H, *J* = 1.3 Hz); 1.83 (br d, 3H, *J* = 1.6 Hz); 1.91 (br s, 3H); 4.27 (dq, 2H, *J* = 1.0, 6.3 Hz); 5.36-5.38 (m, 1H); 5.99 (tq, 1H, *J* = 1.5, 6.4 Hz); 7.36-7.71 (m; 10H). ^{13}C-NMR (75 MHz) $CDCl_3$: 17.8 (CH_3); 19.2 (Cq); 21.0 (CH_3); 24.9 (CH_3); 26.8 (CH_3); 60.9 (CH_2); 85.3 (Cq); 94.1 (Cq); 105.3 (CH); 119.5 (Cq); 127.7 (CH), 129.6 (CH); 133.6 (Cq); 135.1 (CH); 135.6 (CH); 148 (Cq). MS (CI/Isobutane): *m/z (%)* = 389.2 ($[M+H]^+$,19); 331.1 (65); 311 (21); 199.1 (56); 133.2 (100). IR (NaCl; cm^{-1}): 1057; 1115; 1427; 1589-1620; 2188; 3073.

(2Z)-3,7-dimethylocta-2,6-dien-4-ynol (7Z)

In a solution of (*2Z*)-1-tert-butyldiphenylsilyloxy-3,7-dimethylocta-2,6-dien-4-yne **6*Z*** (0.210 g, 0.54 mmol) in anhydrous THF (5 mL) was added tetrabutylammonium fluoride (0.65 mL, 1M in THF, 0.65 mmol, 1.2 eq.). The mixture was stirred 3h and was hydrolyzed by an aqueous saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The desired product **7*Z*** (0.075 g, 92%) was obtained after flash chromatography (cyclohexane/EtOAc: 4/1) as a yellowish oil.

(2E)-3,7-dimethylocta-2,6-dien-4-ynol (7E)

In a solution of (*2E*)-1-tert-butyldiphenylsilyloxy-3,7-dimethylocta-2,6-dien-4-yne **6*E*** (0.210 g, 0.54 mmol) in anhydrous THF (5 mL) was added tetrabutylammonium fluoride (0.65 mL, 1M in THF, 0.65 mmol, 1.2 eq.). The mixture was stirred 3h and was hydrolyzed by an aqueous saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The desired product **7*E*** (0.071 g, 88%) was obtained after flash chromatography (cyclohexane/EtOAc: 4/1) as slightly yellow oil.

Taxifolial and Isotaxifolial D Synthesis Through Cross-Coupling Reactions

(2Z)-3,7-dimethylocta-2,6-dien-4-ynol (7Z)

To a solution of 1-bromo-2-methylpropene (0.750 g, 5.55 mmol, 1.1 eq.) in anhydrous and degassed Et_2NH (10 mL) were successively added at 0°C $PdCl_2(PPh_3)_2$ (0.080 g 0.11 mmol, 0.02 eq.), CuI (0.107 g, 0.56 mmol, 0.10 eq.) and a solution of (*2Z*)-3-methylpent-2-en-3-ynol **3*Z*** (0.587 g, 6.11 mmol, 1 eq.) in 20 mL of anhydrous and degassed Et_2NH. The initially slightly yellow solution gradually darkened. After disappearance of the starting material as judged from TLC (3 to 4 h), a saturated aqueous solution of ammonium chloride was added at 0°C. After extraction with diethyl ether, the combined organic layers were washed with water, dried over Na_2SO_4, concentrated. The dark oil was purified by flash chromatography (cyclohexane/EtOAc: 4/1) to give pure product **7*Z*** (0.724 g, 79%).

^{1}H-NMR (300 MHz) $CDCl_3$: 1.73 (s, 1H); 1.83 (br d, 3H, *J* = 1.5 Hz); 1.90-1.92 (m, 6H); 4.33 (dq, 2H, *J* = 1.1, 6.8 Hz); 5.38-5.41 (m, 1H); 5.82 (tq, 1H, *J* = 1.5, 6.8 Hz). ^{13}C-NMR (75 MHz) $CDCl_3$: 21.1 (CH_3); 23.4 (CH_3); 24.9 (CH_3); 61.4 (CH_2); 89.6 (Cq); 92.9 (Cq); 105.2 (CH); 121.6 (Cq); 134.1 (CH); 149.1 (Cq). MS (EI): *m/z (%)* = 150.2 ($[M]^+$, 92); 135.1 (83); 107.2 (70); 91.1 (100); 79.1 (58). IR (NaCl; cm^{-1}): 1048; 1376; 1440; 2928; 3358.

(2E)-3,7-dimethylocta-2,6-dien-4-ynol (7E):

To a solution of 1-bromo-2-methylpropene (1.02 g, 7.55 mmol, 1.1 eq.) in anhydrous and degassed Et_2NH (10 mL) were successively added at 0°C $PdCl_2(PPh_3)_2$ (0.096 g 0.137 mmol, 0.02 eq.), CuI (0.131 g, 0.688 mmol, 0.10 eq.) and a solution of (*2E*)-3-methylpent-2-en-3-ynol **3*E*** (0.660 g, 6.87 mmol, 1 eq.) in anhydrous and degassed Et_2NH (20 mL). The initially slightly yellow solution gradually darkened. After disappearance of the starting material as judged from TLC (3 to 4 h), a saturated aqueous solution of ammonium chloride was added at 0°C. After extraction with diethyl ether, the combined organic layers were washed with water dried over Na_2SO_4, concentrated. The crude orange-brown oil was purified by flash chromatography (cyclohexane/EtOAc: 4/1) to give pure **7*E*** (0.473 g, 45%) as slightly yellow oil.

^{1}H-NMR (300 MHz) $CDCl_3$: 1.35 (s, 1H); 1.82 (br d, 3H, *J* = 1.6 Hz); 1.86 (dt, 3H, *J* = 0.8, 1.5 Hz); 1.90 (br s, 3H); 4.23 (d, 2H, *J* = 6.9 Hz); 5.35-5.37 (m, 1H); 5.95 (tq, 1H, *J* = 1.5, 6.9 Hz). ^{13}C-NMR (75 MHz) $CDCl_3$: 17.8 (CH_3); 21.0 (CH_3); 24.9 (CH_3); 59.3 (CH_2); 86.2 (Cq); 93.7 (Cq); 105.2 (CH); 121.6 (Cq); 133.9 (CH); 148.8 (Cq). MS (EI): *m/z (%)* = 150.2 ($[M]^+$, 80); 135.1 (83); 107.2 (72); 91.1 (100); 79.1 (52). IR (NaCl; cm^{-1}): 1050, 1375, 1432, 2930, 3358.

Taxifolial D (= (2Z)-3,7-dimethylocta-2,6-dien-4-ynal)

To a solution of dienynol **7*Z*** (0.130 g, 0.865 mmol) in anhydrous CH_2Cl_2 (5 mL), was added anhydrous MnO_2 (0.650 g, 7.477 mmol, 8.6 eq.). The solution was stirred overnight. The mixture was then filtrated through a pad of Celite®. Solvent evaporation gave **Taxifolial D** (0.123 g, 96%) as slightly yellow oil.

^{1}H-NMR (300 MHz) $CDCl_3$: 1.87 (br d, 3H, *J* = 1.4 Hz); 1.93 (br s, 3H); 2.12 (d, 3H, *J* = 1.4 Hz); 5.45-5.58 (m, 1H); 6.09 (dq, 1H, *J* = 1.4, 8.3 Hz); 10.03 (d, 1H, *J* = 8.3 Hz). ^{13}C-NMR (75 MHz) $CDCl_3$: 21.6 (CH_3); 25.1 (CH_3); 25.2 (CH_3); 88.7 (Cq); 99.3 (Cq); 104.7 (CH); 133.6 (CH); 143.2 (Cq); 153.3 (Cq); 192.9 (CH). MS (CI/isobutane): *m/z (%)* = 149.1 ($[M+H]^+$, 100), 133.2 (19). IR (NaCl; cm^{-1}): 1140; 1216; 1585; 1664; 2182; 2849-3019.

IsoTaxifolial D (= (2E)-3,7-dimethylocta-2,6-dien-4-ynal)

To a solution of dienynol **7*E*** (0.129 g, 0.859 mmol) in anhydrous CH_2Cl_2 (5 mL), was added anhydrous MnO_2 (0.649 g, 7.465 mmol, 8.7 eq.). The solution was stirred overnight in the absence of light. The mixture was filtrated through a pad of Celite®. Solvent evaporation gave **Isotaxifolial D** (0.121 g, 95%) as slightly yellow oil.

^{1}H-NMR (300 MHz) $CDCl_3$: 1.87 (br d, 3H, *J* = 1.7Hz); 1.93 (br s, 3H); 2.31 (d, 3H, *J* = 1.4 Hz); 5.44-5.47 (m, 1H); 6.16 (dq, 1H, *J* = 1.4, 8.0 Hz); 10.01 (d, 1H, *J* = 8.0 Hz). ^{13}C-NMR (75 MHz) $CDCl_3$: 18.6 (CH_3); 21.4 (CH_3); 25.2 (CH_3); 93.5 (Cq); 98.1 (Cq); 104.9 (CH); 132.4 (CH); 141.5 (Cq); 153.4 (Cq); 190.2 (CH). MS (CI/isobutane): *m/z (%)* = 149.1 ($[M+H]^+$, 100), 133.2 (17). IR (NaCl; cm^{-1}): 1140; 1216; 1585; 1664; 2182; 2849-3019.

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