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An efficient stereoselective approach to silylated polyunsaturated γ-alkylidene butenolides

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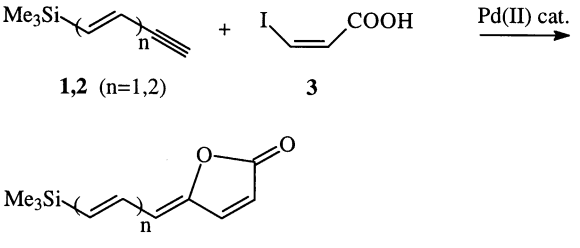
Abstract—An efficient and stereoselective synthetic approach to a variety of polyunsaturated γ-alkylidene butenolides has been developed, starting from readily available silylated and polyunsaturated terminal alkynes. The palladium-catalysed tandem cross-coupling/cyclization reaction of the alkynes with the (*Z*)-3-iodo-2-propenoic acid leads directly to polyunsaturated (*Z*)-γ-alkylidene butenolides with a high degree of stereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

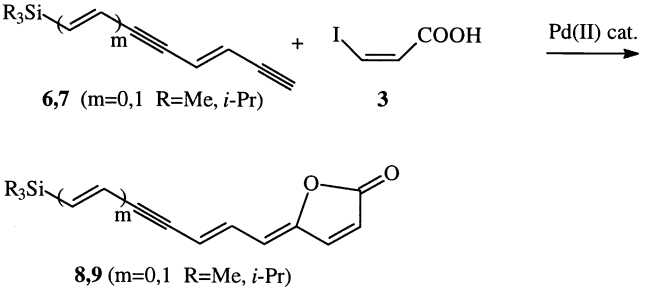
A large number of natural products of medicinal and biological interest contain the butenolide moiety.[1] In particular, a wide variety of stereodefined γ-alkylidene butenolides have been isolated from natural sources and have shown interesting biological activities such as freelingyne[2] and tetrenolin[3] which display antibiotic activity, or dihydroxerulin,[4] a potent inhibitor of the biosynthesis of cholesterol. Therefore, an increasing amount of attention has been focused on the synthesis of stereodefined γ-alkylidene butenolides.[5] Various methods lead to the γ-alkylidene butenolide moiety in a stereoselective manner, such as the Ag- or the Pd-catalysed lactonization reactions of 4-alkynoic acids,[6–13] which involve stereoselective *trans* addition reactions. Moreover, the recent Pd-catalysed tandem cross-coupling/lactonization process[14] converting terminal alkynes and (*Z*)-β-haloacrylic acids directly into (*Z*)-γ-alkylidene butenolides appears to be a highly selective procedure.

In our previous studies dealing with the synthesis of stereodefined polyenes[15] we have devised new methodology for the synthesis of a series of natural compounds[16–21] with a conjugated unsaturated structure, starting from unsaturated bis-silyl derivatives. In connection with this type of synthetic work, we now report an efficient and stereoselective approach to a variety of silylated polyunsaturated (*Z*)-γ-alkylidene butenolides, which can be successfully elaborated for the construction of the above natural compounds.

Our strategy was based upon Pd(II) catalysed cross-coupling/cyclization reactions, using the same catalytic system reported in the literature,[14] but with a different molar ratio of the reagents, between various enynes **1**,**2** and polyenediynes **6**,**7** and (*Z*)-3-iodo-2-propenoic acid,[22] leading directly to polyunsaturated butenolides, with a high stereoselectivity (97–98%), as outlined in Eqs. (1) and (2).



(1)



(2)

In order to realize the synthesis of butenolides with different unsaturations, such as butenolides **4** and **5**, presenting only conjugated double bonds, or butenolides **8** and **9**, with conjugated double and triple bonds, we have devised rapid

Keywords: silicons and compounds; stereoselective synthesis; enynes; alkylidene butenolides.

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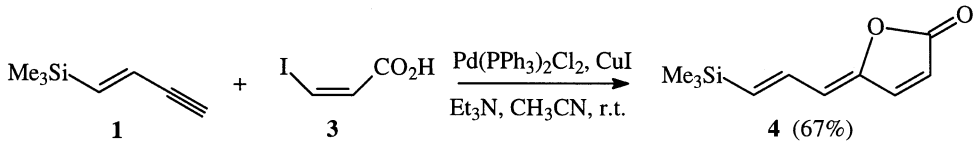


Scheme 1.

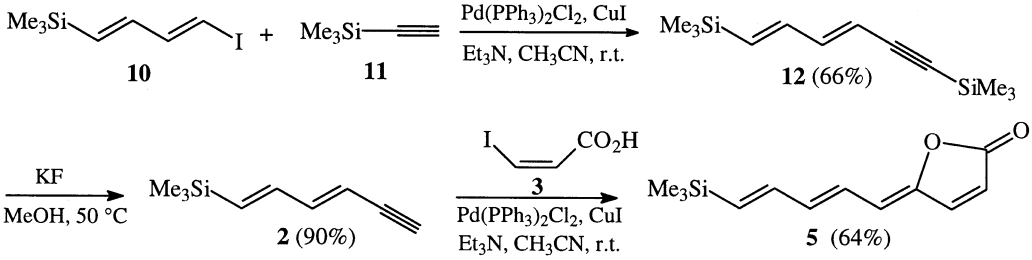
and efficient synthetic sequences leading to the appropriate terminal alkynes **1**,**2** and **6**,**7**, the key starting compounds for the synthesis of the butenolides.

2. Results and discussion

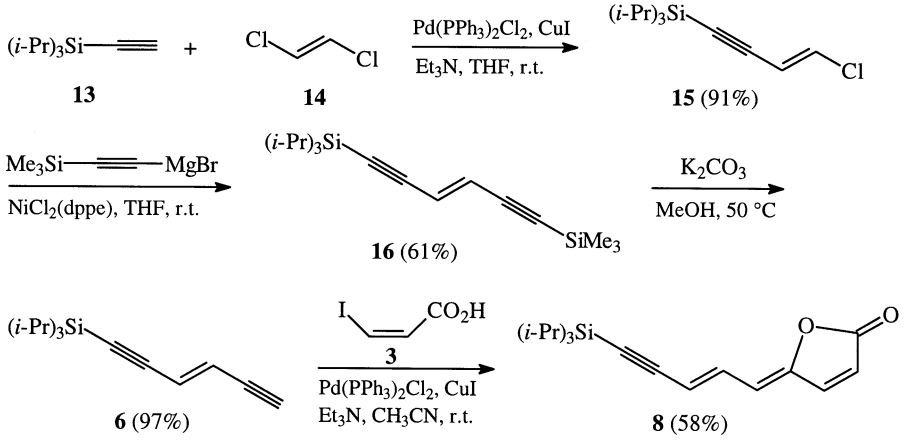
To synthesize the butenolide **4** (n=1) it was sufficient to start from the readily available mono-silylated enyne **1**[23] (n=1). As depicted in Scheme 1, the cross-coupling[24] reaction between the enyne **1** and the iodoacid **3** was performed at room temperature in the presence of the Pd(II) catalyst in acetonitrile as solvent, (molar ratio **1**/**3**/$Pd(PPh_3)_2Cl_2$/CuI/Et_3N=1.5:1:0.02:0.04:30) leading directly to the butenolide **4** in good yield (67%) and with high stereoselectivity (98%, with Z configuration of the exocyclic double bond, as determined by ^1H NMR spectroscopy). According to the procedure reported in the literature,[14] the same reaction afforded the butenolide **4** with a lower stereoselectivity value (80%).

To obtain the butenolide **5** (n=2), it was necessary to synthesise the monosilylated dienyne **2** (n=2), which, in turn, can be obtained by desilylation of the bis-silylated dienyne **12**. Thus, we have realized a more stereoselective procedure leading to compound **12** and alternative to that reported,[25] based upon (Scheme 2) the coupling reaction between the trimethylsilylacetylene and the silylated conjugated iododiene **10**, prepared according to our procedure.[26] Indeed, the dienyne **12** has been obtained in 66% yield and in high stereoselectivity (95%). The subsequent selective desilylation reaction led to the dienyne **2** in 90% yield. Finally, by the coupling reaction of the dienyne **2** with the iodoacid **3**, with the same catalytic system, the butenolide **5** was obtained in 64% yield (98% diastereomeric purity).

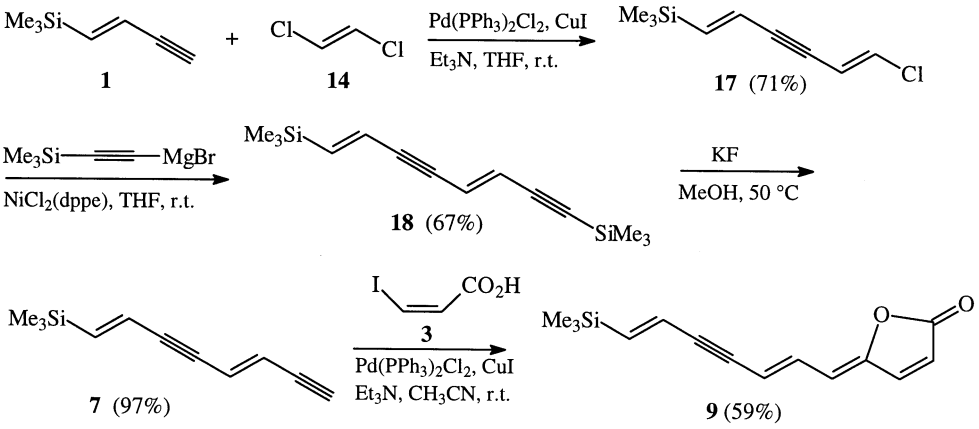
To introduce on the butenolide skeleton different unsaturations, i.e. double and triple bonds, it was necessary to prepare the appropriate polyenediynes. Thus, in the case of the butenolide **8** (m=0, R=i-Pr), the first step of the synthetic sequence depicted in Scheme 3 required a coupling reaction between the triisopropylsilylacetylene **13** and the (*E*)-dichloroethene **14** in the presence of the Pd(II) catalyst, in THF as solvent, which led to the (*E*)-chloro enyne **15** in 91% yield (98% of isomeric purity). By a subsequent coupling reaction of the compound **15** with the Grignard reagent of the trimethylsilylacetylene, in the presence of a Ni(II) catalyst, in THF, the bis-silylated endiyne **16** was obtained in 61% yield. It is worth noting that it was necessary to use the Grignard reagent in this



Scheme 2.



Scheme 3.



Scheme 4.

coupling reaction, in the presence of a Ni(II) catalyst, and not the simple acetylene in the presence of a Pd(II) catalyst (longer reaction times were required, ≈4 days). Moreover, it was necessary to introduce two different silyl groups on the endiyne moiety, in order to perform a selective desilylation reaction. Indeed, some attempts to desilylate selectively the endiyne presenting the same trimethylsilyl groups failed. Thus, the compound **16** was selectively desilylated with K_2CO_3 in MeOH at 50°C, leading to product **6**, employed in the final step. The butenolide **8** was obtained in 58% yield and with a stereoselectivity of 98%.

In the case of the butenolide **9** (m=1, R=Me), which presents an additional and terminal double bond with respect to the butenolide **8**, as illustrated in Scheme 4, it was sufficient to start from the monosilylated enyne **1** which was coupled with the dichloroethene **14**, in the presence of the Pd(II) catalyst, to give the (*E*,*E*)-chloro dienyne **17** in 71% yield.

In the subsequent step, the coupling reaction of compound **17** with the Grignard reagent of the trimethylsilylacetylene in the presence of the Ni(II) catalyst led to 67% yield of the diendiyne **18** with high stereoselectivity (97%). The usual desilylation reaction, followed by the final coupling of the desilylated compound **7** with the iodoacid **3** afforded the desired compound **9** in 59% yield (diastereomeric purity=97%).

In conclusion, the procedure described here appears to be a useful route to stereodefined polyunsaturated γ-alkylidene butenolides, which, in principle, are useful intermediates in the synthesis of natural compounds with a more extended conjugated system via electrophilic substitution reactions of the silyl group. Moreover, the ready availability of the silyl derivatives employed, the simplicity of the operations involved and the high selectivity are additional features making the procedure very promising.

3. Experimental

Macherey–Nagel silica gel (60, particle size 0.040–0.063 mm) for column chromatography and Macherey–Nagel aluminum sheets with silica gel 60 F_{254} for TLC were used. GC analysis was performed on a Hewlett-Packard 5890 series II gas chromatograph equipped with a SE-30 (methylsilicone, 30 m×0.25 mm id) capillary column. GC/mass-spectrometry analysis was performed on a Shimadzu GCMS-QP5000 gas chromatograph–mass spectrometer equipped with a MDN-1 capillary column (methylsilicone, 30 m×0.25 mm id). IR spectra were recorded on a Perkin–Elmer FT-IR 1710 spectrometer. ^{1}H NMR spectra were recorded in deuterochloroform on a Bruker AM 500 spectrometer at 500 MHz. ^{13}C NMR spectra were recorded in deuterochloroform on a Bruker AM 500 spectrometer at 125.7 MHz. Elemental analyses were recorded on a Carlo Erba EA 1108 elemental analyser. Solvents were dried before use as follows: acetonitrile was distilled over molecular sieves, tetrahydrofuran was distilled from sodium.

3.1. Synthesis of (*Z*)-γ-alkylidene butenolide 4

3.1.1. (*Z*)-5-[(2*E*)-3-Trimethylsilyl-2-propenylidene]-5*H*-furan-2-one (4). A CH_3CN solution (1 mL) of enyne **1**[23] (0.5 g, 4.03 mmol) was added at room temperature, under nitrogen, to a stirred mixture of (*Z*)-3-iodo-2-propenoic acid **3** (0.53 g, 2.69 mmol), Et_3N (7.27 g, 71.8 mmol), CuI (0.02 g, 0.107 mmol) and $Pd(PPh_3)_2Cl_2$ (0.04 g, 0.054 mmol) in CH_3CN (2 mL). After reaction completion (12 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and extracted with ethyl acetate (3×10 mL). The organic extracts were washed with water (3×10 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (10% ethyl acetate/petroleum ether) led to the *title compound* **4** (0.35 g, 67% yield, diastereomeric purity=98%) as a thick brown oil; [Found: C, 61.7; H, 7.3. $C_{10}H_{14}O_2Si$ requires C, 61.81; H, 7.26%]; ν_{max} (neat) 3104, 2894, 1780, 1740, 1541, 1330, 1248, 1124, 995, 943, 839 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.39 (1H, d, J=5.4 Hz, CH=C*H*–C=O), 7.05 (1H, dd, J=18.5, 10.8 Hz, C*H*=CH–Si), 6.31 (1H, dd, J=18.5, 1.0 Hz, CH=C*H*–Si), 6.20 (1H, dd, J=5.4, 0.7 Hz, C*H*=CH–C=O) 5.80 (1H, d like, J=10.8 Hz, C*H*=C–O), 0.14 (9H, s, Si*Me*$_3$); δ_C (125.7 MHz, $CDCl_3$) 169.40, 148.17, 143.67, 143.56, 135.83, 119.18, 116.26, −1.66; MS m/z 194 (M^+, 18), 179 (26), 166 (11), 152 (8), 151 (55), 135 (13), 133 (9), 123 (9), 109 (12), 105 (12), 99

(7), 97 (7), 95 (31), 92 (14), 91 (20), 83 (9), 82 (18), 77 (10), 76 (8), 75 (100), 73 (57), 69 (11), 68 (14), 67 (10), 59 (24), 55 (15), 54 (11), 53 (17), 45 (76), 43 (65%).

3.2. Synthesis of (*Z*)-γ-alkylidene butenolide 5

3.2.1. (3*E*,5*E*)-(1,6)-Bis(trimethylsilyl)-3,5-hexadien-1-yne (12).[25] A CH_3CN solution (1 mL) of (1*E*,3*E*)-4-trimethylsilyl-1-iodo-1,3-butadiene **10**[26] (0.51 g, 2.02 mmol) was added at room temperature, under nitrogen, to a stirred mixture of ethynyltrimethylsilane **11** (0.3 g, 3.05 mmol), Et_3N (4.36 g, 43.1 mmol), CuI (0.0152 g, 0.081 mmol) and $Pd(PPh_3)_2Cl_2$ (0.0285 g, 0.041 mmol) in CH_3CN (1 mL). After reaction completion (1 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and extracted with ethyl acetate (3×10 mL). The organic extracts were washed with water (3×10 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by percolation on florisil column (petroleum ether as eluent) led to the *title compound* **12** (0.3 g, 66% yield, diastereomeric purity=95%) as a colourless oil.

3.2.2. (3*E*,5*E*)-(6)-Trimethylsilyl-3,5-hexadien-1-yne (2). KF (0.78 g, 13.51 mmol) was added to a MeOH solution (3 mL) of compound **12** (0.3 g, 1.35 mmol). The reaction mixture was stirred for 1 h at 50°C, then, after cooling at room temperature, quenched with water (10 mL) and extracted with diethyl ether (3×20 mL). The organic extracts were dried over Na_2SO_4 and the residue was recovered removing the solvent by distillation. The *title compound* **2** was obtained in 90% yield (0.184 g, diastereomeric purity=95%) as a colourless oil, pure for the next reaction; [Found: C, 72.0; H, 9.5. $C_9H_{14}Si$ requires C, 71.92; H, 9.39%]; ν_{max} (neat) 3312, 2960, 2926, 2855, 2176, 1462, 1261, 864, 839 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.66 (1H, dd, *J*=15.4, 10.4 Hz, C*H*=CH), 6.53 (1H, dd, *J*=18.1, 10.4 Hz, C*H*=CH–Si), 6.03 (1H, d, *J*=18.1 Hz, CH=C*H*–Si), 5.60 (1H, dd, *J*=15.4, 2.2 Hz, CH=C*H*) 3.06 (1H, d, *J*=2.2 Hz, C≡C-*H*), 0.08 (9H, s, Si*Me*$_3$); MS *m*/*z* 150 (M^+, 10), 136 (9), 135 (65), 109 (12), 107 (28), 95 (6), 83 (11), 73 (10), 72 (6), 69 (7), 59 (60), 58 (45), 57 (12), 55(11), 53 (23), 45 (25), 44 (10), 43 (100%).

3.2.3. (*Z*)-5-[(2*E*,4*E*)-5-Trimethylsilyl-2,4-pentadienylidene]-5*H*-furan-2-one (5). A CH_3CN solution (1 mL) of dienyne **2** (0.16 g, 1.07 mmol) was added at room temperature, under nitrogen, to a stirred mixture of (*Z*)-3-iodo-2-propenoic acid **3** (0.14 g, 0.71 mmol), Et_3N (2.32 g, 23 mmol), CuI (0.005 g, 0.028 mmol) and $Pd(PPh_3)_2Cl_2$ (0.01 g, 0.014 mmol) in CH_3CN (1 mL). After reaction completion (12 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and extracted with ethyl acetate (3×10 mL). The organic extracts were washed with water (3×10 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (20% ethyl acetate/petroleum ether) led to the *title compound* **5** in 64% yield (0.1 g, diastereomeric purity=98%) as a brown oil; [Found: C, 65.4; H, 7.3. $C_{12}H_{16}O_2Si$ requires C, 65.41; H, 7.32%]; ν_{max} (neat) 2959, 2924, 1778, 1751, 1537, 1261, 1250, 1104, 1003, 937, 839 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37 (1H, d, *J*=5.3 Hz, CH=C*H*–C=O), 6.75 (1H, dd, *J*=15.1, 11.6 Hz, C*H*=CH), 6.66 (1H, dd, *J*=18.2, 10.4 Hz, C*H*=CH–Si), 6.48 (1H, dd, *J*=15.1, 10.4 Hz, CH=C*H*) 6.18 (1H, d, *J*=5.3 Hz, C*H*=CH–C=O), 6.13 (1H, d, *J*=18.2 Hz, CH=C*H*–Si) 5.87 (1H, d, *J*=11.6 Hz, C*H*=C–O), 0.12 (9H, s, Si*Me*$_3$); δ_C (125.7 MHz, $CDCl_3$) 169.33, 149.40, 143.38, 142.63, 140.85, 140.07, 125.58, 118.83, 114.69, −1.47; MS *m*/*z* 220 (M^+, 27), 205 (11), 192 (9), 191 (7), 178 (10), 177 (54), 161 (10), 151 (12), 131 (30), 118 (9), 117 (13), 103 (25), 95 (11), 91 (10), 82 (11), 81 (27), 77 (19), 75 (81), 74 (10), 73 (100), 61 (16), 59 (36), 55 (15), 54 (13), 53 (17), 45 (72), 43 (57%).

3.3. Synthesis of (*Z*)-γ-alkylidene butenolide 8

3.3.1. (*E*)-4-Triisopropylsilyl-1-chloro-1-buten-3-yne (15). A solution of ethynyltriisopropylsilane **13** (2.5 g, 13.7 mmol) in THF (23 mL) was added dropwise at room temperature, under nitrogen, to a stirred mixture of (*E*)-1,2-dichloroethene **14** (6.64 g, 68.54 mmol), Et_3N (2.08 g, 20.55 mmol), CuI (0.10 g, 0.55 mmol) and $Pd(PPh_3)_2Cl_2$ (0.19 g, 0.27 mmol) in THF (22 mL). After reaction completion (2 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (50 mL), and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with water (3×50 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by percolation on florisil column (petroleum ether as eluent) led to the *title compound* **15** (3.01 g, 91% yield, isomeric purity=98%) as a yellowish oil; [Found: C, 64.2; H, 9.6. $C_{13}H_{23}ClSi$ requires C, 64.29; H, 9.55%]; ν_{max} (neat) 3074, 2943, 2893, 2867, 2169, 1581, 1464, 1243, 1224, 1071, 1018, 997, 916, 883, 848 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.56 (1H, d, *J*=14.1 Hz, C*H*=CH), 5.96 (1H, d, *J*=14.1 Hz, CH=C*H*), 1.07 [21H, s, Si(*i*-Pr)$_3$]; MS *m*/*z* 244 (M^{+2}, 1), 242 (M^+, 4), 227 (1), 201 (36), 200 (17), 199 (99), 173 (14), 171 (29), 159 (15), 157 (40), 145 (28), 143 (70), 131 (40), 129 (100), 121 (22), 119 (16), 117 (21), 115 (18), 113 (16), 105 (19), 103 (22), 95 (24), 93 (78), 91 (15), 81 (17), 79 (53), 65 (21), 63 (46), 59 (19), 55 (15), 53 (27), 45 (17), 43 (53%).

3.3.2. (*E*)-6-Triisopropylsilyl-1-trimethylsilyl-3-hexen-1,5-diyne (16). A solution of the Grignard reagent of the ethynyltrimethylsilane (0.54N, 55.8 mmol) in THF (103 mL) was slowly added dropwise at room temperature, under nitrogen, to a stirred mixture of compound **15** (3.0 g, 12.4 mmol) and the catalyst $NiCl_2$(dppe) (0.88 g, 1.67 mmol) in THF (35 mL). After reaction completion (4 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (80 mL), and extracted with ethyl acetate (3×50 mL). The organic extracts were washed with water (3×50 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (silica gel, petroleum ether as eluent) led to the *title compound* **16** (2.3 g, 61% yield, isomeric purity=98%) as a yellow oil; [Found: C, 71.1; H, 10.5. $C_{18}H_{32}Si_2$ requires C, 70.97; H, 10.59%]; ν_{max} (neat) 3035, 2960, 2945, 2894, 2867, 2175, 2128, 1463, 1251, 1094, 1073, 1018, 997, 936, 883, 844 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.03 (1H, d, *J*=16.1 Hz, C*H*=CH), 5.99 (1H, d, *J*=16.1 Hz, CH=C*H*), 1.04 [21H, s, Si(*i*-Pr)$_3$], 0.16 (9H, s, Si*Me*$_3$); MS *m*/*z* 304 (M^+, 4), 289 (7), 263 (7), 262 (20), 261 (70), 233 (12), 219 (23), 205 (18), 193 (43), 177 (7), 159 (20), 145 (19), 135 (6), 109 (6), 97 (8), 96 (7), 95 (99), 88 (51), 83 (16), 81 (14), 73 (100), 59 (50), 53 (10), 45 (25), 43 (26%).

3.3.3. (*E*)-6-Triisopropylsilyl-3-hexen-1,5-diyne (6). K_2CO_3 (13.6 g, 98.68 mmol) was added to a MeOH solution (30 mL) of compound **16** (1.0 g, 3.29 mmol). The reaction mixture was stirred for 1 h at 50°C, then, after cooling at room temperature, quenched with an aqueous solution of HCl (1N, 30 mL) and extracted with ethyl ether (3× 30 mL). The organic extracts were washed with water (3×30 mL), dried over Na_2SO_4 and concentrated under vacuum. The *title compound* **6** (0.74 g, 97% yield, isomeric purity=98%) was obtained as a brown oil, pure for the subsequent reaction; [Found: C, 77.4; H, 10.3. $C_{15}H_{24}Si$ requires C, 77.51; H, 10.41%]; ν_{max} (neat) 3310, 3038, 2953, 2893, 2868, 2172, 2124, 1463, 1260, 1079, 1019, 997, 937, 883 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.09 (1H, dd, *J*=16.1, 0.6 Hz, C*H*═CH), 5.97 (1H, dd, *J*=16.1, 2.3 Hz, CH═C*H*), 3.14 (1H, dd, *J*=2.3, 0.6 Hz, C≡C–H) 1.05 [21H, s, Si(*i*-Pr)$_3$]; MS *m/z* 232 (M^+, 2), 190 (19), 189 (100), 161 (32), 147 (51), 145 (19), 133 (41), 121 (13), 119 (64), 105 (15), 103 (14), 93 (17), 83 (20), 69 (12), 67 (15), 59 (34), 55 (13), 53 (74), 45 (16), 43 (46%).

3.3.4. (*Z*)-5-[(2*E*)-5-Triisopropylsilyl-2-penten-4-ynylidene]-5*H*-furan-2-one (8). A CH_3CN solution (1 mL) of endiyne **6** (0.3 g, 1.29 mmol) was added at room temperature, under nitrogen, to a stirred mixture of (*Z*)-3-iodo-2-propenoic acid **3** (0.17 g, 0.86 mmol), Et_3N (2.47 g, 24 mmol), CuI (0.006 g, 0.034 mmol) and $Pd(PPh_3)_2Cl_2$ (0.012 g, 0.017 mmol) in CH_3CN (2 mL). After reaction completion (1.5 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and extracted with ethyl acetate (3×10 mL). The organic extracts were washed with water (3×10 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (20% ethyl acetate/petroleum ether) led to the *title compound* **8** (0.15 g, 58% yield, diastereomeric purity=98%) as a brown oil; [Found: C, 71.4; H, 8.6. $C_{18}H_{26}O_2Si$ requires C, 71.47; H, 8.66%]; ν_{max} (neat) 3104, 2954, 2115, 1777, 1741, 1541, 1330, 1248, 1124, 1068, 995, 943, 839 cm^{-1}; δ_H (500 MHz, $CDCl_3$)7.37 (1H, d, *J*=5.4 Hz, CH═C*H*–C═O), 7.11 (1H, dd, *J*= 15.6, 11.5 Hz, C*H*═CH), 6.23 (1H, d, *J*=5.4 Hz, C*H*═CH–C═O), 5.92 (1H, d, *J*=15.6 Hz, CH═C*H*), 5.86 (1H, d, *J*=11.5 Hz, C*H*═C–O), 1.05 [21H, s, Si(*i*-Pr)$_3$]; δ_C (125.7 MHz, $CDCl_3$) 168.93, 149.38, 142.76, 134.58, 119.90, 117.14, 113.34, 105.93, 99.27, 18.52, 11.19; MS *m/z* 302 (M^+, 12), 274 (1), 260 (22), 259 (100), 244 (1), 231 (12), 217 (13), 203 (7), 189 (30), 175 (9), 173 (7), 161 (7), 145 (15), 131 (9), 129 (12), 128 (10), 127 (10), 115 (9), 102 (36), 91 (9), 87 (17), 81 (14), 75 (33), 73 (22), 67 (11), 61 (14), 59 (17), 55 (10), 53 (16), 45 (34), 43 (32%).

3.4. Synthesis of (*Z*)-γ-alkylidene butenolide 9

3.4.1. (1*E*,5*E*)-6-Trimethylsilyl-1-chloro-1,5-hexadien-3-yne (17). A solution of (*E*)-4-trimethylsilyl-3-buten-1-yne **1** (0.57 g, 4.61 mmol) in THF (5 mL) was slowly added dropwise, at room temperature, under nitrogen, to a stirred mixture of (*E*)-1,2-dichloroethene **14** (2.23 g, 23.06 mmol), Et_3N (0.7 g, 6.92 mmol), CuI (0.035 g, 0.184 mmol) and $Pd(PPh_3)_2Cl_2$ (0.065 g, 0.092 mmol) in THF (7 mL). After reaction completion (1.5 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (20 mL), and extracted with ethyl acetate (3×20 mL). The organic extracts were washed with water (3×30 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by percolation on florisil column (petroleum ether as eluent) led to the *title compound* **17** (0.605 g, 71% yield, diastereomeric purity=93%) as a yellowish oil; [Found: C, 58.6; H, 7.0. $C_9H_{13}ClSi$ requires C, 58.51; H, 7.09%]; ν_{max} (neat) 3074, 2957, 2898, 2190, 1560, 1250, 1230, 1210, 975, 916, 865, 842 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.52 (1H, d, *J*=13.8 Hz, CH═C*H*–Cl), 6.48 (1H, d, *J*=19.3 Hz, CH═C*H*–Si), 6.05 (1H, dd, *J*=13.8, 1.8 Hz, C*H*═CH–Cl), 6.03 (1H, dd, *J*=19.3, 1.8 Hz, C*H*═CH–Si), 0.10 (9H, s, Si*Me*$_3$); MS *m/z* 186 (M^{+2}, 4), 184 (M^+, 11), 169 (28), 158 (14), 145 (36), 143 (100), 133 (9), 117 (11), 105 (7), 93 (23), 91 (11), 73 (21), 65 (17), 63 (33), 59 (89), 53 (14), 45 (30), 43 (43%).

3.4.2. (3*E*,7*E*)-1,8-Bis(trimethylsilyl)-3,7-octadien-1,5-diyne (18). A solution of trimethylsilylethynylmagnesium bromide (0.43N, 10.32 mmol) in THF (24 mL) was slowly added dropwise at room temperature, under nitrogen, to a stirred mixture of compound **17** (0.605 g, 3.48 mmol) and the catalyst $NiCl_2$(dppe) (0.16 g, 0.31 mmol) in THF (6 mL). After reaction completion (8 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (30 mL), and extracted with ethyl acetate (3×30 mL). The organic extracts were washed with water (3×30 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (silica gel, petroleum ether) led to the *title compound* **18** (0.57 g, 67% yield, diastereomeric purity=97%) as a yellow oil; [Found: C, 68.1; H, 9.0. $C_{14}H_{22}Si_2$ requires C, 68.22; H, 9.00%]; ν_{max} (neat) 3034, 2958, 2899, 2160, 2119, 1589, 1560, 1250, 1210, 1191, 1074, 975, 935, 844 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.49 (1H, d, *J*=19.1 Hz, CH═C*H*–Si), 6.14 (1H, dd, *J*=16.0, 2.0 Hz, C*H*═CH), 6.08 (1H, dd, *J*=19.1, 2.0 Hz, C*H*═CH–Si), 5.96 (1H, d, *J*=16.0 Hz, CH═C*H*), 0.19 (9H, s, Si*Me*$_3$), 0.09 (9H, s, Si*Me*$_3$); MS *m/z* 246 (M^+, 13), 231 (28), 215 (5), 205 (23), 191 (4), 173 (8), 159 (5), 145 (9), 131 (3), 117 (3), 108 (11), 95 (9), 83 (7), 73 (100), 59 (27), 45 (33), 43 (18%).

3.4.3. (3*E*,7*E*)-8-Trimethylsilyl-3,7-octadien-1,5-diyne (7). KF (1.34 g, 23.06 mmol) was added to a MeOH solution (6 mL) of compound **18** (0.57 g, 2.31 mmol). The reaction mixture was stirred for 1 h at 50°C, then, after cooling at room temperature, quenched with water (10 mL) and extracted with ethyl acetate (3×20 mL). The organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The *title compound* **7** (0.39 g, 97% yield, diastereomeric purity=97%) was obtained as a brown oil, pure for the next reaction; [Found: C, 75.9; H, 8.1. $C_{11}H_{14}Si$ requires C, 75.79; H, 8.10%]; ν_{max} (neat) 3294, 2955, 2898, 2179, 1590, 1250, 1210, 1097, 975, 839 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 6.50 (1H, d, *J*=19.2 Hz, CH═C*H*–Si), 6.20 (1H, dd, *J*=15.8, 2.2 Hz, C*H*═CH), 6.07 (1H, dd, *J*=19.2, 2.2 Hz, C*H*═CH–Si), 5.94 (1H, dd, *J*=15.8, 2.5 Hz, CH═C*H*), 3.18 (1H, d, *J*=2.5 Hz, ≡C–H), 0.10 (9H, s, Si*Me*$_3$); MS *m/z* 174 (M^+, 18), 160 (9), 159 (58), 143 (5), 133 (63), 131 (24), 119 (6), 105 (12), 83 (23), 73 (15), 67 (15), 59 (100), 55 (11), 53 (28), 45 (27), 43 (55%).

3.4.4. (*Z*)-5-[(2*E*,6*E*)-7-Trimethylsilyl-2,6-eptadien-4-ynylidene]-5*H*-furan-2-one (9). A CH_3CN solution (1 mL) of

endiyne **7** (0.2 g, 1.15 mmol) was added at room temperature, under nitrogen, to a stirred mixture of (*Z*)-3-iodo-2-propenoic acid **3** (0.15 g, 0.77 mmol), Et_3N (2.91 g, 28.6 mmol), CuI (0.0058 g, 0.03 mmol) and $Pd(PPh_3)_2Cl_2$ (0.01 g, 0.0153 mmol) in CH_3CN (1 mL). After reaction completion (2 h), the mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and extracted with ethyl acetate (3×10 mL). The organic extracts were washed with water (3×10 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (30% ethyl acetate/petroleum ether) led to the *title compound* **9** (0.11 g, 59% yield, diastereomeric purity= 97%) as a pale yellow oil; [Found: C, 68.9; H, 6.7. $C_{14}H_{16}O_2Si$ requires C, 68.81; H, 6.60%]; ν_{max} (neat) 3135, 2956, 2160, 1780, 1747, 1600, 1538, 1333, 1261, 1102, 1069, 1021, 957, 839 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37 (1H, d, *J*=5.4 Hz, CH═C*H*–C═O), 7.06 (1H, dd, *J*=15.5, 11.6 Hz, C*H*═CH), 6.53 (1H, d, *J*=18.9 Hz, CH═C*H*–Si) 6.22 (1H, d, *J*=5.4 Hz, C*H*═CH–C═O), 6.12 (1H, dd, *J*=18.9, 2.1 Hz, C*H*═CH–Si), 6.01 (1H, dd, *J*=15.5, 2.1 Hz, CH═C*H*), 5.87 (1H, d, *J*=11.6 Hz, C*H*═C–O), 0.10 (9H, s, Si*Me*$_3$); δ_C (125.7 MHz, $CDCl_3$) 168.78, 149.19, 147.42, 142.50, 133.57, 122.68, 119.61, 116.85, 113.29, 96.59, 89.16, −2.03; MS *m*/*z* 244 (M^+, 55), 229 (18), 216 (10), 215 (10), 203 (11), 202 (11), 201 (56), 186 (10), 185 (31), 183 (12), 175 (15), 173 (15), 170 (12), 169 (11), 155 (42), 145 (29), 142 (23), 141 (41), 127 (16), 115 (26), 105 (12), 101 (19), 93 (15), 87 (27), 83 (11), 75 (83), 73 (67), 63 (20), 61 (25), 59 (81), 55 (25), 54 (16), 53 (39), 45 (100), 43 (87%).

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