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Palladium-Catalyzed Reaction of (E) and (Z)-Dichloroethenes with 1-Alkynes. An Efficient Stereospecific Synthesis of (E) and (Z)-Enediynes.

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Abstract: The stereospecific sequential substitution of (E) and (Z)-dichloroethenes with 1-alkynes leads to (E) and (Z)-enediynes in high yield.

The synthesis of conjugated enynes and enediynes has recently received much attention since this structural moiety is found in several natural products.[1,2] In particular, the (Z)-enediyne structure is present in a novel class of antitumor antibiotics [3] (esperamycins, [4] calicheamycins, [5] dynemycin, [6] neocarzinostatin [7] and C 1027 chromophore [8]). Furthermore, enynes and enediynes are efficient precursors to dienes and trienes having a defined geometry.[9]

An efficient way to enynes has been realized (i) by reaction of vinylmetals with haloalkynes [10,12] or (ii) by reaction of vinyl halides with metallated terminal alkynes.[13-15] The Stephens Castro coupling [16] of terminal alkynes in the presence of palladium complexes and copper halide is an efficient and chemoselective procedure[17,9,18]. The utilization of commercially available (E) and (Z)-dichloroethenes appears to be interesting since it would lead, by sequential substitution, to chloroenynes [19] and then to enediynes.[9b,20] However, by using the Sonogashira's conditions ($PdCl_2(PPh_3)_2$, CuI in diethylamine) [17], low yields (12-20%) of chloroenynes **3** and **7** were obtained. We have found that both the nature of the catalyst and the amine are critical for the success of the reaction. In the case of (E)-dichloroethene, the use of tetrakis (triphenylphosphine) palladium in benzene containing piperidine (Figure 1) leads to high yields (88-92%) of (E)-chloroenynes **3**

(table I). In the case of (Z)-dichloroethene, the use of n-butylamine, instead of piperidine, is preferable (Figure 2) and gives (Z) chloroenynes **7** [19] in 76-98%yields (Table II). An excess of dichloroethenes is used in order to avoid the formation of the disubstituted products **5** and **8** ($R^1 = R^2$). THF can also be employed instead of benzene but it gives slightly lower yields (82%) of coupling product **7** (Table III). The reaction is stereospecific as in the case of Pd-catalysed reactions of vinyl halides .[21]

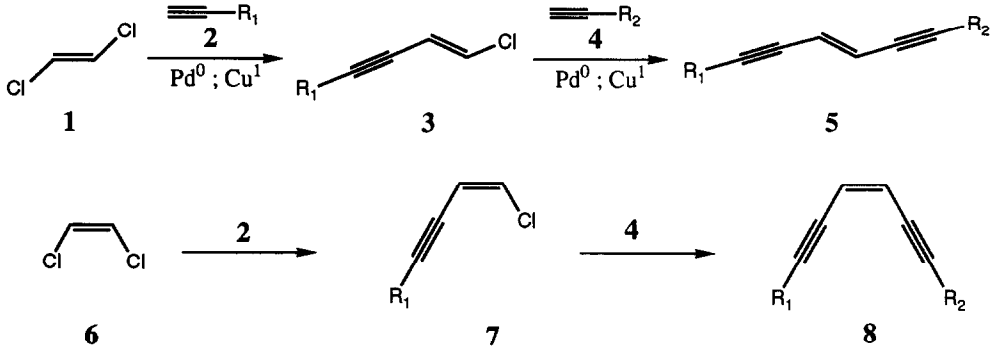
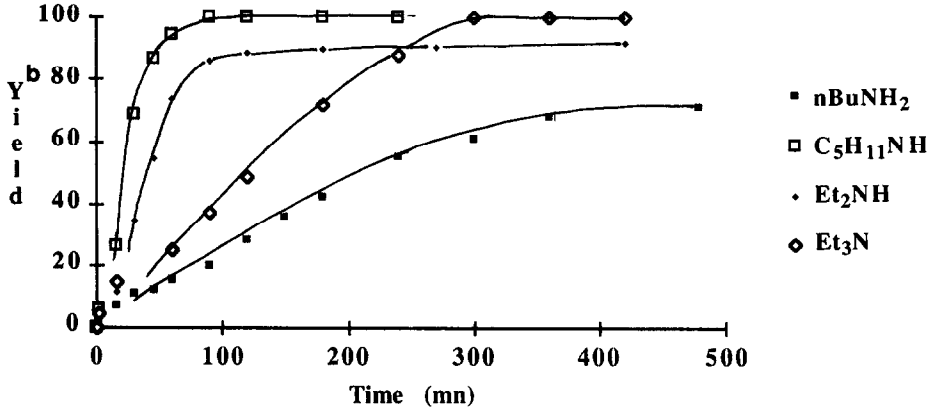


Figure 1: Reaction of (E)-1,2-dichloroethene with 1-hexyne in the presence of different amines (a)



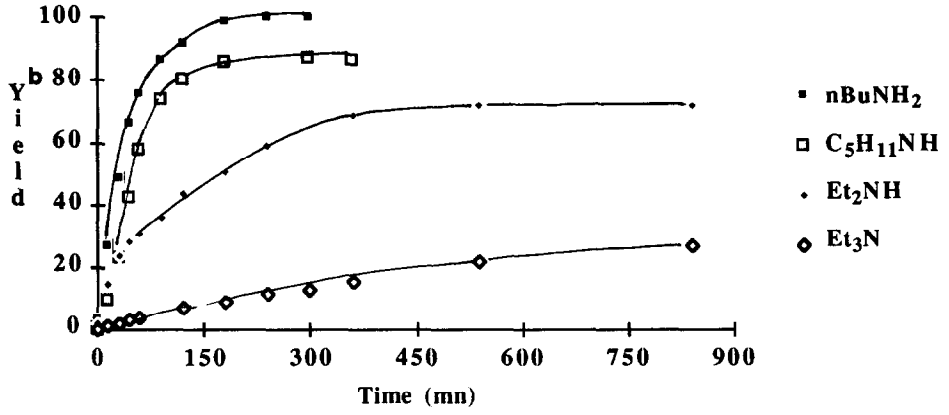
(a) $Pd(PPh_3)_4$ 5% ; CuI 10%; 2 equiv. of amine; 5 equiv. of (E)-1,2-dichloroethene in benzene at 20°C.
(b) Yield determined by G.P.C. analysis with internal reference (dodecane).

Table I: Reaction of (E)-1,2-dichloroethene with 1-alkynes[(a)].

entry	R^1	Yield **3** (%)
a	C_4H_9	93[(b)]
b	C_5H_{11}	92
c	$SiMe_3$	76
d	$CH(OH)C_5H_{11}$	92[(c)]
e	CH_2OH	88

(a) $Pd(PPh_3)_4$ 5 %; CuI 10 %; 2 equiv. of piperidine; 5 equiv. of (E)-dichloroethene in benzene 2h at 20°C unless otherwise indicated; **(b)**: a 94% yield was obtained when the reaction was conducted (20°C, 6h) in the presence of triethylamine instead of piperidine; (c) a 92% yield was also obtained in the presence of $Cl_2Pd(PPh_3)_2$/DIBAH instead of $Pd(PPh_3)_4$.

Figure 2: Reaction of (Z)-1,2-dichloroethene with 1-hexyne in the presence of different amines **(a)**



(a) 5% $Pd(PPh_3)_4$; 10% CuI; 2 equiv. of amine; 2 equiv. of (Z)-1,2-dichloroethene in benzene at 20°C.

(b) Yield determined by G.P.C. analysis with internal reference (dodecane).

Table II: Reaction of (Z)-1,2-dichloroethene with 1-alkynes[a]

entry	R^1	Yield **7** (%)
a	C_4H_9	86
b	C_5H_{11}	78
c	$C(CH_3)_2NH_2$	95
d	$SiMe_3$	76
e	$(CH_2)_3Cl$	93[b,c]

(a) $Pd(PPh_3)_4$ 5 % ; CuI 10 % ; 2 equiv. of butylamine; 2 equiv. of (Z)-dichloroethene in benzene 5h at 20°C; **(b)** by using 2.5 % $Cl_2Pd(PPh_3)_2$; 3 % CuI in Et_2NH as solvent[17] 3h at 20°C, a 12% yield was obtained. **(c)** by using $Pd(PPh_3)_4$ (5%) without CuI, 20h in refluxing propylamine, a 10% yield was obtained.

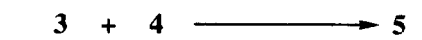
Table III: Reaction of 1-alkynes with (Z)-1,2-dichloroethene in different solvents [a].

Solvent	R_1	Time (h)	Yield **7** (%)
Benzene	$(CH_2)_2COOMe$	3	98
Toluene	$(CH_2)_2COOMe$	4	65
Benzene	$(CH_2)_3Cl$	2	92
THF	$(CH_2)_3Cl$	6	82

(a) $Pd(PPh_3)_4$ 5 %; CuI 10 %; 2 equiv. of n butylamine; 2 equiv. of (Z)-1,2-dichloroethene at 20°C.

Further reaction of (E) and (Z)-chloroenynes **3** and **7** with 1-alkynes leads stereospecifically to (E) and (Z)-enediynes **5** and **8** by using the same catalysts (tetrakis (triphenylphosphine) palladium and copper iodide) in benzene containing n-butylamine or piperidine (Tables IV and V).

Table IV: Preparation of (E) enediynes **5**[a]



entry	Enyne **3**	R_2	equiv. of **4**	Yield **5** (%)
a	**3b**	$SiMe_3$	2	95
b	**3b**	$(CH_2)_2COOMe$	1.2	89[b]
c	**3a**	C_5H_{11}	2	92

(a) 5 % $Pd(PPh_3)_4$; 10 % CuI; 2 equiv. of piperidine in benzene 9h at 20°C; **(b)** in the presence of 5% of $Cl_2Pd(PhCN)_2$ (instead of $Pd(PPh_3)_4$) in piperidine as solvent[18]

Table V: Preparation of (Z)-enediynes **8**[(a)]

7 + **4** ⟶ **8**

entry	Enyne **7**	R_2	equiv. of **4**	Yield **8** (%)
a	7a	$(CH_2)_2OH$	2	85
b	7a	$(CH_2)_2COOMe$	1	90
c	7a	$SiMe_3$	1.5	85
d	7b	CH_2OH	2	50

(a) $Pd(PPh_3)_4$ 5 %; CuI 10 %; 2 equiv. of n-butylamine in benzene 4h at 20°C.

When (Z)-dichloroethene was treated with an excess (2.3 equiv.)[22] of 1-alkyne in the presence of $Pd(PPh_3)_4$, CuI and n-butylamine in benzene[19, 9b], the symmetrical enediynes **8** (R^1=R^2) were obtained in good yield.

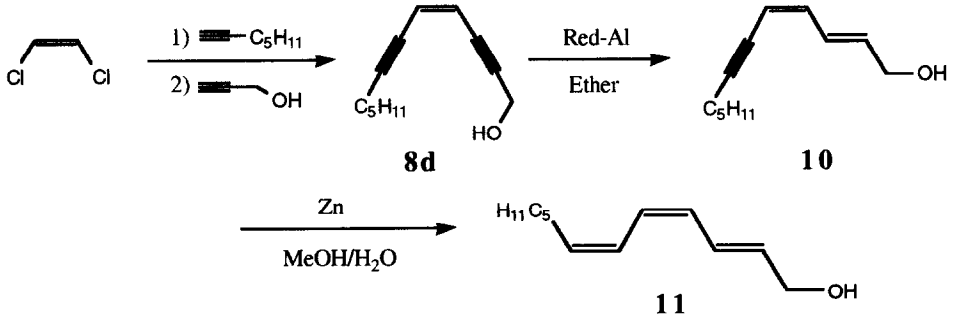
TableVI: Preparation of (Z)-symmetrical enediynes **8** (R^1=R^2) **(a)**

6 + **2** ⟶ **8** (R^1=R^2)

entry	R^1=R^2	equiv. of **2**	Yield **8** (R^1=R^2) (%)
a	$(CH_2)_2COOMe$	2.3	97
b	$(CH_2)Cl$	2.3	98
c	C_4H_9	2.3	87
d	$CH_2N(CH_3)_2$	2	85
e	$SiMe_3$	2.5	98

(a) $Pd(PPh_3)_4$ 5 %; CuI 10 % ; 2 equiv of n-butylamine in benzene at 20°C for 3h.

The enediynes are efficient precursors to conjugated trienes since a triple bond is easily reduced into a (Z) double bond by activated zinc[23].When a propargyl alcohol is present, the adjacent triple bond can also be transformed into a (E) double bond by using lithium aluminium hydride or Red-Al [R] as reducing agents[24-25].



An example illustrates the efficiency of the procedure: The enediyne **8d** was prepared (50%) by reaction of (1Z)-1- chloro-non-1-en-3-yne **7b** with propargylic alcohol in the presence of palladium-copper catalysts. Reduction of **8d** with Red-Al^R in ether at room temperature gives the (E,Z)-dienol **10** in 83% yield. Reduction of **10** with activated zinc gives the pure (E,Z,Z)-trienol **11** in 86% yield.

Experimental Section

^{1}H NMR spectra were recorded on a Brucker VM 250 instrument.The following abbreviations are used for spin multiplicity: s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quadruplet and m=multiplet.
Mass spectra were determined on a Nermag R 10/10 instrument in the NH_3 chemical ionisation mode.
I.R spectra were recorded on a Perkin Elmer Model 599 spectrophotometer and are reported in wave numbers(cm^{-1}).Analytical T.L.C.was performed on 0.25 mm precoated silica gel plates purchased from E.Merck.Products were purified using the flash chromatography technique on Kieselgel 60 (230-400 mesh ASTM, 0.040-0.063 mm) purchased from E.Merck.Commercial grade reagents and solvents were used as supplied with the following exceptions: Methylene dichloride, piperidine, triethylamine and benzene were distilled over CaH_2; pentane over P_2O_5; ether and tetrahydrofuran over sodium-benzophenone ketyl.Reactions sensitive to oxygen or moisture were conducted under an argon atmosphere.

General procedure for the preparation of the (E)-chloroenynes 3: To a mixture of (E)-1,2-dichloroethene (4.35g, 45 mmol), $Pd(PPh_3)_4$ (0.52g, 0.45 mmol), piperidine (1.53g, 18 mmol) and cuprous iodide (0.171g 0.9 mmol) the alkyne **2** (9 mmol) in C_6H_6 (5 ml) is added dropwise with stirring. After 2h at room temperature, the mixture is poured into a saturated aqueous solution of ammonium chloride and extracted with ether. The organic layer is washed with brine, dried ($MgSO_4$) and concentrated. Triphenylphosphine is precipitated with a minimum volume of ether/pentane (50/50). The crude product is purified by flash chromatography.

(1E)-1-chloro-oct-1-en-3-yne (3a) : purified by flash chromatography (pentane). NMR ^{1}H (ppm): 6.41 (H-1; dt; J_{1-2} = 13.5 Hz; J_{1-5} = 0.50 Hz); 5.9 (H-2; dt; J_{2-1} = 13.7 Hz ; J_{2-5} = 2.3 Hz); 2.3 (H-5; tdd; J_{5-6} = 5.9 Hz; J_{5-2} = 2.35 Hz; J_{5-1} = 0.45 Hz); 1.60 to 1.32 (4H-6,H-7; massif); 0.91 (H-8; t; J_{8-7} = 6.3 Hz).Anal. calcd. for $C_8H_{11}Cl$: C 67.37 ; H 7.77. Found: C 67.31; H 7.78.

(1E)-1-chloro non-1-en-3-yne (3b): purified by distillation $Eb_{(40\ mm)}$=85°C. NMR ^{1}H (ppm): 6.44 (H-1; d; J_{1-2} = 13.9Hz); 5.92 ((H-2; dt; J_{2-1} = 13.9Hz; J_{2-5} = 2.3Hz); 2.3 (H-5; td; J_{5-6} = 7.0Hz; J_{5-2} = 2.3Hz); 1.65 to 1.24 (H-6 to H-8; m); 0.91 (H-9; t; J_{9-8} = 6.9Hz). NMR ^{13}C (ppm): 128.6(C-1); 114.25 (C-2); 93.4 (C-3); 75.6 (C-4); 31.0 (C-7); 28.1 (C-6); 22.1 (C-8); 19.3 (C-5); 13.9 (C-9). IR (neat): 2960; 2850; 2210; 1590; 920. MS (m/e): 121 ((M-Cl)$^+$; 100%); 127 (^{35}Cl; M-C_2H_5)$^+$; 129 (^{37}Cl; M-C_2H_5)$^+$; 141 (^{35}Cl; M-CH3)$^+$; 143 (^{37}Cl; M-CH_3)$^+$; 156 (^{35}Cl; M)$^+$; 158 (^{37}Cl; M)$^+$. Anal. calcd. for $C_9H_{13}Cl$: C 69.03; H 8.30. Found: ; C 69.21; H 8.39.

(1E)-1-chloro-4-(trimethylsilyl)-but-1-en-3-yne (3c): purified by flash chromatography (pentane). NMR ^{1}H (ppm): 6.56 (H-1; d; J_{1-2} = 14 Hz); 5.92 (H-2; d; J_{2-1} = 14 Hz); 0.17 (3Me; s). NMR ^{13}C (ppm): 131.4 (C-1); 113.7 (C-2); 99.4, 97.5 (C-3, C-4); -0.45 (3 $\underline{C}H_3$). Anal. calcd. for $C_7H_{11}SiCl$: C 52.98; H 6.98. Found: C 52.89; H 7.08.

(1E)-1-chloro-5-hydroxy-dec-1-en-3-yne (3d)[26]: purified by flash chromatography (ethyl acetate/cyclohexane, 5/95). NMR ^{1}H (ppm): 6.42 (H-1; d; J_{1-2} = 13 Hz); 5.80 (H-2; dd; J_{2-1} = 13 Hz; J_{2-5} = 2 Hz); 4.27 (H-5; td; J_{5-6} = 6.5 Hz; J_{5-2} = 2 Hz); 2.4 (OH; s); 1.80 to 1.65 (H-6; m); 1.55 to 1.25 (H-7 to H-9; m); 0.90 (H-10; t; $J1_{0-9}$ = 6,7 Hz). NMR ^{13}C (ppm): 130.5 (C-1); 113.3 (C-2); 93.1 (C-3); 79.8 (C-4); 62.8 (C-5); 37.6 (C-6); 31.4 (C-8); 24.7 (C-7); 22.4 (C-9); 13.8 (C-10). IR (neat): 3340; 3060; 1580; 1120; 920. MS (m/e): 186 (^{35}Cl; M$^+$; 100 %,); 188 (^{37}Cl; M$^+$); 204 (^{35}Cl; M+18)$^+$. Anal. calcd. for $C_{10}H_{15}OCl$: C 64.34 ; H 8.10. Found: C 64.17 ; H 8.05.

(4E)-5-chloro-pent-4-en-2-yn-1-ol (3e): purified by flash chromatography (methanol/ methylene dichloride, 1/99). NMR ^1H (ppm): 6.56 (H-1; dd; J_{1-2} = 13.5 Hz; J_{1-5} = 0.5 Hz); 6.0 (H-2; dt; J_{2-1} = 13.5 Hz; J_{2-5} = 2 Hz); 4.4 (H-5; d; J_{5-2} = 2Hz). NMR ^{13}C (ppm): 130.8 (C-1); 113.0 (C-2); 89.8 (C-3); 80.3 (C-4); 50.7 (C-5) IR (neat): 3350; 3070; 3020; 2210; 1570; 970. MS (m/e): 115 $(M-1)^+$; 116 (^{35}Cl; M^+; 100 %); 118 (^{37}Cl, M^+). Anal. calcd. for C_5H_5OCl: C 51.57; H 4.30. Found: C 51.52; H 4.38.

General procedure for the preparation of (Z)-chloroenyne 7: To a solution of (Z)-1,2-dichloroethene (5.8g, 60 mmol) in benzene (40 ml), $Pd(PPh_3)_4$ (1.73g, 1.5 mmol), n-butylamine (4.4g, 60 mmol) and terminal alkyne **2** (30 mmol) are rapidly added. After 10 min., cuprous iodide (0.57g ; 3 mmol) is introduced into the stirred solution; the reaction is exothermic and the flask is cooled in a water bath. After 5h at room temperature the mixture is hydrolyzed with a saturated aqueous solution of ammonium chloride and extracted with Et_2O. The organic layer is washed with brine, dried ($MgSO_4$) and concentrated. The major part of triphenylphosphine is precipitated with a minimum volume of ether/pentane (50/50). The crude product is purified by flash chromatography.

(1Z)-1-chloro oct-1-en-3-yne (7a): purified by flash chromatography (methylene dichloride/cyclohexane, 20/80). NMR ^1H (ppm): 6.35 (H-1; d; J_{1-2} = 7.2 Hz); 5.90 (H-2; dt; J_{2-1} = 7.3 Hz; J_{2-5} = 2.18 Hz); 2.42 (H-5; td; J_{5-6} = 6.8 Hz; J_{5-2} = 2.17 Hz); 1.64 to 1.37 (H-6, H-7; m); 0.93 (3H-8; t; J_{8-7} = 7.05 Hz). NMR ^{13}C (ppm): 126.5 (C-1); 112.3 (C-2); 99.0 (C-3); 74.5 (C-4); 30.4 (C-6); 21.7 (C-5); 19.2 (C-7); 13.4 (C-8). IR (neat): 3080; 2950; 2220; 1600, 1450; 750. Anal. calcd. for $C_8H_{11}Cl$: C 67.37; H 7.77. Found: C 67.29; H 7.83.

(1Z)-1-chloro non-1-en-3-yne (7b): purified by distillation $Eb_{(0.5\ mm)}$ = 70°C. NMR ^1H (ppm): 6.26 (H-1; d; J_{1-2} = 7.3Hz); 5.85 (H-2; dt; J_{2-1} = 7.3Hz; J_{2-5} = 2.1Hz); 2.39 (H-5; td; J_{5-6} = 7.1Hz; J_{5-2} = 2.1Hz); 1.58 (H-6; m); 1.50 to 1.25 (H-7, H-8; m); 0.92 (H-9; t; J_{9-8} = 6.9Hz). NMR ^{13}C (ppm):126.6 (C-1); 112.4 (C-2); 99.3 (C-3); 74.5 (C-4); 30.9 (C-7); 28.2 (C-6); 22.1 (C-8); 19.5 (C-5); 13.7 (C-9). IR (neat): 3080; 2950; 2200; 1590; 1450. MS (m/e): 79^+ (100%); 127 (^{35}Cl, M-Et)$^+$; 129 (^{37}Cl, M-Et)$^+$; 141 (^{35}Cl, M-Me)$^+$; 156 (^{35}Cl, M)$^+$.

(1Z)-1-chloro-5-amino-5-methyl-hex-1-en-3-yne (7c): purified by chromatography (alumine, methylene dichloride/pentane, 25/75). NMR ^1H (ppm): 6.25 (H-1; d; J_{1-2} = 7.6Hz); 5.58 (H-2; d; J_{2-1} = 7.5 Hz); 1.42 ($N\underline{H}_2$; s); 1.05 (2Me; s). NMR ^{13}C (ppm): 128.9 (C-1); 111.6 (C-2); 105.3 (C-3); 73.5 (C-4); 45.3 (C-5); 31.0 ($2\underline{C}H_3$). IR (neat): 3360; 2990; 2220; 1440; 1335; 700. MS (m/e): 128 $(M-NH_2)^+$; 144 $(M+1)^+$. Anal. calcd. for $C_7H_{10}Cl$ C 58.54; H 7.02. Found: C 58.43; H 7.11.

(1Z)-1-chloro-4-trimethylsilylbut-1-en-3-yne (7d): purified by flash chromatography (pentane). NMR ^1H (ppm): 6.45 (H-1; d; J_{1-2} = 7Hz); 5.95 (H-2; d; J_{2-1} = 7Hz); 0.15 (H-5; s). Anal. calcd. for $C_7H_{11}SiCl$: C 52.98; H 6.98. Found: C 52.90; H 6.91.

(1Z)-1-chloro-5-hydroxy-dec-1-en-3-yne (7e): purified by flash chromatography (ethyl acetate/cyclohexane, 5/95). NMR ^1H (ppm): 6.44 (H-1; d; J_{1-2} = 7.5Hz); 5.86 (H-2; dd; J_{2-1} = 7.5Hz; J_{2-5} = 2Hz); 4.58 (1H-5; td; J_{5-6} = 6.5Hz; J_{5-2} = 2Hz); 2.84 (OH; s); 1.1 to 1.9 (H-6 to H-9; massif); 0.88 (H-10; t; J_{10-9} = 6.7Hz). NMR ^{13}C (ppm): 128.4 (C-1); 111.5 (C-2); 98.7 (C-3); 78.1 (C-4); 62.5 (C-5); 34.3 (C-6); 31.2 (C-8); 24.6 (C-7); 22.3 (C-9); 13.7 (C-10). IR (neat): 3350; 3050; 2900; 2870; 2150; 1580; 700. MS (m/e): 186 (M+); 204 ($(M+18)^+$, ^{35}Cl); 206 ($(M+18)^+$, ^{37}Cl). Anal. calcd. for $C_{10}H_{15}OCl$: C 64.34; H 8.1. Found: C 64.23; H 8.21.

General procedure for the preparation of (E) enediynes 5: To a solution of pure (E) chloroenyne **3** (20 mmol) in benzene (10ml) at room temperature, $Pd(PPh_3)_4$ (1.15g, 1mmol), piperidine (3.4 g, 40 mmol) and terminal alkyne **4** (proportion indicated in table IV) are added. Cuprous iodide (0.38g, 2 mmol) is introduced in the stirred solution. The reaction is monitored by thin layer chromatography.(# 9h) and the mixture is poured into a saturated aqueous solution of ammonium chloride and extracted with ether. The organic layer is washed with brine, dried over $MgSO_4$ and the solvent is removed in vacuo. The crude product is purified by flash column chromatography.

(3E)-1-(trimethylsilyl)-undec-3-en-1,5-diyne (5a): purified by flash chromatography (pentane).

NMR ^1H (ppm): 6.08 (H-4; dt; J_{4-3} = 16Hz; J_{4-7} = 2Hz); 5.92 (H-3; d; J_{3-4} = 16Hz); 2.35 (H-7; dt; J_{7-8} = 7Hz; J_{7-4} = 2Hz); 1.64 to 1.22 (H-8 to H-10; m); 0.90 (H-11; t; J_{11-10} = 7Hz); 0.18 ($(Me)_3$; s). NMR ^{13}C (ppm): 122.7 (C-3); 119.2 (C-4); 103.3 (C-2); 98.7 (C-1); 96.7 (C-5); 78.9 (C-6); 31.0 (C-9); 28.1 (C-8); 22.1 (C-10); 19.6 (C-7); 13.9 (C-11); -0.1 (Me_3). IR (neat): 2940; 2200; 2160; 2120; 1300; 1100; 935; 760. MS (m/e): 203 $(M-CH_3)^+$; 219 $(M+1)^+$; 236 $(M+18)^+$. Anal. calcd. for $C_{14}H_{22}Si$: C 77.03 ; H 10.08. Found: C 77.18 ; H 10.01.

Methyl (6Z) tetradec-6-en-4,8-diynoate (5b): purified by flash chromatography (cyclohexane/ethyl acetate, 90/10). NMR ^1H (ppm): 5.87 (H-6; H-7; m); 3.7 (OMe; s); 2.6 (H-2; H-3; m); 2.32 (H-10; td; J_{10-11} = 7Hz; J_{10-7} = 1.2Hz); 1.6 to 1.2 (H-11 to H-13; m); 0.9 (H-14; t; J_{14-13} = 7.1Hz). NMR ^{13}C (ppm): 172.2 (C-1); 121.0 (C-6); 119.6 (C-7); 95.4 (C-5); 92.2 (C-8); 79.6 (C-4); 78.9 (C-9); 51.7 (OMe); 33.2 (C-2); 31.0 (C-12); 28.2 (C-11); 22.1 (C-13); 19.5 (C-10); 15.4 (C-3); 13.9 (C-14). IR (neat): 3400; 2920; 2860; 2220; 1740; 1435.MS (m/e): 217 $(M-Me)^+$; 233 $(M+1)^+$; 250 $(M+18)^+$.

General procedure for the preparation of (Z)-enediynes 8 (Table V): To a solution of pure chloroenyne **7** (20 mmol) in benzene (10 ml), $Pd(PPh_3)_4$ (1.15g, 1 mmol), n-butylamine (3g, 40 mmol) and terminal alkyne **4** (proportion indicated in Table V) are added. Copper (I) iodide (0.38g, 2 mmol) is introduced in the stirred solution. The reaction is monitored by thin layer chromatography (# 4h). The mixture is poured into a saturated aqueous solution of ammonium chloride and extracted with ether. The organic phase is washed with brine, dried over $MgSO_4$ and the solvent is removed *in vacuo*. The crude product is purified by flash column chromatography.

(5Z)-dodec-5-en-3,7-diyn-1-ol (8a): purified by flash chromatography (methylene dichloride). NMR ^1H (ppm): 5.84 (H-5; d; J_{5-6} = 11Hz; J_{5-2} = 2Hz); 5.77 (H-6; td; J_{6-5} = 11Hz; J_{6-9} = 2Hz); 3,79 (H-1; dd; J_{1-2} = J_{1-OH} = 6Hz); 2.68 (H-2; td; J_{2-1} = 6Hz; J_{2-5} = 2Hz); 2.43 (2H-9; td; J_{9-10} = 6.5Hz; J_{9-6} = 2Hz); 2.15 (OH; t; J_{OH-1} = 6Hz); 1.52 (H-10, H-11; m); 0.94 (H-12; t; J_{12-11} = 7Hz). NMR ^{13}C (ppm): 119.2 (C-5); 117.9 (C-6); 97.6 (C-4); 93.4 (C-7); 79.4 (C-3); 77.9 (C-8); 60.3 (C-1) ; 30.1 (C-2); 23.4 (C-9); 21.3 (C-10); 18.8 (C-11); 13.0 (C-12). IR (neat): 3400; 2950; 2220; 1050. MS (m/e): 177 $(M+1)^+$; 194 [$(M+18)^+$, 100 %]. Anal. calcd. for $C_{12}H_{16}O$: C 81.77; H 9.15. Found: C 81.88; H 9.02.

Methyl (6Z)-tridec-6-en-4,8-diynoate (8b): purified by flash chromatography (methylene dichloride/cyclohexane, 50/50). NMR ^1H (ppm): 5.82 (H-6; dt; J_{6-7} = 11Hz; J_{6-3} = 2Hz); 5.74 (H-7; dt; J_{7-6} = 11Hz; J_{7-10} = 2Hz); 3.72 (OMe; s); 2.72 (H-2; m); 2.62 (H-3; m); 2.43 (H-10; m); 1.52 (H-11, H-12; m); 0.94 (H-13; t; J_{13-12} = 7Hz). NMR ^{13}C (ppm): 171.6 (C-1); 119.3 (C-6); 118.0 (C-7); 97.8 (C-5); 94.7 (C-8); 78.4 (C-4); 77.8 (C-9); 51.2 (OMe); 32.8 (C-2); 30.3 (C-11); 21.4 (C-10); 18.9 (C-3); 15.2 (C-12); 13.1 (C-13). IR (neat): 3050; 2950; 2240; 1750. SM (m/e): 219 $(M+1)^+$; 236 [$(M+18)^+$, 100 %]. Anal. calcd. for $C_{14}H_{18}O_2$: C 77.03; H 8.31. Found: C 77.15; H 8.35.

(3Z)-1-(trimethylsilyl) dec-3-en-1,5-diyne (8c): purified by flash chromatography (pentane). NMR ^1H (ppm): 5.84 (1H; dt; H-7; J_{7-8} = 10.9Hz; J_{7-4} = 2.1Hz); 5.76 (1H; d; H-8; J_{8-7} = 10.9Hz); 2.42 (2H;t d; H-4; J_{4-3} = 6.8Hz; J_{4-7} = 2.1Hz); 1.64 to 1.37 (4H; m; H-2; H-3); 0.93 (3H; t; H-1; J_{1-2} = 7.2Hz); 0.26 to 0.13 (3Me; m). RMN ^{13}C (ppm): 121.4 (C-8); 118.0 (C-7); 102.2 (C-9); 101.3 (C-6); 99.1 (C-10); 78.1 (C-5); 30.6 (C-3); 21.7 (C-4); 19.3 (C-2); 13.5 (C-1 ; -0.29 (C-11). Anal. calcd. for $C_{13}H_{20}Si$: C 76.40; H 9.86. Found: C 76.29; H 9.77.

General procedure for the preparation of (Z)-enediynes 8 (R^1=R^2), Table VI: To a flask, cooled in a water-ice bath, containing (Z)-1-2-dichloroethene (1.46g, 15 mmol), $Pd(PPh_3)_4$ (0.867g, 0.75 mmol), n-butylamine (5.03g, 68.8 mmol) and the alkyne **2** (34.4 mmol) in benzene (15 ml), copper (I) iodide (0.286g, 1.5 mmol) is added. After the reaction time indicated in the table, the mixture is poured into a saturated aqueous solution of ammonium chloride and extracted with ether. The organic phase is washed with brine, dried on $MgSO_4$ and the solvent is removed in vacuo. Triphenylphosphine is precipitated with pentane/ether (50/50). Flash column chromatography gives the desired compound **8** (R^1=R^2).

Dimethyl (6Z)-dodec-6-en-4,8-diyn-1,12 dioate (8, R^1=R^2=$(CH_2)CO_2Me$): purified by flash chromatography (cyclohexane/ethyl acetate, 50/50). NMR ^1H (ppm): 5.78 (H-6,H-7; s); 3.73 (2 OMe; s); 2.74

(H-2, H-11; m); 2.62 (H-3, H-10; m). NMR ^{13}C (ppm) : 171.6 (C-1; C-12); 118.7 (C-6; C-7); 95.2 (C-5; C-8); 78.2 (C-4; C-9); 51.2 (C-13; C-14); 32.8 (C-2; C-11); 15.1 (C-3; C-10). IR (neat): 2960; 2220; 1750; 1450; 1200. S.M. (m/e): 249 $(M+1)^+$; 265 [$(M+18)^+$, 100 %]. Anal. calcd for $C_{14}H_{16}O_4$: C 67.72; H 6.49. Found: C 67.67; H 6.41.

(6Z)-1;12-dichloro-dodec-6-en-4,8-diyne (8, R^1=R^2=$(CH_2)_2Cl$): purified by flash chromatography (cyclo-hexane/methylene dichloride 50/50). NMR ^1H (ppm): 5.84 (H-6, H-7; t; $J_{6-3} = J_{7-10} = 0.8Hz$); 3.80 (H-3, H-10; t; $J_{3-2} = J_{10-11} = 6.25Hz$); 2.67 (H-1, H-12; t; $J_{1-2} = J_{12-11} = 6.6Hz$); 2.08 (H-2, H-11; quintet; $J_{2-1} = J_{2-3} = J_{11-10} = J_{11-12} = 6.5Hz$). NMR ^{13}C (ppm): 118.9 (C-6; C-7); 95;40 (C-5; C-8); 79.0 (C-4; C-9); 43.30 (C-1; C-12); 31.0 (C-2; C-11); 16.8 (C-3; C-10). IR (neat): 3020; 2960; 2220; 1660; 1430; 750. SM (m/e): 228 [$(M+1)^+$; 2 ^{35}Cl]; 230 [$(M+1)^+$ ^{35}Cl, ^{37}Cl]; 246 $(M+18)^+$. Anal. calcd. for $C_{12}H_{14}Cl_2$: C 62.90; H 6.16. Found: C 62.78; H 6.14.

(7Z)-tetradec-7-en-5,9-diyne (8, R^1=R^2=C_4H_9): purified by flash chromatography (methylene dichloride /cyclohexane 20/80). NMR ^1H (ppm): (ppm) : 5;77 (H-7, H-8; s); 2.42 (H-11, H-4; t; $J_{4-3} = J_{11-12} = 6.5Hz$); 1.52 (H-2; H-3; H-12; H-13; m); 0.93 (H-1, H-14; t; $J_{1-2} = J_{14-13} = 7Hz$). NMR ^{13}C (ppm): 118.6 (C-7; C-8); 97.0 (C-6; C-9); 78.2 (C-5; C-10); 30.5 (C-3; C-12); 21.6 (C-2; C-13); 19.1 (C-4; C-11); 13.2 (C-1; C-14). IR (neat): 3020; 2940; 1680; 1460. Anal. calcd. for $C_{14}H_2O$: C 89.29; H 10.70. Found: C 89.12; H 10.83.

(4Z)-1,8-(N,N,N',N' tetramethyl 1,8-diamino) oct-4-en-2, 6-diyne (8,R^1=R^2=$CH_2N(CH_3)_2$: purified by flash chromatography (methylene dichloride/methanol 50/50). NMR ^1H (ppm): 5.75 (H-4, H-5; s); 3.4 (H-1, H-8; s); 2,3 (4 Me; s). NMR ^{13}C (ppm) : 128.3 (C-4; C-5); 93.9 (C-3; C-6); 79.0 (C-2; C-7); 48.3 (C-1; C-8); 43.8 (4 Me). SM (m/e): 102 $(M-2N(Me)_2)^+$; 146 $(M-N(Me)_2)^+$; 191 $(M+1)^+$. Anal. calcd. for $C_{12}H_{18}N_2$: C 75.74; H 9.53. Found: C 75.81; H 9.46.

(3Z)-1,6-bis(trimethylsilyl)hex-3-en-2,5-diyne (8, R^1=R^2=$SiMe_3$): For the preparation of this product, trimethylsilyl acetylene was slowly added to the reaction mixture in order to avoid the formation of bis(trimethylsilyl) butadiyne. Purified by flash chromatography (pentane/ether 90/10).
NMR ^1H (ppm): 5.88 (H-3, H-4; s); 0,20 (6 Me; s). NMR ^{13}C: (ppm) : 120.5 (C-3; C-4) ; 102.9 (C-2;.C-5) ; 101.9 (C-1; C-6) ; -0.21 (C-7; C-8). Anal. calcd. for $C_{12}H_{20}Si_2$: C 65.37; H 9.14. Found: C 65.49; H 9.19.

(4Z)-dodec-4-en-2,6-diyn-1-ol (8d): Prepared from propargyl alcohol and (1Z)-1-chloro-non-1-en-3-yne **7b** according to the general procedure for the preparation of (Z)-enediynes **8**.(Table V). Purified by flash chromatography (pentane and ether/pentane, 15/85)
NMR ^1H (ppm): 5.84 (H-5; d; $J_{5-4} = 10.9Hz$): 5.76 (H-4; d; $J_{4-5} = 10.96Hz$); 4.45 (H-1; s); 2.39 (H-8; td; $J_{8-9} = 7.05Hz$; $J_{8-5} = 1.5Hz$); 2.08 (OH; s); 1.57 (H-9; quintet; $J_{9-8} = J_{9-10} = 7.12Hz$); 1.58 to 1.23 (H-10, H-11; m); 0.90 (H-12; t; $J_{12-11} = 6.7Hz$). NMR ^{13}C (ppm): 120.7 (C-4); 117.3 (C-5); 99.2 (C-6); 93.9 (C-3); 82.9 (C-7); 77.9 (C-2); 51.4 (C-1); 30.9 (C-10); 28.15 (C-9); 22.1 (C-8); 19.6 (C-11); 13.85 (C-12).
IR (neat): 3350; 2910; 2850; 2200; 1150. MS (m/e): 105 ($M-C_5H_{11})^+$, 100%); 119 $(M-C_4H_9)^+$; 176 (M^+); 194 $(M+18)^+$. Anal calcd for $C_{12}H_{16}O$: C 81.81 ; H 9.09 Found: C 81.71 ; H 9.13.

(2E,4Z) Dodeca-2-4-dien-6-yn-1-ol 10: To a solution of Red-Al^R [15] (1.24 ml, 4.3 mmol) in ether (2ml) at 5°C, a solution of enediyne **8d** (0.390g, 2.2mmol) in ether (2ml) is added slowly. After stirring for 1h at 0°C, the mixture is hydrolyzed with an ice/water solution of sulfuric acid 2M, extracted with ether (2x30ml), washed with water (2x25ml). The organic layer is dried over $MgSO_4$, concentrated and purified by flash chromatography (silica gel, ether/pentane, 20/80) (0.327g, 83%).
NMR ^1H (ppm): 6.78 (H-3; ddt; $J_{3-2} = 15.3Hz$; $J_{3-4} = 10.9Hz$; $J_{3-1} = 0.94Hz$); 6.32 (H-4; t; $J_{4-5} = 10.8Hz$); 5.97 (H-2; dt; $J_{2-3} = 15.4Hz$; $J_{2-1} = 5.6Hz$); 5.46 (H-5; d; $J_{5-4} = 10.8Hz$); 4.25 (H-1; dd; $J_{1-2} = 5.3Hz$; $J_{1-3} = 0.8Hz$); 2.38 (H-8; td; $J_{8-9} = 6.9Hz$; $J_{8-5} = 2.2Hz$); 1.87 5OH; sl); 1;65 to 1.49 (H-11; m); 1.49 to 1.25 (H-9, H-10; m); 0.90 (H-12; t; $J_{12-11} = 6.9Hz$). NMR ^{13}C (ppm): 137.7 (C-4); 134.4 (C-2); 128.4 (C-3); 110.5 (C-5); 97.4 (C-6); 78.7 (C-7); 63.3 (C-1); 31.1 (C-10); 28.2 (C-11); 22.2 (C-9); 19.6 (C-8); 13.9 (C-12).
IR (neat): 3300; 2910; 2200; 1450; 970. MS (m/e): 161 ($(M-OH)^+$, 100%); 178$(M)^+$; 196 $(M+18)^+$.

(2E,4Z,6Z)-dodeca-2,4,6-trien-1-ol 11: To a suspension of activated zinc (13g) prepared as previously described[23, 9c] in MeOH/H_2O 50/50 (60ml), is added a solution of dienyne **10** (0.200g, 1.12 mmol) in methanol/water 50/50 (2ml). After stirring at room temperature for 16h, the mixture is filtered through a pad of Celite, washed with MeOH (2x20ml); the combined solutions are concentrated to 1/3 of the original volume and extracted with ether (3x30ml). The organic layer is washed with water (2x30ml), and dried over $MgSO_4$. After evaporation of the solvent and flash chromatography (silica gel, ether/pentane 15/85) the trienol (E,Z,Z) **11** is obtained in 86% yield (0.174g).NMR ^1H (ppm): 6.74 (H-3; ddt; J_{3-2} = 15.2Hz; J_{3-4} = 10.9Hz; J_{3-1} = 1.1Hz); 6.45 (H-5; t; $J_{5-4} = J_{5-6}$ = 11.1Hz); 6.28 (H-4; t; $J_{4-5} = J4_{-3}$ = 10.95Hz); 6.01 (H-6; t; $J_{6-5} = J_{6-5}$ = 11.0Hz); 5.87 (H-2; dt; J_{2-3} = 15.2Hz); J_{2-1} = 5.9Hz); 5.56 (H-7; dt; J_{7-6} = 10.7Hz; J_{7-8} = 7.6Hz); 4.23 (H-1; d; J_{1-2} = 5.7Hz); 2.2 (H-8; q; $J_{8-9} = J_{8-7}$ = 7.6Hz); 1.7 (OH); 1.48 to 1.2 (H-9 to H-11; m); 0.88 (H-12; t; J_{12-11} = 6.6Hz). NMR ^{13}C (ppm): 134.1 (C-7); 132.8 (C-2); 127.8 (C-6); 126.5 (C-4); 125.0 (C-5); 123.2 (C-3); 63.4 (C-1); 31.4 (C-10); 29.2 (C-11); 27.5 (C-8); 22.5 (C-9); 14.0 (C-12). IR (neat): 3300; 2940; 2905; 1450; 1080. MS (m/e): 163 ($(M-OH)^+$, 100%); 180 (M^+); 198 $(M+18)^+$.

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