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A General Access to Optically Pure Epoxypolyynes: Asymmetric Synthesis of Antifeedant Natural Products

D. Grandjean, P. Pale* and J. Chuche

Laboratoire de Chimie Organique Physique, associé au CNRS, Université de Reims-Champagne-Ardenne, BP 347, 51100 Reims, France.

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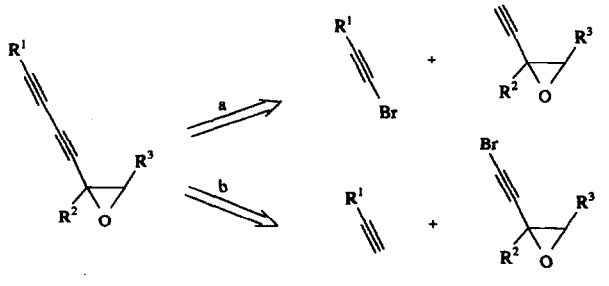
Abstract: A general asymmetric approach toward cis-epoxypolyynes is described using optically pure (2R, 3S)-5-bromo-2,3-epoxy-4-pentyn-1-ol **1a** as the key intermediate. From this intermediate, the synthesis of 2 epoxy polyyne natural products was carried out in 6 steps with a 42% overall yield.

INTRODUCTION

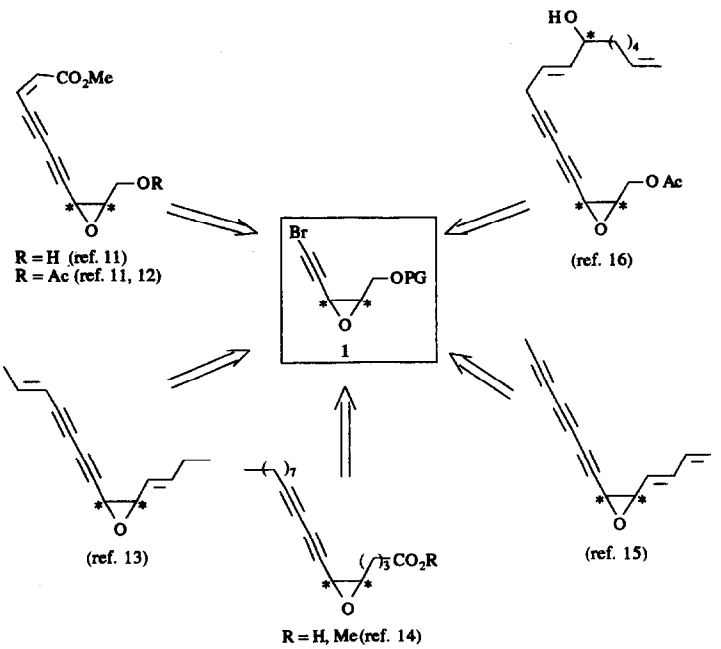
Polyynes and polyenynes are often encountered as secondary metabolites in higher plants, mainly from the Compositae and Umbelliferae families.[1-4] These polyacetylenic natural compounds also occur in higher fungi such as the Basidiomycetes.[1] Biosynthetically these natural products evolve from fatty acids[5] and often involve further oxidation leading to epoxypolyynes and/or their hydroxyl derivatives.

As these epoxypolyyne compounds are key intermediates, often exhibiting interesting biological activities, we embarqued on a program devoted to the asymmetric synthesis of such natural products. To date, only a small number of syntheses leading to these compounds have been described,[1] none of which refer to an asymmetric route. A general and convergent approach to *cis*-epoxypolyynes might rely on the coupling of two acetylenic fragments (Scheme 1). Although dissymmetric coupling can be obtained from two terminal acetylenes,[6] higher selectivities and yields are usually obtained when a bromoacetylene is



Scheme 1

coupled with a terminal acetylene, the so-called Cadiot-Chodkiewicz reaction.[7,8] When applied to the retrosynthetic analysis of naturally occurring polyacetylene epoxides, the Cadiot-Chodkiewicz reaction led to two strategies, one involving the coupling of a halogenated acetylene with an ethynyloxirane (Scheme 1, route a) the other one based on the coupling of a halogenoacetylenic epoxide with a terminal acetylene (Scheme 1, route b). As we have already demonstrated, bromoethynyl epoxides[9] can be conveniently obtained optically pure starting from enantiomerically pure (2*S*, 3*R*)-4-butyryloxy-2,3-epoxy-1-butanol,[10] the total synthesis of chiral *cis*-epoxypolyynes could be realized by the coupling of *cis*- 5-bromo-2,3-epoxy-4-pentyn-1-ol derivatives **1** to suitably substituted terminal acetylenes (Scheme 2).



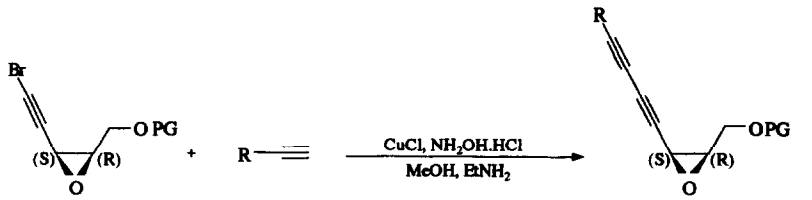
Scheme 2 (PG = protective group)

RESULTS AND DISCUSSION:

To demonstrate the efficiency of the above route and in order to determine suitable reaction conditions, we first performed preliminary experiments with commercialy available terminal acetylenes. Due to the basic and nucleophilic nature of the reaction conditions usually required for the Cadiot-Chodkiewicz coupling, opening of the oxirane, especially for α-unsaturated oxiranes, and/or Payne rearrangement[17] were

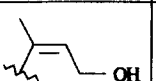
anticipated as the major source of side reactions during the coupling of bromoethynyl epoxides with terminal alkynes. Therefore the search for optimized conditions were critical for the success of the planned strategy.

Two different terminal acetylenes were choosen: 1-hexyne **2**, as the simplest representative member of 1-alkynes and (*Z*)-3-methyl-2-penten-4-yn-1-ol **3**. This commercially available enynol alkyne was selected as a model for the synthesis of complex polyyne natural products, since it contains functionalities similar to that found in the natural products, especially the double bond (Scheme 2). With the planned strategy (Scheme 2), double bond isomerization should be avoided during the coupling step. The results are disclosed in Table 1.

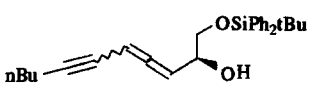


bromoethynyl epoxides **1a-c** epoxydiynes **4a-b, 6a**

Table 1: Cadiot-Chodkiewicz Coupling Reaction between Bromoethynyl Epoxides and Terminal Acetylenes.

Entry	Bromoethynyl Epoxide (PG)	R	Temp.(°C)	Yields[a]	Products
1	**1a** ($SiPh_2tBu$)	nBu **2**	25[b]	57%[c]	**4a** + **5a** (27%)
2	**1a** ($SiPh_2tBu$)	nBu **2**	10	66%[c]	**4a** + **5a** (< 5%)
3	**1a** ($SiPh_2tBu$)	nBu **2**	0	91%	**4a**
4	**1b** (COPr)	nBu **2**	0	84%	**4b**
5	**1c** (H)	nBu **2**	0	96%	**4c**
6	**1a** ($SiPh_2tBu$)	 **3**	25[b]	50%[d]	**6a**
7	**1a** ($SiPh_2tBu$)		0	84%	**6a**

5a



a) yield of isolated products; b) as the initial reaction was exothermic, the actual temperature was higher at the beginning of the reaction; c) minor polar by-products were also formed; d) several unidentified products were formed from which only the expected product was characterized.

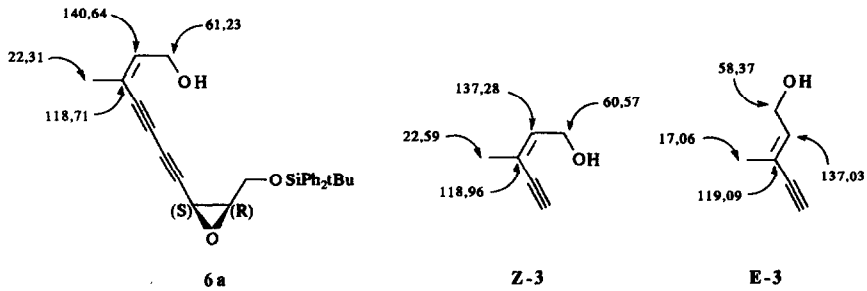
When the standard Cadiot-Chodkiewicz conditions[18] were used with **1a** and the 1-hexyne **2** at room temperature, a rapid reaction occured as evidenced by the color changes of the reaction mixture after the addition of **1a**. Notwithstanding, TLC analysis showed the formation of a multitude of products, in which the expected product was eventually detected. However, when **1a** and 5-hexyn-1-ol **2** were both added to a mixture of copper chloride, hydroxylammonium hydrochloride and ethylamine in methanol and water at room temperature (Table 1, entry 1), a highly exothermic reaction took place. The starting materials were rapidly consummed and within 15 mn, two new major products were formed, together with some polar compounds. From this mixture, the expected product **4a** was isolated in 57 % yield. The structure of **4a** was clearly evidenced from NMR and IR spectra analysis. ^{1}H NMR spectrum showed the disappearance of the terminal acetylenic proton and the presence of a butyl chain connected to an unsaturated system. ^{13}C NMR spectrum revealed the presence of the expected diyne function with four small singlet signals at 65.42, 71.03, 71.21 and 81.56 ppm. This structure was confirmed by the IR spectrum with an absorption at 2260 cm^{-1}, characteristic of a diyne. The second product **5a** required a more detailed investigation to reveal its structure. From ^{1}H and ^{13}C NMR spectra, its was evident that a hexynyl chain was present in the structure, and that the epoxy part had disappeared. Instead, the ^{1}H NMR spectrum showed the presence of an hydroxyl proton, a highly coupled proton at 4.25 ppm and two protons at low field (5.57 and 5.41 ppm). COSY and decoupling experiments showed that these two protons were both coupled together with a rather small coupling constant (6.4 Hz), one was coupled with the methyne adjacent proton at 4.25 ppm (6.2 Hz), and both exhibited long range coupling with methylene protons at 2.1 ppm. ^{13}C NMR spectra finally allowed to suggest an allenic structure for **5a**, with a characteristic singlet signal at 211.5 ppm and two doublets at 94.6 ppm and 79.0 ppm. The IR spectrum confirmed this attribution with the characteristic absorption of allene at 1940 cm^{-1}. The origin of this allenynol **5a** is still unclear.[19]

The fact that almost no opening of the oxirane by the excess of ethylamine or methanol occured in these conditions prevented improvement of the yield by modifying the relative amount of reagents.[20] We finally found that a careful control of the reaction temperature effectively prevented rearrangement and oxirane opening. At 10°C (water bath), the yield of the coupling product increased but side reaction products were still present (Table 1, entry 2). However , at ice bath temperature, the desired coupled compound **4a** was almost the sole product (Table 1, entry 3).

In these conditions, the coupling reaction became insensitive to the nature of the protecting group (ester vs silyl group; Table 1, entry 4 vs 3) and even unprotected bromoethynyl epoxyalcohol, **1c**, could be cleanly coupled with alkyne (Table 1, entry 5).

When the Cadiot-Chodkiewicz coupling reaction was performed between **1a** and (*Z*)-3-methyl-2-penten-4-yn-1-ol **3** at room temperature (Table 1, entry 6), the expected product **6a** was obtained in only 50 % yield. A collection of minor by-products was also formed, but no attempt was undertook to isolate them. In the conditions defined above, **6a** was isolated in good yield (Table 1, entry 7). No isomerization of the double bond occured during the coupling reaction as evidenced by the comparison of the ^{1}H and ^{13}C NMR spectra of the coupling product **6a** and the NMR spectra of both (*E*) and (*Z*)-3-methyl-2-penten-4-yn-

1-ol **3**. In the ^1H NMR spectrum of **6a**, the chemical shift of the methylene group adjacent to the double bond is analogous to the one observed for the (*Z*) isomer of **3** (4.28 ppm compared to 4.31 ppm for (*Z*)-**3** and 4.18 ppm for (*E*)-**3**) (Scheme 3). The ^{13}C NMR data are more conclusive. The corresponding carbon signal, C-1 in **6a**, is observed at 61.23 ppm, a value close to the one measured for (*Z*)-**3**: 60.57 ppm (compared to 58.37 ppm for (*E*)-**3**). The chemical shift of the carbon of the methyl group borne by the double bond in **6a** is almost identical to the one in (*Z*)-**3** , 22.31 ppm and 22.59 ppm respectively (compared to 17.06 ppm for (*E*)-**3**).

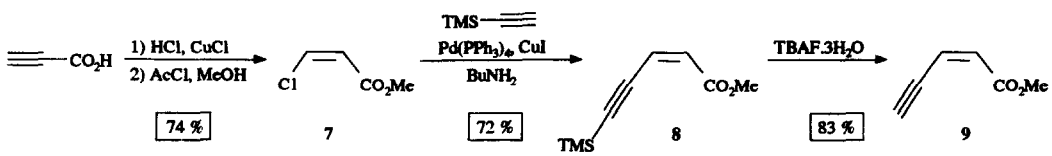


Scheme 3

These results indicate that, providing the above modifications were applied, the Cadiot-Chodkiewicz coupling can be carried out without isomerization of a double bond, even a conjugated one, and that the integrity of the epoxide can be preserved during the reaction. The reaction conditions also proved to be compatible with protected as well as unprotected bromoethynylepoxyalcohols.

To illustrate the effectiveness of this method, we then synthesized the (8*S*, 9*R*) enantiomer of methyl (2*Z*)-8,9-epoxy-10-hydroxy-4,6-decadiyn-2-enoate **10c** and its acetate **10d** (Scheme 2).[21] Both are natural products isolated from the Compositaes *Chrysothamnus nauseus* and *C. parryi*, and both exhibit insect antifeedant activity.[11,12] To the best of our knowledge, no synthesis of these compounds has yet been reported. The copper catalyzed coupling reaction described above between (2*R*, 3*S*)-5-bromo-2,3-epoxy-4-pentyn-1-ol **1**, protected or not, and the *Z* isomer of methyl 2-penten-4-ynoate should provide us with the desired natural products.

Methyl (*Z*)-2-penten-4-ynoate **9** was prepared from propiolic acid (Scheme 4). Copper catalyzed

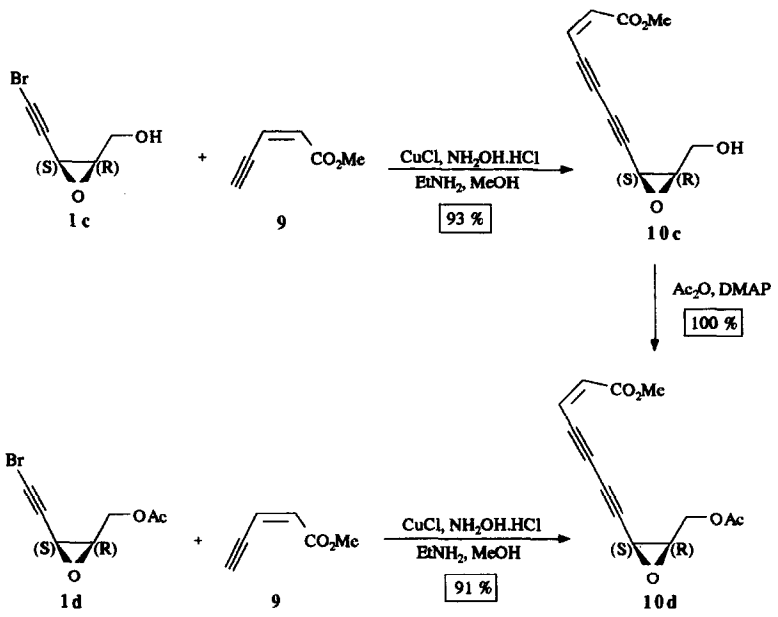


Scheme 4

addition of hydrochloric acid to propiolic acid followed by esterification with methanol in the presence of a catalytic amount of acetyl chloride only produced the *Z* isomer **7**.[22] Palladium catalyzed coupling of **7** with trimethylsilylacetylene[23-24] provided the enyne **8** in good yield (72 %) without isomerization of the double bond. Subsequent desilylation with TBAF.$3H_2O$ furnished the required methyl (*Z*)-2-penten-4-ynoate **9** in 44 % overall yield (4 steps).

This enyne **9** was then coupled with the unprotected (2*R*, 3*S*)-5-bromo-2,3-epoxy-4-pentyn-1-ol **1c** under the conditions used for the enyne model **3** (Table 1, entry 7). From this reaction the optically active epoxyendiyne **10c** was isolated in 93 % yield ($[\alpha]_D^{22}$ + 64°, c 0.27 in CH_2Cl_2) (Scheme 5). Since an ester protective group was tolerated during the Cadiot-Chodkiewicz reaction in the conditions we used (*cf.* Table 1, entry 4), direct coupling of **7** with the acetate of (2*R*, 3*S*)-5-bromo-2,3-epoxy-4-pentyn-1-ol **1d**,[9,10] was envisaged. The corresponding acetate **10d** was obtained either by acetylation of **10c** with DMAP in ether in quantitative yield or effectively by direct coupling of the acetate **1d** with **9** in 91 % yield ($[\alpha]_D^{22}$ + 18°, c 0.32 in CH_2Cl_2) (Scheme 5).

Both compounds **10c** and **10d** proved to be spectroscopically identical to the natural products.[11,12] The optical purity of **10d** was determined by ^1H NMR in the presence of $Eu(hfc)_3$ and showed the presence of a single enantiomer. In the absence of an optical rotation for the natural products **10c** and **10d**, the optical purity of synthetic **10c** and **10d** was inferred from the ^1H NMR data and from the optical purity of (2*R*, 3*S*)-5-bromo-2,3-epoxy-4-pentyn-1-ol **1c**.



Scheme 5

CONCLUSION

In conclusion, we have developed an efficient synthetic route to α-polyunsaturated oxirane derivatives which allow excellent yields and high optical purities to be obtained. The application of these chiral α-unsaturated oxiranes to the first total synthesis of the naturally occuring antifeedant methyl (2*Z*, 8*S*, 9*R*)-8,9-epoxy-10-hydroxy-4,6-decadiyn-2-enoate **10c** and the corresponding acetate **10d** in optically pure form has been also demonstrated.

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EXPERIMENTAL SECTION

General remarks: All melting points are uncorrected. IR spectra were recorded on a Philips SP3-300 infrared spectrophotometer. NMR spectra were recorded with a Bruker AC-300 spectrometer at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C or with a Bruker AC-250 spectrometer at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C. ^{1}H NMR chemical shifts are expressed in parts per million downfield relative to internal tetramethylsilane ($\delta = 0$). Splitting patterns are assigned as: s, singlet; d, doublet; t, triplet; q, quartet; sext, sextet, m, multiplet. ^{13}C NMR were recorded using the central peak of the $CDCl_3$ signal as the internal standard ($\delta = 77.00$) or the central peak of the C_6D_6 signal as the internal standard ($\delta = 128.00$). Mass spectra were recorded on a JEOL D300 mass spectrometer at 70 ev. Optical rotations were measured using a Perkin-Elmer polarimeter at the sodium D line and reported as follow: $[\alpha]_D^{22}$ (concentration in g/100 ml, solvent, ee %). All reactions were monitored by thin-layer chromatography using 0.25 mm E. Merck silica gel plates (60 F_{254}) with a mixture of petroleum ether (PE) and ethyl acetate (AE) as eluent. Flash column chromatography was performed on silica gel Merck 60 (particle size 0.040-0.063 mm). Ether was distilled from sodium/benzophenone; methanol from sodium. *n*-Butylamine and benzene were distilled from calcium hydride.

The optically pure *cis*- 5-bromo-2,3-epoxy-4-pentyn-1-ol derivatives **1a-d** were obtained starting from enantiomerically pure (2*S*, 3*R*)-4-butyryloxy-2,3-epoxy-1-butanol [9-10] through a three step sequence followed by protecting group modification.[25]

All other reagents were commercially available from either Janssen or Aldrich, except (*Z*)-3-methyl-2-penten-4-yn-1-ol **3** which is available from Fluka.

General procedure for the Cadiot-Chodkiewicz coupling of oxyranyl bromoacetylenes:

The terminal acetylene (1.1 eq.) followed by the bromoethynylepoxide (1 eq.) were added to a stirred solution of CuCl (0.05 eq.), $NH_2OH.HCl$ (0.3 eq.) and $EtNH_2$ (70 % in H_2O, 1ml/mmol) in MeOH (1 ml/mmol) cooled to 0 °C. If the solution turned blue, more $NH_2OH.HCl$ was added. After 10 min at 0 °C Et_2O was added and the phases separated. The aqueous layer was further extracted three times with Et_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered then concentrated *in vacuo*. The crude product was purified by flash column chromatography.

(2*R*, 3*S*)-1-*tert*-Butyldiphenylsilyloxy-2,3-epoxy-4,6-undecadiyne: 4a
(148 mg, 91 %) as a colourless oil. TLC R_f 0.47 (PE-EA : 95-5); $[\alpha]_D^{22}$ + 13° (c 0.42, CH_2Cl_2, ee >99 %); IR (thin film) 2260, 1590, 1460, 1430, 1140, 1110, 820, 750 cm^{-1}; ^1H NMR (C_6D_6) δ : 0.63-0.73 (3H, m), 1.07-1.20 (4H, m), 1.17 (9H, s), 1.77-1.84 (2H, m), 2.94 (1H, ddd, J = 5.4, 4.9, 3.9 Hz), 3.02 (1H, d, J = 3.9 Hz), 3.95 (1H, dd, J = 11.5, 4.9 Hz), 3.99 (1H, dd, J = 11.5, 5.4 Hz), 7.20-7.32 (6H, m), 7.72-7.84 (4H, m); ^{13}C NMR (C_6D_6) δ 13.5, 18.9, 19.4, 22.0, 27.0, 30.1, 44.3, 58.1, 63.8, 65.4, 71.0, 71.2, 81.6, 128.1, 130.0, 133.5, 136.0; mass spectrum, m/e (intensity) 359 (M^+-57, 100), 329 (73), 223 (25), 199 (38), 163 (42), 135 (31), 105 (25). Anal. Calcd. for $C_{27}H_{32}O_2Si$: C, 77.84; H, 7.74. Found : C, 77.67; H, 7.89.

1-*tert*-Butyldiphenylsilyloxy-3,4-undecadien-6-yn-2-ol: 5a
colourless oil. TLC R_f 0.4 (PE-EA : 90-10); IR (CCl_4) 3500, 2210, 1940, 1420, 1250, 1100, 1005, 700 cm^{-1}; ^1H NMR (C_6D_6) δ 0.76 (3H, t, J = 7.2 Hz), 1.15 (9H, s), 1.20-1.50 (4H, m), 2.1-2.2 (2H, m), 3.62 (1H, dd A part of an AB system, J = 10.2, 5.7 Hz), 3.69 (1H, dd B part of an AB system, J = 10.2, 4.4 Hz), 4.25 (2H, dddd, J = Hz), 5.41 (1H, ddt, J = 6.4, 6.2, 1.4 Hz) 5.57 (1H, ddt, J = 6.4, 2.3, 2.3 Hz), 7.20-7.32 (6H, m), 7.72-7.84 (4H, m); ^{13}C NMR (C_6D_6) δ 13.6, 19.4, 22.1, 27.0, 30.9, 67.9, 70.2, 73.2, 79.0, 92.5, 94.6, 128.5, 130.4, 133.5, 135.9, 211.5.

(2*R*, 3*S*)-1-Butyryloxy-2,3-epoxy-4,6-undecadiyne: 4b
(96 mg, 84 %) as a colourless oil. TLC R_f 0.73 (PE-EA : 90-10); $[\alpha]_D^{22}$ + 9° (c 0.55, CH_2Cl_2, ee >99 %); IR (thin film) 2260, 1750, 1250, 1180 cm^{-1}; ^1H NMR (C_6D_6) δ 0.67 (3H, m), 0.75 (3H, t, J = 7.4 Hz), 1.07-1.22 (4H, m), 1.47 (2H, sext, J = 7.4 Hz), 1.85 (2H, td, J = 7.2, 0.7 Hz), 2.01 (2H, t, J = 7.4 Hz), 2.88 (1H, ddd, J = 6.6, 4.0, 4.0 Hz), 3.02 (1H, dt, J = 4.0, 0.7 Hz), 4.11 (1H, dd, J = 12.2, 6.6 Hz), 4.31 (1H, dd, J = 12.2, 4.0 Hz); ^{13}C NMR (C_6D_6) δ 13.5, 13.6, 18.5, 18.9, 22.0, 30.1, 35.7, 43.9, 55.3, 63.4, 65.1, 70.2, 71.4, 82.1, 172.5.

(2*R*, 3*S*)-2,3-Epoxy-4,6-undecadiyn-1-ol: 4c
(110 mg, 96 %) as a colourless oil. TLC R_f 0.49 (PE-EA : 70-30); $[\alpha]_D^{22}$ + 50° (c 0.38, CH_2Cl_2, ee >99 %); IR (thin film) 3350, 2260, 1230, 1050, 910, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (3H, t, J = 7.2

Hz), 1.35-1.60 (4H, m), 2.10 (OH), 2.28 (2H, t, J = 7.2 Hz), 3.30 (1H, ddd, J = 6.2, 4.2, 4.2 Hz), 3.58 (1H, d, J = 4.0 Hz), 3.82 (1H, dd, J = 12.4, 6.2 Hz), 3.93 (1H, dd, J = 12.4, 4.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.4, 18.9, 21.9, 30.0, 44.6, 57.8, 62.0, 64.2, 69.4, 71.0, 82.0.

(2*Z*, 8*S*, 9*R*)-10-(*tert*-Butyldiphenylsilyloxy)-8,9-epoxy-3-methyl-4,6-decadiyn-2-en-1-ol: 6a

(132 mg, 84 %) as a yellow oil. TLC R_f 0.49 (EP-EA : 70-30); $[\alpha]_D^{22}$ + 6° (c 0.65, CH_2Cl_2, ee >99 %); IR (thin film) 3420, 2230, 1590, 1460, 1425, 1100, 830, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s), 1.84 (OH), 1.87 (3H, dt, J = 1.2, 1.2 Hz), 3.32 (1H, td, J = 5.0, 4.0 Hz), 3.56 (1H, d, J = 4.0 Hz), 3.90 (2H, d, J = 5.0 Hz), 4.28 (2H, dq, J = 6.9, 1.2 Hz), 6.04 (1H, tq, J = 6.9, 1.2 Hz), 7.35-7.47 (6H, m), 7.65-7.73 (4H, m); ^{13}C NMR ($CDCl_3$) δ 19.2, 22.3, 26.7, 44.5, 58.4, 61.2, 63.1, 69.9, 76.3, 77.8, 78.0, 118.7, 127.7, 129.8, 133.0, 135.5, 140.6; mass spectrum, m/e (intensity) 373 (M^+-57, 3), 241 (56), 223 (27), 199 (63), 163 (100), 135 (21), 105 (25), 77 (21). Anal. Calcd for $C_{27}H_{30}O_3Si$: C, 75.31; H, 7.02. Found : C, 75.57; H, 7.03.

Synthesis of the naturally occuring antifeedants:
(8*S*, 9*R*) methyl (2*Z*)-8,9-epoxy-10-hydroxy-4,6-decadiyn-2-enoate 10c and
(8*S*, 9*R*) methyl (2*Z*)-8,9-epoxy-10-acetoxy-4,6-decadiyn-2-enoate 10d:

Methyl (*Z*)-3-chloro-2-propenoate: 7

2-Propynoic acid (10 ml, 162 mmol) was added dropwise to a stirred solution of aqueous HCl (12 M, 26 ml, 312 mmol, 1.92 eq.) and CuCl (0.964 g, 9.74 mmol, 0.06 eq.) cooled to 0 °C and the reaction mixture was then stirred at this temperature for 10 h. The aqueous layer was then extracted several times with $CHCl_3$ and the combined organic extracts concentrated *in vacuo* to give a pale yellow solid which was recristallized to afford (*Z*)-3-chloro-2-propenoic acid (13.5 g, 78 %) as a white solid: mp : 60 °C (hexane). TLC R_f 0.31 (PE-EA : 50-50); IR ($CHCl_3$) 1690, 1610, 1400, 1330, 1275, 1240, 1120, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.27 (1H, d, J = 9.0 Hz), 6.87 (1H, d, J = 9.0 Hz), 9.5 (CO_2H); ^{13}C NMR ($CDCl_3$) δ 120.7, 135.4, 168.7.

AcCl (0.50 ml, 7.03 mmol, 0.07 eq.) was added slowly to a stirred solution of (*Z*)-3-chloro-2-propenoic acid (10.50 g, 98.58 mmol) in MeOH (50 ml) at O °C. The reaction mixture was allowed to warm to rt and stirred for 24 h at this temperature before addition of aqueous $NaHCO_3$. After extraction with CH_2Cl_2, drying over anhydrous $MgSO_4$, filtration and concentration *in vacuo*, 7 was obtained as a pale yellow oil which was chromatographically pure (11.3 g, 95 %). TLC R_f 0.60 (PE-EA : 80-20); IR (thin film) 1725, 1625, 1430, 1345, 1280, 1230, 1175, 990, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.77 (3H, s), 6.24 (1H, d, J = 8.3 Hz), 6.78 (1H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 50.9, 120.6, 132.2, 163.2.

Methyl (*Z*)-5-trimethylsilyl-2-penten-4-ynoate: 8

7 (8.7 g, 72.18 mmol, 2.5 eq.) was added to a stirred solution of tetrakis(triphenylphosphine)palladium (1.67 g, 1.44 mmol, 0.05 eq.) in C_6H_6 (30 ml) under argon in the dark at rt. After 15 min, a solution of trimethylsilylacetylene (4 ml, 28.87 mmol) and $BuNH_2$ (4.3 ml, 43.31 mmol, 1.5 eq.) followed by CuI (0.274 g, 1.44 mmol, 0.05 eq.) were added. After stirring for 6 h at rt, aqueous NH_4Cl was added and the two phases separated. The aqueous layer was then extracted twice with Et_2O and the combined organic phases dried over anhydrous $MgSO_4$, filtered then concentrated *in vacuo*. The resulting black oil was purified by flash column chromatography to afford **8** (3.79 g, 72 %) as a yellow oil. TLC R_f 0.51 (PE-EA : 90-10); IR (thin film) 2140, 1735, 1720, 1600, 1440, 1400, 1390, 1245, 1220, 1180, 1165, 1040, 995, 840, 810, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.22 (9H, s), 3.74 (3H, s), 6.08 (1H, d, J = 12.0 Hz), 6.13 (1H, d, J = 12.0 Hz); ^{13}C NMR ($CDCl_3$) δ -0.5, 51.3, 100.6, 108.2, 122.7, 129.1, 164.8. Anal. Calcd. for $C_9H_{14}O_2Si$: C, 59.30; H, 7.74. Found : C, 59.24; H, 7.95.

Methyl (*Z*)-2-penten-4-ynoate: 9

TBAF.$3H_2O$ (0.346 g, 1.1 mmol, 0.25 eq.) was added in a single portion to a stirred solution of **8** (0.80 g, 4.39 mmol) in Et_2O-THF (10 ml-4 ml) at rt. After 5 min, H_2O (5 ml) was added and the reaction was then extracted with Et_2O, dried and concentrated *in vacuo* to afford the crude product which was purified by flash column chromatography (pentane-Et_2O : 90-10) to give **9** as a pale yellow oil (0.400 g, 83 %). TLC R_f 0.34 (PE-EA : 90-10); IR (thin film) 3280, 2100, 1730, 1620, 1440, 1390, 1290, 1220, 1180, 1000, 820 cm^{-1}; ^1H NMR (C_6D_6) δ 3.23 (1H, dd, J = 2.7, 0.7 Hz), 3.34 (3H, s), 5.57 (1H, dd, J = 11.6, 2.7 Hz), 5.80 (1H, dd, J = 11.6, 0.9 Hz); ^{13}C NMR (C_6D_6) δ 50.9, 79.8, 89.6, 121.7, 130.6, 164.2.

Methyl (2*Z*, 8*S*, 9*R*)-8,9-epoxy-10-hydroxy-4,6-decadiyn-2-enoate: 10c

(140 mg, 93 %) as a white solid: mp : 58 °C (EP-Et_2O : 9-1). TLC R_f 0.24 (PE-EA : 60-40); $[\alpha]_D^{22}$ + 64° (c 0.27, CH_2Cl_2, ee >99 %); IR ($CHCl_3$) 3600, 3460, 2210, 2130, 1720, 1600, 1440, 1400, 1290, 1170, 1030, 890, 810 cm^{-1}; ^1H NMR (C_6D_6) δ 1.30 (OH), 2.72 (1H, ddd, J = 5.8, 4.8, 4.0 Hz), 2.95 (1H, d, J = 4.0 Hz), 3.29 (3H, s), 3.42 (1H, dd, J = 12.4, 5.8 Hz), 3.47 (1H, dd, J = 12.4, 4.8 Hz), 5.42 (1H, d, J = 11.5 Hz), 5.77 (1H, d, J = 11.5 Hz); ^{13}C NMR (C_6D_6) δ 44.2, 51.3, 58.5, 62.0, 70.1, 74.7, 82.5, 84.7, 121.0, 132.6, 164.2. Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found : C, 64.16; H, 4.82.

Methyl (2*Z*, 8*S*, 9*R*)-10-acetoxy-8,9-epoxy-4,6-decadiyn-2-enoate: 10d

By using the modified Cadiot-Chodkiewicz coupling described above: **10d** was obtained as a yellow oil (154 mg, 91 %).

By direct acetylation of **10c**:

DMAP (32 mg, 0.266 mmol, 1.1 eq.) and Ac_2O (25 ml, 0.266 mmol, 1.1 eq.) were added to a stirred solution of **10c** (50 mg, 0.242 mmol) in Et_2O (2 ml) at rt . After 10 min, the reaction mixture was filtered and the Et_2O removed *in vacuo*. The crude oil was then purified by flash column chromatography to afford

4b in quantitative yield (60 mg). TLC R_f 0.38 (PE-EA : 70-30); $[\alpha]_D^{22}$ + 18° (c 0.32, CH_2Cl_2, ee >99 %); IR (thin film) 2220, 2140, 1750, 1730, 1610, 1440, 1400, 1370, 1230, 1180, 1040, 820 cm^{-1}; ^1H NMR (C_6D_6) δ 1.64 (3H, s), 2.83 (1H, ddd, J = 6.6, 4.1, 4.0 Hz), 2.99 (1H, d, J = 4.1 Hz), 3.32 (3H, s), 3.99 (1H, dd, J = 12.3, 6.6 Hz), 4.20 (1H, dd, J = 12.3, 4.0 Hz), 5.47 (1H, d, J = 11.4 Hz), 5.81 (1H, d, J = 11.4 Hz); ^{13}C NMR (C_6D_6) δ 20.1, 43.8, 51.2, 55.5, 63.3, 70.4, 75.0, 81.1, 84.3, 120.6, 132.9, 164.0, 169.7; mass spectrum, m/e (intensity) : 248 (M^+, <1), 175 (76), 146 (74), 131 (100), 103 (57), 87 (43). Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found : C, 62.85; H, 4.82.

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19 Further works are now in progress to clearly establish the reasons of the formation of allenynols, such as **5a**, from either epoxydiynes, such as **4a**, or bromoethynyl allenols derived from *in situ* isomerization of bromo-ethynylepoxides, *e. g.* **1a-c**.

20 Control experiments showed that it was indeed the case.

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25 The sequence was reported in a preliminary communication.[21] Experimental details will be described elsewhere.