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A NEW APPROACH TO CONJUGATED DIENES SYNTHESIS OF THE PHEROMONES OF *LOBESIA BOTRANA* AND *BOMBYX MORI*

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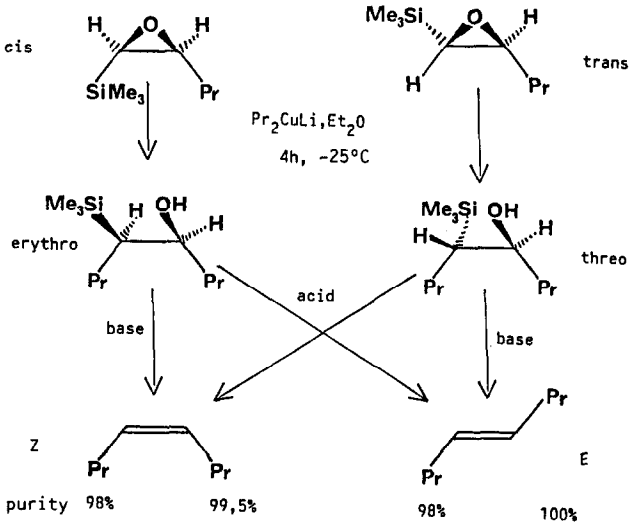
Summary - Cis or trans epoxysilanes are regio and stereoselectively opened by Z-alkenyl cuprates, in the presence of $BF_3.OEt_2$, affording erythro or threo β-hydroxy silanes respectively. These are, in turn, transformed into E-Z conjugated dienes of high stereoisomeric purity by acidic or basic elimination. The method serves to synthetize the pheromones of *Lobesia botrana* and *Bombyx mori*.

The conjugated diene system is a common pattern in many natural products and particularly in the carbon framework of numerous insect sex pheromones[1]. Due to our interest in this field, we have already investigated, and published, various ways of obtention of conjugated dienes[2] and their application to the synthesis of pheromones of Lepidoptera[3]. We describe herein another approach based on the Peterson-Hudrlik reaction[4].

The Peterson olefination reaction has already been applied to the synthesis of dienic pheromones[5]. However, to our knowledge, the Hudrlik version of this reaction[6] has not been used so far with alkenyl cuprates for this purpose.

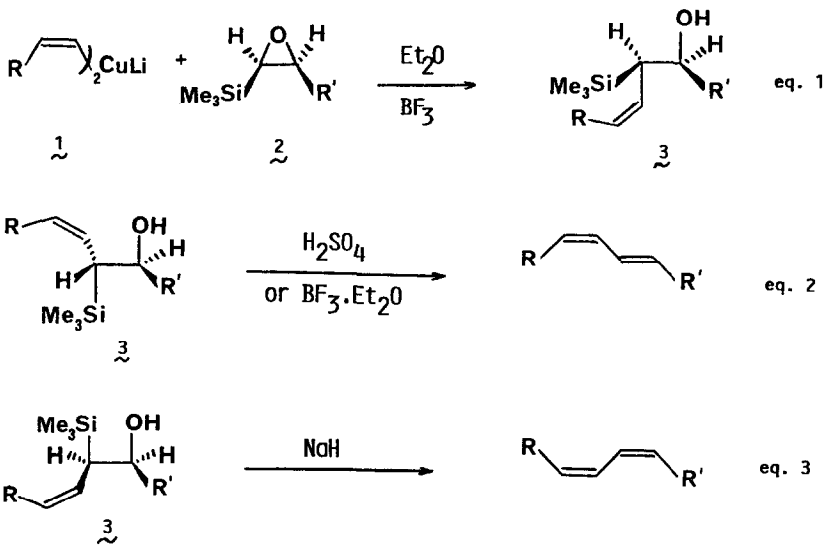
According to this version an organocuprate reagent reacts regio- and stereoselectively with epoxysilanes by anti attack on the carbon bearing the silicon atom, affording a β-hydroxy silane. (Scheme A)



Scheme A

The most fascinating point of this reaction sequence is that from a common intermediate, the erythro or the threo β-hydroxysilane, two isomeric olefins may be obtained at will, and with a very high degree of stereoisomeric purity.

This possibility is quite useful for the synthesis of dienic pheromone where, it is often desirable to test independently the different stereoisomers for biological studies. In this context, an approach, such as the one described in scheme B, would be half as much time consuming.



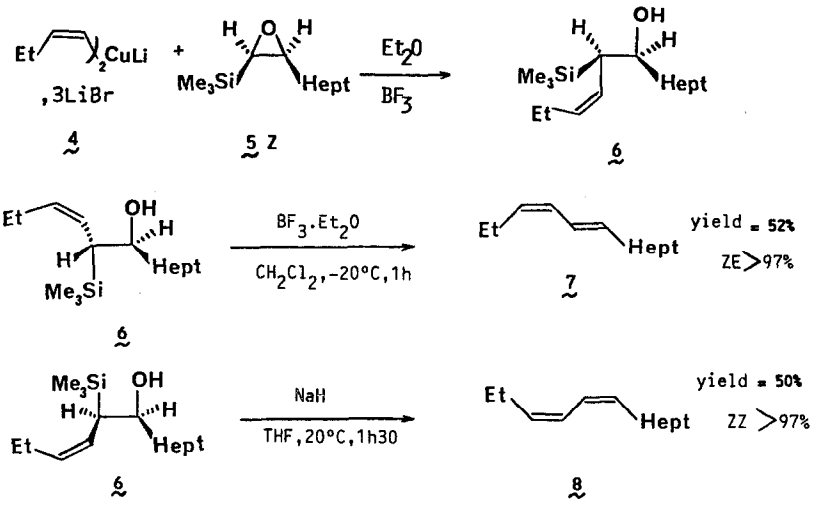
Scheme B

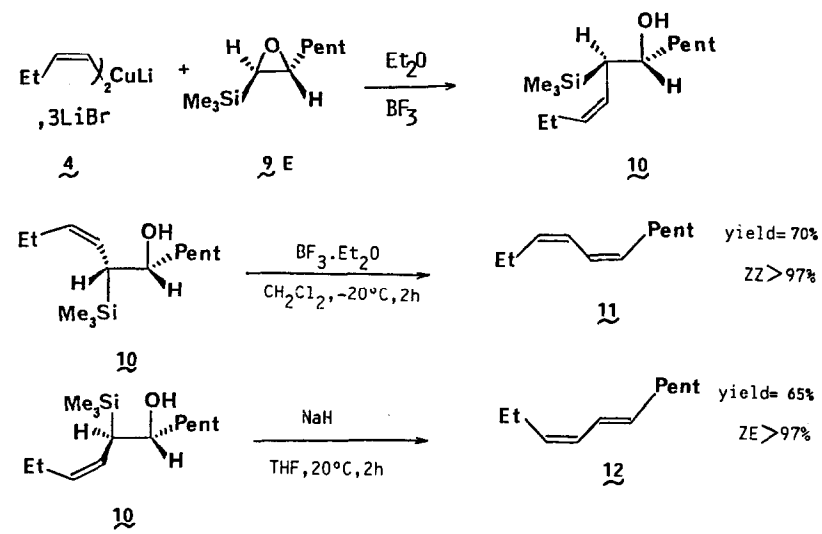
Some years ago[7], we have unsuccesfully explored this approach, which has been, now, reexamined with more success.

In view of scheme B, it is quite easy to understand the reasons which explain our initial failure with alkenyl cuprate reagents 1. Although cuprate reagents are well known for their high reactivity towards epoxides[8], alkenyl cuprates 1 are among the least reactive ones[9]. On the other hand, epoxysilanes 2 are quite crowded epoxides and therefore not easily opened. In our initial experiments, the reaction schown in eq. 1 could not be run at -25°C, as described by Hudrlik for dialkyl cuprates[6], and we had to raise the temperature to 0°C at least. Even at 0°C, the reaction was quite slow and part of the cuprate 1 was thermally decomposed to the symmetric dienes[10]. However, the main problem was the high lability of the trimethylsilyl group in an allylic position[11]. It was not possible to stop the reaction and to isolate the desired intermediate 3. Instead, the lithium (or copper) alcoholate was sufficiently reactive[12], at 0°C, to undergo *in situ* a syn β-elimination, as shown in eq. 3. With this type of elimination the newly created double bond had the same stereochemistry as that of the starting vinyl silane, the precursor of the epoxy-silane. In fact this result was exactly the contrary of what we wished to do, *viz* a reversal of the stereochemistry of the starting vinyl silane.

The solution to our problems came only recently, when we discovered the highly efficient boron trifluoride assisted opening of epoxides by organocopper and cuprate reagents[13]. Even poorly reactive epoxides, such as cyclohexene oxide, are opened and substituted by various cuprates reagents, as hindered as, for example, dimesityl cuprate, and at low temperature (-78° to -60°C).

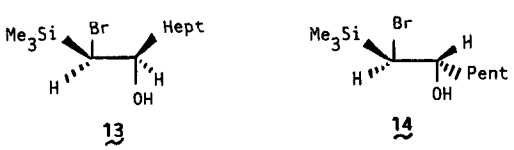
Under these new conditions, both epoxy-silanes 5 and 9 are now smoothly opened by Z-butenyl cuprate 4 to afford respectively homoallylic alcohols 6 and 10 (see scheme C).



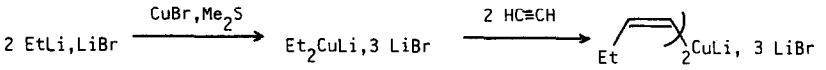


Scheme C

In both cases the reaction is regio- and stereoselective, despite the presence of a strong Lewis acid. On the contrary, its presence permits to run the reaction at a temperature low enough so that no syn β-elimination can occur, as was the case in its absence. The low temperature avoids also the possible anti β-elimination, which is also performed with BF_3,Et_2O (see below). The only detected by-product were the bromohydrins 13 and 14, (in 10-15% yield).



The formation of these compounds arises from the presence of LiBr, which in turn takes its origin from the mode of obtention of Z-butenyl cuprates (by the carbocupration reaction)[9] :



In our original paper[13b], we preferred to use, for the opening of epoxides, lithium cyanocuprates $R_2CuCNLi_2$ which avoid the presence of lithium halides. Unfortunately these cuprates are too basic and unsuitable for the carbocupration reaction.

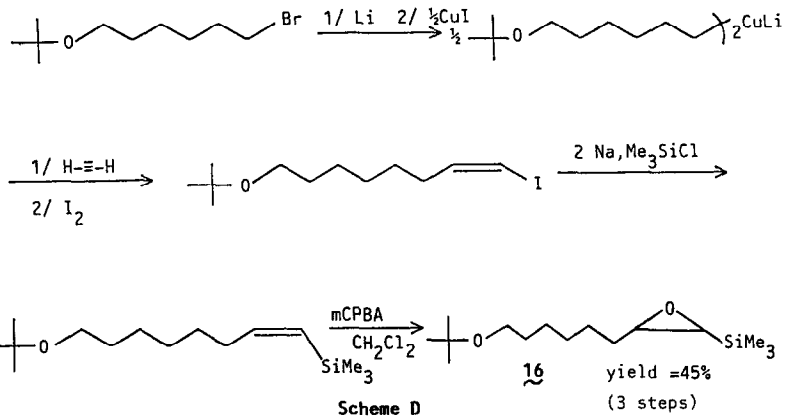
Nevertheless, halohydrins 13 and 14 are easily removed in the next stage of the reaction sequence : the β-elimination. The erythro β-hydroxysilane 6, when treated with BF_3,Et_2O in methylene chloride for 1 h at -20°C, undergoes an anti β-elimination, giving rise to the expected Z,E diene 7, in 52% overall isolated yield. Its stereoisomeric purity was > 97% as checked by capillary gas chromatography. The same erythro β-hydroxysilane 6, when treated with 1 eq. NaH, in THF, at room temperature for 1 h 30, undergoes a syn β-elimination. The Z,Z diene 8 is obtained in 50% overall yield with a stereoisomeric purity >97%.

In a similar manner the threo β-hydroxysilane 10 is transformed into the Z,Z diene 11, by acidic treatment, in 70% yield overall yield and with excellent stereoisomeric purity (> 97%). Crude 10 was also transformed into the Z,E diene 12, under basic conditions, in 65% yield and > 97% purity.

Thus the overall process - opening of epoxide and elimination - is entirely stereoselective.

These results establish the vialibity of this methodology as a general way for the obtention of highly pure conjugated dienes. Its synthetic utility is illustrated by the synthesis of two insect sex pheromones.

The synthesis of (E,Z)-7,9-dodecadienyl acetate 15, the pheromone of the European grape-vine moth *Lobesia botrana*[3,14] was undertaken with cis epoxysilane 16. This functionalized epoxysilane 16, was, in turn, prepared by a carbocupration/iodination sequence[15] followed by a Wurtz-Fittig silylation[16] and an epoxidation with mCPBA, as shown in scheme D.

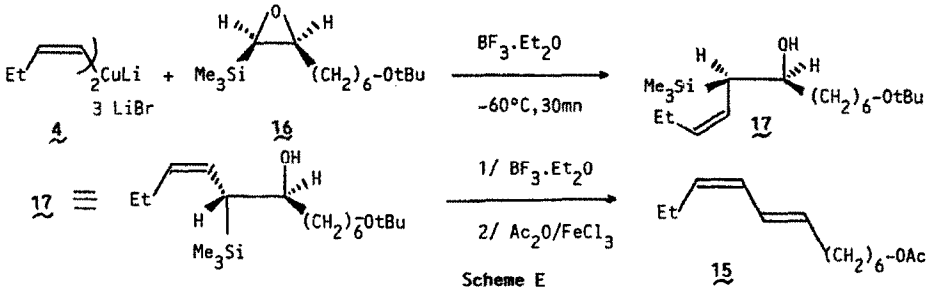


Scheme D

The yield of 16 in this overall process is 45% and its cis purity > 99% (no trans isomer was detected by GC or NMR).

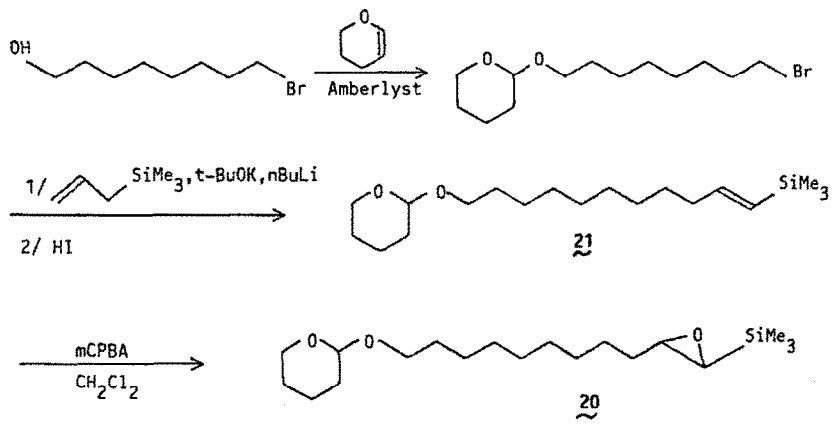
Z-Butenyl cuprate 4, prepared by carbocupration, was then reacted with 16, in the presence of BF_3,Et_2O, and the crude erythro β-hydroxy-silane 17 submitted directly to the anti β-elimination conditions. The resulting crude E,Z diene 18 still has its terminal hydroxy functionality protected as a tert-butoxy ether. The deprotection-acetylation step was done under mild conditions according to our recent procedure ($Ac_2O/FeCl_3$ in Et_2O)[17] which does not destroy nor isomerise the conjugated diene system (see scheme E).

Thus, the desired pheromone 15 was obtained in 62% overall isolated yield and with a 96.5% stereoisomeric purity.



Scheme E

Bombykol, (E,Z)-10,12-hexadenadienyl acetate 19 is the sex pheromone of the silkworm moth *Bombyx mori* [14]. Its synthesis was undertaken with a trans functionalized epoxysilane 20, which was prepared by epoxidation of E-alkenyl silane 21, itself obtained by the method of Chan[18] (see scheme F)

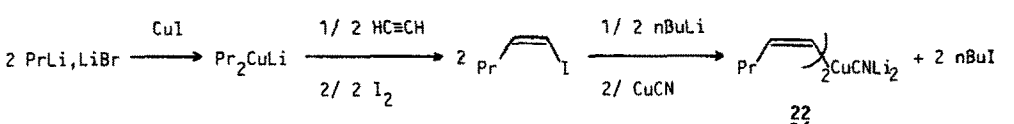


yield = 54% (3 steps)

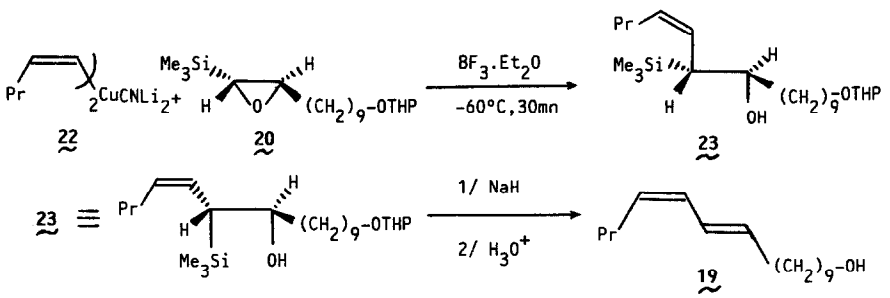
Scheme F

In this manner 20 was obtained in 54% overall yield (based on 1-bromo-8-octanol) and in a >99% isomeric purity. This synthetic approach permits the use of a halohydrin (bromooctanol) having an even number of carbon atoms (less expensive). An approach such as the one used in the synthesis of the pheromone of *Lobesia botrana* would have required a halohydrin with an odd number of carbon atoms (less available).

Another modification was also applied to the synthesis of Bombykol 19 : the required Z-pentenyl cuprate 22 was only indirectly obtained from carbocupration in order to avoid the presence of lithium bromide and therefore the competitive formation of bromohydrins such as 13 or 14.



Cuprate 22 reacts easily with epoxide 20, with the assistance of BF_3,Et_2O, and the obtained crude threo β-hydroxysilane 23 is submitted to syn elimination conditions. After deprotection of the terminal hydroxy functionality, bombykol 19 is obtained in 75% overall isolated yield and with a 97.5% stereoisomeric purity.



Scheme G

The above syntheses of pheromones examplify the synthetic potential of this new methodology for the obtention of conjugate dienes (or even polyenes). It should be pointed out that, reversal of the -elimination conditions would have afforded the Z,Z isomers of these pheromones.
It is also noteworthy that the system $R_2CuLi/BF3$ is chemoselective towards epoxides : the acetal protection of the alcohol functionality remains untouched in 20, although such a cleavage reaction is known to occur[13a].

Acknoledgements -
The authors thank Prof. J. Normant for stimulating discussions and the C.N.R.S. (U.A. 473) for financial support.

EXPERIMENTAL -

^1H NMR spectra were recorded on a Jeol NH100 apparatus ($CDCl_3$; δ ppm from TMS).
^{13}C NMR on a Jeol FX90Q ($CDCl_3$; δ ppm from TMS).
IR spectra were obtained on a Perkin Elmer model 457 spectrometer.
GLPC analyses were performed on a Carlo Erba chromatograph model G1 and 2150 using a 3 m glass column (10% SE30 on silanized chromosorb G 80/100 mesh or Carbowax 20M) and 25m capilarry glass column (OV 101).
The gas chromatograph was coupled to an integrator Hitachi D2000.

Preparation of alkenylsilanes -

(Z)-1-Nonenyl trimethylsilane
This compound is prepared as described in ref. 19.
To a solution of 20 mmol of Z-dinonenyl cuprate[15] in 100 ml Et_2O, are successively added, at -50°C, 80 ml THF, 3.6 ml HMPT (hexamethyl phosphoric triamide)[2] (20 mmol), 4 g NEt_3 (40 mmol) then 2.17 g trimethylchlorosilane (20 mmol). The mixture is stirred for 3 h at room temperature, hydrolyzed with 50 ml 1N HCl and after standard work up the crude product is distilled. Yield : 80%. B.p. : 43°C/0.01 mmHg.
IR(neat) cm^{-1} : 1600, 1245, 835, 760
^1H NMR : 6.22(dt,1H) ; 5.37(d,1H) ; J : 14Hz ; 0.08(s,9H)
^{13}C NMR : 149.3 and 128.7 (C=C) ; 0.3 ($SiMe_3$)

8-t-Butyloxy (Z)1-octenyl trimethylsilane
8-t-Butyloxy-1-hexyl lithium is prepared in Et_2O from 8-t-Butyloxy-1-hexyl bromide and Li metal. This organolithium reagent is used for the carbocupration-iodination sequence, exactly as described in ref. 15. 8-t-Butyloxy (Z)1-octenyl iodide : B.p. : 95°C/10^{-2} mmHg
IR(neat) cm^{-1} : 3065, 1610, 725
^1H NMR($CDCl_3$) : 6.15(m,2H) ; 3.32(t,2H) ; 1.18(s,9H)
^{13}C NMR($CDCl_3$) : 141.1(CH=) ; 82.2(ICH=) ; 72.1(-C-O) ; 61.3(CH_2-O)
This alkenyl iodide is coupled with Me_3SiCl and Na in THF, according to ref. 16. The title compound may be used directly in the epoxidation step. A small sample was distilled : B.p. : 75°C/10^{-2} mmHg.
IR(neat) cm^{-1} : 1600, 1460, 1245, 1200, 835, 760
^1H NMR : 6.3(dt,1H) ; 5.45(d,1H) ; 3.31(t,2H) ; 1.17(s,9H) ; 0.11(s,9H).
^{13}C NMR : 149.1(CH=) ; 128.7(SiCH=) ; 0.3(Me_3Si)
Anal. : $C_{15}H_{32}O_5$: 256.50. Calc. C 70.24, H 12.57. Found C 70.10, H 12.64

(E)1-Heptenyl trimethylsilane
Prepared in 77% yield as described in ref. 18. B.p. 95°C/50 mmHg
IR(neat) cm^{-1} : 1610, 1245, 985, 835
^1H NMR : 6.11(dt,1H) ; 5.65(d,1H) ; J=18.5Hz ; 0.05(s,9H)
^{13}C NMR : 14.73(-CH=) ; 129.6(SiCH=) ; -1.1(Me_3Si)

11-Tetrahydropyranyloxy (E)1-Undecenyl trimethylsilane
Prepared according to ref. 18. The crude product is used in the epoxidation step.
IR(neat) cm^{-1} : 1245, 1030, 985, 835
^1H NMR : 6.03(dt,1H) ; 5.61(d,1H) ; J : 18.5Hz ; 4.58(m,1H) ; 0.05(s,9H)
^{13}C NMR : 147.2(-CH=) ; 129.5(SiCH=) ; 98.5(O-CH-O) ; -1.1(Me_3Si).

Preparation of epoxy-silanes

General procedure :
To a solution of m-peroxybenzoic acid (mCPBA) (30 mmol) in CH_2Cl_2(100 ml) are added 30 mmol (4.2 g) of powdered Na_2HPO_4, then, at room temperature, a solution of the alkenyl silane (20 mmol) in CH_2Cl_2 (10 ml). The mixture is stirred 3-5 h, until no starting material is left. After filtration, the organic phase is washed with aqueous Na_2SO_3, dried over $MgSO_4$ and concentrated in vacuo.

Cis epoxysilane 5
Yield : 82%. B.p. 70°C/10^{-2} mmHg
IR(neat) cm^{-1} : 1250, 845
^1H NMR : 3.09(m,1H) ; 2.19(d,1H) ; J : 5.2 Hz ; 0.13 (s,9H)
^{13}C NMR : 57.7(-CH-O) ; 50.6(Si-CHO) ; -1.7(Me_3Si)
Anal. $C_{12}H_{26}OSi$: 214.42. Calc. C 67.22, H 12.22. Found C 67.13, H 12.27

Cis epoxysilane 16
Purified by column chromatography on SiO_2 (eluent : cyclohexane/Et_2O : 95/5)
IR(neat) cm^{-1} : 1460, 1245, 1200, 835
^1H NMR : 3.35(t,2H) ; 3.05(m,1H) ; 2.09(d,1H) ; J : 6 Hz ; 1.1(s,9H) ; 0.13(s,9H)
^{13}C NMR : 72.1(-C-O) ; 61.3(CH_2O) ; 57.4(-CHO) ; 50.2(SiCHO) ; -1.7(Me_3Si)
Anal. $C_{15}H_{32}O_2Si$: 272.50. Calc. C 66.12, H 11.84. Found C 66.08, H 11.96

Trans epoxysilane 9
Yield : 83%. B.p. 41°C/10^{-1} mmHg
IR(neat) cm^{-1} : 1250, 870, 845
^1H NMR : 2.8(m,1H) ; 1.97(d,1H) ; J : 3.5Hz ; 0.05(s,9H)
^{13}C NMR : 56.1(-CHO-) ; 51.6(SiCHO-) ; -3.6(Me_3Si)
Anal. $C_{10}H_{22}OSi$: 186.37. Calc. C 64.45, H 11.88. Found C 64.40, H 11.96

Trans epoxysilane 20
Purified by column chromatography on SiO_2 (eluent : CH_2Cl_2)
IR(neat) cm^{-1} : 1245, 1030, 879, 845
^1H NMR : 4.58(m,1H) ; 3.2-4.0(m,4H) ; 2.8(m,1H) ; 1.98(d,1H)
^{13}C NMR : 98.4(-OCHO-) ; 67.3(CH_2O) ; 61.7(CH_2O) ; 55.9(-CHO-) ; 51.1(SiCHO-) ; -3.7(Me_3Si)

Reaction of epoxides with Z-alkenyl cuprates

- Z-Butenyl cuprate 4 is prepared by carbocupration of HC≡CH according to ref. 15. Acetylene (750 ml, 33 mmol) is bubbled into an ethereal solution (100 ml) of diethyl cuprate (30 mmol of EtLi + 16 mmol CuBr,Me_2S), cooled at -45°C. The reaction is exothermic and the solution turns green. After 30 mn at -20°C the obtained Z-butenyl cuprate 4 is ready for further use.

- Z-Pentenyl cyanocuprate 22 is prepared as follows : an ethereal solution (75 ml) of Z-1-iodo pentene[15] (31 mmol) is cooled to -65°C. n-Butyl lithium (30 mmol, 1.6 M in hexane) is added, and the solution stirred for 10 mn at -50°C. CuCN (16 mmol) is added at once and the mixture is stirred at -50°C until all solid material has dissolved (0.5-1h). The solution of cuprate 22 is ready for further use.

- To either of the above cuprate solutions, are added, at -78°C, the desired epoxysilane (10 mmol) dissolved in Et_2O (30 ml). After sitrring for 30 mn, a solution of $BF_3.Et_2O$ (12 mmol) in Et_2O (30 ml) is slowly added dropwise. The reaction is exothermic and care should be taken that the temperature does not rise above -70°C. After 1 h at this temperature, the mixture is hydrolyzed with 50 ml aqueous NH_4Cl and 15 ml aqueous NH_3, stirred 1 h at +20°C and the salts filtered. The aqueous layer is extracted with Et_2O (2 x 100 ml) and the organic phases dried over Na_2SO_4. The crude β-hydroxysilane which cannot be purified is used for the basic (syn) or acidic (anti) elimination.

β-Hydroxy silane 6
IR(neat) cm^{-1} : 3430, 1245, 84
^1H NMR : 5.5(m,2H) ; 3.8(m,1H) ; 0.4(s,9H)
^{13}C NMR : 132.2(-CH=) ; 125.5(-CH=) ; 72.1(CHOH) ; -1.8(Me_3Si)

β-Hydroxy silane 10
IR(neat) cm^{-1} : 3430, 1245, 840
^1H NMR : 5.1-5.5(m,2H) ; 3.7(m,1H) ; 0.04(s,9H)
^{13}C NMR : 132.0(-CH=) ; 126.2(-CH=) ; 73.5(CHOH) ; -1.6(Me_3Si)

β-Hydroxy silane 17
IR(neat) cm^{-1} :3430,1460, 1245, 1200, 835
^1H NMR : 5.2-5.6(m,2H) ; 3.7(m,1H) ; 3.31(t,2H) ; 1.16(s,9H) ; 0.04(s,9H)
^{13}C NMR : 131.7(-CH=) ; 125.5(-CH=) ; 72.2(-C-O) ; 71.9(CHOH) ; 61.4(CH_2-O) ; -1.8(Me_3Si)

β-Hydroxy silane 23
IR(neat) cm^{-1} : 3430, 1245, 1030, 840
^1H NMR : 4.9-5.5(m,2H) ; 4.5(m,1H) ; 3.2-3.8(m,3H) ; 0.04(s,9H)
^{13}C NMR : 129.3(-CH=) ; 127.5(-CH=) ; 98.6(OCH-O) ; 73.4(CHOH) ; 67.4 and 61.7(CH_2O) ; -1.5(Me_3Si)

Eliminations reactions -

Acidic elimination (anti) :
To the crude -hydroxy silane (10 mmol) in CH_2Cl_2 (200 ml), cooled at -40°C, is added $BF_3.Et_2O$ (20 mmol) diluted in CH_2Cl_2 (30 ml). After stirring at -20°C for 2 h, a mixture of aqueous NH_4Cl and NH_3 (70 ml + 30 ml) is added. The aqueous layer is extracted with CH_2Cl_2 (100 ml) and the combined organic phases are dried over $MgSO_4$. The crude diene is purified by column chromatography on SiO_2.

Basic elimination (syn) :
To a suspension of NaH (20 mmol) in THF (200 ml) is added the crude -hydroxy silane (10 mmol) in THF (100 ml) at room temperature. After 2 h the mixture is hydrolyzed with aqueous NH_4Cl (100 ml). The aqueous layer is extracted twice with Et_2O (2 x 100 ml) and the combined organic phases are dried over $MgSO_4$. The crude diene is purified by column chromatography on SiO_2.

(Z,E)3,5-Tridecadiene 7
IR(neat) cm^{-1} : 3010, 1655, 980, 945, 725
^1H NMR : 6.4(dd,1H) ; 6.0(dd,1H) ; 5.7(dt,1H) ; 5.4(dt,1H) ; J_E : 15 Hz, J_Z : 11Hz
^{13}C NMR : 134.6 ; 131.5 ; 128.2 and 125.6 (-CH=)
Anal. $C_{13}H_{24}$: 180.33. Calc. C 86.59, H 13.41. Found : C 86.49 H 13.36

(Z,Z)3,5-Tridecadiène 8
IR(neat) cm^{-1} : 3020, 3005, 1600, 715
^1H NMR : 6.2(m,2H) ; 5.4(m,2H)
^{13}C NMR : 133.4 ; 132.0 ; 123.6 and 123.2(-CH=)

(Z,Z)-3,5 Undecadiene 11
Litt. ref. 20
IR(neat) cm^{-1} : 3020, 3005, 1600, 715
^1H NMR : 6.25(m,2H) ; 5.5(m,2H)
^{13}C NMR : 133.5 ; 132.1 ; 123.5 and 123.1 (-CH=)

(Z,E)-3,5-Undecadiene 12
Litt. ref. 20
IR(neat) cm^{-1} : 3010, 1655, 980, 945, 725
^1H NMR : 6.29(dd,1H) ; 5.90(dd,1H) ; 5.64(dt,1H) ; 5.29(dt,1H)
^{13}C NMR : 134.6 ; 131.5 ; 128.2 and 125.8 (-CH=)

(E,Z)-7,9-Dodecadien-1-yl acetate 15
The deprotection of the tert-butyl group and the subsequent acetylation were performed as described in ref. 17.
The crude diene (10 mmol) is dissolved in Et_2O (100 ml) and acetic anhydride (8 ml, 80 mmol) is added, followed by anhydrous $FeCl_3$ (160 mg, 1 mmol). The mixture is stirred overnight at room temperature, until completion, then quenched with aqueous Na_2HPO_4 (100 ml). The aqueous layer is extracted twice with Et_2O (2 x 100 ml) and the combined organic phases washed with aqueous $NaHCO_3$ (50 ml), then dried over $MgSO_4$. The pheromone 15 is purified on SiO_2 column chromatography (eluent : cyclohexane/EtOAc : 95/5), and then distilled. B.p. 71-72°C/10^{-2} mmHg. Litt. ref. 21.
IR(neat) cm^{-1} : 1740, 1655, 980, 945, 725
^1H NMR : 6.26(dd,1H) ; 5.86(dd,1H) ; 5.6(dt,1H) ; 5.25(dt,1H) ; J_E : 15 Hz, J_Z : 10.5 Hz; 4.01(t,2H) ; 1.99(s,3H)
^{13}C NMR : 170.7(-COO-) ; 134.1 ; 131.5 ; 128.1 and 125.8 (-CH=) ; 65.4(CH_2-O-)

(E,Z) 10,12-Hexadecadien-1-ol 19
The deprotection step was performed as described in ref. 20. The crude THP protected diene was dissolved in 100 ml EtOH and pyridinium paratoluene sulfonate (250 mg, 1 mmol) is added. The solution is stirred at room temperature overnight, then heated at 50°C for 2 h. The solvents are evaporated and the crude residue purified on SiO_2 column chromatography (eluent : cyclohexane/Et_2O : 70/30). Litt. ref. 21.

IR(neat) cm^{-1} : 3320, 3010, 1650, 1030, 980, 945, 745
^1H NMR : 6.30(dd,1H) ; 5.95(dd,1H) ; 5.64(dt,1H) ; 5.29(dt,1H) ; J_E : 15 Hz ; J_Z : 10.7 Hz ; 3.59(t,2H)
^{13}C NMR : 134.7 ; 129.9 ; 129.1 and 125.9 (-CH=) ; 63.0(CH_2O-).

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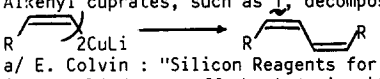

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