Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Trail-Following in Termites: Stereoselective Syntheses of (Z)-3-Dodecen-1-ol, (3Z,6Z)-3,6-Dodecadien-1-ol and (3Z,6Z,8E)-3,6,8-Dodecatrien-1-ol

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Published online: 23 Sep 2006.

To cite this article: Laura Argenti , Fabio Bellina , Adriano Carpita , Elena Rossi & Renzo Rossi (1994) Trail-Following in Termites: Stereoselective Syntheses of (Z)-3-Dodecen-1-ol, (3Z,6Z)-3,6-Dodecadien-1-ol and (3Z,6Z,8E)-3,6,8-Dodecatrien-1-ol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:16, 2281-2297, DOI: 10.1080/00397919408019053

To link to this article: http://dx.doi.org/10.1080/00397919408019053

SYNTHETIC COMMUNICATIONS, 24(16), 2281-2297 (1994)

TRAIL-FOLLOWING IN TERMITES: STEREOSELECTIVE SYNTHESES OF (*Z*)-3-DODECEN-1-OL, (3*Z*,6*Z*)-3,6-DODECADIEN-1-OL AND (3*Z*,6*Z*,8*E*)-3,6,8-DODECATRIEN-1-OL[1]

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Abstract: (*Z*)-3-Dodecen-1-ol (**4**), a candidate trail-following semiochemical for several termite species, was synthetized by (*Z*)-stereoselective reduction of 3-dodecyn-1-ol (**8**). (3*Z*,6*Z*)-3,6-Dodecadien-1-ol (**6**), which is a structural analogue of **4**, was prepared by a reaction sequence in which the key step was the cross-coupling between 5-(*tert*-butyldimethylsilyloxy)-2-pentyn-1-yl *p*-toluenesulfonate (**11**) and 1-heptyne (**12**), in the presence of CuI, NaI and K_2CO_3. Finally, (3*Z*,6*Z*,8*E*)-3,6,8-dodecatrien-1-ol (**3**), which is a non-species-specific trail-following pheromone of termites, was prepared by a convergent synthesis in which compound **11** and (*E*)-3-hepten-1-yne (**18**) were used as key intermediates.

The ability of termites to lay pheromone trails is well documented[2]. However, due to the small quantity of pheromone present in the termites's sternal gland or in the trail, only a few semiochemicals, which are responsible for eliciting trail-following behavior, have been yet identified. These trail-active components

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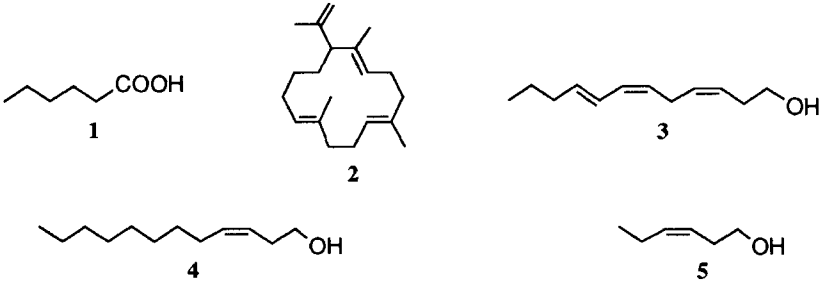
include hexanoic acid (**1**), neocembrene 1 (**2**) and (*3Z, 6Z,8E*)-3,6,8-dodecatrien-1-ol (**3**), which are natural trail pheromone components for *Zootermopsis nevadensis*[3], several *Nasutitermes species*[4] and *Reticulitermes virginicus*[5], respectively. Interestingly, compound **3** is a non-species-specific semiochemical, being also attractive to other *Reticulitermes* spp. and to termites of other genera, *i.e. Amitermes, Coptotermes, Schedorhinotermes,* and *Trinervitermes*[6].



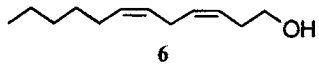
1 2 3 4 5

It has also been hypotesized that compound **3**, or an alcohol related to (*Z*)-3-dodecen-1-ol (**4**), is one component of the trail-active extracts from several African termites such as some *Trinervitermes* and *Amitermes* spp., *Machrotermes michaelseni, Schedorhinotermes mossambicus* and *Reticulitermes lucifugus*[6b]. In fact, it has been found that the threshold concentrations of compound **4** eliciting trail-following behavior in *R. lucifugus* and *R. virginicus* are $\times 10^{-11}$g/5 cm trail and 2×10^{-11}g/5 cm trail, respectively[6b]. Moreover, it has been observed that extracts of various East African termites are followed by *R. lucifugus* with the same sensitivity level as the extract of its own species[6b].

These data and the fact that *Kalotermes flavicollis* and *Microcerotermes edentatus* respond to (*Z*)-3-hexen-1-ol (**5**), but not to the (*Z*)-2 isomer of this compound, thus suggested that the (*Z*)-3 double bond appears to be important for the response of several termite species including *R. lucifugus* in non-species-specific trail-following behavior[6b].

Recently, we began a study to develop a method suitable for monitoring and/or trapping termite species present in Italy. In particular, our attention was devoted to *R. lucifugus*, a species present in Central-Southern Italy and Veneto, which

establishes itself in the wood-structures of houses, in musea and libreries, where it causes irreparable damages. In conjunction with this study, we explored the possibility for using synthetic conspecific trail-following pheromone components and/or their structural analogues for monitoring and/or trapping this termite species, and, on the basis of the above mentioned literatura data, we took into consideration as possible candidates (*Z*)-3-dodecen-1-ol (**4**), (*3Z,6Z*)-3,6-dodecadien-1-ol (**6**) and (*3Z,6Z,8E*)-3,6,8-dodecatrien-1-ol (**3**).

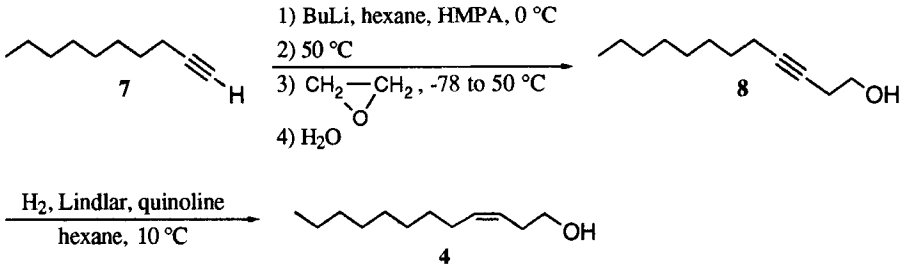


6

In this paper we report expeditious and highly stereoselective syntheses of these compounds on a gram scale starting from commercially available materials.

(*Z*)-3-Dodecen-1-ol (**4**), which is also a female sex-pheromone component of the apple ermine moth, *Yponomeuta malinellus*[7], was stereoselectively prepared according to the simple reaction sequence depicted in Scheme 1[8].

SCHEME 1



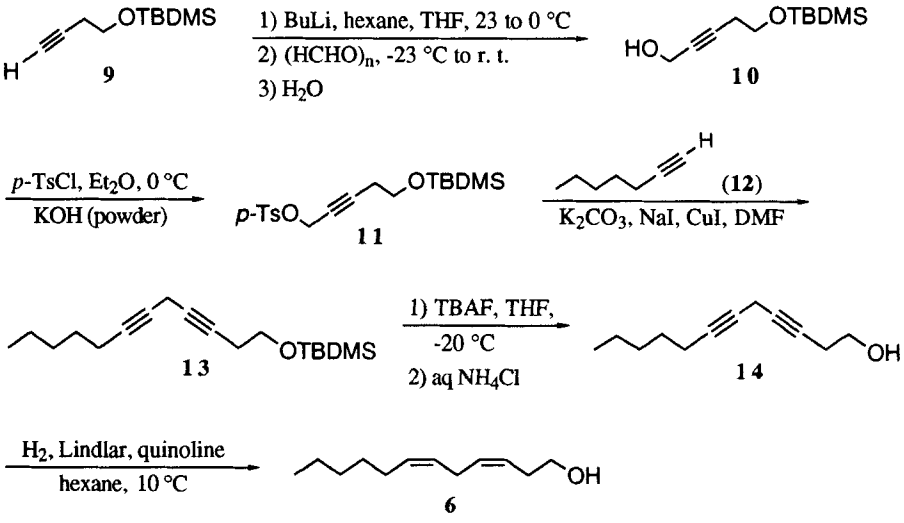
4

Thus, reaction of the lithium salt of 1-decyne (**7**) with ethylene oxide in HMPA at 20 to 50 °C, followed by hydrolysis, gave 3-decyn-1-ol (**8**)[9] in 71 % yield. Then, hydrogenation of an hexane solution of **8** at 10 °C and atmospheric pressure over Lindlar catalyst partially poisoned with quinoline gave in 78 % yield compound **4** having stereoisomeric purity higher than 99 %.

The synthesis of (*3Z,6Z*)-3,6-dodecadien-1-ol (**6**)[10] was carried out by the reactions illustrated in Scheme 2. In particular, 4-(*tert*-butyldimethylsilyloxy)-

1-butyne (**9**), which was prepared according to the standard procedure[11] from commercially available 3-butyn-1-ol, was converted into the corresponding lithium salt by reaction with butyllithium in THF. Homologation of this salt with dry paraformaldehyde gave in 75 % yield compound **10**, which was tosylated with *p*-toluensulfonyl chloride and powdered KOH in Et_2O at 0 °C[12,13] to afford compound **11** in 97 % yield. This propargylic tosylate was then coupled with 1-heptyne (**12**) according to a recently described general procedure for the chemoselective synthesis of functionalized 1,4-alkadiynes[14].

SCHEME 2



Thus, compound **11** was reacted with 2.0 equiv of **12** in DMF solution at room temperature, in the presence of 1.88 equiv of finely ground anhydrous K_2CO_3, 1.88 equiv of NaI and 0.94 equiv of CuI, to give 1-(*tert*-butyldimethylsilyloxy)-3,6-dodecadiyne (**13**) in 87 % yield.

Some attempts were then carried out to convert selectively compound **13** into the corresponding 3,6-diyn-1-ol, **14**, by reaction with tetrabutylammonium fluoride (TBAF) in THF, followed by treatment with an aqueous NH_4Cl solution. We observed that, when the reaction between **13** and TBAF was carried out at a

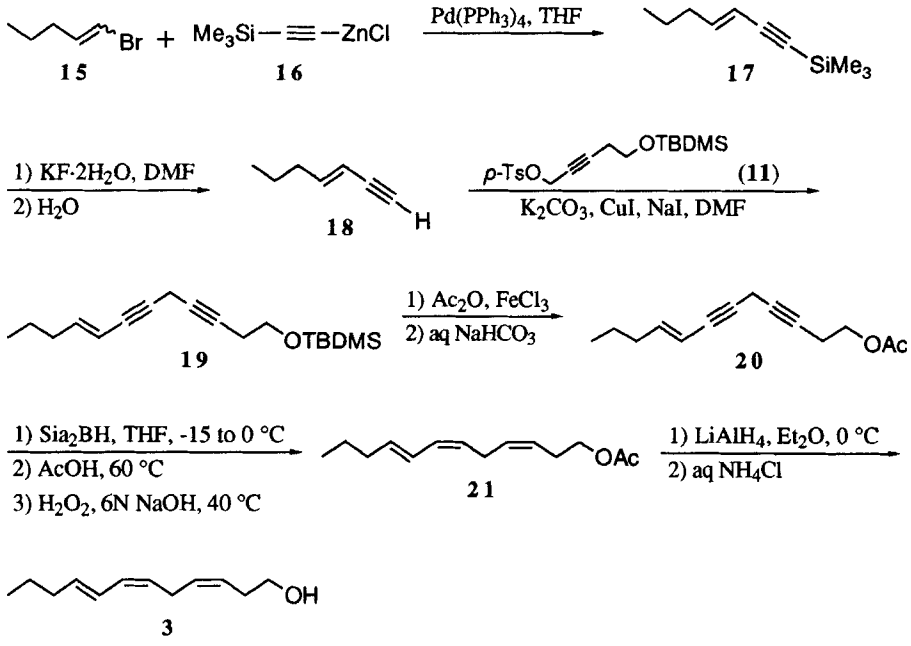
temperature higher than -10 °C, compound **14** resulted to be contaminated by not negligible amounts of regioisomers[15]. However, when the reaction between **13** and 2.1 equiv of TBAF in THF was carried out at -20 °C for 1.1 h, it was possible to obtain selectively the desired 3,6-diyn-1-ol, **14**, in 73 % yield.

Finally, stereoselective partial reduction of **14** by hydrogenation over Lindlar catalyst partially poisoned by quinoline led in 68 % isolated yield to the skipped dienol, **6**, having stereoisomeric purity higher than 98 %.

The synthetic route followed to prepare (*3Z,6Z,8E*)-3,6,8-dodecatrien-1-ol (**3**) is illustrated in Scheme 3[16]. In this route (*E*)-3-hepten-1-yne (**18**) and compound **11**, which were used as key intermediates, were coupled, according to a procedure similar to that employed to prepare **13**, to give the (*E*)-enediyne **19** containing the C-12 skeleton of compound **3**. The precursor to **18**, *i.e.* (*E*)-1-trimethylsilyl-3-hepten-1-yne (**17**), was prepared according to a general procedure for the highly diastereoselective synthesis of (*E*)-1-trimethylsilyl-3-en-1-ynes[17]. In particular, an easily available diastereomeric mixture of 1-bromo-1-pentene (**15**), which contained n equiv of (*E*)-**15**, was reacted with 1.07 × n equiv of trimethylsilylethynylzinc chloride (**16**) in THF at room temperature, in the presence of a catalytic quantity of $Pd(PPh_3)_4$, to give in 72 % yield compound **17** having stereoisomeric purity higher than 98 %. Compound **17** was then reacted with $KF{\cdot}2H_2O$ in DMF at room temperature to give **18** in 62 % yield. This eneyne was coupled with **11** using a modification of the procedure employed to prepare **13** in which 1.0 equiv of **18** were reacted with 1.30 equiv of **11** in DMF at room temperature, in the presence of 2.25 equiv of finely ground anhydrous K_2CO_3, 2.24 equiv of NaI and 0.94 equiv of CuI. This reaction afforded in *ca.* 83 % yield compound **19**, which was directly converted in 79 % yield into the corresponding acetate **20** by reaction with a molar excess of acetic anhydride and 0.15 equiv of anhydrous ferric chloride at room temperature. Treatment of **20** with disiamylborane, followed by protonolysis and reaction with 30 wt. % hydrogen peroxide in the presence of 6 N NaOH, gave, after purification of the crude reaction mixture by MPLC on silica gel, (*3Z,6Z,8E*)-3,6,8-dodecatrien-1-yl acetate (**21**) in 72 % yield. Finally, reaction of **21** with a molar excess of $LiAlH_4$ in Et_2O at 0 °C,

followed by hydrolysis, and purification of the crude reaction mixture by MPLC on silica gel, gave in 96 % yield the desired trienol **3** having chemical and stereoisomeric purity higher than 99.5 %.

SCHEME 3



EXPERIMENTAL

GLC analyses were performed on a Dani 6500 gas-chromatograph with a PTV injector and equipped with a Perkin Elmer LCI-100 integrator. Two types of capillary columns were used: a AT-35 bonded FSOT column (30 m × 0.25 mm i.d.) and a SE-30 bonded FSOT column (30 m × 0.25 mm i.d.).

TLC analyses were performed using plastic sheets Merck silica gel 60 F_{254}.

Purifications by MPLC were performed on a Büchi 681 instrument, using a Bischoff 8100 differential refractometer as detector.

GLC/MS analyses were performed using a Q-mass 910 spectrometer interfaced with a Perkin-Elmer 8500 gas-chromatograph.

^1H NMR spectra were recorded on a Varian XL 100, a Varian Gemini 200 MHz or a Varian VXR 300 MHz spectrometer using TMS as an internal standard. ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer.

All reactions of air and water sensitive materials were performed in flame dried glassware under an atmosphere of argon. Air and water sensitive solutions were transferred with hypodermic syringes or double-ended needles.

$Pd(PPh_3)_4$ was prepared from $PdCl_2$, PPh_3 and hydrazine dihydrochloride in DMSO according to the literature [18]. 4-(*tert*-Butyldimethylsilyloxy)-1-butyne (**9**) [b.p. 78 - 79 °C/22 Torr] was prepared starting from 3-butyn-1-ol by the standard procedure[11]. The spectral properties of compound **9** were in very good agreement with those previously reported[12].

*3-Dodecyn-1-ol (**8**)*

A 1.74 M hexane solution of butyllithium (46.3 ml, 80.5 mmol) was added dropwise to a solution of 1-decyne (**7**) (11.54 g, 83.5 mmol) in dry HMPA (50 ml) maintained at 0 °C. The resulting mixture was stirred for 15 minutes at room temperature and for 0.5 h at 50 °C and then cooled to -80 °C. Ethylene oxide (4.56 ml, 93.4 mmol) was added and the mixture was allowed to warm up to room temperature. It was then stirred for 1.5 h at this temperature and for 2 h at 50 °C, cooled to room temperature and partially concentrated at 25 Torr. The residue was diluted with hexane, poured into a large excess of ice water and extracted with hexane. The organic extract was washed with water, dried, concentrated *in vacuo* and fractionally distilled to give compound **8** (11.52 g, 78 % yield based on butyllithium): b.p. 84.5 - 85 °C/0.15 Torr. ^1H NMR ($CDCl_3$, 200 MHz), δ: 3.68 (2 H, t, J = 6 Hz, H-1), 2.43 (2 H, tt, J = 6 and 2 Hz, H-2), 2.16 (2 H, tt, J = 7 and 2 Hz, H-5), 1.94 (1 H, br s, OH), 1.58 - 1.12 (12 H, br m, H-6, H-7, H-8, H-9, H-10 and H-11), 0.88 ppm (3 H, t, J = 6 Hz, H-12). MS, m/z (%): 153 (1), 139 (1), 135 (2), 121 (3), 107 (9), 97 (22), 93 (13), 81 (21), 55 (68), 41 (100). Anal. Calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.20; H, 12.45.

(Z)-3-Dodecen-1-ol (4)

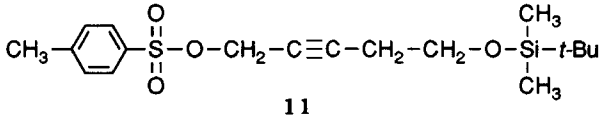
Compound **8** (4.55 g, 24.96 mmol) was hydrogenated at 10 °C over Lindlar catalyst (0.60 g) in hexane (20 ml) containing quinoline (2 drops). Absorption of hydrogen ceased after 1 h. The catalyst was filtered off and the filtrate was washed with dilute HCl and water, dried and fractionally distilled to give compound **4** (4.18 g, 91 % yield): b.p. 68 - 69 °C/0.02 Torr (lit[19] b.p. 110 - 130 °C/14 Torr). ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 5.56 (1 H, dtt, J = 11, 7 and 1 Hz, H-4), 5.35 (1 H, dtt, J = 11, 7 and 1 Hz, H-3), 3.63 (2 H, t, J = 7 Hz, H-1), 2.32 (2 H, q, J = 7 Hz, H-2), 2.05 (2 H, q, J = 7 Hz, H-5), 1.56 (1 H, br s, OH), 1.40 - 1.21 (12 H, br m, H-6, H-7, H-8, H-9, H-10 and H-11), 0.88 ppm (3 H, t, J = 7 Hz, H-12). ^{13}C NMR ($CDCl_3$, 50.3 MHz), δ: 133.4 (C-4), 125.0 (C-3), 62.3 (C-1), 31.9 (C-10), 30.8 (C-2), 29.8, 29.6, 29.3 (C-6, C-8 and C-9), 27.4 (C-5), 22.7 (C-11), 14.1 ppm (C-12). MS, m/z (%): 166 (1), 138 (1), 124 (1), 110 (2), 96 (6), 95 (5), 82 (11), 81 (10), 55 (50), 41 (100). Anal. Calcd. for $C_{12}H_{24}O$: C, 78.19; H, 13.12. Found: C, 78.35; H, 13.30. GLC analysis showed that compound **4** had stereoisomeric purity higher than 99 %.

5-(tert-Butyldimethylsilyloxy)-2-pentyn-1-ol (10)

4-(*tert*-Butyldimethylsilyloxy)-1-butyne (**9**) (18.78 g, 102 mmol) was dissolved in THF (300 ml) and the solution was cooled to -23 °C. A 1.75 M hexane solution of butyllithium (60.5 ml, 106 mmol) was added dropwise maintaining the temperature at -23 °C and the resulting mixture was stirred at 0 °C for 2 h. It was then cooled to -23 °C and dry paraformaldehyde (4.80 g, 153 mmol) was added in five portions. The mixture was stirred for 1 h at -23 °C, then warmed to 0 °C over several hours and stirred at room temperature for 12 h. It was then poured into a large excess of ice water and extracted with Et_2O. The organic extracts were washed with brine until neutrality, dried and concentrated under reduced pressure. The residue was fractionally distilled to give compound **10** (16.37 g, 75 % yield): b.p. 117 - 118 °C/2 Torr. ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 4.24 (2 H, dt, J = 6 and 2 Hz, H-1), 3.73 (2 H, t, J = 7 Hz, H-5), 2.44 (2 H, tt, J = 7 and 2 Hz, H-4), 2.00 (1 H, t, J = 6 Hz, OH), 0.90 (9 H, s, *t*-Bu), 0.06 ppm (6 H, s, $SiMe_2$).

*5-(*tert*-Butyldimethylsilyloxy)-2-pentyn-1-yl* p-*toluensulfonate (***11***)*

Compound **10** (14.34 g, 67 mmol) and *p*-toluensulfonyl chloride (15.25 g, 80 mmol) were dissolved in dry Et_2O (130 ml) and the solution was cooled to -10 °C. Finely powdered KOH (37.59 g, 670 mmol) was added in five equal portions at 5 minute intervals, maintaining the temperature below 0 °C. The mixture was then stirred at 0 °C for 1 h and poured into ice water (500 ml). The organic phase was removed and the aqueous residue was extracted repeatedly with Et_2O. The combined organic extracts were washed with brine until neutrality, dried and concentrated *in vacuo* at 10 °C to give compound **11** (24.05 g, 97 % yield). ^1H NMR ($CDCl_3$, 200 MHz), δ: 7.81 (2 H, d, J = 8 Hz, H-6' and H-2'), 7.34 (2 H, dm, J = 8 Hz, H-5' and H-3'), 4.68 (2 H, t, J = 2 Hz, H-5), 3.60 (2 H, t, J = 7 Hz, H-1), 2.45 (3 H, s, H-7'), 2.30 (2 H, tt, J = 7 and 2 Hz, H-2), 0.87 (9 H, s, Si-C(CH_3)$_3$), 0.03 ppm (6 H, s, $SiMe_2$).



11

Compound **11**, which had spectral properties in good agreement with those previously reported[12], was used in the next step without any further purification.

*1-(*tert*-Butyldimethylsilyloxy)-3,6-dodecadiyne (***13***)*

Anhydrous and finely ground K_2CO_3 (11.56 g, 83.6 mmol), NaI (12.53 g, 83.6 mmol) and CuI (7.96 g, 41.8 mmol) were suspended in dry DMF (55 ml) with stirring. 1-Heptyne (**12**) (8.51 g, 88.5 mmol) and a solution of compound **11** (16.29 g, 44.3 mmol) in dry DMF (33 ml) were sequentially added and the resulting mixture was stirred for 28 h at room temperature. It was then poured into a large excess of a mixture of a saturated aqueous NH_4Cl solution and NH_4OH (pH 8) and the resulting mixture, after stirring for 0.5 h at room temperature, was extracted with Et_2O. The organic extract was washed with a saturated aqueous NH_4Cl solution, dried and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of hexane and benzene (9 : 1 *v*/*v*) as eluant, to give compound **13** (11.33 g, 87 % yield). ^1H NMR

($CDCl_3$, 200 MHz), δ: 3.71 (2 H, t, J = 7 Hz, H-1), 3.11 (1 H, quint, J = 2 Hz, H-5), 2.38 (2 H, tt, J = 7 and 2 Hz, H-2), 2.15 (2 H, tt, J = 7 and 2 Hz, H-8), 1.18 - 1.15 (6 H, m, H-9, H-10 and H-11), 0.99 - 0.75 (12 H, m, $SiC(CH_3)_3$ and H-12), 0.07 ppm ((6 H, s $SiMe_2$). MS, m/z (%): 236 (12), 235 (59), 179 (25), 161 (22), 159 (25), 133 (18), 105 (27), 75 (78), 57 (58), 41 (100). Anal. Calcd. for $C_{18}H_{32}OSi$: C, 73.90; H, 11.02. Found: C, 73.86; H, 11.46.

*3,6-Dodecadiyn-1-ol (**14**)*

A 1.0 M THF solution of TBAF (43.1 ml, 43.1 mmol) was slowly added to a solution of compound **13** (6.00 g, 20.5 mmol) in THF (23 ml) maintained at -20 °C and the resulting mixture was stirred at this temperature for 1.1 h. A large excess of a saturaed aqueous NH_4Cl solution was added and the resulting mixture was extracted with Et_2O. The organic extract was dried and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, using a mixture of benzene and Et_2O (95 : 5 v/v) as eluant, to give compound **14** (2.65 g, 73 % yield). ^1H NMR ($CDCl_3$, 200 MHz), δ: 3.71 (2 H, t, J = 6 Hz, H-1), 3.14 (2 H, quint, J = 2 Hz, H-5), 2.45 (2 H, tt, J = 6 and 2 Hz, H-2), 2.15 (2 H, tt, J = 7 and 2 Hz, H-8), 1.59 -1.18 (6 H, m, H-9, H-10 and H-11), 0.90 ppm (3 H, t, J = 7 Hz, H-12). MS, m/z (%): 163 (1), 147 (2), 145 (1), 135 (3), 131 (3) 121 (9), 117 (16), 105 (31), 91 (73), 31 (100). Anal. calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.99; H, 10.45.

*(3Z,6Z)-3,6-Dodecadien-1-ol (**6**)*

Compound **14** (2.0 g, 11.2 mmol) was hydrogenated at 10 °C over Lindlar catalyst (1.1 g) in hexane (30 ml) containing quinoline (6 drops). Absorption of hydrogen ceased after *ca.* 1 h. The catalyst was filtered off and the filtrate was washed with 5 % HCl and brine, dried and concentrated *in vacuo*. GLC/MS of the residue showed the presence of a new substance subsequently identified as compound **6** together with minor amounts (*ca.* 4 %) of other compounds. This residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (70 : 30 v/v) as eluant. Concentration of the first eluted chromatographic fractions allowed to obtain compound **6** (1.06 g, 52 % yield). ^1H NMR ($CDCl_3$, 300 MHz), δ: 5.54 (1 H, dtt, J = 11, 7 and 1 Hz, H-4), 5.40 (1 H, dtt, J = 11, 7 and 1 Hz, H-7), 5.39 (1

H, dtt, J = 11, 7 and 1 Hz, H-3), 5.32 (1 H, dtt, J = 11, 7 and 1 Hz, H-6), 3.65 (2 H, t, J = 7 Hz, H-1), 2.82 (2 H, t, J = 7 Hz, H-5), 2.35 (2 H, q, J = 7 Hz, H-2), 2.05 (2 H, q, J = 7 Hz, H-8), 1.60 (1 H, s, OH), 1.43 - 1.19 (6 H, m, H-9, H-10, H-11), 0.89 ppm (3 H, t, J = 7 Hz, H-12). ^{13}C NMR ($CDCl_3$, 50.3 MHz), δ: 131.5 (C-7), 130.6 (C-4), 127.4 (C-6), 125.3 (C-3), 62.3 (C-1), 31.5 (C-10), 30.8 (C-2), 29.3 C-9), 27.2 (C-8), 25.8 (C-5), 22.6 (C-11), 14.1 ppm (C-12). MS, m/z (%): 182 (1), 164 (1), 132 (2), 121 (3), 107 (4), 95 (5), 93 (10), 79 (27), 41 (54), 31 (100). Anal. Calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.91 ; H, 12.24. GLC analysis showed that compound **6** had stereoisomeric purity higher than 99 %.

On the other hand, concentration of the last eluted chromatographic fractions allowed to obtain 93 % stereoisomerically pure **6** (0.33 g) Thus, compound **6** was obtained in 68 % overall yield.

(E)/(Z)-1-Bromo-1-pentene (**15**)

This stereoisomeric mixture was prepared according to a reported general procedure[20]. In particular, to a solution of 1-pentene (41.31 g, 0.589 mol) in dry CH_2Cl_2 (240 ml) cooled to -50 °C was slowly added bromine (30.21 ml, 0.589 mol). The mixture was stirred at -50 °C for 0.5 h, then warmed up to room temperature, washed with a saturated aqueous $NaHCO_3$ solution and water, dried and concentrated *in vacuo*. To a suspension of the residue in mineral oil (b.p. > 250 °C) (640 ml) and Aliquat 336 (5.90 g) was added finely ground KOH (41.40 g, 0.737 mol). The mixture was maintained at 85 °C for 3 h, then further finely ground KOH (7.97 g, 0.142 mol) and Aliquat 336 (1.60 g) were added. After 3 h at 85 °C the reaction products were distilled at 5 Torr. The distillate was dried and fractionally distilled through a Fischer RE 200 column to give (*E*)/(*Z*)-**15** (22.7 g, 26 % yield) (*E*/*Z* = 76 : 24): b.p. 118 - 124 °C. ^1H NMR ($CDCl_3$, 100 MHz), δ: 6.18 - 5.91 (2 H, m, H-1 and H-2), 2.21 - 1.98 (2 H, m, H-3), 1.56 - 1.31 (2 H, m, H-4), 0.91 ppm (3 H, t, J = 6.9 Hz, H-5).

(E)-1-Trimethylsilyl-3-hepten-1-yne (**17**)

Trimethylsilylacetylene (19.45 g, 198 mmol) was slowly added to a 0.68 M THF solution of ethylmagnesium bromide (291 ml, 198 mmol) maintained at 40 -

45 °C. After the addition was complete the mixture was refluxed for 1 h, then cooled to room temperature and added to an ice-cooled solution of dry $ZnCl_2$ (26.98 g, 198 mmol) in THF (200 ml). A degassed solution of (*E*)/(*Z*)-**15** (41.58 g, 279 mmol) (*E*/*Z* = 76 : 24) and $Pd(PPh_3)_4$ (5.64 g, 4.87 mmol) in THF (220 ml), which was prepared immediately prior to use, was added to this mixture maintained at 0 °C and the resulting mixture was stirred for 5 h at room temperature. After this period a GLC analysis showed that *ca.* 95 % of (*E*)-**15** had been consumed. The reaction mixture was then poured into cold 1 N HCl and extracted with Et_2O. The organic extract was washed with brine, filtered on Celite, dried and partially concentrated under reduced pressure. The residue was diluted with pentane, filtered on Celite and the filtrate was concentrated under reduced pressure. The new residue was purified by MPLC on silica gel, using pentane as eluant, to give compound **17** (23.71 g, 72 % yield): b.p. 87 °C/ 17 Torr. ^{1}H NMR (CCl_4, 100 MHz), δ: 6.13 (1 H, dt, J = 16 and 7 Hz, H-4), 5.39 (1 H, d, J = 16 Hz, H-3), 2.33 - 1.87 (2 H, br m, H-5), 1.80 - 1.16 (2 H, br m, H-6), 0.95 (3 H, t , J = 7 Hz, H-7), 0.17 ppm (9 H, s, $SiMe_3$). MS, *m*/*z* (%): 166 (16), 152 (15), 151 (100), 109 (12), 107 (5), 95 (5), 83 (11), 73 (20), 59 (26), 43 (7). GLC analysis showed that compound **17** had stereoisomeric purity higher than 98 %. The spectral properties of this compound were in good agreement with those previously reported[17].

*(E)-3-Hepten-1-yne (***18***)*

Potassium fluoride dihydrate (24.63 g, 261.6 mmol) was added to a solution of **17** (21.76 g, 130.8 mmol) in DMF (260 ml) and the resulting mixture was stirred for 2 h at room temperature, poured into cold 3 N HCl (800 ml) and extracted with pentane. The organic extract was washed with 3 N HCl and brine, dried, concentrated at atmospheric pressure and fractionally distilled. ^{1}H NMR and GLC analyses of the various fractions (13.85 g) showed that they contained compound **18** contaminated by different amounts of silyl derivatives derived from the reaction and/or the subsequent work up. The fraction having b.p. 101 - 102 °C had 90 % chemical purity. ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 6.25 (1 H, dt, J = 16 and 7 Hz, H-4), 5.45 (1 H, dq, J = 16 and 2 Hz, H-3), 2.76 (1 H, d, J = 2 Hz, H-1), 2.09 (2 H, qd, J = 7 and 2 Hz, H-5), 1.43 (2 H, sext, J = 7 Hz, H-6), 0.91 ppm (3 H, t, J = 7.0 Hz,

H-7). The yield of **18**, based on the ^1H NMR analysis of the collected fractions, was 62 %. These collected fractions were used in the next step without any further purification.

*(E)-1-(*tert*-Butyldimethylsilyloxy)-8-dodecen-3,6-diyne (**19**)*

Anydrous and finely ground K_2CO_3 (25.20 g, 182.3 mmol), NaI (27.19 g, 181.4 mmol) and CuI (14.61 g, 76.7 mmol) were suspended in dry DMF (100 ml) with stirring. Compound **18** contaminated by the silyl derivatives obtained during its preparation (13.46 g, containing 81.2 mmol of pure **18**) and a solution of compound **11** (38.91 g, 105.6 mmol) in dry DMF (70 ml) were sequentially added and the resulting mixture was stirred for 72 h at room temperature. After this period it was poured into a large excess of a mixture of a saturated aqueous NH_4Cl solution and NH_4OH (pH 8) and the resulting mixture, after stirring for 0.5 h at room temperature, was repeatedly extracted with Et_2O. The organic extract was washed with a mixture of a saturated aqueous NH_4Cl solution and NH_4OH (pH 8) and filtered. The filtrate was washed with water, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel using a mixture of hexane and benzene (94 : 6 *v*/*v*) as eluant. Concentration of the intermediate chromatographic fractions allowed to obtain 97 % chemically pure **19** (8.06 g). On the other hand, concentration of the first and the last eluted chromatographic fractions allowed to recover 73 % chemically pure **19**, which was purified by a second MPLC on silica gel, using a mixture of hexane and benzene (92 : 8 *v*/*v*) as eluant. Concentration of the intermediate chromatographic fractions allowed to obtain compound **19** having chemical purity higher than 94 % (11.42 g). The overall yield of **19** based on **18** was 83 %. ^1H NMR ($CDCl_3$, 200 MHz), δ: 6.11 (1 H, dt, J = 16 and 7 Hz, H-9), 5.44 (1 H, dtt, J = 16 and 1 Hz, H-8), 3.71 (2 H, t, J = 7 Hz, H-1), 3.24 (2 H, q, J = 2 Hz, H-5), 2.38 (2 H, tt, J = 7 and 2 Hz, H-2), 2.06 (2 H, qd, J = 7 and 1 Hz, H-10), 1.40 ((2 H, sext, J = 7 Hz, H-11), 0.90 (3 H, t, J = 7 Hz, H-12), 0.9) (9 H, s, $SiC(CH_3)_3$), 0.07 ppm (6 H, s, $SiMe_2$). MS, *m*/*z* (%): 233(9), 159 (3), 151 (5), 75 (7), 73 (6), 59 (25), 43 (42), 42 (36), 41 (64), 29 (100). Anal. Calcd. for $C_{18}H_{30}OSi$: C, 74.42; H, 10.41. Found: C, 74.32; H, 10.22.

(E)-Dodecen-3,6-diyn-1-yl acetate (**20**)

Anhydrous ferric chloride (1.29 g, 7.95 mmol) was added in one portion to a stirred mixture of compound **19** (15.44 g, 53.1 mmol) and freshly distilled acetic anhydride (33.41 g, 327.3 mmol) cooled to 0 °C and the resulting mixture was stirred at this temperature for 20 minutes. After this period GLC analysis of a sample of the reaction mixture diluted with hexane and washed with a saturated aqueous $NaHCO_3$ solution showed the presence of a new compound and that **19** had completely reacted. Thus, the reaction mixture was poured into a large excess of ice water and repeatedly extracted with hexane. The collected organic extracts were washed with water, a saturated aqueous $NaHCO_3$ solution and water, dried, filtered and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (95 : 5 *v*/*v*) as eluant, to give compound **20** (9.18 g, 79 % yield). ^1H NMR ($CDCl_3$, 200 MHz), δ: 6.13 (1 H, dt, J = 16 and 7 Hz, H-9), 5.45 (1 H, dtt, J = 16, 2 and 1 Hz, H-8), 4.14 (2 H, t, J = 7 Hz, H-1), 3.25 (2 H, q, J = 2 Hz, H-5), 2.51 (2 H, tt, J = 7 and 2 Hz, H-2), 2.07 (3 H, s, $COCH_3$), 2.06 (2 H, dq, J = 7 and 1 Hz, H-10), 1.40 (2 H, sext, J = 7 Hz, H-11), 0.90 ppm (3 H, t, J = 7 Hz, H-12). MS, *m*/*z* (%): 175 (2), 161 (1), 147 (3), 143 (4), 129 (7), 128 (11), 115 (13), 105 (3), 91 (6), 43 (100). Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.15; H, 8.41. GLC analysis showed that compound **20** had chemical and stereoisomeric purity higher than 96 %.

(3Z,6Z,8E)-3,6,8-Dodecatrien-1-yl acetate (**21**)

2-Methyl-2-butene (7.10 g, 101.3 mmol) was slowly added to a solution of borane-methylsulfide complex (4.89 ml, 48.9 mmol) in THF (52 ml) cooled to -20 °C. The mixture was stirred for 2 h at room temperature, then it was cooled to -10 °C and portionwise added to a solution of compound **20** (4.10 g, 18.78 mmol) in THF (30 ml) maintained at -10 °C. The resulting mixture was stirred for 6 h at 0 °C, then acetic acid (13.74 ml, 240 mmol) was added and the resulting mixture was heated under stirring to 60 °C and maintained at this temperature for 6 h. After evaporation of the volatile substances (25 °C/15 Torr, 0.5 h) the mixture was diluted with THF (50 ml), cooled to 0 °C and 6 N NaOH (75.5 ml, 453 mmol) was slowly added. The resulting mixture was warmed up to room temperature and 30 wt. %

H_2O_2 (16,00 ml, 158 mmol) was added dropwise, maintaining the temperature below 40 °C. After completion of the addition it was further stirred for 40 minutes at 40 °C. The mixture was then cooled to room temperature, water was added and the aqueous layer was saturated with NaCl. The organic phase was separated and the aqueous layer was extracted repeatedly with Et_2O. The combined organic extracts were washed twice with brine and water until neutrality, dried and concentrated *in vacuo*. The residue, which was analyzed by TLC and GLC/MS, was purified by MPLC on silica gel using benzene as eluant, to give compound **21** (3.01 g, 72 % yield). ^1H NMR ($CDCl_3$, 200 MHz), δ: 6.32 (1 H, ddq, J = 15, 11 and 1 Hz, H-8), 5.97 (1 H, t, J = 11 Hz, H-7), 5.69 (1 H, dt, J = 15 and 7 Hz, H-9), 5.52 (1 H, dtt, J = 11, 7 and 1 Hz, H-4), 5.39 (1 H, dtt, J = 11, 7 and 1 Hz, H-3), 5.24 (1 H, dt, J = 11 and 7 Hz, H-6), 4.08 (2 H, t, J = 7 Hz, H-1), 2.93 (2 H, t, J = 7 Hz, H-5), 2.42 (2 H, q, J = 7 Hz, H-2), 2.09 ((2 H, q, J = 7 Hz, H-10), 2.05 (3 H, s, $COCH_3$), 1.42 (2 H, sext, J = 7 Hz, H-11), 0.91 ppm (3 H, t, J = 7 Hz, H-12). ^{13}C NMR ($CDCl_3$, 50.3 MHz), δ: 171.0 (CO), 135.4 (C-9), 130.7 (C-4), 129.2 (C-7), 127.0 (C-6), 125.4 (C-3 or C-4), 125.0 (C-4 or C-3), 63.8 (C-1), 35.0 (C-10), 26.9 (C-2), 26.1 (C-5), 22.5 (C-11), 20.9 ($CO\underline{C}H_3$), 13.7 ppm (C-12). MS, m/z (%): 222 (10), 162 (6), 133 (5), 119 (10), 105 (8), 91 (13), 80 (7), 79 (9), 43 (100), 41 (20). Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.47; H, 10.15. GLC analysis showed that compound **21** had chemical and stereoisomeric purity higher than 96 %.

(3Z,6Z,8E)-3,6,8-dodecatrien-1-ol (3)

A solution of compound **21** (2.86 g, 12.86 mmol) in dry Et_2O (15 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.02 g, 26.87 mmol) in Et_2O (30 ml) maintained at 0 °C. The resulting mixture was stirred at 0 °C for 3 h, then poured into a large excess of a saturated aqueous NH_4Cl solution cooled to 0 °C and extracted repeatedly with Et_2O. The organic extract was washed with brine until neutrality, dried and concentrated under reduced pressure. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (70 : 30 v/v), to give compound **3** (2.22 g, 96 % yield). ^1H NMR ($CDCl_3$, 200 MHz), δ: 6.32 (1 H, ddq, J = 15, 11 and 1 Hz, H-8), 5.98 (1 H, br t, J = 11 Hz, H-7), 5.69 (1 H, dt, J = 15 and 7 Hz, H-9), 5.56 (1 H, dtt, J = 11, 7 and 1 Hz, H-4), 5.41 (1 H, dtt, J = 11, 7 and 1 Hz, H-

3), 5.25 (1 H, br dt, J = 11 and 7 Hz, H-6), 3.65 (2 H, q, J = 6 Hz, H-1), 2.95 (2 H, t, J = 7 Hz, H-5), 2.37 (2 H, dt, J = 7 and 6 Hz, H-2), 2.09 (2 H, q, J = 7 Hz, H-10), 1.68 (1 H, t, J = 6 Hz, OH), 1.42 (2 H, sext, J = 7 Hz, H-11), 0.91 ppm (3 H, t, J = 7 Hz, H-12). ^{13}C NMR ($CDCl_3$, 50.3 MHz), δ: 135.3 (C-9), 131.0 (C-4), 129.0 (C-7), 127.1 (C-6), 125.7 (C-3), 125.4 (C-8), 62.2 (C-1), 34.9 (C-10), 30.8 (C-2), 26.1 (C-5), 22.5 (C-11), 13.8 ppm (C-12). MS, m/z (%): 180 (19), 162 (3), 133 (6), 121 (4), 119 (19), 105 (20), 91 (26), 79 (13), 41 (26), 31 (100). GLC and ^{1}HNMR analyses showed that compound **3** had chemical and stereoisomeric purity higher than 99.5 %. The spectral properties of this compound were in very good agreement with those previously reported[16c].

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(Received in the UK 14 February 1994)