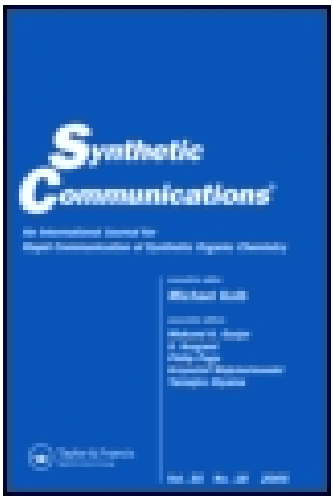

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Candidate Trail Attractants of Reticulitermes lucifugus: Stereoselective Syntheses of (3Z, 6E, BE)-(3Z, 6E, 8Z)- and (3Z, 6Z, 8Z)-3,6,8 -Dodecatrien-1-OL[1]

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CANDIDATE TRAIL ATTRACTANTS OF *Reticultermes lucifugus*: STEREOSELECTIVE SYNTHESES OF (3Z, 6E, 8E)- (3Z, 6E, 8Z)- AND (3Z, 6Z, 8Z)- 3, 6, 8 -DODECATRIEN-1-OL[1]

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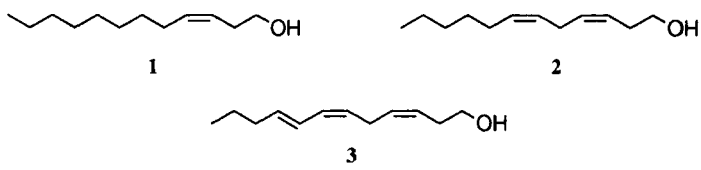
Abstract: Stereoselective syntheses on a gram scale of (3*Z*,6*E*,8*E*)-, (3*Z*,6*E*,8*Z*)- and (3*Z*,6*Z*,8*Z*)-3,6,8-dodecatrien-1-ol, **8**, **9** and **10**, respectively, are described. A key step of the synthesis of **8** consisted of a copper-mediated coupling reaction between 4-(2-tetrahydropyranyloxy)-1-butynylmagnesium bromide (**15**) and the mesyl ester of (2*E*,4*E*)-2,4-octadien-1-ol (**14**). A similar copper-mediated reaction between **15** and the mesyl ester of (*E*)-2-octen-4-yn-1-ol (**19**) was used to construct the C-12 carbon skeleton of **9**. On the other hand, the synthesis of **10** was based on a palladium-promoted reaction between (*Z*)-1-bromo-1-pentene (**23**) and the organozinc bromide derived from 3,6-heptadiyn-1-yl acetate (**27**).

Reticulitermes lucifugus is a termite present in several regions of Italy, which is responsible for serious damages to the wood-structures of houses, musea, libreries and monumental buildings.[2] In conjunction with our studies on the development of a safe method for monitoring and/or controlling this pest, we explored the possibility for using for this purpose interspecific trail-following pheromone components of termites, their structural analogues as well as naturally-occurring trail

attractants.[3-7] In fact, unfortunately the trail-following pheromone of R. *lucifugus* has not been so far characterized. Since it had been suggested that a (*Z*)-3 carbon-carbon double bond in an unsaturated linear primary alcohol is important for the response of several termites species including *R. lucifugus* in non-species-specific trail-following behavior,[8] we synthesized (*Z*)-3-dodecen-1-ol (**1**), (3*Z*,6*Z*)-3,6-dodecadien-1-ol (**2**) and (3*Z*,6*Z*,8*E*)-3,6,8-dodecatrien-1-ol (**3**) as possible trail-following substances.[3]

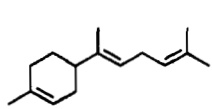


1 2 3

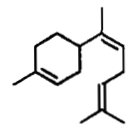
Compound **3**, which is a trail pheromone component of *R. virginicus*,[9] *Coptotermes formosanus*[10] and *R. speratus*[11], has also been isolated from workers and alates of *R. santonensis*.[12] Moreover, this compound proved to be attractive to termites of other genera.[8,13]

Some years ago it was also reported that in the stems with foliage of the chinese date, *Zizyphus jujuba,* are present compounds which were shown to be trail attractants for *R. lucifugus*.[14] These substances were identified as α- and β-bisabolenes, but their stereochemistry was not elucidated.[14] Thus, we developed efficient and selective syntheses either of racemic (*E*)-α-, (*Z*)-α- and β-bisabolenes, (*E*)-**4**, (*Z*)-**4** and **5**, respectively,[4] as well as of highly enantiomerically enriched (*S*)-**5**.[5,6] More recently, we also prepared a sample of highly enantiomerically enriched (*R*)-**5** by a synthetic route in which (*R*)-4-methyl-3-cyclohexene carboxylic acid, (*R*)-**6**, which was the key intermediate, was obtained via a highly diastereoselective $TiCl_4$-catalyzed Diels-Alder reaction between isoprene and the acrylate of commercial (*S*)-N-methyl-2-hydroxysuccinimide (**7**).[7]

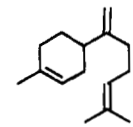
Preliminary bioactivity tests in laboratory, which were carried out by Prof. G. Sbrenna at the University of Ferrara (Italy), showed that compounds (*R*)(*S*)(*E*)- and (*R*)(*S*)(*Z*)-**4**, (*R*)(*S*)-, (*S*)- and (*R*)-**5** exhibited low bioactivity for larvae of



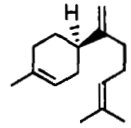
(*R*)(*S*)(*E*)-**4**



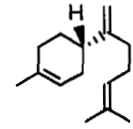
(*R*)(*S*)(*Z*)-**4**



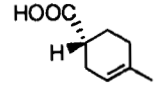
(*R*)(*S*)-**5**



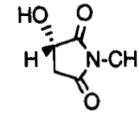
(*R*)-**5**



(*S*)-**5**



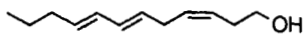
(*R*)-**6**



(*S*)-**7**

R. lucifugus. On the contrary, compounds **1**, **2** and **3**, proved to be highly bioactive and their order of bioactivity was **3** >> **1** > **2**. In particular, 5 µl of an hexane solution of 10^{-14} µl of **3**, when laid on a straight paper strip 5 cm in lenght, induced larvae of *R. lucifugus* to cover back and forward this strip more than 3 times during 3 sec. In fact, 17 cm / larva were covered during 30 sec. High, although lower bioactivity was also observed for a concentration of 10^{-16} µl/ 5 cm trail.

These encouraging results induced us to synthesize stereoselectively the three other stereoisomers of **3**, which are characterized by a *Z* carbon-carbon double bond in the 3-position, and then to test their bioactivity. Herein, we wish to report the stereoselective syntheses on a gram scale of these substances, *i.e.* (3*Z*,6*E*,8*E*)-, (3*Z*,6*E*,8*Z*)- and (3*Z*,6*Z*,8*Z*)-3,6,8-dodecatrien-1-ol, **8**, **9** and **10**, respectively, as well as the results of a preliminary bioassay concerning compound **8**.



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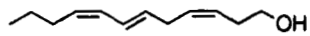

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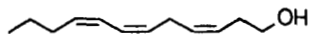

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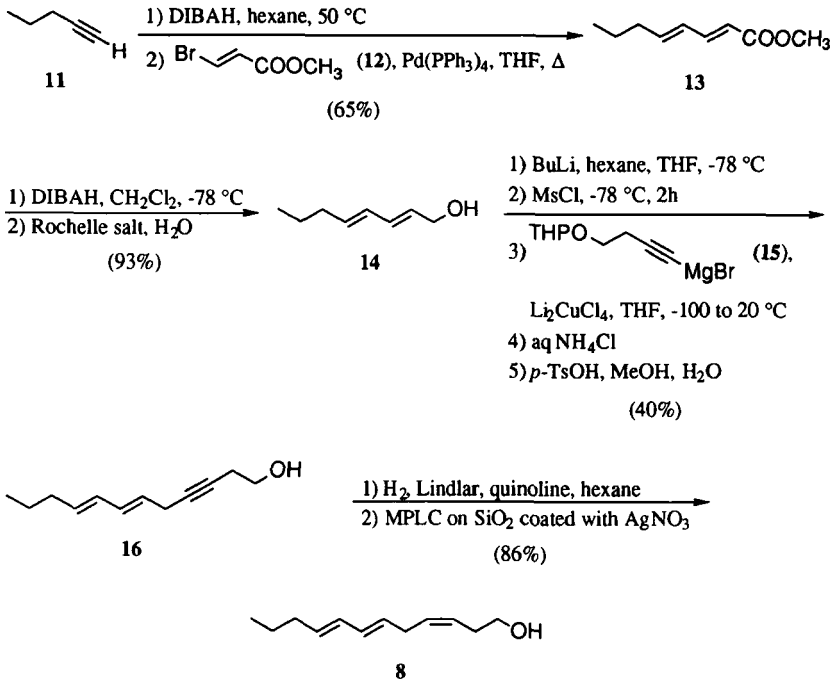
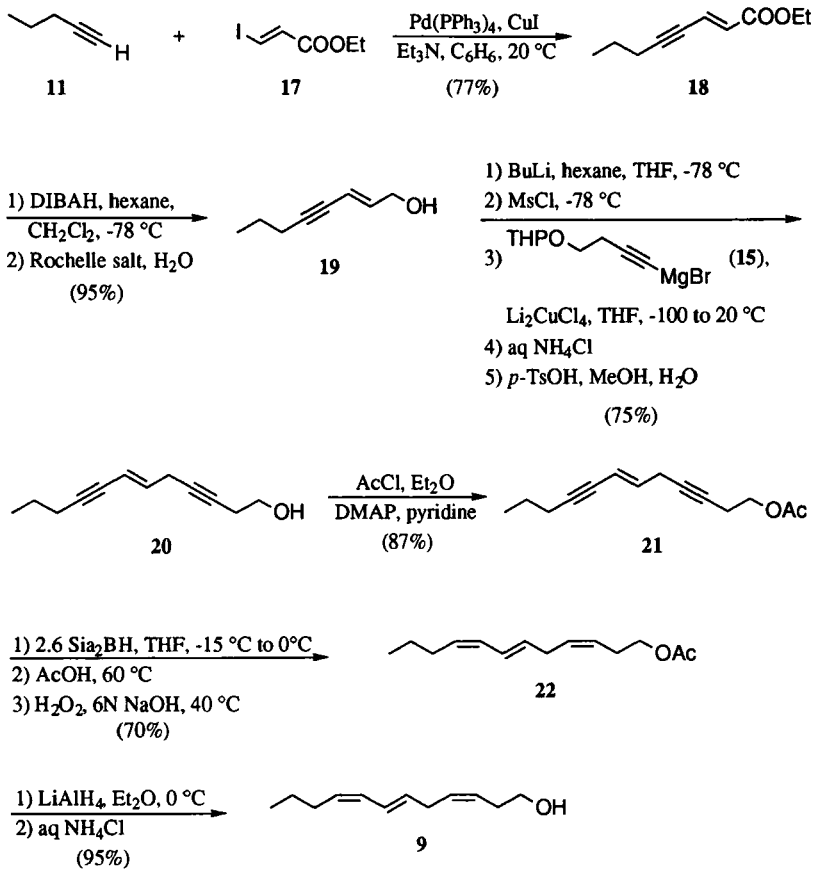


SCHEME 1

It must be noted that these compounds, which are known in the literature,[15] have not been previously stereoselectively prepared. They had been synthesized on a very small scale by a Wittig olefination reaction followed by separation of the desired stereoisomers by recycle high performance liquid chromatography methods.[15]

We synthesized compound **8**, which has been identified as a minor trail-following component of *C. formosanus*,[10] from 1-pentyne (**11**) according to the reaction sequence reported in Scheme 1. Thus, reaction of **11** with diisobutylalane (DIBAH) in hexane at 50 °C followed by cross-coupling of the (*E*)-1-alkenylalane so obtained with methyl (*E*)-3-bromopropenoate (**12**), in the presence of a catalytic quantity of $Pd(PPh_3)_4$, gave methyl (2*E*,4*E*)-2,4-octadienoate (**13**) in 65 % yield. This ester was



SCHEME 2

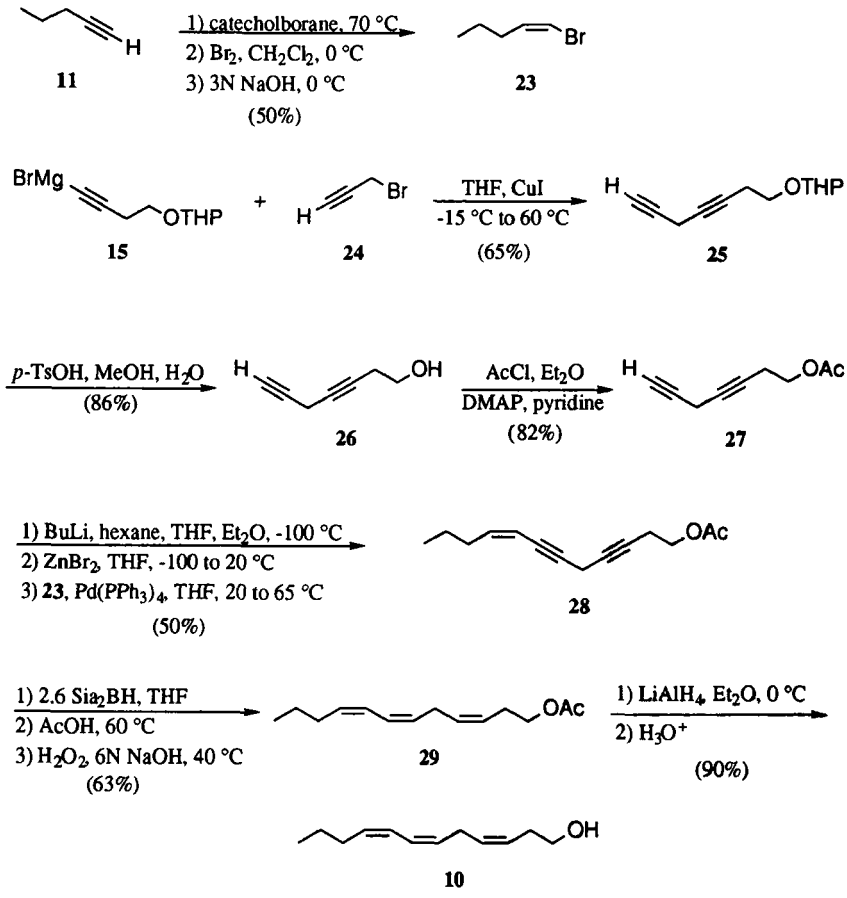
converted in 93 % yield to the corresponding dien-1-ol **14** by reduction with DIBAH in CH_2Cl_2 at - 78 °C. Then, sequential treatment of a THF solution of **14** with 1.1 equiv of butyllithium at -78 °C, 1.1 equiv of methanesulfonyl chloride, a THF solution of 2.0 equiv of 4-(2-tetrahydropyranyloxy)-1-butynylmagnesium bromide (**15**) and, finally, with a THF solution of 0.05 equiv of Li_2CuCl_4,[16] afforded crude (6*E*,8*E*)-1-(2-tetrahydropyranyloxy)-6,8-dodecadien-3-yne.[17]

This product was hydrolyzed to the correponding alcohol **16** in 40 % overall yield. Finally, stereoselective partial reduction of **16** by hydrogenation over Lindlar catalyst poisoned with quinoline, followed by purification of the crude reaction product by MPLC on silica gel coated with $AgNO_3$, allowed to obtain in 86 % yield the desired trien-1-ol **8** having stereoisomeric purity higher than 95 %.

The synthesis of (3*Z*,6*E*,8*Z*)-3,6,8-dodecatrien-1-ol (**9**) was carried out by the reactions sequence illustrated in Scheme 2. Thus, palladium- and copper-mediated coupling between **11** and 0.87 equiv of ethyl (*E*)-3-iodopropenoate (**17**), in the presence of 3.3 equiv of Et_3N in benzene solution at room temperature,[18] gave ethyl (*E*)-3-octen-4-ynoate (**18**) in 77 % yield.

This ester was converted in 95 % yield to the corresponding alcohol **19** by reduction with DIBAH in CH_2Cl_2 at - 78 °C. Then, sequential treatment of **19** with 1.1 equiv of butyllithium in hexane at - 78 °C, 1.1 equiv of methanesulfonyl chloride, a solution of 2.5 equiv of **15** in THF and Et_2O and finally with a THF solution of 4 mol % Li_2CuCl_4 at -100 °C, followed by warming up the reaction mixture to room temperature, gave a crude reaction product, which was mainly constituted of 1-(2-tetrahydropyranyloxy)-1-butyne and (*E*)-6-1-(2-tetrahydropyranyloxy)-6-dodecen-3,8-diyne. This crude product, on treatment with methanol and water, in the presence of a catalytic amount of *p*-toluenesulfonic acid at 90 °C, followed by purification by fractional distillation of the resulting hydrolysis mixture, gave (*E*)-6-dodecen-3,8-diyn-1-ol (**20**) in 75 % yield. Reaction of an Et_2O solution of this alcohol with acetyl cloride, in the presence of pyridine and a catalytic amount of 4-dimethylaminopyridine, afforded chemically and stereoisomerically pure **21** in 87 % yield. Treatment of this acetate with 2.6 equiv od disiamylborane, followed by protonolysis and reaction with 30 wt % H_2O_2 in the presence of 6 N NaOH, gave, after purification of the crude reaction product by MPLC on silica gel, (3*Z*,6*E*,8*Z*)-3,6,8-dodecatrien-1-yl acetate (**22**) in 70 % yield. Finally, reaction of **22** with $LiAlH_4$ in Et_2O at 0 °C, followed by hydrolysis and purification of the crude reaction product by distillation, gave in 95 % yield chemically pure trien-1-ol **9** having stereoisomeric purity higher than 98.5 %.

The synthetic route followed to prepare (3*Z*,6*Z*,8*Z*)-3,6,8-dodecatrien-1-ol (**10**) is illustrated in Scheme 3. In this route the C-12 skeleton of **10** was constructed by a highly chemoselective and stereospecific palladium-mediated cross-coupling reaction between (*Z*)-1-bromo-1-pentene (**23**) and the highly functionalized organozinc bromide derived from 3,6-heptadiyn-1-yl acetate (**27**). Compound **23**, having *ca.* 95



SCHEME 3

% stereoisomeric purity, was synthesized in 50 % yield according to a procedure[19] which involved the reaction between **11** and catecholborane, addition of bromine to a CH_2Cl_2 solution of the catechol ester of the alkenylboronic acid so obtained and treatment of the reaction mixture with aqueous NaOH. On the other hand, compound **27** was so prepared. Reaction of a THF solution of **15** with propargyl bromide (**24**) in the presence of a catalytic quantity of CuI afforded 1-(2-tetrahydropyranyloxy)-3,6-heptadiyne (**25**) in 65 % yield.[20]

Hydrolysis of this derivative with methanol and water, in the presence of a small amount of *p*-toluenesulfonic acid, gave in 86 % yield the corresponding diyn-1-ol **26**, which, on treatment with acetyl chloride in Et_2O solution in the presence of pyridine and a catalytic quantity of dimethylaminopyridine, was converted to **27** in 82 % yield. Then, according to a general procedure for the preparation of highly functionalized aryl and alkenylorganometallics,[21] 1.05 equiv of butyllithium in hexane were added to a solution of **27** in THF / Et_2O (4 : 1) maintained at -100 °C. After 3 minutes, a solution of 1.15 equiv of $ZnBr_2$ in THF was added and the resulting mixture was allowed to warm up to room temperature. A solution of 1.2 equiv of **23** and 0.05 equiv of $Pd(PPh_3)_4$ in THF was then added and the mixture was stirred for 16 h at 20 °C and for 48 h at 50 °C. Purification of the crude reaction product by MPLC on silica gel provided (*Z*)-8-dodecen-3,6-diyn-1-yl acetate (**28**) in 50 % yield. Finally, a reaction sequence very similar to that used to prepare compound **9** from **21**, gave the desired trien-1-ol **10** in 56.7 % yield based on **28**. GLC and ^1H NMR analyses showed that this compound had stereoisomeric purity higher than 95 %.

It is worthwhile mentioning that a preliminary bioactivity test carried out by Prof. G. Sbrenna showed that compound **8** exhibits trail-following activity comparable to that of (3*Z*,6*Z*,8*E*)-3,6,8-dodecatrien-1-ol (**3**). In fact, 10^{-10} µl / 5 cm trail of compound **8** induced larvae of *R. lucifugus* to cover back and forward a straight paper strip 5 cm in lenght more than 4 times during 30 sec. Interestingly, also a concentration of 10^{-14} µl / 5 cm trail of this compound showed a good efficacy. In fact, *ca.* 10 cm / larva were covered during 30 sec. Unfortunately, bioassays concerning compounds **9** and **10** have not been so far performed.

In conclusion, highly chemo- and stereoselective syntheses on a gram scale of compounds **8**, **9** and **10**, which represent three stereoisomers of (3*Z*,6*Z*,8*E*)-3,6,8-dodecatrien-1-ol (**3**), a main trail-following pheromone component of several termites, have been developed. The first of these substances, which is a minor trail-following pheromone component of *C. formosanus*,[10] has proven to possess a bioactivity for larvae of *R. lucifugus*, which is comparable to that of compound **3**.

EXPERIMENTAL

All reactions of air and water sensitive materials were performed in flame dried glassware under an atmosphere of argon or nitrogen. Air and water sensitive

solutions were transferred with hypodermic syringes or double-ended needles. GLC analyses were performed on a Dani 6500 gas-chromatograph with a PTV injector and equipped with a Dani data station 86.01. Two types of capillary columns were used: a SE-30 bonded FSOT column (30 m x 0.25 mm i.d.) and an AT-Wax bonded FSOT column (30 m x 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 a Q-mass 910 spectrometer interfaced with a Perkin-Elmer 8500 gas-chromatograph. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard.

The following compounds were prepared according to the literature: $Pd(PPh_3)_4$[22], methyl (*E*)-3-bromopropenoate (**12**),[23] 1-(2-tetrahydropyranyloxy)-3-butyne,[24] ethyl (*E*)-3-iodopropenoate (**17**),[25] and 1-(2-tetrahydropyranyloxy)-3,6-heptadiyne (**25**).[20]

Methyl (2E,4E)-2,4-octadienoate (13)

A 1.0 M hexane solution of diisobutylalane (DIBAH) (88.2 ml, 88.2 mmol) was added dropwise to 1-pentyne (**11**) (8.70 ml, 88.1 mmol) maintained at 20 °C. The resulting mixture was stirred for 0.5 h at 20 °C and for 5 h at 50 °C and then cooled to room temperature. This solution and methyl (*E*)-3-bromopropenoate (**12**) (16.0 g, 97.0 mmol) were sequentially added to a stirred solution of $Pd(PPh_3)_4$ (4.75 g, 4.11 mmol) in THF (80 ml) and the resulting mixture was stirred for 0.5 h at 20 °C and for 0.5 h under reflux. After this period, a GLC analysis of a sample of the reaction mixture, which was hydrolyzed with cold 3 N HCl, showed that the reaction was complete. Thus, the reaction mixture was cooled under stirring to - 20 °C and an excess of 3 N HCl was dropwise added during 45 minutes. The resulting mixture was allowed to warm up to 20 °C and extracted with Et_2O. The organic extract was washed with water 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 (97 : 3 *v/v*) as eluant. The chromatographic fractions, which contained the desired cross-coupled product, were combined and fractionally distilled to give stereoisomerically pure **13** (8.77 g, 65 % yield): b.p. 101 °C / 15 Torr. ^{1}H NMR

($CDCl_3$): δ 7.42 (1H, dd, J = 15.2 and 10.7 Hz, H-3), 5.86 (1H, dd, J = 14.9 and 10.7 Hz, H-4), 5.85 (1H, d, J = 15.2 Hz, H-2), 5.65 (1H, dt, J = 14.9 and 7.0 Hz, H-5), 3.46 (3H, s, OCH_3), 1.76 (2H, q, J = 7.0 Hz, H-6), 1.15 (2H, sext, J = 7.0 Hz, H-7), 0.73 ppm (3H, t, J = 7.0 Hz, H-8). These NMR data were in satisfactory agreement with those reported in the literature.[26] Anal. Calcd for $C_9H_{14}O_2$: C, 70.15; H, 9.09. Found: C, 69.92; H, 9.12.

*(2E,4E)-2,4-Octadien-1-ol (**14**)*

A 1 M hexane solution of DIBAH (234 ml, 234 mmol) was added dropwise over 0.5 h to a solution of compound **13** (17.6 g, 114.2 mmol) in CH_2Cl_2 (730 ml), which was stirred at - 78 °C. After completion of the addition the mixture was stirred for 4.5 h at - 78 °C. Methanol (16 ml) and a saturated aqueous solution of potassium sodium tartrate (200 ml) were sequentially added dropwise and the resulting mixture was allowed to warm up to room temperature. After stirring for additional 40 minutes, the mixture was repeatedly extracted with Et_2O. The combined organic extracts were washed with brine, dried, concentrated and distilled to give pure **14** (12.72 g, 93 % yield): b.p. 100-101 °C/ 15 Torr (Lit[27] b.p. 70-73 °C/ 2.0 Torr). ^1H NMR ($CDCl_3$): δ 6.20 (1H, dd, J = 14.7 and 10.4 Hz, H-3), 6.03 (1H, dd, J = 14.8 and 10.4 Hz, H-4), 5.70 (1H, dt, J = 14.7 and 6.0 Hz, H-1), 2.39 (1H, br s, OH), 2.06 (2H, q, J = 7.3 Hz, H-6), 1.41 (2H, sext, J = 7.3 Hz, H-7), 0.90 ppm (3H, t, J = 7.3 Hz, H-8). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.97; H, 11.03.

*(6E,8E)-6,8-Dodecadien-3-yn-1-ol (**16**)*

A 1.85 M solution of butyllithium (24.4 ml, 45.15 mmol) was added dropwise to a solution of compound **14** (5.18 g, 41.05 mmol) in THF (245 ml), which was stirred at - 78 °C. After 0.5 h, methanesulfonyl chloride (3.50 ml, 45.20 mmol) was added in one portion and the resulting mixture was stirred at - 78 °C for 2 h. A solution of 4-(2-tetrahydropyranyloxy)-1-butynylmagnesium bromide (**15**) in THF, which was prepared by treatment of a solution of 1-(2-tetrahydropyranyloxy)-3-butyne (13.1 g, 85 mmol) in THF (136) with a 1.25 M THF solution of ethylmagnesium bromide (81.6 mmol), was next transferred rapidly via cannula into the reaction mixture cooled to - 100 °C under stirring. A 0.1 M THF solution of Li_2CuCl_4 (20.5 ml, 2.05 mmol) was then added and the resulting mixture was allowed to warm up to room

temperature over 2.5 h, stirred at this temperature for 4 h and then poured into a large excess of saturated aqueous NH_4Cl solution buffered to pH 8 with NH_4OH. After stirring for 0.5 h at room temperature, the mixture was extracted repeatedly with Et_2O and the combined organic extracts were washed with a saturated aqueous NH_4Cl solution and brine, dried and concentrated *in vacuo*. The residue was diluted with methanol (200 ml), which contained *p*-toluenesulfonic acid (1.3 g), and the resulting solution was refluxed until completion of the reaction. It was then cooled to 20 °C and concentrated *in vacuo*. The residue was diluted with Et_2O and a large excess of brine was added. The mixture was extracted repeatedly with Et_2O and the combined organic extracts were washed with water until neutrality, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (65 : 35 *v*/*v*) as eluant, to give compound **16** (2.92 g, 40 % yield). ^1H NMR ($CDCl_3$): δ 6.23 (1H, dd, J = 14.9 and 10.3 Hz, H-8), 6.03 (1H, dd, J = 14.8 and 10.3 Hz, H-7), 5.65 (1H, dt, J = 14.9 and 7.2 Hz, H-9), 5.53 (1H, dt, J = 14.8 and 5.8 Hz, H-6), 3.71 (2H, t, J = 6.2 Hz, H-1), 2.98 (2H, brd, J = 2.5 Hz, H-5), 2.47 (2H, tt, J = 6.2 and 2.5 Hz, H-2), 2.05 (2H, q, J = 7.2 Hz, H-10), 1.85 (1H, brs, OH), 1.41 (2H, sext, J = 7.2 Hz, H-11), 0.90 ppm (3H, t, J = 7.2 Hz, H-12). MS, *m*/*z* (%): 178 (0.2), 177 (2), 130 (5), 116 (16), 104 (41), 91 (18), 90 (100), 78 (42), 76 (39). Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.71; H, 10.28. GLC analysis showed that compound **16** had chemical purity higher than 95 %.

*(3Z,6E,8E)-3,6,8-Dodecatrien-1-ol (**8**)*

Compound **16** (1.77 g, 9.94 mmol) was hydrogenated at 5 °C over Lindlar catalyst (1.0 g) in hexane (40 ml) containing quinoline (3 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 concentrated *in vacuo*. The residue was purified by MPLC on silica gel coated with 10 % $AgNO_3$, using a mixture of hexane and ethyl acetate (70 : 30 *v*/*v*) as eluant, to give compound **8** (1.54g, 86 % yield). ^1H NMR ($CDCl_3$): δ 6.04 (1H, ddt, J = 14.7, 10.0 and 1.0 Hz, H-7), 5.99 (1H, ddt, J = 14.1, 10.0 and 1.0 Hz, H-8), 5.75 - 5.50 (3H, m, H-4, H-6 and H-9), 5.44 (1H, ddt, J = 10.8, 6.8 and 1.3 Hz, H-3), 3.64 (2H, t, J = 6.8 Hz, H-1), 2.84 (2H, t, J = 6.6 Hz, H-5), 2.33 (2H, q, J = 6.8 Hz, H-2), 2.03 (2H, q, J = 7.3 Hz, H-10), 1.75 (1H, brs, OH), 1.39 (2H, sext, J = 7.3 Hz, H-11), 0.89 ppm (3H, t, J = 7.3 Hz, H-12). ^{13}C NMR ($CDCl_3$): δ

133.0, 130.9, 130.2, 129.6, 126.2, 34.7, 30.7, 30.5, 22.5 and 13.7 ppm. MS, *m/z* (%): 181 (2), 180 (16), 137 (5), 119 (13), 105 (26), 91 (52), 79 (36), 67 (26), 55 (100). The ^{1}H NMR and ^{13}C NMR data were in satisfactory agreement with those previously reported.[15]

Ethyl (E)-2-octen-4-ynoate (18)

Ethyl (*E*)-3-iodopropenoate (**17**) (29.6 g, 131 mmol) and 1-pentyne (**11**) (10.2 g, 150 mmol) were sequentially added to a suspension of $Pd(PPh_3)_4$ (7.57 g, 6.55 mmol), CuI (3.74 g, 19.65 mmol) and Et_3N (50.9 g, 500 mmol) in benzene (300 ml), which was stirred at 20 °C. The resulting mixture was stirred for additional 6 h at room temperature, then diluted with Et_2O and poured into a large excess of a saturated aqueous NH_4Cl solution buffered to pH 8 with NH_4OH. The mixture was extracted repeatedly with Et_2O and the combined organic extracts were washed with an aqueous NH_4Cl solution and water, dried and concentrated under reduced pressure. The residue was diluted with hexane (400 ml) and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was fractionally distilled to give chemically and stereoisomerically pure **18** (16.85 g, 77 % yield): b.p. 57 °C / 0.25 Torr. ^{1}H NMR ($CDCl_3$): δ 6.76 (1H, dt, J = 15.9 and 2.2 Hz, H-3), 6.14 (1H, d, J = 15.9 Hz, H-2), 4.20 (2H, q, J = 7.2 Hz, OCH_2), 2.35 (2H, td, J = 7.1 and 2.2 Hz, H-6), 1.58 (2H, sext, J = 7.1 Hz, H-7), 1.29 (3H, t, J = 7.2 Hz, O-C-CH_3), 1.00 ppm (3H, t, J 7.1 Hz, H-8). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.98; H, 8.63.

(E)-2-Octen-4-yn-1-ol (19)

A 1 M hexane solution of DIBAH (212 ml, 212 mmol) was added dropwise over 1 h to a solution of compound **18** (16.0 g, 96.26 mmol) in CH_2Cl_2 (630 ml), which was stirred at - 78 °C. The resulting reaction mixture was allowed to warm up to room temperature over 7 h, then it was cooled to - 20 °C. Methanol (15 ml) and saturated aqueous solution of potassium sodium tartrate (300 ml) were sequentially added dropwise and the mixture was allowed to warm up to 20 °C. After stirring for additional 40 minutes, it was repeatedly extracted with Et_2O and the combined organic extracts were washed with brine, dried and concentrated under reduced pressure. The residue was fractionally distilled to give chemically and stereoisomerically pure **19** (11.21 g, 95 % yield): b.p. 109 °C / 11 Torr. ^{1}H NMR

($CDCl_3$): δ 6.15 (1H, dt, J = 15.8 and 5.4 Hz, H-2), 5.71 (1H, d quint, J = 15.8 and 1.9 Hz, H-3), 4.14 (2H, br t, J = 5.4 Hz, H-1), 2.60 (1H, br t, J = 5.4 Hz, OH), 2.28 (2H, td, J = 7.1 and 1.9 Hz, H-6), 1.55 (2H, sext, J = 7.1 Hz, H-7), 0.99 ppm (3H, t, J = 7.1 Hz, H-8). Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.73. Found: C, 77.01; H, 9.85.

*(E)-6-Dodecen-3,8-diyn-1-ol (**20**)*

A 1.92 M hexane solution of butyllithium (26.35 ml, 50.6 mmol) was added dropwise to a solution of compound **19** (5.70 g, 46.0 mmol) in THF (250 ml), which was stirred at - 78 °C. After 0.5 h, methanesulfonyl chloride (3.92 ml, 50.6 mmol) was added in one portion and the resulting mixture was stirred at - 78 °C for 2.5 h. A solution of 4-(2-tetrahydropyranyloxy)-1-butynylmagnesium bromide (**15**) (120 mml) in a *ca.* 2.7 : 1 mixture of THF and Et_2O (320 ml), which was cooled to - 20 °C, was next transferred rapidly via cannula into the reaction mixture cooled to - 100 °C under stirring. A 0.1 M THF solution of Li_2CuCl_4 (18.4 ml, 1.84 mmol) was then added and the resulting mixture was allowed to warm up to room temperature over 3 h and stirred at this temperature for additional 3 h. It was then poured into a large excess of a saturated aqueous NH_4Cl solution buffered to pH 8 with NH_4OH and extracted repeatedly with Et_2O. The combined organic extracts were washed with aqueous NH_4Cl solution and brine, dried and concentrated *in vacuo*. The residue was diluted with methanol (170 ml) and water (20 ml), which contained *p*-toluenesulfonic acid (3.2 g) and 35 % HCl (0.5 ml). The resulting solution was refluxed until completion of the reaction, cooled to room temperature and concentrated *in vacuo*. The residue was diluted with Et_2O (300 ml) and the solution so obtained was washed with water until neutrality, dried and concentrated *in vacuo*. The residue was fractionally distilled to give stereoisomerically pure **20** (6.08 g, 75 % yield based on **19**): b.p. 96-97 °C / 0.03 Torr. ^1H NMR ($CDCl_3$): δ 6.01 (1H, dt, J = 15.7 and 5.1 Hz, H-6), 5.76 (1H, d quint, J = 15.7 and 2.0 Hz, H-7), 3.70 (2H, t, J = 6.3 Hz, H-1), 3.00 (2H, br dd, J = 5.1 and 2.0 Hz, H-5), 2.46 (2H, tt, J = 6.3 and 2.0 Hz, H-2), 2.27 (2H, td, J = 7.1 and 2.0 Hz, H-10), 2.02 (1H, br s, OH), 1.55 (2H, sext, J = 7.1 Hz, H-11), 0.99 ppm (3H, t, J = 7.1 Hz, H-12). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.21; H, 9.52. GLC analysis showed that this compound had chemical purity higher than 96.5 %.

(E)-6-Dodecen-3,8-diyn-1-yl acetate (21)

A solution of acetyl chloride (2.91 g, 37.09 mmol) in Et_2O (15 ml) was added dropwise to a solution of compound **20** (5.23 g, 29.67 mmol), 4-dimethylamino-pyridine (0.27 g, 2.23 mmol) and pyridine (3.52 g, 55.5 mmol) in Et_2O (45 ml), which was stirred at 0 °C. The resulting mixture was stirred at 20 °C for 0.5 h and then refluxed for 12 h. It was then cooled to room temperature, diluted with Et_2O, poured into a large excess of cold water and extracted repeatedly with Et_2O. The combined organic extracts were washed with cold 5 % HCl, a saturated aqueous $NaHCO_3$ solution and water, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (93 : 7 *v/v*) as eluant, to give chemically and stereoisomerically pure **21** (6.43 g, 87 % yield). ^1H NMR ($CDCl_3$): δ 6.00 (1H, dt, J = 5.8 and 5.0 Hz, H-6), 5.78 (1H, d quint, J = 15.8 and 2.0 Hz, H-7), 4.15 (2H, t, J = 6.9 Hz, H-1), 2.97 (2H, br dd, J = 5.0 and 2.0 Hz, H-5), 2.53 (2H, tt, J = 6.9 and 2.0 Hz, H-2), 2.27 (2H, td, J = 7.1 and 2.0 Hz, H-10), 2.08 (3H, s, $COCH_3$), 1.55 (2H, sext, J = 7.1 Hz, H-11), 0.99 ppm (3H, t, J = 7.1 Hz, H-12). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.17; 8.71.

(3Z,6E,8Z)-3,6,8-Dodecatrien-1-yl acetate (22)

2-Methyl-2-butene (11.14 g, 158.8 mmol) was slowly added to a solution of borane-methyl sulfide complex (7.67 ml, 76.7 mmol) in THF cooled to - 20 °C and the mixture was stirred for 2 h at room temperature. It was then cooled to - 10 °C and a solution of compound **21** (6.43 g, 29.45 mmol) in THF (42 ml) was added dropwise over 0.5 h. The resulting mixture was stirred for 6.5 h at 0 °C, then acetic acid (21.5 ml, 376 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, 45 minutes), the mixture was diluted with THF (50 ml), cooled to 0 °C and 6 N NaOH (118 ml, 710 mmol) was slowly added. The mixture was warmed up to room temperature and 30 wt % H_2O_2 (33.2 ml, 327.7 mmol) was added dropwise maintaining the reaction temperature below 40 °C. The mixture was then cooled to room temperature, brine was added and the resulting mixture 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 was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (96 : 4 v/v)

as eluant, to give compound **22** (4.61 g, 70 % yield). ^{1}H NMR ($CDCl_3$): δ δ 6.33 (1H, ddd, J = 14.6, 10.9 and 1.0 Hz, H-7), 5.96 (1H, t, J = 10.9 Hz, H-8), 5.62 (1H, dt, J = 14.6 and 6.5 Hz, H-6), 5.60-5.25 (3H, m, H-3, H-4 and H-9), 4.08 (2H, t, J = 6.8 Hz, H-1), 2.87 (2H, t, J = 6.5 Hz, H-5), 2.40 (2H, q, J = 6.8 Hz, H-2), 2.14 (2H, q, J = 7.0 Hz, H-10), 2.04 (3H, s, $COCH_3$), 1.41 (2H, sext, J = 7.0 Hz, H-11), 0.92 ppm (3H, t, J = 7.0 Hz, H-12). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.34; H, 10.05. GLC and ^{1}H NMR analyses showed that compound **22** had chemical and stereoisomeric purity higher than 98 %.

*(3Z,6E,8Z)-3,6,8-Dodecatrien-1-ol (**9**)*

A solution of compound **22** (3.81 g, 17.14 mmol) in Et_2O (15 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.36 g, 35.81 mmol) in Et_2O (45 ml) maintained at 0 °C. The resulting mixture was stirred for 4 h at this temperature, diluted with Et_2O, 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 *in vacuo*. The residue was fractionally distilled to give chemically pure **9** (2.94 g, 95 % yield): b.p. 79-80 °C / 0.03 Torr. ^{1}H NMR ($CDCl_3$): δ 6.34 (1H, ddq, J = 15.0, 11.0 and 1.2 Hz, H-7), 5.96 (1H, t, J = 11.0 Hz, H-8), 5.63 (1H, dt, J = 15.0 and 6.9 Hz, H-6), 5.63-5.48 (1H, m, H-4), 5.49 (1H, dtt, J = 10.8, 6.8 and 1.3 Hz, H-3), 3.65 (2H, t, J = 6.8 Hz, H-1), 2.89 (2H, t, J = 6.9 Hz, H-5), 2.35 (2H, q, J = 6.8 Hz, H-2), 2.14 (2H, dq, J = 7.3 and 1.4 Hz, H-1), 2.89 (2H, t, J = 6.9 Hz, H-5), 2.35 (2H, q, J = 6.8 Hz, H-2), 2.14 (2H, dq, J = 7.3 And 1.4 Hz, H-10), 1.64 (1H, br s, OH), 1.40 (2H, sext, J = 7.3 Hz, H-11), 0.92 ppm (3H, t, J = 7.3 Hz, H-12). ^{13}C NMR ($CDCl_3$): δ 131.8, 130.6, 130.2, 128.4, 126,2, 126.1, 62.2, 30.9, 30.9, 29.7, 22.8 and 13.7 ppm. The spectral properties of this compound, which had stereoisomeric purity higher than 98.5 %, were in satisfactory agreement with those previously reported.[15]

*(Z)-1-Bromo-1-pentene (**23**)*

1-Pentyne (**11**) (8.78 g, 129 mmol) was added dropwise to catecholborane (15.47 g, 129 mmol) and the mixture was stirred for 45 minutes at room temperature and for 3 h at 70 °C. It was then cooled to room temperature, diluted with CH_2Cl_2 (125 ml) and the solution was cooled under stirring to 0 °C. A solution of bromine (41.2 g,

258 mmol) in CH_2Cl_2 (30 ml) was added dropwise and the resulting mixture was stirred at 0 °C for 1 h. Then 3 N NaOH (86 ml, 258 mmol) was added and the mixture was stirred at 0 °C for 4 h, poured into a large excess of water and extracted repeatedly with CH_2Cl_2. The combined organic extracts were filtered, washed with water until neutrality, dried and concentrated under reduced pressure at 20 °C. The residue was fractionally distilled to give compound **23** (9.60 g, 50 % yield): b.p. 68-70 °C / 150 Torr (Lit[28] b.p. 41 °C / 92 mm). The spectral properties of this compound were in good agreement with those previously reported.[28] GLC and ^1H NMR analyses showed that this compound had stereoisomeric purity higher than 94 %.

*3,6-Heptadiyn-1-ol (**26**)*

A solution of 1-(2-tetrahydropyranyloxy)-3,6-heptadiyne (**25**) (53.36 g, 278 mmol) in methanol (440 ml) and water (44 ml), which contained *p*-toluenesulfonic acid (4.2 g), was refluxed for 5.5 h. It was then cooled to room temperature and concentrated under reduced pressure (190 Torr). The residue was diluted with Et_2O and washed repeatedly with brine. The organic extract was dried and concentrated under reduced pressure and the residue was fractionally distilled to give **26** (25.9 g, 86 % yield): b.p. 104 °C / 18 Torr. ^1H NMR ($CDCl_3$): δ 3.71 (2H, t, J = 6.3 Hz, H-1), 3.18 (2H, q, J = 2.5 Hz, H-5), 2.45 (2H, tt, J = 6.3 and 2.5 Hz, H-2), 2.10 (1H, br s, OH), 2.09 ppm (1H, t, J = 2.5 Hz, H-7). MS, *m/z* (%): 108 (1), 107 (10), 89 (5), 79 (21), 78 (31), 77 (18), 63 (11), 53 (18), 52 (100). Anal. Calcd for C_7H_8O: C, 77.78; H, 7.46. Found: C, 77.95; H, 7.21.

*3,6-Heptadiyn-1-yl acetate (**27**)*

A solution of acetyl chloride (18.05 g, 230 mmol) in Et_2O (20 ml) was added dropwise to a solution of compound **26** (21.8 g, 201 mmol), 4-dimethylaminopyridine (1.22 g, 10 mmol) and pyridine (20.2 ml, 250 mmol) in Et_2O (280 ml), which was stirred at 0 °C. The resulting mixture was stirred for 0.5 h at 0 °C, for 12 h at 20 °C and refluxed for 4 h. It was then cooled to 20 °C, diluted with Et_2O and poured into a large excess of water. The resulting mixture was extracted repeatedly with Et_2O and the combined organic extracts were washed with cold 5 % HCl, a saturated aqueous $NaHCO_3$ solution and water, dried and concentrated under reduced pressure. Fractional distillation of the residue gave compound **27** (24.8 g, 82 %

yield): b.p. 113 °C / 17 Torr. ^{1}H NMR ($CDCl_3$): δ 4.15 (2H, t, J = 6.9 Hz, H-1), 3.16 (2H, q, J = 2.5 Hz, H-5), 2.51 (2H, tt, J = 6.9 Hz and 2.5 Hz, H-2), 2.08 (1H, t, J = 2.5 Hz, H-7), 2.07 (3H, s, $COCH_3$). MS, *m/z* (%): 119 (1), 91 (3), 90 (28), 89 (20), 65 (5), 63 (6), 51 (3), 50 (19), 43 (100). Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.86; H, 6.52.

*(Z)-8-Dodecen-3,6-diyn-1-yl acetate (**28**)*

A 1.95 M hexane solution of butyllithium (17.8 ml, 34.7 mmol) was added dropwise over 5 minutes to a solution of compound **27** (4.95 g, 33.0 mmol) in a mixture of THF and Et_2O (4 : 1, 103 ml), which was stirred at - 100 °C. The resulting solution was stirred for 3 minutes at - 100 °C and a THF solution (50 ml) of dry $ZnBr_2$ (8.63 g, 38.3 mmol) was added. After the mixture was stirred for 1 h at - 100 °C it was allowed to warm up to room temperature. A solution of compound **23** (5.96 g, 40.0 mmol) and $Pd(PPh_3)_4$ (2.08 g, 1.8 mmol) in THF (60 ml), which had been shortly before prepared, was added and the resulting mixture was stirred for 16 h at room temperature and for 48 h under reflux. It was then cooled, poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O. The combined organic extracts were filtered, washed with water, dried and concentrated *in vacuo*. The residue was diluted with hexane (500 ml) and filtered over Celite. The filtrate was concentrated *in vacuo* and 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 **28** (3.59 g, 50 % yield). ^{1}H NMR ($CDCl_3$): δ 5.89 (1H, dt, J = 10.8 and 7.3 Hz, H-9), 5.44 (1H, d quint, J = 10.8 and 1.4 Hz, H-8), 4.15 (2H, t, J = 7.0 Hz, H-1), 3.31 (2H, br q, J = 2.2 Hz, H-5), 2.52 (2H, tt, J = 7.0 and 2.2 Hz, H-2), 2.27 (2H, dq, J = 7.3 and 1.4 Hz, H-10), 2.08 (3H, s, $COCH_3$), 1.43 (2H, sext, J = 7.3 Hz, H-11), 0.93 ppm (3H, t, J = 7.3 Hz, H-12). MS, *m/z* (%): 176 (0.1), 175 (0.5), 147 (1), 129 (2), 128 (3), 115 (2), 51 (4), 44 (3), 43 (100).Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.29; H, 8.45. ^{1}H NMR and GLC/MS analyses showed that compound **28** was 97.5 % chemically pure and had stereoisomeric purity higher than 95 %.

*(3Z,6Z,8Z)-3,6,8-Dodecatrien-1-yl acetate (**29**)*

2-Methyl-2-butene (5.36 g, 76.6 mmol) was added dropwise to a solution of borane-methylsulfide complex (3.70 ml, 37.0 mmol) in THF (35 ml) cooled to - 20 °C.

The mixture was stirred for 2 h at room temperature and then cooled to - 10 °C. A solution of compound **28** (3.15 g, 14.2 mmol) in THF (20 ml) was added dropwise over 0.5 h and the resulting mixture was stirred for 6 h at 0 °C. Acetic acid (10.4 ml, 18.2 mmol) was added and the resulting mixture was stirred at 60 °C for 6 h. After evaporation of the volatile substances (25 °C / 20 Torr, 40 minutes), the mixture was diluted with THF (35 ml), cooled to 0 °C and 6 N NaOH (57 ml, 342 mmol) was slowly added. The resulting mixture was warmed up to room temperature and 30 wt % H_2O_2 (16.0 ml, 158 mmol) was added dropwise, maintaining the reaction temperature below 40 °C. After completion of the addition, the mixture was stirred for 40 minutes at 40 °C, cooled to 20 °C, diluted with brine and extracted repeatedly with Et_2O. The combined organic extracts were washed with brine and water until neutrality, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (96 : 4 *v/v*) as eluant, to give compound **29** (3.16 g, 63 % yield). ^1H NMR ($CDCl_3$): δ 6.37 - 6.19 (2H, m, H-7 and H-8), 5.61 - 5.29 (4H, m, H-3, H-4, H-6 and H-9), 4.08 (2H, t, J = 6.7 Hz, H-1), 2.94 (2H, t, J = 7.3 Hz, H-5), 2.41 (2H, q, J = 6.7 Hz, H-2), 2.16 (2H, q, J = 7.2 Hz, H-10), 2.05 (3H, s, $COCH_3$), 1.42 (2H, sext, J = 7.2 Hz, H-11), 0.92 ppm (3H, t, J = 7.2 Hz, H-12). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.32; H, 10.41. GLC analysis showed that compound **29** was 95 % stereoisomerically pure.

*(3Z,6Z,8Z)-3,6,8-Dodecatrien-1-ol (**10**)*

A solution of compound **29** (1.29 g, 5.8 mmol) in Et_2O (5 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.0 g, 5.26 mmol) in Et_2O (25 ml), which was maintained at 0 °C. The resulting mixture was stirred for 4 h at 0 °C, the, poured into a large excess of a saturated aqueous NH_4Cl solution and extracted repeatedly with Et_2O. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (70 : 30 v/v) as eluant, to give compound **10** (0.94 g, 90 % yield). ^1H NMR ($CDCl_3$): δ 6.38 - 6.18 (2H, m, H-7 and H-8), 5.65 - 5.31 (4H, m, H-3, H-4, H-6 and H-9), 3.65 (2H, br t, J = 6.5 Hz, H-1), 2.97 (2H, t, J = 7.3 Hz, H-5), 2.36 (2H, q, J = 6.5 Hz, H-2), 2.16 (2H, q, J = 7.3 Hz, H-10), 1.66 (br s, OH), 1.42 (2H, sext, J = 7.3 Hz, H-11), 0.92 ppm (3H, t, J = 7.3 Hz, H-12). ^{13}C NMR ($CDCl_3$): δ 132.8, 130.8, 129.2, 125.9, 124.1, 123.5, 62.3, 30.9, 29.6, 26.0, 22.8, 13.8 ppm. The

spectral properties of this compound, which was 95 % stereoisomerically pure, were in satisfactory agreement with those previously reported.[15]

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