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Synthesis of Tricyclopolyprenols *via* a Radical Addition and a Stereoselective Elimination. Part I: Methodology

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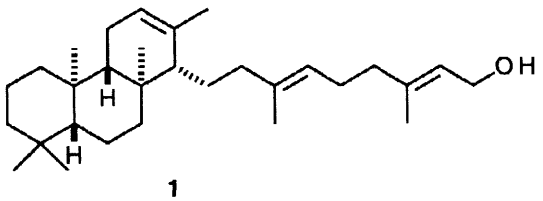
Abstract: The feasibility of a synthesis of tricyclopolyprenols based on the addition of the isocopalen-15-yl radical either to a 2-methylene-3-hydroxy alkenenitrile or to a methyl 2-methylene-3-hydroxy alkenoate – both prepared by a Baylis-Hillman reaction – is examined. When two model adducts, a β-acetoxy nitrile and a β-mesyloxy ester, were subjected to an elimination reaction, the former gave a *trans* α,β-unsaturated nitrile whereas the latter gave a *cis* α,β-unsaturated ester. The reduction of the ancillary cyano or methoxycarbonyl groups into a methyl is also described.

The synthesis of tricyclopolyprenols, the hypothetical precursors of a family of tricyclic geoterpanes,[1] has been undertaken to allow the evaluation of their membrane reinforcing properties,[2] since it has been proposed that these compounds might have been membrane constituents in primitive microorganisms.[3]



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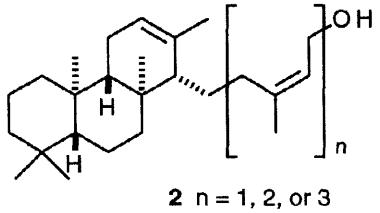

2 n = 1, 2, or 3

This programme has led to the synthesis of (*E,E*)-tricyclohexaprenol **1** as well as to that of three tricyclopolyprenols **2** bearing a side chain made respectively of one, two and three (*Z*) isoprenic units.[4] (*E,E*)-tricyclohexaprenol had been synthesised earlier by Corey[5] on the one hand and by one of us on the other.[6] In the latter synthesis, the side chain was introduced stepwise on the hindered C-15 of isocopal-12-en-15-ol **3** prepared in three steps from natural copalic acid. This has allowed for some flexibility since it has also resulted in a synthesis of (*Z,Z*)-tricyclohexaprenol.[7]

In the syntheses considered here, we planned to take advantage of radical chemistry[8] to introduce the side chain in one step, *i.e.* to add the isocopalenyl radical, obtained from isocopal-12-en-15-yl iodide **4**, to an alkenic side chain precursor **5** (Scheme 1). The hydroxy group of compound **5** would later allow the formation of a double bond and the reduction of the electron withdrawing group (EWG) into a methyl would complete the synthesis.

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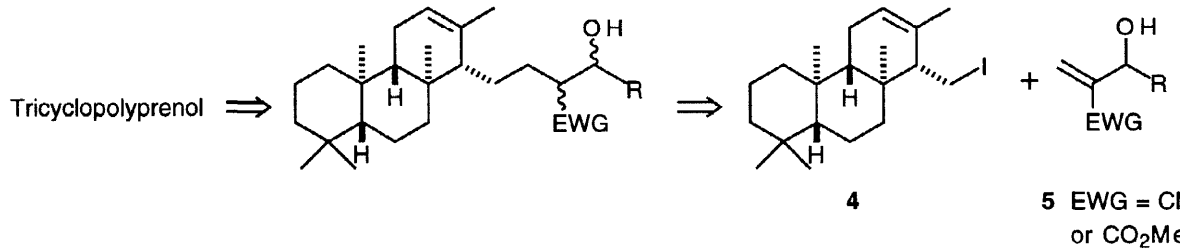
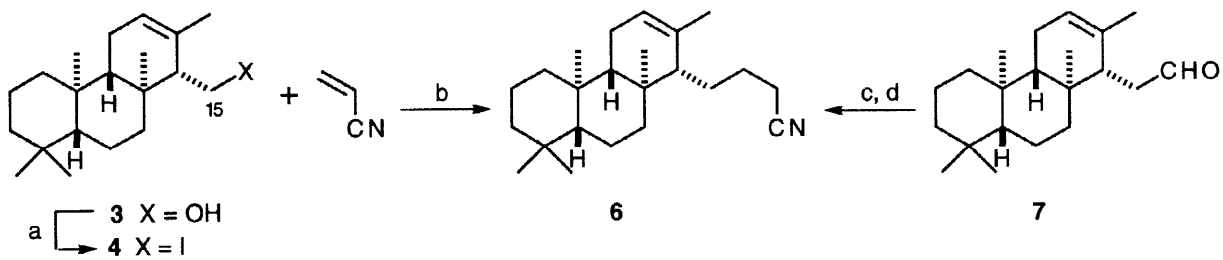
A successful synthesis along these lines implied: a) that we were able to prepare isocopalenyl iodide from isocopalenol, being aware that elimination was a likely side reaction;[6] b) that the homoallylic isocopalenyl radical did not rearrange before addition;[9] c) that the elimination reaction proceeded with reasonable selectivity; d) that we were able to transform the EWG into a methyl without loss of the double bond configuration. We show below in several preliminary experiments how we have been able to fulfill these requirements. The following paper describes the syntheses of four tricyclopolyprenols by means of the methodology outlined here.

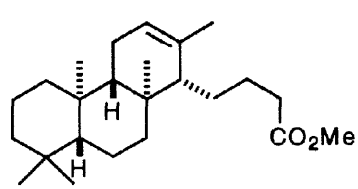


Scheme 1

We rapidly found out that up to 70% of isocopal-12-en-15-yl iodide **4** accompanied by only small amounts of isocopala-12,14-diene could be obtained by treatment of the alcohol **3**[6] with iodine and triphenylphosphine in ether and hexamethylphosphoramide (HMPA).[10] We then checked if the addition of the homoallylic isocopalenyl radical to acrylonitrile occurs without radical rearrangement and found that the so obtained nitrile was identical (GC, IR, ^{1}H-NMR) to the nitrile **6** prepared from the aldehyde **7**[6] by a Wittig reaction followed by the reduction of the conjugated double bond (Scheme 2). The same addition could also be performed on methyl acrylate and gave the ester **8**, but not on allyltributyltin[11] or on methallyl phenyl sulfone[12] which would have allowed shorter syntheses.



Scheme 2. a) I_2, PPh_3, Et_2O, HMPA, 0 °C, 0.5 h, then r. t., 6 h (70%); b) *n*-Bu_3SnH, Et_2O, hv (100 W tungsten lamp), 2 h (79%); c) $(EtO)_2P(O)CHNaCN$, THF, DMSO, r. t., 2 h (67%); d) Mg, MeOH, r. t., 1.5 h (85%).



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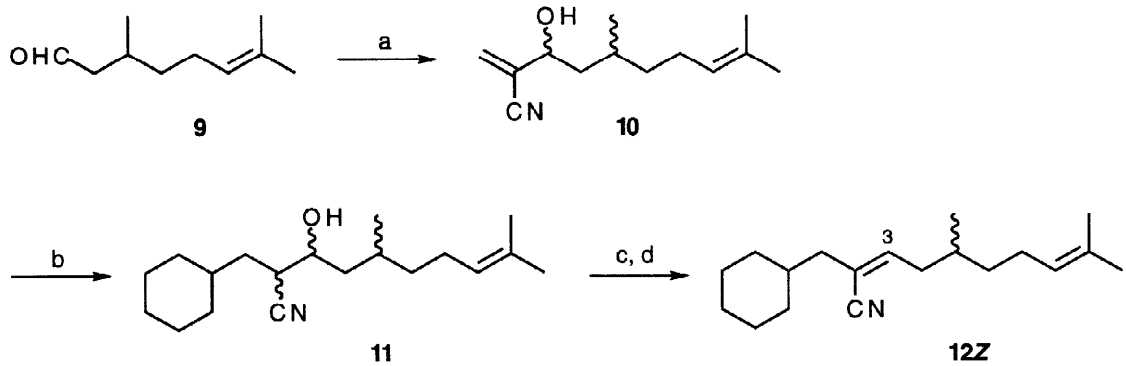
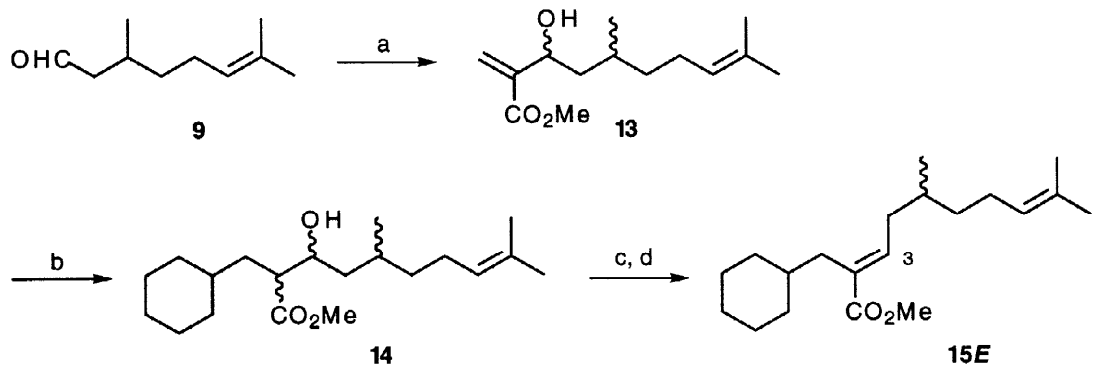
We then examined the configuration of the double bonds formed by elimination of the activated hydroxy groups of a model 3-hydroxy nitrile and 3-hydroxy ester. To this end we prepared the 3-hydroxy-2-methylene alkenenitriles **10** by subjecting citronellal **9** to a Baylis-Hillman reaction[13] with acrylonitrile, and 1,4-diazabicyclo[2.2.2]octane (DABCO) as

a catalyst, and added the cyclohexyl radical (from cyclohexyl bromide) to the compounds **10**. The so obtained hydroxy nitriles **11** were then mesylated and treated with 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) to give a 28/72 *E*/*Z* mixture[14] of the α,β-unsaturated nitriles **12** separable by column chromatography. When the hydroxy nitriles **11** were acetylated, the selectivity of the elimination reaction was even better (*E*/*Z* = 15/85)[14] (Scheme 3).



Scheme 3. a) acrylonitrile, DABCO, 21 days (90%); b) cyclohexyl bromide, *n*-Bu_3SnH, Et_2O, hv (300 W tungsten lamp), 9 h (53%); c) Ac_2O, 4-(dimethylamino)pyridine (DMAP), toluene, r. t., 0.5 h; d) DBU, toluene, reflux, 56 h (89%; **12Z/12E** = 85/15).

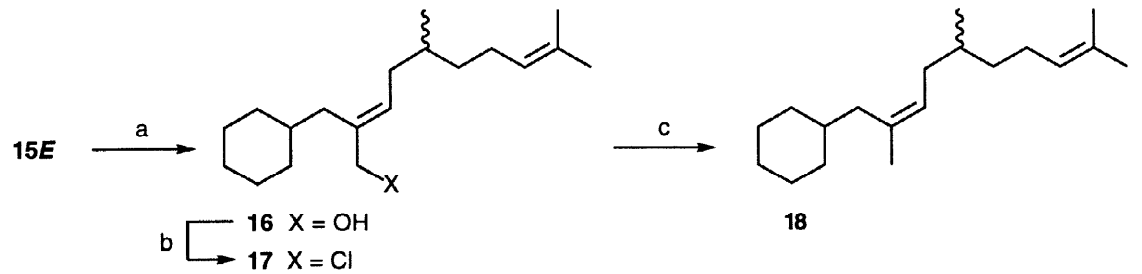
On the other hand, we prepared in the same way the hydroxy esters **14** from the methyl 3-hydroxy-2-methylene alkenoates **13** obtained by a Baylis-Hillman reaction on citronellal and methyl acrylate in the presence of quinuclidin-3-ol.[15] Mesylation followed by treatment with DBU led this time to a separable 93/7 *E*/*Z* mixture[16] of the α,β-unsaturated esters **15**, a result that could not be improved when acetylated **14** was used (Scheme 4). This selectivity can be attributed primarily to steric factors – a methoxycarbonyl is larger than a methylene which is larger than a cyano group – although other factors may also contribute.[17]



Scheme 4. a) methyl acrylate, quinuclidin-3-ol, 35 days (88%); b) cyclohexyl bromide, *n*-Bu_3SnH, Et_2O, hv (300 W tungsten lamp), 24 h (38%); c) MsCl, NEt_3, CH_2Cl_2, 0 °C, 0.25 h; d) DBU, toluene, reflux, 9 h (94%, **15E/15Z** = 93/7)

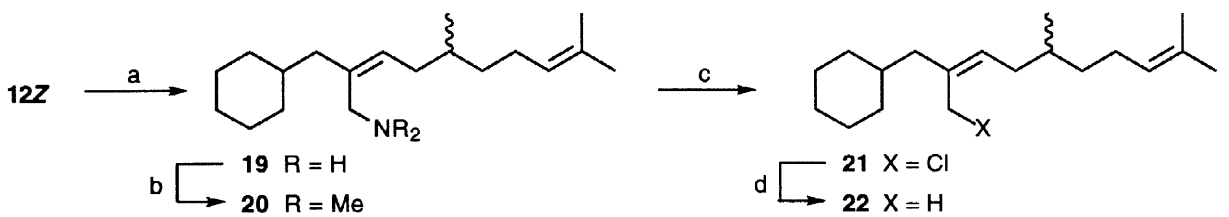
This unexpected result opened the way to tricyclopolyprenols with either *E* or *Z* side chains, provided that the reduction of the ancillary cyano and methoxycarbonyl groups into methyls could be performed with satisfactory yields and without loss of double bond configuration. The ester **15*E*** could easily be transformed first into the alcohol **16** (di-isobutylaluminium hydride [DIBAH], toluene) and then into the chloride **17** (CCl_4, PPh_3)

which was reduced into the diene **18** with lithium triethylborohydride[18] (Scheme 5). The reduction of the α,β-unsaturated nitrile **12Z** however, was somewhat more delicate. An attempt to transform the nitrile into an aldehyde (DIBAH, acidic hydrolysis) occured, not quite unexpectedly, with partial loss of the double bond configuration. This outcome led us to



Scheme 5. a) DIBAH, toluene, –78 °C, 0.5 h (88%); b) CCl_4, PPh_3, reflux, 8 days; c) $LiBHEt_3$, THF, r. t., 6 h (steps b + c = 75%).

reduce the nitrile **12Z** into the amine **19** with aluminium hydride,[19] having in mind to convert the amino group into a leaving group. One way to achieve this transformation, which is more difficult and hence less common than that of an alcohol, is to activate the nitrogen with two arylsulfonyl moieties. But apart from being sometimes difficult to prepare, disulfonimides also require rather vigorous conditions for their nucleophilic displacement with an halide[20] or an hydride.[21] Therefore we turned to a von Braun-type reaction. The preliminary transformation of the primary amine **19** into the tertiary amine **20** could be performed under mild conditions by treatment first with formaldehyde and methanol and



Scheme 6. a) AlH_3, Et_2O, 0 °C, 1.25 h (63%); b) $(CH_2O)_n$, MeOH, 65 °C, 2 h; then $NaBH_3CN$, r. t., 0.3 h (79%); c) $ClCO_2Et$, K_2CO_3, toluene, 0 °C, 4 days; d) $LiBHEt_3$, THF, r. t., 1 h (c + d = 71%).

then with sodium cyanoborohydride.[22] Reaction of the amine **20** with ethyl chloroformate[23] gave the corresponding chloride **21** which when exposed to lithium triethylborohydride led to the diene **22** (Scheme 6). It should be pointed out that when this reaction sequence was carried out without purification of the intermediates, the overall yield from the nitrile **12Z** was 58%.

With these reactions at hand the synthesis of the tricyclopolyprenols **1** and **2** was within reach. It is reported in the following paper.

EXPERIMENTAL SECTION

General Techniques. The melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. IR spectra were obtained from carbon tetrachloride solutions on a Perkin-Elmer 881 or a Bruker Spectrafile FT-IR spectrophotometer. NMR spectra were recorded, unless otherwise stated, in chloroform-d

solutions on a Bruker WP-200SY or a Bruker AM-400 instrument. Mass spectra were recorded on a LKB 9000S spectrometer. High-resolution mass spectra (HRMS) were recorded on a Varian Mat 311 spectrometer at the Centre Régional de Mesures Physiques de l'Ouest, Rennes. Elemental analyses were performed at the Institut Charles Sadron and at the Institut de Chimie, both at Strasbourg. All reactions were run under a positive pressure of dry argon. All organic extracts were dried over magnesium sulfate and the solvents were removed with a Büchi rotary evaporator. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium / benzophenone ketyl, *N,N*-dimethylformamide (DMF) from phosphorus pentaoxide, dichloromethane, dimethyl sulfoxide (DMSO), pyridine and toluene from calcium hydride. Distilled diethyl ether (without 2,6-di-*t*-butyl-4-methylphenol) was used for the extraction and chromatography of the compounds used in the radical reactions. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous compounds. All reactions were monitored by thin-layer chromatography on Kieselgel 60 F_{254} silica gel plates (Merck, 0.25 mm thickness) using ethanolic *p*-anisaldehyde (5 ml *p*-anisaldehyde, 100 ml acetic acid, and 50 ml sulfuric acid in 850 ml ethanol) or 10% ethanolic phosphomolybdic acid as spray reagent. Column chromatography (flash) was performed on Kieselgel 60 silica gel (Merck, 40-63 μm particle size). Gas phase chromatographic analyses (GC) were conducted on a Carlo Erba 4130 chromatograph equiped with a FID detector and a fused silica capillary column (CP Sil 5 CB, 10 m x 0.33 mm or J & W - DB 5, 15 m x 0.32 mm).

Isocopal-12-en-15-yl iodide 4. A solution of triphenylphosphine (2.70 g, 10.3 mmol) in HMPA (3.6 ml, 20.6 mmol) was added to a stirred solution of iodine (2.89 g, 11.4 mmol) in ether (29 ml) at 0 °C. After 30 min isocopal-12-en-15-ol **3** (1.0 g, 3.4 mmol) in ether (30 ml) was added to the yellow suspension and the medium was allowed to warm to room temperature and was stirred for 6 h. It was then diluted with ether and an ice-cold saturated $NaHCO_3$ solution was added. The organic phase was washed with aqueous Na_2SO_3, 10% H_2SO_4, water, saturated $NaHCO_3$ and again with water until neutral. It was then dried, concentrated, and chromatographed on a silica gel column (eluent: hexane). Recrystallisation (ether-methanol) afforded the iodide **4** (0.96 g, 2.4 mmol, 70%) as white crystals. mp 92-94 °C. IR: 2932, 1446, 1391 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.76, 0.81 (2 s, 2 x 3 H), 0.86 (s, 6 H), 1.91 (d, *J* = 1.2 Hz, 3 H), 2.50 (m, 1 H), 2.94 (dd, *J* = 10.4, 7.4 Hz, 1 H), 3.51 (dd, *J* = 10.4, 1.6 Hz, 1 H), 5.41 (br s, 1 H). ^{13}C-NMR (50 MHz) δ: 2.8, 14.0, 15.6, 18.5, 18.7, 21.6, 21.7, 22.6, 33.1, 33.4, 37.4, 38.7, 39.8, 40.6, 41.9, 55.0, 56.0, 59.1, 123.6, 132.7. MS m/z: 400 (M^+, 1%), 385 (2), 273 (100), 217 (10), 191 (20), 137 (17).

Isocopal-12-ene-15-propionitrile 6. ***From the iodide 4.*** Acrylonitrile (0.75 ml, 10.0 mmol) and tributyltin hydride (70 μl, 0.5 mmol) were added to a stirred solution of iodide **4** (40 mg, 0.10 mmol) in ether (3 ml) and were irradiated with a 100 W tungsten lamp for 2 h. Concentration and column chromatography (hexane/ether 30/1) afforded the nitrile **6** (26 mg, 0.079 mmol, 79%). mp 118.5-119 °C (colourless needles from ether-methanol). IR: 2934, 2249, 1445, 1388 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.73, 0.82, 0.86, 0.87 (4 s, 4 x 3 H), 1.66 (br s, 3 H), 1.75-2.05 (m, 4 H), 2.34 (t, *J* = 6.8 Hz, 2 H), 5.39 (br s, 1 H). ^{13}C-NMR (100 MHz) δ: 14.3, 15.5, 17.6, 18.5, 18.7, 21.7, 21.9, 22.8, 26.4, 27.6, 33.1, 33.4, 36.8, 37.2, 39.8, 40.8, 41.9, 54.9, 55.0, 56.3, 119.7, 122.8, 133.9. MS m/z: 327.3 (M^+, 21%), 312.3 (4), 192.2 (100), 191.2 (32), 177.2 (82), 122.2 (24). ***From the aldehyde 7.*** 0.5 M Dimsyl sodium in DMSO (1.8 ml) was added to diethyl cyanomethylphosphonate (161 μl, 1.0 mmol) in DMSO (1 ml) and the mixture was stirred for 1 h at room temperature. This solution (1.1 ml, 0.33 mmol) was added to a solution of the aldehyde **7** (70 mg, 0.23 mmol) in THF (1.0 ml) and stirred for 2 h at room temperature. The reaction mixture was diluted with ether, washed with aqueous NH_4Cl and brine, dried, and concentrated. Two column chromatographies (first with dichloromethane, then with hexane/ether 95/5) afforded the expected *Z* and *E* α,β-unsaturated nitriles (50 mg, 0.15 mmol, 67%). IR: 2930, 2220, 1630, 1440, 1380 cm^{-1}. ^{1}H-NMR (200 MHz) δ: (*Z* isomer) 0.78, 0.82, 0.86, 0.89 (4 s, 4 x 3 H), 1.62 (br s, 3 H), 1.82-2.05 (m, 4 H), 2.37-2.65 (m, 2 H), 5.27 (dt, *J* = 10.9, 1.7 Hz, 1 H), 5.45 (br s, 1 H), 6.50-6.62 (ddd, *J* = 10.9, 7.8, 6.5 Hz, 1 H); (*E* isomer) 0.75, 0.82, 0.86, 0.88 (4 s, 4 x 3 H), 1.59 (br s, 3 H), 1.80-2.02 (m, 4 H), 2.18 (dt, *J* = 16.1, 7.8 Hz, 1 H), 2.42 (dm, *J* = 16.1 Hz, 1 H), 5.33 (dt, *J* = 16.4, 1.7 Hz, 1 H), 5.44 (br s, 1 H), 6.73-6.88 (ddd, *J* = 16.4, 7.8, 6.2 Hz, 1 H). Magnesium turnings (90 mg, 3.7 mmol) were added to a stirred solution of the α,β-unsaturated nitriles (28 mg, 0.086 mmol) in dry methanol (2 ml). After 1.5 h at room temperature, the supernatant was separated from the magnesium in excess which was washed with additionnal methanol. Ice-cold water was then added to the combined methanol phases followed by enough 10% HCl to reach neutrality. After extraction with ether, the

combined organic phases were washed with saturated $NaHCO_3$ and brine, dried, concentrated and chromatographed on a silica gel column (hexane/ether 95/5) to give the nitrile **6** (24 mg, 0.073 mmol, 85%) which was identical (IR, ^{1}H-NMR, GC) to the nitrile obtained above from the iodide **4**.

Methyl isocopal-12-ene-15-propionate 8. Methyl acrylate (300 µl, 3.3 mmol) and tributyltin hydride (110 µl, 0.4 mmol) were added to a stirred solution of the iodide **4** (100 mg, 0.25 mmol) in ether (7 ml) and the mixture was irradiated with a 300 W tungsten lamp for 4.5 h. Concentration and column chromatography (hexane/ether 10/1) afforded the ester **8** (36 mg, 0.10 mmol, 40%). IR: 2932, 1739, 1459, 1437, 1385, 1207, 1172 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.71, 0.81, 0.86, 0.87 (4 s, 4 x 3 H), 1.68 (br s, 3 H), 1.80-2.00 (m, 4 H), 2.32 (m, 2 H), 3.67 (s, 3 H), 5.36 (br s, 1 H). ^{13}C-NMR (100 MHz) δ: 14.3, 15.5, 18.5, 18.8, 21.7, 21.9, 22.8, 26.6, 27.3, 33.1, 33.4, 34.5, 36.8, 37.2, 39.9, 40.7, 41.9, 51.4, 55.1, 55.3, 56.3, 122.2, 134.8, 174.1. Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found C, 80.1; H, 11.3.

5,9-Dimethyl-3-hydroxy-2-methylenedec-8-enenitriles 10. Citronellal **9** (1.8 ml, 10.0 mmol), acrylonitrile (1.0 ml, 15.0 mmol), and DABCO (120 mg, 1.0 mmol) were stirred at room temperature for 21 days. The acrylonitrile in excess was removed in vacuo and the residual oil was diluted with ether, washed with 10% HCl and with water, and dried. Concentration and column chromatography (hexane/ether 8/2) afforded the α,β-unsaturated nitriles **10** (1.87 g, 9.0 mmol, 90%) as a yellow oil. IR: 3614, 3480, 2920, 2226, 1620, 1450, 1378, 944 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.95 (br d, J = 6.3 Hz, 3 H), 1.60 (br s, 3 H), 1.68 (br s, 3 H), 1.99 (m, 2 H), 4.31 (m, 1 H), 5.08 (tq, J = 7.1, 1.4 Hz, 1 H), 5.96 (s, 1 H), 5.97 and 6.00 (2 d, J = 1.1 Hz, 1 H). Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found C, 75.1; H, 10.4; N, 6.7.

Methyl 5,9-dimethyl-3-hydroxy-2-methylenedec-8-enoates 13. Citronellal **9** (2.0 ml, 11.0 mmol), methyl acrylate (1.5 ml, 16.7 mmol), and quinuclidin-3-ol (140 mg, 1.1 mmol) were stirred at room temperature for 35 days. The methyl acrylate in excess was removed in vacuo and the residual oil was diluted with ether and washed with 10% HCl and with water, and dried. Concentration and column chromatography (hexane/ether 8/2) afforded the α,β-unsaturated esters **13** (2.34 g, 9.7 mmol, 88%) as a colourless oil. IR: 3620, 3552, 2920, 1718, 1630, 1440, 1334, 1300, 1196, 1152, 956 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.93, 0.95 (2 d, J = 6.3 Hz, 3 H), 1.60 (br s, 3 H), 1.67 (br s, 3 H), 1.97 (m, 2 H), 2.45, 2.56 (2 br d, J = 6.9 Hz, 1 H), 3.78 (s, 3 H), 4.48 (m, 1 H), 5.09 (t quint., J = 7.1, 1.4 Hz, 1 H), 5.78, 5.81 (2 t, J = 1.1 Hz, 1 H), 6.20 (d, J = 1.0 Hz, 1H). Anal. Calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found C, 69.7; H, 9.9.

1-Cyclohexyl-5,9-dimethyl-3-hydroxydec-8-ene-2-carbonitriles 11. A stirred solution of the α,β-unsaturated nitriles **10** (830 mg, 4.0 mmol) and of cyclohexyl bromide (5.0 ml, 40.6 mmol) in ether (30 ml) was irradiated with a 300 W tungsten lamp for 1 h as a solution of tributyltin hydride (4.7 ml, 17.5 mmol) in ether (10 ml) was added. After the end of the addition, the irradiation was continued for 8 h. Then aqueous KF (15 ml) was added to the reaction mixture which was stirred for 12 h. The solid tin compounds were filtered off and the filtrate was concentrated, dissolved in ether and dried. Concentration and column chromatography (hexane/ether 8/2) afforded unreacted **10** (304 mg, 1.5 mmol, 38%), and the nitriles **11** (615 mg, 2.1 mmol, 53%) as a colourless oil. IR: 3622, 3474, 2928, 2240, 1450, 1378 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.90-0.99 (m, 3 H), 1.61 (br s, 3 H), 1.68 (br s, 3 H), 1.99 (m, 2 H), 2.60-2.85 (m, 1 H), 3.65-3.87 (m, 1 H), 5.08 (br t, J = 7 Hz, 1 H). Anal. Calcd for $C_{19}H_{33}NO$: C, 78.29; H, 11.41; N, 4.81. Found C, 77.7; H, 11.5; N, 4.7.

Methyl 1-cyclohexyl-5,9-dimethyl-3-hydroxydec-8-ene-2-carboxylates 14. The same procedure as for **11** was used to treat a solution of the α,β-unsaturated esters **13** (854 mg, 3.55 mmol) and of cyclohexyl bromide (4.4 ml, 35.5 mmol) in ether (10 ml) with a solution of tributyltin hydride (3.0 ml, 11.2 mmol) in ether (10 ml). Total irradiation time: 24 h. Column chromatography (hexane/ether 9/1) gave unreacted **13** (383 mg, 1.6 mmol, 45%) and the esters **14** (441 mg, 1.36 mmol, 38%) as a colourless oil. IR: 3620, 3564, 2928, 1716, 1448, 1192, 1164 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.91 (t, J_{app} = 6.6 Hz, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.96 (m, 2 H), 2.22-2.42 (m, 1 H), 2.49-2.60 (m, 1 H), 3.71 (s, 3 H), 3.81-3.93 (m, 1 H), 5.09 (br t, J = 7 Hz, 1 H). Anal. Calcd for $C_{20}H_{36}O_3$: C, 74.02; H, 11.18. Found C, 73.7; H, 11.2.

1-Cyclohexyl-5,9-dimethyldeca-2,8-diene-2-carbonitriles 12. ***Via mesylates.*** Triethylamine (0.35 ml, 2.5 mmol) and methanesulfonyl chloride (0.19 ml, 2.4 mmol) were added to a stirred solution of the hydroxy nitriles **11** (291 mg, 1.0 mmol) in dichloromethane (10 ml) at 0 °C. After 15 min, the reaction medium

was washed successively with 10% HCl, saturated $NaHCO_3$ and brine, and dried. After concentration, the crude mesylates were dissolved in toluene (80 ml) and refluxed as DBU (4.0 ml, 27.6 mmol) was added. After refluxing for an extra hour, the reaction medium was cooled to room temperature, diluted with ether, washed with 10% HCl and with brine until neutral, dried and concentrated to give a 72/28 mixture of the α,β-unsaturated nitriles **12Z/12*E***.[14] Column chromatography (hexane/ether 8/2) gave a mixture of the nitriles **12** (255 mg, 0.93 mmole, 93%). Another column chromatography (hexane/ether 250/1) allowed the separation of pure **12*Z*** (183 mg, 0.67 mmol, 67%) and pure **12*E*** (71 mg, 0.26 mmol, 26%). ***Via acetates.*** Acetic anhydride (100 µl, 1.1 mmol) and DMAP (13 mg, 0.11 mmol) were added to a stirred solution of the hydroxy nitriles **11** (103 mg, 0.35 mmol) in toluene (5 ml). After 30 min at room temperature, the medium was diluted with ether (50 ml), washed with 0.01 M HCl and with brine, dried, and concentrated. DBU (300 µl, 2.0 mmol) was then added to the so-obtained crude acetates in toluene (5 ml) and the solution was refluxed for 56 h. The reaction medium was cooled to room temperature, diluted with ether, washed with 10% HCl and with brine, dried, and concentrated to give a 85/15 mixture of the α,β-unsaturated nitriles **12Z/12*E***.[14] Column chromatography (hexane/ether 9/1) afforded a mixture of the nitriles **12** (86 mg, 0.31 mmol, 89%) which could be separated as above by another column chromatography. Nitrile **12*Z*** (Colourless oil; more mobile isomer). IR: 2928, 2216, 1638, 1448, 1378 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.92 (d, J = 6.7 Hz, 3 H), 1.60 (s, 3 H) 1.68 (br s, 3 H), 1.98 (m, 2 H), 2.08 (d, J = 7.0 Hz, 2 H), 2.14-2.44 (m, 2 H), 5.07 (tt, J = 7.1, 1.3 Hz, 1 H), 6.09 (t, J = 7.7 Hz, 1 H). Anal. Calcd for $C_{19}H_{31}N$: C, 83.45; H, 11.43; N, 5.12. Found C, 83.4; H, 11.5; N, 5.0. Nitrile **12*E*** (Colourless oil; less mobile isomer). IR: 2928, 2214, 1632, 1448, 1378 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.90 (d, J = 6.6 Hz, 3 H), 1.60 (s, 3 H), 1.68 (br s, 3 H), 1.90-2.40 (m, 6 H; includes a doublet [J = 7.1 Hz] at 2.07), 5.07 (br t, J = 7.1 Hz, 1 H), 6.39 (t, J = 7.5 Hz, 1 H).

Methyl 1-cyclohexyl-5,9-dimethyldeca-2,8-diene-2-carboxylates 15. ***Via mesylates.*** Same procedure as above for **12**. The mesylates were prepared by treating the hydroxy esters **14** (48 mg, 0.15 mmol) in dichloromethane (3 ml) with triethylamine (420 µl, 3.0 mmol) and with methanesulfonyl chloride (210 µl, 2.7 mmol). The crude mesylates and DBU (150 µl, 1.0 mmol) in toluene (10 ml) were then refluxed for 9 h to give a 93/7 mixture of the α,β-unsaturated esters **15*E*/15*Z***.[16] Column chromatography (hexane/ether 9/1) allowed the separation of pure **15*E*** (40 mg, 0.13 mmol, 87%) and pure **15*Z*** (3 mg, 0.01 mmol, 7%). ***Via acetates.*** Same procedure as above for **12**. The acetates were prepared by treating the hydroxy esters **14** (116 mg, 0.36 mmol) in toluene (5 ml) with acetic anhydride (95 µl, 1.0 mmol) and with DMAP (12 mg, 0.10 mmol). The crude acetates and DBU (300 µl, 2.0 mmol) in toluene (5 ml) were then refluxed for 6 days to give a 88/12 mixture of the α,β-unsaturated esters **15*E*/15*Z***.[16] Column chromatography (hexane/ether 8/2) afforded a mixture of the esters **15** (91 mg, 0.29 mmol, 81%) which could be separated as above by another column chromatography (hexane/ether 9/1). Ester **15*E*** (Colourless oil; less mobile isomer). IR: 2928, 1710, 1630, 1436, 1288, 1268, 1250, 1204 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.90 (d, J = 6.6 Hz, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.90-2.30 (m, 6 H; includes a doublet [J = 7.0 Hz] at 2.19), 3.72 (s, 3 H), 5.08 (br t, J = 7.1 Hz, 1 H), 6.81 (t, J = 7.4 Hz, 1 H). Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found C, 78.1; H, 11.3. Ester **15*Z***. ^{1}H-NMR (200 MHz) δ: 5.79 (t, J = 7.5 Hz, 1 H).

(*E*)-[1-Cyclohexyl-5,9-dimethyldeca-2,8-diene]-2-methanol 16. 1 M DIBAH in toluene (700 µl, 0.70 mmol) was added to a cold (–78 °C) solution of the ester **15*E*** (102 mg, 0.33 mmol) in toluene (15 ml). The mixture was stirred for 30 min at –78 °C, hydrolysed with aqueous NH_4Cl (5 ml) and a few drops of 10% HCl, and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated. Column chromatography (hexane/ether 8/2) gave the alcohol **16** (80 mg, 0.29 mmol, 88%) as a colourless oil. IR: 3620, 2926, 1448, 1376 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 0.88 (d, J = 6.5 Hz, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.80-2.15 (m, 6 H; includes a doublet [J = 7.4 Hz] at 1.98), 4.02 (br s, 2 H), 5.09 (br t, J = 6.3 Hz, 1 H), 5.49 (t, J = 7.1 Hz, 1 H). Anal. Calcd. for $C_{19}H_{34}O$: C, 81.95; H, 12.31. Found C, 81.6; H, 12.4.

(*Z*)-1-Cyclohexyl-2,5,9-trimethyldeca-2,8-diene 18. A solution of the alcohol **16** (46 mg, 0.16 mmol) and of triphenylphosphine (105 mg, 0.40 mmol) in carbon tetrachloride (4 ml) was refluxed for 8 days. It was then diluted with dichloromethane, washed with water and dried. Concentration afforded 100 mg of the chloride **17** containing 14% of unreacted alcohol **16** (determined by ^{1}H-NMR). ^{1}H-NMR (200 MHz) δ: 0.87 (d, J = 6.5 Hz, 3 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 1.78-2.14 (m, 6 H; includes a doublet [J = 7.2 Hz] at 2.07), 4.04 (s, 2 H), 5.08 (tt, J = 7.1, 1.3 Hz, 1 H), 5.61 (t, J = 7.2 Hz, 1 H). 1 M Lithium triethylborohydride

in THF (6.0 ml, 6.0 mmol) was added over 4 h to a stirred solution of the crude chloride **17** in THF (10 ml). After the end of the addition, the solution was stirred for another 2 h, diluted with ether, and quenched with water. The aqueous phase was extracted with ether, and the combined organic phases were dried and concentrated. Column chromatography (hexane/ether 8/2) gave unreacted alcohol **16** (6 mg, 0.02 mmol, 13%) and the diene **18** (32 mg, 0.12 mmol, 75% yield from **16**) as a colourless oil. IR: 2926, 1446, 1376 cm^{-1}. ^1H-NMR (200MHz) δ: 0.86 (d, J = 6.5 Hz, 3 H), 1.60 (s, 3 H), 1.67 (d, J = 1.3 Hz, 3 H), 1.68 (s, 3 H), 1.75-2.08 (m, 4 H), 1.89 (d, J = 7.3 Hz, 2 H), 5.10 and 5.18 (tt, J = 7.1, 1.3 Hz, and t, J = 7.0 Hz, 2 H). ^{13}C-NMR (100 MHz) δ: 17.6, 19.6, 24.1, 25.7, 26.5, 26.7, 33.4, 33.5, 35.2, 36.3, 36.9, 39.7, 125.0, 125.1, 131.0, 134.4. MS m/z: 262.3 (M^+, 36%), 219.2 (3), 206.2 (5), 179.2 (6), 166.2 (18), 149.1 (11), 137.2 (16), 123.2 (35), 109.2 (100).

(*Z*)-[1-Cyclohexyl-5,9-dimethyldeca-2,8-diene]-2-methanamine 19. 0.4 M Aluminium hydride in ether was prepared by adding $AlCl_3$ (178 mg, 1.34 mmol) to ice-cold 1 M $LiAlH_4$ in ether (4 ml). The mixture was stirred at 0 °C for 2 h. Then the solid LiCl was allowed to settle and the supernatant 0.4 M aluminium hydride solution (3.6 ml, 1.4 mmol) was added to a solution of the nitrile **12*Z*** (78 mg, 0.28 mmol) in ether (5 ml) at 0 °C. The reaction mixture was stirred for 1.25 h, diluted with ether and cautiously hydrolysed with water. The organic phase was washed with aqueous sodium potassium tartrate, 10% HCl, saturated $NaHCO_3$ and brine, and dried. Concentration and column chromatography (eluent: hexane/ether 5/5, then chloroform/methanol 5/5) afforded the amine **19** (50 mg, 0.18 mmol, 63%). IR: 3370, 2926, 1616, 1448, 1376, 1116, 828 cm^{-1}. ^1H-NMR (200 MHz) δ: 0.86 (d, J = 6.5 Hz, 3 H), 1.59 (br s, 3 H), 1.67 (br s, 3 H), 1.80-2.12 (m, 6 H; includes a doublet [J = 7.4 Hz] at 1.96), 3.21 (br s, 2 H), 5.08 and 5.16 (br t and t, J = 7.1 and 7.4 Hz, 2 H).

(*Z*)-[1-Cyclohexyl-5,9,N,N-tetramethyldeca-2,8-diene]-2-methanamine 20. Paraformaldehyde (30 mg) was added to a solution of the amine **19** (38 mg, 0.14 mmol) in methanol (5 ml). After 2 h at 65 °C, the reaction medium was cooled to room temperature and was treated with sodium cyanoborohydride (31 mg, 0.49 mmol) for 20 min. Water was then added to the reaction and the methanol was removed in vacuo. After extraction with ether, the organic phases were washed with brine, dried, concentrated, and chromatographed on a silica gel column (hexane/ether 8/2) to afford the dimethylamine **20** (33 mg, 0.11 mmol, 79%). IR: 2928, 2815, 2766, 1449, 1024 cm^{-1}. ^1H-NMR (200 MHz) δ: 0.86 (d, J = 6.5 Hz, 3 H), 1.60 (s, 3 H) 1.68 (s, 3 H), 1.82-2.18 (m, 6 H; includes a doublet [J = 6.9 Hz] at 1.94), 2.16 (s, 6 H), 2.78 (s, 2 H), 5.09 (br t, J = 7.1 Hz, 1 H), 5.28 (t, J = 7.3 Hz, 1 H). Anal. Calcd for $C_{21}H_{39}N$: C, 82.55; H, 12.87; N, 4.58. Found C, 82.1; H, 12.9; N, 4.4.

(*E*)-1-Cyclohexyl-2,5,9-dimethyldeca-2,8-diene 22. Ethyl chloroformate (240 µl, 2.5 mmol) and potassium carbonate (25 mg, 0.18 mmol) were added to a solution of the dimethylamine **20** (23 mg, 0.075 mmol) in toluene (3 ml) at 0 °C. The mixture was then allowed to react at room temperature. After 2 days, extra ethyl chloroformate (100 µl, 1.0 mmol) and potassium carbonate (10 mg, 0.072 mmol) were added. After another 2 days, the reaction was diluted with ether, washed with water, dried, and concentrated to give the crude chloride **21** (36 mg). ^1H-NMR (200 MHz) δ: 0.88 (d, J = 6.5 Hz, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.86-2.20 (m, 6 H; includes a doublet [J = 7.1 Hz] at 2.03), 4.05 (s, 2 H), 5.09 (br t, J = 7.1 Hz, 1 H), 5.36 (t, J = 7.5 Hz, 1 H). 1 M Lithium triethylborohydride in THF (2.0 ml, 2.0 mmol) was added at room temperature to a solution of the crude chloride **21** in THF (10 ml). After 1 h, the mixture was diluted with ether and hydrolysed with water. The aqueous phase was extracted with ether and the combined organic phases were washed with brine, dried, concentrated and chromatographed on a silica gel column (hexane) to afford the diene **22** (14 mg, 0.053 mmol, 71% yield from the dimethylamine **20**; 35% from nitrile **12*Z***) as a colourless oil. It should be noted that when the transformation of the nitrile **12*Z*** (25 mg, 0.091 mmol) into the diene **22** (14 mg, 0.053 mmol) was carried out without purification of the intermediate compounds, the overall yield was 58%. IR: 2927, 1447, 1376 cm^{-1}. ^1H-NMR (200 MHz) δ: 0.86 (d, J = 6.5 Hz, 3 H), 1.55 (s, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.72-2.08 (m, 6 H; includes a doublet [J = 7.0 Hz] at 1.85), 5.09 (br t, J = 7.2 Hz, 2 H). ^{13}C-NMR (100 MHz) δ: 16.1, 17.6, 19.6, 25.7, 26.4, 26.7, 33.3, 33.4, 35.2, 35.6, 36.8, 48.3, 124.6, 125.0, 130.9, 134.1. MS m/z: 262.3 (M^+, 35%), 219.2 (3), 206.2 (6), 179.2 (8), 166.2 (18), 149.1 (31), 137.2 (18), 123.2 (38), 109.2 (100), 95.2 (54). Anal. Calcd for $C_{19}H_{34}$: C, 86.94; H, 13.06. Found C, 86.3; H, 13.1.

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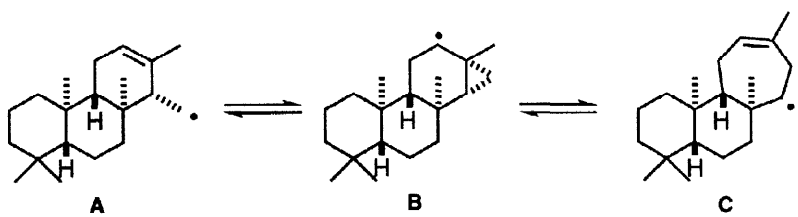
REFERENCES AND NOTES

1. Aquino-Neto, F. R.; Restle, A.; Connan, J.; Albrecht, P.; Ourisson, G. *Tetrahedron Lett.* **1982**, *23*, 2027-2030. Ekweozor, C. M.; Strausz, O. P. *Ibid.* **1982**, *23*, 2711-2714. Moldowan, J. M.; Seifert, W. K.; Gallegos, E. J. *Geochim. Cosmochim. Acta* **1983**, *47*, 1531-1534. Heissler, D.; Ocampo, R.; Albrecht, P.; Riehl, J. J.; Ourisson, G. *J. Chem. Soc., Chem. Commun.* **1984**, 496-498. González Sierra, M.; Cravero, R. M.; Laborde, M. A.; Rúveda, E. A. *Ibid.* **1984**, 417-418; *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1227-1231.
2. Krajewski-Bertrand, M. A.; Hayer, M.; Wolff, G.; Milon, A.; Albrecht, A. M.; Heissler, D.; Nakatani, Y; Ourisson, G. *Tetrahedron* **1990**, *46*, 3143-3154; Krajewski-Bertrand, M.-A.; Milon, A.; Nakatani, Y.; Ourisson, G. *Biochim. Biophys. Acta* **1992**, *1105*, 213-220.
3. Ourisson, G.; Albrecht, P.; Rohmer, M. *Trends Biochem. Sci.* **1982**, *7*, 236-239. Ourisson, G.; Albrecht, P. *Acc. Chem. Res.* **1992**, *25*, 398-402. Ourisson, G.; Nakatani, Y. *Chemistry & Biology* **1994**, *1*, 11-23.
4. See following paper. Preliminary communications: a) Heissler, D.; Jenn, T.; Nagano, H. *Tetrahedron Lett.* **1991**, *32*, 7587-7590. b) Jenn, T.; Heissler, D. *Ibid.* **1992**, *33*, 7227-7228.
5. Corey, E. J.; Burk, R. M. *Tetrahedron Lett.* **1987**, *28*, 6413-6416.
6. Heissler, D.; Ladenburger, C. *Tetrahedron* **1988**, *44*, 2513-2521.
7. Ladenburger, C; Heissler, D. *J. Chem. Research (S)* **1991**, 330.
8 Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986, pp. 36-140. Curran, D. P. *Synthesis* **1988**, 417-439; Radical addition reactions. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon Press: Oxford, vol. 4, 1991; pp. 715-777.
9. We dreaded that the homoallylic radical **A** could rearrange into the radical **C** before adding to the activated double bond. However, the results obtained by others with the radical deriving from 3-(bromomethyl)-cyclohex-1-ene led us to be reasonably optimistic: Friederich, E. C.; Holmstead, R. L. *J. Org. Chem.* **1972**, *37*, 2550-2554.



A **B** **C**

10. Haynes, R. K.; Holden, M. *Aust. J. Chem.* **1982**, *35*, 517-524. Wiley, G. A.; Hershkowitz, R.L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964-965.
11. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829-5831. Kosugi, M.; Kurino, K.; Takayama, K.; Migita, T. *J. Organometal. Chem.* **1973**, *56*, C11-C13. Grignon, J.; Pereyre, M. *Ibid.* **1973**, *61*, C33-C35.
12. Keck, G. E.; Tafesh, A. M. *J. Org. Chem.* **1989**, *54*, 5845-5846. Keck, G. E.; Byers, J. H. *Ibid.* **1985**, *50*, 5442-5444.

13. a) Baylis, A. B.; Hillman, M. E. D. *German Patent* **1972**, 2155113; *Chem. Abstr.* **1972**, *77*, 34174q. b) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795-796. c) Amri, H.; Villieras, J. *Tetrahedron Lett.* **1986**, *27*, 4307-4308. d) Basavaiah, D.; Gowriswari, V. V. L. *Synth. Commun.* **1987**, *17*, 587-591. e) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653-4670. f) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001-8062.
14. Determined by 200 MHz ^{1}H-NMR on the alkenic H-3 triplet which was at δ = 6.09 for the nitrile **12*Z*** and at δ = 6.39 for the nitrile **12*E***.
15. Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P. T. *Synth. Commun.* **1988**, *18*, 495-500.
16. Determined by 200 MHz ^{1}H-NMR on the alkenic H-3 triplet which was at δ = 6.81 for the ester **15*E*** and at δ = 5.79 for the ester **15*Z***.
17. In recent years, several papers have described the obtention of stereodefined trisubstituted alkenes from Baylis-Hillman adducts by nucleophilic substitution reactions; for a review see ref. 13f, pp. 8023-8035. See also: Piettre, S.; Heathcock, C. H. *Science* **1990**, *248*, 1532-1534. Heathcock, C. H.; Piettre, S.; Ruggeri, R. B.; Ragan, J. A.; Kath, J. C. *J. Org. Chem.* **1992**, *57*, 2554-2566.
18. Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1-12.
19. Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464-1472.
20. DeChristopher, P. J.; Adamek, J. P.; Lyon, G. D.; Galante, J. J.; Haffner, H. E.; Boggio, R. J.; Baumgarten, R. J. *J. Am Chem. Soc.* **1969**, *91*, 2384-2385. Andersen, N. H.; Uh, H. S. *Synth. Commun.* **1972**, *2*, 297-302.
21. Hutchins, R. O.; Kandasamy, D.; Dux, F.; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259-2267.
22. Kapnang, H.; Charles, G.; Sondengam, B. L.; Hentchoya Hémo, J. *Tetrahedron Lett.* **1977**, 3469-3472. Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673-1674. Sondengam, B. M.; Hentchoya Hémo, J.; Charles, G. *Tetrahedron Lett.* **1973**, 261-263.
23. Kometani, T.; Shiotani, S.; Mitsuhashi, K. *Chem. Pharm. Bull.* **1976**, *24*, 342-349. Mornet, R.; Gouin, L. *Synthesis*, **1977**, 786-787. Kapnang, H.; Charles, G. *Tetrahedron Lett.* **1983**, *24*, 3233-3236. For a review, see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1-7.