44. Vitamin-B_{12}-Catalyzed C,C-Bond Formation. Synthesis of a California Red Scale Pheromone[1])

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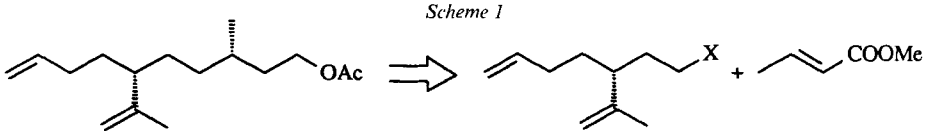
A mixture of (3*S*,6*R*)- and (3*R*,6*R*)-3-methyl-6-(1-methylethenyl)dec-9-enyl acetate (**1a** and **1b**, respectively) – **1a** being a pheromone of the California red scale – is synthesized in 14 steps from (+)-(*R*)-limonene (**4**). The key step is the reductive vitamin-B_{12}-catalyzed coupling of (*R*)-5-(2-iodoethyl)-6-methylhept-6-en-2-one ethylene acetal (**8**) and methyl crotonate (**3**).

Introduction. – The cobalamin-catalyzed, light-assisted electroreduction of organic halides in presence of *Michael*-type olefins is a procedure to form C,C bonds by conjugate radical addition [1]. To examine the scope and limitation of this reaction, the synthesis of the mixture of (3*S*,6*R*)- and (3*R*,6*R*)-3-methyl-6-(1-methylethenyl)dec-9-enyl acetate (**1a** and **1b**, resp.) – **1a** being a pheromone of the California red scale *Aonidiella aurantii* (MASKELL)[2]) – was studied. The strategy was based on the coupling of an enantiomerically pure (*R*)-configurated alkyl halide of type **2** with methyl crotonate (**3**; *Scheme 1*).

Scheme 1



1a **2** **3**

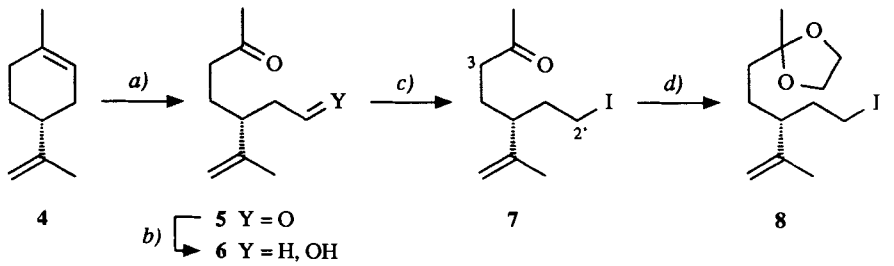
Results and Discussion. – The C_{10}-building block of type **2** was derived from (+)-(*R*)-limonene (**4**) (*Scheme 2*). Partial ozonolysis of **4** followed by reductive workup with Me_2S [3] gave the ketoaldehyde **5** whose CHO group was selectively reduced with Li[AlH-(*t*-BuO)$_3$] [4] to afford the hydroxyketone **6**. An attempt to transform **6** into the corresponding bromoketone using *N*-bromosuccinimide (NBS) and PPh_3 [5] failed; but with *N*,*N*′-dicyclohexyl-*N*-methylcarbodiimidium iodide (DCC·MeI) [6], it was smoothly converted to the iodoketone **7** which was then protected as its 1,3-dioxolane derivative **8**.

The C,C-coupling between **8** and crotonate **3** in presence of Cbl(I) (molar ratio 1:160:0.2) was achieved by potentiostatic electroreduction under irradiation of visible light. To that end, a solution of **8** and **3** in 0.2M $LiClO_4$/DMF was slowly added to the

[1]) Part of the Ph. D. Thesis of *L. A.*, University of Berne, 1992.

[2]) For previous syntheses of the pheromone *cf.* [2].

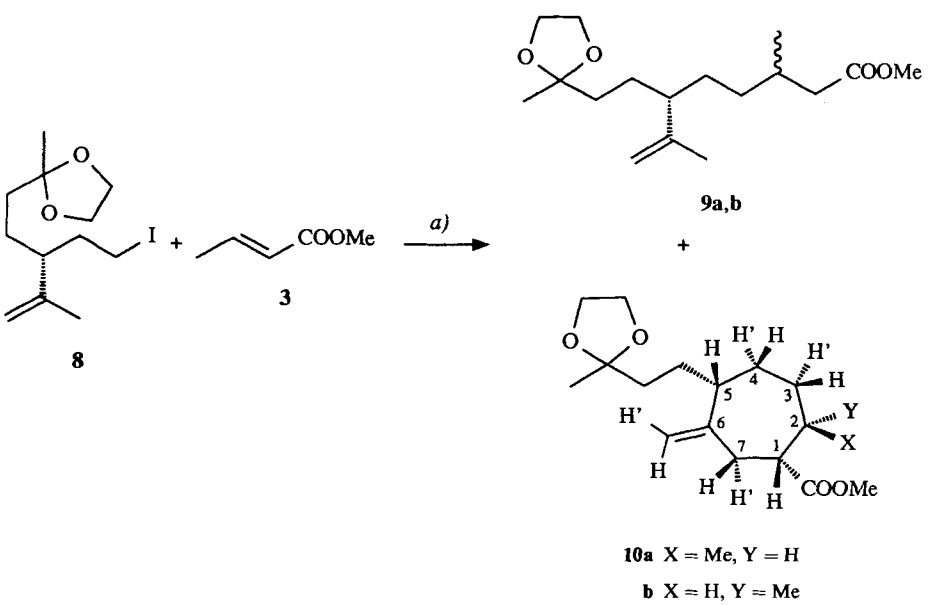
Scheme 2



a) 1) O_3, MeOH, −78°; 2) Me_2S, MeOH, 0°. *b*) Li[AlH(*t*-BuO)$_3$], THF, −70°, 4 h; 52% yield from **4**. *c*) DCC · MeI, THF, r.t., 22 h; 86% yield. *d*) $(CH_2OH)_2$, pyridinium toluene-4-sulfonate, C_6H_6, reflux, 5 h; 91% yield.

cathode compartment of a H-type cell at −1.2 V (*vs.* SCE), containing **3**, 0.2M $LiClO_4$/DMF, and Cbl(I) (obtained by previous electroreduction from hydroxo-Cbl(III)-hydrochloride), in such a rate that the color of the catholyte stayed brown-green (Cbl(I)). After the current had dropped to the back-ground value (consumption of *ca.* 1.4 F/1 equiv. of **8**), the mixture was worked up. Two constitutionally different compounds **9** and **10** in a ratio of *ca.* 2:1, each a *ca.* 1:1 mixture of 2 diastereoisomers **9a**, **b** and **10a**, **b** (GC) were obtained in 90% combined yield with respect to **8** (*Scheme 3*). The isomers **10a**, **10b**, and the mixture **9a**, **b** of acyclic diastereoisomers were separated by HPLC.

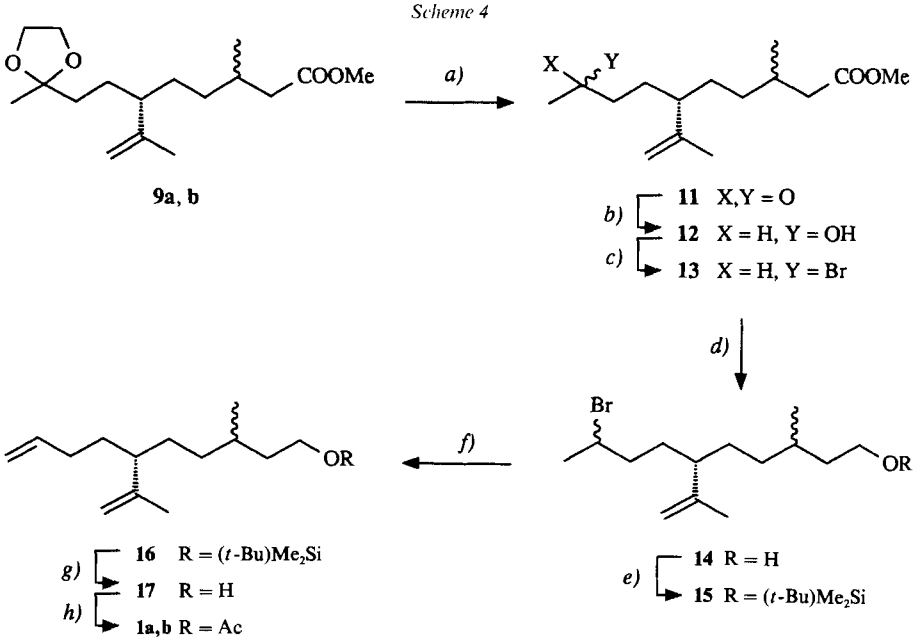
Scheme 3



a) Electrolysis: 0.23 equiv. of Cbl(III), 160 equiv. of **3**, 1 equiv. of **8**, 7 equiv. of AcOH, 0.2M $LiClO_4$/DMF, −1.2 V (*vs.* SCE), *hv*, 8°; 90% yield; **9**/**10** *ca.* 2:1, **a**/**b** *ca.* 1:1, HPLC separation.

The acetal **9a, b** was first converted *via* **11** and **12** to the corresponding bromide **13**, followed by the transformation of the ester group to the primary alcohol **14** by classical procedures (*Scheme 4*). The latter was protected as silyl ether (→ **15**). On this stage, the regioselective transformation of the *sec*-alkyl bromide to the terminal olefin (**15** → **16**) was achieved by the use of lithium 2,2,6,6-tetramethylpiperidinate in presence of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) and [12]crown-4 [7]. Deprotection (→ **17**) and acetylation afforded the mixture **1a**/**1b** (ratio *ca.* 0.7:1) in an overall yield of 16% from **4**.

Scheme 4

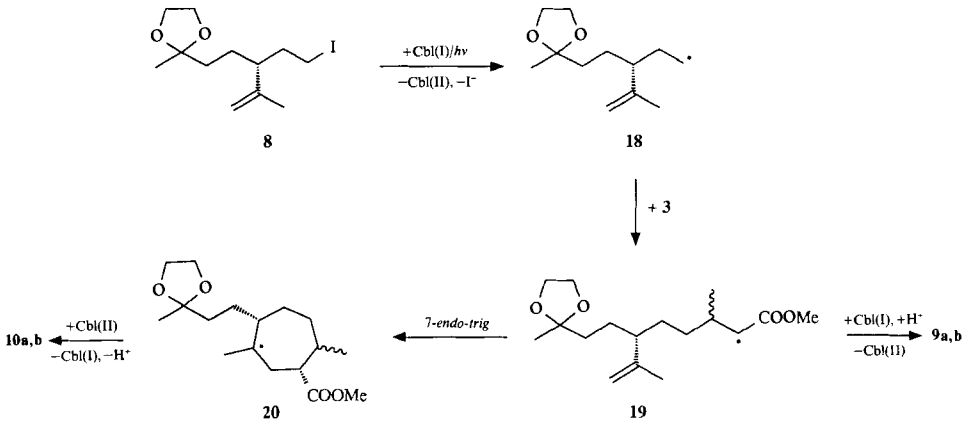


a) H_2O, Me_2CO, pyridinium toluene-4-sulfonate, 60°, 3 h; 98% yield. *b*) $Zn[BH_3(CN)]_2$, Et_2O, r.t., 4 h; 99% yield. *c*) Im_2CO, MeCN, 3-bromoprop-1-ene, 80°, 2 h; 77% yield. *d*) DIBAH, toluene, −15°, 4 h; 95% yield. *e*) (*t*-Bu)Me_2SiCl, DBU, CH_2Cl_2, r.t., 2 h; quant. yield. *f*) Lithium 2,2,6,6-tetramethylpiperidinate, TMEDA, [12]crown-4, THF, −75°, 30 min, 0°, 2 h; 95% yield. *g*) $Bu_4NF \cdot 3H_2O$, THF, r.t., 20 h; quant. yield. *h*) Ac_2O, Py, r.t., 18 h; quant. yield.

This material showed the same spectral data (IR, ^{1}H-NMR, ^{13}C-NMR) as published for (3*RS*,6*RS*)-3-methyl-6-(1-methylethenyl)dec-9-en-1-yl acetate [2b] and proved to be undistinguishable by GC/MS from an authentic sample of a mixture **1a**/**1b** provided by *Anderson* from *Sandoz Crop Protection*.

The constitution of **10a** and **10b** was confirmed by GC/MS, ^{1}H-NMR, ^{13}C-NMR, and 1D-TOCSY (total correlation spectroscopy). The signals of highest mass in the GC/MS at *m/z* 281 ($[M - Me]^+$) correspond to $[C_{16}H_{25}O_4]^+$. The ^{1}H-NMR and ^{13}C-NMR spectra showed the presence of signals of an exocyclic olefinic CH_2 group, but the absence of signals of an allylic Me group at *ca.* 1.6 ppm in the ^{1}H-NMR and at *ca.* 17.5 ppm in the ^{13}C-NMR. Based on ^{1}H-NOE's (see *Exper. Part*), the configuration of **10a** and **10b** are tentatively assigned.

Scheme 5



The competitive formation of **9** and **10** needs a comment (*Scheme 5*). The reaction sequence is started by the electrochemical reduction of Cbl(III) to dark-green Cbl(I). As a strong nucleophile, it undergoes a S_N2 reaction with the primary alkyl iodide **8** to form a red alkylcob(III)alamin [9]. Irradiation by visible light causes (reversible) Co–C bond cleavage to brown Cbl(II) and the highly reactive primary alkyl radical **18**. Since **18** is not quenched by fast intramolecular reactions[3]), it adds to methyl crotonate (**3**; present in high concentration) leading to the two diastereoisomeric *sec*-alkyl radicals **19**, and by recombination with Cbl(II) to the corresponding *sec*-alkylcob(III)alamins. Radicals **19**, obtained directly or by photolysis of the red alkylcob(III)alamins, may further react in two different ways, strongly depending on the reaction conditions. In presence of protons and a high concentration of Cbl(I) (color of the solution being dark brown-green caused by slow addition of **8** to the reaction mixture) reductive protonation of **19** to **9** dominates [10]. If, however, the concentration of Cbl(I) is very low (color of the solution being red caused by fast addition of **8** to the reaction mixture) 7-*endo-trig* cyclization of **19** to **20**, followed by hydro-cobalt elimination to **10**, clearly dominates. Thus, fine tuning of the reaction conditions allows a control of the competing formation of **9** or **10**.

The authors are indebted to Dr. *R. J. Anderson, Sandoz Crop Protection*, for providing a sample of a mixture **1a**/**1b**. They are grateful to Prof. *U. P. Schlunegger* and his group for the MS and GC/MS, Prof. *H. Arm* and his group for GC and HPLC, and PD Dr. *P. Bigler* and his group for NMR measurements, all from the University of Berne. This work was financially supported by the *Swiss National Science Foundation*.

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[3]) Under the reaction conditions described, alkyl iodides like **2** – carrying a terminal olefinic double bond instead of the protected carbonyl group as in **8** – undergo intramolecular radical cyclizations. The unprotected iodoketone **7** mainly reacts by hydrogenolysis of the halide, most likely *via* a 1,5-H shift of H at C(3) to C(2′) (*Scheme 2*), followed by reductive protonation of the electrophilic C(3) radical. This 1,5-H shift is favored, since a transition state may be reached allowing maximum overlap between the p-orbital of the C(2′) radical and the colinear arrangement of the H–C(3) σ-orbital with the C=O π^*-orbital. A corresponding 1,5-H shift in **18** (*Scheme 5*) from the allylic methyl group to C(2′) is disfavored, since colinearity of the H–C σ-orbital with the C=C π^*-orbital in the transition state would imply a highly strained conformation [9].

Experimental Part

General. Vitamin B_{12a} (= hydroxocobalamine-hydrochloride; pyrogen-free *Fr. Ph. BP*, 10.7% loss on drying, < 2% cyanocobalamine) from *Roussel Uclaf*; BuLi (2.5M) in hexane from *Aldrich*, titrated as described in [11]; DIBAH (1M) in hexane from *Aldrich*; anh. $ZnCl_2$ (techn.) from *Alfa Products*; MeCN (HPLC quality) from *Romil Chemicals*; *N,N'*-dicyclohexyl-*N*-methylcarbodiimidium iodide was prepared as described in [6a]; all other reagents and solvents from *Fluka*: $Li[AlH(t\text{-}BuO)_3]$ and $NaBH_3CN$, pract.; other reagents, *purum* grade. The solvents were dried before use as described in [12] where appropriate. Ar was bubbled during 45 min through the 0.2M $LiClO_4$/DMF before use. Ozonolysis: a O_3/O_2 mixture was generated with a *Fischer* ozoniser. Electrolysis: see

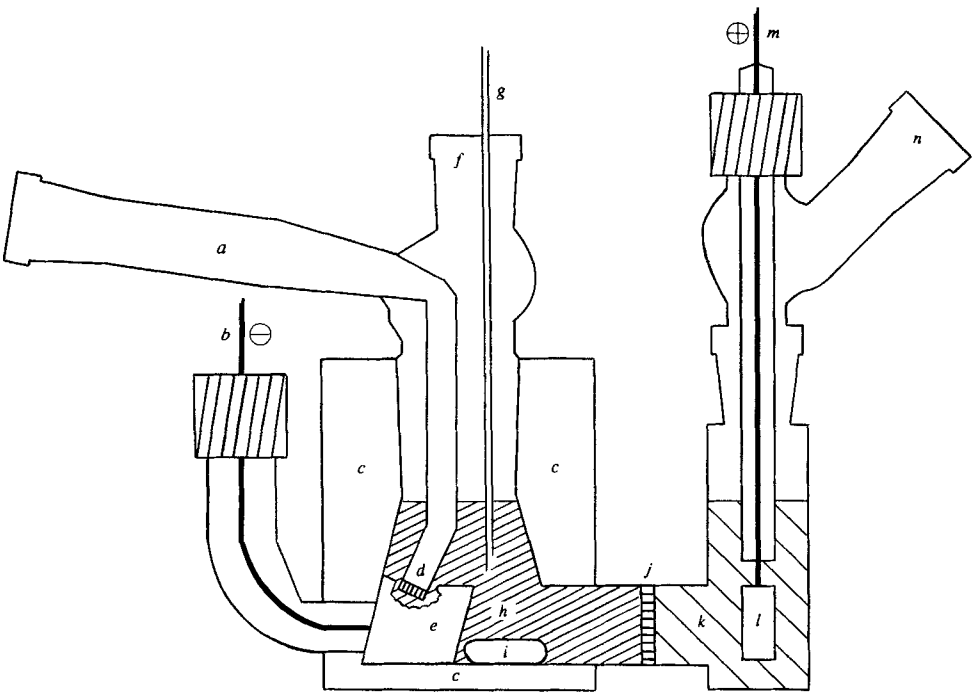

Figure. *Equipment for Electrolysis. a*) Salt-bridge for reference electrode, electrolyte: *ca.* 0.2M $LiClO_4$/DMF; saturated-calomel reference electrode (SCE), *Metrohm AG*, CH–9101 Herisau, joined up an electrolyte vessel of 90 mm length filled with sat. KCl/H_2O (diaphragm: *G5* sintered-glass frit.) *b*) Pt-wire connecting the cathode *e* and the (–)-pole of the potentiostate *Amel* model 550, potentiostate/galvanostate, *Apparecchiature di Misura Elettroniche*, I–20127 Milano. *c*) Cooling jacket (in- and outlet not drawn). *d*) Diaphragm: *G4* sintered-glass frit, 2 mm thick. *e*) Cathode: carbon felt (*Sigratherm felt GFA 5*, *Sigri Elektrodengraphit GmbH*, D–8901 Meitingen, 60 × 20 × 3 mm^3). *f*) Ground-glass joint for two-necked head (for Ar-bubbler and septum for syringe). *g*) Syringe needle for addition of reactand. *h*) Cathode compartment, content *ca.* 50 ml. *i*) Magnetic stirring bar. *j*) Diaphragm: *G3* sintered-glass frit, 3 mm thick. *k*) Anode compartment, content *ca.* 20 ml. *l*) Anode: Pt-sheet 19 × 7 mm^2. *m*) Pt-wire to the (+)-pole of the potentiostate. *n*) Ground-glass joint for Ar-bubbler.

Figure. Anal. GC: *Hewlett-Packard-5794* gas chromatograph; 20-m *Duran* glass cap. column coated with *SE-54* (*df* = 0.15 μm), temp. program from 40 to 250° at a rate of 3°/min; flame-ionization detector (FID). Anal. TLC: precoated plates, silica gel *60* F_{254} from *Merck*, detection with H_2SO_4/vanilline. Column chromatography (CC): silica gel for flash chromatography from *Baker*. HPLC: *Altex-100* solvent metering pump with preparative head, flow rate 14 ml/min; *Refractor Monitor LDC 1107* refractive index detector; *Condition I*: silica gel *Du Pont*, 7 μm, 23 mm × 250 mm, hexane/*t*-BuOMe 9:1; *Condition II*: silica gel *LiChrosorb Si 60* from *Merck*, 5 μm, 10 mm × 250

mm, hexane/*t*-BuOMe 85:15 + 0.1% (*v/v*) Et_3N; t_R in min. $[\alpha]_D$: *Perkin-Elmer* polarimeter. IR: *Perkin-Elmer-782* spectrometer. ^{1}H-NMR: *Varian EM 360L* (60 MHz) and *Bruker AM-400 WB* (400 MHz; if not stated); solvent $CDCl_3$; δ in ppm rel. to TMS (= 0 ppm) as internal standard, *J* in Hz. NOE: irradiated H→affected H's. ^{13}C-NMR: *Bruker AM-400 WB* (100.61 MHz); solvent $CDCl_3$, TMS (= 0 ppm) as internal standard. EI-MS: *Varian-MAT-CH-7-A* spectrometer, ionization energy 70 eV.

(R)-4-Methyl-3-(3-oxobutyl)pent-4-enal (**5**). O_3 (42 mmol/h) was bubbled through a soln. of (+)-(*R*)-limonene (**4**; 22.48 g, 165 mmol) and pyridine (3.8 g, 48 mmol) in MeOH (130 ml) at −72°. Immediately after **4** was completely consumed (GC), Ar was bubbled through the soln. for 30 min, then Me_2S (16 g, 258 mmol) was added and the soln. stirred overnight at −40°, allowed to warm up to r.t., and diluted with H_2O (600 ml). The H_2O phase was separated and extracted 5 times with $CHCl_3$ (100 ml). The combined org. phase was dried (Na_2SO_4) and evaporated. The residue was diluted with Et_2O (200 ml) and the soln. washed with 5% HCl/brine (20 ml), sat. $NaHCO_3$ soln. (20 ml), and brine (3 × 20 ml), dried (Na_2SO_4), and evaporated. The bright yellowish green oily residue (24.5 g) was subjected to CC (280 g of SiO_2/*ca.* 8 g of residue, AcOEt/pentane 1:4). Bulb-to-bulb distillation (80°/0.01 Torr) afforded 17.93 g (65%) of **5**. Colorless oil. R_f (AcOEt/hexane 1:3) 0.33. $[\alpha]_D^{20} = +15.3$ (*c* = 3.06, $CHCl_3$). IR (film): 3077*m*, 2965*s* (sh), 2940*s*, 2900*s* (sh), 2830*m*, 2725*m*, 1720*s* (br.), 1647*s*, 1440*s*, 1414*s*, 1367*s*, 1240*m*, 1230*m*, 1190*m*, 1162*s*, 1127*m*, 1100*m*, 1070*m*, 1020*m*, 897*s*. ^{1}H-NMR (60 MHz): 9.76 (*m*, 1 H); 4.84 (*m*, 2 H); 3.0–1.4 (*m*, 7 H); 2.13 (*s*, 3 H); 1.67 (br. *s*, 3 H). MS: 132 (1, $[M - 2\,H_2O]^+$), 108 (2), 107 (7), 95 (3), 93 (3), 92 (3), 91 (2), 83 (2), 82 (5), 81 (2), 79 (3), 71 (5), 69 (5), 68 (2), 67 (10), 59 (2), 58 (10), 55 (10), 53 (3), 44 (2), 43 (71), 42 (2), 41 (17), 40 (2), 39 (7), 32 (22), 29 (4), 28 (100), 18 (25).

(R)-5-(2-Hydroxyethyl)-6-methylhept-6-en-2-one (**6**). A soln. of $Li[AlH(t\text{-}BuO)_3]$ (5.28 g, 20.7 mmol) in THF (15 ml) was added within 10 min dropwise at −70° to a soln. of **5** (3.49 g, 20.7 mmol) in THF (25 ml). After stirring for 4 h at −70° and for 45 min at 0°, the mixture was diluted with Et_2O (50 ml) and acidified by adding ice-cooled 2M HCl (35 ml). The H_2O phase was separated and extracted with Et_2O (6 × 30 ml). The combined org. phase was washed with sat. $NaHCO_3$ soln. (20 ml) and brine (3 × 50 ml), dried (Na_2SO_4), and evaporated. The residue (3.5 g) was subjected to CC in two portions (SiO_2 (120 g), pentane/Et_2O 1:3). Bulb-to-bulb distillation (90°–150°/0.001 Torr) afforded 2.818 g (80%) of **6**. Colorless oil. R_f (hexane/Et_2O 1:3) 0.32. $[\alpha]_D^{20} = +3.93$ (*c* = 7.4, $CHCl_3$). IR (film): 3420*s* (br.), 3077*m*, 2940*s*, 2880*s*, 1716*s*, 1646*m*, 1445*m*, 1413*m*, 1368*s*, 1230*m*, 1190*m*, 1162*m*, 1055*s*, 1030*m*, 1010*m* (sh), 892*s*. ^{1}H-NMR: 4.75 (*m*, 2 H); 3.54 (*m*, 2 H); 3.41 (br. *s*, 1 H); 2.37 (*t*, *J* = 7.52, 2 H); 2.22–2.15 (*m*, 1 H); 2.12 (*s*, 3 H); 1.72–1.5 (*m*, 4 H); 1.6 (br. *s*, 3 H). ^{13}C-NMR: 209.0; 145.9; 112.2; 60.0; 42.8; 40.9; 35.6; 29.5; 26.2; 17.1. MS: 152 (12, $[M - H_2O]^+$), 137 (10), 134 (16), 126 (6), 125 (4), 122 (18), 121 (10), 119 (10), 111 (8), 109 (22), 108 (20), 107 (17), 106 (3), 97 (14), 95 (15), 94 (5), 93 (12), 84 (3), 83 (44), 82 (12), 81 (13), 79 (19), 77 (3), 71 (19), 70 (4), 69 (21), 68 (10), 67 (28), 58 (14), 57 (3), 56 (3), 55 (22), 53 (7), 43 (100), 41 (22), 39 (5).

(R)-5-(2-Iodoethyl)-6-methylhept-6-en-2-one (**7**). DCC·MeI (13.03 g, 37.41 mmol) was added to a soln. of **6** (2.58 g, 15.18 mmol) in THF (150 ml). The red violet mixture was stirred for 22 h at r.t. in the dark and thereafter evaporated at 40°/12 Torr. The residue was diluted with pentane (150 ml) and washed with MeOH/H_2O 4:1 (3 × 80 ml). The combined MeOH/H_2O phase was extracted with pentane (5 × 100 ml), the combined pentane phase dried (Na_2SO_4) and evaporated, and the residue (24.8 g) purified by CC in 4 portions (SiO_2 (120 g), pentane/Et_2O 6:1). Bulb-to-bulb distillation (100°–140°/0.01 Torr) afforded 3.67 g (86%) of **7**. Tear-gas-like colorless oil. R_f (hexane/Et_2O 6:1) 0.28. $[\alpha]_D^{20} = -33.4$ (*c* = 5.23, $CHCl_3$). IR (film): 3074*m*, 2965*m*, 2940*s*, 2894*m*, 1718*s*, 1646*m*, 1440*m*, 1423*m*, 1415*m* (sh), 1378*m* (sh), 1367*s*, 1355*m* (sh), 1228*m*, 1170*m*, 1162*m* (sh), 895*s*. ^{1}H-NMR: 4.82 (*m*, 2 H); 3.17 (*m*, 1 H); 2.99 (*m*, 1 H); 2.37 (*t*, *J* = 7.53, 2 H); 2.22–2.15 (*m*, 1 H); 2.12 (*s*, 3 H); 1.85 (*m*, 2 H); 1.70–1.53 (*m*, 2 H); 1.58 (br. *s*, 3 H). ^{13}C-NMR: 207.8; 144.0; 113.6; 46.8; 40.8; 36.4; 29.7; 25.7; 17.0; 4.4. MS: 262 (6, $[M - H_2O]^+$), 222 (1), 155 (4), 154 (2), 153 (32), 136 (4), 135 (50), 128 (3), 109 (6), 107 (9), 96 (4), 95 (54), 93 (11), 83 (2), 81 (8), 79 (7), 71 (11), 69 (3), 68 (3), 67 (25), 58 (6), 57 (5), 55 (13), 53 (5), 44 (2), 43 (100), 41 (11), 39 (3).

(R)-5-(2-Iodoethyl)-6-methylhept-6-en-2-one Ethylene Acetal (**8**). A soln. of **7** (2.14 g, 7.6 mmol), ethanediol (2.67 g, 43 mmol) and pyridinium toluene-4-sulfonate (0.148 g, 0.58 mmol) in benzene (70 ml) was refluxed for 5 h with H_2O separation by a *Dean-Stark* trap. After the first 1.5 h, the *Dean-Stark* trap was filled with 4-Å molecular sieves. Excess solvent was then removed *in vacuo* at 40°, Et_2O (60 ml) added, and the mixture washed with sat. $NaHCO_3$ soln./brine 1:1 (40 ml). The H_2O layer was extracted with Et_2O (3 × 50 ml), the combined org. phase washed with brine (2 × 30 ml) and dried (Na_2SO_4), and the solvent distilled off. The residue (2.78 g) was purified by CC (SiO_2 (83 g), pentane/Et_2O 19:1) and bulb-to-bulb distilled (125°/0.001 Torr): 2.23 g (91%) of **8**. Slightly yellowish oil. R_f (hexane/Et_2O 19:1) 0.41. $[\alpha]_D^{20} = -31.15$ (*c* = 4.34, $CHCl_3$). IR (film): 3073*m*, 2980*s*, 2946*s*, 2880*s*, 1646*m*, 1450*s*, 1376*s*, 1343*m*, 1332*m*, 1315*m*, 1299*m*, 1250*s*, 1224*s*, 1172*s*, 1136*s*, 1102*s*, 1062*s*, 1048*s* (sh), 946*m*, 892*s*, 860*s*. ^{1}H-NMR: 4.8 (*m*, 2 H); 3.93 (*m*, 4 H); 3.17 (*m*, 1 H); 3.0 (*m*, 1 H); 2.16 (*m*, 1 H); 1.83 (*m*, 2 H); 1.58 (br. *s*, 3 H); 1.58–1.40 (*m*, 4 H); 1.29 (*s*, 3 H). ^{13}C-NMR: 144.9; 113.4; 109.9; 64.6; 47.8; 36.9; 36.7; 26.9; 23.7; 17.5; 4.9.

MS: 309 (2, $[M - Me]^+$), 262 (7), 135 (7), 115 (3), 107 (3), 105 (4), 99 (13), 95 (3), 88 (5), 87 (100), 86 (3), 81 (3), 79 (3), 71 (3), 67 (4), 59 (4), 55 (4), 43 (25).

Methyl (3RS,6S)-3,7-Dimethyl-6-[3,3-(ethylenedioxy)butyl]oct-7-enoate (**9**) *and Methyl (1R,2R,5S)- and (1R,2S,5S)-5-[3,3-(Ethylenedioxy)butyl]-2-methyl-6-methylidene Cycloheptanoate* (**10a** and **10b**, resp.). To the cathode compartment of an electrochemical H-type cell (see *Fig.*) containing C-felt (60 × 20 × 3 mm^3) as cathode material and 0.2M $LiClO_4$/DMF (30 ml) was added vitamin B_{12a} (164 mg, 0.12 mmol, 0.23 equiv. rel. to **8**). The anode compartment was charged with 0.2M $LiClO_4$/DMF (10 ml). Vitamin B_{12a} was reduced to Cbl(I) at −1.5 V (*vs.* SCE) until the current had dropped to a constant level of *ca.* 1.5 mA and the color had changed from red to dark brownish green. The potential was set to −1.2 V (*vs.* SCE), and AcOH (0.2 ml) and methyl crotonate (**3**; 4.1 g, 41 mmol) were added to the cathode compartment. The cathode compartment was irradiated by a 400-W halogen lamp at a distance of *ca.* 20 cm. A soln. of **3** (4 g, 40 mmol) and **8** (166 mg, 0.51 mmol) in 0.2M $LiClO_4$/DMF (total volume 10 ml) was added slowly by syringe (syringe-pump addition, outlet of the syringe needle below the level of the soln.) within 6 h at +8°. The color of the soln. remained dark brown green[4]). After the current had dropped from *ca.* 7 mA during the reaction to a constant background level of *ca.* 1.5 mA after 12 h, the mixture was diluted with brine (300 ml) and H_2O (60 ml). The H_2O phase was extracted with Et_2O (5 × 100 ml). The combined org. phase was washed twice with brine (150 ml), dried (Na_2SO_4) and evaporated. The residue was subjected to CC (SiO_2 (18 g), Et_2O/pentane 3:10). Bulb-to-bulb distillation (180°/0.001 Torr) afforded 136 mg (90%) of **9**/**10** 1.8:1 (2 diastereoisomers in each case, ratio *ca.* 1:1). The combined distillate of several parallel runs was purified by HPLC under *Condition I*, yielding *Fractions 1–4*. *Fr. 1* contained **10b** (t_R *ca.* 19.3–21), *Fr. 2* **9a**, **b** (t_R *ca.* 21–22), *Fr. 3* **10a** (t_R *ca.* 22–24.5), and *Fr. 4* **10a** (t_R *ca.* 24.5–32.5). Isolation of **10a** and **10b**: the distillate was separated by HPLC under *Condition II* yielding *Fr. A–C*. *Fr. A* (t_R *ca.* 10.4–10.9) was resubmitted to HPLC (*Condition II*; → *Fr. A1–A3*). *Fr. A1* contained **10b**. *Fr. C* (t_R *ca.* 11.3–12.2) was subjected to the same procedure (→ *Fr. C1–C3*). *Fr. C3* contained **10a**.

9a: GC: t_R 49.02. GC/MS: 283 (0.2, $[M - Me]^+$), 237 (0.2), 236 (0.5), 161 (0.4), 159 (0.3), 145 (1), 123 (1), 122 (2), 121 (2), 119 (3), 107 (5), 99 (5), 93 (3), 87 (100), 81 (4), 79 (3), 71 (3), 69 (6), 67 (5), 59 (8), 55 (11), 43 (47), 41 (12).

9b: GC: t_R 49.19. GC/MS: 283 (0.3, $[M - Me]^+$), 237 (0.2), 236 (1), 161 (0.4), 159 (0.2), 145 (1), 123 (1), 122 (3), 121 (3), 119 (3), 107 (6), 99 (6), 93 (3), 87 (100), 81 (3), 79 (3), 71 (4), 69 (4), 67 (7), 59 (10), 55 (12), 43 (53), 41 (12).

10a: GC: t_R 52.19. $[\alpha]_D^{20} = +7.3$ ($c = 1.22$, CCl_4). IR (CCl_4): 3075*w*, 2980*m*, 2955*s*, 2930*s*, 2880*m*, 1740*s*, 1640*w*, 1460*m*, 1437*m*, 1375*m*, 1160*s*, 1145*m*, 898*m*. ^{1}H-NMR: 4.88 (*m*, CH–C(6)); 4.74 (*m*, CH′–C(6)); 3.9 (*m*, OCH_2CH_2O); 3.66 (*s*, MeO); 2.2 (*m*, CH_2(7)); 2.15 (*m*, H–C(5)); 1.96 (*m*, *td*-like, $J \approx 11, 4$, H–C(1)); 1.88 (*m*, H–C(4)); 1.71 (*m*, H–C(2)); 1.63 (*m*, H–C(2′)); 1.55 (*m*, H′–C(3)); 1.48 (*m*, H–C(2′)); 1.41 (*m*, H–C(1′)); 1.25 (*s*, H–C(4′)); 1.24 (*m*, H–C(1′)); 1.2 (*m*, H′–C(4)); 1.09 (*m*, H–C(3)); 0.82 (*m*, *d*-like, $J \approx 7$, Me–C(2)). NOE: 4.88→4.74, 2.2, 1.96; 4.74→4.88, 2.15; 1.96→2.2; 1.88→2.15, 1.55, 1.2; 0.82→1.96, 1.71, 1.55. ^{13}C-NMR: 176.7 (*C*OOMe); 150.9 (C(6)); 114.6 (CH_2–C(6)); 110.1 (C(3′)); 64.6 (OCH_2CH_2O); 56.6 (C(1)); 51.5 (MeO); 46.5 (C(5)); 39.5 (C(2)); 36.9 (C(2′)); 34.0 (C(7)); 33.4 (C(3)); 32.1 (C(4)); 30.2 (C(1′)); 23.8 (C(4′)); 22.0 (Me–C(2)). GC/MS: 281 (0.2, $[M - Me]^+$), 235 (0.2), 234 (1), 175 (1), 174 (1), 160 (1), 159 (2), 145 (1), 135 (1), 121 (2), 119 (3), 99 (4), 93 (5), 87 (100), 81 (3), 79 (4), 71 (2), 69 (2), 67 (3), 59 (6), 55 (9), 43 (44), 41 (8).

10b: GC: t_R 52.69 $[\alpha]_D^{20} = -39.8$ ($c = 1.93$, CCl_4). IR (CCl_4): 3080*w*, 2985*m*, 2955*s*, 2930*s*, 2880*m*, 1740*s*, 1640*w*, 1460*m*, 1448*m*, 1435*m*, 1377*m*, 1165*s*, 1063*m*, 897*m*. ^{1}H-NMR: 4.8 (*m*, CH–C(6)); 4.76 (*m*, CH′–C(6)); 3.9 (*m*, OCH_2CH_2O); 3.63 (*s*, MeO); 2.42 (*m*, H–C(7)); 2.29 (*m*, H′–C(7)); 2.19 (*m*, H–C(1)); 2.16 (*m*, H–C(5)); 1.98 (*m*, H–C(2)); 1.68 (*m*, H–C(4)); 1.62 (*m*, H–C(3)); 1.57 (*m*, CH_2(2′)); 1.51 (*m*, H–C(1′)); 1.39 (*m*, H′–C(4)); 1.38 (*m*, H–C(1′)); 1.34 (*m*, H′–C(3)); 1.27 (*s*, Me(4′)); 0.86 (*d*, $J = 7.1$, Me–C(2)). NOE: 4.8→4.76, 2.42, 2.29; 4.76→4.8, 2.16; 3.9→1.27; 2.42→4.8, 2.29, 2.19; 2.29→4.8, 2.42; 2.19→2.42, 1.98; 2.16→4.76, 1.68; 1.98→1.68, 0.86; 1.68→2.16, 1.98, 1.39; 1.27→3.9; 0.86→2.19, 1.98. ^{13}C-NMR: 176.3 (*C*OOMe); 149.8 (C(6)); 112.5 (CH_2–C(6)); 110.2 (C(3′)); 64.6 (OCH_2CH_2O); 52.5 (C(1)); 51.3 (MeO); 44.4 (C(5)); 37.1 (C(2′)); 36.1 (C(7)); 34.3 (C(2)); 31.4 (C(3)); 30.2 (C(4)); 28.6 (C(1′)); 23.8 (C(4′)); 21.5 (Me–C(2)). GC/MS: 281 (0.4, $[M - Me]^+$), 235 (0.4), 234 (2), 175 (2), 174 (3), 161 (1), 159 (3), 145 (1), 135 (2), 121 (2), 119 (3), 99 (4), 93 (7), 87 (100), 81 (4), 79 (5), 71 (4), 69 (3), 67 (4), 59 (11), 55 (12), 43 (52), 41 (10).

Methyl (3RS,6S)-3,7-Dimethyl-6-(3-oxobutyl)oct-7-enoate (**11**). A soln. of **9** (219 mg, 0.73 mmol), pyridinium toluene-4-sulfonate (78 mg, 0.3 mmol), and H_2O (10 drops) in acetone (10 ml) was refluxed for 2.5 h. Excess solvent was removed at r.t./12 Torr, Et_2O (40 ml) added, the mixture washed with sat. $NaHCO_3$ soln. (10 ml) and

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[4]) If the addition of **8** proceeded too fast or stepwise in portions, the color changed temporarily from dark brown green (Cbl(I)) to red (alkyl-Cbl(III)), reaction conditions that favored the formation of **10** on the cost of **9**.

brine (2 × 10 ml), the org. phase dried (Na_2SO_4), and the solvent distilled off. Bulb-to-bulb distillation (130°–150°/0.001 Torr) afforded 182 mg (98%) of **11**. Colorless oil. R_f (AcOEt/hexane 1:19) 0.19 (twice developed).

Methyl (3RS,6S)-6-[(3RS)-3-Hydroxybutyl]-3,7-dimethyloct-7-enoate (**12**). To a suspension of $NaBH_3CN$ (59 mg, 0.93 mmol) and $ZnCl_2$ (68 mg, 0.5 mmol) in Et_2O (3 ml) was added at r.t. a soln. of **11** (182 mg, 0.72 mmol) in Et_2O (4 ml). After stirring for 4 h, the mixture was diluted with Et_2O (30 ml) and washed with 0.1M KIO_3 (10 ml). The H_2O phase was extracted with Et_2O (5 × 20 ml), the combined org. phase washed with brine (10 ml) and dried (Na_2SO_4), and the Et_2O distilled off. Bulb-to-bulb distillation (160°/0.001 Torr) afforded 183 mg (99%) of **12**. Colorless oil. R_f (Et_2O/hexane 1:1) 0.27; R_f (Et_2O/hexane 3:11) 0.17.

Methyl (3RS,6S)-6-[(3RS)-3-Bromobutyl]-3,7-dimethyloct-7-enoate (**13**). A soln. of **12** (183 mg, 0.71 mmol), Im_2CO (154 mg, 0.94 mmol) and 3-bromoprop-1-ene (1.23 g, 10.16 mmol) in MeCN (5 ml) was stirred for 30 min at r.t. and then heated at 90° for 2 h. The mixture was diluted with Et_2O (35 ml) and washed with brine. The H_2O phase was extracted with Et_2O (5 × 20 ml) and the combined org. phase washed with ice-cooled 1M HCl, sat. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated. The oily residue consisted mainly of the (alkoxycarbonyl)imidazole of **12** (R_f (Et_2O/hexane 3:11) 0.11; *cf.* R_f of **12**). This residue was taken up in MeCN (1 ml), 3-bromoprop-1-ene (2 ml) and Im_2CO (*ca.* 10 mg) were added, and the mixture was heated at 100° for 4 h. After workup as described above, the residue was purified by CC (SiO_2, (40 g), Et_2O/pentane 1:12) and bulb-to-bulb distilled (150°/0.001 Torr): 174 mg (77%) of **13**. Colorless oil. R_f (Et_2O/hexane 1:1) 0.78.

(3RS,6S)-6-[(3RS)-3-Bromobutyl]-3,7-dimethyloct-7-en-1-ol (**14**). To a soln. of **13** (155 mg, 0.48 mmol) in toluene (6 ml) at −15°, 1M diisobutylaluminium hydride (DIBAH)/hexane (2 ml, 2 mmol) was added dropwise by syringe. After stirring for 4 h at r.t., the mixture was quenched by dropwise (syringe) addition of toluene/MeOH 1:1 (2 ml) followed by 2M HCl (2 ml). The H_2O phase was separated and extracted with Et_2O (5 × 20 ml), the combined org. phase washed with sat. $NaHCO_3$ soln. (15 ml) and brine (2 × 20 ml), dried, and evaporated, and the crude product purified by CC (SiO_2 (11 g), Et_2O/pentane 1:2). Bulb-to-bulb distillation (170°/0.001 Torr) afforded 134 mg (95%) of **14**. Colorless oil. R_f (Et_2O/hexane 1:2) 0.31.

(3RS,6S)-6-[(3RS)-3-Bromobutyl]-3,7-dimethyloct-7-en-1-yl (tert-Butyl)dimethylsilyl Ether (**15**). To a soln. of **14** (65 mg, 0.22 mmol) and (*t*-Bu)Me_2SiCl (85 mg, 0.57 mmol) in CH_2Cl_2 (1.5 ml) was added 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU; 155 mg, 1 mmol). After stirring for 2 h at r.t., the mixture was filtered over SiO_2 (2.5 g, deactivated by 1 drop of Et_3N) with CH_2Cl_2. The solvent of the filtrate was removed at 40°/10 Torr: 90 mg (quant.) of **15**. Slightly yellowish oil. R_f (hexane) 0.27.

(tert-Butyl)dimethylsilyl (3RS,6R)-3-Methyl-6-(1-methylethenyl)dec-9-en-1-yl Ether (**16**). To 2.3M BuLi (1 ml) at 0° were added *N,N,N',N'*-tetramethylethylenediamine (TMEDA; 282 mg, 2.4 mmol) and 2,2,6,6-tetramethylpiperidine (365 mg, 2.6 mmol). After stirring for 45 min at 0°, the solvent was distilled off at r.t./10 Torr. The residue was cooled to 0°, diluted with THF (2 ml), and immediately cooled to −78°. A soln. of [12]crown-4 (461 mg, 2.6 mmol) in THF (1 ml) was added within 30 s. After 1 min, a soln. of **15** (33 mg, 0.08 mmol) in THF (1.5 ml) was added by syringe. After stirring for 30 min at −78° and for 2 h at 0°, the mixture was diluted with Et_2O (15 ml) and H_2O (20 ml). To the aq. phase NaCl was added and this phase extracted with Et_2O (5 × 10 ml). The combined org. phase was washed with 1M HCl/brine (5 ml), sat. $NaHCO_3$ soln. (20 ml), and brine (20 ml), dried (Na_2SO_4), and evaporated: 24.5 mg (95%) of **16**. Colorless oil. R_f (Et_2O/hexane 1:19) 0.91.

(3RS,6R)-3-Methyl-6-(1-methylethenyl)dec-9-en-1-ol (**17**). A soln. of **16** (24.5 mg, 0.075 mmol) and $Bu_4NF \cdot 3H_2O$ (300 mg, 0.9 mmol) in THF (3 ml) was stirred for 20 h at r.t., then diluted with Et_2O (20 ml) and washed with brine (30 ml). The H_2O phase was extracted with Et_2O (5 × 20 ml), the combined org. phase dried (Na_2SO_4) and evaporated, and the residue purified by CC (SiO_2 (3 g), Et_2O/pentane 1:2): 15.7 mg (quant.) of **17**. R_f (Et_2O/hexane 1:1) 0.39; R_f (Et_2O/hexane 1:2) 0.22. ^{1}H-NMR: 5.78 (*m*, 1 H); 4.97 (*m*, 1 H); 4.89 (*m*, 1 H); 4.71 (*m*, 1 H); 4.63 (*m*, 1 H); 3.63 (*m*, 2 H); 2.01–1.86 (*m*, 3 H); 1.55 (br. *s*, 3 H); 1.61–1.15 (*m*, 9 H); 1.07–0.98 (*m*, 1 H); 0.85 (*d*-like, J = 6.6, 1.5 H); 0.84 (*d*-like, J = 6.6, 1.5 H). ^{13}C-NMR: 147.3; 147.0; 139.0; 114.1; 111.8; 111.7; 61.1; 47.1; 46.9; 40.0; 39.6; 34.9; 34.6; 32.7; 32.6; 31.6; 30.6; 30.4; 29.6; 19.7; 19.5; 17.8; 17.6.

(3RS,6R)-3-Methyl-6-(1-methylethenyl)dec-9-en-1-yl Acetate (**1a**/**1b**). A soln. of **17** (15.7 mg, 0.074 mmol) in pyridine (0.5 ml) and Ac_2O (0.25 ml) was stirred for 18 h at r.t., diluted with Et_2O (20 ml), and washed with 2M HCl (15 ml). The H_2O phase was extracted with Et_2O (4 × 15 ml), the combined org. phase washed with sat. $NaHCO_3$/brine 1:1 and brine, dried (Na_2SO_4), and evaporated, and the crude product purified by CC (SiO_2, (4.6 g), Et_2O/pentane 3:200) and bulb-to-bulb distilled (100°/0.01 Torr): 18.8 mg (quant.) of **1a**/**1b**. Colorless oil. R_f (Et_2O/hexane 1:40) 0.25. GC: t_R 38.28 and 38.47, ratio 0.73:1. $[\alpha]_D^{20} = -8.03$ (c = 1.88, $CHCl_3$). IR ($CHCl_3$): 3078*m*, 2960*s*, 2932*s*, 2875*m*, 2860*m*, 1744*s*, 1644*m*, 1455*m*, 1367*s*, 1049*m*, 1035*m*, 995*m*, 892*s*. ^{1}H-NMR: 5.77 (br. *m*, H–C(9)); 4.96 (*m*, H–C(10) *cis* to C(8)); 4.9 (*m*, H–C(10) *trans* to C(8)); 4.72 (*m*, H–C(2')); 4.63 (*m*, H–C(2')); 4.05 (*m*, CH_2(1)); 2.04–1.85 (*m*, H–C(6), CH_2(8)); 2.01 (*s*, Ac); 1.54 (br. *s*, Me–C(1')); 1.65–1.16, 1.06–0.98 (*m*, CH_2(2), CH(3), CH_2(4), CH_2(5), CH_2(7)); 0.87 (*d*, J = 6.5, Me–C(3)); 0.86 (*d*, J = 6.5, Me–C(3)). ^{13}C-NMR:

171.1; 147.1; 147.0; 139.0; 114.2; 111.8; 111.7; 63.0; 62.9; 47.0; 46.8; 35.6; 35.1; 34.6; 34.4; 32.7; 32.5; 31.6; 31.6; 30.5; 30.4; 29.9; 29.6; 20.9; 19.6; 19.3; 17.7; 17.6. GC/MS (t_R 38.28): 209 (0.1, $[M - Ac]^+$), 192 (0.3), 178 (0.2), 177 (0.4), 165 (0.2), 164 (1), 163 (2), 149 (7), 135 (9), 123 (9), 122 (5), 121 (7), 110 (5), 109 (24), 108 (6), 107 (14), 96 (7), 95 (38), 94 (8), 93 (20), 91 (5), 83 (12), 82 (27), 81 (100), 80 (12), 79 (19), 77 (5), 70 (6), 69 (51), 68 (21), 67 (62), 66 (5), 57 (11), 56 (8), 55 (63), 54 (4), 53 (10), 44 (5), 43 (86), 42 (6), 41 (45), 40 (7), 39 (11). GC/MS (t_R 38.47): 209 (0.1, $[M - Ac]^+$), 192 (0.2), 178 (0.1), 177 (1), 165 (0.2), 164 (1), 163 (2), 149 (6), 135 (8), 123 (8), 122 (5), 121 (6), 110 (6), 109 (23), 108 (6), 107 (14), 96 (7), 95 (38), 94 (8), 93 (18), 91 (5), 83 (12), 82 (27), 81 (100), 80 (11), 79 (19), 77 (4), 70 (6), 69 (63), 68 (21), 67 (63), 66 (5), 57 (12), 56 (9), 55 (71), 54 (5), 53 (11), 44 (4), 43 (91), 42 (5), 41 (49), 40 (5), 39 (11).

This material showed the same spectral data (IR, ^{1}H-NMR, ^{13}C-NMR) as published for (3*RS*,6*RS*)-3-methyl-6-(1-methylethenyl)dec-9-en-1-yl acetate in [2b] and proved to be undistinguishable by GC/MS from an authentic sample of **1a**/**1b** 1:1 provided by Dr. *R. J. Anderson* from *Sandoz Crop Protection*.

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