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# A Versatile and Convenient Protocol for the Stereocontrolled Synthesis of Olefinic Insect Pheromones

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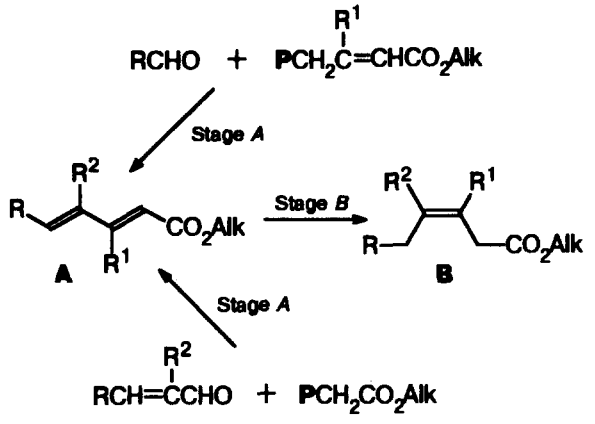
**Abstract**—A combination of the Horner–Emmons synthesis of alkyl 2,4-dienoates with their hydrogenation over complex L·Cr(CO)$_3$ catalysts (L = 3CO or arene) provides a versatile, stereocontrolled and operationally simple approach to the (*Z*)-disubstituted, (*Z*)-trisubstituted, (*E*)-trisubstituted alkenes and skipped (*Z*,*Z*)-disubstituted diolefins with a homoallylic type of functionally. This protocol, sometimes supplemented by an enzymatic hydrolysis, was successfully applied to the synthesis of configurationally pure (gp ≥ 98%) pheromones of the furniture carpet beetle, dry bean beetle, rusty grain beetle, square-necked grain beetle and of a trail-following pheromone mimic for subterranean termites. Copyright © 1996 Elsevier Science Ltd

## Introduction

The stereobiology of pheromone reception cannot be properly understood without studying the activity of individual stereoisomers, and in the case of the widespread olefinic insect pheromones this necessity was realized long ago.[1] Today, their ever-growing plethora seems to be matched by numerous synthetic methods elaborated by modern organic chemists for the regio- and stereocontrolled formation of the double C—C bonds.[2] Nevertheless, certain relatively complex structural types of olefinic pheromones still can be a stimulus for developing new ways of obtaining them by highly selective, yet operationally simple reactions. Among such targets are (3*Z*)-alkenoic acids and their macroheterocyclic derivatives, (*Z*)- and (*E*)-trisubstituted alkenes with a homoallylic pattern of functional substitution, and skipped (*Z*,*Z*)-disubstituted diolefins.

Recently[3,4] we proposed a practical and flexible approach to such systems based on a two-stage sequence which unites the Horner–Emmons synthesis of the appropriately substituted alkyl 2,4-dienoates[5] and the increasingly popular 1.4-*cis* addition of $H_2$ to conjugated dienes catalysed by chromium carbonyl complexes.[6] By varying the synthesis of alkyl 2,4-dienoates (stage A) and carefully selecting the conditions of hydrogenation for various types of diene substrates (stage B) we obtained a number of configurationally pure pheromones belonging to the above-mentioned structural types (Scheme 1). In some of these syntheses enzymatic hydrolysis of the ester intermediates (stage C) was also included in the protocol.

Application of this methodology is illustrated below by the syntheses of five insect behaviour-controlling substances of various molecular complexity.




**Scheme 1.** P = $(AlkO)_2P(O)$; R = Alk, AlkC≡C or H, $R^1$ = Me (if $R^2$ = H) or H, $R^2$ = H or Alk (if $R^1$ = H).

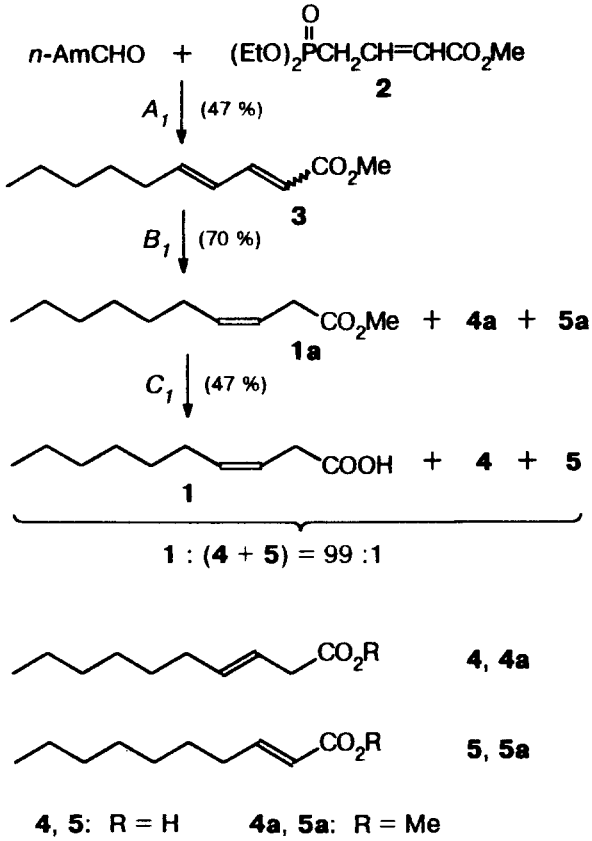
## Results and Discussion

### (3*Z*)-Alkenoic acids

**(3*Z*)-Decenoic acid (1).** This olefin was shown to be the aggregation pheromone of the furniture carpet beetle, *Anthrenus flavipes* (Dermestidae),[7] otherwise known as the 'museum beetle'. Later, **1** was identified as one of the urinary fatty acid catabolites in humans.[8] The required geometry of the double bond in **1** was asserted by the *cis* hydrogenation of the C≡C bond of its acetylenic precursor.[7,8] This technique afforded the specimens containing up to 96% of the (*Z*) isomer,[8] the precursor being prepared by the double alkylation of acetylene and subsequent oxidation.

Alternatively, we obtained **1** in three steps starting from *n*-hexanal and methyl 4-(diethylphosphono) crotonate (**2**). Their condensation in the presence of $NaNH_2$ in THF afforded methyl 2,4-decadienoate (**3**),

which contained the (3*E*,4*E*) and (2*Z*,4*E*) isomers in the proportion 9:1. Both stereoisomers were consumed when **3** was hydrogenated over $Cr(CO)_6$ in hexane (180 °C, 50 atm) to give methyl (3*Z*)-decenoate (**1a**), its (*E*) isomer (**4a**) and methyl (2*E*)-decenoate (**5a**) in the proportions 96:1:3. Mild alkaline hydrolysis of this mixture with KOH in aqueous MeOH liberated the target acid **1** from **1a**. Unfortunatley, this proces was accompanied by partial isomerisation of **1a** to **5a** due to which the geometric purity of **1** was lowered in comparison to **1a**. According to the $^1$H NMR spectrum, the ratio of the isomeric acids **1**, **4** and **5** in the specimen thus obtained was 93:1:6.



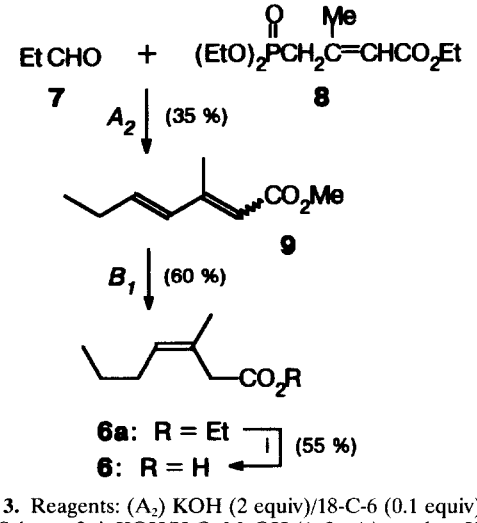

**Scheme 2.** Reagents: ($A_1$) $NaNH_2$/THF, 5–20 °C; ($B_1$) $H_2$-$Cr(CO)_6$/hexane, 180 °C; ($C_1$) PPL/$H_2O$ (pH 7.0):DMF (1:1, v/v), rt, 80% conversion.

In order to avoid this isomerization, which was obviously due to the alkaline medium, we made use of an early observation[9] that porcine pancreatic lipase (PPL) under strictly neutral conditions hydrolyses the esters of (2*E*)-alkenoic acids much slower than their unconjugated $\Delta^3$ isomers. In fact, at the 80% conversion the PPL-catalysed hydrolysis of **1a** at pH 7.0 in 0.1 M phosphate buffer–DMF (1:1, v/v) afforded a specimen of the acid **1** of 99% geometrical purity (against the 96% gp of the ester **1a**), whereas the admixture of the less reactive **5a** accumulated in the unconverted material. The yield of **1** thus obtained was 15.5% over three steps of the synthesis (Scheme 2).

**3-Methyl-(3*Z*)-heptenoic acid (6).** The females of *Callosobruchus maculatus* (Bruchidae) produce compound **6** as one of the two components of their sex pheromone.[10] No details of the apparently non-selective synthesis of this acid were disclosed, except that **6** was isolated from a mixture of isomers obtained by conventional Reformatsky, Wittig and Horner–Emmons reactions.[10] Although *C. maculatus* is an important pest of dry beans and other stored legumes, we are not aware of any other synthesis of compound **6** ever since its identification.

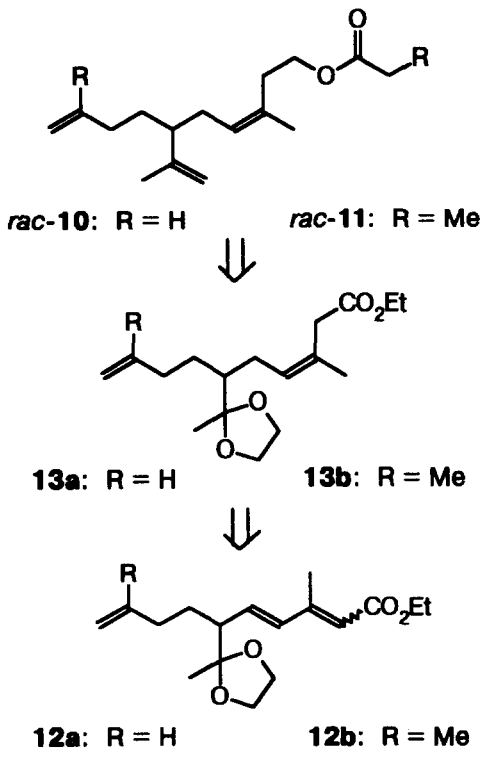
Our synthesis of **6** starts from propanal (**7**) and ethyl 4-(diethylphosphono)-3-methyl-2-butenoate (**8**). Their condensation under the conditions of phase transfer catalysis afforded ethyl 3-methyl-2,4-heptadienoate (**9**) as a mixture of (2*E*,4*E*) and (2*Z*,4*E*) isomers. Subsequent 1,4-*cis* hydrogenation of **9** over $Cr(CO)_6$ in hexane (180 °C, 80 atm) cleanly gave the olefinic ester **6a** of very high (99%) geometrical purity as the only low-molecular product. Unlike the case of **1a**, the trisubstituted double bond in **6a** did not migrate upon mild alkaline hydrolysis, whereas the ester group of **6a** was less reactive. As a result, the gp of **6** thus obtained was 99%, albeit at the expense of its chemical yield which was 11.4% over three steps (Scheme 3).

By comparing the syntheses of **1** and **6** one can notice that in the latter case the stereoselectivity of stage B is higher and so is the selectivity of alkaline hydrolysis of the resulting esters. This shows the potential of 1,4-*cis* hydrogenation of conjugated dienes of the type A for the synthesis of geometrically pure (*Z*)-trisubstituted olefins with a homoallylic pattern of functional substitution. Very recently[4] we proved the feasibility of this approach by synthesizing the sex pheromones of the Californian red scale (**10**) and white peach scale (**11**) via almost identical intermediates **12a,b** and **13a,b** obtained by the same protocol.



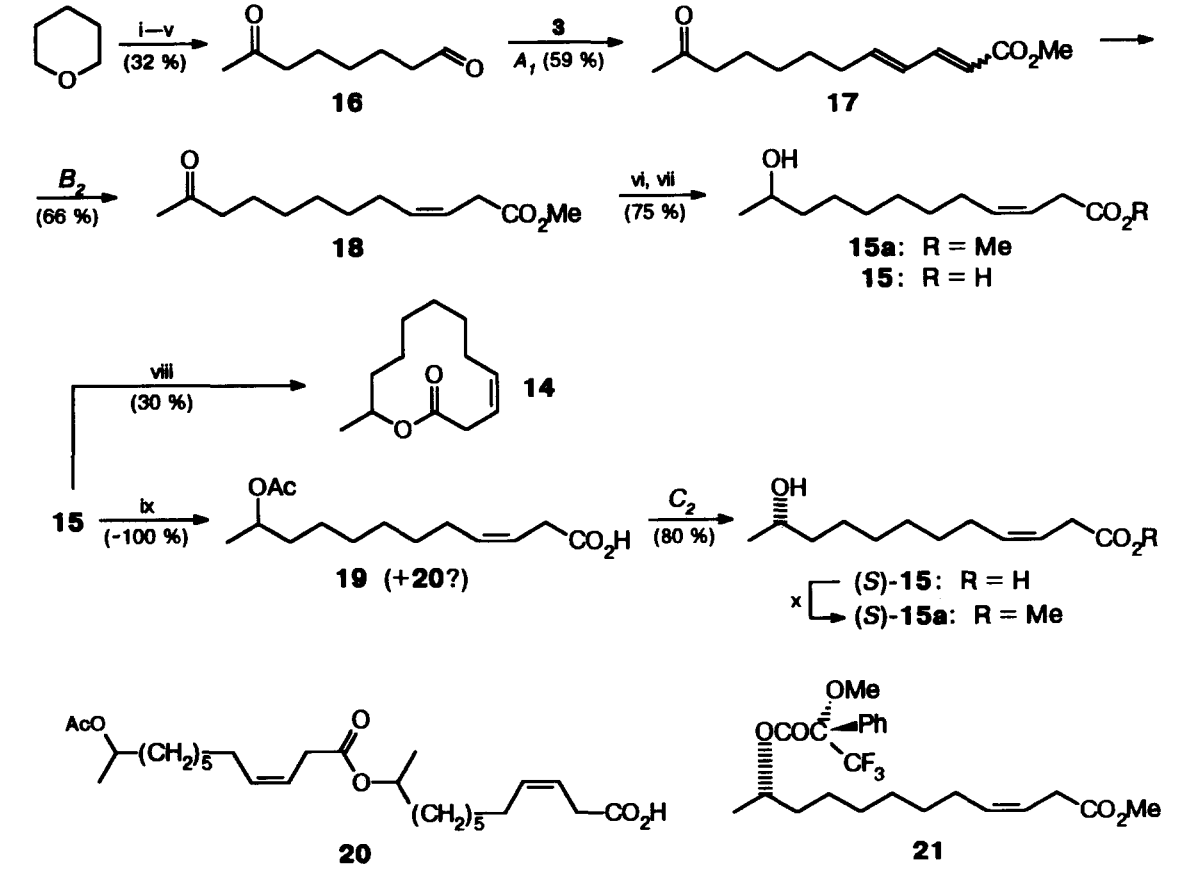

**Scheme 3.** Reagents: ($A_2$) KOH (2 equiv)/18-C-6 (0.1 equiv)/PhH, rt; ($B_1$) cf. Scheme 2; i. KOH/$H_2O$:MeOH (1:3, v/v), rt, then HCl aq.

***rac*-Ferrulactone II (14) and (3*Z*,11*S*)-11-hydroxy-3-dodenoic acid [(*S*)-15].** Two species of cucujid




grain beetles, *Cryptolestes ferrugineus* and *Orzaephilus mercator*, produce the (*S*) and (*R*) enantiomers of (3*Z*)-dodecen-11-olide (**14**), respectively, as obligatory components of their aggregation pheromone blends.[11] All syntheses of these lactones, whether in racemic or optically active form, converge on the formation of 11-hydroxy-(3*Z*)-dodecenoic acid (**15**), which is the nearest precursor of **14**; natural forms of the pheromones were prepared by employing either (*S*)-**15** or (*R*)-**15** instead of racemic **15**. Only two principal strategies were so far adopted for introducing the (*Z*)-disubstituted double bond into the molecule of **15**: partial *cis* hydrogenation of the C≡C bond in acetylenic intermediates[12] and stereoselective Wittig olefination of 8-(tetrahydropyranyloxy)nonanal with a masked or unprotected β-carboxyethylidenephosphorane[13] or else with a β,β-dialkoxyethylidenephosphorane[14] under the conditions favouring the formation of *cis*-olefins.

Our synthesis of the acid **15** started from tetrahydropyran (THP), which was converted into 7-oxooctanal (**16**) in five conventional steps in a 32% yield overall.[15] The condensation of **16** with phosphonate **2** afforded methyl 11-oxo-2,4-dodecadienoate (**17**) containing the (2*E*,4*E*) and (2*Z*,4*E*) isomers in the ratio 90:10. The hydrogenation of this diene over $(\eta^6\text{-PhCO}_2\text{Me})\text{Cr(CO)}_3$ in acetone (120 °C,



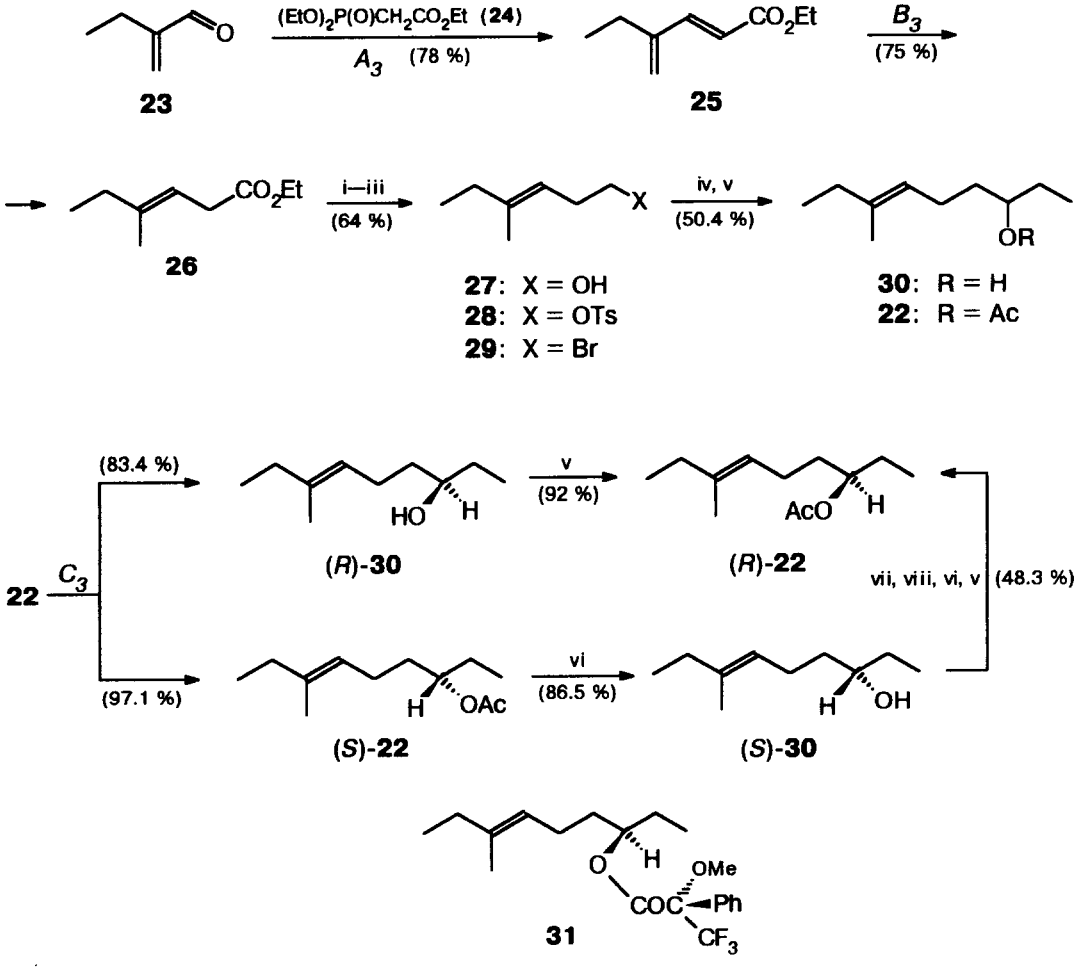

**Scheme 4.** Reagents: (i) AcCl–$ZnCl_2$, 100 °C; (ii) NaI/$Me_2CO$, 60 °C; (iii) $AcCH_2CO_2Et$, $K_2CO_3$–18-C-6/dioxane:$H_2O$ (~30:1, v/v), 70–80 °C; (iv) NaOH aq, rt, then $H_2SO_4$, Δ; (v) PCC–NaOAc/$CH_2Cl_2$, rt; ($A_1$) cf. Scheme 2; ($B_2$) $H_2$-$(\eta^6\text{-PhCO}_2\text{Me})\text{Cr(CO)}_3$/$Me_2CO$, 120 °C; (vi) $NaBH_4$/EtOH, rt; (vii) NaOH aq, rt; (viii) $(\alpha\text{-}C_5H_4NS)_2$–$PPh_3$/MeCN, then $AgClO_4$/*p*-xylene, 135 °C; (ix) $Ac_2O$–DMAP, rt; ($C_2$) PPL–$H_2O$ (pH 7), rt, 25% conversion; (x) $CH_2N_2$/$Et_2O$, rt.

80 atm) afforded the expected (*Z*)-olefine **18** of high geometrical purity (99% by GC and $^{13}C$ NMR). Subsequent reduction of this key intermediate with $NaBH_4$ gave the respective hydroxy ester (**15a**), which was hydrolysed in situ by careful addition of KOH to give the target hydroxy acid **15** in 75% yield (over two steps).[16] Lactonization of **15** according to the known procedure[12b] afforded racemic lactone **14**. The overall yield of **14** was 8.6% from the hydroxy aldehyde **16** (five steps, in four operations) or 2.7% from tetrahydropyran (Scheme 4).

Acetylation of **15** with $Ac_2O$–DMAP resulted in the respective acetoxy acid (**19**) contaminated with a practically inseparable admixture (ca. 15%) with almost the same $R_f$ on silica gel and very similar signals in the $^1H$ NMR spectrum of the mixture. Assuming this acidic admixture to be an enzymatically hydrolysable dimeric ester, such as **20**, we subjected the crude acetoxy acid **19** to the PPL-catalysed hydrolysis in 0.1 M phosphate buffer at pH 7.0. The hydrolysis was arrested at the 25% conversion with a view of achieving the kinetic resolution of the easily hydrolysable (11*S*) component of **19** and both its (11*R*) antipode and contaminant **20**. In fact, at this conversion depth the hydrolysis afforded the dextrorotatory (3*Z*,11*S*)-11-hydroxy-3-dodecenoic acid [(*S*)-**15**] of reasonable optical purity (ee 66–67%). This value of ee was found from the $[\alpha]_D$ of our specimen of (*S*)-**15** as well as from the $^1H$ and $^{19}F$ NMR spectra of the (*S*)-MTPA derivative **21** obtained from the respective specimen of methyl ester, (*S*)-**15a**. Since (*S*)-**15** is the ultimate intermediate in all the syntheses of the lactone (*S*)-**14** ('ferrulactone II'), our preparation of (*S*)-**15** represents a formal synthesis of (*S*)-**14** from the aldehyde **16** in ca. 1.5% yield.

**(3*R*,6*E*)-3-Acetoxy-7-methyl-6-nonene ('Quadrilure').** The 1,4-*cis* addition of $H_2$ to unconjugated dienes as a route to (*E*)-trisubstituted olefins has received little attention from synthetic organic chemists, although its effectiveness was clearly demonstrated in the stereocontrolled synthesis of juvenile hormone $C_{16}$ (JH III) by Yamamoto et al.[17] Our synthesis of quadrilure, the aggregation pheromone of the square-necked grain beetle *Cathartus quadricollis* (Bostrichidae), is yet another example of successful application of this reaction to the synthesis of (*E*)-trisubstituted olefins.

In previous syntheses of this pheromone, (*R*)-**22**, the required configuration of the double bond was asserted




**Scheme 5.** Reagents: ($A_3$) $K_2CO_3$ aq, rt; ($B_3$) $H_2$-($\eta^6$-$C_{10}H_8$)$Cr(CO)_3$/THF, 50 °C; (i) $LiAlH_4/Et_2O$; (ii) TsCl/Py; (iii) NaBr/DMF, 60 °C; (iv) Mg/THF (40 °C), then **7** (20 °C); (v) $Ac_2O$/Py, rt; ($C_3$) PPL–$H_2O$ (pH 6.8); rt, 50% conversion; (vi) KOH/MeOH, rt; (vii) MsCl–$NEt_3/CH_2Cl_2$, 0–5 °C; (viii) AcOK/DMF, 90–100 °C.

by various methods, such as the $S_N2'$ substitution of allylic acetates upon copper-catalysed cross-coupling,[18] stereospecific ring opening of cyclic vinyl ethers via an 2,3-alkyl shift in transient• organonickelates,[19] palladium-catalysed cross-coupling of organoboranes with (*E*)-trisubstituted vinyl bromides (prepared by stereocontrolled fragmentation of 1,2-dibromoalkanoic acids)[20] and the isolation of the (*E*)-trisubstituted olefinic precursor from its mixture with (*Z*) isomer by fractional crystallisation.[21] All of these ways involve rather tedious synthetic operations.

By contrast, the protocol based on the Horner–Emmons olefination/1,4-*cis* hydrogenation appears to be quite simple. The reaction of commercially available 2-ethylacrolein (**23**) with equally available triethyl phosphonoacetate (**24**) in a concd aq solution of $K_2CO_3$ took place easily to give ethyl 4-methylene-(2*E*)-hexenoate (**25**) in a good yield. This diene was hydrogenated over ($\eta^6$-naphthalene)$Cr(CO)_3$ in acetone at 45–50 °C and 70 atm, and the resulting olefinic ester **26** was converted into the homoallylic bromide **29** in three conventional operations via alcohol **27** and tosylate **28**. The Grignard reaction of bromide **29** with propanal and acetylation of the olefinic carbinol **30** afforded the racemic form of the pheromone (**22**) in 18.8% yield over seven steps (Scheme 5).[22] The geometrical purity of compounds **26**, **27** and **30**, assessed by GC, $^1H$ and $^{13}C$ NMR spectroscopy, was not less than 98%.

Partial hydrolysis of the racemic acetate **22** at pH 6.8 (0.1 M phosphate buffer, rt, conversion 50±2%) followed by column chromatography resulted in a clean separation of the levorotatory alcohol (*R*)-**30** ($[\alpha]_D$ −9.71°, in $CDCl_3$) from the slow-reacting (*S*)-**22**; the yields of (*R*)-**30** and (*S*)-**22** were 83.4 and 97.1%, respectively. Acetylation of (*R*)-**30** gave the pheromone (*R*)-**22** of satisfactory enantiomeric purity (ee 93–94%), as could be concluded from its specific rotation ($[\alpha]_D$ +8.92°, in $CHCl_3$) and the $^{19}F$ NMR spectrum of the (*S*)-MTPA ester of alcohol (*R*)-**30** (**31**). The overall yield of this specimen of (*R*)-**22** was 38.3%.

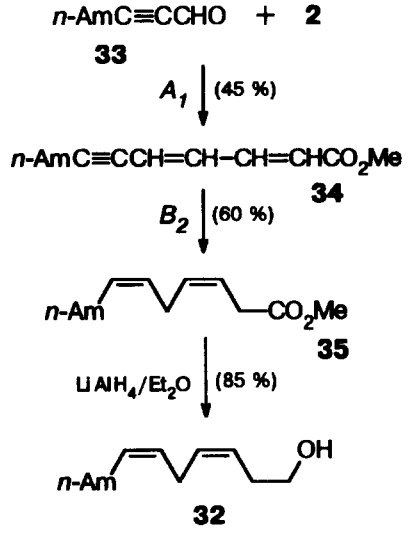
Saponification of the crude (*S*)-**22** recovered after partial enzymatic hydrolysis liberated the dextrorotatory alcohol (*S*)-**30**. This material was used for obtaining an additional crop of (*R*)-**22** by a four-step sequence (cf. ref 18) comprising an intermolecular $S_N2$ reaction (ROMs→ROAc) as the key step. In our hands, under recommended conditions the inversion reaction proceeded with moderate selectivity and resulted in a mixture of acetates [(*R*)-**22** > (*S*)-**22**] and respective formates with unidentified hydrocarbons. Chromatographically inseparable acetate/formate fraction was saponified to give a specimen of (*R*)-**30** with $[\alpha]_D$ −5.11°. A portion of it was transformed to the respective specimen of **31** which had, according to its NMR $^{19}F$ spectrum, only 50% optical purity. Acetylation of this specimen of (*R*)-**30** afforded a sample of (*R*)-**22** with $[\alpha]_D$ +4.78° (ee ca. 50%) in 20.2% yield over six steps from **22**.

Thus, the overall yield of the first crop of (*R*)-**22** with gp ≥ 98% and ee ≥ 93%) from the starting aldehyde **23** was 4.7% and that of the additional crop (gp ≥ 98% and ee ca. 50%) was 2.5%. Due to the operational simplicity of all the steps involved, this synthesis of the pheromone (*R*)-**22** may be useful for its large-scale preparation.

**(*Z*,*Z*)-3,6-Dodecadien-1-ol.** 'Skipped' (*Z*,*Z*)-disubstituted dienes are characteristic of certain families of *Lepidoptera* (Arctiidae, Geometridae), *Coleoptera* (Cucujidae) and *Isoptera* (Rhinotermitidae). With a view of apprising the applicability of our two-step protocol to the formation of such bond systems we synthesised (*Z*,*Z*)-3,6-dodecadien-1-ol (**32**), which is a potent trail-following pheromone mimic for *Reticulitermes virginicus* and other subterranean termites of this genus,[23] as well as a model compound for the study of lipoxy-catalysed lipid oxidation.[24,25]

Previously, dienol **32** was synthesised either by the copper-catalysed coupling of terminal alkynes with propargylic electrophiles followed by partial hydrogenation of resulting 1,4-diynes[26,27] or by the Wittig *cis*-olefination of alkanals with phosphoranes derived from (*Z*)-configurated homoallylic halides.[24–26] Since the isolated C≡C bonds are cleanly hydrogenated to (*Z*)-alkenes over ($\eta^6$-arene)$Cr(CO)_3$ complexes,[28] it seemed plausible that the skipped diene moiety of **32** could be formed upon the addition of two molecules of $H_2$ to the conjugated dienyne system, provided that the affinity of the triple bond towards such catalysts is weaker than that of the diene system and no migration of π-bonds occurs during the process.

In fact, the reaction of 2-octynal (**33**)[29] with phosphonocrotonate **2** gave, in a fair yield, the conjugated dienyne **34** (a 7:3 mixture of two stereoisomers), which was subjected to hydrogenation over ($\eta^6$-$PhCO_2Me$)$Cr(CO)_3$ in acetone to give the




**Scheme 6.** Reagents: ($A_1$) cf. Schemes 1 and 3; ($B_2$) cf. Scheme 1.

skipped (*Z*,*Z*)-diene **35** in 60% yield. The reduction of **35** with $LiAlH_4$ afforded the target dienol **32** in a

good yield. Both the chemical and geometrical purity of compounds **35** and **32** exceeded 98% (GC, $^1H$ and $^{13}C$ NMR data). Thus, starting from the easily accessible alkynal **33**, the pheromone mimic **32** was obtained just in three steps in 23.4% overall yield (Scheme 6). Presently we are not aware of successful application of 1,4-*cis* hydrogenation of conjugated dienynes to the synthesis of other skipped (*Z*,*Z*)-diolefins.

## Conclusion

The examples given here show that a combination of the Horner–Emmons synthesis of alkyl 2,4-dienoates with 1,4-*cis* hydrogenation over chromium carbonyl complexes is a flexible and operationally simple strategy for the stereocontrolled synthesis of olefinic insect pheromones and other unsaturated biomolecules. It appears that in many cases the disclosed protocol may be a method of choice for the large-scale preparation of configurationally pure alkenes.

## Experimental

### Methods and materials

All boiling points are uncorrected. GC analyses were performed with an LKhM-8 MD gas chromatograph equipped with a flame ionization detector and two 2000 × 3 mm glass columns packed with 5% Carbowax 20M or XE-60 on Chromaton N-AW-DMCS ($N_2$ as the carrier gas, 30 mL $min^{-1}$; injector temperature 225 °C, oven temperature 100–150 °C). $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker WM-250 instrument at 250 and 67.5 MHz, respectively. $^{19}F$ NMR spectra were obtained at 188.3 MHz in $CDCl_3$ (using $CFCl_3$ as the external reference) with a Bruker-200P instrument. Specific rotations were measured using a JASCO-DIP 360 polarimeter. Silicagel L (40–100 μm) was used for column chromatography.

Porcine pancreatic lipase (47.8 U $mg^{-1}$) was supplied by Olainpharm, Latvia, 2,2′-dipyridyl disulfide and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid were purchased from Fluka AG. Phosphonates **2** and **8** were prepared by a modified procedure of Gedye et al.[30] Aldehyde **33** was obtained according to the known procedure.[29] ($\eta^6$-Methyl benzoate)chromium tricarbonyl was prepared according to Mahaffy et al.,[31] ($\eta^6$-naphthalene)chromium tricarbonyl was obtained according to Rieke et al.[32]

**Methyl 2,4-decadienoate (3).** A solution of hexanal (1.2 mL, 10 mmol) and phosphonate **2** (2.36 g, 10 mmol) in abs THF (20 mL) was added dropwise during 10 min to a stirred suspension of $NaNH_2$ (0.41 g, 10.5 mmol) in THF (20 mL) at 5 °C. The mixture was stirred for 30 min at 5 °C and for additional 30 min at room temperature and then poured into the saturated aqueous solution of $NaHCO_3$ (100 mL). The product was extracted with benzene (4 × 15 mL), the extract was successively washed with water and brine, dried over $CaCl_2$ and concentrated under reduced pressure. The remainder was distilled to give the diene ester **3**, a colourless oil with bp 120–125 °C (10 torr) and $n_D^{20}$ 1.4928. Yield: 0.9 g (47%); (2*E*,4*E*):(2*Z*,4*E*) = 90:10. Spectral characteristics of the specimen thus obtained practically coincided with those reported earlier.[33]

**Methyl (3*Z*)-decenoate (1a).** The diene ester **3** (1.3 g) was dissolved in dry hexane (15 mL) and hydrogenated in a stainless steel autoclave (capacity 50 mL) in the presence of chromium hexacarbonyl (0.25 g, 16 mol %) at 180 °C and ca. 80 atm (initial pressure of $H_2$ 50 atm) during 3 h. The reaction mass was filtered and the filtrate was concentrated under reduced pressure. Subsequent distillation at 106 °C (10 torr) afforded crude olefinic ester **1a** as a colourless oil with $n_D^{20}$ 1.4429. Yield: 0.96 g. The comparison of the GC data with $^1H$ NMR spectrum of crude **1a** revealed the presence of (3*E*) isomer (**4a**) and (2*E*) isomer (**5a**) in the proportions **1a**:**4a**:**5a** 96:1:3. Hence, the yield of **1a** was 70%. $^{13}C$ NMR ($CDCl_3$): δ 14.2 (C-10), 22.7 (C-9), 27.4 (C-5), 29.0 (C-6), 29.4 (C-7), 41.6 (C-8), 32.7 (C-2), 51.6 (OMe), 120.9 (C-3), 133.4 (C-4).

**(3*Z*)-Decenoic acid (1).**

**Procedure A.** The ester **1a** of 96% purity (0.2 g) was added at room temperature to a stirred solution of KOH (0.3 g) in a mixture of water (0.3 mL) and MeOH (1.0 mL) and left to react for 20 min. The reaction mass was acidified to pH 2 with 1 M HCl and extracted with $Et_2O$ (4 × 2.5 mL), the combined extracts were washed with water and brine, dried over $MgSO_4$ and concentrated under reduced pressure to leave the acid **1** as a colourless oil. Yield: 0.14 g (78%). $^1H$ NMR spectrum of **1** practically coincided with previously reported data.[7] The ratio of isomeric acids in the specimen thus obtained (**1**:**4**:**5**) was 93:1:6.

**Procedure B.** The same specimen of the ester **1a** (0.16 g, ca. 0.8 mmol), PPL (0.2 g), 0.1 M phosphate buffer with pH 7.0 (0.5 mL) and freshly distilled DMF (0.5 mL) were mixed together and stirred for 16 h at room temperature; the pH was kept at 7.0 by continuous neutralization of the liberated acid with 0.25 M NaOH. When 2.70 mL of this solution was consumed (27 mg NaOH, 80% conversion of **1a**), the mixture was filtered through a pad of Celite, diluted with water and extracted with $Et_2O$ (3 × 5 mL) to remove the unconverted **1a**. The aqueous layer was acidified and extracted with $Et_2O$. Further work up was performed as described above (procedure A) to afford another specimen of the acid **1** which was 99% pure. Yield: 0.070 g (47%).

The ethereal extract upon evaporation in vacuo left an oily residue (0.025 g) in which the ratio of isomeric esters **1a**:**4a**:**5a** was ca. 62:10:28.

**Ethyl 3-methyl-2,4-heptadienoate (9).** The diene ester **9**, bp 133–136 °C (40 torr), $n_D^{20}$ 1.4900, was prepared from equimolar amounts of propanal (**7**) and phospho-

nate **8** according to an earlier procedure.[5a] Yield: 35%; (2*E*,4*E*):(2*Z*,4*E*) = 61:39 (GC and $^1$H NMR data). $^{13}$C NMR ($CDCl_3$) δ 13.0 (C-7), 14.1 ($OCH_2\underline{Me}$), 13.6 [C-3—Me, (2*E*,4*E*)-isomer] > 20.8 [C-3—Me, (2*Z*,4*E*)-isomer], 25.9 > 26.2 (C-6), 59.3 ($O\underline{C}H_2$), 115.8 < 117.6 (C-5), 126.8 < 132.7 (C-4), 138.5 > 140.1 (C-2), 151.0 < 152.4 (C-3), 166.2 < 167.0 (C-1).[34]

**Ethyl 3-methyl-(3*Z*)-heptenoate (6a).** The diene ester **9** (1.10 g) in hexane (8 mL) was hydrogenated in the presence of $Cr(CO)_6$ (0.25 g, 17 mol %) at 180 °C and 80 atm during 3 h. The reaction mass was worked up as described above for the preparation of **1a**. The oily residue was distilled from a short-path distillation flask to afford the ester **6a** of 99% purity (GC and $^1$H NMR data), bp 90–93 °C (15 torr). Yield: 0.67 g (60%). $^1$H NMR ($CDCl_3$) δ 0.89 (3H, t, *J* = 7.5 Hz), 1.22 (3H, t, *J* = 7.0 Hz), 1.36 (2H, d t, *J* = 7.5 Hz, 6-$H_2$), 1.75 (3H, s, 3-Me), 1.99 (2H, br q, *J* = 7.0 Hz, 5-$H_2$), 3.01 (2H, s, 2-$H_2$), 4.21 (2H, q, *J* = 7.0 Hz, $OCH_2$), 5.34 (1H, m, 4-H).

**3-Methyl-(3*Z*)-heptenoic acid (6).** To a solution of KOH (0.2 g, 3.5 mmol) in MeOH–$H_2O$ (4 mL, 3:1, v/v) the ester **6a** (0.51 g, 3 mmol) was added and the mixture was stirred at room temperature for 2 h, diluted with water (5 mL) and extracted with $Et_2O$ (3 × 3 mL). The aqueous layer was acidified with 1 M HCl to pH 2 and reextracted with $Et_2O$ (4 × 3 mL). This ethereal extract was dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue was distilled in vacuo to give the acid **6** of 99% purity ($^1$H NMR data), bp 120–122 °C (20 torr). $^1$H NMR ($CDCl_3$) δ 0.89 (3H, t, *J* = 7.5 Hz, 7-$H_3$), 1.35 (2H, d t, *J* = 7.5 Hz, 6-$H_2$), 1.78 (3H, s, 3-Me), 2.0 (2H, br q, *J* = 7.0 Hz, 5-$H_2$), 3.08 (2H, s, 2-$H_2$), 5.38 (1H, br t, *J* = 7.0 Hz, 4-$H_2$), 10.45 (1H, br s, $CO_2H$).

**7-Oxooctanal (16).**

**1-Acetoxy-5-chloropentane.** Vacuum-dried anhydrous $ZnCl_2$ (8.0 g, 60 mmol) was mixed with anhydrous tetrahydropyran (56.5 g, 0.66 mol) at 0–5 °C and freshly distilled acetyl chloride (47.1 g, 0.60 mol) was added in several portions to the mixture at such a pace as to keep the reaction temperature below 25–30 °C. Then the reaction mixture was heated for 1 h on the water bath, cooled to 20–25 °C, diluted with benzene (100 mL), and washed with water (100 mL) and saturated aqueous $NaHCO_3$ solution. The organic layer was dried with $CaCl_2$ and concentrated under reduced pressure. Distillation of the oily residue gave 1-acetoxy-5-chloropentane, bp 102–105 °C (15 torr). Yield: 78.3 g (82%).

**1-Hydroxyoctan-7-one.** 1-Acetoxy-5-chloropentane (55 g, 0.37 mol) and vacuum-dried NaI (110 g, 0.73 mol) were dissolved in 500 mL of freshly dried anhydrous acetone and the mixture was stirred and refluxed for 48 h; by this time the conversion of the starting chloride was ca. 95% (GC data). The precipitated NaCl was removed by filtration and washed with cold anhydrous $Me_2CO$, the filtrate and washings were combined and concentrated under reduced pressure and the concentrate was diluted with anhydrous dioxane (300 mL) to precipitate the excess NaI. The filtrate, which contained mainly the intermediate 1-acetoxy-5-iodopentane, was mixed with ethyl acetoacetate (55 g, 0.42 mol), anhydrous $K_2CO_3$ (120 g, 0.9 mol), 18-crown-6 (1.5 g) and water (10 mL). This mixture was stirred for 2 h at 75–80 °C until the disappearance of the iodide from the thickening reaction mass (GC control) and filtered warm. The solid inorganic precipitate was dissolved in water to liberate upon dissolution a little oil which was added to the filtrate. The combined organic solution was concentrated in vacuo and the residue was stirred for 40 min with aqueous NaOH (50 g in 450 mL of water) at 20–25 °C. Then concentrated $H_2SO_4$ (*d* = 1.86, 70 g) in water (70 mL) was added dropwise to the alkaline hydrolysate and the mixture was refluxed until after the evolution of $CO_2$ had ceased (ca. 2.5 h). After cooling, the reaction medium was made alkaline with solid $Na_2CO_3$ and extracted with $Et_2O$ (4 × 75 mL). The extract was washed with water and brine, dried with $MgSO_4$ and evaporated. The oily residue was distilled to give pure 1-hydroxyoctan-7-one, bp 115–117 °C (3 torr) or 150–153 °C (15 torr), $n_D^{20}$ 1.5589. Yield: 29 g (60% overall from 1-acetoxy-5-chloropentane).

**The oxidation of 1-hydroxyoctan-7-one.** To a stirred suspension of pyridinium chlorochromate (8 g, 37 mmol) and anhydrous NaOAc (1.2 g) in dry $CH_2Cl_2$ (50 mL) a solution of the title ketol (3.6 g, 25 mmol) in $CH_2Cl_2$ (10 mL) was added at room temperature under the atmosphere of argon and the stirring was continued for 3 h. The reaction mixture was diluted with $Et_2O$ (100 mL), the organic supernatant was decanted from the solidified inorganic residue and filtered through a small pad of silica gel (ca. 5 g). The filtrate and ethereal washings were combined and evaporated, and the remainder was distilled under reduced pressure to give the pure keto aldehyde **16**, bp 105–108 °C (10 torr), $n_D^{17}$ 1.4419. Yield: 2.3 g (65%). The value of $n_D^{20}$ (1.4405) and $^1$H NMR spectrum [δ 2.10 (3H, s) and 9.85 (1H, t)] were compatible with the previously reported data (cf. ref 35).

**Methyl 11-oxo-2,4-dodecadienoate (17).** The keto aldehyde **16** (1.60 g, 11.2 mmol) and phosphonate **2** (2.70 g, 11.3 mmol) were dissolved together in 20 mL of abs THF and added at 0–5 °C to a stirred suspension of $NaNH_2$ (4.56 g, 11.7 mmol) in THF (20 mL) over 30 min. The stirring was continued for 30 min at this temperature and then for 1 h at 20–22 °C. The reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ and extracted with $Et_3O$ (4 × 25 mL). The combined extracts were dried over $CaCl_2$ and evaporated to leave an oily residue which was fractionated in vacuo to afford the diene keto ester **17**, bp 150–155 °C (4 torr). Yield: 1.50 g (59%); (2*E*,4*E*):(2*Z*,4*E*) 90:10 (GC and $^1$H NMR data). $^{13}$C NMR ($CDCl_3$) δ 23.2 (C-9), 28.21 and 28.38 (C-8 and C-7), 29.6 (C-12), 32.5 (C-6), 43.2 (C-10), 51.1 (OMe),

118.6 (C-2), 128.3 (C-4), 144.2 (C-5), 145.0 (C-3), 167.3 (C-1), 208.6 (C-11).

**Methyl 11-oxo-(3Z)-dodecenoate (18).** The diene keto ester **17** (1.5 g), degassed, peroxide-free anhydrous acetone (9 mL) and ($\eta^6$-$PhCO_2Me$)$Cr(CO)_3$ (0.25 g, 14 mol%) were loaded, under an atmosphere of argon, into the carefully dried stainless steel autoclave which was afterwards closed and filled three times with $H_2$ (up to 10 atm $H_2$). Then $H_2$ (initial pressure 60 atm) was delivered and the process was carried out at 120–125 °C and ca. 80 atm over 2 h. Acetone was distilled from the reaction product under reduced pressure, the residue was taken into 20 mL of dry benzene and passed through a pad of silica gel (ca. 3 g) in order to remove the green-coloured products of the catalyst decomposition. Evaporation of the eluate followed by the vacuum distillation gave the required (3Z)-olefin **18** of 99% geometrical purity (GC and $^1$H NMR data), bp 120–125 °C (3 torr). Yield: 1.0 g (66%). $^{13}$C NMR ($CDCl_3$) δ 23.8 (C-9), 27.65 (C-5), 29.0, 29.1, 29.2 (C-8, C-7, C-6), 29.8 (C-12), 32.8 (C-2), 43.7 (C-10), 51.7 (OMe), 121.0 (C-3), 133.4 (C-4), 177.3 (C-1), 208.1 (C-11).

***rac*-11-Hydroxy-(3Z)-dodecenoic acid (15).** The keto ester **18** (1.0 g, 4.4 mmol), was dissolved in 50% aqueous EtOH (6 mL) and reduced with $NaBH_4$ (0.20 g, 5.3 mmol) added portionwise during 1 h under stirring; by that time **18** was fully consumed (GC data). Without being isolated, the intermediate *rac*-methyl 11-hydroxy-(3Z)-dodecenoate (**15a**) was treated with KOH (0.3 g, 5.3 mmol) in water (2 mL), and stirring was continued for 30 min at room temperature. The reaction medium was diluted with water (6 mL), extracted with $Et_2O$ to remove neutral impurities and carefully acidified to pH 2.0 with diluted HCl to avoid the foaming. The acidic broth was extracted with $Et_2O$ (5 × 3 mL), the combined extracts were washed with brine, dried with $MgSO_4$ and evaporated to leave the crude hydroxy acid **15** as a colourless oil with $n_D^{20}$ 1.4630. According to its $^1$H NMR spectrum, which was identical to those published earlier,[12c,e,g,14] this product was practically pure and, therefore, it was used in the next step without further purification. Yield: 0.70 g (75% overall from **18**). IR (film), ν: 3390 s, 3020, 2935, 2860, 1722 s, 1465, 1375, 1265, 1100, 1035, 880, 805 cm$^{-1}$. $^{13}$C NMR ($CDCl_3$) δ 23.5 (C-12), 25.7 (C-5), 27.3 (C-9), 27.6, 29.5 (C-6, C-8), 30.2 (C-7), 38.5 (C-2), 42.6 (C-10), 68.1 (C-11), 118.7 (C-4), 135.0 (C-3), 185.3 (C-1).

***rac*-(3Z)-Dodecen-11-olide (14).** The hydroxy acid **15** (0.43 g, 2 mmol), 2,2′-dipyridyl disulfide (0.88 g, 4 mmol) and $PPh_3$ (1.05 g, 4 mmol) were dissolved together in absolute acetonitrile (20 mL) and stirred at 20–25 °C for 2 h under the atmosphere of argon. The mixture was diluted with absolute *p*-xylene (100 mL) and added dropwise over 6 h (under argon) to the boiling mixture of freshly prepared dry $AgClO_4$ (2.08 g, 10 mmol) with 200 mL of *p*-xylene. The reaction mass was refluxed for additional 6 h, cooled and filtered through a short column of silica gel (5 g). The filtrate was concentrated under reduced pressure and the viscous residue was distilled in a quick-distillation/sample collection tube at 130–170 °C (bath temperature) and 20 torr. The distillate was chromatographed on a column filled with 6 g of $SiO_2$ using the hexane–$Et_2O$ gradient system (100:0→90:10) as the eluent to afford the racemic lactone **14**, a colourless oil with $n_D^{20}$ 1.4785. This specimen was about 99% pure (GC and $^1$H NMR data). Yield: 118 mg (30%). $^{13}$C NMR ($CDCl_3$) δ 19.6 (C-12), 23.9–29.2 (C-5, C-9, C-6, C-8, C-7), 36.2 (C-2), 40.1 (C-10), 73.1 (C-11), 121.5 (C-4), 135.0 (C-3), 173.0 (C-1).

**(3Z,11*S*)-11-Hydroxy-3-dodecenoic acid [(*S*)-15].**

***rac*-11-Acetoxy-(3Z)-dodecenoic acid (19).** Racemic hydroxy acid **15** (0.21 g), acetic anhydride (2 mL), dry pyridine (0.5 mL) and 4-dimethylaminopyridine (50 mg) were mixed together and left overnight at room temperature. The excess $Ac_2O$ was removed under reduced pressure. The remainder was dissolved in $Et_2O$ (10 mL) and the solution was successively washed with water (3 × 3 mL), 10% aqueous $CuSO_4$ (acidified to pH 3 with 1 N $H_2SO_4$) and brine, dried with $MgSO_4$ and evaporated at 45–50 °C (25 torr). The residue was chromatographed on a column with 6 g of silica gel. Elution with hexane:AcOEt (3:1, v/v) gave a colourless oil, which consisted of the acetoxy acid **19** (ca. 95% by $^1$H NMR) contaminated with an admixture which upon TLC analysis on the Silufol plates had practically the same $R_f$ values as **19** in several solvent systems (two overlapping spots, $\Delta R_f$ ca. 0.05). IR (film) ν: 3400–3290 s, 3030, 2940, 1745 s, 1712 s, 1460, 1375, 1245 s, 1105, 1040, 880, 800 cm$^{-1}$. Yield: 0.26 g (ca. 100%). $^1$H NMR ($CDCl_3$) δ 1.18 (3H, d, $J$ = 7 Hz, 12-$H_3$), 1.25–1.62 (10H, m, 6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 1.89 (2H, m, 5-$H_2$), 2.01 (3H, s, OCOMe), 3.21 (2H, d, $J$ = 7 Hz, 2-$H_2$), 4.96 (1H, m, 11-H), 5.44–5.76 (2H, m, 3-H and 4-H), 10.4 (1H, br s, COOH). Signals attributable to the tentative structure **20** were also observed at δ 1.15 (d), 2.04 (s), 3.16 (d), 3.24 (m), 5.01 (m) with integral intensities of ca. 10–15% of those of the respective main signals, but none at δ larger than 6 ppm.

**Enzymatic hydrolysis of the acetate 19.** Crude racemic acetate **19** (0.2 g, ca. 0.78 mmol) and PPL (0.15 g) were dispersed in 6 mL of 0.1 M phosphate buffer (pH 7.0) by vigorous stirring. After 48 h of stirring at room temperature and pH 7.0 (maintained by gradual addition of 1 M NaOH), the reaction mass was decanted from the bulk of PPL, the supernatant was filtered through a small pad of Celite, acidified to pH 3.0 with 1 M HCl and extracted with $Et_2O$ (3 × 10 mL). The extract was washed with brine (3 × 5 mL), dried with $MgSO_4$ and evaporated. The oily residue (0.19 g) was chromatographed on a column with 6 g of $SiO_2$ using $CHCl_3$ and $CHCl_3$:MeOH (99:1, v/v) as eluents to give first the unconverted acetate (150 mg) and then the target hydroxy acid, (*S*)-**15**, as a clean, chromatographically pure oil with $n_D^{22}$ 1.4632 and $[\alpha]_D^{22}$ +7.33° (*c* 0.5, $CHCl_3$). Yield: 33.5 mg (80.1% at

25% conversion) [lit.: $[\alpha]_D + 5.8°$ for a specimen of less than 88% ee[12f] or $[\alpha]_D + 11.5°$ for a specimen containing ca. 15% of the (2*E*) isomer,[13b] both in $CHCl_3$].

**Determination of optical purity of (*S*)-15.** The acid (*S*)-**15** (20 mg) was dissolved in MeOH (0.2 mL) and titrated with freshly distilled ethereal solution of $CH_2N_2$ until the persistent light-yellow colouration. The solvents were evaporated to leave the chromatographically pure methyl ester (*S*)-**15a** as a colourless oil. Yield: 21 mg (100%). This amount (0.09 mmol) was dissolved in $CCl_4$ (30 μL) and transformed into the (*S*)-MTPA derivative of (*S*)-**15a** according to the reported procedure,[36b] the work up being performed according to a later modification.[37] The resulting ester (**21**) was isolated as a colourless, chromatographically pure gum. $^1$H NMR ($CDCl_3$) δ: 1.18 (3H, d, $J$ = 7 Hz), 1.25–1.68 (10H, m, 6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 1.89–2.12 (2H, m, 5-$H_2$), 3.07 (2H, d, $J$ = 5.2 Hz, 2-$H_2$), 3.49 (3H, s, C*—OMe), 3.61 (3H, s, $CO_2$Me), 4.98 (1H, m, 11-H), 5.44–5.51 (2H, m, 3-H and 4-H), 7.25–7.45 (5H, m, Ph). $^{19}$F NMR ($CDCl_3$) δ 70.649 [(*R*,*S*)-diastereomer], 70.629 [(*S*,*S*)-diastereomer]. From the ratio of peak areas in the $^{19}$F NMR spectrum ($\sigma_{RS}:\sigma_{SS}$ = 17:83) the enantiomeric purity of the methyl ester (*S*)-**15a**, and hence of the acid (*S*)-**15**, was estimated to be 66%; this is compatible with the ratio of $[\alpha]_D$ values found for (*S*)-**15** in this (+7.33°) and an earlier work (+11.4°).[12d]

**Ethyl 4-methylene-(2*E*)-hexenoate (25).** A mixture of triethyl phosphonoacetate **24** (16.2 g, 0.072 mol), $K_2CO_3$ (17.2 g, 0.117 mol) and water (12 mL) with 2-ethylacrolein **23** (5.1 g, 0.061 mol) was stirred at room temperature for 10 h and then worked up according to the relevant procedure.[38] The ethereal extract was dried with $CaCl_2$ and evaporated. The residue was fractionated in vacuo to give the diene **25** as a colourless oil with bp 85–86 °C (10 torr) and $n_D^{20}$ 1.4818. Yield: 7.3 g (78%). $^1$H NMR ($CDCl_3$) δ 0.98 (3H, t, $J$ = 7.5 Hz, 6-$H_3$), 1.19 (3H, t, $J$ = 7.2 Hz, $OCH_2$Me), 2.23 (2H, br q, $J$ = 7.5 Hz, 5-$H_2$), 4.20 (2H, q, $J$ = 7.2 Hz, $OCH_2$Me), 5.30 (1H, br s, =$CH_2$), 5.34 (1H, br s, =$CH_2$), 5.90 (1H, d, $J$ = 15.5 Hz, 2-H), 7.30 (1H, d, $J$ = 15.5 Hz, 3-H).

**Ethyl 4-methyl-(3*E*)-hexenoate (26).** A stainless steel autoclave (50 mL) was loaded under argon with the diene **25** (4.3 g) and ($\eta^6$-naphthalene)chromium tricarbonyl (0.4 g, 5.6 mol %) in degassed, peroxide-free THF (8 mL). The autoclave was closed and filled three times with $H_2$ (up to 10 atm). Then dry $H_2$ was delivered at 70 atm and the process was carried out at 45–50 °C over 3 h. The reaction mass was concentrated under reduced pressure and the residue was submitted to vacuum distillation to afford the olefinic ester **26** as a colourless oil with bp 84–85 °C (20 torr) and $n_D^{20}$ 1.4381. Yield: 3.2 g (75%). $^1$H NMR ($CDCl_3$) δ 0.98 (3H, t, $J$ = 7.5 Hz, 6-$H_3$), 1.23 (3H, t, $J$ = 7.2 Hz, $OCH_2$Me), 1.62 (3H, br s, 4-Me), 2.04 (2H, br q, $J$ = 7.5 Hz, 5-$H_2$), 3.03 (2H, br d, $J$ = 7.0 Hz, 2-$H_2$), 4.11 (2H, q, $J$ = 7.2 Hz, $OCH_2$Me), 5.30 (1H, t m, $J$ = 7.0 Hz, $J'$ ca. 1 Hz, 3-H). $^{13}$C NMR ($CDCl_3$) δ 12.4 (C-6), 14.1 ($OCH_2$Me), 16.1 (4-Me), 32.14 (C-5), 33.6 (C-2), 60.3 ($OCH_2$), 114.5 (C-3), 140.6 (C-4), 172.4 (C-1).

**4-Methyl-(3*E*)-hexen-1-ol (27).** To a stirred suspension of $LiAlH_4$ (0.76 g, 20 mmol) in $Et_2O$ (10 mL) a solution of the ester **26** (3.12 g, 20 mmol) in $Et_2O$ (7 mL) was added under argon. After 3 h of stirring at 20–25 °C the reaction mixture was refluxed for 30 min, then cooled and carefully quenched with 1 M HCl. The organic layer was separated, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Vacuum distillation of the residue gave the homoallylic alcohol **27** as a colourless oil, bp 74–78 °C (30 torr), $n_D^{20}$ 1.4529. Yield: 1.94 g (85%). $^1$H NMR ($CDCl_3$) δ 0.98 (3H, t, $J$ = 7.5 Hz, 6-$H_3$), 1.62 (3H, s, 4-Me), 2.02 (2H, br q, $J$ = 7.5 Hz, 5-$H_2$), 2.10 (1H, br s, OH), 2.25 (2H, d t, $J$ = 6.8 Hz, $J'$ = 7.0 Hz, 2-$H_2$), 3.60 (2H, t, $J$ = 6.8 Hz, 1-$H_2$), 5.10 (1H, m, $J$ = 7.0 Hz, $J'$ ca. 1 Hz, 3-H). $^{13}$C NMR ($CDCl_3$) δ 12.6 (C-6), 16.0 (4-Me), 31.4 (C-2), 32.4 (C-5), 62.3 (C-1), 118.4 (C-3), 140.1 (C-4).

**1-Bromo-4-methyl-(3*E*)-hexene (29).** *p*-Toluenesulfonyl chloride (6.0 g, 31 mmol) was added portionwise during 30 min to a chilled (−10 °C) and agitated solution of alkenol **27** (2.4 g, 21 mmol) and pyridine (3.5 g) in $CHCl_3$ (20 mL), and the reaction mixture was left overnight at 0 °C. Methanol (2 mL) was added to destroy the excess of TsCl and after a short exposure (30 min) the mixture was poured into ice-cold water. The non-ionic products were extracted with $Et_2O$ (3 × 15 mL), the extract was washed with 1.5 M HCl (2 × 15 mL) and saturated aqueous $NaHCO_3$, dried with $MgSO_4$ and concentrated. The crude tosylate **28** contaminated with TsOMe (TLC and $^1$H NMR data) was dissolved in DMF (30 mL) and stirred at 50–60 °C for 3 h with powdered NaBr (12 g, 116 mmol). The reaction mixture was diluted with water (50 mL) and extracted with hexane (5 × 20 mL). The extract was dried over $CaCl_2$ and the volatiles were removed under atmospheric pressure by distilling them through a small Vigreux column. The residue was fractionated in vacuo to afford practically pure bromide **29** as a colourless oil with bp 107–108 °C (100 torr) and $n_D^{20}$ 1.4770. Yield: 2.80 g (75.2%). $^1$H NMR ($CDCl_3$) δ 1.00 (3H, t, $J$ = 7.5 Hz, 6-$H_3$), 1.64 (3H, s, 4-Me), 2.03 (2H, br q, $J$ = 7.5 Hz, 5-$H_2$), 2.57 (2H, d t, $J$ = 6.8 Hz, $J'$ = 7.0 Hz, 2-$H_2$), 3.34 (2H, t, $J$ = 6.8 Hz, 1-$H_2$), 5.12 (1H, m, $J$ = 7.0 Hz, 3-H).

***rac*-7-Methyl-(6*E*)-nonen-3-ol (30).** Magnesium turnings (0.81 g) in THF (17 mL) were activated by adding $CH_3I$ (0.2 mL) and a portion of the bromide **31** (0.5 g) and stirring the mixture at 35–40 °C. When the reaction had started, the rest of bromide **29** (2.1 g, 14.6 mmol in all) was added within 20 min while the temperature was maintained at 35–40 °C. The stirring was continued for additional 30 min at 40 °C in order to complete the formation of the Grignard reagent. Then freshly distilled propanal **7** (0.8 g, 13.8 mmol)

was added dropwise at ca. 20 °C and the mixture was stirred for 1.5 h. The reaction was quenched with saturated aqueous $NH_4Cl$ and the product was extracted with $Et_2O$ (5 × 10 mL). The extract was dried with $MgSO_4$, the solvents were distilled under reduced pressure through a small Vigreux column and the residue was fractionated in vacuo to give the alcohol **30** as a colourless oil, bp 98–101 °C (15 torr), $n_D^{20}$ 1.4550. Yield: 1.40 g (56%) [lit.[20] bp 99–102 °C (18 torr), $n_D^{21}$ 1.4489]. $^1H$ NMR ($CDCl_3$) δ 0.93 (3H, t, $J$ = 7.3 Hz, 1-$H_3$), 0.97 (3H, t, $J$ = 7.3 Hz, 9-$H_3$), 1.42–1.54 (4H, m, 2-$H_2$ and 4-$H_2$), 1.62 (3H, br s, 7-Me), 1.70 (1H, br s, OH), 1.98 (2H, br q, $J$ = 7.3 Hz, 8-$H_2$), 2.13 (2H, m, 5-$H_2$), 3.53 (1H, m, 3-H), 5.13 (1H, t q, $J$ = 7.1 Hz, $J'$ = 1.5 Hz, 6-H). $^{13}C$ NMR ($CDCl_3$) δ 9.74 (C-1), 12.60 (C-9), 15.7 (7-Me), 24.15 (C-5), 30.1 (C-2), 32.26 (C-8), 36.8 (C-4), 72.9 (C-3), 122.7 (C-6), 137.29 (C-7).

***rac*-3-Acetoxy-7-methyl-(6*E*)-nonene (22).** A mixture of alcohol **30** (1.40 g, 9 mmol), pyridine (2 mL) and acetic anhydride (2.05 g, 20 mmol) was left overnight at 20–25 °C and worked up according to an earlier procedure.[18] The product, a colourless oil with bp 55–57 °C (12 torr) and $n_D^{20}$ 1.4330, was not less than 98% pure (GC and $^1H$ NMR data). Yield: 1.60 g (90%). All spectral characteristics of this product practically coincided with those reported earlier[18,19] for compound **22**. $^{13}C$ NMR ($CDCl_3$) δ 9.6 (C-1), 12.75 (C-9), 15.9 (7-Me), 21.45 (COMe), 24.1 (C-5), 28.0 (C-2), 32.95 (C-8), 75.3 (C-3), 122.3 (C-6), 137.4 (C-7), 180.2 (—O—C=O).

**(3*R*,6*E*)-7-Methyl-6-hexen-3-ol [(*R*)-30].**

**Enzymatic hydrolysis of the acetate 22.** The racemic acetate **22** (1.39 g, 7 mmol) was dispersed in 10 mL of 0.1 M phosphate buffer (pH 6.8) by vigorous magnetic stirring, powdered PPL (0.70 g) was added to the emulsion, and the stirring was continued for 35 h at room temperature (20–25 °C). During this period the pH was maintained at 6.8–7.0 by gradual addition of 1 M NaOH. When the ratio between the product and unconverted acetate was ca. 36:64 (GC and TLC control), the reaction practically stopped. After further 24 h of incubation a new portion of PPL (0.35 g) was added to accelerate the hydrolysis. As a result, in the next 10 h the conversion of the substrate attained 50±2% (GC and column chromatography data). The reaction mass was filtered through a column of Celite (5 g), the filtrate was extracted with hexane (4 × 5 mL), the tarry deposit on the column was also washed with hexane, the extract and washings were combined, dried with $MgSO_4$ and evaporated under reduced pressure. The oily residue (1.26 g) was chromatographed on a column with 40 g of silica gel. Elution with hexane:$Et_2O$ (9:1, v/v) afforded the slow-reacting fraction of the starting acetate, i.e. (*S*)-**22** (0.680 g, yield 97.1%). Subsequent elution with hexane:$Et_2O$ (1:1, v/v) gave the alcohol (*R*)-**30** as a colourless oil with $n_D^{20}$ 1.4492 and $[\alpha]_D^{20}$ −9.71° (*c* 1.02, in $CHCl_3$) [lit.[20] $n_D^{21}$ 1.4489 and $[\alpha]_D^{21}$ −10.8° (*c* 0.3, in $CHCl_3$)]. Yield: 0.460 g (83.4%). IR, $^1H$ and $^{13}C$ NMR spectra of this specimen were almost identical to those of the racemic alcohol **30**.

**Determination of optical purity of (*R*)-30.** The alcohol (*R*)-**30** (15.6 mg, 0.12 mmol) was dissolved in $CCl_4$ (30 μL) and transformed into its (*S*)-MTPA derivative according to the reported procedure.[36] Subsequent work up was performed according to a later modification[37] to afford the respective ester **31** as a colourless, chromatographically pure gum. $^1H$ NMR ($CDCl_3$) δ 0.93 (3H, t, $J$ = 7.3 Hz, 1-$H_3$), 0.975 (3H, t, $J$ = 7.3 Hz, 9-$H_3$), 1.43–1.53 (4H, m, 2-$H_2$ and 4-$H_2$), 1.62 (3H, s, 7-Me), 1.98 (2H, m, 8-$H_2$), 2.13 (2H, m, 5-$H_2$), 3.56 (3H, s, C*—OMe), 5.14 (2H, m, 6-H), 7.38–7.62 (5H, m, Ph). $^{19}F$ NMR ($CDCl_3$) δ 71.223 [(*R*,*S*)-diastereomer], 71.513 [(*S*,*S*)-diastereomer]. From the ratio of peak areas in the $^{19}F$ NMR spectrum ($\sigma_{RS}$:$\sigma_{SS}$ = 96.5:3.5) enantiomeric purity of (*R*)-**30** was found to be 93%; this is compatible with the ratio of $[\alpha]_D$ values found for (*R*)-**30** in this (−9.71°) and an earlier work (−10.8° or +10.4° for the two antipodes of assumingly 100% enantiomeric purity).[20]

**(3*R*,6*E*)-3-Acetoxy-7-methyl-6-nonene [(*R*)-22].**

**Specimen I.** Alcohol (*R*)-**30** obtained as disclosed above (312 mg, 2 mmol) was acetylated exactly as in the case of racemic alcohol **30**. The resulted acetate (*R*)-**22**, a colourless oil with $n_D^{20}$ 1.4332 and $[\alpha]_D^{20}$ +8.92° (*c* 1.00, in $CHCl_3$), had the same spectral characteristics as compound **22** [lit.[20] $[\alpha]_D^{20}$ +9.59° (*c* 1.09, in $CHCl_3$), $n_D^{21}$ 1.4331]. Yield: 364 mg (92%).

**Specimen II.** This specimen [$n_D^{20}$ 1.4330, $[\alpha]_D^{20}$ +4.78° (*c* 0.65, in $CHCl_3$)] was obtained from the crude acetate (*S*)-**22**, i.e. from the acetate fraction recovered after the partial enzymatic hydrolysis of **22**. This transformation comprised the following operations:

(1) To a stirred solution of KOH (168 mg, 2.5 mmol) in MeOH (5 mL) crude (*S*)-**22** (0.40 g, ca. 2.04 mmol) was added. After 6 h of stirring at room temperature the mixture was cooled to 0–5 °C, neutralized with AcOH and concentrated under reduced pressure. The remainder was agitated with 15 mL of water and extracted with $Et_2O$ (5 × 10 mL). The extract was dried over $MgSO_4$ and evaporated to leave an oil (0.32 g), which was chromatographed on a column with silica gel (15 g). Elution with hexane:$Et_2O$ (3:1, v/v) afforded chromatographically pure (GC, TLC) alcohol (*S*)-**30**. Yield: 270 mg (86.5%).

(2) Alcohol (*S*)-**30** (270 mg, 1.73 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and treated with mesyl chloride (0.3 mL, 4 mmol) and $NEt_3$ (0.7 mL, 5 mmol) at +5 °C. After 30 min of stirring at this temperature the reaction mixture was quenched with 5 mL of ice-cold water and extracted with $Et_2O$ (5 × 5 mL). The combined organic phase was washed with water, dried with $MgSO_4$ and evaporated under reduced pressure to afford crude (3*R*,6*E*)-7-methyl-3-methylsulfonyloxy-6-nonene as a colourless oil. Yield: 0.4 g (ca. 100%). IR (film): 1350 and 1150 $cm^{-1}$ (no bands at 3500–3200 $cm^{-1}$).

(3) The above mesylate (0.4 g, 1.7 mmol) was dissolved in dry DMF (10 mL) and contacted with anhydrous KOAc (1.0 g, ca. 10 mmol) for 2 h at 90–100 °C. The reaction mass was worked up according to an earlier procedure.[18] Column chromatography on silica gel (10 g, elution with hexane:$Et_2O$ (from 9:1 to 1:1, v/v) afforded a fraction of hydrocarbons (50 mg) and 230 mg of a more polar fraction. The latter was saponified with KOH (85 mg) in MeOH (3 mL) at 20–25 °C (3 h). Subsequent chromatography on a column with 5 g of $SiO_2$ [elution with hexane:$Et_2O$ (5:1→1:1)] gave chromatographically pure specimen of alcohol (*R*)-**30** with $n_D^{20}$ 1.4486 and $[\alpha]_D^{20}$ −5.11° (*c* 1.00, in $CHCl_3$). Yield: 150 mg (55.5% over three steps). A part of this specimen (20 mg) was converted to the corresponding specimen of the (*S*)-MTPA derivative **31**, which displayed almost the same $^1H$ NMR spectrum as that given above for the first specimen of **31**. $^{19}F$ NMR ($CDCl_3$) δ 71.233 and 71.511. The ratio of peak areas ($\sigma_{RS}$:$\sigma_{SS}$) in the $^{19}F$ NMR spectrum was 75:25, from which enantiomeric excess in the second specimen of (*R*)-**30** was estimated to be ca. 50%.

(4) The specimen of (*R*)-**30** thus obtained was acetylated according to the standard procedure (vide infra) to give the acetate (*R*)-**22** (specimen II) in 87.6% yield.

**Methyl 2,4-dodecadien-6-ynoate (34).** A solution of 2-octynal **33** (2.0 g, 16.1 mmol) and phosphonate **2** (3.9 g, 16.4 mmol) in THF (20 mL) was added at 0–5 °C over 30 min to a stirred suspension of $NaNH_2$ (0.65 g, 16.5 mmol) in THF (20 mL). The mixture was stirred for 0.5 h at 0–5 °C and for an additional hour at room temperature and then poured into saturated aqueous solution of $NaHCO_3$ (100 mL) and extracted with $Et_2O$ (4 × 20 mL). The extract was dried over $CaCl_2$ and concentrated under reduced pressure. The viscous oily residue was fracationated in vacuo to afford the dienyne **34** as a colourless oil, bp 120–135 °C (4 torr), $n_D^{20}$ 1.5380. Yield: 1.20 g (36%), (2*E*,4*E*):(2*Z*,4*E*) 70:30 (GC and $^1H$ NMR data). $^{13}C$ NMR ($CDCl_3$) δ 14.0 (C-12), 19.5 (C-8), 22.0 (C-11), 28.3 (C-9), 31.0 (C-10), 51.5 (OMe), 79.5 (C-7), 98.0 (C-6), 120.1, 121.2, 137.0, 143.2 [diene moiety of (2*E*,4*E*)-**3**], 118.1, 122.3, 135.1, 140.4 [diene moiety of (2*Z*,4*E*)-**3**]. This unstable material was used without delay in the next step.

**Methyl (*Z*,*Z*)-3,6-dodecadienoate (35).** The dienyne ester **34** (1.03 g, 5 mmol) in degassed, peroxide-free acetone (8 mL) and ($\eta^6$-$PhCO_2Me$)$Cr(CO)_3$ (0.22 g, ca. 16 mol %) were loaded (under argon) into the stainless steel autoclave which was flushed several times with $H_2$ (up to 10 atm). Then $H_2$ was delivered to the system (initial pressure 60 atm) and the hydrogenation was carried out at 120 °C and 80 atm over 2 h. Subsequent standard work up afforded the 'skipped' diene **35** as a colourless oil, bp 90–95 °C (3 torr). Yield: 0.63 g (60%). $^1H$ NMR ($CDCl_3$) δ 0.83 (3H, t, $J$ = 7.0 Hz, 12-$H_3$), 1.15–1.39 (6H, m, 11-$H_2$, 10-$H_2$, 9-$H_2$), 1.96 (2H, m, 8-$H_2$), 2.74 (2H, degenerated d d, $J$ = 6.0 Hz, 5-$H_2$), 3.07 (2H, d, $J$ = 6.0 Hz, 2-$H_2$), 3.65 (3H, s, OMe), 5.28 (2H, m, CH=CH), 5.53 (2H, m, CH=CH). $^{13}C$ NMR ($CDCl_3$) δ 14.0 (C-12), 22.6 (C-11), 25.7 (C-5), 27.2 (C-8), 29.21 (C-9), 31.5 (C-10), 32.7 (C-2), 51.6 (OMe), 121.0 (C-3), 126.7 (C-4), 130.8 and 131.6 (C-6 and C-7).

**(*Z*,*Z*)-3,6-Dodecadien-1-ol (32).** To a stirred suspension of $LiAlH_4$ (0.12 g, 3 mmol) in $Et_2O$ (3 mL) a solution of the ester **35** (0.53 g, 2.5 mmol) in $Et_2O$ (7 mL) was added under argon, the mixture was stirred for 2 h at room temperature and quenched with 1 M HCl. The organic layer was separated, washed with aqueous $NaHCO_3$ and brine, dried with $MgSO_4$ and concentrated under reduced pressure. The remainder was distilled in vacuo to give the target dienol **32** as a colourless oil, bp 90–95 °C (3 torr). Yield: 0.39 g (85%). $^1H$ NMR ($CDCl_3$) δ 0.90 (3H, t, $J$ = 7.2 Hz, 12-$H_3$), 1.23–1.50 (6H, m, 9-$H_2$, 10-$H_2$, 11-$H_2$), 2.01 (2H, m, 8-$H_2$), 2.34 (2H, d d d, $J$ = 6 Hz, $J'$ = 1.5 Hz, 5-$H_2$), 2.69 (2H, m, 2-$H_2$), 3.61 (2H, t, $J$ = 7.0 Hz, 1-$H_2$), 4.3 (1H, br s, OH), 5.35–5.50 (4H, m, 3-H, 4-H, 6-H, 7-H). $^{13}C$ NMR ($CDCl_3$) δ 14.2 (C-12), 22.6 (C-11), 25.8 (C-5), 27.3 (C-8), 29.3 (C-9), 30.8 (C-2), 31.6 (C-10), 62.3 (C-1), 125.3 (C-3), 127.0 (C-4), 130.7 (C-7), 131.5 (C-6). These data are very close to those reported earlier.[26,27]

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15. For the description of the sequence THP→$Cl(CH_2)_5OAc$ →$I(CH_2)_5OAc$→$MeCO(CH_2)_6OH$→**16** see Experimental (entry 7-Oxooctanal, **16**).

16. Earlier[3a] the ester **16a** was prepared by reducing the keto ester **19** with $NaBH_4$ and subjecting the resulting hydroxy diene to 1,4-*cis* hydrogenation over $Cr(CO)_6$ in benzene (180 °C, 80 atm). Both the yield (60%) and geometrical purity (gp 96%) of the ester **16a** thus obtained were inferior to those attained upon the hydrogenation of **19** over ($\eta^6$-$PhCO_2Me$)$Cr(CO)_3$ in $Me_2CO$ at 120 °C (80 atm) and subsequent reduction of the keto group.

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22. Earlier[3b] the hydrogenation step (**27**→**28**) was performed in $Me_2CO$ at 120 °C and 80 atm using ($\eta^6$-$PhCO_2Me$)$Cr(CO)_3$ as the catalyst. By replacing the latter by ($\eta^6$-naphthalene)$Cr(CO)_3$ it was possible to enhance the yield of **28** from 60 to 75%, which brought about an 1.25-fold increase of the overall yield of racemic quadrilure (**24**).

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