Reviews

Stereospecific 1,4-*cis*-hydrogenation of conjugated dienes, dienynes, and dienediynes catalyzed by chromium carbonyl complexes in stereocontrolled syntheses of physiologically active olefins

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Synthesis of insect pheromones provides a good illustration of versatility, flexiblility, and practical convenience of the chromium carbonyl complexes-mediated 1,4-*cis*-hydrogenation of conjugated dienes as the tool for for stereocontrolled construction of di-, tri-, and tetrasubstituted olefins and nonconjugated dienes. A new strategy for synthesizing homoconjugated *all-Z*-dienes and trienes by hydrogenation of diene-alkyne conjugated systems using the same catalysts is proposed.

Key words: dienes, dienynes, dienediynes, hydrogenation, chromium carbonyl complexes, stereocontrolled synthesis, olefins, pheromones, fragrances.

1. Introduction and background

Biological properties of stereoisiomeric olefins depend substantially on the configuration of the C=C bond. Therefore, development of new methods of stereocontrolled synthesis of olefins is a topical problem of organic chemistry and molecular biology. 1,4-*cis*-Hydrogenation of conjugated dienes catalyzed by carbonyl chromium complexes (see Ref. 1, a review) is among the best methods for stereoselective construction of olefins, *e.g.*, the transformation of diene ester **1** into (*Z*)-alk-3-enoate **2** (Scheme 1).

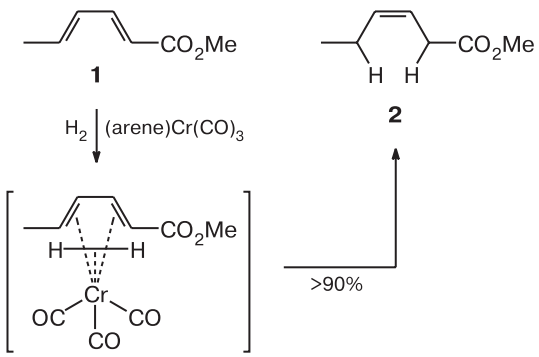
This publication summarizes the authors´ research (1991—2001) into stereocontrolled synthesis of mono- and polyolefins based on the above strategy. The potential of this method has been demonstrated in the synthesis of olfactorily active olefins (fragrance compounds and insect pheromones) where 1,4-*cis*-hydrogenation of dienes was employed as the key step. The former review[1] appeared almost 10 years ago, and no reviews on this reaction have been published in Russian. Therefore, a breif overview of its characteristic features could be useful.

Depending on the type of substitution in the initial substrate, this reaction gives rise to 1,2-disubstituted *Z*-olefins, trisubstituted *Z*- or *E*-olefins, and tetrasubstituted *Z*- and *E*-olefins (Scheme 2).

The mechanism of 1,4-cis-hydrogenation of dienes (Scheme 3) had been considered by the inventors of

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1237—1255, August, 2002.

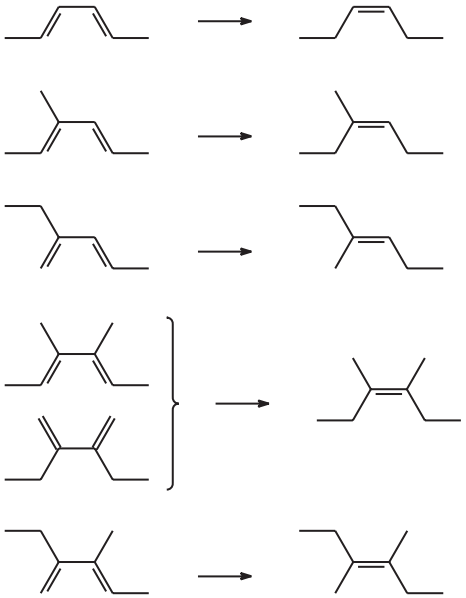
Scheme 1



arene = PhH, $PhCO_2Me$, PhOMe, $C_{10}H_8$.

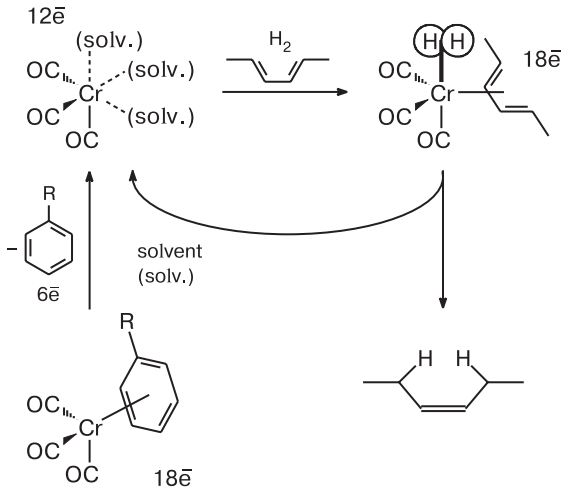
Reagents and conditions: 5 mol % $(arene)Cr(CO)_3$, 50 atm, 160 °C (see Table 1).

Scheme 2



this reaction.[2,3] After thermal dissociation of the $(\eta^6\text{-arene})Cr(CO)_3$ complex, the arene ligand is replaced by solvent molecules. In the labile species thus formed, which is designated conventionally as «$Cr(CO)_3$», three coordination vacancies of Cr^0 accommodate a diene molecule and an H_2 molecule. In the substrate—catalyst—H_2 reaction complex, the diene adopts the *s-cis*-conformation, and the addition of the H_2 molecule to the ends of the diene system occurs in the Cr^0 coordination sphere to give an alkene. Simultaneously, the $Cr(CO)_3$ species returns to the catalytic cycle. Actually, this species is the true reaction catalyst, while the $(\eta^6\text{-arene})Cr(CO)_3$ complex is only the catalyst precursor.

Scheme 3



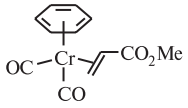
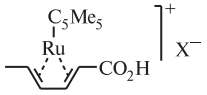
The driving forces of the process are the tendency toward restoration of the stable 18-electron configuration of the chromium atom, which is affected upon thermal dissociation of the η^6-arene complex, and the higher affinity of the bidentate dienic π-ligand to the «$Cr(CO)_3$» species compared to that of the solvent.

This mechanism has been confirmed using 1,4-*cis*-deuteration of diene **1**. In the product **2**-d_2 obtained according to Scheme 1, almost the whole isotope label is distributed in equal parts between the two allylic CH_2 units; in the case of hydrogenation by H_2 — D_2 mixtures, the proportion of olefin **2**-d_2 in the product reflects to the content of D_2 in the initial gas mixture, which indicates the absence of protium-deuterium exchange in the reaction complex.[3]

1,4-cis-Hydrogenation catalysts: advantages and limitations. Initially, 1,4-*cis*-hydrogenation of diene **1** was performed in the presence of $(\eta^6$-arene)tricarbonylchromium complexes, which ensured the formation of methyl (*Z*)-hex-3-enoate **2** with 94—98% regio- and stereoselectivity.[2,3] Later, the range of ligands has been extended (Table 1).[4—10] The temperature at which the absorption of hydrogen starts depends appreciably on the π-ligand and on the solvent, because they dictate the ease of thermal dissociation of the hapto-complex to give the active species «$Cr(CO)_3$».

By 1990, owing to the studies of Japanese chemists, 1,4-*cis*-hydrogenation became a convenient tool for the stereoselective synthesis of olefins.[11—18] The catalysts $MBZ \cdot Cr(CO)_3$ (MBZ is η^6-$PhCO_2Me$), active at 120 °C in acetone, and $NP \cdot Cr(CO)_3$ (NP is η^6-naphthalene), active at 45 °C in THF,[1] had found the most extensive use. Both of them ensure almost 100% selectivity. The advantages of $MBZ \cdot Cr(CO)_3$ are the simplicity of its preparation and stability in air, while the drawback of this catalyst is the relatively high temperature of its

Table 1. Hydrogenation of methyl sorbate **1** to give methyl (*Z*)-hex-3-enoate **2** in the presence of chromium and ruthenium hapto-complexes

Entry	Complex	Solvent	*T*/°C	p_{H_2} /atm	τ/h	The fraction of **2** in the product[a] (%)	Refs.
1	$Cr(CO)_6$	Hexane	180	50	3	93	4
2	$(\eta^6\text{-PhH})Cr(CO)_3$	Cyclohexane	165	48	8	94	2
3	$(\eta^6\text{-PhH})Cr(CO)_3$	CH_2Cl_2	165	48	0.5	94	2
4	$(\eta^6\text{-PhH})Cr(CO)_3$	Acetone	165	48	0.5	92	5
5	$(\eta^6\text{-PhMe})Cr(CO)_3$	Cyclohexane	150	48	7	94	2
6	MBZ•$Cr(CO)_3$	Cyclohexane	150	48	2	99	2
7	MBZ•$Cr(CO)_3$	Acetone	100	70	16	94	1
8	$(\eta^6\text{-Phenanthrene})Cr(CO)_3$	Cyclohexane	150	48	0.3	97	5
9	$(\eta^6\text{-}C_7H_7)$[b]$Cr(CO)_3$	Cyclohexane	120	31	1	98	6
10	$(\eta^6\text{-PhOMe})Cr(CO)_3$	THF	120	60	5	100	7
11	$[\eta^6\text{-1,4-}C_6H_4(OMe)_2]Cr(CO)_3$	THF	120	60	5	100	7
12	$[\eta^6\text{-1,2-}C_6H_4(OMe)_2]Cr(CO)_3$	THF	90	60	5	100	7
13	$[\eta^6\text{-1,2,3-}C_6H_3(OMe)_3]Cr(CO)_3$	THF	80	60	5	100	7
14	$[\eta^6\text{-4-MeOC}_6H_4CO_2Me]Cr(CO)_3$	THF	90	60	5	100	7
15	NP•$Cr(CO)_3$	Decalin	120	4	Not indicated[c]		8
16	NP•$Cr(CO)_3$	THF	40	4	Not indicated[c]		8
17	NP•$Cr(CO)_3$	Acetone	27	4	Not indicated[c]		8
18		THF	20	1	1	100	9
19		$(HOCH_2)_2$— —Me_3COMe	60	10—60	1.5	96	10

[a] The impurities other than the initial diene are other alkenes and/or their saturated analogs.
[b] Cycloheptatrienyl.
[c] The study contains only kinetic data.

dissociation, which may decrease the selectivity of 1,4-*cis*-hydrogenation to ~90%.

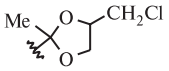
The NP•$Cr(CO)_3$ catalyst is virtually free from these drawbacks; however, it is more expensive and its synthesis and storage are more difficult. This catalyst is preferred in the case of labile or polyfunctional substrates.

The commercially available chromium hexacarbonyl is the least efficient catalyst. It is thermally more stable, and, therefore, it is activated only at 160—190 °C. However, even under these conditions, the selectivity can exceed 90% with an almost complete conversion of the diene. Thus hydrogenation of hexa-2,4-dien-1-ol at 190—200 °C and at an H_2 pressure of 80 atm furnishes (*Z*)-hex-3-en-1-ol (**3**) in 93% yield with a geometric purity of ~98%.[19—21] Systematic research into the $Cr(CO)_6$-catalyzed hydrogenation of substrates having an oxygen-containing functional group in the α-position to the diene moiety[4,21—29] (Table 2) showed that esters of sorbic acid are converted into target alkyl (*Z*)-hex-3-enoates with good selectivity (Table 2, entries 1—4), while for the acid itself or some other derivatives, the selectivity is low (entries 5—8, R ≠ Alk).[27] Undesirable impurities appear due to thermal isomerization of the initially formed 3(*Z*)-products.[29] Good results were obtained with 1,4-*cis*-hydrogenation of alcohols, ethers, and acetals/ketals (see Table 2, entries 9—17, 20—21).

In the $(\eta^2\text{-MeO}_2CCH{=}CH_2)Cr(C_6H_6)(CO)_2$ complex, the η^6-bond with the benzene ligand is weaker than the η^2-bond with methyl acrylate.[9] In hydrogenation of diene **1** (see Table 1, entry 18), this catalyst is active even at 20 °C and 1 atm of H_2. The readily available tris(acetonitrile)tricarbonylchromium $(MeCN)_3Cr(CO)_3$, which performs 1,4-*cis*-hydrogenation of diene hydrocarbons at 45 °C and 1.5 atm, seems to be a promising catalyst.[31]

Apart from Cr^0 carbonyl complexes, similar Mo, W, and Co complexes also catalyze 1,4-*cis*-hydrogenation of dienes, but the selectivity is relatively low with these metals.[32] Only a ruthenium hapto-complex (see Table 1, entry 19) can ensure a selectivity of 1,4-*cis*-hydrogenation of methyl sorbate **1** and sorbic alcohol[10] equal to that of $L_nCr(CO)_3$ (96—99%).

Table 2. 1,4-*cis*-Hydrogenation of functionally substituted dienes of the RCH=CH—C(R´)=CHX type (100 mmol of the diene in 20 mL of hexane, 2—5 mmol of $Cr(CO)_6$, 50—80 atm of H_2, 160—180 °C, 2—4 h)

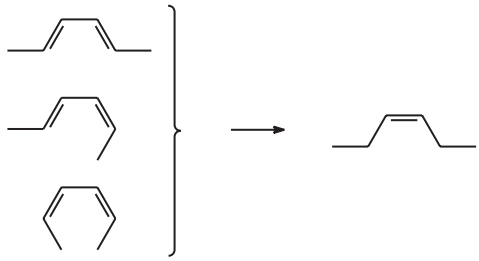
Entry	R	R´	X	Conversion	The fraction of 3*Z*-olefin[a]	Yield[b]	Refs.
				%			
1	Me	H	CO_2Me	100	87—93	59	4, 27
2	C_5H_{11}	H	CO_2Me	100	96	70	27, 30
3	Et	Me[c]	CO_2Et	100	99	60	28, 30
4	4-$MeOC_6H_4$	Me[c]	CO_2Et	92	92	63	28
5	Me	H	CO_2H	100	12 (94[d])	40 (74[d])	27, 29
6	Me	H	CO_2K	100	36	58	27, 29
7	Me	H	CO_2SiMe_3	100	34	58	27, 29
8	Me	H	CO_2CH_2OMe	100	31 (100[d])	63 (77[d])	27, 29
9	Me	H	CH_2OH	99	98	84	4, 21
10	Me	H	CH(OH)Me	99	96	82	4, 22
11	Me	H	$C(OH)Me_2$	98	97	81	4, 22
12	Me	H	C(OH)MePh	98	96	68	4, 22
13	H	H	CH_2OH	100	94	38[e]	24
14	C_3H_7	H	CH_2OH	96	94	62	4, 23
15	Ph	H	CH_2OH	98	98	86	4
16	Me	H	CH(OMe)Me	92	91	65	4
17	Me	H	$CH_2OCH(Me)OEt$	99	98	86	25
18	Me	H	CH_2OAc	12	12	Not determined	4, 21
19	Me	H	C(O)Me	50	12	Not determined	4
20	Me	H		100	99	85	4, 25
21	Me	H	$CH(OEt)_2$	100	97	78	25

[a] According to GLC and/or NMR, the products isolated by distillation contain also 3*E*- and 2*E*-isomers and (more rarely) saturated counterparts of the target olefin.
[b] The yield after distillation.
[c] In the initial diene, the isomer ratio was 2*E*,4*E* : 2*Z*,4*E* = ~65 : 35.
[d] For comparison, the results obtained at 120 °C in acetone with the MBZ·$Cr(CO)_6$ catalyst are given in parentheses.
[e] Hydrogenation was accompanied by polymerization.

Dependence of the reactivity of 1,4-cis-hydrogenation substrates on their structure. The scope of 1,4-*cis*-hydrogenation as a method for stereoselective synthesis of linear and branched monoolefins from conjugated dienes can be seen from Scheme 2. The configuration of the double bonds in the initial diene influences only the rate of the process but not the stereochemistry, because 1,4-*cis*-hydrogenation of *E,E*-, *E,Z*-, and *Z,Z*-stereoisomers of the diene yields the same product (Scheme 4).

The rates of hydrogenation of *E,Z*- and, especially, *Z,Z*-dienes are lower than that observed for the *E,E*-isomer. This can be explained by steric congestion hampering the formation of the reaction complex in the former stereoisomers. Under relatively mild conditions, only the *E,E*-isomer can be hydrogenated, while the *E,Z*-isomer either remains unchanged or undergoes migration of the double bond.[17,18] The 1,4-*cis*-hydrogenation method is also suitable for stereoselective synthesis

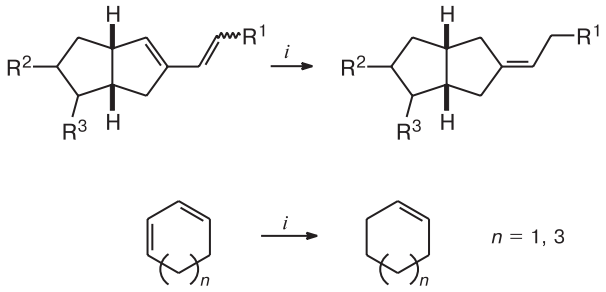
Scheme 4



of exocyclic olefins[11—17] and partial hydrogenation of some cyclic dienes[33] (Scheme 5).

A substantial limitation of the method comes from the degree of substitution at the terminal carbon atoms of the diene system. Namely, each of them must not bear more than one substituent. Otherwise, the diene

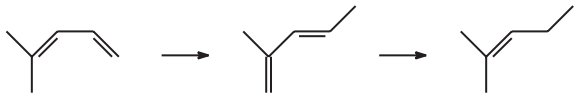
Scheme 5



i. $H_2/(\eta^6$-arene$)Cr(CO)_3$.

isomerizes, and it is the less substituted isomer that undergoes 1,4-*cis*-hydrogenation (Scheme 6).[32] This is in line with the known[12,33] ability of the $L_nCr(CO)_3$ complexes to induce migration of double bonds in conjugated and homoconjugated dienes at elevated temperatures in the absence of H_2.

Scheme 6



The prospects of scaling 1,4-cis-hydrogenation of conjugated dienes. Despite the high preparative value of 1,4-*cis*-hydrogenation, so far it has remained a tool of the laboratory synthesis. In the case of dienes with complex structures, the scale of synthesis does not normally exceed 1 g (see Ref. 1 and references therein). A batch of ~0.5—2 moles is considered to be large for 1,4-*cis*-hydrogenation in an autoclave.[19,29,34] The problems of synthesis and regeneration of catalysts have not yet been solved to an extent that would enable the use of 1,4-*cis*-hydrogenation on an industrial scale. Even the use of the simplest catalyst, $Cr(CO)_6$, is profitable only for the manufacture of particularly valuable chemicals, the annual demand for which is satisfied by several hundreds kg or less.

Large-scale testing of $Cr(CO)_6$ as a 1,4-*cis*-hydrogenation catalyst has shown that the hydrogenation is accompanied by fast self-heating of the reaction mixture as soon as the temperature of the onset of H_2 absorption has been reached.[29] In these cases, the amount of $Cr(CO)_6$ used can be decreased. The key factors determining the hydrogenation rate include the substrate concentration and the mole fraction of the catalyst in the reaction mixture. For a particular autoclave equipment, the amount of catalyst can be decreased only to a certain limit, below which the reaction no longer proceeds. This is due to the destruction of the catalyst by traces of oxygen, which is difficult to remove completely upon the standard procedure that consists in evacuation—filling with argon followed by hydrogen admission—discharge. Therefore, one has to take into account the fact that a part of the catalyst should be sacrificed for the ultimate removal of oxygen traces. The products of oxidative destruction of the catalyst ("chromium earths") do not usually affect the course of the major process.*

Thus, with rational selection of reaction conditions, 1,4-*cis*-hydrogenation in the presence of $Cr(CO)_6$ is an attractive method for the stereoselective synthesis of olefins in small-scale manufacturing of highly valuable chemicals. As regards catalysts such as $L_nCr(CO)_3$, their use in laboratory syntheses depends mainly on the accessibility of the diene substrate.

2. New developments in the 1,4-*cis*-hydrogenation methodology

Our studies in the stereoselective synthesis of functionalized mono- and polyolefins based on 1,4-*cis*-hydrogenation of dienes were carried out along three directions. *1.* Extension of the Frankel synthesis of monoolefins to a new range of objects and development of efficient routes for the preparation of required substrates. *2.* Elaboration of the strategy for the synthesis of nonconjugated polyolefins using 1,4-*cis*-hydrogenation as the key step of the target-directed synthesis. *3.* Development of a new method for the synthesis of homoconjugated linear di- and triolefins *via* synchronous 1,4-*cis*-hydrogenation of the diene system and 1,2-*syn*-hydrogenation of the triple bond in conjugated dienynes and dienediynes in the presence of chromium carbonyl complexes, and elaboration of the routes for the preparation of these substrates.

By the early 1990-s, 1,4-*cis*-hydrogenation of dienes as a method of stereocontrolled olefin synthesis had been successfully used in the target-directed syntheses of pharmacologically active compounds (modified cyclic eicosanoids,[11—17] their analogs,[35] and precursors[36]), fragrance compounds,[18—21] an insect juvenile hormone,[37] and alkaloids.[38] In the vast majority of cases, linear dienes served as the substrates for 1,4-*cis*-hydrogenation (see Ref. 1).

The procedures and synthetic algorithms for the preparation of mono- and polyolefins considered below where 1,4-*cis*-hydrogenation of dienes served as the key step, have been developed in our studies dealing with the preparation of unsaturated olfactorily active compounds. The latter include a group of fragrance compounds (FC), namely, the analogs of (*Z*)-hex-3-en-1-ol **3**, and various insect pheromones (IP) of the aliphatic series.

* More detailed consideration of this problem and some useful recommendations can be found in the Thesis, Ref. 29.

For an adequate estimate of the physiological activity of olefinic FC and IP, it is necessary that the isomeric purity of the compounds be as high as possible. The Frankel reaction affords exactly this type of product; therefore, it is expedient to use this reaction for the preparation of these compounds. Of the numerous known methods for the synthesis of conjugated dienes,[39] three types of reactions are used most often to prepare the required substrates: (*1*) elimination reactions occurring without a change in the carbon skeleton; (*2*) olefination of carbonyl compounds by organophosphorus or organoselenium compounds, and (*3*) cross-coupling of vinylic electrophiles and nucleophiles to give the central single C—C bond.

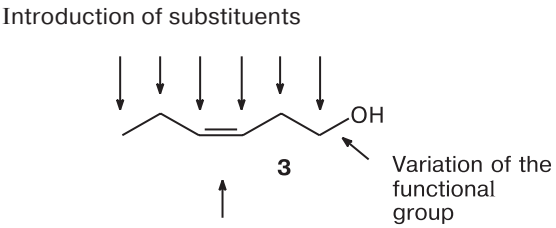
For the syntheses of FC and IP described in this section, diene substrates were prepared most often by the first and the second processes. Optimization of the Horner—Wadsworth—Emmons (HWE) synthesis of dienes provided the reaction conditions that permitted the synthesis of 2*E*,4*E*- and 2*Z*,4*E*-isomers of 3-methylalka-2,4-dienoates with contents of up to 96% and 85%, respectively.[40,41] An efficient pathway to linear diene systems is oxidative elimination of arylselenenic acids from α-selenyl-substituted esters of aliphatic acids[42,43] or acetals,[44] for the synthesis of which improved procedures were developed.

2.1. Synthesis of the leaf alcohol and its analogs

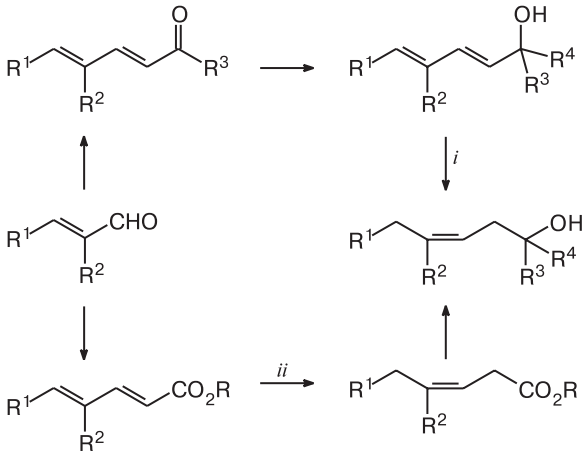
(*Z*)-Hex-3-en-1-ol or the leaf alcohol (**3**) is a valuable natural FC with a "fresh-green odor".[45] A topical task for the chemical fragrance industry in Russia, namely, the replacement of expensive compound **3** by a more readily available synthetic FC with similar properties (and higher technical and economic qualities!) involved elucidation of the factors that determine these properties. To this end, it was necessary to identify the dependence of the odor on the structure of the FC molecule (see reviews[46]). The first step toward the solution of this problem was to synthesize a representative number of analogs of alcohol **3** as the lead for subsequent structural modifications (Scheme 7).

Such a synthetic program required simple and efficient protocols to give geometrically pure analogs of alcohol **3** with different types of substitution at the C=C bond[47] and various oxygen-containing functions.[48] The 1,4-*cis*-hydrogenation proved to be the most reliable technique both for the construction of *Z*-disubstituted or *Z*- and *E*-trisubstituted olefins (Scheme 8) and for the synthesis of *Z*-tetrasubstituted olefin analogs of the alcohol (Scheme 9). Of the total of 91 analogs of the leaf alcohol, almost one-third was prepared by this method (15 alcohols[4,22—24,48] and 13 olefins with other oxygen-containing functions[25,27]).

Scheme 7



Scheme 8

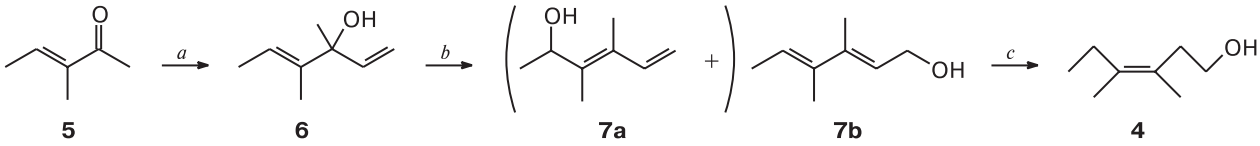


Reagents and yields: *i*. H_2, $Cr(CO)_6$, up to 80% yield, up to 99% purity; *ii*. H_2, MBZ·$Cr(CO)_3$, up to 76% yield, up to 99% purity.

As a result of these studies, the analogs of the leaf alcohol were subjected to organoleptic testing and the results were summarized. The efficiency of this approach directly depended on the accessibility of the starting dienes. These were prepared by aldol condensation or, more selectively, by the HWE or Wittig reaction[28,40,41] (Schemes 10 and 11). The organophosphorus pathway proved to be especially advantageous in the stereocontrolled synthesis of trisubstituted olefins. Tetrasubstituted olefin **4**, which was difficult to obtain by other routes, could be prepared in only three steps starting from 3-methylpent-3-en-2-one (**5**), which results from condensing acetaldehyde with methyl ethyl ketone (see Scheme 9).[23] The allylic rearrangement of the corresponding dialkenyl alcohol **6** in the presence of ammonium molybdate affords a mixture of two isomeric diene alcohols **7a** and **7b**, but the reaction mixture can be subjected directly to the subsequent hydrogenation without resolving the components.*

* It is more expedient to carry out chromatographic purification of primary alcohol **4** from secondary alcohols at the end of the process, after the key step.

Scheme 9



Reagents and conditions: *a*. CH_2=CHMgBr; *b*. $(NH_4)_2MoO_4$, Δ; *c*. H_2, $Cr(CO)_6$.

The organoleptic assessment of the analogs of alcohol **3** and matching the odor to the molecular structure showed that the best substitutes should be selected among alkenols with a total number of atoms of 6—8 in which at least one of the alkyl substituents is located in the β-position to the double bond. The greater the deviations from the structure of **3** (see Scheme 7), the less the similarity to the standard "green" odor. Of the series of close analogs of alcohol **3** evaluated as promising substitutes for the leaf alcohol, some compounds were prepared by 1,4-*cis*-hydrogenation.

2.2. Stereocontrolled synthesis of insect pheromones

Pheromones (volatile metabolites of insects that control their intra-species behavior) help to increase the efficiency and environmental safety of combating the agricultural and food stock pests. The synthesis of IP in order to validate the structure attributed to them or for practical purposes of pest control is the subject of numerous publications (see reviews and monographs[49]). The high specificity of the reception of natural IP by each species and, as a consequence, situations where the IP attractant activity was lost (due to contamination of the synthetic specimen with positional or configurational isomer) stipulate the use of highly chemo-, regio-, and steroselective reactions in the pheromone synthesis. Hence, despite the considerable progress in the strategy of the selective synthesis of olefins,[49,50] the quest for rational methods for stereocontrolled synthesis of olefins does not stop.

Due to structural diversity and rather simple structures, unsaturated IP are excellent targets for the application and extension of the 1,4-*cis*-hydrogenation strategy. We appear to be the first to use stereospecific 1,4-*cis*-hydrogenation of conjugated dienes in the target-directed pheromone synthesis. The examples given below attest to the benefit of using this strategy in the preparation of IP.*

* Due to the limited size of the review, references to identification and to known syntheses of insect pheromones are given only in special cases. Comparison of the insect pheromone syntheses described below with the studies of other researchers can be found, as a rule, in our publications cited in this review (1994—2002).

2.2.1. Horner—Wadsworth—Emmons olefination / catalytic 1,4-cis-hydrogenation as a two-step protocol for the synthesis of (Z)-alk-3-enoic acids and their derivatives

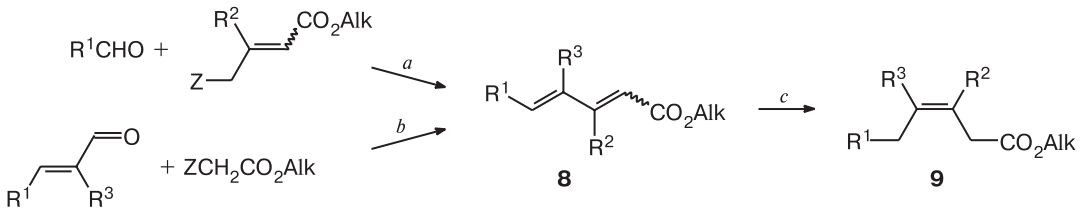
Olefins with an oxygen-containing functional group in the homoallylic position are not uncommon among IP. In particular, (*Z*)-alk-3-enoic acids and their derivatives are either pheromones for several coleopterous species or intermediates of their synthesis. The most popular methods used for the synthesis of these acids include (*1*) partial hydrogenation of the triple bond in 3-alkynoic acids and related systems and (*2*) Wittig *cis*-olefination of aldehydes.[49,51] However, the former procedure is unsuitable for stereoselective synthesis of compounds with alkyl substituents at the double bond, while the latter does not always ensure a high (90—100%) content of the required stereoisomer in the product.

We proposed a versatile two-step protocol for the preparation of esters of 3-substituted (*Z*)- and (*E*)-alk-3-enoic acids,[28] which included the HWE synthesis of alka-2,4-dienoates and 1,4-*cis*-hydrogenation of these substrates in the presence of $Cr(CO)_6$ or $(\eta^6$-ArH$)Cr(CO)_3$ (Scheme 10). The dienic substrates of the general type **8** were prepared by olefinating AlkCHO or ArCHO with allylphosphonates $(AlkO)_2P(O)CH_2C(R)$=$CHCO_2Alk$ (method *a*) or by condensing α,β-alkenals with alkyl phosphonoacetates (method *b*). By varying the positions of substituents in substrate **8** through appropriate selection of starting aldehydes and phosphonates, one can prepare either *Z*- or *E*-trisubstituted olefins **9** at the 1,4-*cis*-hydrogenation step (*c*). In the case of 1,4-*cis*-hydrogenation of linear alka-2,4-dienoates **8** (R^2 = R^3 = H), (*Z*)-alk-3-enoates are formed almost exclusively, the reaction selectivity being somewhat lower than that in the hydrogenation of 3-substituted alkadienoates.[27,30]

Synthesis of (Z)-dec-3-enoic acid (10). This acid is an aggregation pheromone of the museum carpet beetle *Anthrenus flavipes* (Dermestidae), which damages valuable cultural and historical exhibits and collections. This acid appeared to be a simple object for evaluating the efficiency of the strategy in question (Scheme 11).[27,30]

The yield of the diene substrate **12** proved to depend appreciably on the reaction conditions. The highest yield of **12** (47%) was attained under conditions indicated in Scheme 11, whereas a yield of 96% was reached

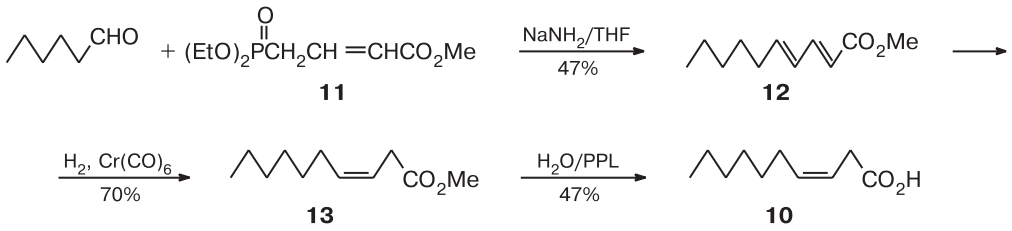
Scheme 10



R^1 = H, Alk, Ar; R^2 = Me or H; R^3 = H or Alk; Z = $(AlkO)_2P(O)$.

a, *b* is Horner—Wadsworth—Emmons olefination of aldehydes; *c* is 1,4-*cis*-hydrogenation.

Scheme 11



later by using LiOH in combination with molecular sieves.[52]

1,4-*cis*-Hydrogenation of diene **12** catalyzed by $Cr(CO)_6$ (see Table 2, entry 2) furnished methyl (*Z*)-dec-3-enoate (**13**) containing only a minor impurity of 3*E*- and 2*E*-isomers (1 and 3%, respectively).[27] Mild alkaline hydrolysis of this product afforded a specimen of the target acid **10** in which the fraction of the 2*E*-isomer has increased to 6%. The loss of the pH-sensitive acid **10** could be avoided by making use of Brockerhoff´s data [53] that hydrolysis of alkenoic esters catalyzed by porcine pancreatic lipase (PPL) at pH ~6.5—7 proceeds more readily for nonconjugated isomers than for esters of α,β-unsaturated acids. Mild hydrolysis of ester **13** in the presence of PPL up to a 70—90% degree of conversion gave rise to 99% pure acid **10**, while the admixture of methyl (*E*)-dec-2-enoate was left entirely in the neutral fraction. Thus, the last step was combined with simultaneous purification of the pheromone. The total yield of pheromone **10** was 15.5% over three synthetic steps.

Synthesis of (Z)-dodec-3-en-11-olide. The (3*Z*,11*S*)- and (3*Z*,11*R*)-stereoisomers of dodec-3-en-11-olide (ferrulactone II, **14**) are active components of the pheromone bouquets produced by the rusty grain beetle *Cryptolestes ferrugineus* and the grain beetle *Oryzaephilus mercator,* respectively. The known methods for the synthesis of (+)-, (−)-, and (±)-**14** are based on either partial *syn*-hydrogenation of acetylene precursors or *Z*-stereoselective Wittig olefination (see above). In both cases, the synthesis is completed by macrolactonization of (*Z*)-11-hydroxydodec-3-enoic acid (**15**).

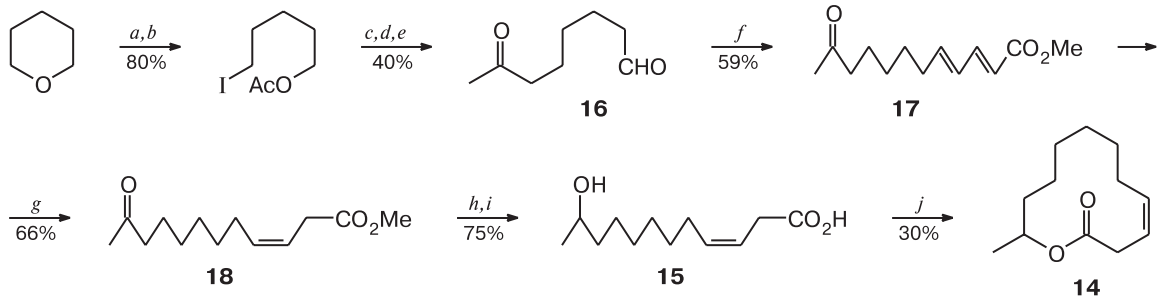
We demonstrated[27,30] the efficiency of an alternative strategy for the construction of the double bond in lactone **14**. 7-Oxooctanal (**16**) served as the aldehyde component in the HWE reaction. As expected, its keto group remained practically unaffected under the chosen conditions of olefination (Scheme 12).

The reaction of oxo aldehyde **16** with phosphonate **11** gave ester **17**, which contained up to 90% of the 2*E*,4*E*-isomer. Subsequent 1,4-*cis*-hydrogenation of dienoate **17** catalyzed by MBZ•$Cr(CO)_3$ resulted in *Z*-olefin **18** with ~99% content of the major substance. After reduction of the oxo group and hydrolysis of the intermediate 11-hydroxy ester, the key hydroxy acid **15** was subjected to lactonization by a known procedure[54] (in parallel with our experiments, this step was significantly improved by other researchers[55]). The overall yield of the target product with ~99% content of lactone **14** was 8.6% over five synthetic steps starting with oxo aldehyde **16**.

Synthesis of (Z)-3-methylhept-3-enoic acid. (*Z*)-3-Methylhept-3-enoic acid (**19**) is one of the two components of the sex pheromone produced by females of the four-spotted dried-bean bruchid beetle *Callosobruchus maculatus F.* (Bruchidae). Unlike the nonbranched analog **10**, a stereoselective approach to the formation of *Z*-trisubstituted Δ^3-double bond by traditional methods in this case is less obvious. The use of the general algorithm (Scheme 10, pathway *a*) allowed the first stereoselective synthesis of pheromone **19** in only three steps (Scheme 13)[27,30].

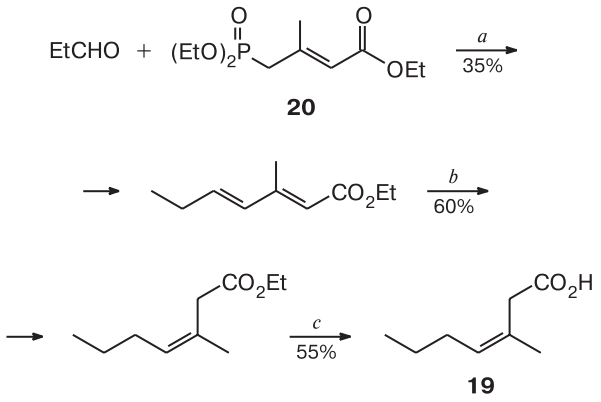
Olefination of propanal with isoprenoid C_5-phosphonate **20** was carried out using a convenient proce-

Scheme 12



Reagents and conditions: *a*. AcCl—$ZnCl_2$, 100 °C; *b*. NaI/Me_2CO; *c*. $MeCOCH_2CO_2Et$—K_2CO_3—18-crown-6/dioxane—H_2O (~30 : 1), 70—80 °C; *d*. 1) NaOH (aq), 2) H_2SO_4, Δ; *e*. PCC—AcONa/CH_2Cl_2; *f*. Phosphonate **11**—$NaNH_2$/THF; *g*. H_2 (60 atm), MBZ • $Cr(CO)_3$/Me_2CO, 120 °C; *h*. $NaBH_4$/EtOH; *i*. 1) KOH (aq), 2) HCl; *j*. 1) (α-$C_5H_4NS)_2$—PPh_3/MeCN, 2) $AgClO_4$/xylene, 135 °C.

Scheme 13



Reagents: *a*. KOH/PhH/18-C-6; *b*. H_2—$Cr(CO)_6$; *c*. 1) KOH/H_2O, 2) HCl (aq).

dure involving phase transfer catalysis. Subsequent 1,4-*cis*-hydrogenation (see Table 2, entry 3) and alkaline hydrolysis steps furnished the target pheromone with 99% purity. In contrast to ester **13**, in this case, the hydrolysis was not accompanied by the migration of the double bond to the α-position relative to the carbonyl.

Synthesis of sex pheromones of the California red scale and white peach scale. The major component of the sex pheromone of the California red scale *Aonidiella aurantii* (**21a**) and the sex pheromone of the white peach scale *Pseudaulacaspis pentagona* (**21b**) are the acetate and propionate, respectively, of homologous alcohols **22a** and **22b** having *Z*-configuration of the trisubstituted double bond. Of the known methods for the preparation of these compounds, the synthesis including stereocontrolled [2,3]-sigmatropic rearrangement[56] is the most interesting (for other methods, see a review[50b]).

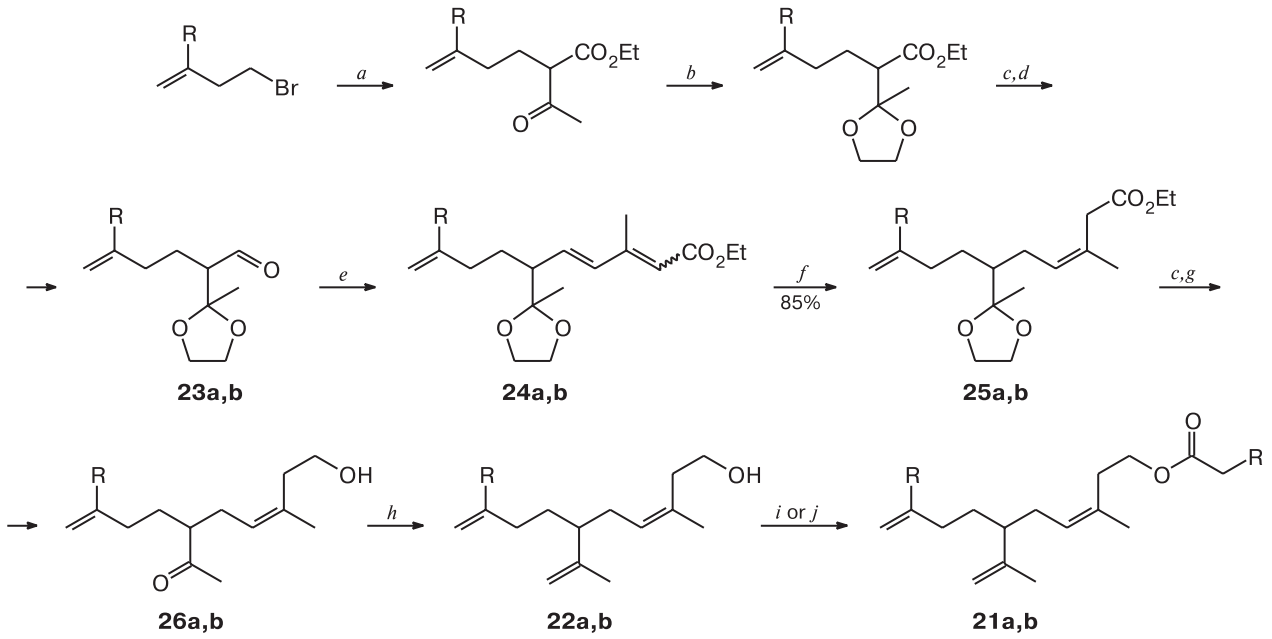
We proposed a new strategy for the synthesis of pheromones **21a** and **21b**, the key step of which is stereospecific 1,4-*cis*-hydrogenation of their diene precursors catalyzed by chromium carbonyl complexes (Scheme 14).[57] Aldehydes **23a,b**, prepared by the same route from readily available building blocks, ethyl acetoacetate and homoallylic alcohols CH_2=$CRCH_2CH_2OH$ (R = H or Me), were condensed with C_5-phosphonate **20** under phase transfer catalysis conditions. This gave dieneoates **24a,b** with a ratio of 2*E*,4*E*- to 2*Z*,4*E*-isomers of ~65 : 35.

The key step, 1,4-*cis*-hydrogenation of dienoates **24a,b**, was performed using the MBZ • $Cr(CO)_3$ catalyst. Hydrogenation of both (2*E*,4*E*)-**24** and (2*Z*,4*E*)-**24** gave rise to the same *Z*-olefin **25** with a degree of conversion and geometrical purity close to 100%. The Wittig reaction was employed to transform the acetyl group in compounds **26a,b** into the isopropenyl group, which completed the synthesis. This protocol does not involve laborious chemical operations and utilizes more readily available reagents than the known processes comparable in efficiency.

Synthesis of (E)-3-acetoxy-7-methyl-non-6-ene. (3*R*,6*E*)-3-Acetoxy-7-methylnon-6-ene ((*R*)-**27**, quadrilure) is the aggregation pheromone of the grain beetle *Cathartus quadricollis* (Bostrichidae), a widespread granary pest. Among stereoselective methods for the synthesis of **27**, of greatest interest is the route that includes replacement of the oxygen atom in dihydro-4*H*-pyran ring catalyzed by a nickel complex.[58] Other syntheses of quadrilure (see references in Ref. 30) are multistep procedures inappropriate for the preparation of large amounts of the material.

We developed a pathway to racemic quadrilure (±)-**27** in which 1,4-*cis*-hydrogenation was used to construct the *E*-trisubstituted double bond (Scheme 15).[28,30] In this protocol, ester **28**, prepared by olefination of commercially available 2-ethyl acrolein (**29**) with triethyl phosphonoacetate, served as the diene substrate. The NP • $Cr(CO)_3$ complex, active in THF even at 45—50 °C, proved to be the best catalyst for hydrogenation of the reactive diene **28**[30] to give the key

Scheme 14



R = H (**a**), Me (**b**)

Reagents, conditions, and yields: *a*. $MeC(O)CH_2CO_2Et$—EtONa/EtOH, yield 55% (**a**), 60% (**b**); *b*. $HO(CH_2)_2OH$—TsOH/PhH, Δ, yield 78% (**a**), 63% (**b**); *c*. $LiAlH_4/Et_2O$; *d*. PCC/CH_2Cl_2, yield 87% (**a**), 85% (**b**); *e*. $(EtO)_2P(O)CH_2C(Me)=CHCO_2Et$ (**20**)—KOH/18-C-6/PhH, 20 °C, yield 69% (**a**), 72% (**b**); *f*. H_2 (80 atm)—$MBZ \cdot Cr(CO)_3/Me_2CO$, 120 °C; *g*. H_2O—Me_2CO (1 : 3)/$H_2C_2O_4$ (cat), yield 52% (**a**), 63% (**b**); *h*. $Ph_3P=CH_2$/THF—DMSO, 20 °C; *i*. Ac_2O/Na_2CO_3; *j*. $(EtCO)_2O/Na_2CO_3$, yield 45% (**a**), 42% (**b**). Overall yield 4.3% (**21a**), 4.0% (**21b**).

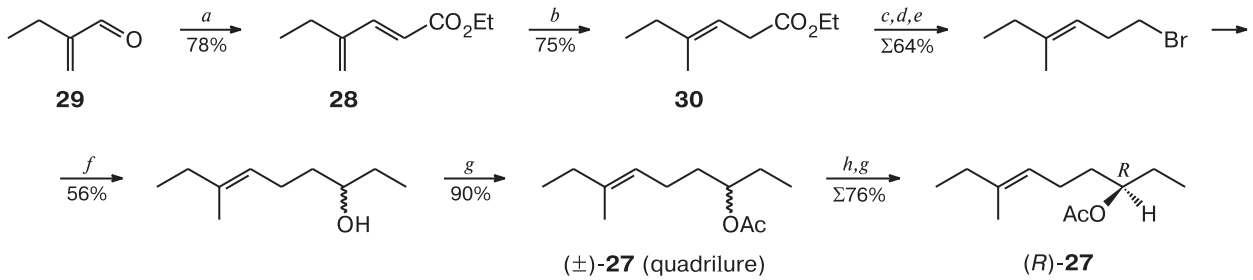
(*E*)-4-methylhex-3-enoate (**30**) in 75% yield. The use of the $MBZ \cdot Cr(CO)_3$—acetone system (120—125 °C) provided a 59% yield of alkene **30** and the process was accompanied by polymerization. In the presence of $Cr(CO)_6$ at 180 °C, 1,4-*cis*-hydrogenation resulted in the corresponding saturated analog (20%).[29]

Further transformation of olefin **30** into the target product was accomplished by simple procedures (see Scheme 15) in which the double bond geometry remained unchanged. The overall yield of (±)-quadrilure from ethyl acrolein **29** amounted to 18.8% over the seven steps of the synthesis. Partial hydrolysis of acetate (±)-**27** catalyzed by PPL up to ~50% conversion depth, followed by acetylation of the resulting optically active alcohol, afforded the natural *R*-form of the pheromone with an enantiomeric purity of ≥93%.

2.2.2. Organoselenium approach to conjugated dienes — intermediates in the synthesis of insect pheromones

A unique feature of organic selenides is the ability to be transformed into olefins under mild conditions (see

Scheme 15



Reagents and conditions: *a*. $(EtO)_2P(O)CH_2CO_2Et$—K_2CO_3/H_2O; *b*. H_2 (70 atm)—$NP \cdot Cr(CO)_3$/THF, 50 °C; *c*. $LiAlH_4/Et_2O$; *d*. TsCl—Py; *e*. NaBr/DMF, 60 °C; *f*. 1) Mg/THF, 2) EtCHO; *g*. Ac_2O/Py; *h*. H_2O—PPL (pH 7).

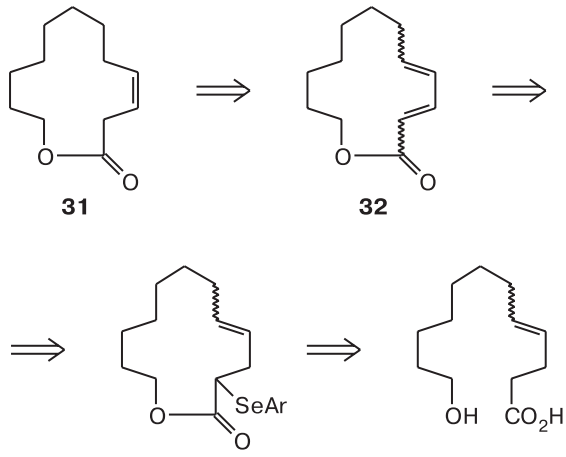
reviews[59]). Examples of using selenium chemistry in the synthesis of conjugated dienes are few in number; actually, these are the same reactions giving olefins but from molecules that already have an additional double bond in the required position. Two general methods that implement these processes are known: (*1*) oxidative elimination of an arylselenyl group[60] and (*2*) elimination of vicinal selenide and hydroxy groups on treatment with acidic reagents.[61]

Our studies have demonstrated that the organoselenium approach is quite useful for the synthesis of conjugated dienes, such as those employed in total syntheses of some pheromones.

New approaches to the synthesis of (Z)-dodec-3-en-12-olide. (*Z*)-Dodec-3-en-12-olide (**31**) is the principal component of the aggregation pheromone of the flat grain beetle *Cryptolestes pusillus*. Of all known unsaturated macrocyclic lactones representing pheromones of cucujid beetles, this compound has the simplest structure and, therefore, represents a convenient model for testing new synthetic protocols for the preparation of such compounds. Previously known syntheses of olefinic macrolides, in particular, **31** included lactonization of the corresponding hydroxy acids whose *Z*-alkene bonds were, in turn, formed either by partial *syn*-hydrogenation of the C≡C bond[62] or by the Wittig reaction.[55]

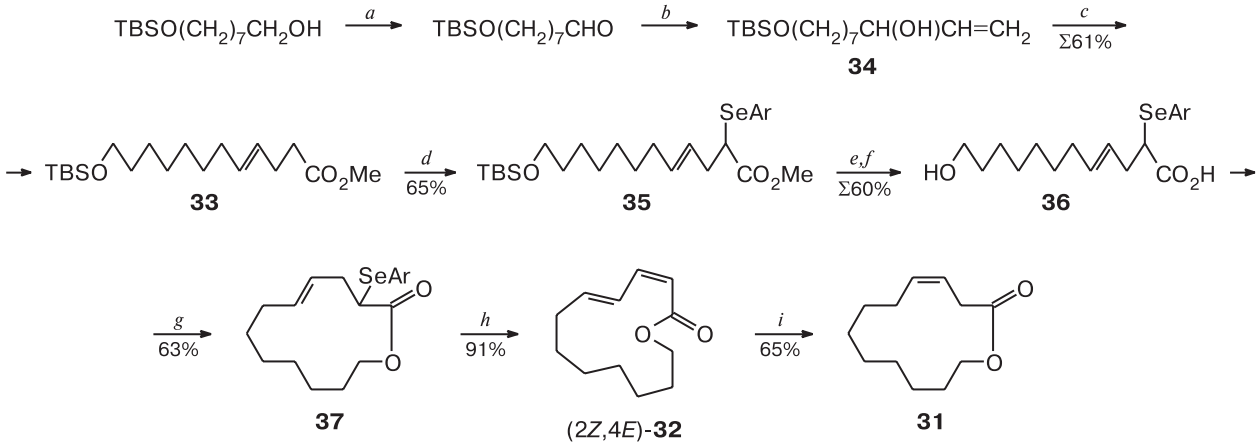
On the basis of the Frankel reaction, we developed two original routes,[43,63] in which *Z*-configuration of the double bond in lactone **31** was ensured by 1,4-*cis*-hydrogenation of the derivatives of 12-hydroxydodeca-2,4-dienoic acid, in particular, 1→12 lactone (**32**). The most obvious pathways to dienoic esters are either inapplicable or difficult to implement in the synthesis of macrolides. However, we anticipated that oxidative elimination of the arylselenyl group from the more readily available macrolactone with one C=C bond could give the α,β:γ,δ-conjugated dienolide system (Scheme 16).[43] To realize this pathway, it was necessary to obtain ω-hydroxy-γ-alkenoic acid derivatives.

Scheme 16



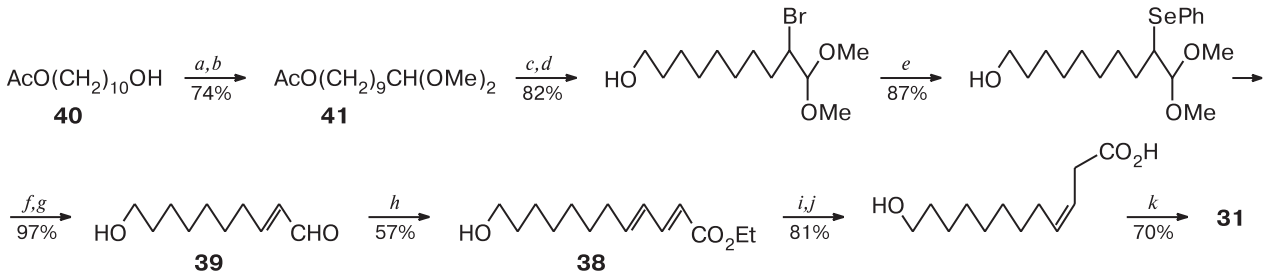
The required key derivative of 12-hydroxydodec-4-enoic acid **33** was readily prepared from a conventionally obtained monoprotected diol **34** (Scheme 17). α-Selenation of ester **33** with bis(4-methoxyphenyl) diselenide using an original procedure[42] yielded selenide **35**. Transformation of functional groups in **35** resulted in α-selenated hydroxy acid **36**, whose cyclization afforded arylsenenyl-substituted lactone **37** in an overall yield of 25% based on ester **33**.

Scheme 17



Reagents and conditions: *a*. NaBr—$NaHCO_3$ (aq)/CH_2Cl_2/4-AcNH-TEMPO (−2e$^-$, 2.0 F mol^{-1}), ~20 °C; *b*. CH_2=CHMgBr/THF; *c*. $MeC(OMe)_3$—H^+, 115 °C; *d*. 1) LDA/THF, −78 °C, 2) $(4\text{-}MeOC_6H_4)_2Se_2$; *e*. Bu_4NF/THF; *f*. 1) KOH/H_2O—MeOH, 2) HCl (aq); *g*. Ph_3P—DEAD/PhMe, ~20 °C; *h*. H_2O_2/THF, ~20 °C; *i*. H_2—NP•$Cr(CO)_3$/THF, 45 °C, 40 atm.

Scheme 18



Reagents and conditions: *a*. NaBr—$NaHCO_3$ (aq)/CH_2Cl_2/4-AcNH-TEMPO ($-2e^-$, 4.5 F mol^{-1}); *b*. $MeC(OMe)_3/H^+$; *c*. Br_2/CH_2Cl_2; *d*. $MeOH/K_2CO_3$; *e*. PhSeK/DMSO, 90 °C; *f*. H_2O_2/THF; *g*. H_3O^+; *h*. $(EtO)_2P(O)CH_2CO_2Et—K_2CO_3/H_2O$, 20 °C; *i*. H_2—MBZ • $Cr(CO)_3/Me_2CO$, 120 °C; *j*. 1) KOH/MeOH—H_2O, 2) HCl (aq); *k*. Ph_3P—DEAD/PhMe, 20 °C.

Oxidative elimination of arylselenyl group from compound **37** proceeded smoothly to give (2*Z*,4*E*)-dodeca-2,4-dien-12-olide (**32**) in 91% yield, instead of the expected *E,E*-isomer. This stereochemical outcome can be explained by lesser conformational strain in the transition state leading to *syn*-elimination of ArSeOH; as a result, the 2*Z*-configured double bond is formed.

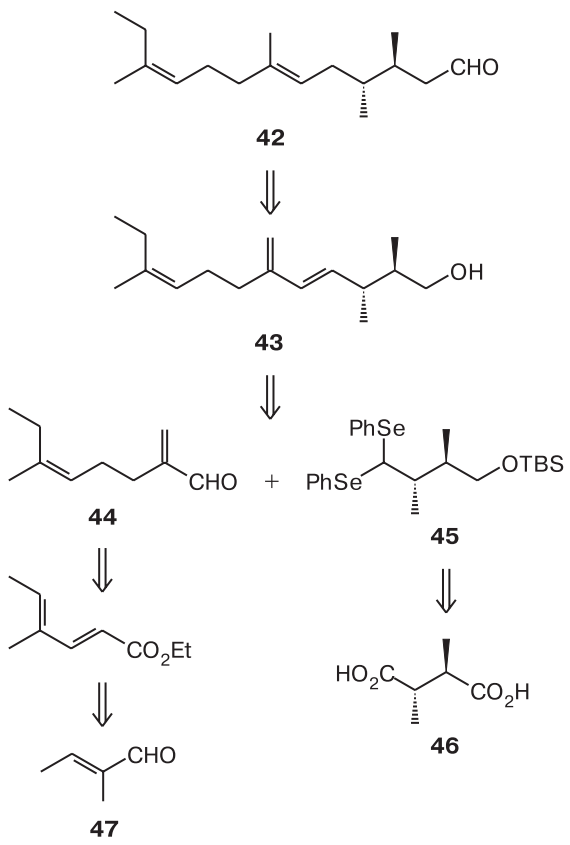
1,4-*cis*-Hydrogenation of diene lactone **32** in the presence of NP • $Cr(CO)_3$ proceeded to completion, and the target pheromone **31** was isolated in 65% yield. This result is of interest because the *Z,E*-diene system of lactone **32** appears to be prone to coordination with Cr^0 in the transition state. The overall yield of pheromone **31** in this route was 10.5% over nine synthetic steps.[43] The proposed method represents a conceptually new approach to the synthesis of macrocyclic (*Z*)-alk-3-enolides.

In another synthesis of pheromone **31**, acyclic diene ester **38** was used as the key intermediate (Scheme 18).[63] Diene **38** was prepared by olefinating of 10-hydroxy-2-decenal (**39**) (synthesized in seven steps from 1,10-decanedione monoacetate (**40**) *via* acetal **41**) with phosphoryl acetate. The passage from **41** to enal **39** was implemented using an original method of transforming 1,1-dialkoxyalkanes into α,β-alkenals (bromination,[44] nucleophilic selenation,[64] oxidative elimination, hydrolysis). By this route, lactone **31** was obtained in eleven steps in 16.5% overall yield.

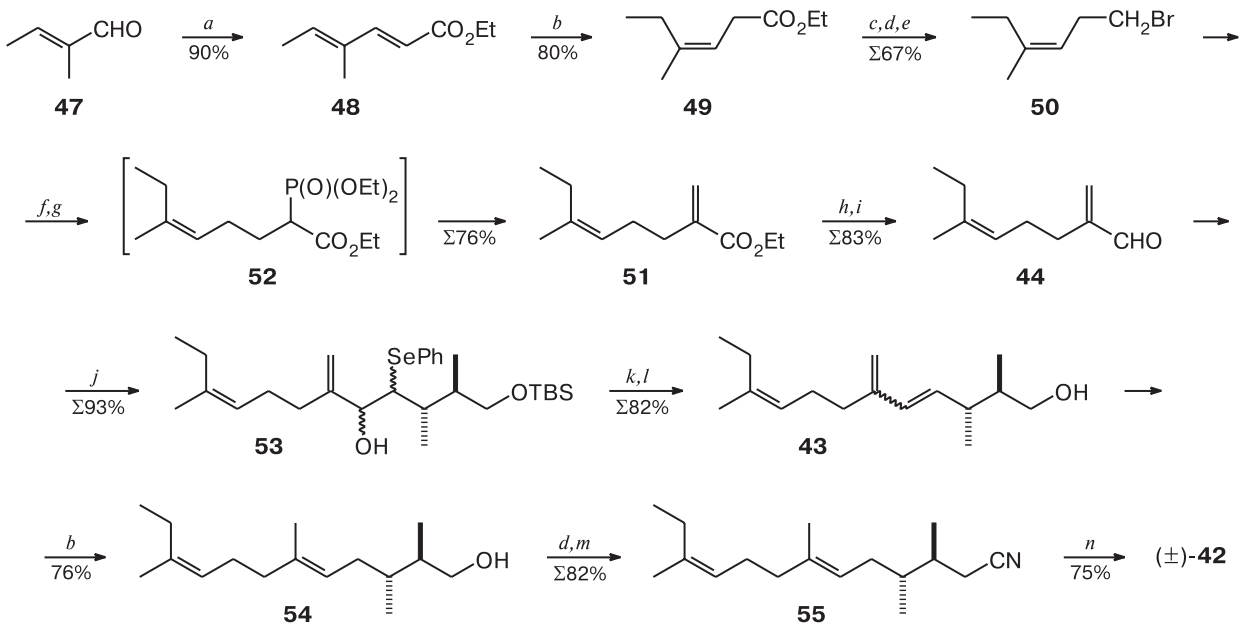
Synthesis of (±)-faranal: introduction of two isolated trisubstituted double bonds with E- and Z-configurations. The tiny pharaoh´s ant *Monomorium pharaonis* L. is a vehicle of salmonellosis and postoperative infections in hospitals. Its trail pheromone, (3*S*,4*R*,6*E*,10*Z*)-3,4,7,11-tetramethyltrideca-6,10-dienal (faranal, **42**), produced by pharaoh´s worker ants, is a promising tool for controlling the population of these insects. Previously, the addition of organocuprate reagents to monosubstituted alkynes has been the method of choice for the construction of both double bonds of faranal in the required configuration.[65,66] Other methods (see Ref. 50b) did not always ensure high stereoselectivity, which makes it necessary to separate the isomeric products with closely similar properties.

We proposed[67] a new strategy for the synthesis of racemic faranal (3*S**,4*R**)-**42**. The strategy is based on 1,4-*cis*-hydrogenation of properly substituted diene intermediates, which ensures stereospecific construction of both trisubstituted C=C bonds. Retrosynthetic analysis of faranal (Scheme 19) implies the hydrogenation of a conjugated diene of the type **43**. This can be prepared by olefination of the corresponding 2-substituted acrolein

Scheme 19



Scheme 20



Reagents and conditions: *a*. NaH—$(EtO)_2P(O)CH_2CO_2Et$/PhH; *b*. H_2—NP·$Cr(CO)_3$/THF, 70 °C (50 atm); *c*. $LiAlH_4$; *d*. TsCl/Py; *e*. NaBr/DMFA, 50 °C; *f*. NaH—$(EtO)_2P(O)CH_2CO_2Et$/DMSO, 50 °C; *g*. CH_2O—K_2CO_3; *h*. DIBAL (2 equiv.), −30 °C; *i*. 1) $(COCl)_2$—DMSO/CH_2Cl_2, −50 °C, 2) Et_3N; *j*. 1) BuLi/THF, −78 °C, 2) **45**; *k*. MsCl—Et_3N/CH_2Cl_2; *l*. Bu_4NF/THF; *m*. NaCN/DMSO, 50 °C; *n*. DIBAL/PhMe, −15 °C.

44 with the *Z*-configured alkene chain. It was planned to carry out the olefination by organoselenium Krieff´s method,[61a] which is equivalent to the Wittig strategy, but less sensitive to the nature of the substrate. This strategy implied the synthesis of selenoacetal **45** from commercially available *meso*-2,3-dimethylsuccinic acid (**46**).

The "left-hand" part of faranal, dienal **44**, was constructed starting with tiglic aldehyde (**47**) (Scheme 20), which was subjected to HWE olefination. The resulting dienoate **48** was 1,4-*cis*-hydrogenated to give ethyl (*Z*)-4-methylhex-3-enoate (**49**), which was converted into homoallylic bromide **50**. Successive one-pot treatment of triethyl phosphonoacetate with two different electrophiles afforded the 2-substituted acrylate **51**. Transition from this compound to dienal **44** took place uneventfully.

In order to introduce the second, *E*-configured double bond in the middle of the faranal molecule, aldehyde **44** was coupled with *erythro*-4-(*tert*-butyl)dimethylsilyloxy-2,3-dimethylbutanal selenoacetal (**45**)* by way of Krieff´s reaction pathway[61a] (Scheme 20, step *j*) in which the replacement of one PhSe group in the selenoacetal by lithium yields a carbanion stabilized by the second phenylselenyl group. The 1,2-addition of the carbanion to enal **44** gave β-hydroxy selenide **53** (a mixture of four diastereomers). Elimination of vicinal PhSe and HO groups with subsequent removal of the (*tert*-butyl)dimethylsilyl group afforded a mixture of 4*E*- and 4*Z*-isomers of conjugated diene **43** in the ratio $E : Z \approx 3 : 2$. Subsequent 1,4-*cis*-hydrogenation of this stereoisomer mixture resulted in individual 5*E*,9*Z*-diolefin **54**. This product was converted into (±)-faranal **42** by a known[68] route *via* nitrile **55**. The isomeric purity of the resulting sample of **42** was 94.5% (capillary GLC data).

Thus, 1,4-*cis*-hydrogenation of conjugated dienes proved to be an efficient reaction for the stereospecific construction of both (6*E*)- and (10*Z*)-trisubstituted double bonds of faranal **42**. The overall yield of (±)-faranal was 14.9% over fifteen steps based on tiglic aldehyde **47**.

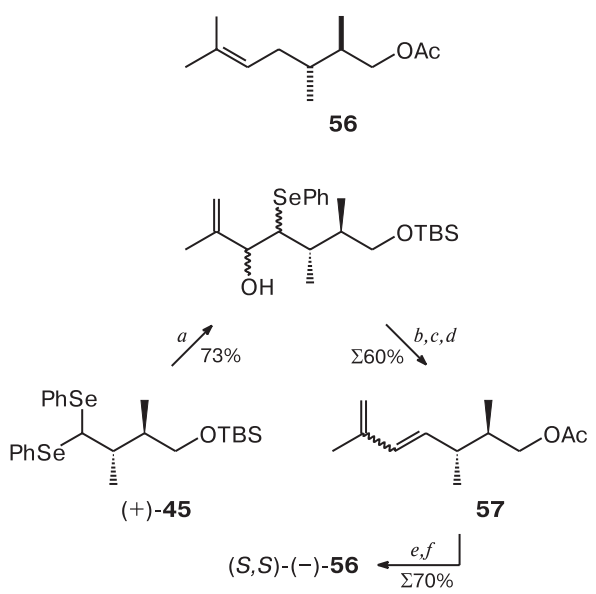
Synthesis of (2S,3S)-2,3,6-trimethylhept-5-en-1-ol ((−)-lasiol). Lasiol (**56**) is the major component of the secretion of mandibular glands of the ant *Lasius meridionalis*. Both optically active forms are known for molecule **56**.[69] Like faranal (**42**), molecule **56** contains an *erythro* fragment with two vicinal Me groups and a remote trisubstituted double bond, but its structure is markedly simpler. We synthesized the *S*,*S*-(−)-stereoisomer of alcohol **56** from optically active selenoacetal **45** * (Scheme 21)[70] using a strategy similar to that

* The synthesis of racemic selenoacetal **45** from commercially available *meso*-2,3-dimethylsuccinic acid (in 27% yield over seven steps) was described in the same publication.[67]

* The dextrorotatory acetal **45** was synthesized in the same way as the (±)-form used in the synthesis of (±)-faranal[67] (see above) with the difference that the intermediate *meso*-diol was asymmetrized using the PPL lipase.[70]

described above for introducing the internal double bond into the faranal backbone.

Scheme 21



Reagents and conditions: *a*. 1) BuLi/THF, −78 °C, 2) CH_2=CH(Me)CHO; *b*. MsCl—Et_3N/CH_2Cl_2; *c*. Bu_4NF/THF; *d*. Ac_2O—DMAP, chromatography; *e*. H_2—NP·$Cr(CO)_3$/THF, 50 °C (50 atm); *f*. K_2CO_3/MeOH.

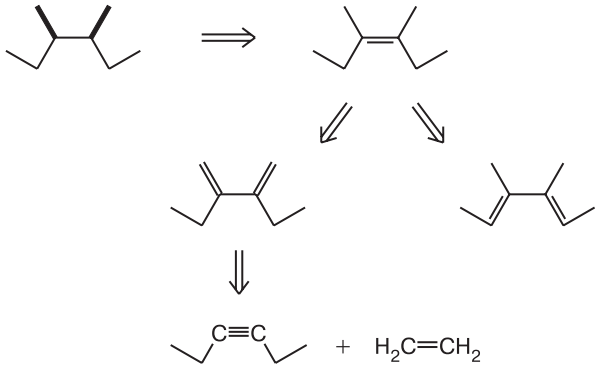
The proposed route is of interest, because in this case stereospecific 1,4-*cis*-hydrogenation of diene **57** is used to form a trisubstituted C=C bond in which *E,Z*-isomerism is degenerate.

2.2.3. Alkene-alkyne metathesis/1,4-cis-hydrogenation as a short approach to Z-tetrasubstituted olefins and their saturated analogs with erythro-configuration

Synthesis of erythro-5-benzyloxy-2,3-dimethylpentan-1-ol. The construction of a vicinal *erythro*-dimethyl fragment of faranal (**42**) or lasiol (**56**) is an interesting independent task. Previously, such duly configured synthons were prepared by multistep routes from compounds with a known arrangement of required substituents[69,70] or by stereospecific addition of tiglylmanganese chloride to methyl crotonate.[71]

We showed[72] that the required configuration of the —CH(Me)—CH(Me)— fragment could be attained upon 1,2-*syn*-hydrogenation of the corresponding *Z*-tetrasubstituted olefins. It was enticing to use 1,4-*cis*-hydrogenation of conjugated dienes of the dimethylene or dialkylidene types to prepare the tetrasubstituted olefins suitable for this purpose (Scheme 22). Convenient methods for the synthesis of dienes of the former type (by employing propargyl substrates and ethylene) were recently developed due to the progress in intermolecular alkene—alkyne metathesis.[73,74]

Scheme 22



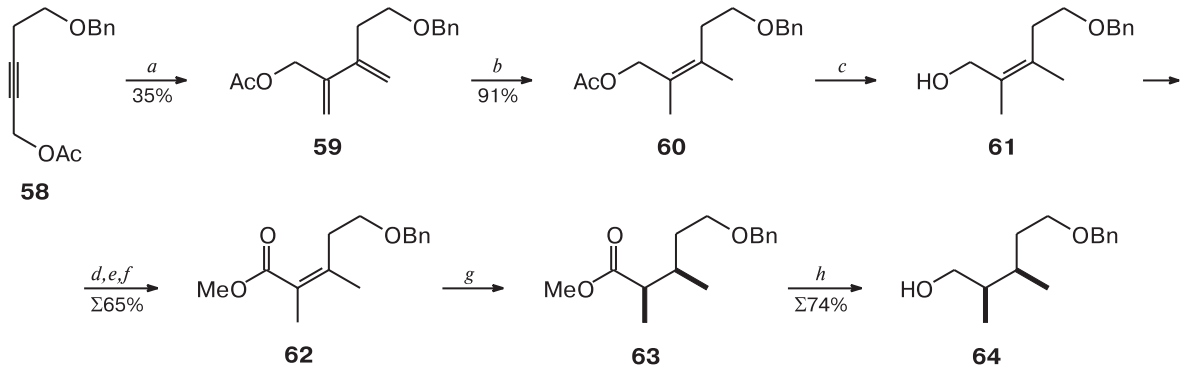
To verify this assumption, readily available 1-acetoxy-5-benzyloxypent-2-yne (**58**), which supplies the required number of carbon atoms to the backbone of the selected starting synthon **59** and contains an ether group (which may complicate the course of co-metathesis) at a sufficient distance from the reaction center, was introduced in the metathesis with ethylene on the Grubbs catalyst II[75] (Scheme 23).

Under optimal conditions of intermolecular ethylene—alkyne cometathesis,[73] compound **58** was transformed into diene **59**, the conversion depth being at most 43% due to the known[74] reversibility of metathesis processes. Attempts to increase the conversion by performing the process in an autoclave under pressure led to the opposite result, that is, the degree of conversion diminished.

Subsequent 1,4-*cis*-hydrogenation of diene **59** in the presence of NP·$Cr(CO)_3$ proceeded smoothly to give *Z*-tetrasubstituted olefin **60**. Attempts at *syn*-hydrogenation of the double bond in acetate **60** or in the corresponding allylic alcohol **61** in the presence of Raney nickel gave mainly the product that correesponded to hydrogenolysis of the allylic C—O bond. In order to minimize hydrogenolysis, alcohol **61** was subjected to stepwise oxidation to give the respective carboxylic acid, which was then converted into ester **62**. Hydrogenation of *Z*-tetrasubstituted acrylate **62** over Raney nickel did not affect the ester group and yielded a 90% pure specimen of *erythro*-isomer **63**. The relative arrangement of the methyl groups in compound **63** was proved by converting this compound into the benzyloxy-substituted alcohol **64**. Debenzylation of the alcohol (H_2—Pd/C) afforded the known *erythro*-2,3-dimethylpentane-1,5-diol. The *erythro*-configured alcohol **64** is a promising synthon *en route* to faranal (**42**) and lasiol (**56**).

Thus, the sequence of metathesis and 1,4-*cis*-hydrogenation reactions catalyzed by transition metal com-

Scheme 23



Reagents and conditions: *a*. C_2H_4—PhCH=$RuCl_2(PCy_3)_2$ (cat.)/CH_2Cl_2, ~20 °C; *b*. H_2—NP·$Cr(CO)_3$/THF, 45 °C (1 atm); *c*. MeOH—K_2CO_3, ~20 °C; *d*. 1) $(COCl)_2$—DMSO/CH_2Cl_2, −50 °C, 2) Et_3N; *e*. $NaClO_2$/1-methylcyclohexene—Bu^tOH—Na_2HPO_4 (aq), ~20 °C; *f*. CH_2N_2/Et_2O; *g*. H_2—Ni/Pr^iOH, ~20 °C (15 atm); *h*. $LiAlH_4/Et_2O$.

plexes appears to be a convenient strategy for the preparation of functionalized *Z*-tetrasubstituted olefins. When coupled with catalytic 1,2-*syn*-hydrogenation of the C=C bond, this algorithm can serve as a simple pathway to *vic*-dimethylated saturated synthon with the *erythro*-configuration.

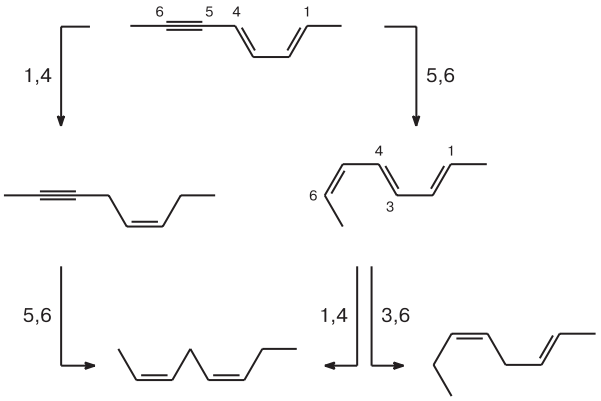
3. Hydrogenation of conjugated alkyne—diene systems: a new strategy for the synthesis of methylene-separated *all-Z*-polyenes

(η^6-Arene)tricarbonylchromium complexes catalyze not only 1,4-*cis*-hydrogenation of dienes but also 1,2-*syn*-hydrogenation of alkynes. Unlike the hydrogenations catalyzed by other transition metals, the latter results in *Z*-disubstituted alkenes with ~100% geometric purity without any alkane impurities.[1,76]

Hydrogenation of molecules in which the diene system is conjugated with an acetylene fragment has not been studied previously. The order of addition of hydrogen to each of the neighboring reaction sites is important from both preparative and mechanistic standpoints. If the diene fragment is the first to undergo hydrogenation (1,4-*cis*) so that the resulting *Z*-double bond is removed from conjugation, hydrogenation of the triple bond is expected to give a methylene-divided *Z,Z*-diene. Conversely, the initial hydrogenation of the triple bond (1,2-*syn*) should give rise to a conjugated triene, which can subsequently be converted along two parallel pathways to give a product mixture (Scheme 24).

We found that the reaction follows the former route. Hence, the affinity of Cr^0 to the diene system is higher than to the C≡C bond. Thus, hydrogenation of conjugated diene-acetylene systems can serve as a new method for the synthesis of methylene-separated *Z,Z*-diolefins.

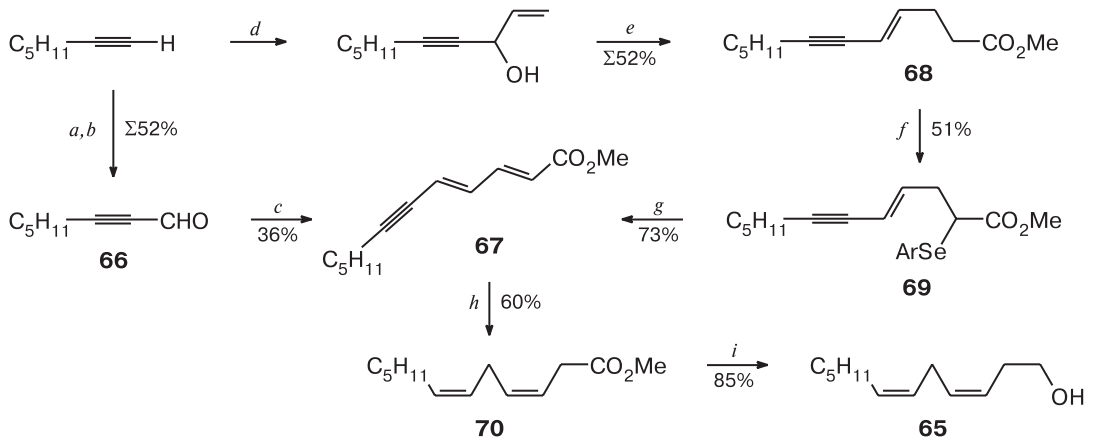
Scheme 24



Substructures of this type are encountered in many biologically active natural compounds, namely, in polyunsaturated fatty acids and the products of their metabolism, in prostaglandins, and related eicosanoids, as well as in the pheromones from the Lepidopterous and Coleopterous orders (see a review[77]). Evidently, the accessibility of the initial conjugated dienynes is a key factor in the approach in question.

Synthesis of (Z,Z)-dodeca-3,6-dien-1-ol. This diene alcohol (**65**) is a mimic of the trail pheromone produced by the workers of subterranean termite *Reticulitermes virginicus*. It proved to be a convenient object for testing this approach to methylene-separated polyenes. For the synthesis of compound **65** (Scheme 25),[28,30] hept-1-yne was converted into oct-2-ynal (**66**) in two simple steps; this aldehyde was olefinated by phosphoryl crotonate **11** to give dienyne ester **67** (2*E*,4*E* : 2*E*,4*Z* = 70 : 30) in an overall yield of 18.7% (over three steps). An alternative organoselenium pathway[42] that included the preparation and Claisen—Johnson rearrangement of a vinylalkynyl-

Scheme 25



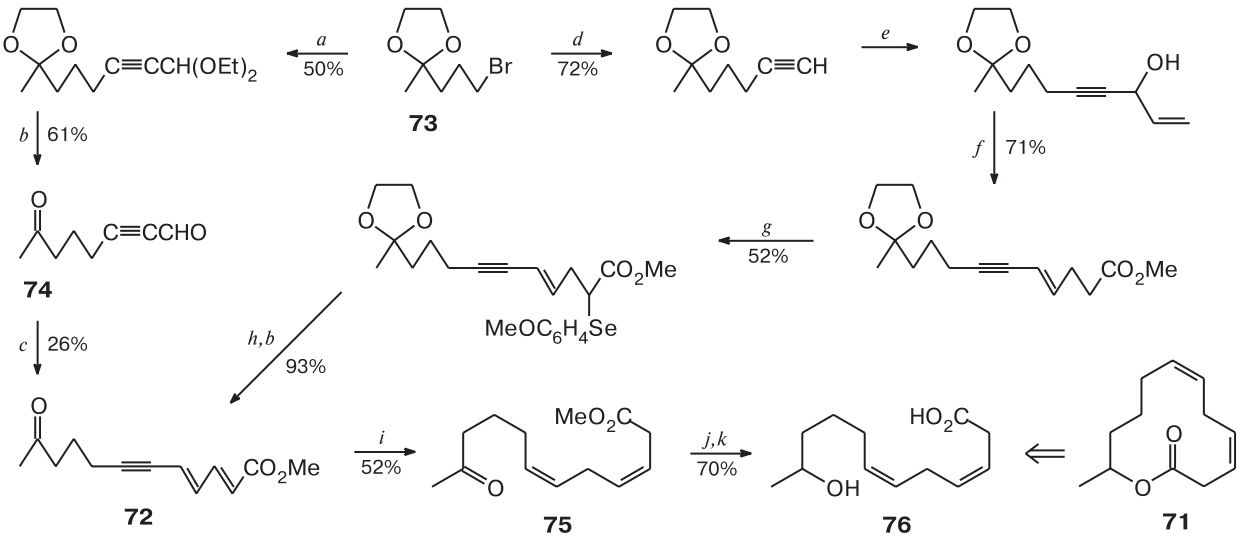
Reagents and conditions: *a*. 1) EtMgBr, 2) $CH(OEt)_3$; *b*. H_2O—$(HO_2C)_2$ (cat.)/Me_2CO, Δ; *c*. Phosphonate **11**—$NaNH_2$/THF, 0 °C; *d*. 1) BuLi/THF, 2) CH_2=CHCHO, 0 °C; *e*. $MeC(OMe)_3$—$EtCO_2H$/PhMe, 115 °C; *f*. 1) LDA—THF, −78 °C, 2) $(4\text{-}MeOC_6H_4)_2Se_2$; *g*. H_2O_2/THF, ~20 °C; *h*. H_2—MBZ·$Cr(CO)_3$/Me_2CO, 120 °C (80 атм); *i*. $LiAlH_4/Et_2O$.

carbinol, arylselenation of the resulting enyne ester **68**, and oxidative elimination of ArSeOH from selenide **69** resulted in dienyne **67** in a somewhat better overall yield (19.7% over four steps) and with a higher ratio of the 2*E*,4*E*-isomer to 2*E*,4*Z*-isomers (93 : 7).

Hydrogenation of dienyne ester **67** up to termination of H_2 absorption has produced individual 3*Z*,6*Z*-dienoate **70**, whose subsequent reduction afforded the target (*Z*,*Z*)-dodeca-3,6-dien-1-ol (**65**) of 98% purity.

Formal synthesis of (Z,Z)-dodeca-3,6-dien-11-olide. Subsequently, the new strategy was utilized in the synthesis of a more complex compound, (*Z*,*Z*)-dodeca-3,6-dien-11-olide (**71**), the aggregation pheromone of the cucujid beetles *Oryzaephilus surinamensis* (the Surinamese grain beetle, a dangerous granary pest) and *O. mercator* (Scheme 26).[44,78] The key intermediate of this synthesis, the dienyne oxo ester **72**, was prepared from accessible 2-(3-bromopropyl)-2-methyldioxolane (**73**) using either

Scheme 26



Reagents and conditions: *a*. $NaC{\equiv}CCH(OEt)_2/NH_3$ (liq.)—THF; *b*. H_2—$(HO_2C)_2$ (cat.)/Me_2CO, Δ; *c*. phosphonate **11**—$NaNH_2$/THF, 0 °C; *d*. $HC{\equiv}CLi/(NH_2CH_2)_2$—DMSO, 20 °C; *e*. 1) BuLi—THF, 2) CH_2=CHCHO, 0 °C; *f*. $MeC(OMe)_3$—$EtCO_2H$ (cat.)/PhMe, 115 °C; *g*. 1) LDA/THF, −78 °C, 2) $(4\text{-}MeOC_6H_4)_2Se_2$; *h*. H_2O_2/THF, 20 °C; *i*. H_2—MBZ·$Cr(CO)_3$/Me_2CO, 120 °C; *j*. $NaBH_4$/EtOH—H_2O; *k*. 1) KOH/EtOH—H_2O, 2) HCl (aq).

the phosphonate[44] or organoselenium[78] algorithm (three or six steps, overall yield ~8 or ~25%, respectively).

Hydrogenation of dienyne **72** in the presence of MBZ•$Cr(CO)_3$ afforded the methylene-separated *Z,Z*-diolefinic oxo ester **75**. The two-step transformation of oxo ester **75** into the known hydroxy acid **76** (the immediate precursor of pheromone **71**) was carried out as a one-pot synthesis. The preparation of acid **76** completes the formal synthesis of macrolide **71**. The yield of compound **76** calculated on the basis of bromide **73** amounted to 9% (the organoselenium strategy). The known syntheses of intermediate **76** (and, hence, lactone **71**) are multistep and laborious procedures (see reviews[48d,77]).

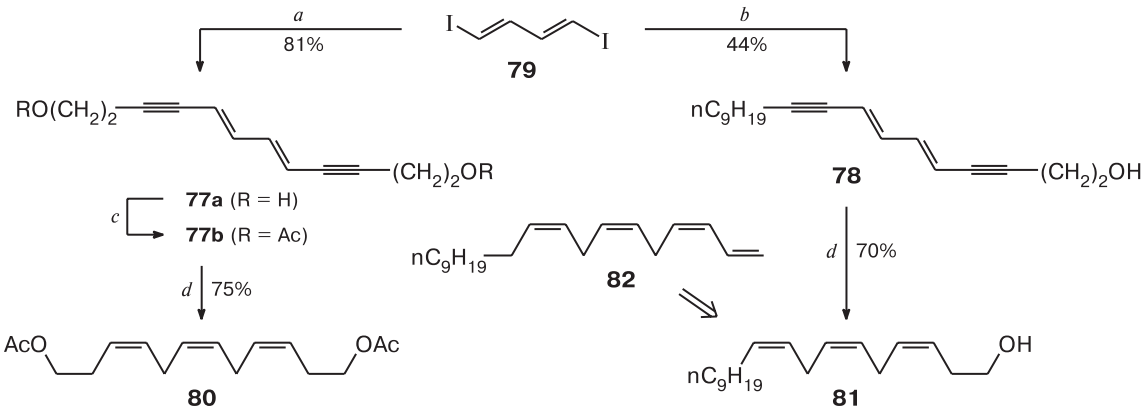
Hydrogenation of conjugated 3,5-diene-1,7-diyne systems catalyzed by chromium carbonyl complexes as a pathway to (Z,Z,Z)-1,4,7-trienes. Formal synthesis of the pheromone of winter moth Operophtera brumata. In order to extend the scope of the new strategy of obtaining methylene-separated *Z*-polyenes, we studied hydrogenation of other substrates containing conjugated double and triple bonds, namely, symmetrical (**77a,b**) and asymmetrical molecules (**78**) with acetylene fragments in positions 1 and 4 of the diene system (Scheme 27).[79] As the starting compound, we used (*E,E*)-1,4-diiodobuta-1,3-diene (**79**),[80] which is readily prepared by the reaction of acetylene with iodine in MeOH in the presence of Na_2PtCl_6. The synthesis of dienediynes of types **77** and **78** included the cross-coupling of diiodide **79** with two terminal alkynes according to a modified Sonogashira´s method.[81]

Using this procedure, symmetrical dienediyne **77a** was prepared in a good yield from but-3-yn-1-ol and diiodide **79**; this product was then converted into diacetate **77b**. When preparing an asymmetrical dienediyne, it is expedient to use terminal alkynes with different polarities, because in this case the components of the reaction mixture can be separated by column chromatography. For example, consecutive one-pot cross-coupling of diiodide **79** with but-3-yn-1-ol and undec-1-yne gave nonadeca-5,7-diene-3,9-diyn-1-ol (**78**) in 44% yield.

Analysis of the products obtained upon hydrogenation of dienediynes **77b** and **78** under mild conditions (with NP•$Cr(CO)_3$ as the catalyst) showed that methylene-separated *Z,Z,Z*-trienes **80** and **81** are the major products. However, the selectivity of hydrogenation of substrates **77b** and **78** did not exceed 75% after complete conversion of initial substrates. The side products had the same carbon skeleton as trienes **80** and **81**, but contained only two double bonds separated by two or more methylene groups. Apparently, this result can be explained by the fact that carbonyl chromium complexes induce slow isomerization of 1,4-dienes into conjugated isomers,[12,33,82] which undergo 1,4-*cis*-hydrogenation in a hydrogen atmosphere. The difference between the selectivities of synchronous hydrogenation of conjugated dienyne esters **66**, **72** and dienediynes **77b** and **78** might be due to unequal stabilities of the main reaction products, *i.e.*, homoconjugated (*all-Z*)-polyenes: triolefins are isomerized more easily than diolefins under similar conditions. One cannot rule out that a statistically more probable process for the products of incomplete hydrogenation of dienediynes is isomerization of the $C{\equiv}C{-}CH_2{-}CH{=}CH$ fragment into the vinylallene system, $CH{=}C{=}CH{-}CH{=}CH$, which is potentially able to add H_2 in the presence of NP•$Cr(CO)_3$.

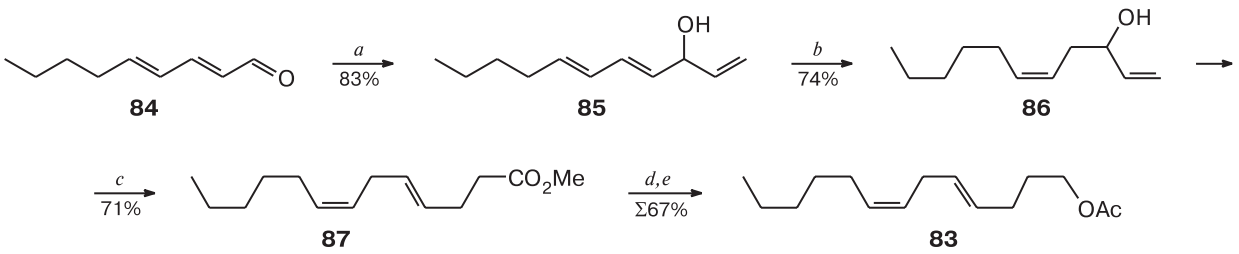
(*Z,Z,Z*)-Nonadeca-3,6,9-trienol (**81**) is a key intermediate in the known[83] synthesis of (*Z,Z,Z*)-nonadeca-1,3,6,9-tetraene (**82**), the sex pheromone of winter moths *Operophtera brumata* (a widespread fruit-tree pest). Thus, the short synthesis of triene **81** is equivalent to formally

Scheme 27



Reagents and conditions: *a*. $PdCl_2(PPh_3)_2$, PPh_3/pyrrolidine, 20 °C, 2 equiv. $HC{\equiv}C(CH_2)_2OH$; *b*. $PdCl_2(PPh_3)_2$, PPh_3/pyrrolidine, 20 °C, 1 equiv. $HC{\equiv}C(CH_2)_2OH$ + 1 equiv. $C_9H_{19}C{\equiv}CH$; *c*. Ac_2O—Py; *d*. H_2—NP•$Cr(CO)_3$/THF, 45 °C, 50 atm.

Scheme 28



Reagents and conditions: *a*. CH_2=CHMgBr/THF; *b*. H_2—MBZ·$Cr(CO)_3$/Me_2CO, 125 °C, 80 atm; *c*. $MeC(OMe)_3$, H^+, Δ; *d*. $LiAlH_4$; *e*. Ac_2O.

the total synthesis of pheromone **82** in which all building blocks have been obtained from acetylene. Although such a method of obtaining of homoconjugated *Z*,*Z*,*Z*-trienes requires further optimization (to increase hydrogenation selectivity), there are grounds to regard it as a new strategy for the synthesis of this type of compound.

Table 3. Summary of the results on the stereocontrolled synthesis of olefins based on the Frankel reaction (see Sections 2—4 of the review)

Synthesized olefin	General type of the initial compound	Key reagents other than H_2—"$Cr(CO)_3$"	Yield (the number of steps in the algorithm)	Refs
R⁄⁄C(FG)	RCHO	$(EtO)_2P(O)CH_2CO_2Alk$	33—39 (2)	27, 28, 30
		CH_2=CHMgBr, $MeC(OMe)_3$, Ar_2Se_2	25 (5)	42
	RCH=CHCHO	$(EtO)_2P(O)CH_2CO_2Alk$	46 (2)	63
		MeC(O)R´	13—22 (2)	22
	RCH_2CH_2CHO	$(EtO)_2P(O)CH_2CO_2Alk$, Ph_2Se_2	32 (6)	63
R⁄⁄C(FG)	RCHO	$(EtO)_2P(O)CH_2CO_2Alk$	21—59 (2)	27, 30, 57
R⁄⁄C(FG)	R⁄⁄CHO	$(EtO)_2P(O)CH_2CO_2Alk$	72 (2)	67
R⁄⁄R¹	R⁄⁄CHO	$(EtO)_2P(O)CH_2CO_2Alk$	58 (2)	28, 30
		or $(PhSe)_2CH$—R´	31—58 (3)	67, 70
R⁄⁄R¹	R⁄⁄O	CH_2=CHMgBr	15 (3)	23
	R⁄⁄OAc	CH_2=CH_2	32 (2)	72
C(FG)⁄⁄R	RC≡CCHO	$(EtO)_2P(O)CH_2CO_2Alk$	13—22 (2)	30, 78
	RC≡CH	CH_2=CHCHO, $MeC(OMe)_3$, Ar_2Se_2	12—18 (5)	42
R¹⁄⁄R²	R^1C≡CH R^2C≡CH	I—CH=CH—CH=CH—I	22—49 (2)	79
R⁄⁄C(FG)	R⁄⁄CHO	CH_2=CHMgBr, $MeC(OMe)_3$	43 (3)	84

4. New approach to the preparation of methylene-separated *Z*,*E*-dienes

Synthesis of (4E,7Z)-trideca-4,7-dien-1-yl acetate. *(4E,7Z)*-Trideca-4,7-dien-1-yl acetate (**83**), one of the two components of the sex pheromone of potato moth *Phtorimaea operculella*, is a relatively rare example of a natural 1,4-diene with differently configured double bonds. Two stereochemical tasks are involved in the synthesis of compound **83**, namely, the formation of a *Z*-configured Δ^7-bond and a *E*-configured Δ^4-bond separated by one CH_2 unit. In the previous works dealing with the synthesis of diene **83** (see monographs[59a,b]), these problems were mainly solved by traditional methods.

We proposed a simple scheme for the preparation of pheromone **83** from commercially available 2,4-nonadienal **84** (Scheme 28).[84] The key step of the synthesis is 1,4-*cis*-hydrogenation of the conjugated diene system in 1,4,6-trien-3-ol **85** catalyzed by the MBZ•$Cr(CO)_3$ complex. This gives rise to *Z*-olefin **86**. Further transformation of alcohol **86** into the target product **83** was based on the Claisen—Johnson reaction, which ensures high configurational purity of the incoming *vic*-disubstituted $\Delta^{4(E)}$-bond of compound **87** and completes the three-step protocol for constructing the homoconjugated *E*,*Z*-diene. The purity of the resulting pheromone **83** was at least 95% (capillary GLC data).

Thus, *(E,Z)*-trideca-4,7-dien-1-yl acetate (**83**) was prepared in only five preparatively convenient steps in 29% yield based on the starting nonadienal **84**.

5. Conclusion

Our research confirmed that the synthesis of insect pheromones is actually a convenient testing ground for the development of methods and protocol for the stereocontrolled construction of olefinic bonds of different types based on 1,4-*cis*-hydrogenation of dienes as the key step. The results obtained by the authors while using and furthering this strategy of olefin synthesis are summarized in Table 3.

The type of substitution and double bond configuration in final olefins are determined by the type of substitution at the double bonds in the diene. Synthetic strategy used to prepare particular compounds included most often olefination of a carbonyl compound followed by 1,4-*cis*-hydrogenation of the resulting conjugated diene.[27,28,30,57,67,78] Another convenient approach to conjugated dienes is based on the successive Claisen—Johnson reaction, α-selenation of alkyl 4-alkenoates, and oxidative elimination of the seleno group.[42,43,63] The previously unknown hydrogenation of conjugated acetylene-diene systems in the presence of carbonyl chromium complexes is a new approach to the construction of methylene-separated (*all-Z*)-polyenes.[28,31,78,79] Interesting opportunities provided by application of the Frankel reaction to diene systems prepared by the Krieff reaction[67,70] and alkene-alkyne metathesis[72] were used. In the latter case, the resulting tetrasubstituted alkenes hold good prospects for the synthesis of saturated *vic*-disubstituted functional compounds with *erythro*-configurations.

The developed methods promote the design of improved synthetic protocols for the preparation of olfactory-active olefins such as fragrance compounds and insect pheromones.

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Received January 21, 2002
in revised form June 28, 2002