α,ω-Dicarbonyl 1,5-unsaturated isoprenoids with (*Z*)- and (*E*)-configured Δ-bonds in the synthesis of low-molecular-weight bioregulators

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Syntheses carried out with participation of the author of terpenoids, polyprenols, prenylcarboxylic acids, insect pheromones, and juvenoids based on α,ω-dicarbonyl 1,5-unsaturated isoprenoid compounds with (*Z*)- and (*E*)-configurations, obtained by controlled ozonolysis of isoprene cyclic oligomers and polyisoprene rubbers, are considered.

Key words: isoprene cyclic oligomers, (*Z*)- and (*E*)-1,5-polyisoprenes, controlled (selective, partial) ozonolysis, synthesis of acyclic terpenoids, polyprenols, prenylcarboxylic acids, pheromones, juvenoids.

The interest in terpenoids and compounds containing terpene fragments is due to the fact that these substances exhibit various important activities in living organisms.[1] One approach to the synthesis of representatives of, for example, pheromones, juvenoids, polyprenols, and polyprenylacetic acids is based on the use of isoprenoid synthetic blocks.[2—7]

We synthesized terpenoid 1,5-polyenes, pheromones, juvenoids, polyprenols, and prenylcarboxylic acids starting from α,ω-dicarbonyl (*Z*)- or (*E*)-1,5-unsaturated isoprenoids, prepared by selective ozonolysis of isoprene cyclic oligomers and polyisoprene rubbers.

1,5-Unsaturated isoprenoid synthons based on partial ozonolysis of regular isoprene cyclooligomers and 1,5-polyisoprenes

Study of the ozonolysis of cyclodimers of 1,3-dienes[8] made it possible to find conditions for selective cleavage of one multiple bond in the starting diene or triene. When the latter are ozonized in cyclohexane in the presence of two molar equivalents of methanol, the selectivity of monoozonolysis does not decrease markedly until 0.9 equiv. of O_3 has been supplied. Under these conditions, the peroxide product of ozonolysis, which is more polar than the starting olefin, separates from the solution, which is favorable for monoozonolysis. The subsequent hydrogenation of peroxides in acetone over Lindlar catalysts affords the corresponding unsaturated acyclic α,ω-dioxo derivatives in 70—85% yields.[9] In the case of ozonolysis of cyclic dienes and trienes containing both (*E*)- and (*Z*)-configured double bonds, it involves the (*E*)-substituted double bond with high selectivity[10]; in addition, for the partial ozonolysis of 1-methyl-1*Z*,5*Z*-cyclooctadiene, containing both di- and trisubstituted double bonds, it was shown[11,12] that ozone attacks predominantly the more substituted bond.

This approach was employed to convert cyclodiene **1** into (*Z*)-4-methyl-8-oxonon-4-enal (**2**) (Scheme 1).[9] Treatment of the peroxide product of partial ozonolysis of diene **1** with potassium borohydride gave diol **3** (which was then converted into diacetate **4**).[11] Monoacetal **5**, which is formed selectively on treatment of compound **2** with methanol in the presence of ammonium chloride[9] possesses a greater synthetic potential.

Similarly, partial ozonolysis of cyclotriene **6** was used to prepare keto aldehyde **7**, acetal **8**, and diol **9**; the latter was converted into diacetate **10** [13] (see Scheme 1).

In order to prepare C_{10}-terpenoid keto aldehyde with (*E*)-configuration, the amount of ozone delivered in the ozonization of trimer **6** was increased to an equimolar amount (further increase in the consumption of O_3 resulted in nonproportionally fast accumulation of the product of exhaustive ozonization of **6**) and, after the pool of keto aldehydes had been converted into a mixture of keto acetals, keto acetal **8** and *E*-6-methyl-9,9-dimethoxynon-5-en-2-one (**11**) were isolated by vacuum distillation in 54 and 20% yields, respectively.[14] When keto acetal **8** is ozonized under the same conditions as the starting triene **6**, absorption of 0.7 equiv. of O_3 results in a mixture of keto acetals **8** and **11** in 44 : 56 ratio. Thus, successive ozonization of trimer **6** and C_{15}-keto acetal **8**, prepared from it, allows the synthesis of (*E*)-monoene C_{10}-keto acetal **11** in a yield reaching 40% based on the initial **6**.[14]

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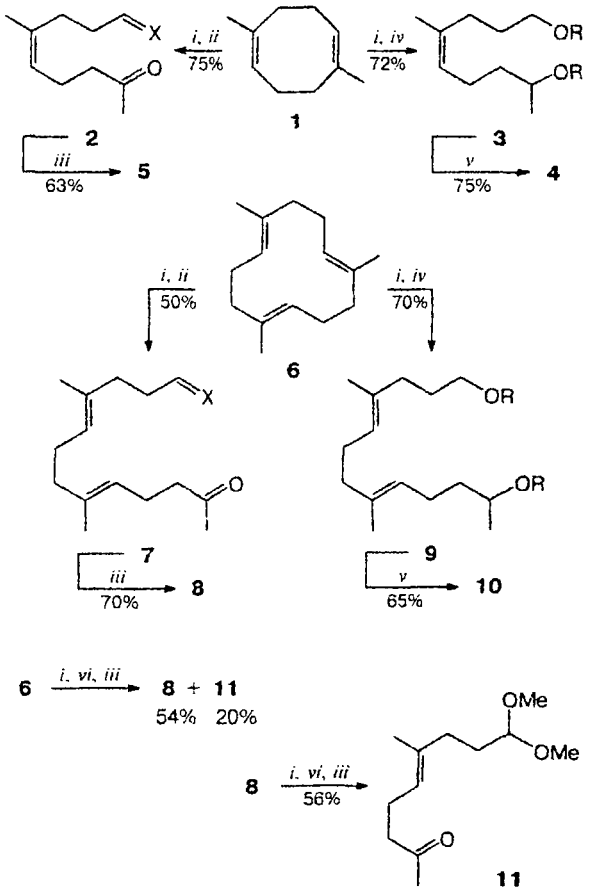
Scheme 1



X = O (**2**, **7**), $(OMe)_2$ (**5**, **8**); R = H (**3**, **9**), Ac (**4**, **10**)

Reagents and conditions: *i.* O_3/*cyclo*-C_6H_{12}—MeOH, 5 °C; *ii.* H_2/Pd—$CaCO_3$—PbO/Me_2CO; *iii.* MeOH/NH_4Cl; *iv.* KBH_4/MeOH; *v.* Ac_2O/Py; *vi.* Pd—$CaCO_3$—PbO/MeOH.

Conditions have been found for the transformation of (*Z*)-1,5-polyisoprene **12** (natural rubber and SKI-3 synthetic rubber) into (*Z*)-1,5-oligoisoprene-α,ω-diols (**13**)[15] by selective ozonolysis followed by reduction of oligomeric ozonides. The transformation of diols into bis(trimethylsilyl) (TMS) ethers or diacetates with subsequent vacuum distillation yields individual TMS ethers **14**—**18** and, correspondingly, diacetates **4**, **19**—**22** with exceptionally regular (*Z*)-1,5-polyprenoid structure and the number of isoprene units (*n*) ranging from one to five[16] (Scheme 2).

It was also found that partial ozonolysis of polymer **12** followed by reduction of the peroxides by either hydrogen over Lindlar catalyst or dimethyl sulfide gives rise to oligomeric ω-*C*-acetyl-(*Z*)-1,5-polyene aldehydes (**23**), which were then converted into a mixture of the corresponding dimethyl acetals. Individual (*Z*)-1,5-polyene isoprenoid keto acetals **5** and **24**—**27** with numbers of isoprene units (*n*) of 1 to 5 were isolated by vacuum fractionation.[17] Similarly, based on the partial ozonolysis of (*E*)-1,5-polyisoprene **28** (natural gutta-percha or its synthetic analog), a new approach to the synthesis of acyclic α,ω-bifunctional regular (*E*)-1,5-oligoisoprenoids was developed.[18] After transformation of the mixture of oligomeric isoprenol diols **29** into their bis-TMS ethers or diacetates, bis-TMS ethers **30** and **31** and diacetates **10**, **32**, and **33** were isolated by vacuum distillation[19] (see Scheme 2).

Synthesis of terpenoid 1,5-polyenes

Selective ozonolysis of isoprene cyclic dimer and trimer and (*Z*)- and (*E*)-1,5-polyisoprenes opened up a simple route to terpenoid 1,5-polyenes. Selective olefination of keto aldehydes **2** and **7** involving the aldehyde group gave (*Z*)-geranyl- (**34**) and (*E*,*E*)-farnesylacetone (**35**)[20] (Scheme 3). The reaction of the latter compound or its perhydro derivative (**36**) with vinylmagnesium bromide, together with ozonolysis of cyclotrimer **6** and olefination of C_{15}-keto aldehyde **7**, constitute a new approach to the synthesis of (*E*,*E*)-geranyllinalool (**37**) and isophytol (**38**), which are isoprenoid synthons for the synthesis of α-tocotrienol and α-tocopherol.[21]

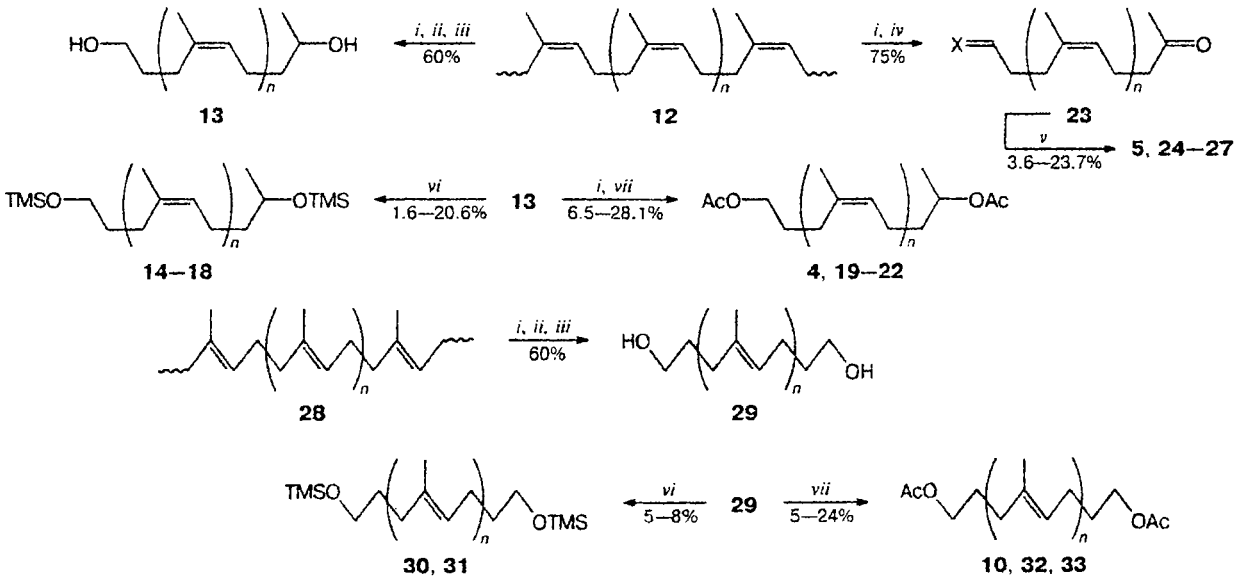
This approach using keto aldehydes **39** and **40**, prepared in two steps from bis-TMS ethers **30** and **15** or from diacetates **10** and **19**, was employed to synthesize (*E*)-geranyl- (**41**) and (*Z*,*Z*)-farnesylacetone (**42**), respectively[19] (see Scheme 3).

Keto aldehyde **2** served as the starting compound for the preparation of keto ester **43**, which was used in the synthesis of modified prostaglandins[22] (Scheme 4). Selective protection of the aldehyde group in keto aldehydes **2** and **7** permitted olefination of these compounds at the oxo group. The resulting acetals **44** and **48** were used to prepare oligoolefins **45**—**47** and **49**, which possess a carbon skeleton and functional groups needed for electrophilic cyclization (to chromene structures)[23] (see Scheme 4).

Selective transformations of keto acetals **11** and **8** served as the basis for a new method of stereospecific synthesis of (*E*,*E*)-farnesol (2*E*-**54**) and geranylgeraniol (2*E*-**55**)[14] (Scheme 5). Olefination of **11** and **8** by the α-silylated carbanion generated from ethyl TMS-acetate resulted in the synthesis of a mixture of esters **50** and **51**, respectively (2*E*/*Z*-isomer ratio ~ 55 : 45). Their isomerization on treatment with Pr^iONa resulted in stereoisomers 2*E*-**50** and 2*E*-**51** as a mixture of ethyl and isopropyl esters, whose acid hydrolysis followed by olefination gave ethyl (*E*,*E*)-farnesoate (2*E*-**52**) and geranylgeranate (2*E*-**53**). Their selective reduction yielded target terpenols 2*E*-**54** and 2*E*-**55** (see Scheme 5).

The interest in the derivatives of prenols and prenylcarboxylic acids is due to their high and versatile physiological activities.[4]

Scheme 2

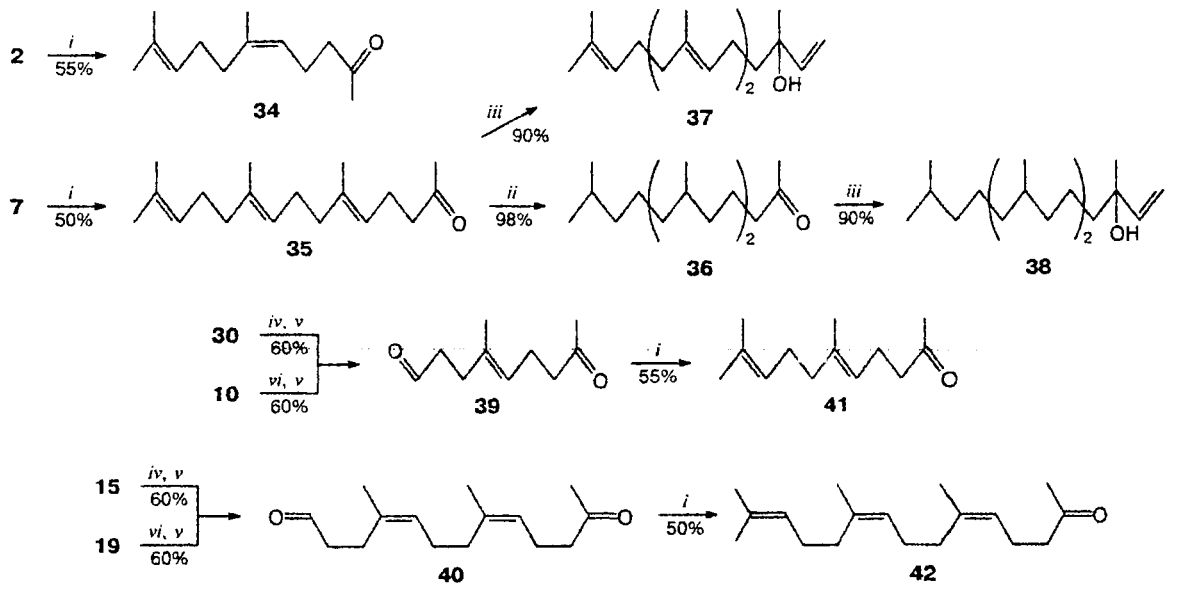


n = (8–9)·10^3 (**12**), (2–3)·10^3 (**28**), 0–5 (**13**, **23**), 0–3 (**29**), 1 (**4**, **5**, **10**, **14**, **30**), 2 (**15**, **19**, **24**, **31**, **32**), 3 (**16**, **20**, **25**, **33**), 4 (**17**, **21**, **26**), 5 (**18**, **22**, **27**); X = O (**23**), $(OMe)_2$ (**5**, **24–27**)

Reagents and conditions: *i.* O_3/PhH–MeOH, –20 °C; *ii.* H_2/Pd–$CaCO_3$–PbO; *iii.* DIBAH/PhH, –80 °C; MeOH–PhH, 8 °C; MeOH–H_2O; *iv.* Me_2S; *v.* MeOH/PhH/NH_4Cl; *vi.* TMSCl/Py/PhH; *vii.* Ac_2O/Py.

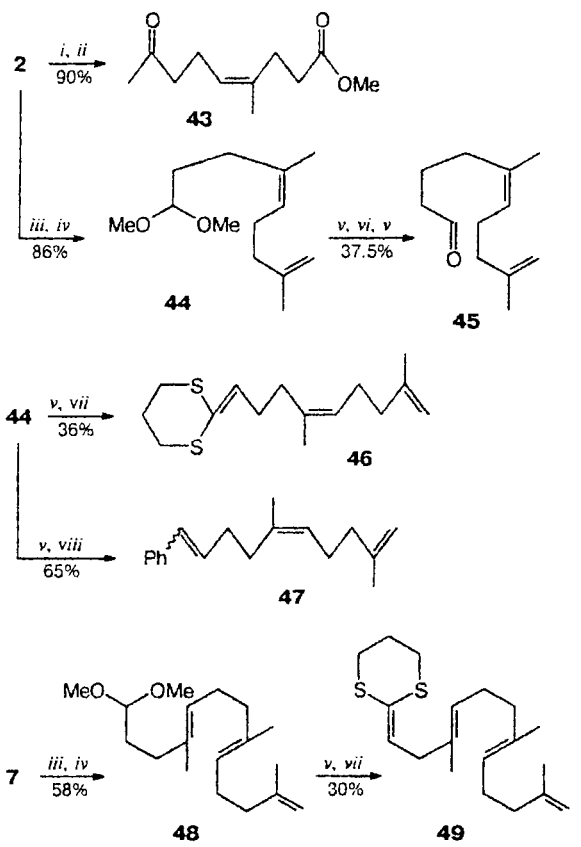
Keto acetals **11** and **8** served as convenient starting compounds for the synthesis of esters of 2,3-dihydro derivatives of prenylic acids. For this purpose, they were converted into methyl (**52a**, **53a**), ethyl (**52b**, **53b**), and isopropyl (**52c**, **53c**) farnesoates and geranylgeranates (see Scheme 5). Hydrogenation of esters **52a–c** and

Scheme 3



Reagents and conditions: *i.* Pr^iPh_3PBr/Bu^nLi/THF–*n*-C_6H_{14}, –40→25 °C, –78→25 °C; *ii.* H_2/10%Pd–C, EtOH; *iii.* CH_2=CHMgBr/THF; *iv.* EtOH/HCl–H_2O; *v.* $(COCl)_2/Et_3N/Me_2SO$–CH_2Cl_2, –60 °C; *vi.* EtOH/NaOH–H_2O.

Scheme 4



Reagents and conditions: *i.* $AgNO_3/KOH/H_2O$—EtOH; *ii.* CH_2N_2/Et_2O; *iii.* $MeOH/NH_4Cl$; *iv.* $MePh_3PBr/Bu^tOK/THF$, −30→25 °C; *v.* $TsOH/Me_2CO$(aq.); *vi.* $MeOCH_2Ph_3PCl/Bu^nLi/THF$—$n$-$C_6H_{14}$, −20 to −10→25 °C; *vii.* S=⟨S⟩ /$(EtO)_3P$; *viii.* $BnPh_3PCl/Bu^nLi/Et_2O$—n-C_6H_{14}.

53a—c by an equimolar amount of hydrogen in the presence of platinum black[25] proved to be the best procedure for preparing target 2,3-dihydro derivatives **60a—c** and **61a—c** (see Scheme 5).

An alternative pathway to esters **60a—c** and **61a—c**,* based on condensation of keto acetals **11** and **8** with diethyl malonate, was also found[25] (see Scheme 5). Selective reduction of the Δ^2-bond in diesters **62** and **63** was easily accomplished by treating these compounds with $NaBH_4$, which gave 2,3-dihydro derivatives **64** and **65**. By standard operations including decarboxylation of diesters **66** and **67**, the latter were converted into esters **60b** and **61b**, whose overall yields were 23—27% based on the starting keto acetals **11** and **8**.

To prepare other esters (**60a,c** and **61a,c**), compounds **66** and **67** were hydrolyzed and the corresponding geminal dicarboxylic acids were decarboxylated. Monocarboxylic acids **68** and **69** thus formed were esterified *via* the corresponding acid chlorides to give esters **60a,c** and **61a,c** in 8—10% yields based on the starting keto acetals **11** and **8** [25] (see Scheme 5).

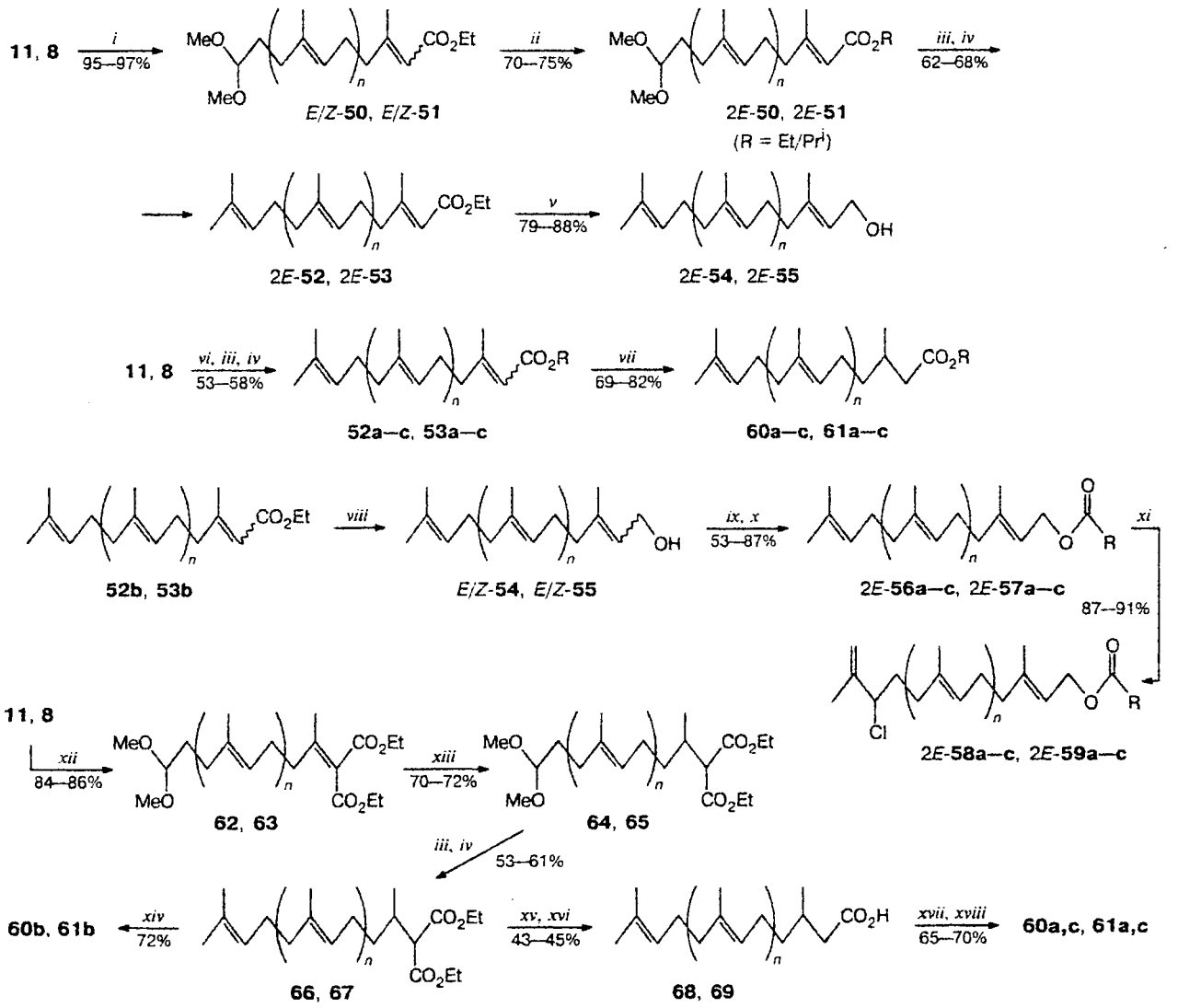
We propose a synthesis of chlorinated acylprenols based on esters **52b** and **53b**. Reduction of these isomer mixtures with DIBAH at low temperatures occurred highly selectively involving the Δ^2-bond and gave mixtures of 2*E*/*Z*-farnesols (**54**) and 2*E*/*Z*-diterpenols (**55**), which were then converted by treatment with the corresponding acyl chlorides into acetates **56a**, **57a**, propionates **56b**, **57b**, and isovalerates **56c**, **57c** with a 2*E*/*Z*-isomer ratio (70 : 30) identical to that observed in the initial esters **52b** and **53b**. Chromatography gave virtually exclusively stereoisomers 2*E*-**56a—c** and 2*E*-**57a—c** (the content of 2*Z*-isomer was ≤5%). Their treatment with SO_2Cl_2 afforded the target chlorinated derivatives 2*E*-**58a—c** and 2*E*-**59a—c** in high yields [24] (see Scheme 5).

Blocks of isoprenoid units having specified terminal functional groups and double bonds with a definite geometry in a specified position required for the synthesis of physiologically active polyprenols, which are exceptionally important in the biosynthesis of carbohydrate-containing biopolymers,[26] were prepared by oxidative cleavage of the terminal double bond in acyclic terpenoids including selective ozonolysis of the isopropylidene group in linear isoprenoid compounds.[27,28] The isoprenoid blocks **24** and **25**, obtained by partial ozonolysis of rubber and gutta-percha, are quite promising in this respect; this was demonstrated by the synthesis of the racemic octaprenol wtttccccsOH and nonaprenol wtttccccsOH based on these compounds [29] (Scheme 6). To carry out this synthesis using the previously developed procedure for controlled aldol condensation,[30] compounds **24** and **25** were converted into isoprenoid aldehyde blocks **76** and **77** *via* esters **70** and **71** (2*Z*/*E* = 3 : 2), alcohols **72** and **73**, and the corresponding benzyl ethers **74** and **75** (see Scheme 6).[29]

Condensation of aldehydes **76** and **77** with the lithium derivatives of the isoprenoid aldimine **78** resulted in disubstituted (*E*)-acroleins **79** and **80**, which were more than 95% stereochemically pure according to the data of ^1H NMR spectra. The subsequent hydride reduction of **79** and **80** to carbinols **81** and **82** and their deoxygenation yielded benzyl ethers **83** and **84**, whose debenzylation gave rise to the target polyprenols **85** and **86** (see Scheme 6). The stereochemical purity of the isoprenoid blocks[31] and polyprenols **85** and **86**, synthesized by ozonolysis of rubbers, was confirmed by analysis of the ^{13}C NMR spectra resorting to information derived from the published studies of the isomeric farnesyl esters[32] as well as farnesols and farnesyl bromides synthesized from them.[28]

* The acid corresponding to esters **61a—c** possesses strong hepatoprotecting activity.[4]

Scheme 5



n = 1 (**50**, **52a–c**, **54**, 2*E*-**56a–c**, 2*E*-**58a–c**, **60a–c**, **62**, **64**, **66**, **68**); 2 (**51**, **53a–c**, **55**, 2*E*-**57a–c**, 2*E*-**59a–c**, **61a–c**, **63**, **65**, **67**, **69**); R = Me (**52a**, **53a**, 2*E*-**56a**, 2*E*-**57a**, 2*E*-**58a**, 2*E*-**59a**, **60a**, **61a**); Et (**52b**, **53b**, 2*E*-**56b**, 2*E*-**57b**, **58b**, **59b**, **60b**, **61b**); Me_2CH (**52c**, **53c**, **60c**, **61c**); Me_2CHCH_2 (2*E*-**56c**, 2*E*-**57c**, 2*E*-**58c**, 2*E*-**59c**)

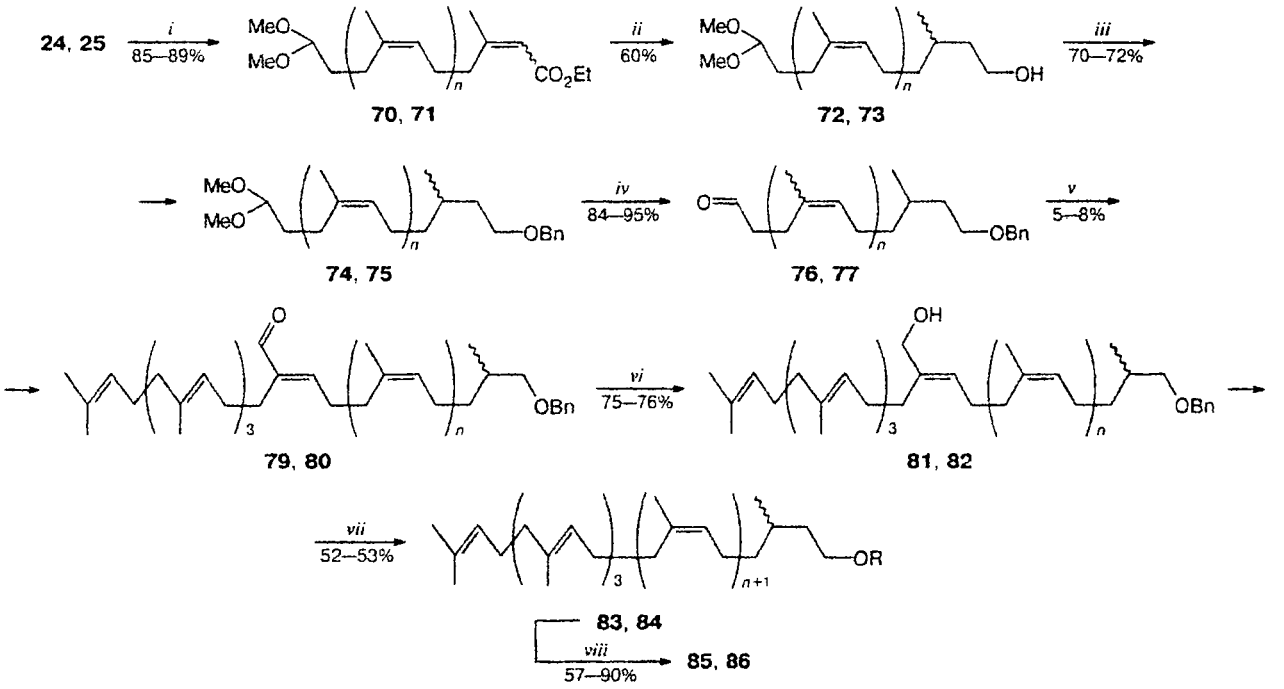
Reagents and conditions: *i*. $TMSCH_2CO_2Et$/LDA/THF, −75→20 °C; *ii*. Pr^iONa/Pr^iOH; *iii*. $TsOH \cdot Py/Me_2CO—H_2O$; *iv*. Pr^iPh_3PBr/Bu^nLi/THF, n-C_6H_{14}, −78→20 °C; *v*. $LiAl(OBu^t)H_3/Et_2O$, 0 °C; *vi*. $TMSCH_2CO_2R$ (R = Me, Et, Pr^i)/LDA/THF; *vii*. H_2/Pt/EtOH; *viii*. DIBAH/Et_2O—n-C_6H_{14}, −78→20 °C; *ix*. RCOCl (R = Me, Et, Me_2CHCH_2)/Py; *x*. SiO_2/10% $AgNO_3$; *xi*. SO_2Cl_2/Py/CH_2Cl_2, −60→0 °C; *xii*. $CH_2(CO_2Et)_2$/Py—piperidine, 120 °C; *xiii*. $NaBH_4$/MeOH; *xiv*. LiI/DMF, 150 °C; *xv*. NaOH/EtOH; *xvi*. $MeO(C_2H_4O)_2Me$/quinoline, 160 °C; *xvii*. SO_2Cl_2/DMF; *xviii*. ROH (R = Me, Pr^i).

Synthesis of isoprenoid analogs of juvenile hormones

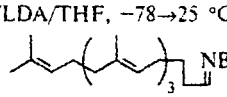
Five native insect juvenile hormones (JH) have been identified by now.[3] All of them are 10,11-epoxy derivatives of farnesylic acid or its homologs. Natural analogs of JH, referred to as juvenoids, have been found in plants. A large number of JH analogs have been synthesized. 2,4-Dienoates, of which esters of C_{15}-isoprenoid acid are best known, merit special attention.[33]

We developed a synthesis of racemic juvenile hormone JH-III (**89**), based on the above-described transformation of isoprene trimer **6** into keto acetal **11** [34] (Scheme 7). Olefination of **11** gave a mixture of esters **87** (2*E*/*Z*-isomer ratio ~ 3 : 2) in a high yield; this was converted into methyl farnesoates **52a** (isomer mixture

Scheme 6



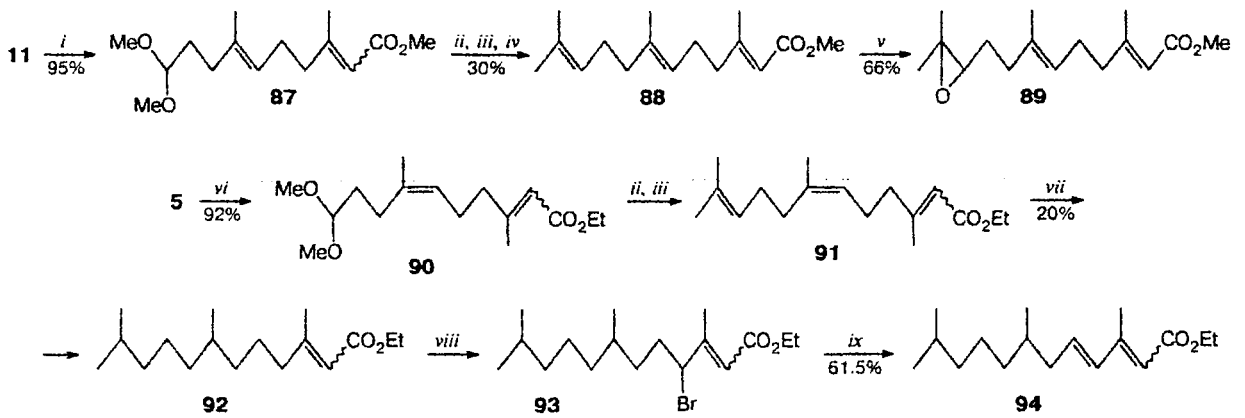
n = 2 (**24**, **70**, **72**, **74**, **76**, **79**, **81**, **83**, **85**); 3 (**25**, **71**, **73**, **75**, **77**, **80**, **82**, **84**, **86**); R = Bn (**83**, **84**), H (**85**, **86**)

Reagents and conditions: *i*. $TMSCH_2CO_2Et/LDA/THF$, −78→25 °C; *ii*. $Li/NH_3/(CH_2CH_2O)_2—Et_2O$, −40 °C, EtOH; *iii*. BnCl/NaH; *iv*. $TsOH/Me_2CO—H_2O$; *v*.  (**78**)/LDA/$Et_2O—n$-C_6H_{14}, −70→−25 °C; *vi*. $NaBH_4$/EtOH; *vii*. $Py \cdot SO_3$/THF; $LiAlH_4$; *viii*. Li/NH_3, −35 °C; NH_4Cl.

at the Δ^2-bond) *via* two steps. Column chromatography on $SiO_2—AgNO_3$ afforded 2*E*,6*E*-isomer **88**, which was converted into the target epoxide **89**. The overall yield of JH-III based on keto acetal **11** was 12%.

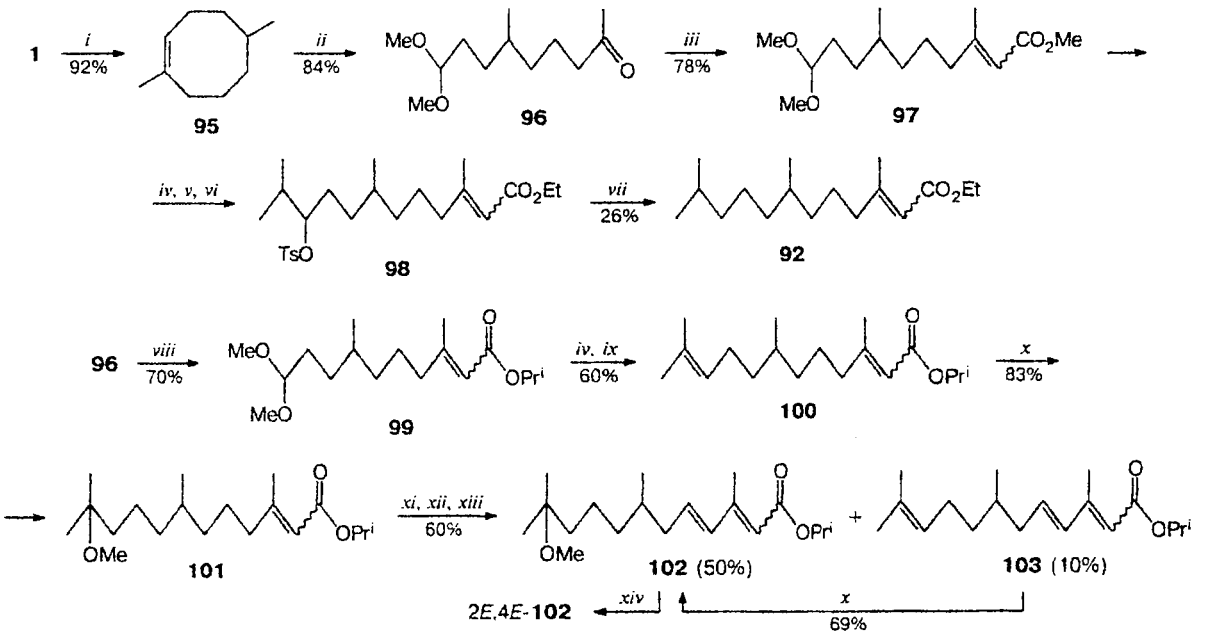
Keto acetal **5** served as the starting compound in the synthesis of ethyl 3,7,11-trimethyldodeca-2*E*,4*E*-dienoate (**94**), the juvenoid hydroprene[35] (see Scheme 7). The synthesis includes ethoxycarbonylmethylenation of **5** and

Scheme 7



Reagents and conditions: *i*. $TMSCH_2CO_2Me/LDA/THF$; *ii*. $TsOH \cdot Py/Me_2CO—H_2O$; *iii*. $Me_2C{=}PPh_3$; *iv*. $SiO_2/AgNO_3$; *v*. NBS/THF, K_2CO_3; *vi*. $TMSCH_2CO_2Et/LDA/THF$; *vii*. $Et_3SiH/CF_3CO_2H/CH_2Cl_2$; *viii*. $NBS/Bz_2O/CCl_4$; *ix*. Li_2CO_3/LiBr/DMF.

Scheme 8



Reagents and conditions: *i.* H_2/Pt/MeOH; *ii.* O_3/MeOH, −75 °C; H_2/Pd–$CaCO_3$–PbO; NH_4Cl; *iii.* $TMSCH_2CO_2Et$/LDA/THF; *iv.* TsOH · Py/Me_2CO–H_2O; *v.* $Me_2CHMgBr/Et_2O$; *vi.* TsCl/Py; *vii.* Zn/NaI/THF; *viii.* $TMSCH_2CO_2Pr^i$/LDA/THF; *ix.* $Me_2C{=}PPh_3$/THF; *x.* $Hg(OAc)_2$/MeOH; $NaBH_4$/NaOH; SiO_2; *xi.* NBS/Bz_2O/CCl_4; *xii.* Li_2CO_3/LiBr/DMF; *xiii.* SiO_2; *xiv.* HPLC.

transformation of the mixture of decadienoates **90** into 2*E*/*Z*,6*Z*-ethyl farnesoates (*E*/*Z*-**91**), which are selectively transformed into α,β-unsaturated esters *E*/*Z*-**92** under conditions of ionic hydrogenation. Compounds **92** were converted (*via* bromide **93**) into a product consisting of 2*E*,4*E*- and 2*Z*,4*E*-stereoisomers (ratio 77 : 23). The individual 2*E*,4*E*-isomer **94** was isolated by preparative HPLC.

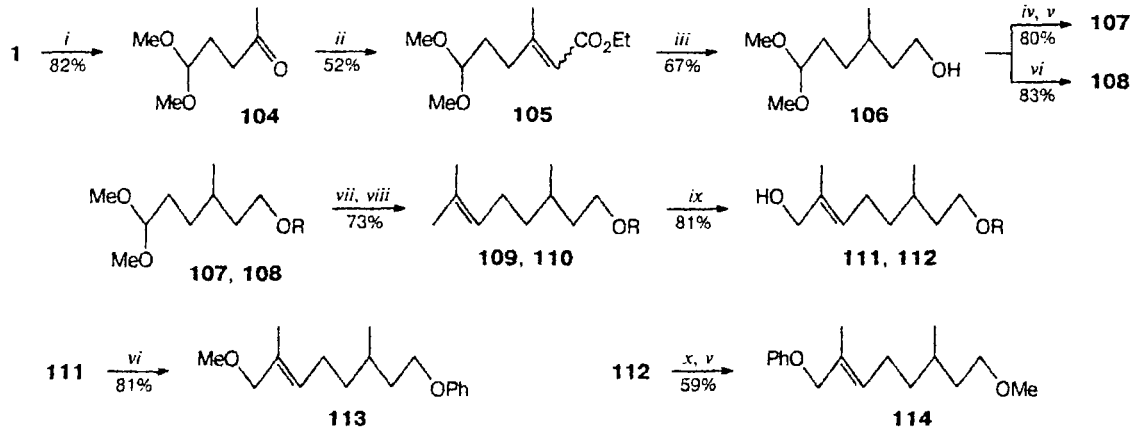
The key synthon **92** was also prepared from cyclodimer **1** *via* a somewhat different route[35] (Scheme 8). According to this Scheme, diene **1** was hydrogenated to olefin **95**, whose ozonization afforded the saturated analog (**96**) of keto aldehyde **2** in 84% yield. Petersen ethoxycarbonylmethylenation of keto acetal **96** gave a mixture (2*E*/*Z* ~ 55 : 45) of ethyl 3,7-dimethyldecenoates (**97**). Acetal esters **97** were converted *via* three steps into tosyloxy derivatives **98**, whose reduction resulted ultimately in the desired synthon **92**.

Keto acetal **96** was also employed in the synthesis of isopropyl 3,7,11-trimethyl-11-methoxydodeca-2*E*,4*E*-dienoate (*E*,*E*-**102**), the juvenoid methoprene[36] (see Scheme 8). To this end, keto acetal **96** was subjected to Petersen olefination to give a mixture of 3,7-dimethyldecenoates (**99**) (*E*/*Z* ~ 1 : 1). The subsequent removal of the acetal protection and Wittig olefination of the intermediate aldehydes afforded a mixture of isomeric 3,7,11-trimethyldodecadienoates (**100**), which was then converted into 11-methoxy derivatives **101**. Their allylic bromination followed by dehydrobromination of the bromides gave a mixture (85 : 15) of dienoates **102** and demethoxylation products **103**. Trienoates **103** were converted into dienoates **102** in a way similar to that used in the case of dienoates **100**. Finally, the yield of the target product **102** was 15% based on the initial isoprene dimer **1**. The individual isomer 2*E*,4*E*-**102** was isolated by preparative HPLC.

Diethers of 2,6-dimethyloct-2*E*-ene-1,8-diol (**113**, **114**), possessing a high juvenoid activity with respect to *Culex* mosquito larvae, were synthesized from the product of exhaustive ozonolysis of isoprene dimer **1**, namely, levulinic aldehyde dimethylacetal (**104**)[37] (Scheme 9). Petersen ethoxycarbonylmethylenation of keto acetal **104** yielded a mixture of ethyl 3-methylhexenoates **105** (2*E*/*Z* ~ 1 : 1). The subsequent reduction with Li in NH_3 was accompanied by hydrogenation of the Δ^2-bond and gave alcohol **106**, which was converted in two steps into 6-phenoxy derivative **107**. *O*-Methylation of alcohol **106** yielded 3-methyl-1,6,6-trimethoxyhexane (**108**). Acetals **107** and **108** were then converted into 8-phenoxy- (**109**) and 8-methoxy-2,6-dimethyloct-2-enes (**110**), respectively.

Allylic oxidation of olefins **109** and **110** resulted in 8-phenoxy- (**111**) and 8-methoxy-2,6-dimethyloct-2*E*-en-1-ols (**112**), respectively. The former was converted

Scheme 9



R = Ph (**107**, **109**, **111**); Me (**108**, **110**, **112**)

Reagents and conditions: *i.* O_3/MeOH; H_2/Pd–$CaCO_3$–PbO; NH_4Cl; *ii.* $TMSCH_2CO_2Et$/LDA/THF; *iii.* Li/NH_3, −40 °C, EtOH; *iv.* TsCl/Py; *v.* NaH/PhOH/DMSO; *vi.* NaH/MeI/DMSO; *vii.* TsOH · Py/Me_2CO–H_2O; *viii.* $Me_2C{=}PPh_3$/THF; *ix.* $Bu^tOOH/SeO_2/CH_2Cl_2$; *x.* PBr_3/Py/Et_2O.

into 1-methoxy-8-phenoxy derivative (**113**), and the latter was transformed into 1-phenoxy-8-methoxy derivative (**114**) *via* the intermediate bromide. The yield of target diethers **113** and **114** was ~16% based on keto acetal **104**.

Synthesis of pheromones of isoprenoid nature

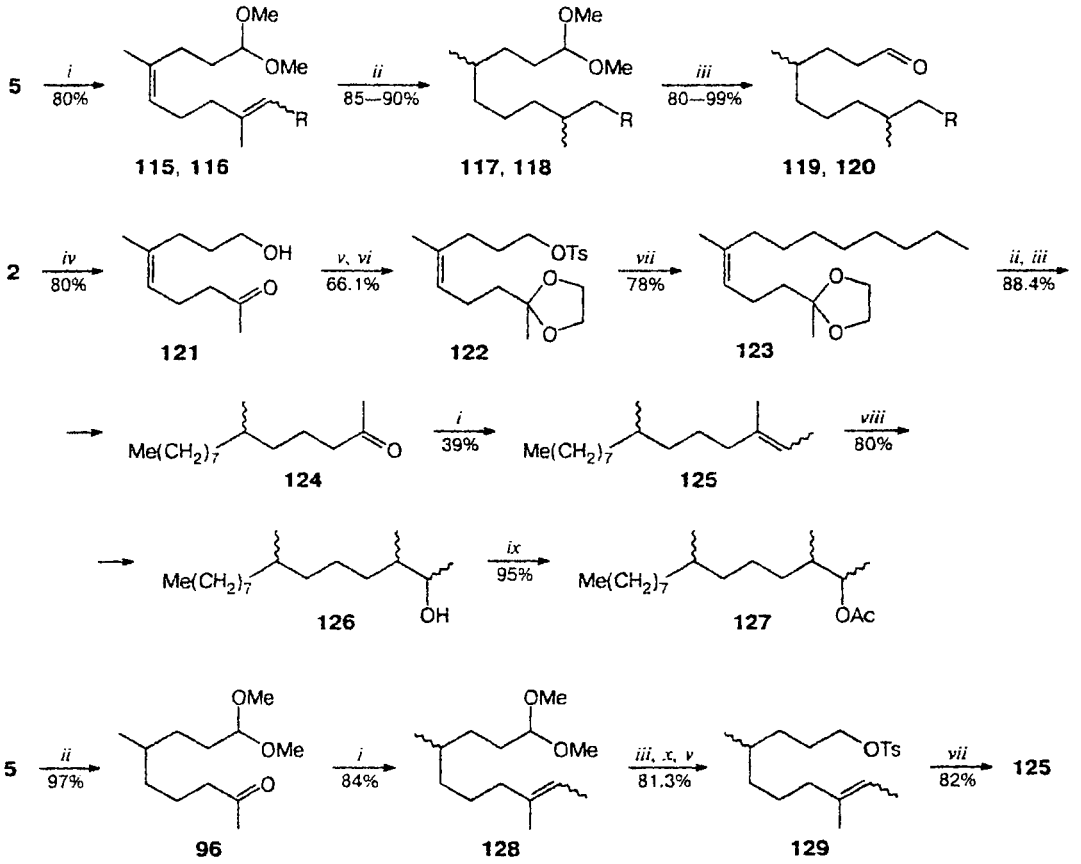
Isoprenoid C_{10}- and C_{15}-keto aldehydes and keto acetals are convenient synthons for the preparation of pheromones, whose structure incorporates isoprene fragments. Based on keto acetal **5**, we developed one of the shortest syntheses of 4,8-dimethyldecanal (**119**) and its noranalog, 4,8-dimethylnonanal (**120**)[38] (Scheme 10). Compound **119** is formed as a mixture of diastereomers, one of which, the (4*R*,8*R*)-diastereomer, is an aggregation pheromone of mealworm (*Tribolium castaneum* and *T. confusum*). Olefination of keto acetal **5** with ethylidene- or methylidenetriphenylphosphorane gave rise to the corresponding diene acetals **115** and **116**. Exhaustive hydrogenation of these compounds gave the saturated acetals **117** and **118** corresponding to these dienes. Hydrolysis of these products afforded the target bishomo- (**119**) and homocitronellals (**120**). Their total yield amounted to 45–60% based on isoprene dimer **1**.

Selective reduction of keto aldehyde **2** using $NaBH(OAc)_3$ led to hydroxy ketone **121** and thus opened up a new synthetic route[39] (see Scheme 10) to a mixture of diastereomeric (±)-3,7-dimethylpentadecan-2-ols (**126**), whose acetates (**127**) were active as sex pheromones of four species of pine sawflies of the *Diprion* and *Neodiprion* genera. According to Scheme 10, hydroxy ketone **121** was converted *via* intermediate compounds **122** and **123** into ketone **124**, whose olefination occurs nonstereospecifically yielding a mixture of alkenes (**125**) (*E*/*Z* ~ 1 : 1). Hydroboration of alkenes **125** is regioselective and yields the target alcohol **126** (an equimolar mixture of 2*R*/*S*,3*R*/*S*,7*S*/*R*- and 2*S*/*R*,3*R*/*S*,7*S*/*R*-diastereomers), which was then converted into the corresponding acetate **127**. The yield of diprionyl acetate **127** was ~15% based on the initial isoprene dimer **1**.

Alkenes **125**, preceding diprionol **126** (see Scheme 10), were also prepared[40] by a shorter route and in higher yield starting from keto acetal **5** (see Scheme 10). This modification of the synthetic scheme included olefination of derivative **96** as the key stage. The dimethoxyalkenes **128** thus obtained (*Z*/*E*-isomer ratio ~ 4 : 1) were readily converted into tosylates **129** over three unambiguous steps. Coupling of these products with allylmagnesium bromide occurred smoothly to give the required alkenes **125**.

The use of consecutive olefination steps, namely, olefination of keto acetal **5** with one phosphorane and, after the removal of the acetal protection, olefination of the corresponding aldehyde with another phosphorane opened up a new, much shorter pathway to long-chain 1,5-dimethylated branched alkanes, among which pheromones of several species of insects have been identified. Thus coupling of **5** with $C_5H_{11}CH{=}PPh_3$ gave diene acetal **130**. The aldehyde **133** formed upon the removal of the acetal protection was involved in one more Wittig condensation, namely with $PrCH{=}PPh_3$, which gave rise to triene **136**, whose exhaustive hydrogenation yielded 7,11-dimethyloctadecane (**139**)[41] (a mixture of diastereomers active as an oviposition attractant of the yellow-fever mosquito *Aedes aegypti*) (Scheme 11). The total yield of alkane **139** was 20% based on isoprene dimer **1**.

Scheme 10



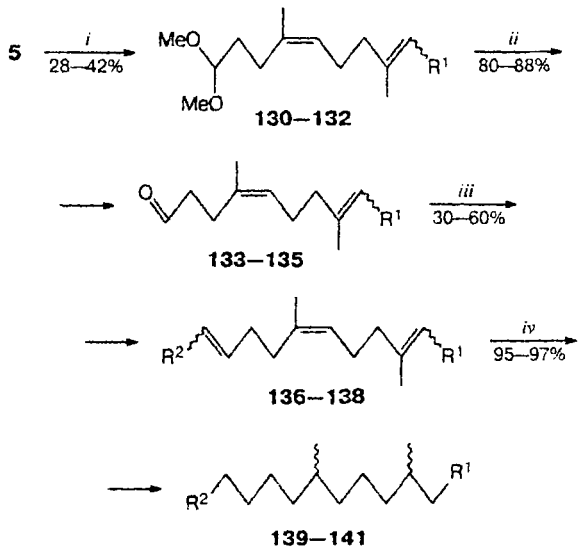
R = Me (**115**, **117**, **119**); H (**116**, **118**, **120**)

Reagents and conditions: *i.* $RCH{=}PPh_3$/THF (R = Me, H); *ii.* H_2/Pd—C/EtOH; *iii.* TsOH · Py/Me_2CO—H_2O; *iv.* $NaBH(OAc)_3$/PhH; *v.* TsCl/Py; *vi.* $(CH_2OH)_2$/TsOH/PhH; *vii.* $Me(CH_2)_4MgBr/Li_2CuCl_4/Et_2O$—THF; *viii.* B_2H_6/THF; H_2O_2/NaOH; *ix.* Ac_2O/Py; *x.* $NaBH_4$/MeOH.

This approach was used to prepare 15,19-dimethyltriacontane (**140**)[42] (a mixture of diastereomers exhibiting properties of an attractant of the stable fly *Stomoxys calcitrans*) (see Scheme 11). Olefination of **5** afforded diene acetal **131**, and repeated olefination of aldehyde **134** resulted in triene **137**, whose hydrogenation completed the synthesis of the target alkane **140**. 17,21-Dimethylheptatriacontane (**141**)[43] was synthesized (as a mixture of diastereomers exhibiting activity as a sex attractant of the tsetse fly *Glossina morsitans morsitans*) according to the same scheme (*via* intermediate compounds **132**, **135**, and **138**) using different phosphoranes (see Scheme 11).

In the case of C_{15}-isoprenoid keto aldehyde **7**, selective olefination involving the aldehyde group was successfully carried out. The triene ketones obtained in this reaction in ~60% yield were readily separated from tetraene hydrocarbons, formed simultaneously upon diolefination of **7** (up to 10%), by adsorption chromatography on SiO_2. Repeated olefination of the triene ketones occurred smoothly to give the required tetraenes in high yields; exhaustive hydrogenation completed the synthesis of the target 1,5,9-trimethylated branched long-chain hydrocarbons. This approach was employed to develop a three-step procedure[44] for the synthesis of diastereomeric trimethylated branched triacontanes **151**—**153**, which had been isolated from the ova of the tobacco hawk-moth *Manduca sexta L.* and prepared previously in seven steps. The intermediate triene ketones **142**—**144** were purified from tetraenes **145**—**147** and then involved in repeated olefination; the products **148**—**150** thus obtained were converted into target hydrocarbons, 13,17,21-trimethyltri- (**151**), 13,17,21-trimethylpenta- (**152**), and 13,17,21-trimethylheptatriacontanes (**153**), containing three isoprene residues in the chain (Scheme 12). The

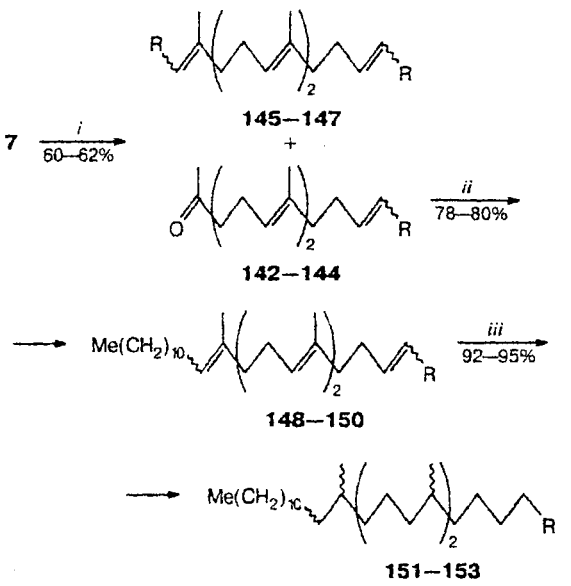
Scheme 11



R^1 = $Me(CH_2)_4$ (**130**, **133**, **136**, **139**), $Me(CH_2)_{12}$ (**131**, **134**, **137**, **140**), $Me(CH_2)_{14}$ (**132**, **135**, **138**, **141**);
R^2 = $Me(CH_2)_2$ (**136**, **139**), $Me(CH_2)_9$ (**137**, **140**), $Me(CH_2)_{11}$ (**138**, **141**)

Reagents and conditions: *i.* $R^1CH{=}PPh_3$/THF (R^1 = $Me(CH_2)_4$, $Me(CH_2)_{12}$, $Me(CH_2)_{14}$)); *ii.* 5% HCl/Me_2CO; *iii.* $R^2CH{=}PPh_3$/THF (R^2 = $Me(CH_2)_2$, $Me(CH_2)_9$, $Me(CH_2)_{11}$); *iv.* H_2/Pd–C/EtOH.

Scheme 12



R = $Me(CH_2)_7$ (**142**, **145**, **148**, **151**); $Me(CH_2)_9$ (**143**, **146**, **149**, **152**); $Me(CH_2)_{11}$ (**144**, **147**, **150**, **153**)

Reagents and conditions: *i.* $RCH{=}PPh_3$/THF–C_6H_{14} (R = $Me(CH_2)_7$, $Me(CH_2)_9$, $Me(CH_2)_{11}$); SiO_2; *ii.* $Me(CH_2)_{11}CH{=}PPh_3$/THF–C_6H_{14}; *iii.* H_2/Pd–C/EtOH.

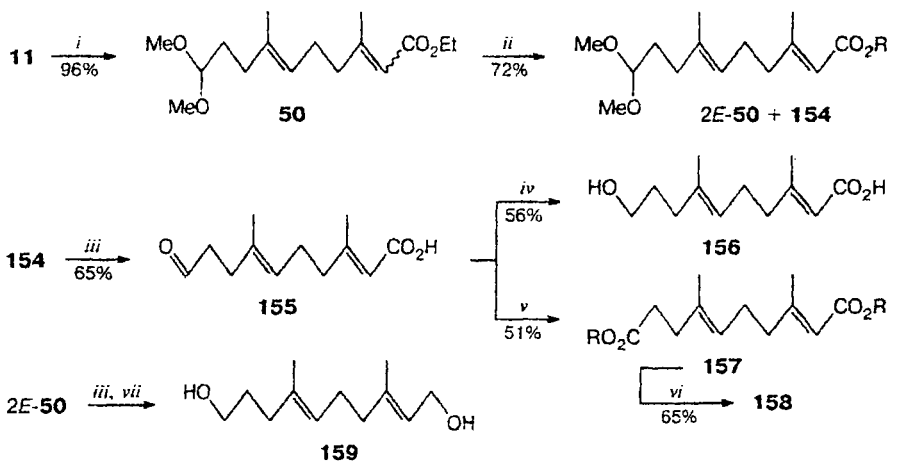
overall yield of alkanes **151**–**153** over three steps exceeded 40%.

Terpenoid C_{10}-keto acetal **11**, the product of ozonolysis of trimer **6** at two multiple bonds, proved to be a convenient synthon for the synthesis of α,ω-bifunctional bishomoterpenoid components of the sex pheromone of the danaide butterfly *Danaus plexippus* and *D. chrysippus* males. The synthesis of 3,7-dimethyl-10-hydroxydeca-2*E*,6*E*-dienoic acid (**156**), 3,7-dimethyldeca-2*E*,6*E*-diene-1,10-dioic acid (**157**), its dimethyl ester (**158**), and 3,7-dimethyldeca-2*E*,6*E*-diene-1,10-diol (**159**) that we developed includes ethoxycarbonylmethylenation of **11** and isomerization of the Δ^2-bond in ester **50** [45] (Scheme 13). Hydrolysis of the acetal group in compound **154** afforded aldehydo acid **155**, whose hydride reduction resulted in the target hydroxy acid **156**; oxidation by the Jones reagent yielded two other pheromone components, diacid **157** and ester **158**. Diol **159** was prepared by the hydrolysis of esters 2*E*-**50** followed by the reduction of the resulting mixture of oxo esters. The total yields of target compounds **156**, **157**, **158**, and **159** based on keto acetal **11** amounted to 10, 9, 6, and 31%, respectively.

The bis-homoterpenoid 4,8-dimethyl-10-hydroxydeca-4*E*,8*E*-dienoic acid (**161**), isomeric to hydroxy acid **156** and the acyclic precursor of ferrulactone I, a macrolide component of the aggregation pheromone of the rust-red grain beetle *Cryptolestes ferrugineus*, was synthesized from ester 2*E*-**50** by two methods.[46] According to one method, ester 2*E*-**50** was reduced to give alcohol **160**, which was then transformed into the target hydroxy acid **161** (Scheme 14), whose yield was 66% based on ester 2*E*-**50**. In the alternative route, ester 2*E*-**50** was converted into intermediate acid ester **162** in two steps. If a mixture of *E*/*Z*-**50** (~3 : 2) is involved in these transformations instead of 2*E*-**50**, the admixture of the 4*E*,8*Z*-isomer in the resulting hydroxy acid **161** is only ~2%.

The product of exhaustive ozonolysis of trimer **6** (or dimer **1**), keto acetal **104**, was used to prepare the racemic form of the potential biogenetic precursor of the sex pheromone of the Comstock mealybug (*Pseudococcus comstoki*) and its structural isomer 2,6-dimethylhepta-1,6-dien-3-ol acetate (**165**), whose activity is half that of the natural product 3*R*-**166**. Wittig methylenation of keto acetal **104** gave 4-methylpent-4-enal acetal (**163**), which was readily converted into aldehyde **164**; condensation of this product with isoproprenylmagnesium bromide and acetylation of the intermediate Mg alkoxide gave finally the target dienyl acetate **165** [47] (see Scheme 14). The total yield of

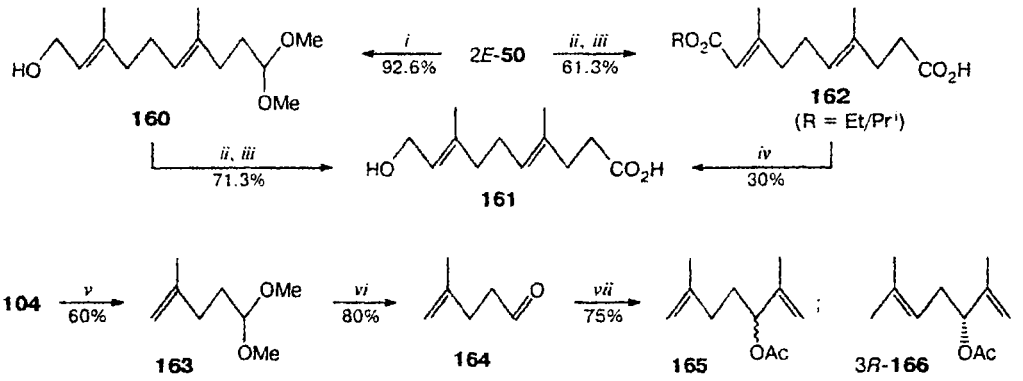
Scheme 13

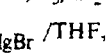


R = H (**154**, **157**), Me (**158**), Et/Pr^i (2*E*-**50**)

Reagents and conditions: *i*. $TMSCH_2CO_2Et$/LDA; *ii*. Pr^{i}ONa/Pr^{i}OH; *iii*. TsOH · Py/Me_2CO—H_2O; *iv*. $NaBH_4$/MeOH; *v*. H_2CrO_4/Me_2CO; *vi*. MeOH/TsOH; *vii*. LiAl(Bu^{t}O)H_3/Et_2O.

Scheme 14



Reagents and conditions: *i*. DIBAH/Et_2O, −75 °C; *ii*. TsOH · Py/Me_2CO—H_2O; *iii*. $AgNO_3$/NaOH; *iv*. LiAl(Bu^{t}O)H_3/Et_2O, 0 °C; *v*. $MePh_3PBr$/Bu^{t}OK/THF, −30 °C; *vi*. 5% HCl/Me_4NCl/Et_2O—Me_2CO; *vii*.  /THF, 0 °C; AcCl, 0→25 °C.

attractant **165** was ~30% based on the initial isoprene oligomer.

Thus, isoprenoid keto aldehydes and their monoacetals, which can easily be obtained by ozonolysis of readily available cyclic oligomers and isoprene polymers, are convenient bifunctional blocks, synthons for diverse biologically active compounds. This was illustrated in this review in relation to the synthesis of terpenoids, polyprenols, prenylcarboxylic acids, and insect pheromones and juvenoids.

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