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SYNTHESIS OF METHYL-BRANCHED LOW-MOLECULAR-MASS INSECT BIOREGULATORS FROM THE PRODUCTS OF THE ACID DECYCLIZATION OF 4-METHYLTETRA-HYDROPYRAN

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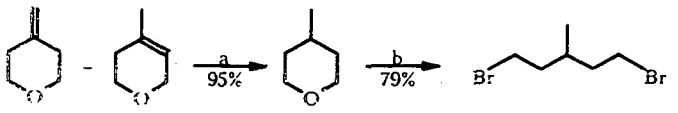
This review generalizes work on the chemoselective synthesis of racemic methyl-branched insect pheromones and the juvenoid hydroprene from 1,5-bifunctional 3-methylpentanes produced by the acid opening of the ring of 4-methyltetrahydropyran.

In many species of insects, chemical communication is achieved by means of chiral compounds. The molecules of four natural juvenoid hormones and also those of some of their most active synthetic analogs are also chiral. In the past 20-25 years, in order to elucidate the nature of the reception of chiral pheromones numerous syntheses of these substances in enantiomerically pure forms have been made, and the response reactions of many species of insects to each of the possible stereoisomers have been studied [1, 2]. It has been established that the efficiency of the attraction of many insect species producing chiral hormones increases 2- to 1000-fold if, in place of a racemic mixture, the enantiomer with the absolute configuration of the natural pheromone is used. An analogous situation is encountered in the field of synthetic juvenoids, where the difference in the hormonal activities of the enantiomers amounts to several orders of magnitude and the more active of them is more than twice as active as the racemate. The accumulated results of biotests enable us to judge to what extent the technologically more accessible racemic analogs are capable of replacing the natural optically active low-molecular-mass insect bioregulators. Examples where one of the enantiomers is biologically active and its antipode does not exert inhibiting properties are particularly attractive. In these cases it is also possible to use the racemate, although a larger dose of the latter is required to achieve the same effect.

We have developed a new approach to the synthesis of such racemic methyl-branched insect pheromones and of the juvenoid hydroprene from 4-methyltetrahydropyran (**3**) – the sole product of the hydrogenation of a mixture of 4-methylenetetrahydropyran (**1**) and 4-methyl-5,6-dihydro-2-pyran (**2**), which are components of the "dihydropyran fraction," a waste from the industrial manufacture of isoprene through the stage of cleaving the intermediate 4,4-dimethyl-1,3-dioxan under conditions of acid catalysis [3-6]. The opening of the pyran ring of (**3**) takes place under the action of acids, and different products are obtained with different reagents. Thus, under the action of $HBr-H_2SO_4$ on the cyclic ether (**3**) the dibromide (**4**) is formed [7], while other conditions ($AcBr-ZnCl_2$) lead to the bromoacetate (**5**) from which it is easy [8-11] to obtain the α,ω-bifunctional compounds (**6-8**), which are used in the synthesis of a number of low-molecular-mass insect bioregulators [7-16].



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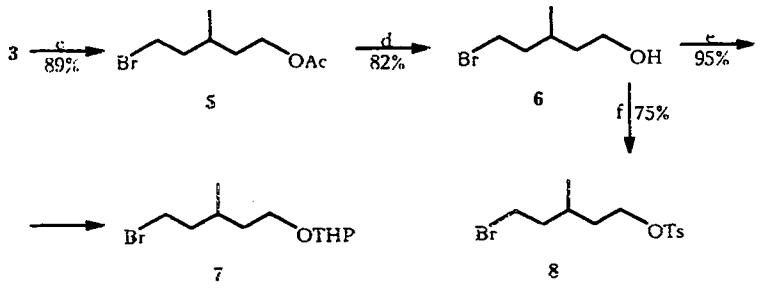
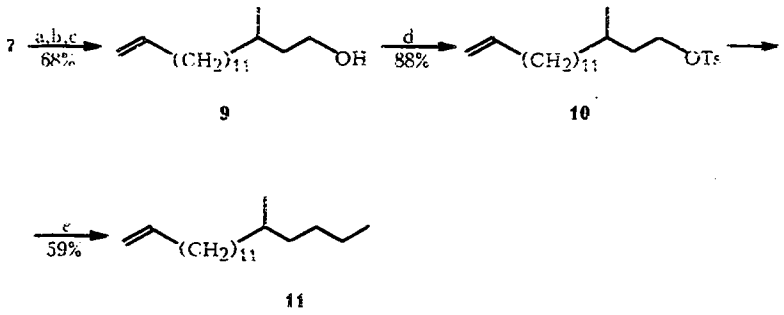


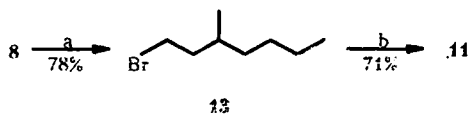
a. H_2, Ni; b. $HBr-H_2SO_4$; c. AcBr, $ZnCl_2$; d. TsOH / MeOH-H_2O;
e. DHP, TsOH; f. TsCl / Py

In our previous schemes [10] for the synthesis of the pheromone of the leaf miner peach moth (*Lyonetia clerkella*), which has the structure of 14-methyloctadec-1-ene (**11**), the initial compounds were derivatives (**7**) and (**8**). The interaction of the Grignard reagent generated from the bromide (**7**) with 1-bromoundec-10-ene (**12**) in the presence of the complex CuI-bpy* gave, after acid hydrolysis, the alcohol (**9**) the ethylation of which in the form of the corresponding tosylate (**10**) with a lithiocuprate reagent led to the desired pheromone (**11**) in an overall yield of 22%, calculated on the initial (**3**).



a. Mg; b. $(CH_2)_9Br$(**12**) / CuI-bpy; c. TsOH / MeOH-H_2O;
d. TsCl / Py; e. Et_2CuLi

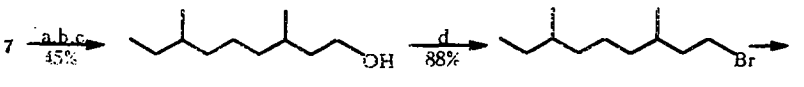
A higher overall yield of the pheromone (**11**) (30%) was obtained from the bromotosylate (**8**), for which conditions (Et_2O, −30°C) have been found for selective alkylation by diethyl lithiocuprate at the tosyl group. The bromide obtained (**13**) was then subjected to Wurtz coupling with (**12**).



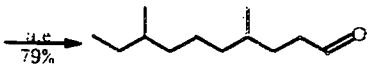
a. Et_2CuLi; b. **12** / Mg

The bromide (**7**) has also been used in the synthesis of racemic 4,8-dimethyldecanal (**16**), which exhibits a high attractiveness for the confused and the rust-red flour beetles (*Tribolium confusum* and *T. castaneum*). The construction of the 1,5-dimethyl-branched carbon skeleton of the desired pheromone has been realized in three ways [8]. According to the first, bromide (**7**) was converted into the Grignard reagent and coupled with 1-bromo-2-methylbutanol (**17**). The resulting alcohol (**14**) was converted into the bromide (**15**), the formulation of the magnesium derivative of which led to pheromone (**16**) with an overall yield of 21%, calculated on the cyclic ether (**3**).

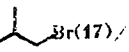
*bpy — 2,2′-bipyridyl.



14 15



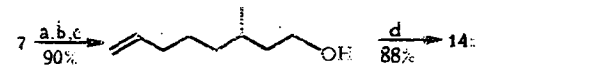
16

a. Mg; b.  Br(17)/ CuI-bpy; c. TsOH/ MeOH-H_2O;

d. HBr-H_2SO_4; e. DMF

According to the second route, bromide (**7**) was cross-coupled with allyl bromide, and the alkenol obtained (**18**) was converted into the dimethyl-branched alcohol (**14**) by means of the regiospecific carboalumination reaction with triethylaluminum catalyzed by Cp_2ZrCl_2. In spite of the fact that the conversion of (**7**) into (**14**) took place in two stages, its yield was higher than in the one-stage conversion described above (79 and 45%, respectively). According to [17], if, instead of carboalumination, the alkene (**18**) was subjected to carbomagnation, then, together with the main product (**14**), about 5% of the unsaturated alcohol (**19**) was formed, but this was easily eliminated in the following stage when alcohol (**14**) was converted into the bromide (**15**) and the unsaturated alcohol (**19**) into the easily separated dibromo derivative (**20**).

The most rational method proved to be the formation of the key alcohol (**14**) from the bromoacetate (**5**) and its coupling with 1-bromomagnesio-2-methylbutane at −15°C, taking place selectively and with high yield. In this case the overall yield of pheromone (**16**) was 52%, calculated on the initial (**3**).



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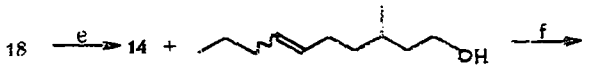

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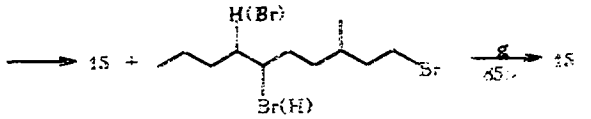
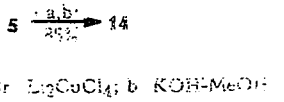


20

a. Mg; b.  Br/CuI-bpy; c. TsOH/MeOH-H_2O;

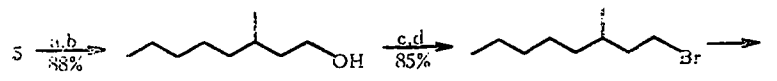
d. Et_3Al - Cp_2ZrCl_2; e. Et_2Mg / Cp_2ZrCl_2.

f. HBr-H_2SO_4; g. SiO_2

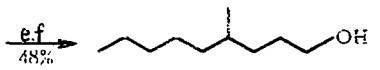


a.  Li_2CuCl_4; b. KOH-MeOH

The racemic analog (**23**) of the sex pheromone of the yellow mealworm beetle (*Tenebrio molitor* L.), identified as 4R-methylnonan-1-ol has been synthesized from the bromoacetate (**5**) by its selective alkylation to 3-methyloctan-1-ol (**21**), followed by homologization via the magnesium derivative of the corresponding bromide (**22**).



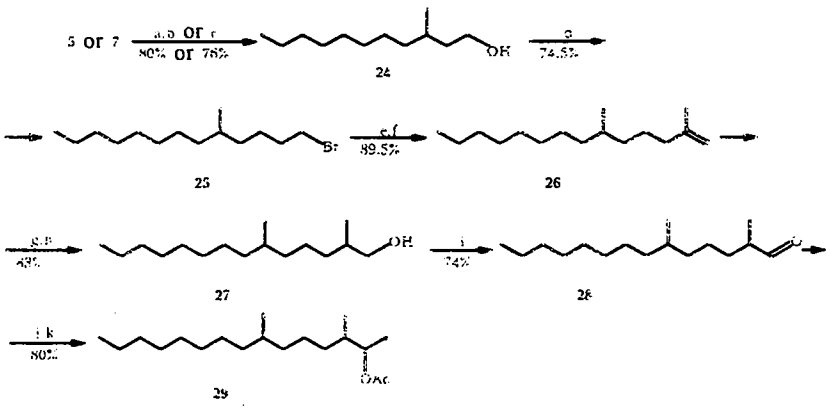
21 22

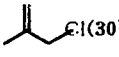


23

a. PrMgBr - Li_2CuCl_4; b. KOH-MeOH; c. TsCl / Py; d. LiBr;
e. Mg; f. CH_2O

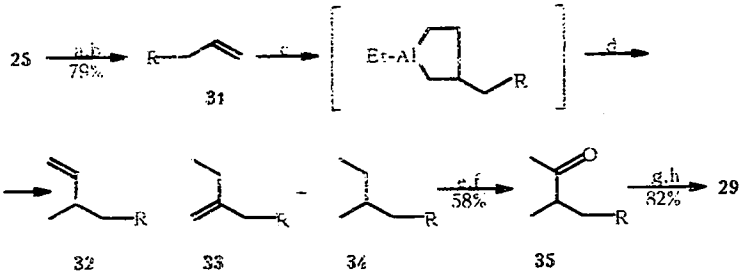
The natural sex pheromone of pine sawflies of the genera *Diprion* and *Neodiprion* has been identified as 3,7-dimethylpentadecan-2-ol acetate with the (2S,3S,7S)-configuration. In addition, it is known that the corresponding racemic mixture of acetates (**29**) with the *erythro*-arrangement of the substituents at the C^2 and C^3 atoms also exhibits appreciable biological activity. A synthesis of (**29**) based on chemoselective transformations of bromohydrin derivatives (**5**) and (**7**) is extremely practical [9]. The coupling of each of them with *n*-hexylmagnesium bromide in the presence of $LiCuCl_4$, followed by hydrolysis, gave one and the same compound – 3-methylundecan-1-ol (**24**), its yield from the bromoacetate being somewhat higher and amounting to 80%. The further transformation of alcohol (**24**), including its bromination and the coupling of the resulting bromide (**25**) with methallyl chloride (**30**), led to 2,6-dimethyltetradec-1-ene (**26**). Its anti-Markovnikov hydration via an organoboron intermediate gave the individual primary alcohol (**27**), which was then oxidized to the aldehyde (**28**), and the condensation of this with MeMgI at 20°C led, after the working up of the reaction mixture, to the desired attractant (**29**) in the form of a mixture (7:3) of *erythro*- and *threo*-isomers with a yield of 22% (calculated on (**3**)).

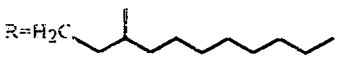


a. $n\text{-}C_6H_{13}MgBr$ - Li_2CuCl_4; b. TsOH / MeOH-H_2O; c. KOH-MeOH;
d. HBr-H_2SO_4; e. Mg; f.  Cl(**30**) / CuI-bpy
g. $NaBH_4$-BF_3·OEt_2 ; h. H_2O_2-NaOH; i. PCC; j. MeMgI; k. Ac_2O

Thus, the scheme of synthesis developed enables diprionyl acetate (**29**) to be obtained in the form of a racemic mixture with a predominant content (70%) of the active *erythro*-isomer.

Another route to the synthesis of diprionyl acetate (**29**) [13] is based on the reductive β-vinylation of α-olefins [18]. The initial terminal alkene (**31**) for the realization of this approach was obtained through the bromide (**25**). The vinylation of (**31**) led to a mixture of 3,7-dimethylpentadec-1-ene (**32**), its isomer (**33**), and the corresponding alkane (**34**), the catalytic interaction of which with oxygen gave an individual oxidation product – the methyl ketone (**35**). The hydride reduction of the latter, followed by acetylation, led to the pheromone (**29**) with an overall yield of 13%, calculated on the initial (**3**), the ratio of *erythro*- and *threo*-isomers being 1:1.



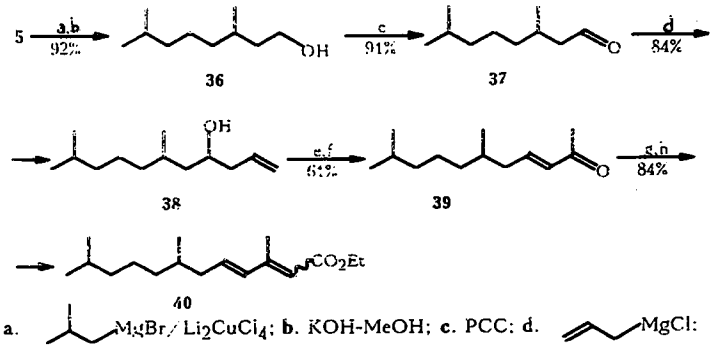


a. Mg; b.  / CuI-bpy; c. $AlEt_3$ / Cp_2ZrCl_2;

d.  / $Ni(acac)_2$ / PPh_3 / Bu^i_2AlH; e. O_2 / $PdCl_2$-CuCl;

f. SiO_2; g. $NaBH_4$; h. Ac_2O / Py

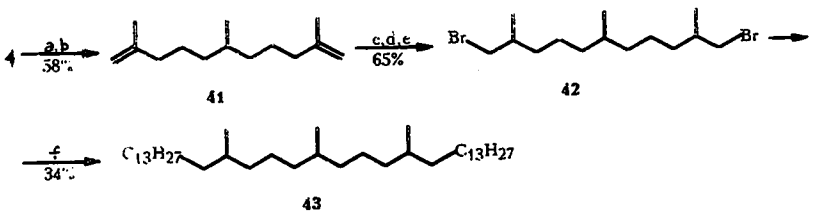
The active principle of the widely known juvenoid preparation hydroprene is ethyl 3,7,11-trimethyldodeca-2E,4E-dienoate (**40**). We have realized a new route to the synthesis of the dienoate (**40**) from the bromoacetate (**5**), using its capacity for chemoselective interaction with cuprate reagents [11]. The coupling of (**5**) with isobutylmagnesium bromide in the presence of Li_2CuCl_4 took place without affecting the acetate group and led (after saponification) to tetrahydrogeraniol (**36**). Its oxidation and the condensation of the resulting aldehyde (**37**) with allylmagnesium chloride gave the homoallyl secondary alcohol (**38**), the oxidation of which with oxygen in the presence of $PdCl_2$-CuCl, followed by treatment with acid, led to 6,10-dimethylundec-3E-en-2-one (**39**), which was converted by the Iotsich–Preobrazhenskii reaction [19] into the desired compound (**40**) in the form of a mixture (7:3) of the 2E,4E- and 2Z,4E- stereoisomers. The overall yield of hydroprene (**40**) in this six-stage synthesis was 31%, calculated on the initial (**3**).



a. ; b. KOH-MeOH; c. PCC; d. ;

e. O_2 / $PdCl_2$-CuCl; f. HCl; g. EtOC≡CMgBr; h. H_2SO_4

The symmetrical methyl-branched dibromide (**4**) has proved to be a convenient synthon for (±)-15,19,23-trimethylheptatriacontane – the sex pheromone of the tsetse fly (*Glossina morsitans morsitans*). The synthesis of pheromone (**43**) consisted [7] in the growth of the skeleton of the dibromide (**4**) simultaneously at both ends via its dimagnesium derivative, and the subsequent repetition of the same operation with the symmetrical trimethyl-branched dibromide (**42**), obtained by the hydroboration–bromination reaction of the diolefin (**41**). In the final account, passage from the initial dibromide (**4**) to the desired pheromone by the scheme developed was achieved in only three stages, with an overall yield of 12%.



a. Mg; b. **30** / CuI-bpy; c. B_2H_6; d. Br_2; e. MeONa;
f. $C_{13}H_{27}MgBr$ / CuI-bpy

Thus, we have revealed new possibilities for the chemoselective synthesis of racemic methyl-branched pheromones and of the juvenoid hydroprene from 1,5-bifunctional 3-methylpentanes – products of the acid decyclization of the industrially available 4-methyltetrahydropyran.

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*The particular Akad. Nauk concerned is not specified and has not been identified – Translator.