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SYNTHESIS OF MACROLIDE PHEROMONES

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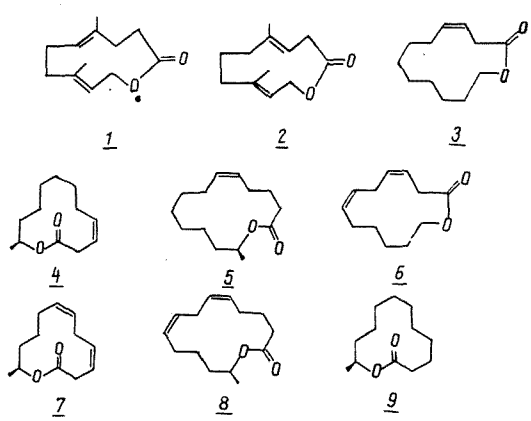
This review considers pathways for the synthesis of macrocyclic lactones (macrolides) identified as components of pheromones of insects of the order Coleoptera (Cucujidae), genera Cryptolestes *and* Oryzaephilus *– granary pests.*

Interest in the synthesis of macrolides is due above all to the fact that highly active bioregulators are found among the compounds of this class [1, 2]. In the mid-eighties, macrolide components were identified in the secretions of insects of the order Coleoptera (Cucujidae), genera *Cryptolestes* and *Oryzaephilus*, which are pests of grain stores [3-7]. Somewhat later [8], a macrolide component was found in the pheromone of the Caribbean fruit fly *Anastrepa suspensa* – a pest of citrus fruits. At the present time eight macrolide pheromones have been identified. Of them, two (**1**, **2**) have an isoprenoid structure with two double bonds in the ring, while three (**3-5**) are monoenic, and three (**6-8**) are dienic. In addition, the saturated macrolide (**9**) – dihydrorecifeiolide has been detected in the extraction mixture obtained during the isolation of the pheromone of the rusty grain beetle *Cryptolestes ferrugineus* [3].



As a rule, the strategy of the synthesis of macrolide pheromones is based on the preparation of an acyclic precursor – a hydroxycarboxylic acid – followed by its cyclization. Recently, a method of enzymatic macrolactonization has been used in the synthesis of four macrolide pheromones [8].

SYNTHESIS OF ISOPRENOID MACROLIDES

4,8-Dimethyldeca-4E,8E-dienolide (**1**) (ferrulactone I) has been identified as the main component of the aggregation pheromone of the rusty grain beetle *Cryptolestes ferrugineus* [3]. The maximum attractive activity is possessed by a mixture of ferrulactone I (**1**) and ferrulactone II (**4**) in a ratio of 9:1 [9].

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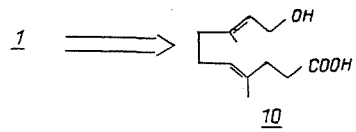
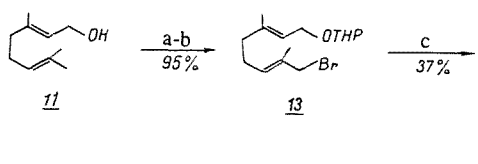
The majority of syntheses of the eleven-membered macrolide (**1**) are based on the lactonization of 10-hydroxy-4,8-dimethyldeca-4E,8E-dienoic acid (**10**) [8, 10-13], for which a number of methods of synthesis have been described [14, 15]:



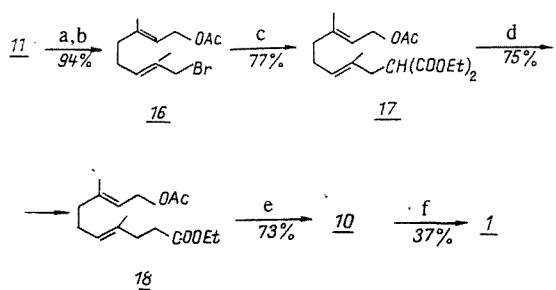
The isoprenoid structure of ferrulactone I (**1**) determined the choice of geraniol (**11**) [10-12, 16] and farnesol (**12**) [13] as the initial compounds for its synthesis. When geraniol is used, the carbon chain must be extended from its tail by two carbon atoms, while farnesol must be shortened by three carbon atoms.

In the first synthesis of macrolide (**1**) [10], the key stage was the alkylation of the ω-bromo derivative (**13**) of geraniol with the lithium salt of 2,4,4-trimethyl-2-oxazoline (**14**), with the subsequent hydrolysis of the oxazoline (**15**). The overall yield was 4.4%, calculated on the initial (**11**):



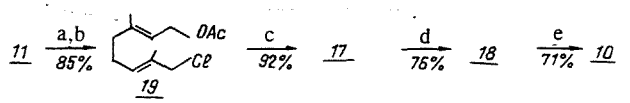
Reagents: a) DHP/TsOH, Et_2O; b) $CBr_4 \cdot PPh_3/Et_2O$, 23°C, 20 h;
c) $Li^+ {}^-CH_2$  , THF, −78°C, 0.5 h; d) MeI;
e) 1N NaOH, 20°C, 20 h; f) 10% HCl;
g) BID/PPh_3, PhMe, −10°C, 2 h; boil., 2 h

In the following syntheses, the same authors [10] made use of the alkylation of geraniol bromoacetate (**16**) with the aid of sodiomalonic ester, leading in high yield to compound (**17**), the decarboxylation of which gave the acetoxyester (**18**). In this case, the overall yield of macrolide (**1**) amounted to 15.5%, calculated on the geraniol (**11**):



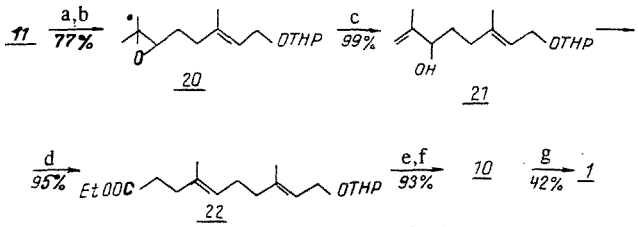
Reagents: a) Ac_2O/Py; b) $CBr_4 \cdot PPh_3/Et_2O$, 23°C, 20 h;
c) $Na^+ {}^-CH(COOEt)_2$/EtOH; d) NaCl/Me_2SO/H_2O, 160 °C;
e) NaOH/dioxane; f) BID/PPh_3, PhMe, −10 °C, 2 h;
boil., 2 h

The use of a palladium catalyst in the condensation of chloride (**19**) with sodiomalonic ester enabled the yield of compound (**17**) to be raised to 92% [14]. The overall yield of hydroxy acid (**10**) amounted to 42%, calculated on the geraniol (**11**):



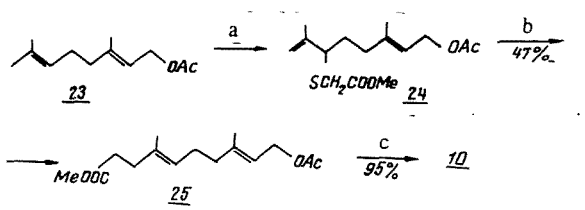
Reagents: a) Ac_2O/Py; b) $COCl_2/DMF$, c) $NaCH(COOEt)_2$/ PPh_3·$Pd(OAc)_2$, $EtOH$; d) $LiCl/DMF$, H_2O; e) $KOH/MeOH$

In the synthesis of ferrulactone I via the epoxide of the THP ether of geraniol (**20**), use was made of the Claisen rearrangement for the alcohol (**21**) [11], leading almost quantitatively to the ester (**22**), the proportion of the (E,E)-isomer in which exceeded 99% according to the results of GLC analysis. The overall yield of (**1**), calculated on the initial (**11**) was 28%:



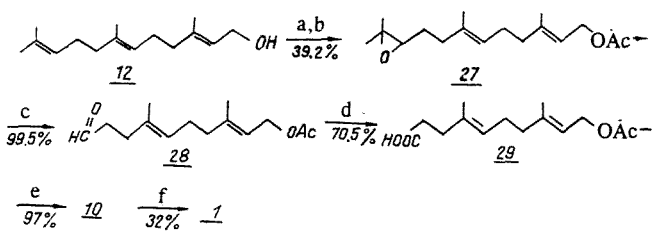
Reagents: a) $DHP/TsOH$, Et_2O; b) $MCPBA/AcONa$, CH_2Cl_2; c) $(i\text{-}PrO)_3Al/PhMe$; d) $MeC(OEt)_3/EtCOOH$, 135 °C; e) $Py\cdot TsOH/EtOH$; f) $KOH/MeOH$; g) BID /Ph_3P, $PhMe$

Another approach to the synthesis of ferrulactone I [12] is based on the use of a sigmatropic rearrangement of the activated allyl sulfide (**24**), obtained by the interaction of geranyl acetate (**23**) with the sulfenyl chloride derivative of methyl acetate (**26**). The rearrangement of the thioester (**24**), catalyzed by strong bases, led to a mixture of the *E/Z*-isomers of the acetoxy ester (**25**) the saponification of which gave the desired hydroxy acid (**10**) in the form of a mixture of isomers (4*E/Z* = 85:15):



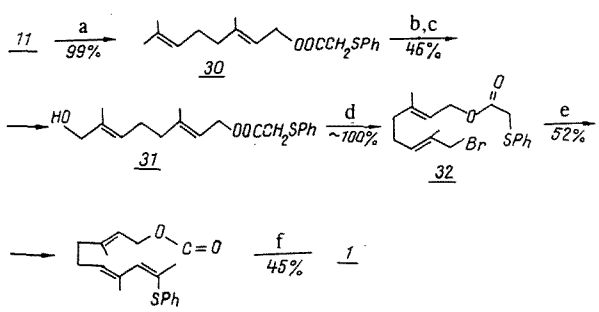
Reagents: a) $ClCH_2COOMe$; b) $t\text{-}BuOK/DMF$; c) $KOH/MeOH/H_2O$

The synthetic task of shortening the carbon chain of farnesol (**12**) was achieved by the destructive oxidation of the epoxide of farnesyl acetate (**27**) with periodic acid [13]. The aldehyde (**28**), obtained in almost quantitative yield, was transformed into ferrulactone I by oxidation with the Jones reagent, followed by alkaline hydrolysis of the acetate (**29**) and lactonization of the hydroxy acid (**10**) with the aid of bis(4-tert-butyl-N-isopropylimidazol-2-yl) disulfide (BID). The overall yield of lactone (**1**) was 8.8%, calculated on the initial (**12**):



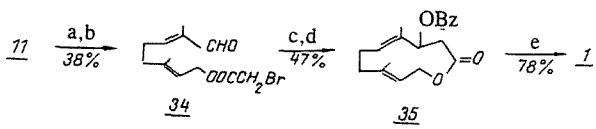
Reagents: a) Ac_2O/Py; b) NBS; c) $HIO_4\cdot 2H_2O/THF$, Et_2O; d) H_2CrO_4/acetone; e) $KOH/MeOH$; f) BID/PPh_3, $PhMe$

In a number of syntheses of ferrulactone I, cyclization was effected through ω,ω'-bifunctional esters [10, 16]. Thus, the intramolecular alkylation of 8-bromogeraniol phenylthioacetate (**32**) under the action of sodium hydride gave a 52% yield of the macrolide (**33**), the desulfurization of which led to ferrulactone I [10]. The acyclic precursor (**32**) was obtained from geraniol through the phenylthiocetate (**30**) and the allyl alcohol (**31**). The overall yield of (**1**) amounted to 10.6%, calculated on the initial geraniol:



Reagents: a) $PhSCH_2COCl/Py$, CH_2Cl_2; b) SeO_2/Py, $EtOH$; c) $NaBH_3CN$; d) $CBr_4 \cdot PPh_3/Et_2O$; e) $NaH/HMPA$; f) Raney Ni/$EtOH$

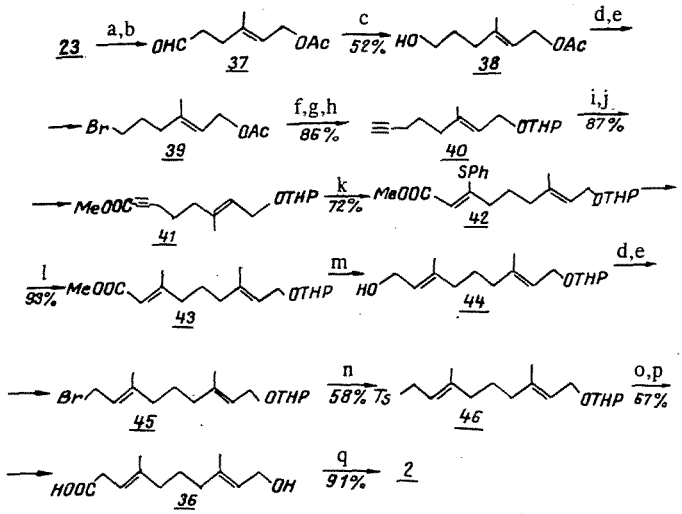
In a short synthesis of ferrulactone I from geraniol, the intramolecular cyclization of 8-bromoacetoxy-2,6-dimethylocta-2E,6E-dienal (**34**) was initiated with samarium iodide [16]. The selective allyl deacylation of the resulting macrolide (**35**) was carried out in the presence of SmI_2 with the addition of pivalic acid. The overall yield of (**1**) amounted to 14%, calculated on the initial (**11**).



Reagents: a) $BrCH_2COBr/Et_3N$; b) t-$BuOOH/SeO_2$-SiO_2; c) SmI_2/THF; d) $BzCl/DMAP$, 20 °C; e) SmI_2 pivalic acid/$HMPA$, THF

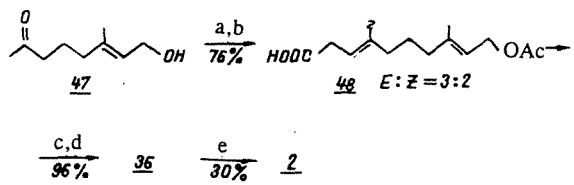
One of the four components of the sex pheromone of the Caribbean fruit fly *Anastrepha suspensa* has been identified as 4,8-dimethyldeca-3E,8E-dien-10-olide (suspensolide) (**2**) [17], isomeric with ferrulactone I. The difference between them amounts to the position of one of the double bonds. This fact determined the choice of geraniol as the starting material for the synthesis of of suspensolide (**2**), as well [18].

The head part of the geraniol molecule corresponds to the tail fragment of the acyclic precursor of suspensolide – 10-hydroxy-4,8-dimethyldeca-3E,8E-dienoic acid (**36**). For the construction of the carbon skeleton of the latter, geranyl acetate (**23**) was cleaved at the $\Delta^{6,7}$ bond, and the resulting aldehyde (**37**) was then transformed successively into the alcohol (**38**) and the bromide (**39**). Coupling the latter with lithium acetylide gave the alkenyne (**40**), which, in the form of the lithium salt, was coupled with methyl chloroformate. The stereoselective addition of thiophenol to the triple bond of compound (**41**) led to the phenylthioalkene (**42**), the interaction of which with methylmagnesium bromide gave the ester (**43**). The latter was converted into sulfone (**46**) through the intermediate alcohol (**44**) and bromide (**45**). The addition of carbon dioxide to the carbanion obtained from the sulfone (**46**), with the subsequent elimination of the tosyl sulfone group by means of sodium amalgam, yielded the acyclic precursor (**36**). The desired product was obtained with a yield of 9.1% by the lactonization of (**36**), using Mitsunobu's method [19]. The overall yield of suspensolide (**2**) was 1.4%, calculated on the (**23**) [18].



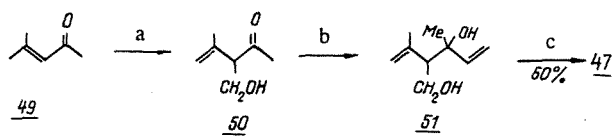
Reagents: a) OsO_4/N-methylmorpholine - N-oxide; b) $NaIO_4$
c) $Li\,AlH(t\text{-}BuO)_3$; d) $TsCl/Py$; e) $LiBr$/acetone
f) $HC{\equiv}CLi/NH_3$ (liquid), DMSO; g) $NaOH/MeOH$;
h) $DHP/TsOH, Et_2O$; i) $BuLi/THF$, j) $ClCOOMe$;
k) $PhSH$; l) $MeMgBr/CuI, Et_2O$; m) $LiAlH_4/Et_2O$;
n) $TsCl/DMF$; o) $BuLi/CO_2$; p) $Na\text{-}Hg$;
q) $EtOOCN{=}NCOOEt/Ph_3P$, PhMe

A short synthesis of the acyclic precursor (**36**) of suspensolide has been achieved from 8-hydroxy-6-methyloct-6E-en-2-one (**47**). The Wittig olefination of its acetate gave the acetoxy acid (**48**) and subsequent alkaline hydrolysis led to the desired hydroxy acid (**36**) in the form of a mixture of (E/Z)-isomers (3:2) from which the E-isomer was isolated by HPLC [20]. The macrolactonization of hydroxy acid (**36**) was achieved with the aid of diethyl azodicarboxylate and gave a 30% yield of the desired suspensolide (**2**) (stereochemical purity 94%) [21, 22].



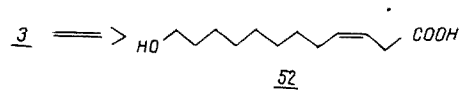
Reagents: a) AcO_2/Py, 20°C, 5 h; b) $Ph_3P^+CH_2CH_2COOHCl^-$/ DMSO, THF, 30°C, 10 h; c) NaOH/MeOH, d) HPLC; e) $EtOOCN{=}NCOOEt/PhPh_3, C_6H_6$

The synthon (**47**), obtained from mesityl oxide (**49**) via the intermediate compounds (**50**) and (**51**) [23], consisted of a 3:2 mixture of (E/Z)-isomers, which was separated in the form of acetates by liquid chromatography:

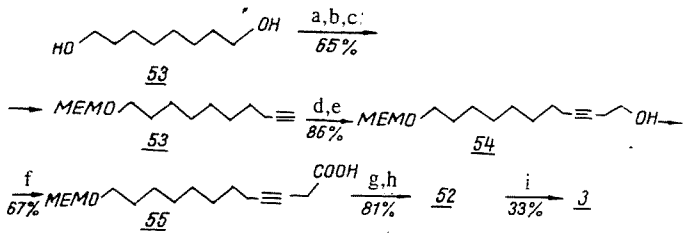


Reagents: a) $CH_2O/Et_2O/H^+$; b) $H_2C{=}CHMgBr/THF$;
c) NMP/Δ

The main component of the aggregation pheromone of the flat grain beetle *Cryptolestes pusillus*, identified as dodec-3Z-en-12-olide (**3**), has been synthesized by the cyclization of 12-hydroxydodec-3Z-enoic acid (**52**).

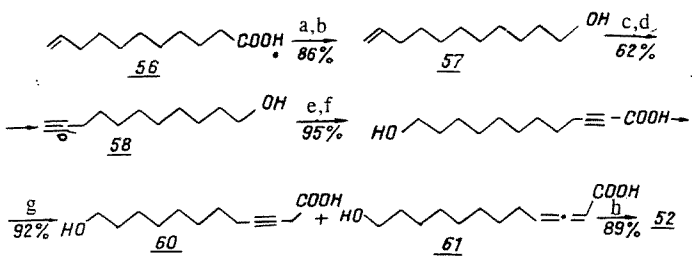


The first synthesis of macrolide (**3**) [24] was achieved by the sucessive growth of the skeleton of octane-1,8-diol (**53**) with the aid of acetylene and ethylene oxide. The C_{12} synthon obtained (**54**) was oxidized (Jones method) to the acid (**55**) and, by reduction of the triple bond to a (Z)-double bond, was transformed into the hydroxy acid (**52**), the lactonization of which by Corey's method gave the desired macrolide (**3**) with a yield of 33%. Its overall yield, calculated on the initial diol (**53**) was 10.3%:



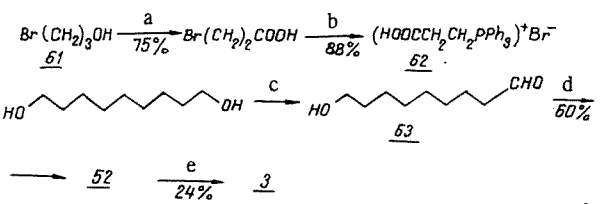
Reagents: a) HBr; b) $MEMCl/i\text{-}Pr_2EtN$, CH_2Cl_2;
c) $HC{\equiv}CLi/NH_3$(liquid); d) $EtMgBr/Et_2O$; e)  ;
f) H_2CrO_4/acetone; g) $H_2O/HCl/THF$; h) $H_2/Ni\text{-}P2$;
i) $(PyS)_2/Ph_3P/MeCN$, xylene

On synthesis from the readily available undec-10-enoic aicd (**56**) via the intermediates (**57-61**) a 45% overall yield of the hydroxy acid (**52**) was obtained [25]:



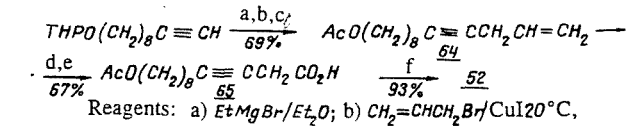
Reagents: a) $MeOH/TsOH$; b) $i\text{-}Bu_2AlH$; c) Br_2/CH_2Cl_2;
d) KOH/18-crown-12; e) $BuLi$; f) CO_2;
g) $LiNH_2/NH_3/THF$; h) $H_2/Ni\text{-}P2$

When the Z-double bond was constructed by the Wittig reaction with 8-hydroxynonanal (**63**) and the phosphonium salt (**62**), the overall yield of the desired macrolide (**3**) was 9.5%, calculated on the initial bromohydrin (**61**) [26]:



Reagents: a) H_2CrO_4/ acetone ; b) $Ph_3P/MeCN$, boil, 8 h;
c) $t\text{-}BuOCrO_3H$; d) $t\text{-}BuOK$/(62), DMF, 0 °C, 3 h;
e) $(PyS)_2/Ph_3P$, p-xylene, boil., 2 h

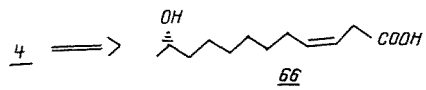
A new approach has been proposed to the synthesis of 3Z-unsaturated ω-hydroxy carboxylic acids that is based on the partial ozonolysis of acetates of aliphatic alcohols with a terminal 1,4-enyne fragment [27]. Thus, the ozonolyis of tridec-12-en-9-yn-1-yl acetate (**64**) gave a high yield of 12-acetoxydodec-3-enoic acid (**65**), readily converted in two stages into the desired hydroxy acid (**52**) [27]:



Reagents: a) $EtMgBr/Et_2O$; b) $CH_2{=}CHCH_2Br$/CuI 20 °C, c) Ac_2O/Py; d) O_3/c-C_6H_{12}–AcOH, 5 °C, e) H_2CrO_4/acetone; 0–20 °C; f) H_2/Ni–P2, 20 °C; 2 h

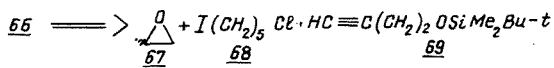
A minor component of the aggregation pheromone of the rusty grain beetle *Cryptolestes ferrugineus* has been given the name ferrulactone II and has been identified as a chiral monoenic 12-membered lactone with a (S,Z)-configuration – dodec-3Z-en-11S-olide (**4**) [3] – which is present in the two-component pheromone of the merchant grain beetle *Oryzaephilus mercator* [6].

Known syntheses of ferrulactone II (**4**) are based on the lactonization of an acyclic precursor – 11S-hydroxydodec-3Z-enoic acid (**66**):

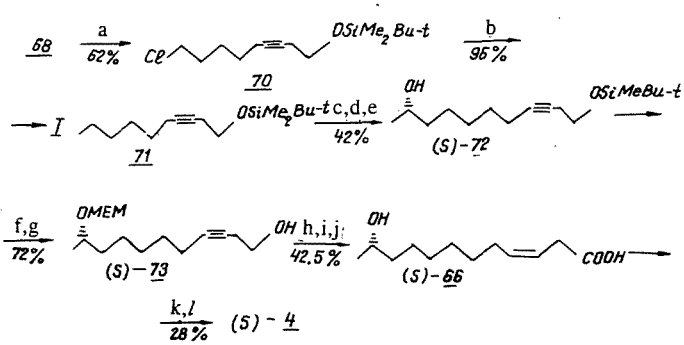


In addition, by enzymatic macrolactonization it has been possible to obtain the (S)-macrolide (**4**) from the racemic hydroxy acid (**66**) [8].

In the first of the published syntheses of hydroxy acid (**66**) [10] the chiral center was introduced with the optically active (S)-(propylene oxide) (**67**). In the construction of the carbon skeleton of (**66**) use was also made of synthons (**68**) and (**69**):

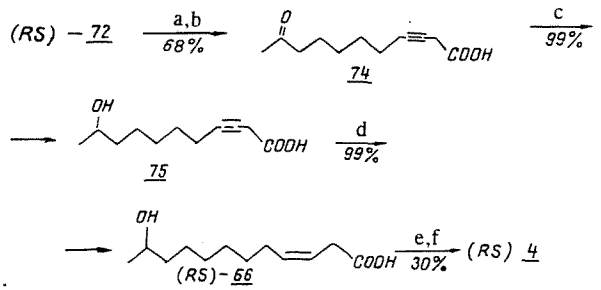


The realization of this plan of synthesis was performed in accordance with the scheme shown. Selective coupling of the dihalide (**68**) with the lithium salt of alkyne (**69**) and then, after conversion of the chloride (**70**) into the corresponding iodide (**71**), with (S)-(propylene oxide) gave the alcohols (**72**) and (**73**) having the (S)-configuration. The Jones oxidation of the latter and reduction of the triple bond to a Z-double bond gave the desired (S)-(hydroxy acid) (**66**), the lactonization of which by Corey's method led to (S)-ferrulactone II with a yield of 28%. The overall yield of macrolide (**4**) was 2.1%, calculated on the initial dihalide (**68**). The (R)-isomer was obtained in an overall yield of 1.3% by the same scheme, using (R)-(propylene oxide).



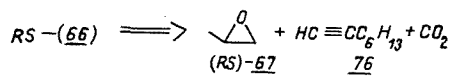
Reagents: a) (**69**)$BuLi/THF,HMPA$; b) NaI/acetone; c) Mg/THF; d) CuI; e)  ; f) $MEMCl/i\text{-}Pr_2CHCH_2NH_2$; g) $AcOH/H_2O/THF$; h) H_2CrO_4/ acetone; i) $ZnBr_2/CH_2Cl_2$; j) H_2/Ni–P2; k) $(PyS)_2PPh_3$/ $MeCN$; l) $AgClO_4$/p-xylene

In the synthesis of racemic ferrulactone (II) (using racemic propylene oxide), the alcohol (RS)-(**72**) was converted into the keto acid (**74**), which was reduced to the hydroxy acid (**75**) and then transformed into the lactone (**4**), the overall yield of which, calculated on the dihalide (**68**) was 5.1% [10]:

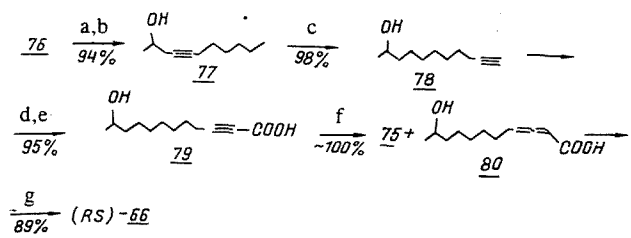


Reagents: a) $(t\text{-}Bu)_4NCl/H_2O/THF$, 23°C, 1 h; b) H_2CrO_4/ acetone ; c) $NaBH_4/EtOH$; d) $H_2/Ni\text{-}P2$; e) $(PyS)_2$/ $PPh_3/MeCN$; f) $AgClO_4$/ p-xylene

The racemic hydroxy acid (**66**) was also obtained by a $C_8 + C_3 + C_1$ scheme [25]:

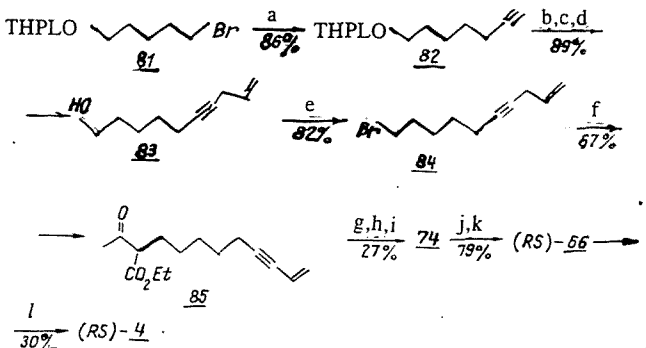


The alkylation of oct-1-yne (**76**) with propylene oxide, followed by the isomerization of the alkynone (**77**) into the terminal alkyne (**78**) and carboxylation of the latter, gave 11-hydroxydodec-2-ynoic acid (**79**). The action of sodium amide in liquid ammonia on the latter gave a mixture of the alk-3-ynoic and alka-2,3-dienoic acids (**75** and **80**) the hydrogenation of which led to a single product – the racemic hydroxy acid (**66**), the overall yield of which amounted to 78%, calculated on the initial oct-1-yne (**76**) [25]:



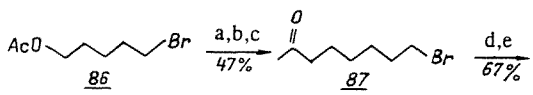
Reagents: a) $BuLi/HMPT$, THF; b)  ; c) $NH_2(CH_2)_3NHNa/NH_3$; d) $BuLi/THF$; e) CO_2; f) $NaNH_2/THF$; g) $H_2/Ni\text{-}P2$

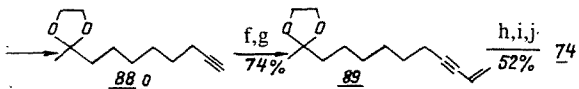
A scheme using the partial ozonolysis of ω-acetyl derivatives of 1,4-alkenynes has been proposed for the synthesis of the (±)-(hydroxy acid) (**66**) [28]. Starting from the tetrahydropyranyl (THPL) derivative of the bromohydrin (**81**), the enyne bromide (**84**) was synthesized via the intermediate alkyne (**82**) and alkenyne (**83**), and its coupling with acetoacetic ester gave 3-ethoxycarbonyl-2-oxotridec-12-en-9-yne (**85**), which was subjected to ozonolysis and then to Jones oxidation and deethoxycarbonylation, leading to the acetylenic keto acid (**74**) and then to the desired (±)-(hydroxy acid) (**66**) [28]:



Reagents: a) $CH{\equiv}CH/NH_2Na$/liquid NH_3; b) $EtMgB_r/Et_2O$; c) ≈Br/ $CuI\,Et_2O$; d) $TsOH/MeOH$; e) $Br_2 \cdot PPh_3/CCl_4$; f) $CO_2Et/EtONa/EtOH$; g) O_3/c-C_6H_{12}/AcOH; h) H_2CrO_4/acetone; i) $LiCl$/DMSO/H_2O; j) $NaBH_4/EtOH$; k) H_2/Ni-P2; l) 2,2'-dipyridyl disulfide /PPh_3/MeCN

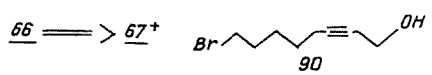
A somewhat different pathway for the synthesis of keto acid (**74**), starting from the acetate of bromohydrin (**86**), has been realized [28]. In this case it was the enyne (**89**), obtained by a five-stage transformation of the initial (**86**) through the intermediates (**87**) and (**88**), that was subjected to ozonization:



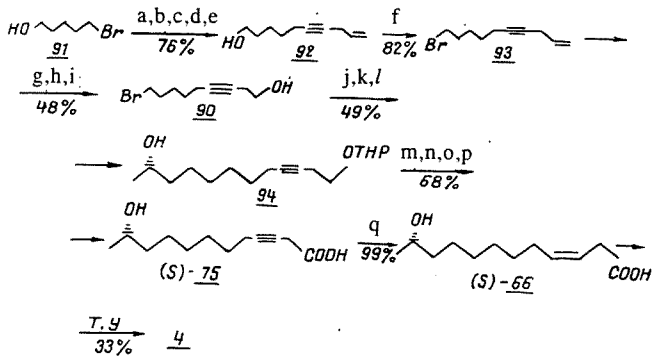


Reagents: a) ≈$CO_2Et/EtONa/EtOH$; b) $TsCl/Py$; c) $NaBr$/acetone; d) $(CH_2OH)_2$ $TsOH/Py{\cdot}TsOH$/benzene, boil, 35 h; e) $HC{\equiv}CH/NH_2Na$/liquid NH_3/THF/DMSO; f) $EtMgBr/Et_2O$; g) ≈Br/CuI/THF; h) O_3/c-C_6H_{12}/AcOH; i) H_2CrO_4/acetone; j) HCl/acetone

An effective synthesis of the (S)-(hydroxy acid) (**66**) has been achieved from (S)-(propylene oxide) (**67**) and the C_9 synthon 9-bromonon-3-yn-1-ol (**90**) [29]:

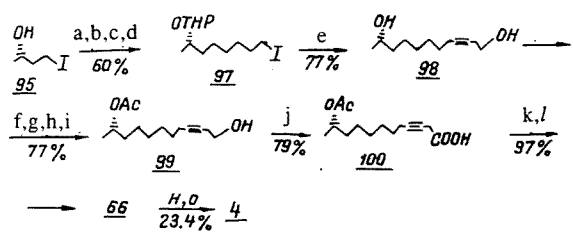


The C_9 fragment (**90**) was obtained by the successive growth of the carbon chain of the readily available 5-bromopentan-1-ol (**91**) with the aid of acetylene and allyl bromide. The C_{10}-allylic alcohol (**92**) obtained in this way was transformed into the required C_9 synthon (**90**) by partial ozonolysis of the enynic bromide (**93**). The Wurtz coupling of the bromohydrin (**90**) with (S)-(propylene oxide) so obtained was performed in the cuprate variant and led with a yield of 50% to the chiral diol (**94**). Its further tranformation consisted in the selective oxidation of the primary hydroxy group and the (Z)-hydrogenation of the (S)-hydroxyalkynoic acid (**75**). The overall yield of the desired (S)-(hydroxy acid) (**66**) was 3.0% and that of ferrulactone II (**4**) 1.0%, calculated on the initial bromohydrin (**91**):



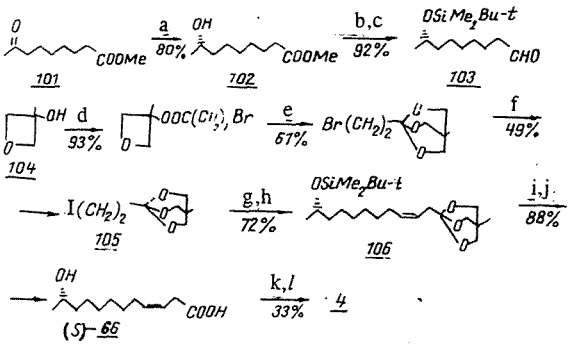
Reagents: a) DHP/TsOH, Et_2O; b) $HC{\equiv}CLi/NH_3$/DMSO, THF; c) EtMgBr/THF; d) $H_2C{=}CHCH_2Br$; e) TsOH/MeOH; f) $Br_2{\cdot}PPh_3/CCl_4$; g) O_3/MeOH; h) $NaBH_4$; i) DHP/TsOH, Et_2O; j) Mg/THF; k) CuBr/Me_2S; l) (67), -40 °C; m) Ac_2O/Py; n) Py·TsOH/Et_2O; o) H_2CrO_4/acetone; p) K_2CO_3/MeOH; q) H_2/Ni-P2; r) $(PyS)_2/Ph_3P$, MeCN; s) $AgClO_4$/ p-xylene

Japanese authors [13] used the THP ether of 4-iodobutan-2S-ol (**95**) as the chiral synthon. The carbon skeleton of the hydroxy acid (**66**) was constructed by coupling the iodide (**95**) with the Grignard reagent obtained from the chlorohydrin (**96**), and then the iodide (**97**) with the lithium salt of the acetylene (**69**). The C_{12} synthon (**98**) so obtained was transformed into the desired product (**66**) through the intermediates (**99**) and (**100**) as shown in the scheme given. The overall yield of ferrulactone II (**4**) was 6.3%, calculated on the initial chiral synthon (**95**).



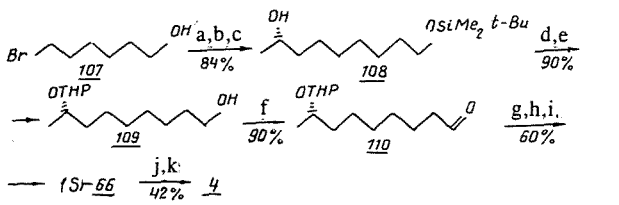
Reagents: a) DHP/TsOH, Et_2O; b) $Cl(CH_2)_4OH$ (96)/MgOPr/Mg; c) TsCl/Py; d) NaI/Me_2CO; e) (69)/BuLi/THF; f) $Ph_2SiBu\text{-}tCl$, imidazole; g) H_2O/AcOH, THF; h) Ac_2O/Py; i) 46% HF/MeOH; j) H_2CrO_4/acetone; k) K_2CO_3/MeOH; l) H_2/Ni-P2; m) $(PyS)_2/Ph_3P$, MeCN; n) $AgClO_4$/ p-xylene

In the construction of the (Z)-alkenyl skeleton of optically active ferrulactone II with the use of the Wittig reaction, the chiral hydroxy aldehyde (**103**) was synthesized from the readily available keto ester (**101**) by the asymmetric reduction of the keto group to an alcohol group with the aid of the heat-stable enzyme alcohol dehydrogenase of *Thermoanaerobium brockii* (TBADM) with the subsequent hydride reduction of the ester group in the (S)-chiral hydroxyester (**102**) to an aldehyde group [30]. The phosphorane necessary for the olefination of the aldehyde (**103**) was generated from the 3-iodoorthopropionate (**105**), obtained from the oxetane (**104**). The olefination of the aldehyde (**103**) yielded the (Z)-alkene (**106**) contaminated with 10% of the (E)-isomer. Removal of the orthoester protective group led to the (S)-(hydroxy acid) (**66**) the lactonization of which by Corey's method gave the desired macrolide (**4**), the overall yield of which was 15.3%, calculated on the initial keto ester (**101**).



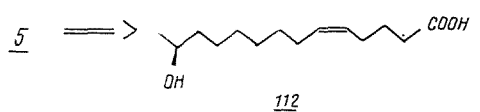
Reagents: a) TBADM; b) t-$BuMe_2SiCl$; c) $LiAlH_4$; d) $Br(CH_2)_2COCl/Py, THF$; e) $BrF_3 \cdot Et_2O/CH_2Cl_2$, 0 °C, 3 h; f) $NaI/DMF, NaHCO_3$, 100 °C, 2 h; g) Ph_3P; h) (103); i) $H_2SO_4/MeOH$; j) KOH; k) $(PyS)_2/Ph_3P/MeCN$; l) $AgClO_4$/p-xylene

The (S)-(hydroxy acid) (**66**) was synthesized by the olefination of the chiral hydroxy aldehyde (**110**), obtained from the bromohydrin (**107**) (via the intermediates **108** and **109**) and (S)-(propylene oxide) with the aid of the phosphorane generated from the 3-bromo orthoester (**111**) with an overall yield of 17%, calculated on the initial (**107**) [31, 32]:



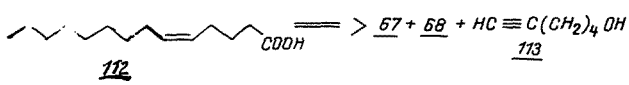
Reagents: a) $ClSiMe_2t$-Bu/imidazole/DMF; b) Mg/THF; c) (S)-67/$CuBr \cdot Me_2S$; d) THP/TsOH·Py/CH_2Cl_2; e) Bu_4NF/THF; f) PCC/AcONa/CH_2Cl_2; g) $Br(CH_2)_2$ (111)/PPh_3; h) Bu Li/THP/HMPA; i) TsOH·Py/EtOH; j) 2,2'-dipyridyl disulfide/PPh_3/$AgClO_4$/MeCN/ o-$Me_2C_6H_4$; k) HPLC

A minor component of the aggregation pheromone of the flat grain beetle *Cryptolestes pusillus* [76]* and of the flour mill grain beetle *Cryptolestes turcicus* [80]*, identified as tetradec-5Z-en-13S-olide (**134**), has been synthesized by the lactonization of 13S-hydroxytetradec-5Z-enoic acid (**112**) [77, 78, 81, 82]*.



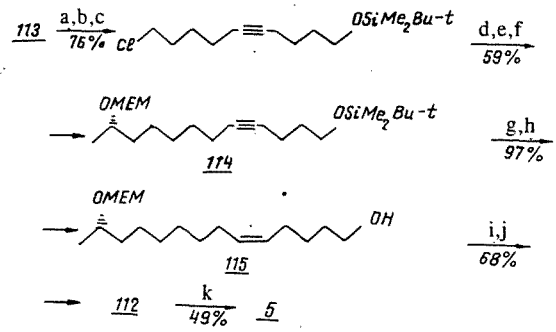
Optically active synthons – (S)-(propylene oxide) (**67**) [24] or 3S-hydroxybutanoic acid [33] – were used to construct the chiral fragment of the hydroxy acid (**112**).

In the synthesis of the hydroxy acid (**112**) by a ($C_6 + C_5 + C_3$) scheme the starting compounds used were hex-5-yn-1-ol (**113**), the dihalide (**68**), and (S)-(propylene oxide) (**67**) [24]:



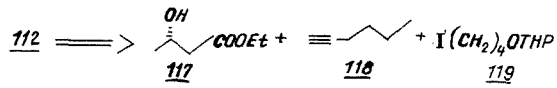
*[sic]. The given list of references ends at No. 49 – Translator.

The growth of the carbon chain of the initial alkynol (**113**) was achieved by successive coupling with the above-mentioned synthons (**67**) and (**68**) in accordance with the scheme shown below. The C_{14} synthon (**114**) obtained via the (Z)-alkenediol (**115**) was transformed into the desired hydroxy acid (**112**). Its lactonization was carried out with the aid of 2-chloro-N-methylpyridinium iodide (**116**) and gave the macrolide (**5**) in 49% yield. The overall yield of the pheromone, calculated on the initial hexynone (**113**) amounted to 14%.

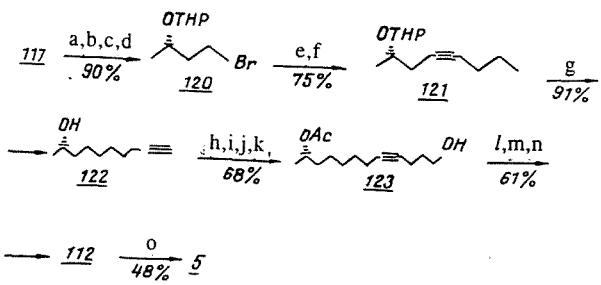


Reagents: a) *t*-Bu$Me_2SiCℓ$; b) *BuLi*/Et_2O; c) (**68**); d) *Mg*/*THF*; e) (**67**); f) *MEMCℓ*; g) H_2/*Ni-P2*; h) *AcOH*/H_2O; i) H_2CrO_4/acetone; j) H_2O/*HCℓ*, *THF*; k) (**116**)/*MeCN*

When ethyl 3S-hydroxybutynoate (**117**) was used as the chiral source, the following plan of synthesis was chosen:



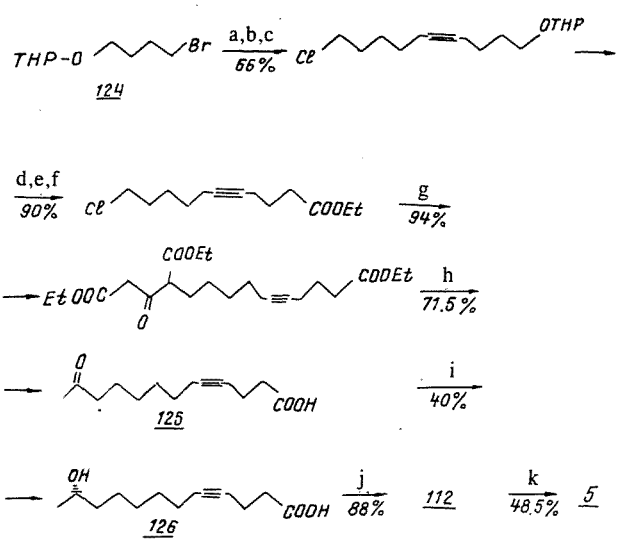
For its realization, the chiral hydroxy ester (**117**) was converted into the bromide (**120**), the coupling of which with lithium hexynylide gave the alkyne (**121**), and this was converted into the terminal alkyn-2S-ol. The coupling of the lithium salt of the latter with the iodohydrin THP ether (**119**) led to the chiral alkynediol (**123**), which was converted in four stages into the desired macrolide (**5**). The overall yield of the pheromone was 13.4%, calculated on the initial (**117**) [33]:



Reagents: a) *i*-$Bu_2AℓH$/Et_2O; b) *TsCℓ*/*Py*; c) *NaBr*/acetone; d) *DHP*/*TsOH*, Et_2O; e) (**118**)/*BuLi*/Et_2O; f) *TsOH*/Et_2O; g) $NH_2(CH_2)_3NH_2$/$NaNH_2$; h) *BuLi*, i) (**119**); j) Ac_2O/*Py*; k) *TsOH*/Et_2O; *l*) H_2CrO_4/acetone; m) *NaOH*/*MeOH*; n) H_2/*Ni-P2*; o) (**116**)/*MeCN*

The chiral hydroxy acid (**112**) has been obtained by the asymmetric reduction of the keto acid (**125**) with the aid of immobilized bakers' yeast (IBY) [34, 35]. The keto acid (**125**) was synthesized by the succesive coupling of the THP ether of 4-bromobutanol (**124**) with lithium acetylenide, 5-iodo-1-chloropentane, and the magnesium derivative of diethyl ketoglutarate. The enantiospecific reduction of keto acid (**125**) gave the hydroxy acid (**126**) with a yield of 40% and an optical purity of 95%.

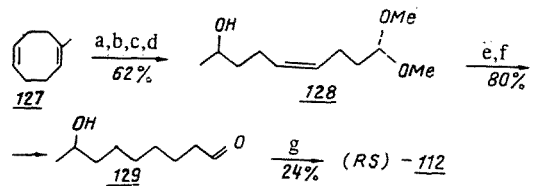
After hydrogenation over Ni-P2 and lactonization of the hydroxy acid (**112**), the desired macrolide (**5**) was obtained with an overall yield of 6.6%, calculated on the initial bromide (**124**).



Reagents: a) $HC{\equiv}CLi/DMSO/(NH_2CH_2)_2$; b) $BuLi/THF$; c) $Cl(CH_2)_5I$; d) $TsOH/MeOH$; e) H_2CrO_4/acetone; f) $EtOH/TsOH$; g) $EtOOCH_2CCH_2COOEt/Mg(OEt)_2$; h) KOH/H_2O, $(C_{16}H_{33}Me_3)^+Br^-$; i) IBY/glucose, H_2O; j) H_2/Ni-P2; k) (**116**)/MeCN

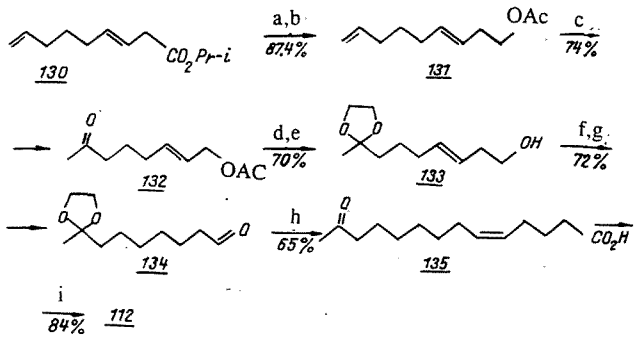
Enzymatic macrocyclization of the (R)-methyl ester of the racemic hydroxy acid (**112**) gave macrolide (**5**) with the (R)-configuration, a component of the pheromone of the flat grain beetle *Cryptolestes pusillus* [8].

Two approaches have been developed for the synthesis of the racemic acid (**112**) [36]. One of them is based on the selective ozonolysis of 1-methylcyclo-1Z,5Z-diene (**127**) – a copolymer of butadiene and isoprene – leading to the product of the cleavage of the diene at its trisubstituted double bond [37-39]. The dimethyl acetal of 8-hydroxynon-4Z-enal (**128**) so obtained was hydrogenated, and the resulting hydroxy acetal was hydrolyzed to give the hydroxy aldehyde (**129**), and the olefination of this with 4-carboxybutylidenetriphenylphosphorane led to the desired (Z)-(hydroxy acid) (**112**), the overall yield of which, calculated on the initial cyclodiene (**127**) was 11.9% [36].



Reagents: a) O_3/c-C_6H_{12}-MeOH, 5°C; b) H_2/Pd-$CaCO_3$-PbO; c) $NH_4Cl/MeOH$, 20°C, 36 h; d) $NaBH_4/MeOH$; e) H_2/Ni-Ra, 25°C, 80 atm, 3 h; f) $TsOH \cdot Py$/acetone-H_2O, boil. 2 h; g) $[Ph_3P(CH_2)_4COOH]^+Br^-$/$NaN(SiMe_3)_2/THF$

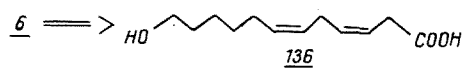
In the other approach to the synthesis of hydroxy acid (**112**) the starting compound was a product of the telomerization of butadiene and carbon monoxide – nona-3E,8-dienoate (**130**) [36]. Its reduction with diisobutylaluminum hydride followed by acetylation led to a high yield of the dienic acetate (**131**) [40]. The oxidation of the latter with molecular oxygen in the presence of $PdCl_2-CuCl$ gave the acetoxy ketone (**132**), which was converted into the acetal of the correponding hydroxy ketone (**133**). Its hydrogenation and subsequent oxidation led to the keto aldehyde monoacetal (**134**), the olefination of which was conducted under the same conditions as for the hydroxy aldehyde (**129**), although the yield of olefination product – the Z-unsaturated keto acid (**135**) – was substantially higher. Hydride reduction of the keto acid led smoothly to the desired (±)-(hydroxy acid) (**112**). Its overall yield amounted to 17.8%, calculated on the initial dienoate (**130**) [36].



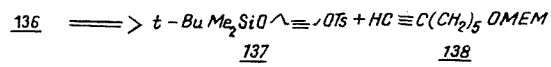
Reagents: a) i-Bu_2AlH; b) Ac_2O/Py; c) $O_2/PdCl_2$-$CuCl/DMF$; d) $(CH_2OH)_2/Py$·$TsOH$/benzene, boil. 30h; e) $KOH/MeOH$, boil. 2h; f) H_2/Pd-$C/AcOEt$, 10 h; g) PCC/CH_2Cl_2; h) $[Ph_3P(CH_2)_4COOH]^+Br^-/NaN(SiMe_3)_2/THF$; i) $NaBH_4$/EtOH

SYNTHESIS OF 1,4-DIENIC MACROLIDES

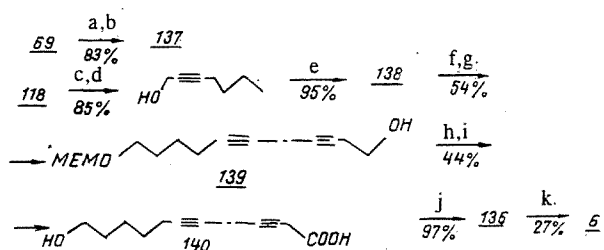
The synthesis of dodeca-3Z,6Z-dien-12-olide (**6**), which has been identified as a component of the pheromone of the saw-toothed grain beetle *Oryzaephilus surinamensis* [6] has been effected by the lactonization of an acyclic precursor – 12-hydroxydodeca-3Z,6Z-dienoic acid (**136**) [41]:



A $C_5 + C_7$ scheme of synthesis was used for the hydroxy acid (**136**) [41]:

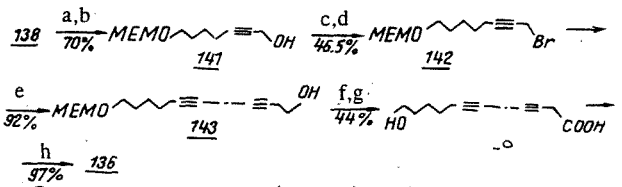


Both alkynic synthons (**137**) and (**138**) were obtained by formylation of substrates (**68**) and (**118**), respectively. Coupling the alkyne (**138**) and the tosylate (**137**) gave the selectively protected diynic diol (**139**), the oxidation of which and the hydrogenation of the resulting diynic acid (**140**) led to the desired (Z,Z)-dienic hydroxy acid (**136**), the lactonization of which produced the macrolide (**6**) with an overall yield of 2.8%, calculated on the initial hexyne (**118**) [41].



Reagents: a) $(HCHO)_n$; b) $TsCl/Py$; c) Li/NH_3; d) K_2CO_3/$NH_2(CH_2)NH_2$; e) $MEMCl$; f) $BuLi$/(**137**); g) $TsOH/Et_2O$; h) H_2CrO_4/acetone; i) HCl/H_2O, THF; j) H_2/Ni-P2; k) (**116**)/$MeCN$

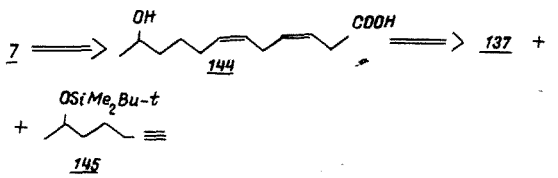
In the other scheme for synthesizing hydroxy acid (**136**) [25], the MEM ether (**138**) was brought into condensation with formaldehyde. The resulting alkynol (**141**) was converted into the bromide (**142**). Its coupling with the dimagnesium derivative of but-3-yn-1-ol gave the selectively protected diynic diol (**143**), which was oxidized by the Jones method and then, by reduction of the triple bonds to (Z)-double bonds, was transformed into the desired hydroxy acid (**136**), the overall yield of which was 14%, calculated on the initial (**138**):



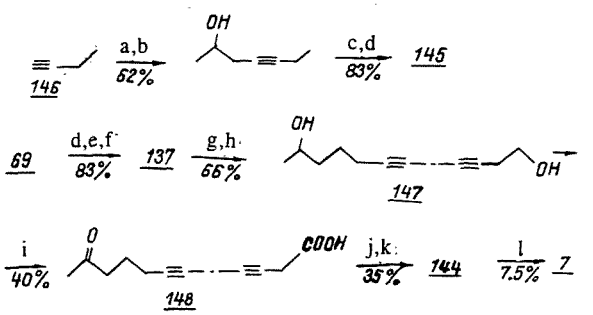
Reagents: a) BuLi/THF; b) HCHO; c) TsCl/KOH, Et_2O; d) LiBr/acetone; e) $BrMgO(CH_2)_2C{\equiv}CMgBr/CuBr$, HMPA; f) H_2CrO_4/acetone; g) HCl/THF, H_2O; h) H_2/Ni-P2

One of the components of the aggregation pheromone of the grain beetles *Oryzaephilus mercator* and *O. surinamensis,* which has been identified as dodeca-3Z,6Z-dien-11-olide (7) [6], possesses a chiral center. However, it has been shown that the chirality of the macrolide (7) does not affect its biological activity [6], and it is therefore desirable to synthesize it in the racemic form.

Two syntheses of macrolide (7) from its acyclic precursor (**144**) are known. In the first of them, a $C_5 + C_7$ scheme was used for the synthesis of hydroxy acid (**144**) [41]:

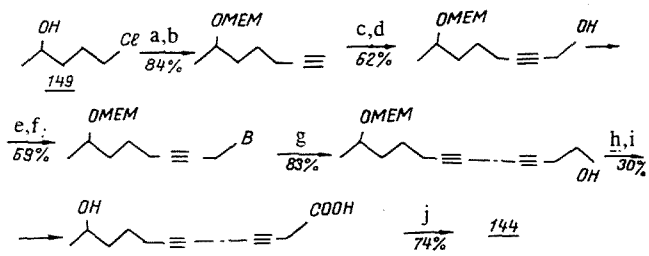


The alkyne (**145**), obtained by coupling but-1-yne (**146**) with propylene oxide, followed by isomerization, was coupled with the C_7 synthon (**137**), obtained by the formylation of but-3-yn-1-ol (**69**). The resulting diol (**147**) was subjected to Jones oxidation, and and the diynic keto acid (**148**) formed was converted in two stages into the (Z,Z)-(hydroxy acid) (**144**), the cyclization of which led to the desired macrolide (7) with a yield of 7.5%, its overall yield, calculated on the alkynol (**69**), being 0.57%.



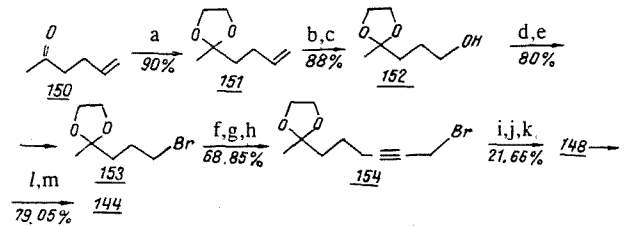
Reagents: a) Li/NH_3; b) (RS)-67; c) KOH/$NH_2(CH_2)_3NH_2$; d) t-BuMe$_2$SiCl; e) HCHO; f) TsCl/Py; g) (145)/EtMgBr/CuI; h) HCl; i) H_2CrO_4/acetone; j) $NaBH_4$; k) H_2/Ni-P2; l) (116)/MeCN

In the other synthesis [25], the acyclic precursor (**144**) was obtained by the successive growth of the carbon chain of 5-chloropentan-1-ol (**149**) with the aid of acetylene, formaldehyde, and the alkynol (**69**). The overall yield of the hydroxy acid (**144**) was 6.6% calculated on the initial (**149**).



Reagents: a) MEMCℓ; b) HC≡CLi/Et_2O; c) BuLi; d) HCHO; e) TsCℓ/Py; f) LiBr/acetone; g) **69**/BuLi; h) H_2CrO_4/acetone; i) HCℓ/H_2O/THF; j) H_2/Ni-P2

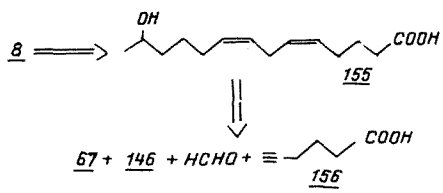
The most rational of the known methods is the synthesis of hydroxy acid (**144**) from the readily available allylacetone (**150**) [42]: the ozonolysis of its acetal (**151**) gives a high yield of the alcohol (**152**), which is converted into the bromide (**153**). The subsequent transformation of (**153**) into the alkynic bromide (**154**) and the coupling of the latter with the magnesium derivative of the alkynol (**69**) led to the diynic keto acid (**148**) – a precursor of the hydroxy acid (**144**) [42]:



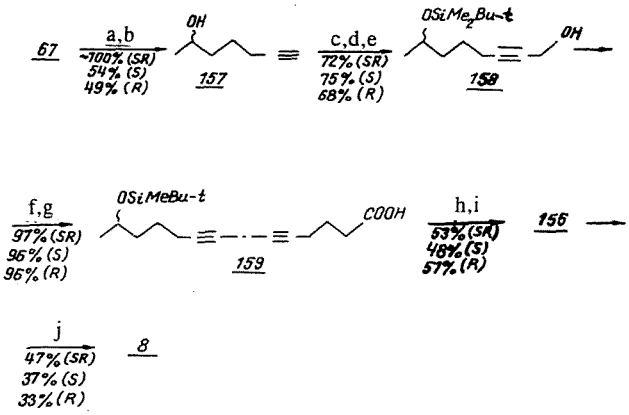
Reagents: a) $(CH_2OH)_2$/TsOH·Py, C_6H_6; b) O_3/AcOH, c-C_6H_{12}; c) $NaBH_4$/EtOH; d) Ts Cℓ/Py; e) NaBr/DMF; f) $LiC{\equiv}CCH_2Li/NH_3$ (liquid); g) Ts Cℓ/Py; h) NaBr/DMF; i) **69**/EtMgBr/THF; j) TsOH/MeOH; k) $H_2C_2O_4$/Me_2CO; l) $NaBH_4$/EtOH; m) H_2/Ni-P2

The macrolide tetradeca-5Z,8Z-dien-13-olide (**8**), which has been identified as a component of the aggregation pheromones of the grain beetles *Cryptolestes turcicus* [7] and *Oryzaephilus surinamensis* [6] has been synthesized both in optically active and in racemic forms. As a result, it was found that the racemic form is more active [7].

In the synthesis [41] of the enantiomers of macrolide (**8**), the chiral source used was (S)- or (R)-(propylene oxide) (**67**). But-1-yne (**146**), formaldehyde, and 5-hexynoic acid (**156**) have also been used for the construction of the carbon skeleton of hydroxy acid (**155**).

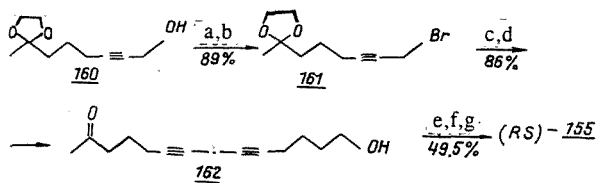


The coupling of (**67**) and (**146**), followed by the displacement of the triple bond to the terminal position, gave the alkynol (**157**), which, in the form of the silyl derivative, was brought into condensation with formaldehyde. This gave the alcohol (**158**), the tosylate of which was coupled with hex-5-ynoic acid (**156**). Selective hydrogenation of the triple bond in the hydroxy acid (**159**) and removal of the silyl protection led to the desired hydroxy acid (**155**) of the (S)-, (R)-, or (RS)-configuration as the case may be. Macrolactonization of the hydroxy acid (**155**) formed 37, 33, or 47% of the (S)-, (R)- or (SR)-macrolides (**8**), respectively [41]:



Reagents: a) (146)/BuLi; b) $K_2CO_3/NH_2(CH_2)_3NH_2$;
c) t-BuMe$_2$SiCl; d) BuLi/THF; e) HCHO;
f) TsCl/Py; g) (156)/BuLi; h) H_2/Ni-P2;
i) HCl/H_2O/THF; j) (116)/MeCN

The synthesis of the racemic precursor (**155**) started from the C_8 alkynyl hydroxy ketone (**160**). Its conversion into the bromide (**161**) and the coupling of the latter with hex-5-yn-1-ol gave the C_{14} dienic hydroxy ketone (**162**) the Jones oxidation of which, followed by hydride reduction of the keto group and Z-hydrogenation of the triple bonds, gave the desired Z,Z-dienic hydroxy acid (**155**) with an overall yield of 38%, calculated on the (**160**) [25]:

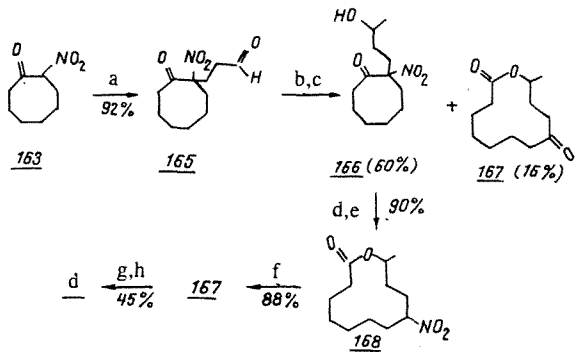


Reagents: a) TsCl/KOH; b) LiBr; c) $HO(CH_2)_4C{\equiv}CH$/EtMgBr;
d) H_2SO_4/acetone; e) H_2CrO_4/acetone;
f) $NaBH_4$; g) H_2/Ni-P_2

SYNTHESIS OF DIHYDRORECIFEIOLIDE

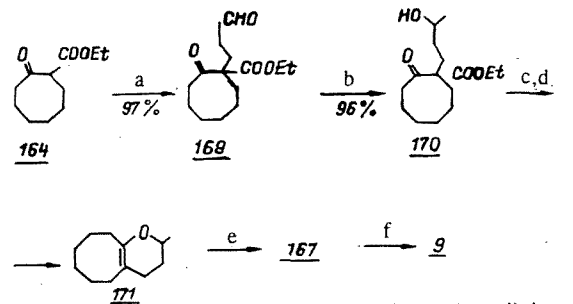
In the mid-eighties, syntheses of racemic dodecan-11-olide (dihydrorecifeiolide) (**9**) achieved by the transformation of nitro (**163**) [43] or carboxy (**164**) [44] derivatives of cyclooctanone were published.

In the first of theses syntheses [43], the initial 2-nitrocyclooctanone was alkylated with acrolein by the Michael reaction. The resulting aldehyde (**165**) was methylated by the action of MeTi(OPr-*i*)$_2$ and, after treatment with acid, a mixture was obtained of the alcohol (**166**) and the keto derivative of the macrolide (**167**), which was separated chromatographically. Cleavage of the eight-membered ring in the nitroalcohol (**166**) was effected by boiling with tetrabutylammonium fluoride (TBAF) in THF, giving the twelve-membered macrolide (**168**), which was converted into macrolide (**167**) and then into the desired macrolide (**9**). The overall yield of (±)-dihydrorecifeiolide (**9**) was 26.5%, calculated on the initial (**163**):



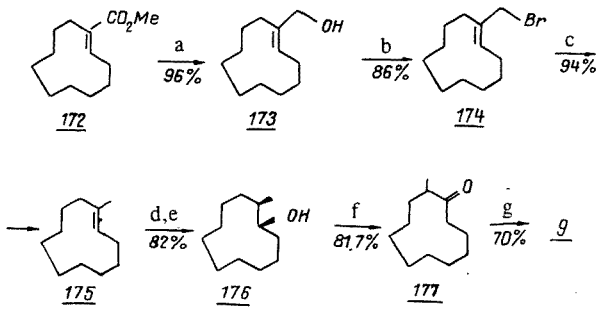
Reagents: a) $H_2C{=}CHCHO/Ph_3P$, THF, 20°C, 1 h;
b) $MeTi(OPr\text{-}i)_2$/THF, 20°C, 2 h;
c) HCl/Et_2O; d) TBAF/THF, boil., 1 h;
e) $AcOH/H_2O$, 0°C; f) $MeONa/TiCl_3$/MeOH, 20°C, 0,5 h; g) $TsNHNH_2/TsOH\cdot H_2O$/DMF, 100°C, 15-20 min; h) $NaBH_4CN$/c-C_6H_{12}, boil., 4h

In the second synthesis [44], an analogous transformation to expand the ring was performed for 2-ethoxycarbonylcyclooctanone (**164**). Its alkylation with acrolein gave the aldehyde (**169**), and the condensation of the latter with dimethyldiisopropoxytitanium gave the alcohol (**170**), which, by heating with Bu_4NF, was converted into the bicyclic compound (**171**). Oxidative cleavage of the latter with the aid of *m*-chloroperbenzoic acid (MCPBA) led to the macrolide (**167**) and then to the desired compound (**9**) with a higher overall yield than in the preceding synthesis [49%, calculated on the initial (**164**)].



Reagents: a) $H_2C{=}CHCHO/PH_3P$, THF; b) $Me_2Ti(OPr\text{-}i)_2/TiCl_3$/THF; c) Bu_4NF/THF; d) boil., 3 h;
e) MCPBA/CH_2Cl_2, 20°C, 5 min; f) $TsNHNH_2/(Ph_3P)_2CuBH_4$, boil, 4 h

A synthesis has recently been published [45] of macrolide (**9**) by the transformation of methyl cycloundec-1-enecarboxylic acid (**172**), obtainable from cyclododecene [46]. The eleven-membered ester (**172**) was converted in three stages through the intermediate alcohol (**173**) and bromide (**174**) into 1-methylcycloundec-1-ene (**175**), predominantly of the (E)-configuration. The presence of the (Z)-isomer of (**175**) (15%) was shown in the ^{13}C NMR spectrum. Hydroboration of cyclene (**175**) took place regiospecifically, and after oxidation of the organoboron intermediate the secondary alcohol (**176**) with the *cis*- orientation of the CH_3 and OH groups in the ring (confirmed by ^1H and ^{13}C NMR spectra) was obtained, and this was then oxidized to the ketone (**177**) by the Bayer–Villiger reaction, conducted with the aid of a new reagent – decanepersulfonic acid (DPSA) [47]. The overall yield of macrolide (**9**) was 36.4%, calculated on the cyclic ester (**172**).



Reagents: a) $i\text{-}Bu_2AlH/Et_2O$, -70°C, b) $CBr_4 \cdot PPh_3/Et_2O$;
c) $LiAlH_4/THF$; d) $NaBH_4/BF_3 \cdot Et_2O$;
e) $H_2O_2/NaOH$; f) $H_2C_2O_4/Me_2CO$;
g) DSPA/CCl_4

Thus, it may be concluded from the publications considerd that up to the present time macrolide pheromones have been obtained predominantly by cyclizing the corresponding hydroxy carboxylic acids, although there are examples of the use of a method of intramolecular condensation catalyzed by palladium complexes in the synthesis of macrolides that has been developed by Trost et al. [48, 49].

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