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USE OF ENYNE COMPOUNDS IN THE SYNTHESIS OF INSECT PHEROMONES

G. Yu. Ishmuratov, N. M. Ishmuratova, V. N. Odinokov, and G. A. Tolstikov

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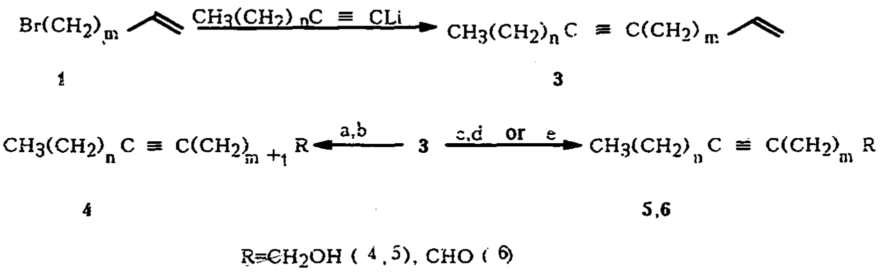
A new approach has been developed to the synthesis of monogenic insect pheromones with acetogenin and macrolide structures, using the low reactivity of ozone and of 9-borabicyclo[3.3.1]nonane towards an acetylenic function as compared with a vinyl function.

Ozone and 9-borabicyclo[3.3.1]nonane (9-BBN) are widely used reagents for organic synthesis, including that of insect pheromones [1-10]. An extremely interesting property of these compounds is their surprising inertness in relation to disubstituted acetylenes as compared with vinyl olefins [11-13], which has enabled us to propose a new approach to the synthesis of monogenic insect pheromones with acetogenin and macrolide structures.

In the synthesis of pheromones of insects of the order Lepidoptera, consisting, as a rule, of unsaturated alcohols, acetates, and aldehydes [8], use is most frequently made of the so-called "acetylene" route, which consists in coupling alkali metal alkynylides with alkyl halides having an oxygen-containing functional group in the ω- position [6, 8, 9, 14-16], followed by the stereoselective reduction of the triple bond to a double carbon–carbon bond with the (Z)- or the (E)- configuration.



a. 9-BBN ; b. $H_2O_2/AcONa$; c. O_3 ; d. $NaBH_4$; e. Me_2S

We have developed an alternative approach [17-21] that is based on the condensation of lithium alkynylides (2) with ω-bromoalkenes (1) and substantially expands the synthetic possibilities of the "acetylene" route. The terminal double bond in the coupling product (3), introduced from the ω-bromoalkene (1), is smoothly transformed into the required oxygen function, for example, by hydration via an organoboron intermediate, giving the corresponding alkyn-1-ol (4) or by reductive ozonolysis with the formation (depending on the method of treating the peroxide product of ozonolysis) of an alkyn-1-ol (5) or an alkynal (6) with a carbon chain one atom shorter than in the alkenyne precursor (3).

This approach has been used in the synthesis of dodec-8Z- and -8E-enyl acetates (12 and 13) — components of the pheromone of the plum fruit moth (*Grapholitha funebrana*) and the oriental fruit moth (*Grapholitha molesta*). By coupling 1-bromohept-6-ene (7) with lithium pent-1-ynylide (the reaction being performed in liquid ammonia in the presence 5-10% by volume of a mixture of THF and DMSO) the enyne (8) was obtained with a yield of 89%, and, with the aid of the hydroboration reaction, it was converted into the alkynyl alcohol (9). Hydrogenation of the latter over a deactivated nickel catalyst

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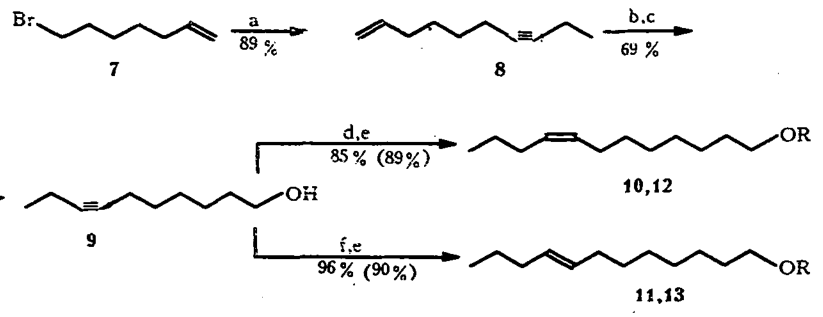
Institute of Organic Chemistry, Ufa Scientific Center of the Russian Academy of Sciences. Translated from Khimiya Prirodnykh Soedinenii, Vol. 33, No. 1, pp. 34-41, January-February, 1997. Original article submitted April 17, 1996.

gave the alk-Z-enyl alcohol (**10**), while reduction with sodium in liquid ammonia led to dodec-8E-en-1-ol (**11**). Acetylation of the alcohols (**10**) and (**11**) led, respectively, to the pheromones (**12**) and (**13**). The level of the main stereoisomers in each of them was not less than 96% (GLC results).

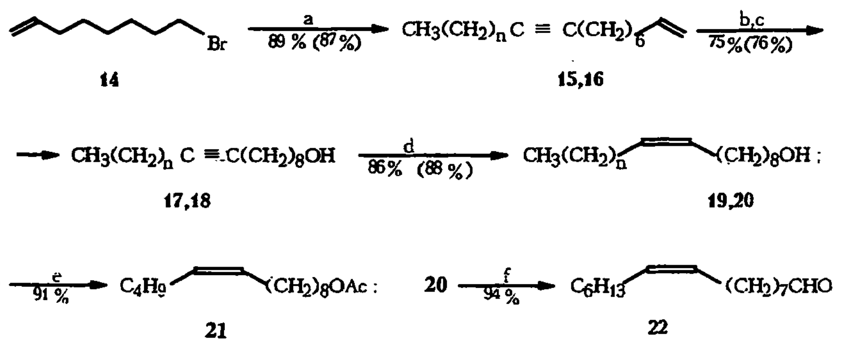


R = H (**10,11**), Ac (**12,13**)

a. PrC $\equiv$ CLi ; b. 9-BBN ; c. H_2O_2/AcONa ; d. H_2/Ni - P_2 ; e. Ac_2O/Py ; f. Na/NH_3

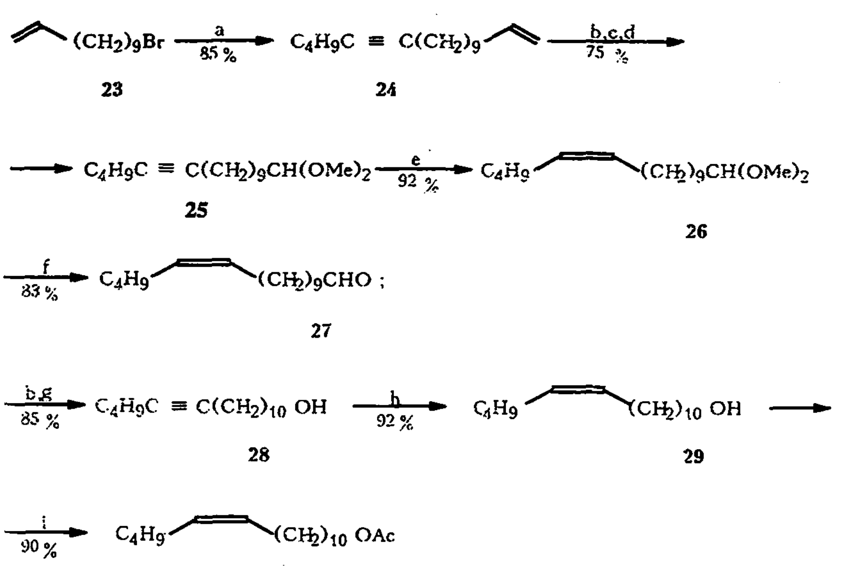
Analogously, the coupling of 1-bromooct-7-ene (**14**) with lithium hex-1-ynylide and oct-1-ynylide gave tetradec-1-en-9-yne (**15**) and hexadec-1-en-9-yne (**16**), respectively. The hydroboration of each of them led (after the oxidation of the organoboron intermediates) to the corresponding acetylenic alcohols (**17**) and (**18**), the catalytic hydrogenation of which gave the alk-Z-enic alcohols (**19**) and (**20**). The acetylation of tetradec-9Z-en-1-ol (**19**) led to the pheromone of the pine beauty moth (*Panolis flammea*) (**21**), while the oxidation of hexadec-9Z-en-1-ol gave a component (**22**) of the pheromone of the bollworm (*Heliothis armigera*) [17].

Hexadec-11Z-enal (**27**) and hexadec-11Z-en-1-yl acetate (**30**) — components of the pheromone of the bollworm (*Heliothis armigera)* and of the cabbage moth (*Mamestra brassicae)* — have been synthesized [17-21] via heptadec-1-en-12-yne (**24**), obtained by the interaction of the undecenyl bromide (**23**) with lithium hex-1-ynylide. The enyne (**24**) was ozonized, and, after the working up of the peroxide product of ozonolysis with dimethyl sulfide and methanol, we obtained the alkynic acetal (**25**), readily transformed by selective hydrogenation over a Lindlar catalyst into the alk-Z-enic acetal (**26**) and then into the desired aldehyde (**27**). Ozonolysis of the enyne (**24**) followed by reduction with sodium tetrahydroborate gave the alkynol (**28**), which was converted into the alk-Z-enic alcohol (**29**) by the hydromagnation reaction [22]. The desired acetate (**30**) was obtained by acetylating the alcohol (**29**). According to capillary GLC, the aldehyde (**27**) and the acetate (**30**) each contained not less than 95% of the main stereoisomer. It must be mentioned that the aldehyde (**27**) contained about 3% of the saturated compound.



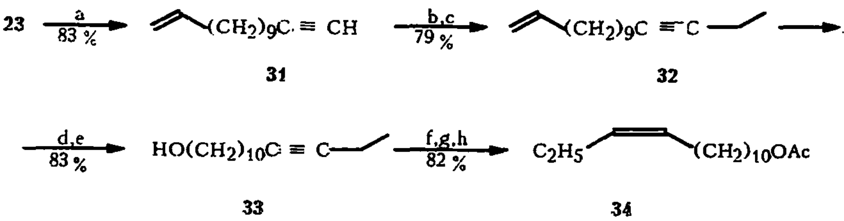
n=3 (**15,17,19**); 5 (**16,17,20**)

a. $CH_3(CH_2)_nC \equiv CLi$: b. 9-BBN : c. H_2O_2/AcONa : d. H_2/Ni - P_2 : e. Ac_2O/Py : f. PCC



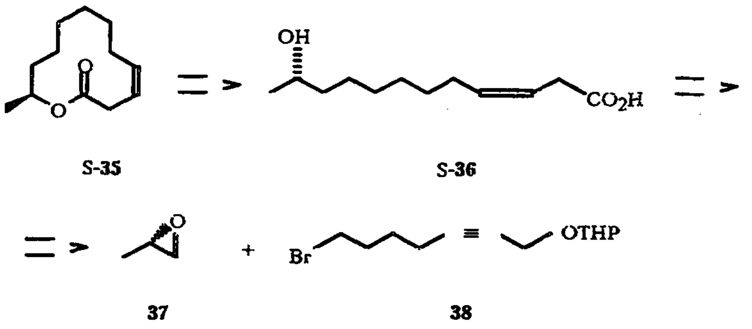
a. $C_4H_9C \equiv CLi$; b. $O_3/c\text{-}C_6H_{12}$, MeOH: c. Me_2S: d. MeOH/TsOH:
e. $H_2/Pd - CaCO_3 - PbO$: f. PPTS/H_2O: g. $NaBH_4$; h. iBuMgBr/Cp_2TiCl_2; i. Ac_2O/Py

The synthesis of the pheromone of the green oak tortrix (*Tortrix viridiana*), having the structure of tetradec-11Z-en-1-nyl acetate (34) was based [19] on the ozonolytic cleavage of the double bond in pentadec-1-en-12-yne (32), obtained by the ethynylation of the undecenyl bromide (23), followed by the ethylation of the resulting tridec-1-en-12-yne (31). Ozonolysis of the enyne (32) took place exclusively at the double bond, and, after reduction of the peroxidic ozonolysis product with sodium tetrahydroborate, gave tetradec-11-yn-1-ol (33), converted by reduction with 9-BBN followed by acetylation [7] into the desired pheromone (34) exclusively with the (Z)- configuration.

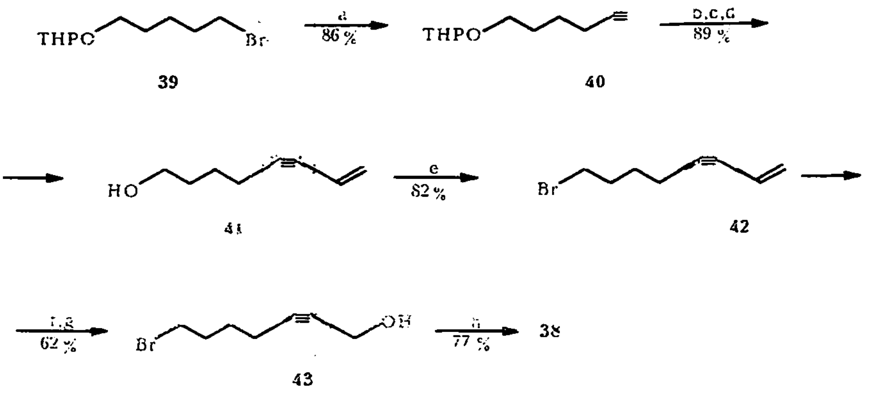


a. $HC \equiv CLi$; b. $LiNH_2$; c. EtBr ; d. $O_3/c - C_6H_{12}$,MeOH ;
e. $NaBH_4$; f. 9- BBN ; g. AcOH ; h. Ac_2O/Py

As a rule, natural macrolide pheromones and their analogs are obtained by the intramolecular cyclization of ω-hydroxy carboxylic acids with the appropriate structure [23-30]. A new effective synthesis of optically pure (S)-dodec-3Z-en-11-olide (ferrulactone II) (S-35) — a component of the aggregation pheromone of the rust-red grain beetle (*Cryptolestes ferrugineus*) — developed together with workers at the N. D. Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, is based on the macrolactonization of the (S)-acid (S-36) obtained by means of a cross-coupling reaction of the acetylenic block synthon (38) with optically active (S)-1,2-epoxypropane (37).

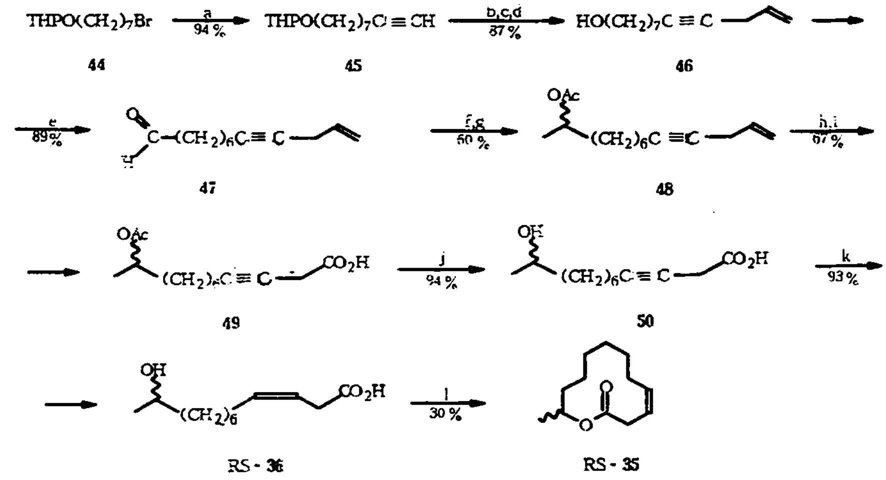


The synthesis of the acetylenic C_5-synthon (38) was achieved by the successive growth of the linear chain of the available THP ether of 5-bromopentan-1-ol (39). Standard condensation of the latter with lithium acetylenide gave a high yield of the THP ether of the alkynol (40), the Wurtz coupling of which, in the form of the copper derivative, with allyl bromide led equally effectively, after elimination of the protective group, to the 1-en-4-ynol (41) and then to the bromide (42). Conversion of the $C_{10}-$(42) [sic] into the required C_5-block synthon (38) was smoothly achieved by the partial ozonolysis of (42) giving, after hydride reduction of the intermediate peroxidic products, the homopropargyl α,ω-bromohydrin (43), which was readily converted into the desired bromoether (38) with an overall yield of 30%, calculated on the initial (39).

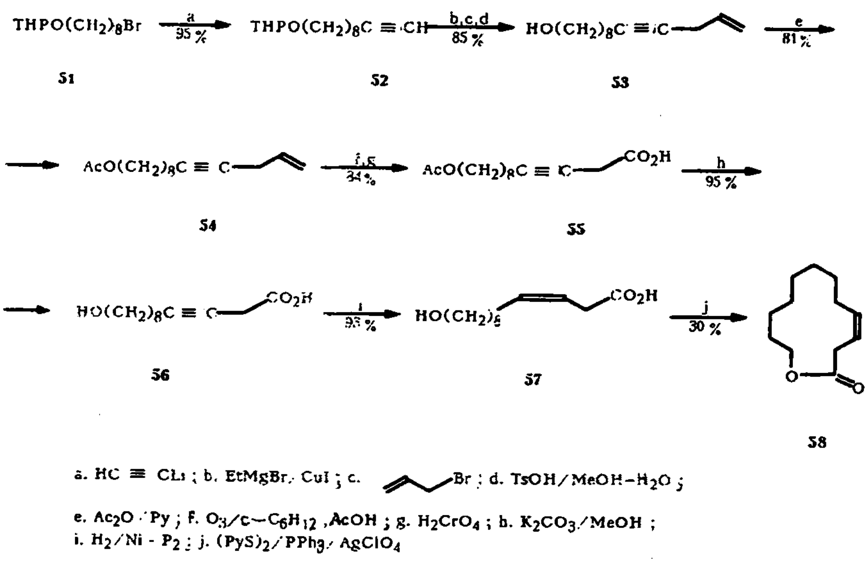


a. HC ≡ CLi ; b. EtMgBr/CuI ; c. Br ; d. TsOH · MeOH - H_2O ;
e. Br_2 · PPh_3 ; f. O_3 / c-C_6H_{12}, MeOH ; g. $NaBH_4$; h. DHP / TsOH

Since racemic ferrulactone II (RS-35) is also biologically active [24], its synthesis, as well, is of practical importance. We have developed a new approach [32, 33] to an acyclic precursor of the pheromone — 11(RS)-hydroxydodec-3Z-enoic acid (RS-36), using in one of the key stages the partial ozonolysis of acetate (48) with a 1-en-4-yne fragment. In this case, the initial compound was the THP ether of 7-bromoheptan-1-ol (44), the transformation of which into the required methylene-separated alkenyne (48) began by condensation with lithium acetylenide, followed by the interaction of the intermediate alkynol THP ether (45) with allyl bromide. The enynic alcohol (46) was converted into the corresponding aldehyde (47), condensation of which with methylmagnesium iodide and treatment with acetic anhydride gave the enynic acetate (48). Partial ozonolysis of the latter took place exclusively at the double bond and, after oxidation of the peroxidic product with the Jones reagent, led to 11(RS)-acetoxydodec-3-ynoic acid (49). Alkaline hydrolysis of the acetate (49), followed by catalytic hydrogenation of the hydroxyalkynoic acid (50) obtained, completed the synthesis of the racemic alk-Z-enoic acid (RS-36), the overall yield of which, calculated on the initial bromohydrin (44) amounted to 25.5%. Cyclization of the hydroxy acid (RS-36) under standard conditions [25] gave the desired macrolide (RS-35).



a. HC ≡ CLi ; b. EtMgBr/CuI ; c. Br ; d. TsOH /MeOH - H_2O ;
e. PCC ; f. MeMgI ; g. Ac_2O ; h. O_3/c-C_6H_{12}, MeOH ; i. H_2CrO_4 ;
j. K_2CO_3/MeOH ; k. H_2 Ni - P_2 ; l. $(PyS)_2$/PPh_3/$AgClO_4$



12-Hydroxydodec-3Z-enoic acid (**57**) — the acyclic precursor of dodec-3Z-en-12-olide (**58**), a component of the aggregation pheromone of the flat grain beetle (*Cryptolestes pusillis*) [32] — has been synthesized by analogous transformations but through fewer stages and with a far higher overall yield (48.5%) from the THP ether of 8-bromooctan-1-ol (**51**) via the intermediate compounds (**52-56**).

Thus, we have found new prospects for the "acetylene" route in the synthesis of pheromones, based on the selective transformation of enyne compounds with a terminal double bond in ozonolysis reactions followed by hydroboration with 9-borabicyclo[3.3.1]nonane.

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