

SYNTHESIS OF Z-ISOMERIC INSECT SEX PHEROMONE COMPONENTS VIA ETHENOLYSIS OF 1,5-CYCLOOCTADIENE

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Abstract- A novel syntheses of Z-5-decenol, Z-5-decenyl acetate, Z-7-dodecenol, Z-7-dodecenyl acetate, Z-9-tricosene, Z-7,8-epoxy-2-methyloctadecane which are sex pheromone components of *Lepidoptera* and *Diptera* orders, have been realized via stereoselective cometathesis of 1,5-cyclooctadiene with ethylene in the presence of $\text{MoCl}_5/\text{SiO}_2\text{-SnMe}_4$ as a key reaction. The main cometathesis product, 1,Z-5,9-decatriene, has been converted into pheromone components mentioned above by regioselective partial hydroboration or hydrozirconation with help of 9-BBN and Cp_2ZrHCl , correspondingly. The protonolysis of the obtained zirconosene derivative gave 1,Z-5-decadiene. Hydroboration-oxidation or hydroboration- C_2 -homologation of the latter led to Z-5- or Z-7 monoene pheromone components. Hydroboration-iodination of terminal double bond in 1,Z-5,9-decatriene, and further cross-coupling of the obtained iodine derivative with convenient lithium cuprates resulted in Z-9-tricosene, the main sex pheromone component of House Fly (*Musca Domestica*), or in 2-methyl-Z-7-octadecene, the precursor of Gypsy Moth (*Lymantria Dispar*) sex attractant. © 1999 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Sex pheromone compositions of more than 600 insect species are known.¹ Among them there are pests dangerous for forests, cereals, orchards, greenhouses, storages, etc. The most understood ones are sex pheromones of *Lepidoptera*, *Diptera*, and *Hymenoptera*. Sex pheromones of *Lepidoptera* consists of long chain ($\text{C}_{10}\text{-C}_{18}$) unsaturated mainly Z-isomeric acetates, alcohols, and aldehydes having double bonds in 3-13 positions; more rarely esters or epoxydes occur. *Diptera* sex pheromones compositions often contain long chain Z-monoenic hydrocarbons. Various schemes have been proposed for preparation of these substances.¹⁻⁵ As a rule they are based on stereoselective variants of Wittig reaction or on transformation of triple bond into Z-double bond. The use of "silazid-technique" in a Wittig reaction allows one to obtain Z-isomers with 98 % stereochemical purity.⁶ Hydrogenation of the alkynes on the "P-2 Ni-eda" ⁷ or Lindlar catalysts ³ at low temperature achieves Z-isomers with 99 % purity. About the same stereo-selectivity has been observed with hydroboration-protonolysis of alkynes by BBN^{8,9} as well as with carbocupration by copper reagents.¹⁰ Synthesis of structures consisting of 100 % Z-configuration are possible if the initial compounds have cis - double bond. For example, oleic (Z-9-octadecenoic) and eruc (Z-13-docosenoic) acids have been used for preparation of Z-9-tricosene.^{11,12} It

seems that the approach based on Z-4-octene α,ω -bifunctional derivatives, which can be obtained by partial oxidation of 1,5-cyclooctadiene, has also good prospects.^{13,14}

Olefin metathesis and cometathesis reactions offer a general and effective approach for assembling unsaturated long chain compounds of desired length and double bond position. These compounds are well suited as precursors for various natural compounds.¹⁵⁻²², particularly pheromone components.¹⁵⁻²⁰ Our data and results of other authors show that this route using commercial raw materials, as well as accessible heterogeneous catalysts is a technologically perspective one. There are two variants of this strategy based on metathesis or cometathesis of enic functional derivatives ²³⁻²⁶ as well as on olefin hydrocarbons with further functionalization.¹⁵⁻²² Until recently metathetical route to insect sex pheromone components has been realized via cometathesis of linear olefins or functionalized olefins such as esters containing terminal or internal double bonds.²³⁻²⁶ It should be mentioned that this version of metathetical approach is very short, but has serious drawbacks. Metathesis catalysts are very sensitive to certain functional groups therefore this strategy must plan accordingly. Commercial significance of needed initial olefin functional derivatives is also limited. Only oleic, eruc and 10-undecenoic esters can be considered as to some extent accessible raw materials. The other drawback implies that olefin metathesis of linear

structures is a typical equilibrium process leading as a rule to final mixtures containing preferentially trans isomers (up to 84 %).²⁷ Meanwhile, biological activity of many natural compounds depends dramatically on their stereoisomer content. In many cases just cis isomers as predominant components have enough high activity.²

Earlier we have used cometathesis of cycloolefins with α -olefins as a general approach to preparation of 1, Δ -dienes, precursors of monoenic sex pheromone components having a double bond in 6-11 positions.¹⁵⁻¹⁷ The size of starting cycloolefin defines internal double bond position in the target diene. The length of the latter is defined by total number of C - atoms in the cycloolefin and α -olefin. We have found cometathesis conditions for cycloolefins C₅, C₇, and C₈ where 1,Z- Δ - diene content decreased from 79 to 63 % and selectivity decreased from 86 to 60 % at the increase of cycloolefin conversion from 3 to 80 %¹⁵. 1,6-, 1,8- and 1,9- dienes have been regioselectively transformed into the corresponding alcohols by hydroboration-oxidation with help of 9-BBN.^{15,16} However the synthesis of 7-monoenic components is impossible to realize by the same scheme because cyclohexene is practically incapable to be involved in cometathesis with α -olefins.¹⁶ We proposed two-step scheme for synthesis of 1,7-dienes based on the cometathesis of cyclopentene with available α -olefins and subsequent hydroboration-carbonylation of obtained 1,6-dienes.¹⁶ For example, we have used initial cyclopentene and 1-hexene for preparation of 7-dodecenol. At the cometathesis reaction conditions providing Z-isomer formation (6 °C) we achieved 59 % content of 1,Z-6-undecadiene.¹⁵

It should be noted that synthesis of 5-monoenic pheromone components is rather difficult in

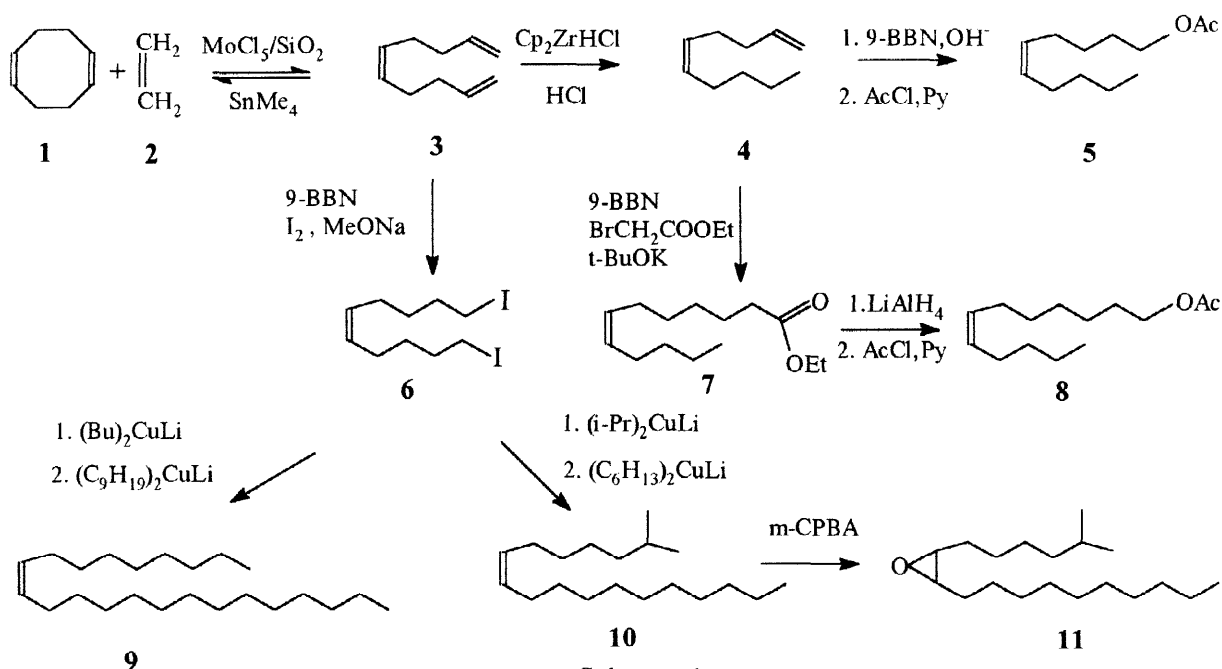
commercial sense because of inaccessibility of starting cyclobutene.

It is known that Z-5-decenol (Z-5-DOL), Z-5-decenyl acetate (Z-5-DA), Z-7-dodecenol (Z-7-DDOL), Z-7-dodecenyl acetate (Z-7-DDA) are pheromone constituents of more than 50 species of insects from *Lepidoptera* order.² The pheromone compositions of such dangerous pests as Looper family (*Noctuidae*) contain the enic compounds mention above. These components are the most typical for subfamily of Cut Loopers (*Agrotinae*) such as Turnip Moth (*Agrotis Segetum*), Black Cutworm (*A. Ipsilon*), Common Cutworm (*A. Fucosa*), etc., which are omnivorous pests of winter crop, cotton and others.²⁸ Racemic Z-7,8-epoxy-2-methyloctadecane (disparlure) is a sex attractant for Gypsy Moth (*Limantria Dispar*)²⁹, and Z-9-tricosene (muscalure) is a component of House Fly (*Musca Domestica*) pheromone.³⁰

In this work we propose a novel syntheses of pheromone components mentioned above via stereoselective ethenolysis of 1,5-cyclooctadiene (COD) in the presence of MoCl₅/SiO₂-SnMe₄.

RESULTS AND DISCUSSION

We have found that cometathesis of COD **1** and ethylene **2** in the presence of MoCl₅/SiO₂-SnMe₄³¹ at 20 °C, ethylene pressure 25 atm, mole ratio COD:Mo = 500 and reaction time 24 h resulted in 1,Z-5,9-decatriene **3** as a main product (68.4 %) with stereopurity 98.8 % at 80 % COD conversion. The stereoselectivity was very high at partial COD conversion (at 50 and 20 % conversion- 99.3 and 99.7 % stereopurity, correspondingly). The triene **3** has been hydrozirconated in combination with protonolysis.³² As a result 1,Z-5-decadiene **4** has been obtained with high yield and selectivity (Scheme 1).



Scheme 1

We offer a simple one pot technique of hydrozirconation which consists in the formation of Cp_2ZrHCl in the presence of triene **3**, by dropping of LiAlH_4 in THF to Cp_2ZrCl_2 . If twofold excess of **3** was used, only *Z*-5-decene as an impurity has been found along with the target **4** after protonolysis of zirconocene derivatives. According to literature and our data, internal double bonds are substantially less active in hydroboration by 9-BBN than terminal ones.^{33,16} Therefore, *Z*-5-decene did not react and can be easily separated. This allows to obtain target products of high purity. It is important from practical point of view because at the process of hydrozirconation-protonolysis formed Cp_2ZrCl_2 can be separated and used again.³² It should be noted that we were unsuccessful in obtaining **4** selectively by the hydroboration-protonolysis combination. In all cases we received mixture of **3**, **4** and 5-decene. Perhaps it is due to the fact that at high temperature (180–220 °C) realkylation reaction takes place along with protonolysis. At the same time the protonolysis of zirconocene derivatives carries out with high selectivity at 0 °C.³²

There are two routes using **4** (Scheme 1). Hydroboration-oxidation of the diene **4** with subsequent acetylation of *Z*-5-DOL lead to *Z*-5-DA **5**. Hydroboration- C_2 -homologation with help of $\text{BrCH}_2\text{COOEt}$ ³⁴ resulted in *Z*-7-dodecenoate **7**. Reduction of the latter and acetylation of obtained *Z*-7-DDOL gave *Z*-7-DDA **8**.

1,*Z*-5,9-decatriene **3** can be smoothly transformed into mono- or bifunctional derivatives having the same or different functional groups, via well known methods of bororganic chemistry.³⁵ In this work we have used combination of hydroboration-iodination³⁶ with further cross-coupling of obtained iodine derivative with convenient lithium cuprates.^{37,38} Cross-coupling of diiodine derivative **6** with lithium cuprates gave low yields of target olefins **9** and **10**. Therefore, we have used 10-iodo-1,*Z*-5-decadiene for cross-coupling at first step, and then procedures hydroboration-iodination-cross-coupling were repeated again. In this cases we obtained **9** and **10** with yields 40–70 %.

It should be noted that this strategy using 1,*Z*-5,9-decatriene as a precursor for the synthesis of *Z*-isomeric insect sex pheromone components can be also useful for preparation of other long chain or macrocyclic natural compounds.

EXPERIMENTAL

NMR spectra were recorded with a Bruker MSL-300 instrument in CDCl_3 . IR spectra were taken in thin layers with a Specord IR-75 instrument. Ms spectra were recorded using a Kratos MS-80 mass spectrometer (electron energy 70 eV). GLC analysis were performed with a LKhM8 MD chromatograph fitted with a flame ionization detector (50 m × 0.16 mm column packed with SE-30 on silica or 50 m × 0.2

mm with SKTFP; H_2 was used as carrier gas). The gas chromatograph was coupled with integrator IC-26. Determination of stereo-isomeric content was based on GLC and NMR (^1H and ^{13}C) data. The starting materials were purified over LiAlH_4 , Na, CaH_2 , or 5 Å molecular sieves as well as all reactions were carried out under high purity argon.

Ethenolysis of 1,5-cyclooctadiene

In a steel reactor equipped with a magnetic stirrer, pressure gauge and a device for charging reagents and sampling the reaction mixture, $\text{MoCl}_5/\text{SiO}_2$ (10 g, 1.5 mmol of Mo) and COD **1** (81 g, 0.75 mol) were placed. The ethylene **2** pressure was increased up to 25 atm, then the tetramethyltin (1.07 g, 6.0 mmol) solution in toluene 93 g saturated with ethylene at 27 atm, was added from special vessel. After 24 h the reaction mixture was separated from catalyst by filtration. Rectification resulted in 55 g of triene **3**. **B. p.** 169 °C at 760 torr. **MS** (70 eV): *m/z* (rel. int.) 136 [$\text{M}]^+$ (**3**), 41 [$\text{M}-95]^+$. $^1\text{H-NMR}$ (CDCl_3): δ 2.15 (m, 8H, $\text{CH}_2\text{-CH=}$), 4.9 (t, 4H, $\text{CH}_2\text{=CH-}$), 5.39 (t, 2H, $-\text{CH}=\text{CH-}$), 5.8 (m, 2H, $-\text{CH}=\text{CH}_2$). $^{13}\text{C-NMR}$ (CDCl_3): δ 26.98 ($\text{CH}_2\text{-CH=CH}$), 34.01 ($\text{CH}_2\text{=CH-CH}_2$), 114.83 ($\text{CH}_2\text{=CH}$), 129.57 ($\text{CH}=\text{CH}$), 138.47 ($\text{CH}_2\text{=CH}$). **IR** ν_{max} cm^{-1} : 730 (Z H-C=C-H), 1640 (C=C).

Hydrozirconation-protonolysis

Cp_2ZrCl_2 (10 g, 34.2 mmol) in 100 ml THF and triene **3** (9.3 g, 68.4 mmol) were placed into glass flask equipped by stirrer, condenser and funnel. Then 37.6 ml of 0.455 M solution LiAlH_4 in THF was added from the funnel by drops for 1 h. The mixture was stirred for 1 h, and then THF and unreacted **3** were removed in vacuum. 50 ml of hexane was added to remainder, and then 35 ml of 5 % HCl was added by drops. Water layer was separated. Solution of **4** in hexane was neutralized with K_2CO_3 , washed by water, and dried on MgSO_4 . After removing of hexane in vacuo, 4.2 g of diene **4** was obtained (90 % yield). **MS** (70 eV): *m/z* (rel. int.) 138 [$\text{M}]^+$ (**5**), 41 [$\text{M}-95]^+$ (100). $^1\text{H-NMR}$ (CDCl_3): δ 0.85 (t, 3H, $\text{CH}_3\text{-CH}_2$), 1.29 (m, 4H, $\text{CH}_2\text{-CH}_2$), 2.15 (m, 6H, $\text{CH}_2\text{-CH=}$), 4.9 (t, 2H, $\text{CH}_2\text{=CH-}$), 5.39 (t, 2H, $-\text{CH}=\text{CH-}$), 5.8 (m, 1H, $-\text{CH}=\text{CH}_2$).

Hydroboration-iodination

To suspension of 9-BBN (24.4 g, 0.1 mol) in 100 ml THF at 6 °C was added triene **3** (55 g, 0.4 mol) and the mixture was stirred until the suspension disappeared. Then mixture was warmed to room temperature and stirred for 1 h. After cooling to -20 °C the solutions of MeONa (10.8 g, 0.2 mol) in 100 ml MeOH and I_2 (50.8 g, 0.2 mole) in 150 ml THF were added dropwise. After removing of solvents, remainder was extracted with hexane. Organic layer was washed by water, and was dried on MgSO_4 . After removing of hexane and distillation in vacuo 10-iodo-1,*Z*-5-decadiene 18.6 g was obtained with 35 % yield. **B. p.** 125 °C at 15 torr.

¹H-NMR (CDCl₃): δ 1.3–2.2 (m, 10H, CH₂), 3.18 (t, 2H, CH₂-I), 4.9 (t, 2H, CH₂=CH-), 5.39 (t, 2H, -CH=CH-), 5.8 (m, 1H, -CH=CH₂).

Cross-coupling

The suspension of CuBr 1.3 g (9.0 mmol) and LiCl 0.78 g (18.0 mmol) in 30 ml THF was stirred at room temperature until a solution was obtained. This solution was cooled to -70 °C and lithium reagent (18 mmol) was added. After 1 h iodine derivative (7.5 mmol) was added and the mixture was warmed to room temperature, and stirred for 2 h, and then was hydrolysed with 30 ml of 5 % HCl aq. The organic phase was neutralized with K₂CO₃, washed by water, and dried on MgSO₄. After removing of solvents the desired dienes (5.3–4.8 mmol) were obtained.

Procedures of hydroboration-oxidation, hydroboration-C₂-homologation, reduction by LiAlH₄, acetylation of alcohols by AcCl/Py were described by us in detail^{15–17} and epoxydation of **10** into **11** was described in.²⁹

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