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Stereoselective Cometathesis of 1,5-Cyclooctadiene with Ethylene as an Efficient Pathway to *Z*-Ene Biologically Active Natural Products

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The molecules of many biologically active natural products of animal and plant origin contain unsaturated, long-chain or macrocyclic hydrocarbon structures with *Z*-configuration of the double bond. This is especially typical of the structures of many insect pheromones. Indeed, the vast majority of sex pheromones of the lepidoptera insects contain mainly or exclusively *Z*-monoene acetates, alcohols, aldehydes or, more rarely, acids, esters, ketones, or epoxides [1–3]. The pheromones of the dipterous insects often contain *Z*-unsaturated C_{23}–C_{29} hydrocarbons [1–3]. Macrocyclic lactones and ketones have been encountered in the signal compounds of the coleoptera insects and some mammals and in the plant fragrance compounds [1–3].

The syntheses of the above-mentioned compounds are normally based on *Z*-stereoselective versions of the Wittig reaction or the transformation of a triple bond into a *Z*-double bond [1–3]. The use of sodium hexamethyldisilazide (–78°C) in phosphorane syntheses provides *Z*-isomers with a purity of up to 98% [4]. In the partial hydrogenation of acetylene derivatives catalyzed by the "P-2 Ni-en" [5] or Lindlar catalysts at low temperatures, the stereoselectivity is 99% [1]. Approximately the same stereochemical purity was attained in hydroboration of alkynes with 9-BBN followed by protolysis [6], or in carbocupration of acetylene compounds [7]. These highly stereoselective methods of fine organic chemistry, which have become classical, still suffer from substantial drawbacks. They are rather labor-consuming as they include 7 to 9 steps and require difficult-to-obtain initial compounds and, often, toxic reagents.

The use of catalytic cometathesis of olefins makes the syntheses much simpler; in this case, they employ readily available raw materials and convenient heterogeneous catalysts [8–10].

Previously, we proposed a general, fairly efficient approach (consisting of 2 or 3 steps) to the synthesis of monoene complexes of pheromones having a double bond at the 6- and 8–11-positions [9, 10]. The approach is based on the cometathesis of C_5 or C_7–C_{10} cycloolefins with C_4–C_8 α-olefins followed by regioselective hydroboration–oxidation of the resulting 1,Δ-diene. The position of the internal double bond in the 1,Δ-diene and, hence, in the target pheromone molecule is dictated by the number of carbon atoms in the cycloolefin plus one, and the chain length equals the sum of the carbon atoms present in the cycloolefin and the α-olefin [9, 10]. A drawback of this approach is that mixtures of *E*- and *Z*-isomers are formed in all cases. In the metathesis or cometathesis of linear olefins and their functional derivatives, irrespective of the type of catalyst system and the degree of conversion, thermodynamically favorable *E*-isomers are predominantly produced (80–84%) [11]. We showed that cometathesis of α-olefins with cycloolefins (C_5, C_7–C_9) gives mainly 1,*Z*-Δ-dienes (up to 70%) for incomplete conversions of cycloolefins [12]. However, in some cases, this does not suffice for the preparation of exact replicas of natural mixtures without a special step of resolution into individual stereoisomers. It is noteworthy that the synthesis of 5- and 7-monoene components of pheromones by this method is difficult because in the former case, the initial cyclobutene is not readily available and in the latter case, the initial cyclohexene is virtually inert toward metathesis.

Herein, we used readily available cyclooctadiene (COD) and ethylene for the preparation of *Z*-5-, *Z*-7-, and other *Z*-monoene components of pheromones.

We showed for the first time that the cometathesis of COD with ethylene carried out in the presence of heterogeneous Mo-containing catalysts developed in our previous works [13, 14] (Scheme 1) proceeds with high stereoselectivity (up to 99.7%). The resulting 1,*Z*-5,9-decatriene (table) was used as a multipurpose intermediate for the synthesis of pheromone components with *Z*-configuration of the double bond (Scheme 2).

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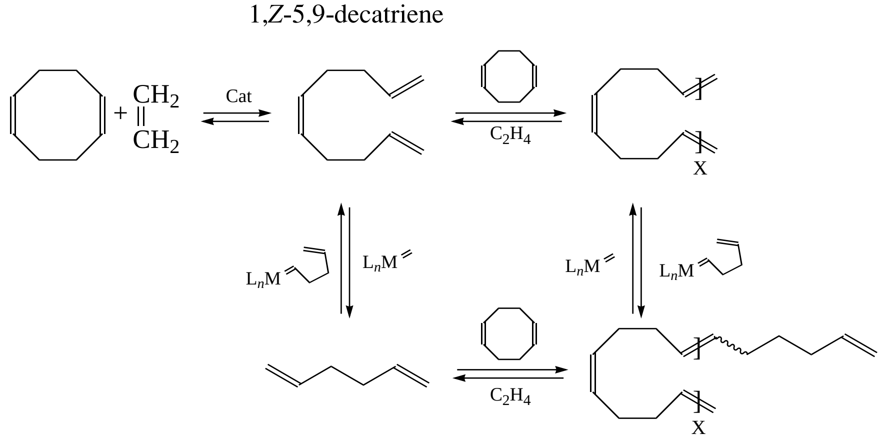
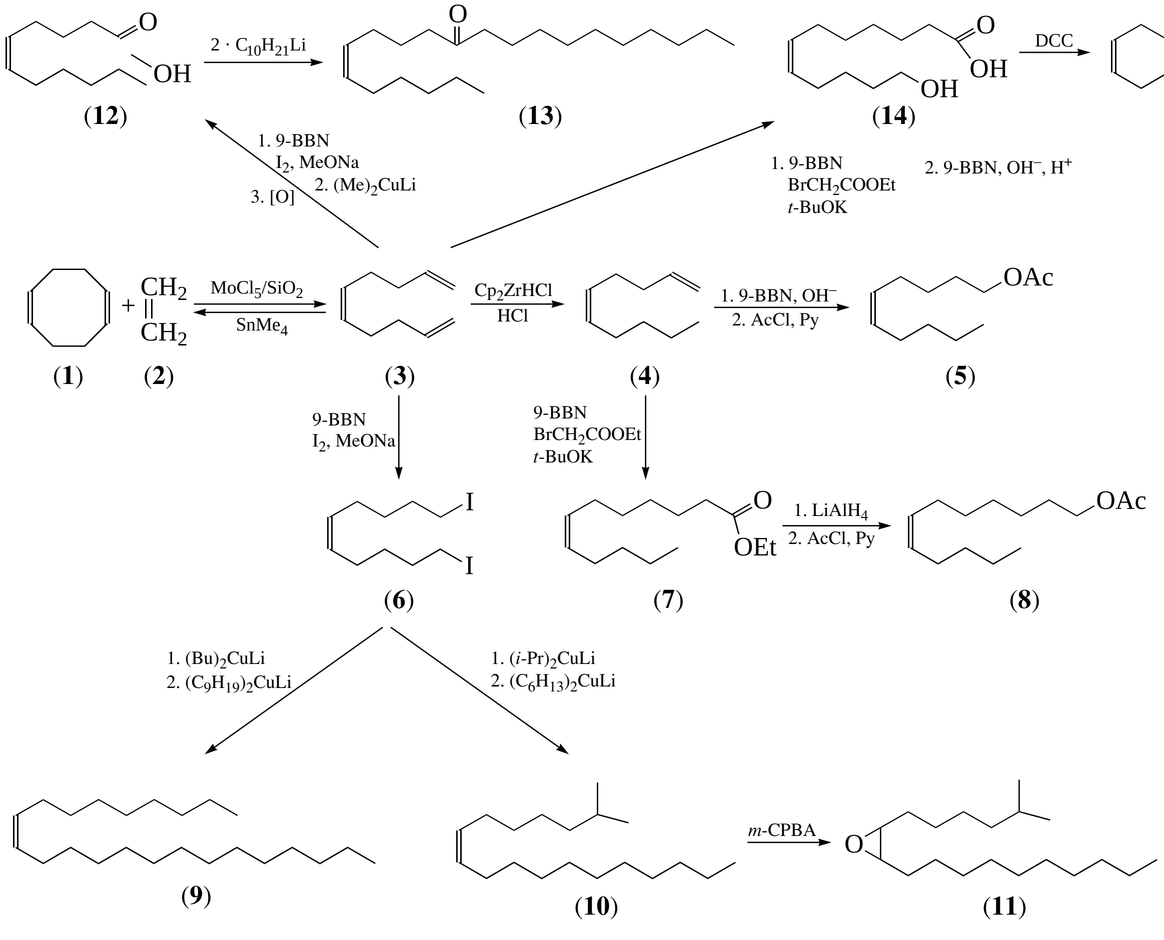


Scheme 1. Cometathesis of COD and ethylene.



Scheme 2. Synthesis of *Z*-ene biologically active natural products.

The table presents cometathesis conditions and data on the process chemo- and stereoselectivity. It can be seen that the stereoselectivity with respect to the *Z*-isomer reaches 99.6–99.7% (table, run 2). Even for high degrees of COD conversion (80–87%, table, run 1), the content of 1,*Z*-5,9-decatriene equals 99.0–98.6%. Such a high stereoselectivity is observed for the first time in olefin metathesis. It is comparable to or even higher than the stereoselectivity attained in the classical methods mentioned above. However, when the degree of COD conversion is close to 100% (table, run 5), the stereochemical composition of 1,5,9-decatriene approaches

Dependence of the yield and chemo- and regioselectivity on the cometathesis conditions

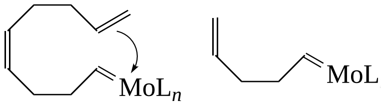
Run	T, °C	Mo : COD : $SnMe_4$: $SiCl_4$ molar ratio	Ethylene pressure, atm	Degree of COD conversion, wt %	Time, h	Selectivity: $C_{6:2}/\Sigma$ cometathesis products, wt %	Selectivity: $C_{10:3}/\Sigma$ cometathesis products, wt %	Yield of $C_{6:2}$ relative to COD, wt %	Yield of $C_{10:3}$ relative to COD, wt %	Stereoselectivity for 1,*Z*-5,9-decatriene, wt %
1	23	1 : 500 : 4	25	80.0	24	17.0	68.4	20.6	68.9	99.0
1	23	1 : 500 : 4	25	87.0	120	21.6	67.0	28.5	73.4	98.6
2	23	1 : 1000 : 8	25	23.0	24	2.3	92.0	0.8	26.7	99.7
2	23	1 : 1000 : 8	25	40.0	94	3.0	90.0	1.8	45.4	99.6
3	60	1 : 1000 : 8 : 8	25	54.0	2	11.5	80.0	9.4	54.4	99.0
3	60	1 : 1000 : 8 : 8	25	67.7	24	14.8	73.7	15.2	62.9	98.8
4	80	1 : 1000 : 8 : 8	25	71.0	2	16.0	68.0	17.2	60.8	97.7
4	80	1 : 1000 : 8 : 8	25	80.0	24	19.5	56.0	23.7	56.4	95.9
5	20	1 : 100 : 4	10	99.5	48	34.8	24.8	52.6	31.1	21.0

Note: The $MoCl_5/SiO_2–SnMe_4$ catalyst system was used in runs 1, 2, and 5; the $MoCl_5/SiO_2–SnMe_4–SiCl_4$ system was used in runs 4 and 5; no solvent was used in run 1; and toluene (1 : 1 by weight relative to COD) was used in runs 2–5.

the thermodynamic equilibrium (*Z*/*E* = 21/79). The chemoselectivity also appreciably decreases. In all experiments (table), 1,5-hexadiene ($C_{6:2}$) is formed together with the major product, 1,5,9-decatriene ($C_{10:3}$). The total content of these products is 75.5–94.3% for COD conversions of 23 to 87%; when the degree of COD conversion is 99.5%, the content decreases to 59.6% (run 5). In the latter case, unlike other experiments, 1,5-hexadiene is the major reaction product and the reaction stereoselectivity is the lowest. Evidently, for incomplete conversion, 1,*Z*-5,9-decatriene is mainly formed directly from COD and ethylene with the participation of carbene sites of type a (figure), which produce the *Z*-isomer. In the case of complete COD conversion, the type a carbene sites are virtually missing, while the metal carbene sites of type b (figure) accomplish degenerate metathesis of 1,*Z*-5,9-decatriene. As a consequence, the *E*-isomer is accumulated. Since high *Z*-stereoselectivity is observed even with a rather high content of 1,5-hexadiene (it is formed with the participation of active sites b), sites a can be assumed to be more stable than sites b due to coordination of the terminal double bond to the molybdenum atom (figure).

As noted above, the main cometathesis product, i.e., 1,*Z*-5,9-decatriene (**3**) (Scheme 2), has been used as a versatile intermediate for the synthesis of *Z*-ene monofunctional and bifunctional derivatives (Scheme 2). Indeed, the synthesized *Z*-5-decenyl acetate (**5**), *Z*-7-dodecenyl acetate (**8**) (Scheme 2), and the corresponding alcohols are contained in sex pheromones of more than 60 species of the Lepidoptera insects [1–3], including those of the polytrophic insects of the noctuid (Noctiudae) family and the Agrotinae subfamily, whose typical representative is the turnip moth (Agrotis segetum), a pest of winter crops, maize, cotton, and other types of crops. Racemic *Z*-7,8-epoxy-2-methyloctadecane (disparlure) (**11**) is a sex attractant of the gipsy moth (Lymantria dispar), which is a greenwood and garden vermin, while heneicos-*Z*-6-ene-11-one (**13**) is the major component of the sex pheromone of the moth Orgiya pseudotsugata, a coniferous forest pest. *Z*-9-Tricosene (**9**) is the major component of the sex pheromone of the typhoid fly (Musca domestica), *Z*-5-dodecen-12-olide (**15**) is a component of the aggregation pheromones of Cucujidae beetles, and *Z*-5-undecenoic acid (**12**) (Scheme 2) is a part of the sex pheromones of insects (Anghrenus verbasci) that damage stuffed animals in zoological museums [1–3].

Z-5-Decenol, *Z*-7-dodecenol, and their acetates **5** and **8** were prepared (Scheme 2) starting from *Z*-5-decadiene (**4**), which was synthesized by the regioselective hydrozirconation of triene **3** by the Schwartz reagent



(a) (b)

Structure of the catalyst active sites.

[15] (Cp_2ZrHCl) followed by protolysis of the zirconocene derivative. We proposed a simple procedure for the hydrozirconation of triene **3**, according to which Cp_2ZrHCl is synthesized in the presence of triene **3** and hydrozirconation takes place simultaneously with the formation of Cp_2ZrHCl. To increase the selectivity of the hydrozirconation step, we used a twofold excess of **3**. After the reaction, the remaining triene **3** was evaporated *in vacuo* and the residue containing a nonvolatile zirconocene derivative was subjected to protolysis by hydrogen chloride. It is significant from the practical standpoint that this gives Cp_2ZrCl_2, which can be isolated and re-used. Hydroboration of diene **4** with 9-BBN affords an intermediate borane which is oxidized to give *Z*-5-decenol or made to react with $BrCH_2COOEt$ in the presence of Bu^tOK to yield ester **7** with the carbon chain elongated by two atoms (Scheme 2). Subsequently, ester **7** is reduced by $LiAlH_4$, giving rise to *Z*-7-dodecenol, whose acetylation affords acetate **8**.

Yet another route of transformations of triene **3** is related to the hydroboration–iodination protocol. The reaction of triene **3** with 9-BBN followed by iodination in the presence of MeONa yields iodinated compound **6**, which undergoes cross-coupling with an appropriate lithium cuprate derivative to give *Z*-9-tricosene (**9**) or 2-methyl-*Z*-7-octadecene (**10**) (Scheme 2), whose epoxidation results in *Z*-7,8-epoxy-2-methyloctadecane (**11**) (Scheme 2). It is worth noting that the cross-coupling of diiodo derivative **6** with lithium cuprate reagents gave target products **9** and **10** in low yields. Therefore, to increase the yield, monoiodinated derivatives were used in the same hydroboration–iodination and cross-coupling sequence of steps. The same strategy was employed to prepare *Z*-5-undecenoic acid (**12**). First, 1,*Z*-5-undecadiene was subjected to the hydroboration–oxidation sequence, giving *Z*-5-undecenol, which was then converted into *Z*-5-undecenoic acid (**12**) (Scheme 2); this acid is a component of the pheromone of Anghrenus verbasci and, simultaneously, can serve as an intermediate in the synthesis of heneicos-*Z*-6-en-11-one (**13**) (Scheme 2), which is the sex pheromone of the moth Orgiya pseudotsugata.

One more application of triene **3** is for the preparation of bifunctional derivatives, in particular, α,ω-hydroxy acids, precursors of macrocyclic lactones. Thus, a protocol including successive hydroboration–C_2-homologization or hydroboration–oxidation and protolysis steps results in α,ω-hydroxy-*Z*-7-dodecenoic acid (**14**), an intermediate *en route* to *Z*-5-dodecenolide (**15**) (Scheme 2).

Thus, the first stereoselective cometathesis of COD and ethylene allowed us to develop a new effective strategy for the preparation of a number of *Z*-ene mono- and bifunctional derivatives which represent practically valuable biologically active natural products or their precursors.

EXPERIMENTAL

The purity of solvents, initial compounds, and products was checked and the reactions were monitored by GLC using an LKhM-8MD chromatograph with a flame ionization detector, an ITs-26 integrating device, a 50 m × 0.2 mm column, the SKTFP or SE-300 stationary phase, and H_2 as the carrier gas. ^1H and ^{13}C NMR spectra were recorded on a Bruker MSL-300 spectrometer in $CDCl_3$; the chemical shifts were referred to TMS. IR spectra were measured on a Specord IR-75 instrument in thin films. Mass spectra (EI) were run on a Kratos MS-80 (70 eV). The stereoisomer composition was determined on the basis of GLC and ^{13}C NMR data. All the reactions and the pretreatment of initial compounds and solvents were carried out under high-purity argon using $LiAlH_4$ as the drying agent. Pure compounds were characterized by mass, ^1H and ^{13}C NMR, and IR spectra.

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