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Synthesis of 2-Butyl-4,9-decadienoic and 2-Butyl-4,9-dimethyl-4,9-decadienoic Acids, Structural Analogues of Cygerol

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Abstract—2-Butyl-4,9-decadienoic and 2-butyl-4,9-dimethyl-4,9-decadienoic acids, structural isomers of 2-cyclohexylgeranylacetic acid, which is an active component of the wound healing ointment cygerol, have been synthesized. Hydrocarbon chains C_{10} have been obtained by the one-pot method of formation of long-chain hydrocarbons, namely, by the telomerization reaction of 1,3-dienes with nucleophiles catalyzed by palladium complexes. A heterogeneous palladium–zeolite catalyst has been used for the first time in telomerization of isoprene with piperidine.

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Active bacteriostatic agents of monoterpene structure 2-cyclohexyl-5,9-dimethylcapric acid and 2-cyclohexyl-5,9-dimethyl-4,8-decadienoic acid (2-cyclohexylgeranylacetic acid) are components of the wound healing ointment cygerol. The bacteriostatic activity of substituted terpenylacetic acids is known to depend on the branching of substituents. The substitution of the octadiene group for the terpenyl group should also change the bacteriostatic activity.

A one-pot method for obtaining a monoterpene structure is telomerization of isoprene with nucleophiles. Inasmuch as this method affords terpenoids with both natural and artificial hydrocarbon skeletons, it can be used for obtaining modified cygerol for the purpose of searching for more efficient and economical wound-healing drugs.

The simplest method of synthesis of cygerol analogues with a small number of stages is based on telomerization of isoprene and butadiene with ethyl acetoacetate by Scheme 1. Telomerization of butadiene with ethyl acetoacetate was carried out as described in [1]. Product **1** is formed with 62% selectivity and is easy to isolate by distillation of the reaction mixture. Alkylation of telomer **1** with butyl bromide in the presence of sodium hydride produces compound **2** in high yield. The further synthesis of a cygerol analogue—2-butyl-4,9-dimethyl-4,9-decadienoic acid (**3**)—was carried out without isolation of the decarbonylation product. The latter, after saponification of the ethoxycarbonyl group by Scheme 1, gives product **3** with an overall yield of 40%. The structure of **3** was proved by NMR.

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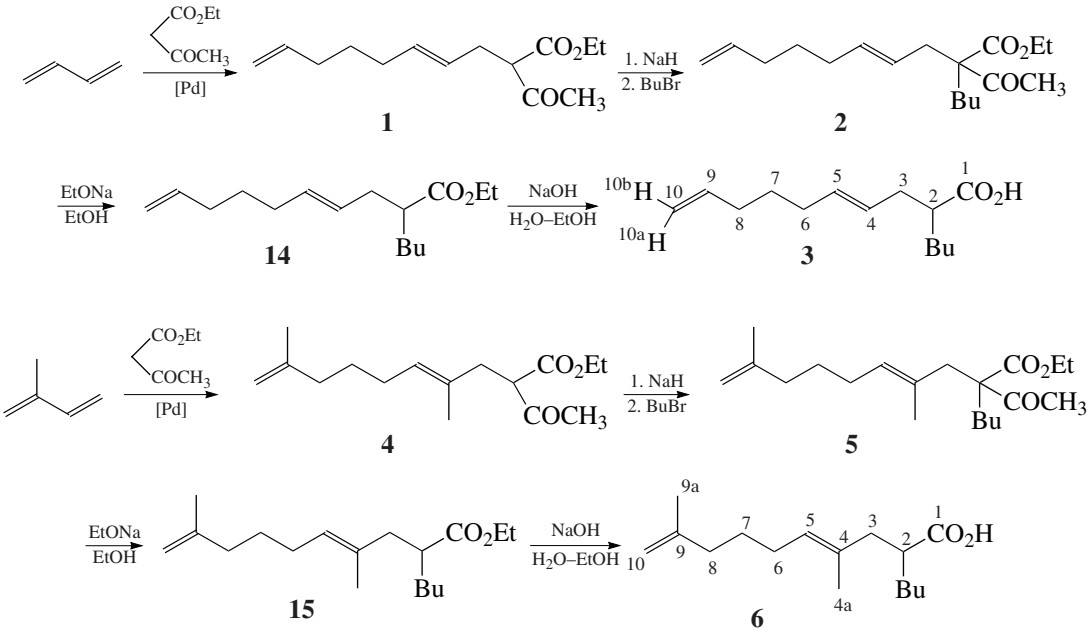
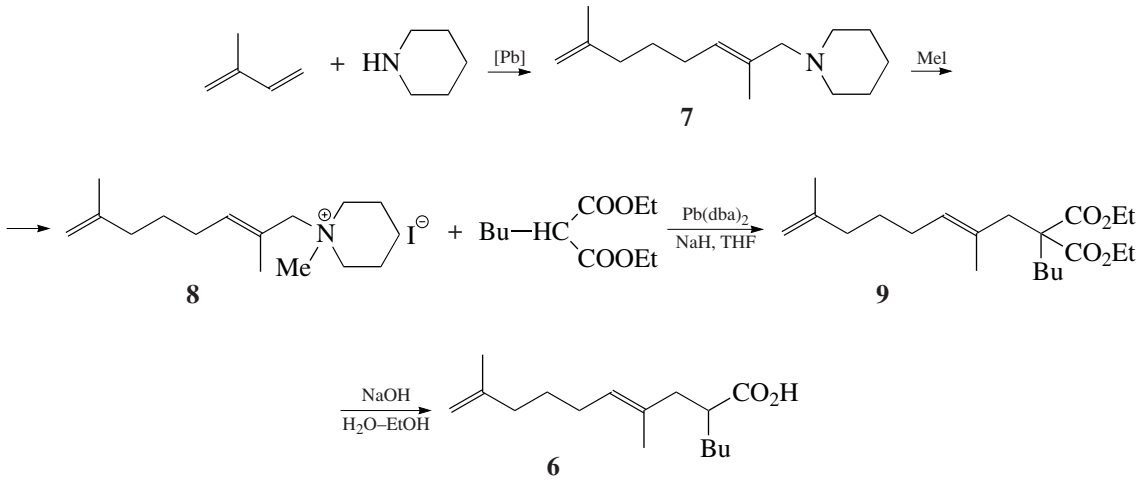
The synthesis based on the telomer of isoprene with ethyl acetoacetate (**4**) by an analogous scheme turned out to be a more complicated process. Telomer **4** was obtained as described in [2]; however, the alkylation of the α position is not quite smooth (the conversion of the initial telomer is only 58%), presumably due to steric hindrances created by the methyl group for the nearest double bond.

Attempts to isolate product **5** by distillation showed that it partially decomposed at high temperatures, which significantly decreased its yield. Therefore, product **5** was not isolated; rather, the crude product was saponified and then decarboxylated. Inasmuch as purification led to considerable losses of the target product and the latter contained an impurity of skeletal isomers (as MS-GC analysis showed), we used an alternative scheme of synthesis of compound **6** from the telomer of isoprene with piperidine (**7**) (Scheme 2). The telomerization carried out as described in [3] gave telomer **7** with 89% selectivity. The $Pd(dba)_2$-catalyzed allyl alkylation of diethyl butylmalonate by salt **8**, obtained by quaternization of telomer **7**, is smooth and gives compound **9** with a high selectivity (up to 91%). The saponification and decarboxylation of ester **9** were carried out in one stage by treatment with a fourfold excess of NaOH in a water–alcohol medium followed by heating at 170°C, which yields acid **6** (Scheme 2).

Inasmuch as the state-of-the-art metal-complex homogeneous telomerization of isoprene with amines affords isomers **7** and **10**–**12** with a high selectivity [3, 4], whereas telomerization of isoprene with C-nucleophiles does not yield all analogous skeletal isomers, the use of Scheme 2 opens up new possibilities for synthesis of modified biologically active cygerol analogues with different branching of the terpenyl chain. This



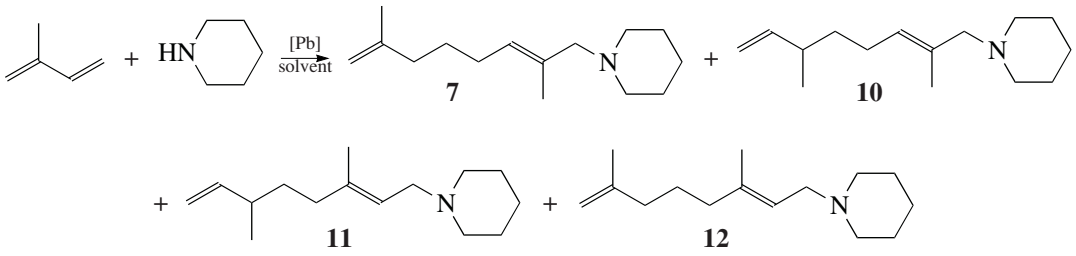
Scheme 1.



Scheme 2.

scheme was previously used for synthesizing 2-cyclohexylgeranyl- and nerylacetic acids [6].

Since the industrial use of homogeneous catalysts is economically inexpedient, we studied the possibility of using zeolite-supported heterogeneous catalysts for telomerization of isoprene with piperidine in comparison with the known method of preparation of a telomer mixture under homogeneous conditions [4], which affords all four possible skeletal isomers (**7**, **10**–**12**) (Scheme 3) in a mixture with 5–10% of corresponding *cis* isomers. To prepare a heterogeneous catalyst, we used the $Pd(NH_3)_4Cl_2$ complex deposited on the Z_{4366}/H^+ zeolite (H form). The resulting catalyst was characterized by X-ray powder diffraction and X-ray absorption spectroscopy (XANES). According to X-ray powder diffraction, the H form of an MFI zeolite (a crystalline zeolite with micropores of ~0.55 nm in size) was used as the support. The X-ray diffraction patterns of the pristine zeolite and the Pd-containing catalyst (both initial and spent) are similar; however, for the modified zeolite containing the palladium complex, the lines are slightly shifted toward small angles and their intensities are somewhat redistributed. This can be associated with some increase in the unit cell parameters of the zeolite caused by the fact that the cationic palladium ammine complex occupies ion-exchange positions of the zeolite. The XANES spectra are consistent with the Pd^{2+} state in the catalyst (the absorption



Scheme 3.

edge shift relative to Pd^0 was ~8 eV). Palladium does not noticeably change its state in the course of catalysis. The Pd content estimated from the intensity of resonant X-ray fluorescence was 0.4 wt % in the initial catalyst and 0.05 wt % in the spent catalyst; i.e., the palladium concentration decreases eightfold after the first catalytic cycle. This is evidence of a considerable catalyst entrainment, despite its rather strong binding to the matrix. Heterogeneous catalytic reactions were carried out for a long time in MeCN or MeOH in the presence of phosphorus-containing ligands. No products formed in the absence of these ligands. At temperatures <100°C, the presence of zeolite catalysts does not ensure telomerization; therefore, the reaction were carried out at 120°C in an autoclave. The results are summarized in the table.

The yield of the desired products (**7**, **10**–**12**) was no more than 2%. When the process was carried out in MeOH in the presence of Ph_3P, telomer **11** was not identified; at the same time, no byproducts typical of such reactions (isoprene dimers, isoprene and piperidine adducts, high telomers) were observed. The overall content of corresponding *cis* isomers was no more than 0.5%. Notwithstanding the low yield of the products, the use of zeolite catalysts in this reaction is promising since all possible side reactions are suppressed and the isomer composition of telomers is considerably changes depending on the phosphorus ligand used. This opens up new possibilities in selective synthesis of skeletal isomers of terpenoids.

Thus, we showed that the synthesis of 2-butyl-4,9-decadienoic acid from telomers of butadiene with ethyl acetoacetate is smooth, whereas it is more expedient to synthesize 2-butyl-4,9,dimethyl-4,9-decadienoic acid from the telomer of isoprene with piperidine by Scheme 2. Telomerization of isoprene with piperidine on zeolite-supported palladium complexes revealed some advantages of these catalysts over homogeneous palladium complexes, namely, the absence of byproducts and a narrower composition of the formed telomer products.

EXPERIMENTAL

Ethyl acetoacetate and diethyl butylmalonate were distilled before use, and butadiene was recondensed twice through a KOH tube. Isoprene and piperidine were distilled over KOH. GLC analysis was carried out on an LKhM-8MD (5) chromatograph (steel column 2 m long, 15% SKTFT-50 on Chromatone N-AW) and a Finnigan-9001 chromatograph (capillary column 30 m long, DB 5.625) at a programming rate of 8 K/min in the range from 50 to 200°C and of 12 K/min in the range from 200 to 310°C; $C_{21}H_{44}$ was used as the internal reference. Mass spectrometry/gas chromatography analysis was carried out on an Analytical VG-7070E mass spectrometer at 70 eV and an ion source temperature of 150°C. Before GLC and MS-GC analyses, the acids were preliminarily methylated with diazomethane. The resulting isomers were identified by GLC on a capillary column by comparing their retention times with those of the described samples. The ^1H NMR spectra were recorded on Bruker Avance-300 and Avance-400 spectrometers ($CDCl_3$, TMS as the internal

Conditions of telomerization of isoprene with piperidine in the presence of catalysts

Solvent, mL	Catalyst	Isoprene, mmol	Piperidine, mmol	Isoprene : piperidine ratio	Temperature, °C	Time, h	Yield, %	Isomer ratio, **7** : **10** : **11** : **12**
MeOH 37.5	$Pd(acac)_2$ (1.25 mmol) : Ph_3P = 1 : 2	375	350	1 : 0.9	60–70	53	61	2.5 : 3.4 : 2.9 : 1
MeCN 12.5	Zeolite Z_{4366}/H^+ + Pd 0.5% 1 g $(EtO)_3P$ 0.17 g	100	50	2 : 1	120	37	0.36	3.2 : 4.7 : 4.7 : 1
MeOH 7.5	Zeolite Z_{4366}/H^+ + Pd 0.5% 0.1 g Ph_3P 0.13 g	75	37.5	2 : 1	120	96	1.2	2.6 : 1.7 : 0 : 1

reference). X-ray powder diffraction patterns were recorded on a DRON-3 automated powder diffractometer (CuK_α radiation; scan speed, 1 deg/min; angle increment, 0.05°). The Pd *K*-edge XANES spectra of the Pd–zeolite catalyst were recorded at the STM station at the Kurchatov Center of Synchrotron Radiation and Nanotechnologies (Si(111) monochromator, scintillation detector).

Ethyl 2-acetyl-2-butyl-4,9-dimethyl-4,9-decadienoate (2). To a solution of 2.38 g (10 mmol) of ether **1** in 10 mL of THF, 0.29 g (12 mmol) of NaH was added under an argon atmosphere. The mixture was heated under reflux for 1 h and cooled, and 1.37 g (10 mmol) of BuBr was added. The mixture was refluxed for another 6 h, and then 30 mL of water was added. The product was extracted with ether. The extract was dried by Na_2SO_4, and the solvent was removed by evaporation to give 2.3 g of product **2** (75% purity according to GLC).

Ethyl 2-butyl-4,9-decadienoate (14). A two-neck flask was loaded with 2.1 g of crude ester **2**, 0.2 g of sodium ethylate, and 60 mL of absolute ethanol. The formed ethyl acetate was distilled off while the mixture was heated. After the reaction was completed, most alcohol was removed in vacuum, and dilute hydrochloric acid was added to the residue. The product was extracted with hexane, dried by Na_2SO_4. The yield was 1.8 g of the crude product.

2-Butyl-4,9-decadienoic acid (3). To the ester obtained at the previous stage, 0.3 g NaOH, 1 mL of water, and 0.65 mL of ethanol were added. The mixture was stirred without heating for 1 h and then heated under reflux for 2 h. The alcohol was removed in vacuum, water was added to the residue, and the product was extracted with a hexane–ether mixture. The aqueous phase was acidified, the oil was separated, and the aqueous layer was extracted with ether and dried over $MgSO_4$. The ether was evaporated. After distillation, 0.75 g (40% with respect to initial telomer **1**) of acid **3** with bp 140–142°C/2 mmHg. MS-GC analysis of acid **3** (carried out after it was methylated with diazomethane) showed 95% purity of the sample synthesized.

MS of methylated acid **3** (*m*/*z*, I_{rel}, %): 238 [M^+] (3), 207 (5), 182 (2), 123 (10), 109 (25), 87 (100). ^{1}H NMR, δ, ppm: 0.88 (t, 3H, $^{Bu}CH_3$, J = 6.8); 1.29 (m, 4H, 2 $^{Bu}CH_2$); 1.42 (tt, 2H, $^7CH_2$, J = 7.25); 1.45 and 1.59 (AB quartet, 2H, $^{Bu}\underline{CH_2}$–^{2}CH, J = 1.42); 2.00 (m, 4H, $^8CH_2$, $^6CH_2$, J_{8-9} = 6.65, J_{6-7} = 6.80); 2.18 and 2.30 (AB quartet, 2H, $^3CH_2$, J = 14.2); 2.38 (m, 1H, ^{2}CH); 4.91–5.00 (m, 2H, $^{10}CH_2$, J_{a-b} = 1.93, J_{9-a} = 10.2, J_{9-b} = 17.15); 5.33 and 5.47 (AB quartet, 2H, ^{3}CH, ^{4}CH, J = 15.23, trans), 5.72–5.82 (m, 1H, ^{9}CH, J_{9-8} = 6.65, J_{9-a} = 10.2, J_{9-b} = 17.17). Signals were assigned using a 2D ^{1}H–^{1}H COSY spectrum (400 MHz, $CDCl_3$).

Ethyl 2-acetyl-2-butyl-4,9-dimethyl-4,9decadienoate (5). To a solution of 2.5 g (9.4 mmol) (**4**) in 10 mL of THF, 0.3 g (11.3 mmol) of NaH was added under an argon atmosphere. The mixture was heated under reflux for 4.5 h and cooled; then, 1.29 g (9.4 mmol) of BuBr was added. The mixture was heated under reflux for 38 h. Water was added into the flask, and the product was extracted with ether and dried with Na_2SO_4. GLC analysis showed that the conversion of the initial ester was 60%. The yield was 3.2 g of crude compound **5**.

Ethyl 2-butyl-4,9-dimethyl-4,9-decadienoate (**15**) and 2-butyl-4,9-dimethyl-4,9-decadienoic acid (**6**) were prepared by the above procedures for acid **3**. MS-GC analysis of acid **6** (carried out after it was methylated with diazomethane) showed 80% purity of the sample synthesized.

MS of methylated acid **6** (*m*/*z*, I_{rel}, %): 266 [M^+] (4), 235 (8), 210 (11), 151 (34), 137 (27), 81 (100). ^{1}H NMR, δ, ppm: 0.9 (t, 3H, $^{Bu}CH_3$, J = 6.8); 1.29 (m, 4H, $^{Bu}CH_2$, $^{Bu}CH_2$); 1.42 (m, 2H, $^7CH_2$); 1.45 and 1.59 (m, 2H $^{Bu}\underline{CH_2}$–^{2}CH); 1.7 (s, 3H, $^{4a}CH_3$); 2.00 (m, 4H, $^8CH_2$, $^6CH_2$); 2.18 and 2.30 (AB quartet, 2H, $^3CH_2$, J = 14.2); 2.2 (s, 3H, $^{9a}CH_3$); 2.18 and 2.30 (m, 2H, $^3CH_2$); 2.38 (m, 1H, ^{2}CH); 4.70–4.83 (m, 2H, $^{10}CH_2$); 5.35 (t, 1H, ^{3}CH).

Synthesis of the palladium catalyst applied to a zeolite matrix. A ferroaluminosilicate zeolite of the MFI type was obtained by hydrothermal crystallization of a gel consisting of the sources of Si (A-300 Aerosil, sodium silicate), Na (sodium hydroxide, sodium silicate), Fe (ferric chloride), Zn (zinc acetate, and B (boric acid) in the presence of tetrapropylammonium bromide at 150°C for 82 h. After filtration and washing with water, the zeolite in the Na form was treated with a 1 M NH_4NO_3 solution (80°C, 4 × 30 min), dried at 120°C, and calcined at 540°C for 6 h. The resulting H-zeolite was impregnated with a solution of $Pd(NH_3)_4Cl_2$, dried at 120°C, and calcined at 400°C for 3 h. Elemental analysis (%): Na, 0.033; Al, 19.1; Si, 29.4; Zn, 1.12; Fe, 0.38; B, 0.003; Pd, 0.48.

General procedure of telomerization of isoprene with piperidine in the presence of zeolite catalysts. Under an argon flow, a steel autoclave was charged with (1) 1 g of a zeolite (Z_{4366}/H^+ + 0.5% Pd), 7.5 mL of acetonitrile, 5.1 g (75 mmol) of isoprene, 5.9 g (70 mmol) of piperidine, and 0.166 g (1 mmol) of $(EtO)_3P$; (2) 0.1 g of a zeolite (Z_{4366}/H^+ + 0.5% Pd), 7.5 mL of methanol, 5.1 g (75 mmol) isoprene, 3.19 g (37.5 mmol) of piperidine, and 0.13 g (1 mmol) of Ph_3P. The reaction was carried out under the conditions specified in the table. Suspensions were filtered. The solvent and unreacted isoprene were removed in vacuum. The residue was distilled at T_b = 110–116°C/2 mmHg. The yield was 0.04 g (0.36%) and 0.1 g (1.2%) of telomers prepared by procedure (1) and (2), respectively.

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