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Studies on Annelation of (+)-2-Caranone

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Summary. The Michael reaction of (+)-2-caranone (**1**) with methyl vinyl ketone, ethyl vinyl ketone or methyl acrylate was utilized for synthesis of corresponding diketones **4** and **5** and keto ester **8**. These compounds were subjected to cyclization to obtain the sesquiterpenoid systems.

Keywords. Annelation; Michael reaction; Sesquiterpenoids.

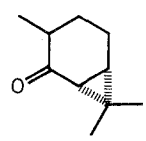
Untersuchungen über die Annelierung von (+)-2-Karanon

Zusammenfassung. Die Michaelreaktion von (+)-2-Karanon mit Methylvinylketon, Ethylvinylketon oder Methylakrylat wurde zur Synthese der entsprechenden Diketone **4** und **5** und des Ketoesters **8** genutzt. Diese Verbindungen wurden weiterhin einer Zyklisierung unterworfen, um zu Sesquiterpenoidstrukturen zu gelangen.

Introduction

Cyclic sesquiterpenes, occurring in many natural products, exhibit often very interesting biological and fragrant properties. Some of them found application as odoriferous substances in cosmetic industry and as pesticides with antifeedant properties.

Our synthesis of the sesquiterpenoid skeleton utilized the relatively easily available chiral, monoterpenic ketone, (+)-2-caranone (**1**), obtained according to Baeyer [1], for the annelation reaction with methyl vinyl ketone (*MVK*), ethyl vinyl ketone (*EVK*) or methyl acrylate.



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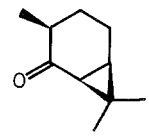

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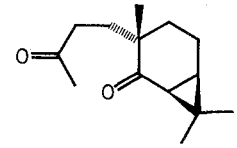

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The results obtained were compared with those of Bates et al. [2] and Caine and Gupton [3], who applied an enantiomer of compound **1**, (−)-2-caranone (**2**) for the Michael reaction with *EVK*.

Experimental Part

Melting points are given uncorrected. IR spectra were taken on a Perkin Elmer 621 apparatus. ^{1}H-NMR (100 MHz) spectra were measured on a Tesla BS-497 and ^{1}H (300.13 MHz), ^{13}C (75.47 MHz) NMR spectra on a Bruker CPX 300 spectrometer (*HMDSO* or *TMS* as standard, CCl_4 or $CDCl_3$ as solvent, concentration ca. 10%). High resolution MS analysis was carried out on a MAT 711 spectrometer connected with a SS 100 data system.

Analytical thin-layer chromatography (TLC) was carried out on Silica gel 60 F-254 (Merck), column chromatography of the "flash" type on Silica gel G, type 60 (Merck). Petroleum ether refers to the fraction with boiling point 30–60°C.

(+)-*2-Caranone* (**1**) was prepared according to Baeyer [1]. B.p. 60–63°C (1 mm Hg), $[\alpha]_D^{20} = +137.6$, $n_D^{20} = 1.4780$. IR (CCl_4): 1 670 cm^{-1}. ^{1}H-NMR (300 MHz, *TMS*, $CDCl_3$) $\delta = 1.042$ (d, 3 H, CH_3-C 3, $J = 6.5$ Hz), 1.043 (m, 1 H, H-C 6), 1.154 (s, 3 H, CH_3-C 7), 1.209 (s, 3 H, CH_3-C 7), 1.453 (d, 1 H, H-C 1, $J = 7.5$ Hz), 1.603 (m, 2 H), 1.830 (m, 1 H), 2.057 (m, 2 H). ^{13}C-NMR (*TMS*, $CDCl_3$) $\delta =$ 15.5, 16.6, 18.9, 27.7, 29.4, 32.0, 35.3, 35.5, 43.3, 211.6. High resolution MS: 152.1202, calcd. for $C_{10}H_{16}O$: 152.1202.

3,7,7-Trimethyl-3β-(3-oxobutyl)bicyclo[4.1.0]heptan-2-one[1] (**4**)

To a solution of **1** (15.20 g, 0.10 mol) and KOH (0.25 g, 4.50 mmol) in ethanol (250 ml), *MVK* (12 ml, 0.15 mol) was added dropwise at 0–5°C under nitrogen. The reaction mixure was stirred at room temp. for 10 h and then refluxed for 1 h. Then it was diluted with water (200 ml), acetic acid was added to *pH* 7 and the solvent was evaporated. The residue was extracted with methylene chloride, the extract was washed with aqueous $NaHCO_3$ and water and then dried (Na_2SO_4). The residue after evaporation of CH_2Cl_2 was purified by column chromatography (eluent: petroleum ether – diethyl ether, 8 : 2, *v/v*). Diketone **4** (17.60 g) was obtained in 80% yield as a pale yellow oil. IR (CCl_4): 1 715, 1 685 cm^{-1}. ^{1}H-NMR (300 MHz, *TMS*, $CDCl_3$) $\delta = 0.920$ (s, 3 H, CH_3-C 3), 1.072 (s, 3 H, CH_3-C 7), 1.116 (s, 3 H, CH_3-C 7), 1. 234 (m, 1 H, H-C 6), 1.321 (d, 1 H, H-C 1, $J = 7.6$ Hz), 1.568 (m, 4 H), 1.861 (m, 1 H), 2.025 (m, 1 H), 2.138 (s, 3 H, CH_3-C 3′), 2.355 (m, 2 H). ^{13}C-NMR (*TMS*, $CDCl_3$) $\delta = 15.8$, 17.3, 20.5, 22.9, 25.0, 29.7, 30.0, 30.4, 32.1, 33.2, 38.0, 44.9, 207.8, 212.6. High resolution MS: 222.1619, calcd. for $C_{14}H_{22}O_2$: 222.1621.

3,7,7-Trimethyl-3β-(3-oxopentyl)bicyclo[4.1.0]heptan-2-one (**5**)

The reaction was carried out as above, using *EVK* (15 ml, 0.15 mol) instead of *MVK*. Diketone **5** (19.60 g) was obtained in 83% yield as an yellow oil. IR (CCl_4): 1 720, 1 695 cm^{-1}. ^{1}H-NMR (300 MHz, *TMS*, $CDCl_3$) $\delta = 0.925$ (s, 3 H, CH_3-C 3), 1.032 (t, 3 H, CH_3-C 4′, $J = 7.3$ Hz), 1.076 (s, 3 H, CH_3-C 7), 1.118 (s, 3 H, CH_3-C 7), 1.234 (m, 1 H, H-C 6), 1.325 (d, 1 H, H-C 1, $J = 7.5$ Hz), 1.569 (m, 4 H), 1.845 (m, 1 H), 2.056 (m, 1 H), 2.372 (m, 4 H). ^{13}C-NMR (*TMS*, $CDCl_3$) $\delta =$ 7.8, 15.9, 17.3, 20.5, 23.0, 25.0, 29.7, 30.5 32.1, 33.3, 36.0, 36.8, 45.0, 210.7, 212.8. High resolution MS: 236.1775, calcd. for $C_{15}H_{24}O_2$: 236.1778.

(4aR,7S)-7-(1-Acetoxy-1-methylethyl)-4a-methyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (**6**)

To a solution of diketone **4** (0.96 g, 4.32 mmol) in benzene (70 ml), pyrrolidine (0.35 ml, 4.30 mmol) and then acetic acid (0.26 ml, 4.32 mmol) were added. The mixture was heated to boiling and water was azeotropically distilled off for 5 h. After cooling to room temp., sodium acetate (2 g) and 50% acetic acid (40 ml) were added to a mixture. After 10 min the mixture was diluted with petroleum

[1] The nomenclature of IUPAC is applied. However, for reason of simplicity the numbers of atoms in the Experimental Part follow Figs. 2 and 3

ether (20 ml) and the organic layer was separated and dried (Na_2SO_4). The crude product after evaporation of the solvent was purified by column chromatography (eluent: petroleum – diethyl ether, 9 : 1, *v/v*). Keto ester **6** (0.86 g) was obtained in 75% yield. M.p. 49–51°C. IR (CCl_4): 1 730, 1 670, 1 640, 1 250 cm^{-1}. ^{1}H-NMR (100 MHz, *HMDSO*$_{ext.}$, CCl_4) δ = 1.50 (s, 3 H, CH_3-C 10), 1.72 (s, 6 H, $(CH_3)_2$-C 11), 1.94 (m, 3 H), 2.18 (m, 4 H), 2.22 (s, 3 H, CH_3-C 12), 2.50 (m, 4 H), 5.92 (s, 1 H, H-C 4). $C_{16}H_{24}O_3$ (264.4): calcd. C 72.7, H 9.2; found: C 72.9, H 9.1.

(4aR, 7S)-7-(1-Hydroxy-1-methylethyl)-4a-methyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (**7**)

To a solution of keto ester **6** (2.52 g, 0.01 mol) in ethanol (30 ml), KOH (0.92 g, 0.02 mol) was added. The reaction mixture was refluxed for 3 h, then diluted with water (20 ml) and ethanol was distilled off. The residue was extracted with methylene chloride and the extract was dried (Na_2SO_4). After removal of the solvent, the crude product was purified by column chromatography (eluent: petroleum ether – diethyl ether, 7 : 3, *v/v*). Hydroxyketone **7** (2.00 g) was obtained in 95% yield as a colorless oil. IR (CCl_4): 3 580–3 200, 1 670, 1 620 cm^{-1}. ^{1}H-NMR (100 MHz, *HMDSO*$_{ext.}$, CCl_4) δ = 1.43 (s, 3 H, CH_3-C 10), 1.46 (s, 3 H, CH_3-C 11), 1.50 (s, 3 H, CH_3-C 11), 1.70 (m, 3 H), 2.10 (m, 4 H), 2.60 (m, 4 H), 3.20 (s, 1 H, HO-C 11), 5.95 (s, 1 H, H-C 4). $C_{14}H_{22}O_2$ (222.3): calcd. C 75.6, H 10.0; found: C 75.6, H 10.2.

3β-(2-Methoxycarbonylethyl)-3,7-7-trimethylbicyclo[4.1.0]heptan-2-one (**8**)

To a solution of **1** (3.04 g, 0.02 mol), in diethyl ether (30 ml) and *tert.*-butyl alcohol (30 ml), potassium *tert.*-butoxide (2.19 g, 18.00 mmol) was added at 0°C under nitrogen. After 10 min methyl acrylate (2.16 ml, 24.00 mmol) in diethyl ether (5 ml) was added dropwise to the mixture, which was left at room temp. for 16 h. Then the mixture was diluted with water and neutralized (*pH* 7). The solvent was distilled off and the aqueous layer was extracted with methylene chloride. The extract was washed with aqueous $NaHCO_3$ and water and then dried (Na_2SO_4). After removal of methylene chloride, the crude residue was purified by column chromatography (eluent: petroleum ether – diethyl ether, 9 : 1, *v/v*). Keto ester **8** (3.80 g) was obtained in 80% yield as an yellow syrup. IR (CCl_4): 1 735, 1 685, 1 190 cm^{-1}. ^{1}H-NMR (100 MHz, *HMDSO*$_{ext.}$, CCl_4) δ = 1.14 (s, 3 H, CH_3-C 3), 1.32 (s, 3 H, CH_3-C 7), 1.40 (s, 3 H, CH_3-C 7), 1.46 (m, 1 H, H-C 6), 1.52 (d, 1 H, H-C 1, J = 7.0 Hz), 1.87 (m, 4 H), 2.20 (m, 2 H), 2.36 (m, 2 H), 3.86 (s, 3 H, CH_3O-C 3′). $C_{14}H_{22}O_3$ (238.3): calcd. C 70.6, H 9.3; found: C 70.6, H 9.2.

3β-(2-Carboxyethyl)-3,7,7-trimethylbicyclo[4.1.0]heptan-2-one (**9**)

A solution of keto ester **8** (2.38 g, 0.01 mol) in 2 *N* NaOH (10 ml) was stirred for 1 h. The mixture was acidified with 10% H_2SO_4 at 5–10°C to *pH* 1. The aqueous solution was extracted with methylene chloride and the extract was dried (Na_2SO_4). After removal of the solvent, the crude product was purified as above (eluent: petroleum ether – diethyl ether, 8 : 2, *v/v*). Keto acid **9** (2.02 g) was obtained in 90% yield as a dark viscous oil. IR (CCl_4): 3 100, 1 700, 1 200 cm^{-1}. ^{1}H-NMR (100 MHz, *HMDSO*$_{ext.}$, CCl_4) δ = 1.18 (s, 3 H, CH_3-C 3), 1.32 (s, 3 H, CH_3-C 7), 1.40 (s, 3 H, CH_3-C 7), 1.44 (m, 1 H, H-C 6), 1.57 (d, 1 H, H-C 1, J = 7.0 Hz), 1.90 (m, 4 H), 2.14 (m, 1 H), 2.28 (m, 1 H), 2.42 (m, 2 H), 11.22 (s, 1 H, H – OOC). $C_{13}H_{20}O_3$ (224.3): calcd. C 69.6, H 9.0; found: C 69.4, H 8.9.

(4aR, 7S)-7-Isopropenyl-4a-methyl-4a,5,6,7-tetrahydrochroman-2-one (**10**) *and*
(4aR, 7S)-7-(1-acetoxy-1-methylethyl)-4a-methyl-4a,5,6,7-tetrahydrochroman-2-one (**11**)

A solution of keto acid **9** (1.12 g, 5.00 mmol), and sodium acetate (0.82 g, 0.01 mol) in acetic anhydride (20 ml) was refluxed for 3 h. Acetic acid was destilled off and the residue was extracted continuously with diethyl ether for 6 h. The extract was dried (Na_2SO_4) and evaporated to give a crude product

which was purified by column chromatography (eluent: petroleum ether – diethyl ether, 9:1, *v/v*). Lactones **10** and **11** (0.89 g) (a ratio of 4:1 was calculated from the capillary GC spectrum) were obtained in 70% yield. Further purification (as above) gave pure **10** (a colorless oil) and **11** (a pale yellow oil).

10. IR (CCl_4): 1745, 1630 cm^{-1}. ^{1}H-NMR (300 MHz, *TMS*, $CDCl_3$) δ = 1.203 (s, 3H, CH_3-C10), 1.566 (m, 2H), 1.716 (s, 3H, CH_3-C11), 1.749 (m, 4H), 2.695 (m, 2H), 2.889 (m, 1H, H-C7), 4.751 (d, 1H, H-C12, J = 1.4 Hz), 4.759 (d, 1H, H-C12, J = 1.4 Hz), 5.198 (d, 1H, H-C6, J = 2.5 Hz). High resolution MS: 206.1306, calcd. for $C_{13}H_{18}O_2$: 206.1307.

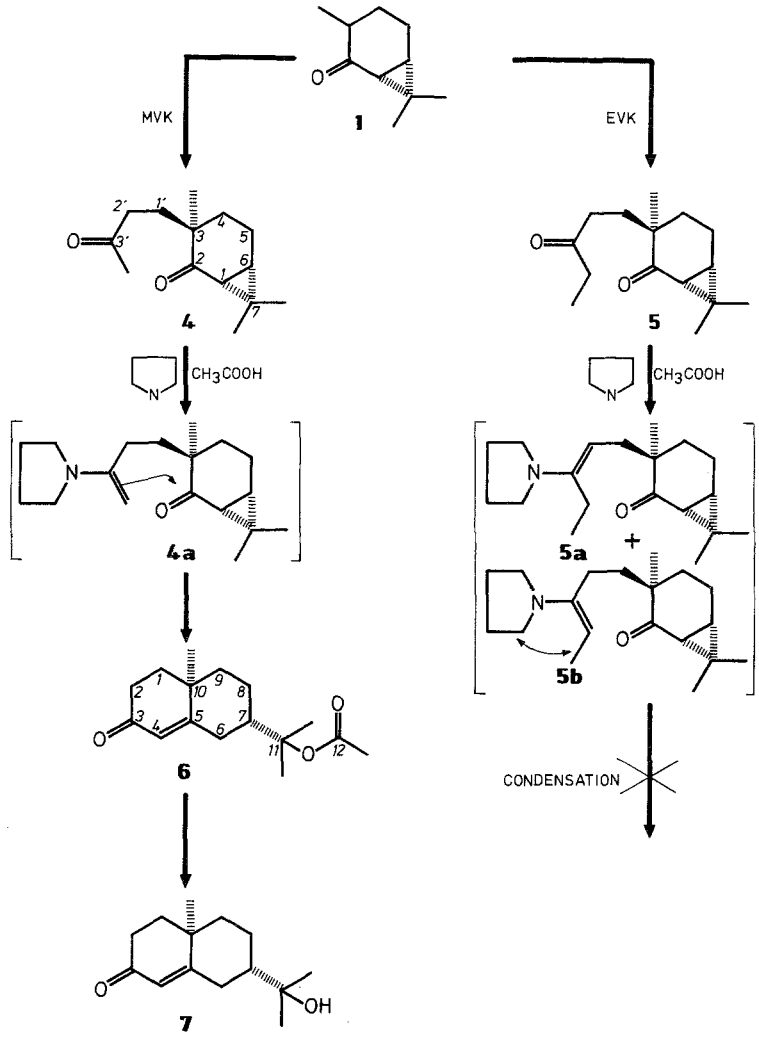
11. IR (CCl_4): 1720, 1675, 1245 cm^{-1}. ^{1}H-NMR (100 MHz, *HMDSO*$_{ext.}$, CCl_4) δ = 1.44 (s, 3H, CH_3-C10), 1.63 (s, 3H, CH_3-C11), 1.68 (s, 3H, CH_3-C11), 1.90 (m, 6H), 2.22 (s, 3H, CH_3-C12), 2.82 (m, 2H), 3.14 (m, 1H, H-C7), 5.42 (d, 1H, H-C6, J = 2.5 Hz). High resolution MS: 266.1515, calcd. for $C_{15}H_{22}O_4$: 266.1518.

(4aR,7S)-7-Isopropenyl-1,4a-dimethyl-4,4a,5,6,7,8-hexahydro-2(3H)-naphthalenone (**12**)

To a solution of lactone **10** (1.00 g, 4.80 mmol) and anhydrous diethyl ether (40 ml), a solution of C_2H_5MgBr [prepared from 0.24 g, (0.01 mol) of Mg and 1.09 g (0.01 mol) of C_2H_5Br] was added during 5 min at 0°C. The mixture was stirred for 1 h, then water (25 ml) was added and the ether evaporated. The residue was dissolved in ethanol (30 ml) and 1 *N* NaOH (15 ml) was added. The mixture was stirred at room temp. for 3 h and then extracted with methylene chloride. The extract was dried (Na_2SO_4) and evaporated. Crude dienone **12** (0.40 g, 40%, a yellow oil) was purified as usually (eluent: hexane – diethyl ether, 8:2, *v/v*). IR (CCl_4): 1660, 1615 cm^{-1}. ^{1}H-NMR (300 MHz, *TMS*, $CDCl_3$) δ = 1.223 (s, 3H, CH_3-C10), 1.680 (m, 6H), 1.779 (s, 3H), 1.822 (s, 3H), 2.061 (m, 2H), 2.399 (qd, 1H, H_e-C2, J = 17.0, 5.7, and 4.7 Hz), 2.529 (qd, 1H, H_a-C2, J = 16.9, 13.0, and 5.7 Hz), 2.736 (m, 1H, H-C7), 4.779 (d, 1H, H-C12, J = 1.4 Hz), 4.781 (d, 1H, H-C12, J = 1.4 Hz). ^{13}C-NMR (*TMS*, $CDCl_3$) δ = 10.9, 20.7, 22.5, 26.9, 33.0, 33.8, 35.9, 37.5, 41.9, 46.0, 109.2, 128.9, 149.2, 162.1, 199.1. High resolution MS: 218.1669, calcd. for $C_{15}H_{22}O$: 218.1672.

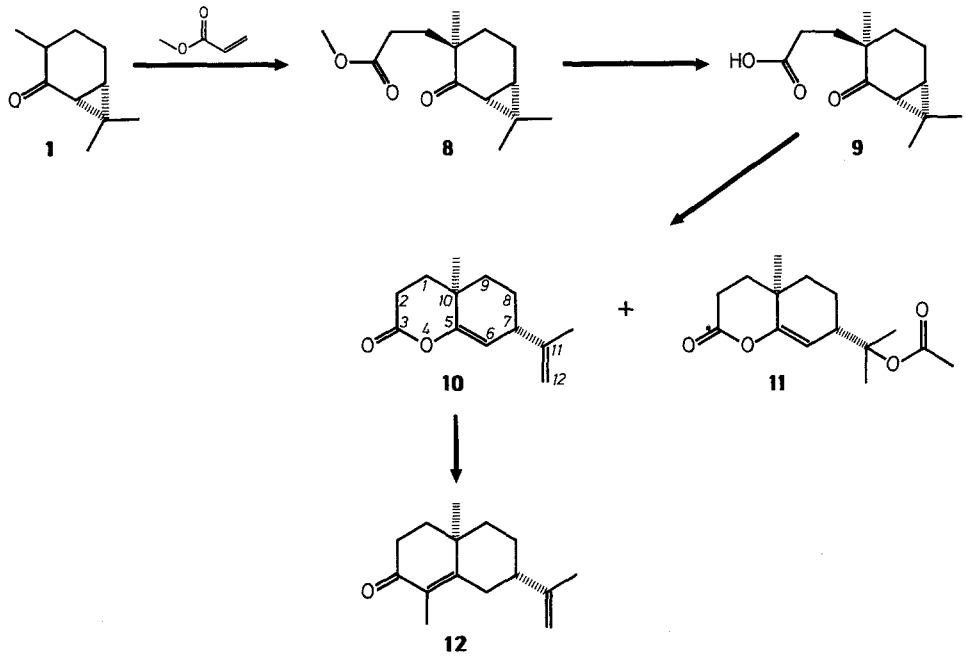
Results and Discussion

The Michael reaction of (+)-2-caranone (**1**) with methyl vinyl ketone (*MVK*) or ethyl vinyl ketone (*EVK*) led to diketones **4** and **5**, respectively. Cyclization of **4** or **5** was initially carried out under alkaline conditions (KOH in ethanol, $NaOC_2H_5$ in ethanol, *t-Bu*OK in *tert.*-butyl alcohol), the unreacted substrate being separated. Similar results were obtained by Bates et al. [2] and Caine and Gupton [3] in the case of cyclization of diketone **3**. Another factor, enabling cyclization of similar diketones, was the application of pyrrolidine in acetic acid [4]. However, only diketone **4** underwent cyclization by this method and in the case of diketone **5** only the substrate itself was isolated. This fact can be explained that intermediate enamine, formed during cyclization of **4**, gives more active and more preferable isomer **4a** with the less substituted ethylenic bond. Thus, the nucleophilic agent formed is situated in convenient position enabling condensation [5] running with simultaneous cleavage of the cyclopropane ring. Formation of keto ester **6** as result of cyclization was univocally supported by the ^{1}H-NMR spectrum, which does not exhibit the cyclopropane protons but contains a six-proton singlet at lower field (δ = 1.72) derived from the $-C-(CH_3)_2-O-$ grouping. The three-proton singlet at δ = 2.22 indicates the presence of the acetate group. Probably the formation of the ester grouping consist in the opening of the cyclopropane ring and formation of a tertiary carbonium ion which is attacked by acetate ion present in solution. The position of cleavage of the cyclopropane ring and thereby the position of



binding the $-C-(CH_3)_2-OCOCH_3$ grouping and its configuration was established on the ground of X-ray analysis [6]. This analysis completely confirms the hypothesis of Caine and Gupton [3] that cleavage of the cyclopropane ring in the compounds of this type consists in the breaking of the C 1–C 7 bond. Additionally, on the basis of X-ray analysis of compound **6**, where the angular methyl group is in α-position at C 10, the configuration of **4** and **5** was established. This configuration is in full agreement with the fact that attack of *MVK* or *EVK* on compound **1** should take place from the opposite side of the cyclopropane ring [7]. Further alkaline hydrolysis of keto ester **6** afforded hydroxyketone **7**, which is an interesting analog of nor-carisone, in a yield of 95%. In the case of cyclization of diketone **5** we assume that interactions disturbing coplanarity of π-electrons at the carbon atoms and the free pair of electrons at the nitrogen atom influenced the formation of intermediate enamine. Thus, only the presence of the isomer **5a**, making impossible further condensation, is possible [8].

By alkylation of **1** with methyl acrylate in strong alkaline medium (*t-Bu*OK/*t-Bu*OH), keto ester **8** was obtained, which gave after hydrolysis keto acid **9**. Com-



pound **9** was subjected to lactonization in the presence of sodium acetate and acetic anhydride to give a mixture (4 : 1) of lactones **10** and **11**. During this process cleavage of the cyclopropane ring also occurs by breaking the C 1–C 7 bond and the mechanism of formation of lactones obtained agrees with earlier suggestions concerning formation of keto ester **6**. Lactone **10** was subjected to the Fujimoto-Belleau [9, 10] reaction with Grignard reagent (C_2H_5MgBr) to give dienone **12**, whose configuration was established on the basis of ^{13}C-NMR analysis.

The sesquiterpenoid compounds obtained (**6**, **7**, **10**, **11**, **12**) are convenient substrates for further functionalization by means of microorganisms. The results of these studies will be the subject of further publications.

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