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Cyclopropanation of Methyl (2*E*)-3-[(1*R*,6*S*)-7,7-Dimethyl-2-oxo-3-oxabicyclo[4.1.0]hept-4-en-4-yl]prop-2-enoate with Dichlorocarbene and Diazomethane

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Abstract—Cyclopropanation of methyl (2*E*)-3-[(1*R*,6*S*)-7,7-dimethyl-2-oxo-3-oxabicyclo[4.1.0]hept-4-en-4-yl]prop-2-enoate with dichlorocarbene occurred at the endocyclic double bond, while its reaction with diazomethane in the presence of $Pd(acac)_2$ involved the exocyclic double bond. The resulting lactones reacted with sodium methoxide in methanol via opening of one cyclopropane fragment.

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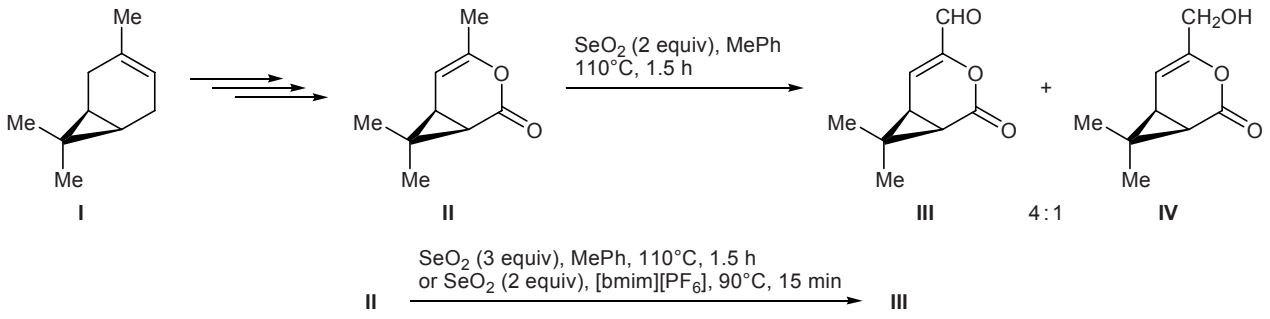
(1*R*,6*S*)-4,7,7-Trimethyl-3-oxabicyclo[4.1.0]hept-4-en-2-one (**II**) is available via a series of oxidative transformations of (+)-3-carene (**I**) and is used as intermediate product in syntheses of biologically active compounds having a *cis*-2,3-disubstituted 1,1-dimethylcyclopropane fragment [1–4]. It was shown previously that allylic oxidation of compound **II** with 2 equiv of selenium(IV) oxide in boiling toluene is regioselective: it occurs at the methyl group at the double C=C bond and gives a mixture of aldehyde **III** and alcohol **IV** at a ratio of 4 : 1 [5] (Scheme 1). Increase in the amount of the oxidant to 3 equiv or the use of ionic liquid ([bmim][PF_6]) as reaction medium (2 equiv of SeO_2) ensures selective formation of oxidation product **III**. The oxidation of enol lactone **II** with SeO_2 in ionic liquid is characterized by a considerably shorter time, higher yield of aldehyde **III**, and simpler isolation procedure. When the oxidation of **II** in [bmim][PF_6] was performed under milder conditions (50°C), the reaction was slower, and an approximately equimolar mixture of aldehyde **III** and alcohol **IV** was formed in 2 h.

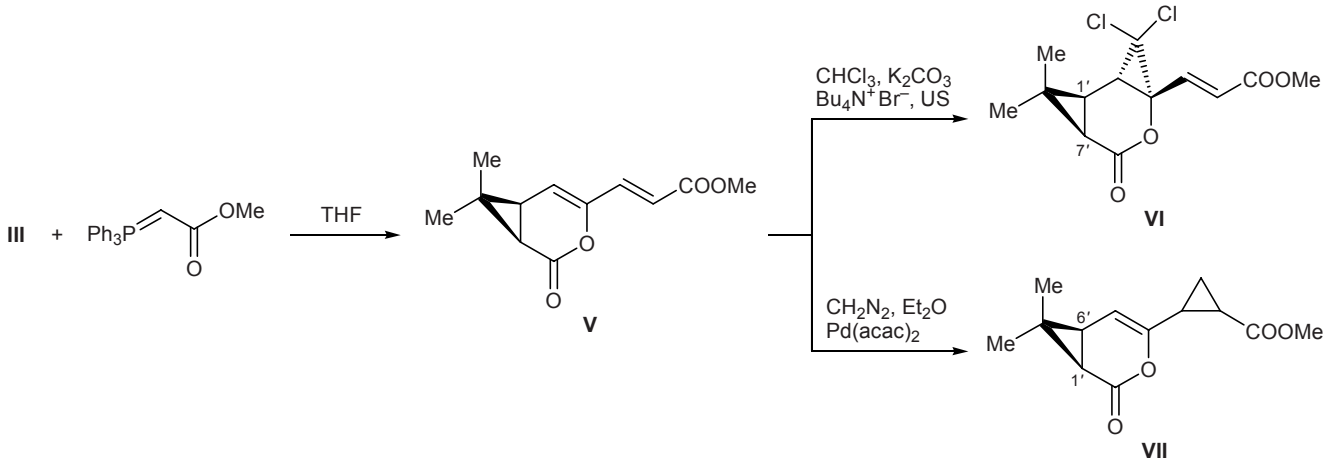
Introduction of oxygen-containing functional groups into the allylic position of molecule **II** considerably extends its synthetic potential. In the present work we examined the reactivity of double bonds in the Wittig olefination product of aldehyde **III**, dienoate **V**, in [1+2]-cycloadditions of dichlorocarbene and diazomethane and performed some transformations of the cyclopropanation products, which led to (1*R*)-*cis*-substituted cyclopropanecarboxylic acid derivatives.

It was found that the reactivity of double bonds in compound **V** toward cyclopropanation depends on the

Scheme 1.



Scheme 2.



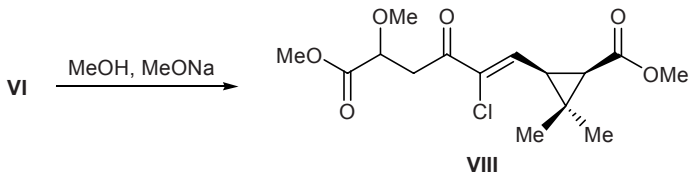
reagent nature. In the reaction with dichlorocarbene the endocyclic double C=C bond was more active. The ^{1}H NMR spectrum of adduct **VI** thus formed (Scheme 2) contained no signal at δ 5.73 ppm, which is typical of olefinic proton in the cyclohexene ring of initial compound **V**, and signals from two quaternary carbon atoms appeared in the ^{13}C NMR spectrum at δ_C 67.57 (CCl_2) and 65.27 ppm (C^4). Ultrasonic activation in the synthesis of lactone **VI** considerably shortened the reaction time (from 24 to 6 h); as a result, the contribution of tarring processes was reduced, and the yield of the final product increased. The reaction of **V** with diazomethane in the presence of a catalytic amount of bis(acetylacetonato)palladium(II) involved the double C=C bond conjugated with the ester group. The corresponding adduct (compound **VII**) showed in the ^{1}H NMR spectrum no signals at δ 6.29 and 6.98 ppm, which were present in the spectrum of initial compound **V** (two doublets) due to protons at the exocyclic double bond. Instead, upfield multiplet signals appeared due to methylene protons in the newly formed cyclopropane fragment.

Lactone **VII** was formed as a mixture of two diastereoisomers at a ratio of ~3:1 (*cis* and *trans* substitution in the newly formed cyclopropane ring). Its ^{1}H NMR spectrum (C_6D_6) contained double signals from the methoxy group and proton at the double bond, δ, ppm: 3.26 s and 3.31 s (3:1) (3H, OCH_3), 4.58 d and 4.61 d (1:3) (1H, 5′-H′, $J_1 = J_2 = 5.0$ Hz). Likewise, some carbon signals in the ^{13}C NMR spectrum were also doubled.

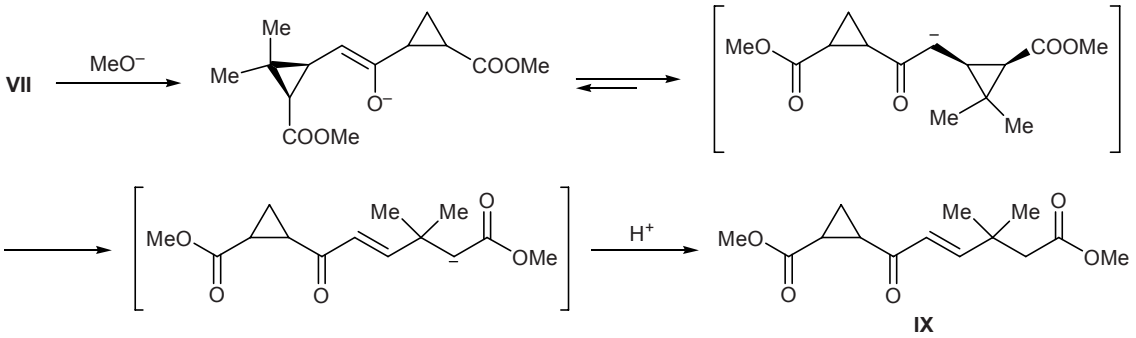
Treatment of compound **VI** with sodium methoxide in methanol resulted in opening of the lactone and dichlorocyclopropane rings and nucleophilic addition of methanol at the double bond with formation of diester **VIII** (Scheme 3). In the ^{1}H NMR spectrum of **VIII** we observed no doublets from protons at the double bond in the α-position with respect to the ester group, but a singlet at δ 3.45 ppm and a doublet at δ 7.44 ppm were present. These signals belong, respectively, to protons in the methoxy group and proton at the double bond resulting from opening of the dichlorocyclopropane fragment. Analogous opening of dichlorocyclopropane ring was observed previously in the reaction of dichlorocarbenylation product of lactone **II** with alkali [3].

The reaction of adduct **VII** with sodium methoxide under analogous conditions involved opening of the lactone and dimethylcyclopropane rings with formation of oxo diester **IX** (Scheme 4). Methanolysis of **VII** in the presence of *p*-toluenesulfonic acid gave compound **X** as a result of opening of only the lactone fragment, while both cyclopropane rings remained unchanged (Scheme 5).

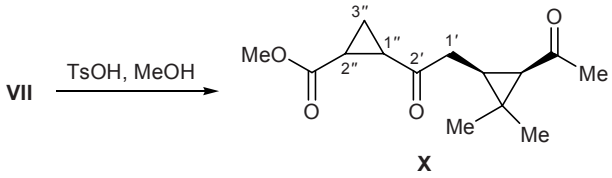
Scheme 3.



Scheme 4.



Scheme 5.



Thus the results of our study are consistent with published data [6–8] according to which the direction of [2+1]-cycloaddition of carbenes to conjugated dienoates is determined by the reagent nature and substituents at the double bond. We also demonstrated the known ability of cyclopropane derivatives to undergo various skeletal rearrangements.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75.46 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as reference. The IR spectra were obtained in the range from 400 to 4000 cm^{-1} on a Specord M-80 instrument from samples prepared as thin films. The optical rotations were measured from solutions in chloroform on a Perkin–Elmer 241 MS polarimeter. GLC analyses were performed on a Chrom-5 chromatograph equipped with a 1200×3-mm column packed with 5% of SE-30 on Chromaton N-AW-DMSC (0.16–0.20 mm); oven temperature 50–300°C; carrier gas helium. A UZDN-2T ultrasonic dispenser (44 kHz, 400 W) equipped with an immersion probe with a conical adapter was used for ultrasonic treatment of reaction mixtures.

(1*R*,6*S*)-7,7-Dimethyl-2-oxo-3-oxabicyclo[4.1.0]-hept-4-ene-4-carbaldehyde (III). Selenium(IV) oxide, 0.14 g (1.3 mmol), was added in portions to a mixture of 0.1 g (0.65 mmol) of enol lactone **II** and 1 ml of 1-butyl-3-methylimidazolium hexafluorophosphate(V) [bmim][PF_6] under stirring at 90°C. The mixture was stirred for 15 min, cooled to room temperature, and extracted with diethyl ether. The extract was washed with water, dried over Na_2SO_4, and evaporated, and the residue was purified by chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 0.08 g (78%), colorless crystals, mp 122–124°C; published data [5]: mp 119–121°C; $[\alpha]_D^{20}$ = +70.3° (*c* = 0.85). The ^{1}H and ^{13}C NMR spectra of the product were identical to those reported previously [5].

Methyl (2*E*)-3-[(1*R*,6*S*)-7,7-dimethyl-2-oxo-3-oxabicyclo[4.1.0]hept-4-en-4-yl]prop-2-enoate (V). Methyl (triphenyl-λ^5-phosphanylidene)acetate, 2 g (6.06 mmol), was added to a solution of 1 g (6.02 mmol) of aldehyde **III** in 30 ml of anhydrous tetrahydrofuran, and the mixture was stirred for 6 h. The solvent was distilled off, and the residue was purified by chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 0.82 g (82%), colorless crystals, mp 80–81°C, $[\alpha]_D^{20}$ = –42.9° (*c* = 0.28). IR spectrum, ν, cm^{-1}: 1624, 1675 (C=C); 1724, 1751 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.12 s and 1.33 s (3H each, CH_3), 1.91 d.d (1H, 6′-H, $J_{6',1'}$ = 7.3, $J_{6',5'}$ = 5.2 Hz), 2.04 d (1H, 1′-H, *J* = 7.3 Hz), 3.76 s (3H, OCH_3), 5.73 d (1H, 5′-H, *J* = 5.2 Hz), 6.29 d (1H, 2-H, *J* = 15.5 Hz), 6.98 d (1H, 3-H, *J* = 15.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.37 and 26.46 (CH_3), 25.21 ($C^{7'}$), 29.75 and 29.92 ($C^{1'}$, $C^{6'}$), 51.50 (OCH_3), 110.48 ($C^{5'}$), 118.21 (C^2), 135.29 (C^3), 146.44 ($C^{4'}$), 165.07 and 166.72 (C^1, $C^{2'}$). Found, %: C 64.53; H 6.02. $C_{12}H_{14}O_4$. Calculated, %: C 64.86; H 6.31.

Methyl (2*E*)-3-[(1*R*,7*R*)-3,3-dichloro-8,8-dimethyl-6-oxo-5-oxatricyclo[5.1.0.0^{2,4}]oct-4-yl]prop-2-enoate (VI). Compound **V**, 0.5 g (2.25 mmol), was dissolved in 10 ml of anhydrous chloroform, 0.15 g (0.46 mmol) of tetrabutylammonium bromide and 2.58 g (18.70 mmol) of potassium carbonate were added, and the mixture was stirred for 6 h under ultrasonic activation. The mixture was diluted with ethyl acetate, washed with water, and dried over Na_2SO_4. The solvent was distilled off, and the residue was purified by chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 0.56 g (84%), colorless crystals, mp 73–75°C, $[\alpha]_D^{20}$ = +19.4° (*c* = 0.31). IR spectrum, ν, cm^{-1}: 560, 590 (C–Cl); 1650 (C=C); 1730, 1755 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.12 s and 1.25 s (3H each, CH_3), 1.74 d (1H, 7′-H, *J* = 7.9 Hz), 1.9 d.d (1H, 1′-H, $J_{7',1'}$ = 7.9, $J_{1',2'}$ = 1.1 Hz), 2.29 d (1H, 2′-H, *J* = 1.1 Hz), 3.77 s (1H, OCH_3), 6.43 d (1H, 2-H, *J* = 15.4 Hz), 6.81 d (1H, 3-H, *J* = 15.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.85 and 26.90 (CH_3), 25.69 ($C^{1'}$), 26.98 ($C^{7'}$), 27.80 ($C^{8'}$), 31.81 ($C^{2'}$), 51.85 (OCH_3), 65.27 ($C^{4'}$), 67.57 ($C^{3'}$), 123.79 (C^2), 140.51 (C^3), 165.13 and 165.56 (C^1, $C^{6'}$). Found, %: C 51.00; H 4.45; Cl 23.10. $C_{13}H_{14}Cl_2O_4$. Calculated, %: C 51.15; H 4.59; Cl 23.28.

Methyl 2-[(1*R*,6*S*)-7,7-dimethyl-2-oxo-3-oxabicyclo[4.1.0]hept-4-en-4-yl]cyclopropane-1-carboxylate (VII). A solution of 0.1 g (0.45 mmol) of diene **V** and 0.0022 g (0.007 mmol) of $Pd(acac)_2$ in 1.5 ml of diethyl ether was cooled to 5–10°C, 3 ml of a 0.45 M solution of diazomethane in diethyl ether was added over a period of 30 min under stirring, and the mixture was stirred for 30–40 min and passed through a thin layer of aluminum oxide. The solvent was distilled off, and the residue was subjected to chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 0.087 g (82%), colorless oily liquid, $[\alpha]_D^{20}$ = –215.8° (*c* = 0.17). IR spectrum, ν, cm^{-1}: 1640 (C=C); 1730, 1753 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.00 s and 1.26 s (3H each, CH_3), 1.36 m (2H, CH_2), 1.73 d.d (1H, 6′-H, $J_{6',1'}$ = 7.6, $J_{6',5'}$ = 5.0 Hz), 1.84 d (1H, 1′-H, *J* = 7.6 Hz), 1.96 m (1H, 1-H), 2.08 m (1H, 2-H), 3.68 s (3H, OCH_3), 5.25 d (1H, 5′-H, *J* = 5.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 12.57 (C^3), 15.45 and 26.63 (CH_3), 19.36 (C^1), 22.85 (C^2), 23.60 ($C^{7'}$), 28.99 and 29.18 ($C^{1'}$, $C^{6'}$), 51.89 (OCH_3), 98.54 ($C^{5'}$), 148.19 ($C^{4'}$), 166.24 ($C^{2'}$), 173.26 (C=O). Found, %: C 65.91; H 6.49. $C_{13}H_{16}O_4$. Calculated, %: C 66.10; H 6.78.

Methyl (1*R*,3*R*)-3-[(1*Z*)-2-chloro-5-methoxy-5-methoxycarbonyl-3-oxopent-1-en-1-yl]-2,2-dimethylcyclopropane-1-carboxylate (VIII). Compound **VI**, 0.32 g (0.96 mmol), was added to 6.4 ml of a 5% solution of sodium methoxide in methanol, and the mixture was stirred for 2 h. The mixture was filtered, the filtrate was evaporated, the residue was dissolved in ethyl acetate, the solution was washed with water until neutral washings, dried over Na_2SO_4, and evaporated, and the residue was subjected to chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 0.3 g (87%), colorless oily liquid, $[\alpha]_D^{20}$ = +27.6° (*c* = 0.16). IR spectrum, ν, cm^{-1}: 1590 (C–Cl); 1640 (C=C); 1700, 1730, 1735 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.31 s and 1.33 s (3H each, CH_3), 2.08 d (1H, 1-H, *J* = 8.3 Hz), 2.33 d.d (1H, 3-H, $J_{1,3}$ = 8.3, $J_{3,1'}$ = 9.5 Hz), 3.10 d.d (1H, 4′-H, ^2J = 17.3, ^3J = 4.4 Hz), 3.23 d.d (1H, 4′-H, ^2J = 17.3, ^3J = 8.4 Hz), 3.45 s (3H, 5′-OCH_3), 3.67 s and 3.77 s (3H each, OCH_3), 4.32 d.d (1H, 5′-H, ^3J = 4.4, 8.4 Hz), 7.44 d (1H, 1′-H, *J* = 9.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.14 and 28.44 (CH_3), 30.06 (C^2), 32.66 (C^1), 34.19 (C^3), 41.07 ($C^{4'}$), 51.71 and 52.19 ($COOCH_3$), 58.92 (5′-OCH_3), 76.14 ($C^{5'}$), 133.96 ($C^{2'}$), 138.66 ($C^{1'}$), 170.67 and 172.29 (C=O), 189.42 ($C^{3'}$). Found, %: C 53.93; H 6.50; Cl 10.71. $C_{15}H_{21}ClO_6$. Calculated, %: C 54.14; H 6.32; Cl 10.68.

Methyl 2-[(2*E*)-4,4-dimethyl-5-methoxycarbonyl-1-oxopent-2-en-1-yl]cyclopropane-1-carboxylate (IX). Compound **VII**, 0.085 g (0.36 mmol), was added to 1.7 ml of a 5% solution of sodium methoxide in methanol, and the mixture was stirred for 2 h. The mixture was then filtered, the filtrate was evaporated, the residue was dissolved in ethyl acetate, the solution was washed with water until neutral washings, dried over Na_2SO_4, and evaporated, and the residue was subjected to chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 0.076 g (80%), colorless oily liquid. IR spectrum, ν, cm^{-1}: 1635 (C=C); 1710, 1732 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.17 s (6H, CH_3), 1.43 m (2H, 3-H), 2.19 m (1H, 2-H), 2.38 s (2H, 4′-H) 2.64 m (1H, 1′-H), 3.60 s and 3.67 s (3H each, OCH_3), 6.14 d (1H, 2′-H, *J* = 15.1 Hz), 6.94 d (1H, 3′-H, *J* = 15.1 Hz). Found, %: C 62.95; H 7.51. $C_{14}H_{20}O_5$. Calculated, %: C 62.69; H 7.46.

Methyl (1*R*,3*S*)-3-{2-[2-methoxycarbonylcyclopropyl]-2-oxoethyl}-2,2-dimethylcyclopropane-1-carboxylate (X). A solution of 0.25 g (1 mmol) of lactone **VII** and 0.19 g (1.1 mmol) of *n*-toluenesulfonic acid in 6 ml of anhydrous methanol was stirred for 6 h. The solvent was distilled off, the residue was dissolved in 30 ml of ethyl acetate, the solution was washed with

water (3×5 ml) and dried over Na_2SO_4, the solvent was distilled off, and the residue was subjected to chromatography on silica gel using petroleum ether–ethyl acetate (9:1) as eluent. Yield 0.23 g (82%), colorless oily liquid, $[\alpha]_D^{20} = -59°$ (c = 0.19). IR spectrum, ν, cm^{-1}: 1715, 1731, 1737 (C=O). ^1H NMR spectrum, δ, ppm: 1.14 s and 1.20 s (3H each, CH_3), 1.41 m (2H, 3″-H), 1.45 d.t (1H, 3-H, $J_{3,1'a}$ = 6.2, $J_{3,1'b}$ = 6.5, $J_{3,1}$ = 8.6 Hz), 1.58 d.t (1H, 1-H, $J_{1,3}$ = 8.6, $J_{1,1'a}$ = 1.2, $J_{1,1'b}$ = 1.2 Hz), 2.15 m (1H, 2″-H), 2.47 m (1H, 1″-H), 3.04 d.d.d (1H, 1′-H_a, ^2J = 18.5, $J_{1'a,3}$ = 6.2, $J_{1'a,1}$ = 1.2 Hz), 3.09 d.d.d (1H, 1-H_b, ^2J = 18.5, $J_{1'b,3}$ = 6.5, $J_{1'b,1}$ = 1.2 Hz), 3.62 s and 3.71 s (3H each, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 14.21 and 28.50 (CH_3); 16.84 ($C^{3''}$); 25.05 (C^2); 23.76, 27.35, 28.01, and 28.97 (CH); 38.13 ($C^{1'}$); 51.16 and 52.06 (OCH_3); 172.24 and 172.42 (C=O, ester); 206.66 (C=O). Found, %: C 62.05; H 7.48. $C_{14}H_{20}O_5$. Calculated, %: C 62.69; H 7.46.

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