ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 2, pp. 191–197. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © N.K. Selezneva, F.A. Gimalova, R.F. Valeev, M.S. Miftakhov, 2009, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 2, pp. 198–204.

Carvone Hydrochloride in the Synthesis of Thiazole-Containing C^{11}-C^{21}-Block of Epithilones *gem*-Dimethylcyclopropane Analogs

N. K. Selezneva, F. A. Gimalova, R. F. Valeev, and M. S. Miftakhov

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Ufa, 450054 Russia
e-mail: bioreg@anrb.ru

Received April 13, 2009

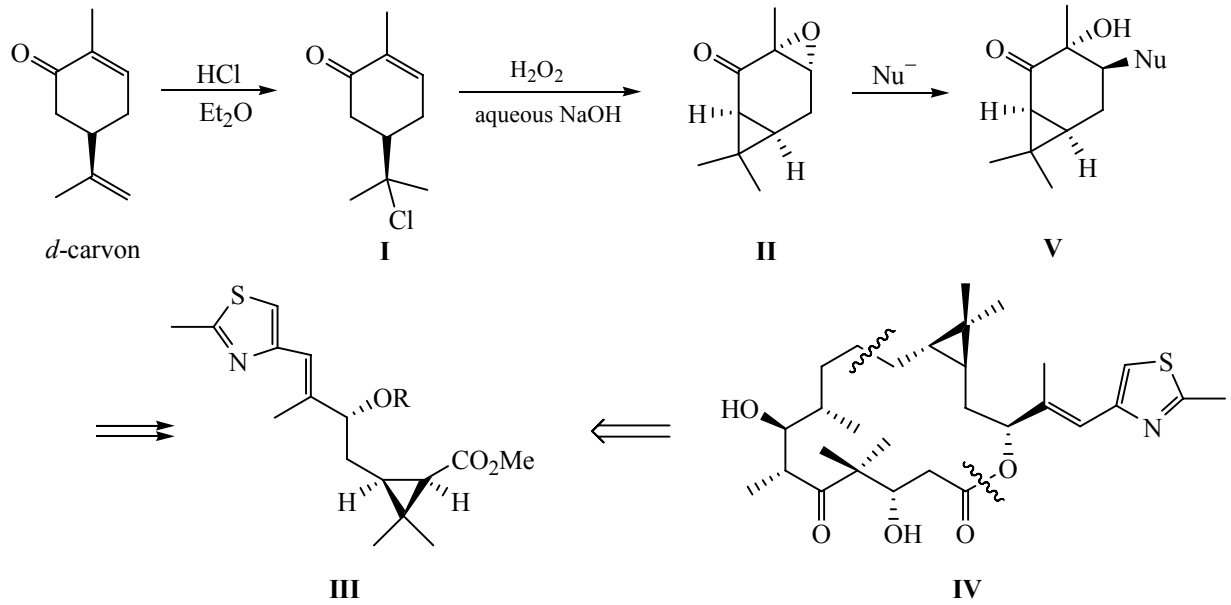
Abstract—Starting with R-(–)-carvone hydrochloride a synthesis was developed of the key chiral block for the epothilones *gem*-dimethylcyclopropane analog.

DOI: 10.1134/S1070428010020089

Nowadays epothilones and their analogs attract exclusive interest as the most promising class of compounds with the taxol-like mechanism of anticancer action [1–3]. Among modified substances more stable and less toxic carbaanalogs of epothilone are prominent, where the epoxy ring is replaced by a cyclopropane cycle [4, 5]. In this respect we are interested in the synthesis of new *gem*-dimethylcyclopropane analogs of epothilones. The previously obtained from carvone hydrochloride (**I**) [6] epoxycyclopropane derivative **II** [7] we planned to use in the synthesis of a chiral block **III,** the precursor of epothilones *gem*-dimethylcyclo-propane analogs **IV** [8]. The preparation of structures **III** we presumed to perform by the nucleophilic opening of the epoxy ring followed by the cleavage of α-ketol **V** effected by $Pb(OAc)_4$ and fusion of the thiazole fragment by Wittig–Horner procedure (Scheme 1).

However our numerous attempts at the regioselective

Scheme 1.



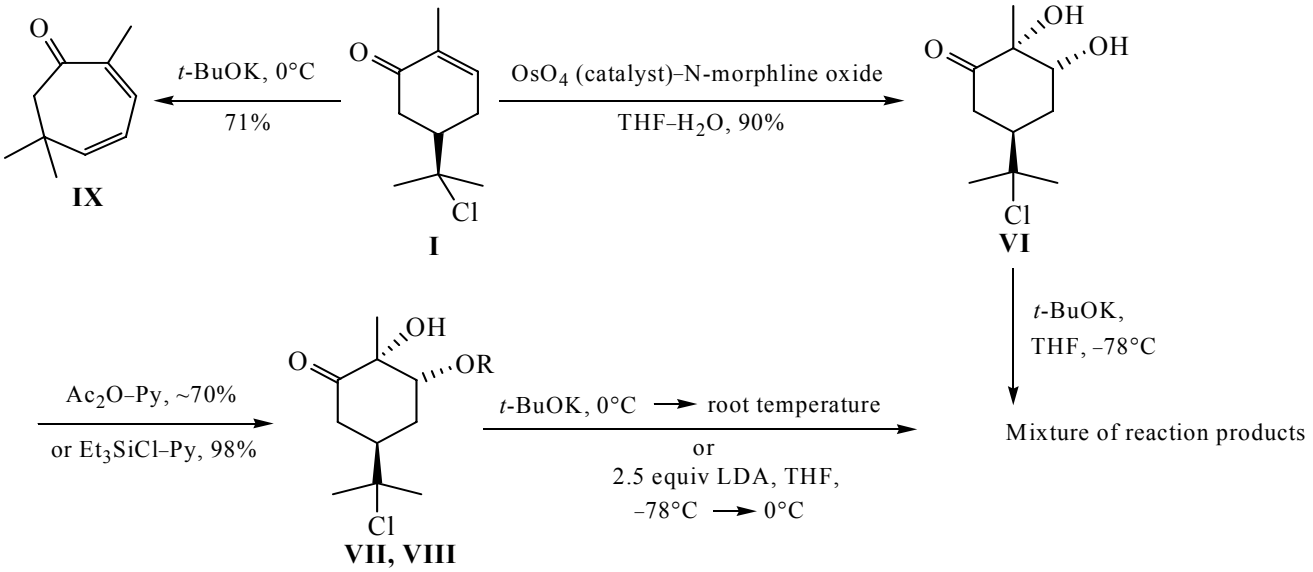
opening of the epoxy ring in compound **II** with versatile O-, N-nucleophiles (aqueous NaOH; BnONa–BnOH, 80°C; NaN_3, DMF, NH_4Cl, 80°C; $BnNH_2$, 20°C) did not result in the preparatively plausible process with regard to selectivity and yield of reaction products **V**. Therefore we decided to proceed from preliminary opened diol forms of compound **II**, in particular, from compound **VI** obtained by dihydroxylation of carvone derivative **I** with OsO_4 (catalyst)–morpholine N-oxide [9]. In this event also the attempts on intramolecular cyclization of compound **VI** even under controlled mild conditions led prevailingly to side reactions of retroaldol cleavage etc. giving a mixture of products. Monoacetate **VII** in the deprotonation with LDA under the indicated conditions did not afford the cyclization product, and *t*-BuOK reacted both with compound **VII** and monosilyl derivative **VIII** analogously to diol **VI** yielding an intractable mixture of substances. The attempt to involve into the cyclization with the help of *t*-BuOK directly compound **I** instead of the expected caren-2-one led to the formation in a high yield of eucarvone (**IX**) (Scheme 2).

Therefore we decided to work with completely protected derivative of diol **VI**. Although compound **VI** did not react with carbonylimidazole, the performance of the acetonide protection was quite easy. Obtained acetonide **X** proved to be more stable and less subject to side reactions. The experiments on intramolecular cyclization using LDA, the system NaOH–aqueous H_2O_2 and *t*-BuOK led to the formation of cyclopropane derivative **XI** and enone **XII** respectively. As seen, in the experiment with the hydroperoxide anion a good yield of compound **XI** was obtained (80%) (Scheme 3).

The next important stage of the synthesis was the hydrolysis of the acetonide protection in compound **XI**. Under the standard hydrolysis conditions of the acetonide group (aqueous mineral acids, organic solvent, heating) the three-carbon ring suffered destruction providing several compounds. A more unambiguous result was obtained by methanolysis of compound **XI** assisted by montmorilonite resin K-10 affording in 75% yield transformed diol **XIII**. At the use of acetone as solvent enone **XII** was obtained (Scheme 4).

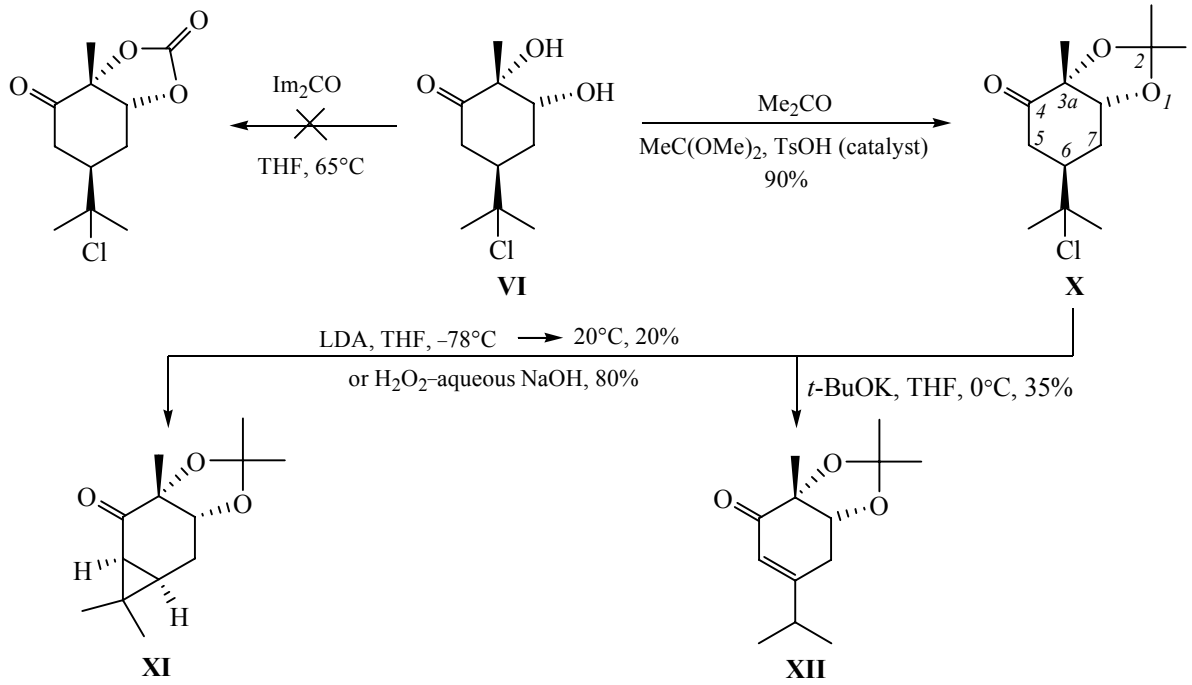
The difficulties found on the way to ketol **V** both from compounds **VI–VIII** (the formation in basic media of the products of α- and β-ketol decomposition and their subsequent transformations) and from acetonide **XI** (lability of the cyclopropane ring under the conditions of acid hydrolysis of acetals) forced us to develop alternative routes to the target structures **III**. In particular, we decided first "neutralize" the highly reactive ketol fragment in the substrates by first olifination by Wittig reaction with a thiazole-containing phosphonate and only afterwards begin to build up the cyclopropane fragment of molecule **III**. To this end the monosilylated ketodiol **VIII** was treated with lead tetraacetate in a mixture benzene–methanol [10] to obtain methyl ester **XIV**. The

Scheme 2.

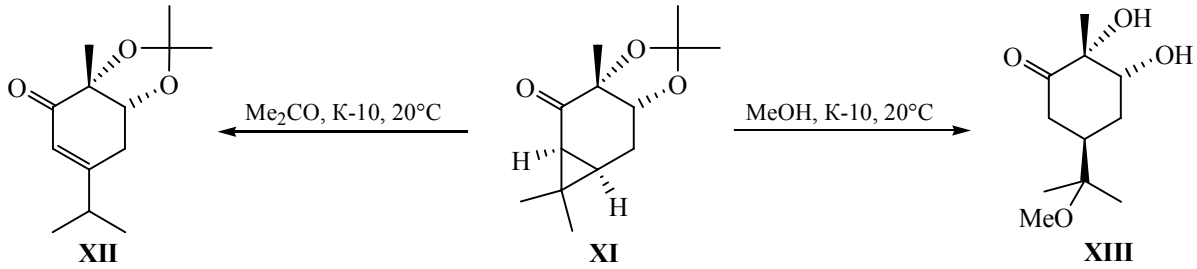


R = Ac (**VII**), $SiEt_3$ (**VIII**).

Scheme 3.



Scheme 4.



condensation of the latter with the anion of phosphonate **XV** in THF at –78°C we obtained olefin **XVI** that underwent clear intramolecular cyclization into cyclopropane derivative **XVII** at dehydrohalogenation by treating with sodium hexamethyldisilazide in THF at –78°C (Scheme 5).

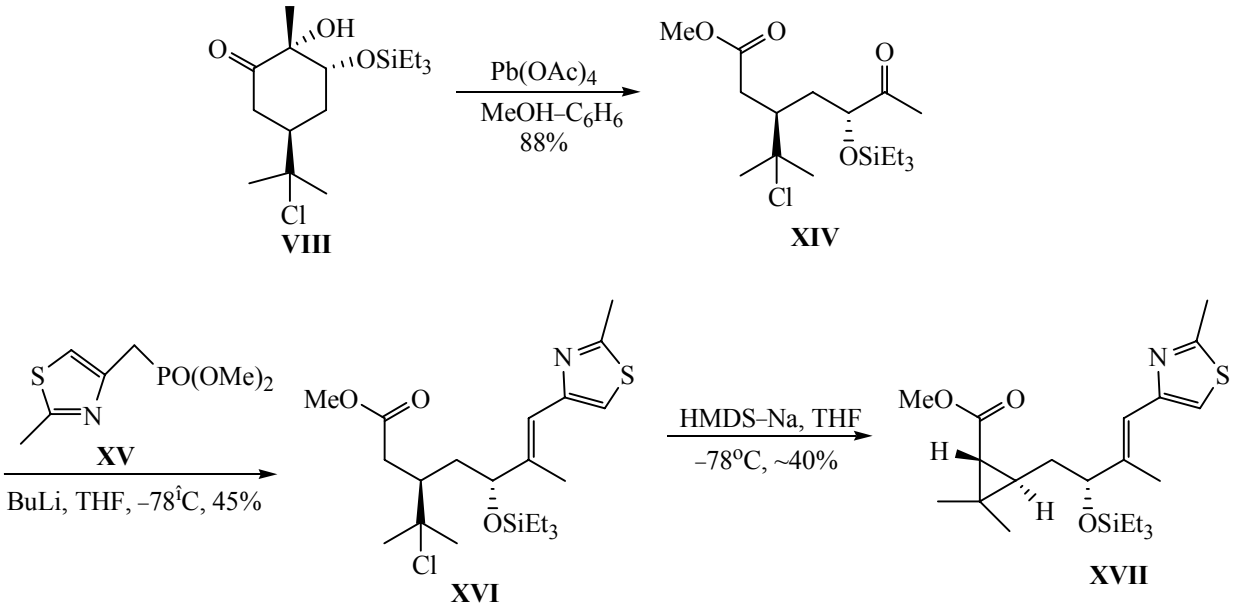
Thus based on *d*-carvone we prepared the key C^{11}–C^{21}-block for the synthesis of the *gem*-dimethylcyclopropane analog of epothilones.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer IR Prestige-21 Shimadzu from thin films. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequencies 300.13 and 75.47 MHz respectively, internal reference TMS. The specific rotation was measured on a polarimeter Perkin Elmer-341. Mass spectra were taken on an instrument Shimadzu LCMS-2010 under chemical ionization conditions under atmospheric pressure and electrons energy 20 eV with the registration of both positive and negative ions. The mobile liquid phase a mixture MeOH–water, 50:50, flow rate 0.03 or 0.05 ml/min.

(2*R*,3*R*,5*R*)-2,3-Dihydroxy-2-methyl-5-(1-chloro-1-methylethyl)cyclohexan-1-one (VI). To a stirred solution of 1.0 g (5.36 mmol) of chloride **I** in 10 ml of a mixture acetone–water, 4:1, was added in succession 1 mg of OsO_4 and 15 min later 1.5 g (11.11 mmol)of morpholine N-oxide. The reaction mixture was stirred for 8 h, acetone was distilled off, to the residue was added a saturated solution of Na_2SO_3, the mixture was stirred

Scheme 5.



for 30 min, then the products were extracted into EtOAc, the extract was dried with $MgSO_4$ and evaporated. The solid residue was recrystallized from a mixture petroleum ether–ethyl acetate to obtain 0.97 g (82%) of compound **VI**. Colorless crystals, mp 96–97°C, $[\alpha]_D^{20}$ +43.4° (*C* 1.335, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3427, 2924, 2852, 1722, 1458, 1386, 1369, 1260, 1240, 1141, 1085, 1047, 883, 567. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 s (3H each, CH_3), 1.58 s and 1.63 s (3H each each, *gem*-CH_3), 2.03 t (1H, *J* 12.8 Hz) and 2.30 m (1H, C^4H_2), 2.43 m (1H, CH), 2.67–2.70 m (2H, C^6H_2), 2.98 br.s (1H, OH), 4.07 t (1H, OCH, *J* 2.7 Hz), 4.21 s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 23.08 (CH_3), 29.34 (C^4), 31.16 and 31.45 (*gem*-CH_3), 38.55 (C^6), 44.75 (C^5), 74.22 ($C^{1'}$), 75.03 (C^3), 78.13 (C^2), 212.95 (C=O).

(2*R*,3*R*,5*R*)-2-Hydroxy-2-methyl-3-oxo-5-(1-chloro-1-methylethyl)cyclohexyl acetate (VII). To a stirred solution of 0.1 g (0.45 mmol) of diol **VI** in 2 ml of pyridine was added 0.45 ml (4.40 mmol) of acetic anhydride, and the stirring was carried out till complete consumption of the initial compound (TLC monitoring). Then 5 ml of ice water was added, the product was extracted into $CHCl_3$, the extract was dried with $MgSO_4$, the solvent was evaporated, the reaction product was subjected to column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1:2). Yield 0.08 g (67%). Colorless oily fluid, $[\alpha]_D^{20}$ +0.2° (*C* 0.97, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 s (3H each, CH_3), 1.59 s and 1.60 s (3H each each, *gem*-CH_3), 2.03 s (3H each, CH_3CO), 2.21 m (3H each, CH, CH_2), 2.74 m (2H, C^6H_2), 3.76 s (1H, OH), 5.34 br.s (1H, OCH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.94 (CH_3), 23.44 (CH_3CO), 29.33 (C^4), 31.10 and 31.22 (*gem*-CH_3), 38.99 (C^6), 45.55 (C^5), 74.50 (C^2), 76.56 ($C^{1'}$), 77.18 (C^1), 169.74 (CH_3CO), 210.95 (C=O).

(2*R*,3*R*,5*R*)-2-Hydroxy-2-methyl-3-triethylsilyloxy-5-(1-chloro-1-methylethyl)cyclohexan-1-one (VIII). To a stirred solution of 0.3 g (1.36 mmol) of diol **VI** in 3 ml of pyridine was added 0.36 ml (2.04 mmol) of Et_3SiCl, and the stirring was carried out till complete consumption of the initial compound (~2 h, TLC monitoring). Then , the solvent was evaporated, the resudue was subjected to column chromatography on silica gel (eluent EtOAc–petroleum ether, 1:5). Yield 0.45 g (98%). Colorless oily fluid, $[\alpha]_D^{20}$ –7.2° (*C* 1.55, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.56 q (6H, CH_2Si, *J* 7.96 Hz), 0.89 t (9H, CH_3, *J* 7.96 Hz), 1.36 s (3H each, CH_3), 1.54 s and 1.57 s (3H each each, *gem*-CH_3), 2.03 m (2H, C^4H_2), 2.36 m (1H, CH), 2.60 d (1H, *J* 3.5 Hz) and 2.67 d.d (1H, C^6H_2, *J* 13.9, ^2J 15.0 Hz), 3.51 s (1H, OH), 4.02 t (1H, OCH, *J* 2.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 4.70 ($SiCH_2$), 6.72 (CH_3), 22.52 (CH_3), 31.19 and 31.24 (*gem*-CH_3), 32.11 (C^4), 39.10 (C^6), 45.17 (C^5), 73.10 ($C^{1'}$), 77.64 (C^3), 78.44 (C^2), 212.42 (C=O).

2,6,6-Trimethylcyclohepta-2,4-dien-1-one (IX). To a solution of 0.3 g (1.6 mmol) of chloride **I** in 10 ml of anhydrous THF at 0°C was added 0.27 g (2.40 mmol) of *t*-BuOK. The reaction mixture was stirred for ~4 h (TLC

monitoring), then it was decomposed by adding a saturated solution of NH_4Cl, the reaction product was extracted into chloroform, the extract was dried with $MgSO_4$, and evaporated, the residue was subjected to column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 3) to obtain 0.17 g (71%) of eucarvone (**IX**). Colorless oily fluid. IR spectrum, ν, cm^{-1}: 3019, 2959, 2926, 2868, 1647, 1458, 1420, 1364, 1260, 1238, 1179, 1119, 866, 810, 731. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.06 C (6H, *gem*-CH_3), 1.92 s (3H each, CH_3), 2.65 s (2H, C^7H_2), 5.77 d.d (1H, $=C^4H$, *J* 8.1, 11.5 Hz), 5.97 d (1H, $=C^{3H\ each}$, *J* 11.7 Hz), 6.48 d.d 1H, $=C^5H$, *J* 1.2, 8.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.92 (CH_3), 26.93 (*gem*-CH_3), 33.14 (C^6), 54.13 (C^7), 122.13 (C^4), 133.92 (C^3), 138.39 (C^2), 148.85 (C^5), 200.06 (C=O). Mass spectrum, *m/z*: 151 $[M + H]^+$, 123 $[M + H–C_2H_4]^+$, 107, 192 $[M + H + CH_3CN]^+$, 149 $[M – H]^–$, 165, 181 $[M – H + CH_3OH]^–$.

(3a*R*,6*R*,7a*R*)-2,2,3a-Trimethyl-6-(1-chloro-1-methylethyl)tetrahydro-1,3-benzodioxol-4(3a*H*)-one (X). To a solution of 0.4 g (1.8 mmol) of diol **VI** and 0.4 ml (3.37 mmol) of dimethoxypropane in 5 ml of anhydrous acetone was added 30 mg of TsOH. The reaction mixture was stirred till complete consumption of the initial compound (~15 h, TLC monitoring), then 0.1 g of anhydrous $NaHCO_3$ was added, the stirring was continued for 15 min, the solution was filtered, and acetone was distilled off. The residue was diluted with CH_2Cl_2, the solution obtained was washed with brine, dried with $MgSO_4$, and evaporated. The solid residue was recrystallized from a mixture EtOAc–petroleum ether, 1:10, to obtain 0.38 g (80%) of acetonide **X**. Colorless crystals, mp 98–100°C, $[\alpha]_D^{20}$ +4.4° (*C* 1.43, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2995, 2960, 2932, 2914, 2852, 1724, 1462, 1394, 1368, 1294, 1267, 1240, 1227, 1205, 1171, 1142, 1111, 1056, 1031, 995, 931, 885, 835, 721, 711, 596, 569, 514. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.37 s, 1.38 s (3H eacheach, CMe_2), 1.40 s (3H each, CH_3), 1.59 C, 1.63 s (3H eacheach, *gem*-CH_3), 1.96 d.t.d (1H, *J* 2.87, 2.65, 2.87, 11.9 Hz), 2.27 m (1H, C^7H_2), 2.45 m (1H, *J* 12.8, 13.7 Hz), 2.69 d.t (1H, C^5H_2, *J* 2.88, 13.9 Hz), 2.48 m (1H, C^6H), 4.19 t (1H, OCH, *J* 2.65 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 19.42 (CH_3), 26.69, 26.97 (CMe_2), 27.57 (C^7), 30.98, 31.08 (*gem*-CH_3), 41.48 (C^5), 43.87 (C^6), 72.26 ($C^{1'}$), 80.82 (C^{7a}), 82.04 (C^{3a}), 108.48 (C^2), 211.05 (C=O). Found, %: C 59.38; H 7.86; Cl 13.70. $C_{13}H_{21}ClO_3$. Calculated, %: C 59.88; H 8.12; Cl 13.60.

(3a*R*,6a*R*)-2,2,3a,5,5-Pentamethylhexahydro-4*H*-cyclopropane[4,5]benzo[1,2-*d*]-1,3-dioxol-4-one (XI). *a.* To a stirred solution of 0.07 ml (0.99 mmol) of diisopropylamine in 5 ml of anhydrous THF at–78°C under an argon atmosphere was added dropwise 0.65 ml of 2.0 N BuLi solution. The reaction mixture was stirred for 15 min at –78°C, then it was warmed to –10°C and stirred over 15 min, then it was cooled to–78°C, and 0.1 g (0.38 mmol) of acetonide **X** in 2 ml of anhydrous THF was added dropwise, the mixture was stirred for 30 min at –78°C, then it was warmed to 0°C and stirred for 2 h. Then 2–3 ml of saturated NH_4Cl solution was added, the mixture was stirred for 10 min, THF was evaporated, and the residue was treated with $CHCl_3$ (3 × 5 ml). The combined organic solutions were washed with brine, dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 4). Yield 0.02 g (23%).

b. To a stirred solution of 0.06 g (0.23 mmol) of acetonide **X** in 2 ml of anhydrous MeOH at 0°C was added dropwise 0.18 ml of 47% H_2O_2 solution, then was slowly added 0.22 ml of 4 N NaOH solution. The reaction mixture was warmed to room temperature and stirred for 8 h. Then 3 ml of H_2O was added, the reaction product was extracted into CH_2Cl_2, the extract was dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 3). Yield 0.04 g (80%). Colorless oily fluid, $[\alpha]_D^{20}$ –323.2° (*C* 1.02, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.95 s, 1.27 s (3H each, *gem*-CH_3), 1.16 s (3H each, CH_3), 1.35 s, 1.38 s (3H each, CMe_2), 1.43 m (1H, CH), 1.51 m (1H, CH), 1.57 m (1H), 2.48 d.d.d.d (1H, CH_2, *J* 3.2, 3.5, 3.2, 3.2 Hz), 4.09 t (1H, OCH, *J* 2.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 17.18 (CH_3), 18.63, 26.31 (*gem*-CH_3), 19.15 (C^5), 22.99 (C^{5a}), 24.96 (C^6), 27.78, 28.13 (CMe_2), 31.83 (C^{4a}), 80.03 (C^{3a}), 81.06 (C^{6a}), 109.42 (C^2), 208.48 (C=O).

(3a*R*,7a*R*)-6-Isopropyl-2,2,3a-trimethyl-7,7a-dihydro-1,3-benzodioxol-4-(3a*H*)-one (XII). To a stirred solution of 0.1 g (0.38 mmol) of acetonide **X** in 2 ml of anhydrous THF was added 0.085 g (0.76 mmol) of *t*-BuOK, and the mixture was stirred at room temperature till complete consumption of the initial compound (TLC monitoring). Then 2–3 ml of saturated NH_4Cl solution was added, the mixture was stirred for 10 min, THF was evaporated, and the residue was treated with $CHCl_3$ (3 × 5 ml). The combined organic solutions were washed with brine, dried with $MgSO_4$, and evaporated. The residue was subjected to column chromatography on SiO_2 (eluent EtOAc–petroleum ether, 1 : 3). Yield 0.03 g (35%). Colorless oily fluid, $[\alpha]_D^{20}$ –

16.2° (*C* 0.905, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2968, 2931, 2873, 1676, 1634, 1456, 1411, 1371, 1336, 1280, 1242, 1213, 1172, 1109, 1074, 991, 883, 844, 804, 514. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 d (6H, *gem*-CH_3, *J* 6.8 Hz), 1.28 s (3H each, CH_3), 1.35 s, 1.38 s (3H each, $CM\varepsilon_2$), 2.44 q (1H, CH, *J* 6.6, 6.8 Hz), 2.67 d.d.d.d (1H, *J* 2.2, 2.4, 4.0, 2.3, 2.1, 4.0, 19.4 Hz), 2.79 d.d (1H, C^7H_2, *J* 1.6, 19.4 Hz), 4.25 d.d (1H, OCH, *J* 1.8, 2.2, 4.0 Hz), 5.93 C (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.85 (CH_3), 15.13, 15.46 (*gem*-CH_3), 21.52, 22.01 ($CM\underline{\varepsilon}_2$), 23.76 ($C^7$), 30.19 (CH), 73.28 ($C^{7a}$), 74.67 ($C^{3a}$), 103.00 ($C^2$), 116.12 ($C^5$), 161.02 ($C^6$), 194.76 (C=O). Mass spectrum, *m/z*: 255 [*M* – H + MeOH]$^+$, 225 [*M* + H]$^+$, 167 [*M* + H – Me_2CO]$^+$, 165 [*M* – H – Me_2CO]$^-$, 125 [*M* + H – Me_2CO – CH_2=$CHCH_3$]$^+$.

(2*R*,3*R*)-2,3-Dihydroxy-2-methyl-5-(1-methoxy-1-methylethyl)cyclohexan-1-one (XIII). To a solution of 0.05 g (0.22 mmol) of compound **XI** in 2 ml of MeOH was added 0.03 g of cation-exchanger K-10, and the mixture was stirred for 24 h at room temperature. Then the reaction mixture was filtered through a silica gel bed, evaporated, the residue was subjected to column chromatography on silica gel (eluent EtOAc–petroleum ether, 1:3). Yield 0.03 g (75%). Colorless oily fluid, $[\alpha]_D^{20}$ +38.6° (*C* 0.46, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3458, 2972, 2933, 2829, 1715, 1458, 1427, 1383, 1366, 1304, 1249, 1168, 1149, 1128, 1047, 957, 854, 692, 590. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.19 s, 1.20 s (3H each, *gem*-CH_3), 1.38s (3H each, CH_3), 1.64 m (1H, CH), 1.92 d.d (1H, *J* 13.5, 12.8 Hz), 2.13 d (1H, CH_2, *J* 12.8 Hz), 2.40–2.60 m (2H, C^6H_2), 2.91 s (1H, OH), 3.22 s (3H each, OCH_3), 4.09 s (1H, OCH), 4.26 br.s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.56 (CH_3), 22.65, 23.33 (*gem*-CH_3), 28.56 (C^4), 37.72 (C^6), 41.97 (C^5H), 49.12 (OCH_3), 74.96 ($C^{1'}$), 75.95 (C^3), 78.22 (C^2), 214.17 (C=O).

Methyl (3*R*,5*R*)-6-oxo-5-(triethylsilyloxy)-3-(1-chloro-1-methylethyl)heptanoate (XIV). To a stirred solution of 0.65 g (1.94 mmol) of compound **VIII** in 20 ml of anhydrous mixture MeOH–benzene, 1 : 1, was added 3.46 g (7.77 mmol) of lead tetraacetate. The reaction mixture was stirred for 15 min, then 3–4 drops of ethylene glycol and 10 ml of water was added, and the mixture was stirred for 10 min. The reaction product was extracted into EtOAc, the combined organic extracts were dried with $MgSO_4$, the solvent was evaporated. The residue was subjected to column chromatography on silica gel (eluent EtOAc–petroleum ether, 1 : 5). Yield 0.62 g (88%). Colorless oily fluid, $[\alpha]_D^{20}$ +9.42° (*C* 3.81, $CHCl_3$). IR spectrum, ν, cm^{-1}:

2955, 2912, 2878, 1735, 1717, 1458, 1435, 1415, 1373, 1352, 1294, 1240, 1194, 1159, 1113, 1105, 1011, 978, 889, 826, 743, 729, 594, 571, 516. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.58 q (6H, CH_2Si, *J* 7.76 Hz), 0.93 t (9H, CH_3, *J* 7.74 Hz), 1.48 s and 1.53 s (3H each, *gem*-CH_3), 2.15 s (3H each, C^7H_3), 1.58 d.d (1H, *J* 6.41, 2.21 Hz), 2.00 d.d.d (1H, C^4H_2, *J* 2.21, 6.41, ^2J 17.2 Hz), 2.24 m (1H, CH), 2.36 d.d (1H, *J* 4.76, 15.93 Hz) and 2.60 d.d (1H, C^2H_2, *J* 6.41, 15.92 Hz), 3.66 s (3H each, OCH_3), 4.05 d.d (1H, OCH, *J* 6.6, 7.5 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 4.63 ($SiCH_2$), 6.71 (CH_3), 24.65 (C^7H_3), 30.11, 30.91 (*gem*-CH_3), 36.55 (C^4), 36.78 (C^2), 43.22 (C^3), 51.77 (OCH_3), 73.93 ($C^{1'}$), 77.89 (C^5), 173.11 ($CO_2M\varepsilon$), 211.15 (C=O).

Methyl (3*R*,5*R*,6*E*)-6-methyl-7-(2-methyl-1,3-thiazol-4-yl)-5-(triethylsiliyloxy)-3-(1-chloro-1-methylethyl)hept-6-enoate (XVI). To a solution of 0.09 g (0.41 mmol) of phosphonate **XV** in 5 ml of anhydrous THF at –78°C under an argon atmosphere was added under stirring 0.3 ml (9.0 mmol) of 3 N solution of BuLi in hexane. The reaction mixture was stirred for 30 min, then at –78°C was added dropwise a solution of 0.1 g (0.27 mmol) of ketone **XIV** in 5 ml of THF. The reaction mixture was warmed to room temperature and stirred over 2 h. Then a saturated NH_4Cl solution was added, THF was distilled off from the water layer, the reaction products were extracted into EtOAc (3×10 ml), the combined extracts were dried with $MgSO_4$ and evaporated. The residue was subjected to column chromatography on silica gel (eluent EtOAc–petroleum ether, 1 : 3). Yield 0.034 g (45%). Colorless oily fluid. $[\alpha]_D^{20}$ –13.3° (*C* 0.9, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2953, 2912, 2875, 1732, 1458, 1436, 1414, 1361, 1238, 1165, 1112, 1076, 1004, 974, 844, 741, 729, 686. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.59 q (6H, CH_2Si, *J* 7.76 Hz), 0.94 t (9H, CH_3, *J* 7.5 Hz), 1.51 s, 1.55 s (3H each, *gem*-CH_3), 1.55–1.72 m (1H, C^4H_2), 2.02 s (3H each, CH_3), 2.18–2.30 m (2H, C^4H_2, C^3H), 2.47 d.d (1H, *J* 4.14 and 16.29 Hz), 2.63 d.d (1H, C^2H_2, *J* 7.98 and 16.29 Hz), 2.71 s (3H each, $CH_{3thiazole}$), 3.66 C (3H each, OCH_3), 4.24 t (1H, OCH, *J* 6.7 Hz), 6.47 C (1H, =CH), 6.96 C (1H, $=CH_{thiazole}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 4.74 ($SiCH_2$), 6.84 (CH_3), 13.36 (CH_3), 19.17 ($CH_{3thiazole}$), 30.35, 30.69 (*gem*-CH_3), 37.05 (C^4), 38.41 (C^2), 44.08 (C^3), 51.67 (OCH_3), 74.47 ($C^{1'}$), 78.21 (C^5), 115.42 (C^7), 120.24 ($=CH_{thiazole}$), 141.19 (C^6), 152.89 ($C^4{}_{thiazole}$), 164.32 ($C^2{}_{thiazole}$), 173.42 (CO_2Me).

Methyl (1*R*,3*R*)-2,2-dimethyl-3-[(2*R*,3*E*)-3-methyl-4-(2-methyl-1,3-thiazol-4-yl)-2-(triethylsilyloxy)but-3-en-1-yl]cyclopropane-carboxylate (XVII). To a solution of 0.03 g (0.065 mmol) of ester **XVI** in 2 ml of THF at –78°C was added dropwise 0.06 ml (0.12 mmol)of 2 M solution of sodium hexamethyldisilazide in THF. The reaction mixture was stirred at this temperature over 1.5 h, then it was warmed to the room temperature, decomposed by adding a saturated NH_4Cl solution, THF was distilled off, the reaction products were extracted into EtOAc. The combined extracts were dried with $MgSO_4$ and evaporated. The residue was subjected to column chromatography on silica gel (eluent EtOAc–petroleum ether, 1 : 9). Yield 0.01 g (36%). Colorless oily fluid, $[\alpha]_D^{20}$ –165.0° (*C* 0.867, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.60 q (6H, CH_2Si, *J* 7.76 Hz), 0.95 t (9H, CH_3, *J* 7.76 Hz), 1.12 s, 1.19 s (3H each, *gem*-CH_3), 1.45 d.d.d (1H, $C^{3H\,each}$, *J* 6.7, 6.5, 7.0 Hz), 1.62 d.d.d (1H, $C^{1'}H_2$, *J* 5.7, 7.5, ^2J 14.0 Hz), 1.71 m 1H, C^1H, *J* 7.0 Hz), 1.74 d.d.d (1H, $C^{1'}H_2$, *J* 6.2, 6.5, 14.0 Hz), 2.0 s (3H each, CH_3), 2.71 s (3H each, $CH_{3thiazole}$), 3.61 s (3H each, OCH_3), 4.18 d.d (1H, OCH, *J* 6.2 and 5.7 Hz), 6.47 s (1H, =CH), 6.92 s (1H, $=CH_{thiazole}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 4.76 ($SiCH_2$), 6.87 (CH_3), 13.98 (CH_3), 19.20 ($CH_{3thiazole}$), 20.79, 21.51 (*gem*-CH_3), 27.32 (C^2), 30.53 (C^1), 32.48 (C^3), 35.84 ($C^{1'}$), 51.21 (OCH_3), 78.39 ($C^{2'}$), 115.09 ($=CH_{thiazole}$), 118.79 ($C^{4'}$), 141.99 ($C^{3'}$), 153.08 ($C^4{}_{thiazole}$), 164.29 ($C^2{}_{thiazole}$), 173.13 (CO_2Me). Mass spectrum, *m/z*: 424 $[M + H]^+$, 292 $[M + H - HOSiEt_3]^+$.

The study was carried out under a financial support of the Federal Agency on Science and Innovations and of the Council of grants of the President of the Russian Federation (project NSh-1725.2008.3).

REFERENCES

1. Hцfle, G., Bedorf, N., Steinmetz, H., Schomburg, D., Gerth, K., and Reichenbach, H., *Angew. Chem., Int. Ed.,* 1996, p. 1567.
2. Watkins, E.B., Chittiboyina, A.G., and Avery, M.A., *Eur. J. Org. Chem*., 2006, p. 4071.
3. Feyen, F., Cachoux, F., Gertsch, L., Wartmann, M., and Altmann, K.-H., *Acc. Chem. Res*., 2008, vol. 41, p. 21.
4. Sachoux, F., Izarno, T., Wartmann, M., and Altmann, K.-H., *Synlett*., 2006, p. 1384.
5. Nicolaou, K.C., Ritzen, A., Namoto, K., Buey, R.M., Diaz, J.F., Andreu, J.M., Wartmann, M., Altmann, K.-H., O-Brate, A., and Giannakakou, P., *Tetrahedron*, 2002, vol. 58, p. 6413.
6. Wolinsky, J., Hamsher, J.J., and Hutchins, R.O., *J. Org. Chem*., 1970, vol. 35, p. 207.
7. Mass, D.D., Blagg, M., and Wiemer, D.F., *J. Org. Chem*., 1984, vol. 49, p. 853.
8. Selezneva, N.K., *Cand. Sci. (Chem.) Dissertation*, 2008, Ufa.
9. Van, Rheenen, V., Kelly, R.C., and Cha, D.Y., *Tetrahedron Lett.,* 1976, p. 1973.
10. Baer, E., *J. Am. Chem. Soc*., 1942, vol. 64, p. 1416.