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Stereoselective Synthesis of Steroids and Related Compounds, V[1]

Synthesis of (±)-Chokol A by a Tandem Michael-Addition/Dieckmann Cyclization

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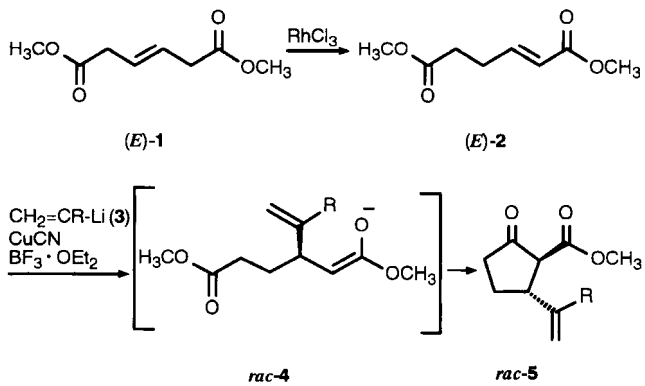
A total synthesis of (±)-chokol A (*rac*-**12**) was accomplished in five steps by starting from the α,β-unsaturated ester (*E*)-**2** in an overall yield of 24%. The key step of this synthesis is the tandem conjugate addition/Dieckmann cyclization of the cuprate derived from vinyl bromide **9** with the α,β-unsaturated ester (*E*)-**2**.

(−)-Chokol A is a fungitoxic modified sesquiterpene isolated from the stromata of timothy grass *Phleum pratense* infected by the pathogenic fungus *Epichloe typhina*. Isolated for the first time in 1985 by Yoshihara et al.[2], (−)-chokol A and the more active chokols B, C[3], D and G[4] have recently received special attention due to their fungitoxic properties[5].

So far, two syntheses for racemic chokol A (**12**) and two enantioselective ones have been described. In 1986 Oppolzer et al. reported on a 12-step synthesis of racemic chokol A[6] with an overall yield of 3%. Key step of this synthesis was a stereoselective magnesium-ene reaction. In 1988 Lawler and Simpkins synthesized (±)-chokol A (**12**) in six steps via a conjugate addition/alkylation reaction in an overall yield of 32%[7]. Unfortunately, the use of toxic and carcinogenic HMPTA could not be avoided. Moreover, the conjugate addition step remains problematic since the yield varies between 30−52%. In 1987 Mash presented the first asymmetric synthesis of (−)-chokol A[8]. Key step of this synthesis was a diastereoselective cyclopropanation of a chiral ketal. The overall yield was 9% over 13 steps with an enantiomeric excess of approximately 80%. The last synthesis of (−)-chokol A was described by Suzuki et al. in 1992[9]. They converted the well-established (*R*)-2,3-*O*-isopropylideneglyceraldehyde[10] in 21 steps into (−)-chokol A with an overall yield of 4%.

The successful synthesis of (±)-chokol A (*rac*-**12**) described in this paper is based on a tandem addition/Dieckmann cyclization reaction of organometallic reagents with the α,β-unsaturated diester (*E*)-**2**[11,12,13]. (*E*)-**2** has been previously prepared by palladium-catalyzed dimerization of methyl acrylate[12] or by a sodium ethoxide-induced equilibration of ester (*E*)-**1**[14]. In our hands, this isomerization afforded a 57:35:8 mixture of (*E*)-**2**, (*E*)-**1** and the 1,4-methanol adduct of (*E*)-**2** which could not be separated by chromatography. Therefore, the rhodium-catalyzed isomerization[15] of (*E*)-**1** was investigated. In almost quantitative yield a 92:4:2:2 mixture of (*E*)-**2** and isomers was obtained. Obviously, this ratio reflects the thermodynamical equilibrium ratio[12].

Since the results presented in this communication are only preliminary studies of asymmetric syntheses of the chokols the addition of vinylmagnesium bromide in the presence of $BF_3 \cdot Et_2O$ was investigated according to protocols from Helmchen et al.[16] and Oppolzer et al.[17] for their successful asymmetric 1,4-addition reactions. The tandem conjugate addition/Dieckmann cyclization reaction of vinylmagnesium bromide with α,β-unsaturated ester (*E*)-**2** in the presence of copper(I) bromide and $BF_3 \cdot Et_2O$ afforded the β-keto ester *rac*-**5a**[12] in only 14% yield. Therefore, the use of vinyllithium in the 1,4-addition process was required. In our hands, the most efficient procedure for the preparation of vinyllithium compounds is the transmetalation of the corresponding tetravinyltin derivatives with methyllithium. Tetramethyltin, which is liberated in this process, can be easily removed by evaporation after workup of the reaction mixture.



3 - 5	R	Yield of 5 (%)
a	H	81
b	CH_3	52
c	$(CH_2)_3OSi\,tBuPh_2$	77

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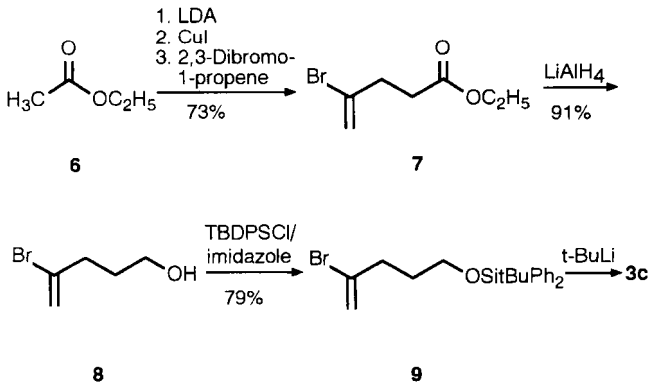
Consequently, 1 equivalent of tetravinyltin[18] was treated with 4 equivalents of methyllithium and the formed vinyllithium was allowed to react with 2 equivalents of tri-*n*-butylphosphane, 2 equivalents of copper(I) iodide, 2 equivalents of $BF_3 \cdot Et_2O$, and subsequently with 1 equivalent of (*E*)-**2** to afford, after aqueous workup and chromatography, 81% of the β-keto ester *rac*-**5a**.

Still, this reaction remains cumbersome since 2 equivalents of tri-*n*-butylphosphane have to be used for the stabilization of the organocuprate and have to be removed later on by chromatography. Therefore, the use of cyanide-stabilized cuprates[19] was investigated. 1.25 equivalents of tetraisopropenyltin were treated with 5 equivalents of methyllithium and allowed to react with 5 equivalents of copper(I) cyanide, 5 equivalents of $BF_3 \cdot Et_2O$, and subsequently with 1 equivalent of (*E*)-**2** to afford, after aqueous workup and chromatography, 52% of the 3-isopropenyl-substituted β-keto ester *rac*-**5b**[20].

Encouraged by this result, a synthesis of the vinyllithium compound **3c** was performed basically according to Simpkins' protocol[7]. Ethyl acetate (**6**) was lithiated with LDA and alkylated with 2,3-dibromo-1-propene in the presence of 1.5 equivalents of copper(I) iodide to afford ethyl 4-bromo-4-pentenoate (**7**) in 73% yield. After reduction of the ester group with lithium aluminum hydride to alcohol **8** (91%) and subsequent protection of the alcohol function as its *tert*-butyldiphenylsilyl ether, the vinyl bromide **9** was obtained in 79% yield.

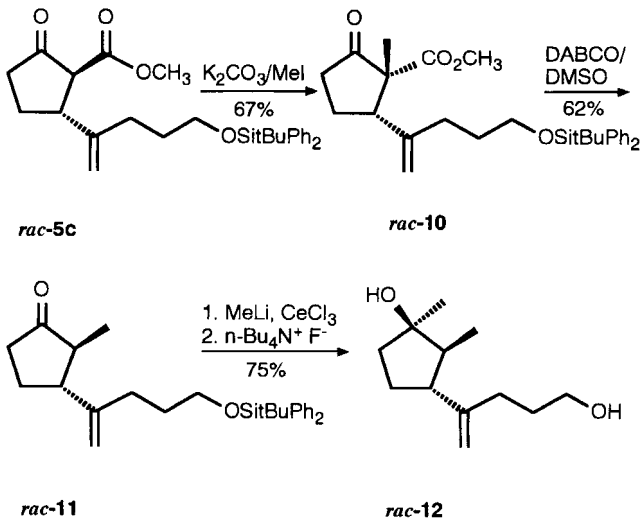
The transformation of vinyl bromide **9** into its corresponding tin derivative via a Grignard reaction turned out to be problematic. This Grignard reaction occurred sluggishly and consequently only 12% of the tin derivative could be isolated. Therefore, a bromine lithium exchange of vinyl bromide **9** was attempted with 2 equivalents of *tert*-butyllithium[7,21].



6 **7** **8** **9**

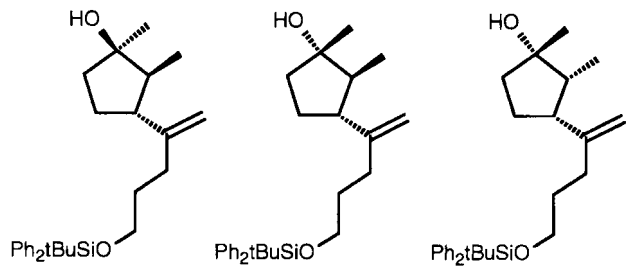
The addition of a cuprate, prepared from 10 equivalents of the vinyllithium compound **3c**, 10 equivalents of copper(I) cyanide and 10 equivalents of $BF_3 \cdot Et_2O$, to the α,β-unsaturated ester (*E*)-**2** afforded the β-keto ester *rac*-**5c** in 77% yield. When 2, 3 or 5 equivalents of this cuprate were used for the conjugate addition the β-ketoester *rac*-**5c** could be isolated in only 25%, 31% or 37% yield.

Finally, β-keto ester *rac*-**5c** could be easily converted into (±)-chokol A (*rac*-**12**) in four steps. Methylation of β-keto



rac-**5c** *rac*-**10** *rac*-**11** *rac*-**12**

ester *rac*-**5c** with methyl iodide/potassium carbonate in acetone afforded β-keto ester *rac*-**10** in 67% yield as a 4:1 mixture of C-2 epimers. Demethoxycarbonylation of β-keto ester *rac*-**10** and its corresponding C-2 epimer to the cyclopentanone *rac*-**11** was best achieved by using DABCO[22]. Cyclopentanone *rac*-**11** was isolated in 62% yield as a 94:6 mixture of *rac*-**11** and its *cis* isomer. When magnesium bromide or lithium bromide were used for the demethoxycarbonylation, the yield of *rac*-**11** dropped down to 19%.



rac-**13a** *rac*-**13b** *rac*-**13c**

The introduction of the C-1 methyl group was achieved by using an organocerium reagent by analogy with Mash's[8] and Suzuki's[9] protocols. Cyclopentanone *rac*-**11** was treated with an organocerium reagent prepared from 2.6 equivalents of anhydrous cerium(III) chloride and 2.4 equivalents of methyllithium to afford the alcohols *rac*-**13** as a 77:16:7 mixture of diastereomers. According to Suzuki et al.[9] the diastereomers *rac*-**13a** and *rac*-**13b** result from an α- or a β-attack of the organocerium reagent on the carbonyl group of ketone *trans*-**11**. The third diastereomer *rac*-**13c** evidently results from a β-attack of the organocerium reagent on the carbonyl group of ketone *cis*-**11**, since a 94:6 mixture of *trans*/*cis*-**11** was applied to this reaction. Since these three diastereomers were not separable by chromatography, this mixture of diastereomers was submitted directly to desilylation with tetra-*n*-butylammonium fluoride to afford 76% of (±)-chokol A (*rac*-**12**) diastereomerically pure after chromatography. The spectroscopical data

of *rac*-**12** are in full agreement with the data reported for the natural product[2].

The synthesis of racemic chokol A described in this communication proceeds in only five steps starting from the α,β-unsaturated ester (*E*)-**2** with an overall yield of 24%. Furthermore, this method allows us to perform an enantioselective synthesis since an asymmetric conjugate addition to a diester like (*E*)-**2** with a chiral alcohol component of the α,β-unsaturated ester function should yield after cyclization and transesterfication the β-keto ester **5c** virtually enantiomerically pure[16,17]. In first preliminary studies an asymmetric addition of a cuprate derived from the organolithium compound **3c** to a diester containing the Helmchen auxiliary[16] as a chiral component could be achieved in 79% yield with a diastereomeric excess of >95%[23]. Another approach towards (−)-chokol A which is under current investigation applies cuprates bearing a chiral ligand for the conjugate addition to diester (*E*)-**2**[24].

A drawback of this synthesis and of syntheses accomplished before[7,8,9] appears to be the low diastereoselectivity observed in the addition of the methylcerium reagent to the keto group at C-1. Therefore, the design and synthesis of more selective organocerium reagents seem to be necessary[1]. The evaluation of methylcerium dichloride and its chiral modifications in C−C bond forming reactions is under current investigation.

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Experimental

Infrared (IR) spectra: Perkin-Elmer 298 spectrometer. – NMR spectra: Varian XL 200, VXR 200 or Bruker AMX 300 spectrometer for ^1H and ^{13}C NMR and a Bruker MSL 400 spectrometer for ^{119}Sn NMR. Chemical shifts are given in δ values by using tetramethylsilane as an internal standard for ^1H and ^{13}C NMR and tetramethyltin for ^{119}Sn NMR. – Mass spectra: Varian MAT 731 or 311 A spectrometers. – TLC analyses: Polygram Sil G/UV_{254} silica gel plates. Silica gel (30−60 μm) from Macherey and Nagel was used for flash chromatography. – Combustion analyses: Microanalytical laboratory of the University of Göttingen. – All reactions were carried out under argon. All reagents were purified and dried if necessary before use. THF was freshly distilled from $LiAlH_4$ prior to use. Et_2O was distilled from sodium. Solvents, used for organometallic reactions, were degassed prior to use.

Dimethyl(E)-3-Hexene-1,6-dioate (**1**): To a suspension of 10.0 g (70 mmol) of (*E*)-3-hexenedioic acid in 30 ml of methanol 1.5 g of H_2SO_4 was added, and the mixture was heated under reflux for 20 h. The solvent was removed in vacuo (50°C/10 Torr) and the residue dissolved in 50 ml of iced water and 50 ml of diethyl ether. The layers were separated, and the aqueous layer was reextracted twice with 50-ml portions of diethyl ether. The combined organic layers were extracted once with 50 ml of an aqueous $NaHCO_3$ solution and twice with 50-ml portions of H_2O and dried with $MgSO_4$. The solvent was removed in vacuo (30°C/10 Torr) and the crude product **1** purified by bulb-to-bulb distillation. 8.54 g (71%) of the diester **1** was obtained as a colorless liquid. – B.p. 75−80°C/0.01 Torr. – IR (neat): $\tilde{\nu}$ = 1735 cm^{-1} (C=O). – ^1H NMR (200 MHz, $CDCl_3$): δ = 3.04−3.16 (m; 4H, CH_2), 3.69 (s; 6H, OCH_3), 5.66−5.74 (m; 2H, CH=CH). – $C_8H_{12}O_4$ (172.2): calcd. C 55.76, H 7.02; found C 55.83, H 7.09.

Dimethyl (E)-2-Hexene-1,6-dioate (**2**): To a solution of 8.54 g (49.6 mmol) of diester **1** in 60 ml of methanol 0.40 g (1.49 mmol) of rhodium trichloride trihydrate was added at room temp., and the solution was stirred in a sealed glas tube for 36 h at 100°C. During this period metallic rhodium precipitated like a mirror on the inside surface of the glass tube. The solution was filtered through a short pad of Celite in order to remove the catalyst and the Celite was rinsed with 70 ml of diethyl ether. The solvent was removed in vacuo (50°C/10 Torr) and the crude product **2** purified by bulb-to-bulb distillation. 8.39 g (>95%) of the diester **2** was obtained as a colorless liquid. A GC-MS analysis indicated a purity of 92%. All minor components proved to be isomers of **2**. – B.p. 75−80°C/0.01 Torr. – IR (neat): $\tilde{\nu}$ = 1730 (C=O), 1715 (C=CH−C=O), 1650 cm^{-1} (C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 2.36−2.58 [m; 4H, $(CH_2)_2$], 3.65 (s; 3H, 6-OCH_3), 3.69 (s; 3H, 1-OCH_3), 5.82 (ddd, $^3J_{trans}$ = 15.7 Hz, ^4J = 1.8 und 1.3 Hz; 1H, 2-H), 6.90 (dt, $^3J_{trans}$ = 15.7 Hz, ^3J = 6.6 Hz; 1H, 3-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.24 (C-5), 32.22 (C-4), 51.48 and 51.76 (OCH_3), 121.86 (C-2), 146.94 (C-3), 166.72 (C-1), 172.65 (C-6). – MS (70 eV): *m/z* (%) = 172 (1) [M^+], 140 (100) [$M^+ - CH_4O$], 113 (22) [$M^+ - CH_3COO$], 108 (63) [$M^+ - 2\ CH_4O$], 81 (54) [$M^+ - CH_3COO - CH_4O$]. – $C_8H_{12}O_4$ (172.2): calcd. C 55.76, H 7.02; found C 55.89, H 7.04.

Preparation of Tetraisopropenyltin: 2.41 g (98.8 mmol) of magnesium was suspended in 15 ml of THF at room temp., and 0.5 ml of 2-bromo-1-propene was added. When the formation of isopropenylmagnesium bromide started, which was indicated by precipitating magnesium bromide and increase in reaction temp. up to 30°C, a solution of additional 9.5 g (82.6 mmol overall) of 2-bromo-1-propene in 40 ml of THF was added dropwise with stirring in such a manner that the reaction temp. was maintained at about 60°C. After the addition of 2-bromo-1-propene was completed the reaction mixture was heated under reflux for 2 h. A solution of 3.81 g (14.6 mmol) of tin tetrachloride in 15 ml of isopentane was added at room temp. within 10 min, and stirring was continued under reflux for additional 19 h. Then 20 ml of aqueous 10% hydrochloric acid was added at 0°C with stirring. After the magnesium bromide was completely dissolved the layers were separated, and the aqueous layer was extracted twice with 50-ml portions of diethyl ether. The combined organic layers were reextracted with 30 ml of an aqueous $NaHCO_3$ solution and 30 ml of H_2O and dried with $MgSO_4$. The solvent was removed in vacuo (30°C/200 Torr), and the crude tetraisopropenyltin purified by distillation. 3.83 g (93%) of tetraisopropenyltin was obtained as a colorless liquid. – B.p. 81−83°C/10 Torr. – IR (neat): $\tilde{\nu}$ = 3020 (C=C−H), 1590 cm^{-1} (C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.88−2.16 (m, $^4J_{H/H}$ = 1.6 Hz, $^3J_{Sn/H}$ = 24.2 Hz; 3H, CH_3), 5.00−5.38 (m, $^2J_{H/H}$ = 2.8 Hz, $^4J_{H/H}$ = 1.3 Hz, $^3J_{Sn/H} \approx$ 36 Hz; 1H, H−C=C), 5.39−6.26 (m, $^2J_{H/H}$ = 2.8 Hz, $^4J_{H/H}$ = 1.7 Hz, $^3J_{Sn/H} \approx$ 80 Hz; 1H, H−C=C). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 26.93 ($^2J_{Sn/C}$ = 26.0 Hz, CH_3), 127.99 ($^2J_{Sn/C}$ = 16.7 Hz, C=CH_2), 147.22 ($^1J_{Sn/C}$ = 231.8 Hz, C=CH_2). – ^{119}Sn NMR (149.2 MHz, $CDCl_3$): δ = −145.08 ($^1J_{Sn/C}$ = 231.8 Hz, $^2J_{Sn/C-3}$ = 26.0 Hz, $^2J_{Sn/C-2}$ = 16.7 Hz). – MS (70 eV): *m/z* (%) = 283 (1) [M^+], 243 (100) [$M^+ - C_3H_5$], 203 (28) [$M^+ - 2\ C_3H_5$], 161 (30) [$M^+ - 3\ C_3H_5$], 120 (27) [Sn^+]. – $C_{12}H_{20}Sn$ (282.9): calcd. C 50.91, H 7.13; found C 51.05, H 7.17.

Preparation of Organolithium Compounds **3a** *and* **3b**. – *General Procedure:* 10 mmol of methyllithium (6.25 ml of a 1.64 N solution

in diethyl ether) was added dropwise with stirring at room temp. to a solution of 2.5 mmol of the tetraorganotin compound in 15 ml of diethyl ether and stirring was continued at ambient temp. for 1 h.

Preparation of Organolithium Compound **3c**: 40 mmol of *tert*-butyllithium (14.3 ml of a 2.8 N solution in pentane) was added dropwise with stirring at −90°C to a solution of 20 mmol of the vinyl bromide **9** in 40 ml of diethyl ether within 45 min and stirring was continued for 90 min.

Methyl trans-5-Oxo-2-vinylcyclopentanecarboxylate (*rac*-**5a**): 1.01 g (5 mmol) of tri-*n*-butylphosphane was added with stirring at room temp. to a suspension of 0.95 g (5 mmol) of copper(I) iodide in 10 ml of diethyl ether, and stirring was continued at ambient temp. for 1 h. A solution of 10 mmol of vinyllithium (**3a**) in diethyl ether, prepared from 0.57 g (2.5 mmol) of tetravinyltin and 10 mmol of methyllithium according to the general procedure given above, was added dropwise via a syringe with stirring at −70°C. The clear yellow solution was allowed to warm up to −40°C within 30 min and then cooled down again to −70°C. 0.65 ml (5 mmol) of $BF_3 \cdot Et_2O$ and after 15 min a solution of 0.44 g (2.5 mmol) of ester (*E*)-**2** in 5 ml of diethyl ether were added with stirring at −70°C. The reaction mixture was allowed to warm up to −40°C within 12 h, then 20 ml of an aqueous NH_4Cl solution was added and the reaction mixture was allowed to warm up to room temp. Solid material was removed by filtration, the layers were separated, and the aqueous layer was extracted three times with 20-ml portions of diethyl ether. The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo (10°C/15 Torr). After flash chromatography (silica gel, 50 g) of the residue with ethyl acetate/pentane (1:8) 0.34 g (81%) of *rac*-**5a** was obtained as a colorless oil; R_f = 0.20, diastereomeric purity: >95%. − IR (neat): $\tilde{\nu}$ = 3065 (C=C−H), 1750 (C=O), 1735 (O−C=O), 1635 cm^{-1} (C=C). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.58−1.84 and 2.17−2.58 (2 m; 4H, cyclopentyl H), 3.03 (dd, *J* = 11.5 and 1.0 Hz; 1H, 1-H), 3.13−3.34 (m; 1H, 2-H), 3.77 (s; 3H, OCH_3), 5.10 (ddd, J_{cis} = 10.0 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz; 1H, CH=CH_2), 5.17 (ddd, J_{trans} = 17.0 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz; 1H, CH=CH_2), 5.85 (ddd, J_{trans} = 17.0 Hz, J_{cis} = 10.0 Hz und *J* = 6.5 Hz; 1H, C*H*=CH_2). − ^{13}C NMR (20 MHz, $CDCl_3$): δ = 27.22 and 38.03 (CH_2), 44.93 (C-2), 52.30 (OCH_3), 60.76 (C-1), 115.79 (CH=*C*H_2), 138.42 (*C*H=CH_2), 169.18 (O−C=O), 210.57 (C-5). − $C_9H_{12}O_3$ (168.1): calcd. C 64.25, H 7.20; found C 64.03, H 7.12.

Methyl trans-2-Isopropenyl-5-oxocyclopentanecarboxylate (*rac*-**5b**): A solution of 10 mmol of isopropenyllithium (**3b**) in diethyl ether, which was prepared from 0.71 g (2.5 mmol) of tetraisopropenyltin and 10 mmol of methyllithium according to the general procedure given above, was added dropwise via a syringe with stirring at −60°C to a suspension of 0.90 g (10 mmol) of copper(I) cyanide in 20 ml of diethyl ether and stirring was continued at −30°C for 10 min. The clear yellow solution was cooled down to −70°C, then 1.28 ml (10 mmol) of $BF_3 \cdot Et_2O$ and after 15 min a solution of 0.34 g (2.0 mmol) of ester (*E*)-**2** in 15 ml of diethyl ether were added with stirring at −70°C. After the reaction mixture was allowed to warm up to room temp. within 12 h, 30 ml of an aqueous NH_4Cl solution was added. Solid material was removed by filtration through a short pad of Celite, the layers were separated and the aqueous layer was extracted twice with 20-ml portions of diethyl ether. The combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo (10°C/200 Torr). After flash chromatography (silica gel, 60 g) of the residue with diethyl ether/petroleum ether (2:3) 0.19 g (52%) of *rac*-**5b** was obtained as a colorless oil; R_f = 0.27, diastereomeric purity: >95%. − IR (neat): $\tilde{\nu}$ = 1750 (C=O), 1720 cm^{-1} (O−C=O). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.76 (s; 3H, CH_3=C), 2.06−2.94 (m; 5H, cyclopentyl H), 3.08−3.24 (m; 1H, 1-H), 3.75 (s; 3H, OCH_3), 4.70−4.86 (m; 2H, C=CH_2). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.37 (*C*H_3=C), 26.34 (C-3), 38.33 (C-4), 47.70 (C-2), 52.46 (OCH_3), 59.68 (C-1), 111.14 (C=*C*H_2), 144.15 (*C*=CH_2), 169.54 (O−C=O), 211.01 (C-5). − MS (70 eV): *m/z* (%) = 182 (26) [$M^+ - CH_4O$], 123 (85) [$M^+ - COOCH_3$], 67 (100) [$C_5H_7^+$], 55 (58) [$C_3H_3O^+$], 41 (97) [$C_3H_5^+$]. − $C_{10}H_{14}O_3$ (182.2): calcd. C 65.85, H 7.74; found C 65.78, H 7.65.

Methyl trans-2-{1-[3-(tert-Butyldiphenylsilyloxy)propyl]vinyl}-5-oxocyclopentanecarboxylate (*rac*-**5c**): A solution of 20 mmol of the organolithium compound **3c** in diethyl ether, which was prepared from 8.40 g (20 mmol) of the vinyl bromide **9** and 40 mmol of *tert*-butyllithium according to the procedure given above, was added dropwise via a cannula with stirring at −70°C to a suspension of 1.80 g (20 mmol) of copper(I) cyanide in 50 ml of diethyl ether and stirring was continued at −30°C for about 2 h until all of the copper(I) cyanide was dissolved. The clear yellow solution was cooled down to −70°C, 2.55 ml (20 mmol) of $BF_3 \cdot Et_2O$ and after 15 min a solution of 0.34 g (2.0 mmol) of ester (*E*)-**2** in 20 ml of diethyl ether were added with stirring at −70°C. After the reaction mixture was allowed to warm up to −10°C within 12 h and to room temp. within 3 h, 30 ml of an aqueous NH_4Cl solution was added. Solid material was removed by filtration through a short pad of Celite, the layers were separated, and the aqueous layer was extracted twice with 20-ml portions of diethyl ether. The combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo (30°C/10 Torr). After flash chromatography (silica gel, 220 g) of the residue with diethyl ether/petroleum ether (1:2) 0.71 g (77%) of *rac*-**5c** was obtained as a colorless oil; R_f = 0.38, diastereomeric purity: >95%. − IR (neat): $\tilde{\nu}$ = 3060−3030 (C=C−H), 1755 (C=O), 1730 (O−C=O), 1650 cm^{-1} (C=C). − ^1H NMR (200 MHz, $CDCl_3$): δ = 1.04 [s; 9H, $C(CH_3)_3$], 1.56−1.90 (m; 4H, 3-H and 2′-H), 2.09−2.55 (m; 4H, 4-H and 1′-H), 3.14−3.24 (m; 2H, 1-H and 2-H), 3.67 (t, *J* = 6.3 Hz; 2H, OCH_2), 3.71 (s; 3H, OCH_3), 4.82 (br. s; 2H, C=CH_2), 7.33−7.42 (m; 6H, *m*- and *p*-phenyl H), 7.61−7.67 (m; 4H, *o*-phenyl H). − ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.17 [*C*$(CH_3)_3$], 26.81 [$C(C{H_3})_3$], 26.87 (C-2′), 30.43 and 30.80 (C-3 and C-1′), 38.34 (C-4), 46.57 (C-2), 52.43 (OCH_3), 59.94 (C-1), 63.25 (C-3′), 109.44 (C=*C*H_2), 127.58 (*m*-phenyl C), 129.55 (*p*-phenyl C), 133.85 (phenyl C), 135.50 (*o*-phenyl C), 148.34 (*C*=CH_2), 169.45 (O−C=O), 211.01 (C-5). − MS (70 eV): *m/z* (%) = 464 (1) [M^+], 407 (12) [$M^+ - CH_4O$], 283 (63) [$C_2H_4OSiPh_2tBu^+$], 199 (100) [Ph_2SiOH^+]. − $C_{28}H_{36}O_4Si$ (464.7): calcd. C 72.37, H 7.81; found C 72.48, H 7.88.

Ethyl 4-Bromo-4-pentanoate (**7**): To a solution of 0.12 mol of *n*-butyllithium (75.2 ml of a 1.67 N solution in hexane) in 100 ml of THF 12.2 g (0.12 mol) of diisopropylamine was added with stirring at −70°C and stirring was continued at room temp. for 10 min. The solution was cooled down to −70°C and 9.6 g (0.11 mol) of ethyl acetate (**6**) was added, and stirring was continued for 15 min. This solution of the lithium enolate of **6** was added via a cannula to a suspension of 31.2 g (0.17 mol) of copper(I) iodide in 300 ml of THF at −50°C, and stirring was continued at −30°C for 10 min. To this dark green solution 26.2 g (0.13 mol) of 2,3-dibromo-1-propene was added at −50°C, and stirring was continued at −30°C for 1 h. The reaction mixture was allowed to warm to room temp. and then poured into a mixture of 500 ml of a saturated aqueous NH_4Cl solution and 100 ml of an aqueous ammonia solution with stirring. The layers were separated, and the ethereal layer was extracted twice with 200-ml portions of H_2O. The solvent was

removed in vacuo (30°C/20 Torr) and the residue dissolved in 100 ml of diethyl ether. This heterogeneous solution was extracted with 20 ml of 1 N hydrochloric acid, twice with 20-ml portions of H_2O, then with 20 ml of an aqueous $NaHCO_3$ solution, once again with 20 ml of H_2O and dried with $MgSO_4$. The diethyl ether was removed in vacuo (30°C/20 Torr) and after bulb-to-bulb distillation of the residue 16.5 g (73%) of ester **7** was obtained as a colorless liquid; R_f = 0.50 (diethyl ether/petroleum ether, 1:4). – B.p. 90°C/10 Torr. – IR (neat): $\tilde{\nu}$ = 3085 (C=C–H), 1730 (O–C=O), 1625 cm^{-1} (C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.1 Hz; 3H, OCH_2CH_3), 2.57 (dt, J = 7.5 Hz and 1.2 Hz; 2H, 3-H), 2.77 (t, J = 7.5 Hz; 2H, 2-H), 4.18 (q, J = 7.1 Hz; 2H, OCH_2), 5.44 (d, ^2J = 1.7 Hz; 1H, HC=C), 5.63 (dt, ^2J = 1.7 Hz, ^4J = 1.2 Hz; 1H, HC=C). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 14.21 (OCH_2CH_3), 32.99 (C-3), 36.65 (C-2), 60.62 (OCH_2), 117.60 (C-5), 132.26 (C-4), 171.95 (C-1). – MS (70 eV): *m/z* (%) = 127 (55) [M^+ – Br], 99 (100) [M^+ – Br – C_2H_4]. – $C_7H_{11}BrO_2$ (207.0): calcd. C 40.57, H 5.35; found C 40.82, H 5.56.

4-Bromo-4-pentenol (**8**): A solution of 16.51 g (79.8 mmol) of ester **7** in 60 ml of diethyl ether was added dropwise at –10°C to a stirred suspension of 3.03 g (79.9 mmol) of lithium aluminum hydride in 100 ml of diethyl ether, and stirring was continued at –10°C for 1 h. Then about 10 ml of 1 N hydrochloric acid was added carefully, until the aluminum salts were dissolved completely. The layers were separated, the aqueous layer was extracted twice with 20-ml portions of diethyl ether, the combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo (20°C/10 Torr). Afte bulb-to-bulb distillation of the residue 12.0 g (91%) of alcohol **8** was obtained as a colorless liquid; R_f = 0.38 (diethyl ether/petroleum ether, 2:1). – B.p. 95–100°C/10 Torr. – IR (neat): $\tilde{\nu}$ = 3600–3100 (OH), 1625 cm^{-1} (C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.41 (br. s; 1H, OH), 1.81 (tt, J = 7.6 and 6.3 Hz; 2H, 2-H), 2.53 (dt, ^3J = 7.6 Hz, ^4J = 1.0 Hz; 2H, 3-H), 3.67 (t, J = 6.3 Hz; 2H, 1-H), 5.40 (d, ^2J = 1.3 Hz; 1H, HC=C), 5.60 (dt, ^2J = 1.3 Hz, ^4J = 1.0 Hz; 1H, HC=C). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 30.66 (C-2), 37.65 (C-3), 61.01 (C-1), 116.82 (C-5), 133.81 (C-4). – MS (70 eV): *m/z* (%) = 85 (72) [M^+ – Br], 67 (100) [M^+ – Br – H_2O]. – C_5H_9BrO (165.0): calcd. C 36.39, H 5.50; found C 36.52, H 5.71.

2-Bromo-5-(tert-butyldiphenylsilyloxy)-1-pentene (**9**): To a solution of 11.5 g (0.17 mol) of imidazole and 2.57 g (21.1 mmol) of 4-(dimethylamino)pyridine (DMAP) in 300 ml of DMF 22.0 g (80.0 mmol) of *tert*-butylchlorodiphenylsilane was added dropwise with stirring, and stirring was continued at room temp. for 45 min. Then 12.0 g (72.7 mmol) of alcohol **8** was added and stirring was continued for 48 h. The solvent was removed in vacuo (50°C/10 Torr) and the residue dissolved in 100 ml of diethyl ether. The layers were separated, the ethereal layer was extracted with 50-ml portions of 2 N HCl, an aqueous $NaHCO_3$ solution and an aqueous NaCl solution and dried with $MgSO_4$. The solvent was removed in vacuo (30°C/10 Torr) and after bulb-to-bulb distillation of the residue 24.1 g (79%) of the silyl-protected alcohol **9** was obtained as a colorless liquid; R_f = 0.40 (diethyl ether/petroleum ether, 1:50). – B.p. 150–160°C/0.02 Torr. – IR (neat): $\tilde{\nu}$ = 3060–3020 (aromat. C–H), 1950, 1880, 1815 and 1580 (aromat. C=C), 1640 cm^{-1} (C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.04 [s; 9H, $C(CH_3)_3$], 1.73 (tt, J = 6.5 Hz and 6.5 Hz; 2H, 4-H), 2.55 (t, J = 6.5 Hz; ^4J = 1.7 Hz; 2H, 3-H), 3.67 (t, J = 6.5 Hz; 2H, 5-H), 5.37 (d, ^2J = 1.6 Hz; 1H, HC=C), 5.53 (dt, ^4J = 1.7 Hz, ^2J = 1.6 Hz; 1H, HC=C), 7.33–7.42 (m; 6H, *m*- and *p*-phenyl H), 7.62–7.67 (m; 4H, *o*-phenyl H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.22 [$C(CH_3)_3$], 26.86 [$C(CH_3)_3$], 30.87 (C-4), 37.91 (C-3), 62.27 (C-5), 116.66 (C-2), 127.64 (*o*-phenyl C), 129.60 (*p*-phenyl C), 133.81 (phenyl C), 134.28 (C-1), 135.53 (*m*-phenyl C). – MS (70 eV): *m/z* (%) = 347 and 345 (55) [M^+ – C_4H_9], 263 and 261 (100) [Ph_2SiBr^+], 199 (37) [Ph_2SiOH^+], 77 (18) [$C_6H_5^+$]. – $C_{21}H_{27}BrOSi$ (420.4): calcd. C 62.56, H 6.75; found C 62.60, H 6.76.

Methyl cis-2-{1-[3-(tert-Butyldiphenylsilyloxy)propyl]vinyl}-1-methyl-5-oxocyclopentanecarboxylate (*rac*-**10**): A suspension of 0.67 g (1.44 mmol) of β-keto ester *rac*-**5c**, 0.27 g (1.95 mmol) of K_2CO_3 and 0.14 ml (2.23 mmol) of methyl iodide in 10 ml of acetone was stirred at room temp. for 5 d. A TLC analysis indicating that starting material *rac*-**5c** was not completely consumed at this point. Therefore, 50 mg of K_2CO_3 and 0.05 ml of methyl iodide were added, and stirring was continued at room temp. for additional 24 h. The solvent was removed in vacuo (30°C/10 Torr) and the residue dissolved in 20 ml of diethyl ether and 10 ml of H_2O. The layers were separated, the aqueous layer was extracted twice with 10-ml portions of diethyl ether and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo (30°C/10 Torr) and after flash chromatography (silica gel, 75 g) of the residue with diethyl ether/petroleum ether (1:3) 0.46 g (67%) of β-keto ester *rac*-**10** was obtained as a colorless oil; R_f = 0.39, diastereomeric ratio *cis*:*trans* = 4:1. – IR (neat): $\tilde{\nu}$ = 3075–3010 (aromat. C–H), 1745 (C=O), 1725 (O–C=O), 1630 (C=C), 1580 cm^{-1} (aromat. C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.05 [s; 9H, $C(CH_3)_3$], 1.40 (s; 3H, CH_3), 1.66–2.70 (m; 9H, 2-H, 3-H, 4-H, 1′-H and 2′-H), 3.56 (s; 3H, OCH_3), 3.67 (t, J = 6.3 Hz; 2H, OCH_2), 4.84 and 4.89 (2 br. s; 2H, $C=CH_2$), 7.34–7.43 (m; 6H, *m*- and *p*-phenyl H), 7.61–7.67 (m; 4H, *o*-phenyl H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.14 [$C(CH_3)_3$], 20.13 (CH_3), 24.54 (C-2′), 26.79 [$C(CH_3)_3$], 30.92 and 32.47 (C-3 and C-1′), 37.61 (C-4), 51.79 (C-2), 53.88 (OCH_3), 60.01 (C-1), 63.30 (C-3′), 111.04 ($C=CH_2$), 127.56 (*m*-phenyl C), 129.53 (*p*-phenyl C), 133.81 (phenyl C), 135.48 (*o*-phenyl C), 146.99 ($C=CH_2$), 170.72 (O–C=O), 215.64 (C-5). – MS (70 eV): *m/z* (%) = 421 (11) [M^+ – C_4H_9], 389 (1) [M^+ – C_4H_9 – CH_4O], 199 (100) [Ph_2SiOH^+]. – $C_{29}H_{38}O_4Si$ (478.4): calcd. C 72.81, H 8.01; found C 72.98, H 7.96.

trans-3-{1-[3-(tert-Butyldiphenylsilyloxy)propyl]vinyl}-2-methylcyclopentanone (*rac*-**11**): A solution of 0.22 g (1.5 mmol) of DABCO in 5 ml of DMSO was preheated to 120°C. At this temp. a solution of 0.20 g (0.42 mmol) of β-keto ester *rac*-**10** in 1 ml of DMSO was added and the progress of the reaction was monitored by TLC analysis. After 8 h the reaction mixture was cooled down to room temp. and 15 ml of pentane, 10 ml of diethyl ether and 10 ml of 1 N hydrochloric acid were added.The layers were separated, the aqueous layer was extracted twice with 25-ml portions of diethyl ether, and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo (30°C/10 Torr) and after flash chromatography (silica gel, 35 g) of the residue with diethyl ether/petroleum ether (1:4) 0.11 g (62%) of the 3-substituted 2-methylcyclopentanone *rac*-**11** was obtained as a colorless oil; R_f = 0.45 (diethyl ether/petroleum ether, 1:1), diastereomeric ratio *cis*:*trans* = 6:94. – IR (neat): $\tilde{\nu}$ = 3050–3030 (aromat. C–H), 1730 (C=O), 1630 (C=C), 1580 cm^{-1} (aromat. C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.02 (d, J = 6.7 Hz; 3H, CH_3), 1.05 [s; 9H, $C(CH_3)_3$], 1.59–2.50 (m; 10H, 2-H, 3-H, 4-H, 5-H, 1′-H and 2′-H), 3.70 (t, J = 6.2 Hz; 2H, OCH_2), 4.84 (m; 2H, $C=CH_2$), 7.32–7.43 (m; 6H, *m*- and *p*-phenyl H), 7.62–7.74 (m; 4H, *o*-phenyl H). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 12.41 (CH_3), 19.18 [$C(CH_3)_3$], 26.83 [$C(CH_3)_3$], 27.41, 29.81 and 31.07 (C-4, C-1′ and C-2′), 37.30 (C-5), 48.13 (C-2), 51.34 (C-3), 63.39 (C-3′), 109.32 ($C=CH_2$), 127.59 (*m*-phenyl C), 129.56 (*p*-phenyl C), 133.90 (phenyl C), 135.53 (*o*-phenyl C), 149.19 ($C=CH_2$), 220.22 (C-1). – MS (70 eV): *m/z* (%) = 363 (5) [M^+ – C_4H_9], 45 (100) [$C_2H_5O^+$]. – $C_{27}H_{36}O_2Si$ (420.7): calcd. C 77.09, H 8.63; found C 77.20, H 8.52.

3-{1-[3-(tert-Butyldiphenylsilyloxy)propyl]vinyl}-1,2-dimethylcyclopentanol (*rac*-**13**): 0.20 g (0.54 mmol) of $CeCl_3 \cdot 7\ H_2O$ was powdered and dried at 140°C/0.05 Torr for 3 h. This anhydrous cerium(III) chloride was suspended in 3 ml of THF, and the suspension was stirred at room temp. for 2 h. At −70°C 0.5 mmol of methyllithium (0.30 ml of a 1.64 N solution in diethyl ether) was added and stirring was continued for 30 min. To the resulting yellow suspension a solution of 88 mg (0.21 mmol) of ketone *rac*-**11** in 1 ml of THF was added, and stirring was continued at −70°C for 3 h. Within 1 h the reaction mixture was allowed to warm up to room temp. and 10 ml of a saturated aqueous NH_4Cl solution was added. Solid material was removed by filtration through a short pad of Celite, the Celite was rinsed with 200 ml of diethyl ether and the ethereal solution was dried with $MgSO_4$. The solvent was removed in vacuo (30°C/10 Torr) and after flash chromatography (silica gel, 18 g) of the residue with diethyl ether/petroleum ether (1:2) 90 mg (98%) of *rac*-**13** was obtained as a colorless oil; R_f = 0.27 (diethyl ether/petroleum ether, 1:1), diastereomeric ratio = 11.2:2.4:1. – IR (neat): $\tilde{\nu}$ = 3600–3100 (O–H), 3050 (aromat. C–H), 1630 (C=C), 1580 cm^{-1} (aromat. C=C). – ^1H NMR (300 MHz, C_6D_6): δ = 0.60 (br. s; 1H, OH), [0.78, 0.80], 0.85 (d, *J* = 6.9 Hz; 3H, 2-CH_3), 1.05 (s; 3H, 1-CH_3), 1.27 [s; 9H, $C(CH_3)_3$], 1.36–1.50 (m; 1H, 4-H_a), 1.53–1.68 (m; 3H, 2-H and 5-H), 1.72–1.80 (m; 2H, 2′-H), 1.80–1.98 (m; 1H, 4-H_b), 2.08 (br. t, *J* = 5.2 Hz; 2H, 1′-H), 2.46 (dt, *J* = 11.2 Hz and 6.8 Hz; 1H, 3-H), 3.68 (t, *J* = 6.2 Hz; 2H, OCH_2), 4.71 and 4.75 (2 m; 2H, C=CH_2), 7.34–7.42 (m; 6H, *m*- and *p*-phenyl H), 7.64–7.70 (m; 4H, *o*-phenyl H); signals of minor diastereomers in brackets. – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = [9.60], 10.66, [12.94] (2-CH_3), 19.24 [*C*(CH_3)$_3$], 26.57 (1-CH_3), 26.88 [C(*C*H_3)$_3$], 28.54, 29.77 and 31.27 (C-4, C-1′ and C-2′), [39.31], 39.94, [40.55] (C-5), [47.23], 47.49, [48.50] (C-2), 51.97, [52.34] (C-3), 63.64 (C-3′), [77.20], 80.27 (C-1), 108.12, [108.24, 109.38] (C=*C*H_2), 127.56 (*o*-phenyl C), 129.49 (*p*-phenyl C), 134.03 (phenyl C), 135.54 (*m*-phenyl C), [150.01, 151.26], 151.35 (*C*=CH_2); signals of minor diastereomers in brackets. – MS (70 eV): *m/z* (%) = 421 (2) [M^+ – CH_3], 379 (6) [M^+ – C_4H_9], 199 (100) [Ph_2SiOH^+]. – $C_{28}H_{40}O_2Si$ (436.4): calcd. C 77.06, H 9.24; found C 76.96, H 9.07.

3-[1-(3-Hydroxypropyl)vinyl]-1,2-dimethylcyclopentanol [(±)-Chokol A] (*rac*-**12**): A solution of 61 mg (0.14 mmol) of *rac*-**13** and 87 mg (0.28 mmol) of tetra-*n*-butylammonium fluoride (TBAF) in 1 ml of THF was stirred at room temp. for 5 h. Then 10 ml of diethyl ether and 5 ml of H_2O were added, the layers were separated, the aqueous layer was extracted twice with 5-ml portions of diethyl ether, and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo (30°C/100 Torr) and after flash chromatography (silica gel, 5 g) of the residue with diethyl ether 21 mg (76%) of (±)-chokol A (*rac*-**12**) was obtained as a colorless oil; R_f = 0.28 (diethyl ether), diastereomeric purity after chromatography: >95%. – IR (neat): $\tilde{\nu}$ = 3600–3100 (O–H), 3050 (C=C–H), 1660 cm^{-1} (C=C). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz; 3H, 2-CH_3), 1.28 (s; 3H, 1-CH_3), 1.30–2.08 (m; 11H, 2-H, 4-H, 5-H, 1′-H, 2′-H and 2 × OH), 2.39 (m; 1H, 3-H), 3.67 (t, *J* = 6.8 Hz; 2H, CH_2OH), 4.78 (m; 2H, C=CH_2). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 10.62 (2-CH_3), 26.55 (1-CH_3), 28.70 (C-2′), 30.07 (C-1′), 31.06 (C-4), 39.82 (C-5), 47.48 (C-2), 51.65 (C-3), 62.80 (C-3′), 80.29 (C-1), 108.23 (C=*C*H_2), 151.19 (*C*=CH_2). – MS (70 eV): *m/z* (%) = 198 (2) [M^+], 180 (20) [M^+ – H_2O], 43 (100) [$C_2H_3O^+$]. – $C_{12}H_{22}O_2$ (198.2): calcd. C 72.66, H 11.19; found C 72.71, H 10.97.

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