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Enantioselective Synthesis of Calcitriol A-Ring Fragments

*Hans-Joachim Knölker,** *Achim Ecker*, and *Petra Struwe*

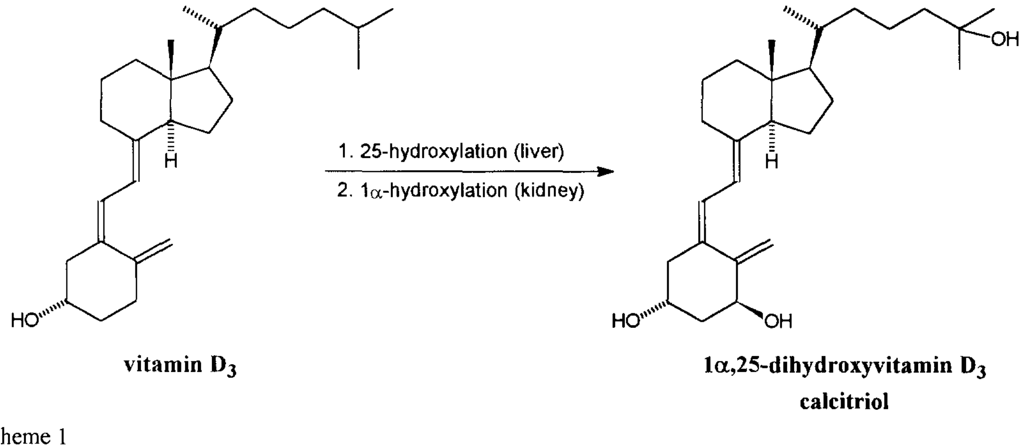
Institut für Organische Chemie, Universität Karlsruhe, Richard-Willstätter-Allee, D-76131 Karlsruhe, Germany

*Andreas Steinmeyer,** *Gunnar Müller*, and *Günter Neef*

Forschungslaboratorien, Schering AG Berlin, Müllerstraße 170-178, D-13342 Berlin, Germany

Abstract: Commercial (*S*)-(+)-carvone is transformed to a calcitriol A-ring synthon in 24% overall yield by a highly efficient 11-step sequence. The route is designed to enable the large scale production of enantiopure A-ring precursors for the synthesis of calcitriol analogues.

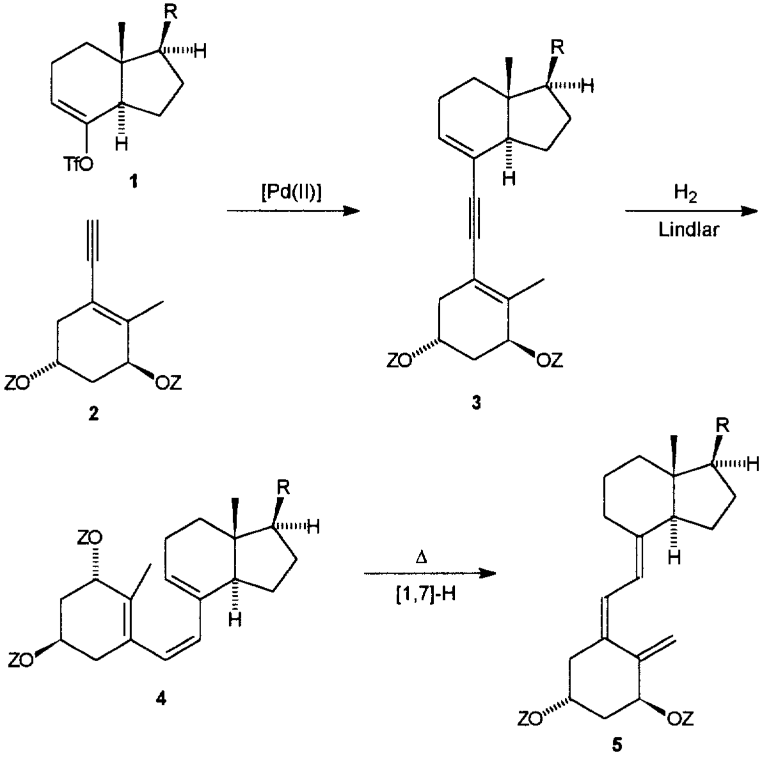
The hormonally active steroid hormone 1α,25-dihydroxyvitamin D_3 (calcitriol) is produced from vitamin D_3 by two sequential hydroxylations in liver and kidney (Scheme 1). These findings and the biological activity of calcitriol led to the development of diverse strategies directed towards its total synthesis.[1]



Scheme 1

The physiological role of calcitriol was extensively investigated in recent years.[2] Besides acting as a regulator of calcium and phosphorous homeostasis, calcitriol was found to inhibit proliferation and to induce differentiation of various cell types such as keratinocytes, tumor cells or lymphocytes. Due to the manifestation of severe hypercalcemia in the doses relevant for therapeutic application the usefulness of calcitriol for the treatment of diseases like certain cancers or disorders of the immune system is rather limited. Therefore, significant efforts have been made to develop novel calcitriol analogues, which should exhibit the beneficial activity on cell growth but on the other hand are devoid of the undesired calcium mobilizing potential.[3]

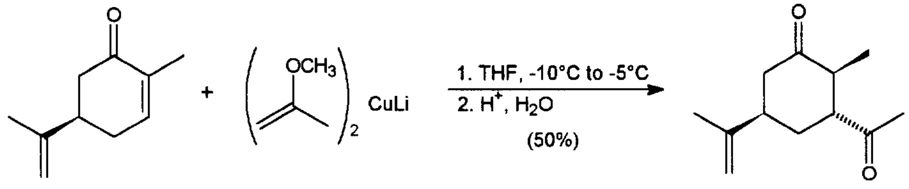
An attractive synthetic approach is based on the earlier work of Lythgoe.[4] More recently Mouriño has improved this concept remarkably (Scheme 2).[5] The key reaction is the palladium(II)-catalyzed coupling of the steroid CD-ring fragment **1** and an A-ring enyne **2**. Lindlar hydrogenation of the triple bond of the dienyne **3** and subsequent thermally induced 1,7-hydrogen shift of **4** lead to the 1α-hydroxyvitamin D skeleton **5**. By proper choice of the CD-ring portion a variety of modified side chains could be introduced.



Scheme 2

Stimulated by the elegant syntheses of A-ring fragments by Mouriño,[5] Baggiolini,[6] Okamura,[7] and Takano[8] we have been interested in developing a novel synthetic approach to this crucial building block suitable for industrial manufacturing. For this purpose commercial (*S*)-(+)-carvone appeared to be an excellent and cheap chiral starting material, since it has already been used for the synthesis of a broad range of natural products.[9] We envisaged the conjugate addition of a functional group to the enone of (*S*)-(+)-carvone. Our strategy was to achieve a simultaneous conversion of this functional group and the already existing isopropenyl group after ozonolysis into a protected hydroxy group *via* a Baeyer-Villiger oxidation.

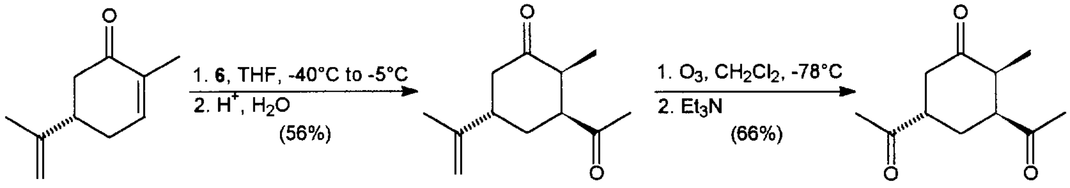
Heathcock reported the addition of lithium di(α-methoxyvinyl)cuprate **6** to (*R*)-(−)-carvone, which provided after hydrolysis the acetyl derivative **7** as a single diastereoisomer (Scheme 3).[10] In analogy to related reactions reported previously[11] the addition of the nucleophile occurred *anti* to the isopropenyl group. The configuration of the methyl group relative to the acetyl group was assigned as *anti*, thus leading to the assignment as (2*S*,3*R*,5*R*)-3-acetyl-2-methyl-5-(1-methylethenyl)cyclohexanone 7.



(R)-(-)-carvone **6** **7**

Scheme 3

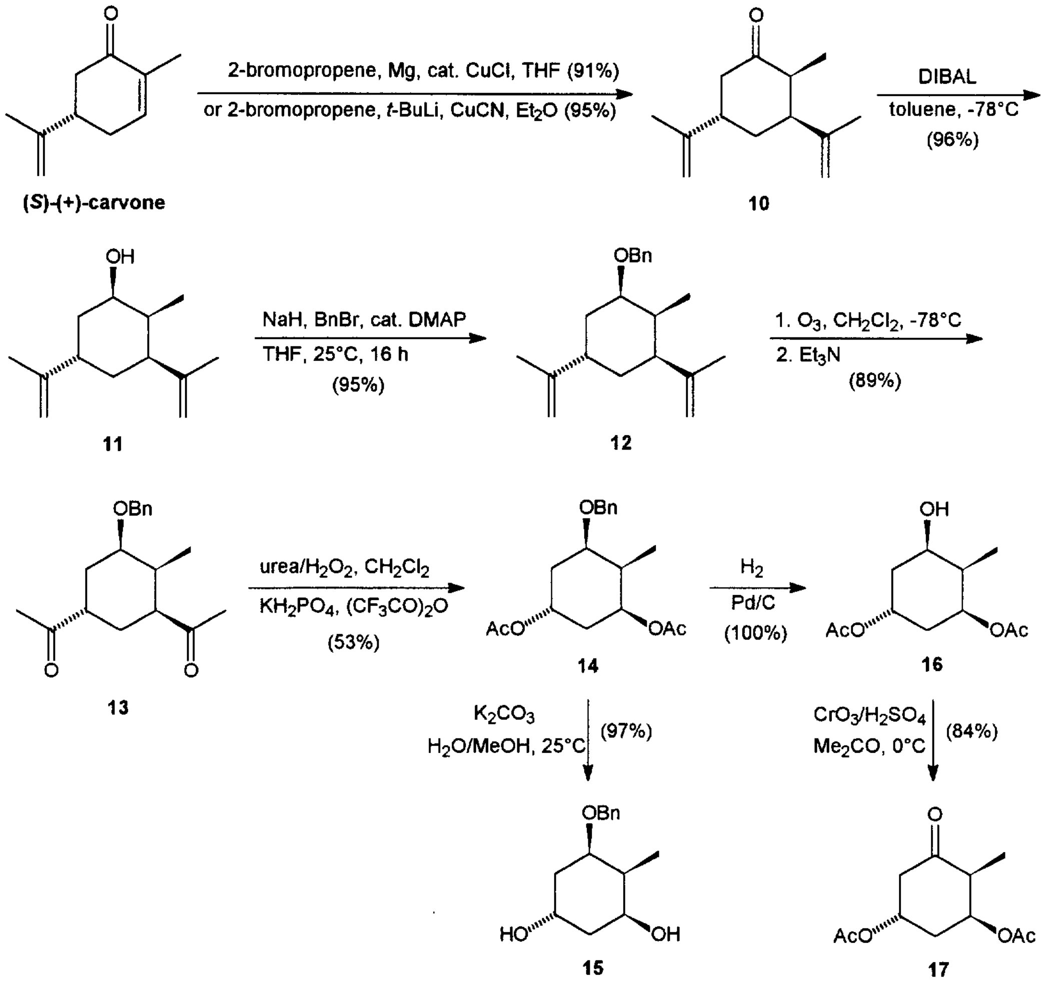
We performed the addition of the cuprate **6** to (*S*)-(+)-carvone at -40 to -5°C (Scheme 4). The ^{1}H NMR and ^{13}C NMR spectra revealed that the product **8** was obtained essentially as one diastereoisomer. However, based on the X-ray crystal structure investigation of a later derivative of our studies *(vide infra)* we propose a *cis* arrangement of the methyl substituent and the acetyl group.[12] Thus, the structure assignment of our product led to (2*S*,3*S*,5*S*)-3-acetyl-2-methyl-5-(1-methylethenyl)cyclohexanone **8**. Ozonolysis of **8** and reductive workup with triethylamine[13] provided the triketone **9**. Chemoselectivity in the projected Baeyer-Villiger oxidation to a diacetoxy derivative could not be achieved due to decomposition as well as the preferential oxidation of the ring carbonyl to a lactone.[14]



(S)-(+)-carvone **8** **9**

Scheme 4

In order to circumvent this problem, we decided to introduce a second isopropenyl group by a 1,4-addition to (*S*)-(+)-carvone (Scheme 5). This would provide the opportunity to achieve a chemoselective transformation of the ring carbonyl group prior to the conversion of the isopropenyl to acetyl groups by a simultaneous ozonolysis. Reaction of (*S*)-(+)-carvone with isopropenylmagnesium bromide in the presence of catalytic amounts of cuprous chloride afforded the ketone **10**. Alternatively, the stereospecific conjugate addition of an isopropenyl group could be achieved by using the cuprate prepared from 2-bromopropene, *t*-BuLi, and CuCN.[15] The attack of the organometallic reagent in either case was directed by the isopropenyl group at C-5 and occurred stereoselectively from the β-face of the molecule.[11] The C-2 methyl substituent was orientated *syn* relative to the isopropenyl group at C-3 of **10**. These stereochemical assignments were confirmed by an X-ray analysis of a derivative at a later stage of our synthesis. Reduction of the ketone **10** with sodium borohydride in methanol at 0°C provided in 92% yield a 14 : 1 mixture of diastereoisomers in favor of the β-carbinol **11** from which 84% of isomerically pure **11** could be obtained by chromatography at silica gel. For selectivity reasons the ketone **10** was reduced with diisobutylaluminum hydride (DIBAL) at -78°C. This procedure afforded in 96% yield exclusively the β-carbinol **11**, which was subsequently converted to the benzyl ether **12**. In the following steps the two isopropenyl units in 3- and 5-position could be manipulated simultaneously, finally leading to the biologically required calcitriol hydroxy groups (Scheme 5).



Scheme 5

Ozonolysis of **12** followed by reductive workup with triethylamine[13] gave the diacetyl derivative **13** which was subjected to a double Baeyer-Villiger oxidation. Usually rather harsh conditions (*e.g.* 3-chloroperoxybenzoic acid or trifluoroperacetic acid) are required for efficient conversions in the Baeyer-Villiger reaction.[16] These methods resulted to a large extent in decomposition of substrate **13**. Finally, the mild procedure reported by Heaney and coworkers,[17] using the urea–hydrogen peroxide adduct and trifluoroacetic anhydride, gave access to the diacetate **14**. Compound **14** represents the only crystalline derivative in the whole synthetic sequence. Therefore, we decided to confirm the stereochemistry at this stage by an X-ray analysis. Slow crystallization of **14** from pentane/diethyl ether afforded colorless crystals which were suitable for an X-ray crystal structure determination (Figure 1). All configurational assignments made earlier based solely on the ^{1}H and ^{13}C NMR spectra are unequivocally confirmed by this crystal structure: the 1,3-*trans* direction of the isopropenyl group on conjugate addition of the organometallic reagent to (*S*)-(+)-carvone, the *cis* arrangement of the C-2 methyl and the C-3 isopropenyl group, and the stereoselectivity of the DIBAL reduction.

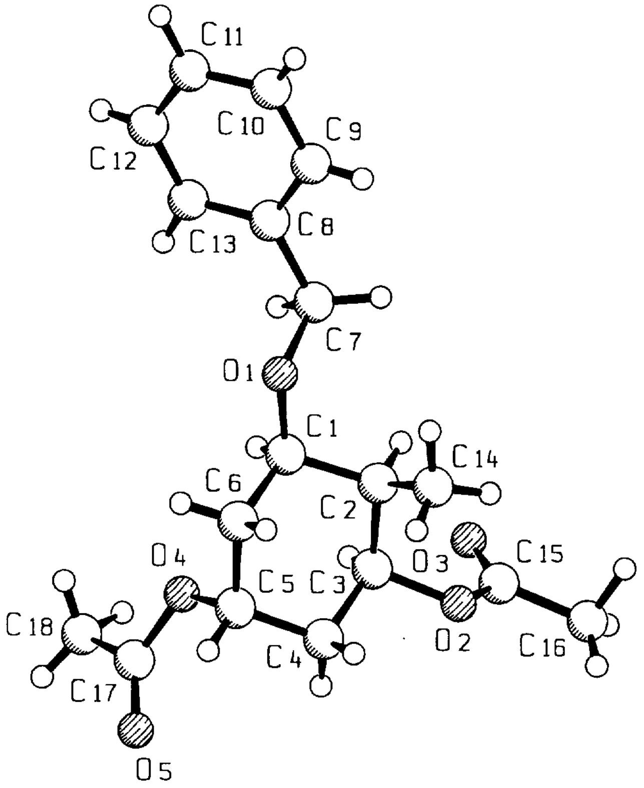
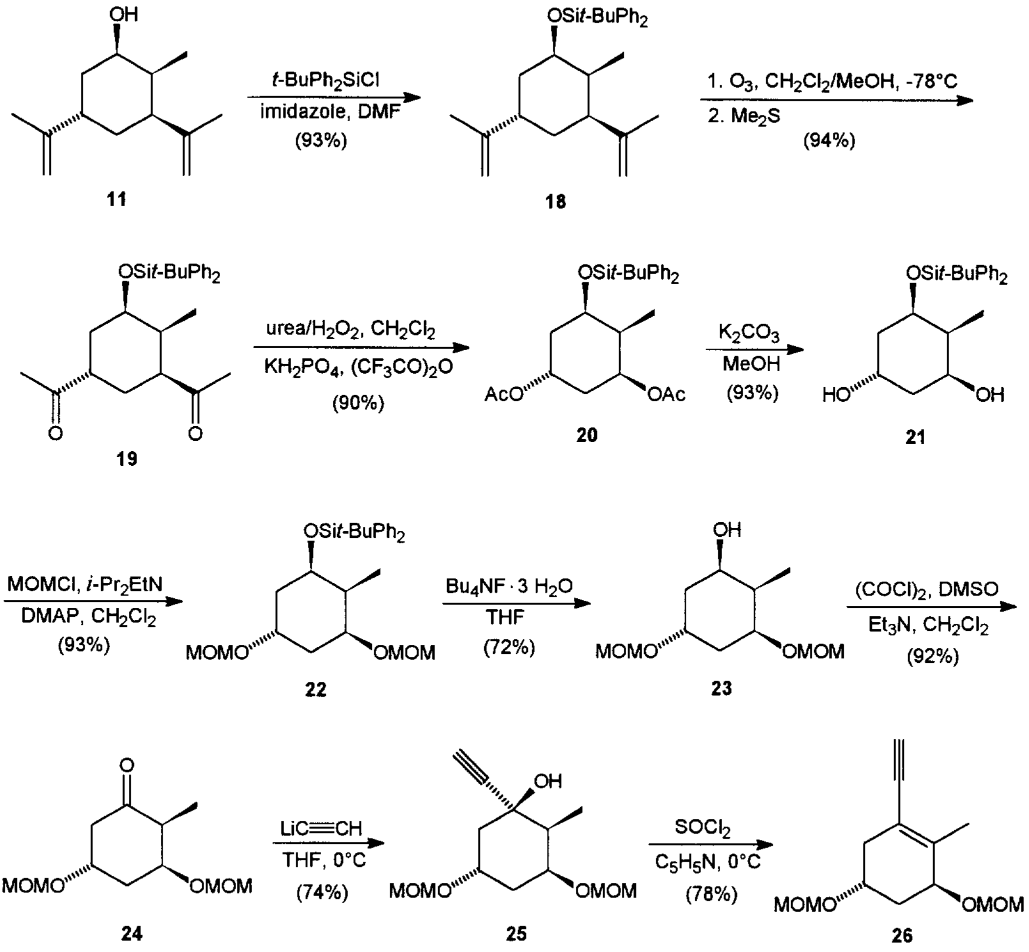


Figure 1. Molecular structure of the diacetate **14** in the crystal (monoclinic, space group $P2_1$).

The feasibility to achieve a chemoselective deliberation of the *trans* diol moiety was demonstrated by hydrolysis of the diacetate **14** to the diol **15** (Scheme 5). Cleavage of the benzyl protecting group of **14** by catalytic hydrogenation to the carbinol **16** and subsequent Jones oxidation[18] provided the ketone **17**, which represents a direct precursor of the A-ring building block **2**.

In an alternative sequence the protection of the alcohol was performed with a silyl protecting group (Scheme 6). Transformation of the carbinol **11** to the *t*-butyldiphenylsilyl ether **18** followed by ozonolytic cleavage of the alkenes afforded the diacetyl derivative **19**. Using Heaney's procedure[17] a double Baeyer-Villiger reaction was accomplished in a clean transformation to the diacetate **20**. For the subsequent reaction steps a more stable protecting group for the hydroxy groups at C-3 and C-5 was required. Thus, the diacetate **20** was hydrolyzed to the diol **21** which was without further purification directly transformed into the di(methoxymethyl) ether **22**. Chromatography of the crude diol **21** was found to result in considerable loss of material. Fluoride induced cleavage of the silyl ether followed by Swern oxidation[19] of the carbinol **23** provided the ketone **24**. Treatment of **24** with lithium acetylide gave the propargylic alcohol **25** as a single diastereoisomer. Based on the stereoselectivity observed on DIBAL reduction of **10** the configuration at C-1 was assigned as *R*, resulting from approach of the alkyne unit *anti* to the methyl group at C-2. Finally, dehydration of **25** with thionyl chloride in pyridine provided the desired A-ring fragment **26**, which has been used before by Mouriño for the construction of vitamin D derivatives.[20]



Scheme 6

Alternatively, by using *t*-butyldimethylsilyl protecting groups the diol **15** was transformed into the di(*t*-butyldimethylsilyl) analogue of the alkyne **26**,[21] which was previously described by Okamura as a precursor for Vitamin D derivatives.[7]

In conclusion, the enantiopure calcitriol A-ring fragment **26** is now accessible by an 11-step sequence which is accomplished in an excellent overall yield of 24%, starting from commercial (*S*)-(+)-carvone. Since all reaction steps involve low-price and easy-to-handle reagents an upscaling for industrial production should be feasible.

EXPERIMENTAL SECTION

All reactions were carried out using anhydrous and degassed solvents under an inert gas atmosphere (argon). Chromatography: Baker or Merck silica gel (0.03-0.06 mm). Melting points: Büchi 535. $[\alpha]_D$-Values: Perkin-Elmer 241. IR: Bruker IFS-88 and Perkin-Elmer PE-621. ^{1}H NMR and ^{13}C NMR: Bruker AC-300 and AM-400, General Electric QE-300; internal standard: tetramethylsilane or chloroform; δ in ppm; coupling constants in Hz. Mass spectra: Finnigan: MAT-90 and TSQ-700; ionization potential: 70 eV. Elemental analyses: Heraeus CHN-Rapid and Schering Analytical Department.

(2*S*,3*S*,5*S*)-3-(Acetyl)-2-methyl-5-(1-methylethenyl)cyclohexanone (8)

A 1.7 M solution of *t*-butyllithium in pentane (117.6 ml, 200 mmol) was added slowly to a solution of methylvinyl ether (14.0 g, 240 mmol) in THF (100 ml) at -60°C. After the addition, the reaction mixture was warmed to 0°C and the clear solution was cooled again to -40°C. This solution of α-methoxyvinyllithium was added slowly to cuprous bromide • dimethyl sulfide complex (20.6 g, 100 mmol) in THF (100 ml) at -40°C. The reaction mixture was stirred for 30 min and a solution of (*S*)-(+)-carvone (10.9 ml, 10.5 g, 70.0 mmol) in THF (20 ml) was added. The reaction mixture was gradually warmed (stirring for 30 min at -40°C, subsequently for 30 min at -10°C, and for 75 min at -5°C) and then quenched with a sat. solution of ammonium chloride and a small amount of *conc.* hydrochloric acid (pH control!). The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine and dried over magnesium sulfate. Evaporation of the solvent and distillation (100°C/0.01 bar) of the residue afforded the acetyl derivative **8** as a yellow oil, yield: 7.65 g (56%). IR (film): ν = 2971, 2936, 2876, 1707, 1670, 1645, 1451, 1378, 1251, 1213, 1167, 1053, 983, 963, 945, 897 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (dd, *J* = 6.7, 1.8, 3 H), 1.58 (s, 3 H), 1.63 (d, *J* = 7.6, 2 H), 1.84-1.90 (m, 1 H), 1.97-2.02 (m, 1 H), 2.06 (d, *J* = 1.4, 3 H), 2.22-2.56 (m, 2 H), 3.26 (m, 1 H), 4.61 (m, 2 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 12.1 (CH_3), 20.4 (CH_3), 29.9 (CH_3), 31.2 (CH_2), 40.2 (CH), 45.0 (CH), 45.1 (CH_2), 54.0 (CH), 110.2 (CH_2), 146.7 (C), 209.0 (CO), 209.7 (CO). MS (42°C): *m/z* (%) = 194 (M^+, 40), 151 (85), 123 (22), 121 (17), 109 (62), 107 (12), 97 (25), 95 (20), 93 (13), 91 (11), 85 (66), 55 (54), 43 (100). HRMS: Calc. for $C_{12}H_{18}O_2$ (M^+): 194.1307, found: 194.1293.

(2*S*,3*S*,5*S*)-3,5-Diacetyl-2-methylcyclohexanone (9)

A stream of ozone/oxygen was passed through a solution of the acetyl derivative **8** (2.80 g, 14.4 mmol) in dichloromethane (20 ml) at -78°C until the blue color of the solution persisted. After purging with nitrogen, triethylamine (4.0 ml, 28.8 mmol) was added and the mixture was allowed to warm to room temperature (stirring for about 2 h). The dichloromethane solution was washed with a saturated solution of ammonium chloride, with brine, and dried over magnesium sulfate. Removal of the solvent and chromatography (diethyl ether) of the residue on neutral aluminum oxide (deactivated with 3% H_2O) provided the triketone **9** as a yellow oil, yield: 1.81 g (66%). IR (KBr): ν = 2928, 2876, 2855, 2037, 1709, 1458, 1422, 1385, 1364, 1354, 1268, 1251, 1230, 1178, 1165, 1140, 1097, 1077, 1048, 972, 946, 907, 880, 854, 810, 779, 625 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.7, 3 H), 2.00-2.09 (m, 1 H), 2.17 (s, 3 H), 2.19 (m, 1 H), 2.22 (s, 3 H), 2.31-2.64 (m, 3 H), 2.97 (m, 1 H), 3.36-3.45 (m, 1 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 12.2 (CH_3), 27.8 (CH_2), 28.3 (CH_3), 30.4 (CH_3), 41.1 (CH_2), 45.0 (CH), 46.5 (CH), 53.3 (CH), 207.7 (CO), 208.4 (CO), 210.0 (CO). MS (25°C): *m*/*z* (%) = 196 (M^+, 21), 154 (17), 153 (32), 111 (60), 109 (26), 99 (22), 98 (12), 85 (25), 71 (10), 69 (10), 55 (28), 43 (100). HRMS: Calc. for $C_{11}H_{16}O_3$ (M^+): 196.1099, found: 196.1080.

(2*S*,3*S*,5*S*)-2-Methyl-3,5-di(1-methylethenyl)cyclohexanone (10)

a) *Grignard reaction*

Magnesium turnings (10.5 g, 0.43 mol) were placed in THF (120 ml) at room temperature. A solution of 2-bromopropene (54.5 g, 0.45 mol) in THF (400 ml) was added slowly. The mixture was stirred until all magnesium was dissolved. Cuprous chloride (800 mg, 6 mmol) was added rapidly at 0°C and stirring was continued for 30 min. Subsequently, a solution of (*S*)-(+)-carvone (50 g, 0.33 mol) in THF (300 ml) was added and the reaction mixture was stirred at r. t. overnight. The mixture was poured into an aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Filtration and evaporation of the solvent followed by chromatography (ethyl acetate/hexane) on silica gel gave the ketone **10** as a colorless oil, yield: 57.8 g (91%). Spectral data, see below.

b) *Cuprate addition*

A 1.7 M solution of *t*-butyllithium in pentane (95 ml, 0.16 mol) was added slowly to a solution of 2-bromopropene (9.7 g, 80 mmol) in diethyl ether (160 ml) at -78°C. After stirring for 1 h, cuprous cyanide (3.6 g, 40 mmol) was added and the mixture was allowed to warm to -20°C over a period of 30 min. Finally, the reaction flask was recooled to -78°C and (*S*)-(+)-carvone (4.5 g, 30 mmol) in diethyl ether (15 ml) was added. The mixture was gradually warmed to r. t., quenched with an aqueous solution of ammonium chloride, and subsequently extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. Filtration and evaporation of the solvent followed by chromatography (ethyl acetate/hexane) on silica gel provided the ketone **10** as a colorless oil, yield: 5.5 g (95%). $[\alpha]_D^{20}$ = + 2.5° (c = 0.475, $CHCl_3$). IR ($CHCl_3$): ν = 3088, 2974, 2939, 1704, 1646, 1451, 1377, 901 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 7, 3 H), 1.70 (s, 3 H), 1.73 (s, 3 H), 1.82 (m, 1 H), 2.00 (m, 1 H), 2.30 (dd, *J* = 14.5, 10, 1 H), 2.53 (dd, *J* = 14.5, 5, 1 H), 2.61 (m, 1 H), 2.67 (m, 1 H), 2.72 (m, 1 H), 4.52 (s, 1 H), 4.72 (s, 1 H), 4.80 (br s, 1 H), 4.92 (br s, 1 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 12.0 (CH_3), 21.1 (CH_3), 23.7 (CH_3), 31.9 (CH_2), 40.3 (CH), 44.9 (CH_2), 46.4 (CH), 47.0 (CH), 110.5 (CH_2), 112.8 (CH_2), 143.9 (C), 147.3 (C), 213.7 (CO). MS (EI): *m*/*z* (%) = 192 (M^+, 27), 175 (10), 149 (32), 134 (58), 95 (55), 83 (100). Anal. Calc. for $C_{13}H_{20}O$: C, 80.81; H, 10.50. Found: C, 80.96; H, 10.61.

(1*R*,2*S*,3*S*,5*S*)-2-Methyl-3,5-di(1-methylethenyl)cyclohexanol (11)

A solution of ketone **10** (51 g, 0.26 mol) in toluene (1.0 l) was treated with a 1.1 M solution of DIBAL in hexane (290 ml, 0.32 mol) at -78°C. After stirring for 30 min, water (60 ml) and isopropanol (5 ml) were added and stirring was continued overnight. Removal of the precipitate by filtration, evaporation of the solvent, and purification of the residue by chromatography gave the alcohol **11** as a colorless oil, yield: 49.1 g (96%). $[\alpha]_D^{20}$ = + 12.6° (c = 0.500, $CHCl_3$). IR ($CHCl_3$): ν = 3608, 3451, 3087, 3008, 2971, 2943, 1642, 1448, 1376, 1053, 894 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 7, 3 H), 1.70 (s, 3 H), 1.65 (m, 4 H), 1.73 (s, 3 H), 1.97 (br d, J = 13, 1 H), 2.20 (m, 2 H), 2.49 (m, 1 H), 3.99 (dt, J = 11.5, 4, 1 H), 4.65 (s, 1 H), 4.81 (br s, 2 H), 4.90 (br s, 1 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 5.0 (CH_3), 22.3 (CH_3), 22.8 (CH_3), 24.9 (CH_2), 30.5 (CH_2), 36.6 (CH), 38.2 (CH), 41.0 (CH), 69.3 (CH), 109.6 (CH_2), 110.5 (CH_2), 146.5 (C), 147.3 (C). MS (EI): *m/z* (%) = 194 (M^+, 13), 176 (22), 161 (21), 133 (55), 107 (52), 81 (55), 41 (100). Anal. Calc. for $C_{13}H_{22}O$: C, 80.36; H, 11.41. Found: C, 80.51; H, 11.59.

(1*R*,2*S*,3*S*,5*S*)-2-Methyl-3,5-di(1-methylethenyl)-1-phenylmethoxycyclohexane (12)

A solution of the alcohol **11** (3.54 g, 18.3 mmol) in THF (50 ml) was added to a suspension of sodium hydride (80%, 1.8 g, 60 mmol) in THF (50 ml) and the mixture was stirred for 15 min at room temperature. DMAP (0.1 g, 1 mmol) and benzyl bromide (6.40 g, 37.4 mmol) were added and the mixture was stirred for 16 h at room temperature. Brine was added and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate and the solvent was evaporated. Chromatography (hexane) of the residue on silica gel provided the benzyl ether **12** as a colorless oil, yield: 4.93 g (95%). IR (film): ν = 3085, 3031, 2967, 2941, 2878, 1643, 1497, 1453, 1374, 1351, 1328, 1312, 1259, 1204, 1163, 1119, 1095, 1074, 1028, 992, 972, 890, 735, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, J = 7.1, 3 H), 1.67-1.75 (m, 3 H), 1.71 (s, 3 H), 1.72 (s, 3 H), 2.02-2.05 (m, 1 H), 2.12-2.15 (m, 1 H), 2.40 (m, 1 H), 2.49 (m, 1 H), 3.70 (dt, J = 12.2, 4.4, 1 H), 4.48 (d, J = 11.9, 1 H), 4.60 (d, J = 11.9, 1 H), 4.66 (s, 1 H), 4.73 (s, 1 H), 4.84 (ddd, J = 10.2, 2.8, 1.4, 2 H), 7.23-7.37 (m, 5 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 5.6 (CH_3), 22.4 (CH_3), 22.7 (CH_3), 25.3 (CH_2), 28.0 (CH_2), 33.4 (CH), 38.3 (CH), 40.9 (CH), 69.7 (CH_2), 76.3 (CH), 109.8 (CH_2), 110.6 (CH_2), 127.3 (CH), 127.4 (2 CH), 128.3 (2 CH), 139.2 (C), 146.7 (C), 147.4 (C). MS (20°C): *m/z* (%) = 284 (M^+, 32), 176 (12), 133 (13), 107 (20), 93 (12), 92 (44), 91 (100). HRMS: Calc. for $C_{20}H_{28}O$ (M^+): 284.2140, found: 284.2154.

(1*R*,2*S*,3*S*,5*S*)-3,5-Diacetyl-2-methyl-1-phenylmethoxycyclohexane (13)

A stream of ozone/oxygen was passed through a solution of the benzyl ether **12** (3.9 g, 14 mmol) in dichloromethane (80 ml) at -78°C until the blue color of the solution persisted. After purging with nitrogen, triethylamine (5.3 ml, 40 mmol) was added and the mixture was allowed to warm to room temperature (stirring for about 2 h). After addition of water, the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, the solvent was evaporated, and the residue was purified by chromatography (hexane/ethyl acetate, 1:1) on silica gel to afford the diacetyl derivative **13** as a colorless oil, yield: 3.58 g (89%). IR (film): ν = 3065, 3032, 2948, 2875, 2253, 1708, 1497, 1454, 1359, 1314, 1275, 1243, 1213, 1178, 1133, 1113, 1097, 1043, 1028, 993, 913, 735, 700, 648 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, J = 7.0, 3 H), 1.67-1.89 (m, 4 H), 2.11 (s, 3 H), 2.13 (s, 3 H), 2.59-2.66 (m, 2 H), 2.85 (m, 1 H), 3.64 (dt, J = 11.6, 4.2, 1 H), 4.50 (d, J = 11.7, 1 H), 4.59 (d, J = 11.7, 1 H), 7.27-7.36 (m, 5 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 7.1 (CH_3), 21.1 (CH_2), 26.5 (CH_2), 28.0 (CH_3), 28.2 (CH_3), 33.3 (CH), 45.5 (CH), 49.8 (CH), 70.2 (CH_2), 76.0 (CH), 127.5 (2 CH), 127.6 (CH), 128.4 (2 CH), 138.6 (C), 209.7 (CO), 211.1 (CO). MS (60°C): *m/z* (%) = 288 (M^+, 1), 245 (22), 197 (10), 179 (10), 137 (12), 91 (100), 43 (43). HRMS: Calc. for $C_{18}H_{24}O_3$ (M^+): 288.1725, found: 288.1715.

(1*S*,2*R*,3*R*,5*R*)-1,5-Diacetoxy-2-methyl-3-phenylmethoxycyclohexane (14)

To a solution of the diacetyl derivative **13** (3.40 g, 11.8 mmol) in dichloromethane (160 ml) potassium dihydrogen phosphate (32.1 g, 236 mmol) and urea/hydrogen peroxide adduct (22.6 g, 240 mmol) were added at 0°C. Trifluoroacetic anhydride (12.6 g, 60 mmol) was added slowly while the temperature of the reaction mixture was kept below 20°C. After stirring for 2 h at 20°C, the mixture was hydrolyzed with a saturated solution of sodium bicarbonate and the aqueous layer was extracted with dichloromethane. The combined organic layers were successively washed with a saturated solution of sodium bisulfite, brine, and water and dried over magnesium sulfate. Removal of the solvent and chromatography (hexane/ethyl acetate, 3:2) of the residue on silica gel provided the diacetate **14** (colorless crystals, yield: 1.79 g, 47%) as the less polar fraction and a mixture (4:1 according to the ^{13}C NMR spectrum) of the two regioisomeric monoacetates (light yellow oil, yield: 368 mg, 1.21 mmol, 10%) as the more polar fraction. The mixture of monoacetates was resubmitted to the reaction conditions described above and transformed to the diacetate **14** (yield: 201 mg, 52%).

14: Colorless crystals, yield: 1.99 g (53%), m.p. 74°C. $[\alpha]_D^{20} = -3.1°$ (c = 0.82, $CHCl_3$). IR (film): ν = 2964, 2872, 1736, 1497, 1454, 1371, 1316, 1247, 1217, 1182, 1127, 1102, 1047, 1027, 739, 698, 608 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 7.0, 3 H), 1.76-1.89 (m, 4 H), 2.02 (s, 3 H), 2.06 (s, 3 H), 2.60 (m, 1 H), 3.80 (dt, *J* = 10.4, 4.5, 1 H), 4.48 (d, *J* = 11.6, 1 H), 4.54 (d, *J* = 11.6, 1 H), 5.10 (dt, *J* = 4.5, 7.8, 1 H), 5.20 (m, 1 H), 7.24-7.34 (m, 5 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 6.2 (CH_3), 21.2 (CH_3), 21.3 (CH_3), 30.2 (CH_2), 30.5 (CH_2), 35.3 (CH), 68.0 (CH), 70.1 (CH), 70.2 (CH_2), 74.0 (CH), 127.4 (2 CH), 127.5 (CH), 128.3 (2 CH), 138.5 (C), 170.2 (CO), 170.4 (CO). MS (90°C): *m*/*z* (%) = 320 (M^+, 0.3), 200 (8), 169 (14), 154 (14), 110 (10), 109 (22), 94 (22), 91 (100), 81 (10), 43 (27). HRMS: Calc. for $C_{18}H_{24}O_5$ (M^+): 320.1624, found: 320.1612. Anal. Calc. for $C_{18}H_{24}O_5$: C, 67.47; H, 7.55. Found: C, 67.43; H, 7.55.

X-Ray crystal structure determination of 14

Crystal data

Formula: $C_{18}H_{24}O_5$; M = 320.37; crystal color and habit: colorless sticks; crystal size: 0.75 • 0.25 • 0.175 mm; monoclinic; space group: $P2_1$; a = 10.228(6) Å, b = 7.191(3) Å, c = 12.440(6) Å; $\alpha = \gamma = 90°$, $\beta = 104.66(3)°$; V = 885.2(8) Å^3; Z = 2, ρ_{calc} = 1.202 g/cm^3; μ = 0.087 mm^{-1}; F(000) = 344.

Data collection

The data were collected on a STOE STADI-4 diffractometer using Mo-K_α radiation (λ = 0.71069 Å); T = 293(2) K; θ range: 1.69-26.96°; reflections collected: 7077; independent reflections: 3842.

Solution and refinement

The structure was solved by direct methods (SHELXS-86) and refined anisotropically by full-matrix least squares based on all unique F^2 (SHELXL-93); data/restraints/parameters: 3841/1/304; data-to-parameter ratio: 12.6:1; R_1 = 0.0376, wR_2 = 0.0904 [$I>2\sigma(I)$]; maximal residual electron density: 0.103 e/Å^3.[22]

The program SCHAKAL-92 has been used for the graphical representation of the crystal structure (E. Keller, A computer program for the graphic representation of molecular and crystallographic models, Universität Freiburg, Germany, 1992).

Table 1. Atomic coordinates (• 10^4) and equivalent isotropic displacement parameters ($Å^2$ • 10^3) for **14**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	3317(2)	4442(3)	7050(2)	58(1)
O(1)	3884(2)	6272(3)	7208(1)	71(1)
C(7)	4918(3)	6464(6)	8227(2)	91(1)
C(8)	5874(2)	7984(4)	8082(2)	66(1)
C(9)	5824(3)	9702(5)	8549(3)	82(1)
C(10)	6696(4)	11110(5)	8419(4)	106(1)
C(11)	7616(4)	10807(7)	7823(3)	106(1)
C(12)	7689(3)	9136(9)	7366(3)	115(1)
C(13)	6833(3)	7709(6)	7507(3)	94(1)
C(2)	2571(2)	3882(4)	7928(2)	65(1)
C(14)	1490(4)	5285(6)	8033(4)	93(1)
C(3)	2039(2)	1910(4)	7639(2)	62(1)
O(2)	1226(1)	1330(3)	8396(1)	77(1)
C(15)	1836(2)	425(3)	9315(2)	62(1)
O(3)	3004(2)	9(3)	9560(2)	89(1)
C(16)	881(4)	11(6)	10016(3)	89(1)
C(4)	1122(2)	1724(4)	6480(2)	66(1)
C(5)	1793(2)	2466(3)	5612(2)	61(1)
O(4)	2930(1)	1288(2)	5550(1)	66(1)
C(6)	2373(2)	4397(4)	5889(2)	62(1)
C(17)	2726(2)	-160(4)	4852(2)	68(1)
O(5)	1639(2)	-544(4)	4293(2)	116(1)
C(18)	3994(3)	-1170(5)	4870(3)	82(1)

Table 2. Bond lengths [Å] of **14**.

C(1)-O(1)	1.432(3)	C(1)-C(6)	1.521(3)
C(1)-C(2)	1.535(3)	O(1)-C(7)	1.438(3)
C(7)-C(8)	1.508(4)	C(8)-C(13)	1.367(4)
C(8)-C(9)	1.372(4)	C(9)-C(10)	1.386(5)
C(10)-C(11)	1.354(6)	C(11)-C(12)	1.339(6)
C(12)-C(13)	1.388(6)	C(2)-C(14)	1.527(4)
C(2)-C(3)	1.529(4)	C(3)-O(2)	1.465(3)
C(3)-C(4)	1.514(3)	O(2)-C(15)	1.326(3)
C(15)-O(3)	1.194(3)	C(15)-C(16)	1.495(4)
C(4)-C(5)	1.515(3)	C(5)-O(4)	1.456(3)
C(5)-C(6)	1.515(4)	O(4)-C(17)	1.338(3)
C(17)-O(5)	1.185(3)	C(17)-C(18)	1.481(4)

Table 3. Bond angles [°] of **14**.

O(1)-C(1)-C(6)	106.7(2)	O(1)-C(1)-C(2)	113.6(2)
C(6)-C(1)-C(2)	111.1(2)	C(1)-O(1)-C(7)	113.0(2)
O(1)-C(7)-C(8)	108.5(2)	C(13)-C(8)-C(9)	117.4(3)
C(13)-C(8)-C(7)	122.1(3)	C(9)-C(8)-C(7)	120.5(3)
C(8)-C(9)-C(10)	120.9(3)	C(11)-C(10)-C(9)	120.2(4)
C(12)-C(11)-C(10)	119.8(3)	C(11)-C(12)-C(13)	120.4(3)
C(8)-C(13)-C(12)	121.2(4)	C(14)-C(2)-C(3)	114.2(3)
C(14)-C(2)-C(1)	112.9(3)	C(3)-C(2)-C(1)	106.7(2)
O(2)-C(3)-C(4)	105.8(2)	O(2)-C(3)-C(2)	109.8(2)
C(4)-C(3)-C(2)	113.8(2)	C(15)-O(2)-C(3)	118.3(2)
O(3)-C(15)-O(2)	124.4(2)	O(3)-C(15)-C(16)	124.1(3)
O(2)-C(15)-C(16)	111.5(2)	C(3)-C(4)-C(5)	111.4(2)
O(4)-C(5)-C(4)	110.1(2)	O(4)-C(5)-C(6)	105.9(2)
C(4)-C(5)-C(6)	112.5(2)	C(17)-O(4)-C(5)	119.5(2)
C(5)-C(6)-C(1)	110.7(2)	O(5)-C(17)-O(4)	122.1(2)
O(5)-C(17)-C(18)	125.6(3)	O(4)-C(17)-C(18)	112.3(2)

(1*S*,2*S*,3*R*,5*S*)-2-Methyl-3-phenylmethoxycyclohexane-1,5-diol (15)

A solution of the diacetate **14** (402 mg, 1.26 mmol) in methanol (5 ml) was added slowly to a solution of K_2CO_3 (800 mg, 5.8 mmol) in methanol (10 ml) and water (1 ml). The reaction mixture was stirred for 15 min at r. t., poured into water, and extracted with diethyl ether. The combined organic layers were washed with brine and dried over magnesium sulfate. Evaporation of the solvent in vacuo afforded the diol **15** as a colorless oil (the crude product was pure enough for characterization and further transformations; chromatography on silica gel resulted to a large extent in decomposition), yield: 288 mg (97%). $[\alpha]_D^{20} = -12.0°$ (c = 0.81, $CHCl_3$). IR (film): ν = 3403, 3089, 3064, 3031, 2933, 1721, 1497, 1454, 1420, 1369, 1345, 1315, 1263, 1213, 1127, 1097, 1063, 1028, 988, 941, 815, 739, 698, 654, 621 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 7.1, 3 H), 1.35 (ddd, *J* = 13.3, 11.1, 2.1, 1 H), 1.44 (ddd, *J* = 13.3, 11.1, 2.7, 1 H), 1.70 (m, 1 H), 2.27 (m, 1 H), 2.42 (m, 1 H), 2.93 (br s, 1 H), 3.45 (br s, 1 H), 3.76 (m, 1 H), 3.85 (m, 1 H), 4.21 (m, 1 H), 4.38 (d, *J* = 11.6, 1 H), 4.65 (d, *J* = 11.6, 1 H), 7.27-7.35 (m, 5 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 13.8 (CH_3), 37.1 (CH_2), 38.2 (CH), 42.7 (CH_2), 62.1 (CH), 71.5 (CH_2), 72.1 (CH), 80.0 (CH), 127.6 (2 CH), 127.8 (CH), 128.5 (2 CH), 137.8 (C). MS (20°C): *m*/*z* (%) = 218 ($M^+ - H_2O$, 8), 200 (5), 110 (27), 109 (12), 108 (44), 107 (16), 94 (18), 92 (15), 91 (100), 81 (13), 57 (10), 43 (64). HRMS: Calc. for $C_{14}H_{18}O_2$ ($M^+ - 18$): 218.1307, found: 218.1318.

(1*R*,2*R*,3*S*,5*R*)-3,5-Diacetoxy-2-methylcyclohexanol (16)

10% Palladium on activated carbon (50 mg) was added to a solution of the diacetate **14** (135 mg, 0.42 mmol) in methanol (5 ml). The mixture was stirred vigorously at room temperature under an hydrogen atmosphere (1.2 atm) until no further hydrogen uptake was detected. Filtration through a short path of Celite and evaporation of the solvent provided the carbinol **16** as a colorless oil, yield: 97 mg (100%). $[\alpha]_D^{20}$ = + 15.8° (c = 0.83, $CHCl_3$). IR (film): ν = 3458, 2969, 1738, 1439, 1372, 1247, 1175, 1124, 1086, 1031, 988, 951, 932, 913, 880, 802, 708, 670, 645, 608 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 7.1, 3 H), 1.57-1.64 (m, 2 H), 1.86-1.97 (m, 2 H), 1.93 (s, 3 H), 1.98 (s, 3 H), 2.04 (m, 1 H), 2.70 (br s, 1 H), 3.91 (m, 1 H), 5.03-5.11 (m, 2 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 9.0 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 32.1 (CH_2), 35.2 (CH_2), 37.5 (CH), 66.7 (CH), 68.6 (CH), 72.0 (CH), 170.0 (CO), 170.2 (CO). MS (40°C): *m/z* (%) = 170 (M^+ - CH_3COOH, 2), 152 (3), 110 (100), 95 (11), 85 (20), 83 (40), 82 (10), 81 (23), 74 (56), 59 (78), 45 (44), 43 (82). HRMS: Calc. for $C_9H_{14}O_3$ (M^+ – 60): 170.0943, found: 170.0953.

(2*S*,3*S*,5*S*)-3,5-Diacetoxy-2-methylcyclohexanone (17)

To a solution of the carbinol **16** (98 mg, 0.43 mmol) in acetone (10 ml) the Jones reagent ([O] = 8 M, 0.3 ml)[18] was added at 0°C until the orange color of the solution persisted. After stirring at 0°C for 30 min, the excess of the Jones reagent was destroyed by addition of isopropanol, the mixture was diluted with water and extracted with diethyl ether. The combined organic layers were washed with a saturated solution of sodium bicarbonate and dried over magnesium sulfate. Removal of the solvent in vacuo gave the ketone **17** as a colorless oil, yield: 82 mg (84%). $[\alpha]_D^{20}$ = + 3.6° (c = 0.86, $CHCl_3$). IR (film): ν = 3622, 3465, 2981, 2940, 1744, 1680, 1451, 1431, 1373, 1313, 1243, 1202, 1162, 1118, 1056, 1035, 980, 968, 925, 889, 864, 735, 655, 603 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.8, 3 H), 1.90-2.05 (m, 1 H), 1.97 (s, 3 H), 1.98 (s, 3 H), 2.35-2.43 (m, 2 H), 2.55 (m, 1 H), 2.83 (ddd, *J* = 14.0, 5.2, 2.1, 1 H), 5.14 (m, 1 H), 5.34 (m, 1 H). ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 10.1 (CH_3), 20.7 (CH_3), 21.0 (CH_3), 34.7 (CH_2), 46.2 (CH_2), 47.2 (CH), 67.8 (CH), 71.9 (CH), 169.7 (CO), 170.0 (CO), 205.7 (CO). MS (35°C): *m/z* (%) = 168 (M^+ - CH_3COOH, 9), 126 (5), 109 (15), 108 (100), 107 (11), 82 (36), 81 (11), 80 (18), 79 (15), 68 (14), 43 (57). HRMS: Calc. for $C_9H_{12}O_3$ (M^+ – 60): 168.0786, found: 168.0775.

(1*R*,2*S*,3*S*,5*S*)-2-Methyl-3,5-di(1-methylethenyl)-1-(1,1-dimethylethyl)diphenylsiloxycyclohexane (18)

A solution of the alcohol **11** (49 g, 0.25 mol), imidazole (34 g, 0.50 mol), and *t*-butyldiphenylsilyl chloride (103 g, 0.38 mol) in DMF (512 ml) was stirred for 6 h at room temperature. After addition of brine, the mixture was extracted with ethyl acetate. The combined organic layers were washed several times with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by chromatography (ethyl acetate/hexane) on silica gel afforded the silyl ether **18** as a colorless oil, yield: 100.1 g (93%). $[\alpha]_D^{20}$ = + 24.8° (c = 0.765, $CHCl_3$). IR ($CHCl_3$): ν = 3073, 2933, 2858, 1642, 1589, 1473, 1446, 1428, 1378, 1112, 1083, 894 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 7, 3 H), 1.08 (s, 9 H), 1.43 (s, 3 H), 1.58 (s, 3 H), 1.60 (m, 2 H), 1.73 (m, 2 H), 1.84 (m, 1 H), 2.08 (m, 1 H), 2.34 (m, 1 H), 3.98 (dt, *J* = 11.5, 4, 1 H), 4.19 (s, 1 H), 4.54 (br s, 1 H), 4.60 (s, 1 H), 4.78 (br s, 1 H), 7.38 (m, 6 H), 7.69 (m, 4 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 5.5 (CH_3), 19.2

(C), 22.3 (CH_3), 22.5 (CH_3), 24.8 (CH_2), 27.1 (3 CH_3), 30.8 (CH_2), 36.7 (CH), 38.6 (CH), 40.9 (CH), 70.8 (CH), 109.3 (CH_2), 110.3 (CH_2), 127.5 (4 CH), 129.5 (2 CH), 134.6 (C), 134.7 (C), 135.8 (4 CH), 146.5 (C), 147.7 (C). MS (EI): *m/z* (%) = 375 (M^+ – *t*-butyl, 23), 333 (5), 297 (5), 255 (4), 199 (100), 181 (17), 135 (15), 77 (17), 57 (54). Anal. Calc. for $C_{29}H_{40}OSi$: C, 80.50; H, 9.32. Found: C, 80.32; H, 9.30.

(1*R*,2*S*,3*S*,5*S*)-3,5-Diacetyl-2-methyl-1-(1,1-dimethylethyl)diphenylsiloxycyclohexane (19)

A stream of an ozone/oxygen mixture (200 l oxygen/h = 0.17 mol ozone/h, generated by a Fischer ozonisator) was passed through a solution of the silyl ether **18** (54 g, 0.12 mol) in dichloromethane (1.68 l) and methanol (560 ml) at -78°C until the blue color of the solution persisted (about 1.5 h). After purging with nitrogen, dimethyl sulfide (18.7 g, 0.30 mol) was added and the mixture was allowed to warm to room temperature. Brine was added and extraction with ethyl acetate was carried out. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the solvent was evaporated. Chromatographical purification (ethyl acetate/hexane) on silica gel provided the diketone **19** as a colorless oil, yield: 51.3 g (94%). $[\alpha]_D^{20}$ = + 85.7° (c = 0.525, $CHCl_3$). IR ($CHCl_3$): ν = 3012, 2961, 2680, 1705, 1473, 1428, 1362, 1113, 861 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 7, 3 H), 1.08 (s, 9 H), 1.69 (s, 3 H), 1.79 (m, 2 H), 1.98 (s, 3 H), 2.26 (m, 1 H), 2.58 (dt, *J* = 12.5, 4, 1 H), 2.63 (m, 1 H), 3.81 (dt, *J* = 11.5, 4, 1 H), 7.42 (m, 6 H), 7.69 (m, 4 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 6.5 (CH_3), 19.2 (C), 19.8 (CH_2), 27.1 (3 CH_3), 27.3 (CH_3), 27.8 (CH_3), 29.3 (CH_2), 36.1 (CH), 45.8 (CH), 49.7 (CH), 70.6 (CH), 127.7 (4 CH), 129.8 (2 CH), 134.1 (2 C), 135.7 (4 CH), 209.8 (CO), 210.8 (CO). MS (EI): *m/z* (%) = 379 (M^+ – *t*-butyl, 94), 335 (5), 301 (2), 251 (6), 199 (100), 181 (10), 135 (17), 77 (10), 43 (30). Anal. Calc. for $C_{27}H_{36}O_3Si$: C, 74.27; H, 8.31. Found: C, 74.32; H, 8.42.

(1*R*,2*S*,3*S*,5*S*)-3,5-Diacetoxy-2-methyl-1-(1,1-dimethylethyl)diphenylsiloxycyclohexane (20)

To a solution of the diketone **19** (42 g, 96 mmol) in dichloromethane (1.0 l) potassium dihydrogen phosphate (65.8 g, 0.48 mol) and urea/hydrogen peroxide adduct (45 g, 0.48 mol) were added at room temperature. Subsequently, trifluoroacetic anhydride (25.2 g, 0.12 mol) was added slowly. After stirring at 40°C for 2 h and overnight at room temperature, the mixture was poured carefully into an aqueous solution of sodium bicarbonate and then diluted with dichloromethane. The organic layer was washed with a solution of sodium sulfite and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Chromatographical purification (ethyl acetate/hexane) on silica gel gave the diacetate **20** as a colorless oil, yield: 37.5 g (90%). $[\alpha]_D^{20}$ = + 0.4° (c = 1.335, $CHCl_3$). IR ($CHCl_3$): ν = 3012, 2962, 2659, 1732, 1473, 1428, 1370, 1250, 1112, 1036 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 7, 3 H), 1.08 (s, 9 H), 1.72 (s, 4 H), 1.80 (s, 3 H), 2.06 (s, 3 H), 2.36 (m, 1 H), 3.99 (dt, *J* = 11.5, 4, 1 H), 5.00 (ddd, *J* = 10, 5, 4, 1 H), 5.07 (m, 1 H), 7.39 (m, 6 H), 7.65 (d, *J* = 8, 4 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 6.5 (CH_3), 19.2 (C), 21.1 (CH_3), 21.3 (CH_3), 26.9 (3 CH_3), 30.0 (CH_2), 33.2 (CH_2), 38.5 (CH), 67.8 (CH), 68.5 (CH), 70.2 (CH), 127.6 (4 CH), 129.7 (2 CH), 133.7 (C), 134.1 (C), 135.8 (4 CH), 169.8 (CO), 170.3 (CO). MS (EI): *m/z* (%) = 411 (M^+ – *t*-butyl, 16), 351 (15), 309 (10), 241 (100), 199 (75), 181 (32), 135 (13), 93 (25), 43 (30). Anal. Calc. for $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74. Found: C, 70.01; H, 7.71.

(1*S*,2*S*,3*R*,5*S*)-2-Methyl-3-(1,1-dimethylethyl)diphenylsiloxycyclohexane-1,5-diol (21)

A solution of the diacetate **20** (14.9 g, 31.8 mmol) in methanol (500 ml) was treated with K_2CO_3 (20 g, 0.15 mol) and the mixture was heated at reflux for 1 h. After cooling to room temperature, the mixture was poured into brine and extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo to afford the diol **21** as a light yellow oil (the compound was pure enough for the following reaction), yield: 11.4 g (93%). $[\alpha]_D^{20} = -13.4°$ (c = 1.010, $CHCl_3$). IR ($CHCl_3$): ν = 3609, 3497, 3012, 2933, 2860, 1734, 1473, 1428, 1376, 1260, 1112, 1059, 997 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 7, 3 H), 1.09 (s, 9 H), 1.40 (m, 1 H), 1.44 (dd, *J* = 10.5, 4, 1 H), 1.57 (m, 1 H), 2.00 (m, 1 H), 2.31 (m, 1 H), 3.50 (d, *J* = 10, 1 H), 3.89 (m, 1 H), 4.10 (m, 1 H), 4.40 (m, 1 H), 7.41 (m, 6 H), 7.69 (m, 4 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 19.7 (C), 27.3 (3 CH_3), 38.9 (CH), 41.2 (CH_2), 42.4 (CH_2), 62.5 (CH), 72.5 (CH), 75.3 (CH), 127.7 (4 CH), 129.8 (2 CH), 132.5 (C), 133.4 (C), 135.8 (2 CH), 135.9 (2 CH). MS (EI): *m/z* (%) = 385 (M^+ + 1, 3), 367 (4), 327 (12), 309 (19), 199 (100), 139 (56), 111 (15), 93 (15), 58 (20). Anal. Calc. for $C_{23}H_{32}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.91; H, 8.40.

(1*R*,2*S*,3*S*,5*S*)-3,5-Di(methoxymethoxy)-2-methyl-1-(1,1-dimethylethyl)diphenylsiloxycyclohexane (22)

A solution of the diol **21** (10.7 g, 27.9 mmol) in dichloromethane (600 ml) was treated with *N*,*N*-diisopropylethylamine (10.8 g, 83.7 mmol), methoxymethyl chloride (6.7 g, 83.7 mmol), and DMAP (1.02 g, 8.4 mmol) and then stirred at r. t. overnight. The mixture was poured into brine and extracted with dichloromethane. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by chromatography (ethyl acetate/hexane) on silica gel to provide the ether **22** as a yellow oil, yield: 12.3 g (93%). $[\alpha]_D^{20} = -10.2°$ (c = 0.700, $CHCl_3$). IR ($CHCl_3$): ν = 3012, 2933, 2891, 1734, 1473, 1428, 1378, 1229, 1111, 1044, 976 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 7, 3 H), 1.08 (s, 9 H), 1.58 (m, 3 H), 1.73 (br d, *J* = 6, 1 H), 2.28 (m, 1 H), 3.15 (s, 3 H), 3.31 (s, 3 H), 3.78 (dt, *J* = 11, 4, 1 H), 3.83 (m, 1 H), 4.08 (m, 1 H), 4.21 (d, *J* = 6, 1 H), 4.29 (d, *J* = 6, 1 H), 4.59 (s, 2 H), 7.39 (m, 6 H), 7.69 (m, 4 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 5.6 (CH_3), 19.4 (C), 27.1 (3 CH_3), 31.3 (CH_2), 32.9 (CH_2), 39.4 (CH), 55.0 (CH_3), 55.2 (CH_3), 68.7 (CH), 69.9 (CH), 72.7 (CH), 94.4 (CH_2), 94.8 (CH_2), 127.5 (4 CH), 129.5 (2 CH), 134.3 (C), 134.5 (C), 135.8 (4 CH). MS (EI): *m/z* (%) = 411 (M^+ - CH_3OCH_2O, 1), 349 (3), 323 (10), 309 (18), 213 (22), 199 (8), 135 (5), 45 (100). Anal. Calc. for $C_{27}H_{40}O_5Si$: C, 68.61; H, 8.53. Found: C, 68.57; H, 8.43.

(1*R*,2*R*,3*S*,5*R*)-3,5-Di(methoxymethoxy)-2-methylcyclohexanol (23)

A mixture of the ether **22** (6.4 g, 13.5 mmol) and tetra-*n*-butylammonium fluoride trihydrate (5.28 g, 20 mmol) in THF (150 ml) was stirred at room temperature overnight. Brine was added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the solvent was evaporated. Purification of the residue by chromatography (ethyl acetate/hexane) on silica gel afforded the alcohol **23** as a colorless oil, yield: 2.30 g (72%). $[\alpha]_D^{20} = +10.3°$ (c = 0.660, $CHCl_3$). IR ($CHCl_3$): ν = 3522, 3012, 2935, 2826, 1456, 1428, 1380, 1152, 1102, 1042, 916 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 7, 3 H), 1.43 (dd, *J* = 12, 4, 1 H), 1.52 (dd, *J* = 12, 5, 1 H), 1.78 (m, 1 H), 2.33 (m, 2 H), 3.00 (d, *J* = 10, 1 H), 3.36 (s, 3 H), 3.40 (s, 3 H), 3.91 (m, 2 H), 4.10 (m, 1 H), 4.60 (d, *J* = 6, 1 H), 4.67 (d, *J* = 6, 1 H), 4.70 (d, *J* = 6, 1 H), 4.73 (d, *J* = 6, 1 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 13.5 (CH_3), 36.3 (CH_2), 38.2 (CH), 39.8 (CH_2), 55.3 (CH_3), 55.8 (CH_3), 68.1 (CH), 71.8 (CH), 78.6 (CH), 94.9 (CH_2), 95.7 (CH_2). MS (EI): *m/z* (%) = 189 (M^+ – CH_3OCH_2, 2), 157 (8), 140 (12), 117 (27), 77 (24), 56 (30), 45 (100). Anal. Calc. for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.51; H, 9.58.

(2*S*,3*S*,5*S*)-3,5-Di(methoxymethoxy)-2-methylcyclohexanone (24)

A solution of oxalyl chloride (1.27 g, 10 mmol) in dichloromethane (50 ml) was treated with dimethylsulfoxide (1.56 g, 20 mmol) at -78°C. After stirring for 20 min, the alcohol **23** (1.90 g, 8.10 mmol) in CH_2Cl_2 (5 ml) was added and the mixture was stirred for 15 min at -30°C. Subsequently, triethylamine (4.04 g, 40 mmol) was added and the mixture was allowed to warm to r. t. After dilution with dichloromethane, the solution was acidified with 1 N HCl. The aqueous layer was reextracted with dichloromethane, the combined organic layers were washed with brine, dried over sodium chloride, filtered, and concentrated in vacuo. Purification of the residue by chromatography (ethyl acetate/hexane) on silica gel gave the ketone **24** as a colorless foam, yield: 1.72 g (92%). $[\alpha]_D^{20}$ = + 2.1° (c = 0.795, $CHCl_3$). IR ($CHCl_3$): ν = 3012, 2938, 2892, 1717, 1450, 1378, 1229, 1149, 1104, 1045, 915 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 7, 3 H), 1.82 (br dd, *J* = 12, 10, 1 H), 2.40 (dd, *J* = 12, 10, 1 H), 2.53 (m, 2 H), 2.87 (ddd, *J* = 12, 5, 2, 1 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 4.09 (m, 1 H), 4.14 (m,1 H), 4.58 (d, *J* = 6, 1 H), 4.68 (s, 2 H), 4.69 (d, *J* = 6, 1 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 10.6 (CH_3), 36.5 (CH_2), 48.2 (CH_2), 48.8 (CH), 55.4 (CH_3), 55.8 (CH_3), 72.2 (CH), 77.8 (CH), 95.2 (CH_2), 95.9 (CH_2), 207.9 (CO). MS (EI): *m/z* (%) = 187 (M^+ – CH_3OCH_2, 3), 170 (7), 156 (12), 126 (18), 108 (15), 85 (75), 57 (40), 45 (100). Anal. Calc. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.69; H, 8.59.

(1*R*,2*S*,3*S*,5*S*)-1-Ethynyl-3,5-di(methoxymethoxy)-2-methylcyclohexanol (25)

At 0°C THF (50 ml) was saturated with acetylene for 20 min. Subsequently, a 2.5 M solution of *n*-butyllithium in hexane (11.8 ml, 29.5 mmol) was added dropwise and the mixture was stirred for 20 min. Then the ketone **24** (1.37 g, 5.9 mmol) in THF (5 ml) was added and stirring was continued for 2 h. The mixture was poured into an aqueous solution of ammonium chloride and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the solvent was evaporated. Purification of the residue by chromatography (ethyl acetate/hexane) on silica gel provided the alkyne **25** as a colorless oil, yield: 1.13 g (74%). $[\alpha]_D^{20}$ = – 4.5° (c = 0.750, $CHCl_3$). IR ($CHCl_3$): ν = 3490, 3308, 3013, 2937, 1454, 1381, 1229, 1155, 1095, 1034, 920 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 7, 3 H), 1.47 (br t, *J* = 12, 1 H), 1.72 (dd, *J* = 12, 11, 1 H), 1.87 (dq, *J* = 7, 4, 1 H), 2.43 (m, 1 H), 2.45 (s, 1 H), 2.61 (br d, *J* = 12, 1 H), 3.38 (s, 3 H), 3.42 (s, 3 H), 3.80 (s, 1 H), 3.98 (m, 1 H), 4.07 (tt, *J* = 10.5, 4, 1 H), 4.60 (d, *J* = 6, 1 H), 4.64 (d, *J* = 6, 1 H), 4.70 (d, *J* = 6, 1 H), 4.73 (d, *J* = 6, 1 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ = 12.3 (CH_3), 36.8 (CH_2), 42.4 (CH), 46.4 (CH_2), 55.3 (CH_3), 56.1 (CH_3), 67.9 (CH), 70.9 (C), 71.8 (C), 78.5 (CH), 86.4 (CH), 95.0 (CH_2), 95.9 (CH_2). MS (CI/NH_3): *m/z* (%) = 276 (M^+ + 18, 10), 258 (M^+, 6), 250 (38), 218 (10), 188 (100), 171 (38), 108 (10). Anal. Calc. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.37; H, 8.59.

(3*S*,5*R*)-1-Ethynyl-3,5-di(methoxymethoxy)-2-methylcyclohexene (26)

A solution of the alkyne **25** (258 mg, 1 mmol) in pyridine (10 ml) was treated with thionyl chloride (357 mg, 3 mmol) at 0°C. The mixture was stirred for 10 min, poured into water, and extracted with ethyl acetate. The combined organic layers were washed with a solution of sodium bicarbonate and brine and dried over sodium sulfate. Filtration, removal of the solvent, and chromatography of the residue (ethyl acetate/hexane) on silica gel afforded the enyne **26** as a colorless oil, yield: 187 mg (78%). $[\alpha]_D^{20} = -47.1°$ (c = 1.125, $CHCl_3$). IR ($CHCl_3$): $\nu = 3305, 3013, 2936, 1442, 1384, 1229, 1150, 1101, 1045, 915\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.72$ (ddd, $J = 15, 10, 5$, 1 H), 2.00 (br s, 3 H), 2.18 (m, 2 H), 2.60 (dd, $J = 15, 4$, 1 H), 3.10 (s, 1 H), 3.38 (s, 3 H), 3.43 (s, 3 H), 3.99 (m, 1 H), 4.11 (m, 1 H), 4.67 (d, $J = 6$, 1 H), 4.70 (s, 2 H), 4.78 (d, $J = 6$, 1 H). ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): $\delta = 18.9$ (CH_3), 34.7 (CH_2), 36.7 (CH_2), 55.3 (CH_3), 55.7 (CH_3), 69.0 (CH), 74.9 (CH), 77.5 (C), 83.1 (CH), 95.2 (CH_2), 96.1 (CH_2), 115.6 (C), 141.2 (C). MS (CI/NH_3): *m/z* (%) = 258 ($M^+ + 18$, 20), 241 ($M^+ + 1$, 2), 228 (10), 196 (100), 136 (25), 119 (27). Anal. Calc. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.11; H, 8.45.

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