The First Synthesis of (4*S*,5*R*,6*R*)-5,6-Dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carboxylic Acid

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A putative acid metabolite of a novel highly effective antiparkinsonian agent, (4*S*,5*R*,6*R*)-5,6-dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carboxylic acid (**5**), was synthesized for the first time. Several synthetic approaches based on different transformations of O-bearing monoterpenoids of the pinane and *p*-menthane series were developed and tested in the course of the study. Acid **5** was synthesized starting from a commercially available monoterpenoid, (−)-verbenone, in a total yield of 4.4% over eight steps.

Introduction. – Previously, we found that monoterpenoid (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**1**) exhibits high antiparkinsonian activity *in vivo* combined with low acute toxicity [1][2], which makes it highly promising for further research. One of the most important tasks in the development of new drugs is the investigation of their metabolism using usually a combination of chromatography and MS analyses. In the case of monoterpenoids, this task is complicated by the fact that it is often very difficult to relate reliably the MS spectrum to the monoterpenoid structure in the absence of the MS data for individual compounds and even to determine their molecular weights. All this makes it necessary to synthesize a set of possible metabolites of **1** (*Fig.*).

Based on the available literature data on the metabolism of monoterpenoids of the *p*-menthane series [3–6], the formation of products of hydroxylation of Me groups and subsequent oxidation to corresponding acids may be expected. It should be noted that the presence of several functional groups of comparable reactivity and three

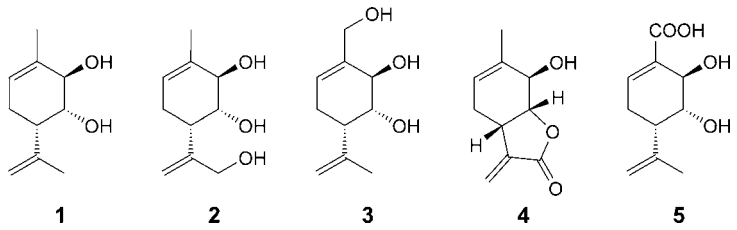


Figure. *Structures of* **1**–**5**

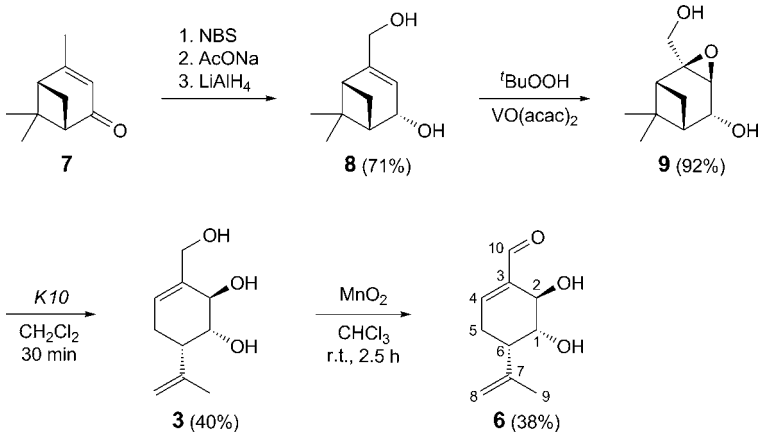
asymmetric centers in **1** causes considerable difficulties in planning and performing its transformations [7][8]. However, previously, we successfully synthesized a number of derivatives of **1** (triols **2** [9] and **3** [10], and lactone **4** [11]) that can be considered as possible metabolites. The aim of this work was the synthesis of carboxylic acid **5**.

Results and Discussion. – *Synthesis Based on Triol* **3**. Given the structures of the previously synthesized compounds **2**–**4**, an approach to the synthesis of **5** seems quite obvious and can include stepwise oxidation of triol **3** first to aldehyde **6** and then to acid **5**. Triol **3** was synthesized starting from (−)-verbenone (**7**) according to the procedure described in [10] *via* the intermediate formation of diol **8** with the pinane scaffold, its oxidation to epoxide **9**, and subsequent isomerization of the epoxide to the product with the *p*-menthane scaffold, catalyzed by *Montmorillonite K10* clay (*Scheme 1*). However, further oxidation of **3** was faced with difficulties associated primarily with insufficient selectivity of transformations due to the presence of two allylic OH groups and a vicinal diol moiety in the molecule that undergo rather easily oxidative transformations. For example, significant resinification and the formation of a complex product mixture that lacked the corresponding aldehyde were observed in the *Swern* oxidation of triol **3**. Compound **6** could be obtained in the acceptable yield of 38% by the oxidation of **3** under neutral conditions using MnO_2 in $CHCl_3$ (*Scheme 1*).

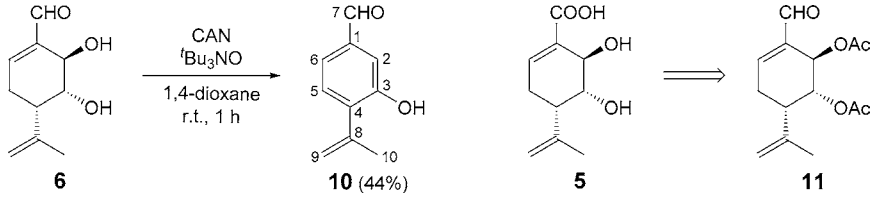
Currently, there are a number of oxidative systems that enable the selective oxidation of the CHO to the COOH group in complex polyfunctional compounds [12–15]. We used those that might be suitable for the oxidation of the substrate containing OH groups and a conjugated C=C bond.

Oxidation of aldehyde **6** using the $^tBu_3NO/(NH_4)_2Ce(NO_3)_6$ (CAN) system resulted in the formation of the aromatic product **10** (44% yield) instead of the target acid **5** (*Scheme 2*). All attempts to obtain acid **5** by the oxidation of **6** with Ag_2O under very different conditions were unsuccessful: the reaction did not occur without base, whereas a complex mixture of products was formed in the presence of even a small amount of base. The use of $NaClO_2$ as oxidant made it possible to adjust the conditions,

Scheme 1. *Syntheses of Triol* **3** *and Aldehyde* **6**



Scheme 2. *Transformations of* **6** *and Structure of* **11**



under which the formation of **5** in trace amounts (<1–2%) was observed on the background of significant resinification.

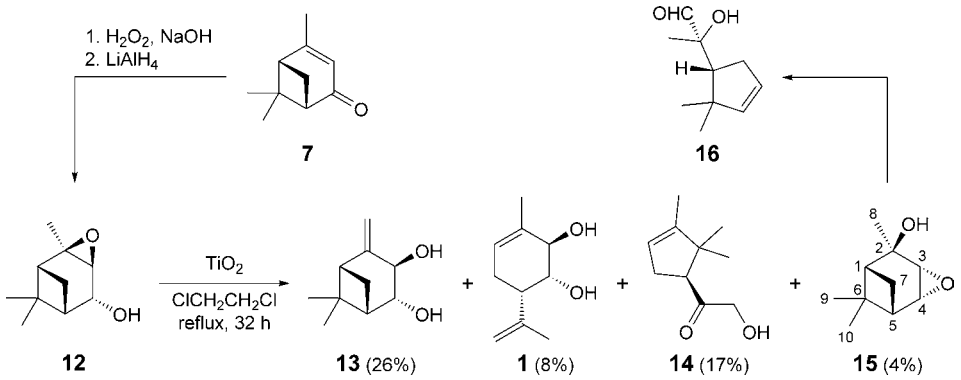
Therefore, oxidation of **6** containing free OH groups did not lead to the desired result that prompted us to the synthesis and use of **11** as precursor for acid **5**, in which OH groups were protected as AcO groups (*Scheme 2*).

Synthesis of Aldehyde **11**. The synthesis of **11** was carried out starting from the epoxide of (−)-*cis*-verbenol (**12**) that, in turn, can be obtained from (−)-verbenone (**7**) by the consecutive epoxidation and reduction in accordance with the procedure described in [16] (*Scheme 3*). Previously, we found that the use of TiO_2 as catalyst enables isomerization of epoxide **12** to diol **13** with preservation of the pinane scaffold [17], which, in general, is not a trivial task.

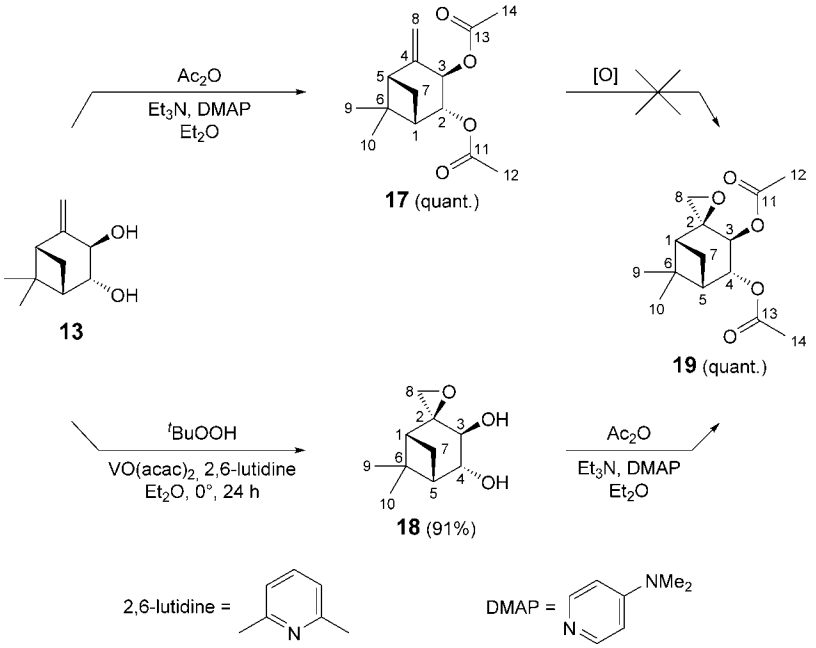
During the synthesis of **13**, it was found that reducing the amount of solvent (from 15 ml of $ClCH_2CH_2Cl$ per 0.1 g of epoxide **12** [17] to 55 ml of $ClCH_2CH_2Cl$ per 4 g of **12** in the present work) led to a decrease in the yield of the desired product **13** from 40 to 26%. However, in addition to the expected compounds **1**, **13**, and **14**, rearranged epoxide **15**, not described previously, was isolated under these conditions. This compound is of interest, because it was previously suggested as possible intermediate in the formation of hydroxyaldehyde **16** from the epoxide of (−)-*cis*-verbenol **12** [18]. Indeed, epoxide **15** turns slowly into hydroxyaldehyde **16** upon storage at room temperature (*Scheme 3*).

Acylation of diol **13** furnished **17** in quantitative yield (*Scheme 4*), but attempts to conduct the epoxidation of diacetate **17** using AcOOH or *m*-chloroperoxybenzoic acid

Scheme 3. *Synthesis and Rearrangements of (−)*-cis-*Verbenol Epoxide* (**12**)



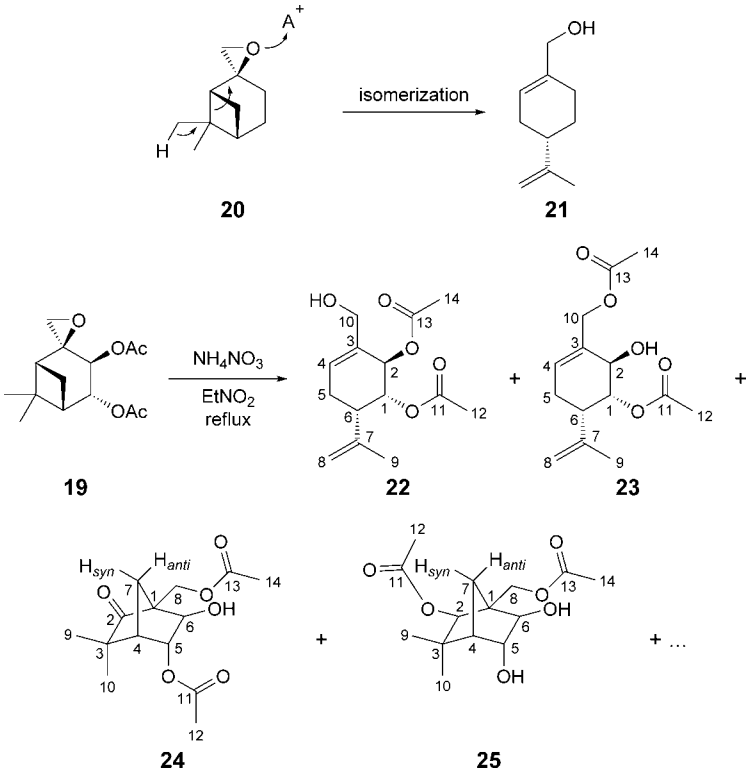
Scheme 4. *Synthesis of* **19**



(*m*-CPBA) under different conditions did not provide a positive result, probably due to steric reasons. Therefore, we had to interchange the steps, with the epoxidation of **13** being conducted first, followed by acylation. The reaction of **13** with ^{t}BuOOH in the presence of $VO(acac)_2$ in boiling toluene for 40 min resulted in the formation of a mixture of aldehydes due to the secondary reactions of epoxide opening and isomerization. An improved method that involved conducting the epoxidation in ether at 0° using ^{t}BuOOH in the presence of $VO(acac)_2$ and 2,6-lutidine [19] provided the desired epoxide **18** in 91% yield after purification by column chromatography (SiO_2). The acylation of epoxide **18** furnished diacetate **19** in quantitative yield (*Scheme 4*).

Although isomerization of the epoxide of *β*-pinene (**20**) to perillyl alcohol (**21**) (*Scheme 5*) is well studied [7], this is not true for derivatives of monoterpenoid **20**. Acid-activated *Montmorillonite* clays are often used as catalyst for reactions of monoterpenoids [20]. Surprisingly, epoxide **19** appeared to be stable in the presence of *Montmorillonite K10* clay in CH_2Cl_2, while carrying out the reaction without the solvent led to the formation of a complex product mixture containing only a small amount of **22**. Similarly, isomerization of epoxide **19** in the presence of TsOH and *N*-methylpyrrolidone mixtures in various ratios in CH_2Cl_2 provided a complex mixture of products with a small amount of product **22**. The largest, but not very high, content of **22** in a reaction product mixture was achieved during isomerization in the presence of NH_4NO_3, according to a method [21], which was previously used successfully for the isomerization of the epoxide of *β*-pinene to perillyl alcohol ([4-(prop-1-en-2-yl)cyclohex-1-en-1-yl]methanol). $EtNO_2$ was chosen instead of $MeNO_2$ as solvent to increase the reaction rate due to a higher boiling point, but even in this case, complete

Scheme 5. *Transformations of* **19** *in the Presence of* NH_4NO_3



conversion was achieved only after 10 h of boiling. As a result, we obtained a complex mixture of products that was used for isolation of the desired compound **22** (11%), its regioisomer **23** (7%), and products **24** (10%) and **25** (5%) with the bornane scaffold (*Scheme 5*).

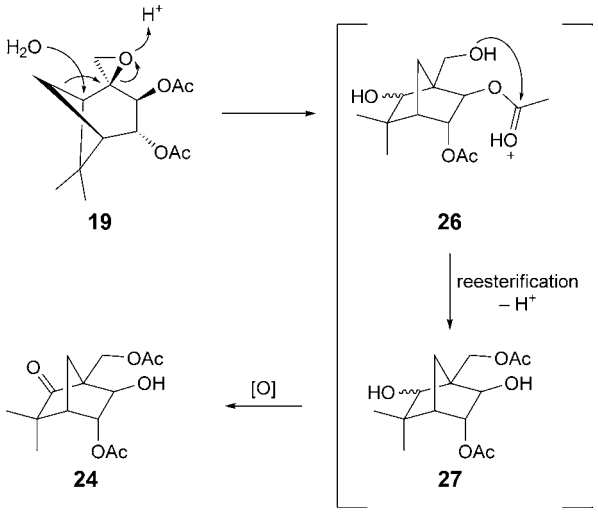
The formation of **24** may occur according to *Scheme 6*, including acid-catalyzed isomerization (with addition of H_2O) of epoxide **19** to an intermediate with the bornane scaffold, **26**, intramolecular transesterification to **27**, and subsequent oxidation to product **24**. Compound **25** is presumably also formed starting from intermediate **27** *via* intra- or intermolecular transfer of an AcO group.

Oxidation of **22** using MnO_2 in $CHCl_3$ for 6 h afforded the desired protected aldehyde **11** in 78% yield (*Scheme 7*).

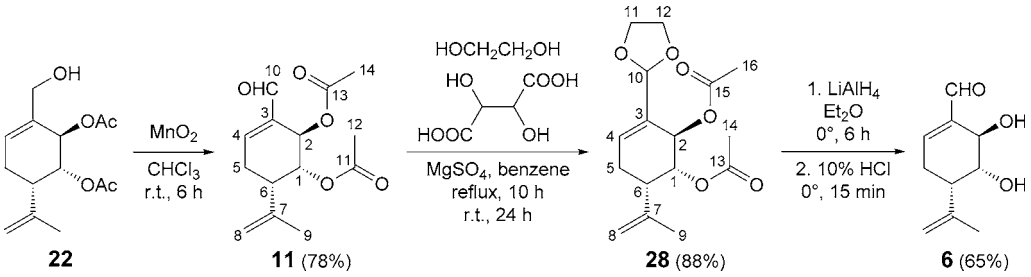
Unfortunately, attempts to oxidize **11** to a carboxyl compound for its further saponification to the desired acid **5** failed either using Ag_2O or $NaClO_2$ as oxidant or using the *Corey* method [22] or its modification with Me_3SiCN instead of NaCN [23].

Although **11** can be converted into derivative **28** in good yield (88%) under conditions reported earlier [24], and then, after removal of protective groups, aldehyde **6** can be obtained in 65% yield (*Scheme 7*), the synthetic value of this approach for the production of **6** is not high due to a large number of steps and a low yield in the isomerization step.

Scheme 6. *Possible Mechanism of the Formation of* **24**



Scheme 7. *Transformations of* **22**

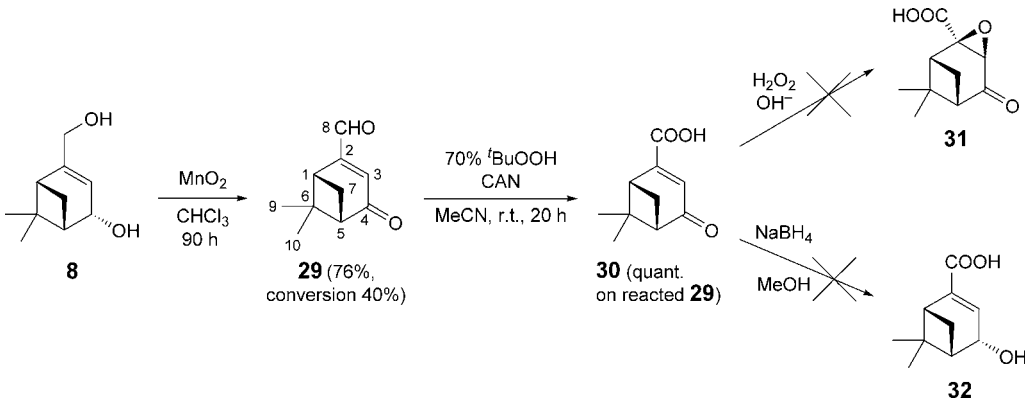


Synthesis of Acid **5**. Since the first two approaches were unsuccessful, we developed an alternative procedure for the synthesis of acid **5**, based on diol **8** with the pinane scaffold that we used previously in the synthesis of triol **3** (*Scheme 1*).

Oxidation of **8** using MnO_2 in $CHCl_3$ produced ketoaldehyde **29** in 76% yield (*Scheme 8*). It should be noted that **29** appeared to be unstable at room temperature, which should be considered when planning and carrying out synthesis with its participation. The oxidation of **29** was carried out using the ^{t}BuOOH/CAN system for 20 h. Conversion of **29** was 43%, and the yield of the desired acid **30** was quantitative based on reacted **29**. However, attempts to epoxidize **30** for production of **31** or reduction for the synthesis of hydroxy acid **32** were unsuccessful.

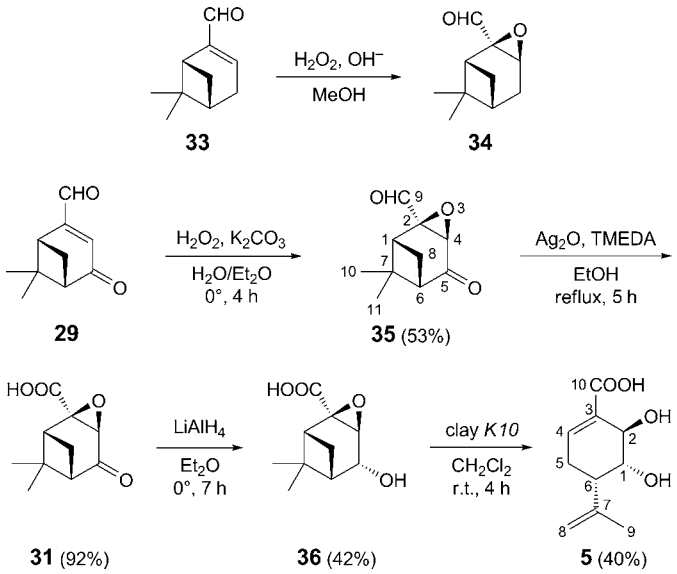
Therefore, we had to follow the way that initially seemed to be the most complex one and involved selection of conditions for the epoxidation of unstable ketoaldehyde **29**, followed by oxidation of the CHO to the COOH group in the presence of the epoxy function in order to obtain key acid **31**. The use of the H_2O_2/NaOH/MeOH/H_2O system, which was previously exploited for the synthesis of **34** from myrtenal (**33**;

Scheme 8. *Synthesis of Ketoacid* **30**



Scheme 9) [25], at 0° for the epoxidation led, in the case of **29**, to a mixture of several products with a small amount of **35**, which also appeared to be unstable under column chromatography conditions. Based on the method from [26] that was previously used for the epoxidation of C=C bonds conjugated with two C=O groups by means of H_2O_2 and involved the use of K_2CO_3 as base and acetone as solvent, in the presence of a small amount of H_2O, we varied the ratio of all components of the mixture and the reaction conditions. However, we were not able to achieve simultaneously the complete conversion and the absence of condensation products. At the same time, replacing acetone with the H_2O/Et_2O biphasic system allowed us to find conditions furnishing **35** in 53% yield (*Scheme 9*).

Scheme 9. *Synthesis of Acid* **5**



Use of the *t*BuOOH/CAN system, which we successfully exploited for conversion of **29** to acid **30**, appeared to be ineffective for the oxidation of **35**. Epoxy keto acid **31** could be obtained by the oxidation of **35** using Ag_2O in the presence of tetramethylethylenediamine (TMEDA). The product yield was 92% (*Scheme 9*). The reduction of **31** using $LiAlH_4$ furnished **36** in 42% yield. Finally, isomerization of epoxide **36** in the presence of *K10* clay provided the desired acid **5** in 40% yield. The yield of **5** over eight steps on (−)-verbenone (**7**) basis was 4.4%.

Conclusions. – The synthesis of the putative metabolite of antiparkinsonian agent **1**, (4*S*,5*R*,6*R*)-5,6-dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carboxylic acid (**5**), was developed and conducted for the first time. The yield of **5** over eight steps based on (−)-verbenone (**7**) was 4.4%. Methods for producing large amounts of O-bearing monoterpenoids with pinane and *p*-menthane scaffolds, which to the best of our knowledge were not previously described in the literature, were developed in the course of this study. For most of the reactions, various synthetic approaches were tested, and methods to obtain desired products in acceptable yields and with acceptable selectivity were chosen.

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Experimental Part

General. Reagents and solvents were purchased from commercial suppliers and used as received. Dry solvents were obtained according to standard procedures. Column chromatography (CC): silica gel (SiO_2; 60–200 μm, *Macherey–Nagel*). GC: *7820A* gas chromatograph (*Agilent Tech.*, *USA*); detector, FID; *HP-5* capillary column (0.25 mm × 30 m × 0.25 μm); carrier gas, He (flow rate, 2 ml min^{-1}; flow division, 99 : 1). Optical rotations: *polAAr 3005* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-500* apparatus (500.13 and 125.76 MHz, resp.); in $CDCl_3$, $CCl_4/CDCl_3$ 1 : 1, or $CDCl_3/CD_3OD$ 10 : 1 (depending on solubility); δ in ppm rel. to residual $CHCl_3$ (δ(H) 7.24, δ(C) 76.90), *J* in Hz. The structure of the products was determined by analyzing the ^{1}H- and ^{13}C-NMR spectra, ^{1}H,^{1}H-double-resonance, ^{13}C,^{1}H-type 2D-COSY (*J*(C,H) = 160) and COLOC (*J*(C,H) = 10) spectra. HR-EI-MS: *DFS Thermo Scientific* spectrometer (70 eV, full scan mode (*m*/*z* 15–500), direct sample administration); in *m*/*z*. Spectral and analytical investigations were carried out at Collective Chemical Service center of Siberian Branch of the Russian Academy of Sciences.

(4S,5R,6R)-5,6-Dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carbaldehyde (**6**). (1*R*,2*R*,6*S*)-3-(Hydroxymethyl)-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**3**; $[\alpha]_D^{28} = -42.3$ ($c = 0.35$, $CHCl_3$)) was obtained from (−)-verbenone (**7**; $[\alpha]_D^{25} = -210.5$ ($c = 0.77$, $CHCl_3$); *Aldrich*) according to the procedure described in [10]. MnO_2 was prepared by the following method. Hot solns. of $MnSO_4 \cdot 5\ H_2O$ (6.74 g) in H_2O (20 ml) and NaOH (2.4 g) in H_2O (6 ml) were added simultaneously dropwise over 10–15 min to a soln. of $KMnO_4$ (4.94 g) in H_2O (40 ml) heated to 75–80°. The mixture was stirred at 75–80° for 100 min. Then, it was cooled and filtered. The precipitate was washed with H_2O (6 × 40 ml), acetone (4 × 40 ml), and Et_2O (3 × 30 ml) and dried in a stream of air on the filter to give 7.76 g MnO_2 reagent. $CHCl_3$ was washed with sat. $NaHCO_3$, dried ($CaCl_2$), and distilled over P_2O_5. MnO_2 reagent (754 mg) was added to a soln. of (1*R*,2*R*,6*S*)-3-(hydroxymethyl)-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**3**; 64.3 mg, 0.349 mmol) in $CHCl_3$ (10 ml). The mixture was stirred at r.t. for 2.5 h and then filtered. The precipitate was washed with $CHCl_3$ (7 × 10 ml). The solvent was distilled off to give (4*S*,5*R*,6*R*)-5,6-dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carbaldehyde (**6**; 17.2 mg, 0.0944 mmol, 38% on reacted triol **3**). In addition, the precipitate was washed with EtOH (3 × 5 ml). The solvent was distilled off to give starting triol **3** (19.2 mg, 0.104 mmol, conversion 70%). ^{1}H-NMR ($CDCl_3$): 1.86 (br. *s*, Me(9)); 2.35 (*ddd*, ^2J =

18.0, $J(5_{eq},4) = 5.4$, $J(5_{eq},6) = 3.4$, H_{eq}–C(5)); 2.52–2.66 (*m*, H_{ax}–C(5), H–C(6)); 4.05 (br. *s*, H–C(1)); 4.53 (br. *s*, H–C(2)); 4.88 (br. *s*, 1 H of CH_2(8)); 5.03–5.05 (*m*, all $J \leq 2.0$, 1 H of CH_2(8)); 7.00 (*dd*, $J(4,5_{eq}) = 5.4$, $J(4,5_{ax}) = 2.3$, H–C(4)); 9.51 (*s*, H–C(10)). ^{13}C-NMR: 22.63 (*q*, C(9)); 25.87 (*t*, C(5)); 40.14 (*d*, C(6)); 65.32 (*d*, C(2)); 69.37 (*d*, C(1)); 111.96 (*t*, C(8)); 139.76 (*s*, C(3)); 144.73 (*s*, C(7)); 152.27 (*d*, C(4)); 194.28 (*d*, C(10)). HR-EI-MS: 182.0931 (M^+, $C_{10}H_{14}O_3^+$; calc. 182.0937).

3-Hydroxy-4-(prop-1-en-2-yl)benzaldehyde (**10**). A soln. of **6** (6.4 mg, 0.035 mmol) in 1,4-dioxane (2 ml) was added to a soln. of CAN (1.9 mg, 3.5 μmol) and 10% ^{t}Bu$_3$NO · H$_2$O (0.2 ml, 0.091 mmol) in 1,4-dioxane (1 ml). The mixture was stirred at r.t. for 1 h. Na_2SO_3 (50 mg) and brine (3 ml) were added. The mixture was extracted with $CHCl_3$ (3 × 5 ml). The combined extract was washed with the soln. (7 ml) obtained by addition of conc. HCl to brine (10 ml) and decantation from precipitate of fallen NaCl. Then the extract was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off. The residue was chromatographed (SiO_2 (0.6 g); hexane/AcOEt) to afford 3-hydroxy-4-(prop-1-en-2-yl)benzaldehyde (**10**; 2.5 mg, 0.154 mmol, 44%). ^{1}H-NMR ($CDCl_3$): 2.13 (*dd*, *J*(10,9) = 1.5, 0.9, Me(10)); 5.20–5.21 (*m*, all $J \leq 1.6$, 1 H of CH_2(9)); 5.47 (*dq*, *J*(9,9) = 1.6, *J*(9,10) = 1.5, 1 H of CH_2(9)); 5.77 (br. *s*, OH); 7.28 (*d*, *J*(5,6) = 7.6, H–C(5)); 7.39 (*d*, *J*(2,6) = 1.6, H–C(2)); 7.40 (*dd*, *J*(6,5) = 7.6, *J*(6,2) = 1.6, H–C(6)); 9.92 (*s*, H–C(7)). ^{13}C-NMR: 25.26 (*q*, C(10)); 116.02 (*d*, C(2)); 117.10 (*t*, C(9)); 121.83 (*d*, C(6)); 128.48 (*d*, C(5)); 136.71 (*s*, C(1)); 141.21 (*s*, C(4)); 143.04 (*s*, C(8)); 152.53 (*s*, C(3)); 191.51 (*d*, C(7)).

(1S,2R,3R,5R)-6,6-Dimethyl-4-methylidenebicyclo[3.1.1]heptane-2,3-diol (**13**), *(1S,2R,4R,5R,6R)-5,7,7-Trimethyl-3-oxatricyclo[4.1.1.0^{2,4}]octan-5-ol* (**15**). (−)-*cis*-Verbenol epoxide (**12**; 70% ee) was obtained from (−)-verbenone (**7**; $[\alpha]_D^{25} = -210.5$ (*c* = 0.77, $CHCl_3$); *Aldrich*) according to the procedure described in [16]. TiO_2 (*Degussa AG*; *Aerolyst 7708*, anatase > 70%, $S_{BET} = 45$ m^2 g^{-1}) was grinded to powder and calcined at 225° for 10 h. A soln. of (−)-*cis*-verbenol epoxide (**12**; 4.001 g, 23.78 mmol) in anh. $ClCH_2CH_2Cl$ (35 ml) was added to a suspension of TiO_2 (2.309 g, 28.9 mmol) in $ClCH_2CH_2Cl$ (30 ml). The mixture was stirred under reflux for 32 h. The mixture was concentrated to 5 ml and filtered through a column (SiO_2 (17 g); AcOEt). The solvent was distilled off. The residue (3.90 g) was separated by CC (SiO_2 (19 g); AcOEt/hexane, gradient) to give (1*S*,2*R*,3*R*,5*R*)-6,6-dimethyl-4-methylidenebicyclo[3.1.1]heptane-2,3-diol (**13**; 1.050 g, 6.24 mmol, 26%), (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**1**; 317 mg, 1.88 mmol, 8%), 2-hydroxy-1-[(1*S*)-2,2,3-trimethylcyclopent-3-en-1-yl]ethanone (**14**; 695 mg, 4.13 mmol, 17%), and (1*S*,2*R*,4*R*,5*R*,6*R*)-5,7,7-trimethyl-3-oxatricyclo[4.1.1.0^{2,4}]octan-5-ol (**15**; 143 mg, 0.850 mmol, 4%). The spectral characteristics of **1** and **14** corresponded to those described in [16].

Data of Compound **15**: ^{1}H-NMR ($CDCl_3$): 1.17 (*s*, Me(10)); 1.18 (*s*, Me(9)); 1.43 (*d*, $^2J = 9.7$, H_{anti}–C(7)); 1.45 (*s*, Me(8)); 1.83 (*ddd*, *J*(1,5) = 5.5, $J(1,7_{syn}) = 5.0$, *J*(1,3) = 2.1, H–C(1)); 2.19 (*ddd*, *J*(5,1) = 5.5, $J(5,7_{syn}) = 5.0$, *J*(5,4) = 4.6, H–C(5)); 2.23 (*ddd*, $^2J = 9.7$, $J(7_{syn},1) = J(7_{syn},5) = 5.0$, H_{syn}–C(7)); 2.88 (*dd*, *J*(3,4) = 4.1, *J*(3,1) = 2.1, H–C(3)); 3.60 (*dd*, *J*(4,5) = 4.6, *J*(4,3) = 4.1, H–C(4)). ^{13}C-NMR: 23.45 (*q*, C(10)); 25.33 (*q*, C(8)); 29.60 (*t*, C(7)); 30.96 (*q*, C(9)); 39.86 (*s*, C(6)); 40.19 (*d*, C(5)); 53.57 (*d*, C(3)); 53.68 (*d*, C(1)); 59.44 (*d*, C(4)); 72.29 (*s*, C(2)).

(1S,2R,3R,5R)-6,6-Dimethyl-4-methylidenebicyclo[3.1.1]heptane-2,3-diyl Diacetate (**17**). Et_3N (0.20 ml, 1.44 mmol), Ac_2O (0.10 ml, 1.06 mmol), and 4-(dimethylamino)pyridine (DMAP; 0.3 mg, 2.5 μmol) were added to a soln. of **13** (19.2 mg, 0.114 mmol) in Et_2O (5 ml). The mixture was left for 14 h. H_2O (5 ml) was added, and the mixture was stirred for 5 min, then the aq. phase was separated off. The procedure was repeated. The org. phase was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off to give (1*S*,2*R*,3*R*,5*R*)-6,6-dimethyl-4-methylidenebicyclo[3.1.1]heptane-2,3-diyl diacetate (**17**; 28.7 mg, 0.114 mmol, quantitatively). ^{1}H-NMR ($CDCl_3$): 0.87 (*s*, Me(9)); 1.27 (*s*, Me(10)); 1.30 (*d*, $^2J = 10.7$, H_{anti}–C(7)); 2.01 (*s*, Me(12)); 2.07 (*s*, Me(14)); 2.24 (*ddd*, $J(1,7_{syn}) = 6.7$, *J*(1,5) = 5.4, *J*(1,2) = 3.8, H–C(1)); 2.48 (*ddd*, $^2J = 10.7$, $J(7_{syn},5) = 6.7$, $J(7_{syn},1) = 5.6$, H_{syn}–C(7)); 2.54 (*dd*, $J(5,7_{syn}) = 5.6$, *J*(5,1) = 5.4, H–C(5)); 4.92–4.93 (*m*, all $J < 2.0$, 1 H of CH_2(8)); 5.00 (*dd*, *J*(8,3) = 1.6, $^2J = 1.1$, 1 H of CH_2(8)); 5.08 (*dd*, *J*(2,1) = 3.8, *J*(2,3) = 2.0, H–C(2)); 5.69 (*ddd*, *J*(3,2) = 2.0, *J*(3,8) = 1.6, 1.6, H–C(3)). ^{13}C-NMR: 21.09 (*q*, C(12)); 21.15 (*q*, C(14)); 23.82 (*q*, C(9)); 26.07 (*q*, C(10)); 27.07 (*t*, C(7)); 39.20 (*s*, C(6)); 44.68 (*d*, C(1)); 50.97 (*d*, C(5)); 72.51 (*d*, C(3)); 79.09 (*d*, C(2)); 113.06 (*t*, C(8)); 148.30 (*s*, C(4)); 170.00 (*s*, C(11)); 170.23 (*s*, C(13)).

*(1*R*,2*S*,3*S*,4*R*,5*S*)-6,6-Dimethylspiro[bicyclo[3.1.1]heptane-2,2′-oxirane]-3,4-diol* (**18**). A soln. of **13** (900 mg, 5.35 mmol) in Et_2O was cooled to 0°. 2,6-Lutidine (0.25 ml, 8.08 mmol) and $VO(acac)_2$ (98.1 mg, 0.370 mmol) were added to the soln. Then, a 5.5M soln. of *t*BuOOH in hexane (18.5 ml, 102 mmol) was added dropwise over 3 min. The mixture was stirred at 0° for 1 h then it was put in the refrigerator for 23 h. The color of the mixture changed from saturated red-pink to bright yellow-orange. The mixture was washed with brine (2 × 150 ml). The aq. phase was extracted with AcOEt (3 × 100 ml). The combined org. phase was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off. The residue was purified by CC (SiO_2 (50 g); AcOEt/hexane, gradient) to give (1*R*,2*S*,3*S*,4*R*,5*S*)-6,6-dimethylspiro[bicyclo[3.1.1]heptane-2,2′-oxirane]-3,4-diol (**18**; 895 mg, 4.86 mmol, 91%). $[\alpha]_D^{23} = +2.30$ ($c = 0.667$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.08 (*s*, Me(9)); 1.28 (*s*, Me(10)); 1.39 (*d*, $^2J = 10.8$, H_{anti}–C(7)); 1.60 (*dd*, $J(1,7_{syn}) = 5.4$, $J(1,5) = 5.2$, H–C(1)); 2.21 (*ddd*, $J(5,7_{syn}) = 6.8$, $J(5,1) = 5.2$, $J(5,4) = 3.5$, H–C(5)); 2.34 (*ddd*, $^2J = 10.8$, $J(7_{syn},5) = 6.8$, $J(7_{syn},1) = 5.4$, H_{syn}–C(7)); 2.85 (br. *s*, HO–C(4)); 2.86 (*d*, $^2J = 4.6$, 1 H of CH_2(8)); 2.91 (br. *s*, HO–C(3)); 2.97 (*d*, $^2J = 4.6$, 1 H of CH_2(8)); 4.08 (*dd*, $J(4_{eq},5) = 3.5$, $J(4_{eq},3_{eq}) = 2.7$, H–C(4)); 4.10 (br. *s*, H–C(3)). ^{13}C-NMR: 23.44 (*q*, C(9)); 25.82 (*t*, C(7)); 26.65 (*q*, C(10)); 39.57 (*s*, C(6)); 47.27 (*d*, C(5)); 48.14 (*d*, C(1)); 55.53 (*t*, C(8)); 63.17 (*s*, C(2)); 73.85 (*d*, C(3)); 79.48 (*d*, C(4)). HR-EI-MS: 166.0985 ($[M - H_2O]^+$, $C_{10}H_{14}O_2^+$; calc. 166.0994).

*(1*R*,2*S*,3*S*,4*R*,5*S*)-6,6-Dimethylspiro[bicyclo[3.1.1]heptane-2,2′-oxirane]-3,4-diyl Diacetate* (**19**). Et_3N (6.20 ml, 44.6 mmol), Ac_2O (6.20 ml, 65.6 mmol), and DMAP (10 mg, 82 μmol) were added to a soln. of **18** (895 mg, 4.86 mmol) in Et_2O (100 ml). The mixture was left for 24 h. The solvent was distilled off. The residue was purified by CC (SiO_2 (40 g); AcOEt/hexane, gradient (0–100%)) to give (1*R*,2*S*,3*S*,4*R*,5*S*)-6,6-dimethylspiro[bicyclo[3.1.1]heptane-2,2′-oxirane]-3,4-diyl diacetate (**19**; 1.305 g, 4.86 mmol, quantitatively). $[\alpha]_D^{26} = -5.83$ ($c = 0.480$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.06 (*s*, Me(9)); 1.28 (*s*, Me(10)); 1.51 (*dd*, $J(1,7_{syn}) = 5.5$, $J(1,5) = 5.2$, H–C(1)); 1.55 (*d*, $^2J = 11.2$, H_{anti}–C(7)); 2.02 (*s*, Me(14)); 2.08 (*s*, Me(12)); 2.30 (*ddd*, $J(5,7_{syn}) = 6.8$, $J(5,1) = 5.2$, $J(5,4) = 3.8$, H–C(5)); 2.41 (*ddd*, $^2J = 11.2$, $J(7_{syn},5) = 6.8$, $J(7_{syn},1) = 5.5$, H_{syn}–C(7)); 2.59 (*d*, $^2J = 5.4$, 1 H of CH_2(8)); 3.03 (*d*, $^2J = 5.4$, 1 H of CH_2(8)); 5.17 (*dd*, $J(4_{eq},5) = 3.8$, $J(4_{eq},3_{eq}) = 1.8$, H–C(4)); 5.31 (*d*, $J(3_{eq},4_{eq}) = 1.8$, H–C(3)). ^{13}C-NMR: 20.53 (*q*, C(12)); 21.08 (*q*, C(14)); 23.28 (*q*, C(9)); 24.76 (*t*, C(7)); 26.06 (*q*, C(10)); 39.67 (*s*, C(6)); 44.25 (*d*, C(5)); 48.27 (*d*, C(1)); 54.27 (*t*, C(8)); 60.74 (*s*, C(2)); 71.91 (*d*, C(3)); 78.32 (*d*, C(4)); 169.88 (*s*, C(13)); 170.20 (*s*, C(11)). HR-EI-MS: 267.1228 ($[M - H]^+$, $C_{14}H_{19}O_5^+$; calc. 267.1227).

*(1*R*,2*R*,6*S*)-3-(Hydroxymethyl)-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diyl Diacetate* (**22**). NH_4NO_3 (0.145 g, 1.81 mmol) was added to a soln. of **19** (90 mg, 0.335 mmol) in $EtNO_2$ (6 ml). The mixture was heated under reflux for 4 h; NH_4NO_3 which appeared higher than the level of soln. was periodically returned to the mixture. The solvent was distilled off. A sat. soln. of $NaHCO_3$ (10 ml) was added. The resulting mixture was extracted with AcOEt (3 × 10 ml). The combined extract was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off. The residue was separated by CC (SiO_2 (9 g); AcOEt/hexane, gradient) to give the starting material **19** (18 mg, 0.067 mmol, conversion 80%) and (1*R*,2*R*,6*S*)-3-(hydroxymethyl)-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diyl diacetate (**22**; 21 mg, 0.078 mmol, 29% on reacted **19**). $[\alpha]_D^{28} = -23.9$ ($c = 0.813$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.78 (br. *s*, Me(9)); 1.98 (*s*, Me(12)); 2.10 (*s*, Me(14)); 2.13 (*dddt*, $^2J = 17.7$, $J(5_{eq},6_{ax}) = 5.2$, $J(5_{eq},4) = 5.2$, $J(5_{eq},10) = 1.3$, H_{eq}–C(5)); 2.34–2.42 (*ddm*, $^2J = 17.7$, $J(5_{ax},6_{ax}) = 11.2$, H_{ax}–C(5)); 2.46 (br. *dd*, $J(6_{ax},5_{ax}) = 11.2$, $J(6_{ax},5_{eq}) = 5.2$, H–C(6)); 3.97 (br. *d*, $^2J = 13.2$, 1 H of CH_2(10)); 4.00–4.05 (*dm*, $^2J = 13.2$, other $J \leq 2.0$, 1 H of CH_2(10)); 4.74 (br. *s*, 1 H of CH_2(8)); 4.85–4.87 (*m*, all $J \leq 2.0$, 1 H of CH_2(8)); 5.23 (*dd*, $J(1_{eq},2_{eq}) = 2.8$, $J(1_{eq},6_{ax}) = 2.0$, H–C(1)); 5.28 (*dd*, $J(2_{eq},1_{eq}) = 2.8$, $J(2_{eq},5_{ax}) = 1.1$, H–C(2)); 6.05 (*ddt*, $J(4,5_{eq}) = 5.2$, $J(4,5_{ax}) = 2.4$, $J(4,10) = 1.2$, H–C(4)). ^{13}C-NMR: 20.69 (*q*, C(12)); 20.92 (*q*, C(14)); 22.19 (*q*, C(9)); 24.93 (*t*, C(5)); 39.30 (*d*, C(6)); 64.02 (*t*, C(10)); 67.15 (*d*, C(2)); 69.72 (*d*, C(1)); 111.58 (*t*, C(8)); 129.68 (*d*, C(4)); 132.37 (*s*, C(3)); 143.90 (*s*, C(7)); 169.83 (*s*, C(11)); 170.77 (*s*, C(13)). HR-EI-MS: 268.1306 (M^+, $C_{14}H_{20}O_5^+$; calc. 268.1305).

*Isomerization of (1*R*,2*S*,3*S*,4*R*,5*S*)-6,6-Dimethylspiro[bicyclo[3.1.1]heptane-2,2′-oxirane]-3,4-diyl Diacetate* (**19**). NH_4NO_3 (4.80 g, 60 mmol) was added to a soln. of **19** (1.134 g, 4.227 mmol) in $EtNO_2$ (65 ml). The mixture was heated under reflux for 10 h; NH_4NO_3 which appeared higher than the level of soln. was periodically returned to the mixture. The solvent was distilled off. A soln. of $NaHCO_3$ (5%, 60 ml) and brine (10 ml) were added. The resulting mixture was extracted with AcOEt (6 × 20 ml). The combined extract was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off. The

residue was separated repeatedly by CC (SiO_2 (4.5–20 g); AcOEt/hexane, gradient (0–100% and 0–35%) as the first eluents and with eluents of constant concentrations (22% for **22** and **24**, 17% for **23**, and 21% for **25**)) to give (1*R*,2*R*,6*S*)-3-(hydroxymethyl)-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diyl diacetate (**22**; 126.7 mg, 0.472 mmol, 11.2%), [(1*R*,4*S*,5*R*)-5-(acetyloxy)-6-hydroxy-3,3-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methyl acetate (**24**; 118.6 mg, 0.442 mmol, 10.4%), [(4*S*,5*R*,6*R*)-5-(acetyloxy)-6-hydroxy-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl]methyl acetate (**23**; 82.4 mg, 0.307 mmol, 7.3%), and [(1*R*,2*R*,4*S*,5*R*)-2-(acetyloxy)-5,6-dihydroxy-3,3-dimethylbicyclo[2.2.1]hept-1-yl]methyl acetate (**25**; 61.3 mg, 0.228 mmol, 5.4%)). It should be noted that the mixture contained ten unidentified products in an amount of 1–7%.

Data of Compound **23**: $[\alpha]_D^{26} = -82.4$ ($c = 0.153$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.79 (br. *s*, Me(9)); 1.98, 2.06 (2*s*, Me(12,14)); 2.13 (*ddd*, $^2J = 18.0$, $J(5_{eq}, 4) = 5.3$, $J(5_{eq}, 6_{ax}) = 5.1$, H_{eq}–C(5)); 2.32–2.40 (*ddm*, $^2J = 18.0$, $J(5_{ax}, 6_{ax}) = 11.2$, H_{ax}–C(5)); 2.54 (br. *dd*, $J(6_{ax}, 5_{ax}) = 11.2$, $J(6_{ax}, 5_{eq}) = 5.1$, H–C(6)); 4.02 (br. *s*, H–C(2)); 4.54 (*d*, $^2J = 12.4$, 1 H of CH_2(10)); 4.69 (br. *d*, $^2J = 12.4$, 1 H of CH_2(10)); 4.73 (br. *s*, 1 H of CH_2(8)); 4.85–4.87 (*m*, all $J \leq 2.0$, 1 H of CH_2(8)); 5.19 (*dd*, $J(1_{eq}, 2_{eq}) = 2.8$, $J(1_{eq}, 6_{ax}) = 2.1$, H–C(1)); 6.03–6.05 (*dm*, $J(4, 5_{eq}) = 5.3$, other $J \leq 1.5$, H–C(4)). ^{13}C-NMR: 20.82, 20.89 (2*q*, C(12,14)); 22.20 (*q*, C(9)); 25.41 (*t*, C(5)); 37.96 (*d*, C(6)); 66.29 (*t*, C(10)); 66.83 (*d*, C(2)); 72.45 (*d*, C(1)); 111.39 (*t*, C(8)); 131.04 (*s*, C(3)); 131.10 (*d*, C(4)); 144.39 (*s*, C(7)); 170.32, 170.92 (2*s*, C(11,13)). HR-EI-MS: 208.1093 ($[M - AcOH]^+$, $C_{12}H_{16}O_3^+$; calc. 208.1094).

Data of Compound **24**: $[\alpha]_D^{24} = -0.39$ ($c = 1.017$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.10 (*s*, Me(9)); 1.15 (*s*, Me(10)); 2.00, 2.05 (2*s*, Me(12,14)); 1.98–2.07 (*m*, CH_2(7)); 2.54 (*ddd*, $J(4, 5_{exo}) = 4.3$, $J(4,7) = 2.3$, $J(4, 7) = 1.7$, H–C(4)); 3.34 (*d*, J(OH, 6_{endo}) = 2.5, HO–C(6)); 3.68 (*ddd*, $J(6_{endo}, 5_{exo}) = 3.2$, $J(6_{endo}$, OH) = 2.5, $J(6_{endo}, 7_{syn}) = 2.0$, H–C(6)); 4.33 (*d*, $^2J = 11.6$, 1 H of CH_2(8)); 4.39 (*d*, $^2J = 11.6$, 1 H of CH_2(8)); 4.79 (*dd*, $J(5_{exo}, 4) = 4.3$, $J(5_{exo}, 6_{endo}) = 3.2$, H–C(5)). ^{13}C-NMR: 20.64, 20.77 (2*q*, C(12, 14)); 21.63 (*q*, C(10)); 25.05 (*q*, C(9)); 31.84 (*t*, C(7)); 46.75 (*d*, C(4)); 47.44 (*s*, C(3)); 59.61 (*t*, C(8)); 62.17 (*s*, C(1)); 74.55 (*d*, C(6)); 86.29 (*d*, C(5)); 170.90, 171.82 (2 *s*, C(11,13)); 216.77 (*s*, C(2)). HR-EI-MS: 284.1252 (M^+, $C_{14}H_{20}O_6^+$; calc. 284.1254).

Data of Compound **25**: $[\alpha]_D^{26} = -59.9$ ($c = 0.377$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.01 (*s*, Me(9)); 1.28 (*s*, Me(10)); 1.58 (*ddd*, $^2J = 11.1$, $J(7_{anti}, 2_{endo}) = 1.8$, $J(7_{anti}, 4) = 1.2$, H_{anti}–C(7)); 1.72 (*ddd*, $^2J = 11.1$, $J(7_{syn}, 6_{endo}) = 2.6$, $J(7_{syn}, 4) = 2.0$, H_{syn}–C(7)); 2.01, 2.07 (2 *s*, Me(12,14)); 2.19 (*ddd*, $J(4, 5_{exo}) = 4.2$, $J(4, 7_{syn}) = 2.0$, $J(4, 7_{anti}) = 1.2$, H–C(4)); 3.63 (*ddd*, $J(6_{endo}, 5_{exo}) = 3.5$, $J(6_{endo}$, OH) = 2.1, $J(6_{endo}, 7_{syn}) = 2.6$, H–C(6)); 3.75 (*d*, J(OH, 6_{endo}) = 2.1, HO–C(6)); 4.04 (*d*, $^2J = 11.5$, 1 H of CH_2(8)); 4.52 (*d*, $^2J = 11.5$, 1 H of CH_2(8)); 4.59 (*dd*, $J(5_{exo}, 4) = 4.2$, $J(5_{exo}, 6_{endo}) = 3.5$, H–C(5)); 4.73 (*d*, $J(2_{endo}, 7_{anti}) = 1.8$, H–C(2)). ^{13}C-NMR: 20.58, 20.90 (2*q*, C(12, 14)); 24.01 (*q*, C(9)); 25.88 (*q*, C(10)); 33.11 (*t*, C(7)); 44.47 (*s*, C(3)); 49.29 (*d*, C(4)); 55.35 (*s*, C(1)); 60.13 (*t*, C(8)); 75.06 (*d*, C(6)); 85.26 (*d*, C(5)); 89.44 (*d*, C(2)); 171.46, 171.53 (2*s*, C(11,13)). HR-EI-MS: 251.1272 ($[M - H_2O - OH]^+$, $C_{14}H_{19}O_4^+$; calc. 251.1278).

*(1*R*,2*R*,6*S*)-3-Formyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diyl Diacetate* (**11**). $CHCl_3$ was washed with sat. $NaHCO_3$, dried ($CaCl_2$), and distilled over P_2O_5. A soln. of **22** (11.8 mg, 44.0 μmol) in $CHCl_3$ (5 ml) was added to a suspension of freshly prepared (as described for the synthesis of **6**) MnO_2 reagent (164.8 mg) in $CHCl_3$ (5 ml). The mixture was stirred at r.t. for 6 h. The precipitate was filtered off. The solvent was distilled off to afford (1*R*,2*R*,6*S*)-3-formyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diyl diacetate (**11**; 9.2 mg, 34.5 μmol, 78%). $[\alpha]_D^{25} = -8.0$ ($c = 0.25$, $CHCl_3$). ^{1}H-NMR (CCl_4/$CDCl_3$ 1:1): 1.81 (br. *s*, Me(9)); 1.96 (*s*, Me(12)); 2.05 (*s*, Me(14)); 2.44 (*ddd*, $^2J = 18.0$, $J(5_{eq}, 6_{ax}) = 5.0$, $J(5_{eq}, 4) = 5.0$, H_{eq}–C(5)); 2.48 (br. *dd*, $J(6_{ax}, 5_{ax}) = 10.3$, $J(6_{ax}, 5_{eq}) = 5.0$, H–C(6)); 2.61 (*dddd*, $^2J = 18.0$, $J(5_{ax}, 6_{ax}) = 10.3$, $J(5_{ax}, 4) = 2.4$, $J(5_{ax}, 2_{eq}) = 1.3$, H_{ax}–C(5)); 4.74 (br. *s*, 1 H of CH_2(8)); 4.89–4.91 (*m*, all $J \leq 2.0$, 1 H of CH_2(8)); 5.30 (*dd*, $J(1_{eq}, 2_{eq}) = 2.8$, $J(1_{eq}, 6_{ax}) = 1.3$, H–C(1)); 5.57 (*dd*, $J(2_{eq}, 1_{eq}) = 2.8$, $J(2_{eq}, 5_{ax}) = 1.3$, H–C(2)); 7.12 (*dd*, $J(4, 5_{eq}) = 5.0$, $J(4, 5_{ax}) = 2.4$, H–C(4)); 9.48 (*s*, H–C(10)). ^{13}C-NMR: 20.55 (*q*, C(12)); 20.68 (*q*, C(14)); 22.33 (*q*, C(9)); 26.30 (*t*, C(5)); 39.18 (*d*, C(6)); 63.50 (*d*, C(2)); 67.91 (*d*, C(1)); 112.04 (*t*, C(8)); 136.65 (*s*, C(3)); 143.21 (*s*, C(7)); 152.62 (*d*, C(4)); 168.30 (*s*, C(13)); 168.53 (*s*, C(11)); 190.78 (*d*, C(10)). HR-EI-MS: 164.0829 ($[M - AcOH - Ac]^+$, $C_{10}H_{12}O_2^+$; calc. 164.0832).

*(1*R*,2*R*,6*S*)-3-(1,3-Dioxolan-2-yl)-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diyl Diacetate* (**28**). Benzene was dried by azeotropic distillation. $HOCH_2CH_2OH$ (27.6 mg, 0.444 mmol), tartaric acid (6.8 mg, 45.3 μmol), and $MgSO_4$ (102.4 mg, 0.85 mmol) were added to a soln. of **11** (23.1 mg, 86.7 μmol) in anh. benzene (8 ml). The mixture was heated under reflux for 10 h and was left at r.t. for 24 h. Then, it was

subjected to CC (SiO_2 (2 g); 30% AcOEt in hexane) to afford (1*R*,2*R*,6*S*)-3-(1,3-dioxolan-2-yl)-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diyl diacetate (**28**; 23.8 mg, 76.7 μmol, 88%). ^{1}H-NMR ($CDCl_3$): 1.77–1.78 (*m*, all $J \leq 2.0$, Me(9)); 1.97, 2.05 (2*s*, Me(14, 16)); 2.20 (*ddd*, $^2J = 18.3$, $J(5_{eq}, 4) = J(5_{eq}, 6_{ax}) = 5.2$, H_{eq}–C(5)); 2.34–2.42 (*ddm*, $^2J = 18.3$, $J(5_{ax}, 6_{ax}) = 11.5$, other $J \leq 2.5$, H_{ax}–C(5)); 2.55 (br. *dd*, $J(6_{ax}, 5_{ax}) = 11.5$, $J(6_{ax}, 5_{eq}) = 5.2$, H–C(6)); 3.79–3.92, 3.96–4.02 (*m*, CH_2(11,12)); 4.73 (br. *s*, 1 H of CH_2(8)); 4.85–4.87 (*m*, all $J \leq 2.0$, 1 H of CH_2(8)); 5.18 (*dd*, $J(1_{eq}, 2_{eq}) = 2.8$, $J(1_{eq}, 6_{ax}) = 2.0$, H–C(1)); 5.19 (*s*, H–C(10)); 5.50 (*dd*, $J(2_{eq}, 1_{eq}) = 2.8$, $J(2_{eq}, 5_{ax}) = 1.2$, H–C(2)); 6.35 (*dd*, $J(4, 5_{eq}) = 5.2$, $J(4, 5_{ax}) = 2.3$, H–C(4)). ^{13}C-NMR: 20.69, 21.08 (2*q*, C(14,16)); 22.13 (*q*, C(9)); 25.05 (*t*, C(5)); 38.88 (*d*, C(6)); 64.29 (*d*, C(2)); 65.06, 65.10 (2*t*, C(11, 12)); 69.12 (*d*, C(1)); 104.55 (*d*, C(10)); 111.44 (*t*, C(8)); 129.68 (*s*, C(3)); 134.59 (*d*, C(4)); 143.94 (*s*, C(7)); 169.27, 169.63 (2*s*, C(13,15)). HR-EI-MS: 309.1325 ($[M-H]^+$, $C_{16}H_{21}O_6^+$; calc. 309.1333).

(4S,5R,6R)-5,6-Dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carbaldehyde (**6**). A soln. of **28** (12.5 mg, 40.3 μmol) in anh. Et_2O (5 ml) was added dropwise over 3 min to a suspension of $LiAlH_4$ (5.2 mg, 0.137 mmol) in Et_2O (5 ml). The mixture was stirred at 0° for 6 h. H_2O (0.5 ml) was added dropwise followed by 10% HCl (2 ml). The mixture was vigorously stirred at 0° for 15 min, then, the layers were separated. The aq. phase was extracted with AcOEt (3 × 2 ml). The combined org. phase was washed with sat. $NaHCO_3$ soln. and dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off to afford (4*S*,5*R*,6*R*)-5,6-dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carbaldehyde (**6**; 4.8 mg, 26.3 μmol, 65%).

(1R,5S)-6,6-Dimethyl-4-oxobicyclo[3.1.1]hept-2-ene-2-carbaldehyde (**29**). (1*S*,2*S*,5*R*)-4-(Hydroxymethyl)-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ol (**8**; $[\alpha]_D^{24} = -23.6$ ($c = 0.37$, $CHCl_3$)) was obtained from (−)-verbenone (**7**; $[\alpha]_D^{25} = -210.5$ ($c = 0.77$, $CHCl_3$); *Aldrich*) according to the procedure described in [10]. $CHCl_3$ was washed with sat. $NaHCO_3$, dried ($CaCl_2$), and distilled over P_2O_5. Freshly prepared (as described for the synthesis of **6**) MnO_2 reagent (7.76 g) was added to a soln. of **8** (792.2 mg, 4.715 mmol) in $CHCl_3$ (300 ml). The mixture was stirred continuously for 90 h. The precipitate was filtered off and washed with $CHCl_3$ (4 × 30 ml). The solvent was carefully distilled off to afford (1*R*,5*S*)-6,6-dimethyl-4-oxobicyclo[3.1.1]hept-2-ene-2-carbaldehyde (**29**; 591.4 mg, 3.606 mmol, 76%). It appeared that **29** is unstable by keeping at r.t. on air. It is necessary to keep the substance under Ar atmosphere at $< -10°$. $[\alpha]_D^{26} = -166.4$ ($c = 0.667$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.90 (*s*, Me(10)); 1.53 (*s*, Me(9)); 2.01 (*d*, $^2J = 9.8$, H_{anti}–C(7)); 2.80 (*ddd*, $J(5, 1) = 6.3$, $J(5, 7_{syn}) = 5.5$, $J(5,3) = 1.8$, H–C(5)); 2.90 (*ddd*, $^2J = 9.8$, $J(7_{syn}, 1) = J(7_{syn}, 5) = 5.5$, H_{syn}–C(7)); 3.10 (*ddd*, $J(1, 5) = 6.3$, $J(1, 7_{syn}) = 5.5$, $J(1, 3) = 1.5$, H–C(1)); 6.46 (*dd*, $J(3, 5) = 1.8$, $J(3, 1) = 1.5$, H–C(3)); 9.83 (*s*, H–C(8)). ^{13}C-NMR: 21.94 (*q*, C(10)); 26.21 (*q*, C(9)); 39.96 (*d*, C(1)); 40.23 (*t*, C(7)); 53.73 (*s*, C(6)); 59.11 (*d*, C(5)); 134.82 (*d*, C(3)); 160.88 (*s*, C(2)); 191.60 (*d*, C(8)); 203.44 (*s*, C(4)). HR-EI-MS: 164.0834 (M^+, $C_{10}H_{12}O_2^+$; calc. 164.0832).

(1R,5S)-6,6-Dimethyl-4-oxobicyclo[3.1.1]hept-2-ene-2-carboxylic Acid (**30**). A 70% aq. soln. of ^{t}BuOOH (0.40 ml, 3.1 mmol) was added to a soln. of CAN (34.7 mg, 0.063 mmol) and **29** (34.3 mg, 0.209 mmol) in MeCN (3 ml). The mixture was stirred at r.t. for 20 h. A sat. $NaHCO_3$ soln. (12 ml) was added. The resulting mixture was extracted with AcOEt (2 × 3 ml). The combined extract was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off to afford the starting material **29** (19.5 mg, 0.119 mmol, conversion 43%). The aq. phase was diluted with 2M HCl (15 ml) and extracted with AcOEt (5 × 5 ml). The combined extract was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off to afford (1*R*,5*S*)-6,6-dimethyl-4-oxobicyclo[3.1.1]hept-2-ene-2-carboxylic acid (**30**; 16.2 mg, 0.0899 mmol, quantitatively calculated on reacted **29**). ^{1}H-NMR ($CDCl_3$): 0.98 (*s*, Me(10)); 1.55 (*s*, Me(9)); 2.10 (*d*, $^2J = 9.7$, H_{anti}–C(7)); 2.78 (br. *dd*, $J(5, 1) = 6.3$, $J(5, 7_{syn}) = 5.5$, H–C(5)); 2.92 (*ddd*, $^2J = 9.7$, $J(7_{syn}, 1) = J(7_{syn}, 5) = 5.5$, H_{syn}–C(7)); 3.09 (br. *dd*, $J(1, 5) = 6.3$, $J(1, 7_{syn}) = 5.5$, H–C(1)); 6.71 (br. *s*, H–C(3)); 7.85 (br. *s*, HO–C(8)). ^{13}C-NMR: 22.00 (*q*, C(10)); 26.36 (*q*, C(9)); 40.77 (*t*, C(7)); 43.33 (*d*, C(1)); 54.46 (*s*, C(6)); 58.59 (*d*, C(5)); 130.51 (*d*, C(3)); 154.93 (*s*, C(2)); 170.11 (*s*, C(8)); 203.28 (*s*, C(4)). HR-EI-MS: 180.0780 (M^+, $C_{10}H_{12}O_3^+$; calc. 180.0781).

(1R,2R,4R,6S)-7,7-Dimethyl-5-oxo-3-oxatricyclo[4.1.1.0^{2,4}]octane-2-carbaldehyde (**35**). A 35% soln. of H_2O_2 (1.34 ml, 15.7 mmol) was added to a soln. of calcined K_2CO_3 (104.2 mg, 0.755 mmol) in H_2O (11.7 ml) and cooled to 0°, then a cooled soln. of **29** (375.4 mg, 2.29 mmol) in Et_2O (52 ml) was added over 5 min and the mixture was vigorously stirred (1000 rpm) at 0° for 4 h. A soln. of Na_2SO_3 (4.17 g, 33.1 mmol) in 20 ml H_2O was added. The mixture was stirred for 3 min, and the aq. layer was separated.

NaCl (4.17 g) was added to the aq. phase which was then extracted with CH_2Cl_2 (4 × 10 ml). The combined org. phases were dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off to afford (1*R*,2*R*,4*R*,6*S*)-7,7-dimethyl-5-oxo-3-oxatricyclo[4.1.1.$0^{2,4}$]octane-2-carbaldehyde (**35**; 219 mg, 1.22 mmol, 53%). ^{1}H-NMR ($CDCl_3$): 0.87 (*s*, Me(11)); 1.46 (*s*, Me(10)); 2.03 (*d*, ^2J = 10.8, H_{anti}–C(8)); 2.40 (*dddd*, ^2J = 10.8, $J(8_{syn}, 1) = J(8_{syn},6) = 6.3$, $J(8_{syn}, 9) = 0.8$, H_{syn}–C(8)); 2.51 (*ddd*, $J(6, 8_{syn}) = 6.3$, $J(6, 1) = 5.5$, $J(6, 4) = 1.7$, H–C(6)); 2.87 (*dd*, $J(1, 8_{syn}) = 6.3$, $J(1,6) = 5.5$, H–C(1)); 3.66 (*dd*, $J(4, 6) = 1.7$, $J(4, 1) = 0.8$, H–C(4)); 9.08 (*d*, $J(9, 8_{syn}) = 0.8$, H–C(9)). ^{13}C-NMR: 20.82 (*t*, C(8)); 21.45 (*q*, C(11)); 25.90 (*q*, C(10)); 38.41 (*d*, C(1)); 50.65 (*s*, C(7)); 55.24 (*d*, C(4)); 57.00 (*d*, C(6)); 63.64 (*s*, C(2)); 195.34 (*d*, C(9)); 201.17 (*s*, C(5)).

*(1*R*,2*R*,4*R*,6*S*)-7,7-Dimethyl-5-oxo-3-oxatricyclo[4.1.1.$0^{2,4}$]octane-2-carboxylic Acid* (**31**). EtOH was freshly distilled over BaO. A soln. of $AgNO_3$ (765.7 mg, 4.57 mmol) in H_2O (10 ml) was added over 3 min under stirring to a soln. of NaOH (480.7 mg, 12.0 mmol) in H_2O (10 ml) then the mixture was stirred for additional 5 min. The soln. was decanted, the precipitate was washed with H_2O (10 ml) under stirring for 2–3 min. H_2O was removed by decantation. The procedure was repeated 5 times. Then, the precipitate was washed in a similar way with EtOH (4 × 10 ml). EtOH (60 ml) and TMEDA (0.80 ml, 5.36 mmol) were added to the mixture. The suspension was stirred for 20 min, then, it was left to stay without stirring for 14 h. A soln. of **35** (67.1 mg, 0.373 mmol) in EtOH (40 ml) was added. The mixture was heated under reflux for 5 h. The precipitate was filtered off and the solvent was distilled off. Brine (100 ml) and conc. HCl (4.0 ml) were added to the residue. The resulting mixture was extracted with $CHCl_3$ (4 × 30 ml). The combined extract was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off. The residue (103 mg) was purified by CC (SiO_2 (4.5 g); 70% $CHCl_3$ in hexane and EtOH (0–10%)/$CHCl_3$, gradient) to afford (1*R*,2*R*,4*R*,6*S*)-7,7-dimethyl-5-oxo-3-oxatricyclo[4.1.1.$0^{2,4}$]octane-2-carboxylic acid (**31**; 67.4 mg, 0.344 mmol, 92%). $[\alpha]_D^{23} = -74.2$ ($c = 0.690$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 0.99 (*s*, Me(11)); 1.47 (*s*, Me(10)); 2.03 (*d*, ^2J = 10.8, H_{anti}–C(8)); 2.41 (*ddd*, ^2J = 10.8, $J(8_{syn}, 1) = J(8_{syn},6) = 6.3$, H_{syn}–C(8)); 2.51 (*ddd*, $J(6, 8_{syn}) = 6.3$, $J(6, 1) = 5.5$, $J(6, 4) = 1.7$, H–C(6)); 2.94 (*dd*, $J(1, 8_{syn}) = 6.3$, $J(1, 6) = 5.5$, H–C(1)); 3.69 (*d*, $J(4, 6) = 1.7$, H–C(4)); 8.39 (br. *s*, HO–C(9)). ^{13}C-NMR: 21.34 (*t*, C(8)); 21.61 (*q*, C(11)); 26.12 (*q*, C(10)); 40.78 (*d*, C(1)); 50.98 (*s*, C(7)); 56.70 (*d*, C(6)); 57.15 (*d*, C(4)); 57.98 (*s*, C(2)); 173.07 (*s*, C(9)); 202.33 (*s*, C(5)). HR-EI-MS: 196.0734 (M^+, $C_{10}H_{12}O_4^+$; calc. 196.0730).

*(1*R*,2*R*,4*S*,5*R*,6*S*)-5-Hydroxy-7,7-dimethyl-3-oxatricyclo[4.1.1.$0^{2,4}$]octane-2-carboxylic Acid* (**36**). A soln. of **31** (113.3 mg, 0.578 mmol) in anh. Et_2O (30 ml) was added dropwise over 5 min to a suspension of $LiAlH_4$ (82.2 mg, 2.166 mmol) in Et_2O (30 ml) at 0°. The mixture was stirred at 0° for 7 h. H_2O (3 ml) was added dropwise followed by brine (3 ml), and then, the layers were separated. The aq. phase was extracted with Et_2O (10 ml). The combined org. phase was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off to afford a mixture of products of secondary transformations (38.2 mg, *ca.* 34%). Brine (15 ml), H_2O (5 ml), and conc. HCl (1 ml) were added to the aq. phase. The resulting mixture was extracted with AcOEt (4 × 15 ml). The combined org. phase was dried (Na_2SO_4). The desiccant was filtered off and the solvent was distilled off to afford (1*R*,2*R*,4*S*,5*R*,6*S*)-5-hydroxy-7,7-dimethyl-3-oxatricyclo[4.1.1.$0^{2,4}$]octane-2-carboxylic acid (**36**; 48.2 mg, 0.243 mmol, 42%). $[\alpha]_D^{22} = -44.9$ ($c = 0.820$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.12 (*s*, Me(11)); 1.37 (*s*, Me(10)); 1.43 (*d*, ^2J = 10.8, H_{anti}–C(8)); 1.99 (*dddd*, $J(6,8_{syn}) = 7.2$, $J(6,1) = 5.0$, $J(6,5) = 3.1$, $J(6,4) = 2.2$, H–C(6)); 2.13 (*ddd*, ^2J = 10.8, $J(8_{syn},6) = 7.2$, $J(8_{syn},1) = 6.2$, H_{syn}–C(8)); 2.62 (*dd*, $J(1,8_{syn}) = 6.2$, $J(1,6) = 5.0$, H–C(1)); 3.58 (*d*, $J(4,6) = 2.2$, H–C(4)); 4.22 (*d*, $J(5,6) = 3.1$, H–C(5)). ^{13}C-NMR: 21.74 (*t*, C(8)); 21.82 (*q*, C(11)); 26.61 (*q*, C(10)); 40.29 (*d*, C(1)); 40.40 (*s*, C(7)); 46.30 (*d*, C(6)); 59.17 (*d*, C(4)); 59.20 (*s*, C(2)); 69.63 (*d*, C(5)); 173.17 (*s*, C(9)). HR-EI-MS: 180.0783 ($[M - H_2O]^+$, $C_{10}H_{12}O_3^+$; calc. 180.0781).

*(4S,5*R*,6*R*)-5,6-Dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carboxylic Acid* (**5**). CH_2Cl_2 was distilled over P_2O_5 and passed through Al_2O_3. A soln. of **36** (34.2 mg, 0.173 mmol) in CH_2Cl_2 (25 ml) was added to a stirred suspension of clay *K10* (345 mg, calcined over 3 h at 100–105°) in CH_2Cl_2 (25 ml). The mixture was stirred at r.t. for 4 h. Then, AcOEt (50 ml) was added and the mixture was stirred for 10 min. The clay was filtered off, the solvent was distilled off. The residue (22.4 mg) was separated by CC (SiO_2 (1 g); EtOH/$CHCl_3$, gradient (0–100%)) to afford (4*S*,5*R*,6*R*)-5,6-dihydroxy-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carboxylic acid (**5**; 13.7 mg, 0.0692 mmol, 40%) containing a little amount of impurities. An additional purification was carried out by CC (SiO_2 (1 g); EtOH/$CHCl_3$, gradient (0–10%)) to afford **5** (7.0 mg) of analytical purity. $[\alpha]_D^{29} = -43.8$ ($c = 0.347$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$/

CD_3OD 10:1): 1.82 (br. *s*, Me(9)); 2.16–2.24 (*m*, H_{eq}–C(5)); 2.38–2.49 (*m*, H_{ax}–C(5), H–C(6)); 4.01 (br. *s*, H–C(1)); 4.40 (br. *s*, H–C(2)); 4.83 (br. *s*, 1 H of CH_2(8)); 4.95–4.97 (*m*, all $J \leq 2.0$, 1 H of CH_2(8)); 7.18 (br. *d*, $J(4, 5_{eq}) = 5.2$, H–C(4)). ^{13}C-NMR: 22.32 (*q*, C(9)); 25.21 (*t*, C(5)); 36.11 (*d*, C(6)); 66.98 (*d*, C(2)); 69.63 (*d*, C(1)); 111.51 (*t*, C(8)); 129.08 (*s*, C(3)); 143.46 (*d*, C(4)); 145.02 (*s*, C(7)); 169.40 (*s*, C(10)). HR-EI-MS: 198.0889 (M^+, $C_{10}H_{14}O_4^+$; calc. 198.0887).

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