Enantioselective Synthesis of 3-Methylcarbapentofuranose Derivatives, Based on a Chemoenzymatic Procedure

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The enantioselective synthesis of 3-methylcarbapentofuranose derivatives through the use of a racemic substituted cyclopentenylcarboxylate as the carbon building block and a number of stereoselective transformations is described. All of the stereogenic centres of these derivatives are directed by the two stereogenic centres created early in the key cyclopentene moiety by a lipase-catalysed enantioselective acetylation.

Introduction

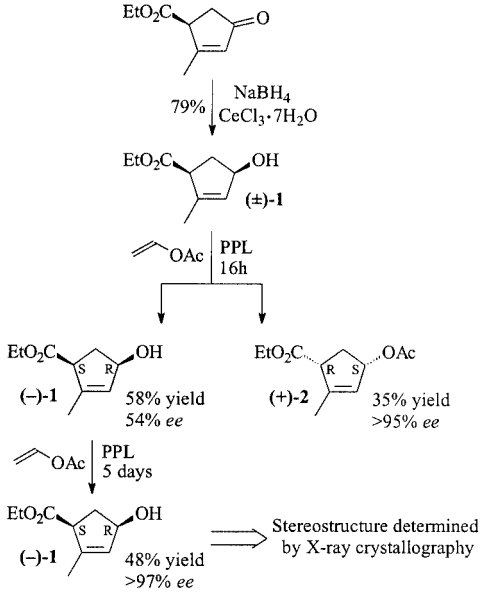
Polyoxygenated cyclopentanes are referred to as carbasugars, since they may be viewed as furanose mimics in which the ring oxygen atom has been replaced by a methylene group.[1] The lack of the glycosidic bond renders them chemically and enzymatically more stable than the natural sugar derivatives[2] and thus biologically resistant.[3] Biological activity can be achieved by use of the carbocyclic sugar itself or by incorporation of the carbasugar fragment into other natural or synthetic molecules such as, for instance, aristeromycin[4] and neplanocin A[5] or carbovir[6] and abacavir,[7] respectively.

The synthesis of carbasugars has accordingly been intensely investigated. Other than the modification of carbohydrates,[8] one of the most widely used synthetic procedures for the preparation of optically active carbocyclic sugars is the modification of achiral or racemic starting materials.[9] In particular, the use of lipase-catalysed kinetic resolution or asymmetrization of suitable building blocks has received increasing attention.[10] Together with the type and further substitution of the bases,[11,12] the most relevant modifications that enhance antitumor and antiviral properties are related to the nature and number of substituents on the carbapentofuranose subunit, and intense synthetic researches are still in progress.[13]

Here we describe a straightforward enantioselective approach for the preparation of optically active 3-methylcarbapentofuranose derivatives **3**−**7** (see Scheme 3) that uses the cyclopentenylcarboxylate **1** as carbon building block. All of the stereogenic centres in **3**−**7** are established through direction by the two stereogenic centres created in the cyclopentene moiety by an enzymatic resolution.

Results and Discussion

The readily available[14] ethyl 2-methyl-4-oxocyclopent-2-ene-1-carboxylate was converted into the hydroxy ester **(±)-1** in 79% yield by Luche reduction with $NaBH_4$/$CeCl_3 \cdot 7H_2O$ in methanol (overall yield 93%, *cis*/*trans* = 6:1, easily separated by column chromatography). Treatment of **(±)-1** with vinyl acetate in the presence of porcine pancreas lipase[15,16] (PPL, Fluka) gave the results outlined in Scheme 1.



Scheme 1. Lipase-catalysed kinetic resolution of racemic **1**

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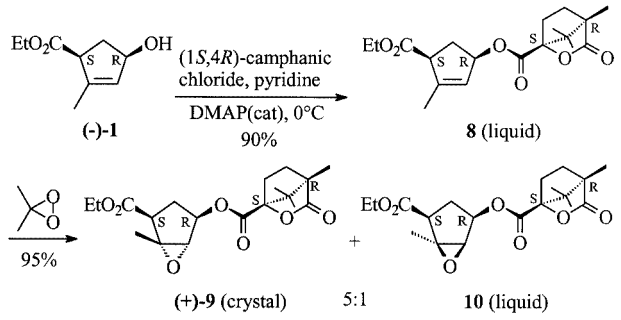
The progress of the reaction was monitored by capillary GC. In parallel, the enantiomeric excess (*ee*) was determined by the ratio of the peak areas obtained by GC separation on a chiral phase (see Exp. Sect.). The enantiomers of the remaining alcohol and those of the produced acetate were perfectly separated. After 16 h at room temp., the active enzyme was recovered for reuse by filtration. Concentration of the filtrate and column chromatography on silica gel afforded 58% of the unreactive alcohol (1*S*,4*R*)-**1** (54% *ee*) and a 35% yield of the (1*R*,4*S*)-acetate **2** (> 95% *ee*). This acetate **(+)-2** was not stable and slowly degraded during the course of the reaction (theoretical yield: 42%). The remaining alcohol was again subjected to enzymatic transesterification under the same conditions with the recovered enzyme. The progress of the reaction was monitored by chiral phase analytical GC until one enantiomer of the starting material had been completely consumed. After 5 d, (1*S*,4*R*)-alcohol **(−)-1** was obtained in 48% overall yield (> 97% *ee*). By this methodology, **(−)-1** could be prepared in multigram quantities. The absolute configuration of this alcohol was established by X-ray crystallography by the sequence shown in Scheme 2, by the use of (1*S*,4*R*)-camphanic chloride[17,18] as a chiral auxiliary.



Scheme 2

Treatment of alcohol **(−)-1** with (1*S*,4*R*)-camphanic chloride afforded the derivative **8** in 90% yield, but as a syrupy liquid that we were unable to crystallise despite numerous attempts. This difficulty was overcome by epoxidation of the double bond of **8**. Thus, exposure of **8** to dimethyldioxirane (DMDO)[19] afforded the readily separable crystalline epoxide **9** and the liquid epoxide **10** in 95% yield and in a ratio of 5:1. Recrystallization of **(+)-9** (solvent: diethyl ether/petroleum ether) gave single crystals, the ORTEP view of which is shown in Figure 1.

With the absolute configuration of the hydroxy ester **(−)-1** confirmed, the different pathways for the synthesis of 3-methylcarbapentofuranose derivatives **3**−**7** are outlined in Scheme 3. It is also possible to start from the enantiomeric hydroxy ester **(+)-1**, obtained by MeOH/K_2CO_3 hydrolyse of acetate **(+)-2**, and so the other enantiomers of **3**−**7** are also accessible.

Reduction with $LiAlH_4$ or $VO(acac)_2$-catalysed hydroxy-directed epoxidation[20] of **(−)-1** afforded diol **(−)-11** or the epoxide **(−)-15**, respectively, with excellent yields. These

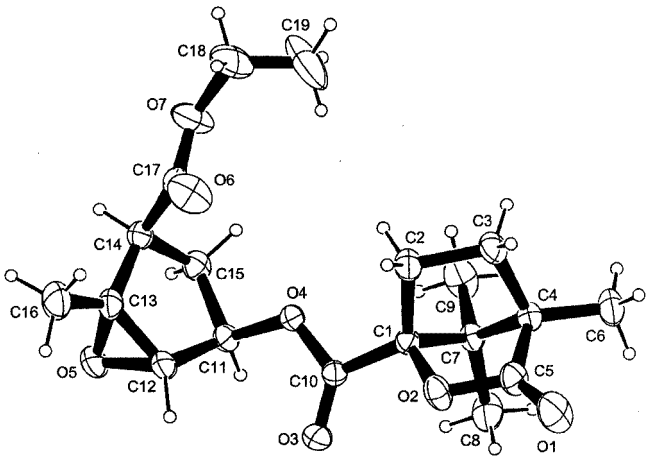
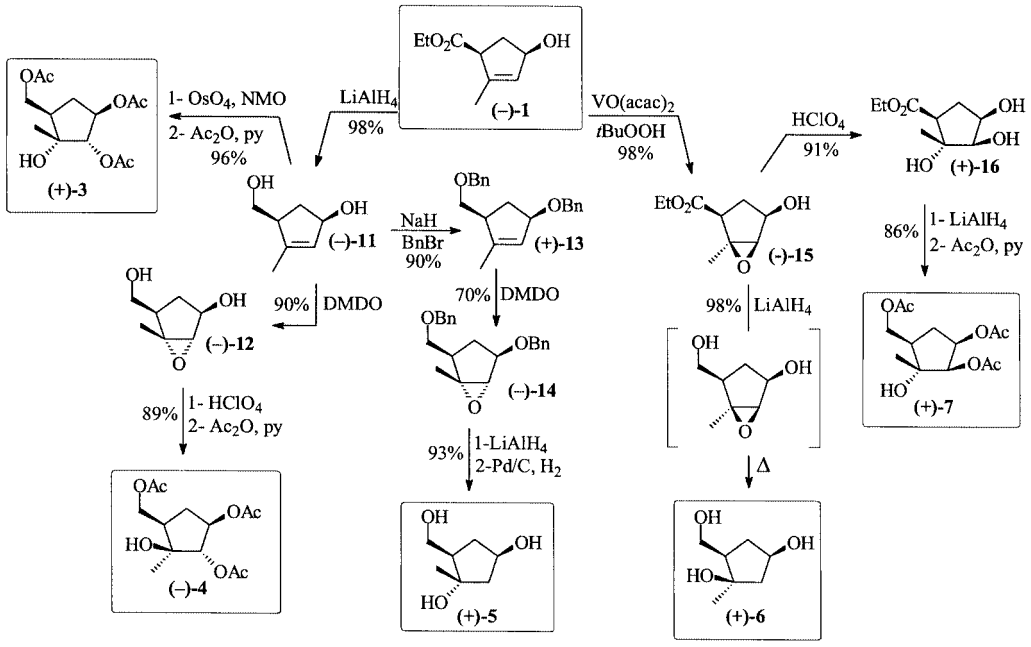


Figure 1. ORTEP view of epoxycamphanate (+)-**9**

two products were the subunits that allowed the synthesis of the different carbasugar derivatives.

cis-Dihydroxylation of **(−)-11** by OsO_4 (4 mol-% in water)/NMO in acetone/water (3:1), followed by peracetylation of the crude reaction mixture, gave the triacetate **(+)-3** as a single stereomer in an overall yield of 96% for the two steps. NOESY cross-peaks (Figure 2) between 2-H and 6-H_b and between 5-CH_2 and 2-H, showed that the *cis* dihydroxylation gave the *trans* product exclusively. This is in concordance with the stereoselectivity observed in the *cis* hydroxylation of *cis*-3,5-disubstituted cyclopentenes bearing one (or two) hydroxy (or acetoxy) groups.[21] In other respects, epoxidation of the double bond of **(−)-11** by the dimethyldioxirane (DMDO) methodology afforded a 9:1 mixture of **(−)-12** and its *cis* stereomer, easily separated by column chromatography, in quantitative yield. The stereochemistry of these derivatives was unambiguously assigned by the fact that partial reduction of **(−)-15** with $LiAlH_4$ at room temperature (see Scheme 3) afforded the corresponding diol without opening of the oxirane ring. The ^1H and ^{13}C NMR spectra of this intermediate diol were exactly those of the minor *cis* stereomer of **(−)-12**. Treatment of **(−)-12** with aqueous perchloric acid, followed by peracetylation with Ac_2O/pyridine, resulted in the sole formation of triacetate **(−)-4** in 89% yield. The NOESY spectrum (Figure 2) showed correlations between 6-H_b and 2-H and between 1-H and 3-Me. This means that these groups are positioned on the same sides, respectively. This result clearly showed that the attack of the oxygen nucleophile must have taken place at the more encumbered carbon atom. The origin of this selectivity was attributed to stabilization of the developed positive charge in the activated oxirane ring.

To synthesize triol **(+)-5**, diol **(−)-11** was first protected as the dibenzyl ether **(+)-13**, in order to avoid the Payne rearrangement that might take place under the basic conditions created by addition of the metal hydride.[22] Dimethyldioxirane (DMDO) epoxidation of the double bond of **(+)-13** gave the expected epoxide **(−)-14** in 70% yield, together with other by-products easily removed by column chromatography. In the following step, epoxide **(−)-14** was regiose-



Scheme 3

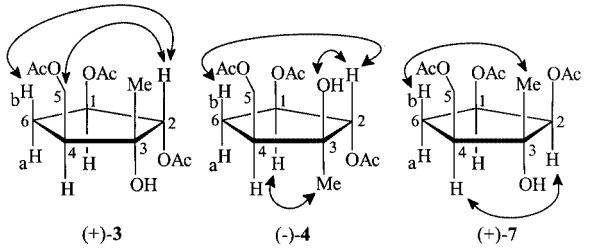


Figure 2. Selected NOESY interactions for carbasugar derivatives **(+)-3**, **(−)-4**, and **(+)-7**

lectively reduced with $LiAlH_4$ in Et_2O/THF (2:1) at 50 °C to afford a mixture of the expected alcohol and partially monodebenzylated diols. The benzyl protecting groups of the crude mixture were subjected to hydrogenolysis at 1 atm pressure with 10% Pd/C as a catalyst and methanol as a solvent, affording the target triol **(+)-5** in 93% overall yield.

Reduction of **(−)-15** with $LiAlH_4$ in refluxing Et_2O yielded 98% of **(+)-6** as a single regioisomer. As in the previous case of **(−)-12**, treatment of **(−)-15** with aqueous perchloric acid regioselectively afforded the triol **(+)-16** in 91% yield. Derivative **(+)-16** was reduced with $LiAlH_4$ in THF at room temp., and the crude reaction mixture was converted into the corresponding triacetates with Ac_2O/pyridine to afford **(+)-7** in 86% overall yield. Pronounced NOESY correlations (Figure 2) between 6-H_b and 3-Me and between 4-H and 2-H established the spatial proximities of these substituents.

Conclusion

In summary, approaches to the synthesis of 3-methylcarbapentofuranose derivatives in enantiopure form have been developed, starting from a readily available racemic cyclopentene building block, and by the use of a lipase-catalysed enantioselective acetylation as the key step by which the first two stereogenic centres are created. These are used to direct the formation of the remaining stereogenic centres in the carbocyclic framework. The reactions proceed with very high yields and stereoselectivities.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, D_2O, or C_6D_6 solutions with Bruker AM 300 or Bruker AM 200 spectrometers (Bruker AM 500 and Bruker AM 400 spectrophotometers for COSY and NOESY experiments). Infrared spectra were obtained as films or as KBr pellets with a Perkin−Elmer 1600 FT-IR spectrophotometer. Routine monitoring of reactions was performed with Merck silica gel 60 F_{254} aluminium-supported TLC plates. Column chromatography was performed with silica gel 60 (230−400 mesh) and pentane/diethyl ether gradients as eluents, unless stated otherwise. GC analyses were carried out with a Chrompack 9001 on a WCOT fused silica column (25 m × 0.32 mm i.d.; CP-Wax-52 CB stationary phase; N_2 carrier gas: 50 kPa). Determinations of enantiomeric excesses were carried out on a MEGADEX DETTBSβ fused silica column (30 m × 0.25 mm i.d.; N_2 carrier gas: 75 kPa). Specific rotations were recorded with a Perkin−Elmer 341 polarimeter. Microanalyses were performed with a ThermoFinnigan EA 1112 analyzer at our University. Melting points were not corrected and were determined by use of a Büchi Totolli apparatus. Unless otherwise stated, the solutions were dried with magnesium sulfate and the solvents were removed under reduced pressure in a rotary evaporator.

Ethyl *cis*-4-Hydroxy-2-methylcyclopent-2-ene-1-carboxylate [(±)-1]: A solution of ethyl 2-methyl-4-oxocyclopent-2-ene-1-carboxylate (4.0 g, 23.8 mmol) and $CeCl_3 \cdot 7H_2O$ (10.7 g, 28.6 mmol) in absolute EtOH (300 mL) was stirred at room temp. for 1 h. The solution

was cooled to −90 °C and treated with $NaBH_4$ (2.3 g, 60.8 mmol) in two portions. The reaction mixture was stirred for an additional 2.5 h before being concentrated under reduced pressure to provide a residue that was partitioned between 200 mL of water and 350 mL of CH_2Cl_2. After separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel to afford 3.2 g (79%) of pure (±)-**1** and 0.6 g (14%) of *trans*-**1**. Alcohol **1**: IR (neat): $\tilde{\nu}$ = 3502, 3055, 1722, 1640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.72 (br. s, 1 H), 4.62 (br. t, *J* = 8.6 Hz, 1 H), 4.22 and 4.14 (ABX_3, *J* = 13.4, 7.2 Hz, 2 H), 3.22 (d, *J* = 8.1 Hz, 1 H), 2.61 (d, *J* = 11.0 Hz, 1 H, OH), 2.34 (ddd, *J* = 14.3, 8.1, 7.2 Hz, 1 H), 1.97 (d, *J* = 14.3 Hz, 1 H), 1.78 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.6 (C), 142.5 (C), 131.7 (CH), 76.2 (CH), 61.2 (CH_2), 52.8 (CH), 38.2 (CH_2), 15.4 (CH_3), 14.2 (CH_3) ppm. $C_9H_{14}O_3$ (170.2): calcd. C 63.51, H 8.29; found C 63.19, H 8.21. *trans*-**1**: IR (neat): $\tilde{\nu}$ = 3383, 3037, 1727, 1646, 1182 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.60 (br. s, 1 H), 4.97−4.91 (m, 1 H), 4.16 and 4.10 (ABX_3, *J* = 11.2, 7.2 Hz, 2 H), 3.59−3.50 (m, 1 H), 2.53 (ddd, *J* = 14.0, 7.2, 4.4 Hz, 1 H), 1.95 (ddd, *J* = 13.8, 8.3, 3.4 Hz, 1 H), 1.77 (br. s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2 (C), 142.2 (C), 131.3 (CH), 76.5 (CH), 60.6 (CH_2), 53.0 (CH), 38.8 (CH_2), 15.4 (CH_3), 14.1 (CH_3).

General Procedure for the Lipase-Catalysed Acylation of (±)-1: A mixture of (±)-**1** (1.84 g, 10.8 mmol) and PPL (530 mg) in 22 mL of vinyl acetate was magnetically stirred at room temp. and the progress of the reaction was monitored by GC on a chiral column. After 16 h and 35% conversion, the GC chromatogram showed that the formed ethyl (1*R*,4*S*)-4-acetoxy-2-methylcyclopent-2-ene-1-carboxylate [(+)-**2**] had an enantiomeric excess of > 95%. The reaction was stopped by filtration. Removal of the solvent, followed by separation on a silica gel column, yielded 1.18 g (64%) of (−)-**1** (54% *ee*) and 775 mg (35%) of acetate (+)-**2** (*ee* > 95%). (+)-**2**: $[\alpha]_D^{25}$ = +19.4 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3036, 1744, 1732, 1647, 1183 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.62−5.58 (m, 1 H), 5.60−5.56 (m, 1 H), 4.19 and 4.13 (ABX_3, *J* = 10.8, 7.2 Hz, 2 H), 3.32−3.26 (m, 1 H), 2.60 (dt, *J* = 14.5, 8.0 Hz, 1 H), 2.13 (dt, *J* = 14.5, 4.8 Hz, 1 H), 2.03 (s, 3 H), 1.82 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1 (C), 171.1 (C), 144.7 (C), 127.1 (CH), 78.7 (CH), 60.8 (CH_2), 52.2 (CH), 34.5 (CH_2), 21.2 (CH_3), 15.7 (CH_3), 14.2 (CH_3) ppm. $C_{11}H_{16}O_4$ (212.2): calcd. C 62.25, H 7.60; found C 61.97, H 7.52. The unreactive alcohol (−)-**1** (*ee* = 54%) was again subjected to lipase-catalysed acylation under the same conditions with the recovered active enzyme and the progress of the reaction was monitored by chiral GC. After 5 d, GC analysis showed that one enantiomer had been completely consumed. The reaction was stopped by filtration. Removal of the solvent, followed by silica gel column chromatography, yielded 0.87 g of alcohol (−)-**1** (48% overall yield from (±)-**1**). *ee* > 97%, $[\alpha]_D^{25}$ = −143.3 (*c* = 1.0, $CHCl_3$). The ^1H and ^{13}C NMR spectroscopic data are identical with those reported for (±)-**1**.

Camphanate Derivative 8: (−)-(1*S*,4*R*)-Camphanic chloride (Fluka; 210 mg, 0.97 mmol) was added at 0 °C under argon to a solution of (−)-**1** (100 mg, 0.59 mmol) and DMAP (10 mg, 0.08 mmol) in pyridine (10 mL). The cooling bath was removed, and the solution was stirred at room temp. The reaction was monitored by TLC and was complete within 26 h. The mixture was diluted with CH_2Cl_2 and was then sequentially washed with water, 1 N HCl (until pH = 2), saturated $NaHCO_3$ solution, and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was subjected to column chromatography and afforded the camphanate derivative **8** (187 mg, 90%). IR (neat): $\tilde{\nu}$ = 3037, 1794, 1770, 1750, 1656 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.72−5.66 (m, 1 H), 5.65−5.61 (m, 1 H), 4.19 and 4.14 (ABX_3, *J* = 11.1, 7.2 Hz, 2 H), 3.35−3.28 (m, 1 H), 2.66 (ddd, *J* = 16.2, 8.7, 7.5 Hz, 1 H), 2.40 (ddd, *J* = 15.0, 10.8, 4.5 Hz, 1 H), 2.19 (ddd, *J* = 14.5, 4.5, 3.4 Hz, 1 H), 2.06−1.87 (m, 2 H), 1.85 (s, 3 H), 1.66 (ddd, *J* = 13.4, 9.3, 4.3 Hz, 1 H), 1.55 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 1.09 (s, 3 H), 1.05 (s, 3 H), 0.95 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.1 (C), 172.6 (C), 167.3 (C), 145.9 (C), 126.3 (CH), 91.0 (C), 80.2 (CH), 60.9 (CH_2), 54.8 (C), 54.1 (C), 52.2 (CH), 34.5 (CH_2), 30.5 (CH_2), 29.0 (CH_2), 16.8 (CH_3), 16.7 (CH_3), 15.8 (CH_3), 14.2 (CH_3), 9.7 (CH_3) ppm. $C_{19}H_{26}O_6$ (350.4): calcd. C 65.13, H 7.48; found C 65.26, H 7.52.

Epoxycamphanate Derivatives 9 and 10: A freshly generated dimethyldioxirane solution (5 mL, 0.072 M in acetone, 0.36 mmol) was added in one portion at −20 °C to a stirred solution of **8** (100 mg, 0.29 mmol) in acetone. The reaction mixture was kept for 3 h at this temperature, and the mixture was then allowed to warm slowly to room temp. After 12 h, the solvent was removed and the crude mixture was subjected to column chromatography to obtain 80% of **(+)-9** (85 mg, 0.23 mmol) as a solid and 15% of **10** (16 mg, 0.04 mmol) as an oil. Crystallization of **(+)-9** from petroleum ether/diethyl ether afforded white crystals. Compound **(+)-9**: M.p. 86−87 °C. $[\alpha]_D^{25}$ = +10.9 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1782, 1769, 1663, 1201 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$)]: δ = 5.26 (d, *J* = 5.9 Hz, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 3.43 (s, 1 H), 2.97 (dd, *J* = 8.6, 1.3 Hz, 1 H), 2.48−2.31 (m, 1 H), 2.25−1.79 (m, 4 H), 1.71−1.55 (m, 1 H), 1.53 (s, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.06 (s, 3 H), 1.01 (s, 3 H), 0.92 (s, 3 H) ppm. $C_{19}H_{26}O_7$ (366.4): calcd. C 62.28, H 7.15; found C 62.09, H 7.11. Compound **10**: IR (neat): $\tilde{\nu}$ = 1788, 1772, 1761, 1148 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.17 (td, *J* = 8.6, 1.4 Hz, 1 H), 4.24 and 4.16 (ABX_3, 2 H, *J* = 11.3, 7.2 Hz), 3.70−3.50 (m, 1 H), 2.79 (dd, *J* = 10.4, 8.2 Hz, 1 H), 2.52−2.19 (m, 2 H), 2.10−1.79 (m, 3 H), 1.74−1.57 (m, 1 H), 1.55 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 0.95 (s, 3 H) ppm.

X-ray Diffraction Analysis of (+)-9: $C_{19}H_{26}O_7$, *M* = 366.41. The colourless single crystals were analysed at 298 K with a Bruker Nonius Kappa-CCD automated four-circle diffractometer by use of graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Crystal data: monoclinic, space group $P2_1$, *a* = 7.2424(5), *b* = 6.5204(2), *c* = 20.740 (1) Å, β = 97.380(2)°, *V* = 971.30(9) $Å^3$, *Z* = 2, D_X = 1.253 g/cm^3, *F*(000) = 392, and μ(Mo-K_α) = 0.09 cm^{-1}. Of the 1938 independent reflections collected, 1693 reflections with $I > 3.0\sigma(I)$ were used for the structure determination. The final refinement converged with *R* = 0.048 and *Rw* = 0.055 for 233 parameters. CCDC-186516 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

(1*R*,4*S*)-4-(Hydroxymethyl)-3-methylcyclopent-2-en-1-ol [(−)-11]: A solution of **(−)-1** (150 mg, 0.88 mmol) in dry diethyl ether (10 mL) was slowly added at −20 °C to a stirred slurry of $LiAlH_4$ (70 mg, 1.76 mmol) in dry diethyl ether (2 mL). The solution was allowed to warm to room temp. After 1 h, Celite (2 g) and $Na_2SO_4 \cdot 10H_2O$ (2 g) were added and the solution was stirred for a further 30 min. The mixture was filtered through a pad of $MgSO_4$ and concentrated. Column chromatography of the oil afforded 110 mg (98%)

of pure **(−)-11**. $[\alpha]_D^{25} = -13.1$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3339, 3037, 1646, 1049 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.67 (br. s, 1 H), 4.57 (br. d, J = 6.7 Hz, 1 H), 3.75 and 3.58 (ABX, J = 10.5, 2.9, 2.8 Hz, 2 H), 2.57 (br. d, J = 8.8 Hz, 1 H), 2.36 (ddd, J = 13.9, 8.8, 6.7 Hz, 1 H), 1.77 (br. s, 3 H), 1.61 (d, J = 13.7 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 144.4 (C), 129.6 (CH), 74.7 (CH), 60.7 (CH_2), 49.0 (CH), 38.0 (CH_2), 14.6 (CH_3) ppm. $C_7H_{12}O_2$ (128.2): calcd. C 65.60, H 9.44; found C 65.26, H 9.58.

(1*R*,2*R*,3*S*,4*R*)-3,4-Diacetoxy-2-hydroxy-2-methylcyclopentylmethyl Acetate [(+)-3]: *N*-Methylmorpholine *N*-oxide (137 mg, 1.17 mmol) and a solution of OsO_4 (4% in H_2O, few drops) were added to a solution of **(−)-11** (100 mg, 0.78 mmol) in acetone/H_2O (3:1, 10 mL). After the mixture had been stirred for 3.5 h at room temp., the solvents were removed. Pyridine (10 mL) and Ac_2O (5.0 mL, 50 mmol) were added to the crude material, which was stirred at room temp. After 1 d, the solvents were removed and the residue was partitioned between CH_2Cl_2 (30 mL) and H_2O (20 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Column chromatography afforded **(+)-3** as a solid in 96% overall yield (215 mg, 0.75 mmol) from **(−)-11**. An analytical sample was recrystallized from diethyl ether. M.p. 71−72 °C. $[\alpha]_D^{25} = +6.1$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3486, 1730, 1230, 1038 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.14 (ddd, J = 11.6, 6.4, 5.2 Hz, 1 H, 1-H), 4.94 (d, J = 5.1 Hz, 1 H, 2-H), 4.19 and 4.03 (ABX, J = 11.3, 6.7, 5.5 Hz, 2 H, 5-H), 2.56 (dt, J = 14.1, 8.8 Hz, 1 H, 6-H_a), 2.29 (dq, J = 8.3, 6.4 Hz, 1 H, 4-H), 2.11 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 1.36 (ddd, J = 14.4, 8.1, 6.6 Hz, 1 H, 6-H_b), 1.24 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.8 (C), 170.3 (C), 170.2 (C), 82.2 (CH), 77.3 (C), 75.8 (CH), 64.0 (CH_2), 44.4 (CH), 30.9 (CH_2), 21.4 (CH_3), 20.9 (CH_3), 20.8 (2 × CH_3) ppm. $C_{13}H_{20}O_7$ (288.3): calcd. C 54.16, H 6.99; found C 54.31, H 7.11.

(1*S*,2*R*,4*R*,5*R*)-4-(Hydroxymethyl)-5-methyl-6-oxabicyclo-[3.1.0]hexan-2-ol [(−)-12]: A freshly generated dimethyldioxirane solution (50 mL, 0.065 M in acetone, 3.30 mmol) was added in one portion at −20 °C to a stirred solution of **(−)-11** (250 mg, 1.95 mmol) in acetone. The reaction mixture was kept for 2 h at this temperature, and the mixture was then allowed to warm slowly to room temp. After 24 h, the reaction was complete and the solvent was removed. Purification by chromatography on silica gel afforded 90% of **(−)-12** (253 mg, 1.76 mmol) and 10% of *cis*-**12** (27 mg, 0.19 mmol). **(−)-12**: $[\alpha]_D^{25} = -28.1$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3422, 1139, 1031 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.17 (br. d, J = 5.5 Hz, 1 H), 3.90 and 3.63 (ABX, J = 10.2, 2.2, 2.1 Hz, 2 H), 3.26 (br. s, 1 H), 2.30−2.05 (m, 2 H), 1.51 (br. s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 70.8 (CH), 65.3 (CH), 65.1 (C), 62.6 (CH_2), 42.8 (CH), 36.3 (CH_2), 14.9 (CH_3) ppm. $C_7H_{12}O_3$ (144.2): calcd. C 58.32, H 8.39; found C 57.99, H 8.50. Minor compound ***cis*-12**: IR (neat): $\tilde{\nu}$ = 3428, 1127, 1042 cm^{-1}. ^1H NMR (200 MHz, D_2O): δ = 4.28 (td, J = 8.9, 1.4 Hz, 1 H), 3.75 and 3.56 (ABX, J = 11.3, 7.0, 5.9 Hz, 2 H), 3.38 (br. s, 1 H), 2.25−2.10 (m, 1 H), 1.98 (dt, J = 12.2, 7.9 Hz, 1 H), 1.37 (s, 3 H), 0.96 (ddd, J = 12.1, 9.6, 8.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 71.3 (CH), 66.8 (CH), 66.1 (C), 61.6 (CH_2), 43.1 (CH), 31.1 (CH_2), 16.0 (CH_3).

(1*R*,2*S*,3*S*,4*R*)-3,4-Diacetoxy-2-hydroxy-2-methylcyclopentylmethyl Acetate [(−)-4]: Epoxide **(−)-12** (90 mg, 0.63 mmol) was suspended in H_2O (5 mL), and perchloric acid (70% in water, 0.1 mL) was added at room temp. After the mixture had been stirred for 1 d, Amberlyst® A-21 resin (1.5 g) was added and the suspension was stirred for a further 20 min. The reaction mixture was filtered through a pad of $MgSO_4$ and concentrated. Pyridine (3 mL) and Ac_2O (0.5 mL, 5 mmol) were added to the crude material, which was stirred at room temp. for 5 h. Solvents were removed and purification of the residue by column chromatography afforded **(−)-4** as a colourless oil in 89% overall yield (160 mg, 0.55 mmol). $[\alpha]_D^{25} = -24.4$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3472, 1729, 1229, 1039 cm^{-1}. ^1H NMR (400 MHz, C_6D_6): δ = 5.20 (d, J = 5.0 Hz, 1 H, 2-H), 5.11 (td, J = 8.1, 5.0 Hz, 1 H, 1-H), 4.42 and 4.18 (ABX, J = 11.2, 7.0, 6.2 Hz, 2 H, 5-H), 2.55 (br. s, 1 H, OH), 2.23 (dt, J = 12.9, 7.5 Hz, 1 H, 6-H_a), 1.89 (dq, J = 13.5, 6.9 Hz, 1 H, 4-H), 1.72−1.63 (m, 1 H, 6-H_b), 1.70 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.0 (C), 170.9 (C), 170.4 (C), 86.2 (CH), 77.7 (C), 75.9 (CH), 63.4 (CH_2), 44.7 (CH), 31.7 (CH_2), 23.2 (CH_3), 20.9 (CH_3), 20.9 (CH_3), 20.7 (CH_3) ppm. $C_{13}H_{20}O_7$ (288.3): calcd. C 54.16, H 6.99; found C 54.45, H 6.90.

(3*R*,5*S*)-3-Benzyloxy-5-(benzyloxymethyl)-1-methylcyclopent-1-ene (+)-13: Compound **(−)-11** (350 mg, 2.73 mmol), diluted in diethyl ether (5 mL), was added at 0 °C to a stirred suspension of sodium hydride (660 mg, 50 wt.% in oil, 13.7 mmol) in dry diethyl ether (10 mL). After 20 min, tetrabutylammonium iodide (37 mg, 0.10 mmol) and benzyl bromide (1.3 mL, 10.9 mmol) were added and the reaction mixture was allowed to warm to room temp. After 2 d, the reaction was complete, and $Na_2SO_4 \cdot 10H_2O$ (3.5 g) and NH_4Cl (300 mg) were added. The solution was stirred for a further 15 min and concentrated. The residue was chromatographed on silica gel to afford **(+)-13** as a colourless oil in 90% yield (756 mg, 2.45 mmol). $[\alpha]_D^{25} = +18.5$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3063, 3030, 1641, 1600, 1135 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.18 (m, 10 H), 5.59−5.55 (m, 1 H), 4.55−4.45 (m, 4 H), 4.50−4.43 (m, 1 H), 3.60 and 3.39 (ABX, J = 8.9, 7.5, 5.3 Hz, 2 H), 2.72−2.61 (m, 1 H), 2.36 (dt, J = 13.7, 7.6 Hz, 1 H), 1.77 (br. s, 3 H), 1.72 (dt, J = 13.7, 3.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.2 (C), 138.9 (C), 138.4 (C), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH_3), 127.4 (CH), 127.3 (CH), 126.9 (CH), 82.8 (CH), 73.7 (CH_2), 73.1 (CH_2), 70.4 (CH_2), 47.2 (CH), 34.9 (CH_2), 15.6 (CH_3) ppm. $C_{21}H_{24}O_2$ (308.4): calcd. C 81.78, H 7.84; found C 81.51, H 7.91.

(1*S*,2*R*,4*R*,5*R*)-2-Benzyloxy-4-(benzyloxymethyl)-6-oxabicyclo-[3.1.0]hexane [(−)-14]: A freshly generated dimethyldioxirane solution (31 mL, 0.064 M, 1.99 mmol) was added in one portion at −20 °C to a stirred solution of **(+)-13** (250 mg, 0.81 mmol) in acetone. The reaction mixture was kept at this temperature for 2 h, and the mixture was then allowed to warm slowly to room temp. After 15 h, the reaction was complete, and the solvent was removed. The oily residue was purified by column chromatography on silica gel to give 336 mg of **(−)-14** (70% yield). **(−)-14**: $[\alpha]_D^{25} = -1.5$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3089, 3032, 1127, 1045 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.23 (m, 10 H), 4.63−4.42 (m, 4 H), 4.08−4.04 (m, 1 H), 3.65 and 3.47 (ABX, J = 8.8, 8.3, 7.4 Hz, 2 H), 3.33 (br. s, 1 H), 2.48−2.40 (m, 1 H), 1.83−1.76 (m, 2 H), 1.48 (br. s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2 (2 × C), 128.3 (4 × CH), 127.6 (3 × CH), 127.5 (3 × CH), 79.1 (CH), 73.1 (CH_2), 71.8 (CH_2), 71.2 (CH_2), 66.1 (C), 63.4 (CH), 42.1 (CH), 31.1 (CH_2), 16.0 (CH_3) ppm. $C_{21}H_{24}O_3$ (324.4): calcd. C 77.75, H 7.46; found C 78.06, H 7.41.

(1*S*,3*R*,5*R*)-5-(Hydroxymethyl)-1-methylcyclopentane-1,3-diol [(+)-5]: Compound **(−)-14** (100 mg, 0.31 mmol) was added with vigorous stirring to a refluxing mixture of dry Et_2O/THF (2:1, 9 mL) and $LiAlH_4$ (95 mg, 2.50 mmol). The mixture was continuously

stirred under reflux for 4 d. After the mixture had been cooled in an ice bath, Celite (2.5 g) and $Na_2SO_4 \cdot 10H_2O$ (2.5 g) were added. After 20 min, the reaction mixture was filtered through a pad of $MgSO_4$ and concentrated. MeOH (5 mL) and 5 mol% Pd/C (1 mg) was added to the crude material and the suspension was flushed with H_2. After stirring for 1 d at room temp., the mixture was filtered, washed with MeOH (5 mL) and concentrated. Column chromatography afforded **(+)-5** as a colourless oil in 93% overall yield (42 mg, 0.29 mmol). $[\alpha]_D^{25} = +18.5$ (c = 1.0, MeOH). IR (neat): $\tilde{\nu}$ = 3358, 1205, 1109, 1068 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 4.39 (quint, 1 H, J = 7.1 Hz), 3.77 and 3.53 (ABX, J = 11.0, 8.5, 5.7 Hz, 2 H), 2.39 (dt, J = 13.4, 7.5 Hz, 1 H), 2.13 (dd, J = 14.0, 7.6 Hz, 1 H), 2.09 (dq, J = 8.1, 5.6 Hz, 1 H), 1.65 (dd, J = 14.2, 6.3 Hz, 1 H), 1.34 (ddd, J = 13.4, 6.5, 2.7 Hz, 1 H), 1.26 (s, 3 H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 79.6 (C), 70.2 (CH), 63.1 (CH_2), 51.0 (CH), 49.8 (CH_2), 37.9 (CH_2), 24.0 (CH_3).

Ethyl (1*S*,2*S*,4*R*,5*R*)-4-Hydroxy-1-methyl-6-oxabicyclo[3.1.0]hexane-2-carboxylate [(−)-15]: A mixture of allylic alcohol **(−)-1** (50 mg, 0.29 mmol) and $VO(acac)_2$ (0.16 mg) in benzene (5 mL) was heated at reflux under argon for 10 min. *t*BuOOH (1.6 mL, 0.5 M in benzene, 0.80 mmol) was added, and the mixture was stirred under reflux for 20 h. After cooling, the solution was diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$, water and brine. The organic layer was dried and concentrated, and the residue was purified by column chromatography to afford **(−)-15** as a white solid in 98% yield (53 mg, 0.285 mmol). M.p. 86−87 °C. $[\alpha]_D^{25} = -13.6$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3451, 1735, 1247, 1127 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.32−4.19 (m, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.27 (d, J = 1.3 Hz, 1 H), 2.70 (dd, J = 10.2, 8.2 Hz, 1 H), 2.17 (dt, J = 13.2, 8.0 Hz, 1 H), 1.65 (ddd, J = 13.2, 10.2, 8.3 Hz, 1 H), 1.52 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.2 (C), 71.4 (CH), 64.8 (CH), 63.2 (C), 60.8 (CH_2), 46.6 (CH), 32.0 (CH_2), 16.9 (CH_3), 14.2 (CH_3) ppm. $C_9H_{14}O_4$ (186.2): calcd. C 58.05, H 7.58; found C 57.80, H 7.68.

(1*R*,3*R*,5*R*)-5-(Hydroxymethyl)-1-methylcyclopentane-1,3-diol [(+)-6]: Compound **(−)-15** (100 mg, 0.54 mmol) in diethyl ether (5 mL) was added with vigorous stirring to a refluxing mixture of dry Et_2O (10 mL) and $LiAlH_4$ (80 mg, 2.16 mmol). The mixture was stirred under reflux for 23 h. After the mixture had been cooled in an ice bath, Celite (3 g) and $Na_2SO_4 \cdot 10H_2O$ (3 g) were added. After 20 min, the reaction mixture was filtered through a pad of $MgSO_4$ and concentrated. The residue was purified by column chromatography to give 77 mg (98%) of pure **(+)-6**. $[\alpha]_D^{25} = +7.2$ (c = 1.0, MeOH). IR (neat): $\tilde{\nu}$ = 3346, 1213, 1124, 1061 cm^{-1}. ^1H NMR (200 MHz, D_2O): δ = 4.20 (qd, J = 7.0, 4.8 Hz, 1 H), 3.76 and 3.53 (ABX, J = 10.9, 8.0, 5.5 Hz, 2 H), 2.22 (dt, J = 13.0, 7.3 Hz, 1 H), 2.04 (dd, J = 14.3, 7.3 Hz, 1 H), 1.90−1.72 (m, 1 H), 1.65 (dd, J = 14.3, 4.6 Hz, 1 H), 1.46 (ddd, J = 12.8, 10.9, 6.4 Hz, 1 H), 1.25 (s, 3 H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 79.8 (C), 71.0 (CH), 62.6 (CH_2), 50.1 (CH_2), 49.8 (CH), 38.3 (CH_2), 27.3 (CH_3).

Ethyl (1*S*,2*R*,3*R*,4*R*)-2,3,4-Trihydroxy-2-methylcyclopentane-1-carboxylate [(+)-16]: Perchloric acid (70% in water, 0.1 mL) was added at room temp. to epoxide **(−)-15** (100 mg, 0.54 mmol), suspended in H_2O (5 mL). After the mixture had been stirred for 3 d, Amberlyst® A-21 resin (1.5 g) was added. After 20 min, the reaction mixture was filtered through a pad of $MgSO_4$ and concentrated. Column chromatography afforded 100 mg (91%) of **(+)-16** as a solid. M.p. 62−63 °C. $[\alpha]_D^{25} = +33.3$ (c = 1.0, MeOH). IR (KBr): $\tilde{\nu}$ = 3439, 1731, 1233, 1172 cm^{-1}. ^1H NMR (200 MHz, D_2O): δ = 4.15 (q, J = 7.0 Hz, 2 H), 4.15−4.05 (m, 1 H), 3.71 (d, J = 6.4 Hz, 1 H), 2.73 (dd, J = 10.5, 9.1 Hz, 1 H), 2.29 (dt, J = 14.4, 8.2 Hz, 1 H), 1.84 (ddd, J = 14.4, 10.6, 5.2 Hz, 1 H), 1.21 (t, J = 7.2 Hz, 3 H), 1.08 (s, 3 H) ppm. ^{13}C NMR (50 MHz, D_2O): δ = 175.7 (C), 80.9 (C), 79.8 (CH), 68.4 (CH), 62.7 (CH_2), 50.9 (CH), 32.3 (CH_2), 18.0 (CH_3), 14.2 (CH_3).

(1*R*,2*R*,3*R*,4*R*)-3,4-Diacetoxy-2-hydroxy-2-methylcyclopentylmethyl Acetate [(+)-7]: A solution of **(+)-16** (100 mg, 0.49 mmol) in dry THF (5 mL) was slowly added at 0 °C to a stirred slurry of $LiAlH_4$ (38 mg, 1.00 mmol) in dry THF (2 mL). The solution was allowed to warm to room temp. After 1 h, H_2O (1 mL) was added and the mixture was concentrated. Pyridine (8 mL) and Ac_2O (2.0 mL, 20 mmol) were added to the crude material, and the mixture was stirred at room temp. After 2 d, solvents were removed and purification of the residue by column chromatography afforded **(+)-7** as a colourless oil in 86% overall yield (121 mg, 0.42 mmol). $[\alpha]_D^{25} = +7.2$ (c = 1.0, MeOH). IR (neat): $\tilde{\nu}$ = 3489, 1733, 1237, 1049 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.32 (dt, J = 8.5, 5.7 Hz, 1 H, 1-H), 4.92 (d, J = 6.2 Hz, 1 H, 2-H), 4.17 and 4.07 (ABX, J = 11.0, 7.8, 6.7 Hz, 2 H, 5-H), 2.43 (dt, J = 14.4, 8.6 Hz, 1 H, 6-H_a), 2.22 (dq, J = 9.6, 7.7 Hz, 1 H, 4-H), 2.06 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 1.99 (s, 3 H, CH_3), 1.46 (ddd, J = 15.2, 9.9, 5.5 Hz, 1 H, 6-H_b), 1.21 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.9 (C), 170.6 (C), 170.0 (C), 80.2 (CH), 78.8 (C), 69.6 (CH), 64.6 (CH_2), 43.7 (CH), 31.8 (CH_2), 20.9 (CH_3), 20.8 (CH_3), 20.6 (CH_3), 18.2 (CH_3) ppm. $C_{13}H_{20}O_7$ (288.3): calcd. C 54.16, H 6.99; found C 54.43, H 7.02.

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