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Stereoselective synthesis of (3*S*,5*S*,6*S*)-tetrahydro-6-isopropyl-3,5-dimethylpyran-2-one; a *C*5-epimer of a component of a natural sex pheromone of the wasp *Macrocentrus grandii*, the larval parasitoid of the European corn borer *Ostrinia nubilalis*

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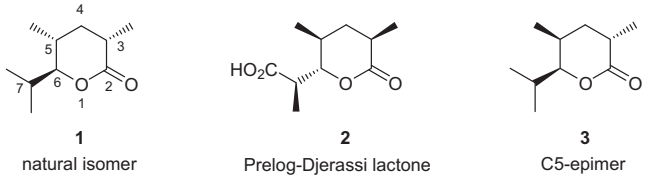
ABSTRACT

(3*S*,5*S*,6*S*)-Tetrahydro-6-isopropyl-3,5-dimethylpyran-2-one, a *C*5-epimer of a component of the natural sex pheromone of the wasp *Macrocentrus grandii*, the larval parasitoid of the European corn borer *Ostrinia nubilalis*, was synthesized starting from methyl L-valinate. The transformation includes a Kulinkovich cyclopropanation reaction, a cationic cyclopropyl-allyl rearrangement of cyclopropyl methanesulfonate, a diastereoselective alkylation of Oppolzer's (*N*-propionyl)-(2*R*)-bornane-10,2-sultam and a diastereoselective hydrogenation using Wilkinson's catalyst as the key steps.

1. Introduction

One of the methods used for controlling the European corn borer (*Ostrinia nubilalis* Hübner) population is the pheromonal attraction of its natural entomophage, the larval parasitoid *Macrocentrus grandii* Goidanich. The sex pheromone of this predacious wasp is comprised of (3*S*,5*R*,6*S*)-tetrahydro-6-isopropyl-3,5-dimethylpyran-2-one **1**, (9*Z*,13*Z*)-9,13-heptacosadiene and (*Z*)-4-tridecenal.[1] The last two components are synergists for lactone **1**.[1,2] Compound **1** has a structural similarity to the Prelog–Djerassi lactone **2** (Fig. 1), a well-known product of the oxidative degradation of methymycin, neomethymycin, narbomycin, picromycin and a number of other microbial macrolide antibiotics.[3]



1 natural isomer

2 Prelog-Djerassi lactone

3 C5-epimer

Figure 1.

In 1993, Liu et al. synthesized[4] both enantiomers of lactone **1**. They found that (3*S*,5*R*,6*S*)-**1** was as attractive as natural **1**, while (3*R*,5*S*,6*R*)-**1**[2] was several times less active and showed no inhibitory action. It is known that the bioactivity of pheromones may be very dependent on the enantiomeric and diastereomeric composition of the components,[5] and it is not always the pure stereoisomer that shows maximum activity. For instance the natural component of the pheromone of German cockroach *Blattella germanica* (3*S*,11*S*)-3,11-dimethylnonacosan-2-one was the least effective amongst the three other synthetic isomers.[5a,6] Sometimes the enantiomeric or the diastereomeric mixture is more active than the individual stereoisomers.[5] The male-produced aggregation pheromone of the red-flour beetle *Tribolium castaneum* (4*R*,8*R*)-4,8-dimethyldecanal (tribolure)[7] is as active as the natural pheromone, while a mixture of (4*R*,8*R*)- and (4*R*,8*S*)-isomers in a ratio of 4:1 is about 10 times more active.[5a,8] Similar structure–activity relationships were also observed for other insect pheromones.[5] Thus, the synthesis of individual, including unnatural isomers and components of the pheromones, to study the structure–activity relationships for the various stereoisomers and mixtures thereof is an urgent problem that must be solved prior to the practical application of these pheromones.

Several approaches to the stereoselective synthesis of lactone **1** have already been reported.[4,9] There are two publications that describe the synthesis and isolation of the *C*3-epimers of **1** in enantiomerically pure[9a] and racemic[9d] forms. Other diastereomers of **1** including the *C*5-epimer **3** are unknown. Since we are interested in monitoring and managing the maize pests using pheromones, as well as developing methods for pheromone synthesis via hydroxycyclopropane intermediates, we proposed a retrosynthetic scheme for obtaining heptanolide **3** through the unsaturated lactone **4** as the key precursor. The main difference of the proposed

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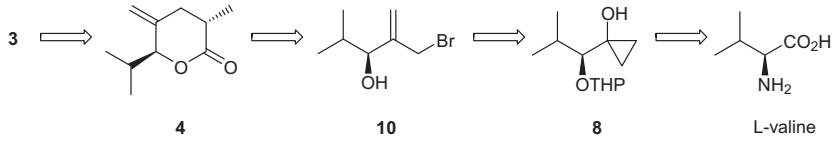


Scheme 1. Retrosynthetic analysis of **3**.

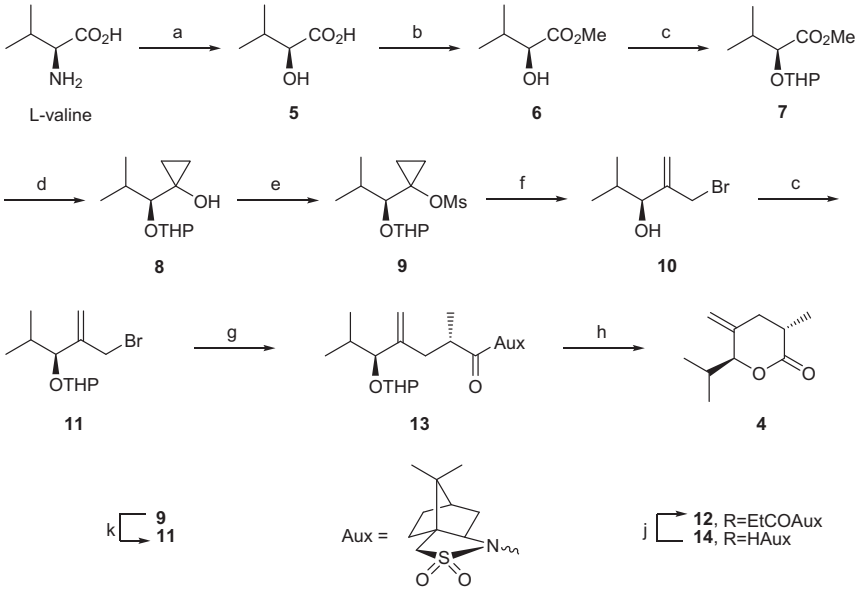
synthetic way from the previously reported syntheses of compounds **1** and **4**[9b] is the use of carboxylic ester cyclopropanation with RMgBr/Ti(O*i*-Pr)$_4$ (Kulinkovich reaction)[10] followed by $MgBr_2$-induced cationic cyclopropyl-allyl rearrangement[11] of the cyclopropyl methanesulfonate to form the C4–C7 carbon skeleton of the target molecule (Scheme 1). The C2–C3 carbon fragment of lactone **3** was formed *via* diastereoselective alkylation of Oppolzer's *N*-acylsultam.[12] It should be noted that cyclopropanols are readily accessible by a Kulinkovich reaction, and the products of their transformations have been previously used in the synthesis of a number of pheromones.[13]

2. Results and discussion

The key compound **3** was obtained from the available natural amino acid L-valine. The latter was transformed into L-valinic acid **5** by a Van Slyke reaction[14] (Scheme 2). The extractive esterification of **5** with methanol in the presence of *p*-toluenesulfonic acid gave methyl L-valinate **6** in 97% ee. Cyclopropanol **8** was synthesized by tetrahydropyranylation of the free hydroxyl group in the hydroxyester **6** followed by Kulinkovich cyclopropanation of the methoxycarbonyl group in compound **7** with EtMgBr catalysed by Ti(O*i*-Pr)$_4$ under the previously reported conditions for THP-protected hydroxyesters.[13e,i,15] Next, **8** was converted into methanesulfonate **9** (97% ee of deprotected **9**). The latter was involved in a $MgBr_2$-promoted cationic cyclopropyl-allyl rearrangement[11] proceeding with simultaneous removal of the tetrahydropyranyl protecting group.[13e,16]

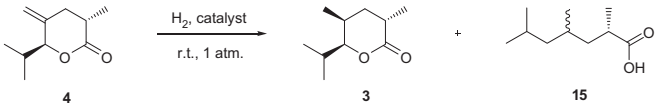
Re-tetrahydropyranylation of the hydroxyl group in **10**, followed by diastereoselective alkylation of the the sodium enolate derived from Oppolzer's *N*-propionylsultam **12** with the alkyl bromide **11**, led to imide **13**. Removal of the tetrahydropyranyl protection was avoided by adding 1 equiv of Hünig's base to the reaction mixture to suppress the formation of acidic impurities.[17] The reaction proceeded without a loss of enantiomeric purity of the asymmetric centre at the oxy-group. Full conversion was achieved in 4 h (TLC control). Alkylation of **12** by the allyl bromide **11** in the presence of HMPTA was not observed at −78 to −50 °C[12] and was very slow at temperatures above −50 °C (incomplete conversion in 20 h). The addition of TBAI[12] significantly accelerated the alkylation. The reaction begins at −78 °C (TLC control) and at −50 °C is complete in 5 h. It was found to be more convenient to use a small excess (0.3 equiv) of the allyl bromide **11** with respect to sultam **12**, because otherwise a chromatographically inseparable mixture of the desired product **13** and starting sultam **12** was formed. The use of more than 1 equiv of NaHMDS at this stage resulted in the dialkylation of **12** with a second alkyl group introduced into the methylene unit activated by the carbonyl and sulfonic groups.[12]

Hydrolysis of imide **13** under mild conditions, followed by the extraction of the chiral auxiliary (AuxH) **14** by chloroform, the acid-catalysed removal of the THP-protection and the 'one-pot' lactonization with a 3 M HCl solution gave the unsaturated δ-valerolactone **4** with 90% de (by GC–MS). The use of 6 M HCl solution at the last stage of this transformation led to some epimerization of the C3 stereocentre. Hydrogenation of the exocyclic double bond in the lactone **4** using palladium on carbon or platinum black at rt and 1 atm pressure of H_2 proceeded along with the reductive cleavage of the C–O bond at the allyl position to give (2*S*,4*RS*)-2,4,6-trimethylheptanoic acid **15** (see Table 1). Highly chemoselective and diastereoselective hydrogenation took place when using Wilkinson's catalyst[18] and gave (3*S*,5*S*,6*S*)-tetrahydro-6-isopropyl-3,5-dimethylpyran-2-one **3** (de >98% from GC–MS, 98% yield), the *C*5-epimer of **1**. The same diastereomer was detected (by ^{1}H



Scheme 2. Reagents and conditions: (a) Ref. 14a, 96%; (b) MeOH, *p*-TsOH·H_2O, CCl_4, 10 h, 82%; (c) DHP, PPTS, CH_2Cl_2, 1 h, 92%; (d) EtMgBr, Ti(O*i*-Pr)$_4$, THF, Et_2O, 3 h, 75%; (e) MsCl, Et_3N, CH_2Cl_2, 1 h, 99%; (f) $MgBr_2$, Et_2O, $CHCl_3$, 2 h, 71%; (g) **12**, NaHMDS, Bu_4NI, HMPTA, then **11**, THF, 5 h, 77%; (h) (i) H_2O_2, LiOH, 12 h; (ii) extraction of **14**, $CHCl_3$, 89%; (iii) HCl, H_2O, 1 h, 84% over two synthetic steps; (j) NaH, EtCOCl, PhMe, 4 h, 81%; (k) $MgBr_2$, Hünig's base, Et_2O, $CHCl_3$, 4 h, 84%.

Table 1
Hydrogenation of lactone **4** using various catalysts



4 3 15

Catalyst, solvent	Ratio[a] of products (%)	
	3	**15**
5% Pd/C, EtOAc	13	87
Pt black, EtOAc	15	85
Pt black, *n*-C_6H_{14}	63	37
$(Ph_3P)_3RhCl$, C_6H_6	>99	<1

[a] By ^{1}H MNR spectra.

NMR) as the main one in reaction mixtures after the hydrogenation on palladium and platinum catalysts. In contrast to the crystalline natural isomer **1**,[9a] the epimeric product **3** is a liquid at room temperature.

The stereochemical result of the hydrogenation was established by NMR. For the spatially proximal methyl groups and hydrogen atoms in compound **3**, a positive Overhauser effect was observed (Fig. 2). The spin–spin coupling constants between hydrogen atoms in lactone **3** were determined by ^{1}H-homodecoupling NMR experiments and corresponded to those described in the literature for compounds with a similar structure.[19] Furthermore, the chemical shifts of some hydrogen atoms in the ^{1}H NMR spectrum of **3** differed substantially from those described for the natural isomer **1**.[9a,20] The data obtained clearly support the proposed structure

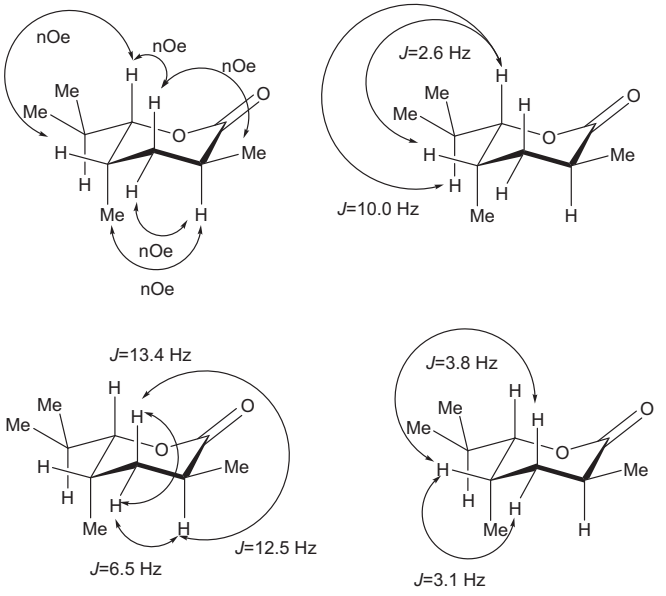


Figure 2. Key NOESY correlations and ^{1}H spin–spin coupling constants of the lactone **3**.

of **3** with equatorial substituents at the C3 and C6 positions, and an axial substituent at the C5 position.

We also studied the diastereoselectivity of the hydrogenation for the acyclic allylic alcohol **16** (Scheme 3) obtained by the acid-catalysed methanolysis of **13**. The use of Wilkinson's catalyst resulted in the formation of *syn*-diastereoisomer **17** (de 90% from ^{1}H NMR).

The hydroxyl group in **16** had no stereodirecting effect on the hydrogenation of the double bond at these conditions.[21] The hydroxyl-directed *anti*-selective high pressure hydrogenation of **16** on a cationic rhodium(I) catalyst[21a] or the other similar catalytic systems[21b] can potentially be used for the synthesis of the natural isomer **1**. Saponification of the saturated imide **17** followed by lactonization in an acidic medium, as described above for **13**, led to lactone **3** (de 90%, from GC–MS). The spectroscopic characteristics of **3** were in agreement with those previously obtained for the product of the hydrogenation of **4**.

3. Conclusion

The first stereoselective synthesis of (3*S*,5*S*,6*S*)-tetrahydro-6-isopropyl-3,5-dimethylpyran-2-one **3**, a *C*5-epimer of a component of the natural sex pheromone of the wasp *M. grandii*, was developed starting from the readily available L-valine. The best overall linear sequence consisted of 10 preparative stages with an overall yield of 25%. The organocatalytic synthesis of the natural isomer **1** and comparative biological studies of **1** and **3** are currently in progress.

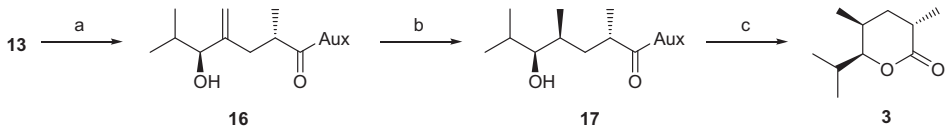
4. Experimental

4.1. General

Solvents were dried over standard drying agents and were distilled prior to use. TLC was performed on aluminium-backed plates coated with Silica Gel 60; chromatograms were visualised with a Ce/Mo reagent followed by heating. Column chromatography was performed using Merck 60 silica gel (70–230 mesh). Flash column chromatography was carried out on Silica Gel 60 (230–240 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ ($CHCl_3$ at δ = 7.26 ppm for ^{1}H NMR and $CHCl_3$ at δ = 77.0 ppm for ^{13}C NMR as internal standard) using a Bruker AC 400 spectrometer. The 1D g-NOESY, HMQC, HMBC and ^{1}H-homodecoupling experiments were performed on the same spectrometer. The FT-IR spectra were recorded using a Vertex 70 spectrometer. Optical rotations were measured at 20 ± 2 °C using a CM-3 polarimeter (scale factor: 0.05°). GC–MS analyses were performed using a Hewlett Packard 5890/5972 mass spectrometer with ionization by electron impact (70 eV), with helium as the carrier gas, and capillary column 50 m × 0.20 mm HP Innovax.

4.2. (*S*)-Methyl 2-hydroxy-3-methylbutanoate 6[22]

Methanol (14.5 mL, 360 mmol) and *p*-TsOH·H_2O (0.68 g, 3.6 mmol) were added to a solution of (*S*)-valinic acid[14a] **5** (14.20 g, 120 mmol) in CCl_4 (40 mL). The resulting mixture was



16 17 3

Scheme 3. Reagents and conditions: (a) MeOH, *p*-TsOH·H_2O, 0.5 h, 93%; (b) H_2, $(Ph_3P)_3RhCl$, C_6H_6, 7 h, 90%; (c) (i) H_2O_2, LiOH, 12 h; (ii) extraction of **14**, $CHCl_3$, 89%; (iii) HCl, H_2O, 1 h, 87% over two synthetic steps.

refluxed for 10 h under anhydrous conditions. Next, the mixture was cooled to rt, washed with water (15 mL), saturated aqueous $NaHCO_3$ (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was distilled to give methyl ester **6** (13.03 g, 82%) as a colourless oil; bp 62–63 °C/15 Torr; $[\alpha]_D$ = +23.7 (*c* 1.00, $CHCl_3$), lit.[14b] $[\alpha]_D$ = +24.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.82 (d, *J* = 6.9 Hz, 3H, 3-Me), 0.98 (d, *J* = 6.9 Hz, 3H, 3-Me), 2.03 (sept. of d, *J* = 6.9, 3.6 Hz, 1H, 3-H), 2.83 (d, *J* = 6.2 Hz, 1H, OH), 3.75 (s, 3H, CO_2Me), 4.01 (dd, *J* = 6.2, 3.6 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$) δ 15.9, 18.6, 32.1, 52.2, 75.0, 175.3; IR (film) ν_{max}: 3483, 1735 cm^{-1}.

4.2.1. Determination of the enantiomeric purity of 6

The ee value of **6** was determined by Mosher's method[23] from the integral intensities of the doublets of the 2-H protons at δ = 5.01 and 5.03 ppm in the ^{1}H NMR spectra of the (*S*)- and (*RS*)-MTPA esters. The enantiomeric excess of the compound **6** was 97%.

4.3. (*S*)-Methyl 3-methyl-2-(tetrahydro-2*H*-pyran-2-yloxy) butanoate 7[22a]

3,4-Dihydro-2*H*-pyran (11.2 mL, 123 mmol) and PPTS (0.70 g, 2.8 mmol) were added to a stirred solution of **6** (12.48 g, 94.5 mmol) in CH_2Cl_2 (150 mL) at rt. The resulting mixture was stirred for 1 h at rt, quenched with aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give the THP-protected methyl ester **7** (18.79 g, 92%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 0.90 (d, *J* = 6.9 Hz, 1.5H, 3-Me), 0.97 (d, *J* = 6.9 Hz, 1.5H, 3-Me), 0.99 (d, *J* = 6.9 Hz, 3H, 3-Me), 1.00 (d, *J* = 6.9 Hz, 1.5H, 3-Me), 1.44–1.62 (m, 3H, $CH_2CH_2CH_2$ in tetrahydropyran), 1.64–1.76 (m, 2H, $CH_2CH_2CH_2$ in tetrahydropyran), 1.78–1.90 (m, 1H, $CH_2CH_2CH_2$ in tetrahydropyran) 2.01 (d of sept., *J* = 7.2, 6.9 Hz, 0.5H, 3-H), 2.11 (sept. of d, *J* = 6.9, 5.6 Hz, 0.5H, 3-H), 3.39–3.46 (m, 0.5H, CH_2O in tetrahydropyran), 3.47–3.54 (m, 0.5H, CH_2O in tetrahydropyran), 3.65 (d, *J* = 7.2 Hz, 0.5H, 2-H), 3.72 (s, 1.5H, CO_2Me), 3.72 (s, 1.5H, CO_2Me), 3.79–3.93 (m, 1H, CH_2O in tetrahydropyran), 4.10 (d, *J* = 5.6 Hz, 0.5H, 2-H), 4.60 (t, *J* = 3.6 Hz, 0.5H, OCHO in tetrahydropyran), 4.63 (t, *J* = 3.3 Hz, 0.5H, OCHO in tetrahydropyran); ^{13}C NMR ($CDCl_3$) δ 17.8, 18.2 (×2), 18.9, 19.1, 19.3, 25.2, 25.4, 30.3 (×2), 31.4, 31.5, 51.2, 51.5, 62.0, 62.5, 78.6, 83.6, 96.6, 100.9, 164.7, 164.9; IR (film) ν_{max}: 1752 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.01; H, 9.41.

4.4. 1-((*S*)-2-Methyl-1-(tetrahydro-2*H*-pyran-2-yloxy)propyl) cyclopropanol 8

A solution of ethylmagnesium bromide prepared from magnesium (3.89 g, 162 mmol) and ethyl bromide (12.3 mL, 165 mmol) in a mixture of THF (160 mL), Et_2O (160 mL) and benzene (20 mL) was added to a stirred solution of ester **7** (10.00 g, 46.3 mmol) and Ti(O*i*-Pr)$_4$ (7.0 mL, 23.2 mmol) in THF (100 mL) at 10–13 °C over the course of 3 h. The mixture was concentrated in vacuo, diluted with CH_2Cl_2 (100 mL), quenched with aqueous NH_4Cl (30 mL) and filtered. The filter cake was washed thoroughly with CH_2Cl_2. The filtrate was washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give cyclopropanol **8** (7.64 g, 75%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 0.47–0.55 (m, 1H, CH_2CH_2 in cyclopropane), 0.56–0.65 (m, 1H, CH_2CH_2 in cyclopropane), 0.68–0.75 (m, 1H, CH_2CH_2 in cyclopropane), 0.80–0.92 (m, 1H, CH_2CH_2 in cyclopropane), 0.97 (d, *J* = 2.7 Hz, 1.5H, 3-Me), 0.98 (d, *J* = 2.7 Hz, 1.5H, 3-Me), 1.01 (d, *J* = 1.5 Hz, 1.5H, 3-Me), 1.03 (d, *J* = 1.5 Hz, 1.5H, 3-Me), 1.47–1.67 (m, 4H, $CH_2CH_2CH_2$ in tetrahydropyran), 1.70–1.91 (m, 2H, $CH_2CH_2CH_2$ in tetrahydropyran), 2.05 (d of sept., *J* = 7.3, 1.5 Hz, 0.5H, 3-H), 2.21 (d of sept., *J* = 9.1, 2.6 Hz, 0.5H, 3-H), 2.69 (d, *J* = 7.3 Hz, 0.5H, 2-H), 2.80 (d, *J* = 9.1 Hz, 0.5H, 2-H), 3.12 (s, 0.5H, OH), 3.34 (s, 0.5H, OH), 3.45–3.53 (m, 1H, CH_2O in tetrahydropyran), 3.89–4.01 (m, 1H, CH_2O in tetrahydropyran), 4.60 (dd, *J* = 6.1, 2.6 Hz, 0.5H, OCHO in tetrahydropyran), 5.11 (t, *J* = 3.3 Hz, 0.5H, OCHO in tetrahydropyran); ^{13}C NMR ($CDCl_3$) δ 11.0, 11.6, 12.8, 13.6, 19.2 (×2), 19.3, 20.0, 20.1, 20.8, 25.2, 25.4, 29.9, 30.9, 31.1, 31.6, 54.1, 55.7, 62.1, 63.9, 85.0, 89.7, 93.5, 100.5; IR (film) ν_{max}: 3435, 3090 cm^{-1}. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.21; H, 10.28.

4.5. 1-((*S*)-2-Methyl-1-(tetrahydro-2*H*-pyran-2-yloxy)propyl) cyclopropyl methanesulfonate 9

Methanesulfonyl chloride (4.2 ml, 54.3 mmol) was added dropwise to a stirred solution of cyclopropanol **8** (8.31 g 38.8 mmol) and triethylamine (16.2 mL, 116.4 mmol) in dry ether (270 mL) at 0 °C. The reaction mixture was stirred for 1 h at rt, quenched with water (120 mL) and extracted with ether (3 × 70 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The methanesulfonate **9** was isolated as a colourless oil (11.21 g, 99%) using flash column chromatography on silica gel (petroleum ether/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.62–0.72 (m, 0.5H, CH_2CH_2 in cyclopropane), 0.80–0.95 (m, 1H, CH_2CH_2 in cyclopropane), 0.98 (d, *J* = 6.7 Hz, 1.5H, 3-Me), 1.03 (d, *J* = 6.9 Hz, 1.5H, 3-Me), 1.06 (d, *J* = 6.9 Hz, 1.5H, 3-Me), 1.10 (d, *J* = 6.7 Hz, 1.5H, 3-Me), 1.13–1.27 (m, 0.5H, CH_2CH_2 in cyclopropane), 1.46–1.85 (m, 6H, $CH_2CH_2CH_2$ in tetrahydropyran), 2.07 (d of sept., *J* = 8.4, 6.7 Hz, 0.5H, 3-H), 2.14 (d of sept., *J* = 9.0, 6.9 Hz, 0.5H, 3-H), 2.92 (d, *J* = 8.4 Hz, 0.5H, 2-H), 3.08 (d, *J* = 9.0 Hz, 0.5H, 2-H), 3.16 (s, 1.5H, $MeSO_2$), 3.20 (s, 1.5H, $MeSO_2$), 3.42–3.52 (m, 1H, CH_2O in tetrahydropyran), 3.77–3.86 (m, 0.5H, CH_2O in tetrahydropyran), 4.11–4.19 (m, 0.5H, CH_2O in tetrahydropyran), 4.55 (t, *J* = 3.6 Hz, 0.5H, OCHO in tetrahydropyran), 5.27 (t, *J* = 3.3 Hz, 0.5H, OCHO in tetrahydropyran); ^{13}C NMR ($CDCl_3$) δ 9.4, 10.8, 12.1, 12.4, 19.0, 19.2, 19.6, 19.7, 20.0, 20.2, 25.3, 25.4, 30.2, 30.5, 31.7, 31.9, 39.4, 39.8, 62.3, 62.5, 65.0, 68.2, 81.2, 87.2, 94.7, 100.6; IR (film) ν_{max}: 3093, 1476 cm^{-1}. Anal. Calcd for $C_{13}H_{24}O_5S$: C, 53.40; H, 8.27. Found: C, 53.49; H, 8.33.

4.5.1. Determination of the enantiomeric purity of deprotected 9

An analytical sample was prepared by the acid-catalysed deprotection of the second hydroxyl group in compound **9**. The ee value of deprotected **9** was determined by Mosher's method[23] from the integral intensities of the doublets of the 2-H protons at δ = 4.68 and 4.72 ppm in the ^{1}H NMR spectra of the (*S*)- and (*RS*)-MTPA esters. The enantiomeric excess of deprotected **9** was 97%.

4.6. (*S*)-2-(Bromomethyl)-4-methylpent-1-en-3-ol 10

A solution of $MgBr_2$, prepared from magnesium (1.79 g, 74.5 mmol) and 1,2-dibromoethane (3.0 mL, 74.5 mmol) in diethyl ether (75 mL), was added to a stirred solution of methanesulfonate **9** (5.44 g, 18.6 mmol) in $CHCl_3$ (65 mL) at reflux. The reaction mixture was then refluxed for 2 h, cooled to 0 °C and quenched with water (80 mL). The organic layer was separated from the aqueous one, and the latter was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Compound **10** was isolated by column chromatography on silica gel (2.55 g, 71%) as a yellowish oil; $[\alpha]_D$ = +13.7 (*c* 2.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (d, *J* = 6.8 Hz, 3H, 4-Me), 0.95 (d, *J* = 6.8 Hz, 3H, 4-Me), 1.69 (d, *J* = 4.7 Hz, 1H, OH), 1.69 (sept., *J* = 6.8 Hz, 1H, 4-H),

1.69 (sept. of d, J = 6.8, 4.7 Hz, 1H, 4-H), 3.96–4.00 (m, 1H, C*H*HBr), 4.02–4.06 (m, 1H, CH*H*Br), 4.07 (dd, J = 4.7, 4.7 Hz, 1H, 3-H), 5.28–5.31 (m, 1H, C=C*H*H), 5.37–5.39 (m, 1H, C=CH*H*); ^{13}C NMR ($CDCl_3$) δ 16.8, 19.6, 31.5, 32.8, 78.0, 117.1, 146.8; IR (film) ν_{max}: 3424, 3090, 1643 cm^{-1}. Anal. Calcd for $C_7H_{13}BrO$: C, 43.54; H, 6.79. Found: C, 43.48; H, 6.72.

4.7. 2-((*S*)-2-(Bromomethyl)-4-methylpent-1-en-3-yloxy)-tetrahydro-2*H*-pyran 11

3,4-Dihydro-2*H*-pyran (1.3 mL, 14.4 mmol) and PPTS (0.08 g, 0.33 mmol) were added to a stirred solution of alcohol **10** (2.15 g, 11.1 mmol) in CH_2Cl_2 (30 mL) at rt. The mixture was stirred for 1 h, quenched with aqueous $NaHCO_3$ (15 mL) and extracted with $CHCl_3$ (3×20 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether/ethyl acetate) to give the THP-protected allyl bromide **11** (2.84 g, 92%) as a yellowish oil; ^{1}H NMR ($CDCl_3$) δ 0.87 (d, J = 4.3 Hz, 1.5H, 4-Me), 0.89 (d, J = 4.3 Hz, 1.5H, 4-Me), 0.93 (d, J = 6.7 Hz, 1.5H, 4-Me), 1.01 (d, J = 6.7 Hz, 1.5H, 4-Me), 1.43–1.63 (m, 4H, $CH_2CH_2CH_2$ in tetrahydropyran), 1.64–1.74 (m, 1H, $CH_2CH_2CH_2$ in tetrahydropyran), 1.75–1.96 (m, 2H, 4-H, $CH_2CH_2CH_2$ in tetrahydropyran), 3.36–3.45 (m, 0.5H, 3-H), 3.45–3.53 (m, 0.5H, 3-H), 3.70–3.75 (m, 0.5H, CH_2O in tetrahydropyran), 3.75–3.83 (m, 0.5H, CH_2O in tetrahydropyran), 3.84–3.94 (m, 2H, CH*H*Br, CH_2O in tetrahydropyran), 3.98–4.04 (m, 0.5H, C*H*HBr), 4.04–4.11 (m, 0.5H, C*H*HBr), 4.53–4.60 (m, 1H, OCHO in tetrahydropyran), 5.22–5.24 (m, 0.5H, C=CH_2), 5.24–5.28 (m, 0.5H, C=CH_2), 5.35–5.40 (m, 0.5H, C=CH_2), 5.45–5.50 (m, 0.5H, C=CH_2); ^{13}C NMR ($CDCl_3$) δ 18.3, 18.8, 19.3 (×2), 19.5, 19.7, 25.3, 25.5, 30.5, 30.6, 31.1, 31.2, 31.3, 32.6, 62.0, 62.9, 82.1, 85.6, 94.5, 100.2, 120.0, 117.9, 144.9, 143.5; IR (CCl_4) ν_{max}: 3089, 1643 cm^{-1}. Anal. Calcd for $C_{12}H_{21}BrO_2$: C, 51.99; H, 7.64. Found: C, 52.06; H, 7.78.

4.8. 8,8-Dimethyl-1-{(2*S*)-2-methyl-4-[(1*S*)-2-methyl-1-(tetrahydro-2*H*-pyran-2-yloxy)propyl]pent-4-enoyl}hexahydro-3a,6-methano-2,1-benzisothiazole 2,2-dioxide 13

A 1 M solution of NaHMDS in THF (8.3 mL, 8.3 mmol) was added over the course of 15 min to a stirred solution of (*N*-propionyl)-(2*R*)-bornane-10,2-sultam **12** (0.20 M in THF, 41.5 mL) and TBAI (0.61 g, 1.65 mmol) at -78 °C. The reaction mixture was kept at this temperature for 1 h under stirring. A solution of the allyl bromide **11** (4.98 M in HMPTA, 2.2 mL) was then added dropwise to the stirring reaction mixture. The cooling bath was replaced by an octane–liquid nitrogen bath (−50 °C). The reaction mixture was stirred at −50 °C for 4 h and then slowly (1 h) warmed to −25 °C, quenched with water (80 mL), warmed to rt and extracted with ether (4 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Compound **13** (3.58 g, 77%) was isolated by column chromatography on silica gel (petroleum ether/ethyl acetate) as a colourless viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.76 (d, J = 6.7 Hz, 3H, 6-Me), 0.89 (d, J = 6.7 Hz, 1.5H, 6-Me), 0.95 (s, 3H, CH_3 in bornane), 1.04 (d, J = 5.6 Hz, 1.5H, 6-Me), 1.12 (s, 1.5H, CH_3 in bornane), 1.14 (s, 1.5H, CH_3 in bornane), 1.17 (t, J = 5.6 Hz, 1.5H, 2-Me), 1.19 (t, J = 5.4 Hz, 1.5H, 2-Me), 1.27–2.22 (m, 14H, 3 × CH_2 in bornane, CH in bornane, $CH_2CH_2CH_2$ in tetrahydropyran, 6-H), 2.39–2.50 (m, 1H, 3-H), 2.68–2.77 (m, 1H, 3-H), 3.31–3.52 (m, 4H, CH_2S, CHN in bornane, 2-H), 3.54 (d, J = 7.4 Hz, 0.5H, 5-H), 3.66 (d, J = 8.7 Hz, 0.5H, 5-H), 3.76–3.91 (m, 2H, CH_2O in tetrahydropyran), 4.51 (dd, J = 3.3, 2.8 Hz, 0.5H, OCHO in tetrahydropyran), 4.56 (dd, J = 3.3, 2.8 Hz, 0.5H, OCHO in tetrahydropyran), 4.95–4.98 (m, 0.5H, C=CH_2), 4.99–5.01 (m, 0.5H, C=CH_2), 5.00–5.04 (m, 0.5H, C=CH_2), 5.12–5.16 (m, 0.5H, C=CH_2); ^{13}C NMR ($CDCl_3$) δ 16.7, 17.2, 18.3, 19.1, 19.3, 19.4, 19.8, 19.9, 20.6 (×2), 20.8, 25.4, 25.5, 26.4, 28.8, 30.1 30.5, 30.8, 31.0, 32.8, 32.9, 35.1, 36.6, 37.1, 37.2, 38.4 (×2), 44.5, 44.6, 47.7 (×2), 48.2, 48.4, 52.9, 53.1, 62.0, 62.9, 65.1, 65.4 (×2), 84.7, 87.2, 94.4, 100.1, 112.4, 114.3, 144.4, 146.1, 172.6, 175.8; IR (CCl_4) ν_{max}: 3086, 1701, 1649 cm^{-1}. Anal. Calcd for $C_{25}H_{41}NO_5S$: C, 64.21; H, 8.84. Found: C, 64.17; H, 8.76.

4.9. (3*S*,6*S*)-Tetrahydro-6-isopropyl-3-methyl-5-methylene-pyran-2-one 4[9b]

At first, $LiOH{\cdot}H_2O$ (403 mg, 9.69 mmol) and 34% aq H_2O_2 (1.3 mL, 19.2 mmol) were added to a stirred solution of **13** (1.12 g, 2.40 mmol) in THF (16 mL) and water (4 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 16 h at rt. Then water (10 mL) and $CHCl_3$ (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The aqueous layer was acidified with 3 M HCl to pH 1, stirred for 1 h at rt and extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate extracts were washed with water, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under reduced pressure. Compound **4** (359 mg, 84%) was isolated by column chromatography on silica gel (petroleum ether/ethyl acetate) as a colourless oil; $[\alpha]_D$ = +34.1 (*c* 2.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96 (d, J = 6.5 Hz, 3H, 7-Me), 1.02 (d, J = 6.5 Hz, 3H, 7-Me), 1.24 (d, J = 6.9 Hz, 3H, 3-Me), 2.00 (d of sept., J = 6.9, 6.5 Hz, 1H, 6-H), 2.16–2.25 (m, 1H, 4-H), 2.66–2.81 (m, 2H, 3-H, 4-H), 4.50 (d, J = 6.9 Hz, 1H, 6-H), 4.97–5.39 (m, 1H, C=C*H*H), 5.05–5.10 (m, 1H, C=CH*H*); ^{13}C NMR ($CDCl_3$) δ 17.2, 17.6, 19.2, 32.9, 34.4, 35.1, 88.3, 113.4, 138.9, 174.6; IR (CCl_4) ν_{max}: 3086, 1742, 1655 cm^{-1}; MS (EI): *m/z* (%) = 168 (M^+, 4.8), 125 (100.0), 97 (80.0), 41 (41.9). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.34; H, 9.64.

4.10. (2*S*)-2,4,5-Trimethylheptanoic acid 15

A solution of unsaturated lactone **4** (200 mg, 1.19 mmol) in ethyl acetate (4 mL) was stirred under a hydrogen atmosphere in the presence of Pt black (23 mg) for 2 h. The mixture was filtered and concentrated under reduced pressure. The residue was diluted with petroleum ether (3 mL), water (3 mL) and Et_3N (0.18 mL). The aqueous layer was separated and extracted with petroleum ether. The resulting aqueous layer was acidified with 3 M HCl to pH 1 and extracted with petroleum ether. The extract was washed with brine and concentrated under reduced pressure. Flash column chromatography of the residue on silica gel (petroleum ether/ethyl acetate) gave the saturated carboxylic acid **15** (161 mg, 79%) as a colourless viscous oil; ^{1}H NMR ($CDCl_3$) δ 0.79–0.91 (m, 9H, 4-Me, 6-Me, 6′-Me), 0.95–1.03 (m, 1H, 6-H), 1.06–1.14 (m, 1H, 5-H), 1.16 (d, J = 7.2 Hz, 1.5H, 2-Me), 1.18 (d, J = 7.4 Hz, 1.5H, 2-Me), 1.31–1.40 (m, 1H, 5-H), 1.45–1.59 (m, 1H, 4-H), 1.59–1.74 (m, 2H, 3-H, 3′-H), 2.50–2.66 (m, 1H, 2-H), 11.20 (br s, CO_2H); ^{13}C NMR ($CDCl_3$) δ 16.7, 17.8, 19.4, 19.8, 22.1, 22.2 23.2, 23.3, 25.0, 25.1, 28.0, 28.3, 36.9, 37.1, 41.1, 41.4, 46.7 (×2), 182.8, 183.0; IR (CCl_4) ν_{max}: 2960, 1707 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.80; H, 11.73.

4.11. (3*S*)-2-[(2*S*)-3-(8,8-Dimethyl-2,2-dioxidotetrahydro-3*a*,6-methano-2,1-benzisothiazol-1(4*H*)-yl)-2-methyl-3-oxopropyl]-4-methylpent-1-en-3-ol 16

At first, *p*-TsOH·H_2O (95 mg, 0.50 mmol) was added to a stirred solution of **13** (2.31 g, 4.95 mmol) in MeOH (100 mL) at rt. The mixture was refluxed for 0.5 h, cooled to rt and then Et_3N (0.07 mL, 0.50 mmol) was added. Methanol was evaporated under reduced pressure, and the residue was purified by column

chromatography (petroleum ether/ethyl acetate) to give imide **16** (1.76 g, 93%) as a colourless viscous oil; $[\alpha]_D = -6.9$ (*c* 2.70, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.78 (d, *J* = 6.9, Hz, 3H, 6-Me), 0.95 (d, *J* = 6.9 Hz, 3H, 6′-Me), 0.95 (s, 3H, Me in bornane), 1.13 (s, 3H, Me′ in bornane), 1.18 (d, *J* = 6.5, Hz, 3H, 2-Me), 1.30–1.42 (m, 2H, CHC*H*HC*H*H in bornane), 1.70–1.79 (m, 1H, 6-H), 1.81–1.92 (m, 3H, C*H*CH*H*CH*H* in bornane), 2.02–2.06 (m, 2H, CHC*HH*CH in bornane), 2.18 (dd, *J* = 13.8, 5.1 Hz, 1H, 3-H), 2.29 (d, *J* = 2.9 Hz, 1H, OH), 2.41 (dd, *J* = 13.8, 9.8 Hz, 1H, 3′-H), 3.33–3.42 (m, 1H, 2-H), 3.42 (d, *J* = 13.8 Hz, 1H, C*H*HS in bornane), 3.49 (d, *J* = 13.8 Hz, 1H, CH*H*S in bornane), 3.71 (dd, *J* = 7.2, 2.9 Hz, 1H, 5-H), 3.88 (dd, *J* = 6.4, 6.1 Hz, 1H, CHN in bornane), 4.88–4.92 (m, 2H, C=CH_2); ^{13}C NMR ($CDCl_3$) δ 17.6, 18.1, 19.5, 19.9, 20.8, 26.3, 31.4, 33.0, 37.0, 38.5, 39.6, 44.7, 47.4, 48.2, 53.2, 65.6, 81.5, 113.7, 147.8, 176.0; IR (CCl_4) ν_{max}: 3561, 3078, 1700, 1645 cm^{-1}. Anal. Calcd for $C_{20}H_{33}NO_4S$: C, 62.63; H, 8.67. Found: C, 62.71; H, 8.71.

4.12. (3*S*,4*S*,6*S*)-7-(8,8-Dimethyl-2,2-dioxidotetrahydro-3*a*,6-methano-2,1-benzisothiazol-1(4*H*)-yl)-2,4,6-trimethyl-7-oxoheptan-3-ol 17

A solution of **16** (1.35 g, 3.52 mmol) and freshly prepared Wilkinson's catalyst[14] $(Ph_3P)_3RhCl$ (0.81 g, 0.88 mmol) in dry benzene (70 mL) was stirred under a hydrogen atmosphere (1 bar) at rt for 7 h. The solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to give **17** (1.28 g, 94%) as a pale yellow oil, which was shown to be isomerically homogenous by TLC and ^1H NMR. A portion (250 mg) of this sample was chromatographed on silica (petroleum ether/ethyl acetate) to give a pure **17** as a colourless viscous oil (240 mg); $[\alpha]_D = -8.8$ (*c* 2.22, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.82 (d, *J* = 6.8, Hz, 3H, 6-Me), 0.86 (d, *J* = 6.4, Hz, 3H, 4-Me), 0.95 (d, *J* = 6.9, Hz, 3H, 6′-Me), 0.96 (s, 3H, Me in bornane), 1.15 (s, 3H, Me′ in bornane), 1.16 (d, *J* = 6.5, Hz, 3H, 2-Me), 1.30–1.43 (m, 3H, CHC*H*HC*H*H in bornane, OH), 1.49–1.55 (m, 1H, 3-H), 1.62–1.73 (m, 3H, 3′-H, 4-H, 6-H), 1.81–1.92 (m, 3H, C*H*CH*H*CH*H* in bornane), 2.01–2.09 (m, 2H, CHC*HH*CH in bornane), 3.11–3.19 (m, 2H, 2-H, 5-H), 3.43 (d, *J* = 13.8 Hz, 1H, C*H*HS in bornane), 3.49 (d, *J* = 13.8 Hz, 1H, CH*H*S in bornane), 3.88 (dd, *J* = 6.4, 6.4 Hz, 1H, CHN in bornane); ^{13}C NMR ($CDCl_3$) δ 12.7, 17.0, 18.7, 19.1, 19.8, 21.1, 26.4, 31.2, 32.7, 32.9, 37.6, 38.7, 39.3, 44.7, 47.7, 48.2, 53.2, 65.4, 79.3, 176.7; IR (CCl_4) ν_{max}: 3569, 1698 cm^{-1}. Anal. Calcd for $C_{20}H_{35}NO_4S$: C, 62.30; H, 9.15. Found: C, 62.23; H, 9.25.

4.13. (3*S*,5*S*,6*S*)-Tetrahydro-6-isopropyl-3,5-dimethylpyran-2-one 3

A solution of freshly prepared Wilkinson's catalyst (208 mg, 0.22 mmol) in dry benzene (4 mL) was degassed and then stirred under a hydrogen atmosphere (1 bar) at rt for 30 min. A solution of the unsaturated lactone **4** (252 mg, 1.50 mmol) in benzene (2 mL) was added, and the mixture was stirred under a hydrogen atmosphere (1 bar) at rt for 3 h. The solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to give the target lactone **3** (250 mg, 98%) as a colourless liquid; $[\alpha]_D = -11.4$ (*c* 2.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.5 Hz, 3H, 7-Me), 0.98 (d, *J* = 7.2 Hz, 3H, 5-Me), 1.07 (d, *J* = 6.5 Hz, 3H, 7′-Me), 1.29 (d, *J* = 7.2 Hz, 3H, 3-Me), 1.66 (ddd, *J* = 13.4, 12.5, 3.8 Hz, 1H, 4-Hax), 1.81 (d of sept., *J* = 10.0, 6.5 Hz, 1H, 7-H), 1.91 (ddd, *J* = 13.4, 6.5, 3.1 Hz, 1H, 4-Heq), 2.14 (m, 2.09–2.17, 1H, 5-H), 2.60 (ddd, *J* = 12.5, 7.2, 6.5 Hz, 1H, 3-H), 3.82 (dd, *J* = 10.0, 2.6 Hz, 1H, 6-H); ^{13}C NMR ($CDCl_3$) δ 10.5, 17.8, 17.9, 19.7, 27.8, 30.1, 31.1, 36.4, 89.4, 174.5; IR (CCl_4) ν_{max}: 1738 cm^{-1}; MS (EI): *m/z* (%) = 170 (M^+, 1.4), 127 (41.4), 56 (100.0), 43 (96.0). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.53; H, 10.71.

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