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Asymmetric synthesis of 2-alkyl-3-thiazoline carboxylates: stereochemistry of the MnO_2-mediated oxidation of *cis*- and *trans*-2-alkyl-thiazolidine-(4*R*)-carboxylates

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Abstract—The asymmetric synthesis of a series of 3-thiazoline carboxylates, **2**, was effected by MnO_2 oxidation of the corresponding *cis*/*trans* thiazolidines, **1**. The stereochemistry of the oxidation reaction was studied using NMR and chiral GC analyses. Compounds **2** were obtained with enantiomeric excesses (e.e.s) in the range of 40–100%.

1. Introduction

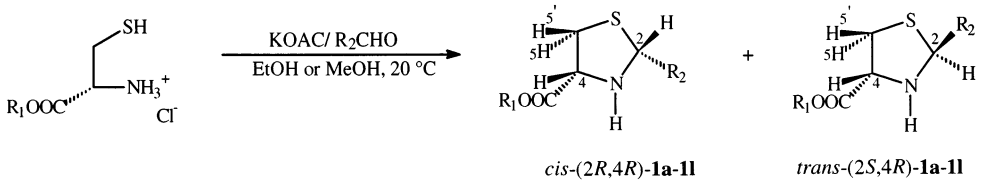
Alkyl thiazolines are widely studied in food and flavorings chemistry.[1] More than 30 thiazoline structures have now been identified from natural sources and foods,[2] particularly in cooked meat[1,3] and in certain exotic fruit such as lychees.[4] There has also been considerable industrial interest related to these compounds, due to their ability to enhance the flavor and/or aroma of various consumable materials, including foodstuffs.[5]

The preparation of 3-thiazolines has been reported through the Asinger reaction,[6] a multi-component process between an α-mercaptoketone, an aldehyde and ammonia. Recently, Martens et al.[7] proposed the only reported example of asymmetric synthesis of 3-thiazolines by a modified Asinger procedure, using in combination with an α-chloro-substituted aldehyde or ketone, aqueous ammonia, sodium hydrogenosulfide and a second homochiral aldehyde. 3-Thiazolines were obtained in yields of between 27 and 85% with diastereoisomeric ratios in the range of 1/1–19/1. However, the reaction was efficient only with bulky aldehydes and high diastereoisomeric ratios were obtained only with very bulky substituents.

We recently proposed a novel strategy for the synthesis of 4-carboxy-2-substituted 3-thiazolines of the type **2**, parallel to the biosynthetic route, in which thiazolidines were selectively oxidized to 3-thiazolines by MnO_2 (Scheme 3).[8] The obtained heterocycles contain a stereogenic center at C(2). In the study presented herein, we focus on the asymmetric synthesis of the 3-thiazolines **2**. Analysis of the 3-thiazoline products by NMR and chiral GC showed that e.e.s in the range of 40–100% were obtained.

2. Results and discussion

Thiazolidines, **1a**–**1l**, were easily obtained in yields of 80–95% from the condensation of L- or (*R*)-cysteine



Scheme 1. Thiazolidine synthesis.

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ethyl or methyl esters (or their ammonium salts) and an alkyl aldehyde derivative under slightly basic conditions[9,10] (Scheme 1, Table 1). This condensation afforded **1** as a mixture of diastereomers, *cis*-(2*R*,4*R*)-**1** and *trans*-(2*S*,4*R*)-**1**′ (Scheme 1), which could not be separated. An equilibrium resulting from epimerization at C(2) occurs between **1** and **1**′ (Scheme 2).[11]

The ^{1}H NMR of the mixture of the two isomers **1** and **1**′ was studied. NMR proved to be the best method of analysis; the spectra of the *cis*/*trans* isomers showed distinct signals for the two isomers, and the C(2) protons were well resolved in all of the spectra obtained. We performed 2D NOESY experiments to determine the absolute configuration of the C(2) center, which showed a C(4)H to C(2)H correlation which was adequate for determining the *cis*/*trans* configuration. The major isomer presented an interaction between C(2)H and C(4)H, while the C(4)H proton was correlated with C(5)H in the minor isomer. The space-proximity of the C(2)H and C(4)H protons gave evidence for a *cis* configuration of the ester and R_2 groups in the main isomer **1**. The absolute configuration of C(4), determined by the starting material, was (*R*) and the absolute configuration of C(2) was also (*R*) for the *cis* isomer. In all of the cases examined (Table 1), the *cis* isomers predominated in $CDCl_3$ at room temperature.

The *cis*/*trans* ratios were not dependent on the temperature; however, they were strongly dependent on the nature of the solvent (Table 2). In $CDCl_3$, CD_3OD and CD_3CN, the major isomer for **1**/**1**′h was the *cis* isomer. However, in DMSO-d_6, the *trans* diastereoisomer predominated after complete equilibration.

The oxidation of methyl or ethyl 2-alkyl-thiazolidine-4(*R*)-carboxylates, **1**/**1**′, with an excess of MnO_2 in CH_3CN at 50°C led to a mixture of 3-thiazolines **2a**–**2l** and thiazole **3** (Scheme 3). After column purification, 3-thiazolines were obtained in moderate to good yields (Table 3). Apart from our studies, these series of heterocycles, **2a**–**2l**, possessing an ester substituent at the 4-position have not, to our knowledge, been described. Upon oxidation compounds **2** lost the C(4) stereogenic center, but present a stereogenic center at C(2). Although we initially expected e.e.s of **2** to be in the same range as the *cis*/*trans* ratios obtained for **1**/**1**′ mixtures, the e.e.s of compounds **2** were found to be much higher in most cases. The e.e.s were measured by ^{1}H NMR, by the use of the chiral shift reagent, tris-[3(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium(III), Eu(tfc)$_3$ (Table 3). In all cases, a shift and a good separation of the C(2)H protons occurred, the separation being around 0.15–0.25 ppm. The e.e.s were also determined by chiral GC using Chiraldex B-PH as the column. The results obtained by chiral GC were comparable (±5%) to those obtained by NMR.

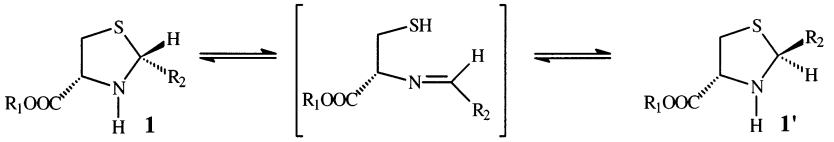
Table 2. Variation of the *cis*/*trans* ratios of ethyl 2-ethyl-thiazolidine-(4*R*)-carboxylate, **1**/**1**′**h**, as a function of the solvent, at 20°C

Solvent	Ratio *cis*/*trans* (%)
$CDCl_3$	67/33
CD_3OD	52/48
CD_3CN	6/4
DMSO-d_6	46/54

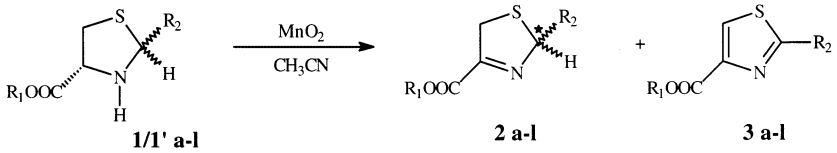
Table 1. Synthesis of thiazolidines **1**/**1**′

Entry	Compound **1**/**1**′	R_1	R_2	Isolated yield of **1**/**1**′ (%)	Ratio *cis*/*trans*[c] (%)
1	**1**/**1**′**a**	Me	Me	90[a]	61/39
2	**1**/**1**′**b**	Me	Et	89[a]	62/38
3	**1**/**1**′**c**	Me	*n*-Pr	82[a]	68/32
4	**1**/**1**′**d**	Me	*i*-Pr	94[a]	70/30
5	**1**/**1**′**e**	Me	*n*-Bu	90[b]	69/31
6	**1**/**1**′**f**	Me	*i*-Bu	93[a]	71/29
7	**1**/**1**′**g**	Et	Me	93[a]	71/29
8	**1**/**1**′**h**	Et	Et	90[a]	67/33
9	**1**/**1**′**i**	Et	*n*-Pr	92[a]	69/31
10	**1**/**1**′**j**	Et	*n*-Bu	89[b]	69/31
11	**1**/**1**′**k**	*i*-Pr	Et	90[b]	69/31
12	**1**/**1**′**l**	*i*-Pr	*i*-Pr	89[b]	62/38

[a] Compounds obtained by condensation of L-cysteine ethyl or methyl esters and aldehydes.
[b] Compounds obtained by esterification of the corresponding thiazolidine-(4*R*)-carboxylic acids.
[c] Ratios determined by ^{1}H NMR, in $CDCl_3$ at 20°C.

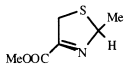
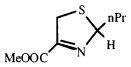
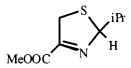
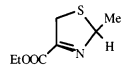
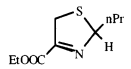
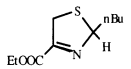
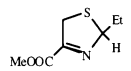
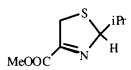
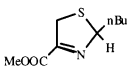
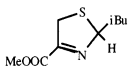
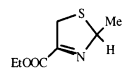
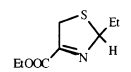
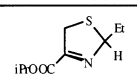
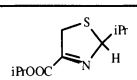


Scheme 2. Thiazolidine epimerization.



Scheme 3. MnO_2-mediated oxidation of thiazolidines **1**/**1′a–l**.

Table 3. MnO_2-mediated oxidation of thiazolidines **1**/**1′**

Entry	Starting	MnO_2[a)]	Product	Isolated Yield of 2 (%)	E.e.[b)] (%)
1	**1/1'a**	A		58	74
2	**1/1'c**	"		55	71
3	**1/1'd**	"		64	14
4	**1/1'g**	"		54	2
5	**1/1'i**	"		60	83
6	**1/1'j**	"		60	81
7	**1/1'b**	B		55	80
8	**1/1'd**	"		56	90
9	**1/1'e**	"		60	100
10	**1/1'f**	"		49	91
11	**1/1'g**	"		50	73
12	**1/1'h**	"		68	95
13	**1/1'k**	"		52	94
14	**1/1'l**	"		56	40

a) A: MnO_2 precipitated hydrate (Prolabo) 20 equivalents.
B: MnO_2 suitable for use in batteries (Aldrich) 15 equivalents.
b) Ee's measured by ^1H NMR ($CDCl_3$, 20 °C) in the presence of 10 % $Eu(tfc)_3$.

Steric hindrance at C(2) and C(4) appears to be important to the stereochemical outcome of the reaction and affected the e.e. value of the product markedly (entries 13 and 14).

We observed that the MnO_2 source also had a marked influence on the stereoselectivity of this heterogeneous process. Several grades of MnO_2 were tested: Precipitated MnO_2 hydrate (Prolabo) and MnO_2 suitable for use in batteries (Aldrich) gave the best yields. MnO_2 obtained by a modified Attenburrow procedure[12] afforded a much lower yield of **2**, and MnO_2 powder (Acros) led to very low oxidation efficiencies. Even though MnO_2 hydrate and battery grade MnO_2 were comparable in conversion efficiencies, they did not afford the same asymmetric control. The oxidation of **1**

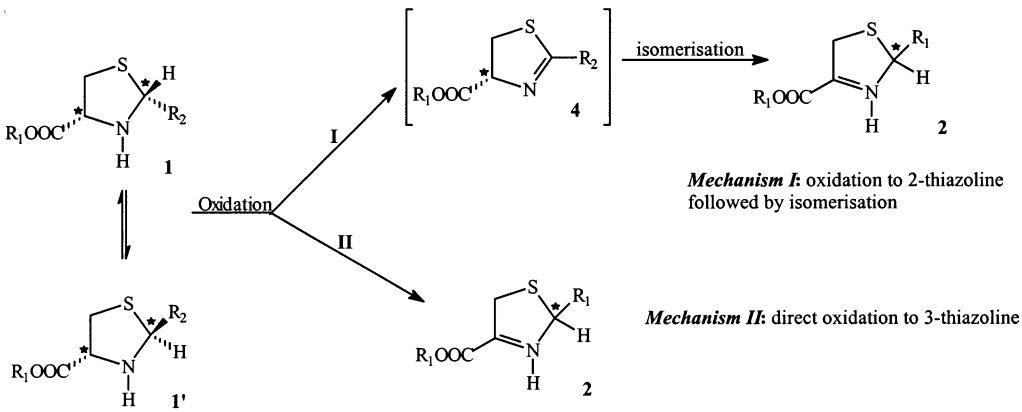
with MnO_2 hydrate (method A) led to 3-thiazolines with widely variable e.e.s in the range 2–83% as shown in Table 3. In contrast, method B using battery grade MnO_2 gave good, reproducible results, with e.e.s in the range 73–100% (except for entry 14). For the two methods, comparing entries 3, 8, 4 and 11 the e.e. differences are considerable. Thus, in the case of ethyl 2-methyl-3-thiazoline-4-carboxylate, the e.e. was 2% with MnO_2 hydrate, but increased to 73% by the use of the battery grade MnO_2 as oxidant. Previous reports have also indicated that the structure and reactivity of active manganese dioxide used as an oxidizing agent in organic synthesis was strongly dependent on the method of its preparation.[13,14] The differences in asymmetric induction obtained in the oxidation of **1**/**1′** to **2** emphasize the importance of the grade of MnO_2 used.

A series of racemic ethyl or methyl thiazolidine-(4*RS*)-carboxylates (±)-**1**/**1′** were oxidized with battery grade MnO_2 (method B). Compounds **1b**/**1′b**, **1h**/**1′h** and **1i**/**1′i** were obtained by reaction of DL-cysteine with alkyl aldehydes, followed by esterification of the carboxylic acid function. The obtained 3-thiazolines, **2b**, **2h** and **2i**, had e.e.s in the range of 1–4% according to ^1H NMR analysis in the presence of $Eu(tfc)_3$.

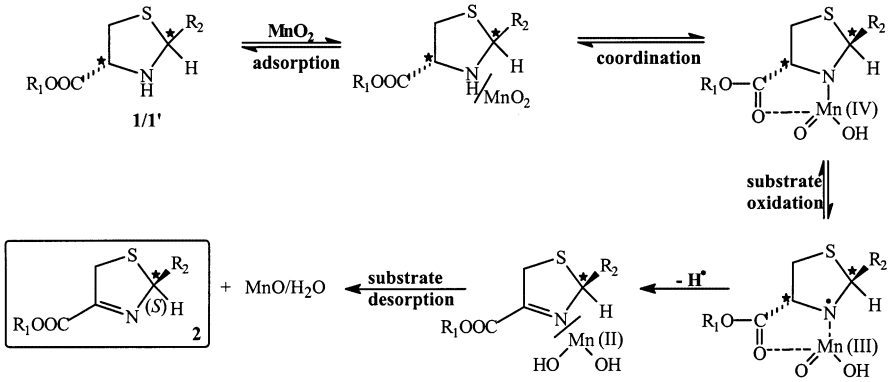
Two possible mechanisms can be considered to explain the asymmetric induction from **1**/**1′** to **2**. In the first mechanism, **I** (Scheme 4), a first oxidation of thiazolidine **1**/**1′** to a homochiral 2-thiazoline intermediate **4** can be considered, followed by isomerization of **4** with chirality transfer to 3-thiazoline **2**. The second mechanism **II** (Scheme 4) involves the direct N–C(4) oxidation of the **1**/**1′** to 3-thiazoline **2**. In this case, to explain the high asymmetric induction found for **2**, we have to consider a fast equilibrium between **1** and **1′**, and enhanced reactivity of one of the diastereomers **1** or **1′**. In order to differentiate between the possible pathways **I** and **II**, several experiments were carried out. To check the possibility of mechanism **I**, we prepared 2-thiazolines **4** by an Ru-catalyzed/TBHP oxidation of **1**/**1′**, which occurred with good regioselectivities (>95%).[15] In particular, ethyl 2-methyl-2-thiazoline-(4*R*)-carboxylate **4b** (R_1 = Et and R_2 = Me) was prepared in 36% yield and treated with MnO_2 under the same reaction conditions as those of Table 3 (method B). No 3-thiazoline **2b** was formed, and only the corresponding thiazole **3b** could be isolated. We also prepared the proposed intermediate **4b** by condensing L-cysteine ethyl ester with ethyl acetimidate.[16] Here again, oxidation with different quantities of MnO_2 (3–10 equiv.) led to thiazole **3b** in all cases. These observations indicate that the isomerization from 2-thiazolines to 3-thiazolines does not take place under the reaction conditions. Therefore, mechanism **I** can be excluded. To further eliminate this pathway **I**, the MnO_2-mediated oxidation of a 2,2-dialkyl-substituted thiazolidine-(4*R*)-carboxylate was carried out. However, the reaction led to decomposition of the heterocycle and no mechanistic considerations could be concluded from the experiment.

According to these experimental data, only mechanism **II** seems plausible. A dynamic process involving equilibration between **1** and **1′** under the reaction conditions, with one diastereoisomer reacting at a faster rate than the other, could account for the enhanced enantioselectivity of the products relative to the initial diastereoisomeric mixture.

Precise elucidation of the mechanism of oxidation by manganese dioxide is difficult because of the nature of the heterogeneous reaction involved. The difficulties encountered in studying these reactions result from the structure of the oxidant, particularly the relationship of its surface-active sites toward the substrate and its stereoelectronic factors. Previous studies on the oxidation mechanism by MnO_2 suggested the presence of an adsorptive process.[13] The reaction pathway involves adsorption of the substrate onto the surface of the oxide, followed by its radical-type oxidation and desorption of the product. Accordingly, we present in Scheme 5 a plausible oxidation mechanism involving Mn(IV) and Mn(III) species. The adsorption of **1**/**1′** onto the MnO_2 surface occurs with an N–Mn(IV)-coordination. The further coordination of ester to the Mn species should enhance the stability of the intermediate diastereomer in which the R_2 substituent at C(2) has *trans* (or (*S*)) configuration. The oxidative electron transfer with the intermediate formation of an Mn(III)/N-centered radical species loses $H^\bullet$ to give the imine–Mn(II) complex. Desorption then affords the product



Scheme 4. Oxidation pathways.



Scheme 5. Proposed mechanism.

2, in which the stereogenic center at C(2) is proposed to have (*S*) configuration. The e.e.s of the different 3-thiazolines were measured, but the absolute configurations are not known at this time.

3. Conclusion

We have presented a new and practical asymmetric synthesis of alkyl 3-thiazoline-4-carboxylates **2** with high e.e.s by MnO_2-mediated oxidation of the corresponding chiral thiazolidines **1**/**1**′. The asymmetric induction was strongly dependent upon the source of the manganese dioxide. The use of MnO_2 suitable for use in batteries (Aldrich) led to the best results with high e.e. For several alkyl substituents, the e.e.s lie in the range 73–100%. MnO_2 coordination to the ester and the amine groups of **1**/**1**′ can be considered, followed by the direct selective N–C(4) dehydrogenation to **2**. The coordination of MnO_2 to either **1** or **1**′ occurs with high diastereoselectivity under kinetic control.

4. Experimental

4.1. General

All solvents and reagents were purchased from commercial suppliers and used as received unless otherwise indicated. ^1H and ^{13}C NMR data were recorded on a Bruker AC 200 FT spectrometer, at room temperature, with 40 mg of product in 0.5 mL $CDCl_3$ and TMS as internal standard. 2D ^1H NMR spectra were recorded on a Bruker AMX 400 spectrometer. Acquisition and processing parameters for NOESY experiments: data points in F1: 256 and F2: 1024, mixing time: 1–2 s, zero filling: 1024. Chemical shifts are reported in δ ppm.

GC analysis was carried out using an HP-5890 gas chromatograph. GC–MS analysis was accomplished by using an HP-5890 chromatograph coupled to a 5970A mass selective detector. Mass spectra were obtained by electron ionization at 70 eV and source temperature of 250°C. High resolution mass spectra (HRMS) were measured on a Fisons-FG-prospec magnetic spectrometer.

Chromatographic separations were performed using 70–260 mesh (SDS) silica gel eluted with mixed solvent of hexane and ether by changing the ratios from 9/1 to 4/1, 7/3 and finally to 6/4. Thin-layer chromatography was carried out on SDS precoated silica plates (60/15 μm layer thickness).

4.2. Thiazolidine synthesis

4.2.1. Condensation of L-cysteine ethyl or methyl ester with aldehydes. To a stirred solution of L-cysteine ethyl ester hydrochloride (10 mmol) and potassium acetate (0.98 g, 10 mmol) in alcohol (30 mL), a solution of freshly distilled aldehyde in alcohol (10 mL) was added at 0°C. After stirring for 4 h at 0°C, the reaction mixture was filtered off and the solvent evaporated under reduced pressure. The crude product was washed with a saturated solution of aqueous NaCl (15 mL) and extracted three times with CH_2Cl_2 (3×15 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated. A colorless oil was obtained.

4.2.2. Esterification of thiazolidine-(4*R*)-carboxylic acids. Thiazolidine-(4*R*)-carboxylic acids were obtained by the reaction of L-cysteine with aldehydes using the method of Schubert.[17] To a stirred solution of 2-substituted thiazolidine-(4*R*)-carboxylic acid (0.1 mol) in absolute alcohol (methanol, ethanol or *iso*-propanol) was added thionyl chloride in small portions at 0°C. The mixture was stirred at room temperature for 12 h and stirred under reflux for 1 h. The reaction mixture was filtered and the solvent evaporated under reduced pressure. The crude product was dissolved in H_2O, neutralized with a saturated solution of aqueous K_2CO_3 and extracted three times with CH_2Cl_2 (3×20 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated. A colorless oil was obtained. Experimental and spectroscopic data for compounds **1**/**1**′ have already been reported.[18,19] However, the relative positions of the different protons in ^1H NMR for the *cis*/*trans* isomers have not been fully described. We therefore only give here the detailed ^1H NMR spectra of these compounds.

4.2.3. Methyl 2-methyl-thiazolidine-(4*R*)-carboxylates 1a/1′a. ^1H NMR: δ 1.5 (d, 3H, CH_{3trans}, $J=6.3$ Hz), 1.6 (d, 3H, CH_{3cis}, $J=6.2$ Hz), 2.2 (s, 2H, N-$H_{cis\ and\ trans}$),

2.9 (td, 1H, H-5$_{cis}$, J=0.8 and 9.5 Hz), 3.1 (dd, 1H, H-5$_{trans}$, J=6 and 10.7 Hz), 3.3 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.7 (2s, 6H, OC$H_{3cis\ and\ trans}$), 3.85 (1H, H-4$_{cis}$), 4.2 (t, 1H, H-4$_{trans}$, J=6.6 Hz), 4.5 (q, 1H, H-2$_{cis}$, J=6.2 Hz), 4.75 (q, 1H, H-2$_{trans}$, J=6.3 Hz).

4.2.4. Methyl 2-ethyl-thiazolidine-(4*R*)-carboxylates 1b/1′b. ^{1}H NMR: δ 0.95 (t, 3H, CH$_2$CH_{3trans}, J=7.4 Hz), 1 (3H, t, CH$_2$CH_{3cis}, J=7.4 Hz), 1.6, 1.7 and 1.9 (3m, 4H, CH_2CH$_{3cis\ and\ trans}$), 2.2 (s, 2H, N-$H_{cis\ and\ trans}$), 2.8 (t, 1H, H-5$_{cis}$, J=10 Hz), 3 (dd, 1H, H-5$_{trans}$, J=6.4 and 10.6 Hz), 3.2 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.7 (s, 3H, OCH_{3cis}), 3.75 (s, 3H, OCH_{3trans}), 3.8 (dd, 1H, H-4$_{cis}$, J=6.4 and 9.6 Hz), 4.1 (t, 1H, H-4$_{trans}$, J=6.6 Hz), 4.4 (dd, 1H, H-2$_{cis}$, J=5.7 and 7 Hz), 4.55 (dd, 1H, H-2$_{trans}$, J=6 and 7.6 Hz).

4.2.5. Methyl 2-propyl-thiazolidine-(4*R*)-carboxylates 1c/1′c. ^{1}H NMR: δ 0.85 (t, 3H, (CH$_2$)$_2$CH_{3trans}, J=7.2 Hz), 0.9 (t, 3H, (CH$_2$)$_2$CH_{3cis}, J=7.2 Hz), 1.4, 1.55, 1.7 and 1.85 (4m, 8H, CH_2CH_2CH$_{3cis\ and\ trans}$), 2.2 (s, 2H, N-$H_{cis\ and\ trans}$), 2.8 (dd, 1H, H-5$_{cis}$, J=9.5 and 10.1 Hz), 3 (dd, 1H, H-5$_{trans}$, J=6.2 and 10.6 Hz), 3.2 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.7 (s, 3H, OCH_{3trans}), 3.72 (s, 3H, OCH_{3cis}), 3.8 (dd, 1H, H-4$_{cis}$), 4,1 (t, 1H, H-4$_{trans}$, J=6.6 Hz), 4,45 (dd, 1H, H-2$_{cis}$, J=5.7 and 7.2 Hz), 4.6 (dd, 1H, H-2$_{trans}$, J=5.7 and 7.2 Hz).

4.2.6. Methyl 2-isopropyl-thiazolidine-(4*R*)-carboxylates 1d/1′d. ^{1}H NMR: δ 0.9, 0.95, 1 and 1.05 (4d, 12H, CH(CH_3)$_{2cis\ and\ trans}$, J=6.2 Hz, 6.7 Hz, 6.7 Hz, 6.6 Hz), 1.75 (octuplet, 1H, CH(CH$_3$)$_{2trans}$, J=6.7 Hz), 1.9 (octuplet, 1H, CH(CH$_3$)$_{2cis}$, J=6.7 Hz), 2.2 (s, 2H, N-$H_{cis\ and\ trans}$), 2.7 (t, 1H, H-5$_{cis}$, J=9.8 Hz), 2.95 (dd, 1H, H-5$_{trans}$, J=6.2 and 10.6 Hz), 3.1 (dd, 1H, H-5$_{trans}$, J=6.7 and 10.6 Hz), 3.2 (dd, 1H, H-5′$_{cis}$, J=6.9 and 10.6 Hz), 3.7 (s, 3H, OCH_{3trans}), 3.75 (3H, OCH_{3cis}), 3.8 (dd, 1H, H-4$_{cis}$), 4.05 (t, 1H, H-4$_{trans}$, J=6.4 Hz), 4.3 (d, 1H, H-2$_{cis}$, J=7.2 Hz), 4.45 (d, 1H, H-2$_{trans}$, J=7.7 Hz).

4.2.7. Methyl 2-butyl-thiazolidine-(4*R*)-carboxylates 1e/1′e. ^{1}H NMR: δ 0.9 (2t, 6H, (CH$_2$)$_2$C$H_{3cis\ and\ trans}$), 1.4, 1.8 and 2 (3m, 12H, (CH_2)$_2$CH$_{3cis\ and\ trans}$), 2.3 (s, 2H, N-$H_{cis\ and\ trans}$), 2.8 (dd, 1H, H-5$_{cis}$, J=9.5 and 10.3 Hz), 3.05 (dd, 1H, H-5$_{trans}$, J=6.3 and 10.6 Hz), 3.3 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.8 (2s, 6H, OC$H_{3cis\ and\ trans}$), 3.85 (dd, 1H, H-4$_{cis}$, J=7 and 10.1 Hz), 4.15 (t, 1H, H-4$_{trans}$, J=6.6 Hz), 4.5 (dd, 1H, H-2$_{cis}$, J=5.7 and 7.2 Hz), 4.65 (dd, 1H, H-2$_{trans,}$ J=5.7 and 7.4 Hz).

4.2.8. Methyl 2-isobutyl-thiazolidine-(4*R*)-carboxylates 1f/1′f. ^{1}H NMR: δ 1 (4d, 12H, CH$_2$CHC$H_{3cis\ and\ trans}$), 1.8 (m, 6H, CH_2CHCH$_{3cis\ and\ trans}$), 2.25 (s, 2H, N-$H_{cis\ and\ trans}$), 2.85 (dd, 1H, H-5$_{cis}$, J=9.4 and 10.2 Hz), 3.1 (dd, 1H, H-5$_{trans}$, J=6.1 and 10.7 Hz), 3.3 (m, 2H, H-5$_{cis\ and\ trans}$), 3.7 (s, 6H, OCH_{3trans}), 3.75 (s, 3H, OCH_{3cis}), 3.8 (dd, 1H, H-4$_{cis}$), 4.15 (t, 1H, H-4$_{trans}$, J=6.2 Hz), 4.5 (dd, 1H, H-2$_{cis}$), 4.75 (dd, 1H, H-2$_{trans}$, J=6.2 and 7.6 Hz).

4.2.9. Ethyl 2-methyl-thiazolidine-(4*R*)-carboxylates 1g/1′g. ^{1}H NMR: δ 1.3 (2t, 6H, OCH$_2$C$H_{3cis\ and\ trans}$), 1.5 (dd, 3H, CH_{3trans}, J=1.1 and 6.3 Hz), 1.6 (dd, 3H, CH_{3cis}, J=0.9 and 6.1 Hz), 2.9 (td, 1H, H-5$_{cis}$, J=1.2 and 9.5 Hz), 3.1 (dd, 1H, H-5$_{trans}$, J=6.1 and 10.7 Hz), 3.3 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.8 (t, 1H, H-4$_{cis}$, J=7.2 Hz), 4.2 (m, 8H, OCH_2CH$_{3cis\ and\ trans}$, H-4$_{trans}$, N-$H_{cis\ and\ trans}$), 4.55 (qd, 1H, H-2$_{cis}$, J=1.1 and 6.2 Hz), 4.8 (q, 1H, H-2$_{trans}$, J=6.4 Hz).

4.2.10. Ethyl 2-ethyl-thiazolidine-(4*R*)-carboxylates 1h/1′h. ^{1}H NMR: δ 0.95 (t, 3H, CH$_2$CH_{3trans}, J=7.4 Hz), 1 (t, 3H, CH$_2$CH_{3cis}, J=7.4 Hz), 1.25 (6H, 2t, OCH$_2$C$H_{3cis\ and\ trans}$), 1.8 (2m, 2H, CH_2CH$_{3cis\ and\ trans}$), 2.6 (m, 2H, N-$H_{cis\ and\ trans}$), 2.8 (dd, 1H, H-5$_{cis}$, J=1.2 and 9.5 Hz), 2.95 (dd, 1H, H-5$_{trans}$), 3.2 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.75 (1H, dd, H-4$_{cis}$, J=7.1 and 9.3 Hz), 4.05 (t, 1H, H-4$_{trans}$, J=6.6 Hz), 4.15 (m, 4H, OCH_2CH$_{3cis\ and\ trans}$), 4.4 (1H, dd, H-2$_{cis}$, J=5.5 and 6.4 Hz), 4.55 (dd, 1H, H-2$_{trans}$, J=6 and 7.7 Hz).

4.2.11. Ethyl 2-propyl-thiazolidine-(4*R*)-carboxylates 1i/1′i. ^{1}H NMR: δ 0.9 (t, 6H, (CH$_2$)$_2$C$H_{3cis\ and\ trans}$, J=7.2 Hz), 1.2 (2t, 6H, OCH$_2$C$H_{3cis\ and\ trans}$, J=7.2 Hz), 1.4 and 1.6 (2m, 2H, CH$_2$CH_2CH$_{3cis\ and\ trans}$), 1.7 and 1.9 (2m, 2H, CH_2CH$_2$CH$_{3cis\ and\ trans}$), 2.2 (s, 2H, N-$H_{cis\ and\ trans}$), 2.7 (t, 1H, H-5$_{cis}$, J=9.8 Hz), 2.9 (dd, 1H, H-5$_{trans}$, J=6.5 and 10.6 Hz), 3.2 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.7 (dd, 1H, H-4$_{cis}$, J=7 and 9.4 Hz), 4 (t, 1H, H-4$_{trans}$, J=6.7 Hz), 4.15 (m, 4H, OCH_2CH$_{3cis\ and\ trans}$), 4.4 (dd, 1H, H-2$_{cis}$, J=5.7 and 7.2 Hz), 4.6 (t, 1H, H-2$_{trans}$, J=6.8 Hz).

4.2.12. Ethyl 2-butyl-thiazolidine-(4*R*)-carboxylates 1j/1′j. ^{1}H NMR: δ 0.9 (2t, 12H, (CH$_2$)$_3$C$H_{3cis\ and\ trans}$), 1.3 (2t, 3H, OCH$_2$C$H_{3cis\ and\ trans}$, J=7.2 Hz), 1.5, 1.8 and 2 (3m, 12H, (CH_2)$_3$CH$_{3cis\ and\ trans}$), 2.3 (s, 2H, N-$H_{cis\ and\ trans}$), 2.85 (dd, 1H, H-5$_{cis}$, J=9.5 and 10.2 Hz), 3.1 (dd, 1H, H-5$_{trans}$, J=6.5 and 10.6 Hz), 3.3 (m, 2H, H-5′), 3.8 (dd, 1H, H-4$_{cis}$, J=7 and 9.4 Hz), 4.1 (t, 1H, H-4$_{trans}$, J=6.7 Hz), 4.25 (m, 4H, OCH_2CH$_{3cis\ and\ trans}$), 4.5 (dd, 1H, H-2$_{cis}$, J=5.7 and 7.2 Hz), 4.65 (dd, 1H, H-2$_{trans}$).

4.2.13. Isopropyl 2-ethyl-thiazolidine-(4*R*)-carboxylates 1k/1′k. ^{1}H NMR: δ 0.95 (t, 3H, CH$_2$CH_{3trans}, J=7.2), 1.05 (t, 3H, CH$_2$CH_{3cis}, J=7.5 Hz), 1.25 (2d, 12H, OCH(CH_3)$_{2cis\ and\ trans}$, J=2.2 Hz), 1.6, 1.8 and 2 (3m, 4H, CH_2CH$_{3cis\ and\ trans}$), 2.5 (2s, 2H, N-$H_{cis\ and\ trans}$), 2.8 (t, 1H, H-5$_{cis}$, J=9.7 Hz), 2.95 (dd, 1H, H-5$_{trans}$, J=6.9 and 10.5 Hz), 3.3 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.8 (dd, 1H, H-4$_{cis}$, J=7 and 9.4 Hz), 4 (t, 1H, H-4$_{trans}$, J=6.9 Hz), 4.45 (dd, 1H, H-2$_{cis}$, J=5.8 and 7.5 Hz), 4.6 (dd, 1H, H-2$_{trans}$, J=6.5 and 7.2 Hz), 5.1 (m, 2H, CH(CH$_3$)$_{2cis\ and\ trans}$).

4.2.14. Isopropyl 2-isopropyl-thiazolidine-(4*R*)-carboxylates 1l/1′l. ^{1}H NMR: δ 0.95 (2d, 12H, CH(CH_3)$_{2cis\ and\ trans}$, J=7 Hz), 1.22 (d, 12H, OCH(CH_3)$_{2cis\ and\ trans}$), 1.6 (m, 2H, CH(CH$_3$)$_{2cis\ and\ trans}$), 2.5 (2s, 2H, N-$H_{cis\ and\ trans}$), 2.75 (t, 1H, H-5$_{cis}$, J=9.5 Hz), 2.9 (dd, 1H, H-5$_{trans}$, J=6.7 and 10.5 Hz), 3.2 (m, 2H, H-5′$_{cis\ and\ trans}$), 3.7 (dd, 1H, H-4$_{cis}$, J=7.1 and 7.3 Hz), 4 (t, 1H, H-4$_{trans}$, J=6.8 Hz), 4.5 (dd, 1H, H-2$_{cis}$, J=5.7 and 7.3 Hz), 4.6 (dd, 1H, H-2$_{trans,}$ J=6.5 and 7.2 Hz), 5.05 (m, 2H, CH(CH$_3$)$_{2cis\ and\ trans}$).

4.3. Synthesis of 3-thiazolines

A mixture of *cis*- and *trans*-thiazolidines **1**/**1′** (5 mmol) was stirred in CH_3CN (50 mL) in the presence of MnO_2 (Prolabo, 20 equiv. or Aldrich, 15 equiv.). The reaction was followed by GC or TLC. The crude mixture was filtered over Celite. Solvent evaporation was followed by purification by column chromatography on silica gel, with hexane–ether mixture as the eluent.

4.3.1. Methyl 2-methyl-3-thiazoline-4-carboxylate 2a. ^{1}H NMR: δ 1.7 (d, 3H, CH_3, J=7.6 Hz), 3.9 (s, 3H, OCH_3), 4.2 (dd, 2H, H-5 and H-5′, J=0.4 and 14 Hz), 5.9 (m, 1H, H-2). ^{13}C NMR: δ 24.96, 43.33, 53.33, 79.06, 161.83, 162.16. GC–MS: 159 (M^+, 43.6), 144 (88.2), 126 (13.6), 112 (100), 100 (19.6), 98 (15), 74 (15.6), 68 (21.4), 59 (46.8), 58 (15), 45 (23.9), 42 (21.1), 41 (14.9). HRMS calcd for $C_6H_9O_2NS$: 159.0354. Observed: 159.0350.

4.3.2. Methyl 2-ethyl-3-thiazoline-4-carboxylate 2b. ^{1}H NMR: δ 1 (t, 3H, CH_2CH_3, J=7.4 Hz), 1.9 and 2.1 (2m, 2H, CH_2CH_3), 3.9 (s, 3H, OCH_3), 4.2 (m, 2H, H-5 and H-5′), 5.85 (m, 1H, H-2). ^{13}C NMR: δ 10.48, 31.39, 42.56, 53.29, 85.74, 162, 162.19. GC–MS: 173 (M^+, 45), 144 (66), 114 (23.9), 113 (14.7), 112 (100), 100 (11.7), 73 (10.3), 68 (17.1), 59 (52.1), 46 (10.2), 45 (21.6), 42 (18.6), 41 (26.7).

4.3.3. Methyl 2-propyl-3-thiazoline-4-carboxylate 2c. ^{1}H NMR: δ 0.9 (t, 3H, $(CH_2)_2CH_3$, J=7.1 Hz), 1.5 (m, 2H, $CH_2CH_2CH_3$), 1.75 and 2.1 (2m, 2H, $CH_2CH_2CH_3$), 3.9 (s, 3H, OCH_3), 4.1 (d, 1H, H-5, J=1.7 Hz), 4.12 (d, 1H, H-5, J=2.8 Hz), 5.8 (m, 1H, H-2). ^{13}C NMR: δ 13.82, 19.70, 40.57, 42.49, 53.27, 84.22, 161.83, 162.22. GC–MS: 187 (M^+, 31.4), 154 (34.7), 144 (23.2), 140 (37.4), 113 (24.5), 112 (100), 84 (20.7), 59 (54), 55 (18.4), 54 (16.3), 45 (23.8), 49 (19.4). HRMS calcd for $C_8H_{13}O_2NS$: 187.0667. Observed: 187.0665.

4.3.4. Methyl 2-isopropyl-3-thiazoline-4-carboxylate 2d. ^{1}H NMR: δ 0.9 and 1.05 (2d, 6H, $CH(CH_3)_2$, J=6.6 and 6.8 Hz), 2.3 (m, 1H, C$H(CH_3)_2$), 3.9 (s, 3H, OCH_3), 4.1 (t, 1H, H-5, J=1.1 Hz), 4.1 (d, 1H, H-5, J=1 Hz), 5.8 (m, 1H, H-2). ^{13}C NMR: δ 17.54, 19.83, 34.92, 42.38, 53.26, 91.01, 162.01, 162.23. GC–MS: 187 (M^+, 28.4), 145 (43.4), 144 (11.6), 113 (100), 112 (42.4), 85 (16.6), 59 (33), 55 (11.7), 45 (12.5), 41 (14.9). HRMS calcd for $C_8H_{13}O_2NS$: 187.0667. Observed: 187.0656.

4.3.5. Methyl 2-butyl-3-thiazoline-4-carboxylate 2e. ^{1}H NMR: δ 0.9 (t, 3H, $(CH_2)_3CH_3$, J=7 Hz), 1.4 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.8 and 2.1 (2m, 2H, $CH_2(CH_2)_2CH_3$), 3.9 (s, 3H, OCH_3), 4.15 (m, 2H, H-5), 5.8 (m, 1H, H-2). ^{13}C NMR: δ 13.86, 22.31, 28.37, 38.06, 42.34, 53.11, 84.32, 161.66, 162.08. GC–MS: 201 (M^+, 11), 168 (100), 154 (35.3), 144 (18.1), 142 (16.5), 127 (14.8), 113 (25.3), 112 (80.8), 108 (15.9), 59 (58.7), 54 (15.8), 45 (21.8), 42 (23.1), 41 (42.8). HRMS calcd for $C_9H_{15}O_2NS$: 201.0823. Observed: 201.0821.

4.3.6. Methyl 2-isobutyl-3-thiazoline-4-carboxylate 2f. ^{1}H NMR: δ 1 (2d, 6H, $(CH_2(CH_3)_2$, J=6.6 and 6.8 Hz), 1.6, 1.75 and 2.1 (3m, 3H, CH_2CH $(CH_3)_2$), 3.9 (s, 3H, OCH_3), 4.2 (m, 2H, H-5), 5.8 (m, 1H, H-2). ^{13}C NMR: δ 13.86, 22.31, 28.37, 38.06, 42.34, 53.11, 84.32, 161.66, 162.08. GC–MS: 201 (M^+, 15.1), 169 (11.5), 168 (100), 154 (22.7), 113 (22.9), 112 (60.5), 108 (19.4), 84 (16.5), 45 (12), 42 (14.9), 41 (24.8).

4.3.7. Ethyl 2-methyl-3-thiazoline-4-carboxylate 2g. ^{1}H NMR: δ 1.4 (t, 3H, OCH_2CH_3, J=7.1 Hz), 1.7 (d, 3H, CH_3, J=6.7 Hz), 4.25 (2d, 2H, H-5 and H-5′, J=4.1 and 5.9 Hz), 4.4 (q, 2H, OCH_2CH_3, J=7.1 Hz), 5.8 (m, 1H, H-2). ^{13}C NMR: δ 14.11, 24.84, 45.22, 62.55, 78.98, 161.64, 162.01. GC–MS: 173 (M^+, 28.6), 158 (72.4), 130 (15.8), 112 (100), 100 (15.9), 74 (16.5), 73 (13.2), 68 (18.8), 59 (17.3), 55 (15), 45 (18.5), 41 (12.6).

4.3.8. Ethyl 2-ethyl-3-thiazoline-4-carboxylate 2h. ^{1}H NMR: δ 1 (t, 3H, OCH_2CH_3, J=7.2 Hz), 1.35 (td, 3H, CH_2CH_3, J=0.6 and 7.2 Hz), 1.8 and 2.1 (2m, 2H, CH_2CH_3), 4.15 (m, 2H, H-5 and H-5′), 4.35 (q, 2H, OCH_2CH_3, J=7.2 Hz), 5.8 (m, 1H, H-2). ^{13}C NMR: δ 10.47, 14.22, 31.39, 42.59, 62.63, 87.78, 161.79, 162.79. GC–MS: 187 (M^+, 28.7), 130 (14.6), 114 (24.7), 113 (13.9), 112 (100), 87 (12), 86 (35.8), 82 (11.3), 68 (14.6), 59 (12.6), 57 (11), 54 (13), 45 (17.3), 41 (27.3). HRMS calcd for $C_8H_{13}O_2NS$: 187.0667. Observed: 187.0667.

4.3.9. Ethyl 2-propyl-3-thiazoline-4-carboxylate 2i. ^{1}H NMR: δ 0.9 (t, 3H, $(CH_2)_2CH_3$, J=7.3), 1.35 (t, 3H, OCH_2CH_3, J=7.2 Hz), 1.5 (m, 2H, $CH_2CH_2CH_3$), 1.75 and 2.1 (2m, 2H, $CH_2CH_2CH_3$), 4.15 (2d, 2H, H-5 and H-5′, J=1.8 and 2.9 Hz), 4.35 (q, 2H, OCH_2CH_3, J=7.1 Hz), 5.85 (m, 1H, H-2). ^{13}C NMR: δ 13.80, 14.22, 19.70, 40.58, 42.49, 62.59, 84.24, 161.79, 162.12. GC–MS: 201 (M^+, 28.6), 168 (33.3), 158 (29.1), 154 (33.9), 130 (15.2), 128 (32.7), 126 (17.7), 113 (25.1), 112 (100), 98 (13.9), 94 (12.8), 86 (42.9), 82 (20.9), 59 (14.7), 55 (19.8), 54 (20.2), 45 (17.4), 41 (15). HRMS calcd for $C_9H_{15}O_2NS$: 201.0823. Observed: 201.0837.

4.3.10. Ethyl 2-butyl-3-thiazoline-4-carboxylate 2j. ^{1}H NMR: δ 0.9 (t, 3H, $(CH_2)_3CH_3$, J=7 Hz), 1.4 (t, 3H, OCH_2CH_3, J=7.1 Hz), 1.4 (m, 4H, $CH_2(CH_2)_2CH_3$), 1.8 and 2.1 (2m, 2H, $CH_2(CH_2)_2CH_3$), 4.15 (m, 2H, H-5 and H-5′), 4.35 (q, 2H, OCH_2CH_3, J=7.1 Hz), 5.8 (m, 1H, H-2). ^{13}C NMR: δ 14.02, 14.23, 22.46, 28.56, 38.22, 42.51, 62.62, 84.53, 161.82, 162.10. GC–MS: 215 (M^+, 5), 182 (100), 171 (31.9), 168 (32.8), 158 (14.2), 142 (24.9), 112 (87.2), 108 (14.1), 101 (15.4), 100 (15.8), 86 (31), 59 (14.2), 54 (14.7), 45 (16.8), 41 (31.4). HRMS calcd for $C_{10}H_{17}O_2NS$: 215.1054. Observed: 215.0980.

4.3.11. Isopropyl 2-ethyl-3-thiazoline-4-carboxylate 2k. ^{1}H NMR: δ 1 (t, 3H, CH_2CH_3, J=7.3 Hz), 1.35 (d,

6H, $OCH(CH_3)_2$, $J=6.3$ Hz), 1.8 and 2.1 (2m, 2H, CH_2CH_3), 4.2 (dd, 2H, H-5), 5.2 (octuplet, 1H, $OCH(CH_3)_2$, $J=6.3$ Hz), 5.8 (1H, m, H-2). ^{13}C NMR: δ 10.51, 21.78, 31.42, 42.60, 70.61, 85.82, 161.34, 162.56. GC–MS: 201 (M^+, 28.3), 172 (20.1), 172 (20.1), 159 (22.4), 130 (100), 126 (10.9), 114 (27.1), 113 (19.2), 112 (75.2), 87 (19.2), 86 (31.5), 59 (13), 45 (18.9), 43 (56.6).

4.3.12. Isopropyl 2-isopropyl-3-thiazoline-4-carboxylate 2l. ^1H NMR: δ 0.9 and 1.05 (2d, 6H, $CH(CH_3)_2$, $J=6.6$ and 6.8 Hz), 1.35 (d, 6H, $OCH(CH_3)_2$, $J=6.3$ Hz), 2.3 (m, 1H, $CH(CH_3)_2$), 4.1 (m, 2H, H-5), 5.2 (octuplet, 1H, $OCH(CH_3)_2$, $J=6.3$), 5.8 (m, 1H, H-2). ^{13}C NMR: δ 17.42, 19.96, 21.79, 34.84, 42.41, 70.56, 91.04, 161.35, 162.57. GC–MS: 215 (M^+, 18.8), 130 (27.3), 114 (27.3), 114 (12.7), 113 (100), 112 (41.5), 86 (12.7), 85 (10.6), 55 (17.3), 45 (13), 43 (65.8), 41 (31.5).

4.4. Synthesis of ethyl 2-methyl-2-thiazoline-(4*R*)-carboxylate 4b

A mixture of L-cysteine ethyl ester hydrochloride (1.85 g, 0.01 mol), ethyl acetimidate hydrochloride[20] (1.72 g, 0.01 mol) and dry triethylamine (1.01 g, 0.1 mol) in CH_2Cl_2 (20 mL) was stirred overnight at room temperature. CH_2Cl_2 was removed in vacuo and saturated aqueous NaCl (20 mL) was added and the solution was extracted three times with dry diethyl ether (3×20 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated to afford the title compound as a colorless oil (1.7 g, 98%). ^1H NMR: δ 1.3 (t, 3H, OCH_2CH_3, $J=7.2$ Hz), 2.3 (d, 3H, CH_3, $=1.7$ Hz), 3.6 (m, 2H, H-5 and H-5′), 4.3 (qd, 2H, OCH_2CH_3, $J=1.3$ and 7.2 Hz), 5.1 (tq, 1H, H-4, 1.7 and 9.4 Hz). ^{13}C NMR: δ 14.29, 20.40, 36.42, 61.82, 78.43, 170.13, 170.94. GC–MS: 173 (M^+, 0.3), 100 (100), 86 (11), 59 (41.3), 58 (9.6), 42 (7.5).

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