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Cyclic sulfates as useful tools in the asymmetric synthesis of 1-aminocyclopropane-1-carboxylic acid derivatives

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ABSTRACT

The enantiomers of 4-(2-methoxyethyl)-1,3,2-dioxathiolane-2,2-dioxide and 4-(methoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide have been used as 'epoxide-like' synthons during the asymmetric alkylation of oxazinone-derived glycine equivalents. Using a fully stereoselective synthesis, eight stereoisomers of the *spiro* derivatives of the glycine equivalents were obtained. The relative configurations of the *spiro* compounds obtained were easily determined using nuclear magnetic resonance spectroscopy and two dimensional nuclear Overhauser effect experiments. Additionally, one of the *spiro* derivatives obtained was hydrolyzed to its corresponding amino acid, which was a derivative of 1-aminocyclopropano-1-carboxylic acid, a very important building block that is present in many compounds, which have interesting biological activity.

1. Introduction

In 2004, according to the literature, more than 20% of drugs belonging to the top 200 sales were based on compounds that possess a peptidic nature.[1] In addition, more than 200 peptides, proteins, and antibodies were launched for sale in 2010.[2] At the same time 40% of failures in clinical trials are caused by the low bioavailability and poor pharmacokinetics of the test compounds.[2] In particular, compounds that possess a peptidic nature have several drawbacks due to their rapid proteolysis and measures have to be taken to modify their structure in order to improve their pharmacokinetic properties, for example, the introduction of unnatural amino acids into their structure.[1–3]

1-Aminocyclopropane-1-carboxylic acid building blocks are present in many compounds, which have interesting biological activity (Fig. 1). The first example of a compound containing the 1-aminocyclopropane-1-carboxylic acid building block was cytotrienin A, an ansamycin-type anticancer drug, which was isolated from a species of *Steptomyces*.[4] Cytotrienin A induces apoptosis in human promyelocytic leukemia HL-60 cell line.[5] Another important example is the modification of the antiviral agent, Valacyclovir, which is an ester derivative of Acyclovir. Valacylovir is the L-valine ester of Acyclovir (prodrug) and has an oral bioavailability that is 5-fold higher than the original drug as a result of this modification. Using 1-aminocyclopropane-1-carboxylic acid instead of L-valine has allowed even better pharmacokinetic properties to be obtained.[6] 1-Aminocyclopropane-1-carboxylic acid is also found as a part of Simeprevir, an inhibitor of NS3/4A protease inhibitors, which was registered in 2014 as a new drug to treat hepatitis C.[7–9] 1-Aminocyclopropane-1-carboxylic acid was also used in investigations to improve the biological activity in factor Xa inhibitors[10] and atypical retinoids (anti-tumor activity).[11]

Therefore, it is necessary to search for new synthetic methods and various derivatives of 1-aminocyclopropane-1-carboxylic acid, which may be used as building blocks to improve the pharmacokinetic properties of biologically active compounds.

This work is a continuation of our efforts directed toward methods for the asymmetric synthesis of aminocycloalkane carboxylic acid derivatives.[12,13] The synthesis of the stereoisomers of 1-aminocyclopropane-1-carboxylic acid derivatives were based on glycine equivalent **1**, which was developed by Wanner et al.[14] Herein, we have focused our attention on cyclic sulfates **2** and **3** as they are emerging as important 'epoxide-like' synthons and should lead us to obtain the target compounds **4** and **5** with excellent diastereoselectivity. Compounds **4** and **5** can be hydrolyzed to their corresponding amino acids **6** and **7** (Scheme 1).

2. Results and discussion

2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethanol **8** and (2,2-dimethyl-1,3-dioxolan-4-yl)methanol **9** were selected as starting materials

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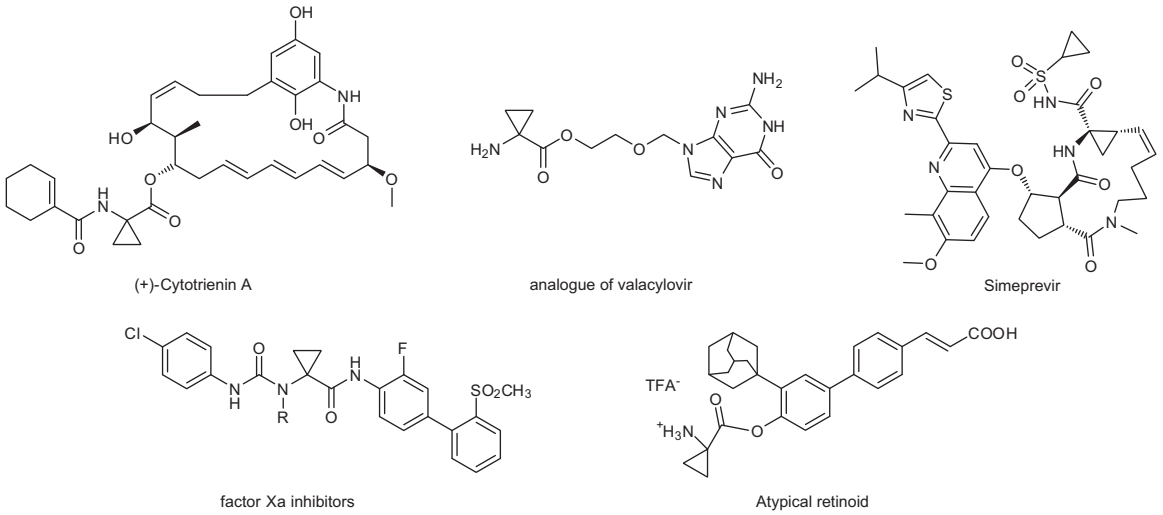
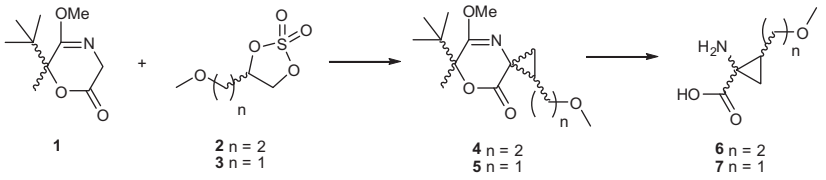


Figure 1. Examples of using 1-aminocyclopropane-1-carboxylic acids derivatives as a building block.



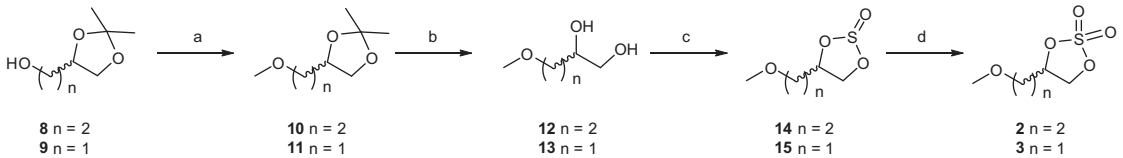
Scheme 1. Scheme of planned synthesis.

to prepare sulfates **2** and **3**, since they are both easily available in a single enantiomeric form. Firstly, **8** and **9** were converted into their methoxy derivatives **10** and **11** using methyl iodine and potassium hydroxide in dimethyl sulfoxide as a solvent.[15] The deprotection to give compounds **12** and **13** was carried out in a mixture of 1 M hydrochloric acid and acetone.[16] Compounds **12** and **13** were reacted with thionyl chloride to give cyclic sulfites **14** and **15**, which were further oxidized using sodium periodate and a catalytic amount of ruthenium trichloride to their corresponding cyclic sulfates **2** and **3**.[17,18] In this way a racemic mixture and two enantiomers of compound **2**, and a racemic mixture of compound **3** and enantiomer (*S*)-**3** were obtained.

The as-prepared cyclic sulfates **2** and **3** were used as the alkylating agents of glycine equivalents (*S*)-**1** and (*R*)-**1**. The deprotonation agent, sodium *bis*(trimethylsilyl)amide (NaHMDS) was used. The enantiomer of the glycine equivalent **1** was deprotonated at −30 °C for 30 min, the cyclic sulfate **2** or **3** was added and the reaction mixture stirred for 2 h. The last portion of NaHMDS was added dropwise for 1 h after which the mixture was stirred overnight and purified (Scheme 2).

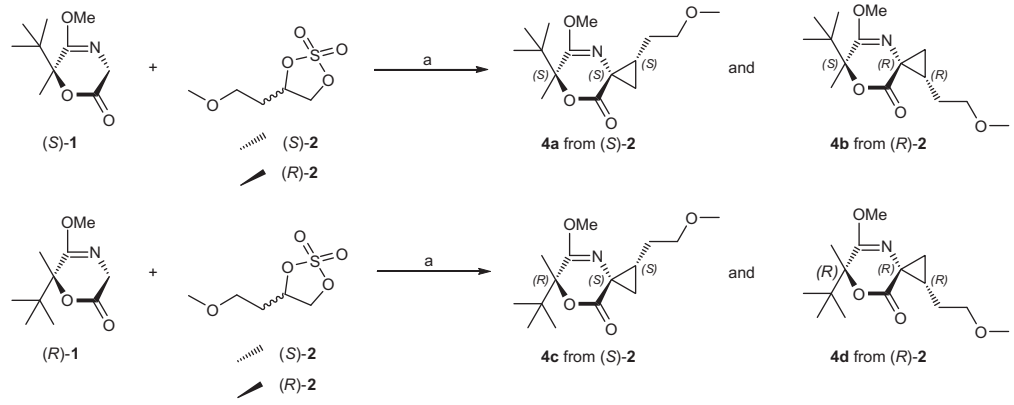
When a racemic mixture of compound **2** was used, two stereoisomers of compound **4** were obtained (as determined by proton nuclear magnetic resonance ^{1}H NMR spectroscopy). The separation of these stereoisomers was not easy to carry out and so we decided to use the single enantiomers of compound **2**, which were easily obtained from the enantiomers of 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol **8**. This led us to obtain four stereoisomers of the *spiro*-derivatives **4** as single diastereoisomers in good yields (44–51%) (Scheme 3).

The relative configurations within compound **4** were determined using NMR spectroscopy based on the nuclear Overhauser effects (NOEs) experiments with the absolute configurations determined by the absolute configuration of **1**.[12,13,19] The most important interaction observed was between the protons of the *tert*-butyl group with methoxyethyl group (compounds **4a** and **4d**) or the absence of these interactions (compounds **4b** and **4c**) (Fig. 2). In each reaction only one stereoisomer of compound **4** was formed and its stereoselectivity was dependent on the absolute configuration of the cyclic sulfate. We obtained two pairs of enantiomers of compound **4** in series I: from glycine equivalent



a: MeI, KOH; DMSO, RT; 24 h
b: 1 M HCl; acetone; reflux; 1 h
c: $SOCl_2$; $CHCl_3$; 0°C-reflux; 1 h
d: $NaIO_4$, $RuCl_3xH_2O$; $CHCl_3$; MeCN, H_2O; 0°C-RT; 3 h

Scheme 2. Synthesis of cyclic sulfate **2** and **3**.



Scheme 3. Products of the alkylation of glycine equivalent **1** with cyclic sulfite **2**—series I.

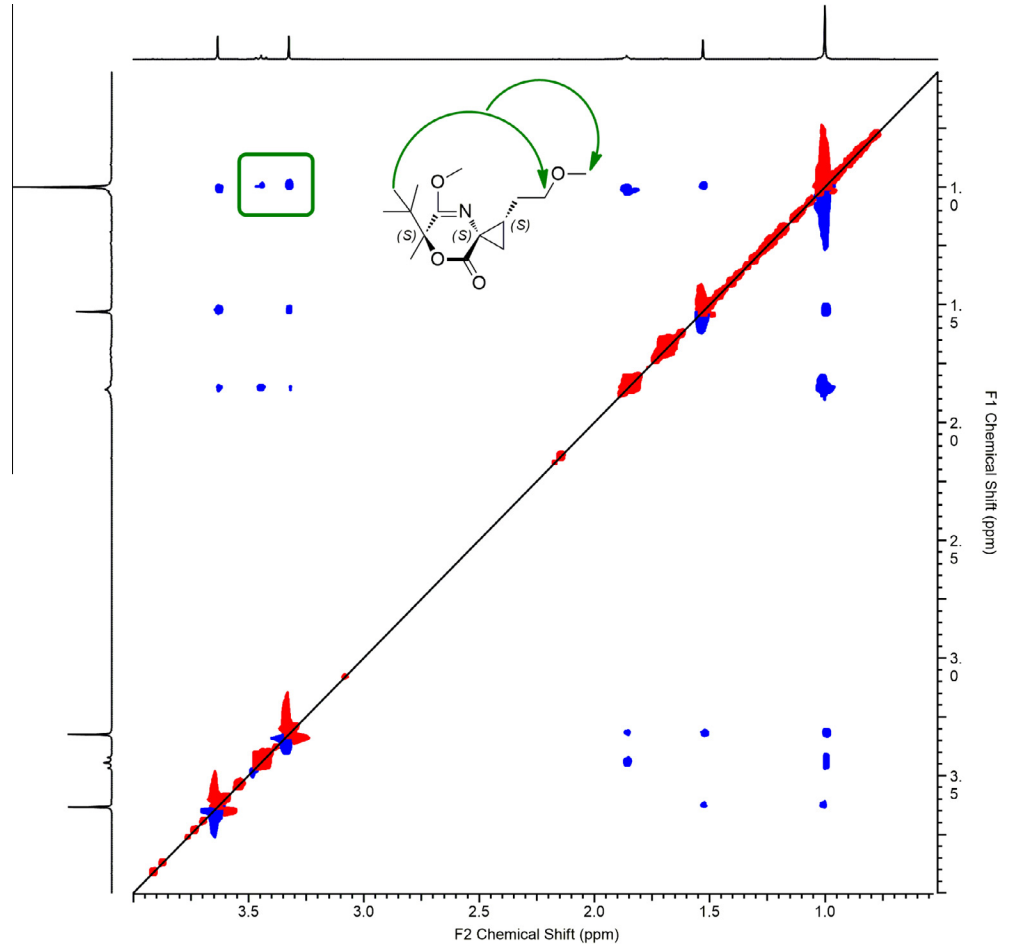
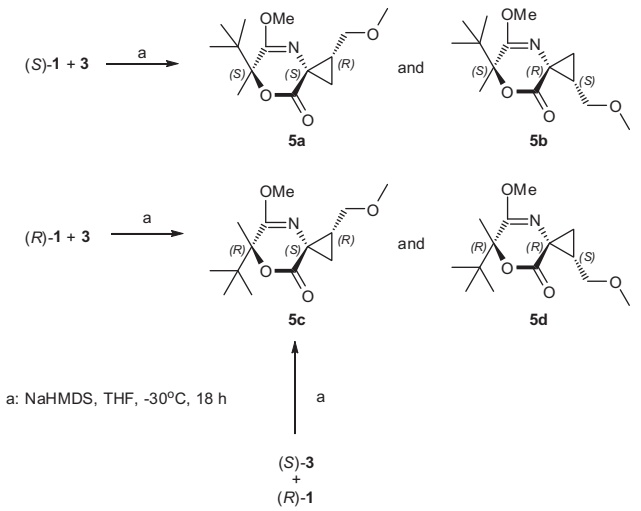


Figure 2. Sample of NOESY spectra for compound **4a**.

(*S*)-**1** and cyclic sulfate (*S*)-**2**, we obtained compound **4a**, which was the enantiomer of compound **4d** obtained from glycine equivalent (*R*)-**1** and cyclic sulfate (*R*)-**2**. From glycine equivalent (*S*)-**1** and cyclic sulfate (*R*)-**2** we obtained compound **4b**, which was the enantiomer of compound **4c** obtained from the reaction between glycine equivalent (*R*)-**1** and cyclic sulfate (*S*)-**2**.

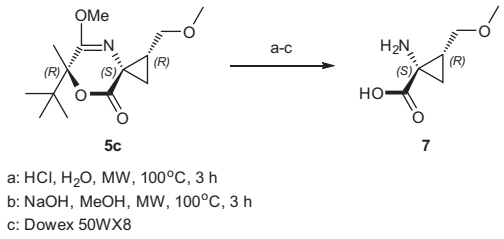
On the other hand, when we used a racemic mixture of compound **3**, two diastereoisomers of compound **5** were also obtained, which were easily separated using simple column chromatography. The same situation was observed for both enantiomers of glycine equivalent **1**. After separation of the stereoisomers of compound **5**, the absolute configuration at position C-3 was determined using the NOE experiments and similar interactions were observed; the absolute configuration at position in C-1 was determined by comparison to the first series and was also confirmed after the reactions using the enantiomers of compound **3** (Scheme 4).

In the final stage, a two-step hydrolysis was employed to provide the free amino acid **7**. The reactions were carried out in



Scheme 4. Products of the alkylation of glycine equivalent **1** with cyclic sulfite **3**—series II.

pressure tubes using microwave heating. Compound **5c** was first dissolved in a mixture of water and hydrochloric acid, and then heated in a microwave at 100 °C for 3 h. This process resulted in the complete cleavage of the imidate functionality. Next, the cleavage obtained was treated with sodium hydroxide in methanol at 100 °C for 3 h to hydrolyze the remaining ester functionality. After work-up with 2 M hydrochloric acid and subsequent purification by ion exchange chromatography, the free (1*S*,2*R*)-1-amino-2-(methoxymethyl)cyclopropanecarboxylic acid **7** was obtained (Scheme 5).



Scheme 5. Hydrolysis to free amino acid.

3. Experimental

3.1. General

All experiments were carried out in oven-dried glassware under a dry argon atmosphere and standard vacuum techniques were used. Analytical grade chemicals were obtained from commercial sources and used without further purification. Solvents were dried under a dry argon atmosphere using standard methods and were freshly distilled before use. Thionyl chloride was distilled under low pressure up to three weeks before use. Chromatography was performed with silica gel (Sigma Aldrich Si_{60} 0.040–0.063 mm). Thin layer chromatography (TLC) was performed on precoated silica gel 60–F_{254} plates (Merck). The products were detected on the TLC plates by one of the following methods/detection reagents or a combination of them: UV light, ammonium cerium(IV)heptamolybdate (5% $(NH_4)\times Mo_7O_{24}$ and 0.2% $Ce(SO_4)_2$ dissolved in 400 mL of a 5% H_2SO_4 solution), ninhydrin (0.3 g ninhydrin dissolved in 100 mL *n*-propanol and 3 mL acetic acid). Reactions under microwave irradiation were carried out using a Discover LabMate (CEM Corporation). Optical rotations were measured on a polarimeter Jasco, model P-2000 using a sodium lamp, emitting light at a wavelength of 589 nm and a 10 cm polametric tube. Elemental analyses (C, H, N) were performed on an Elementar Vario EL III (Elementar Analysensystem, Hanau, Germany). NMR spectra were measured in $CDCl_3$ or D_2O on a Varian Mercury-VX 300 spectrometer operating at 300.08 MHz (^{1}H) and 75.46 MHz (^{13}C). Chemical shifts (δ in ppm) were referenced to the lock signal of the solvent. Coupling constants, *J*, are expressed in Hz. Sample concentrations were in the range of 20 mg/ml. All spectra were acquired at ambient temperature, for each ^{1}H NMR spectrum, 16 scans were accumulated with spectral width of 4.2 kHz and 32 k data points. ^{13}C NMR spectra were recorded with spectroscopic width of 18 kHz and 64 k data points. All 2D experiments were performed using standard pulse sequences of spectrometer. Spectral widths of the ^{1}H and ^{13}C dimensions were 2.7 kHz and 13.5 kHz respectively, data matrix for FT 1 k × 1 k Mixing time for NOESY experiment was 500 ms.

3.2. Synthesis

3.2.1. General procedure 1

Acetonide **8** or **9** (13.7 mmol) was dissolved in 10 mL of DMSO, after which powdered KOH was added (1.00 g, 17.8 mmol), and the mixture was stirred for 30 min. Next, MeI (1.00 mL, 16.4 mmol) was added and mixture was stirred at room temperature for 24 h. In the next step, the mixture was dissolved in 20 mL of water and extracted with diethyl ether (3 × 30 mL). Each organic layers was washed with brine (1 × 30 mL), combined, dried over anhydrous Na_2SO_4, and evaporated. The obtained product **10** or **11** was used in the next step without purification.

3.2.2. General procedure 2

Methoxy acetonide **10** or **11** (5 mmol) was dissolved in 15 mL of acetone after which 12 ml of 1 M HCl were added. The mixture was stirred at reflux for 1 ho, and then evaporated. Product **12** or **13** was purified by column chromatography using ethyl acetate as the eluent.

3.2.3. General procedure 3

Thionyl chloride (0.95 mL, 14.5 mmol) was added to a suspension of the enantiomer of 4-methoxybutane-1,2-diol **12** (1.06 g, 8.83 mmol) in chloroform (16 mL) and the solution was refluxed for 1 h. Next, the solution was cooled to 0 °C, and acetonitrile (10 mL), $NaIO_4$ (2.00 g, 9.35 mmol), $RuCl_3{\cdot}H_2O$ (0.01 g, 0.05 mmol) and water (15 mL) were added. The resulting mixture was stirred for 3 h, and then diluted with diethyl ether (20 mL) and water (10 mL). The organic layer was washed with water (3 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated in a vacuum. The crude product was kept under argon in a freezer because of its fragility without purification.

3.2.4. General procedure 4

Thionyl chloride (0.57 mL, 8.7 mmol) was added to a suspension of 3-methoxypropane-1,2-diol **13** (0.63 g, 5.94 mmol) in chloroform (9 mL) and the solution was refluxed for 1 h. Next, the solvent was evaporated in vacuo and the remaining oil was purified by column chromatography using diethyl ether.

3.2.5. General procedure 5

To a solution of 4-(methoxymethyl)-1,3,2-dioxathiolane 2-oxide **15** (0.58 g, 3.81 mmol) in a mixture of acetonitrile (5 mL) and chloroform (5 mL) was added $NaIO_4$ (1.20 g, 5.65 mmol), followed by $RuCl_3{\cdot}H_2O$ (0.01 g, 0.05 mmol) and water (7 mL). The

resulting mixture was stirred for 3 h, and then diluted with diethyl ether (15 mL) and water (10 mL). The organic layer was washed with water (3 × 15 mL), saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, and evaporated in a vacuum. The crude product (oil) was purified by flash chromatography using diethyl ether.

3.2.6. General procedure 6

A solution of glycine equivalent (0.20 g, 1.00 mmol) in THF (4 mL) was cooled to −30 °C, treated with NaHMDS (1 M in hexane, 1.2 mL, 1.00 mmol), and stirred for 30 min. Next, cyclic sulfate **2** or **3** (1.50 mmol) dissolved in 1 mL of THF was added and the stirring was continued for 1.5 h, after which NaHMDS (1 M in hexane, 1.2 mL, 1.00 mmol) was added dropwise (for approximately 1 h). The reaction was stirred at −30 °C overnight. The reaction was quenched by the addition of a phosphate buffer pH = 7.0 (6 mL), and allowed to warm to room temperature. The inorganic layer was extracted with diethyl ether (4 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was purified by column chromatography using petroleum ether/ethyl acetate 7:3.

3.3. Synthesis of series I

3.3.1. (*S*)-4-(2-Methoxyethyl)-2,2-dimethyl-1,3-dioxolane (*S*)-10

Product was obtained according to general procedure 1, from (*S*)-**8** (2.00 g, 13.7 mmol). Yield: 2.06 g (94%, 12.8 mmol) as a yellow oil. TLC: R_f = 0.52 (petroleum ether/ethyl acetate 7:3). $C_8H_{16}O_3$ (160.21). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.32 (s, 3H, CH_3C), 1.37 (s, 3H, CH_3C), 1.74–1.88 (m, 2H, CH_2CH_2CH), 3.30 (s, 3H, CH_3O), 3.40–3.46 (m, 2H, OCH_2CH_2), 3.52 (dd, J = 7.95, 7.44 Hz, 1H, $CHCH_2O$), 4.02 (dd, J = 7.95, 5.90 Hz, 1H, $CHCH_2O$), 4.09–4.20 (m, 1H, CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 25.71 (CH_3C), 26.89 (CH_3C), 33.72 (CH_2CH_2CH), 58.66 (CH_3O), 69.36 ($CHCH_2O$), 69.55 (OCH_2CH_2), 73.70 (CH), 108.52 ($(CH_3)C$) ppm.

3.3.2. (*R*)-4-(2-Methoxyethyl)-2,2-dimethyl-1,3-dioxolane (*R*)-10

Product was obtained according to general procedure 1, from (*R*)-**8** (2.00 g, 13.7 mmol). Yield: 2.00 g (91%, 12.5 mmol) as a yellow oil. TLC: R_f = 0.53 (petroleum ether/ethyl acetate 7:3). $C_8H_{16}O_3$ (160.21). NMR data were identical to those of the enantiomer (*S*)-**10**.

3.3.3. (*S*)-4-Methoxybutane-1,2-diol (*S*)-12

Product was obtained according to general procedure 2, from (*S*)-**10** (1.71 g, 11.7 mmol). Yield: 1.08 g (84%, 9.00 mmol) as a yellow oil. TLC: R_f = 0.15 (ethyl acetate). $C_5H_{12}O_3$ (120.15) calcd C, 49.98; H, 10.07; found: C, 50.11; H, 10.12. $[\alpha]_D^{20}$ = −8.4 (*c* 1.280, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.65–1.87 (m, 2H, CH_2CH_2CH), 2.51 (br s, 2H, OH), 3.36 (s, 3H, CH_3O), 3.46–3.54 (m, 1H, OCH_2CH_2), 3.56–3.63 (m, 3H, $OCH_2CH_2CHCH_2$), 3.86–3.94 (m, 1H, CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 32.99 (CH_2CH_2CH), 58.92 (CH_3O), 66.47 ($CHCH_2O$), 70.65 (OCH_2CH_2), 71.13 (CH) ppm.

3.3.4. (*R*)-4-Methoxybutane-1,2-diol (*R*)-12

Product was obtained according to general procedure 2, from (*R*)-**10** (1.72 g, 11.7 mmol). Yield: 0.96 g (75%, 8.00 mmol) as a yellow oil. TLC: R_f = 0.175 (ethyl acetate). $C_5H_{12}O_3$ (120.15) calcd C, 49.98; H, 10.07; found: C, 50.20; H, 10.23. $[\alpha]_D^{20}$ = +8.3 (*c* 1.170, CH_2Cl_2). NMR data were identical to those of the enantiomer (*S*)-**12**.

3.3.5. (*S*)-4-(2-Methoxyethyl)-1,3,2-dioxathiolane-2,2-dioxide (*S*)-2

Product was obtained according to general procedure 3, from (*S*)-**12** (1.06 g, 8.83 mmol). Yield: 1.21 g (75%, 6.65 mmol) as a yellow oil. TLC: R_f = 0.55 (diethyl ether). $C_5H_{10}O_5S$ (182.19) calcd C, 32.96; H, 5.53; S, 17.60; found: C, 33.10; H, 5.61; S, 17.74. $[\alpha]_D^{20}$ = −14.5 (*c* 1.270, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.06–2.22 (m, 2H, CH_2CH_2CH), 3.33 (s, 3H, CH_3O) 3.47–3.60 (m, 2H, OCH_2CH_2), 4.46 (dd, J = 8.85, 8.34 Hz, 1H, $CHCH_2O$), 4.73 (dd, J = 8.98, 5.90 Hz, 1H, $CHCH_2O$), 5.06–5.19 (m, 1H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 32.50 (CH_2CH_2CH), 58.96 (CH_3O), 67.39 ($CHCH_2O$), 73.50 (OCH_2CH_2), 81.25 (CH) ppm.

3.3.6. (*R*)-4-(2-Methoxyethyl)-1,3,2-dioxathiolane-2,2-dioxide (*R*)-2

Product was obtained according to general procedure 3, from (*R*)-**12** (0.93 g, 7.74 mmol). Yield: 0.93 g (66%, 5.10 mmol) as a yellow oil. TLC: R_f = 0.55 (diethyl ether). $C_5H_{10}O_5S$ (182.19) calcd C, 32.96; H, 5.53; S, 17.60; found: C, 32.81; H, 5.69; S, 17.32. $[\alpha]_D^{20}$ = +15.5 (*c* 1.310, CH_2Cl_2). NMR data were identical to those of the enantiomer (*S*)-**2**.

3.3.7. (1*S*,3*S*,6*S*)-6-(*tert*-Butyl)-5-methoxy-1-(2-methoxyethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 4a

Product was obtained according to general procedure 6, from glycine equivalent (*S*)-**1** and (*S*)-**2**. Yield: 0.14 g (44%, 0.44 mmol) as a yellow oil. TLC: R_f = 0.65 (petroleum ether/ethyl acetate 7:3). $C_{15}H_{25}NO_4$ (283.36) calcd: C, 63.58; H, 8.89; N, 4.94; found: C, 63.49; H, 8.93; N, 4.87. $[\alpha]_D^{20}$ = +0.6 (*c* 1.952, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.97–1.03 (m, 10H, $((CH_3)_3$, $CCH_2CH_3OCH_3$), 1.53 (s, 3H, CH_3C), 1.67–1.75 (m, 1H, $CCH_2CH_3OCH_3$), 1.82–1.91 (m, 3H, CCH_2CH), 3.33 (s, 3H, CH_2OCH_3), 3.45 (t, J = 6.67 Hz, 2H, CH_2CH_2O), 3.63 (s, 3H, OCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 20.81 (CH_3C), 25.46 ($(CH_3)_3$), 27.34 ($CHCH_2CH_2$), 28.10 (CCH_2-CH), 29.17 (CCH_2CH), 39.44 ($((CH_3)_3C)$,), 41.70 (CCH_2CH), 52.84 (CH_3O), 58.65 (CH_3OCH_2), 71.93 (CH_2OCH_3), 88.33 (CH_3C), 161.35 ($COCH_3$), 171.44 (CO) ppm.

3.3.8. (1*R*,3*R*,6*S*)-6-(*tert*-Butyl)-5-methoxy-1-(2-methoxyethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 4b

Product was obtained according to general procedure 6, from glycine equivalent (*S*)-**1** and (*R*)-**2**. Yield: 0.15 g (50%, 0.50 mmol) as a yellow oil. TLC: R_f = 0.65 (petroleum ether/ethyl acetate 7:3). $C_{15}H_{25}NO_4$ (283.36) calcd: C, 63.58; H, 8.89; N, 4.94; found: C, 63.51; H, 8.77; N, 4.84. $[\alpha]_D^{20}$ = +6.6 (2.572, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.93 (dd, J = 7.05, 4.23 Hz, 1H, $CCH_2CH_3OCH_3$), 1.00 (s, 9H, $(CH_3)_3$), 1.51 (s, 3H, CH_3C), 1.73 (dd, J = 9.49, 4.10 Hz, 1H, $CCH_2CH_3OCH_3$), 1.83–2.00 (m, 3H, CCH_2CH), 3.32 (s, 3H, CH_2OCH_3), 3.42 (t, J = 6.80 Hz, 2H, CH_2CH_2O), 3.63 (s, 3H, OCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 20.81 (CH_3C), 25.46 ($(CH_3)_3$), 27.34 ($CHCH_2CH_2$), 28.10 (CCH_2CH), 29.17 (CCH_2CH), 39.44 ($((CH_3)_3C$), 41.70 (CCH_2CH), 52.84 (CH_3O), 58.65 (CH_3OCH_2), 71.93 (CH_2OCH_3), 88.33 (CH_3C), 161.35 ($COCH_3$), 171.44 (CO) ppm.

3.3.9. (1*S*,3*S*,6*R*)-6-(*tert*-Butyl)-5-methoxy-1-(2-methoxyethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 4c

Product was obtained according to general procedure 6, from glycine equivalent (*R*)-**1** and (*S*)-**2**. Yield: 0.16 g (51%, 0.51 mmol) as a yellow oil. TLC: R_f = 0.65 (petroleum ether/ethyl acetate 7:3). $C_{15}H_{25}NO_4$ (283.36) calcd C, 63.58; H, 8.89; N, 4.94; found: C, 63.67; H, 8.94; N, 4.81. $[\alpha]_D^{20}$ = −6.9 (*c* 2.474, CH_2Cl_2). NMR data were identical to those of the enantiomer **4b**.

3.3.10. (1*R*,3*R*,6*R*)-6-(*tert*-Butyl)-5-methoxy-1-(2-methoxyethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 4d

Product was obtained according to general procedure 6, from glycine equivalent (*R*)-**1** and (*R*)-**2**. Yield: 0.16 g (51%, 0.51 mmol) as a yellow oil. TLC: R_f = 0.65 (petroleum ether/ethyl acetate 7:3). $C_{15}H_{25}NO_4$ (283.36) calcd: C, 63.58; H, 8.89; N, 4.94; found: C, 63.65; H, 8.73; N, 5.04. $[\alpha]_D^{20}$ = −0.7 (*c* 2.466, CH_2Cl_2). NMR data were identical to those of the enantiomer **4a**.

3.4. Synthesis of series II

3.4.1. 4-(Methoxymethyl)-2,2-dimethyl-1,3-dioxolane 11

Product was obtained according to general procedure 1, from **9** (1.80 g, 13.7 mmol). Yield: 1.81 g (91%, 12.5 mmol) as a yellow oil. TLC: R_f = 0.69 (petroleum ether/ethyl acetate 7:3). $C_7H_{14}O_3$ (146.18). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.34 (s, 3H, CH_3C), 1.41 (s, 3H, CH_3C), 3.37 (s, 3H, CH_3O), 3.39–3.50 (m, 2H, CH_3OCH_2CH), 3.68 (dd, J = 8.21, 6.41 Hz, 1H, $CHCH_2O$), 4.03 (dd, J = 8.21, 6.41 Hz, 1H, $CHCH_2O$), 4.21–4.31 (m, 1H, CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 25.33 (CH_3C), 26.73 (CH_3C), 59.33 (CH_3O), 66.62 ($CHCH_2O$), 73.74 (OCH_2CH), 74.57 (CH), 109.41 ((CH_3)C) ppm.

3.4.2. (*S*)-4-(Methoxymethyl)-2,2-dimethyl-1,3-dioxolane (*S*)-11

Product was obtained according to general procedure 1, from **9** (0.90 g, 6.85 mmol). Yield: 0.77 g (78%, 5.34 mmol) as a yellow oil. TLC: R_f = 0.69 (petroleum ether/ethyl acetate 7:3). $C_7H_{14}O_3$ (146.18). NMR data were identical to those of the compound **11**.

3.4.3. 3-Methoxypropane-1,2-diol 13

Product was obtained according to general procedure 2, from **11** (1.75 g, 12.0 mmol). Yield: 0.95 g (75%, 9.00 mmol) as a yellow oil. TLC: R_f = 0.2 (ethyl acetate). $C_4H_{10}O_3$ (106.12) calcd: C, 45.27; H, 9.50; found: C, 45.20; H, 9.36. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.51 (br s, 2H, OH), 3.39 (s, 3H, CH_3O), 3.44–3.50 (m, 2H, OCH_2CH), 3.58–3.66, (m, 1H, $OCHCH_2O$), 3.67–3.74 (m, 1H, $OCHCH_2O$), 3.83–3.91 (m, 1H, CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 59.17 (CH_3O), 63.94 ($CHCH_2O$), 70.62 (OCH_2CH), 74.14 (CH) ppm.

3.4.4. (*R*)-3-Methoxypropane-1,2-diol (*R*)-13

Product was obtained according to general procedure 2, from (*S*)-**11** (0.77 g, 5.26 mmol). Yield: 0.46 g (82%, 4.31 mmol) as a yellow oil. TLC: R_f = 0.2 (ethyl acetate). $C_4H_{10}O_3$ (106.12) calcd: C, 45.27; H, 9.50; found: C, 45.10; H, 9.40. $[\alpha]_D^{20}$ = −2.2 (c 1.065, CH_2Cl_2). NMR data were identical to those of the compound **13**.

3.4.5. 4-(Methoxymethyl)-1,3,2-dioxathiolane 2-oxide 15

Product was obtained according to general procedure 4, from **13** (0.63 g, 5.94 mmol). Yield: 0.59 g (66%, 3.92 mmol) as a yellow oil. TLC: R_f = 0.80 (diethyl ether). $C_4H_8O_4S$ (152.17) calcd: C, 31.57; H, 5.30; S, 21.07; found: C, 31.87; H, 5.20; S, 20.87. Mixture of diastereoisomers 60:40. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.39 (s, 3H, CH_3O), 3.47–3.58 (m, 2H, CH_3OCH_2CH), 4.29 (dd, J = 8.34, 5.26 Hz, 1H, $CHCH_2$), 4.70 (dd, J = 8.46, 6.67 Hz, 1H, $CHCH_2$), 5.01–5.09 (m, 1H, CH) (diastereoisomers 1); 3.42 (s, 3H, CH_3O), 3.68–3.81 (m, 2H, CH_3OCH_2CH), 4.48–4.57 (m, 2H, $CHCH_2$), 4.59–4.67 (m, 1H, CH) (diastereoisomers 2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 59.52 (CH_3O), 68.67 ($CHCH_2O$), 70.93 (CH_3OCH_2), 78.32 (CH) (diastereoisomers 1); 59.52 (CH_3O), 69.11 ($CHCH_2O$), 72.62 (CH_3OCH_2), 80.98 (CH) (diastereoisomers 2).

3.4.6. (4*S*)-4-(methoxymethyl)-1,3,2-dioxathiolane 2-oxide (4*S*)-15

Product was obtained according to general procedure 4, from (*R*)-**13** (0.39 g, 3.68 mmol). Yield: 0.38 g (68%, 2.50 mmol) as a yellow oil. TLC: R_f = 0.81 (diethyl ether). $C_4H_8O_4S$ (152.17) calcd: C, 31.57; H, 5.30; S, 21.07; found: C, 31.77; H, 5.21; S, 21.01. $[\alpha]_D^{20}$ = −42.6 (c 1.295, CH_2Cl_2). Mixture of diastereoisomers 60:40. NMR data were identical to those of the compound **15**.

3.4.7. 4-(Methoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide 3

Product was obtained according to general procedure 5, from (4*S*)-**15** (0.32 g, 2.1 mmol). Yield: 0.27 g (77%, 1.62 mmol) as a yellow oil. TLC: R_f = 0.50 (diethyl ether). $C_4H_8O_5S$ (168.17) calcd: C, 28.57; H, 4.79; S, 19.07; found: C, 28.35; H, 4.89; S, 19.17. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.43 (s, 3H, OCH_3), 3.70 (d, J = 4.87 Hz, 2H, CH_3OCH_2), 4.59 (dd, J = 8.85, 7.05 Hz, 1H, $CHCH_2$), 4.71 (dd, J = 8.85, 6.54 Hz, 1H, $CHCH_2$), 4.99–5.09 (m, 1H, CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 59.75 (CH_3O), 69.67 ($CHCH_2O$), 69.99 (CH_3OCH_2), 79.92 (CH) ppm.

3.4.8. (*S*)-4-(Methoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide (*S*)-3

Product was obtained according to general procedure 5, from (4*S*)-**15** (0.32 g, 2.1 mmol). Yield: 0.27 g (77%, 1.62 mmol) as a yellow oil. TLC: R_f = 0.50 (diethyl ether). $C_4H_8O_5S$ (168.17) calcd: C, 28.57; H, 4.79; S, 19.07; found: C, 28.39; H, 4.67; S, 18.93. $[\alpha]_D^{20}$ = −7.4 (c 1.365, CH_2Cl_2). NMR data were identical to those of the compound **3**.

3.4.9. (1*R*,3*S*,6*S*)-6-(*tert*-Butyl)-5-methoxy-1-(methoxymethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 5a and (1*S*,3*R*,6*S*)-6-(*tert*-butyl)-5-methoxy-1-(methoxymethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 5b

Product was obtained according to general procedure 6, from glycine equivalent (*S*)-**1** and **3**. Stereoisomer **5a** and **5b** were separated using column chromatography. Total yield: 0.143 g (53%, 0.53 mmol) as a yellow oil. $C_{14}H_{23}NO_4$ (269.34).

Compound **5a**: Yield: 0.076 g (28%, 0.28 mmol) TLC: R_f = 0.70 (petroleum ether/ethyl acetate 7:3). $C_{14}H_{23}NO_4$ (269.34) calcd: C, 62.43; H, 8.61, N, 5.20; found: C, 62.59; H, 8.83, N, 5.24. $[\alpha]_D^{20}$ = +4.9 (c 2.000, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.00 (s, 9H, $(CH_3)_3$), 1.12 (dd, J = 7.69, 4.10 Hz, 1H, CCH_2CH), 1.52 (s, 3H, CH_3C), 1.87 (dd, J = 9.49, 4.10 Hz, 1H, CCH_2CH), 2.08–2.16 (m, 1H, CH), 3.29 (s, 3H, CH_2OCH_3), 3.54 (dd, J = 6.80, 4.49 Hz, 2H, $CHCH_2O$), 3.63 (s, 3H, OCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 20.77 (CH_3C), 25.42 (CCH_2CH), 25.45 (($CH_3)_3$), 30.46 (CCH_2CH), 39.71 (($CH_3)_3C$), 41.95 (CCH_2CH), 52.83 (CH_3O), 58.22 (CH_2OCH_3), 70.58 (CH_2OCH_3), 88.52 (CH_3C), 161.63 ($COCH_3$), 171.00 (CO) ppm.

Compound **5b**: Yield: 0.067 g (25%, 0.25 mmol) TLC: R_f = 0.63 (petroleum ether/ethyl acetate 7:3). $C_{14}H_{23}NO_4$ (269.34) calcd: C, 62.43; H, 8.61, N, 5.20; found: C, 62.40; H, 8.75, N, 5.17. $[\alpha]_D^{20}$ = +33.7 (c 1.872, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.97–1.02 (m, 10H, $(CH_3)_3$, CCH_2CH), 1.51 (s, 3H, CH_3C), 1.74 (dd, J = 9.75, 4.36 Hz, 1H, CCH_2CH), 2.18–2.29 (m, 1H, CH), 3.32 (s, 3H, CH_2OCH_3), 3.58–3.67 (m, 5H, $CHCH_2O$, OCH_3) ppm.

^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 20.51 (CH_3C), 24.66 (CCH_2CH), 25.49 (($CH_3)_3$), 30.26 (CCH_2CH), 39.74 (($CH_3)_3C$), 41.87 (CCH_2CH), 52.84 (CH_3O), 58.29 (CH_2OCH_3), 70.28 (CH_2OCH_3), 88.41 (CH_3C), 161.66 ($COCH_3$), 170.93 (CO) ppm.

3.4.10. (1*R*,3*S*,6*R*)-6-(*tert*-Butyl)-5-methoxy-1-(methoxymethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 5c and (1*S*,3*R*,6*R*)-6-(*tert*-butyl)-5-methoxy-1-(methoxymethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 5d

Product was obtained according to general procedure 6, from glycine equivalent (*R*)-**1** and **3**. Stereoisomer **5c** and **5d** were separated using column chromatography. Total yield: 0.137 g (50%, 0.50 mmol) as a yellow oil. $C_{14}H_{23}NO_4$ (269.34).

Compound **5c**: Yield: 0.061 g (22%, 0.22 mmol) TLC: R_f = 0.60 (petroleum ether/ethyl acetate 7:3). $C_{14}H_{23}NO_4$ (269.34) calcd: C, 62.43; H, 8.61; N, 5.20; found: C, 62.24; H, 8.79; N, 5.04. $[\alpha]_D^{20}$ = −34.0 (c 1.714, CH_2Cl_2). NMR data were identical to those of the compound **5b**.

Compound **5d**: Yield: 0.076 g (28%, 0.28 mmol) TLC: R_f = 0.71 (petroleum ether/ethyl acetate 7:3). $C_{14}H_{23}NO_4$ (269.34) calcd: C, 62.43; H, 8.61; N, 5.20; found: C, 62.59; H, 8.82; N, 5.27. $[\alpha]_D^{20}$ = −4.2 (c 2.144, CH_2Cl_2). NMR data were identical to those of the compound **5c.**

3.4.11. (1*R*,3*S*,6*R*)-6-(*tert*-Butyl)-5-methoxy-1-(methoxymethyl)-6-methyl-7-oxa-4-azaspiro[2.5]oct-4-en-8-one 5c

Product was obtained according to general procedure 6, from glycine equivalent (*R*)-**1** (0.10 g, 0.5 mmol) and (*S*)-**3**. Yield: 0.074 g (55%, 0.28 mmol) as a yellow oil. TLC: R_f = 0.62 (petroleum ether/ethyl acetate 7:3). $C_{14}H_{23}NO_4$ (269.34) calcd C, 62.43; H, 8.61; N, 5.20; found: C, 62.31; H, 8.47; N, 5.27. $[\alpha]_D^{20} = -34.3$ (*c* 1.288, CH_2Cl_2). NMR data were identical to those of the compound **5b**.

3.4.12. (1*S*,2*R*)-1-Amino-2-(methoxymethyl)cyclopropanecarboxylic 7

Concentrated HCl (0.72 mL, 8 mmol) was added to a solution of **5c** (0.060 g, 0.22 mmol) in 0.35 mL of water and the reaction mixture was stirred for 3 h at 100 °C in a microwave. The solvent was then removed in vacuo and the residue was treated with methanol (1 mL) and NaOH (0.4 g, 8 mmol), and then stirred at 100 °C for 3 h in a microwave. The solvent was removed in vacuo, after which water was added (3 mL), and the alkaline solution was washed with diethyl ethyl (2 × 3 mL), adjusted to pH 2 by addition of 2 M HCl and again washed with diethyl ether (2 × 3 mL). The acidic aqueous solution was finally subjected to ion-exchange chromatography (Dowex 50 WX 8 cation exchange resin) to afford the title compound **7** (elution with H_2O until the eluent was neutral and free of chloride, then elution with 10% aqueous NH_3). Yield: 0.030 g (94%, 0.21 mmol) as a beige solid, mp decomposition over 150 °C; $C_6H_{11}NO_3$ (145.16). Calcd: C, 49.65; H, 7.64; N, 9.65; found: C, 49.75; H, 7.77; N, 59.60. $[\alpha]_D^{20} = -18.6$ (*c* 0.485, EtOH/H_2O 1:1). ^{1}H NMR (300 MHz, D_2O) δ = 1.05–1.13 (m, 1H, CCH_2CH), 1.39 (dd, *J* = 10.00, 6.16 Hz, 1H, CCH_2CH), 1.76–1.87 (m, 1H, CCH_2-C*H*), 3.23 (s, 3H, OCH_3), 3.43 (dd, *J* = 11.28, 7.44 Hz, 1H, CH_2OCH$_3$), 3.72 (dd, *J* = 11.16, 5.00 Hz, 1H, CH_2OCH$_3$) ppm. ^{13}C NMR (75.5 MHz, D_2O) δ = 22.21 (CCH_2CH), 24.56 (CH), 39.06 (*C*COOH), 57.86 (CH_2OCH_3), 68.86 (CH_2OCH_3), 174.59 (COOH) ppm.

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