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Synthesis of Functionalized γ-Spirolactone and 2-Oxabicyclo[3.3.0]octane Derivatives from Nucleophilic Oxirane Ring Opening☆

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Abstract—Methyl 1-(2-oxiranylmethyl)-2-oxo-1-cyclopentanecarboxylate (**4**) was subjected to the nucleophilic ring opening reaction, leading to the formation of the functionalized 2-oxaspiro[4.4]nonane and 2-oxabicyclo[3.3.0]octane derivatives, which are important structural sub-unit present in several classes of bioactive compounds. The products obtained were characterized on the basis of spectral data, including 1D and 2D NMR. © 2000 Elsevier Science Ltd. All rights reserved.

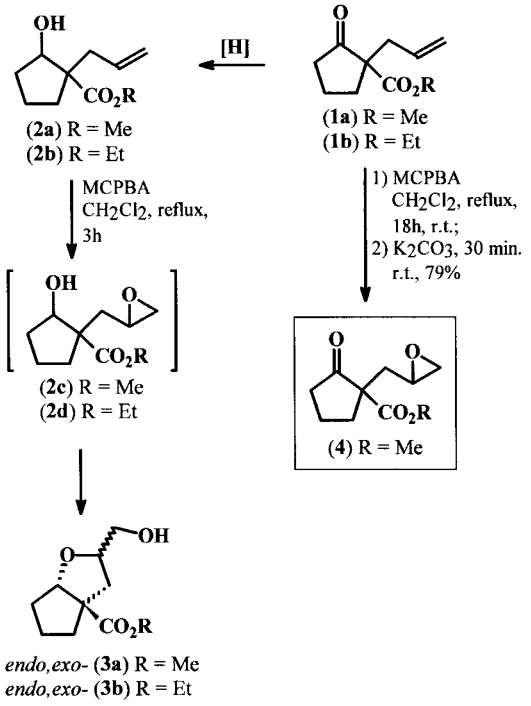
Introduction

The spiro γ-butyrolactone framework has proved to be an important structural sub-unit present in several classes of bioactive substances, e.g. anti-convulsants[1] and anti-tumorals,[2,3] and conformationally semirigid diacylglycerol mimics.[4]

The epoxy function constitutes one of the most important groups in organic synthesis. Ready availability and ability to react with a large variety of nucleophiles make this function a valuable tool for the construction of two adjacent stereogenic centers, once the regiochemistry of the oxirane ring opening process can be driven by steric factors or by manipulation of the reaction mechanism.[5]

In previous papers, we described the diastereo[6,7] and enantiofacial[8,9] selective reduction of alkyl 1-allyl-2-oxo-1-cyclopentanecarboxylate derivatives (**1a**–**b**) to the corresponding cyclopentanol derivatives (**2a**–**b**) and (**2c**–**d**), which are intermediates in the construction of 2-oxabicyclo[3.3.0]octane synthons[10] (**3a**–**b**) useful in the synthesis of new bioactive compounds (Scheme 1).[11,12]

In this work, we report our studies on the nucleophilic ring opening reactions of methyl 1-(2-oxiranylmethyl)-2-oxo-1-cyclopentanecarboxylate (**4**), by using different nucleophiles in an intermolecular or intramolecular process. In



Scheme 1.

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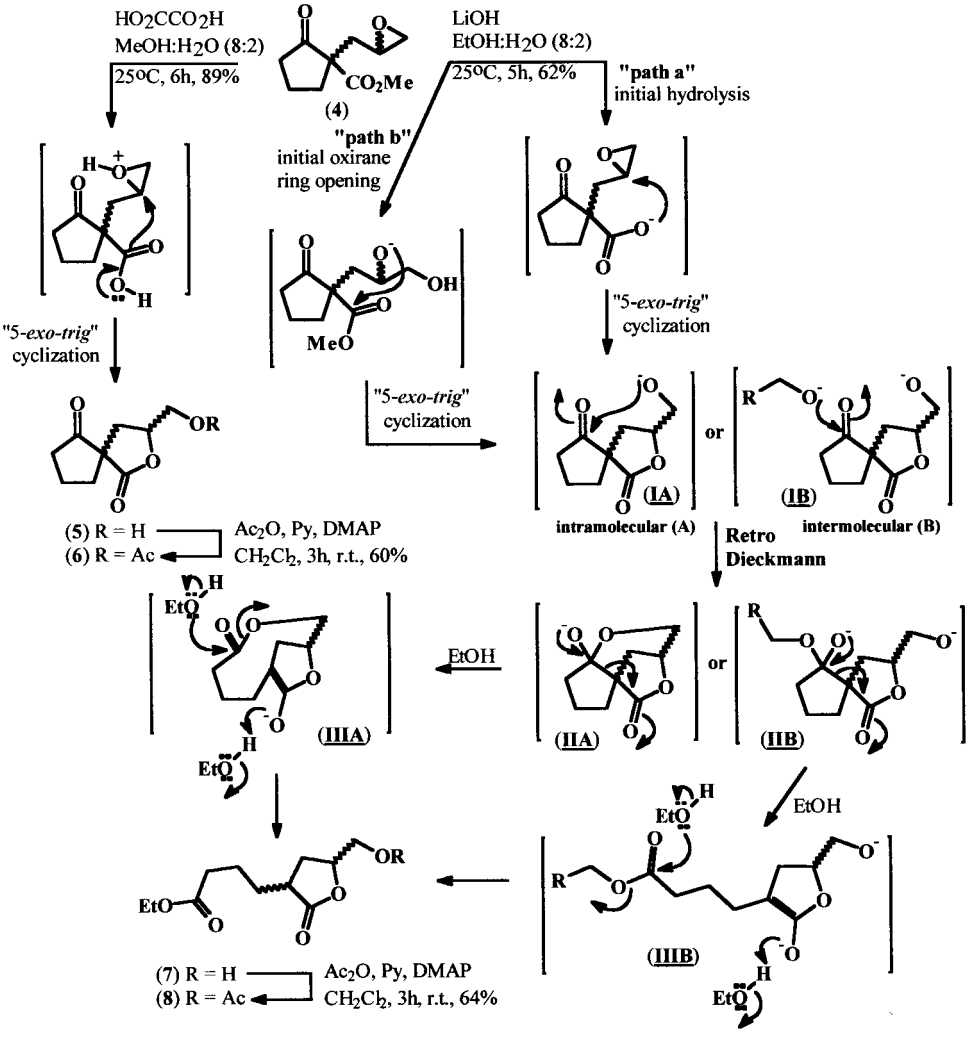
order to investigate the factors related to the reactivity of the oxirane ring of (**4**), we studied the following reactions: (a) acid and base catalyzed methyl ester hydrolysis; (b) reduction of the keto-carbonyl group with sodium borohydride, either in the presence or in the absence of calcium chloride; (c) the nucleophilic azide anion reaction; (d) the nucleophilic cyanide anion reaction.

Results

We started our synthesis from methyl 1-allyl-2-oxo-1-cyclopentanecarboxylate (**1a**) prepared in 90% yield, through the alkylation of commercially available methyl 2-oxocyclopentanecarboxylate[13] with allyl bromide, as previously described.[14] The conversion of β-keto-ester (**1a**) into the corresponding epoxy ketone, methyl 1-(2-oxiranylmethyl)-2-oxo-1-cyclopentanecarboxylate (**4**), was accomplished under standard conditions[15] by the treatment with 3-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane at 25°C, giving a mixture of two diastereomers in a 1:1 ratio (Scheme 1). The structure of epoxy-ketone (**4**) was characterized by spectroscopic methods.[16] The presence of the oxirane ring in the two products was identified in the ^{13}C NMR spectra (HBBD and DEPT) of the mixture by signals corresponding to methine (CH) at δ_C 48.8 and 49.2 and methylene carbons (CH_2) at δ_C 46.9 and 46.7. Next, epoxy ketone (**4**) was submitted to the reactions summarized in Scheme 2.

Initially, the treatment of the epoxy-ketone derivative (**4**) with oxalic acid in weakly nucleophilic media, e.g. methanol/water (8:2), led to the hydrolysis of the methyl ester followed by acid catalyzed '5-*exo-trig*' cyclization[17] of the carboxylic acid intermediate, furnishing a 1:1 diastereomeric mixture of γ-spirolactone derivative (**5**), in 89% yield. The IR spectrum of (**5**) showed characteristic bands due to the hydroxyl group at ν_{max} 3439 cm^{-1} and carbonyl groups at ν_{max} 1764 and 1730 cm^{-1} attributed to γ-lactone and ketone groups, respectively. Comparative analysis of the HBBD- and DEPT-^{13}C NMR spectra of **5** confirmed the presence of these carbonyl groups by the signals at δ_C 175.6 and 175.3 (lactone) and 214.4 and 214.3 (ketone), along with the additional signals corresponding to two quaternary, two methine monooxygenated and ten methylene (two monooxygenated) sp^3 carbon atoms (vide experimental). The conversion of the spirocyclic compound (**5**) into the corresponding monoacetate (**6**) by the treatment with acetic anhydride in the presence of pyridine (Scheme 2) was used to confirm structure **5** through the comparative



Scheme 2.

analysis of ^{1}H and ^{13}C NMR spectral data, including the results obtained from the homonuclear 2D $^{1}H-^{1}H$-COSY and heteronuclear 2D $^{1}H-^{13}C$-COSY NMR spectra.

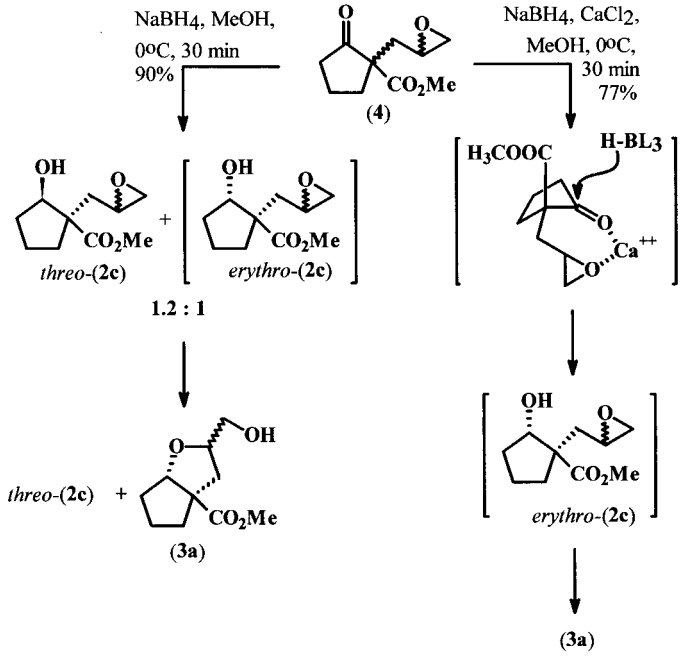
The employment of basic hydrolysis conditions on the epoxide-ester (**4**) using lithium hydroxide[18] in ethanol/water mixture (8:2) at 25°C enabled the competition between the hydroxide anion attack on the less hindered carbon of the epoxide (path b) and the ester carbonyl group (path a), as summarized in Scheme 2. In either case, the expected product would be the γ-spirolactone (**5**), obtained from the acid hydrolysis of compound (**4**). Instead of furnishing the spiro derivative (**5**) as the final product, this procedure gave a diastereomeric mixture of the γ-butirolactone derivative, ethyl 4-[5-hydroxymethyl-2-oxo-tetrahydro-3-furanyl]butanoate (**7**), in 62% yield, probably as a result of a retro-Dieckmann reaction[19] of **5**. This process, which was promoted by the intramolecular (**A**) or intermolecular (**B**) attack of the alkoxide intermediate **I** on the keto-carbonyl group, could furnish the intermediates **IIA** or **IIB**, which led to enolates **IIIA** or **IIIB**, respectively, after cleavage of C–C bond. Compound **7** could be formed from **III**, by the protonation of the enolate group and the solvent mediated hydrolysis (Scheme 2). The careful analysis of ^{1}H and ^{13}C NMR spectroscopic data of the spirocyclic derivative (**7**) and the corresponding acetate (**8**) (Scheme 2) permitted its unambiguous structural characterization.

Chemoselective reduction of the ketone function from the epoxy-ketone derivative (**4**) using sodium borohydride in methanol,[6,7] at 0°C, furnished a mixture of *cis*-2-oxabicyclo[3.3.0]octane derivatives *endo*,*exo*-(**3a**) and *threo*-epoxy alcohol (**2c**), with a ratio of 1:1.2, respectively (Scheme 3). Moreover, the sodium borohydride reduction in the presence of calcium chloride[6,7,20] led to the formation of the bicyclic derivatives *endo*,*exo*-(**3a**) in 77% yield. Considering that only the cyclopentanol derivative (**2c**) with the *erythro*-configuration apparently reacts spontaneously with the lateral epoxide group to afford **3a**, the exclusive synthesis of **3a** using $CaCl_2$ can be rationalized by the selective blockage of one face of the ketone carbonyl group due its coordination with the calcium ion assisted by the oxirane ring, followed by hydride attack on less hindered face giving diastereoselectively the alcohol *erythro*-(**2c**).

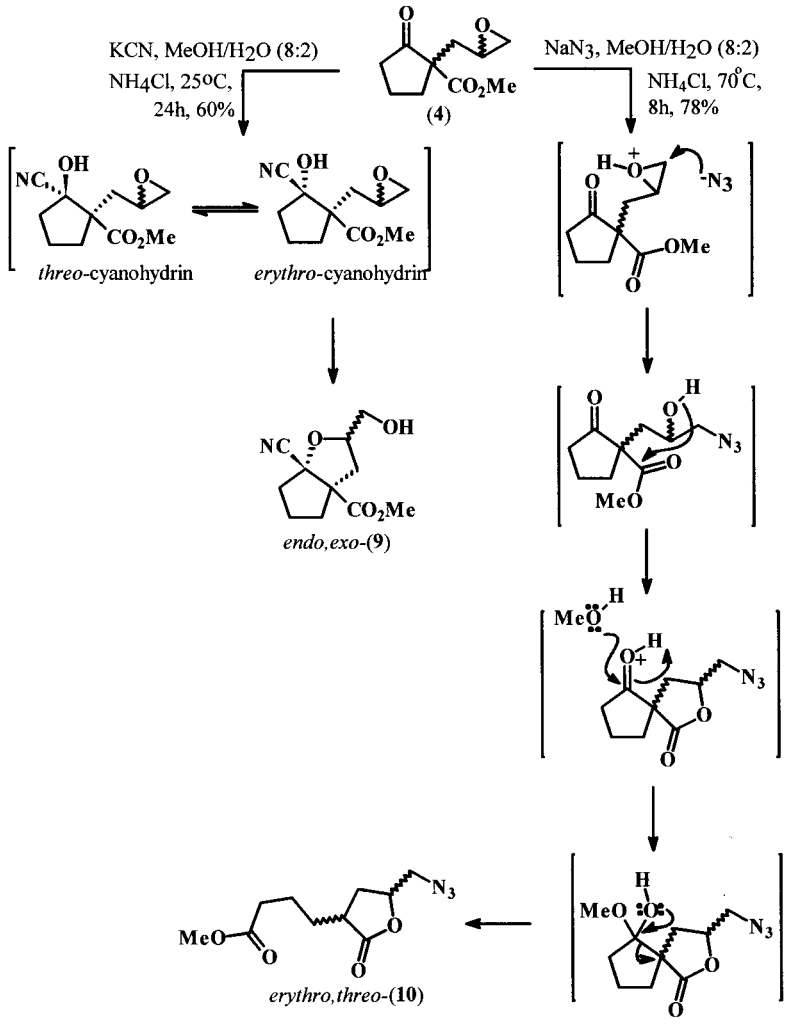
Afterwards, the epoxy-ketone derivative (**4**) was treated with classical nucleophiles, e.g. cyanide and azide anions. The regioselective reaction profile of these nucleophiles with **4** was dependent on their hard–soft character, e.g. the softer base cyanide ion reacts with the softer ketone carbonyl group, leading to the formation of cyanohydrin intermediates. On the other hand, the treatment of **4** with a harder base azide ion leads exclusively to the attack of the harder and less hindered terminal carbon atom on the epoxide moiety (Scheme 4).

Thus, the acid catalyzed reaction of **4** with equimolar amounts of cyanide anion in aqueous methanol media[21] furnished, in 60% yield, the *endo*,*exo*-cyano *cis*-2-oxabicyclo[3.3.0]octane derivatives (**9**), as a result of the stereoselective nucleophilic attack of the hydroxyl group of the *erythro*-cyanohydrin intermediate (Scheme 4) on the neighboring oxirane group. Due to the interconvertibility character of the ketone-cyanohydrin derivatives, the *threo*-cyanohydrin intermediate presenting the unfavorable *trans* relationship between hydroxyl and oxirane groups, was not detected since the conversion of *erythro*-cyanohydrin intermediate into the 2-oxabicyclic derivatives (**9**) shifts the ketone-cyanohydrin equilibrium to the formation of the *erythro*-diastereomer (Scheme 4).

Finally, the epoxy-ketone (**4**) was submitted to the azidolysis reaction (Scheme 4) by treatment with sodium azide in acidic media,[22] furnishing the azido γ-lactone derivatives (**10**), in 78% yield. The formation of **10** could be rationalized by nucleophilic attack of the azide anion on



Scheme 3.



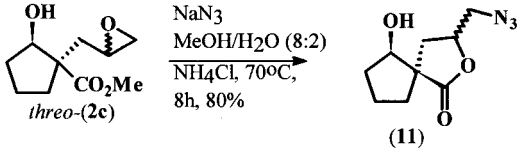
Scheme 4.

the epoxide group and lactonization of the azido-alcohol intermediate with the methyl ester, followed by solvent mediated acid catalyzed cyclopentanone ring opening (Scheme 4).

This acid catalyzed retro-Dieckmann reaction was confirmed by subjecting the *threo*-epoxide-alcohol derivative (**2c**) to the same azidolysis protocol, which furnished the expected azido γ-spirolactone derivative (**11**) as the only product, in 65% yield (Scheme 5).

Conclusion

The study involving the nucleophilic ring opening of the methyl 1-(2-oxiranylmethyl)-2-oxo-1-cyclopentanecarboxylate (**4**) resulted in the discovery of useful synthetic methodologies which facilitated the preparation of functionalized γ-spirolactone and 2-oxabicyclo[3.3.0]octane derivatives in good yields.



Scheme 5.

Experimental

Infrared (IR) spectra were obtained on a Perkin–Elmer 1600-T spectrometer, using sodium chloride cell. One-(1D) and two-dimensional (2D) ^{1}H and ^{13}C NMR spectra were determined in deuterated solvents containing ca. 1% tetramethylsilane as an internal standard on a Bruker Avance DRX-500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) and AC-200 T (^{1}H: 200 MHz; ^{13}C: 50 MHz) spectrometers. Splitting patterns were as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; qt, quintet; m, multiplet; br, broad. Microanalysis data was obtained with a Perkin–Elmer 240 analyzer, using a Perkin–Elmer AD-4 balance. The progress of all reactions was monitored by TLC which was performed on 2.0×5.0 cm aluminum sheets precoated with silica gel 60 (HF-254, Merck) to a thickness of 0.25 mm. The spots of developed chromatograms were visualized by ultraviolet light (254–265 nm) and exposure to iodine vapor. For column chromatography, Merck silica

gel (70–230 mesh) was used. Solvents used in reactions were dried, redistillated prior to use and stored over 3–4 Å molecular sieves.

Synthesis of methyl 1-(2-oxiranylmethyl)-2-oxo-1-cyclopentanecarboxylate (4). To a solution of 2-allyl-2-carbomethoxycyclopentanone (**1a**) (1.00 g, 5.5 mmol) in CH_2Cl_2 (65 mL) at 25°C, was added 60% *m*-CPBA (1.90 g, 6.6 mmol) and the resulting mixture was stirred at 25°C for 18 h. Then, potassium carbonate (1.38 g, 10 mmol) was added and the reaction mixture was stirred for an additional 30 min. Next, the mixture was filtered and the filtrate was washed with water (30 mL). Drying of the organic layer over anhydrous sodium sulfate and removal of the solvent under reduced pressure led to the formation of a residue which was purified by silica-gel column chromatography with a mixture of *n*-hexane–ethyl acetate (60:40) to furnish, in 79% yield, a 1:1 diastereomeric mixture of the epoxy-ketone derivative (**4**), as a colorless oil. IR (NaCl) ν_{max}: 2958, 1749, 1727, 1437, 1319, 1232, 1162, 1090, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 2.88–2.98 and 3.02–3.11 (m, CH– in oxirane ring); 1.95–2.10 (m, $COCH_2CH_2CH_2$, in cyclopentane ring); 2.30–2.40 (m, $COCH_2$ CH_2CH_2– in cyclopentane ring) 2.60 and 2.45 (m, CH_2); 2.75 (m, CH_2 in oxirane ring); 3.72 and 3.74 (s, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 214.1 and 213.9 (C=O); 171.1 and 171.0 (COO); 58.7 and 58.7 (COCCOO); 48.8 and 48.5 (CH- in oxirane ring); 32.9 and 32.5 ($COCH_2CH_2CH_2$, in cyclopentane ring); 19.4 and 19.3 ($COCH_2CH_2CH_2$, in cyclopentane ring); 36.3 and 36.2 ($COCH_2CH_2CH_2$ in cyclopentane ring); 37.6 and 37.2 ($COCCH_2$); 46.5 and 46.4 (CH_2– in oxirane ring); 52.3 (OCH_3). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.63; H, 7.04.

Synthesis of 3-hydroxymethyl-2-oxaspiro[4.4]nonane-1,6-dione (5). *Acid Hydrolysis of 4:* A solution of **4** (0.198 g, 1 mmol) and oxalic acid (0.27 g, 3 mmol) in MeOH/H_2O mixture (8:2) (5 mL) was stirred at 25°C for 6 h. The organic solution was evaporated, diluted with CH_2Cl_2 (20 mL) and neutralized with 10% aqueous K_2CO_3. The organic extract was washed with brine (20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded an oily residue, which after purification by silica-gel column chromatography with a mixture of *n*-hexane–ethyl acetate (50:50) furnish **5** in 89% yield, as a colorless oil. IR (NaCl) ν_{max}: 3439.3, 2954.9, 2883.2, 1764.1, 1730.1 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H 4.61 and 4.76 (m, CH– in lactone); 2.50–2.40, 2.00–1.70 (m, $COCH_2CH_2CH_2$, in cyclopentane ring); 2.23 and 1.88 (m, $COCH_2CH_2CH_2$, in cyclopentane ring); 2.45–2.20 (m, $COCH_2CH_2CH_2$, in cyclopentane ring); 2.42–2.36 and 2.05–1.99 (m, CH_2– in lactone); 3.80 (dl, J=12.3 Hz), 3.72 (dd, J=12.3, 5.4 Hz) and 3.89 (dl, J=12.5 Hz), 3.56 (dl, J=12.5 Hz) CH_2OH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 214.4 and 214.3 (C=O); 57.2 and 58.3 (COCCOO); 175.6 and 175.3 (COO); 78.6 and 78.9 (CH– in lactone); 35.7 and 34.2 ($COCH_2CH_2CH_2$, in cyclopentane ring); 19.5 and 19.8 ($COCH_2CH_2CH_2$, in cyclopentane ring); 37.5 and 37.4 ($COCH_2CH_2CH_2$, in cyclopentane ring); 33.7 and 33.5 (CH_2– in lactone); 64.0 and 63.0 (CH_2OH). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.78; H, 6.70.

Synthesis of 1,6-dioxo-2-oxaspiro[4.4]non-3-ylmethyl acetate (6). A solution of **5** (0.10 g, 0.54 mmol), pyridine (0.098 g,1.24 mmol), Ac_2O (0.11 g, 1.08 mmol) and 4-DMAP (cat.) in CH_2Cl_2 (5 mL) was stirred for 3 h at 25°C. Next, the organic solution was exhaustively washed with saturated aqueous $CuSO_4$ and dried (Na_2SO_4) affording, after removal of the solvent, the acetate (**6**) in 60% yield, as yellow oil. ^{13}C NMR ($CDCl_3$, 50 MHz) δ_C: 213.7 and 213.2 (C=O); 57.4 and 56.5 (COCCOO); 174.0 and 175.0 (COO); 170.3 and 170.3 (COO); 75.3 and 75.1 (CH– in lactone); 33.9 and 33.7 ($COCH_2CH_2CH_2$); 19.5 and 19.2 ($COCH_2CH_2CH_2$); 34.2 and 34.9 ($COCH_2CH_2CH_2$); 37.5 and 37.5 (CH_2– in lactone); 64.8 and 64.4 (CH_2OAc); 20.6 and 20.5 (CH_3). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.46; H, 6.33.

Synthesis of ethyl 4-(5-hydroxymethyl-2-oxotetrahydro-3-furanyl)butanoate (7). *Basic Hydrolysis of 4:* A solution of **4** (0.198 g, 1.0 mmol) and LiOH (0.073 g, 3 mmol) in EtOH/H_2O mixture (8:2) (5 mL) was stirred at 25°C for 5 h. After removal of the solvent, the reaction mixture was diluted with water, acidified by the addition of 10% aqueous HCl followed by extraction with CH_2Cl_2 (3×20 mL). The organic layer was washed with brine (15 mL) and dried (Na_2SO_4) affording, after removal of the solvent, a residue which was purified by silica-gel column chromatography with a mixture of *n*-hexane–ethyl acetate (60:40) to furnish **7** in 62% yield, as a colorless oil. IR (NaCl) ν_{max}: 3444.2, 2939.8, 2872.8, 1761.5, 1732.2 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 4.55 and 4.46 (m, $CHCH_2OH$, in lactone); 2.62 and 2.69 (m, CHCOO, in lactone); 2.28 (t, J=8 Hz, $OOCCH_2CH_2CH_2$); 1.65–1.71 (m, $OOCCH_2CH_2CH_2$); 1.86, 1.45 (m, $OOCCH_2CH_2CH_2$); 1.80, 2.30 and 1.98, 2.30 (m, CH_2– in lactone); 3.84 and 3.58 (m, CH_2OH); 4.07 (q, OCH_2CH_3); 1.21 (t, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 173.2 (COO); 179.4 and 178.4 (COO, in lactone); 78.9 and 78.6 ($CHCH_2OH$, in lactone); 40.5 and 39.3 (CHCOO, in lactone); 33.9 and 33.8 ($OOCCH_2CH_2CH_2$); 22.6 and 22.6 ($OOCCH_2CH_2CH_2$); 30.6 and 29.8 ($OOCCH_2CH_2CH_2$); 29.6 and 29.5 (CH_2– in lactone); 64.4 and 63.6 (CH_2OH); 60.4 (OCH_2CH_3); 14.2 (OCH_2CH_3). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.32; H, 7.93.

Synthesis of ethyl 4-(5-methylcarbonyloxymethyl-2-oxotetrahydro-3-furanyl)butanoate (8). A solution of **7** (0.100 g, 0.5 mmol), pyridine (0.08 g, 0.87 mmol), Ac_2O (0.10 g, 1 mmol) and 4-DMAP (cat.) in CH_2Cl_2 (5 mL) was stirred for 3h at 25°C. Next, the organic solution was exhaustively washed with saturated aqueous $CuSO_4$ and dried (Na_2SO_4) affording, after removal of the solvent, the acetate (**8**) in 64% yield, as yellow oil. ^{13}C NMR ($CDCl_3$, 50 MHz) δ_C: 172.8 (COO); 178.2 and 177.5 (COO, in lactone); 75.3 and 74.9 ($CHCH_2OH$, in lactone); 39.9 and 38.6 (CHCOO, in lactone); 29.7 and 29.5 ($OOCCH_2CH_2CH_2$); 22.3 ($OOCCH_2CH_2CH_2$); 33.6 and 33.5 ($OOCCH_2CH_2CH_2$); 30.2 (CH_2– in lactone); 65.2 and 64.6 (CH_2OAc). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.40; H, 7.46.

Synthesis of methyl *threo*-2-hydroxy-1-(2-oxiranylmethyl)-cyclopentane-1-carboxylate (2c) and 3-*endo*,

***exo*-Hydroxymethyl-5-carbomethoxy-2-oxabicyclo[3.3.0]-octane (3a).** *Sodium borohydride reduction of epoxide-ketone (**4**):* $NaBH_4$ (0.038 g, 1 mmol) was added to a solution of **4** (0.198 g, 1 mmol) in methanol (5 mL) at 0°C. After 30 min the reaction mixture was poured into 10% aqueous NH_4Cl solution (15 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried (Na_2SO_4) afforded after removal of the solvent a crude reaction product which consists in a mixture of (**2c**) and (**3a**) obtained in 90% yield, as a colorless oil.

*Sodium borohydride reduction of epoxide-ketone (**4**), in the presence of $CaCl_2$:* Calcium chloride (0.224 g, 2 mmol) was added to a solution of **4** (0.198, 1 mmol) in methanol (5 mL) at 25°C. After 30 min, the resulting mixture was cooled to 0°C and $NaBH_4$ (0.038 g, 1 mmol) was added. Vigorous gas evolution occurred. After stirring for 30 min at 0°C, the reaction mixture was poured into 10% aqueous NH_4Cl solution (15 mL) and the extracted with ethyl acetate (3×20 mL). The combined organic layers were dried (Na_2SO_4) affording, after removal of the solvent, an oily residue which was purified by silica-gel column chromatography with a mixture of *n*-hexane–ethyl acetate (55:35) to furnish the functionalized bicyclic derivative (**3a**) in 77% yield, as a colorless oil.

Methyl *threo*-2-hydroxy-1-(2-oxiranylmethyl)-cyclopentane-1-carboxylate (2c). IR (NaCl) ν_{max}: 3450.2, 2953.4, 1725.2, 1439.2, 1219.6 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ_H: 4.04 (m, HOC*H*, in cyclopentane ring); 2.94 (m, CH– in oxirane ring); 1.56–1.96 (m, $HOCCH_2CH_2CH_2$ in cyclopentane ring); 2.75 (dd, *J*=4.61, 5.38 Hz), 2.42 (dd, *J*=4.61, 2.31 Hz) (CH_2– in oxirane ring); 3.71 (s, OCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ_C: 175.7 (COO); 79.2 (HO*C*H, in cyclopentane ring); 49.1 (CH-7, in oxirane ring); 56.9 (C-2); 31.0 ($HOCCH_2CH_2CH_2$ in cyclopentane ring); 20.2 ($HOCCH_2CH_2CH_2$ in cyclopentane ring); 31.9 ($HOCCH_2CH_2CH_2$ in cyclopentane ring); 39.0 (CH_2– in lactone); 46.5 (CH_2 in oxirane ring); 51.7 (OCH_3). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.04; H, 8.11.

3-*endo*,*exo*-Hydroxymethyl-5-carbomethoxy-2-oxabicyclo-[3.3.0]octane (3a). IR (NaCl) ν_{max}: 2954, 1771, 1734, 1444, 1356, 1282 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H 4.69 (t, *J*=3.4 Hz) and 4.51 (d, *J*=5.3 Hz) (OC*H*, in cyclopentane ring); 4.17 and 3.93 (m, C*H*CH_2OH); 2.16, 1.72 and 1.96, 1.72 (m, $OCCH_2CH_2CH_2$, in cyclopentane ring); 1.75 and 1.74 (m, $OCCH_2CH_2CH_2$ in cyclopentane ring); 1.82 and 1.87, 1.58 (m, $OCCH_2CH_2CH_2$ in cyclopentane ring); 2.38 (dd, *J*=8.0, 12.9 Hz), 1.87 (dd, *J*=6.3, 12.9 Hz) and 2.48 (dd, *J*=5.1, 12.6 Hz), 1.59 (t, *J*=12.6 Hz) (CH_2– in lactone); 3.78 (dd, *J*=2.5, 11.9 Hz), 3.53 (dd, *J*=4.5, 11.9 Hz) and 3.63 (dd, *J*=2.8, 11.5 Hz), 3.50 (dd, *J*=6.0, 11.5 Hz) (CH_2OH); 3.69 and 3.68 (s, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 176.4 and 176.7 (COO); 88.9 and 89.2 (OCH– in cyclopentane ring); 80.2 and 80.2 (*C*HCH_2OH); 60.5 and 60.4 (CO*C*COO); 37.9 and 37.5 ($OCCH_2CH_2CH_2$ in cyclopentane ring); 25.2 and 24.3 ($OCCH_2CH_2CH_2$ in cyclopentane ring); 34.5 and 33.7 ($OCCH_2CH_2CH_2$ in cyclopentane ring); 39.2 and 39.0 (CH_2– in lactone); 64.1 and 63.4 (CH_2OH); 52.2 and 52.3 (OCH_3). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 60.02; H, 7.98.

Synthesis of 1-cyano-3-*endo*,*exo*-hydroxymethyl-5-carbomethoxy-2-oxabicyclo[3.3.0]octane (9). A solution of **4** (0.198 g, 1 mmol) in 5 mL of the mixture of MeOH/H_2O (8:2) containing KCN (0.065 g, 1 mmol) and NH_4Cl (0.12 g, 2 mmol), was stirred for 24 h at 25°C. The reaction mixture was concentrated, diluted with water (20 mL) and extracted with Et_2O (20 mL) furnishing, after drying (Na_2SO_4) and evaporation of the solvent, the crude cyanobicyclic derivative (**9**) as yellow oil. After purification by using silica-gel column chromatography employing a mixture of *n*-hexane–ethyl acetate (60:40%), compound (**9**) was obtained in 60% yield. IR (NaCl) ν_{max}: 3453, 2954, 2885, 2239, 1732, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 4.28 and 4.24 (m, C*H*CH_2OH); 2.40, 1.80 (m, $OCCH_2CH_2CH_2$, in cyclopentane ring); 1.95, 1.80 (m, $OCCH_2CH_2CH_2$, in cyclopentane ring); 2.30, 1.88 (m, $OCCH_2CH_2CH_2$, in cyclopentane ring); 2.68, 2.06 (dd, *J*=9.2, 13.2 Hz; 6.3, 13.2-CH_2-6) and 2.74, 1.71 (dd, *J*=5.4, 12.8 Hz; 10.6, 12.8, CH_2-6); 3.72, 3.64 (dd, *J*=3.3, 12.1 Hz; 5.9, 12.1, CH_2OH) and 3.85, 3.59 (dd, *J*=2.3, 12.4 Hz; 4.6, 12.4, CH_2OH); 3.78 and 3.79 (s, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 172.7 and 173.0 (COO); 119.2 and 118.8 (CN); 82.3 and 81.9 (*C*HCH_2OH); 86.9 and 88.2 (CN*C*O); 65.9 and 66.6 (CO*C*COO); 37.0 and 38.2 ($OCCH_2CH_2CH_2$, in cyclopentane ring); 24.4 and 23.9 ($OCCH_2CH_2CH_2$, in cyclopentane ring); 39.7 and 39.4 ($OCCH_2CH_2CH_2$, in cyclopentane ring); 36.9 and 37.7 (CH_2– in lactone); 63.9 and 62.5 (CH_2OH); 53.0 and 53.1 (OCH_3). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.61; H, 6.79; N, 6.14.

Synthesis of methyl 4-(5-azidomethyl-2-oxotetrahydro-3-furanyl)butanoate (10). A solution of the **4** (0.198g, 1 mmol) in 5 mL of MeOH/H_2O mixture (8:2) containing NaN_3 (0.195 g, 3 mmol) and NH_4Cl (0.12 g, 2 mmol) was stirred for 18 h at 70°C. The reaction mixture was concentrated, diluted with water (20 mL) and extracted with Et_2O (20 mL) furnishing, after drying (Na_2SO_4) and evaporation of the solvent a crude oily residue. After purification by using silica-gel column chromatography employing a mixture of *n*-hexane–ethyl acetate (55:35%), the butyrolactone derivative (**10**) was obtained in 78% yield, as a yellow oil. IR (NaCl) ν_{max}: 2954, 2106, 1771, 1734, 1444, 1356, 1282 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 4.47 and 4.57 (m, C*H*CH_2N_3, in lactone); 2.59 and 2.61 (m, C*H*COO, in lactone); 1.47, 1.87 and 2.10, 2.20 (m, $OOCCH_2CH_2CH_2$); 1.64–1.68 (m, $OOCCH_2CH_2CH_2$); 2.30 (t, *J*=7.3 Hz $OOCCH_2CH_2CH_2$); 1.65, 2.40 (m, CH_2– in lactone); 3.53, 3.39(m, CH_2N_3); 3.61 (s, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 173.4 (COO); 177.4 and 178.1 (COO, in lactone); 76.3 and 75.9 (*C*HCH_2N_3, in lactone); 40.2 and 38.7 (*C*HCOO, in lactone); 29.8 and 30.5 ($OOCCH_2CH_2CH_2$); 22.5 and 22.5 ($OOCCH_2CH_2CH_2$); 33.6 and 33.5 ($OOCCH_2CH_2CH_2$); 31.3 (CH_2– in lactone); 53.6 and 54.4 (CH_2N_3); 51.5 (OCH_3). Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.85; H, 6.32; N, 17.51.

Synthesis of 3-azido methyl-6-hydroxy-2-oxaspiro[4.4]-nonane (11). A solution of the (**2c**) (0.200 g, 1 mmol) in

5 mL of MeOH/H_2O mixture (8:2) containing NaN_3 (0.195 g, 3 mmol) and NH_4Cl (0.12 g, 2 mmol) was stirred for 12 h at 70°C. The reaction mixture was concentrated, diluted with water (20 mL) and extracted with Et_2O (20 mL) furnishing after drying (Na_2SO_4) and evaporation of the solvent, the spirocyclic derivative (**11**) in 65% yield, as a yellow oil. IR (NaCl) ν_{max}: 3397, 2955, 2875.3, 2106, 1753, 1644, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ_H: 4.68 (m, C*H* in cyclopentane ring) 4.06 (m, C*H*CH_2N_3, in lactone); 3.55 (m, C*H*$_2N_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ_C: 179.3 and 180.0 (COO, in lactone); 80.8 and 79.6 (*C*H in cyclopentane ring); 75.7 and 75.5 (*C*HCH_2N_3, in lactone); 53.4 and 54.0 (CH_2N_3); 39.0 and 37.4 (CH_2– in lactone); 20.9 and 20.7 (HOCHCH_2*C*H_2CH_2). Anal. Calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.11; H, 6.25; N, 19.82.

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References

1. Peterson, E. M.; Xu, K.; Holland, K. D.; McKeon, A. C.; Rothman, S. M.; Ferrendelli, J. A.; Covey, D. F. *J. Med. Chem.* **1994**, *37*, 275–286.
2. Kupchan, S. M.; Dessertine, A. L.; Blaylock, B. T.; Bryan, R. F. *J. Org. Chem.* **1974**, *39*, 2477–2482.
3. Trost, B. M.; Balkovec, J. M.; Mao, M. K.-T. *J. Am. Chem. Soc.* **1983**, *105*, 6755–6757.
4. Lee, L.; Wang, S.; Milne, G. W. A.; Sharma, R.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. *J. Med. Chem.* **1996**, *39*, 29–35.
5. Hayakawa, H.; Okada, N.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1999**, *40*, 4589–4592; Calvani, F.; Crotti, P.; Gardelli, C.; Pineeschi, M. *Tetrahedron* **1994**, *50*, 12999–13022; Smith, J. G. *Synthesis* **1984**, 629–656.
6. Fraga, C. A. M.; Barreiro, E. J. *Synth. Comm.* **1995**, *25*, 1133–1144.
7. Teixeira, L. H. P.; Barreiro, E. J.; Fraga, C. A. M. *Synth. Comm.* **1997**, *27*, 3241–3257.
8. Fraga, C. A. M.; Barreiro, E. J. *Chirality* **1996**, *8*, 305–310.
9. Fraga, C. A. M.; Silva, E. F.; Ramos, M. C. K. V.; Aquino Neto, F. R.; Barreiro, E. J. *Chirality* **1997**, *9*, 321–324.
10. Barreiro, E. J.; Garcia, V. L. *An. Acad. Brasil. Ciênc.* **1985**, *57*, 417428; *Chem. Abstr.* **1985**, *106*, 138176d.
11. Fraga, C. A. M.; Miranda, A. L. P.; Barreiro, E. J. *Chem. Pharm. Bull.* **1996**, *44*, 2157–2161.
12. Peçanha, E. P.; Fraga, C. A. M.; Sant'Anna, C. M. R.; Miranda, A. L. P.; Barreiro, E. J. *Il Farmaco* **1998**, *53*, 327–336.
13. Purchased from Aldrich Chemical Co., Milwaukee, Wis., USA.
14. Barco, A.; Benetti, S.; Pollini, G. P. *Synthesis* **1976**, 316–318.
15. Swern, D. *Org. Reactions* **1953**, *7*, 378–433.
16. Haral, G. *NMR Spectroscopy*, Wiley: New York, 1994.
17. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736; Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476–482.
18. Meanwell, N. A.; Rosenfel, M. J.; Trehan, A. K.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Gamberdella, M.; Zavoico, G. B.; Seiler, S. M. *J. Med. Chem.* **1992**, *35*, 3483–3497.
19. Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1–203.
20. Fujii, H.; Oshina, K.; Utimoto, K. *Chem. Lett.* **1992**, 967–970.
21. Kergomard, A.; Veschanbre, H. *Tetrahedron Lett.* **1976**, *45*, 4069–4072.
22. Azzena, F.; Calvani, F.; Crotti, P.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 10601–10626; Colombini, M.; Crotti, P.; Di Bussolo, V.; Favero, L.; Gardelli, C.; Macchia, F.; Pineschi, M. *Tetrahedron* **1995**, *51*, 8089–8112.