From Renewable Levulinic Acid to a Diversity of 3-(Azol-3-yl) Propanoates

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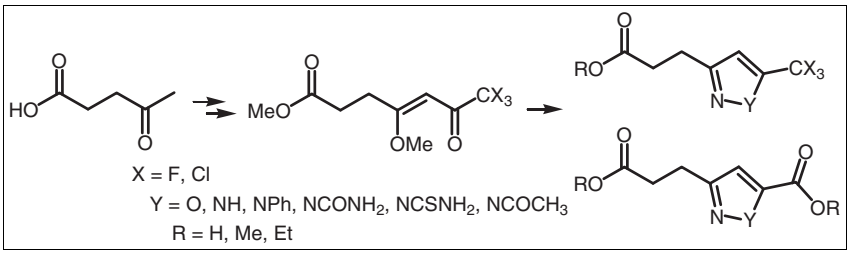
Received March 21, 2012
DOI 10.1002/jhet.1774
Published online 3 December 2013 in Wiley Online Library (wileyonlinelibrary.com).



Efficient heterocyclization of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-4-heptenoate and methyl 7,7,7-trichloro-4-methoxy-6-oxo-4-heptenoate into isoxazole and pyrazole derivatives that represent a new type of glutamate-like 3-(trihalomethylated-1,2-azol-3-yl)propanoate is reported. Preparation of the key methyl 7,7,7-trihalo-4-methoxy-6-oxohept-4-enoate precursors from levulinic acid is also described. The synthetic potential of this synthetic protocol was indicated by the production of several methyl and ethyl 3-(isoxazol-3-yl) propanoates and 3-(1*H*-pyrazol-3-yl)propanoates, and the respective acid derivatives, in good (70–95%) yields. The crystal structure for ethyl 5-(3-ethoxy-3-oxopropyl)-1*H*-pyrazole-3-carboxylate (**10c**) has been determined by monocrystal X-ray diffraction analysis. The N–H···H intermolecular hydrogen bonds join the molecules into catamer.

J. Heterocyclic Chem., **51**, 733 (2014).

INTRODUCTION

The azole rings are an important framework in pharmaceuticals and agricultural chemicals and for the development of new functional materials [1–6]. For example, (*S*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) is a classic AMPA receptor agonist, and a large number of heterocyclic Glu analogs, most of which are derived from AMPA, are potent and selective agonists at AMPA receptors. The 3-heteroaryl-propanoates are important targets for the development of potent and selective AMPA antagonists and represent potential drugs for cerebral ischemia or epilepsy. Good results were observed for ethyl 3-(2-ethoxycarbonyl-1*H*-imidazol-4-yl) propenoate and its saturated derivative at micromolar concentrations (Fig. 1)[7]. The synthesis of new drugs targeting the glutamatergic system is also important for the treatment of mood disorders [8–10].

We have systematically used the acetal acylation method for the synthesis of a wide range of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones [11–13]. These 1,3-dielectrophilic precursors have proved to be important building blocks for the regiospecific synthesis of heterocyclic compounds bearing trihalo methyl/carboxyl groups with important pharmacological and synthetic applications [14–17]. Levulinic acid (4-oxopentanoic acid, LA) is an important fine organic material from renewable sources and presents us with an attractive acetyl group [18–22]. Our continuing interest in functionalized 1,3-dielectrophilic compounds led us to study a new aspect of the application of the acetal acylation method for producing methyl 7,7,7-trifluoro-4-methoxy-6-oxo-4-heptenoate (**1**) and methyl 7,7,7-trichloro-4-methoxy-6-oxo-4-heptenoate (**2**) [23].

With this in mind, we designed and synthesized a series of new 3-(azol-3-yl)propanoates from precursors **1** and **2**, which were obtained by the trihaloacylation of methyl 4,4-dimethoxypentanoate derived from levulinic acid.

RESULTS AND DISCUSSION

Methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoates (**1**, **2**) were synthesized, according with previous publications, from the reaction of methyl 4,4-dimethoxypentanoate with trifluoroacetic anhydride or trichloroacetyl chloride (Scheme 1) [11].

To prepare isoxazole derivatives, precursors **1** and **2** were reacted with hydroxylamine hydrochloride in different reaction conditions. When the reaction was performed in pyridine in a molar ratio of 1:1.2:1.2 using methanol or ethanol under reflux, we obtained the methyl (5-trihalomethyl-5-hydroxy-4,5-dihydroisoxazol-3-yl) propanoates **3b** and **4b**

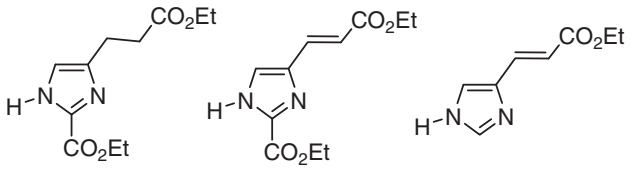
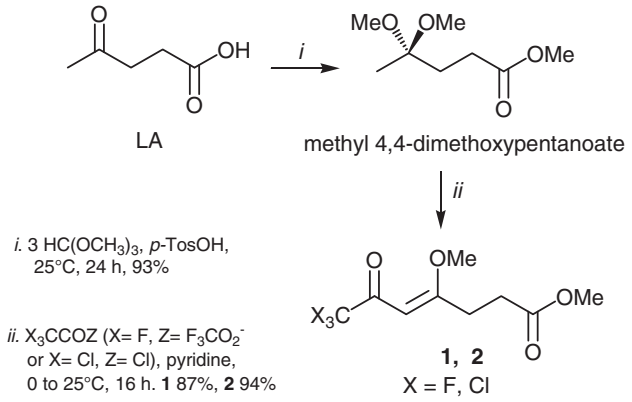
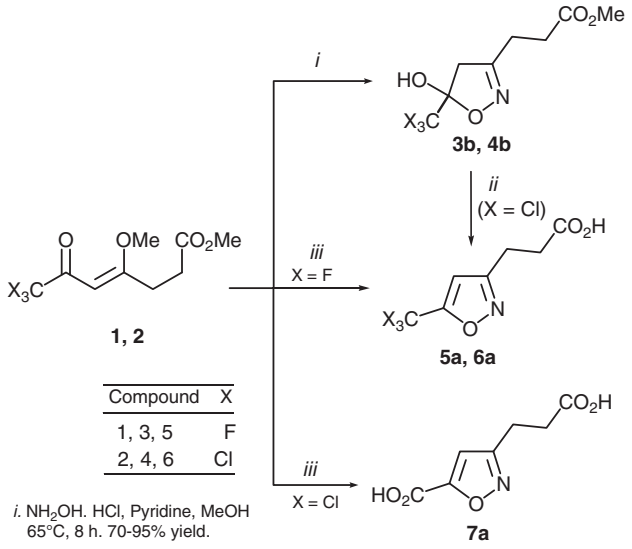


Figure 1. 3-(Imidazol-4-yl)propanoates and propenoates as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonists.

Scheme 1. Process to acylate exclusively methyl site.



Scheme 2. Synthesis of isoxazole derivatives.



Compound	X
1, 3, 5	F
2, 4, 6	Cl

in 90–95% yields (Scheme 2). These compounds were obtained as colorless crystalline solids, after purification by recrystallization from hexane.

Compounds **3b** and **4b** were characterized as dihydroisoxazoles by $^1H/^{13}C$ NMR spectra in $CDCl_3$. The ^1H NMR spectra of **3b** and **4b** exhibit two doublet signals assignable to diastereotopic hydrogens at the 4-C position of the isoxazole, with typical chemical shift values (**3b**, δ 3.1–3.37 ppm and a $J_{H–H}$ coupling constant of 18.3 Hz; **4b**, δ 3.23–3.66 ppm, $J_{H–H}$ = 18.5 Hz). Interestingly, the two methylenes of the propanoate chain were characterized as a broad singlet signal at δ 2.7 ppm. Compounds **3b** and **4b** were reacted with sulfuric acid for dehydration/aromatization of the isoxazole ring. After 4-h stirring at 40°C, we isolated the aromatic derivatives **5a** and **6a**, both resulting from dehydration at the isoxazole ring and hydrolysis of the ester function of the acid. The 3-(5-trihalomethylisoxazol-3-yl) propanoic acids (**5a**, **6a**) were obtained as colorless solids after purification by recrystallization from acetone. The ^1H NMR spectrum of **5a** exhibits a singlet at δ 6.63 ppm for the aromatic isoxazole 4-H. The aromatic isoxazole was also confirmed by observation of ^{13}C NMR signals at δ 162.6, δ 105.5, and δ 159 ppm for 3-C, 4-C, and 5-C, respectively. Assignment of 5-C was easy because it resonates as a quartet, with a characteristic $^2J_{CF}$ = 42.6 Hz [13,24,25].

Reacting **1** with hydroxylamine hydrochloride in aqueous medium to obtain propanoic acid **5a** in one step was successful; after 24 h under reflux, pure propanoic acid **5a** (Scheme 2) was isolated. However, the same reaction conditions for precursor **2** lead to the propanoic acid **7a**, which is derived from three steps: the aromatization of the isoxazole ring, the hydrolysis of ester function, and finally the hydrolysis of trichloromethyl to a carboxylic moiety. This was confirmed by a ^1H NMR spectrum in DMSO, which exhibits a singlet signal at δ 7.08 ppm representing the aromatic isoxazole 4-H and a broad singlet at 10.58 ppm representing the carboxyl group at the 5-C position of the isoxazole ring. A ^{13}C NMR spectrum exhibits two signals at δ 164.2 and δ 173.7 ppm, both for carboxyl groups [26,27].

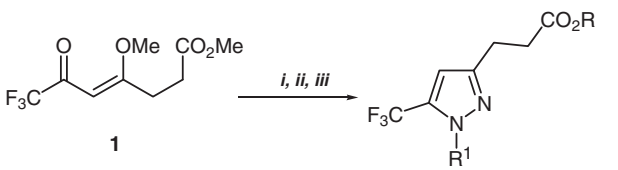
The cyclocondensation of **1** with hydrazine monohydrate was performed in a molar ratio of 1:1.2 using water, methanol, or ethanol as the solvent [28–30]. All mixtures were stirred at 65°C for 12 h; the solvent was evaporated under reduced pressure; and the products were dissolved in $CHCl_3$, dried with Na_2SO_4, and isolated. When these reactions were performed in acid medium, pyrazole **8** was obtained. When the reaction was conducted in ethanol, **9** promoted the transesterification of the methyl ester (CO_2Me) into ethyl ester (CO_2Et); when the reaction was conducted in water, **9** promoted the hydrolysis of the methyl ester to carboxylic acid. The 3-(5-trifluoromethyl pyrazol-3-yl) propanoic acid (**8a**) was obtained in pure form as a colorless solid; alkyl 3-(5-trifluoromethylpyrazol-3-yl)propanoates (**8b**, **c**) were obtained in pure form as yellow-red oils. The ^1H NMR spectra of **8a–c** exhibit a singlet around δ 6.4–6.6 ppm for the aromatic pyrazole 4-H. The aromatic pyrazole also was confirmed by the observation of ^{13}C NMR signals at δ 144, δ 101, and δ 141 ppm for 3-C, 4-C,

and 5-C, respectively. The assignment of 5-C was easy because it resonates as a quartet, with a characteristic $^2J_{CF} = 33.7$ Hz. Reactions between **1** and hydrazine hydrochloride produced 1*H*-pyrazoles **8a–c** in low yields and used the large excess amount of hydrazine only under pyridine assistance.

Cyclocondensations between precursor **1** and free phenylhydrazine to form pyrazoles were performed in a molar ratio of 1:1.2 using water, methanol, or ethanol as the solvent [31]. All mixtures were initially stirred for 1 h at 0–5°C and after for 12 h at 25°C, and the solvent was evaporated under vacuum. The residue was dissolved in chloroform and washed with water two times, and methyl 3-(5-trifluoromethyl-1-phenyl-1*H*-pyrazol-3-yl)propanoate (**9b**) was obtained in pure form as red-brown oil. At this condition, transesterification did not occur; to obtain pyrazoles **9a** and **9c**, the cyclization reaction between **1** and phenylhydrazine hydrochloride was performed in water or ethanol. The mixtures were stirred at reflux for 8 h. This led to the formation of ethyl 3-(5-trifluoromethyl-1-phenylpyrazol-3-yl)propanoate (**9c**) in a good (68%) yield. This cyclocondensation in water to obtain **9a** creates a complex mixture of products with proposed structures supported by mass and ^{1}H/^{13}C NMR spectra. The ^{1}H NMR spectra of **9b** and **c** exhibit a singlet at 6.4–6.6 ppm representing the aromatic pyrazole 4-H and multiplet signals at high field 2.7–3.0 ppm for propanoate methylenes. Aromatic pyrazoles are also confirmed through ^{13}C NMR signals at δ 151, δ 108, and δ 132 ppm for 3-C, 4-C, and 5-C, respectively. Assignment of 5-C was straightforward because it resonates as a quartet, with characteristic $^2J_{CF} = 38$ Hz. Similarly, the use of free phenyl hydrazine improved the yield compared with the phenylhydrazine hydrochloride previously tested (Scheme 3).

The cyclocondensations between **2** and hydrazines were conducted in two ways. First, our goal was to retain the trichloromethyl group allowing us to obtain trichloromethyl-1*H*-pyrazoles; second, we conducted one-pot cyclocondensation and hydrolysis of trichloromethyl to the carboxyl group and obtained 1*H*-pyrazole carboxylates [32].

Scheme 3. Synthesis of aromatic trifluoromethyl-1*H*-pyrazoles.



i. NH_2NHR^1. H_2O, ROH (R =H, Me, Et) 65°C, 8-12 h.

ii. NH_2NHPh, MeOH 0 to 5 °C, 30 min. then reflux °C, 8 h (**9b**).

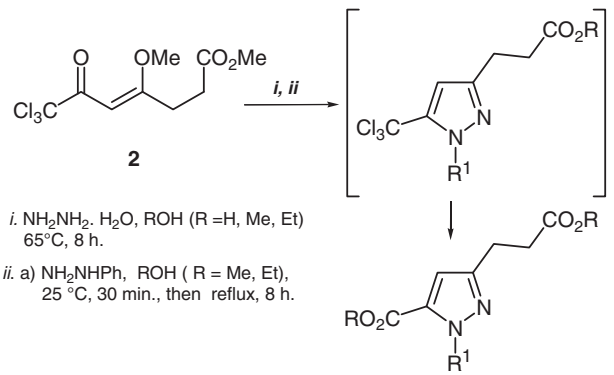
iii. $NH_2NHPh.HCl$, EtOH 0 to 5 °C, 30 min. then reflux °C, 8 h (**9c**).

Compound	R^1	R	yield (%)
8a	H	H	93
8b	H	Me	94
8c	H	Et	77
9b	Ph	Me	94
9c	Ph	Et	68

However, despite our best efforts to retain CCl_3, all reactions of **2** and $RNHNH_2$ (R=H or Ph) produced some proportion of 1*H*-pyrazole-5-carboxylate. Even using aprotic solvent at low temperature, we obtained a mixture of trichloromethylpyrazole and its respective carboxyl derivatives. The 1*H*-pyrazole-5-carboxylates **11b** and **c** were prepared pure in water or alcoholic (MeOH or EtOH) solvent at 70°C (Scheme 4). Products **10a–c** and **11b** and **c** were isolated as colorless crystalline solids. The structures of isolated compounds were assigned by MS and ^{1}H/^{13}C NMR spectroscopy data. X-ray diffraction enabled us to observe that compound **10c** exists as tautomer ethyl 5-(3-methoxy-3-oxopropyl)-1*H*-pyrazole-3-carboxylate, which is crystallized as a catemer along the *ab* plane [33] (Fig. 2). Condensation of **2** with phenylhydrazine in water at 70°C produced a mixture of the 1,5- and 1,3-regioisomers **11a** and **12a**.

To expand sampling diversity from LA, we conducted condensations between precursors **1** and **2** and semicarbazide hydrochloride, thiosemicarbazide, and methyl hydrazine carboxylate (Scheme 5). These reactions proceeded smoothly in MeOH to produce the respective methyl 3-(5-hydroxy-5-trihalomethyl-4,5-dihydro-1*H*-pyrazol-3-yl) propanoates (**13b–18b**). The acyl substituent at the N1-position guarantees the stability of 5-trihalomethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole products because of the electron-withdrawing effect of the amide carbonyl group. Dehydration of propanoates **13b–18b** could not be achieved without the parallel hydrolysis of the N1carboxyls. The ^{1}H NMR spectra of **13b–18b** exhibit two doublet signals assignable to diastereotopic hydrogens at the 4-C position of the 1*H*-pyrazole, with values typical of chemical shifts, δ 3.2–3.7 ppm, and the coupling constant $J_{H-H} = 19$ Hz.

Scheme 4. Synthesis of 1*H*-pyrazole-5-carboxylate.



i. NH_2NH_2. H_2O, ROH (R =H, Me, Et) 65°C, 8 h.

ii. a) NH_2NHPh, ROH (R = Me, Et), 25 °C, 30 min., then reflux, 8 h.

Compound	R^1	R	yield (%)
10a	H	H	93
10b	H	Me	94
10c	H	Et	77
11b	Ph	Me	94
11c	Ph	Et	68

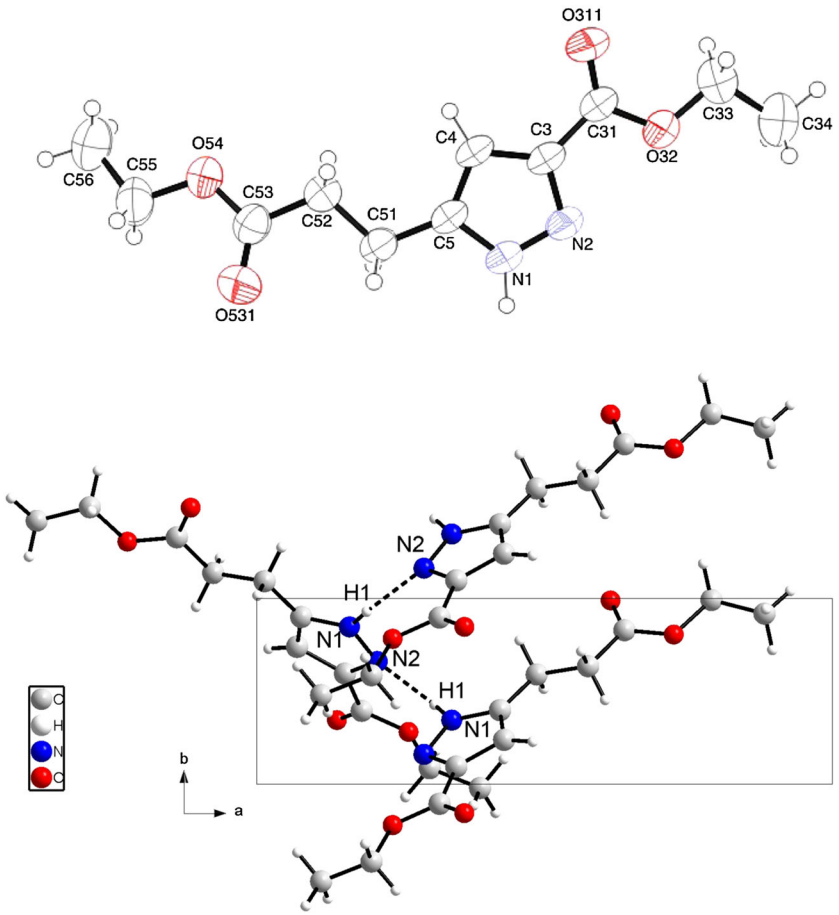
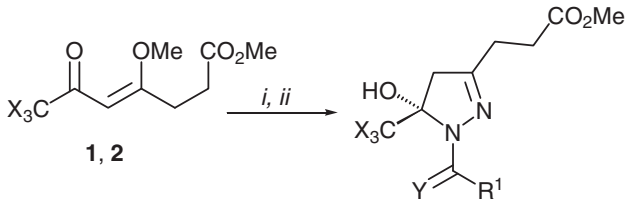


Figure 2. X-ray structure of **10c**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Scheme 5. 5-Trihalomethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles.



i. $NH_2NHCONH_2.HCl$, Py, $MeOH/H_2O$, 65 °C, 18 h.
ii. $NH_2NHC(=Y)R^1$, MeOH, 50 °C, 18 h.

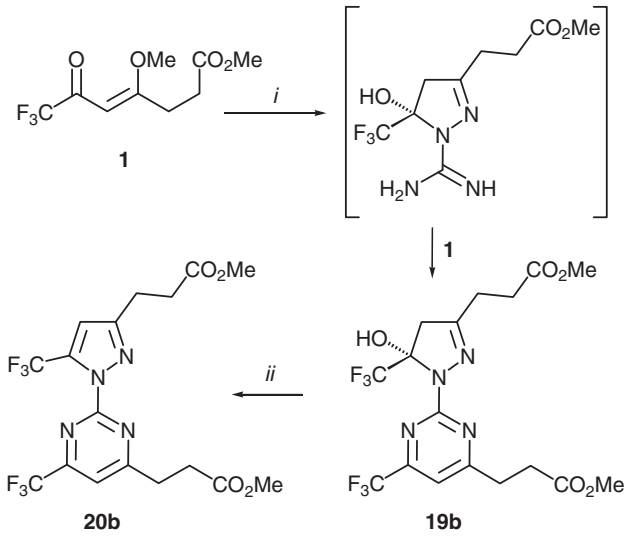
13b-18b

	X	Y	R^1
13b	F	O	NH_2
14b	Cl	O	NH_2
15b	F	S	NH_2
16b	Cl	S	NH_2
17b	F	O	OMe
18b	Cl	O	OMe

Again, as in 4,5-dihydroisoxazole, the two methylenes of the propanoate chain were characterized as a broad singlet signal at δ 2.7 ppm. The structure of the 5-trihalomethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole was also supported by MS and ^{13}C NMR data.

Finally, precursor **1** was reacted with tetraelectrophilic aminoguanidine hydrochloride [34,35]. Several conditions were tested for obtaining methyl 3-(1-carboxyamidino-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-3-yl) propanoate, and even under large excess of aminoguanidine, we always obtained pyrazolyl–pyrimidine **19b**. Then, we allowed precursor **1** to react with aminoguanidine in a 2:1 molar proportion between **1** and aminoguanidine hydrochloride in MeCN and, after purification by recrystallization from hexane, obtained **19b** as a pure colorless solid in 65% yield (Scheme 6). The structure of **19b** was determined by MS and $^1H/^{13}C$ NMR spectral data. The product methyl 3-{2-[5-hydroxy-3-(3-methoxy-3-oxopropyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-6-trifluoromethyl pyrimidin-4-yl}propanoate (**19b**) was dehydrated to its respective bis-aromatic pyrazolyl–pyrimidine, **20b**, using H_2SO_4 98%. The methyl 3-{2-[3-(3-methoxy-3-oxopropyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-6-(trifluoromethyl)pyrimidin-4-yl}propanoate (**20b**) was obtained as a colorless solid when precipitated from cooled diluted acid solution. We were unable to obtain some product from precursor **2** and aminoguanidine hydrochloride.

Scheme 6. Synthesis of pyrazolyl–pyrimidine derivatives.



i. $NH_2NH(C{=}NH)NH_2.HCl$, Py, MeOH, 65 °C, 18 h.
ii. H_2SO_4 98%, 40 °C, 4 h.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were collected at 300 K using a 5-mm dual probe on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.62 MHz (UFSM, Santa Maria, RS, Brazil)). Chemical shifts (δ) are quoted in parts per million (ppm) from TMS, and coupling constants (*J*) are given in Hz. Melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus (Barnstead Thermoline, Dubuque, IA). Mass spectra were registered in an Agilent HP 5973 MSD connected to a HP 6890 GC and interfaced using a Pentium PC (Agilent Technologies, Santa Clara, CA). The GC was equipped with a split–splitless injector, cross-linked to an HP-5 capillary column (30 m, 0.32 mm i.d.), and helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil). The diffraction measurements were performed by graphite monochromatized Mo Kα radiation with $k = 0.71073$ Å on a Bruker SMART CCD diffractometer [36]. The structure was solved with direct methods using the SHELXS-97 program [37] and refined on F2 by full-matrix least-squares using the SHELXL-97 package [38]. The absorption correction was performed by Gaussian methods [39]. Anisotropic displacement parameters for nonhydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3), 0.97 Å (methylene CH_2), 0.98 Å (methine CH), 0.93 Å (aromatic CH), and 0.82 Å (OH) using a riding model. The hydrogen isotropic thermal parameters were kept equal to Uiso (H) = *v*Ueq (carrier C atom), with $v = 1.5$ for methyl groups and $v = 1.2$ otherwise. The valence angles C–C–H and H–C–H of methyl groups were set to 109.5°, and the H atoms were allowed to rotate around the C–C bond. The molecular graph was prepared using ORTEP3 for Windows [40]. Crystallographic data for the structure of **10c** have been deposited with the Cambridge Crystallographic Data Centre and allocated deposition number CCDC 849417. Copies of the data can be obtained free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax 44-1223-336033 or via http://www.ccdc.cam.ac.uk).

Methyl 3-(5-hydroxy-5-trihalomethyl-4,5-dihydroisoxazol-3-yl) propanoates (3b and **4b**). A solution of methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoate **1** or **2** (5 mmol), hydroxylamine hydrochloride (7.5 mmol), and pyridine (7.5 mmol) in MeOH or EtOH (10 mL) was stirred for 8 h at 65°C. The solvent was removed, and the residue was dissolved in $CHCl_3$ (20 mL) and washed with HCl 10% (10 mL). The solution was dried over Na_2SO_4, and the solvent was evaporated, producing **3b** or **4b**. The products were purified by recrystallization in hexane. **3b** (850 mg, 70%), mp 78–79°C, ^1H NMR ($CDCl_3$, 400 MHz) δ 2.7 (large s, 4H, $2CH_2$), 3.1 (d, $J = 18.2$ Hz, 1H, H4), 3.37 (d, $J = 18.2$ Hz, 1H, H4), 3.72 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.2 (CH_2), 30.4 (CH_2), 45.6 (C-4), 52.6 (OMe), 103.3 (q, $J_{C-F} = 34.3$ Hz, C-5), 122.3 (q, $J_{C-F} = 283.8$ Hz, CF_3), 158.8 (C-3), 173.5 (C=O). MS [*m*/*z*(%)] 241 (M^+, <5), 224 (–OH, 14), 210 (–OMe, 100), 182 (–C(O)OMe, 55), 172 (–CF_3, 39), 164 (26), 140 (74), 112 (40), 68 (CF_3, 46), 59 (78). $C_8H_{10}F_3NO_4$: C, 39.80; H, 4.07; N, 5.64; found C, 39.50; H, 4.17; N, 5.74. **4b** (1.4 g, 95%), mp 80–82°C, ^1H NMR ($CDCl_3$, 400 MHz) δ 2.71 (large s, 4H, $2CH_2$), 3.23 (d, $J = 18.5$ Hz, 1H, H4), 3.66 (d, $J = 18.5$ Hz, 1H, H4), 3.71 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.1 (CH_2), 30.1 (CH_2), 46.5 (C4), 52.1 (CH_3), 100.8 (CCl_3), 110.8 (C5), 159 (C3), 172.8 (C=O). MS [*m*/*z*(%)] 289 (M^+, <5), 274 (–OH, 5), 258 (–OMe, 18), 172 (–CCl_3, 28), 140 (100), 87 (28), 59 (61). *Anal.* Calcd for $C_8H_{10}Cl_3NO_4$: C, 33.07; H, 3.47; N, 4.82; found C, 33.17; H, 3.48; N, 4.79.

3-(5-Trifluoromethylisoxazol-3-yl)propanoic acid (5a). A solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-4-heptenoate **1** (5 mmol) and hydroxylamine hydrochloride (7.5 mmol) in H_2O (10 mL) was stirred for 12 h at reflux. The solution was extracted with $CHCl_3$ (3 × 10 mL). The organic solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the pure propanoic acid **5a** (750 mg, 72%). Decomposed at >180°C, ^1H NMR (DMSO-d_6, 400 MHz) δ 2.86 (t, $J = 6.9$ Hz, 2H, CH_2), 3.08 (t, $J = 7.0$ Hz, 2H, CH_2), 6.63 (s, 1H, H4). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3 (CH_2), 31.7 (CH_2), 105.5 (C4), 118.0 (q, $J_{C-F} = 270$ Hz, CF_3), 159 (q, $J_{C-F} = 43$ Hz, C5), 162.6 (C3), 178.0 (C=O). MS [*m*/*z*(%)] 191 (−OH, 25), 163 (−C(O)OH, 15), 140 (−CF_3, <5), 94 (53), 68 (CF_3, 100). *Anal.* Calcd for $C_7H_6F_3NO_3$: C, 40.2; H, 2.89; N, 6.70; found C, 40.17; H, 3.00; N, 6.65.

3-(5-Trichloromethylisoxazol-3-yl)propanoic acid (6a). To the respective 4,5-dihydroisoxazole **4b** (1 mmol) was added H_2SO_4 98% (2.5 mL) at 50°C. The mixture was stirred for 4 h. After the acidic solution was diluted with cooled water, the precipitated solid was filtered and dried over $CaCl_2$ under vacuum, which gave the pure propanoic acid **6a** (200 mg, 69%). Decomposed at >180°C, ^1H NMR (D_2O, 400 MHz) δ 2.65 (t, $J = 7.2$ Hz, 2H, CH_2), 2.91 (t, $J = 7.2$ Hz, 2H, CH_2), 7.1 (s, 1H, H-4). ^{13}C NMR (D_2O, 100 MHz): δ 21.7 (CH_2), 31.4 (CH_2), 110.1 (C-4), 108.2 (CCl_3), 160.6 (C-5), 160.5 (C-3), 173 (C=O). MS [*m*/*z*(%)] 258 (M^+, <5), 239 (−OH, 10), 221 (−Cl, 100), 68 (23), 55 (14). *Anal.* Calcd for $C_7H_6Cl_3NO_3$: C, 32.53; H, 2.34; N, 5.42; found C, 32.45; H, 2.50; N, 5.4.

3-(2-Carboxyethyl)isoxazole-5-carboxylic acid (7a). A solution of methyl 7,7,7-trichloro-4-methoxy-6-oxo-4-heptenoate **2** (5 mmol) and hydroxylamine hydrochloride (7.5 mmol) in H_2O (10 mL) was stirred for 12 h at reflux. The solution was extracted with $CHCl_3$ (3 × 10 mL). The organic solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the pure propanoic acid **7a** (785 mg, 85%). Decomposed at >200°C, ^1H NMR (DMSO-d_6, 400 MHz): δ 2.65 (s, 2H, CH_2), 2.89 (s, 2H, CH_2), 7.08 (s, 1H, H4), 10.32 (bulky s, OH). ^{13}C NMR

(DMSO-d_6, 100 MHz) δ 21.7 (CH_2), 31 (CH_2), 109.6 (C4), 158.4 (C5), 161.3 (C3), 164.3 (C═O), 173.8 (C═O). *Anal*. Calcd for $C_7H_7NO_5$: C, 48.25; H, 3.81; N, 7.57; found C, 48.2; H, 3.95; N, 7.45.

3-(5-Trifluoromethyl-1*H*-pyrazol-3-yl)propanoic acid (8a). A solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-4-heptenoate **1** (5 mmol) and hydrazine monohydrate (5 mmol) in H_2O (10 mL) was stirred for 12 h at reflux. The solution was extracted with $CHCl_3$ (3 × 10 mL). The organic solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the pure propanoic acid **8a** (975 mg, 93%). mp 88–89°C, ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.61 (t, J = 7.5 Hz, 2H, CH_2), 2.87 (t, J = 7.5 Hz, 2H, CH_2), 6.46 (s, 1H, H-4), 12.27 (s, OH), 13.35 (s, NH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.3 (CH_2), 32.7 (CH_2), 101.5 (C4), 121 (q, J_{C-F} = 268 Hz, CF_3), 141 (q, J_{C-F} = 34 Hz, C5), 144.3 (C3), 173.3 (C═O). MS [m/z(%)] 208 (M^+ 57), 191 (−OH, <5), 163 (−COOH, 100), 143 (−CF_3, 41), 101 (32), 75 ($CH_2CH_2C(O)OH$, 39), 69 (CF_3, 12), 67 (11), 55 (<5). *Anal*. Calcd for $C_7H_7F_3N_2O_2$: C, 40.39; H, 3.39; N, 13.46; found C, 40.4; H, 3.45; N, 13.15.

Alkyl 3-(5-trifluoromethyl-1*H*-pyrazol-3-yl)propanoates 8b and **8c**. A solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-4-heptenoate **1** (5 mmol) and hydrazine monohydrate (5 mmol) in MeOH (10 mL, **8b**) or EtOH (10 mL, **8c**) was stirred for 8 h at 65°C. The solvent was removed, and the residue was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (10 mL). The solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the pure respective alkyl propanoate **8b** (1.0 g, 94%), as red-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.7 (t, J = 6.8 Hz, 2H, CH_2), 3.02 (t, J = 6.8 Hz, 2H, CH_2), 3.72 (s, OMe), 6.35 (s, 1H, H4). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6 (CH_2), 33.27 (CH_2), 52.3 (OMe), 102.3 (C4), 121.4 (q, J_{C-F} = 268 Hz, CF_3), 143.1 (q, J_{C-F} = 38 Hz, C5), 144.1 (C3), 173.6 (C═O). MS [m/z(%)] 222 (M^+, 14), 163 (−C(O)OCH_3, 100), 69 (CF_3, <5). *Anal*. Calcd for $C_8H_9F_3N_2O_2$: C, 43.25; H, 4.08; N, 12.61; found C, 43.4; H, 4.15; N, 12.35.

8c (1.1 g, 77%), as red-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, J = 7.1 Hz, 3H, Me), 2.68 (t, J = 6.8 Hz, 2H, CH_2), 3.01 (t, J = 6.8 Hz, 2H, CH_2), 4.17 (q, 2H, OCH_2), 6.35 (s, 1H, H4). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2 (Me), 20.6 (CH_2), 33.5 (CH_2), 61.4 (OCH_2), 102.3 (C4), 121.5 (q, J_{C-F} = 268 Hz, CF_3), 143.1 (q, J_{C-F} = 37 Hz, C5), 144.1 (C3), 173.3 (C═O). MS [m/z(%)] 236 (M^+, 43), 191 (–OEt, 14), 162 (–C(O)OEt, 100), 149 (32), 69 (CF_3, <5). *Anal*. Calcd for $C_9H_{11}F_3N_2O_2$: C, 45.77; H, 3.81; N, 11.86; found C, 45.85; H, 3.95; N, 11.55.

Alkyl 3-(1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl) propanoates 9b and **9c**. To a stirred solution of methyl 7,7,7-fluoro-4-methoxy-6-oxo-4-heptenoate **1** (5 mmol) in MeOH (5 mL) was added a solution of phenylhydrazine (5 mmol) in MeOH (5 mL) at 0–5°C. Then, the mixture was stirred for 8 h at reflux. After that, the solution was dried with Na_2SO_4 and filtered, and the solvent was removed, which gave the pure respective alkyl propanoate **9b** (1.4 g, 94%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.73 (t, J = 7.2 Hz, 2H, CH_2), 3.02 (t, J = 7.2 Hz, 2H, CH_2), 3.68 (s, 3H, OMe), 6.62 (s, 1H, H4), 7.44 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6 (CH_2), 33.6 (CH_2), 52.1 (Me), 108.3 (C4), 120.1 (q, J_{C-F} = 269 Hz, CF_3), 127.5 (q, J_{C-F} = 39 Hz, C-5), 152 (C3), 173 (C═O). MS [m/z(%)] 298 (M^+, 28), 267 (–OMe, 16), 239 (–C(O)OMe, 100), 77 (Ph, 47). *Anal*. Calcd for $C_{14}H_{13}F_3N_2O_2$: C, 57.69; H, 4.84; N, 8.97; found C, 57.83; H, 4.97; N, 8.8.

For **9a** and **9c** was used a solution of phenylhydrazine hydrochloride (5 mmol) in water or EtOH repeating the same procedure. **9c** (1.1 g, 68%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.2 (t, 3H, Me), 2.58 (t, J = 7.5 Hz, 2H, CH_2), 2.96 (t, J = 7.4 Hz, 2H, CH_2), 4.1 (q, 2H, OCH_2), 6.45 (s, 1H, H4), 7.45 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14 (Me), 21.4 (CH_2), 32.7 (CH_2), 60.8 (OCH_2), 103.4 (C4), 121.3 (q, J_{C-F} = 269 Hz, CF_3), 142.7 (q, J_{C-F} = 38 Hz, C-5), 125.3–138.6 (m, 5H, Ph), 143.8 (C3), 171.6 (C═O). MS [m/z(%)] 312 (M^+, 64), 267 (–OEt, 25), 239 (–C(O)OEt, 100), 77 (Ph, 35).$C_{15}H_{15}F_3N_2O_2$: C, 56.38; H, 4.39; N, 9.39; found C, 56.6; H, 4.57; N, 9.3.

3-(2-Carboxyethyl)-1*H*-pyrazole-5-carboxylic acid (10a). A solution of methyl 7,7,7-trichloro-4-methoxy-6-oxo-4-heptenoate **2** (5 mmol) and hydrazine monohydrate (6 mmol) in H_2O (5 mL) was stirred for 8 h at reflux. The solution was extracted with $CHCl_3$ (3 × 10 mL). The organic solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the pure propanoic acid **10a** (625 mg, 68%). Decomposed at >150°C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.59 (t, J = 7.5 Hz, 2H), 2.83 (t, J = 7.5 Hz, 2H), 6.5 (s, 1H, H4), 11.2 (bulky s, 3H, NH, OH). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3 (CH_2), 33.1 (CH_2), 106.2 (C4), 140.6 (C5), 146.4 (C3), 162.4 (C═O), 173.4 (C═O). *Anal*. Calcd for $C_7H_8N_2O_4$: C, 45.66; H, 4.38; N, 15.21; found C, 45.45; H, 4.64; N, 15.5.

Alkyl 3(5)-(3-alkoxy-3-oxopropyl)-1*H*-pyrazole-5(3)-carboxylates 10b and **10c**. A solution of methyl 7,7,7-trichloro-4-methoxy-6-oxo-4-heptenoate **2** (5 mmol) and hydrazine monohydrate (5 mmol) in MeOH (10 mL, **10b**) or EtOH (10 mL, **10c**) was stirred for 8 h at reflux. The solvent was removed, and the residue was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (10 mL). The solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the respective alkyl carboxylate. The products were purified by recrystallization in hexane. **10b** (985 mg, 93%). mp 60–61°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.7 (t, J = 7 Hz, 2H, CH_2), 3.03 (t, J = 7.1 Hz, 2H, CH_2), 3.7 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.62 (s, 1H, H4). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (CH_2), 33.7 (CH_2), 52.4 (2OMe), 107.1 (C4), 141.4 (C5), 146.5 (C3), 162.6 (C═O), 173.6 (C═O). MS [m/z(%)] 212 (M^+, 20), 181 (–OMe, 22), 152 (–C(O)OMe, 29), 121 (–OMe, 100), 94 (–C(O)OMe, 5), 79 (17), 66 (23). *Anal*. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20; found C, 50.92; H, 5.73; N, 13.15.

10c (1.05 g, 87%). mp 87–88°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, 3H, J = 7.1 Hz, Me), 1.28 (t, 3H, J = 7.1 Hz, Me), 2.61 (t, 2H, J = 7.1 Hz, CH_2), 2.96 (t, 2H, J = 7.1 Hz, CH_2), 4.07 (t, 2H, J = 7.1 Hz, OCH_2), 4.28 (q, 2H, J = 7.1 Hz, OCH_2), 6.55 (s, 1H, H4), 10.03 (bulky s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (Me), 14.2 (CH_3), 21.5 (CH_2), 33.5 (CH_2), 60.8 (OCH_2), 61.0 (OCH_2), 106.7 (C-4), 140.7 (C-5), 146.7 (C-3), 161.4 (C═O), 172.9 (C═O). MS [m/z(%)] 240 (M^+ 11), 195 (–OEt), 167 (–CO_2Et, 33), 149 (53), 121 (100), 79 (23), 66 (24), 53 (24). *Anal*. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66; found C, 55.17; H, 6.77; N, 11.60.

Alkyl 3-(3-methoxy-3-oxopropyl)-1-phenyl-1*H*-pyrazole-5-carboxylates 11b and **11c**. A solution of methyl 7,7,7-trichloro-4-methoxy-6-oxo-4-heptenoate **2** (5 mmol) phenylhydrazine hydrochloride (5 mmol) in MeOH (10 mL, **11b**) or EtOH (10 mL, **11c**) was stirred for 30 min at 25°C and after for 8 h at reflux. The solvent was removed, and the residue was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (10 mL). The solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the respective alkyl carboxylate. The products were purified by recrystallization in hexane. **11b** (1,4 g, 94%). mp 44–45°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (t, J = 7.5 Hz, 2, CH_2), 3.05 (t, J = 7.5 Hz, 2H, CH_2), 3.71 (s, 3H, OMe), 3.78 (s, 3H, OMe), 6.85 (s, 1H, H4), 7.43 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.5 (CH_2), 33.6 (CH_2), 51.9 (OMe), 52.1 (OMe), 111.5 (C4), 126–140.3 (Ph), 133.6 (C5), 151.7 (C3), 159.7 (C═O), 173.4

(C═O). MS [*m*/*z*(%)] 288 (M^+, 32), 257 (–OMe, 14), 229 (–C(O)OMe, 100), 77 (Ph, 23). *Anal*. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72; found C, 62.55; H, 5.75; N, 9.85.

11c (1.47 g, 93%). mp 59–60°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.2 (t, 3H, Me), 1.36 (t, 3H, Me), 2.58 (t, J = 7.5, 2H, CH_2), 2.93 (t, J = 7.5 Hz, 2H, CH_2), 4.08 (q, J = 7.2 Hz, 2H, OCH_2), 4.38 (q, J = 7.2 Hz, 2H, OCH_2), 6.73 (s, 1H, H4), 7.43 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.3 (Me), 14.6 (Me), 21.7 (CH_2), 33.6 (CH_2), 61.0 (OCH_2), 61.2 (OCH_2), 107.9 (C4), 126.1–143.9 (Ph), 139.1 (C5), 144.2 (C3), 162.7 (C═O), 171.9 (C═O). MS [*m*/*z* (%)] 316 (M^+, 53), 271 (–OEt, 50), 243 (–CO_2 Et, 49), 197 (100), 171 (57), 77 (Ph, 48). *Anal*. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85; found C, 64.55; H, 6.45; N, 8.75.

Methyl 3-(1-carbamoyl-5-hydroxy-5-trifluoro [chloro]methyl-4,5-dihydro-1*H*-pyrazol-3-yl)propanoates 13b and **14b**. A solution of methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoates **1** or **2** (5 mmol), semicarbazide hydrochloride (6 mmol), and pyridine (6 mmol) in MeOH (3 mL) : H_2O (9 mL) was stirred for 18 h at 65°C. MeOH was removed, and aqueous residue was extracted with $CHCl_3$ (3 × 10 mL) and washed with HCl 10% solution (10 mL). The solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the respective alkyl propanoates **13b** and **14b**. The products were purified by recrystallization in hexane. **13b** (1.4 g, 98%). mp 106–107°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.66 (bulky s, 4H, $2CH_2$), 3.13 (d, J = 19 Hz, 1H, H4), 3.3 (d, J = 19 Hz, 1H, H4), 3.7 (s, 3H, OMe), 5.95 (s, 2H, NH_2), 6.32 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.93 (CH_2), 30.05 (CH_2), 46.59 (C4), 52.01 (Me), 90.73 (q, J = 34 Hz, C-5), 123.25 (q, J = 286 Hz, CF_3), 154.98 (C3), 156.75 ($CONH_2$), 172.66 (CO_2Me). MS [*m*/*z*(%)] 283 (M^+, 6), 239 (–$CONH_2$, <44), 222 (–OH, 17), 209 (OMe, 17), 191 (-CO_2 Me), 171 (–CF_3, 76), 162 (52), 139 (100), 111 (61), 97 (57), 69 (CF_3, 12), 55 (19). *Anal*. Calcd for $C_9H_{12}F_3N_3O_4$: C, 38.17; H, 4.27; N, 14.84; found C, 38.37; H, 4.18; N, 14.45.

14b (1.58 g, 95%). mp 114–115°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.68 (s, 4H, $2CH_2$), 3.28 (d, J = 19 Hz, 1H, H4), 3.56 (d, J = 19 Hz, 1H, H4), 3.7 (s, 3, OMe), 7.60 (s, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.0 (CH_2), 30.0 (CH_2), 49.2 (C4), 51.9 (OMe), 100.6 (C5), 104.2 (CCl_3), 157.3 (C3), 157.8 ($CONH_2$), 172.3 (CO_2Me). *Anal*. Calcd for $C_9H_{12}Cl_3N_3O_4$: C, 32.50; H, 3.64; N, 12.64; found C, 31.88; H, 3.54; N, 12.85.

Methyl 3-(1-carbamothioyl-5-hydroxy-5-(trihalome thyl)-4,5-dihydro-1*H*-pyrazol-3-yl)propanoates 15b, **16b**. A solution of methyl 7,7,7-trihalo-4-methoxy-6-oxo- 4-heptenoate **1** or **2** (5 mmol) and thiosemicarbazide (6 mmol) in MeOH (10 mL) was stirred for 18 h at 65°C. The solvent was removed, and the residue was dissolved in $CHCl_3$ (20 mL) and washed with H_2O (10 mL). The solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the methyl propanoates **15b** and **16b**. The products were purified by recrystallization in hexane. **15b** (1.15 g, 76%). mp 111–112°C, ^{1}H NMR ($CDCl_3$, 400 MHz), δ 2.68 (s, 4H, $2CH_2$), 3.28 (d, J = 19 Hz, 1H, H4), 3.37 (d, J = 19 Hz, 1H, H4), 3.7 (s, 3H, OMe), 6.27 (s, OH), 7.08 (s, NH_2), 7.93 (s, NH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (CH_2), 29.8 (CH_2), 47.1 (C4), 52.1 (Me), 92.5 (q, J = 34 Hz, C5), 123.2 (q, J = 290 Hz, CF_3), 157.3 (C3), 172.2 (C═O), 177.1 (C═S). MS [*m*/*z*(%)] 299 (M^+, 91), 282 (–NH_2, <5), 268 (–S, 14), 238 (–$CSNH_2$), 222 (–H_2O, <5), 208 (–OMe, 22), 180 (–HCO_2Me), 171 (–CF_3, 71), 139 (100), 97 (45), 69 (CF_3, 17), 60 (52), 55 (17). *Anal*. Calcd for $C_9H_{12}F_3N_3O_3S$: C, 36.12; H, 4.27; N, 14.84; found C, 38.37; H, 4.18; N, 14.45.

16b (1.30 g, 73%). mp 131–132°C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.7 (m, 4H), 3.36 (d, J = 19 Hz, 1H, H-4), 3.62 (d, J = 19 Hz, 1, H4), 3.69 (s, 3H, OMe), 9.0 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.3 (CH_2), 30.0 (CH_2), 50.0 (C-4), 52.2 (OMe), 102.4 (C5), 104.3 (CCl_3), 159.4 (C3), 172.4 (C═O), 179.2 (C═S). *Anal*. Calcd for $C_9H_{12}Cl_3N_3O_3S$: C, 31.01; H, 3.47; N, 12.05; found C, 31.06; H, 3.54; N, 12.05.

Methyl 3-(3-methoxy-3-oxopropyl)-5-trifluoro[chloro] methyl-1*H*-pyrazole-1-carboxylate 17b, **18b**. A solution of methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoate **1** or **2** (2 mmol) and hydrazine methyl carboxylate (2.4 mmol) in methanol (10 mL) was stirred for 18 h at 25°C. The solvent was removed, and the residue was dissolved in $CHCl_3$ (10 mL) and washed with water (10 mL). The solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the pure respective methyl propanoate **17b** (480 mg, 79%). mp 81–82°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.68 (s, 4H, $2CH_2$), 3.16 (d, $J_{H–H}$ = 19.1 Hz, 1H, H4), 3.30 (d, $J_{H–H}$ = 19.1 Hz, 1H, H4), 3.70 (s, 3H, OMe), 3.89 (s, 3H, OMe). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7 (CH_2), 30.3 (CH_2), 45.6 (C4), 51.9 (OMe), 53.8 (OMe), 90.7(q, $^2J_{C–F}$ = 34 Hz, C5), 123 (q, $J_{C–F}$ = 286.5 Hz, CF_3), 153.8 (C3), 156.2 (NCO_2Me), 172.4 (CO_2Me). MS [*m*/*z*(%)] 298 (M^+, <5), 280 (40), 221 (49), 177 (100), 125 (90), 69 (CF_3, 15), 59 (37). *Anal*. Calcd for $C_{10}H_{13}F_3N_2O_5$: C, 40.28; H, 4.39; N, 9.39; found C, 40.4; H, 4.5; N, 9.65.

18b (485 g, 70%). mp 73–74°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70 (s, 4H, $2CH_2$), 3.28 (d, $J_{H–H}$ = 19.11 Hz, 1H, H4), 3.56 (d, $J_{H–H}$ = 19.11 Hz, 1H, H4), 3.70 (s, 3H, OMe), 3.88 (s, 3H, OMe), 6.84 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (CH_2), 30.3 (CH_2), 48.5 (C4), 51.9 (OMe), 53.7 (OMe), 100.2 (C5), 103.5 (CCl_3), 155.0 (C3), 158.3 (NCO_2Me), 172.3 (CO_2Me). MS [*m*/*z*(%)] 348 (M^+, <5), 319 (M^+ + 4-Cl, <5), 317 (M^+ + 2-Cl, 11), 315, (M^+ – Cl, 11), 283 (<5), 229 (60), 197 (42), 153 (66), 111 (100), 59 (26). *Anal*. Calcd for $C_{10}H_{13}Cl_3N_2O_5$: C, 34.56; H, 3.77; N, 8.06; found C, 34.4; H, 3.90; N, 8.22.

Methyl 3-{2-[5-hydroxi-3-(3-metoxy-3-oxopropyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-yl]-6-(tri fluo romethyl) pyrimidin-4-yl)propanoate (19b). A solution of methyl 7, 7,7-fluoro-4-methoxy-6-oxo-4-heptenoate **1** (4 mmol) and aminoguanidine hydrochloride (2 mmol) in acetonitrile (10 mL) was stirred for 24 h at 80°C. After the solvent was removed and the residue was dissolved in chloroform (20 mL) and washed with water (2 × 10 mL), the organic solution was dried with Na_2SO_4, and the solvent was evaporated, which gave the bismethyl propanoate **19b**. The product was purified by recrystallization in hexane. **19b** (530 mg, 56%). mp 89–90°C, ^{1} NMR ($CDCl_3$, 400 MHz) δ 2.74 (m, 6H, $3CH_2$), 3.09 (m, 2H, CH_2), 3.22 (d, $J_{H–H}$ = 19.0 Hz, 1H, H4), 3.37 (d, $J_{H–H}$ = 19.0 Hz, 1H, H4), 3.65 (s, 3H, OMe), 3.66 (s, 3H, OMe), 7.0 (s, 1H, H pyrimidine). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (CH_2), 30.4 (CH_2), 31.1 (CH_2), 32.3 (CH_2), 46.4 (C-4), 51.9 (2 OMe), 92.0 (q, $^2J_{C–F}$ = 33.7 Hz, C-5), 108.4 (q, $^3J_{C–F}$ = 2.6 Hz, C4′), 120.1 (q, $^1J_{C–F}$ = 275.0 Hz, CF_3), 123.4 (q, $^1J_{C–F}$ = 288.0 Hz, CF_3), 155.0 (q, $^2J_{C–F}$ = 36.4 Hz, C-5′), 156.0 (C-3), 158.8 (C-1′), 172.5 (C═O), 172.6 (C═O), 172.9 (C-3′). MS [*m*/*z*(%)] 472 (M^+, 42), 441 (–OCH_3, 39), 403 (–CF_3, 95), 363 (71), 339 (100), 190 (57). *Anal*. Calcd for $C_{17}H_{18}F_6N_4O_5$: C, 43.23; H, 3.84; N, 11.86; found C, 43.4; H, 3.92; N, 11.72.

Methyl 3-{2-[3-(3-metoxy-3-oxopropyl)-5-trifluoromethyl-1*H*-pyrazol-1-yl]-6-(trifluoro methyl)pyrimidin-4-yl)propanoate (20b). To the product **19b** (1 mmol) was added concentrated sulfuric acid 98% (3 mL). The mixture was stirred for 4 h at 40°C, the acidic solution was diluted with cooled water, and the precipitate was

filtered and dried over calcium chloride under vacuum, which gave the pure methyl propanoate **20b** (390 mg, 86%). mp 98°C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.78 (t, 2H, J_{H-H} = 7.4 Hz, CH_2), 2.96 (t, 2H, J_{H-H} = 7.4 Hz, CH_2), 3.11 (t, 2H, J_{H-H} = 7.4 Hz, CH_2), 3.26 (t, 2H, J_{H-H} = 7.0 Hz, CH_2), 3.68 (s, 3H, OMe), 3.72 (s, 3H, OMe), 6.82 (s, 1H, H4, pyraz), 7.53 (s, 1H, H4 pyrym). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (CH_2), 31.0 (CH_2), 32.5 (CH_2), 32.9 (CH_2), 51.8 (OMe), 51.9 (OMe), 114.8 (C-4), 114.8 (C4), 119.2 (q, $^1J_{C-F}$ = 268.0 Hz, CF_3), 120.0 (q, $^1J_{C-F}$ = 275.0 Hz, CF_3), 134.5 (q, $^2J_{C-F}$ = 40.0 Hz, C-5), 154.3 (C3), 155.7 (C-1), 156.6 (q, $^2J_{C-F}$ = 37.0 Hz, C-5), 172.5 (C=O), 172.9 (2C=O), 174.7 (C-3). MS [*m*/*z*(%)] 454 (M^+, 30), 423 (–OCH_3, 33), 395 (–C(O)OCH_3, 39), 383 (–CF_3, 100), 335 (68), 315 (34), 289 (24), 173 (13), 78 (13), 59 (42). *Anal*. Calcd for $C_{17}H_{16}F_6N_4O_4$: C, 44.94; H, 3.55; N, 12.33; found C, 45.15; H, 3.70; N, 12.42.

CONCLUSIONS

This work presents a convenient method for obtaining novel glutamate-like 3-(azolyl)propanoates from renewable precursor LA and demonstrates that methyl 1,1,1-trihalo-4-methoxy-6-oxo-4-heptenoate compounds are versatile substrates in heterocyclic chemistry. The high synthetic potential of these accessible reagents has numerous applications in the synthesis of heterocyclic products, with structures that have been determined by NMR experiments and X-ray diffraction analysis. Furthermore, we obtained important dicarboxyl derivatives from cyclocondensation between methyl 1,1,1-trichloro-4-methoxy-6-oxo-4-heptenoate and 1,2-dinucleophilic hydroxylamine and hydrazine. These derivatives show interesting nootropic activity in rats.

Acknowledgments. Financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS grant PqG 06/2010 no 1016236) is acknowledged. The Bruker X-ray diffractometer was funded by infrastructure grant from the Financiadora de Estudos e Projetos (CT-INFRA/FINEP). We thank CNPq for fellowships.

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