DOI: 10.1002/adsc.201000142

Michael Reaction of Nitroalkanes with β-Nitroacrylates under a Solid Promoter: Advanced Regio- and Diastereoselective Synthesis of Nitro-Functionalized α,β-Unsaturated Esters and 1,3-Butadiene-2-carboxylates

Alessandro Palmieri,[a] Serena Gabrielli,[a] and Roberto Ballini[a,*]

[a] "*Green Chemistry Group*", School of Sciences and Technologies, Chemistry Division, University of Camerino, via S. Agostino 1, 62032 Camerino, Italy
Fax: (+39)-(0)737-402-297; phone: (+39)-(0)737-402-270; e-mail: roberto.ballini@unicam.it

Received: February 23, 2010; Published online: June 8, 2010

Abstract: A new class of nitro-functionalized α,β-unsaturated esters has been prepared by a regio- and diastereoselective Michael addition of nitroalkanes to β-nitroacrylates, performed at room temperature, under carbonate on polymer as promoter, and in the presence of ethyl acetate as eco-friendly solvent. Moreover, by the modular choice of the reaction conditions the method allows the synthesis of 1,3-butadiene-2-carboxylates.

Keywords: 1,3-butadiene-2-carboxylates; Michael addition; β-nitroacrylates; nitroalkanes; solid-supported promoter; α,β-unsaturated esters

Introduction

One of the main issues in today's world is the development of new eco-sustainable processes and, in particular in the field of organic chemistry, this issue is undoubtedly the production of new fine chemicals. In this context, a very important answer is achieved by the use of solid-supported reagents (SSR) which, thanks their peculiarity, represent a viable and convenient alternative to traditional synthetic processes realized under homogeneous conditions.[1] In addition, solid promoters are often able to produce a consistent increase in the reactivity and selectivity of the related processes so that their utilization becomes mandatory for a successful synthetic procedure. On this basis, conjugate addition of nucleophiles to electron-poor alkenes represents a test benchmark for a considerable number of solid promoters that may work either by activating the nucleophilic reagent (basic supports) or the alkene moiety (acidic supports).[2] Among all the electron-poor olefins, nitroalkenes are surely the strongest Michael acceptors[3] and, in particular, β-nitroacrylates show fascinating ability as precursors of a variety of fine chemicals.[4]

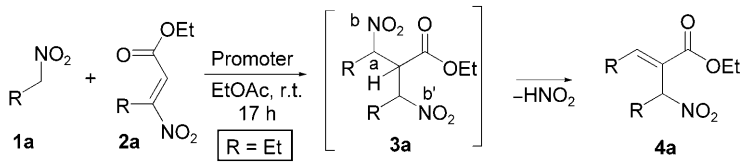
α,β-Unsaturated esters are useful chemical entities in organic synthesis[5] which can be further functionalized by Michael or Diels–Alder reactions, giving access to important targets of considerable interest, mainly in the synthesis of natural products.[6] α,β-Unsaturated esters are usually accessible through (i) Knovenagel condensation of active methylene esters with aldehydes,[7] (ii) condensation of alkyl acetates with aldehydes followed by dehydration,[8] (iii) Reformastsky reaction with aldehydes followed by elimination of the resultant hydroxy esters,[9] or (iv) Wadsworth-Emmons olefination of carbonyl derivatives.[10] However, within this scenario, new efficient procedures for their synthesis and the need for new classes of α,β-unsaturated esters, particularly for the polyfunctionalized ones, would be welcome, especially taking into account the advantages offered by the syntheses on solid supports.

Results and Discussion

For many years, we have been investigating the use of unconventional reaction media that could replace harmful reaction conditions while maintaining the highest chemical efficiency.[11] As a continuation of our interest in the chemistry of nitro compounds and in the use of solid bases, we have investigated the Michael addition of nitroalkanes to β-nitroacrylates, for the production of a new class of nitro-functionalized α,β-unsaturated esters, promoted by carbonate on polymer.[12]

As reported in Table 1, firstly we tested, as a sample reaction, the conjugate addition of 1-nitropro-

Table 1. Screening of different promoters.



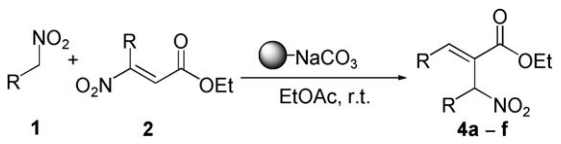
Promoter	g (mequiv. of base)	Yield [%][a] of **4a**	*dr* (*E*/*Z*)
Carbonate on polymer support	0.286 (1)	81	96:4
Amberlyst A21	1 (~2.5)	35	92:8
TBD on polymer	0.676 (1)	33	93:7
Basic Al_2O_3	1	traces	
Na_2CO_3	0.106 (1)	traces	

[a] Yield of pure isolated product.

pane **1a** to the acrylate **2a** under a variety of basic solid promoters and in the presence of ethyl acetate as eco-friendly solvent.[13]

The reaction allows, *via* elimination of nitrous acid from the adduct **3a**, the formation of the nitro α,β-unsaturated ester **4a** as a diastereomeric mixture (with high prevalence of the *E* isomer, >90%) and the best yields (81%) were obtained by using carbonate on polymer as promoter. It is evident that from **3a** two different eliminations could be observed, one involving the hydrogen *a* and the nitro group *b*, the other one the elimination of the hydrogen *a* and the nitro group *b′*. However, from this point of view, due to the same nature of the alkyl group (R = Et) in the nitroalkane **1a** and in the β-nitroacrylate **2a**, the adduct **3a** produces the same α,β-unsaturated ester **4a**. In order to verify the generality of our method, we extended the use of carbonate on polymer to a variety of other substrates and, as reported in Table 2, good yields were obtained even with functionalized nitroalkanes, so that polyfunctionalized α,β-unsaturated esters can be synthesized under very mild reaction conditions.

Table 2. Michael reaction for the synthesis of unsaturated esters **4a–f**.



Entry	R	Yield [%][a] of **4**	Reaction time (h)
a	Et	81	18
b	*n*-Bu	80	17
c	*n*-C_5H_{11}	80	17
d	$Ph(CH_2)_2$	81	17
e	$MeOCO(CH_2)_4$	70	18
f	$AcO(CH_2)_3$	55	19

[a] Yield of pure isolated product.

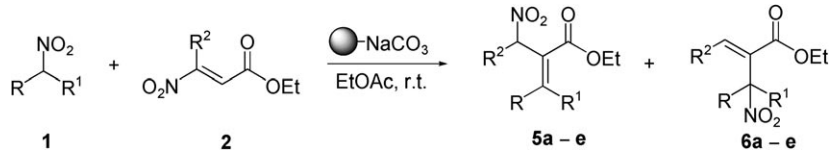
The reaction was then applied to the conjugate addition of nitroalkanes **1** possessing the alkyl group R^1 different from the alkyl group R^2 in the β-nitroacrylate **2**, and a mixture of regioisomers **5** and **6** was obtained, in which the elimination of nitrous acid derived from the nitro group, bearing to the incoming nitroalkane **1**, is strongly favoured (**5**/**6** > 3) (Table 2).

The trend of the reaction can be explained by the possible mechanism of the conjugate addition of **1** to **2** (Scheme 1), in which the nitronate anion **A**, generated by deprotonation of the nitroalkane **1**, reacts with β-nitroacrylate **2** affording the Michael adduct **B**, which allows (*path a*) an intramolecular substitution (similarly to those described by Gomez-Sanchez et al.[14] for analogous compounds) and formation of the isoxazole *N*-oxide **C**, that after protonation (giving **D**) and intramolecular elimination, affords the nitronate form **E** which is prone to convert into the regioisomer **5**. The formation of regioisomeric product **6**, can be rationalized by the competitive *path b*, in which the Michael adduct **B** is involved in an intramolecular acid-base equilibrium, giving the regioisomeric nitronate anion **F**. This intermediate, as above reported for the corresponding adduct **B**, gives the intramolecular substitution with the formation of heterocycle **H**, which affords, similarly as reported for the intermediate **C**, the products **6**.

The distribution of the products, suggests that the reaction is under kinetic control, in which the intramolecular substitution rate is higher with the respect to the acid-base thermodynamic equilibrium rate; or else the distribution of the products **5** and **6** should be around 1:1. In addition the formation, exclusively, of the regioisomer **6**, starting from secondary nitroalkanes, is explained by their incompatibility with the *path b* (see structures **H–J**).

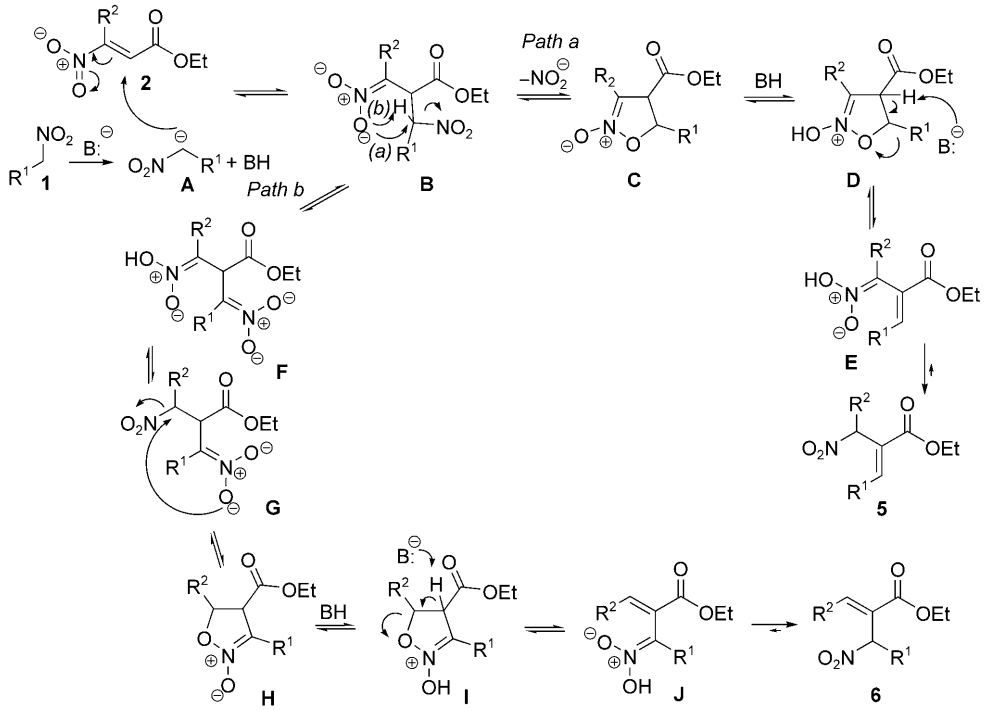
It is important to point out that synthetic potential of the compounds **4–6** is strongly increased by the presence of the nitro group, since it can favour the generation of stabilized carbanions under basic condi-

Table 3. Michael reaction for the synthesis of unsaturated esters **5** and **6a–e**.



Entry	R	R^1	R^2	Yield [%][a] of **5**+**6** (ratio)[b]	Reaction time [h]
a	Me	Me	*n*-C_5H_{11}	63 (100:0)	48
b	H	Et	*n*-C_5H_{11}	62 (75:25)	18
c	H	*n*-C_5H_{11}	Et	76 (80:20)	17
d	H	*n*-C_5H_{11}	Me	55 (75:25)	17
e	H	$Ph(CH_2)_2$	Me	72 (80:20)	17

[a] Yield of pure isolated product.
[b] Regioisomeric ratio was defined by ^{1}H NMR studies.

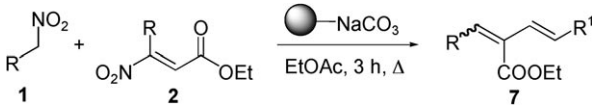


Scheme 1. Proposed reaction mechanism.

tions and, consequently, the formation of new C/C bonds.[15] Moreover, the nitro group can be converted into a variety of other functionalities.[16]

As a further development of our method, we found a new procedure for the synthesis of 1,3-butadiene-2-carboxylates, simply by a small modification of the reaction conditions. In fact, as reported in Table 4, the conjugate addition of **1** to **2** under refluxing EtOAc, and in the presence of an excess (2.5 equivalents) of carbonate on polymer, allows a double elimination of nitrous acid with the formation of the dienes **7** in satisfactory to good overall yields (64–76%).

Table 4. One-pot preparation of conjugate dienes **7a–d**.



Entry	R	R^1	Yield [%][a] of **7** (*EE*:*ZE* ratio)
a	Et	Me	75 (80:20)
b	*n*-C_5H_{11}	*n*-C_4H_9	76 (80:20)
c	*n*-C_6H_{13}	*n*-C_5H_{11}	73 (80:20)
d	$Ph(CH_2)_2$	$PhCH_2$	64 (75:25)

[a] Yield of pure isolated product.

In addition, although the presence of two conjugate double bonds, in the final compounds **7** could allow four different diastereomers, only two of them were observed. On the basis of NMR and NOE studies on the compound **7b** the configurations of the diastereomers were defined as *E/E* and *Z/E*, with a high predominance for the former. In particular, the configuration of the C-1′/C-2′ double bound was assigned on the basis of H-1′,H-2′ coupling constant (15.8 Hz for both the diastereomers), while the configuration of C-2/C-3 double bond was defined by the NOE correlation between H-4 and protons H-1′ and H-2′ (Figure 1).

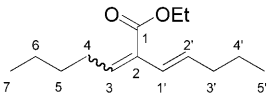


Figure 1. Compound **7b**.

The stereochemistry was confirmed by comparison of the ^{1}H NMR spectra of **7a** with those reported in literature.[17]

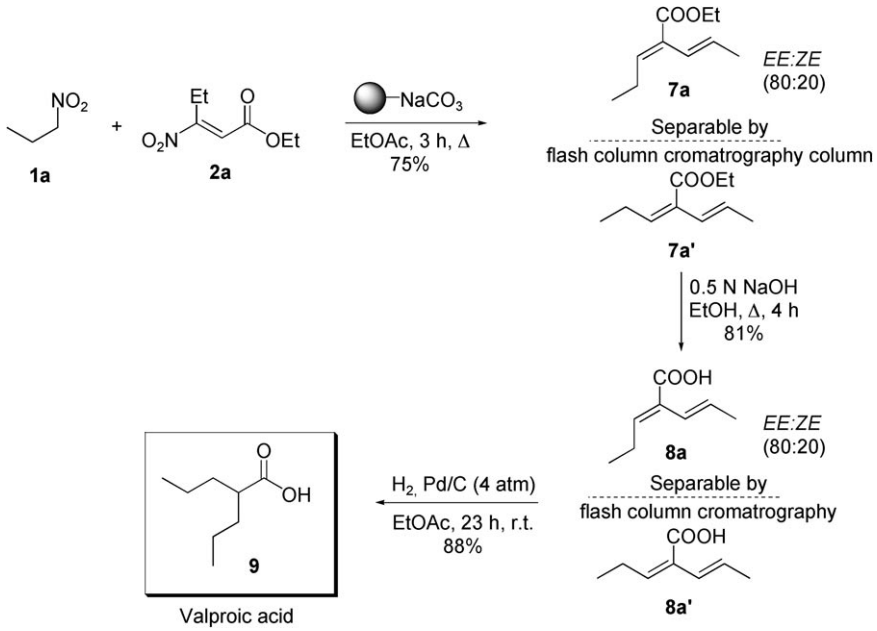
1,3-Butadiene-2-carboxylates **7** are a very important class of molecules since they have been throughly studied in recent years as potential starting materials for organic synthesis, in particular for various [4+2]cycloadditions, and a number of these compounds have proven to be valuable precursors for functionalized alkyl 1-cyclohexene-1-carboxylates,[18–22] naturally occurring cyclopentanoid terpenic acids,[23] biologically important litsenolides,[24] and α-alkylidenebutyrolactone natural products.[25]

Moreover, our procedure can be applied to a new, efficient preparation of valproic acid (VPA) **9** and its main metabolite (*E*)-2-[(*E*)-prop-1-enyl]pent-2-enoic acid **8a** (Scheme 2).

Valproic acid is a widely used drug for the treatment of epilepsy.[26,27] Metabolism of VPA occurs mainly in the liver and several complex metabolic pathways have been presented and of great interest are a series of diunsaturated metabolites.[28–30] However one of these, the compound **8a**, is the most frequently found in patient serum and urine samples[31] and it possesses anticonvulsant activity in mice.[32,33]

In order to undertake metabolic and pharmacokinetic studies of **8a**, methods of syntheses that would yield significant quantities of this diene, were required.[17]

Thus, our synthetic approach for the synthesis of compound **9** and its metabolite **8a**, consists in a three-step pathway. The first step involves the reaction of 1-nitropropane **1a** with β-nitroacrylate **2a**, allowing the formation of the corresponding diunsaturated ester **7** [mainly isolated as a pair of diastereomers **7a** (*EE*) and **7a′** (*ZE*), in 80:20 ratio]. These diastereomers can be separated by flash chromatography, or alternatively used as mixture to be converted into the corresponding pair of diunsaturated acids (**8a** and **8a′**). This step, performed under refluxing 0.5 N aqueous solution of NaOH and in the presence of ethanol, affords (after four hours) the diastereomeric acids **8a** and **8a′** in 81% yield. It is important to point out that our synthesis shows remarkable advantages with respect to those reported in literature,[17] where the same transformation was realized, after refluxing for 48 h, in 52% yield. The diastereomeric acids **8** can be



Scheme 2. Synthetic pathway to valproic acid (**9**) and its metabolite **8a**.

easily separated by flash chromatography (hexanes-ethyl actetate 80:20) with the isolation of metabolite **8a** in 65% yield. Alternatively, the mixture can be subject to catalytic hydrogenation with the formation of valproic acid **9** in 88% yield.

Finally, we focused our investigation on the recovery and reuse of the promoter, after reactivation,[34] in the model reaction (**1a**+**2a**→**4a**), with the following results: reaction 81%, 1st recycle 76%, 2nd recycle 75%.

Conclusions

In conclusion, we have found a new approach for the regio- and diastereoselective synthesis of nitro-functionalized α,β-unsaturated esters under eco-friendly conditions (due to the use of eco-compatible solvent, solid and recycling promoter, and room temperature). In addition, by the modular choice of the reaction conditions, even 1,3-butadiene-2-caroboxylates can be obtained in high diastereoselectivity. Finally, the efficient syntheses of both valproic acid and its main metabolite have been realized as a representative application of our results.

Experimental Section

General Remarks

General ^{1}H NMR spectra were recorded at 400 MHz on a Varian Mercury Plus 400 in $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ as solvent. Micro analyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. IR spectra were recorded with a Perkin–Elmer Paragon 500 FT-IR. GLC analyses were performed with an SE-54 fused silica capillary column (25 m, 0.32 mm internal diameter), FID detector and nitrogen as carrier gas.GS-MS analyses were carried out by means of the EI technique (70 eV).

Typical Procedure for the Synthesis of Compounds 4, 5 and 6

To a stirred solution of the opportune nitroalkane **1** (1.1 mmol) and the β-nitroacrylate **2** (1 mmol) in ethyl acetate (2 mL), the carbonate on polymer support (286 mg, 1 mmol) was added. The resulting heterogeneous mixture was stirred at room temperature for the required time (the reaction progress was monitored by TLC, Table 2), then the promoter was filtered off, washing with EtOAc. Finally the filtrate was concentrated under vacuum to give the crude products **4–6** which were purified by flash chromatography column (hexane-ethyl acetate).

(*E*)-Ethyl 2-(1-nitropropyl)pent-2-enoate (4a): Colorless oil. IR (neat): ν = 1238, 1365, 1552, 1647, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 3H, *J* = 7.7 Hz), 1.11 (t, 3H, *J* = 7.7 Hz), 1.26 (t, 3H, *J* = 7.3 Hz), 2.04–2.40 (m, 3H), 2.48–2.61 (m, 1H), 4.18 (q, 2H, *J* = 7.3 Hz), 5.14 (dd, 1H, *J* = 6.0, 9.0 Hz), 7.14 (t, 1H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9, 13.0, 14.2, 22.3, 24.5, 61.3, 83.7, 126.7, 151.1, 165.2; EI-MS (70 eV): *m/z* = 186, 169, 141, 123, 95 (100), 81, 67, 55, 41, 29; anal. calcd. for $C_{10}H_{17}NO_4$ (215.25): C 55.80, H 7.96, N 6.51; found: C 55.99, H 8.03, N 6.44.

(*E*)-Ethyl 2-(1-nitropentyl)hept-2-enoate (4b): Colorless oil. IR (neat): ν = 1240, 1368, 1552, 1648, 1717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.92 (m, 6H), 1.10–1.51 (m, 8H), 1.23 (t, 3H, *J* = 7.3 Hz), 1.98–2.11 (m, 1H), 2.12–2.33 (m, 2H), 2.41–2.55 (m, 1H), 4.15 (q, 2H, *J* = 7.3 Hz), 5.18 (dd, 1H, *J* = 6.0, 9.0 Hz), 7.10 (t, 1H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.2, 22.6, 22.7, 28.6, 28.7, 30.7, 30.9, 61.3, 82.5, 127.4, 149.9, 165.2; EI-MS (70 eV): *m/z* = 225, 179, 151, 123, 109, 95 (100), 81, 67, 55, 41, 29; anal. calcd. for $C_{14}H_{25}NO_4$ (271.35): C 61.97, H 9.29, N 5.16; found: C 62.09, H 9.40, N 5.08.

(*E*)-Ethyl 2-(1-nitrohexyl)oct-2-enoate (4c): Colorless oil. IR (neat): ν = 1238, 1367, 1552, 1649, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–0.93 (m, 6H), 1.17–1.38 (m, 10H), 1.26 (t, 3H, *J* = 7.3 Hz), 1.42–1.57 (m, 2H), 2.00–2.14 (m, 1H), 2.15–2.35 (m, 2H), 2.43–2.56 (m, 1H), 4.19 (q, 2H, *J* = 7.3 Hz), 5.21 (dd, 1H, *J* = 6.0, 8.6 Hz), 7.14 (t, 1H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.3, 22.5, 22.6, 26.2, 28.3, 29.0, 31.2, 31.6, 31.7, 61.4, 82.5, 127.4, 150.0, 165.2; EI-MS (70 eV): *m/z* = 253, 207, 179, 137, 123, 109 (100), 95, 81, 67, 55, 41, 29; anal. calcd. for $C_{16}H_{29}NO_4$ (299.41): C 64.18, H 9.76, N 4.68; found: C 64.31, H 9.65, N 64.19.

(*E*)-Ethyl 2-(1-nitro-3-phenylpropyl)-5-phenylpent-2-enoate (4d): Colorless oil. IR (neat): ν = 1246, 1369, 1551, 1603, 1648, 1712, 3028, 3063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, 3H, *J* = 7.3 Hz), 2.18–2.47 (m, 3H), 2.63 (t, 2H, *J* = 7.3 Hz), 2.66–2.83 (m, 2H), 2.86–2.98 (m, 1H), 4.21 (q, 2H, *J* = 7.3 Hz), 5.15 (t, 1H, *J* = 7.3 Hz), 7.09–7.33 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 30.5, 32.5, 32.8, 34.5, 61.5, 81.4, 126.6, 126.7, 128.0, 128.5, 128.6, 128.8, 128.9, 140.0, 140.2, 148.6, 165.0; EI-MS (70 eV): *m/z* = 320, 231, 185, 117, 105, 91 (100), 77, 65; anal. calcd. for $C_{22}H_{25}NO_4$ (367.44): C 71.91, H 6.86, N 3.81; found: C 72.03, H 6.99, N 3.73.

(*E*)-6-Ethyl 1,11-dimethyl 7-nitroundec-5-ene-1,6,11-tricarboxylate (4e): Colorless oil. IR (neat): ν = 1171, 1369, 1552, 1648, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.46 (m, 3H), 1.26 (t, 3H, *J* = 7.3 Hz), 1.48–1.59 (m, 1H), 1.60–1.74 (m, 4H), 1.97–2.14 (m, 1H), 2.18–2.39 (m, 6H), 2.47–2.69 (m, 1H), 3.65 (s, 3H), 3.66 (s, 3H), 4.18 (q, 2H, *J* = 7.3 Hz), 5.20 (dd, 1H, *J* = 6.0, 8.5 Hz), 7.11 (t, 1H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 24.6, 24.7, 26.0, 28.0, 28.6, 30.9, 33.7, 33.8, 51.7, 51.8, 61.5, 82.2, 127.7, 149.2, 164.9, 173.8; EI-MS (70 eV): *m/z* = 356, 338, 279, 261, 235, 201, 163 (100), 135, 111, 79, 55, 29; anal. calcd. for $C_{18}H_{29}NO_8$ (387.42): C 55.80, H 7.54, N 3.62; found: C 55.93, H 7.66, N 3.55.

(*E*)-5-(Ethoxycarbonyl)-6-nitronon-4-ene-1,9-diyl diacetate (4f): Colorless oil. IR (neat): ν = 1237, 1365, 1551, 1648, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, 3H, *J* = 7.3 Hz), 1.51–1.79 (m, 3H), 1.81–1.90 (m, 1H), 2.04 (s, 6H), 2.05–2.21 (m, 1H), 2.26–2.47 (m, 2H), 2.55–2.72 (m, 1H), 4.05–4.13 (m, 4H), 4.19 (q, 2H, *J* = 7.3 Hz), 5.25 (dd, 1H, *J* = 6.4, 8.6 Hz), 7.14 (t, 1H, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.0, 21.1, 25.7, 25.8, 27.6, 27.9,

61.7, 63.5, 63.6, 81.8, 128.0, 148.6, 164.8, 171.1, 171.2; EI-MS (70 eV): m/z = 313, 267, 225, 207, 183, 165, 147, 119, 91, 43 (100), 29; anal. calcd. for $C_{16}H_{25}NO_8$ (359.37): C 53.47, H 7.01, N 3.90; found: C 53.59, H 6.90, N 3.98.

Ethyl 3-nitro-2-(propan-2-ylidene)octanoate (5a): Colorless oil. IR (neat): ν = 1242, 1364, 1553, 1638, 1721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, 3H, J = 7.3 Hz), 1.23–1.34 (m, 9H), 1.88–1.99 (m, 1H), 1.96 (s, 3H), 2.05 (s, 3H), 2.29–2.41 (m, 1H), 4.12–4.27 (m, 2H), 5.25 (t, 1H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.2, 22.2, 22.5, 23.8, 26.0, 31.5, 31.6, 61.0, 85.2, 124.4, 149.6, 166.6; EI-MS (70 eV): m/z = 186, 169, 141, 123, 95 (100), 81, 67, 55, 41, 29; anal. calcd. for $C_{13}H_{23}NO_4$ (257.33): C 60.68, H 9.01, N 5.44; found: C 60.81, H 9.13, N 5.35.

Mixture of regioisomeric compounds 5b and 6b (75:25): Colorless oil. IR (neat): ν = 1247, 1365, 1552, 1639, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82–0.93 (m, 3H), 0.93 (t, 0.75H, J = 7.7 Hz), 1.12 (t, 2.25H, J = 7.7 Hz), 1.19–1.38 (m, 8.5H), 1.43–1.56 (m, 0.5H), 2.00–2.42 (m, 3H), 2.43–2.63 (m, 1H), 4.14–4.24 (m, 2H), 5.14 (dd, 0.25H, J = 6.0, 8.9 Hz), 5.21 (dd, 0.75H, J = 6.0, 8.9 Hz), 7.11 (t, 0.75H, J = 7.7 Hz), 7.16 (t, 0.25H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 13.1, 14.1, 14.3, 22.4, 22.5, 22.6, 24.6, 26.2, 28.3, 29.0, 31.2, 31.6, 31.7, 61.4, 82.5, 83.8, 127.1, 150.2, 151.0, 165.2, 165.3.

Mixture of regioisomeric compounds 5c and 6c (80:20): Colorless oil. IR (neat): ν = 1246, 1365, 1551, 1639, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.91 (m, 3H), 0.93 (t, 2.4H, J = 7.7 Hz), 1.12 (t, 0.6H, J = 7.7 Hz), 1.20–1.37 (m, 7.4H), 1.43–1.55 (m, 1.6H), 2.01–2.39 (m, 3H), 2.43–2.61 (m, 1H), 4.13–4.23 (m, 2H), 5.14 (dd, 0.8H, J = 6.0, 8.9 Hz), 5.21 (dd, 0.2H, J = 6.0, 8.9 Hz), 7.11 (t, 0.2H, J = 7.7 Hz), 7.16 (t, 0.8H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 13.1, 14.1, 14.3, 22.4, 22.5, 22.6, 24.6, 26.2, 28.3, 29.0, 31.2, 31.6, 31.7, 61.4, 82.5, 83.8, 127.1, 150.2, 151.0, 165.2, 165.3.

Mixture of regioisomeric compounds 5d and 6d (75:25): Colorless oil. IR (neat): ν = 1242, 1364, 1551, 1638, 1718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.92 (m, 3H), 1.20–1.37 (7.5H), 1.43–1.56 (m, 1.5H), 1.77 (d, 2.25H, J = 6.9 Hz), 1.92 (d, 0.75H, J = 7.3 Hz), 2.02–2.34 (m, 1.75H), 2.44–2.56 (m, 0.25H), 4.15–4.22 (m, 2H), 5.24 (dd, 0.25H, J = 6.0, 8.9 Hz), 5.32 (q, 0.75H, J = 7.3 Hz), 7.06 (t, 0.75H, J = 7.7 Hz), 7.24 (q, 0.25H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.2, 14.8, 17.8, 22.5, 22.6, 26.1, 28.3, 28.8, 31.2, 31.6, 31.7, 61.4, 77.9, 82.2, 128.9, 144.5, 148.6, 165.0, 165.1.

Mixture of regioisomeric compounds 5e and 6e (80:20): Colorless oil. IR (neat): ν = 1244, 1364, 1551, 1638, 1713, 3025, 3061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.30 (m, 3H), 1.57 (d, 2.4H, J = 7.3 Hz), 1.70 (d, 0.6H, J = 7.3 Hz), 2.32–3.03 (m, 4H), 4.15–4.24 (m, 2H), 5.17–5.25 (m, 1H), 7.11 (t, 0.8H, J = 7.7 Hz), 7.14–7.34 (m, 5.2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.2, 14.4, 17.4, 30.8, 32.4, 32.6, 34.5, 61.3, 61.4, 77.8, 81.0, 126.7, 128.5, 128.6, 128.7, 128.8, 128.9, 129.5, 140.0, 140.3, 144.9, 146.9, 164.8.

Typical Procedure for the Synthesis of Compounds 7

To a stirred solution of the respective nitroalkane **1** (1.1 mmol) and the β-nitroacrylate **2** (1 mmol) in ethyl acetate (4 mL), the carbonate on polymer support (715 mg, 2.5 mmol) was added. The resulting heterogeneous mixture was stirred three hours at reflux, then, after cooling at room temperature, the catalyst was filtered off, washing with EtOAc. Finally the filtrate was concentrated under vacuum to give the crude products **7** which were purified by flash chromatography column (hexane-toluene 7:3).

(*E*)-Ethyl 2-[(*E*)-prop-1-enyl]pent-2-enoate (7a): Colorless oil. IR (neat): ν = 1714, 1651, 1629, 1603, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (t, 3H, J = 7.3 Hz), 1.30 (t, 3H, J = 7.3 Hz), 1.82 (dd, 3H, J = 1.3, 6.4 Hz), 2.25–2.34 (m, 2H), 4.20 (q, 2H, J = 7.3 Hz), 6.02 (dq, 1H, J = 6.4, 15.8 Hz), 6.14 (dd, 1H, J = 1.3, 15.8 Hz), 6.55 (t, 1H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 14.4, 19.3, 22.2, 60.7, 123.5, 130.0, 131.1, 143.1, 167.9; EI-MS (70 eV): m/z = 168 (M^+), 140, 123, 111, 95 (100), 79, 67, 55, 39, 29; anal. calcd. for $C_{10}H_{16}O_2$ (168.23): C 71.39, H 9.59; found: C 71.50, H 9.68.

(*Z*)-Ethyl 2-[(*E*)-prop-1-enyl]pent-2-enoate (7a′): Colorless oil. IR (neat): ν = 1716, 1648, 1603, 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (t, 3H, J = 7.3 Hz), 1.33 (t, 3H, J = 7.3 Hz), 1.75 (dd, 3H, J = 1.3, 6.8 Hz), 2.17–2.27 (m, 2H), 4.26 (q, 2H, J = 7.3 Hz), 5.63–5.77 (m, 2H), 6.01 (dd, 1H, J = 1.3, 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.5, 18.5, 23.2, 60.8, 126.6, 129.2, 131.1, 137.7, 168.4; EI-MS (70 eV): m/z = 168 (M^+), 140, 123, 111, 95 (100), 79, 67, 55, 39, 29; anal. calcd. for $C_{10}H_{16}O_2$ (168.23): C 71.39, H 9.59; found: C 71.21, H 9.47.

(*E*)-Ethyl 2-[(*E*)-pent-1-enyl]hept-2-enoate (7b): Colorless oil. IR (neat): ν = 1716, 1650, 1627, 1602, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.95 (m, 6H), 1.29 (t, 3H, J = 7.3 Hz), 1.30–1.49 (m, 6H), 2.12 (q, 2H, J = 7.3 Hz), 2.27 (q, 2H, J = 7.3 Hz), 4.20 (q, 2H, J = 7.3 Hz), 6.00 (dt, 1H, J = 6.8, 15.8 Hz), 6.11 (d, 1H, J = 15.8 Hz), 6.58 (t, 1H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 14.1, 14.5, 22.6, 22.7, 28.6, 31.4, 35.9, 60.7, 122.4, 130.6, 136.3, 142.0, 168.0; EI-MS (70 eV): m/z = 224 (M^+), 195, 179, 167, 149, 139, 121, 111, 95 (100), 79, 67, 55, 41, 29; anal. calcd. for $C_{14}H_{24}O_2$ (224.34): C 74.95, H 10.78, found: C 75.07, H 10.89.

(*Z*)-Ethyl 2-((*E*)-pent-1-enyl)hept-2-enoate (7b′): Colorless oil. IR (neat): ν = 1714, 1652, 1631, 1600, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.93 (m, 6H), 1.27–1.46 (m, 6H), 1.33 (t, 3H, J = 7.3 Hz), 2.05 (q, 2H, J = 7.3 Hz), 2.21 (q, 2H, J = 7.3 Hz), 4.27 (q, 2H, J = 7.3 Hz), 5.66 (dt, 1H, J = 6.8, 15.8 Hz), 5.74 (t, 1H, J = 7.3 Hz), 6.00 (d, 1H, J = 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.1, 14.5, 22.6, 29.6, 31.7, 35.2, 60.7, 128.1, 131.8, 133.8, 136.4, 168.5; EI-MS (70 eV): m/z = 224 (M^+), 195, 179, 167, 149, 139, 121, 111, 95 (100), 79, 67, 55, 41, 29; anal. calcd. for $C_{14}H_{24}O_2$ (224.34): C 74.95, H 10.78; found: C 74.79, H 10.67.

(*E*)-Ethyl 2-[(*E*)-hex-1-enyl]oct-2-enoate (7c): Colorless oil. IR (neat): ν = 1718, 1647, 1628, 1605, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.94 (m, 6H), 1.31 (t, 3H, J = 7.3 Hz), 1.27–1.51 (m, 10H), 2.16 (q, 2H, J = 7.3 Hz), 2.28 (q, 2H, J = 7.3 Hz), 4.21 (q, 2H, J = 7.3 Hz), 6.01 (dt, 1H, J = 6.4, 16.2 Hz), 6.13 (d, 1H, J = 15.8 Hz), 6.59 (t, 1H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 14.2, 14.5, 22.4, 22.7, 28.8, 28.9, 31.6, 31.8, 33.5, 60.7, 122.2, 130.6, 136.5, 141.9, 167.9; EI-MS (70 eV): m/z = 252 (M^+), 209, 181, 163, 139, 109, 93, 79 (100), 67, 55, 41; anal. calcd.

for $C_{16}H_{28}O_2$ (252.39): C 76.14, H 11.18; found: C 76.36, H 11.31.

(*Z*)-Ethyl 2-[(*E*)-hex-1-enyl]oct-2-enoate (7c′): Colorless oil. IR (neat): ν = 1716, 1649, 1625, 1601, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.92 (m, 6H), 1.33 (t, 3H, *J* = 7.3 Hz), 1.23–1.48 (m, 10H), 2.08 (q, 2H, *J* = 6.8 Hz), 2.20 (q, 2H, *J* = 7.3 Hz), 4.27 (q, 2H, *J* = 7.3 Hz), 5.67 (dt, 1H, *J* = 6.8, 16.2 Hz), 5.74 (t, 1H, *J* = 7.7 Hz) 6.00 (d, 1H, *J* = 16.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 14.3, 14.5, 22.5, 22.7, 29.2, 29.8, 31.5, 31.7, 32.8, 60.7, 128.0, 132.0, 133.8, 136.4, 168.5; EI-MS (70 eV): *m*/*z* = 252 (M^+), 209, 181, 163, 139, 109, 93, 79 (100), 67, 55, 41, 29; anal. calcd. for $C_{16}H_{28}O_2$ (252.39): C 76.14, H 11.18; found: C 75.97, H 10.98.

Diastereomeric mixture of compounds (*E*)-ethyl 5-phenyl-2-[(*E*)-3-phenylprop-1-enyl]pent-2-enoate (7d) and (*Z*)-ethyl 5-phenyl-2-[(*E*)-3-phenylprop-1-enyl]pent-2-enoate (7d′): Colorless oil. IR (neat): ν = 3062, 3027, 1715, 1602, 1239, 1178 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.35 (m,3H), 2.55–2.64 (m, 2H), 2.71–2.79 (m, 2H), 3.44 (d, 0.5H, *J* = 6.8 Hz), 3.49 (d, 1.5H, *J* = 5.1 Hz), 4.17–4.29 (m, 2H), 5.82–5.93 (m, 0.5H), 6.02–6.23 (m, 1.75), 6.70 (t, 0.75H, *J* = 7.7 Hz), 7.11–7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 14.5, 30.9, 31.6, 35.3, 35.6, 39.3, 40.1, 60.8, 60.9, 123.5, 126.1, 126.2, 126.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 130.5, 130.9, 133.4, 133.7, 134.9, 136.4, 140.0, 140.1, 141.2, 141.3, 141.4, 167.5, 168.0.

Typical Procedure for the Synthesis of Compounds 8

A mixture of unsaturated esters **7a** and **7a′** (2.6 mmol) was dissolved in EtOH (10 mL), then 0.5 N NaOH (50 mL) was added at room temperature. The solution was refluxed for 4 h and concentrated to 1/3 of the volume. Water (100 mL) was added and the solution was washed with EtOAc (3× 10 mL). The aqueous phase was acidified to pH 1 by 2 N HCl, then extracted with EtOAc (5×20 mL), washed with brine (20 mL) and dried over Na_2SO_4. After filtration the solvent was removed under reduced pressure and the crude acid **8** was purified by flash chromatography (hexanes-ethyl acetate 80:20) affording, separately, the diastereomers **8a** and **8a′** in an 80:20 ratio.

(*E*)-2-[(*E*)-Prop-1-enyl]pent-2-enoic acid (8a): Colorless oil. IR (neat): ν = 3506–2361 (bs), 1698, 1619, 1253, 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, 3H, *J* = 7.7 Hz), 1.84 (d, 3H, *J* = 5.1 Hz), 2.28–2.38 (m, 2H), 6.02–6.16 (m, 2H), 6.79 (t, 1H, *J* = 7.7 Hz), 12.10 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 19.3, 22.6, 122.9, 129.0, 131.9, 146.5, 173.5; EI-MS (70 eV): *m*/*z* = 140 (M^+), 125, 111, 95 (100), 79, 67, 55, 39; anal. calcd. for $C_8H_{12}O_2$ (140.18): C 68.54, H 8.63; found: C 68.71, H 8.78.

(*Z*)-2-[(*E*)-Prop-1-enyl]pent-2-enoic acid (8a′): Colorless oil. IR (neat): ν = 3513–2352 (bs), 1695, 1616, 1252, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, 3H, *J* = 7.7 Hz), 1.77 (dd, 3H, *J* = 1.3, 6.4 Hz), 2.37–2.46 (m, 2H), 5.87 (dq, 1H, *J* = 6.4, 15.8 Hz), 5.99 (t, 1H, *J* = 7.7 Hz), 6.08 (d, 1H, *J* = 15.8 Hz), 11.69 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 18.6, 23.4, 127.2, 128.6, 131.0, 142.4, 173.9; EI-MS (70 eV): *m*/*z* = 140 (M^+, 100), 125, 111, 95, 79, 67, 55, 39; anal. calcd. for $C_8H_{12}O_2$ (140.18): C 68.54, H 8.63; found: C 68.73, H 8.77.

Typical Procedure for the Synthesis of Valproic Acid (9)

To a solution of the diastereomeric mixture of the diunsaturated acid **8** (1.36 mmol) in EtOAc (14 mL), 10% Pd/C (200 mg) was added. The suspension was hydrogenated (4 atm) under stirring at room temperature for 23 h. Then the catalyst was filtered off through a pad of celite washing with EtOAc. Finally, after evaporation of the solvent, the pure product, 2-propylpentanoic acid (**9**) was obtained; yield: 88%; colorless oil. IR (neat): ν = 3380–2375 (bs), 1707, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, 6H, *J* = 7.3 Hz), 1.26–1.51 (m, 6H), 1.56–1.68 (m, 2H), 2.33–2.42 (m, 1H), 11.85 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 20.8, 34.6, 45.4, 183.5. EI-MS (70 eV) *m*/*z*: 115, 102, 73 (100), 55, 41, 29; anal. calcd. for $C_8H_{16}O_2$ (144.21): C 66.63, H 11.18; found: C 66.75, H 11.27.

Acknowledgements

Financial support from the University of Camerino and MIUR Italy (National Project "Sintesi organiche ecosostenibili mediate da nuovi sistemi catalitici") are gratefully acknowledged.

References

[1] a) K. Rueck-Braun, T. H. E. Freysoldt, F. Wierschem, *Chem. Soc. Rev.* **2005**, *34*, 507–516; b) G. Sartori, R. Ballini, F. Bigi, G. Bosica, R. Maggi, P. Righi, *Chem. Rev.* **2004**, *104*, 199–250; c) C. Chung, Y. Wan, P. H. Toy, *Tetrahedron: Asymmetry* **2004**, *15*, 387–399; d) M. H. Valkenberg, C. de Castro, W. F. Hoelderich, *Green Chem.* **2002**, *4*, 88–93; e) J. H. Clark, *Acc. Chem. Res.* **2002**, *35*, 791–797; f) A. Solinas, M. Taddei, *Synthesis* **2007**, 2409–2453.

[2] a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**; b) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806.

[3] a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; b) V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, D. A. Efremov, *Nitroalkenes Conjugated Nitro Compounds*, Wiley, Chichester, **1994**.

[4] R. Ballini, S. Gabrielli, A. Palmieri, *Curr. Org. Chem.* **2010**, *14*, 65–83.

[5] a) E. J. Corey, X. M. Cheng, *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, **1989**; b) T. L. Ho, *Tactics of Organic Synthesis*, Wiley, New York, **1994**; c) *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, Vol. 4, **1991**.

[6] a) J. Ap Simon, *The Total Synthesis of Natural Products*, John Wiley & Sons, New York, **1998**; b) J. R. Hwu, G. H. Hakimelahi, C. T. Chou, *Tetrahedron Lett.* **1992**, *33*, 6469–6472; c) P. Galatsis, D. J. Parks, *Tetrahedron Lett.* **1994**, *35*, 6611–6614.

[7] A. C. Cope, C. M. Hoffman, *J. Am. Chem. Soc.* **1941**, *63*, 3456–3459.

[8] A. Galat, *J. Am. Chem. Soc.* **1946**, *68*, 376–377.

[9] a) R. L. Shriner, *Org. React.* **1947**, *1*, 1–37; b) C. R. Hauser, D. S. Breslow, *Org. Synth. Coll. Vol. 4*, **1963**, 444–450.
[10] a) W. S. Wadsworth, W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738; b) W. S. Wadsworth, *Org. React.* **1977**, *25*, 73–253; c) J. S. Wojciech, *Acc. Chem. Res.* **1983**, *16*, 411–417; d) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.
[11] a) G. Sartori, R. Ballini, F. Bigi, G. Bosica, R. Maggi, P. Righi, *Chem. Rev.* **2004**, *104*, 199–250; b) R. Ballini, A. Palmieri, *Curr. Org. Chem.* **2006**, *10*, 2145–2169; c) R. Ballini, L. Barboni, A. Palmieri, *Synlett* **2007**, 3019–3021; d) R. Ballini, G. Bosica, A. Palmieri, F. Pizzo, L. Vaccaro, *Green Chem.* **2008**, *10*, 541–544; e) R. Ballini, S. Gabrielli, A. Palmieri, M. Petrini, *Tetrahedron* **2008**, *64*, 5435–5441.
[12] The carbonate on polymer support (Amberlite® IRA 900 $NaCO_3^-$ form) was purchased from Sigma–Aldrich and used directly without any manipulation. The promoter containing ~20% of water and has a loading of ~3.5 mmol g^{-1} of $NaCO_3^-$.
[13] K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry, M. Stefaniak, *Green Chem.* **2008**, *10*, 31–36.
[14] M. P. D. Alcàntara, F. C. Escribano, A. Gòmez-Sànchez, M. J. Diànez, M. D. Estrada, A. Lòpez-Castro, S. Pérez-Garrido, *Synthesis* **1996**, 64–70.
[15] a) G. Rosini, R. Ballini, *Synthesis* **1988**, 833–847; b) G. Rosini, in: *Comprehensive Organic Synthesis*, (Ed.: B. M. Trost), Pergamon, New York, **1992**, pp 321–340; c) G. Rosini, R. Ballini, M. Petrini, E. Marotta, P. Righi, *Org. Prep. Proced. Int.* **1990**, *22*, 707–746; d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–971.
[16] a) D. Seebach, E. W. Colvin, F. Lehr, T. Weller, *Chimia* **1979**, *33*, 1–18; b) N. Ono, in: *The Nitro Group in Organic Synthesis*, Wiley, New York, **2001**; c) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047.
[17] R. D. Lee, K. Kassahum, F. S. Abbott, *J. Pharm. Sci.* **1989**, *78*, 667–671.
[18] J. M. McIntosh, R. A. Sieler, *J. Org. Chem.* **1978**, *43*, 4431–4433.
[19] T. Mandai, H. Yokoyama, T. Miki, H. Fokuda, H. Kobata, M. Kawada, *Chem. Lett.* **1980**, 1057–1060.
[20] L. L. Sydness, L. Skattebol, C. B. Chapleo, D. G. Leppard, K. L. Svanholt, A. S. Dreiding, *Helv. Chim. Acta* **1975**, *58*, 2061–2073.
[21] O. Goldberg, A. S. Dreiding, *Helv. Chim. Acta* **1976**, *59*, 1904–1910.
[22] H. M. R. Hoffmann, J. Rabe, *Angew. Chem.* **1983**, *95*, 795–796; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 795–796.
[23] T. Hudlicky, R. P. Short, B. C. Ranu, J. M. Revol, *J. Org. Chem.* **1983**, *48*, 4453–4461.
[24] A. S. Kende, B. H. Toder, *J. Org. Chem.* **1982**, *47*, 163–167.
[25] C. Harcken, R. Brükner, *Tetrahedron Lett.* **2001**, *42*, 3967–3971.
[26] O. Dulac, D. Steru, E. Rey, A. Perret, M. Arthuis, *Brain Dev.* **1986**, *8*, 47–52.
[27] G. Olmos-Garcia deAlba, J. M. Valdez, *Clin. Electroencephalogr.* **1986**, *17*, 14–20.
[28] G. R. Granneman, S. I. Wang, J. M. Machinist, J. W. Kesterson, *Xenobiotica* **1984**, *14*, 375–387.
[29] A. W. Rettenmeier, W. P. Gordon, K. S. Prickett, R. H. Ley, J. S. Lockard, K. E. Thummel, T. A. Baille, *Drug Metab. Dispos.* **1986**, *14*, 443–453.
[30] F. S. Abbott, J. Kassam, J. M. Orr, K. Farrell, *Clin. Pharmacol. Ther.* **1986**, *40*, 94–100.
[31] F. S. Abbott, J. Kassam, A. Acheampong, S. Ferguson, S. Panesar, R. Burton, K. Farrell, J. Orr, *J. Chromatogr.* **1986**, *375*, 285–298.
[32] J. W. Kesterson, G. R. Granneman, J. M. Machinist, *Hepatology* **1984**, *4*, 1143–1152.
[33] F. S. Abbott, A. A. Acheampong, *Neuropharmacology* **1988**, *27*, 287–294.
[34] G. Cardillo, M. Orena, G. Porzi, S. Sandri, *Synthesis* **1981**, 793–794.

