Comparative study of the *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide chemical and electrochemical syntheses†

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In order to show the advantages and limitations of organic electrosynthesis in the total synthesis of a natural product, one of the promising green chemistry techniques in organic chemistry, the synthesis of *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide (**3**) was undertaken. Chemical and electrochemical routes that use the same intermediates were used to carry out the syntheses. Four reactions were compared from a green chemistry point of view in the synthesis of **3**: (a) alcohol to aldehyde oxidation, (b) the Horner–Emmons reaction, (c) carboxylic acid amidation with triphenylphosphonium ions and (d) the Wittig reaction. All the electrolyses were carried out in non-divided cells at a constant current. The electrochemical method in the oxidation reaction of alcohols and the carboxylic acid amidation gave better yields (95% and 67%, respectively) than the corresponding chemical reactions. The Horner–Emmons reaction gave the same yields in both techniques (80–85%); however, the electrochemical method was more environmentally friendly, due to the fact that the base used was electrogenerated, avoiding corrosive and sensitive base manipulation. Finally, the electrochemical Wittig reaction was unsuccessful in the different experimental conditions attempted, and only the chemical method produced the target product. This study demonstrated that organic electrochemistry can be a reliable method for the synthesis of important intermediates, but not all electrochemical reactions can compete with the already well-established methods of organic chemistry.

Introduction

Unsaturated *N*-isobutylamides such as spilanthol **1** and α-sanshoöl **2** are natural products found in plants of *Echinacea*,[1] *Salmea*,[2] *Spilanthes*,[3] and *Asarum* species[4] from the *Compositae*, *Piperaceae*, and *Rutaceae* families.[5] These compounds have anaesthetic,[6,7] anti-inflammatory,[8] potent mosquito larvicidal,[9] cannabinoid type-2 (CB2) receptor antagonistic,[10] insecticidal,[3,11] and antihelmitic[12] properties. Low stability of the natural unsaturated *N*-isobutyl-amides has been reported;[13] therefore, derivatives were required that are better suited to the environmental conditions. In addition, in order to carry out further studies of the biological activity, it is necessary to obtain these products in larger quantities than those isolated from natural sources. *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide **3** was chemically prepared in our laboratories several years ago.[14] Our preliminary studies using the *Artemia salina* biological test[15] showed that this compound was more stable than natural products **1** and **2**, and 74 times more active. Compound **3** has also been prepared by hydrogenation of natural unsaturated *N*-isobutylamides and it has been applied to flavor mixtures due to its organoleptic properties.[16]

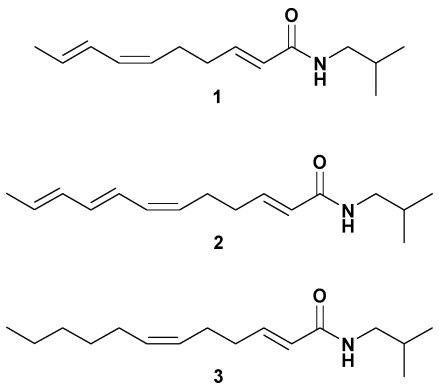

Fig. 1 *N*-isobutyl-amides with biological activity.

Organic chemistry generally uses specific methods for the synthesis of natural products such as enzymatic, photochemical and organometallic catalytic processes.[17] One of the methods that has not been widely used in organic chemistry is organic electrosynthesis, and it is rare to find a report that describes electrochemical steps in a total synthesis.[18] Synthetic organic electrochemistry nowadays offers many electrochemical versions for almost all types of classical chemical reactions.[19] The use of organic electrochemistry opens a non-traditional way of synthesizing molecules[19a,19b,20] and has important characteristics that make it attractive for synthetic green chemistry applications.[21] In organic electrosynthesis the electron becomes a reactant, thus, its use opens the possibility of replacing toxic

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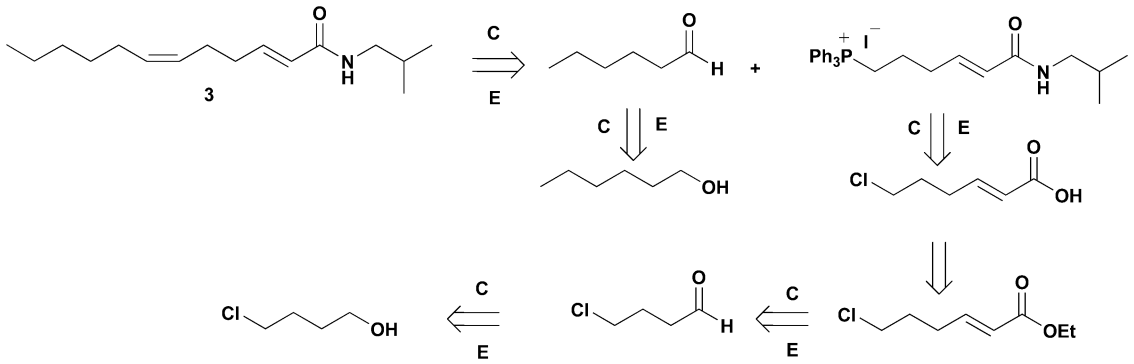


Scheme 1 Retrosynthetic analysis of compound **3**. C: chemical reaction, E: electrochemical reaction.

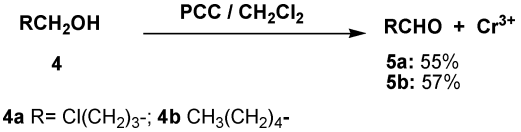
redox reagents, using catalytic quantities of expensive redox mediators *via* electroregenerating reactions, electrogenerating *in situ* stoichiometric amounts of dangerous reagents, using ionic liquids which are the conducting media and solvents in electrochemistry, and opens the possibility of following the reactions by electroanalytical techniques. These features are in agreement with some of the basic principles of green chemistry.

Therefore, in this contribution the synthetic route previously used[14] for the synthesis of compound **3** was optimized and compared from the green chemistry point of view, using both electrochemical (E) and chemical (C) synthetic routes. The retrosynthetic pathway depicted in Scheme 1 was followed for the synthesis of this compound. In this strategy, the most important intermediates can be obtained by organic electrochemistry and by classical organic chemistry reactions, a fact that allowed us to compare both methodologies. Four reactions were evaluated during the synthesis of **3**: (a) alcohol to aldehyde oxidation, (b) the Horner–Emmons reaction, (c) carboxylic acid amidation with triphenylphosphonium ions and (d) the Wittig reaction.

Results and discussion

Oxidation of alcohols (4) to aldehydes (5)

The first intermediate required in the synthesis of compound **3** is the 4-chlorobutaldehyde (**5a**); hexanal (**5b**) was used later in the synthesis route. Both aldehydes were obtained from the oxidation of their corresponding alcohols (**4a** and **4b**). Among the classical methodologies for this oxidation (PCC,[22] DMSO/$(COCl)_2$,[23] Dess–Martin,[24] TPAP[25]), the reaction with PCC[26] was chosen for the chemical comparison because nowadays it is frequently used.[27] The reaction of PCC with alcohols **4a** and **4b** gave the corresponding aldehydes in 55% and 57% yields, respectively (Scheme 2). The work-up of this reaction requires a high quantity of anhydrous ether and the final mixture is a very viscous brown tar, which made isolation of the aldehydes



Scheme 2 Chemical oxidation of alcohols **4a** and **4b** using PCC reagent.

difficult. In addition, the use of chromium salt requires a special treatment for the residual wastewaters due to its toxicity.

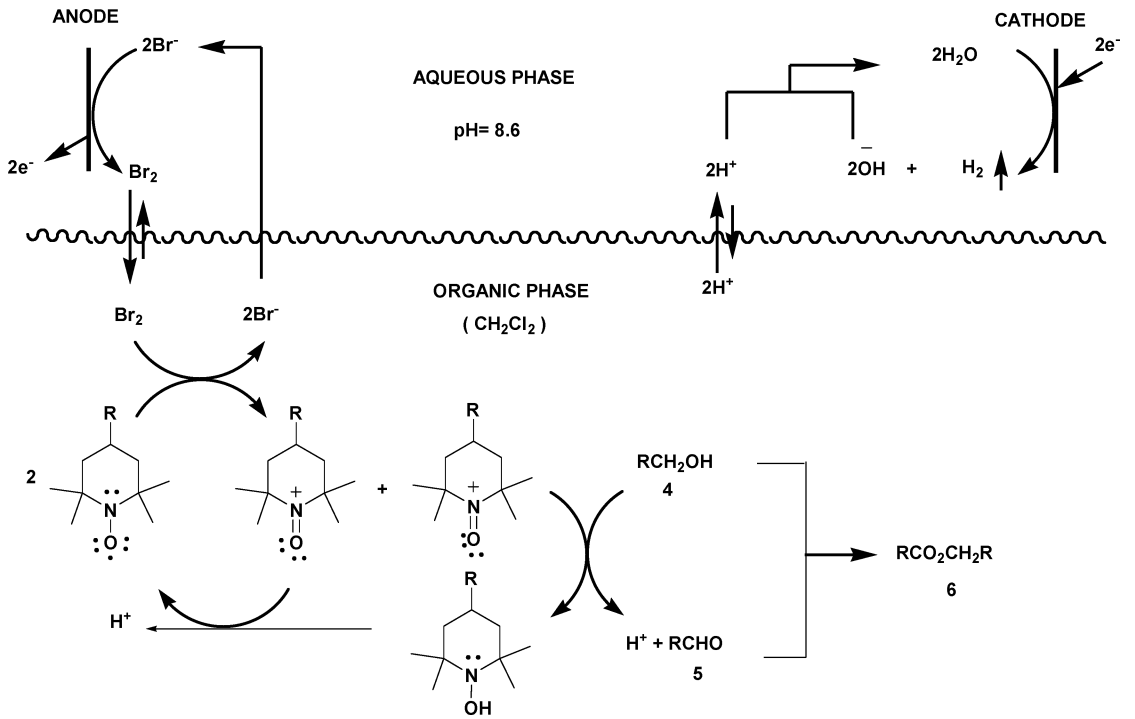
Direct electrochemical oxidation of alcohols requires a very high positive potential and the reaction is not selective.[28] Therefore, an indirect electrochemical reaction allowed us to carry out the oxidation at lower potential values, with a higher rate of reaction and higher selectivity.[29] This methodology requires a regenerable redox catalyst (mediator) that is used to transport electrons between the electrode and the compound to be oxidized. The selective electrochemical oxidation of alcohols to aldehydes was carried out by means of the electrocatalytic reaction with radical 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO) as a redox catalyst (1% mol) by a double mediator electrochemical reaction (Scheme 3).[30,31]

In this reaction the primary oxidant, a halogen, was obtained by electrochemically oxidizing chloride or bromide ions, which are regenerated during the reaction. When chlorine was used (Table 1, entries 1–3), aldehyde production was very low and, even in the presence of a mixture of bromide and chloride ions or at higher temperatures, the yield did not substantially increase.[32] Better results were obtained when bromine was used as the primary oxidant (Table 1, entries 4–9). At 25 °C, the yield of the isolated aldehyde was lower; thus, all the other reactions were carried out at 0 °C. Three TEMPO derivatives were studied demonstrating that TEMPO and TEMPO-4-OBz were the better mediators for the reaction. Due to the higher cost of TEMPO-4-OBz, TEMPO was selected as the mediator in the macroelectrolysis. When the alcohol was added to the electrolysis cell at the beginning of the reaction, aldehyde **5a** was produced in high yields (94%). The ester (**6**) was observed as a secondary product, and its quantity depended on the alcohol used. Thus, when **4a** was electrolyzed only traces of **6a** were observed; when **4b** was used, 28% of ester was produced. Consequently, it was decided to add the alcohol in three portions during the electrolysis of **4b**, observing an improvement in the production of aldehyde **5b** reaching a 95% yield (Table 1, entry 9). An additional advantage of the electrochemical method is its self-indicator end of reaction property; the reaction became orange due to the presence of bromine when the alcohol was almost totally consumed. The fact that the reaction was carried out in a biphasic system led to easier isolation of the final products, since they accumulated in the organic layer. Nevertheless, it is not possible to use electron-rich aromatic rings or unsaturated alcohols since they suffer halogenation during the oxidation.[33]

Table 1 Indirect electrooxidation of alcohols **4a** and **4b** using the TEMPO double mediator system[a]

Exp.	Alcohol	X-TEMPO	Temperature/°C	Primary oxidant		Products (%)[b]		
				NaCl/M	KBr/M	**4**	**5**	**6**
1	4-Chlorobutanol (**4a**)	X = H	0	0.85	0.0	87	13	T[d]
2	**4a**	X = H	0	0.85	0.01	80	20	T[d]
3	**4a**	X = H	25	0.85	0.01	94	6	T[d]
4	**4a**	X = H	0	0	1.46	6	94	T[d]
5	**4a**	X = H	25	0	1.46	75	10	15
6	**4a**	X = 4-Oxo	0	0	1.46	100	—	—
7	**4a**	X = 4-OBz	0	0	1.46	7	93	0
8	1-Hexanol (**4b**)	X = H	0	0	1.46	5	67	28
9	**4b**[c]	X = H	0	0	1.46	T[d]	95	5

[a] Carried out using 10 mmol of alcohols **4**, 0.1 mmol of TEMPO (1% mol) derivatives in CH_2Cl_2 (50 mL) and aqueous solution (100 mL) of the halogen salt. The pH was adjusted to 8.6 by saturation with $NaHCO_3$. The reaction was stopped after the passage of 2.3 F mol^{-1} at a current density of 70 mA cm^{-2} using a carbon anode (12 cm^2) and a Ti cathode (12 cm^2). [b] Determined from the reaction mixture by ^1H NMR. [c] The alcohol was added in three parts during the reaction. [d] Traces.

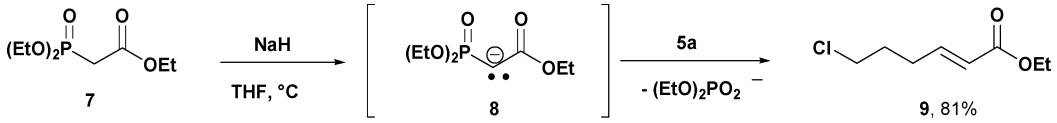


Scheme 3 General mechanism of the indirect electrooxidation of alcohols using the TEMPO(⁺)/TEMPO(•) and $Br_2/Br(^-)$ double mediator biphasic system.

When the yields obtained for the selective oxidation of alcohols to aldehydes are compared using the chemical (55–57%) and the electrochemical (94–95%) methods, the latter one is more advantageous. From an environmental and safety point of view, the electrochemical method is superior, because the use of toxic metals (Cr^{VI}) is avoided, catalytic quantities of mediator are used, the bromine used in the reaction is stoichiometrically electrogenerated and is never manipulated and, finally, hydrogen is generated as the final product together with the aldehyde. Practical advantages such as selective oxidation to aldehydes, the use of distilled solvents in biphasic aqueous-organic media instead of pure dry solvents, the easiness of separation of the products of reaction (concentrated in the organic layer), self-monitoring of the end of reaction and shorter reaction times make the electrocatalytic method a truly attractive alternative.

Synthesis of the ethyl-6-chloro-2(*E*)-hexenoate (9) *via* a Horner–Emmons reaction

The second reaction to be compared was the production of the α,β-(*E*)-unsaturated ester (**9**) using the Horner–Emmons reaction,[34] a variant of the classical Wittig methodology,[35] which uses an aldehyde and the triethyl phosphonoacetate carbanion (**8**). The chemical version was attempted with NaH, which is a base typically used in this reaction, and the previously obtained 4-chlorobutanal (**5a**) (Scheme 4).[36]



Scheme 4 Chemical synthesis of compound **9** using a Horner–Emmons reaction.

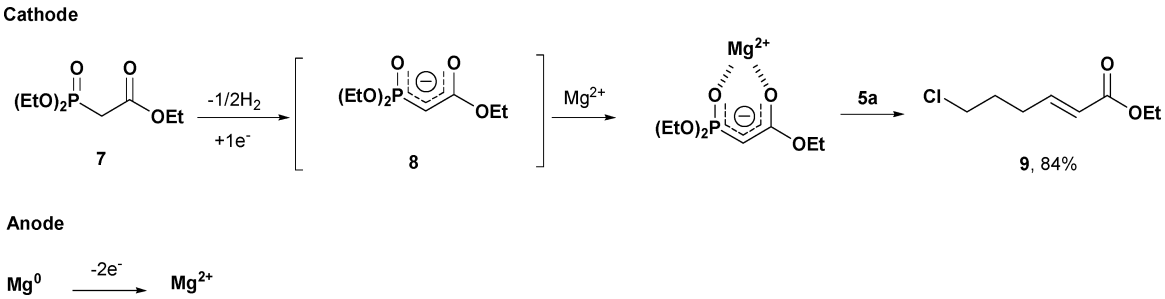
The chemical reaction produced a yield (81%), which is in agreement with the data reported in literature.[36] As a limitation, during the course of the reaction the mineral oil used for the stabilization and conservation of NaH turned very viscous, impeding the magnetic stirring of the reaction. Because NaH is very sensitive fresh base is always required. The corrosive properties of this compound also impose special manipulation precautions such as an inert atmosphere and dry solvents.

The electrochemical Horner–Emmons reaction was carried out using the galvanostatic non-divided cell with a sacrificial anode methodology for the electrogeneration of triethyl phosphonoacetate carbanion (**8**).[37] This method does not use a strong base, since the cathode plays the role of base when it reduces to hydrogen the acidic protons of triethyl phosphonoacetate (Scheme 5). The electrochemical cell filled with the electrolytic solution (Et_4NBF_4, 0.03 M dissolved in DMF) was fitted with concentric electrodes using a Pt electrode as the cathode and an Mg rod as the anode. Aldehyde and triethyl phosphonoacetate were added at the beginning of the electrolysis. The Mg^{2+} ions produced at the anode stabilized the carbanion, a fact that permits the reaction to be carried out at lower reduction potentials decreasing the energy required for the transformation.[37] Moreover, by using a non-divided cell and a sacrificial electrode, we were able to use a lower quantity of the supporting electrolyte; the ionic species electrogenerated during the reaction favors the conductivity of the medium.

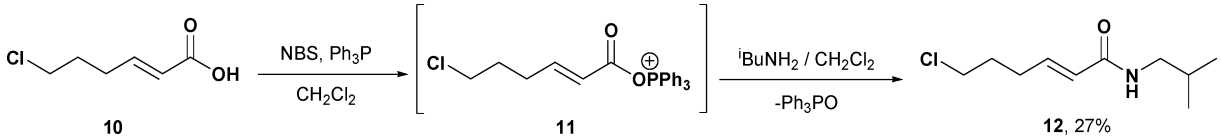
Aldehyde **5a** was added at the beginning of the electrolysis in order to favor its reaction with the triethyl phosphonoacetate carbanion as soon as the latter is formed. During electrolysis, small bubbles could be observed on the cathode surface. After reaction work-up and column separation ethyl-6-chloro-2(*E*)-hexenoate **9** was obtained in 84% yield. The reaction was stereospecific because the *Z* isomer was never detected by ^{1}H NMR in the reaction mixture. The chemical and electrochemical yields were practically the same but the electrochemical methodology is safer since it eliminates the use and manipulation of a strong, corrosive, and sensitive base. The use of a galvanostatic non-divided cell assures simplicity, a fact that is appreciated by the organic chemist. Reports in the literature mention that the Horner–Emmons reaction carried out in a divided cell[38] typically has a 60% yield; therefore, the reaction in a non-separated cell fitted with a sacrificial anode, as used in this study, is more efficient. When acetonitrile was used as solvent or aluminium as the sacrificial anode, the reaction did not work efficiently.

Synthesis of the *N*-isobutyl-6-chloro-(2*E*)-hexenamide (12)

Saponification of ester **9** with LiOH/THF[39] and further acidification yielded 88% of carboxylic acid **10**. The amidation of carboxylic acid **10** requires its activation, which was carried out using the acyloxytriphenylphosphonium ion **11** (P^V), generated chemically and electrochemically by oxidizing triphenylphosphine (P^{III}). In the chemical version Fröyen's methodology was used.[40] The reaction consisted of oxidizing Ph_3P with *N*-bromo- or *N*-chlorosuccinimide (NBS or NCS) in the presence of the carboxylic acid producing **11** *in situ*.[41] Later on, the amine was gradually added until two equivalents were reached. This chemical synthesis of **12** gave us, after several attempts, an optimized yield of 27% (Scheme 6). Other final products of the reaction were: oxidant (NBS) and the corresponding reduced product, triphenylphosphine, its oxide, and the remaining starting material. This mixture is complicated to purify and requires



Scheme 5 Proposed mechanism for the electrosynthesis of α,β-(*E*)-unsaturated ester **9**. Pt cathode, +1e$^-$, charge = 1 F mol^{-1}, current density = 2 mA cm^{-2}, 0.03 M Et_4NBF_4 in DMF; Mg rod as sacrificial anode in undivided cell.



Scheme 6 Chemical amidation of **10** using Fröyen's methodology.

large quantities of solvent for the column chromatography separation.

The electrochemical process takes advantage of the redox properties or the organophosphorus compounds which can be exploited in electrosynthesis.[42] Thus, phosphonium ions can be electrogenerated directly at the anode and activate carboxylic acids generating their derivatives in a redox-substitution reaction. In this reaction, the typical behavior of triphenylphosphine as a nucleophile is changed to an electrophile by an electrochemical umpolung process, which is very useful in electrosynthetic procedures.[20a] Triphenylphosphine showed an anodic peak at 1.3 V *vs.* Ag/AgCl[43] that increased its current value with the addition of aliquots of carboxylic acid **10** (Fig. 2). This increment in current is provoked by the fast consumption of the cation-radical of the triphenylphosphine by the nucleophilic attack of the carboxylic acid generating **11**, a reaction that favors the electrochemical step.[44] In this way, the possibility of producing the acyloxytriphenylphosphonium ion **11** by oxidation of triphenylphosphine in the presence of **11** was demonstrated. Isobutylamine and carboxylic acid **10** were electrochemically inactive in the experimental conditions used.

The macroelectrolysis was carried out in a galvanostatic non-divided cell using platinum electrodes in CH_2Cl_2 using 2,6-lutidinium perchlorate ($LutClO_4$) as a supporting electrolyte. At the anode the triphenylphosphine is oxidized, whereas at the cathode, the supporting electrolyte is reduced to hydrogen and the corresponding base (Scheme 7). This base traps the protons liberated during the amidation process, maintaining a neutral media during the process.[45]

After several electrolyses (Table 2), the best conditions were 32 °C (CH_2Cl_2 boils at 34 °C in Mexico City), low current density values (1.31 mA cm^{-2}), and the addition of the amine in three portions during the electrolysis (Table 2, entry 5). In this way, the electrochemical reaction yield (67%) was 2.5 times the yield obtained by means of a chemical reaction. Since the anode replaces the oxidizing agent, the separation of the reaction mixture is easier to carry out. A minor inconvenience of the electrochemical reaction is the use of $LutClO_4$, which is not commercial but can be very easily prepared and purified (see the Experimental).

Table 2 Electrochemical amidation of 6-chloro-2(*E*)-hexenoic acid (**10**) using as electrogenerated acyloxytriphenylphosphonium ion[a]

Exp.	Temperature/°C	Current density/ mA cm^{-2}	Amine added	Yield (%)[b]
1	20	1.31	At the beginning	5
2	32	1.31	At the beginning	24
3	32	1.31	At the end	32
4	32	2.28	At the end	37
5	32	1.31	In three parts	67

[a] Platinum anode (13.7 cm^2), platinum cathode (24.4 cm^2), charge consumed: 2.4 F mol^{-1} of acid (**7**) 1 mM, Ph_3P 2 mM, $^iBuNH_2$ 4 mM, supporting electrolyte: $LutClO_4$ (2 mM) in CH_2Cl_2 (35 mL). [b] Yield corresponding to isolated product.

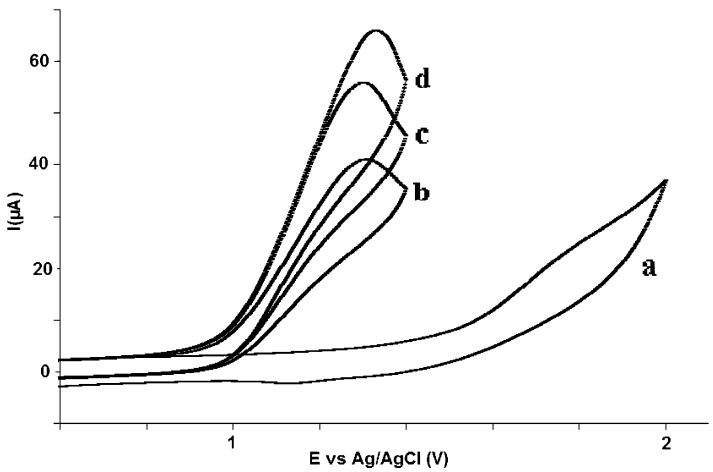
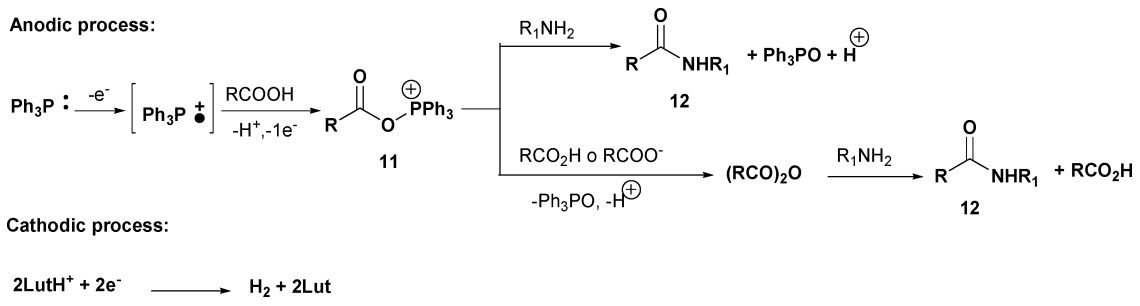
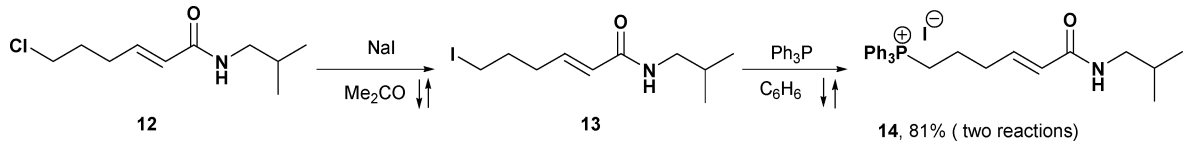


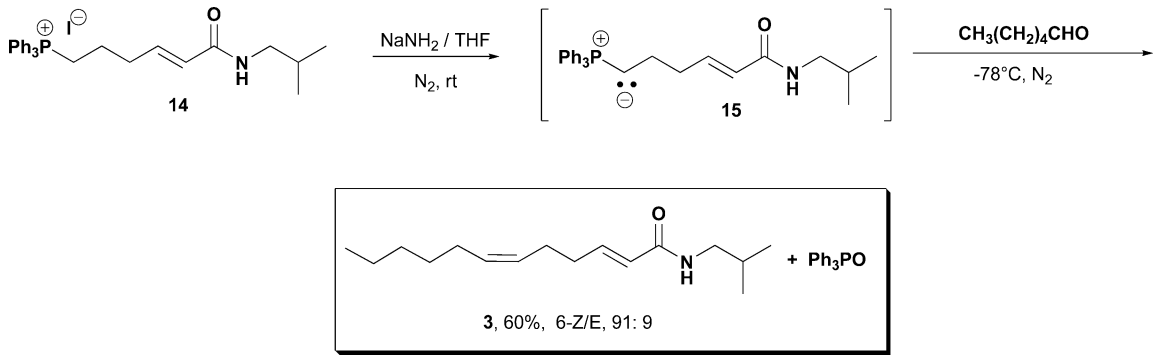
Fig. 2 Cyclic voltammetry using a Pt disk (1 mm diam.) as a working electrode, a Pt wire as an auxiliary electrode and Ag/AgCl as a reference electrode at 50 mV s^{-1}. (a) Supporting electrolyte, $LutClO_4$ 0.1M in CH_2Cl_2; (b) triphenylphosphine, 5 mM; (c) as (b) plus 6-chloro-2(*E*)-hexenoic acid (**10**) 5 mM; (d) as (b) plus 6-chloro-2(*E*)-hexenoic acid (**10**) 10 mM.



Scheme 7 Proposed mechanism for amide electrosynthesis *via* an electrogenerated acyloxytriphenylphosphonium ion.



Scheme 8 Preparation of the Wittig salt **14**.



Scheme 9 Synthesis of compound **3** using a Wittig reaction.

Preparation of *N*-isobutyl-(2*E*, 6*Z*)-dodecadienamide (3) *via* a Wittig reaction

With compound **12** in hand a Wittig reaction was attempted to generate target compound **3**. In order to perform the reaction, the corresponding Wittig salt of compound **12** was produced substituting the chlorine atom with an iodine atom using the Finkelstein method.[46] This generated compound **13** quantitatively (Scheme 8), and it was used without purification. Later on, the reaction of **13** with Ph_3P in benzene produced 81% of the Wittig salt **14**.

The stereoselective Wittig reaction[35] of **14** with hexanal (**5b**), obtained in a previous step, was the fourth reaction compared during the synthetic route of the target compound **3**. The *Z* alkene is required in the final product because the biological activity depends on the stereochemistry of this double bond.[5,47] This stereochemistry is favored when the reaction mixture is free of the salts generated during the ylide production.[48] The chemical reaction was performed using sodium amide as the strong base in THF, generating the phosphorous ylide (**15**) (Scheme 9). Efficient mixing of the reaction was needed to generate the ylide, therefore the reaction was carried out inside an essay tube closed with a septum and was ultrasonically stirred. Once ylide was formed and the salts were separated, it was reacted at −78 °C with the hexanal diluted in THF. After work-up, compound **3** was obtained in a 60% yield and ^{13}C NMR showed a ratio *Z*/*E* 91 : 9 for the C-6 double bond.

The electrochemical Wittig reaction requires electrogeneration of the corresponding ylide **15**. Two different approaches were attempted: (a) a direct electroreduction of the protons next to the phosphonium group and (b) the use of an electrogenerated base (EGB). The cyclic voltammetry of salt **14** demonstrated the possibility of using the first approach (Fig. 3). Salt **14** showed a reduction peak on Pt electrode at −1.95 V *vs.* Ag/AgCl in a system containing ACN/Bu_4NBr 0.1 M. This peak could be attributed to the reduction of the protons next to the phosphonium group. Hexanal in the same analysis media did not show any cathodic signal. When hexanal was added to the solution containing salt **14**, a slight increment in the current of **14** was observed. With this analytical background the preparative direct reduction of **14** was carried out using the same electrolyte in the presence of hexanal with a divided cell and a platinum cathode. The electrochemical reaction produced a mixture of compounds and the NMR analysis of the major components showed products corresponding to the cleavage of the P–C bond and Ph_3P (Scheme 10).[49] After the negative results of the direct reduction, we decided to use the second approach, which involved the electrogeneration of a base at the cathode.

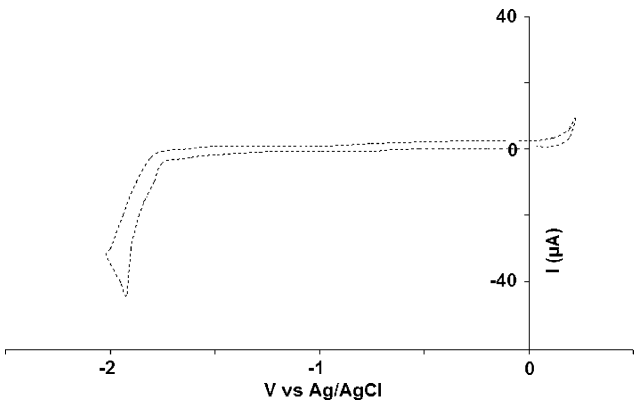
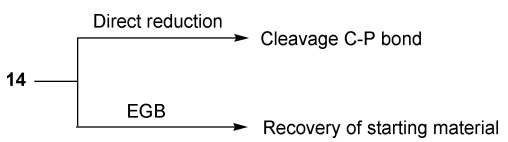


Fig. 3 Cyclic voltammetry of the Wittig salt **14** (6 mM) in Bu_4NBr 0.1 M/ACN, WE: Pt, AE: Pt, RE: Ag/AgCl, $v = 100$ mV s^{-1}.



Scheme 10 Cathodic behavior of salt **14** using direct electroreduction and electrogenerated base.

The use of electrogenerated bases has been widely discussed in the electrosynthetic literature[50] and the most common pro-bases used in Wittig reactions were essayed in our experiments. Azobenzene,[51] trityl,[52] and hexamethyldisilazane[53] were used as pro-bases using the described experimental procedures in an electrolysis divided cell. Using one equivalent or an excess of pro-base and one equivalent of salt **14**, in all our attempts we never observed the typical intense red color of the ylide **15** and the starting material was recovered without change. Stronger bases such as acetonitrilate (ACN^-) can be electrogenerated,[54] but they require higher reduction potential values that provoke the direct reduction of **14** promoting the C–P bond cleavage.

In this synthetic step, only the chemical Wittig reaction was able to produce the final compound **3** in a 60% yield. Despite the fact that cyclic voltammetry showed that salt **14** was electroreducible, the induced reaction was not useful for the ylide synthesis and the same result was obtained when an EGB was used.

Conclusions

In this work the synthesis of *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide **3** was carried out both by a chemical and an electrochemical methodology, comparing the different green chemistry aspects of four reactions: (a) alcohol oxidation to aldehydes (PCC *vs.* TEMPO), (b) the Horner–Emmons reaction, (c) carboxylic acid amidation with triphenylphosphonium ions and (d) the Wittig reaction (Scheme 11). The electrochemical route did not work for the Wittig reaction. The overall yield of amide **12** (the first three steps of the synthesis) is 10% by the chemical route and 46% by the electrochemical pathway. Until here, the electrosynthetic pathway is clearly superior to the chemical one not only in terms of performance (yield) but also in being more environmentally friendly. It is also important to remark that in a total synthesis scheme, electrosynthetic methods are complementary to currently used chemical methods since not all the electrochemical reactions are efficient. Thus, combining the best electrochemical/chemical reactions a global yield of 22% can be reached, instead of a very low 5% by the chemical route. A synthetic organic chemist can easily carry out the electrochemical reactions used in the synthetic route, due to the fact that they are carried out at a constant current and in a non-divided cell. Thus, no sophisticated equipment was required, the major obstacle perceived by chemists when the methodology is selected. A convenient choice of the synthetic methodology using the best chemical or electrochemical methodologies, can improve substantially the total synthesis yield of organic compounds, keeping a green chemistry philosophy along the synthetic route.

Experimental

General

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. THF was stirred in sodium for 2 h in an ultrasonic bath and distilled. DMF was dried over phosphorus pentoxide and distilled at reduced pressure. CH_2Cl_2 was dried with CaH_2 at reflux for 3 h and distilled. Et_4NBF_4 was dried at night in an Alberhaldren apparatus before use. $LutClO_4$, was prepared by adding 70% $HClO_4$ (164 g) dropwise to 2,6-lutidine (110 g) at 0 °C. The crystals were filtered, recrystallized from AcOEt–EtOH, dried under reduced pressure at room temperature, and stored in a desiccator. Prior to its use $LutClO_4$ was dried in an Alberhadren apparatus. Other supporting electrolytes were obtained from commercial sources and were dried under reduced pressure at 100 °C in the same apparatus.

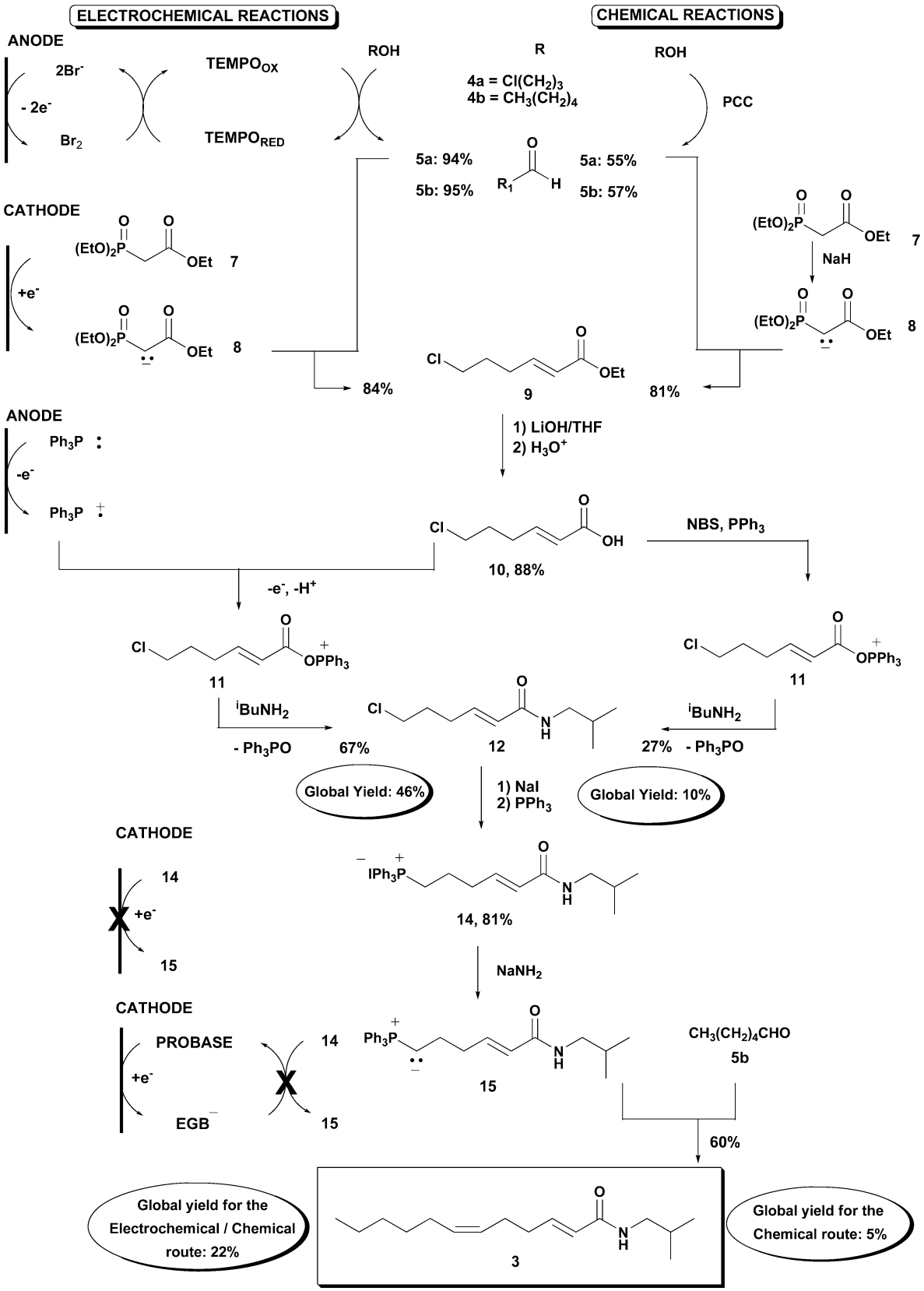
Melting points were determined on a Fisher-Johns apparatus. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured with a Varian Unity (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane in $CDCl_3$; *J* values are given in Hz. The following abbreviations are used: s, singlet; d, doublet; q, quartet; dd, doublet of doublets; t, triplet; m, multiplet; bs, broad signal. MS were recorded on a JEOL JMS-AX 505HA spectrometer by electron impact (EI). UV spectra were recorded in a Shimadzu U-160 spectrophotometer. Infrared spectra were recorded in film technique using a Nicolet Magna 750 spectrophotometer. The cyclic voltammetry and the preparative electrolysis were performed with EG & G PAR potentiostat Model 273A. The cyclic voltammetry was performed on a vitreous carbon disk electrode (3 mm diameter) using an Ag/AgCl reference electrode and a platinum wire as a counter-electrode. Platinum cylindrical gauze and titanium plate were used as cathodes in the preparative electrolysis, while magnesium rod, platinum cylindrical gauze and carbon plate were used as anodes. Thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Merck Silica gel 60 F_{254}). Column chromatography was performed on silica gel (Macherey-Nagel 230–400 mesh).

Chemical oxidation of alcohols 4a and b to aldehydes

In a round bottom-flask fitted with a reflux condenser PCC (89.6 g, 0.415 mol) and anhydrous CH_2Cl_2 (450 mL) were added. The alcohol **4** (0.277 mol) dissolved in anhydrous CH_2Cl_2 was slowly added. The mixture was magnetically stirred during 2.5 h at room temperature. Later, anhydrous diethylether (500 mL) was added to the reaction mixture. Black insoluble residue was washed with more anhydrous diethylether. The organic solution was passed through a short florisil® column followed by removal of solvent at reduced pressure. The aldehyde was purified by distillation at reduced pressure.

4-Chlorobutyraldehyde (5a). Colorless oil, bp. 77 °C (38 mm Hg) 16 g, 55%. IR (film, ν/cm^{-1}): 2710, CHO; 1715, CO. ^1H NMR: 2.10 (q, 2H, $CH_2CH_2CH_2$, J = 6.9), 2.67 (td, 2H, CH_2CHO, J = 6.9, 0.9), 3.6 (t, 2H, CH_2Cl, J = 6.3), 9.8 (t, 1H, CHO, J = 0.9). EI-MS m/z (rel. int. %): $[M + 2]^+$ 92(4), $[M]^+$ 90(12), 55(53), 42(81), 31(100).

Hexanal (5b). colorless oil, bp. 63–65 °C (60 mm Hg) 15.2 g, 57%. IR (film, ν/cm^{-1}): 2700, CHO; 1736, CO. ^1H NMR: 0.9 (t, 3H, CH_3, J = 6.9), 1.66–1.31 (m, 6H, $3CH_2$), 2.42 (td, 2H, CH_2CHO, J = 7.5, 2.0), 9.77 (t, 1H, CHO, J = 2.0). EI-MS m/z (rel. int. %): $[M]^+$ 100(1), 77(20), 56(83), 44(100), 41(72).



Scheme 11 Summary of the electrochemical (left) and chemical (right) routes used for the synthesis of *N*-isobutyl-(2*E*, 6*Z*)-dodecadienamide **3**.

Electrooxidation of alcohols 4a and b to aldehydes

Alcohol (10 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (15.6 mg, 0.1 mmol) were dissolved in CH_2Cl_2 (50 mL) in an electrolysis vessel. To this solution was added aqueous NaCl or NaBr (100 mL) saturated with $NaHCO_3$. Into the upper layer (aqueous) of the resulting biphasic mixture the electrodes were immersed in a parallel disposition: a centered carbon electrode (6 cm^2) was used as anode and two titanium electrodes (6 cm^2) behaved as the cathodes. The mixture was electrolyzed under a constant current of 70 mA cm^{-2} with a moderate stirring. The electrolysis was stopped when 2.3 F mol^{-1} of electricity were passed and organic phase was separated from aqueous phase using a separation funnel. The organic layer was purified with successive washes with 10% HCl (20 mL) containing NaI (0.25 g), 10% sodium thiosulfate (20 mL) and brine (20 mL). After that, the CH_2Cl_2 layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was analyzed by ^{1}H NMR in order to quantify the aldehyde. The product was purified by distillation at reduced pressure in a Kugelrohr. 4-Chlorobutaldehyde (**5a**) 0.96 g, 94%; hexanal (**5b**) 0.91 g, 95%.

Chemical synthesis of ethyl-6-chloro-2-*E*-hexenoate (9)

In a dry N_2 purged round flask, NaH was added (60% dispersion in mineral oil, 0.483 g, 11.96 mmol) in dry THF (15 mL). Triethylphosphonoacetate **7** (2.7 g, 11.96 mmol) dissolved in dry THF (5 mL) was added dropwise at 0 °C. This addition was carried out over 30 min and later the mixture was stirred for 1.5 h at the same temperature. After this time, a solution of **5a** (1.27 g, 11.96 mmol) in dry THF (5 mL) was added dropwise at 0 °C. The reaction mixture was allowed to slowly warm to room temperature and was stirred for 2 h at this temperature. The solvent was evaporated and the resulting residue was diluted with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried; evaporated and resulting oil was purified by column chromatography (hexane-EtOAc 95 : 5) to give **9** as oil (2.11 g, 81%). IR (film, ν/cm^{-1}): 1720, C=O; 1656, C=C. UV λ_{max}/nm (ε/L mol^{-1} cm^{-1}) (MeOH): 209 (246). ^{1}H NMR: 1.26 (t, 3H, CH_3, J = 7.2), 1.80–1.96 (m, 2H, CH_2), 2.30–2.40 (m, 2H, allylic-CH_2), 3.52 (t, 2H, CH_2Cl, J = 6.4), 4.16 (q, 2H, OCH_2, J = 7.2), 5.84 (d, 1H, CHCO, J = 15.6), 6.89 (dt, 1H, CH_2CH=CH, J = 15.6, 6.9). ^{13}C NMR: 14.2, 29.1, 30.6, 43.9, 60.2, 122.4, 146.8, 166.0. EI-MS, m/z (rel. int. %): $[M + 2]^+$ 178 (17), $[M]^+$ 176 (45), 150 (11), 148 (38), 131 (100), 99 (62), 67 (26), 55 (20), 41 (26), 33 (34), 29 (17).

Electrochemical synthesis of ethyl-6-chloro-2-*E*-hexenoate (9)

Into a previously N_2 purged (5 min) one-compartment cell, equipped with a concentric cylindrical Pt gauze as cathode (15 cm^2) and the magnesium rod as anode (12 cm^2), a solution containing anhydrous DMF (30 mL), the aldehyde **5a** (0.2 mol L^{-1}), Et_4NBF_4 (0.03 mol L^{-1}) and triethyphosphonoacetate **7** (0.1 mol L^{-1}) were added. The mixture was magnetically stirred under nitrogen and electrolyzed with 1 F mol^{-1} of electricity at constant current (2 mA cm^{-2}), the solution was maintained in the electrolysis cell for 0.5 h at room temperature under inert atmosphere. Lately, saturated NH_4Cl solution (50 mL) was added to the mixture reaction and extracted repeatedly with diethylether (3 × 25 mL). The organic fraction was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated by means of a rotatory evaporator. The product was purified by column chromatography (hexane–EtOAc, 95 : 5). The product was obtained as colorless oil (0.45 g, 84%).

Preparation of 6-chloro-(2*E*)-hexenoic acid (10)

To a solution of ester **9** (2.72 g, 15.45 mmol) dissolved in THF (20 mL) was added a solution of $LiOH{\cdot}H_2O$ in water (10 mL, 0.71 g, 17 mmol). The resulting mixture was stirred at room temperature for 22 h. THF was evaporated, and then to the residue was added 10% $NaHCO_3$ solution (3 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 15 mL), acidulated with 10% HCl until pH 4 and extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were put together, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated by means of a vacuum rotatory evaporator. The residue was purified by crystallization from hexane to give **10** (2.02 g, 88%) as white crystals (mp 36–37 °C). IR (KBr, ν/cm^{-1}): 2966 broad, O–H; 1697, C=O; 1655, C=C. UV λ_{max}/nm (EtOH): 207.2. ^{1}H NMR: 1.96 (q, 2H, H-5, J = 6.9), 2.42 (c, 2H, H-4 J = 6.9), 3.56 (t, 2H, H-6, J = 6.3), 5.9 (dt, 1H, H-2, J = 15.6, 1.5), 7.06 (dt, 1H, H-3, J = 15.6, 6.9). ^{13}C NMR: 29.3, 30.5, 43.8, 121.8, 149.9, 171.8. EI-MS, m/z (rel. int. %): $[M + 2]^+$ 150 (4.5) $[M]^+$ 148, 99 (100).

Chemical synthesis of *N*-isobutyl-6-chloro-(2*E*)-hexenamide (12)

To a stirred solution of triphenylphosphine (0.67 g, 2.55 mmol) and acid **10** (0.37 g, 2.5 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C, was added *N*-bromosuccinimide (NBS, 0.5 g, 2.8 mmol) in one portion. The mixture was stirred for 20 min letting it slowly reach room temperature. Isobutylamine (0.52 mL, 5.25 mmol) in anhydrous CH_2Cl_2 (4 mL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature in inert atmosphere (N_2). Next, to the mixture was added CH_2Cl_2 (20 mL) and it was washed in an extraction funnel with water (15 mL), 10% HCl (15 mL), saturated $NaHCO_3$ (15 mL), and finally with brine (15 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated at reduced pressure. The crude product was purified by column chromatography (hexane–AcOEt, 4 : 2) and crystallized from diethylether–hexane to give **12** (0.137 g, 27%) as white solid (mp 56–57 °C). IR (KBr, ν/cm^{-1}): 3297, NH; 3084, H–C=C; 2800–2990 C–H; 1668, CH=CH; 1625, CO. UV λ_{max}/nm (EtOH): 210.4. ^{1}H NMR: 0.93 (d, 6H, CH_3, J = 6.6 Hz), 1.88–1.74 (m, 1H, CH), 1.93 (q, 2H, CH_2 C**H**$_2$$CH_2$, J = 7.8 Hz), 2.35 (c, 2H, C**H**$_2$CH=CH, J = 7.2 Hz), 3.15 (t, 2H, CH_2N, J = 6.9), 3.55 (t, 2H, CH_2Cl, J = 6.6 Hz), 5.58 (s, broad, 1H, NH), 5.84 (dt, 1H, CH=C**H**CO, J = 15.3, 1.5 Hz), 6.80 (dt, 1H, C**H**–CH=C, J= 15.3, 6.9 Hz). ^{13}C NMR: 20.07, 28.5, 28.9, 30.85, 44.0, 46.8, 124.8, 142.3, 165.6. EI-MS, m/z (rel. int. %): $[M + 2]^+$ 205 (6.5), $[M]^+$ 203 (19.3), 190 (3.3), 188 (10), 162 (4), 150 (5.6), 148 (17.1), 133 (33), 131 (100), 60 (12.1).

Electrochemical synthesis of *N*-isobutyl-6-chloro-(2*E*)-hexenamide (12)

A solution of triphenylphosphine (0.524 g, 2 mmol), acid **10** (0.15 g, 1 mmol), ^{i}BuNH$_2$ (0.15 mL, 1.5 mmol, added in three parts during the electrolysis) and $LutClO_4$ (0.41 g, 2 mmol)

in dry deoxygenated (N_2) CH_2Cl_2 (35 mL) was placed in the electrolysis cell equipped with a two concentric cylindrical Pt gauze electrodes (15 cm^2 and 10 cm^2). The mixture was electrolyzed at 32 °C under N_2 atmosphere and at 1.31 mA cm^{-2} until 2.4 F mol^{-1} with respect to the acid **10** had passed. The solution was washed with 10% HCl (15 mL), brine (15 mL), 10% $NaHCO_3$ (15 mL) and finally with brine (15 mL). The organic layer was dried with anhydrous Na_2SO_4 and evaporated at reduced pressure. The crude product was purified by column chromatography (hexane–EtOAc, 4 : 2) and crystallized from diethylether–hexane to give **12** as a white solid (0.136 g, 67%).

Synthesis of Wittig salt (14)

A mixture of anhydrous NaI (previously dried in the rotary evaporator under house vacuum for 2 h at 80 °C, 32 g, 213 mmol), anhydrous acetone (250 mL) and chloro compound **12** was heated to reflux for 18 h. The reaction mixture was cooled and the precipitate was filtered out. The solid residue was washed with acetone and the acetone washes were put together with the filtrate. This solution was evaporated in the rotary evaporator under reduced pressure. The organic mixture was dissolved in ethyl acetate and was washed with brine and sodium thiosulfate solution (5%) to decolorize. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated by means of a vacuum rotatory evaporator. This crude product **13** was used without purification in the next step.

In a 250 mL round-bottom flask equipped with reflux condenser was dissolved triphenylphosphine (25.7 g, 98.2 mmol) in benzene (75 mL). Compound **13** was added to the solution and was heated to reflux for 24 h. After this time, the reaction was cooled down at 10 °C and the Wittig salt was separated by filtration. The solid was washed with hexane and then recrystallized from ethanol–EtOAc producing **14** (43.6 g, 81% yield) as white crystals (mp 187–188 °C). IR (KBr, ν, cm^{-1}): 1706, C=O; 1655, C=C. ^{1}H NMR: 0.92 (d, 6H, $3CH_3$, $J = 6.6$), 1.7–2.0 (m, 3H, $CH_2CH_2CH_2$, CH), 2.5–2.7 (m, 2H, CCH_2CH=C), 3.1 (t, 2H, $NHCH_2$, $J = 6.6$), 3.4–3.6 (m, 2H, CH_2P), 6.4 (d, 1H, CH_2CH=C**H**CO, $J = 15$), 6.6 (dt, 1H, CH_2CH=CH), 7.5 (s, 1H, NH), 7.6–8.0 (m, 15H, H aromatics). ^{13}C NMR: 19.9, 28.1, 31.3, 31.6, 46.5, 46.7, 118.2, 127.3, 130.2, 133.7, 134.9, 139.2, 166.4.

Preparation of *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide (3)

The dry Wittig salt **14** (1.2 g, 2.14 mmol) and an excess of commercial $NaNH_2$ powder (0.34 g, 8.6 mmol) were transferred to a dry test tube. The tube was previously closed with a septum and parafilm® and was N_2 purged. THF was added *via* syringe to prepare 0.2 mol L^{-1} solution of **14**. This reaction mixture was ultrasonically stirred in N_2 atmosphere for 20 min. During this time the ylide was formed and the solution took a brick red color. The N_2 line was removed and the tube was centrifuged to sediment the salts. The supernatant solution containing the salt-free ylide was transferred *via* a cannula to a dry round-bottom flask at −78 °C. To this solution was slowly added hexanal (0.204 g, 2.02 mmol) dissolved in dry THF (11 mL). The reaction mixture was stirred for 15 min at −78 °C and then the mixture was allowed to reach room temperature. After an hour at this temperature, water was added and three extractions with diethylether were carried out. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated by means of a vacuum rotatory evaporator. The residue was purified by column chromatography (hexane–AcOEt, 4 : 1) to give **3** as yellow oil (307 mg, 60%). IR (film, ν/cm^{-1}): 3288, NH; 3082, 309, H–C=C; 2850–2960, CH_3, CH_2, CHO; 1670, C=C; 1632, CO. UV $\lambda_{max.}$/nm: 212.5. ^{1}H NMR: 0.88–0.93 (m, 9H, $3CH_3$), 1.4–1.6 (m, 6H, $CH_3CH_2CH_2CH_2$), 1.8 (m, 1H, CH, $J = 6.9$ Hz), 2.0 (c, 2H, CH_2CH_2CH=CH, $J = 6.6$ Hz), 2.1–2.3 (m, 4H, CH=CHCH_2CH_2CH=CH), 3.1 (t, 2H,$NHCH_2CH_2$, $J = 6.6$ Hz), 5.3–5.5 (m, 2H, CH=CH, *Z* isomer), 5.85 (dt, 1H, CH=C**H**CO, $J = 15.3$, 1.2 Hz), 6.09 (s, NH), 6.81 (dt, 1H, CH_2CH=CHCO, $J = 15.3$, 6.3 Hz). ^{13}C NMR: 13.9, 20.0, 22.4, 25.9, 27.1, 28.4, 29.1, 31.3, 32.1, 46.8, 123.9, 127.9, 131.0, 143.5, 166.1. EI-MS, *m*/*z* (rel. int. %): 251 (32) $[M]^+$, 179 (59), 141 (100), 69 (85), 55 (57), 41 (44). HRMS FAB$^+$ *m*/*z* requires $C_{16}H_{30}NO$ $[M - H]^+$ 252.2327, found 252.2324.

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