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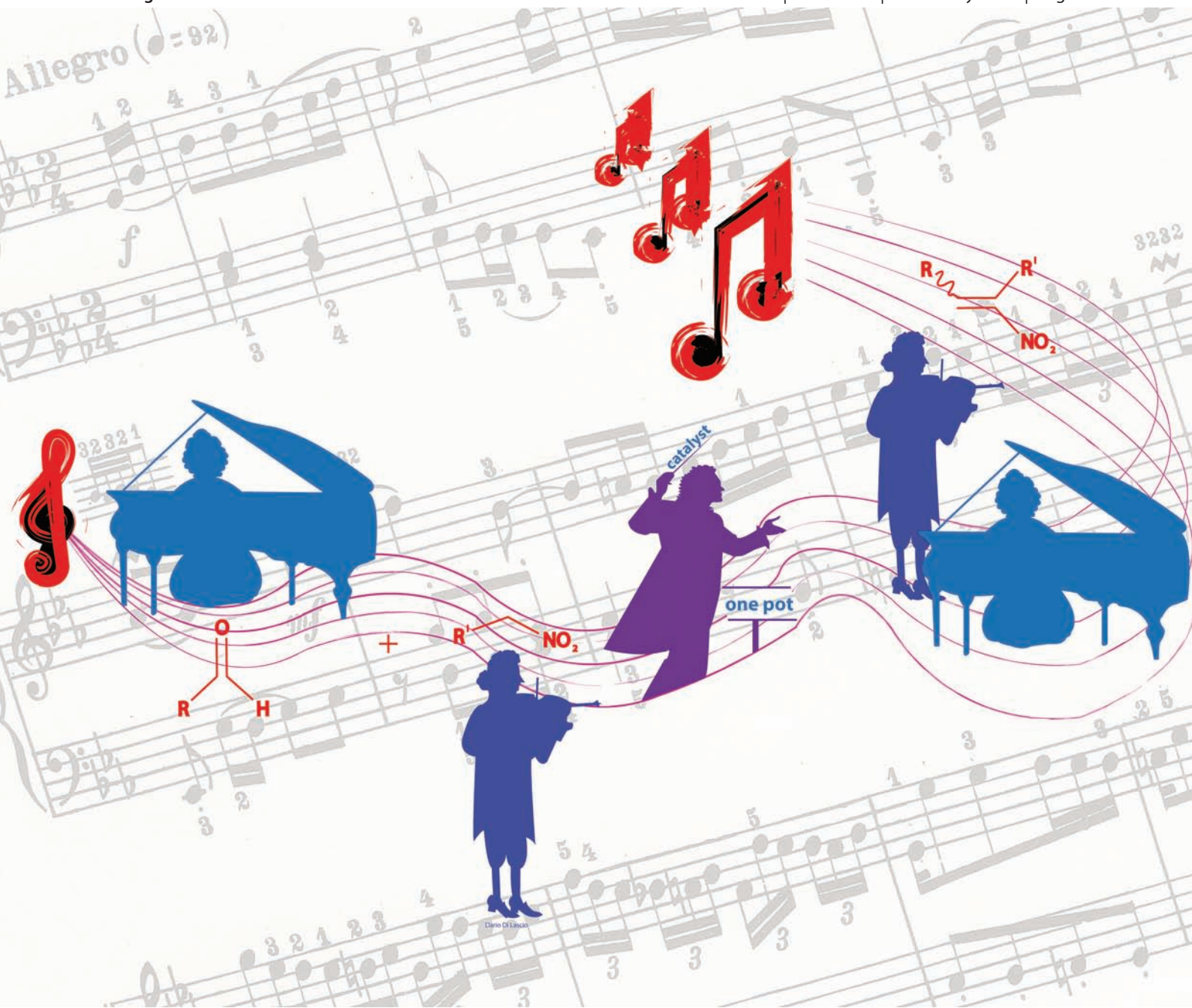

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PAPER

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PAPER

Domino reactions for the synthesis of various α-substituted nitro alkenes†

Stefania Fioravanti,* Lucio Pellacani* and Maria Cecilia Vergari

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Efficient one-pot methods for the synthesis of variously functionalised conjugated nitro alkenes have been reported. Despite the utility in different fields of these compounds, only a few multi-step syntheses have been reported in the literature, giving the target compounds in low overall yields. α-Nitro acrylates or cinnamates, α-nitro α,β-unsaturated ketones and, most importantly, aromatic and heteroaromatic (*E*)- 2-nitro allylic alcohols, compounds characterised by a well-known anticancer activity, were obtained in high yields and high diastereomeric purity by a domino condensation-dehydration process.

Introduction

The synthesis of conjugated nitro alkenes has been a challenge for many years because of their importance in terms either of their application as biological and pharmacologically active substances or of their synthetic utility in organic chemistry as key intermediates in the construction of more complex molecules.[1]

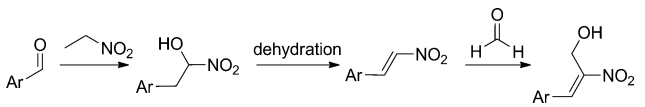
The synthetic versatility of these derivatives arises from the powerful electron-withdrawing effect of the nitro substituent that make them hard electrophiles and, therefore, good Michael acceptors[2] as well as efficient dienophiles in Diels-Alder reactions;[3] moreover, the nitro group can be converted into many other functionalities by simple transformations.[4]

Despite the utility in different fields of these compounds, to the best of our knowledge, just few syntheses were reported in the literature by a multi-step synthesis,[1a,5] resulting in low overall yields of the desired compounds. As is well known, the most common preparation of nitro alkenes involves a two-step reaction that strongly decreases the overall yield of their synthesis. In fact, a Henry reaction[6] leading to a C–C bond formation between a carbonyl compound and a nitro alkane,[7] followed by a dehydration step, often performed under harsh conditions, was required to obtain the target compounds.

Recently, we reported the use of activated 4 Å molecular sieves and piperidine as catalyst as a simple and efficient one-pot method to obtain unfunctionalised conjugated nitro alkenes in good yields.[8] Furthermore, nitro allylic *O*-nosyl hydroxylamines were successfully achieved starting from 2-nitro allylic alcohols, compounds easily obtained by our fast one-pot synthetic methodology.[9]

Concerning the 2-nitro allylic alcohols (hydroxymethyl nitro alkenes) recent studies have demonstrated their significant biological activity. In fact, Panda et coll. found that these kind of compounds present anticancer activity towards HeLa cells, when an aromatic group directly bound to the C=C is present.[10]

Aromatic and heteroaromatic (*E*)-2-nitro allylic alcohols were synthesized by a three-step procedure tested under different reaction conditions and involving in sequence a Henry condensation, a nitroaldol dehydration, and finally a Morita-Baylis-Hillman reaction (MBHR)[11] performed in the presence of aqueous formaldehyde (Scheme 1).[12]



Scheme 1 Aryl 2-nitro allylic alcohols by multi-step procedures.

The compounds were obtained in moderate to good yields, but it is necessary to stress that the reported data are referred only to the MBHR final step.

Results and discussion

Continuing our studies on the synthesis of functionalised conjugated nitro alkenes, the possibility of obtaining very interesting aromatic or heteroaromatic nitro allylic alcohols starting from 2-nitroethanol and different suitable aldehydes, by a high-throughput one-pot methodology, was considered.

Thus, 2-nitroethanol was reacted over 4 Å molecular sieves, in the presence of a catalytic amount of piperidine, with aromatic or heteroaromatic aldehydes **1a–g** under an inert atmosphere (Ar) at reflux of anhydrous toluene (Method **A**). The results are reported in Table 1.

As reported in Table 1, the domino reactions proceed with high stereoselectivity, giving only the (*E*)-2-nitro allylic alcohols **2a–g** with high purity and in very good overall yields, as confirmed by NMR analyses. We want to stress that when we performed the reaction without 4 Å molecular sieves, not under inert atmosphere and at room temperature, the expected products were obtained in

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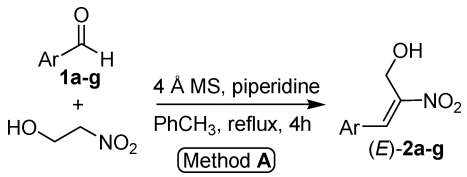
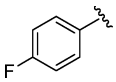
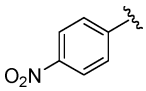
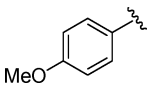
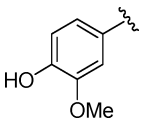
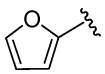
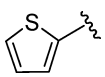
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for all the new compounds. See DOI: 10.1039/c1ob06260c

Table 1 Stereoselective one-pot synthesis of (*E*)-2-nitro allylic alcohols



Entry	1	Ar	2	Yield (%)[a]
1	**a**		**a**	70
2	**b**		**b**	65
3	**c**		**c**	60
4	**d**		**d**	65
5	**e**		**e**	50
6	**f**		**f**	95
7	**g**		**g**	85

[a] After filtration of the crude mixture on celite.

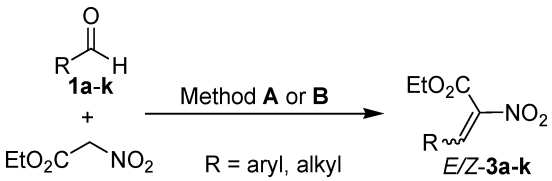
low yields, with the Henry adduct intermediates in the ^{1}H NMR spectra of the crude mixtures being distinctly present. Therefore, the higher temperature, the inert atmosphere and the use of 4 Å molecular sieves are conditions absolutely required to obtain total conversion and complete intermediate dehydration.

Buoyed by these results, the synthetic methodology has been applied to other different functionalised α-nitro alkenes for the synthesis of them are often required complex and few efficient procedures, involving even toxic and expensive reagents.[13]

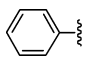
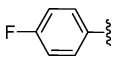
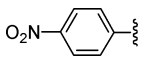
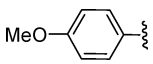
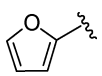
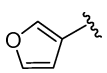
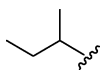
Thus, ethyl nitroacetate was considered as the ideal methylene compound for obtaining interesting α-nitro cinnamates and acrylates, known as versatile building blocks in organic synthesis and widely used due to their reactivity as good Michael acceptors and to the possibility of transforming either the nitro or the ester group into many other functional groups.[13b,14]

The reactions were performed by following Method **A**, but starting from several aryl or alkyl aldehydes the procedure failed and the synthesis starting from these last compounds required some changes, using Et_3N instead of piperidine as base, $ZrCl_4$ as catalyst and THF as solvent (Method **B**). The results are reported in Table 2.

Table 2 One-pot synthesis of α-nitro acrylates and cinnamates



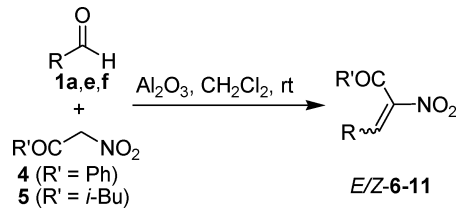
A: 4 Å MS, piperidine, $PhCH_3$, reflux, 4 h
B: 4 Å MS, Et_3N, $ZrCl_4$, THF, reflux, 4-48 h

Entry	1	Ar	Method	3	*E*/*Z* ratio[a]	Yield (%)[b]
1	**a**		**A** **B**	**a**	50:50 50:50	50 83
2	**b**		**A**	**b**	50:50	76
3	**c**		**B**	**c**	40:60	84[d]
4	**d**		**B**	**d**	35:65	95[e]
5	**f**		**A**	**f**	40:60	95
6	**g**		**A**	**g**	40:60	83
7	**h**		**A**	**h**	30:70	97
8	**i**		**A** **B**	**i**	40:60 40:60	51 91
9	**j**		**B**	**j**	30:70	95[d]
10	**k**		**B**	**k**	30:70	86[c]

[a] By ^{1}H NMR analysis on the crude mixture. [b] After purification on silica gel. [c] After 48 h. [d] After 24 h. [e] After 4 h.

As shown in Table 2, the expected α-nitro cinnamates **3a–i** and acrylates **3j**,**k** were obtained in all cases as *E*/*Z* mixtures in good to excellent yields, the stereoselectivity of the reaction decreasing as a function of the starting aldehydes. The *Z* isomer is almost always the major one. Surprisingly, following Method **A**, the one-pot condensation reactions do not take place starting from aldehydes **1c**,**d** (entries 3, 4) and **1j**,**k** (entries 9, 10). In effect, only when starting from **1d** and performing the reaction under Method **A**, the corresponding α-nitro cinnamate **3d** was observed but only in very low yields (< 5%). Then, the reactions on these substrates were attempted replacing piperidine with Et_3N or using basic alumina as both base and dehydrating agent,[15] but also under these conditions the expected compounds were not observed.

Table 3 Synthesis of (*E*/*Z*)-α-nitro α,β-unsaturated ketones



Entry	Alkene	R	R′	Time (h)	*E*/*Z* ratio[a]	Yield (%)[b]
1	**6**	*i*-Bu	Ph	16	85:15	85
2	**7**	*sec*-Bu		60	80:20	70
3	**8**	2-Furyl		72	95:5	65
4	**9**	*i*-Bu	*i*-Bu	20	10:90	93
5	**10**	*sec*-Bu		48	20:80	60
6	**11**	2-Furyl		16	40:60	85

[a] By ^{1}H NMR analysis on the crude mixture. [b] After purification on silica gel.

Therefore, by changing a synthetic method reported in the literature[13a] involving the use of very toxic $TiCl_4$, Method **B** was successfully developed, maintaining the presence of 4 Å molecular sieves as dehydrating agents, using Et_3N as base and, most importantly, adding $ZrCl_4$ as Lewis acid. $ZrCl_4$ was chosen as catalyst, instead of $TiCl_4$, being easier to handle, stronger Lewis acid, cheaper and more environmentally friendly.[16]

Under these different conditions, the reactions were kept at reflux of anhydrous THF and led to the expected *E*/*Z* compounds in excellent yields (Table 2, entries 1, 3, 4, 8, 9 and 10).

This unexpected reactive behaviour of aryl aldehydes **1c**, **d** and alkyl aldehydes **1j**, **k** might be due to the strong ability of $ZrCl_4$ to stabilize the negative charge on the oxygen atom, thus maximising the electrophilicity of the aldehyde carbon.

Continuing our studies on the possible one-pot strategies to synthesise different functionalised nitro alkenes, we found, to the best of our knowledge, that only one method to obtain α-nitro α,β-unsaturated ketones was reported, involving an acid-catalysed reaction between heteroaromatic aldehydes and nitro carbonyl compounds in the presence of $SOCl_2$ or acetic acid at reflux of benzene.[17]

In light of the greater reactivity of nitro ketones as active methylene compounds with respect to nitro esters, a direct base Al_2O_3-catalysed synthesis of α-nitro α,β-unsaturated ketones was attempted. By following reported procedures,[18] compounds **1a**, **e**, **f** were reacted with the commercially available nitromethyl phenyl ketone (**4**) and with the isobutyl nitromethyl ketone (**5**), the last one synthesised starting from isovaleraldehyde and nitromethane, by a procedure reported in the literature.[19,20] The results of the Al_2O_3-catalysed Knoevenagel condensations are reported in Table 3.

After filtration of Al_2O_3, (*E*/*Z*)-α-nitro α,β-unsaturated ketones were obtained in very good yields and high purity, as detected by NMR spectra. Starting from **4**, the *E* isomer is always the major one, while starting from **5** the stereoselective outcome was inverted, giving the *Z* isomer as the major one (entries 4–6).

The presence of an aryl group as substituent of the C=O increases the stability of the *E* isomer as a consequence of a high coplanarity with the alkene π system.[21] Noteworthy, the nitro alkenes derived from alkyl ketones show a stereoselectivity analogous but emphasised to that observed for the nitro alkenes derived from ethyl nitroacetate (see Table 2). In fact, the stability of the *Z* isomer probably arises from a weak intramolecular C–H···O hydrogen bond formation,[22] which is favoured with the acyl group with respect to the nitro group, as reported in the literature.[23]

We want to stress that the higher diastereoselective induction either for *E* or *Z* isomers is observed when an electronic effect (entry 3) or a steric hindrance (entry 4), respectively, are present on both reagents.

Conclusions

In this paper we present new and efficient one-pot methods for the synthesis of α-substituted nitro alkenes, important compounds for their application in organic synthesis[24] and for their biological significance. In particular, we devised a one-pot synthesis of aryl (*E*)-nitro allylic alcohols, characterised by a known anticancer activity. Moreover, our methodology allows to obtain these compounds in high yields and high diastereomeric purity. Despite their potential use and application in many fields, only a few examples of synthetic procedure to obtain these compounds have been reported in the literature so far.

Experimental section

General remarks

All reactions requiring dry conditions were performed in flame dried glassware under inert atmosphere (Ar). All the commercial available reagents [(aldehydes **1a–k**, 2-nitroethanol, ethyl nitroacetate and nitromethyl phenyl ketone (**4**)] and the anhydrous solvents were purchased from *Aldrich* and used without further purification. Molecular sieves type 4 Å (beads, diameter 1.7–2.4 mm, *Aldrich*) were activated by heating at 280 °C for 2 h under vacuum. Basic Al_2O_3 (70–230 mesh ASTM) were purchased from *Fluka*. The reactions were monitored by ^{1}H NMR analysis. Flash chromatography were performed on Merck silica gel (60, particle size: 0.040–0.063 mm).^{1}H NMR and ^{13}C NMR spectra were recorded on a VARIAN XL-300 spectrometer at room temperature. $CDCl_3$ was used as the solvent and $CHCl_3$ as the internal standard. FT-IR spectra were recorded on a Perkin–Elmer 1600 spectrophotometer in $CHCl_3$ as the solvent. HRMS analyses were performed using a Micromass Q-TOF Micro quadrupole-time of flight (TOF) mass spectrometer equipped with an ESI source and a syringe pump. The experiments were conducted in the positive ion mode. Isobutyl nitromethyl ketone (**5**)[25] was synthesised, according to the procedure reported in the literature.[19,20] **2a**,**b**, **d–g**,[10] **2c**,[26] **3a**,[27] **3c**,[28] **3b**,**d**,**f**,**g**,[13a] **3h**,**i**,[29] **3j**,[30] and **8**[17] are known compounds.

General procedure for the one-pot synthesis of (*E*)-nitro allylic alcohols 2a–g (Method A)

A solution of 2-nitroethanol (228 mg, 2.5 mmol) and an aromatic or heteroaromatic aldehyde **1a–g** (2.5 mmol) in anhydrous $PhCH_3$ (12 mL) was added under Ar in a round-bottom flask containing previously activated 4 Å molecular sieves (5 g). A catalytic amount of piperidine was added (10% mol) and the reactions, followed by the ^{1}H NMR analysis, were kept at reflux for 4 h. The crude

mixtures were filtered under inert atmosphere (Ar or N_2) through a plug of celite to remove the molecular sieves using CH_2Cl_2 as eluent and the solvents were evaporated under vacuum. The products were purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2 for **2a**,**g**; 7:3 for **2b**,**d**,**f**; 25:75 for **2c**; 85:15 for **2e**.)

General procedure for the one-pot synthesis of α-nitro acrylates and cinnamates 3a,b,f–i

For the synthesis of title compounds the general procedure before reported (Method **A**) was followed. The products were purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 7:3 for **3a**; 9:1 for **3b**; 8:2 for **3g**,**h**; 85:15 for **3i**. **3f** was purified using hexane/dichloromethane = 4:6 as eluent).

General procedure for the one-pot synthesis of α-nitro acrylates and cinnamates 3c,d,j,k (Method B)

To a solution of ethyl nitroacetate (266 mg, 2 mmol) and an aromatic or aliphatic aldehyde (2.4 mmol) in anhydrous THF (8 mL), kept at 0 °C under Ar in a round-bottom flask containing previously activated 4 Å molecular sieves (5 g), zirconium tetrachloride (932 mg, 4 mmol) was added. The mixtures were kept stirring at 0 °C for 10 min, then a solution of triethylamine (808 mg, 8 mmol) in anhydrous THF (8 mL) was added dropwise for 15 min. The reaction mixtures were refluxed until the ^{1}H NMR analysis showed the disappearance of ethyl nitroacetate (see Table 2). The crude mixtures were filtered through a plug of celite to remove the molecular sieves using THF as eluent and the solvent was evaporated under vacuum. Thus, the residues were recovered with 10 mL of Et_2O and 15 mL of water were added. After extraction (three times with diethyl ether), the collected organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The products were purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2 for **3c**; 9:1 for **3j**. **3d** was purified using as eluent hexane/dichloromethane = 1:1).

Ethyl (*E*/*Z*)-4-methyl-2-nitrohex-2-enoate (*E*/*Z*-3k). Isolated yield 86%. Pale yellow oil. Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 95:5). ν_{max} cm^{-1} 2932, 1740, 1662, 1530. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.01 (d, *J* = 11.2 Hz, 1H, minor isomer), 6.63 (d, *J* = 11.1 Hz, 1H, major isomer), 4.36 (q, *J* = 7.1 Hz, 2H, minor), 4.31 (q, *J* = 7.1 Hz, 2H, major), 2.69–2.54 (m, 1H, minor), 2.44–2.33 (m, 1H, major), 1.58–1.38 (m, 4H), 1.35 (t, *J* = 7.1 Hz, 3H, minor), 1.32 (t, *J* = 7.1 Hz, 3H, major), 1.12 (d, *J* = 6.7 Hz, 3H, minor), 1.10 (d, *J* = 6.6 Hz, 3H, major), 0.90 (t, *J* = 7.4 Hz, 3H, minor), 0.88 (t, *J* = 7.4 Hz, 3H, major). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.9 (minor isomer), 158.7 (major isomer), 147.4 (2C), 144.4 (2C), 62.6 (major), 62.5 (minor), 35.1 (major), 34.6 (minor), 29.1 (minor), 28.9 (major), 19.2 (minor), 19.0 (major), 13.9 (major), 13.8 (minor), 11.5 (2C). HRMS: *m*/*z* [M + Na]$^+$ calcd. for $C_9H_{15}NNaO_4$ 224.0899, found 224.0893.

General procedure for the synthesis of conjugated (*E*/*Z*)-α-nitro ketones 6–11

To a solution of nitro compound **4** or **5** (2 mmol) and an aromatic or aliphatic aldehyde (2.5 mmol) in CH_2Cl_2 (5 mL), 2 g of basic Al_2O_3 were added and the mixtures were kept stirring at room temperature. The reactions were followed by ^{1}H NMR analyses (see Table 3). Then, the mixtures were filtered off and the solvent was evaporated under vacuum to give the crude mixtures. The products were purified by flash chromatography on silica gel (**8** was purified using as eluent hexane/dichloromethane = 3:7).

(*E*/*Z*)-5-Methyl-2-nitro-1-phenylhex-2-en-1-one (*E*/*Z*-6). Isolated yield 85%. Pale yellow oil. Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 9:1). ν_{max} cm^{-1} 2954, 1679, 1598, 1536. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89–7.85 (m, 2H, major isomer), 7.77–7.74 (m, 2H, minor isomer), 7.67–7.61 (m, 2H), 7.56–7.48 (m, 5H), 6.64 (t, *J* = 7.8 Hz, 1H, minor), 2.38 (dd, *J* = 6.9 Hz, 7.7 Hz, 2H, minor), 2.13 (dd, *J* = 6.8 Hz, 8.2 Hz, 2H major), 1.95–1.81 (m, 2H), 1.00 (d, *J* = 6.7 Hz, 6H, minor), 0.90 (d, *J* = 6.7 Hz, 6H, major). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.5 (2C), 141.4 (major isomer), 141.1 (minor isomer), 135.6 (minor), 135.5 (major), 134.6 (2C), 133.6 (2C), 129.1 (2C, major), 129.0 (2C, major), 128.9 (2C, minor), 128.8 (2C, minor), 37.2 (minor), 36.3 (major), 28.3 (major), 28.2 (minor), 22.4 (2C, minor), 22.3 (2C, major). HRMS: *m*/*z* [M + Na]$^+$ calcd. for $C_{13}H_{15}NNaO_3$ 256.0950, found 256.0955.

(*E*/*Z*)-4-Methyl-2-nitro-1-phenylhex-2-en-1-one (*E*/*Z*-7). Isolated yield 75%. Pale yellow oil. Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). ν_{max} cm^{-1} 2932, 1679, 1598, 1530. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90–7.86 (m, 2H, major isomer), 7.76–7.73 (m, 2H, minor isomer), 7.67–7.61 (m, 2H), 7.54–7.48 (m, 4H), 7.29 (d, *J* = 11.5 Hz, 1H, major). 6.37 (d, *J* = 10.5 Hz, 1H, minor), 2.35–2.20 (m, 2H), 1.52–1.42 (m, 4H), 1.16 (d, *J* = 6.6 Hz, 3H, minor), 1.09 (d, *J* = 6.6 Hz, 3H, major), 0.86 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 186.9 (2C), 146.8 (major isomer), 146.7 (minor isomer), 135.6 (2C), 134.6 (2C), 133.6 (2C), 129.1 (2C, major), 129.0 (2C, major), 128.9 (2C, minor), 128.8 (2C, minor), 35.5 (minor), 34.5 (major), 29.2 (2C), 19.3 (2C), 11.8 (minor), 11.7 (major). HRMS: *m*/*z* [M + Na]$^+$ calcd. for $C_{13}H_{15}NNaO_3$ 256.0950, found 256.0954.

(*E*/*Z*)-2,8-Dimethyl-5-nitronon-5-en-4-one (*E*/*Z*-9). Isolated yield 93%. Pale yellow oil. Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 85:15). ν_{max} cm^{-1} 2958, 1698, 1653, 1555. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16 (t, *J* = 8.1 Hz, 1H, minor isomer), 6.67 (t, *J* = 7.9 Hz, 1H, major isomer), 2.50 (d, *J* = 6.9 Hz, 2H, minor), 2.44 (d, *J* = 6.8 Hz, 2H, major), 2.18 (dd, *J* = 6.9 Hz, 8.1 Hz, 2H, minor), 2.11 (dd, *J* = 6.9 Hz, 7.8 Hz, 2H, major), 1.88–1.74 (m, 4H), 0.90 (d, *J* = 6.7 Hz, 12H), 0.89 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.1 (minor isomer), 189.9 (major isomer), 153.1 (2C), 137.1 (2C), 46.1 (2C), 36.9 (minor), 36.8 (major), 28.2 (minor), 27.9 (major), 25.3 (minor), 24.9 (major), 24.4 (2C), 24.2 (2C), 22.3 (2C), 22.2 (minor), 22.1 (major). HRMS: *m*/*z* [M + Na]$^+$ calcd. for $C_{11}H_{19}NNaO_3$ 236.1263, found 236.1266.

(*E*/*Z*)-2,7-Dimethyl-5-nitronon-5-en-4-one (*E*/*Z*-10). Isolated yield 60%. Pale yellow oil. Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 9:19). ν_{max} cm^{-1} 2957, 1698, 1649, 1558. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.97 (d, *J* = 11.4 Hz, 1H, minor isomer), 6.45 (d, *J* = 10.9 Hz, 1H, major isomer), 2.55 (d, *J* = 7.0 Hz, 2H, minor), 2.49 (d, *J* = 6.9 Hz, 2H, major), 2.44–2.28 (m, 2H), 2.26–2.10 (m, 2H), 1.52–1.40 (m, 4H), 1.10 (d, *J* = 6.6 Hz, 3H, major), 1.09 (d, *J* = 6.8 Hz, 3H, minor),

0.95 (d, J = 6.6 Hz, 12H), 0.88 (t, J = 7.5 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.0 (2C), 147.4 (2C), 142.7 (2C), 46.2 (2C), 35.3 (major isomer), 34.2 (minor isomer), 29.3 (minor), 29.1 (major), 25.0 (major), 24.5 (minor), 22.4 (2C, major), 22.3 (2C, minor), 19.4 (minor), 19.2 (major), 11.7 (minor), 11.6 (major). HRMS: m/z [M + Na]$^+$ calcd. for $C_{11}H_{19}NNaO_3$ 236.1263, found 236.1269.

(*E*/*Z*)-1-(Furan-2-yl)-5-methyl-2-nitrohex-1-en-3-one (*E*/*Z*-11). Isolated yield 85%. Yellow oil. Purified by flash chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2). ν_{max} cm^{-1} 2964, 1691, 1634, 1544. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (s, 1H minor isomer), 7.64–7.63 (m, 1H, major isomer), 7.63–7.61 (m, 1H, minor), 7.23 (s, 1H, major), 7.06 (d, J = 3.6 Hz, 1H, minor), 6.95 (d, J = 3.6 Hz, 1H, major), 6.61–6,57 (m, 2H), 2.71 (d, J = 6.7 Hz, 2H, minor), 2.54 (d, J = 6.9 Hz, 2H, major), 2.40–2.17 (m, 2H), 1.02 (d, J = 6.7 Hz, 6H, minor), 0.98 (d, J = 6.7 Hz, 6H, major). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.7 (2C), 148.2 (2C), 145.3 (2C), 122.4 (2C), 121.8 (minor isomer), 121.2 (major isomer), 118.1 (2C), 113.8 (minor), 113.4 (major), 51.6 (minor), 45.6 (major), 25.0 (major), 23.9 (minor), 22.4 (2C, major), 22.3 (2C, minor). HRMS: m/z [M + Na]$^+$ calcd. for $C_{11}H_{13}NNaO_4$ 246.0742, found 246.0748.

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