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Exploring the versatility of the Johnson–Claisen rearrangement: access to functionally versatile δ-ethoxycarbonyl-α,β-unsaturated nitriles

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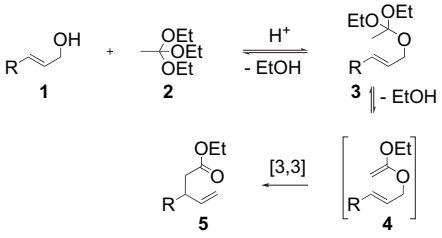
ABSTRACT

A practical entry into δ-ethoxycarbonyl-α,β-unsaturated nitriles is described. α,β-Unsaturated aldehydes were converted to cyanohydrins, by employing either KCN in aqueous acid, or by using TMSCN with catalytic K_2CO_3, followed by acid hydrolysis of the TMS ether. These cyanohydrins underwent a Claisen rearrangement employing a modified Johnson–Claisen protocol to yield unsaturated nitriles in good yields and with moderate *E*/*Z* selectivity.

1. Introduction

Carbon–carbon bond forming reactions are fundamental tools in synthetic organic chemistry. Foremost among these is the Claisen rearrangement, which describes a thermally allowed concerted rearrangement of an allyl vinyl ether into an unsaturated aldehyde or ketone.[1] The numerous variants of the Claisen rearrangement attest to the importance of this powerful transformation. Of the different modifications, the Johnson–Claisen variant is a well-established and reliable method for converting allylic alcohols into γ,δ-unsaturated esters.[2,3] The effectiveness of this method can be attributed to the execution of several steps in a one-pot procedure, without recourse to strictly anhydrous conditions. The standard procedure typically involves heating an allylic alcohol in the presence of an excess of orthoester (typically trimethyl or triethyl ortho acetate) and a catalytic amount of a weak protic acid at temperatures ranging from 140 to 200 °C.[3] As depicted in Scheme 1, an allylic alcohol **1** condenses with the orthoester **2** under acid catalysis to form a mixed orthoester intermediate **3** (which is generally not isolated). This process is however reversible and the equilibrium can be shifted in the forward direction by distilling off the low-boiling alcohol by-product. Further acid-catalysed elimination of alcohol from **3** gives a ketene acetal intermediate **4**, which subsequently undergoes a thermal [3,3] sigmatropic rearrangement to give a γ,δ-unsaturated ester **5**.[2]



Scheme 1. The Johnson–Claisen rearrangement.

While useful, the Johnson–Claisen rearrangement requires rather harsh reaction conditions[4] and these high reaction temperatures, acid catalysis and long reaction times may not always be compatible with sensitive substrates. To date, development of methodology for milder reaction conditions has received limited attention. Johnson–Claisen reactions performed under microwave irradiation are reported to reduce reaction times and improve yields, however they too are performed at elevated temperatures.[5] For some time we have been interested in developing methodology to reduce these harsh reaction conditions of the Johnson–Claisen reaction and we have recently reported a variation, promoted by triisobutylaluminium (TIBAL), that occurs at room temperature (Scheme 2).[6] We wished to complement this methodology by

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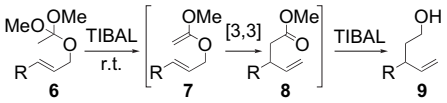
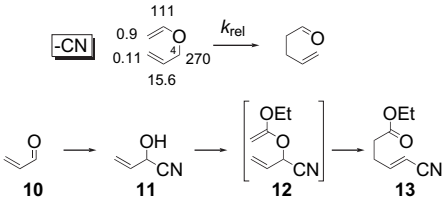
examining an alternative approach, which did not require TIBAL, and so would be compatible with substrates containing reducible functional groups.



Scheme 2. A room temperature triisobutylaluminium-promoted Johnson–Claisen rearrangement.[6]

Substituent effects on the rate of the Claisen rearrangement have been extensively investigated, both experimentally and theoretically.[7–10] The most impressive substituent-induced rate enhancement of the Claisen rearrangement is observed for the 4-cyano-substituted allyl vinyl ether, which leads to a 270-fold rate enhancement, relative to an unsubstituted allyl vinyl ether.[7,8] Remarkably, this impressive increase in rate caused by a 4-cyano substituent appears never to have been exploited synthetically. We therefore sought to apply the rate enhancement promoted by the 4-cyano group to the Johnson–Claisen rearrangement, with the expectation that by lowering the activation energy of this reaction, it could be executed under milder conditions and so be applied to thermally-sensitive substrates (Scheme 3).



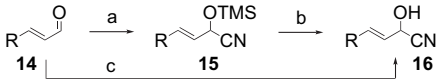
Scheme 3. Effects of cyano substituents on the rate of the Claisen reaction, relative to the unsubstituted allyl vinyl ether, and proposed Johnson–Claisen rearrangement of allylic cyanohydrins.

Retro-synthetically the starting substrate for a Johnson–Claisen reaction bearing a 4-cyano substituent (**12**) is an allylic cyanohydrin **11**, readily prepared from enal **10**, and the expected product would be a thermodynamically stable δ-alkoxycarbonyl-α,β-unsaturated nitrile **13** (Scheme 3). δ-Alkoxycarbonyl-α,β-unsaturated nitriles **13** are potentially very versatile synthetic intermediates in organic chemistry. These densely functionalised molecules may find use as precursors for further synthetic transformations such as conjugate additions and carbon–carbon double-bond reactions, and are also capable of a multitude of functional group transformations at both the nitrile and ester functionalities.

Surprisingly, the Johnson–Claisen reaction has not yet been applied to allylic cyanohydrins. In view of the potential for milder reaction conditions, combined with the utility of δ-alkoxycarbonyl-α,β-unsaturated nitriles, we decided to explore the Johnson–Claisen rearrangement of allylic cyanohydrins. Herein we report our results.

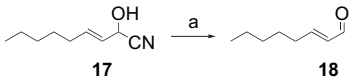
2. Results and discussion

Syntheses of allylic cyanohydrins **16** are frequently accomplished by the reaction of an α,β-unsaturated aldehyde **14** with HCN, generally formed in situ from KCN and aqueous acid. Usually, the reaction equilibrium favours formation of products, but yields can be maximised by adding TMSCN and trapping the cyanohydrin irreversibly as its TMS ether **15**. The TMS group of **15** can then be readily hydrolysed with mild acid to give the cyanohydrins **16**. We utilised both methods to synthesise a range of allylic cyanohydrin substrates, and found that addition of TMSCN and then deprotection to the cyanohydrins, albeit over two steps, gave consistently better yields (Scheme 4).



Scheme 4. Reagents and conditions: (a) TMSCN, K_2CO_3, neat, rt, 6 h; (b) 5% HCl, MeCN, rt; (c) KCN, 16% HCl, Et_2O, rt, 3 h.

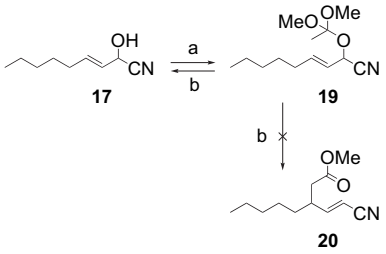
As a model substrate for the Johnson–Claisen reaction, we examined the allylic cyanohydrin **17**, readily prepared from 2-octenal **18**. To our dismay, subjecting **17** to the standard Johnson–Claisen conditions (excess of triethyl ortho acetate, catalytic propionic acid at reflux) resulted in a complex mixture with the predominant product being the α,β-unsaturated aldehyde **18** from which the cyanohydrin was derived (Scheme 5). Trace amounts of the desired δ-alkoxycarbonyl-α,β-unsaturated nitrile were formed and isolated by flash column chromatography, however yields were poor. Employing strictly anhydrous conditions increased the yield of the rearranged nitrile only slightly. We tried using commonly employed solvents such as toluene, xylene and DMF with limited improvements. Both trimethyl ortho acetate and triethyl ortho acetate were tested along with catalysts such as acetic acid, trifluoroacetic acid, sulfuric acid and hydroquinone without any major improvement in yields. Various reaction temperatures and times were trialled along with changing the order of reagent addition to the reaction and the number of molar equivalents of orthoester, all without significant improvement in yields. Different allylic cyanohydrins were also tested but they all decomposed to their respective enals. The reaction was also tested in a microwave reactor using conditions similar to those we had trialled under conventional heating, and with equally limited success. A literature search revealed a report by Gerrits et al. who found that cyanohydrins rapidly decompose in water and simple alcohols to give the parent aldehyde.[11] We thought it likely that the low-boiling alcohol evolved during the Johnson–Claisen reaction, in conjunction with the high reaction temperatures, was responsible for the decomposition of the cyanohydrins. We therefore tried a protocol, which used trimethyl ortho acetate and activated 4 Å sieves, so that we could remove the methanol as it was formed. Unfortunately we did not observe a significant improvement in yield. Removal of the low-boiling alcohol by-product under standard refluxing conditions was ineffective, and so we tested a Dean–Stark type attachment containing 4 Å molecular sieves under both atmospheric and reduced pressure, however there were no significant gains in yield.



Scheme 5. Reagents and conditions: (a) $MeC(OEt)_3$, H^+(cat.), Δ.

Clearly a change of approach was required; we sought then to eliminate methanol from an isolated allylic mixed orthoester **19** (Scheme 6),[12] forming the mixed ketene acetal, which we expected would immediately undergo sigmatropic rearrangement to the Claisen product **20**.[6] This method would minimise exposure of the allylic cyanohydrin to the destabilising low-boiling alcohol. The standard Johnson–Claisen rearrangement utilises protic acid to eliminate a molecule of alcohol from the mixed orthoester to form the mixed ketene acetal intermediate. We added **19** to a solution of toluene and propionic acid at reflux (Scheme 6), predominantly yielding again regenerated allylic cyanohydrin **17** and forming only a small quantity of the rearranged ester **20**. This suggested that

there was a greater likelihood of elimination of the allylic alcohol moiety from **19**, rather than methanol, as was required to form the mixed ketene acetal intermediate.

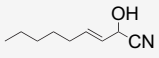
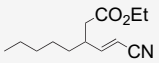
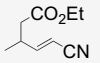
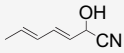
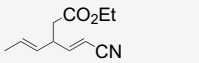
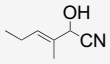
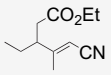
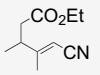
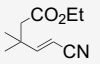
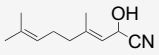
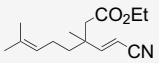
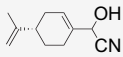
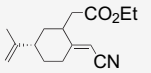
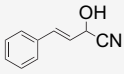
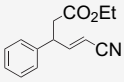
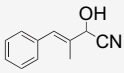
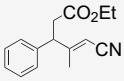
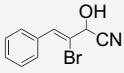
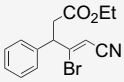
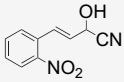
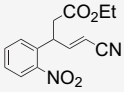


Scheme 6. Reagents and conditions: (a) $CH_2{=}C(OMe)_2$, neat, rt, 30 min; (b) propionic acid, toluene, Δ.

We then decided to carefully examine the decomposition of the allylic cyanohydrin **17** by ^{1}H NMR spectroscopy. The allylic cyanohydrin was added to an NMR tube containing trialkyl ortho acetate and propionic acid in toluene-d_8 and the temperature was increased to 80 °C. Spectra were then acquired during several hours. To our delight we discovered that the addition of an *excess* of propionic acid drastically slowed the rate of cyanohydrin decomposition. After optimising the reaction conditions we found that the best yields of the δ-ethoxycarbonyl-α,β-unsaturated nitrile products were obtained by employing an excess of triethyl ortho acetate and a large excess of propionic acid in xylenes at 130 °C. Whilst rearranged product **20** could be observed at temperatures as low as 90 °C, efficient conversion required higher reaction temperatures. We are now pleased to report a modified Johnson–Claisen protocol, which we have applied to various allylic cyanohydrins, as shown in Table 1.

The reaction products predominantly consisted of the desired δ-ethoxycarbonyl-α,β-unsaturated nitriles, however they also contained smaller amounts of allylic aldehyde and ethyl propionate. That the expected α,β-unsaturated nitriles had in fact formed was confirmed by peaks in the ^{13}C NMR spectra of the products at around 117 ppm, along with peaks at around 171 ppm, typical for ethyl esters. Characteristic bands in the IR spectra at

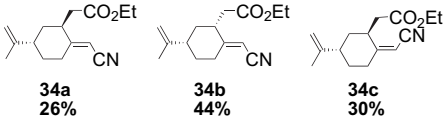
Table 1
Yields and isomer ratios of δ-ethoxycarbonyl-α,β-unsaturated nitriles

Entry	Cyanohydrin		Yield, % (method)[a]	δ-Ethoxycarbonyl-α,β-unsaturated nitriles[b]		Ratio[c] (*Z*/*E*)	Yield,[d] %
1		**17**	96 (A)		**20**	24:76	76
2		**21**	72 (A)		**22**	24:76	66[e]
3		**23**	62 (B)		**24**	30:70	59
4		**25**	90 (B)		**26**	24:76	73
5		**27**	78 (B)		**28**	26:74	73
6		**29**	60 (B)		**30**	7:93	76
7		**31**	72 (B)		**32**	7:93	76
8		**33**	73 (B)		**34**	30:70	75
9		**35**	78 (A)		**36**	22:78	73
10		**37**	63 (A)		**38**	20:80	40
11		**39**	13 (A)		**40**	100:0	13
12		**41**	50 (B)		**42**	—	0

[a] Method A: KCN, aq HCl, Et_2O, rt. Method B: (i) TMSCN, K_2CO_3, rt (ii) aq HCl, MeCN, rt.
[b] Optimised method: $EtCO_2H$ (12.3 equiv), $MeC(OEt)_3$ (24 equiv), xylenes, Δ, 24 h.
[c] The *E*/*Z* ratio was measured by ^{1}H NMR spectroscopy.
[d] Isolated uncorrected yields.
[e] Lower yield due to evaporative losses.

around 2200 cm^{-1} for the nitrile group (and at around 1730 cm^{-1} for the ethyl ester functional group) were also observed. As is typical for cyanohydrins, nitrile bands in the IR spectra of the starting materials were very weak or not observed. Isolation of the δ-ethoxycarbonyl-α,β-unsaturated nitriles was readily achieved by flash column chromatography. Presumably the large excess of protic acid decreases the amount of free ethanol by sequestering it as ethyl propionate, thereby limiting the likelihood of the cyanohydrin reconverting to the aldehyde. Anhydrous conditions were necessary for the reactions to proceed in high yields; all of the reagents were dried by distillation prior to reaction, the cyanohydrin was dried under high vacuum, and the xylene was dried over molecular sieves.

The majority of allylic cyanohydrins we examined were converted to δ-ethoxycarbonyl-α,β-unsaturated nitriles in yields greater than 70%. The unsaturated nitrile products are very stable and NMR analysis showed that storage at room temperature for several months did not lead to decomposition. Allylic cyanohydrins possessing di-, and tri-substituted alkenes were capable of rearrangement and the reaction conditions are compatible with the presence of an additional double bond and a benzyl group. The Johnson–Claisen rearrangement of allylic cyanohydrins (entries 1–10) predominantly led to formation of the *E*-isomer. The *E*-selectivity of the reaction is fairly consistent for entries 1–5, 9 and 10. Interestingly, allylic cyanohydrins possessing β-disubstituted double bonds (entries 6 and 7) yielded higher proportions of the *E*-isomers of the products. The geometry around the double bonds of compounds **38** and **40** were confirmed by NOESY experiments. Notably, the reaction seems to be sensitive to an increased steric hindrance around the double bond imposed by an aromatic group and methyl group, leading to a low yield of **38**. In comparison, the absence of a methyl group at the α-position did little to hinder the reaction as shown for product **36**, however further increase in steric bulk by replacement of the methyl group with a bromo-group as in **39** led to a further reduction in yield. The absolute stereochemistry of the isomers of compound **34** has not been unequivocally determined; however it has been tentatively assigned on the basis of COSY and NOESY correlations. The minor isomer was able to be partially purified from the other isomers and is assigned the following structure **34a**. The remaining two isomers, which were unable to be separated chromatographically have been assigned the following structures **34b** and **34c** (Fig. 1).



34a 26% **34b** 44% **34c** 30%

Figure 1. Stereochemical assignments of isomers **34a–c**.

3. Conclusion

The Johnson–Claisen reaction fails for allylic cyanohydrins when the standard conditions are employed. The reaction may be successfully accomplished, however, by using a large excess of acid catalyst and a large excess of triethyl ortho acetate in hot xylenes, giving good yields of δ-ethoxycarbonyl-α,β-unsaturated nitriles. These reactions can be performed on a diverse range of allylic cyanohydrins and display moderate *E*/*Z* selectivity.

4. Experimental

4.1. General experimental

All NMR experiments were recorded on Bruker AVANCE 500, 400 or 300 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) on a δ scale, and referenced to the residual solvent peak (^{1}H NMR 7.24 ppm, ^{13}C NMR 77.0 ppm for $CDCl_3$; ^{1}H NMR 7.15 ppm, ^{13}C NMR 128 ppm for C_6D_6; ^{1}H NMR 1.94 ppm, ^{13}C NMR 118.3 for CD_3CN). Coupling constants (*J*) are reported in hertz. Melting points were determined on a Stuart SMP11 Melting Point apparatus and are uncorrected. Low- and high-resolution EIMS were measured on a Finnigan MAT 900 XL-Trap mass spectrometer in positive ionisation mode. LR-ESI data were recorded on a Bruker HCT 3D Ion Trap and HR-ESI data were recorded on a Bruker MicrOTof-Q with the DIONEX Ultimate 3000 LC in positive electrospray ionisation mode. GC/MS data were recorded on a Shimadzu GC-17A Ver.3, mass spectrometer. IR spectra were recorded on a Perkin–Elmer FT-IR spectrometer (Spectrum 2000) and are only reported for the rearranged nitriles, because cyanohydrins have a very weak nitrile stretching frequency.[13] Spectroscopic data for the allylic cyanohydrins have generally been previously reported. Unfortunately, all the allylic cyanohydrins underwent dehydrocyanation when subjected to GC–MS or ESI-MS, using acetonitrile, methanol or diethyl ether as the solvent. Notably, mass spectral data are frequently not reported for cyanohydrins.[14–18] In addition, several accounts, which have reported mass spectral data, identify peaks corresponding to dehydrocyanation of cyanohydrins.[19–23] All of the unsaturated aldehydes were purchased from Sigma–Aldrich, except for (*E*)-3,7-dimethylocta-2,6-dienal (geranial) and 3-methylbut-2-enal, which were prepared from known literature procedures.[24] Only the NMR resonances of the major product isomers are reported. Light petroleum refers to the fraction boiling at 40–60 °C.

4.2. General procedure for the preparation of allylic cyanohydrins Method A

The general procedure of Anderson et al.[25] was used for the preparation of allylic cyanohydrins. The preparation of 2-hydroxy-3-pentenenitrile **21** is representative. A chilled (0 °C) solution of potassium cyanide (*CAUTION*, highly toxic; 9.83 g, 151 mmol) in water (20 mL) was added dropwise over 10 min to a stirred and chilled solution (−10 °C, ice/salt bath) of (*E*)-but-2-enal (5.00 mL, 4.23 g, 60.4 mmol) in diethyl ether (40 mL). Hydrochloric acid (40 mL, 16% aqueous) was added dropwise to the reaction over 2 h. The reaction was allowed to warm to room temperature and stir for 3 h. The ether layer was separated from the aqueous layer and washed with distilled water (2×100 mL), before being dried over $MgSO_4$, filtered and evaporated in vacuo to afford a yellow oil. The title compound was purified by flash column chromatography (20% EtOAc in light petroleum), to yield a colourless oil (4.19 g, 72%), R_f 0.38 (20% EtOAc in light petroleum). δ_H (500 MHz, $CDCl_3$) 6.07 (1H, dqd, *J* 15.3, 6.6, 1.4 Hz), 5.61 (1H, ddq, *J* 15.3, 6.1 and 1.8 Hz), 4.90 (1H, m), 1.77 (3H, m); δ_C (125 MHz, $CDCl_3$) 132.9, 125.0, 118.5, 61.7, 17.5. NMR data are in agreement with that previously reported.[15]

*4.2.1. (E)-2-Hydroxynon-3-enenitrile (**17**).* The title compound was prepared as indicated in the representative procedure (Method A). Flash column chromatography (10% EtOAc in light petroleum) afforded the pure cyanohydrin as a colourless oil (990 mg, 96%). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.40; H, 10.08; N, 9.28, R_f 0.3 (10% EtOAc in light petroleum). δ_H ($CDCl_3$, 400 MHz) 6.06 (1H, dtd, *J* 15.4, 6.8 and 1.2 Hz), 5.59 (1H, ddt, *J* 15.4, 6.0 and 1.5 Hz), 4.92 (1H, m), 2.35 (1H, br s), 2.09 (2H, m,), 1.43–1.36 (2H, m), 1.35–1.22 (4H, m), 0.87 (3H, br t, *J* 6.9 Hz). δ_C ($CDCl_3$, 400 MHz) 138.2, 123.7, 118.4, 61.9, 31.7, 31.3, 28.1, 22.4, 13.9. NMR data are in agreement with that previously reported.[26]

*4.2.2. (E)-2-Hydroxy-4-phenylbut-3-enenitrile (**35**).* The title compound was prepared as indicated in the representative procedure (Method A). Purification by trituration with hexane gave a white solid (469 mg, 78%), mp 71–72 °C (lit.[27] mp 73–74 °C). δ_H (500 MHz, $CDCl_3$) 7.42–7.39 (2H, m), 7.37–7.30 (3H, m), 6.91 (1H, dd, *J* 15.9 Hz

and 1.3 Hz), 6.25 (1H, dd, *J* 15.9 Hz and 5.9 Hz), 5.15 (1H, br d, *J* 5.6 Hz), 2.60 (1H, br s). δ_C (125 MHz, $CDCl_3$) 135.4, 134.6, 129.1, 128.8, 127.1, 122.2, 118.0, 61.9. NMR data are in agreement with that previously reported.[16,17]

*4.2.3. (E)-2-Hydroxy-3-methyl-4-phenylbut-3-enenitrile (**37**).* The title compound was prepared as indicated in the representative procedure (Method A). Purification by flash column chromatography (25% Et_2O in light petroleum), gave a waxy white solid (1.49 g, 63%), mp 28–29 °C, R_f 0.13 (20% Et_2O in light petroleum). δ_H (500 MHz, $CDCl_3$) 7.38–7.34 (2H, m), 7.29–7.26 (3H, m), 6.79 (1H, br s), 5.01 (1H, s), 2.51 (1H, br s), 2.02 (3H, d, *J* 1.4 Hz). δ_C (125 Hz, $CDCl_3$) 135.7, 131.8, 130.3, 129.0, 128.4, 127.7, 118.1, 67.2, 14.2. NMR data are in agreement with that previously reported.[22]

*4.2.4. (Z)-3-Bromo-2-hydroxy-4-phenylbut-3-enenitrile (**39**).* The title compound was prepared as indicated in the representative procedure (Method A). Purification by flash column chromatography (20% Et_2O in light petroleum) to yield a waxy light-yellow solid (300 mg, 13%), mp 51–52 °C. Anal. Calcd for $C_{10}H_8BrNO$: N, 5.88; C, 50.45; H, 3.39. Found: N, 5.77; C, 50.31; H, 3.29, R_f 0.12 (20% Et_2O in light petroleum). δ_H (400 MHz, C_6D_6) 7.35–7.32 (2H, m), 7.07–7.00 (3H, m), 6.72 (1H, s), 4.22 (1H, d, *J* 8.2 Hz), 1.88 (1H, d, *J* 8.2 Hz). δ_C (100 MHz, C_6D_6) 134.0 131.9, 129.4, 129.2, 128.5, 118.9, 117.1, 67.4. LRMS showed peaks corresponding only to the enal.

4.3. General procedure for the preparation of allylic cyanohydrins Method B

The general procedure of He et al.[28] was used for the preparation of allylic cyanosilyl ethers. The preparation of the silyl-protected cyanohydrin **25** is representative. Dried potassium carbonate (4.2 mg, 0.03 mmol) was added to a 10 mL flask, which was subsequently heated with a heat-gun to ensure dry reaction conditions. Once the flask was cooled under high vacuum it was placed under argon. (*E*)-2-Methylpent-2-enal (0.12 mL, 0.1 g, 1 mmol) and TMSCN (0.15 mL, 0.12 g, 1.2 mmol) were then added and the reaction was stirred vigorously. The reaction became warm. After 6 h TLC indicated complete consumption of the starting material. The title compound was concentrated under reduced pressure and purified by flash column chromatography (20% Et_2O in light petroleum) yielding a light pink oil in quantitative yield (200 mg), R_f 0.79 (20% Et_2O in light petroleum). δ_H (500 MHz, C_6D_6) 5.37 (1H, triplet of quintets, *J* 7.2 and 1.2 Hz), 4.42 (1H, br s), 1.75 (2H, quintet, *J* 7.5 Hz), 1.58 (3H, m), 0.74 (3H, t, *J* 7.5 Hz), 0.03 (9H, s); δ_C (125 MHz, C_6D_6) 132.1, 130.7, 119.0, 67.6, 21.1, 13.4, 11.8, −0.44. ESI-MS *m*/*z* 220 $(M+Na)^+$ HRMS calculated for $C_{10}H_{19}NOSiNa^+$ 220.1128, found 220.1127.

3-Methyl-2-(trimethylsilyloxy)hex-3-enenitrile (1.66 g, 8.5 mmol) was stirred in a solution of 5% HCl (aqueous, 1 mL in CH_3CN (10 mL)) until TLC indicated complete removal of the silyl ether. TMSOH, CH_3CN and water were then removed in vacuo, purification by flash column chromatography (20% Et_2O in light petroleum) afforded (*E*)-2-hydroxy-3-methylhex-3-enenitrile **25** as a light-yellow oil (96 mg, 90%), R_f 0.14 (20% Et_2O in light petroleum). δ_H (500 MHz, $CDCl_3$) 5.73 (1H, m), 4.81 (1H, s), 2.08 (2H, m), 1.77 (3H, m), 0.99 (3H, t, *J* 7.6 Hz); δ_C (125 MHz, $CDCl_3$) 133.6, 129.2, 118.4, 66.9, 21.1, 13.4, 12.3. NMR data are in agreement with that previously reported.[26]

*4.3.1. (3E,5E)-2-Hydroxyhepta-3,5-dienenitrile (**23**).* The title compound was prepared as indicated in the representative procedure (Method B) with the following exception: the silyl ether was immediately carried onto the next step without purification. Deprotected cyanohydrin was purified by flash column chromatography (30% Et_2O in light petroleum) to yield the product as a yellow oil (480 mg, 62%), R_f 0.21 (30% Et_2O in light petroleum). δ_H (300 MHz, C_6D_6) 6.14 (dd *J* 15.2 and 10.4 Hz), 5.72–5.63 (1H, m), 5.46–5.34 (1H, m), 5.05 (dd, *J* 15.0 and 5.6 Hz), 4.10 (1H, br t, *J* 7.0 Hz), 1.44 (3H, m), 1.24 (1H, br d, *J* 7.0 Hz). δ_C (100 MHz, C_6D_6) 134.8, 133.4, 129.7, 123.7, 118.4, 61.4, 18.0. NMR data are in general agreement with that previously reported.[11,23]

4.3.2. (E)-3,7-Dimethylocta-2,6-dienal. The enal was prepared from geraniol using literature procedures[24] and purified by Et_3N-washed silica flash column chromatography (2% Et_3N in 2:8 Et_2O/light petroleum) to afford the product as a clear oil (750 mg, 85%), R_f 0.63 (20% Et_2O in light petroleum). δ_H (400 MHz, C_6D_6) 9.86 (1H, d, *J* 7.8 Hz), 5.82 (1H, m), 4.94 (1H, m), 1.86 (2H, m), 1.74 (2H, m), 1.59 (3H, d, *J* 0.8 Hz), 1.51 (3H, d, *J* 1.2 Hz), 1.42 (3H, s). δ_C (100 MHz, C_6D_6) 189.7, 161.2, 132.3, 127.7, 123.3, 40.4, 25.9, 25.6, 17.6, 16.8. NMR data are in general agreement with that previously reported.[29]

4.3.3. (E)-4,8-Dimethyl-2-(trimethylsilyloxy)nona-3,7-dienenitrile. The title compound was prepared as indicated in the representative procedure (Method B). Purified by flash column chromatography (20% Et_2O in light petroleum) to yield a pink oil (267 mg, 76%), R_f 0.9 (20% Et_2O in light petroleum). δ_H (400 MHz, $CDCl_3$) 5.32 (1H, doublet of sextets, *J* 8.4 and 1.3 Hz), 5.08 (1H, d, *J* 8.4 Hz), 5.04 (1H, m), 2.13–2.02 (4H, m), 1.70 (3H, d, *J* 1.4 Hz), 1.66 (3H, d, *J* 1.2), 1.58 (3H, s), 0.19 (9H, s). δ_C (100 MHz, $CDCl_3$) 142.7, 132.3, 123.2, 120.7, 119.4, 58.5, 39.2, 25.9, 25.7, 17.7, 16.8, −0.1. NMR data are in agreement with that previously reported.[30]

*4.3.4. (E)-2-Hydroxy-4,8-dimethylnona-3,7-dienenitrile (**31**).* The title compound was prepared as indicated in the representative procedure (Method B). Purified by flash column chromatography (20% EtOAc in light petroleum) to yield a clear yellow oil (170 mg, 95%), R_f 0.3 (15:10:75 EtOAc/$CHCl_3$/light petroleum). δ_H (400 MHz, $CDCl_3$) 5.39 (1H, doublet of sextets, *J* 5.9 and 1.3 Hz), 5.11 (1H, dd, *J* 8.5 and 6.0 Hz), 5.06–5.02 (1H, m), 2.14 (1H, d, *J* 8.4 Hz), 2.19–2.03 (4H, m), 1.75 (3H, d, *J* 1.4 Hz), 1.67 (3H, d, *J* 1.1 Hz), 1.59 (3H, br s). δ_C (100 MHz, $CDCl_3$) 145.7, 132.5, 123.0, 119.2 (2C), 58.0, 39.2, 25.9, 25.6, 17.7, 16.9. NMR data are in agreement with that previously reported.[23]

4.3.5. (E)-3-Methyl-2-(trimethylsilyloxy)pent-3-enenitrile. The title compound was prepared as indicated in the representative procedure (Method B). Purified by flash column chromatography (20% Et_2O in light petroleum) to yield a pink oil (1.3 g, 99%), R_f 0.82 (20% Et_2O in light petroleum). δ_H (400 MHz, $CDCl_3$) 5.71 (1H, m), 4.75 (1H, m), 1.73 (3H, quintet, *J* 1.2 Hz), 1.65 (3H, m), 0.18 (9H, s). δ_C (100 MHz, $CDCl_3$) 131.4, 125.1, 118.9, 67.2, 13.3, 11.8, −0.34. ESI-MS *m*/*z* 206 $(M+Na)^+$ HRMS calculated for $C_9H_{17}NOSiNa^+$ 206.0972, found 206.0970.

*4.3.6. (E)-2-Hydroxy-3-methylpent-3-enenitrile (**27**).* The title compound was prepared as indicated in the representative procedure (Method B). Purified by flash column chromatography (20% EtOAc in light petroleum) to yield a clear yellow oil (620 mg, 79%), R_f 0.13 (20% Et_2O in light petroleum). δ_H (400 MHz, $CDCl_3$) 5.82 (1H, m), 4.81 (1H, m), 2.80 (1H, m), 1.77 (3H, m), 1.67 (3H, m). δ_C (100 MHz, $CDCl_3$) 130.5, 126.3, 118.5, 66.8, 13.3, 12.1. NMR data are in general agreement with that previously reported.[17]

4.3.7. (E)-4-(2-Nitrophenyl)-2-(trimethylsilyloxy)but-3-enenitrile. The title compound was prepared as indicated in the representative procedure (Method B). Purification by flash column chromatography (100% DCM) gave a yellow oil, which crystallised upon standing to a yellow solid (610 mg, 63% yield), mp 51–52 °C, R_f 0.33 (20% Et_2O in light petroleum). Anal. Calcd for $C_{13}H_{16}N_2O_3Si$: C, 56.50; H, 5.84; N, 10.14. Found: C, 56.71; H, 5.66; N, 10.28. δ_H (500 MHz, $CDCl_3$) 8.01 (1H, dd, *J* 8.2 and 1.3 Hz), 7.61–7.56 (2H, m),

7.48–7.45 (1H, m), 7.31 (1H, br dd, *J* 15.5 and 1.5 Hz), 6.13 (1H, dd, *J* 15.5 and 5.8 Hz), 5.14 (1H, dd, *J* 5.8 and 1.5 Hz), 0.26 (9H, s). δ_C (125 MHz, $CDCl_3$) 147.8, 133.5, 131.2, 129.7, 129.3, 129.1, 128.5, 124.8, 118.0, 61.8, −0.2. ESI-MS *m*/*z* 299 $(M+Na)^+$ HRMS calculated for $C_{13}H_{16}N_2O_3SiNa^+$ 299.0822, found 299.0828.

*4.3.8. (E)-2-Hydroxy-4-(2-nitrophenyl)but-3-enenitrile (**41**).* The title compound was prepared as indicated in the representative procedure (Method B). Purification by flash column chromatography (50% EtOAc in light petroleum) gave a yellow solid (350 mg, 80% yield), mp 80–81 °C. Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.77; H, 3.61; N, 13.44, R_f 0.63 (50% EtOAc in light petroleum). δ_H (400 MHz, CD_3CN) 7.97 (1H, m), 7.71–7.66 (2H, m), 7.55–7.51 (1H, m), 7.25 (1H, m), 6.30 (1H, dd, *J* 15.7 and 5.6 Hz), 5.25 (1H, dd, *J* 5.6 and 1.6 Hz). δ_C (100 MHz, CD_3CN,) 148.8, 134.5, 131.7, 130.3, 129.9, 129.7, 129.3, 125.5, 119.6, 61.5. Due to the instability of this compound the ^{13}C NMR spectrum was collected at 10 °C. The carbon attached to the nitro group was very deshielded, and only observable by using 30 mg of compound and the following pulse settings, p1=5.95 μs, D1=10 s, ns=216.

4.3.9. 3-Methylbut-2-enal. This enal was prepared from 3-methylbut-2-enol using known procedures[24] and purified by flash column chromatography (30% Et_2O in light petroleum) to yield a clear volatile oil (1.96 g, 65%), R_f 0.9 (30% Et_2O in light petroleum). δ_H (400 MHz, $CDCl_3$) 9.94 (1H, d, *J* 8.1 Hz), 5.86 (1H, doublet of septets, *J* 8.1 and 1.3 Hz), 2.15 (3H, d, *J* 1.3 Hz), 1.96 (3H, d, *J* 1.3 Hz). δ_C (100 MHz, $CDCl_3$) 191.1, 160.5, 128.1, 27.2, 18.9. NMR data are in general agreement with that previously reported.[29]

4.3.10. 4-Methyl-2-(trimethylsilyloxy)pent-3-enenitrile. The title compound was prepared as indicated in the representative procedure (Method B). Purification by flash column chromatography (20% Et_2O in light petroleum) yielded the product as a pink oil (1.24 g, 95%), R_f 0.81 (20% Et_2O in light petroleum). δ_H (400 MHz, $CDCl_3$) 5.33 (1H, doublet of septets, *J* 8.6 and 1.4 Hz), 5.06 (1H, d, *J* 8.5 Hz), 1.76 (3H, d, *J* 1.4 Hz), 1.71 (3H, d, *J* 1.4 Hz), 0.19 (9H, s). δ_C (100 MHz, $CDCl_3$) 139.5, 120.9, 119.4, 58.4, 25.6, 18.3, −0.1. ESI-MS *m*/*z* 206 $(M+Na)^+$ HRMS calculated for $C_9H_{17}NOSiNa^+$ 206.0972, found 206.0970.

*4.3.11. 2-Hydroxy-4-methylpent-3-enenitrile (**29**).* The title compound was prepared as indicated in the representative procedure (Method B). Purification by flash column chromatography (20% EtOAc in light petroleum) gave the product as a yellow oil (500 mg, 63%), R_f 0.13 (20% Et_2O in light petroleum). δ_H (400 MHz, C_6D_6) 4.94 (1H, doublet of septets, *J* 8.4 and 1.4 Hz), 4.36 (1H, br dd, *J* 8.3 and 5.8 Hz), 1.26 (3H, br d, *J* 1.3 Hz), 1.21 (1H, br d, *J* 5.9 Hz), 1.12 (3H, br d, *J* 1.3 Hz). δ_C (100 MHz, C_6D_6) 140.2, 120.2, 119.2, 57.7, 24.8, 17.5. NMR data are in general agreement with that previously reported.[17]

4.3.12. (S,R)-2-((S)-4-(Prop-1-en-2-yl)cyclohex-1-enyl)-2-(trimethylsilyloxy)acetonitrile. The title compound was prepared as indicated in the representative procedure (Method B). Purification by flash column chromatography (20% Et_2O in light petroleum) to yield the product as a yellow oil, as a 1:1 mixture of diastereomers (780 mg, 78%), R_f 0.91 (20% Et_2O in light petroleum). δ_H (400 MHz, C_6D_6) 5.70 (1H, m), 5.64 (1H, m), 4.74 (2H, m), 4.67 (2H, m), 4.44 (2H, m), 2.10–1.58 (12H, m), 1.53 (6H, m), 1.25–1.19 (2H, m), 0.06 and 0.05 (9H, 2s). δ_C (100 MHz, C_6D_6) 149.0, 148.9, 133.7, 133.4, 126.9, 126.5, 118.9, 118.8, 109.4, 109.3, 66.0, 65.9, 40.8, 40.7, 30.5, 30.4, 27.2, 27.1, 24.5, 24.2, 20.7, 20.6, −0.42, −0.44. ESI-MS *m*/*z* 272 $(M+Na)^+$ HRMS calculated for $C_{14}H_{23}NOSiNa^+$ 272.1441, found 272.1439.

*4.3.13. (S,R)-2-Hydroxy-2-((S)-4-(prop-1-en-2-yl)cyclohex-1-enyl)acetonitrile (**33**).* The title compound was prepared as indicated in the representative procedure (Method B). Purification by flash column chromatography (30% Et_2O in light petroleum) gave the product as a light-yellow oil, as a 1:1 mixture of diastereomers (510 mg, 93%), R_f 0.2 (30% Et_2O in light petroleum). δ_H (400 MHz, $CDCl_3$) 6.09–6.05 (2H, m), 4.83 (2H, br t, *J* 7.5 Hz), 4.74 (2H, quintet, *J* 1.5 Hz), 4.70 (2H, m), 2.28–1.88 (14H, m), 1.73–1.72 (6H, m), 1.55–1.46 (2H, m). δ_C (100 MHz, $CDCl_3$) 148.7 (2×C), 132.5, 132.4, 128.2, 128.0, 118.23, 118.19, 109.3 (2×C), 65.5, 65.4, 40.4, 40.3, 30.31, 30.29, 27.0, 26.9, 24.7, 24.6, 20.73, 20.71. NMR data are in agreement with that previously reported.[31,32]

4.4. General procedure for the preparation of δ-ethoxycarbonyl-α,β-unsaturated nitriles

Freshly distilled propionic acid (4.1 equiv) was added to a solution containing allylic cyanohydrin (100 mg, freshly prepared and dried), triethyl ortho acetate (freshly distilled, 8 equiv) and xylenes (30 mL, dried over molecular sieves). The solution was immediately heated to 135–140 °C for 24 h whilst under an atmosphere of argon. During this time a further two additions of triethyl ortho acetate (8 equiv) and propionic acid (4.1 equiv) were made to the reaction, such that the total amount of triethyl ortho acetate added equalled 24 equiv and the total amount of propionic acid was 12.3 equiv. The reaction mixture was then cooled to room temperature and concentrated to give a yellow oil. Purification of the product was achieved by flash column chromatography.

*4.4.1. (E)-Ethyl 3-(2-cyanovinyl)octanoate (**20**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (10% EtOAc in light petroleum) gave the title compound a yellow oil as a mixture of *Z*/*E* (24:76) isomers (125 mg, 76%), R_f 0.38 (10% EtOAc in light petroleum). IR neat ν (cm^{-1}) 2224, 1731. δ_H (400 MHz, $CDCl_3$) 6.53 (1H, dd, *J* 16.4 and 8.9 Hz), 5.34 (1H, dd, *J* 16.4 and 1.0 Hz), 4.11 (2H, q, *J* 7.1 Hz), 2.69–2.62 (1H, m), 2.41 (1H, dd, *J* 15.6 and 5.6 Hz), 2.29 (1H, dd, *J* 15.6 and 8.6 Hz), 1.42–1.18 (8H, m), 1.23 (3H, t, *J* 7.1 Hz), 0.87 (3H, t, *J* 7.0 Hz). δ_C (100 MHz, $CDCl_3$) 171.3, 157.7, 117.2, 100.4, 60.7, 40.0, 38.7, 33.6, 31.5, 26.5, 22.4, 14.2, 13.9. ESI-MS *m*/*z* 246 $(M+Na)^+$ HRMS calculated for $C_{13}H_{21}NO_2Na^+$ 246.1465, found 246.1466.

*4.4.2. (E)-Ethyl 5-cyano-3-methylpent-4-enoate (**22**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (20% Et_2O in light petroleum) gave the title compound as a clear oil, as a mixture of *Z*/*E* (24:76) isomers (113 mg, 66%), R_f 0.21 (20% Et_2O in light petroleum). IR neat ν (cm^{-1}) 2224, 1730. δ_H (400 MHz, $CDCl_3$) 6.65 (1H, dd, *J* 16.4 and 7.4 Hz), 5.34 (1H, dd, *J* 16.4 and 1.4 Hz), 4.12 (2H, q, *J* 7.2 Hz), 2.84 (1H, septet of doublets, *J* 7.0 and 1.4 Hz), 2.35 (1H, d *J* 7.2 Hz), 2.34 (1H, d, *J* 7.0 Hz), 1.24 (3H, t, *J* 7.1 Hz), 1.10 (3H, d, *J* 6.8 Hz). δ_C (100 MHz, $CDCl_3$) 171.1, 158.5, 117.2, 99.3, 60.7, 40.0, 34.1, 18.6, 14.2. ESI-MS *m*/*z* 190 $(M+Na)^+$ HRMS calculated for $C_{11}H_{17}NO_2Na^+$ 190.0838, found 190.0837.

*4.4.3. (E)-Ethyl 3-((E)-2-cyanovinyl)hex-4-enoate (**24**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (20% Et_2O in light petroleum) gave the title compound as a clear oil, as a mixture of *Z*/*E* (30:70) isomers (83 mg, 59%), R_f 0.21 (20% Et_2O in light petroleum). IR neat ν (cm^{-1}) 2222, 1731. δ_H (400 MHz, $CDCl_3$) 6.64 (1H, dd, *J* 16.4 and 7.0 Hz), 5.55 (1H, dqd, *J* 15.3, 6.5 and 1.0 Hz), 5.36 (1H, dd, *J* 16.4 and 1.5 Hz), 5.28 (1H, ddq, *J* 15.3, 7.5 and 1.6 Hz), 4.12 (2H, q, *J* 7.1 Hz), 3.35 (1H, br quintet, *J* 6.9 Hz), 2.43 (1H, d, *J* 7.0 Hz), 2.42 (1H, d, *J* 7.6 Hz), 1.67 (3H, ddd, *J* 6.5, 1.7, 0.8 Hz), 1.23 (3H, t, *J* 7.1 Hz). δ_C (100 MHz, $CDCl_3$) 170.8, 156.1, 129.2, 128.4, 117.2, 100.1,

60.8, 42.3, 38.6, 18.0, 14.2. ESI-MS *m*/*z* 216 $(M+Na)^+$ HRMS calculated for $C_{11}H_{15}NO_2Na^+$ 216.0995, found 216.0994.

*4.4.4. (E)-Ethyl 5-cyano-3-ethyl-4-methylpent-4-enoate (**26**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (10% EtOAc in light petroleum) gave the title compound as a clear oil, as a mixture of *Z*/*E* (24:76) isomers (122 mg, 73%), R_f 0.27 (10% EtOAc in light petroleum). IR neat ν (cm^{-1}) 2218, 1731. δ_H (400 MHz, $CDCl_3$) 5.16 (1H, m), 4.13–4.07 (2H, m), 2.64–2.57 (1H, m), 2.42 (1H, dd, *J* 15.3 and 6.2 Hz), 2.34 (1H, dd, *J* 15.3 and 8.8 Hz), 1.98 (3H, d, *J* 1.1), 1.53–1.38 (2H, m), 1.22 (3H, t, *J* 7.1 Hz), 0.82 (3H, t, *J* 7.4 Hz). δ_C (100 MHz, $CDCl_3$) 171.4, 165.7, 116.8, 97.0, 60.7, 46.1, 38.1, 25.9, 17.4, 14.2, 11.5. ESI-MS *m*/*z* 218 $(M+Na)^+$ HRMS calculated for $C_{11}H_{17}NO_2Na^+$ 218.1151, found 218.1146.

*4.4.5. (E)-Ethyl 5-cyano-3,4-dimethylpent-4-enoate (**28**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (20% Et_2O in light petroleum) gave the title compound as a clear oil, as a mixture of *Z*/*E* (26:74) isomers (120 mg, 73%), R_f 0.22 (20% Et_2O in light petroleum). IR neat ν (cm^{-1}) 2218, 1730. δ_H (400 MHz, $CDCl_3$) 5.16 (1H, quintet, *J* 1.0 Hz), 4.11 (2H, q, *J* 7.1 Hz), 2.81 (1H, sextet of doublets, *J* 7.0 and 0.6 Hz), 2.42 (1H, dd, *J* 15.3 and 7.4 Hz), 2.32 (1H, dd, *J* 15.3 and 7.3 Hz), 2.03 (3H, d, *J* 1.1 Hz), 1.23 (3H, t, *J* 7.1 Hz) and 1.10 (3H, d, *J* 6.9 Hz). δ_C (100 MHz, $CDCl_3$) 171.3, 167.4, 116.9, 95.5, 60.7, 39.5, 38.6, 18.9, 18.3, 14.2. ESI-MS *m*/*z* 204 $(M+Na)^+$ HRMS calculated for $C_{15}H_{23}NO_2Na^+$ 204.0995, found 204.0998.

*4.4.6. (E)-Ethyl 5-cyano-3,3-dimethylpent-4-enoate (**30**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (20% Et_2O in light petroleum) gave the title compound as a clear oil, as a mixture of *Z*/*E* (7:93) isomers (123 mg, 76%), R_f 0.3 (20% Et_2O in light petroleum). IR neat ν (cm^{-1}) 2224, 1729. δ_H (400 MHz, $CDCl_3$) 6.81 (1H, d, *J* 16.6 Hz), 5.27 (1H, d, *J* 16.6 Hz), 4.10 (2H, q, *J* 7.1 Hz), 2.33 (2H, s), 1.23 (3H, t, *J* 7.1 Hz), 1.16 (6H, s). δ_C (100 MHz, $CDCl_3$) 170.4, 162.6, 117.5, 97.2, 60.5, 45.9, 37.0, 26.1, 14.2. ESI-MS *m*/*z* 204 $(M+Na)^+$ HRMS calculated for $C_{10}H_{15}NO_2Na^+$ 204.0995, found 204.0998.

*4.4.7. (E)-Ethyl 3-(2-cyanovinyl)-3,7-dimethyloct-6-enoate (**32**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (20% Et_2O in light petroleum) gave the title compound as a clear oil, as a mixture of *Z*/*E* (7:93) isomers (115 mg, 76%), R_f 0.42 (20% Et_2O in light petroleum). IR neat ν (cm^{-1}) 2224, 1730. δ_H (400 MHz, $CDCl_3$) 6.76 (1H, d, *J* 16.7 Hz), 5.25 (1H, d, *J* 16.7 Hz), 5.01 (1H, m), 4.12–4.07 (2H, m, AB system), 2.38 (1H, d, *J* 14.2 Hz), 2.32 (1H, d, *J* 14.2 Hz), 1.93–1.82 (2H, m), 1.65 (3H, m), 1.56 (3H, m), 1.46 (2H, br t, *J* 8.7 Hz), 1.23 (3H, t, *J* 7.2 Hz), 1.15 (3H, s). δ_C (100 MHz, $CDCl_3$) 170.4, 162.0, 132.4, 123.2, 117.6, 98.0, 60.5, 44.3, 40.2, 40.1, 25.6, 22.7, 22.4, 17.6, 14.2. ESI-MS *m*/*z* 272 $(M+Na)^+$ HRMS calculated for $C_{15}H_{23}NO_2Na^+$ 272.1621, found 272.1618.

*4.4.8. Ethyl 2-((1S,5S,E)-2-(cyanomethylene)-5-(prop-1-en-2-yl)cyclohexyl)acetate (**34**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (20% Et_2O in light petroleum) gave the title compound as a yellow oil, as mixture of *Z*/*E* (30:70) isomers, where the trans isomer was a mixture of diastereomers (106 mg, 75%), R_f 0.38 (20% Et_2O in light petroleum). The minor trans isomer (26% of the total product) was partially purified from the other isomers and tentatively assigned the above structure based on NOESY and COSY correlations of the allylic proton. IR neat ν (cm^{-1}) 2218, 1731. δ_H (400 MHz, $CDCl_3$) 5.11 (1H, d, *J* 1.9 Hz), 4.72 (1H, quintet, *J* 1.4 Hz), 4.67 (1H, appears as a septet, *J* 0.8 Hz), 4.20–4.08 (2H, m), 3.57 (1H, m), 2.56 (2H, d, *J* 7.9 Hz), 2.40 (1H, br tdd, *J* 13.7, 4.9 and 2.0 Hz), 2.31–2.24 (2H, m), 1.94 (1H, m), 1.86 (1H, m), 1.68 (3H, m), 1.59 (1H, m), 1.32 (1H, br td, *J* 12.9 and 4.1 Hz), 1.26 (3H, *J* 7.1 Hz). δ_C (100 MHz, $CDCl_3$) 170.9, 167.8, 116.2, 109.7, 94.2, 60.9, 38.5, 37.6, 37.5, 36.4, 32.7, 31.7, 20.7, 14.1. ESI-MS *m*/*z* 270 $(M+Na)^+$ HRMS calculated for $C_{15}H_{21}NO_2Na^+$ 270.1465, found 270.1463.

*4.4.9. (E)-Ethyl 5-cyano-3-phenylpent-4-enoate (**36**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (20% Et_2O in light petroleum) gave the title compound as a yellow oil, as a mixture of *Z*/*E* (22:78) isomers (100 mg, 73%), R_f 0.16 (10% EtOAc in light petroleum). IR neat ν (cm^{-1}) 2224, 1729. δ_H (400 MHz, $CDCl_3$) 7.35–7.31 (2H, m), 7.29–7.23 (1H, m), 7.16–7.13 (2H, m), 6.84 (1H, dd, *J* 16.4 and 7.0), 5.27 (1H, dd, *J* 16.4 and 1.6), 4.13–4.05 (2H, m, AB system and peak mixing with *cis* isomer), 4.00 (1H, qd, *J* 7.3 and 1.6), 2.75 (2H, m), 1.18 (3H, t, *J* 7.1). δ_C (100 MHz, $CDCl_3$) 170.6, 156.2, 139.0, 129.1, 127.8, 127.6, 117.0, 100.6, 60.9, 45.0, 39.1, 14.1. ESI-MS *m*/*z* 252 $(M+Na)^+$ HRMS calculated for $C_{14}H_{15}NO_2Na^+$ 252.0995, found 252.0996.

*4.4.10. (E)-Ethyl 5-cyano-4-methyl-3-phenylpent-4-enoate (**38**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (10% EtOAc in light petroleum) gave the product as a clear oil, as mixture of *Z*/*E* (20:80) isomers (70 mg, 40%), R_f 0.24 (10% EtOAc in light petroleum). IR neat ν (cm^{-1}) 2219, 1730. δ_H (500 MHz, $CDCl_3$) 7.34–7.29 (2H, m), 7.27–7.25 (1H, m), 7.15–7.12 (2H, m), 5.28 (1H, quintet, *J* 1.1 Hz), 4.10–4.02 (2H, m, AB system), 3.96 (1H, br t, *J* 7.8), 2.81 (1H, dd, *J* 15.5 and 8.2 Hz), 2.75 (1H, dd, *J* 15.5 and 7.5), 1.94 (3H. d, *J* 1.0 Hz), 1.16 (3H, t, *J* 7.3). δ_C (125 MHz, $CDCl_3$) 170.8, 165.2, 139.1, 128.9, 127.7, 127.6, 116.8, 96.1, 60.9, 49.2, 38.1, 19.9, 14.1. The stereochemistry was confirmed with the aid of a NOESY experiment. ESI-MS *m*/*z* 266 $(M+Na)^+$ HRMS calculated for $C_{15}H_{17}NO_2Na^+$ 266.1151, found 266.1146.

*4.4.11. (Z)-Ethyl 4-bromo-5-cyano-3-phenylpent-4-enoate (**40**).* The title compound was prepared as indicated in the representative procedure. Purification by flash column chromatography (10% EtOAc in light petroleum) gave the product as a single isomer, as a clear yellow oil (14 mg, 13%), R_f 0.2 (10% EtOAc in light petroleum). IR neat ν (cm^{-1}) 2227, 1729. δ_H (500 MHz, $CDCl_3$) 7.37–7.30 (3H, m), 7.22–7.19 (2H, m), 6.01 (1H, d, *J* 0.9 Hz), 4.32 (1H, br t, *J* 7.5 Hz), 4.14–4.06 (2H, m, AB system), 3.05 (1H, dd, *J* 16.1 and 7.9 Hz), 2.86 (1H, dd, *J* 16.1 and 7.3 Hz), 1.18 (3H, dd, *J* 7.5 and 7.0 Hz). δ_C (100 MHz, $CDCl_3$) 170.1, 152.3, 137.4, 129.1, 128.3, 127.7, 115.7, 103.1, 61.2, 51.7, 38.3, 14.1. Stereochemistry confirmed with the aid of a NOESY experiment. ESI-MS *m*/*z* 330 $(M+Na)^+$ HRMS calculated for $C_{14}H_{14}BrNO_2Na^+$ 330.0100, found 330.0107.

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