Claisen-Johnson Orthoester Rearrangement of γ-Hydroxy α,β-Unsaturated Ketones and Nitriles

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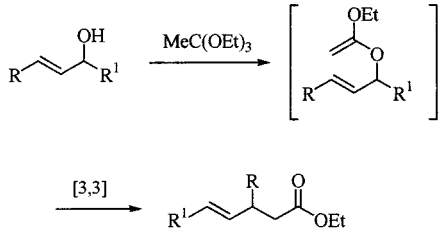
Unsaturated γ-hydroxy ketones **3** and γ-hydroxy nitriles **7** are readily converted into 4-oxo esters **4** and 3-cyano esters **8** by means of a Claisen–Johnson orthoester rearrangement, using triethyl orthoacetate in xylene at reflux. The obtained ester derivatives can be selectively reduced at the carbonyl and cyano groups to afford the corresponding lactones **5** and pyrrolidinones **14**.

Introduction

The Claisen rearrangement belongs to a class of synthetic transformations, namely the sigmatropic shifts, capable of producing a consistent structural modification of the molecular framework with concomitant creation of a new carbonyl function.[1] The widespread application of this synthetic procedure is also due to the outstanding degree of stereoselectivity, arising from the highly ordered transition states, observed in the newly formed carbon−carbon bonds.[2] Of various modified protocols for this [3,3] rearrangement, the Johnson orthoester variant has attained considerable importance since, starting from allylic alcohols, it ultimately results in the synthesis of γ,δ-unsaturated esters (Scheme 1).[3]



Scheme 1. Claisen-Johnson rearrangement of allylic alcohols

The Johnson procedure also takes advantage of a rate acceleration in the sigmatropic rearrangement observed when electron-donating substituents are present at the C-2 position in the allyl vinyl ether.[4] Although a large variety of different substrates have been tested in the Johnson rearrangement, the utilization of allylic alcohols in which the double bond is conjugated with an electron-withdrawing group has received very little attention.[5] The expected products of a Claisen−Johnson rearrangement carried out on γ-hydroxy α,β-unsaturated derivatives are 1,3- and 1,4-difunctionalized molecules, that represent very useful building blocks suitable for the synthesis of many interesting targets.[6]

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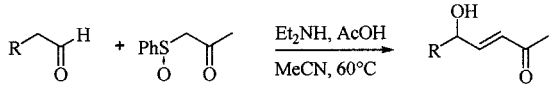
Results and Discussion

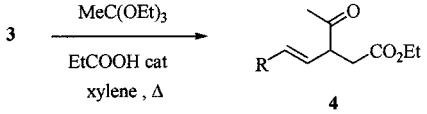
Recently we reported the Claisen rearrangement of γ-hydroxyvinyl sulfones through their ketene acetal derivatives, ensuring the highly stereoselective synthesis of (*E*)-3-phenylsulfonyl-4-alkenoic esters.[7] In order to test the feasibility of this process for the synthesis of functionalized 4-oxo esters, we prepared unsaturated hydroxy ketones **3** using the methodology of Nokami, as described in Scheme 2.[8]



1 **2** **3**

Scheme 2. Synthesis of hydroxy ketones **3** from aldehydes **1** and oxo sulfoxide **2**

These hydroxy derivatives undergo a [3,3] sigmatropic shift when heated at reflux with an excess of triethyl orthoacetate in xylene in the presence of a catalytic amount of propionic acid, giving the corresponding oxo esters **4** in good yields and with high (*E*) stereoselectivity (Scheme 3 and Table 1).[9]



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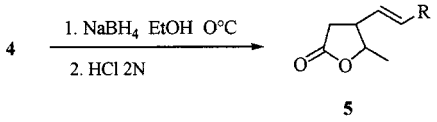
Scheme 3. Claisen-Johnson rearrangement of hydroxy ketones **3**

Table 1. Synthesis of hydroxy ketones **3** and oxo esters **4**

Entry	Aldehyde **1** R	Hydroxy ketone **3** Yield (%)	Oxo ester **4** Yield (%)
a	n-C_6H_{13}	64	81
b	$Cl(CH_2)_4$	76	70
c	*i*Pr	80	74
d	$BnO(CH_2)_3$	84	78
e	$CH_2{=}CH(CH_2)_6$	69	63

  1434−193X/01/0204−0713 $ 17.50+.50/0

It is interesting to note that, in spite of the acidic conditions and the high temperature of the process, no conjugation of the double bond to the carbonyl group is observed. The 3-alkenyl oxo esters **4** obtained in this way present some interesting structural features, since they might be obtained by a regioselective Michael addition of an alkenyl carbanion to alkyl 4-oxo-2-pentenoates. However, such conjugate additions invariably result in the opposite regioisomer, since attack at the 2-position is strongly preferred for electronic reasons.[10] Therefore, the orthoester rearrangement of hydroxy ketones **3** represents a valuable route to an interesting class of functionalized dicarbonyl derivatives. A selective reduction of the carbonyl group in oxo esters **4** with sodium borohydride in ethanol provides an alternative approach for the synthesis of 3-alkenyl-γ-butyrolactones **5** as a mixture of diastereomers separable by column chromatography (Scheme 4 and Table 2).



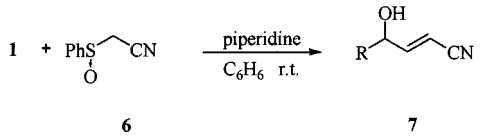
Scheme 4. Reduction of oxo esters **4** to lactones **5**

Table 2. Synthesis of butyrolactones **5**

Entry	Oxo ester	Lactone	*d.r.*[a]	Yield (%)
1	**4a**	**5a**	60:40	95
2	**4b**	**5b**	65:35	92
3	**4c**	**5c**	60:40	88

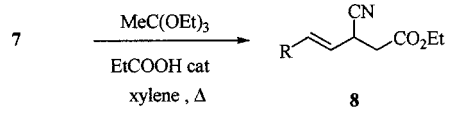
[a] Diastereomeric ratio was evaluated by ^{1}H NMR analysis.

Preparation of lactones **5** by conventional methods is not a trivial task; indeed, most synthetic approaches available in literature, concern the preparation of simple vinyl derivatives.[11] γ-hydroxyalkene nitriles **7** have been prepared starting from (phenylsulfinyl)acetonitrile (**6**) using a strategy resembling that used for hydroxy ketones **3** (Scheme 5).[12]



Scheme 5. Synthesis of hydroxy nitriles **7** from aldehydes **1** and cyano sulfoxide **6**

The rearrangement of nitriles **7** was carried out under the usual conditions, enabling the corresponding cyano esters **8** to be synthesized in good yield (Scheme 6 and Table 3).



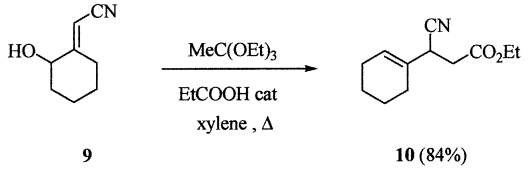
Scheme 6. Claisen-Johnson rearrangement of hydroxy nitriles **7**

Table 3. Synthesis of hydroxy nitriles **7** and cyano esters **8**

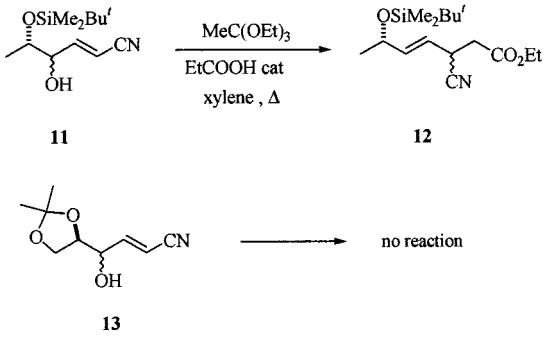
Entry	Aldehyde **1** R	Hydroxy nitrile **7** Yield (%)	Cyano ester **8** Yield (%)
a	*n*-C_6H_{13}	80	81
b	$Cl(CH_2)_4$	78	73
c	*i*Pr	74	75
d	$BnO(CH_2)_3$	72	85
e	$CH_2{=}CH(CH_2)_6$	66	87
f	$PhCH_2$	60	85

Particularly interesting was the behavior displayed by hydroxy nitrile **9**, prepared from cyclohexanone. This showed a reactivity comparable to derivatives **7** obtained from aldehydes, and gave the rearranged product **10** in 84% yield (Scheme 7).

An appealing opportunity is offered by the utilization of chiral aldehydes for the preparation of derivatives **3** and **7**. Unfortunately, hydroxy nitrile **11** (Scheme 8), prepared from (*S*)-3-(*tert*-butyldimethylsilyloxy)butanal, was obtained with very low diastereoselectivity (*dr* 65:35) and consequently the rearranged product **12** was produced with the same diastereomeric ratio maintained, although in good yield.



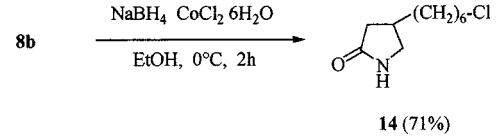
Scheme 7. Claisen−Johnson rearrangement of hydroxy nitrile **9**, derived from cyclohexanone



Scheme 8. Claisen−Johnson rearrangement of optically active hydroxy nitrile **11**

A similar trend was observed for nitrile **13**, prepared with poor selectivity (*dr* 60:40) from (*R*)-3,4-*O*-isopropylidene-

3,4-dihydroxybutanal. This even failed to react with triethyl orthoacetate to give the intermediate ketene acetal. This lack of reactivity is probably due to steric crowding around the hydroxy group. Chemoselective reduction of the cyano group in compound **8** offered the potential to provide 2-pyrrolidinone derivatives, and this synthetic route was exploited using sodium borohydride as reducing agent in the presence of cobalt dichloride (Scheme 9).[13]



Scheme 9. Chemoselective reduction of cyano ester **8b** to lactam **14**

Under these conditions, cyano ester **8b** was converted into pyrrolidinone **14**, with a concomitant reduction of the carbon−carbon double bond observed. A base-assisted migration of the double bond had evidently occurred, so that a complete reduction of the intermediate α,β-unsaturated nitrile had taken place.

In conclusion, the Johnson orthoester rearrangement of hydroxy ketones **3** and hydroxy nitriles **7** produces unsaturated oxo esters **4** and cyano esters **8** in good yields. These rearranged products are amenable to further synthetic transformations, selective reduction of the oxo or cyano groups giving butyrolactones or pyrrolidinones, respectively.

Experimental Section

General: Microanalyses were performed with a Model EA 1108 CHNS-O analyzer from Fisons Instruments. − IR spectra were recorded with a Perkin−Elmer 1310 spectrometer. − ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ with a Varian VXR 300. − Mass spectra were recorded with a Hewlett-Packard GC/MS 5970 by means of the EI technique (70 eV). − Reaction progress was monitored by TLC or GLC with a Carlo Erba Fractovap 4160, with a capillary column of fused silica (0.32 mm × 25 m), stationary phase SE54. − The solvents were distilled before use. All chemicals used were obtained commercially. − Flash chromatography was performed on Merck silica gel (0.040−0.063 mm). − 6-Chlorohexanal (**1b**),[14] 5-(benzyloxy)pentanal (**1d**),[15] (phenylsulfinyl)propan-2-one (**2**),[8] and (phenylsulfinyl)acetonitrile (**6**)[12] were prepared as previously described.

Synthesis of Hydroxy Ketones 3: Aldehyde **1** (12 mmol), diethylamine (10 mmol), and acetic acid (10 mmol) were successively added at room temperature to a solution of oxo sulfoxide **2** (10 mmol) in acetonitrile (30 mL). After stirring for 2 h at 60 °C, the solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (40 mL). The solution was washed with 2 N HCl (3 × 5 mL) and brine, and the organic phase was then dried with $MgSO_4$. After evaporation of the solvent at reduced pressure, the residue was purified by flash chromatography, affording the pure product **3**.

(*E*)-5-Hydroxy-3-undecen-2-one (3a): Yield 1.18 g, 64%; oil. − IR (film): $\tilde{\nu}$ = 3500, 1680 cm^{-1}. − ^{1}H NMR: δ = 0.88 (t, 3 H, *J* = 6.8 Hz, CH_3CH_2), 1.14−1.44 (m, 8 H, $CH_2CH_2CH_2CH_2$), 1.55−1.61 (m, 3 H, OH, $CHCH_2$), 2.28 (s, 3 H, CH_3CO), 4.27−4.36 (m, 1 H, C*H*COH), 6.26 (dd, 1 H, *J* = 1.4, 16.0 Hz, C*H*=), 6.77 (dd, 1 H, *J* = 5.0, 16.0 Hz, C*H*=). − $C_{11}H_{20}O_2$ (184.3): calcd. C 71.70, H 10.24; found C 71.77, H 10.20.

(*E*)-9-Chloro-5-hydroxy-3-nonen-2-one (3b): Yield 1.45 g, 76%; oil. − IR (film): $\tilde{\nu}$ = 3500, 1680 cm^{-1}. − ^{1}H NMR: δ = 1.45−1.72 (m, 4 H, CH_2CH_2), 1.74−1.89 (m, 3 H, OH, $CHCH_2$), 2.29 (s, 3 H, CH_3CO), 3.55 (t, 2 H, *J* = 6.0 Hz, $ClCH_2$), 4.32−4.37 (m, 1 H, C*H*COH), 6.28 (dd, 1 H, *J* = 1.4, 15.8 Hz, C*H*=), 6.76 (dd, 1 H, *J* = 5.0, 16.0 Hz, C*H*=). − $C_9H_{15}ClO_2$ (190.7): calcd. C 56.69, H 7.93; found C 56.75, H, 7.92.

(*E*)-5-Hydroxy-6-methyl-3-hepten-2-one (3c): Yield 1.14 g, 80%; oil. − IR (film): $\tilde{\nu}$ = 3500, 1680 cm^{-1}. − ^{1}H NMR: δ = 0.93 (d, 3 H, *J* = 1.0 Hz, CH_3CH), 0.97 (d, 3 H, *J* = 1.2 Hz, CH_3CH), 1.80−1.89 (m, 2 H, OH, CH_3CHCH_3), 2.28 (s, 3 H, CH_3CO), 4.09−4.15 (m, 1 H, C*H*COH), 6.28 (dd, 1 H, *J* = 1.6, 16 Hz, C*H*=), 6.78 (dd, 1 H, *J* = 5.0, 16.0 Hz, C*H*=). − $C_8H_{14}O_2$ (142.2): calcd. C 67.57, H, 9.92; found C 67.54, H 9.98.

(*E*)-8-Benzyloxy-5-hydroxy-3-octen-2-one (3d): Yield 2.08 g, 84%; oil. − IR (film): $\tilde{\nu}$ = 3500, 1680 cm^{-1}. − ^{1}H NMR: δ = 1.60−1.85 (m, 5 H, OH, CH_2CH_2), 2.27 (s, 3 H, CH_3CO), 3.54 (t, 2 H, *J* = 3.6 Hz, CH_2OBn), 4.27−4.41 (m, 1 H, C*H*COH), 4.54 (s, 2 H, CH_2Ar), 6.29 (dd, 1 H, *J* = 1.6, 16.0 Hz, C*H*=), 6.77 (dd, 1 H, *J* = 4.6, 15.8 Hz, C*H*=), 7.32−7.37 (m, 5 H, arom.). − $C_{15}H_{20}O_3$ (248.3): calcd. C 72.55, H 8.12; found C 72.52, H 8.15.

(*E*)-5-Hydroxy-3,12-tridecadien-2-one (3e): Yield 1.45 g, 69%; oil. − IR (film): $\tilde{\nu}$ = 3500, 1680 cm^{-1}. − ^{1}H NMR: δ = 1.15−1.45 [m, 10 H, $(CH_2)_5$], 1.55−1.65 (m, 3 H, OH, $CHCH_2$), 2.28 (s, 3 H, CH_3CO), 4.31−4.34 (m, 1 H, C*H*COH), 4.90−4.96 (m, 2 H, CH_2=),5.74−5.82 (m, 1 H, CH=CH_2), 6.27 (dd, 1 H, *J* = 1.6, 16 Hz, C*H*=), 6.77 (dd, 1 H, *J* = 5.0, 16 Hz, C*H*=). − $C_{13}H_{22}O_2$ (210.3): calcd. C 74.24, H 10.54; found C 74.30, H 10.56.

Synthesis of Oxo Esters 4: Hydroxy ketone **3** (5 mmol) was suspended in xylene (15 mL), and triethyl orthoacetate (15 mmol) was added. A catalytic amount of propanoic acid (3 drops) was added and the suspension was refluxed for 5 h. After evaporation of the solvent at reduced pressure, the crude oxo ester **4** was purified by flash chromatography [hexane/ethyl acetate (7:3)].

Ethyl (*E*)-3-Acetylundec-4-enoate (4a): Yield 1.03 g, 81%; oil. − IR (film): $\tilde{\nu}$ = 1735, 1710 cm^{-1}. − ^{1}H NMR: δ = 0.88 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 1.20−1.34 [m, 11 H, $CH_3(CH_2)_4$], 1.97−2.10 (m, 2 H, =$CHCH_2CH_2$), 2.20 (s, 3 H, CH_3CO), 2.36 (dd, 1 H, *J* = 5.4, 16.8 Hz, $COCH_2$), 2.85 (dd, 1 H, *J* = 8.8, 16.6 Hz, $COCH_2$), 3.51−3.62 (m, 1 H, COC*H*), 4.10 (q, 2 H, *J* = 7.2 Hz, CH_3CH_2O), 5.20−5.32 (m, 1 H, C*H*=), 5.62−5.76 (m, 1 H, C*H*=). − $C_{15}H_{26}O_3$ (254.4): calcd. C 70.83, H 10.30; found C 70.77, H 10.28.

Ethyl (*E*)-3-Acetyl-9-chlorononon-4-enoate (4b): Yield 0.95 g, 70%; oil. − IR (film): $\tilde{\nu}$ = 1735, 1710 cm^{-1}. − ^{1}H NMR: δ = 1.24 (t, 3 H, *J* = 7.2 Hz, CH_3CH_2O), 1.48−1.85 (m, 4 H, $CH_2CH_2CH_2Cl$), 2.01−2.19 (m, 2 H, =$CHCH_2CH_2$), 2.21 (s, 3 H, CH_3CO), 2.25−2.43 (m, 1 H, $COCH_2$), 2.86 (dd, 1 H, *J* = 9.0, 16.8 Hz, $COCH_2$), 3.50−3.61 (m, 3 H, CH_2Cl, COC*H*), 4.11 (q, 2 H, *J* = 7.0 Hz, CH_3CH_2O), 5.25−5.38 (m, 1 H, C*H*=), 5.61−5.72 (m, 1 H, C*H*=). − $C_{13}H_{21}ClO_3$ (260.8): calcd. C 59.88, H 8.12; found C 59.82, H 8.09.

Ethyl (*E*)-3-Acetyl-6-methylhept-4-enoate (4c): Yield 0.78 g, 74%; oil. − IR (film): $\tilde{\nu}$ = 1735, 1710 cm^{-1}. − ^{1}H NMR: δ = 0.97 (d, 6 H, *J* = 6.8 Hz, CH_3CHCH_3), 1.23 (t, 3 H, *J* = 7.0 Hz, CH_3CH_2O), 2.20 (s, 3 H, CH_3CO), 2.22−2.41 (m, 2 H, $COCH_2$), 2.75−2.90 (m, 1 H, CH_3CHCH_3), 3.30−3.57 (m, 1 H, COC*H*),

4.10 (q, 2 H, J = 7.2 Hz, CH_3CH_2O), 5.15−5.28 (m, 1 H, C*H*=), 5.66 (dd, 1 H, J = 6.8, 15.4 Hz, C*H*=). − $C_{12}H_{20}O_3$ (212.3): calcd. C 67.89, H 9.50; found C 67.95, H 9.47.

Ethyl (*E*)-3-Acetyl-8-benzyloxyoct-4-enoate (4d): Yield 0.99 g, 78%; oil. − IR (film): $\tilde{\nu}$ = 1735, 1710 cm^{-1}. − ^1H NMR: δ = 1.23 (t, 3 H, J = 7.2 Hz, CH_3CH_2O), 1.65−1.75 (m, 2 H, CH_2CH_2OBn), 2.08−2.31 (m, 2 H, =CHCH_2), 2.18 (s, 3 H, CH_3CO), 2.33 (dd, 1 H, J = 5.2, 16.6 Hz, COCH_2), 2.84 (dd, 1 H, J = 9.0, 16.8 Hz, COCH_2), 3.45 (t, 2 H, J = 6.4 Hz, CH_2OBn), 3.54−3.57 (m, 1 H, COC*H*), 4.10 (q, 2 H, J = 7.2 Hz, CH_3CH_2O), 4.49 (s, 2 H, CH_2Ph), 5.25−5.32 (m, 1 H, C*H*=), 5.57−5.74 (m, 1 H, C*H*=), 7.30−7.35 (m, 5 H, arom.). − $C_{19}H_{26}O_4$ (318.4): calcd. C 71.67, H 8.23; found C 71.61, H, 8.28.

Ethyl (*E*)-3-Acetyltrideca-4,12-dienoate (4e): Yield 0.88 g, 63%; oil. − IR (film): $\tilde{\nu}$ = 1735, 1710 cm^{-1}. − ^1H NMR: δ = 1.24 (t, 3 H, J = 7.2 Hz, CH_3CH_2O), 1.25−1.59 (m, 8 H, $CH_2CH_2CH_2CH_2$), 1.97−2.18 (m, 4 H, =CHCH_2,CH_2CH=), 2.20 (s, 3 H, CH_3CO), 2.30−2.41 (m, 1 H, COCH_2), 2.85 (dd, 1 H, J = 9.0, 16.8 Hz, COCH_2), 3.55−3.58 (m, 1 H, COC*H*), 4.10 (q, 2 H, J = 7.0 Hz, CH_3CH_2O), 4.90−5.04 (m, 2 H, =CH_2), 5.27 (dd, 1 H, J = 9.0, 15.4 Hz, CHC*H*=), 5.62−5.83 (m, 2 H, =C*H*, C*H*=). − $C_{17}H_{28}O_3$ (280.4): calcd. C 72.82, H 10.06; found C 72.77, H, 9.99.

Synthesis of Lactones 5: Oxo ester **4** (2 mmol) was dissolved in ethanol (15 mL), and $NaBH_4$ (2 mmol) was then added at 0 °C. Stirring was continued for 3 h at 0 °C and the reaction mixture was then quenched by adding 2 N HCl (5 mL). The mixture was then extracted with dichloromethane (3 × 20 mL), and the organic phase was dried with $MgSO_4$. After evaporation of the solvent at reduced pressure, the residue was purified by flash chromatography (hexane/ethyl acetate, 9:1), giving pure lactones **5**.

5-Methyl-4-[(*E*)-oct-1-enyl]dihydrofuran-2(3*H*)-one (5a): Diastereomer A: yield 0.24 g, 57%; oil. − IR (film): $\tilde{\nu}$ = 1770 cm^{-1}. − ^1H NMR: δ = 0.88 (t, 3 H, J = 6.6 Hz, CH_3CH_2), 1.22−1.36 (m, 8 H, $CH_2CH_2CH_2CH_2$), 1.39 (d, 3 H, J = 6.2 Hz, CH_3CH), 1.97−2.07 (m, 2 H, =CHCH_2), 2.32−2.49 (m, 1 H, C*H*CH=), 2.59−2.72 (m, 2 H, COCH_2), 4.17−4.24 (m, 1 H, OC*H*), 5.22−5.33 (m, 1 H, =C*H*), 5.53−5.64 (m, 1 H, =C*H*). − $C_{13}H_{22}O_2$ (210.3): calcd. C 74.24, H 10.54; found C 74.30, H 10.52. − Diastereomer B: yield 0.16 g, 38%; oil. − IR (film): $\tilde{\nu}$ = 1770 cm^{-1}. − ^1H NMR: δ = 0.88 (t, 3 H, J = 6.6 Hz, CH_3CH_2), 1.14−1.68 (m, 11 H, CH_3CH, $CH_2CH_2CH_2CH_2$), 1.98−2.08 (m, 2 H, =CHCH_2), 2.41 (dd, 1 H, J = 7.2, 17.4 Hz, COCH_2), 2.65 (dd, 1 H, J = 8.0, 17.2 Hz, COCH_2), 3.08−3.16 (m, 1 H, C*H*CH=), 4.64−4.71 (m, 1 H, CH_3C*H*), 5.26−5.38 (m, 1 H, =C*H*), 5.49−5.63 (m, 1 H, =C*H*). − $C_{13}H_{22}O_2$ (210.3): calcd. C 74.24, H 10.54; found C 74.19, H 10.50.

4-[(*E*)-6-Chlorohex-1-enyl]-5-methyldihydrofuran-2(3*H*)-one (5b): Diastereomer A: yield 0.26 g, 60%; oil. − IR (film): $\tilde{\nu}$ = 1770 cm^{-1}. − ^1H NMR: δ = 1.40 (d, 3 H, J = 6.0 Hz, CH_3CH), 1.49−1.81 (m, 4 H, CH_2CH_2), 2.02−2.13 (m, 2 H, =CHCH_2), 2.33−2.50 (m, 1 H, C*H*CH=), 2.60−2.74 (m, 2 H, COCH_2), 3.54 (t, 2 H, J = 6.4 Hz, CH_2Cl), 4.18−4.25 (m, 1 H, OC*H*), 5.35−5.38 (m, 1 H, =C*H*), 5.53−5.64 (m, 1 H, =C*H*). − $C_{11}H_{17}ClO_2$ (216.7): calcd. C 60.97, H 7.91; found C 61.01, H 7.95. − Diastereomer B: yield 0.14 g, 32%; oil. − IR (film): $\tilde{\nu}$ = 1770 cm^{-1}. − ^1H NMR: δ = 1.26 (d, 3 H, J = 6.6 Hz, CH_3CH), 1.30−1.82 (m, 4 H, CH_2CH_2), 2.04−2.14 (m, 2 H, =CHCH_2), 2.42 (dd, 1 H, J = 7.0, 17.2 Hz, COCH_2), 2.66 (dd, 1 H, J = 8.0, 17.4 Hz, COCH_2), 3.10−3.17 (m, 1 H, C*H*CH=), 3.54 (t, 2 H, J = 6.4 Hz, CH_2Cl), 4.65−4.72 (m, 1 H, OC*H*), 5.38−5.43 (m, 1 H, =C*H*), 5.50−5.61 (m, 1 H, =C*H*). − $C_{11}H_{17}ClO_2$ (216.7): calcd. C 60.97, H 7.91; found C 61.05, H 7.99.

5-Methyl-4-[(*E*)-3-methylbut-1-enyl)dihydrofuran-2(3*H*)-one (5c): Diastereomer A: yield 0.18 g, 53%; oil. − IR (film): $\tilde{\nu}$ = 1770 cm^{-1}. − ^1H NMR: δ = 0.99 (d, 6 H, J = 6.8 Hz, CH_3CHCH_3), 1.39 (d, 3 H, J = 6.2 Hz, OCHCH_3), 2.20−2.49 (m, 2 H, C*H*CH=, CH_3C*H*CH_3), 2.60−2.73 (m, 2 H, COCH_2), 4.17−4.24 (m, 1 H, OC*H*), 5.18−5.30 (m, 1 H, =C*H*), 5.58 (dd, 1 H, J = 6.6, 15.4 Hz, =C*H*). − $C_{10}H_{16}O_2$ (168.2): calcd. C 71.39, H 9.59; found C 71.33, H 9.63. − Diastereomer B: yield 0.12 g, 35%; oil. − IR (film): $\tilde{\nu}$ = 1770 cm^{-1}. − ^1H NMR: δ = 0.99 (d, 6 H, J = 17.2 Hz, CH_3CHCH_3), 1.25 (d, 3 H, J = 6.2 Hz, OCHCH_3), 2.21−2.35 (m, 1 H, CH_3C*H*CH_3), 2.42 (dd, 1 H, J = 7.2, 17.3 Hz, COCH_2), 2.65 (dd, 1 H, J = 8.0, 17.3 Hz, COCH_2), 3.07−3.15 (m, 1 H, C*H*CH=), 4.62−4.75 (m, 1 H, OC*H*), 5.22−5.34 (m, 1 H, =C*H*), 5.54 (dd, 1 H, J = 7.0, 15.4 Hz, =C*H*). − $C_{10}H_{16}O_2$ (168.2): calcd. C 71.39, H 9.59; found C 71.30, H 9.55.

Synthesis of Hydroxy Nitriles 7, 11, and 13: Aldehyde **1** (12 mmol) and piperidine (10 mmol) were added at room temperature to a solution of sulfoxide **6** (10 mmol) in benzene (30 mL). After stirring for 2 h at the same temperature, the organic solution was washed with 2 N HCl (3 × 5 mL) and brine (2 × 5 mL).The organic phase was dried with $MgSO_4$ and, after evaporation of the solvent at reduced pressure, the residue was purified by flash chromatography to afford the pure product **7**.

(*E*)-4-Hydroxydec-2-enenitrile (7a): Yield 1.35 g, 80%; oil. − IR (film): $\tilde{\nu}$ = 3435, 2929, 2858, 2227 cm^{-1}. − ^1H NMR: δ = 0.88 (t, 3 H, J = 4.8 Hz, CH_3), 1.22−1.44 (m, 8 H, $CH_2CH_2CH_2CH_2$), 1.51−1.73 (m, 3 H, O*H*, CH_2CH), 4.30−4.34 (m, 1 H, OC*H*), 5.67 (dd, 1 H, J = 2.0, 16.2 Hz, =C*H*), 6.75 (dd, 1 H, J = 4.0, 16.2 Hz, =C*H*). − $C_{10}H_{17}NO$ (167.2): calcd. C 71.81, H 10.25, N 8.37; found C 71.86, H 10.21, N 8.41.

(*E*)-8-Chloro-4-hydroxyoct-2-enenitrile (7b): Yield 1.35 g, 78%; oil. − IR (film): $\tilde{\nu}$ = 3435, 2929, 2858, 2227 cm^{-1}. − ^1H NMR: δ = 1.53−1.65 (m, 4 H, CH_2CH_2), 1.78−1.92 (m, 3 H, O*H*, CH_2CH), 3.56 (t, 2 H, J = 6.4 Hz, CH_2Cl), 4.22−4.31 (m, 1 H, OC*H*), 5.69 (dd, 1 H, J = 2.0, 16.2 Hz, =C*H*), 6.76 (dd, 1 H, J = 4.0, 16.2 Hz, =C*H*). −$C_8H_{12}NClO$ (173.6): calcd. C 55.34, H 6.97, N 8.07; found C 55.39, H 7.03, N 8.04.

(*E*)-4-Hydroxy-5-methylhex-2-enenitrile (7c): Yield 0.92 g, 74%; oil. − IR (film): $\tilde{\nu}$ = 3435, 2929, 2858, 2227 cm^{-1}. − ^1H NMR: δ = 0.89−1.08 (m, 6 H, CH_3CHCH_3), 1.74−1.93 (m, 2 H, O*H*, CH_3C*H*CH_3), 4.10−4.16 (m, 1 H, OC*H*), 5.69 (dd, 1 H, J = 2.0, 16.4 Hz, =C*H*), 6.76 (dd, 1 H, J = 4.0, 16.2 Hz, =C*H*). − $C_7H_{11}NO$ (125.2): calcd. C 67.17, H 8.86, N 11.19, found C 67.21, H, 8.90 N 11.15.

(*E*)-7-Benzyloxy-4-hydroxyhept-2-enenitrile (7d): Yield 1.66 g, 72%; oil. − IR (film): $\tilde{\nu}$ = 3435, 2929, 2858, 2227. − ^1H NMR: δ = 1.57−1.85 (m, 4 H, CH_2CH_2), 3.56 (t, 2 H, J = 5.2 Hz, CH_2O), 3.82−3.56 (d, 1 H, J = 4.6 Hz, OC*H*), 4.28−4.31 (m, 1 H, O*H*), 4.53 (s, 2 H, CH_2Ph), 5.66 (dd, 1 H, J = 2.2, 16.2 Hz, =C*H*), 6.71 (dd, 1 H, J = 3.6, 16 Hz, =C), 7.24−7.42 (m, 5 H, arom.). −$C_{14}H_{17}NO_2$ (231.3): calcd. C 72.70, H 7.41, N 6.06; found C 72.74, H, 7.37, N 6.02.

(*E*)-4-Hydroxydodeca-2,11-dienenitrile (7e): Yield 1.28 g, 66%; oil. − IR (film): $\tilde{\nu}$ = 3435, 2929, 2858, 2227 cm^{-1}. − ^1H NMR: δ = 1.34−1.44 (m, 8 H, $CH_2CH_2CH_2CH_2$), 1.51−1.59 (m, 3 H, O*H*, CH_2CH), 2.00−2.06 (m, 2 H, =CHCH_2), 4.29−4.32 (m, 1 H, OC*H*), 4.91−5.05 (m, 2 H, CH_2=), 5.67 (dd, 1 H, J = 2.2, 16.4 Hz,

CHC*H*=), 5.74−5.88 (m, 1 H, CH_2=C*H*), 6.75 (dd, 1 H, *J* = 4.0, 16.2 Hz, =C*H*CN). −$C_{12}H_{19}NO$ (193.3): calcd. C 74.57, H 9.91, N 7.25; found C 74.63, H 9.96, N 7.22.

(*E*)-4-Hydroxy-5-phenylpent-2-enenitrile (7f): Yield 1.04 g, 60%; oil. − IR (film): $\tilde{\nu}$ = 3435, 2929, 2858, 2227 cm^{-1}. − ^1H NMR: δ = 2.20 (br. s, 1 H, O*H*), 2.73−2.97 (m, 2 H, PhCH_2), 4.49−4.53 (m, 1 H, OC*H*), 5.67 (dd, 1 H, *J* = 2.0, 16.2 Hz, CHC*H*=), 6.78 (dd, 1 H, *J* = 3.8, 16.2 Hz, =C*H*CN), 7.18−7.40 (m, 5 H, arom.). − $C_{11}H_{11}NO$ (173.2): calcd. C 76.28, H 6.40, N 8.09; found C 76.23, H 6.44, N 8.03.

(*E*)-(5*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-hydroxyhex-2-enenitrile (11): Yield 1.64 g, 68%; oil. − IR (film): $\tilde{\nu}$ = 3435, 2929, 2858, 2227 cm^{-1}. − Diastereomer A: ^1H NMR: δ = 0.07 (s, 6 H, SiCH_3), 0.89 [s, 9 H, C(CH_3)$_3$], 1.09 (d, 3 H, *J* = 6.2 Hz, CH_3), 2.48 (d, 1 H, *J* = 4.0 Hz, O*H*), 3.82−3.93 (m, 1 H, C*H*OSi), 3.99−4.09 (m, 1 H, C*H*OH), 5.68−5.71 (m, 1 H, CHC*H*=), 6.72−6.77 (m, 1 H, = C*H*CN). Diastereomer B: ^1H NMR: δ = 0.09 (s, 6 H, SiCH_3), 0.90 [s, 9 H, C(CH_3)$_3$],), 1.22 (d, 3 H, *J* = 6.2 Hz, CH_3), 2.59 (d, 1 H, *J* = 6.0 Hz, O*H*), 3.68−3.81 (m, 1 H, C*H*OSi), 4.18−4.28 (m, 1 H, C*H*OH), 5.76−5.79 (m, 1 H, CHC*H*=), 6.64−6.69 (m, 1 H, = C*H*CN). − $C_{12}H_{23}NO_2Si$ (241.4): calcd. C 59.71, H 9.60, N 5.80; found C 59.77, H, 9.63, N 5.77.

(*E*)-4-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-hydroxybut-2-enenitrile (13): Yield 1.41 g, 77%; oil. − IR (film): $\tilde{\nu}$ = 3435, 2929, 2858, 2227 cm^{-1}. − ^1H NMR: δ = 1.35 (s, 3 H, CH_3C), 1.44 (s, 3 H, CH_3C), 1.77 (br. s, 1 H, O*H*), 3.81−4.03 (m, 2 H, OCH_2), 4.08−4.15 (m, 1 H, OC*H*), 4.35−4.45 (m, 1 H, C*H*OH), 5.79 (dd, 2 H, *J* = 1.8, 16.4 Hz, CHC*H*=), 6.78 (dd, 2 H, *J* = 3.4, 16.2 Hz, = C*H*CN). − $C_9H_{13}NO_3$ (183.2): calcd. C 59.00, H 7.15, N 7.65; found C 58.96, H, 7.18, N 7.61.

Synthesis of Cyano Esters 8: Hydroxy nitrile **7** (5 mmol) was suspended in xylene (15 mL), and then triethyl orthoacetate (15 mmol) was added. A catalytic amount of propanoic acid (3 drops) was added and the suspension was refluxed for 8 h. After evaporation of the solvent at reduced pressure, the crude oxo ester **4** was purified by flash chromatography (hexane/ethyl acetate, 7:3).

Ethyl (*E*)-3-Cyanoundec-4-enoate (8a): Yield 0.96 g, 81%; oil. − IR (film): $\tilde{\nu}$ = 2225, 1730 cm^{-1}. − ^1H NMR: δ = 0.88 (t, 3 H, *J* = 6.8 Hz, CH_3CH$_2$CH$_2$), 1.27−1.40 (m, 8 H, CH_2CH_2CH_2CH_2), 1.28 (t, 3 H, *J* = 7.2 Hz, CH_3CH$_2$O), 2.05 (m, 2 H, =CHCH_2), 2.60 (dd, 1 H, *J* = 7.2, 16.4 Hz, COCH_2), 2.75 (dd, 1 H, *J* = 7.4, 16.4 Hz, COCH_2), 3.61−3.83 (m, 1 H, C*H*CN), 4.20 (q, 2 H, *J* = 7.2 Hz, CH$_3$CH_2O), 5.35 (dd, 1 H, *J* = 6.4, 15.3 Hz, C*H*= CHCH$_2$), 5.84−5.93 (m, 1 H, CH=C*H*CH$_2$). − $C_{14}H_{23}NO_2$ (237.3): calcd. C 70.85, H 9.77, N 5.90; found C 70.89, H 9.74 N 5.87.

Ethyl (*E*)-9-Chloro-3-cyanonon-4-enoate (8b): Yield 0.89 g, 73%; oil. − IR (film): $\tilde{\nu}$ = 2225, 1730 cm^{-1}. − ^1H NMR: δ = 1.28 (t, 3 H, *J* = 7.0 Hz, CH_3CH$_2$O), 1.50−1.61 (m, 2 H, CH$_2$CH_2CH$_2$CH$_2$Cl), 1.70−1.81 (m, 2 H, CH$_2$CH$_2$CH_2CH$_2$Cl), 2.05−2.12 (m, 2 H, CH_2CH$_2$CH$_2$CH$_2$Cl), 2.60 (dd, 1 H, *J* = 7.4, 16.4 Hz, COCH_2), 2.76 (dd, 1 H, *J* = 7.2, 16.4 Hz, COCH_2), 3.53 (t, 2 H, *J* = 6.4 Hz, CH_2Cl), 3.67−3.71 (m, 1 H, C*H*CN), 4.20 (q, 2 H, *J* = 7.2 Hz, CH$_3$CH_2O), 5.39 (m, 1 H, *J* = 6.3, 15.4, C*H*=CHCH$_2$), 5.84−5.93 (m, 1 H, CH=C*H*CH$_2$). − $C_{12}H_{18}ClNO_2$ (243.7): calcd. C 59.14, H 7.44, N 5.75; found C 59.19, H 7.40, N 5.74.

Ethyl (*E*)-3-Cyano-6-methylhept-4-enoate (8c): Yield 0.73 g, 75%; oil. − IR (film): $\tilde{\nu}$ = 2225, 1730 cm^{-1}. − ^1H NMR: δ = 0.99 (d, 6 H, *J* = 6.8 Hz, CH_3CHCH_3), 1.28 (t, 3 H, *J* = 7.2 Hz, CH_3CH$_2$O), 2.30−2.34 (m, 1 H, CH$_3$C*H*CH$_3$), 2.60 (dd, 1 H, *J* = 7.2, 16.2 Hz, COCH_2), 2.75 (dd, 1 H, *J* = 7.4, 16.2 Hz, COCH_2), 3.66−3.69 (m, 1 H, C*H*CN), 4.20 (q, 2 H, *J* = 7.2 Hz, CH$_3$CH_2O), 5.32 (dd, 1 H, *J* = 6.4, 15.4 Hz, C*H*=CHCH$_2$), 5.87 (dd, 1 H, *J* = 6.7, 15.4 Hz, CH=C*H*CH$_2$). − $C_{11}H_{17}NO_2$ (195.3): calcd. C 67.66, H 8.78, N 7.17. found C 67.61, H 8.82, N 7.14.

Ethyl (*E*)-8-Benzyloxy-3-cyanooct-4-enoate (8d): Yield 1.28 g, 85%; oil. − IR (film): $\tilde{\nu}$ = 2225, 1730 cm^{-1}. − ^1H NMR: δ = 1.28 (t, 3 H, *J* = 7.2 Hz, CH_3CH$_2$O), 1.66−1.77 (m, 2 H, CH_2CH$_2$OBn), 2.12−2.19 (m, 2 H, =CHCH_2), 2.57 (dd, 1 H, *J* = 7.0, 16.4 Hz, COCH_2), 2.73 (dd, 1 H, *J* = 7.4, 16.4 Hz, COCH_2), 3.46 (t, 2 H, *J* = 6.2 Hz, CH_2OBn), 3.65−3.69 (m, 1 H, C*H*CN), 4.19 (q, 2 H, *J* = 7.2 Hz, CH$_3$CH_2O), 4.50 (s, 2 H, CH_2Ph), 5.36 (dd, 1 H, *J* = 6.3, 15.4 Hz, C*H*=CHCH$_2$), 5.85−5.93 (m, 1 H, CH=C*H*CH$_2$), 7.27−7.36 (m, 5 H, arom.). − $C_{18}H_{23}NO_3$ (301.4): calcd. C 71.73, H 7.69, N 4.65; found C 71.69, H 7.72, N 4.66.

Ethyl (*E*)-3-Cyanotrideca-4,12-dienoate (8e): Yield 1.31 g, 87%; oil. − IR (film): $\tilde{\nu}$ = 2225, 1730 cm^{-1}. − ^1H NMR: δ = 1.28 (t, 3 H, *J* = 7.2 Hz, CH_3CH$_2$O), 1.26−1.41 (m, 8 H, CH_2CH_2CH_2CH_2), 1.99−2.06 (m, 4 H, =CHCH_2, CH_2CH=), 2.60 (dd, 1 H, *J* = 7.2, 16.4 Hz, COCH_2), 2.75 (dd, 1 H, *J* = 7.4, 16.4 Hz, COCH_2), 3.67−3.70 (m, 1 H, C*H*CN), 4.19 (q, 2 H, *J* = 7.2 Hz, CH$_3$CH_2O), 4.91−5.04 (m, 2H CH=CH_2), 5.39 (dd, 1 H, *J* = 6.6, 15.4 Hz C*H*= CHCH$_2$), 5.79−5.92 (m, 2 H, =C*H*CH$_2$, CH$_2$C*H*=). − $C_{16}H_{25}NO_2$ (263.4): calcd. C 72.97, H 9.57, N 5.32; found C 73.05, H 9.60, N 5.29.

Ethyl (*E*)-3-Cyano-6-phenylhex-4-enoate (8f): Yield 1.03 g, 85%; oil. − IR (film): $\tilde{\nu}$ = 2225, 1730 cm^{-1}. − ^1H NMR: δ = 1.26 (t, 3 H, *J* = 7.2 Hz, CH_3CH$_2$O), 2.62 (dd, 1 H, *J* = 7.4, 16.4 Hz, COCH_2), 2.77 (dd, 1 H, *J* = 7.4, 16.4 Hz, COCH_2), 3.40 (d, 2 H, *J* = 7.0 Hz, CH_2Ph), 3.70−3.75 (m, 1 H, C*H*CN), 4.18 (q, 2 H, *J* = 7.2 Hz, CH$_3$CH_2O), 5.43 (dd, 1 H, *J* = 6.4, 15.4 Hz, C*H*=CHCH$_2$), 6.00−6.11 (m, 1 H, CH=C*H*CH$_2$), 7.13−7.35 (m, 5 H, arom.). − $C_{15}H_{17}NO_2$ (243.3) calcd. C 74.05, H 7.04, N 5.76; found C 74.09, H 7.00, N 5.79.

Ethyl 3-Cyano-3-cyclohex-1-enylpropanoate (10): Yield 0.87 g, 84%; oil. − IR (film): $\tilde{\nu}$ = 2225, 1730 cm^{-1}. − ^1H NMR: δ = 1.27 (t, 3 H, *J* = 7.2 Hz, CH_3CH$_2$O), 1.53−1.70 (m, 4 H, CH_2CH_2), 1.99−2.05 (m, 4 H, CH_2CH=CCH_2), 2.58−2.82 (m, 2 H, COCH_2), 3.59 (t, 1 H, *J* =7.4 Hz, C*H*CN), 4.19 (q, 2 H, *J* = 7.2 Hz, CH$_3$CH_2O), 5.78−5.80 (m, 1 H, C*H*=). − $C_{12}H_{17}NO_2$ (207.3): calcd. C 69.54, H 8.27, N 6.76; found C 69.59, H 8.23, N 6.80.

Ethyl (*S*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-3-cyanohex-4-enoate (12): Yield 0.37 g, 60%; oil. − IR (film): $\tilde{\nu}$ = 2225, 1730 cm^{-1}. − ^1H NMR: δ = 0.04 (d, 3 H, *J* = 2.6 Hz, CH_3CH), 0.9 (s, 9 H, *t*Bu), 1.19 (s, 3 H, CH_3Si), 1.22 (s, 3 H, CH_3Si), 1.28 (t, 3 H, *J* = 7.0 Hz, CH_3CH$_2$O), 2.55−2.77 (m, 2 H, COCH_2), 3.71−3.75 (m, 1 H, C*H*CN), 4.19 (q, 2 H, *J* = 7.0 Hz, CH$_3$CH_2O), 4.30−4.35 (m, 1 H, C*H*OSi), 5.30−5.63 (m, 1 H, CHC*H*=), 5.89−5.99 (m, 1 H, CHCH=C*H*). − $C_{16}H_{29}NO_3Si$ (311.5): calcd. C 61.69, H 9.38, N 4.50; found C 61.74, H 9.34, N 4.45.

4-(6-Chlorohexyl)pyrrolidin-2-one (14): $NaBH_4$ (0.155 g, 4.1 mmol) was added at 0 °C with stirring to a solution of $CoCl_2 \cdot 6\,H_2O$ (0.95 g, 4 mmol) in ethanol (6 mL). After 15 min, nitrile **8b** (0.49 g, 2 mmol), dissolved in ethanol (8 mL), was added dropwise at 0 °C. $NaBH_4$ (1.51 g, 40 mmol) was then added portionwise over a period of 4 h and, after a total stirring time of 6 h at 0 °C, the mixture was quenched with water (10 mL) and filtered through Celite. The Celite pad was washed with ethanol (3 × 20 mL) and the solution was concentrated at reduced pressure. The residue was dis-

solved in ethyl acetate (60 mL) and washed with 10% aqueous NH_4OH (2 × 8 mL) and brine (10 mL), and finally dried with $MgSO_4$. After evaporation of the solvent at reduced pressure, the residue was purified by flash chromatography (hexane/ethyl acetate/ethanol, 60:35:5) to afford 0.29 g of pyrrolidinone **14** (71%); oil. – IR (film): $\tilde{\nu}$ = 1715 cm^{-1}. – ^1H NMR: δ = 1.23–1.49 [m, 10 H, $(CH_2)_5$], 1.67–1.78 (m, 1 H, C*H*), 1.94–2.04 (m, 1 H, CH_2N), 2.33–2.45 (m, 1 H, CH_2N), 2.94–3.03 (m, 1 H, $COCH_2$), 3.42–3.46 (m, 1 H, $COCH_2$), 3.51 (t, 2 H, *J* = 6.6 Hz, CH_2Cl), 6.68 (br. s, 1 H, N*H*). – $C_{10}H_{18}ClNO$ (202.7): calcd. C 59.25, H 8.45, N 6.91; found C 59.23, H 8.41, N 6.93.

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