Radical addition to ynol ethers — A convenient procedure for the stereoselective preparation of α-iodo enol ethers in neutral conditions

Fanny Longpré, Natalia Rusu, Maxime Larouche, Rana Hanna, and Benoit Daoust

Abstract: α-Iodo enol ethers, precursors of acyl anion equivalents, are not easily prepared. Herein we report that addition of activated iodoalkanes to ynol ethers under mild and neutral radical reaction conditions leads to α-iodo enol ethers in moderate to excellent yields with high stereoselectivity. The reaction can be carried out in various solvents at different temperatures. The methodology allows the preparation of β-alkylated and β,β-dialkylated α-iodo enol ethers. Reduction of the carbon-iodine bond of these species leads to the corresponding enol ethers with good yields.

Key words: ynol ethers, enol ethers, radical addition, stereoselective.

Résumé : Les α-iodoéthers d'énol, des précurseurs d'équivalents d'anions acyles, sont difficiles à préparer. Cet article présente nos résultats de notre étude sur l'addition d'iodoalcanes activés sur des éthers d'ynol. Cette réaction, qui conduit à des α-iodoéthers d'énol avec des rendements allant de bons à excellents, s'effectue en milieu neutre et dans des conditions réactionnelles très douces. De plus, cette réaction est très stéréosélective. La réaction peut être effectuée dans différents solvants, à différentes températures. Cette méthodologie permet de préparer des α-iodoéthers d'énol β-alkylés et β,β-dialkylés. La réduction du lien carbone-iode de ces composés permet d'isoler des éthers d'énol avec de bons rendements.

Mots-clés : éthers d'ynol, éthers d'énol, addition radicalaire, stéréosélectif.

[Traduit par la Rédaction]

Introduction

α-Halo enol ethers are interesting precursors of substituted enol ethers and are also umpolungs for acyl groups (1). Transmetallation of the α-halo enol ether halogen atom produces α-alkoxy vinyl anions that have shown versatile applications in organic synthesis (2, 3). These halogenated species were also used in cross-coupling reactions (4). However, very few methods exist for preparing these useful α-halo enol ethers (2, 5). Most of them require the use of strong bases or the intermediacy of α-alkoxy vinylstannane compounds. Recently, Yu and Jin developed a more convenient method using in situ produced hydrohalic acids (2). These then react with ynol ethers to produce α-halo enol ethers with good to excellent yields. Unfortunately, this method requires acidic reaction conditions that are known to be deleterious to a number of α-halo enol ethers (1). Also, only *mono* β-alkylated α-halo enol ethers can be prepared by this method. As a consequence, the development of a new methodology for the preparation of β-alkylated and β,β-dialkylated α-halo enol ethers under neutral and mild reaction conditions emerges as an important and challenging synthetic endeavor.

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Results and discussion

Our strategy for the preparation of α-iodo enol ethers is outlined in Scheme 1. We hypothesized that intermediate electrophilic radical **2** formed by homolytic cleavage of iodinated active methylene **1** (Z = CO_2Et, CN, $CONH_2$) would add to the electron-rich β-carbon of **3** to give trans radical adduct **4**. The anti attack leading to trans radical **4** should be favored for stereoelectronic reasons (6). The use of iodides, which are efficient halogen-atom transfer agents, should ensure rapid trapping of vinyl radical **4** before its interconversion leading to *E*-isomer **5** with stereoselection (7).

We first examined the radical addition of ethyl iodoacetate (**1a**) to ethoxyacetylene (**3a** ; R = ethyl, R′ = H), the only commercially available ynol ether. In CH_2Cl_2 at room temperature (Table 1, entry 1), completion of the reaction was observed within 15 min using Et_3BO_2 as radical initiator. We were very happy to isolate 97% of the expected adduct **5a** with complete stereoselectivity. Indeed, only the *E*-isomer could be observed in NMR spectra and GCMS chromatographs (*E*/*Z* > 99:1). This result not only supports our hypothesis about the ability of ynol ethers to accept electrophilic radicals but also confirms the slow interconversion of vinyl radical **4** (see Scheme 1). We were very pleased to observe that low temperature (–78 °C) had no important effect on the reaction efficiency (entry 2, 90% yield). We then tested an ynol ether possessing a more sterically de-

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Scheme 1.

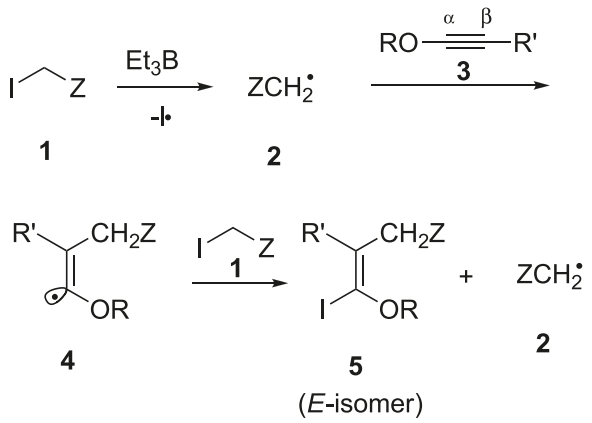
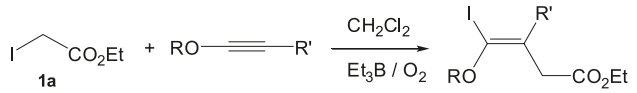


Table 1. Addition of ethyl iodoacetate (**1a**) to ynol ethers **3a**–**3d**, **3g**, and **3h** in CH_2Cl_2.



3a (R = Et, R' = H)
3b (R = menthyl, R' = H)
3c (R = adamantyl, R' = H)
3d (R = menthyl, R' = Me)
3e (R = menthyl, R' = iPr)
3f (R = menthyl, R' = sBu)
3g (R = Et, R' = SitBuMe$_2$)
3h (R = Et, R' = SitBuPh$_2$)

5a (R = Et, R' = H)
5b (R = menthyl, R' = H)
5c (R = adamantyl, R' = H)
5d (R = menthyl, R' = Me)
5e (R = menthyl, R' = iPr)
5f (R = menthyl, R' = sBu)
5e (R = Et, R' = SitBuMe$_2$)
5f (R = Et, R' = SitBuPh$_2$)

Entry	Substrate	Temp.[a]	Product	Yield[b] (%)	*E*/*Z* ratio[c,d]
1	**3a**	RT	**5a**	97	> 99:1
2	**3a**	–78 °C	**5a**	90	> 99:1
3	**3b**	RT	**5b**	75	> 99:1
4	**3b**	–78 °C	**5b**	70	> 99:1
5	**3c**	RT	**5c**	0	–
6	**3d**	RT	**5d**	72	> 99:1
7	**3d**	–78 °C	**5d**	70	> 99:1
8	**3g**	RT	**5g**	0	–
9	**3h**	RT	**5h**	0	–

Note: Reaction time: 2 h in all cases except for entry 1 (15 min).
[a]RT = room temperature.
[b]Isolated yield based on **3**.
[c]The *E*-isomer was easily detected by ^{1}H and ^{13}C NMR, TLC, and GCMS ; we could not detect the presence of any of the *Z*-isomers with these methods.
[d]The geometries of the double bond of **5a** and **5b** were determined by the characteristic coupling constants of their reduced counterparts **6a** and **6b** (see Table 4). The geometry of the double bond of **5d** was determined by NOESY spectra of the reduced counterpart **6d**.

manding group attached to the oxygen atom: menthoxyethyne **3b** (R = menthyl, R′ = H) (8). As one can see from entries 3 and 4, the reaction with **3b** proceeds with good yields (75% and 70%) and complete stereoselectivity at RT and at –78 °C. When we tried an ynol ether with even more sterically demanding adamantyl group (**3c** ; R = adamantyl, R′ = H) (9), no desired adduct was observed (entry 5); only the starting material was recovered.

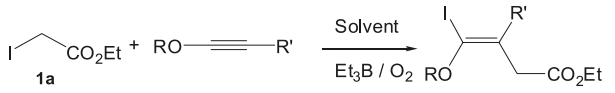
These results suggest that the menthyl group might be the steric limit on the oxygen side of the ynol ether for our reaction to occur. We then decided to prepare a series of substituted menthoxyethyne (R = menthyl) possessing groups with increasing bulkiness at the β-position. First, 1-menthoxypropyne **3d** (R = menthyl, R″ = Me) was tested (8). The radical reaction between **3d** and ethyl iodoacetate occured with yields comparable to those obtained with **3b** (entries 6 and 7, 72% and 70% yield). Again, complete stereocontrol of the double bond was observed. We then decided to install groups possessing secondary carbon at the β-position. Isopropyl was our first choice. We examined the possibility of producing compound **3e** (R = menthyl, R″ = *i*-Pr) by reacting menthoxyethyne **3b** with triisopropylborane (10) using Greene's protocol (8). Unfortunately, we were not able to isolate the desired product. Though TLC revealed the presence of a new compound with an R_f characteristic of ynol ethers, compound **3e**, if ever produced, seemed to be very unstable and degradation was observed before any characterization could be performed. We also tried to prepare compound **3f** (R = menthyl, R′ = *s*-Bu) according to Greene's protocol (8). In that case, the desired compound **3f** could be obtained and isolated, though it showed a very high propensity to decomposition. We submitted this freshly produced ynol ether to our radical reaction conditions. Unfortunately, compound **3f** decomposed before any addition reaction could occur. Hoping that highly encumbered triple bonds would be easier to handle, we tried to prepare very crowded ynol ethers **3g** (R = Et, R′ = Si-*t*-BuMe$_3$) and **3h** (R = Et, R′ = Si-*t*-BuPh$_3$) (11). Fortunately, these compounds were chemically stable and could thus be isolated and purified. However, radical addition of these two ynol ethers with ethyl iodoacetate did not produce the desired adducts **5g**–**5h** (entries 8 and 9, 0% yield in both cases). Only the starting materials were recovered.

Other solvents were then assessed (Table 2) for the reaction involving ethyl iodoacetate (**1a**) and ynol ether **3b**. In benzene (entry 1), the reaction took place with a slightly better yield (80%) compared to CH_2Cl_2 (Table 1, entry 3). In hexanes, acetone, and DMSO (Table 2, entries 2, 3, and 4), the yields were slightly lower (51%–65%). Reaction did not occur in THF (entry 5, 0% yield).

It is of note that when volatile solvents were used (for example, CH_2Cl_2 or hexanes), no aqueous work-up was required, thus reducing the risk of hydrolysis of iodo vinyl ethers **5**. The adducts **5** must be isolated by carefully evaporating the solvent and Et_3B with a nitrogen gas flow. Indeed, we observed that rotary evaporation dramatically accelerated decomposition of these highly functionalized adducts.

Table 3 summarizes results of radical addition of two other iodinated active methylenes towards ynol ether **3d** in CH_2Cl_2. Entries 1, 2, and 3 reveal that iodoacetonitrile added to ynol ether **3d** at different temperatures (RT, 0 °C and –78 °C) with poorer yields (49%–57%) than ethyl iodoacetate (**1a**). Here again, only one isomer of the double bond was observed. Iodoacetamide (entries 4, 5, and 6) added to ynol ether **3d** with modest yields (18%–30%) but with high stereoselection. We also tried the addition of two other α-iodo carbonyl compounds, namely diethyl iodomalonate and 1-iodopropan-2-one. Unfortunately, both iodinated compounds failed to react with ynol ethers **3a** and **3b**. Brominated activated methylenes $BrCH_2CO_2Et$, $BrCH_2CN$, and $BrCH(CO_2Et)_2$ were also reacted with ynol

Table 2. Addition of ethyl iodoacetate **1a** to ynol ethers **3b** in different solvents at room temperature.

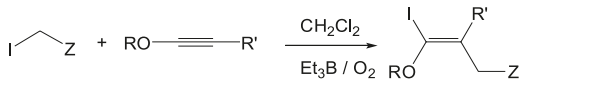


3b (R = menthyl, R' = H) **5b** (R = menthyl, R' = H)

Entry	Solvent	Reaction time (h)	Yield[a] of **5b** (%)	*E*/*Z* ratio
1	Benzene	2	80	> 99:1
2	Hexanes	2	65	> 99:1
3	DMSO	1	51	> 99:1
4	Acetone	1	60	> 99:1
5	THF	1	0	—

[a]Isolated yield based on **3b**.

Table 3. Addition of iodinated active methylenes **1b** and **1c** to ynol ether **3d** in CH_2Cl_2.



1b (R = CN) **3d** (R = menthyl, R' = Me) **5i** (R = menthyl, R' = Me, Z = CN)
1c (R = $CONH_2$) **5j** (R = menthyl, R' = Me, Z = $CONH_2$)

Entry	Temp.[a]	Iodinated compound	Product	Yield	*E*/*Z* ratio[b]
1	RT	**1b**	**5i**	57	> 99:1
2	0 °C	**1b**	**5i**	51	> 99:1
3	–78 °C	**1b**	**5i**	49	> 99:1
4	RT	**1c**	**5j**	30	> 99:1
5	0 °C	**1c**	**5j**	25	> 99:1
6	–78 °C	**1c**	**5j**	18	> 99:1

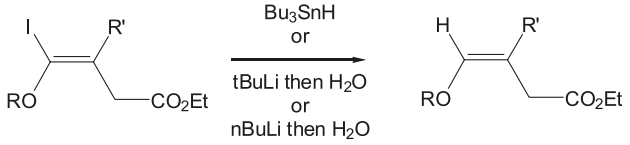
Note: Reaction time of 2 h in all cases.
[a]RT = room temperature
[b]The geometry of double bonds of **5i** and **5j** were determined by NOESY spectra.

ethers **3a** and **3b**. In all cases, only the starting materials were recovered.

The radical nature of this new methodology was confirmed using a radical scavenger. Addition of *tert*-butylphenylnitrone to a mixture of **1a** and **3a** followed by Et_3B addition gave ~ 0% yield of the desired adduct.

To demonstrate the usefulness of α-iodo enol ethers, we performed C–I bond reductions of adducts **5a**, **5b**, and **5d** (Table 4). Di and trisubstituted cis enol ethers were obtained with modest to excellent yields (15%–96%) using tributyltin hydride, *n*-BuLi or *t*-BuLi as reducing agents. The desired compounds **6a**, **6b**, and **6d** were all isolated with complete stereoretention. A one-pot procedure involving radical addition of ethyl iodoacetate **1a** to ynol ether **3d** followed by Bu_3SnH reduction without isolation of the intermediate iodo enol ether **5d** did not lead to the desired reduced compound **6d** (0% yield).

Table 4. Formation of di- and trisubstituted enol ethers **6a**, **6b**, and **6d** from deiodination of **5a**, **5b**, and **5d**.



5a (R = Et, R' = H)
5b (R = menthyl, R' = H)
5d (R = menthyl, R' = Me)

6a (R = Et, R' = H)
6b (R = menthyl, R' = H)
6d (R = menthyl, R' = Me)

Entry	Substrate	Reducing agent	Product	Yield[a] (%)	*E*/*Z* ratio[b]
1	**5a**	Bu_3SnH[c]	**6a**	96%	> 99:1
2	**5a**	*t*-BuLi[d]	**6a**	70%	> 99:1
3	**5b**	Bu_3SnH[c]	**6b**	15%	> 99:1
4	**5b**	*t*-BuLi[d]	**6b**	69%	> 99:1
5	**5b**	*n*-BuLi[e]	**6b**	16%	> 99:1
6	**5d**	*t*-BuLi[d]	**6d**	72%	> 99:1

[a]Isolated yields.
[b]The geometries of the double bond of **6a**–**6b** were determined by their characteristic coupling constants. The geometry of the double bond of **6d** was determined by NOESY spectra.
[c]Bu_3SnH 1.2 eq., benzene, 1–3 h, RT.
[d]*t*-BuLi 1.2 eq, THF, –78 °C, 0.5 h.
[e]*n*-BuLi 1.2 eq., THF, –78 °C, 0.5 h.

Conclusion

In conclusion, we demonstrated, for the first time, that activated methylenes add to ynol ethers in neutral radical conditions. The yields obtained vary from moderate to excellent. The diastereoselectivity of the addition is very high in all cases. The possibility of avoiding the aqueous work-up represents a great advantage over existing methods for preparing hydrolysis-sensitive α-iodo enol ethers. The latter are interesting precursors of substituted enol ethers and are acyl anion equivalents. This method is one of the very few that allowed the stereo-controlled formation of α-iodo β,β-disubstituted enol ether (12). We are now working on the radical addition of activated iodoalkanes to silyl ynol ethers. This should allow us to prepare stereocontrolled β,β-disubstituted silyl enol ethers, enolate equivalents, known to be difficult to prepare (13).

Experimental[2]

All reactions requiring anhydrous conditions were conducted under positive nitrogen atmosphere in oven-dried glassware and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via standard syringe techniques. All solvents were distilled prior to use, except for anhydrous tetrahydrofuran (THF) that was used as received from Sigma-Aldrich (SureSeal). *n*-Butyllithium (1.6 mol/L solution in hexanes) and *tert*-butyllithium (1.7 mol/L solution in pentane) were purchased from Sigma-Aldrich and titrated prior to use (diphenylacetic

[2]Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 3776. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

acid end-point in dry THF). Tributyltin hydride, ethoxyacetylene (40% in hexanes), and triethylborane (1 mol/L in hexane) were also purchased from Sigma-Aldrich and used as received. Flash chromatography was performed on triethylamine pretreated Merck silica gel 60 (0.040–0.063 mm) using compressed air pressure. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F 54 plates previously treated with triethylamine. ^{1}H NMR spectra were recorded on a Varian 200 MHz NMR spectrometer using $CDCl_3$ (δ = 7.26 ppm) or CD_3COCD_3 (δ = 2.09 ppm) as the reference. ^{13}C NMR were recorded at 50.3 MHz using $CDCl_3$ (δ = 77.1 ppm), CD_3COCD_3 (δ = 30.6 ppm), or C_6D_6 (δ = 128.6 ppm) as the reference. NMR data are reported as follows: chemical shift in ppm, multiplicity (d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets), number of protons, and coupling constants in Hertz. IR spectra were recorded on a Nicolet Impact 420 spectrophotometer. Gas chromatography – mass spectra (GC–MS) were recorded on an Agilent model 6890N. High-resolution mass spectra (HRMS) were recorded on a ZAB-2F model VG apparatus.

Preparation of starting materials

The preparation and characterization of menthoxyethyne (**3b**), 1-menthoxypropyne (**3d**), and 1-menthoxy-3-methylpentyne (**3f**) have been reported previously (8). Compounds **3c** (9) and **3g** (11) have also been prepared and characterized previously (9). Ethoxyacetylene (**3a**) is commercially available.

Ethoxyethynyl(1,1-dimethylethyl)diphenylsilane (3h)

The preparation of the title compound was carried out according to the procedure described by Pericas and co-workers for the synthesis of similar compounds (10*b*). Under inert atmosphere, *n*-BuLi (3 mL, 1.50 mol/L in *n*-hexane, 4.60 mmol) was added dropwise to a solution of ethoxyacetylene (40% in hexanes, 1 mL, 4.18 mmol) in anhydrous THF (2.9 mL) at 0 °C over a period of 10 min. The mixture was stirred for 1.5 h and hexamethylphosphoric triamide (0.81 mL) was added. After 10 min, *tert*-butyldiphenylsilyl chloride (1.17 mL, 4.51 mmol) was added. The cooling bath was removed and the mixture was stirred overnight at room temperature. The reaction mixture was poured on a mixture of ice (3 g) and *n*-hexane (6 mL). The organic layer was separated, and the aqueous layer was extracted twice with *n*-hexane (4 mL). The combined organic layers were washed with brine (4 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was chromatographed through silica gel (pretreated with 1% *v*/*v* of triethylamine) eluting with hexane to give 90% yield of **3h** as a colorless oil.

IR (cm^{-1}): 3065, 3048, 2959, 2929, 2891, 2857, 2174, 1427, 1103. ^{1}H NMR ($CDCl_3$) δ: 8.09 (m, 4H), 7.58 (m, 6H), 4.38 (q, 2H, *J* = 7.0 Hz), 1.60 (t, 3H, *J* = 7.0 Hz), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 14.7, 19.0, 27.6, 33.0, 75.6, 113.0, 128.0, 129.6, 135.0, 136.0. HRMS calcd. for $C_{20}H_{24}SiO$ (+NH_4): 326.1940; found : 326.1931

General procedure for radical addition of iodoalkanes to ynol ethers

In a 10 mL round-bottomed flask, 0.28 mmol of ynol ether and 1.5 equiv. of the appropriate iodoalkane were dissolved in 2 mL of freshly distilled solvent at the desired temperature. Triethylborane (1.0 mol/L in hexane) was added (100 μL) to initiate the radical chain process. Triethylborane (100 μL) was then added every 15 min until no starting material was detectable by TLC. The solvent was removed by a gentle flow of dry nitrogen gas. The crude product was *rapidly* purified by flash chromatography using 100% hexanes to 10% acetone–hexanes (the contact time with the silica gel must be less than 15 min to avoid decomposition).

α-Iodo enol ethers **5a**, **5b**, **5d**, **5i**, and **5j** were not fully characterized because of their instability. HRMS could not be recorded. In most cases, recording ^{13}C NMR spectra was not possible. When using diluted solutions in the NMR tube, the long acquisition time led to decomposition before ^{13}C spectra could be recorded. Concentrating the solution (to reduce the time required to obtain the ^{13}C NMR) accelerated decomposition, thus precluding the recording of the spectra. However, the stable reduced parents of **5a**, **5b**, and **5d**, the enol ethers **6a**, **6b**, and **6d**, were fully characterized.

The geometry of double bonds was determined by NOESY spectra for compounds **5d**, **5i**, **5j**, and **6d**. For the reduced compounds **6a** and **6b**, the geometry of the double bonds was determined with the help of the characteristic cis-isomer coupling constants.

(*E*)-Ethyl 4-ethoxy-4-iodobut-3-enoate (5a)

Yellow oil. IR (cm^{-1}): 3018, 2952, 2915, 1731, 1629, 1454. ^{1}H NMR (CD_3COCD_3) δ: 1.22 (m, 6H), 2.80 (m, 1H), 3.12 (d, 1H, *J* = 7.0 Hz), 3.77 (q, 2H, *J* = 7.4 Hz), 4.09 (q, 2H, *J* = 7.0 Hz), 5.53 (t, 1H, *J* = 7.2Hz). MS: 157 (M^+ – I), 129, 101, 99, 83, 73, 55.

(*E*)-Ethyl 4-iodo-4-menthoxybut-3-enoate (5b)

Yellow oil. IR (cm^{-1}): 3017, 2960, 2922, 1735, 1633, 1451. ^{1}H NMR (CD_3COCD_3) δ: 0.80–2.20 (m, 21H), 3.12 (d, 2H, *J* = 7.4 Hz), 3.67 (td, 1H, *J* = 5.5 and 10.9 Hz), 4.11 (q, 2H, *J* = 7.0 Hz), 5.54 (td, 1H, *J* = 1.6 and 7.0 Hz). MS: 267 (M^+ – I), 139, 123, 95, 83, 69, 55.

(*E*)-Ethyl 4-iodo-4-menthoxy-3-methylbut-3-enoate (5d)

Yellow oil. IR (cm^{-1}): 2955, 2921, 2868, 1734, 1636, 1457, 1180. ^{1}H NMR (CD_3COCD_3) δ: 0.80–2.20 (m, 24H), 3.11 (d, 1H, *J* = 15.6 Hz), 3.37 (d, 1H, *J* = 15.6 Hz), 3.66 (td, 1H, *J* = 4.3 and 10.9 Hz), 4.13 (q, 2H, *J* = 7.0 Hz). ^{13}C NMR (CD_3COCD_3) δ: 13.9, 16.2, 20.3, 21.8, 23.4, 23.7, 25.6, 31.5, 34.3, 37.1, 39.6, 47.1, 60.3, 82.1, 116.6, 120.5, 170.1. MS: 281 (M^+ – I), 270, 142, 83, 69, 55.

(*E*)-Ethyl 4-iodo-4-menthoxy-3-methylbut-3-enenitrile (5i)

Yellow oil. IR (cm^{-1}): 2953, 2917, 2865, 2246, 1636, 1454. ^{1}H NMR ($CDCl_3$) δ: 0.80–2.2 (m, 21H), 3.36–3.57 (m, 2H), 3.75 (td, 1H, *J* = 4.7 and 10.5 Hz). ^{13}C NMR (CD_3COCD_3) δ: 16.1, 19.7, 20.3, 21.7, 22.5, 23.4, 25.6,

31.6, 34.2, 39.7, 47.0, 82.9, 116.1, 116.8. MS: 234 (M^+ – I), 139, 97, 83, 69, 55.

(*E*)-Ethyl 4-iodo-4-menthoxy-3-methylbut-3-enamide (5j)

Yellow oil. IR (KBr, cm^{-1}): 3433, 3187, 2962, 2867, 1662, 1461, 1386, 1126. ^{1}H NMR ($CDCl_3$) δ: 0.80–2.20 ppm (m, 21H), 3.05–3.26 (m (apparent q), 2H), 3.73 (td, 1H, J = 4.5 and 10.9 Hz), 6.20–6.40 (br, 1H), 6.60–6.80 (br, 1H).

General procedure for tributyltin hydride reduction of α-iodoenol ethers

In a 10 mL round-bottomed flask, 0.250 mmol of freshly prepared α-iodoenol ether was dissolved in 1.5 mL of benzene along with 0.300 mmol (87 mg, 80 μL) of tributyltin hydride (1.2 eq.). Triethylborane (1.0 mol/L in hexane) was added (100 μL) to initiate the radical chain process. Triethylborane (100 μL) was then added every 15 min until no starting material was detectable by TLC (1–3 h). A saturated aqueous solution of $NaHCO_3$ was poured into the reaction mixture. After the aqueous layer was extracted with Et_2O (3×), the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered through a pad of silica-KF, and concentrated. The crude product was purified by flash chromatography using 100% hexanes to 10% acetone–hexanes.

General procedure for *n*-butyllithium and *tert*-butyllithium reduction of α-iodoenol ethers

In a 10 mL round-bottomed flask, 0.250 mmol of freshly prepared α-iodoenol ether was dissolved in 5 mL of anhydrous THF. The reaction mixture was cooled to –78 °C and 0.300 mmol (1.2 eq.) of freshly titrated BuLi was added dropwise. After 30 min (when TLC confirms that the reaction was completed), 1 mL of distilled water was added dropwise. The cooling bath was removed and the reaction mixture was stirred for another 10 min. A saturated aqueous solution of $NaHCO_3$ was poured into the reaction mixture. After the aqueous layer was extracted with Et_2O (3×), the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography using 100% hexanes to 10% acetone–hexanes.

(*Z*)-Ethyl 4-ethoxybut-3-enoate (6a)

Yellow oil. IR (cm^{-1}): 3047, 2978, 2944, 2884, 1730, 1666, 1381, 1323, 1245, 1177, 1109. ^{1}H NMR ($CDCl_3$) δ: 1.22 (m, 6H), 3.11 (dd, 2H, J = 1.6 and 7.0 Hz), 3.79 (q, 2H, J = 7.0 Hz), 4.08 (q, 2H, J = 7.0 Hz), 4.53 (q, 1H, J = 7.0 Hz), 6.06 (dt, 1H, J = 1.6 and 6.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.4, 15.4, 30.0, 60.7, 68.0, 98.1, 147.0, 172.7. MS: 158, 127, 99, 85, 57. HRMS calcd. for $C_8H_{14}O_3$: 158.0943; found: 158.0935

(*Z*)-Ethyl 4-menthoxybut-3-enoate (6b)

Yellow oil. IR: 3009, 2944, 1742, 1450, 1022. ^{1}H NMR ($CDCl_3$) δ: 0.76 (d, 3H, J = 6.6 Hz), 0.80–2.20 (m, 21H), 3.11 (dd, 2H, J = 1.6 and 7.0 Hz), 3.39 (td, 1H, J = 4.3 and 10.9 Hz), 4.13 (q, 2H, J = 7.0 Hz), 4.51 (q, 1H, J = 7.0 Hz), 6.13 (dt, 1H, J = 1.6 and 6.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 14.3, 16.4, 17.8, 20.5, 22.2, 23.8, 31.7, 34.2, 35.0, 41.9, 47.7, 60.1, 80.8, 106.2, 142.0, 171.2. MS: 268, 138, 123, 97, 83, 69, 55. HRMS calcd. for $C_{16}H_{28}O_3$: 268.2038; found: 268.2028

(*Z*)-Ethyl 4-menthoxy-3-methylbut-3-enoate (6d)

Yellow oil. IR (cm^{-1}): 3005, 2956, 2868, 1740, 1456, 1364, 1253, 1178, 1136, 1038. ^{1}H NMR ($CDCl_3$) δ: 0.80–2.20 (m, 24H), 3.05–4.20 (m, 5H), 6.04 (m, 1H). ^{13}C NMR δ (C_6D_6) δ: 14.0, 16.1, 18.0, 20.5, 22.0, 24.1, 26.0, 31.2, 34.0, 34.8, 41.3, 48.0, 60.0, 81.0, 107.0, 141.2, 171.0. MS: 219, 202, 173, 145, 127, 101. HRMS calcd. for $C_{17}H_{30}O_3$: 282.2195; found: 282.2193

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