Tetrahedron 67 (2011) 92–99

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Intramolecular regioselective addition of radicals and carbanions to ynol ethers. A strategy for the synthesis of exocyclic enol ethers

Rana Hanna, Benoit Daoust *

Département de Chimie-Biologie, Université du Québec à Trois-Rivières, Trois-Rivières, Québec, Canada G9A 5H7

ARTICLE INFO

Article history:
Received 4 October 2010
Received in revised form 3 November 2010
Accepted 3 November 2010
Available online 11 November 2010

Keywords:
Ynol ethers
Enol ethers
Radical cyclization
Anionic cyclization
Alkyllithiums
Vinyllithiums

ABSTRACT

The scope and limitations of radical and anionic cyclization reactions involving halo ynol ethers have been investigated. 5-*exo* and 6-*exo* radical cyclizations of 6-iodo and 7-iodo ynol ethers proceeded well when the oxygen of the ynol ether was bearing an ethyl group. Exocyclic iodoenol ethers resulting from these cyclizations were highly unstable and decomposed rapidly. Li–I exchange of iodo ynol ethers proceeded smoothly at −78 °C. 6-Alkoxy-5-hexynyllithiums underwent regiospecific 5-*exo*-dig anionic cyclization to produce five-membered rings bearing an exocyclic enol ether moiety. The cyclized vinyllithium intermediate was successfully trapped with electrophiles to afford functionalized cycloalkoxyalkylidene derivatives in modest to good yields. 7-Alkoxy-6-heptynyllithiums did not cyclize via a 6-*exo* anionic process.

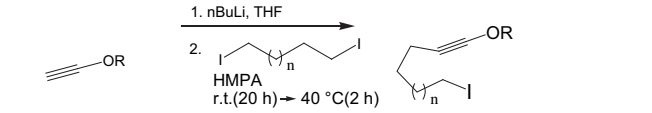
1. Introduction

Formation of carbocycles is one of the most important endeavors in organic chemistry. A simple approach to this synthetic problem is the intramolecular addition of a reactive center to a CC multiple bond acceptor. Additions to alkynes are especially interesting since they generally lead to exocyclic unsaturated compounds. Radical[1,2] and anionic[3–5] additions to alkynes have been studied. Some of these cyclization reactions were performed on functionalized alkynes,[4,5] but very few on alkoxylated alkynes (ynol ethers).[6–8] In our ongoing research program dedicated to the development of functionalized ynol ethers,[9,10] we decided to explore the scarcely studied addition of radical and anionic reactive centers to ynol ethers.

2. Results and discussion

2.1. Preparation of models

Models with different R groups and different carbon saturated chains were prepared (compounds **2a**–**d**, see Scheme 1). Our strategy consisted in preparing 6- and 7-iodo ynol ethers, and not bromoynol ethers. This choice was made since it is known that (i) radical formation is easier with iodoalkanes than it is with bromoalkanes[9] and (ii) alkylmetals are formed more cleanly starting from iodinated compounds than brominated ones.[3]



1 (R = Et, menthyl))

2a (R = Et, n=1) (75% yield)
2b (R = Menthyl, n=1) (90% yield)
2c (R = Et, n=2) (89% yield)
2d (R = Menthyl, n=2) (75% yield)

Scheme 1.

Models **2a** and **2c** were prepared by alkylating the deprotonated ethoxyethyne (**1** (R=Et), commercially available) with 1,4-diiodobutane or 1,5-diiodopentane, in the presence of HMPA. Yields were, respectively, 75 and 89%. In the absence of HMPA, yields dropped to less than 10%.

Models **2b** and **2d** were first prepared using a two-step sequence. First, ynol ether **1** (R=menthyl) was prepared from menthol, using Greene's protocol (KH and TCE then BuLi and H_2O).[11] It was then transformed to the desired iodinated compounds using the procedure described in the previous paragraph, with comparable yields (90 and 75%, respectively). Compounds **2b** and **2d** could also be synthesized from menthol without isolation of β-unsubstituted ynol

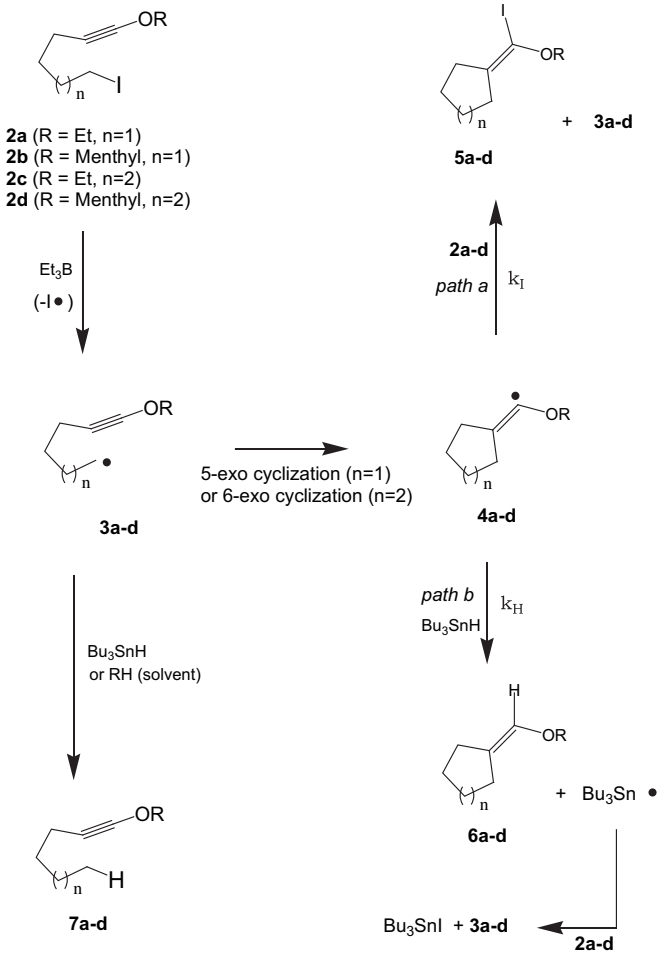
* Corresponding author. Tel.: +819 376 5011; fax: +819 376 5084; e-mail address: Benoit.Daoust@uqtr.ca (B. Daoust).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.11.024

ether **1** (R=menthyl) (KH and TCE then BuLi and diiodoalkane). With this procedure, **2b** was prepared with 90% yield and **2d** was prepared with 45% yield. It should be noted that menthylated ynol ethers **2b** and **2d** are stable at −5 °C for more than a week. Ethylated ynol ethers **2a** and **2c** are stable at −5 °C for only a few days.

2.2. Radical cyclization

Scheme 2 illustrates the expected radical cyclization mechanism for models **2a**–**d**. Upon treatment with Et_3B initiator, compound **2** should produce alkyl radical **3**. Cyclization would lead to vinyl radical **4**. In the absence of an H-transfer agent, abstraction of iodine from the starting material should form iodoenol ether **5** (path a). In the presence of an H-transfer agent (e.g., Bu_3SnH), path b, leading to **6**, is also possible. Also possible is a transfer of H to radical **3** prior to cyclization leading to **7**.



Scheme 2.

Since the best solvent for intermolecular addition of carbon-centered radicals to ynol ethers[9,10] is known to be dichloromethane, this solvent was chosen to begin the present investigation.

*2.2.1. Compound **2a**.* The radical reaction was performed by adding radical initiator Et_3B to a 0.05 M CH_2Cl_2 solution of **2a** at room temperature. The results are presented in Table 1. Low concentration (0.05 M) of ynol ether **2a** was used to favor intramolecular processes over intermolecular processes. In entry 1, 0.3 equiv of Et_3B was added every 15 min for 2 h. After 24 h, a modest 9% yield of the desired compound was observed. The experiment was repeated

Table 1
Intramolecular radical addition of **2a** in CH_2Cl_2[a,b]

Entry	Bu_3SnH added (total equiv)[c]	Reaction time (h)	Temp (°C)	Yields[d] (%)	
				5a	**6a**
1	0	24	23	9	0
2	0	24	23	10	0
3	0	4	40	0[e]	0
4	1.2	0.25	23	0[e]	0
5	1.2	6	−78	40	0
6	2	6	−78	85	0
7	4	6	−78	45	30

[a] Concentration of **2a**: 0.05 M.
[b] The radical initiator, Et_3B 1.0 M/hexanes, was added every 15 min (100 μL) for the first 2 h (except for entry 2 where it was added for the first 4 h).
[c] Bu_3SnH (0.3 equiv) was added every hour until the amount of equivalents was reached.
[d] Yields obtained by ^1H NMR (internal standard: diphenylmethane).
[e] Product degradation.

but Et_3B was then added every 15 min for the first 4 h. The yield did not improve significantly (10%, entry 2). In both reactions, the remaining material was a mixture of decomposition products and unreacted **2a**. When heated at reflux (entry 3), the starting product did not survive the reaction conditions.

In view of these unsatisfying results, it was decided to use a hydride transfer agent, Bu_3SnH. It was hoped that Bu_3SnH would improve the intramolecular addition by generating a more efficient radical chain or by acting as a better radical initiator. The product generally expected from a tin hydride radical chain reaction is the hydrogenated compound (here, compound **6a**, see Scheme 1). This is explained by that fact that reaction of the alkyl radical with tin hydride is generally faster than abstraction of iodide from the starting material (k_H is generally $>k_I$, see Scheme 1). However, the case is different with cyclized vinyl radicals. Curran demonstrated that for these radicals k_I is at least three times faster than k_H.[1] In our case, it is most probable that alkoxylated vinyl radicals will behave the same way, thus favoring the production of **5a** over **6a**.

To avoid reduction of radical **3a** to **7a** (see Scheme 1) prior to its cyclization to **4a**, small quantities of Bu_3SnH (0.3 equiv) were added every hour (entry 4). In these conditions, at room temperature, compound **2a** reacted very rapidly and led to a complex mixture of products. At −78 °C (entry 5), a 40% conversion of iodinated carbocycle **5a** was observed. Reduced cyclized compound **6a** could not be detected. By adding a total of 2 equiv of Bu_3SnH, the conversion went up to 85% (entry 6). Adding 4 equiv of Bu_3SnH (entry 7) finally led to the reduced product with 30% yield. Still, 45% of the iodinated compound was obtained. Adding more Bu_3SnH led to more conversion to **6a** (observed in the ^1H NMR of the crude reaction mixture), however, because of tin compounds this precluded the recording of any NMR conversion yield or isolation of any expected products.

As observed by Curran with other vinyl radicals,[1] it must be concluded that in the present case, k_I is larger than k_H. This radical cyclization is therefore very exothermic and most probably irreversible (another reason why any thermodynamically favored six-membered ring products were not observed). Volatility might also contribute to the very small amount of **6a** observed. Indeed, compound **6a** seemed to be more volatile than **5a**, as suggested when entry 7, Table 1, was allowed to have a very long evaporation time (1 h instead of the regular 5 min evaporation). In that case, the yield of **6a** fell to 5% while the yield of **5a** decreased only to 40%.

Other solvents were also assessed (Table 2) for the cyclization of compound **2a** in the presence of Bu_3SnH. In benzene (entry 1) at room temperature, the reaction took place with a lower conversion (50%) than in CH_2Cl_2 at −78 °C (Table 1, entry 6). In hexanes and in acetone (entries 2–5), the reaction was much slower and led to lower conversions (0–21%). Reaction did not occur in THF (entries 6

Table 2
Intramolecular radical addition of **2a** in different solvents[a,b,c]

Entry	Solvent	Reaction time (h)	Temp (°C)	Yields[d] (%)	
				5a	**6a**
1	Benzene	24	23	50	0
2	Hexanes	6	−78	5	0
3	Hexanes	24	23	18	0
4	Acetone	6	−78	0	0
5	Acetone	24	23	21	0
6	THF	6	−78	0	0
7	THF	24	23	0	0

[a] Concentration of **2a**: 0.05 M.
[b] The radical initiator, Et_3B 1.0 M/hexanes, was added every 15 min (100 μL) for the first 2 h.
[c] Bu_3SnH (0.3 equiv) was added every hour until a total of 2 equiv was reached.
[d] Yields obtained by ^1H NMR (internal standard: diphenylmethane).

and 7, 0% conversion). A lot of decomposition products were observed in reactions performed at room temperature.

The desired compound **5a** was unstable. It decomposed rapidly when in contact with air. Dissolved in deoxygenated acetone-d_6, the product was just stable enough to record a ^1H NMR and thus confirm its structure (no ^{13}C NMR could be recorded). The structure of **5a** was also confirmed indirectly: rapidly after its formation (without purification), compound **5a** was treated with BuLi (see anionic cyclization, below) and suffered a trans-metallation. Quenching with deoxygenated methanol afforded stable **6a**. Comparison with spectroscopic literature data of this compound confirmed its structure.[6]

*2.2.2. Compound **2b**.* Compound **2b** was first reacted using the experimental conditions allowing the best cyclization conversion for iodo ynol ether **2a** (see Table 1 entry 6). Entry 1 of Table 3 presents this result.

Table 3
Intramolecular radical addition of **2b**[a,b]

Entry	Solvent	Bu_3SnH added[c] (equiv)	Temp (°C)	Reaction time (h)	Product	Yields[d] (%)
1	CH_2Cl_2	2	−78	6	**5b**	9
2	CH_2Cl_2	2	0	8	**5b**	14
3	CH_2Cl_2	2	23	24	**5b**	20
4	CH_2Cl_2	4	23	24	**5b**	20
5	Benzene[e]	2	80	0.5	**5b**	0[f]

[a] Concentration of **2b**: 0.05 M.
[b] The radical initiator, Et_3B 1.0 M/hexanes, was added every 15 min (100 μL) for the first 2 h.
[c] Bu_3SnH (0.3 equiv) was added every hour until the amount of equivalents was reached.
[d] Yields obtained by ^1H NMR (internal standard: diphenylmethane).
[e] $(PhCO_2)_2$ as initiator: 0.10 equiv added entirely at the beginning of the reaction.
[f] Product degradation.

With only 9% of the desired compound, one can see that these conditions were not optimal for compound **2b**. Since the reaction seemed to be very slow at −78 °C, it was then performed at 0 °C and room temperature (entries 2 and 3). Yields were slightly better, but still very modest (a lot of decomposition was observed at room temperature). In order to speed up the reaction, the amount of Bu_3SnH was increased to 4 equiv (entry 4). Even after 24 h, yields did not improved. This low reactivity prompted us to perform the reaction in refluxing benzene (using benzoyl peroxide as initiator). After 30 min of reflux, compound **2b** had completely decomposed (entry 5). Note that in none of these experiments could any hydrogenated cyclized compound **6b** be detected. One can see that the ynol ether bearing the menthyl group (**2b**) cyclized more slowly than the one bearing the ethyl group (**2a**). Whether the effect of the menthyl group was steric and/or electronic is difficult to establish. Compound **5b** was also unstable and decomposed rapidly when in contact with air. Dissolved in deoxygenated acetone-d_6, the product was stable long enough to record a ^1H NMR and thus confirm its structure (no ^{13}C NMR could be recorded).

*2.2.3. Compound **2c**.* Intramolecular radical addition of compound **2c** was also investigated. Here, the 6-*exo* cyclization should be favored over the 7-*endo* process. Since this 6-*exo* cyclization is known to be slower than 5-*exo*, lower conversions than those observed for compound **2a** were expected. Results of this cyclization are gathered in Table 4.

Table 4
Intramolecular radical addition of **2c** in CH_2Cl_2[a,b]

Entry	Bu_3SnH[c] (total equiv)	Reaction time (h)	Temp (°C)	Product	Yields[d] (%)
1	0	24	23	**5c**	0
2	2	6	23	**5c**	5
3	2	24	23	**5c**	50
4	2	6	−78	**5c**	78

[a] Concentration of **2c**: 0.05 M.
[b] The radical initiator, Et_3B 1.0 M/hexanes, was added every 15 min (100 μL) for the first 2 h.
[c] Bu_3SnH (0.3 equiv) was added every hour until the amount of equivalents was reached.
[d] Yields obtained by ^1H NMR (internal standard: diphenylmethane).

Entry 1 shows that without Bu_3SnH, at room temperature, the reaction did not take place (0% conversion; a mixture of degradation products and starting material was obtained). In the presence of Bu_3SnH, after 6 h (entry 2), only a very low yield (5%) of **5c** could be obtained (along with a little decomposition). After 24 h (entry 3), a 50% conversion and a lot of degradation was observed. At −78 °C (entry 4), the reaction was cleaner and conversion increased to 78%. Surprisingly, the conversion observed for this 6-*exo* cyclization was similar to the one obtained for the 5-*exo* cyclization (Table 1 entry 6). Neither 7-*endo* product nor cyclized and uncyclized reduced products (**6c** and **7c**) were observed.

The six-membered ring compound **5c** is more stable than its five-membered ring cousin **5a**. It was possible to purify and isolate **5c** with a 45% yield. However, once the spectral data were recorded (few hours), the product decomposed.

*2.2.4. Compound **2d**.* Compound **2d**, when submitted to various radical reaction conditions (2–24 h reactions, −78 °C–80 °C, 0 to 2 equiv of Bu_3SnH), was completely refractory to cyclization. In all cases, 0% conversion was recorded. Only a mixture of degradation and starting materials could be observed.

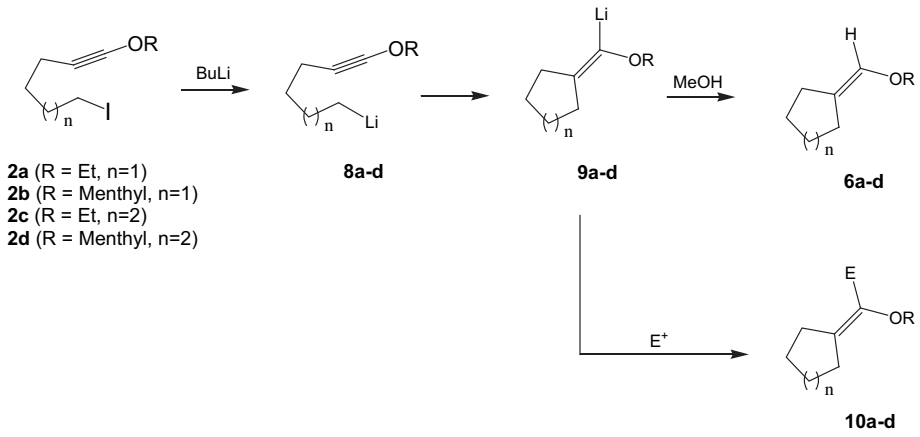
Note that in none of the above Bu_3SnH experiments could any uncyclized reduced compound **7a–d** be detected, though careful TLC, GC–MS, and NMR analyses were performed. It thus seemed that once formed, the radical isomerized to its cyclic counterpart much more rapidly than it reacted with Bu_3SnH, even for the 6-*exo* radical cyclization (production of **5c**).

2.3. Anionic cyclization

Radical cyclization showed interesting results, but failed to work well with some models. Another drawback of this radical reaction was the difficulty to functionalize the cyclized vinyl radical by trapping it with an atom-transfer reagent. Even with large amounts of Bu_3SnH in the mixture, no product resulting from the hydrogenation of radicals could be detected.

It was then decided to assess the cyclization of our models **2a–d** through an anionic pathway. Since Bailey showed that Li–I exchange proceed smoothly with iodoalkynes,[3] it was thought that a similar metal–halogen exchange could take place for compounds

2a–**d**. This process should allow ynol ethers **2a**–**d** to be transformed to alkyllithiums **8a**–**d** (see Scheme 3) that should be stable in solution at −78 °C.[3] The latter, upon warming to room temperature under inert atmosphere, should isomerize to cyclized vinyllithiums **9a**–**d**. Quenching with MeOH should lead to **6a**–**d**. An important advantage of the anionic cyclization over the radical cyclization was the possibility of functionalizing the cyclized vinyl anion **9a**–**d** by reaction with various electrophiles (other than MeOH) in order to produce **10a**–**d**.

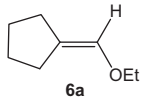
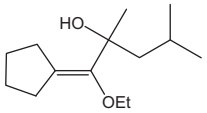
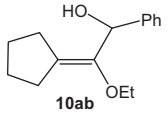
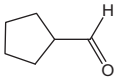
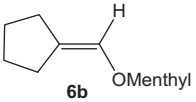
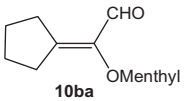
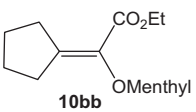
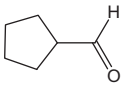


Scheme 3.

*2.3.1. Compound **2a**.* Before investigating any cyclization reaction, it was needed to verify if the required Li–I exchange could be successfully performed. Treatment of a solution of 6-iodo-1-ethoxyhexyne **2a** in hexanes–ethyl ether (3:2 by vol) with 2.2 equiv of n-butyllithium (*n*-BuLi) in hexanes at −78 °C cleanly generated the corresponding acetylenic alkyllithium **8a** as demonstrated by the fact that quenching the reaction mixture at −78 °C with an excess of deoxygenated methanol afforded 1-ethoxyhexyne **7a** in 90% isolated yield. Note that this experimental procedure slightly differs from Bailey's protocol for Li–I exchange of iodoalkynes. While Bailey used *t*-BuLi to perform Li–I exchange, it was decided here to use the more easy to handle n-BuLi. Bailey's procedure using the more reactive *t*-BuLi was also tested; we obtained the same compound **7a**, with a slightly lower yield (74%). This result convinced us to continue using the more easy to handle *n*-BuLi. Knowing that ynol ether alkyllithiums can be prepared by low-temperature lithium–iodine exchange, the intramolecular cyclization investigation was undertaken.

The study first began by treating compound **2a** with *n*-BuLi at −78 °C. Warming the reaction mixture to room temperature allowed the alkyllithium intermediate **8a** to cyclize and afford vinyl anion **9a**. After 2.5 h at room temperature, deoxygenated methanol was added to quench anion **9a** and led to cyclized compound **6a**. After work-up, only a very small quantity of **6a** (<5%) could be isolated, most probably due to its high volatility. Nevertheless, it was just enough to record ^{1}H and ^{13}C NMR spectra. Comparison with literature spectroscopic data[6] confirmed the structure of **6a**. The experiment was then repeated, but instead of isolating the desired compound, an NMR yield of the crude reaction mixture was recorded and a 87% yield was observed (Table 5, entry 1). No 6-*endo* cyclization product could be detected. It is clear that the kinetically favored attack at the β-carbon of the alkoxyacetylene moiety leading to the smaller ring system largely overcomes the 'expected' nucleophilic addition at the more electrophilic α-carbon site. In addition, the exclusive formation of a five-membered ring via 5-*exo* cyclization of this 6-alkoxy-5-hexynyllithiums is in agreement with the fact that intramolecular additions of organometallic reagents to unsaturated bonds invariably form the smaller ring.[3,7,8,12–14]

Table 5
Intramolecular anionic addition of **2a**,**b**[a]

Entry	Starting material	Electrophile (equiv)	Yield[b] (%)	Product
1	**2a**	MeOH (3)	87	 **6a**
2	**2a**	*i*-BuCOMe (6)	70	 **10aa**
3	**2a**	PhCHO (6)	71	 **10ab**
4	**2a**	MeOH (3) then $HClO_4$	71	
5	**2b**	MeOH (3)	90	 **6b**
6	**2b**	DMF (6)	70	 **10ba**
7	**2b**	$ClCO_2Et$ (6)	68	 **10bb**
8	**2b**	MeOH (3) then $HClO_4$	77	

[a] Alkyllithium **8a**,**b** was generated at −78 °C by the addition of 2.2 equiv of *n*-BuLi to a solution of **2a**,**b** in hexanes–diethyl ether (3:2 by vol), the cooling bath was removed after 10 min, and the mixture was allowed to warm and stand at room temperature for 2.5 h after which period the mixture was recooled to −78 °C and the required amount of equivalents of the electrophile was added.

[b] Isolated yields except for entry 1 (NMR yield).

Alkyllithium propensity to preferentially add to β-carbon of the alkoxyacetylene moiety has also been observed in intermolecular reactions.[15] Note that this same compound cyclized, via a radical pathway, with a very similar 85% yield (see Table 1, entry 6).

As discussed previously, an advantage of the anionic technique of cyclization was the possibility of functionalizing the cyclized anion by reaction with electrophiles. Instead of adding MeOH after 2.5 h at room temperature, electrophiles were added. After stirring for 1 h, work-up and isolation led to functionalized compounds (Table 5, entries 2 and 3).

These carbonyl reagents were selected to make sure that the final product possessed a molecular weight high enough to avoid any volatility problem. Yields were good in both cases (70–71% yield).

Note that these reactions were also tested in hexanes, with no Et_2O added. Yields dropped to ~0%. The low reactivity in hexanes might be due to the fact that alkyllithiums are known to be highly aggregated in hexanes, forming dimers and tetramers. Better results were obtained with ether since this solvent is known to dissociate alkyllithium aggregates.

Efficient formation of exocyclic enol ether **6a** led us to examine the possibility of developing a carboxaldehyde synthesis, since hydrolysis of **6a** should lead to cyclopentane carboxaldehyde (Table 5, entry 4). Compound **2a** was treated with BuLi at −78 °C, warmed to room temperature and quenched with methanol to afford **6a**. After 2 h of stirring, 35% $HClO_4$ was added dropwise.[16,17] After work-up, a 71% yield of cyclopentane carboxaldehyde was observed. This result demonstrates that it is possible to transform, in one-step, 6-iodo ynol ethers to cyclopentane carboxaldehydes.

*2.3.2. Compound **2b**.* Prior to intramolecular investigation, as for compound **2a**, it was imperative to make sure that Li–I exchange of compound **2b** was successful before embarking on cyclization reactions. Treatment of a solution of 6-iodo-1-menthoxyhexyne **2b** in hexanes:ethyl ether (3:2 by vol) with 2.2 equiv of *n*-butyllithium (*n*-BuLi) in hexane at −78 °C cleanly generated the corresponding alkyllithium **8b** and produced, after addition of deoxygenated methanol, 1-menthoxyhexyne **7b** with 90% yield.

Investigation of the anionic cyclization of compound **2b** was then undertaken. Results are gathered in Table 5 (entries 5–8). With MeOH as electrophile (entry 5), one can see that the isolated yield was very high 90% (no problems of volatility). No 6-*endo* cyclization product could be detected. This reaction was also performed in hexanes. Here also, yields dropped to ~0%.

In this case, the starting material not being volatile (compared to **2a**), it was thought that the cyclized vinyl anion could be quenched with electrophiles allowing addition of more versatile low molecular weight moieties. Reaction of cyclized anion **9b** with 6 equiv of DMF led to 70% yield of **10ba** (entry 6). Chloroformate quenching of the isomerized anion produced 68% of the functionalized cyclized product **10bb** (entry 7).

One must note that this very same compound (**2b**) cyclized, under radical reaction conditions, with only 20% yield (see Table 3, entries 3 and 4).

As for compound **6a**, the possibility of transforming in situ compound **6b** to cyclopentane carboxaldehyde was tested (Table 5, entry 8). Following the same procedure as described above, iodo ynol ether **2b** was transformed into the desired carboxaldehyde with 77% yield.

*2.3.3. Compound **2c**.* First, it was confirmed that Li–I exchange of **2c** was efficient using the above described method (BuLi −78 °C and quench with MeOH; yield of **7c**=89%). The reaction was repeated and the alkyllithium was allowed to warm to room temperature in order for cyclization to occur. After 2.5 h, deoxygenated MeOH was added. Since volatility was again a problem here, an NMR yield was recorded. Only 20% yield of **6c** was observed (spectral data identical to literature[18–20]). However, for the first time in these reactions, a 80% yield of the dehalogenated uncyclized product **7c** was observed. Longer reaction times (4–6 h) did not lead to better results (<20% yield of the desired **6c**).

Adding lithiophilic Lewis bases to the reaction medium was then tried. It has been demonstrated that Lewis bases can break organolithium aggregates and facilitate isomerization to cyclized vinyllithiums.[14] Two Lewis bases were tested: TMEDA and THF. Again, no increase in the yield of the desired compound was observed.

*2.3.4. Compound **2d**.* First, formation of alkyllithium **8d** was assessed as before. Reduced uncyclized **7d** was obtained with 91% yield. Cyclization of **2d** led to only 15% of the desired compound **6d** (after 2 h at room temperature and quenching with MeOH). The major compound was uncyclized **7d** (>50%). Unfortunately, after much effort, the two compounds could not be separated. Here also, increasing the reaction time (4–6 h) did lead to better yields. Addition of Lewis bases (TMEDA, THF) did not improve cyclization efficiency.

In all, it must be concluded that while 5-*exo* anionic cyclization to ynol ethers was efficient (yields up to 90%), its 6-*exo* counterpart was quite difficult to achieve (yields lower than 20%).

Note that performing the metal–halogen exchange using Mg instead of BuLi did not allow the desired cyclization to occur. At −78 °C, 0 °C, 23 °C, and at reflux in ether, all these experiments were unsuccessful.

3. Conclusion

The radical cyclization of iodo ynol ethers has shown some synthetic limitations, mainly due to the instability of the iodoenol ethers produced. However, it was shown that 5-*exo* cyclization can be efficient with 6-iodo-1-ethoxyhexyne. Anionic 5-*exo* cyclization of iodo ynol ethers led to exocyclic methylene compounds with yields ranging from good to excellent. Functionalization of cyclized vinyllithiums produced interesting difunctionalized exomethylenes. Attempts to cyclize 7-iodo-1-alkoxyheptyne in a 6-*exo* fashion were not efficient.

This method represents a novel strategy for the synthesis of functionalized five-membered ring carbocycles. In particular, it represents a rare entry into the formation of functionalized alkoxyalkylidenes. Via hydrolysis of the latter, this method is also a new entry to the synthesis of cyclopentane carboxaldehydes.

4. Experimental procedures

4.1. General

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). Alkyllithium solutions were purchased from Sigma–Aldrich and titrated prior to use (diphenylacetic acid endpoint 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 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) or CD_3COCD_3 (δ=30.6 ppm) as the reference. NMR data are reported as follows: chemical shifts in parts per million, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, td=triplet of doublets, m=multiplet), number of protons, and coupling constants in hertz. IR spectra were recorded on a Nicolet Impact 420 spectrophotometer. Gas chromatography—low resolution mass spectra (GC-LRMS) were recorded on an Agilent model 6890 N. HRMS were recorded on an Agilent HPLC model 1200 using a TOF 6210 detector.

Products **6a**,[6] **6c**,[18–20] and **7c**[21] are known compounds and show identical analytic data to reported data in the literatures. Analytical data of product **7a** were identical to those of an authentic sample (obtained from Aurora Fine Chemicals). Products **5a**, **5b**, and **5c** were not sufficiently stable to allow HRMS characterization.

4.2. General procedure for the syntheses of iodo ethoxy alkynes

n-BuLi (6.9 mmol, dissolved in hexanes, freshly titrated with diphenylacetic acid) was added dropwise at −78 °C under nitrogen atmosphere to a solution containing 6.16 mmol of EtOC≡CH 40% in hexanes and 7 mL of THF. After stirring for 1 h, 13.55 mmol of HMPA was added and the solution was stirred for another 15 min. A solution of 4.93 mmol of diiodoalkane (diiodobutane or diiodopentane) in 1 mL of THF was then added. The cooling bath was removed and the solution was stirred at room temperature overnight. The reaction mixture was then heated at 45 °C for 3 h. Once the reaction mixture had cooled to room temperature, 10 mL of water was added. After stirring for 30 min, the organic layer was separated. The aqueous phase was extracted twice with diethyl ether. The organic layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. Crude product was then purified with flash chromatography using hexanes as eluent.

*4.2.1. 6-Iodo-1-ethoxyhexyne (**2a**).* Colorless oil; 75% yield; FTIR (NaCl, ν_{max}, cm^{-1}): 2974, 2933, 2878, 2248, 1443, 1388; ^1H NMR ($CDCl_3$, δ ppm): 1.25(t, *J*=7.0 Hz, 3H), 1.45(m, 2H), 1.90(m, 2H), 2.15 (t, *J*=7.0 Hz, 2H), 3.15(t, *J*=7.0 Hz, 2H), 4.0(q, *J*=7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, δ ppm): 6.9, 14.6, 16.5, 30.5, 32.7, 36.7, 74.1, 90.0; LRMS (*m*/*z*, relative intensity): 252 (M^+, 100); HRMS: calcd for $C_8H_{13}IO$: 252.0011; found: 252.0018.

*4.2.2. 7-Iodo-1-ethoxyheptyne (**2c**).* Colorless oil; 89% yield; FTIR (NaCl, ν_{max}, cm^{-1}): 2963, 2944, 2868, 2264, 1456, 1380, 1232, 1032, 880; ^1H NMR ($CDCl_3$, δ ppm): 1.25(t, *J*=5.8 Hz, 3H), 1.48(m, 4H), 1.80 (m, 2H), 2.11(t, *J*=4.6 Hz, 2H), 3.15(t, *J*=7.0 Hz, 2H), 4.00(q, *J*=5.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, δ ppm): 7.2, 14.6, 17.3, 28.7, 29.9, 33.3, 37.1, 74.1, 89.8; LRMS (*m*/*z*, relative intensity): 266 (M^+, 100); HRMS: calcd for $C_9H_{15}IO$: 266.0168; found: 266.0162.

4.3. General procedure for the syntheses of iodo menthoxy alkynes

At room temperature and under nitrogen atmosphere, 12.5 mmol of menthol in 25 mL of THF was added dropwise to a solution containing 24.4 mmol of oil-free KH suspended in 25 mL of THF. When hydrogen evolution had ceased, the reaction mixture was cooled to −50 °C and 12.5 mmol of TCE dissolved in 15 mL of THF was slowly added. Once the addition was completed, the cooling bath was removed and the solution was stirred for 1 h at room temperature. The reaction mixture was then cooled to −78 °C and a freshly titrated solution of BuLi (30.0 mmol) was added dropwise. After stirring for 30 min at −78 °C and 30 min at −50 °C, 40.5 mmol of HMPA was added. After stirring for 15 min, the following solution was added: 25 mmol of diiodoalkane (diiodobutane or diiodopentane) in 5.4 mL of THF. The cooling bath was removed and stirred at room temperature for 24 h under nitrogen atmosphere. The solution was then treated with 15 mL of water. The layers were separated. The aqueous phase was extracted thrice with hexanes. The combined organic layers were successively washed with water and brine, and dried over anhydrous $MgSO_4$. Crude product was then purified with flash chromatography using hexanes as eluent.

*4.3.1. 6-Iodo-1-menthoxyhexyne (**2b**).* Yellowish oil; 90% yield; FTIR (NaCl, ν_{max}, cm^{-1}): 2960, 2930, 2875, 2258, 1448, 1100, 945, 895, 840; ^1H NMR ($CDCl_3$, δ ppm): 0.75–1.22(m, 16H), 1.30–1.70(m, 4H), 1.92(m, 2H), 2.17(m, 2H), 3.2(t, *J*=7.0 Hz, 2H), 3.85(m, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 6.8, 16.6, 16.7, 20.9, 22.3, 23.5, 26.1, 30.6, 31.1, 32.8, 34.3, 37.4, 39.9, 47.0, 87.2, 88.6; HRMS: calcd for $C_{16}H_{27}IO$: 362.1107; found: 362.1100.

*4.3.2. 7-Iodo-1-menthoxyheptyne (**2d**).* Colorless oil; 45% yield; FTIR (NaCl, ν_{max}, cm^{-1}): 2976, 2932, 2867, 2263, 1451, 1383, 1113; ^1H NMR ($CDCl_3$, δ ppm): 0.75–1.22(m, 16H), 1.40(m, 4H),1.50–1.95(m, 2H), 2.00–2.12(m, 4H), 3.15(t, *J*=7.0 Hz, 2H), 3.70(m, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 6.8, 16.6, 16.7, 20.9, 22.3, 23.5, 26.1, 28.1, 30.6, 31.1, 32.8, 34.3, 38.1, 39.9, 47.0, 87.0, 88.2; HRMS: calcd for $C_{17}H_{29}IO$: 376.1263; found: 376.1253.

4.4. General procedure for radical cyclization of iodo alkoxy alkynes in absence of Bu_3SnH

In a 25 mL round-bottomed flask, 0.42 mmol of iodo alkoxy alkyne (**2a**–**d**) was dissolved in 5.4 mL of solvent. The flask was secured with a septum through which a needle was inserted (to let O_2 activate the Et_3B initiator). At this point, depending on selected conditions (see Tables 1–5), the reaction mixture was maintained at room temperature or at 40 °C. 0.126 mmol of Et_3B (1 M in hexanes) was added every 15 min for the first 6 h of reaction. After the required reaction time (see Tables 1–5), the solvent was removed in vacuo while the flask was maintained below 5 °C. The compound was rapidly purified by flash chromatography using pentane as eluent.

4.5. General procedure for radical cyclization of iodo alkoxy alkynes in presence of Bu_3SnH

In a 25 mL round-bottomed flask, 0.42 mmol of iodo alkoxy alkyne (**2a**–**d**) was dissolved in 5.4 mL of solvent. The flask was secured with a septum through which a needle was inserted (to let O_2 activate the Et_3B initiator). At this point, depending on selected conditions (see Tables 1–5), the reaction mixture was cooled to −78 °C or maintained at room temperature. Bu_3SnH (0.108 mmol) and 0.126 mmol of Et_3B (1 M in hexanes) were added. Aliquots of Bu_3SnH (0.108 mmol) were added every hour for the first 4 h of reaction. Et_3B (0.126 mmol) was added every 15 min for the first 6 h of reaction. After the required reaction time (see Tables 1–5), diethyl ether (10–20 mL) was added. DABCO (1.26 mmol, 0.14 g; 2 equiv of DABCO per equivalent of Bu_3SnH) was then added. The reaction mixture was titrated with an iodine solution (0.1 M in ether) until persistence of the iodine brown coloration. The solution was then poured on a 1 cm pad of SiO_2 and eluted with diethyl ether (30 mL). The solvents were removed using rotary evaporation while the flask was maintained below 5 °C. The compound was rapidly purified by flash chromatography using pentane as eluent.

*4.5.1. (Ethoxyiodomethylene)cyclopentane (**5a**).* Yellowish oil; 85% NMR yield, 4% isolated yield; unstable, decomposes before complete characterization; FTIR (NaCl, ν_{max}, cm^{-1}): 2975, 2868, 2928,

1664,1455, 1384, 1109; ^{1}H NMR (acetone-d_6, δ ppm): 0.90(t, J=7.0 Hz, 3H), 1.30(t, J=5.8 Hz, 4H), 2.10(m, J=5.8 Hz, 4H), 4.00(q, J=7.0 Hz, 2H); LRMS (m/z, relative intensity): 252 (5).

*4.5.2. (Menthoxyiodomethylene)cyclopentane (**5b**).* Yellowish oil; 20% NMR yield, 5% isolated yield; unstable, decomposes before complete characterization; FTIR (NaCl, ν_{max}, cm^{-1}): 2982, 2855, 2941, 1661,1448, 1377, 1101; ^{1}H NMR (acetone-d_6, δ ppm): 0.70–1.05 (m, 9H), 1.20–1.40(m, 6H), 1.45–1.70(m, 5H), 1.90–2.15(m, 2H), 2.20–2.33(m, 4H), 3.68 (m, 1H); LRMS (m/z, relative intensity): 362 (5).

*4.5.3. (Ethoxyiodomethylene)cyclohexane (**5c**).* Colorless oil; 78% NMR yield, 45% isolated yield (72 mg); slightly more stable than **5a**, ^{13}C NMR could be recorded, HRMS could not be recorded; FTIR (NaCl, ν_{max}, cm^{-1}): 2985, 2925, 2862, 1642,1470, 1378, 1029; ^{1}H NMR (acetone-d_6, δ ppm): 0.88(t, J=7.0 Hz, 3H), 1.20–1.50(m, 6H), 2.10(t, J=5.6 Hz, 4H), 4.00(q, J=7.0 Hz, 2H); ^{13}C NMR (acetone-d_6, δ ppm): 13.6, 13.9, 17.0, 22.2, 57.0, 73.8, 89.5; LRMS (m/z, relative intensity): 266 (80).

4.6. General procedure for dehalogenation of iodo alkoxy hexynes (Li–I exchange assessment)

A 0.1 M solution of 0.27 mmol iodo ynol ether (**2a**–**d**) in hexanes-Et$_2$O was deoxygenated by bubbling N_2 for 5 min. The mixture was cooled to −78 °C. A solution of freshly titrated *n*-BuLi in hexanes (0.57 mmol) was added dropwise. The solution was stirred for 10 more minutes at −78 °C and 2–3 mL of deoxygenated methanol was added in order to quench the uncyclized alkyllithium. The reaction mixture was poured on 2 mL of water. The layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and evaporated in vacuo. The crude product (**7a**–**d**) was purified with flash chromatography using hexanes as eluent.

Compound **7a** was obtained in 90% yield. Analytical data of this compound were identical to those of an authentic sample (obtained from Aurora Fine Chemicals). Compound **7c** was obtained in 89% yield. This compound is a known compound and showed identical analytic data to reported data in the literature.[21]

*4.6.1. 1-Menthoxyhexyne (**7b**).* Colorless oil; 90% yield; FTIR (NaCl, ν_{max}, cm^{-1}): 2957, 2928, 2864, 2262, 1455; ^{1}H NMR (CDCl$_3$, δ ppm): 3.69 (td, J=4.7 and 10.9 Hz, 1H), 2.05–2.30 (m, 4H), 1.65 (m, 2H), 1.30–1.50 (m, 6H), 1.00–1.22 (m, 2H), 0.80–0.96 (m, 13H); ^{13}C NMR (CDCl$_3$, δ ppm): 13.6, 16.3, 17.0, 20.6, 21.9, 22.2, 23.3, 25.8, 31.6, 32.0, 34.1, 38.0, 39.6, 46.8, 86.8, 87.9; HRMS: calcd for $C_{16}H_{28}O$: 236.2140; found: 236.2139.

*4.6.2. 1-Menthoxyheptyne (**7d**).* Colorless oil; 91% yield; FTIR (NaCl, ν_{max}, cm^{-1}): 2955, 2926, 2865, 2266, 1456; ^{1}H NMR (CDCl$_3$, δ ppm): 3.69 (td, J=4.3 and 10.5 Hz, 1H), 2.07–2.28 (m, 4H), 1.61–1.68 (m, 2H), 1.01–1.50 (m, 10H), 0.80–0.96 (m, 13H); ^{13}C NMR (CDCl$_3$, δ ppm): 14.0, 16.3, 17.3, 20.6, 22.0, 22.2, 23.3, 25.8, 29.6, 31.1, 31.6, 34.1, 38.1, 39.6, 46.8, 86.8, 87.9; HRMS: calcd for $C_{17}H_{30}O$: 250.2297; found: 250.2294.

4.7. General procedure for anionic cyclization of iodo alkoxy hexynes and functionalization of the resulting vinyllithium

A 0.1 M solution of 0.27 mmol iodo ynol ether in hexanes–Et$_2$O was deoxygenated by bubbling N_2 for 5 min. The mixture was cooled to −78 °C. A solution of freshly titrated *n*-BuLi in hexanes (0.57 mmol) was added dropwise. The solution was stirred for 10 more minutes at −78 °C and then the cooling bath was removed. The reaction mixture was stirred 2.5 h at room temperature in order for the cyclization to occur. The cyclized vinyllithium solution was cooled to −78 °C and an excess of electrophile (typically 6 equiv, see Table 5) was added. After the addition, the cooling bath was removed and the reaction mixture was stirred at room temperature for 4 h.

*4.7.1. 1-Cyclopentylidene-1-ethoxy-2,4-dimethylpentan-2-ol (**10aa**).* At −78 °C, the vinyllithium solution, prepared as described above, was treated with 6 equiv of anhydrous methyl isobutyl ketone. The cooling bath was removed and the solution was stirred for 2 h at room temperature. The reaction mixture was poured into 2 mL of water. The layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and evaporated in vacuo. The crude product was purified with flash chromatography using hexanes–acetone 99:1 as eluent; colorless oil; 70% yield (43 mg); FTIR (NaCl, ν_{max}, cm^{-1}): 3350, 2932, 2853,1656, 1456, 1384; ^{1}H NMR (CDCl$_3$, δ ppm): 0.80–1.00(m, 6H), 1.10–1.41 (m, 7H), 1.45–1.80(m, 5H), 2.00–2.42(m, 6H), 4.01(q, J=4.0 Hz, 2H); ^{13}C NMR (CDCl$_3$, δ ppm): 17.8, 17.9, 19.1, 20.8, 25.9, 26.6, 27.1, 30.3, 39.0, 63.4, 76.6, 117.8, 135.9; LRMS (m/z, relative intensity): 226 (M$^+$, 100); HRMS: calcd for $C_{14}H_{26}O_2$: 226.1933; found: 226.1934.

*4.7.2. 2-Cyclopentylidene-2-ethoxy-1-phenylethanol (**10ab**).* At −78 °C, the vinyllithium solution, prepared as described above, was treated with 2 equiv of anhydrous benzaldehyde. The cooling bath was removed and the solution was stirred overnight at room temperature. The reaction mixture was poured on 2 mL of water. The layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were successively washed with 3×8 mL NaHSO$_3$ 8%, water and brine, dried over anhydrous MgSO$_4$, and evaporated in vacuo. The crude product was purified with flash chromatography using hexanes–acetone 99.5:0.5 as eluent; colorless oil; 71% yield (45 mg); FTIR (NaCl, ν_{max}, cm^{-1}): 3350, 3060, 3023, 2959, 2927,2844, 1656, 1597,1491, 1464, 1384; ^{1}H NMR (CDCl$_3$, δ ppm): 0.90–1.60(m, 7H), 2.03–2.20(m, 5H), 4.02(q, J=4.0 Hz, 2H), 5.20(s, 1H), 7.32–7.59(m, 3H), 8.00–8.12(m, 2H); ^{13}C NMR (CDCl$_3$, δ ppm): 19.2, 20.7, 25.4, 30.1, 30.2, 64.1, 70.6, 118.9, 127.8, 128.4, 128.6, 137.1, 153.7; HRMS: calcd for $C_{15}H_{20}O_2$: 232.1463; found: 232.1463.

*4.7.3. (Menthoxymethylene)cyclopentane (**6b**).* At −78 °C, the vinyllithium solution, prepared as described above, was quenched with 1.62 mmol of deoxygenated and anhydrous MeOH. The cooling bath was removed and the solution was stirred for 30 min at room temperature. The reaction mixture was poured into 2 mL of water. The layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and evaporated in vacuo. The crude product was purified with flash chromatography using hexanes as eluent; colorless oil; 90% yield (57 mg); FTIR (NaCl, ν_{max}, cm^{-1}): 3477, 2959, 2859,1684, 1456, 1384; ^{1}H NMR (CDCl$_3$, δ ppm): 0.70–1.05(m, 9H), 1.20–1.40(m, 6H), 1.45–1.71(m, 5H), 1.90–2.10 (m, 2H), 2.11–2.35(m, 4H), 3.32(m, 1H), 6.02 (s, 1H); ^{13}C NMR (CDCl$_3$, δ ppm): 16.2, 21.8, 23.7, 26.0, 26.5, 29.4, 31.8, 34.7, 41.8, 48.0, 54.1, 81.1, 120.2, 136.5; LRMS (m/z, relative intensity): 236 (M$^+$, 100); HRMS: calcd for $C_{16}H_{28}O$: 236.2140; found: 236.2131.

*4.7.4. (Menthoxycarboxaldehydemethylene)cyclopentane (**10ba**).* At −78 °C, the vinyllithium solution, prepared as described above, was treated with 6 equiv of anhydrous DMF. The cooling bath was removed and the solution was stirred for 3.5 h at room temperature. The reaction mixture was poured into 2 mL of water. The layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, and evaporated in vacuo. The crude

product was purified with flash chromatography using hexanes–acetone 95:5 as eluent; yellowish oil; 70% yield (50 mg); FTIR (NaCl, ν_{max}, cm^{-1}): 2959, 2859, 2720,1720, 1675, 1456, 1390; ^1H NMR ($CDCl_3$, δ ppm): 0.70–1.03(m, 9H), 1.05–1.43(m, 6H), 1.45–1.85(m, 7H), 1.90–2.01(m, 4H), 4.00(m, 1H), 9.75(s, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 16.5, 21.4, 23.9, 26.5, 26.8, 30.1, 31.4, 36.1, 41.8, 48.4, 55.1, 85.4, 136.0, 148.9, 195.1; HRMS: calcd for $C_{17}H_{28}O_2$: 264.2089; found: 264.2077.

*4.7.5. (Carboethoxymenthoxymethylene)cyclopentane (**10bb**).* At −78 °C, the vinyllithium solution, prepared as described above, was treated with 6 equiv of anhydrous $ClCO_2Et$. The cooling bath was removed and the solution was stirred for 2.5 h at room temperature. The reaction mixture was poured on 2 mL of water. The layers were separated. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The crude product was purified with flash chromatography using hexanes–acetone 99:1 as eluent; colorless oil; 68% yield (56 mg); FTIR (NaCl, ν_{max}, cm^{-1}): 2932, 2853, 1734,1656, 1456, 1384; ^1H NMR ($CDCl_3$, δ ppm): 0.81–1.09(m, 9H), 1.20–1.42(m, 9H), 1.60–1.78(m, 5H), 1.82–2.00(m, 2H), 2.11–2.20(m, 4H), 3.68(m, 1H), 4.23(q, J=7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, δ ppm): 15.1, 16.4, 21.3, 24.6, 26.1, 27.3, 30.5, 31.3, 36.0, 43.2, 50.0, 55.1, 61.3, 85.4, 128.7, 141.9, 165.1; HRMS: calcd for $C_{19}H_{32}O_3$: 308.2351; found: 308.2358.

4.8. Hydrolysis of 2a and 2b. Formation of cyclopentane carboxaldehyde

A 0.1 M solution of 0.27 mmol iodo ynol ether (**2a** or **2b**) in hexanes-Et_2O was deoxygenated by bubbling N_2 for 5 min. The mixture was cooled to −78 °C. A solution of freshly titrated *n*-BuLi in hexanes (0.57 mmol) was added dropwise. The solution was stirred for 10 more minutes at −78 °C and then the cooling bath was removed. The reaction mixture was stirred 2 h at room temperature in order for the cyclization to occur. MeOH (6 equiv) was added and the reaction mixture was stirred for another 30 min at room temperature. To this solution were added 1–2 drops of 35% perchloric acid. The reaction mixture was stirred for 18 h at room temperature, diluted with ether, and quenched with 5% $NaHCO_3$. The ethereal layer was washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation with a bath temperature maintained at 0 °C. Comparison of NMR signals of this crude material with the commercially available cyclopentane carboxaldehyde confirmed the structure of cyclopentane carboxaldehyde. The crude mixture revealed a 71% NMR yield starting with **2a** and a 77% NMR yield starting with **2b**.

4.9. NMR yields

In an NMR tube, the crude addition mixture and a known quantity of diphenylmethane (internal standard) were dissolved in $CDCl_3$. The yield was obtained by comparing the integration of the CH_2 signal of diphenylmethane (3.9 ppm) with the integration of the ethoxy CH_2 signal for products **5a**, **5c**, **6a**, and **7c** (~4.0 ppm) or with the R_2CHOalkynyl signal for compound **5b** (3.3 ppm).

Acknowledgements

Acknowledgements is made to the Natural Sciences and Engineering Council of Canada for financial support.

References and notes

1. Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265.
2. Curran, D. P.; Kim, D. *Tetrahedron* **1991**, *47*, 6171.
3. Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080.
4. Cooke, M. P. J.; Gopal, D. *J. Org. Chem.* **1994**, *59*, 260.
5. Cooke, M. P. J. *J. Org. Chem.* **1993**, *58*, 6833.
6. Ohnuki, T.; Yoshida, M.; Simamura, O. *Chem. Lett.* **1972**, 797.
7. Funk, R. L.; Bolton, G. L.; Brummond, K. M.; Ellestad, K. E.; Stallman, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 7023.
8. Gralla, G.; Wibbeling, B.; Hoppe, D. *Org. Lett.* **2002**, *4*, 2193.
9. Longpre, F.; Rusu, N.; Larouche, M.; Hanna, R.; Daoust, B. *Can. J. Chem.* **2008**, *86*, 970.
10. Lemoine, P.; Daoust, B. *Tetrahedron Lett.* **2008**, *49*, 6175.
11. Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919.
12. Cooke, M. P. J. *J. Org. Chem.* **1984**, *49*, 1144.
13. Cooke, M. P. J.; Widener, R. K. *J. Org. Chem.* **1987**, *52*, 1381.
14. Bailey, W. F.; Kbanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720.
15. Kooyman, J. G.; Hendriks, H. P. G.; Montijn, P. P.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 69.
16. Mehta, G.; Rao, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 8015.
17. Ye, Q.; Grunewald, G. L. *J. Med. Chem.* **1989**, *32*, 478.
18. Rudler, H.; Parlier, A.; Durand-Réville, T.; Martin-Vaca, B.; Audouin, M.; Garrier, E.; Certal, V.; Vaissermann, J. *Tetrahedron* **2000**, *56*, 5001.
19. Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 448.
20. Newman, M. S.; Okorodudu, O. M. *J. Org. Chem.* **1969**, *34*, 1220.
21. Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* **1972**, *1*, 393.