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Synthetic and Computational Studies of Acyl Radical Cyclizations with β-Alkoxyacrylates: Formal Synthesis of (±)-Longianone†

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An investigation into the cyclization of acyl radicals with mono- and disubstituted β-alkoxyacrylates is described. Ether-tethered acyl radicals, generated directly from the corresponding aldehyde, undergo cyclization to form dioxaspiro heterocyclic systems including 1,7-dioxaspiro[4,4]nonane-4,8-dione and 1,8-dioxaspiro[5,4]decane-5,9-dione. This strategy is applied to a concise formal synthesis of the fungal metabolite longianone. Density functional theory calculations provide insight into the chemistry of the acyl radicals in this study.

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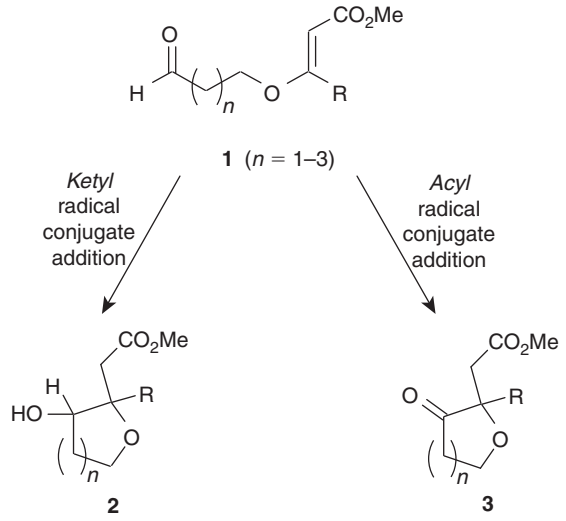
Introduction

Among the variety of functional groups used as radical precursors, the straightforward synthetic accessibility of aldehydes makes such substrates convenient and versatile precursors for radical reactions. Commonly, reductive conditions using either tributyltin hydride[1] or samarium(II) iodide[2] are applied to precursors such as **1** (Scheme 1), resulting in ketyl radical formation and subsequent cyclization to generate cyclic secondary alcohols, e.g. **2**, in which two new asymmetric centres are created. Such a cyclization strategy has seen regular application in natural products synthesis,[3] particularly in the preparation of polycyclic ethers. Examples of ketyl radical cyclizations with β-disubstituted acrylates (e.g. **1**, R ≠ H) are somewhat less common, but in such cases a quaternary asymmetric centre can be generated.[4]

Unlike the formation and subsequent cyclization of *ketyl* radicals generated from aldehydes, the direct generation of *acyl* radicals from aldehydes is far less common. More typically, the generation of acyl radicals is achieved either via thio- or selenoester precursors, by carbonylation of alkyl radicals, or through fragmentation processes.[5] The usual tin-mediated conditions associated with selenoesters and the necessary high-pressure conditions used in carbonylation procedures are seen as drawbacks to the widespread application of these conditions. Few practical examples of the direct generation of acyl radicals from aldehydes and their subsequent addition or cyclization have been reported. This is in part due to the existence of unfavourable polar effects in the transition state for H-atom transfer. However, the use of polarity-reversal catalysis can overcome this hurdle.[6] Tsujimoto and coworkers reported the intermolecular addition of acyl radicals to electron-deficient alkenes in the presence of benzoyl peroxide as radical initiator and using *N*-hydroxyphthalimide (NHPI) as a polarity-reversal catalyst.[7] Yoshikai and coworkers have described an intramolecular hydroacylation process using *tert*-dodecanethiol as catalyst and 2,2′-azobis(isobutyronitrile)



Scheme 1. Radical cyclization strategies towards cyclic ethers from aldehyde precursors.

†Dedicated to the memory of Athel Beckwith, an inspirational scientist, teacher and mentor.

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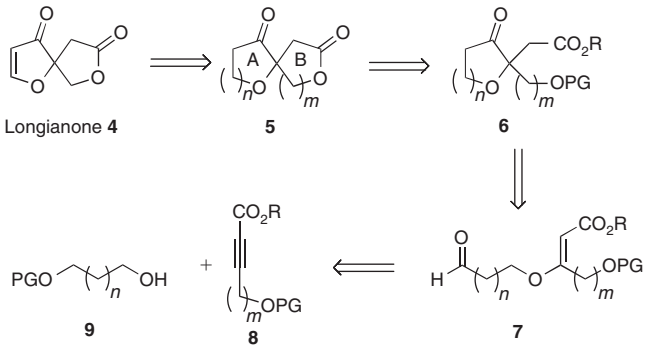
(AIBN) (or 1,1′-azobis(cyclohexanecarbonitrile) (ABCN)) initiation.[8] Although carbocyclic structures have been prepared in this way, the formation of heterocyclic compounds under such conditions does not appear to have been reported.

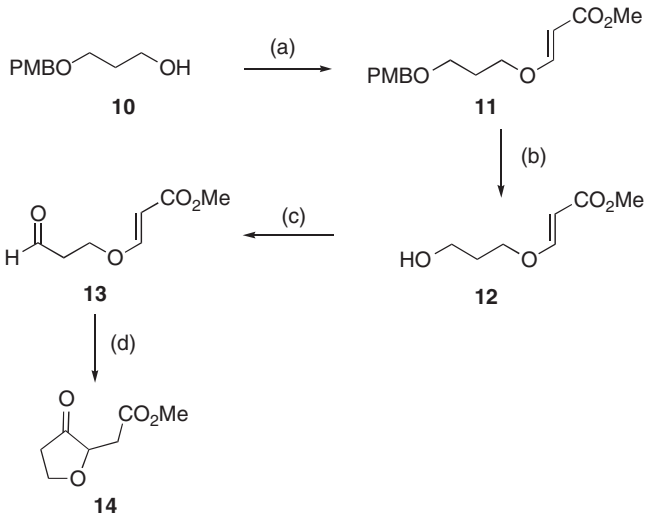
We have an ongoing interest in developing an understanding of the fundamental reactivity of acyl and related radicals and their application to synthesis,[9] especially as these radicals can often 'masquerade' as electrophiles.[10] One of us recently reported the application of aldehyde-containing substrates as radical precursors in cyclization reactions with β-alkoxyacrylates.[11] In a continuation of these investigations, we sought to explore the possibility of direct acyl radical formation from aldehyde precursors and their subsequent cyclization to generate novel heterocycles. Specifically, we planned to use β-disubstituted acrylates (e.g. **1**, R ≠ H) that would, on cyclization, give functionalized tetrahydrofuran-3-one products, e.g. **3** ($n = 1$) that may be further transformed to dioxaspirocyclic systems.

Results and Discussion

Dioxaspirocyclic systems, of varying ring sizes, are present in several naturally occurring structure classes.[12] The simplest example is longianone **4**, a fungal metabolite from *Xylaria longiana*,[13] which we considered an ideal target to demonstrate the feasibility, or otherwise, of using acyl radical cyclizations for the preparation of spirocycles. The proposed general synthetic strategy towards spirocycles, e.g. longianone **4**, is shown in Scheme 2. Thus, the intermediate β-disubstituted acrylate **7** may undergo acyl radical generation and cyclization to form the 2,2-disubstituted furan **6**, while subsequent deprotection of the primary alcohol and lactonization to form the B-ring completes the spirocyclic framework in **5**. The cyclization substrate **7** should be available from the precursor alcohol **9** and acetylene **8**, with the choice of chain lengths (n, $m = 1$, 2) dictating the ultimate size of the spirocyclic ring system in **5**. Dioxaspirocycle **5** ($n = m = 1$) has been prepared as a precursor to longianone **4** in both previous syntheses of this metabolite, with final conversion to **4** being achieved either by an α-selenation–oxidation–elimination sequence[14] or by direct oxidation using stabilized 2-iodoxybenzoic acid (IBX).[15]



Scheme 2. Retrosynthetic analysis of spirocyclic systems **5**. PG = protecting group.

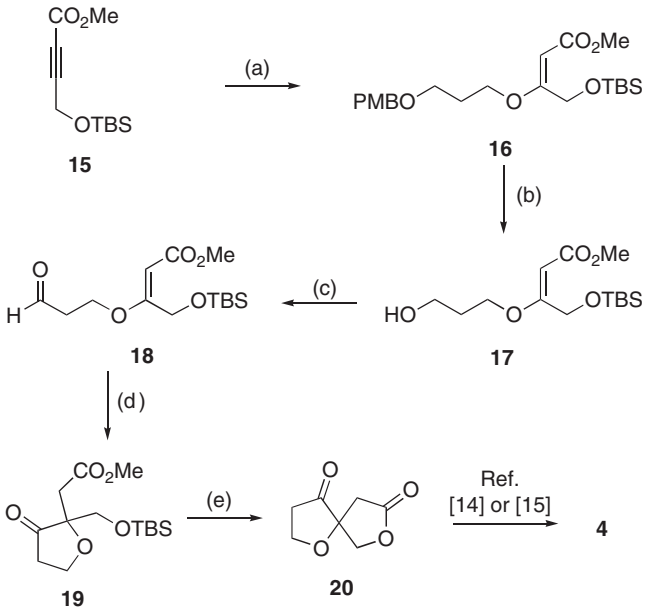


Scheme 3. Reagents and conditions: (a) methyl propiolate, PMe_3 (1 M in THF, 0.2 equiv.), CH_2Cl_2, 0°C, 45 min (98%); (b) DDQ, CH_2Cl_2, H_2O, 0°C, 3 h (75%); (c) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 4 h (72%); (d) *tert*-dodecanethiol (0.3 equiv.), ABCN (0.3 equiv.), toluene, reflux, 18 h. PMB = *para*-methoxybenzyl.

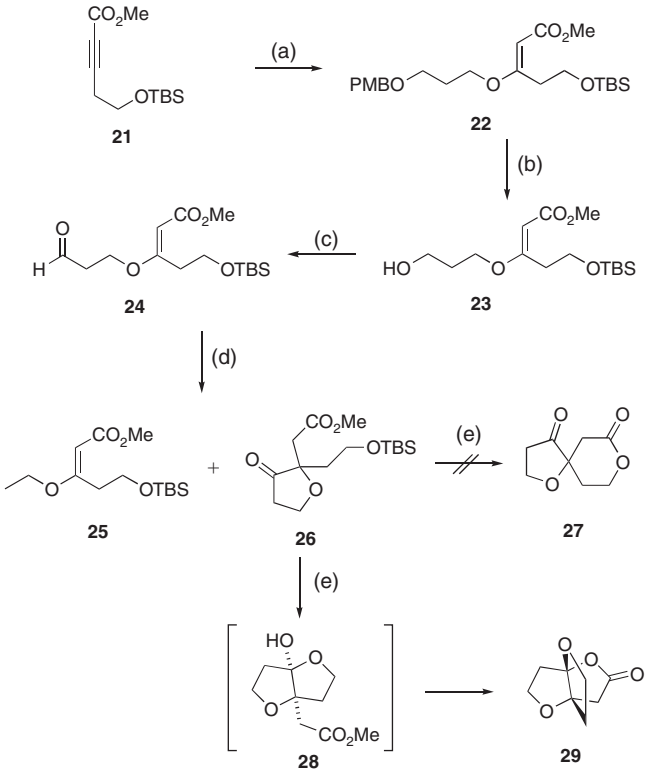
Before attempting the acyl radical cyclization using hindered substrates such as **7**, we sought to investigate whether simpler β-alkoxyacrylates would undergo the expected cyclization with acyl radicals generated directly from aldehydes under the reported conditions.[7,8] The aldehyde **13** (Scheme 3), a potential acyl radical precursor, was prepared from the monoprotected diol **10** by first reacting with methyl propiolate in the presence of trimethylphosphine[16] to form the (*E*)-β-alkoxyacrylate **11**, which was then deprotected and subsequently oxidized to the aldehyde **13** (53% yield over three steps). First, applying conditions developed by Ishii (benzoyl peroxide/NHPI/toluene, 80°C)[7] led to aldehyde **13** being recovered essentially unchanged.

Turning to Tomioka's methodology,[8] the aldehyde **13** was heated in toluene with ABCN initiation and using *tert*-dodecanethiol as the polarity-reversal catalyst. A complex mixture of products was recovered from the reaction, with the expected cyclized product **14** being a minor component of the mixture. It may be concluded that the low yields of heterocycle **14** result from the more electron-rich nature of the acrylate substrate **13**, which may lead to polymerization. Additionally, thiyl radicals are known to add to olefins,[17] a process that is more favourable for electron-rich double bonds. Aware of the possibility of competitive decarbonylation occurring, the anticipated product formed from such a process (enol-ether **38**, *vide infra*) was prepared. However, spectroscopic comparison of the enol-ether **38** with the product mixture formed from reaction of **13** (Scheme 3) indicated that enol-ether **38** was not present.

Undeterred by the modest success in achieving direct acyl radical formation and cyclization using aldehyde **13**, we pursued a β-disubstituted system as an acyl radical precursor. Initially targeting the bis-furanone spirocyclic system that leads to longianone **4**, the aldehyde intermediate **18** was prepared from acetylene **15** (Scheme 4). Thus, conjugate addition of monoprotected 1,3-propanediol with acetylene **15**, followed by deprotection and oxidation gave the aldehyde substrate **18**. Treating aldehyde **18** under the thiol-mediated radical cyclization conditions gave a less complex product mixture than obtained previously for the monosubstituted substrate. The sole product isolated from the reaction was shown to be the tetrahydrofuran-3-one **19**, formed from successful acyl radical cyclization. Characteristic signals in the ^1H NMR spectrum of **19** included two pairs of doublets at δ 2.57 and 2.71 (J 16.5 Hz) and δ 3.58 and 3.70 (J 10.1 Hz) from the exocyclic methylene groups. The success in forming the cyclized product **19** from the



Scheme 4. Reagents and conditions: (a) **10**, PMe_3 (1 M in THF, 0.25 equiv.), CH_2Cl_2, 0°C to rt, 2 h (91%); (b) DDQ, CH_2Cl_2, H_2O, 0°C, 3 h (98%); (c) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 4 h (70%); (d) *tert*-dodecanethiol (0.3 equiv.), ABCN (0.3 equiv.), toluene, reflux, 15 h (28%); (e) 10-CSA, $CHCl_3$, MeOH, 2 days (61%). TBS = *tert*-butyldimethylsilyl, PMB = *para*-methoxybenzyl.



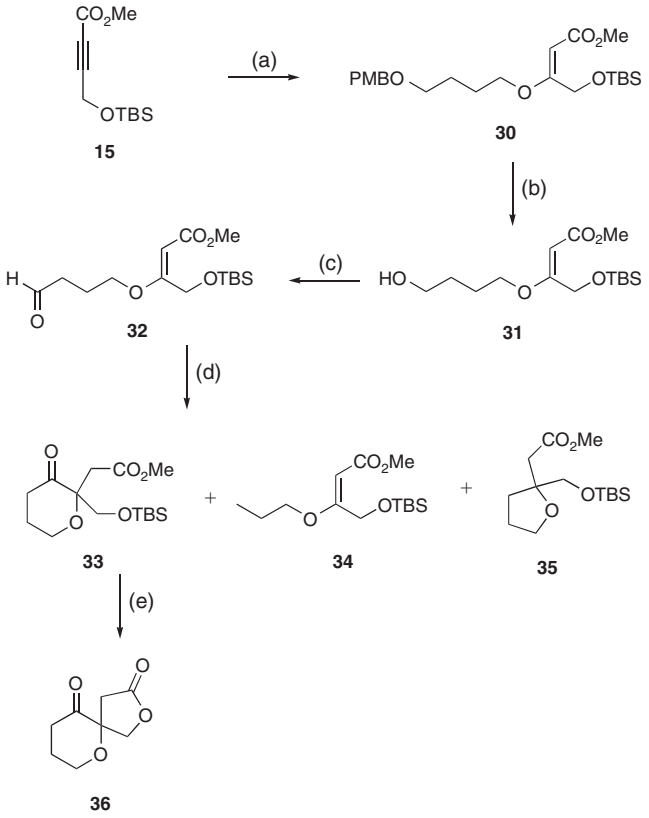
Scheme 5. Reagents and conditions: (a) **10**, PMe_3 (1 M in THF, 0.25 equiv.), CH_2Cl_2, 0°C to room temperature (rt), 2 h (84% (*E*)-isomer, 6% (*Z*)-isomer); (b) DDQ, CH_2Cl_2, H_2O, 0°C, 2 h (95%); (c) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 2 h (77%); (d) *tert*-dodecanethiol (0.3 equiv.), ABCN (0.6 equiv.), toluene, reflux, 21 h (**25**, 42%; **26**, 36%); (e) 10-CSA, $CHCl_3$, MeOH, 20 h (71%). TBS = *tert*-butyldimethylsilyl, PMB = *para*-methoxybenzyl.

β-disubstituted acrylate **18** is consistent with our earlier proposals that the sulfur radical may be reacting directly with the less-hindered double bond in **13** (Scheme 3) in preference to hydrogen abstraction from the aldehyde group, or that polymerization of **13** may be occurring.

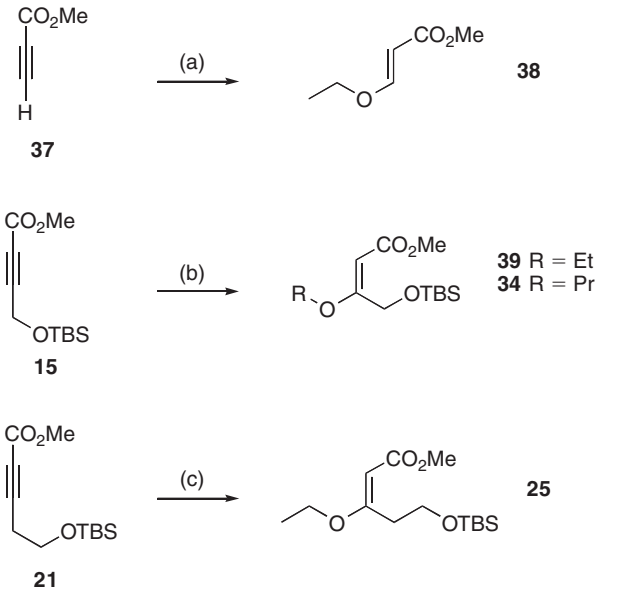
Treatment of **19** with camphorsulfonic acid (CSA) in methanol/chloroform leads to removal of the silyl group and lactonization to give the dioxaspirononane **20** (dihydrolongianone). The structure of **20** could be confirmed by spectroscopic comparison (^1H and ^{13}C NMR) with the same product derived from hydrogenation of naturally occurring longianone **4**.[13] Preparation of dihydrolongianone **20**, which has previously been converted to longianone **4**,[14,15] completes a formal synthesis of this natural product. Notably, in the originally reported synthesis of longianone **4** by Steel,[14] the spiro system was formed by cyclization of a vinyl radical generated from a terminal acetylene using Bu_3SnH, with subsequent ozonolysis of the resultant exocyclic methylene group giving **20**. The reported intention of applying an acyl radical cyclization using a selenoester precursor was not able to be realised owing to the instability of the proposed intermediates. Thus, the direct formation of acyl radicals from aldehydes, as demonstrated in the present work, may serve as an alternative methodology in situations where the formation of selenoesters, or other acyl radical precursors, is not viable.

As an extension of this acyl radical cyclization procedure, we sought to prepare dioxaspiro systems of varying ring sizes. It was expected that heterocycle **27** (Scheme 5), having an expanded lactone ring, could be prepared from the homologous acetylene **21**. Hetero-Michael addition of alcohol **10** with acetylene **21** gave the (*E*)-acrylate **22**, which was then deprotected and oxidized to generate the cyclization precursor **24** in 61% yield over the three steps. Applying the radical cyclization conditions under polarity-reversal catalysis led to the isolation of two products in a combined yield of 78%. The first product was identified as the expected tetrahydrofuranone **26** resulting from acyl radical cyclization. The ^1H NMR spectrum of **26** included a pair of doublets at δ 2.72 and 2.82 (J 16.4 Hz) from the isolated methylene group while the remaining eight methylene protons gave clearly resolved multiplets between δ 1.70 and 4.28. The second product from this reaction, isolated in 42% yield, was the enol-ether **25**. This product clearly derives from decarbonylation and subsequent reduction of the acyl radical generated from **24**. Confirmation of the identity of **25** was achieved by spectroscopic analysis and comparison with an authentic sample prepared directly from acetylene **21** and ethanol (Scheme 7). The formation of **25** is somewhat surprising given that the corresponding decarbonylated product that would be formed from aldehyde **18** (Scheme 4) was not observed. This was confirmed by preparing an authentic sample of the enol-ether **39** (Scheme 7) to show, by spectroscopic comparison, that it was not part of the crude reaction mixture formed from the radical cyclization reaction of aldehyde **18**. Exposure of silyl ether **26** to acid, however, failed to form the dioxaspiro system **27**. Instead, the novel propellane **29** was isolated in 71% yield. Presumably the product **29** is formed by trapping of the intermediate acetal **28** formed after deprotection of the primary alcohol in **26**.[18]

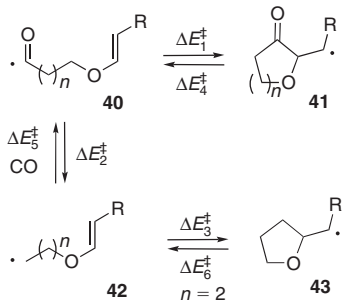
As a final demonstration of the application of this strategy, the isomeric system **36** (Scheme 6) was prepared. Thus, disubstituted acrylate **30** was prepared from acetylene **15** and monoprotected 1,4-butanediol. Removal of the *para*-methoxybenzyl (PMB) group and subsequent oxidation of the



Scheme 6. Reagents and conditions: (a) 4-(4-methoxybenzyloxy)butan-1-ol, PMe_3 (1 M in THF, 0.25 equiv.), CH_2Cl_2, 0°C to room temperature (rt), 1 h (87%); (b) DDQ, CH_2Cl_2, H_2O, 0°C, 2 h (96%); (c) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 3 h (97%); (d) *tert*-dodecanethiol (0.3 equiv.), ABCN (0.8 equiv.), toluene, reflux, 42 h (**33**, 32%; **34**, 26%; **35**, 19%); (e) 10-CSA, $CHCl_3$, MeOH, 2 days (75%). TBS = *tert*-butyldimethylsilyl, PMB = *para*-methoxybenzyl.



Scheme 7. Reagents and conditions: (a) EtOH, PMe_3 (1 M in THF, 0.2 equiv.), CH_2Cl_2, 0°C, 1 h (94%); (b) EtOH or *n*-PrOH, PMe_3 (1 M in THF, 0.5 equiv.), CH_2Cl_2, 0°C to room temperature (rt), 1.5 h (83% for **39**, 84% for **34**); (c) EtOH, PMe_3 (1 M in THF, 0.7 equiv.), CH_2Cl_2, 0°C to rt, 5 h (86%). TBS = *tert*-butyldimethylsilyl.



n	R	$\Delta E_1^{\ddagger}$	$\Delta E_2^{\ddagger}$	$\Delta E_3^{\ddagger}$	$\Delta E_4^{\ddagger}$	$\Delta E_5^{\ddagger}$	$\Delta E_6^{\ddagger}$
1	H	61.6	78.3	–	97.5	25.7	–
1	CO_2Me	52.3	76.2	–	95.5	26.4	–
2	H	68.8	75.3	50.7	107.4	26.5	106.5
2	CO_2Me	57.5	73.3	43.3	105.9	25.7	116.1

kJ mol^{-1} (BHandHLYP/6−311++G(d,p)).

Scheme 8.

primary alcohol **31** gave the aldehyde **32** (81% yield over three steps). Given that the previously described acyl radical cyclization of aldehyde **24**, which involves a 5-*exo* process, was prone to competitive decarbonylation, it was expected that the 6-*exo* cyclization of aldehyde **32** might be less successful. However, treating the aldehyde **32** under similar radical reaction conditions to those used previously led to formation of the pyran **33** in 32% yield, only marginally lower than the 36% yield obtained from the 5-*exo* cyclization of aldehyde **24**. The decarbonylated product **34** was also isolated from the reaction mixture (26% yield) and its structure confirmed by comparison with an authentic sample prepared directly from conjugate addition of propanol with acetylene **15** (Scheme 7). A third product was identified as the tetrahydrofuran **35** (19% yield) that is formed via 5-*exo* cyclization of the primary radical generated after decarbonylation of **32**. Finally, exposure of **33** to CSA catalyzed desilylation and formation of the γ-lactone ring and completed the 6,5 dioxaspiro system **36**.

In order to provide further insight into this chemistry, we sought recourse to computational techniques. To that end, the cyclization and decarbonylation chemistries of the acyl radicals **40** (Scheme 8) were investigated using *ab initio* and density functional theory (DFT) techniques as described below. Radical **40** can undergo intramolecular homolytic addition chemistry to afford the ketone **41**, or it can decarbonylate via an α-scission process to afford **42**, which, depending on chain length, can undergo further cyclization to afford the tetrahydrofuranylalkyl radical **43**.

Searching of the relevant potential energy surfaces located structures **40**–**43**, and these proved to correspond to minima on the respective potential energy surface (Scheme 8). Transition states for the cyclization of radicals **40** are displayed in Fig. 1, and transition states for the decarbonylation of **40** leading to **42**, and those for subsequent cyclization to **43** are not shown; however, full geometric details are available in the Accessory Publication. Energy barriers calculated at the BHandHLYP/6–311++G(d,p) level of theory are listed in Scheme 8. Data obtained at other levels of theory are provided in the Accessory Publication, together with the Gaussian Archive entries for all optimized structures in this study.

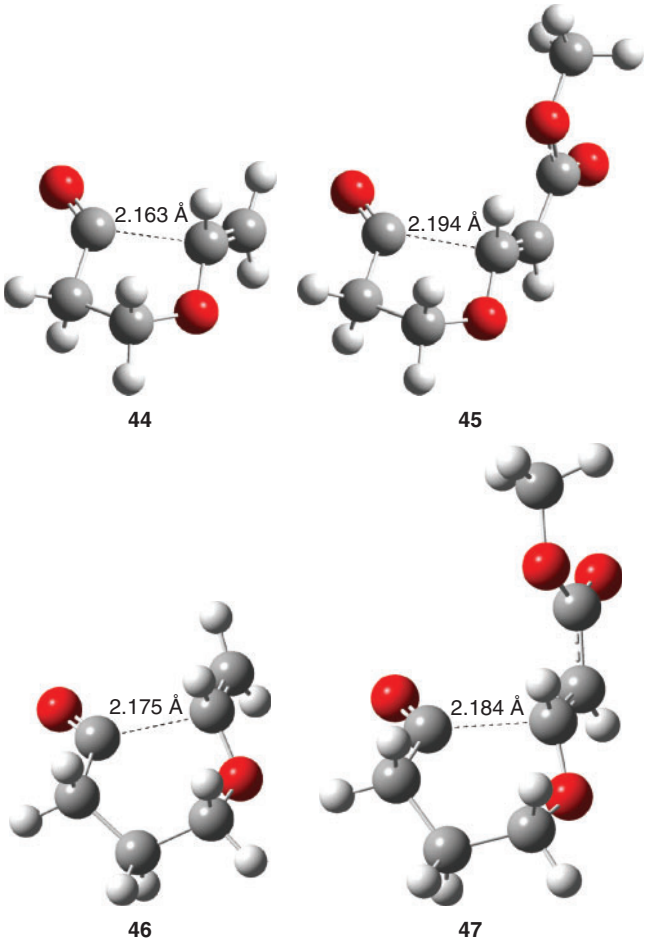
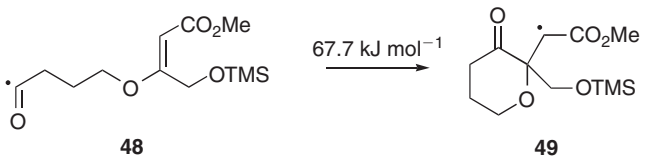


Fig. 1. BHandHLYP/6–311++G(d,p) optimized geometries of the transition states **44**–**47** involved in the cyclization of acyl radicals **40**.

Fig. 1 reveals that the transition states **44**–**47** adopt similar chair-like conformations to those of the parent 5-hexenyl and 6-heptenyl radicals,[19] with key separations of between 2.16 and 2.19 Å at the BHandHLYP/6–311++G(d,p) level of theory.

Not unexpectedly, BHandHLYP/6–311++G(d,p) calculated energy barriers ($\Delta E_1^{\ddagger}$) (Scheme 8) reveal that the cyclization reactions of radicals **40** to form five-membered radicals **41** ($n = 1$) are favoured over their six-membered counterparts ($n = 2$) by ~5–7 kJ mol^{-1}; values for $\Delta E_1^{\ddagger}$ of 61.6 and 52.3 kJ mol^{-1} are calculated for the former radicals, with values of 68.8 and 57.5 kJ mol^{-1} calculated for the analogous six-membered ring-forming reactions. As expected, the chemistry of the esters (R = CO_2Me) is also calculated to proceed more readily than that of the corresponding parent system (R = H), consistent with acyl radicals reacting as nucleophilic radicals towards alkenes.[9c]

All decarbonylation reactions are calculated to proceed with very similar barriers ($\Delta E_2^{\ddagger}$) of ~73–78 kJ mol^{-1}. In the case of **40** ($n = 1$, R = CO_2Me) cyclization is calculated to be strongly preferred (by more than 20 kJ mol^{-1}) over decarbonylation and this is consistent with experimental observations. For **40** ($n = 2$, R = H), cyclization and decarbonylation are calculated to take place with barriers that are within ~6 kJ mol^{-1} of each other, whereas the corresponding ester ($n = 2$, R = CO_2Me) is predicted to ring-close with a barrier ($\Delta E_1^{\ddagger}$) within ~15 kJ mol^{-1} of the barrier ($\Delta E_2^{\ddagger}$) for decarbonylation. As evident in the data provided in Scheme 8, all cyclization reactions are calculated to be significantly exothermic, while the decarbonylation reactions are predicted to be endothermic by ~50 kJ mol^{-1}.



Scheme 9.

Unfortunately, no kinetic data are available for either the cyclization or decarbonylation reactions of the 'parent' radicals **40** (R = H); however, it is instructive to compare the decarbonylation data with those obtained for the decarbonylation of the propanoyl radical, which was determined to lose carbon monoxide with an activation energy of ~62 kJ mol^{-1} in the gas phase.[20] Clearly, our calculated energy barriers for decarbonylation are slightly overestimated; however, we believe that they are nevertheless instructive from a qualitative perspective.

In order to provide an explanation for the products observed when aldehyde **32** was subjected to the standard reaction conditions, we next turned our attention to the chemistry of the analogous silylated acyl radical **48** (Scheme 9). The inclusion of the silylated substituent on the alkene serves to significantly raise the energy barrier for ring-closure to 67.7 kJ mol^{-1} at the same level of theory as employed previously. When compared with the barrier for decarbonylation (73.3 kJ mol^{-1}), it is clear that decarbonylation is now competitive with cyclization; these calculations are consistent with the experimental observations for the ring-closure of aldehyde **32**. In this case, one might expect that in the absence of a trapping agent (e.g. Bu_3SnH), rapid 5-*exo* cyclization of the decarbonylated radical will lead to the tetrahydrofuran (**35**).

Conclusions

We have thus demonstrated that acyl radicals, formed directly from the corresponding aldehyde, undergo cyclization to β-disubstituted acrylates under polarity-reversal catalysis. The formation of 2,2-disubstituted tetrahydrofuranones and tetrahydropyranones has been achieved, with moderate yields for the acyl radical cyclization of these hindered systems resulting from a competitive decarbonylation pathway being available. This strategy has given access to a range of dioxaspiro systems and been successfully applied to a formal synthesis of longianone **4**. The convenient preparation of aldehyde precursors and the simple and benign reaction conditions employed in this acyl radical cyclization should allow this procedure to be of wider applicability. Further studies in this area are currently in progress.

Experimental

*Representative Synthetic Procedure: Synthesis of Dihydrolongianone **20***

*(E)-Methyl 4-(tert-Butyldimethylsilyloxy)-3-(3-(4-methoxybenzyloxy)propoxy)but-2-enoate **16***

To a solution of alcohol **10** (2.33 g, 11.9 mmol) and trimethylphosphine (1 M in THF, 3.6 mL) in dichloromethane (60 mL) at 0°C was added acetylene **15** (3.25 g, 14.2 mmol) in dichloromethane (20 mL) dropwise over 20 min. The solution was allowed to warm to ambient temperature over 30 min and stirred for a further 1 h. Saturated NH_4Cl (75 mL) was added,

and the mixture extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (ethyl acetate/petrol 1:9) gave the (*E*)-acrylate **16** (4.57 g, 91%) as a colourless oil.

m/z (high-resolution electrospray ionization (HR-MS ESI) MS) 425.2349. $C_{22}H_{37}O_6Si$ $[M+H]^+$ requires 425.2354, δ_H ($CDCl_3$, 500 MHz) 0.07 (6H, s), 0.90 (9H, s), 2.03 (2H, m), 3.58 (2H, t, *J* 6.1), 3.67 (3H, s), 3.80 (3H, s), 3.89 (2H, t, *J* 6.3), 4.42 (2H, s), 4.80 (2H, s), 5.01 (1H, s), 6.87 (2H, d, *J* 8.8), 7.24 (2H, d, *J* 8.8). δ_C ($CDCl_3$, 125 MHz) −5.3 (CH_3), 18.4 (C), 25.8 (CH_3), 29.1 (CH_2), 50.8, 55.2 (CH_3), 60.5, 65.5, 66.1, 72.7 (CH_2), 91.0, 113.8, 129.2 (CH), 130.3, 159.2, 167.5, 172.3 (C). ν_{max}/cm^{-1} 2930, 1713, 1627, 1613, 1513, 1247, 1142, 1092, 1048. GC-MS (retention time, R_t 38.25 min) *m/z* 424.3 ($[M]^+$, 1%), 367.2 (16), 121.1 (100).

(E)-Methyl 4-(tert-Butyldimethylsilyloxy)-3-(3-hydroxypropoxy)but-2-enoate **17**

To a solution of PMB ether **16** (4.30 g, 10.1 mmol) in a mixture of dichloromethane/water (20:1, 105 mL) cooled to 0°C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (3.00 g, 13.2 mmol) and the solution was stirred rapidly for 3 h. Saturated $NaHCO_3$ (100 mL) was added and the mixture was extracted with chloroform (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (ethyl acetate/petrol 1:4) gave the alcohol **17** (3.01 g, 98%) as a colourless oil.

m/z (HR-MS ESI) 305.1779. $C_{14}H_{29}O_5Si$ $[M+H]^+$ requires 305.1779. δ_H ($CDCl_3$, 500 MHz) 0.10 (6H, s), 0.91 (9H, s), 2.01 (2H, m), 3.67 (3H, s), 3.82 (2H, t, *J* 5.6), 3.97 (2H, t, *J* 5.9), 4.83 (2H, s), 5.04 (1H, s). δ_C ($CDCl_3$, 125 MHz) −5.4 (CH_3), 18.4 (C), 25.9 (CH_3), 31.2 (CH_2), 50.9 (CH_3), 60.5, 60.6, 67.1 (CH_2), 91.1 (CH), 167.4, 171.9 (C). ν_{max}/cm^{-1} 3459, 2930, 1714, 1626, 1143, 1048. GC-MS (R_t 24.12 min) *m/z* 304.1 ($[M]^+$, 1%), 247.1 (93), 215.1 (39), 189.1 (61), 157.0 (100), 129.0 (37), 89.1 (23), 75.1 (48), 73.1 (29).

(E)-Methyl 4-(tert-Butyldimethylsilyloxy)-3-(3-oxopropoxy)but-2-enoate **18**

To a solution of alcohol **17** (550 mg, 1.81 mmol) in CH_2Cl_2 (4 mL) was added $PhI(OAc)_2$ (698 mg, 2.17 mmol) and (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) (28 mg, 0.18 mmol) and the mixture was stirred at ambient temperature for 4 h. After removal of the solvent under vacuum, the remaining residue was purified by flash column chromatography (ethyl acetate/petrol 1:4) to give aldehyde **18** (380 mg, 70%) as a colourless oil.

m/z (HR-MS ESI) 303.1622. $C_{14}H_{27}O_5Si$ $[M+H]^+$ requires 303.1622. δ_H ($CDCl_3$, 500 MHz) 0.06 (6H, s), 0.89 (9H, s), 2.90 (2H, td, *J* 6.1 and 1.2), 3.68 (3H, s), 4.13 (2H, t, *J* 6.1), 4.80 (2H, s), 5.06 (1H, s), 9.82 (1H, t, *J* 1.2). δ_C ($CDCl_3$, 125 MHz) −5.3 (CH_3), 18.3 (C), 25.8 (CH_3), 42.4 (CH_2), 51.0 (CH_3), 60.3, 61.9 (CH_2), 91.8 (CH), 167.1, 171.7 (C), 198.9 (CH). ν_{max}/cm^{-1} 2930, 1714, 1628, 1142, 1104, 1049. GC-MS (R_t 22.88 min) *m/z* 302.1 ($[M]^+$, 1%), 245.1 (63), 189.1 (50), 157.0 (38), 129.0 (100), 89.1 (42), 75.1 (28), 73.1 (36).

Methyl 2-(2-((tert-Butyldimethylsilyloxy)methyl)-3-oxotetrahydrofuran-2-yl)acetate **19**

A solution of aldehyde **18** (750 mg, 2.48 mmol), *tert*-dodecanethiol (175 μL, 0.74 mmol) and 1,1′-azobis(cyclohexanecarbonitrile) (182 mg, 0.74 mmol) in toluene (5 mL) was flushed with argon for 30 min. The solution was then heated at reflux for 15 h. After removal of the solvent under vacuum, flash column chromatography (ethyl acetate/petrol 1:4) gave tetrahydrofuranone **19** (210 mg, 28%) as a colourless oil.

m/z (HR-MS ESI) 303.1621. $C_{14}H_{27}O_5Si$ $[M+H]^+$ requires 303.1622. δ_H ($CDCl_3$, 500 MHz) 0.02 (3H, s), 0.04 (3H, s), 0.86 (9H, s), 2.50 (1H, ddd, *J* 18.1, 8.7 and 5.6), 2.57 (1H, d, *J* 16.5), 2.71 (1H, d, *J* 16.5), 2.79 (1H, ddd, *J* 18.1, 9.2 and 7.0), 3.58 (1H, d, *J* 10.1), 3.65 (3H, s), 3.70 (1H, d, *J* 10.1), 4.31 (1H, m), 4.34 (1H, m). δ_C ($CDCl_3$, 125 MHz) −5.8, −5.6 (CH_3), 18.1 (C), 25.7 (CH_3), 36.6, 38.5 (CH_2), 51.9 (CH_3), 65.1, 68.0 (CH_2), 82.3, 170.2, 216.1 (C). ν_{max}/cm^{-1} 2930, 1741, 1254, 1135, 1078. GC-MS (R_t 20.49 min) *m/z* 287.1 ($[M-15]^+$, 1%), 271.1 (30), 245.1 (81), 227.1 (31), 215.1 (34), 171.0 (100), 153.0 (31), 129.0 (66), 89.0 (69), 73.1 (56), 59.0 (23).

1,7-Dioxaspiro[4,4]nonane-4,8-dione (Dihydrolongianone) **20**

To the silyl ether **19** (200 mg, 0.69 mmol) in chloroform (5 mL) and methanol (3 mL) was added 10-CSA (113 mg, 0.49 mmol), and the mixture was stirred at ambient temperature for 24 h. After removal of the solvent under vacuum, the remaining residue was resuspended in chloroform (5 mL) and stirring was continued for 21 h. Saturated $NaHCO_3$ (10 mL) was added and the mixture was extracted with chloroform (3 × 5 mL), the combined organic layers dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (ethyl acetate/petrol 1:1) gave dihydrolongianone **20** (63 mg, 61%) as a colourless oil.

m/z (HR-MS ESI) 157.0495. $C_7H_9O_4$ $[M+H]^+$ requires 157.0495. δ_H ($CDCl_3$, 500 MHz) 2.63 (1H, dd, *J* 17.9 and 0.9), 2.64 (2H, m), 2.79 (1H, d, *J* 17.9), 4.22 (1H, m), 4.27 (1H, m), 4.31 (1H, d, *J* 10.1), 4.34 (1H, dd, *J* 10.1 and 0.9). δ_C ($CDCl_3$, 125 MHz) 35.8, 37.6, 63.2, 74.2 (CH_2), 84.2, 173.1, 211.9 (C). ν_{max}/cm^{-1} 2927, 1777, 1754, 1158, 1029, 1012. GC-MS (R_t 12.35 min) *m/z* 156.1 ($[M]^+$, 7%), 126.0 (84), 100.0 (26), 98.0 (100).

The spectroscopic data (^1H and ^{13}C NMR) for **20** are in accord with reported data.[13,15]

Computational Methods

Ab initio and DFT calculations were carried using the *Gaussian 03* program.[21] Geometry optimizations were performed with standard gradient techniques at HF and BHandHLYP levels of theory, using restricted and unrestricted methods for closed- and open-shell systems, respectively. All ground and transition states were verified by vibrational frequency analysis. Optimized geometries and energies for all transition structures in this study (Gaussian Archive entries) are available in the Accessory Publication.

Accessory Publication

General experimental details, full experimental procedures, spectroscopic data for compounds **11**–**13**, **22**–**26**, **29**–**36** and **38**, **39**, and Gaussian Archive entries for all *ab initio* and DFT optimized structures in this work are available from the Journal's website.

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