A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2024** (2) 202312079

Generation and reversible cyclisation of furfurylic radicals

Wilfred J. M. Lewis, Elizabeth J. Rayment, and Jeremy Robertson*

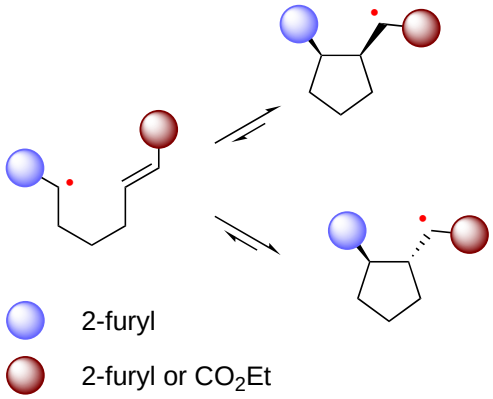
Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, United Kingdom
Email: jeremy.robertson@chem.ox.ac.uk

Dedicated with respect to Professor Samir Z. Zard

Received 09-12-2023 **Accepted Manuscript** 10-10-2023 **Published on line** 10-20-2023

Abstract

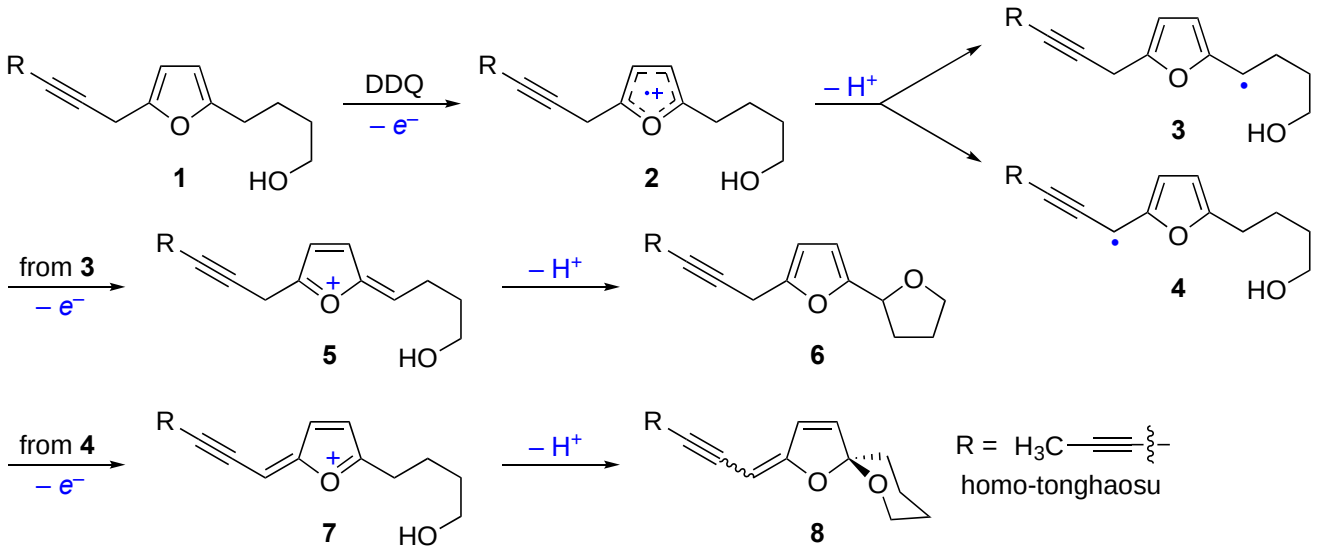
The chemistry of free radical intermediates has undergone a renaissance with the recent advent of alternatives to toxic, stoichiometric reagent systems and thermal reaction conditions. In this context, we describe an attempt to effect an isomerisation reaction comprising overall 5-*exo*-*trig* radical cyclisation preceded and followed by electron and proton transfer steps. In a follow-up study the 5-*exo*-*trig* cyclisation of furfurylic radicals, generated unambiguously by classical methods, is here shown to be synthetically viable, reversible, and equally effective with either an electron-deficient or an electron-rich alkene component. The experimental results are compared with DFT transition state and ground state energy calculations.



Keywords: Radical cyclisation, furan α-radicals, electron transfer catalysis, cyclopentanes, DFT calculations.

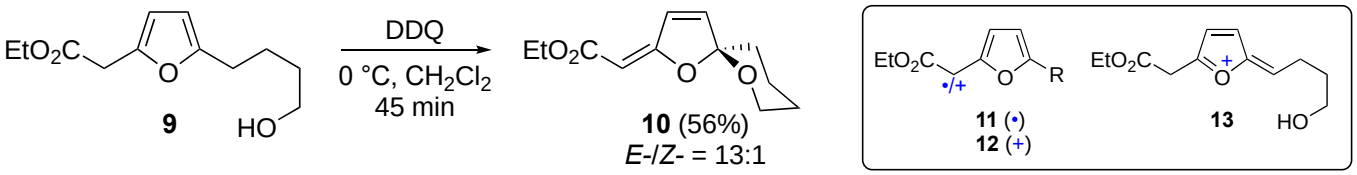
Introduction

In the key step of our synthesis of homo-tonghaosu (**8**, Scheme 1),[1] deprotonation of one of the furyl-methylene positions in 2,5-dialkylated furan radical cation **2** was proposed to occur regioselectively to give the more stabilised radical **4** from which loss of an electron would result in an extended oxonium ion **7** to give the spirocyclic product **8** rather than the linked bicyclic isomer **6**. That the desired outcome was observed did not, however, rule out the possibility of direct hydride abstraction since the conjugating alkynyl substituent would also favour cation **7**.

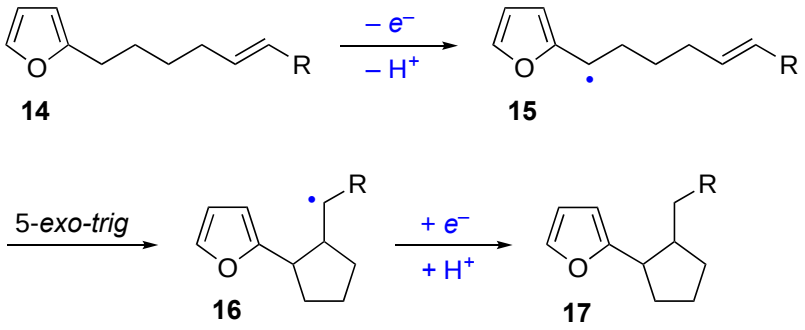


Scheme 1. Oxidative cyclisation of a 2-(4-hydroxybutyl)furan derivative leading to homo-tonghaosu proposed to proceed via furfurylic radical **4** and the derived extended oxonium ion **7**.

In subsequent work, the mechanism of the analogous reaction of ester **9** (Scheme 2),[2] leading to spiroacetal **10**, is more consistent with formation of a radical intermediate, rather than a cation, as the committing step[3,4,5,6,7] since the carbonyl system can contribute to captodative stabilisation[8,9] of radical **11** but is expected to destabilise the equivalent cation **12** with respect to the isomeric cation **13**. With this in mind, we speculated that a substrate of general structure **14** (Scheme 3) might be induced to isomerise in an overall catalytic process as shown, with a 5-*exo*-*trig* radical cyclisation[10] separating the removal and addition of an electron and a proton. This paper describes an evaluation of this proposal.

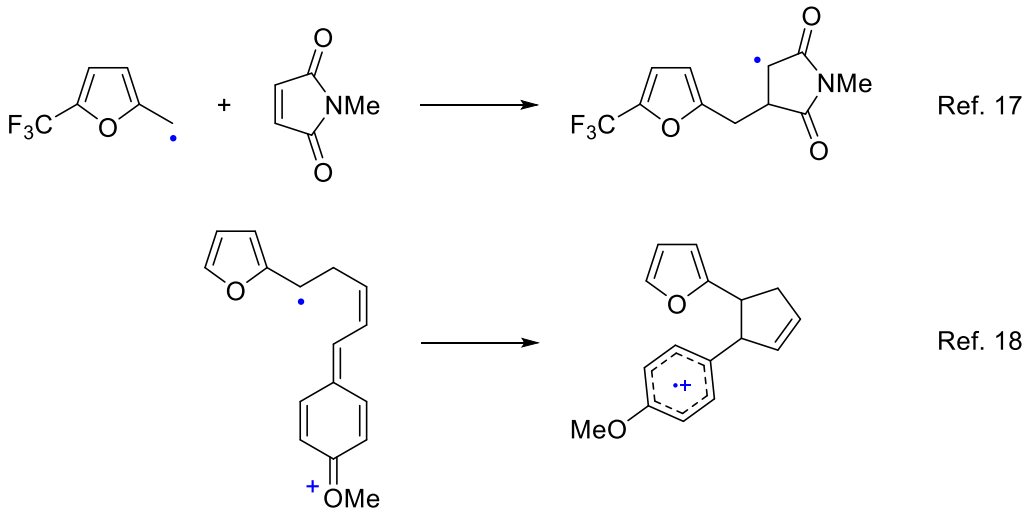


Scheme 2. The formation of spiroacetal **10**, rather than a linked bicyclic isomer (*cf.* **6**), supports initial overall loss of H• rather than H⁻.



Scheme 3. A proposed catalytic cycloisomerisation of substrate **14** to cyclopentane **17**.

The intermolecular addition of furyl-*acyl* (furoyl) radicals[11] to activated alkenes is reported,[12,13,14] and there are instances of direct reduction of *bona fide* furfurylic radicals,[15,16] but their addition to alkenes (either inter- or intramolecularly) does not seem to have been studied systematically; two potential examples are summarised in Scheme 4.[17,18] In contrast, benzylic free radicals undergo homolytic cyclisation as expected, with the 5-*exo-trig* mode being kinetically preferred relative to 6-*endo-trig* ($k_{5\text{-}exo}/k_{6\text{-}endo}$ > 20 @ 70 °C). This cyclisation is reversible such that the cyclohexyl and cyclopentylmethyl products are formed in similar quantities when the reaction is effected with a low concentration (0.01 M) of tributyltin hydride.[19] Given that a free radical generated at the α-position in a 2-alkyl furan (i.e. a furfurylic free radical) is significantly more stabilised than an analogous benzylic radical,[20] its cyclisation might well be slow and the ratio of cyclised to open-chain radicals unfavourable.

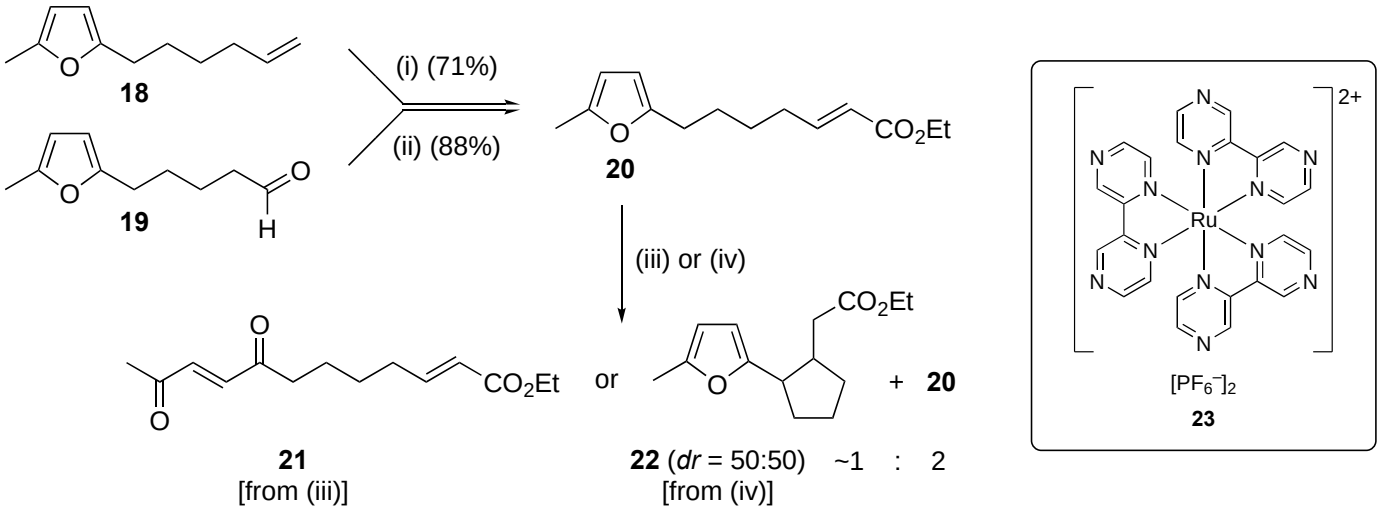


Scheme 4. Inter- and intramolecular addition of furfurylic radicals to double bonds.

Results and Discussion

A suitable substrate with which to test the proposal in Scheme 3 requires the terminal R-substituent to: (i) support unambiguous initial oxidation of the electron-rich furan ring; (ii) activate the alkene kinetically towards 5-*exo-trig* mode addition of the 'nucleophilic' furfurylic radical **15**;[21,22,23] and (iii) favour the reduction of radical **16**. An obvious candidate was identified (**20**, Scheme 5), which was readily prepared either by cross-

metathesis of alkene **18**[24] or Horner–Wadsworth–Emmons olefination of aldehyde **19**.[25] The 5-methyl substituent was included to minimise potential side-reactions arising from the intermolecular capture of radical intermediates and to afford a more readily oxidised furan.[26] Initial efforts centred on a photoredox catalysis approach, using tris(2,2'-bipyrazyl)ruthenium(II) hexafluorophosphate **23** and irradiation with blue light.[27] None of the trials gave any evidence of cyclisation and, unless oxygen was purged from the reaction mixture, the photocatalyst acted merely to sensitise oxidation by singlet oxygen to form enedione **21**.[28] Partial validation of the concept, however, was obtained by irradiating an acetonitrile solution of the substrate in the presence of tetrabutylammonium decatungstate (TBADT)[29] which returned a 2:1 mixture of starting material and cyclised product **22** after 21 h.

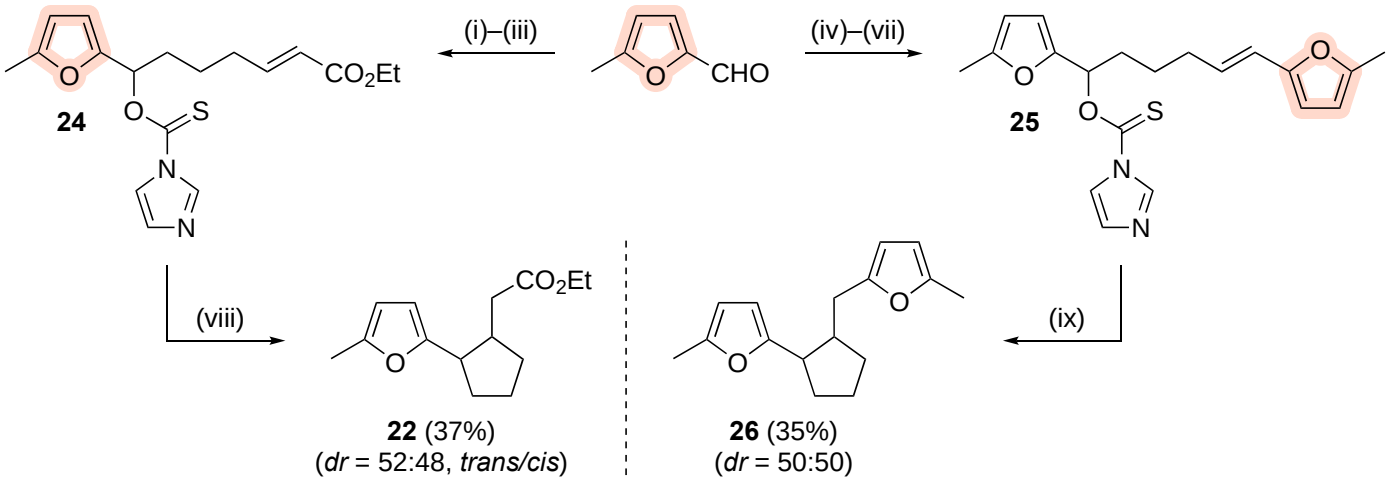


Scheme 5. (i) Ethyl acrylate, Hoveyda–Grubbs II catalyst (1 mol %), toluene, reflux, 50 min; (ii) triethyl phosphonoacetate, LiCl, DBU, CH_3CN, RT, 17 h; (iii) O_2, **23** (1 mol %), pyridine, *hv* (λ_{max} = 480 nm), aq. CH_3CN, RT, 3 h; (iv) TBADT (2 mol %), *hv* (λ_{max} = 365 nm), CH_3CN, RT, 21 h.

The lack of cyclisation with catalyst **23** and the low conversion to a cyclic product with TBADT, coupled with the stability of the furfurylic radical led to doubts about the viability of the 5-*exo*-*trig* cyclisation. To probe this step, two precursors **24** and **25** were prepared, as shown in Scheme 6, for site-specific radical generation by the Barton–McCombie method.[30] The substrate **25** bearing a terminal 5-methylfuryl substituent was designed on the basis that both the initiating and cyclised radicals would benefit from the same degree of stabilisation and, thus: (i) the relative rates of quenching by the hydrogen atom source would be comparable, and (ii) any equilibrium between them would be driven towards the cyclised radical by virtue of the exothermicity associated with forming the new C–C σ-bond at the expense of the π-component of the alkene.

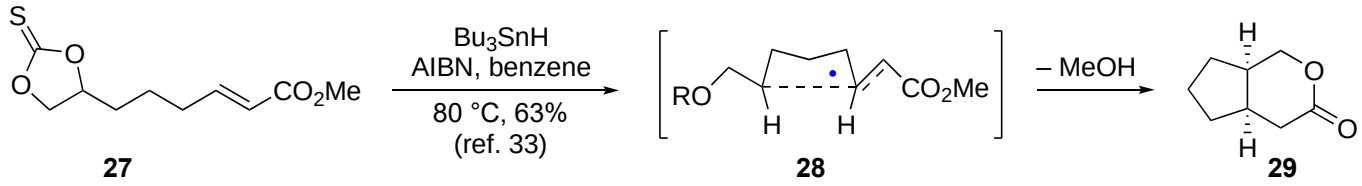
The reactions progressed to cyclised products with similar rates under the conditions used for the two substrates, although the cyclisation from **25** was more efficient at 110 °C than 80 °C and using triphenyltin hydride rather than tributyltin hydride. In each case, successful radical initiation required the reaction mixtures to be deoxygenated and, at a 5.0 mM substrate concentration, for all reaction components to be combined at the outset, rather than added slowly via syringe pump. The reactions were clean, but separation of the tin-containing impurities by chromatography was inefficient, resulting in reduced isolated yields. The cyclised products **22** and **26** were each generated as an approximately equimolar mixture of *trans* and *cis* diastereomers as ascertained by NOE studies (Supplementary Material, Figure S1). Less than 10% of the

product of direct reduction **20** was present (NMR) in the reaction mixture from **24**, and from substrate **25** no direct reduction product was observed.



Scheme 6. (i) CH_2=CH$(CH_2)_3$MgBr, THF, 0 °C, 1 h (49%); (ii) ethyl acrylate, Hoveyda–Grubbs II catalyst (1 mol %), $CHCl_3$, reflux, 40 min (88%); (iii) thiocarbonyldiimidazole, DMAP, CH_2Cl_2, 0 °C, 2.5 h (86%); (iv) HO$(CH_2)_5P^+Ph_3$ $Br^–$, BuLi, *i*-Pr_2NH, THF/toluene, 0 °C, 1 h (28%); (v) $PhI(OAc)_2$, TEMPO (5 mol%), $NaHCO_3$, CH_2Cl_2, RT, 24 h (50%); (vi) 5-methyl-2-furyllithium, THF, –78 °C to RT, 17 h (95%); (vii) as for (iii) (48%); (viii) Bu_3SnH, AIBN, benzene, reflux, 5.5 h; (ix) Ph_3SnH, AIBN, toluene-d_8, reflux, 1 h.

Simplistic application of the Beckwith–Houk stereochemical model for 5-*exo*-*trig* radical cyclisations suggests that the kinetic product of cyclisations of substrates **24** and **25** should be the *cis* isomer;[31,32] for example, in a close reported precedent, cyclisation of cyclic thionocarbonate **27** (Scheme 7) under conditions similar to those employed here formed the *cis*-fused bicyclic lactone exclusively.[33] The formation of *trans/cis* mixtures suggests that either: (i) steric interactions between the furan and terminal group (=CHCO$_2$Et or =CHfuran) disfavour the 'chair'/diequatorial transition state arrangement (*cf.* **28**); or (ii) furfurylic radicals cyclise reversibly.[34]



Scheme 7. Exclusive formation of a *cis*-1,2-cyclopentane from 5-*exo*-*trig* radical cyclisation.

DFT calculations were performed to provide some insight into the cyclisation of substrate **24** (Supplementary Material). The computed enthalpies of formation of the cyclised product **22'** diastereomers (methyl ester for simplicity) imply a small thermodynamic preference (2.9 kJ mol^{-1}) for the *trans* diastereomer (Figure 1), in close agreement with the observed ratio. Next, transition state calculations were performed on both 'chair' (~*anti*-butene) and 'boat' (~*gauche*-butene) conformers, considering the formation of *cis* and *trans* cyclised products from each. The transition state conformations selected and their relative weighting are shown in Table 1. Summing the conformer populations leading to the *cis* and *trans* cyclised product diastereomers gives a predicted 43:57 ratio in favour of the *trans* isomer. Since predictions of the major diastereomer under both kinetic and equilibrating conditions are qualitatively in agreement with the slight preference for the *trans* diastereomer observed experimentally, the computational investigation shed little light on the process.

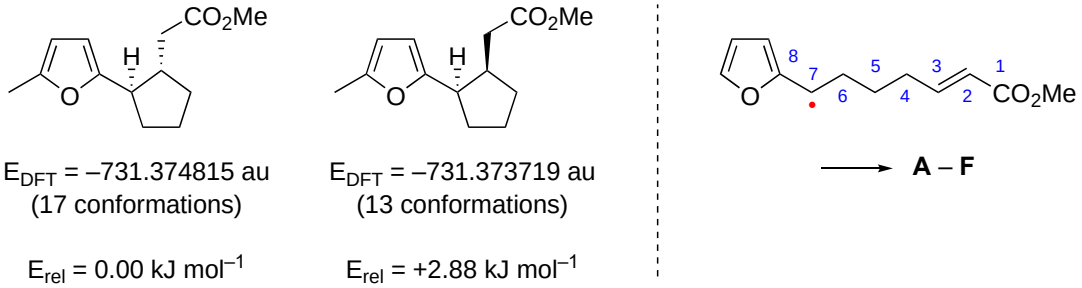
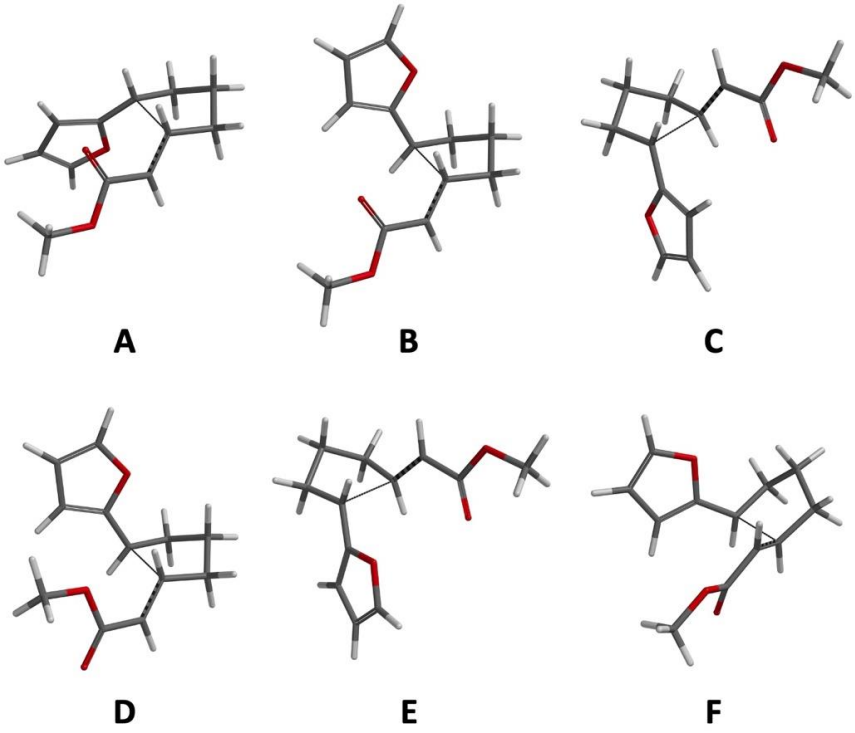


Figure 1. DFT energies (B3LYP/6-31G*) for *trans*- and *cis*-**22'**. Atom numbering in a simplified radical – lacking the furan 5-methyl substituent and with the methyl ester in place of ethyl – leading to transition state conformations **A** – **F**.

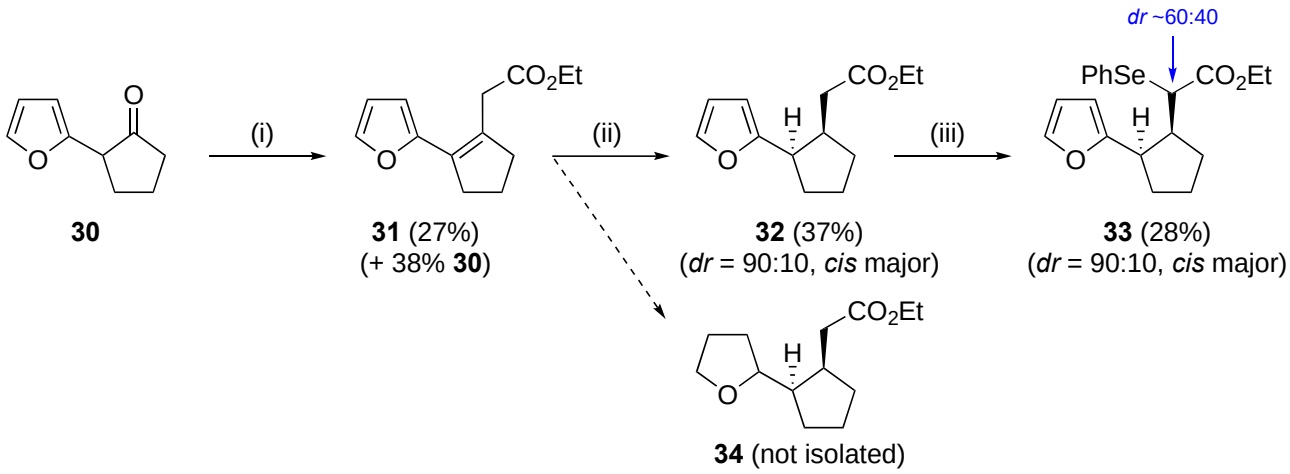
The reaction was therefore probed by examining the homolytic reactions of substrate **33** (Scheme 8), prepared as the major *cis* diastereomer (Supplementary Material, Figure S2) in three steps from 2-(2-furyl)cyclopentanone **30**.[35,36] The steps in this sequence were not optimised since sufficient radical precursor **33** was obtained, but low yields were encountered in every step. The Wittig reaction used to append the carboxymethylene fragment was only ~50% complete at the time the product was isolated; the catalytic hydrogenation proved difficult to control as the furan ring in the product **32** was reduced at a similar rate to the cyclopentenyl double bond, the crude product comprising a 41:59 ratio of **32** and THF derivative **34**; and reaction of **32** sequentially with LDA and phenylselenenyl bromide – both freshly prepared – returned a crude product mixture containing significant quantities of unconverted starting material **32**.

Table 1. Transition state conformations for the 5-*exo-trig* cyclisation of methyl (*E*)-7-(2-furyl)hept-2-enoate (7-yl radical), their DFT energies (B3LYP/6-31G*), relative population, and selected structural parameters



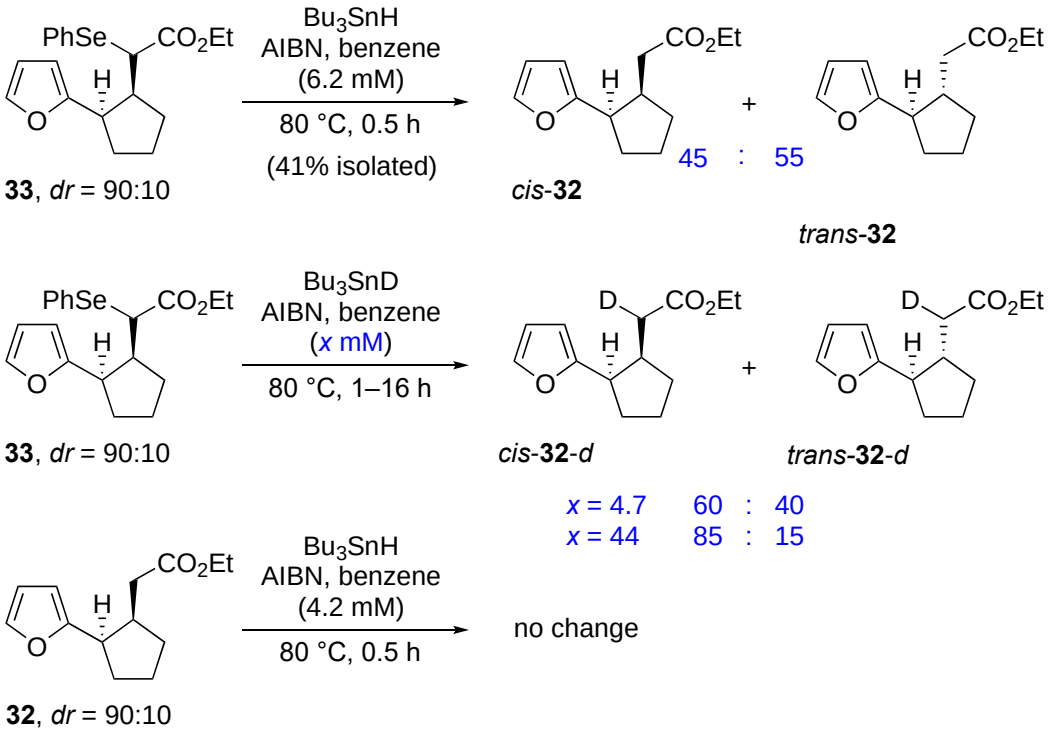
Conformation[a]	E_{DFT} / au[b]	E_{rel} / kJ mol^{-1} (Conformer %)[c]	|θ| (C5–C4–C3–C2)	r(C3–C7) / Å	r(C2–C8) / Å
A (*anti-cis*)	–691.899207	0.00 (41.5)	144°	2.14	3.18
B (*anti-trans*)	–691.898954	+0.664 (33.6)	139°	2.15	3.74
C (*gauche-trans*)	–691.897832	+3.61 (12.8)	83°	2.15	3.74
D (*anti-trans*)	–691.897226	+5.20 (7.46)	144°	2.15	3.71
E (*gauche-trans*)	–691.896148	+8.03 (3.07)	91°	2.16	3.69
F (*gauche-cis*)	–691.895419	+9.95 (1.62)	103°	2.14	3.18

[a] *anti* and *gauche* refer to the conformational disposition of C2=C3 and C4–C5 bonds as viewed along the C3–C4 bond; [b] DFT energies are reported for a transition state calculation for each conformer (**A**–**F**); [c] Boltzmann-weighted population for each conformer within the ensemble **A**–**F** calculated at 370 K.



Scheme 8. (i) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 22 h; (ii) H_2, 10% Pd/C (2.2 mol %), EtOH, RT, 16 h; (iii) LDA, THF, –78 °C, 0.5 h then PhSeBr, –78 °C, 2 h.

Three key experiments were performed with selenide **33** (Scheme 9). In the first, treatment with tributyltin hydride under similar conditions to those used for the radical cyclisations in Scheme 6 gave no evidence of ring-opened products (*cf.* **20**), but the *cis*/*trans* ratio of cyclopentane diastereomers eroded substantially from 90:10, leading to a slight majority of the *trans* diastereomer (dr = 45:55). Then, reactions with tributyltin deuteride (67% deuterium component) resulted only in deuterated products bearing deuterium adjacent to the ester. At a roughly 5 mM reaction concentration, the ratio of *cis*/*trans* diastereomers was noticeably reduced, to 60:40. On the other hand, when the reaction was run with a tenfold increase in concentration, approximately the same *cis*/*trans* diastereomer ratio (85:15) of ester α-deuterated products was returned. Finally, the configurational stability of the product was confirmed by subjecting the (major) *cis* cyclopentane **32** to the radical reaction conditions which resulted in no change. This reaction included phenethyl bromide, which was reduced to ethylbenzene, confirming an operative reductive radical chain reaction, and hence the stability of **32** towards radical intermediates and heating to 80 °C. Taken together, the evidence supports a reversible ring-opening/cyclisation process in which the equilibrium strongly favours the cyclised radical.



Scheme 9. Experiments supporting a reversible ring-opening/cyclisation from **33** to **32** and, hence, reversible cyclisation of the radical derived from substrate **24**.

Conclusions

This study demonstrates that despite the extended conjugation and stabilisation of furfurylic radicals, their 5-*exo*-*trig* cyclisation onto activated alkenes is a synthetically viable process. At the low (~5 mM) substrate concentrations typical for radical reactions very little directly reduced product is obtained, and the reaction is equally effective when the accepting alkene bears an electron withdrawing (ester) or electron releasing (furan) substituent. The cyclisation step appears to be fully reversible, with product configuration determined by the relative stability of the diastereomers. The results reported in this work provide some confidence that further investigation of substrates such as **20** might enable their radical cyclisation to be achieved without recourse to toxic organotin reagents or, indeed, any stoichiometric reagents at all.

Experimental Section

General details. All solvents for anhydrous reactions were obtained dry from Grubbs solvent dispenser units after being passed through an activated alumina column under argon. THF was additionally distilled from sodium/benzophenone ketyl under argon. Commercially available reagents were, in general, used as supplied. "Petrol" refers to the fraction of light petroleum ether boiling in the range of 30–40 °C; "ether" refers to diethyl ether. Unless stated otherwise, all reactions were carried out in oven-dried glassware and under an inert atmosphere (N_2 or Ar as specified). Silica gel chromatography was carried out using Geduran Silicagel 60, particle size 40–63 μm. Thin-layer chromatography (TLC) was conducted after all reactions whenever practical,

using Merck aluminium-backed Silicagel 60 F254 fluorescent treated silica; visualisation was enabled by UV light (λ_{max} = 254 nm) and staining with $KMnO_4$, vanillin, or anisaldehyde solutions to give the retention factors (R_f) quoted. Compound names are as generated by PerkinElmer ChemDraw Professional 22.2. Melting points (mp) were recorded (uncorrected) in degrees Celsius (°C), using a Griffin MFB-700-010U melting point apparatus. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film on a diamond ATR module. Only selected absorption maxima (ν_{max}) are reported, in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded using Bruker AVIIIHD-400 and AVDIIIHD-500 spectrometers using the solvents specified. Chemical shifts are quoted in ppm downfield of tetramethylsilane (δ = 0) and referenced in MestReNova to the appropriate solvent peak: $CDCl_3$, 7.26/77.16; C_6D_6, 7.16/128.06. Coupling constants (*J*) are quoted in Hz, rounded to the nearest 0.5 Hz. All ^1H NMR spectra are reported as follows: ppm (number of protons, multiplicity, coupling constants). High-resolution mass spectra (HRMS) were recorded by the staff at the Chemistry Research Laboratory (University of Oxford) using a Bruker Daltonics MicroTOF spectrometer; mass-to-charge ratios (*m*/*z*) are reported in Daltons.

Ethyl 2-[5-(4-hydroxybutyl)furan-2-yl]acetate (9). To a dark green solution of $FeSO_4·7H_2O$ (600 mg, 2.16 mmol) and 2-(4-hydroxybutyl)furan[37] (100 mg, 0.713 mmol) in DMSO (10 mL) was added a solution of ethyl iodoacetate (169 µL, 1.43 mmol) in DMSO (2 mL). The resulting mixture was stirred at RT for 5 min then H_2O_2 solution (0.85 mL, 35% in water, 8.8 mmol) was added dropwise. The resulting red mixture was stirred at RT for 14 h then diluted with water (15 mL) and ether (15 mL). The aqueous layer was extracted with ether (3 × 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (petrol/ethyl acetate, 80:20) furnished the title compound as a colourless oil (113 mg, 70%). R_f 0.25 (petrol/ethyl acetate, 50:50); IR (thin film) ν_{max}/cm^{-1} 3419br, 2940m, 1739s, 1566m, 1226w, 1031s; ^1H NMR (500 MHz, $CDCl_3$) δ_H 6.09 (1H, d, *J* = 3.0 Hz), 5.92 (1H, d, *J* = 3.0 Hz), 4.18 (2H, q, *J* = 7.0 Hz), 3.65 (2H, t, *J* = 6.0 Hz), 3.63 (2H, s), 2.62 (2H, t, *J* = 7.5 Hz), 1.68–1.75 (2H, m), 1.59–1.65 (2H, m), 1.26 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 169.9, 155.7, 146.0, 108.6, 105.9, 62.7, 61.2, 34.4, 32.3, 27.9, 24.3, 14.3; HRMS (ESI+) *m/z* $[M+Na]^+$ calcd for $C_{12}H_{18}NaO_4$, 249.1097; found, 249.1097.

(*E*)-Ethyl 2-(1,6-dioxaspiro[4.5]dec-3-en-2-ylidene)acetate (*E*-10) and (*Z*)-ethyl 2-(1,6-dioxaspiro[4.5]dec-3-en-2-ylidene)acetate (*Z*-10). To a stirred solution of furan derivative **9** (160 mg, 0.707 mmol) in dichloromethane (10.5 mL) at 0 °C was added a solution of DDQ (352 mg, 1.56 mmol) in dichloromethane (17 mL). The mixture was stirred for 45 min, then the reaction was quenched by cannula transfer into a stirred solution of saturated aqueous $Na_2S_2O_3·xH_2O$ (50 mL); stirring was continued for 20 min and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 x 25 mL) and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic portions were dried ($MgSO_4$), filtered, and concentrated. The products were isolated by flash chromatography (petrol/ether, 80:20) as colourless oils (***E*-10**, 83 mg, 52%; ***Z*-10**, 6.0 mg, 4%). Data for ***E*-10** – R_f 0.20 (petrol/ether, 90:10); IR (thin film) ν_{max}/cm^{-1} 2949s, 1702s, 1647s, 1584m, 1444m; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.36 (1H, d, *J* = 6.0 Hz), 6.43 (1H, dd, *J* = 6.0, 1.5 Hz), 5.32–5.33 (1H, m), 4.16 (2H, q, *J* = 7.0 Hz), 4.00 (1H, td, *J* = 11.5, 3.5 Hz), 3.84–3.88 (1H, m), 1.62–2.00 (6H, m), 1.27 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.6, 167.8, 142.1, 125.8, 111.5, 91.4, 64.6, 59.7, 32.3, 24.4, 19.4, 14.5; HRMS (ESI+) *m/z* $[M+Na]^+$ calcd for $C_{12}H_{16}NaO_4$; 247.0941, found 247.0938. Data for ***Z*-10** – R_f (petrol/ether; 80:20) 0.30; IR (thin film) ν_{max}/cm^{-1} 2950s, 1711s, 1648s, 1590w, 1444w; ^1H NMR (400 MHz, $CDCl_3$) δ_H 6.38 (1H, d, *J* = 5.5 Hz), 6.22 (1H, d, *J* = 5.5 Hz), 4.95 (1H, s), 4.16 (2H, q, *J* = 7.0 Hz) part overlayed by 4.12 (1H, td, *J* = 12.0, 3.5 Hz), 3.82–3.89 (1H, m), 2.01–2.13 (1H, m), 1.63–1.68 (5H, m), 1.28 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 167.4, 166.0, 141.2, 128.2, 114.2, 91.0, 64.7, 59.6, 32.4, 24.5, 19.3, 14.5; HRMS (ESI+) *m/z* $[M+Na]^+$ calcd for $C_{12}H_{16}NaO_4$; 247.0941, found 247.0943.

Ethyl (*E*)-7-(5-methylfuran-2-yl)hept-2-enoate (20)

By cross-metathesis. To a solution of alkene **18** (200 mg, 1.22 mmol) in toluene (7 mL) was added ethyl acrylate (260 µL, 2.40 mmol). The mixture was deoxygenated by bubbling Ar through for 10 min. Hoveyda–Grubbs II catalyst (33 mg, 52.7 µmol) was added and the mixture heated to reflux on a preheated oil bath for 45 min, after which time the mixture was cooled and transferred to a silica gel column for chromatography (petrol → petrol/ether, 90:10) to afford the title compound as a colourless oil (143 mg, 50%).

By Masamune–Roush olefination. To a suspension of LiCl (64.0 mg, 1.51 mmol) in dry acetonitrile (6 mL) at RT and under Ar was added sequentially triethyl phosphonoacetate (145 µL, 0.731 mmol) and DBU (110 µL, 0.736 mmol). The mixture was stirred for 10 min, then a solution of aldehyde **19** (100 mg, 0.602 mmol) in dry acetonitrile (300 µL) was added. The mixture was stirred at RT for 16 h, then diluted with water (60 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to afford the title compound as a geranium-scented colourless oil (125 mg, 88%). R_f 0.65 (petrol/ether, 80:20); IR (thin film) ν_{max}/cm^{-1} 2934w, 1718s, 1654w, 1178s, 779s; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.95 (1H, dt, *J* = 15.5, 7.0 Hz), 5.85–5.78 (2H, m) overlaying 5.81 (1H, dt, *J* = 15.5, 1.5 Hz), 4.18 (2H, q, *J* = 7.0 Hz), 2.57 (2H, t, *J* = 7.5 Hz), 2.28–2.17 (2H, m) overlaying 2.25 (3H, s), 1.71–1.58 (2H, m), 1.55–1.47 (2H, m), 1.28 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.8, 154.2, 150.4, 149.1, 121.6, 105.9, 105.6, 60.3, 32.0, 27.9, 27.8, 27.6, 14.4, 13.6; HRMS (APCI+, NH_3) *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}O_3$, 237.1485; found, 237.1484.

Ethyl (2*E*)-8,11-dioxododeca-2,9-dienoate (21). A vial containing a stirred solution of pyridine (75 µL, 0.931 mmol), tris(2,2'-bipyrazyl)ruthenium(II) hexafluorophosphate (3.5 mg, 4.01 µmol) and enoate ester **20** (100 mg, 0.423 mmol) in acetonitrile (3.5 mL) and water (0.84 mL) was sealed with a septum and O_2 was bubbled from a balloon through the mixture. The solution was irradiated at RT by a blue LED lamp (λ_{max} = 480 nm) for 3 h then transferred directly to a silica gel column for chromatography (petrol/ether, 50:50) which afforded an impure sample of the title compound as a colourless oil (72 mg, contains ~30 mol % pyridine). R_f 0.10 (petrol/ether, 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.92, 4.16 (2H, qd, *J* = 7.0, 1.0 Hz), 2.66 (2H, t, *J* = 7.0 Hz), 2.36 (3H, q, *J* = 1.0 Hz), 2.22 (2H, br q, *J* = 7.0 Hz), 1.76–1.57 (2H, m), 1.57–1.39 (2H, m), 1.27 (3H, td, *J* = 7.0, 1.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 200.3, 198.5, 166.7, 148.4, 137.1, 137.1, 121.9, 60.3, 41.1, 32.0, 28.3, 27.5, 23.2, 14.4; HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}O_4$, 253.1434; found, 253.1436.

1-(5-Methylfuran-2-yl)hex-5-en-1-ol (S1). To a suspension of Mg (228 mg, 9.38 mmol) in THF (0.5 mL) under Ar was added 1,2-dibromoethane (50 µL, 0.58 mmol). The mixture was heated to reflux and a solution of 5-bromopent-1-ene (710 µL, 6.00 mmol) in THF (9.5 mL) added slowly until the mixture was seen briefly to go cloudly, at which point addition was stopped and the heat source removed. The remaining bromide solution was added slowly over 1 h, then the mixture was heated to reflux for 30 min, then cooled to 0 °C. A solution of 5-methylfurfural (780 µL, 7.84 mmol) in THF (40 mL) was added dropwise and the mixture stirred at 0 °C for 1 h. The mixture was then quenched with saturated aqueous NH_4Cl solution (15 mL) and diluted with water (50 mL). The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic phases were washed with water (10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (petrol → petrol/ether, 70:30) to afford the title compound as a pale yellow oil (928 mg, 86%). R_f 0.70 (dichloromethane/ethyl acetate, 90:10); IR (thin film) ν_{max}/cm^{-1} 3354br, 1020m, 996m, 910m, 783m; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.09 (1H, d, *J* = 3.0 Hz), 5.89 (1H, dq, *J* = 3.0, 1.0 Hz), 5.80 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz), 5.01 (1H, app dq, *J* = 17.0, 1.5 Hz), 4.95 (1H, ddt, *J* = 10.0, 2.5, 1.0 Hz), 4.60 (1H, td, *J* = 7.0, 4.0 Hz), 2.28 (3H, d, *J* = 1.0 Hz), 2.13–2.05 (2H, m), 1.88–1.81 (2H, m), 1.61–1.49 (1H, m), 1.48–1.35 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.0, 151.8, 138.7, 114.9, 106.8, 106.1, 67.8, 35.0, 33.6, 25.1, 13.7; HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{11}H_{17}O_2$, 181.1223; found, 181.1226.

Ethyl (*E*)-7-hydroxy-7-(5-methylfuran-2-yl)hept-2-enoate (S2). A solution of alkene **S1** (117 mg, 0.649 mmol) in toluene (7 mL) was deoxygenated by bubbling Ar through for 5 min then ethyl acrylate (360 µL, 3.32 mmol) and Hoveyda–Grubbs II catalyst (71.0 mg, 113 µmol) was added. The resulting mixture was heated to reflux under Ar in a preheated oil bath for 40 min, after which time the mixture was concentrated to 1 mL the diluted to 4 mL with petrol. The solution was transferred directly to a silica gel column for chromatography (petrol → petrol/ether, 60:40) to afford the title compound as a pale pink oil (144 mg, 88%). R_f 0.15 (petrol/ether 70:30); IR (thin film) ν_{max}/cm^{-1} 3428br, 1716s, 1652m, 1185s, 1040s, 1020s, 784s; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.94 (1H, dt, *J*=15.5, 7.0 Hz), 6.09 (1H, d, *J* = 3.0 Hz), 5.89 (1H, dq, *J* = 3.0, 1.0 Hz), 5.81 (1H, dt, *J* = 15.5, 1.5 Hz), 4.60 (1H, td, *J* = 7.0, 5.0 Hz), 4.17 (2H, q, *J* = 7.0 Hz), 2.28 (3H, d, *J* = 1.0 Hz), 2.24 (2H, qd, *J* = 7.0, 1.5 Hz), 1.85 (2H, dt, *J* = 8.0, 7.0 Hz), 1.70–1.56 (1H, m), 1.56–1.40 (2H, m), 1.28 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.8, 154.7, 151.9, 148.8, 121.8, 107.0, 106.1, 67.7, 60.3, 34.9, 32.0, 24.2, 14.4, 13.7; HRMS (APCI+, NH_3) *m/z* $[M+NH_4]^+$ calcd for $C_{14}H_{24}NO_4$, 270.1700; found, 270.1695.

Ethyl (*E*)-7-[(1*H*-imidazole-1-carbonothioyl)oxy]-7-(5-methylfuran-2-yl)hept-2- enoate (24). To a solution of thiocarbonyl diimidazole (85.0 mg, 0.477 mmol) in dichloromethane (0.8 mL) at 0 °C and under N_2 was added DMAP (22.0 mg, 0.180 mmol) and a solution of alcohol **S2** (40.0 mg, 0.158 mmol) in dichloromethane (0.8 mL). The mixture was stirred at 0 °C for 35 min then transferred directly to a silica gel column for column chromatography (dichloromethane → dichloromethane/methanol, 95:5) to afford the title compound as a yellow oil (49.5 mg, 86%). R_f 0.35 (dichloromethane/methanol, 95:5); IR (thin film) ν_{max}/cm^{-1} 1715s, 1692s, 1654w, 1287m, 1270m, 1214s, 884s; ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.99 (1H, d, *J* = 1.5 Hz), 7.02 (1H, t, *J* = 1.5 Hz), 6.91 (1H, dt, *J* = 15.5, 7.0 Hz), 6.87 (1H, dd, *J* = 2.0, 1.0 Hz), 5.99 (1H, d, *J* = 3.0 Hz), 5.81 (1H, dt, *J* = 15.5, 1.5 Hz), 5.66 (1H, dq, *J* = 3.0, 1.0 Hz), 4.76 (1H, dd, *J* = 9.0, 6.5 Hz), 4.04 (2H, q, *J* = 7.0 Hz), 1.95 (3H, d, *J* = 1.0 Hz), 1.90–1.80 (1H, m), 1.75–1.68 (3H, m), 1.25–1.10 (2H, m), 0.98 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, C_6D_6) δ_C 166.0, 165.2, 152.6, 150.5, 147.8, 135.5, 131.5, 122.4, 115.8, 109.4, 106.9, 60.1, 43.7, 33.5, 31.4, 25.9, 14.3, 13.4; HRMS (APCI+, NH_3) *m/z* $[M–C_4H_3N_2OS]^+$ calcd for $C_{14}H_{19}O_3$, 235.1329; found 235.1320.

Ethyl 2-[(5-methylfuran-2-yl)cyclopentyl]acetate (22). To a solution of radical precursor **24** (18.0 mg, 49.7 µmol) in benzene (7 mL) was added a solution of AIBN (~1 mg, ~6 µmol) in benzene (9 mL). The mixture was deoxygenated by bubbling Ar through for 10 min and tributyltin hydride (16.5 mg, 55.5 µmol) added. The mixture was heated to reflux under Ar for 5.5 h and was then cooled and concentrated then purified by column chromatography [silica gel containing 10% by weight of KF; petrol → petrol/ether, 94:6] to afford a mixture containing a little of the directly-reduced compound **20** (<10%) and the diastereomers of the title compound (*trans*/*cis*, 52:48 by ^{1}H NMR integration) as a colourless oil (4.3 mg, 37%). R_f 0.30 (petrol/ether, 90:10); IR (thin film) ν_{max}/cm^{-1} 2956m, 1735s, 1178m, 1023m, 781m; ^{1}H NMR (500 MHz, C_6D_6) δ_H 5.88 (0.5H, d, *J* = 3.0 Hz, *trans*), 5.80 (0.5H, d, *J* = 3.0 Hz, *cis*), 5.78–5.76 (0.5H, m, *trans*), 5.76–5.73 (0.5H, m, *cis*), 3.95 (1H, q, *J* = 7.0 Hz, *cis*), 3.91 (1H, q, *J* = 7.0 Hz, *trans*), 3.22 (0.5H, q, *J* = 7.5 Hz, *cis*), 2.68–2.61 (0.5H, m, *cis*), 2.60 (0.5H, d, *J* = 4.0 Hz, *trans*), 2.58–2.47 (1H, m, both), 2.23 (0.5H, dd, *J* = 16.0, 6.5 Hz, *cis*), 2.15–2.11 (0.5H, m, 0.5H, *trans*), 2.09 (0.5H, d, *J* = 4.0 Hz, *cis*), 2.08–2.04 (0.5H, m, *trans*), 2.02 (1.5H, d, *J* = 1.0 Hz, *trans*), 2.01 (1.5H, d, *J* = 1.0 Hz, *cis*), 1.90–1.84 (0.5H, m, *trans*), 1.82–1.75 (2H, m, both), 1.75–1.66 (0.5H, m, *cis*), 1.61–1.52 (0.5H, m, *trans*), 1.52–1.42 (1H, m, both), 1.42–1.31 (0.5H, m, *cis*), 1.28–1.16 (0.5H, m, *trans*), 0.95 (1.5H, t, *J* = 7.0 Hz, *cis*), 0.93 (1.5H, t, *J* = 7.0 Hz, *trans*); ^{13}C NMR (126 MHz, C_6D_6) δ_C 172.7, 172.3, 156.3, 155.9, 150.7, 150.6, 107.0, 106.3, 106.2, 105.7, 60.0, 59.9, 45.2, 42.3, 41.7, 40.6, 39.3, 36.4, 32.3, 32.1, 31.4, 29.9, 23.9, 23.7, 14.3 (two peaks), 13.5; HRMS (APCI+, NH_3) *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}O_3$, 237.1485; found, 237.1492.

6-(5-Methylfuran-2-yl)hex-5-en-1-ol (S3). To a suspension of 5-hydroxypentyl triphenylphosphonium bromide (19.9 g, 46.4 mmol) in toluene under N_2 was added toluene (10 mL) and THF (35 mL). The mixture was cooled to 0 °C and butyllithium (37.3 mL, 2.5 M in hexanes, 93.8 mmol) was added over 2 h while the mixture was

shaken vigorously. Diisopropylamine (13.5 mL, 96.3 mmol) was added, followed by 5-methylfurfural (5.1 mL, 51.3 mmol) over 5 min. The mixture was stirred for 1 h and the reaction mixture acidified to pH 5 by adding saturated aqueous NH_4Cl solution. The organic phase was concentrated, and the residue purified by column chromatography (petrol → petrol/ether, 50:50) to afford the title compound as a mixture of diastereomers (*Z*-/*E*-, 70:30 by ^{1}H NMR integration) and as a golden oil (2.32 g, 28%). R_f 0.20 (dichloromethane/methanol, 98:2); IR (thin film) ν_{max}/cm^{-1} 3343br, 2928s, 2860m, 1020s, 781s; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H [data for ***Z*-S3**] 6.17–6.02 (2H, m), 5.96 (1H, dt, *J* = 2.0, 1.0 Hz), 5.45 (1H, dt, *J* = 11.5, 7.5 Hz), 3.65 (2H, t, *J* = 6.5 Hz), 2.46 (2H, qd, *J* = 7.5, 2.0 Hz), 2.30 (3H, d, *J* = 1.0 Hz), 1.83 (1H, br s), 1.68–1.58 (2H, m), 1.58–1.47 (2H, m) [resonances for ***E*-S3** were visible at: 6.17–6.02 (1H, m), 5.99 (1H, d, *J* = 3.0 Hz), 5.91 (1H, dq, *J* = 3.0, 1.0 Hz), 3.63 (2H, t, *J* = 6.5 Hz), 2.28 (3H, d, *J* = 1.0 Hz), 2.19 (2H, q, *J* = 7.0 Hz)]; ^{13}C NMR (101 MHz, $CDCl_3$) δ_C [data for ***Z*-S3**] 151.8, 151.2, 129.3, 117.7, 110.0, 107.2, 62.8, 32.4, 28.9, 25.7, 13.8; [data for ***E*-S3**] 151.7, 151.2, 127.9, 119.1, 107.3, 107.1, 62.8, 32.5, 32.2, 25.5, 13.7; HRMS (APCI+, NH_3) *m/z* $[M+H]^+$ calcd for $C_{11}H_{17}O_2$, 181.1223; found, 181.1226.

(*E*)-6-(5-Methylfuran-2-yl)hex-5-enal (S4). To a solution of alcohol **S3** (700 mg, 3.88 mmol) in dichloromethane (53 mL) was added $NaHCO_3$ (1.63 g, 19.4 mmol). The mixture was cooled to 0 °C, placed under N_2, and light was excluded from the reaction vessel with aluminium foil. A solution of TEMPO (31.0 mg, 0.198 mmol) in dichloromethane (5 mL) was added dropwise then a solution of bis(acetoxy)iodobenzene (175 mg, 0.543 mmol) in dichloromethane (20 mL) was added over 1 h via syringe pump. The foil was removed from the outside of the reaction vessel, and the mixture warmed to RT and stirred for 24 h. The reaction mixture was washed successively with saturated aqueous $Na_2S_2O_3{\cdot}xH_2O$ solution (2 × 30 mL), water (20 mL) and brine (20 mL), and the organic phase was separated and dried ($MgSO_4$), then concentrated and the residue purified by column chromatography (petrol → petrol/ether, 80:20) to afford the aldehyde as a mixture of diastereomers (*E*-/*Z*-, 70:30 by ^{1}H NMR integration) and as a yellow oil (350 mg, 51%). A portion of this material (100 mg, 0.561 mmol) was converted into the (*E*)-isomer (*dr* = 95:5) via dissolution in benzene (4.5 mL) and the sequential addition to this mixture of K_2CO_3 (13.5 mg, 0.098 mmol) and a solution of I_2 (13.5 mg, 0.0532 mmol) in benzene (1.5 mL). The mixture was stirred in the dark (aluminium foil) for 1 h at RT, after which time the mixture was shaken vigorously with saturated aqueous $Na_2S_2O_3{\cdot}xH_2O$ solution (2 × 1 mL). The organic phase was passed through a plug of Na_2SO_4, then concentrated to afford the title compound as a yellow oil (94 mg, 94%). R_f 0.60 (dichloromethane); IR (thin film) ν_{max}/cm^{-1} 2926w, 1724s, 1020m, 996w, 785s; ^{1}H NMR (500 MHZ, C_6D_6) δ_H 9.25 (1H, t, *J* = 1.5 Hz), 6.06–6.02 (2H, m), 5.96 (1H, d, *J* = 3.0 Hz), 5.80 (1H, br dq, *J* = 3.0, 1.0 Hz), 2.02 (3H, d, *J* = 1.0 Hz), 1.87–1.81 (2H, m), 1.75 (2H, td, *J* = 7.5, 1.5 Hz), 1.38 (2H, quin, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, C_6D_6) δ_C 200.4, 152.1, 151.5, 127.1, 120.1, 108.0, 107.6, 43.0, 32.2, 21.8, 13.5; HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{11}H_{15}O_2$, 179.1067; found, 179.1070.

(*E*)-1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-ol (S5). To 2-methylfuran (95.0 µL, 1.05 mmol) in THF (2 mL) at 0 °C and under Ar was added butyllithium (316 µL, 2.5 M in hexanes, 0.790 mmol) dropwise. The mixture was stirred for 2.5 h, then cooled to −78 °C. A solution of **(*E*)-S4** (94 mg, 0.527 mmol) in THF (0.63 mL) was added, and the resulting mixture was warmed to RT and stirred over 16 h, then quenched with saturated aqueous NH_4Cl solution (1 mL) and extracted with ethyl acetate (3 × 2 mL). The combined organic phases were washed with brine (3 mL), dried (Na_2SO_4), filtered and concentrated to afford the title compound as a pale-yellow oil (130 mg, 95%). R_f 0.10 (petrol/ether, 80:20); IR (thin film) ν_{max}/cm^{-1} 3389br, 2944w, 1020s, 962m, 782s; ^{1}H NMR (400 MHz, C_6D_6) δ_H 6.21 (1H, dt, *J* = 16.0, 7.0Hz), 6.09 (1H, dt, *J* = 16.0, 1.5 Hz), 5.96 (1H, d, *J* = 3.0 Hz), 5.94 (1H, d, *J* = 3.0 Hz), 5.79 (1H, dq, *J* = 3.0, 1.0 Hz), 5.75 (1H, dq, *J* = 3.0, 1.0 Hz), 4.42 (1H, t, *J* = 7.0 Hz), 2.07–1.96 (8H, m), 1.81–1.72 (2H, m), 1.61–1.48 (1H, m), 1.48–1.33 (1H, m), 1.23 (1H, br s); ^{13}C NMR (101 MHz, C_6D_6) δ_C 128.1 (from HSQC), 119.6, 107.7, 107.5, 106.6, 106.4, 67.8, 35.5, 32.9, 25.8, 13.5, 13.4 (resonances for

two 4° carbons were not resolved); HRMS (APCI+, NH_3) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}O_3$, 261.1485; found, 261.1487.

***O*-[1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-yl]-[1*H*]-imidazole-1-carbothioate (25).** A solution of alcohol **S5** (50.0 mg, 0.192 mmol) and DMAP (28.0 mg, 0.229 mmol) in dichloromethane (1 mL) was transferred into a solution of thiocarbonyl diimidazole (103 mg, 0.578 mmol) in dichloromethane (1 mL) at 0 °C. The resulting mixture was stirred at 0 °C under N_2 in the dark (aluminium foil) for 2.25 h and then transferred directly to a silica gel column for purification by chromatography (petrol → petrol/ether, 60:40) to afford the title compound as a yellow oil (34.0 mg, 48%). R_f 0.10 (dichloromethane); IR (thin film) ν_{max}/cm^{-1} 1692s, 1216s, 885s; ^{1}H NMR (400 MHz, C_6D_6) δ_H 8.00 (1H, t, *J* = 1.0 Hz), 7.04 (1H, t, *J* = 1.5 Hz), 6.87 (1H, dd, *J* = 1.5, 1.0 Hz), 6.18–6.09 (2H, m), 6.04 (1H, d, *J* = 3.0 Hz), 5.96 (1H, d, *J* = 3.0 Hz), 5.80–5.77 (1H, m), 5.69–5.66 (1H, m), 4.87 (1H, dd, *J* = 8.5, 7.0 Hz), 2.07–1.92 (9H, m), 1.92–1.81 (1H, m), 1.42–1.31 (2H, m); ^{13}C NMR (101 MHz, C_6D_6) δ_C 165.3, 152.5, 152.1, 151.5, 150.8, 135.5, 131.4, 127.2, 120.0, 115.8, 109.3, 108.0, 107.6, 106.8, 43.9, 33.5, 32.4, 27.4, 13.5, 13.4; HRMS (ESI+) *m/z* $[M–C_4H_3N_2OS]^+$ calcd for $C_{16}H_{19}O_2$, 243.1380; found, 243.1381.

2-Methyl-5-{[2-(5-methylfuran-2-yl)cyclopentyl]methyl}furan (26). A solution of radical precursor **25** (34.0 mg, 0.092 mmol), triphenylstannane (48.5 mg, ~60% by ^{1}H NMR integration, 0.0829 mmol), and AIBN (3.0 mg, 0.018 mmol) in toluene-d_8 (0.95 mL) was degassed via three freeze-pump-thaw cycles under Ar. The solution was heated to reflux for 30 min, after which time additional solutions of triphenylstannane (22.5 mg, ~60% by ^{1}H NMR integration, 0.0385 mmol) in toluene-d_8 (0.25 mL) and AIBN (1.5 mg, 0.0091 mmol) in toluene-d_8 (0.2 mL) were added. Heating was continued for a further 35 min, and the cooled mixture was transferred directly to a silica gel column for purification by chromatography (pentane) to afford the title compound (*dr* = 50:50 by ^{1}H NMR integration) as a colourless oil (8.0 mg, 36%). R_f 0.80 (pentane); IR (thin film) ν_{max}/cm^{-1} 2951s, 2922s, 2873m, 1568s, 1219s, 1021s, 778s; ^{1}H NMR (400 MHz, C_6D_6) δ_H 5.91–5.62 (4H, m), 3.15 (0.5H, q, *J* = 7.5 Hz), 2.96–2.87 (0.5H, m), 2.71–2.63 (1H, m), 2.57–2.49 (0.5H, m), 2.49–2.38 (1H, m), 2.32 (0.5H, dd, *J* = 15.0, 10.0 Hz), 2.07–2.03 (6H, m), 1.95–1.87 (1H, m), 1.85–1.67 (2H, M), 1.65–1.54 (1H, m), 1.53–1.41 (1H, m), 1.39–1.29 (1H, m); ^{13}C NMR (101 MHz, C_6D_6) δ_C 157.0, 156.0, 154.4, 153.9, 150.5, 150.5, 150.3, 150.2, 107.0, 106.8, 106.4, 106.3, 106.3 (2 peaks), 106.2, 105.4, 45.2, 44.9, 43.2, 42.4, 33.2, 32.3, 32.2, 31.2, 30.2, 29.8, 24.1, 23.5, 13.6 (2 peaks), 13.5 (2 peaks); HRMS (ESI+) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}O_2$, 245.1536; found, 245.1537.

Ethyl 2-[2-(furan-2-yl)cyclopent-1-en-1-yl]acetate (31). To a solution of carbethoxymethylenetriphenylphosphorane (232 mg, 0.666 mmol) in benzene (0.75 mL) under Ar was added via syringe 2-(furan-2-yl)cyclopentanone **30** (100 mg, 0.666 mmol). The mixture was heated to reflux for 20 h, then the cooled mixture was transferred directly to a silica gel column for purification by chromatography (petrol → petrol/ether, 95:5) to afford the title compound, as a variable mixture of alkene regioisomers in which the tetrasubstituted alkene isomer usually dominated, as a colourless to pale orange oil (41 mg, 28%; 46% based on recovered ketone **30**). R_f 0.30(petrol/ether, 92:8); IR (thin film) ν_{max}/cm^{-1} 1732s, 1655w, 1177s, 1155s, 1035m, 1009m, 732s; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 (1H, d, *J* = 2.0Hz), 6.37 (1H, dd, *J* = 3.5, 2.0 Hz), 6.24 (1H, d, *J* = 3.5 Hz), 4.16 (2H, q, *J* = 7.0 Hz), 3.59 (2H, t, *J* = 1.5 Hz), 2.74–2.68 (2H, m), 2.58 (2H, br t, *J* = 7.0 Hz), 1.94 (2H, quin, *J* = 7.5 Hz), 1.26 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.6*, 152.6*, 141.6, 131.0*, 128.1*, 110.9, 107.7, 60.7, 38.1, 35.8, 34.7, 22.2, 14.4 (starred resonances from a 500 MHz spectrum of a mixed-isomer sample); HRMS (APCI+, NH_3) *m/z* $[M+H]^+$ calcd for $C_{13}H_{17}O_3$, 221.1172; found, 221.1174.

Ethyl 2-[2-(furan-2-yl)cyclopentyl]acetate (32). From alkene **31** Alkene **31** (206 mg, 0.935 mmol) was added to a suspension of Pd/C (22 mg, 10 wt.% Pd, 20 μmol) in ethanol (10 mL). A three-way valve was attached, and the mixture was frozen by immersing the reaction vessel in liquid N_2. The flask was filled with N_2 via three pump-fill cycles. A balloon of H_2 was attached to the three-way valve and the flask refilled with H_2 via three pump-fill cycles. The mixture was allowed to thaw, stirred for 16 h, re-frozen in liquid N_2, and the flask refilled

with N_2 via five pump-fill cycles. After thawing, the mixture was passed through a short plug of Celite®, rinsing through with ethanol (20 mL). The combined filtrates were concentrated, and the residue purified by column chromatography (petrol → petrol/ether, 95:5) to afford the title compound (76.0 mg, 37%) as a floral-smelling colourless oil, and as a mixture of diastereomers (*cis/trans*, ~90:10 by ^{1}H NMR integration). The mass balance in this reaction comprised the THF derivative **34** (not isolated).

From selenide 33. A solution of selenide **33** (24.0 mg, 0.0636 mmol) in benzene (5 mL) was deoxygenated by bubbling Ar through for 5 min. A solution of AIBN (1.0 mg, 6.1 µmol) in benzene (1 mL) was similarly deoxygenated and added to the selenide solution. The resulting mixture was heated to reflux in a preheated oil bath and a deoxygenated solution of tributyltin hydride (20 mg, 0.068 mmol) in benzene (4 mL) was added over 1 h. An additional portion of AIBN (1.0 mg, 6.1 µmol) in deoxygenated benzene (1 mL) was added and reflux was continued for a further 1 h. The mixture was then cooled, concentrated, and purified by column chromatography (benzene) to afford the title compound (6.0 mg, 42%) as a colourless oil, and as a mixture of diastereomers (*trans/cis*, 55:45 by ^{1}H NMR integration). Data for *cis*-**32**: R_f 0.30 (petrol/ether, 90:10); IR (thin film) ν_{max}/cm^{-1} 2961w, 1734s, 1164m, 731w; ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.05 (1H, dd, *J* = 2.0, 1.0 Hz), 6.06 (1H, dd, *J* = 3.0, 2.0 Hz), 5.82 (1H, dt, *J* = 3.0, 1.0 Hz), 4.00–3.86 (2H, m), 3.20 (1H, q, *J* = 7.5 Hz), 2.65–2.56 (1H, m), 2.14 (1H, dd, *J* = 16.0, 6.5 Hz), 2.00 (1H, dd, *J* = 16.0, 9.0 Hz), 1.79–1.68 (4H, m), 1.48–1.33 (2H, m), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, C_6D_6) δ_C 172.6, 157.7, 141.3, 110.2, 106.3, 59.9, 41.6, 40.8, 36.3, 31.4, 29.9, 23.7, 14.3; HRMS (APCI+, NH_3) *m/z* $[M+H]^+$ calcd for $C_{13}H_{19}O_3$, 223.1329; found 223.1328. NMR data for *trans*-**32** (assigned by subtraction of the data for *cis*-**32** in a sample from the radical reaction): R_f 0.30 (petrol/ether, 90:10); ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.09 (1H, dd, *J* = 2.0, 1.0 Hz), 6.09 (1H, dd, *J* = 3.0, 2.0 Hz), 5.90 (1H, d, *J* = 3.0 Hz), 3.97–3.88 (2H, m), 2.55–2.42 (3H, m), 2.13–2.06 (1H, m), 1.90–1.35 (6H, m), 0.93 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, C_6D_6) δ_C 172.2, 158.2, 141.3, 110.3, 104.8, 60.0, 45.0, 42.4, 39.3, 32.3, 32.0, 23.9, 14.3.

Ethyl 2-[2-(furan-2-yl)cyclopentyl]-2-(phenylselanyl)acetate (33). To a solution of diisopropylamine (48 µL, 0.34 mmol) in THF (0.5 mL), cooled to 0 °C under Ar, was added butyllithium (0.175 mL, 1.6 M in hexanes, 0.280 mmol) dropwise. The reaction mixture was stirred for 15 min, then cooled to –78 °C and a solution of *cis*-**32** (57.0 mg, 0.256 mmol) in THF (0.2 mL) added slowly. The mixture was stirred for 30 min at −78 °C, during which time separate solutions were prepared of diphenyldiselenide (45 mg, 0.14 mmol) in THF (0.5 mL) and Br_2 (100 µL, 1.95 mmol) in THF (7.0 mL), both under Ar. A portion of the Br_2 solution (0.5 mL, ~0.14 mmol Br_2) was added to the vigorously stirred diphenyldiselenide solution at RT. A rapid colour change of the diphenyldiselenide solution from yellow to dark brown was observed. Stirring was continued for 5 min, after which time the resulting mixture was transferred to the cold enolate solution dropwise via syringe. The mixture was stirred for 2 h, and the reaction was then quenched by the addition of saturated aqueous $Na_2S_2O_3{\cdot}xH_2O$ solution (2 mL) and saturated aqueous NH_4Cl solution (3 mL). The mixture was then allowed to warm to RT and was extracted with ether (3 × 5 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (petrol/toluene, 80:20 to petrol/toluene/ether, 78:20:2) to give two part-separated α-ester diastereomers of the title compound (both *cis*-cyclopentanes) as a yellow oil (16 mg + 12 mg, 28%). Data for both diastereomers: R_f 0.10 (petrol/ether, 98:2); IR (thin film) ν_{max}/cm^{-1} 2960w, 1725s, 1147m, 737s, 692m; HRMS (EI+) *m/z* $[M]^+$ calcd for $C_{19}H_{22}O_3Se$, 378.0729; found, 378.0727. NMR data for major diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ_H 7.62–7.56 (2H, m), 7.00–6.94 (4H, m), 6.03 (1H, dd, *J* = 3.0, 2.0 Hz), 6.00 (1H, dd, *J* = 3.0, 1.0 Hz), 3.97–3.75 (2H, m), 3.56 (1H, ddd, *J* = 8.5, 7.0, 2.0 Hz), 3.43 (1H, d, *J* = 11.5 Hz), 2.63–2.53 (1H, m), 2.06–1.95 (1H, m), 1.95–1.82 (1H, m), 1.83–1.60 (4H, m), 1.56–1.43 (1H, m), 0.82 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, C_6D_6) δ_C 172.3, 157.3, 141.3, 135.8, 129.1, 110.2, 107.4, 60.5, 46.4, 46.2, 41.2, 31.1, 29.7, 23.9, 14.0 (two phenyl resonances obscured by solvent

signal). NMR data for minor diastereomer: ^{1}H NMR (400 MHz, C_6D_6) δ_H 7.66–7.62 (2H, m), 7.01 (1H, dd, *J* = 2.0, 1.0 Hz), 6.98–6.92 (3H, m), 6.00 (1H, dd, *J* = 3.0, 2.0 Hz), 5.79 (1H, dd, *J* = 3.0, 1.0 Hz), 3.96–3.84 (2H, m), 3.52–3.46 (1H, m), 3.36 (1H, d, *J* = 11.5 Hz), 2.69 (1H, tt, *J* = 11.5, 7.5 Hz), 2.24–2.14 (1H, m), 1.86–1.62 (4H, m), 1.41–1.29 (1H, m), 0.90 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, C_6D_6) δ_C 172.4, 157.4, 141.5, 136.2, 129.1, 128.5, 110.2, 107.0, 60.3, 46.7, 45.9, 40.8, 31.9, 31.2, 23.8, 14.1 (one phenyl resonance obscured by solvent signal).

Ethyl 2-[2-(furan-2-yl)cyclopentyl]acetate-*d* (32-*d*). To a solution of selenide **33** (13.5 mg, 35.8 µmol) in benzene (0.3 mL) was added a solution of tributyltindeuteride (13 mg, ~60% deuterium content, ~27 µmol) in benzene (0.2 mL) and a solution of AIBN (0.6 mg, 3.7 µmol) in benzene (0.23 mL). The mixture was degassed via three freeze-pump-thaw cycles and then heated to reflux for 1 h. An additional portion of tributyltindeuteride (6.5 mg, ~60% deuterium content, ~13 µmol) in benzene (0.1 mL) was added and the mixture returned to reflux for a further 45 min. The mixture was then concentrated and the residue purified by column chromatography (pentane → pentane/ether, 95:5) to afford the title compound (4.5 mg, 56%), a colourless oil, as a mixture of diastereomers (*cis/trans*, 85:15 by ^{1}H NMR integration). ^{2}H NMR (92 MHz, C_6H_6; referenced to C_6D_6 added as an internal standard, @ 7.16 ppm) δ_D 2.18 (br s), 1.77 (br s), 1.65 (br s); NMR data for *cis*-**32-*d*** (assigned by comparison with *cis*-**32**): ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.05 (1H, dd, *J* = 2.0, 1.0 Hz), 6.06 (1H, dd, *J* = 3.0, 2.0 Hz), 5.81 (1H, d, *J* = 3.0 Hz), 3.94 (1H, q, *J* = 7.0 Hz), 3.93 (1H, q, *J* = 7.0), 3.19 (1H, qd, *J* = 7.5, 3.0 Hz), 2.64–2.58 (1H, m), 2.13 (0.5H, dd, *J* = 16.0, 6.5 Hz) and 2.00 (0.5H, dd, *J* = 16.0, 9.0 Hz, residual CH_2CO_2Et overlaying C**H**D multiplets), 1.80–1.66 (4H, m), 1.49–1.34 (2H, m), 0.94 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, C_6D_6) δ_C 172.6, 157.7, 141.3, 110.2, 106.3, 59.9, 41.7, 40.7, 36.3 (residual CH_2CO_2Et), 36.0 (t, *J* = 20 Hz), 31.4, 29.9, 23.7, 14.3; NMR data for *trans*-**32-*d*** (assigned by comparison with *trans*-**32**): ^{1}H NMR (500 MHz, C_6D_6) δ_H 7.09 (1H, dd, *J* = 2.0, 1.0 Hz), 6.09 (1H, dd, *J* = 3.0, 2.0 Hz), 5.90 (1H, dd, *J* = 3.0, 1.0 Hz), 3.97–3.89 (2H, m, obscured by resonances for *cis*-isomer), 2.56–2.43 (2.5H, m), 2.14–2.05 (0.5H, m), 1.86–1.33 (6H, m), 0.93 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, C_6D_6) δ_C 172.2, 158.2, 141.3, 110.3, 104.8, 60.0, 45.0, 42.4, 39.2 (residual CH_2CO_2Et), 39.0 (t, *J* = 20 Hz), 38.9 (t, *J* = 20 Hz), 32.3, 32.0, 23.9, 14.3; HRMS (APCI+, NH_3) *m/z* $[M+H]^+$ calcd for $C_{13}H_{18}DO_3$, 224.1391; found, 224.1391.

Acknowledgements

WJML was supported by the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/ 1).

Supplementary Material

Copies of ^{1}H and ^{13}C NMR data for all compounds; selected NOESY data, DFT workflow.

References

1. Robertson, J.; Naud, S. *Org. Lett.* **2008**, *10*, 5445. https://doi.org/10.1021/ol802138t
2. Rayment, E. J. *Chemistry Part II Thesis,* University of Oxford, 2009.
3. Höfler, C.; Rüchardt, C. *Liebigs Ann. Recl.* **1996**, 183.

https://doi.org/10.1002/jlac.199619960206
4. Baciocchi, E.; Giacco, T. D.; Elisei, F.; Lanzalunga, O. *J. Am. Chem. Soc.* **1998**, *120*, 11800. https://doi.org/10.1021/ja9820902
5. Yamamoto, S.; Sakurai, T.; Yingjin, L.; Sueishi, Y. *Phys. Chem. Chem. Phys.* **1999**, *1*, 833. https://doi.org/10.1039/a807337f
6. Fukuzumi, S.; Ohkubo, K.; Tokuda, Y.; Suenobu, T. *J. Am. Chem. Soc.* **2000**, *122*, 4286. https://doi.org/10.1021/ja9941375
7. Wurche, F.; Sicking, W.; Sustmann, R.; Klärner, F.-G.; Rüchardt, C. *Chem. Eur. J.* **2004**, *10*, 2707. https://doi.org/10.1002/chem.200305686
8. Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem. Int. Ed.* **1979**, *18*, 917. https://doi.org/10.1002/anie.197909171
9. Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148. https://doi.org/10.1021/ar00113a004
10. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6059. https://doi.org/10.1021/ja00772a020
11. Chatgilialoglu, C.; Lunazzi, L.; Macciantelli, D.; Placucci, G. *J. Am. Chem. Soc.* **1984**, *106*, 5252. https://doi.org/10.1021/ja00330a036
12. Liu, Y.; Liu, X.; Zhang, Y. *Tetrahedron Lett.* **2003**, *44*, 1667. https://doi.org/10.1016/S0040-4039(03)00030-3
13. Guindeuil, S. *PhD Thesis*, CNRS-École Polytechnique, 2006.
14. Wang, C.-M.; Song, D.; Xia, P.-J.; Wang, J.; Xiang, H.-Y.; Yang, H. *Chem. Asian J.* **2018**, *13*, 271. https://doi.org/10.1002/asia.201701738
15. Saitman, A. *PhD Thesis*, University of California – San Diego, 2013.
16. Liang, X.-T.; Sun, B.-C.; Liu, C.; Li, Y.-H.; Zhang, N.; Xu, Q.-Q.; Zhang, Z.-C.; Han, Y.-X.; Chen, J.-H.; Yang, Z. *J. Org. Chem.* **2021**, *86*, 2135. https://doi.org/10.1021/acs.joc.0c02494
17. Cuadros, S.; Horwitz, M. A.; Schweitzer-Chaput, B.; Melchiorre, P. *Chem. Sci.* **2019**, *10*, 5484. https://doi.org/10.1039/C9SC00833K
18. Maeta, N.; Kamiya, H.; Okada, Y. *J. Org. Chem.* **2020**, *85*, 6551. https://doi.org/10.1021/acs.joc.0c00544
19. Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6064. https://doi.org/10.1021/ja00772a020
20. Adam ,W.; Emmert, O.; Harrer, H. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 687. https://doi.org/10.1039/a607513d
21. Giese, B.; Meister, J. *Angew. Chem. Int. Ed.* **1977**, *16*, 178. https://doi.org/10.1002/anie.197701781
22. Giese, B.; He, J.; Mehl, W. *Chem. Ber.* **1988**, *121*, 2063. https://doi.org/10.1002/cber.19881211127
23. Giese, B. *Angew. Chem. Int. Ed.* **1983**, *22*, 753. https://doi.org/10.1002/anie.198307531
24. Firmenich, R.; Firmenich, G.; Firmenich R. E.; Firmenich, F. H.; GB 1,099,382, 1965.
25. Groen, M. B.; Hindriksen, B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 59. https://doi.org/10.1002/recl.19851040206

26. The half-wave potentials of furan and 2,5-dimethylfuran are 1.70 V and 1.20 V, respectively. Eberson, L.; Nyberg, K. *J. Am. Chem. Soc.* **1966**, *88*, 1686.
27. The reduction potential for **23***/**23**$^{-}$ = +1.45 V. Haga, M.-A.; Dodsworth, E. S.; Eryavec, G.; Seymour, P.; Lever, A. B. P. *Inorg. Chem.* **1985**, *24*, 1901.
28. *Cf.* Plutschack, M. B.; Seeberger, P. H.; Gilmore, K. *Org. Lett.* **2017**, *19*, 30. https://doi.org/10.1021/acs.orglett.6b03237
29. Tzirakis, M. D.; Lykakis, I. N.; Orfanopoulos, M. *Chem. Soc. Rev.* **2009**, *38*, 2609. https://doi.org/10.1039/b812100c
30. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. https://doi.org/10.1039/p19750001574
31. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373. https://doi.org/10.1016/S0040-4039(01)80821-2
32. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959 https://doi.org/10.1021/jo00382a001
33. Rondot, B.; Durand, T.; Girard, J. P.; Rossi, J. C.; Schio, L.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1983**, *34*, 8245. https://doi.org/10.1016/S0040-4039(00)61401-6
34. Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*, VCH, Weinheim, 1996. https://doi.org/10.1002/9783527615230
35. Duval, O.; Gomès, L. M. *Tetrahedron Lett.* **1988**, *29*, 3243. https://doi.org/10.1016/0040-4039(88)85132-3
36. Duval, O.; Gomès, L. M. *Tetrahedron* **1989**, *45*, 4471. https://doi.org/10.1016/S0040-4020(01)89082-7
37. Sun, M.; Deng, Y.; Batyreva, E.; Sha, W; Salomon, R. G. *J. Org. Chem.* **2002**, *67*, 3575. https://doi.org/10.1021/jo0105383