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

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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\textsuperscript{11} to activated alkenes is reported,\textsuperscript{12,13,14} and there are instances of direct reduction of \textit{bona fide} furfurylic radicals,\textsuperscript{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.\textsuperscript{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 ($k_{5\text{-}exo}/k_{6\text{-}endo} > 20 @ 70 ^\circ C$). 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.\textsuperscript{19} Given that a free radical generated at the $\alpha$-position in a 2-alkyl furan (i.e. a furfurylic free radical) is significantly more stabilised than an analogous benzylic radical,\textsuperscript{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;\textsuperscript{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\textsuperscript{24} or Horner–Wadsworth–Emmons olefination of aldehyde 19\textsuperscript{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\textsuperscript{26}. Initial efforts centred on a photoredox catalysis approach, using tris(2,2′-bipyrazyl)ruthenium(II) hexafluorophosphate 23 and irradiation with blue light\textsuperscript{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\textsuperscript{28}. Partial validation of the concept, however, was obtained by irradiating an acetonitrile solution of the substrate in the presence of tetrabutylammonium decatungstate (TBADT)\textsuperscript{29} which returned a 2:1 mixture of starting material and cyclised product 22 after 21 h.

![Scheme 5](image)

**Scheme 5.** (i) Ethyl acrylate, Hoveyda–Grubbs II catalyst (1 mol %), toluene, reflux, 50 min; (ii) triethyl phosphonoacetate, LiCl, DBU, CH\textsubscript{3}CN, RT, 17 h; (iii) O\textsubscript{2}, 23 (1 mol %), pyridine, hv (\(\lambda\text{max} = 480\) nm), aq. CH\textsubscript{3}CN, RT, 3 h; (iv) TBADT (2 mol %), hv (\(\lambda\text{max} = 365\) nm), CH\textsubscript{3}CN, 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\textsuperscript{30}. The substrate 25 bearing a terminal 5-methylfuranyl 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 \(\sigma\)-bond at the expense of the \(\pi\)-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 \textit{trans} and \textit{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.

\[
\begin{align*}
\text{Scheme 6. (i) CH}_2=\text{CH}(&\text{CH}_2)_3\text{MgBr, THF, 0 °C, 1 h (49%); (ii) ethyl acrylate, Hoveyda–Grubbs II catalyst (1 mol %), CHCl}_3, \text{reflux, 40 min (88%); (iii) thiocarbonyldiimidazole, DMAP, CH}_2\text{Cl}_2, 0 °C, 2.5 h (86%); (iv) HO(CH}_2)_5\text{P}^+\text{Ph}_3 \text{Br}^-, \text{BuLi, i-Pr}_2\text{NH, THF/toluene, 0 °C, 1 h (28%); (v) PhI(OAc)}_2, \text{TEMPO (5 mol%), NaHCO}_3, \text{CH}_2\text{Cl}_2, \text{RT, 24 h (50%); (vi) 5-methyl-2-furyllithium, THF, –78 °C to RT, 17 h (95%); (vii) as for (iii) (48%); (viii) Bu}_3\text{SnH, AIBN, benzene, reflux, 5.5 h; (ix) Ph}_3\text{SnH, AIBN, toluene-d}_8, \text{reflux, 1 h.}}
\end{align*}
\]

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;\textsuperscript{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.\textsuperscript{33} The formation of trans/cis mixtures suggests that either: (i) steric interactions between the furan and terminal group (=CHCO}_2\text{Et or }=\text{CHfuran) disfavour the ‘chair’/diequatorial transition state arrangement (cf. 28); or (ii) furfurylic radicals cyclise reversibly.\textsuperscript{34}

\[
\begin{align*}
\text{Scheme 7. Exclusive formation of a cis-1,2-cyclopentane from 5-exo-trig radical cyclisation.}
\end{align*}
\]
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

<table>
<thead>
<tr>
<th>Conformation</th>
<th>E_{DFT} / au</th>
<th>E_{rel} / kJ mol^{-1}</th>
<th></th>
<th>( \theta )</th>
<th>r(C3–C7) / Å</th>
<th>r(C2–C8) / Å</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (anti-cis)</td>
<td>-691.899207</td>
<td>0.00 (41.5)</td>
<td>144°</td>
<td>2.14</td>
<td>3.18</td>
<td></td>
</tr>
<tr>
<td>B (anti-trans)</td>
<td>-691.898954</td>
<td>+0.664 (33.6)</td>
<td>139°</td>
<td>2.15</td>
<td>3.74</td>
<td></td>
</tr>
<tr>
<td>C (gauche-trans)</td>
<td>-691.897832</td>
<td>+3.61 (12.8)</td>
<td>83°</td>
<td>2.15</td>
<td>3.74</td>
<td></td>
</tr>
<tr>
<td>D (anti-trans)</td>
<td>-691.897226</td>
<td>+5.20 (7.46)</td>
<td>144°</td>
<td>2.15</td>
<td>3.71</td>
<td></td>
</tr>
<tr>
<td>E (gauche-trans)</td>
<td>-691.896148</td>
<td>+8.03 (3.07)</td>
<td>91°</td>
<td>2.16</td>
<td>3.69</td>
<td></td>
</tr>
<tr>
<td>F (gauche-cis)</td>
<td>-691.895419</td>
<td>+9.95 (1.62)</td>
<td>103°</td>
<td>2.14</td>
<td>3.18</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 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.
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 furfuryl 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 (N₂ 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 KMnO₄, 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 ¹³C 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: CDCl₃, 7.26/77.16; CD₂Cl₂, 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 FeSO₄·7H₂O (600 mg, 2.16 mmol) and 2-(4-hydroxybutyl)furan³⁷ (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 H₂O₂ 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 (MgSO₄), filtered, and concentrated. Flash chromatography (petrol/ethyl acetate, 80:20) furnished the title compound as a colourless oil (113 mg, 70%). R₇ 0.25 (petrol/ethyl acetate, 50:50); IR (thin film) ν_{max}/cm⁻¹ 3419br, 2940m, 1739s, 1566m, 1226w, 1031s; ¹H NMR (500 MHz, CDCl₃) δ₁H 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); ¹³C NMR (126 MHz, CDCl₃) δ₁C 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 C₁₂H₂₈NaO₄ 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 Na₂S₂O₃·xH₂O (50 mL); stirring was continued for 20 min and the layers were separated. The organic layer was was washed with saturated aqueous NaHCO₃ solution (2 x 25 mL) and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic portions were dried (MgSO₄), 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 – R₇ 0.20 (petrol/ether, 90:10); IR (thin film) ν_{max}/cm⁻¹ 2949s, 1702s, 1647s, 1584m, 1444m; ¹H NMR (400 MHz, CDCl₃) δ₁H 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); ¹³C NMR (101 MHz, CDCl₃) δ₁C 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 C₁₂H₁₆NaO₄; 247.0941, found 247.0938. Data for Z-10 – R₇ 0.20 (petrol/ether, 80:20) 0.30; IR (thin film) ν_{max}/cm⁻¹ 2950s, 1711s, 1648s, 1590w, 1444w; ¹H NMR (400 MHz, CDCl₃) δ₁H 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); ¹³C NMR (101 MHz, CDCl₃) δ₁C 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 C₁₂H₁₆NaO₄; 247.0941, found 247.0943.
Ethyl (E)-7-(5-methylfuran-2-yl)hept-2-enolate (20)

By cross-metathesis. To a solution of alkenes 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 (2H, 1H, 1H) at 0.5 mL/m, 2H, 3H, then transferred directly to a silica gel column for chromatography (petrol/ether, 50:50) which afforded the title compound as a geranium-scented colourless oil (125 mg, 88%). Rf 0.65 (petrol/ether, 80:20); IR (thin film) νmax/cm⁻¹ 2934w, 1718s, 1178s, 779s; ¹H NMR (400 MHz, CDCl₃) δH 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); ¹³C NMR (101 MHz, CDCl₃) δC 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⁺, NH₃) m/z [M+H]⁺ calculated for C₁₂H₂₂O₃. 237.1485; found, 237.1484.

Ethyl (2E)-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 O₂ was bubbled from a balloon through the mixture. The solution was irradiated at RT by a blue LED lamp (λmax = 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). Rf 0.10 (petrol/ether, 50:50); ¹H NMR (400 MHz, CDCl₃) δH 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); ¹³C NMR (101 MHz, CDCl₃) δC 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]⁺ calculated for C₁₃H₂₂O₄, 253.1436; 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 cloudy, 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 NH₄Cl 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 (MgSO₄), 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%). Rf 0.70 (dichloromethane/ethanol acetate, 90:10); IR (thin film) νmax/cm⁻¹ 3354br, 1020m, 996m, 910m, 783m; ¹H NMR (400 MHz, CDCl₃) δH 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); ¹³C NMR (101 MHz, CDCl₃) δC 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]⁺ calculated for C₁₃H₁₇O₂, 181.1223; found, 181.1226.
Ethyl (E)-7-hydroxy-7-(5-methylfuranc-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%). Rf 0.15 (petrol/ether 70:30); IR (thin film) νmax/cm⁻¹ 3428br, 1716s, 1652m, 1185s, 1040s, 1020s, 784s; 1H NMR (400 MHz, CDCl₃) δH 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); 13C NMR (101 MHz, CDCl₃) δC 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+, NH₃) m/z [M+NH₄⁺]⁺ calcld for C₁₄H₂₄NO₄, 270.1700; found, 270.1695.

Ethyl (E)-7-[(1H-imidazole-1-carboxyloxy)-7-(5-methylfuranc-2-yl)hept-2-enoate (24). To a solution of thiocarboxylyl diimidazole (85.0 mg, 0.477 mmol) in dichloromethane (0.8 mL) at 0 °C and under N₂ 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%). Rf 0.35 (dichloromethane/methanol, 95:5); IR (thin film) νmax/cm⁻¹ 1715s, 1692s, 1654w, 1287m, 1270m, 1214s, 884s; 1H NMR (500 MHz, C₆D₆) δH 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); 13C NMR (126 MHz, C₆D₆) δC 166.0, 165.2, 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+, NH₃) m/z [M–C₃H₇N₂O⁺]⁺ calcld for C₁₄H₁₉O₃, 235.1329; found 235.1320.

Ethyl 2-[(5-methylfuranc-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 1H NMR integration) as a colourless oil (4.3 mg, 37%). Rf 0.30 (petrol/ether, 90:10); IR (thin film) νmax/cm⁻¹ 2956m, 1735s, 1178m, 1023m, 781m; 1H NMR (500 MHz, C₆D₆) δH 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); 13C NMR (126 MHz, C₆D₆) δC 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+, NH₃) m/z [M+H⁺]⁺ calcld for C₁₄H₂₁O₃, 237.1485; found, 237.1492.

6-(5-Methylfuranc-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 N₂ 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 NH₄Cl 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 (E/Z, 70:30 by ¹H NMR integration) and as a golden oil (2.32 g, 28%). Rf 0.20 (dichloromethane/methanol, 98:2); IR (thin film) ν_max/cm⁻¹ 3343br, 2928s, 2860m, 1020s, 781s; ¹H NMR (400 MHz, CDCl₃) δ_H [data for ⁻S⁻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⁻S⁻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)]; ¹³C NMR (101 MHz, CDCl₃) δ_C [data for ⁻S⁻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⁻S⁻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+, NH₃) m/z [M+H]^+ calcd for C₁₃H₁₂O₂, 181.1223; found, 181.1226.

(E)-6-(5-Methylfuran-2-yl)hex-5-en-1-ol (S⁵). To a solution of alcohol S₃ (700 mg, 3.88 mmol) in dichloromethane (53 mL) was added NaHCO₃ (1.63 g, 19.4 mmol). The mixture was cooled to 0 °C, placed under N₂, 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 Na₂S₂O₃·xH₂O solution (2 × 30 mL), water (20 mL) and brine (20 mL), and the organic phase was separated and dried (MgSO₄), 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 ¹H 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 K₂CO₃ (13.5 mg, 0.098 mmol) and a solution of I₂ (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 Na₂S₂O₃·xH₂O solution (2 × 1 mL). The organic phase was passed through a plug of Na₂SO₄, then concentrated to afford the title compound as a yellow oil (94 mg, 94%). Rf 0.60 (dichloromethane); IR (thin film) ν_max/cm⁻¹ 2926w, 1724s, 1020m, 996w, 785s; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 C₁₃H₁₇O₂, 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 NH₄Cl solution (1 mL) and extracted with ethyl acetate (3 × 2 mL). The combined organic phases were washed with brine (3 mL), dried (Na₂SO₄), filtered and concentrated to afford the title compound as a pale-yellow oil (130 mg, 95%). Rf 0.10 (petrol/ether, 80:20); IR (thin film) ν_max/cm⁻¹ 3389br, 2944w, 1020s, 962m, 782s; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (101 MHz, CDCl₃) 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+, NH₃) m/z [M+H]+ calcd for C₁₆H₂₁O₃, 261.1485; found, 261.1487.

O-[1,6-Bis(5-methylfuran-2-yl)hex-5-en-1-yl]-1H-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 N₂ in the dark (aluminium foil) for 2.2 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%). Rf 0.10 (dichloromethane); IR (thin film) νₘₐₓ/cm⁻¹ 1692s, 1216s, 885s; ¹H NMR (400 MHz, C₆D₆) δH 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); ¹³C NMR (101 MHz, C₆D₆) δC 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–C₄H₆N₂O₅]+ calcd for C₁₆H₁₉O₂, 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), triphenylstanannane (48.5 mg, ~60% by ¹H NMR integration, 0.0829 mmol), and AIBN (3.0 mg, 0.018 mmol) in toluene–d₈ (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 triphenylstanannane (22.5 mg, ~60% by ¹H NMR integration, 0.0385 mmol) in toluene–d₈ (0.25 mL) and AIBN (1.5 mg, 0.0091 mmol) in toluene–d₈ (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 ¹H NMR integration) as a colourless oil (8.0 mg, 36%). Rf 0.80 (pentane); IR (thin film) νₘₐₓ/cm⁻¹ 2951s, 2922s, 2873m, 1568s, 1219s, 1021s, 778s; ¹H NMR (400 MHz, C₆D₆) δH 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); ¹³C NMR (101 MHz, C₆D₆) δC 157.0, 156.0, 154.4, 153.9, 150.5, 150.5, 150.5, 150.3, 150.2, 150.2, 150.0, 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 C₁₆H₁₉O₂, 243.1536; found, 245.1537.

Ethyl 2-[2-(furan-2-yl)cyclopent-1-en-1-yl]acetate (31). To a solution of carbethoxymethyleneetriphenylphosphorane (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 tetrastubstituted alkene isomer usually dominated, as a colourless to pale orange oil (41 mg, 28%; 46% based on recovered ketone). Rf 0.30 (petrol/ether, 92:8); IR (thin film) νₘₐₓ/cm⁻¹ 1732s, 1655w, 1177s, 1155s, 1035m, 1009m, 732s; ¹H NMR (400 MHz, CDCl₃) δH 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); ¹³C NMR (101 MHz, CDCl₃) δC 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+, NH₃) m/z [M+H]+ calcd for C₁₃H₁₇O₃, 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 N₂. The flask was filled with N₂ via three pump-fill cycles. A balloon of H₂ was attached to the three-way valve and the flask refilled with H₂ via three pump-fill cycles. The mixture was allowed to thaw, stirred for 16 h, re-frozen in liquid N₂, and the flask refilled.
with N₂ 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 ¹H 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 ¹H NMR integration). Data for cis-32: Rf 0.30 (petrol/ether, 90:10); IR (thin film) νmax/cm⁻¹ 2961w, 1734s, 1164m, 731w; ¹H NMR (500 MHz, C₆D₆) δH 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); ¹³C NMR (126 MHz, C₆D₆) δC 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+, NH₃) m/z [M+H]⁺ calcld for C₁₃H₁₉O₃, 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): Rf 0.30 (petrol/ether, 90:10); ¹H NMR (500 MHz, C₆D₆) δH 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); ¹³C NMR (126 MHz, C₆D₆) δC 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-(phenylselenanyl)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 Br₂ (100 μL, 1.95 mmol) in THF (7.0 mL), both under Ar. A portion of the Br₂ solution (0.5 mL, ~0.14 mmol Br₂) 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 Na₂S₂O₃·xH₂O solution (2 mL) and saturated aqueous NH₄Cl 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 (MgSO₄), 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: Rf 0.10 (petrol/ether, 98:2); IR (thin film) νmax/cm⁻¹ 2960w, 1725s, 1147m, 737s, 692m; HRMS (EI+) m/z [M⁺]⁺ calcld for C₁₉H₂₂O₃Se, 378.0729; found, 378.0727. NMR data for major diastereomer: ¹H NMR (400 MHz, C₆D₆) δH 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); ¹³C NMR (101 MHz, C₆D₆) δC 172.3, 157.3, 141.3, 135.8, 129.1, 110.2, 107.4, 60.5, 46.4, 46.2, 41.2, 41.1, 31.1, 29.7, 23.9, 14.0 (two phenyl resonances obscured by solvent.
NMR data for minor diastereomer: $^1$H NMR (400 MHz, CD$_6$OD) $\delta$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, CD$_6$D) $\delta$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). $^1$H NMR (92 MHz, CD$_6$D$_2$; referenced to CD$_3$OD as an internal standard, @ 7.16 ppm) $\delta$H 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, CD$_6$D$_2$) $\delta$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, dd, $J = 7.5, 3.0$ 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$_2$CO$_2$Et overlaying CHD 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, CD$_6$D$_2$) $\delta$C 172.6, 157.7, 141.3, 110.2, 106.3, 59.9, 41.7, 40.7, 36.3 (residual CH$_2$CO$_2$Et), 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, CD$_6$D$_2$) $\delta$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, CD$_6$D$_2$) $\delta$C 172.2, 158.2, 141.3, 110.3, 104.8, 60.0, 45.0, 42.4, 39.2 (residual CH$_2$CO$_2$Et), 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.

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**Supplementary Material**

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

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