DOI: 10.1002/ejoc.200700367

Investigating Direct Access to 2-Oxospiro[4.5]decanones via 6π-Electrocyclisation

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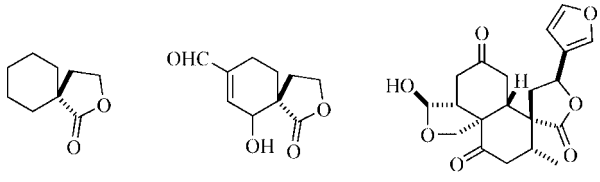
Keywords: 2-Oxospiro[4.5]decan-1-one / Spirolactones / Microwave irradiation / Electrocyclic reactions / Calculations

The 2-oxospiro[4.5]decan-1-one (or spiro-γ-lactone) structural motif is contained within a number of natural products, for example, the clerodane family of diterpenes. Methods to construct this structural motif are somewhat limited and usually involve multiple functional group interconversions. A novel synthetic approach to this system utilising 6π-electrocyclisation has been identified and associated density functional calculations performed. Details of the scope, limitations, and ramifications of this methodology are discussed.

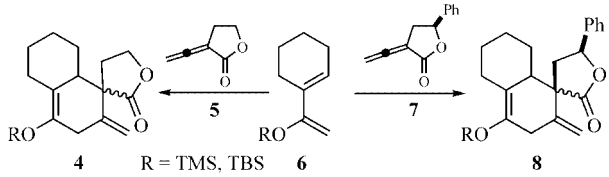
The 2-oxospiro[4.5]decan-1-one (**1**) structural motif exists within a number of natural product groups [e.g. canangone (**2**),[1] teusalvin A (**3**)[2]], of which the clerodanes[3] (i.e. **3**) are a major contributor (Figure 1).



1 Canangone **2** Teusalvin A **3**

Figure 1. Examples of the 2-oxospiro[4.5]decan-1-one structural motif in nature.

Considering the usual mode of 2-oxospiro[4.5]decan-1-one construction is to assemble the lactone portion at a later stage,[4–14] which often involves multiple steps, we contemplated the approach of initial γ-lactone inclusion (i.e. construction of the six-membered ring at the later stage). Although this approach presents limitations it does open additional avenues for constructing the 2-oxospiro[4.5]-decan-1-one structural motif (**1**) directly. In this regard we are only aware of two examples that fit this criterion.[15–16] Of note is the Diels–Alder approach reported by Jung et al.[15] in which allenic lactones **5** and **7** were treated with diene **6** affording the 2-oxospiro[4.5]decan-1-ones **4** and **8** (Scheme 1).



Scheme 1. Diels–Alder approach to the 2-oxospiro[4.5]decan-1-one structural motif.

With these examples in mind, it seemed reasonable that a 6π-electrocyclisation approach to the six-membered ring (i.e. 2-oxospiro[4.5]decan-1-ones of type **4** and **8**) was worthy of investigation. For example, the lactone trienes **9** and **10**, via thermal or photochemical conditions, could be transformed into cyclised adducts **11** (**12**) and **13** (**14**), which then have the potential to undergo [1,5]-hydrogen shifts, affording the dienes **15** (**16**) and **17** (**18**). An additional advantage to this approach would be the relative stereocontrol of the products as described by the Woodward–Hoffmann principles[17–19] (Scheme 2).

To test the viability of this method a suite of compounds of type **9** were synthesised in good to excellent yields by Sonogashira coupling[20–22] of the corresponding alkyne, followed by partial hydrogenation to give the *cis*-alkenes **28**–**31**, **38**–**40** (Scheme 3), as well as **45** and **46** (Scheme 4).

The partial hydrogenation of these systems was at times capricious, however, neither diimide or boron mediated reduction gave satisfactory results. Furthermore, all attempts to reduce **27** to **31** failed. Though direct synthesis of the aromatic dienes and trienes through Stille coupling is an appealing route, it was found that the triflate **23** did not react with vinyl stannanes at temperatures low enough to

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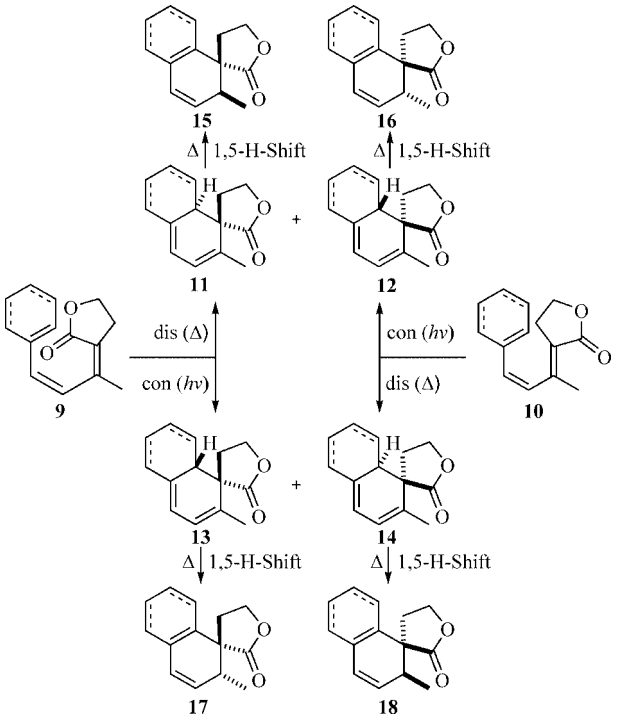
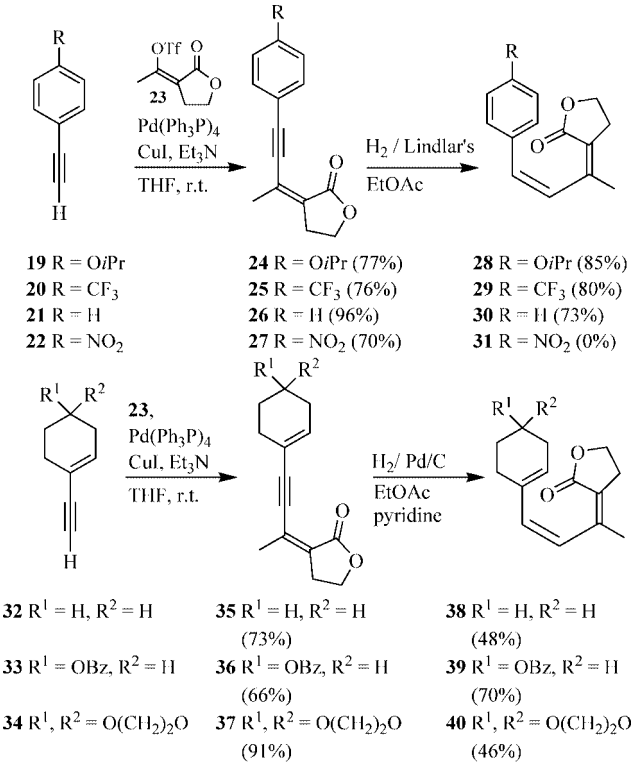
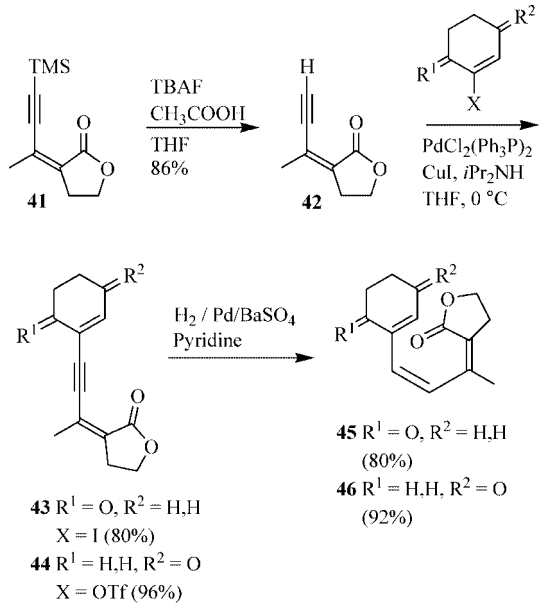


Scheme 2. Electrocyclisation approach to the 2-oxospiro[4.5]decan-1-one structural motif.

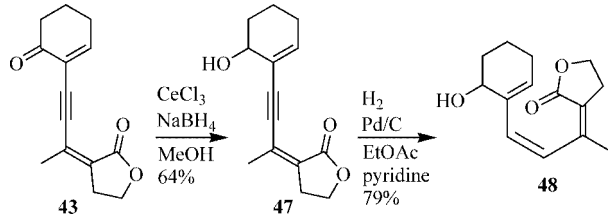


Scheme 3. Construction of trienes **28**–**31** and **38**–**40** by Sonogashira/partial hydrogenation sequence.

avoid significant isomerisation of the *cis*-alkene. Luche reduction[23] of the enone **43** to give **47**, followed by partial hydrogenation gave allylic alcohol **48** in good yield (Scheme 5).



Scheme 4. Synthesis of trienes **45** and **46**.

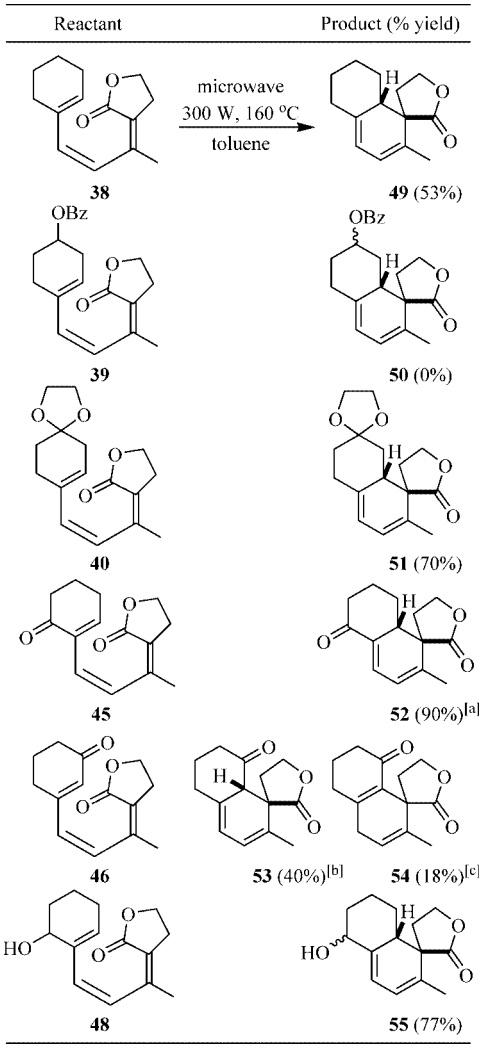


Scheme 5. Synthesis of triene **48** via Luche reduction and partial hydrogenation.

Surprisingly, all of the aromatic substrates failed to undergo cyclisation when exposed to either light (broad spectrum, 254 and 300 nm, with and without I_2), conventional heating (up to 220 °C) or microwave irradiation (up to 220 °C) (toluene, diphenyl ether, toluene/SiO_2). Even flash vacuum pyrolysis (up to 600 °C) failed. The only observable products were due to partial double bond isomerisation. This lack of success was somewhat intriguing as there is literature precedent on related systems.[24–26]

Success, however, was found in the cyclisation of the non-aromatic triene substrates **38**, **40**, **45**, **46**, and **48** (Table 1). The optimal conditions for cyclisation were found to be microwave irradiation in toluene at 300 W with a maximum reaction temperature of 160 °C, which gave cyclised product in good yield. For reasons unknown, the benzoyl-substituted **39** failed to react. Triene **45**, however, cyclised at only 100 °C to give **52** in excellent yield, the structure of which was confirmed by X-ray crystallography (Figure 2). We attribute this reactivity to a lowering of the transition state through a capto-dative effect,[27] induced by the electron-withdrawing effect of the ketone substituent with respect to the β-carbon.

Table 1. 6π Electrocyclisation of trienes **38**–**40**, **45**–**46**, and **48**.



[a] Reaction performed at 100 °C. [b] Non-isolated yield calculated by ^{1}H NMR spectroscopy. [c] Isolated from attempted purification using silica gel and neutral Al_2O_3 chromatography.

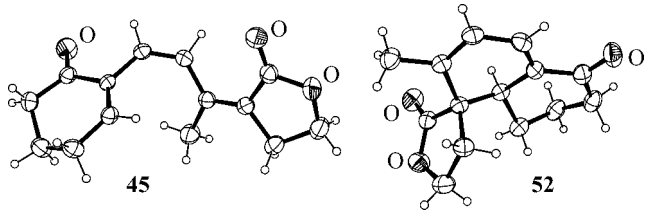
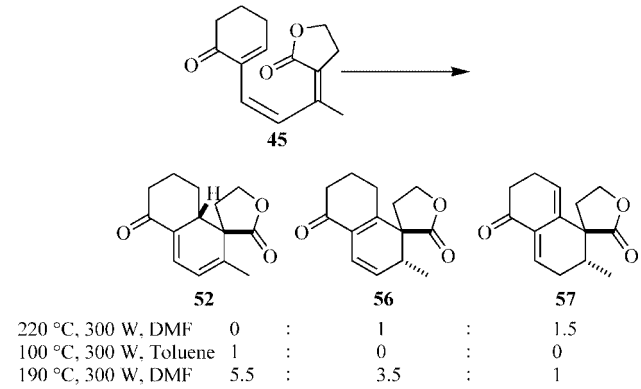


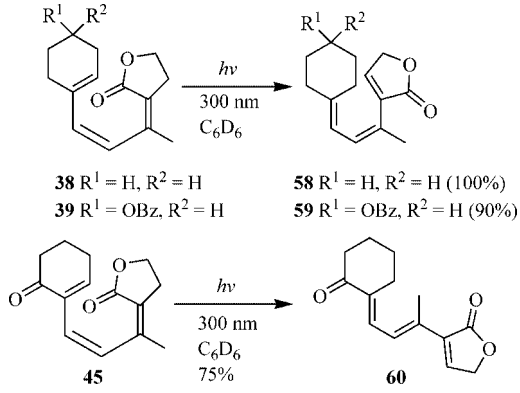
Figure 2. Molecular structure of compounds **45** and **52** (30% probablity ellipsoids).

Adding further to the utility of this reaction, it was found that a rearrangement of **52** could be driven at higher temperatures (Scheme 6). If the temperature was elevated to 220 °C (MW) using dimethylformamide as solvent the [1,5]-hydrogen shift product **56** could be obtained along with the isomeric diene **57** (1:1.5, 96%), which was separable using silver nitrate impregnated silica gel chromatography.[28] Lowering the temperature to 190 °C using dimethylformamide as solvent gave rise to all three products **52**, **56** and **57**. The unexpected formation of **57** can most likely be attributed to dimethylformamide slowly decomposing at high temperature affording dimethylamine which catalysed the isomerisation.



Scheme 6. Thermal and base-catalysed rearrangements of **52**.

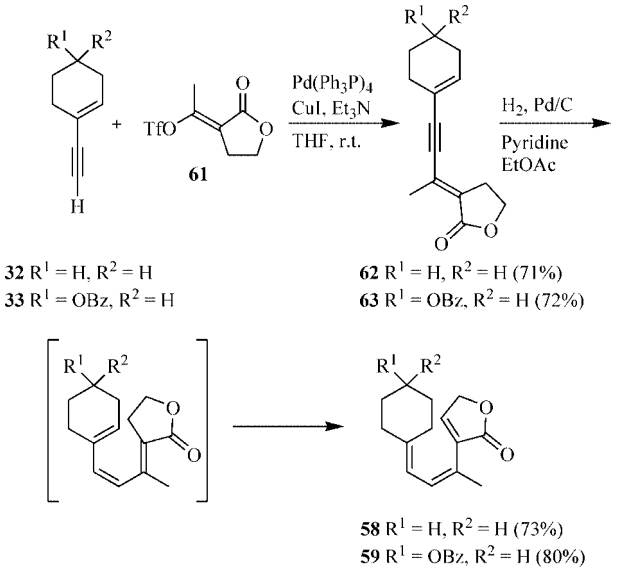
In an attempt to obtain the opposite relative stereochemistry, the trienes **38**, **39**, and **45** were subjected to photochemical irradiation. Suprisingly, when irradiated at 300 nm only the products of a [1,7]-hydrogen shift were obtained, i.e. **58**, **59**, and **60**, respectively (Scheme 7). Irradiation at 254 nm gave a gross mixture of products resulting from isomerisation of the double bonds.



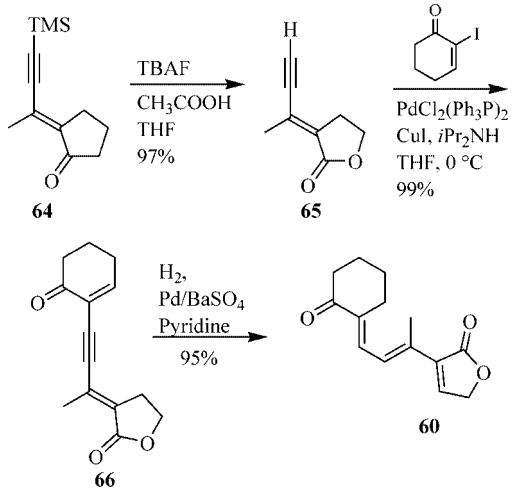
Scheme 7. Photochemical irradiation of trienes **38**, **39**, and **45**.

Attempts to synthesise the *trans*-lactones fell to a similar fate. While the Sonogashira couplings of triflate **61** with acetylenes **32** and **33** proceeded in good yield to give **62** and **63** respectively, partial hydrogenation did not afford the desired triene, but the products of [1,7]-hydrogen shift, **58** and **59**, respectively (Scheme 8).

This was also the case in the partial hydrogenation of **66** (Scheme 9). Although [1,7]-hydrogen shifts are known to occur in preference to 6π-electrocyclisation[29] it is also known that subjection to high temperatures drives cyclisation,[30] however, subjecting **58** to increased temperatures failed to afford any cyclised material.



Scheme 8. Attempted synthesis of *trans*-lactones from substrates **62** and **63**.



Scheme 9. Attempted synthesis of *trans*-lactones from substrate **66**.

To add further understanding to these results, a computational study was undertaken in which heats of formation of starting materials, the products of the electrocyclisation and the [1,5]-hydrogen shifts, and the transition states for these transformations were examined. Thus, unrestricted geometry optimisations including full frequency calculations were performed at the B3LYP/6-31g(d) level of theory.[31] Although other functionals (viz. MPW1K) perform better in the calculation of barrier heights for pericyclic reactions they give only poor results for reaction enthalpies.[32–33] The enthalpies of formation were calculated using an atomisation scheme at standard conditions (25 °C, 1 atm) using unscaled frequencies.[34] Calculations have been carried out for both the thermal and the photochemical pathways,[35] results of which are summarised in Figure 3. Detailed results as well as structural representations and atomic coordinates for all calculated structures can be found in the Supporting Information.

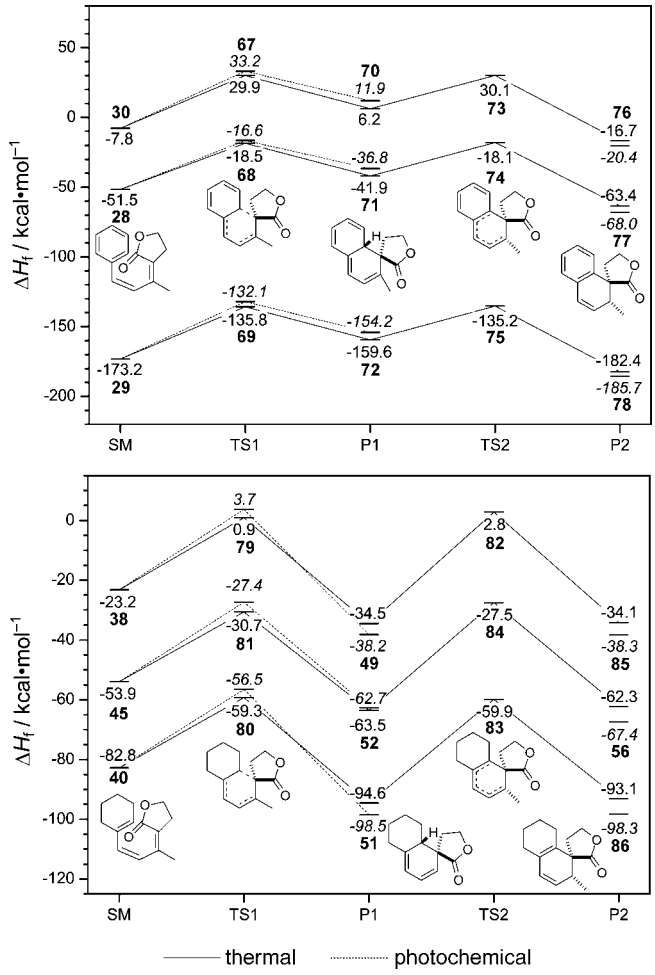


Figure 3. Calculated energy profiles for the cyclisation reactions of compounds **28**–**30** (top) and for the saturated series **38**, **40**, and **45** (bottom). Enthalpy values in italics refer to the photochemical pathway.

The calculated enthalpies of activation ($\Delta\Delta H$) for the electrocyclisations were predicted to range from 33.0 to 37.7 kcal/mol for thermally induced processes and to be 34.9–41.1 kcal/mol for photochemical induction for the aromatic compounds **28**–**30**. The reaction enthalpies leading to the electrocyclisation products **70**–**72** were predicted to be endothermic by ca. 10–20 kcal/mol owing to the lack of the aromatic stabilisation. For the photochemical processes,[35] the predicted cyclisation barriers are ca. 2–4 kcal/mol higher than for the thermal processes. Calculations performed on the hexatrienes **38**, **40**, and **45** on the other hand predicted exothermic cyclisation processes and significantly lower activation energies for the thermal pathway (23.2–24.1 kcal/mol) and the photochemical induced processes (26.3–26.9 kcal/mol).

Additionally, the enthalpies of the transition states for the [1,5]-shifts of the thermal cyclisation products have been calculated, to compare the activation enthalpy with experimentally determined values for unsubsituted 1,3-cyclohexadiene ($\Delta\Delta H$ = 39.0 kcal/mol for interconversions of 2-*d*-1,3-cyclohexadiene;[36] similar values have been obtained for

1,4-d_2-1,3-cyclohexadiene[37] and by calculations[38]), which is considerably higher than that for the 6π-electrocyclisation of the unsubstituted (*Z*)-hexa-1,3,5-triene ($\Delta\Delta H$ = 29.1 kcal/mol determined experimentally;[39] calculations on various levels of theory agreed with this[32]). However, in the aromatic series **28**–**30**, these activation enthalpies are predicted to be much smaller (23.8–24.4 kcal/mol) owing to the energetically unfavourable cyclisation products **67**–**69** which already possess rather high ground state energies. For the saturated compounds **38**, **40**, and **45**, the activation enthalpies ($\Delta\Delta H$ of 35.1–37.3 kcal/mol) are in line with those for the unsubstituted parent system.

Although the activation energies for the [1,5]-shifts of the saturated system are predicted to be significantly higher than those for the aromatic system, these processes are still considered feasible, since the absolute values of the enthalphies for TS2 barely differ from those for TS1 in this series. Thus, when the system is provided with enough energy to cross the first barrier (TS1) it should suffice for the second transition state. For the aromatic compounds **28**–**30**, however, the second barrier height is only lower due to the non-stabilised electrocyclisation products **70**–**72**. The energy to cross TS1 constitutes the highest barrier in these systems and the height of this barriers renders the reaction of the aromatic systems impossible.

In conclusion, it has been found that 2-oxospiro[4.5]-decanones can be constructed by 6π-electrocyclisation, however, only certain hexatrienes are amenable to this process, which concur with theoretical predictions.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV300 (300.13 MHz; 75.47 MHz), AV400 (400.13 MHz; 100.62 MHz) and a DRX500 (500.13 MHz; 125.77 MHz) in deuteriochloroform ($CDCl_3$) or hexadeuteriobenzene (C_6D_6) unless otherwise stated. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. High and low resolution EI mass spectroscopic data were obtained with a KRATOS MS 25 RFA. Electrospray negative and positive ion mass spectra were measured in methanol solutions with a Finigan Mat 900 XL-Trap. Microanalyses were performed by the University of Queensland Microanalytical Service. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. Tetrahydrofuran was freshly distilled from a sodium/benzophenone still. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected.

Typical Sonogashira Procedure (Compounds 24–27, 35–37, and 62–63)

(*Z*)-3-(4-Cyclohexenylbut-3-yn-2-ylidene)dihydrofuran-2(3*H*)-one (35): A solution of triflate **23**[40] (175 mg, 0.67 mmol) and 1-ethynylcyclohexene (**32**) (100 mg, 0.94 mmol) was added to copper iodide (13 mg, 0.07 mmol) and tetrakis(triphenylphosphane)palladium (39 mg, 0.04 mmol) in anhydrous tetrahydrofuran (6 mL) and anhydrous triethylamine (0.29 mL, 2.03 mmol) by cannula under argon. The reaction was degassed (freeze-thawed) and stirred for 1.5 h, after which time the reaction was diluted with brine (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phase was washed with saturated ammonium chloride solution (2 × 10 mL) and then dried with magnesium sulfate. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (1:1 petroleum ether/diethyl ether) to give the title compound **35** as a white powder (106 mg, 73% yield). The powder was recrystallised from dichloromethane/petroleum ether to give colourless needles. M.p. 44–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.64 (m, 4 H), 1.98 (t, *J* = 1.8 Hz, 3 H), 2.05–2.20 (m, 4 H), 2.85–2.95 (m, 2 H), 4.22–4.27 (m, 2 H), 6.22–6.25 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 22.1, 22.8, 25.8, 27.8, 28.7, 63.9, 85.9, 102.4, 120.8, 127.2, 128.7, 137.5, 168.4 ppm. MS (EI): *m*/*z* (%) = 217 (15), 216 (100) [M$^+$], 215 (20), 210 (14), 187 (14), 173 (20), 157 (19), 145 (24), 143 (28), 131 (18), 130 (15), 129 (38), 128 (36), 117 (23), 115 (39), 105 (23), 93 (14), 91 (53), 80 (17), 79 (32), 78 (19), 77 (47). HRMS (EI): calcd. for $C_{14}H_{16}O_2$: (M$^+$) 216.1150, found 216.1149.

Typical Procedure for Partial Hydrogenation (Compounds 28–30)

(*Z*)-3-[(*Z*)-4-(4-Isopropoxyphenyl)but-3-en-2-ylidene]dihydrofuran-2(3*H*)-one (28): Lindlar's catalyst (30 mg, 5% palladium poisoned with lead) was added to a solution of **24** (250 mg, 0.93 mmol) in freshly distilled ethyl acetate (10 mL) and the vessel was flushed with hydrogen gas and stirred for 1.5 h. The mixture was filtered through Celite®, the solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (1:1 petroleum ether/diethyl ether) to give the title compound **28** as a pale yellow powder (213 mg, 85% yield). The powder was recrystallised from diethyl ether/petroleum ether to give large pale yellow needles. M.p. 54–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.1 Hz, 6 H), 1.77 (br. s, 3 H), 2.89–2.94 (m, 2 H), 4.33–4.37 (m, 2 H), 4.52 (sept, *J* = 6.1 Hz, 1 H), 6.63 (d, *J* = 12.2 Hz, 1 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 7.07 (d, *J* = 12.2 Hz, 1 H), 7.10 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.5, 22.0, 27.9, 64.5, 69.8, 115.3, 121.7, 127.4, 129.7, 130.3, 132.8, 147.9, 157.5, 169.8 ppm. MS (EI): *m*/*z* (%) = 273 (19), 272 (94) [M$^+$], 230 (36), 215 (15), 202 (100), 185 (25), 184 (25), 172 (18), 171 (81), 157 (40), 153 (11), 141 (13), 128 (23), 115 (20), 107 (20), 77 (18). HRMS (EI): calcd. for $C_{17}H_{20}O_3$ (M$^+$) 272.1412, found 272.1406.

Typical Procedure for Partial Hydrogenation (Compounds 38–40, 48, and 58–59)

(*Z*)-3-[(*Z*)-4-Cyclohexenylbut-3-en-2-ylidene]dihydrofuran-2(3*H*)-one (38): 10% palladium on carbon (4 mg) and 1 drop of pyridine was added to the dienyne **35** (40 mg, 0.19 mmol) in distilled ethyl acetate (2 mL). The vigorously stirring mixture was flushed with hydrogen gas and stirred for 1 h. The mixture was filtered, and the solvent removed in vacuo. The residue was subjected to the same reaction conditions a further 3 times after which time the ratio between starting material and desired product was approximately 1:1 by ^{1}H NMR spectroscopy. The residue was purified by silica gel column chromatography (2:1 petroleum ether/diethyl ether) to give the title compound **38** as a colourless oil (19 mg, 48% yield, 92:8 *Z*/*E*). ^{1}H NMR (400 MHz, C_6D_6): δ = 1.33–1.52 (m, 4 H), 1.67 (dt, *J* = 1.7, 0.6 Hz, 3 H), 1.86–2.00 (m, 6 H), 3.50–3.55 (m, 2 H), 5.58 (m, 1 H), 5.97 (d, *J* = 11.9 Hz, 1 H), 7.35 (d, *J* = 11.9 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, C_6D_6): δ = 21.2, 22.3, 22.9, 26.0, 27.6, 28.5, 63.6, 122.0, 127.3, 128.6, 136.0, 136.2, 146.5, 168.9 ppm. MS (EI): *m*/*z* (%) = 218 (47) [M$^+$], 203 (87), 190 (31), 185 (15), 173 (16), 172 (100), 159 (20), 146 (17), 145 (92), 144 (23), 131 (54), 130 (14), 129 (32), 128 (21), 118 (31), 117 (36), 115 (23), 105 (28), 91 (45), 77 (24). HRMS (ESI, pos.): calcd. for $C_{14}H_{18}NaO_2$ [M + Na]$^+$ 241.1204, found 241.1201.

Typical Sonogashira Procedure (Compounds 43–44, and 66)

(*Z*)-3-[4-(6-Oxocyclohexenyl)but-3-yn-2-ylidene]dihydrofuran-2(3*H*)-one (43): Diisopropylamine (0.43 mL, 3.07 mmol) was added

to a solution of the enyne **42** (210 mg, 1.54 mmol), 2-iodocyclohex-2-enone[41] (230 mg, 1.04 mmol), $PdCl_2(Ph_3P)_2$ (37 mg, 0.05 mmol), and copper iodide (20 mg, 0.11 mmol) in anhydrous tetrahydrofuran (10 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min, and then diluted with diethyl ether (20 mL), and the organic phase was washed with 1 M HCl solution (1 × 5 mL), and brine (1 × 5 mL), and then dried with magnesium sulfate. The residue was purified by silica gel column chromatography (14:1 diethyl ether/petroleum ether) to give the title compound **43** as a white powder (191 mg, 80% yield). The powder was recrystallised from dichloromethane/petroleum ether to give large colourless needles. M.p. 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00–2.07 (m, 2 H), 2.08 (t, J = 1.8 Hz, 3 H), 2.46–2.52 (m, 4 H), 2.95–3.01 (m, 2 H), 4.30–4.34 (m, 2 H), 7.48 (t, J = 4.5 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 22.2, 22.7, 26.6, 27.8, 38.0, 64.1, 90.3, 94.5, 125.1, 128.1, 128.9, 156.4, 168.3, 195.2 ppm. MS (EI): m/z (%) = 230 (24) [$M^{+\cdot}$], 207 (14), 84 (22). HRMS (ESI, pos.): calcd. for $C_{14}H_{14}NaO_3$ [M + Na]$^+$ 253.0841, found 253.0835. $C_{14}H_{14}O_3$ (230.25): calcd. C 73.03, H 6.13; found C 72.95, H 6.17.

Typical Procedure for Partial Hydrogenation (Compounds 45–46, and 60)

(*Z*)-3-[(*Z*)-4-(6-Oxocyclohexenyl)but-3-en-2-ylidene]dihydrofuran-2(3*H*)-one (45): Palladium on barium sulfate (5 mg) in distilled methanol (1 mL) was purged with hydrogen, and the solution became black. Dienyne **43** (20 mg, 0.09 mmol) in pyridine (2 mL) was added and the reaction was stirred for 10 min, after which time the solution was filtered through celite. The solvent was removed in vacuo and the residue was subjected to the same conditions. The residue was purified by silica gel column chromatography (5:1 diethyl ether/petroleum ether) to give the title compound **45** as a white powder (16 mg, 80% yield), which was recrystallised from dichloromethane/petroleum ether to give small colourless needles. M.p. 95–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.87 (dt, J = 1.7, 0.6 Hz, 3 H), 1.98–2.05 (m, 2 H), 2.38–2.43 (m, 2 H), 2.45–2.50 (m, 2 H), 2.86–2.93 (m, 2 H), 4.32–4.36 (m, 2 H), 6.35–6.41 (m, 1 H), 6.75–6.80 (m, 1 H), 7.14–7.21 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.3, 22.6, 26.6, 27.9, 38.3, 64.5, 122.5, 128.1, 130.5, 137.2, 146.7, 149.2, 169.6, 198.1 ppm. MS (ESI, pos.): m/z = 255 [M + Na]$^+$. HRMS (ESI, pos.): calcd. for $C_{14}H_{16}NaO_3$ [M + Na]$^+$ 255.0997, found 255.0994.

Typical Procedure for Cyclisation (Compounds 49, 51–55)

2′-Methyl-4,5,5′,6′,7′,8′,8′a-heptahydrospiro[furan-3(2*H*),1′(7′*H*)-naphthalene]-2-one (49): A solution of triene **38** (19 mg, 0.09 mmol) in dry toluene (0.5 mL) was heated under microwave irradiation for 20 min (maximum temperature 160 °C, 300 W). The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (2:1 petroleum ether/diethyl ether) to give the title compound **49** as a colourless oil (10 mg, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24–1.37 (m, 3 H), 1.68–1.76 (m, 2 H), 1.76 (d, J = 1.1 Hz, 3 H), 1.81–1.86 (m, 1 H), 1.90 (ddd, J = 13.9, 9.7, 7.8 Hz, 1 H), 2.12–2.21 (m, 1 H), 2.43 (bd, J = 16.8 Hz, 1 H), 2.72 (ddd, J = 13.6, 8.8, 4.6 Hz, 1 H), 2.78–2.84 (m, 1 H), 4.14 (m, 1 H), 4.29–4.35 (m, 1 H), 5.58–5.62 (m, 1 H), 5.68 (bd, J = 5.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.8, 24.6 (2 C), 25.4, 27.8, 32.0, 42.8, 52.2, 66.3, 118.8, 121.3, 133.7, 136.1, 181.4 ppm. MS (ESI): m/z = 241 [M + Na]$^+$. HRMS (ESI, pos.): calcd. for $C_{14}H_{18}NaO_2$: [M + Na]$^+$ 241.1204, found 241.1203.

Supporting Information (see also the footnote on the first page of this article): Detailed results of DFT calculations and associated coordinates. Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all compounds.

Acknowledgments

The authors thank The University of Queensland for financial support.

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Received: April 24, 2007
Published Online: July 24, 2007

