Pergamon

Tetrahedron 55 (1999) 9333–9340

TETRAHEDRON

1,5-Diketones from 3,4-Dihydropyranones: An Application in the Synthesis of (±)-α-Herbertenol

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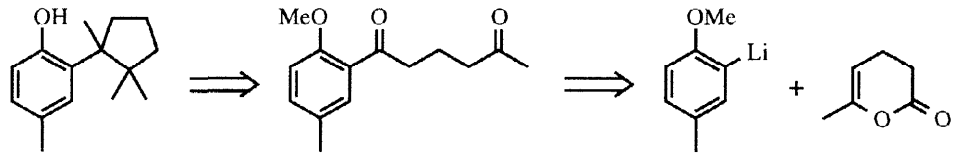
Received 30 March 1999; revised 12 May 1999; accepted 27 May 1999

Abstract: An approach to 1,5-diketones involving the addition of organolithium reagents to 3,4-dihydropyranones is described. Good yields are obtained when reactions are quenched with trimethylsilyl chloride prior to hydrolytic work up and the organolithium reagent contains a Lewis basic group adjacent to the carbon to lithium bond. The method has been applied in a short synthesis of the fungicidal sesquiterpene (±)-α-herbertenol. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Ketones; Lithium and compounds; Pyrones; Terpenes and terpenoids; Titanium and compounds.

INTRODUCTION

As part of a programme directed towards the total synthesis of α-herbertenol **1**,[1-3] a fungicidal sesquiterpene found in a wide variety of liverworts,[3] we required a rapid method of synthesising 1,5-diketone **2**. Though such compounds are conventionally prepared by the oxidative cleavage of cyclopentenes or the conjugate addition of enolates to α,β-unsaturated ketones,[4,5] these and related methodologies[6] were deemed unsuitable for our purpose since they would lengthen the projected synthesis considerably (Scheme 1). We therefore decided to pursue a more speculative approach based on the addition of an organolithium intermediate **3** to 3,4-dihydropyranone **4** (Scheme 1). In this *Paper* we describe our realisation of that objective, some further applications of the method and its use as a key step in a short synthesis of (±)-α-herbertenol.



1 **2** **3** **4**

Scheme 1

RESULTS AND DISCUSSION

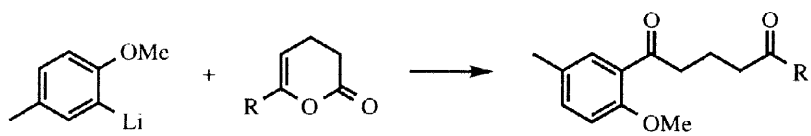
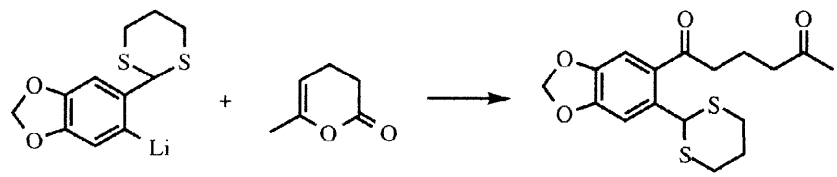
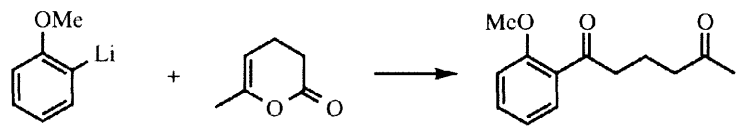
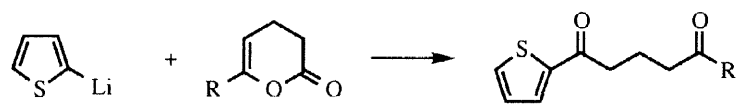
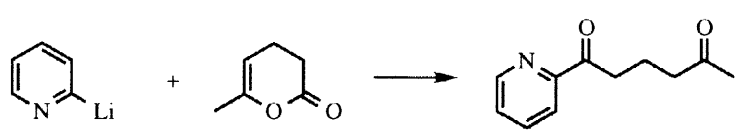
Initial attempts to synthesise diketone **2** through the union of aryllithium **3** and dihydropyranone **4** met with limited success. Conducting reactions in THF or diethyl ether, at various temperatures (between -90°C and -50°C) and using either *n*-butyllithium or *t*-butyllithium to effect metal - halogen exchange commonly gave the desired adduct **2** in yields ranging from 15% to 55%. Unfortunately, the yield of diketone obtained from a

PII: S0040-4020(99)00495-0

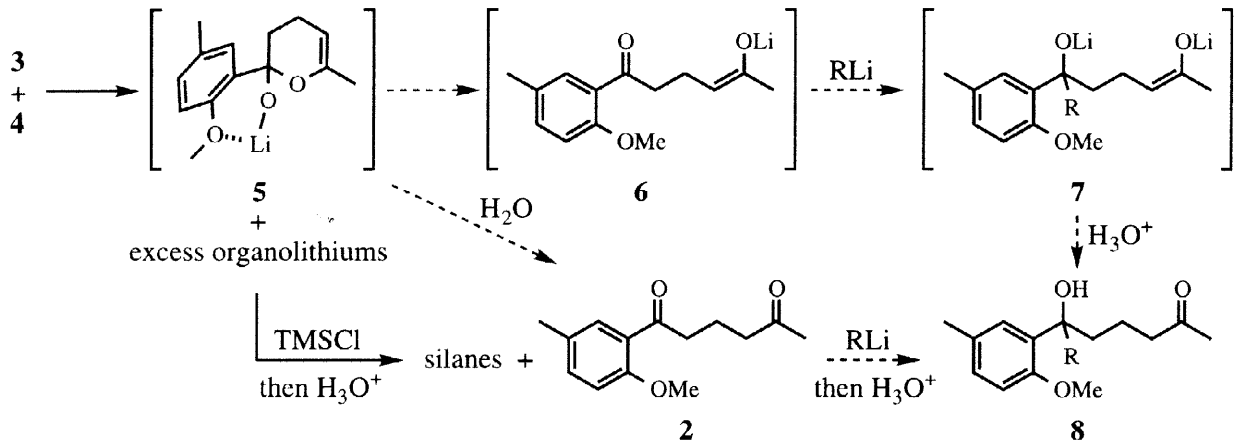
particular set of experimental conditions was seldom reproducible. This observation, together with the isolation of side products arising from over addition of organolithiums to **4**, led us to conclude that the work up procedure was greatly influencing the outcome of individual reactions.

Our awareness that a related problem, mono-addition of organolithium reagents to carboxylic acids, had been overcome through the simple expedient of adding trimethylsilyl chloride to the reaction mixture prior to hydrolytic work up, prompted us to use this tactic to our advantage.[7] Thus, when dihydropyranone **4** was added to a THF solution of organolithium **3** maintained at -78°C, and the reaction quenched after 15 minutes with TMSCl, a 77% yield of diketone **2** was given after work up. Moreover, this yield was reproducible and varied little with small changes to the reaction conditions. The method was successfully applied to other substrates and these results are summarised in the Table below.

Table: Examples of 1,5-Diketone Synthesis through Union of an Organolithium and a 3,4-Dihydropyranone

Entry	Overall Reaction	Yield
A **B**		R = Me, 77% R = Ph, 52%
C		92%
D		57%
E **F**		R = Me, 73% R = Ph, 46%
G		32%

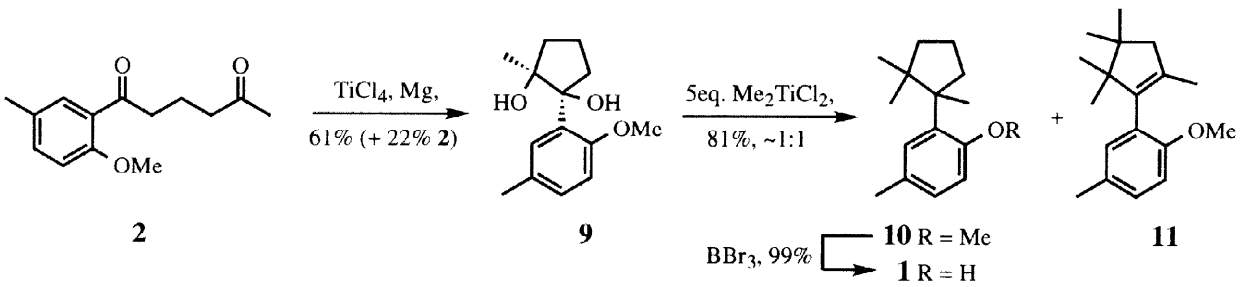
Generally, good yields were obtained when the organolithium reagent bore a donor atom adjacent to the carbon to lithium bond. Presumably this stabilises the first formed adduct (*e.g.* **5**) through an intramolecular Lewis acid - Lewis base interaction. In turn, *in situ* collapse (to **6**) and over addition (to **7**) are prevented (Scheme 2). In the absence of such donor groups yields are poor, as evinced by the 10% yield of diketone obtained when **4** and phenyllithium were united under the aforementioned conditions.



Scheme 2

A Short Synthesis of (±)-α-Herbertenol

Our plan to transform diketone **2** into (±)-α-herbertenol **1** envisioned a low valent titanium induced pinacolic coupling reaction to diol **9**,[8] followed by treatment with dimethyltitanium dichloride to install the adjacent quartenary centres,[9] and boron tribromide to unmask the phenol.[1a] Indeed, these steps proceeded without incident (Scheme 3) though an unprecedented side reaction involving Reetz's reagent is worthy of comment.[10] For exposure of diol **9** to Me_2TiCl_2 led to equimolar quantities of the desired dimethylated product **10** and the tetramethylated product **11**! Presumably formation of **11** involves a series of carbometallation and dehydrometallation reactions, a hypothesis we are currently investigating.



Scheme 3

CONCLUSIONS

We have shown that 3,4-dihydropyranones can serve as useful synthons of 1,5-diketones. Good yields are obtained when the reaction is quenched with TMSCl prior to hydrolytic work up and the organolithium intermediate bares a donor atom adjacent to the carbon to lithium bond. Our observations and inferences concerning the mechanistic course of the reaction are summarised in Scheme 2. A short synthesis of (±)-α-herbertenol which uses this transformation as a key step is also presented (Scheme 3).

ACKNOWLEDGEMENTS

The authors thank the EPSRC for a Quota studentship (to JCH) and the EPSRC mass spectrometry service at Swansea for their provision of some HRMS data.

EXPERIMENTAL SECTION

GENERAL REMARKS

Melting points were obtained using a Mel-Temp (II) apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam SP800 spectrometer. IR spectra were recorded on a Perkin Elmer 1600 series Fourier transform infrared spectrometer using NaCl cells. NMR spectra were recorded on a Bruker AC300 (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C). Chemical shifts (δ_H) are reported as values in parts per million relative to tetramethylsilane (δ_H 0.00, δ_C 0.00) or residual $CHCl_3$ (δ_H 7.27, δ_C 77.2). Low resolution mass spectra were recorded using atmospheric pressure chemical ionisation (APCI), positive ion, on a Micromass platform quadropole mass analyser with an electrospray ion source. High resolution mass spectra were recorded on a variety of instruments either in house or at the EPSRC mass spectrometry centre, Swansea.

All reactions were magnetically stirred, conducted under a nitrogen atmosphere using flame dried glassware and monitored by thin layer chromatography using Macherey-Nagel Alugram Sil G/UV$_{254}$ precoated aluminium foil plates of layer thickness 0.25mm. Compounds were visualised firstly by UV irradiation, then by exposure to iodine vapour and finally by heating plates exposed to solutions of phosphomolybdic acid in ethanol. Column chromatography was performed on Sorbsil 60 silica (230-400 mesh), slurry packed and run under low pressure. THF was dried and degassed by refluxing over sodium wire using benzophenone ketyl as indicator. All reagents were used as supplied. 6-Methyl-3,4-dihydropyran-2-one was prepared by treatment of 4-acetylbutyric acid with thionyl chloride according to the procedure of Paquette.[11] 6-Phenyl-3,4-dihydropyran-2-one was prepared by treatment of 4-benzoylbutyric acid with oxalyl chloride according to the procedure of Bhatt.[12] 2-Bromo-4-methylanisole was prepared in 98% yield by stirring an acetone solution of 2-bromo-4-methylphenol (40 mmol), MeI (60 mmol) and potassium carbonate (60 mmol) at 50°C for 12h. 2-Bromo-4-methylphenol was prepared by treatment of *p*-cresol with tetrabutylammonium tribromide according to the procedure of Kajigaeshi.[13]

GENERAL PROCEDURE

t-BuLi (12 mL of a 1.4M solution in pentane, 16.8 mmol) was added dropwise over 5 min to a cooled (-78°C) solution of the arylbromide (7.0 mmol) in THF (40 mL). The reaction was allowed to warm to ambient temperature, stirred for 1 h, then cooled to -78°C. Freshly distilled 3,4-dihydropyranone (10.5 mmol) dissolved in THF (10 mL) was then added *via* syringe over 5 min. After a further 15 min, trimethylsilyl chloride (7.0 mL, 55 mmol) was added and the reaction mixture allowed to warm to RT over 1 h. The reaction mixture was partitioned between dilute HCl (1M, 40 mL) and ether (80 mL), the aqueous phase was extracted with ether (2 x 80 mL) and the combined organic phases were then washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (and recrystallisation for solids) to give the product.

1-(2-Methoxy-5-methylphenyl)-1,5-hexanedione **2** (Table entry A)

Prepared using the general procedure with 2-bromo-4-methylanisole (1.407 g, 7.0 mmol), THF (40 mL), ^{t}BuLi (12.0 mL, 1.4 M in pentane, 16.8 mmol), **4** (1.177 g, 10.5 mmol in 10 mL THF), TMSCl (7.0 mL, 55 mmol). Purification by column chromatography (silica using 20% ether in petrol) gave the title compound as a colourless oil (1.260 g, 5.4 mmol, 77% yield). **FT-IR** (thin film) ν_{max}, 2945 m, 1715 s, 1675 s, 1610 m, 1580 w, 1500 s, 1465 m, 1405 m, 1285 m, 1250 s, 1180 m, 1160 m and 1025 m cm^{-1}; **UV** (MeOH) λ_{max} (ε), 314 (2000), 248 (3900) and 223 (3800) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.47 (1H, d, *J* = 2.4 Hz, Ar*H*), 7.25 (1H, ddq, *J* = 8.5, 2.4, 0.7 Hz, Ar*H*), 6.85 (1H, d, *J* = 8.5 Hz, Ar*H*), 3.86 (3H, s, OC*H*$_3$), 3.00 (2H, t, *J* = 7.1 Hz, C*H*$_2$CO), 2.52 (2H, t, *J* = 7.1 Hz, C*H*$_2$CO), 2.30 (3H, brs, ArC*H*$_3$), 2.15 (3H, s, C*H*$_3$CO) and 1.96 (2H, quintet, *J* = 7.1 Hz, CH$_2$C*H*$_2$CH$_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 209.0 (s), 202.5 (s), 156.7 (s), 134.1 (d), 130.6 (d), 130.1 (s), 128.0 (s), 111.7 (d), 55.7 (q), 43.1 (t), 42.7 (t), 30.0 (q), 20.4 (q) and 18.6 (t) ppm; **LRMS** (APCI), 252 (5%, [M+NH$_4$]$^+$) and 235 (100%, MH$^+$); **HRMS** (EI), Calcd. for $C_{14}H_{18}O_3$: 234.1256; Found: M$^+$ 234.1249.

1-(2-Methoxy-5-methylphenyl)-5-phenyl-1,5-pentanedione (Table entry B)

Prepared using the general procedure with 2-bromo-4-methylanisole (0.200 g, 1.0 mmol), THF (30 mL), ^{t}BuLi (1.7 mL, 1.4 M in pentane, 2.4 mmol), 6-phenyl-3,4-dihydropyran-2-one (0.261 g, 1.5 mmol in 5 mL THF), TMSCl (1.0 mL, 8 mmol). Purification by column chromatography (silica using 20% ether in petrol) and

recrystallisation from petrol gave the title compound as a white solid (0.155 g, 0.5 mmol, 52% yield). **MP** (petrol) 70-71°C; **CHN** Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.74; H, 6.76; **FT-IR** (nujol mull) ν_{max}, 2920 s, 1680 m, 1660 m, 1605 w, 1575 w, 1495 m, 1460 s, 1395 m, 1375 m, 1280 m, 1245 m, 1225 m, 1180 m and 1170 m cm^{-1}; **UV** (MeOH) λ_{max} (ε), 314 (2100) and 247 (8400) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.99-7.95 (2H, m, 2 x Ar*H*), 7.57-7.40 (4H, m, 4 x Ar*H*), 7.23 (1H, ddq, *J* = 8.4, 2.2, 0.6 Hz, Ar*H*), 6.83 (1H, d, *J* = 8.4 Hz, Ar*H*), 3.82 (3H, s, OCH_3), 3.10 (2H, t, *J* = 7.1 Hz, COCH_2), 3.06 (2H, t, *J* = 7.1 Hz, COCH_2), 2.28 (3H, brs, ArCH_3) and 2.13 (2H, quintet, *J* = 7.1 Hz, $CH_2CH_2CH_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 202.6 (s), 200.2 (s), 156.7 (s), 137.1 (s), 134.1 (d), 133.1 (d), 130.6 (d), 130.0 (s), 128.7 (2 x d), 128.2 (2 x d), 128.0 (s), 111.7 (d), 55.7 (q), 42.9 (t), 38.0 (t), 20.4 (q) and 19.2 (t) ppm; **LRMS** (APCI), 314 (70%, $[M+NH_4]^+$), 297 (35%, MH^+) and 182 (100%); **HRMS** (EI), Calcd. for $C_{19}H_{20}O_3$: 296.1412; Found: M^+ 296.1412.

1-[6-(1,3-Dithian-2-yl)-1,3-benzodioxol-5-yl]-1,5-hexanedione (Table entry C)

Prepared using the general procedure with aryl bromide (0.638 g, 2.0 mmol), THF (30 mL), ^{n}BuLi (0.96 mL, 2.5 M in hexanes, 2.4 mmol), **4** (0.336 g, 3.0 mmol in 5 mL THF), TMSCl (2.0 mL, 16 mmol). Purification by column chromatography (silica, 30-60% ether in petrol) gave the title compound as a colourless oil (0.649 g, 1.8 mmol, 92% yield). **FT-IR** (thin film) ν_{max}, 2900 m, 1715 s, 1680 s, 1610 m, 1505 s, 1485 s, 1420 m, 1370 s, 1270 s, 1240 s, 1180 m, 1090 m and 1035 s, cm^{-1}; **UV** (MeOH) λ_{max} (ε), 289 (6500) and 237 (12800) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.31 (1H, s, Ar*H*), 7.10 (1H, s, Ar*H*), 6.09 (1H, s, SC*H*S), 6.04 (2H, s, OCH_2O), 3.15-3.05 (2H, m, SCH_2), 2.94-2.84 (4H, m, SCH_2 & COCH_2), 2.57 (2H, t, *J* = 7.0 Hz, COCH_2), 2.16 (1H, m, SCH_2CHH), 2.16 (3H, s, COCH_3), 1.99 (2H, quintet, *J* = 7.0 Hz, $COCH_2CH_2$) and 1.96-1.86 (1H, m, SCH_2CHH) ppm; **^{13}C NMR** (75 MHz, C_6D_6) δ_C, 206.7 (s), 201.7 (s), 150.6 (s), 147.5 (s), 134.9 (s), 131.0 (s), 110.5 (d), 108.9 (d), 102.1 (t), 47.5 (d), 42.2 (t), 40.7 (t), 32.3 (2 x t), 29.5 (q), 25.4 (t) and 18.8 (t) ppm; **LRMS** (APCI), 353 (100%, MH^+); **HRMS** (EI), Calcd. for $C_{17}H_{20}O_4S_2$: 352.0803; Found: M^+ 352.0815.

1-(2-Methoxyphenyl)-1,5-hexanedione (Table entry D)

Prepared using the general procedure with *o*-bromoanisole (0.374 g, 2.0 mmol), THF (40 mL), ^{t}BuLi (3.4 mL, 1.4 M in pentane, 4.8 mmol), **4** (0.336 g, 3.0 mmol in 5 mL THF), TMSCl (2.0 mL, 16 mmol). Purification by column chromatography (silica, 20-30% ether in petrol) gave the title compound as a pale yellow oil (0.251 g, 1.1 mmol, 57% yield). **FT-IR** (thin film) ν_{max}, 3075 w, 3000 w, 2945 m, 2840 w, 1715 s, 1675 s, 1600 s, 1580 m, 1485 s, 1465 s, 1435 s,, 1285 s, 1245 s, 1115 m and 1025 m cm^{-1}; **UV** (MeOH) λ_{max} (ε), 300 (2900), 245 (6300) and 220 (3600) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.67 (1H, app dd, *J* = 7.5, 1.8 Hz, Ar*H*), 7.45 (1H, td, *J* = 7.5, 1.8 Hz, Ar*H*), 6.99 (1H, td, *J* = 7.5, 0.9 Hz, Ar*H*), 6.97 (1H, td, *J* = 7.5, 0.9 Hz, Ar*H*), 3.89 (3H, s, OCH_3), 3.01 (2H, t, *J* = 7.1 Hz, CH_2CO), 2.53 (2H, t, *J* = 7.1 Hz, CH_2CO), 2.14 (3H, s, CH_3CO) and 1.97 (2H, quintet, *J* = 7.1 Hz, $CH_2CH_2CH_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 208.9 (s), 202.3 (s), 158.7 (s), 133.6 (d), 130.3 (d), 128.4 (s), 120.8 (d), 111.7 (d), 55.6 (q), 43.0 (t), 42.7 (t), 30.0 (q) and 18.5 (t) ppm; **LRMS** (APCI), 238 (40%, $[M+NH_4]^+$) and 221 (100%, MH^+); **HRMS** (EI), Calcd. for $C_{13}H_{16}O_3$: 220.1099; Found: M^+ 220.1092.

1-(2-Thienyl)-1,5-hexanedione (Table entry E)

A solution of thiophene (0.168 g, 2.0 mmol) in THF (30 mL) was cooled to -78°C and ^{t}BuLi (1.7 mL, 1.5 M in pentane, 2.5 mmol) was added. The reaction was stirred for 1 h then a solution of **4** (0.261 g, 1.5 mmol) in THF (5 mL) was added. After 10 min TMSCl (1.0 mL, 8 mmol) was added and the reaction was allowed to warm to RT over 1 h. Dilute hydrochloric acid (1 M, 20 mL) was added, the reaction mixture was stirred for 15 min then extracted with ether (3 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by column chromatography (silica, 20 - 40% ether in petrol) and recrystallisation from petrol to give white crystals (0.288 g, 1.5 mmol, 73% yield). **MP** (petrol) 57-59°C (Lit.[14] 66-67°C); **CHN** Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.10; H, 6.06; **FT-IR** (nujol mull) ν_{max}, 2920 s, 2850 s, 1705 s, 1660 s, 1520 w and 1455 m cm^{-1}; **UV** (MeOH) λ_{max} (ε), 282 (6700) and 259 (8400) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.72 (1H, dd, *J* = 3.7, 1.1 Hz, Ar*H*), 7.62 (1H, dd, *J* = 5.0,

1.1 Hz, Ar*H*), 7.12 (1H, dd, *J* = 5.0, 3.7 Hz, Ar*H*), 2.94 (2H, t, *J* = 7.1 Hz, COCH_2), 2.56 (2H, t, *J* = 7.1 Hz, COCH_2), 2.14 (3H, s, COCH_3) and 2.00 (2H, quintet, *J* = 7.1 Hz, $CH_2CH_2CH_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 208.5 (s), 192.9 (s), 144.3 (s), 133.7 (d), 132.1 (d), 128.3 (d), 42.6 (t), 38.2 (t), 30.1 (q) and 18.6 (t) ppm; **LRMS** (APCI), 197 (100%, MH^+) and 111 (25%, [M-$(CH_2)_3$COMe]$^+$); **HRMS** (EI), Calcd. for $C_{10}H_{12}O_2S$: 196.0558; Found: M^+ 196.0578.

5-Phenyl-1-(2-thienyl)-1,5-pentanedione (Table entry F)

A solution of thiophene (0.084 g, 1.0 mmol) in THF (30 mL) was cooled to -78°C and ^{t}BuLi (0.8 mL, 1.4 M in pentane, 1.1 mmol) was added. The reaction was stirred for 1 h then a solution of 6-phenyl-3,4-dihydropyranone (0.261 g, 1.5 mmol) in THF (5 mL) was added. After 10 min TMSCl (1.0 mL, 8 mmol) was added and the reaction was allowed to warm to RT over 1 h. Dilute hydrochloric acid (1 M, 20 mL) was added, the reaction mixture was stirred for 15 min then extracted with ether (3 x 60 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product was purified by column chromatography (silica, 20% ether in petrol) and recrystallisation from petrol to give white needles (0.119 g, 0.5 mmol, 46% yield). **MP** (petrol) 62-63°C; **CHN** Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.41; H, 5.42; **FT-IR** (nujol mull) ν_{max}, 2920 s, 2855 s, 1685 m, 1650 m, 1590 w, 1520 w, 1460 m, 1445 m and 1420 m cm^{-1}; **UV** (MeOH) λ_{max} (ε), 286 (10000) and 248 (18000) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 8.02-7.95 (2H, m, 2 x Ar*H*), 7.76 (1H, d, *J* = 3.4 Hz, thiophene-*H*), 7.63 (1H, d, *J* = 4.8 Hz, thiophene-*H*), 7.60-7.42 (3H, m, 3 x Ar*H*), 7.14 (1H, dd, *J* = 4.8, 3.4 Hz, thiophene-*H*), 3.13 (2H, t, *J* = 7.0 Hz, CH_2CO), 3.07 (2H, t, *J* = 7.0 Hz, CH_2CO) and 2.21 (2H, quintet, *J* = 7.0 Hz, $CH_2CH_2CH_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 199.9 (s), 193.0 (s), 144.4 (s), 136.9 (s), 133.7 (d), 133.3 (d), 132.2 (d), 128.8 (2 x d), 128.3 (d), 128.2 (2 x d), 38.4 (t), 37.6 (t) and 19.2 (t) ppm; **LRMS** (APCI), 276 (25%, [M+NH_4]$^+$), 259 (100%, MH^+), 182 (70%, [MH-Ph]$^+$) and 126 (30%, [MH-CH_2CH_2COPh]$^+$); **HRMS** (EI), Calcd. for $C_{15}H_{14}O_2S$: 258.0715; Found: M^+ 258.0717.

1-(2-Pyridinyl)-1,5-hexanedione (Table entry G)

Prepared using the general procedure with 2-bromopyridine (0.316 g, 2.0 mmol), THF (30 mL), ^{n}BuLi (0.96 mL, 2.5 M in hexanes, 2.4 mmol), **4** (0.336 g, 3.0 mmol in 3 mL THF), TMSCl (2.0 mL, 16 mmol). Purification by column chromatography (silica, 40% ether in petrol) and recrystallisation from petrol gave the title compound as a colourless crystals (0.121 g, 0.63 mmol, 32% yield). **MP** (petrol) 48-50°C; **CHN** Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.59; H, 6.82; N, 7.10; **FT-IR** (nujol mull) ν_{max}, 2920 s, 2850 s, 1710 m, 1690 m, 1580 w and 1455m cm^{-1}; **UV** (MeOH) λ_{max} (ε), 269 (4500) and 239 (3900) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 8.65 (1H, ddd, *J* = 4.8, 1.7, 1.0 Hz, Ar*H*), 8.01 (1H, dt, *J* = 7.7, 1.0 Hz, Ar*H*), 7.82 (1H, td, *J* = 7.7, 1.7 Hz, Ar*H*), 7.45 (1H, ddd, *J* = 7.7, 4.8, 1.0 Hz, Ar*H*), 3.24 (2H, t, *J* = 7.2 Hz, CH_2CO), 2.55 (2H, t, *J* = 7.2 Hz, CH_2CO), 2.14 (3H, s, CH_3CO) and 2.00 (2H, quintet, *J* = 7.2 Hz, $CH_2CH_2CH_2$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 208.6 (s), 201.5 (s), 153.4 (s), 149.1 (d), 137.1 (d), 127.3 (d), 121.9 (d), 43.0 (t), 36.9 (t), 30.0 (q) and 18.1 (t) ppm; **LRMS** (APCI), 192 (100%, MH^+); **HRMS** (CI), Calcd. for $C_{11}H_{13}NO_2$: 191.0946; Found: M^+ 191.0929.

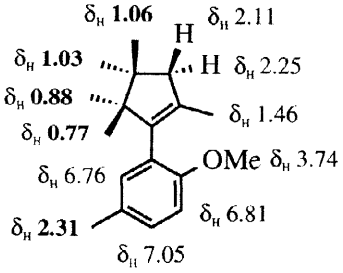
2-(1*S**,2*S**-Dihydroxy-2-methylcyclopentyl)-1-methoxy-4-methyl-benzene **9**

Magnesium turnings (0.972 g, 40 mmol) in dry THF (80 mL) were cooled to -78°C and $TiCl_4$ (4.4 mL, 40 mmol) added dropwise over 2 min. The reaction mixture was allowed to warm to RT and stirred for 2 h. The reaction was cooled to -40°C and the diketone **2** (0.937 g, 4.0 mmol) in dry THF (5 mL) was added. The temperature was kept at -40°C for 2 h then quenched with water (30 mL) and extracted with ether (6 x 50 mL). The combined ethereal layers were concentrated then washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (silica, 25% ether in petrol) gave firstly **9** as a colourless oil (0.580 g, 2.5 mmol, 61% yield) then recovered starting material **2** (0.203 g, 22% yield). **FT-IR** (thin film) ν_{max}, 3480 brs, 2965 s, 1610 w, 1500 s, 1455 m, 1375 m, 1295 m, 1230 s, 1180 m, 1115 m, 1025 m, 970 m and 810 m cm^{-1}; **UV** (MeOH) λ_{max} (ε), 290 (1900), 284 (2000) and 238 (1900) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.08-7.04 (2H, m, 2 x Ar*H*), 6.85 (1H, dd, *J* = 6.7, 2.2 Hz, Ar*H*), 4.87 (1H, brs, O*H*), 3.89 (3H, s, OCH_3), 3.49 (1H, brs, O*H*), 2.46-

2.34 (1H, m), 2.31 (3H, s, ArC*H*$_3$), 2.24-1.93 (3H, m), 1.83-1.63 (2H, m) and 0.99 (3H, s, CC*H*$_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 155.1 (s), 131.1 (s), 130.7 (s), 129.2 (d), 129.0 (d), 111.9 (d), 85.9 (s), 81.8 (s), 56.1 (q), 38.3 (t), 37.4 (t), 25.6 (q), 20.9 (q) and 20.0 (t) ppm; **LRMS** (APCI), 236 (30%, M$^+$), 235 (35%, [M-H]$^+$) and 219 (100%, [MH-H_2O]$^+$); **HRMS** (EI), Calcd. for $C_{14}H_{20}O_3$: 236.1412; Found: M$^+$ 236.1426.

1-Methoxy-4-methyl-2-(1,2,2-trimethylcyclopentyl)-benzene **10** and
1-Methoxy-4-methyl-2-(2,4,4,5,5-pentamethylcyclopent-1-enyl)-benzene **11**

A solution of $TiCl_4$ (0.90 mL, 8.2 mmol) in dry dichloromethane (20 mL) was cooled to 0°C and dimethylzinc (4.0 mL, 2.0 M in toluene, 8.0 mmol) was added cautiously. After 10 min the diol **9** (0.189 g, 0.8 mmol) was added. After a further 14 h water (10 mL) was added. The product was extracted with dichloromethane (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by chromatography (silica, 10% ether in petrol) to give **10** as a colourless oil (79 mg, 0.34 mmol, 43%) and **11** as a colourless oil (78 mg, 0.30 mmol, 38%). DATA for **10**: **FT-IR** (thin film) ν_{max}, 2955 s, 2875 s, 1605 w, 1500 s, 1465 s, 1370 m, 1285 m, 1245 s, 1175 m, 1065 m, 1035 s and 805 s cm^{-1}; **UV** (MeOH) λ_{max} (ε), 286 (2700), 279 (3000) and 232 (4800) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.15 (1H, d, J = 2.2 Hz, Ar*H*), 7.00 (1H, ddq, J = 8.2, 2.2, 0.8 Hz, Ar*H*), 6.79 (1H, d, J = 8.2 Hz, Ar*H*), 3.78 (3H, s, OC*H*$_3$), 2.64-2.51 (1H, m), 2.32 (3H, brs, ArC*H*$_3$), 1.83-1.64 (4H, m), 1.62-1.50 (1H, m), 1.39 (3H, s, C*H*$_3$), 1.19 (3H, s, C*H*$_3$) and 0.72 (3H, s, C*H*$_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 156.9 (s), 136.1 (s), 129.8 (d), 128.9 (s), 127.1 (d), 111.7 (d), 55.0 (q), 51.3 (s), 44.3 (s), 42.2 (t), 40.0 (t), 27.7 (q), 26.1 (q), 23.2 (q), 21.1 (q) and 20.7 (t) ppm; **LRMS** (APCI), 232 (100%, M$^+$), 165 (80%) and 163 (70%, [ArH+MeCN]$^+$); **HRMS** (EI), Calcd. for $C_{16}H_{24}O$: 232.1827; Found: M$^+$ 232.1825. These data were consistent with those previously reported in the literature.[3c] DATA for **11**: **FT-IR** (thin film) ν_{max}, 2960 s, 2905 s, 2865 m, 2830 m, 1500 s, 1465 m, 1250 s, 1230 s, 1140 m, 1040 m and 805 m cm^{-1}; **UV** (MeOH) λ_{max} (ε), 287 (3600), 281 (3800) and 233 (5200) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.05 (1H, ddq, J = 8.4, 2.2, 0.7 Hz, Ar*H*), 6.81 (1H, d, J = 8.4 Hz, Ar*H*), 6.76 (1H, d, J = 2.2 Hz, Ar*H*), 3.74 (3H, s, OC*H*$_3$), 2.31 (3H, brs, ArC*H*$_3$), 2.25 (1H, d + fine splitting, J = 15.4 Hz, C*H*H), 2.11 (1H, d + fine splitting, J = 15.4 Hz, CH*H*), 1.46 (3H, s, C*H*$_3$), 1.06 (3H, s, C*H*$_3$), 1.03 (3H, s, C*H*$_3$), 0.88 (3H, s, C*H*$_3$) and 0.77 (3H, s, C*H*$_3$) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 156.2 (s), 140.9 (s), 132.9 (s), 132.1 (d), 129.0 (s), 128.1 (d), 127.6 (s), 110.9 (d), 55.8 (q), 52.0 (s), 51.3 (t), 43.4 (s), 25.5 (q), 24.2 (q), 23.0 (q), 20.8 (q), 20.7 (q) and 15.4 (q) ppm; **LRMS** (EI), 258 (25%, M$^+$) and 243 (100%, [M-Me]$^+$); **HRMS** (EI), Calcd. for $C_{18}H_{26}O$: 258.1984; Found: M$^+$ 258.1980; **n.O.e.**



Irradiation of δ_H	Caused a n.O.e. enhancement at δ_H
2.31	7.05 (4%), 6.76 (5%)
1.06	2.25 (2%), 2.11 (4%), 0.77 (2%)
1.03	2.25 (3%), 2.11 (2%)
0.88	6.76 (7%), 2.25 (1%)
0.77	6.76 (3%), 3.74 (2%), 1.06 (2%)

4-Methyl-2-(1,2,2-trimethylcyclopentyl)-phenol: (±)-α-Herbertenol **1**

Prepared through modification of the procedure of McOmie and West.[15] To a solution of the substrate **10** (0.120 g, 0.5 mmol) in dry dichloromethane (30 mL) at -78°C was added BBr_3 (0.55 mL, 1.0 M in dichloromethane, 0.6 mmol). The reaction was allowed to warm to RT, stirred for 16 h then quenched with water (10 mL) and extracted with ether (3 x 50 mL). The combined ethereal layers were washed with brine (10 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica, 10% - 20% ether in petrol) to give **1** as colourless oil (0.112 g, 0.5 mmol, 99% yield). **FT-IR** (CH_2Cl_2) ν_{max}, 3585 m, 2960 s, 2875 m, 1605 w, 1505 m, 1465 w, 1405 w, 1270 s and 1265 s cm^{-1}; **UV** (EtOH) λ_{max} (ε), 290 inf (2100), 282 (3500) and 235 (6100) nm; **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H, 7.13 (1H, d, J = 1.5 Hz, Ar*H*), 6.90 (1H, dd, J = 8.0, 1.5 Hz, Ar*H*), 6.60 (1H, d, J

= 8.0 Hz, Ar*H*), 4.66 (1H, brs, O*H*), 2.72-2.56 (1H, m), 2.30 (3H, brs, ArCH_3), 1.85-1.53 (5H, m), 1.44 (3H, s, CH_3), 1.22 (3H, s, CH_3) and 0.80 (3H, s, CH_3) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C, 152.4 (s), 133.2 (s), 130.2 (d), 129.2 (s), 127.4 (d), 116.9 (d), 51.1 (s), 44.8 (s), 41.4 (t), 39.6 (t), 27.2 (q), 25.7 (q), 23.1 (q), 21.1 (q) and 20.5 (t) ppm; **LRMS** (APCI), 218 (100%, M^+); **HRMS** (CI), Calcd. for $C_{15}H_{22}O$: 218.1671; Found: M^+ 218.1678. These data were consistent with those previously reported in the literature.[3]

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