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Synthesis of 4-azacyclopent-2-enones and 5,5-dialkyl-4-azacyclopent-2-enones

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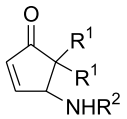
Abstract—Three different methods are reported for the preparation of 4-azacyclo-2-enones **1**, two of which allow the preparation of the compounds in optically active form. In addition, a facile route to 4-aza-5,5-dimethylcyclopent-2-enones **2** is disclosed.

1. Introduction

4-Aza-cyclopentenones **1** and **2** are potentially interesting scaffolds for parallel synthesis/combinatorial chemistry and are possibly useful building blocks for the construction of carbocyclic nucleosides.[1] Paradoxically, little work has been reported in the literature concerning the synthesis of such compounds.[2] In our laboratories we were keen to access these materials in racemic and optically active form in connection with our studies concerning the anti-viral activity of simple cyclopentenones.[3]



(**1**) R^1 = H; R^2 = alkyl, aryl or protecting group
(**2**) R^1 = CH_3; R^2 = alkyl, aryl or protecting group

2. Results and discussion

Initially, the earlier studies of Harris attracted our attention.[4] Harris showed that 4-hydroxycyclopent-2-enone **3** could be converted into the urethane **4** which itself was transformed into the 4-anilino-compound **8** (with loss of CO_2) on treatment with triethylamine (Scheme 1). We found that the same two-step transformation could be applied more broadly and, for example, was accomplished by reacting hydroxyketone **3** with *N*-tosylisocyanate to afford compound **5** (44%), which was converted into the desired product **9** (68%) on treatment with base. Similarly the compound **10** was prepared in 42% overall yield through the intermediate formation of urethane **6**.

The synthesis of the phenoxycarbonyl compound **11** suffered from a low yield (27%) in the first step, although the rearrangement/decarboxylation of **7** proceeded in almost quantitative yield. Interestingly, reaction of the alcohol **3** with chloroacetyl isocyanate gave the rearranged product **12** directly in 40% yield.

Overall, this pathway suffered from some drawbacks. First, the overall yields were only modest to good. In addition, the decarboxylative rearrangements of some other intermediates (for example those derived by reaction of **3** with cyclohexyl- or *tert*-butyl-isocyanate) were capricious and none of the desired product could be detected. One of our target compounds, 4-*tert*-butoxycarbonylaminocyclopent-2-enone **13** could not be obtained. Finally, the hydroxyketone **3** is not readily available in optically active form,[5] and therefore access to optically active compounds was not facile.

The second methodology investigated, specifically to prepare compound **13**, involved, in the first step, the cycloaddition of the nitroso-compound derived from **14** and cyclopentadiene (Scheme 2) to furnish the bicyclic compound **15**. This proceeded as reported previously,[6,7] as

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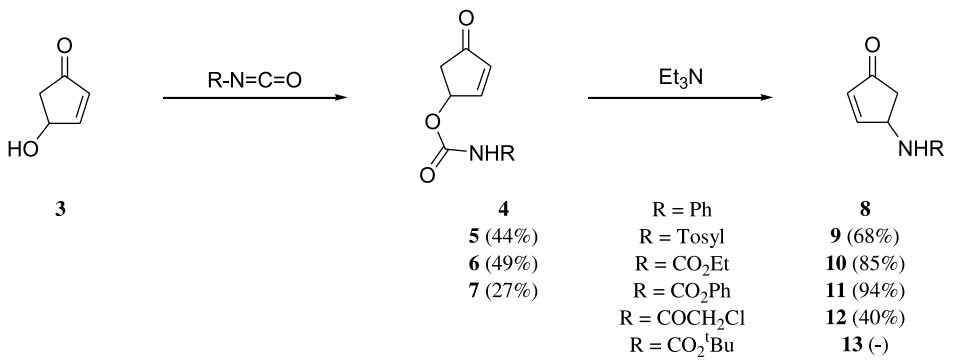
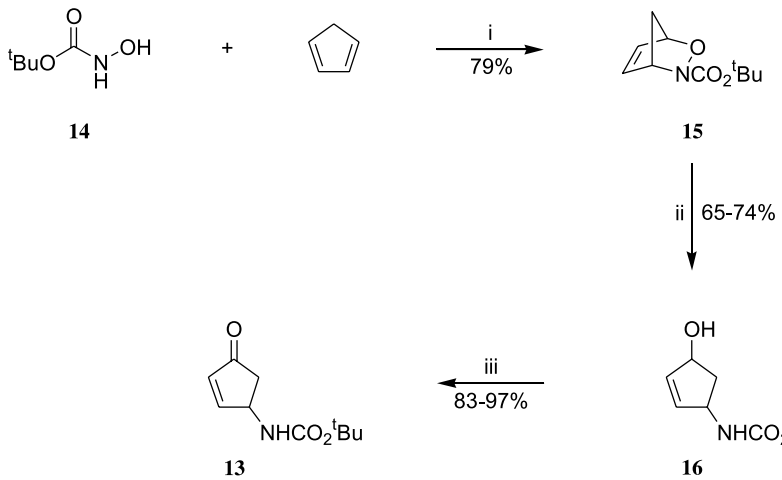


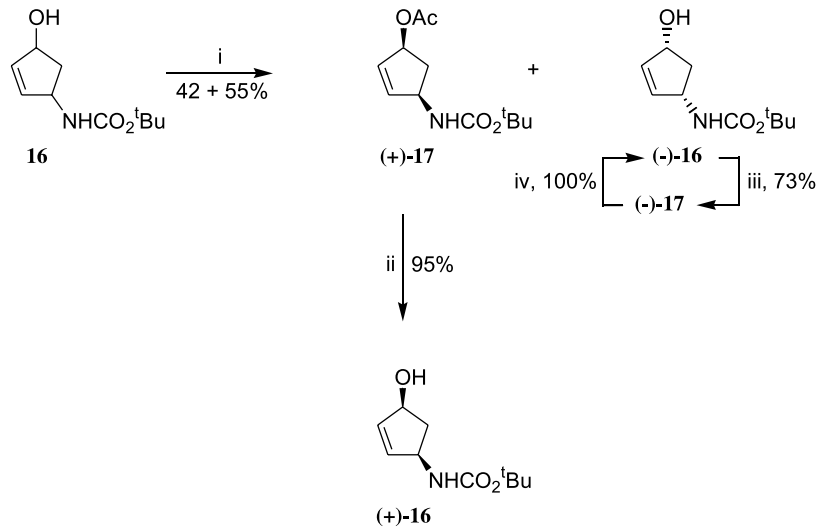
Scheme 1.



Scheme 2. Reagents and conditions: (i) $(n\text{-Bu})_4NIO_4$, CH_2Cl_2, 1 h, 79%; (ii) $Mo(CO)_6$, CH_3CN, H_2O, then $NaBH_4$, reflux, 3 h, 65%; OR Na/Hg, Na_2HPO_4, C_2H_5OH, 0 °C, 1.5 h, 74%; (iii) PCC, CH_2Cl_2, 4 Å mol. sieve, 2 h, 83%; OR TEMPO, H_5IO_6, CH_2Cl_2, 2.5 h, 97%.

did the N–O bond cleavage using $Mo(CO)_6$.[6] However, we were anxious to find a replacement for the latter reagent and we found that sodium amalgam was a suitable alternative,[8] leading to a cleaner reaction providing the protected amino alcohol **16** in 74% yield in a protocol more suitable for scale-up. Oxidation of the alcohol **16** to the enone **13** proceeded smoothly using pyridinium chlorochromate, or periodate and a catalytic amount of TEMPO.[9]

The intermediacy of alcohol **16** in this pathway suggested this might be a suitable substrate for enzyme-controlled kinetic resolution.[10] Incubation with Amano PS-C II lipase



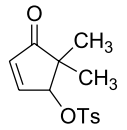
Scheme 3. Reagents and conditions: (i) Amano PS-C II lipase, CH_2CHOAc, CH_2Cl_2, 35 °C, 72 h, 42% of (+)-**17** and 55% of (−)-**16**; (ii) LiOH, C_2H_5OH, H_2O, 4 h, 95%; (iii) CH_3COCl, CH_2Cl_2, 0 °C, 18 h, 84%; Amano PS-C II lipase, $(CH_3)_2CO$, pH 7.4 buffer, 35 °C, 54 h, 73% of (−)-**17** and 20% of (+)-**16**; (iv) LiOH, C_2H_5OH, H_2O, 100%.

in dichloromethane containing vinyl acetate gave the acetate (+)-**17** (42%) and recovered alcohol (−)-**16** (55%) after the biotransformation, followed by work-up in a conventional manner (Scheme 3). The recovered alcohol (−)-**16** was acetylated and this acetate (−)-**17** was hydrolysed in phosphate buffer using Amano PS-C II lipase to give optically enriched (−)-**17** (73%) and alcohol (+)-**16** (20%). The acetate (+)- and (−)-**17** were readily hydrolysed to the alcohols (+)- and (−)-**16**, respectively. The optical purities were measured as 92 and 99% ee by GC employing a chiral column after oxidation to (+)- and (−)-**13**, respectively.

To circumvent the loss of material at the stage of the kinetic resolution a new method was sought to provide optically active **16** that was less wasteful in material. The initial findings of this initiative are reported here but full details will be reported elsewhere. First, the readily available *meso*-diacetate **18** could be mono-substituted by using $HN(CO_2^tBu)_2$ and a palladium catalyst to give the racemic acetate **19**.[11] Treatment of **19** with TFA then gave the acetate **17** is very short order.

Furthermore, the monoacetate **20** could be prepared from the corresponding *meso*-diacetate **18** using an enzyme-catalysed hydrolysis.[12] This hydroxyester **20** was then directly converted into the bis-protected amine **21** using similar conditions.[13] Mono-deprotection of **21** was then effected, to provide the protected amine **16** with a enantiomeric excess of 98% in only 3 high yielding transformations (Scheme 4).

The preparation of compounds of type **2** involved another novel transformation in the key step. 2-Methylcyclopentane-1,3-dione was converted into 4-hydroxy-5,5-dimethylcyclopent-2-enone as prescribed by Yamada et al.[14] and reaction of this alcohol with *para*-toluenesulfonyl chloride gave the tosylate **22**. Reaction of **22** with the appropriate amine gave the amines **23**-**25** directly in 65–74% yield. It is likely that the reaction proceeds through conjugate addition of the amine to the enone and secondary rearrangement through an aziridinium species, rather than direct attack at the neopentyl centre. In accord with this postulate, reaction of tosylate **22** with hexanethiol gave, under mild conditions, the conjugate addition products **28** and **30** and the enone **26** (ratio 1:1:2). Heating the major conjugate adduct **28** (*trans*-stereochemistry) furnished the enone **26** in high yield, but the *cis*-isomer **30** remained unchanged after prolonged heating under the same conditions. In a similar manner, under the appropriate reaction conditions, octanethiol and the tosylate **22** gave a mixture of Michael adducts **29** and **31** as well as the enone **27** in a ratio of 5:4:8. Heating **29** in dichloromethane for 1 h afforded **27** in 89% yield whereas, **31** was stable under these conditions.



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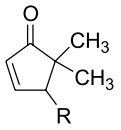
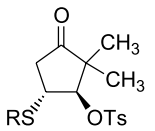
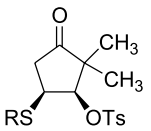


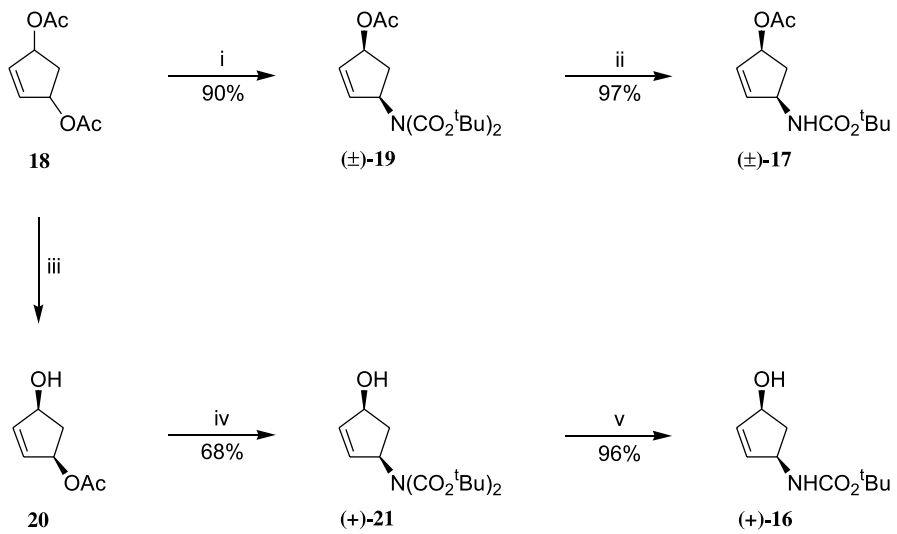
(**23**) R = $N(CH_3)CH_2Ph$
(**24**) R = $N[CH_2CH_2]_2O$
(**25**) R = $N[CH_2CH_2]_2NC_6H_4F$
(**26**) R = SC_6H_{13}
(**27**) R = SC_8H_{17}





28 R = C_6H_{13} **30**
29 R = C_8H_{17} **31**

In conclusion, the preparation of 4-azacyclopentenones according to the method of Harris has been used to access compounds **8**-**12**. The route does not allow the preparation of the *N*-Boc derivative **13**. However, this compound can be made from the alcohol **16**, kinetic resolution of **16** using a lipase allows access to optically active material. However, the preferred route to optically active **13** involves conversion of the monoester **20** into the diprotected amine **21** in the



Scheme 4. Reagents and conditions: (i) $Pd_2(dba)_3$, dppf, $NH(Boc)_2$, BSA, THF, 50 °C, 12 h, 90%; (ii) TFA, CH_2Cl_2, 20 h, 97%; (iii) see Ref. 12; (iv) $Pd_2(dba)_3$, dppf, $NH(Boc)_2$, BSA, THF, 45 °C, 3 h, 68%; (v) TFA, CH_2Cl_2, 20 h, 96%.

key step. The scope of the latter transformation is under active investigation.

3. Experimental

3.1. General

Starting materials were purchased from commercial sources and were used without further purification. Dichloromethane was distilled from calcium hydride and tetrahydrofuran was distilled from sodium benzophenone ketyl. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using a Varian Gemini 2000 spectrometer. Optical rotation measurements were recorded using an Optical Activity, Polaar 2001 polarimeter at 589 nm and quoted in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was performed under moderate pressure using silica gel—ICN 32-63, 60 Å. Analytical HPLC measurements were performed on a Gilson HPLC machine using an OD column and GC measurements were performed on a Shimadzu GC-14AH machine using a Lipodex E (Macherey-Nagel) column.

3.1.1. 3-(4-Oxocyclopent-2-enyl)-4-methylphenylsulfonyl carbamic acid (9).[15] *p*-Tolylsulfonyl isocyanate (2.94 g, 14.9 mmol) was added to a solution of the enone **3** (1.46 g, 14.9 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 5 h. The dichloromethane was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 40% ethyl acetate in hexane) to afford the compound **5** (1.93 g, 6.54 mmol, 44%) as a light yellow solid; R_f 0.25 (50% ethyl acetate in hexane); δ_H (400 MHz, $CDCl_3$) 7.87–7.76 (2H, m, Ar*H*), 7.39–7.32 (3H, m, C*H*=CHC=O, Ar*H*), 6.20 (1H, dd, *J*=5.6, 1.8 Hz, CH=C*H*C=O), 4.96 (1H, d, *J*=9.1 Hz, N*H*), 4.63 (1H, m, C*H*OR), 2.58 (1H, dd, *J*=18.8, 6.7 Hz, C*H*H), 2.45 (3H, s, ArCH_3), 1.98 (1H, dd, *J*=18.8, 2.5 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.3 (s), 160.9 (d), 145.7 (s), 144.3 (s), 137.2 (s), 136.0 (d), 130.1 (d), 127.2 (d), 53.6 (d), 42.1 (t), 21.6 (q).

A catalytic amount of triethylamine (3–4 drops) was added to a solution of the enone **5** (148 mg, 0.50 mmol) in dry chloroform (5 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 4 h. The chloroform was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 40% ethyl acetate in hexane) to afford the title compound **9** (86 mg, 0.34 mmol, 68%) as a white crystalline solid; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J*=8.2 Hz, Ar*H*), 7.37 (1H, dd, *J*=5.7, 2.4 Hz, C*H*=CHC=O), 7.35 (2H, d, *J*=8.2 Hz, Ar*H*), 6.20 (1H, dd, *J*=5.7, 1.8 Hz, CH=C*H*C=O), 4.80 (1H, d, *J*=9.2 Hz, N*H*), 4.60 (1H, m, C*H*NH), 2.55 (1H, dd, *J*=18.8, 6.7 Hz, C*H*H), 2.45 (3H, s, ArCH_3), 1.95 (1H, dd, *J*=18.8, 2.6 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.1 (s), 160.7 (d), 144.3 (s), 137.3 (s), 136.1 (d), 130.1 (d), 127.2 (d), 53.6 (d), 42.2 (t), 21.6 (q); *m*/*z* (CI) 269 ([MNH_4]$^+$, 100%), 252 ([MH]$^+$, 20). Found [MH]$^+$ 252.0699 ([MH]$^+$ $C_{12}H_{14}NO_3S$ requires 252.0694).

3.1.2. (4-Oxocyclopent-2-enyl)-carbamic acid ethyl ester (10). Ethoxycarbonyl isocyanate (0.90 mL, 8.72 mmol) was added to a solution of the enone **3** (1.08 g, 11.0 mmol) in dry dichloromethane (20 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 5 h. The dichloromethane was removed in vacuo, then filtered through a short pad of silica eluting with a 2:1 mixture of dichloromethane and petrol to give the crude product **6** (1.16 g, 5.45 mmol, 49%) as a brown oil, which was taken on without further purification.

Triethylamine (0.84 mL, 6.03 mmol) was added to a solution of the crude enone **6** (1.16 g, 5.45 mmol) in dry chloroform (20 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 3 h. The chloroform was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 50% ethyl acetate in hexane) to afford the title compound **10** (0.78 g, 4.62 mmol, 85%) as a white crystalline solid; R_f 0.3 (50% ethyl acetate in hexane); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, m, C*H*=CHC=O), 6.25 (1H, m, CH=C*H*C=O), 5.00 (1H, br. s, N*H*), 4.91 (1H, br. s, C*H*NH), 4.15 (2H, q, *J*=7.1 Hz, CH_2CH$_3$), 2.86 (1H, dd, *J*=18.7, 6.5 Hz, C*H*H), 2.18 (1H, dd, *J*=18.7, 2.4 Hz, CH*H*), 1.26 (3H, t, *J*=7.1 Hz, CH$_2$CH_3); δ_C (100 MHz, $CDCl_3$) 206.2 (s), 161.7 (d), 155.9 (s), 135.4 (d), 61.4 (t), 51.4 (d), 42.3 (t), 14.5 (q); *m*/*z* (CI) 187 ([MNH_4]$^+$, 100%), 170 ([MH]$^+$, 92), 169 ([M]$^+$, 14). Found [MH]$^+$ 170.0814 ([MH]$^+$ $C_8H_{12}NO_3$ requires 170.0817).

3.1.3. (4-Oxocyclopent-2-enyl)-carbamic acid phenyl ester (11). Phenoxycarbonyl isocyanate (1.60 mL, 12.1 mmol) was added to a solution of the enone **3** (1.18 g, 12.0 mmol) in dry dichloromethane (15 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 24 h. The dichloromethane was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate in hexane) to afford the compound **7** (0.85 g, 3.26 mmol, 27%) as a white solid; R_f 0.4 (50% ethyl acetate in hexane); δ_H (400 MHz, $CDCl_3$) 7.60 (1H, dd, *J*=5.7, 2.4 Hz, C*H*=CHC=O), 7.38 (2H, t, *J*=7.9 Hz, Ar*H*), 7.23 (1H, t, *J*=7.5 Hz, Ar*H*), 7.14 (2H, m, Ar*H*), 6.30 (1H, dd, *J*=5.7, 1.7 Hz, CH=C*H*C=O), 5.33 (1H, m, N*H*), 5.07 (1H, m, C*H*OR), 2.93 (1H, dd, *J*=18.8, 6.8 Hz, C*H*H), 2.28 (1H, dd, *J*=18.8, 2.5 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.8 (s), 161.2 (d), 154.0 (s), 150.7 (s), 135.8 (d), 129.4 (d), 125.7 (d), 121.4 (d), 120.5 (s), 51.6 (d), 42.0 (t).

Triethylamine (0.23 mL, 1.65 mmol) was added to a solution of the enone **7** (0.41 g, 1.57 mmol) in dry chloroform (10 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo to afford the title compound **11** (0.32 g, 1.47 mmol, 94%) as a copper coloured solid; R_f 0.4 (50% ethyl acetate in hexane); mp 111–112 °C (EtOAc/hexane); δ_H (400 MHz, $CDCl_3$) 7.58 (1H, dd, *J*=5.6, 2.4 Hz, C*H*=CHC=O), 7.40–7.33 (2H, m, Ar*H*), 7.247.19 (1H, m, Ar*H*), 7.15–7.10 (2H, m, Ar*H*), 6.29 (1H, dd, *J*=5.6, 1.8 Hz, CH=C*H*C=O), 5.28 (1H, br. s, N*H*), 5.09–5.01 (1H, m, C*H*NH), 2.91 (1H, dd, *J*=18.6, 6.8 Hz, C*H*H), 2.27 (1H, dd, *J*=18.6, 2.2 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.7 (s), 161.1 (d), 153.9 (s), 150.7 (s),

135.8 (d), 129.4 (d), 125.7 (d), 121.4 (d), 51.6 (d), 42.0 (t); *m/z* (CI) 235 ($[MNH_4]^+$, 100%), 218 ($[MH]^+$, 16), 217 ($[M]^+$, 0.3). Found $[MH]^+$ 218.0824 ($[MH]^+$ $C_{12}H_{12}NO_3$ requires 218.0817).

3.1.4. 2-Chloro-*N*-(4-oxocyclopent-2-enyl)-acetamide (12). Chloroacetyl isocyanate (0.84 g, 9.86 mmol) was added to a solution of the enone **3** (0.96 g, 9.80 mmol) in dry dichloromethane (10 mL) under a nitrogen atmosphere and the reaction mixture was stirred at room temperature for 20 h. The dichloromethane was removed in vacuo and the crude product was purified by flash chromatography (SiO_2, 20% ethyl acetate in hexane) to afford the title compound **12** (0.68 g, 3.92 mmol, 40%) as a white solid; R_f 0.5 (ethyl acetate); mp 99–100 °C (EtOAc/hexane); δ_H (400 MHz, $CDCl_3$) 7.53 (1H, dd, *J*=5.6, 2.4 Hz, C*H*═CHC═O), 6.71 (1H, s, N*H*), 6.33 (1H, dd, *J*=5.6, 1.8 Hz, CH═C*H*C═O), 5.31–5.23 (1H, m, C*H*NH), 4.09 (2H, s, CH_2Cl), 2.91 (1H, dd, *J*=18.8, 6.8 Hz, C*H*H), 2.22 (1H, dd, *J*=18.8, 2.7 Hz, CH*H*); δ_C (100 MHz, $CDCl_3$) 205.5 (s), 165.8 (s), 160.6 (d), 136.2 (d), 50.0 (d), 42.4 (t), 41.7 (t); *m/z* (CI) 191 ($[MNH_4]^+$, 100%), 174 ($[MH]^+$, 39), 173 ($[M]^+$, 3.7). Found $[MH]^+$ 174.0321 ($[MH]^+$ $C_7H_9NO_2Cl$ requires 174.0322).

3.1.5. 2-Oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylic acid *tert*-butyl ester (15).[6] Water (5 mL) and sodium carbonate (23.9 g, 0.23 mol) were added to a suspension of hydroxylamine hydrochloride (24.0 g, 0.35 mol) in diethyl ether (150 mL). The suspension was stirred at room temperature for 1 h, then cooled to 0 °C. Subsequently, a solution of di-*tert*-butyl dicarbonate (50.2 g, 0.23 mol) in diethyl ether (50 mL) was added dropwise over 30 min and the suspension was allowed to warm up to room temperature, then stirred for 3 h. Upon completion of reaction, the mixture was filtered and washed with ether (2×100 mL). The filtrate was evaporated to dryness to yield a colourless oil. Upon addition of cyclohexane, compound **14** was crystallised as colourless needles (27.2 g, 0.20 mol, 89%, 2 crops).

Tetra-*n*-butylammonium periodate (2.0 g, 4.67 mmol) was added to a solution of freshly cracked cyclopentadiene (0.46 g, 6.97 mmol) in dichloromethane (15 mL). *tert*-Butyl-*N*-hydroxycarbamate **14** (0.62 g, 4.67 mmol) was added portionwise over 5 min and the solution was stirred for 1 h at room temperature. Upon completion of reaction, the organic solution was washed successively with sodium thiosulfate (10% aq. soln., 2×50 mL) and sodium hydrogen carbonate (sat'd. aq., 80 mL), then dried over anhydrous magnesium sulfate, filtered and concentrated to give a crude black oil. Flash chromatography (SiO_2, 20% ethyl acetate in petrol) gave the bicyclic adduct **15** (0.73 g, 3.71 mmol, 79%) as a yellow oil, which solidified upon standing in the freezer; δ_H (400 MHz, $CDCl_3$) 6.41 (2H, m, C*H*═C*H*), 5.20 (1H, m, C*H*NBoc), 4.98 (1H, m, C*H*ON), 1.98 (1H, dt, *J*=8.5, 1.9 Hz, C*H*H), 1.73 (1H, m, CH*H*), 1.46 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 158.6 (s), 134.1 (d), 132.9 (d), 83.5 (d), 81.8 (s), 65.0 (d), 48.1 (t), 28.2 (q).

3.1.6. (4-Hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester (16). *Method A*.[6] Molybdenum hexacarbonyl (1.46 g, 5.53 mmol) was added to a solution of the bicycle **15** (0.70 g, 3.55 mmol) in a 7:1 mixture of acetonitrile and water (24 mL). The suspension was stirred for 10 min at room temperature, then sodium borohydride (0.07 g, 1.85 mmol) was added and the suspension was heated under reflux for 3 h. Upon completion of reaction, the mixture was allowed to cool to room temperature, filtered through a celite® plug, and evaporated to dryness to give a dark oil. Flash chromatography (SiO_2, 50% ethyl acetate in petrol) gave the alcohol **16** (0.46 g, 2.31 mmol, 65%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 6.02–5.96 (1H, m, C*H*═CH), 5.85 (1H, dd, *J*=5.5, 1.2 Hz, CH═C*H*), 4.82–4.67 (2H, m), 4.47–4.39 (1H, m), 2.75 (1H, dt, *J*=14.4, 7.7 Hz, C*H*H), 2.63–2.57 (1H, m, CH*H*), 1.56–1.50 (1H, m, O*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 155.2 (s), 136.1 (d), 134.2 (d), 79.6 (s), 75.3 (d), 55.0 (d), 41.5 (t), 28.4 (q); *m/z* (CI). Found $[MH]^+$ 200.1285 ($[MH]^+$ $C_{10}H_{18}NO_3$ requires 200.1287).

Method B. Disodium hydrogen phosphate (42.3 g, 0.30 mol) was added to a solution of the bicycle **15** (16.9 g, 85.7 mmol) in ethanol (230 mL). After cooling to 0 °C, freshly prepared and pulverised sodium amalgam (150 g, 5% sodium, 0.33 mol) was added in one portion (CAUTION: EXOTHERM). However, after stirring for 1 h at 0 °C some starting material remained, so further amalgam (50 g, 0.11 mol) was added. Further stirring at 0 °C for 30 min allowed full consumption of starting material, so the reaction mixture was then filtered through a celite® plug. The filtrate was then diluted with water (350 mL) and extracted with dichloromethane (3×100 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate, and evaporated in vacuo to give the alcohol **16** (12.7 g, 63.7 mmol, 74%) as a pale yellow oil of suitable purity to be taken on and with identical data to the material prepared via the previous method.

3.1.7. (4-Oxocyclopent-2-enyl)-carbamic acid *tert*-butyl ester (13). *Method A*. 4 Å powdered, activated, molecular sieves (0.50 g) and pyridinium chlorochromate (0.60 g, 2.78 mmol) were successively added to a solution of the alcohol **16** (0.46 g, 2.31 mmol) in anhydrous dichloromethane (20 mL). The suspension was stirred for 2 h at room temperature. Upon completion of reaction, the mixture was filtered over a short silica gel column (50% ethyl acetate in petrol) to give the ketone **13** (0.38 g, 1.93 mmol, 83%) as a white solid; δ_H (400 MHz, $CDCl_3$) 7.51 (1H, m, C*H*═CHC═O), 6.21 (1H, dd, *J*=5.7, 0.7 Hz, CH═C*H*C═O), 4.94 (2H, m, N*H*+C*H*NH), 2.83 (1H, m, C*H*H), 2.17 (1H, m, CH*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 206.9 (s), 162.6 (d), 155.5 (s), 135.5 (d), 80.6 (s), 51.5 (d), 42.7 (t), 28.7 (q); *m/z* (EI). Found $[M]^+$ 197.1057 ($[M]^+$ $C_{10}H_{15}NO_3$ requires 197.1052).

Method B. TEMPO (91 mg, 0.58 mmol) and periodic acid (14.6 g, 64.0 mmol) were successively added to a solution of the alcohol **16** (11.5 g, 57.7 mmol) in dichloromethane (250 mL). The suspension was stirred for 2.5 h at room temperature. The reaction mixture was poured onto sodium thiosulfate (sat'd. aq., 300 mL) (CAUTION: EXOTHERM), the phases separated and the aqueous phase extracted with dichloromethane (3×500 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate, and evaporated in vacuo to give the ketone **13** (11.0 g,

55.8 mmol, 97%) as a white solid of suitable purity to be taken on and with identical data to the material prepared via the previous method.

3.1.8. (2*S*,4*R*)-Acetic acid 4-*tert*-butoxycarbonylamino-cyclopent-2-enyl ester ((+)-17) and (2*S*,4*R*)-(4-hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((−)-16).[10] Vinyl acetate (7.0 mL, 76 mmol) and PS-C II Amano lipase (1.51 g) were successively added to a solution of the racemic alcohol (±)-**16** (1.51 g, 7.59 mmol) in anhydrous dichloromethane (40 mL) and the slurry was stirred for 72 h at 35 °C. The mixture was filtered and evaporated to dryness to give a yellow oil. Flash chromatography (SiO_2, 50% ethyl acetate in petrol) gave the optically active acetate (+)-**17** (0.76 g, 3.15 mmol, 42%) and the optically enriched alcohol (−)-**16** (0.82 g, 4.12 mmol, 55% recovery). Crystallisation from petroleum ether afforded the optically active acetate (+)-**17** (0.64 g) as white orthorhombic crystals, whose stereochemistry was elucidated by obtaining an X-ray structure; δ_H (400 MHz, $CDCl_3$) 5.97 (1H, d, J=5.6 Hz, C*H*=CH), 5.92 (1H, d, J=5.6 Hz, CH=C*H*), 5.54–5.48 (1H, m, C*H*OAc), 4.66 (2H, br. s, N*H*+C*H*NH), 2.81 (1H, dt, J=14.5, 7.3 Hz, C*H*H), 2.02 (3H, s, O_2CCH_3), 1.51 (1H, dt, J=14.5, 4.0 Hz, CH*H*), 1.44 (9H, s, $CO_2C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 170.5 (s), 155.0 (s), 136.9 (d), 132.0 (d), 79.5 (s), 77.4 (d), 54.3 (d), 38.6 (t), 28.3 (q), 21.1 (q); *m*/*z* (CI) 242 ($[MH]^+$, 15%), 182 ($[MH-AcOH]^+$, 34), 142 ($[MH_2-CO_2C(CH_3)_3]^+$, 77), 126 ($[MH-NHBoc]^+$, 100). Found $[MH]^+$ 242.1394 ($[MH]^+$ $C_{12}H_{20}NO_4$ requires 242.1392).

3.1.9. (2*R*,4*S*)-(4-Hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((+)-16). Lithium hydroxide monohydrate (0.17 g, 4.05 mmol) was added to a solution of the optically active acetate (+)-**17** (0.64 g, 2.66 mmol) in 75% aqueous ethanol (40 mL). The solution was stirred for 4 h at room temperature. Upon completion of reaction, the mixture was partitioned between water (40 mL) and ethyl acetate (40 mL), and the aqueous layer was further extracted with ethyl acetate (2×30 mL). The combined organic layers were washed successively with sodium hydrogen carbonate (sat'd. aq., 40 mL), water (40 mL) and brine (40 mL), then dried over anhydrous magnesium sulfate and evaporated to give the optically active alcohol (+)-**16** (0.50 g, 2.51 mmol, 95%) as a light yellow oil, which solidified upon standing at room temperature; $[\alpha]_D$=+64.0 (*c* 1.0, $CHCl_3$); and gave identical data to the racemic material described in Section 3.1.6.

3.1.10. (2*R*)-(4-Oxocyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((+)-13). 4 Å powdered, activated, molecular sieves (0.50 g) and pyridinium chlorochromate (0.65 g, 3.02 mmol) were successively added to a solution of the optically active alcohol (+)-**16** (0.50 g, 2.54 mmol) in anhydrous dichloromethane (20 mL). The suspension was stirred for 1.5 h at room temperature. Upon completion of reaction, the mixture was filtered over a short silica gel column (50% ethyl acetate in petrol) to give the optically active cyclopentenone (+)-**13** (0.40 g, 2.03 mmol, 80%) as a white solid; ee=92% (determined by chiral GC (Lipodex; 140 °C; t_R (+)-**13**=19.0 min)); $[\alpha]_D$=+71.0 (*c* 1.0, $CHCl_3$); which gave identical data to the racemic material described in Section 3.1.7.

3.1.11. (2*R*,4*S*)-Acetic acid 4-*tert*-butoxycarbonylamino-cyclopent-2-enyl ester ((−)-17). A solution of acetyl chloride (0.53 mL, 7.45 mmol) in anhydrous dichloromethane (10 mL) was added slowly to a solution of the enriched alcohol (−)-**16** (1.13 g, 5.68 mmol) in a mixture of pyridine (10 mL) and anhydrous dichloromethane (10 mL), cooled to 0 °C. The mixture was stirred overnight at 0 °C. Upon completion of reaction, the mixture was evaporated and diluted with ethyl acetate (200 mL), then washed with citric acid (10% aq. soln., 200 mL). The aqueous layer was then extracted with ethyl acetate (150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered and evaporated to give a yellow oil. Flash chromatography (SiO_2, 50% ethyl acetate in petrol) gave the optically enriched acetate (−)-**17** (1.15 g, 4.77 mmol, 84%) as a yellow oil, which showed identical spectroscopic data to its enantiomer (+)-**17** as described in Section 3.1.8.

PS-C II Amano lipase (1.15 g) was added to an emulsion of the enriched acetate (−)-**17** (1.15 g, 4.77 mmol) in a mixture of acetone (20 mL) and phosphate buffer (c=0.1 M, pH=7.4, 20 mL). The slurry was stirred for 54 h at 35 °C. The mixture was filtered and evaporated to dryness to give a yellow oil. Flash chromatography (SiO_2, 50% ethyl acetate in petrol) gave in the order of elution, the optically active acetate (−)-**17** (0.84 g, 3.49 mmol, 73% recovery), and the optically enriched alcohol (+)-**16** (0.19 g, 0.95 mmol, 20%).

3.1.12. (2*S*,4*R*)-(4-Hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((−)-16). Lithium hydroxide monohydrate (0.22 g, 5.24 mmol) was added to a solution of the optically active acetate (−)-**17** (0.84 g, 3.49 mmol) in 75% aqueous ethanol (48 mL). The solution was stirred overnight at room temperature. Upon completion of reaction, the mixture was partitioned between water (50 mL) and ethyl acetate (50 mL), and the aqueous layer was further extracted with ethyl acetate (2×50 mL). The combined organic layers were washed successively with sodium hydrogen carbonate (sat'd. aq., 50 mL), water (50 mL) and brine (50 mL), then dried over anhydrous magnesium sulfate and evaporated to give the optically active alcohol (−)-**16** (0.70 g, 100%) as a light yellow oil, which solidified upon standing at room temperature; $[\alpha]_D$=−67.0 (*c* 1.0, $CHCl_3$); and gave identical data to the racemic material described in Section 3.1.6.

3.1.13. (2*S*)-(4-Oxocyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((−)-13). 4 Å powdered, activated, molecular sieves (0.75 g) and pyridinium chlorochromate (0.91 g, 4.22 mmol) were successively added to a solution of the optically active alcohol (−)-**16** (0.70 g, 3.52 mmol) in anhydrous dichloromethane (30 mL). The suspension was stirred for 1 h at room temperature. Upon completion of reaction, the mixture was filtered over a short silica gel column (50% ethyl acetate in petrol) to give the optically active cyclopentenone (−)-**13** (0.55 g, 2.79 mmol, 79%) as a white solid; ee=99% (determined by chiral GC (Lipodex; 140 °C; t_R (−)-**13**=18.4 min)); $[\alpha]_D$=−72.0 (*c* 1.0, $CHCl_3$); which gave identical data to the racemic material described in Section 3.1.7.

3.1.14. (2*RS*,4*SR*)-Acetic acid 4-*tert*-butoxycarbonylaminocyclopent-2-enyl ester ((±)-17). 1,1′-Bis(diphenylphosphino)ferrocene (1.43 g, 2.28 mmol), tris(dibenzylideneacetone)dipalladium (554 mg, 0.61 mmol) and anhydrous, oxygen-free tetrahydrofuran (90 mL) were added to dry reaction vessel, under an atmosphere of nitrogen, to give a very dark purple solution. After stirring for 20 min at room temperature, the solution turned dark orange/brown. Di-*tert*-butyl iminodicarboxylate (22.4 g, 0.10 mol) and the *meso*-diacetate **18** (19.0 g, 0.10 mol) were added and the resulting mixture was quickly degassed by placing under reduced pressure, then backfilling with nitrogen. *N*, *O*-Bis(trimethylsilyl)acetamide (21.0 g, 0.10 mol) was then added and a further 3 degassing cycles carried out. The resulting solution was heated to 50 °C for 12 h, when tlc analysis showed the reaction to be complete. Diethyl ether (200 mL) was then added and the mixture was poured onto ammonium chloride (sat'd., aq., 100 mL). The phases were then separated and the aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 12% ethyl acetate in hexane) gave the mono-substituted product **19** (31.7 g, 92.8 mmol, 90%) as a white solid; δ_H (400 MHz, $CDCl_3$) 5.98 (1H, dt, J=5.6, 1.7 Hz, C*H*=CH), 5.82 (1H, dt, J=5.6, 2.2 Hz, CH=C*H*), 5.59–5.53 (1H, m, C*H*OAc), 5.14–5.08 (1H, m, C*H*N), 2.84 (1H, dt, J=13.3, 8.0 Hz, C*H*H), 2.04 (3H, s, O_2CCH_3), 1.93 (1H, dt, J=13.3, 6.6 Hz, CH*H*), 1.49 (18H, s, $N[CO_2C(CH_3)_3]_2$); which was taken on without further characterisation.

Trifluoroacetic acid (15.3 g, 0.13 mol) was added to a solution of this product **19** (31.3 g, 91.7 mmol) in dichloromethane (450 mL) at 0 °C. The mixture was then stirred for 20 h. Sodium hydrogen carbonate (sat'd., aq., 400 mL) was then added, the phases separated and the aqueous phase extracted with dichloromethane (3×20 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 25% ethyl acetate in hexane) gave the mono-Boc product (±)-**17** (21.5 g, 89.1 mmol, 97%) as a pale yellow oil, which gave identical data to the enantiomerically enriched material prepared by the method in Section 3.1.8.

3.1.15. (2*R*,4*S*)-(4-Hydroxycyclopent-2-enyl)-carbamic acid *tert*-butyl ester ((+)-16). 1,1′-Bis(diphenylphosphino)ferrocene (80 mg, 0.14 mmol), tris(dibenzylideneacetone)dipalladium (32 mg, 35 μmol) and anhydrous, oxygen-free tetrahydrofuran (4 mL) were added to dry reaction vessel, under an atmosphere of nitrogen, to give a very dark purple solution. After stirring for 15 min at room temperature, the solution turned dark orange/brown. This solution was added, via cannula, to a solution of di-*tert*-butyl iminodicarboxylate (0.75 g, 3.45 mmol) and the mono-acetate **20** (0.50 g, 3.42 mmol) in anhydrous, oxygen-free tetrahydrofuran (4 mL) and the resulting mixture was quickly degassed by placing under reduced pressure, then backfilling with nitrogen. *N*, *O*-Bis(trimethylsilyl)acetamide (0.84 g, 4.14 mmol) was then added and a further 2 degassing cycles carried out. The resulting solution was heated to 45 °C for 3 h, when tlc analysis showed the reaction to be complete. This was then filtered through a short pad of silica and the filtrate was treated with a solution of tetrabutylammonium fluoride in tetrahydrofuran and washed with brine. The organics were then dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 25% ethyl acetate in hexane) gave the mono-substituted product **21** (714 mg, 2.39 mmol, 68%) as a white solid; mp 54–55 °C (EtOAc/hexane); δ_H (400 MHz, $CDCl_3$) 6.04 (1H, dt, J=5.4, 2.3 Hz, C*H*=CH), 5.76 (1H, dd, J=5.4, 2.3 Hz, CH=C*H*), 5.09 (1H, app. dq, J=9.3, 2.3 Hz, C*H*N), 4.60 (1H, m, C*H*OH), 3.53 (1H, br. d, J=11.0 Hz, O*H*), 2.68 (1H, ddd, J=15.1, 9.3, 7.9 Hz, C*H*H), 1.85 (1H, dt, J=15.1, 2.3 Hz, CH*H*), 1.49 (18H, s, $N[CO_2C(CH_3)_3]_2$); δ_C (100 MHz, $CDCl_3$) 153.3 (s), 136.8 (d), 131.4 (d), 82.8 (s), 75.7 (d), 60.2 (d), 38.8 (t), 28.0 (q); *m*/*z* (CI). Found $[MNa]^+$ 322.1642 ($[MNa]^+$ $C_{15}H_{25}NO_5Na$ requires 322.1630). Found: C, 60.4; H, 8.6; N, 4.4, $C_{15}H_{25}NO_5$ requires C, 60.2; H, 8.4; N, 4.7%.

Trifluoroacetic acid (0.41 g, 3.60 mol) was added to a solution of this product **21** (0.71 g, 2.37 mmol) in dichloromethane (12 mL) at 0 °C. The mixture was then stirred for 20 h. Sodium hydrogen carbonate (sat'd., aq., 12 mL) was then added, the phases separated and the aqueous phase extracted with dichloromethane (3×20 mL). The combined organic extracts were then dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 50% ethyl acetate in hexane) gave the mono-Boc product (+)-**16** (452 mg, 2.27 mmol, 96%) as a pale yellow oil; ee=98% (determined by chiral HPLC (OD; 5% ethanol in hexane; t_R (+)-**16**=8.1 min; t_R (−)-**16**=7.3 min)); which gave identical data to the racemic material prepared by the method in Section 3.1.6.

3.1.16. Toluene-4-sulfonic acid 5,5-dimethyl-4-oxocyclopent-2-enyl ester (22). *p*-Toluenesulfonyl chloride (477 mg 2.50 mmol) was added to a solution of 4-hydroxy-5,5-dimethylcyclopent-2-enone (252 mg, 2.00 mmol) and 4-dimethylaminopyridine (366 mg, 3.00 mmol) in dichloromethane (6 mL) and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (Si_2O, dichloromethane) to give the tosylate **22** (500 mg, 1.78 mmol, 89%) as a white solid; mp 74–75 °C (Et_2O/hexane); ν_{max}(film)/cm^{-1} 2976, 1727, 1598; δ_H (400 MHz, $CDCl_3$) 7.85 (2H, d, J=8.1 Hz, Ar*H*), 7.40 (2H, d, J=8.1 Hz, Ar*H*), 7.28 (1H, dd, J=6.0, 2.3 Hz, C*H*=CHC=O), 6.27 (1H, dd, J=6.0, 1.4 Hz, CH=C*H*C=O), 5.20–5.19 (1H, m, C*H*OTs), 2.48 (3H, s, ArCH_3), 1.04 (3H, s, CCH_3), 1.03 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 208.5 (s), 155.5 (d), 145.5 (s), 134.9 (d), 133.3 (s), 130.1 (d), 127.9 (d), 86.2 (d), 47.3 (s), 22.3 (q), 21.7 (q), 20.7 (q); *m*/*z* (CI) 298 ($[MNH_4]^+$, 43%). Found $[MNH_4]^+$ 298.1113 ($[MNH_4]^+$ $C_{14}H_{20}NO_4S$ requires 298.1113). Found: C, 60.0; H, 5.7, $C_{14}H_{16}O_4S$ requires C, 60.0; H, 5.8%.

3.1.17. 4-(Benzylmethylamino)-5,5-dimethylcyclopent-2-enone (23). Benzyl methylamine (34 μL, 0.26 mmol) was added to a solution of tosylate **22** (33 mg, 0.12 mmol) in ethanol (12 mL) and the reaction was heated at reflux for 48 h. The reaction was allowed to cool and the solvent removed in vacuo. The crude product was dissolved in

diethyl ether (10 mL) and $NaHCO_3$ (sat'd., aq., 10 mL) added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 10% ethyl acetate in hexane) gave the title compound **23** (20 mg, 87 μmol, 74%) as a colourless oil; ν_{max}(film)/cm^{-1} 1712; δ_H (400 MHz, $CDCl_3$) 7.66 (1H, dd, *J*=6.0, 2.4 Hz, C*H*=CHC=O), 7.37–7.25 (5H, m, Ar*H*), 6.24 (1H, dd, *J*=6.0, 1.9 Hz, CH=C*H*C=O), 3.72 (2H, s, CH_2Ar), 3.62 (1H, t, *J*=2.2 Hz, C*H*N), 2.30 (3H, s, NCH_3), 1.19 (3H, s, CCH_3), 1.08 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 213.1 (s), 160.6 (d), 139.4 (s), 132.8 (d), 128.4 (d), 128.3 (d), 127.1 (d), 74.3 (d), 60.2 (t), 48.2 (s), 40.3 (q), 26.4 (q), 20.1 (q); *m*/*z* (CI) 230 ([MH]$^+$, 100%). Found [MH]$^+$ 230.1553 ([MH]$^+$ $C_{15}H_{20}NO$ requires 230.1545).

3.1.18. 5,5-Dimethyl-4-morpholin-4-yl-cyclopent-2-enone (24). Morpholine (35 μL, 0.40 mmol) was added to a solution of tosylate **22** (50 mg, 0.18 mmol) in ethanol (18 mL) and the reaction was heated at reflux for 48 h. The reaction was allowed to cool and the solvent removed in vacuo. The crude product was dissolved in diethyl ether (5 mL) and $NaHCO_3$ (sat'd., aq., 5 mL) added. The layers were separated and the aqueous layer was extracted with diethyl ether (2×5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 50% ethyl acetate in hexane) gave the title compound **24** (23 mg, 0.12 mmol, 66%) as a pale orange oil; ν_{max}(film)/cm^{-1} 1713; δ_H (400 MHz, $CDCl_3$) 7.65 (1H, dd, *J*=6.0, 2.4 Hz, C*H*=CHC=O), 6.24 (1H, dd, *J*=6.0, 1.9 Hz, CH=C*H*C=O), 3.75–3.65 (4H, m, 2×CH_2), 3.35 (1H, t, *J*=2.2 Hz, C*H*N), 2.63 (4H, t, *J*=4.6 Hz, 2×CH_2), 1.15 (3H, s, CCH_3), 1.11 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 213.0 (s), 159.4 (d), 133.3 (d), 76.1 (d), 67.6 (t), 52.9 (t), 48.3 (s), 26.6 (q), 20.6 (q); *m*/*z* (CI) 196 ([MH]$^+$, 100%). Found [MH]$^+$ 196.1340 ([MH]$^+$ $C_{11}H_{18}NO_2$ requires 196.1337).

3.1.19. 4-[4-(4-Fluorophenyl)-piperazin-1-yl]-5,5-dimethylcyclopent-2-enone (25). 1-(4-Fluorophenyl)-piperazine (83 mg, 0.46 mmol) was added to a solution of tosylate **22** (60 mg, 0.21 mmol) in ethanol (20 mL) and the reaction was heated at reflux for 19 h. The reaction was allowed to cool and the solvent removed in vacuo. The crude product was dissolved in diethyl ether (5 mL) and $NaHCO_3$ (sat'd., aq., 5 mL) added. The layers were separated and the aqueous layer was extracted with diethyl ether (2×5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and evaporated in vacuo. Flash chromatography (SiO_2, 25% ethyl acetate in hexane) gave the title compound **25** (41 mg, 0.14 mmol, 65%) as a colourless oil; ν_{max}(film)/cm^{-1} 1712, 1510, 1236; δ_H (400 MHz, $CDCl_3$) 7.68 (1H, dd, *J*=6.0, 2.5 Hz, C*H*=CHC=O), 6.99–6.93 (2H, m, Ar*H*), 6.89–6.84 (2H, m, Ar*H*), 6.25 (1H, dd, *J*=6.0, 1.8 Hz, CH=C*H*C=O), 3.44 (1H, t, *J*=2.2 Hz, C*H*N), 3.15–3.06 (4H, m, 2×CH_2), 2.83–2.74 (4H, m, 2×CH_2), 1.17 (3H, s, CCH_3), 1.13 (3H, s, CCH_3); δ_C (100 MHz, $CDCl_3$) 213.2 (s), 159.7 (d), 158.8 (s), 148.3 (s), 133.3 (d), 118.3 (d), 115.9 (d), 75.7 (d), 52.2 (t), 51.0 (t), 48.3 (s), 26.8 (q), 20.5 (q); *m*/*z* (CI) 289 ([MH]$^+$, 100%). Found [MH]$^+$ 289.1720 ([MH]$^+$ $C_{17}H_{22}FN_2O$ requires 289.1716).

3.1.20. 4-Hexylsulfanyl-5,5-dimethylcyclopent-2-enone (26), *trans*-2,2-dimethyl-4-hexylsulfanyl-3-*O*-*para*-toluenesulfonylcyclopentanone (28) and *cis*-2,2-dimethyl-4-hexylsulfanyl-3-*O*-*para*-toluenesulfonyl-cyclopentanone (30). A solution of DBU (0.16 mL, 1.07 mmol) and hexanethiol (0.15 mL, 1.07 mmol) in dry tetrahydrofuran (1 mL) was added to a solution of tosylate **22** (300 mg, 1.07 mmol) in dry tetrahydrofuran (2 mL). The reaction mixture was stirred for 1 min before solvent was removed at 0 °C. Flash chromatography of the residue (SiO_2, 2%, then 5% ethyl acetate in hexane) afforded the enone **26** (104 mg, 0.46 mmol, 43%) as a yellow viscous oil; ν_{max}(film)/cm^{-1} 1709; δ_H (300 MHz, $CDCl_3$) 7.50 (1H, dd, *J*=5.8, 2.5 Hz, C*H*=CHC=O), 6.16 (1H, dd, *J*=5.8, 1.9 Hz, CH=C*H*C=O), 3.66 (1H, dd, *J*=2.5, 1.9 Hz, C*H*S), 2.57 (2H, t, *J*=7.4 Hz, SCH_2), 1.64–1.55 (2H, m, SCH$_2$CH_2), 1.47–1.20 (6H, m, (CH_2)$_3$CH$_3$), 1.18 (3H, s, CCH_3), 1.16 (3H, s, CCH_3), 0.90 (3H, t, *J*=6.7 Hz, CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 215.5 (s), 161.2 (d), 131.0 (d), 57.6 (d), 47.6 (s), 32.4 (t), 31.4 (t), 29.7 (t), 28.5 (t), 25.2 (t), 22.5 (q), 22.2 (q), 13.9 (q); *m*/*z* (EI) 226 ([M]$^+$, 5%), 109 ([M−SC$_6$H$_{13}$]$^+$, 100). Found [M]$^+$ 226.1392 ([M]$^+$ $C_{13}H_{22}OS$ requires 226.1391); then the *trans*-3,4-disubstituted cyclopentanone **28** (98 mg, 0.25 mmol, 23%) as a white solid; mp 34–35 °C (EtOAc/hexane); ν_{max}(film)/cm^{-1} 1747; δ_H (300 MHz, $CDCl_3$) 7.88–7.84 (2H, m, Ar*H*), 7.40–7.35 (2H, m, Ar*H*), 4.75 (1H, d, *J*=6.0 Hz, C*H*OTs), 3.35 (1H, m, C*H*S), 2.92 (1H, dd, *J*=19.2, 9.0 Hz, C*H*HC=O), 2.52–2.40 (5H, m, SCH_2, ArCH_3), 2.29 (1H, dd, *J*=19.2, 8.1 Hz, CH*H*C=O), 1.57–1.41 (2H, m, SCH$_2$CH_2), 1.40–1.21 (6H, m, (CH_2)$_3$CH$_3$), 1.20 (3H, s, CCH_3), 1.00 (3H, s, CCH_3), 0.89 (3H, t, *J*=6.9 Hz, CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 215.3 (s), 145.2 (s), 134.0 (s), 129.9 (d), 128.1 (d), 90.6 (d), 49.9 (s), 42.8 (d), 42.0 (t), 31.8 (t), 31.3 (t), 29.3 (t), 28.4 (t), 23.4 (t), 22.4 (q), 21.5 (q), 19.2 (q), 13.9 (q). Found: C, 60.3; H, 7.7, $C_{20}H_{30}O_4S_2$ requires C, 60.3; H, 7.6%; and finally, the corresponding *cis*-iosmer **30** (90 mg, 0.23 mmol, 21%) as a white solid; mp 37–38 °C (diethyl ether/hexane); ν_{max}(film)/cm^{-1} 1746; δ_H (300 MHz, $CDCl_3$) 7.88–7.84 (2H, m, Ar*H*), 7.35–7.32 (2H, m, Ar*H*), 5.00 (1H, d, *J*=4.4 Hz, C*H*OTs), 3.56–3.48 (1H, m, C*H*S), 2.69 (1H, dd, *J*=18.7, 8.1 Hz, C*H*HC=O), 2.53–2.37 (6H, m, SCH_2, ArCH_3, CH*H*C=O), 1.55–1.41 (2H, m, SCH$_2$CH_2), 1.40–1.20 (6H, m, (CH_2)$_3$CH$_3$), 1.10 (3H, s, CCH_3), 1.07 (3H, s, CCH_3), 0.89 (3H, t, *J*=6.8 Hz, CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 215.9 (s), 144.9 (s), 134.2 (s), 129.6 (d), 128.2 (d), 88.4 (d), 51.0 (s), 42.5 (d), 42.0 (t), 32.0 (t), 31.4 (t), 29.4 (t), 28.5 (t), 23.6 (t), 22.5 (q), 21.6 (q), 19.4 (q), 14.0 (q); *m*/*z* (EI) 398 ([M]$^+$, 8%), 226 ([M−TsOH]$^+$, 24), 171 ([TsO]$^+$, 33), 155 ([Ts]$^+$, 29), 109 ([M−TsOHSC$_6$H$_{13}$]$^+$, 27). Found [M]$^+$ 398.1582 ([M]$^+$ $C_{20}H_{30}O_4S_2$ requires 398.1586). Found: C, 60.4; H, 7.6, $C_{20}H_{30}O_4S_2$ requires C, 60.3; H, 7.6%.

3.1.21. Conversion of *trans*-2,2-dimethyl-4-hexylsulfanyl-3-*O*-*p*-toluenesulfonyl-cyclopentanone (28) to 4-hexylsulfanyl-5,5-dimethylcyclopent-2-enone (26). A solution of **28** (15.8 mg, 40 μmol) in dichloromethane (1 mL) was refluxed for 1 h. The solvent was removed in vacuo and flash chromatography (SiO_2, 2.5% ethyl acetate in hexane) of the residue afforded enone **26** (8.3 mg, 37 μmol, 93%) as a yellow viscous oil; which showed identical spectroscopic data to the material obtained by the

procedure described above in Section 3.1.20. Thiol adduct **30** remained unchanged even after prolonged refluxing (10 h) under the same conditions.

3.1.22. 4-Octylsulfanyl-5,5-dimethylcyclopent-2-enone (27), *trans*-2,2-dimethyl-4-octylsulfanyl-3-*O*-*para*-toluenesulfonylcyclopentanone (29) and *cis*-2,2-dimethyl-4-octylsulfanyl-3-*O*-*para*-toluenesulfonylcyclopentanone (31). A solution of DBU (0.16 mL, 1.07 mmol) and *n*-octanethiol (0.19 mL, 1.07 mmol) in dry tetrahydrofuran (1 mL) was added to a solution of tosylate **22** (300 mg, 1.07 mmol) in dry tetrahydrofuran (2 mL). The reaction mixture was stirred for 10 min, then evaporated in vacuo. Flash chromatography of the residue (SiO_2, 2%, then 5% ethyl acetate in hexane) afforded the enone **27** (0.11 g, 0.43 mmol, 40%) as a yellow viscous oil; ν_{max}(film)/cm^{-1} 1709; δ_H (300 MHz, $CDCl_3$) 7.50 (1H, dd, J=5.8, 2.5 Hz, C*H*=CHC=O), 6.15 (1H, dd, J=5.8, 1.9 Hz, CH=C*H*C=O), 3.66 (1H, dd, J=2.5, 1.9 Hz, C*H*S), 2.56 (2H, t, J=7.4 Hz, SCH_2), 1.67–1.55 (2H, m, SCH_2CH_2), 1.45–1.20 (10H, m, $(CH_2)_5CH_3$), 1.18 (3H, s, CCH_3), 1.16 (3H, s, CCH_3), 0.88 (3H, t, J=6.7 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 212.6 (s), 161.3 (d), 131.1 (d), 57.6 (d), 47.5 (s), 32.3 (t), 31.7 (t), 29.7 (t), 29.1 (t), 29.0 (t), 28.8 (t), 25.2 (t), 22.5 (q), 22.1 (q), 13.9 (q); *m*/*z* (EI) 254 ($[M]^+$, 2%), 109 ($[M-SC_8H_{17}]^+$, 100). Found $[M]^+$ 254.1703 ($[M]^+$ $C_{15}H_{26}OS$ requires 254.1704); then the *trans*-3,4-disubstituted cyclopentanone **29** (0.12 g, 0.28 mmol, 26%) as a white solid; mp 58–59 °C (EtOAc/hexane); ν_{max}(film)/cm^{-1} 1748; δ_H (300 MHz, $CDCl_3$) 7.88–7.84 (2H, m, Ar*H*), 7.39–7.35 (2H, m, Ar*H*), 4.75 (1H, d, J=6.0 Hz, C*H*OTs), 3.35 (1H, m, C*H*S), 2.92 (1H, dd, J=19.1, 9.0 Hz, C*H*HC=O), 2.60–2.40 (5H, m, SCH_2, ArCH_3), 2.30 (1H, dd, J=19.1, 8.0 Hz, CH*H*C=O), 1.60–1.41 (2H, m, SCH_2CH_2), 1.40–1.21 (10H, m, $(CH_2)_5CH_3$), 1.20 (3H, s, CCH_3), 1.00 (3H, s, CCH_3), 0.89 (3H, t, J=6.7 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 215.2 (s), 145.1 (s), 133.9 (s), 129.9 (d), 128.1 (d), 90.6 (d), 49.9 (s), 42.8 (d), 42.0 (t), 31.9 (t), 31.8 (t), 29.4 (t), 29.1 (t), 28.8 (t), 23.5 (t), 22.6 (q), 21.6 (q), 19.2 (q), 14.0 (q). Found: C, 61.8; H, 8.1, $C_{22}H_{34}O_4S_2$ requires C, 61.9; H, 8.0%; and finally, the corresponding *cis*-iosmer **31** (96 mg, 0.23 mmol, 21%) as a white solid; mp 50–51 °C (diethyl ether/hexane); ν_{max}(film)/cm^{-1} 1747; δ_H (300 MHz, $CDCl_3$) 7.87–7.84 (2H, m, Ar*H*), 7.36–7.32 (2H, m, Ar*H*), 5.00 (1H, d, J=4.3 Hz, C*H*OTs), 3.56–3.48 (1H, m, C*H*S), 2.68 (1H, dd, J=18.7, 8.1 Hz, C*H*HC=O), 2.53–2.37 (6H, m, SCH_2, ArCH_3, CH*H*C=O), 1.60–1.41 (2H, m, SCH_2CH_2), 1.40–1.18 (10H, m, $(CH_2)_5CH_3$), 1.10 (3H, s, CCH_3), 1.07 (3H, s, CCH_3), 0.89 (3H, t, J=6.7 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 215.9 (s), 144.9 (s), 134.2 (s), 129.6 (d), 128.2 (d), 88.4 (d), 51.0 (s), 42.5 (d), 42.0 (t), 32.1 (t), 31.8 (t), 29.5 (t), 29.2 (t), 28.9 (t), 23.7 (t), 22.6 (q), 21.6 (q), 19.5 (q), 14.0 (q); *m*/*z* (EI) 426 ($[M]^+$, 5%), 254 ($[M-TsOH]^+$, 7), 155 ($[Ts]^+$, 28), 109 ($[M-TsOHSC_8H_{17}]^+$, 46). Found $[M]^+$ 426.1895 ($[M]^+$ $C_{22}H_{34}O_4S_2$ requires 426.1899). Found: C, 61.9; H, 8.1, $C_{22}H_{34}O_4S_2$ requires C, 61.9; H, 8.0%.

3.1.23. Conversion of *trans*-2,2-dimethyl-4-octylsulfanyl-3-*O*-*p*-toluenesulfonyl-cyclopentanone (29) to 4-octylsulfanyl-5,5-dimethylcyclopent-2-enone (27). A solution of **29** (17 mg, 40 μmol) in dichloromethane (1 mL) was refluxed for 1 h. The solvent was removed in vacuo and flash chromatography (SiO_2, 2.5% ethyl acetate in hexane) of the residue afforded enone **27** (9 mg, 35 μmol, 89%) as a yellow viscous oil; which showed identical spectroscopic data to the material obtained by the procedure described above in Section 3.1.22. Thiol adduct **31** remained unchanged even after prolonged refluxing (10 h) under the same conditions.

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