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Evaluation of a new linker system cleaved using samarium(II) iodide. Application in the solid phase synthesis of carbonyl compounds

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A new linker design for solid phase synthesis has been developed that is cleaved under mild, neutral conditions using samarium(II) iodide. The feasibility of the linker approach has been illustrated in the solid phase synthesis of ketones and amides using an oxygen linker. Insights into the mechanism of the samarium(II) iodide cleavage reaction are described and the potential of a sequential cleavage carbon–carbon bond forming process is assessed.

Introduction

Solid phase organic synthesis remains an important tool for synthetic chemists who wish to prepare collections of compounds in an efficient manner.[1] At the heart of solid phase synthesis lie linker groups.[2] The design of new linker strategies is crucial to the continued development of the field. Our interest in new linker systems for synthesis has led us to develop ephedrine-based linkers for asymmetric solid phase synthesis.[3] Furthermore, we have demonstrated the potential of the chemistry for asymmetric library synthesis.[3b] Here we report the evaluation of a potential family of linkers cleaved using electron-transfer reagents such as samarium(II) iodide (SmI_2).[4] The new linker can be described as being *traceless*, the most common definition of which is when an aliphatic or aromatic proton is introduced at the point of cleavage.[2c,d] Traceless linkers are often the most useful type of linker as no residual functionality is left at the point of attachment.

Cleavage of the linker described here relies on the well-established reduction of α-heteroatom substituted carbonyl compounds with SmI_2 (Fig. 1). In 1986, Molander carried out the first detailed studies on the reduction of α-heterosubstituted ketones[5a] and α,β-epoxy ketones.[5b] Shortly afterwards, Inanaga reported conditions for the reduction of the analogous ester substrates using the SmI_2–HMPA reagent system.[5c,d] The reduction of α-heterosubstituted amides has only recently been reported by Simpkins.[6]

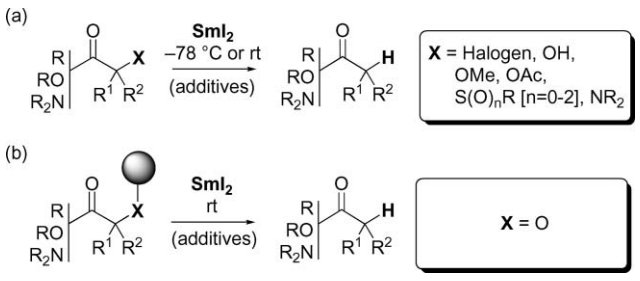


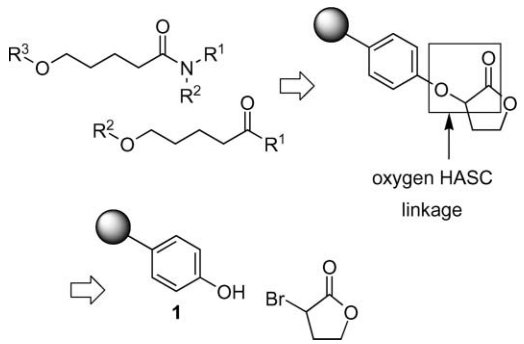
Fig. 1 (a) The reduction of α-heteroatom substituted carbonyl compounds with SmI_2: (b) The α-Hetero-Atom Substituted Carbonyl or HASC linker strategy.

The mild, neutral conditions of the SmI_2 process and its applicability to different classes of carbonyl compound have allowed the reaction to be employed extensively in organic synthesis, often on complex substrates bearing sensitive functionality. The reaction has recently found application in a variety of areas[7] including natural product synthesis,[8] the stereoselective preparation of unsaturated esters and amides, including isotopically labelled analogues,[9] and the development of new methods for asymmetric protonation.[10] We felt the impressive specificity of the reducing agent for the α-heteroatom substituted carbonyl motif would be an ideal feature for a new linker system.

In our linker approach, if the 'X' group in Fig. 1 represents a heteroatom linkage to solid support, then the overall reaction represents cleavage from the support and introduction of a proton at the point of cleavage. We refer to this new class of linker as an α-Hetero-Atom Substituted Carbonyl or HASC linker.[11] In this article we describe in detail the realisation of our linker approach and illustrate its application in the solid-phase synthesis of acyclic carbonyl compounds using an oxygen-based HASC linker.[12]

Results and discussion

At the outset of our studies few examples of the use of SmI_2 in solid-phase chemistry had been described.[13] It was therefore important not only to assess the feasibility of our proposed linker system but also to further verify the compatibility of the reagent with polymeric supports. We therefore decided to begin our studies by investigating the solid phase synthesis of simple amides and ketones from γ-butyrolactone immobilized by an oxygen linkage α to the lactone carbonyl (Scheme 1).



Scheme 1 An approach to simple amides and ketones from an immobilized lactone.

As shown in Scheme 1, we chose to establish the linkage through the reaction of a phenol resin with an α-halo carbonyl compound. This immobilisation approach was selected due to the ready availability of α-halo carbonyl compounds and the

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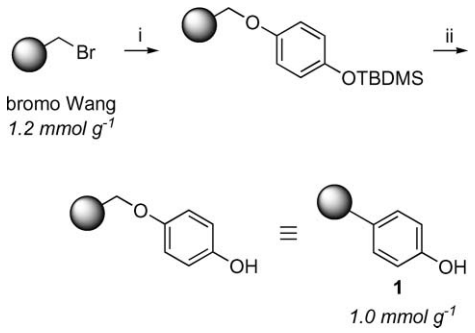
predicted ease of the etherification reaction with phenols. Phenol resin **1** was readily prepared from commercially available bromo Wang resin in two steps and in good overall yield (Scheme 2).

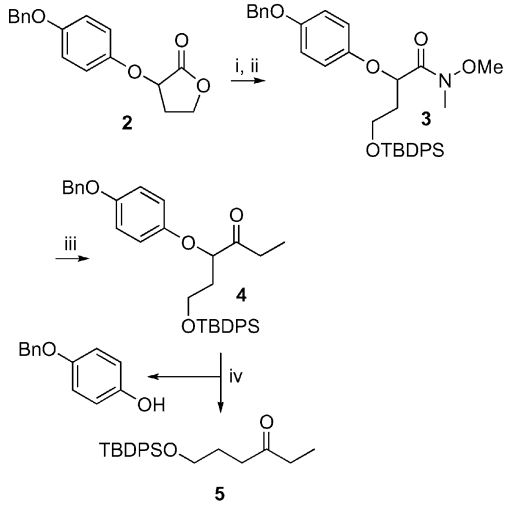


Scheme 2 *Reagents and conditions*: i, 4-TBDMSOC$_6$H$_4$OH 4 eq, NaH 5 eq, DMF, rt, 18 h; ii, TBAF (1 M in THF) 6 eq, THF, rt, 15 h (resin re-treated under the same conditions): Overall yield ~80%.

The loading of phenol resin **1** was determined by cleavage with TFA–CH_2Cl_2 (1 : 1) and isolation of hydroquinone, in conjunction with bromine elemental analysis of the resin.

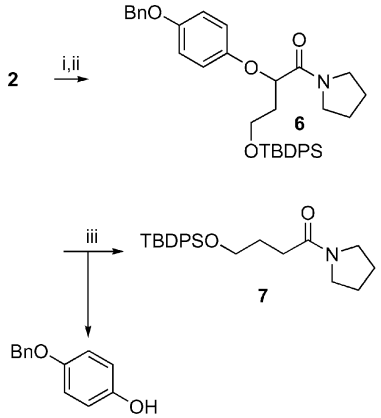
Before solid phase studies were begun, solution model studies using benzyloxyphenol as a model for resin **1** were carried out. The reaction of benzyloxyphenol with α-bromo-γ-butyrolactone (K_2CO_3, DMF, 18-crown-6, 60 °C, 24 h) gave lactone **2** in 74% yield. Ring-opening and Weinreb amide formation followed by protection of the primary hydroxyl group then gave **3** (Scheme 3). Finally, reaction with EtMgCl gave ketone **4**, a model substrate for the samarium(II) cleavage reaction, in good overall yield. Pleasingly, treatment of **4** with samarium(II) iodide at 0 °C resulted in complete conversion to ketone **5** (93% isolated yield) and benzyloxyphenol (90% isolated yield) in less than 5 min. This sequence shows the potential of our linker approach and illustrated the compatibility of the linkage with strongly basic and Lewis acid conditions. In addition, the link proved to be stable during the addition of Grignard reagents to the amide carbonyl group. The solution model studies also suggested the possibility of recovering and reusing the phenol resin **1**.

We also carried out solution phase model studies to assess the feasibility of preparing amides. Lactone **2** was ring-opened with pyrrolidine under Lewis acid conditions and protected to give amide **6**, a solution phase model for an immobilised amide. Cleavage of α-heteroatom substituents in amide substrates has been found to be more difficult than for analogous ketones.[6]



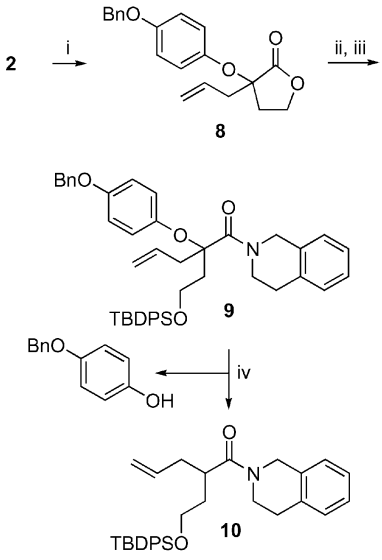
Scheme 3 *Reagents and conditions*: i, AlMe$_3$ 3 eq, NH(Me)(OMe)·HCl 3 eq, toluene, rt to 50 °C; ii, TBDPSCl 2 eq, imidazole 4 eq, DMF, rt, 79% (2 steps); iii, EtMgCl 2.5 eq, THF, 0 °C to rt, 72%; iv, SmI_2 3 eq, THF, 0 °C, <5 min: ketone **5** 93%, benzyloxyphenol 90%.

In the only previous example of the reduction of α-alkoxy amides, prior to our work, Simpkins reported that LiCl[14] was an efficient promoter of the reaction.[6] In our systems, the use of LiCl often led to incomplete cleavage of the α-aryloxy group. After a brief study, we found that the use of DMPU as an additive in the reduction gave excellent results.[15] Treatment of **6** with samarium(II) iodide and DMPU at room temperature resulted in complete conversion to amide **7** (81% isolated yield) and benzyloxyphenol (83% isolated yield) after 2 h (Scheme 4).



Scheme 4 *Reagents and conditions*: i, AlMe$_3$ 3 eq, pyrrolidine 3 eq, toluene, rt to 50 °C; ii, TBDPSCl 2 eq, imidazole 4 eq, DMF, rt, 71% (2 steps); iii, SmI_2 6 eq, DMPU 16 eq, THF: amide **7** 81%, benzyloxyphenol 83%.

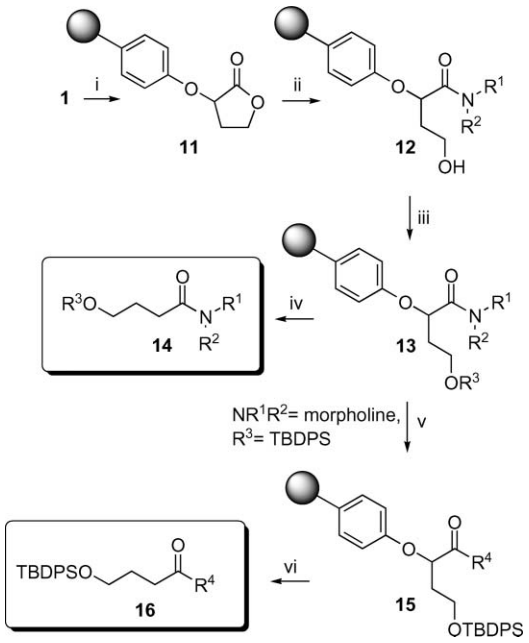
Finally, we investigated the introduction of additional diversity using our model system. Lactone **2** was alkylated (LDA, THF, −45 °C, allyl bromide), ring-opened with 1,2,3,4-tetrahydroisoquinoline at 50 °C and protected to give amide **9**. We were pleased to find that treatment of **9** with samarium(II) iodide and DMPU at 50 °C for 2 h resulted in complete conversion to amide **10** (76% isolated yield) and benzyloxyphenol (95% isolated yield), thus illustrating the feasibility of preparing more substituted carbonyl compounds using the approach (Scheme 5).



Scheme 5 *Reagents and conditions*: i, LDA 1.4 eq, THF, −45 °C, 30 min then allyl bromide −45 °C to rt, 72%; ii, AlMe$_3$ (2.0 M in hexane) 3 eq, 1,2,3,4-tetrahydroisoquinoline·HCl, 3 eq, toluene, rt to 50 °C, 24 h; ii, TBDPSCl 2 eq, imidazole 4 eq, DMF, rt, 78% (2 steps); iii, SmI_2 7 eq, DMPU 16 eq, THF: amide **10** 76%, benzyloxyphenol 95%.

Satisfied that our linker approach was feasible, we considered solid phase routes from immobilised γ-butyrolactone **11** to simple, functionalised carbonyl compounds which embraced a

variety of reaction conditions. The key aspects of the routes are illustrated in Scheme 6. Lewis acid mediated ring-opening of **11** with a variety of secondary amines was carried out followed by subsequent silylation or acetylation of the resultant alcohols **12** (see Scheme 6). In addition, *tert*-butyldiphenylsilyl-protected morpholine amides were converted to ketones **15** by reaction with Grignard reagents. Immobilised amide substrates **13**, and ketone substrates **15** underwent smooth cleavage from the resin when exposed to the conditions developed in our model solution phase studies. Amide and ketone products were obtained in moderate to good overall yields and purities (Fig. 2). Crucially, we have found that the link can be cleaved in the presence of ester groups (**14c** and **14d**), thus illustrating the mild and neutral nature of the cleavage conditions.

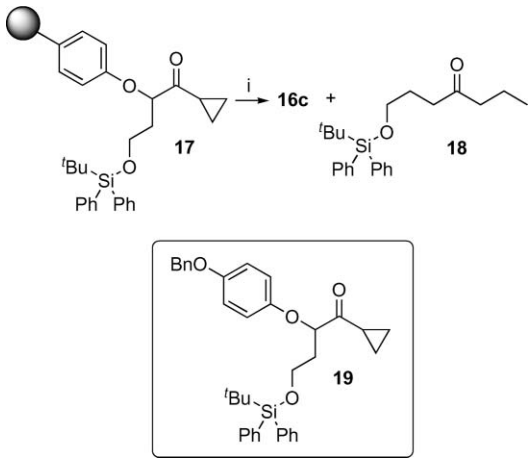


Scheme 6 *Reagents and conditions*: i, α-bromo-γ-butyrolactone 10 eq, K_2CO_3 16 eq, DMF, 60 °C, 18 h; ii, pyrrolidine/morpholine/1,2,3,4-tetrahydroisoquinoline 6 eq, $AlMe_3$ (2 M in hexanes) 6 eq, toluene, 50 °C, 20–24 h; iii, TBDPSCl 4 eq, imidazole 8 eq, DMF, rt, 16 h *or* Ac_2O 10 eq, pyridine, rt, 20 h; iv, SmI_2 5 eq, DMPU 16 eq, THF, rt or 50 °C, 6–12 h; v, *i*-PrMgCl/BnMgCl/*c*-PrMgBr 6 eq, THF, 0 °C to rt; 20 h; vi, SmI_2 4 eq, THF, rt, 4–6 h.

No aqueous work up is necessary on completion of the reduction. Products were conveniently separated from DMPU and inorganic by-products by simple filtration through a short column of silica gel, after which they were found to give satisfactory ^1H and ^{13}C NMR spectra. Standard, flash chromatography was required to separate the more polar acetates **14c** and **14d** from DMPU. Unfortunately, attempts to utilize the approach illustrated in Scheme 5 to access more substituted amide products gave poor yields of product. This was due to the inefficiency of the lactone alkylation step on solid phase.

In an attempt to improve the overall yields obtained using the linker system, we investigated the use of Brown's phenol resin, prepared by Friedel–Crafts acylation of polystyrene followed by Baeyer–Villiger rearrangement and ester hydrolysis.[16] We felt this phenol resin might prove more robust than **1** and lead to higher yields in the solid phase sequences. The synthesis of morpholine amide **14a** using Brown's phenol resin however gave the product in a similar yield after 4 steps (18%).

The synthesis of cyclopropyl ketone **16c** was designed to probe the mechanism of cleavage from the resin. If the SmI_2 cleavage reaction proceeds through the generation of a cyclopropylmethyl radical anion, fragmentation of the cyclopropane would be expected to occur.[17] Treatment of **17** with SmI_2 gave a 6 : 1 mixture of ring-closed (**16c**) and ring-opened product (**18**) (Scheme 7). Preparation of the solution phase model compound **19** allowed us to study the cleavage in more detail. Careful titration of **19** with SmI_2 gave **16c** in 72% (isolated yield) and benzyloxyphenol (79% isolated yield), with no trace of ring-opened product **18** by ^1H NMR. This indicates that the isolation of small amounts of **18** from the solid phase reaction results from over-reduction of the cleaved product **16c**.[18]



Scheme 7 *Reagents and conditions*: i, SmI_2 1 eq (based on theoretical loading), THF, rt, 3 h: 6 : 1 ratio of **16c** : **18**, 18% (5 steps from **1**).

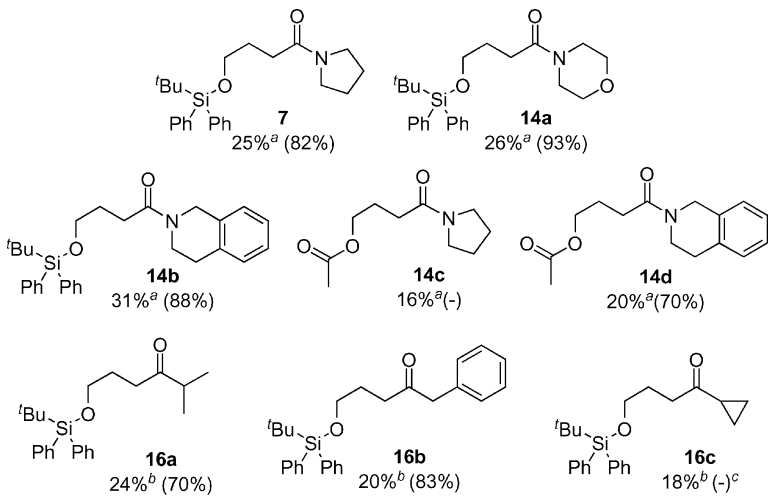


Fig. 2 Amide and ketone products obtained. HPLC purities (254 nm) are given in parentheses after chemical yields. [a]Overall yield for 4 steps from **1**. [b]Overall yield for 5 steps from **1**. [c]Obtained as a 6 : 1 mixture of ring-closed (**16c**) and ring-opened (**18**) product.

The isolation of **16c**, where the cyclopropyl ring is intact, suggests that a radical is not formed at the carbonyl carbon during cleavage (*cf.* **20**).[17,18] This appears to indicate that cleavage occurs by direct reduction of the carbon–oxygen link, to give a radical such as **21**, rather than by elimination of the α-heteroatom substituent after reduction of the carbonyl.[5] To the best of our knowledge, direct reduction of an α-substituent in ketone substrates, has not previously been proposed (Fig. 3).[19]

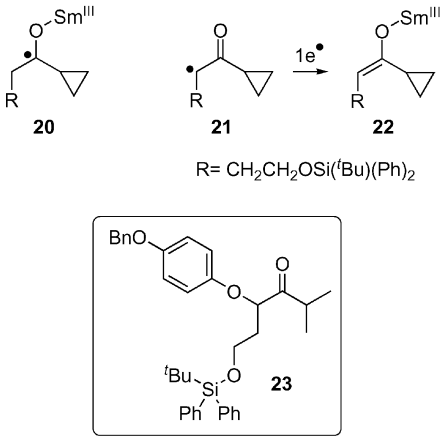


Fig. 3 Proposed mechanism of cleavage.

To probe the nature of the reactive intermediate formed upon cleavage, the reduction of solution phase model **23** was carried out under various conditions. In the presence of 1 eq of MeOD, ketone **16a** was isolated with complete deuterium incorporation α to the carbonyl group. Reduction of **23** using SmI_2 in d_8-THF gave unlabelled ketone **16a**. Finally, reduction of **23** followed by quenching with MeOD after 2 minutes gave only 36% deuterium incorporation. These experiments suggest the intermediacy of a samarium(III) enolate (*cf.* **22**) that is protonated rather than a radical (*cf.* **21**) that is quenched by hydrogen atom capture from solvent. Our studies also suggest that the intermediate enolate readily undergoes protonation even under 'anhydrous' conditions.

As previously mentioned, our solution model studies suggested the possibility of recovering and reusing the phenol resin **1** without the need for chemical reactivation. To investigate the feasibility of recycling **1**, the resin from the synthesis of morpholine amide **14a** (26%) was washed, dried and reused in the preparation of pyrrolidine amide **7**. Unfortunately, upon cleavage with SmI_2, **7** was isolated in a disappointing overall yield (5%). This preliminary study shows that recycling of the support is currently not practical.

To increase the potential of our new linker approach, we sought to evaluate a multidirectional cleavage strategy in which the intermediate samarium(III) enolate formed upon cleavage could be trapped with electrophiles. In principle, this would allow a single resin bound intermediate to furnish a variety of products depending upon the electrophile employed in the cleavage step, thus effectively amplifying the size of any synthetic library.

The intermolecular trapping of samarium(III) enolates with electrophiles has relatively limited precedent.[20] Arguably the most elegant application of such chemistry to date is Skrydstrup's selective alkylation of peptides *via* reductive samariation.[21]

We chose to investigate the sequential cleavage–enolate trapping by returning to a solution phase model system. After optimization, treatment of ketone **23** with SmI_2–DMPU at −78 °C, employing cyclohexanone and tetrahydropyran-4-one as electrophiles, gave aldol adducts **24** and **25** in excellent yield (78% and 76% respectively). No products were obtained if the carbon electrophile was not employed as an *in situ* trap. DMPU was also found to be essential for successful reaction and the use of higher temperatures was found to result in significant retro-aldol reaction. Sequential cleavage–Michael addition was less successful. Adduct **26** was obtained in an unoptimised yield of 11% after cleavage in the presence of methyl acrylate[22] (Scheme 8).

Although of synthetic and mechanistic interest, we feel the conditions required for successful cleavage–trapping are unlikely to lead to a practical solid-phase protocol. Improved HASC linker systems better suited to multidirectional cleavage are currently under development in our laboratory.

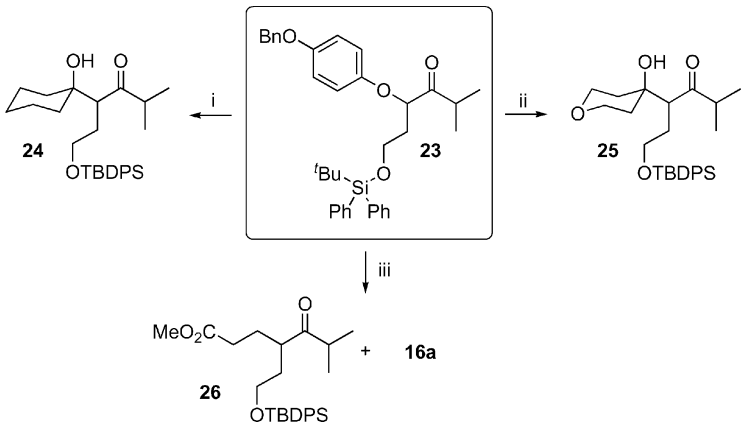
Conclusions

In summary, we have developed and evaluated a new linker design for solid phase synthesis. Our linker strategy is based on the mild, neutral reduction of α-heteroatom substituted carbonyl compounds using samarium(II) iodide. The feasibility of the linker approach has been illustrated initially in solution and then in a solid phase approach to ketones and amides using an oxygen linker. Insights into the mechanism of the samarium(II) iodide cleavage reaction have been made during our studies. Finally, we have assessed the potential of a sequential cleavage, carbon–carbon forming process.

Experimental

General considerations

All experiments were performed under an atmosphere of Ar or N_2, using anhydrous solvents, unless stated otherwise. Reactions



Scheme 8 *Reagents and conditions*: i, SmI_2 6 eq, DMPU 24 eq, cyclohexanone 16 eq, THF, −78 °C, 45 min, 78% (**24**), 10% (**23**), benzyloxyphenol recovered in 86% yield. ii, SmI_2 6 eq, DMPU 20 eq, tetrahydropyran-4-one 16 eq, THF, −78 °C, 1 h, 76% (**25**), 12% (**16a**), benzyloxyphenol recovered in 100% yield. iii, SmI_2 4.4 eq, methyl acrylate 2.2 eq, 0 °C to rt, 11% (**26**), 86% (**16a**), benzyloxyphenol recovered in 91% yield.

were carried out using oven-dried glassware. THF was distilled from sodium–benzophenone. CH_2Cl_2, Et_2O and *i*-Pr_2NH were distilled from CaH_2. Et_3N was distilled from CaH_2 and stored over KOH and under Ar–N_2. HMPA and DMPU were dried by refluxing with CaH_2 followed by fractional distillation under reduced pressure. Commercially available bromo-Wang resin with a loading of 1.2 mmol g^{-1} was employed throughout. Reactions on immobilized substrates were carried out in round-bottomed flasks and agitated by slow stirring, or in Bond Elut cartridges fitted with polyethylene frits and agitated by rotation on a blood tube rotator. In general, resin was washed with THF (30 mL), THF : H_2O (2 : 1) (3 × 30 mL), THF : H_2O (1 : 1) (3 × 30 mL), THF : H_2O (1 : 2) (3 × 30 mL), THF (2 × 30 mL), then alternate washings with CH_2Cl_2 (3 × 30 mL) and MeOH (3 × 30 mL), finishing with THF (2 × 30 mL). The resin was then left to dry for 10 min under water pump pressure before being dried for 6 h under high vacuum. THF used for washing resin was distilled prior to use. ^{1}H NMR and ^{13}C NMR were recorded on a Fourier transform spectrometer with chemical shift values being reported in ppm relative to residual chloroform ($\delta_H = 7.27$ or $\delta_C = 77.2$) as internal standard unless otherwise stated. NMR signals were assigned using DEPT-135, HMQC and COSY spectra. All coupling constants (*J*) are reported in Hertz (Hz). IR spectra were recorded using a Fourier transform spectrometer. Mass spectra and microanalyses were recorded at the University of Glasgow and the University of Manchester. HPLC data was obtained using an Xterra MS C18 7 μm column (19 × 150 mm) at 254 nm wavelength using mixtures of 0.1% TFA in acetonitrile and 0.1% TFA in water were used as the solvent systems. Samarium(II) iodide was prepared by the method of Imamoto[23] with the modification that the samarium–iodine suspension in THF was heated at 60 °C rather than at reflux.

4-(*tert*-Butyldimethylsilyloxy)phenol[24]. Imidazole (4.08 g, 60.0 mmol) and TBDMSCl (4.50 g, 30.0 mmol) were added to a solution of benzyloxyphenol (3.00 g, 15.0 mmol) in DMF (30 mL) at room temperature and the mixture stirred for 4 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (30 mL) and distilled H_2O (20 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 50 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give crude product *O*-*tert*-butyldimethylsilyl benzyloxyphenol (4.71 g, 15.0 mmol, 100%) as a white crystalline solid which was used without further purification: ν_{max} ATR/cm^{-1} 3044 (w), 2931(s), 1508 (s), 1258 (S) and 1103 (m); δ_H (400 MHz; $CDCl_3$) 0.18 (6H, s, $(CH_3)_2Si$), 0.98 (9H, s, $SiC(CH_3)_3$), 5.00 (2H, s, $ArCH_2O$), 6.75–6.87 (4H, m, ArH) and 7.30–7.52 (5H, m, ArH); δ_C (100 MHz; $CDCl_3$) −4.5 ($Si(CH_3)_2$ × 2), 18.2 ($SiC(CH_3)_3$), 25.7 (3 × $C(CH_3)_3$), 70.6 ($ArCH_2$), 115.6 (ArCH × 2), 120.6 (ArCH × 2), 127.5 (ArCH × 2), 127.8 (ArCH), 128.5 (ArCH × 2), 137.3 (ArC × 2) and 138.1 (ArC); LRMS (EI^+) 314.2 (M^+ 98%), 257 (21), 223 (77), 91 (66) and 73 (55); HRMS calculated for $C_{19}H_{26}O_2Si$ 314.1702, found 314.1699.

To a solution of *O*-*tert*-butyldimethylsilyl benzyloxyphenol (4.71 g, 15.0 mmol) in ethanol (45 mL) was added 10% Pd/C (0.70 mg, 15% weight) under hydrogen (balloon) and the reaction stirred at room temperature for 5 h. The reaction mixture was then poured onto a short column of silica gel and eluted with 40% EtOAc/petroleum ether, which upon concentration *in vacuo* gave 4-(*tert*-butyldimethylsilyloxy)phenol (3.33 g, 14.8 mmol, 99%) as a white crystalline solid: m.p. 57–59 °C; ν_{max} ATR/cm^{-1} 3271 (b), 2928 (m), 1505 (s), 1216 (s) and 1096 (m); δ_H (400 MHz; $CDCl_3$) 0.17 (6H, s, $(CH_3)_2Si$), 0.98 (9H, s, $SiC(CH_3)_3$), 4.56 (1H, br s, OH) and 6.68–6.74 (4H, apparent s, ArH); δ_C (100 MHz; $CDCl_3$) −4.5 ($Si(CH_3)_2$ × 2), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$ × 3), 115.9 (ArCH × 2), 120.8 (ArCH × 2), 149.4 (ArC) and 149.8 (ArC); Anal. calculated for $C_{12}H_{20}O_2Si$: C, 64.24; H, 8.98%. Found: C, 64.30; H, 8.97%.

Wang supported 4-(*tert*-butyldimethylsilyloxy)phenol. 4-(*tert*-Butyldimethylsilyloxy)phenol (9.95 g, 44.4 mmol) was added to a flask containing a suspension of bromo Wang resin (9.25 g, 11.1 mmol) which had been pre-swollen in DMF (100 mL). NaH (1.33 g, 55.5 mmol) was subsequently added and the mixture stirred slowly at room temperature. After 12 h the resin was filtered, washed and dried according to the standard washing procedure, to give Wang supported 4-(*tert*-butyldimethylsilyloxy)phenol: ν_{max} ATR/cm^{-1} 3026 (w), 2918 (w), 1603 (m), 1508 (s) and 1219 (s).

Wang phenol resin 1. Wang supported 4-(*tert*-butyldimethylsilyloxy)phenol (4.50 g, 4.64 mmol) was swollen in THF (15 mL) in a 25 mL Bond Elut cartridge. TBAF (1.0 M in THF, 27.8 mL, 27.8 mmol) was then added and the mixture rotated at room temperature for 18 h. The resin was then filtered, washed and dried according to the standard washing procedure. Re-treatment of the resin under the same reaction conditions gave **1**: ν_{max} ATR/cm^{-1} 3025 (m) O–H, 2914 (w), 1602 (m), 1506 (s) and 1219 (m).

Determination of loading of resin 1. Phenol resin **1** (249 mg, 0.288 mmol) was swollen in CH_2Cl_2 (1 mL). TFA (1 mL) was subsequently added and the reaction stirred slowly at room temperature for 1.5 h. The suspension was then filtered and the resin washed with CH_2Cl_2 (3 × 15 mL). The washings were collected and concentrated *in vacuo* to give hydroquinone (26 mg, 0.236 mmol, 82%). The loading of resin **1** was therefore approximately 0.96 mmol g^{-1}, 82% that of the maximum theoretical loading (1.17 mmol g^{-1}). This result was confirmed by microanalysis of resin **1** which found 16% bromine content, corresponding to approximately 84% loading.

3-(4-Benzyloxyphenoxy)dihydrofuran-2-one 2. K_2CO_3 (3.46 g, 25.0 mmol) was added to a solution of α-bromo-γ-butyrolactone (1.66 mL, 20.0 mmol) and 4-benzyloxyphenol (1.00 g, 4.99 mmol) in DMF (75 mL) and the mixture stirred at room temperature for 16 h. The reaction was quenched with aqueous saturated NH_4Cl (50 mL) and distilled H_2O (40 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 30 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Recrystallisation from methanol gave **2** (1.02 g, 3.59 mmol, 72%) as a white crystalline solid: mp 116–117 °C; ν_{max} KBr/cm^{-1} 2923 (s), 1782 (s) C=O, 1507 (s), 1296 (s), 1234 (s) and 1189 (s); δ_H (400 MHz; $CDCl_3$) 2.47 (1H, apparent dq, *J* 8.1, 13.1 Hz, 1H from CH_2CH_2OC=O), 2.64–2.70 (1H, m, 1H from CH_2CH_2OC=O), 4.31–4.37 (1H, m, 1H from CH_2OC=O), 4.49–4.55 (1H, m, 1H from CH_2OC=O), 4.84 (1H, apparent t, *J* 7.8 Hz, CHC=O), 5.03 (2H, s, $ArCH_2$), 6.91–7.01 (4H, m, ArH) and 7.33–7.44 (5H, m, ArH); δ_C (100 MHz; $CDCl_3$) 29.8 (CH_2CH_2OC=O), 65.3 (CH_2OC=O), 70.6 ($ArCH_2$), 73.5 (CHC=O), 115.8 (ArCH × 2), 117.4 (ArCH × 2), 127.4 (ArCH × 2), 127.9 (ArCH), 128.6 (ArCH × 2), 137.0 (ArC), 151.6 (ArC), 154.3 (ArC) and 195.5 (C=O); LRMS (EI^+) 284.1 (M^+, 22%) 91 (99), 85 (3), 65 (6) and 43 (10); Anal. calculated $C_{17}H_{16}O_4$: C, 71.82; H, 5.67%. Found: C, 71.76; H, 5.68%.

2-(4-Benzyloxyphenoxy)-4-(*tert*-butyldiphenylsilyloxy)-*N*-methoxy-*N*-methylbutyramide 3. $AlMe_3$ (2.0 M in hexanes, 3.18 mmol, 1.59 mL) was added dropwise to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (310 mg, 3.18 mmol) in toluene (6 mL) at 0 °C and the reaction warmed to room temperature. After 0.5 h at room temperature the reaction mixture was once again cooled to 0 °C and lactone **2** (300 mg, 1.06 mmol) was added to the reaction mixture. The reaction mixture was then allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with K/Na tartrate (20 mL) and distilled H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give crude 2-(4-benzyloxyphenoxy)-4-hydroxy-*N*-methoxy-*N*-methylbutyramide as a clear yellow oil (345 mg, 1.00 mmol, 100%) which was used without further purification: δ_H

(400 MHz; $CDCl_3$) 2.04–2.13 (2H, m, $CH_2CHC{=}O$), 3.15 (3H, s, NCH_3), 3.52 (3H, s, $NOCH_3$), 3.75–3.86 (2H, m, CH_2OH), 4.93 (2H, s, $ArCH_2$), 5.08 (1H, m, $CHC{=}O$), 6.81 (4H, apparent s, ArH) and 7.07–7.35 (5H, m, ArH). Imidazole (272 mg, 4.00 mmol) and TBDPSCl (520 μL, 2.00 mmol) were added to a solution of 2-(4-benzyloxyphenoxy)-4-hydroxy-*N*-methoxy-*N*-methylbutyramide (345 mg, 1.00 mmol) in DMF (3 mL) and the reaction stirred at room temperature for 12 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (20 mL) and distilled H_2O (10 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 30 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification by column chromatography (silica, 30% EtOAc–petroleum ether) gave **3** (461 mg, 0.790 mmol, 79%) as a clear colourless oil: ν_{max} neat/cm^{-1} 3069 (s), 2858 (s), 1737 (s) C=O, 1508 (s), 1210 (m) and 1096 (s); δ_H (400 MHz; $CDCl_3$) 0.96 (9H, s, $(CH_3)_3CSi$), 1.99–2.09 (2H, m, $CH_2CHC{=}O$), 3.12 (3H, s, NCH_3), 3.60 (3H, s, $NOCH_3$), 3.75 (1H, apparent quintet, *J* 4.9 Hz, 1H from CH_2OSi), 3.91 (1H, dt, *J* 4.5, 9.6 Hz, 1H from CH_2OSi), 4.94 (2H, s, $ArCH_2O$), 5.24 (1H, dd, *J* 8.5, 3.5 Hz, $CHC{=}O$), 6.79 (4H, apparent s, ArH), 7.17–7.34 (11H, m, ArH) and 7.49–7.58 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 19.2 ($C(CH_3)_3$), 26.7 ($C(CH_3)_3$ × 3), 32.5 (NCH_3), 35.2 ($CH_2CHC{=}O$), 59.4 (CH_2OSi), 61.6 ($NOCH_3$), 70.6 ($PhCH_2O$), 71.9 ($CHC{=}O$), 115.8 (ArCH × 2), 116.6 (ArCH × 2), 127.4 (ArCH × 2), 127.6 (ArCH × 4), 127.8 (ArCH), 128.5 (ArCH × 2), 129.6 (ArCH × 2), 133.3 (ArC), 133.5 (ArC), 135.5 (ArCH × 4), 137.2 (ArC), 138.1 (ArC), 152.5 (ArC) and 153.5 (C=O); LRMS (EI^+) 583.2 (M^+, 18%), 526 (80), 135 (41) and 91 (100); HRMS calculated for $C_{35}H_{41}O_5Si$, 583.2754, found 583.2751.

4-(4-Benzyloxyphenoxy)-6-(*tert*-butyldiphenylsilyloxy)hexan-3-one 4. Ethyl magnesium bromide (1.0 M in THF, 550 μL, 0.550 mmol) was added dropwise to a solution of **3** (53 mg, 0.091 mmol) in THF (1 mL) at 0 °C over a period of 6.5 h. The reaction mixture was then allowed to warm to room temperature overnight. The reaction was quenched with aqueous saturated NH_4Cl (5 mL) and distilled H_2O (3 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 10 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification by column chromatography (silica, 30% EtOAc–petroleum ether) gave **4** (36 mg, 0.065 mmol 72%) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 2929 (w), 2856 (w), 1714 (m) C=O, 1504 (s), 1225 (s) and 1105 (s); δ_H (400 MHz; $CDCl_3$) 0.92 (3H, t, *J* 6.8 Hz, $CH_3CH_2C{=}O$), 0.95 (9H, s, $(CH_3)_3CSi$),1.85–2.01 (2H, m, $CH_2CHC{=}O$), 2.40 (1H, dq, *J* 7.3, 18.6 Hz, 1H from $CH_2C{=}O$), 2.55 (1H, dq, *J* 7.3, 18.6 Hz, 1H from $CH_2C{=}O$), 3.69–3.80 (2H, m, CH_2OSi), 4.71 (1H, dd, *J* 4.0, 9.2 Hz, $CHC{=}O$), 4.91 (2H, s, $ArCH_2O$), 6.71–6.83 (4H, m, ArH), 7.18–7.36 (11H, m, ArH) and 7.48–7.58 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 7.1 (CH_3CH_2), 19.1 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3$ × 3), 30.8 ($CH_2C{=}O$), 35.3 ($CH_2CHC{=}O$), 59.3 (CH_2OSi), 70.6 ($ArCH_2O$), 80.2 ($CHC{=}O$), 115.9 (ArCH × 4), 125.8 (ArC), 127.5 (ArCH × 2), 127.6 (ArCH × 2), 127.7 (ArCH × 2), 127.9 (ArCH), 128.6 (ArCH × 2), 129.6 (ArCH), 129.7 (ArCH), 133.4 (ArC), 135.5 (ArCH × 4), 137.1 (ArC), 152.3 (ArC), 153.4 (ArC) and 213.0 (C=O); LRMS (EI^+) 552.2 (M^+, 3%), 417 (35), 219 (12), 199 (10), 135 (17) and 91 (100); HRMS calculated for $C_{35}H_{40}O_4Si$ 552.2696, found 552.2692.

6-(*tert*-Butyldiphenylsilyloxy)hexan-3-one 5. Ketone **4** (21 mg, 0.04 mmol) was dissolved in THF (0.50 mL) and methanol (0.43 mL). SmI_2 (0.1 M in THF, 1.20 ml, 0.12 mmol) was then added dropwise to the mixture at 0 °C and the resulting solution allowed to warm to room temperature. After 45 min, the reaction was quenched with aqueous saturated $NaHCO_3$ (10 mL) and distilled H_2O (5 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 10 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification by column chromatography (silica, 5% EtOAc–petroleum ether) gave **5** (13 mg, 0.037 mmol, 93%) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 3071 (w), 2932 (m), 2858 (m), 1716 (s) C=O, 1110 (s); δ_H (400 MHz; $CDCl_3$) 1.05 (3H, t, *J* 7.3 Hz, $CH_3CH_2C{=}O$), 1.06 (9H, s, $C(CH_3)_3$), 1.84 (2H, m, $CH_2CH_2C{=}O$), 2.42 (2H, q, *J* 7.3 Hz, $CH_3CH_2C{=}O$), 2.53 (2H, t, *J* 6.1 Hz, $CH_2CH_2C{=}O$), 3.67 (2H, t, *J* 7.3 Hz, CH_2OSi), 7.36–7.45 (6H, m, ArH) and 7.64–7.67 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 7.8 (CH_3), 19.2 ($C(CH_3)_3$), 26.7 ($CH_2CH_2C{=}O$), 26.8 ($C(CH_3)_3$ × 3), 35.9 ($CH_3CH_2C{=}O$), 38.7 ($CH_2CH_2C{=}O$), 63.1 (CH_2OSi), 127.6 (ArCH × 4), 129.6 (ArCH × 2), 133.8 (ArC × 2), 135.5 (ArCH × 4) and 211.5 (C=O); LRMS (CI^+) 355.2 ($(M + H)^+$, 99%), 297 (92), 277 (80), 199 (13) and 99 (50); HRMS calculated for $C_{22}H_{31}O_2Si$ 355.2093, found 355.2092.

2-(4-Benzyloxyphenoxy)-4-(*tert*-butyldiphenylsilyloxy)-1-(pyrrolidin-1-yl)-butan-1-one 6. $AlMe_3$ (2.0 M in hexane, 2.78 mL, 5.55 mmol) was added dropwise to a solution of pyrrolidine (463 μL, 5.55 mmol) in toluene (3 mL) and the solution stirred at room temperature for 20 min. A solution of lactone **2** (525 mg, 1.85 mmol) in toluene (13 mL) was then added dropwise to the mixture and the reaction heated to 50 °C overnight. The reaction was quenched carefully with 1 M HCl (5 mL) at 0 °C and distilled H_2O (10 mL) was subsequently added. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give crude 2-(4-benzyloxyphenoxy)-4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one (592 mg, 1.67 mmol, 90%) as a clear yellow oil which was used without further purification: δ_H (400 MHz; $CDCl_3$) 1.74–1.95 (4H, m, CH_2CH_2N × 2), 2.13–2.23 (2H, m, CH_2CH_2OH), 3.34–3.68 (4H, m, CH_2N × 2), 3.82–3.92 (2H, m, CH_2OH), 4.86 (1H, apparent t, *J* 6.5 Hz, $CHC{=}O$), 5.02 (2H, s, $ArCH_2O$), 6.83–6.91 (4H, m, ArH) and 7.15–7.44 (5H, m, ArH).

tert-Butyldiphenylsilyl chloride (869 μL, 3.34 mmol) and imidazole (421 mg, 6.68 mmol) were added to a solution of 2-(4-benzyloxyphenoxy)-4-hydroxy-1-(pyrrolidin-1-yl)butan-1-one (592 mg, 1.67 mmol) in DMF (3 mL) and the solution stirred at room temperature for 3.5 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (5 mL) and distilled H_2O (2 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 30 mL), the organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (silica, 40% EtOAc–petroleum ether) gave **6** (785 mg, 1.32 mmol, 79%,) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 3069 (m), 2930 (s), 2879 (s), 1633 (s) C=O, 1227 (s) and 1107 (s); δ_H (400 MHz; $CDCl_3$) 0.95 (9H, s, $(CH_3)_3Si$), 1.68–1.86 (4H, m, $CH_2CH_2NC{=}O$ × 2), 2.01–2.06 (2H, m, $CH_2CHC{=}O$), 3.34–3.50 (4H, m, CH_2N × 2), 3.73–3.89 (2H, m, CH_2OSi), 4.88 (1H, t, *J* 6.5 Hz, CH), 4.94 (2H, s, $PhCH_2O$), 6.23–6.82 (4H, m, ArH), 7.17–7.36 (11H, m, ArH) and 7.48–7.58 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 19.1 ($(CH_3)_3CSi$), 23.6 (CH_2CH_2N), 26.3 (CH_2CH_2N), 26.8 ($C(CH_3)_3$ × 3), 34.9 (CH_2CH_2OSi), 46.0 (CH_2N), 46.3 (CH_2N), 59.7 (CH_2OSi), 70.6 (CH_2Ph), 74.6 (CH), 115.8 (ArCH × 2), 116.2 (ArCH × 2), 127.4 (ArCH × 2), 127.6 (ArCH × 2), 127.7 (ArCH × 2), 127.9 (ArCH × 2), 128.5 (ArCH × 2), 129.6 (ArCH × 2), 129.7 (ArCH), 133.3 (ArC), 133.5 (ArC), 135.5 (ArCH × 2), 137.2 (ArC), 152.2 (ArC), 153.4 (ArC), 169.7 (C=O); LRMS (FAB^+) 617.7 ($(M + Na)^+$100%), 595 (39), 537 (71), 338 (53), 135 (69) and 92 (54); HRMS calculated for $C_{37}H_{43}NO_4SiNa$, 616.2859, found 616.2866.

4-(*tert*-Butyldiphenylsilyloxy)-1-(pyrrolidin-1-yl)butan-1-one 7. SmI_2 (0.1 M solution in THF, 4.00 mL, 0.400 mmol) was added to a solution of amide **6** (54 mg, 0.091 mmol) and DMPU (154 μL, 1.28 mmol) and MeOH (1.05 mL) in THF (0.2 mL). The reaction mixture was then stirred for 2 h and was quenched with aqueous saturated $NaHCO_3$ (10 mL) and

distilled H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (silica, 50% EtOAc–petroleum ether) gave **7** as a clear colourless oil (29 mg, 0.073 mmol, 81%): ν_{max} (neat)/cm^{-1} 2931 (s), 2858 (s), 1644 (s) C=O, 1428 (s) and 1111 (s); δ_H (400 MHz; $CDCl_3$) 1.06 (9H, s, $C(CH_3)_3$), 1.81–1.98 (6H, m, $CH_2CH_2NC{=}O$ × 2, $CH_2CH_2C{=}O$), 2.39 (2H, t, *J* 7.6 Hz, $CH_2C{=}O$), 3.32 (2H, apparent t, *J* 6.8 Hz, 2H from $CH_2NC{=}O$), 3.38 (2H, apparent t, *J* 6.8 Hz, 2H from $CH_2NC{=}O$), 3.66 (2H, t, *J* 6.0 Hz, CH_2OSi), 7.36–7.45 (6H, m, ArH) and 7.65–7.67 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 19.2 ($C(CH_3)_3$), 24.4 ($CH_2CH_2C{=}O$), 26.1 ($CH_2CH_2NC{=}O$), 26.8 ($(CH_3)_3C$ × 3), 27.8 ($CH_2CH_2NC{=}O$), 31.1 ($CH_2C{=}O$), 45.5 ($CH_2NC{=}O$), 46.5 ($CH_2NC{=}O$), 63.2 (CH_2OSi), 127.6 (ArCH × 4), 129.6 (ArCH × 2), 133.9 (ArC), 135.5 (ArCH × 4), 138.1 (ArC) and 171.4 (C=O); LRMS (CI$^+$) 396.3 ((M + H)$^+$11%), 338 (100) and 318 (22); HRMS calculated for $C_{24}H_{34}NO_2Si$, 396.2359, found 396.2358. Further elution gave benzyloxyphenol (15 mg, 0.075 mmol, 83%) as a pale yellow solid.

3-Allyl-3-(4-benzyloxyphenoxy)dihydrofuran-2-one 8. *n*-BuLi (1.6 M in hexane, 154 µl, 0.250 mmol) was added dropwise to a solution of diisopropylamine (35 µl, 0.250 mmol) in THF (1 ml) at −45 °C and the solution stirred for 30 min. A solution of lactone **2** (50 mg, 0.176 mmol) in THF (1 ml) was then added *via* cannula at −45 °C to the LDA solution. After 30 min, allyl bromide (76 µl, 0.88 mmol) was added and the reaction mixture allowed to warm to room temperature. The reaction was quenched with aqueous saturated NH_4Cl (10 mL) and distilled H_2O (5 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 10 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification by column chromatography (silica, CH_2Cl_2) gave **8** (42 mg, 1.13 mmol, 72%) as a pale yellow oil: ν_{max} (neat)/cm^{-1} 2985 (w), 2916 (w), 1774 (s) C=O, 1643 (w) C=C, 1502 (s), 1203 (m), 1012 (s); δ_H (400 MHz; $CDCl_3$) 2.27–2.34 (1H, m, CH_2CH_2O), 2.47–2.57 (2H, m, 1 H from CH_2CH_2O and 1H from $CH_2{=}CHCH_2$), 2.77 (1H, dd, *J* 14.7, 7.1 Hz, 1 H from $CH_2{=}CHCH_2$), 4.18–4.27 (2H, m, CH_2O), 5.00 (2H, s, $ArCH_2O$), 5.18–5.29 (2H, m, $CH_2{=}CH$), 5.81–5.91 (1H, m, $CH_2{=}CH$), 6.85–6.98 (4H, m, ArH) and 7.30–7.42 (5H, m, ArH); δ_C (100 MHz; $CDCl_3$) 31.3 ($CH_2CH_2OC{=}O$), 39.2 ($CH_2{=}CHCH_2$), 64.9 ($CH_2OC{=}O$), 70.4 ($ArCH_2$), 82.2 ($CC{=}O$), 115.5 (ArCH × 2), 120.4 ($CH{=}CH_2$), 123.3 (ArCH × 2), 127.5 (ArCH × 2), 128.0 (ArCH), 128.5 (ArCH × 2), 131.1 ($CH_2{=}CH$), 136.8 (ArC), 147.8 (ArC), 155.6 (ArC) and 175.7 (C=O); LRMS (EI$^+$) 324.1 (M$^+$, 18%); HRMS calculated for $C_{20}H_{20}O_4$ 324.1362, found 324.1359; Anal. calculated for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21%. Found: C, 73.75; H, 6.21%.

2-(4-Benzyloxyphenoxy)-2-[2-(*tert*-butyldiphenylsilyloxy)-ethyl]-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)pent-4-en-1-one 9. $AlMe_3$ (2.0 M in hexane 0.39 ml, 0.767 mmol) was added to a solution of 1,2,3,4-tetrahydroisoquinoline·HCl (130 mg, 0.767 mmol) in toluene (1 ml) and the solution stirred at room temperature for 20 min. Lactone **8** (83 mg, 0.256 mmol) in toluene (1 ml) was then added dropwise *via* cannula to the reaction mixture which was then heated to 50 °C for 24 h. The reaction was quenching using 1.0 M HCl (2 mL) which was added dropwise at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was then washed with distilled H_2O (20 mL) dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product 2-(4-benzyloxyphenoxy)-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-(2-hydroxyethyl)pent-4-en-1-one (117 mg, 0.256 mmol) as a pale yellow oil which was used without further purification.

Imidazole (71 mg, 1.04 mmol) and TBDPSCl (135 µl, 0.519 mmol) were added to a solution of 2-(4-benzyloxyphenoxy)-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-(2-hydroxyethyl)pent-4-en-1-one (117 mg, 0.256 mmol) in DMF (1 ml) and the mixture stirred at room temperature overnight. The reaction was quenched with aqueous saturated $NaHCO_3$ (20 mL) and distilled H_2O (10 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 15 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification by column chromatography (silica, 10% EtOAc–petroleum ether) gave **9** (138 mg, 0.198 mmol, 78% over 2 steps) as a pale yellow oil:ν_{max} (neat)/cm^{-1} 3069 (m), 2930 (s), 2857 (s), 1633 (s) C=O, 1504 (s) C=C, 1428 (m), 1206 (s), 1108 (s); (complex mixture of rotamers) δ_H (400 MHz; $CDCl_3$) 0.99–1.09 (9H, m), 2.36 (1H, apparent quintet, J 7.3 Hz), 2.48–2.79 (4H, m), 2.93–2.99 (1H, m), 3.62–3.75 (2H, m), 3.98–4.11 (2H, m), 4.64–4.81 (2H, m), 4.94–5.12 (4H, m), 5.69–5.71 (1H, m), 6.33–6.84 (4H, m), 6.93–7.21 (4H, m), 7.32–7.41 (11H, m) and 7.59–7.74 (4H, m); LRMS (FAB$^+$) 718 ((M + Na)$^+$10%), 696 (10), 496 (16), 440 (34), 418 (100), 197 (90); HRMS (FAB$^+$,M + Na$^+$) calculated for $C_{45}H_{49}O_4NSiNa$ 718.3333, found 718.3329.

2-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)pent-4-en-1-one 10. SmI_2 (0.1 M solution in THF, 2.38 ml, 0.238 mmol) was added to a solution of amide **9** (24 mg, 0.034 mmol) in DMPU (66 µl, 0.544 mmol) and THF (0.2 ml) and the reaction stirred for 2 h. The reaction was quenched with aqueous saturated $NaHCO_3$ (15 ml) and distilled H_2O (10 ml). The aqueous layer was extracted with EtOAc (3 × 20 ml), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (silica, 30% EtOAc–petroleum ether) gave **10** (13 mg, 0.026 mmol, 76%) as a clear colourless oil: ν_{max} KBr/cm^{-1} 3070 (m), 2929 (s), 1689 (s) C=O, 1643 (s), ($CH{=}CH_2$), 1428 (s) and 1110 (m); δ_H (400 MHz; $CDCl_3$) 1.07 (9 H, s, $C(CH_3)_3$), 1.70–1.77 (1H, m, 1H from $CH_2CHC{=}O$), 1.90–1.98 (1H,m, 1H from $CH_2CHC{=}O$), 2.18–2.25 (1H, m, 1H from $CH_2CH{=}CH_2$), 2.39–2.49 (1H, m, $CH_2CH{=}CH_2$), 2.81–2.89 (2H, m, $CH_2CH_2NC{=}O$), 2.19–3.29 (1H, m, $CHC{=}O$), 3.60–3.86 (4H, m, CH_2OSi, $CH_2CH_2NC{=}O$), 4.69–4.83 (2H, m, $ArCH_2NC{=}O$), 4.95–5.10 (2H, m, $H_2C{=}CH$), 5.71–5.84 (1H, m, $H_2C{=}CH$), 6.96–7.23 (4H, m, ArH), 7.28–7.46 (6H, m, ArH), 7.59–7.68 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 19.2 ($C(CH_3)_3$), 26.9 ($C(CH_3)$), 28.8 ($CH_2CH_2NC{=}O$), 29.8 ($CH_2CH_2NC{=}O$), 35.2 ($CH_2CH_2C{=}O$), 36.6 ($CH_2CH{=}CH_2$), 37.5 ($CHC{=}O$), 39.9 ($CH_2CH_2NC{=}O$), 43.3 ($CH_2CH_2NC{=}O$), 44.3 ($ArCH_2$), 47.4 ($ArCH_2$), 61.4 (CH_2OSi), 61.5 (CH_2OSi), 116.5 ($CH_2{=}CH$), 126.1 (ArCH), 126.3 (ArCH), 126.5 (ArCH × 2), 126.7 (ArCH), 127.6 (ArCH), 127.7 (ArCH), 128.3 (ArCH), 128.8 (ArCH), 129.6 (ArCH), 129.7 (ArCH × 2), 132.9 (ArC), 133.8 (ArC), 134.2 (ArC), 135.2 (ArC), 135.5 (ArCH × 2), 136.0 ($CH_2{=}CH$), 136.1 ($CH_2{=}CH$), 174.2 (C=O), 174.3 (C=O); LRMS (CI$^+$) 498 ((M + H)$^+$15%); HRMS (EI$^+$,M$^+$) calculated for $C_{32}H_{39}O_2NSi$ 497.2754, found 497.2750. Further elution gave 4-benzyloxyphenol (6.5 mg, 0.032 mmol, 95%) as a pale yellow solid.

Wang supported 3-(4-hydroxyphenoxy)dihydrofuran-2-one 11. Phenol resin **1** (1.31 g, 1.26 mmol) was swollen in DMF (30 mL). α-Bromo-γ-butyrolactone (1.67 mL, 20.2 mmol) was then added followed by K_2CO_3 (1.74 g, 12.6 mmol) and the reaction mixture stirred slowly at 60 °C for 24 h. The resin was then drained, washed and dried according to the standard washing procedure to give solid supported lactone **11**: ν_{max} KBr/cm^{-1} 3024 (w), 2922 (w), 1787 (s) C=O, 1610 (s), 1507 (s) and 1220 (s).

General procedure for the ring opening of immobilised lactone 11 to give supported amides 12

Wang supported 4-hydroxy-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one. $AlMe_3$ (2.0 M in hexane, 1.5 mL,

3.00 mmol) was added dropwise to a solution of morpholine (262 μL, 3.00 mmol) in toluene (2 mL) and mixture was stirred for 20 minutes at room temperature. The solution was then added *via* cannula to a suspension of lactone resin **11** (559 mg, 0.498 mmol) in toluene (5 mL) and the reaction stirred slowly at 50 °C for 14 h. The resin was then drained, washed and dried according to the standard washing procedure to give Wang supported 4-hydroxy-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one: ν_{max} ATR/cm^{-1} 3026 (w), 2922 (w), 1631 (m) C=O, 1610 (m), 1583 (w), 1504 (s) and 1205 (s).

General procedure for the TBDPS protection of alcohols 12 to give solid supported amides 13

Wang supported 4-(*tert*-butyldiphenylsilyloxyl)-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one. TBDPSCl (520 μL, 2.00 mmol) was added to a suspension of Wang supported 4-hydroxy-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one (0.498 mmol), pre-swollen in DMF (5 mL) in a Bond Elut cartridge. Imidazole (252 mg, 4.00 mmol) was then added and the mixture rotated at room temperature for 18 h. The resin was then filtered, washed and dried according to the standard washing procedure to give Wang supported 4-(*tert*-butyldiphenylsilyloxyl)-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one:ν_{max} KBr/cm^{-1} 2922 (w), 2852 (w), 1643 (w) C=O, 1612 (m), 1585 (w), 1504 (s), 1290 (s) and 1219 (s).

General procedure for the cleavage of amides

4-(*tert*-Butyldiphenylsilyloxy)-1-(morpholin-4-yl)butan-1-one 14a. DMPU (967 μL, 8.00 mmol) was added to a suspension of Wang supported 4-(*tert*-butyldiphenylsilyloxyl)-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one (0.498 mmol), in THF (3 mL). SmI_2 (0.1 M in THF, 25 mL, 2.50 mmol) was added dropwise and the mixture stirred slowly for 12 h. The reaction mixture was then filtered and washed with THF (100 mL) and concentrated *in vacuo* to give the crude product as a yellow oil. The crude mixture was then filtered through a short pad of silica gel (using 50% EtOAc–petroleum ether), to give **14a** (54 mg, 0.131 mmol, 26% for 4 steps from phenol resin **1**, HPLC purity 93%) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 2856 (m), 1651 (s) C=O, 1428 (m), 1271 (w) and 1113 (s); δ_H (400 MHz; $CDCl_3$) 0.92 (9H, s, $C(CH_3)_3$), 1.84–1.91 (2H, m, CH_2CH_2C=O), 2.40 (2H, t, *J* 7.6 Hz, CH_2C=O) 3.42 (2H, apparent t, *J* 4.8 Hz, CH_2NC=O), 3.61–3.68 (6H, m, CH_2O × 2 and CH_2NC=O), 3.72 (2H, t, *J* 5.9 Hz, CH_2OSi), 7.34–7.44 (6H, m, ArH) and 7.62–7.65 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 19.2 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$ × 3), 28.2 (CH_2CH_2C=O), 29.8 (CH_2C=O), 41.9 (CH_2N), 45.9 (CH_2N), 63.1 (CH_2OSi), 66.6 (CH_2O), 66.9 (CH_2O), 127.7 (ArCH × 4), 129.7 (ArCH × 2), 133.8 (ArC × 2), 135.5 (ArCH × 4) and 171.6 (C=O); LRMS (CI$^+$) 412.3 ((M + H)$^+$, 3%), 354 (100), 334 (12), 156 (8); HRMS calculated for $C_{24}H_{34}O_3NSi$, 412.2308, found 412.2311.

4-(*tert*-Butyldiphenylsilyloxy)-1-(pyrrolidin-1-yl)butan-1-one 7. The precursor resin (0.445 mmol) gave **7** (44 mg, 0.111 mmol, 25% overall yield for 4 steps from phenol resin **1**, HPLC purity 82%) as a pale yellow oil.

4-(*tert*-Butyldiphenylsilyloxy)-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)butan-1-one 14b. The precursor resin (0.478 mmol) gave **14b** (68 mg, 0.149 mmol, 31% overall yield for 4 steps from phenol resin **1**, HPLC purity 88%) as a pale yellow oil; ν_{max} (neat)/cm^{-1} 3069 (m), 2930 (s), 1692 (s), 1648 (s), 1427 (s) and 1109 (s); (mixture of rotamers) δ_H (400 MHz; $CDCl_3$) 1.08 (9H, s, $C(CH_3)_3$), 1.91–1.99 (2H, m, CH_2CH_2C=O), 2.51–2.57 (2H, m, CH_2C=O), 2.84–2.90 (2H, m, CH_2CH_2NC=O), 3.68 (2H, t, *J* 5.9 Hz, CH_2NC=O, major rotamer), 3.76–3.79 (2H, m, CH_2OSi), 3.84 (2H, t, *J* 5.0 Hz, CH_2NC=O, minor rotamer), 4.62 (2H, s, $ArCH_2NC$=O minor rotamer), 4.74 (2H, s, $ArCH_2NC$=O major rotamer), 7.06–7.24 (4H, m, ArH), 7.36–7.45 (6H, m, ArH) and 7.66–7.76 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 19.2 ($SiC(CH_3)_3$, 26.9 ($C(CH_3)_3$ × 3), 28.2 (CH_2CH_2C=O), 28.5 (CH_2CH_2NC=O), 29.5 (CH_2CH_2NC=O), 29.9 (CH_2C=O), 30.2 (CH_2C=O), 39.6 (CH_2NC=O), 43.2 (CH_2NC=O), 44.2 ($ArCH_2NC$=O), 47.3 ($ArCH_2NC$=O), 63.2 (CH_2OSi), 125.9 (ArCH), 126.3 (ArCH), 126.4 (ArCH), 126.5 (ArCH), 126.7 (ArCH), 126.8 (ArCH), 127.6 (ArCH × 2), 128.2 (ArCH), 128.9 (ArCH), 129.6 (ArCH × 2), 132.7 (ArC), 133.7 (ArC), 133.8 (ArC), 134.1 (ArC), 134.8 (ArC), 135.2 (ArC), 135.5 (ArCH × 2) and 171.8 (C=O); LRMS (CI$^+$) 458.3 ((M + H)$^+$, 18%), 400 (100), 380 (12), 202 (7); HRMS (EI$^+$, M$^+$) calculated for $C_{29}H_{35}O_2NSi$, 457.2437, found 457.2433.

General procedure for the acetylation of alcohols 12

Wang supported 4-acetoxy-2-(4-hydroxyphenoxy)-1-(pyrrolidin-1-yl)butan-1-one. Acetic anhydride (481 μL, 5.10 mmol) was added to a Bond Elut cartridge containing a suspension of Wang supported 4-hydroxy-2-(4-hydroxyphenoxy)-1-(pyrrolidin-1-yl)-butan-1-one (0.502 mmol) in pyridine (2 mL) at room temperature and the reaction mixture rotated for 18 h. The resin was then filtered, washed and dried according to the standard washing procedure to give Wang supported 4-acetoxy-2-(4-hydroxyphenoxy)-1-(pyrrolidin-1-yl)butan-1one: ν_{max} KBr/cm^{-1} 3025 (w), 2923 (w), 1740 (s) C=O, 1612 (s) C=O, 1505 (s) and 1223 (m).

General procedure for cleavage of acetates from resin

4-Acetoxy-1-(pyrrolidin-1-yl)butan-1-one 14c[25]. SmI_2 (0.1 M solution in THF, 30.6 mL, 3.06 mmol) was added to a suspension of Wang supported 4-acetoxy-2-(4-hydroxyphenoxy)-1-(pyrrolidin-1-yl)butan-1-one (0.502 mmol) in THF (2 mL) and DMPU (987 μL, 8.16 mmol) at room temperature. The mixture was then stirred slowly at room temperature for 2.5 h. The reaction mixture was filtered and the resin washed with THF (100 mL). The filtrate and washings were then concentrated *in vacuo*. Purification by column chromatography (silica, 10% MeOH–EtOAc) gave **14c** (16 mg, 0.080 mmol, 16% overall yield for 4 steps from phenol resin **1**) as a clear colourless oil: ν_{max} KBr/cm^{-1} 2972 (m), 2877 (m), 1732 (s) C=O, 1618 (s) C=O, 1452 (s), 1244 (s) and 1038 (s); δ_H (400 MHz; $CDCl_3$) 1.83–2.04 (6H, m, CH_2CH_2C=O, CH_2CH_2NC=O × 2), 2.05 (3H, s, CH_3C=O), 2.34 (2H, t, *J* 7.4 Hz, CH_2C=O), 3.42 (2H, t, *J* 6.9 Hz, CH_2NC=O), 3.47 (2H, t, *J* 6.9 Hz, CH_2NC=O) and 4.15 (2H, t, *J* 6.4 Hz, CH_2O); δ_C (100 MHz; $CDCl_3$) 21.0 (CH_3C=O), 24.0 (CH_2CH_2C=O), 24.4 (CH_2CH_2NC=O), 26.1 (CH_2CH_2NC=O), 30.9 (CH_2C=O), 45.7 (CH_2NC=O), 46.5 (CH_2NC=O), 64.0 (CH_2O), 170.4 (OC=O) and 171.1 (NC=O), LRMS (EI$^+$) 199.1 (M$^+$, 25%), 113 (100), 98 (25), 70 (56), 43 (33); HRMS calculated for $C_{10}H_{17}NO_3$, 199.1208, found 199.1207.

4-Acetoxy-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)butan-1-one 14d. SmI_2 (0.1 M solution in THF, 21.9 mL, 2.19 mmol) was added to a suspension of Wang supported 4-acetoxy-2-(4-hydroxyphenoxy)-1-(3,4-dihydro-1*H*-isoquinolin-2-yl)butan-1-one (0.555 mmol) in THF (2 mL) and DMPU (1.06 mL, 8.77 mmol) at room temperature. The mixture was then stirred slowly for 2.5 h. The reaction mixture was filtered and the resin washed with THF (100 mL). The filtrate and washings were then concentrated *in vacuo*. Purification by column chromatography (silica, 50% EtOAc–petroleum ether) gave amide **14d** (29 mg, 0.111 mmol, 20% overall yield for 4 steps from phenol resin **1**, HPLC purity 70%) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 2934 (m), 1736 (s), 1645 (s), 1242 (s) and 1040 (s); (mixture of rotamers) δ_H (400 MHz; $CDCl_3$) 1.73–2.08 (5H, m, CH_2CH_2C=O, CH_3C=O), 2.47 (2H, m, CH_2C=O), 2.86 (2H, t, *J* 6.0 Hz, CH_2CH_2N minor rotamer), 2.91 (2H, t, *J* 5.8 Hz, CH_2CH_2N major rotamer), 3.69 (2H, t, *J* 6.0 Hz, CH_2NC=O major rotamer), 3.84 (2H, t, *J* 6.0 Hz,

$CH_2NC{=}O$ minor rotamer), 4.15 (2H, t, *J* 6.2 Hz, CH_2O), 4.63 (2H, s, $ArCH_2N$ minor rotamer), 4.74 (2H, s, $ArCH_2N$ major rotamer) and 7.10–7.22 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 20.9 ($CH_3C{=}O$), 24.2 ($CH_2CH_2C{=}O$), 28.5 (CH_2CH_2N), 29.4 (CH_2CH_2N), 29.8 ($CH_2C{=}O$), 30.0 ($CH_2C{=}O$), 39.7 ($CH_2NC{=}O$), 43.1 ($CH_2NC{=}O$), 44.2 ($ArCH_2NC{=}O$), 47.2 ($ArCH_2NC{=}O$), 63.9 (CH_2O), 126.0 (ArCH), 126.3 (ArCH), 126.5 (ArCH), 126.6 (ArCH), 126.7 (ArCH), 126.9 (ArCH), 128.2 (ArCH), 129.0 (ArCH), 132.4 (ArC), 133.5 (ArC), 134.0 (ArC), 135.1 (ArC), 170.7 (NC=O), 170.8 (NC=O) and 171.0 ($CH_3OC{=}O$); LRMS (EI^+) 261.2 (M^+, 21%), 201 (28), 145 (40), 132 (100), 104 (34), 43 (34); HRMS calculated for $C_{15}H_{19}NO_3$, 261.1365, found 261.1367.

General procedure for the formation of immobilised ketones

Wang supported 5-(*tert*-butyldiphenylsilyloxy)-3-(4-hydroxyphenoxy)-1-phenylpentan-2-one. Benzyl magnesium chloride (2.0 M in THF, 1.59 mL, 3.18 mmol) was added dropwise at 0 °C to a suspension of Wang supported 4-(*tert*-butyldiphenylsilyloxyl-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one (0.516 mmol) in THF (1.5 mL) and the reaction stirred slowly at 0 °C overnight during which time the reaction warmed to room temperature. The reaction was then quenched using acetone (40 mL), to destroy any excess Grignard reagent present, and distilled water (10 mL). The resin was then filtered, washed and dried according to the standard washing procedure to give Wang supported 5-(*tert*-butyldiphenylsilyloxy)-3-(4-hydroxyphenoxy)-1-phenylpentan-2-one: ν_{max} KBr/cm^{-1} 2926 (w), 1721 (w) C=O, 1613 (s), 1509 (s) and 1221 (m).

Wang supported 6-(*tert*-butyldiphenylsilyloxy)-4-(4-hydroxyphenoxy)-2-methylhexan-3-one. Wang supported 4-(*tert*-butyldiphenylsilyloxyl-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one (0.589 mmol), was treated with *i*-PrMgCl (2.0 M in THF, 1.77 mL, 3.54 mmol) to give Wang supported 6-(*tert*-butyldiphenylsilyloxy)-4-(4-hydroxyphenoxy)-2-methylhexan-3-one: ν_{max} KBr/cm^{-1} 3025 (w), 2925 (w), 1721 (m) C=O, 1612 (s), 1506 (s) and 1223 (s).

Wang supported 4-(*tert*-butyldiphenylsilyloxy)-1-cyclopropyl-2-(4-hydroxyphenoxy)butan-1-one 17. A crystal of iodine was added to a suspension of magnesium powder (244 mg, 10.2 mmol) in minimal THF (0.3 mL). Cyclopropyl bromide (817 μL, 10.2 mmol) was then added dropwise with THF (9.7 mL) and the mixture warmed until Grignard formation began. The mixture was then heated at reflux for approximately 50 min by which time all the magnesium had been consumed. A portion of the cyclopropyl Grignard reagent (3 mL, 3.06 mmol) was added dropwise at 0 °C to a suspension of Wang supported 4-(*tert*-butyldiphenylsilyloxyl)-2-(4-hydroxyphenoxy)-1-(morpholin-4-yl)butan-1-one (0.499 mmol) in THF (1.5 mL) and the reaction stirred slowly at 0 °C overnight during which time the reaction warmed to room temperature. The reaction was then quenched using acetone, to destroy any excess Grignard reagent present, and distilled water (10 ml). The resin was then filtered, washed and dried according to the standard washing procedure to give resin **17**: ν_{max} KBr/cm^{-1} 2922 (w), 2854 (w), 1697 (w) C=O, 1637 (m), 1612 (s), 1508 (s) and 1221 (m).

General procedure for the cleavage of ketones

5-(*tert*-Butyldiphenylsilyloxy)-1-phenylpentan-2-one 16b. SmI_2 (0.1 M solution in THF, 15.9 mL, 1.59 mmol) was added to a suspension of Wang supported 5-(*tert*-butyldiphenylsilyloxy)-3-(4-hydroxyphenoxy)-1-phenylpentan-2-one (0.516 mmol) in THF (2 mL) at 0 °C. The mixture was then stirred slowly and allowed to warm to room temperature over 6 h. The reaction mixture was filtered and the resin washed with THF (100 mL). The filtrate and washings were then concentrated *in vacuo*. Further filtration through a short pad of silica gel (10% EtOAc–petroleum ether) removed the inorganic by-products and gave **16b** (43 mg, 0.103 mmol, 20% overall yield for 5 steps from phenol resin **1**, HPLC purity 83%) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 3069 (w), 2930 (m), 2857 (m), 1713 (s) C=O and 1112 (s); δ_H (400 MHz; $CDCl_3$) 0.94 (9H, s, $C(CH_3)_3$), 1.69–1.75 (2H, m, $CH_2CH_2C{=}O$), 2.49 (2H, t, *J* 7.3 Hz, $CH_2CH_2C{=}O$), 3.55 (2H, t, *J* 6.1 Hz, CH_2OSi), 3.59 (2H, s, $ArCH_2C{=}O$), 7.10–7.36 (11H, m, ArH) and 7.53–7.55 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 19.2 ($C(CH_3)_3$), 26.5 ($CH_2CH_2C{=}O$), 26.8 ($C(CH_3)_3$ × 3), 38.3 ($CH_2CH_2C{=}O$), 50.2 ($ArCH_2C{=}O$), 62.8 (CH_2OSi), 126.9 (ArCH), 127.6 (ArCH × 4), 128.7 (ArCH × 2), 129.4 (ArCH × 2), 129.6 (ArCH × 2), 133.8 (ArC × 2), 134.4 (ArC), 135.5 (ArCH × 4) and 208.3 (C=O); LRMS (FAB^+) 417.2 ($(M + H)^+$ 21%), 359 (100), 199 (47), 161 (84), 135 (41) and 92 (44); HRMS calculated for $C_{27}H_{33}O_2Si$, 417.2250, found 417.2246.

2-Methyl-6-(*tert*-butyldiphenylsilyloxy)hexan-3-one 16a. Wang supported 6-(*tert*-butyldiphenylsilyloxy)-4-(4-hydroxyphenoxy)-2-methylhexan-3-one (0.589 mmol) gave **16a** (52 mg, 0.141 mmol, 24% overall yield for 5 steps from phenol resin **1**, HPLC, purity 70%) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 3071 (m), 2962 (s), 2859 (s), 1712 (s) C=O and 1110 (s); δ_H (400 MHz; $CDCl_3$) 1.06 (9H, s $C(CH_3)_3$), 1.10 (6H, d, *J* 7.0 Hz, $(CH_3)_2CHC{=}O$), 1.82 (2H, m, $CH_2CH_2C{=}O$), 2.58 (3H, m, $CH_2C{=}O$ and $(CH_3)_2CHC{=}O$), 3.68 (2H, t, *J* 6.1 Hz, CH_2OSi), 7.36–7.46 (6H, m, ArH) and 7.65–7.67 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 18.3 ($(CH_3)_2CH$ × 2), 19.2 ($C(CH_3)_3$), 26.6 ($CH_2CH_2C{=}O$), 26.8 ($C(CH_3)_3$ × 3), 36.5 ($CH_2C{=}O$), 40.9 ($(CH_3)_2CHC{=}O$), 63.0 (CH_2OSi), 127.6 (ArCH × 4), 129.6 (ArCH × 2), 133.8 (ArC × 2), 135.5 (ArCH × 4) and 214.7 (C=O); LRMS (CI^+) 369.3 ($(M + H)^+$ 18%), 311 (100), 291 (27), 199 (23) and 113 (24); HRMS calculated for $C_{23}H_{33}O_2Si$, 369.2250, found 369.2248.

1-Cyclopropyl-4-(*tert*-butyldiphenylsilyloxy)butan-1-one 16c. SmI_2 (0.1 M solution in THF, 9.78 mL, 0.978 mmol) was added to a suspension of resin **17** (0.499 mmol) in THF (1.5 mL) at 0 °C. The mixture was then stirred slowly and allowed to warm to room temperature over 2.5 h. The reaction mixture was filtered and the resin washed with THF (100 mL). The filtrate and washings were then concentrated *in vacuo*. Further filtration through a short pad of silica gel (10% EtOAc–petroleum ether) removed the inorganic by-products and gave a 6 : 1 mixture of ring-closed (**16c**) and ring-opened (**18**) product (33 mg, 0.090 mmol, 18% overall yield for 5 steps from phenol resin **1**) as a clear colourless oil: For **16c**; ν_{max} (neat)/cm^{-1} 3070 (w), 2913 (m), 2858 (m), 1699 (s) C=O and 1111 (s); δ_H (400 MHz; $CDCl_3$) 0.88–0.92 (2H, m, $(CH_2)_2CHC{=}O$), 0.98–1.02 (2H, m, $(CH_2)_2CHC{=}O$), 1.07 (9H, s, $C(CH_3)_3$), 1.84–1.96 (3H, m, $CHC{=}O$ and $CH_2CH_2C{=}O$), 2.68 (2H, t, *J* 7.2 Hz, $CH_2C{=}O$), 3.70 (2H, t, *J* 6.2 Hz, CH_2OSi), 7.37–7.45 (6H, m, ArH) and 7.66–7.68 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 10.6 ($(CH_2)_2CHC{=}O$ × 2), 19.2 ($C(CH_3)_3$), 20.1 ($CHC{=}O$), 26.8 ($CH_2CH_2C{=}O$), 26.9 ($C(CH_3)_3$ × 3), 39.7 ($CH_2C{=}O$), 63.0 (CH_2OSi), 127.6 (ArCH × 4), 129.6 (ArCH × 2), 133.8 (ArC × 2), 135.5 (ArCH × 4) and 210.8 (C=O); LRMS (FAB^+) 367.2 ($(M + H)^+$ 10%), 309 (100), 199 (78), 111 (86) and 74 (85); HRMS calculated for $C_{23}H_{31}O_2Si$, 367.2093, found 367.2090.

For **18**; ν_{max} (ATR)/cm^{-1} 2935(s), 1713(s) C=O, 1427(m) and 1096(s); δ_H (500 MHz; $CDCl_3$) 0.93 (3H, t, *J* 6.0 Hz, CH_3), 1.07 (9H, s, $C(CH_3)_3$), 1.61 (2H, apparent sextet, *J* 6.0 Hz, CH_2CH_3), 1.85 (2H, quintet, *J* 5.9 Hz, CH_2), 2.40 (2H, t, *J* 5.9 Hz, $CH_3CH_2CH_2C(O)$), 2.54 (2H, t, *J* 5.9 Hz, $CH_2C(O)$), 3.69 (2H, t, *J* 5.9 Hz, CH_2O), 7.38–7.44 (6H, m, ArH) and 7.66–7.7.68 (4H, m, ArH); δ_C (75 MHz; $CDCl_3$) 13.7 (CH_3), 17.3 (CH_2CH_3), 19.2 (SiC), 26.6 (CH_2), 26.8 ($C(CH_3)_3$), 39.0 ($CH_2C(O)$), 44.8 ($CH_3CH_2CH_2C(O)$), 63.0 (CH_2O), 127.6 (ArCH × 4), 129.6 (ArCH × 2), 133.8 (ArC × 2), 135.5 (ArCH × 4) and 211.1 (C=O); LRMS (CI^+) 369 ($(M + H)^+$ 100%), 311 (50), 291 (20)

and 113 (30); HRMS calculated for $C_{23}H_{32}O_2Si$, 368.2166, found 368.2170.

2-(4-Benzyloxyphenoxy)-4-(*tert*-butyldiphenylsilyloxy)-1-cyclopropylbutan-1-one 19. A crystal of iodine was added to a suspension of magnesium metal (219 mg, 9.12 mmol) in a minimal amount of THF (0.5 mL). Cyclopropyl bromide (703 μL, 9.12 mmol) was then added dropwise followed by THF (9.5 mL) and the resulting mixture heated at reflux for 1 h until the magnesium had been consumed. A portion of the resultant Grignard reagent (1.67 mL, 1.52 mmol) was then added dropwise to a solution of 2-(4-benzyloxyphenoxy)-4-(*tert*-butyldiphenylsilyloxy)-1-(morpholin-4-yl)butan-1-one (230 mg, 0.377 mmol) in THF (4 mL) and the reaction mixture stirred at room temperature for 12 h. The reaction was quenched using aqueous saturated NH_4Cl (40 mL) and distilled H_2O (20 mL). The aqueous solution was extracted using 30% EtOAc–petroleum ether (3 × 30 mL), the organic layers combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (silica, 5% EtOAc–petroleum ether) gave **19** (177 mg, 0.313 mmol, 83%) as a clear colourless oil; ν_{max} (neat)/cm^{-1} 3070 (s), 2858 (s), 1697 (s) C=O, 1506 (s), 1226 (m) and 1111 (s); δ_H (400 MHz; $CDCl_3$) 0.82–1.08 (13H, m, 2 × (C*H*$_2$)$_2$CHC=O, 3 × C(CH$_3$)$_3$), 2.03–2.18 (2H, m, C*H*$_2$CH$_2$OSi), 2.25–2.32 (1H, m, (CH$_2$)C*H*C=O), 3.81–3.86 (1H, m, 1H from CH$_2$OSi), 3.93 (1H, dt, *J* 4.8, 9.6 Hz, 1H from CH$_2$OSi), 4.84 (1H, dd, *J* 3.8, 9.3 Hz, OCHC=O), 5.03 (2H, s, PhCH$_2$), 6.79–6.91 (4H, m, ArH), 7.29–7.45 (11H, m, ArH) and 7.58–7.67 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 11.8 ((*C*H$_2$)$_2$CHC=O × 2), 16.3 ((CH$_2$)$_2$*C*HC=O), 19.2 (*C*(CH$_3$)$_3$), 26.8 (C(*C*H$_3$)$_3$ × 3), 35.3 (*C*H$_2$CH$_2$OSi), 59.4 (CH$_2$OSi), 70.6 (PhCH$_2$O), 80.6 (O*C*HC=O)), 115.8 (ArCH × 2), 116.1 (ArCH × 2), 117.1 (ArC), 127.5 (ArCH × 2), 127.6 (ArCH × 2), 127.7 (ArCH × 2), 127.9 (ArCH), 128.5 (ArCH × 2), 129.6 (ArCH × 2), 133.4 (ArC), 135.5 (ArCH × 4), 137.2 (ArC), 152.6 (ArC), 153.4 (ArC) and 212.3 (C=O); LRMS (FAB$^+$) 587.2 ((M + Na)$^+$ 18%), 197 (19), 135 (37) and 92 (100); HRMS calculated for $C_{36}H_{40}O_4SiNa$, 587.2594, found 587.2591.

4-(4-Benzyloxyphenoxy)-6-(*tert*-butyldiphenylsilyloxy)-2-methylhexan-3-one 23. *i*-PrMgCl (2.0 M, in THF 1.59 mL, 3.18 mmol) was added dropwise at 0 °C to a solution of amide **6** (643 mg, 1.08 mmol) in THF (10 mL) and the reaction stirred slowly at 0 °C overnight, during which time the reaction warmed to room temperature. The reaction was quenched with aqueous saturated NH_4Cl (30 mL) and distilled H_2O (10 mL). The aqueous layer was extracted with 30% EtOAc–petroleum ether (3 × 30 mL), the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification by column chromatography (silica, 5% EtOAc–petroleum ether) gave **23** (501 mg, 0.883 mmol, 82%) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 3070 (s), 2931 (s), 1714 (s) C=O, 1506 (s), 1227 (m) and 1111 (s); δ_H (400 MHz; $CDCl_3$) 0.97 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CHC=O), 1.03 (9H, s, (CH$_3$)$_3$CSi), 1.12 (3H, d, *J* 6.8 Hz, (C*H*$_3$)$_2$CHC=O), 1.94–2.01 (1H, m, 1H from C*H*$_2$CH$_2$OSi), 2.07–2.13 (1H, m, 1H from C*H*$_2$CH$_2$OSi), 3.01 (1H, apparent septet, *J* 6.8 Hz, (CH$_3$)$_2$C*H*C=O), 3.77–3.82 (1H, m, 1H from CH$_2$OSi), 3.89 (1H, dt, *J* 4.4, 9.7 Hz, CH$_2$OSi), 4.90 (1H, dd, *J* 3.7, 9.5 Hz, OCHC=O), 5.03 (2H, s, ArCH$_2$), 6.80–6.90 (4H, m, ArH), 7.28–7.45 (11H, m, ArH) and 7.56–7.66 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 18.1 (CH(*C*H$_3$)$_2$), 19.1 (CH(*C*H$_3$)$_2$ and *C*(CH$_3$)$_3$), 26.8 (C(*C*H$_3$)$_3$ × 3), 35.3 (*C*H$_2$CH$_2$OSi), 35.9 ((CH$_3$)$_2$*C*HC=O), 59.5 (CH$_2$OSi), 70.6 (ArCH$_2$O), 79.7 (O*C*HC=O)), 115.9 (ArCH × 2), 116.2 (ArCH × 2), 127.5 (ArCH × 2), 127.6 (ArCH × 2), 127.7 (ArCH × 2), 127.9 (ArCH), 128.5 (ArCH × 2), 129.6 (ArCH), 129.7 (ArCH), 133.3 (ArC), 133.4 (ArC), 135.5 (ArCH × 4), 137.2 (ArC), 152.6 (ArC), 153.5 (ArC) and 215.6 (C=O); LRMS (EI$^+$) 566.2 (M$^+$ 8%) 431 (89), 233 (26), 199 (20), 135 (27) and 91 (100); HRMS calculated for $C_{36}H_{42}O_4Si$, 566.2852, found 566.2853.

6-(*tert*-Butyldiphenylsilyloxy)-4-(1-hydroxycyclohexyl)-2-methylhexan-3-one 24. Cyclohexanone (50 μL, 0.480 mmol) and DMPU (58 μL, 0.480 mmol) were added to a solution of ketone **23** (19 mg, 0.034 mmol) in THF (0.5 mL). SmI_2 (0.1 M in THF, 1.2 mL, 0.120 mmol) was then added and the reaction mixture stirred at −78 °C. After 15 min the reaction mixture changed from a dark blue to a yellow/orange colour and further portions of DMPU (29 μL, 0.240 mmol) and SmI_2 (0.1 M in THF, 0.6 mL, 0.060 mmol) were subsequently added. The reaction was stirred for a further 25 minutes before being quenched with aqueous saturated NH_4Cl (8 mL) and distilled H_2O (3 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), the organic extracts combined, dried (Mg_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (silica, 5% EtOAc–petroleum ether) gave starting ketone **23** (2 mg, 0.004 mmol, 10%) as a clear colourless oil. Further elution then gave **24** as a clear colourless oil (12.5 mg, 0.027 mmol, 78%): ν_{max} ATR/cm^{-1} 3485 (b), 2929 (s), 2856 (m), 1691 (s) C=O, 1464 (m) and 1107 (s); δ_H (400 MHz; $CDCl_3$) 1.01 (3H, d, *J* 6.8 Hz, (CH(C*H*$_3$)$_2$), 1.08 (3H, d, *J* 6.9 Hz, (CH(C*H*$_3$)$_2$), 1.08 (9H, s, C(CH$_3$)$_3$), 1.12–1.76 (11H, m, 1H from C*H*$_2$CH$_2$OSi, C*H*$_2$C(OH) × 2, C*H*$_2$CH$_2$C(OH) × 2, C*H*$_2$CH$_2$CH$_2$C(OH)), 1.98–2.04 (1H, m, 1H from C*H*$_2$CH$_2$OSi), 2.76 (1H, septet, *J* 6.9 Hz, C*H*(CH$_3$)$_2$), 2.98 (1H, dd, *J* 4.3, 8.2 Hz, CH$_2$C*H*C=O), 3.33 (1H, s, OH), 3.53–3.59 (1H, m, 1H from CH$_2$OSi), 3.69 (1H, apparent quintet, *J* 5.5 Hz, 1H from CH$_2$OSi), 7.37–7.46 (6H, m, ArH) and 7.64–7.67 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 17.2 (CH(*C*H$_3$)$_2$), 17.7 (CH(*C*H$_3$)$_2$), 19.2 (*C*(CH$_3$)$_3$), 21.5 (CH$_2$), 21.9 (CH$_2$), 25.7 (CH$_2$), 26.9 (C(*C*H$_3$)$_3$ × 3), 30.3 (*C*H$_2$CH$_2$OSi), 34.8 (*C*H$_2$C(OH)), 37.4 (*C*H$_2$C(OH)), 42.5 (*C*H(CH$_3$)$_2$), 53.8 (*C*HC=O), 62.4 (CH$_2$OSi), 72.7 (C(OH)), 127.7 (ArCH × 4), 129.7 (ArCH × 2), 133.5 (ArC × 2), 135.5 (ArCH × 4) and 221.9 (C=O). LRMS (FAB$^+$) 467.3 ((M + H)$^+$ 7%) 311 (24), 193 (100), 135 (23) and 72 (28); HRMS calculated for $C_{29}H_{43}O_3Si$, 467.2981, found 467.2981. Further elution then gave 4-benzyloxyphenol (6 mg, 0.030 mmol, 86%) as a pale yellow solid.

6-(*tert*-Butyldiphenylsilyloxy)-4-(4-hydroxytetrahydropyran-4-yl)-2-methylhexan-3-one 25. Tetrahydro-4*H*-pyran-4-one (133 μL, 1.44 mmol) and DMPU (174 μL, 1.44 mmol) were added to a solution of ketone **23** (50 mg, 0.088 mmol) in THF (0.5 mL). SmI_2 (0.1 M in THF, 3.6 mL, 0.36 mmol) was then added and the reaction mixture stirred at −78 °C. After 25 minutes the reaction mixture changed from a dark blue to a yellow/orange colour and further portions of DMPU (66 μL, 0.720 mmol) and SmI_2 (1.80 mL, 0.180 mmol) were added. The reaction was stirred for a further 25 min before being quenched with aqueous saturated NH_4Cl (8 mL) and distilled H_2O (4 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), the organic extracts combined, dried (Mg_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (silica, 2% EtOAc–petroleum ether) gave ketone **23** (4 mg, 0.011 mmol, 12%) as a clear colourless oil. Further elution then gave 4-benzyloxyphenol (18 mg, 0.090 mmol, 100%) as a pale yellow solid. Further elution gave **25** (32 mg, 0.068 mmol, 76%) as a clear, colourless oil: ν_{max} ATR/cm^{-1} 3473 (b), 2958 (m), 2931 (m), 1691 (m) C=O, 1468 (m) and 1103 (s); δ_H (400 MHz; $CDCl_3$) 1.01 (3H, d, *J* 6.9 Hz, CH(C*H*$_3$)$_2$), 1.08 (9H, s, C(C*H*$_3$)$_3$), 1.09 (3H, d, *J* 7.2 Hz, CH(C*H*$_3$)$_2$), 1.33–1.43 (2H, m, C*H*$_2$C(OH)CH), 1.55 (1H, dd, *J* 1.5, 13.3 Hz, 1H from C*H*$_2$C(OH)CH), 1.64–1.76 (2H, m, 1H from C*H*$_2$(OH)CH, 1H from C*H*$_2$CH$_2$OSi), 1.98–2.07 (1H, m, C*H*$_2$CH$_2$OSi), 2.75 (1H, septet, *J* 6.9 Hz, C*H*(CH$_3$)$_2$), 2.86 (1H, dd, *J* 4.4, 8.0 Hz, CHC=O), 3.54–3.60 (2H, m, 1H from CH$_2$OSi), 3.60 (1H, d, *J* 2.1 Hz, OH), 3.70–3.82 (5H, m, 1H from CH$_2$OSi, C*H*$_2$O × 2), 7.37–7.47 (6H, m, ArH) and

7.64–7.66 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 16.9 ($CH(CH_3)_2$), 17.9 ($CH(CH_3)_2$), 19.1 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3 \times 3$), 29.8 ($CH_2CHC{=}O$), 35.4 ($CH_2C(OH)$), 37.8 ($CH_2C(OH)$), 42.4 ($CH(CH_3)_2$), 54.0 ($CHC{=}O$), 62.1 (CH_2OSi), 63.4 ($CH_2O \times 2$), 70.1 ($CH_2C(OH)$), 127.7 (ArCH × 4), 129.8 (ArCH × 2), 133.3 (ArC × 2), 135.5 (ArCH × 4) and 221.9 (C=O). LRMS (CI^+) 469.4 ($(M + H)^+$ 11%) 451 (10), 369 (5), 195 (7) and 57 (100); HRMS calculated for $C_{28}H_{41}O_4Si$, 469.2774, found 469.2773.

4-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-methyl-5-oxoheptanoic acid methyl ester 26. SmI_2 (0.1M solution in THF, 1.2 mL, 0.120 mmol) was added dropwise to a solution of ketone **23** (31 mg, 0.055 mmol) in methyl acrylate (54 μL, 0.060 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred for 20 minutes before further portions of both methyl acrylate (54 μL, 0.600 mmol) and SmI_2 (0.1 M in THF, 1.20 mL, 0.120 mmol) were added and the solution stirred for a further 20 minutes. The reaction was quenched with aqueous saturated $NaHCO_3$ (5 mL) and distilled H_2O (2 mL). The aqueous layer was extracted with EtOAc, the organic extracts combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography (silica, 30% EtOAc–petroleum ether) gave ketone **16a** (19 mg, 0.052 mmol, 86%) as a clear colourless oil. Further elution then gave **26** as a (3 mg, 0.007 mmol, 11%) as a clear colourless oil: ν_{max} (neat)/cm^{-1} 2931 (m), 1738 (s), 1708 (s), 1427 (m) and 1108 (s); δ_H (400 MHz; $CDCl_3$) 1.04 (3H, d, *J* 6.9 Hz, $CH(CH_3)_2$), 1.06 (9H, s, $C(CH_3)_3$), 1.07 (3H, d, *J* 6.9 Hz, $CH(CH_3)_2$), 1.49–1.55 (1H, m, 1H from CH_2CH_2OSi), 1.63–1.71 (1H, m, 1H from $CH_2CH_2CO_2CH_3$), 1.78–1.96 (2H, m, 1H from CH_2CH_2OSi and 1H from $CH_2CH_2CO_2CH_3$), 2.14–2.32 (2H, m, $CH_2CO_2CH_3$), 2.73 (1H, septet, *J* 6.9 Hz, $CH(CH_3)_2$), 3.00 (1H, apparent quintet, *J* 6.6 Hz, CHC=O), 3.56–3.69 (5H, m, CH_2OSi and CO_2CH_3), 7.36–7.46 (6H, m, ArH) and 7.63–8.36 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 17.9 ($CH(CH_3)_2$), 18.1 ($CH(CH_3)_2$), 19.1 ($C(CH_3)_3$), 25.9 ($CH_2CH_2CO_2CH_3$), 26.8 ($C(CH_3)_3 \times 3$), 31.6 ($CH_2CO_2CH_3$), 34.0 (CH_2CH_2OSi), 40.1 ($CH(CH_3)_2$), 44.9 ($CHC{=}O$), 51.6 (CO_2CH_3), 61.3 (CH_2OSi), 127.7 (ArCH × 4), 129.7 (ArCH × 2), 133.5 (ArC), 135.5 (ArCH × 4), 138.1 (ArC), 173.5 (CO_2CH_3) and 217.1 (C=O); LRMS (FAB^+) 455.3 ($(M + H)^+$ 10%), 397 (45), 199 (100) and 135 (35); HRMS calculated for $C_{27}H_{39}O_4Si$ 455.2618, found 455.2614; Further elution gave 4-benzyloxyphenol (11 mg, 0.055 mmol, 91%) as a pale yellow solid.

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