Efficient Synthesis of Quaternary α-Hydroxy Acids by Alkylation of α-Ketoamide-Derived Dienediolates

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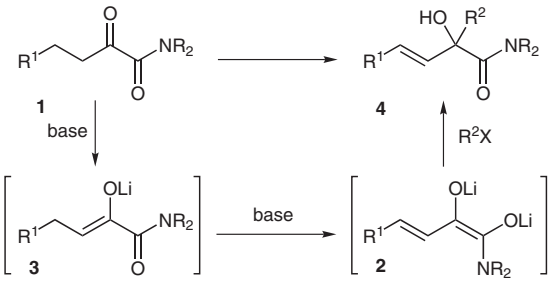
Dedicated to Professor Steven Ley, FRS, on the occasion of his 60th birthday

Abstract: Double deprotonation of α-ketoamides generates dienediolates, which undergo regioselective α-alkylation to yield α-substituted-α-hydroxy-β,γ-unsaturated amides. 1,2-Disubstituted alkenes are generated exclusively as the *E*-isomer. 1,1-Disubstituted and 1,1,2-trisubstituted olefins can also be prepared. The amides can be readily converted to the corresponding acids.

Key words: ketoamides, alkylations, dianions, hydroxy acids, stereoselective olefin synthesis

The α-hydroxy-α,α-disubstituted carboxyl function is a commonly found motif in both natural and synthetic targets of biological interest. Examples of the former range from relatively simple structures such as the nitrogenase co-factor component (*R*)-homocitrate[1] and the anti-collagenolytic fukinolic and cimifugic acids[2] to complex natural products such as the squalene synthase inhibiting zaragozic acids (squalestatins).[3] The motif can also be found in pharmaceuticals such as the anti-androgen bicalutamide[4] (marketed as Casodex® for the treatment of prostate cancer) and agrochemicals such as the insecticidal sodium channel blocker indoxacarb[5] (Avaunt®). There has therefore been much interest in the development of methods for the construction of these motifs. One of the most popular approaches involves the α-alkylation of substituted glycolate equivalents, particularly where the control of absolute stereochemistry can be enforced. The work of Seebach[6] and Ley[7] on chiral relay-based approaches and Seebach[6] and Evans[8] on alkylation/aldol reactions of tartaric acid-derived enolates has been particularly widely adopted.

We became interested in the possibility of an alternative approach to the generation of α-hydroxy-α,α-disubstituted carboxylic acids, centred on the chemistry of dienediolates. Specifically, we envisaged that double deprotonation of α-ketoamides **1** would lead to the formation of dienediolates **2** by way of the intermediate monoenolate **3**. Regioselective α-alkylation would then lead to the β,γ-unsaturated α-alkyl,α-hydroxy amides **4** (Scheme 1). This chemistry was attractive to us for several reasons. Firstly, the starting ketoamides are trivial to prepare; secondly, the olefin generated serves as a useful handle for the introduction of further functionality; and thirdly, the presence of a terminal substituent R^1 other than hydrogen allows for the simultaneous generation of a second stereochemical element in the form of olefin geometry. All of these factors combine to add significant molecular complexity to a simple educt in a single operation.



Scheme 1 Proposed synthesis of α-alkyl α-hydroxy amides by alkylation of dienediolates derived from α-ketoamides.

In fact, a preliminary investigation of such an approach appeared in the literature some years ago. In 1986 Koft reported the alkylation of dianions generated by treatment of diethyl 2-ketobutyramide (**1**, $NR_2 = NEt_2$, $R^1 = H$) with LDA–HMPA.[9] The reaction was only successful with primary alkyl halides (29–67% yield), did not work with benzylic halides, and usually returned some unreacted starting material. To our knowledge, this work has not been followed up since. We felt that these preliminary results were encouraging and that the method would have great synthetic potential if the deprotonation protocol could be improved (complete deprotonation; avoid carcinogenic HMPA) and the range of ketoamide substrates and reactive electrophiles expanded significantly. We report here the results of our studies in this area.

Initially, we focused upon optimisation of the deprotonation conditions. Treatment of diethyl 2-ketobutyramide with 2.2 equivalents of LDA and 6 equivalents of LiCl in THF at 0 °C, followed by alkylation with iodomethane gave a ca. 1:1 mixture of product to starting material. The use of LTMP as base was more effective, giving a ca. 2.5:1 mixture of product and starting material when used alone and a ca. 4:1 mixture when used with added LiCl.[10] Finally, we found that the use of 3 equivalents of LTMP and 6 equivalents of LiCl at 0 °C gave a clean alkylation reaction with < 8% returned starting material. We also investigated the influence of the nature of the carboxyl sub-

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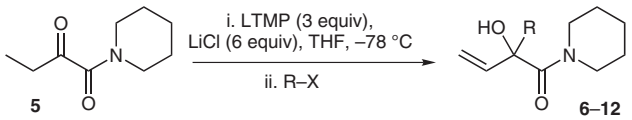
stituent on the reaction. Attempted formation of dienediolates of α-ketoesters was unsuccessful even at –78 °C, with the liberation of the alcohol substituent indicating that an α-elimination pathway was operating. The use of anilides was similarly unsuccessful, but other aliphatic amides could be used. Our further studies have focused upon piperidinyl amides, owing to the ease of preparation of higher substituted substrates in this series (see below).

Having identified our optimal reaction conditions, we then examined the scope of the reaction in terms of electrophile. Thus, the dienediolate from piperidinyl 2-oxobutyramide **5** (prepared in 92% yield by DCC coupling of piperidine and 2-oxobutyric acid) was treated with a range of alkylating agents and the results are shown in Scheme 2, Table 1.



Scheme 2

Table 1 Reaction of Piperidinyl 2-Ketobutyrate-Derived Dianionic Dienediolates with a Range of Electrophiles

Entry	RX	Product	Yield (%)
1	CH_3I	**6**	63
2	CH_2=$CHCH_2Br$	**7**	55
3	$PhCH_2Br$	**8**	51
4	(4-MeOPh)CH_2Br	**9**	71
5	$CH_3CH_2CH_2I$	**10**	74
6	$(CH_3)_2CHCH_2Br$	**11**	62
7	$(CH_3)_2CHI$	**12**	54

Some aspects of these results are worthy of discussion. In all cases, the crude reaction mixtures consist almost exclusively of the alkylation products and so the moderate isolated yields in some cases may reflect loss of the highly polar materials on chromatography. Whilst simple primary alkyl electrophiles worked well, as expected from the precedent of Koft (entries 1, 2 and 5), we were pleased to find that under our reaction conditions the use of benzylic electrophiles was well tolerated (entries 3 and 4). This may be a consequence of the reaction conditions: Koft does not state conditions for his alkylations, but indicates that products of benzyl carbenoid formation were observed. Under our conditions, alkylation proceeds on warming from –78 °C to 0 °C and only minor formation of carbenoid products was seen. It is also noteworthy that, despite the strongly basic nature of the dienediolates, efficient alkylation is also observed with β-branched primary alkyl and secondary alkyl electrophiles, which might be expected to be prone to elimination (entries 6 and 7 respectively).

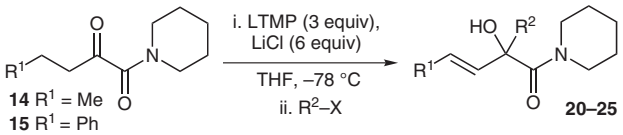
We next wished to investigate the generality of the process with respect to the substitution pattern of the dienediolate. This required the preparation of diverse α-ketoamides, which we accomplished by selective monosubstitution of dipiperidinyl oxalamide **13** with Grignard reagents or organolithiums (Scheme 3, Table 2).[11] This process ought to be applicable to the preparation of other α-ketoamides, but we found that the reactions of tetraethyl oxalamide with hindered organometallics were much less efficient.

Scheme 3

Table 2 Synthesis of Diverse α-Ketoamides from Oxalamide **13**

Entry	RM	Product	Yield (%)
1	CH_3CH_2MgBr	**5**	88
2	$CH_3CH_2CH_2MgBr$	**14**	90
3	$PhCH_2CH_2MgBr$	**15**	88
4	$(CH_3)_2CHMgCl$	**16**	50
5	*c*-$C_6H_{11}MgCl$	**17**	53
6	$CH_3CH_2(CH_3)CHLi$	**18**	67
7	$(CH_3)_2CHCH_2MgBr$	**19**	79

With these materials in hand, we first investigated the generation of 1,2-disubstituted alkenes in the alkylation reactions (Scheme 4, Table 3). Koft reported one example of methylation of *N*,*N*-diethyl 2-oxopentamide to yield selectively the *E*-isomer in 38% yield.[9] Under our reaction conditions, methylation of the piperidinyl analogue **14** gave a 66% yield of the alkylated product **20** as a single *E*-isomer, although an extended period at room temperature was required for full deprotonation. Alkylations of **14** with iodopropane and allyl bromide were similarly successful and stereoselective. The presence of an aryl group as the R^1 substituent was also probed in substrate **15**; although the reactions were slightly lower yielding the regio- and stereoselectivities of the alkylations mirrored those of the alkyl series.



Scheme 4

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Table 3 Synthesis of *E*-Disubstituted Olefins by Alkylation of Ketoamide-Derived Dienediolates

Entry	R^1	R^2X	Product	Yield (%)
1	Me	CH_3I	**20**	66
2	Me	$CH_3CH_2CH_2I$	**21**	82
3	Me	CH_2=$CHCH_2Br$	**22**	62
4	Ph	CH_3I	**23**	61
5	Ph	$CH_3CH_2CH_2I$	**24**	65
6	Ph	CH_2=$CHCH_2Br$	**25**	46

The selective formation of the *E*-isomer can be rationalised by minimisation of $A_{1,3}$-strain in the deprotonation of the intermediate monoenolate by placement of the hydrogen substituent proximal to the oxyanion in preference to the C4-substituent (Me, Ph; Figure 1).

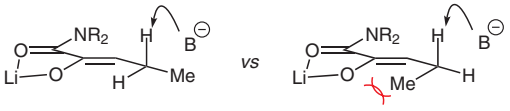
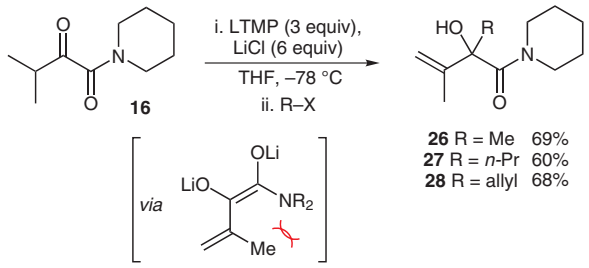


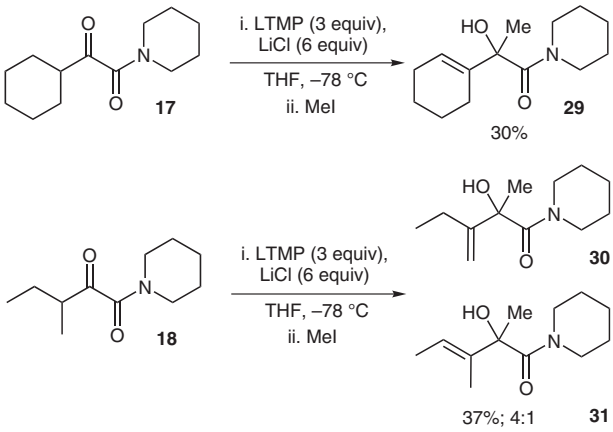
Figure 1 Rationalisation of the stereochemical outcome of dienediolate formation.

Attention then turned to the generation of 1,1-disubstituted olefins by alkylation of dienediolates derived from ketoamide **16**. As shown in Scheme 5, clean alkylation was observed with iodomethane, iodopropane and allyl bromide, indicating that the presence of the additional C3-substituent is not an impediment to the second deprotonation, despite the unavoidable development of $A_{1,3}$-strain in the resulting dienediolate.



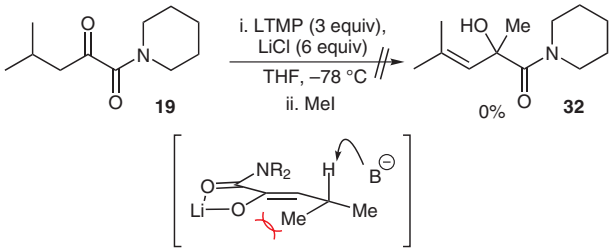
Scheme 5 Alkylation of dienediolates derived from ketoamide **16**.

Finally, we wished to examine the possibility of generating trisubstituted olefins in the alkylation reaction, utilising substrates **17**–**19**. The alkylation of the cyclohexyl-substituted ketoamide **17** required an extended period for dienediolate formation (23 h, cf 1 h for **15** and **16**) and generated the endocyclic olefin **29** in a moderate 30% yield (Scheme 6). Although deprotonation of the *sec*-butyl-substituted ketoamide **18** proceeded under normal conditions, a similarly modest 37% yield was obtained in the alkylation. As expected, an inseparable mixture of two regioisomeric products **30** and **31** was obtained in a ratio of 4:1. These arise from the availability of two non-identical sets of protons for removal in the intermediate enolate, with deprotonation at the methyl substituent dominating over the ethyl group.



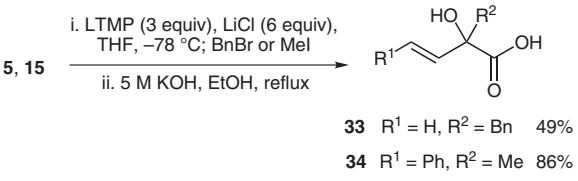
Scheme 6 Alkylation of dienediolates derived from ketoamides **17** and **18**.

All attempts to generate dienediolates from the ketoamide **19** were, however, unsuccessful (Scheme 7). It appears that the strain associated with accommodating an 'inside' substituent in the reactive conformation for deprotonation is prohibitively high.



Scheme 7 Failure of attempted alkylations of ketoamide **19**.

Finally, we wished to demonstrate that substitution chemistry was feasible at the hindered α-quaternary tertiary amides. Basic hydrolyses of the crude reaction mixtures leading to α-hydroxyamides **8** and **23** were carried out. Following extractive workup, the clean α-hydroxyacids **33** and **34** were isolated in 49% and 86% yields, respectively, over the two steps (Scheme 8).



Scheme 8 Preparation of free α-hydroxy acids.

In summary, we have conducted a detailed examination of the scope and limitations of the alkylation reactions of dienediolates derived from readily prepared α-ketoamides.

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We have identified optimised conditions for the formation of reactive dienediolates, which widens the scope of acceptable electrophiles, gives improved yields and avoids the undesirable use of HMPA. We have also demonstrated that products containing monosubstituted, *E*-1,2- and 1,1-disubstituted and 1,1,2-trisubstituted olefins can be accessed, but that the formation of 1,2,2-trisubstituted olefins is unsuccessful. Further studies on synthetic applications of these useful building blocks will be reported in due course.

All reactions were carried out under an atmosphere of dry N_2 and carried out using oven-dried glassware unless otherwise stated. THF and Et_2O were distilled from sodium benzophenone ketyl; CH_2Cl_2 and toluene from CaH_2; TMP from NaOH. All other reagents and solvents were purified by standard procedures or were used as obtained from commercial sources as appropriate. Light petroleum ether (PE) used had a bp range of 40–60 °C, unless otherwise stated and was distilled prior to use. Flash chromatography was carried out using silica gel (35–70 μm particles). TLC was carried out on commercially available pre-coated plates (Merck silica Kieselgel 60F254) and visualised by UV fluorescence or $KMnO_4$ dip. Melting points were measured using a Reichert hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer FT-IR infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM 300 FT spectrometer using an internal deuterium lock. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AM 300 FT spectrometer. Chemical shifts are quoted in ppm downfield of TMS and values of coupling constants (*J*) are given in Hz. Mass spectra were recorded using electrospray techniques on a Micromass LCT KA111 spectrometer (nominal) and a Waters LCT time-of-flight spectrometer (accurate). Microanalyses were determined in microanalytical laboratories at the Department of Chemistry, University of Leeds.

Synthesis of α-Ketoamides: 1-Piperidin-1-ylbutane-1,2-dione (5); Typical Procedure

A solution of oxalamide **13** (10.0 g, 44.6 mmol) in THF (100 mL) was cooled to 0 °C under N_2. EtMgBr (3 M in Et_2O, 17.9 mL, 53.6 mmol) was added dropwise and the reaction was allowed to warm to r.t. over 18 h. The orange solution was cooled to 0 °C and 3 M HCl (50 mL) was added cautiously. The solution was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to return a yellow oil. Flash chromatography eluting with PE–EtOAc (2:1) gave the α-ketoamide **5** (6.66 g, 88%) as a pale yellow oil; R_f 0.30 (PE–EtOAc, 1:1).

IR (neat): 1710 (C=O), 1634 (NC=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.56 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.32 (t, *J* = 5.4 Hz, 2 H, NCH_2), 2.78 (q, *J* = 7.3 Hz, 2 H, CH_2CH_3), 1.56–1.72 [m, 6 H, $NCH_2(CH_2)_3$], 1.14 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.8 (C=O), 166.4 (NC=O), 47.2 (NCH_2), 42.8 (NCH_2), 33.9 (CH_3CH_2), 26.8, 25.7, 24.8 [$NCH_2(CH_2)_3$], 7.3 (CH_3CH_2).

MS (ESI+): *m*/*z* = 184 [M$^+$ + H].

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.60; H, 9.15; N, 8.55.

1-Piperidin-1-ylpentane-1,2-dione (14)

Prepared according to the typical procedure on a 22.3 mmol scale, using *n*-PrMgBr (2 M in Et_2O, 26.8 mmol); R_f 0.28 (PE–EtOAc, 2:1).

IR (neat): 1709 (C=O), 1643 (NC=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.56 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.33 (t, *J* = 5.4 Hz, 2 H, NCH_2), 2.72 (t, *J* = 7.4 Hz, 2 H, $CH_2CH_2CH_3$), 1.57–1.71 [m, 8 H, $CH_2CH_2CH_3$, $NCH_2(CH_2)_3$], 0.97 (t, *J* = 7.4 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.2 (C=O), 166.3 (NC=O), 47.1 (NCH_2), 42.8, 42.5 (NCH_2, $C{=}OCH_2$), 26.8, 25.7, 24.8 [$NCH_2(CH_2)_3$], 16.8 (CH_3CH_2), 14.1 (CH_3).

MS (ESI+): *m*/*z* = 184 [M$^+$ + H].

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.60; H, 9.45; N, 7.70.

4-Phenyl-1-piperidin-1-ylbutane-1,2-dione (15)

Prepared according to the typical procedure on a 22.3 mmol scale, using $PhCH_2CH_2MgBr$ (1.1 M in Et_2O, 33.5 mmol); mp 42–46 °C; R_f 0.21 (PE–Et_2O, 1:1).

IR ($CHCl_3$): 1713 (C=O), 1635 (NC=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.30 (m, 5 H, Ph), 3.53 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.16 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.10 (app dt, *J* = 2.1, 7.2 Hz, 2 H, CH_2), 2.99 (t, *J* = 7.2 Hz, 2 H, CH_2), 1.45–1.68 [m, $NCH_2(CH_2)_3$, 6 H].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.2 (C=O), 165.9 (NC=O), 140.6 (C_q), 129.0 (CH), 128.8 (CH), 126.7 (CH), 47.0 (NCH_2), 42.8 (NCH_2), 41.9 (CH_2), 29.2 (CH_2), 26.7, 25.7, 24.7 [$NCH_2(CH_2)_3$].

MS (ESI+): *m*/*z* = 245 [M$^+$ + H].

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.40; H, 7.70; N, 5.70.

3-Methyl-1-piperidin-1-ylbutane-1,2-dione (16)

Prepared according to the typical procedure on an 8.9 mmol scale, using *i*-PrMgCl (2.0 M in Et_2O, 17.9 mmol); R_f 0.24 (PE–EtOAc, 3:1).

IR (neat): 1710 (C=O), 1634 (NC=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.58 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.29 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.18 [sept, *J* = 7.1 Hz, 1 H, $CH(CH_3)_2$], 1.58–1.72 [m, $NCH_2(CH_2)_3$, 6 H], 1.16 [d, *J* = 7.1 Hz, 6 H, $CH(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.2 (C=O), 166.5 (NC=O), 47.2 (NCH_2), 42.7 (NCH_2), 37.9 [$CH(CH_3)_2$], 26.7, 25.7, 24.7 [$NCH_2(CH_2)_3$], 17.1 [$CH(CH_3)_2$].

MS (ESI+): *m*/*z* = 184 [M$^+$ + H].

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.35; H, 9.20; N, 7.90.

1-Cyclohexyl-2-piperidin-1-ylethane-1,2-dione (17)

Prepared according to the typical procedure on an 8.9 mmol scale, using CyMgCl (2.0 M in Et_2O, 17.9 mmol); mp 32–35 °C; R_f 0.30 (PE–EtOAc, 3:1).

IR ($CHCl_3$): 1704 (C=O), 1639 (NC=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.57 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.29 (t, *J* = 5.4 Hz, 2 H, NCH_2), 2.87–2.97 (m, 1 H, CHC=O), 1.12–1.96 [m, 16 H, $NCH_2(CH_2)_3$, 5 × CH_2].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.6 (C=O), 166.6 (NC=O), 47.3 (HCC=O), 47.2 (NCH_2), 42.6 (NCH_2), 27.5, 26.8, 26.2, 25.8, 24.8 [$NCH_2(CH_2)_3$, 5 × CH_2].

MS (ESI+): *m*/*z* = 224 [M$^+$ + H].

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.80; H, 9.55; N, 6.20.

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3-Methyl-1-piperidin-1-ylpentane-1,2-dione (18)
A solution of oxalamide **13** (2.0 g, 8.9 mmol) in THF (20 mL) was cooled to –78 °C under N_2. *s*-BuLi (1.3 M in cyclopentane, 6.9 mL, 8.9 mmol) was added dropwise and the reaction was stirred at –78 °C for 1 h before allowing to warm to r.t. over 18 h. The yellow solution was cooled to 0 °C and 2 M HCl (20 mL) was added cautiously. The solution was extracted with EtOAc (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to return a yellow oil. Flash chromatography eluting with PE–EtOAc (6:1) gave the α-ketoamide **18** (1.17 g, 67%) as a colourless oil; R_f 0.32 (PE–EtOAc, 3:1).

IR (neat): 1706 (C=O), 1634 (NC=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.58 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.31 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.02 (sext, *J* = 6.9 Hz, 1 H, CHC=O), 1.81 (dp, *J* = 7.4, 14.9 Hz, 1 H, CH_3CHHCH), 1.50–1.73 [m, 6 H, $NCH_2(CH_2)_3$], 1.38 (dp, *J* = 7.4, 14.9 Hz, 1 H, CH_3CHHCH), 1.13 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$), 0.96 (t, *J* = 7.4 Hz, 3 H, CH_3CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.5 (C=O), 166.1 (NC=O), 46.7 (NCH_2), 44.3 (CH), 42.4 (NCH_2), 26.3, 25.4, 24.4, 24.3 [$NCH_2(CH_2)_3$, CH_2], 14.0 (CH_3CH), 11.5 (CH_3CH_2).

MS (ESI+): *m*/*z* = 198 [M^+ + H].

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.00; H, 9.60; N, 7.25.

4-Methyl-1-piperidin-1-ylpentane-1,2-dione (19)
Prepared according to the typical procedure on an 8.9 mmol scale, using *i*-BuMgBr (2.0 M in Et_2O, 10.7 mmol); R_f 0.25 (PE–EtOAc, 5:1).

IR (neat): 1708 (C=O), 1639 (NC=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.56 (t, *J* = 5.4 Hz, 2 H, NCH_2), 3.34 (t, *J* = 5.4 Hz, 2 H, NCH_2), 2.63 (d, *J* = 6.8 Hz, 2 H, $CHCH_2C$=O), 2.21 [sept, *J* = 6.7 Hz, 1 H, $CH(CH_3)_2$], 1.58–1.71 [m, 6 H, $NCH_2(CH_2)_3$], 0.98 [d, *J* = 6.7, 6 H, $CH(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.8 (C=O), 166.2 (NC=O), 49.4 (CH_2C=O), 47.1 (NCH_2), 42.8 (NCH_2), 26.8, 25.8, 24.8 [$NCH_2(CH_2)_3$], 24.2 (CH), 23.0 (2 × CH_3).

MS (ESI+): *m*/*z* 198 [M^+ + H].

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.80; H, 9.50; N, 7.30.

Alkylation of α-Ketoamides: 2-Hydroxy-2-methyl-1-piperidin-1-ylbut-3-en-1-one (6); Typical Procedure
A flask charged with LiCl (150 mg, 3.55 mmol) was flame-dried under vacuum then purged with N_2. THF (2 mL) and 2,2,6,6-tetramethylpiperidine (300 μL, 1.78 mmol) were added and the mixture cooled to –78 °C before a solution of *n*-BuLi (1.6 M in hexanes, 1.11 mL, 1.78 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, then a solution of α-ketoamide **5** (100 mg, 0.59 mmol) in THF (2 mL) was added. The mixture was stirred at 0 °C for 30 min then recooled to –78 °C before adding MeI (184 μL, 2.96 mmol). The reaction mixture was allowed to slowly warm to r.t. over 20 h, then quenched with sat. aq NH_4Cl solution (5 mL), diluted with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Flash chromatography eluting with PE–EtOAc (2:1) gave the product **6** (69 mg, 63%) as a pale yellow oil; R_f 0.34 (PE–EtOAc, 1:1).

IR (neat): 3378 (OH), 1615 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.03 (dd, *J* = 10.3, 17.4 Hz, 1 H, CH_2=C*H*), 5.34 (d, *J* = 17.4 Hz, 1 H, CH*H*=CH), 5.27 (d, *J* = 10.3 Hz, 1 H, CH*H*=CH), 5.19 (s, 1 H, OH), 3.54 (m, 4 H, 2 × NCH_2), 1.55–1.68 [m, 9 H, $NCH_2(CH_2)_3$, CH_3].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2 (C=O), 140.5 (CH_2=*C*H), 115.7 (CH_2=CH), 73.2 (C_q), 48.0, 45.4 (br, 2 × NCH_2), 26.2, 24.7, 24.6 [$NCH_2(CH_2)_3$, CH_3].

MS (ESI+): *m*/*z* = 184 [M^+ + H].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{18}NO_2$: 184.1338; found: 184.1345.

2-Hydroxy-1-piperidin-1-yl-2-vinylpent-4-en-1-one (7)
R_f 0.20 (PE–EtOAc, 4:1).

IR (neat): 3368 (OH), 1622 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.04 (dd, *J* = 10.7, 17.3 Hz, 1 H, CH_2=C*H*C), 5.80–5.87 (m, 1 H, CH_2=C*H*CH_2), 5.39 (d, *J* = 17.3 Hz, 1 H, CH*H*=CHC), 5.27 (d, *J* = 10.7 Hz, 1 H, CH*H*=CHC), 5.14 (d, *J* = 11.5 Hz, 1 H, CH*H*=$CHCH_2$) 5.13 (d, *J* = 15.8 Hz, 1 H, C*H*H=$CHCH_2$), 4.94 (s, 1 H, OH), 3.55 (m, 4 H, 2 × NCH_2), 2.62 (d, *J* = 7.0 Hz, 2 H, CH_2CHCH_2), 1.53–1.67 [m, 6 H, $NCH_2(CH_2)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7 (C=O), 139.7 (C_qCH=CH_2), 133.2 (H_2C=*C*HCH_2), 119.1 (H_2C=CHCH_2), 116.3 (C_qCH=*C*H_2), 75.6 (C_q), 47.2, 45.5 (br, 2 × NCH_2), 42.7 (H_2C=CH*C*H_2), 26.2, 24.7 [$NCH_2(CH_2)_3$].

MS (ESI+): *m*/*z* = 210 [M^+ + H].

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.60; H, 9.30; N, 6.40.

2-Benzyl-2-hydroxy-1-piperidin-1-ylbut-3-en-1-one (8)
Mp 83–88 °C; R_f 0.20 (PE–EtOAc, 4:1).

IR ($CHCl_3$): 3368 (OH), 1624 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.26 (m, 5 H, Ph), 6.13 (dd, *J* = 10.7, 17.4 Hz, 1 H, CH_2=C*H*), 5.42 (d, *J* = 17.4 Hz, 1 H, CH*H*=CH), 5.30 (d, *J* = 10.7 Hz, 1 H, CH*H*=CH), 4.81 (s, 1 H, OH), 3.29–3.66 (m, 4 H, 2 × NCH_2), 3.16 (s, 2 H, $PhCH_2$), 1.57–1.66 [m, 6 H, $NCH_2(CH_2)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7 (C=O), 140.0 (*C*H=CH_2), 136.1 (C_q), 130.7 (CH), 128.4 (CH), 127.3 (CH), 116.6 (*C*H_2=CH), 76.6 (Cq), 46 (br, NCH_2), 44.1 (Ph*C*H_2), 26.0, 24.8 [$NCH_2(CH_2)_3$].

MS (ESI+): *m*/*z* = 260 [M^+ + H].

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.80; H, 8.30; N, 5.30.

2-Hydroxy-2-(4-methoxybenzyl)-1-piperidin-1-ylbut-3-en-1-one (9)
Mp 79–82 °C; R_f 0.27 (PE–EtOAc, 3:1).

IR ($CHCl_3$): 3368 (OH), 1623 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.6 Hz, 2 H, ArH), 6.80 (d, *J* = 8.6 Hz, 2 H, ArH), 6.12 (dd, *J* = 10.6, 17.4 Hz, 1 H, CH_2=C*H*), 5.41 (d, *J* = 17.4 Hz, 1 H, CH*H*=CH), 5.30 (d, *J* = 10.6 Hz, 1 H, CH*H*=CH), 4.83 (s, 1 H, OH), 3.77 (s, 3 H, OMe), 3.64 (m, 4 H, 2 × NCH_2), 3.13 (d, *J* = 15.0 Hz, 1 H, PhCH*H*), 3.08 (d, *J* = 15.0 Hz, 1 H, PhC*H*H), 1.57–1.67 [m, 6 H, $NCH_2(CH_2)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (C=O), 158.9 (C_q), 140.0 (*C*H=CH_2), 131.7 (CH), 128.1 (C_q), 116.6 (CH=*C*H_2), 113.9 (CH), 76.7 (C_q), 55.5 (OMe), 47 (br, NCH_2), 43.1 (Ph*C*H_2), 26.1, 24.8 [$NCH_2(CH_2)_3$].

MS (ESI+): *m*/*z* = 290 [M^+ + H].

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.30; H, 8.25; N, 4.70.

2-Hydroxy-1-piperidin-1-yl-2-propylbut-3-en-1-one (10)
R_f 0.33 (PE–EtOAc, 3:1).

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IR (neat): 3367 (OH), 1622 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.96 (dd, *J* = 10.5, 17.4 Hz, 1 H, C*H*=CH_2), 5.31 (d, *J* = 17.4 Hz, 1 H, CH=C*H*H), 5.18 (s, 1 H, OH), 5.17 (d, *J* = 10.5 Hz, 1 H, CH=CH*H*), 3.48 (br m, 4 H, 2 × NCH_2), 1.71–1.79 (m, 2 H, C*HH*CH_2CH_3), 1.42–1.69 [m, 7 H, CHHCH*H*CH_3, $NCH_2(CH_2)_3$], 1.01–1.19 (m, 1 H, CHHC*H*HCH_3), 0.86 (t, *J* = 7.3 Hz, 3 H, $CHHCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0 (C=O), 138.9 (*C*H=CH_2), 114.7 (CH=*C*H_2), 74.6 (C_q), 46.1, 44.5 (br, 2 × NCH_2), 38.5 (*C*$H_2CH_2CH_3$), 24.8, 23.3 [$NCH_2(CH_2)_3$], 15.8 (*C*H_2CH_3), 13.3 (CH_2CH_3).

MS (ESI+): *m*/*z* = 212 [M^+ + H].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{22}NO_2$: 212.1651; found: 212.1654.

2-Hydroxy-4-methyl-1-piperidin-1-yl-2-vinylpentan-1-one (11)
R_f 0.17 (PE–EtOAc, 3:1).

IR (neat): 3354 (OH), 1622 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.02 (dd, *J* = 10.6, 17.3 Hz, 1 H, CH_2=C*H*), 5.37 (dd, *J* = 0.8, 17.3 Hz, 1 H, C*H*H=CH), 5.28 (s, 1 H, OH), 5.22 (dd, *J* = 0.8, 10.6 Hz, 1 H, CH*H*=CH), 3.50 (br m, 4 H, 2 × NCH_2), 1.80–1.88 (m, 3 H, $CHCH_2$), 1.56–1.78 [m, 6 H, $NCH_2(CH_2)_3$], 0.98 (d, *J* = 6.1 Hz, 3 H, C*H*$_3$CH), 0.87 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C=O), 140.9 (CH_2=*C*H), 115.8 (*C*H_2=CH), 75.8 (C_q), 47 (br, NCH_2), 46.3 (*C*H_2CH), 45 (br, NCH_2), 26.0, 24.7 [$NCH_2(CH_2)_3$], 24.9, 24.6, 24.1 (*C*H_3*C*H*C*H_3).

MS (ESI+): *m*/*z* = 225 [M^+ + H].

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.00; H, 10.05; N, 6.05.

(*E*)-2-Hydroxy-2-isopropyl-1-piperidin-1-ylbut-3-en-1-one (12)
R_f 0.20 (PE–EtOAc, 3:1).

IR (neat): 3341 (OH), 1622 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.11 (dd, *J* = 10.6, 17.0 Hz, 1 H, CH_2=C*H*), 5.47 (dd, *J* = 1.2, 17.0 Hz, 1 H, C*H*H=CH), 5.27 (dd, *J* = 1.2, 10.6 Hz, 1 H, CH*H*=CH), 5.19 (s, 1 H, OH), 3.56 (br m, 4 H, 2 × NCH_2), 2.10 (sept, *J* = 6.6 Hz, 1 H, CH), 1.56–1.71 [m, 6 H, $NCH_2(CH_2)_3$], 0.99 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.84 (d, *J* = 6.6 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C=O), 139.0 (*C*H=CH_2), 117.8 (CH=*C*H_2), 79.0 (C_q), 47.0 (br, 2 × NCH_2), 34.2 (CH), 26.2, 24.8 [$NCH_2(CH_2)_3$], 17.2 (CH_3), 16.9 (CH_3).

MS (ESI+): *m*/*z* = 212 [M^+ + H].

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.00; H, 9.90; N, 6.65.

2-Hydroxy-2-methyl-1-piperidin-1-ylpent-3-en-1-one (20)
Prepared according to the typical procedure except that after the addition of α-ketoamide **14**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; R_f 0.38 (PE–EtOAc, 1:1).

IR (neat): 3381 (OH), 1621 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.80 (dq, *J* = 6.4, 15.6 Hz, 1 H, CH_3C*H*=CH), 5.66 (dd, *J* = 1.4, 15.6 Hz, 1 H, CH_3CH=C*H*), 5.19 (s, 1 H, OH), 3.52 (br m, 4 H, 2 × NCH_2), 1.74 (dd, *J* = 1.4, 6.4 Hz, 3 H, C*H*$_3$CH=CH), 1.51–1.66 [m, 9 H, $NCH_2(CH_2)_3$, CH_3].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4 (C=O), 133.4 (H*C*=$CHCH_3$), 126.7 (HC=*C*HCH_3), 72.3 (C_q), 47.7, 45.0 (br, 2 × NCH_2), 25.9, 24.4 [$NCH_2(CH_2)_3$], 24.8 (*C*H_3C_q), 17.9 (*C*H_3CH=CH).

MS (ESI+): *m*/*z* = 198 [M^+ + H].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{19}NO_2Na$: 220.1313; found: 220.1315.

(*E*)-2-Hydroxy-1-piperidin-1-yl-2-propylpent-3-en-1-one (21)
Prepared according to the typical procedure except that after the addition of α-ketoamide **14**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; R_f 0.29 (PE–EtOAc, 4:1).

IR (neat): 3366 (OH), 1619 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.80 (dq, *J* = 6.4, 15.6 Hz, 1 H, CH_3CH=CH), 5.67 (dd, *J* = 1.3, 15.6 Hz, 1 H, CH_3CH=C*H*), 5.26 (s, 1 H, OH), 3.55 (br m, 4 H, 2 × NCH_2), 1.46–1.82 [m, 12 H, $NCH_2(CH_2)_3$, C*HH*C*H*HCH_3; including 1.73 (dd, *J* = 1.3, 6.4 Hz, 3 H, C*H*$_3$CH=CH)], 1.03–1.20 (m, 1 H, CHHCH*H*CH_3), 0.92 (t, *J* = 7.2 Hz, 3 H, C*H*$_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6 (C=O), 133.3 (CH_3CH=*C*H), 127.0 (CH_3*C*H=CH), 75.2 (C_q), 47.6, 45.1 (br, 2 × NCH_2), 40.1 (*C*$H_2CH_2CH_3$), 25.9, 24.4 [$NCH_2(CH_2)_3$], 18.0 (*C*H_3CH=CH), 16.9 ($CH_2CH_2CH_3$), 14.3 ($CH_2CH_2CH_3$).

MS (ESI+): *m*/*z* = 226 [M^+ + H].

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.00; H, 10.50; N, 6.25.

(*E*)-2-Allyl-2-hydroxy-1-piperidin-1-ylpent-3-en-1-one (22)
Prepared according to the typical procedure except that after the addition of α-ketoamide **14**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; R_f 0.20 (PE–EtOAc, 4:1).

IR (neat): 3362 (OH), 1621 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.78–5.86 (m, 2 H, CH_3C*H*=CH, CH_2C*H*=CH_2), 5.69 (dd, *J* = 1.3, 15.4 Hz, 1 H, CH_3CH=C*H*), 5.12 (d, *J* = 11.8 Hz, 1 H, CH_2CH=CH*H*), 5.11 (d, *J* = 15.4 Hz, 1 H, CH_2CH=C*H*H), 5.08 (s, 1 H, OH), 3.34–3.81 (br m, 4 H, 2 × NCH_2), 2.61 (dd, *J* = 6.4, 14.1 Hz, 1 H, CH_2CH=C*H*H), 2.57 (dd, *J* = 7.7, 14.1 Hz, 1 H, CH_2CH=CH*H*), 1.74 (dd, *J* = 1.3, 6.4 Hz, 3 H, C*H*$_3$CH=CH), 1.54–1.72 [m, 6 H, $NCH_2(CH_2)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9 (C=O), 133.0, 132.6, 127.3 (3 × =CH), 118.4 (CH=*C*H_2), 75.1 (C_q), 47.6, 45.1 (br, 2 × NCH_2), 42.7 (*C*H_2CH=CH_2), 25.8, 24.5 [$NCH_2(CH_2)_3$], 18.0 (CH_3).

MS (ESI+): *m*/*z* = 224 [M^+ + H].

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{22}NO_2$: 224.1651; found: 224.1556.

(*E*)-2-Hydroxy-2-methyl-4-phenyl-1-piperidin-1-ylbut-3-en-1-one (23)
Prepared according to the typical procedure except that after the addition of α-ketoamide **15**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; mp 110–113 °C; R_f 0.14 (PE–EtOAc, 3:1).

IR ($CHCl_3$): 3364 (OH), 1622 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.40 (m, 5 H, Ph), 6.68 (d, *J* = 16.2 Hz, 1 H, CH), 6.37 (d, *J* = 16.2 Hz, 1 H, CH), 5.31 (s, 1 H, OH), 3.58 (br m, 4 H, 2 × NCH_2), 1.54–1.65 [m, 9 H, $NCH_2(CH_2)_3$; including 1.65 (s, 3 H, CH_3)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0 (C=O), 136.3 (C_q), 131.3, 130.5 (HC=CH), 128.6 (CH), 128.0 (CH), 126.6 (CH), 72.7 (C_q), 47.6, 45.5 (br, 2 × NCH_2), 25.9, 24.3 [$NCH_2(CH_2)_3$], 25.2 (CH_3).

MS (ESI+): *m*/*z* = 260 [M^+ + H].

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.80; H, 8.35; N, 5.35.

2-Hydroxy-1-piperidin-1-yl-2-[(*E*)-styryl]pentan-1-one (24)
Prepared according to the typical procedure except that after the addition of α-ketoamide **15**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; R_f 0.36 (PE–EtOAc, 3:1).

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IR (neat): 3363 (OH), 1615 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.40 (m, 5 H, Ph), 6.70 (d, *J* = 16.1 Hz, 1 H, CH), 6.38 (dd, *J* = 2.2, 16.1 Hz, 1 H, CH), 5.37 (d, *J* = 2.2 Hz, 1 H, OH), 3.59 (br m, 4 H, 2 × NCH_2), 1.82–1.99 (m, 2 H, $CH_2CH_2CH_3$), 1.55–1.66 [m, 7 H, $NCH_2(CH_2)_3$, CH_2CHHCH_3], 1.13–1.28 (m, 1 H, CH_2CHHCH_3), 0.97 (t, *J* = 7.3 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3 (C=O), 136.6 (C_q), 131.1, 130.9 (HC=CH), 128.6 (CH), 127.9 (CH), 126.5 (CH), 75.5 (C_q), 46.2 (br, 2 × NCH_2), 40.4 ($CH_2CH_2CH_3$), 26.0, 24.4 [$NCH_2(CH_2)_3$], 17.0 ($CH_2CH_2CH_3$), 14.3 ($CH_2CH_2CH_3$).

MS (ESI+): *m*/*z* = 288 [M^+ + H].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{25}NO_2Na$: 310.1783; found: 310.1796.

2-Hydroxy-1-piperidin-1-yl-2-[(*E*)-styryl]pent-4-en-1-one (25)

Prepared according to the typical procedure except that after the addition of α-ketoamide **15**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; R_f 0.30 (PE–EtOAc, 3:1).

IR (neat): 3365 (OH), 1622 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.40 (m, 5 H, Ph), 6.70 (d, *J* = 16.2 Hz, 1 H, HC=CH), 6.38 (d, *J* = 16.2 Hz, 1 H HC=CH), 5.82–5.95 (m, 1 H, H_2C=CH), 51.4–5.19 (m, 2 H, H_2C=CH), 5.07 (s, 1 H, OH), 3.58 (br m, 4 H, 2 × NCH_2), 2.72 (d, *J* = 7.2 Hz, 2 H, CH_2CH=CH_2), 1.42–1.63 [m, 6 H, $NCH_2(CH_2)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5 (C=O), 136.4 (C_q), 132.8 (CH), 131.0 (CH), 130.5 (CH), 128.6 (CH), 128.0 (CH), 126.5 (CH), 118.9 (CH=CH_2), 75.5 (C_q), 47.2 (br, 2 × NCH_2), 43.2 (CH_2CH=CH_2), 25.9, 24.4 [$NCH_2(CH_2)_3$].

MS (ESI+): *m*/*z* = 286 [M^+ + H].

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{23}NO_2Na$: 308.1626; found: 308.1639.

2-Hydroxy-2,3-dimethyl-1-piperidin-1-ylbut-3-en-1-one (26)

Prepared according to the typical procedure except that after the addition of α-ketoamide **16**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; mp 89–91 °C; R_f 0.16 (PE–EtOAc, 4:1).

IR ($CHCl_3$): 3368 (OH), 1621 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.30 (s, 1 H, OH), 5.14 (s, 1 H, CH), 5.04 (s, 1 H, CH), 3.53 (br m, 4 H, 2 × NCH_2), 1.74 (s, 3 H, CH_3C=CH_2), 1.42–1.70 [m, 9 H, $NCH_2(CH_2)_3$; including 1.56 (s, 3 H, CH_3)].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8 (C=O), 146.8 (C_q), 111.9 (CH_2), 74.8 (C_q), 47.0, 44.8 (br, 2 × NCH_2), 25.8, 24.3 [$NCH_2(CH_2)_3$], 23.7 (CH_3COH), 18.7 (CH_3C=CH_2).

MS (ESI+): *m*/*z* = 198 [M^+ + H].

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.10; H, 10.00; N, 6.80.

2-Hydroxy-3-methyl-1-piperidin-1-yl-2-propylbut-3-en-1-one (27)

Prepared according to the typical procedure except that after the addition of α-ketoamide **16**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; R_f 0.25 (PE–EtOAc, 4:1).

IR (neat): 3355 (OH), 1622 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.28 (s, 1 H, OH), 5.12 (s, 1 H, CH), 5.03 (s, 1 H, CH), 3.32–3.91 (br m, 4 H, 2 × NCH_2), 1.78–1.98 (m, 2 H, $CH_2CH_2CH_3$), 1.73 (s, 3 H, CH_3), 1.24–1.70 [m, 7 H, $NCH_2(CH_2)_3$, CH_2CHHCH_3], 1.00–1.09 (m, 1 H, CH_2CHHCH_3), 0.95 (t, *J* = 6.9 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.1 (C=O), 147.3 (C_q), 112.1 (CH_2), 77.7 (C_q), 47.3, 45.3 (br, 2 × NCH_2), 38.3 ($CH_2CH_2CH_3$), 26.3, 24.8 [$NCH_2(CH_2)_3$], 19.4 (CH_3C=CH_2), 17.5 ($CH_2CH_2CH_3$), 14.9 ($CH_2CH_2CH_3$).

MS (ESI+): *m*/*z* = 226 [M^+ + H].

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.00; H, 10.55; N, 6.25.

2-Hydroxy-2-isopropenyl-1-piperidin-1-ylpent-4-en-1-one (28)

Prepared according to the typical procedure except that after the addition of α-ketoamide **16**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; R_f 0.23 (PE–EtOAc, 4:1).

IR (neat): 3366 (OH), 1634 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.75–5.89 (m, 1 H, CH), 5.06–5.14 (m, 5 H, 2 × alkene CH_2, OH), 3.29–3.57 (br, 4 H, 2 × NCH_2), 2.77 (dd, *J* = 5.6, 13.8 Hz, 1 H, $CHHCH$=CH_2), 2.63 (dd, *J* = 8.2, 13.8 Hz, 1 H, $CHHCH$=CH_2), 1.74 (3 H, CH_3), 1.43–1.67 [m, 6 H, $NCH_2(CH_2)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4 (C=O), 146.8 (C_q), 133.7 (CH), 118.8 (CH_2=CH), 112.2 (CH_2=C), 77.7 (C_q), 47.2, 45.0 (br, 2 × NCH_2), 41.1 (CH_2CH=CH_2), 26.2, 24.8 [$NCH_2(CH_2)_3$], 19.4 (CH_3).

MS (ESI+): *m*/*z* = 224 [M^+ + H].

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.70; H, 9.75; N, 6.20.

2-Cyclohex-1-enyl-2-hydroxy-1-piperidin-1-ylpropan-1-one (29)

Prepared according to the typical procedure except that after the addition of α-ketoamide **17**, the reaction was stirred at 25 °C for 23 h before cooling to –78 °C; R_f 0.26 (PE–EtOAc, 4:1).

IR (neat): 3367 (OH), 1618 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.81–5.88 (m, 1 H, CH), 5.29 (s, 1 H, OH), 3.33–3.78 (br m, 4 H, 2 × NCH_2), 2.01–2.28 (m, 4 H, CH_2CH=CCH_2), 1.35–1.85 [m, 13 H, CH_3, 2 × CH_2, $NCH_2(CH_2)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (C=O), 139.8 (C_q), 123.3 (CH), 75.3 (C_q), 46.9, 44.7 (br, 2 × NCH_2), 26.4, 25.6, 24.8, 24.6, 23.1, 22.6 [$NCH_2(CH_2)_3$, 4 × CH_2], 23.7 (CH_3).

MS (ESI+): *m*/*z* = 238 [M^+ + H].

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.80; H, 10.05; N, 5.60.

3-Ethyl-2-hydroxy-2-methyl-1-piperidin-1-ylbut-3-en-1-one (30) and (*E*)-2-Hydroxy-2,3-dimethyl-1-piperidin-1-ylpent-3-en-1-one (31)

Prepared according to the typical procedure except that after the addition of α-ketoamide **18**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C; R_f 0.20 (PE–EtOAc, 3:1).

IR (neat; mixture of **30** and **31**): 3367 (OH), 1633 (C=O) cm^{-1}.

Major Isomer 30

^1H NMR (300 MHz, $CDCl_3$): δ = 5.24 (s, 1 H, OH), 5.17 (s, 1 H, C=C*HH*), 4.99 (s, 1 H, C=C*HH*), 3.40–3.55 (br m, 4 H, 2 × NCH_2), 2.10–2.20 (m, 1 H, CH_3CHH), 1.72–1.80 (m, 1 H, CH_3CHH), 1.49–1.62 [m, 9 H, $NCH_2(CH_2)_3$, CH_3], 1.01 (t, *J* = 7.3 Hz, 3 H, CH_3CH_2).

Minor Isomer 31

^1H NMR (300 MHz, $CDCl_3$): δ = 5.63 (q, *J* = 6.7 Hz, 1 H, CH_3CH=C), 5.24 (s, 1 H, OH), 3.40–3.55 (br m, 4 H, 2 × NCH_2), 1.60 (d, *J* = 6.7 Hz, 3 H, CH_3CH=C), 1.49–1.62 [m, 12 H, $NCH_2(CH_2)_3$, 2 × CH_3].

^{13}C NMR (75 MHz, $CDCl_3$; mixture of **30** and **31**): δ = 173.8, 173.5 (2 × C=O), 152.9 (C_q), 137.8 (C_q), 120.7 (CH), 109.5 (CH_2), 76.1,

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75.6 (2 × C_q), 47.4, 45.2 (4 × NCH_2), 26.2, 24.8, 24.0 [2 × $NCH_2(CH_2)_3$, CH_3CH_2], 24.3, 23.9, 13.9, 13.0, 12.3 (5 × CH_3).

MS (ESI+): *m/z* = 212 [M^+ + H].

HRMS: *m/z* [M + H]$^+$ calcd for $C_{12}H_{22}NO_2$: 212.1651; found: 212.1642.

2-Benzyl-2-hydroxybut-3-enoic Acid (33)

A flask charged with LiCl (1.50 g, 35.5 mmol) was flame-dried under vacuum then purged with N_2. THF (10 mL) and 2,2,6,6-tetramethylpiperidine (3.01 mL, 17.8 mmol) were added and the mixture was cooled to –78 °C before a solution of *n*-BuLi (1.6 M in hexanes, 1.11 mL, 17.8 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, then a solution of α-ketoamide **5** (1.00 g, 5.9 mmol) in THF (10 mL) was added. The mixture was stirred at 0 °C for 30 min then recooled to –78 °C before adding BnBr (3.5 mL, 29.6 mmol). The reaction mixture was allowed to slowly warm to r.t. over 20 h, then quenched with sat. aq NH_4Cl solution (20 mL), diluted with water (25 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was dissolved in absolute EtOH (10 mL) and 5 M KOH (15 mL) and heated to reflux for 24 h. The reaction mixture was cooled to 25 °C before adding Et_2O (25 mL). The organic phase was separated and further extracted with 2 M KOH (2 × 25 mL). The combined basic aqueous phases were ice-cooled then acidified with concd HCl (15 mL) and extracted with Et_2O (5 × 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure to return the acid **33** (554 mg, 49%) as a pale yellow solid. An analytical sample was recrystallised from toluene to return a white solid; mp 120–123 °C.

IR (diamond transmission cell): 3450 (OH), 2961 (COOH), 1732 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.04–7.17 (m, 5 H, Ph), 6.14 (dd, *J* = 10.5, 17.1 Hz, 1 H, CH_2=C*H*), 5.53 (dd, *J* = 1.0, 17.1 Hz, 1 H, CH*H*=CH), 5.27 (dd, *J* = 1.0, 10.5 Hz, 1 H, C*H*H=CH), 3.22 (d, *J* = 13.6 Hz, 1 H, PhC*H*H), 2.96 (d, *J* = 13.6 Hz, 1 H, PhCH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3 (C=O), 138.2 (*C*H=CH_2), 135.4 (C_q), 130.7 (CH), 128.7 (CH), 127.6 (CH), 116.4 (CH=*C*H_2), 78.4 (C_q), 45.5 ($PhCH_2$).

HRMS: *m/z* [M – H]$^+$ calcd for $C_{11}H_{11}O_3$: 191.0708; found: 191.0699.

(*E*)-2-Hydroxy-2-methyl-4-phenylbut-3-enoic Acid (34)

Method as above except that after the addition of α-ketoamide 1**5**, the reaction was stirred at 25 °C for 1 h before cooling to –78 °C and addition of MeI (1.84 mL, 29.6 mmol). Hydrolysis was performed as previously described to return the acid **34** (979 mg, 86%) as a brown solid. An analytical sample was recrystallised from toluene to return a white solid; mp 133–137 °C.

IR (diamond transmission cell): 3428 (OH), 2933 (COOH), 1719 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, MeOD): δ = 7.09–7.31 (m, 5 H, Ph), 6.66 (d, *J* = 16.1 Hz, 1 H, HC=C*H*), 6.34 (d, *J* = 16.1 Hz, 1 H, *H*C=CH), 1.47 (s, 3 H, CH_3).

^{13}C NMR (75 MHz, MeOD): δ = 178.3 (C=O), 138.3 (C_q), 133.3 (CH), 130.4 (CH), 129.9 (CH), 129.0 (CH), 127.9 (CH), 75.9 (C_q), 27.2 (CH_3).

HRMS: *m/z* [M – H]$^+$ calcd for $C_{11}H_{11}O_3$: 191.0708; found: 191.0692.

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