Supplemental Information

Enantioselective synthesis of γ-alkyl β-hydroxy α-amino acids via asymmetric transfer hydrogenation: application to MeBmt

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All air or moisture sensitive reactions were performed under a positive pressure of nitrogen, using oven-or flame dried glassware where stated. Anhydrous solvents were purchased from Sigma-Aldrich (St. Louis, MO). ‘Normal phase chromatography’, column chromatography, or gradient column chromatography refers to automatic purification using a ‘Tyledyne ISCO CombiFlash® Rf+’ system with pre-loaded silica gel ‘Redisep RF flash columns’ of an appropriate size. Preparative HPLC purification was performed on a Waters semi-preparative HPLC system (Waters Corp., Milford, MA). The column used was a Phenomenex Luna C18 (5 micron, 30 x 75 mm; Phenomenex, Inc., Torrance, CA) at a flow rate of 45.0 mL/min. The mobile phase consisted of acetonitrile and water (each containing 0.1% trifluoroacetic acid). A gradient of 10% to 50% acetonitrile over 8 min was used during the purification. Automated fraction collection was triggered by UV detection at 220 nM. Analytical analysis was performed on an Agilent LC/MS (Agilent Technologies, Santa Clara, CA). A Phenomenex Luna C18 column (3 micron, 3 x 75 mm) was used at a temperature of 50 °C. Purity determination was performed using an Agilent diode array detector for both Method 1 and Method 2.

Method 1: A 7-min gradient of 4% to 100% acetonitrile (containing 0.025% trifluoroacetic acid) in water (containing 0.05% trifluoroacetic acid) was used with an 8-min run time at a flow rate of 1.0 mL/min.

Method 2: A 3-min gradient of 4% to 100% acetonitrile (containing 0.025% trifluoroacetic acid) in water (containing 0.05% trifluoroacetic acid) was used with a 4.5-min run time at a flow rate of 1.0 mL/min. Retention time (RT) and m/z for M+1 is reported, occasionally (M+Na) is observed exclusively.

Mass determination was performed using an Agilent 6130 mass spectrometer with electrospray ionization in the positive mode.

$^1$H and $^{13}$C NMR spectra were recorded on Varian 400 MHz spectrometers (Agilent Technologies, Santa Clara, CA). Signals are described as singlets (s), doublets (d), triplets (t), quadruplets (q), septuple (sept), doublet of doublets (dd) and doublet of triplets (dt). Spectra were analysed in MestReNova.

Single-crystal X-ray diffraction studies were carried out by Dr. Curtis Moore at the UCSD Crystallography Lab using a Bruker D8 Platinum$^{135}$ CCD diffractometer equipped with Cu K$_\alpha$ radiation ($\lambda = 1.5478$). A 0.217 x 0.053 x 0.051 mm piece of a colorless rod was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 125(2) K using $\phi$ and $\omega$ scans. Crystal-to-detector distance was 45 mm using variable exposure time (2s-5s) depending on $\theta$ with a scan width of 2.0°. Data collection was 98.4% complete to 68.00° in $\theta$. A total of 33864 reflections were collected covering the indices, -11<=h<=10, -12<=k<=14, -19<=l<=19. 3547 reflections were found to be symmetry independent, with a R$_{int}$ of 0.0549. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P212121. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.
All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson’s method with a Flack parameter of 0.050(34).

Chiral chromatographic analysis was performed by Agilent 1200 series HPLC using an analytical Chiralpak AD column (4.6 mm x 250 mm; 5 µm). The mobile phase consisted of ethanol and hexanes containing 0.1% diethylamine.

Optical rotations were measured on a PerkinElmer model 341 polarimeter with a 10cm cell
Supplementary Figure 1: Preparation of β-keto esters and amides

**Synthesis of β-keto esters, structures 6a-c**

\[
\text{AlkylCl} \xrightarrow{\text{TiCl}_4 \text{ NMe-Imidazole}} \text{AlkylOMe} \\
\text{DCM, -45°C} \\
R^1 = \text{Bz, CBz} \quad R^2 = \text{H, Me}
\]

**Synthesis of β-keto anilides, structures 15-17**

\[
\text{Alkyl} \xrightarrow{\text{MgBr}_2 \text{OEt}_2 \text{N(iPr)}_2\text{Et}} \text{AlkylSPh} \\
\text{DCM, RT, 30min} \\
R^1 = \text{Bz, CBz, FMOC}
\]

\[
\text{AlkylSPh} \xrightarrow{\text{AgO} \text{CF}_3} \text{AlkylNHR^2} \\
\text{H}_2\text{NR^2, THF, RT}
\]
Supplementary Table S1. Survey of catalysts for optimization of ATH DKR. ND - Not determined, aIsolated yield following aqueous workup and column chromatography dr - diastereomer ratio (2S,3R):(2R,3R), er - enantiomer ratio (2S,3R):(2R,3S). Structures of catalysts A-F given below table. Entry 7: Long reaction times resulted in decomposition of product. Full consumption of starting material was noted for entries 7 and 8.
General procedures

General procedure ‘A’ for Ti-Crossed Claisen

In general, an acyl chloride (25.4 mmol) was added to a stirring solution of a glycine derivative (25.4 mmol) and 1-methyl-1H-imidazole (2.426 mL, 30.4 mmol) in DCM (50 mL) at -45 °C under N₂. Stirring was continued for 10 minutes, then TiCl₄ (9.79 mL, 89 mmol) and diisopropylethylamine (17.72 mL, 101 mmol) were successively added to the mixture which was stirred at -45 °C for a further 1 hour. The mixture was quenched with water (100 mL), then extracted with EtOAc (2x). The combined extracts were washed with water, brine, dried over MgSO₄ filtered and concentrated in vacuo. Purification by gradient normal phase chromatography yielded the title compound.

General procedure ‘B’ for thioester formation

In general, to the carboxylic acid (22.40 mmol) in DCM (50 mL) at 0°C was added isobutyl chloroformate (3.22 mL, 24.64 mmol), benzenethiol (5.03 mL, 49.3 mmol) and triethylamine (6.24 mL, 44.8 mmol). The reaction was allowed to warm to room temperature and stirred until completion. The reaction was diluted with Et₂O (30 mL) to facilitate precipitation of triethylamine HCl, the salt was filtered off and the filter cake was washed with Et₂O, (50 mL). Volatiles were removed under rotary evaporation. The residue was taken up in EtOAc, and washed with 1N HCl, 1N NaOH, and brine. Organics were dried over MgSO₄ and concentrated in vacuo, followed by purification by gradient normal phase chromatography to afford the thoioester.

General procedure ‘C’ for thioester crossed Claisen

In general, under N₂ at 0°C, magnesium bromide diethyl etherate (1.27 g, 4.91 mmol) was added to a stirred solution of the respective N-acyl benzotriazole (1.402 mmol) in DCM (6 mL), followed by the addition of the respective thioester nucleophile (1.402 mmol) and diisopropylethylamine (0.979 mL, 5.61 mmol). The ice-bath was removed, and the reaction was allowed to warm to ambient temperature, then left to stir overnight (18h). Upon completion, the reaction was again cooled to 0-5°C, then 10% aqueous HCl (8 mL) was added dropwise. Stirring was continued for 5 min and the mixture was partitioned between EtOAc (30 mL) and H₂O (20 mL). The aqueous phase was extracted with EtOAc (2 x 20 mL) and the combined organic extracts were washed with brine, dried over MgSO₄, and concentrated in vacuo. The crude β-ketoester products were are purified by gradient column chromatography.
General procedure ‘D’ for ATH DKR in emulsions\textsuperscript{3}
Under N\textsubscript{2}, to a solution of an appropriate β-keto derivative (7.60 mmol) in DCM (25 mL) was added sodium formate solution (5N, 50 mL) followed by tetrabutylammonium iodide (5.61 g, 15.19 mmol) and pre-activated Ru-ATH DKR catalyst (0.760 mmol, 10 % loading). After stirring for 40 hours the reaction was added to a separatory funnel and diluted with EtOAc and sat. NaHCO\textsubscript{3}, then the organic phase was separated and the aqueous was extracted with twice more with EtOAc. The combined extracts were dried (MgSO\textsubscript{4}) and the crude oil was purified by gradient column chromatography, yielding β-hydroxy reduction products.

General procedure ‘E’ for thioester substitution\textsuperscript{2}
To a stirred solution of the appropriate β-keto thioester (0.281 mmol) and aniline (31.4 mg, 0.338 mmol) in THF (2 mL) was added silver trifluoroacetate (63.4 mg, 0.309 mmol). The reaction was stirred until complete, diluted with 20 mL of EtOAc and passed through a pad of Celite to remove silver salts. The filtrate was concentrated followed by purification by gradient flash chromatography over silica gel affording the corresponding β-keto anilide.

General procedure ‘F’ for synthesis of N-acyl benzotriazoles\textsuperscript{4}
SOCl\textsubscript{2} (157 µl, 2.146 mmol) was added to a stirred solution of 1H-benzo[d][1,2,3]triazole (929 mg, 7.80 mmol) in DCM (9 mL), in one portion at room temperature; stirring was continued for 30 min. The appropriate carboxylic acid (1.951 mmol) in DCM (1 mL) was added to the reaction mixture, followed by almost immediate precipitation of 1H-benzo[d][1,2,3]triazole HCl. Stirring was continued overnight, then the white precipitate was filtered off and washed with DCM. The combined DCM filtrates were evaporated and the crude N-acylbenzotriazole was purified by silica gel flash chromatography.
Methyl-3-hydroxy-4-methyl-2-(N-methylbenzamido)pent-2-enoate, 6a

Following general procedure A, isobutyryl chloride (0.506 mL, 4.83 mmol) was coupled to N-benzoyl-N-methylglycinate (1.0 g, 4.83 mmol) with 1-methyl-1H imidazole (0.462 mL, 5.79 mmol), TiCl₄ (1.862 mL, 16.89 mmol) and diisopropylamine (3.37 mL, 19.30 mmol) in DCM (10 mL) at -45 °C under N₂. The crude oil was purified by column chromatography to yield methyl-3-hydroxy-4-methyl-2-(N-methylbenzamido)pent-2-enoate 6a as a white solid (0.575 g, 2.075 mmol, 43 % yield)

LCMS RT (Method 2) 3.24-3.4 min (m/z 278.1)

¹H NMR (400 MHz, CDCl₃) δ 12.16 (d, J = 1.5 Hz, 1H), 7.51 – 7.23 (m, 6H), 3.83 – 3.80 (m, 3H), 3.16 (s, 3H), 2.81 – 2.70 (m, 1H), 1.11 (d, J = 6.8, 3H), 0.77 (d, J = 6.7, 3H)

¹³C NMR (101 MHz, CDCl₃) δ 180.97, 172.64, 170.86, 136.07, 129.72, 127.92, 126.74, 108.16, 52.16, 37.32, 29.15, 20.38, 17.72.

HRMS (ESI) m/z calcd for [M + H]⁺ 278.1392, found 278.1384.

Methyl 2-benzamido-4-methyl-3-oxopentanoate, 6b

Following general procedure A, isobutyryl chloride (2.66 mL, 25.4 mmol) was coupled with methyl 2-benzamidoacetate (4.9 g, 25.4 mmol) using 1-methyl-1H-imidazole (2.426 mL, 30.4 mmol), TiCl₄ (9.79 mL, 89 mmol) and diisopropylethylamine (17.72 mL, 101 mmol). Purification by gradient normal phase chromatography afforded 6b (3.61 g, 13.70 mmol, 54 % yield) as a colourless oil.

LCMS RT (Method 2) 3.14 min (m/z 264.1)

¹H NMR (400 MHz, CDCl₃) δ 7.84 – 7.79 (m, 2H), 7.52 – 7.46 (m, 1H), 7.44 – 7.38 (m, 2H), 7.35 (d, J = 6.5 Hz, 1H), 5.59 (d, J = 6.7 Hz, 1H), 3.78 (s, 3H), 3.19 – 3.02 (m, 1H), 1.21 (d, J = 7.1 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 205.02, 166.94, 166.76, 132.98, 132.05, 128.59, 127.23, 61.03, 53.26, 38.76, 18.81, 17.66.

HRMS (ESI) m/z calcd for [M + H]⁺ 264.1230, found 264.1226.
Methyl-2-(((benzyloxy)carbonyl)(methyl)amino)-3-hydroxy-4-methylpent-2-enoate, 6c

Following general procedure A, isobutyryl chloride (0.442 mL, 4.21 mmol) was coupled to methyl N-((benzyloxy)carbonyl)-N-methylglycinate (1.0 g, 4.21 mmol) with 1-methyl-1H-imidazole (0.403 mL, 5.06 mmol), TiCl$_4$ (1.627 mL, 14.75 mmol) and diisopropylethylamine (2.94 mL, 16.86 mmol) at -45 °C under N$_2$. The crude oil was purified by column chromatography to yield methyl-2-(((benzyloxy)carbonyl)(methyl)amino)-3-hydroxy-4-methylpent-2-enoate, 6c (0.492 g, 1.602 mmol, 38 % yield) as a colourless oil.

LCMS RT (Method 2) 3.64 min (m/z 308.1)

$^1$H NMR (400 MHz, CDCl$_3$) enol (major) δ 12.19 (s, 1H), 7.49 – 7.11 (m, 5H), 5.17 – 5.01 (m, 2H), 3.77 – 3.62 (m, 3H), 3.03 – 2.95 (m, 3H), 2.84 – 2.75 (m, 1H), 1.13 – 0.97 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 206.64, 180.66, 171.11, 156.63, 136.69, 128.33, 127.87, 127.74, 105.57, 67.21, 51.81, 37.72, 29.11, 18.88.

Methyl (2S,3S)-2-benzamido-3-hydroxy-4-methylpentanoate, 8b

Following general procedure D, methyl 2-benzamido-4-methyl-3-oxopentanoate 6b (2 g, 7.60 mmol) underwent ATH DKR with pre-activated Ru(p-cymene)[(S,S)-Ts-DPEN] (0.140 g, 0.228 mmol, 3 % loading). The crude oil was purified by gradient column chromatography yielding (2S,3S)-methyl 2-benzamido-3-hydroxy-4-methylpentanoate 8b (1.794 g, 6.76 mmol, 89 % yield), a colourless oil, as an inseparable mixture of syn and anti diasteromers (15:85 by NMR). Major isomer (anti) reported:

LCMS RT (Method 2) 2.89 min (m/z 266.1)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.82 – 7.75 (m, 2H), 7.52 – 7.43 (m, 1H), 7.43 – 7.34 (m, 2H), 7.29 – 7.20 (m, 1H), 4.93 (dd, $J =$ 7.6, 3.4 Hz, 1H), 3.76 (s, 3H), 3.63 – 3.51 (m, 1H), 3.27 (d, $J =$ 7.7 Hz, 1H), 1.77 (dsept, $J =$ 8.5, 6.7 Hz, 1H), 0.99 (t, $J =$ 6.5 Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.37, 167.41, 133.41, 131.91, 128.57, 127.16, 78.71, 55.80, 52.51, 31.38, 19.08.

HRMS (ESI) m/z calcd for [M + H]$^+$ 266.1392, found 266.1327.
**S-phenyl 2-(N-methylbenzamido)ethanethioate**

Following general procedure B, N-benzoyl-N-methylglycine (3 g, 15.53 mmol) was transformed into its phenylthioester derivative using, isobutyl chloroformate (2.333 g, 17.08 mmol), triethylamine (3.142 g, 31.6 mmol) and thiophenol (3.76 g, 34.2 mmol). After workup, the crude was purified by gradient column chromatography to yield the title compound (3.54 g, 12.42 mmol, 80 % yield) as a colourless oil, which solidified on standing.

**LCMS RT (Method 2)** 3.55 min (m/z 308.1)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.73 – 7.31 (m, 10H), 4.55 (s, 1.4H), 4.24 (s, 0.6 H), 3.13 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 194.86, 171.97, 135.18, 134.76, 130.02, 129.67, 129.34, 128.48, 127.07, 57.02, 39.14.

HRMS (ESI) m/z calculated for [M + Na]$^+$ 308.0716, found 308.0720.

**S-phenyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)ethanethioate**

Following general procedure B, 2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)acetic acid (5 g, 16.06 mmol) was transformed into its derived phenyl thioester with isobutyl chloroformate (2.309 mL, 17.67 mmol) benzenethiol (3.60 mL, 35.3 mmol) and triethylamine (4.48 mL, 32.1 mmol). Following aqueous work-up the material was purified by gradient column chromatography (0-30 % EtOAc in hexanes) to afford the title compound (1.07 g, 2.65 mmol, 17 % yield)

**LCMS RT (Method 2)** 3.83 min (m/z 404.1 (M+H), 426.1 (M+Na))

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.76 (dd, $J = 7.7, 3.0$ Hz, 2H), 7.60 (dd, $J = 18.7, 7.5$ Hz, 2H), 7.44 – 7.24 (m, 9H), 4.53 – 4.44 (m, 2H), 4.29 (s, 1H), 4.34 – 4.21 (m, 1H), 4.16 (s, 1H), 3.08 (d, $J = 1.9$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 196.0, 143.81, 141.31, 134.70, 134.60, 129.57, 129.27, 127.71, 127.08, 125.01, 124.93, 119.99, 68.05, 58.61, 47.23, 36.50.

HRMS (ESI) m/z calcd for [M + H]$^+$ 404.1315, found 404.1298.
S-phenyl 2-(((benzyloxy)carbonyl)(methylamino)ethanethioate, 22

Following general procedure B, 1, 2-(((benzyloxy)carbonyl)(methylamino)acetic acid (5 g, 22.40 mmol) was transformed into its phenyl thioester with isobutyl chloroformate (3.22 mL, 24.64 mmol) thiophenol (5.03 mL, 49.3 mmol) and triethylamine (6.24 mL, 44.8 mmol). After workup the crude was purified by gradient column chromatography (10-30 % EtOAc in hexanes) to yield 22 (6.27 g, 19.88 mmol, 89 % yield) as a colourless oil.

**LCMS RT (Method 2)** 3.57 min (m/z 316.1)

**1H NMR (400 MHz, CDCl3)** δ 7.46 – 7.26 (m, 10H), 5.19 (d, J = 6.9 Hz, 2H), 4.29 (s, 1H), 4.20 (s, 1H), 3.09 (s, 3H).

**13C NMR (101 MHz, CDCl3)** δ 196.04, 195.74, 156.59, 155.76, 136.36, 136.25, 134.70, 134.61, 129.58, 129.55, 129.27, 128.50, 128.11, 128.01, 127.86, 126.52, 77.33, 77.01, 76.70, 67.77, 67.73, 58.65, 58.47, 36.58, 35.81. **HRMS (ESI)** m/z calcd for [M + H]+ 316.1002, found 316.1013.

1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-methylpropan-1-one, 10b

Following general procedure F, isobutyric acid (2 g, 88.11 mmol) was transformed into its N-acetyl benzotriazole using SOCl2 (1.823 mL, 24.97 mmol) and 1H-benzo[d][1,2,3]triazole (10.82 g, 91 mmol) in DCM (114 mL). The product was purified by gradient column chromatography using 5-10 % EtOAc/hexane to yield 10b (3.741 g, 19.77 mmol, 87 % yield) as a pale, straw coloured, free flowing oil.

**LCMS RT (Method 2)** 3.50 min (no m/z in +ve mode)

**1H NMR (400 MHz, CDCl3)** δ 8.28 (dd, J = 8.2, 1.3 Hz, 1H), 8.10 (dd, J = 8.2, 1.3 Hz, 1H), 7.63 (td, J = 8.3, 7.8, 1.5 Hz, 1H), 7.53 – 7.44 (m, 1H), 4.14 (hept, J = 6.9 Hz, 1H), 1.42 (d, J = 6.9 Hz, 6H).

**13C NMR (101 MHz, CDCl3)** δ 176.61, 146.14, 131.28, 130.29, 126.03, 120.06, 114.55, 33.96, 19.07.
S-phenyl 4-methyl-2-(N-methylbenzamido)-3-oxopentanethioate, 12a

Following general procedure C, 1-(1Hbenzo[d][1,2,3]triazol-1-yl)-2-methylpropan-1-one (265 mg, 1.402 mmol) in DCM (6 mL), was coupled to S-phenyl 2-(N-methylbenzamido)ethanethioate (400 mg, 1.402 mmol) using MgBr$_2$.diethyl etherate (1.27 g, 4.91 mmol) and diisopropylethylamine (0.979 mL, 5.61 mmol). The crude material was purified by gradient column chromatography to give the title compound (379 mg, 1.065 mmol, 76 % yield) as a colourless oil which solidified upon standing.

**LCMS RT (Method 2)** 3.64 min (m/z 356.0)

$^1$H NMR (400 MHz, CDCl$_3$) (Mixture of rotamers and tautomers, major enol product reported) $\delta$ 12.79 (d, $J = 1.5$ Hz, 1H), 7.69 – 7.57 (m, 2H), 7.46 (s, 5H), 7.43 – 7.30 (m, 3H), 3.37 (s, 3H), 2.54 (heptd, $J = 6.5$, 1.8 Hz, 1H), 1.14 (d, $J = 6.8$ Hz, 3H), 0.69 (d, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.17, 180.01, 172.73, 135.36, 135.19, 135.06, 130.23, 129.89, 129.35, 129.20, 128.53, 127.93, 127.52, 126.87, 126.43, 116.65, 41.35, 38.66, 36.61, 30.26, 29.90, 29.68, 24.66, 20.54, 19.36, 19.23, 17.60.

HRMS (ESI) m/z calcd for [M + H]$^+$ 356.1320, found 356.1437.

S-phenyl-2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-4-methyl-3-oxopentanethioate, 12b

Following general procedure C, 1-(1Hbenzo[d][1,2,3]triazol-1-yl)-2-methylpropan-1-one (1.117 g, 5.90 mmol) was coupled to S-phenyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)ethanethioate (2.5 g, 6.20 mmol) using magnesium bromide diethyl etherate (4.57 g, 17.70 mmol) and diisopropylethylamine in DCM (23 mL). The crude material was purified by gradient column chromatography (0-30 % EtOAc-hexane), giving the title compound (570 mg, 1.204 mmol, 20 % yield) as a colourless, mobile oil. Rotameric, keto enol.

**LCMS RT (Method 2)** 4.0 min (m/z 474.7)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.85 (d, $J = 1.5$ Hz, 1H), 7.81 – 7.71 (m, 2H), 7.65 – 7.49 (m, 2H), 7.46 – 7.30 (m, 7H), 7.28 – 7.21 (m, 2H), 4.51 (dd, $J = 10.3$, 7.4 Hz, 1H), 4.31 (dd, $J = 10.4$, 7.2 Hz, 1H), 4.19 (t, $J = 7.3$ Hz, 1H), 3.16 (s, 3H), 2.67 (sep, $J = 6.8$, 1.5 Hz, 1H), 1.10 (dd, $J = 6.8$ Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 195.09, 170.01, 156.34, 143.69, 143.64, 141.26, 141.23, 135.23, 135.16, 129.67, 129.14, 129.13, 127.73, 127.71, 127.18, 127.09, 126.55, 125.21, 125.19, 125.00, 124.87, 119.91, 114.17, 68.41, 47.50, 47.15, 38.00, 36.61, 29.98, 29.94, 19.38, 19.04, 18.82.
S-phenyl 2-(((benzylhydroxycarbonyl)(methyl)amino)-4-methyl-3-oxopentanethioate, 12c

Following general procedure C, 1-(1H-benzo[d]1,2,3triazol-1-yl)-2- methylpropan-1-one (1.143 g, 6.04 mmol) was coupled to S-phenyl 2-(((benzylhydroxycarbonyl)(methyl)amino)ethanethioate (2 g, 6.34 mmol) using magnesium bromide diethyl etherate (5.46 g, 21.14 mmol) and diisopropylethylamine (4.22 mL, 24.16 mmol) in DCM (24.16 mL). The crude material was purified by gradient column chromatography (15-30 % EtOAc-hexane) giving the title compound (2.165 g, 5.62 mmol, 93 % yield) as a colourless, mobile oil. Rotameric, keto enol.

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \( \delta 12.89 - 12.74 \text{ (m, 1H), 7.53 - 7.21 \text{ (m, 10H), 5.29 - 5.13 \text{ (m, 2H), 3.25 - 3.20 \text{ (m, 3H), 2.62 \text{ (ttd, \text{J} = 8.3, 6.5, 1.5 Hz, 1H)\text{, 1.08 \text{ (dd, \text{J} =6.8, 0.7 Hz, 6H).}}}}}} \]

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3 \] \( \delta 195.00, 194.65, 180.38, 179.41, 156.27, 136.34, 135.24, 135.12, 129.63, 129.58, 129.17, 129.13, 128.49, 128.40, 128.12, 128.07, 128.05, 127.90, 126.84, 126.76, 114.04, 67.89, 67.78, 38.36, 38.09, 30.07, 29.85, 19.31, 18.98, 18.69. \]

HRMS (ESI) \( m/z \) calcd for [M + H]^+ 386.1421, found 386.1427.

N-methyl-N-(4-methyl-1,3-dioxo-1-(phenylamino)pentan-2-yl)benzamide, 13

Following general procedure E, S-phenyl 4-methyl-2-(N-methylbenzamido)-3-oxopentanethioate (100 mg, 0.281 mmol) underwent substitution with aniline (31.4 mg, 0.338 mmol) and silver trifluoroacetate (63.4 mg, 0.309 mmol). The crude material was purified by gradient flash chromatography (15-35 % EtOAc/Hexanes) over silica gel affording 13 (89 mg, 0.264 mmol, 94 % yield) as a pale yellow oil. Rotameric, keto/enol.

LCMS RT (Method 1) 3.49 min (m/z 339.1)

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \] \( \delta 14.07 \text{ (s, 1H), 9.72 \text{ (keto, s, 0.3H) 8.41 \text{ (s, 1H), 7.63 \text{ (d, \text{J} = 8.6 Hz, 2H), 7.48 - 7.30 \text{ (m, 6H), 7.21 \text{ (dd, \text{J} = 12.9, 7.3 14Hz, 2H), 5.55 \text{ (keto, s, 0.3H) 3.20 \text{ (s, 3H), 3.11 \text{ (s, 1H), 2.47 - 2.33 \text{ (m, 1H), 1.09 \text{ (d, \text{J} = 6.8 Hz, 3H), 0.50 \text{ (d, \text{J} = 6.7 Hz, 3H).}}}}}}}} \]

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3 \] \( \delta 180.04, 173.32, 168.77, 136.91, 134.49, 130.56, 130.52, 129.07, 129.01, 128.48, 128.04, 127.46, 125.10, 121.31, 119.99, 109.05, 38.07, 29.36, 20.51, 17.64. \]

HRMS (ESI) \( m/z \) calcd for [M + H]^+ 339.1703, found 339.1712.
(9H-fluoren-9-yl)methylmethyl(4-methyl-1,3-dioxo-1-(phenylamino)pentan-2-yl)carbamate, 14

Following general procedure E, S-phenyl 2-(((9Hfluoren-9-yl)methoxy)carbonyl) (methyl)amino)4-methyl-3 oxopentanethioate (370mg, 0.781 mmol) underwent substitution with aniline (109 mg, 1.172 mmol) and silver trifluoroacetate (224 mg, 1.016 mmol) in THF (5.2 mL). The crude material was purified by gradient flash chromatography (15-35 % EtOAc/Hexanes) over silica gel affording 14 (193 mg, 0.422 mmol, 54 % yield). Rotameric, keto/enol.

LCMS RT (Method 2) 3.85, 4.01 min (m/z 457.2)

$^1$H NMR (400 MHz, CDCl$_3$) δ 14.23 (s, 1H), 7.80 – 7.70 (m, 1H), 7.69 – 7.60 (m, 2H), 7.56 – 7.45 (m, 2H), 7.45 – 7.40 (m, 1H), 7.39 – 7.32 (m, 3H), 7.31 – 7.22 (m, 2H), 7.22 – 7.10 (m, 2H), 7.06 (t, $J$ = 7.5 Hz, 1H), 4.55 – 4.34 (m, 1H), 4.28 (d, $J$ = 7.3 Hz, 2H), 3.12 (d, $J$ = 29.3 Hz, 3H), 2.68 – 2.53 (m, 1H), 1.17 (d, $J$ = 6.7 Hz, 3H), 1.02 (d, $J$ = 6.8 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 180.16, 168.61, 156.94, 143.55, 142.87, 141.11, 136.76, 129.01, 128.96, 127.76, 127.71, 127.12, 127.08, 125.03, 124.88, 124.82, 121.16, 120.18, 119.94, 119.90, 47.14, 46.78, 38.00, 36.63, 29.64, 24.68, 23.37, 19.67, 18.87.

HRMS (ESI) m/z calcd for [M + H]$^+$ 457.2122, found 457.2122.

Benzyl methyl(4-methyl-1,3-dioxo-1-(phenylamino)pentan-2-yl)carbamate, 9

Following general procedure E, S-phenyl 2-(((benzyloxy)carbonyl) (methyl)amino)-4-methyl-3-oxopentanethioate (370mg, 0.960 mmol) underwent substitution with aniline (134 mg, 1.440 mmol) and silver trifluoroacetate (276 mg, 1.248 mmol) in THF (6.4 mL). The crude material was purified by gradient flash chromatography (15-35 % EtOAc/Hexanes) over silica gel affording 9 (325 mg, 0.883 mmol, 92 % yield). Rotameric, keto/enol

LCMS RT (Method 2) 3.61, 3.78 min (m/z 369.2)

$^1$H NMR (400 MHz, CDCl$_3$) δ 14.01 (d, $J$ = 1.4 Hz, 1H), 7.70 – 6.96 (m, 11H), 5.31 – 4.98 (m, 2H), 3.13 (s, 3H), 2.55 (sept, $J$ = 7.0, 6.4 Hz, 1H), 1.06 (dd, $J$ = 66.1, 6.8 Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 13C NMR (101 MHz, cdcl3) δ 179.93, 168.55, 128.97, 128.56, 128.24, 128.11, 124.81, 120.82, 67.87, 38.10, 29.59, 19.58, 18.73.

HRMS (ESI) m/z calcd for [M + H]$^+$ 369.1814, found 369.1810.
N-((2S,3R)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)-Nmethyl benzamide, 15

Following general procedure D, N-methyl-N-(4-methyl-1,3-dioxo-1-phenylamino)pentan-2-yl)benzamide (50 mg, 0.147 mmol) underwent ATH DKR to afford 15 (1.9 mg, 5.8 µmol, 3.8 % yield) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.87 (s, 1H), 7.53 (dd, $J = 15.0$, 8.0 Hz, 4H), 7.45 (p, $J = 6.6$ Hz, 3H), 7.34 (t, $J = 7.8$ Hz, 2H), 7.13 (t, $J = 7.4$ Hz, 1H), 5.17 (d, $J = 4.8$ Hz, 1H), 4.06 – 3.99 (m, 1H), 3.16 (s, 3H), 1.96 (dq, $J = 13.3$, 6.6 Hz, 1H), 1.12 (d, $J = 6.6$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 178.65, 174.00, 137.42, 130.87, 129.06, 128.57, 127.88, 124.66, 120.07, 75.61, 74.03, 30.56, 19.34, 18.26.

(9H-fluoren-9-yl)methyl((2S,3R)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl) carbamate, 16

Following general procedure D, (9H-fluoren-9-yl)methylmethyl(4-methyl-1,3-dioxo-1-phenylamino)pentan-2-yl)carbamate (50 mg, 0.11 mmol) underwent ATH DKR to yield 16 (9.0 mg, 19.8 µmol, 18 % yield) as a white solid.

LCMS RT (Method 2) 3.77 min (m/z 459.2)

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.15 (s, 1H), 7.75 (dd, $J = 7.6$, 4.9 Hz, 2H), 7.60 – 7.52 (m, 2H), 7.52 – 7.44 (m, 2H), 7.41 – 7.25 (m, 5H), 7.21 – 7.06 (m, 2H), 4.67 (d, $J = 5.5$ Hz, 1H), 4.52 (qd, $J = 10.6$, 6.7 Hz, 2H), 4.26 (t, $J = 6.7$ Hz, 1H), 3.93 (d, $J = 8.5$ Hz, 1H), 3.47 (s, 1H), 3.06 (s, 3H), 1.82 – 1.66 (m, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.94, 158.30, 143.69, 143.44, 141.36, 137.22, 128.99, 127.83, 127.08, 124.82, 120.25, 120.03, 75.17, 68.11, 47.25, 36.61, 30.21, 24.66, 23.33, 19.56, 17.77.

HRMS (ESI) m/z calcd for [M + H] 459.2278, found 459.2288.
**Benzyl((2S,3R)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl) carbamate, 17**

Following general procedure D, benzyl methyl(4-methyl-1,3-dioxo-1 (phenylamino) pentan-2 yl)carbamate 9 (50mg, 0.136 mmol) underwent ATH DKR with pre-formed [(R,R)- Teth-TsDpen Ru] (7.92 mg, 0.014 mmol) and TBAI (122 mg, 0.330 mmol) in in a DCM/HCO$_2$Na emulsion. The crude is purified by gradient column chromatography to yield 17 (32.2 mg, 0.087 mmol, 64 % yield) as a white solid.

**LCMS RT (Method 2) 3.38 min (m/z 371.1)**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.20 (s, 1H), 7.43 (d, $J$ = 7.6 Hz, 2H), 7.40 – 7.26 (m, 7H), 7.14 – 7.09 (m, 1H), 5.27 – 5.14 (m, 2H), 4.79 – 4.70 (m, 1H), 3.99 – 3.91 (m, 1H), 3.56 (d, $J$ = 4.4 Hz, 1H), 3.13 (s, 3H), 1.81 (m, $J$ = 6.7 Hz, 1H), 0.99 (d, $J$ = 6.7 Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.10, 158.45, 129.00, 128.60, 128.24, 127.77, 124.71, 120.06, 77.00, 75.21, 68.15, 30.22, 19.49, 17.87

**HRMS (ESI) m/z calcd for [M + H] 371.1965, found 371.1963.**

$^2$S, 3R) $\left[\alpha\right]_D^{20} -118.7$ (c 1.00, CHCl$_3$)

$^2$R, 3S) $\left[\alpha\right]_D^{20} +109.3$ (c 1.00, CHCl$_3$) [Using (S, S)-catalyst]
(4E)-N-((S)-2-hydroxy-1-phenylethyl)-2-methylhex-4-enamide, 19/epi-19

To a solution of (E)-2-methylhex-4-enoeic acid (rac-20) (prepared according to Rich et al.\(^6\)) (2.5 g, 19.51 mmol) in DCM was added HATU (8.90 g, 23.41 mmol) and DIPEA (4.09 mL, 23.41 mmol). After allowing 5 minutes for preactivation, (S)-2-amino-2-phenylethanol (3.48 g, 25.4 mmol) was added and the reaction was stirred overnight. The solvent was removed by rotary evaporation, then the crude was dissolved in EtOAc and washed with 1N HCl, 1N NaOH and brine. Organics were dried over MgSO\(_4\), filtered, evaporated and purified by column chromatography (30 % EtOAc in Hexanes) to yield (E)-N-((S)-2-hydroxy-1-phenylethyl)-2-methylhex-4-enamide (4.36 g, 17.63 mmol, 90 % yield) as a separable mixture of diastereomers.

**LCMS RT (Method 2)** 2.89 min (m/z 248.1)

**HRMS (ESI)** m/z calcd for [M + H] 248.1645, found 248.1647.

(2R,4E)-N-((S)-2-hydroxy-1-phenylethyl)-2-methylhex-4-enamide, 19

\[ \alpha \]\(^D\)\(_{20}\) +23.0 (c 1.00, CHCl\(_3\))

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.39 – 7.22 (m, 5H), 6.23 (d, J = 7.1 Hz, 1H), 5.51 – 5.38 (m, 1H), 5.32 (dddt, J = 15.1, 6.8, 5.2, 1.5 Hz, 1H), 5.03 (dt, J = 7.1, 4.9 Hz, 1H), 3.84 (td, J = 5.0, 4.4, 1.4 Hz, 2H), 2.96 – 2.88 (m, 1H), 2.35 – 2.20 (m, 2H), 2.15 – 2.01 (m, 1H), 1.59 (dq, J = 6.3, 1.2 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H).

\(^1^3\)C NMR (101 MHz, CDCl\(_3\)) 176.67, 139.03, 128.82, 128.12, 127.79, 127.73, 126.66, 66.69, 55.72, 41.73, 37.34, 17.90, 17.43.

(2S,4E)-N-((S)-2-hydroxy-1-phenylethyl)-2-methylhex-4-enamide, epi-19

\[ \alpha \]\(^D\)\(_{20}\) +41.1 (c 1.00, CHCl\(_3\))

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.39 – 7.13 (m, 5H), 6.73 (d, J = 7.1 Hz, 1H), 5.51 – 5.27 (m, 2H), 5.01 – 4.86 (m, 1H), 3.71 (d, J = 5.2 Hz, 2H), 3.49 (s, 1H), 2.24 (h, J = 7.1 Hz, 2H), 2.03 (q, J = 10.5, 9.4 Hz, 1H), 1.69 – 1.56 (m, 3H), 1.04 (d, J = 6.6 Hz, 3H).

\(^1^3\)C NMR (101 MHz, CDCl\(_3\)) 176.85, 139.31, 128.64, 128.17, 127.55, 126.62, 66.11, 55.66, 41.33, 37.18, 17.96, 17.28.
(2R,4E)-2-methylhex-4-enoic acid, 20
A solution of (2R,4E)-N-((S)-2-hydroxy-1-phenylethyl)-2-methylhex-4-enamide 19 (1 g, 4.04 mmol) in 6N H$_2$SO$_4$ in 60 mL (H$_2$O/Dioxane) was heated to 80°C for 3 hours, then the reaction was cooled to room temperature. The reaction was diluted with water (50 mL), extracted with DCM and dried with Mg$_2$SO$_4$. The volatiles were removed under reduced pressure to yield (R,E)-2-methylhex-4-enoic acid, 20 (0.503 g, 3.92 mmol, 97 % yield) as a translucent, yellow oil.

$[\alpha]_D^{20}$ -13.9 (c 1.00, CHCl$_3$) (Lit. $[\alpha]_D^{RT}$ -10.2 in Et$_2$O)

LCMS RT (Method 1) 2.95 min (no m/z in +ve mode)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.65 (d, J = 3.7 Hz, 1H), 5.57 – 5.44 (m, 1H), 5.44 – 5.31 (m, 1H), 2.49 (m, J = 6.9 Hz, 1H), 2.43 – 2.30 (m, 1H), 2.13 (ddt, J = 12.9, 8.1, 7.1, 1.1 Hz, 1H), 1.65 (dq, J = 6.3, 1.2 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 182.54, 127.76, 127.49, 39.52, 36.32, 17.88, 16.22.

(R,E)-1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-methylhex-4-en-1-one, 21
Following general procedure F. SOCl$_2$ (157 $\mu$l, 2.146 mmol) was added to a stirred solution of 1H-benzo[d][1,2,3]triazole (929 mg, 7.80 mmol) in DCM (9 mL), in one portion at room temperature. Stirring was continued for 30 min. (R,E)-2-methylhex-4-enolic acid (250mg, 1.951 mmol) in DCM (1 mL) was added to the reaction mixture, followed by almost immediate precipitation of 1H-benzo[d][1,2,3]triazole.HCl. The reaction mixture was agitated to continue stirring (precipitate forms). Stirring was continued overnight. The white precipitate was filtered off and washed with DCM, then the combined DCM filtrates were evaporated and the crude product was purified by column chromatography (100 % DCM) to yield 21 (422mg, 1.841 mmol, 94 %).

$[\alpha]_D^{20}$ – 64.5 (c 1.00, CHCl$_3$)

LCMS RT (Method 1) 3.68 min (m/z 230.1)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.29 (dt, J = 8.3, 1.0 Hz, 1H), 8.11 (dt, J = 8.3, 1.0 Hz, 1H), 7.64 (ddd, J = 8.3, 7.1, 1.0 Hz, 1H), 7.49 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H), 5.57 – 5.37 (m, 2H), 4.13 (h, J = 6.9 Hz, 1H), 2.68 – 2.55 (m, 1H), 2.41 – 2.29 (m, 1H), 1.61 – 1.54 (m, 3H), 1.38 (d, J = 6.9 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.80, 146.17, 131.21, 130.27, 128.34, 127.00, 126.03, 120.05, 114.57, 39.35, 36.54, 17.85, 16.78.
S-phenyl (4R,6E)-2-(((benzyloxy)carbonyl)(methyl)amino)-4-methyl-3-oxooct-6-enethioate, 23

To a stirred solution of (2R,4E)-1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-methylhex-4-en-1-one 21 (385 mg, 1.679 mmol) in anhydrous DCM (6.72 mL) under cooling with an ice bath was added S-phenyl 2-(((benzyloxy)carbonyl)(methyl)amino)ethanethioate 22 (556 mg, 1.763 mmol) followed by magnesium bromide diethyl etherate (1518 mg, 5.88 mmol) and N,N-diisopropylethylamine (1.231 mL, 7.05 mmol). The ice bath was removed and the reaction was allowed to warm to room temperature, monitored by TLC and stirred for 24h. At this point the reaction was re-cooled to 0°C and slowly quenched by the initially dropwise addition of 1N HCl (10 mL). Stirring was continued with cooling for 5 minutes, then the ice bath was removed. The reaction was diluted with brine and EtOAc, the organic phase was separated and the aqueous was again extracted with EtOAc. The combined organic extracts were dried over MgSO₄ and evaporated to yield an oil which was purified by gradient column chromatography (0-30 % EtOAc in Hexanes) to yield 23 as a colourless oil (426mg, 1.001 mmol, 60 % yield).

**LCMS RT(Method 2)**  4.03 min (m/z 426.1)

**¹H NMR (400 MHz, CDCl₃)** δ 7.70 – 6.94 (m, 10H), 5.46 (dd, J = 13.6, 6.9 Hz, 1H), 5.37 – 5.20 (m, 2H), 5.07 (dd, J = 25.8, 12.4 Hz, 1H), 3.18 (d, J = 16.7 Hz, 3H), 2.57 – 2.37 (m, 1H), 2.23 (ddt, J = 26.6, 12.6, 7.1 Hz, 1H), 2.11 – 1.96 (m, 1H), 1.65 – 1.52 (m, 3H), 1.04 (dd, J = 59.9, 7.2 Hz, 3H).

**¹³C NMR (101 MHz, CDCl₃)** δ 195.05, 194.91, 178.81, 178.66, 156.30, 156.16, 136.35, 136.31, 135.25, 135.14, 129.66, 129.60, 129.18, 129.15, 128.50, 128.41, 128.36, 128.15, 128.08, 128.02, 127.97, 127.87, 127.82, 127.81, 127.58, 127.56, 126.76, 126.72, 115.04, 114.67, 38.60, 38.35, 38.12, 36.66, 36.40, 36.28, 35.59, 17.82, 17.33, 17.00, 16.53.

**HRMS (ESI)** m/z calcd for [M + H] 426.1734, found 426.1744.
Benzyl methyl((4R, 6E)-4-methyl-1,3-dioxo-1-(phenylamino)oct-6-en-2-yl)carbamate, 24

To a solution of S-phenyl (4R,6E)-2(((benzyloxy)carbonyl)(methyl)amino)-4-methyl-3-oxooct-6 enethioate 23 (300mg, 0.705 mmol) and aniline (77 μl, 0.846 mmol) in THF (5 mL) at room temperature was added silver trifluoroacetate (187 mg, 0.846 mmol) with stirring. Precipitation of Ag salts requires efficient stirring. Upon completion the reaction was diluted with EtOAc and filtered through Celite. Volatiles were removed by rotary evaporation and the crude material was purified by gradient flash chromatography (5-35% EtOAc/Hexanes) over silica gel affording 24 (261 mg, 0.641 mmol, 91 % yield).

Rotameric, keto/enol

^1^H NMR (400 MHz, CDCl3) δ 14.01 (s, 1H) 7.54 – 7.19 (m, 9H), 7.18 – 7.07 (m, 1H), 5.58 – 5.29 (m, 2H), 5.23 – 4.95 (m, 2H), 3.19 – 3.02 (m, 3H), 2.40 (d, J = 6.9 Hz, 1H), 2.35 – 2.22 (m, 1H), 2.12 – 1.98 (m, 1H), 1.63 – 1.56 (m, 3H), 1.04 (dd, J = 65.2, 6.8 Hz, 3H).

^13^C NMR (101 MHz, CDCl3) δ 179.14, 168.45, 156.12, 128.98, 128.60, 128.56, 128.24, 128.10, 128.01, 127.56, 124.83, 120.83, 68.25, 67.87, 38.32, 36.78, 36.36, 17.92, 17.82.

HRMS (ESI) m/z calcd for [M + H] 409.2122, found 409.2131

Benzyl ((2S,3R,4R,6E)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)oct-6-en-2-yl)(methyl)carbamate, 25

To benzyl methyl((4R,E)-4-methyl-1,3-dioxo-1-(phenylamino)oct-6-en-2-yl)carbamate, 24 (26mg, 0.064 mmol) under N2 was added DCM (0.5 mL), [(R,R)-Teth-TsDpenRu] (3.72 mg, 6.36 μmol) followed by TBAI (47 mg, 0.127 mmol) and 0.5 mL of a 5N solution of HCO2Na in H2O. The reaction was sealed and stirred at ~1400 RPM for 48 hours. Following complete consumption of the starting material, the reaction was diluted with 3 mL of sat. NaHCO3, then extracted with 2x3 mL of EtOAc. The organics were combined, dried over MgSO4 and purified by gradient column chromatography to yield 25 (10.3 mg, 0.025 mmol, 61 % yield).

^1^H NMR (400 MHz, CDCl3) δ 8.18 (s, 1H), 7.65 – 7.15 (m, 9H), 7.16 – 7.08 (m, 1H), 5.46 (qd, J = 15.3, 7.1 Hz, 2H), 5.28 – 5.11 (m, 2H), 4.77 (d, J = 4.6 Hz, 1H), 4.10 – 3.96 (m, 1H), 3.93 – 3.78 (m, 1H), 3.14 (s, 3H), 2.39 (d, J = 13.6 Hz, 1H), 2.01 – 1.89 (m, 1H), 1.71 – 1.60 (m, 4H), 0.88 (d, J = 6.7 Hz, 3H).

^13^C NMR (101 MHz, CDCl3) δ 169.40, 158.45, 137.18, 136.11, 128.99, 128.89, 128.60, 128.23, 127.74, 127.13, 124.72, 120.11, 74.33, 68.16, 60.34, 35.35, 35.06, 33.32, 18.01, 15.82.

HRMS (ESI) m/z calcd for [M + H] 411.2278, found 411.2290

(2S, 3R, 4R) [α]_D^20: -81.8 (c 1.00, CHCl3)

(2R, 3S, 4R) [α]_D^20: +107.6 (c 1.00, CHCl3) [Using (S, S)-catalyst]
(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoic acid, MeBmt — 2. Benzyl(E)-(3-hydroxy-4-methyl-1-oxo-1-(phenylamino)oct-6-en-2-yl)(methyl)carbamate 25 (20mg, 0.049 mmol) was added to 0.5 mL of 2N KOH, in a sealed reaction vessel and heated to 80°C by means of an oil bath, followed by overnight stirring. The following day the reaction was cooled to room temperature and diluted with 2 mL of water, then extracted with 2x2 mL Et₂O. The resultant aqueous layer was acidified with DOWEX ion exchange resin, which was washed with water. The amino acid was eluted with 1M aq. NH₃ in H₂O, to yield 1 as an off-white solid (9.2 mg, 0.023 mmol, 46 % yield) whose data were in accordance with previously reported spectra.⁵

LCMS RT (Method 2) 2.24 min (m/z 202.1).

¹H NMR (400 MHz, D₂O) δ 5.40 (qd, J = 15.4, 7.0 Hz, 2H), 3.55 (t, J = 5.6 Hz, 1H), 3.43 (s, 1H), 3.31 (d, J = 5.5 Hz, 1H), 2.56 (s, 2H), 2.45 (s, 3H), 2.15 (d, J = 14.0 Hz, 1H), 1.78 – 1.69 (m, 1H), 1.57 (tt, J = 6.3, 3.2 Hz, 1H), 1.52 (d, J = 5.9 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H).

HRMS (ESI) m/z calcd for [M + H]⁺ 202.1438, found 202.1441.

Benzyl (1-cyclopropyl-1,3-dioxo-3-(phenylamino)propan-2-yl)(methyl)carbamate

Following general procedure E, S-phenyl 2-(((benzyloxy)carbonyl)(methyl)amino)-3-cyclopropyl-3-oxopropanethioate (107mg, 0.281 mmol) underwent substitution with aniline (31.4 mg, 0.338 mmol) and silver trifluoroacetate (63.4 mg, 0.309 mmol). The crude material was purified by gradient flash chromatography (15-35 % EtOAc/Hexanes) over silica gel affording the title compound (86.5 mg, 0.236 mmol, 84 % yield) as a clear colourless oil. Rotameric, keto/enol.

LCMS RT (Method 2) 3.65min (m/z 367.2)

¹H NMR (400 MHz, CDCl₃) δ 14.13 (s, 1H), 9.48 (d, J = 65.8 Hz, 1H), 7.59 – 7.18 (m, 9H), 7.16 – 7.07 (m, 1H), 5.28 – 5.03 (m, 2H), 3.16 (d, J = 26.7 Hz, 3H), 1.52 – 0.61 (m, 5H).

¹³C NMR (101 MHz, CDCl₃) δ 189.08, 168.19, 136.76, 136.40, 128.99, 128.95, 128.51, 128.23, 127.94, 124.66, 124.54, 120.71, 120.09, 67.76, 37.70, 11.22, 7.96, 7.61.

HRMS (ESI) m/z calcd for [M + H] 367.1652, found 367.1652.
Following general procedure D, benzyl (1-cyclopropyl-1,3-dioxo-3-(phenylamino)propan-2-yl)(methyl)carbamate (49.7 mg, 0.136 mmol) underwent ATH DKR with pre-formed [(R,R)-Teth-TsDpen Ru] (7.92 mg, 0.014 mmol) and TBAI (122 mg, 0.330 mmol) in in a DCM/HCO$_2$Na emulsion. The crude is purified by gradient column chromatography to yield the title compound (39.1 mg, 0.106 mmol, 78 % yield) as a white solid.

**LCMS RT (Method 2)** 3.11 min (m/z 369.1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.28 (s, 1H), 7.56 – 7.25 (m, 9H), 7.17 – 7.08 (m, 1H), 5.19 (s, 2H), 4.71 (d, $J$ = 6.5 Hz, 1H), 3.80 (s, 1H), 3.59 (d, $J$ = 14.2 Hz, 2H), 3.01 (s, 3H), 1.05 – 0.97 (m, 1H), 0.48 (d, $J$ = 31.3 Hz, 3H), 0.32 (s, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 178.43, 169.2, 129.02, 128.59, 128.26, 127.90, 124.77, 120.21, 73.88, 68.01, 64.26, 32.80, 14.81, 2.61, 1.80.

HRMS (ESI) m/z calcd 369.1809 for [M + H], found 369.1802.

**28:** (2S, 3R) $\lbrack \alpha \rbrack_D^{20}$: -23.8 (c 1.00, CHCl$_3$) [Using (S, S)-catalyst]

**29:** (2R, 3S) $\lbrack \alpha \rbrack_D^{20}$: +19.2 (c 1.00, CHCl$_3$)

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Benzyl (1-cyclobutyl-1,3-dioxo-3-(phenylamino)propan-2-yl)(methyl)carbamate

Following general procedure E, S-phenyl 2-(((benzoxyl)carbonyl)(methyl)amino)-3-cyclobutyl-3-oxopropanethioate (111mg, 0.281 mmol) underwent substitution with aniline (31.4 mg, 0.388 mmol) and silver trifluoroacetate (63.4 mg, 0.309 mmol). The crude material was purified by gradient flash chromatography (15-35 % EtOAc/Hexanes) over silica gel affording the title compound (82 mg, 0.224 mmol, 80 % yield) as a clear colourless oil. **Rotameric, keto/enol.**

**LCMS RT (Method 2)** 3.65min (m/z 381.1)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 14.10 (s, 1H), 9.31 (s, 1H), 7.57 – 7.09 (m, 10H), 5.12 (m, 2H), 3.09 (s, 3H), 2.47 – 1.70 (m, 7H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 176.41, 168.40, 136.67, 128.99, 128.55, 128.27, 128.18, 127.92, 124.79, 120.80, 120.09, 67.71, 43.33, 38.03, 35.33, 25.32, 18.28.

HRMS (ESI) m/z calcd for [M + H] 381.1809, found 381.1815.
Following general procedure D, benzyl (1-cyclobutyl-1,3-dioxo-3-(phenylamino)propan-2-yl)(methyl)carbamate (50.3 mg, 0.136 mmol) underwent ATH DKR with pre-formed [(R,R)-Teth-TsDpen Ru] (7.92 mg, 0.014 mmol) and TBAI (122 mg, 0.330 mmol) in a DCM/HCO$_2$Na emulsion. The crude was purified by gradient column chromatography to yield the title compound (27 mg, 0.073 mmol, 54 % yield) as a white solid.

**LCMS RT (Method 2)** 3.07 min (m/z 383.2).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14 (s, 1H), 7.71 – 6.95 (m, 10H), 5.18 (s, 2H), 4.48 (s, 1H), 4.04 (s, 1H), 3.55 (s, 1H), 2.97 (s, 3H), 2.50 (s, 1H), 2.17 – 1.62 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.83, 169.32, 129.01, 128.63, 128.32, 127.92, 120.16, 71.98, 68.11, 65.95, 34.76, 23.95, 23.23, 18.04.

**HRMS (ESI)** m/z calcd 383.1965 for [M + H], found 383.1967.

30: (2S, 3R) $[\alpha]$$_{D}^{20}$: +53.2 (c 1.00, CHCl$_3$)

31: (2R, 3S) $[\alpha]$$_{D}^{20}$: -60.2 (c 1.00, CHCl$_3$) [Using (S, S)-catalyst]
Methyl-3-hydroxy-4-methyl-2-(N-methylbenzamido)pent-2-enoate, 6a
Methyl 2-benzamido-4-methyl-3-oxopentanoate, 6b
Methyl-2-(((benzylloxy)carbonyl)(methyl)amino)-3-hydroxy-4-methylpent-2-enoate, 6c

1H NMR (400 MHz, Chloroform-d): 12.19 (s, 1H), 7.49 – 7.31 (m, 5H), 5.17 – 5.01 (m, 2H), 3.77 – 3.62 (m, 2H), 3.03 – 2.95 (m, 2H), 2.04 – 2.79 (m, 2H), 1.33 – 0.97 (m, 6H).

13C NMR (100 MHz, CDCl3): 206.64, 180.66, 171.11, 156.63, 136.69, 128.33, 127.87, 127.74, 105.57, 67.21, 51.81, 37.72, 30.11, 16.96.
Methyl (2S,3S)-2-benzamido-3-hydroxy-4-methylpentanoate, 8b
S-phenyl 2-(N-methylbenzamido)ethanethioate
S-phenyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino) ethane thioate
S-phenyl 2-(((benzyloxy)carbonyl)(methyl)amino)ethanethioate, 22
1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-methylpropan-1-one, 10b

$^{1}H$ NMR (600 MHz, CDCl$_3$) δ 8.28 (d, $J$ = 8.1 Hz, 1H), 8.30 (d, $J$ = 8.1 Hz, 1H), 7.81 (t, $J$ = 7.7 Hz, 1H), 7.88 (d, $J$ = 7.7 Hz, 1H), 4.14 (t, $J$ = 11.8 Hz, 1H), 1.42 (d, $J$ = 6.9 Hz, 6H).

$^{13}$C NMR (150 MHz, CDCl$_3$): 176.39, 164.12, 131.27, 130.28, 128.55, 128.56, 114.56, 33.99, 21.06.
S-phenyl 4-methyl-2-(N-methylbenzamido)-3-oxopentanethioate
S-phenyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)-4-methyl-3-oxopentanethioate

$^1$H NMR (400 MHz, Chloroform-d): 8 12.85 (d, J = 1.5 Hz, 1H), 7.81 – 7.71 (m, 2H), 7.49 (m, 2H), 7.19 – 7.00 (m, 5H), 5.36 (dd, J = 10.3, 7.2 Hz, 1H), 4.20 (sept, J = 6.8, 1.5 Hz, 1H), 3.16 (s, 3H), 2.67 (sept, J = 6.8 Hz, 1H), 1.30 (d, J = 6.8 Hz, 6H).
S-phenyl-2(((benzoyloxy)carbonyl)(methyl)amino)-4-methyl-3-Oxopentanethioate

$\text{S-phenyl-2(((benzoyloxy)carbonyl)(methyl)amino)-4-methyl-3-Oxopentanethioate}$

$^1$H NMR (400 MHz, Chloroform-d) δ 2.99 – 3.34 (m, 4H), 7.35 – 7.37 (m, 1H), 5.39 – 5.37 (m, 2H), 3.25 – 3.30 (m, 3H), 2.62 (s, 1H), J = 8.5, 6.5, 5.5 Hz (3H), 1.08 (s, 3H), J = 9.8, 6.8, 3.8 Hz (6H).

$^13$C NMR (100 MHz, CDCl$_3$) δ 195.90, 194.05, 180.56, 178.45, 166.27, 138.54, 135.34, 134.43, 130.58, 129.46, 128.40, 128.31, 128.05, 127.98, 126.92, 126.84, 126.80, 126.76, 126.64, 126.04, 125.80, 125.31, 124.13, 120.70, 119.57, 119.35, 118.64, 118.60, 118.34, 118.09, 117.98, 117.85, 117.67, 117.60, 117.55, 117.49, 117.44, 117.39, 117.34, 117.19.
N-methyl-N-(4-methyl-1,3-dioxo-1-(phenylamino)pentan-2-yl)benzamide, 13

$^{1}H$ NMR (400 MHz, Chloroform-$d$) δ 8.41 (s, 1H), 7.63 (d, $J = 8.6$ Hz, 2H), 7.48 - 7.30 (m, 4H), 7.22 (d, $J = 12.8$ Hz, 2H), 6.55 (s, 1H), 5.20 (s, 2H), 3.01 (s, 3H), 1.16, 3.87 - 3.33 (m, 1H), 1.09 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.7$ Hz, 3H).

$^{13}C$ NMR (100 MHz, Chloroform-$d$) δ 173.32, 166.67, 139.99, 134.49, 130.50, 129.07, 128.04, 127.46, 125.10, 123.31, 119.99, 108.05, 39.37, 29.36, 20.51, 17.64.
(9H-fluoren-9-yl)methylmethyl(4-methyl-1,3-dioxo-1(phenylamino)pentan-2-yl)carbamate, 14
Benzyl methyl(4-methyl-1,3-dioxo-1-(phenylamino)pentan-2-yl)carbamate, 9

$^1$H NMR (400 MHz, Chloroform-d) δ 14.01 (s), 8.98 (t, J = 1.4 Hz, 1H), 7.30 – 6.96 (m, 1H), 5.31 – 4.96 (m, 2H), 3.11 (s, 3H), 2.58 (t, J = 7.1 Hz, 1H), 1.00 (dd, J = 6.6 Hz, 1H).

$^13$C NMR (100 MHz, Chloroform-d) δ 175.91, 166.95, 128.97, 128.55, 128.08, 128.15, 124.02, 123.02, 47.87, 36.10, 29.39, 19.98, 18.53.
N-((2S,3R)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)-N-methyl benzamide, 15
(9H-fluoren-9-yl)methyl((2S,3R)-3-hydroxy-4-methyl-1-oxo-1-(phenyl amino)pentan-2-yl)(methyl) carbamate, 16
Benzyl ((2S,3R)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl) carbamate, 17
(2R,4E)-N-((S)-2-hydroxy-1-phenylethyl)-2-methylhex-4-enamide – 19
(2S,4E)-N-((S)-2-hydroxy-1-phenylethyl)-2-methylhex-4-enamide – epi-19
(2R,4E)-2-methylhex-4-enoic acid, 20
(2R,4E)-1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-methylhex-4-en-1-one, 21

1H NMR (499 MHz, cdcl3): δ 175.90, 146.17, 131.23, 130.27, 128.34, 127.50, 126.00, 124.05, 114.57, 30.35, 36.54, 17.85, 16.78.
S-phenyl (4R,6E)-2-(((benzyloxy)carbonyl)(methyl)amino)-4-methyl-3-oxooct-6-enethioate, 23
Benzyl methyl((4R,6E)-4-methyl-1,3-dioxo-1 (phenylamino)oct-6-en-2-yl) carbamate, 24
Benzyl ((2S,3R,4R,6E)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)oct-6-en-2-yl)(methyl)carbamate, 25
(2S,3R,4R,E)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoic acid, MeBmt, 2
### MS Zoomed Spectrum

**Cpd 1: +ESI Scan (2.007, 2.090-2.123 min, 4 Scans) Frag=175.0V ACR008-002.d Subtract**

| m/z | Calc m/z | Diff (ppm) | z | Abund | Formula | Ion |
|-----|----------|------------|---|-------|---------|-----|
| 202.1441 | 202.1438 | 1.68 | 1 | 559168.3 | C10H20NO3 | (M+H)+ |
| 202.1441 | 202.1441 | 0.0 | 1 | 559168.3 | C10H20NO3 | (M+H)+ |
| 203.1477 | 203.1477 | 0.0 | 1 | 564770.8 | C10H20NO3 | (M+H)+ |
| 204.1573 | 204.1573 | 0.0 | 1 | 570373.2 | C10H20NO3 | (M+H)+ |
| 205.1670 | 205.1670 | 0.0 | 1 | 575975.5 | C10H20NO3 | (M+H)+ |
| 224.1289 | 224.1289 | 0.0 | 1 | 575975.5 | C10H20NO3 | (M+H)+ |
| 225.1299 | 225.1300 | 0.42 | 1 | 581582.0 | C10H20NO3 | (M+H)+ |
| 227.1328 | 227.1333 | 0.22 | 1 | 587184.3 | C10H20NO3 | (M+H)+ |
| 227.1377 | 227.1377 | 0.22 | 1 | 587184.3 | C10H20NO3 | (M+H)+ |

--- End Of Report ---
Benzyl (1-cyclopropyl-1,3-dioxo-3-(phenylamino)propan-2-yl)(methyl)carbamate
syn-benzyl-(1-cyclopropyl-1-hydroxy-3-oxo-3-(phenylamino)propan-2-yl)(methyl) carbamate, 28/29
(1H-benzo[d][1,2,3]triazol-1-yl)(cyclobutyl)methanone

$^1$H NMR (400 MHz, Chloroform-$d$): $\delta$ 8.30 (d, $J = 8.3$, 3H), 8.09 (d, $J = 8.3$, 0H), 7.61 (d, $J = 8.3$, 1H), 7.11 (d, $J = 7.1$, 1H), 7.48 (d, $J = 7.48$, 1H), 4.53 (p, $J = 4.53$, 1H), 3.09 – 4.97 (m, 4H), 2.64 – 2.41 (m, 4H), 2.26 – 2.14 (m, 1H), 2.09 – 1.97 (m, 1H).

$^13$C NMR (100 MHz, Chloroform-$d$): $\delta$ 179.98, 146.09, 131.20, 130.21, 129.98, 120.01, 114.39, 39.02, 25.25, 18.46.
Benzyl (1-cyclobutyl-1,3-dioxo-3-(phenylamino)propan-2-yl)(methyl)carbamate
syn-Benzyl(-1-cyclobutyl-1-hydroxy-3-oxo-3-(phenylamino)propan-2-yl)(methyl)carbamate, 30/31
Chiral analysis of benzyl (3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl)carbamate - 17

Racemic sample was synthesized according to general procedures C and E utilizing isobutyraldehyde in place of 1-{1H-benzo[d][1,2,3]triazol-1-yl}-2-methylpropan-1-one, yielding a mixture of two diastereomers. Racemic chiral HPLC sample was taken from a chromatography fraction that appeared to have approximate equal quantities of both diastereomers as judged by TLC. A purified sample of diastereomer A (later identified as anti after comparison to X-ray sample) was able to be obtained by column chromatography. Diastereomer B was identical to samples obtained by ATH DKR of (17) by NMR.
Racemic benzyl (3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl)carbamate
benzyl (3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl)carbamate – 17 Diastereomer A (anti).
NMR Diastereomer analysis

Mixture of diastereomer A+B

Electronic overlay of purified diastereomers in Mestrenova
Chiral HPLC chromatograms from Table S1

S1. Entry 1 – Cat. A. Ru(p-cymene)[(R,R)-Ts-DPEN]
S1. Entry 2 – Cat B. Ru[(R,R)-TsDPEN](mesitylene)

Additional Info: Peak(s) manually integrated

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Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254.8 Ref=off

| # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|--------------|------|-------------|--------------|--------------|--------|
| 1 | 3.710        | VV   | 0.1229      | 210.01619    | 23.81942     | 2.6470 |
| 2 | 4.144        | VB   | 0.2128      | 7609.24658   | 552.01428    | 95.9070|
| 3 | 5.089        | BB   | 0.1233      | 114.71864    | 14.33808     | 1.4459 |

Totals: 7933.98141 590.17178
S1. Entry 3 – Cat C. Ru(p-cymene)[(R,R)-Fs-DPEN]

Additional Info: Peak(s) manually integrated

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254.8 Ref=off

| Peak RetTime Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|------------------|-------------|--------------|--------------|-------|
| 1                | 3.709 VV    | 0.1241       | 266.12659    | 30.65196 | 2.9646 |
| 2                | 4.145 VB    | 0.2150       | 8724.49609   | 632.09247 | 96.4854 |
| 3                | 5.096 BB    | 0.1288       | 51.54995     | 6.21606  | 0.5700 |

Totals: 9046.17263 668.96049
S1. Entry 4 – Cat D.

Additional Info: Peak(s) manually integrated

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254.8 Ref=off

| Peak RetTime | Type | Width | Area [mAU*s] | Height [mAU] | Area % |
|--------------|------|-------|--------------|--------------|--------|
| 1 3.712 VV   |      | 0.1346| 81.20387     | 8.41102      | 1.8248 |
| 2 4.149 VB   |      | 0.2162| 4356.22412   | 313.41925    | 97.8943|
| 3 5.111 BB   |      | 0.1279| 12.49660     | 1.46000      | 0.2808 |

Totals: 4449.92460 323.29027
**S1. Entry 5 – Cat E.**

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**Area Percent Report**

Sorted By: Signal  
Multiplier: 1.0000  
Dilution: 1.0000  
Do not use Multiplier & Dilution Factor with ISTDs

**Signal 1: DAD1 B, Sig=254.8 Ref=off**

| Peak | RetTime | Type | Width | Area   | Height | Area % |
|------|---------|------|-------|--------|--------|--------|
| 1    | 3.717   | VV   | 0.1101| 213.86124 | 28.33149 | 3.8773 |
| 2    | 4.151   | VB   | 0.2102| 5256.19922 | 373.53464 | 95.2949 |
| 3    | 5.124   | BB   | 0.1911| 45.66090  | 3.26519  | 0.8278 |

Totals: 5515.72135 405.13132
### Additional Info: Peak(s) manually integrated

**DAD1 B, Sig=254,8 Ref=off (ACR/ACR008-067 2016-07-22 13-10-52.D)**

**ADC1 A, PDR-Chiral Advanced Laser Polarimeter (ACR/ACR008-067 2016-07-22 13-10-52.D)**

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### Area Percent Report

**Sorted By**: Signal  
**Multiplier**: 1.0000  
**Dilution**: 1.0000  
**Sample Amount**: 10.00000 [ng/ul] (not used in calc.)  
Do not use Multiplier & Dilution Factor with ISTDs

**Signal 1: DAD1 B, Sig=254,8 Ref=off**

| #  | RetTime | Type | Width | Area [mAU^2] | Height [mAU] | Area [%] |
|----|---------|------|-------|--------------|--------------|---------|
| 1  | 3.689   | VV   | 0.1759| 90.92557     | 7.17465      | 0.5394  |
| 2  | 4.146   | VB   | 0.2124| 1.64092e4   | 1208.93835   | 97.3400 |
| 3  | 5.077   | BB   | 0.2405| 68.40959    | 3.79225      | 0.4058  |
| 4  | 6.599   | BB   | 0.4382| 289.07190   | 8.10368      | 1.7148  |
Benzyl(2S,3R)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl)carbamate, 17

Additional Info : Peak(s) manually integrated

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Area Percent Report
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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,8 Ref-off

| # | RetTime | Type | Width | Area | Height | Area
|---|---------|------|-------|------|--------|------|
| 1 | 3.959   | Vu   | 0.1052| 5546.01025| 816.80585 | 99.2462 |
| 2 | 4.451   | Vu   | 0.1567| 42.12186  | 3.35081  | 0.7538  |

Totals : 5588.13211 820.15665

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Benzyl ((2R,3S)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl)carbamate, 26

Additional Info: Peak(s) manually integrated

DAD1 B, Sig=254,8 Ref=off (ACR008-003_7 2017-08-23 09-53-35055-0501.D)

ADC1 A, PDR-Chiral Advanced Laser Polarimeter (ACR008-003_7 2017-08-23 09-53-35055-0501.D)

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,8 Ref=off

| Peak RetTime Type | Width | Area    | Height | Area % |
|------------------|-------|---------|--------|--------|
| #                | [min] | [mAU*s] | [mAU]  |       |
| 1                | 3.902 | 0.1294  | 102.07346 | 10.68969 | 1,1223 |
| 2                | 4.466 | 0.1441  | 8992.65723 | 970.45032 | 98.8777 |

Totals: 9094.73068 981.14001
Benzyl ((1S,2R)-1-cyclopropyl-1-hydroxy-3-oxo-3-(phenylamino)propan-2-yl)(methyl)carbamate, 29

Additional Info: Peak(s) manually integrated

Area Percent Report

Sorted By: Signal
Multiplier: 1.0000
Dilution: 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,8 Ref-off

| Peak | RetTime | Type | Width | Area | Height | Area |
|------|---------|------|-------|------|--------|------|
| 1    | 3.888   | VV   | 0.0935| 8717.10742| 1463.34253| 62.9210 |
| 2    | 4.250   | VV   | 0.1445| 5136.93750| 523.57275| 37.0790 |

Totals: 1.38540e4 1986.91528

75
Benzyl ((1R,2S)-1-cyclopropyl-1-hydroxy-3-oxo-3-(phenylamino)propan-2-yl)(methyl)carbamate, 28
Benzyl ((1S,2R)-1-cyclobutyl-1-hydroxy-3-oxo-3-(phenylamino)propan-2-yl)(methyl)carbamate, 31

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| # | RetTime | Type | Width  | Area    | Height | Area % |
|---|---------|------|--------|---------|--------|--------|
| 1 | 9.960   | MM   | 0.3452 | 3745.04492 | 180.81860 | 18.2473 |
| 2 | 14.237  | MM   | 1.1620 | 1.67787e4 | 240.65768 | 81.7527 |
```

Totals: 2.05238e4 421.47629
Benzyl ((1R,2S)-1-cyclobutyl-1-hydroxy-3-oxo-3-(phenylamino)propan-2-yl)(methyl)carbamate, 30
Benzyl ((2S,3R,4R,E)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)oct-6-en-2-yl)(methyl)carbamate, 25
benzyl \((2R,3S,4R,E)-3\text{-hydroxy-4-methyl-1-\text{oxo}-1-}\text{(phenylamino)oct-6-en-2-yl}(\text{methyl})\text{carbamate, 27}\)
X-Ray crystallography – experimental summary

Compound name: benzyl ((2S,3R)-3-hydroxy-4-methyl-1-oxo-1-(phenylamino)pentan-2-yl)(methyl)carbamate

CCDC Deposition number: 1897285

The single crystal X-ray diffraction studies were carried out on a Bruker D8 Platinum\textsuperscript{135} CCD diffractometer equipped with Cu Kα radiation (λ = 1.5478). A 0.217 x 0.053 x 0.051 mm piece of a colorless rod was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 125(2) K using φ and α scans. Crystal-to-detector distance was 45 mm using variable exposure time (2s-5s) depending on θ with a scan width of 2.0°. Data collection was 98.4% complete to 68.00° in θ. A total of 33864 reflections were collected covering the indices, -11<=h<=10, -12<=k<=14, -19<=l<=19. 3547 reflections were found to be symmetry independent, with a R\text{int} of 0.0549. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be \textit{P2}_1\textit{2}_1\textit{2}_1. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. All other hydrogen atoms (H-bonding) were located in the difference map. Their relative positions were restrained using DFIX commands and their thermals freely refined. The absolute stereochemistry of the molecule was established by anomalous dispersion using the Parson’s method with a Flack parameter of 0.050(34). Crystallographic data are summarized in Table 1.

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Table 1. Crystal data and structure refinement for NIH18.

| Property                        | Value                      |
|---------------------------------|----------------------------|
| Identification code             | NIH18                      |
| Empirical formula               | C21 H26 N2 O4              |
| Molecular formula               | C21 H26 N2 O4              |
| Formula weight                  | 370.44                     |
| Temperature                     | 125 K                      |
| Wavelength                      | 1.54178 Å                  |
| Crystal system                  | Orthorhombic               |
| Space group                     | P2_12_12                 |
| Unit cell dimensions            | a = 10.2972(4) Å, α = 90° |
|                                 | b = 11.7362(4) Å, β = 90° |
|                                 | c = 16.2355(6) Å, γ = 90° |
| Volume                          | 1962.06(12) Å³             |
| Z                               | 4                          |
| Density (calculated)            | 1.254 Mg/m³                |
| Absorption coefficient          | 0.707 mm⁻¹                 |
| F(000)                          | 792                        |
| Crystal size                    | 0.217 x 0.053 x 0.051 mm³  |
| Crystal color, habit            | Colorless Rod              |
| Theta range for data collection | 4.649 to 68.273°           |
| Index ranges                    | -11≤h≤10, -12≤k≤14, -19≤l≤19 |
| Reflections collected           | 33864                      |
| Independent reflections         | 3547 [R(int) = 0.0549, R(sigma) = 0.0205] |
| Completeness to theta = 68.000°| 98.4 %                     |
| Absorption correction           | Semi-empirical from equivalents |
| Max. and min. transmission      | 0.3201 and 0.2018          |
| Refinement method               | Full-matrix least-squares on F² |
| Data / restraints / parameters  | 3547 / 2 / 255             |
| Goodness-of-fit on F²           | 1.086                      |
| Final R indices [I>2sigma(I)]   | R1 = 0.0252, wR2 = 0.0636  |
| R indices (all data)            | R1 = 0.0256, wR2 = 0.0639  |
| Absolute structure parameter    | 0.05(3)                    |
| Extinction coefficient          | n/a                        |
| Largest diff. peak and hole     | 0.113 and -0.179 e.Å⁻³     |
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