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J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/acs.joc.6b01284 • Publication Date (Web): 22 Jul 2016

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Asymmetric Synthesis of 2-Substituted Azetidin-3-ones via Metalated SAMP/RAMP Hydrazones

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2-Substituted azetidin-3-ones can be prepared in good yields and enantioselectivities (up to 85% *ee*) by a one-pot procedure involving the metalation of the SAMP/RAMP hydrazones of *N*-Boc-azetidin-3-one, reaction with a wide range of electrophiles, including alkyl, allyl and benzyl halides and carbonyl compounds, followed by hydrolysis using oxalic acid.

Azetidines are an important class of azaheterocyle which has attracted considerable interest in recent years as a structural motif within drug discovery. They possess a broad range of biological activities,¹ and provide a means of introducing molecular rigidity, novelty and improved pharmacological profiles in lead optimization programmes.² Substituted azetidines are present in several natural products and compounds patented for pharmaceutical applications, including the marketed drug Azelnidipine,³ Penaresidin A,^{1b,4} antithrombotics⁵ and GLPG1690 (Figure 1).⁶ Whilst a number of methods have been developed for the preparation of azetidines,⁷ only limited methods exist for the stereocontrolled synthesis of chiral derivatives. These include rhodium or copper catalyzed N-H insertion reactions of diazoketones derived from α -amino acids,⁸ gold-catalyzed oxidative cyclization of chiral *N*-propagylsulfonamides,⁹ nickel-catalyzed cross coupling of organozinc reagents with chiral aziridines,¹⁰ lithiation-electrophilic substitution of *tert*-butoxythiocarbonyl (Botc) protected azetidine in the presence

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of a chiral ligand,¹¹ through imino-aldol reactions of ester enolates with chiral aldimines,¹² and via the organocatalyzed synthesis of α -chloro aldehydes.¹³ These approaches either have limited scope, involve multiple steps with low overall yield, or introduce the azetidine substituent early on in the synthesis thereby reducing the efficiency by which structure activity (SAR) relationships can be explored. In particular, the asymmetric routes do not provide sufficiently general methods to 2-substituted azetidin-3-ones.

Figure 1. Examples of biologically active 3-oxygenated azetidines



To provide both a general and short asymmetric synthesis of 2-substituted azetidin-3-ones, and thus increase the diversity of chiral azetidine building blocks available, we decided to explore the SAMP/RAMP hydrazone methodology developed by Enders,¹⁴ which we recently applied to the asymmetric synthesis of 2-substituted oxetan-3-ones.¹⁵ This could allow a rather direct and efficient access to a broad range of 2,3-disubstituted azetidines,¹⁶ and other pharmaceutically relevant nitrogen heterocycles.¹⁷

Our proposed strategy from commercial *N*-Boc-azetidin-3-one is depicted in Scheme 1. The α lithiation and alkylation of selected *N*-protected azetidines is well documented, providing further encouragement for this study.¹⁸ In this Note, we demonstrate how a variety of chiral 2-substituted

azetidin-3-ones can be prepared in high ee in one-pot by the metalation/alkylation of the SAMP/RAMP hydrazones derived from N-Boc-azetidin-3-one, offering a procedurally straightforward route to these pharmaceutically relevant building blocks.

Scheme 1. Proposed route to chiral 2-substituted azetidin-3-ones



The SAMP hydrazone (S)-1 was prepared in quantitative yield by treatment of SAMP with an excess of commercially available N-Boc-azetidin-3-one at 55 °C without solvent (Table 1). The corresponding (R)-enantiomer was made using RAMP in an identical fashion. In order to optimize the metalation of (S)-1, a screen of different lithium bases, metalation times, solvents and concentrations was performed, where the lithiated intermediate was quenched with deuterated methanol. The conversion of 1 to 2 was estimated by mass spectrometry, and deuterated product 2 isolated by chromatography (Table 1). Initial reactions using 1.1 equivalents of either ^tBuLi or LDA in THF indicated a higher yield of **2** using ¹BuLi (entries 1 and 2, Table 1). A decrease in the metalation time to 1 h led to an increase to 73% yield (entry 4). This finding perhaps suggests that the lithiated heterocycle has moderate stability under these reaction conditions. By reducing the reaction concentration to 0.1 mM, and reverting to a 2 h metalation time, a further improvement in yield to 77% was achieved (entry 6). No improvement in yield was observed when a mixture of THF and pentane was used as solvent (entry 7). With a highest yield of 77% for 2 using ^tBuLi as the base (THF, metalation time 2 h, concentration 0.1 mM, entry 6), we decided to explore use of easier to handle "BuLi under the same reaction conditions. Satisfyingly, this led to a further small improvement in yield (entry 8).

Table 1. Optimization of conditions for lithiation of SAMP hydrazone (S)-1



^a isolated yield after chromatography. ^b determined by mass spectrometry.

Having identified practical conditions for the lithiation of **1**, we turned our attention to the optimization of the yield and stereoselectivity for the subsequent alkylation step with allyl bromide. An initial reaction using the best lithiation conditions and 1.2 equivalents of allyl bromide gave hydrazone **3** in 66% yield after chromatography (Scheme 2). Hydrolysis of **3** using aqueous oxalic acid provided ketone (*S*)-**4** in 75% yield (50% over 2 steps) and 81% *ee* (as determined by chiral GC). The racemic ketone **4** was prepared from achiral hydrazone **5** using the same general approach.^{19,20}

Scheme 2. Synthesis of enantiomerically enriched and racemic N-Boc-2-allyl-azetidin-3-one (4)

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We briefly examined the use of alternative nitrogen protecting groups in this chemistry. The alternative SAMP hydrazone **6** derived from *N*-benzhydrylazetidin-3-one produced **7** in low 20% yield after hydrolysis, indicating that the Boc group is a better N-protecting group for this chemistry (Scheme 3).

Scheme 3. Synthesis of (S)-N-benzhydryl-2-allyl-azetidin-3-one (7)



By performing the two-step sequence from 1 to (*S*)-4 in one-pot, omitting isolation of the hydrazone intermediate 3, ketone (*S*)-4 was prepared in comparable overall yield (48%) with no erosion of stereoselectivity (81% *ee*) (entry 1, Table 2). For convenience, all subsequent reactions to optimize the yield and enantioselectivity were performed using this one-pot method. A switch to diethyl ether as solvent proved detrimental to the yield (entry 2), and introduction of the additive TMEDA led to a drop in *ee* (entry 3). Performing the lithiation at a higher temperature of -40 °C gave no product (entry 4), and a change in solvent to 1:1 THF:pentane led to an improvement in selectivity but a slight decrease in yield (entry 5). Finally, a much improved 67% yield and high *ee* was achieved by maintaining the reaction

temperature at -78 °C for two hours after addition of the electrophile prior to warming to room temperature (entry 6). Using RAMP derived (*R*)-1, the opposite enantiomer (*R*)-4 was produced in an identical 81% *ee* (see Experimental).



^a*ee* determined by chiral GC analysis (see Supporting Information). ^b1.1 eq TMEDA was used. EA = electrophile added.

Having established conditions for the one-pot preparation of (*S*)-**4** from (*S*)-**1** in good yield and high *ee*, we sought to establish the scope of the alkylation step (Table 3). A representative range of electrophiles including alkyl, allyl and benzyl halides, benzaldehyde and acetone were screened. Satisfyingly, additional allyl bromides were found to react in good yield and high selectivity (entries 3 and 4), as did both primary and secondary alkyl iodides (entries 5 and 6). The stereoselectivity for each iodide was found to reflect its steric demand, with the most hindered, $(CH_3)_2CHI$, giving the highest *ee* of 85% (entry 6). A much lower *ee* was observed with benzyl bromide, which suggests a different mechanism is operating with this electrophile, possibly involving electron transfer (entry 7). Reaction of the

lithiated intermediate with acetone gave alcohol **14** in good yield and high enantioselectivity (entry 9) although low selectivity was seen with benzaldehyde (entry 8). Preliminary attempts to make 2,2-disubstituted derivatives by repetition of the deprotonation/alkylation sequence have not been fruitful.





^a*ee* determined by chiral GC analysis. ^b*ee* determined by chiral HPLC analysis. In all cases, racemic samples were prepared from achiral hydrazone **5** for comparison purposes.^c(R)-**1** was reacted. See Supporting Information for GC and HPLC conditions and chromatograms. ^dobtained as an inseparable 3:2 mixture of diastereomers.

The absolute configuration of the major enantiomer of **14** was established by performing a Pictet-Spengler reaction on ketone **14** with _L-tryptophan methyl ester, using reaction conditions developed previously.²¹ The major ester **15** was separated from the reaction mixture in 81% yield, and was converted to amide **16**. X-ray crystal structure analysis of **16** unambiguously determined the (*S*)-configuration of the azetidine C2 stereocenter of **14** (Scheme 4, Supporting Information).





The stereochemical outcome of the alkylation of SAMP hydrazone (S)-1 is in accordance with previous studies by Enders *et al*, and can be explained by preferential attack of a conformationally rigid and

chelated $E_{C=C}Z_{C-N}$ azaenolate by the electrophile from the less sterically hindered *Si* face (Scheme 5).²² The sense of asymmetric induction in the other alkylations reported herein was made by analogy.

Scheme 5. Proposed mechanism of formation of the major enantiomer of 14



In conclusion, we have developed a practical and efficient asymmetric synthesis of 2-substitutedazetidin-3-ones in high enantiomeric excesses via a one-pot procedure involving the alkylation of the lithiated SAMP hydrazone of *N*-Boc-azetidin-3-one. Reactions with allyl bromides, alkyl iodides and carbonyl compounds were found to be high yielding (50-74% over 2 steps) and stereoselective (up to 85% *ee*). These products are expected to be useful in the preparation of novel 2,3-disubstituted azetidine containing scaffolds and other heterocycles used in drug discovery programs.

EXPERIMENTAL SECTION

NMR assignments were deduced using 2D experiments (COSY, HMBC and HMQC).

(S)-3-(2-(Methoxymethyl)-N-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-tert-butylcarboxylate (1)

(*S*)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (537 µl, 4.00 mmol) was added dropwise to *N*-Bocazetidin-3-one (822 mg, 4.80 mmol). The mixture was heated to 55 °C for 16 h, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 3:1, hexane:ethyl acetate) to give (*S*)-1 (1.13 g, 100%) as a pale yellow oil, R_f (3:1, hexane:ethyl acetate) 0.31; $[\alpha]_D^{26}$ +23.4 (*c* 0.12, CHCl₃); υ_{max} (film)/cm⁻¹ 2929, 2867, 1703, 1457, 1365, 1087, 940, 859, 767; δ_H (400 MHz, CDCl₃) 4.76–4.68 (1H, m, NC*H*H), 4.64–4.52 (3H, m, NCH*H*, NCH₂), 3.50 (1H, dd, *J* = 8.0, 4.0 Hz, CHHOCH₃), 3.44–3.39 (2H, m, CHHOCH₃, NCH), 3.38 (3H, s, CH₂OCH₃), 3.33–3.26 (1H, m, NCHH), 2.79 (1H, q, J = 8.0 Hz, NCHH), 1.98–1.84 (3H, m, CHH, CH₂), 1.78–1.69 (1H, m, CHH), 1.46 (9H, s, C(CH₃)₃); δ_{C} (100 MHz, CDCl₃) 156.2 (C=O), 135.9 (C=N), 80.1 (*C*(CH₃)₃), 74.9 (*C*H₂OCH₃), 65.2 (NCH), 61.4 (NCH₂), 60.4 (NCH₂), 59.3 (CH₂OCH₃), 52.5 (NCH₂), 28.4 (C(CH₃)₃), 25.9 (CH₂), 22.7 (CH₂); MS (ES⁺) *m*/*z* 284 (MH⁺); HRMS (ESI/TOF-Q) m/*z*: [M + H]⁺ Calcd for C₁₄H₂₆N₃O₃ 284.1969; Found 284.1972.

(R)-3-(2-(Methoxymethyl)-N-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-tert-butylcarboxylate (1)

(*R*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine (269 μl, 2.00 mmol) was added dropwise to *N*-Bocazetidin-3-one (411 mg, 2.40 mmol). The mixture was heated to 55 °C for 16 h, and and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 3:1, hexane:ethyl acetate) to give (*R*)-1 (540 mg, 95%) as a pale yellow oil, R_f (3:1, hexane:ethyl acetate) 0.24; $[\alpha]_D^{29} -21.2$ (*c* 0.11, CHCl₃); ν_{max} (film)/cm⁻¹ 2979, 2930, 2888, 2835, 1687, 1460, 1364, 1146, 1105, 941, 858, 767; δ_H (400 MHz, CDCl₃) 4.77–4.68 (1H, m, NCHH), 4.65–4.53 (3H, m, NCHH, NCH₂), 3.54-3.46 (1H, m, CHHOCH₃), 3.45–3.35 (2H, m, CHHOCH₃, NCHCH₂OCH₃), 3.38 (3H, s, CH₂OCH₃), 3.34–3.26 (1H, m, NCHHCH₂), 2.79 (1H, q, *J* = 8.1 Hz, NCHHCH₂), 1.98–1.83 (3H, m, CHH, CH₂), 1.79–1.69 (1H, m, CHH), 1.46 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 156.2 (C=O), 135.9 (C=N), 80.1 (*C*(CH₃)₃), 74.9 (*C*H₂OCH₃), 65.1 (NCH), 61.4 (NCH₂), 59.3 (CH₂OCH₃), 52.5 (NCH₂CH₂), 28.3 (C(*C*H₃)₃), 25.9 (CH₂), 22.7 (CH₂); MS (ES⁺) *m*/z 284 (MH⁺); HRMS (ESI/TOF-Q) m/z: [M + H]⁺ Calcd for C₁₄H₂₆N₃O₃ 284.1969: Found 284.1964.

N,*N*-*Dimethyl*-*N*'-*azetidine*-3-*ylidinehydrazine*-1-*tert*-*butylcarboxylate* (5)

N,*N*-Dimethyl hydrazine (304 μ l, 4.00 mmol) was added dropwise to *N*-Boc-azetidin-3-one (822 mg, 4.80 mmol). The mixture was heated to 65 °C for 16 h, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 1:1, hexane:ethyl acetate) to give **5** (784

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mg, 92%) as a pale yellow oil, R_f (1:1, hexane:ethyl acetate) 0.53; v_{max} (film)/cm⁻¹ 2974, 2864, 1700, 1452, 1388, 1365, 1124, 1016, 940, 859, 765; δ_H (400 MHz, CDCl₃) 4.71 (2H, t, J = 2.7 Hz, NCH₂), 4.57 (2H, t, J = 2.7 Hz, NCH₂), 2.70 (6H, s, N(CH₃)₂), 1.46 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 156.1 (C=O), 138.4 (C=N), 80.2 (*C*(CH₃)₃), 61.6 (NCH₂), 61.0 (NCH₂), 45.8 (N(CH₃)₂), 28.3 (C(CH₃)₃); MS (ES⁺) *m*/*z* 236 (MNa⁺); HRMS (ESI/TOF-Q) m/*z*: [M + Na]⁺ Calcd for C₁₀H₁₉N₃O₂Na 236.1369; Found 236.1365.

(S)-3-(2-(Methoxymethyl)-N-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-benzhydryl (6)

(*S*)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (671 μl, 5.00 mmol) was added dropwise to 1benzhydrylazetidin-3-one (1.42 g, 6.00 mmol). The mixture was heated to 90 °C for 16 h, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 3:1, hexane:ethyl acetate) to give **6** (1.76 g, 100%) as an orange oil, R_f (3:1, hexane:ethyl acetate) 0.37; $[\alpha]_D^{25}$ +33.5 (*c* 0.106, CHCl₃); υ_{max} (film)/cm⁻¹ 2926, 2875, 2825, 1686, 1599, 1451, 1115, 1091, 950, 742, 700; δ_H (400 MHz, CDCl₃) 7.44 (4H, d, *J* = 7.6 Hz, ArH), 7.31-7.24 (4H, m, ArH), 7.23-7.16 (2H, m, ArH), 4.53 (1H, s, NCH), 4.00 (2H, s, NCH₂), 3.92 (2H, s, NCH₂), 3.54-3.48 (1H, m, CHHOCH₃), 3.41–3.28 (2H, m, CHHOCH₃, NCHCH₂), 3.36 (3H, s, CH₂OCH₃), 3.23–3.15 (1H, m, NCHHCH₂), 2.68 (1H, q, *J* = 8.3 Hz, NCHHCH₂), 1.96–1.85 (1H, m, CHH), 1.85–1.75 (2H, m, CH₂), 1.73-1.62 (1H, m, NCHH); δ_C (125 MHz, CDCl₃) 142.53 (C=N), 142.51 (C, Ar), 128.6 (CH, Ar), 127.4 (CH, Ar), 127.32 (CH, Ar), 127.28 (CH, Ar), 127.25 (CH, Ar), 77.4 (NCH), 75.1 (CH₂OCH₃), 65.3 (NCHCH₂), 64.9 (NCH₂), 64.5 (NCH₂), 59.3 (CH₂OCH₃), 53.0 (NCH₂CH₂), 26.0 (CH₂), 22.6 (CH₂); MS (ES⁺) *m/z* 350 (MH⁺); HRMS (ESI/TOF-Q) m/z: [M + H]⁺ Calcd for C₂₂H₂₈N₃O 350.2227; Found 350.2221.

(S)-2-Allyl-1-benzyhydrylazetidin-3-one (7)

n-Butyllithium (2.35 M solution in hexanes, 187 μ l, 0.44 mmol) was added dropwise to a stirred solution of **6** (140 mg, 0.40 mmol) in anhydrous THF (4 ml) at -78 °C under nitrogen. After 2 h at -78 **ACS Paragon Plus Environment**

 $^{\circ}$ C, allyl bromide (42 µl, 0.48 mmol) was added by syringe, and the solution maintained at this temperature for 2 h before warming slowly to RT over 18 h. Saturated aqueous oxalic acid solution (4 ml) was added and the solution stirred vigorously at RT for 20 h. The reaction mixture was diluted with diethyl ether (50 ml) and the layers were separated. The organic layer was washed with brine (25 ml), saturated aqueous sodium bicarbonate (25 ml), dried (MgSO₄), filtered and the solvent removed in vacuo. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave 7 (22 mg, 20%) as a pale yellow oil, R_f (7:1, hexane: ethyl acetate) 0.53; $[\alpha]_D^{24}$ +6.50 (c 0.100, CHCl₃); υ_{max} $(\text{film})/\text{cm}^{-1}$ 3063, 2932, 2819, 1804, 1599, 1453, 1429, 920, 743, 698; δ_{H} (400 MHz, CDCl₃) 7.90-6.95 (10H, m, ArH), 5.74-5.52 (1H, m, CH₂CH=CH₂), 5.01-4.75 (2H, m, CH₂CH=CH₂), 4.53 (1H, s, NCH), 4.18-3.90 (2H, m, NCHH, NCHCH₂), 3.61 (1H, d, *J* = 16.2 Hz, NCHH), 1.96-1.80 (2H, m, NCHCH₂); δ_C (125 MHz, CDCl₃) 204.4 (C=O), 142.5 (C, Ar), 142.3 (C, Ar), 133.3 (CH₂CH=CH₂), 128.7 (CH, Ar), 128.5 (CH, Ar), 128.3 (CH, Ar), 127.8 (CH, Ar), 127.4 (CH, Ar), 127.3 (CH, Ar), 117.5 (CH₂CH=CH₂), 84.7 (NCHCH₂), 77.3 (NCH), 72.9 (NCH₂), 35.0 (NCHCH₂); MS (ES⁺) m/z 278 (MH⁺); HRMS (ESI/TOF-Q) m/z: $[M + H]^+$ Calcd for C₁₉H₂₀NO 278.1539; Found 278.1541; 7% *ee* (determined by chiral HPLC on a Chiralpak AD-H column (0.46cm ø x 25 cm), 99:1 hexane:propan-2-ol, 0.5 ml/min, T $= 25^{\circ}$ C, detection wavelength = 224 nm, see Supporting Information).

Two-Step Synthesis of (S)-4:

(2S)-2-(Methoxymethyl)-N-[2-(S)-allylazetidine-3-ylidine-1-tert-butylcarboxylate]-1-pyrrolidinamine (3)

n-Butyllithium (2.45 M solution in hexanes, 180 μ l, 0.44 mmol) was added dropwise to a stirred solution of (*S*)-1 (113 mg, 0.40 mmol) in anhydrous THF (4 ml) at –78 °C under nitrogen. After 2 h at – 78 °C, allyl bromide (42 μ l, 0.48 mmol) was added by syringe, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with ether (40 ml), and washed with water (10 ml) and brine (10 ml). The organic layer was dried (MgSO₄), filtered, and concentrated under

reduced pressure. The residue was purified by flash column chromatography (SiO₂, 3:1, hexane:ethyl acetate) to give **3** (85 mg, 66%) as a pale yellow oil, R_f (3:1, hexane:ethyl acetate) 0.34; v_{max} (film)/cm⁻¹ 2925, 2870, 1703, 1477, 1457, 1390, 1365, 1129, 1030, 913, 768; δ_H (400 MHz, CDCl₃) major isomer, 5.73-5.86 (1H, m, CH₂CH=CH₂), 5.19-5.07 (2H, m, CH₂CH=CH₂), 5.01-4.91 (1H, m, NCHCH₂CH=CH₂), 4.48-4.40 (1H, m, NCHH), 4.37 (1H, dd, *J* = 13.6, 3.4 Hz, NCHH), 3.52 (1H, dd, *J* = 9.1, 4.1 Hz, CHHOCH₃), 3.46-3.25 (3H, m, CHHOCH₃, NCHCH₂, NCHHCH₂), 3.37 (3H, s, CH₂OCH₃), 2.81-2.60 (1H, m, NCHHCH₂), 2.66 (1H, q, *J* = 8.3 Hz, CHHCH=CH₂), 2.55-2.46 (1H, m, CHHCH=CH₂), 2.06-1.83 (3H, m, NCHH, NCH₂), 1.71-1.63 (1H, m, NCHH), 1.47 (9H, s, C(CH₃)₃); δ_C (176 MHz, CDCl₃) 155.2 (C=O), 141.8 (C=N), 132.2 (CH₂CH=CH₂), 118.0 (CH₂CH=CH₂), 79.2 (C(CH₃)₃), 75.1 (CH₂OCH₃), 72.4 (NCHCH₂CH=CH₂), 65.3 (NCHCH₂OCH₃), 58.5 (CH₂OCH₃), 53.0 (NCH₂CH₂), 33.0 (CH₂CH=CH₂), 27.7 (C(CH₃)₃), 26.0 (CH₂), 22.3 (CH₂), azetidine CH₂ not observed; MS (ES⁺) *m*/z 346 (MNa⁺); HRMS (ESI/TOF-Q) m/z: [M + Na]⁺ Calcd for C₁₇H₂₉N₃O₃Na 346.2101; Found 346.2101.

(S)-2-(Allyl-3-oxoazetidine)-1-tert-butyl carboxylate (4)

To (*S*)-**3** (61 mg, 0.19 mmol) was added saturated aqueous oxalic acid (1.5 ml) and diethyl ether (2.5 ml), and the reaction stirred vigorously at room temperature for 18 h. The reaction mixture was diluted with diethyl ether (50 ml), and the layers separated. The organic layer was washed with brine (25 ml), saturated aqueous sodium bicarbonate (25 ml), dried (MgSO₄), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave (*S*)-**4** (30 mg, 75%) as a pale yellow oil; R_f (7:1, hexane: ethyl acetate) 0.32; $[\alpha]_D^{25}$ +55.4 (*c* 0.106, CHCl₃); v_{max} (film)/cm⁻¹ 3082, 2979, 2928, 1822, 1704, 1479, 1458, 1392, 1365, 1177, 1124, 923, 772; δ_H (400 MHz, CDCl₃) 5.91-5.73 (1H, m, CH₂CH=CH₂), 5.24-5.12 (2H, m, CH₂CH=CH₂), 5.01-4.87 (1H, m, NCHCH₂), 4.67 (1H, d, *J* = 16.6 Hz, NCHH), 4.47 (1H, dd, *J* = 16.6, 2.2 Hz, NCHH), 2.72-2.61 (1H, m, NCHCHH), 2.61-2.51 (1H, m, NCHCHH), 1.49 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 199.9 (C=O),

155.9 (C=O), 131.6 (CH₂CH=CH₂), 119.3 (CH₂CH=CH₂), 82.2 (NCHCH₂), 80.8 (*C*(CH₃)₃), 69.1 (NCH₂), 34.1 (NCH*C*H₂), 28.3 (C(CH₃)₃); MS (ES⁺) m/z 234 (MNa⁺); HRMS (ESI/TOF-Q) [M + Na]⁺ Calcd for C₁₁H₁₇NO₃Na 234.1101; Found 234.1093; 81% *ee* (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 110°C, P = 15 psi, H₂ carrier gas, see Supporting Information).

One-Pot Synthesis of (S)-4, 8-13: General Procedure.

n-Butyllithium (2.5 M solution in hexanes, 1.1 eq) was added dropwise to a stirred solution of (*S*)-**1** or (*R*)-**1** (0.40 mmol) in anhydrous THF (4 ml) at -78 °C under nitrogen. After 2 h at -78 °C, the electrophile (1.2 eq) was added by syringe, and the solution was stirred at -78 °C for 2 h before warming slowly to room temperature over 18 h. Saturated aqueous oxalic acid solution (4 ml) was added and the solution stirred vigorously at room temperature for 20 h. The reaction mixture was diluted with diethyl ether (50 ml) and the layers separated. The organic layer was washed with brine (25 ml), saturated aqueous sodium bicarbonate (25 ml), dried (MgSO₄), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography gave the 2-substituted azetidin-3-ones as detailed below.

(S)-2-(Allyl-3-oxoazetidine)-1-tert-butyl carboxylate (4)

(*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 µl, 0.44 mmol), anhydrous THF (4 ml) and allyl bromide (42 µl, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave (*S*)-**4** (57 mg, 67%) as a pale yellow oil; R_f (7:1, hexane: ethyl acetate) 0.32; $[\alpha]_D^{25}$ +52.7 (*c* 0.112, CHCl₃); v_{max} (film)/cm⁻¹ 3082, 2979, 2928, 1822, 1704, 1479, 1458, 1392, 1365, 1177, 1124, 923, 772; δ_H (400 MHz, CDCl₃) 5.91-5.73 (1H, m, CH₂CH=CH₂), 5.24-5.12 (2H, m, CH₂CH=CH₂), 5.01-4.87 (1H, m, NCHCH₂), 4.67 (1H, d, *J* = 16.6 Hz, NCHH), 4.47 (1H, dd, *J* = 16.6, 2.2 Hz, NCHH), 2.72-2.61 (1H, m, NCHCHH),

2.61-2.51 (1H, m, NCHCH*H*), 1.49 (9H, s, C(CH₃)₃); δ_{C} (125 MHz, CDCl₃) 199.9 (C=O), 155.9 (C=O), 131.6 (CH₂CH=CH₂), 119.3 (CH₂CH=CH₂), 82.2 (NCHCH₂), 80.8 (*C*(CH₃)₃), 69.1 (NCH₂), 34.1 (NCH*C*H₂), 28.3 (C(CH₃)₃); MS (ES⁺) *m/z* 234 (MNa⁺); HRMS (ESI/TOF-Q) m/z: [M + Na]⁺ Calcd for C₁₁H₁₇NO₃Na 234.1101; Found 234.1093; 81% *ee* (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 110°C, P = 15 psi, H₂ carrier gas, see Supporting Information).

(*R*)-2-(*Allyl-3-oxoazetidine*)-1-tert-butyl carboxylate (4)

(*R*)-1 (113 mg, 0.40 mmol), *n*-butyllithium (2.35 M solution in hexanes, 187 µl, 0.44 mmol), anhydrous THF (4 ml) and allyl bromide (42 µl, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave (*R*)-4 (46 mg, 55%) as a pale yellow oil; $[\alpha]_D^{30}$ –47.4 (*c* 0.116, CHCl₃); 81% *ee* (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 110°C, P = 15 psi, H₂ carrier gas, see Supporting Information).

(S)-2-((3-Methylbut-2-en-1-yl)-3-oxoazetidine)-1-tert-butyl carboxylate (8)

(*S*)-**1** (113 mg, 0.40 mmol), *n*-butyllithium (2.35 M solution in hexanes, 187 µl, 0.44 mmol), anhydrous THF (4 ml) and 3,3-dimethylallyl bromide (56 µl, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave (*S*)-**8** (51 mg, 53%) as a pale yellow oil, R_f (7:1, hexane: ethyl acetate) 0.39; $[\alpha]_D^{25}$ +30.3 (*c* 0.125, CHCl₃); υ_{max} (film)/cm⁻¹ 2977, 2927, 1821, 1701, 1365, 1176, 1129, 856, 772; δ_H (400 MHz, CDCl₃) 5.18 (1H, t, J = 7.2 Hz, CH₂CH=C(CH₃)₂), 4.94-4.86 (1H, m, NCHCH₂), 4.64 (1H, d, J = 16.5 Hz, NCHH), 4.45 (1H, dd, J = 16.6, 4.1 Hz, NCHH), 2.61-2.51 (2H, m, NCHCH₂), 1.72 (3H, s, CH₂CH=C(CH₃)(CH₃)), 1.63 (3H, s, CH₂CH=C(CH₃)(CH₃)), 1.49 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 200.6 (C=O), 155.9 (C=O), 136.3 (CH=C(CH₃)₂), 116.9 (CH=C(CH₃)₂), 82.8 (NCHCH₂), 80.6 (C(CH₃)₃), 68.9 (NCH₂),

28.6 (NCH*C*H₂), 28.3 (C(*C*H₃)₃), 25.9 (CH=C(*C*H₃)(CH₃)), 17.9 (CH=C(CH₃)(*C*H₃)); MS (ES⁺) m/z262 (MNa⁺); HRMS (ESI/TOF-Q) m/z: [M + Na]⁺ Calcd for C₁₃H₂₁NO₃Na 262.1414; Found 262.1415; 81% *ee* (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 140°C, P = 15 psi, He carrier gas, see Supporting Information).

(S)-2-(Phenylallyl-3-oxoazetidine)-1-tert-butyl carboxylate (9)

(*S*)-1 (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 µl, 0.44 mmol), anhydrous THF (4 ml) and 3-bromo-1-phenyl-1-propene (95 mg, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave (*S*)-**9** (85 mg, 74%) as a pale yellow oil, R_f (7:1, hexane: ethyl acetate) 0.36; $[\alpha]_D^{19}$ +71.3 (*c* 0.122, CHCl₃); v_{max} (film)/cm⁻¹ 2976, 2929, 1822, 1699, 1494, 1391, 1365, 1129, 966, 743, 693; δ_H (400 MHz, CDCl₃) 7.40-7.19 (5H, m, ArH), 6.51 (1H, d, *J* = 15.8 Hz, CH₂CH=CHAr), 6.24-6.13 (1H, m, CH₂CH=CH), 5.04-4.97 (1H, m, NCHCH₂), 4.67 (1H, d, *J* = 16.6 Hz, NCHH), 4.48 (1H, dd, *J* = 16.6, 4.3 Hz, NCHH), 2.88-2.77 (1H, m, NCHCHH), 2.76-2.64 (1H, m, NCHCHH), 1.48 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 199.9 (C=O), 155.9 (C=O), 136.9 (C, Ar), 134.4 (CH₂CH=CH), 128.6 (CH, Ar), 127.5 (CH, Ar), 126.3 (CH, Ar), 122.8 (CH₂CH=CH), 82.4 (NCHCH₂), 80.9 (*C*(CH₃)₃), 69.2 (NCH₂), 33.4 (NCHCH₂), 28.3 (C(CH₃)₃); MS (ES⁺) *m/z* 310 (MNa⁺); HRMS (ESI/TOF-Q) m/z: [M + Na]⁺ Calcd for C₁₇H₂₁NO₃Na 310.1414; Found 310.1412; 77% *ee* (determined by chiral HPLC on a Chiralcel OJ column (0.46cm ø x 25 cm), 97:3 hexane:propan-2-ol, 0.5 ml/min, T = 25°C, detection wavelength = 254 nm, see Supporting Information).

(S)-2-(Propyl-3-oxoazetidine)-1-tert-butyl carboxylate (10)

(S)-1 (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 μ l, 0.44 mmol), anhydrous THF (4 ml) and 1-iodopropane (47 μ l, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave (S)-10 (43 mg,

50%) as a pale yellow oil, R_f (7:1, hexane: ethyl acetate) 0.41; $[α]_D^{19}$ +54.8 (*c* 0.104, CHCl₃); v_{max} (film)/cm⁻¹ 2964, 2934, 2875, 1819, 1701, 1478, 1458, 1389, 1365, 1138, 1119, 774; δ_H (400 MHz, CDCl₃) 4.93-4.86 (1H, m, NCHCH₂), 4.68 (1H, d, *J* = 16.7 Hz, NCHH), 4.51 (1H, dd, *J* = 16.7, 4.3 Hz, NCH*H*), 1.87-1.77 (2H, m, NCHCH₂), 1.60-1.37 (2H, m, CH₂CH₂CH₃), 1.49 (9H, s, C(CH₃)₃), 0.95 (3H, t, *J* = 7.3 Hz, CH₂CH₂CH₃); δ_C (125 MHz, CDCl₃) 201.1 (C=O), 156.3 (C=O), 82.9 (NCHCH₂), 80.7 (*C*(CH₃)₃), 68.9 (NCH₂), 32.4 (NCH*C*H₂), 28.3 (C(*C*H₃)₃), 18.1 (CH₂CH₂CH₃), 13.9 (CH₂CH₂CH₃); MS (ES⁺) *m*/*z* 236 (MNa⁺); HRMS (ESI/TOF-Q) m/*z*: [M + Na]⁺ Calcd for C₁₁H₁₉NO₃Na 236.1257; Found 236.1254; 79% *ee* (determined by chiral GC analysis on a CP-ChiraSil-DEX CB 25m x 0.25mm x 0.25µm column, T = 130°C, P = 18 psi, He carrier gas, see Supporting Information).

(S)-2-(Isopropyl-3-oxoazetidine)-1-tert-butyl carboxylate (11)

(*S*)-1 (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 µl, 0.44 mmol), anhydrous THF (4 ml) and 2-iodopropane (48 µl, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave (*S*)-11 (44 mg, 52%) as a colourless yellow oil, R_f (7:1, hexane: ethyl acetate) 0.40; $[\alpha]_D^{28}$ +85.2 (*c* 0.260, CHCl₃); v_{max} (film)/cm⁻¹ 2966, 2931, 2875, 1818, 1704, 1460, 1387, 1366, 1174, 1120, 776; δ_H (500 MHz, CDCl₃) 4.76-4.71 (1H, m, NCHCH(CH₃)₂), 4.65 (1H, d, *J* = 16.7 Hz, NCHH), 4.44 (1H, dd, *J* = 16.7, 4.3 Hz, NCH*H*), 2.17 (1H, octet, *J* = 6.7 Hz, NCHCH(CH₃)₂), 1.49 (9H, s, NCHCH(CH₃)₃), 1.04 (3H, d, *J* = 6.9 Hz, NCHCH(CH₃CH₃)); δ_C (125 MHz, CDCl₃) 201.0 (C=O), 156.7 (C=O), 88.4 (NCHCH(CH₃)₂), 80.8 (*C*(CH₃)₃), 69.4 (NCH₂), 30.0 (NCHCH(CH₃)₂), 28.3 (C(CH₃)₃), 18.2 (CH(*C*H₃)CH₃)), 1.7.7 (CH(CH₃)*C*H₃)); MS (ES⁺) *m*/*z* 236 (MNa⁺); HRMS (ESI/TOF-Q) m/*z*: [M + Na]⁺ Calcd for C₁₁H₁₉NO₃Na 236.1257; Found 236.1255; 85% *ee* (determined by chiral GC analysis on a CP-ChiraSil-DEX CB 25m x 0.25mm x 0.25µm column, T = 130°C, P = 18 psi, He carrier gas, see Supporting Information).

(S)-2-(Benzyl-3-oxoazetidine)-1-tert-butyl carboxylate (12)

(S)-1 (113 mg, 0.40 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 µl, 0.44 mmol), anhydrous THF (4 ml) and benzyl bromide (57 µl, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 7:1, hexane: ethyl acetate) gave (*S*)-12 (60 mg, 57%) as a pale yellow oil, R_f (7:1, hexane: ethyl acetate) 0.31; $[\alpha]_D^{19}$ +65.5 (*c* 0.103, CHCl₃); v_{max} (film)/cm⁻¹ 2955, 2915, 2850, 1820, 1695, 1498, 1392, 1367, 1176, 1125, 776, 717, 703; δ_H (400 MHz, CDCl₃) 7.33-7.17 (5H, m, ArH), 5.15-5.09 (1H, m, NCHCH₂), 4.54 (1H, d, *J* = 16.6 Hz, NCHH), 4.05 (1H, dd, *J* = 16.6, 4.3 Hz, NCHH), 3.20 (1H, dd, *J* = 14.2, 6.4 Hz, NCHCHH), 3.11 (1H, dd, *J* = 14.2, 4.1 Hz, NCHCH*H*), 1.48 (9H, s, C(CH₃)₃); δ_C (125 MHz, CDCl₃) 199.8 (C=O), 155.6 (C=O), 135.5 (C, Ar), 129.8 (CH, Ar), 128.5 (CH, Ar), 127.0 (CH, Ar), 83.2 (NCHCH₂), 80.8 (*C*(CH₃)₃), 69.0 (NCH₂), 35.8 (NCHCH₂), 28.3 (C(CH₃)₃); MS (ES⁺) *m*/*z* 284 (MNa⁺); HRMS (ESI/TOF-Q) m/*z*: [M + Na]⁺ Calcd for C₁₅H₁₉NO₃Na 284.1257; Found 284.1266; 33% *ee* (determined by chiral HPLC on a Chiralcel OD column (0.46cm ø x 25 cm), 99:1 hexane:propan-2-ol, 0.5 ml/min, T = 23°C, detection wavelength = 254 nm, see Supporting Information).

(S,R)- and (S,S)-2-(-Hydroxy(phenyl)methyl-3-oxoazetidine)-1-tert-butyl carboxylate (13)

(*S*)-1 (113 mg, 0.4 mmol), *n*-butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and benzaldehyde (49 µL, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 4:1, hexane: ethyl acetate) gave (*S*)-13 (79 mg, 71%) as a yellow oil and inseparable 1.5:1 mixture of diastereomers; R_f (4:1, hexane: ethyl acetate) 0.29; v_{max} (film)/cm⁻¹ 3414, 2978, 2927, 1824, 1678, 1455, 1393, 1367, 1171, 1145, 1119, 768, 733; δ_H (500 MHz, CDCl₃) 7.38-7.29 (12.5H, m, ArH,), 5.27-5.18 (1H, m, NCHCH), 5.17-5.12 (1.5H, m, NCHCH), 5.10-5.03 (2.5H, m, NCHCH), 4.65 (2H, d, *J* = 16.5 Hz, NCHH, NCHH), 4.52 (1H, br s, COH), 4.47 (3H, dd, *J* = 16.5, 3.5 Hz, NCHH, NCHH), 1.50 (9H, s, C(CH₃)₃), 1.44 (13.5H, s,

C(CH₃)₃); δ_{C} (125 MHz, CDCl₃) 195.8 (CO), 195.6 (CO), 156.9 (COO), 156.3 (COO), 138.8 (C, Ar), 138.6 (C, Ar), 128.5 (CH, Ar), 128.42 (CH, Ar), 128.40 (CH, Ar), 128.1 (CH, Ar), 126.8 (CH, Ar), 126.5 (CH, Ar), 87.8 (NCHCH), 87.7 (NCHCH), 82.0 (C(CH₃)₃), 81.8 (C(CH₃)₃), 73.4 (NCHCH), 72.6 (NCHCH), 70.0 (NCH₂), 69.8 (NCH₂), 28.3 (C(CH₃)₃), 28.1 (C(CH₃)₃); MS (ES⁺) *m/z* 300 (MNa⁺); HRMS (ESI/TOF-Q) m/z: [M + Na]⁺ Calcd. for C₁₅H₁₉NO₄Na 300.1206; Found 300.1204; 31% (major diastereomer), 17% (minor diastereomer) *ee* (determined by chiral HPLC on a Chiralpak IA column (0.46cm \emptyset x 25 cm), 95:5 hexane:propan-2-ol, 0.5 ml/min, T = 25°C, detection wavelength = 254nm, see Supporting Information).

(S)-2-((2-Hydroxypropan-2-yl)-3-oxoazetidine)-1-tert-butyl carboxylate (14)

(*S*)-1 (113 mg, 0.40 mmol), *n*-butyllithium (2.35 M solution in hexanes, 187 µl, 0.44 mmol), anhydrous THF (4 ml) and acetone (36 µl, 0.48 mmol) were reacted according to the general procedure. Purification by flash column chromatography (SiO₂, 3:1, hexane: ethyl acetate) gave (*S*)-14 (54 mg, 59%) as a colourless oil, R_f (3:1, hexane: ethyl acetate) 0.34; $[\alpha]_D^{27}$ +38.2 (*c* 0.114, CHCl₃); v_{max} (film)/cm⁻¹ 3459, 2955, 2912, 2872, 2850, 1826, 1472, 1391, 1371, 1114, 1095, 717; δ_H (400 MHz, CDCl₃) 4.90-4.84 (1H, m, NCHCOH), 4.70 (1H, d, *J* = 16.6 Hz, NCHH), 4.56-4.47 (1H, m, NCHH), 1.51 (9H, s, C(CH₃)₃), 1.33 (3H, s, C(CH₃)(CH₃)OH), 1.30 (3H, s, C(CH₃)(CH₃)OH); δ_C (125 MHz, CDCl₃) 197.2 (C=O), 156.9 (C=O), 91.2 (NCHCOH), 82.0 (*C*(CH₃)₃), 71.2 (*C*(CH₃)₂OH), 70.0 (NCH₂), 28.2 (C(*C*H₃)₃), 26.1 C(*C*H₃)OH), 24.3 (C(CH₃)(*C*H₃)OH); MS (ES⁺) *m/z* 252 (MNa⁺); HRMS (ESI/TOF-Q) m/z: [M + Na]⁺ Calcd for C₁₁H₁₉NO₄Na 252.1206; Found 252.1204; 78% *ee* (determined by chiral HPLC on a Chiralcel OJ column (0.46cm ø x 25 cm), 9:1 hexane:propan-2-ol, 0.5 ml/min, T = 25°C, detection wavelength = 254 nm, see Supporting Information).

(2R,3S,3'S)-2-(2-Hydroxypropan-2-yl)-2',3',4',9'-tetrahydrospiro[azetidine-3,1'-pyrido[3,4b]indole]-1-tert-butyl-3'-methyl-dicarboxylate (15)

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To a stirred solution of 14 (123 mg, 0.54 mmol) in dry CH₃CN (6 ml) was added L-tryptophan methyl ester (142 mg, 0.65 mmol) and I₂ (6.8 mg, 0.027 mmol), and the mixture stirred at reflux for 18 h. The reaction mixture was cooled to room temperature and the solvent removed under reduced pressure. The residue was dissolved in EtOAc (20 ml), and washed with saturated Na₂S₂O₃ solution (10 ml), saturated sodium bicarbonate solution (10 ml) and brine (10 ml). The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography (SiO₂, 7:3, petroleum ether: ethyl acetate) gave 15 (188 mg, 81%) as a cream solid; m.p. 118-120 °C; R_f (7:3, petroleum ether: ethyl acetate) 0.46; $[\alpha]_{D}^{26}$ -44.0 (c 0.100, CHCl₃); v_{max} (film)/cm⁻¹ 3347, 2975, 2939, 2848, 1734, 1677, 1500, 1456, 1380, 1366, 1144, 1133, 747, 736; δ_H (300 MHz, CDCl₃) 8.40-8.25 (1H, br s, NH), 7.49 (1H, d, J = 7.7 Hz, ArH), 7.36 (1H, d, J = 8.0 Hz, ArH), 7.21 (1H, td, J = 7.6, 1.2 Hz, ArH), 7.15-7.10 (1H, m, ArH), 4.56 (1H, s, NCHC(CH₃)₂OH), 4.09 (1H, d, J = 8.6, NCHH), 3.98 (1H, d, J = 8.7, NCHH), 3.84 $(3H, s, CO_2CH_3)$, 3.70 (1H, dd, J = 11.2, 4.1 Hz, NHCHCH₂), 3.11 (1H, dd, J = 15.2, 4.1 Hz, NHCHCHH), 2.82 (1H, dd, J = 15.2, 11.2 Hz, NHCHCHH), 1.52 (9H, s, C(CH₃)₃), 1.49 (3H, s, C(CH₃)(CH₃)OH), 1.25 (3H, s, C(CH₃)(CH₃)OH), piperidine NH and OH not observed; $\delta_{\rm C}$ (125 MHz, CDCl₃) 172.9 (C=O), 158.0 (C=O), 136.4 (C, Ar), 134.2 (C, Ar), 126.7 (C, Ar), 122.6 (CH, Ar), 120.1 (CH, Ar), 118.4 (CH, Ar), 111.2 (CH, Ar), 109.3 (C, Ar), 81.2 (C(CH₃)₃), 77.6 (NCHC(CH₃)₂OH), 72.1 (NC(CH₃)₂OH), 63.9 (NCH₂), 56.4 (NHC), 53.6 (CO₂CH₃), 52.4 (NHCHCH₂), 28.4 (C(CH₃)₃), 26.4 $(C(CH_3)(CH_3)OH)$, 26.3 $(C(CH_3)(CH_3)OH)$, 25.2 $(NHCHCH_2)$; MS (ES^+) m/z 430 (MH^+) ; HRMS $(ESI/TOF-Q) m/z: [M + H]^+ Calcd for C_{23}H_{32}N_3O_5 430.2336; Found 430.2333.$

(2R,3S,3'S)-2-(2-Hydroxypropan-2-yl)-2',3',4',9'-tetrahydrospiro[azetidine-3,1'-pyrido[3,4-b]indole]-1-tert-butyl carboxylate-3'-N-methyl carboxamide (16)

A solution of **15** (40 mg, 0.0931 mmol) and 33% methylamine in ethanol (10 ml) were stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (SiO₂, ethyl acetate) to give **16** (29 mg, 73%) as a cream

solid; m.p. 247-248 °C; R_f (ethyl acetate) 0.30; $[\alpha]_D^{22} -91.3$ (*c* 0.260, CHCl₃); v_{max} (film)/cm⁻¹ 3291, 2972, 1657, 1393, 1366, 1133, 741; δ_H (500 MHz, CDCl₃) 8.14 (1H, br s, NH), 7.49 (1H, d, *J* = 7.9 Hz, ArH), 7.35 (1H, d, *J* = 8.1 Hz, ArH), 7.22 (1H, t, *J* = 7.5 Hz, ArH), 7.14 (1H, t, *J* = 7.4 Hz, ArH), 6.63-6.58 (1H, br m, NH), 4.53 (1H, s, CHC(CH₃)₂OH), 4.02 (1H, d, *J* = 8.7 Hz, CHHN), 3.97 (1H, d, *J* = 8.7 Hz, CHHN), 3.55-3.50 (1H, m, NCHCO), 3.21 (1H, dd, *J* = 15.6, 4.4 Hz, CHHCHCO), 2.92 (3H, d, *J* = 4.9 Hz, NCH₃), 2.74 (1H, dd, *J* = 15.6, 11.3 Hz, CHHCHCO), 2.69-2.50 (1H, br s, OH), 1.51 (12H, br s, C(CH₃)₃ and C(CH₃)(CH₃)OH), 1.26 (3H, s, C(CH₃)(CH₃)OH), piperidine NH not observed; δ_C (125 MHz, CDCl₃) 173.1 (C=O), 158.0 (C=O), 136.4 (C, Ar), 134.1 (C, Ar), 126.8 (C, Ar), 122.8 (CH, Ar), 120.2 (CH, Ar), 118.6 (CH, Ar), 111.2 (CH, Ar), 109.6 (C, Ar), 81.4 (C(CH₃)₃), 77.0 (CHCMe₂OH), 72.0 (CMe₂OH), 63.2 (CH₂N), 56.4 (CH₂CNH), 55.1 (CHCO), 28.3 (C(CH₃)₃), 26.8 (CH₃), 26.6 (CH₃), 26.2 (CH₃), 25.6 (CH₂CHCO); MS (ES⁺) *m*/z 252 (MNa⁺); HRMS (ESI/TOF-Q) m/z; [M + Na]⁺ Calcd for C₂₃H₃₂N₄O₄Na 451.2316; Found 451.2315.

ASSOCIATED CONTENT

Supporting Information

Copies of ¹H and ¹³C NMR spectra of compounds **1** and **3-16**, the X-ray crystal structure of compound **16**, and copies of chiral GC and HPLC chromatograms of racemic and enantiomerically enriched **4** and **7-14**. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

We thank the EPSRC and the University of Warwick for financial support. We are grateful to Professor Martin Wills and Dr. Roy Hodgkinson for providing advice and access to chiral GC and HPLC instruments. The Oxford Diffraction Gemini XRD system for X-ray structure determination was obtained, through the Science City Advanced Materials project: Creating and Characterizing Next Generation Advanced Materials, with support from Advantage West Midlands.

REFERENCES

(1) For examples see: (a) Melloni, P.; Della Torre, A.; Meroni, M.; Ambrosini, A.; Rossi, A. C. J. Med. Chem. 1979, 22, 183. (b) Kobayashi, J.; Cheng, J-F.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. J. Chem. Soc., Perkin Trans. 1 1991, 1135. (c) Frigola, J.; Torrens, A.; Castrillo, J. A.; Mas, J.; Vañó, D.; Berrocal, J. M.; Calvet, C.; Salgado, L.; Redondo, J.; García-Granda, S.; Valentí, E.; Quintana, J. R. J. Med. Chem. 1994, 37, 4195. (d) Kim, J-S.; Kim, J-C.; Lee, S.; Lee, B-H.; Cho, K. Y.; Aquatic Botany 2006, 85, 1. (e) Faust, M. R.; Höfner, G.; Pabel, J.; Wanner, K. T. Eur. J. Med. Chem. 2010, 45, 2453. (f) Pérez-Faginas, P.; Aranda, M. T.; García-López, M. T.; Snoeck, R.; Andrei, G.; Balzarini, J.; González-Muñiz, R. Bioorg. Med. Chem. 2011, 19, 1155. (g) Nakamura, T.; Asano, M.; Sekiguchi, Y.; Mizuno, Y.; Tamaki, K.; Nara, F.; Kawase, Y.; Yabe, Y.; Nakai, D.; Kamiyama, E.; Urasaki-Kaneno, Y.; Shimozato, T.; Doi-Komuro, H.; Kagari, T.; Tomisato, W.; Inoue, R.; Nagasaki, M.; Yuita, H.; Oguchi-Oshima, K.; Kaneko, R.; Nishi, T. Eur. J. Med. Chem. 2012, 51, 92. (h) Glawar, A. F. G.; Jenkinson, S. F.; Thompson, A. L.; Nakagawa, S.; Kato, A.; Butters, T. D.; Fleet, G. W. J. ChemMedChem 2013, 8, 658. (i) Yun, J.; Han, M.; Song, C.; Cheon, S. H.; Choi, K.; Hahn, H-G. Bioorg. Med. Chem. Lett. 2014, 24, 3234.

(2) For example see: Burkhard, J. A.; Guérot, C.; Knust, H.; Carreira, E. M. Org. Lett. 2012, 14, 66.

(3) Oizumi, K.; Nishino, H.; Koike, H.; Sada, T.; Miyamoto, M.; Kimura, T. Japan. J. Pharmacol.

, *51*, 57.

(4) Reddy, B. V. S.; Kishore, Ch.; Reddy, A. S. Tetrahedron Lett. 2014, 55, 49.

(5) Gerlach, K.; Priepke, H.; Wienen, W.; Schuler-Metz, A.; Nar, H. PCT Appl. **2008**, WO 2008135525, A2 20081113.

(6) Desroy, N.; Joncour, A.; Bock, X.; Housseman, C.; Peixoto, C.; Bienvenu, N.; Labeguere, V.;

Cherel, L.; Annoot, D.; Christophe, T. Abstracts of Papers, 251st ACS National Meeting, 2016, San

Diego, CA, United States, 13-17th March.

(7) For reviews of azetidine synthesis see: (a) Cromwell, N. H.; Philips, B. Chem. Rev. 1979, 79, 331.

(b) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. Chem. Rev. 2002, 102, 29. (c)

Brandi, A.; Cicchi, S.; Cordero, F. M. Chem. Rev. 2008, 108, 3988. For recent examples of azetidine

synthesis see: (d) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. J. Am. Chem. Soc. 2011,

133, 17634. (e) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. J. Am. Chem. Soc. 2012, 134, 3. (f) Narhe,

B. D.; Sriramurthy, V.; Yadav, V. K. Org. Biomol. Chem. 2012, 10, 4390. (g) Biswas, T.; Mukherjee, J.

P.; Chattopadhyay, S. K. Tetrahedron: Asymmetry 2012, 23, 1416. (h) Miao, D-B.; Dong, C-P.; Zhang,

M.; Ren, W-L.; Meng, Q.; Sun, X-Q.; Yang, H-T. J. Org. Chem. 2013, 78, 4329. (i) Alcaide, B.;

Almendros, P.; Aragoncillo, C.; Gómez-Campillos, G. Adv. Synth. Catal. 2013, 355, 2089. (j) Martínez,

R. F.; Fleet, G. W. J. Tetrahedron: Asymmetry 2014, 25, 373. (k) Burke, E. G.; Schomaker, J. M.

Angew. Chem. Int. Ed. 2015, 54, 12097. (1) Han, S.; Zard, S. Z. Tetrahedron 2015, 71, 3680. (m)

Dowling, M. S.; Fernando, D. P.; Hou, J.; Liu, B.; Smith, A. C. J. Org. Chem. 2016, 81, 3031.

(8) (a) Podlech, J.; Seebach, D. Helv. Chim. Acta 1995, 78, 1238. (b) Wang, J.; Hou, Y.; Wu, P. J.

Chem. Soc., Perkin Trans. 1 1999, 2277. (c) Hanessian, S.; Fu, J-M. Can J. Chem. 2001, 79, 1812. (d)

Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. J. Org. Chem. 2002, 67, 3169. (e) Burtoloso, A. C. B.;

Correia, C. R. D. Tetrahedron Lett. 2004, 45, 3355. (f) Burtoloso, A. C. B.; Correia, C. R. D. J. Organomet. Chem. 2005, 5636.

(9) Ye, L.; He, W.; Zhang, L. Angew. Chem. Int. Ed. 2011, 50, 3236.

(10) Jensen, K. L; Nielsen, D. U.; Jamison, T. F. Chem. Eur. J. 2015, 21, 7379.

(11) Hodgson, D. M.; Mortimer, C. L.; McKenna, J. M. Org. Lett. 2015, 17, 330.

(12) Ghorai, M. K.; Das, S.; Das, K.; Kumar, A. Org. Biomol. Chem. 2015, 13, 9042.

(13) Senter, T. J.; O'Reilly, M. C.; Chong, K. M.; Sulikowski, G. A; Lindsley, C. W. *Tetrahedron Lett*.**2015**, *56*, 1276.

(14) For a review on SAMP/RAMP-hydrazones see: Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.;Enders, D. *Tetrahedron* 2002, *58*, 2253.

(15) Geden, J. V.; Beasley, B. O.; Clarkson, G. J.; Shipman, M. J. Org. Chem. 2013, 78, 12243.

(16) For examples see: (a) Barré, B.; Gonnard, L.; Campagne, R.; Reymond, S.; Marin, J.; Ciapetti, P.;

Brellier, M.; Guérinot, A.; Cossy, J. Org. Lett. 2014, 16, 6160. (b) Parmar, D.; Henkel, L.; Dib, J.;

Rueping, M. Chem. Commun. 2015, 51, 2111. (c) Dobi, Z.; Holczbauer, T.; Soós, T. Org. Lett. 2015, 17, 2634.

(17) For examples see: (a) Ishida, N.; Yuhki, T.; Murakami, M. Org. Lett. 2012, 14, 3898. (b) Ho, K. Y.

T.; Aïssa, C. Chem. Eur. J. 2012, 18, 3486. (c) Kumar, P.; Louie, J. Org. Lett. 2012, 14, 2026. (d)

Ishida, N.; Shimamoto, Y.; Yano, T.; Murakami, M. J. Am Chem. Soc. 2013, 135, 19103. (e) Thakur,

A.; Facer, M. E.; Louie, J. Angew. Chem. Int. Ed. 2013, 52, 12161.

(18) (a) Hodgson, D. M.; Kloesges, J. Angew. Chem. Int. Ed. 2010, 49, 2900. (b) Parisi, G.; Capitanelli,

E.; Pierro, A.; Romanazzi, G.; Clarkson, G. J.; Degennaro, L.; Luisi, R. Chem. Comm. 2015, 51, 15588.

(c) Jackson, K. E.; Mortimer, C. L.; Odell, B.; McKenna, J. M.; Claridge, T. D. W.; Paton, R. S.;

Hodgson, D. M. J. Org. Chem. 2015, 80, 9838. (d) Rayner, P. J.; Smith, J. C.; Denneval, C.; O'Brien,

P.; Clarke, P. A.; Horan, R. A. J. Chem. Comm. 2016, 52, 1354.

(19) The overall yield of racemic ketone **4** prepared by the two-step alkylation/hydrolysis sequence from achiral hydrazone **5** was found to be lower (47%). We speculate that the methoxy group of SAMP hydrazone **1** aids metalation via a complex-induced proximity effect (CIPE).

(20) Attempts to form racemic **4** by direct formation of the enolate of *N*-Boc-azetidin-3-one with ^{*t*}BuLi at -78 $^{\circ}$ C, with subsequent trapping with allyl bromide, gave the carbinol as a result of direct addition of the organolithium to the ketone.

(21) Beasley, B. O.; Alli-Balogun, A.; Clarkson, G. J.; Shipman, M. Tetrahedron Lett. 2014, 55, 541.

(22) (a) Hazelard, D.; Fadel, A. Tetrahedron: Asymmetry 2005, 16, 2067. (b) Koch, R. Org. Biomol.

Chem. 2011, 9, 2885.