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Synthesis of chiral bicyclic azetidine derivatives

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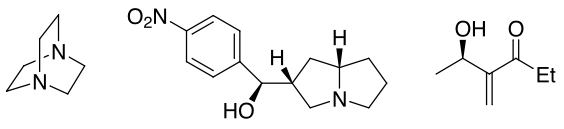
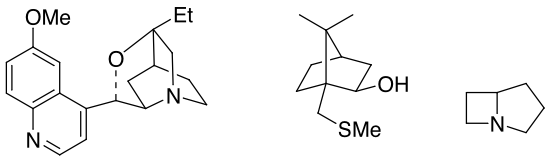
Abstract—(2*S*)-*N*-Benzoyl-2-azetidinecarboxylic acid was converted into several derivatives of (5*R*)-1-azabicycloheptane via lactamization of 3-((2*R*)-azetidine)propanoic acid, subsequent aldol reaction and reduction. The structures of three stereoisomers of (5*R*)-3-(hydroxy-(4-nitrophenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one were determined by X-ray crystallography. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The Baylis–Hillman reaction is a convenient process for the preparation of a β-hydroxy-α-methylene-ketone, -nitrile or -ester, etc. in one step from an α,β-unsaturated ketone, acrylonitrile or an acrylic ester and an aldehyde.[1] The reaction is mediated by a tertiary amine and DABCO (**1**) is the most common catalyst employed. Whilst the Baylis–Hillman reaction of chiral aldehydes or chiral Michael acceptors has been shown to proceed, in some cases, with high diastereoselectivities, the development of chiral catalysts for the Baylis–Hillman reaction is less well developed. Hirama and Markó have, respectively, reported the use of chiral derivatives of diazabicyclo[2.2.2]octane[2] and of quinidine or cinchonine[3] as enantioselective catalysts. However, these authors observed only modest levels of enantioselectivities (ee 11–47% and 6–45%, respectively) and the requirement to use elevated pressures (3–10 kbar) to ensure acceptable conversions. We have published a two step procedure to effect the enantioselective (ee 50–96%) Baylis–Hillman reaction of an aldehyde with an α-methylene-ketone via a tandem Michael addition/aldol reaction of (phenylthio)- or (phenylselenyl)-trimethylsilane catalysed by a chiral borane Lewis acid followed by oxidative elimination.[4] Soai and co-workers described the use of (*S*)-BINAP as a catalyst for the enantioselective (ee 9–44%) Baylis–Hillman reaction of pyrimidine-5-carbaldehydes with acrylate esters.[5] We have also reported the use of pyrrolizidine (azabicyclo[3.3.0]heptane) derivatives as alternative chiral catalysts.[6] For example, hydroxyamine **2** mediated the Baylis–Hillman reaction of electron deficient aldehydes with ethyl vinyl ketone to provide the adducts **3** (17–93%; 21–78% ee). Recently, Hatakeyama and co-workers have reported that the catalytic enantioselective Baylis–Hillman reaction of 1,1,1,3,3,3-hexafluoro-2-propyl acrylate with aldehydes mediated by the quinidine derivative **4** proceed with excellent enantioselectivities (91–99% ee).[7] Additionally, the hydroxy sulfide **5** has been used as a catalyst in the presence of titanium tetrachloride to produce Baylis–Hillman adducts (ee <74%).[8] Herein we report the synthesis of derivatives of 1-azabicyclo[3.2.0]heptane **6** and their assay as catalysts for Baylis–Hillman reactions. We considered that such tertiary amines might be more active than pyrrolizidine systems since the nitrogen lone pair is more accessible due to the increased pyramidalization. We were concerned, in this venture, to seek to alleviate the slow kinetics of most amine and phosphine catalysts for the Baylis–Hillman reaction.



1 **2** **3**



4 **5** **6**

2. Results and discussion

Initially we sought to prepare derivatives of amine **6** from a chiral β-lactam precursor by reduction to the corresponding azetidine and elaboration of the 5-membered ring. Reduction of β-lactam **7** with excess chloroalane[9] in diethyl ether gave the corresponding azetidinemethanol **8** with simultaneous reduction of the ester (89%). This amine was most conveniently isolated as its 4-toluenesulfonate salt. Azetidinemethanol **8** was examined as a potential catalyst

Keywords: azetidine; azetidinone; bicyclic heterocyclic compounds; Baylis–Hillman reactions; aldol reactions.

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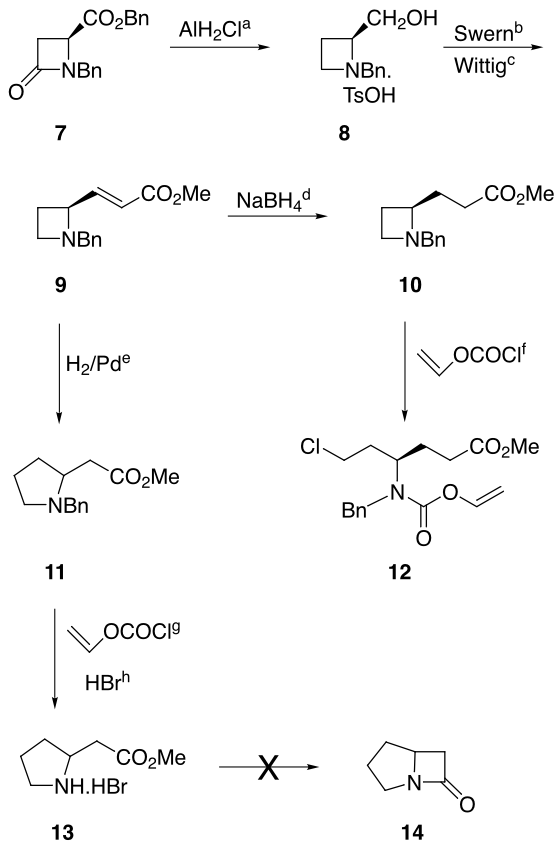
for the Baylis–Hillman reaction but was found to be ineffective in catalyzing the reaction of 2-nitrobenzaldehyde with ethyl vinyl ketone. Swern oxidation of alcohol **8**, followed by in situ Wittig homologation[10] gave the unsaturated ester **9** in 68% overall yield. We planned to effect hydrogenation of the alkene with simultaneous hydrogenolysis of the benzyl ester, hence setting up the system for closure to the corresponding 1-azabicyclo[3.2.0]-heptan-2-one. When alkene **9** was submitted to hydrogenation, a complex mixture of products was obtained, among which the pyrrolidine **11** (20%) could be isolated. Presumably this arose from scission of the allylic C–N bond followed by Michael addition to the α,β-unsaturated ester. Presumably strain in the azetidine ring accelerates this unfortunate event. The structure of pyrrolidine **11** was unequivocally assigned by 2-dimensional NMR spectroscopy. No *N*-debenzylated compounds were detected in any of these experiments.

We next sought to convert pyrrolidine **11** into the bicyclic β-lactam **14**. Debenzylation of amine **11** was achieved by reaction with vinyl chloroformate[11] to afford the corresponding carbamate in 78% yield. This was cleaved by reaction with hydrogen bromide in acetic acid[12] to yield the salt **13** as a white crystalline solid (76%). Unfortunately, all attempts to elaborate the β-lactam **14** by cyclization of the amino ester derived from bromide **13** were unsuccessful. This lactam **14** is a known compound[13] which was previously prepared in low yields and which readily polymerizes on standing.[14] In contrast to the hydrogenation reaction, reaction of the α,β-unsaturated ester **9** with sodium borohydride in methanol gave the azetidine ester **10** in 72% yield. The structure of **10** was assigned spectroscopically and unequivocally confirmed by reaction of the derived enol silane with phenylselenyl bromide, Se-oxidation in the presence of 4-toluenesulfonic acid and *syn*-elimination of the selenoxide to reform the starting unsaturated ester **9** (43%). Unfortunately, attempted deprotection of amine **10** with vinyl chloroformate resulted in azetidine ring scission and the formation of intractable mixtures including the carbamate **12** (48%). Other debenzylation techniques all proved ineffective thereby precluding further transformations to the desired bicyclic amine.

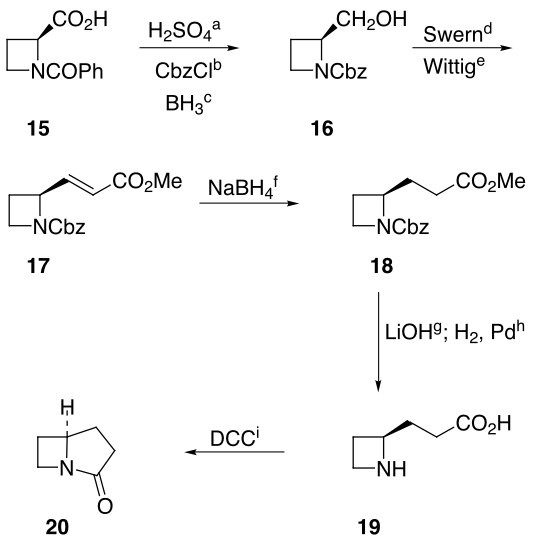
In the light of the problems associated with the synthesis of derivatives of amine **6** from a β-lactam, we sought an alternative route to the required bicyclic amines. Our planning was brought to sharp focus by the receipt of a generous gift of (2*S*)-*N*-benzoylazetidinecarboxylic acid **15**[15] by Chirotech Technology Limited. (2*S*)-*N*-Benzoyl-azetidinecarboxylic acid **15** (95.1% ee) was recrystallized from water to obtain material with an enantiomeric purity of 98.4% as determined by chiral HPLC. Hydrolysis of amide **15** with aqueous sulfuric acid gave the corresponding acid, which was Cbz protected and reduced with borane to produce the azetidinemethanol derivative **16** in 59% overall yield.[16] (Schemes 1 and 2). Subsequent Swern oxidation and direct Wittig homologation in situ gave the unsaturated ester **17** (67%) which was reduced without rearrangement to ester **18** (100%) by treatment with sodium borohydride and copper(I) chloride in methanol.[17] Ester **18** was saponified by reaction with lithium hydroxide, followed by acidification with potassium hydrogensulfate to provide the corresponding carboxylic acid in 87% yield. Subsequent debenzylation by hydrogenation over palladium in methanol gave the desired amino-acid **19** as a stable white crystalline solid in 93% yield. In contrast, attempted synthesis of the corresponding methyl ester by the direct hydrogenolysis of carbamate **18** resulted in extensive decomposition. Cyclization of the amino acid **19** was carried out using dicyclohexyl carbodiimide[18] in dichloromethane to provide the surprisingly volatile γ-lactam **20** (51%).



Reagents and conditions: (a) $LiAlH_4$, $AlCl_3$, Et_2O, Δ; $TsOH.H_2O$ (89%); (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C; (c) $Ph_3P{=}CHCO_2CH_3$, 0 °C (68%); (d) $NaBH_4$, MeOH (72%); (e) H_2, Pd/C, MeOH, (20%); (f) $CH_2{=}CHOCOCl$, CH_2Cl_2, 0 °C (48%); (g) $CH_2{=}CHOCOCl$, CH_2Cl_2, 0 °C (78%); (h) 45% HBr, AcOH (76%).

Scheme 1.

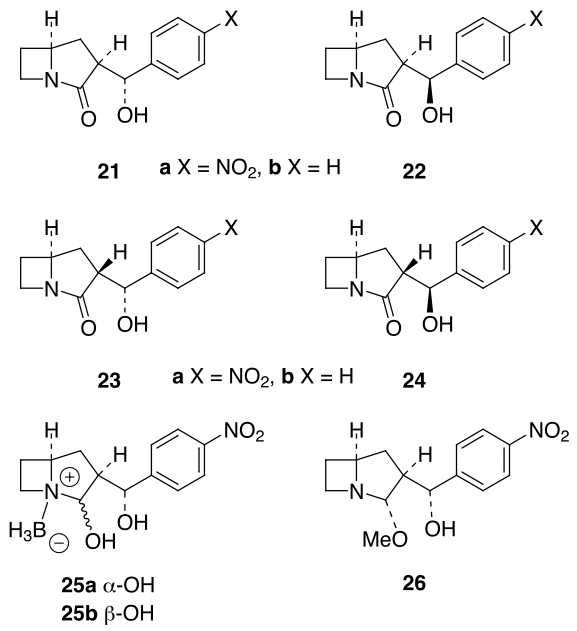
Our next objective towards the synthesis of the target potential Baylis–Hillman catalyst was the introduction of the aromatic side chain via an aldol reaction and subsequent reduction of the γ-lactam to the corresponding amine. Thus reaction of the lithium enolate, derived from lactam **20** and lithium 2,2,6,6-tetramethylpiperidide, with a premixed solution of boron trifluoride etherate and 4-nitrobenzaldehyde in THF gave a mixture of four diastereoisomeric β-hydroxy-lactams **21a**–**24a** (67%). Repeated chromatography afforded the pure isomers **21a** (20%) and **22a** (6%), whilst **23a** and **24a** (41%) were obtained as a mixture. Separation of a sample of the isomer mixture on a chromatotron and recrystallization gave a sample of the



Reagents and conditions: (a) H_2SO_4, H_2O, Δ; (b) CbzCl, $NaHCO_3$, H_2O; (c) BH_3.THF, THF, 0 °C (59% 3 steps); (d) $(COCl)_2$, DMSO, Et_3N, -78 to -40°C; (e) $Ph_3P{=}CHCO_2CH_3$, 0 °C (67% 2 steps); (f) $NaBH_4$, CuCl, MeOH, 0 °C (99%); (g) LiOH, dioxane, H_2O; $KHSO_4$, H_2O (87%); (h) H_2, Pd/C, MeOH (93%); (i) DCC, CH_2Cl_2 (51%).

Scheme 2.

single isomer **24a**. X-Ray crystallographic analyses of **21a** (Fig. 1), **22a** (Fig. 2) and **24a** (Fig. 3) allowed for an assignment of the stereochemistry for all four stereoisomers. It is clear from these results that the aldol reaction occurred preferentially on the less hindered *exo*-face of the bicyclic lactam **20**, as had been observed for the analogous 1-azabicyclo[3.3.0]octane system.[6] Isomer **21a** has the same absolute configuration as the 1-azabicyclo[3.3.0]octane analog **2** and was thus chosen for further investigation.



Reduction of lactam **21a** with borane–dimethyl sulfide in THF at reflux gave a mixture of the borane-complexed

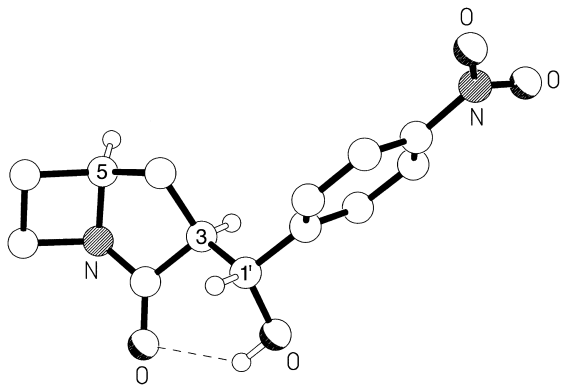


Figure 1. The molecular structure and absolute configuration of **21a**. The intramolecular O–H···O hydrogen bond has O···O, H···O distances of 2.77 and 2.07 Å with an O–H···O angle of 134°.

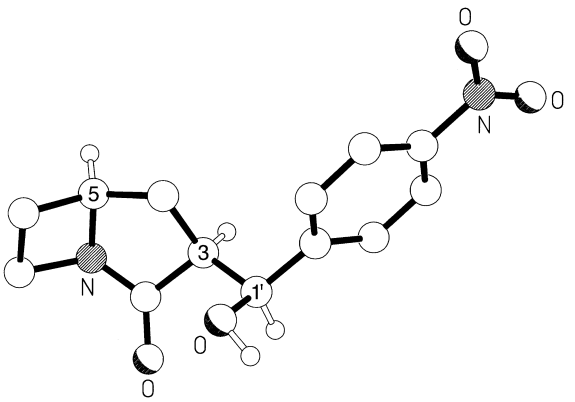


Figure 2. The structure and absolute configuration of **22a**. The hydroxy group forms an intermolecular O–H···O hydrogen bond to the carbonyl oxygen of a screw-related molecule; the O···O, H···O distances are 2.73 and 1.83 Å with an O–H···O angle of 176°.

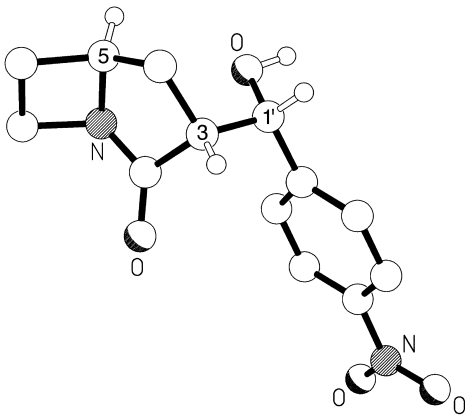


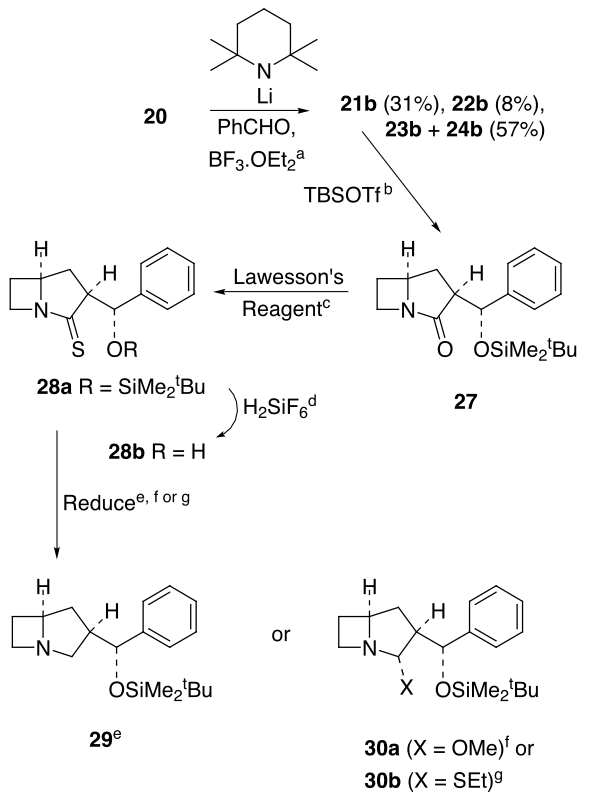
Figure 3. The structure and absolute configuration of **24a**. The hydroxy group forms an intermolecular O–H···O hydrogen bond to the carbonyl oxygen of a screw-related molecule; the O···O, H···O distances are 2.77 and 1.87 Å with an O–H···O angle of 173°.

hemi-aminals **25a** and **25b** rather than the required bicyclic amine–borane complex. The hemi-aminals **25a** and **25b** showed characteristic NMR signals at 97.7 ppm in the ^{13}C spectrum and −17 ppm in the ^{11}B NMR spectrum. The ratio of epimers **25a** and **b** varied with the temperature of the borane reduction. Reduction in THF at reflux gave **25a** and

b (3:1 ratio, 84%), differing in their configuration at the C-2 centre. In contrast, reduction at room temperature gave only one diastereoisomer but upon heating of the crude product the other diastereoisomer was generated, probably via a ring opening-ring closing mechanism. The stereochemistry of epimers **25a** and **b** was tentatively assigned on the basis of their ^{1}H NMR spectra. In view of the vicinal proton couplings observed for the two isomers (4.4 and 8.9 Hz) and by application of the Karplus equation, the configuration at C-2 was assigned as *S* for **25a** (J=8.9 Hz) and *R* for **25b** (J=4.4 Hz). The ^{1}H NMR spectrum of **25b** also revealed the existence of hydrogen bonding, which accounted for the difference in polarity between the two. Methanolysis of the borane complex **25a** in the presence of toluenesulfonic acid gave the methoxy derivative **26** (75%). Attempts to further reduce **25a** and **b** to the corresponding bicyclic amine using borane were unsuccessful. Presumably, formation of the requisite iminium ion was sufficiently disfavoured by the azetidine ring strain.

The presence of the aromatic nitro group in lactam **21a** precluded the use of other more potent reducing agents. As a result investigations continued with the aldol product derived from lactam **20** and benzaldehyde. Sequential reaction of lactam **20** with lithium 2,2,6,6-tetramethylpiperidide and benzaldehyde as above gave the adducts **21b**–**24b** (96% combined yield) (Scheme 3). Their stereochemistries were assigned by comparison of ^{1}H NMR spectra with those of γ-lactams **21a**–**24a**. Attempted reduction of lactam **21b** using lithium aluminum hydride gave intractable mixtures of products. Protection of the hydroxyl group in lactam **21b** with *t*-butyldimethylsilyl triflate[19] gave ether **27** (82%) which was subjected to thionation using Lawesson's reagent,[20] 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, to provide the thionolactam **28a** in 81% yield. Deprotection of the silyl ether **28a** using hexafluorosilicic acid[21] in acetonitrile gave the corresponding alcohol **28b** (80%). Reduction of the thionolactam **28a** using Raney nickel in ethanol at reflux[22] was a fickle reaction but gave variable yields (0–100%) of the unstable bicyclic amine **29**. The reproducibility of the yield of the reaction to produce **29** was the least capricious with freshly prepared Raney nickel. Alternatively, reduction of the thionolactam **28a** using sodium borohydride in methanol gave the methoxy derivative **30a** (32%) whereas reduction via S-ethylation and sodium cyanoborohydride reduction[23] gave the corresponding sulfide **30b** (50%).

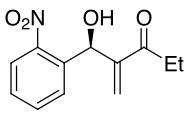
The small sample of the tertiary amine **29** was examined as a catalyst for the Baylis–Hillman reaction of 2-nitrobenzaldehyde with ethyl vinyl ketone at −30°C. The ketone was rapidly consumed over 2 h to provide the adduct **31** (70, 26% ee). It was clear from the rate of reaction that azabicyclo[3.2.0]heptane is more nucleophilic than azabicyclo[3.3.0]octane since the same Baylis–Hillman reaction with the catalyst **2** was significantly slower.[6] This enhancement in catalytic activity is probably the result of increased pyramidalization of the nitrogen atom imposed by the 4-membered ring. However, significant difficulties in the reduction of the key γ-lactam **21b** precluded further investigations and significantly reduced the attractiveness of these azabicyclo[3.2.0]heptanes as catalysts. Nonetheless, the use of ring-fused azetidines may remain a valuable



Reagents and conditions: (a) lithium tetramethylpiperidide, THF, -78 to -30 °C; PhCHO, $BF_3.OEt_2$, -78 °C (96%); (b) ^{t}BuMe$_2$SiOTf, 2,6-lutidine, CH_2Cl_2 (82%); (c) PhMe, Lawesson's reagent, Δ (81%); (d) H_2SiF_6, MeCN, 0 °C (80%); (e) Raney nickel, EtOH, Δ; (f) $NaBH_4$, $NiCl_2.6H_2O$, MeOH (32%); (g) $Et_3O.BF_4$, CH_2Cl_2, 0 °C; $NaBH_3CN$, MeOH (50%).

Scheme 3.

strategy for the development of nucleophilic catalysts in cases where the synthetic challenges can be overcome.



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3. Experimental

3.1. General

Chiral analytical HPLC was carried out using hexanes and EtOH mixtures using a ATI Unicam Crystal 200 quaternary pump with an ATI Unicam Crystal 240 diode array detector (210–350 nm). Chiral separations were achieved using Diacel Chiracel OD-H and Diacel Chirapak AD columns. All manipulations of air or moisture sensitive materials were carried out in oven or flame dried glassware under N_2 using purified[24] and dried solvents (PhMe, THF, Et_2O, CH_2Cl_2). Solvents for chromatography (EtOAc, CH_2Cl_2, MeOH, and Et_2O) were ACS reagent grade or GPR grade and were used

as received except hexanes, which was distilled before use. Et_3N, diisopropylamine and pyridine were distilled from CaH_2 under N_2. PhCHO, 2,2,6,6-tetramethylpiperidine, Me_3SiCl and 2,6-lutidine were redistilled. 2-Nitrobenzaldehyde and 4-nitrobenzaldehyde were filtered through silica with hexanes and evaporated before use. Flash chromatography was carried out on BDH silica gel 60, 230–400.

3.1.1. Benzyl (4*S*)-1-benzyl-2-oxoazetidine-4-carboxylate (7). Dibenzyl L-aspartate 4-toluenesulfonate[25] (60.0 g, 0.124 mol), Na_2CO_3 (65.7 g, 0.62 mol) and $PhCH_2Br$ (14.75 mL, 0.124 mol) in DMF (250 mL) was stirred for 12 h. The mixture was diluted with H_2O (300 mL) and extracted with Et_2O (4×20 mL). The combined organic phases were washed with H_2O (10 mL) and dried (Na_2SO_4). Filtration and rotary evaporation gave an oil, which was dissolved in Et_2O and treated with 45% HBr in AcOH (22.5 mL). The white precipitate was collected by filtration, and dried in vacuo, to yield dibenzyl *N*-benzyl-L-aspartate hydrobromide (52.8 g, 91%), mp 152–154°C. This salt was dissolved in H_2O (100 mL) and K_2CO_3 (34.6 g, 0.25 mol) was added and the mixture was stirred for 30 min. It was extracted with Et_2O (3×20 mL) and the combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). Filtration and rotary evaporation gave dibenzyl *N*-benzyl-L-aspartate (34.35 g, 80%) as an oil, which was carried on without further purification. *t*-BuMgCl in Et_2O (2.0 M; 51.0 mL, 0.102 mol) was added slowly with stirring to the amine in Et_2O (700 mL) at 0°C and stirring continued for 10 h. Saturated aqueous NH_4Cl (300 mL) was added and the aqueous phase extracted with Et_2O (3×30 mL). The combined organic phases were washed with H_2O (20 mL) and dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 5:1) gave lactam **7** (14.35 g, 55%) as a yellow oil: R_f 0.5 (hexanes/EtOAc 3:1); $[\alpha]_D^{20}=-39.6$ (c=2.1, $CHCl_3$); IR (neat) 1760, 1184, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.18 (m, 10H), 5.14 (s, 2H), 4.77 (d, 1H, J=14.9 Hz), 4.15 (d, 1H, J=14.9 Hz), 3.97 (dd, 1H, J=2.5, 5.6 Hz), 3.22 (dd, 1H, J=5.6, 14.5 Hz), 3.05 (dd, 1H, J=2.5, 14.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 165.7, 135.0, 134.8, 128.9, 128.8, 128.6, 128.5, 129.0, 67.3, 50.1, 45.7, 41.9; CI-MS *m/e* 313 $[M+NH_4]^+$, 296 $[M+H]^+$, 204, 108, 91; HRMS calcd for $C_{18}H_{18}NO_3$: 296.1287, found: 296.1291. Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.19; H, 5.81; N, 4.74. Found: C, 72.99; H, 5.87; N, 4.72.

3.1.2. (2*S*)-1-Benzylazetidine-2-methanol (8).[26] $AlCl_3$ (9.5 g, 71.4 mmol) was slowly added over 20 min with stirring to $LiAlH_4$ (2.7 g, 71.0 mmol) in Et_2O (50 mL) and the resulting mixture was heated to reflux for 30 min. β-Lactam **7** (4.2 g, 14.2 mmol) in Et_2O (20 mL) was slowly added with stirring and reflux continued for 4 h. After cooling to room temperature, EtOAc (5 mL) and ethanolamine (30 mL) were added and the mixture stirred overnight. After filtration to remove the aluminum salts, the filtrate was extracted with CH_2Cl_2 (4×20 mL). The combined organic phases were washed with brine (30 mL) and dried (Na_2SO_4). Filtration and rotary evaporation gave an oil (3.6 g), which was dissolved in Et_2O (15 mL), prior to the addition of $TsOH{\cdot}H_2O$ (2.2 g, 1.1 equiv.) in THF (10 mL) and the mixture stirred for 30 min. Rotary evaporation gave an oil, which, upon trituration with Et_2O, gave *(2S)-1-benzylazetidine-2-methanol 4-toluenesulfonate* (4.4 g, 89%) as a yellow solid. An aliquot was treated with K_2CO_3 in H_2O for 30 min and the aqueous layer was extracted with CH_2Cl_2 and dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (EtOAc) gave a sample of the free base azetidine **8** as a yellow oil: $[\alpha]_D^{20}=-17.6$ (c=0.5, $CHCl_3$); IR (neat) 3391, 1495, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H), 3.69 (d, 1H, J=12.8 Hz), 3.59 (d, 1H, J=12.8 Hz), 3.47–3.41 (m, 2H), 3.35–3.28 (m, 2H), 2.95 (m, 1H), 2.25–2.15 (m, 1H), 2.04–1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.7, 128.4, 127.3, 66.8, 62.1, 61.8, 51.4, 18.6; CI-MS *m/e* 178 $[M+H]^+$, 146, 108, 91; HRMS calcd for $C_{11}H_{16}NO$: 178.1232, found: 178.1230. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.53; H, 8.54; N, 7.91. Found: C, 74.29; H, 8.51; N, 7.61.

3.1.3. Methyl (2*S*)-3-(1-benzylazetidin-2-yl)prop-2*E*-enoate (9). DMSO (0.6 mL, 8.6 mmol) was added dropwise with stirring to oxalyl chloride (0.5 mL, 5.7 mmol) in CH_2Cl_2 (10 mL) at −78°C. After 20 min, (2*S*)-1-benzylazetidine-2-methanol 4-toluenesulfonate (1.0 g, 2.8 mmol) in CH_2Cl_2 (5 mL) was slowly added and the mixture was allowed to warm up to −35°C over 2 h. Et_3N (2.0 mL, 14.3 mmol) was added and the resulting suspension was stirred for 1 h, allowing the temperature to rise to 0°C. $Ph_3P{=}CHCO_2Me$ (2.9 g, 8.7 mmol) was added and the mixture was warmed to room temperature and stirred overnight. Aqueous NaOH (0.5 M; 40 mL) was added and the aqueous phase separated, extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 3:1) gave azetidine **9** (0.44 g, 68%) as a yellow oil: R_f 0.5 (hexanes/EtOAc 3:1); $[\alpha]_D^{21}=-92.0$ (c=0.2, $CHCl_3$); IR (neat) 1723, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H), 6.93 (dd, 1H, J=5.6, 15.6 Hz), 5.96 (dd, 1H, J=1.3, 15.6 Hz), 3.81–3.76 (m, 1H), 3.74 (d, 1H, J=12.7 Hz), 3.72 (s, 3H), 3.44 (d, 1H, J=12.7 Hz), 3.31–3.27 (m, 1H), 2.92–2.86 (m, 1H), 2.23–2.15 (m, 1H), 2.08–1.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 149.1, 137.7, 128.8, 128.3, 127.1, 120.3, 65.4, 62.1, 51.5, 51.3, 24.9; CI-MS *m/e* 232 $[M+H]^+$, 140, 91; HRMS calcd for $C_{14}H_{17}NO_2$: 232.1337, found: 232.1345.

3.1.4. Methyl 1-benzyl-2-pyrrolidineacetate (11).[27] Enone **9** (0.046 g, 0.20 mmol), MeOH (5 mL) and 10% Pd/C (5 mg) were hydrogenated (1 atm) for 10 h at room temperature, filtered through Celite and washed with MeOH and EtOAc. Rotary evaporation and chromatography (hexanes/EtOAc 3:1; EtOAc) gave pyrrolidine **11** (0.010 g, 20%) as a pale yellow oil: R_f 0.2 (hexanes/EtOAc 3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H), 3.98 (d, 1H, J=12.9 Hz), 3.67 (s, 3H), 3.28 (d, 1H, J=12.9 Hz), 2.92–2.86 (m, 2H), 2.67 (dd, 1H, J=4.3, 14.9 Hz), 2.37 (dd, 1H, J=8.7, 14.9 Hz), 2.22–2.12 (m, 1H), 2.10–2.01 (m, 1H), 1.78–1.58 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 139.3, 128.8, 128.2, 126.9, 60.8, 58.7, 53.9, 51.5, 39.5, 30.9, 22.2; CI-MS *m/e* 234 $[M+H]^+$, 108, 91; HRMS calcd for $C_{14}H_{19}NO_2$: 234.1494, found: 234.1485.

3.1.5. Ethenyl 2-((methoxycarbonyl)methyl)pyrrolidine-1-carboxylate. Vinyl chloroformate (0.08 mL, 0.93 mmol)

was added with stirring to pyrrolidine **11** (0.14 g, 0.60 mmol) in CH_2Cl_2 (3 mL) at 0°C. After 10 h, saturated aqueous $NaHCO_3$ (3 mL) was added, the organic phase was separated and the aqueous phase further extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried (Na_2SO_4), filtered, rotary evaporated and chromatographed (hexanes/EtOAc 4:1) to give ethenyl 2-((methoxycarbonyl)methyl)pyrrolidine-1-carboxylate (0.10 g, 78%) as a pale yellow oil containing a mixture of rotamers: R_f 0.3 (hexanes/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22, 7.19 (dd, 1H, J=3.1, 6.3 Hz), 4.80–4.74 (m, 1H), 4.45–4.42 (m, 1H), 4.33–4.20 (m, 1H), 3.67 (s, 3H), 3.49–3.44 (m, 2H), 2.78, 2.97 (dd, 1H, J=3.9, 4.3, 15.3 Hz), 2.41–2.31 (m, 1H), 2.16–2.06 (m, 1H), 1.93–1.85 (m, 2H), 1.83–1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.5, 151.8, 142.24, 142.20, 95.5, 95.2, 54.6, 54.1, 51.7, 51.6, 46.7, 46.5, 39.2, 37.8, 31.3, 30.5, 23.5, 22.6; CI-MS *m/e* 214 $[M+H]^+$, 187, 170; HRMS calcd for $C_{10}H_{15}NO_4$: 214.1079, found: 214.1076.

3.1.6. Methyl 2-pyrrolidineacetate hydrobromide (13). Ethenyl 2-((methoxycarbonyl)methyl)-pyrrolidine-1-carboxylate (0.10 g, 0.47 mmol) was allowed to stand in HBr/AcOH (45%; 0.12 mL, 0.67 mmol) at 0°C for 3 h. Evaporation of all the AcOH gave a yellow solid which, upon trituration with Et_2O, gave bromide salt **13** (0.08 g, 76%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.4 (bs, 1H), 9.08 (bs, 1H), 4.00–3.93 (m, 1H), 3.75 (s, 3H), 3.47 (m, 2H), 3.24 (dd, 1H, J=7.3, 17.3 Hz), 2.92 (dd, 1H, J=5.9, 17.3 Hz), 2.33–2.27 (m, 1H), 2.17–2.01 (m, 2H), 1.85–1.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 56.3, 52.5, 45.2, 35.7, 30.3, 23.4; CI-MS *m/e* 144 $[(M-HBr)+H]^+$; HRMS calcd for $C_7H_{14}NO_2$: 144.1024, found: 144.1027.

3.1.7. Methyl (2*R*)-3-(1-benzylazetidin-2-yl)propanoate (10). $NaBH_4$ (2.72 g, 71.6 mmol, 28 equiv.) was added in successive portions of 2 equiv. with stirring every 30 min to enone **9** (0.59 g, 2.55 mmol) in MeOH (15 mL). The mixture was concentrated in vacuo, and the resulting residue was taken up in CH_2Cl_2 (10 mL) and washed with H_2O (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic phases were washed with H_2O and dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 3:1) gave azetidine **10** as a pale brown oil (0.43 g, 72%): R_f 0.1 (hexanes/EtOAc 3:1); $[\alpha]_D^{18}=-34.5$ (c=0.8, $CHCl_3$); IR (neat) 1739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (m, 5H), 3.72 (d, 1H, J=12.7 Hz), 3.65 (s, 3H), 3.46 (d, 1H, J=12.7 Hz), 3.34–3.18 (m, 2H), 2.81 (m, 1H), 2.34–2.21 (m, 2H), 2.06–1.98 (m, 1H), 1.90–1.74 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 128.8, 128.3, 127.0, 65.8, 62.7, 51.5, 51.4, 30.7, 29.7, 23.2; CI-MS *m/e* 234 $[M+H]^+$, 91; HRMS calcd for $C_{14}H_{19}NO_2$: 234.1494, found: 234.1490.

3.1.8. Conversion of methyl (2*R*)-3-(1-benzylazetidin-2-yl)propanoate (10) into methyl (2*S*)-3-(1-benzylazetidin-2-yl)prop-2*E*-enoate (9) by selenoxide elimination. *n*-BuLi in hexanes (2.5 M; 0.137 mL, 0.34 mmol) was added with stirring to $(Me_3Si)_2NH$ (0.076 mL, 0.34 mmol) in THF (0.78 mL) at −78°C. After 30 min, Me_3SiCl (0.022 mL, 0.17 mmol) followed by an aliquot of the $LiN(SiMe_3)_2$ in THF (0.5 mL) were added with stirring to the azetidine **10** (0.02 g, 0.0086 mmol) in THF (1.5 mL) at −78°C. The mixture was allowed to stand at −78°C for 30 min and allowed to warm up to room temperature over 30 min. Rotary evaporation at 40°C and trituration with Et_2O gave the crude enol silane as a colourless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.22 (m, 5H), 3.75 (m, 1H), 3.65 (m, 1H), 3.52, 3.48 (2s, 3 H), 3.48–3.43 (m, 1H), 3.37–3.21 (m, 1H), 3.18–3.13 (m, 1H), 2.81–2.70 (m, 1H), 2.18–2.08 (m, 2H), 2.05–1.80 (m, 2H), 0.24, 0.19 (2s, 9H). PhSeBr (0.02 g) in THF (1 mL) and $Me_3S{\cdot}Me_3SiF_2$ (0.024 g) in THF (1 mL) were added with stirring to the enol silane in THF (2 mL) at −78°C. After 30 min at −78°C and 12 h at −4°C, the reaction mixture was quenched with saturated aqueous NH_4Cl (2 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×4 mL) and the combined organic phases were washed with H_2O (4 mL) and dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 3:1; MeOH) gave the α-phenylselenide (0.02 g, 60%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.24 (m, 10H), 3.63, 3.59 (2s, 3H), 3.87–3.80 (m, 1H), 3.38–3.22 (m, 2H), 3.78–3.65 (m, 2H), 2.30–1.78 (m, 5H); *m/e* (CI) 390 $[M^{+\cdot}]$; HRMS calcd for $C_{20}H_{23}NO_2Se$: 390.0977, found: 390.0975. $TsOH{\cdot}H_2O$ (0.02 g, 0.10 mmol) in THF (6 mL) was added with stirring to the α-phenylselenide (0.045 g, 0.12 mmol) in CH_2Cl_2 (2 mL). After 30 min, rotary evaporation and trituration with Et_2O gave the crude azetidine 4-toluenesulfonate salt (0.047 g, 0.08 mmol, 72%). 3-$ClC_6H_4CO_3H$ (0.026 g, 0.15 mmol) was added with stirring to an aliquot (0.042 g, 0.07 mmol) in CH_2Cl_2 (1 mL) at 0°C. After 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL) and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3×3 mL) and the combined organic phases were dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 4:1) gave the unsaturated ester **9** (0.012 g, 72%) as a colourless oil.

3.1.9. Methyl 4-(*N*-benzyl-*N*-ethenyloxycarbonyl)amino-6-chlorohexanoate (12). Vinyl chloroformate (0.08 mL, 0.93 mmol) was added with stirring to azetidine **10** (0.14 g, 0.60 mmol) in CH_2Cl_2 (3 mL) at 0°C. After 10 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL) and the aqueous phase was separated and extracted with CH_2Cl_2 (3×5 mL) and the combined organic phases were dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 4:1) gave **12** (0.10 g, 48%) as a yellow oil containing a mixture of rotamers: R_f 0.5 (hexanes/EtOAc 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 6H), 4.84–4.77 (m, 1H), 4.60–4.34 (m, 3H), 3.94–3.86 (m, 1H), 3.68 (s, 3 H), 3.51–3.35 (m, 2H), 2.60–2.43 (m, 2H), 2.13–1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 142.4, 142.3, 137.10, 128.7, 128.1, 127.8, 127.5, 95.7, 60.1, 59.8, 51.7, 51.11, 51.06, 44.94, 43.93, 31.2, 36.3, 33.4, 30.8; CI-MS *m/e* 357 $[M+NH_4]^+$, 340 $[M+H]^+$.

3.1.10. (2*S*)-1-Benzoylazetidine-2-carboxylic acid (15). Acid **15** (193.5 g, 0.94 mol, 95.1% ee) in H_2O (500 mL) was heated with stirring until dissolved (68°C) and was allowed to slowly cool to room temperature. When the first crystals started to appear (internal temperature 64°C) a small amount of acid **15** (99.7% ee) was added and the resulting

suspension was allowed to stir overnight. The white crystals were collected by filtration and washed with H_2O to give purified **15** (183.5 g, 95%, 98.4% ee): mp 115–119°C (lit.[15] mp 118–121°C); $[\alpha]_D^{23}=-193.8$ (c=1.0, MeOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.56 (bs, 1H), 7.86–7.45 (m, 5H), 5.34–5.18 (m, 1H), 4.56–4.37 (m, 2H), 2.95–2.53 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.2, 171.2, 132.4, 128.8, 127.9, 62.9, 51.9, 19.7; CI-MS *m/e* 206 $[M+H]^+$; HRMS calcd for $C_{11}H_{12}NO_3$: 206.0817, found: 206.0805. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.36; H, 5.41; N, 6.85.

3.1.11. (2*S*)-1-Benzyloxycarbonyl-2-azetidinemethanol (16). Concentrated H_2SO_4 (6 mL) was added dropwise with stirring to amide **15** (15.0 g, 73.2 mmol) in H_2O (120 mL) and the mixture was heated to reflux for 24 h. The mixture was allowed to cool to room temperature and stirred overnight to allow precipitation of $PhCO_2H$, which was removed by filtration and washed with H_2O. The filtrate was extracted with EtOAc and the aqueous layer was treated with Amberlite IRA-67 (120 g) to pH 7. The Amberlite was removed by filtration and washed with H_2O. Rotary evaporation of the combined aqueous layers gave a yellow solid, which was suspended in hot MeOH and allowed to cool to room temperature, filtered and washed with MeOH to give *(2S)-azetidinecarboxylic acid* (6.0 g, 81%) as a white crystalline solid: mp 205–210°C; $[\alpha]_D^{26}=-116.3$ (c=1.0, H_2O); IR (neat) 3431, 1640 cm^{-1}; ^{1}H NMR (270 MHz, D_2O) δ 10.05 (s, 1H), 4.82–4.70 (m, 1H), 4.13–3.79 (m, 2H), 2.86–2.39 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 174.1, 59.1, 42.9, 23.4; CI-MS *m/e* 119 $[M+NH_4]^+$, 102 $[M+H]^+$; HRMS calcd for $C_4H_8NO_2$: 102.0555, found: 102.0550. Anal. Calcd for $C_4H_7NO_2$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.21; H, 6.97; N, 13.81. Benzyl chloroformate (1.70 mL, 11.88 mmol) was added with stirring to (2*S*)-azetidinecarboxylic acid (1.0 g, 9.9 mmol) in dioxane (5 mL) and saturated aqueous $NaHCO_3$ (15 mL). After stirring overnight, the mixture was rotary evaporated and the residue dissolved in H_2O (10 mL) and extracted with Et_2O (1×20 mL). The aqueous layer was acidified to pH 1 with $KHSO_4$ and extracted with EtOAc (3×20 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated in vacuo to yield *(2S)-1-(benzyloxycarbonyl)azetidinecarboxylic acid*[16] (1.81 g, 78%) as a colourless oil: $[\alpha]_D^{24}=-97.1$ (c=1.2, $CHCl_3$); IR (neat) 3113, 1757, 1660, 1416 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.37 (bs, 1H), 7.36 (m, 5H), 5.16 (s, 2H), 4.82–4.72 (m, 1H), 4.05–4.00 (m, 2H), 2.57–2.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 157.5, 135.94, 128.6, 128.3, 128.1, 67.5, 60.6, 47.6, 20.6; CI-MS *m/e* 253 $[M+NH_4]^+$, 236 $[M+H]^+$, 108, 91; HRMS calcd for $C_{12}H_{14}NO_4$: 236.0923, found: 236.0926. BH_3·THF (16 mL, 1.0 M in THF, 16.0 mmol) was slowly added with stirring to (2*S*)-1-(benzyloxycarbonyl)azetidinecarboxylic acid (1.81 g, 7.7 mmol) in THF (10 mL) at 0°C and the mixture was allowed to warm up to room temperature and stirred overnight. Hydrochloric acid (2 M; 10 mL) was added and stirring was continued for 1 h. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried (Na_2SO_4). Filtration and rotary evaporation gave alcohol **16** (1.58 g, 93%) as a colourless oil: R_f 0.2 (hexanes/EtOAc 1:1); $[\alpha]_D^{17}=-22.0$ (c=0.7, $CHCl_3$); IR (neat) 3420, 1694, 1422, 1354 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 5.13 (s, 2H), 4.58–4.53 (m, 1H), 4.02–3.78 (m, 4H), 3.68–3.64 (m, 1H), 2.31–1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 136.3, 128.6, 128.2, 128.1, 66.7, 65.4, 63.6, 46.9, 18.5; CI-MS *m/e* 239 $[M+NH_4]^+$, 222 $[M+H]^+$, 108, 91; HRMS calcd for $C_{12}H_{16}NO_3$: 222.1130, found: 222.1128.

3.1.12. Methyl (2*R*)-3-((1-benzyloxycarbonyl)azetidin-2-yl)propanoate (18). DMSO (0.76 mL, 10.71 mmol) was slowly added with stirring to oxalyl chloride (0.62 mL, 7.14 mmol) in CH_2Cl_2 (10 mL) at −78°C. After 20 min, alcohol **16** (0.78 g, 3.53 mmol) in CH_2Cl_2 (10 mL) was added and the mixture was allowed to warm up to −40°C over 2 h. Et_3N (2.5 mL, 17.85 mmol) was added followed by CH_2Cl_2 (20 mL) and the mixture was warmed to 0°C over 1 h. $Ph_3P{=}CHCO_2Me$ (2.4 g, 7.18 mmol) was added and the mixture stirred at room temperature overnight. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous layer was separated, extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 3:1) gave enoate **17** (0.65 g, 67%) as a yellow oil: R_f 0.2 (hexanes/EtOAc 3:1); $[\alpha]_D^{29}=-173.4$ (c=1.0, $CHCl_3$); IR (neat) 1713, 1412, 1351 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.05 (dd, 1H, J=5.5, 15.6 Hz), 6.04 (d, 1H, J=15.6 Hz), 5.12 (s, 2H), 4.94–4.87 (m, 1H), 4.06–3.92 (m, 2H), 3.77 (s, 3H), 2.60–2.48 (m, 1H), 2.15–2.04 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 156.5, 146.5, 136.5, 128.5, 128.1, 127.9, 121.0, 66.8, 61.2, 51.7, 46.7, 23.1; CI-MS *m/e* 293 $[M+NH_4]^+$, 276 $[M+H]^+$, 169, 108, 91; HRMS calcd for $C_{15}H_{18}NO_4$: 276.1236, found: 276.1238. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.43; H, 6.23; N, 5.09. Found: C, 65.49; H, 6.27; N, 5.03. $NaBH_4$ was added in 4 portions (4×0.44 g, 11.58 mmol) every 30 min to CuCl (0.87 g, 1.5 equiv.) and **17** (1.62 g, 5.89 mmol) in MeOH (20 mL) at 0°C. Rotary evaporation gave a dark solid residue which was taken up in CH_2Cl_2 (15 mL), filtered through Celite and washed with CH_2Cl_2. The filtrate was washed with H_2O (10 mL) and dried (Na_2SO_4). Filtration and rotary evaporation gave ester **18** (1.60 g, 98%) as a yellow oil: R_f 0.3 (hexanes/EtOAc 3:1); $[\alpha]_D^{24}=-44.3$ (c=0.9, $CHCl_3$); IR (neat) 1738, 1712, 1414, 1350, 1133 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 5.11 (s, 2H), 4.40–4.31 (m, 1H), 3.98–3.85 (m, 2H), 3.67 (s, 3H), 2.43–2.32 (m, 3H), 2.30–1.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 156.9, 136.8, 128.5, 128.0, 66.5, 61.5, 51.6, 46.6, 30.8, 29.7, 22.0; CI-MS *m/e* 295 $[M+NH_4]^+$, 278 $[M+H]^+$, 170, 91; HRMS calcd for $C_{15}H_{20}NO_4$: 278.1392, found: 278.1382. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.91; N, 5.05. Found: C, 65.20; H, 6.95; N, 5.24.

3.1.13. (2*R*)-3-((1-benzyloxycarbonyl)azetidin-2-yl)propanoic acid. LiOH (0.05 g, 1.14 mmol) was added with stirring to ester **18** (0.29 g, 1.05 mmol) in H_2O (1 mL) and dioxane (1 mL). After 2 h, rotary evaporation gave a white solid that was dissolved in H_2O (5 mL) and acidified to pH 1 with $KHSO_4$. The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic layers were dried (Na_2SO_4). Filtration and rotary evaporation gave *(2R)-3-((1-benzyloxycarbony)azetidin-2-yl)propanoic acid* (0.24 g, 87%) as a colourless oil: R_f 0.3 (EtOAc); $[\alpha]_D^{26}=-33.2$ (c=1.2, $CHCl_3$); IR (neat) 1707, 1420, 1353, 1137 cm^{-1}; ^{1}H

NMR (300 MHz, $CDCl_3$) δ 10.64 (bs, 1H), 7.40–7.29 (m, 5H), 5.11 (s, 2H), 4.43–4.34 (m, 1H), 3.99–3.86 (m, 2H), 2.47–2.23 (m, 3H), 2.21–1.84 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 157.2, 136.5, 128.5, 128.1, 128.0, 66.8, 61.3, 46.7, 30.8, 30.3, 22.1; CI-MS *m/e* 281 $[M+NH_4]^+$, 264 $[M+H]^+$, 108, 91; HRMS calcd for $C_{14}H_{18}NO_4$: 264.1236, found: 264.1236. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.57; H, 6.48; N, 5.21.

3.1.14. (2*R*)-3-(Azetidin-2-yl)propanoic acid (19). (2*R*)-3-((1-Benzyloxycarbony)azetidin-2-yl)propanoic acid (0.24 g, 0.91 mmol), MeOH (15 mL) and 10% Pd/C (100 mg) were hydrogenated (1 atm) at room temperature overnight. The solids were removed by filtration through Celite and washed with MeOH when rotary evaporation gave an oil, which was triturated with Et_2O to provide amino acid **19** (0.110 g, 93%) as a white solid: mp 97–107°C; $[\alpha]_D^{27}=-26.5$ (*c*=0.8, MeOH); IR (neat) 3485, 3250, 1767, 1642, 1567, 1401 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 4.39–4.31 (m, 1H), 3.99–3.78 (m, 2H), 2.63–2.44 (m, 2H), 2.32–2.15 (m, 3H), 1.94–1.81 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 179.7, 60.4, 41.4, 33.6, 29.6, 24.4; CI-MS *m/e* 130 $[M+H]^+$; HRMS calcd for $C_6H_{12}NO_2$: 130.0868, found: 130.0870. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.78; H, 8.59; N, 10.85. Found: C, 55.69; H, 8.59; N, 10.79.

3.1.15. (5*R*)-1-Azabicyclo[3.2.0]heptan-2-one (20). Dicyclohexyl carbodiimide (1.00 g, 4.85 mmol) was added with stirring to amino acid **19** (0.50 g, 3.87 mmol) in CH_2Cl_2 (20 mL) and a few drops of MeOH and the mixture was stirred for 5 days. The mixture was filtered and the residue was extracted with CH_2Cl_2. The combined organic phases were rotary evaporated and chromatographed (Et_2O) to give lactam **20** (0.24 g, 51%) as a yellow oil: R_f 0.1 (EtOAc); IR (neat) 1698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (app quintet, 1H, *J*=7.0 Hz), 4.04–3.97 (m, 1H), 3.91 (dt, 1H, *J*=4.3, 9.6 Hz), 2.63–2.52 (m, 2H), 2.43–2.36 (m, 1H), 2.32–2.18 (m, 2H), 2.07–1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 61.9, 49.7, 32.2, 31.4, 31.2; CI-MS *m/e* 112 $[M+H]^+$, 83; HRMS calcd for $C_6H_{10}NO$: 112.0762, found: 112.077.

3.1.16. Aldol reaction of (5*R*)-1-azabicyclo[3.2.0]heptan-2-one (20) with 4-nitrobenzaldehyde. *n*-BuLi in hexanes (1.6 M; 1.10 mL, 1.80 mmol) was added dropwise with stirring to 2,2,6,6-tetramethylpiperidine (0.30 mL, 1.81 mmol) in THF (2 mL) at −78°C and the mixture was allowed to warm up to 0°C for 20 min. The mixture was recooled to −78°C when γ-lactam **20** (0.12 g, 1.08 mmol) in THF (6 mL) was added and the mixture allowed to warm up to −30°C. The mixture was recooled to −78°C and a premixed solution of 4-nitrobenzaldehyde (0.32 g, 2.12 mmol) in THF (10 mL) and $BF_3{\cdot}OEt_2$ (0.26 mL, 2.12 mmol) cooled to 0°C was added and the resulting suspension allowed to warm up to −20°C. Saturated aqueous NH_4Cl (10 mL) was added and the organic layer was separated. The aqueous layer was further extracted with EtOAc (3×10 mL) and the combined organic layers were dried (Na_2SO_4). Filtration, rotary evaporation and chromatography twice (hexanes/EtOAc 1:1; EtOAc) gave (3*S*,5*R*,1′*R*)-3-(hydroxy-(4-nitrophenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one (**21a**) (0.057 g, 20%) as a yellow crystalline solid: mp 122–126°C (Et_2O/hexanes): R_f 0.6 (EtOAc); $[\alpha]_D^{26}=-9.7$ (*c*=0.7, $CHCl_3$); IR (neat) 3471, 1680, 1605, 1516, 1348 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, 2H, *J*=8.8 Hz), 7.58 (d, 2H, *J*=8.7 Hz), 5.56 (bs, 1H), 4.91 (d, 1H, *J*=9.6 Hz), 4.37 (app quintet, 1H, *J*=6.9 Hz), 4.16–4.02 (m, 2H), 2.90–2.79 (m, 1H), 2.72–2.62 (m, 1H), 2.40–2.28 (m, 1H), 2.13–2.04 (m, 1H), 1.89–1.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.0, 148.7, 147.7, 127.4, 123.8, 75.4, 59.8, 49.9, 48.4, 36.0, 31.4; CI-MS *m/e* 280 $[M+NH_4]^+$, 263 $[M+H]^+$, 245; HRMS calcd for $C_{13}H_{15}N_2O_4$: 263.1032, found: 263.1032. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.52; H, 5.38; N, 10.69. Found: C, 59.33; H, 5.29; N, 10.58. *Crystal data for* **21a**: $C_{13}H_{14}N_2O_4$, *M*=262.3, orthorhombic, $P2_12_12_1$ (no. 19), *a*=5.764(1), *b*=9.394(1), *c*=23.151(1) Å, *V*=1253.4(1) Å^3, *Z*=4, D_c=1.390 g cm^{-3}, μ (Cu Kα)=0.87 mm^{-1}, *T*=293 K, colourless needles; 1243 independent measured reflections, F^2 refinement, R_1=0.037, wR_2=0.098, 1125 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq128°$], 177 parameters. The absolute chirality of **21a** could not be determined from the X-ray analysis, but was assigned by internal reference to C5. CCDC 186323. Further elution gave *(3S,5R,1′S)-3-(hydroxy-(4-nitrophenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one* (**22a**) (0.016 g, 6%) as a yellow crystalline solid: mp 100–108°C (Et_2O/hexane): R_f 0.5 (EtOAc); $[\alpha]_D^{18}=-68.6$ (*c*=0.5, $CHCl_3$); IR (neat) 3355, 1680, 1518, 1347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, 2H, *J*=8.7 Hz), 7.56 (d, 2H, *J*=8.8 Hz), 5.49 (d, 1H, *J*=2.13 Hz), 4.39 (app quintet, 1H, *J*=6.9 Hz), 4.17–4.00 (m, 2H), 3.14–3.06 (m, 1H), 2.68–2.58 (m, 1H), 2.40–1.92 (m, 3H), 1.70 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7, 149.3, 147, 126.3, 123.7, 69.2, 59.7, 50.2, 50.0, 31.3, 30.6; CI-MS *m/e* 280 $[M+NH_4]^+$, 263 $[M+H]^+$; HRMS calcd for $C_{13}H_{15}N_2O_4$: 263.1032, found: 263.1032. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.52; H, 5.38; N, 10.69. Found: C, 59.63; H, 5.43; N, 10.51. *Crystal data for* **22a**: $C_{13}H_{14}N_2O_4$, *M*=262.3, monoclinic, $P2_1$ (no. 4), *a*=9.267(1), *b*=5.437(1), *c*=12.491(1) Å, β=92.77(1)°, *V*=628.7(1) Å^3, *Z*=2, D_c=1.385 g cm^{-3}, μ (Cu Kα)=0.87 mm^{-1}, *T*=293 K, colourless platy needles; 1163 independent measured reflections, F^2 refinement, R_1=0.048, wR_2=0.125, 983 independent observed reflections [$|F_o|>4\sigma_{(|Fo|)}$], $2\theta\leq127°$], 177 parameters. The absolute chirality of **22a** could not be determined from the X-ray analysis, but was assigned by internal reference to C5. CCDC 186324. Further elution gave a mixture of *(3R,5R,1′R)-3-(hydroxy-(4-nitrophenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one* (**23a**) and *(3R,5R,1′S)-3-(hydroxy-(4-nitrophenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one* (**24a**) (0.115 g, 41%) as a yellow oil: R_f 0.3 (EtOAc); IR (neat) 3374, 1674, 1518, 1347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23–8.20 (m, 4H), 7.58–7.54 (m, 4H), 5.25 (d, 1H, *J*=3.3 Hz), 4.96 (d, 1H, *J*=7.4 Hz), 4.54–4.44 (m, 1H), 4.25–3.87 (m, 5H), 3.38 (d, 1H, *J*=3.0 Hz), 3.08 (d, 1H, *J*=4.2 Hz), 2.93–2.85 (m, 2H), 2.61–2.47 (m, 2H), 2.38–1.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 149.3, 148.3, 147.7, 147.3, 127.4, 126.6, 123.7, 123.6, 74.1, 72.1, 61.1, 60.4, 53.2, 52.4, 50.7, 50.6, 32.8, 32.0, 31.8, 30.84; CI-MS *m/e* 280 $[M+NH_4]^+$, 263 $[M+H]^+$; HRMS calcd for $C_{13}H_{15}N_2O_4$: 263.1032, found: 263.1040. Separation of a sample of the isomer mixture on a chromatotron (hexanes/EtOAc 4:1 to 0:1) and recrystallization (Et_2O/hexanes) gave a sample of

the single isomer **24a**. *Crystal data for* **24a**: $C_{13}H_{14}N_2O_4$, M=262.3, orthorhombic, $P2_12_12_1$ (no. 19), a=5.219(1), b=10.842(1), c=22.804(1) Å, V=1290.4(1) Å^3, Z=4, D_c=1.350 g cm^{-3}, μ (Cu Kα)=0.85 mm^{-1}, T=293 K, colourless platy needles; 1283 independent measured reflections, F^2 refinement, R_1=0.036, wR_2=0.093, 1147 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq128°$], 177 parameters. The absolute chirality of **24a** could not be determined from the X-ray analysis, but was assigned by internal reference to C5. CCDC 186325.

3.1.17. (1*S*,2*S*,3*S*,5*R*,1′*R*)-3-(Hydroxy-(4-nitrophenyl)-methyl)-1-azabicyclo[3.2.0]heptan-2-ol·borane (25a) and (1*S*,2*R*,3*S*,5*R*,1′*R*)-3-(hydroxy-(4-nitrophenyl)-methyl)-1-azabicyclo[3.2.0]heptan-2-ol·borane (25b). BH_3·THF (1.0 mL, 1.0 M in THF, 1.0 mmol) was added to **21a** (0.050 g, 0.19 mmol) in THF (4 mL) and the mixture was heated to reflux for 2 h. The reaction was quenched with MeOH when rotary evaporation and chromatography (hexanes/EtOAc 1:1) gave borane **25b** as a yellow oil: R_f 0.9 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 2H, J=8.8 Hz), 7.56 (d, 2H, J=8.8 Hz), 5.03 (d, 1H, J=5.7 Hz), 4.83 (app t, 1H, J=4.4 Hz), 4.68 (d, 1H, J=5.0 Hz), 4.27 (dt, 1H, J=6.9, 10.1 Hz), 3.99–3.94 (m, 1H), 3.47–3.41 (m, 2H), 2.81–2.72 (m, 1H), 2.61–2.52 (m, 1H), 2.09–2.00 (m, 1H), 1.90–1.80 (m, 2H), 1.72–1.40 (bs, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 147.6, 127.0, 124.0, 91.7, 72.9, 70.9, 50.4, 49.7, 34.4, 21.8; CI-MS *m/e* 279 [M+BH_3]$^+$, 265 [M+H]$^+$. Further elution gave borane **25a** (0.046 g, 84%) as a yellow solid: mp 108–114°C: R_f 0.8 (EtOAc); $[\alpha]_D^{26}$=−43.4 (c=1.4, $CHCl_3$); IR (neat) 3448, 2961, 2926, 2382, 2315, 2270, 1604, 1518, 1359, 1165, 856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26–8.24 (d, 2H, J=8.7 Hz), 7.59–7.56 (d, 2H, J=8.7 Hz), 4.94 (d, 1H, J=8.3 Hz), 4.84 (d, 1H, J=8.9 Hz), 4.18–4.10 (m, 2H), 4.00–3.92 (m, 1H), 3.77–3.70 (m, 2H), 2.76–2.67 (m, 1H), 2.58–2.49 (m, 1H), 2.07–1.60 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 130.9, 127.3, 123.8, 97.7, 75.2, 70.4, 60.5, 52.7, 31.5, 22.6; CI-MS *m/e* 279 [(M−BH_3)+H]$^+$, 265 [M+H]$^+$. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 56.09; H, 6.88; N, 10.07. Found: C, 56.12; H, 6.77; N, 9.96.

3.1.18. (2*S*,3*S*,7*R*,1′*R*)-3-(1-Hydroxy-(4-nitrophenyl)-methyl)-2-methoxy-1-azabicyclo[3.2.0]-heptane (26). TsOH (0.041 g, 0.22 mmol) was added to borane-complex **25a** (0.03 g, 0.11 mmol) in MeOH (2 mL). After 8 h, rotary evaporation and trituration with Et_2O gave a white solid which was dissolved in H_2O (2 mL) and Na_2CO_3 (0.029 g, 0.27 mmol) added. After stirring overnight, the aqueous layer was extracted with CH_2Cl_2 (3×3 mL) and the combined organic layers were dried (Na_2SO_4). Filtration and evaporation gave **26** (0.023 g, 75%) as a yellow solid: mp 110–115°C; $[\alpha]_D^{19}$=−49.2 (c=1.0, $CHCl_3$); IR (neat) 3393, 1604, 1518, 1347 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, 2H, J=8.6 Hz), 7.55 (d, 2H, J=8.6 Hz), 4.87 (d, 1H, J=9.4 Hz), 4.27 (d, 1H, J=7.3 Hz), 4.04–3.86 (m, 2H), 3.56–3.34 (m, 1H), 3.34 (s, 3H), 2.60–2.50 (m, 1H), 2.36–2.29 (m, 1H), 1.92–1.62 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 127.2, 126.6, 123.7, 107.8, 76.5, 64.4, 55.9, 55.8, 55.7, 35.7, 24.2; CI-MS *m/e* 279 [M+H]$^+$; HRMS calcd for $C_{14}H_{19}N_2O_4$: 279.1345, found: 279.1354. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.4; H, 6.52; N, 10.07. Found: C, 60.39; H, 6.42; N, 9.88.

3.1.19. Aldol reaction of (5*R*)-1-azabicyclo[3.2.0]heptan-2-one (20) with benzaldehyde. *n*-BuLi in hexanes (2.5 M; 2.16 mL, 5.62 mmol) was added with stirring to 2,2,6,6-tetramethylpiperidine (0.95 mL, 5.63 mmol) in THF (5 mL) at −78°C and the mixture was kept at 0°C for 40 min. The mixture was recooled to −78°C and γ-lactam **20** (0.25 g, 2.25 mmol) in THF (6 mL) was added and the mixture allowed to warm up to −30°C. The mixture was recooled to −78°C and a premade solution of PhCHO (0.68 mL, 6.76 mmol) in THF (5 mL) and BF_3·OEt_2 (0.86 mL, 6.76 mmol) at 0°C was added. The resulting suspension was allowed to warm up to −20°C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was separated and extracted with EtOAc (3×10 mL) and the combined organic layers were dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 2:1; 1:1, 1:2; EtOAc) gave *(3S,5R,1′R)-3-(hydroxy-(phenyl)methyl)-1-azabicyclo[3.2.0]-heptan-2-one* (**21b**) (0.15 g, 31%) as a white crystalline solid: mp 90–105°C: R_f 0.6 (EtOAc); $[\alpha]_D^{19}$=+33.3 (c=0.6, $CHCl_3$); IR (neat) 1677, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5H), 5.37 (bs, 1H), 4.78 (d, 1H, J=9.7 Hz), 4.36 (app quintet, 1H, J=6.9 Hz), 4.14–4.01 (m, 2H), 2.98–2.87 (m, 1H), 2.64 (dt, 1H, J=6.8, 11.6 Hz), 2.37–2.25 (m, 1H), 2.12–2.03 (m, 1H), 1.92–1.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 141.4, 128.5, 128.1, 126.6, 76.2, 59.8, 49.8, 48.5, 36.1, 31.4; CI-MS *m/e* 218 [M+H]$^+$, 200, 111; HRMS calcd for $C_{13}H_{16}NO_2$: 218.1181, found: 218.1183. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.96; N, 6.45. Found: C, 71.90; H, 7.05; N, 6.27. Further elution gave *(3S,5R,1′S)-3-(hydroxy-(phenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one* (**22b**) (0.037 g, 8%) as a white crystalline solid: mp 79–85°C: R_f 0.5 (EtOAc); $[\alpha]_D^{19}$=−104.7 (c=0.4, $CHCl_3$); IR (neat) 3425, 1691, 1451, 1368 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.28 (m, 5H), 5.40 (m, 1H, J=2.4 Hz), 4.37 (app quintet, 1H, J=6.8 Hz), 4.12–3.96 (m, 2H), 3.11–3.04 (m, 1H), 2.90 (d, 1H, J=3.1 Hz), 2.60 (dt, 1H, J=7.0, 11.2 Hz), 2.38–2.22 (m, 2H), 2.01–2.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.7, 141.8, 128.4, 127.2, 125.4, 70.2, 60.2, 50.6, 50.6, 31.7, 31.1; CI-MS *m/e* 218 [M+H]$^+$, 111; HRMS calcd for $C_{13}H_{16}NO_2$: 218.1181, found: 218.1178. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.96; N, 6.45. Found: C, 71.82; H, 7.07; N, 6.32. Further elution gave a mixture of *(3R,5R,1′R)-3-(hydroxy-(phenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one* (**23b**) and *(3R,5R,1′S)-3-3-(hydroxy-(phenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one* (**24b**) (0.28 g, 57%) as a colourless oil: R_f 0.2 (EtOAc); IR (neat) 3374, 1671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.29 (m, 10H), 5.17 (d, 1H, J=3.6 Hz), 4.80 (d, 1H, J=8.3 Hz), 4.47–4.28 (m, 2H), 4.10–3.92 (m, 4H), 3.1 (bs, 1H), 2.90–2.85 (m, 3H), 2.57–2.50 (m, 2H), 2.40–2.27 (m, 3H), 2.12–1.95 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 184.1, 141.9, 141.3, 128.5, 128.4, 128.2, 127.6, 126.7, 125.8, 75.3, 73., 61.8, 61.1, 53.3, 52.6, 50.6, 50.5, 34.7, 33.4, 31.7, 31.3; CI-MS *m/e* 218 [M+H]$^+$, 111; HRMS calcd for $C_{13}H_{16}NO_2$: 218.1181, found: 218.1183.

3.1.20. (3*S*,5*R*,1′*R*)-3-((*t*-Butyldimethylsilyloxy)-(phenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-one (27). 2,6-Lutidine (0.24 mL, 2.1 mmol), followed by *t*-BuMe_2SiOTf (0.24 mL, 1.05 mmol) were added with stirring to lactam **21b** (0.11 g, 0.51 mmol) in CH_2Cl_2 (2 mL) at −78°C and

the mixture was allowed to warm up to room temperature. Saturated aqueous NH_4Cl (4 mL) was added, the aqueous phase was separated and extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). Filtration, rotary evaporation and chromatography (hexanes/EtOAc 5:1) gave lactam **27** (0.14 g, 82%) as a colourless oil: R_f 0.8 (hexanes/EtOAc 3:1); $[\alpha]_D^{20}=-28.2$ ($c=1.7$, $CHCl_3$); IR (neat) 1707, 1470, 1252, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.23 (m, 5H), 5.31 (d, 1H, $J=4.6$ Hz), 4.28 (app quintet, 1H, $J=6.8$ Hz), 3.96–3.88 (m, 1H), 3.71 (dt, 1H, $J=4.1$, 9.5 Hz), 3.18–3.10 (m, 1H), 2.38–2.15 (m, 2H), 1.73–1.51 (m, 2H), 0.90 (s, 9H), 0.11 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 142.2, 127.8, 127.3, 127.2, 73.4, 59.8, 51.4, 50.2, 32.1, 31.2, 25.8, 18.2, −4.8, −5.0; MS-CI *m/e* 332 $[M+H]^+$, 91; HRMS calcd for $C_{19}H_{30}NO_2Si$: 332.2046, found: 332.2050. Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.84; H, 8.82; N, 4.23. Found: C, 69.02; H, 8.92; N, 4.33.

3.1.21. (3*S*,5*R*,1′*R*)-3-((*t*-Butyldimethylsilyloxy)-(phenyl)methyl)-1-azabicyclo[3.2.0]heptane-2-thione (28a). Lawesson's reagent (0.072 g, 0.18 mmol) was added with stirring to lactam **27** (0.12 g, 0.36 mmol) in PhMe (4 mL) and the mixture was heated to reflux for 1 h. Rotary evaporation and chromatography (hexanes/EtOAc 5:1) gave thiolactam **28a** (0.10 g, 81%) as a yellow oil: R_f 0.7 (hexanes/EtOAc 5:1); $[\alpha]_D^{20}=-64.4$ ($c=0.9$, $CHCl_3$); IR (neat) 1418, 1252, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.21 (m, 5H), 5.74 (d, 1H, $J=3.5$ Hz), 4.59 (app quintet, 1H, $J=7.1$ Hz), 4.39–4.31 (m, 1H), 4.08–4.00 (m, 1H), 3.40–3.32 (m, 1H), 2.51–2.29 (m, 2H), 1.90–1.78 (m, 1H), 1.54–1.42 (m, 1H), 0.89 (s, 9H), 0.14 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 142.2, 128.2, 127.6, 127.2, 74.6, 66.8, 61.8, 55.6, 35.7, 30.5, 25.9, 18.2, −4.7, −4.8; CI-MS *m/e* 348 $[M+H]^+$, 290; HRMS calcd for $C_{19}H_{30}NOSSi$: 348.1817, found: 348.1826. Anal. Calcd for $C_{19}H_{29}NOSSi$: C, 65.67; H, 8.42; N, 4.03. Found: C, 65.73; H, 8.26; N, 3.95.

3.1.22. (3*S*,7*R*,1′*R*)-3-(1-Hydroxy-(phenyl)methyl)-1-azabicyclo[3.2.0]heptan-2-thione (28b). H_2SiF_6 in CH_3CN (1%; 0.7 mL) was added with stirring to thiolactam **28a** (0.08 g, 0.24 mmol) in CH_3CN (2.5 mL) at 0°C. After 2 h at room temperature, saturated aqueous $NaHCO_3$ (2 mL) was added and the aqueous phase was separated and extracted with EtOAc (3×5 mL). The combined organic phases were dried (Na_2SO_4), filtered, rotary evaporated and chromatographed (hexanes/EtOAc 4:1) to yield the desired alcohol **28b** (0.045 g, 80%) as a yellow oil: R_f 0.4 (hexanes/EtOAc 3:1); $[\alpha]_D^{22}=+198.4$ ($c=0.3$, $CHCl_3$); IR (neat) 3334, 1473, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5H), 5.98 (d, 1H, $J=1.3$ Hz), 4.85 (d, 1H, $J=9.2$ Hz), 4.67–4.58 (m, 1H), 4.47–4.25 (m, 2H), 3.30–3.20 (m, 1H), 2.69–2.59 (m, 1H), 2.36–2.25 (m, 1H), 2.06–1.92 (m, 1H), 1.79–1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 141.3, 128.6, 128.2, 127.1, 76.5, 67.4, 59.3, 55.3, 39.1, 30.4; CI-MS *m/e* 234 $[M+H]^+$; HRMS calcd for $C_{13}H_{16}NOS$: 234.0953, found: 234.0947. Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.93; H, 6.49; N, 6.01. Found: C, 67.16; H, 6.76; N, 5.79.

3.1.23. (3*R*,7*R*,1′*R*)-1-Aza-3-(1-(*tert*-butyldimethylsilyloxy)-(phenyl)methyl)bicyclo[3.2.0]heptane (29). Raney Ni in EtOH (prewashed with H_2O (2×) and EtOH (6×)) was added with stirring to thiolactam **28a** (0.02 g, 0.06 mmol) in EtOH (5 mL) and the mixture was heated to reflux for 1 h. The mixture was filtered through Celite and washed with EtOH. Rotary evaporation gave tertiary amine **29** (capricious reaction, 0–100%) as a yellow oil: IR (neat) 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.25 (m, 5H), 4.68 (d, 1H, $J=6.0$ Hz), 3.97–3.78 (m, 2H), 3.20–3.09 (m, 2H), 2.63–2.44 (m, 3H), 2.00–1.63 (m, 3H), 0.91 (s, 9H), 0.06 (s, 3H), −0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 128.0, 127.2, 126.0, 77.3, 65.9, 60.9, 57.3, 53.5, 36.4, 25.8, 23.9, 18.2, −4.5, −5.1; CI-MS *m/e* 318 $[M+H]^+$; HRMS calcd for $C_{19}H_{32}NOSi$: 318.2253, found: 318.2260.

3.1.24. (2*S*,3*S*,7*R*,1′*R*)-3-(1-*tert*-Butyldimethylsilyloxy)-(phenyl)methyl)-2-methoxy-1-azabicyclo-[3.2.0]heptane (30a). $NaBH_4$ (0.1 g, 2.8 mmol) was added slowly with stirring to $NiCl_2{\cdot}6H_2O$ (0.22 g, 0.9 mmol) and thiolactam **28a** (0.04 g, 0.11 mmol) in MeOH (1 mL) and THF (0.3 mL) at 0°C. After 2 h, the reaction mixture was filtered through Celite, washed with MeOH, the filtrate was rotary evaporated and the residue was partitioned between H_2O and CH_2Cl_2. The combined organic layers were washed with H_2O and dried (Na_2SO_4). Filtration, rotary evaporation and chromatography ((CH_2Cl_2/NH_4OH 5:1)/MeOH 30:1) gave **30a** (0.012 g, 32%) as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 4.83 (d, 1H, $J=5.8$ Hz), 4.00–3.96 (m, 1H), 3.95 (d, 1H, $J=6.0$ Hz), 3.68 (dt, 1H, $J=3.9$, 8.3 Hz), 3.33 (app. q, 1H, $J=8.5$ Hz), 3.11 (s, 3H), 2.60–2.47 (m, 2H), 2.04–1.61 (m, 3H), 0.91 (s, 9H), 0.06 (s, 3H), −0.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 127.8, 127.1, 126.5, 104.2, 75.3, 64.5, 58.2, 55.4, 53.6, 35.1, 25.8, 24.4, 18.2, −4.6, −5.1; CI-MS *m/e* 348 $[M+H]^+$; HRMS calcd for $C_{20}H_{34}NO_2Si$: 348.2359, found: 348.2366.

3.1.25. (2*S*,3*S*,7*R*,1′*R*)-3-(1-*tert*-Butyldimethylsilyloxy)-(phenyl)methyl)-2-ethylthio-1-azabicyclo-[3.2.0]heptane (30b). $Et_3O^+BF_4^-$ (0.013 g, 0.07 mmol) in CH_2Cl_2 (1 mL) was added dropwise with stirring to **28a** (0.02 g, 0.06 mmol) in dry CH_2Cl_2 (1 mL) at 0°C and the mixture was warmed up to room temperature. The solution was recooled to 0°C, $NaBH_3CN$ (0.02 g, 0.3 mmol) in MeOH (1 mL) was added and the mixture allowed to warm up to room temperature. After 5 h, rotary evaporation and chromatography ((CH_2Cl_2/NH_4OH 5:1)/MeOH 30:1) gave **30b** as a yellow oil (0.012 g, 50%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 4.96 (d, 1H, $J=5.4$ Hz), 4.05–3.96 (m, 1H), 3.78–3.62 (m, 2H), 3.05–3.02 (m, 1H), 2.60–2.46 (m, 4H), 2.15–2.10 (m, 1H), 1.77–1.69 (m, 2H), 1.25 (t, 3H, $J=7.4$ Hz), 0.92 (s, 9H), 0.07 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 127.8, 127.4, 127.0, 76.2, 75.0, 65.3, 58.6, 56.5, 34.5, 25.9, 25.5, 23.8, 18.2, 14.7, −4.7, −5.0; CI-MS *m/e* 378 $[M+H]^+$, 316; HRMS calcd for $C_{21}H_{36}NOSSi$: 378.2287, found: 378.2287.

3.1.26. 2-(Hydroxy-(2-nitrophenyl)methyl)pent-1-en-3-one (31).[6] 2-Nitrobenzaldehyde (0.086 g, 0.57 mmol) and ethyl vinyl ketone (0.047 mL, 0.47 mmol) were added with stirring to amine **29** (0.015 g, 0.05 mmol) in CH_2Cl_2 (1 mL) at −35°C and the mixture was stirred for 2 h. Rotary evaporation and chromatography (hexanes/EtOAc 4:1) gave

ester **31** (0.075 g, 68%; 26% ee: Diacel Chiracel OD-H column, hexanes/EtOH 95:5) as a yellow oil: R_f 0.3 (hexanes/EtOAc 4:1); IR (neat) 3467, 1679, 1528, 1321 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.46 (m, 4H), 6.25–6.17 (m, 2H), 5.75 (d, 1H, J=0.86 Hz), 3.53 (bs, 1H), 2.77 (dq, 2H, J=1.5, 7.3 Hz), 1.12 (t, 3H, J=7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 148.4, 148.0, 136.6, 133.5, 128.9, 128.5, 125.2, 124.7, 67.8, 31.2, 8.1; CI-MS *m/e* 253 $[M+NH_4]^+$, 236 $[M+H]^+$; HRMS calcd for $C_{12}H_{14}NO_4$: 236.0923, found: 236.0921.

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