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Enantiodivergent synthesis of N-protected azetidine-2-carboxylic acid

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ABSTRACT

A new route to both enantiomers of *N*-tosyl-azetidine-2- carboxylic acid has been developed from (*R*)-2-cyclohexylideneglyceraldehyde which proceeded with good overall yield and excellent enantiomeric purity.

1. Introduction

Azetidine-2-carboxylic acid (aze) **1** (Fig. 1), a naturally occurring[1] but non-proteinogenic amino acid, has found extensive application as; (i) a proline mimic,[2] (ii) part-structure of naturally occurring compounds[3] such as mugineic acid[4] and its congeners **2**–**4**; (iii) building block in amino acid and β-lactam synthesis;[5] (iv) roles in the design and synthesis of modified peptides,[6] and (v) incorporation into pharmaceutically important[7] compounds such as the thrombin inhibitors melagratran **5** and exenta **6**,[8a,b] the analgesic compound **7**,[8c] as an ACE inhibitor,[9] cell cytotoxic agent and radiosensitizer.[10] Both enantiomers of this important amino acid have also found application in the area of asymmetric synthesis as chiral catalysts and/or auxiliaries in transformations such as Diels–Alder reactions,[11] Michael additions,[12] cyclopropanations,[13] α-aminations of ketones[14] and ketone reductions[15] among others. Various substituted azetidine-2-carboxylic acid derivatives have also proven to be important in many respects.[16]

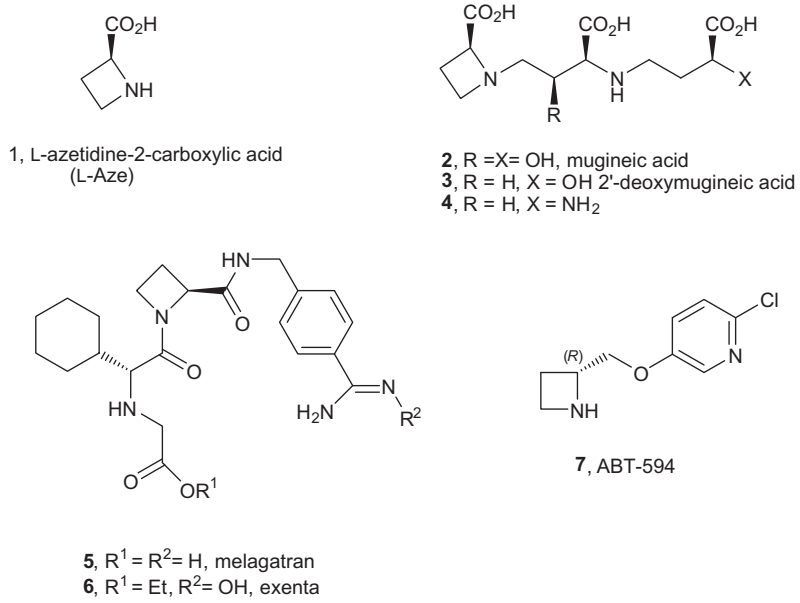

Figure 1. Selected biologically active compounds accommodating derivatives of azetidine-2-carboxylic acid **1**.

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Thus, several elegant routes to this important amino acid either in the racemic form[17] or as the (*S*)-enantiomer[16i,18] have been developed. However, to the best of our knowledge only one synthesis of both enantiomers of azetidine-2-carboxylic acid has been reported[19] excluding several known resolution procedures. We became interested in the development of a common route to both enantiomers of this α-amino acid from a common source and using a common set of reactions in continuation of our interest[20] in the synthesis of natural and non-natural α-amino acids of significance. Herein, we report a new synthetic route to both enantiomers of *N*-tosyl-azetidine -2-carboxylic acid.

2. Results and discussion

The allylation of α-chiral imines has been extensively studied as a route for the synthesis of homoallylic amines.[21] We have recently reported a diastereodivergent synthesis of homoallylic amines from the allylation of an imine derived from (*R*)-2-cyclohexylideneglyceraldehyde **8**.[22] We opted to study the allylation of chiral imine **9** (Scheme 1), obtainable from **8**, for the synthesis of the corresponding homoallylic amines **10** and **11**, identified as potential precursors of the title compounds.

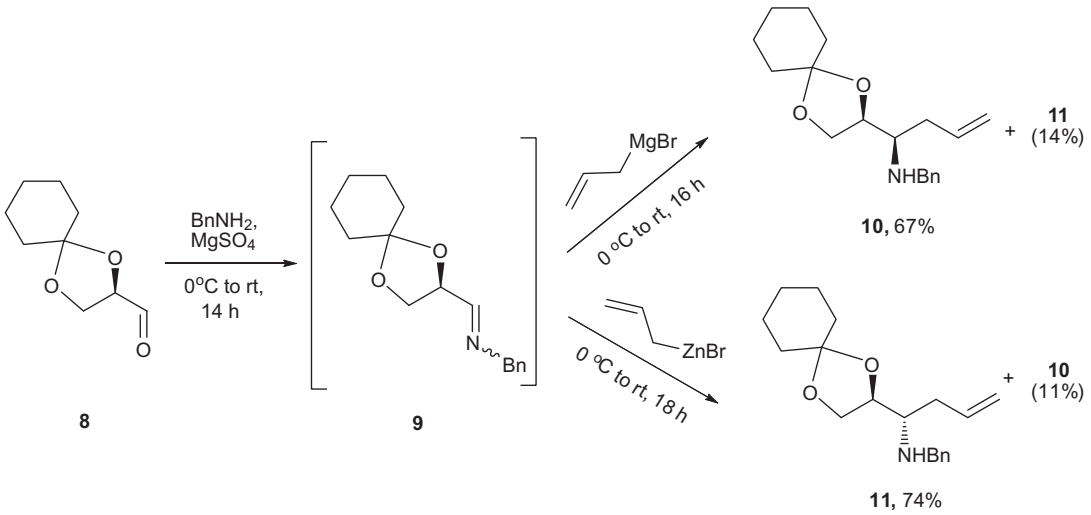
Thus, imine **9** was prepared by dehydrative condensation of benzylamine with aldehyde **8** in the presence of powdered magnesium sulfate in near quantitative yield and was treated with allylmagnesium bromide under optimized conditions to give a separable mixture of the expected homoallylic amines **10** and **11** in a ratio of ~5:1 in a combined yield of 81%. Similarly, when a solution of the imine **9** was treated with allylzinc bromide (prepared in situ from allyl bromide and zinc powder), the amines **10** and **11** were obtained in a comparable yield but with a reversal of selectivity favouring the other isomer. Although the complementary mode of these addition reactions was an advantage, the assignment of stereochemistry at the newly formed stereocentre in each of these amines at this stage could not be made with certainty because of the fact that the nature of diastereoselection in imine addition reactions is known to be dependent on several factors.[23] However, the following synthetic work (Scheme 2) unambiguously established the configuration of the amines **10** and **11** to be *syn*- and *anti*-respectively.

The amine **10** was protected as its Cbz derivative **12** in readiness for a one-carbon degradation of the olefinic unit through ozonolysis and in situ reduction of the resulting aldehyde to deliver the desired primary alcohol **13** in an overall yield of 73% over three steps. Simultaneous reductive removal of the Cbz and benzyl groups from **13** then smoothly produced amine **14**. N-heterocyclisation of this γ-amino alcohol using a tosyl chloride–KOH combination[24] led to the formation of the azetidine derivative **15** possibly through an intermediate *N*,*O*-ditosylate (not isolated). Acid mediated deprotection of the cyclohexylidene acetal moiety in compound **15** cleanly produced diol **16** which was transformed into a carboxyl function under Sharpless' protocol[25] using $NaIO_4$ and a catalytic amount of $RuCl_3$. *N*-Tosylazetidine-2-carboxylic acid **17**, thus produced, was esterified with methyl iodide in the presence of caesium carbonate to obtain the corresponding methyl ester **18**. The latter showed a specific rotation {$[\alpha]_D$ = +141.9 (*c* 0.4, $CHCl_3$)} which is close in magnitude but opposite in sign to that reported[26] for (*S*)-*N*-(4-methylphenyl)sulfonyl-2-azetidinecarboxylic acid methyl ester {$[\alpha]_D$ = −144.3 (*c* 1.4, $CHCl_3$)}. The configuration of the nitrogen-bearing stereogenic centre in each of the compounds **10** and **12**–**18** thus followed from this specific rotation comparison. The synthesis of compound **18** proceeded in a linear sequence of seven steps from **11** in an overall yield of 24%.

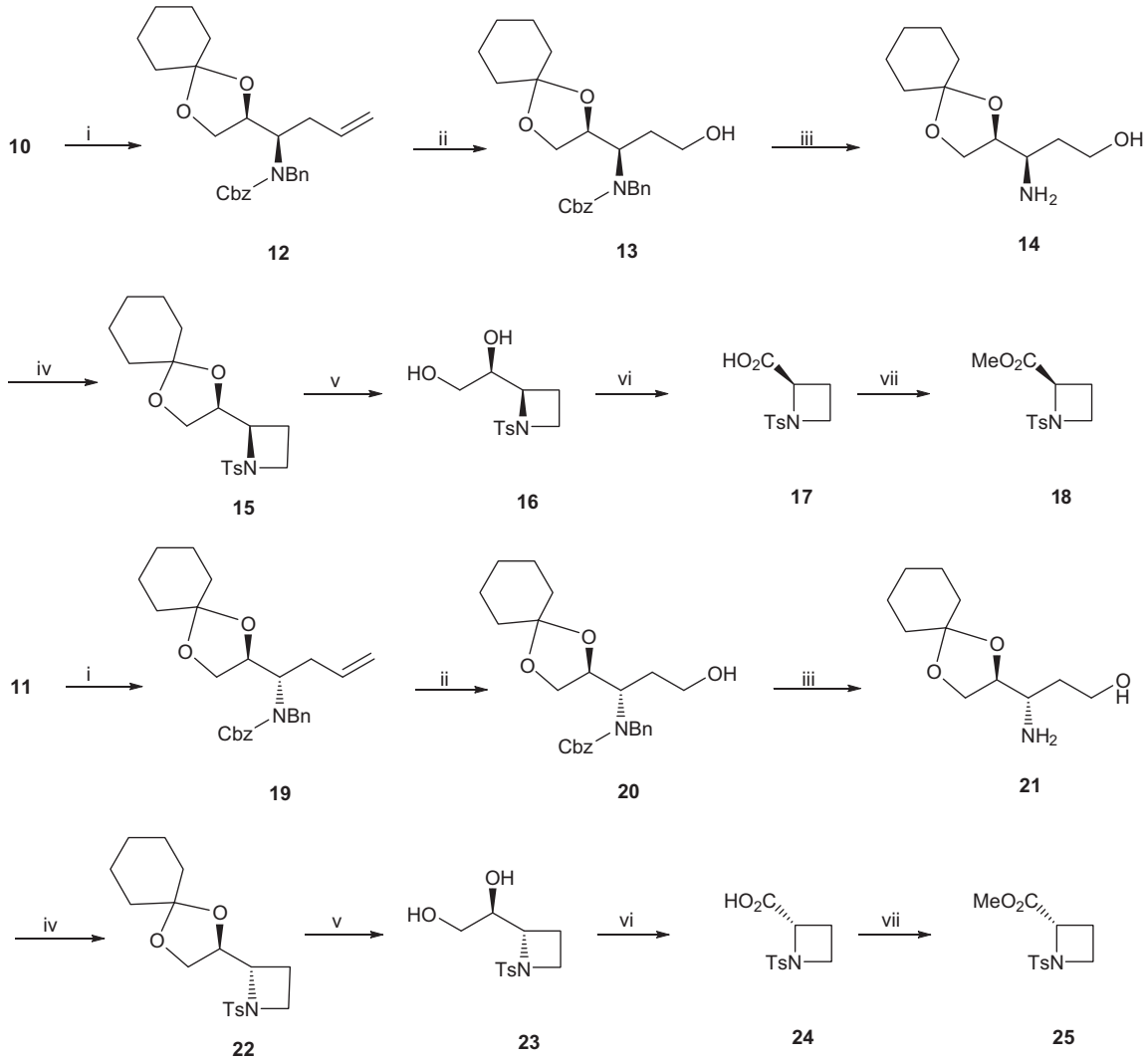
Similarly, the *anti*-homoallylic amine **11** was transformed into (*S*)-azetidine-2-carboxylic acid derivative **25** in an overall yield of 20.3% over seven steps through the intermediates **19**–**24** following an identical sequence of reactions detailed above for the conversion of **10**–**18**. The enantiomeric purity of each of the enantiomeric *N*-tosyl-azetidine-2-carboxylic acid derivatives was determined from chiral HPLC studies on a CHIRALPAK AD-H column using 20% 2-propanol in hexane as eluent and the enenatiomeric excess values were recorded to be 95% and 93% respectively for **17** and **24**.

3. Conclusion

In conclusion, we have demonstrated a concise synthesis of both enantiomers of *N*-tosyl-azetidine-2-carboxylic acid starting from a single source and using a common set of reactions. The synthesis involves the use of easily available reagents and simple reaction conditions. The approach involves the utilization of an initial divergency in the allylation step of the chiral imine **9** for an ultimate enantiodivergent synthesis of the title compounds, which does not have much precedence. It may therefore complement the existing methodologies and hence find application.



Scheme 1. Preparation of the homoallylic amines **10** and **11**.



Scheme 2. Reagents and conditions: (i) Cbz-Cl, $NaHCO_3$, rt, 6 h, **12** (91%), **19** (87%); (ii) O_3, Me_2S, and then $NaBH_4$, **13** (81%), **20** (79%); (iii) H_2, $Pd(OH)_2$, MeOH, rt, 8 h, **14** (89%), **21** (94%); (iv) TsCl, KOH (powder), THF, reflux, 6 h, **15** (64%), **22** (61%); (v) HCl (6 M),THF, rt, 5 h, **16** (86%), **23** (85%); (vi) $NaIO_4$, $RuCl_3$, rt, 3 h, **17** (73%), **24** (68%); (vii) MeI, Cs_2CO_3, DMF, rt, 12 h, **18** (91%), **25** (89%).

4. Experimental

4.1. General

Column chromatography was performed on silica gel, Merck grade 230–400 mesh and neutral alumina. Reactions were monitored by thin-layer chromatography; TLC plates were visualized with UV, in an iodine chamber, or with vaniline solution, unless noted otherwise. Melting points were recorded in open capillaries and are uncorrected. Optical rotations were measured on a Rudolph Autopol-IV polarimeter purchased from a DST grant. IR spectra were recorded on a Perkin–Elmer Spectrum-1 instrument using KBr disks, chloroform solution or as neat. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer, operating at 400 and 100 MHz, respectively. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for ^1H NMR and $^{13}CDCl_3$ (77.0 ppm) for ^{13}C NMR. The following abbreviations were used to denote the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, ddd = doublet of double doublet, dt = doublet of triplet, br = broad, etc. HRMS were performed in a JEOL-JNM mass spectrometer and obtained from a paid source. THF, Toluene, benzene and ether were freshly distilled under argon from a purple solution of sodium benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

4.1.1. (*R*)-*N*-Benzyl-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine 10 and (*S*)-*N*-benzyl-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine 11

A stirred solution of aldehyde **8** (0.50 g, 2.9 mmol) in dry THF (10 mL) was cooled to 5 °C and anhydrous $MgSO_4$ (1.5 g, excess) followed by a solution of freshly distilled benzylamine (0.5 ml, 4.5 mmol) in THF (6 mL) were added over 10 min. The reaction mixture was then allowed to warm to rt and stirred for 14 h. It was filtered and the filtrate was then concentrated in vacuo to produce the crude imine derivative **9** as viscous yellowish liquid which was used for next step without any purification. The crude imine was then taken in dry THF (4.5 mL) and was cooled to −30 °C before adding a solution of allylmagnesium bromide [1.0 (M) in diethyl ether, 4.6 mL] under nitrogen atmosphere. It was stirred at 0 °C for 4 h and then at rt for 16 h. It was cooled back to 0 °C and quenched by the slow addition of aqueous NH_4Cl solution (5%, 10 mL). The reaction mixture was concentrated and then diluted with water (25 mL) before extracting with EtOAc

(2 × 25 mL). The combined organic layer was washed successively with water (2 × 50 mL) and brine (50 mL), and then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to leave a crude product which on flash column chromatography using EtOAc in petroleum ether (1:19) provided the diastereomeric amine derivatives, in the order **11** (0.125 g, 14%) followed by **10** (0.592 g, 67%) each as a pale yellow liquid. Data for **10**: R_f: 0.5 (petroleum ether/EtOAc 19/1), $[\alpha]_D^{25} = -12.0$ (*c* 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.36 (m, 4H), 7.24–7.22 (m, 1H), 5.88–5.74 (m, 1H), 5.11 (d, *J* = 7.2 Hz, 1H), 5.06 (s, 1H), 4.10 (q, *J* = 6.7 Hz, 1H), 4.01–3.94 (m, 1H), 3.90 (s, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.71 (t, *J* = 7.4 Hz, 1H), 2.70 (q, *J* = 6.3 Hz, 1H), 2.33–2.23 (m, 1H), 2.17–2.07 (m, 1H), 1.69–1.58 (m, 9H), 1.39 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 135.0, 128.4, 128.2, 126.9, 117.5, 109.5, 77.9, 66.4, 58.6, 51.5, 37.6, 35.1, 34.9, 25.2, 24.1, 24.0. IR (neat) ν_{max} 3332, 2933, 2857, 1644, 1450, 1103, 926 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 302 (M^++H, 100). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65; Found: C, 75.97; H, 9.17; N, 4.52. Data for **11**: R_f: 0.5 (petroleum ether/EtOAc 24/1). $[\alpha]_D$ = +18.0 (*c* 2.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (m, 4H), 7.24–7.21 (m, 1H), 5.88–5.77 (m, 1H), 5.13 (d, *J* = 6.8 Hz, 1H), 5.09 (s, 1H), 4.05–3.99 (m, 2H), 3.91–3.84 (m, 2H), 3.76 (d, *J* = 13.2 Hz, 1H), 2.80 (q, *J* = 5.6 Hz, 1H), 2.32 (t, *J* = 6.4 Hz, 2H), 1.62–1.56 (m, 8H), 1.49 (br s, 1H), 1.39 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 134.9, 128.4, 128.1, 126.9, 117.9, 109.3, 77.3, 66.5, 58.2, 51.8, 36.3, 35.2, 34.9, 25.2, 24.0, 23.8. IR (neat) ν_{max} 3330, 2935, 2861, 1639, 1449, 1103, 928 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 302 (M^++H, 100). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65; Found: C, 75.86; H, 9.26; N, 4.74.

4.1.2. (*S*)-*N*-Benzyl-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine 11 and (*R*)-*N*-benzyl-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-en-1-amine 10

The crude imine derivative **9** (2.16 g, 8.34 mmol) was taken in dry THF (9 mL) and was added dropwise to a stirred solution of allylzinc bromide [excess, prepared in situ from allyl bromide (2.34 mL) and Zn dust (1.89 g) in dry THF (22 mL)] under a nitrogen atmosphere at 0 °C and stirred for 16 hours at room temperature. It was again cooled to 0 °C and quenched with aqueous NH_4Cl solution (5%, 20 mL). The reaction mixture was concentrated, diluted with water (25 mL) and then extracted with EtOAc (2 × 25 mL). The combined organic layer was washed successively with water (2 × 50 mL) and brine (50 mL), and then dried over anhydrous Na_2SO_4. It was filtered and the filtrate was concentrated under reduced pressure to leave a crude product which on column chromatography on flash silica gel using EtOAc in petroleum ether (1:19) as eluent provided the diastereomeric amine derivatives, in the order **11** (1.97 g, 74%) followed by the minor isomer **10** (0.29 g, 11%). Compounds **10** and **11** displayed nearly identical spectroscopic data as recorded before.

4.1.3. Benzyl-(*R*)-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-enyl(benzyl)carbamate 12

At first, $NaHCO_3$ (0.75 g), water (0.15 mL) and benzyl chloroformate (0.41 mL, 1.99 mmol) were sequentially added to a stirred solution of the compound **10** (0.50 g, 1.66 mmol) in EtOAc (12 mL) and the resulting mixture was stirred at rt for 6 h. It was then diluted with water (25 mL) and further extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with water (2 × 50 mL) followed by brine (50 mL). The organic extract was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuo to leave a crude product which on column chromatography on silica gel using EtOAc in petroleum ether (1:49) provided the product **12** as a colourless liquid (0.66 g, 91%). R_f: 0.5 (petroleum ether/EtOAc: 97/3), $[\alpha]_D^{25} = +4.3$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.10 (m, 10H), 5.59–5.55 (m, 1H), 5.25–5.10 (m, 2H), 5.01–4.87 (m, 2H), 4.64 (dd, *J* = 16 and 29.6 Hz, 1H), 4.49 (d, *J* = 23.6 Hz, 1H), 4.29 (d, *J* = 6.4 Hz, 1H), 4.13–3.87 (m, 2H), 3.61 (t, *J* = 8 Hz, 1H), 2.46–2.42 (m, 1H), 2.19–2.15 (m, 1H), 1.57–1.37 (m, 8H),1.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7 (157.2), 138.9 (138.7), 136.6, 134.4 (134.1), 128.5, 128.2 (128.3), 128.1, 127.7 (127.8), 127.4, 126.9 (127.0), 117.7, 109.5, 75.9 (76.0), 67.1 (67.4), 66.8 (67.0), 59.5, 48.4, 36.2, 34.9, 34.0 (34.4), 25.2, 24.0, 23.8. IR (neat) ν_{max} 3065, 3032, 2935, 2861, 1698, 1450, 1413, 1250, 1229, 1100 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 458 (M^++Na, 100). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22; Found: C, 74.58; H, 7.71; N, 3.11.

4.1.4. Benzyl benzyl-((*R*)-3-hydroxy-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)propyl) carbamate 13

Ozone was bubbled through a pre-cooled (−78 °C) solution of 12 (600 mg, 1.38 mmol) in a solvent mixture of CH_2Cl_2: methanol (4:1, 25 mL) containing a pinch of $NaHCO_3$ until the pale blue colour persisted. The excess ozone was flushed off with oxygen and dimethyl sulfide (0.75 mL) was added. The reaction mixture was warmed to 0 °C and stirred at the same temperature for 6 h. The reaction mixture was filtered through Celite and the filter cake was washed thoroughly with EtOAc (30 mL). Evaporation of the solvent under reduced pressure yielded the crude aldehyde (596 mg) which was taken in dry methanol (6 mL) and cooled to 0 °C. Sodium borohydride (79 mg, 2.07 mmol) was added in one portion and stirring was continued for 7 h at rt. The reaction mixture was quenched by the dropwise addition of saturated NH_4Cl solution (4 mL) at 0 °C and then it was concentrated, diluted with water (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed sequentially with water (2 × 25 mL) and brine (25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to leave a crude product and column chromatographic purification on silica gel using EtOAc in petroleum ether (2:3) yielded compound **13** as a colourless liquid (491 mg, 81%). R_f: 0.4 (petroleum ether/EtOAc: 7/3), $[\alpha]_D^{25} = +20.0$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.25 (m, 10H), 5.25–5.14 (m, 2H), 4.57 (dd, *J* = 18.2, 15.6 Hz, 2H), 4.28 (t, *J* = 6.8 Hz, 1H), 4.19 (d, *J* = 6.4 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.67 (t, *J* = 7.2 Hz, 1H), 3.43 (s, 1H), 3.35–3.20 (m, 1H), 2.57 (br s, 1H), 1.75 (s, 2H), 1.59–1.45 (m, 8H), 1.38 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 138.6, 136.3, 128.5, 128.1, 128.0, 127.9, 127.7, 127.3, 110.0, 75.5, 67.6, 67.2, 58.3, 56.8, 36.3, 35.0, 32.0, 25.1, 23.9, 23.8. IR (neat) ν_{max} 3454, 2936, 2862, 1692, 1450, 1417, 1331, 1221, 1109 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 462 (M^++Na, 100). Anal. Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19; Found: C, 71.24; H, 7.81; N, 3.05.

4.1.5. (*R*)-3-Amino-3-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)propan-1-ol 14

Palladium hydroxide on carbon (Pearlman's catalyst, 25 mg) was added to a solution of compound **13** (0.48 g, 1.09 mmol) in EtOAc (10 mL) at rt and the heterogeneous mixture was stirred under hydrogen atmosphere for 8 h. It was then filtered through Celite and the filter cake was thoroughly washed with EtOAc (30 mL). The combined filtrate was concentrated in vacuo to leave a crude mass which was purified by chromatography over neutral alumina using 80% EtOAc in petroleum ether as eluent to furnish the product **14** as a colourless liquid (0.21 g, 89%). R_f: 0.4 (petroleum ether/EtOAc/methanol: 5/4/1), $[\alpha]_D^{25} = -6.95$ (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.03 (t, *J* = 7.5 Hz, 1H), 3.93 (q, *J* = 6.4 Hz, 1H), 3.84 (t, *J* = 5.2 Hz, 2H), 3.64 (t, *J* = 7.2 Hz, 1H), 2.93–2.88 (m, 1H), 2.82 (br s, 3H), 1.59–1.49 (m, 10H), 1.48–1.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.9, 79.7, 66.3, 62.3, 55.2, 36.3, 34.7,

34.5, 25.1, 24.0, 23.8. IR (neat) ν_{max} 3371, 2936, 2862, 1696, 1367, 1164 cm^{-1}. HRMS (TOF MS ES+): obsd 216.1594 (M+H); calcd 216.1599.

4.1.6. (*R*)-2-((*S*)-1,4-Dioxaspiro[4.5]decan-2-yl)-1-tosylazetidine 15

p-Toluenesulfonyl chloride (1.30 g, 6.84 mmol) and anhydrous KOH dust (0.37 g, 6.84 mmol) were added sequentially into a solution of the amino alcohol **14** (0.49 g, 2.28 mmol) in dry THF (25 mL) under a nitrogen atmosphere. The resulting mixture was heated at reflux for 6 h, and then allowed to come to rt. It was diluted with water (25 mL) before being extracted with EtOAc (2 × 25 mL). The combined organic layer was washed sequentially with HCl (1 N, 50 mL), aqueous $NaHCO_3$ solution (10%, 50 mL), water (2 × 50 mL) and brine (50 mL). It was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to leave a crude product which was purified by column chromatography on silica gel using EtOAc in petroleum (1:9) as eluent to provide the compound **15** as a colourless gummy liquid. (0.51 g, 64%). R_f: 0.5 (petroleum ether/EtOAc: 9/1), $[\alpha]_D^{25} = +91.5$ (*c* 0.79, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 2H), 4.39 (s, 1H), 4.25–4.20 (m, 1H), 4.10 (t, *J* = 7.3 Hz, 2H), 3.72–3.68 (m, 1H), 3.56 (q, *J* = 8.2 Hz, 1H), 2.46 (s, 3H), 2.19–2.13 (m, 1H), 1.93–1.86 (m, 1H), 1.57 (s, 8H), 1.39 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 131.7, 129.7, 128.4, 110.1, 75.3, 64.3, 62.9, 48.0, 36.2, 34.2, 25.1, 24.0, 23.7, 21.6, 17.0. IR (neat) ν_{max} 2932, 2860, 1339, 1156, 1098, 1037 cm^{-1}. HRMS (TOF MS ES+): obsd 374.1403 (M^++Na); calcd 374.1402.

4.1.7. (*S*)-1-((*R*)-1-Tosylazetidin-2-yl) ethane-1,2-diol 16

At first, HCl (6 M, 6 mL) was added dropwise to a solution of **15** (0.45 g, 1.28 mmol) in THF (6 mL), and the resulting reaction mixture was stirred at rt for 5 h. It was then diluted with water (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed successively with aqueous $NaHCO_3$ solution (10%, 50 mL), water (2 × 50 mL) and brine (50 mL). The EtOAc extract was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuo to leave a crude product which on column chromatography over silica gel using EtOAc in petroleum ether (2:3) as eluent provided compound **16** as a colourless gummy solid (0.30 g, 86%). R_f: 0.5 (petroleum ether/EtOAc: 4/6), $[\alpha]_D^{25} = +102.5$ (*c* 0.86, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 4.01 (q, *J* = 7.5 Hz, 1H), 3.88 (s, 2H), 3.73 (d, *J* = 9.3 Hz, 2H), 3.54 (q, *J* = 8.4 Hz, 2H), 2.48 (s, 3H), 2.33 (s, 1H), 2.09–1.98 (m, 1H), 1.93 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 130.4, 130.0, 128.6, 74.6, 65.8, 61.9, 48.1, 21.6, 18.3. IR (neat) ν_{max} 3412, 2925, 2888, 1598, 1355, 1160, 1092 cm^{-1}. HRMS (TOF MS ES+): obsd 294.0775 (M^++Na); calcd 294.0776.

4.1.8. (*R*)-1-Tosylazetidine-2-carboxylic acid 17

Sodium metaperiodate (0.44 g, 2.07 mmol) was added to a solution of diol **16** (0.14 g, 0.52 mmol) in a mixture of CCl_4 (2.6 mL), CH_3CN (2.6 mL) and water (4 mL). The reaction mixture was vigorously stirred at rt for 5 min and then ruthenium trichloride (4 mg, 2.5 mol %) was added to it. Stirring was continued for 3 h. It was then diluted with CH_2Cl_2 (15 mL) and extracted with aqueous $NaHCO_3$ solution (1 M, 20 mL). This aqueous layer was washed with ether and carefully acidified with saturated aqueous $KHSO_4$ solution. The acidified solution was then extracted with EtOAc (2 × 25 mL) and the combined organic layer was washed sequentially with water (2 × 25 mL) and brine (25 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to leave a crude product which on column chromatography on silica gel using EtOAc in petroleum ether (3:2) yielded the carboxylic acid **17** as a colourless solid (0.96 g, 73%). R_f: 0.4 (petroleum ether/EtOAc 3/7), Mp: 135–137 °C, $[\alpha]_D^{25} = +148.3$ (*c* 0.59, $CHCl_3$), lit.[26b] $[\alpha]_D = -154.7$ (*c* 1, $CHCl_3$), for (*S*)-enantiomer; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.12 (br s, 1H), 4.46 (t, *J* = 8.0 Hz, 1H), 3.66 (t, *J* = 8.0 Hz, 2H), 2.40 (s, 3H), 2.46–2.36 (m, 1H), 2.28–2.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 145.1, 131.2, 130.1, 128.4, 60.6, 47.7, 21.7, 19.8. IR (KBr) ν_{max} 3413, 2923, 1722, 1707, 1348, 1161, 1094 cm^{-1}. HRMS (TOF MS ES^+): obsd 278.0465 (M^++Na); calcd 278.0463.

4.1.9. (*R*)-Methyl 1-tosylazetidine-2-carboxylate 18

Methyl iodide (0.06 mL, 0.94 mmol) was added dropwise to a stirred solution of **17** (0.06 g, 0.23 mmol) in dry DMF (3 mL) at 0 °C under a nitrogen atmosphere and then anhydrous Cs_2CO_3 (0.15 g, 0.47 mmol) was added to the reaction mixture in one portion. Stirring was continued for 12 h at rt and then diluted with water (25 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed successively with water (2 × 25 mL) and brine (25 mL). The organic extract was then dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated in vacuo to leave a crude product which was purified by column chromatography on silica gel using EtOAc in petroleum ether (1:9) solvent to provide compound **18** as a colourless solid (0.058 g, 91%). R_f: 0.6 (petroleum ether/EtOAc: 4/1), Mp: 99–100 °C, $[\alpha]_D^{25} = +141.9$ (*c* 0.37, $CHCl_3$), lit.[26a] $[\alpha]_D = -144.3$ (*c* 1.435, $CHCl_3$), for the (*S*)-enantiomer; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.60 (t, *J* = 8.6 Hz, 1H), 3.87 (q, *J* = 8.4 Hz, 1H), 3.76- 3.73 (m, 1H), 3.72 (s, 3H), 2.45 (s, 3H), 2.41–2.34 (m, 1H), 2.32–2.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 143.7, 132.8, 129.2, 127.8, 60.1, 52.0, 47.3, 21.1, 19.0. IR (KBr) ν_{max} 2925, 2854, 1739, 1348, 1159, 1091 cm^{-1}.

4.1.10. Benzyl (*S*)-1-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)but-3-enyl (benzyl) carbamate 19

Compound **19** was prepared from **11** by following the procedure described for **12**. Yield: 87%. R_f: 0.5 (petroleum ether/EtOAc 49/1). $[\alpha]_D^{25} = +22.95$ (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.19 (m, 10H), 5.73–5.59 (m, 1H), 5.23–5.14 (m, 2H), 5.04–4.94 (m, 2H), 4.56 (d, *J* = 16 Hz, 1H), 4.35 (d, *J* = 16 Hz, 1H), 4.14 (br s, 1H), 3.98 (br s, 1H), 3.71 (br t, 1H), 3.55–3.45 (m, 1H), 2.52 -2.42 (m, 2H), 1.56–1.53 (m, 8H), 1.44–1.35 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 138.7, 136.5, 135.0, 128.4, 128.1, 127.9, 127.6, 127.4, 127.2, 117.3 (117.2), 110.2, 76.8, 67.6, 67.3 (67.2), 59.5, 48.4, 36.4 (36.3), 34.8, 33.1, 25.1, 24.0, 23.7. IR (neat) ν_{max} 3032, 2935, 2860, 1699, 1450, 1421, 1225, 1100, 1040, 926 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 458 (M^++Na, 100), 474 (M^++K, 10). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22; Found: C, 74.57; H, 7.77; N, 3.37.

4.1.11. Benzyl benzyl((*S*)-3-hydroxy-1-((*S*)-1,4-dioxaspiro[4.5]-decan-2-yl) propyl) carbamate 20

Compound **20** was prepared from **19** by following the procedure described for **13**. Yield: 79%. R_f: 0.5 (petroleum ether/EtOAc: 7/3), $[\alpha]_D^{25} = +2.9$ (*c* 0.80, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.22–7.28 (m, 10H), 5.21–5.16 (m, 2H), 4.59 (d, *J* = 15.6 Hz, 1H), 4.42 (d, *J* = 15.6 Hz, 1H), 4.24 (br s, 1H), 3.77 (t, *J* = 7.2 Hz, 1H), 3.59–3.51 (m, 2H), 3.45–3.38 (m, 1H), 2.10–1.92 (m, 1H), 1.82–1.71 (m, 1H), 1.57 (br s, 6H), 1.45–1.43 (m, 4H), 1.36 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 138.4, 136.1, 128.5, 128.4, 128.2, 128.1, 127.6, 127.3, 110.5, 67.9, 67.2, 58.8, 56.1, 42.0, 36.1, 34.6, 30.9, 27.0, 25.1, 24.0, 23.7. IR (neat) ν_{max} 3482, 2936, 1698, 1450, 1416, 1163, 1102, 1039, 929, 771, 699 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 462 (M^++Na, 100), 478 (M^++K,10). Anal. Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19; Found: C, 71.22; H, 7.69; N, 3.02.

4.1.12. (*S*)-3-Amino-3-((*S*)-1,4-dioxaspiro[4.5]decan-2-yl)propan-1-ol 21

Compound **21** was prepared from **20** by following the procedure described for **14**. Yield: 94%. R_f: 0.5 (petroleum ether/EtOAc/methanol: 5/4/1), $[\alpha]_D^{25} = +6.4$ (*c* 0.78, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 4.02 (t, *J* = 7.6 Hz, 1H), 3.97 (q, *J* = 6.4 Hz, 1H), 3.84 (dd, *J* = 4.4 and 6.4 Hz, 2H), 3.75 (dd, *J* = 6.0 and 7.6 Hz, 1H) 3.02–3.07 (m, 1H), 2.26 (br s, 3H), 1.71 (qd, *J* = 4.0 and 14.4 Hz, 1H), 1.62–1.52 (m, 8H), 1.53–1.43 (m, 1H), 1.42–1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.8, 79.2, 65.0, 62.4, 54.0, 36.1, 34.5, 34.3, 25.1, 24.0, 23.7. IR (neat) ν_{max} 3788, 3351, 2934, 2860, 1600, 1449, 1366, 1163, 1103, 929 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 216 (M^++H, 100), 238 (M^++Na, 10).

4.1.13. (*S*)-2-((*S*)-1,4-Dioxaspiro[4.5]decan-2-yl)-1-tosylazetidine 22

Compound **22** was prepared from **21** by following the procedure described for **15**. Yield: 61%. R_f: 0.6 (petroleum ether/EtOAc: 9/1), $[\alpha]_D^{25} = -77.0$ (*c* 0.82, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 4.33 (q, *J* = 6.4 Hz, 1H), 4.07 (dd, *J* = 6.0 and 8.4 Hz, 1H), 3.88 (q, *J* = 7.6 Hz, 1H), 3.80 (dd, *J* = 6.0 and 8.8 Hz, 1H), 3.75 (dt, *J* = 4.4 and 8.0 Hz, 1H), 3.61 (q, *J* = 8.0 Hz, 1H), 2.46 (s, 3H), 2.27–2.20 (m, 1H), 1.99–1.95 (m, 1H), 1.57–1.52 (m, 8H), 1.43–1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 132.1, 129.8, 128.3, 110.0, 77.2, 66.4, 63.9, 48.1, 36.2, 34.7, 25.1, 24.0, 23.7, 21.6, 18.2. IR (neat) ν_{max} 2934, 2859, 1335, 1163, 1100, 1039, 927, 815, 676 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 374 (M^++Na, 100). Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99; Found: C, 61.66; H, 7.33; N, 3.82.

4.1.14. (*S*)-1-((*S*)-1-Tosylazetidin-2-yl)ethane-1,2-diol 23

Compound **23** was prepared from **22** by following the procedure described for **16**. Yield: 85%. R_f: 0.5 (petroleum ether/EtOAc: 1/1), $[\alpha]_D^{25} = -45.6$ (*c* 0.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 4.05 (dt, *J* = 4.0 and 8.0 Hz, 1H), 3.94–3.88 (m, 1H), 3.78–3.68 (m, 3H), 3.54 (q, *J* = 8.4 Hz, 1H), 2.80 (d, *J* = 5.2 Hz, 1H), 2.48 (s, 3H), 2.32–2.25 (m, 1H), 2.14–2.11 (m, 1H), 1.92–1.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 131.1, 130.0, 128.5, 72.4, 65.2, 62.6, 48.3, 21.6, 17.2. IR (neat) ν_{max} 3509, 3408, 2970, 2919, 2878, 1598, 1332, 1154, 1098 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 294 (M^++Na, 100), 272 (M^++H, 10). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16; Found: C, 53.19; H, 6.40; N, 5.03.

4.1.15. (*S*)-1-Tosylazetidine-2-carboxylic acid 24

Compound **24** was prepared from **23** by following the procedure described for **17**. Yield: 68%. R_f: 0.4 (petroleum ether/EtOAc 3/7), Mp: 133–136 °C, $[\alpha]_D^{25} = -149.2$ (*c* 0.62, $CHCl_3$), lit.[26b] $[\alpha]_D = -154.7°$ (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 4.50 (t, *J* = 8.4 Hz, 1H), 3.76–3.66 (m, 2H), 2.48 (s, 3H), 2.53–2.43 (m, 1H), 2.33–2.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 145.1, 130.9, 130.1, 128.5, 60.7, 47.7, 21.7, 19.8. IR (neat) ν_{max} 2923, 2853, 1705, 1435, 1340, 1163, 1094, 7734, 683 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 278 (M^++Na, 100), 256 (M^++H, 15).

4.1.16. (*S*)-methyl 1-tosylazetidine-2-carboxylate 25

Compound **25** was prepared from **24** by following the procedure described for **18**. Yield: 89%. R_f: 0.6 (petroleum ether/EtOAc: 4/1), Mp: 97–99 °C, $[\alpha]_D^{25} = -146.5$ (*c* 0.51, $CHCl_3$), lit.[26a] $[\alpha]_D = -144.3°$ (*c* 1.435 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.60 (t, *J* = 8.8 Hz, 1H), 3.87 (q, *J* = 8.4 Hz, 1H), 3.76–3.73 (m, 1H), 3.72 (s, 3H), 2.45 (s, 3H), 2.42–2.35 (m, 1H), 2.32–2.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 144.2, 133.3, 129.7, 128.2, 60.6, 52.4, 47.8, 21.6, 19.5. IR (neat) ν_{max} 3437, 2924, 2853, 1742, 1438, 1347, 1161, 1092, 680 cm^{-1}. MS (TOF MS ES+): *m*/*z* (%) = 292 (M^++Na, 100), 270 (M^++H, 40).

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