A Multikilogram-Scale Synthesis of (*R*)-Methyl 2-[(1*r*,4*R*)-4-(*tert*-Butoxycarbonylamino)cyclohexyl]-2-(2-nitrophenylsulfonamido)acetate – A Doubly Protected Building Block with Three Points of Variation

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Abstract: A robust and scalable synthesis of (*R*)-methyl 2-[(1*r*,4*R*)-4-(*tert*-butoxycarbonylamino)cyclohexyl]-2-(2-nitrophenylsulfonamido)acetate is reported. This serves as a scaffold for the preparation of *trans*-substituted aminocyclohexanes. The key synthetic step is the reduction of D-4-hydroxyphenylglycine, or a protected equivalent, to achieve the required regiochemistry across the cyclohexyl ring.

Key words: chirality, diastereoselectivity, hydrogenation, protecting groups, reduction

Functionalised amino-substituted cyclohexanes are useful building blocks for medicinal chemistry. Compounds containing the general structure **1**, where R^2 is either an amide or alkylamino group, have shown activity against biological targets such as TACE,[1] Factor Xa,[2] antibacterials,[3] MMP,[4] and dipeptidyl peptidase IV.[5]

We required access to kilogram quantities of a suitable building block, which would allow us to vary any of the three positions indicated by R^1, R^2, and R^3 in structure **1** (Figure 1). We chose to focus our efforts on synthesising a building block of structure **2** with the amines protected as nosyl (2-nitrosulfonyl) and Boc. The presence of an ester would allow access to amides and alkyl substitution. We report herein an optimised synthesis, which has been progressed to deliver a single *trans*-diastereomer **2**, on a multikilogram scale.

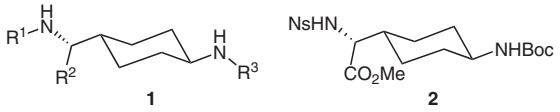
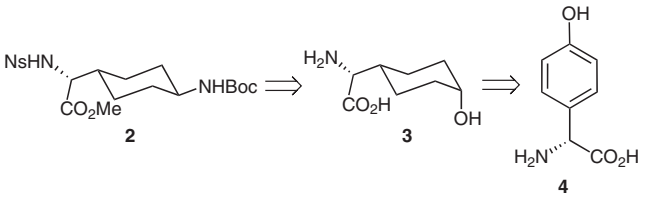


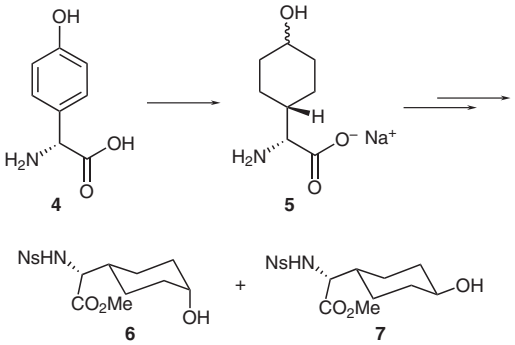
Figure 1 Structures of building blocks **1** and **2**

Our retrosynthetic strategy is shown in Scheme 1. The key step is the reduction of the readily available D-4-hydroxyphenylglycine (**4**) to give the *cis*-diastereomer **3**, which enables installation of the correct *trans*-orientation of the nitrogen in **2** after esterification, protection, activation, and displacement with an ammonia equivalent.



Scheme 1 Retrosynthetic analysis of methyl (*R*)-2-[(1*r*,4*R*)-4-(*tert*-butoxycarbonylamino)cyclohexyl]-2-(2-nitrophenylsulfonamido)acetate

D-4-Hydroxyphenylglycine (**4**) was reduced by hydrogenolysis with rhodium under basic conditions to a 1:1 mixture of the *cis*/*trans*–diastereomers,[6] **5** (Scheme 2), which were easily separated by chromatography following esterification and amine protection to give **6** and **7**.



Scheme 2 Reduction of **4** and separation of diastereomers

Reduction of the *N*-Boc **8**[7] derivative under neutral conditions is reported to give predominantly the *cis*-diastereomer[8] and in our hands gave a 10:1 *cis*/*trans* ratio of diastereomers **9** (Scheme 3), with cyclohexane **10** being observed as the major impurity. On scale-up to 75 grams, reactions progressed smoothly with **6** being isolated in 50% overall yield from **8**, after esterification and protecting group swap. However, when the scale was increased to 750 grams, the yield reduced to 25% due to formation of previously undetected decarboxylated material **11**.

It was hypothesised that if the reduction were performed on the *N*-Boc methyl ester **12** (Scheme 4), the formation of the decarboxylated product **11** would be suppressed.

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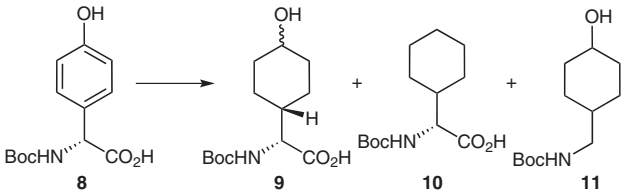
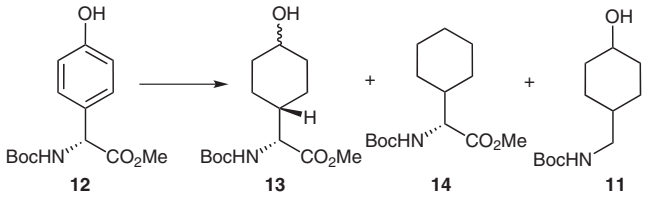


Scheme 3 Reduction of *N*-Boc acid

N-Boc-D-4-hydroxyphenylglycine methyl ester (**12**) was prepared from **4** (Scheme 5) in two steps without chromatography on a scale up to 12 kilograms. Initial experiments showed that the reduction of the ester was much slower than the acid, resulting in an increased formation of dehydroxylated compound **14**. To address this, a screen of reaction conditions was undertaken using acetic acid as solvent as this was found to increase the rate of reaction. Raney nickel was reported[9] to give predominantly the *trans*-diastereomer and little reaction is reported with palladium or ruthenium[9] so we focused on platinum and rhodium catalysts. Table 1 summarises the findings.



Scheme 4 Reduction of *N*-Boc ester and associated impurities

Table 1 Screening of Reduction Conditions[a]

Entry	Solvent	Catalyst	Catalyst loading	Ratio of products **13**:**14**:**11**
1	AcOH	PtO_2	2.5 mol%	11:7:0[b]
2	AcOH[c]	PtO_2	5 mol%	11:9:2[d]
3	AcOH	Rh (5% on Al_2O_3)	10 wt%[e]	9:1:0[d]
4	AcOH	Rh (5% on Al_2O_3)	5 wt%[e]	7:1:5[b,f]
5	MeOH	Rh (5% on Al_2O_3)	10 wt%[e]	16:3:0[g]

[a] Note: All reactions were run at 30–35 °C and 5 bar H_2 pressure.
[b] By ^1H NMR spectroscopy.
[c] Pressure: 20 bar.
[d] Isolated.
[e] Wt% compared to quantity of starting material used.
[f] Remaining starting material: 45%.
[g] By HPLC after protecting group swap.

Reactions with platinum oxide resulted in the formation of a large amount of **14** (Table 1, entry 1) and increasing the catalyst loading and pressure (Table 1, entry 2) also had a detrimental effect resulting in increased quantities of **14**. This prompted investigations into how **14** may be formed. Subjecting **13** to identical reduction conditions resulted in no further reaction, therefore we concluded that **14** was not formed from dehydration of **13**, but during the reduction from dehydration of the partially reduced phenyl ring. Furthermore, when our best conditions with platinum oxide were scaled to 70 grams, we observed very slow reactions resulting in the formation of **11** from the prolonged reaction times. This was attributed to reduced reactor head space on a larger scale resulting in inefficient mixing of hydrogen gas.[9]

Using rhodium on alumina under the conditions given in Table 1, entry 3, improved the reaction giving 90% isolated yield of **13** with little formation of **14** and an acceptable *cis*/*trans* ratio of 4.5:1. Unfortunately, we were unable to achieve an acceptable conversion with less than 10 wt% of rhodium catalyst (Table 1, entry 4); lowering the catalyst charge resulted in incomplete reactions and formation of **11**.

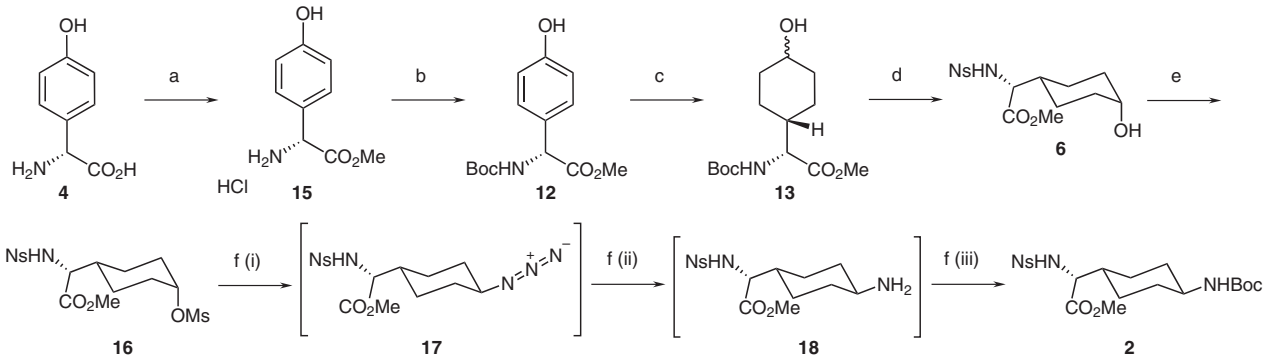
The reaction was scaled successfully to 1 kilogram giving **13** in 90% yield with simple removal of **14** by flash silica chromatography. Methanol was used for scales over 1 kilogram (Table 1, entry 5) as removal of acetic acid by evaporation and aqueous workup was deemed impractical for further scaling. The *cis*/*trans* ratio was found to increase slightly to 5.2:1 on a larger scale using methanol as solvent, although with slightly increased amounts of dehydroxylated impurity **14**.

The complete synthesis of building block **2** is shown in Scheme 5. *N*-Boc-D-4-hydroxyphenylglycine methyl ester (**12**) was prepared from **4** in two steps[10] without chromatography on a scale up to 12 kilograms, then subjected to the reduction conditions as described above to give **13**.

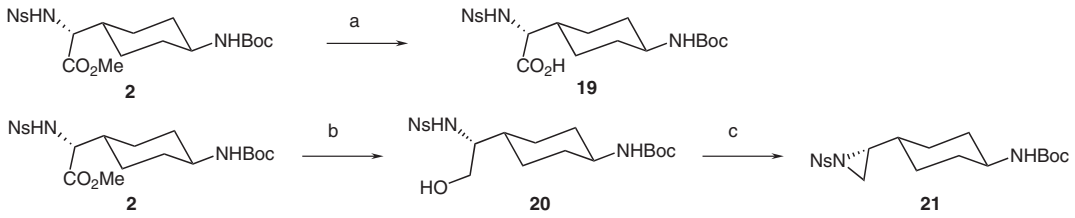
Removing the *N*-Boc protection from **13** using hydrogen chloride (Scheme 5), gave a hydrochloride salt that was difficult to isolate, while deprotection with trifluoroacetic acid gave significant amounts of the trifluoroacetate ester on the free hydroxy group. To avoid these issues, the protecting group swap from *N*-Boc to *N*-nosyl was carried out as a one-pot procedure. The excess hydrogen chloride was neutralised with triethylamine before the addition of 2-nitrobenzenesulfonyl chloride. Chromatographic separation of the *cis*- and *trans*-diastereomers provided **6** in 52% yield. An attempt was made to activate the alcohol via nosylation as part of the same step but this proved unsuccessful. Therefore mesylate **16** was obtained in 78% yield after filtration through a silica pad and methanol slurry.

It was found that the crude reaction mixture from the reduction step containing a mix of *cis*/*trans*-diastereomers **13** and cyclohexyl impurity **14**, could be taken through the protecting group swap and mesylation steps with standard workup conditions and no purification. Mesylate **16** could then be isolated cleanly via a slurry with methanol to remove cyclohexyl impurity **14** and other organic impurities, followed by recrystallisation from methyl *tert*-butyl ether (MTBE) to remove the *trans*-diastereomer. This removed the need for chromatography on a large scale, but with a 15% drop in overall yield.

The *cis*-mesylate **16** was converted to the *trans*-*N*-Boc amine **2** via a three stage, one-pot telescoped procedure. At first, the mesylate **16** was displaced with sodium azide



Scheme 5 Synthesis of **2**. *Reagents and conditions*: (a) AcCl, MeOH, 0 to 55 °C, 18 h, 99%; (b) Boc_2O, Et_3N, CH_2Cl_2, 25 °C, 20 h, 88%; (c) Rh/Al_2O_3, AcOH, H_2, 5 bar, 35 °C, 18 h, 90%; (d) i. HCl, 1,4-dioxane, 25 °C, 3 h, ii. 2-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, 20 °C, 18 h, 52%; (e) MsCl, Et_3N, CH_2Cl_2, 20 °C, 1 h, 78%; (f) i. NaN_3, DMF, 55 °C, 16 h, ii. Ph_3P, EtOAc, H_2O, 65 °C, 3 h, iii. Boc_2O, Et_3N, CH_2Cl_2, 25 °C, 18 h, 69%.



Scheme 6 Further functionalisation of **2**. *Reagents and conditions*: (a) 2 M aq NaOH, MeOH, 50 °C, 1 h, 86%; (b) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 66%; (c) DIAD, Ph_3P, THF, 0 to 20 °C, 2 h, 65%.

in DMF giving the *trans*-azide **17**. Isolation of **17** was avoided by drowning out the reaction mixture into water and then extracting the azide into ethyl acetate before subjecting it to reduction using Staudinger conditions[11] to give amine **18**. The triphenylphosphine oxide formed in the reaction proved difficult to remove by chromatography on a large scale, so was removed by aqueous extraction. The amine **18** was extracted into aqueous hydrochloric acid leaving the triphenylphosphine oxide remaining in the organic phase.

The aqueous extract was neutralised with ammonia and amine **18** was extracted into dichloromethane. This solution was treated directly with di-*tert*-butyl dicarbonate to give **2** in 69% yield. This removal of chromatography was significant as building block **2** could be synthesised on large scale without any chromatographic stages.

Protected building block **2** can be further functionalised in a number of ways and serves as a versatile intermediate, which has three handles for derivatisation (Scheme 6). The carboxylic acid **19** can be released by simple hydrolysis in 86% yield, and the ester can be reduced with diisobutylaluminum hydride to afford the alcohol **20** in 66% yield after chromatography. The nosyl and Boc groups can be removed independently[12] giving flexibility as to which nitrogen is unveiled first. The nosyl group also makes the nitrogen acidic allowing aziridine **21** to be synthesised via Mitsunobu[13] chemistry.

In conclusion, we have shown a practical and scaleable synthesis of **2**, allowing kilogram quantities to be prepared in good yield with no chromatography. Compound **2** can be selectively diversified in each functionalised position providing a versatile building block for medicinal chemistry.

CAUTION: The handling and use of low-molecular-weight nitro compounds (e.g., 2-nosyl) can be dangerous due to their potentially energetic character. Compounds containing nitro functionality should be first prepared on a small scale and their properties tested for safety by appropriate means (Differential Scanning Calorimetry, BAM Fallhammer test, Carius tube test, etc.). It is recommended that anyone wishing to replicate this chemistry should perform their own safety testing and further testing should most definitely be performed prior to any scale-up.

CAUTION: The handling and use of sodium azide can be dangerous due its potentially explosive character. Before use, users should consult the handbook on chemical hazards.[14]

Solvents were not dried before use. The catalyst used for the phenyl ring reduction was 5% Rh on Al_2O_3, powder type 524, purchased from Johnson Matthey. Reactions were monitored by either TLC, LC-MS, or GC-MS. Glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm (Merck) were used for TLC analyses. LC-MS spectra were recorded using a Waters 2790 separation module fitted with a Waters 2996 photodiode array detector and a Waters micromass ZQ mass detector. GC-MS were recorded using Agilent Technologies 6890N network GC system fitted with an Agilent Technologies 5975 inert XL mass selective detector. ^{1}H NMR spectra were recorded at 400, 500, and 700 MHz using TMS as an internal standard in $CDCl_3$. All HRMS were recorded on a Thermo Fisher LTQ-FT fitted with a 7.2T magnet. Reactions were performed in either 10 L, 20 L, or 50 L jacketed glass vessels, or 250 L glass-lined reactors for the larger scale reactions. The phenyl ring reduction was performed in a 5 L or 20 L glass jacketed vessels capable of withstanding the pressure required or a 300 L autoclave for the largest scale reaction. All reactors used an appropriately sized

heater/chiller unit to provide reaction temperature control. Racemic samples of **16** and **20** were prepared using the same route and the chirality was checked via chiral HPLC using an Agilent 1100 system fitted with a photodiode array detector and a 5 μm Chiralpak AD-H column. No racemisation was found and none of the *cis*-diastereomer was detected, copies of the spectra can be found in the Supporting Information. As the chirality was checked part way through and at the end of the synthesis with no found degradation, it was deemed unnecessary to perform a check on chirality at every stage in the synthesis.

Methyl (*R*)-2-Amino-2-(4-hydroxyphenyl)acetate Hydrochloride (15)

AcCl (1.85 L, 26.02 mol) was added dropwise over a period of 1 h to D-(–)-4-hydroxyphenylglycine (1.45 kg, 8.67 mol) suspended in MeOH (14 L) and cooled to 0 °C under N_2. The resulting solution was stirred at 0 °C for 30 min, then heated to 55 °C, and stirred at this temperature for 18 h. The reaction mixture was cooled to 20 °C and the solvent evaporated under vacuum to give the title compound **15** as a white solid; yield: 1.87 kg (99%); mp 180 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ = 3.73 (s, 3 H), 5.00 (s, 1 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 8.72 (s, 2 H), 9.53 (s, 1 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{12}NO_3$: 182.08117; found: 182.08115.

(*R*)-Methyl 2-(*tert*-Butoxycarbonylamino)-2-(4-Hydroxyphenyl)acetate (12)

Et_3N (1.25 L, 9.01 mol) was added dropwise to **15** (1.87 kg, 8.58 mol) suspended in CH_2Cl_2 (15 L). The mixture was warmed to 25 °C and stirred for 5 min; then a solution of di-*tert*-butyl dicarbonate (1.97 kg, 9.01 mol) in CH_2Cl_2 (4 L) was added dropwise over a period of 45 min. The reaction mixture was stirred at 25 °C for 20 h and then washed with H_2O (19 L). The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated under vacuum. The resulting solid was slurried with MTBE (3.80 L) for 1 h, the precipitate collected by filtration, washed with further MTBE (2 L), and dried under vacuum to give the title compound **12** (1.82 kg). The mother liquors were evaporated under vacuum and the solid was triturated with MTBE (850 mL). The precipitate was collected by filtration, washed with further MTBE (850 mL), and dried under vacuum to give a second crop of title compound **12** (297 g); total yield: 2.11 kg (88%); white solid; mp 139 °C.

^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ = 1.39 (s, 9 H), 3.63 (s, 3 H), 5.06 (d, *J* = 7.7 Hz, 1 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 6.91 (s, 1 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 9.08 (s, 1 H).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}NO_5$: 282.13360; found: 282.13361.

Methyl (*R*)-2-(*tert*-Butoxycarbonylamino)-2-(4-hydroxycyclohexyl)acetate (13)

Compound **12** (1.05 kg, 3.73 mol) and 5% Rh on Al_2O_3 (105 g) in AcOH (10 L) were stirred under an atmosphere of H_2 at 5 bar and 35 °C for 18 h. The reaction mixture was filtered through dicalite and the solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (10 L) and washed with sat. aq $NaHCO_3$ (10 L). The aqueous layer was re-extracted with CH_2Cl_2 (5 L), then the combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was passed through a silica pad, washing first with 10% EtOAc in isohexane, then eluting the desired product with 10% MeOH in CH_2Cl_2. Solvents were evaporated under vacuum to give the title compound **13** as a yellow gum, which was used without further purification; yield: 965 g (90%).

Larger-Scale Method: Compound **12** (5.0 kg, 17.8 mol) and 5% Rh on Al_2O_3 (0.5 kg) in MeOH (100 L) were stirred under an atmosphere of H_2 at 5 bar and 35 °C for 18 h. The reaction mixture was filtered through dicalite and the solvent was evaporated under vacuum to give the title compound **13** (3.4 kg, 66%), which was used in the next step without further purification.

Methyl (*R*)-2-[(1*s*,4*S*)-4-Hydroxycyclohexyl]-2-(2-nitrophenylsulfonamido)acetate (6)

A solution of 4 M HCl in 1,4-dioxane (4.10 L, 16.43 mol) was added dropwise to **13** (944 g, 3.28 mol) in 1,4-dioxane (1.90 L) and stirred at 25 °C for 3 h. The reaction mixture was diluted with CH_2Cl_2 (6.60 L) and cooled to 5 °C. Et_3N (3.21 L, 23.00 mmol) was slowly added over a period of 20 min, then the mixture was stirred at 5 °C for 15 min. 2-Nitrobenzenesulfonyl chloride (874 g, 3.94 mol) was added portionwise over a period of 5 min at 5 °C, then the reaction mixture was warmed to 20 °C, and stirred for 18 h. The mixture was washed with H_2O (14.5 L) and the aqueous layer was re-extracted with CH_2Cl_2 (9.50 L). The combined organics were washed with 50% sat. brine (9.50 L) and dried ($MgSO_4$), then filtered, and the solvents evaporated. Purification by flash chromatography (isohexane–acetone, 13:7) gave the title compound **6** as a cream solid; yield: 636 g (52%); mp 78–84 °C.

IR (mull): 3495–3160, 3050–2790, 1740, 1555, 1480, 1395, 1180 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ = 1.04–1.24 (m, 4 H), 1.31–1.40 (m, 1 H), 1.47–1.65 (m, 5 H), 2.96 (s, 3 H), 3.59–3.67 (m, 1 H), 4.06–4.16 (m, 1 H), 6.29 (d, *J* = 9.9 Hz, 1 H), 6.63 (dt, *J* = 7.7, 1.4 Hz, 1 H), 6.76 (dt, *J* = 7.7, 1.3 Hz, 1 H), 7.06 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.79 (dd, *J* = 7.9, 1.4 Hz, 1 H)

^{13}C NMR (175 MHz, DMSO-d_6, 69 °C): δ = 170.44, 147.05, 133.64, 132.74, 131.88, 129.56, 123.73, 63.73, 60.01, 51.14, 38.20, 31.37, 31.29, 22.78, 22.17.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}N_2O_7S$: 373.10640; found: 373.10660.

Larger-Scale Method: A solution of 4 M HCl in 1,4-dioxane (12.90 L, 51.52 mol) was added dropwise to **13** (3.0 kg, 10.44 mol) in 1,4-dioxane (5.90 L) and the reaction mixture was stirred at 25 °C for 2 h. The mixture was diluted with CH_2Cl_2 (20.70 L) and cooled to 5 °C. Et_3N (10.06 L, 72.10 mmol) was slowly added over a period of 1 h, followed by the addition of 2-nitrobenzenesulfonyl chloride (2.74 kg, 12.31 mol) portionwise over a period of 30 min at 5 °C. The reaction mixture was warmed to 20 °C and stirred for 3 h. The mixture was washed with H_2O (44.5 L) and the aqueous layer was re-extracted with CH_2Cl_2 (29.6 L). The combined organics were washed with 50% sat. brine (29.6 L), dried ($MgSO_4$), filtered, and the solvents evaporated to give the title compound **6** (3.5 kg, 90%), which was used in the next step without further purification.

Methyl (*R*)-2-[(1*s*,4*S*)-4-(Methylsulfonyloxy)cyclohexyl]-2-(2-nitrophenylsulfonamido)acetate (16)

A solution of MsCl (249 mL, 3.22 mol) in CH_2Cl_2 (900 mL) was added dropwise over a period of 30 min to a stirred solution of **6** (1.09 kg, 2.92 mol) and Et_3N (610 mL, 4.38 mol) in CH_2Cl_2 (10 L) cooled to 5 °C under N_2. The solution was warmed to 20 °C and stirred for 1 h, and then washed with H_2O (10 L). The aqueous layer was re-extracted with CH_2Cl_2 (10 L) and the combined organics were washed with 50% sat. brine (10 L), dried ($MgSO_4$), filtered, and the solvents evaporated. The crude product was slurried with MeOH (3.40 L) for 10 min, the precipitate was collected by filtration, washed with MeOH (1.0 L) and Et_2O (1.70 L), and dried under vacuum to give the title compound **16** as a white solid; yield: 1.02 kg (78%); mp 117–119 °C.

Chiral HPLC: 1 mg/mL; UV: λ_{max} = 254 nm; Chiralpak AS column, 5 μm silica, 4.6 mm diameter, 250 mm length; eluent: 50:50:0.1 mixture of heptanes–EtOH–Et_3N; 100% chirally pure.

IR (mull): 3305, 3050–2790, 1740, 1550, 1470, 1355, 1180 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.65 (m, 6 H), 1.66–1.87 (m, 1 H), 2.01–2.10 (m, 2 H), 2.96 (s, 3 H), 3.37 (s, 3 H), 3.86–4.08 (m, 1 H), 4.92 (s, 1 H), 6.00 (d, *J* = 9.7 Hz, 1 H), 7.57–7.78 (m, 2 H), 7.83–7.91 (m, 1 H), 7.95–8.10 (m, 1 H).

^{13}C NMR (175 MHz, DMSO-d_6, 69 °C): δ = 170.13, 147.02, 133.69, 132.69, 131.91, 129.59, 123.72, 77.46, 59.92, 51.28, 37.74, 37.54, 29.24, 29.22, 22.67, 21.93.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_9S_2$: 451.08395; found: 451.08447.

Larger-Scale Method: MsCl (0.62 L, 7.98 mol) was added dropwise over a period of 30 min to a stirred solution of **6** (3.5 kg, 9.40 mol) and Et_3N (1.51 L, 10.88 mol) in CH_2Cl_2 (27 L) cooled to 5 °C under N_2. The solution was warmed to 20 °C and stirred for 1 h, and then washed with H_2O (27 L). The aqueous layer was re-extracted with CH_2Cl_2 (27 L) and the combined organics were washed with 50% sat. brine (27 L), dried ($MgSO_4$), filtered, and the solvents evaporated. The crude product was slurried with MeOH (5.4 L) for 1 h at 25 °C, then the precipitate was collected by filtration, and washed with MeOH (2.1 L) and MTBE (2.7 L). The solid was recrystallised from a mixture of MTBE (13.5 L) and EtOAc (5.4 L) to give the title compound **16** as a white solid; yield: 1.54 kg (38%).

Methyl (*R*)-2-[(1*r*,4*R*)-4-(*tert*-Butoxycarbonylamino)cyclohexyl]-2-(2-nitrophenylsulfonamido)acetate (2)

NaN_3 (780 g, 11.97 mol) was added to **16** (3.00 kg, 6.66 mol) in DMF (15 L) and heated to 55 °C for 16 h. The reaction mixture was cooled to 20 °C, diluted with H_2O (45 L), and extracted with EtOAc (30 L). The aqueous layer was re-extracted with EtOAc (30 L), then the combined organics were dried ($MgSO_4$), and filtered. To the filtrate was added Ph_3P (2.10 kg, 7.99 mol) and the solution was heated to 65 °C for 90 min. H_2O (6 L) was added and the reaction mixture was stirred at 65 °C for a further 90 min, then cooled to 20 °C, and extracted with 1.5 M aq HCl (4 × 12 L). The combined aqueous layers were washed with CH_2Cl_2 (3 × 30 L) then the aqueous layer was basified with liquid ammonia (9 L) and extracted with CH_2Cl_2 (30 L). The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, and then treated with Et_3N (1.39 L, 9.99 mol) and di-*tert*-butyl dicarbonate (1.60 kg, 7.33 mol). The mixture was stirred at 25 °C for 18 h and washed with H_2O (30 L). The aqueous layer was re-extracted with CH_2Cl_2 (30 L), then the combined organics were dried ($MgSO_4$), filtered, and the solvent evaporated under vacuum. The crude solid was slurried with isohexane (9 L) and the precipitate collected by filtration and dried under vacuum to give the title compound **2** as a yellow solid; yield: 2.10 kg (69%); mp 108–118 °C.

IR (mull): 3020–2790, 1690, 1555, 1520, 1470, 1365, 1190 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–1.27 (m, 4 H), 1.37 (s, 9 H), 1.53–1.85 (m, 3 H), 1.85–2.10 (m, 2 H), 3.19–3.35 (m, 1 H), 3.36 (s, 3 H), 3.84–4.03 (m, 1 H), 4.28 (s, 1 H), 5.99 (d, *J* = 9.9 Hz, 1 H), 7.62–7.73 (m, 2 H), 7.81–7.90 (m, 1 H), 7.94–8.04 (m, 1 H).

^{13}C NMR (175 MHz, DMSO-d_6, 69 °C): δ = 170.26, 154.43, 147.01, 133.62, 132.77, 131.86, 129.56, 123.69, 77.04, 60.24, 51.22, 48.69, 38.53, 31.57, 31.54, 27.92, 27.27, 26.67.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{30}N_3O_8S$: 472.17481; found: 472.17554.

(*R*)-2-[(1*r*,4*R*)-4-(*tert*-Butoxycarbonylamino)cyclohexyl]-2-(2-nitrophenylsulfonamido)acetic Acid (19)

Aq 2 M NaOH (5.30 mL, 10.60 mmol) was added dropwise to **2** (1 g, 2.12 mmol) suspended in MeOH (5 mL). The resulting solution was stirred at 50 °C for 1 h, then cooled to 20 °C, and the MeOH evaporated under vacuum. The aqueous residues were acidified to pH 4 with 1 M aq citric acid and the resulting precipitate was collected by filtration, washed with H_2O (10 mL), and dried under vacuum to give the title compound **19** as a white solid; yield: 0.84 g (86%); mp 225 °C (dec.).

IR (mull): 3480–3150, 3050–2790, 1690, 1540, 1455, 1365, 1170 cm^{-1}.

^{1}H NMR (700 MHz, pyridine-d_5, 67 °C): δ = 1.25–1.38 (m, 2 H), 1.44–1.71 (m, 11 H), 1.96–2.11 (m, 2 H), 2.11–2.21 (m, 3 H), 3.61 (s, 1 H), 4.45 (d, *J* = 5.66 Hz, 1 H), 6.63 (s, 1 H), 7.45–7.59 (m, 2 H), 7.79 (d, *J* = 7.34 Hz, 1 H), 8.34 (d, *J* = 7.27 Hz, 1 H).

^{13}C NMR (175 MHz, DMSO-d_6, 69 °C): δ = 171.04, 154.46, 147.12, 133.42, 133.06, 131.98, 129.58, 123.85, 77.00, 60.84, 48.95, 31.86, 31.80, 27.96, 27.54, 26.44.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{28}N_3O_8S$: 458.15916; found: 458.15976.

tert-Butyl (1*R*,4*r*)-4-[(*R*)-2-Hydroxy-1-(2-nitrophenylsulfonamido)ethyl]cyclohexylcarbamate (20)

DIBAL-H (1 M solution in toluene, 567 mL, 0.57 mol) was added dropwise over 30 min to **2** (63.6 g, 0.13 mol) in CH_2Cl_2 (640 mL) cooled to –10 °C under N_2. The resulting solution was stirred at 0 °C for 2 h, then quenched by dropwise addition of MeOH (64 mL). The mixture was cooled to 0 °C and a 4.5% w/v aq solution of Rochelle's salt (800 mL) was added. The mixture was warmed to 20 °C and stirred for 1 h, then diluted with CH_2Cl_2 (320 mL), and filtered through Celite. The organic layer was separated and dried ($MgSO_4$), filtered, and the solvent evaporated under vacuum. Purification by flash chromatography (isohexane–EtOAc, gradient of 100:0 to 60:40) gave the title compound **20** as a yellow solid; yield: 39.5 g (66%); mp 196 °C (dec.).

Chiral HPLC: 1 mg/mL; UV: λ_{max} = 254 nm; Chiralpak AS column, 5 μm silica, 4.6 mm diameter, 250 mm length; eluent: 80:20:0.1 mixture of heptanes–EtOH–Et_3N; 100% chirally pure.

IR (mull): 3600–3120, 3050–2790, 1685, 1530, 1450, 1370–1320, 1250, 1170 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75–1.13 (m, 4 H), 1.35 (s, 9 H), 1.40–1.51 (m, 1 H), 1.59–1.65 (m, 1 H), 1.67–1.83 (m, 2 H), 1.83–1.99 (m, 2 H), 3.13–3.29 (m, 2 H), 3.44–3.64 (m, 2 H), 4.26 (s, 1 H), 5.49 (d, *J* = 8.3 Hz, 1 H), 7.61–7.71 (m, 2 H), 7.73–7.85 (m, 1 H), 8.00–8.11 (m, 1 H).

^{13}C NMR (175 MHz, DMSO-d_6, 69 °C): δ = 154.44, 147.09, 133.82, 133.24, 131.81, 129.61, 123.64, 76.98, 60.90, 59.74, 49.11, 37.32, 32.05, 32.03, 27.95, 27.58, 26.48.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{30}N_3O_7S$: 444.17990; found: 444.18042.

tert-Butyl (1*R*,4*r*)-4-[(*R*)-1-(2-Nitrophenylsulfonyl)aziridin-2-yl)cyclohexylcarbamate (21)

Diisopropyl azodicarboxylate (DIAD, 21.0 mL, 107 mmol) was added dropwise to **20** (39.4 g, 89 mmol) and Ph_3P (28.0 g, 107 mmol) in THF (400 mL) cooled to –5 °C under N_2. The resulting solution was stirred at 0 °C for 1 h, then warmed to 20 °C, and stirred for 30 min. Further Ph_3P (14.0 g, 53.5 mmol) and DIAD (10.5 mL, 53.5 mmol) were added and the mixture was stirred at 20 °C for 10 min, then the solvents were evaporated under vacuum (water bath kept below 35 °C). Purification by flash chromatography (isohexane–EtOAc, gradient of 100:0 to 70:30) gave the title compound **21** as a white solid; yield: 24.5 g (65%); mp 152 °C (dec.).

IR (mull): 3050–2790, 1700, 1550, 1470, 1390 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.98–1.10 (m, 5 H), 1.35 (s, 9 H), 1.43–1.55 (m, 1 H), 1.56–1.65 (m, 1 H), 1.64–1.81 (m, 2 H), 2.58–2.70 (m, 1 H), 2.66–2.75 (m, 1 H), 3.09 (s, 1 H), 6.63 (d, *J* = 7.7 Hz, 1 H), 7.86–7.94 (m, 1 H), 7.94–8.01 (m, 1 H), 7.99–8.09 (m, 1 H), 8.09–8.17 (m, 1 H).

^{13}C NMR (175 MHz, DMSO-d_6, 69 °C): δ = 154.44, 147.78, 135.21, 132.11, 130.42, 129.23, 124.02, 77.02, 48.78, 44.91, 37.24, 33.47, 31.34, 31.25, 27.91, 27.56, 27.32.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{28}N_3O_6S$: 426.16933; found: 426.16916.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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