# A Practical Synthesis of (*S*)-*tert*-Butyl 3-Methyl-1,4-diazepane-1-carboxylate, the Key Intermediate of Rho–Kinase Inhibitor K-115

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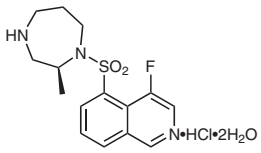
**Abstract:** A practical synthesis of (*S*)-*tert*-butyl 3-methyl-1,4-diazepane-1-carboxylate has been established for supplying this key intermediate of Rho–kinase inhibitor K-115 in a multikilogram production. The chiral 1,4-diazepane was constructed by intramolecular Fukuyama–Mitsunobu cyclization of a *N*-nosyl diamino alcohol starting from the commercially available (*S*)- or (*R*)-2-aminopropan-1-ol. In the same manner, an enantiomeric pair of a structural isomer were prepared for demonstration of the synthetic utility.

**Key words:** 1,4-diazepane, Fukuyama–Mitsunobu cyclization, cation-exchange resin, asymmetric molecule, Rho–kinase inhibitor

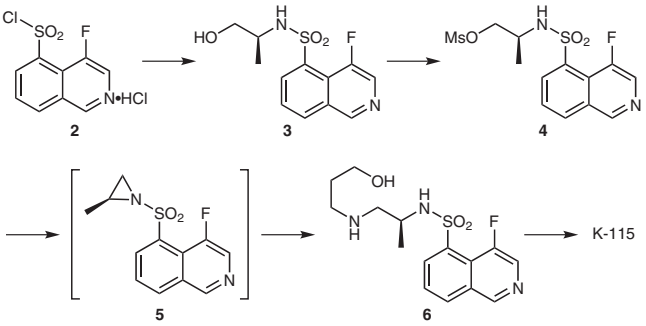
(*S*)-4-Fluoro-5-[(2-methyl-1,4-diazepan-1-yl)sulfonyl]isoquinoline hydrochloride dihydrate (**1**), K-115[1] (Figure 1), a highly potent and selective Rho–kinase inhibitor having the (*S*)-2-methyl-1,4-diazepane moiety, is a promising candidate for the treatment of ocular hypertension with intraocular pressure-lowering activity and neuroprotection of retinal ganglion cells injured in glaucoma.[2] The *S* configuration at the 2-position on the 1,4-diazepane ring of K-115 plays the pivotal role for expressing the physiological feature.



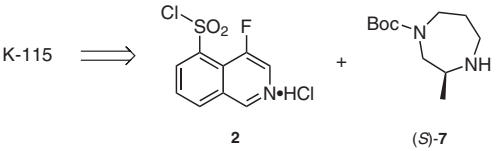

K-115 (**1**)

**Figure 1**

Recently, we have reported the practical synthesis of K-115 in a multikilogram production. This straightforward synthesis was accomplished without protection and deprotection steps and was well-acceptable from a synthetic methodology viewpoint (Scheme 1).[3] However, in consideration of the convenience and robust large-scale production of an Active Pharmaceutical Ingredient, many improvements were needed, including a reduction in the number of synthetic steps, control of the impurity profile and improved cost-performance. In particular, the placement of the expensive 4-fluoroisoquinoline-5-sulfonyl chloride (**2**) in the early step of the linear synthesis was not acceptable to us. Therefore, we had to develop an efficient, alternative synthesis. In order to solve the above-mentioned issues, we addressed the convergent synthesis of K-115 and the requisite production of (*S*)-*tert*-butyl 3-methyl-1,4-diazepane-1-carboxylate [(*S*)-**7**] (Scheme 2).




**Scheme 1** Linear production method for K-115




**Scheme 2** Convergent production method for K-115

Several papers have described the preparation of chiral 2-substituted 1,4-diazepane derivatives. Interestingly, a Merck group reported the large-scale synthesis of MK-4305, but the enantiopure substituted 5-methyl-1,4-diazepane derivative was supplied by the diastereomeric salt resolution of the racemate with dibenzoyl-D-tartaric acid in a low yield.[4] As well, others have reported small-scale preparations by the reduction of dioxo-1,4-diazepanes[5] and the creation of libraries of compounds (under microwave irradiation conditions) in the solid phase.[6] Franzyk and co-workers reported the first study of the solution-phase synthesis via the ring opening of activated aziridines;[7] however, this methodology started with a substituted aminoethanol with 3 equivalents of 2-nitrobenzenesulfonyl chloride (2-nosyl chloride, 2-NsCl) in order to generate the hazardous *N*-nosylaziridine. This excess of 2-nosyl chloride is unacceptable due to cost constraints. Furthermore, the procedure demanded a complicated handling in the workup and HPLC purification. The application and utility of these methodologies are limited and the outlined

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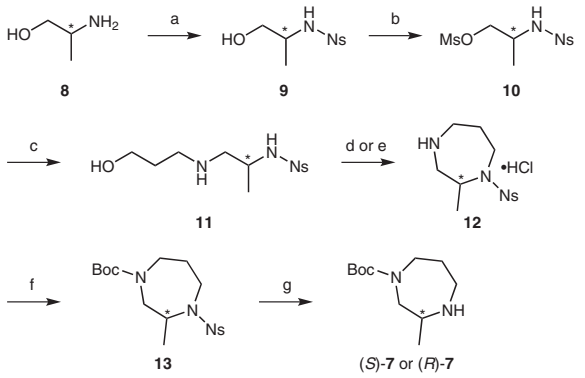
problems should be addressed prior to multikilogram-scale production. Next, we searched the patent literature[8a] for the synthesis of (*S*)-**7**; however, the patent-disclosed intermediate prior to cyclization could easily be decomposed[8b] due to the participation of the carbamate group, with significant deterioration of the chemical yield.

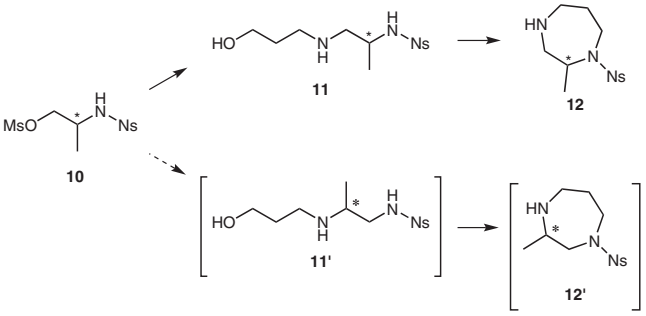
Herewith, our attention was focused on the protection of the diamine derivative and the cyclization step to form the 1,4-diazepane ring. Then, we revised our reported procedure to provide enantiopure (*S*)-**7**. For our synthetic plan, the strategy for the construction of the 1,4-diazepane ring was based in a similar way on a Fukuyama–Mitsunobu *N*-alkyl cyclization reaction;[9] however, in the place of 4-fluoroisoquinoline-5-sulfonyl chloride (**2**), we chose to use 2-nosyl chloride.

According to the literature, we started the selective protection of the amino group of (*S*)-2-aminopropan-1-ol (**8**) with the nosyl group which could be easily removed by thiophenol under basic conditions;[10] however, it was too difficult to control the mononosylation under the conventional basic conditions. Thus, bisnosylation of **8** simultaneously occurred to afford the *N*,*O*-bisnosylate, accompanied by a small amount of the *N*-nosylaziridine.[7,11] After investigating the basic conditions for providing the mononosylate **9**, we succeeded in obtaining (*S*)-**9** in 76% yield by the use of sodium hydrogen carbonate as a base in tetrahydrofuran–water (Scheme 3).




**Scheme 3** *Reagents and conditions*: (a) 2-NsCl, $NaHCO_3$, THF, $H_2O$: (*S*)-**9** (76%), (*R*)-**9** (65%); (b) MsCl, NMM, $CH_2Cl_2$: (*S*)-**10** (91%), (*R*)-**10** (89%); (c) 3-aminopropan-1-ol, MeCN: (*S*)-**11** (93%), (*R*)-**11** (100%); (d) DIAD, $Ph_3P$, THF: (*S*)-**12** (40%), (*R*)-**12** as free base (64%); (e) DIAD, $Ph_3P$, THF, then Amberlyst® 15: (*R*)-**12** (88%); (f) $Boc_2O$, $K_2CO_3$, EtOH, $H_2O$: (*S*)-**13** (87%), (*R*)-**13** (98%); (g) PhSH, $K_2CO_3$, MeCN: (*S*)-**7** (86%), (*R*)-**7** (70%).

We next conducted the O-mesylation of **9** to afford the *N*-nosyl-*O*-mesylate (*S*)-**10** in 91% yield. Due to the high cost of 2-nosyl chloride and atom economy, we opted for the two-step process of nosylation–mesylation rather than bisnosylation in our multikilogram-scale synthesis. Then, the prepared *N*-nosyl-*O*-mesylate **10** was treated with 3 equivalents of 3-aminopropan-1-ol to afford the N-alkylated diamino alcohol **11** in a high yield. In this procedure, we avoided handling the hazardous *N*-nosylaziridine and also reduced the amounts of 2-nosyl chloride and 3-aminopropan-1-ol.[12] As previously discussed, there exists the potential for formation of the activated aziridine in situ (see **5**, Scheme 1). In general, the 2-methyl group on the aziridine ring is expected to control the $S_N2$ nucleophilic attack of 3-aminopropan-1-ol predominantly at the unsubstituted aziridine carbon;[13] however, a few percent of the methyl isomer **11′** (and then **12′**) could be formed from the *N*-nosylaziridine under the influence of the reaction temperature (Scheme 4).[3]




**Scheme 4**

After investigating various conditions for providing the *N*-alkyl derivative **11**, we determined the optimal conditions (Scheme 3). In order to differentiate the two amino groups in the 1,4-diazepane compound **12**, the *N*-nosyl diamine **11** can be protected using the Boc group. Without this protection, however, we conducted the intramolecular Fukuyama–Mitsunobu *N*-alkyl cyclization, which smoothly afforded **12** under mild conditions. Although this reaction is very useful, the drawback was that the product was accompanied by some impurities derived from the spent reagents. In a large-scale production, the problem was how to simplify the isolation of pure (*S*)-**7**. Therefore, we made use of the basicity of **12** and isolated the hydrochloride salt of **12** with the aim of separating it from the soluble organic impurities. We were successful in a multikilogram-scale production; (*S*)-**12** was obtained in 40% yield as a yellow solid. Thus obtained 1,4-diazepane (*S*)-**12** was protected with di-*tert*-butyl dicarbonate ($Boc_2O$) under basic conditions to afford the *N*-*tert*-butoxycarbonyl-*N*′-nosyl-3-methyl-1,4-diazepane (*S*)-**13** in 87% yield. Next, cleavage of the nosyl group with thiophenol and potassium carbonate gave the desired Boc-protected secondary amine (*S*)-**7** in 86% yield (>99.9% ee). Herewith, we have accomplished a practical synthetic method with easy scalability, isolation of crystals or solids, high chemical and enantiomeric purity, and efficient cost, starting from commercially available reagents.

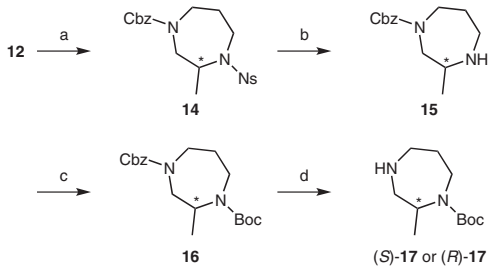
In the same manner, preparation of the enantiomer was also accomplished to give (*R*)-**12** as the free base in 64% yield when using column chromatography.[14] To overcome the low cyclization yield, we adapted an efficient isolation using a cation-exchange resin,[15] Amberlyst® 15. The advantage of the resin is that it simplifies the isolation procedure. We performed this on the *N*-nosyl 1,4-diazepane (*R*)-**12** reaction mixture and easily washed the resin



with organic solvents in order to remove the impurities. The desired product free base (*R*)-**12** was extracted from the resin and was afforded in a quantitative yield after ammonia–methanol elution. Then, the *N*-nosyl 1,4-diazepane was converted into its hydrochloride salt (*R*)-**12** [88% yield from (*R*)-**11**]. The desired (*R*)-**7** was also obtained in high enantiomeric purity (99.8% ee). This resin method provided not only high yield but also minimized the risk of contamination with the potentially toxic Mitsunobu reagents.

Next, we turned our attention to the determination of the enantiopurity and to obtaining authentic samples to detect the potential methyl isomers **17** derived from **11′** and **12′**. In order to obtain the 2-methyl regioisomers, we envisioned the process outlined in Scheme 5. In a straightforward way, the *N*-nosyl group of **12** needs to be converted into the *N*-Boc group. First, we protected **12** as the benzyloxycarbonyl derivative, followed by cleavage of the *N*-nosyl group of **14** to obtain **15**. Next, the free base of **15** was converted into *N*-Boc followed by hydrogenolysis of the Cbz group of **16** to give the desired 2-methyl isomer, (*S*)-**17** (>99.9% ee) or (*R*)-**17** (>99.9% ee).




**Scheme 5** *Reagents and conditions*: (a) CbzCl, $NaHCO_3$, THF, $H_2O$: (*S*)-**14** (97%), (*R*)-**14** (100%); (b) PhSH, $K_2CO_3$, MeCN: (*S*)-**15** (60%), (*R*)-**15** (88%); (c) $Boc_2O$, $K_2CO_3$, EtOH, $H_2O$: (*S*)-**16** (99%), (*R*)-**16** (99%); (d) $H_2$, Pd/C, MeOH: (*S*)-**17** (96%), (*R*)-**17** (74%).

In conclusion, we have established a practical and reliable synthetic method for (*S*)-*tert*-butyl 3-methyl-1,4-diazepane-1-carboxylate [(*S*)-**7**] with a high enantiomeric purity in a multikilogram-scale production. In addition, we have provided viable syntheses of the enantiopure isomer, (*R*)-*tert*-butyl 3-methyl-1,4-diazepane-1-carboxylate [(*R*)-**7**], and an enantiomeric pair of structural isomers, (*S*)-*tert*-butyl 2-methyl-1,4-diazepane-1-carboxylate [(*S*)-**17**] and (*R*)-*tert*-butyl 2-methyl-1,4-diazepane-1-carboxylate [(*R*)-**17**], for the determination of enantiopurity and demonstration of the synthetic utility (Figure 2).

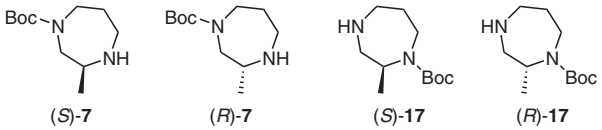



**Figure 2**

This approach has enabled us to make process-scalable products with simple purification techniques without the need for column chromatography. Furthermore, these 1,4-diazepane derivatives are useful and important chiral building blocks and key intermediates for many agents.[16] We are currently developing a concise synthesis of K-115.

Commercially available reagents and solvents were used without further purification. All reactions were carried out under argon or $N_2$ atmosphere unless otherwise noted. TLC analyses were carried out on silica gel 60 $F_{254}$ plates (Merck). Optical rotations were measured on a Jasco P-2200 polarimeter with a sodium (D line) lamp. IR spectra were recorded on a Thermo Nicolet 370 FT-IR spectrometer using a KBr or KCl pellet. $^1H$ and $^{13}C$ NMR spectra were obtained on a Jeol JNM-AL 400 (400 MHz) spectrometer using $CDCl_3$ or DMSO-$d_6$ solvent with tetramethylsilane as internal standard unless otherwise noted. To avoid rotameric mixtures in the NMR spectra, the carbamate samples were recorded at 100 °C (not calibrated) in sealed NMR tubes. Mass spectra were obtained on a Jeol GCmate MS-BU20, Jeol JMS-T100GCV, Waters Xevo G2 QTof or AB SCIEX API 4000 QTRAP instrument. Elemental analyses (C, H, N) were performed using a Yanaco MT-5 analyzer. Melting points were determined in open glass capillaries on a Büchi B-545 melting point apparatus (temperatures not corrected). The enantiopurities were determined by HPLC analysis (Shimadzu LC-10Avp equipment, CHIRALPAK® AD-H column, Daicel Chemical Industries, Ltd.).

**(*S*)-*N*-(1-Hydroxypropan-2-yl)-2-nitrobenzenesulfonamide [(*S*)-9]**

To a soln of (*S*)-(+)-2-aminopropan-1-ol (**8**; 5.10 kg, 67.9 mol) and $NaHCO_3$ (8.80 kg, 105 mol) in $H_2O$ (24.5 L) was gradually added a soln of 2-NsCl (14.7 kg, 65.5 mol) in THF (24.5 L) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 15 h. The mixture was poured into $H_2O$ (30 L), and extracted with EtOAc (3 × 5 L). The combined organic layers were washed with brine (2 × 700 mL), dried over anhyd $MgSO_4$, filtered and concentrated under reduced pressure. The residue was crystallized (EtOAc–petroleum ether) to give (*S*)-**9** as a pale yellow, crystalline solid; yield: 13.1 kg (76%).

Mp 82–83 °C; $[\alpha]_D^{20}$ +100.8 (*c* 1.06, $CHCl_3$); $R_f$ = 0.19 (hexane–EtOAc, 1:1).

IR (KBr): 3558, 3323, 1540, 1527, 1366, 1349, 1174, 1055 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.85 (br s, 1 H, OH), 3.47–3.66 (m, 3 H, $CHCH_2$), 5.48 (d, *J* = 6.8 Hz, 1 H, NH), 7.72–7.79 (m, 2 H, ArH), 7.86–7.92 (m, 1 H, ArH), 8.15–8.20 (m, 1 H, ArH).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 17.7, 52.4, 66.1, 125.4, 130.8, 132.9, 133.6, 134.4, 147.8.

FAB-MS: *m*/*z* = 261 $[M + H]^+$.

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.53; H, 4.65; N, 10.76. Found: C, 41.59; H, 4.60; N, 10.79.

**(*R*)-*N*-(1-Hydroxypropan-2-yl)-2-nitrobenzenesulfonamide [(*R*)-9]**

Yield: 163 g (65%); pale yellow, crystalline solid.

Mp 82–83 °C; $[\alpha]_D^{20}$ –100.7 (*c* 1.09, $CHCl_3$); $R_f$ = 0.19 (hexane–EtOAc, 1:1).

IR (KBr): 3558, 3323, 1541, 1527, 1366, 1349, 1174, 1055 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 2.05 (br s, 1 H, OH), 3.47–3.66 (m, 3 H, $CHCH_2$), 5.57 (d, *J* = 6.8 Hz, 1 H, NH), 7.72–7.79 (m, 2 H, ArH), 7.85–7.90 (m, 1 H, ArH), 8.14–8.20 (m, 1 H, ArH).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 17.7, 52.4, 66.1, 125.4, 130.8, 132.9, 133.6, 134.4, 147.8.

FAB-MS: *m*/*z* = 261 $[M + H]^+$.

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.53; H, 4.65; N, 10.76. Found: C, 41.65; H, 4.59; N, 10.79.

**(*S*)-2-(2-Nitrophenylsulfonamido)propyl Methanesulfonate [(*S*)-10]**

To a soln of (*S*)-**9** (6.20 kg, 23.8 mol) and NMM (3.13 kg, 30.9 mmol) in $CH_2Cl_2$ (32 L) was gradually added a soln of MsCl (3.27 kg, 28.5 mol) in $CH_2Cl_2$ (2 L) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 20 h. To the mixture was added $H_2O$ (10 L), and the precipitated product was collected by filtration and dried under reduced pressure to give (*S*)-**10** as a pale yellow, crystalline solid; yield: 7.30 kg (91%).

Mp 125–126 °C; $[\alpha]_D^{20}$ +34.5 (*c* 0.52, $CHCl_3$); $R_f$ = 0.25 (hexane–EtOAc, 1:1).

IR (KBr): 3340, 1538, 1531, 1368, 1359, 1351, 1187, 1178, 1156 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 3.00 (s, 3 H, $CH_3$), 3.84–3.94 (m, 1 H, CH), 4.11–4.19 (m, 2 H, $CH_2$), 5.54 (d, *J* = 7.6 Hz, 1 H, NH), 7.74–7.80 (m, 2 H, ArH), 7.88–7.94 (m, 1 H, ArH), 8.14–8.20 (m, 1 H, ArH).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 18.0, 37.4, 49.6, 71.4, 125.6, 130.7, 133.1, 133.8, 134.3, 147.8.

FAB-MS: *m*/*z* = 339 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{14}N_2O_7S_2$: C, 35.50; H, 4.17; N, 8.28. Found: C, 35.40; H, 4.07; N, 8.20.

**(*R*)-2-(2-Nitrophenylsulfonamido)propyl Methanesulfonate [(*R*)-10]**

Yield: 187 g (89%); pale yellow, crystalline solid.

Mp 123–125 °C; $[\alpha]_D^{20}$ –34.4 (*c* 0.55, $CHCl_3$); $R_f$ = 0.25 (hexane–EtOAc, 1:1).

IR (KBr): 3341, 1539, 1531, 1368, 1359, 1352, 1186, 1178, 1156 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 3.00 (s, 3 H, $CH_3$), 3.84–3.94 (m, 1 H, CH), 4.11–4.19 (m, 2 H, $CH_2$), 5.55 (d, *J* = 7.8 Hz, 1 H, NH), 7.74–7.81 (m, 2 H, ArH), 7.88–7.94 (m, 1 H, ArH), 8.15–8.19 (m, 1 H, ArH).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 18.0, 37.5, 49.6, 71.5, 125.7, 130.7, 133.1, 133.8, 134.3, 147.9.

FAB-MS: *m*/*z* = 339 $[M + H]^+$.

Anal. Calcd for $C_{10}H_{14}N_2O_7S_2$: C, 35.50; H, 4.17; N, 8.28. Found: C, 35.35; H, 4.07; N, 8.28.

**(*S*)-*N*-{1-[(3-Hydroxypropyl)amino]propan-2-yl}-2-nitrobenzenesulfonamide [(*S*)-11]**

To a soln of 3-aminopropan-1-ol (5.00 kg, 66.6 mol) in MeCN (35 L) was gradually added a soln of (*S*)-**10** (7.00 kg, 20.7 mol) in MeCN (35 L) at r.t. The reaction mixture was stirred for 16 h then concentrated under reduced pressure. To the residue was added $H_2O$ (10 L). The solution was acidified with 6 M HCl until pH 4. The precipitate was filtered off. The filtrate was made alkaline by adding $K_2CO_3$ until pH 9, and then extracted with EtOAc (8 × 3 L). The combined organic layers were dried over anhyd $Na_2SO_4$, filtered and concentrated under reduced pressure to give (*S*)-**11** as a yellow oil; yield: 6.10 kg (93%).

$[\alpha]_D^{20}$ +77.9 (*c* 1.00, $CHCl_3$); $R_f$ = 0.14 ($CHCl_3$–MeOH, 5:1).

IR (KBr): 3330, 2937, 1542, 1365, 1170 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.59–1.70 (m, 2 H, $CH_2$), 2.61 (dd, *J* = 12.6, 7.5 Hz, 1 H, C*H*H), 2.68 (dd, *J* = 12.6, 4.8 Hz, 1 H, C*H*H), 2.75 (dd, *J* = 6.0, 6.0 Hz, 2 H, $CH_2$), 3.32 (br s, 3 H, 2 × NH, OH), 3.54–3.62 (m, 1 H, CH), 3.68–3.76 (m, 2 H, $CH_2$), 7.72–7.78 (m, 2 H, ArH), 7.83–7.89 (m, 1 H, ArH), 8.14–8.18 (m, 1 H, ArH).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 19.4, 31.1, 48.7, 50.2, 54.8, 63.2, 125.3, 130.8, 132.8, 133.5, 134.4, 147.8.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{20}N_3O_5S$: 318.1124; found: 318.1133.

**(*R*)-*N*-{1-[(3-Hydroxypropyl)amino]propan-2-yl}-2-nitrobenzenesulfonamide [(*R*)-11]**

Yield: 174 g (100%); yellow oil.

$[\alpha]_D^{20}$ –77.9 (*c* 1.00, $CHCl_3$); $R_f$ = 0.14 ($CHCl_3$–MeOH, 5:1).

IR (KBr): 3315, 2937, 1541, 1365, 1169 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.61–1.72 (m, 2 H, $CH_2$), 2.65 (dd, *J* = 12.6, 7.5 Hz, 1 H, C*H*H), 2.70 (dd, *J* = 12.6, 4.8 Hz, 1 H, C*H*H), 2.78 (dd, *J* = 6.0, 6.0 Hz, 2 H, $CH_2$), 3.56–3.65 (m, 1 H, CH), 3.61 (br s, 3 H, 2 × NH, OH), 3.71–3.77 (m, 2 H, $CH_2$), 7.71–7.78 (m, 2 H, ArH), 7.83–7.88 (m, 1 H, ArH), 8.15–8.20 (m, 1 H, ArH).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 19.4, 30.9, 48.7, 50.1, 54.7, 63.1, 125.3, 130.8, 132.9, 133.5, 134.4, 147.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{20}N_3O_5S$: 318.1124; found: 318.1140.

**(*S*)-2-Methyl-1-[(2-nitrophenyl)sulfonyl]-1,4-diazepane Hydrochloride [(*S*)-12]**

To a soln of (*S*)-**11** (6.10 kg, 19.2 mol) and $Ph_3P$ (6.50 kg, 24.8 mol) in THF (35 L) was gradually added a soln of DIAD (5.20 kg, 25.7 mol) in THF (5 L) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 18 h. The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (15 L). The solution was acidified with 6 M HCl until pH 4. The precipitated product was collected by filtration and dried under reduced pressure to give (*S*)-**12** as a yellow solid; yield: 2.76 kg (40%).

Mp 146–147 °C; $[\alpha]_D^{20}$ +136.1 (*c* 0.52, MeOH).

IR (KCl): 3333, 2938, 2811, 1532, 1374, 1348, 1160 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 1.09 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.82–2.03 (m, 2 H, $CH_2$), 3.04 (ddd, *J* = 14.5, 9.5, 4.4 Hz, 1 H, C*H*H), 3.13–3.21 (m, 2 H, 2 × C*H*H), 3.39 (dd, *J* = 14.5, 4.4 Hz, 1 H, C*H*H), 3.48 (ddd, *J* = 15.4, 9.5, 4.4 Hz, 1 H, C*H*H), 3.74 (ddd, *J* = 15.4, 4.4, 4.4 Hz, 1 H, C*H*H), 4.32–4.42 (m, 1 H, CH), 7.85–7.94 (m, 2 H, ArH), 8.01 (dd, *J* = 7.2, 1.8 Hz, 1 H, ArH), 8.09 (dd, *J* = 7.2, 1.8 Hz, 1 H, ArH), 9.52 (br s, 2 H, $NH_2$).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 16.2, 26.5, 41.7, 45.6, 50.0, 50.5, 124.3, 129.6, 132.4, 132.6, 134.6, 147.4.

FD-MS: *m*/*z* = 300 $[M + H – HCl]^+$.

Anal. Calcd for $C_{12}H_{18}ClN_3O_4S·H_2O$: C, 40.73; H, 5.70; Cl, 10.02; N, 11.88. Found: C, 40.64; H, 5.63; Cl, 10.03; N, 11.66.

**(*R*)-2-Methyl-1-[(2-nitrophenyl)sulfonyl]-1,4-diazepane [(*R*)-12 Free Base]**

To a soln of (*R*)-**11** (172 g, 542 mmol) and $Ph_3P$ (182 g, 692 mmol) in THF (980 mL) was gradually added a soln of DIAD (140 g, 692 mmol) in THF (140 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 18 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 0 to 9% MeOH–$CHCl_3$) to give the free base (*R*)-**12** as a yellow solid; yield: 104 g (64%).

Mp 86–89 °C; $[\alpha]_D^{20}$ –191.4 (*c* 0.51, $CHCl_3$); $R_f$ = 0.52 ($CHCl_3$–MeOH–aq $NH_3$, 100:9:1).

IR (KBr): 2954, 1540, 1376, 1330, 1155 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.64–1.79 (m, 2 H, $CH_2$), 1.86 (s, 1 H, NH), 2.52 (dd, *J* = 15.1, 9.3 Hz, 1 H, C*H*H), 2.69 (ddd, *J* = 15.1, 9.3, 4.4 Hz, 1 H, C*H*H), 3.08 (ddd, *J* = 15.1, 4.4, 4.4 Hz, 1 H, C*H*H), 3.20 (ddd, *J* = 15.1, 9.3, 4.4 Hz, 1 H, C*H*H), 3.26 (dd, *J* = 14.6, 4.4 Hz, 1 H, C*H*H), 3.85 (ddd,

*J* = 15.5, 4.4, 4.4 Hz, 1 H, C*H*H), 4.08–4.18 (m, 1 H, CH), 7.61–7.71 (m, 3 H, ArH), 8.13–8.19 (m, 1 H, ArH).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 16.9, 32.2, 42.3, 50.1, 54.7, 56.2, 124.1, 130.9, 131.6, 133.2, 134.7, 147.9.

FAB-MS: *m*/*z* = 300 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{17}N_3O_4S$: C, 48.15; H, 5.72; N, 14.04. Found: C, 48.10; H, 5.64; N, 13.92.

**(*R*)-2-Methyl-1-[(2-nitrophenyl)sulfonyl]-1,4-diazepane Hydrochloride [(*R*)-12]**

To a soln of (*R*)-**11** (7.13 g, 22.5 mmol) and $Ph_3P$ (7.08 g, 27.0 mmol) in THF (80 mL) was gradually added DIAD (5.46 g, 27.0 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 12 h. To the mixture was added Amberlyst® 15 (29 g) and the suspension was gently shaken for 9 h at r.t. The resin was filtered and washed with THF (300 mL), followed by MeOH (300 mL), and finally eluted with 7 M $NH_3$ in MeOH (700 mL) to obtain the product. The filtrate was concentrated under reduced pressure to give the crude free base (7.12 g) as an oil. To a soln of 4 M HCl in EtOAc (50 mL) was added a soln of the above product in EtOAc (50 mL) at 0 °C. The precipitated product was collected by filtration and dried under reduced pressure to give (*R*)-**12** as a white solid; yield: 6.66 g (88%).

Mp 146–148 °C; $[\alpha]_D^{20}$ –136.1 (*c* 0.51, MeOH).

IR (KCl): 3334, 2938, 2811, 1532, 1374, 1348, 1160 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 1.08 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.82–2.02 (m, 2 H, $CH_2$), 3.04 (ddd, *J* = 14.5, 9.5, 4.4 Hz, 1 H, C*H*H), 3.12–3.21 (m, 2 H, 2 × C*H*H), 3.39 (dd, *J* = 14.5, 4.4 Hz, 1 H, C*H*H), 3.48 (ddd, *J* = 15.4, 9.5, 4.4 Hz, 1 H, C*H*H), 3.74 (ddd, *J* = 15.4, 4.4, 4.4 Hz, 1 H, C*H*H), 4.31–4.42 (m, 1 H, CH), 7.85–7.94 (m, 2 H, ArH), 8.01 (dd, *J* = 7.2, 1.8 Hz, 1 H, ArH), 8.09 (dd, *J* = 7.2, 1.8 Hz, 1 H, ArH), 9.18 (br s, 1 H, NH), 9.84 (br s, 1 H, NH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 16.3, 26.6, 41.8, 45.7, 50.1, 50.5, 124.4, 129.7, 132.5, 132.7, 134.7, 147.5.

FD-MS: *m*/*z* = 300 $[M + H – HCl]^+$.

Anal. Calcd for $C_{12}H_{18}ClN_3O_4S·H_2O$: C, 40.73; H, 5.70; Cl, 10.02; N, 11.88. Found: C, 40.65; H, 5.60; Cl, 10.06; N, 11.73.

**(*S*)-*tert*-Butyl 3-Methyl-4-[(2-nitrophenyl)sulfonyl]-1,4-diazepane-1-carboxylate [(*S*)-13]**

To a soln of (*S*)-**12** (2.70 kg, 8.04 mol) and $K_2CO_3$ (1.50 kg, 10.9 mol) in EtOH (12 L) and $H_2O$ (12 L) was gradually added $Boc_2O$ (2.00 kg, 9.16 mol) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 2 h. The mixture was concentrated under reduced pressure. To the residue was added $H_2O$ (30 L). The precipitated product was collected by filtration, washed with $H_2O$ and dried under reduced pressure to give (*S*)-**13** as a yellow crystalline solid; yield: 2.80 kg (87%).

Mp 113–114 °C; $[\alpha]_D^{20}$ +105.0 (*c* 1.01, $CHCl_3$); $R_f$ = 0.36 (hexane–EtOAc, 1:1).

IR (KBr): 2976, 1685, 1674, 1542, 1366, 1334, 1170 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.90 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.40 (s, 9 H, *t*-Bu), 1.66–1.74 (m, 2 H, $CH_2$), 3.02–3.13 (m, 1 H, C*H*H), 3.14 (dd, *J* = 15.2, 8.3 Hz, 1 H, C*H*H), 3.20–3.29 (m, 1 H, C*H*H), 3.62 (dd, *J* = 15.2, 4.1 Hz, 2 H, 2 × C*H*H), 3.74 (ddd, *J* = 15.2, 4.1, 4.1 Hz, 1 H, C*H*H), 4.22–4.31 (m, 1 H, CH), 7.78–7.87 (m, 3 H, ArH), 7.97–8.00 (m, 1 H, ArH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 15.1, 27.6, 27.6, 27.6, 28.7, 41.5, 46.4, 51.6, 51.8, 78.4, 123.6, 129.3, 131.7, 132.7, 133.7, 147.2, 153.5.

MS (ESI): *m*/*z* = 400 $[M + H]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{25}N_3O_6SNa$: 422.1362; found: 422.1386.

Anal. Calcd for $C_{17}H_{25}N_3O_6S$: C, 51.11; H, 6.31; N, 10.52. Found: C, 51.05; H, 6.30; N, 10.39.

**(*R*)-*tert*-Butyl 3-Methyl-4-[(2-nitrophenyl)sulfonyl]-1,4-diazepane-1-carboxylate [(*R*)-13]**

Yield: 21.1 g (98%); yellow crystalline solid.

Mp 113–114 °C; $[\alpha]_D^{20}$ –104.8 (*c* 1.00, $CHCl_3$); $R_f$ = 0.36 (hexane–EtOAc, 1:1).

IR (KBr): 2975, 1685, 1674, 1543, 1366, 1334, 1171 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.90 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.40 (s, 9 H, *t*-Bu), 1.66–1.74 (m, 2 H, $CH_2$), 3.01–3.13 (m, 1 H, C*H*H), 3.14 (dd, *J* = 15.2, 8.3 Hz, 1 H, C*H*H), 3.20–3.29 (m, 1 H, C*H*H), 3.62 (dd, *J* = 15.2, 4.1 Hz, 2 H, 2 × C*H*H), 3.74 (ddd, *J* = 15.2, 4.1, 4.1 Hz, 1 H, C*H*H), 4.21–4.31 (m, 1 H, CH), 7.78–7.87 (m, 3 H, ArH), 7.96–8.00 (m, 1 H, ArH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 15.1, 27.6, 27.6, 27.6, 28.7, 41.5, 46.4, 51.6, 51.8, 78.4, 123.6, 129.3, 131.7, 132.7, 133.7, 147.2, 153.5.

MS (ESI): *m*/*z* = 400 $[M + H]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{25}N_3O_6SNa$: 422.1362; found: 422.1370.

Anal. Calcd for $C_{17}H_{25}N_3O_6S$: C, 50.95; H, 6.20; N, 10.45.

**(*S*)-*tert*-Butyl 3-Methyl-1,4-diazepane-1-carboxylate [(*S*)-7]**

To a soln of (*S*)-**13** (2.60 kg, 6.51 mol) and $K_2CO_3$ (1.79 kg, 13.0 mol) in MeCN (20 L) was added PhSH (2.15 kg, 19.5 mol) at r.t. The reaction mixture was stirred at r.t. for 18 h. After the completion of denosylation was monitored by HPLC, the insoluble material was filtered off. The filtrate was concentrated under reduced pressure. To the residue was added ice–water (5 L). The resulting solution was acidified with 2 M HCl until pH 3. The aqueous layer was washed with EtOAc (3 × 500 mL), and was made alkaline with $K_2CO_3$ until pH 9, and then extracted with EtOAc (4 × 1 L). The combined organic layers were dried over anhyd $Na_2SO_4$ and concentrated under reduced pressure to give (*S*)-**7** as a pale yellow oil; yield: 1.20 kg (86%); >99.9% ee (by HPLC).

$[\alpha]_D^{20}$ +8.7 (*c* 1.07, $CHCl_3$); $R_f$ = 0.30 ($CHCl_3$–8 M $NH_3$ in MeOH, 10:1).

IR (KBr): 3317, 2973, 1695, 1418, 1165 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.94 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.40 (s, 9 H, *t*-Bu), 1.52–1.63 (m, 1 H, C*H*H), 1.69–1.79 (m, 1 H, C*H*H), 2.42–2.50 (m, 1 H, C*H*H), 2.60–2.68 (m, 1 H, C*H*H), 2.70–2.79 (m, 1 H, CH), 2.97 (ddd, *J* = 13.8, 4.5, 4.5 Hz, 1 H, C*H*H), 3.17 (ddd, *J* = 13.8, 7.7, 6.1 Hz, 1 H, C*H*H), 3.54 (ddd, *J* = 13.8, 6.1, 6.1 Hz, 1 H, C*H*H), 3.60 (dd, *J* = 13.8, 2.7 Hz, 1 H, C*H*H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 18.9, 27.7, 27.7, 27.7, 29.4, 45.0, 45.1, 53.9, 55.4, 77.6, 154.1.

MS (EI): *m*/*z* = 214 $[M^+]$.

HRMS: *m*/*z* $[M^+]$ calcd for $C_{11}H_{22}N_2O_2$: 214.1681; found: 214.1680.

**(*R*)-*tert*-Butyl 3-Methyl-1,4-diazepane-1-carboxylate [(*R*)-7]**

Yield: 7.95 g (70%); 99.8% ee (by HPLC); pale yellow oil.

$[\alpha]_D^{20}$ –8.6 (*c* 1.13, $CHCl_3$); $R_f$ = 0.30 ($CHCl_3$–8 M $NH_3$ in MeOH, 10:1).

IR (KBr): 3314, 2973, 1691, 1414, 1165 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.95 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.40 (s, 9 H, *t*-Bu), 1.52–1.64 (m, 1 H, C*H*H), 1.69–1.79 (m, 1 H, C*H*H), 2.42–2.50 (m, 1 H, C*H*H), 2.60–2.69 (m, 1 H, C*H*H), 2.71–2.80 (m, 1 H, CH), 2.97 (ddd, *J* = 13.8, 4.5, 4.5 Hz, 1 H, C*H*H), 3.17 (ddd, *J* = 13.8, 7.7, 6.1 Hz, 1 H, C*H*H), 3.54 (ddd,

$J$ = 13.8, 6.1, 6.1 Hz, 1 H, C*H*H), 3.60 (dd, $J$ = 13.8, 2.7 Hz, 1 H, C*H*H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 18.9, 27.7, 27.7, 27.7, 29.4, 45.0, 45.1, 53.9, 55.3, 77.6, 154.1.

MS (EI): $m/z$ = 214 [$M^+$].

HRMS: $m/z$ [$M^+$] calcd for $C_{11}H_{22}N_2O_2$: 214.1681; found: 214.1683.

**(*S*)-Benzyl 3-Methyl-4-[(2-nitrophenyl)sulfonyl]-1,4-diazepane-1-carboxylate [(*S*)-14]**

To a soln of (*S*)-**12** as the free base (5.92 g, 19.8 mmol) and $NaHCO_3$ (2.50 g, 29.8 mmol) in THF (20 mL) and $H_2O$ (20 mL) was gradually added a soln of CbzCl (4.72 g, 27.7 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 15 h. The mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over anhyd $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 0 to 9% MeOH–$CHCl_3$) to give (*S*)-**14** as a yellow oil; yield: 8.36 g (97%).

$[\alpha]_D^{20}$ +91.4 ($c$ 0.78, $CHCl_3$); $R_f$ = 0.34 (hexane–EtOAc, 1:1).

IR (KBr): 2958, 1700, 1543, 1423, 1373, 1159 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.93 (d, $J$ = 6.8 Hz, 3 H, $CH_3$), 1.66–1.74 (m, 2 H, $CH_2$), 3.08–3.34 (m, 3 H, 3 × C*H*H), 3.67–3.81 (m, 3 H, 3 × C*H*H), 4.23–4.33 (m, 1 H, CH), 5.02 (d, $J$ = 12.7 Hz, 1 H, C*H*H), 5.07 (d, $J$ = 12.7 Hz, 1 H, C*H*H), 7.26–7.38 (m, 5 H, ArH), 7.76–7.86 (m, 3 H, ArH), 7.95 (d, $J$ = 7.8 Hz, 1 H, ArH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 15.3, 28.4, 41.3, 46.8, 51.6, 51.8, 65.9, 123.6, 126.9, 126.9, 127.2, 127.8, 127.8, 129.3, 131.7, 132.5, 133.8, 136.5, 147.1, 154.3.

HRMS: $m/z$ [M + H]$^+$ calcd for $C_{20}H_{24}N_3O_6S$: 434.1386; found: 434.1411.

**(*R*)-Benzyl 3-Methyl-4-[(2-nitrophenyl)sulfonyl]-1,4-diazepane-1-carboxylate [(*R*)-14]**

Yield: 65.0 g (100%); yellow oil.

$[\alpha]_D^{20}$ –91.2 ($c$ 0.90, $CHCl_3$); $R_f$ = 0.34 (hexane–EtOAc, 1:1).

IR (KBr): 2959, 1699, 1544, 1424, 1373, 1159 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.93 (d, $J$ = 6.8 Hz, 3 H, $CH_3$), 1.66–1.74 (m, 2 H, $CH_2$), 3.10–3.34 (m, 3 H, 3 × C*H*H), 3.67–3.81 (m, 3 H, 3 × C*H*H), 4.23–4.33 (m, 1 H, CH), 5.02 (d, $J$ = 12.7 Hz, 1 H, C*H*H), 5.07 (d, $J$ = 12.7 Hz, 1 H, C*H*H), 7.27–7.37 (m, 5 H, ArH), 7.76–7.85 (m, 3 H, ArH), 7.95 (d, $J$ = 7.8 Hz, 1 H, ArH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 15.3, 28.3, 41.3, 46.8, 51.6, 51.8, 65.9, 123.5, 126.8, 126.8, 127.1, 127.7, 127.7, 129.3, 131.6, 132.5, 133.7, 136.4, 147.1, 154.3.

HRMS: $m/z$ [M + H]$^+$ calcd for $C_{20}H_{24}N_3O_6S$: 434.1386; found: 434.1407.

**(*S*)-Benzyl 3-Methyl-1,4-diazepane-1-carboxylate [(*S*)-15]**

To a soln of (*S*)-**14** (8.26 g, 19.1 mmol) and $K_2CO_3$ (5.27 g, 38.1 mmol) in MeCN (83 mL) was added PhSH (3.9 mL, 38.1 mol) at r.t. The reaction mixture was stirred at 50 °C for 6.5 h. The mixture was diluted with $H_2O$ (240 mL) and extracted with EtOAc (3 × 80 mL). The combined organic layers were extracted with 2 M HCl (3 × 80 mL). The combined aqueous layers were made alkaline by adding $K_2CO_3$ until pH 12, and then extracted with EtOAc (3 × 80 mL). The combined organic layers were dried over anhyd $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 0 to 18% MeOH–$CHCl_3$) to give (*S*)-**15** as a yellow oil; yield: 2.83 g (60%).

$[\alpha]_D^{20}$ +7.6 ($c$ 0.50, $CHCl_3$); $R_f$ = 0.36 ($CHCl_3$–MeOH–aq $NH_3$, 100:9:1).

IR (KBr): 3318, 2938, 1693, 1422, 1225 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.99 (d, $J$ = 5.9 Hz, 3 H, $CH_3$), 1.61–1.83 (m, 2 H, $CH_2$), 2.54 (ddd, $J$ = 13.8, 10.2, 4.1 Hz, 1 H, C*H*H), 2.81–2.90 (m, 2 H, CH + C*H*H), 3.01 (ddd, $J$ = 13.8, 4.1, 4.1 Hz, 1 H, C*H*H), 3.30 (ddd, $J$ = 14.0, 7.5, 5.9 Hz, 1 H, C*H*H), 3.39 (br s, 1 H, NH), 3.58–3.73 (m, 2 H, 2 × C*H*H), 5.08 (s, 2 H, $CH_2$), 7.26–7.37 (m, 5 H, ArH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 18.4, 28.6, 44.8, 45.1, 53.8, 54.4, 65.6, 126.8, 126.8, 127.1, 127.8, 127.8, 136.8, 154.7.

MS (EI): $m/z$ = 248 [$M^+$].

HRMS: $m/z$ [$M^+$] calcd for $C_{14}H_{20}N_2O_2$: 248.1525; found: 248.1516.

**(*R*)-Benzyl 3-Methyl-1,4-diazepane-1-carboxylate [(*R*)-15]**

Yield: 32.7 g (88%); yellow oil.

$[\alpha]_D^{20}$ –7.9 ($c$ 0.62, $CHCl_3$); $R_f$ = 0.36 ($CHCl_3$–MeOH–aq $NH_3$, 100:9:1).

IR (KBr): 3315, 2934, 1695, 1422, 1224 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.95 (d, $J$ = 5.9 Hz, 3 H, $CH_3$), 1.55–1.79 (m, 2 H, $CH_2$), 1.83 (br s, 1 H, NH), 2.47 (ddd, $J$ = 13.8, 10.2, 4.1 Hz, 1 H, C*H*H), 2.71–2.81 (m, 2 H, CH + C*H*H), 2.97 (ddd, $J$ = 13.8, 4.1, 4.1 Hz, 1 H, C*H*H), 3.28 (ddd, $J$ = 13.8, 7.5, 5.7 Hz, 1 H, C*H*H), 3.57–3.71 (m, 2 H, 2 × C*H*H), 5.08 (s, 2 H, $CH_2$), 7.25–7.37 (m, 5 H, ArH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 19.0, 29.4, 45.2, 45.2, 53.8, 55.4, 65.5, 126.8, 126.8, 127.1, 127.7, 127.7, 136.8, 154.7.

MS (EI): $m/z$ = 248 [$M^+$].

HRMS: $m/z$ [$M^+$] calcd for $C_{14}H_{20}N_2O_2$: 248.1525; found: 248.1512.

**(*S*)-4-Benzyl 1-*tert*-Butyl 2-Methyl-1,4-diazepane-1,4-dicarboxylate [(*S*)-16]**

To a soln of (*S*)-**15** (2.73 g, 11.0 mmol) and $K_2CO_3$ (2.28 g, 16.5 mmol) in EtOH (15 mL) and $H_2O$ (8 mL) was gradually added $Boc_2O$ (3.60 g, 16.5 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 1.5 h. The mixture was diluted with $H_2O$ (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhyd $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 33 to 66% EtOAc–hexane) to give (*S*)-**16** as a white solid; yield: 3.80 g (99%).

Mp 77 °C; $[\alpha]_D^{20}$ +44.6 ($c$ 0.63, $CHCl_3$); $R_f$ = 0.38 (hexane–EtOAc, 2:1).

IR (KBr): 2971, 1697, 1685, 1428, 1259, 1168 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.98 (d, $J$ = 6.8 Hz, 3 H, $CH_3$), 1.36 (s, 9 H, *t*-Bu), 1.51–1.71 (m, 2 H, $CH_2$), 2.92–2.99 (m, 1 H, C*H*H), 2.93 (dd, $J$ = 14.8, 10.8 Hz, 1 H, C*H*H), 2.99 (ddd, $J$ = 14.8, 10.8, 2.0 Hz, 1 H, C*H*H), 3.63–3.71 (m, 1 H, C*H*H), 3.78 (dd, $J$ = 14.8, 6.0 Hz, 1 H, C*H*H), 3.83–3.90 (m, 1 H, C*H*H), 4.29–4.40 (m, 1 H, CH), 5.03 (d, $J$ = 12.7 Hz, 1 H, C*H*H), 5.07 (d, $J$ = 12.7 Hz, 1 H, C*H*H), 7.26–7.36 (m, 5 H, ArH).

$^{13}$C NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 15.6, 27.6, 27.6, 27.6, 27.6, 39.6, 47.5, 47.5, 51.8, 65.7, 78.0, 126.7, 126.7, 127.1, 127.8, 127.8, 136.6, 154.0, 154.2.

MS (EI): $m/z$ = 348 [$M^+$].

HRMS: $m/z$ [$M^+$] calcd for $C_{19}H_{28}N_2O_4$: 348.2049; found: 348.2050.

**(*R*)-4-Benzyl 1-*tert*-Butyl 2-Methyl-1,4-diazepane-1,4-dicarboxylate [(*R*)-16]**

Yield: 45.3 g (99%); pale yellow solid.

Mp 77 °C; $[\alpha]_D^{20}$ –44.0 ($c$ 0.93, $CHCl_3$); $R_f$ = 0.38 (hexane–EtOAc, 2:1).

IR (KBr): 2974, 1690, 1425, 1256, 1166 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.98 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.36 (s, 9 H, *t*-Bu), 1.52–1.70 (m, 2 H, $CH_2$), 2.92–2.99 (m, 1 H, C*H*H), 2.92 (dd, *J* = 14.1, 10.3 Hz, 1 H, C*H*H), 2.99 (ddd, *J* = 14.1, 10.3, 2.5 Hz, 1 H, C*H*H), 3.62–3.71 (m, 1 H, C*H*H), 3.78 (dd, *J* = 14.1, 6.1 Hz, 1 H, C*H*H), 3.82–3.90 (m, 1 H, C*H*H), 4.29–4.40 (m, 1 H, CH), 5.03 (d, *J* = 12.7 Hz, 1 H, C*H*H), 5.07 (d, *J* = 12.7 Hz, 1 H, C*H*H), 7.25–7.36 (m, 5 H, ArH).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 15.6, 27.6, 27.6, 27.6, 27.6, 39.6, 47.5, 47.5, 51.8, 65.6, 77.9, 126.7, 126.7, 127.1, 127.7, 127.7, 136.6, 154.0, 154.1.

MS (EI): *m*/*z* = 348 [$M^+$].

HRMS: *m*/*z* [$M^+$] calcd for $C_{19}H_{28}N_2O_4$: 348.2049; found: 348.2048.

**(*S*)-*tert*-Butyl 2-Methyl-1,4-diazepane-1-carboxylate [(*S*)-17]**

To a soln of (*S*)-**16** (3.70 g, 10.6 mmol) in MeOH (30 mL) was added 10% Pd/C (370 mg). The reaction mixture was stirred at r.t. for 15 h under a hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 1 to 18% MeOH–$CHCl_3$) to give (*S*)-**17** as a pale yellow oil; yield: 2.18 g (96%); >99.9% ee (by HPLC).

$[\alpha]_D^{20}$ +56.8 (*c* 1.13, $CHCl_3$); $R_f$ = 0.33 ($CHCl_3$–MeOH, 5:1).

IR (KBr): 3349, 2974, 1684, 1413, 1173 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.95 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.40 (s, 9 H, *t*-Bu), 1.47–1.57 (m, 2 H, $CH_2$), 2.34 (dd, *J* = 14.3, 10.0 Hz, 1 H, C*H*H), 2.46–2.54 (m, 1 H, C*H*H), 2.64 (br s, 1 H, NH), 2.83–2.93 (m, 2 H, 2 × C*H*H), 3.03 (dd, *J* = 14.3, 5.7 Hz, 1 H, C*H*H), 3.64 (ddd, *J* = 14.3, 3.4, 3.4 Hz, 1 H, C*H*H), 3.92–4.03 (m, 1 H, CH).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 16.2, 27.7, 27.7, 27.7, 30.7, 39.5, 49.3, 51.9, 54.5, 77.4, 154.2.

MS (EI): *m*/*z* = 214 [$M^+$].

HRMS: *m*/*z* [$M^+$] calcd for $C_{11}H_{22}N_2O_2$: 214.1681; found: 214.1682.

**(*R*)-*tert*-Butyl 2-Methyl-1,4-diazepane-1-carboxylate [(*R*)-17]**

Yield: 20.6 g (74%); >99.9% ee (by HPLC); yellow oil.

$[\alpha]_D^{20}$ –56.5 (*c* 1.21, $CHCl_3$); $R_f$ = 0.33 ($CHCl_3$–MeOH, 5:1).

IR (KBr): 3348, 2973, 1685, 1413, 1174 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$, 100 °C): δ = 0.96 (d, *J* = 6.8 Hz, 3 H, $CH_3$), 1.41 (s, 9 H, *t*-Bu), 1.52–1.60 (m, 2 H, $CH_2$), 2.43 (dd, *J* = 14.3, 10.4 Hz, 1 H, C*H*H), 2.51–2.60 (m, 1 H, C*H*H), 2.86–2.99 (m, 2 H, 2 × C*H*H), 3.10 (dd, *J* = 14.3, 5.7 Hz, 1 H, C*H*H), 3.54 (br s, 1 H, NH), 3.66 (ddd, *J* = 14.3, 3.4, 3.4 Hz, 1 H, C*H*H), 3.96–4.07 (m, 1 H, CH).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$, 100 °C): δ = 16.2, 27.8, 27.8, 27.8, 29.9, 39.5, 48.8, 51.2, 53.7, 77.6, 154.1.

MS (EI): *m*/*z* = 214 [$M^+$].

HRMS: *m*/*z* [$M^+$] calcd for $C_{11}H_{22}N_2O_2$: 214.1681; found: 214.1684.

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