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S_N2 reaction of 2-substituted 3-piperidinol mesylate with retention of configuration: application to the asymmetric synthesis of (2*R*,3*S*)-CP-99,994

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Abstract—Starting from protected (*S*)-3-hydroxyglutarimide **2a**, the asymmetric synthesis of (2*R*,3*S*)-CP-99,994 **8** was achieved. The crucial steps were a neighboring group participation leading to pyrrolidino-aziridinium intermediate **25** and the subsequent regioselective ring-opening reaction. In the case where neighboring group participation was not involved, only the eliminated product **15** was obtained.

1. Introduction

2-Substituted 3-hydroxypiperidines and 2-substituted 3-aminopiperidines with different stereochemical patterns are key structural features found in a number of natural products and pharmaceutically interesting compounds.[1,2] Recently, we have shown that protected (*S*)-3-hydroxyglutarimides **1** and **2** (Chart 1) are versatile building blocks for the asymmetric synthesis of 3-hydroxy and 3-amino-piperidines.[3] Starting from **1** and **2**, different methods have been developed for establishing the (2*S*,3*S*)-, (2*R*,3*R*)-, or (2*R*,3*S*)-stereochemistry of 2-substituted 3-hydroxypiperidines, as demonstrated by the asymmetric synthesis of the antimalarial (2*R*,3*S*)-febrifugine **3**,[3a] neurokinin substance P receptor antagonists (2*S*,3*S*)-L-733,060 **4**,[3b] and (2*R*,3*R*)-L-733,061 **5**.[3c] With regards to 3-aminopiperidines,[4,5] the only diastereomer that has been synthesized from the protected (*S*)-3-hydroxyglutarimide **2a** is (2*S*,3*S*)-CP-99,994 **6**,[4] another neurokinin substance P receptor antagonist.[3a] In view of the stereochemical diversity of the bioactive natural[6] and unnatural 2,3-disubstituted piperidines,[1,2,4] and in order to explore the possibility of accessing other stereochemistry pattern[9] from (*S*)-3-hydroxyglutarimides **1** and **2**, we decided to investigate the asymmetric synthesis of (2*R*,3*R*)-CP-99,994 **7** and/or (2*R*,3*S*)-CP-99,994 **8**. Herein, we report the results and some interesting observations made during the investigations.

2. Results and discussion

As an initial target, (2*R*,3*R*)-CP-99,994 **7** was envisioned to be prepared from (2*R*,3S)-**11** via an S_N2 reaction.[7] Thus the known 2-piperidinone **9**,[3c] readily prepared from (*S*)-**2a** by a regio- and *trans*-diastereoselective reductive phenylation, was converted to *N*-Boc protected 3-hydroxypiperidine **10** by a known transformation.[3c] Treatment of **10** with *p*-TsCl in the presence of pyridine gave tosylate **11** in 90% yield (Scheme 1). However, attempts to perform a nucleophilic substitution using *o*-methoxybenzylamine **13** as a nucleophile failed. Most of the starting material was recovered along with a small amount of the eliminated side product **15**. We then tried a more nucleophilic anionic nitrogen nucleophile generated in situ from sulfonamide **16** and potassium *t*-butoxide. Unfortunately, after being stirred in DMF for 3 days at rt, instead of the expected product **18** only the eliminated compound **15** was isolated in 71% yield. It was considered that the failure to perform the nucleophilic substitution might be due to steric hindrance.[8] To reduce the steric hindrance, mesylate **12** was prepared and subjected to a reaction with sodium azide. However, after being stirred at 70–80 °C for 2 days, the eliminated compound **15** was obtained once again as the major product and the desired product **19** was not observed.

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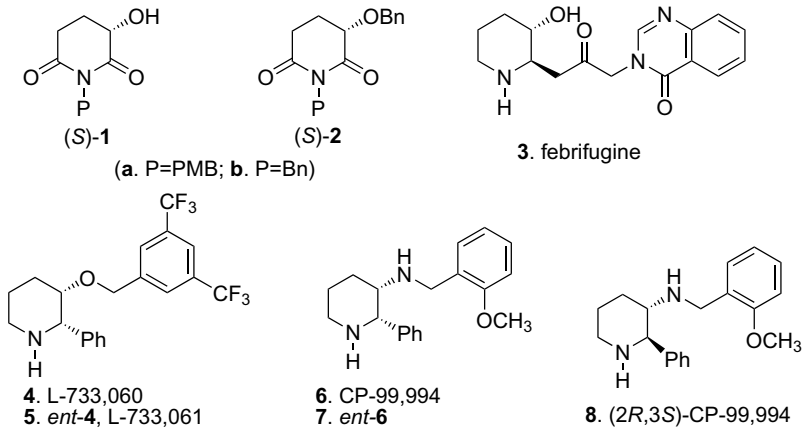
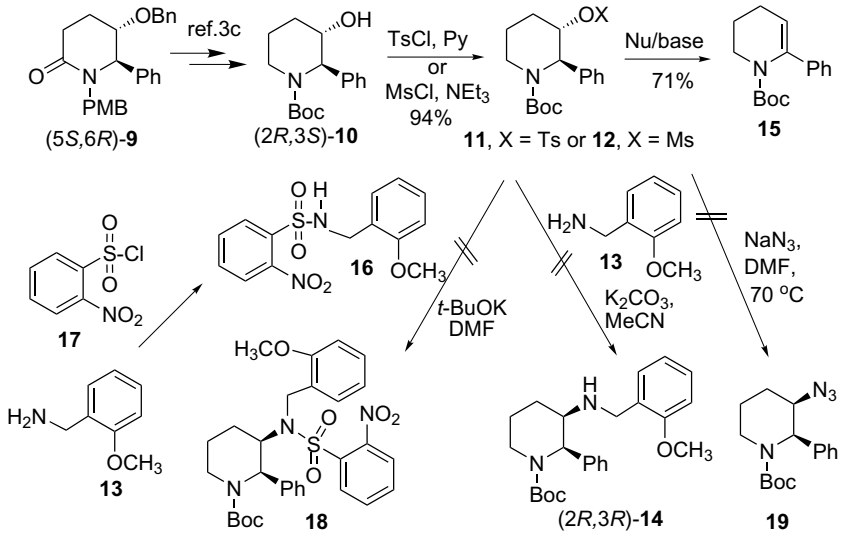
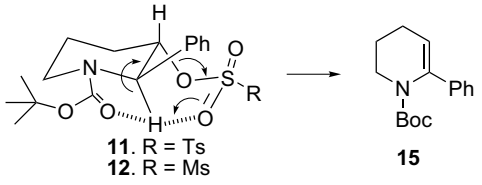


Chart 1. Structures of piperidine building blocks and bioactive 2-substituted 3-hydroxy- and 3-amino-piperidines.



Scheme 1.

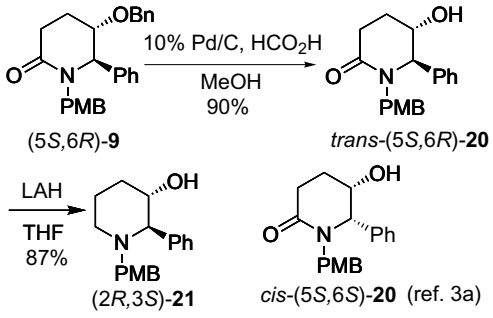
The unexpected facile *syn*-elimination of **11** can be understood in terms of the plausible double dipolar interactions of both Boc carbonyl and sulfonate S=O groups with a benzylic proton, as shown in Scheme 2.



Scheme 2.

At this stage, changing Boc to benzyl as the *N*-protective group was envisioned, in the hope of decreasing the acidity of the proton at the C-2 position, and thus suppressing the elimination reaction. To this end, 2-piperidinone **9** was converted into 2-phenyl-3-hydroxypiperidine **21** via catalytic hydrogenolysis (10% Pd/C, 10% HCO_2H in MeOH, rt, 10 h, yield: 90%) and LAH reduction ($LiAlH_4$, THF, yield: 87%) (Scheme 3).

The conformations of both **20** and **21** deserve comment. *trans*-**20** shows a small (2.6 Hz) vicinal coupling constant between H-5 and H-6 ($J_{5,6}$), which is an indication of a pseudo-equatorial disposition of the two *trans*-protons (Fig. 1). In other words, both the phenyl and the hydroxyl groups in *trans*-**20** are in an axial orientation. This is in agreement with the conformational analysis of substituted 2-piperidinones.[9] In addition, larger $J_{5,6}$ (5.2 Hz) exhibited



Scheme 3.

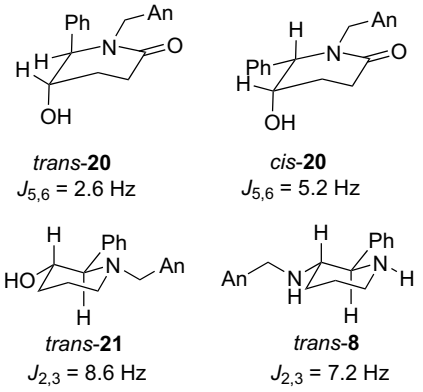
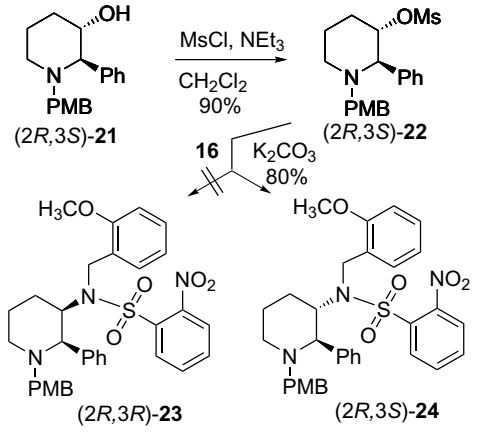


Figure 1. Plausible conformations of *trans*/*cis*-**20**, *trans*-**21** and *trans*-**8**.

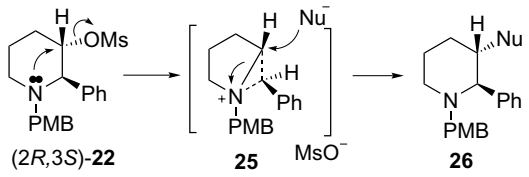
by *cis*-**20**,[3a] having an pseudo-equatorial/axial disposition, is in support of an equatorial/equatorial disposition of the H-5/H-6 in *trans*-**20**. In contrast, the ^{1}H NMR of *trans*-**21** shows a large vicinal coupling constant between H-2 and H-3 ($J_{2,3} = 8.6$ Hz), which may indicate that both the phenyl and the hydroxyl groups are in an equatorial disposition.

Next, treatment of 3-hydroxypiperidine **21** with MsCl at −20 °C for 2 h afforded the desired mesylate **22** as a labile waxy solid (Scheme 4). It was observed that mesylate **22** was unstable at rt, and decomposed during the concentrating procedure. However, the decomposition of **22** can be suppressed at lower temperature (<5 °C). The key nucleophilic substitution was achieved by treating **22** with sulfonamide **16** in the presence of anhydrous K_2CO_3 (MeCN, 30 °C), which gave **24** in 80% yield. The vicinal coupling constant of **24** ($J_{2,3} = 9.7$ Hz) is of the same order as that of 3-hydroxypiperidine **21** ($J_{2,3} = 8.6$ Hz), implying that the obtained product is the *trans*-diastereomer **24** instead of *cis*-diastereomer **23**, which was confirmed by converting **24** into the known *trans*-(2*R*,3*S*)-CP-99,994 **8** (vide infra).



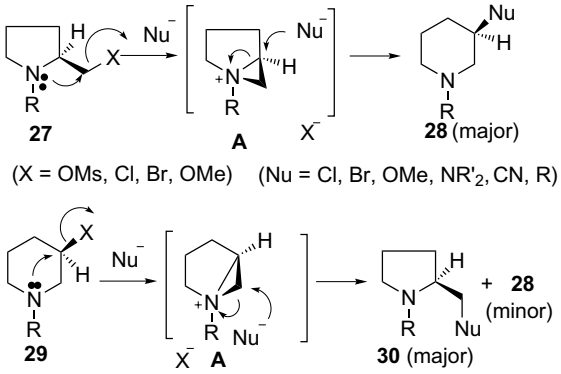
Scheme 4.

The results meant that the configuration at C-3 was conserved during the nucleophilic substitution, which is an indication of neighboring group participation via an aziridinium intermediate **25** (Scheme 5). The neighboring group participation can be used to account for both the successful use of a weak heterogeneous base K_2CO_3 to deprotonate **16** and the instability of mesylate **22**. The fact that only one isomer **24** was obtained indicated that the reaction is highly regio- and diastereoselective.



Scheme 5.

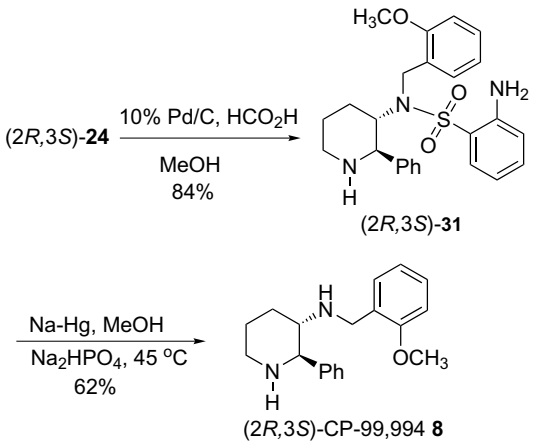
It is worth noting that although the nucleophile-promoted ring expansion reaction of 2-hydroxymethylpyrrolidine mesylates and analogues **27** leading to 3-substituted piperidines **28** as the major products (Scheme 6) is a well-established procedure,[10] formation of the pyrrolidino-aziridinium intermediates **A** from 3-hydroxypiperidine mesylates or analogues **29** is rare,[11] and the subsequent reactions show poor regioselectivity, leading to a mixture of pyrrolidines **30** and piperidines **28** in either ca. 1:1 ratio[11a,b] or with the former being predominant.[11c–e] To the best of our knowledge, only in a highly hindered system has piperidine **28** been predominately formed in good yields.[12]



Scheme 6.

As such, the present study provided a singular example of the anchimeric assistance of the nitrogen atom of piperidine **22** during the substitution reaction, which leads to 3-substituted piperidine **26** with retention of configuration. Thus an efficient method for the transformation of **21** to **24** with retention of configuration was established.

To pursue the synthesis of (2*R*,3*S*)-CP-99,994 **8**, compound **24** was subjected to catalytic hydrogenolytic conditions (Scheme 7) to give product **31**, which was formed with concomitant nitro group reduction. The selection of *o*-nitrobenzenesulfonyl group as the protecting group was made with the intention of taking advantage of Fukuyama's mild deprotection conditions.[13] However, the cleavage of the *o*-aminobenzenesulfonyl group proved to be difficult. An attempt to use SmI_2 as a cleaving agent[14] was unsuccessful. Finally, the procedure described by Trost[15] for

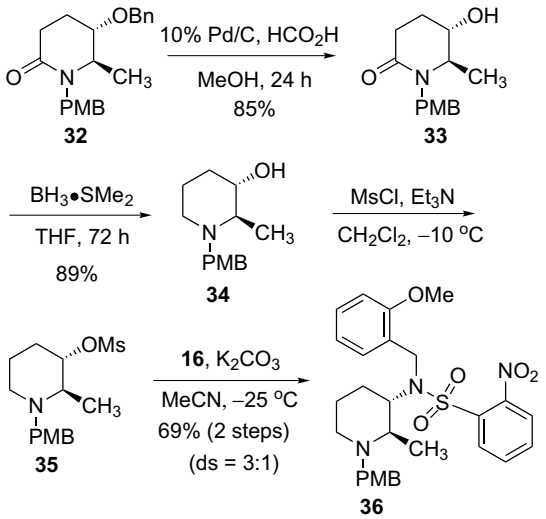


Scheme 7.

de-sulfonation was proven to be effective. The *o*-aminobenzenesulfonyl group in **31** was removed using sodium amalgam in buffered methanolic solution (Na_2HPO_4, MeOH, 45 °C, 2 days), which gave **8** in 62% yield.

The final product (2*R*,3*S*)-**8** shows a larger vicinal coupling constant between H-2 and H-3 ($J_{2,3} = 7.2$ Hz) (cf. Fig. 1) than that of the (2*S*,3*S*)-diastereomer ($J_{2,3} = 2.3$ Hz).[4g] In addition, the specific rotation and mp of (2*R*,3*S*)-**8** {$[\alpha]_D^{20} = +73.4$ (*c* 0.4, MeOH, HCl salt); mp = 247–249 °C (HCl salt)} are in agreement with the data reported for (2*S*,3*R*)-**8** {$[\alpha]_D^{20} = -78$ (*c* 1.0, MeOH, HCl salt); mp = 250 °C (HCl salt)}.[4a] The stereochemistry of **24** has been confirmed to be (2*R*,3*S*), which is in support of the mechanism illustrated in Scheme 5.

To gain insight into the generality of the anchimeric assistance of the nitrogen atom of piperidine **22** during the substitution reaction, a similar reaction of the methyl analogue **35** was investigated (Scheme 8). Thus, the known 2-piperidinone **32**[3c] was debenzylated and reduced to yield 3-piperidinol **34**. Mesylation of **34** gave unstable **35**, which upon treatment with **16** and anhydrous K_2CO_3 in MeCN at −25 °C for 2 days gave the desired *trans*-piperidine **36** and its *cis*-diastereomer in a 3:1 ratio. The similar vicinal coupling constant of piperidine **36** ($J_{2,3} = 9.2$ Hz) compared with that of **24** ($J_{2,3} = 9.7$ Hz) allowed us to assign the *trans*-stereochemistry to **36**. This result showed us that the participation of the nitrogen atom of mesylated 3-piperidinol **35** during the nucleophilic substitution is still the predominant pathway, but is in competition with a normal S_N2 reaction. The observed different outcomes of **22** and **35** can be explained by the synclinal interaction between the *N*-PMB group and the phenyl group in **22**, which favored the aziridinium formation.



Scheme 8.

3. Conclusion

In conclusion, the results from the present study have demonstrated that the S_N2 reaction of 2-substituted 3-piperidinol mesylate with *N*-nucleophiles took place with retention of configuration due to anchimeric assistance of the piperidine nitrogen atom. This represents a singular example where a pyrrolidino-aziridinium ion intermediate is formed starting from a 3-piperidinol mesylate and the subsequent nucleophilic reaction results in a substituted piperidine with high regioselectivity. Using this method, (2*R*,3*S*)-CP-99,994 **8** was obtained from protected (*S*)-3-hydroxyglutarimide **2a** in eight steps. The present method would find application in the asymmetric synthesis of the 5,8-disubstituted indolizidine alkaloids.[16]

4. Experimental

4.1. General

Melting points were determined on a Yanaco MP-500 micromelting point apparatus and are uncorrected. Infrared spectra were measured with a Nicolet Avatar 330 FT-IR spectrometer using film KBr pellet technique. ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker AV400 or a Varian unity +500 spectrometer with tetramethylsilane as the internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by Bruker Dalton Esquire 3000 plus LC–MS apparatus. Optical rotations were measured with a Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out on silica gel (300–400 mesh). THF was distilled over sodium. Dichloromethane was distilled over P_2O_5.

4.1.1. (1*S*,2*R*)-3-(*tert*-Butoxycarbonyl)-2-phenyl-piperidin-1-yl methanesulfonate *trans*-12. To a cooled (−23 °C) solution of **10**[3c] (260 mg, 0.94 mmol) and NEt_3 (0.26 mL, 1.88 mmol) in dry CH_2Cl_2 (10 mL) was added, under a N_2 atmosphere, MsCl (0.11 mL, 1.04 mmol). The mixture was stirred for 2 h at that temperature. The reaction was quenched by the addition of 0.1 M HCl (0.5 mL) and water (10 mL) at that temperature. The aqueous phase was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over anhy-

drous Na_2SO_4, and concentrated under reduced pressure. Flash chromatographic purification (eluent: EtOAc/PE = 1:8) of the residue afforded **12** (314 mg, yield: 94%) as a colorless oil. $[\alpha]_D^{20} = -19.95$ (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 2975, 1691, 1417, 1364, 1175, 1145 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.35 (m, 2H, Ar–*H*), 7.30–7.20 (m, 3H, Ar–*H*), 5.68 (br s, 1H), 5.45 (br s, 1H), 4.20–4.12 (m, 1H), 3.12 (s, 3H, O_3SCH_3), 2.92 (ddd, $J = 13.3$, 13.3, 3.1 Hz, 1H), 2.05–1.97 (m, 1H), 1.96–1.87 (m, 1H), 1.78–1.68 (m, 1H), 1.50–1.40 (m, 1H), 1.45 (s, 9H, $3 \times CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.74 (C=O), 136.51, 128.95 (2C), 127.41, 126.15 (2C), 80.33, 77.78, 57.49, 39.49, 39.05, 28.37 (3C), 25.16, 18.95. MS (ESI) (*m*/*z*): 355 ($M+H^+$, 100%). HRESIMS calcd for $[C_{17}H_{25}NO_5S+H]^+$: 356.1532; found: 356.1525.

4.1.2. 1-(*tert*-Butoxycarbonyl)-2,3-dehydro-2-phenylpiperidine 15. To a solution of **12** (40 mg, 0.11 mmol) and DMF (1.5 mL) was added NaN_3 (60 mg, 0.92 mmol) at room temperature. The mixture was then allowed to warm up to 80 °C and stirred for 48 h at that temperature. The mixture was cooled to room temperature after which water (15 mL) was added to that mixture. The aqueous phase was extracted with Et_2O (5×10 mL) and the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue (eluent: EtOAc/PE = 1:8) yielded **15** (20 mg, yield: 71%) as a colorless oil. IR (film) ν_{max}: 2928, 1692, 1414, 1365, 1170, 1107 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.23 (m, 5H, Ar–*H*), 6.06–5.97 (m, 1H, H-3), 5.90–5.78 (m, 1H), 5.65–5.40 (m, 1H), 4.20–4.00 (m, 1H), 2.92 (ddd, $J = 13.0$, 13.0, 4.0 Hz, 1H), 2.38–2.25 (m, 1H), 2.10–1.98 (m, 1H), 1.45 (s, 9H, $3 \times CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.66 (C=O), 141.32, 128.27 (2C), 127.51, 127.30, 127.21 (2C), 126.22, 79.76, 54.98, 36.65, 28.47 (3C), 24.96. MS (ESI) (*m*/*z*): 260 ($M+H^+$, 100%). HRESIMS calcd for $[C_{16}H_{21}NO_2+H]^+$: 260.1651; found: 260.1647.

4.1.3. (5*S*,6*R*)-5-Hydroxyl-1-(4-methoxybenzyl)-6-phenyl-2-piperidinone *trans*-20. To a solution of **9**[3c] (1.51 g, 3.77 mmol) and formic acid (1 mL) in methanol (10 mL) was added Pd/C (450 mg, 10% Pd). After being stirred overnight at room temperature, the mixture was filtered through silica gel and the solvent was removed under reduced pressure. Flash chromatographic purification of the residue on silica gel (eluent: EtOAc/PE = 1:1) afforded **20** (1.05 g, yield: 90%) as white crystals. Mp 130–131 °C (EtOAc). $[\alpha]_D^{20} = +53.0$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3381, 2935, 1616, 1511, 1474, 1452, 1245, 1174, 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.20 (m, 3H, Ar–*H*), 7.10 (d, $J = 8.0$ Hz, 2H, Ar–*H*), 7.02 (d, $J = 8.5$ Hz, 2H, Ar–*H*), 6.75 (d, $J = 8.5$ Hz, 2H, Ar–*H*), 5.45 (d, $J = 14.8$ Hz, 1H, NCH_2), 4.35–4.28 (m, 1H, H-6), 3.98–3.90 (m, 1H, H-5), 3.71 (s, 3H, OCH_3), 3.25 (d, $J = 14.8$ Hz, 1H, NCH_2), 2.72 (ddd, $J = 18.0$, 10.7, 7.1 Hz, 1H, H-3), 2.48 (ddd, $J = 18.0$, 6.5, 3.4 Hz, 1H, H-3), 2.20–1.90 (br s, 1H, O*H*, D_2O exchangeable), 1.90–1.80 (m, 1H, H-4), 1.76–1.62 (m, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.39 (C=O), 158.87, 138.75, 129.42 (2C), 129.00 (2C), 128.87, 128.01, 126.91 (2C), 113.97 (2C), 69.77, 66.82, 55.24, 47.09, 27.27, 23.19. MS (ESI) (*m*/*z*): 312 ($M+H^+$, 100%). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.31; H, 6.75; N, 4.50. Found: C, 72.98; H, 6.59; N, 4.39.

4.1.4. (2*R*,3*S*)-3-Hydroxyl-1-(4-methoxybenzyl)-2-phenylpiperidine *trans*-21. To a cooled (0–5 °C) suspension of lithium aluminum hydride (501 mg, 13.68 mmol) in dry THF (20 mL) was slowly added, under an N_2 atmosphere, a solution of **20** (820 mg, 2.64 mmol) in dry THF (5 mL). The mixture was stirred at room temperature for 3 h, then warmed to 40 °C and stirred at that temperature for 1 h. The mixture was cooled with an ice-bath, then wet ether (5 mL), a 10% solution of sodium hydroxide (0.4 mL) and H_2O (0.1 mL) were added successively. The mixture was allowed to reach room temperature, stirred for 30 min, and filtered through Celite. After being concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1:2) to afford **21** (680 mg, yield: 87%) as a pale yellow solid. Mp 157–158 °C (acetone). $[\alpha]_D^{20} = -18.5$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3399, 2926, 2789, 1513, 1268, 1239, 1101, 1035 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, $J = 7.0$ Hz, 2H, Ar–*H*), 7.40 (t, $J = 7.3$ Hz, 2H, Ar–*H*), 7.32 (t, $J = 7.3$ Hz, 1H, Ar–*H*), 7.13 (d, $J = 8.4$ Hz, 2H, Ar–*H*), 6.81 (d, $J = 8.4$ Hz, 2H, Ar–*H*), 3.78 (s, 3H, OCH_3), 3.68–3.56 (m, 1H, H-3), 3.60 (d, $J = 13.4$ Hz, 1H, NCH_2), 2.92 (d, $J = 8.6$ Hz, 1H, H-2), 2.95–2.88 (m, 1H, H-6), 2.81 (d, $J = 13.4$ Hz, 1H, NCH_2), 2.15–2.08 (m, 1H, H-6), 1.94 (ddd, $J = 11.8$, 3.1, 2.9 Hz, 1H), 1.74–1.66 (m, 1H), 1.66–1.57 (m, 1H), 1.46–1.35 (m, 1H), 1.40 (br s, 1H, O*H*, D_2O exchangeable). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.39, 141.01, 131.36, 129.66 (2C), 128.81 (3C), 127.93 (2C), 113.41 (2C), 75.87, 73.94, 58.55, 55.21, 52.20, 32.45, 23.31. MS (ESI) (*m*/*z*): 298 ($M+H^+$, 100%). HRESIMS calcd for $[C_{19}H_{23}NO_2+H]^+$: 298.1802; found: 298.1797.

4.1.5. (2*R*,3*S*)-3-[*N*-(2-Methoxybenzyl)-*N*-(2-nitrobenzenesulfonyl)]amino-1-(4-methoxybenzyl)-2-phenylpiperidine *trans*-24. To a cooled (−20 °C) solution of **21** (787 mg, 2.65 mmol) and NEt_3 (0.55 mL, 3.97 mmol) in dry CH_2Cl_2 (20 mL) was added, under an N_2 atmosphere, MsCl (0.25 mL, 3.18 mmol). After being stirred for 2 h at −20 °C, the reaction was quenched by the addition of 0.1 M HCl (0.5 mL) and water (20 mL) at that temperature. The aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Flash chromatographic purification (eluent: EtOAc/PE = 1:4) of the residue afforded unstable **22** as a white solid (890 mg, yield: 90%), which was used in the next step immediately.

A suspension of **16** (640 mg, 1.99 mmol), anhydrous K_2CO_3 (552 mg, 4.00 mmol) in CH_3CN (10 mL) was stirred under an N_2 atmosphere at room temperature for 1 h. To the resulting mixture was added a solution of **22** (500 mg, 1.33 mmol) in dry CH_3CN (5 mL). After being stirred at 30 °C for 24 h, water (10 mL) and CH_2Cl_2 (10 mL) were added successively and the layers were separated. The aqueous phase was extracted with CH_2Cl_2

(3 × 10 mL) and the combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue (eluent: EtOAc/PE = 1:2) yielded **24** (640 mg, yield: 80%) as a yellow solid. Mp 133–135 °C (EtOAc/PE = 3:1). $[\alpha]_D^{20} = -7.1$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 2924, 1544, 1511, 1245, 1161, 1033 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.60–7.50 (m, 3H, Ar–*H*), 7.40–7.15 (m, 9H, Ar–*H*), 6.95–6.85 (m, 2H, Ar–*H*), 6.60–6.50 (m, 3H, Ar–*H*), 4.86 (d, $J = 16.0$ Hz, 1H, NCH_2), 4.72 (d, $J = 16.0$ Hz, 1H, NCH_2), 4.59 (d, $J = 9.7$ Hz, 1H, H-2), 3.90 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.54–3.42 (m, 1H, H-3), 3.36 (d, $J = 12.3$ Hz, 1H, NCH_2), 3.02 (d, $J = 12.3$ Hz, 1H, NCH_2), 2.67–2.56 (m, 1H, H-6), 2.22–2.10 (m, 1H, H-6), 1.95–1.84 (m, 1H, CH_2CH), 1.75–1.57 (m, 1H, CH_2CH), 1.57–1.36 (m, 2H, CH_2CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.29, 156.68, 148.38, 137.32, 134.66, 132.71, 132.30, 131.58, 131.16, 130.13 (2C), 129.76, 129.61, 128.97, 127.94 (2C), 127.78, 125.19, 124.02 (2C), 120.94, 113.24 (2C), 110.30, 67.14, 64.84, 60.70, 55.32, 55.17, 54.43, 44.04, 28.46, 23.79. MS (ESI) (*m*/*z*): 602 ($M+H^+$, 100%). HRESIMS calcd for $[C_{33}H_{35}N_3O_6S+H]^+$: 602.2319; found: 602.2326.

4.1.6. (2*R*,3*S*)-3-[*N*-(2-Aminobenzenesulfonyl)-*N*-(2-methoxybenzyl)]amino-2-phenyl piperidine *trans*-31. To a solution of **24** (620 mg, 1.03 mmol) and formic acid (0.8 mL) in methanol (8 mL) was added Pd/C (150 mg, 10% Pd). After being stirred overnight at room temperature, the mixture was filtered through silica gel and the solvent removed under reduced pressure. Flash chromatographic purification of the residue on silica gel (eluent: EtOAc/PE/$NH_3{\cdot}H_2O$/MeOH = 100:100:1:5) provided **31** (392 mg, yield: 84%) as a yellow waxy solid. $[\alpha]_D^{20} = +91.7$ (*c* 0.2, $CHCl_3$). IR (film) ν_{max}: 3461, 3374, 2942, 1615, 1601, 1484, 1453, 1320, 1242, 1140, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, $J = 7.9$ Hz, 1H, Ar–*H*), 7.37 (d, $J = 7.5$ Hz, 1H, Ar–*H*), 7.24–7.15 (m, 7H, Ar–*H*), 6.85 (t, $J = 7.4$ Hz, 1H, Ar–*H*), 6.80 (d, $J = 8.1$ Hz, 1H, Ar–*H*), 6.64 (m, 2H, Ar–*H*), 5.04 (br s, 2H, NH_2), 4.65 (d, $J = 10.3$ Hz, 1H, H-2), 4.49 (d, $J = 16.0$ Hz, 1H, NCH_2), 4.45 (d, $J = 16.0$ Hz, 1H, NCH_2), 3.79 (s, 3H, OCH_3), 3.60 (ddd, $J = 10.3$, 6.4, 6.4 Hz, 1H, H-3), 2.80 (ddd, $J = 9.3$, 5.5, 5.5 Hz, 1H, H-6), 2.73–2.66 (m, 1H, H-6), 1.92–1.84 (m, 1H, CH_2CH), 1.88 (br s, 1H, N*H*), 1.75–1.66 (m, 2H, CH_2CH_2), 1.64–1.54 (m, 1H, CH_2CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.43, 145.92, 137.19, 133.84, 130.47, 130.18, 129.71 (2C), 128.39, 128.17 (2C), 127.93, 125.85, 122.51, 120.47, 117.64, 117.40, 110.04, 65.44, 58.28, 55.16, 46.21, 42.64, 28.92, 24.80. MS (ESI) (*m*/*z*): 452 ($M+H^+$, 100%). HRESIMS calcd for $[C_{25}H_{29}N_3O_3S+H]^+$: 452.2002; found: 452.2010.

4.1.7. (2*R*,3*S*)-3-(2-Methoxybenzyl)amino-2-phenylpiperidine *trans*-8 (2*R*,3*S*)-CP-99,994. To a mixture of **31** (103 mg, 0.23 mmol), Na–Hg (3.3 g, 5% Na) and Na_2HPO_4 (284 mg, 2.00 mmol) was added methanol (4 mL). The resulting suspension was stirred at 40 °C for 48 h. Water (5 mL) and CH_2Cl_2 (5 mL) were added successively to the resulting mixture, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue (eluent: $CH_2Cl_2/NH_3{\cdot}H_2O$/MeOH = 100:1:3) yielded (2*R*,3*S*)-CP-99,994 **8** (41 mg, yield: 62%) as a colorless oil. $[\alpha]_D^{20} = +73.4$ (*c* 0.4, MeOH, dihydrochloride). IR (neat, free base) ν_{max}: 3350, 2930, 1480, 1230 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, free base): δ 7.54–7.40 (m, 6H, Ar–*H*), 7.10 (d, $J = 7.5$ Hz, 1H, Ar–*H*), 6.90–6.80 (m, 2H, Ar–*H*), 3.82 (s, 3H, OCH_3), 3.73 (d, $J = 13.4$ Hz, 1H, NCH_2), 3.49 (d, $J = 7.3$ Hz, 1H, H-2), 3.43 (d, $J = 13.4$ Hz, 1H, NCH_2), 3.18 (ddd, $J = 7.3$, 7.3, 1.5 Hz, 1H, H-3), 2.93–2.85 (m, 1H, H-6), 2.77–2.69 (m, 1H, H-6), 2.10–1.86 (br s, 2H, N*H*), 1.83 (ddd, $J = 17.5$, 8.1, 5.0 Hz, 1H, CH_2CH_2), 1.75–1.62 (m, 2H, CH_2CH), 1.47 (ddd, $J = 17.5$, 8.1, 8.1 Hz, 1H, CH_2CH_2). ^{13}C NMR (125 MHz, $CDCl_3$, free base): δ 157.74, 142.42, 130.07, 128.49, 128.29 (2C), 128.08 (3C), 127.10, 120.33, 110.18, 66.54, 64.42, 55.15, 47.22, 46.17, 27.97, 24.79. MS (ESI) (*m*/*z*): 297 ($M+H^+$, 100%). HRESIMS calcd for $[C_{19}H_{24}N_2O+H]^+$: 297.1967; found: 297.1961.

4.1.8. (5*S*,6*R*)-5-Hydroxyl-1-(4-methoxybenzyl)-6-methyl-2-piperidinone 33. To a solution of **32**[3c] (850 mg, 2.51 mmol) and formic acid (2.5 mL) in methanol (25 mL) was added Pd/C (300 mg, 10% Pd), and the mixture was stirred overnight at rt. The mixture was filtered through silica gel and the solvent was removed under reduced pressure. Flash chromatographic purification on silica gel (eluent: EtOAc/PE = 1:1) provided **33** (530 mg, 85%) as a colorless oil. $[\alpha]_D^{25} = +64.1$ (*c* 1.6, $CHCl_3$). IR (film) ν_{max}: 3379, 2925, 1613, 1513, 1246, 1177 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (d, $J = 8.5$ Hz, 2H, Ar–H), 6.82 (d, $J = 8.5$ Hz, 2H, Ar–H), 5.16 (d, $J = 15.0$ Hz, 1H, NCH_2), 3.92 (d, $J = 15.0$ Hz, 1H, NCH_2), 3.77 (br s, 1H, H-5), 3.75 (s, 3H, OCH_3), 3.33 (dq, $J = 2.8$, 6.7 Hz, 1H, H-6), 2.85 (d, $J = 3.2$ Hz, 1H, OH, D_2O exchangeable), 2.66 (ddd, $J = 18.2$, 7.4, 2.4 Hz, 1H, H-3), 2.36 (ddd, $J = 18.2$, 7.1, 3.0 Hz, 1H, H-3), 2.00 (ddd, $J = 17.5$, 7.1, 2.4 Hz, 1H, H-4), 1.84 (ddd, $J = 17.5$, 7.4, 3.0 Hz, 1H, H-4), 1.13 (d, $J = 6.7$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.61 (C=O), 158.73, 129.32, 129.05 (2C), 113.88 (2C), 68.17, 57.81, 55.17 (OCH_3), 46.93, 26.89, 23.87, 18.32 (CH_3). MS (ESI): 250 ($M+H^+$, 30), 272 [$(M+23)^+$, 40], 521 [$(2M+23)^+$, 100]. HRESIMS calcd for $[C_{14}H_{19}NO_3+H]^+$: 250.1443; found: 250.1440.

4.1.9. (2*R*,3*S*)-3-Hydroxyl-1-(4-methoxybenzyl)-2-methylpiperidine 34. To a cooled (0 °C) solution of **33** (300 mg, 1.20 mmol) in dry THF (12 mL) was added slowly $BH_3{\cdot}SMe_2$ (0.34 mL, 3.59 mmol) under an N_2 atmosphere. After the mixture had reacted at 0 °C for 72 h, MeOH (2 mL) was added and the mixture was stirred at room temperature for another 3 h. After being concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE = 1:2) to afford **34** (252 mg, 89%) as a waxy solid. $[\alpha]_D^{20} = -32.7$ (*c* 2.1, $CHCl_3$). IR (film) ν_{max}: 3406, 2934, 1512, 1246, 1036 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, $J = 8.5$ Hz, 2H, Ar–H), 6.85 (d, $J = 8.5$ Hz, 2H, Ar–H), 3.78 (s, 3H, OCH_3), 3.64 (d, $J = 13.2$ Hz, 1H, NCH_2), 3.52–3.47 (m, 1H, H-3), 3.40 (d, $J = 13.2$ Hz, 1H,

NCH_2), 2.92 (s, 1H, OH), 2.70–2.62 (m, 1H, H-6), 2.57–2.48 (m, 1H, H-6), 2.25 (dq, $J = 2.8$, 6.6 Hz, 1H, H-2), 1.78–1.66 (m, 2H), 1.53–1.38 (m, 2H), 1.11 (d, $J = 6.6$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.56, 130.74, 129.87 (2C), 113.56 (2C), 70.49, 59.74, 57.75, 55.13 (OCH_3), 46.68 (NCH_2), 27.94, 20.98, 10.28 (CH_3). MS (ESI): 236 ($M+H^+$, 100), 258 [$(M+23)^+$, 5]. HRESIMS calcd for $[C_{14}H_{21}NO_2+H]^+$: 236.1650; found: 236.1644.

4.1.10. (2*R*,3*S*)-3-[*N*-(2-Methoxybenzyl)-*N*-(2-nitrobenzenesulfonyl)amino-1-(4-methoxybenzyl)-2-methylpiperidine 36 and the *cis*-diastereomer. To a cooled (−20 °C) solution of **34** (85 mg, 0.36 mmol) and NEt_3 (0.10 mL, 0.72 mmol) in dry CH_2Cl_2 (4 mL) was added MsCl (0.034 mL, 0.44 mmol) under an N_2 atmosphere. After being stirred for 2 h at the same temperature, the reaction was quenched by the addition of H_2O (6 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. After flash chromatographic purification (eluent: EtOAc/PE = 1:4), unstable **35** (92 mg, 82%) was obtained as a colorless oil, which was used in the subsequent step as it was. A mixture of **16** (95 mg, 0.29 mmol) and anhydrous K_2CO_3 (50 mg, 0.36 mmol) in dry CH_3CN (10 mL) was stirred under an N_2 atmosphere, at −25 °C for 1 h, after which a solution of **35** (92 mg, 0.29 mmol) in dry CH_3CN (2 mL) was added and the resulting mixture was stirred at that temperature for 48 h. Water (8 mL) and CH_2Cl_2 (10 mL) were added successively and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 8 mL) and the combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (eluent: EtOAc/PE = 1:3) of the residue yielded 3**6** (100 mg, yield: 63%) and the *cis*-diastereoisomer (32 mg, yield: 20%) both as yellow waxy solids. Major *trans*-diastereomer **36**: $[\alpha]_D^{25} = -50.4$ (*c* 1.4, $CHCl_3$). IR (film) ν_{max}: 2938, 1544, 1511, 1245, 1162, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.66–7.54 (m, 3H, Ar–H), 7.50 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.21 (t, $J = 7.4$ Hz, 1H, Ar–H), 7.10 (d, $J = 8.6$ Hz, 2H, Ar–H), 6.88 (t, $J = 7.4$ Hz, 1H, Ar–H), 6.82 (d, $J = 8.6$ Hz, 2H, Ar–H), 6.75 (d, $J = 8.3$ Hz, 1H, Ar–H), 4.69 (d, $J = 16.0$ Hz, 1H, NCH_2), 4.55 (d, $J = 16.0$ Hz, 1H, NCH_2), 3.83 (d, $J = 13.5$ Hz, 1H, NCH_2), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.66 (ddd, $J = 9.2$, 9.2, 4.2 Hz, 1H, H-3), 3.20 (d, $J = 13.5$ Hz, 1H, NCH_2), 2.69–2.62 (m, 1H, H-6), 2.32 (dt, $J = 9.2$, 6.1 Hz, 1H, H-2), 1.79 (ddd, $J = 11.3$, 3.6, 3.6 Hz, 1H, H-6), 1.75–1.65 (m, 1H), 1.55–1.38 (m, 3H), 1.02 (d, $J = 6.1$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.44, 156.75, 147.58, 134.24, 133.04, 131.45, 131.34, 130.88 (2C), 130.16, 128.73, 125.53, 123.85, 120.47, 113.43 (2C), 110.13, 110.08, 61.40, 58.51, 56.48, 55.39 (OCH_3), 54.89 (OCH_3), 51.46 (NCH_2), 42.18 (NCH_2), 29.61, 24.25, 16.13 (CH_3). MS (ESI): 540 ($M+H^+$, 100). Anal. Calcd for $C_{28}H_{33}N_3O_6S$: C, 62.32; H, 6.16; N, 7.79; S, 5.94. Found: C, 62.23; H, 6.14; N, 7.59; S, 6.06. Minor *cis*-diastereomer: $[\alpha]_D^{25} = +10.2$ (*c* 2.3, $CHCl_3$). IR (film) ν_{max}: 2960, 1545, 1512, 1245, 1163, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.66–7.54 (m, 3H, Ar–H), 7.52 (d, $J = 7.6$ Hz, 1H, Ar–H), 7.21 (t, $J = 7.5$ Hz, 1H, Ar–H), 7.15 (d, $J = 8.1$ Hz, 2H, Ar–H), 6.90 (t, $J = 7.5$ Hz, 1H, Ar–H), 6.78 (d, $J = 8.4$ Hz, 3H, Ar–H), 4.64 (d, $J = 16.1$ Hz, 1H, NCH_2), 4.58 (d, $J = 16.1$ Hz, 1H, NCH_2), 3.80–3.68 (m, 1H, H-3), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.73 (d, $J = 13.0$ Hz, 1H, NCH_2), 3.30 (d, $J = 13.0$ Hz, 1H, NCH_2), 2.76 (dq, $J = 4.9$, 6.6 Hz, 1H, H-2), 2.57 (ddd, $J = 16.3$, 9.0, 1.6 Hz, 1H, H-6), 2.20 (ddd, $J = 16.3$, 9.1, 1.3 Hz, 1H, H-6), 1.83 (m, 1H), 1.60–1.48 (m, 1H), 1.38–1.22 (m, 2H), 1.17 (d, $J = 6.6$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.46, 156.66, 147.87, 134.15, 133.10, 132.02, 131.32 (2C), 130.87 (2C), 129.52, 128.69, 125.72, 123.83, 120.56, 113.50 (2C), 110.12, 66.69, 61.21, 59.01, 55.20 (OCH_3), 55.12 (NCH_2), 54.61 (OCH_3), 41.65 (NCH_2), 28.08, 24.01, 15.25 (CH_3). MS (ESI): 540 ($M+H^+$, 100). HRESIMS calcd for $[C_{28}H_{33}N_3O_6S+H]^+$: 540.2168; found: 540.2167.

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