DOI: 10.1002/ejoc.200700237

Ring Expansion Induced by DAST: Synthesis of Substituted 3-Fluoropiperidines from Prolinols and 3-Fluoroazepanes from 2-Hydroxymethylpiperidines

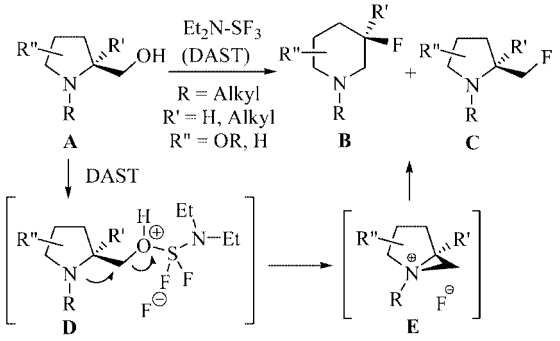
Ingrid Déchamps,[a] Domingo Gomez Pardo,[a] and Janine Cossy*[a]

Keywords: Ring expansion / Rearrangement / Fluorine / Aziridinium / Nitrogen heterocycles

Optically active prolinols can be converted into optically active 3-fluoropiperidines by treatment with DAST. The reaction often produces 2-fluoromethylpyrrolidines as byproducts. The ring expansion was also applied to 2-hydroxypiperidines to produce 3-fluoroazepanes. The rearrangement proceeds via an aziridinium intermediate.

Introduction

The introduction of a fluorine atom in organic molecules strongly modifies their physical, chemical and biological properties.[1] For the past few decades, a variety of fluorinating reagents and methodologies have been developed to fulfil the increasing demand for selective fluorination of organic compounds,[2] among them, *N*,*N*-bis(2-methoxyethyl)aminosulfur trifluoride, $(CH_3OCH_2CH_2)_2NSF_3$ (Deoxofluor)[3] and *N*,*N*-diethylaminosulfur trifluoride (DAST)[4] have emerged as very useful reagents to convert simple alcohols into the corresponding monofluorinated product.[5] The fluorination of optically active alcohols by using these reagents generally proceeds with inversion of configuration (S_N2 mechanism). Furthermore, these reagents are known to initiate rearrangements through anchimeric assistance of an electron-rich group (methoxy,[6] amine,[7] thioester,[8] epoxide,[9] azide,[10] double bond,[11] aromatic ring,[12] ester,[13] amide[14]) present at a vicinal position of the reacting alcohol. These rearrangements can be explained in terms of neighbouring group participation as a result of the formation of a very good leaving group resulting from the reaction of an alcohol moiety with DAST or Deoxofluor. As part of our study of ring expansion of prolinols to piperidines,[15] we would like to report here the rearrangement of optically active prolinols of type **A** into optically active piperidines of type **B** by using DAST.[16] A nonrearranged product of type **C** can also be obtained. The ring expansion is supposed to proceed via an aziridinium intermediate of type **E** resulting from the intramolecular nucleophilic substitution of the nitrogen atom onto the newly formed good leaving group in **D**.[7] The selectivity of the rearrangement, **B** versus **C**, depends on the substitution on the pyrrolidine ring and the steric hindrance at the nitrogen atom (Scheme 1).



Scheme 1. Ring expansion.

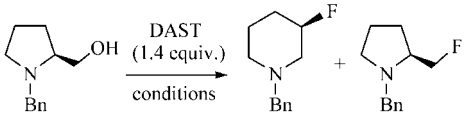
Results and Discussion

Our study started with *N*-benzylprolinol (**1**).[17] This compound was treated with DAST (1.4 equiv.) in THF at 0 °C for 1 h and then for 1 h at room temp. Under these conditions, prolinol **1** was transformed into an inseparable mixture of 3-fluoropiperidine **2** and 2-fluoromethylpyrrolidine **3** in a 57:43[18] ratio in favour of the ring-expanded product **2** with a yield of 60% (Table 1, Entry 1).[7g] To favour the formation of 3-fluoropiperidine **2**, a number of different experimental procedures were examined, and the results are summarized in Table 1. Whatever the solvent used (THF, CH_2Cl_2, cyclohexane or acetone), the ratio **2/3** did not change (Table 1, Entries 1–4). It is worth noting that the use of cyclohexane or acetone led to the formation of byproducts, whereas the reaction was clean in THF and CH_2Cl_2. Modifications of the reaction mixture temperature

[a] Laboratoire de Chimie Organique associé au CNRS, Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (E.S.P.C.I.) – ParisTech, C.N.R.S.
10, rue Vauquelin, 75231 Paris Cedex 05, France
Fax: +33-0140-794-660
E-mail: janine.cossy@espci.fr.

did not change the proportions of **2/3** and byproducts were also formed under these conditions (Table 1, Entries 5 and 6). It is worth noting that an experiment was carried out in the presence of Et_3N (3.0 equiv.) to prevent the eventual protonation of the prolinol during the ring-expansion process. However, no significant evolution of the ratio **2/3** was observed (Table 1, Entry 7).

Table 1. Influence of the experimental conditions on the ratio of **2/3**.

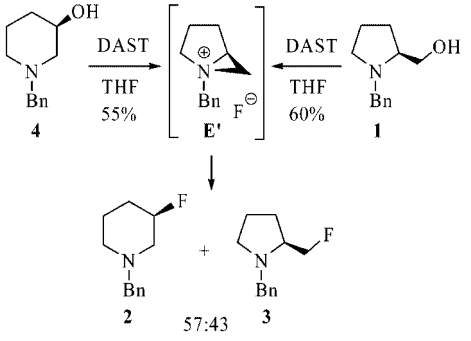


1 **2** **3**

Entry	Solvent	Conditions	Ratio **2/3**
1	THF	1 h at 0 °C, then 1 h at room temp.	57:43
2	CH_2Cl_2	1 h at 0 °C, then 1 h at room temp.	58:42
3	Cyclohexane	1 h at 0 °C, then 1 h at room temp.	59:41
4	Acetone	1 h at 0 °C, then 1 h at room temp.	55:45
5	THF	1 h at 0 °C, then 4 h at 65 °C	55:45
6	THF	3 h from –78 °C to room temp.	58:42
7	THF + Et_3N[a]	1 h at 0 °C, then 1 h at room temp.	56:44

[a] 3.0 equiv. of Et_3N were added.

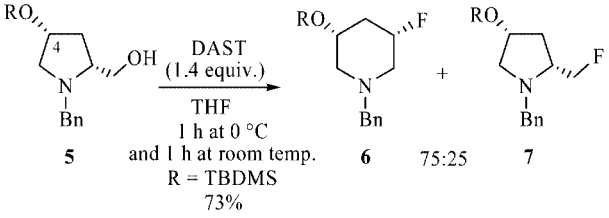
To prove that an aziridinium intermediate of type **D** was involved in the formation of **2** and **3**, piperidin-3-ol **4**[15g] was treated with DAST in THF. After 1 h at 0 °C and 1 h at room temp., compounds **2** and **3** were obtained with similar ratios (**2/3**, 57:43) and yields (55%) compared to those obtained when the reaction was performed on prolinol **1**. These results suggest that, in the presence of DAST, both substrates were converted into the same intermediate, aziridinium **E′**, which was previously postulated in the literature (Scheme 2).[7]



4 **E'** **1** **2** **3**

Scheme 2. Mechanism via an aziridinium intermediate.

The effect of the substituents on the prolinol ring was tested and after treatment with DAST (1.4 equiv., THF, 1 h at 0 °C then 1 h at room temp.), prolinol **5** substituted by a *tert*-butyldimethylsilyl ether at C-4 with a *cis* relative relationship, was converted into an inseparable mixture of 3-fluoropiperidine **6** and 2-fluoromethylpyrrolidine **7** in a 75:25 ratio and in 73% yield (Scheme 3).

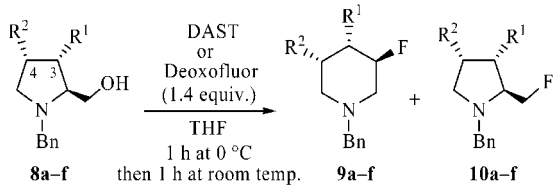


5 **6** **7**

Scheme 3. Rearrangement of prolinol **5**.

As the presence of a silyl ether group seems to influence the selectivity of the rearrangement, the rearrangement of prolinols **8a**–**f**,[19] in which the hydroxy group at C-3 or C-4 is protected, was examined, and the results are reported in Table 2. At first, the substitution by a *tert*-butyldimethylsilyl ether at C-4 with a *trans* relative relationship (prolinol **8a**[15m]) was studied and, interestingly, the observed ratio **9a/10a** increased to 80:20 in favour of the ring-expansion product. The fluorinated products could be separated and isolated in 53 and 8% yield, respectively (Table 2, Entry 1). It is worth noting that when replaced in the ring-expansion conditions (DAST, 1.4 equiv., 1 h at 0 °C then 1 h at room temp.), the isolated ring-expansion product **9a** was not transformed into isomer **10a**. This result shows that there is no equilibrium between the two fluoro products in the presence of DAST and that the reaction is controlled by kinetics under these conditions.[15n] When the *tert*-butyldimethylsilyl ether group was substituted at C-3 with a *trans* relationship, as in prolinol **8b**,[20] an equimolar inseparable mixture of 3-fluoropiperidine **9a** and 2-fluoromethylpyrrolidine **10a** was obtained with a global yield of 55% (Table 2, Entry 2). This result suggests that the presence of the C-3 substituent does not favour the formation of the ring-expansion product. To test the importance of the presence of a silyl ether group at C-4, prolinol **8c** and **8d** were treated with DAST. An important decrease in the selectivity was observed when a methoxy group is present at C-4, as prolinol **8c** was converted into an inseparable mixture of **9c/10c** with a ratio of 55:45 and with a 55% global yield (Table 2, Entry 3). The replacement of the methoxy group by a bulky trityloxy group at C-4 induced an important improvement in the selectivity, since a 75:25 ratio of **9d/10d** was obtained and **9d** and **10d** could be isolated in 33 and 5% yield, respectively (Table 2, Entry 4). The presence of a silyl protecting group on the hydroxy at C-4 seems to lead to better selectivity in favour of the rearranged fluoropiperidines than the use of an alkyl ether group. As an increase in the steric hindrance induced by the protecting group seems to improve the selectivity in favour of the ring expansion, prolinols **8e**[15m] and **8f**[15m] possessing bulky silyl ether groups at C-4 were tested under the ring-expansion conditions. When triisopropylsilyloxyprolinol **8e** was examined, an improved selectivity was obtained with a 89:11 ratio of **9e/10e** in 75 and 9% yield, respectively (Table 2, Entry 5). The better result was obtained with a *tert*-butyldiphenylsilyl group at C-4, as a ratio of 91:9 for **9f/10f** was obtained in favour of the fluoropiperidine (Table 2, Entry 6). It is worth noting that similar results were obtained with Deoxofluor.

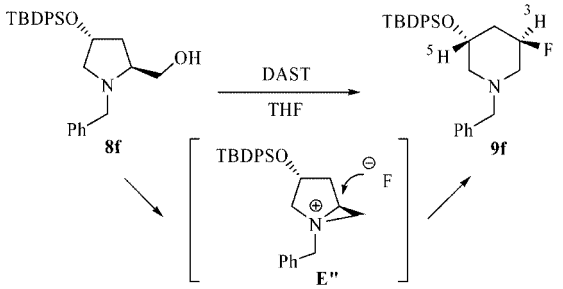
Table 2. Influence of substitution at C-3 and C-4 of the pyrrolidine ring.



Entry	Prolinol	Substituent	DAST Ratio **9/10**, Yield [%]	Deoxofluor Ratio **9/10**, Yield [%]
1	**8a**	R^1 = H R^2 = OTBDMS	**9a/10a**: 80:20, 53/8	**9a/10a**: 60:40, 58/14
2	**8b**	R^1 = OTBDMS R^2 = H	**9b/10b**: 50:50, 55[a]	
3	**8c**	R^1 = H R^2 = OMe	**9c/10c**:55:45, 55[a]	
4	**8d**	R^1 = H R^2 = OTr	**9d/10d**: 75:25, 33/5	
5	**8e**	R^1 = H R^2 = OTIPS	**9e/10e**: 89:11, 75/9	
6	**8f**	R^1 = H R^2 = OTBDPS	**9f/10f**: 91:9, 61/4	**9f/10f**: 91:9, 53/6

[a] Combined yield.

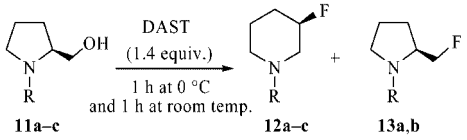
If the rearrangement of prolinol **8f** proceeds via the opening of aziridinium **E″**, a relative *trans* configuration between the *tert*-butyldiphenylsilyl ether at C-5 and the fluorine at C-3 should be obtained in **9f** (Scheme 4). To confirm the configuration of the created centre, the relative relationship between the silyloxy group and the fluorine atom was established by analyzing the ^{1}H NMR spectra of piperidine **9f** and by determining the value of the coupling constants between 3-H and the vicinal protons present at C-2 and C-4, and by determining the value of the coupling constants between 5-H and the vicinal protons present at C-4 and C-6. The equatorial position of the silyl group was confirmed by the signal of 5-H in the ^{1}H NMR spectra, a doublet of doublet of doublet of doublet (dddd) with two rather large coupling constants of 8.0 and 8.0 Hz (typical of H_{axial}–H_{axial} couplings) and two medium coupling constants of 4.0 and 4.0 Hz, which correspond to the H_{axial}–$H_{equatorial}$ constants; in consequence 5-H is axial. The signal that corresponds to 3-H can be described as a "ddddd" with a large coupling constant of 47.7 Hz, which results from the coupling of 3-H with the fluorine atom and smaller coupling constants of 5.0, 5.0, 2.5, 2.5 Hz that are due to $H_{equatorial}$–H_{axial} and $H_{equatorial}$–$H_{equatorial}$ couplings. This analysis allowed us to attribute the (*R*) configuration to the C-3 stereogenic centre. It is worth noting that in the case of piperidine **9a** and **9e**–**f**, the coupling constants for the 3-H proton are too small to be calculated. Moreover, piperidines **9a** and **9e**–**f** were obtained as the only diastereomer; this result is in favour of an aziridinium intermediate hypothesis.



Scheme 4. Aziridinium intermediate and stereochemistry.

As it seems that the rearrangement of prolinols into 3-fluoropiperidines is sensitive to steric hindrance, the variation of the *N*-alkyl substituent of the prolinol was examined. The results are reported in Table 3. The presence of the *N*-*tert*-butylmethyl group has little effect on the ring expansion, as an inseparable mixture of fluoropiperidine **12a** and fluoropyrrolidine **13a** was obtained in a ratio of 60:40, which is similar to the one observed with *N*-benzylprolinol **1** and in 54% yield (Table 3, Entry 1). In the case of a *N*-methyldiphenyl substituent, prolinol **11b** was transformed into a mixture of **12b** and **13b** in a ratio of 76:24 in favour of the ring-expanded product **12b** in 71% yield (Table 3, Entry 2). As an increase in the steric hindrance on the nitrogen atom seems to improve the selectivity of the reaction, *N*-tritylprolinol **11c**[22] was treated with DAST and *N*-trityl-3-fluoropiperidine **12c** was obtained as the only observed product, which was isolated in 64% yield (Table 3, Entry 3).

Table 3. Influence of the substituent on the nitrogen.

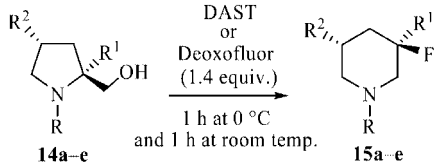


Entry	Prolinol	R	Ratio **12/13**	Yield of **12+13** [%]
1	**11a**[15g]	CH_2tBu	**12a+13a**: 60:40	54
2	**11b**	$CHPh_2$	**12b+13b**: 76:24	71
3	**11c**	CPh_3	**12c**: 100:0	64

When *N*-alkyl-2-alkylprolinols **14a**–**e** were treated with DAST, the ring expansion was very selective as only *N*-alkyl-3-fluoro-3-alkylpiperidines were observed. The optically active *N*-*tert*-butylmethylprolinols **14a**–**c**[23] were converted into the optically active 3-fluoropiperidines **15a**–**c**, respectively (Table 4, Entries 1–3). It is worth noting that when treated with DAST in THF, prolinol **14a** was converted into fluoropiperidine **15a** in a rather low yield of 43% as a result of the volatility of fluoropiperidine **15a**. When the reaction was carried out in CH_2Cl_2 and the distillation of the solvent was carried out at room temp., the

yield was improved to 76% (Table 4, Entry 1). Similar results were obtained with fluoropiperidine **15b**, which could be prepared in 89% yield by using CH_2Cl_2 as the reaction solvent (Table 4, Entry 2). The use of Deoxofluor was also investigated on these prolinols and compounds **15a–c** were obtained with the same selectivity and in comparable yields (68–93%). The replacement of the *N*-*tert*-butylmethyl by an *N*-benzyl group did not affect the selectivity as the *N*-benzyl-3-fluoropiperidine **15d** could be obtained in 30% yield as the unique product of the reaction, when prolinol **14d** was treated with DAST (Table 4, Entry 4). After treatment of prolinol **14e**[15i] with DAST, the fluorinated *N*-methylpiperidine **15e** was formed in 72% yield (Table 4, Entry 5). It is worth noting that in each case, the ^1H NMR spectra of the crude material did not show the presence of any elimination products. The enantiomeric purity of 3-fluoropiperidine **15c** was determined by chiral HPLC. Piperidine **15c** was formed with an enantiomeric excess of 99% when the ring expansion was realized with DAST and with an enantiomeric excess of 93%, when the rearrangement was achieved with Deoxofluor. We have to point out that we were not able to determine the absolute configuration of the stereogenic centres in compounds **15a–e** despite our efforts to crystallize the ammonium salts issued from CSA or tartaric acid, or to functionalize 3-fluoropiperidine **15b** to obtain single crystals for X-ray diffraction. The absolute configuration of the 3-fluoropiperidines was postulated according to our previous results on the rearrangement of amino alcohols in the presence of trifluoroacetic anhydride.[24] However, the possibility of the participation of the neighbouring allyl or benzyl groups cannot be excluded in the case of 3-fluoropiperidines **15b–d**.[25]

Table 4. Influence of the substituent at C-2 of the pyrrolidine ring.

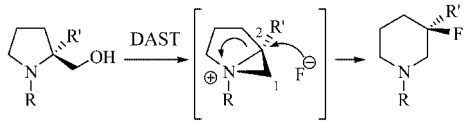


14a–e **15a–e**

Entry	Prolinol	Substituents	DAST Yield [%] (*ee* [%])[c]	Deoxofluor Yield [%] (*ee* [%])[c]
1	**14a**	R = CH_2tBu R^1 = Et R^2 = H	43[a] 76[b]	 68[b]
2	**14b**	R = CH_2tBu R^1 = Allyl R^2 = H	66[a] 89[b]	 85[b]
3	**14c**	R = CH_2tBu R^1 = Bn R^2 = H	87[a] (99)	93 (93)
4	**14d**	R = Bn R^1 = Bn R^2 = H	30[a]	
5	**14e**	R = Me R^1 = Et R^2 = OTBDMS	72[a]	

[a] Conditions: 1 h at 0 °C, then 1 h at room temp., THF. [b] Owing to the volatility of the fluorinated product, CH_2Cl_2 was preferred to THF. [c] The *ee* values were determined by comparison with the racemate on Chiral HPLC: OJ-H, hexane, 0.3 mL/min.

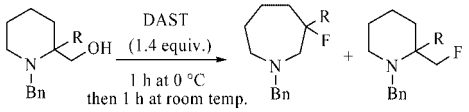
The selective attack of the fluorine anion at the C-2 position of substituted prolinols, which leads exclusively to 3-fluoropiperidines, can be explained by an increase in the length of the C-2–N bond in the aziridinium intermediate; moreover, the presence of a quaternary centre at C-2 results in the stabilization of a partial positive charge at C-2 correlated with a weakened C-2–N bond. In consequence, the cleavage of the C-2–N bond induced by the nucleophilic attack of the fluoride at the more electrophilic carbon is favoured (Scheme 5). The selectivity of the rearrangement when the nitrogen atom is substituted by a bulky protecting group (Table 3, Entry 3), can also be explained in terms of lengthening of the C-2–N bond due to steric constraints.



Scheme 5. Selectivity of the ring expansion.

This ring expansion was also tested to synthesize substituted 3-fluoroazepanes from racemic 2-hydroxymethylpiperidines.[26] The results are reported in Table 5. When *N*-benzyl-2-hydroxymethylpiperidine **16a**[27] was treated with DAST, a mixture of 3-fluoroazepane **17a** and 2-fluoromethylpiperidine **18a** was obtained in a ratio of 70:30 with 51 and 12% yield, respectively (Table 5, Entry 1). By analogy with the prolinols, the 2-hydroxymethylpiperidines substituted by an alkyl group at C-2 were investigated. 2-Alkyl-2-hydroxymethylpiperidines **16b–d** were transformed with high selectivity to 3-fluoroazepanes **17b**, **17c** and **17d**, which were isolated, respectively, in 63, 76 and 76% yield (Table 5, Entries 2–4).

Table 5. Ring expansion applied to 2-hydroxymethylpiperidines.



16a–d **17a–d** **18a**

Entry	Starting Material	R	Ratio **17/18**	Yield [%]
1	**16a**	H	70:30	**17a/18a**: 51/12
2	**16b**	Et	100:0	**17b**: 63
3	**16c**	Allyl	100:0	**17c**: 76
4	**16d**	Bn	100:0	**17d**: 76

Conclusions

We have shown that DAST and Deoxofluor can induce a stereo- and enantioselective rearrangement of prolinols to 3-fluoropiperidines with modest-to-good yield. The presence of a bulky protecting group on the nitrogen atom was shown to improve the selectivity of the rearrangement to

favour the formation of the piperidine. Selective ring expansions were also observed with C-2-alkyl-substituted prolinols and piperidine methanols to produce 3-alkyl-3-fluoropiperidines and 3-alkyl-3-fluoroazepanes.

Experimental Section

General Procedures: DAST and Deoxofluor are commercially available from Aldrich and were used as received. Solvents were distilled. Dry THF and Et_2O were obtained by distillation from sodium and benzophenone; CH_2Cl_2 was dried by distillation from CaH_2. TLC was performed on Merck $60F_{254}$ silica gel plates and visualized either with a UV lamp (254 nm) or by using a solution of $KMnO_4/K_2CO_3$/NaOH in water followed by heating. Flash chromatography was performed with Merck Geduran Si60 silica gel (40–63 μm). Infrared (IR) spectra were recorded with a Bruker TENSOR 27 (IRFT). ^1H NMR spectra at 400 MHz and ^{13}C NMR at 100 MHz were recorded with a Bruker AVANCE 400. ^1H NMR spectra at 300 MHz and ^{13}C NMR at 75 MHz were recorded with a Bruker AC 300. ^1H NMR data are reported as follows: chemical shift in ppm from $SiMe_4$ as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances) and integration. ^{13}C NMR data are reported as follows: chemical shift in ppm from $SiMe_4$ with the solvent as an internal indicator ($CDCl_3$ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH_2, q = CH_3). Mass spectra with electronic impact (EI) were recorded with a Hewlett–Packard tandem 5890A GC (12 m capillary column) – 5971 MS (70 eV). Mass spectra with chemical ionization (CI) and high resolution mass spectra (HRMS) were performed by the Centre de Spectrochimie Organique de l'Ecole Normale Supérieure Ulm (Paris). Optical rotations were measured with a Perkin–Elmer 343 polarimeter in a 10-cm cell.

General Procedure for the Synthesis of *N*-Benzyl-2-hydroxymethylpiperidines 16b-d: To a solution of *N*-benzylpiperidine-2-carboxylic acid methyl ester (4.3 mmol, 1.0 equiv.) in THF (20 mL), cooled to –78 °C, was added LDA (1 M, 4.7 mL, 4.7 mmol, 1.1 equiv.) dropwise, followed by, after 20 min, the alkyl halide. The mixture temperature was then allowed to rise slowly over 3 h till room temp., and the reaction was quenched by the addition of water (20 mL). The aqueous phase was extracted with AcOEt (2 × 40 mL). The organic phase was dried with Na_2SO_4, and the solvents were evaporated in vacuo. After purification by flash chromatography (cyclohexane/AcOEt, 90:10), the obtained alkylated piperidines in a solution of THF (10 mL) were added cautiously at 0 °C to a suspension of $LiAlH_4$ (2 equiv.) in THF (10 mL). After 2 h at room temp., the reaction mixture was cooled to 0 °C and quenched cautiously with a saturated solution of sodium potassium tartrate (10 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The organic phase was dried with Na_2SO_4, and the solvents were evaporated in vacuo. After purification by flash chromatography (cyclohexane/AcOEt, 90:10), piperidine methanols **16b–d** were isolated as colourless oil.

(*N*-Benzyl-2-ethylpiperidin-2-yl)methanol (16b): Yield: 21% (global). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.76 (dd, *J* = 7.7, 7.7 Hz, 3 H, CH_2CH_3), 1.22–1.40 (3 H), 1.42–1.55 (3 H), 1.61 (m, 1 H, 3-H, 4-H, 5-H and CH_2CH_3), 1.83 (dq, *J* = 13.8, 7.7 Hz, 1 H, CH_2CH_3), 2.26 (ddd, *J* = 11.8, 11.8, 3.0 Hz, 1 H, 6-H), 2.60 (m, 1 H, 6-H), 3.00 (d, *J* = 13.6 Hz, 1 H, CH_2Ph), 3.28 (d, *J* = 10.3 Hz, 1 H, CH_2OH), 3.44 (br. s, 1 H, OH), 3.60 (d, *J* = 10.3 Hz, 1 H, CH_2OH), 3.88 (d, *J* = 13.6 Hz, 1 H, CH_2Ph), 7.13–7.27 (5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.2 (q, CH_2CH_3), 19.0 (t), 20.3 (t), 25.9 (t), 29.0 (t, C-3, C-4, C-5 and CH_2CH_3), 46.1 (t, C-6), 52.7 (t, CH_2Ph), 59.5 (s, C-2), 65.1 (t, CH_2OH), 126.8 (d), 128.4 (d), 128.6 (d), 139.1 (s, C_{ar}) ppm. IR (film): $\tilde{\nu}$ = 3424, 2932, 2863, 1494, 1451, 1414, 1363, 1311, 1242, 1122, 1065 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 233 (1) $[M]^{+\cdot}$, 203 (16), 202 (100), 112 (3), 110 (3), 92 (7), 91 (82), 65 (5), 55 (4).

(*N*-Benzyl-2-allylpiperidin-2-yl)methanol (16c): Yield: 31% (global). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.60 (5 H), 1.67 (m, 1 H, 3-H, 4-H and 5-H), 2.04 (dd, *J* = 13.7, 7.4 Hz, 1 H, $CH_2CH{=}CH_2$), 2.26 (ddd, *J* = 11.9, 11.9, 2.7 Hz, 1 H, 6-H), 2.56 (dd, *J* = 13.5, 7.8 Hz, 1 H, $CH_2CH{=}CH_2$), 2.62 (m, 1 H, 6-H), 3.02 (d, *J* = 13.6 Hz, 1 H, CH_2Ph), 3.22 (d, *J* = 10.6 Hz, 1 H, CH_2OH), 3.67 (d, *J* = 10.6 Hz, 1 H, CH_2OH), 3.92 (d, *J* = 13.6 Hz, 1 H, CH_2Ph), 4.97–5.06 (2 H, CH=CH_2), 5.63 (dddd, *J* = 17.1, 9.7, 7.5, 7.5 Hz, 1 H, $CH{=}CH_2$), 7.13–7.26 (5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (t), 25.9 (t), 30.1 (t), 31.7 (t, C-3, C-4, C-5 and $CH_2CH{=}CH_2$), 46.3 (t, C-6), 52.9 (t, CH_2Ph), 59.5 (s, C-2), 65.5 (t, CH_2OH), 117.9 (t, CH=CH_2), 126.9 (d), 128.4 (d), 128.5 (d, C_{Ar}), 133.8 (d, $CH{=}CH_2$), 139.5 (s, C_{ar}) ppm. IR (film): $\tilde{\nu}$ = 3424, 2931, 2861, 2800, 1637, 1603, 1493, 1450, 1413, 1311, 1122, 1051 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 244 (1) $[M - 1]^+$, 215 (9), 214 (53), 205 (10), 204 (69), 92 (8), 91 (100), 65 (6), 55 (3). HRMS: calcd. for $C_{17}H_{24}O_2N$ $[M + H]^+$ 246.1852; found 246.1852.

(*N*-Benzyl-2-benzylpiperidin-2-yl)methanol (16d): Yield: 12% (global). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.52 (2 H), 1.58–1.74 (4 H, 3-H, 4-H and 5-H), 2.49 (ddd, *J* = 12.2, 12.2, 2.3 Hz, 1 H, 6-H), 2.70 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 2.79 (m, 1 H, 6-H), 3.10 (d, *J* = 10.5 Hz, 1 H, CH_2OH), 3.18 (d, *J* = 13.2 Hz, 1 H, CH_2Ph), 3.22 (d, *J* = 13.5 Hz, 1 H, *N*-CH_2Ph), 3.90 (d, *J* = 10.5 Hz, 1 H, CH_2OH), 4.16 (d, *J* = 13.5 Hz, 1 H, *N*-CH_2Ph), 7.13–7.37 (10 H, H_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (t), 25.9 (t), 29.1 (t, C-3, C-4, C-5), 32.9 (t, CH_2Ph), 46.3 (t, C-6), 52.9 (t, *N*-CH_2Ph), 60.5 (s, C-2), 65.3 (t, CH_2OH), 126.3 (d), 127.0 (d), 128.2 (d), 128.5 (d), 128.6 (d), 130.1 (d), 137.7 (s), 139.4 (s, C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 3389, 3028, 2931, 2853, 1492, 1448, 1305, 1127, 1037 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 277 (16), 264 (19) $[M - CH_2OH]^+$, 263 (7), 205 (11), 204 (77), 186 (22), 92 (10), 91 (100), 65 (8). HRMS: calcd. for $C_{20}H_{26}ON$ $[M + H]^+$ 296.2008; found 296.2008.

General Procedure for the Ring Expansion Induced by DAST: To a solution of prolinol (0.5 mmol) in THF or CH_2Cl_2 (5 mL), cooled to 0 °C, was added DAST (0.7 mmol, 1.4 equiv.) dropwise. After 1 h at 0 °C and 1 h at room temp., the reaction mixture was cooled to 0 °C and quenched with a saturated solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with AcOEt (2 × 20 mL). The organic phase was dried with Na_2SO_4, and the solvents were evaporated in vacuo.

(*R*)-*N*-Benzyl-3-fluoropiperidine (2)[7g] and (*S*)-*N*-Benzyl-2-fluoromethylpyrrolidine (3):[7g] Following the general procedure, prolinol **1**[17] {100 mg, 0.52 mmol, 1.0 equiv., $[a]_D^{20}$ = –57.4 (*c* = 1.56, $CHCl_3$)} was treated with DAST (96 μL, 0.78 mmol, 1.4 equiv.) in THF (5 mL). After purification by flash chromatography on silica gel (cyclohexane/AcOEt, 95:5), fluoro compounds **2** and **3** (60 mg, 0.31 mmol, 60%) were obtained as an inseparable mixture. Data for a mixture of **2**+**3**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.98 (4 H^2 and 4 H^3, 4-H^2, 5-H^2, 3-H^3, and 4-H^3), 2.19–2.32 (1 H^2 and 1 H^3, 5-H^3 and 6-H^2), 2.36 (ddd, *J* = 8.1, 7.0, 7.0 Hz, 1 H^2, 2-H), 2.49 (m, 1 H^2, 6-H), 2.78 (m, 1 H^2, 2-H), 2.88 (m, 1 H^3, 2-H), 2.94 (m, 1 H^3, 5-H), 3.48 (d, *J* = 13.1 Hz, 1 H^3, CH_2-Ph), 3.54 (s, 2 H^2,

N-CH_2-Ph), 4.03 (d, *J* = 13.1 Hz, 1 H^3, CH_2-Ph), 4.20–4.40 (2 H^3, 2′-H^3), 4.60 (ddddd, *J* = 48.1, 7.7, 7.7, 3.8, 3.8 Hz, 1 H^2, 3-H^2), 7.20–7.27 (1 H^2 and 1 H^3, H_{Ar}), 7.27–7.35 (4 H^2 and 4 H^3, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.2 (dt, *J* = 8 Hz, C^2-5), 23.1 (t, C^3-4), 27.3 (dt, C^3-3), 30.2 (dt, *J* = 19 Hz, C^2-4), 52.9 (t, C^3-5), 54.7 (t, C^2-6), 57.6 (dt, *J* = 23 Hz, C^2-2), 59.7 (t, CH_2^3-Ph), 62.6 (dd, *J* = 20 Hz, C^3-2), 62.9 (t, CH_2^2-Ph), 86.1 (dt, *J* = 169 Hz, C^3-2′), 88.3 (dd, *J* = 170 Hz, C^2-3), 127.0 (d), 127.1 (d), 128.2 (d), 128.9 (d), 129.1 (d), 137.9 (s), 139.5 (s, C_{Ar}) ppm. IR (film): ṽ = 3028, 2945, 2799, 1495, 1453, 1375, 1349, 1263, 1156, 1105, 1073, 1018, 988 cm^{-1}. Data for **2**: MS (EI, 70 eV): *m*/*z* (%) = 193 (44) [M]$^{+\cdot}$, 192 (42), 172 (2), 160 (2), 146 (6), 132 (4), 117 (6), 116 (54), 102 (45), 92 (19), 91 (100), 89 (4), 73 (3), 65 (16), 55 (5), 51 (3). Data for **3**: MS (EI, 70 eV): *m*/*z* (%) = 193 (13) [M]$^{+\cdot}$, 192 (9), 161 (9), 160 (65), 146 (2), 130 (2), 116 (14), 102 (10), 92 (11), 91 (100), 89 (3), 74 (3), 65 (13), 59 (2), 51 (3).

(3*S*,5*R*)-*N*-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-3-fluoropiperidine (6) and (2*R*,4*R*)-*N*-Benzyl-4-(*tert*-butyldimethylsilanyloxy)-2-fluoromethylpyrrolidine (7): Following the general procedure, prolinol **5**[21] {150 mg, 0.47 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = +42.3 (*c* = 1.22, $CHCl_3$)} was treated with DAST (86 μL, 0.65 mmol, 1.4 equiv.) in THF (5 mL). After purification by flash chromatography on silica gel (cyclohexane/Et_2O, 98:2), fluoro compounds **6** and **7** were obtained as an inseparable mixture (100 mg, 0.31 mmol, 73%). Data for a mixture of **6**+**7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03 (3 H^7, Si-*Me*), –0.01 (3 H^7, Si-*Me*), 0.00 (3 H^6, Si-*Me*), 0.02 (3 H^6, Si-*Me*), 0.80–0.86 (9 H^6 and 9 H^7, *t*Bu^6 and *t*Bu^7), 1.10 (dd, *J* = 14.8, 7.1 Hz, 1 H^7, 3-H), 1.39 (m, 1 H^6, 4-H), 1.60 (m, 1 H^7, 3-H), 1.80–1.95 (2 H^6, 4-H and 6-H), 2.15 (m, 1 H^7, 5-H), 2.35 (m, 1 H^6, 2-H), 2.48 (m, 1 H^7, 5-H), 2.81–2.88 (1 H^6 and 1 H^7, 6-H^6 and 2-H^7), 3.00 (m, 1 H^7, 4-H), 3.05 (m, 1 H^6, 2-H), 3.50 (d, *J* = 13.2 Hz, 1 H^6, CH_2Ph), 3.53 (d, *J* = 13.5 Hz, 1 H^7, CH_2Ph), 3.62 (d, *J* = 13.2 Hz, 1 H^6, CH_2Ph), 3.72 (m, 1 H^6, 5-H), 4.01 (d, *J* = 13.6 Hz, 1 H^7, CH_2Ph), 4.24–4.62 (1 H^6 and 2 H^7, 3-H^6 and 2′-H^7), 7.18–7.34 (5 H^6 and 5 H^7, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (q, Si-*Me*^{7}), –4.8 (q, Si-*Me*^{6}), 18.1 (s, *C*Me$_3^6$ and *C*Me$_3^7$), 25.8 (q, C*Me*$_3^6$), 25.8 (q, C*Me*$_3^7$), 37.8 (dt, *J* = 5 Hz, C^7-3), 41.1 (dt, *J* = 18 Hz, C^6-4), 56.6 (dt, *J* = 26 Hz, C^6-2), 59.3 (t), 60.3 (t), 61.8 (dd, *J* = 61.8 Hz, C^7-2), 62.1 (t), 62.3 (t), 66.3 (dd, *J* = 15 Hz, C^6-5), 71.0 (d, C^7-4), 86.6 (dt, *J* = 169 Hz, -C^7-2′), 86.8 (dd, *J* = 171 Hz, C^6-3), 126.8 (d), 127.2 (d), 128.2 (d), 128.3 (d), 128.6 (d), 128.9 (d), 137.6 (s), 139.3 (s, C_{Ar}) ppm. IR (film): ṽ = 2954, 2929, 2857, 1471, 1383, 1256, 1178, 1148, 1105, 1020 cm^{-1}. Data for **6**: MS (EI, 70 eV): *m*/*z* (%) = 323 (2), 267 (7), 266 (35), 246 (5), 134 (11), 92 (9), 91 (100), 73 (9). Data for **7**: *m*/*z* (%) = 323 (1), 291 (15), 290 (58), 266 (21), 158 (7), 92 (8), 91 (100), 74 (8), 73 (8).

(3*R*,5*R*)-*N*-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-3-fluoropiperidine (9a) and (2*S*,4*R*)-*N*-Benzyl-4-(*tert*-butyldimethylsilanyloxy)-2-fluoromethylpyrrolidine (10a): Following the general procedure, prolinol **8a**[15m] {500 mg, 1.56 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = – 51.1 (*c* = 1.14, $CHCl_3$)} was treated with DAST (245 μL, 2.18 mmol, 1.4 equiv.) in THF (15 mL). After purification by preparative TLC on silica gel (cyclohexane/AcOEt, 95:5), fluoropiperidine **9a** (265 mg, 0.82 mmol, 53%) and fluoromethylpyrrolidine **10a** (39 mg, 0.12 mmol, 8%) were isolated as a white solid and a yellow oil, respectively. Data for **9a**: M.p. 43 °C. $[\alpha]_D^{20}$ = –6.7 (*c* = 0.135, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H, Si-*Me*), 0.03 (s, 3 H, Si-*Me*), 0.83 (s, 9 H, *t*Bu), 1.51 (m, 1 H, 4-H), 1.99–2.29 (m, 3 H, 2-H, 4-H and 6-H), 2.79–2.92 (m, 2 H, 2-H and 6-H), 3.52 (d, *J* = 13.4 Hz, 1 H, CH_2Ph), 3.64 (d, *J* = 13.4 Hz, 1 H, CH_2Ph), 4.06 (dddd, *J* = 9.5, 9.5, 4.5, 4.5 Hz, 1 H, 5-H), 4.80 (dm, *J* = 47.2 Hz, 1 H, 3-H), 7.15–7.40 (5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (q, Si-*Me*), –4.8 (q, Si-*Me*), 18.1 (s, Si-*C*Me$_3$), 25.8 (q, Si-C*Me*$_3$), 38.8 (dt, *J* = 20.2 Hz, C-4), 56.1 (dt, *J* = 20.2 Hz, C-2), 60.2 (t, C-6), 62.3 (t, *C*H_2Ph), 65.1 (d, C-5), 87.9 (dd, *J* = 171.2 Hz, C-3), 127.1 (d), 128.2 (d), 129.0 (d), 137.5 (s, C_{Ar}) ppm. IR (neat): ṽ = 2921, 1460, 1252, 1153, 1090 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 323 (2) [M]$^{+\cdot}$, 308 (3), 266 (31), 246 (4), 191 (4), 134 (11), 92 (9), 91 (100), 75 (4), 73 (10). HRMS: calcd. for $C_{18}H_{31}NFOSi$ [M + H]$^+$ 324.2154; found 324.2151. Data for **10a**: $[\alpha]_D^{20}$ = –16.8 (*c* = 0.62, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, Si*Me*), 0.85 (s, 9 H, *tBu*), 1.81–1.88 (2 H, 3-H), 2.30 (m, 1 H, 5-H), 3.06–3.20 (2 H, 2-H and 5 H), 3.52 (m, 1 H, CH_2Ph), 4.00 (m, 1 H, CH_2Ph), 4.21–4.38 (3 H, 4-H, 2′-H), 7.19–7.32 (5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (q, Si*Me*), 18.0 (s, *C*Me$_3$), 25.8 (q, C*Me*$_3$), 37.5 (dt, *J* = 4 Hz, C-3), 59.9 (t, *C*H_2Ph), 61.8 (dd, *J* = 19 Hz, C-2), 62.5 (t, C-5), 70.3 (d, C-4), 85.8 (dt, *J* = 169 Hz, C-2′), 127.0 (d), 128.3 (d), 128.8 (d), 139.3 (s, C_{Ar}) ppm. IR (film): ṽ = 2954, 2929, 2857, 1471, 1455, 1381, 1255, 1119, 1030, 1008, 913 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 308 (3), 292 (6), 291 (24), 290 (100) [M – CH_2F]$^+$, 266 (8), 158 (11), 92 (6), 91 (86), 75 (12), 74 (14), 56 (8). HRMS: calcd. for $C_{18}H_{31}NFOSi$ [M + H]$^+$ 324.2154; found 324.2154.

(3*S*,4*S*)-*N*-Benzyl-4-(*tert*-butyldimethylsilanyloxy)-3-fluoropiperidine (9b) and (2*S*,3*S*)-*N*-Benzyl-3-(*tert*-butyldimethylsilanyloxy)-2-fluoromethylpyrrolidine (10b): Following the general procedure, prolinol **8b**[19] {24 mg, 0.07 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = –9.3 (*c* = 1.22, $CHCl_3$)} was treated with DAST (15 μL, 0.10 mmol, 1.4 equiv.) in THF (5 mL). After purification by flash chromatography on silica gel (cyclohexane/AcOEt, 95:5), fluoro compounds **9b** and **10b** were obtained as an inseparable mixture (12 mg, 0.38 mmol, 55%). Data for a mixture of **9b**+**10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01–0.02 (6 H^{9b} and 6 H^{10b}, Si-*Me*^{9b} and Si-*Me*^{10b}), 0.81–0.84 (9 H^{9b} and 9 H^{10b}, *t*Bu^{9b} and *t*Bu^{10b}), 1.49–1.64 (1 H^{9b} and 1 H^{10b}, 5-H^{9b} and 4-H^{10b}), 1.76–1.88 (1 H^{9b} and 1 H^{10b}, 5-H^{9b} and 4-H^{10b}), 2.06 (ddd, *J* = 10.8, 10.8, 3.0 Hz, 1 H^{9b}, 6-H), 2.16 (m, 1 H^{9b}, 2-H), 2.54 (m, 1 H^{10b}, 5-H), 2.69–2.58 (1 H^{9b} and 1 H^{10b}, 6-H^{9b} and 2-H^{10b}), 2.83 (m, 1 H^{10b}, 5-H), 2.91 (m, 1 H^{9b}, 2-H), 3.46 (d, *J* = 13.1 Hz, 1 H^{9b}, CH_2Ph), 3.49 (d, *J* = 13.1 Hz, 1 H^{9b}, CH_2Ph), 3.52 (d, *J* = 13.1 Hz, 1 H^{10b}, CH_2Ph), 3.58 (m, 1 H^{9b}, 4-H), 3.93 (d, *J* = 13.1 Hz, 1 H^{10b}, CH_2Ph), 4.37–4.08 (1 H^{9b} and 3 H^{10b}, 3-H^{9b}, 3-H^{10b} and 2′-H^{10b}), 7.15–7.29 (5 H^{9b} and 5 H^{10b}, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8 (q), –4.7 (q), –4.7 (q), –4.6 (q, Si-*Me*^{9b} and Si-*Me*^{10b}), 18.0 (s), 18.1 (s, *C*Me$_3^{9b}$ and *C*Me$_3^{10b}$), 25.8 (q, C*Me*$_3^{9b}$ and C*Me*$_3^{10b}$), 32.0 (t, C^{9b}-5), 33.5 (t, C^{10b}-4), 50.3 (t, C^{9b}-6), 51.9 (t, C^{10b}-5), 54.8 (dt, *J* = 23 Hz, C^{9b}-2), 59.9 (t, *C*H_2^{10b}-Ph), 62.4 (t, *C*H_2^{9b}-Ph), 70.4 (d, C^{10b}-2), 72.0 (dd, *J* = 19 Hz, C^{9b}-4), 73.8 (d, C^{10b}-3), 83.4 (dt, *J* = 171 Hz, C^{10b}-2′), 91.9 (dd, *J* = 171 Hz, C^{9b}-3), 127.0 (d), 127.1 (d), 127.9 (d), 128.3 (d), 128.9 (d), 129.0 (d), 138.0 (s), 139.3 (s, C_{Ar}) ppm. IR (film): ṽ = 3057, 2935, 1596, 1490, 1448, 1375, 1213, 1185, 1070, 1035, 1004 cm^{-1}. Data for **9b**: MS (EI, 70 eV): *m*/*z* (%) = 323 (4) [M]$^{+\cdot}$, 302 (4), 290 (4), 267 (10), 266 (48), 232 (9), 172 (8), 147 (12), 92 (9), 91 (100), 77 (8), 75 (5). Data for **10b**: MS (EI, 70 eV): *m*/*z* (%) = 323 (3) [M]$^{+\cdot}$, 291 (14), 290 (58), 267 (7), 266 (30), 232 (7), 172 (6), 147 (9), 92 (9), 91 (100), 77 (8), 75 (8), 74 (13), 75 (6).

(3*R*,5*R*)-*N*-Benzyl-3-fluoro-5-methoxypiperidine (9c) and (2*S*,4*S*)-*N*-Benzyl-2-fluoromethyl-4-methoxypyrrolidine (10c): Following the general procedure, prolinol **8c** {11 mg, 0.05 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = +33.5 (*c* = 1.34, $CHCl_3$)} was treated with DAST (9 μL, 0.07 mmol, 1.4 equiv.) in THF (3 mL). After purification by flash chromatography on silica gel (cyclohexane/AcOEt, 95:5), fluoro compounds **9c** and **10c** were obtained as an inseparable mixture (6 mg, 0.03 mmol, 55%). Data for a mixture of **9c**+**10c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57–1.70 (1 H^{9c} and 1 H^{10c}, 4-H^{9c} and 3-

H^{10c}), 1.83 (dd, J = 10.3, 9.7 Hz, 1 H^{9c}, 6-H), 2.00 (ddd, J = 9.9, 9.9, 5.4 Hz, 1 H^{9c}, 4-H), 2.15 (m, 1 H^{10c}, 3-H), 2.30 (dd, J = 10.8, 5.2 Hz, 1 H^{10c}, 5-H), 2.43 (m, 1 H^{10c}, 5-H), 2.80–3.03 (1 H^{10c} and 3 H^{9c}, 2-H^{9c}, 6-H^{9c} and 2-H^{10c}), 3.17 (s, 3 H^{10c}, OMe), 3.22–3.31 (4 H^{9c}, 5-H^{9c} and OMe^{9c}), 3.41 (d, J = 13.3 Hz, 1 H^{10c}, CH_2Ph), 3.51 (d, J = 13.2 Hz, 1 H^{9c}, CH_2Ph), 3.56 (d, J = 13.2 Hz, 1 H^{9c}, CH$_2$Ph), 3.75 (m, 1 H^{10c}, 4-H), 4.00 (d, J = 13.3 Hz, 1 H^{10c}, CH_2Ph), 4.32 (ddd, J = 47.4, 9.4, 5.3 Hz, 1 H^{10c}, 2′-H), 4.38 (m, 1 H^{10c}, 2′-H), 4.51 (dm, J = 48.8 Hz, 1 H^{9c}, 3-H), 7.14–7.29 (5 H^{9c} and 5 H^{10c}, H$_{Ar}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 33.2 (t, C^{10c}-3), 36.0 (dt, J = 18 Hz, C^{9c}-4), 55.5 (q, OMe^{9c} and OMe^{10c}), 55.7 (t, C^{10c}-5 or C^{9c}-6), 55.8 (dt, J = 14 Hz, C^{9c}-2), 56.1 (t, C^{10c}-5 or C^{9c}-6), 58.1 (t, CH_2^{10c} -Ph), 60.8 (dd, J = 20 Hz, C^{10c}-2), 61.3 (t, CH_2^{9c} -Ph), 73.2 (dd, J = 13 Hz, C^{9c}-5), 78.3 (d, C^{10c}-4), 85.9 (dt, J = 169 Hz, C^{10c}-2′), 85.8 (dd, J = 172 Hz, C^{9c}-3), 126.0 (d), 126.3 (d), 127.2 (d), 127.3 (d), 127.9 (d), 128.0 (d), 136.5 (s), 137.6 (s) (C$_{Ar}$) ppm. IR (film): $\tilde{\nu}$ = 2944, 2818, 1495, 1454, 1381, 1263, 1179, 1149, 1102, 1028 cm^{-1}. MS (EI, 70 eV): m/z (%) = 223 (5) [M]$^{+\cdot}$, 222 (4), 208 (4), 193 (6), 190 (13), 178 (6), 146 (7), 134 (8), 132 (7), 120 (9), 92 (10), 91 (100), 65 (10).

(3*R*,5*R*)-*N*-Benzyl-3-fluoro-5-trityloxypiperidine (9d) and (2*S*,4*R*)-*N*-Benzyl-4-trityloxy-2-fluoromethylpyrrolidine (10d): Following the general procedure, prolinol **8d** {134 mg, 0.30 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = –14.4 (c = 0.65, CHCl$_3$)} was treated with DAST (56 μL, 0.42 mmol, 1.4 equiv.) in CH_2Cl_2 (10 mL). After purification by preparative TLC on silica gel (cyclohexane/AcOEt, 95:5), fluoropiperidine **9d** (40 mg, 0.09 mmol, 33%) and fluoromethylpyrrolidine **10d** (9 mg, 0.02 mmol, 5%) were isolated. Data for **9d**: $[\alpha]_D^{20}$ = +26.5 (c = 0.26, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.34 (m, 1 H, 4-H), 1.45 (m, 1 H, 4-H), 1.59 (m, 1 H, 6-H), 2.06 (m, 1 H, 6-H), 2.19 (ddd, J = 32.1, 12.5, 2.0 Hz, 1 H, 2-H), 2.66 (ddd, J = 11.5, 11.5, 4.0 Hz, 1 H, 2-H), 3.30 (s, 2 H, CH_2Ph), 3.89 (dddd, J = 8.0, 8.0, 4.0, 4.0 Hz, 1 H, 5-H), 4.66 (dm, J = 46.8 Hz, 1 H, 3-H), 7.09–7.24 (14 H, H$_{Ar}$), 7.34–7.41 (6 H, H$_{Ar}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 36.8 (dt, J = 20 Hz, C-4), 56.3 (dt, J = 21 Hz, C-2), 58.2 (t), 62.2 (t, C-6 and CH_2Ph), 66.9 (d, C-5), 77.3 (s, CPh_3), 87.9 (dd, J = 175 Hz, C-3), 127.0 (d), 127.8 (d), 128.2 (d), 128.7 (d), 128.8 (d), 129.0 (d), 137.6 (s), 144.9 (s) (C$_{Ar}$) ppm. IR (film): $\tilde{\nu}$ = 2921, 2852, 1597, 1491, 1448, 1151, 1059, 1029 cm^{-1}. MS (CI, CH$_4$): m/z (%) = 452 (100) [M + H]$^+$, 432 (20), 271 (9), 244 (23), 244 (86), 210 (19), 208 (14), 192 (28), 167 (17), 127 (9). HRMS: calcd. for $C_{31}H_{31}NFO$ [M + H]$^+$ 452.2390; found 452.2392. Data for **10d**: $[\alpha]_D^{20}$ = –40.7 (c = 0.27, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.54–1.66 (2 H, 3-H), 2.14 (dd, J = 9.7, 6.9 Hz, 1 H, 5-H), 2.50 (dd, J = 9.7, 6.2 Hz, 1 H, 5-H), 2.96 (m, 1 H, 2-H), 3.38 (d, J = 13.0 Hz, 1 H, CH_2Ph), 3.92 (d, J = 13.0 Hz, 1 H, CH_2Ph), 4.06–4.26 (3 H, 4-H and 2′-H), 7.15–7.30 (14 H, H$_{Ar}$), 7.40–7.48 (6 H, H$_{Ar}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 34.9 (dt, J = 5 Hz, C-3), 59.2 (t), 60.3 (t, C-5 and CH_2Ph), 61.3 (dd, J = 19 Hz, C-2), 71.9 (d, C-4), 85.6 (dt, J = 169 Hz, C-2′), 87.1 (s, CPh_3), 126.9 (d), 127.0 (d), 127.8 (d), 128.1 (d), 128.7 (d), 128.9 (d), 138.7 (s), 144.8 (s, C$_{Ar}$) ppm. IR (film): $\tilde{\nu}$ = 3059, 3028, 2942, 2799, 1597, 1492, 1449, 1379, 1219, 1153, 1058, 1029 cm^{-1}. HRMS: calcd. for $C_{31}H_{31}NFO$ [M + H]$^+$ 452.2384; found 452.2384.

(3*R*,5*R*)-*N*-Benzyl-3-fluoro-5-triisopropylsilanyloxypiperidine (9e) and (2*S*,4*R*)-*N*-Benzyl-4-triisopropylsilanyloxy-2-fluoromethylpyrrolidine (10e): Following the general procedure, prolinol **8e**[15m] {232 mg, 0.64 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = –26.4 (c = 0.73, CHCl$_3$)} was treated with DAST (116 μL, 0.89 mmol, 1.4 equiv.) in CH_2Cl_2 (10 mL). After purification by preparative TLC on silica gel (cyclohexane/Et$_2$O, 90:10), fluoropiperidine **9e** (175 mg, 0.48 mmol, 75%) and fluoromethylpyrrolidine **10e** (21 mg, 0.06 mmol, 9%) were isolated. Data for **9e**: $[\alpha]_D^{20}$ = +16.5 (c = 1.20, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.95–1.09 (21 H, CHMe$_3$ and CHMe_3), 1.53 (m, 1 H, 4-H), 2.02 (dd, J = 9.6, 9.6 Hz, 1 H, 6-H), 2.16–2.32 (2 H, 2-H and 4-H), 2.87–2.96 (2 H, 2-H and 6-H), 3.60 (s, 2 H, CH_2Ph), 4.16 (dddd, J = 8.9, 8.9, 4.3, 4.3 Hz, 1 H, 5-H), 4.84 (dm, J = 47.5 Hz, 1 H, 3-H), 7.22–7.34 (5 H, H$_{Ar}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 12.2 (d, CHMe$_3$), 18.0 (q, CH-Me), 39.1 (dt, J = 20 Hz, C-4), 56.1 (dt, J = 20 Hz, C-2), 60.4 (t, C-6), 62.3 (t, CH_2Ph), 65.1 (d, C-5), 88.0 (dd, J = 170 Hz, C-3), 127.1 (d), 128.2 (d), 129.1 (d), 137.6 (s, C$_{Ar}$) ppm. IR (film): $\tilde{\nu}$ = 2942, 2865, 2800, 1462, 1383, 1248, 1155, 1102, 1068, 975 cm^{-1}. MS (EI, 70 eV): m/z (%) = 365 (10) [M]$^{+\cdot}$, 322 (48), 192 (14), 172 (6), 134 (8), 120 (5), 92 (9), 91 (100). HRMS: calcd. for $C_{28}H_{35}NFOSi$ [M + H]$^+$, 366.2623; found 366.2623. Data for **10e**: $[\alpha]_D^{20}$ = –40.7 (c = 0.27, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.01–1.04 (21 H, CHMe_3 and CHMe$_3$), 1.88–1.93 (2 H, 3-H), 2.38 (dd, J = 9.8, 5.5 Hz, 1 H, 5-H), 3.11–3.24 (2 H, 2-H and 5-H), 3.57 (d, J = 13.2 Hz, 1 H, CH_2Ph), 4.03 (d, J = 13.2 Hz, 1 H, CH_2Ph), 4.24–4.43 (3 H, 4-H, 2′-H), 7.21–7.34 (5 H, H$_{Ar}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 11.9 (d, CHMe$_3$), 17.8 (q, CHMe_3), 37.8 (dt, J = 5 Hz, C-3), 59.8 (t, CH_2Ph), 61.7 (dd, J = 19 Hz, C-2), 62.8 (t, C-5), 70.4 (d, C-4), 85.7 (dt, J = 170 Hz, C-2′), 126.8 (d), 128.2 (d), 128.7 (d), 139.1 (s, C$_{Ar}$) ppm. IR (film): $\tilde{\nu}$ = 2942, 2865, 1495, 1463, 1382, 1246, 1119, 1053, 1013 cm^{-1}. MS (EI, 70 eV): m/z (%) = 365 (3) [M]$^{+\cdot}$, 333 (6), 332 (25), 323 (8), 322 (27), 192 (9), 134 (6), 92 (8), 91 (100), 77 (5), 75 (6). HRMS: calcd. for $C_{13}H_{25}NF$ [M + H]$^+$ 366.2620; found 366.2620.

(3*R*,5*R*)-*N*-Benzyl-3-(*tert*-butyldiphenylsilanyloxy)-5-fluoropiperidine (9f) and (2*S*,4*R*)-*N*-Benzyl-4-(*tert*-butyldiphenylsilanyloxy)-2-fluoromethylpyrrolidine (10f): Following the general procedure, prolinol **8f**[15m] {129 mg, 0.29 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = –6.8 (c = 0.81, CHCl$_3$)} was treated with DAST (57 μL, 0.41 mmol, 1.4 equiv.) in THF (10 mL). After purification by preparative TLC on silica gel (cyclohexane/AcOEt, 90:10), fluoropiperidine **9f** (78 mg, 0.18 mmol, 61%) and fluoromethylpyrrolidine **10f** (6 mg, 0.013 mmol, 4%) were isolated. Data for **9f**: $[\alpha]_D^{20}$ = +37.6 (c = 0.35, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.04 (s, 9 H, tBu), 1.67 (m, 1 H, 4-H), 1.98 (m, 1 H, 4-H), 2.15 (m, 1 H, 6-H), 2.40 (ddd, J = 29.1, 12.1, 2.0 Hz, 1 H, 2-H), 2.58–2.74 (m, 2 H, 2-H and 6-H), 3.50 (s, 2 H, CH_2Ph), 4.13 (dddd, J = 8.0, 8.0, 4.0, 4.0 Hz, 1 H, 5-H), 4.83 (ddddd, J = 47.7, 5.0, 5.0, 2.5, 2.5 Hz, 1 H, 3-H), 7.21–7.43 (11 H, H$_{Ar}$), 7.65–7.58 (4 H, H$_{Ar}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.2 (s, CMe_3), 27.0 (q, CMe_3), 38.5 (dd, J = 20 Hz, C-4), 56.3 (dt, J = 21 Hz, C-2), 59.6 (t, C-6), 62.2 (t, CH_2Ph), 66.2 (dd, J = 3 Hz, C-5), 87.7 (dd, J = 170 Hz, C-3), 127.1 (d), 127.6 (d), 127.7 (d), 128.2 (d), 129.0 (d), 129.6 (d), 129.7 (d), 134.2 (s), 134.0 (s), 135.7 (d), 137.6 (s, C$_{Ar}$) ppm. IR (film): $\tilde{\nu}$ = 3069, 2930, 2856, 2800, 1588, 1471, 1427, 1360, 1154, 1105, 1027 cm^{-1}. MS (EI, 70 eV): m/z (%) = 447 (1) [M]$^{+\cdot}$, 392 (7), 391 (27), 390 (82), 201 (8), 199 (10), 192 (7), 191 (6), 183 (9), 181 (6), 170 (5), 135 (7), 92 (8), 91 (100). HRMS: calcd. for $C_{28}H_{35}NFOSi$ [M + H]$^+$ 448.2472; found 448.2473. Data for **10f**: $[\alpha]_D^{20}$ = –3.2 (c = 0.16, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.05 (s, 9 H, CMe_3), 1.68 (m, 1 H, 3-H), 1.92 (ddd, J = 12.8, 8.2, 4.4 Hz, 1 H, 3-H), 2.48 (dd, J = 10.0, 5.0 Hz, 1 H, 5-H), 3.03 (dd, J = 10.0, 5.5 Hz, 1 H, 5-H), 3.22 (m, 1 H, 2-H), 3.60 (d, J = 13.2 Hz, 1 H, CH_2Ph), 4.02 (d, J = 13.2 Hz, 1 H, CH_2Ph), 4.14–4.36 (3 H, 4-H, 2′-H), 7.20–7.44 (12 H, H$_{Ar}$), 7.57–7.65 (3 H, H$_{Ar}$) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 19.1 (s, CMe_3), 26.9 (q, CMe_3), 37.4 (dt, J = 5 Hz, C-3), 59.9 (t, CH_2Ph), 61.8 (dd, J = 19 Hz, C-2), 62.3 (t, C-5), 71.4 (d, C-4), 85.9 (dt, J = 169 Hz, C-2′), 127.0 (d), 127.6 (d), 128.2 (d), 128.8 (d), 129.7 (d), 134.0 (s), 133.9 (s), 135.7 (d, C$_{Ar}$) ppm. IR (film): $\tilde{\nu}$ = 3070, 2930, 2856, 1472, 1428, 1380, 1112, 1009 cm^{-1}. MS (EI, 70 eV): m/z (%) = 447 (1) [M]$^{+\cdot}$, 392 (5), 391

(20), 390 (67), 201 (11), 199 (14), 192 (6), 191 (5), 135 (7), 92 (8), 91 (100). HRMS: calcd. for $C_{13}H_{25}NF$ [M + H]$^+$ 448.2470; found 448.2470.

(*R*)-*N*-(2,2-Dimethylpropyl)-3-fluoropiperidine (12a) and (*S*)-*N*-(2,2-Dimethylpropyl)-2-fluoromethylpyrrolidine (13a): Following the general procedure, prolinol **11a** {55 mg, 0.32 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = –48.2 (*c* = 0.57, $CHCl_3$)} was treated with DAST (59 μL, 0.48 mmol, 1.4 equiv.) in THF (5 mL). After purification by flash chromatography on silica gel (cyclohexane/AcOEt, 95:5), fluoro compounds **12a** and **13a** were obtained as an inseparable mixture (30 mg, 0.17 mmol, 54%). Data for a mixture of **12a** + **13a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 9 H^{12a}, C*Me*$_3$), 0.88 (s, 9 H^{13a}, C*Me*$_3$), 1.39–1.95 (4 H^{12a} and 4 H^{13a}, 4-H^{12a}, 5-H^{12a}, 3-H^{13a}, 4-H^{13a}), 2.06 (s, 2 H^{12a}, C*H*$_2$*t*Bu), 2.26 (d, *J* = 13.5 Hz, 1 H^{13a}, C*H*$_2$*t*Bu), 2.26–2.37 (1 H^{12a} and 1 H^{13a}), 2.43 (m, 1 H^{12a}, 2-H^{12a}, 6-H^{12a} and 5-H^{13a}), 2.47 (d, *J* = 13.5 Hz, 1 H^{13a}, C*H*$_2$*t*Bu), 2.53 (m, 1 H^{12a}, C*H*$_2$*t*Bu), 2.79 (m, 1 H^{13a}, 5-H), 2.88 (m, 1 H^{12a}, 2-H), 3.20 (m, 1 H^{13a}, 2-H), 4.18 (ddd, *J* = 47.9, 9.0, 6.2 Hz, 1 H^{13a}, 2′-H), 4.33 (ddd, *J* = 47.5, 9.0, 4.9 Hz, 1 H^{13a}, 2′-H), 4.56 (ddddd, *J* = 48.8, 12.3, 4.1, 4.1, 4.1 Hz, 1 H^{12a}, 3-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (dt, *J* = 8 Hz, C^{12a}-5), 24.1 (t, C^{13a}-4), 27.3 (dt, *J* = 6 Hz, C^{13a}-3), 27.6 (q, C*Me*$_3^{12a}$), 28.4 (q, C*Me*$_3^{13a}$), 30.1 (dt, *J* = 19 Hz, C^{12a}-4), 32.7 (s, *C*Me$_3^{13a}$), 33.2 (s, *C*Me$_3^{12a}$), 42.3 (t, C^{13a}-5), 55.6 (t, C^{12a}-6), 58.1 (t, *C*H$_2^{13a}$*t*Bu), 60.6 (dt, *J* = 23 Hz, C^{12a}-2), 65.6 (dd, *J* = 20 Hz, C^{13a}-2), 69.7 (t, *C*H$_2^{12a}$*t*Bu), 86.1 (dt, *J* = 169 Hz, C^{13a}-2′), 88.8 (dd, *J* = 170 Hz, C^{12a}-3) ppm. IR (film): $\tilde{\nu}$ = 2951, 2927, 2856, 1465, 1360, 1261, 1206, 1152, 1104, 1027 cm^{-1}. Data for **12a**: MS (EI, 70 eV): *m*/*z* (%) = 173 (2) [M]$^{+\cdot}$, 158 (9), 117 (7), 116 (100), 96 (4), 73 (3), 55 (4). Data for **13a**: MS (EI, 70 eV): *m*/*z* (%) = 173 (3) [M]$^{+\cdot}$, 158 (10), 117 (7), 116 (100), 110 (2), 102 (3), 96 (2), 70 (3), 55 (4).

(*R*)-*N*-Benzhydryl-3-fluoropiperidine (12b) and (*S*)-*N*-Benzhydryl-2-fluoromethylpyrrolidine (13b): Following the general procedure, prolinol **11b** {80 mg, 0.30 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = +28.9 (*c* = 0.28, $CHCl_3$)} was treated with DAST (55 μL, 0.41 mmol, 1.4 equiv.) in CH_2Cl_2 (5 mL). After purification by flash chromatography on silica gel (cyclohexane/AcOEt, 95:5), fluoro compounds **12b** and **13b** were obtained as an inseparable mixture (57 mg, 0.21 mmol, 71%). Data for a mixture of **12b** + **13b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47–1.95 (4 H^{12b} and 4 H^{13b}, 4-H^{12b}, 5-H^{12b}, 3-H^{13b} and 4-H^{13b}), 2.16 (m, 1 H^{12b}, 6-H), 2.26–2.41 (1 H^{12b} and 1 H^{13b}, 2-H^{12b} and 5-H^{13b}), 2.45 (m, 1 H^{12b}, 6-H), 2.74 (m, 1 H^{12b}, 2-H), 2.92 (m, 1 H^{13b}, 5-H), 3.11 (m, 1 H^{13b}, 2-H), 3.98 (ddd, *J* = 47.3, 8.9, 4.7 Hz, 1 H^{13b}, 2′-H), 4.02 (ddd, *J* = 47.9, 8.9, 7.1 Hz, 1 H^{13b}, 2′-H), 4.34 (s, 1 H^{12b}, C*H*Ph$_2$), 4.63 (ddddd, *J* = 48.2, 7.7, 7.7, 3.8, 3.8 Hz, 1 H^{12b}, 3-H), 4.74 (s, 1 H^{13b}, C*H*Ph$_2$), 7.14–7.44 (10 H^{12b} and 10 H^{13b}, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (dt, *J* = 7 Hz, C^{12b}-5), 23.6 (t, C^{13b}-4), 27.6 (t, C^{13b}-3), 30.5 (dt, *J* = 21 Hz, C^{12b}-4), 51.6 (t, C^{12b}-6), 53.0 (t, C^{13b}-5), 56.2 (dt, *J* = 24 Hz, C^{12b}-2), 60.1 (dd, *J* = 24 Hz, C^{13b}-2), 73.4 (d, *C*H^{13b}Ph$_2$), 75.7 (d, *C*H^{12b}Ph$_2$), 85.5 (dt, *J* = 169 Hz, -C^{13b}-2′), 88.7 (dd, *J* = 170 Hz, C^{12b}-3), 126.9 (d), 127.0 (d), 127.2 (d), 128.0 (d), 128.3 (d), 128.5 (d), 142.3 (s), 142.4 (s, C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 3060, 3025, 2944, 2801, 1598, 1491, 1451, 1336, 1304, 1263, 1187, 1154, 1106, 1074, 1015 cm^{-1}. Data for **12b**: MS (EI, 70 eV): *m*/*z* (%) = 269 (19) [M]$^{+\cdot}$, 193 (11), 192 (78), 168 (18), 167 (100), 166 (12), 165 (35), 152 (18), 102 (6), 91 (4). Data for **13b**: MS (EI, 70 eV): *m*/*z* (%) = 269 (6) [M]$^{+\cdot}$, 236 (18), 193 (5), 192 (34), 168 (17), 167 (100), 166 (9), 165 (29), 152 (15), 91 (4).

(*R*)-*N*-Trityl-3-fluoropiperidine (12c): Following the general procedure, prolinol **11c** {1.11 g, 3.2 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = +40.0 (*c* = 1.31, $CHCl_3$)} was treated with DAST (480 μL, 3.6 mmol, 1.4 equiv.) in THF (15 mL). After recrystallization (CH_2Cl_2), fluoropiperidine **12c** (706 mg, 2.0 mmol, 64%) was isolated as a white solid. M.p. 179 °C (CH_2Cl_2). $[\alpha]_D^{20}$ = +7.6 (*c* = 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 100 °C): δ = 1.49 (m, 1 H), 1.66 (m, 1 H), 1.72–1.93 (2 H), 2.03 (m, 1 H, 4-H, 5-H and 6-H), 2.14–2.29 (2 H, 2-H and 6-H), 2.54 (m, 1 H, 2-H), 4.83 (ddddd, *J* = 48.7, 7.1, 7.1, 3.5, 3.5 Hz, 1 H, 3-H), 7.18 (t, *J* = 7.3 Hz, 3 H, H_{Ar}), 7.30 (t, *J* = 7.7 Hz, 6 H, H_{Ar}), 7.43 (d, *J* = 7.9 Hz, 6 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 100 °C): δ = 22.4 (dt, *J* = 6 Hz, C-5), 29.0 (dt, *J* = 20 Hz, C-4), 48.7 (t, C-6), 53.2 (dt, *J* = 23 Hz, C-2), 77.3 (s, *C*Ph$_3$), 87.9 (dd, *J* = 172 Hz, C-3), 126.5 (d), 128.0 (d), 129.3 (d), 142.7 (s) ppm. IR (neat): $\tilde{\nu}$ = 2932, 1594, 1486, 1447, 1183, 1065, 1031, 1003, 971 cm^{-1}. HRMS: calcd. for $C_{24}H_{24}NFNa$ [M + Na]$^+$ 368.1785; found 368.1785.

(*R*)-*N*-(2,2-Dimethylpropyl)-3-ethyl-3-fluoropiperidine (15a): Following the general procedure, prolinol **14a** {256 mg, 1.29 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = –31.7 (*c* = 1.23, $CHCl_3$)} was treated with DAST (236 μL, 1.80 mmol, 1.4 equiv.) in CH_2Cl_2 (15 mL). After purification by flash chromatography (pentane/Et_2O, 95:5), fluoropiperidine **15a** (196 mg, 0.975 mmol, 76%) was isolated as a colourless oil. $[\alpha]_D^{20}$ = +12.6 (*c* = 1.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CHCl_3$): δ = 0.88 (s, 9 H, CC*H*$_3$), 0.93 (t, *J* = 7.5 Hz, 3 H, CH$_2$C*H*$_3$), 1.65–1.43 (3 H, 4-H and 5-H), 1.66–1.79 (3 H, 5-H, C*H*$_2$CH$_3$), 2.02 (d, *J* = 13.7 Hz, 1 H, C*H*$_2$*t*Bu), 2.07 (d, *J* = 13.8 Hz, 1 H, C*H*$_2$*t*Bu), 2.41–2.55 (4 H, 2-H and 6-H) ppm. ^{13}C NMR (100 MHz, $CHCl_3$): δ = 7.0 (dq, *J* = 4 Hz, CH$_2$*C*H$_3$), 22.9 (t, C-5), 27.7 (q, C*C*H$_3$), 29.8 (dt, *J* = 23.0 Hz, *C*H$_2$CH$_3$), 32.7 (dt, *J* = 22.0 Hz, C-4), 33.2 (s, *C*CH$_3$), 56.1 (t, C-6), 63.5 (dt, *J* = 24.0 Hz, C-2), 69.8 (t, *C*H$_2$*t*Bu), 94.8 (ds, *J* = 171.0 Hz, C-3) ppm. IR (film): $\tilde{\nu}$ = 2948, 2865, 2792, 1463, 1359, 1126 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 201 (1) [M]$^{+\cdot}$, 186 (7), 145 (10), 144 (100), 124 (12), 116 (2), 102 (3), 55 (4). HRMS: calcd. for $C_{12}H_{25}NF$ [M + H]$^+$ 202.1971; found 202.1957.

(*S*)-*N*-(2,2-Dimethylpropyl)-3-allyl-3-fluoropiperidine (15b): Following the general procedure, prolinol **14b** {256 mg, 1.21 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = –7.9 (*c* = 1.02, $CHCl_3$)} was treated with DAST (220 μL, 1.70 mmol, 1.4 equiv.) in CH_2Cl_2 (10 mL). After purification by flash chromatography (pentane/Et_2O, 95:5), fluoropiperidine **15b** (229 mg, 1.05 mmol, 89%) was isolated as a colourless oil. $[\alpha]_D^{20}$ = +11.6 (*c* = 1.65, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (9 H, CC*H*$_3$), 1.49 (m, 1 H, 5-H), 1.56–1.62 (2 H, 4-H), 1.71 (m, 1 H, 5-H), 2.03 (d, *J* = 14.8 Hz, 1 H, C*H*$_2$*t*Bu), 2.07 (d, *J* = 14.8 Hz, 1 H, C*H*$_2$*t*Bu), 2.38–2.54 (6 H, 2-H, 6-H and C*H*$_2$CH=CH$_2$), 5.10 (m, 2 H, CH$_2$CH=C*H*$_2$), 5.86 (dddd, *J* = 17.1, 10.1, 7.0, 7.0 Hz, 1 H, CH$_2$C*H*=CH$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7 (dt, *J* = 6 Hz, C-5), 27.8 (q, C*C*H$_3$), 33.9 (dt, *J* = 21 Hz, C-4), 33.2 (s, *C*CH$_3$), 41.7 (dt, *J* = 22 Hz, *C*H$_2$CH=CH$_2$), 56.0 (t, C-6), 63.7 (dt, *J* = 23 Hz, C-2), 69.8 (t, *C*H$_2$*t*Bu), 94.1 (ds, *J* = 173 Hz, C-3), 118.3 (t, CH$_2$CH=*C*H$_2$), 132.7 (dd, *J* = 4 Hz, CH$_2$*C*H=CH$_2$) ppm. IR (film): $\tilde{\nu}$ = 2950, 2865, 2787, 1643, 1466, 1360, 1115, 1023 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 213 (1) [M]$^{+\cdot}$, 198 (7), 157 (11), 156 (100), 136 (6), 115 (13), 114 (11), 76 (3). HRMS: calcd. for $C_{13}H_{25}NF$ [M + H]$^+$ 214.1971; found 214.1960.

(*S*)-*N*-(2,2-Dimethylpropyl)-3-benzyl-3-fluoropiperidine (15c): Following the general procedure, prolinol **14c** {25 mg, 0.10 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = –16.1 (*c* = 0.99, $CHCl_3$)} was treated with DAST (18 μL, 0.13 mmol, 1.4 equiv.) in THF (5 mL). After purification by flash chromatography (cyclohexane/AcOEt, 90:10), fluoropiperidine **15c** (22 mg, 0.084 mmol, 87%) was isolated as a colourless oil. $[\alpha]_D^{20}$ = –4.3 (*c* = 1.75, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 9 H, C*Me*$_3$), 1.44–1.58 (3 H, 4-H and 5-H), 1.69 (m, 1 H, 5-H), 2.04 (d, *J* = 13.8 Hz, 1 H, C*H*$_2$*t*Bu), 2.08 (d, *J* = 13.8 Hz, 1 H, C*H*$_2$*t*Bu), 2.38–2.58 (m, 4 H, 2-H and 6-H), 2.95 (dd, *J* =

19.8, 14.4 Hz, 1 H, CH_2Ph), 3.11 (dd, J = 30.6, 14.4 Hz, 1 H, CH_2Ph), 7.21–7.31 (5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (dt, J = 7 Hz, C-5), 26.8 (q, CMe_3), 31.2 (dt, J = 28 Hz, C-4), 32.2 (s, CMe$_3$), 42.4 (dt, J = 28 Hz, CH$_2$Ph), 55.0 (t, C-6), 63.3 (dt, J = 31 Hz, C-2), 68.8 (t, CH$_2t$Bu), 93.3 (ds, J = 232 Hz, C-3), 125.4 (d), 127.0 (d), 129.5 (d), 135.5 (s) (C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 2945, 2862, 2785, 1605, 1454, 1358, 1112, 1020 cm^{-1}. MS (EI, 70 eV): m/z (%) = 263 (1) [M]$^{+\cdot}$, 248 (6), 207 (15), 206 (100), 186 (13), 115 (5), 96 (12), 91 (28). $C_{17}H_{26}FN$ (263.19): C 77.52, H 9.95, N 5.32; found C 77.13, H 9.73, N 5.34.

(*S*)-*N*-Benzyl-3-benzyl-3-fluoropiperidine (15d): Following the general procedure, prolinol **14d** {43 mg, 0.15 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = +3.6 (c = 0.70, $CHCl_3$)} was treated with DAST (26 μL, 0.18 mmol, 1.4 equiv.) in THF (5 mL). After purification by flash chromatography (cyclohexane/AcOEt, 90:10), fluoropiperidine **15d** (13 mg, 0.045 mmol, 30%) was isolated as a colourless oil. $[\alpha]_D^{20}$ = –3.9 (c = 0.41, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51–1.80 (4 H, 4-H and 5-H), 2.36–2.47 (m, 4 H, 2-H and 6-H), 2.95 (dd, J = 24.8, 14.2 Hz, 1 H, CH_2Ph), 3.02 (dd, J = 24.6, 14.2 Hz, 1 H, CH_2Ph), 3.48 (d, J = 13.2 Hz, 1 H, N-CH_2Ph), 3.54 (d, J = 13.2 Hz, 1 H, N-CH_2Ph), 7.16–7.20 (2 H, H_{Ar}), 7.21–7.29 (4 H, H_{Ar}), 7.30–7.33 (4 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3 (dt, J = 7 Hz, C-5), 32.4 (dt, J = 22 Hz, C-4), 42.4 (dt, J = 23 Hz, CH$_2$Ph), 51.4 (t, C-6), 59.5 (dt, J = 23 Hz, C-2), 61.8 (t, N-CH_2Ph), 93.0 (ds, J = 174 Hz, C-3), 125.5 (d), 126.0 (d), 127.1 (d), 127.2 (d), 128.1 (d), 129.5 (d), 135.3 (s), 137.0 (s, C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 3029, 2943, 2802, 1495, 1354, 1346, 1301, 1116, 1079, 1029 cm^{-1}. MS (EI, 70 eV): m/z (%) = 283 (36) [M]$^{+\cdot}$, 282 (24), 263 (42), 206 (12), 192 (15), 191 (12), 186 (11), 172 (38), 115 (10), 92 (10), 91 (100), 65 (10). HRMS: calcd. for $C_{13}H_{25}NF$ [M + H]$^+$ 284.1815; found 284.1815.

(3*R*,5*R*)-*N*-Methyl-5-(*tert*-butyldiphenylsilanyloxy)-3-ethyl-3-fluoropiperidine (15e): Following the general procedure, prolinol **14e**[15m] {50 mg, 0.13 mmol, 1.0 equiv., $[\alpha]_D^{20}$ = +2.4 (c = 1.36, $CHCl_3$)} was treated with DAST (23 μL, 0.19 mmol, 1.4 equiv.) in THF (5 mL). After purification by flash chromatography (cyclohexane/AcOEt, 80:20), fluoropiperidine **15e** (36 mg, 0.09 mmol, 72%) was isolated as a yellow oil. $[\alpha]_D^{20}$ = +6.6 (c = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 7.5 Hz, 3 H, CH$_2$CH_3), 1.06 (s, 9 H, CMe_3), 1.51–1.63 (3 H, 4-H and CH_2CH$_3$), 1.78–2.00 (2 H, 2-H and 6-H), 2.07 (m, 1 H, 4-H), 2.22 (s, 3 H, *N*-*Me*), 2.75 (m, 1 H, 2-H), 2.87 (m, 1 H, 6-H), 4.12 (dddd, J = 10.1, 10.1, 5.0, 5.1 Hz, 1 H, 5-H), 7.33–7.42 (m, 6 H, H_{Ar}), 7.63–7.67 (m, 4 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.1 (q, CH$_2$$CH_3$), 19.2 (s, CMe$_3$), 27.0 (q, CMe_3), 31.4 (dt, J = 23 Hz, CH_2CH$_3$), 41.4 (dt, J = 22 Hz, C-4), 45.8 (q, *N*-*Me*), 61.7 (dt, J = 21 Hz, C-2), 62.3 (t, C-6), 66.4 (d, C-5), 95.1 (ds, J = 172 Hz, C-3), 127.6 (d), 129.7 (d), 134.1 (s), 135.7 (d, C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 2930, 2856, 2786, 1460, 1427, 1384, 1252, 1180, 1106, 1083, 1048 cm^{-1}. MS (EI, 70 eV): m/z (%) = 399 (2) [M]$^{+\cdot}$, 379 (12), 343 (28), 342 (100), 322 (15), 201 (11), 199 (13), 183 (18), 144 (18), 124 (30), 122 (23), 94 (11), 58 (12). HRMS: calcd. for $C_{31}H_{31}NFO$ [M + H]$^+$ 400.2467; found 400.2467.

***N*-Benzyl-3-fluoroazepane (17a) and *N*-Benzyl-2-fluoromethylpiperidine (18a):** Following the general procedure, piperidine methanol **16a**[27] (120 mg, 0.58 mmol, 1.0 equiv.) was treated with DAST (107 μL, 0.82 mmol, 1.4 equiv.) in CH_2Cl_2 (10 mL). After purification by preparative TLC on silica gel (cyclohexane/AcOEt, 90:10), fluoroazepane **17a** (61 mg, 0.29 mmol, 51%) and fluoromethylpyrrolidine **18a** (15 mg, 0.07 mmol, 12%) were isolated as yellow oils. Data for **17a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (m, 1 H), 1.50–1.70 (3 H, 5-H and 6-H), 1.71–2.10 (2 H, 4-H), 2.57 (2 H), 2.70–2.95 (2 H, 2-H and 7-H), 3.60 (d, J = 13.6 Hz, 1 H, CH_2Ph), 3.66 (d, J = 13.6 Hz, 1 H, CH_2Ph), 4.61 (dm, J = 47.9 Hz, 1 H, 3-H), 7.13–7.30 (5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (dt, J = 9 Hz, C-5), 29.3 (t, C-6), 33.5 (dt, J = 21 Hz, C-4), 56.4 (t, C-7), 59.5 (dt, J = 27 Hz, C-2), 63.1 (t, CH$_2$Ph), 92.6 (dd, J = 181 Hz, C-3), 127.0 (d), 128.2 (d), 128.7 (d), 132.7 (s, C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 3026, 2928, 2860, 1494, 1452, 1353, 1066, 1025 cm^{-1}. MS (EI, 70 eV): m/z (%) = 207 (30) [M]$^{+\cdot}$, 206 (14), 174 (45), 160 (16), 146 (6), 130 (17), 116 (28), 92 (11), 91 (100), 84 (6), 65 (12). HRMS: calcd. for $C_{13}H_{25}NF$ [M + H]$^+$ 208.1496; found 208.1496. Data for **18a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27–1.57 (4 H), 1.65–1.74 (2 H, 3-H, 4-H and 5-H), 2.04 (ddd, J = 11.6, 10.3, 3.2 Hz, 1 H, 6-H), 2.61 (m, 1 H, 2-H), 2.77 (ddd, J = 11.5, 4.2, 4.2 Hz, 1 H, 6-H), 3.34 (d, J = 13.7 Hz, 1 H, CH_2Ph), 4.08 (d, J = 13.7 Hz, 1 H, CH_2Ph), 4.48 (ddd, J = 48.3, 9.9, 3.5 Hz, 1 H, 2′-H), 4.61 (ddd, J = 47.4, 9.9, 5.5 Hz, 1 H, 2′-H), 7.20–7.38 (5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8 (t), 23.5 (t, C-4, C-5), 28.3 (dt, J = 8 Hz, C-3), 52.0 (t, C-6), 59.9 (t, CH$_2$Ph), 60.0 (dd, J = 18 Hz, C-2), 86.4 (dt, J = 169 Hz, C-2′), 126.8 (d), 128.2 (d), 128.9 (d), 139.4 (s, C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 3028, 2934, 2857, 2797, 1494, 1452, 1372, 1339, 1131, 1116, 1082, 1055, 1015 cm^{-1}. MS (EI, 70 eV): m/z (%) = 207 (4) [M]$^{+\cdot}$, 175 (15), 174 (100), 130 (3), 92 (7), 91 (85), 65 (7), 55 (3). HRMS: calcd. for $C_{13}H_{25}NF$ [M + H]$^+$ 208.1496; found 208.1496.

***N*-Benzyl-3-ethyl-3-fluoroazepane (17b):** Following the general procedure, piperidinol **16b** (111 mg, 0.48 mmol, 1.0 equiv.) was treated with DAST (87 μL, 0.67 mmol, 1.4 equiv.) in CH_2Cl_2 (6 mL). After purification by flash chromatography on silica gel (pentane/Et_2O, 90:10), fluoroazepane **17b** (70 mg, 0.30 mmol, 63%) was isolated as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70 (m, 3 H, CH$_2$CH_3), 1.34–1.92 (8 H, 4-H, 5-H, 6-H and CH_2CH$_3$), 2.45 (m, 1 H, 7-H), 2.58 (m, 1 H, 7-H), 2.67–2.73 (2 H, 2-H), 3.57 (d, J = 13.5 Hz, 1 H, CH_2Ph), 3.62 (d, J = 13.5 Hz, 1 H, CH_2Ph), 7.13–7.19 (1 H, H_{Ar}), 7.16–7.28 (4 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.1 (dq, J = 5 Hz, CH$_2$CH_3), 21.6 (dt, J = 5 Hz, C-5), 30.9 (t, C-6), 31.0 (dt, J = 23 Hz), 37.5 (dt, J = 24 Hz, C-4 and CH_2CH$_3$), 57.8 (t, C-7), 63.6 (dt, J = 30 Hz, C-2), 64.0 (t, CH$_2$Ph), 99.8 (ds, J = 168 Hz, C-3), 126.9 (d), 128.1 (d), 128.9 (d), 139.9 (s) ppm. IR (film): $\tilde{\nu}$ = 2926, 1494, 1452, 1351, 1111, 968, 910 cm^{-1}. MS (EI, 70 eV): m/z (%) = 235 (40) [M]$^{+\cdot}$, 215 (16), 200 (17), 186 (10), 174 (11), 160 (47), 158 (11), 146 (13), 144 (15), 134 (25), 120 (19), 92 (11), 91 (100), 65 (11). HRMS: calcd. for $C_{13}H_{25}NF$ [M + H]$^+$ 236.1809; found 236.1809.

***N*-Benzyl-3-allyl-3-fluoroazepane (17c):** Following the general procedure, piperidinol **16c** (110 mg, 0.45 mmol, 1.0 equiv.) was treated with DAST (83 μL, 0.63 mmol, 1.4 equiv.) in CH_2Cl_2 (6 mL). After purification by flash chromatography on silica gel (pentane/Et_2O, 90:10), fluoroazepane **17c** (85 mg, 0.34 mmol, 76%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.52 (2 H), 1.56–1.92 (4 H, 4-H, 5-H, 6-H), 2.26 (ddd, J = 21.5, 7.2, 6.5 Hz, 2 H, CH_2CH=CH$_2$), 2.45 (ddd, J = 12.5, 8.2, 4.4 Hz, 1 H, 7-H), 2.60 (m, 1 H, 7-H), 2.73 (d, J = 15.7 Hz, 2 H, 2-H), 3.67 (s, 2 H, CH_2Ph), 4.99 (m, 1 H, CH$_2$CH=CH_2), 5.06 (m, 1 H, CH$_2$CH=CH_2), 5.77 (dddd, J = 17.2, 10.1, 7.2, 7.2 Hz, 1 H, CH$_2$CH=CH$_2$), 7.21–7.35 (5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (dt, J = 4 Hz, C-5), 30.8 (t, C-6), 38.1 (dt, J = 23 Hz, CH$_2$CH=CH$_2$), 43.9 (dt, J = 23 Hz, C-4), 57.6 (t, C-7), 63.7 (dt, J = 28 Hz, C-2), 63.8 (t, CH$_2$Ph), 98.3 (ds, J = 170 Hz, C-3) 118.3 (t, CH$_2$CH=CH$_2$), 127.0 (d), 128.2 (d), 128.8 (d, C_{Ar}), 133.0 (dd, J = 5 Hz, CH$_2$$C$H=CH$_2$), 139.8 (s, C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 2928, 1641, 1494, 1452, 1351, 1268, 1106, 993 cm^{-1}. MS (EI, 70 eV): m/z (%) = 247 (12) [M]$^{+\cdot}$, 246 (10), 227 (21), 170 (11), 160 (15), 158 (18), 146 (10), 134 (13), 120 (14), 92 (11), 91 (100), 65 (12). HRMS: calcd. for $C_{13}H_{25}NF$ [M + H])$^+$ 248.1809; found 248.1809.

***N*-Benzyl-3-benzyl-3-fluoroazepane (17d):** Following the general procedure, piperidinol **16d** (47 mg, 0.16 mmol, 1.0 equiv.) was treated with DAST (29 μL, 0.22 mmol, 1.4 equiv.) in THF (4 mL). After purification by flash chromatography on silica gel (cyclohexane/AcOEt, 95:5), fluoroazepane **17d** (32 mg, 0.30 mmol, 76%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35–1.53 (2 H), 1.56–1.67 (2 H), 1.70 (m, 1 H), 1.76 (m, 1 H, 4-H, 5-H and 6-H), 2.43 (ddd, J = 12.5, 8.3, 4.5 Hz, 1 H, 7-H), 2.62 (m, 1 H, 7-H), 2.67–2.88 (4 H, 2-H and CH_2Ph), 3.58 (s, 2 H, *N*-CH_2Ph), 7.04–7.29 (10 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (dt, J = 5 Hz, C-5), 30.8 (t, C-6), 30.9 (dt, J = 23 Hz, C-4), 45.2 (dt, J = 21 Hz, *C*H_2Ph), 57.7 (t, C-7), 63.9 (t, *N*-*C*H_2Ph), 64.0 (dt, J = 30 Hz, C-2), 99.2 (ds, J = 171 Hz, C-3), 126.4 (d), 127.0 (d), 128.0 (d), 128.2 (d), 128.9 (d), 130.7 (d), 136.7 (s), 139.8 (s, C_{Ar}) ppm. IR (film): $\tilde{\nu}$ = 3027, 2926, 1603, 1495, 1453, 1263, 1107, 1077, 1009 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 297 (7) $[M]^{+\cdot}$, 278 (9), 277 (41), 186 (48), 160 (11), 129 (8), 120 (16), 115 (11), 92 (9), 91 (100), 65 (10). HRMS: calcd. for $C_{13}H_{25}NF$ $[M + H]^+$ 298.1965; found 298.1965.

Acknowledgments

Johnson & Johnson is greatly acknowledged for financial support (Focus Giving Grant to J. C.)

[1] a) N. C. Craig, A. Chen, K. H. Suh, S. Klee, G. C. Mellau, B. P. Winnewisser, M. Winnewisser, *J. Am. Chem. Soc.* **1997**, *119*, 4789–4790; b) C. R. S. Briggs, M. J. Allen, D. O'Hagan, D. J. Tozer, A. M. Z. Slawin, A. E. Goeta, J. A. K. Howard, *Org. Biomol. Chem.* **2004**, *2*, 732–740; c) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643; d) M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231 and references herein; e) M. Schuler, D. O'Hagan, A. M. Z. Slawin, *Chem. Commun.* **2005**, 4324–4326; f) J. P. Bégué, D. Bonnet-Delpont, *Actual. Chim.* **2006**, *301–302*, 83–87.

[2] P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C.-H. Wong, *Angew. Chem. Int. Ed.* **2005**, *44*, 192–212.

[3] a) G. S. Lal, G. P. Pez, R. J. Pesaresi, F. M. Prozonic, H. Cheng, *J. Org. Chem.* **1999**, *64*, 7048–7054; b) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6119; c) N. Yoneda, *J. Fluorine Chem.* **2004**, *125*, 7–17; d) R. P. Singh, J. M. Shreeve, *Acc. Chem. Res.* **2004**, *37*, 31–44; e) M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2005**, *44*, 214–231; f) X. Bi, *Synlett* **2006**, 2515–2516.

[4] W. J. Middleton, *J. Org. Chem.* **1975**, *40*, 574–578.

[5] For a review on the uses of DAST and Deoxofluor, see: R. P. Singh, J. M. Shreeve, *Synthesis* **2002**, 2561–2578.

[6] a) K. C. Nicolaou, T. Ladduwahetty, J. L. Randall, A. Chucholowski, *J. Am. Chem. Soc.* **1986**, *108*, 2466–2467; b) P. Borrachero-Moya, F. Cabrera-Escribano, M. Gómez-Guillén, F. Madrid-Diaz, *Tetrahedron Lett.* **1997**, *38*, 1231–1234; c) K. Dax, M. Albert, J. Ortner, B. J. Paul, *Carbohydr. Res.* **2000**, *327*, 47–86; d) P. Borrachero, F. Cabrera-Escribano, A. T. Carmona, M. Gómez-Guillén, *Tetrahedron: Asymmetry* **2000**, *11*, 2927–2946.

[7] a) L. Somekh, A. Shanzer, *J. Am. Chem. Soc.* **1982**, *104*, 5836–5837; b) D. Gani, P. B. Hitchcock, D. W. Young, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1363–1372; c) T. Rosen, D. T. W. Chu, I. M. Lico, P. B. Fernandes, K. Marsh, L. Shen, V. G. Cepa, A. G. Pernet, *J. Med. Chem.* **1988**, *31*, 1598–1611; d) R. H. Furneaux, G. J. Gainsford, J. M. Mason, P. C. Tyler, *Tetrahedron* **1995**, *51*, 12611–12630; e) G. V. De Lucca, *J. Org. Chem.* **1998**, *63*, 4755–4766; f) D. F. Hook, F. Gessier, C. Noti, P. Kast, D. Seebach, *ChemBioChem* **2004**, *5*, 691–706; g) C. Ye, J. M. Shreeve, *J. Fluorine Chem.* **2004**, *125*, 1869–1872; h) P. E. Floreancing, S. E. Swalley, J. W. Trauger, P. B. Derwan, *J. Am. Chem. Soc.* **2000**, *122*, 6342–6350.

[8] a) L. S. Jeong, H. R. Moon, S. J. Yoo, S. N. Lee, M. W. Chun, Y.-H. Lim, *Tetrahedron Lett.* **1998**, *39*, 5201–5204; b) A. T. Carmona, P. Borrachero, F. Cabrera-Escribano, J. Diánez, D. Estrada, A. López-Castro, R. Ojeda, M. Gómez-Guillén, S. Pérez-Garrido, *Tetrahedron: Asymmetry* **1999**, *10*, 1751–1764.

[9] a) J. Filmon, D. Grée, R. Grée, *J. Fluorine Chem.* **2001**, *107*, 271–273; b) P. Lakshmipathi, D. Grée, R. Grée, *Org. Lett.* **2002**, *4*, 451–454.

[10] a) S. Castillon, A. Dessinges, R. Faghih, G. Lucaks, A. Olesker, T. T. Thang, *J. Org. Chem.* **1985**, *50*, 4913–4917; b) Y. Vera-Ayoso, P. Borrachero, F. Cabrera-Escribano, A. T. Carmona, M. Gómez-Guillén, *Tetrahedron: Asymmetry* **2004**, *15*, 429–444.

[11] a) S. Rozen, Y. Faust, H. Ben-Yakov, *Tetrahedron Lett.* **1979**, *20*, 1823–1826; b) C. Burnell-Curty, R. Faghih, T. Pagano, R. F. Henry, P. A. Lartey, *J. Org. Chem.* **1996**, *61*, 5153–5154; c) A. Boukerb, D. Grée, M. Laabassi, R. Grée, *J. Fluorine Chem.* **1998**, *88*, 23–27; d) S. Canova, V. Bellosta, S. Mignani, A. Bigot, J. Cossy, *Org. Lett.* **2006**, *8*, 2091–2094.

[12] a) S. E. Boiadjiev, D. A. Lightner, *J. Org. Chem.* **1997**, *62*, 399–404; b) D. J. Hallett, U. Gerhard, S. C. Goodacre, L. Hitzel, T. J. Sparey, S. Thomas, M. Rowley, *J. Org. Chem.* **2000**, *65*, 4984–4993; c) G. L. Grunewald, T. M. Caldwell, Q. Li, K. R. Criscione, *J. Med. Chem.* **2001**, *44*, 2849–2856; d) G. Giannini, M. Marzi, G. P. Moretti, S. Penco, M. O. Tiniti, S. Pesci, F. Lazzaro, F. De Angelis, *Eur. J. Org. Chem.* **2004**, 2411–2420.

[13] a) S. S. Yang, T. R. Beattie, *J. Org. Chem.* **1981**, *46*, 1718–1720; b) C. S. V. Houge-Frydrych, I. L. Pinto, *Tetrahedron Lett.* **1989**, *30*, 3349–3350; c) G. Burrell, J. M. Evans, G. E. Jones, G. Stemp, *Tetrahedron Lett.* **1990**, *31*, 3649–3652; d) S.-J. Shiuey, I. Kulesha, E. G. Baggiolini, M. R. Uskoković, *J. Org. Chem.* **1990**, *55*, 243–247.

[14] a) P. Lafargue, P. Guenot, J. P. Lellouche, *Synlett* **1995**, 171–172; b) A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno, D. R. Williams, *Org. Lett.* **2000**, *2*, 1165–1168; c) T. Nishio, Y. Kurokawa, Y. Narasaki, T. Tokunaga, *Heterocycles* **2006**, *67*, 247–254.

[15] a) J. Cossy, C. Dumas, P. Michel, D. Gomez Pardo, *Tetrahedron Lett.* **1995**, *36*, 549–552; b) J. Cossy, C. Dumas, D. Gomez Pardo, *Synlett* **1997**, 905–906; c) J. Cossy, C. Dumas, D. Gomez Pardo, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1343–1344; d) J. Wilken, M. Kossenjans, W. Saak, D. Haase, S. Pohl, J. Martens, *Liebigs Ann. Recl.* **1997**, 573–579; e) N. Langlois, O. Calvez, *Synth. Commun.* **1998**, *28*, 4471–4477; f) P. W. Davis, S. A. Osgood, N. Hébert, K. G. Sprankle, E. E. Swayze, *Biotechnol. Bioeng.* **1999**, *61*, 143–154; g) J. Cossy, C. Dumas, D. Gomez Pardo, *Eur. J. Org. Chem.* **1999**, 1693–1699; h) P. Michel, A. Rassat, *J. Org. Chem.* **2000**, *65*, 2572–2573; i) J. Cossy, O. Mirguet, D. Gomez Pardo, *Synlett* **2001**, 1575–1577; j) A. Brandi, S. Cicchi, V. Paschetta, D. Gomez Pardo, J. Cossy, *Tetrahedron Lett.* **2002**, *43*, 9357–9359; k) A. Deyine, J.-M. Delcroix, N. Langlois, *Heterocycles* **2004**, *64*, 207–214; l) I. Déchamps, D. Gomez Pardo, P. Karoyan, J. Cossy, *Synlett* **2005**, 1170–1172; m) R. Roudeau, D. Gomez Pardo, J. Cossy, *Tetrahedron* **2006**, *62*, 2388–2394; n) M. Mena, J. Bonjoch, D. Gomez Pardo, J. Cossy, *J. Org. Chem.* **2006**, *71*, 5930–5935; o) I. Déchamps, D. Gomez Pardo, J. Cossy, *Arkivoc* **2007**, 38–45.

[16] I. Déchamps, D. Gomez Pardo, J. Cossy, *Synlett* **2007**, 263–267.

[17] a) S. Itsuno, K. Ito, A. Hirao, S. Nakahama, *J. Chem. Soc. Perkin Trans. 1* **1984**, 2887–2893; b) V. I. Tararov, R. Kadyrov, T. H. Riermeier, A. Boerner, *Synthesis* **2002**, 375–380.

[18] The ratios were calculated after examination of the ^{1}H NMR spectra of the crude material.

[19] These prolinols were prepared by using classical esterification, benzylation, protection and reduction steps. For example of preparation, see ref.[15m]

[20] C. Herdeis, H. P. Hubmann, H. Lotter, *Tetrahedron: Asymmetry* **1994**, *5*, 119–522.

[21] C. Heindl, H. Hübner, P. Gmeiner, *Tetrahedron: Asymmetry* **2003**, *14*, 3153–3172.
[22] J. Bejjani, F. Chemla, M. Audouin, *J. Org. Chem.* **2003**, *68*, 9747–9752.
[23] Prolinols **14a**–**c** were prepared by using Seebach's methods, followed by classical reduction by $LiAlH_4$: D. Seebach, M. Boes, R. Naef, W. B. Schweizer, *J. Am. Chem. Soc.* **1983**, *105*, 5390–5398.
[24] T.-X. Métro, J. Appenzeller, D. Gomez Pardo, J. Cossy, *Org. Lett.* **2006**, *8*, 3509–3512.
[25] Benzyl and allyl neighbouring groups are reported to participate in DAST reactions in the absence of an internal nucleophile, for examples, see: a) D. Haigh, L. J. Jefcott, K. Magge, H. McNab, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2895–2900; b) C. Burnell-Curty, R. Faghih, T. Pagano, R. F. Henry, P. A. Lartey, *J. Org. Chem.* **1996**, *61*, 5153–5154.
[26] Considering the difficulty of preparing optically active 2-hydroxymethylpiperidines, the ring expansion was tested on the racemic starting material.
[27] B. Weber, J. Schwerdtfeger, R. Fröhlich, A. Göhrt, D. Hoppe, *Synthesis* **1999**, 1915.

Received: March 15, 2007
Published Online: July 30, 2007

