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Ring Expansion of Cyclic β-Amino Alcohols Induced by Diethylaminosulfur Trifluoride: Synthesis of Cyclic Amines with a Tertiary Fluorine at C3

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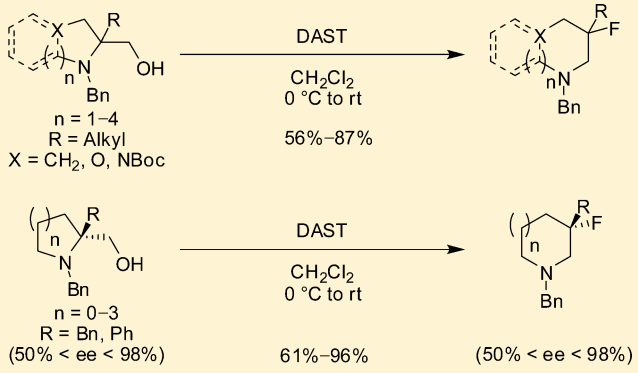
Supporting Information

ABSTRACT: As the replacement of a hydrogen atom by a fluorine atom in a compound can have an important impact on its biological properties, the development of methods allowing the introduction of a fluorine atom is of great importance. The scope and limitations of the ring expansion of cyclic 2-hydroxymethyl amines induced by diethylaminosulfur trifluoride (DAST) to produce cyclic β-fluoro amines was studied as well as the enantioselectivity of the process.



INTRODUCTION

In nature, compounds with fluorine atoms are rare as only 13 compounds have been reported to date.[1] The introduction of a fluorine atom in a molecule can have an important impact on its physical and biological properties due to the high electronegativity, the low polarizability, and the small size of the fluorine atom.[2] In the pharmaceutical industry, about 20% of the prescribed pharmaceuticals and 30% of the leading 30 blockbuster drugs by sales contain a C−F bond.[3,4] In addition, organofluorine compounds have also achieved significant advances in the area of agrochemicals and materials.[5] The majority of commercially available fluorinated compounds contains F-aryl and/or CF_3-aryl moieties; however, since compounds possessing a stereogenic center with a fluorine atom are interesting, chemists have developed new fluorinating reagents as well as ingenious methods for the enantioselective introduction of fluorinated functionality in building blocks or for a late stage fluorination.[6]

A few years ago, we had reported ring expansion of prolinols **A** to the corresponding optically active 3-fluoro piperidines **B** as well as the synthesis of racemic 3-fluoro azepanes **D** from racemic 2-hydroxymethylpiperidines **C**. These ring expansions were achieved by using DAST or Deoxo-Fluor (Scheme 1).[6a,7] The ring expansion is supposed to proceed via an intermediate aziridinium ion **F** resulting from the anchimeric assistance of the nitrogen atom, which expells the leaving group in **E**.

Here, we would like to report that the ring expansion induced by DAST can be generalized to 2-hydroxymethylazepanes, 2-hydroxymethylazocanes, and heterocyclic 2-hydroxymethyl amines such as piperazines **H**, morpholines **I**, and indolines **J** (Figure 1). Furthermore, an enantioselective ring expansion leading to optically active cyclic amines bearing a tertiary fluorine atom at C3 will also be reported.

RESULTS AND DISCUSSION

Ring Expansion of Racemic Cyclic Amino Alcohols. In order to determine the scope and the limitation of the ring expansion induced by DAST, racemic 7- and 8-membered rings **K** were synthetized by using a Schmidt rearrangement applied to cyclic β-keto esters **L** (Scheme 2).[8]

The transformation of β-keto esters **1** (n = 1, 2) to the corresponding cyclic 2-hydroxymethyl amines **4** was achieved. At first, the alkylation of **1** with different alkyl halides was performed (K_2CO_3, RX, acetone, reflux)[9] to produce the *C*-alkylated products **2** in 82% to quantitative yields (Table 1). The obtained alkylated β-keto esters **2** were then submitted to a Schmidt rearrangement using NaN_3 under acidic conditions (H_2SO_4) to afford 7- and 8-membered ring lactams **3**.[10] After reduction ($LiAlH_4$, THF, reflux) and *N*-benzylation (K_2CO_3,

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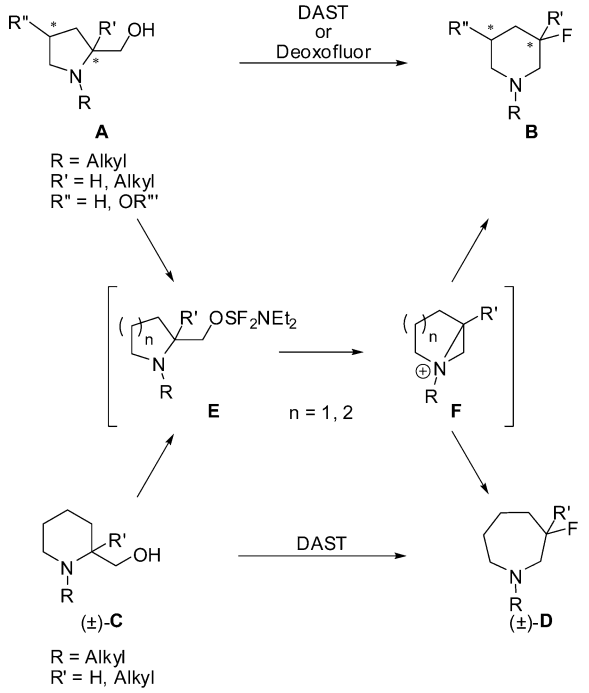
Scheme 1



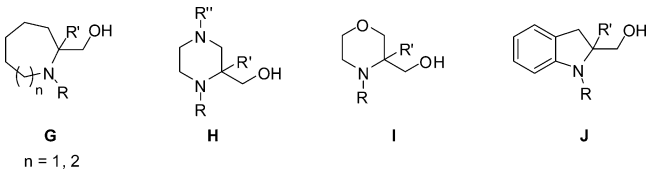
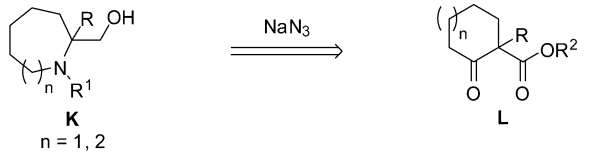


Figure 1. Amino-alcohols considered for the ring expansion.

Scheme 2

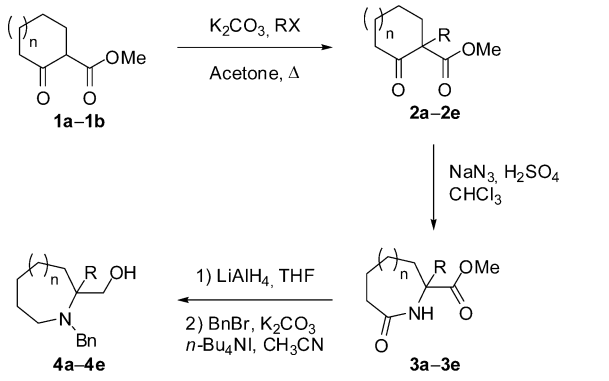


BnBr, *n*-Bu_4NI, CH_3CN, reflux), the corresponding *N*-benzyl 2-hydroxymethylazepanes **4a**–**4c** and azocanes **4d** and **4e** were isolated (yields over 2 steps 13–52%) (Table 1). Noteworthy, the Schmidt rearrangement gave lower yield in 8-membered ring lactams (**3d** and **3e**) than in 7-membered ring lactams (**3a**–**3c**).[11–13]

Compounds **4a**–**4e** were then treated with DAST (1.4 equiv, CH_2Cl_2, 0 °C to rt) to produce the corresponding expanded *β*-fluoro amines **5a**–**5e** in good to excellent yields (58–83%). The best yield was obtained for allylic derivative **5b**, which was isolated in 83% yield. It is worth noting that for a full conversion of **4**, the ring enlargement adducts **5** were the only isolated compounds obtained, and the 2-fluoromethyl cyclic amines **5′** were not detected (Table 2).

In order to study the chemoselectivity of the ring expansion induced by DAST, piperazines, morpholines as well as indolines were examined as substrates. The synthesis of *N*-alkyl-2-hydroxymethylpiperazine **8** was achieved from *N*-Boc-2-carboxylic piperazine **6**. After esterification and *N*-protection (Na_2CO_3, NaOH, H_2O), the corresponding ester **7** was isolated (55%). The alkylation of **7** was then performed by treatment

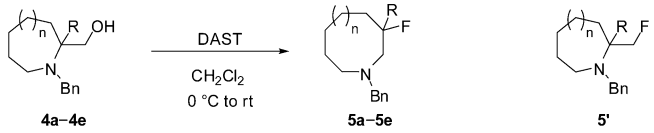
Table 1. Synthesis of Azepanes and Azocanes



entry	*n*	RX	**2** (yield %)	**3** (yield %)	**4** (yield %)
1	1	EtI	**2a** (100)	**3a** (93)	**4a** (42)
2[a]	1	AllylBr	**2b** (96)	**3b** (68)	**4b** (68)
3	1	BnBr	**2c** (97)	**3c** (74)	**4c** (64)
4	2	EtI	**2d** (82)	**3d** (21)	**4d** (62)
5	2	BnBr	**2e** (98)	**3e** (36)	**4e** (42)

[a]For the Schmidt rearrangement, CH_3SO_3H was used.

Table 2. Ring Expansion of Azepanes and Azocanes Induced by DAST



entry	**4** (R, *n*)	**5** (yield %)
1	**4a** (Et, 1)	**5a** (64)
2	**4b** (Allyl, 1)	**5b** (83)
3	**4c** (Bn, 1)	**5c** (65)
4	**4d** (Et, 2)	**5d** (58)
5	**4e** (Bn, 2)	**5e** (62)

with LDA followed by the addition of allyl bromide (THF, −78 °C to rt), and the resulting *C*-alkylated piperazine was reduced by $LiAlH_4$ (THF, rt) to produce 2-hydroxymethylpiperazine **8** (56% for the two chemical steps) (Scheme 3, eq 1).

The synthesis of 2-hydroxymethylmorpholine **12** was achieved within four steps from aminodiol **9**.[14] After reductive amination of **9**, *N*-protected aminodiol **10** was isolated in 56% yield. The transformation of **10** to morpholine **11** was realized in two steps, however in low yield[14] (14%), using chloroacetyl chloride (K_2CO_3, CH_2Cl_2, rt) followed by a basic treatment (*t*-BuOK, *t*-BuOH, reflux). After reduction by Red-Al in toluene, morpholine **12** was isolated (75%) (Scheme 3, eq 2).

2-Hydroxymethylindolines **16a**–**16c** were obtained from indoline carboxylic acid **13** within four steps. After esterification ($SOCl_2$, MeOH, rt) and *N*-protection (BnBr, K_2CO_3, *n*-Bu_4NI, CH_3CN), the indolino-ester **14** was isolated in good yield and then alkylated by treatment with LDA followed by the addition of an alkyl halide (EtI, AllylBr, or BnBr) to produce the corresponding alkylated indolines **15a**–**15c** (60%-88%). The indolines **15a**–**15c** were then reduced by $LiAlH_4$ (THF, rt) to access the desired 2-hydroxymethylindolines **16a**–**16c** (84–100%) (Scheme 3, eq 3).

Compounds **8**, **12**, and **16a**–**16c** were then treated with DAST to obtain respectively and exclusively the ring enlarge-

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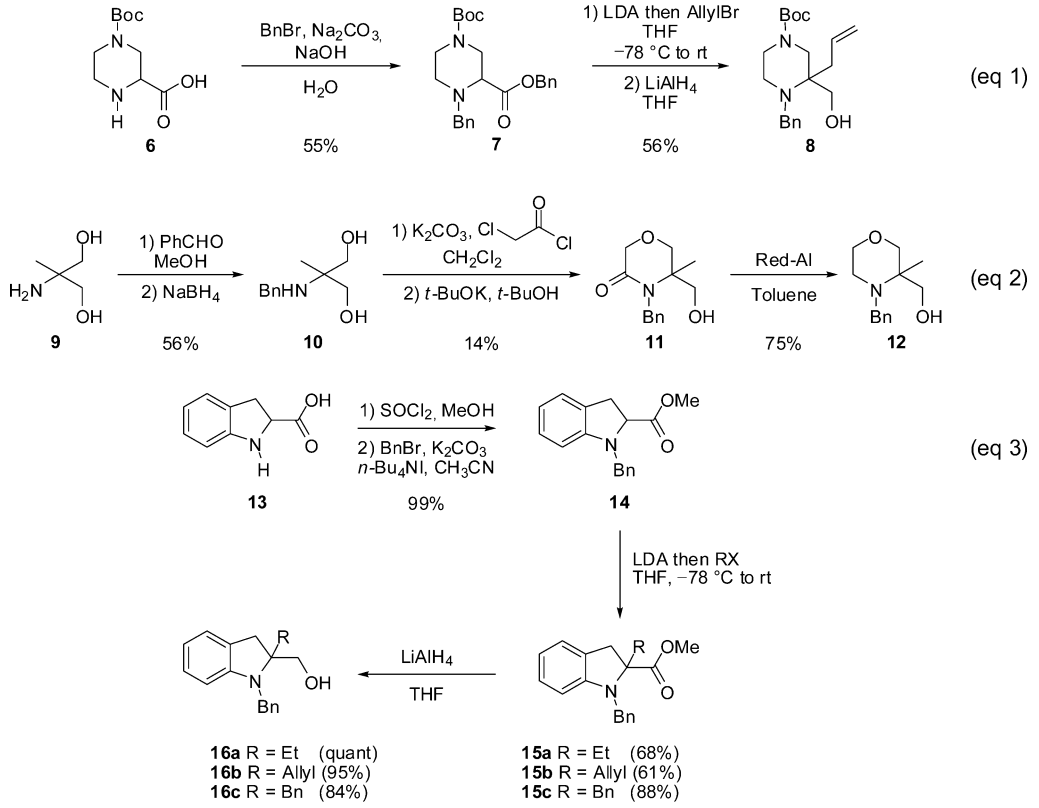
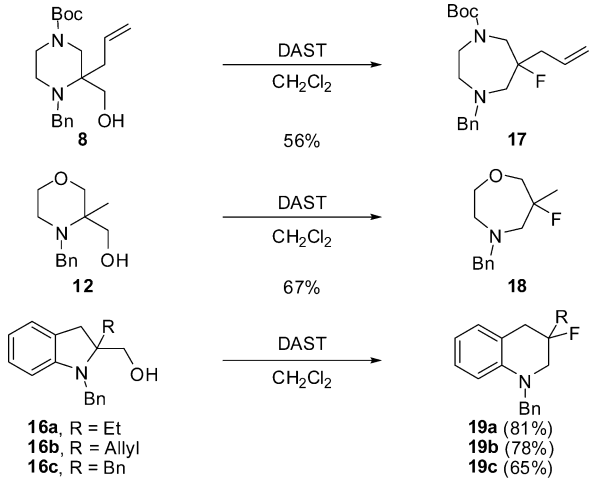
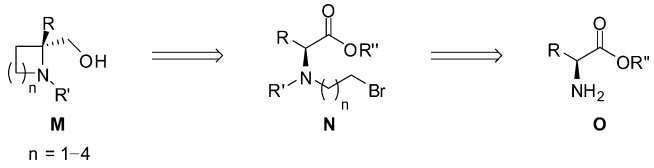
Scheme 3



Scheme 4



Scheme 5



ment adducts **17**, **18**, and **19a**–**19c** in good to excellent yields. The results are reported in Scheme 4.

Ring Expansion of Optically Active Cyclic Amino Alcohols. As previously indicated, we have reported the enantioselective ring expansion of optically active prolinols **A** to the corresponding 3-fluoro piperidines **B** (Scheme 1). In order to generalize this ring expansion to produce optically active β-fluoro pyrrolidines, piperidines, azepanes, and azocanes, possessing a tertiary fluoride at C3, the corresponding optically active 2-hydroxymethylazetidines, pyrrolidines, piperidines, and azepanes were synthetized and treated with DAST. The synthesis of cyclic β-amino alcohols **M** was planned from β-amino ester **O** via the bromo-amino esters **N**, which, after an asymmetric intramolecular cyclization involving the memory of chirality,[15] would produce the precursors of **M** (Scheme 5).

The synthesis of the desired cyclic β-amino alcohols **23a**–**23d** was achieved from amino ester **20**.[16] Amino ester **20** was transformed to the *N*-Boc, *N*-bromoalkylamino esters **21a**–**21d** within three or four steps. After *N*-alkylation (K_2CO_3, DMF, 70 °C) followed by treatment with Boc_2O (1.5 equiv) and *O*-debenzylation (H_2, Pd/C), the hydroxy esters were transformed to the corresponding bromo esters **21a** and **21b** using CBr_4/PPh_3 (Scheme 6, eq 1). To introduce the side chain in compounds **21c** and **21d**, a reductive amination was realized, and after the protection of the amine with a Boc group (1.5 equiv), the treatment with CBr_4 (1.3 equiv) in presence of PPh_3 (1.6 equiv) led to the desired bromo amines **21c** and **21d** (Scheme 6, eq 2 and 3). When these bromide derivatives were treated with potassium hexamethyldisilazide (KHMDS, 1.2 equiv) in DMF at −60 °C for 30 min, the corresponding cyclic amino esters **22a**–**22d** were isolated in yields which varied from 22 to 90% but always with excellent enantiomeric excesses (94–98%).[17] After deprotection (TFA, CH_2Cl_2, rt), *N*-benzylation (BnBr, K_2CO_3, *n*-Bu_4NI, CH_3CN, reflux), and reduction with $LiAlH_4$ (THF, rt), the desired 2-hydroxymethylcyclic amines **23a**–**23d** were isolated in good yields (Scheme 6, eq 4).

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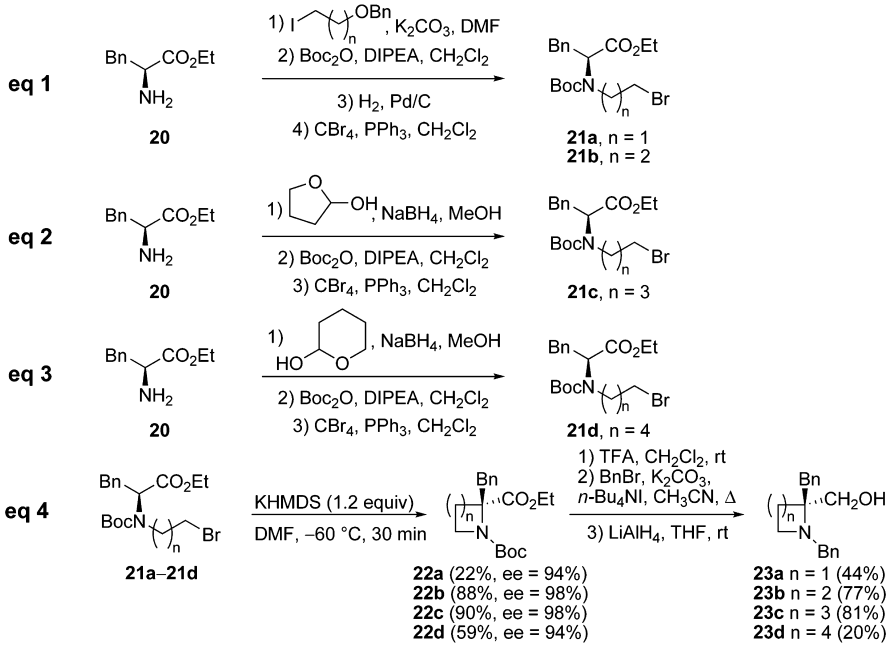
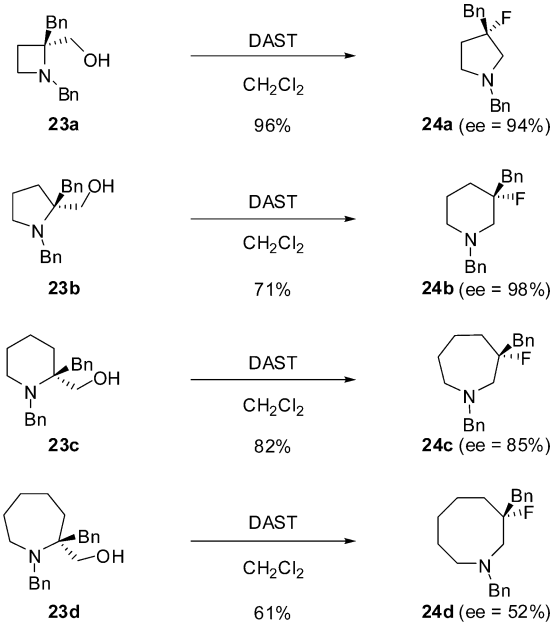
Scheme 6



The cyclic β-amino alcohols **23a–23d** were then treated with DAST (1.4 equiv, CH_2Cl_2, 0 °C to rt), and the corresponding 3-fluorocyclic amines **24a–24d** were isolated in good yields (61–96%).[18] Although the ring expansion of **23a** and **23b** to the corresponding β-fluoro pyrrolidine **24a** and β-fluoro piperidine **24b** is highly enantioselective, an erosion of the enantiomeric excess was noticed for the transformation of **23c** (ee = 98%) to **24c** (ee = 85%), and this erosion was worse for the transformation of **23d** (ee = 94%) to **24d** (ee = 52%) (Scheme 7).

When the size of the cyclic amines **23** increased, the enantioselectivity of the ring expansion decreased. This phenomenon is probably related to the structure of the intermediate aziridinium ion. For cyclic 2-hydroxymethyl amines possessing a small ring such as compounds **P**, the selective attack of the fluorine anion at the C2 position, leading exclusively to the ring expansion adduct **R**, can be explained by a nonsymmetrical intermediate aziridinium ion **Q** in which the C2–N bond is longer than the C2′–N bond (Scheme 8, eq 1). Moreover, the presence of a quaternary center at C2 results in the stabilization of a partially positive charge at C2 correlated with a weakened C2–N bond. Thus, cleavage of the C2–N bond induced by the nucleophilic attack of the fluorine anion at the most electrophilic carbon is favored to afford **R**. When cyclic 2-hydromethyl amines with larger rings such as **S** are involved, the intermediate aziridinium ion **T** can be in equilibrium with a stable intermediate carbocation **U**. As the C2–N bond is longer than it was previously in eq 1, an epimerization of the quaternary center can occur (Scheme 8, eq 2).

Scheme 7



To investigate the formation of an intermediate carbocation, the alkyl group on the quaternary center was replaced by a phenyl, and the rearrangement of 2-hydroxymethylpyrrolidine **28**, which possesses a phenyl substituent at C2, was investigated. Thus, the synthesis of 2-hydroxymethylpyrrolidine **28** was achieved from phenylglycine ethyl ester **25**. After the introduction of the side chain (3-bromopropanol, K_2CO_3, DMF, reflux) and the protection of the amine (Boc_2O, DIPEA, CH_2Cl_2), amino ester **25** was transformed to the bromide derivative **26** (CBr_4, PPh_3, CH_2Cl_2). When the bromide derivative was treated with KHMDS (1.2 equiv) in DMF, the reaction did not go to completion (69% based on resting starting material brsm) and the cyclized product **27** was isolated in a modest yield (19%). The pyrrolidino ester **27** was then transformed within three steps (deprotection, benzylation, reduction) to the desired prolinol **28** with a modest enantiomeric excess (ee = 50%). When **28** was treated with DAST (1.4 equiv) in CH_2Cl_2, the ring enlargement adduct was exclusively obtained in an excellent yield (87%) and with a similar enantiomeric excess than the starting material **28** (Scheme 9). This example showed that the erosion of the enantiomeric excess is related to the ring size of the cyclic

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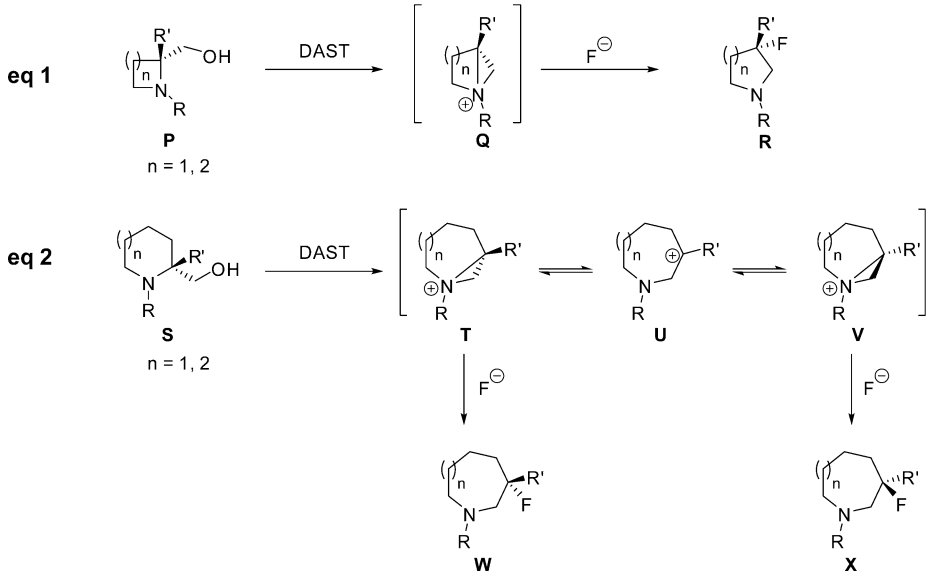
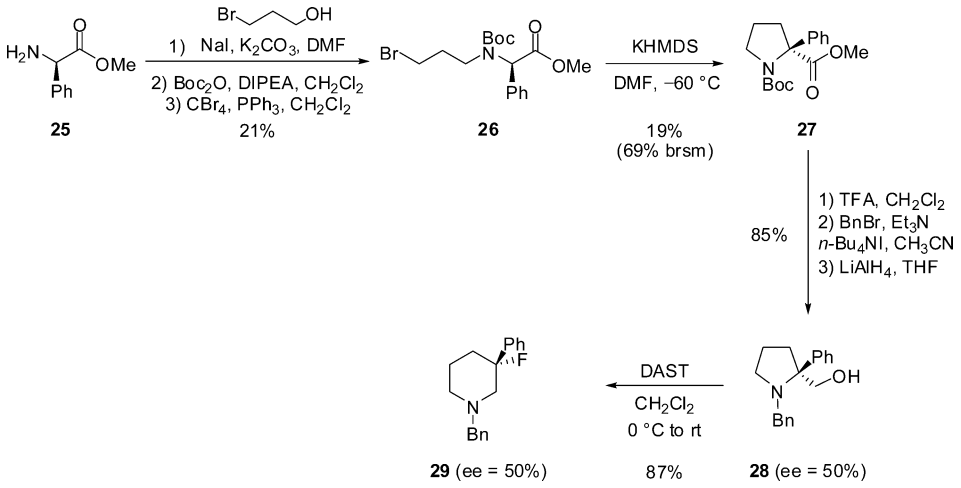
Scheme 8



Scheme 9



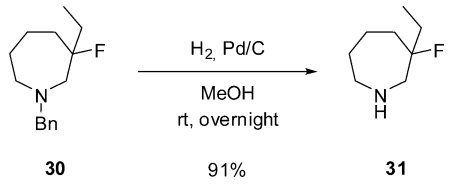
amino alcohols and not to the stability of a possible intermediate carbocation.

It is worth noting that the absolute configuration of the stereogenic center in **24b**·HCl was determined by X-ray diffraction and confirmed the expected absolute configuration of the stereogenic center, which is *R* (see ORTEP in the Supporting Information).

We have to point out that the deprotection of the cyclic *β*-fluoro amines was investigated. When racemic *β*-fluoro azepane **30** was submitted to classical hydrogenolysis conditions (H_2, Pd/C, MeOH, rt), the deprotected fluoroazepane **31** was obtained with an excellent yield of 91% (Scheme 10). This method could be generalized for the deprotection of other *β*-fluoro amines.

In summary, the ring expansion of cyclic 2-hydroxymethyl amines possessing a quaternary center at C2 induced by DAST is a general and highly selective method allowing the formation of cyclic amines with a tertiary fluoride at C3. Furthermore, the ring expansion is highly enantioselective when applied to 2-hydroxymethylazetidines and prolinols, but when applied to cyclic 2-hydroxymethyl amines with larger ring, the enantioselectivity is decreasing. The obtained 3-fluoro cyclic amines can be useful building blocks, as they can be deprotected and then involved in the synthesis of biologically active compounds.

Scheme 10



■ EXPERIMENTAL SECTION

The synthesis of compounds **2a**−**2c**, **2e**, **14**, **22a**−**22d**, and **30** has been already described in the literature.[7,14,19]

All reactions were run under an atmosphere of argon. ^{1}H NMR spectra were recorded on a NMR apparatus at 400 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane as internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances, integration). ^{13}C NMR spectra were recorded on a NMR apparatus at 100 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as internal standard ($CDCl_3$, δ 77.0

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ppm or DMSO-d_6, δ 40.4 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 (MS-EI) were recorded a tandem GC apparatus (12 m capillary column) MS apparatus (70 eV). Infrared (IR) spectra were recorded on an IR apparatus (IRFT); wavenumbers are indicated in cm^{-1}. TLC was performed on $60F_{254}$ silica gel plates and visualized with a UV lamp (254 nm) or by using solutions of $KMnO_4/K_2CO_3$/AcOH in water followed by heating. Column chromatography was performed with silica gel (40−63 μm). High resolution mass spectra (HRMS) were performed by an orbitrap mass spectrometer using a positive electrospray ionization.

General Procedure 1. To a solution of cyclic β-keto ester of type **1** (1 equiv) and alkyl halide (2 equiv) in acetone was added K_2CO_3. After refluxing for 12 h, the reaction media was cooled, filtered through Celite, and washed with CH_2Cl_2. The solvents were removed under reduced pressure, and the crude was purified by flash chromatography on silica gel using a mixture of PE and EtOAc leading to the desired compound of type **2**.

General Procedure 2. To a solution of cyclic β-keto ester of type **2** (1 equiv) and concentrated sulfuric acid in excess (50 equiv) in $CHCl_3$ was added per portions over 2 h NaN_3 (2 equiv). The reaction media was vigorously stirred at rt for 3 h before iced water was added. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel using a mixture of CH_2Cl_2 and EtOAc to obtain the desired lactam of type **3**.

General Procedure 3. To a solution of lactam of type **3** (1 equiv) in THF was added $LiAlH_4$ (5 equiv) at 0 °C. The reaction media was refluxing for 2 h before being hydrolyzed at 0 °C successively by water (10.5 equiv), a 0.15 M aqueous solution of NaOH (10.5 equiv), and water (26.25 equiv). The residue was then filtered over Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure leading to the desired amino alcohol. To a solution of this alcohol (1 equiv) in CH_3CN were successively added BnBr (1.1 equiv), K_2CO_3 (1.5 equiv), and n-Bu_4NI (0.15 equiv). The reaction media was refluxed for 4 h before being concentrated under reduced pressure. The crude was diluted with water/EtOAc 1/1, the layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with a mixture of PE and EtOAc affording the *N*-benzylamino alcohol of type **4**.

General Procedure 4. To a solution of β-amino alcohol (1 equiv) in CH_2Cl_2 was slowly added DAST (1.4 equiv) at 0 °C. The reaction media was stirred 1 h at 0 °C followed by 1 h at rt before a saturated aqueous solution of Na_2CO_3 was added. The layers were separated. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel using a mixture of PE and Et_2O to obtain the fluorinated compound.

General Procedure 5. To a solution of amino ester (1 equiv) in THF was added at −78 °C LDA (1.1 equiv). The reaction media was stirred at this temperature for 20 min. Alkyl halide (1.2 equiv) was added in the reaction media. The temperature was risen slowly at rt over 4 h and water was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel using a mixture of PE and EtOAc leading to the desired compound.

General Procedure 6. To a solution of ester (1 equiv) in THF was added $LiAlH_4$ (2 equiv) at 0 °C. The reaction media was stirred for 2 h at rt before being hydrolyzed at 0 °C successively by water (4.2 equiv), a 0.15 M aqueous solution of NaOH (4.2 equiv), and water (10.5 equiv). The residue was then filtered over Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure leading to the desired amino alcohol.

General Procedure 7. To a solution of the amino ester (1 equiv) in CH_2Cl_2 was added TFA (10 equiv) at 0 °C. The mixture was stirred at rt before a saturated aqueous solution of $NaHCO_3$ was added at 0 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to afford the desired compound.

General Procedure 8. To a solution of the amine (1 equiv) in CH_3CN were successively added BnBr (1.1 equiv), K_2CO_3 (1.5 equiv), and n-Bu_4NI (0.5 equiv). The reaction media was stirred under reflux for 8 h before being cooled. Water was added, and the mixture was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel using a mixture of PE and EtOAc to afford the desired compound.

Methyl 1-Ethyl-2-oxocycloheptanecarboxylate (2d). Prepared according to **General Procedure 1**, **1d** (0.92 mL, 5.9 mmol, 1 equiv) was alkylated by ethyl iodide (0.94 mL, 11.7 mmol, 2 equiv) in acetone (15 mL). The crude was purified by flash chromatography on silica gel (PE/EtOAc 95/5) leading to the desired compound **2d** (958 mg, 4.8 mmol, 82%), isolated as a colorless oil: IR (neat) 2933, 2861, 1734, 1702, 1454, 1224, 1145, 1002 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.60 (s, 3H), 2.50 (m, 1H), 2.36 (m, 1H), 2.02 (m, 1H), 1.90 (m, 2H), 1.66−1.30 (m, 7H), 0.73 (t, 3H, J = 8.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2 (s), 172.8 (s), 63.1 (s), 51.8 (q), 41.9 (t), 32.2 (t), 29.7 (t), 28.2 (t), 25.4 (t), 24.7 (t), 8.9 (q) ppm; MS m/z (%) 198 ($M^{+\cdot}$, 1), 170 (28), 166 (22), 141 (18), 139 (21), 138 (51), 137 (29), 115 (14), 110 (20), 109 (20), 102 (21), 98 (78), 97 (19), 96 (18), 95 (26), 87 (30), 83 (47), 81 (32), 69 (44), 67 (27), 59 (48), 55 (100), 53 (16); HRMS (ESI) *Calcd. for* $C_{11}H_{18}O_3Na$ *(MNa)*$^+$, 221.1148, found 221.1146.

Methyl 2-Ethyl-7-oxoazepane-2-carboxylate (3a). Prepared according to **General Procedure 2**, **2a**[16] (470 mg, 2.55 mmol, 1 equiv) was rearranged in $CHCl_3$ (5 mL). The crude was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc 80/20) affording **3a** (470 mg, 2.36 mmol, 93%), isolated as a white solid: mp 122−124 °C; IR (neat) 3216, 3082, 2937, 1735, 1651, 1435, 1411, 1233, 1205, 1182, 1158, 1119, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (s br, NH), 3.75 (s, 3H), 2.49 (m, 1H), 2.32 (m, 1H), 2.16 (m, 1H), 1.93−1.63 (m, 4H), 1.81 (q, 2H, J = 7.6 Hz), 1.56 (m, 1H), 0.87 (t, 3H, J = 7.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (s), 173.6 (s), 63.6 (s), 52.6 (q), 37.8 (t), 37.4 (t), 33.4 (t), 26.1 (t), 22.9 (t), 8.1 (q) ppm; MS m/z (%) 170 ($M^+ - C_2H_5\cdot$, 1), 142 (16), 140 (100), 97 (42), 95 (32), 82 (20), 67 (11), 56 (28), 55 (61), 54 (12); HRMS (ESI) *Calcd. for* $C_{10}H_{17}NO_3Na$ *(MNa)*$^+$, 222.1101, found 222.1099.

Methyl 2-Allyl-7-oxoazepane-2-carboxylate (3b). To a solution of **2b**[16] (1.21 g, 6.1 mmol, 1 equiv) in $CHCl_3$ (30 mL) were added at 0 °C CH_3SO_3H (3.95 mL, 61 mmol, 10 equiv) and NaN_3 (1.56 g, 24 mmol, 4 equiv). The reaction media was refluxed for 2 h before iced water was added. The media was neutralized by an aqueous solution of ammonia 35% (5 mL). The layers were separated; the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc 80/20) affording **3b** (807 mg, 3.82 mmol, 68%), isolated as a white solid: mp 111−113 °C; IR (neat) 3216, 3079, 2953, 2921, 1736, 1648, 1447, 1405, 1268, 1200, 1172, 1148, 1099, 1058, 993 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (s br, 1H), 5.60 (m, 1H), 5.23 (m, 2H), 3.78 (s, 3H), 2.61 (dddd, 1H, J = 14.1, 6.2, 6.2, and 1.4 Hz), 2.54 (m, 1H), 2.44−2.25 (m, 3H), 1.91 (m, 1H), 1.78−1.67 (m, 2H), 1.60−1.50 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (s), 173.2 (s), 130.7 (d), 121.5 (t), 62.4 (s), 52.6 (q), 45.5 (t), 38.5 (t), 37.7 (t), 26.4 (t), 22.8 (t) ppm; MS m/z (%) 170 ($M^{+\cdot}$−Allyl·, 25), 152 (51), 142 (100), 110 (43), 109 (41), 107 (11), 83 (10), 82 (99), 81 (13), 79 (15), 68 (28), 67 (83), 55 (53), 54 (30), 53 (11); HRMS (ESI) *Calcd. for* $C_{11}H_{17}NO_3Na$ *(MNa)*$^+$, 234.1101, found 234.1099.

Methyl 2-Benzyl-7-oxoazepane-2-carboxylate (3c). Prepared according to **General Procedure 2**, **2c**[16] (500 mg, 2.03 mmol, 1 equiv) was rearranged in $CHCl_3$ (5 mL). The crude was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc 80/20) affording **3c** (386 mg, 1.48 mmol, 74%), isolated as a beige solid: mp 128−130 °C;

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IR (neat) 3198, 3079, 2947, 2865, 1733, 1661, 1440, 1415, 1361, 1267, 1198, 1177, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−6.98 (m, 5H), 5.83 (s br, 1H), 3.67 (s, 3H), 3.14 (d, 1H, J = 13.1 Hz), 2.89 (d, 1H, J = 13.2 Hz), 2.48 (dd, 1H, J = 15.8 and 7.9 Hz), 2.35−2.22 (m, 2H), 1.88 (m, 1H), 1.79 (m, 1H), 1.65 (m, 1H), 1.58−1.46 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (s), 173.2 (s), 136.8 (s), 130.2 (d, 2C), 129.7 (d, 2C), 127.8 (d), 63.8 (s), 52.5 (q), 46.4 (t), 38.8 (t), 37.7 (t), 26.0 (t), 22.8 (t) ppm; MS m/z (%) 261 ($M^{+\cdot}$, 1), 202 (13), 170 (41), 142 (100), 110 (28), 92 (8), 91 (67), 82 (60), 81 (14), 65 (14), 55 (24), 54 (15); HRMS (ESI) *Calcd. for* $C_{15}H_{19}NO_3Na$ $(MNa)^+$, 284.1257, found 284.1259.

Methyl 2-Ethyl-8-oxoazocane-2-carboxylate (3d). Prepared according to **General Procedure 2**, **2d** (594 mg, 3.0 mmol, 1 equiv) was rearranged in $CHCl_3$ (5 mL). The crude was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc 50/50) affording **3d** (135 mg, 0.63 mmol, 21%), isolated as a white solid: mp 128−130 °C; IR (neat) 3203, 3082, 2927, 1730, 1655, 1450, 1400, 1231, 1159, 1131, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (s br, 1H), 3.71 (s, 3H), 2.40−2.18 (m, 3H), 1.85−1.38 (m, 9H), 0.80 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0 (s), 173.6 (s), 64.1 (s), 52.5 (q), 38.5 (t), 35.1 (t), 32.3 (t), 25.7 (t), 24.9 (t), 22.5 (t), 8.2 (q) ppm; MS m/z (%) 213 ($M^{+\cdot}$, 2), 156 (51), 154 (100), 124 (33), 116 (25), 111 (18), 109 (40), 99 (18), 96 (39), 84 (18), 81 (30), 69 (79), 56 (56), 55 (66), 54 (21); HRMS (ESI) *Calcd. for* $C_{11}H_{20}NO_3$ $(MH)^+$, 214.1438, found 214.1437.

Methyl 2-Benzyl-8-oxoazocane-2-carboxylate (3e). Prepared according to **General Procedure 2**, **2e**[16] (520 mg, 2.0 mmol, 1 equiv) was rearranged in $CHCl_3$ (5 mL). The crude was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc 50/50) affording **3e** (200 mg, 0.72 mmol, 36%), isolated as a beige solid: mp 141−143 °C; IR (neat) 3190, 3067, 2933, 1741, 1659, 1453, 1404, 1265, 1227, 1195, 1165, 1099, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−6.99 (m, 5H), 6.39 (s br, 1H), 3.63 (s, 3H), 2.95 (s, 2H), 2.37 (m, 1H), 2.14 (m, 2H), 1.98 (m, 1H), 1.78−1.34 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (s), 173.5 (s), 134.4 (s), 130.4 (d, 2C), 128.5 (d, 2C), 127.3 (d), 64.9 (s), 52.8 (q), 47.5 (t), 36.6 (t), 33.4 (t), 25.6 (t), 24.8 (t), 22.8 (t) ppm; MS m/z (%) 275 ($M^{+\cdot}$, 1), 216 (9), 184 (42), 157 (9), 156 (100), 124 (53), 96 (54), 91 (64), 81 (19), 79 (12), 69 (10), 65 (12), 55 (28), 54 (14); HRMS (ESI) *Calcd. for* $C_{16}H_{21}NO_3Na$ $(MNa)^+$, 298.1414, found 298.1413.

(1-Benzyl-2-ethylazepan-2-yl)methanol (4a). Prepared according to **General Procedure 3**, **3a** (300 mg, 1.51 mmol, 1 equiv) was transformed into **4a** (40%). **4a** was isolated as a colorless oil: IR (neat) 3404, 2924, 2851, 1451, 1355, 1134, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.14 (m, 5H), 3.81 (d, 1H, J = 13.1 Hz), 3.53 (d, 1H, J = 10.3 Hz), 3.48 (d, 1H, J = 10.0 Hz), 3.42 (d, 1H, J = 13.9 Hz), 2.74 (dd, 1H, J = 13.4 and 9.7 Hz), 2.55 (dd, 1H, J = 14.3 and 6.7 Hz), 1.90−1.80 (m, 2H), 1.65−1.41 (m, 6H), 1.17 (m, 2H), 0.86 (t, 3H, J = 7.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9 (s), 128.7 (d, 2C), 128.4 (d, 2C), 126.9 (d), 67.9 (t), 65.4 (s), 53.7 (t), 47.1 (t), 37.6 (t), 31.2 (t), 29.8 (t), 27.1 (t), 23.3 (t), 8.7 (q) ppm; MS m/z (%) 247 ($M^{+\cdot}$, 1), 216 (38), 91 (100), 65 (9); HRMS (ESI) *Calcd. for* $C_{16}H_{26}NO$ $(MH)^+$, 248.20089, found 248.20086.

(2-Allyl-1-benzylazepan-2-yl)methanol (4b). Prepared according to **General Procedure 3**, **3b** (547 mg, 2.59 mmol, 1 equiv) was transformed into **4b** (68%). **4b** was isolated as a yellow oil: IR (neat) 3410, 2923, 2850, 1493, 1451, 1354, 1320, 1144, 1056, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.14 (m, 5H), 5.80 (m, 1H), 5.04 (m, 2H), 3.84 (d, 1H, J = 14.2 Hz), 3.60 (d, 1H, J = 10.7 Hz), 3.48 (d, 1H, J = 13.6 Hz), 3.47 (d, 1H, J = 10.9 Hz), 2.73 (m, 1H), 2.54 (dd, 1H, J = 15.4 and 7.1 Hz,), 2.31 (dd, 1H, J = 14.2 and 7.1 Hz), 2.19 (dd, 1H, J = 13.6 and 7.6 Hz), 1.87−1.13 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6 (s), 134.5 (d), 128.7 (d, 2C), 128.4 (d, 2C), 126.9 (d), 117.9 (t), 68.2 (t), 60.4 (s), 54.1 (t), 47.3 (t), 39.4 (t), 38.3 (t), 31.4 (t), 29.8 (t), 23.3 (t) ppm; MS m/z (%) 259 ($M^{+\cdot}$, 1), 228 (15), 218 (22), 92 (8), 91 (100), 65 (8); HRMS (ESI) *Calcd. for* $C_{17}H_{25}NO$ $(MH)^+$, 260.2009, found 260.2008.

(1,2-Dibenzylazepan-2-yl)methanol (4c). Prepared according to **General Procedure 3**, **3c** (97 mg, 0.37 mmol, 1 equiv) was transformed into **4c** (64%). **4c** was isolated as a colorless oil: IR (neat) 3110, 2914, 2821, 1498, 1448, 1414, 1258, 1173, 1048, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.19 (m, 10H), 4.07 (d, 1H, J = 14.2 Hz), 3.85 (d, 1H, J = 10.5 Hz), 3.75 (d, 1H, J = 9.2 Hz), 3.53 (d, 1H, J = 10.5 Hz), 2.95 (d, 1H, J = 12.0 Hz), 2.88 (d, 1H, J = 12.5 Hz), 2.77 (m, 2H), 1.94−1.22 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (s), 138.1 (s), 130.5 (d, 2C), 128.7 (d, 2C), 128.4 (d, 2C), 128.1 (d, 2C), 126.9 (d), 126.2 (d), 67.7 (t), 63.0 (s), 54.2 (t), 47.0 (t), 40.1 (t), 38.1 (t), 31.2 (t), 29.7 (t), 23.2 (t) ppm; MS m/z (%) 309 ($M^{+\cdot}$, 1), 278 (8), 218 (27), 92 (8), 91 (100), 65 (9); HRMS (ESI) *Calcd. for* $C_{21}H_{28}NO$ $(MH)^+$, 310.2165, found 310.2166.

(1-Benzyl-2-ethylazocan-2-yl)methanol (4d). Prepared according to **General Procedure 3**, **3d** (101 mg, 0.47 mmol, 1 equiv) was transformed into **4d** (62%). **4d** was isolated as a yellow oil: IR (neat) 3373, 2922, 2851, 1452, 1376, 1207, 1119, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.12 (m, 5H), 3.79 (d, 1H, J = 12.5 Hz), 3.60 (d, 1H, J = 10.8 Hz), 3.50 (d, 1H, J = 10.8 Hz), 3.39 (d, 1H, J = 13.3 Hz), 2.98 (m, 1H), 2.56 (ddd, 1H, J = 15.6, 4.6, and 4.6 Hz), 1.84−0.88 (m, 12H), 0.84 (t, 3H, J = 7.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8 (s), 129.4 (d, 2C), 128.2 (d, 2C), 126.9 (d), 67.0 (t), 62.3 (s), 55.1 (t), 47.8 (t), 30.3 (t), 29.7 (t), 27.5 (t), 26.7 (t), 25.8 (t), 24.9 (t), 8.9 (q) ppm; MS m/z (%) 261 ($M^{+\cdot}$, 1), 232 (9), 230 (43), 92 (8), 91 (100), 55 (8); HRMS (ESI) *Calcd. for* $C_{17}H_{28}NO$ $(MH)^+$, 262.21654, found 262.21646.

(1,2-Dibenzylazocan-2-yl)methanol (4e). Prepared according to **General Procedure 3**, **3e** (146 mg, 0.53 mmol, 1 equiv) was transformed into **4e** (42%). **4e** was isolated as a yellow oil: IR (neat) 3429, 3026, 2921, 2850, 1493, 1451, 1357, 1249, 1204, 1115, 1041, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.09 (m, 10H), 4.00 (d, 1H, J = 13.5 Hz), 3.82 (d, 1H, J = 11.3 Hz), 3.52 (d, 1H, J = 13.5 Hz), 3.49 (d, 1H, J = 10.7 Hz), 3.19 (s br, OH), 2.93 (m, 1H), 2.81 (d, 1H, J = 13.5 Hz), 2.70 (d, 1H, J = 14.2 Hz), 2.50 (m, 1H), 1.80−0.57 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7 (s), 138.3 (s), 130.5 (d, 2C), 129.4 (d, 2C), 128.3 (d, 2C), 128.1 (d, 2C), 127.1 (d), 126.1 (d), 67.1 (t), 63.5 (s), 55.9 (t), 48.4 (t), 39.6 (t), 34.7 (t), 30.5 (t), 27.3 (t), 25.8 (t), 25.1 (t) ppm; MS m/z (%) 323 ($M^{+\cdot}$, 1), 292 (10), 232 (35), 92 (7), 91(100), 65 (7); HRMS (ESI) *Calcd. for* $C_{22}H_{30}NO$ $(MH)^+$, 324.2322, found 324.2317.

1-Benzyl-3-ethyl-3-fluoroazocane (5a). Prepared according to **General Procedure 4**, **4a** (100 mg, 0.40 mmol, 1 equiv) was rearranged in CH_2Cl_2 (5 mL) by DAST (75 μL, 0.56 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 90/10) affording **5a** (64 mg, 0.25 mmol, 64%), isolated as a yellow oil: IR (neat) 2921, 2854, 2790, 1452, 1364, 1270, 1124, 1070, 1011 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.11 (m, 5H), 3.71 (d, 1H, J = 13.7 Hz), 3.60 (d, 1H, J = 13.6 Hz), 2.78 (dd, 1H, J = 15.1 and 15.1 Hz), 2.53 (m, 1H), 2.42 (m, 1H), 2.31 (m, 1H), 2.07 (m, 1H), 1.80−1.66 (m, 2H), 1.60−1.14 (m, 7H), 0.86 (t, 3H, J = 7.2 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4 (s), 128.7 (d, 2C), 128.1 (d, 2C), 126.7 (d), 100.3 (ds, J = 169 Hz), 64.1 (t), 59.4 (dt, J = 25 Hz), 54.8 (t), 33.6 (dt, J = 24 Hz), 29.9 (dt, J = 23 Hz), 27, 3 (t), 27.2 (t), 22.7 (dt, J = 10 Hz), 7.28 (dq, J = 5 Hz) ppm; MS m/z (%) 249 ($M^{+\cdot}$, 5), 174 (8), 160 (15), 158 (16), 147 (7), 146 (8), 134 (20), 98 (10), 92 (10), 91 (100), 84 (7), 65 (10); HRMS (ESI) *Calcd. for* $C_{16}H_{25}FN$ $(MH)^+$, 250.1966, found 250.1968.

3-Allyl-1-benzyl-3-fluoroazocane (5b). Prepared according to **General Procedure 4**, **4b** (317 mg, 1.22 mmol, 1 equiv) was rearranged in CH_2Cl_2 (10 mL) by DAST (226 μL, 1.71 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 95/5) affording **5b** (264 mg, 1.01 mmol, 83%), isolated as a yellow oil: IR (neat) 2921, 2854, 2791, 1452, 1347, 1197, 1134, 1070, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.31 (m, 5H), 6.03 (m, 1H), 5.23 (m, 2H), 3.91 (d, 1H, J = 13.2 Hz), 3.82 (d, 1H, J = 13.3 Hz), 3.00 (dd, 1H, J = 14.0 and 14.0 Hz), 2.79 (m, 1H), 2.67−2.49 (m, 3H), 2.46 (ddd, 1H, J = 7.2, 1.3, and 1.3 Hz), 2.27 (m, 1H), 2.06−1.93 (m, 2H), 1.79−1.55 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4 (s), 133.2 (d), 128.9 (d, 2C), 128.3 (d, 2C), 127.0 (d), 118.2 (t), 99.5 (ds, J = 179 Hz), 64.2 (t), 59.4 (dt, J = 43 Hz), 55.0 (t), 42.4 (dt, J = 24 Hz), 34.5 (dt, J = 24 Hz), 27.2 (t), 26.9 (t), 22.5 (dt, J = 9 Hz) ppm; MS m/z (%) 261 ($M^{+\cdot}$, 5), 170 (16), 160 (12), 134 (18), 98

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(11), 92 (11), 91 (100), 84 (7), 65 (11); HRMS (ESI) *Calcd. for* $C_{17}H_{24}FN$ *(MH)*$^+$, 262.1966, found 262.1967.

1,3-Dibenzyl-3-fluoroazocane (5c). Prepared according to **General Procedure 4**, **4c** (155 mg, 0.50 mmol, 1 equiv) was rearranged in CH_2Cl_2 (5 mL) by DAST (92 μL, 0.70 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 90/10) affording **5c** (101 mg, 0.32 mmol, 65%), isolated as a yellow oil: IR (neat) 2918, 2854, 2790, 1452, 1347, 1138, 1076, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.10 (m, 10H), 3.69 (d, 1H, *J* = 13.5 Hz), 3.56 (d, 1H, *J* = 13.8 Hz), 2.88−2.55 (m, 4H), 2.36 (m, 2H), 1.95 (m, 1H), 1.84−1.35 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3 (s), 136.7 (s), 130.6 (d, 2C), 128.8 (d, 2C), 128.2 (d, 2C), 128.1 (d, 2C), 126.8 (d), 126.4 (d), 99.9 (ds, *J* = 173 Hz), 64.1 (t), 59.6 (dt, *J* = 26 Hz), 54.6 (t), 43.7 (dt, *J* = 21 Hz), 34.0 (dt, *J* = 23 Hz), 27.1 (t), 27.0 (t), 22.6 (dt, *J* = 9 Hz) ppm; MS *m*/*z* (%) 311 (M$^{+\cdot}$, 3), 220 (12), 160 (13), 134 (15), 120 (9), 92 (10), 91 (100), 65 (10); HRMS (ESI) *Calcd. for* $C_{21}H_{27}FN$ *(MH)*$^+$, 312.2122, found 312.2121.

1-Benzyl-3-ethyl-3-fluoroazonane (5d). Prepared according to **General Procedure 4**, **4d** (72 mg, 0.28 mmol, 1 equiv) was rearranged in CH_2Cl_2 (4 mL) by DAST (51 μL, 0.39 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 98/2) affording **5d** (43 mg, 0.16 mmol, 58%), isolated as a yellow oil: IR (neat) 2929, 2792, 1453, 1365, 1265, 1192, 1109, 1063, 1027, 1004 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.12 (m, 5H), 3.86 (d, 1H, *J* = 14.2 Hz), 3.46 (d, 1H, *J* = 12.7 Hz), 2.59−2.55 (m, 2H), 2.30−2.17 (m, 3H), 1.74−1.04 (m, 11H), 0.89 (t, 3H, *J* = 6.9 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4 (s), 129.1 (d, 2C), 128.1 (d, 2C), 126.7 (d), 102.4 (ds, *J* = 170 Hz), 63.1 (dt, *J* = 4 Hz), 56.0 (dt, *J* = 22 Hz), 53.7 (t), 28.8 (dt, *J* = 22 Hz), 28.4 (dt, *J* = 23 Hz), 27.3 (t), 22.5 (t), 19.7 (t), 18.2 (dt, *J* = 11 Hz), 7.1 (dq, *J* = 4 Hz) ppm; MS *m*/*z* (%) 263 (M$^{+\cdot}$, 3), 172 (27), 160 (9), 134 (20), 120 (20), 92 (10), 91 (100), 65 (11); HRMS (ESI) *Calcd.* $C_{17}H_{26}FN$ *(MH)*$^+$, 264.2122, found 264.2124.

1,3-Dibenzyl-3-fluoroazonane (5e). Prepared according to **General Procedure 4**, **4e** (50 mg, 0.15 mmol, 1 equiv) was rearranged in CH_2Cl_2 (3 mL) by DAST (28 μL, 0.21 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 98/2) affording **5e** (43 mg, 0.09 mmol, 62%), isolated as a yellow oil: IR (neat) 2928, 2793, 1494, 1453, 1364, 1137, 1063, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.10 (m, 10H), 3.91 (d, 1H, *J* = 13.8 Hz), 3.41 (d, 1H, *J* = 13.8 Hz), 2.84−2.53 (m, 4H), 2.30−2.15 (m, 3H), 1.66−1.09 (m, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3 (s), 136.5 (s), 130.5 (d, 2C), 129.1 (d, 2C), 128.1 (d, 2C), 128.0 (d, 2C), 126.7 (d), 126.4 (d), 102.1 (ds, *J* = 173 Hz), 63.1 (dt, *J* = 3 Hz), 56.1 (dt, *J* = 20 Hz), 53.5 (t), 42.4 (dt, *J* = 20 Hz), 28.3 (dt, *J* = 23 Hz), 27.4 (t), 22.3 (t), 19.3 (t), 18.4 (dt, *J* = 11 Hz) ppm; MS *m*/*z* (%) 325 (1), 234 (20), 172 (6), 160 (6), 134 (13), 120 (16), 92 (9), 91 (100), 65 (10); HRMS (ESI) *Calcd.* $C_{22}H_{29}FN$ *(MH)*$^+$, 326.2278, found 326.2275.

3-Benzyl 1-*tert*-Butyl 4-Benzylpiperazine-1,3-dicarboxylate (7). To a suspension of amino acid **6** (1.00 g, 4.3 mmol, 1 equiv) in water (10 mL) were successively added at 0 °C benzyl bromide (1.54 mL, 13.0 mmol, 3 equiv), Na_2CO_3 (920 mg, 8.7 mmol, 2 equiv), and NaOH (347 mg, 8.7 mmol, 2 equiv). The reaction media was refluxed for 3 h and then cooled and extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (PE/EtOAc 90/10) to afford **7** (985 mg, 2.4 mmol, 55%), isolated as a colorless oil: IR (neat) 2975, 1735, 1693, 1454, 1421, 1365, 1286, 1243, 1146, 1123, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.23 (m, 10H), 5.22 (d, 1H, *J* = 12.2 Hz), 5.15 (d, 1H, *J* = 12.4 Hz), 3.90 (m, 1H), 3.86 (d, 1H, *J* = 13.1 Hz), 3.60 (d, 1H, *J* = 13.7 Hz), 3.56 (m, 2H), 3.22 (m, 2H), 3.08 (m, 1H), 2.36 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (s), 154.4 (s), 137.7 (s), 135.6 (s), 129.1 (d, 2C), 128.6 (d, 2C), 128.3 (d, 2C), 128.2 (d, 2C), 127.5 (d), 127.3 (d), 79.9 (s), 66.4 (t), 61.5 (t), 59.6 (t), 47.8 (t), 46.4 (t), 36.1 (t), 28.3 (q, 3C) ppm; HRMS (ESI) *Calcd.* $C_{24}H_{31}N_2O_4$ *(MH)*$^+$, 411.2278, found 411.2289.

***tert*-Butyl 3-Allyl-4-benzyl-3-(hydroxymethyl)piperazine-1-carboxylate (8).** **7** (902 mg, 2.2 mmol, 1 equiv) was alkylated by LDA 1 M (2.4 mL, 2.4 mmol, 1.1 equiv) with allyl bromide (228 μL, 2.6 mmol, 1.2 equiv) in THF (10 mL) following **General Procedure 5**. The crude was purified by flash chromatography on silica gel (PE/EtOAc 90/10) affording the intermediate piperazine (557 mg, 1.2 mmol, 56%). This intermediate piperazine (494 mg, 1.1 mmol, 1 equiv) was reduced in THF (10 mL) by $LiAlH_4$ (166 mg, 4.4 mmol, 4 equiv) following **General Procedure 6**. Piperazine **8** (387 mg, 1.1 mmol, 100%) was isolated as a yellow oil: IR (neat) 3240, 2975, 1701, 1473, 1245, 1153, 1025 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 100 °C) δ 7.42−7.18 (m, 5H), 5.98 (m, 1H), 5.09 (m, 2H), 4.78 (m, 1H), 4.52 (m, 1H), 4.12 (m, 1H), 3.85 (d, 1H, *J* = 14.6 Hz), 3.72 (d, 1H, *J* = 14.2 Hz), 3.62 (dd, 1H, *J* = 11.4 and 5.0 Hz), 3.55 (dd, 1H, *J* = 11.4 and 3.9 Hz), 3.40−3.18 (m, 4H), 2.48−2.31 (m, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9 (s), 138.4 (s), 133.5 (d), 128.6 (d, 2C), 127.5 (d, 2C), 126.9 (d), 118.9 (t), 80.1 (s), 68.0 (t), 65.1 (t), 59.5 (s), 52.7 (t), 47.5 (t), 45.0 (t), 31.0 (t), 28.4 (q, 3C) ppm; MS *m*/*z* (%) 315 (M$^{+\cdot}$-CH_2OH, 18), 259 (25), 231 (20), 218 (17), 92 (10), 91 (100), 57 (24); HRMS (ESI) *Calcd.* $C_{20}H_{31}N_2O_3$ *(MH)*$^+$, 347.2256, found 347.2258.

2-(Benzylamino)-2-methylpropane-1,3-diol (10). To a solution of **9** (2.10 g, 20 mmol, 1 equiv) in methanol (20 mL) was added benzaldehyde (2.03 mL, 20 mmol, 1 equiv) at 0 °C. The reaction medium was stirred at rt for 2 h before being cooled at 0 °C. $NaBH_4$ (1.18 g, 32 mmol, 1.6 equiv) was added per portions in the medium, which was stirred 10 min before being hydrolyzed by the addition of a 1 M aqueous solution of NaOH (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (EtOAc/MeOH 90/10) leading to **10** (2.18 g, 11.2 mmol, 56%), isolated as a white solid: mp 133−135 °C; IR (neat) 3255, 2925, 1451, 1077, 1053 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 3.67 (s, 2H), 3.50 (s, 4H), 2.78 (s br, 3H), 1.03 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1 (s), 128.6 (d, 2C), 128.4 (d, 2C), 127.2 (d), 67.0 (t), 57.0 (s), 46.0 (t, 2C), 18.3 (q) ppm; HRMS (ESI) *Calcd.* $C_{11}H_{18}NO_2$ *(MH)*$^+$, 196.1332, found 196.1330.

4-Benzyl-5-(hydroxymethyl)-5-methylmorpholin-3-one (11). To a solution of **10** (485 mg, 2.5 mmol, 1 equiv) in CH_2Cl_2 (10 mL) were successively added at 0 °C K_2CO_3 (513 mg, 3.7 mmol, 1.5 equiv) and 2-chloroacetyl chloride (239 μL, 3.0 mmol, 1.2 equiv). The reaction media was stirred at rt for 5 h, and water (10 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, washed successively with water (10 mL), 1 M aqueous solution of HCl (10 mL), and brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude was dissolved in *t*-BuOH (5 mL), and *t*-BuOK (277 mg, 2.5 mmol, 1 equiv) was added to the medium. After refluxing for 3 h, the media was cooled, and a mixture of EtOAc/H_2O 50:50 was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (EtOAc, 100%) affording **11** (83 mg, 0.35 mmol, 14%), isolated as a colorless oil: IR (neat) 3275, 2967, 1685, 1452, 1277, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.11 (m, 5H), 4.65 (d, 1H, *J* = 12.1 Hz), 4.47 (d, 1H, *J* = 11.9 Hz), 4.18 (s, 2H), 3.87 (d, 1H, *J* = 9.0 Hz), 3.55 (d, 1H, *J* = 8.8 Hz), 3.43 (d, 1H, *J* = 9.0 Hz), 3.32 (d, 1H, *J* = 8.6 Hz), 3.04 (s br, 1H), 1.00 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8 (s), 138.5 (s), 128.6 (d, 2C), 127.1 (d, 2C), 127.0 (d), 71.5 (t), 68.0 (t), 65.0 (t), 59.8 (s), 44.6 (t), 18.7 (q) ppm; MS *m*/*z* (%) 235 (M$^{+\cdot}$, 1), 204 (24), 91 (100), 65 (10); HRMS (ESI) *Calcd.* $C_{13}H_{18}NO_3$ *(MH)*$^+$, 236.1208, found 236.1211.

(4-Benzyl-3-methylmorpholin-3-yl)methanol (12). To a solution of **11** (146 mg, 0.62 mmol, 1 equiv) in toluene (2 mL) was added at 0 °C a 3.31 M solution of Red-Al in toluene (563 μL, 1.86 mmol, 1 equiv). The reaction media was stirred at rt for 1 h before being cooled to 0 °C. EtOH (2 mL) and then a 1 M aqueous solution

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of NaOH were added until pH = 12. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layers were combined and acidified with a 1 M aqueous solution of HCl (pH 3). The aqueous layer was separated, and a 1 M aqueous solution of NaOH was added (pH 12). The aqueous layer was extracted with EtOAc (2 × 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (PE/EtOAc 70/30) affording **12** (102.6 mg, 0.46 mmol, 75%), isolated as a colorless oil: IR (neat) 3412, 2961, 2852, 1450, 1126, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.17 (m, 5H), 3.87 (d, 1H, J = 9.9 Hz), 3.73−3.64 (m, 3H), 3.43 (m, 1H), 3.39 (d, 1H, J = 9.1 Hz), 3.12 (d, 1H, J = 8.4 Hz), 3.10 (d, 1H, J = 9.6 Hz), 2.51−2.46 (m, 2H), 1.04 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3 (s), 128.9 (d, 2C), 128.5 (d, 2C), 127.3 (d), 74.0 (t), 67.6 (t), 63.8 (t), 57.1 (s), 53.3 (t), 45.8 (t), 12.9 (q) ppm; MS m/z (%) 221 ($M^{+\cdot}$, 1), 190 (35), 91 (100), 65 (10); HRMS (ESI) *Calcd.* $C_{13}H_{20}NO_2$ $(MH)^+$, 222.1489, found 222.1485.

Methyl 1-Benzyl-2-ethylindoline-2-carboxylate (15a). Prepared according to **General Procedure 5**, **14** (2.36 g, 8.8 mmol, 1 equiv) was alkylated by LDA 1 M (9.5 mL, 9.5 mmol, 1.1 equiv) with ethyl iodide (832 μL, 10.4 mmol, 1.2 equiv) in THF (20 mL). The residue was purified by flash chromatography on silica gel (PE/EtOAc 98/2) affording **15a** (1.78 g, 6.0 mmol, 68%), isolated as an orange oil: IR (neat) 3028, 2950, 1729, 1606, 1485, 1452, 1353, 1233, 1194, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 5H), 7.09 (d, 1H, J = 7.5 Hz), 6.97 (d, 1H, J = 7.5 Hz), 6.66 (ddd, 1H, J = 7.3, 7.3 and 1.0 Hz), 6.15 (d, 1H, J = 7.6 Hz), 4.52 (d, 1H, J = 17.8 Hz), 4.44 (d, 1H, J = 17.1 Hz), 3.65 (s, 3H), 3.58 (d, 1H, J = 16.4 Hz), 3.20 (d, 1H, J = 16.5 Hz), 2.03 (m, 2H), 0.96 (t, 3H, J = 7.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5 (s), 151.0 (s), 139.2 (s), 129.8 (d), 129.0 (d, 2C), 128.4 (d, 2C), 127.5 (d), 126.6 (s), 123.6 (d), 117.5 (d), 106.4 (d), 74.7 (s), 52.1 (q), 48.6 (t), 37.7 (t), 28.0 (t), 8.5 (q) ppm; MS m/z (%) 295 ($M^{+\cdot}$, 1), 236 (39), 91 (100), 65 (8); HRMS (ESI) *Calcd.* $C_{19}H_{21}NO_2Na$ $(MNa)^+$, 318.1465, found 318.1466.

Methyl 2-Allyl-1-benzylindoline-2-carboxylate (15b). Prepared according to **General Procedure 5**, **14** (2.36 g, 8.8 mmol, 1 equiv) was alkylated by LDA 1 M (9.5 mL, 9.5 mmol, 1.1 equiv) with allyl bromide (898 μL, 10.4 mmol, 1.2 equiv) in THF (20 mL). The crude was purified by flash chromatography on silica gel (PE/EtOAc 98/2) affording **15b** (1.65 g, 5.4 mmol, 61%), isolated as an orange oil: IR (neat) 3028, 2950, 1730, 1605, 1485, 1434, 1352, 1250, 1196, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5H), 7.07 (d, 1H, J = 7.0 Hz), 6.97 (dd, 1H, J = 7.7 and 7.7 Hz), 6.67 (dd, 1H, J = 7.6 and 7.6 Hz), 6.16 (d, 1H, J = 7.6 Hz), 5.78 (m, 1H), 5.15 (m, 2H), 4.55 (d, 1H, J = 16.5 Hz), 4.43 (d, 1H, J = 16.6 Hz), 3.67 (s, 3H), 3.52 (d, 1H, J = 15.9 Hz), 3.28 (d, 1H, J = 16.5 Hz), 2.81 (dd, 1H, J = 14.2 and 7.5 Hz), 2.72 (dd, 1H, J = 14.3 and 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (s), 150.9 (s), 139.0 (s), 132.6 (d), 128.5 (d, 2C), 127.5 (d, 2C), 126.7 (d), 126.6 (s), 126.4 (d), 123.7 (d), 119.3 (t), 117.7 (d), 106.6 (d), 73.7 (s), 52.1 (q), 49.0 (t), 39.6 (t), 38.2 (t) ppm; MS m/z (%) 307 ($M^{+\cdot}$, 1), 265 (22), 248 (9), 91 (100), 65 (9); HRMS (ESI) *Calcd.* $C_{20}H_{21}NO_2Na$ $(MNa)^+$, 330.1464, found 330.1465.

Methyl 1,2-Dibenzylindoline-2-carboxylate (15c). Prepared according to **General Procedure 5**, **14**[16] (2.36 g, 8.8 mmol, 1 equiv) was alkylated by LDA 1 M (9.5 mL, 9.5 mmol, 1.1 equiv) with benzyl bromide (1.24 mL, 10.4 mmol, 1.2 equiv) in THF (20 mL). The crude was purified by flash chromatography on silica gel (PE/EtOAc 98/2) affording **15c** (2.79 g, 7.8 mmol, 88%), isolated as an orange oil: IR (neat) 3028, 2949, 1728, 1605, 11484, 1452, 1352, 1268, 1237, 1195, 1081, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.17 (m, 10H), 7.08 (d, 1H, J = 6.8 Hz), 6.98 (dd, 1H, J = 7.5 and 7.5 Hz), 6.69 (ddd, 1H, J = 7.4, 7.4, and 1.0 Hz), 6.19 (d, 1H, J = 7.8 Hz), 4.67 (d, 1H, J = 17.1 Hz), 4.59 (d, 1H, J = 16.9 Hz), 3.66 (s, 3H), 3.54 (d, 1H, J = 13.3 Hz), 3.53 (d, 1H, J = 15.7 Hz), 3.30 (d, 1H, J = 16.0 Hz), 3.16 (d, 1H, J = 13.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (s), 150.4 (s), 139.1 (s), 136.0 (s), 130.4 (d), 128.5 (d, 2C), 128.3 (d, 2C), 127.5 (d, 2C), 126.9 (d, 2C), 126.7 (d), 126.6 (s), 126.5 (d), 123.7 (d), 117.9 (d), 107.1 (d), 75.3 (s), 52.1 (q), 49.0 (t), 40.6 (t), 37.7 (t) ppm; MS m/z (%) 357 ($M^{+\cdot}$, 1), 265 (36), 91 (100), 65 (9); HRMS (ESI) *Calcd.* $C_{24}H_{23}NO_2Na$ $(MNa)^+$, 380.1621, found 380.1626.

(1-Benzyl-2-ethylindolin-2-yl)methanol (16a). Prepared according to **General Procedure 6**, **15a** (1.75 g, 5.93 mmol, 1 equiv) in THF (15 mL) was reduced by $LiAlH_4$ (451 mg, 11.86 mmol, 2 equiv). **16a** (1.58 g, 5.93 mmol, 100%) was isolated as a yellow oil: IR (neat) 3415, 3026, 2965, 2933, 2875, 1604, 1485, 1452, 1354, 1314, 1274, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.26 (m, 5H), 7.10 (d, 1H, J = 7.4 Hz), 7.01 (dd, 1H, J = 7.4 and 7.4 Hz), 6.68 (dd, 1H, J = 6.9 and 6.9 Hz), 6.28 (d, 1H, J = 7.9 Hz), 4.38 (s, 2H), 3.60 (d, 1H, J = 11.7 Hz), 3.53 (d, 1H, J = 11.7 Hz), 3.31 (d, 1H, J = 15.9 Hz), 3.01 (d, 1H, J = 16.4 Hz), 1.81 (s br, OH), 1.79 (qd, 1H, J = 14.9 and 7.5 Hz), 1.55 (qd, 1H, J = 14.8 and 7.4 Hz), 0.88 (t, 3H, J = 7.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4 (s), 139.9 (s), 130.5 (d), 128.9 (d, 2C), 127.3 (d, 2C), 127.1 (s), 126.6 (d), 123.9 (d), 117.3 (d), 106.0 (d), 71.9 (s), 66.3 (t), 46.9 (t), 35.4 (t), 27.0 (t), 8.2 (q) ppm; MS m/z (%) 267 ($M^{+\cdot}$, 5), 236 (37), 9 (100), 65 (10); HRMS (ESI) *Calcd.* $C_{18}H_{21}NONa$ $(MNa)^+$, 290.1515, found 290.1518.

(2-Allyl-1-benzylindolin-2-yl)methanol (16b). Prepared according to **General Procedure 6**, **15b** (1.62 g, 5.27 mmol, 1 equiv) in THF (15 mL) was reduced by $LiAlH_4$ (461 mg, 12.13 mmol, 2 equiv). **16b** (1.41 g, 5.05 mmol, 95%) was isolated as a yellow oil: IR (neat) 3415, 3026, 2918, 1604, 1485, 1452, 1353, 1270, 1141, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 7.10 (d, 1H, J = 7.6 Hz), 7.00 (dd, 1H, J = 7.6 and 7.6 Hz), 6.68 (dd, 1H, J = 7.4 and 7.4 Hz), 6.25 (d, 1H, J = 7.6 Hz), 5.74 (dddd, 1H, J = 14.2, 7.1, 7.1, and 6.5 Hz), 5.16 (m, 1H), 5.09 (m, 1H), 4.45 (d, 1H, J = 16.7 Hz), 4.37 (d, 1H, J = 16.7 Hz), 3.66 (d, 1H, J = 12.2 Hz), 3.58 (d, 1H, J = 11.6 Hz), 3.25 (d, 1H, J = 16.2 Hz), 3.07 (d, 1H, J = 16.2 Hz), 2.53 (dd, 1H, J = 14.2 and 7.1 Hz), 2.33 (dd, 1H, J = 14.2 and 7.6 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8 (s), 139.7 (s), 133.0 (d), 128.9 (d), 127.4 (d, 2C), 127.3 (d, 2C), 127.1 (s), 126.6 (d), 124.1 (d), 118.7 (t), 117.6 (d), 106.4 (d), 71.3 (s), 66.0 (t), 47.1 (t), 38.6 (t), 35.7 (t) ppm; MS m/z (%) 279 ($M^{+\cdot}$, 4), 248 (11), 237 (19), 208 (10), 91 (100), 65 (10); HRMS (ESI) *Calcd.* $C_{19}H_{22}NO$ $(MH)^+$, 280.1696, found 280.1700.

(1,2-Dibenzylindolin-2-yl)methanol (16c). Prepared according to **General Procedure 6**, **15c** (2.65 g, 7.43 mmol, 1 equiv) in THF (15 mL) was reduced by $LiAlH_4$ (565 mg, 14.87 mmol, 2 equiv). **16c** (2.05 g, 6.23 mmol, 84%) was isolated as a yellow oil: IR (neat) 3430, 3026, 2919, 1604, 1483, 1353, 1275, 1138, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.18 (m, 10H), 7.11 (d, 1H, J = 7.1 Hz), 7.02 (dd, 1H, J = 7.5 and 7.5 Hz), 6.70 (dd, 1H, J = 7.1 and 7.1 Hz), 6.30 (d, 1H, J = 8.0 Hz), 4.58 (d, 1H, J = 16.4 Hz), 4.45 (d, 1H, J = 16.5 Hz), 3.79 (d, 1H, J = 10.8 Hz), 3.62 (d, 1H, J = 12.0 Hz), 3.10 (d, 1H, J = 15.5 Hz), 3.06 (d, 1H, J = 12.3 Hz), 3.00 (d, 1H, J = 15.9 Hz), 2.90 (d, 1H, J = 13.3 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3 (s), 139.6 (s), 136.7 (s), 130.5 (d), 128.9 (d, 2C), 128.3 (d, 2C), 127.4 (d, 2C), 127.3 (s), 127.1 (d, 2C), 126.6 (d), 126.5 (d), 124.3 (d), 117.8 (d), 107.1 (d), 72.8 (s), 64.9 (t), 47.4 (t), 38.7 (t), 34.7 (t) ppm; MS m/z (%) 329 ($M^{+\cdot}$, 1), 238 (27), 208 (11), 91 (100), 65 (10); HRMS (ESI) *Calcd.* $C_{23}H_{23}NONa$ $(MNa)^+$, 352.1672, found 352.1673.

***tert*-Butyl 6-Allyl-4-benzyl-6-fluoro-1,4-diazepane-1-carboxylate (17).** Prepared according to **General Procedure 4**, **8** (387 mg, 1.12 mmol, 1 equiv) was rearranged in CH_2Cl_2 (10 mL) by DAST (206 μL, 1.56 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/EtOAc 90/10) affording **17** (220 mg, 0.63 mmol, 56%), isolated as a colorless oil: IR (neat) 2921, 2854, 2791, 1695, 1452, 1347, 1197, 1134, 1070, 1021 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 100 °C) δ 7.36−7.21 (m, 5H), 5.76 (m, 1H), 5.07 (m, 2H), 3.76−3.66 (m, 3H), 3.58−3.45 (m, 2H), 3.26 (m, 1H), 2.80 (m, 1H), 2.76 (m, 1H), 2.66 (m, 2H), 2.46−2.27 (m, 2H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1 (s), 138.9 (s), 131.9 (d), 128.6 (d, 2C), 128.1 (d, 2C), 127.0 (d), 118.9 (t), 98.1 (ds, J = 177 Hz), 78.8 (s), 62.3 (t), 62.0 (dt, J = 28 Hz), 55.5 (t), 55.4 (dt, J = 34 Hz), 52.9 (dt, J = 31 Hz), 49.0 (dt, J = 33 Hz), 27.9 (q, 3C) ppm; MS m/z (%) 348 ($M^{+\cdot}$, 1), 291 (12), 230 (15), 91 (100), 65 (9), 57 (37); HRMS (ESI) *Calcd.* $C_{20}H_{30}N_2O_2F$ $(MH)^+$, 349.22858, found 349.22856.

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4-Benzyl-6-fluoro-6-methyl-1,4-oxazepane (18). Prepared according to **General Procedure 4**, **12** (100 mg, 0.45 mmol, 1 equiv) was rearranged in CH_2Cl_2 (5 mL) by DAST (83.6 μL, 0.63 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/EtOAc 90/10) affording **18** (67 mg, 0.30 mmol, 67%), isolated as a colorless oil: IR (neat) 2938, 1454, 1125, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.15 (m, 5H), 3.90 (dd, 1H, *J* = 13.9 and 10.0 Hz), 3.79 (ddd, 1H, *J* = 9.2, 3.7, and 2.9 Hz), 3.64 (d, 1H, *J* = 13.3 Hz), 3.58 (d, 1H, *J* = 13.3 Hz), 3.56 (dd, 1H, *J* = 25.8 and 13.3 Hz), 3.51 (ddd, 1H, *J* = 16.0, 3.8, and 3.8 Hz), 2.90 (dd, 1H, *J* = 13.0 and 10.3 Hz), 2.73−2.56 (m, 3H), 1.13 (d, 3H, *J* = 16.1 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 (s), 129.0 (d), 128.3 (d), 127.3 (d), 98.0 (ds, *J* = 169 Hz), 78.7 (dt, *J* = 28 Hz), 74.4 (t), 65.0 (dt, *J* = 30 Hz), 63.7 (t), 59.5 (t), 23.1 (dq, *J* = 25 Hz) ppm; MS *m*/*z* (%) 223 ($M^{+\cdot}$, 5), 162 (30), 133 (25), 132 (24), 91 (100), 65 (21); HRMS (ESI) *Calcd.* $C_{13}H_{19}NOF\ (MH)^+$, 224.1445, found 224.1442.

1-Benzyl-3-ethyl-3-fluoro-1,2,3,4-tetrahydroquinoline (19a). Prepared according to **General Procedure 4**, **16a** (534 mg, 2.0 mmol, 1 equiv) was rearranged in CH_2Cl_2 (20 mL) by DAST (369 μL, 2.8 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 98/2) affording **19a** (440 mg, 1.6 mmol, 81%), isolated as a yellow oil: IR (neat) 3027, 2970, 2937, 1602, 1507, 1451, 1354, 1327, 1288, 1247, 1168 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.33−7.00 (m, 7H), 6.82 (ddd, 1H, *J* = 7.3, 7.3, and 1.0 Hz), 6.63 (d, 1H, *J* = 8.3 Hz), 4.27 (s, 2H), 3.22 (m, 1H), 3.06−2.95 (m, 2H), 2.69 (dd, 1H, *J* = 19.2 (H−F) and 16.0 Hz), 1.53 (qd, 2H, *J* = 20.6 (H−F) and 7.3 Hz), 0.93 (t, 3H, *J* = 7.4 Hz) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 144.6 (s), 138.8 (s), 129.9 (d), 128.3 (d), 128.0 (d, 2C), 127.8 (d, 2C), 126.9 (d), 119.3 (s), 117.3 (d), 111.5 (d), 91.7 (ds, *J* = 175 Hz), 56.3 (dt, *J* = 25 Hz), 54.9 (t), 37.6 (dt, *J* = 24 Hz), 30.5 (dt, *J* = 25 Hz), 7.2 (dq, *J* = 6 Hz) ppm; MS *m*/*z* (%) 269 ($M^{+\cdot}$, 35), 192 (10), 178 (7), 158 (7), 92 (12), 91 (100), 65 (14); HRMS (ESI) *Calcd.* $C_{18}H_{21}NF\ (MH)^+$, 270.1652, found 270.1659.

3-Allyl-1-benzyl-3-fluoro-1,2,3,4-tetrahydroquinoline (19b). Prepared according to **General Procedure 4**, **16b** (558 mg, 2 mmol, 1 equiv) was rearranged in CH_2Cl_2 (20 mL) by DAST (369 μL, 2.8 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 98/2) affording **19b** (441 mg, 1.6 mmol, 78%), isolated as a yellow oil: IR (neat) 3017, 2894, 1600, 1508, 1498, 1451, 1289, 1247 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.32−7.00 (m, 7H), 6.81 (ddd, 1H, *J* = 7.3, 7.3, and 0.9 Hz), 6.63 (d, 1H, *J* = 8.0 Hz), 5.90 (m, 1H), 5.11 (d, 1H, *J* = 10.3 Hz), 5.03 (d, 1H, *J* = 17.1 Hz), 4.30 (d, 1H, *J* = 16.9 Hz), 4.24 (d, 1H, *J* = 17.0 Hz), 3.23 (ddd, 1H, *J* = 11.8, 10.5, and 2.3 Hz), 3.06 (ddd, 1H, *J* = 25.6 (H−F), 12.3 and 1.6 Hz), 2.99 (ddd, 1H, *J* = 16.2, 13.6, and 2.4 Hz), 2.75 (dd, 1H, *J* = 28.7 (H−F) and 12.3 Hz), 2.33 (dd, 1H, *J* = 7.3 and 1.0 Hz), 2.28 (dd, 1H, *J* = 7.3, 1.1 Hz) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 144.5 (s), 138.7 (s), 132.1 (dd, *J* = 4.8 Hz), 129.9 (d), 128.8 (d), 128.0 (d, 2C), 127.8 (d, 2C), 126.9 (d), 119.1 (t), 119.1 (s), 117.4 (d), 111.6 (d), 91.2 (ds, *J* = 176 Hz), 56.3 (dt, *J* = 25 Hz), 54.9 (t), 42.2 (dt, *J* = 22 Hz), 37.9 (dt, *J* = 24 Hz) ppm; MS *m*/*z* (%) 281 ($M^{+\cdot}$, 5), 280 (28), 237 (10), 148 (10), 92 (12), 91 (100), 65 (13); HRMS (ESI) *Calcd.* $C_{19}H_{21}NF\ (MH)^+$, 282.1652, found 282.1659.

1,3-Dibenzyl-3-fluoro-1,2,3,4-tetrahydroquinoline (19c). Prepared according to **General Procedure 4**, **16c** (455 mg, 1.38 mmol, 1 equiv) was rearranged in CH_2Cl_2 (15 mL) by DAST (255 μL, 1.93 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 98/2) affording **19c** (299 mg, 0.90 mmol, 65%), isolated as a yellow oil: IR (neat) 3027, 2916, 1602, 1495, 1452, 1353, 1288, 1247, 1079, 1028 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.31−7.06 (m, 11H), 6.93 (d, 1H, *J* = 7.5 Hz), 6.78 (dd, 1H, *J* = 7.0 and 7.0 Hz), 6.63 (d, 1H, *J* = 8.3 Hz), 4.26 (d, 1H, *J* = 17.1 Hz), 4.18 (d, 1H, *J* = 16.8 Hz), 3.24 (ddd, 1H, *J* = 11.8, 9.3, and 2.3 Hz), 3.08 (ddd, 1H, *J* = 22.0 (H−F), 12.0 and 2.0 Hz), 2.96 (m, 1H), 2.84 (d, 2H, *J* = 22.8 (H−F) Hz), 2.79 (dd, 1H, *J* = 24.6 (H−F) and 15.8 Hz) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 144.4 (s), 138.7 (s), 136.0 (s), 130.8 (d), 130.1 (d), 128.8 (d, 2C), 128.5 (d, 2C), 128.3 (d, 2C), 127.9 (d, 2C), 127.1 (d), 127.0 (d), 119.0 (s), 117.4 (d), 111.7 (d), 91.4 (ds, *J* = 177 Hz), 56.5 (dt, *J* = 25 Hz), 54.9 (t), 43.6 (dt, *J* = 22 Hz), 38.0 (dt, *J* = 24 Hz) ppm; MS *m*/*z* (%) 331 ($M^{+\cdot}$, 28), 148 (7), 91 (100), 65 (13); HRMS (ESI) *Calcd.* $C_{23}H_{23}NF\ (MH)^+$, 332.1809, found 332.1807.

(*R*)-(1,2-Dibenzylazetidin-2-yl)methanol (23a). Prepared according to **General Procedure 7**, **22a**[14] (64.2 mg, 0.20 mmol, 1 equiv) was deprotected by TFA in CH_2Cl_2. The β-amino ester obtained was protected by BnBr in CH_3CN following **General Procedure 8**. The β-amino ester was then reduced by $LiAlH_4$ in THF following **General Procedure 6** affording **23a** (44%), isolated as a white solid: mp 119−121 °C; $[\alpha]_D^{20}$ = −4.1 (*c* 1, $CHCl_3$); IR (neat) 3241, 2925, 2853, 1494, 1453, 1310, 1238, 1153, 1063, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.06 (m, 10H), 3.72 (d, 1H, *J* = 12.9 Hz), 3.54 (d, 1H, *J* = 13.0 Hz), 3.21 (d, 1H, *J* = 12.9 Hz), 3.19−3.06 (m, 4H), 2.77 (d, 1H, *J* = 13.0 Hz), 2.06 (m, 1H), 1.87 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4 (s), 136.9 (s), 130.0 (d, 2C), 128.5 (d, 2C), 128.4 (d, 2C), 128.3 (d, 2C), 126.5 (d), 125.5 (d), 70.0 (t), 64.2 (s), 53.8 (t), 48.8 (t), 37.0 (t), 22.7 (t) ppm; MS *m*/*z* (%) 249 ($M^{+\cdot}$-H_2O, 29), 248 (10), 247 (6), 172 (10), 158 (6), 131 (21), 129 (6), 115 (5), 92 (9), 91 (100), 65 (16); HRMS (ESI) *Calcd. for* $C_{18}H_{22}NO\ (MH)^+$, 268.1696, found 268.1701.

(*S*)-(1,2-Dibenzylpyrrolidin-2-yl)methanol (23b). Prepared according to **General Procedure 7**, **22b**[14] (97 mg, 0.29 mmol, 1 equiv) was deprotected by TFA in CH_2Cl_2. The β-amino ester obtained was protected by BnBr in CH_3CN following **General Procedure 8**. The β-amino ester was then reduced by $LiAlH_4$ in THF following **General Procedure 6** affording **23b** (77%), isolated as a beige solid: mp 85−87 °C; $[\alpha]_D^{20}$ = −3.6 (*c* 1, $CHCl_3$); IR (neat) 3165, 3029, 2929, 2854, 1492, 1461, 1370, 1320, 1268, 1201, 1149, 1119, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.18 (m, 10H), 4.05 (d, 1H, *J* = 12.8 Hz), 3.69 (d, 1H, *J* = 10.1 Hz), 3.52 (d, 1H, *J* = 12.5 Hz), 3.47 (d, 1H, *J* = 10.6 Hz), 3.03 (m, 1H), 2.80 (s, 2H), 2.64 (m, 1H), 1.96−1.65 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5 (s), 137.8 (s), 130.3 (d, 2C), 128.6 (d, 2C), 128.5 (d, 2C), 128.3 (d, 2C), 127.1 (d), 126.3 (d), 67.4 (s), 63.2 (t), 52.1 (t), 50.1 (t), 37.1 (t), 30.3 (t), 21.3 (t) ppm; MS *m*/*z* (%) 281 ($M^{+\cdot}$, 0.1), 250 (9), 190 (29), 92 (8), 91 (100), 65 (10); HRMS (ESI) *Calcd. for* $C_{19}H_{24}NO\ (MH)^+$, 282.1853, found 282.1855.

(*S*)-(1,2-Dibenzylpiperidin-2-yl)methanol (23c). Prepared according to **General Procedure 7**, **22c**[14] (300 mg, 0.86 mmol, 1 equiv) was deprotected by TFA in CH_2Cl_2. The β-amino ester obtained was protected by BnBr in CH_3CN following **General Procedure 8**. The β-amino ester was then reduced by $LiAlH_4$ in THF following **General Procedure 6** affording **23c** (81%), isolated as a white solid: mp 103−104 °C; $[\alpha]_D^{20}$ = −6.7 (*c* 1, $CHCl_3$); IR (neat) 3387, 3029, 2935, 2850, 2812, 1495, 1447, 1412, 1365, 1303, 1133, 1050, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.18 (m, 10H), 4.21 (d, 1H, *J* = 13.7 Hz), 3.94 (d, 1H, *J* = 10.8 Hz), 3.28 (d, 1H, *J* = 13.7 Hz), 3.23 (d, 1H, *J* = 13.2 Hz), 3.17 (d, 1H, *J* = 10.1 Hz), 2.85 (m, 1H), 2.75 (d, 1H, *J* = 13.5 Hz), 2.54 (ddd, 1H, *J* = 12.1, 3.0, and 3.0 Hz), 1.78−1.39 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3 (s), 137.7 (s), 130.1 (d, 2C), 129.5 (d, 2C), 129.1 (d, 2C), 128.5 (d, 2C), 126.5 (d), 126.3 (d), 65.2 (t), 60.6 (s), 53.0 (t), 46.3 (t), 37.1 (t), 29.7 (t), 25.8 (t), 20.6 (t) ppm; MS *m*/*z* (%) 264 ($M^{+\cdot}$−$CH_2OH\cdot$, 8), 204 (33), 92 (8), 91 (100), 65 (10); HRMS (ESI) *Calcd. for* $C_{20}H_{26}NO\ (MH)^+$, 296.2009, found 296.2007.

(*S*)-(1,2-Dibenzylazepan-2-yl)methanol (23d). Prepared according to **General Procedure 7**, **22d**[14] (190 mg, 0.52 mmol, 1 equiv) was deprotected by TFA in CH_2Cl_2. The β-amino ester obtained was reduced by $LiAlH_4$ in THF following **General Procedure 6**. The β-amino alcohol was then protected by BnBr in CH_3CN following **General Procedure 8** affording **23d** (20%), isolated as a colorless oil: $[\alpha]_D^{20}$ = −8.5 (*c* 1, $CHCl_3$); IR (neat) 3110, 2914, 2821, 1498, 1448, 1414, 1258, 1173, 1048, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.19 (m, 10H), 4.07 (d, 1H, *J* = 14.2 Hz), 3.85 (d, 1H, *J* = 10.5 Hz), 3.75 (d, 1H, *J* = 9.2 Hz), 3.53 (d, 1H, *J* = 10.5 Hz), 2.95 (d, 1H, *J* = 12.0 Hz), 2.88 (d, 1H, *J* = 12.5 Hz), 2.77 (m, 2H), 1.94−1.22 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5 (s), 138.1 (s), 130.5 (d, 2C), 128.7 (d, 2C), 128.4 (d, 2C), 128.1 (d, 2C), 126.9 (d), 126.2 (d), 67.7 (t), 60.4 (s), 54.2 (t), 47.0 (t), 40.1 (t), 38.1 (t), 31.2 (t), 29.7 (t), 23.2 (t) ppm; MS *m*/*z* (%) 309 ($M^{+\cdot}$, 1),

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278 (8), 218 (27), 92 (8), 91 (100), 65 (9); HRMS (ESI) *Calcd. for* $C_{21}H_{28}NO$ *(MH)*$^+$, 310.2165, found 310.2162.

(*S*)-1,3-Dibenzyl-3-fluoropyrrolidine (24a). Prepared according to **General Procedure 4**, **23a** (18 mg, 0.07 mmol, 1 equiv) was rearranged in CH_2Cl_2 (3 mL) by DAST (12 μL, 0.09 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 80/20) affording **24a** (18 mg, 0.30 mmol, 96%), isolated as a colorless oil: ee = 94% determined by supercritical fluid chromatography on Daicel chiralcel AD-H column (MeOH 3%, flow rate 5 mL/min, t_{maj} = 2.4 min, t_{min} = 2.7 min); $[\alpha]_D^{20}$ = −3.1 (*c* 1, $CHCl_3$); IR (neat) 2969, 2924, 2793, 1454, 1379, 1300, 1261, 1122, 1073, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.11 (m, 10H), 3.55 (s, 2H), 2.94 (d, 2H, *J* = 24.8 (H−F) Hz), 2.74−2.65 (m, 2H), 2.63 (dd, 1H, *J* = 15.5 and 11.9 Hz), 2.53 (m, 1H), 1.92 (ddd, 2H, *J* = 25.9 (H−F), 6.8 and 6.8 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5 (s), 136.5 (s), 130.1 (d, 2C), 128.8 (d, 2C), 128.3 (d, 2C), 128.2 (d, 2C), 127.1 (d), 126.7 (d), 103.4 (ds, *J* = 179 Hz), 64.0 (dt, *J* = 25 Hz), 60.3 (t), 52.8 (t), 44.3 (dt, *J* = 24 Hz), 37.0 (dt, *J* = 23 Hz) ppm; MS *m*/*z* (%) 269 (M$^{+\cdot}$, 21), 268 (11), 192 (7), 191 (6), 178 (11), 133 (16), 132 (18), 92 (13), 91 (100), 65 (17); HRMS (ESI) *Calcd.* $C_{18}H_{21}FN$ *(MH)*$^+$, 270.16525, found 270.16523.

(*R*)-1,3-Dibenzyl-3-fluoropiperidine (24b). Prepared according to **General Procedure 4**, **23b** (48 mg, 0.17 mmol, 1 equiv) was rearranged in CH_2Cl_2 (3 mL) by DAST (31 μL, 0.24 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 90/10) affording **24b** (34 mg, 0.12 mmol, 71%), isolated as a colorless oil: ee = 98% determined by supercritical fluid chromatography on Daicel chiralcel AD-H column (*i*-PrOH 3%, flow rate 5 mL/min, t_{maj} = 2.8 min, t_{min} = 3.4 min); $[\alpha]_D^{20}$ = +13.2 (*c* 1.1, $CHCl_3$); IR (neat) 3028, 2942, 2801, 1494, 1453, 1346, 1300, 1114, 1078, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.23 (m, 10H), 3.62 (d, 1H, *J* = 12.9 Hz), 3.56 (d, 1H, *J* = 13.6 Hz), 3.10 (dd, 1H, *J* = 24.8 (H−F) and 14.3 Hz), 3.02 (dd, 1H, *J* = 25.5 (H−F) and 14.7 Hz), 2.56−2.43 (m, 4H), 1.89−1.59 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 (s), 136.3 (s), 130.6 (d, 2C), 129.2 (d, 2C), 128.3 (d, 2C), 128.1 (d, 2C), 127.1 (d), 126.5 (d), 93.8 (ds, *J* = 175 Hz), 62.8 (t), 60.5 (dt, *J* = 24 Hz), 53.0 (t), 43.5 (dt, *J* = 21 Hz), 33.4 (dt, *J* = 21 Hz), 22.3 (dt, *J* = 6 Hz) ppm; MS *m*/*z* (%) 283 (M$^{+\cdot}$, 23), 282 (13), 206 (8), 192 (11), 191 (7), 172 (5), 146 (6), 134 (11), 92 (11), 91 (100), 65 (11); HRMS (ESI) *Calcd.* $C_{19}H_{23}FN$ *(MH)*$^+$, 284.1809, found 284.1812.

(*R*)-1,3-Dibenzyl-3-fluoroazepane (24c). Prepared according to **General Procedure 4**, **23c** (163 mg, 0.55 mmol, 1 equiv) was rearranged in CH_2Cl_2 (10 mL) by DAST (102 μL, 0.77 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 90/10) affording **24c** (134 mg, 0.45 mmol, 82%), isolated as a colorless oil: ee = 85% determined by supercritical fluid chromatography on Daicel chiralcel AD-H column (MeOH 10%, flow rate 5 mL/min, t_{maj} = 1.7 min, t_{min} = 2.3 min); $[\alpha]_D^{20}$ = +8.2 (*c* 1, $CHCl_3$); IR (neat) 2927, 1494, 1452, 1350, 1106, 1078, 1008 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.18 (m, 10H), 3.73 (s, 2H), 3.04−2.82 (m, 4H), 2.78 (m, 1H), 2.59 (m, 1H), 1.97−1.47 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (s), 136.7 (s), 130.7 (d, 2C), 128.9 (d, 2C), 128.3 (d, 2C), 128.0 (d, 2C), 127.1 (d), 126.4 (d), 99.2 (ds, *J* = 172 Hz), 64.0 (t), 63.9 (dt, *J* = 30 Hz), 57.8 (t), 45.2 (dt, *J* = 22 Hz), 38.0 (dt, *J* = 23 Hz), 30.9 (t), 21.4 (dt, *J* = 4 Hz) ppm; MS *m*/*z* (%) 297 (M$^{+\cdot}$, 12), 296 (3), 191 (7), 206 (5), 186 (11), 160 (17), 147 (6), 146 (7), 134 (20), 132 (6), 120 (15), 115 (6), 92 (9), 91 (100), 84 (8), 70 (6), 65 (12); HRMS (ESI) *Calcd.* $C_{20}H_{25}FN$ *(MH)*$^+$, 298.1965, found 298.1963.

1,3-Dibenzyl-3-fluoroazocane (24d). Prepared according to **General Procedure 4**, **23d** (14 mg, 0.045 mmol, 1 equiv) was rearranged in CH_2Cl_2 (2 mL) by DAST (12 μL, 0.11 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 90/10) affording **24d** (8.5 mg, 0.027 mmol, 61%), isolated as a yellow oil: ee = 52% determined by supercritical fluid chromatography on Daicel chiralcel AD-H column (MeOH 10%, flow rate 5 mL/min, t_{maj} = 2.4 min, t_{min} = 3.0 min); $[\alpha]_D^{20}$ = +2.1 (*c* 1, $CHCl_3$); IR (neat) 2918, 2854, 2790; 1452, 1347, 1138, 1076, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.10 (m, 10H), 3.69 (d, 1H, *J* = 13.5 Hz), 3.56 (d, 1H, *J* = 13.8 Hz), 2.88−2.55 (m, 4H), 2.36 (m, 2H), 1.95 (m, 1H), 1.84−1.35 (m, 7H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3 (s), 136.7 (s), 130.6 (d, 2C), 128.8 (d, 2C), 128.2 (d, 2C), 128.1 (d, 2C), 126.8 (d), 126.4 (d), 99.9 (ds, *J* = 173 Hz), 64.1 (t), 59.6 (dt, *J* = 26 Hz), 54.6 (t), 43.7 (dt, *J* = 21 Hz), 34.0 (dt, *J* = 23 Hz), 27.1 (t), 27.0 (t), 22.6 (dt, *J* = 9 Hz) ppm; MS *m*/*z* (%) 311 (M$^{+\cdot}$, 3), 220 (12), 160 (13), 134 (15), 120 (9), 92 (10), 91 (100), 65 (10); HRMS (ESI) *Calcd. for* $C_{21}H_{27}FN$ *(MH)*$^+$, 312.2122, found 312.2121.

(*R*)-Methyl 2-((3-Bromopropyl)(*tert*-butoxycarbonyl)amino)-2-phenylacetate (26). To a solution of **25** (3.84 g, 19.09 mmol, 1 equiv) in DMF (25 mL) were added 3-bromopropanol (2.57 mL, 28.6 mmol, 1.5 equiv), NaI (248 mg, 1.91 mmol, 0.1 equiv), and K_2CO_3 (5.80 g, 42 mmol, 2.2 equiv). The media was stirred at 70 °C for 2 h before being hydrolyzed by iced water (100 mL). The mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed successively with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (EtOAc/MeOH 90/10) leading to the desired amino alcohol (1.26 g, 5.70 mmol, 30%). To a solution of this alcohol (1.14 g, 5.10 mmol, 1 equiv) in CH_2Cl_2 (10 mL) were successively added Boc_2O (1.33 g, 6.12 mmol, 1.2 equiv) and DIPEA (978 μL, 5.61 mmol, 1.1 equiv). The solution was stirred at rt for 24 h before being hydrolyzed by the addition of a 1 M aqueous solution of hydrochloric acid (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. To a solution of the crude in CH_2Cl_2 (10 mL) were added at 0 °C CBr_4 (2.19 g, 6.63 mmol, 1.3 equiv) and PPh_3 (2.13 g, 8.13 mmol, 1.6 equiv). The mixture was stirred at rt for 2 h before being hydrolyzed by the addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (PE/EtOAc 90/10 to 80/20) leading to **26** (1.38 g, 3.50 mmol, 70% over to steps), isolated as a yellow oil: $[\alpha]_D^{20}$ = +54.2 (*c* 1, $CHCl_3$); IR (neat) 2958, 1743, 1698, 1482, 1054, 1012 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.49−7.20 (m, 5H), 6.01−5.21 (m, 1H), 3.82 (m, 3H), 3.45−3.12 (m, 3H), 2.02−1.32 (m, 12H); ^{13}C NMR (100 MHz, DMSO at 395 K) δ 170.1 (s), 142.2 (s), 134.1 (s), 128.9 (d, 2C), 128.5 (d, 2C), 128.3 (d), 66.5 (s), 62.9 (d), 51.8 (q), 42.6 (t), 28.1 (q, 3C), 23.5 (t), 22.0 (t) ppm; HRMS (ESI) *Calcd. for* $C_{17}H_{25}BrNO_4$ *(MH)*$^+$, 396.0967, found 396.0921.

(*S*)-1-*tert*-Butyl 2-Methyl 2-phenylpyrrolidine-1,2-dicarboxylate (27). To a solution of **26** (1.31 g, 3.4 mmol, 1 equiv) in DMF (32 mL) was slowly added at −60 °C a 0.5 M solution of KHMDS in toluene (8.16 mL, 4.1 mmol, 1.2 equiv). The media was stirred at this temperature for 30 min before being hydrolyzed by the addition of a saturated aqueous solution of NH_4Cl (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed successively with a saturated aqueous solution of $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (PE/Et_2O 80/20 to 70/30) leading to **27** (298 mg, 0.98 mmol, 19%), isolated as a colorless oil: $[\alpha]_D^{20}$ = +14.3 (*c* 1, $CHCl_3$); IR (neat) 3012, 2958, 1734, 1702, 1461, 1238, 1143, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.23 (m, 5H), 3.76 (s, 3H), 3.74−3.68 (m, 2H), 2.60 (m, 1H), 2.27 (m, 1H), 1.89 (m, 1H), 1.65 (m, 1H), 1.24 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (s), 153.9 (s), 140.3 (s), 127.4 (d, 2C), 127.1 (d, 2C), 126.9 (d), 80.2 (s), 71.5 (s), 52.4 (q), 47.8 (t), 43.4 (t), 28.4 (q, 3C), 22.6 (t) ppm; MS *m*/*z* (%) 248 (M$^{+\cdot}$−*t*-Bu·, 1), 246 (M$^{+\cdot}$−CO_2Me·, 20), 190 (35), 147 (11), 146 (100), 117 (15), 77 (7), 57 (93); HRMS (ESI) *Calcd. for* $C_{17}H_{23}NO_4Na$ *(MNa)*$^+$, 328.1519, found 328.1515.

(*S*)-(1-Benzyl-2-phenylpyrrolidin-2-yl)methanol (28). Prepared according to **General Procedure 7**, **27** (242 mg, 0.79 mmol, 1 equiv) was deprotected by TFA in CH_2Cl_2. The β-amino ester was

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then protected by BnBr in CH_3CN following **General Procedure 8**. The β-amino ester obtained was reduced by $LiAlH_4$ in THF following **General Procedure 6** to afford **28** (85%), isolated as a colorless oil: ee = 50% determined by supercritical fluid chromatography on Daicel chiralcel OD-H column (MeOH 15%, flow rate 5 mL/min, t_{maj} = 3.4 min, t_{min} = 4.1 min); $[\alpha]_D^{20}$ = +10.3 (*c* 1, $CHCl_3$); IR (neat) 3414, 3026, 2944, 1494, 1445, 1406, 1363, 1053, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.23 (m, 10H), 4.09 (d, 1H, *J* = 10.1 Hz), 3.91 (d, 1H, *J* = 10.4 Hz), 3.60 (d, 1H, *J* = 13.5 Hz), 3.16 (d, 1H, *J* = 13.5 Hz), 3.10 (ddd, 1H, *J* = 9.3, 7.9, and 3.7 Hz), 2.90 (m, 1H), 2.45 (ddd, 1H, *J* = 13.1, 9.9, and 5.5 Hz), 2.16 (ddd, 1H, *J* = 13.3, 9.1, and 7.1 Hz), 1.95 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6 (s), 140.1 (s), 128.5 (d, 2C), 128.4 (d, 2C), 128.3 (d, 2C), 127.0 (d, 2C), 126.9 (d), 126.6 (d), 69.2 (s), 63.4 (t), 53.8 (t), 52.4 (t), 37.3 (t), 22.8 (t) ppm; HRMS (ESI) *Calcd. for* $C_{18}H_{22}NO$ $(MH)^+$, 268.1696, found 268.1699.

(*R*)-1-Benzyl-3-fluoro-3-phenylpiperidine (29). Prepared according to **General Procedure 4**, **28** (72 mg, 0.26 mmol, 1 equiv) was rearranged in CH_2Cl_2 (3 mL) by DAST (49 μL, 0.37 mmol, 1.4 equiv). The residue was purified by flash chromatography on silica gel (PE/Et_2O 85/15) affording **29** (61 mg, 0.22 mmol, 87%), isolated as a beige solid: ee = 50% determined by supercritical fluid chromatography on Daicel chiralcel OJ-H column (MeOH 5%, flow rate 5 mL/min, t_{maj} = 6.3 min, t_{min} = 7.1 min); $[\alpha]_D^{20}$ = +8.6 (*c* 1, $CHCl_3$); mp 121−123 °C; IR (neat) 2948, 2917, 1447, 1348, 1237, 1160, 1100, 1074, 1030, 1008 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.13 (m, 10H), 3.57 (d, 1H, *J* = 13.2 Hz), 3.51 (d, 1H, *J* = 13.3 Hz), 2.91 (m, 1H), 2.81 (m, 1H), 2.34 (dd, 1H, *J* = 30.4 (H−F) and 12.5 Hz), 2.12 (m, 1H), 2.03−1.91 (m, 2H), 1.76 (m, 1H), 1.56 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (ds, *J* = 21 Hz), 137.6 (s), 129.1 (d, 2C), 128.3 (d, 2C), 128.2 (d, 2C), 127.7 (dd, *J* = 1.5 Hz), 127.1 (d), 124.6 (dd, *J* = 9.6 Hz, 2C), 94.1 (ds, *J* = 177 Hz), 62.8 (t), 62.0 (dt, *J* = 22 Hz), 52.6 (t), 35.0 (dt, *J* = 23 Hz), 21.6 (dt, *J* = 1 Hz) ppm; MS *m*/*z* (%) 269 ($M^{+\cdot}$, 7), 249 ($M^{+\cdot}$-HF, 17), 134 (34), 131 (17), 129 (12), 115 (8), 92 (10), 91 (100), 65 (16); HRMS (ESI) *Calcd. for* $C_{18}H_{21}NF$ $(MH)^+$, 270.16525, found 270.16523.

3-Ethyl-3-fluoroazepane (31). To a solution of **30**[7] (62.8 mg, 0.26 mmol, 1 equiv) in methanol (10 mL) was added Pd/C (6.28 mg, 10%). The reaction media was stirred overnight under hydrogen atmosphere (1 bar) at rt. The mixture was filtered through Celite and washed with CH_2Cl_2 (2 × 10 mL). The solvents were removed under reduced pressure to afford **31** (34.6 mg, 0.24 mmol, 91%), isolated as a colorless oil: IR (neat) 3407, 2835, 1610, 1511, 1247, 1174, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.89 (dd, 1H, *J* = 15.0 and 15.0 Hz), 2.78 (m, 1H), 2.71−2.60 (m, 2H), 1.86 (s br, 1H), 1.81 (m, 1H), 1.65−1.28 (m, 7H), 0.79 (t, 3H, *J* = 7.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.2 (ds, *J* = 169 Hz), 57.1 (dt, *J* = 26 Hz), 50.5 (t), 37.3 (dt, *J* = 24 Hz), 32.1 (dt, *J* = 24 Hz), 31.7 (t), 21.4 (dt, *J* = 5 Hz), 7.4 (dq, *J* = 5 Hz) ppm; MS *m*/*z* (%) 145 ($M^{+\cdot}$, 14), 125 (16), 116 (20), 110 (14), 96 (26), 84 (16), 82 (12), 70 (100), 68 (13), 59 (17), 57 (31), 56 (44), 55 (21), 53 (10); HRMS (ESI) *Calcd. for* $C_8H_{17}NF$ $(MH)^+$, 146.1339, found 146.1337.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR and ^{13}C NMR of compounds described, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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