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Diastereospecific fluorination of substituted azepanes

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ABSTRACT

Fluorination of bioactive compounds is an important step in drug discovery and development. Fluorination has been extensively studied in acyclic systems, carbocycles, and fused heterocycles. However, there is no report on fluorination of azepanes. As azepanes are components of many biologically active substances and natural products. We herein present the first fluorination examples of substituted azepanes. Fluoroazepanes were prepared by deoxyfluorination diastereospecifically in excellent yields. The absolute configuration at the fluorination site was unambiguously assigned by 2D NMR spectroscopy.

1. Introduction

Fluorine is virtually absent in bioactive natural molecules. However, 20% of all drugs approved and 3 of the top 10 best selling drugs in 2011 contain fluorine atom(s).[1] In general, more than 1/5th of all pharmaceuticals and 1/3rd of agrochemicals have at least one fluorine atom.[2] Because fluorine is the most electronegative atom, is small and forms very strong C–F bonds, hydrogen replacement by its bioisosteric fluorine in compounds can lead to profound changes in their physical, chemical, and biological properties.[2d,3] For example, the fluorine *gauche* effect is known to influence the conformation of molecules as a complex function of steric, electrostatic, and stereoelectronic contributors.[4] Thus, fluorination reactions continue to be of interest to organic, medicinal, and agro chemists as evidenced by a growing number of publications in this area.[5] In particular, fluorinated building blocks represent the most efficient entry into diverse structures of fluorinated compounds.[1] Herein, we report the first examples of fluorinated azepanes as new building blocks for diversity generation.

Substituted azepane rings are prevalent in many bioactive natural compounds.[6] Recently, polysubstituted azepane rings and related compounds (iminocyclitols or iminosugars) have attracted considerable attention of medicinal chemists and biologists as they have demonstrated great potential[7] as glycosidase inhibitors and antidiabetics,[8] anticancer,[9] antivirals[10] including HIV,[11] and DNA minor groove binding agents (MGBLs).[12] The added flexibility of a seven membered ring allows functional groups (for instance hydroxyl groups) to adopt a variety of H-bonding positions for protein binding.[13] Unfortunately, despite the important role of azepanes in bioactive molecules[14] and the large potential of fluorinated azepanes in diversity-oriented bioactivity discovery, their preparation has not been reported.

We chose a substituted tetrahydroazepine **7** as our starting model for investigation. The 1,2-*trans*-benzyloxyazido substitution motif in **7** can be easily reduced to 1,2-*trans*-hydroxylamino motif found in many bioactive natural products.[15] The 3-aminoazepane motif is also seen in antitumor *cis*-platin analogs[16] and somatostatin mimics.[17] Therefore fluorinated azepane building blocks from **7** will have wide utility in diversity-oriented synthesis of fluorinated bioactive leads. Many approaches, such as substitution of oxygen with fluorine(s) in carbonyls and replacement of amides with vinyl fluoride[18] have been achieved successfully. Replacement of a hydroxyl group with fluorine has also gained increasing popularity recently, and an increasing number of natural products and bioactive molecules have been synthesized using deoxyfluorination.[19] This strategy was therefore investigated in this study.

The most commonly used nucleophilic fluorinating agents for substituting hydroxyl group with fluorine are diethylaminosulfur trifluoride (DAST),[20] bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor®),[21] Fluorinox, 2,2-difluoro-1,3-dimethyl-imidazolidine (DFI),[22] and perfluoro-1-butanesulfonyl fluoride (PBSF).[23] However, DFI and PBSF being milder reagents require harsher reaction conditions and longer reaction times than DAST and Deoxofluor®. So, we focused our attention on fluorination using

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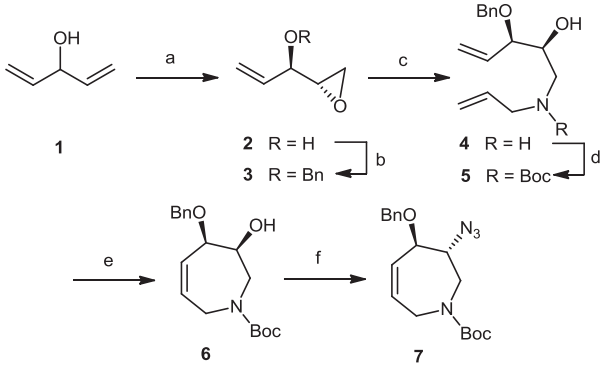
DAST and Deoxofluor®. The general reactivity trend in nucleophilic deoxyfluorination reactions follows the S_N2 pathway with inversion of stereochemistry at the participating stereo-center. However, there are some reports of racemization mainly due to S_N1 competition.[19a,19b] Fluorination reactions of fused heterocycles have been reported before[19d,19e] with S_N2 outcomes. The stereochemical outcomes of deoxyfluorination of substituted azepanes were thus investigated, and we report here deoxyfluorination with retention of stereochemistry due to neighboring group participation.

2. Results and discussion

2.1. Synthesis of tetrahydroazepine 7

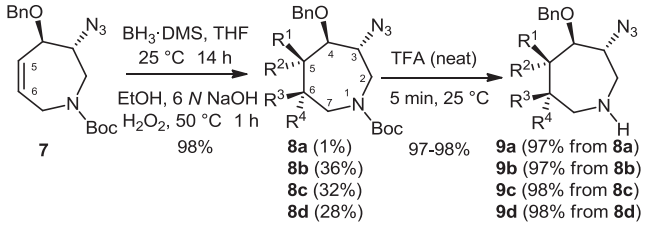
Our investigation started with the preparation of the hydroxyazepanes for use in deoxyfluorination. Disubstituted azepine **7** was synthesized first as the precursor to hydroxyazepanes. The concise six-step protocol (Scheme 1) by Fürstner and Thiel[24] was adopted, starting from divinylcarbinol **1**. Sharpless epoxidation of **1** was performed as described previously[25] and furnished epoxide **2** in excellent optical purity and yield. O-Benzylation was achieved using benzyl bromide before regioselective opening of the oxirane ring of **3** with allylamine to provide diene **4** in 88% yield over two steps. *tert*-Butyloxycarbonyl (Boc) protection of the secondary amine readily provided diene **5**, which served as the precursor for the following ring closing metathesis. Metathesis reaction of **5** was performed by refluxing 0.02 M solution of diene **5** in CH_2Cl_2 in the presence of Grubbs catalyst (5+3 mol %) to afford the desired cycloalkene **6** in 86% yield. Secondary alcohol functionality of **6** was subsequently converted into an azido group with $(PhO)_2P(O)N_3$, diethyl azodicarboxylate, and triphenylphosphine (PPh_3) in THF at room temperature to provide **7** in an overall yield of 54% in six steps.



Scheme 1. Synthesis of tetrahydroazepine **7**. Reagents and conditions: (a) D-(−)-DIPT, cumene hydroperoxide, $Ti(O^iPr)_4$, CH_2Cl_2, −35 °C, 83%, >99% ee; (b) NaH, BnBr, THF, 14 h, rt, 93%; (c) Allylamine (neat), 40 h, 70 °C, 95%; (d) Boc_2O, Et_3N, CH_2Cl_2, 16 h, rt, 96%; (e) Grubbs catalyst, CH_2Cl_2, 42 h, 86%; (f) PPh_3, DEAD, $(PhO)_2P(O)N_3$, THF, 2 h, rt, 89%.

2.2. Hydroboration–oxidation of tetrahydroazepine 7

Tetrahydroazepine **7** then underwent hydroboration (Scheme 2) with borane dimethylsulfide ($BH_3 \cdot SMe_2$) as the boronating agent in THF at 25 °C to furnish hydroxyazepanes **8a**–**d** in 98% overall yield with 2:1 regioselectivity. The mixture of compounds **8a**–**d** was separated by reverse phase HPLC using acetonitrile:water:trifluoroacetic acid (TFA) (from 30:70:0.1 to 60:40:0.1 over 85 min; flow rate: 8.8 mL/min) as a mobile phase to give **8a** (1%), **8b** (36%), **8c** (32%), and **8d** (28%) as colorless oils. The hydroboration exhibited a mild level of regioselectivity (**8a**+**8b**:**8c**+**8d** at 38:62) and a moderate level of diastereofacial selectivity (**8a**+**8c**:**8b**+**8d** at 30:70). It is noteworthy that the diastereoselectivity (1:37 at C5; *cis*:*trans* to C4 substitution) and regioselectivity (C5 to C6 at 1:1.63)



Scheme 2. **8a** and **9a**: R^1=OH, R^2, R^3, R^4=H; **8b** and **9b**: R^2=OH, R^1, R^3, R^4=H; **8c** and **9c**: R^3=OH, R^1, R^2, R^4=H; **8d** and **9d**: R^4=OH, R^1, R^2, R^3=H.

pattern observed is significantly different from the monosubstituted azepine reported previously (diastereoselectivity: 2:1 at C4; *cis*:*trans* to C3 substitution; and regioselectivity: C4 to C5 at 3:1) by Trost et al.[26] The observed difference in selectivity may potentially be due to the *O*-benzyl directing group (at C4) here instead of *N*-Cbz (at C3) used by Trost.

Detailed analysis of ^1H, ^{13}C, and 2D NMR (HSQC, HMBC, COSY, and NOESY) enabled us to unambiguously elucidate the structures of compounds **8a**–**d** (Supplementary data).

The key correlations of **8c** and **8d** are shown in Fig 1 as a representative for the absolute configuration assignment. In **8c**, HMBC and HSQC couplings with C1′ (δ_c 71.7 ppm) and C4 (δ_c 78.7 ppm), respectively, identified H4 at 3.37 ppm. H4 further showed COSY correlations with H5a (δ_H 1.74 ppm) and H5b (δ_H 2.30 ppm), both of which showed correlations to H6 (δ_H 3.97 ppm). Moreover, H4 showed NOE to H6 in its NOESY spectra. However, in **8d** H6 (δ_H 4.14 ppm) did not show any detectable NOE to H4 (δ_H 3.80 ppm), but showed strong NOE to H3 (δ_H 3.70 ppm). Thus, the absolute configuration assignments at C6 in **8c** and **8d** were confirmed to be *S* and *R*, respectively. The same process enabled the assignment at C5 in **8a** and **8b** to be *R* and *S*, respectively. The stereochemistry was further confirmed by *N*-Boc deprotection using neat TFA to furnish compounds **9a**–**d** in quantitative yields (Scheme 2). In the absence of geometric isomers (*cis* and *trans*) of the *N*-Boc group, the assignments of **9a**–**d** were secured by 2D NMR spectroscopy and confirmed the assignment of **8a**–**d** (Supplementary data).

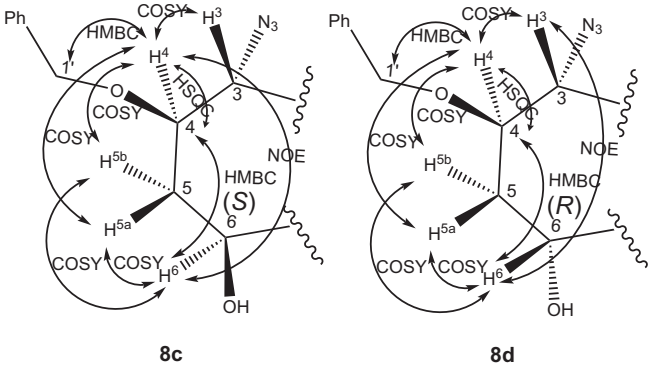


Fig. 1. Key 2D NMR correlations for compound **8c** and **8d**.

2.3. Optimization of hydroboration of 7

While hydroboration of **7** using $BH_3 \cdot SMe_2$ furnished an excellent overall yield of **8a**–**d**, reaction conditions were investigated to examine the regio- and diastereoselectivity of this reaction (Table 1). The conventional condition with borane tetrahydrofuran complex (Table 1, entry 2) gave excellent yield but unsurprisingly, poor diastereoselectivity. On the other hand 9-BBN (Table 1, entry 6) furnished excellent diastereoselectivity but poor yield even after reflux for 48 h. $BH_3 \cdot NMe_3$ after reflux for 48 h (Table 1, entry 4) gave

Table 1
Screening of different hydroborating agents[a]

Entry	Conditions	Yield[b] (%)	Ratio[c]			
			8a	8b	8c	8d
1	BH_3·DMS, 25 °C, 14 h	98	1	37	33	29
2	BH_3·THF, 25 °C, 14 h	81	0	34	31	35
3	BH_3·NMe_3, 25 °C, 24 h	0	0	0	0	0
4	BH_3·NMe_3, 66 °C, 48 h	20	0	49	0	51
5[a]	BH_3·NMe_3, 101 °C, 48 h	0	0	0	0	0
6[a]	BH_3·NMe_3, 110 °C, 48 h	0	0	0	0	0
7	9-BBN, 25 °C, 24 h	0	0	0	0	0
8	9-BBN, 66 °C, 48 h	12	0	1	0	99
9	CatBH, 25 °C, 24 h	0	0	0	0	0
10	CatBH, 66 °C, 48 h	42	0	37	27	36
11[d]	CatBH, 25 °C, 24 h	0	0	0	0	0
12[d]	CatBH, 66 °C, 48 h	14	0	1	51	48
13	PinBH, 25 °C, 24 h	0	0	0	0	0
14	PinBH, 66 °C, 48 h	0	0	0	0	0

[a] All the reactions were carried out in THF except entry 5 (in dioxane) and 6 (in toluene).
[b] Isolated yield of **8** after column chromatography; unreacted **7** was recovered.
[c] Ratio was calculated on the basis of HPLC traces.
[d] 10 mol % $(PPh_3)_3RhCl$ was used.

diastereofacial selectivity but poor yield. Utilization of dioxane and toluene as solvents for BH_3·NMe_3 condition gave only starting material **7** back. More stable hydroborating agents, such as CatBH and PinBH were also employed. As anticipated, at room temperature only starting materials were recovered. However, refluxing in THF after 48 h with CatBH (Table 1, entry 10) furnished a mixture of diastereomers **8b**–**d** in low yield but no improvement in diastereoselectivity.

The addition of rhodium catalyst (Table 1, entry 12) improved regioselectivity, which was consistent with prior studies by Evans et al.[27] but the yield remained low. In the case of PinBH, only starting azepine **7** was recovered (Table 1, entries 13, 14).

With BH_3·SMe_2 as the hydroborating agent, solvents were screened for optimization (Table 2). In non-polar solvents, such as benzene, diethyl ether, chloroform, methylene chloride, and dioxane under reflux for 48 h, only starting materials were recovered. However, toluene (Table 2, entry 2) furnished **8b**–**d** in 19% yield with no significant change in diastereoselectivity to that of THF (Table 2, entry 1). DCE resulted in excellent yields (Table 2, entries 3) with significantly different regioselectivity (C6:C5 at 20:1) compared to 1.63:1 in the case of THF. In acetonitrile, only **7** was recovered (Table 2, entry 4). Overall polar aprotic solvents, such as THF and DCE are the best for this hydroboration reaction, which is in accordance with previous reports on diverse range of substrates, such as styrene, acyclic, carbocyclic, and heterocyclic olefins.[28]

Table 2
Solvent effects in hydroboration of **7**[a]

Entry	Conditions	Yield[b] (%)	Ratio[c]			
			8a	8b	8c	8d
1	THF, 25 °C, 14 h	98	1	37	33	29
2	Toluene, 110 °C, 48 h	19	0	35	30	35
3	DCE, 25 °C, 14 h	98	0	5	40	55
4	MeCN, 82 °C, 48 h	0	0	0	0	0

[a] All reactions were carried out using BH_3·SMe_2 as hydroborating agent.
[b] Isolated yield of **8a**–**d** after column chromatography; unreacted **7** was recovered.
[c] Ratio was calculated on the basis of HPLC traces.

Stabilized boranes, such as CatBH and PinBH with less Lewis-acidity, offer an advantage of better functional group tolerance and ease for storage and handling. However, hydroboration with stabilized boranes usually requires catalytic activation. As such the course of the reaction can be tuned by a catalytic additive. Transition metal-catalyzed addition of CatBH/PinBH to alkenes and alkynes has shown remarkable chemo-,[29] regio-,[27,30] diastereo-,[27,30,31] and enantioselectivities for acyclic, carbocyclic, and heterocyclic substrates.[28a,32] We employed different metal–ligand combinations for hydroboration of azepine **7** to examine their effects on diastereoselectivity. $[Rh(COD)_2Cl]_2$,[33] $Ir(COD)(PCy_3)(Py)PF_6$,[34] $Rh(COD)(DPPB)BF_4$,[33b] and $Rh(COD)(PPh_3)BF_4$[33b] have demonstrated excellent selectivity in styrene hydroboration and were thus investigated in the hydroboration of **7**. In the case of CatBH, $[Rh(COD)_2Cl]_2$, and $Ir(COD)(PCy_3)(Py)PF_6$ furnished a regioselectivity ratio of (C6:C5) of 13.3:1 in moderate yields (Table 3, entries 1–2). $Ir(COD)(PCy_3)(Py)PF_6$ under reflux resulted in higher yield but lower (8:1) regioselectivity (Table 3, entry 3). In the case of PinBH, $Rh(COD)(DPPB)BF_4$, and $Rh(COD)(PPh_3)BF_4$ furnished 10:1 regioselectivity and moderate yields. Recently, Lata and Crudden[28b] have reported the use of Lewis acid additives, such as $Sc(OTf)_3$ and tris(pentafluorophenyl) borone (FAB) for Rh catalyzed hydroboration of acyclic olefins. $Sc(OTf)_3$ and FAB were therefore employed with $Rh(COD)(DPPB)BF_4$ and DCE as solvent. In the case with $Sc(OTf)_3$, **7** was recovered (Table 3, entry 6) while FAB alone furnished 10:1 regioselectivity in good yield with heating (Table 3, entry 8). The best diastereoselectivity (**8d**:**8a**–**c**) obtained in our study (Table 3, entries 1–8) with Rh and Ir catalysts is 2.2:1. Noh et al.[35] have reported excellent enantio- and regioselectivity with the use of ligands (*R*)-DTMB-Segphos and (*S*,*S*,*R*,*R*)-Tangphos in copper(I)-catalyzed hydroboration of styrene and β-substituted vinyl arenes. We investigated these ligands for CuCl catalyzed hydroboration of azepine **7** with PinBH in toluene. (*R*)-DTMB-Segphos furnished **8b**–**d** in 78% yield with 11.5 to 1 regioselectivity (C6:C5) at 70 °C in toluene (Table 3, entry 10) while (*S*,*S*,*R*,*R*)-Tangphos demonstrated 24:1 regioselectivity and 82% yield (Table 3, entry 12). Solvent effects were investigated for this copper-(*S*,*S*,*R*,*R*)-Tangphos catalyzed condition. THF, DCE and $CHCl_3$ did not result in better yield or selectivity. It is noteworthy that although transition metal catalyzed hydroboration has been extensively studied, reports on complex heterocyclic substrates are rare. To our best knowledge, this is the first study of transition metal catalyzed hydroboration of a substituted azepane ring.

2.4. Deoxyfluorination of azepanes 8b–d

Compounds **8b**–**d** were subjected to fluorination reactions (Scheme 3) in the presence of DAST or Deoxofluor® in DCM at 25 °C to provide fluoroazepanes **10b**–**d**, respectively (Table 4, entries 3, 13, and 15). The stereochemical assignments of C5 and C6 in **10b**–**d** were secured by 2D NMR experiments. Furthermore, **10b**–**d** were Boc deprotected to give **11b**–**d** (Scheme 3) to further confirm the stereochemistry at C5 and C6 without *cis*/*trans* isomerism due to the Boc group.

Fluorination using nucleophilic agents, such as DAST is expected to give inversion of stereochemistry at the participating chiral carbon center.[36] However, in our case retention of stereochemistry at C5 and C6 of **10b**–**d** was observed as revealed by 2D NMR data (Supplementary data).

Retention of stereochemistry in such fluorination cases is possible with the assistance of neighboring group participation.[37] In the case of cyclitol derivatives, there are a few reports for retention of stereochemistry explained by double inversion through participation of adjacent 2-methoxyethoxymethyl,[37a] benzyl,[37e] methoxy[37d] groups containing nucleophilic centers or bromomethyl[37d] via bromine anchimeric assistance. Electron rich nitrogen or sulfur containing heterocyclic substrates also demonstrates retention of stereochemistry through formation of aziridinium or episulfonium intermediates.[37c,38] For example, retention of stereochemistry in fluorination of benzyl protected piperidine **12** by hydroxy

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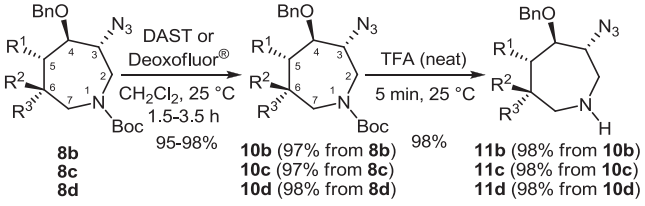
Table 3
Catalyst screening in hydroboration of **7**[a]

Entry	Conditions	Yield[a] (%)	Ratio[b]			
			8a	**8b**	**8c**	**8d**
1	CatBH, 1 mol % $[Rh(COD)_2Cl]_2$, THF, 25 °C, 24 h	43	0	7	52	41
2	CatBH, 5 mol % $Ir(COD)(PCy_3)(Py)PF_6$, THF, 25 °C, 24 h	38	0	7	24	69
3	CatBH, 5 mol % $Ir(COD)(PCy_3)(Py)PF_6$, THF, 66 °C, 14 h	72(70)	0	11	27	62
4	PinBH, 1 mol % $Rh(COD)(PPh_3)BF_4$, DCE, 25 °C, 24 h	40	0	9	33	58
5	PinBH, 1 mol % $Rh(COD)(DPPB)BF_4$, DCE, 25 °C, 24 h	41	0	9	32	59
6	PinBH, 1 mol % $Rh(COD)(DPPB)BF_4$, 2 mol % $Sc(OTf)_3$, DCE, 25 °C, 24 h	0	0	0	0	0
7	PinBH, 1 mol % $Rh(COD)(DPPB)BF_4$, 2 mol % FAB, DCE, 25 °C, 24 h	36	0	12	21	67
8	PinBH, 1 mol % $Rh(COD)(DPPB)BF_4$, 2 mol % FAB, DCE, 70 °C, 14 h	67(63)	0	9	24	67
9	PinBH, 3 mol % CuCl, 3.3 mol % Segphos, 6 mol % NaO^{t}Bu, toluene, 25 °C, 24 h	26	0	5	49	46
10	PinBH, 3 mol % CuCl, 3.3 mol % Segphos, 6 mol % NaO^{t}Bu, toluene, 70 °C, 14 h	78(72)	0	8	38	54
11	PinBH, 3 mol % CuCl, 3.3 mol % Tangphos, 6 mol % NaO^{t}Bu, toluene, 25 °C, 24 h	53	0	4	31	65
12	**PinBH, 3 mol % CuCl, 3.3 mol % Tangphos, 6 mol % NaO^{t}Bu, toluene, 70 °C, 14 h**	**82(80)**	**0**	**4**	**31**	**65**
13	PinBH, 3 mol % CuCl, 3.3 mol % Tangphos, 6 mol % NaO^{t}Bu, toluene, 110 °C, 14 h	86	0	7	35	58
14	PinBH, 3 mol % CuCl, 3.3 mol % Tangphos, 6 mol % NaO^{t}Bu, $CHCl_3$, 61 °C, 14 h	0	0	0	0	0
15	PinBH, 3 mol % CuCl, 3.3 mol % Tangphos, 6 mol % NaO^{t}Bu, DCE, 70 °C, 14 h	14	0	18	40	42
16	PinBH, 3 mol % CuCl, 3.3 mol % Tangphos, 6 mol % NaO^{t}Bu, THF, 66 °C, 14 h	60	0	9	36	55

The entries in bold indicate the most optimal reactions conditions.
[a] 1.5 equiv CatBH or PinBH were used; % conversion based on crude ^{1}H NMR; number in parentheses is isolated yield of **8a**–**d** after column chromatography; unreacted **7** was recovered.
[b] Ratio was calculated on the basis of HPLC traces.

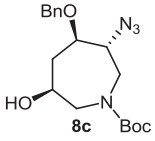
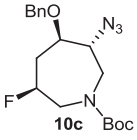
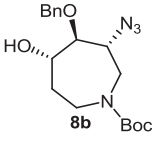
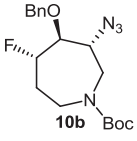
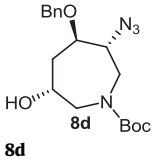
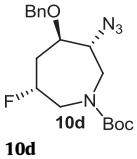


Scheme 3. **8b**: R^1=OH, R^2, R^3=H; **8c**: R^2=OH, R^1, R^3=H; **8d**: R^3=OH, R^1, R^2=H; **10b** and **11b**: R^1=F, R^2, R^3=H; **10c** and **11c**: R^2=F, R^1, R^3=H; **10d** and **11d**: R^3=F, R^1, R^2=H.

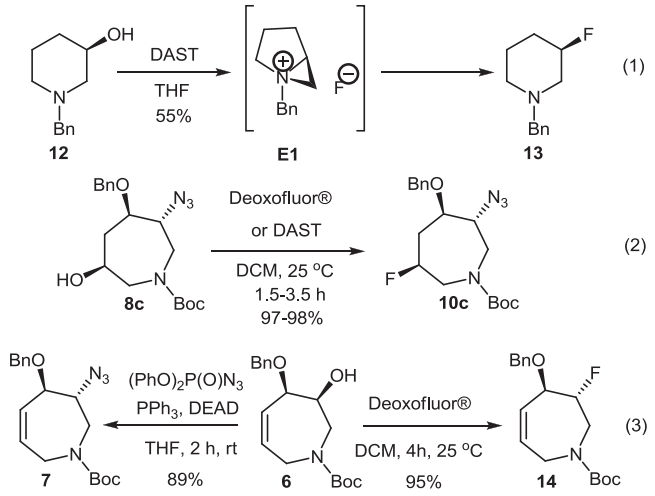
replacement was conferred via an aziridinium intermediate[38] (Scheme 4, Eq. 1) to give **13**. This neighboring group effect from an electron rich nitrogen center by aziridinium formation is not possible in our azepanes **8b**–**d**, given the presence of the *N*-Boc protecting group.

In the case of **8b**–**d**, the retention of stereochemistry can best be explained by the neighboring group effect of the carbamate oxygen (Scheme 4, Eq. 2) via formation of a five (**8c**–**d**) or six (**8b**) membered ring. This would be in accordance with prior examples

Table 4
Deoxyfluorination of compounds **8b**–**d**

Entry	Fluorinating agent	Substrate	Product[a]	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	DAST	 **8c**	 **10c**	CH_2Cl_2	−78	6.5	92
2	DAST	**8c**	**10c**	CH_2Cl_2	0	6.5	89
3	**DAST**	**8c**	**10c**	**CH_2Cl_2**	**25**	**3.5**	>**99**(**97**)
4	DAST	**8c**	**10c**	Toluene	25	14	48[c]
5	DAST	**8c**	**10c**	$CHCl_3$	25	14	5
6	DAST	**8c**	**10c**	*n*-Pentane	25	14	90
7	Deoxofluor®	**8c**	**10c**	CH_2Cl_2	−78	6.5	94
8	Deoxofluor®	**8c**	**10c**	CH_2Cl_2	0	6.5	96
9	**Deoxofluor®**	**8c**	**10c**	**CH_2Cl_2**	**25**	**1.5**	>**99**(**98**)
10	Deoxofluor®	**8c**	**10c**	Toluene	25	14	76[c]
11	Deoxofluor®	**8c**	**10c**	$CHCl_3$	25	14	91
12	Deoxofluor®	**8c**	**10c**	*n*-Pentane	25	14	88
13	**DAST**	 **8b**	 **10b**	**CH_2Cl_2**	**25**	**3.5**	**96**(**95**)
14	**Deoxofluor®**	**8b**	**10b**	**CH_2Cl_2**	**25**	**1.5**	>**99**(**97**)
15	**DAST**	 **8d**	 **10d**	**CH_2Cl_2**	**25**	**4**	**97**(**95**)
16	**Deoxofluor®**	**8d**	**10d**	**CH_2Cl_2**	**25**	**1.5**	>**99**(**97**)

The entries in bold indicate the most optimal reactions conditions.
[a] Only one diastereomer was formed.
[b] Yield was calculated on the basis of HPLC traces; number in parentheses represents isolated yield.
[c] Diastereomeric ratio (**10c**:**10d**) was 98:2.



Scheme 4. (1) Neighboring group effect via an aziridinium intermediate; (2) retention of stereochemistry in deoxyfluorination; (3) inversion of stereochemistry in **6** via S_N2 pathway.

of amide oxygen participation.[37b] Sekar et al.[39] investigated the effect of nitrogen protecting groups for chlorination reaction using PPh_3 and *N*-chorosuccinimide (NCS), which also follows a S_N2 pathway. Their study showed that protecting groups like phenyl, substituted phenyl, and amide exhibit neighboring group participation resulting in retention of stereochemistry from double inversion. However, in their system protecting groups, such as *N*-tosyl or Cbz did not show any neighboring group effect and inversion of stereochemistry was observed. In their study, the substrate used was 2-hydroxy cyclohexylamine, which is quite different from the azepanes here. To test if ring rigidity may influence such neighboring group participation, alcohol **6** was subjected to deoxyfluorination using Deoxofluor® in DCM. Compared to **8c**, **6** may undergo deoxyfluorination with retention of stereochemistry, given that the hydroxyl group is equal distance to the carbamate group as is the case of **8c**. However, due to the presence of the double bond between C5 and C6, the seven-membered ring in **6** is more rigid. The resulting fluoroazepane **14** from **6** was obtained in excellent yield with inversion of stereochemistry (Scheme 4, Eq. 3). It is also noteworthy that alcohol **6** undergoes inversion of stereochemistry to form tetrahydroazepine **7** under mitsunobu conditions following an S_N2 pathway (Scheme 4, Eq. 3). Thus, in spite of being at equicarbon distance to the nitrogen center, the center of substitution in **6** (C3) and **8b**–**d** (C5 or C6) presented different neighboring group effects potentially because of the rigidity of **6** compared to **8b**–**d**. This suggests that retention of stereochemistry in **8b**–**d** deoxyfluorination is dependent on ring rigidity. To the best of our knowledge, this is the first example of carbamate oxygen neighboring group effect for retention of stereochemistry in deoxyfluorination. Given this neighboring group effect, the yields and diastereomeric ratios under other fluorination conditions were examined using **8b**–**d** (Table 4). The deoxyfluorination at lower temperatures resulted in longer reaction times as expected (Table 4, entries 1–3). The diastereospecific conversion was maintained in all cases while different solvents only affected yields. As Deoxofluor®[21,40] is considered a better fluorinating agent than DAST in terms of thermal stability[40b] and reactivity,[40e] deoxyfluorination of **8b**–**d** was also examined using Deoxofluor® (Table 4, entries 7–12, 14, and 16). The yields of fluorination observed in these cases were slightly better than those of DAST.

Significant differences in yields however were observed in toluene and $CHCl_3$ where Deoxofluor® compared to DAST led to much better yields (Table 4, entries 4, 5, 10, and 11). On the other hand, slight racemization (98:2) was observed in the case of toluene with DAST and Deoxofluor® (Table 4, entries 4 and 10).

3. Conclusion

In conclusion, we report here the first practical and efficient diastereospecific fluorination of substituted azepanes in two steps with an overall yield of>95% from a starting tetrahydroazepine **7**. The approach of deoxyfluorination using DAST or Deoxofluor® gave diastereospecific fluorination with retention of stereochemistry, most likely by neighboring group participation from a carbamate. As fluorinated azepanes are important pharmacophores, these fluorinated azepanes should serve as new fluorinated building blocks in drug discovery.

4. Experimental section

4.1. General

All reactions were conducted under N_2 atmosphere. Unless otherwise specified, all reagents were purchased from Sigma–Aldrich and used without further purification. CH_2Cl_2 was obtained from a solvent purification system (Innovative Technology SPS400) and stored over MS 4 Å beads. Ethyl acetate and petroleum ether were distilled before use and the later refers to the fraction collected between 60 °C and 80 °C. THF and toluene were distilled from Na–benzophenone and stored over MS 4 Å beads. $CHCl_3$ was distilled from $CaCl_2$ and stored over MS 4 Å beads in the dark. Anhydrous *n*-pentane was obtained from Sigma–Aldrich and used without further purification. ^{1}H NMR spectra were recorded at 25 °C on either a Bruker DRX600K or DPX400 NMR Spectrometer and are reported in parts per million using the specified solvent as the internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C NMR spectra are reported in ppm using the specified solvent as the internal standard ($CDCl_3$ at 77.16 ppm).

4.2. (2*S*,3*R*)-1,2-Epoxy-4-penten-3-ol (2)

A crushed 4 Å molecular sieves (400 mg) in CH_2Cl_2 (12 mL) was cooled to −35 °C. Pre-cooled (−35 °C) titanium tetraisopropoxide (350 μL, 1.19 mmol) and (*R*,*R*)-(−)-diisopropyl tartrate (330 μL, 1.55 mmol) were added drop wise via syringe. Pre-cooled (−35 °C) divinylcarbinol (1.00 g, 11.9 mmol) and cumene hydroperoxide (3.50 mL, 23.8 mmol) were added drop wise via glass syringe after 30 min. The reaction mixture was allowed to stir at −35 °C for 36 h. Aqueous saturated Na_2SO_4 (1 mL) was added after warming up to room temperature and the mixture was diluted with Et_2O (10 mL). The mixture was then stirred at ambient temperature for 3 h, the resulting slurry was vacuum filtered through a pad of Celite and the resulting yellow solution was concentrated under vacuum at 0 °C to furnish the crude residue, which was subjected to flash chromatography (petroleum ether/EtOAc, 4/1 then 100% Et_2O) to give **2** (990 mg, 83%) as a colorless oil with optical rotation and ^{1}H NMR spectral data matching those reported previously.[25] $[\alpha]_D^{20}$ −50 (*c* 0.73, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.90–5.83 (m, 1H), 5.39 (br d, *J*=17.3 Hz, 1H), 5.26 (d, *J*=10.5 Hz, 1H), 4.34 (br s, 1H), 3.09 (dd, *J*=6.4, 3.0 Hz, 1H), 2.84–2.74 (m, 2H), 2.08 (br, s, 1H).

4.3. (*S*)-2-((*R*)-1-Benzyloxy-allyl)-oxirane (3)

NaH (260 mg, 10.9 mmol) was added slowly to a solution of epoxyalcohol **2** (990 mg, 9.90 mmol) and $(n\text{-Bu})_4NI$ (370 mg, 990 μmol) in THF (22 mL). Benzyl bromide (3.39 g, 19.8 mmol) was added drop wise via syringe after 5 min and the resulting suspension was stirred at ambient temperature for 14 h. The reaction was quenched by drop wise addition of aqueous saturated $NaHCO_3$

(10 mL) and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic phases were dried (Na_2SO_4) before solvent was evaporated to get the residue, which was purified by flash chromatography (petroleum ether/EtOAc, 9/1) to give **3** (1.75 g, 93%) as a colorless oil with optical rotation and ^1H NMR spectral data matching those reported previously.[24] $[\alpha]_D^{20}$ −31.6 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.24 (m, 5H), 5.88–5.77 (m, 1H), 5.38–5.31 (m, 2 H), 4.63 (d, *J*=12.0 Hz, 1H), 4.47 (d, *J*=12.0 Hz, 1H), 3.80 (dd, *J*=7.3, 4.2 Hz, 1H), 3.10–3.06 (m, 1H), 2.76 (dd, *J*=5.2, 4.0 Hz, 1H), 2.67 (dd, *J*=5.2, 2.6 Hz, 1H).

4.4. (2*S*,3*R*)-1-Allylamino-3-benzyloxy-pent-4-en-2-ol (4)

An epoxide **3** (790 mg, 4.15 mmol) was refluxed in freshly distilled allylamine (6.25 mL, 83.0 mmol) for 40 h. Excess allylamine was removed under reduced pressure. The remaining pale yellow oil was amine **4** (980 mg, 95%) with optical rotation and ^1H NMR spectral data matching those reported previously[24] and was pure enough to be used in the next step without further purification. $[\alpha]_D^{20}$ −36.6 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.22 (m, 5H), 5.96–5.75 (m, 2H), 5.36–5.31 (m, 2H), 5.18–5.02 (m, 2H), 4.59 (d, *J*=11.8 Hz, 1H), 4.35 (d, *J*=11.8 Hz, 1H), 3.82–3.73 (m, 2H), 3.30–3.22 (m, 2H), 3.14 (br s, 2H), 2.77 (dd, *J*=12.3, 3.7 Hz, 1H), 2.70–2.63 (m, 1H).

4.5. (2*S*,3*R*)-Allyl-(3-benzyloxy-2-hydroxy-pent-4-enyl)-carbamic acid-*tert*-butyl ester (5)

Di-*tert*-butyl dicarbonate (48.8 mg, 220 μmol) in CH_2Cl_2 (2 mL) was added to a mixture of amine **4** (49.5 mg, 200 μmol) and Et_3N (39.0 μL, 280 μmol) in CH_2Cl_2 (2 mL) at 0 °C and the resulting mixture was stirred at ambient temperature for 2 h. The reaction mixture was quenched by addition of water (2 mL) before the extraction of the aqueous phase with EtOAc (2×5 mL). Successive washing of the combined organic layers with aqueous 2 N HCl (5 mL) and brine (5 mL) followed by drying (Na_2SO_4), evaporation of the solvents and flash chromatography of the residue (petroleum ether/EtOAc, 6/1) gave compound **5** (66.8 mg, 96%) as a colorless oil with optical rotation and ^1H NMR spectral data matching those reported previously.[24] $[\alpha]_D^{20}$ −28.8 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.23 (m, 5H), 5.89–5.68 (m, 2H), 5.39–5.29 (m, 2H), 5.12–5.02 (m, 2H), 4.62 (d, *J*=12.0 Hz, 1H), 4.35 (d, *J*=12.0 Hz, 1H), 3.88–3.67 (m, 4H), 3.41–3.35 (m, 2H), 1.42 (s, 9H).

4.6. (3*S*,4*R*)-4-Benzyloxy-3-hydroxy-2,3,4,7-tetrahydroazepine-1-carboxylic acid-*tert*-butyl ester (6)

Grubbs catalyst (generation I) (11.6 mg, 14.1 μmol, 5 mol %) was added to a solution of diene **5** (98.0 mg, 280 μmol) in CH_2Cl_2 (30 mL). The reaction mixture was refluxed for 20 h when additional Grubbs catalyst (7.00 mg, 8.50 μmol, 3 mol %) was added and solution was refluxed for additional 22 h. Solvent was then evaporated and the residue was subjected to flash chromatography (petroleum ether/EtOAc, 5/1 to 2/1) to provide tetrahydroazepine **6** (77.8 mg, 86%) as a yellow oil with optical rotation and ^1H NMR spectral data matching those reported previously.[24] $[\alpha]_D^{20}$ −78 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.27 (m, 5H), 5.79–5.65 (m, 2H), 4.74–4.61 (m, 1H), 4.58–4.46 (m, 1H), 4.45–4.10 (m, 3H), 4.03–3.90 (m, 1H), 3.82–3.63 (m, 1H), 3.31–3.11 (m, 1H), 2.51 (br s, 1H), 1.41 (s, 9H).

4.7. (3*R*,4*R*)-3-Azido-4-benzyloxy-2,3,4,7-tetrahydroazepine-1-carboxylic acid-*tert*-butyl ester (7)

To a well stirred solution of (3*S*,4*R*)-4-benzyloxy-3-hydroxy-2,3,4,7-tetrahydroazepine-1-carboxylic acid-*tert*-butyl ester **6** (95.8 mg, 300 μmol), PPh_3 (314 mg, 1.20 mmol), and $(PhO)_2P(O)N_3$ (258 μL, 1.20 mmol) in dry THF (7.5 mL) under N_2 atmosphere at 25 °C, diethyl azodicarboxylate (DEAD, 189 μL, 1.20 mmol) was added drop wise via syringe and the resulting mixture was stirred at same temperature until the completion of reaction (monitored by TLC, 4.5 h). The residue obtained by evaporation of reaction mixture under reduced pressure was suspended in EtOAc (15 mL), followed by filtration through a short pad of silica. The filtrate was washed with aqueous 2 N HCl (15 mL), brine (15 mL), and dried over $MgSO_4$. The solvent was evaporated, and the crude was purified by flash chromatography (pentane/*tert*-butylmethylether, 20/1) to afford compound **7** (91.3 mg, 89%) as a pale yellow syrup with optical rotation and ^1H NMR spectral data matching those reported previously.[24] $[\alpha]_D^{20}$ +38 (*c* 8.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.20 (m, 5H), 5.74 (br s, 2H), 4.68–4.55 (m, 2H), 4.25–4.23 (m, 2H), 3.90–3.49 (m, 4H), 1.47 (s, 9H).

4.8. General procedure for hydroboration–oxidation

Borane dimethylsulfide ($BH_3{\cdot}SMe_2$) 2 M solution in THF (78.0 μL, 156 μmol) was added drop wise via syringe to a well stirred solution of olefin **7** (50.0 mg, 145 μmol) in dry THF (150 μL) under N_2 atmosphere at 25 °C. The reaction mixture was allowed to stir at same temperature for 14 h before the addition of EtOH (900 μL), 6 N NaOH (600 μL), and 30% H_2O_2 (300 μL). The mixture was heated at 50 °C for 1 h to ensure complete oxidation. The aqueous layer was saturated with K_2CO_3 to effect the separation of the organic layer. The aqueous layer was then washed with EtOAc (2×2 mL) and the combined organic layers were dried over $MgSO_4$ before evaporation to furnish the crude residue. The crude was subjected to flash chromatography (petroleum ether/EtOAc, 3/1) to give a mixture of diastereomers **8a**–**d** (51.6 mg, 98%). The mixture was then chromatographed on a Phenomenex Gemini C18 column (150×21.20 mm) eluting with MeCN/water/TFA (from 30:70:0.1 to 60:40:0.1 over 85 min; flow rate: 8.80 mL/min; retention time 44.4, 42.0, 37.2, and 40.7 min for **8a**, **8b**, **8c**, and **8d**, respectively) to give **8a** (500 μg, 1%), **8b** (19.1 mg, 36%), **8c** (17.0 mg, 32%), and **8d** (15.0 mg, 28%) as colorless oils in a ratio of 1:37:33:29. It is noteworthy that **8a**–**d** were observed to have rotamers because of *N*-Boc group.

*4.8.1. (3R,4S,5R)-3-Azido-4-benzyloxy-5-hydroxyazepane-1-carboxylic acid-tert-butyl ester (**8a**).* $[\alpha]_D^{20}$ −53 (*c* 0.9, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 3600–3100 (br), 2977, 2930, 2361, 2104, 1684, 1416, 1157, 1088, 1045; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41–7.35 (m, 5H), 5.09–5.08 (t, *J*=10.4 Hz, 1H), 4.69–4.67 (t, *J*=10.6 Hz, 1H), 4.12–4.05 (m, 1H), 3.99–3.80 (m, 2H), 3.60–3.54 (m, 1H), 3.45–3.36 (m, 1H), 3.23–3.09 (m, 2H), 2.16–2.05 (m, 1H), 1.92–1.80 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 137.7, 128.9, 128.5, 128.4, 90.6, 80.6, 76.4, 71.1, 60.6, 48.1, 42.1, 30.3, 28.5; HRMS (ESI): $[M+H]^+$, *m*/*z* calcd for $C_{18}H_{27}N_4O_4$ 363.2039, found 363.2034.

*4.8.2. (3R,4S,5S)-3-Azido-4-benzyloxy-5-hydroxyazepane-1-carboxylic acid-tert-butyl ester (**8b**).* $[\alpha]_D^{20}$ +51.2 (*c* 0.8, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 3600–3100 (br), 2977, 2930, 2361, 2105, 1684, 1416, 1157, 1088, 1045; ^1H NMR (600 MHz, $CDCl_3$) δ 7.41–7.36 (m, 5H), 5.00–4.96 (dd, *J*=11.0, 4.6 Hz, 1H), 4.67–4.63 (t, *J*=10.6 Hz, 1H), 3.80–3.51 (m, 4H), 3.28–3.12 (m, 2H), 3.10–2.96 (m, 1H), 2.48 (br s, 1H), 2.13–2.04 (m, 1H), 1.85–1.72 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.9, 137.6, 128.9, 128.5, 128.4, 87.9, 80.9, 75.9, 70.7, 64.8, 45.0, 42.2, 30.6, 28.5; HRMS (ESI): $[M+H]^+$, *m*/*z* calcd for $C_{18}H_{27}N_4O_4$ 363.2039, found 363.2046.

*4.8.3. (3R,4R,6S)-3-Azido-4-benzyloxy-6-hydroxyazepane-1-carboxylic acid-tert-butyl ester (**8c**).* $[\alpha]_D^{20}$ −49.2 (*c* 0.8, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 3600–3100 (br), 2977, 2930, 2361, 2105, 1684,

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1416, 1157, 1088, 1045; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.34 (m, 5H), 4.68–4.56 (m, 2H), 4.0–3.94 (m, 1H), 3.87–3.78 (m, 1H), 3.69–3.61 (m, 2H), 3.37 (t, J=9.0 Hz, 1H), 3.30 (dd, J=14.9, 5.9 Hz, 1H), 2.90 (q, J=14.9, 8.8 Hz, 1H), 2.54 (br s, 1H), 2.34–2.28 (dd, J=14.8, 5.0 Hz, 1H), 1.79–1.71 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.5, 137.2, 128.6, 128.1, 128.0, 81.2, 78.7, 71.7, 68.3, 64.5, 54.9, 49.7, 37.0, 28.3; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{18}H_{27}N_4O_4$ 363.2039, found 363.2044.

*4.8.4. (3R,4R,6R)-3-Azido-4-benzyloxy-6-hydroxyazepane-1-carboxylic acid-tert-butyl ester (**8d**).* $[\alpha]_D^{20}$ +48.8 (c 0.8, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 3600–3100 (br), 2977, 2930, 2361, 2105, 1684, 1416, 1157, 1088, 1045; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.33 (m, 5H), 4.64–4.52 (m, 2H), 4.21–4.12 (m, 1H), 3.82–3.68 (m, 4H), 3.44–3.33 (m, 2H), 2.08–1.98 (m, 1H), 1.87 (br s, 1H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.2, 137.8, 128.7, 128.1, 128.0, 81.2, 76.1, 71.9, 68.1, 64.9, 55.4, 49.0, 34.6, 28.4; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{18}H_{27}N_4O_4$ 363.2039, found 363.2032.

4.9. Typical procedure for Boc deprotection of 8

(3*R*,4*R*,6*R*)-3-Azido-4-benzyloxy-6-hydroxyazepane-1-carboxylic acid-*tert*-butyl ester **8d** (9.60 mg, 26.5 μmol) was dissolved in TFA (500 μL) at 25 °C. The solution was allowed to stir for 5 min before TFA was vacuum evaporated. The reaction flask was kept under high vacuum (0.005 Torr, 25 °C) for 3 h to remove traces of TFA, and the colorless oil obtained was characterized as (3*R*,4*R*,6*R*)-3-azido-4-benzyloxy-azepane-6-ol **9d** (6.80 mg, 98%).

*4.9.1. (3R,4S,5R)-3-Azido-4-benzyloxyazepane-5-ol (**9a**).* Colorless oil, yield 97%; $[\alpha]_D^{20}$ −57.6 (c 1.0, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 3587, 2341, 1698, 1683, 1636, 1558, 1199, 1132; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 4.77 (d, J=11.5 Hz, 1H), 4.64 (d, J=11.5 Hz, 1H), 4.33 (q, J=4.3 Hz, 1H), 4.14 (t, J=6.8 Hz, 1H), 3.83 (t, J=5.0 Hz, 1H), 3.56–3.47 (m, 3H), 3.22–3.15 (m, 1H), 2.30–2.22 (m, 1H), 2.13–2.04 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.0, 128.9, 128.6, 128.2, 84.9, 73.8, 70.1, 56.6, 47.0, 42.1, 25.7; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{13}H_{19}N_4O_2$ 263.1508, found 263.1505.

*4.9.2. (3R,4S,5S)-3-Azido-4-benzyloxyazepane-5-ol (**9b**).* Colorless oil, yield 97%; $[\alpha]_D^{20}$+56.4 (c 1.0, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 3587, 2341, 1698, 1683, 1636, 1558, 1456, 1199, 1132; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 4.67 (q, J=21.4, 8.2 Hz, 2H), 4.19–4.13 (q, J=3 Hz, 1H), 3.98–3.93 (m, 1H), 3.71 (t, J=8.2 Hz, 1H), 3.51–3.42 (m, 1H), 3.33–3.20 (m, 2H), 3.18–3.09 (m, 1H), 2.80 (br s, 1H), 2.25–2.18(m, 1H), 2.07–1.99 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.0, 128.9, 128.6, 128.2, 82.4, 73.5, 69.3, 60.3, 44.1, 41.4, 25.6; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{13}H_{19}N_4O_2$ 263.1508, found 263.1503.

*4.9.3. (3R,4R,6S)-3-Azido-4-benzyloxyazepane-6-ol (**9c**).* Colorless oil, yield 98%; $[\alpha]_D^{20}$ −55.4 (c 0.9, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 3587, 2341, 1698, 1683, 1636, 1558, 1456, 1199, 1132; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 4.70 (d, J=11.5 Hz, 1H), 4.53 (d, J=11.5 Hz, 1H), 4.21 (br s, 1H), 4.14–4.09 (m, 1H), 3.83 (m, 1H), 3.51 (dd, J=14.2, 3.9 Hz, 1H), 3.43 (dd, J=13.8, 5.2 Hz, 1H), 3.10 (d, J=13.0 Hz, 1H), 3.04 (dd, J=14.2, 5.9 Hz, 1H), 2.26 (dt, J=15.7, 5.9 Hz, 1H), 2.12 (dt, J=15.7, 3.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.0, 128.8, 128.5, 128.3, 77.4, 72.0, 64.6, 61.0, 51.6, 47.2, 34.0; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{13}H_{19}N_4O_2$ 263.1508, found 263.1507.

*4.9.4. (3R,4R,6R)-3-Azido-4-benzyloxyazepane-6-ol (**9d**).* $[\alpha]_D^{20}$ +53.6 (c 1.0, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 3587, 2341, 1698, 1683, 1636, 1558, 1456, 1199, 1132; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.36 (m, 5H), 5.00–4.96 (m, 1H), 4.67–4.63 (m, 1H), 3.79–3.51 (m, 4H), 3.26–3.13 (m, 2H), 3.08–2.97 (m, 1H), 2.48 (br s, 1H), 2.12–2.05 (m, 1H), 1.72–1.84 (br m, 1H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.1, 128.8, 128.4, 128.1, 75.5, 72.2, 63.6, 60.8, 54.1, 47.6, 34.2; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{13}H_{19}N_4O_2$ 263.1508, found 263.1509.

4.10. General procedure for deoxyfluorination of 10

A solution of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor®) (13.4 mg, 60.7 μmol) or diethylaminosulfur trifluoride (DAST) (9.80 mg, 60.7 μmol) in dry DCM (100 μL) was added drop wise via a syringe to a well stirred solution of **8c** (20.0 mg, 55.2 μmol) in dry DCM (100 μL) under N_2 atmosphere at 25 °C. The reaction mixture was allowed to stir at the same temperature until the completion of reaction (monitored by TLC). The reaction mixture was quenched by ice cooled water before the crude was extracted with EtOAc and washed with water and brine. The organic phase was evaporated under reduced pressure after drying over $MgSO_4$ to give the crude product, which was subjected to flash chromatography (petroleum ether/EtOAc, 9/1) to give **10c** (19.5 mg, 97%, using DAST; 19.7 mg, 98%, using Deoxofluor®) as colorless oil.

*4.10.1. (3R,4S,5S)-3-Azido-4-benzyloxy-5-fluoroazepane-1-carboxylic acid-tert-butyl ester (**10b**).* Colorless oil, yield 95% (DAST), 97% (Deoxofluor®); R_f (petroleum ether/EtOAc, 9/1) 0.5; $[\alpha]_D^{20}$ +55.9 (c 1.0, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 2362, 2342, 2109, 1716, 1698, 1541, 1522, 1474, 1457, 1418; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 4.83–4.60 (m, 3H), 3.97–3.84 (m, 1H), 3.80–3.47 (m, 3H), 3.25–3.11 (m, 1H), 3.01–2.87 (m, 1H), 2.23–1.99 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 137.6, 128.6, 128.5, 128.2, 93.6 (d, $^1J_{CF}$=173.1 Hz), 85.2 (d, $^2J_{CF}$=21.2 Hz), 80.9, 75.2, 63.7 (d, $^3J_{CF}$=6.2 Hz), 45.0, 40.9 (d, $^3J_{CF}$=11.4 Hz), 29.7 (d, $^2J_{CF}$=22.4 Hz), 28.5; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{18}H_{26}FN_4O_3$ 365.1989, found 365.2002.

*4.10.2. (3R,4R,6S)-3-Azido-4-benzyloxy-6-fluoroazepane-1-carboxylic acid-tert-butyl ester (**10c**).* R_f (petroleum ether/EtOAc, 9/1) 0.51; $[\alpha]_D^{20}$ −54.1 (c 1.0, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 2361, 2341, 2109, 1716, 1541, 1521, 1473, 1456, 1418; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.34 (m, 5H), 4.93–4.78 (d, $^1J_{HF}$=54.0 Hz, 1H), 4.73 (t, J=11.7 Hz, 1H), 4.60–4.50 (m, 1H), 3.95–3.88 (m, 1H), 3.78–3.38 (m, 5H), 2.40–2.27 (m, 1H), 2.16–1.98 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 137.5, 128.7, 128.2, 88.3 (d, $^1J_{CF}$=171.0 Hz), 81.0, 77.3, 71.7, 64.7, 50.8 (d, $^2J_{CF}$=34.5 Hz), 48.4, 33.1 (d, $^2J_{CF}$=21.0 Hz), 28.4; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{18}H_{26}FN_4O_3$ 365.1989, found 365.1996.

*4.10.3. (3R,4R,6R)-3-Azido-4-benzyloxy-6-fluoroazepane-1-carboxylic acid-tert-butyl ester (**10d**).* R_f (petroleum ether/EtOAc, 9/1) 0.45; $[\alpha]_D^{20}$ +53.4 (c 0.9, CH_2Cl_2); colorless oil, yield 95% (DAST), 97% (Deoxofluor®); IR (film) ν_{max} (cm^{-1}): 2361, 2341, 2109, 1716, 1541, 1521, 1473, 1456, 1418; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.34 (m, 5H), 5.13–5.00 (d, $^1J_{HF}$=48.7 Hz, 1H), 4.62 (s, 2H), 4.15–4.04 (m, 1H), 3.81–3.68 (m, 2H), 3.63–3.57 (m, 1H), 3.32–3.23 (m, 1H), 2.99–2.93 (m, 1H), 2.49–2.42 (m, 1H), 1.85–1.73 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.9, 137.6, 128.7, 128.3, 128.2, 88.5 (d, $^1J_{CF}$=169.7 Hz), 81.1, 77.2, 72.4, 65.1, 51.2 (d, $^2J_{CF}$=25.9 Hz), 47.8, 33.1 (d, $^2J_{CF}$=20.1 Hz), 28.4; HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{18}H_{26}FN_4O_3$ 365.1989, found 365.1994.

4.11. General procedure for Boc deprotection

10b (9.60 mg, 26.3 μmol) was dissolved in TFA (500 μL) at 25 °C. The solution was allowed to stir for 5 min before TFA was vacuum evaporated. The reaction flask was kept under high vacuum (0.005 Torr, 25 °C) for 3 h to remove traces of TFA, and the colorless oily residue obtained was characterized as **11b** (9.20 mg, 98%).

*4.11.1. (3R,4S,5S)-3-Azido-4-benzyloxy-5-fluoroazepane (**11b**).* $[\alpha]_D^{20}$ +60.6 (c 0.8, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 2362, 2341, 2112, 1716,

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1698, 1684, 1671, 1558, 1541, 1521, 1456, 1199; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 4.88 (d, $^1J_{HF}$=45.2 Hz, 1H), 4.72 (q, J=14.8, 11.4 Hz, 2H), 4.04 (t, J=7.7 Hz, 1H), 3.84–3.78 (m, 1H), 3.39–3.08 (m, 4H), 2.35–2.22 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.5, 128.8, 128.6, 128.3, 90.6 (d, $^1J_{CF}$=177.0 Hz), 82.2 (d, $^2J_{CF}$=25.5 Hz), 73.6, 59.9 (d, $^3J_{CF}$=3.0 Hz), 44.7, 40.0 (d, $^3J_{CF}$=9.0 Hz), 26.1 (d, $^2J_{CF}$=22.5 Hz); HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{13}H_{18}FN_4O$ 265.1465, found 265.1463.

*4.11.2. (3R,4R,6S)-3-Azido-4-benzyloxy-6-fluoroazepane (**11c**).* $[\alpha]_D^{20}$ +59.9 (c 1.0, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 2361, 2341, 2111, 1716, 1684, 1671, 1558, 1541, 1521, 1456, 1199; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 5.08 (d, $^1J_{HF}$=44.0 Hz, 1H), 4.76 (d, J=11.6 Hz, 1H), 4.52 (d, J=11.6 Hz, 1H), 4.12 (br s, 1H), 3.96 (br s, 1H), 3.67–3.58 (m, 2H), 3.56–3.44 (m, 1H), 3.42–3.33 (m, 1H), 2.54–2.44 (m, 1H), 2.42–2.30 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.6, 128.9, 128.6, 128.2, 87.5 (d, $^1J_{CF}$=173.1 Hz), 74.9, 71.9, 60.1, 49.5 (d, $^2J_{CF}$=27.4 Hz), 48.2, 31.6 (d, $^2J_{CF}$=20.8 Hz); HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{13}H_{18}FN_4O$ 265.1465, found 265.1471.

*4.11.3. (3R,4R,6R)-3-Azido-4-benzyloxy-6-fluoroazepane (**11d**).* $[\alpha]_D^{20}$ +58.7 (c 0.9, CH_2Cl_2); IR (film) ν_{max} (cm^{-1}): 2362, 2341, 2112, 1698, 1684, 1671, 1558, 1541, 1521, 1456, 1199; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 5.04 (d, $^1J_{HF}$=46.4 Hz, 1H), 4.63 (q, J=11.6, 6.0 Hz, 2H), 4.00–3.93 (m, 1H), 3.93–3.87 (m, 1H), 3.54–3.28 (m, 3H), 3.19–3.12 (q, J=14.4, 6.9 Hz, 1H), 2.54–2.46 (m, 1H), 2.34–2.23 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.0, 128.8, 128.5, 128.2, 85.8 (d, $^1J_{CF}$=171.7 Hz), 75.4 (d, $^3J_{CF}$=9.0 Hz), 72.4, 61.7, 50.9 (d, $^2J_{CF}$=26.6 Hz), 46.4, 31.9 (d, $^2J_{CF}$=21.5 Hz); HRMS (ESI): $[M+H]^+$, m/z calcd for $C_{13}H_{18}FN_4O$ 265.1465, found 265.1469.

4.12. (3*R*,4*R*)-4-Benzyloxy-3-fluoro-2,3,4,7-tetrahydroazepine-1-carboxylic acid-*tert*-butyl (14)

$[\alpha]_D^{20}$ +29.3 (c 1.7, $CHCl_3$); IR (film) ν_{max} (cm^{-1}): 2360, 2345, 2111, 1715, 1699, 1651, 1541, 1522, 1474, 1457, 1418; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.29 (m, 5H), 5.89–5.73 (m, 2H), 5.04 (d, $^1J_{HF}$=66.1 Hz, 1H), 4.91 (d, J=11.9, 1H), 4.64 (q, J=17.5, 11.6 Hz, 1H), 4.04–3.35 (m, 4H), 2.70–2.53 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.9, 136.7, 128.7, 128.2, 128.0, 126.8, 123.6, 112.2 (d, $^1J_{CF}$=219.0 Hz), 80.0, 71.5, 43.5, 41.5 (d, $^2J_{CF}$=17.3 Hz), 40.3 (d, $^2J_{CF}$=21.8 Hz), 28.6; HRMS (ESI): $[M+Na]^+$, m/z calcd for $C_{18}H_{24}FNO_3Na$ 344.1638, found 344.1646.

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Supplementary data

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