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Conformational Regulation of Substituted Azepanes through Mono-, Di-, and Trifluorination

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Substituted azepanes have flexible ring structures and this conformational diversity is important for their bioactivity. We have shown that a single fluorine atom, when installed diastereoselectively on a model azepane ring, can bias its ring to one major conformation. Here the conformational effects of mono-, di-, and trifluorination, as well as hydroxylation, on substituted azepanes have been investigated by ^{1}H NMR spectroscopy and computational modeling in chloroform. Fluorine substitution was found to be more effective than hydroxyl group substitution in reducing conformational disorder; however, multiple fluorinations may not lead to additive conformational control and can result in complex conformational outcomes.

Introduction

Conformational change is frequently observed in receptor-ligand interactions.[1–4] Various models, such as the "induced-fit" mechanism, or its "conformational selection" alternative, and a combined "induced selection" process, have been developed to describe such complexity in molecular recognition.[1] This conformation dynamics, however, renders theoretical prediction of the productive conformation in a ligand-receptor pair difficult, and the details of the dynamic conformational effects that determine the specificity of receptor-ligand interactions remain poorly understood.[2–4] As such, experimental approaches that allow controlled conformational space sampling or manipulation are highly desirable for the rational discovery of specific ligand-receptor interactions.

Several strategies, such as steric directing, electronic attraction and repulsion, stereoelectronic control, and hydrogen-bonding, have been developed to tune the conformation of a ligand molecule.[5–12] More recently, selective fluorination has become an important tool in conformational control, due to the strong and unusual stereoelectronic effects resulting from the C–F bond.[13–16]

We have recently reported the regulatory effects of selective monofluorination on substituted azepanes.[17] Such molecules have been extensively studied as prevalent bioactive epitopes in natural products, or as DNA binders, helix inducers, and sugar mimics,[18] and the introduction of fluorine-based conformatonal control represents an additional avenue through which to access bioactive azepanes.[17b] A series of azepanes with 1,2-*trans* azidobenzyloxy substituents were examined because such compounds can be utilized as building blocks for the synthesis of bioactive natural product analogues with a 1,2-*trans* aminohydroxy moiety. In our model system (Figure 1), disubstituted azepane

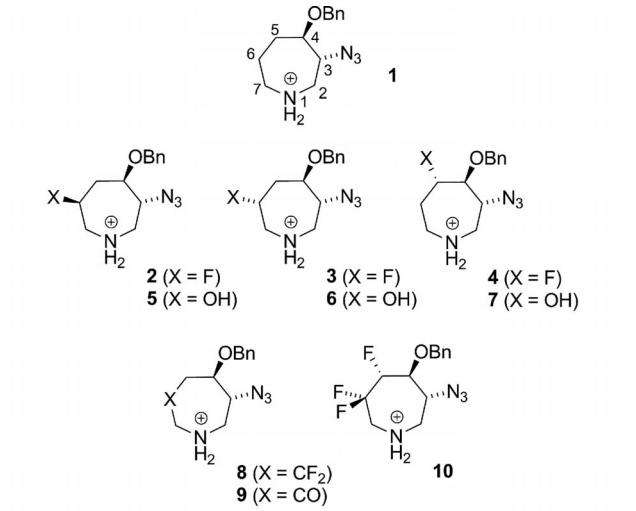

Figure 1. Structures of azepanes **1**–**10**, and the various stereoelectronic effects that are expected to influence their conformations.

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1, with an azido substituent at C3 and an OBn substituent at C4 in a *trans* relationship, was utilized for selective monofluorination at the C6 position. Two monofluorinated azepanes, **2** and **3**, were prepared, with the single fluorine atom in either the 6*S* or 6*R* configuration. This was the first study of fluorine conformational regulation of a seven-membered N-heterocycle, and complemented previous studies of fluorine conformational effects in four-, five-, six-, and eight-membered N-heterocycles.[19–21]

The substituted azepane systems in **2** and **3** have complex conformational properties in which the overall conformational characteristics depend on the interplay of the C3/C4 pseudo-diequatorial vs. pseudo-diaxial preference (Figure 1, insert), the azido *gauche* effect,[22] and the fluorine *gauche* effect.[23] For this model system, parameters for potentially synergistic conformational regulation were investigated and these studies revealed that monofluorination led to a reduction in the ring conformational disorder of the parent azepane **1**. However, only azepane **3**, with the 6*R* configuration (*trans* to the C4–OBn group), was able to furnish one major conformation in which the pseudo-diequatorial preference, the azido *gauche* effect, and the fluorine *gauche* effect were all satisfied concurrently. These results established the diastereospecificity requirement for synergistic conformational control in these azepanes.

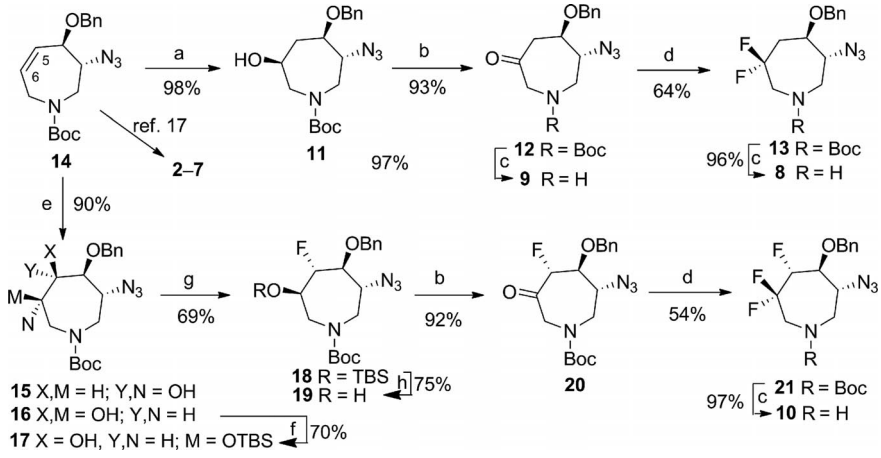
Several new lines of enquiry are addressed here to further understand the complex conformational properties of this azepane system in the solvent chloroform. Because seven-membered nitrogen heterocycles are inherently highly flexible and difficult to control conformationally, this study focused on the conformational outcomes of several fluorine substitution patterns on the same substituted azepane model system to establish the first full profile of the fluorine stereoelectroinc effects on such a ring system. Azepane **4**, in which the fluorine atom is positioned at C5 rather than C6 while maintaining the configuration *trans* to the C4–OBn substituent, is controlled by a different combination of conformational factors. In this case, the C3/C4 pseudo-diequatorial vs. pseudo-diaxial preference operates in close proximity to the C5–fluorine substitution and is potentially moderated by the C5–fluorine/C4–OBn *gauche* effect (Figure 1, inset). Azepanes **5**, **6**, and **7**, which are hydroxyl-substituted counterparts of **2**, **3**, and **4**, respectively, in which an OH group replaces the fluorine, may reveal whether the conformational effects of fluorine at C6 are unique. Azepane **8** was difluorinated at C6 to examine whether an additional fluorine at C6 would maintain or disrupt the diastereospecific conformational bias of azepane **3**. Azepane **9**, as the C6(=O) counterpart of azepane **8**, was prepared so that the effects of an achiral moiety at C6 could be delineated. Finally, azepane **10** was trifluorinated with the 6*S*, 6*R*, and 5*R* configuration to understand the potential limits of conformational bias imposed by multiple fluorination. Together, these substituted azepanes form part of an intricate conformational landscape controlled by single or multiple fluorination.

Results and Discussion

Synthesis of Azepanes 1–10

Azepanes **1** were synthesized by following a reported procedure.[17] Azepanes **2**–**7** were synthesized from the key intermediate *tert*-butyl (3*R*,4*R*)-3-azido-4-benzyloxy-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxylate (**14**) by hydroboration–oxidation (azepanes **5**–**7**) followed by deoxyfluorination (azepanes **2**–**4**) by following our methods.[17a] Azepane **9** was prepared from azepane **11** by oxidation using pyridinium chlorochromate to provide azepane **12**, Boc deprotection of which furnished azepane **9** in quantitative yield. Fluorination of **12** with Deoxofluor furnished azepane **13** in 64% yield and the Boc-deprotected azepane was characterized as **8** (Scheme 1).

Trifluoroazepane **10** was synthesized from **14** in five steps, starting from dihydroxylation of **14** to give a mixture of *syn*-dihydroxy azepanes **15** and **16** for separation by



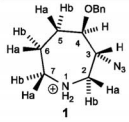
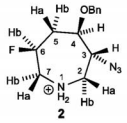
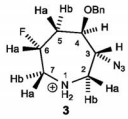
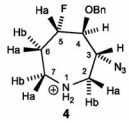
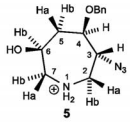
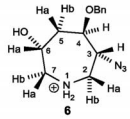
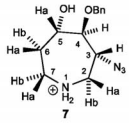
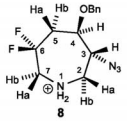
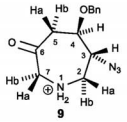
Scheme 1. Synthesis of azepanes **2**–**10**. *Reagents and conditions:* (a) i. BH_3·DMS, THF, 25 °C, 14 h; ii. EtOH, 6 N NaOH, H_2O_2, 50 °C, 1 h (all four diastereomers); **11** (32%);[17a] (b) PCC (1.1 equiv.), MS (4 Å), anhydrous CH_2Cl_2, 25 °C, 1.5 h; (c) TFA, neat, 5 min; (d) Deoxofluor (2.2 equiv.), anhydrous CH_2Cl_2, 0 °C, 10 h; (e) NMO, OsO_4, $(CH_3)_2CO/H_2O$, room temp., 5 h, **15**/**16** (62:38); (f) imidazole, TBSCl, anhydrous DMF, 25 °C, 10 h; (g) Deoxofluor, anhydrous CH_2Cl_2, 0 °C, 8 h; (h) TBAF, anhydrous THF, 45 min.

chromatography. Regioselective TBS monoprotection led to azepane **17** in 70% yield, the fluorination of which afforded its 5*R*-fluoro analogue **18** with inversion of stereochemistry. Azepane **18** then underwent TBS deprotection to furnish fluorohydroxy azepane **19**, followed by oxidation to fluoroketo azepane **20** in excellent yield. Treatment of azepane **20** with Deoxofluor gave the desired trifluoro azepane intermediate **21** and then azepane **10** after Boc deprotection. All azepanes were prepared and analyzed as their trifluoroacetic acid (TFA) salts in $CDCl_3$. The stereochemistry of azepanes **8**–**10** was unambiguously assigned on the basis of HSQC, HMBC, COSY and NOESY 2D NMR experiments, which were analogous to those used for the structure elucidation of azepanes **1**–**7** as described previously.[24] The stereochemical structure assignment was further supported by an X-ray crystal structure of **22** (see Figure 4). Azepane **22** was prepared from **21** by hydrogenation to remove the benzyl protection group and reduce the azido group, followed by amidation to install a *p*-benzyloxy benzoyl group to promote crystalization.[24]

Conformational Analysis and Comparison of Azepanes 2–10

The conformational analysis of azepanes **2**–**9** was based on experimental *J* values obtained from ^{1}H NMR spectra (Table 1).[25] This *J*-based analysis was coupled with molecular modeling and DFT geometry optimizations. Conformers within 3–5 kcal/mol for each azepane were clustered to identify unique ring conformations, as implemented in the program MOE.[26] All of the conformers were subjected to DFT geometry optimization (Turbomole),[27] followed by general *J* calculations as described previously.[25] The experimental *J* values were compared

Table 1. Experimental $^3J_{H,H}$ and $^3J_{H,F}$ values for azepanes **1**–**9**.

Azepanes	Experimental $^3J_{HH}$ [Hz]												
	2a–3	2b–3	3–4	4–5a	4–5b	5a–6a	5a–6b	5b–6a	5b–6b	6a–7a	6a–7b	6b–7a	6b–7b
 **1**	1.5	5.4	5.4	5.4	1.5	6.0	5.9	6.0	1.0	5.9	5.9	5.9	5.9
 **2**	3.5	4.1	6.7	6.0	2.7	16.2	5.1	33.4	4.4	8.0	24.0	4.0	3.0
 **3**	2.8	7.0	7.3	9.0	2.0	2.8	26.5	8.5	8.5	4.0	3.1	30.7	18.3
 **4**	1.0	8.8	7.2	3.0	16.0	2.5	6.0	29.0	14.0	5.0	11.0	4.5	1.5
 **5**	3.3	5.9	6.6	5.1	3.0	n.a.	5.8	n.a.	3.6	n.a.	n.a.	5.4	1.5
 **6**	3.0	4.5	7.2	6.5	2.0	5.0	n.a.	7.5	n.a.	2.7	3.0	n.a.	n.a.
 **7**	1.0	8.0	5.0	4.5	n.a.	1.0	8.0	n.a.	n.a.	5.0	10.0	5.2	4.0
 **8**	2.0	4.8	8.5	10.0	1.0	11.0	29.0	14.0	14.0	9.0	14.0	20.0	9.0
 **9**	2.0	4.1	5.4	7.4	1.2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

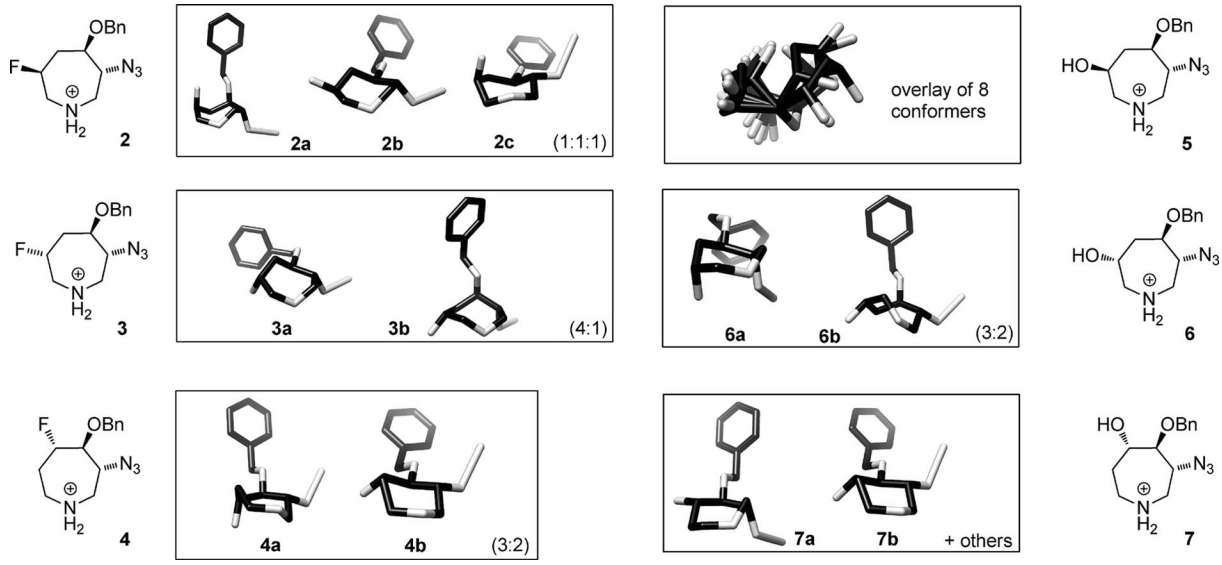


Figure 2. Conformations of azepanes **2**–**7**. Only the major conformer of azepane **3** simultaneously satisfies the C3/C4 pseudo-diequatorial preference, the azido *gauche* effect and the fluorine *gauche* effect.

with the calculated values to identify matching conformers.[24]

Comparison of Azepanes 2 and 3

As described in our preliminary communication,[17] azepane **1** is conformationally disordered, with many contributing conformers. Azepanes **2** and **3** are more conformationally ordered but have dramatically different conformations (Figure 2). Azepane **2** still exhibits considerable disorder in solution, with three low-energy geometries (**2a**–**c**) contributing in a 1:1:1 ratio. In contrast, azepane **3** has one dominant conformer **3a** and one minor conformer **3b** in a 4:1 ratio. Further highlighting the greater extent of conformational biasing in azepane **3**, the two low-energy geometries **3a** and **3b** are quite similar, with the major difference being only a slight change in the C4–C5 dihedral angle, whereas the three low-energy geometries of **2** are very different from one another.

Several factors contribute to the observed conformations of azepanes **2** and **3**; first, a pseudo-diequatorial preference of the benzyloxy and azido substituents (Figure 1, inset); second, an electrostatic charge–dipole interaction between the C–F bond and the ring nitrogen; and third, the azido *gauche* effect. These three conformational effects can act either in synergy or in competition with one another depending on the stereochemistry, and this leads to different conformational outcomes in azepanes **2** and **3**. For example, in azepane **2** the fluorine and the azido groups cannot be simultaneously *gauche* to the ring nitrogen (hence disorder), whereas this is possible for azepane **3** (hence order).

Comparison of Azepanes 3 and 4

Having observed the diastereospecificity requirement for the fluorine atom to exert a greater conformational biasing effect in azepane **3**, azepane **4** was prepared with the fluorine atom at the C5 position while maintaining the relative configuration *trans* to the C4–OBn group to investigate its positional dependence. It was found that azepane **4** adopted two low-energy geometries (**4a** and **4b**, Figure 2) in a ratio of approximately 3:2. The two geometries of **4** are quite similar; in each case the benzyloxy and azido groups are pseudo-equatorial, as expected, whereas perhaps surprisingly the azido group is positioned *anti* to the ring nitrogen in both cases. The major difference between the low-energy geometries of **4** is that the fluorine is *anti* to the benzyloxy group in **4a** but *gauche* in **4b**. This highlights a new influence on the azepane conformation; C–F bonds are known to have a preference for aligning *gauche* to vicinal C–O bonds (Figure 1, inset), due to favorable $\sigma_{CH} \rightarrow \sigma^*_{CF}$ hyperconjugation.[28] However, this preference is very slight and is thus easily overridden in **4a** (Figure 3). This also explains why azepane **4** is more disordered than azepane **3**; a strong F···N^+ interaction is lost whereas only a weak F···OBn interaction is gained. The comparison between the conformational labilities of the major conformers of azepanes **3** and **4** seems to suggest that in azepane **3**, there is synergistic conformational reinforcement between the fluorine *gauche*

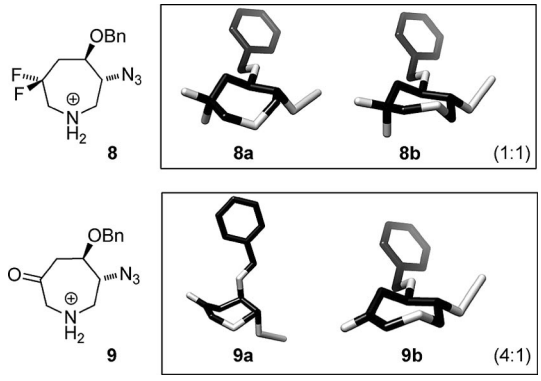


Figure 3. Main conformers of azepanes **8** and **9**.

effect and the azido *gauche* effect, which together dominate the C3/C4 pseudo-diequatorial preference. When this alliance is lost in azepane **4** and replaced by a relatively weak C5–fluorine/C4–OBn *gauche* effect, the C3/C4 pseudo-diequatorial preference becomes dominant.

Comparison of Azepanes 2 and 5

Thus far, some striking differences in conformational behavior have been observed between the fluorinated azepanes **2**–**4** (Figure 2). To investigate whether the various conformational biases are uniquely products of fluorine substitution, or could be reproduced with other electronegative substituents, azepanes **5**–**7**, in which the fluorine atoms were replaced by hydroxy groups, were prepared for investigation.

As discussed above, azepane **2** exhibits some conformational disorder, with three low-energy geometries identified in a 1:1:1 ratio (**2a**–**c**; Figure 2). A similar level of disorder emerged for azepane **5**; most of the $^3J_{H,H}$ values for which (Table 1) were intermediate in magnitude, suggesting significant levels of conformational averaging. Consistent with this, multiple low-energy geometries of **5** were identified by molecular modeling, and no single geometry seemed to dominate in solution. Taken together, the results obtained with azepanes **2** and **5** suggest that placing an electronegative substituent in the *S* configuration at C6 is not particularly effective at reducing conformational disorder because the various conformational influences (Figure 1, inset) are in competition with one another.

Comparison of Azepanes 3 and 6

Azepane **3** has one dominant conformation in solution (Figure 2). Therefore, it was interesting to examine its OH-counterpart, azepane **6**, to determine whether the conformational biasing effect of the fluorine atom could be reproduced with a hydroxyl group. It emerged that azepane **6** does indeed show evidence of significant conformational biasing (Figure 2); in this case, two major geometries (**6a** and **6b**) were observed in a 3:2 ratio. It is noteworthy that the major geometry of azepane **6** (i.e., **6a**) is nearly identical to the major geometry of azepane **3** (i.e., **3a**), with pseudo-diequatorial benzyloxy/azido groups, *gauche* $N^+\cdots N_3$ alignments, and *gauche* $N^+\cdots$F/OH alignments. This suggests a strong similarity between the fluorine and hydroxyl groups of **3** and **6**. However, the hydroxyl group is somewhat less effective than fluorine at biasing the ring conformation, for two reasons. First, the conformer ratio of azepane **3** is much more strongly biased than that of azepane **6** (4:1 vs. 3:2 ratio). Second, the two major geometries of azepane **3** are very similar to one another, whereas the two major geometries of azepane **6** are quite different from one another. In **6b**, the C3/C4 pseudo-diequatorial preference is maintained whereas the azido *gauche* preference became *anti*. The synergy between the fluorine *gauche* and azido *gauche* effects seems to be exclusive to fluorine (azepane **3**) and is not reproduced in the case of an OH substitution (azepane **6**).

Overall, the diastereospecific preference is reproduced in azepanes **5** and **6**, as the 6-OH counterparts of azepanes **2** and **3**, respectively. However, azepanes **5** and **6** are more conformationally disordered than azepanes **2** and **3**.

Comparison of Azepanes 4 and 7

As described above, fluorinated azepane **4** exhibits some conformational biasing, with two closely-related geometries (**4a** and **4b**) dominating in a 3:2 ratio (Figure 2). However the case is quite different for hydroxy derivative **7**. The $^3J_{H,H}$ values of **7** are mostly intermediate in magnitude (Table 1) and, consistent with this, several low-energy geometries of **7** were identified by molecular modeling. A reasonably close match to the experimental $^3J_{H,H}$ values was found by averaging the geometries **7a** and **7b**. Geometry **7a** has *gauche* $N^+\cdots N_3$ and OH···OBn alignments, but does not have pseudo-diequatorial benzyloxy/azido groups. The second low-energy geometry, **7b**, differs from **7a** in its pseudo-diequatorial benzyloxy/azido groups and its *anti* $N^+\cdots N_3$ alignment. Interestingly, the geometry of **7a** closely resembles that of **4a**, suggesting some level of similarity in the effects of fluorine and hydroxy groups in this position. However, a caveat is that no weighted average of **7a** and **7b** actually gave a very good match with the experimental $^3J_{H,H}$ values of **7**,[24] suggesting that at least one other geometry of **7** is involved. Hence, the analysis of **4** and **7** indicates that conformational biasing is enhanced with fluorine at C5 compared with hydroxy group substitution at the same position.

Conformer **7b** was analogous to the minor conformer **4b** with the C3/C4 pseudo-diequatorial preference. The azido *gauche* effect was again not satisfied. The other conformer, **7a**, was not analogous to either **4a** or **4b**. In **7a**, the C3/C4 pseudo-diequatorial preference was not met, and the C5–OH/C4–OBn was *gauche* while satisfying the azido *gauche* effect. The OH group presented a conformational profile that was clearly different to that of fluorine, possibly due to lower levels of electronic repulsion with C5–OH/C4–OBn *gauche* vs. C5–F/C4–OBn *gauche*.

Comparison of Azepanes 3 and 8

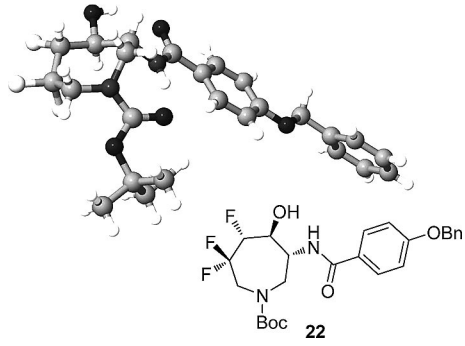
Among all the azepanes examined thus far (**2**–**7**; Figure 2), the monofluorinated azepane **3** clearly experiences the strongest conformational bias. This brings forward the next question of whether incorporating a second fluorine at C6 would further reduce the conformational disorder. To this end, azepane **8** (Figure 3), which was *gem*-difluorinated at C6, was prepared. Interestingly, incorporation of the second fluorine atom actually has a disruptive effect rather than a reinforcing effect, and two equally dominant conformations, **8a** and **8b**, were found in a 1:1 ratio. These two geometries differ from each other by the nitrogen puckering, "down" in **8a** and "up" in **8b**. Structure **8a** is highly reminiscent of the structure of **3a** (Figure 2), but **8b** is not seen in any of the main contributors of azepane **3**. In fact, the conformational disorder in azepane **8** can be readily explained by the $F\cdots N^+$ *gauche* effect; this preference is satisfied in both observed ring puckers of **8**, due to the presence of two fluorine atoms.

Comparison of Azepanes 8 and 9

The *gem*-difluorinated azepane **8** (Figure 3) offered the opportunity to explore another conformational effect of fluorination, which is that the difluoromethylene moiety is often regarded as an isoster of the carbonyl group.[13b] The CF_2 carbon atom can be thought of as having partial sp^2 character, and difluoromethylene-containing compounds typically have C–CF_2–C angles of around 117°. Thus, the *gem*-difluorinated azepane **8** was compared to the "isosteric" carbonyl-containing azepane **9**. It was somewhat difficult to fully elucidate the NMR solution structure of **9** because there are fewer $^3J_{H,H}$ values available (Table 1), nevertheless, two geometries (**9a** and **9b**) were identified that, when combined in a 4:1 ratio, provided a good match with this limited set of experimental $^3J_{H,H}$ values. Geometry **9a** features a *gauche* N_3···N^+ alignment and pseudo-diaxial benzyloxy/azido groups, whereas geometry **9b** features an *anti* N_3···N^+ alignment and pseudo-diequatorial benzyloxy/azido groups; thus, it appears that these two preferences are in competition with one another in azepane **9**. The ring geometry **9a** is not observed in any of the previous azepanes, but there is a striking similarity between **9b** and **8b**. The latter observation reinforces the concept of the *gem*-difluoro moiety as an effective isoster of the carbonyl group.

Azepane 10

Azepane **10** incorporates fluorine atoms at all three sites previously examined in isolation (Figure 1). This molecule was successfully synthesized as described in Scheme 1, however, the NMR solution structure of **10** was too complex for reliable *J* value extraction due to overlapping $^1H/^{19}F$ NMR signals (see the Supporting Information). Therefore, as an alternative measure, the solid-state structure of a crystalline derivative, **22**, was solved (Figure 4). Azepane **22** differs from **10** in several respects: the ring nitrogen is Boc-protected, the benzyl group is absent, and the azido group is replaced with an amide. However, the trifluorination pattern remains intact. The crystal structure of **22** (Figure 4) features a ring geometry that clearly corresponds with our prior expectations. There is a *gauche* alignment between the two nitrogen atoms (dihedral angle 73°), and there is also the maximum possible number of F···N, F···F and F···O *gauche* alignments (one, two and one, respectively, with dihedral angles of 66°, 70°, 44°, and 51°). The particularly small value of 44° for one of the difluoro *gauche* alignments is partially explained by the widened C–CF_2–C angle of 117°, which also fully accords with our expectation. The orientations of the vicinal hydroxy and amide groups are noteworthy; the unusual dihedral angle of 101° seems indicative of some strain, and this accords with our previous observations with azepane **3** (Figure 2) in which competition exists between the azido *gauche* effect and the pseudo-diequatorial preference of the C3/C4 substituents. Overall, the crystal structure of **22** is highly reminiscent of structures **3a** (Figure 2) and **8a** (Figure 3), but it does not resemble either of the low-energy geometries of azepane **4** (Figure 2). This result supports the conclusion that successive introduction of fluorine atoms at different positions of the azepane ring leads to nonadditive conformational outcomes.[29]



22

Figure 4. X-ray structure of **22**.

Conclusions

A series of mono-, di-, and tri-fluorinated azepanes were examined with respect to their conformational properties. Hydroxy-substituted counterparts were also investigated to determine whether the conformational effects were unique to fluorine. As illustrated by the comparison between azepanes **3** and **4**, the synergy between the fluorine *gauche* effect and the other conformational factors is position-dependent, in addition to the diastereospecificity noted earlier.[17b] The OH substitution, while able to follow the same diastereospecificity requirement for reducing conformational disorder, has different and also weaker bias effects that lead to different mixtures of conformational populations. Finally, multiple fluorination may not offer additional conformational bias compared to that of monofluorination, because the introduction of additional fluorine atoms also introduces more opportunities for conflicting conformational effects. Although able to reduce conformational disorder, neither the fluorine nor OH group reduced ring mobility, and variant temperature studies of azepanes **1**–**10** suggested shallow barriers for conformational mobility on the NMR time-scale.[24,30]

Experimental Section

General: All reactions were conducted under an N_2 atmosphere. Unless otherwise specified, all reagents were purchased from Sigma–Aldrich and used without further purification. Deoxofluor was obtained from Matrix Scientific and used without further purification. CH_2Cl_2 was obtained from a solvent purification system (Innovative Technology SPS400) and stored over 4 Å MS beads. Ethyl acetate and petroleum ether (60–80 °C) were distilled before use. THF was distilled from Na/benzophenone and stored over 4 Å MS beads. Anhydrous DMF was obtained from Sigma–Aldrich and used without further purification.

^1H NMR spectra were recorded at 25 °C with either a Bruker DRX600 K or a DPX400 NMR spectrometer and are reported in parts per million (ppm) using the specified solvent as the internal standard ($CDCl_3$ at δ = 7.26 ppm). ^{13}C NMR spectra are reported

in ppm using the specified solvent as the internal standard ($CDCl_3$ at δ = 77.16 ppm). Computational investigations were performed using programs MOE (Molecular Operating Environment 2011.10; Chemical Computing Group), and Turbomole (version 6.3).

Synthesis of Azepanes 1–22: Synthesis of disubstituted tetrahydroazepine **14** was achieved as described previously. Azepanes **1**–**7** and **11** were synthesized from **14** by using our recently reported methods.[17a]

***tert*-Butyl (3*R*,4*R*)-3-Azido-4-benzyloxy-6-oxoazepane-1-carboxylate (12):** Pyridinium chlorochromate (119.6 mg, 0.555 mmol) was added to a well-stirred suspension of **11** (67.0 mg, 0.185 mmol) and 4 Å MS (95.5 mg) in anhydrous CH_2Cl_2 (8.20 mL) under an N_2 atmosphere at 25 °C. The mixture was stirred at the same temperature until the reaction reached completion (50 min; TLC). The reaction mixture was evaporated to dryness and the crude mixture was subjected to flash chromatography (petroleum ether/EtOAc, 4:1) to give **12** (62 mg, 93%; R_f = 0.40) as a colorless oil. $[\alpha]_D^{20}$ = –47.4 (c = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 2369, 2347, 2133, 1725, 1695, 1672, 1559, 1544, 1413, 1147 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 4.68 (d, J = 10.87 Hz, 1 H), 4.48 (d, J = 10.87 Hz, 1 H), 4.28 (br. d, J = 18.11 Hz, 1 H), 3.84 (br. s, 1 H), 3.81–3.70 (m, 2 H), 3.64 (dd, J = 7.10, 6.76 Hz, 1 H), 3.58–3.50 (m, 1 H), 3.02 (d, J = 13.52 Hz, 1 H), 2.85–2.78 (m, 1 H), 1.53 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 208.3, 155.1, 136.8, 128.6, 128.2, 128.1, 81.5, 75.3, 71.4, 63.4, 57.9, 47.3, 42.3, 28.2 ppm. HRMS (ESI): m/z calcd. for $C_{18}H_{25}N_4O_4$ $[M + H]^+$ 361.1876; found 361.1885.

(3*R*,4*R*)-3-Azido-4-benzyloxy-6-oxoazepane (9): Compound **12** (7.2 mg, 19.9 μmol) was dissolved in TFA (500 μL) at 25 °C and the solution was stirred for 5 min before TFA was evaporated under an N_2 flow. 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 **9** (5.0 mg, 97%). $[\alpha]_D^{20}$ = –32.1 (c = 0.8, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 3581, 2349, 1742, 1715, 1690, 1673, 1646, 1550, 1161, 1133 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 5 H), 4.72 (d, J = 11.43 Hz, 1 H), 4.48 (d, J = 11.43 Hz, 1 H), 4.10–4.06 (m, 1 H), 3.91 (d, J = 18.25 Hz, 1 H), 3.90 (t, J = 7.39, 5.38 Hz, 1 H), 3.54 (dd, J = 14.37, 4.05 Hz, 1 H), 3.53 (d, J = 18.22 Hz, 1 H), 3.51 (dd, J = 14.78, 1.2 Hz, 1 H), 3.43 (dd, J = 14.58, 2.02 Hz, 1 H), 3.07 (dd, J = 14.78, 7.39 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 201.3, 136.2, 128.9, 128.7, 128.2, 72.5, 71.8, 60.0, 56.4, 47.5, 41.7 ppm. HRMS (ESI): m/z calcd. for $C_{13}H_{17}N_4O_2$ $[M + H]^+$ 261.1273; found 261.1273.

***tert*-Butyl (5*R*,6*R*)-6-Azido-5-benzyloxy-3,3-difluoroazepane-1-carboxylate (13):** Bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor; 83.7 mg, 0.379 mmol) was added to a solution of **12** (62.0 mg, 0.172 mmol) in anhydrous CH_2Cl_2 (5.1 mL) under an N_2 atmosphere at 0 °C. The mixture was stirred at the same temperature for 10 h, then evaporated to dryness and the crude mixture was subjected to flash chromatography (petroleum ether/EtOAc, 9:1) to give **12** (42.1 mg, 64%, R_f = 0.43) as a colorless oil. It is noteworthy that **13** was obtained exclusively and unreacted **12** was recovered. $[\alpha]_D^{20}$ = –44.1 (c = 1.5, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 2363, 2347, 2109, 1716, 1533, 1520, 1478, 1450, 1419, 1109 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H), 4.68 (d, J = 11.18 Hz, 1 H), 4.57 (d, J = 11.18 Hz, 1 H), 4.05–3.54 (m, 5 H), 3.24–3.14 (m, 1 H), 2.53–2.42 (m, 1 H), 2.28–2.16 (m, 1 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.5, 137.1, 128.7, 128.3, 128.2, 123.0 (d, $^1J_{C,F}$ = 249 Hz), 81.4, 76.2 (d, $^3J_{C,F}$ = 7.40 Hz), 72.0, 63.8, 55.1 (d, $^2J_{C,F}$ = 36.0 Hz), 48.6, 36.9 (d, $^2J_{C,F}$ = 23.83 Hz), 28.3 ppm. HRMS (ESI): m/z calcd. for $C_{18}H_{25}F_2N_4O_3$ $[M + H]^+$ 383.1895; found 383.1900.

(5*R*,6*R*)-6-Azido-5-benzyloxy-3,3-difluoroazepane (8): Yield 96% from **13**; colorless oil; $[\alpha]_D^{20}$ = –53.7 (c = 1.2, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 2392, 2331, 2110, 1700, 1681, 1678, 1550, 1544, 1511, 1486, 1190 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.39–7.30 (m, 5 H), 4.69 (d, J = 11.17 Hz, 1 H), 4.56 (d, J = 11.17 Hz, 1 H), 3.78–3.73 (m, 2 H), 3.29–3.20 (m, 3 H), 3.00 (dd, J = 15.02, 4.60 Hz, 1 H), 2.58–2.41 (m, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 137.0, 128.4, 128.0, 127.9, 122.3 (d, $^1J_{C,F}$ = 244.5 Hz), 75.5 (d, $^3J_{C,F}$ = 7.07 Hz), 71.8, 65.0, 50.7, 56.0 (d, $^2J_{C,F}$ = 32.9 Hz), 36.7 (d, $^2J_{C,F}$ = 25.5 Hz) ppm. HRMS (ESI): m/z calcd. for $C_{13}H_{17}F_2N_4O$ $[M + H]^+$ 283.1370; found 283.1378.

***tert*-Butyl (3*R*,4*S*,5*S*,6*S*)-3-Azido-4-benzyloxy-5,6-dihydroxyazepane-1-carboxylate (15) and *tert*-Butyl (3*R*,4*S*,5*R*,6*R*)-3-Azido-4-benzyloxy-5,6-dihydroxyazepane-1-carboxylate (16):** To a solution of azepane **14** (344.4 mg, 1 mmol) in acetone/water (8:1, 2.45 mL) was added *N*-methyl morpholine-*N*-oxide (351.6 mg, 3 mmol) and OsO_4 (4% w/w in H_2O, 318 μL, 0.05 mmol). The solution was stirred at room temperature for 5 h before addition of EtOAc (15 mL) and a saturated solution of $Na_2S_2O_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2× 5 mL). The combined organic extracts were evaporated to obtain a light-yellow oil, which was subjected to flash column chromatography (EtOAc/petroleum ether, 2:3) to give **15** (211.2 mg, 56%, R_f = 0.22) and **16** (129.4 mg, 34%, R_f = 0.16) as colorless oils.

Compound 15: $[\alpha]_D^{20}$ = +48.6 (c = 1.8, $CHCl_3$). IR (film): $\tilde{\nu}_{max}$ = 3600–3130 (br), 2997, 2933, 2365, 2114, 1680, 1411, 1157, 1088, 1045 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 5 H), 4.95 (d, J = 10.80 Hz, 1 H), 4.62 (d, J = 10.80 Hz, 1 H), 4.33–4.26 (m, 1 H), 4.10–4.00 (m, 1 H), 3.82–3.71 (m, 1 H), 3.64–3.55 (m, 1 H), 3.21 (dd, J = 14.68, 9.84 Hz, 1 H), 3.15 (dd, J = 14.70, 3.82 Hz, 1 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.9, 137.3, 128.9, 128.5, 128.4, 81, 80.9, 75.7, 72.9, 69.6, 64.5, 49.6, 47.6, 28.5 ppm. HRMS (ESI): m/z calcd. for $C_{18}H_{27}N_4O_5$ $[M + H]^+$ 379.1981; found 379.1982.

Compojund 16: $[\alpha]_D^{20}$ = –24.8 (c = 1.6, $CHCl_3$); IR (film): $\tilde{\nu}_{max}$ = 3600–3130 (br), 2997, 2933, 2365, 2114, 1680, 1411, 1157, 1088, 1045 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 5 H), 4.66 (d, J = 4.13 Hz, 2 H), 4.18–4.15 (m, 1 H), 4.00–3.96 (m, 1 H), 3.93–3.88 (m, 1 H), 3.74–3.67 (m, 1 H), 3.61 (dd, J = 15.15, 5.25 Hz, 1 H), 3.54 (d, J = 7.68 Hz, 1 H), 3.45 (dd, J = 15.15, 5.46 Hz, 1 H), 3.29 (dd, J = 14.43, 7.26 Hz, 1 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.0, 137.2, 128.8, 128.4, 128.3, 83.1, 81.1, 73.4, 72.4, 70.4, 61.4, 51.1, 49.7, 28.4 ppm. HRMS (ESI): m/z calcd. for $C_{18}H_{27}N_4O_5$ $[M + H]^+$ 379.1981; found 379.1984.

***tert*-Butyl (3*R*,4*S*,5*S*,6*R*)-3-Azido-4-benzyloxy-6-(*tert*-butyldimethylsilyl)oxy-5-hydroxyazepane-1-carboxylate (17):** A solution of *tert*-butyldimethylsilyl chloride (96.5 mg, 0.641 mmol) in DMF (3.25 mL) was added dropwise by using a syringe to a well-stirred solution of **16** (220 mg, 0.583 mmol) and imidazole (43.6 mg, 0.641 mmol) in DMF (3.25 mL) at 25 °C under an N_2 atmosphere. The reaction mixture was stirred at the same temperature for 10 h, then the reaction was quenched by addition of water (5 mL). The mixture was extracted with EtOAc (3× 10 mL) and the combined organic extracts were washed with water (2× 5 mL) and brine (5 mL) to remove DMF residues and dried ($MgSO_4$) before evaporation under reduced pressure to give the crude mixture, which was subjected to flash chromatography (petroleum ether/EtOAc, 9:1) to give **17** (201.0 mg, 70%, R_f = 0.32) as a colorless oil. It is note-

worthy that **17** was obtained exclusively and unreacted **16** was recovered. $[\alpha]_D^{20}$ = –42.8 (*c* = 0.8, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 3600–3130 (br), 2997, 2933, 2365, 2114, 1680, 1411, 1157, 1088, 1045, 990 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.40–7.27 (m, 5 H), 4.67 (d, *J* = 11.71 Hz, 1 H), 4.63 (d, *J* = 11.71 Hz, 1 H), 4.07 (br. s, 1 H), 4.00–3.84 (m, 3 H), 3.77–3.67 (m, 1 H), 3.42–3.36 (m, 2 H), 2.83 (dd, *J* = 10.58, 3.43 Hz, 1 H), 2.42 (br. s, 1 H), 1.47 (s, 9 H), 0.88 (s, 9 H), 0.08 (d, *J* = 13.93 Hz, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.2, 137.5, 128.6, 128.3, 128.1, 80.6, 80.5, 75.4, 73.0, 70.1, 63.4, 49.6, 49.3, 28.3, 25.8, –4.52, –4.85 ppm. HRMS (ESI): *m/z* calcd. for $C_{24}H_{41}N_4O_5Si$ $[M + H]^+$ 493.2846; found 493.2847.

***tert*-Butyl (3*R*,4*S*,5*R*,6*R*)-3-Azido-4-benzyloxy-6-(*tert*-butyldimethylsilyl)oxy-5-fluoroazepane-1-carboxylate (18):** A solution of Deoxofluor (89.8 mg, 0.406 mmol) was added dropwise by using a syringe to a well-stirred solution of **17** (200.0 mg, 0.406 mmol) in anhydrous CH_2Cl_2 (5.5 mL) under an N_2 atmosphere at 0 °C. The mixture was stirred at the same temperature for 8 h, then evaporated under reduced pressure to give the crude mixture, which was subjected to flash chromatography (petroleum ether/EtOAc, 9:1) to give **18** (138.5 mg, 69%, R_f = = 0.52) as a colorless oil. $[\alpha]_D^{20}$ = –52.1 (*c* = 0.6, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 2997, 2933, 2365, 2114, 1680, 1521, 1473, 1456, 1411, 1157, 1088, 1045, 990 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.32 (m, 5 H), 4.76 (d, *J* = 11.49 Hz, 1 H), 4.65 (d, *J* = 11.49 Hz, 1 H), 4.60 (br. d, $^1J_{H,F}$ = 45.02 Hz, 1 H), 4.09–4.02 (m, 1 H), 3.83–3.76 (m, 1 H), 3.68–3.50 (m, 3 H), 3.40 (br. d, *J* = 14.17 Hz, 1 H), 3.30–3.20 (m, 1 H), 1.48 (s, 9 H), 0.87 (s, 1 H), 0.12 (s, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.1, 137.4, 128.6, 128.4, 128.2, 95.0 (d, $^1J_{C,F}$ = 180.74 Hz), 82.8 (d, $^2J_{C,F}$ = 25.05 Hz), 80.6, 74.0, 70.8 (d, $^2J_{C,F}$ = 25.02 Hz), 63.9 (d, $^3J_{C,F}$ = 3.79 Hz), 47.2 (d, $^3J_{C,F}$ = 4.06 Hz), 46.8, 28.5, 25.9, –4.89, –5.03 ppm. HRMS (ESI): *m/z* calcd. for $C_{24}H_{39}FN_4NaOSi$ $[M + Na]^+$ 517.2622; found 517.2623.

***tert*-Butyl (3*R*,4*S*,5*S*,6*R*)-3-Azido-4-benzyloxy-5-fluoro-6-hydroxyazepane-1-carboxylate (19):** A solution of tetrabutylammonium fluoride (TBAF; 1 M in THF, 80 µL, 80.1 µmol) was added dropwise by using a syringe to a well-stirred solution of **18** (36.0 mg, 72.8 µmol) in anhydrous THF (1 mL) under an N_2 atmosphere at 25 °C. The mixture was stirred at the same temperature until the reaction reached completion (45 min; TLC), then evaporated to dryness and the crude mixture was subjected to flash chromatography (petroleum ether/EtOAc, 4:1) to give **19** (20.8 mg, 75%, R_f = 0.25) as a colorless oil. $[\alpha]_D^{20}$ = –18.2 (*c* = 1.7, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 3600–3130 (br), 2990, 2963, 2365, 2134, 1684, 1526, 1479, 1466, 1419, 1167, 1081, 1042 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5 H), 4.82 (d, *J* = 11.20 Hz, 1 H), 4.69 (d, *J* = 11.20 Hz, 1 H), 4.56 [ddd, *J* = 47.34 ($^1J_{H,F}$), 7.04, 6.84 Hz, 1 H], 4.12–4.00 (m, 1 H), 3.84–3.50 (m, 4 H), 3.44 (br. d, *J* = 15.16 Hz, 1 H), 3.09 (dd, *J* = 14.83, 9.53 Hz, 1 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.0, 137.1, 128.7, 128.6, 128.4, 96.2 (d, $^1J_{C,F}$ = 175.24 Hz), 81.6 (d, $^2J_{C,F}$ = 21.87 Hz), 81.5, 74.9, 71.4 (d, $^2J_{C,F}$ = 23.97 Hz), 62.9 (d, $^3J_{C,F}$ = 6.07 Hz), 48.7 (d, $^3J_{C,F}$ = 6.59 Hz), 47.9, 28.4 ppm. HRMS (ESI): *m/z* calcd. for $C_{18}H_{26}FN_4O_4$ $[M + H]^+$ 381.1938; found 381.1945.

***tert*-Butyl (3*R*,4*S*,5*R*)-3-Azido-4-benzyloxy-5-fluoro-6-oxoazepane-1-carboxylate (20):** Yield 92% from **19**; colorless oil; R_f = 0.42 (petroleum ether/EtOAc, 4:1); $[\alpha]_D^{20}$ = –17.8 (*c* = 0.9, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 2365, 2349, 2119, 1710, 1547, 1527, 1467, 1448, 1424, 1109 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.45–7.30 (m, 5 H), 5.25 [dd, *J* = 48.98 ($^1J_{H,F}$), 8.38 Hz, 1 H], 4.89 (d, *J* = 10.12 Hz, 1 H), 4.71 (d, *J* = 10.12 Hz, 1 H), 4.08 (br. d, *J* = 15.47 Hz, 1 H), 3.94–3.85 (m, 1 H), 3.67–3.50 (m, 3 H), 2.60 (dd, *J* = 14.85, 10.45 Hz, 1 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9 (d, $^2J_{C,F}$ = 17.08 Hz), 154.2, 136.9, 128.9, 128.7, 128.5, 95.6 (d, $^1J_{C,F}$ = 190.8 Hz), 82.5, 81.6 (d, $^2J_{C,F}$ = 19.15 Hz), 76.1, 62.7 (d, $^3J_{C,F}$ = 6.84 Hz), 55.4, 47.9, 28.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{18}H_{23}FN_4NaO_4$ $[M + Na]^+$ 401.1601; found 401.1602.

***tert*-Butyl (4*R*,5*S*,6*R*)-6-Azido-5-benzyloxy-3,3,4-trifluoroazepane-1-carboxylate (21):** Yield 54% from **20**; colorless oil; R_f = 0.54 (petroleum ether/EtOAc, 4:1); $[\alpha]_D^{20}$ = –26.9 (*c* = 1.1, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 2366, 2335, 2109, 1716, 1531, 1529, 1478, 1457, 1415, 1111 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 5 H), 4.87–4.60 (m, 3 H), 4.47 (dd, *J* = 29.2, 15.93 Hz, 1 H), 3.86 (d, *J* = 15.18 Hz, 1 H), 3.81–3.63 (m, 2 H), 3.50–3.33 (m, 1 H), 2.89 (dd, *J* = 14.66, 10.85 Hz, 1 H), 1.49 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 136.8, 128.7, 128.7, 128.5, 119.5 (dd, $^1J_{C,F}$ = 244, $^2J_{C,F}$ = 21.88 Hz), 91.4 (dt, $^1J_{C,F}$ = 187.46, $^2J_{C,F}$ = 27.87 Hz), 82.3, 81.2 (br. s), 75.3, 64.1, 48.8 (t, $^2J_{C,F}$ = 32.9 Hz), 46.5, 28.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{18}H_{23}F_3N_4O_3$ $[M + H]^+$ 401.1722; found 401.1716.

(4*R*,5*S*,6*R*)-6-Azido-5-benzyloxy-3,3,4-trifluoroazepane (10): Yield 97% from **21**; colorless oil; $[\alpha]_D^{20}$ = –29.4 (*c* = 1.3, CH_2Cl_2). IR (film): $\tilde{\nu}_{max}$ = 2396, 2330, 2116, 1709, 1688, 1678, 1557, 1541, 1525, 1480, 1194 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.44–7.34 (m, 5 H), 4.93 [dd, *J* = 44.19 ($^1J_{H,F}$), 14.7 Hz, 1 H], 4.80 (d, *J* = 11.44 Hz, 1 H), 4.73 (d, *J* = 11.44 Hz, 1 H), 4.08 (dd, *J* = 8.71, 8.68 Hz, 1 H), 3.89–3.82 (m, 1 H), 3.67–3.57 (m, 2 H), 3.48 (d, *J* = 14.0 Hz, 1 H), 3.10 (dd, *J* = 14.0, 9.70 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 135.7, 129.0, 128.5, 128.5, 118.4 (dd, $^1J_{C,F}$ = 247.66, $^2J_{C,F}$ = 28.07 Hz), 90.2 (ddd, $^1J_{C,F}$ = 186.03, $^2J_{C,F}$ = 34.98, $^2J_{C,F}$ = 27.82 Hz), 79.6 (dd, $^2J_{C,F}$ = 24.93, $^3J_{C,F}$ = 7.20 Hz), 73.9, 60.6, 45.8 (dd, $^2J_{C,F}$ = 39.76, $^2J_{C,F}$ = 25.66 Hz), 45.6 ppm. HRMS (ESI): *m/z* calcd. for $C_{13}H_{16}F_3N_4O$ $[M + H]^+$ 301.1276; found 301.1278.

***tert*-Butyl (4*R*,5*S*,6*R*)-6-[4-(Benzyloxy)benzamido]-3,3,4-trifluoro-5-hydroxyazepane-1-carboxylate (22):** A solution of **21** (23.3 mg, 58.1 µmol) and trifluoromethanesulfonic acid (4 µL, 58.1 µmol) in MeOH (1.21 mL) was treated with Pd/C (5% w/w). The resulting suspension was stirred under H_2 (1 atm) for 14 h, then the reaction mixture was filtered through a pad of Celite, which was rinsed with MeOH (5× 1 mL). The solvent was evaporated under reduced pressure to give the desired primary amine for use in the next step without further purification. 4-Benzyloxybenzoyl chloride (15.6 mg, 68.1 µmol) was added to the solution of amine and Et_3N (64 µL, 681 µmol) in anhydrous CH_2Cl_2 (0.81 mL) under an N_2 atmosphere. The reaction mixture was stirred for 2 h at 25 °C, then quenched by the addition of MeOH (0.15 mL) and pyridine (0.15 mL). The volatiles were evaporated under vacuum and the residue was dissolved in EtOAc. The organic phase was successively extracted with aqueous 2 N HCl, water, aqueous saturated $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4) and evaporated under vacuum to give the crude mixture, which was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to afford azepane **22** (14.9 mg, 52% over both steps, R_f = 0.37) as white crystals (CCDC-966288). $[\alpha]_D^{20}$ = –11.4 (*c* = 1.0, $CHCl_3$); m.p. 169–172 °C. IR (film): $\tilde{\nu}_{max}$ = 3500–3100 (br), 2360, 1716, 1683, 1652, 1630, 1613, 1518, 1249, 1210, 1171, 1139, 1049, 840, 793, 726, 608 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 4.87 Hz, 1 H), 7.82 (d, *J* = 8.66 Hz, 2 H), 7.45–7.32 (m, 5 H), 7.03 (d, *J* = 8.59 Hz, 2 H), 5.45 (s,1 H), 5.12 (s, 2 H), 4.68 [dddd, *J* = 46.57 ($^1J_{H,F}$), 18.31, 9.42, 1.57 Hz, 1 H], 4.47–4.39 (m, 1 H), 4.30–4.24 (m, 1 H), 4.21–4.10 (m, 2 H), 4.34–4.23 (m, 2 H), 1.51 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.6, 162.0, 156.7, 136.4, 129.3, 128.8, 128.4, 127.6, 125.4, 121.7 [dd, *J* = 252.11

($^1J_{C,F}$), 18.99 ($^3J_{C,F}$) Hz], 114.9, 90.3 [dt, J = 193.17 ($^1J_{C,F}$), 22.29 ($^2J_{C,F}$) Hz], 82.9, 73.2 (d, $^2J_{C,F}$ = 16.55 Hz), 70.3, 57.6 (d, $^3J_{C,F}$ = 5.71 Hz), 52.4 [dd, J = 37.68 ($^2J_{C,F}$), 27.76 ($^2J_{C,F}$) Hz], 48.9, 28.3 ppm. HRMS (ESI): *m/z* calcd. for $C_{25}H_{30}F_3N_2O_5$ [M + H]$^+$ 495.2107; found 495.2104. CCDC-966288 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Conformational Analysis: The conformational analysis was based on the observed J values, which were extracted from the ^{1}H NMR spectra of azepanes in chloroform, in conjunction with computational modeling in chloroform. The conformational search for each azepane was performed as implemented in the program MOE.[26] Conformers were generated by the stochastic method and minimized in the MMFF94X force field with chloroform as the solvent. Conformers within 3–5 kcal/mol in energy were grouped to identify different azepane ring conformations. All representative conformers were subjected to DFT calculations as implemented in the program Turbomole.[27] A DFT geometry optimization [SV(P) basis set at the B3LYP level in COSMO solvent $CHCl_3$] was performed for each conformer.[24] The $^3J_{H,H}$ values were calculated for each conformer ring geometry as described by Haasnoot et al.[25a] The calculated spin–spin coupling constants for each conformer were compared with the experimentally determined values (extracted by simulation with program Bruker TopSpin 3.2) to exclude conformers that were in clear violation and identify valid contributing conformers.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra and conformational analysis details.

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[29] Clearly, the crystal structure of **22** (Figure 4) must be interpreted with some caution because the observed geometry may not represent the global minimum due to crystal lattice packing forces; however, we assume that the observed geometry must at least be among the low-energy geometries of **22**, hence the examination is of value.

[30] Azepanes **1**–**10** were subjected to variant temperature studies from 25 to –60 °C in $CDCl_3$. Azepane **3** was also examined at –85 °C in $(CD_3)_2CO$ with improved NMR lock signal. However, none of the azepane ^1H NMR spectra revealed new conformational equilibria, suggesting low barriers for the conformational interchange.

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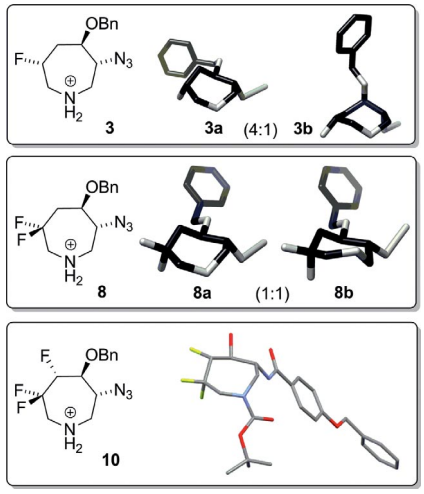
Conformation Analysis

Seven-membered nitrogen heterocycles have flexible ring structures and this conformational diversity is important for their bioactivity. Here the conformational effects of fluorination, as well as hydroxylation, on an azepane model system are investigated by ^{1}H NMR spectroscopy and computational modeling.



Keywords: Conformation analysis / Medium-ring compounds / Fluorine / Density functional calculations / Nucleophilic substitution

