CSIRO PUBLISHING

RESEARCH FRONT

Aust. J. Chem. **2015**, *68*, 50–56
http://dx.doi.org/10.1071/CH14256

Full Paper

Cooperative Conformational Regulation in *N*-Heterocyclic Fluorohydrins

Alpesh Ramanlal Patel[A] *and Fei Liu*[A,B]

[A]Department of Chemistry and Biomolecular Sciences, Macquarie University, Sydney, NSW 2109, Australia.
[B]Corresponding author. Email: fei.liu@mq.edu.au

Seven-membered *N*-heterocycles are flexible ring structures, and their conformational control is important to their bioactivity. Our prior work shows that stereoselective monofluorination, if installed diastereoselectively, can bias a seven-membered, substituted azepane ring to one major conformation. However, multiple fluorination may not provide as much conformational bias due to conflicting effects. Here we show in our model azepane system that fluorohydrins can confer strong conformational bias if the relative configuration of the fluorine and hydroxy substitutent is appropriate to enable cooperative conformational control.

Manuscript received: 24 April 2014.
Manuscript accepted: 16 May 2014.
Published online: 18 July 2014.

Introduction

Chemical diversity manifests in many ways, the most commonly explored being compositional and configurational as seen frequently in diversity-oriented synthesis (DOS).[1–3] Conformational diversity is another source of chemical diversity and important to receptor–ligand interactions and molecular recognition.[4] Conformation dynamics in ligand–receptor interactions is not easily predictable, and experimental approaches that allow measured conformational regulation are necessary for conferring specific ligand–receptor interactions.[5–7] Existing approaches of conformational control, such as steric directing, electronic attraction and repulsion, stereoelectronic control, and hydrogen bonding, have seen great success in tuning ligand conformation.[8,9] Selective fluorination is a recent addition to this repertoire in conformation tuning, due to the strong and unusual stereoelectronic effects resulting from the C–F bond, which include dipole–dipole interactions, charge–dipole interactions, and hyperconjugation effects.[10–13]

We have recently reported the regulatory effects of stereoselective fluorination using a model *N*-heterocyclic azepane system.[14] Substituted azepanes are well recognised bioactive epitopes in medicinal and natural products chemistry, and our introduction of fluorine-based conformational control represents an additional avenue for accessing bioactive azepanes.[15]

In our model system, a disubstituted azepane, with an azido substituent at C3 and an OBn substituent at C4 in *trans* relationship, was able to undergo selective monofluorination at the C6 position.[14a] Our earlier work of conformational control by monofluorination in this substituted azepane system shows that stereoselective monofluorination at the C6 position confers significant conformational bias only if such substitution occurs in the *R* configuration.[14b] Installation of an additional fluorine atom at the same C6 carbon is not conducive to further conformational bias, due to conflicting conformational controls from multiple fluorine atoms.[14c] Here, we describe the findings of conformational control from concurrent fluorine and hydroxy substitution at C5 and C6 in this azepane system (Fig. 1). Three fluorohydrin azepanes, **3**–**5**, were prepared to investigate the conformational outcomes of this azepane ring system. The aim was to investigate the stereochemical requirements for achieving cooperative conformational control for highly substituted fluoroazepanes. This is the first study of conformational regulation of seven-membered azepane fluorohydrins, in which we show how cooperative conformational control can be achieved.

In these tetra-substituted azepanes (Fig. 1), multiple effects exist to influence the conformation of the azepane ring. Notably, the C3/C4 pseudo-diequatorial *v.* pseudo-diaxial preference, the C3 azido *gauche* effect, and the fluorine/hydroxy *gauche* effect are significant contributors.[16,17] These preferences in the order of 1–3 kcal mol^{-1} are comparable in strength, unlike our earlier cases in which strong fluorine/N^{+} *gauche* effects around 6 kcal mol^{-1} from C6 fluorine substitution may dominate in controlling the ring conformation. In the azepanes here, these relatively mild conformational effects may act cooperatively or in conflict, thereby presenting an interesting opportunity for investigating the conformational characteristics that may emerge from cooperative interaction of multiple conformational effects in these highly substituted azepanes.

Results and Discussion

Synthesis of Fluorohydrin Azepanes

The synthesis of the targeted fluorohydrin azepanes **3**–**5** followed the deoxyfluorination strategy starting from dihydroxyazepanes. Dihydroxyazepanes **6** and **10** were synthesised according to the procedure reported previously.[14a] The

synthesis was initiated with the asymmetric epoxidation of divinylcarbinol and involved epoxide ring opening with allyl amine, ring closing metathesis, and dihydroxylation as key steps to afford **6** and **10** in 49 % yield over seven steps. The fluorohydrin azepane **9** was synthesised using the deoxyfluorination procedure with inversion of stereochemistry at C5.[14] Sodium borohydride reduction of azepane **12** furnished a mixture of diastereomers **13** and **11** in a ~9 : 1 ratio. Boc-deprotection using triflouroacetic acid (TFA) afforded the TFA salt of azepanes **1**–**5** from **6**, **10**, **9**, **11**, and **13**, respectively (Scheme 1).

The stereochemistry of azepanes **1**–**13** was secured using HSQC, HMBC, COSY, and NOESY 2D NMR spectroscopy as described previously.[14] The experimental *J* values were extracted via ^{1}H NMR simulation with the use of the program *Bruker TopSpin 3.2* (Table 1). The conformational analysis of azepanes **1**–**5** was based on these experimental *J* values to identify the contributing conformers.[18] Conformation searches were performed as implemented in the program *MOE*, and conformers within 3–5 kcal mol^{-1} for each azepane were clustered to identify unique ring conformations.[19] Each of the unique ring structures was subjected to density functional theory (DFT) geometry optimisations (*Turbomole*),[20] followed by general *J* calculations as described previously.[18] The experimental *J* values were then compared with the calculated values to identify the matching conformers.[21]

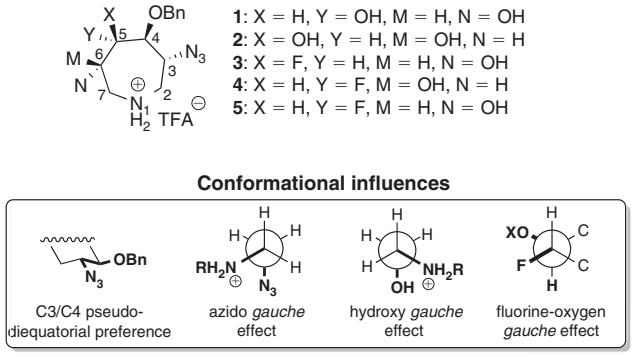


Fig. 1. Structures of azepanes **1**–**5** and the expected contributors of stereoelectronic influence on their conformations.

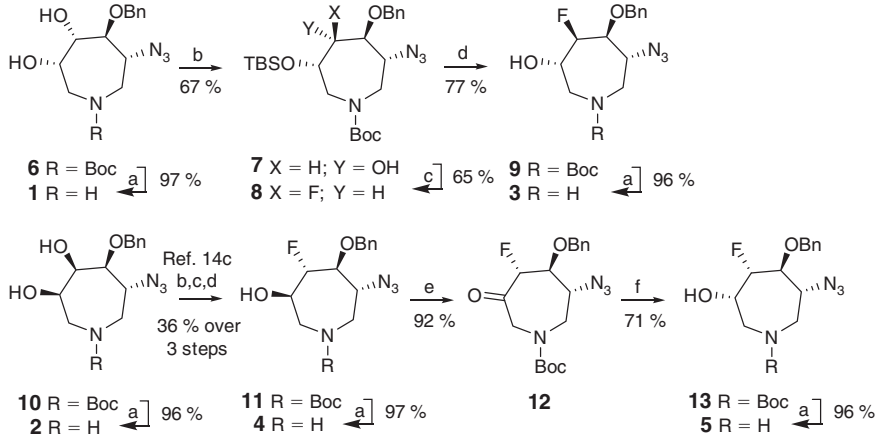
*Conformational Analysis of Fluorohydrin Azepanes **3**–**5** in $CDCl_3$*

*Comparison of Fluorohydrin Azepane **3** with Hydroxyazepane **14***

In our earlier work,[14c] two major conformers for hydroxyazepane **14** were identified (**14a** and **14b** in a 3 : 2 ratio, Fig. 2). In both conformers, the C3/C4 pseudo-diequatorial preference is maintained. However, the azido *gauche* preference was only maintained in the major conformer **14a** but not in **14b**. Fluorohydrin azepane **3** differs from the hydroxyazepane **14** by only the fluorine substitution at C5 *trans* to the C6 hydroxy group. The addition of this fluorine substituent at C5 does not alter the conformational preference of **14**, since the major conformer **3a** is similar to **14a**. In both conformers, the benzyloxy and azido groups are pseudo-diequatorial as expected, and the azido *gauche* and C6-oxygen/C7-nitrogen *gauche* preferences are also satisfied. The minor conformer **3b** is also quite similar to **3a** with the difference mainly due to the puckering of the nitrogen. Interestingly, the addition of fluorine in this case improves the conformational bias only slightly to a 2 : 1 ratio. In the case here, the fluorine substitution at C5 does not appreciably reduce conformational disorder nor change the major conformational preferences.

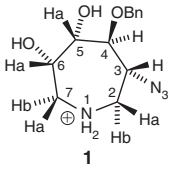
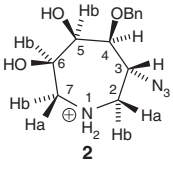
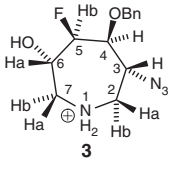
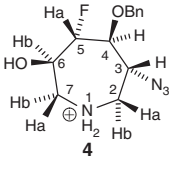
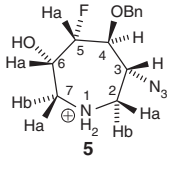
*Comparison of Fluorohydrin Azepanes **4** with Hydroxyazepane **15***

Hydroxyazepane **15** differs from hydroxyazepane **14** only in the configuration of the C6 hydroxy group (Fig. 2). Yet for **15** the conformational disorder was high enough to prevent the identification of major contributors from eight clusters of conformers found by a conformational search.[14c] Similar to **15**, azepane **2**, with an additional C5 hydroxy substitution in the *R* configuration (*cis*-diol), is also too conformationally disordered to permit identification of major conformers out of a dozen distinct ring conformation clusters. However, the addition of one fluorine *trans* to the C6 hydroxy group provided the fluorohydrin **4** with clear conformational bias to one conformer **4a** (Fig. 3). In this conformation, the benzyloxy and azido groups are pseudo-diequatorial as expected, and similar to **3a**, the C5-fluorine/C6-oxygen relationship is *anti* rather than *gauche*. This shows that the cooperativity between the fluorine



Scheme 1. Synthesis of fluorohydrin azepanes **1**–**5**. Reagents and conditions: (a) trifluoroacetic acid (TFA), neat, 5 min; (b) Imidazole, *tert*-butyldimethylsilyl chloride (TBSCl), dry DMF, 25°C, 10 h; (c) Deoxofluor, dry dichloromethane (DCM), 0°C, 8 h; (d) tetrabutylammonium fluoride (TBAF), dry THF, 45 min; (e) pyridinium chlorochromate (PCC) (1.1 equiv.), MS 4 Å, dry DCM, 25°C, 1.5 h; (f) $NaBH_4$, EtOH, 25°C, 1.5 h.

Table 1. Experimental $^3J_{HH}$ and $^3J_{HF}$ values for azepanes 1–5 in $CDCl_3$

Azepanes	Experimental $^3J_{HH}$ and $^3J_{HF}$ (Hz)[A]												
	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**	2.5	7.5	5.5	5.0	n.a.	1.8	n.a.	n.a.	n.a.	3.4	7.5	n.a.	n.a.
 **2**	2.0	6.0	8.0	n.a.	4.0	n.a.	n.a.	n.a.	2.0	n.a.	n.a.	4.0	4.0
 **3**	3.5	4.0	7.1	24.2	1.7	11.0	n.a.	6.0	n.a.	3.0	3.0	n.a.	n.a.
 **4**	2.0	8.9	8.7	2.0	21.4	n.a.	5.9	n.a.	7.0	n.a.	n.a.	6.2	1.4
 **5**	1.9	8.2	7.0	5.8	13.1	2.2	n.a.	19.4	n.a.	1.7	7.5	n.a.	n.a.

[A]The ^{1}H NMR spectrum of azepane **2** in $CDCl_3$ was too broad to allow accurate extraction of specific *J* values therefore the *J* values reported for azepane **2** should be regarded as approximate. n.a.: not applicable.

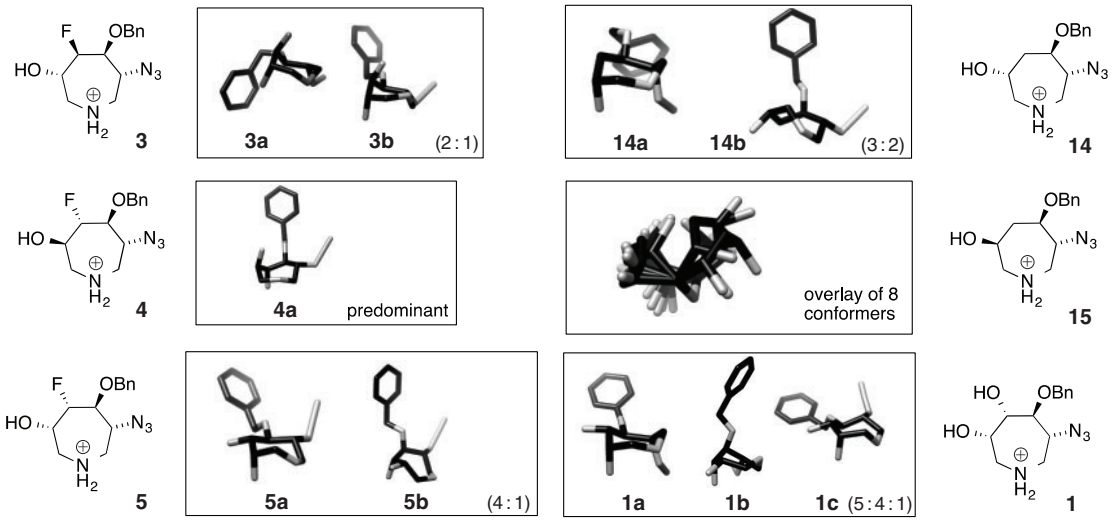


Fig. 2. Major conformers of azepanes **1**, **3**, **4**, and **5**. Azepane **2** was too disordered to allow identification of major conformers. For comparison purposes, the conformers of hydroxyazepanes **14** and **15** are included.[14c] All carbon atoms are shown in black and heteroatoms grey. All hydrogen atoms are omitted for clarity.

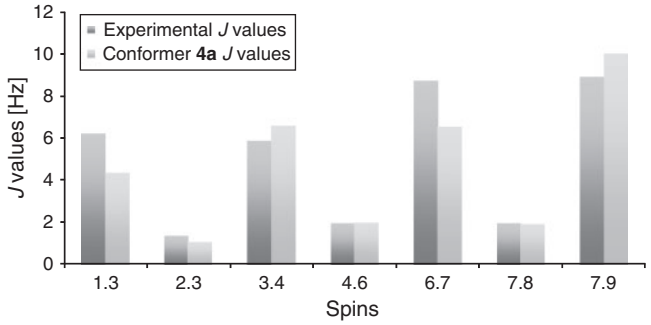


Fig. 3. The well matched experimental and calculated *J* values of conformer **4a** in $CDCl_3$.

and hydroxy substituents in conferring strong conformational bias can be achieved only if the relative stereochemistry of the two groups is appropriate.

*Comparison of Fluorohydrin Azepane **5** with Hydroxyazepane **1***

The comparison between the conformational populations of azepane **5** and **1** reveals interesting effects of the fluorine substitution at C5 (Fig. 2). Both azepanes are tetra-substituted in identical configurations; for azepane **5**, the C5 substitution is a fluorine atom rather than a hydroxy group. Hydroxyazepane **1** has two major conformers **1a** and **1b**, plus one minor conformer **1c**. Conformers **1a** and **1b** are distinct, with different dihedral angles at C3, C4, C5, and C6. Conformer **1a** adopts a chair–boat like geometry, and the C3/C4 pseudo-diequatorial preference is only partly satisfied; however in **1b**, the C3/C4 substituents are in the pseudo-diaxial position. The minor conformer **1c** resembles **1a**, except that the C3/C4 substituents are pseudo-diequatorial and that the azido preference in **1c** is *anti* rather than *gauche*.

Changing the C5 substituent from OH to fluorine appears to significantly alter the conformational landscape of the azepane. In azepane **5**, the conformational disorder is clearly reduced to one major conformer **5a** with one minor conformer **5b** in a 4 : 1 ratio. The conformational preferences are also considerably changed, in that **5a** resembles the minor conformer **1c**, with only slight dihedral differences at C2 and C3. The minor conformer **5b** does not resemble any of the conformational contributors of azepane **1**. For both conformer **5a** and **5b**, the C3/C4 preference is pseudo-diequatorial, and the azido preference is *anti* rather than *gauche*. Both of the C4/C5 and C5/C6 fluorine/OH *gauche* preferences are met in **5a** but not in **5b**. This comparison demonstrates that C5 fluorine substitution is more effective at reducing conformational disorder compared with the hydroxy substituent.

*Cooperative Conformational Regulation in Fluorohydrin Azepane **4***

The tetra-substituted fluorohydrin azepane **4** exhibits strong conformational bias, and this control is the result of all four substituents in an appropriate relative configuration on the azepane ring. One possibility might be that perhaps tetra-substitution generally favours a more ordered ring conformation. However, the conformational properties of azepane **1** are not supportive of such a generalisation. Compared with the mono-hydroxylated azepane **14**, the bis-hydroxylated azepane **1** exhibits a comparable level of conformational disorder if not more. In other words, having an additional hydroxy substituent at C5 does not appreciably confer further conformational bias nor alter the conformational preferences in this azepane. Conformers **14a** and **1a** are in fact quite similar.

In the case of azepane **5**, substitution with fluorine at C5 in the same configuration, however, is able to confer conformational control cooperatively with three other substituents at C3, C4, and C6. Not only is the ring conformation biased to one major conformer but also the conformational preferences in the major conformer are changed. Interestingly, this level of conformational control is absent in fluorohydrin azepane **3**, in which the fluorine substituent is in the opposite configuration. This again reinforces the observation that, given the appropriate configuration in this highly substituted azepane system, fluorine is a stronger director than the hydroxy group. It is also noteworthy that in all three major conformations of the fluorohydrins **3a**, **4a**, and **5a**, the C3/C4 pseudo-diequatorial preference and hydroxy *gauche* effect are satisfied, while the azido *gauche* effect group is consistently lost. In the case of the dihydroxy azepane **1** with two major conformers **1a** and **1b**, the C3/C4 pseudo-diequatorial preference and hydroxy *gauche* effect are either satisfied (**1a**) or lost (**1b**), while the azido *gauche* effect group is consistently satisfied in both **1a** and **1b**. This also suggests that fluorine at C5 is able to control the relative influences of the other conformational factors better than the hydroxy group. However, fluorine alone is not able to achieve conformational regulation at the most optimal level. The best-case scenario of conformational control is found in fluorohydrin azepane **4**, where the C5 fluorine remains in the *S* configuration with the C6 hydroxy group *trans* to the fluorine. In this azepane the cooperativity between the four substituents in conformational control is at the highest level given the appropriate relative configuration of the substituents, resulting in bias to one predominant conformer **4a**.

Solvent Effects

The coupling constants of azepanes **1**–**5** in polar aprotic solvents, such as $(CD_3)_2CO$, CD_3CN, $(CD_3)_2SO$, and protic solvent CD_3OD were also investigated. For bishydroxyazepane **1**, the proton chemical shifts were within 0.5 ppm in different solvents. Small coupling constant deviations of 2–3 Hz appeared in the C3–C5 region; however, the rest of the *J* values were identical in different solvents, suggesting no significant changes in the conformer populations in different solvents. For bishydroxyazepane **2**, the solvent effects were more pronounced. The broad proton signals became more defined with more than one conformer population visible. ^{1}H NMR spectra in $(CD_3)_2CO$ and CD_3CN displayed at least three different conformer populations; while the ^{1}H NMR spectra in CD_3OD and $(CD_3)_2SO$ had one major conformer population with a minor population. It was possible to extract the coupling constants of the major population from the CD_3OD spectrum. Conformational analysis was able to identify two major conformers **2a** and **2b** in a 3 : 2 ratio (Fig. 4). These two conformers adopt similar conformations at C3, C4, and C5; however, the nitrogen puckerings are in opposite directions (up in **2a** but down in **2b**). In the major conformer **2a**, the C6 oxygen prefers to be *gauche* to the ring nitrogen, although the azido preference is *anti* rather than *gauche*.

Azepane **4** and **5** had no significant changes in conformer populations in the solvents studied, and lowering the

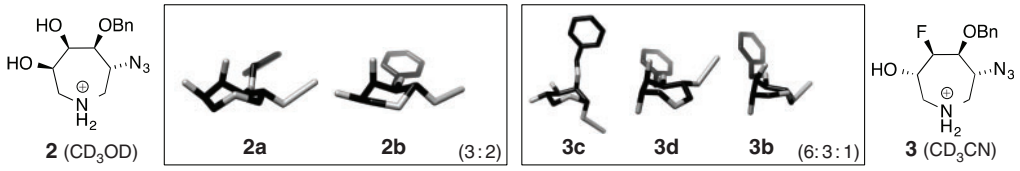


Fig. 4. Major conformers of azepanes **2** in CD_3OD and **3** in CD_3CN. All carbon atoms are shown in black and heteroatoms grey. All hydrogen atoms are omitted for clarity.

temperature did not lead to apparent changes in conformational populations.[21,22] However, azepane **3** in acetonitrile exihibits very different conformational populations (Fig. 4). Only one set was amenable to *J*-based analysis. This population consists of two major conformers **3c** and **3d**, with **3b** being a minor contributor. Interestingly, **3d** is only slightly different from **3a** by virtue of the azido *anti* rather than *gauche* to the ring nitrogen. However, conformer **3c** is a distinct new conformer with the C5 fluorine and C6 hydroxy groups *gauche* and the C3/C4 substituents in pseudo-diaxial positions. These cases demonstrate that some of these highly substituted azepane systems, while conformationally biased, still retain significant conformational mobility and are able to sample very different conformations in different solvents. For seven-membered *N*-heterocycles that are conformationally very diverse, such conformational mobility could not have been predicted prior but only observed experimentally.

Conclusions

In conclusion, a series of fluorohydrin azepanes were examined for their conformational properties. One of their dihydroxy-substituted counterparts was also investigated as a comparison. In such highly substituted seven-membered *N*-heterocyles, positive cooperativity in conformational control was achieved with a C5-*S* fluorine and a C6-*R* hydroxy substituent. Deviation from this configurational profile leads to increased conformational disorder. Replacing the C5-*S* fluorine with a C5-*S* hydroxy substituent also causes loss of conformational bias, suggesting that the C5 fluorine exhibits stronger effects than the hydroxy group in conformational control of this azepane system.

Experimental

General

All reactions were conducted under 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 MS 4 Å beads. Ethyl acetate and petroleum ether were distilled before use and the later refers to the fraction collected between 60 and 80°C. THF was distilled over Na–benzophenone and stored over MS 4 Å beads. Anhydrous DMF 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 (ppm) 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). Computational investigations were performed using programs *MOE* (Molecular Operating Environment 2011.10; Chemical Computing Group), and *Turbomole* (version 6.3).

Synthesis of Azepanes *1*–*13*

Azepanes **6**, **10**–**12** were synthesised according to the procedure described previously.[14]

*(3R,4S,5S,6S)-3-Azido-4-benzyloxy-5,6-dihydroxyazepane (**1**)*

The azepane **6** (13.60 mg, 35.9 μmol) was dissolved in TFA (500 μL) at 25°C. The solution was allowed to stir for 5 min before TFA was evaporated under 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 colourless oily residue obtained was characterised as **1** (9.70 mg, 97 %).

$[\alpha]_D^{20} = +32.3$ (*c* 0.8, CH_2Cl_2). ν_{max} (film)/cm^{-1} 3581, 2349, 1690, 1673, 1646, 1551, 1167, 1130. δ_H (600 MHz, $CDCl_3$) 7.39–7.28 (m, 5H), 4.65 (d, *J* 10.10, 1H), 4.57 (d, *J* 10.10, 1H), 4.34–4.28 (m, 1H), 4.07–3.95 (m, 2H), 3.62–3.53 (m, 1H), 3.38–3.13 (m, 3H), 2.83–2.71 (m, 1H). δ_C (150 MHz, $CDCl_3$) 136.8, 128.9, 128.6, 128.4, 80.6, 74.6, 73.9, 66.1, 59.9, 46.3, 45.1. *m/z* (HRMS ESI) 279.1451; $[M+H]^+$ $C_{13}H_{19}N_4O_3$ requires 279.1457.

*(3R,4S,5R,6S)-3-Azido-4-benzyloxy-6-(*tert*-butyldimethylsilyl)oxy-5-hydroxyazepane-1-carboxylic Acid* tert*-Butyl Ester (**7**)*

A solution of *tert*-butyldimethylsilyl chloride (96.5 mg, 0.641 mmol) in DMF (3.25 mL) was added dropwise via a syringe to a well stirred solution of **6** (220 mg, 0.583 mmol) and imidazole (43.6 mg, 0.641 mmol) in DMF (3.25 mL) at 25°C under N_2 atmosphere. The reaction mixture was allowed to stir at the same temperature for 10 h. The reaction mixture was quenched by addition of water (5 mL) and was extracted with EtOAc (10 mL × 3). The combined organic layer was washed with water (5 mL × 2) and brine (5 mL) to remove DMF residues and dried ($MgSO_4$) before evaporation under reduced pressure to obtain the crude product, which was subjected to flash chromatography (petroleum ether/EtOAc, 9/1) to give **7** (192.4 mg, 67 %, R_f 0.33) as a colourless oil. It is noteworthy that **7** was obtained exclusively and unreacted **6** was recovered. $[\alpha]_D^{20} = +15.1$ (*c* 1.0, CH_2Cl_2). ν_{max} (film)/cm^{-1} 3600–3130 (br), 2997, 2933, 2365, 2114, 1680, 1411, 1157, 1088, 1045, 990. δ_H (600 MHz, $CDCl_3$) 7.39–7.33 (m, 5H), 4.93 (d, *J* 11.11, 1H), 4.60 (d, *J* 11.11, 1H), 4.28–4.25 (m, 1H), 4.02 (dd, *J* 14.28, 5.32, 1H), 3.82–3.70 (m, 2H), 3.62 (br s, 1H), 3.58–3.53 (m, 1H), 3.31 (dd, *J* 14.17, 10.88, 1H), 3.01 (ddd, *J* 13.70, 4.69, 2.86, 1H), 2.60 (br s, 1H), 1.47 (s, 9H), 0.92 (s, 9H), 0.1 (s, 6H). δ_C (150 MHz, $CDCl_3$) 154.7, 137.6, 128.9, 128.4, 128.3, 81.7, 80.7, 75.4, 73.4, 71.4, 64.4, 50.5, 46.0, 28.5, 26.0, −4.53, −4.85. *m/z* (HRMS ESI) 493.2844; $[M+H]^+$ $C_{24}H_{41}N_4O_5Si$ requires 493.2846.

*(3R,4S,5S,6S)-3-Azido-4-benzyloxy-6-(*tert-*butyldimethylsilyl)oxy-5-fluoroazepane-1-carboxylic Acid* tert-*Butyl Ester (**8**)*

A solution of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) (89.8 mg, 0.406 mmol) in dry dichloromethane (DCM) (5.5 mL) was added dropwise via a syringe to a well stirred solution of **7** (200.0 mg, 0.406 mmol) in dry DCM (5.5 mL) under N_2 atmosphere at 0°C. The reaction mixture was allowed to stir at the same temperature for 8 h. 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 obtain the crude product, which was subjected to flash chromatography (petroleum ether/EtOAc, 9/1) to give **8** (130.5 mg, 65 %, R_f 0.52) as a colourless oil. $[\alpha]_D^{20}$ +55.1 (*c* 0.9, CH_2Cl_2). ν_{max} (film)/cm^{-1} 2997, 2933, 2365, 2114, 1680, 1521, 1473, 1456, 1411, 1157, 1088, 1045, 990. δ_H (600 MHz, $CDCl_3$) 7.44–7.28 (m, 5H), 4.80 (d, *J* 10.29, 1H), 4.71 (d, *J* 10.29, 1H), 4.55 (dd, *J* 46.56 ($^1J_{HF}$), 8.47, 1H), 4.43–4.36 (m, 1H), 4.11 (dd, *J* 14.01, 4.75, 1H), 4.01–3.90 (m, 1H), 3.75 (dd, *J* 14.30, 2.45, 1H), 3.53–3.47 (m, 1H), 3.25 (dd, *J* 14.30, 11.33, 1H), 3.02 (dd, *J* 14.01, 12.36, 1H), 1.45 (s, 9H), 0.93 (s, 1H), 0.13 (d, *J* 23.66, 6H). δ_C (150 MHz, $CDCl_3$) 154.6, 137.8, 128.7, 128.6, 128.2, 95.6 (d, $^1J_{CF.}$ 177.79), 81.1, 80.8 (d, $^2J_{CF.}$ 19.18), 75.8, 71.6 (d, $^2J_{CF.}$ 28.23), 63.5 (d, $^3J_{CF.}$ 10.16), 49.4 (d, $^3J_{CF.}$ 12.65), 45.3, 28.5, 25.9, −4.61, −4.83. *m/z* (HRMS ESI) 495.2798; $[M+H]^+$ $C_{24}H_{40}FN_4OSi$ requires 495.2803.

(3R,4S,5R,6S)-3-Azido-4-benzyloxy-5-fluoro-6-hydroxyazepane-1-carboxylic Acid tert-*Butyl Ester (**9**)*

A solution of tetrabutylammonium fluoride (TBAF, 1 M solution in THF, 80 µL, 80.1 µmol) was added dropwise via a syringe to a well stirred solution of **8** (36.0 mg, 72.8 µmol) in dry THF (1 mL) under N_2 atmosphere at 25°C. The reaction mixture was allowed to stir at the same temperature until completion (45 min, TLC). The reaction mixture was evaporated to dryness and the crude obtained was subjected to flash chromatography (petroleum ether/EtOAc, 4/1) to give **9** (21.3 mg, 77 %, R_f 0.24) as a colourless oil. $[\alpha]_D^{20}$ +36.7 (*c* 0.9, CH_2Cl_2). ν_{max} (film)/cm^{-1} 3600–3130 (br), 2990, 2963, 2365, 2134, 1684, 1526, 1479, 1466, 1419, 1167, 1081, 1042. δ_H (600 MHz, $CDCl_3$) 7.39–7.30 (m, 5H), 4.78 (d, *J* 11.80, 1H), 4.74 (br d, $^1J_{HF}$ 45.70, 1H), 4.62 (d, *J* 11.80, 1H), 4.16–4.08 (m, 1H), 4.01 (br d, *J* 15.22, 1H), 3.98 (br d, *J* 17.69, 1H), 3.95 (dd, *J* 14.59, 4.09, 1H), 3.78 (br s, 1H), 3.39 (dd, *J* 15.31, 4.32, 1H), 3.24 (dd, *J* 15.22, 3.72, 1H), 1.48 (s, 9H). δ_C (150 MHz, $CDCl_3$) 157.8, 137.3, 128.7, 128.3, 128.1, 96.5 (d, $^1J_{CF.}$ 176.11), 81.8, 79.5 (d, $^2J_{CF.}$ 22.61), 73.9, 72.6 (d, $^2J_{CF.}$ 24.36), 61.4 (d, $^3J_{CF.}$ 12.05), 52.1 (d, $^3J_{CF.}$ 9.44), 48.8, 28.3. *m/z* (HRMS ESI) 381.1938; $[M+H]^+$ $C_{18}H_{26}FN_4O_4$ requires 381.1938.

*(3R,4S,5R,6S)-3-Azido-4-benzyloxy-5-fluoro-6-hydroxyazepane (**3**)*

The procedure for the synthesis of **1** was followed to give a colourless oil in 96 % yield from **9**; $[\alpha]_D^{20}$ +43.2 (*c* 0.7, CH_2Cl_2). ν_{max} (film)/cm^{-1} 3610–3160 (br), 2999, 2939, 2369, 2134, 1482, 1442, 1410, 1143, 1089, 1012. δ_H (600 MHz, $CDCl_3$) 7.40–7.30 (m, 5H), 5.02 (dd, $^1J_{HF}$ 46.02, 5.69, 1H), 4.75 (d, *J* 11.86, 1H), 4.65 (d, *J* 11.86, 1H), 4.33–4.26 (m, 1H), 4.16 (dd, *J* 24.30, 6.78, 1H), 3.99–3.95 (m, 1H), 3.52 (d, *J* 14.60, 1H), 3.40 (d, *J* 14.09, 1H), 3.42–3.22 (m, 2H). δ_C (150 MHz, $CDCl_3$) 136.5, 128.9, 128.6, 128.3, 93.0 (d, $^1J_{CF.}$ 178.86), 78.0 (d, $^2J_{CF.}$ 19.98), 74.0, 66.6 (d, $^2J_{CF.}$ 26.97), 57.6 (d, $^3J_{CF.}$ 9.21), 50.1 (d, $^3J_{CF.}$ 5.58), 48.2. *m/z* (HRMS ESI) 281.1410; $[M+H]^+$ $C_{13}H_{18}FN_4O_2$ requires 281.1408.

*(3R,4S,5R,6R)-3-Azido-4-benzyloxy-5,6-dihydroxyazepane (**2**)*

The procedure for the synthesis of **1** was followed to give a colourless oil in 96 % yield from **10**; $[\alpha]_D^{20}$ −18.2 (*c* 0.8, CH_2Cl_2). ν_{max} (film)/cm^{-1} 3581, 2349, 1690, 1673, 1646, 1551, 1167, 1130. δ_H (600 MHz, $CDCl_3$) 7.42–7.29 (m, 5H), 4.65 (d, 2H), 4.29–4.23 (m, 1H), 4.06–4.00 (m, 1H), 3.87–3.80 (m, 1H), 3.74–3.69 (m, 1H), 3.48–3.40 (m, 1H), 3.28–3.15 (m, 3H). δ_C (150 MHz, $CDCl_3$) 136.6, 128.9, 128.7, 128.7, 81.8, 73.1, 72.5, 66.3, 58.9, 47.6, 46.6. *m/z* (HRMS ESI) 279.1459; $[M+H]^+$ $C_{13}H_{19}N_4O_3$ 279.1457.

*(3R,4S,5S,6R)-3-Azido-4-benzyloxy-5-fluoro-6-hydroxyazepane (**4**)*

The procedure for the synthesis of **1** was followed to give a colourless oil in 97 % yield from **11**; $[\alpha]_D^{20}$ −22.1 (*c* 0.7, CH_2Cl_2). ν_{max} (film)/cm^{-1} 3610–3160 (br), 2999, 2939, 2369, 2134, 1482, 1442, 1410, 1143, 1089, 1012. δ_H (600 MHz, $CDCl_3$) 7.41–7.34 (m, 5H), 4.85 (dd, $^1J_{HF}$ 44.09, 6.07, 1H), 4.77 (d, *J* 11.33, 1H), 4.67 (d, *J* 11.33, 1H), 4.42–4.37 (m, 1H), 4.24 (dd, *J* 9.01, 8.37, 1H), 3.78 (dd, *J* 21.34, 8.48, 1H), 3.40 (dd, *J* 14.06, 6.03, 1H), 3.36 (d, *J* 14.08, 1H), 3.14 (d, *J* 13.58, 1H), 2.85 (dd, *J* 13.96, 9.50, 1H). δ_C (150 MHz, $CDCl_3$) 136.2, 128.9, 128.9, 128.7, 92.1 (d, $^1J_{CF.}$ 173.7), 82.7 (d, $^2J_{CF.}$ 21.7), 73.8, 66.4 (d, $^2J_{CF.}$ 28.33), 59.5, 46.3, 46.0. *m/z* (HRMS ESI) 281.1411; $[M+H]^+$ $C_{13}H_{18}FN_4O_2$ requires 281.1408.

(3R,4S,5S,6S)-3-Azido-4-benzyloxy-5-fluoro-6-hydroxyazepane-1-carboxylic Acid tert-*Butyl Ester (**13**)*

To a solution of azepane **12** (14.6 mg, 38.7 µmol) in EtOH (0.12 mL) was added sodium borohydride (1.5 mg, 38.7 µmol) and the solution was allowed to stir at room temperature for 1.5 h before addition of EtOAc (5 mL) and brine (2 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL × 2). The combined organic layer was rotary evaporated to obtain the crude mixture, which was subjected to flash column chromatography using 25 % EtOAc/petroleum ether to obtain **13** (10.4 mg, 71 %, R_f 0.24) and **11** (1.2 mg, 8 %, R_f 0.25) as colourless oils. **13**: $[\alpha]_D^{20}$ +15.5 (*c* 1.1, CH_2Cl_2). ν_{max} (film)/cm^{-1} 3600–3130 (br), 2990, 2963, 2365, 2134, 1684, 1526, 1479, 1466, 1419, 1167, 1081, 1042. δ_H (400 MHz, $CDCl_3$) 7.44–7.30 (m, 5H), 4.82–4.67 (m, 3H), 4.44–4.26 (m, 1H), 4.04–3.91 (m, 2H), 3.76 (br d, *J* 13.85, 1H), 3.62–3.53 (m, 1H), 3.24–3.13 (m, 2H), 2.29 (d, *J* 4.98, 1H), 1.46 (s, 9H). δ_C (100 MHz, $CDCl_3$) 154.8, 137.5, 128.7, 128.6, 128.3, 95.6 (d, $^1J_{CF.}$ 176.57), 81.2, 80.3 (d, $^2J_{CF.}$ 21.01), 75.3, 70.2 (d, $^2J_{CF.}$ 22.97), 63.6 (d, $^3J_{CF.}$ 7.24), 48.5 (d, $^3J_{CF.}$ 10.28), 46.4, 28.5. *m/z* (HRMS ESI) 381.1941; $[M+H]^+$ $C_{18}H_{26}FN_4O_4$ requires 381.1938.

*(3R,4S,5S,6S)-3-Azido-4-benzyloxy-5-fluoro-6-hydroxyazepane (**5**)*

The procedure for the synthesis of **1** was followed to give a colourless oil in 96 % yield from **13**; $[\alpha]_D^{20}$ +24.5 (*c* 0.8, CH_2Cl_2). ν_{max} (film)/cm^{-1} 3610–3160 (br), 2999, 2939, 2369, 2134, 1482, 1442, 1410, 1143, 1089, 1012. δ_H (600 MHz,

$CDCl_3$) 7.42–7.35 (m, 5H), 4.81 (ddd, $^1J_{HF}$ 44.79, 5.78, 177, 1H), 4.79 (d, *J* 11.33, 1H), 4.72 (d, *J* 11.33, 1H), 4.52 (dd, *J* 19.41, 7.08, 1H), 4.02 (dt, *J* 12.77, 5.73, 1H), 3.97 (ddd, *J* 6.75, 5.73, 2.35, 1H), 3.61 (ddd, *J* 14.00, 7.54, 2.06, 1H), 3.43–3.39 (m, 2H), 3.34 (d, *J* 13.49, 1H). δ_C (150 MHz, $CDCl_3$) 136.5, 128.9, 128.6, 128.3, 93.0 (d, $^1J_{CF.}$ 178.86), 78.0 (d, $^2J_{CF.}$ 19.98), 74.0, 66.6 (d, $^2J_{CF.}$ 26.97), 57.6 (d, $^3J_{CF.}$ 9.21), 50.1 (d, $^3J_{CF.}$ 5.58), 48.2. *m/z* (HRMS ESI) 281.1410; $[M+H]^+$ $C_{13}H_{18}FN_4O_2$ requires 281.1408.

Supplementary Material

Copies of NMR spectra and conformational analysis details are available on the Journal's website.

Acknowledgement

The authors thank Dr Luke Hunter for helpful suggestions.

References

[1] S. L. Schreiber, *Science* **2000**, *287*, 1964. doi:10.1126/SCIENCE.287.5460.1964

[2] D. S. Tan, *Nat. Chem. Biol.* **2005**, *1*, 74. doi:10.1038/NCHEMBIO0705-74

[3] W. R. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.* **2010**, 1. doi:10.1038/NCOMMS1081

[4] S. Llabrés, J. Juárez, F. Forti, R. Pouplana, F. J. Luque, in *Physico–Chemical and Computational Approaches to Drug Discovery* (Eds J. Luque, X. Barril) **2012**, Ch. 1, pp. 1–22 (The Royal Society of Chemistry: London).

[5] L. Skjaerven, N. Reuter, A. Martinez, *Future Med. Chem.* **2011**, *3*, 2079. doi:10.4155/FMC.11.159

[6] K. K. Frederick, M. S. Marlow, K. G. Valentine, A. J. Wand, *Nature* **2007**, *448*, 325. doi:10.1038/NATURE05959

[7] B. Honarparvar, T. Govender, G. E. Maguire, M. E. Soliman, H. G. Kruger, *Chem. Rev.* **2014**, *114*, 493. doi:10.1021/CR300314Q

[8] J. Rebek, Jr, *Science* **1987**, *235*, 1478. doi:10.1126/SCIENCE.3823899

[9] E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem. Int. Ed.* **2003**, *42*, 1210. doi:10.1002/ANIE.200390319

[10] (a) X.-G. Hu, L. Hunter, *Beilstein J. Org. Chem.* **2013**, *9*, 2696. doi:10.3762/BJOC.9.306
(b) L. Hunter, *Beilstein J. Org. Chem.* **2010**, *6*, 38. doi:10.3762/BJOC.6.38
(c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308. doi:10.1039/B711844A

[11] (a) R. Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 777. doi:10.4155/FMC.09.65
(b) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359. doi:10.1021/JM800219F

[12] N. E. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Slawin, A. M. Teale, D. J. Tozer, R. J. Young, *Angew. Chem. Int. Ed.* **2007**, *46*, 5904. doi:10.1002/ANIE.200700714

[13] H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119. doi:10.1021/CR800388C

[14] (a) A. R. Patel, F. Liu, *Tetrahedron* **2013**, *69*, 744. doi:10.1016/J.TET.2012.10.078
(b) A. R. Patel, G. Ball, L. Hunter, F. Liu, *Org. Biomol. Chem.* **2013**, *11*, 3781. doi:10.1039/C3OB40391B
(c) A. R. Patel, L. Hunter, M. M. Bhadbhade, F. Liu, *Eur. J. Org. Chem.* **2014**, 2584. doi:10.1002/EJOC.201301811

[15] (a) E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832. doi:10.1021/JM401375Q
(b) T. K. Beng, S. M. Wilkerson-Hill, R. Sarpong, *Org. Lett.* **2014**, *16*, 916. doi:10.1021/OL403671S

[16] L.-S. Sonntag, S. Schweizer, C. Ochsenfeld, H. Wennemers, *J. Am. Chem. Soc.* **2006**, *128*, 14697. doi:10.1021/JA0654938

[17] (a) C. R. S. Briggs, M. J. Allen, D. O'Hagan, D. J. Tozer, D. J. A. M. Z. Slawin, A. E. Goeta, J. A. K. Howard, *Org. Biomol. Chem.* **2004**, *2*, 732. doi:10.1039/B312188G
(b) K. B. Wiberg, M. A. Murcko, K. E. Laidig, P. J. MacDougall, *J. Phys. Chem.* **1990**, *94*, 6956. doi:10.1021/J100381A008
(c) C. R. S. Briggs, D. O'Hagan, H. S. Rzepa, A. M. Z. Slawin, *J. Fluor. Chem.* **2004**, *125*, 19. doi:10.1016/J.JFLUCHEM.2003.08.011
(d) D. O'Hagan, C. Bilton, J. A. K. Howard, L. Knight, D. J. Tozer, *J. Chem. Soc., Perkin Trans. 2* **2000**, 605. doi:10.1039/B000205O

[18] (a) C. A. G. Haasnoot, F. A. A. M. DeLeeuw, C. Altona, *Tetrahedron* **1980**, *36*, 2783. doi:10.1016/0040-4020(80)80155-4
Three-bond H–H and H–F coupling constants obey Karplus relationships with the corresponding H–C–C–H and H–C–C–F dihedral angles: 'typical' $^3J_{HH}$ values are 1–3 Hz for *gauche* alignments and 6–9 Hz for *anti* alignments; see (b) A. M. Ihrig, S. L. Smith, *J. Am. Chem. Soc.* **1970**, *92*, 759. doi:10.1021/JA00707A003
'Typical' $^3J_{HF}$ values are 5–15 Hz for *gauche* alignments and 25–35 Hz for *anti* alignments; see (c) C. Thibaudeau, J. Plavec, J. Chattopadhyaya, *J. Org. Chem.* **1998**, *63*, 4967. doi:10.1021/JO980144K
For an example of conformational analysis by NMR and DFT methods, see (d) P. Tähtinen, A. Bagno, K. D. Klika, K. Pihlaja, *J. Am. Chem. Soc.* **2003**, *125*, 4609. doi:10.1021/JA021237T

[19] *MOE (Molecular Operating Environment software)* **2013** (Chemical Computing Group Inc.: Montreal). Available at http://www.chemcomp.com

[20] (a) R. Ahlrichs, M. Bär, M. Häser, H. Horn, C. Kölmel, *Chem. Phys. Lett.* **1989**, *162*, 165. doi:10.1016/0009-2614(89)85118-8
(b) A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571. doi:10.1063/1.463096
(c) O. Treutler, R. Ahlrichs, *J. Chem. Phys.* **1995**, *102*, 346. doi:10.1063/1.469408
(d) A. Klamt, G. Schüürmann, *J. Chem. Soc. Perkin Trans. 2* **1993**, 799. doi:10.1039/P29930000799
(e) M. von Arnim, R. Ahlrichs, *J. Chem. Phys.* **1999**, *111*, 9183. doi:10.1063/1.479510

[21] See Supplementary Material.

[22] Consistent with earlier observations (Ref. [14c]), none of the fluorohydrin azepane ^{1}H NMR spectra revealed new conformational equilibria at different temperatures suggesting low barriers for the conformational interchange.