Synthesis and Conformational Analysis of Cyclic Analogues of Inverse γ-Turns

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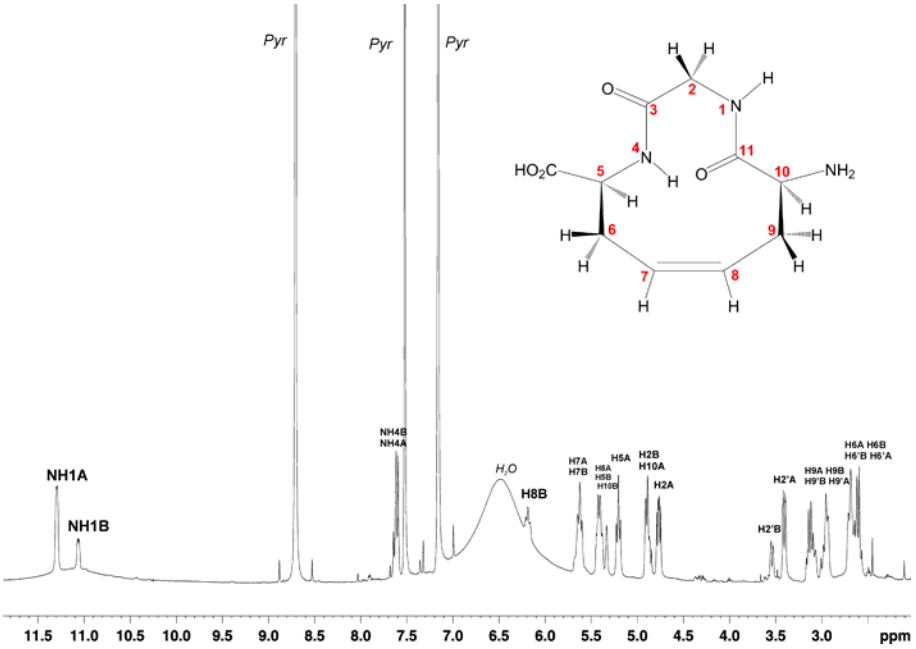


Fig. S1 ^{1}H spectrum of ***Z*-4b** in [^{2}H]$_5$-pyridine at 238 K.

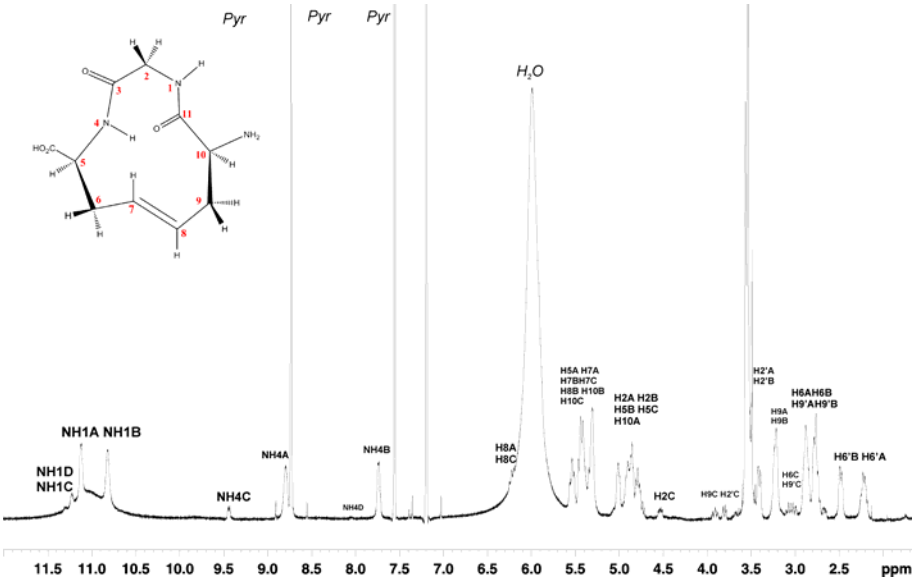


Fig. S2 ^{1}H spectrum of ***E*-4b** in [^{2}H]$_5$-pyridine at 238 K.

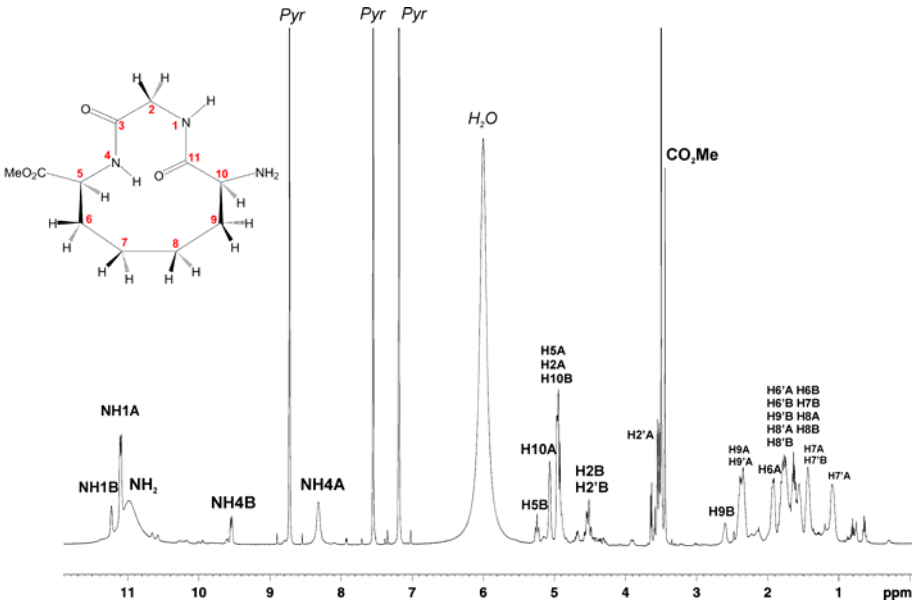


Fig. S3 ^{1}H spectrum of **5** in $[^{2}H]_5$-pyridine at 238 K.

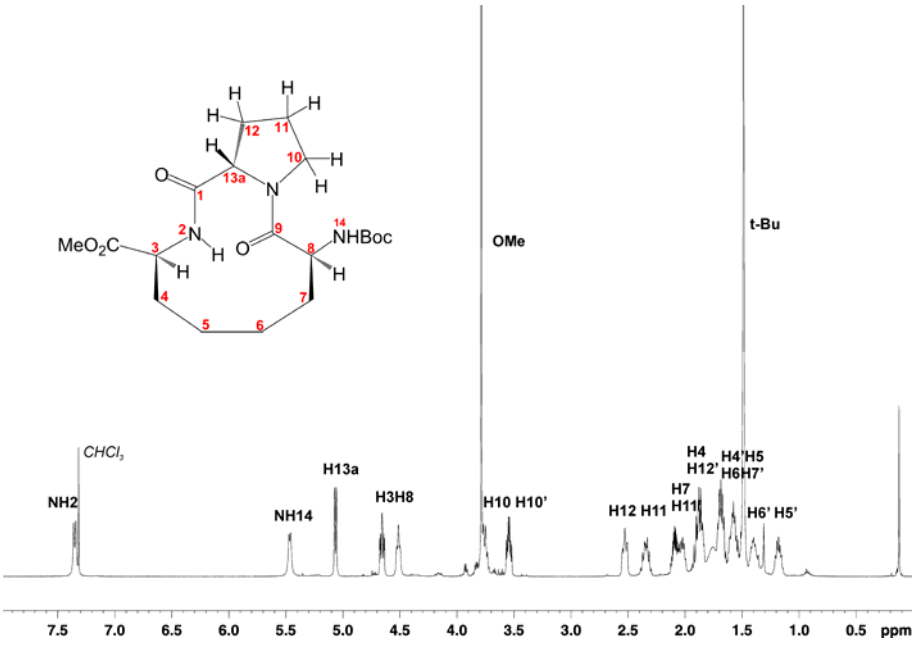
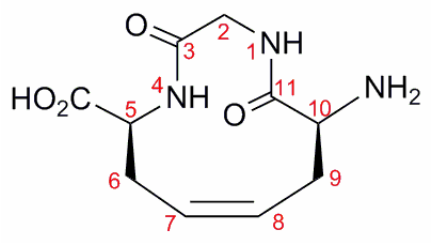


Fig. S4 ^{1}H spectrum of **10** in $CDCl_3$ at 298 K.

Table S1 ^{1}H NMR data for ***Z*-4b** and ***E*-4b** in [^{2}H]$_5$-pyridine at 238 K.

Position	δ_H, multiplicity, J in Hz of ***Z*-4b**		δ_H, multiplicity, J in Hz of ***E*-4b**		
	Conformer A	Conformer B	Conformer A	Conformer B	Conformer C
NH1	11.34, dd, 8.0, 3.7	11.10, dt, 9.3, 3.7	11.00	10.68	11.1, br
2	4.81, dd, 8.0,	4.91, dd, 9.3,	4.66	4.78	4.43, d, 8.7
2′	3.45, dd,	3.58, dd,	3.28	3.40	3.65, d, 5.1
NH4	7.64, d, 10.8	7.67, d, 9.6	8.68	7.62	9.3, d, 8.15
5	5.25, ddd, 11.0, 10.8, 2.6	5.45, m	5.28	4.76	4.6
6	2.69, m	2.64, m	2.68	2.76	2.93, overlap
6′	2.62, m	2.67, m	2.10	2.35	2.5
7	5.64, dt,	5.67, m	5.32	5.22	5.4, overlap
8	5.44, dt,	6.22, dt,	5.86	5.43	6.1, overlap
9	3.12, m	3.06, m	3.12	3.08	3.8, d, 12.8
9′	2.95, m	3.00, m	2.78	2.66	2.87, overlap
10	4.94, m	5.37, m	4.89	5.18	5.2, overlap



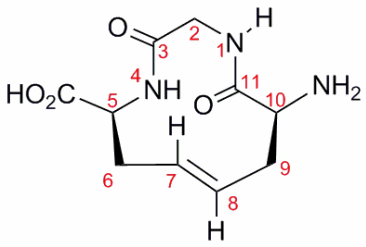


Table S2 Selected NOEs for conformer A of ***Z*-4b** at 238 K and comparison of the calculated inter-proton distances with those derived from the energy minimised molecular dynamics structure.

Proton pair	NOE intensity ratio[(a)]	Calc. distance (Å)	
		NOEs[(b)]	Model
NH4 – H6	14	2.8	2.6
NH1 – H8	18	2.9	3.1
NH1 – H10	5.1	2.3	2.2
H5 – H7	14	2.8	2.7
H8 – H10	14	2.8	2.7

[(a)] 2D volume integral relative to that of H2-H2′ ($V_{H2\text{-}2'}/V_{I\text{-}S}$) quoted to 2 significant figures. [(b)] Calculated distance based on the isolated spin pair approximation.

Table S3 A summary of selected NOEs for conformers A, B and C of ***E*-4b** at 238 K.

Proton pair	Intensity of NOEs		
	***E*-4b** conformer A	***E*-4b** conformer B	***E*-4b** conformer C
NH1 – NH4	-	-	Medium (2.5)
NH1 – H8	Weak (4.3)	Medium (3.6)	-
NH1 – H7	Weak* (3.2)	Weak* (5.1)	-
NH1 – H10	Medium (2.5)	Strong (2.1)	Strong (2.3)
NH1 – H2′	Medium (2.4)	Strong (2.4)	Medium (2.5)
NH4 – H5	Medium (3.0)	Medium (2.9)	Medium (2.3)
NH4 – H6′	Weak (2.9)	Medium (2.7)	Medium (3.0)
NH4 – H2	Strong (2.3)	Medium* (2.3)	Weak (3.6)
NH4 – H2′	-	Weak (3. 6)	Medium (2.3)
H8 – H6	-	Medium (3.0)	-
H8 – H6′	Medium (2.4)	-	-

*NOE not definitive due to peak overlap, NOEs defined qualitatively according to cross peak intensities as weak, medium, or strong. Some averaging of NOEs between conformers A and B was observed. The inter-proton distances (Å) from representative model structures are given in parentheses.

Table S4 ^{1}H NMR data for **5** in [^{2}H]$_5$-pyridine at 238 K.

Position	δ_H, multiplicity, J in Hz of **5**	
	Conformer A	Conformer B
NH1	11.11, dd, 9.5, 2.8	11.24, br
2	4.96, dd, 12.9, 9.5	4.58, dd, 15.5, 7.0
2′	3.56, dd, 12.9, 2.8	4.51, dd, 15.5, 3
NH4	8.33, br	9.56, d, 11.5
5	4.97, overlap	5.26, td, 11.5, 2.5
6	1.94, m	1.78, overlapping
6′	1.65, m	1.78, overlapping
7	1.11, br	1.63, overlapping
7′	1.45, br	1.48, overlapping
8	1.75, overlap	1.78, overlapping
8′	1.57, br	1.78, overlapping
9	2.40, m	2.62, m
9′	2.36, m	1.83, overlapping
10	5.08, br	4.91, br

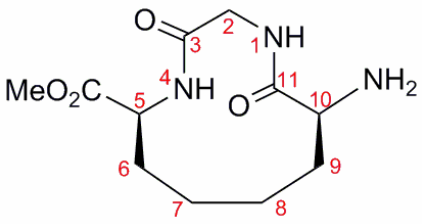


Table S5 Selected NOEs for conformer A of **5** in $[^2H]_5$-pyridine at 238 K and comparison with inter-proton distances as measured from molecular modelling.

Proton pair	Intensity of NOEs	Peak integral ratio from NOEs[(c)]	Calculated distance (Å) from	
			NOEs[(d)]	Modelling
NH1 – H10	strong	2.9	2.1	2.6
NH1 – H2′[(a)]	strong	2.2	2.1	2.4
NH1– H2[(b)]	medium	5.1	2.3	2.9
NH1 – H9′	weak	120	3.9	3.7
NH1– H8′	very weak	330	4.6	4.0
NH4 – H2	strong	4.2	2.2	2.5
NH4 – H6′	weak	330	4.6	2.7
H5– H6	strong	1.1	1.8	2.5
H5 – H6′	strong	1.0	1.8	2.5
H5 – H7′	weak	40	3.1	3.9

[(a)] $J_{(NH1,\ H2'eq)}$ 3 Hz

[(b)] $J_{(NH1,\ H2ax)}$ 9.5 Hz

[(c)] 2D volume integral relative to that of H7-H7′ ($V_{H7\text{-}7'}/V_{I\text{-}S}$) quoted to 2 significant figures. [(d)] Calculated distance based on the isolated spin pair approximation.

Table S6 Selected NOEs for conformer B of **5** in $[^2H]_5$-pyridine at 238K and comparison with inter-proton distances predicted by molecular modelling.

Proton pair	Intensity of NOEs	Peak integral ratio from NOEs[(a)]	Calculated distance (Å) from	
			NOEs[(b)]	Modelling
NH1 – H5	strong	5.3	2.3	2.7
NH1 – H10	strong	10	2.6	2.2
NH1 – H2	strong	12	2.7	2.3
NH4 – H2/H2′	weak	490	5.0	3.8
NH4 – H6	medium	22	3.0	3.1

$^3J_{(NH4,H5)}$ = 11.5 Hz, $^3J_{(NH1,H2ax)}$ = 7 Hz, $^3J_{(NH1,\ H2eq)}$ = 3 Hz.

[(a)] 2D volume integral relative to that of H9-H9′ ($V_{H9\text{-}9'}/V_{I\text{-}S}$) quoted to 2 significant figures. [(b)] Calculated distance based on the isolated spin pair approximation.

Table S7 ^{1}H NMR data for **10** in $CDCl_3$ at 298 K.

Position	δ_H, multiplicity, J in Hz of **10**
NH2	7.30, d, 10.0
3	4.60, ddd, 10, 7.5, 3.0
4	1.80, m
4′	1.61, m
5	1.50, m
5′	1.12, m
6	1.53, m
6′	1.34, m
7	1.96, m
7′	1.64, m
8	4.46, td, 8.0, 2.4
10	3.70, m
10′	3.49, td, 9.5, 4.7
11	2.28, dquintet, 12.7, 8.6
11′	2.04, m
12	2.47, dddd, 12.5, 8.1, 3.4, 1.4
12′	1.83, m
13a	5.01, dd, 7.9, 1.6
NH14	5.43, d, 8.0
OMe	3.73, s
^{t}Bu	1.43, s

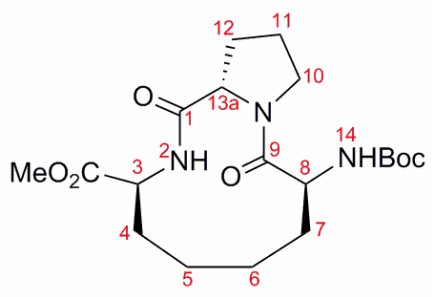


Table S8 Relevant NOEs from the NOESY spectrum of **10** in $CDCl_3$ at 298 K.

Proton pair	Intensity of NOEs	Peak integral ratio from NOEs[(a)]	Calculated distance[(b)] (Å)
NH2 – H13a	strong	4.7	2.4
NH2 – H3	weak	76	3.0
NH2 – H4′	medium	55	3.1
NH2 – H5*	(medium)*	26*	2.3
H12 – H13a	medium	55	2.8
H12′ – H13a	strong	18	2.4
H3 – H4	medium	14	2.4
H3 – H4′	medium	19	2.5
H3 – H5′	medium	140	3.7
H10 – H8	strong	19	2.4
H10′ – H8	medium	10	2.6
H10′ – H7′	strong	30	2.3
H10′ – H5/H6	weak	29	4.8
H10′ – H5′	weak	82	4.7
H10′ – H6′	weak	70	3.7
NH14 – H8	strong	24	2.9

*Overlap with H6; estimated volume

[(a)] 2D volume integral relative to that of H10-H10′ ($V_{H10\text{-}10'}/V_{I\text{-}S}$) quoted to 2 significant figures. [(b)] Calculated distance based on the isolated spin pair approximation

Table S9 Observed ^{3}J-coupling constants and calculated dihedral angles of **10**.

Protons	$^3J_{(H,H)}$, Hz	Calcd. dihedral angles (°)
NH2 – H3	10	166
NH14 – H8	8	146
H3 – H4	7.5	146
H3 – H4′	3	57 or 108
H13a – H12	7.9	150
H13a – H12′	1.6	90 or 77