

# SUPPLEMENTARY INFORMATION

## The most reactive amide as a transition state mimic for *cis-trans* interconversion.

Igor V. Komarov\*, Stanislav Yanik, Aleksandr Yu. Ishchenko, John E. Davies, Jonathan M. Goodman, Anthony J. Kirby\*

\* Corresponding authors. E-mail: ajk1@cam.ac.uk (AJK); ik214@yahoo.com (IVK).

### 1. PDF files

1. Supplementary information: Contents below

2. Crystallographic information:

Checkcifs for compounds 2 and 3.H<sup>+</sup>.BF<sub>4</sub><sup>-</sup>.

### 2. Crystallographic information files

Crystallographic data for compounds 2 and 3.H<sup>+</sup>.BF<sub>4</sub><sup>-</sup>.

(CCDC Deposition nos. 1031183 and 1031182)

### Supplementary information: Contents.

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Figure S14. Results of the HPLC analysis of the reaction mixture (compound 3 and 0.6 equiv. of water in THF-d<sub>8</sub> after 75 min of the hydrolysis) quenched by LiAlH<sub>4</sub> (reflux 5h), aqueous work-up.

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Table S2. Concentrations of 2 (mol/l) and its hydrolysis product vs time.\*

Table S3. Concentration of the twisted amide 3 (mol/l) vs time during the hydrolysis.\*

Table S4. Concentrations of 1'HBF<sub>4</sub> (mol/l) and its hydrolysis product vs time during the hydrolysis.\*

Table S5. Concentrations of 2'HBF<sub>4</sub> (mol/l) and its hydrolysis products vs time during the hydrolysis.\*

Table S6. Concentrations of 3'HBF<sub>4</sub> (mol/l) and 9'HBF<sub>4</sub> vs time during the hydrolysis.\*

## S3. Methods

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- S3.1 General procedures
- S3.2 3-Benzoyl-7-methyl-3-azabicyclo[3.3.1]nonane-7-carboxylic acid ethyl ester (16)
- S3.3 3-Methyl-1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one (2)
- S3.4 7-benzyl 3-tert-butyl 7-methyl-3-aza-bicyclo[3.3.1]nonane-3,7-dicarboxylate
- S3.5 3-(tert-butoxycarbonyl)-7-methyl-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid (20)
- S3.6 tert-butyl 7-(hydroxymethyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonane-3-carboxylate (21)
- S3.7 tert-butyl 7-formyl-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonane-3-carboxylate (23)
- S3.8 3-(tert-butoxycarbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid (24)
- S3.9 Synthesis of compounds 1-3 by pyrolysis of the corresponding NBoc-protected amino acids
- S3.10 Preparation of 1'HBF<sub>4</sub>, 2'HBF<sub>4</sub> and 3'HBF<sub>4</sub>
- S3.11 Kinetic measurements for hydrolysis of 1-3, 1'HBF<sub>4</sub>, 2'HBF<sub>4</sub> and 3'HBF<sub>4</sub>
- S3.12 Quenching of the reaction mixture of compound 3 with water by LiAlH<sub>4</sub> in order to identify the intermediate dimers and oligomers

## S.4 References

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## S.5 Spectroscopic Data. NMR and Mass spectra

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## S1. Calculations

Calculations used Jaguar, version 7.9, from Schrodinger, LLC.

Structures calculated using 6-31++G\*\*/M06-2X

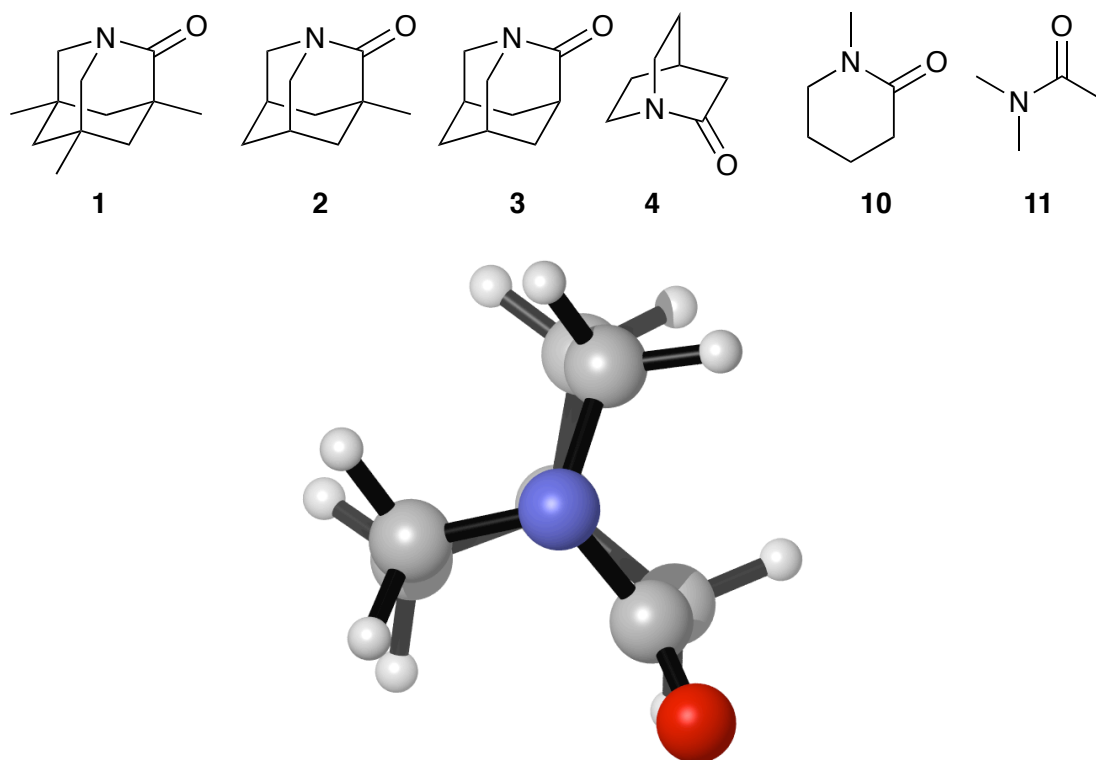


Figure S1: Molecule 4 showing the barrel-distortion of the ground state

Table S1.1 Geometries compared for calculated and crystal structures of twisted amides 1 – 4.

	Selected structural parameters <sup>c</sup>							
Compound	1 xtl	1 <sup>a</sup>	2 xtl	2 <sup>a</sup>	3 <sup>b</sup>	3 <sup>a</sup>	4 <sup>c</sup>	4 <sup>a</sup>
Twist angle $\tau$ , deg	90.5	89.5	90.0	90.8	90.0	90.55	90.0	105.05
$\Sigma$ bond angles at N	325.7	327.4	325.6	327.4	327.1	326.9	327.1	324.2
$\Sigma$ bond angles, C=O	359.9	360.0	359.9	360.0	360	360	360	359.8
C-N bond length, Å	1.475	1.449	1.448	1.449	1.457	1.450	1.433	1.443
C=O bond length, Å	1.196	1.204	1.201	1.204	1.210	1.203	1.183	1.203

Notes. <sup>a</sup> Calculations using 6-31++G\*\*/M06-2X. This work <sup>b</sup> Geometries optimized at the B3LYP/6-31G\* level of theory. Morgan, K. M., et al. *J. Phys. Org. Chem.* **18**, 310-314 (2005). <sup>c</sup> Calculated at the RHF/6-31G\* level. Greenberg, A.; Venzani, C. A. *J. Am. Chem. Soc.* **116**, 6951 (1993).

## Tables S1.2 . Energies and geometries for molecules 1, 2, 3, 4, 10 and 11

### 1.2.1

**E = -598.4854041 minimum**

C1	0.4028043947	-1.5323947107	-1.0223103928
C2	-1.0872723221	-1.5429074286	-1.4285456371
C3	-1.9794608861	-1.0531463291	-0.2782404079
C4	-1.7704532088	-1.9718728726	0.9367647469
C5	-0.2994370370	-1.9679415892	1.3839305709
C6	0.5721191574	-2.4476391038	0.2131682554
H8	-1.3649228829	-2.5673884589	-1.7170292976
H9	-1.2353302162	-0.9072907882	-2.3130803245
H11	-2.4090270267	-1.6354685982	1.7670960592
H12	-2.0808403286	-2.9973561931	0.6863980887
H14	0.2973109627	-3.4741041277	-0.0709245427
H15	1.6285953238	-2.4675587462	0.5159327661
C16	0.1015897768	-0.5138966380	1.6892022521
H17	1.1538287622	-0.4621516866	1.9958635306
H18	-0.5018815500	-0.1113438520	2.5129574672
C19	-1.4966201030	0.3565250379	0.1027366678
H20	-2.0938661445	0.7588439695	0.9312094690
H21	-1.6094151592	1.0425530426	-0.7462258799
C22	0.7443484213	-0.1146430177	-0.5582052266
O23	1.6367233905	0.5480105505	-1.0199465644
N24	-0.0840325369	0.3741236062	0.5255420439
C24	1.3004300228	-1.9708227015	-2.1690768745
H25	2.3523748141	-1.9486204776	-1.8719861712
H26	1.0421566401	-2.9904134171	-2.4750375053
H27	1.1861202600	-1.3067755845	-3.0304352012
C27	-0.0959862277	-2.8474716176	2.6123057668
H28	0.9519673748	-2.8393160929	2.9323614474
H29	-0.7103139754	-2.4988857852	3.4501098235
H30	-0.3760378184	-3.8845460872	2.3968489938
C30	-3.4445205499	-1.0223333869	-0.6979797526
H31	-4.0794552491	-0.6651719811	0.1206248109
H32	-3.5932794526	-0.3596832549	-1.5579337280
H33	-3.7878290354	-2.0240537118	-0.9792520429

### 1.2.2

**E = -519.8834017 minimum**

C1	0.4014317020	-1.5341296137	-1.0231891843
C2	-1.0906195860	-1.5475522493	-1.4311161681
C3	-1.9642444719	-1.0562632388	-0.2703990672
C4	-1.7824967187	-1.9796807255	0.9437261024
C5	-0.3067175825	-1.9580045181	1.3700035047
C6	0.5711723989	-2.4526555075	0.2132618080
H8	-1.3626373650	-2.5725176349	-1.7184211092
H9	-1.2367054337	-0.9135487674	-2.3155825489
H10	-3.0166638862	-1.0317042212	-0.5766878748
H11	-2.4186692761	-1.6420008107	1.7719122234
H12	-2.0898742210	-3.0027256556	0.6920569159
H13	-0.1552328121	-2.5902521933	2.2528244627
H14	0.2964504389	-3.4765454753	-0.0753225111
H15	1.6271702483	-2.4716602199	0.5131961241
C16	0.0985343921	-0.5126653339	1.6944077037
H17	1.1495895166	-0.4579367064	1.9997282421
H18	-0.5052700875	-0.1053186884	2.5139025334
C19	-1.5019499298	0.3581897759	0.1048668042
H20	-2.0936585627	0.7620951074	0.9349247824
H21	-1.6126373879	1.0446963919	-0.7421881838
C22	0.7421529854	-0.1167662527	-0.5556682942
O23	1.6382885908	0.5438456969	-1.0135964946
N24	-0.0862522937	0.3751849178	0.5268193435

C24	1.3003263839	-1.9703429926	-2.1692286595
H25	2.3521958101	-1.9474051282	-1.8713294411
H26	1.0432995329	-2.9899953755	-2.4767338296
H27	1.1865265564	-1.3054468172	-3.0302569969

### 1.2.3

**E = -480.582103      minimum**

C1	0.3866888158	-1.5404805659	-0.9988699692
C2	-1.0952455143	-1.5584494077	-1.4316709729
C3	-1.9626147917	-1.0532414991	-0.2697240800
C4	-1.7837447152	-1.9725224203	0.9488541921
C5	-0.3072326200	-1.9587333344	1.3752221029
C6	0.5690907021	-2.4689584125	0.2219599974
H7	1.0467743895	-1.8280624190	-1.8208183618
H8	-1.3763394871	-2.5821250320	-1.7095846101
H9	-1.2382870400	-0.9278981356	-2.3172867740
H10	-3.0158263123	-1.0224110374	-0.5723287867
H11	-2.4169985083	-1.6271238825	1.7762352178
H12	-2.0983639172	-2.9947460096	0.7028366022
H13	-0.1613820812	-2.5844799068	2.2634594337
H14	0.2852688637	-3.4912059024	-0.0583162337
H15	1.6228487878	-2.4928820558	0.5243030375
C16	0.1063565411	-0.5133866369	1.6910163425
H17	1.1578083673	-0.4628446837	1.9957005085
H18	-0.4942357410	-0.1013039846	2.5105349030
C19	-1.4922819571	0.3612250226	0.1004243530
H20	-2.0830283822	0.7688391735	0.9292863282
H21	-1.6003880987	1.0460284837	-0.7483110818
C22	0.7409189629	-0.1244196343	-0.5666028869
O23	1.6171076953	0.5359907990	-1.0609756013
N24	-0.0747084141	0.3764373052	0.5229272859

### 1.2.4

**E = -403.1749016      minimum**

C1	0.4039605042	-0.6204113828	-0.2436346388
C2	-0.9121140680	0.0317300332	0.2139937450
C3	-0.8193643090	1.5612919209	-0.0645902255
N4	0.5695006435	1.9654465356	-0.3864632056
C5	1.3907565003	1.4459713224	0.6808828307
O6	1.8312823467	2.1453174613	1.5547944889
C7	1.5378882862	-0.0710423639	0.6389569090
C8	0.6756522461	-0.1870184261	-1.6895418805
C9	0.9655757545	1.3370031535	-1.6626995734
H10	0.3460438346	-1.7093412024	-0.1623355061
H11	-1.7605058123	-0.4080610098	-0.3199835506
H12	-1.0667625346	-0.1585367310	1.2821508750
H13	-1.4325762632	1.8464282755	-0.9252014501
H14	-1.1598234281	2.1498621718	0.7901907315
H15	2.5238292674	-0.3334299555	0.2342520880
H16	1.4965943422	-0.4421246213	1.6670803777
H17	1.5269629225	-0.7347685635	-2.1067443416
H18	-0.1947423674	-0.4131267848	-2.3153105495
H19	2.0300755408	1.5404512343	-1.8116741234
H20	0.4290347446	1.8631350329	-2.4574802068

### 1.2.10

**E = -365.1111672      minimum**

C1	-0.4359825147	0.4633233394	-0.9302116277
C2	-1.8881705611	0.4310822795	-1.3949277520
C3	-1.1560646331	-0.0192480007	1.4006852208
C4	-0.2778774893	-0.4863825345	0.2505479334
H5	-0.1628430352	1.4800217560	-0.6196826703
H6	0.2314230552	0.1889167544	-1.7525835954
H7	-2.1058631099	-0.5268209600	-1.8839057425
H8	-2.1139412767	1.2130678779	-2.1229832663
H9	-0.7248383650	0.8874626630	1.8546094998
H10	-1.1942461767	-0.7828191396	2.1864330078
H11	-0.5721223376	-1.4994451333	-0.0504951000
H12	0.7594166640	-0.5337386835	0.5956691971
C13	-2.9166538105	0.5800953746	-0.2834684764
O14	-4.0588380280	0.9333973622	-0.5478283399
C15	-3.4695756573	0.4513954509	2.0789744802
H16	-4.4542219431	0.6518045523	1.6613166292
H17	-3.5069691306	-0.4494996544	2.7001252401
H18	-3.1633247503	1.2973998940	2.7072908287
N19	-2.5287920643	0.2594185919	0.9901553468

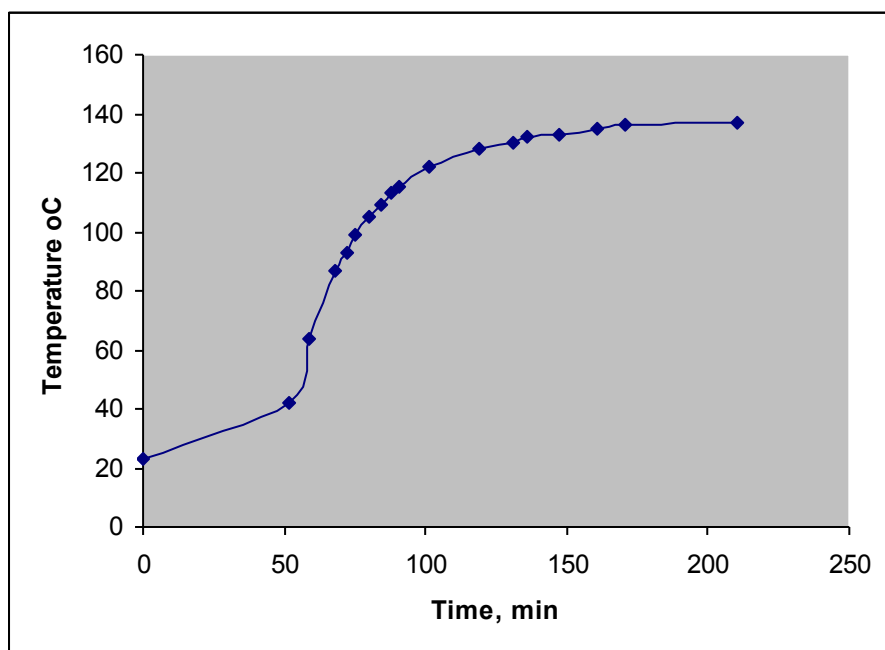
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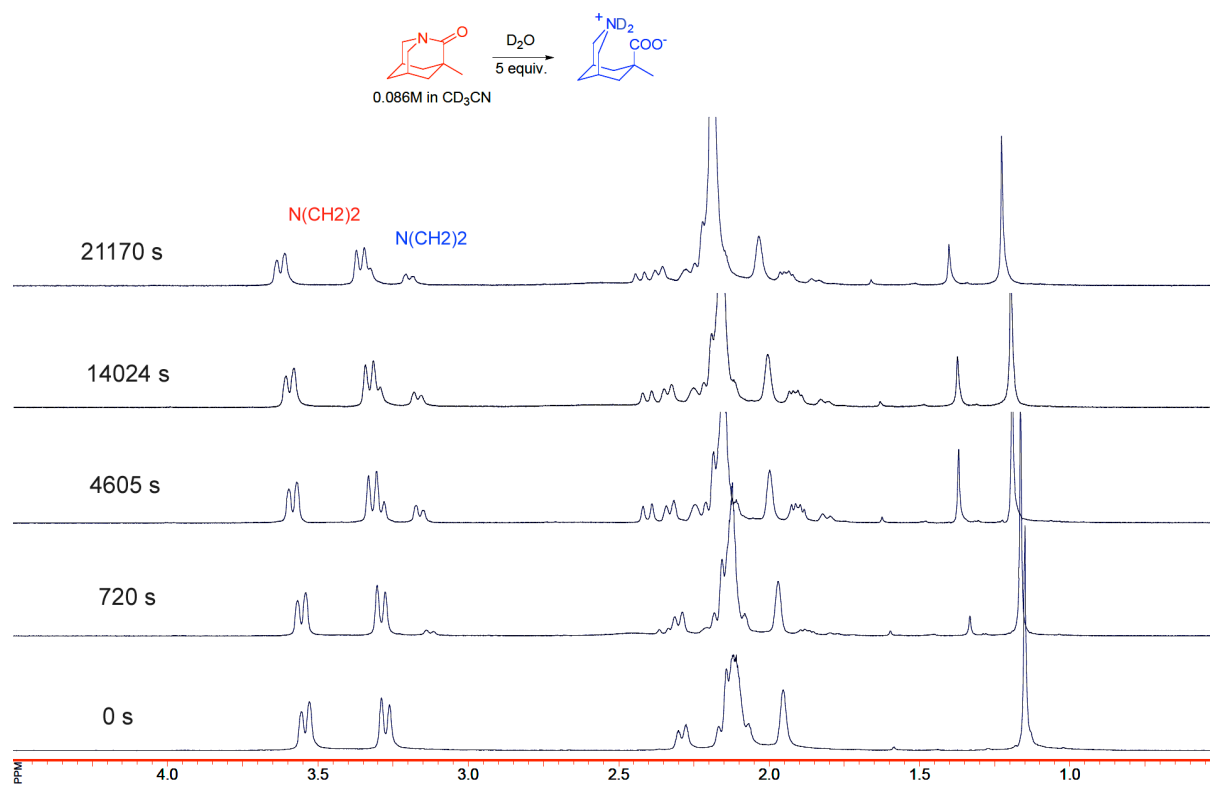
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N2	0.3161632876	-0.5589686281	0.0264634046
O3	-1.6428382887	0.5660875706	-0.1767931429
C6	0.3228466862	1.9116661444	-0.0387775699
H7	-0.4234468352	2.6994282547	-0.1240426154
H8	0.8774884489	2.0413257791	0.8946988692
H9	1.0273398017	1.9933665755	-0.8712374594
C9	-0.3580285715	-1.8440536902	0.0323699552
H10	0.0348553353	-2.4780843643	-0.7704070026
H11	-0.1972311096	-2.3543889067	0.9897215340
H12	-1.4234978871	-1.6816871132	-0.1175152705
C12	1.7514055760	-0.6150599692	0.2105709875
H13	2.2000388224	-1.2613033424	-0.5527088986
H14	2.2014824038	0.3717918011	0.1277461043
H15	1.9991558756	-1.0294150562	1.1961654769

## S2. Kinetic measurements

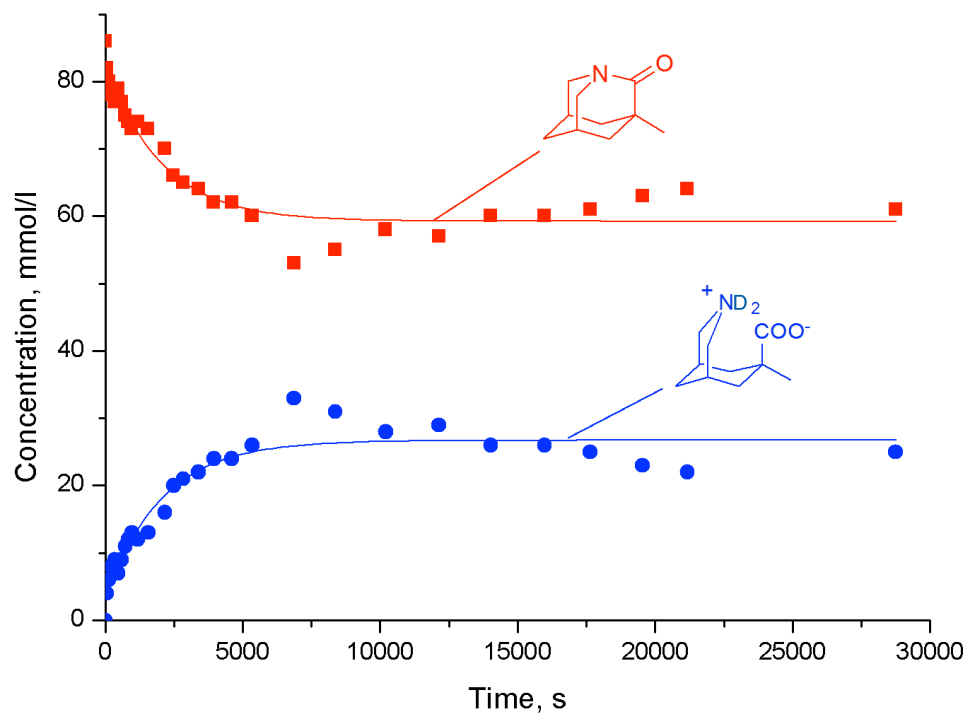
Figure S2. Temperature regime for growing crystals of 3 by pyrolysis of 8 on silica gel.



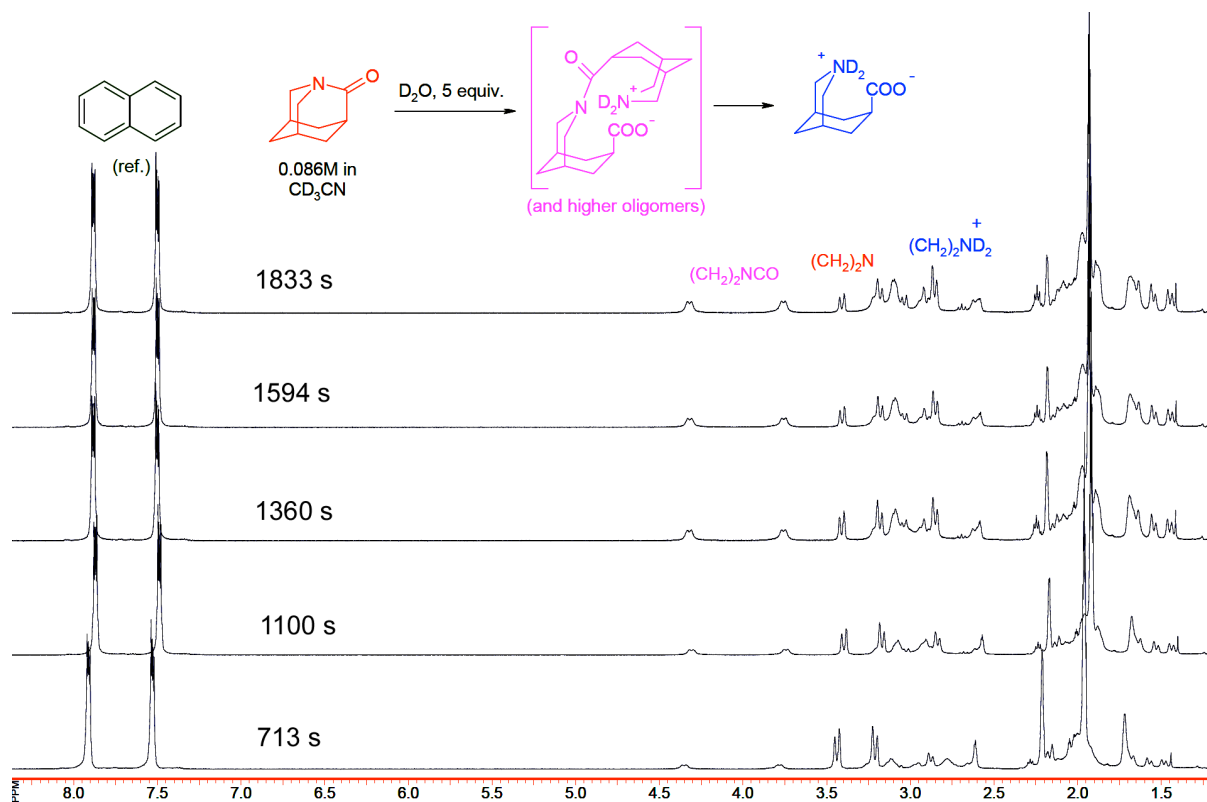
**Figure S3. Representative spectroscopic data set for kinetic measurements, hydrolysis of 2 (0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



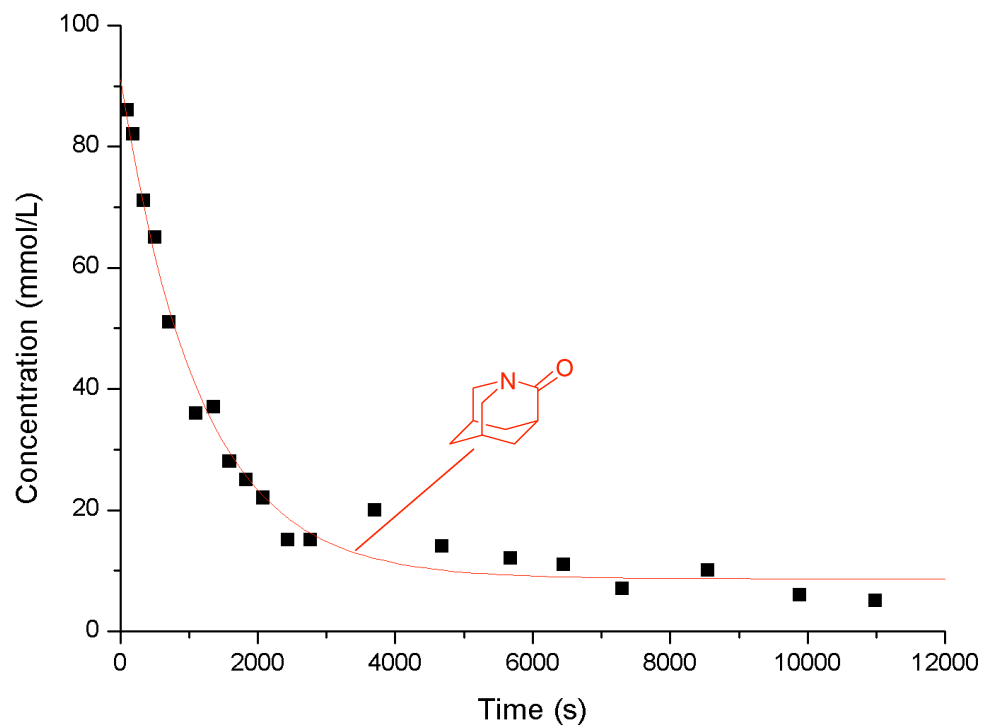
**Figure S4. Concentrations of 2 (mol/l) and 7 vs time in the course of the hydrolysis**  
**(0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



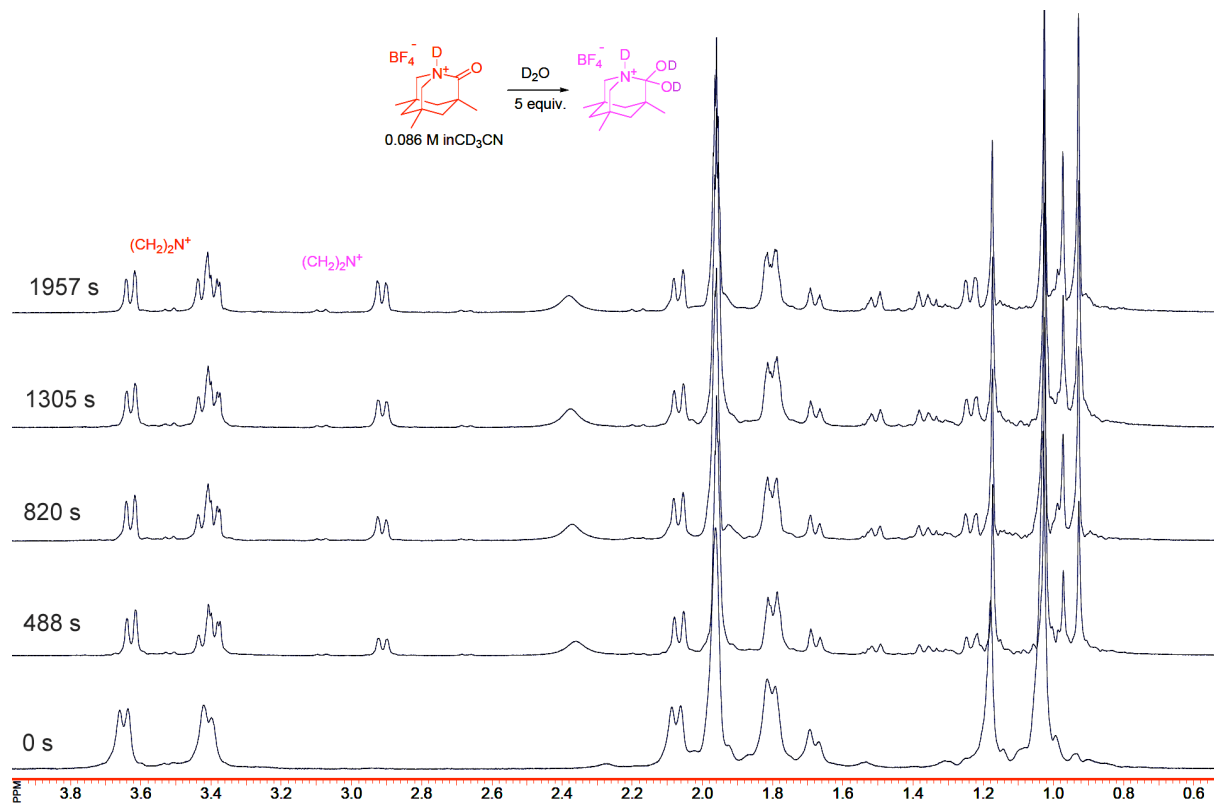
**Figure S5 Representative spectroscopic data set for kinetic measurements, hydrolysis of 3**  
**(0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



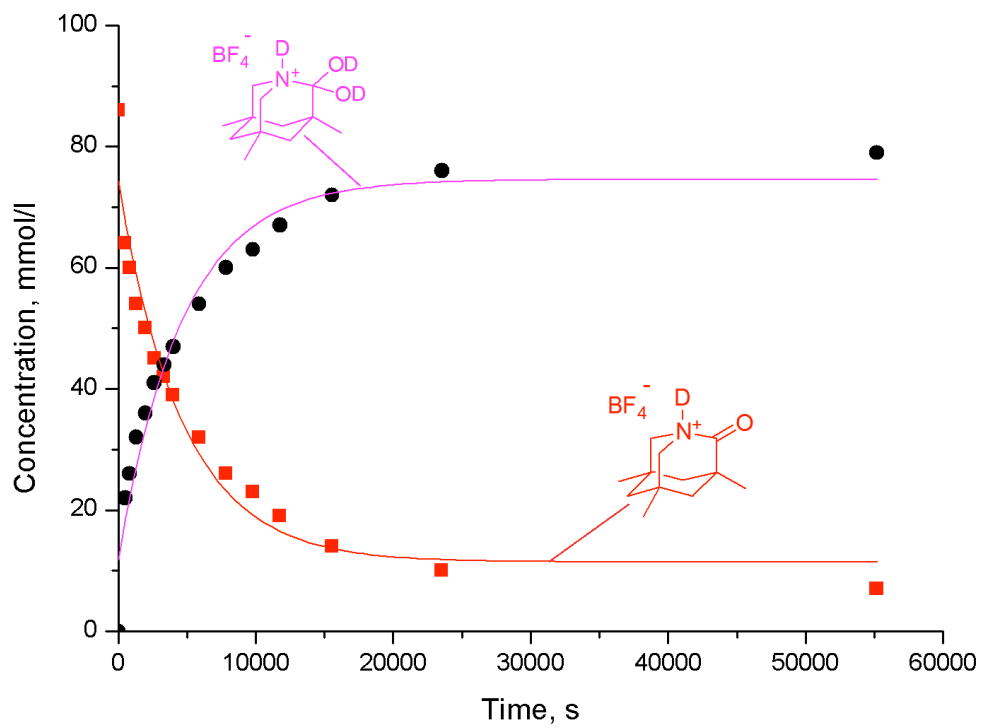
**Figure S6. Concentration of the twisted amide 3 (mol/l) vs time during the hydrolysis**  
**(0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



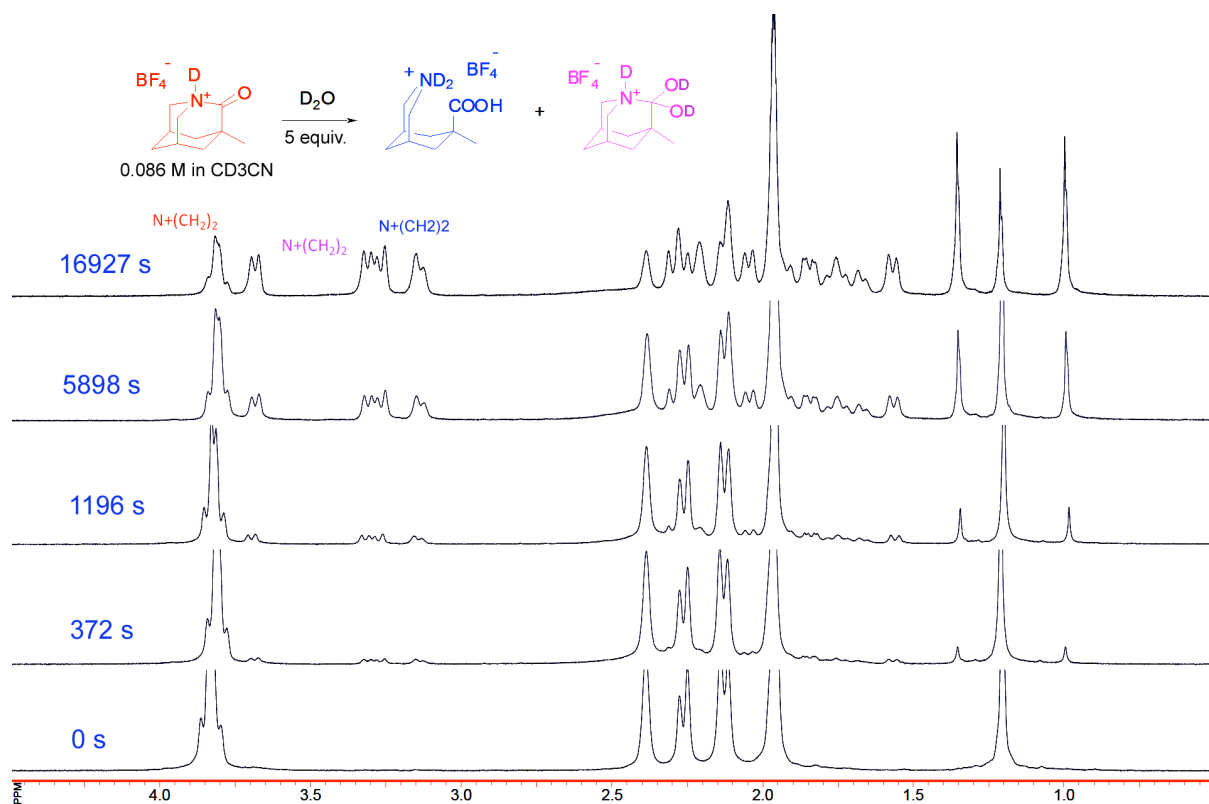
**Figure S7. Representative spectroscopic data set for kinetic measurements, hydrolysis of 1<sup>+</sup>HBF<sub>4</sub> (0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



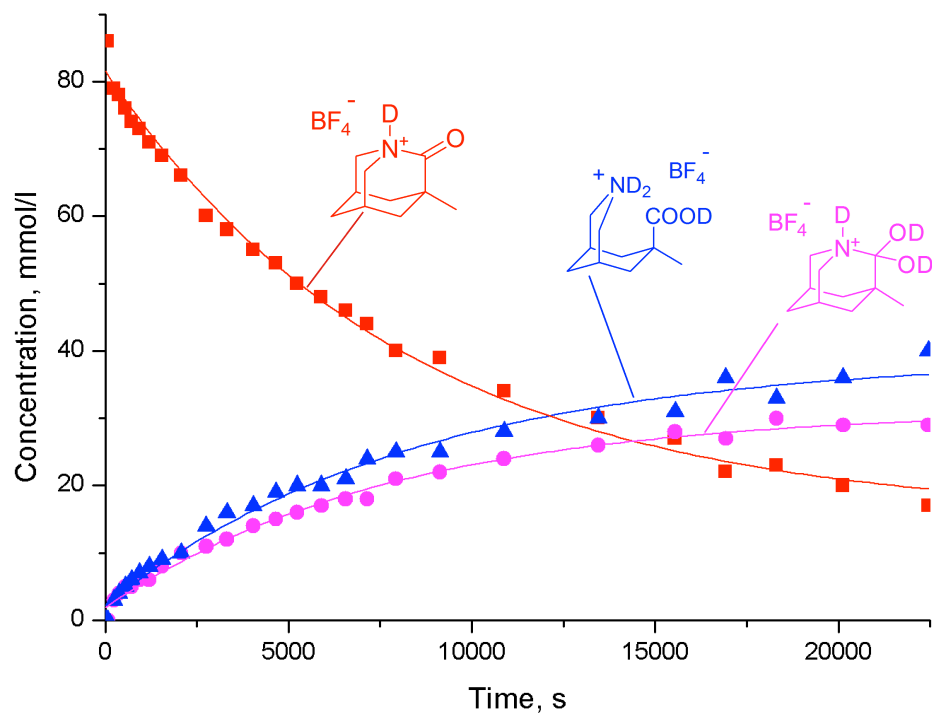
**Figure S8. Concentrations of 1·HBF<sub>4</sub> (mol/l) and 12 vs time during the hydrolysis (0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



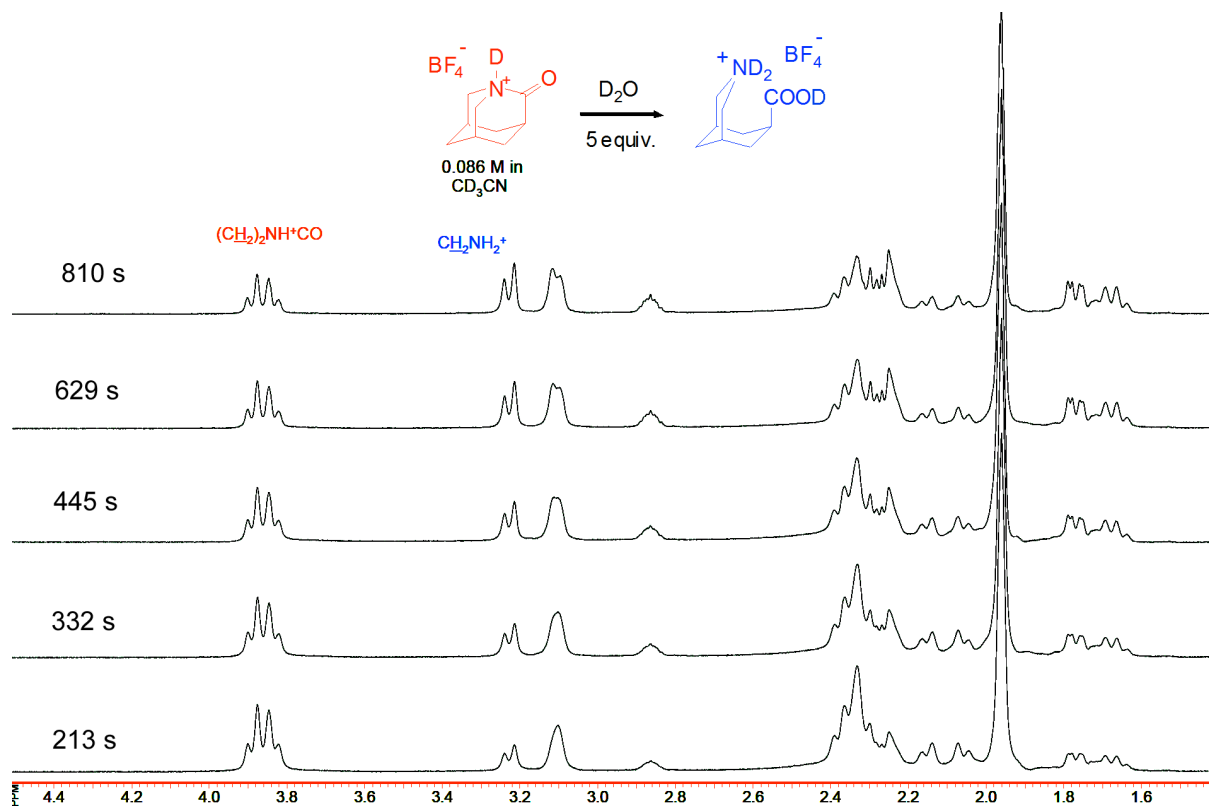
**Figure S9. Representative spectroscopic data set for kinetic measurements, hydrolysis of 2·HBF<sub>4</sub> (0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



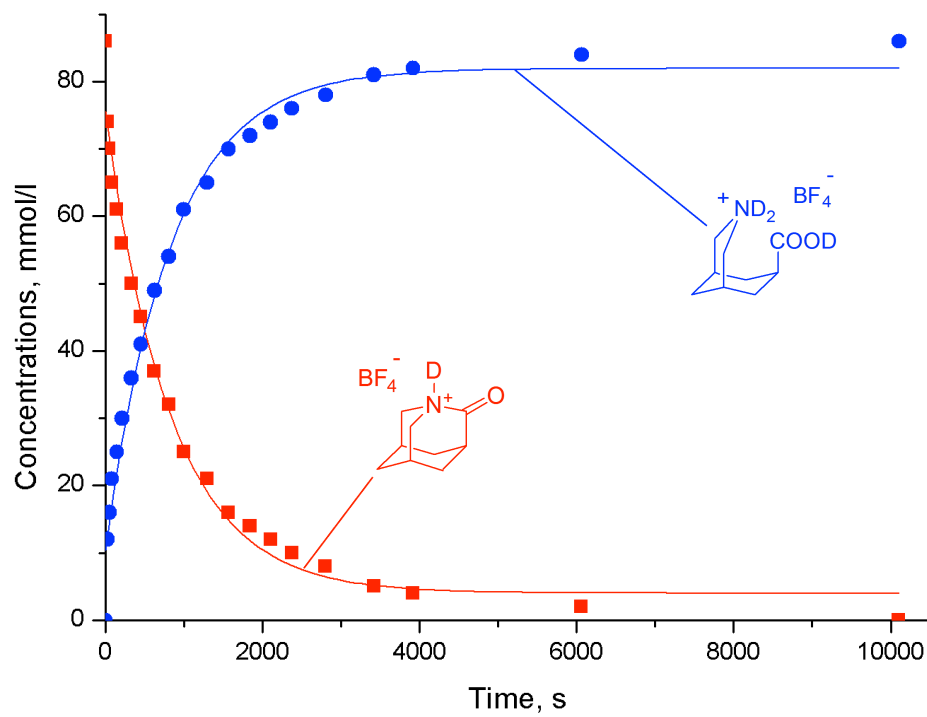
**Figure S10. Concentrations of 2·HBF<sub>4</sub> (mol/l), 7·HBF<sub>4</sub> and 13 vs time during the hydrolysis (0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



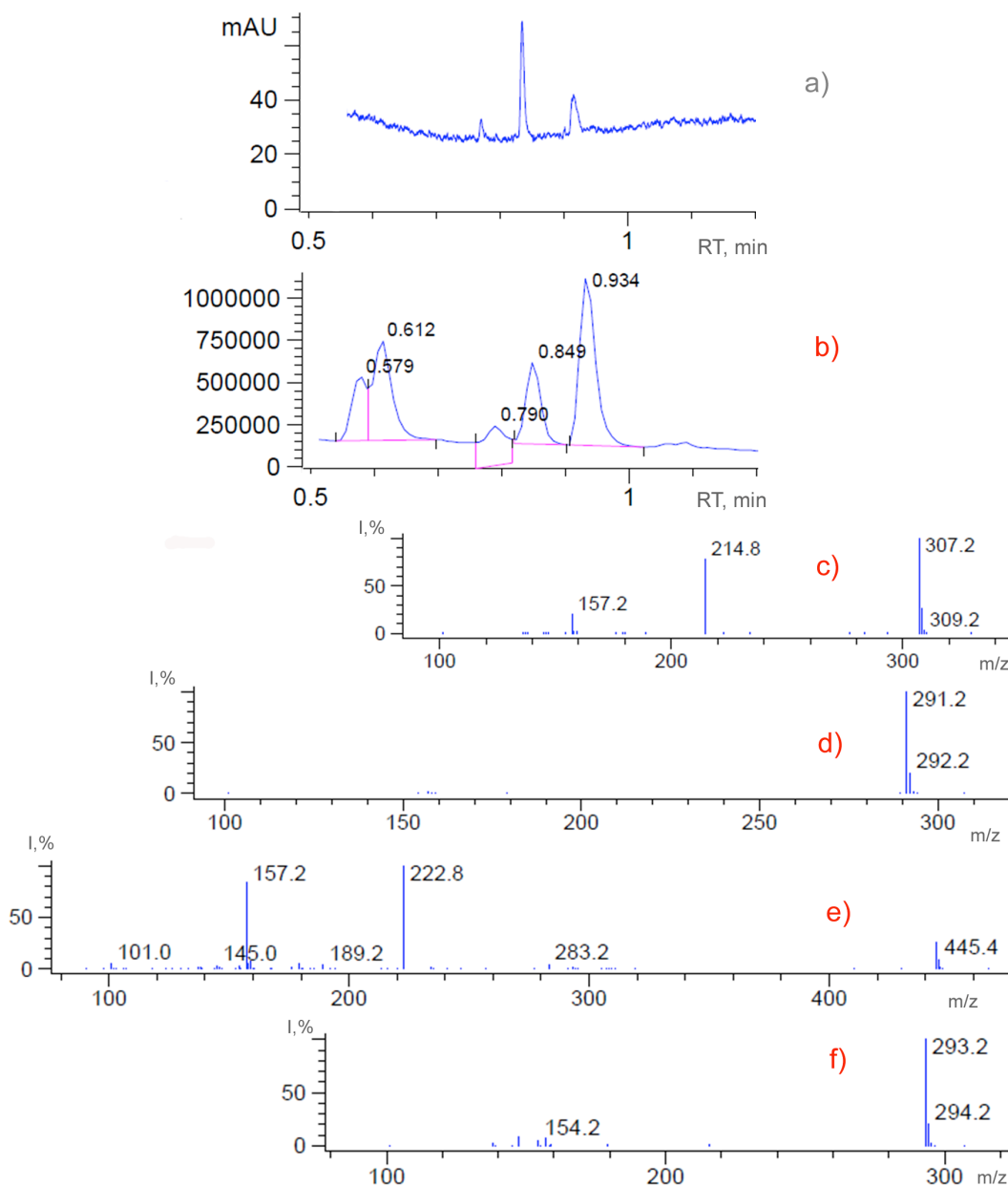
**Figure S11. Representative spectroscopic data set for kinetic measurements, hydrolysis of 3<sup>+</sup>·HBF<sub>4</sub> (0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**



**Figure S12. Concentrations of 3-HBF<sub>4</sub> (mol/l) and 9-HBF<sub>4</sub> vs time during the hydrolysis (0.086M solution in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C)**

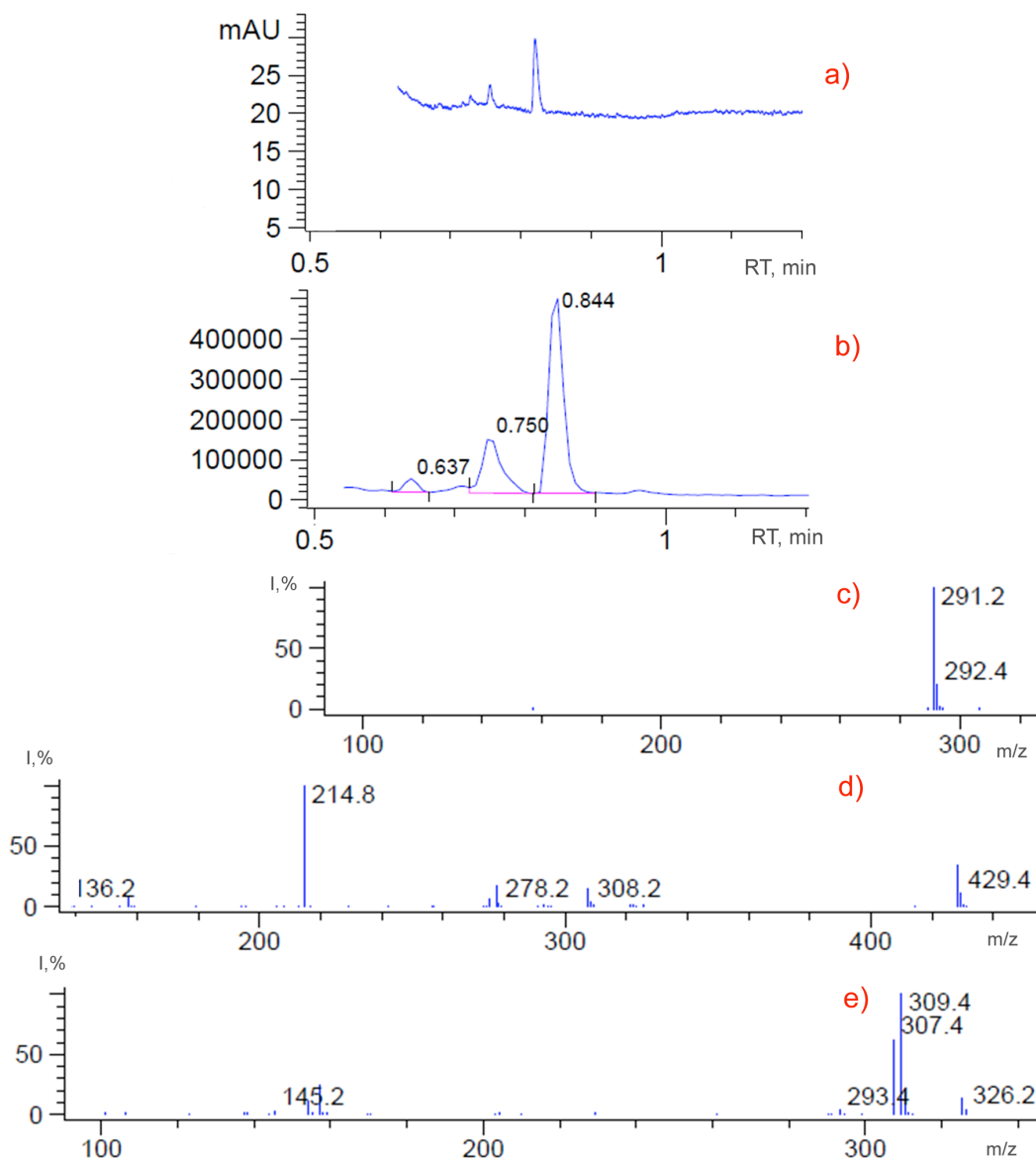


**Figure S13. Results of the HPLC analysis of the reaction mixture (compound 3 and 0.6 equiv. of water in THF- $d_8$  after 75 min of the hydrolysis) quenched by  $LiAlH_4$  (1 h at 23 °C), aqueous work-up.**



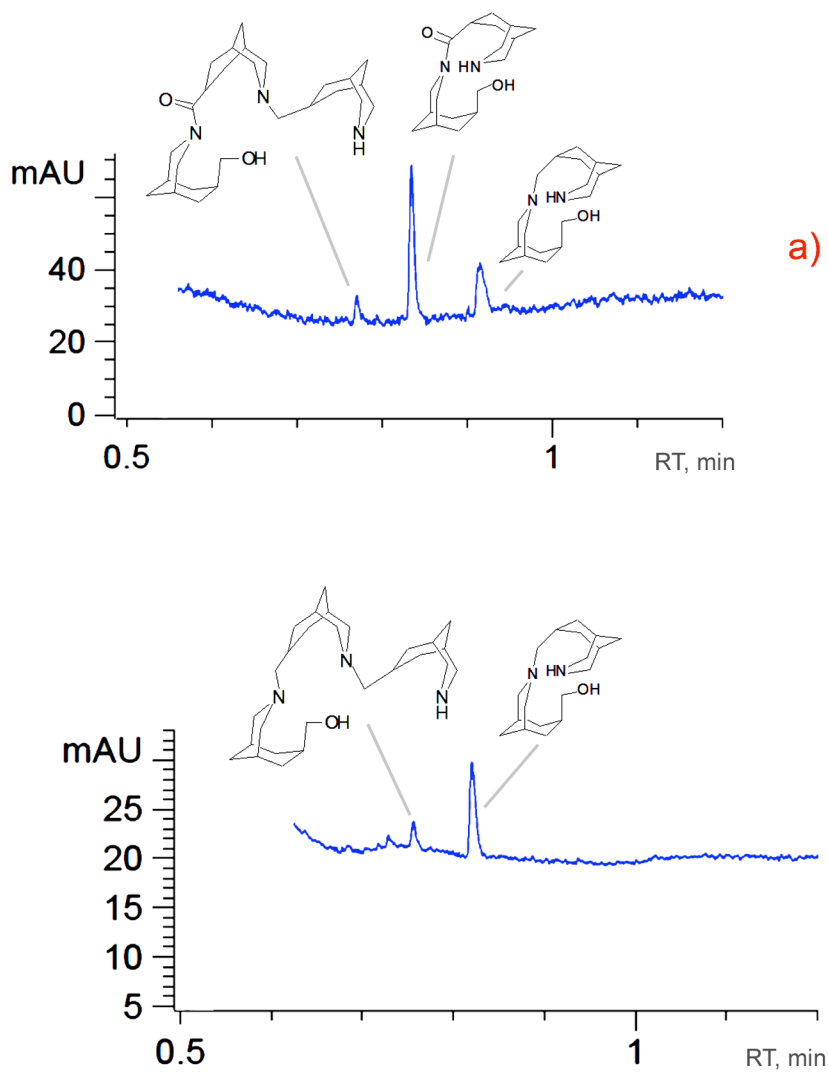
a) HPLC trace, UV detection at 215 nm (Zorbax Eclipse® XDB-C<sub>8</sub> column (4.6 mm x 150 mm) and MeCN/H<sub>2</sub>O (60:40 v/v) as the isocratic eluent); b) HPLC trace (conditions as in a)), MS detection (CI, positive scan); c) Mass-spectrum of the fraction with RT 0.849 min; d) Mass-spectrum of the fraction with RT 0.934 min; e) Mass-spectrum of the fraction with RT 0.790 min; f) Mass-spectrum of the fraction with RT 0.612 min.

**Figure S14. Results of the HPLC analysis of the reaction mixture (compound 3 and 0.6 equiv. of water in THF- $d_8$  after 75 min of the hydrolysis) quenched by  $LiAlH_4$  (reflux 5h), aqueous work-up.**



a) HPLC trace, UV detection at 215 nm (Zorbax Eclipse<sup>®</sup> XDB-C<sub>8</sub> column (4.6 mm x 150 mm) and MeCN/H<sub>2</sub>O (65:35 v/v) as the isocratic eluent); b) HPLC trace (conditions as in a)), MS detection (CI, positive scan); c) Mass-spectrum of the fraction with RT 0.844 min; d) Mass-spectrum of the fraction with RT 0.750 min; e) Mass-spectrum of the fraction with RT 0.637 min.

**Figure S15.** Assignments of the HPLC peaks (UV detection at 215 nm) of the products obtained by  $\text{LiAlH}_4$  quenching of the reaction mixture (compound 3 and 0.6 equiv. of water in  $\text{THF-d}_8$  after 75 min of the hydrolysis); a) 1 h at 23 °C; b) reflux, 5h.



**Table S2. Concentrations of 2 (mol/l) and its hydrolysis product vs time.\***

Nr	Time, s	Concentration of 2, mmol/L	Concentration of 12, mmol/L
1	0	86	0
2	50	82	4
3	131	80	6
4	211	78	8
5	345	77	9
6	471	79	7
7	597	77	9
8	720	75	11
9	840	74	12
10	969	73	13
11	1182	74	12
12	1564	73	13
13	2170	70	16
14	2487	66	20
15	2840	65	21
16	3398	64	22
17	3951	62	24
18	4605	62	24
19	5345	60	26
20	6869	53	33
21	8365	55	31
22	10204	58	28
23	12140	57	29
24	14024	60	26
25	15977	60	26
26	17639	61	25
27	19546	63	23
28	21170	64	22
29	28752	61	25

\* Conditions: 0.086M solution of 2 in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C

**Table S3. Concentration of the twisted amide 3 (mol/l) vs time during the hydrolysis.\***

Nr	Time, s	[3], mmol/l
1	0	86
2	101	86
3	191	82
4	341	71
5	508	65
6	713	51
7	1100	36
8	1360	37
9	1594	28
10	1833	25
11	2078	22
12	2441	15
13	2768	15
14	3702	20
15	4680	14
16	5677	12
17	6453	11
18	7303	7
19	8553	10
20	9892	6
21	10993	5
22	12167	5

\* Conditions: 0.086M solution of 3 in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C

**Table S4. Concentrations of  $1\text{-HBF}_4$  (mol/l) and its hydrolysis product vs time during the hydrolysis.\***

Nr	Time, s	Concentration of $1\text{-HBF}_4$ , mmol/L	Concentration of gemiaminal, mmol/L
1	0	86	0
2	488	64	22
3	820	60	26
4	1305	54	32
5	1957	50	36
6	2623	45	41
7	3327	42	44
8	3988	39	47
9	5878	32	54
10	7831	26	60
11	9785	23	63
12	11754	19	67
13	15560	14	72
14	23548	10	76
15	55181	7	79
16	403618	5	81

\* Conditions: 0.086M solution of  $1\text{-HBF}_4$  in  $\text{CD}_3\text{CN}$ , 5 equivalents of  $\text{D}_2\text{O}$ , 23 °C

**Table S5. Concentrations of 2·HBF<sub>4</sub> (mol/l) and its hydrolysis products vs time during the hydrolysis.\***

<b>N r</b>	<b>Time, s</b>	<b>Concentration of 2·HBF<sub>4</sub>, mmol/L</b>	<b>Concentration of gemiaminal, mmol/L</b>	<b>Concentratio n of acid, mmol/L</b>
1	0	86	0	0
2	71	86	0	0
3	235	79	3	3
4	372	78	4	4
5	545	76	5	5
6	711	74	5	6
7	929	73	6	7
8	1196	71	6	8
9	1542	69	8	9
10	2072	66	10	10
11	2753	60	11	14
12	3318	58	12	16
13	4035	55	14	17
14	4651	53	15	19
15	5233	50	16	20
16	5898	48	17	20
17	6557	46	18	21
18	7146	44	18	24
19	7931	40	21	25
20	9131	39	22	25
21	10875	34	24	28
22	13449	30	26	30
23	15543	27	28	31
24	16927	22	27	36
25	18313	23	30	33
26	20131	20	29	36
27	22450	17	29	40
28	61648	8	34	44

\* Conditions: 0.086M solution of 2·HBF<sub>4</sub> in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C

**Table S6. Concentrations of 3-HBF<sub>4</sub> (mol/l) and 9-HBF<sub>4</sub> vs time during the hydrolysis.\***

Nr	Time, s	[3-HBF <sub>4</sub> ], mmol/l	[9-HBF <sub>4</sub> ], mmol/l
1	0	86	0
2	26	74	12
3	49	70	16
4	81	65	21
5	146	61	25
6	213	56	30
7	332	50	36
8	452	45	41
9	629	37	49
10	810	32	54
11	998	25	61
12	1297	21	65
13	1567	16	70
14	1843	14	72
15	2105	12	74
16	2377	10	76
17	2806	8	78
18	3421	5	81
19	3918	4	82
20	6063	2	84
21	10106	0	86

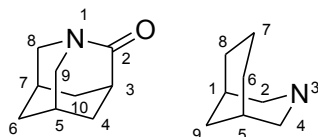
\* Conditions: 0.086M solution of 3-HBF<sub>4</sub> in CD<sub>3</sub>CN, 5 equivalents of D<sub>2</sub>O, 23 °C

### S3. Methods

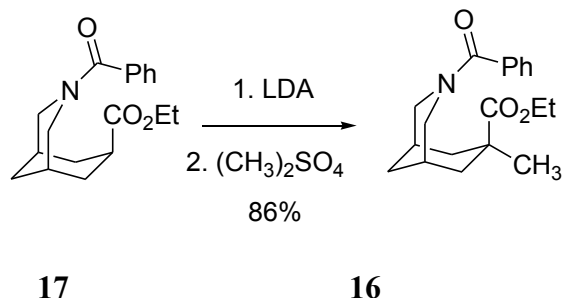
#### S3.1 General procedures

Starting materials were purchased from Merck, Acros, ABCR, Fisher, Enamine. Solvents were purified according to the standard procedures [S1]. Analytical reversed-phase high-performance liquid chromatography (RP-HPLC) was done on an Agilent 1100 HPLC instrument using a Zorbax Eclipse<sup>®</sup> XDB-C<sub>8</sub> column (4.6 mm x 150 mm) and MeCN/H<sub>2</sub>O (60:40 v/v) as the isocratic eluent. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance 300 spectrometer as specified below and referenced to TMS. Mass spectra were recorded either on an Agilent 1100 LC/MSD SL instrument by chemical ionization (CI) or on a GCMS instrument with electron impact ionization (EI). CHN-analysis was done on an Elementar VarioMICRO Cube analyzer. High resolution mass spectra were determined on a Bruker APEX III FTMS (7 T magnet). Infrared spectra were measured on a Perkin Elmer Spectrum 100 FTIR and are reported in reciprocal centimeters (cm<sup>-1</sup>). Melting points were measured on an automated melting point system and are uncorrected. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase. Compound **1** (3,5,7-Trimethyl-1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one) was prepared using the procedures described in [S2] or by sublimation of the corresponding NBoc-protected amino acid, see the procedure below. Synthesis of **8** (exo-3-(tert-butoxycarbonyl)-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid) is described in [S3].

The IUPAC numbering of the polycyclic systems encountered in this work is the following:



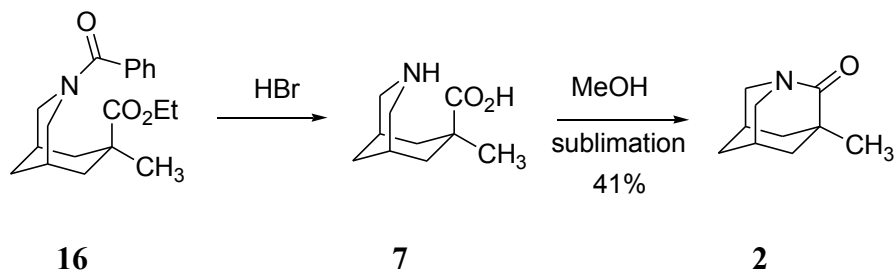
### S3.2 3-Benzoyl-7-methyl-3-azabicyclo[3.3.1]nonane-7-carboxylic acid ethyl ester (16)



A solution of BuLi (17.6 ml of 1.6 M (~15%) in hexanes, 28.2 mmol) was added to a solution of *i*-Pr<sub>2</sub>NH (3.67 ml, 2.64 g, 26.1 mmol in 200 ml of dry Et<sub>2</sub>O) at 0 °C (ice-water bath) under an argon atmosphere. After stirring at 0 °C for ~1 h, a solution of the amide-ester **17** [S4] (3.9 g, 12.9 mmol in 100 ml of dry Et<sub>2</sub>O) was added dropwise, the ice bath was removed, and the solution was stirred for another hour at room temperature. Freshly distilled dimethylsulfate (2.65 ml, 3.52 g, 27.9 mmol) was carefully added to the stirred reaction mixture. The reaction was exothermic, a white precipitate was formed immediately. The stirring continued overnight, the precipitate was filtered off. The filtrate was washed with water, 5% ammonia, 1N HCl, brine, dried (MgSO<sub>4</sub>), and evaporated. The colorless viscous oil obtained (3.5 g, 11.1 mmol, 86% yield) was subjected to the HBr hydrolysis without further purification. An analytical sample was prepared by column chromatography (Silica gel Merck 60, ethyl acetate - hexane, 1:1 mixture as an eluent). Colorless crystals, *R*<sub>f</sub> = 0.34 (SiO<sub>2</sub>, ethyl acetate - hexane, 1:1). <sup>1</sup>H-NMR (δ, CDCl<sub>3</sub>, 500 MHz): 7.48 (dd, *J* = 7.0 and 1.7 Hz, *o*-Ph, 2H), 7.36 (m, *m,p*-Ph, 3H), 4.47 (d, *J* = 13.7 Hz, 2e-H, 1H), 4.23 (dq, *J* = 7.07 and 3.42 Hz, CH<sub>2</sub>CH<sub>3</sub>, 1H), 4.13 (dq, *J* = 7.07 and 3.42 Hz, CH<sub>2</sub>CH<sub>3</sub>, 1H), 3.63 (d, *J* = 12.4 Hz, 4e-H, 1H), 3.04 (dd, *J* = 12.4 and 3.3 Hz, 4a-H, 1H), 3.02 (dd, *J* = 13.7 and 4.1 Hz, 2a-H, 1H), 2.75 (dd, *J* = 14.1 and 1.3 Hz, 6e-H, 1H), 2.63 (dd, *J* = 14.2 and 1.3 Hz, 8e-H, 1H), 2.12 (s, 1-H, 1H), 1.89 (s, 5-H, 1H), 1.61 (m, 9-CH<sub>2</sub>, 2H), 1.47

(dd,  $J=3.3$  and  $14.7$  Hz, 6a-H, 1H), 1.38 (dd,  $J=14.2$  and  $4.1$  Hz, 8a-H, 1H), 1.26 (t,  $J=7.08$  Hz,  $\text{CH}_2\text{CH}_3$ , 3H), 1.15 (s, 7- $\text{CH}_3$ , 3H); Assignments were made with DQF-COSY spectrum.  $^{13}\text{C}$ -NMR ( $\delta$ ,  $\text{CDCl}_3$ , 124.9 MHz): 171.7, 173.3, 137.4, 128.8, 128.2, 126.7, 61.1, 52.5, 46.9, 40.8, 39.2, 38.6, 32.9, 32.3, 28.3, 27.6, 14.0; IR ( $\text{cm}^{-1}$ ,  $\text{CDCl}_3$ ): 2912, 2857 (CH), 1710 (C=O), 1621 (C=O), 1453 (Ph), 1416; MS (EI): 315 ( $\text{M}^+$ , 27%), 286 (4%), 242 (6%), 211 (14%), 210 (100%), 182 (5%), 136 (10%), 105 (85%); HRMS: Calc. For  $\text{C}_{19}\text{H}_{25}\text{NO}_3$  315.1834305, found: 315.18333. 1-D NOE experiment {7- $\text{CH}_3$ }: 6.8a-H - 11%, 6.8e-H - 5%; No NOE was observed between 7- $\text{CH}_3$  and 9- $\text{CH}_2$  protons.

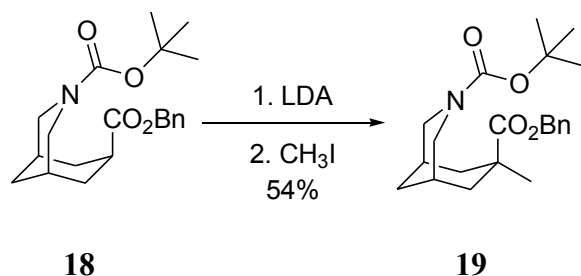
### S3.3 3-Methyl-1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one (2)



Concentrated aq. HBr solution (~45%, 20 ml), was added to the amide-ester **16** (3.5 g, 11.1 mmol) and the mixture was set up for a 6 days reflux under stirring. At the end of this period, all the starting material was dissolved. Then the mixture was evaporated, the product was extracted from the residue with water and after evaporation to ~ 10 ml, pH of the water extract was adjusted to 7.45. Water was evaporated, methanol (5 ml) was added and the solution transferred to a sublimator and carefully evaporated in vacuum without heating (water pump). The residue was then sublimed (60-120 °C, oil pump). The sublimed product was resublimed again (60 °C, oil pump) to obtain white crystals of **2** possessing strong camphor-like smell (0.75 g, 4.5 mmol, 41% yield), m.p. 89-90 °C. Compound **2** can also be recrystallized from toluene or from  $\text{CH}_2\text{Cl}_2$ -hexane mixture (1:1).  $^1\text{H}$ -NMR ( $\delta$ ,  $\text{CDCl}_3$ , 500 MHz): 3.43 (ddd,  $J=13.5$ , 2.2 and 2.2

Hz, 8,9e-H, 2H), 3.23 (d,  $J=13.5$  Hz, 8,9a-H, 2H), 2.12 (dm,  $J=12.7$  Hz, 6e-H, 1H), 2.03 (dm,  $J=13.0$  Hz, 4,10e-H, 2H), 1.93 (dm,  $J=13.0$  Hz, 4,10a-H, 2H), 1.91 (m, 6a-H, 1H), 1.84 (br s, 5,7-H, 2H), 1.05 (s,  $\text{CH}_3$ , 3H) (Assignments proven by COSY);  $^{13}\text{C}$ -NMR ( $\delta$ ,  $\text{CDCl}_3$ , 124.9 MHz): 200.2, 61.4, 46.5, 44.5, 34.3, 28.0, 23.9; IR ( $\text{cm}^{-1}$ ,  $\text{CDCl}_3$ ): 2923, 2857 (CH), 1732 (C=O), 1456, 1297, 1056; Anal. Calc. for  $\text{C}_{10}\text{H}_{15}\text{NO}$ : C, 72.69; H, 9.15; N, 8.48. Found: C, 71.84, H, 9.16, N, 8.46; Crystals suitable for X-ray analysis were obtained by slow sublimation (30-40 °C, 0.1 mm Hg).

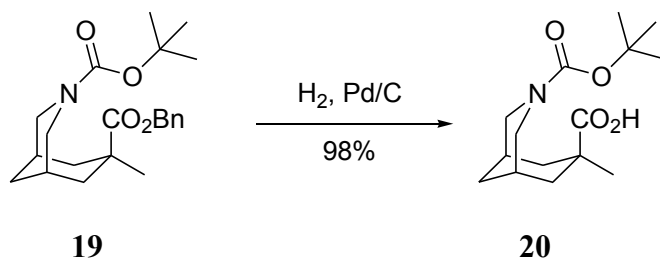
### S3.4 7-benzyl 3-tert-butyl 7-methyl-3-aza-bicyclo[3.3.1]nonane-3,7-dicarboxylate



A solution of BuLi (3.74 ml of 2.46 M in hexanes, 9.2 mmol) was added to a solution of  $i\text{-Pr}_2\text{NH}$  (1.27 ml, 0.923 g, 9.2 mmol in 10 ml of dry THF) at  $-40 \div -20$  °C (propan-2-ol\ liquid nitrogen bath) under an argon atmosphere. After stirring at  $-20$  °C for 30 min, the bath was cooled to  $-78$  °C and the mixture of Boc-aminoacid benzyl ester **18** [S3] (3 g, 8.3 mmol in 30 ml of dry THF) with HMPA (2.5 ml) was added dropwise. The solution was stirred for 30 min after the addition at  $-78$  °C and then the cooling bath was removed. Freshly distilled methyl iodide (1.3 g, 0.57 mL, 9.2 mmol) was carefully added to the stirred reaction mixture at  $-78$  °C. The stirring continued for 8h. Citric acid (10 ml, 10 % solution in water) was added to the reaction mixture at  $0$  °C under stirring. The mixture was extracted with MTBE (3 x 50 mL). Combined extracts were dried over  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure. The residue was purified by flash column chromatography (gradient EtOAc in hexane) to obtain the pure

product (1.674 g, 54% yield).  $^1\text{H-NMR}$  ( $\delta$ ,  $\text{CDCl}_3$ , 500 MHz): 7.25-7.45 (m, Ph, 5H), 5.12 (broad s,  $\text{CHHPh}$ , 1H), 4.98 (broad s,  $\text{CHHPh}$ , 1H), 3.91 (broad s, 2,4-H, 2H), 2.88 (d,  $J = 10$  Hz, 6,8-CH, 2H), 2.68 (d,  $J = 14$  Hz, 6,8-CH, 2H), 1.94 (broad s, 2,4-H, 2H), 1.54 (broad s, 1,5-H, 2H), 1.48 (s, t-Bu, 9H), 1.39-1.36 (AB system, 9- $\text{CH}_2$ , 2H), 1.10 (s, 7- $\text{CH}_3$ , 3H).  $^{13}\text{C-NMR}$  ( $\delta$ ,  $\text{CDCl}_3$ , 124.9 MHz): 175.9, 155.2, 136.5, 128.0, 127.9, 127.4, 79.0, 65.8, 48.3 (broad), 40.8, 38.8, 32.2, 31.9, 28.2, 27.5. GC-MS (EI,  $m/z$ ): 316 ( $\text{M}^+$ -t-Bu), 212 ( $\text{M}^+$ -COOtBu), 182, 166, 137, 108, 91, 79, 57, 44.

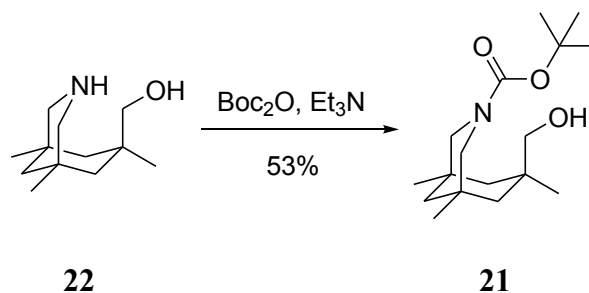
### S3.5 3-(tert-butoxycarbonyl)-7-methyl-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid (**20**)



The Boc-protected aminoacid benzyl ester **19** (4 mmol) was dissolved in THF (50 mL) under an argon atmosphere. Palladium on charcoal (10%, 2 g) was added, the flask was charged with hydrogen gas and the content was shaken under the hydrogen (1 atm) for 8 h. After no starting material was left in the mixture (TLC control, eluent – hexane-EtOAc, 1:1) the catalyst was filtered off and the filtrate was evaporated on a rotary evaporator (with the bath temperature maintained below 80 °C; the Boc protection might cleave off at higher temperatures). The product (1.1 g, 98% yields) was sufficiently pure for further transformations. It was recrystallised from methanol for analytical purpose (m.p. 103-104 °C).  $^1\text{H-NMR}$  ( $\delta$ ,  $\text{CDCl}_3$ , 500 MHz): 6.65 (very broad s, COOH, 1H), 3.93 (broad s, 2,4-H, 2H), 2.86 (d,  $J = 12$  Hz, 2,4-H, 2H), 2.61 (d,  $J = 14$  Hz, 6,8-CH, 2H), 1.93 (broad s, 5,1-H, 2H), 1.55-1.66 (AB system, 9- $\text{CH}_2$ , 2H), 1.47 (s, t-Bu, 9H), 1.41 (d,  $J = 14$  Hz, 6,8-CH, 2H), 1.31 (s, 7- $\text{CH}_3$ , 3H).  $^{13}\text{C-NMR}$  ( $\delta$ ,

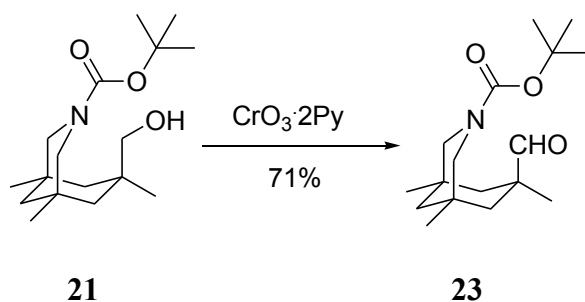
CDCl<sub>3</sub>, 124.9 MHz): 176.6, 155.6, 79.1, 47.8 (broad), 40.1, 38.8, 32.2, 32.1, 28.1, 27.5. Anal. Calc. for C<sub>15</sub>H<sub>25</sub>NO<sub>4</sub>: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.55, H, 8.92, N, 4.98;

**S3.6 tert-butyl 7-(hydroxymethyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonane-3-carboxylate (21)**



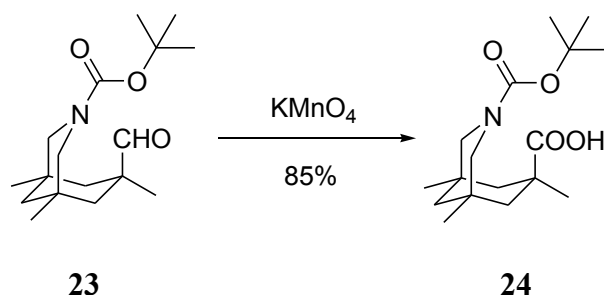
Compound **22** [S2] (2.35 g, 11.9 mmol) was dissolved in dichloromethane (25 mL), and the solution was immersed in an ice water bath. Boc-anhydride (2.18 g, 10 mmol) and triethylamine (1.01 g, 0.73 mL, 10 mmol) were added to the cooled solution under stirring. The reaction mixture was stirred at 0 °C for 3 h, and then left overnight. Dichloromethane (100 mL) was added, the resulting solution was washed with water (25 mL), saturated aq. citric acid solution (25 mL), brine (2 x 25 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated in vacuum, and the residue (colourless oil, 1.88 g, 6.3 mmol, 53% yield) was used in the next step without further purification. <sup>1</sup>H-NMR (δ, CDCl<sub>3</sub>, 500 MHz): 3.62 (broad s, 2,4-H, 2H), 3.21 (s, CH<sub>2</sub>OH, 2H), 2.33 (broad s, 2,4-H, 2H), 1.45 (m, t-Bu+6,8-H+9-H, 12H), 1.07 (d, J = 15 Hz, 6,8-H, 2H), 0.98 (s, 7-CH<sub>3</sub>, 3H), 0.93 (d, J = 14 Hz, 9-H, 1H), 0.90 (s, 1,5-CH<sub>3</sub>, 6H); <sup>13</sup>C-NMR (δ, CDCl<sub>3</sub>, 124.9 MHz): 155.1 (C=O), 79.2 (C(CH<sub>3</sub>)<sub>3</sub>), 72.2 (CH<sub>2</sub>OH), 55.4 (broad), 44.8, 42.5 (broad), 34.4, 30.8, 29.4, 28.1.

**S3.7 tert-butyl 7-formyl-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonane-3-carboxylate (23)**



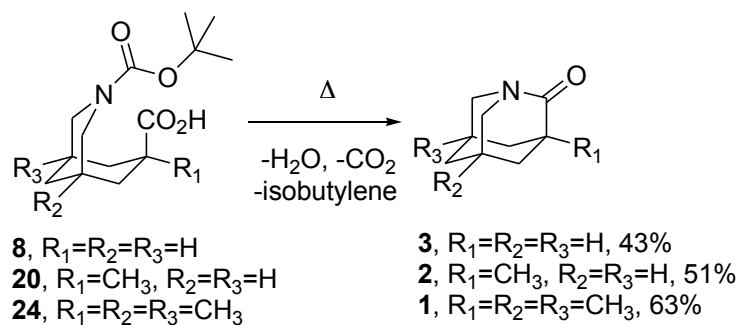
A solution of compound **21** (1.88 g, 6.3 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (40 mL) was added to a magnetically stirred solution of the freshly prepared  $\text{CrO}_3 \cdot 2\text{Py}$  complex [prepared from 3.78 g (37.8 mmol) of  $\text{CrO}_3$  and 6.14 mL (75.6 mmol) of pyridine in 160 mL of dichloromethane]. The mixture was stirred for 30 min at ambient temperature (a black deposit formed). The mixture was then diluted with diethyl ether (400 mL). The solution was decanted from the deposit, which was washed with ether ( $3 \times 50$  mL) by decantation. The combined decanted solutions were transferred to a separating funnel and washed successively with 2% NaOH (80 mL), saturated aq. citric acid solution (80 mL), saturated  $\text{NaHCO}_3$  (80 mL) and brine (80 mL), then dried over  $\text{Na}_2\text{SO}_4$ . Evaporation and column chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ – $\text{CH}_3\text{OH}$ , 9:1) yielded 1.32 g (4.5 mmol, 71% yield) of aldehyde **23**, as colourless crystals; m.p. 91–92 °C. (cryst. from hexane).  $^1\text{H}$ -NMR ( $\delta$ ,  $\text{CDCl}_3$ , 500 MHz): 9.17 (s, CHO, 1H), 3.57 (broad s, 2,4-H, 2H), 2.33 (dd,  $J = 12.5$  and 3 Hz, 2,4-H, 2H), 2.13 (d,  $J = 12.5$  Hz, 6,8-H, 2H), 1.46 (s, t-Bu, 9H), 1.09 (m, 6,8-H+9- $\text{CH}_2$ ), 0.90 (s, 1,5- $\text{CH}_3$ , 6H), 0.83 (s, 7- $\text{CH}_3$ , 3H).  $^{13}\text{C}$ -NMR ( $\delta$ ,  $\text{CDCl}_3$ , 124.9 MHz): 200.6 (CHO), 155.3 (C=O), 79.9 ( $\text{C}(\text{CH}_3)_3$ ), 53.1, 47.1, 44.3, 43.5 (broad), 30.5, 28.7, 28.1, 27.9. IR ( $\text{cm}^{-1}$ , KBr): 2952, 1706 (C=O), 1695 (C=O), 1401, 1297, 1165. Anal. calc. for  $\text{C}_{17}\text{H}_{29}\text{NO}_3$ : C, 69.12; H, 9.89; N, 4.74. Found: C, 69.14, H, 9.83, N, 4.78.

### S3.8 3-(tert-butoxycarbonyl)-1,5,7-trimethyl-3-aza-bicyclo[3.3.1]nonane-7-carboxylic acid (**24**)



The aldehyde **23** (1.32 g, 4.5 mmol) was dissolved in aqueous acetone (1:2, 120 mL), and finely ground  $\text{KMnO}_4$  (1.06 g, 6.7 mmol) was added in several portions to the stirred solution. The mixture was stirred for 30 min at ambient temperature, by which time no starting aldehyde could be detected by TLC ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ – $\text{CH}_3\text{OH}$ , 9:1). The excess oxidant was destroyed with  $\text{Na}_2\text{SO}_3$  (~2 mL of saturated aqueous solution). The mixture was filtered through a Celite pad, which was then washed with methanol and the combined filtrate and washings evaporated. The residue was dissolved in water (80 mL), carefully acidified to pH ~ 5 with conc.  $\text{HCl}$ . The white precipitate formed was filtered and washed with cold water, then dried in a vacuum desiccator (239.6 mg, 85%). The crude product **24** was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2$ – $\text{CH}_3\text{OH}$ , 9 : 1). White crystals, mp 232–235 °C.  $^1\text{H}$ -NMR ( $\delta$ ,  $\text{CDCl}_3$ , 500 MHz): 6.32 (broad s, COOH, 1H), 3.69 (broad s, 2,4-H, 2H), 2.43 (d,  $J$  = 14 Hz, 6,8-H, 2H), 2.35 (d,  $J$  = 12 Hz, 2,4-H, 2H), 1.45 (s, t-Bu, 9H), 1.16 (s, 7- $\text{CH}_3$ , 3H), 1.11 (d,  $J$  = 12 Hz, 9-H, 1H), 1.05 (d,  $J$  = 12 Hz, 9-H, 1H), 0.98 (d,  $J$  = 14 Hz, 6,8-H, 2H), 0.88 (s, 1,5- $\text{CH}_3$ , 6H).  $^{13}\text{C}$ -NMR ( $\delta$ ,  $\text{CDCl}_3$ , 124.9 MHz): 176.4 (COOH), 155.4 (C=O), 79.3 ( $\text{C}(\text{CH}_3)_3$ ), 52.9, 47.2, 45.3, 41.2, 32.5, 30.8, 29.3, 28.2, 28.1. IR ( $\text{cm}^{-1}$ , KBr): 3528 (OH), 2930, 1715 (C=O), 1662 (C=O), 1460, 1408, 1304, 1168. Anal. calc. for  $\text{C}_{17}\text{H}_{29}\text{NO}_4$ : C, 65.57; H, 9.39; N, 4.50. Found: C, 65.44, H, 9.41, N, 4.48.

### S3.9 Synthesis of compounds 1-3 by pyrolysis of the corresponding NBoc-protected amino acids



### General procedure

The pyrolysis/sublimation was carried out in an apparatus consisting of a 50 mL round-bottom flask (standard joint 14.5 mm) attached to a condenser equipped with a central cold-finger. The N-Boc amino-acid (**24**, **20**, or **8**) (0.93 mmol) was dissolved in dry methanol (6 mL) in the 50 mL round-bottom flask. Silica gel (Kieselgel Merck 60, 5-fold amount calculating on the N-Boc amino acid) was added to the solution, and methanol was evaporated on a rotary evaporator (water vacuum pump, 40 °C bath temperature), then the residue dried in vacuum (water vacuum pump, 40 °C bath temperature) for ~30 min. Then the flask was connected to the cold-finger and a vacuum oil pump (~0.5 mm Hg). Connection to vacuum had to be done with great care, because the mixture may produce volatile dust. The flask was immersed completely (up to the upper rim) in an oil bath, and the oil bath heated. Sublimation of the product started at 115 °C (bath temperature). The temperature of the bath increased to 150 °C within 1 h, and then the products were collected on the cold-finger within 4h, while keeping the bath temperature at 150±5 °C.

Compound **1** (**3,5,7-Trimethyl-1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one**) was obtained in 63% yield. Its  $^1\text{H}$ ,  $^{13}\text{C}$ -NMR spectra in  $\text{CDCl}_3$ , IR and analytical data were identical to those described in [S2].  $^1\text{H}$ -NMR ( $\delta$ ,  $\text{CD}_3\text{CN}$ , 500 MHz): 2.90 (dd,  $J = 3.5$  and 13.5 Hz, 8,9-H, 2H), 2.87 (d,  $J = 13.5$  Hz, 8,9-H, 2H), 1.72 (d,  $J = 12.5$  Hz, 4,10-H, 2H), 1.64 (dt,  $J = 2.5$  and 12.5 Hz, 6-H, 1H), 1.56 (dd,  $J = 3.5$  and 12.5 Hz, 4,10-H, 2H), 1.53 (dt,  $J = 2.5$  and 12.5 Hz, 6-H,

1H), 0.97 (s, 3-CH<sub>3</sub>, 3H), 0.81 (s, 5,7-CH<sub>3</sub>, 6H). <sup>13</sup>C-NMR (δ, CD<sub>3</sub>CN, 124.9 MHz): 199.5 (C=O), 65.0, 51.3, 47.5, 42.8, 29.7, 24.1, 22.3.

Compound **2** (**3-methyl-1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one**) was obtained in 51% yield. Its <sup>1</sup>H, <sup>13</sup>C-NMR spectra in CDCl<sub>3</sub>, IR and analytical data were identical to those described above.

<sup>1</sup>H-NMR (δ, CD<sub>3</sub>CN, 500 MHz): 3.39 (d, J = 13 Hz, 8,9-H, 2H), 3.12 (d, J = 13 Hz, 8,9-H, 2H), 2.13 (d, J = 12.5 Hz, 6-H, 1H), 1.70-2.00 (m, 4,10-H+6-H), 1.81 (broad s, 1,5-H, 2H), 1.00 (s, CH<sub>3</sub>, 3H). <sup>13</sup>C-NMR (δ, CD<sub>3</sub>CN, 124.9 MHz): 199.8 (C=O), 60.6, 45.8, 43.9, 33.6, 27.7, 23.1.

Compound **3** (**1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one**) was obtained in 43% yield. White crystals, <sup>1</sup>H-NMR (δ, CD<sub>3</sub>CN, 500 MHz): 3.43 (d, J = 13 Hz, 9,10-H, 2H), 3.20 (d, J = 13 Hz, 9,10-H, 2H), 2.61 (broad s, 3-H, 1H), 2.21 (broad s, 4,8-CH<sub>2</sub>, 4H), 2.17 (d, J = 12.5 Hz, 6-H, 1H), 2.04 (d, J = 12.5 Hz, 6-H, 1H), 1.72 (broad s, 5,7-H, 2H). <sup>13</sup>C-NMR (δ, CD<sub>3</sub>CN, 124.9 MHz): 198.6 (C=O), 60.6, 43.0, 38.5, 34.2, 26.3. IR (cm<sup>-1</sup>, powder, Attenuated Total Reflectance (ATR) mode, run under argon; measurements in KBr or in solvents failed because of the fast hydrolysis of **3** by traces of water): 2906, 2856 (CH), 1734 (C=O), 1452, 1301, 1063, 1020; Anal. Calc. for C<sub>9</sub>H<sub>13</sub>NO: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.46, H, 8.65, N, 9.24; Crystals for X-ray analysis were obtained by pyrolysis of **8** on silica gel as described above, using the oil bath temperature regime shown in Fig. S1.

### S3.10 Preparation of 1·HBF<sub>4</sub>, 2·HBF<sub>4</sub> and 3·HBF<sub>4</sub>

#### *General procedure*

Freshly prepared twisted amide (compound **1**, **2** or **3**, 0.2-0.3 mmol) was dissolved in acetonitrile (distilled over P<sub>2</sub>O<sub>5</sub> before use, ~0.5 mL) in a flame-dried Schlenk flask under argon. One equivalent of HBF<sub>4</sub>·Et<sub>2</sub>O complex was added to the solution by a micro-syringe. After being shaken for 1 min, the mixture was diluted with dry diethyl ether (~5 mL). The white

precipitate formed was filtered under an argon atmosphere and purified by dissolving in dry acetonitrile (~0.5 mL) followed by precipitation from the solution with dry diethyl ether. The purification procedure was repeated twice; the product was finally filtered and dried in vacuum (oil pump) without heating for 5 h. All the three salts obtained (white powders, 30-45% yield) melted above 250 °C with decomposition. Crystals for the X-Ray analysis were grown from concentrated solutions in acetonitrile-diethyl ether mixture (~5:1) by freezing the solutions to -30 °C.

**3,5,7-Trimethyl-1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one, tetrafluoroboric acid salt (1'HBF<sub>4</sub>)** <sup>1</sup>H-NMR (δ, CD<sub>3</sub>CN, 500 MHz): 8.36 (broad s, N<sup>+</sup>H, 1H), 3.65 (d, J = 12 Hz, 9,10-H, 2H), 3.40 (dd, J = 12 and 2.5 Hz, 9,10-H, 2H), 2.07 (d, J = 13 Hz, 4,10-H, 2H), 1.80 (m, 4,10-H+6-H, 3H), 1.68 (d, J = 13 Hz, 6-H, 1H), 1.18 (s, 3-CH<sub>3</sub>, 3H), 1.03 (s, 5,7-CH<sub>3</sub>, 6H). <sup>13</sup>C-NMR (δ, CD<sub>3</sub>CN, 124.9 MHz): 178.0 (C=O), 62.3, 48.0, 44.3, 43.5, 29.9, 22.8, 20.5.

**3-methyl-1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one, tetrafluoroboric acid salt (2'HBF<sub>4</sub>)**, <sup>1</sup>H-NMR (δ, CD<sub>3</sub>CN, 500 MHz): 8.24 (broad s, N<sup>+</sup>H, 1H), 3.85 (d, J = 12.5 Hz, 9,10-H, 2H), 3.80 (d, J = 12.5 Hz, 9,10-H, 2H), 2.39 (broad s, 5,7-H, 2H), 2.26 (d, J = 13 Hz, 4,10-H, 2H), 2.13 (d, J = 13 Hz, 4,10-H+6-H, 3H), 1.96 (m, 6-H, overlapped with acetonitrile residual peak), 1.21 (s, CH<sub>3</sub>, 3H). <sup>13</sup>C-NMR (δ, CD<sub>3</sub>CN, 124.9 MHz): 176.3 (C=O), 59.7, 44.4, 42.4, 29.9, 25.5, 21.0.

**1-azatricyclo[3.3.1.1<sup>3,7</sup>]decan-2-one, tetrafluoroboric acid salt (3'HBF<sub>4</sub>)**, <sup>1</sup>H-NMR (δ, CD<sub>3</sub>CN, 500 MHz): 8.21 (broad s, N<sup>+</sup>H, 1H), 3.90 (d, J = 12 Hz, 9,10-H, 2H), 3.84 (d, J = 12 Hz, 9,10-H, 2H), 3.11 (s, 3-H, 1H), 2.25-2.45 (m, 4,10-CH<sub>2</sub>+5,7-H, 6H), 2.15 (d, J = 12 Hz, 6-H, 1H), 2.06 (d, J = 12 Hz, 6-H, 1H). <sup>13</sup>C-NMR (δ, CD<sub>3</sub>CN, 124.9 MHz): 175.8 (C=O), 59.8, 40.9, 35.3, 30.5, 24.4.

### **S3.11 Kinetic measurements for hydrolysis reactions of 1-3, 1'HBF<sub>4</sub>, 2'HBF<sub>4</sub> and 3'HBF<sub>4</sub>**

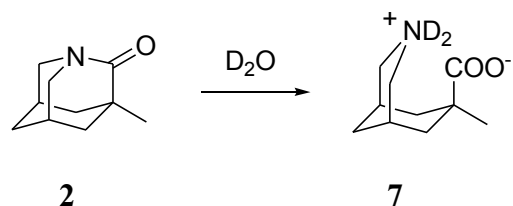
### *General procedure.*

Hydrolysis was carried out in NMR sample tubes, monitored by  $^1\text{H}$ -NMR spectra (recorded by repeated single scans at 23 °C). The reactant concentration was exactly reproduced from [S5] for comparison. In a typical run, the twisted amides or their salts (**1-3**, **1·HBF<sub>4</sub>**, **2·HBF<sub>4</sub>** or **3·HBF<sub>4</sub>**, around 0.1 mmol) were weighed in a flame-dried NMR sample tube under argon. The solvent CD<sub>3</sub>CN (freshly distilled over P<sub>2</sub>O<sub>5</sub> under argon) was added in the amount to obtain 0.086 M solution of the twisted amides or their salts. After recording the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra deuterium oxide (5 equivalents) was added by a micro-syringe, the content of the tube was vigorously shaken, starting immediately the recording of the time. The first  $^1\text{H}$ -NMR spectrum was measured as quickly after the D<sub>2</sub>O addition as practical, then the spectra were measured in 3-10 min intervals, depending on the reaction progress. The spectra were run as single scans, in order to avoid integral-value distortions due to relaxation effects. Typical fragments of the NMR spectra sets for each compound are shown in Figures S2,4,6,8,10. The unambiguously assigned non-overlapping peaks (indicated in the Figures by the labels over the peaks) were carefully integrated; in the case of compound **3** the internal integration reference (carefully weighed amount of naphthalene) was added to the reaction mixture before water addition. The complete data sets (Tables S1-5) were used to build the kinetic curves (Figures S3,5,7,9,11) and calculate the half lives for each compound.

### *Results*

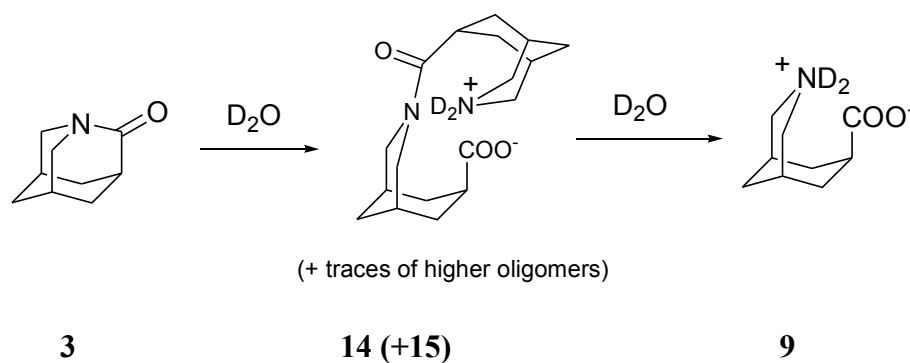
**Compound 1** showed no signs of the hydrolysis under the above described conditions within 700 min.

**Compound 2** hydrolysed with the formation of the corresponding zwitter-ionic amino acid:



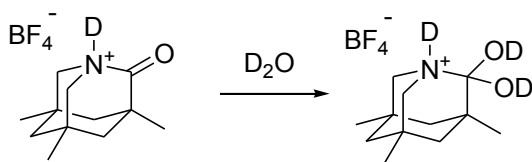
$^1H$ -NMR control of the reaction progress was done by integration of the  $CH_2$  group signals of the twisted amide and the amino acid; typical NMR spectra set are shown in Fig. S2. The reaction reached equilibrium: after 2 days the spectrum showed  $\sim 70\%$  of the twisted amide and  $\sim 30\%$  of the amino acid: the ratio did not change thereafter. The complete data set obtained by the integration of the spectra is shown in the Table S1. The graph (Fig. S3) was constructed using the data, and an exponential fit of the descending curve ( $y = A_1 \cdot \exp(-x/t_1) + y_0$  (R-value 0,92);  $y_0 = 59.26 \pm 0.82$ ;  $A_1 = 23.49 \pm 1.32$ ;  $t_1 = 2036.87 \pm 308.64$ ) yielded the time of the half-transformation for compound **2**, namely, 1019 s or  $\sim 17$  min. Noticeable are *synchronous counter-phase* oscillations of the concentrations of both **2** and **7**. We observed these oscillations in several experiments and are confident that they are not measurement artifacts. The oscillation might indicate non-stationary nature of the processes leading to the equilibrium between **2** and its hydrolysis product.

**Compound 3.** This compound hydrolysed with formation of the corresponding amino acid **9** with intermediate formation of dimer and higher oligomers (**14** and **15**), as shown in the scheme below:



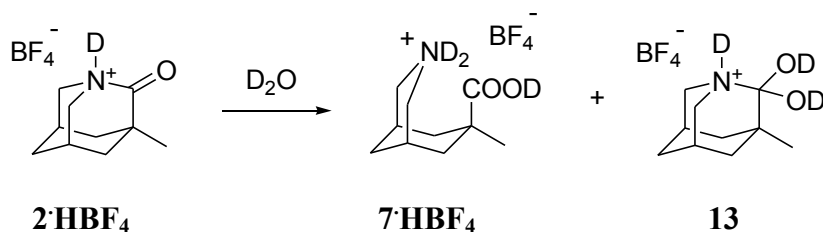
Disappearance of the twisted amide in the course of the hydrolysis was monitored by the integral values of the separately standing  $N-CH_2$  doublet at 3.43 ppm relative to the integral value of the reference compound signals, naphthalene (Fig. S4). Signals from the oligomeric intermediates are visible in each spectrum; they are indicated in the Fig. S4 on the corresponding spectral set. However, as the ratio of different oligomeric intermediates is not known, it was not possible to quantify their concentration changes. The increasing amino acid concentration is also difficult to quantify because of severe NMR signal overlap. Results of the integration of all the measured spectra are shown in the Table S2 and Fig. S5. The half-life of compound **3** is 1011 s or ~16.9 min (calculated using the exponential fit of the data,  $y = A_1 \cdot \exp(-x/t_1) + y_0$  (R-value 0,984);  $y_0 = 8,67 \pm 1,22$ ;  $A_1 = 82,32 \pm 2,31$ ;  $t_1 = 1156,27 \pm 77,38$ ). As for the hydrolysis of compound **2**, oscillations of the twisted amide concentration were observed, indicating the non-stationary nature of the hydrolysis.

**Compound 1·HBF<sub>4</sub>**. This compound hydrolysed with the formation of the protonated tricyclic hemiaminal **12** as the sole product (identified by us previously, see [S2]).



Disappearance of **1·HBF<sub>4</sub>** was monitored by the integral of the N<sup>+</sup>(CH<sub>2</sub>)<sub>2</sub> AB system (its downfield component) relatively to the corresponding N<sup>+</sup>(CH<sub>2</sub>)<sub>2</sub> AB system of the protonated hemiaminal, as shown on the spectra of Fig. S6. The hydrolysis proceeded to completion: only traces of the starting salt could be detected in the mixture after 1 month of the reaction. The integration results and corresponding concentrations are summarized in Table S3. The data were used to build the plot of Fig. S7 and thus calculate the half-life of the compound **1·HBF<sub>4</sub>** under the conditions described above: 3216 s (53.6 min) (exponential fit of the data,  $y = A_1 \cdot \exp(-x/t_1) + y_0$  (R-value 0.96),  $y_0 = 11,45 \pm 2.8$ ;  $A_1 = 62,80 \pm 3.6$ ;  $t_1 = 4671,64 \pm 720.4$ ).

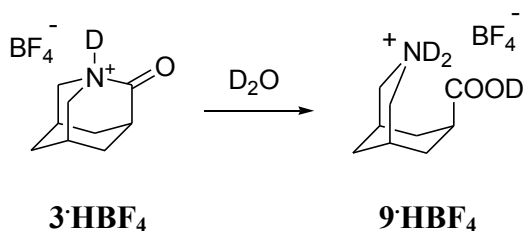
**Compound 2·HBF<sub>4</sub>**. The hydrolysis proceeds with formation of two products **7·HBF<sub>4</sub>** and **13**, as shown in the scheme below:



The hydrolysis did not proceed to completion but reached equilibrium. The equilibrated mixture (after 2 days of reaction) contained ~10% of the starting twisted amide salt. Characteristic signals from the NCH<sub>2</sub> protons were used for integration and calculation of the compound concentrations (see Fig. S8 for a representative spectra set). The results of the integration of all the spectra are summarized in Table S4 and Fig. S9.

The half-transformation time of **2·HBF<sub>4</sub>** calculated using the exponential fit of the data is 6211 s or ~103.5 min ( $y = A_1 \cdot \exp(-x/t_1) + y_0$  (R-value 0.99),  $y_0 = 11,29 \pm 1.6$ ;  $A_1 = 69,61 \pm 1.6$ ;  $t_1 = 9305,84 \pm 535.3$ ).

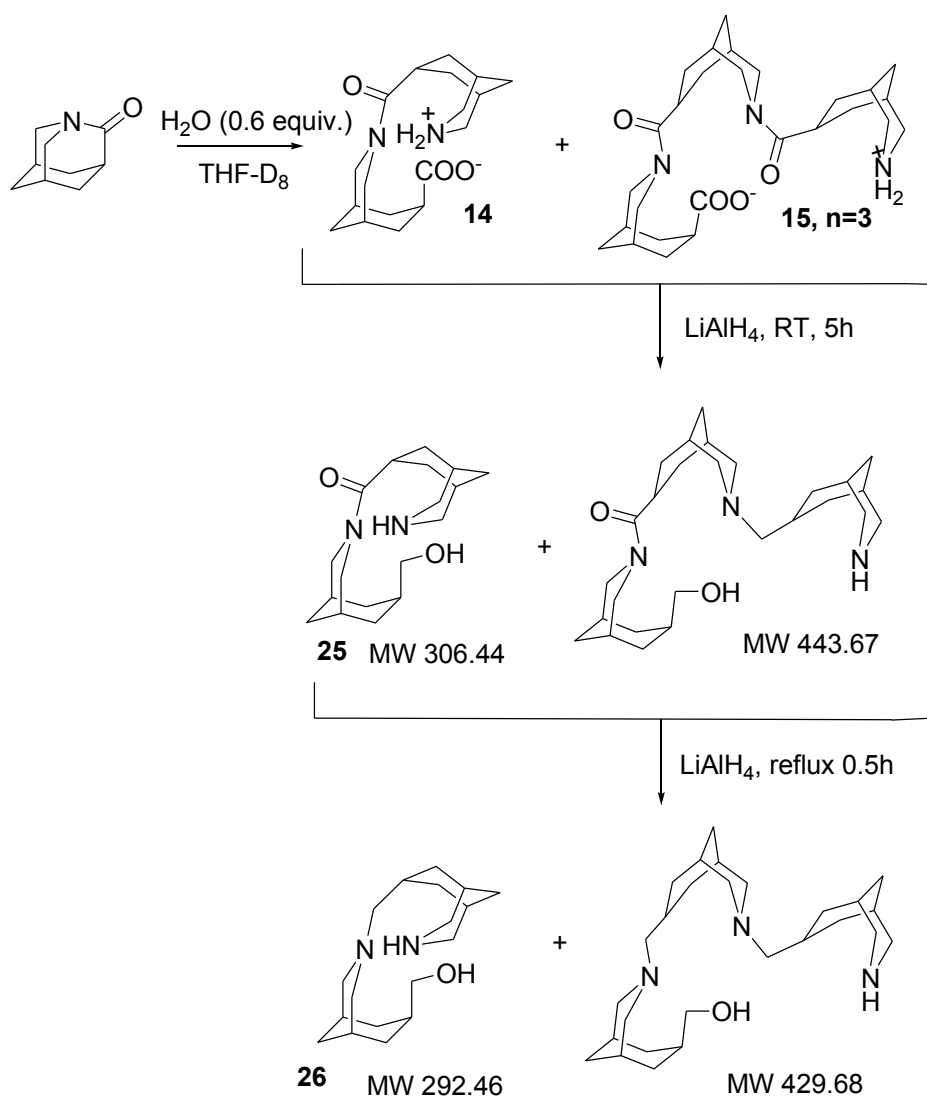
**Compound 3·HBF<sub>4</sub>.** This compound hydrolysed rapidly to the protonated amino acid **9·HBF<sub>4</sub>** only:



Concentrations of both the starting compound and its hydrolysis product can be determined from the <sup>1</sup>H-NMR spectra by the integration of the corresponding NCH<sub>2</sub> proton signals (Fig. S10).

All the results are summarized in the Table S5 and Fig. S11. The half-life of **3·HBF<sub>4</sub>** calculated using the exponential fit of the data is 506 s or ~8.4 min ( $y = A_1 \cdot \exp(-x/t_1) + y_0$  (R-value 0.985),  $y_0 = 4,03 \pm 1,5$ ;  $A_1 = 71,59 \pm 1,96$ ;  $t_1 = 831,21 \pm 65,81$ ).

**S3.12 Quenching of the reaction mixture of compound 3 with water by LiAlH<sub>4</sub> in order to identify the intermediate dimers and oligomers**



The hydrolysis of **3** was carried out in NMR sample tubes using  $\text{THF-d}_8$  as the solvent, to be able to monitor the progress of the reaction. After some experimentation we found that the dimer and higher oligomeric intermediates are formed efficiently in concentrated solutions of **3** in the presence of  $\sim 0.6$  equiv of water. For example, monitoring the reaction mixture contained 48 mg of **3** (0.32 mmol) dissolved in 0.5 mL of  $\text{THF-d}_8$  (making a 0.64 M solution) and 0.5 equiv. of water (3.4  $\mu\text{L}$ ) revealed that a maximal concentration of the intermediates was reached after  $\sim 75$  min at  $23^\circ\text{C}$ . Characteristic signals of  $(\text{CH}_2)_2\text{NC=O}$  protons in  $^1\text{H}$ -NMR spectrum (broad singlets, 4.44 and 3.94 ppm) and two  $\text{C=O}$  peaks in the  $^{13}\text{C}$ -NMR spectrum (at 179.2 and 178.6 ppm) indicated the predominant formation of the dimer **14** under these conditions (see the

spectra in the Supplementary Data section). In order to prove this hypothesis further, the mixture (after 75 min of the hydrolysis) was transferred in a flame-dried Schlenk flask under argon and immediately treated with  $\text{LiAlH}_4$  (60.7 mg, 1.6 mmol). The mixture was stirred under argon for 1 h, then one half of it was taken out, quenched with water (2 mL) and the products were extracted with diethyl ether (5 x 10 mL). The other half of the reaction mixture was refluxed for 5 h, cooled, and quenched with water (2 mL). The products formed were also extracted with diethyl ether (5 x 10 mL). The extracts from both portions were dried over  $\text{Na}_2\text{SO}_4$  and evaporated in vacuum. Both residues were analysed by HPLC. The results (Fig. S12-S13) confirmed the formation of the dimeric intermediate (MS peaks corresponding to partly reduced **25** or completely reduced **26** were detected). Traces of the reduction products formed from the trimeric **15** can also be detected in both cases. Our assignments of the HPLC peaks are shown in the Fig. S14.

Preparative isolation of the dimeric intermediate **14** failed in our hands. On standing in solution or during isolation, the compound either rapidly hydrolysed to the amino acid **9** (in the presence of water) or polymerized (in water-free solutions), forming highly insoluble material.

## S.4 References

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