Supporting Information

Synthesis of Cyclic Peptidosulfonamides by Ring-Closing Metathesis

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¹H NMR (300 MHz) spectra for:

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4	S7		10a	S19		11b	S31		12c	S43		16	S57			
6	S10		10b	S22		11c	S34		13*	S48		18	S63			
7	S13		10c	S25		12a	S37		14	S51		19	S66			

¹³C NMR (75 MHz) spectra for:

3	S5		8	S17		11a	S29		12b	S41		15	S55
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4	S8		10a	S20		11b	S32		12c	S44		16	S58
6	S11		10b	S23		11c	S35		13*	S49		18	S64
7	S14		10c	S26		12a	S38		14	S52		19	S67

2D NMR (300 MHz) spectra for:

3	S6		8	S18		11a	S30		12b	S42		15	S56		20	S70
4	S9		10a	S21		11b	S32		12c	S45		16	S59			
6	S12		10b	S24		11c	S36		13*	S50		18	S65			
7	S15		10c	S27		12a	S38		14	S52		19	S68			

HPLC data for:

16	S60-62
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Modeling data for:

16	S71-74
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* Precursor of **13**

Experimental Section

General Methods. Peptide grade solvents for synthesis were purchased from Biosolve (The Netherlands), 1,1,2 trichloroethane (98%) from Acros. The second generation Grubbs catalyst and α,α -dichlorotoluene were purchased from Aldrich. Reactions were carried out at ambient temperature unless stated otherwise. TLC analysis was performed on Merck pre-coated silicagel 60 F-254 (0.25 mm) plates. Spots were visualized with UV light, ninhydrin, Cl_2 -TDM[10], or KMnO_4 . Solvents were evaporated under reduced pressure at 40°C . Column chromatography was performed on ICN Silica 32-63, $60\text{ \AA}$. ^1H NMR, ^{13}C NMR (75 MHz) and COSY spectra were recorded on a 300 MHz spectrometer. NOESY, HSQC and HMBC spectra were recorded on a 500 MHz spectrometer. Chemical shifts are reported in ppm relative to TMS (0 ppm) for the ^1H NMR and to CDCl_3 (77 ppm) for the ^{13}C NMR as internal standards. All ^1H NMR spectra were interpreted using COSY spectra. ^{13}C NMR spectra were recorded using the attached proton test (APT) pulse sequence. Anal. HPLC runs were performed on an automated HPLC system with an Alltech Absorbosphere C8 column ($90\text{ \AA}$, $5\text{ }\mu\text{m}$, $250\times 4.6\text{ mm}$) at a flow rate of 1 mL/min . The compounds were detected by evaporative light scattering (ELSD). Prep. HPLC runs were performed on a semi-automated HPLC system with an Alltech Absorbosphere C8 column ($90\text{ \AA}$, $10\text{ }\mu\text{m}$, $250\times 22\text{ mm}$) at a flow rate of 12 mL/min . A linear gradient of buffer B (0.085% TFA in $\text{MeCN}/\text{H}_2\text{O}$ 95:5) (anal.: 100% in 20 min, prep.: 100% in 30 min) from buffer A (0.1% TFA in H_2O) (anal.: from 100% buffer A, prep.: from 30% buffer A).

STANDARD IS OBSERVE
H1_data are in file H1

Pulse Sequence: relayh
Solvent: CDCl3
Ambient temperature
File: FmocIscC282020Hallyl-coxy-Isobornanolom
INOVA-500 "nu500"

Relax. delay 1.000 sec
COZY 30-90
Acq. time 0.227 sec
Width 2252.1 Hz
2D Width 2252.1 Hz
2 repetitions
128 increments
OBSERVE H1, 299.9746634 MHz
DATA PROCESSING
Sine bell 0.114 sec
F1 DATA PROCESSING
Sine bell 0.031 sec
F2 size 1024 x 1024
Total time 5 min, 26 sec

STANDARD 1H OBSERVE

Pulse Sequence: relayh
Solvent: CDCl₃
Ambient temperature
File: arylglylasecr2001small-convp-el14141
INSTR: 300 "nmr500"

Melam. delay 1.601 sec
COST 80-98
Acq. time 0.130 sec
NS/ab 1973.7 Hz
2D Width 5973.7 Hz
4 repetitions
128 increments
OBSERVE M1. 399.9748634 MHz
DATA PROCESSING
Sine bell 0.045 sec
F1 DATA PROCESSING
Sine bell 0.031 sec
FT size 312 x 512
Total time 18 min, 3 sec

STANDARD IN ORSERVE

Pulse Sequence: relayh

Solvent: CDCl3

Ambient temperature

File: leu149a1e-cosy-01170

INNOVA-300 "nmr500"

Pulse delay 1.000 sec

CGST 96-90

Acq. time 0.225 sec

Misc 2273.8 Hz

2D Width 2273.8 Hz

4 repetitions

126 increments

CHARGE: M1, 299.9682948 mM*

DATA PROCESSING

Size bell 0.113 sec

F1 DATA 960CH8180

Size bell 0.021 sec

FT size 1024 x 1024

Total time 10 min, 49 sec

STANDARD 1B CHIRKYE

Pulse sequence: zgpg30

Solvent: CDCl3

Ambient temperature

File: 27Feb20230808-diallyl-alk-coey-ali7761

INOVA-500 "cuar330"

Relax. delay 1.500 sec

COFF 90-90

Acq. time 0.143 sec

Wdth 1795.0 Hz

2D width 1795.0 Hz

2 repetitions

128 increments

CHIRKYE W1 299.9683280 MHz

DATA PROCESSING

Sine bell 0.071 sec

F1 DATA PROCESSING

Sine bell 0.021 sec

F2 size 312 x 312

Total time 5 min, 6 sec

STANDARD 1H OBSERVE

Pulse Sequence: relayh

Solvent: CDCl3

Acquire temperature

File: 080801010YCD030NALLM-coxy-411941

INOVA-100 *mas100*

Relax. delay 1.000 sec

CGST 90-90

Acq. time 9.232 sec

Width 2202.2 Hz

2D Width 2202.2 Hz

3 repetitions

128 increments

OBSERVE M1, 299.9483273 MHz

DATA PROCESSING

Sine bell 0.116 sec

F1 DATA PROCESSING

Sine bell 0.031 sec

FT size 1024 x 1024

Total time 5 min. 28 sec

11c

STANDARD IS CHSEVVE

Pulse Sequence: relayph

Solvent: CDCl3

Ambient temperature

File: Ring-CHSEVVE11g1yCHSEVVE11m-conv-el195
INCHV-500 "g101"

Relax. Delay 1.000 sec

CHSEVVE 10-80

Acq. time 0.318 sec

Width 2043.5 Hz

2D Width 2043.5 Hz

4 repetitions

128 increments

CHSEVVE 10. 299.968375 MHz

DATA PROCESSING

Sine bell 0.109 sec

F1 DATA PROCESSING

Sine bell 0.021 sec

F2 size 1024 x 1024

Total time 10 min. 45 sec

STANDARD IN OBSERVE

Pulse Sequence: relayh
 Solvent: CDCl3
 Ambient temperature
 File: N001a01g-000p-01361r
 IN001a-303 "hmc200"

Relax. delay 1.800 sec
 CURE 90-90
 Acq. time 2.114 sec
 Width 1837.2 Hz
 2D Width 1837.2 Hz
 2 repetitions
 128 increments
 OBSERVE M1, 299.8624813 MHz
 DATA PROCESSING
 Slow ball 0.878 sec
 F1 DATA PROCESSING
 Slow ball 0.621 sec
 PT size 512 x 512
 Total time 5 min, 10 sec

Procedures of 13

CONVERTS M1

Pulse Sequence: relayh

Solvent: CDCl3

Ambient temperature

File: NMR-BocAlaAllylMlyCBO3MAL18u-004y-414481

INOVA-300 "nmr303"

Relax. delay 1.000 sec

COET 90-90

Acq. time 0.228 sec

Width 2192.9 Hz

2D Width 2192.9 Hz

8 repetitions

128 increments

CONVERT M1, 299.9483366 MHz

DATA PROCESSING

size 1024 x 1024

F1 DATA PROCESSING

size 1024 x 1024

FT size 1024 x 1024

Total time 21 min, 30 sec

Modeling data for 16

Materials and methods.

Cyclic sulfonamide **16** was modeled on a SGI O₂ workstation with MacroModel 7.0 [1] using the organic builder and the MMFF[2] forcefield. After construction, the structure was minimized on a SGI Origin200 server using Molecular Mechanics with the following settings:

MMFF (planar N's) [2]

PRCG [3]

CCrit 0.01 kJ/mol-Å [4]

iterations > max. [5]

[1] Mohamadi, F., Richards, N. G. J., Guida, W. C., Liskamp, R., Caufield, C., Chang, G., Hendrickson, T., and Still, W. C. (1990) *J. Comput. Chem.* **11**, 440–467

[2] MMFF94, or MMFF for short by Dr. Thomas A. Halgren. Volume 17 of *J. Comput. Chem.* (1996), issues 5-6, contain five articles introducing MMFF94.

[3] Conjugate gradient minimization using the Polak-Ribiere first derivative method with restarts every 3N iterations. Should not find saddle points. Best general minimization method for energy minimization. BatchMin code for carrying out this method is highly vectorized for efficient operation on vector hardware. E. Polak & G. Ribiere, *Revue Francaise Informat. Recherche Operationelle*, 16, 35 (1969).

[4] Convergence criterion - energy, movement or gradient. Default is gradient (first derivative RMS) convergence (criterion = 0.01 kJ/Å).

[5] Iterations/stop, sets the maximum number of iterations that BatchMin will use to energy minimize a structure.

Atom coordinates

79							E = -347.4	kJ/mol
2	2 2	6 1	10 1	0 0	0 0	0 0	-0.058608	-
0.482185	0.220874	0X	2	-0.00900	-0.00900	UNK		
2	1 2	3 1	40 1	0 0	0 0	0 0	-0.628669	-
0.158394	-1.022048	0X	2	-0.15000	-0.15000	UNK		
2	2 1	4 2	41 1	0 0	0 0	0 0	-1.279472	-
1.134415	-1.783141	0X	2	-0.15000	-0.15000	UNK		
2	3 2	5 1	42 1	0 0	0 0	0 0	-1.394817	-
2.437818	-1.303152	0X	2	-0.15000	-0.15000	UNK		
2	4 1	6 2	43 1	0 0	0 0	0 0	-0.867975	-
2.766157	-0.055491	0X	2	-0.15000	-0.15000	UNK		
2	1 1	5 2	7 1	0 0	0 0	0 0	-0.211427	-
1.781376	0.701086	0X	2	0.13300	0.13300	UNK		
25	6 1	8 2	9 2	0 0	0 0	0 0	0.296280	-
2.199088	1.987083	0X	4	0.90700	0.90700	UNK		
15	7 2	0 0	0 0	0 0	0 0	0 0	1.514468	-
2.395525	2.062768	0X	16	-0.52000	-0.52000	UNK		
15	7 2	0 0	0 0	0 0	0 0	0 0	-0.538063	-
2.421480	2.872351	0X	16	-0.52000	-0.52000	UNK		
49	1 1	11 1	20 2	21 2	0 0	0 0	0.670186	
0.824920	1.175826	0X	13	1.44700	1.44700	UNK		
25	10 1	12 1	19 1	0 0	0 0	0 0	2.303110	
0.862934	0.685716	0X	4	-0.84940	-0.84940	UNK		
3	11 1	13 1	22 1	44 1	0 0	0 0	3.326379	
1.506223	1.626399	0X	2	0.35570	0.35570	UNK		
3	12 1	14 1	45 1	46 1	0 0	0 0	3.757987	
0.444435	2.646574	0X	2	0.10520	0.10520	UNK		
49	13 1	15 1	26 2	27 2	0 0	0 0	5.399691	-
0.172783	2.260113	0X	13	1.33280	1.33280	UNK		
25	14 1	16 1	25 1	0 0	0 0	0 0	5.316089	-
0.518752	0.601081	0X	4	-0.84940	-0.84940	UNK		
3	15 1	17 1	47 1	48 1	0 0	0 0	4.295594	-
1.508423	0.211458	0X	2	0.49390	0.49390	UNK		
2	16 1	18 2	49 1	0 0	0 0	0 0	3.700979	-
1.158303	-1.120890	0X	2	-0.28820	-0.28820	UNK		
2	17 2	19 1	50 1	0 0	0 0	0 0	2.997349	-
0.072654	-1.493713	0X	2	-0.28820	-0.28820	UNK		
3	11 1	18 1	51 1	52 1	0 0	0 0	2.575598	
1.155367	-0.737487	0X	2	0.49390	0.49390	UNK		
15	10 2	0 0	0 0	0 0	0 0	0 0	0.040829	
2.053241	0.739441	0X	16	-0.65000	-0.65000	UNK		
15	10 2	0 0	0 0	0 0	0 0	0 0	0.621398	
0.442982	2.567540	0X	16	-0.65000	-0.65000	UNK		
3	12 1	23 1	24 1	53 1	0 0	0 0	2.857274	
2.863070	2.240355	0X	2	0.00000	0.00000	UNK		
3	22 1	54 1	55 1	56 1	0 0	0 0	2.668060	
3.938816	1.157459	0X	2	0.00000	0.00000	UNK		
3	22 1	57 1	58 1	59 1	0 0	0 0	3.864167	
3.428216	3.257168	0X	2	0.00000	0.00000	UNK		
3	15 1	32 1	28 1	60 1	0 0	0 0	6.616413	-
0.595778	-0.172940	0X	2	0.41670	0.41670	UNK		
15	14 2	0 0	0 0	0 0	0 0	0 0	6.308712	
0.936271	2.444387	0X	16	-0.65000	-0.65000	UNK		
15	14 2	0 0	0 0	0 0	0 0	0 0	5.593865	-
1.427770	2.953784	0X	16	-0.65000	-0.65000	UNK		
3	25 1	29 1	61 1	62 1	0 0	0 0	6.746042	
0.746051	-0.947346	0X	2	0.00000	0.00000	UNK		
3	28 1	30 1	31 1	63 1	0 0	0 0	7.441823	
0.676963	-2.326608	0X	2	0.00000	0.00000	UNK		

3	29	1	64	1	65	1	66	1	0	0	0	0	6.607256	-
0.086512	-3.357533				0X	2	0.00000	0.00000	UNK					
3	29	1	67	1	68	1	69	1	0	0	0	0	8.860302	
0.114898	-2.272872				0X	2	0.00000	0.00000	UNK					
2	25	1	34	1	33	2	0	0	0	0	0	0	7.886479	-
0.882244	0.674735				0X	2	0.56900	0.56900	UNK					
15	32	2	0	0	0	0	0	0	0	0	0	0	8.699709	
0.017504	0.910592				0X	16	-0.57000	-0.57000	UNK					
25	32	1	35	1	39	1	0	0	0	0	0	0	8.115205	-
2.171835	1.150437				0X	4	-0.66020	-0.66020	UNK					
3	34	1	36	1	70	1	71	1	0	0	0	0	7.345986	-
3.368334	0.821987				0X	2	0.30010	0.30010	UNK					
3	35	1	37	1	72	1	73	1	0	0	0	0	8.254591	-
4.557841	0.511787				0X	2	0.00000	0.00000	UNK					
3	36	1	38	1	74	1	75	1	0	0	0	0	9.279750	-
4.788642	1.616494				0X	2	0.00000	0.00000	UNK					
3	37	1	39	1	76	1	77	1	0	0	0	0	10.063209	-
3.508983	1.889073				0X	2	0.00000	0.00000	UNK					
3	34	1	38	1	78	1	79	1	0	0	0	0	9.122439	-
2.349503	2.198828				0X	2	0.30010	0.30010	UNK					
41	2	1	0	0	0	0	0	0	0	0	0	0	-0.588903	
0.860570	-1.404982				0X	21	0.15000	0.15000	UNK					
41	3	1	0	0	0	0	0	0	0	0	0	0	-1.713871	-
0.870987	-2.746029				0X	21	0.15000	0.15000	UNK					
41	4	1	0	0	0	0	0	0	0	0	0	0	-1.911359	-
3.192055	-1.893616				0X	21	0.15000	0.15000	UNK					
41	5	1	0	0	0	0	0	0	0	0	0	0	-0.979425	-
3.780024	0.325961				0X	21	0.15000	0.15000	UNK					
41	12	1	0	0	0	0	0	0	0	0	0	0	4.201159	
1.775084	1.021407				0X	21	0.00000	0.00000	UNK					
41	13	1	0	0	0	0	0	0	0	0	0	0	3.828783	
0.823456	3.667548				0X	21	0.00000	0.00000	UNK					
41	13	1	0	0	0	0	0	0	0	0	0	0	3.091506	-
0.417567	2.686951				0X	21	0.00000	0.00000	UNK					
41	16	1	0	0	0	0	0	0	0	0	0	0	4.726107	-
2.510847	0.163692				0X	21	0.00000	0.00000	UNK					
41	16	1	0	0	0	0	0	0	0	0	0	0	3.489794	-
1.579704	0.935920				0X	21	0.00000	0.00000	UNK					
41	17	1	0	0	0	0	0	0	0	0	0	0	3.873379	-
1.915262	-1.885970				0X	21	0.15000	0.15000	UNK					
41	18	1	0	0	0	0	0	0	0	0	0	0	2.689894	-
0.043818	-2.540329				0X	21	0.15000	0.15000	UNK					
41	19	1	0	0	0	0	0	0	0	0	0	0	1.682774	
1.567922	-1.217886				0X	21	0.00000	0.00000	UNK					
41	19	1	0	0	0	0	0	0	0	0	0	0	3.338759	
1.928885	-0.870475				0X	21	0.00000	0.00000	UNK					
41	22	1	0	0	0	0	0	0	0	0	0	0	1.906744	
2.736491	2.768162				0X	21	0.00000	0.00000	UNK					
41	23	1	0	0	0	0	0	0	0	0	0	0	2.318650	
4.877165	1.602507				0X	21	0.00000	0.00000	UNK					
41	23	1	0	0	0	0	0	0	0	0	0	0	3.611563	
4.146237	0.640265				0X	21	0.00000	0.00000	UNK					
41	23	1	0	0	0	0	0	0	0	0	0	0	1.933326	
3.651493	0.404131				0X	21	0.00000	0.00000	UNK					
41	24	1	0	0	0	0	0	0	0	0	0	0	3.579450	
4.440773	3.565228				0X	21	0.00000	0.00000	UNK					
41	24	1	0	0	0	0	0	0	0	0	0	0	3.904818	
2.829730	4.170667				0X	21	0.00000	0.00000	UNK					
41	24	1	0	0	0	0	0	0	0	0	0	0	4.871669	
3.479401	2.831115				0X	21	0.00000	0.00000	UNK					

41	25	1	0	0	0	0	0	0	0	0	0	6.537633	-
1.395795	-0.912130	0X	21	0.00000	0.00000	UNK							
41	28	1	0	0	0	0	0	0	0	0	0	5.749285	
1.173185	-1.115699	0X	21	0.00000	0.00000	UNK							
41	28	1	0	0	0	0	0	0	0	0	0	7.265658	
1.491388	-0.332032	0X	21	0.00000	0.00000	UNK							
41	29	1	0	0	0	0	0	0	0	0	0	7.518842	
1.711836	-2.687086	0X	21	0.00000	0.00000	UNK							
41	30	1	0	0	0	0	0	0	0	0	0	7.059143	-
0.004442	-4.352187	0X	21	0.00000	0.00000	UNK							
41	30	1	0	0	0	0	0	0	0	0	0	6.530548	-
1.151306	-3.118363	0X	21	0.00000	0.00000	UNK							
41	30	1	0	0	0	0	0	0	0	0	0	5.594913	
0.325056	-3.421489	0X	21	0.00000	0.00000	UNK							
41	31	1	0	0	0	0	0	0	0	0	0	9.338455	
0.187777	-3.255985	0X	21	0.00000	0.00000	UNK							
41	31	1	0	0	0	0	0	0	0	0	0	9.477600	
0.679518	-1.567349	0X	21	0.00000	0.00000	UNK							
41	31	1	0	0	0	0	0	0	0	0	0	8.870619	-
0.939918	-1.981412	0X	21	0.00000	0.00000	UNK							
41	35	1	0	0	0	0	0	0	0	0	0	6.700623	-
3.595220	1.677425	0X	21	0.00000	0.00000	UNK							
41	35	1	0	0	0	0	0	0	0	0	0	6.711987	-
3.204853	-0.046344	0X	21	0.00000	0.00000	UNK							
41	36	1	0	0	0	0	0	0	0	0	0	7.649471	-
5.459958	0.368997	0X	21	0.00000	0.00000	UNK							
41	36	1	0	0	0	0	0	0	0	0	0	8.782733	-
4.371053	-0.431928	0X	21	0.00000	0.00000	UNK							
41	37	1	0	0	0	0	0	0	0	0	0	8.769472	-
5.112102	2.531838	0X	21	0.00000	0.00000	UNK							
41	37	1	0	0	0	0	0	0	0	0	0	9.965985	-
5.592122	1.327170	0X	21	0.00000	0.00000	UNK							
41	38	1	0	0	0	0	0	0	0	0	0	10.751407	-
3.664900	2.727033	0X	21	0.00000	0.00000	UNK							
41	38	1	0	0	0	0	0	0	0	0	0	10.671042	-
3.261563	1.009908	0X	21	0.00000	0.00000	UNK							
41	39	1	0	0	0	0	0	0	0	0	0	8.579722	-
2.543026	3.132407	0X	21	0.00000	0.00000	UNK							
41	39	1	0	0	0	0	0	0	0	0	0	9.708811	-
1.439389	2.357735	0X	21	0.00000	0.00000	UNK							