Supplementary Material (ESI) for Green Chemistry

Electronic Supplementary Information

For

Cyclic Dipeptides: Catalyst/Promoter Free Rapid and Environmentally Benign Cyclization of Free Amino Acids

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CONTENTS:

General experimental details

The DKP derivatives are synthesized starting from commercial amino acids. The starting materials are obtained from the commercial sources glycine, L-alanine, D-alanine. L-valine, L-Leucine, L-tyrosine, L-proline, D-proline, trans-4-hydroxy-L-proline, (*S*)-(-)-indoline-2-carboxylic acid and racemic pipecolic acid (Aldrich). All the solvents used from crystallization are of HPLC grade obtained from J.T.Baker (acetonitrile, *N, N* -dimethylformamide). Crystallization experiments were carried out taking a known amount of the compound in respective solvent or mixture of solvents and heated over an oil bath until the mixture turned into a clear solution and allowed to stand at room temperature. The crystallized samples were separated by filtration. Compounds **1-13** were synthesized in single-mode CEM Discover microwave reactor operating at 2450 MHz using 10 ml pressure vessel. Reaction times vary from 8 min to 25 min and temperature from 200°C to 250°C with controlled pressure and power. Molecular masses of the compounds were confirmed either by using Micromass LCT ESI-TOF mass spectrometer in positive ion mode or by VG AutoSpec 3500 HR-MS EI/CI high resolution mass spectrometer. IR spectra were recorded on Bruker Tensor 27 FT-IR using Pike GladiATR attenuated total reflectance (ATR) cell equipped with a diamond crystal plate. Elemental analyses were carried out using Elementar Vario EL III -analysator

Solution NMR measurements

All the liquid state 1D NMR spectra (^{1}H, ^{13}C NMR) were recorded on a Bruker Avance DRX500 NMR spectrometer equipped with 5 mm dual direct detection BBO probehead operating at 500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C, respectively. The ^{1}H and ^{13}C NMR experiments were carried out at 303 K for sample solution in $CDCl_3$ (99.8 %, Aldrich) and ^{1}H the chemical shifts referenced to the trace of $CHCl_3$ (7.26 ppm from int. TMS) or in DMSO-d_6 (99.8 %, Aldrich) with ^{1}H the chemical shifts referenced to the trace of DMSO-d_5 (2.50 ppm from int. TMS). The number of scans was 8, a $\pi/2$

pulse length of 6.0 μs, the flip angle 30°, with recycle delay 2 s, and 64K data points in time domain was collected which was zero filled to 128 K prior to FT. The ^{13}C experiment was performed in composite pulse decoupling mode (waltz16) using a 30° flip angle. 400 scans were acquired with a recycle delay of 2 s. All the ^{13}C spectra were processed with 1 Hz line broadening prior to FT and the chemical shifts referenced to the center peak of DMSO-d_6 heptet (39.50 ppm from int. TMS).

Representative procedure for the synthesis of DKP.

Glycine (324 mg, 4.31 mmol) was taken in a 10 mL microwave reaction vessel and added DMF (2 mL) and subjected for microwave reaction in CEM discover microwave reactor. The pre-stiring time was set to 15 s and the set point temp (220 °C) with hold time of 10 min. The reaction mixture turned clear when the temperature of 220 °C was attained and after 5 min the clear solutions turned into pale yellow and the reaction was stopped. The precipitate obtained upon cooling the reaction mixture to room temperature was filtered and dried to yield 234 mg (95%) of **1**.

Single Crystal X-ray data:

The single crystal data were recorded with a Kappa APEX II diffractometer at –150 °C using graphite monochromatized Mo K_α (λ = 0.71073 Å; 55 kV, 30 mA) radiation. The data were processed with Denzo–SMN v0.97.638[1] and the absorption correction was performed using SADABS.[2] The structures were solved using direct methods (SIR2002[3] and/or SHELXS–97[4]) and refined on F^2 by full matrix least squares techniques (SHELXL–97[4]) using anisotropic displacement parameters for non–hydrogen atoms. Compound dependently hydrogen atoms were either calculated to their positions as riding atoms or taken from the electron density map using isotropic displacement parameters, that were fixed to be 1.2– 1.5 times larger than those of the attached non–hydrogen atom. The program Mercury[5] was used for depicting the crystal structures. The determined crystal structures were compared to the formerly reported structures (when available) in Cambridge structural database (v 5.30+ 2009 updates).[6]

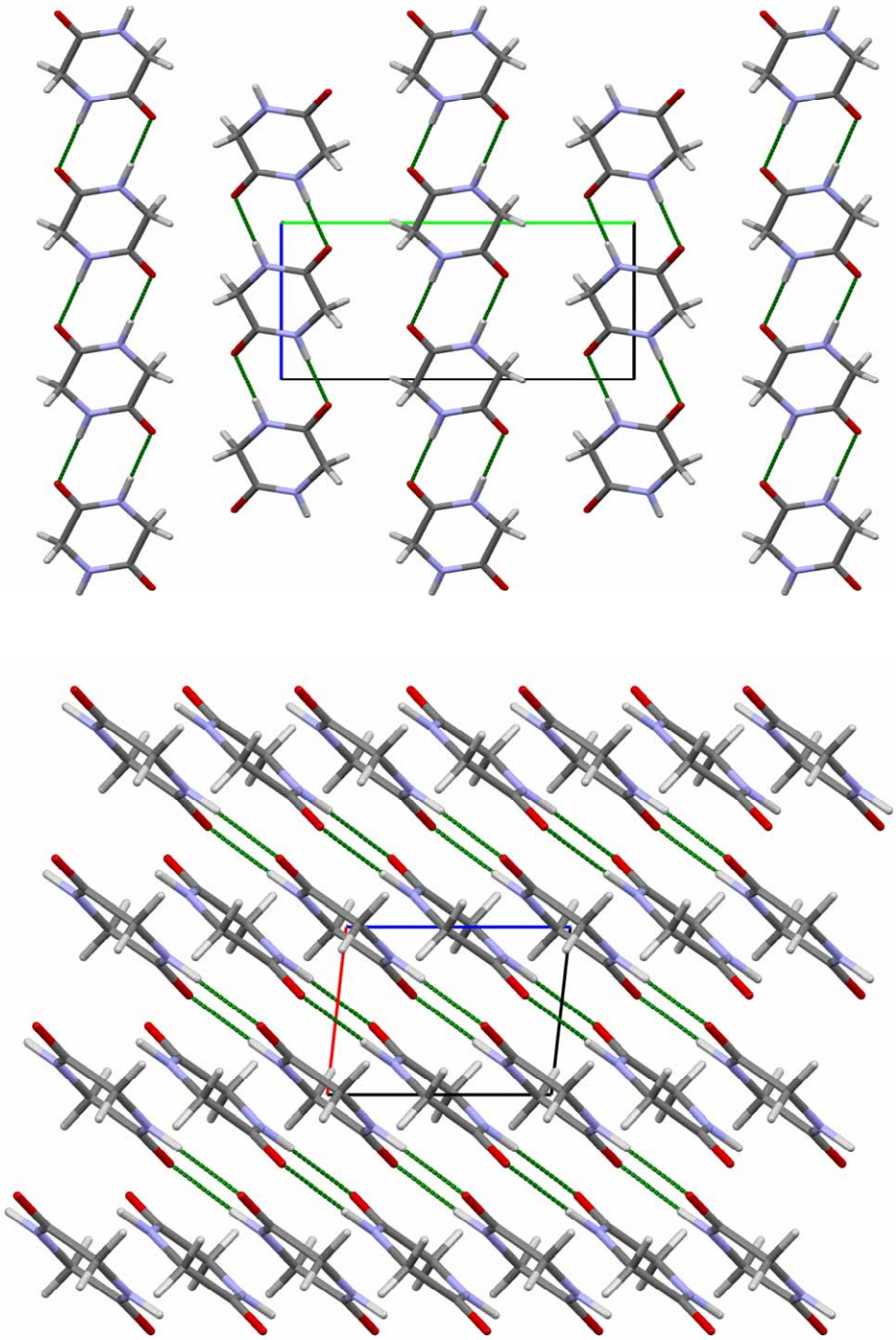

Figure S1. Molecular packing of compound **1** along *a*- (top) and *b*-axis (below). Hydrogen bonding network is shown by dashed green lines.

Table S1. Crystallographic data for compound **1**

Compound	**1**
Formula	$C_4 H_6 N_2 O_2$
MW (g mol^{-1})	114.11
Temp (K)	123±2
Crystal system	Monoclinic
Space group	$P2_1/c$ (No. 14)
a (Å)	3.9045(4)
b (Å)	11.5645(17)
c (Å)	5.1679(7)
β (°)	96.461(8)
V ($Å^3$)	231.87(5)
Z	2
ρ_{calcd} (g cm^{-3})	1.634
μ (mm^{-1})	0.133
F (000)	120
Crystal size (mm^3)	0.24 x 0.24 x 0.30
θ range (deg)	3.52 to 28.50°
Reflections collected	1467
Independent reflections	570
Data/restraints/parameters	570 / 0 / 41
GooF	1.083
R (int)	0.0258
Final R indices [I>2σ(I)]	R_1 = 0.0367
	wR^2 = 0.0852
R indices (all data)	R_1 = 0.0417
	wR^2 = 0.0885
Largest diff. peak/hole (e $Å^{-3}$)	0.28 and -0.20

Table S2. Selected bond distances (Å) and angles (°) and torsion angles for **1**

Compound	**1**
O(1)-C(2)	1.2465(15)
C(4)-N(3)#1	1.4556(15)
C(4)-C(2)	1.5044(17)
C(2)-N(3)	1.3273(17)
N(3)#1-C(4)-C(2)	114.61(10)
O(1)-C(2)-N(3)	122.53(12)
O(1)-C(2)-C(4)	118.31(11)
O(1)-C(2)-N(3)-C(4)#1	-178.36(12)

For **1** (#1) -x+2,-y,-z+1

Table S3. Hydrogen bond distances (Å) and angles (°) for **1**

D-H…A	**d(D-H)**	**d(H…A)**	**d(D…A)**	**<(DHA)**
		1		
N(3)-H(3)...O(1)#2	0.890(16)	1.958(16)	2.8469(15)	177.6(13)
C(4)-H(4B)...O(1)#3	0.9900	2.5100	3.2781(16)	134.00

For **1** (#2) -x+1,-y,-z (#3) x,-y-1/2,z-1/2

Table S4. Crystallographic data for compounds **9**, **11–13.**

Compound	**9**	**11**	**12**	**13**
Formula	$C_{10}H_{14}N_2O_4 \times 2H_2O$	$C_{18}H_{14}N_2O_2$	$C_7H_{10}N_2O_2$	$C_{12}H_{18}N_2O_2$
MW (g mol^{-1})	262.26	290.31	154.17	222.28
Chiral properties	L-form	Racemic	L-form	*meso*
Temp (K)	123±2	123±2	123±2	123±2
Crystal system	Orthorhombic	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$ (No. 19)	$P\ 2_1/c$ (No. 14)	$P2_12_12_1$ (No. 19)	$P2_1$/c (No. 14)
a (Å)	7.7534(16)	10.5612(14)	5.8353(3)	6.0475(7)
b (Å)	8.0651(16)	8.4166(5)	9.6510(6)	7.8473(10)
c (Å)	18.818(4)	15.8706(19)	12.8178(10)	11.2904(12)
β (°)	90	107.860(4)	90	97.541(7)
V (Å^3)	1176.7(4)	1342.7(3)	721.85(8)	531.17(11)
Z	4	4	4	2
ρ_{calcd} (g cm^{-3})	1.480	1.436	1.419	1.390
μ (mm^{-1})	0.123	0.095	0.106	0.095
F (000)	560	608	328	240
Crystal size (mm^3)	0.12 x 0.23 x 0.24	0.08 x 0.12 x 0.36	0.24 x 0.32 x 0.36	0.20x0.28 x0.30
θ range (deg)	2.75 to 28.31	3.84 to 26.00	3.82 to 28.26	3.17 to 28.53
Reflections collected	9344	7809	4138	2989
Independent reflections	2893	2627	1777	1334
Data/restraints /parameters	2893 / 0 / 187	2627 / 0 / 200	1777 / 0 / 140	1334 / 0 / 73
GooF	1.035	1.034	1.073	1.056
R (int)	0.0428	0.1095	0.0434	0.0462
Final R indices [I>2σ(I)]	R1 = 0.0429 wR2 = 0.0841	R1 = 0.0734 wR2 = 0.1142	R1 = 0.0476 wR2 = 0.0991	R1 = 0.0637 wR2 = 0.1325
R indices (all data)	R1 = 0.0557 wR2 = 0.0881	R1 = 0.1714 wR2 = 0.1447	R1 = 0.0637 wR2 = 0.1064	R1 = 0.0985 wR2 = 0.1458
Largest diff. peak/hole (e Å^{-3})	0.25 and -0.19	0.30 and -0.26	0.198 and -0.25	0.33 and -0.24
CCDC	783550	783551	783552	783553

Table S5. Selected bond lengths (Å) and angles (deg), as well as torsion angles (deg) with e.s.d.s for compounds **9**, **11-13**.

Compound	**9**	**11**	**12**	**13**
C(1)-O(1)	1.242(2)	1.227(4)	1.245(2)	1.230(2
C(4)-O(2)	1.241(2)	1.226(4)	1.235(2)	–
C(1)-N(2)	1.326(2)	1.346(5)	1.326(3)	1.339(3)
C(4)-N(5)	1.329(2)	1.350(5)	1.342(3)	–
C(3)-C(4)	1.513(3)	1.513(5)	1.508(3)	–
C(1)-C(6)	1.515(2)	1.516(5)	1.510(3)	–
C(1)-C(2)	–	–	–	1.521(3)
C(3)-N(2)	1.479(2)	1.484(4)	1.472(3)	–
N(2)-C(2)#1	–	–	–	1.465(3)
O(1)-C(1)-N(2)	122.79(17)	125.4(4)	123.15(19)	123.58(18)
O(1)-C(1)-C(6)	122.13(15)	121.9(4)	122.22(18)	–
O(1)-C(1)-C(2)	–	–	–	117.75(18)
N(2)-C(1)-C(6)	115.05(15)	112.8(3)	114.63(18)	–
N(2)-C(1)-C(2)	–	–	–	118.65(17)
N(2)-C(3)-C(4)	112.55(13)	111.5(3)	110.17(16)	–
N(2)#1-C(2)-C(1)	–	–	–	115.14(16)
O(2)-C(4)-N(5)	123.13(18)	124.8(3)	123.5(2)	–
O(2)-C(4)-C(3)	121.07(15)	122.1(3)	122.5(2)	–
N(5)-C(4)-C(3)	115.80(15)	113.0(3)	113.95(17)	–
N(2)-C(3)-C(4)-O(2)	-151.93(16)	-143.3(3)	141.4(2)	
N(2)-C(3)-C(4)-N(5)	28.6(2)	39.2(4)	-38.7(2)	
O(1)-C(1)-C(6)-N(5)	-145.18(17)	-143.6(3)	147.3(2)	
C(13)-C(3)-C(4)-N(5)	–	158.7(3)	–	
C(9)-C(3)-C(4)-N(5)	144.20(17)	–	155.78(19)	
O(1)-C(1)-N(2)-C(7)	6.5(3)	-1.2(6)	2.3(3)	–
O(1)-C(1)-C(2)-N(2)#1	–	–	–	175.44(19)
O(1)-C(1)-C(2)-C(3)	–	–	–	-60.5(2)
O(1)-C(1)-N(2)-C(6)#1	–	–	–	-0.5(3)

For **13**: (#1) -x,-y+1,-z+1

Table S6. Hydrogen bond distances (Å) and angles (°) of compound **9**, **11-13.**

D-H…A	d(D-H)	d(H…A)	d(D…A)	<(DHA)
		9		
O(5W)-H(5AW)...O(6W)	0.87(3)	1.93(3)	2.798(2)	177(3)
O(5W)-H(5BW)...O(2)#1	0.89(3)	1.90(3)	2.790(2)	177(3)
O(6W)-H(6AW)...O(1)#2	0.95(3)	1.74(3)	2.679(2)	170(2)
O(3)-H(3H)...O(5W)#3	0.85(3)	1.96(3)	2.807(2)	173(3)
O(6W)-H(6BW)...O(4)#4	0.86(3)	1.86(3)	2.715(2)	174(3)
O(4)-H(4H)...O(6W)#2	0.91(3)	1.82(3)	2.718(2)	167(3)
C(3)-H(3)...O(2)#5	1.0000	2.3500	3.208(2)	144.00
C(7)-H(7A)...O(3)#6	0.9900	2.5300	3.477(3)	161.00
		11		
C(3)-H(3)...O(1)#1	1.0000	2.4500	3.222(5)	134.00
C(3)-H(3)...O(2)#2	1.0000	2.4900	3.245(5)	132.00
C(8)-H(8)...O(1)	0.9500	2.4500	2.991(6)	116.00
C(8)-H(8)...O(2)#3	0.9500	2.5800	3.345(5)	138.00
C(15)-H(15)...O(1)#4	0.9500	2.3800	3.220(5)	147.00
C(15)-H(15)...O(2)	0.9500	2.4700	3.006(5)	116.00
		12		
N(5)-H(5)...O(1)#1	0.86(3)	1.96(2)	2.815(2)	175(3)
C(3)-H(3)...O(1)#2	0.95(2)	2.55(2)	3.205(3)	126.2(15)
C(6)-H(6A)...O(2)#3	0.98(2)	2.52(3)	3.478(3)	166(2)
		13		
C(6)-H(6A)...O(1)	0.9900	2.3500	2.769(3)	105.00
C(6)-H(6B)...O(1)#2	0.9900	2.4900	3.468(3)	169.00

For **9**: (#1) -x-1,y+1/2,-z+1/2; (#2) x+3/2,-y+1/2,-z; (#3) -x,y-1/2,-z+1/2; (#4) x-1,y,z #5 -x,y+1/2,-z+1/2 #6 -x-1,y-1/2,-z+1/2; For **11**: (#1) -x+1,y+1/2,-z+1/2; (#2) -x+1,y-1/2,-z+1/2; (#3) x,y-1,z; (#4) x,y+1,z; For **12**: (#1) x+5/2,-y+1/2,-z; (#2) x+3/2,-y+1/2,-z; (#3) x+5/2,-y-1/2,-z; For **13**: (#1) -x,-y+1,-z+1; (#2) -x+2,y-1/2,-z-1/2;

Figure S2. Overlay of molecular conformations of compound **11** and enantiopure structure form COSGEX found in CSD

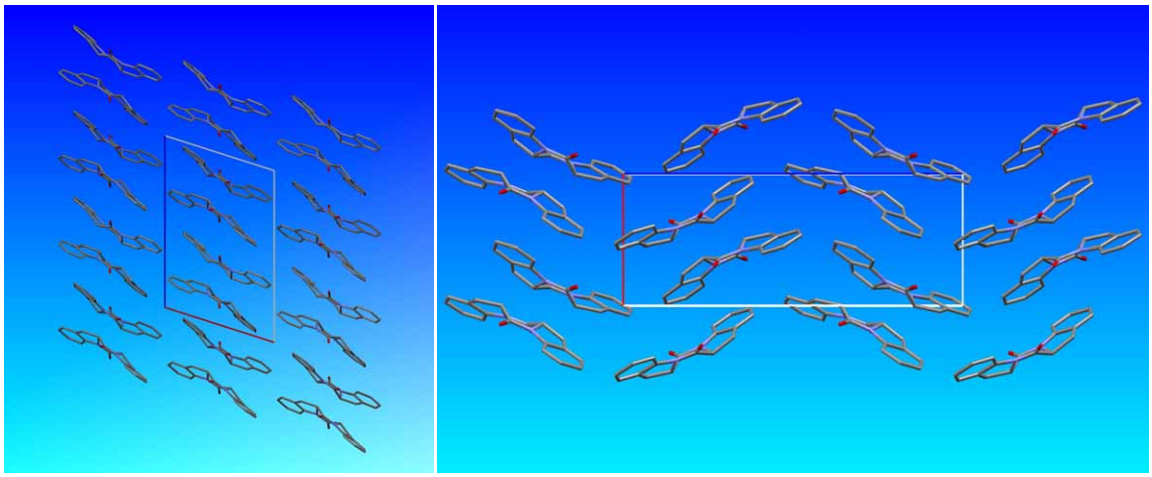

Figure S3. Molecular packing of compound **11** (left) and CSD entry COSGEX (right) viewed along *b*-axis. Hydrogen atoms are omitted for clarity.

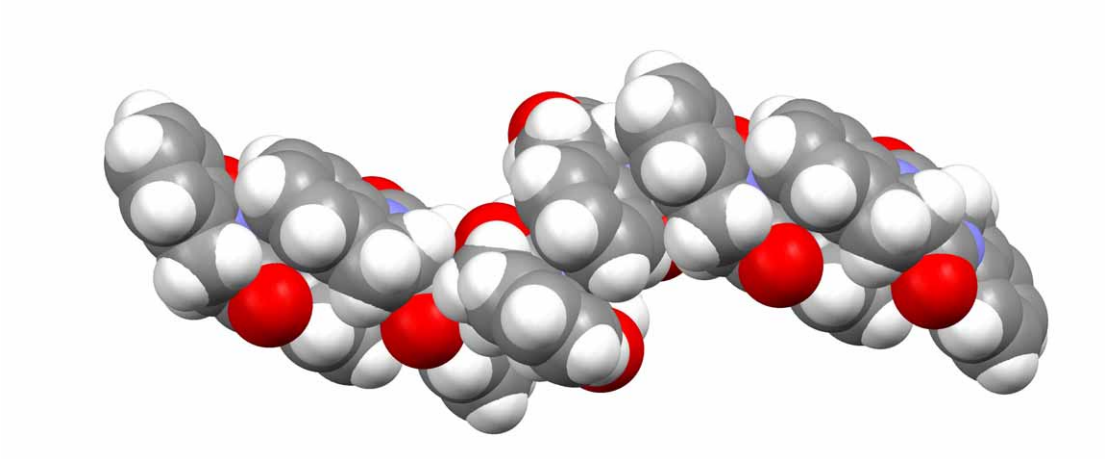

Figure S4. Repeating unit of compound **11.** The two molecules in the middle are pointing towards the viewer and are facing each other.

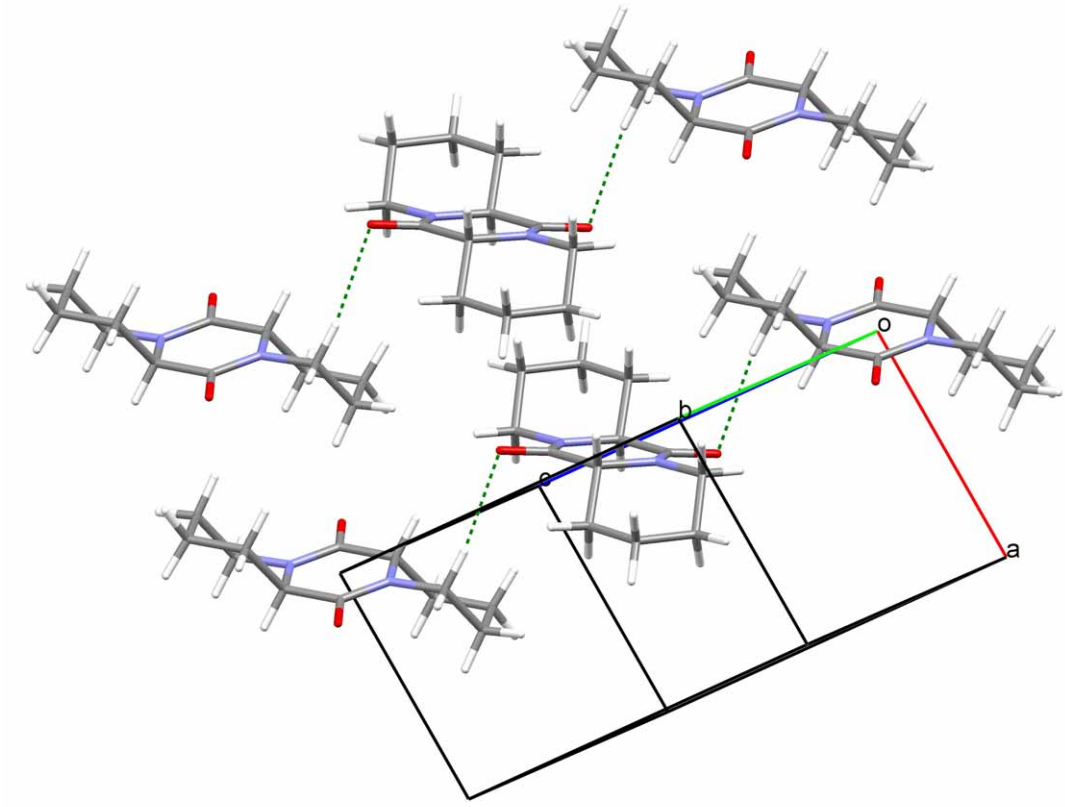

Figure S5. Weak hydrogen bonding network in compound **13**.

Spectral data and microwave reaction profiles of DKP derivatives

2,5-diketopiperazine (1): Scale (324 mg, 4.31 mmol): yield (234 mg mg, 95%); m.p.: 298-301 ^{o}C; ^{1}H NMR (500 MHz, D_2O) δ 3.56 (s, CH_2) ppm; ^{13}C NMR (126 MHz, D_2O) δ 168.47, 43.84 ppm. IR (solid)ν 3040, 2983, 2913, 1667, 1466, 1437, 1336, 1249, 1072, 829, 804 cm^{-1}; HRMAS (*m/z*) calcd for $C_4H_6N_2O_2$ $[M+H]^+$,115.1106; found, 115.9878.

Type: Dynamic

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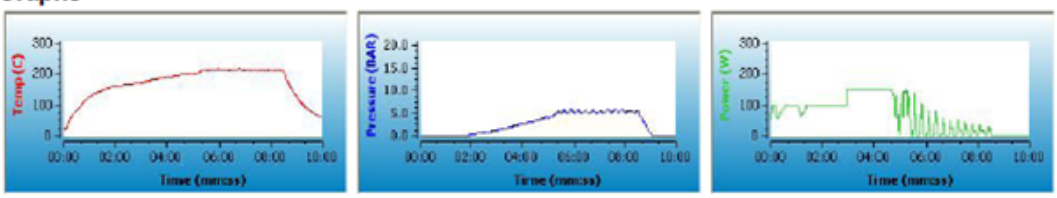
Graphs



Method Summary

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HOT KEY: Changed power from 100 W to 150 W	10/5/2009 1:43:00 PM
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HOT KEY: Changed temp from 200 C to 210 C	10/5/2009 1:45:09 PM
HOT KEY: Changed time from 17:52 to 04:00	10/5/2009 1:46:54 PM
HOT KEY: Changed time from 02:49 to 01:00	10/5/2009 1:48:06 PM
HOT KEY: Changed time from 00:44 to 00:10	10/5/2009 1:48:23 PM
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Cooling/Reaction ended:	10/5/2009 1:50:02 PM

Reaction Completed Successfully!

Maximum temperature:	215 C
Maximum pressure:	6 BAR
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Time at setpoint:	03:49 mm:ss
Time cooling:	01:28 mm:ss

***rac*-3,6-dimethylpiperazine-2,5-dione (2 & 3):** Scale (330 mg, 3.7 mmol); yield (245 mg, 93%); m.p: 260-263 ^{o}C; ^{1}H NMR (500 MHz, D_2O)δ 4.27(q, J = 13.6 Hz, 1H), 4.23 (q, J = 13.5 Hz, 1H), 1.55 (d, J = 6.97 Hz, 3H), 1.52 (d, J = 6.97 Hz, 3H) ppm; ^{13}C NMR (126 MHz, D_2O) δ 171.38, 171.34, 50.42, 50.25, 19.41, 18.33 ppm; IR(solid)ν 3049, 2975, 1688, 1667, 1620, 1590, 1330, 1128, 848 cm^{-1}; HRMAS (*m/z*): calcd for $C_6H_{10}N_2O_2$, $[M+H]^+$: 143.0820; found, 143.085; analysis calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. found C, 50.60; H, 7.12; N, 19.02.

Type: Dynamic

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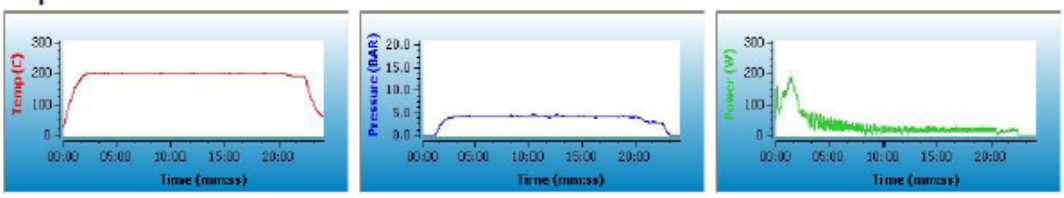
Graphs



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Cooling/Reaction ended:	7/15/2009 10:56:23 AM

Reaction Completed Successfully!

Maximum temperature:	202 C
Maximum pressure:	5 BAR
Time to obtain setpoint:	02:31 mm:ss
Time at setpoint:	20:01 mm:ss
Time cooling:	01:40 mm:ss

***rac*-3,6-diisopropylpiperazine-2,5-dione (4)**: Scale (340 mg, 2.90 mmol); yield (262 mg, 91%); m.p.:259-263 ^{o}C ^{1}H NMR (500 MHz, CD_3OD)δ 3.84 (d, J = 3.0 Hz, 2H), 2.36-2.27 (m, 2H), 1.04 (d, J = 7.5 Hz, 6H), 0.95 (d, J = 7.0 Hz, 6H) ppm; ^{13}C NMR (126 MHz, CD_3OD) δ 171.41, 61.85, 34.61, 19.57, 17.68 ppm; IR (solid) ν 3188, 2964, 1664, 1450, 1349 cm-^{1}; HRMS (*m/z*) calcd for $C_{10}H_{18}N_2O_2$[M.CH_3OH+Na]$^{+}$ 253.1528; found 253.087; analysis calc. for $C_{10}H_{18}N_2O_2$.1/2H_2O: C, 57.95; H, 9.24; N, 13.52. found C, 57.94; H,8.91 ; N, 13.69.

Type: Dynamic

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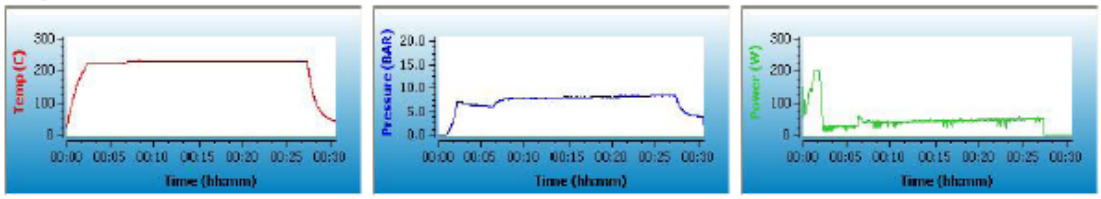
Graphs



Method Summary

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Reaction Completed Successfully!

Maximum temperature:	231 C
Maximum pressure:	9 BAR
Time to obtain setpoint:	02:18 mm:ss
Time at setpoint:	25:02 mm:ss
Time cooling:	03:13 mm:ss

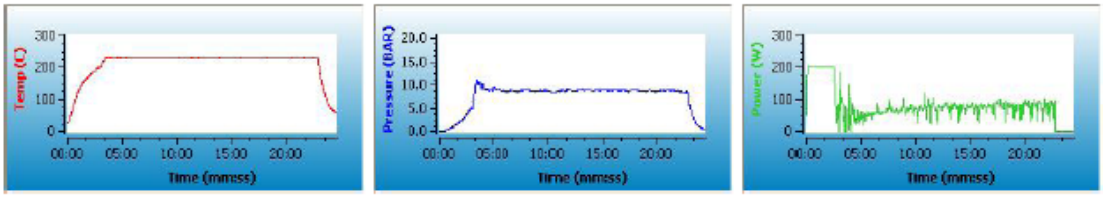
***rac*-cyclo(leucyl-leucine) (5)**: Scale (580 mg, 4.42 mmol); yield (468 mg, 93%); m.p.: 270-272 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (br s, 1H,), 6.49 (br s, 1H), 3.99 (br s,

1H), 3.97 (m, 1H), 2.16 (s,1H), 1.88-1.75 (br m, 4H) 1.67-1.59 (br m, 2H), 0.99 (d, 6H), 0.99 (dd, 2.17, J = 6.27 Hz, 6H), 0.95 (d, 6.27) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.98, 168.86, 53.35, 53.18, 43.39, 42.11, 24.30, 24.22, 23.22, 23.13, 21.30, 21.15 ppm; IR (solid) ν 3088, 2974, 1655, 1445, 1291 cm-^{1}; HRMS (*m/z*) calcd for $C_{12}H_{22}N_2O_2$ $[M.CH_3OH+Na]^+$ 281.1841; found 281.090; analysis calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H 9.80; N 12.38. found C, 63.27; H, 9.58; N, 12.40.

Type: Dynamic

Stage	Temp(C)	Time(mm:ss)	Pressure(BAR)	Power(W)	PowerMAX	Stirring
1	200	20:00	17.2	200	No	High

Graphs



Method Summary

Reaction started:	7/22/2009 9:53:04 AM
Temperature setpoint reached:	7/22/2009 9:55:47 AM
HOT KEY: Changed temp from 200 C to 230 C	7/22/2009 9:56:07 AM
Reaction cooling started:	7/22/2009 10:15:48 AM
Cooling/Reaction ended:	7/22/2009 10:17:31 AM

Reaction Completed Successfully!

Maximum temperature:	235 C
Maximum pressure:	11 BAR
Time to obtain setpoint:	02:43 mm:ss
Time at setpoint:	20:01 mm:ss
Time cooling:	01:43 mm:ss

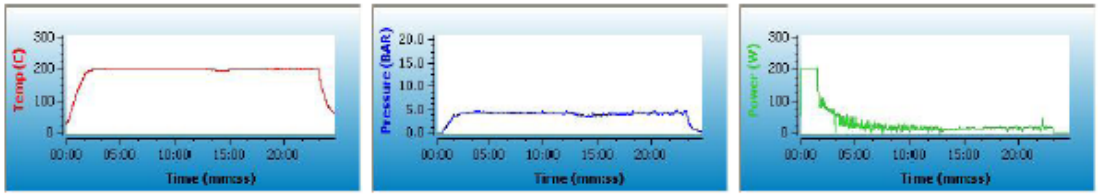
***rac*-cyclo(tyrosyl-tyrosine) (5)**: Scale (296 mg, 1.63 mmol); yield (231mg, 88%); m.p.: 279-280 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 2H), 7.87 (s, 2H), 6.90 (d, J = 8.30Hz, 2H), 6.61(d, J = 8.30 Hz, 2H), 2.88(dd, J = 3.30, 13.70 Hz, 2H), 2.60(dd, J =

4.60, 13.75 Hz, 2H) ppm; ^{1}H NMR (500 MHz, DMSO-d_6 +D_2O) δ 6.89 (d, J = 8.35 Hz), 6.61(d, J = 8.35 Hz), 3.29 (t, J = 3.75 Hz), 2.89 (dd, J = 3.30, 14.0Hz), 2.60 (dd, J = 4.74, 14.0 Hz) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.96, 155.99, 130.97, 125.79, 114.73, 54.78, 36.94 ppm; IR (solid) ν 3229, 3021, 2956, 2923, 1660, 1608, 1593, 1507, 1450, 1360, 1235, 1113, cm^{-1}; HRMS (*m/z*) calcd for $C_{18}H_{18}N_2O_4$ $[M+Na]^+$ 349.1164; found, 349.1162; analysis calcd. for $C_{18}H_{18}N_2O_4.H_2O$: C, 62.78; H, 5.85; N 8.13. found C, 62.99; H, 5.93; N, 8.99.

Type: Dynamic

Stage	Temp(C)	Time(mm:ss)	Pressure(BAR)	Power(W)	PowerMAX	Stirring
1	200	20:00	17.2	200	No	High

Graphs



Method Summary

Reaction started:	7/17/2009 11:04:53 AM
Temperature setpoint reached:	7/17/2009 11:08:03 AM
HOT KEY: Changed stirring from High to Medium	7/17/2009 11:09:53 AM
HOT KEY: Changed stirring from Medium to High	7/17/2009 11:12:23 AM
Reaction cooling started:	7/17/2009 11:28:05 AM
Cooling/Reaction ended:	7/17/2009 11:29:35 AM

Reaction Completed Successfully!

Maximum temperature:	202 C
Maximum pressure:	5 BAR
Time to obtain setpoint:	03:10 mm:ss
Time at setpoint:	20:02 mm:ss
Time cooling:	01:30 mm:ss

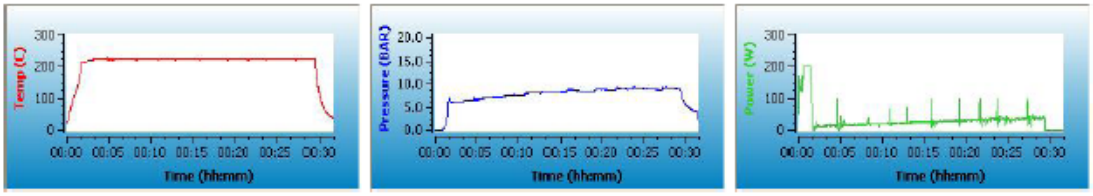
***rac*-octahydrodipyrrolo[1,2-*a*:1′,2-*d*]pyrazine-5,10-dione (7 & 8)):** Scale (250 mg, 2.17 mmol); yield (203 mg, 96%); m .p.:146-148 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16

(t, J = 8.13 Hz, 2H, 5a-H, 10a-H), 3.57-3.49 (m, 4H, 3-CH_2, 8-CH_2), 2.34-2.28 (m, 2H, CH_2), 2.22-2.14 (m, 2H, CH_2), 2.05-1.98 (m, 2H, CH_2), 1.95-1.86 (m, 4H, 2 x CH_2) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.37, 60.54, 45.20, 27.68, 23.34 ppm. IR (solid) ν 2990, 2957, 2877, 1643, 1426, 1334, 1293, 1271, 1150, 875 cm^{-1}; HRMS (*m/z*) calcd for $C_{10}H_{14}N_2O_2$ $[M+H]^+$ 195.1133; found, 195.109; analysis calcd. for $C_{10}H_{14}N_2O_2$: C 61.84; H 7.27; N 14.42. found C, 61.03; H, 7.12; N, 14.26.

Type: Dynamic

Stage	Temp(C)	Time(mm:ss)	Pressure(BAR)	Power(W)	PowerMAX	Stirring
1	220	25:00	17.0	200	No	High

Graphs



Method Summary

Reaction started:	8/11/2009 11:14:26 AM
HOT KEY: Changed temp from 220 C to 230 C	8/11/2009 11:16:25 AM
HOT KEY: Changed temp from 230 C to 225 C	8/11/2009 11:18:45 AM
Temperature setpoint reached:	8/11/2009 11:18:46 AM
HOT KEY: Changed power from 200 W to 100 W	8/11/2009 11:19:07 AM
Reaction cooling started:	8/11/2009 11:43:48 AM
Cooling/Reaction ended:	8/11/2009 11:46:02 AM

Reaction Completed Successfully!

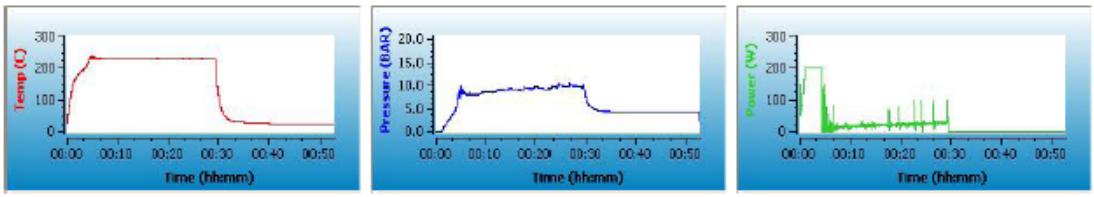
Maximum temperature:	228 C
Maximum pressure:	10 BAR
Time to obtain setpoint:	04:20 mm:ss
Time at setpoint:	25:02 mm:ss
Time cooling:	02:14 mm:ss

(2*R*,4*S*,7*R*,9*S*)-2,7-dihydroxyoctahydrodipyrrolo[1,2-*a*:1′,2′-*d*]pyrazine-5,10-dione (9): Scale (310 mg, 2.36 mmol); yield (257 mg, 96%); m.p.: 243-245 ^{o}C; $[\alpha]^{D}_{25}$ (deg cm^3 g^{-1} dm^{-1}) = -152 (c = 2.0 g cm^{-3} in H_2O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 5.10(br s), 4.51 (dd, J = 6.72, 10.52 Hz), 4.30 (br s), 3.47 (dd, J = 4.37, 12.27), 3.20 (d, J = 12.35 Hz), 2.06 (d, J = 6.75 Hz), 2.04 (d, J = 6.65 Hz), 1.97 (d, J = 4.20 Hz), 1.95 (dd, J = 2.30, 4.50 Hz), 1.93 (d, J = 4.30 Hz) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.30, 67.42, 58.29, 53.38, 36.41 ppm; IR (solid) ν 3401, 3287, 3193, 2965, 2867, 1634, 1464, 1436, 968 cm^{-1}; HRMAS (m/z) calcd for $C_{10}H_{14}N_2O_4$ $[M+Na]^+$ 249.1578; found, 249.0829; analysis calcd. for $C_{10}H_{14}N_2O_4.2H_2O$: C, 45.79; H, 6.91; N 10.68. found C, 45.30; H, 6.74; N, 10.68.

Type: Dynamic

Stage	Temp(C)	Time(mm:ss)	Pressure(BAR)	Power(W)	PowerMAX	Stirring
1	220	25:00	17.2	200	No	High

Graphs



Method Summary

Reaction started:	8/11/2009 11:48:07 AM
HOT KEY: Changed temp from 220 C to 220 C	8/11/2009 11:51:18 AM
HOT KEY: Changed temp from 220 C to 230 C	8/11/2009 11:52:13 AM
Temperature setpoint reached:	8/11/2009 11:52:30 AM
HOT KEY: Changed power from 200 W to 150 W	8/11/2009 11:53:04 AM
HOT KEY: Changed power from 150 W to 100 W	8/11/2009 11:54:17 AM
Reaction cooling started:	8/11/2009 12:17:32 PM
Cooling/Reaction ended:	8/11/2009 12:41:17 PM

Reaction Completed Successfully!

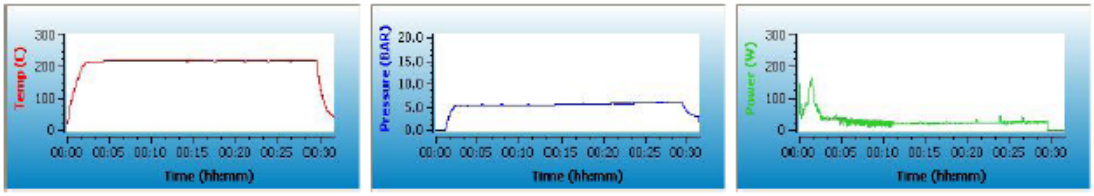
Maximum temperature:	241 C
Maximum pressure:	11 BAR
Time to obtain setpoint:	04:23 mm:ss
Time at setpoint:	25:02 mm:ss
Time cooling:	23:45 mm:ss

(6a,7,13a,14)-tetrahydropyrazino[1,2-*a*:4,5-*a*′]diindol-6,13-dione (11): Scale (190 mg, 1.16); yield (160 mg, 94%); m.p.:250-252 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, J = 7.71 Hz, 2H, 2,9-H), 7.35 (d, J = 7.52 Hz, 1H), 7.25 (t, J = 8.0 Hz, 4H, 3,4,10,11-H), 7.10 (dt, J = 1.06, 7.47 Hz, 2H, 1,8-H), 5.33 (dd, J = 8.8, 16.9 Hz, 2H, 6a, 13a-H), 3.58 (dd, J = 8.8, 16.8 Hz, 2H, 7,14-H), 3.43 (dd, J= 8.8, 16.8 Hz, 2H, 7,14-H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.69, 140.37, 130.09, 127.38, 125.25, 124.36, 114.58, 60.98, 29.14 ppm; IR (solid) ν 3344, 3069, 3050, 2898, 2863, 1793, 1681, 1603, 1483,1462, 1446, 1343, 1315, 1245 776 cm^{-1}; HRMAS: calcd for $C_{18}H_{14}N_2O_2$ $[M+Na]^+$ 313.0952; found, 313.0945; analysis calcd. for $C_{18}H_{14}N_2O_2$): C,74.47; H, 4.86; N 9.65. found C, 74.32; H, 4.69; N, 9.64.

Type: Dynamic

Stage	Temp(C)	Time(mm:ss)	Pressure(BAR)	Power(W)	PowerMAX	Stirring
1	220	25:00	17.2	200	No	High

Graphs



Method Summary

Reaction started:	8/17/2009 11:09:17 AM
Temperature setpoint reached:	8/17/2009 11:13:41 AM
Reaction cooling started:	8/17/2009 11:38:42 AM
Cooling/Reaction ended:	8/17/2009 11:40:47 AM

Reaction Completed Successfully!

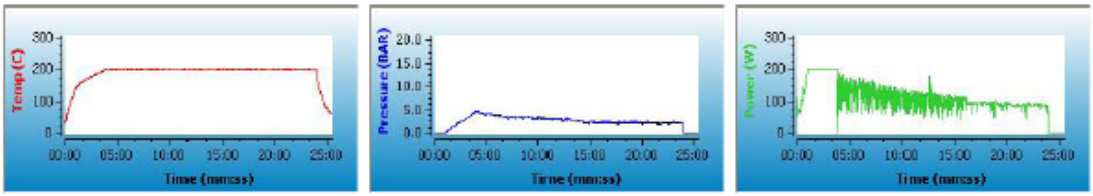
Maximum temperature:	221 C
Maximum pressure:	6 BAR
Time to obtain setpoint:	04:24 mm:ss
Time at setpoint:	25:01 mm:ss
Time cooling:	02:05 mm:ss

(*R*)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (12): Scale (210 mg, 1.22 mmol); yield (186 mg, 99%); m.p.:188-190 ^{o}C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.03 (br s, 1H), 4.11 (t, J = 7.25 Hz, 1H), 3.98(dd, J = 16.4 Hz, 1.05 Hz). 3.50 (dd, 1H), 3.34-3.39 (m, 1H), 3.35-3-31(m, 1H), 2.15-2.10 (m, 1H), 1.87-1.77 (m, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.14, 163.72, 57.89, 45.82, 44.53, 27.75, 21.95 ppm; IR (solid) ν 3162, 2877, 1673, 1643, 1453, 1293, 1111, 1003, 779 cm^{-1}; HRMS calcd for $C_7H_{10}N_2O_2$ $[M+H]^+$ 155.0820; found, 155.053; analysis calcd. for $C_7H_{10}N_2O_2$): C, 54.54; H, 6.54, N,18.17. found C, 54.00; H, 6.38; N, 18.17.

Type: Dynamic

Stage	Temp(C)	Time(mm:ss)	Pressure(BAR)	Power(W)	PowerMAX	Stirring
1	200	20:00	17.2	200	No	High

Graphs



Method Summary

Reaction started:	10/5/2009 2:21:38 PM
Temperature setpoint reached:	10/5/2009 2:25:31 PM
Reaction cooling started:	10/5/2009 2:45:32 PM
Cooling/Reaction ended:	10/5/2009 2:47:06 PM

Reaction Completed Successfully!

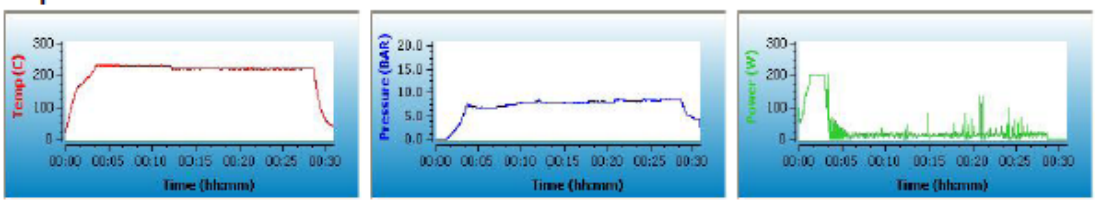
Maximum temperature:	201 C
Maximum pressure:	5 BAR
Time to obtain setpoint:	03:53 mm:ss
Time at setpoint:	20:01 mm:ss
Time cooling:	01:34 mm:ss

(6a*R*, 12a*S*)-octahydrodipyrido[1,2-a:1′,2′-*d*]pyrazine-6,12(2*H*, 6a*H*)-dione (13): Scale (232 mg, 1.79 mmol); yield (185 mg, 93%); m.p.: 245-247 ^{o}C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.70 (t, *J* = 2.05 Hz, 1H), 4.67 (t, *J* = 2.25 Hz, 1H), 3.82 (d, *J* = 2.4Hz, 1H), 3.80 (d, *J* = 1.95Hz, 1H), 2.48(dt, *J* = 13.05 Hz, 3.05 Hz), 2.40 (br d, *J* = 13 Hz), 1.99 (br d, *J* = 13 Hz), 1.61-1-52 (m, 4 H), 1.49, 1.36 (m, 4 H) ppm; ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.24, 58.69, 42.50, 31.82, 24.52 ppm; IR (solid) ν 2967, 1636, 1568, 1447, 767 cm^{-1}; HRMS (*m/z*) calcd for $C_{12}H_{18}N_2O_2$ $[M+H]^+$ 223.1446; found, 223.107; analysis calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. found C, 64.65; H, 8.16; N, 12.56.

Type: Dynamic

Stage	Temp(C)	Time(mm:ss)	Pressure(BAR)	Power(W)	PowerMAX	Stirring
1	220	25:00	17.2	200	No	High

Graphs



Method Summary

Reaction started:	11/23/2009 11:16:21 AM
HOT KEY: Changed temp from 220 C to 230 C	11/23/2009 11:19:42 AM
Temperature setpoint reached:	11/23/2009 11:19:53 AM
HOT KEY: Changed temp from 230 C to 220 C	11/23/2009 11:28:31 AM
HOT KEY: Changed power from 200 W to 100 W	11/23/2009 11:37:44 AM
Reaction cooling started:	11/23/2009 11:44:55 AM
Cooling/Reaction ended:	11/23/2009 11:47:09 AM

Reaction Completed Successfully!

Maximum temperature:	234 C
Maximum pressure:	9 BAR
Time to obtain setpoint:	03:32 mm:ss
Time at setpoint:	25:02 mm:ss
Time cooling:	02:14 mm:ss