Organocatalyzed Multicomponent Synthesis of Pyrazolidinones: the Meldrum's Acid Approach

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I General information

Reactions were performed using oven dried glassware under inert atmosphere of dry argon or nitrogen and monitored by thin-layer chromatography with silica gel 60 F254 pre-coated aluminium plates (0.25 mm). Visualization was performed under UV light and phosphomolybdic acid or $KMnO_4$ oxidation. Chromatographic purification of compounds was achieved with 60 silica gel (40-63 μm).[1]

Solvents and reagents: Toluene and CH_2Cl_2 were dried by refluxing over CaH_2 and then distilled. Unless otherwise noted, all reagent-grade chemicals and solvents were used as supplied (analytical or HPLC grade) without prior purification.

Melting points were measured on a WME Köfler hot-stage with a precision of +/– 2 °C and are uncorrected.

Infrared spectra (IR) were recorded on a PerkinElmer Spectrum 100 Series FT-IR spectrometer. Liquids and solids were applied on the Single Reflection Attenuated Total Reflectance (ATR) Accessories. Data are reported in cm^{-1}.

Optical rotations were determined with a Perkin-Elmer 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g per 100 mL.

^{1}H Spectra (300 or 400 MHz) and **^{13}C NMR spectra** (75 or 100 MHz) were recorded on either a Bruker Advance300 or Advance400 spectrometers. The field was locked by external referencing to the relevant deuteron resonance. Data appear in the following order: chemical shifts in ppm which were referenced to the internal solvent signal, number of protons, multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *dd*, doublet of doublet, *ddd*, doublet of doublet of doublet, *ddt*, doublet of triplet, *m*, multiplet) and coupling constant *J* in Hertz.

Low Resolution Mass Spectra (LRMS) were recorded on a Thermo Electron Corporation ion-trap spectrometer.

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.*, 1978, **43**, 2923-2925.

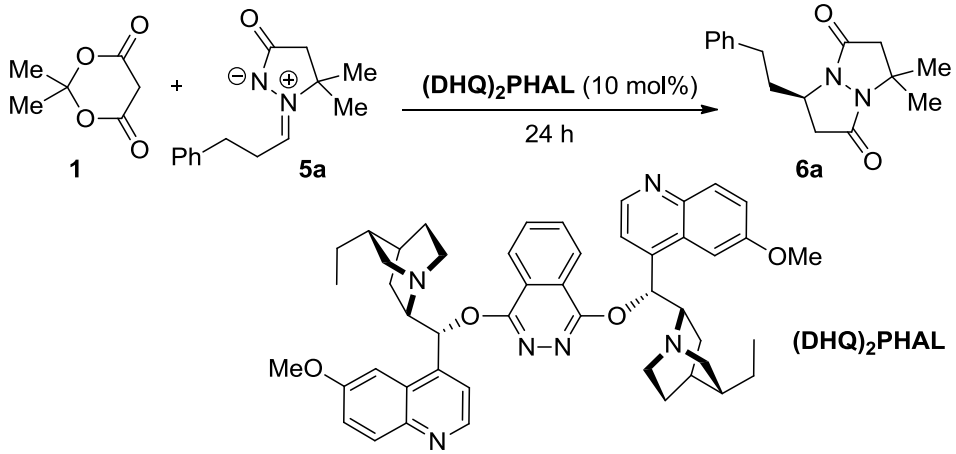
Accurate Mass measurements (HRMS) were performed by the Mass Spectrometry Laboratory of the University of Rouen and were recorded with a Waters LCP 1er XR spectrometer.

Elemental analyses were performed by the microanalysis service of the University of Rouen and were recorded with a Thermo Scientific FLASH 2000 analyzer.

HPLC analyses were performed with Daicel Chiralpak® and Chiralcel® columns (4.6 mm × 250 mm) and a mixture of heptane/*i*-PrOH solvents. A spectrosystem UV 1000 thermofisher detector and a chiral detector (polarimeter) JACSCO OR-1590 were used.

II Optimization of reaction conditions

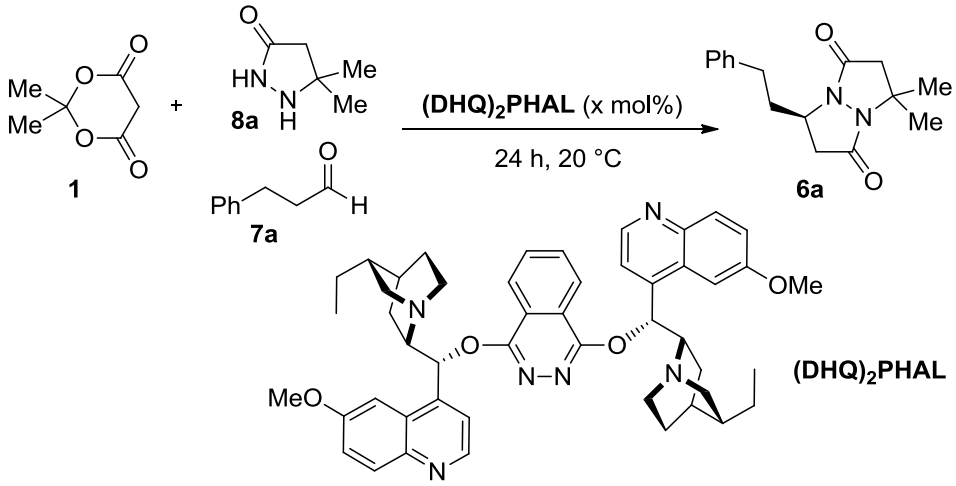
II-1 Solvent selection



Entry	Solvent	T [°C]	Yield [%][b]	*er*[c]
1	Tol/CH_2Cl_2 (3/1)	40	96	86:14
2	Tol/CH_2Cl_2 (3/1)	10	21	97:3
3	Tol/CH_2Cl_2 (3/1)	20	74	92.5:7.5
4	THF	20	68	86:14
5	Dioxane	20	47	95.5:4.5
6	AcOEt	20	68	86:14
7	$PhCF_3$	20	59	89:11
8	MeCN	20	23	90:10
9	DMF	20	0	-
10	*t*-BuOH	20	0	-
11	MeTHF	20	61	83:17
12	$CHCl_3$	20	29	95.5:4.5
13	CH_2Cl_2	20	60	95:5

[a] Reaction conditions: Meldrum's acid **1** (0.1 mmol), azomethine imine **4a** (1 equiv), $(DHQ)_2PHAL$ (0.1 equiv) in 1 mL of solvent during 24 hours. [b] Yield determined by ^1H NMR with an internal standard. [c] Enantiomeric ratios determined by chiral HPLC.

Remark: the use of toluene/CH_2Cl_2 mixture at 20 °C instead of toluene solvent was required to prevent precipitation events leading to erratic outcomes.



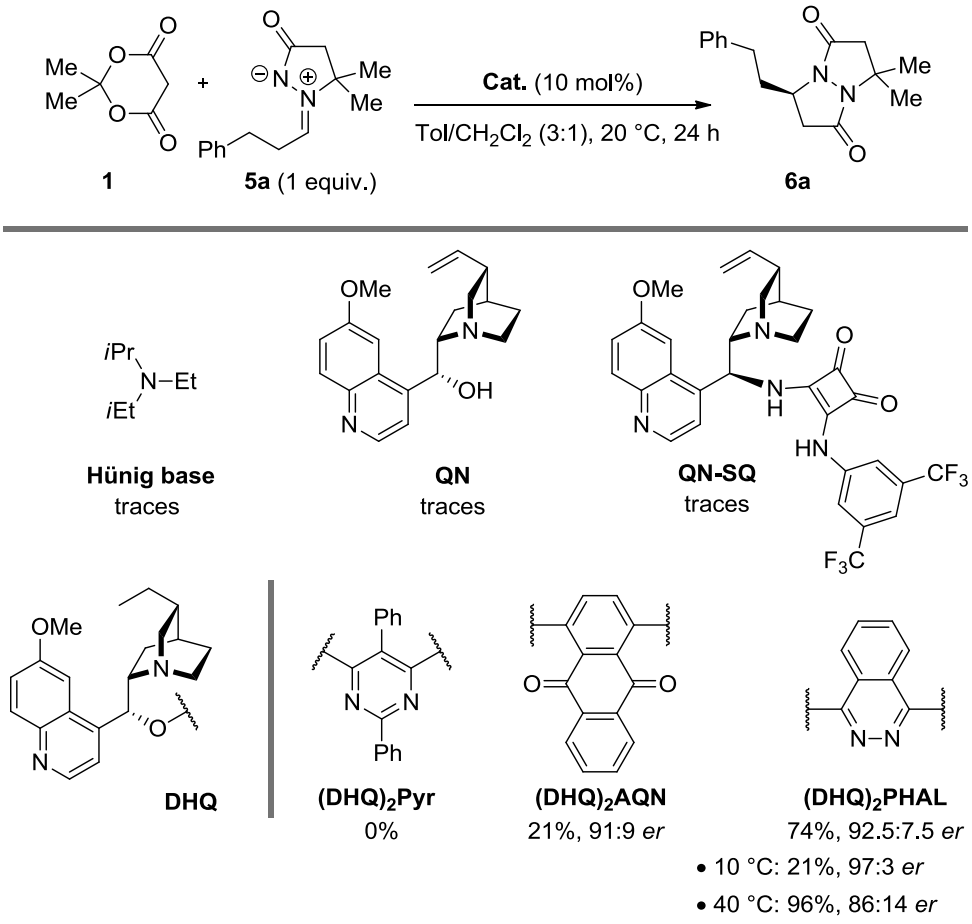
Entry	Solvent	Conc. [M]	$(DHQ)_2PHAL$	Yield [%][b]	*er*[c]
1	Tol/CH_2Cl_2 (3/1)	0.1	10	64	92.5:7.5
2	Tol/CH_2Cl_2 (3/1)	0.25	10	71	90.5:9.5
3	Tol/CH_2Cl_2 (3/1)	0.1	15	74	91:9
4	Tol/CH_2Cl_2 (1/1)	0.1	15	64	92:8
5	Tol/CH_2Cl_2 (1/3)	0.1	15	64	92:8
6	Tol/CH_2Cl_2 (3/1)	0.1	10	91 (48 h)	85:15
7	CH_2Cl_2	0.1	10	53	94:6
8	CH_2Cl_2	0.2	10	52	94.5:5.5
9	CH_2Cl_2	0.2	15	70	92.5:7.5
10	Dioxane	0.2	10	44	91:9
11	DME	0.2	10	59	82:18
13	acetone	0.2	10	65	75:25

[a] Reaction conditions: Meldrum's acid **1** (0.1 mmol), aldehyde **7a** (1 equiv), pyrazolidinone **8a**, $(DHQ)_2PHAL$ (0.1 equiv) in solvent (0.1-0.2 M) during 24 hours at 20 °C. [b] Isolated yield after column chromatography. [c] Enantiomeric ratios determined by chiral HPLC.

It was observed that CH_2Cl_2 as solvent provided slightly better enantiomeric ratio (*er*) than Tol/CH_2Cl_2 (3/1) but led to slower processes in many instances. Moreover, the yield could be nicely improved by running the reaction over 48 hours (entry 6), but a decreased in *er* was observed too.

II-2 Catalyst structure-activity relationship

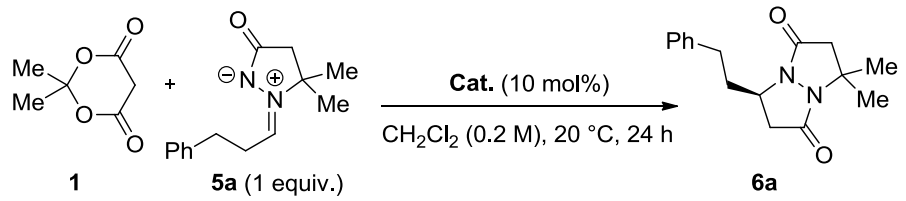
The initial screening of catalyst revealed a unique catalytic behavior of dimeric Sharpless ligands.



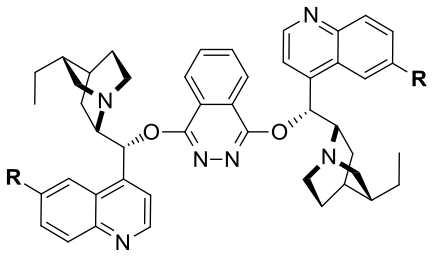
This study was carried out mainly in dichloromethane in order to obtain homogeneous solutions, as long as ammonium salts tend to precipitate in other solvents. As depicted in scheme below, the two quinidine moieties of **$(DHQ)_2PHAL$** are required to obtain both an optimal catalytic activity and enantiomeric ratios.[2,3] The mono-protonated catalyst **$(DHQ)_2PHAL{\cdot}CF_3CO_2H$** provided the closest results to **$(DHQ)_2PHAL$** in terms of *er* and the best yield in comparison to the other catalytic promoters. Worthy of note, an ^1H NMR study of **$(DHQ)_2PHAL$** in the presence of Meldrum's acid **1** demonstrated that the protonation steps are equilibrated and depend of the catalyst/Meldrum's acid ratio; on the

[2] For the synthesis of quaternary ammonium salts, see: Corey, E.J.; Noe, M. C.; S. Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741-8744.
[3] For the synthesis of monomeric catalysts, see: Motorina, I.; Crudden, C. M. *Org. Lett.* **2001**, *3*, 2325-2328.

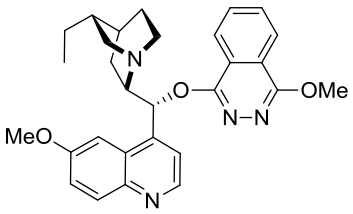
contrary of the mixture between **(DHQ)$_2$PHAL** in the presence of CF_3CO_2H which showed a clear-cut protonation event.



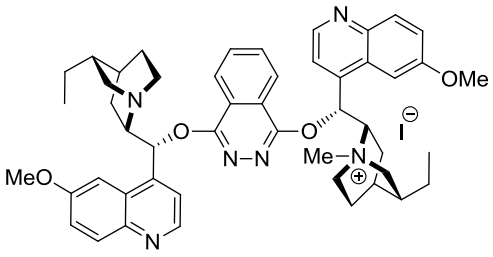
1 **5a** (1 equiv.) **6a**



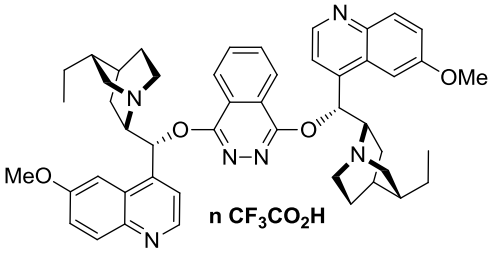
•**(DHQ)$_2$PHAL (R = OMe)**
52%, 94.5:5.5 *er*
74%, 92.5:7.5 *er* (in CH_2Cl_2/Tol: 1/3)
•**(DHCD)$_2$PHAL (R = H)**
45%, 88:12 *e.r.* (in CH_2Cl_2/Tol: 1/3)



(DHQ)PHAL-OMe
Traces



(DHQ)$_2$PHAL-Me
<10%, 89:11 *er*

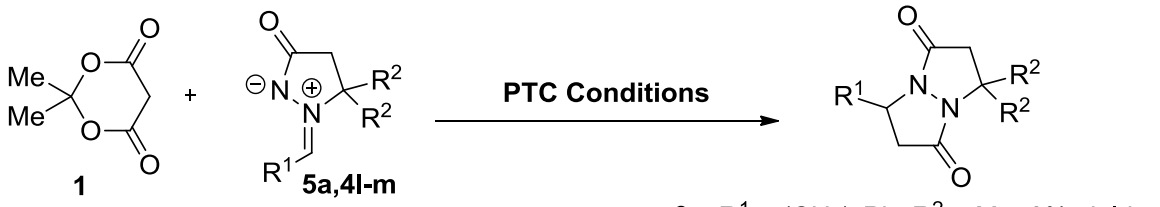


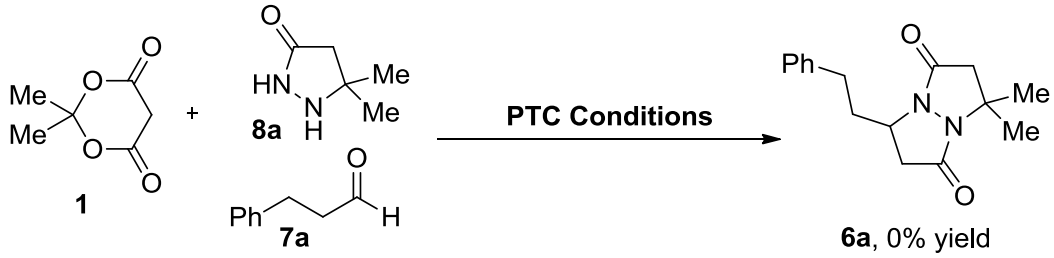
n CF_3CO_2H

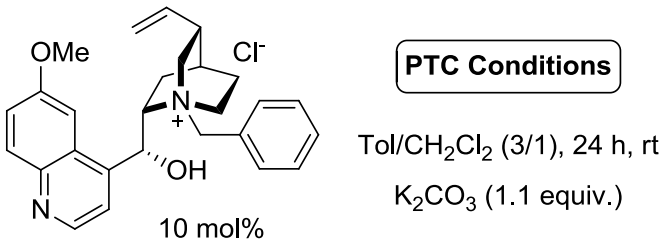
(DHQ)$_2$PHAL + 1 CF_3CO_2H: 25%, 92.5:7.5 *er*
(DHQ)$_2$PHAL + 2 CF_3CO_2H: 10%, 80:20 *er*

II-3 Evaluation of other types of catalysis

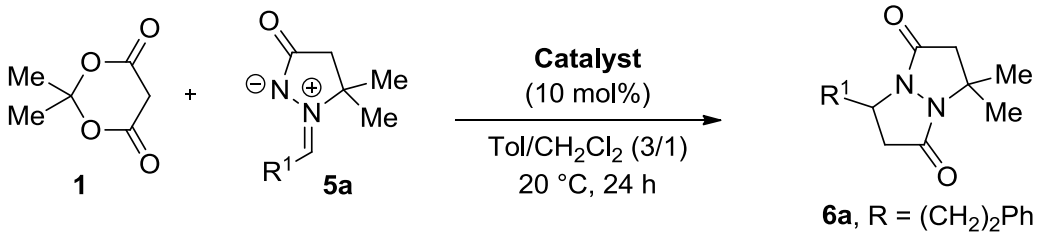
Phase Transfer Catalytic conditions did not lead to significant transformation (see below for an example):





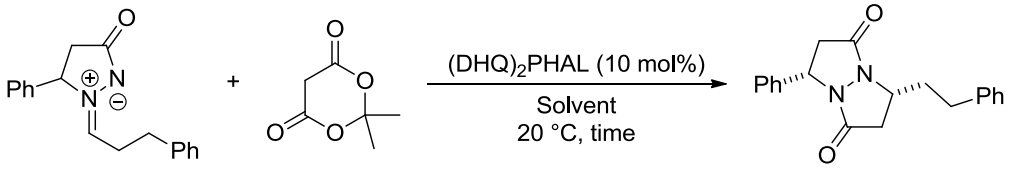


The use of stronger guanidine bases was not efficient to promote the transformation of azomethine imine **4a** into bicyclopyrazolidinones **6**. From ^{1}H NMR analyses, it seems that 40-60% of non-decarboxylated substrate was formed.



II-4 Evaluation of a kinetic resolution approach

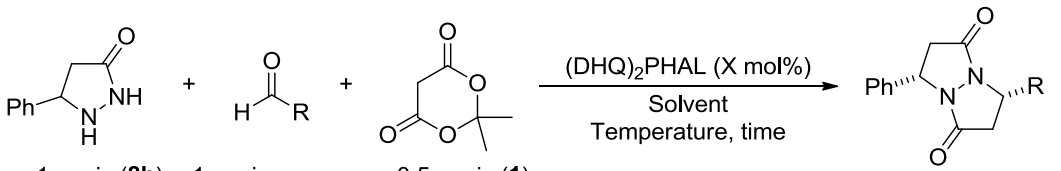
Preliminary investigations of a kinetic resolution approach of either chiral racemic azomethine imine[4] **5p** or by carrying out the multi-component reaction with chiral racemic pyrazolidinone **8b** shows that this catalytic system is unable to differentiate efficaciously the chiral substrates by means of $(DHQ)_2PHAL$ catalyst. During this reaction most of the azomethine imine was consumed.



5p, 1 equiv + 0.5 equiv → dr > 98:2 → **6p**

Solvent	Time (h)	NMR yield (%)[a]	*er*[b]
Tol/CH_2Cl_2 (3/1)	12	9	64:36
CH_2Cl_2	12	<5	-
Tol/CH_2Cl_2 (3/1)	24	13	59:41
CH_2Cl_2	24	20	60:40

[a] Yield of **6p** was determined by ^{1}H NMR with respect to an internal standard and Meldrum's acid **1**. [b] Enantiomeric ratios were determined by chiral HPLC for pyrazolidinone **6p**.



1 equiv (**8b**) + 1 equiv (**7a**, R = $(CH_2)_2Ph$; **7l**, R = Ph) + 0.5 equiv (**1**) → dr > 98:2 → **6p**, R = $(CH_2)_2Ph$; **6o**, R = Ph

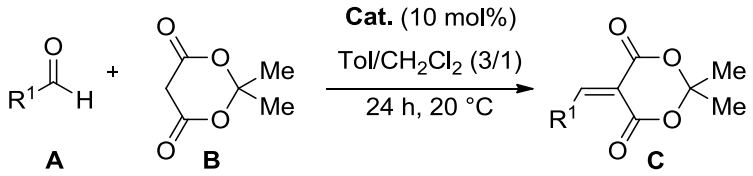
R	Solvent	$(DHQ)_2PHAL$ (mol %)	Temp (°C)	Time (days)	NMR yield[a] (%)	*er*[b]
Ph (**6o**)	CH_2Cl_2	10	0	4	100	64:36
$(CH_2)_2Ph$ (**6p**)	Tol/CH_2Cl_2 (3/1)	15	10	2	44	60:40
$(CH_2)_2Ph$ (**6p**)	CH_2Cl_2	15	10	2	44	66.5:33.5

[a] Yields of **6p** or **6o** were determined by ^{1}H NMR with respect to an internal standard and Meldrum's acid **1**.
[b] Enantiomeric ratios were determined by chiral HPLC for pyrazolidinones **6p** and **6o**.

[4] For previous kinetic resolutions of azomethine imines, see: (a) A. Suárez, C. W. Downey, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11244. (b) M. Wang, Z. Huang, J. Xu, Y. R. Chi, *J. Am. Chem. Soc.* **2014**, *136*, 1214.

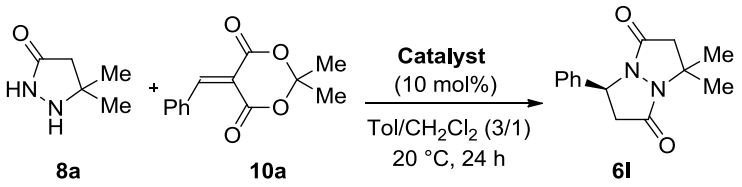
II-5 Pieces of Mechanism from ^{1}H NMR and ESI/MS

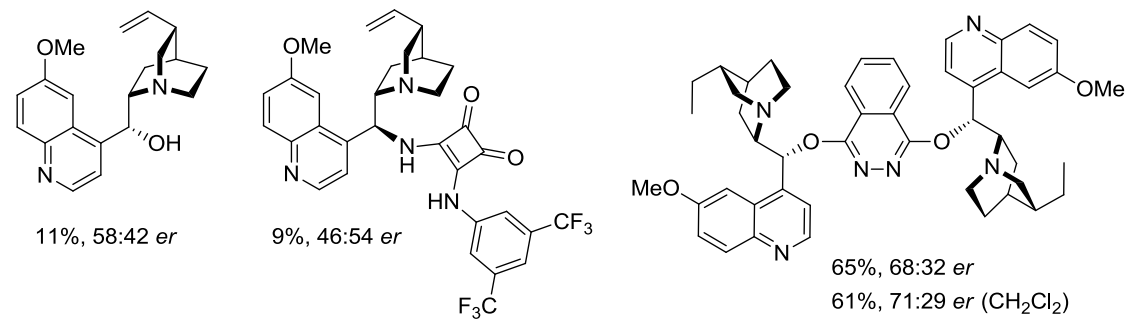
The formation of alkylidene Meldrum's acids **C** is accelerated upon Brønsted base catalysis and **(DHQ)$_2$PHAL** is more competent than Hünig base in that respect.



Cat.	R^1	% determined by NMR with an internal standard	
-	$(CH_2)_2Ph$		7% (**C**)
***i*-Pr$_2$EtN**	$(CH_2)_2Ph$	51% (**B**)	44% (**C**)
(DHQ)$_2$PHAL	$(CH_2)_2Ph$	22% (**B**)	63% (**C**)
(DHQ)$_2$PHAL	Ph	25% (**B**)	72% (**C**)

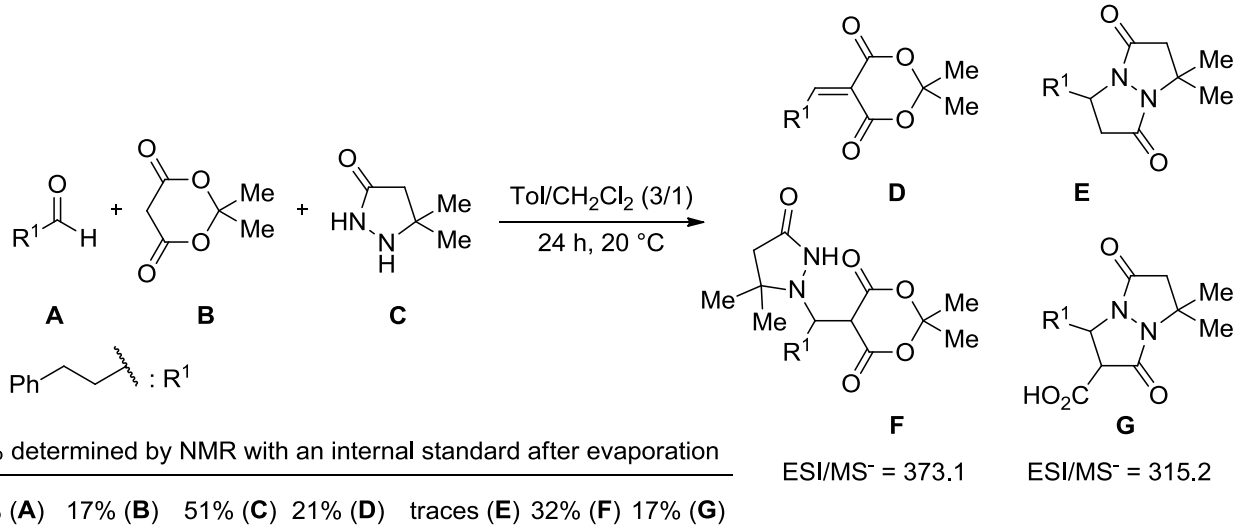
Moreover, some representative test reactions also validated that **(DHQ)$_2$PHAL** is a competence catalyst for the direct aza-Michael step to pre-formed benzylidene Meldrum's acid **10a**.[5] As a piece of mechanism, this reaction promoted by **(DHQ)$_2$PHAL** in CH_2Cl_2 furnished product **6l** with 71:29 *er*, which parallels the outcome of the multicomponent Knoevenagel-aza-Michael-Cyclocondensation (KMC) reaction (see Table 1, entry 14 in the paper, 72.5:27.5 *er*), albeit in lower yield (61% *versus* 80%)





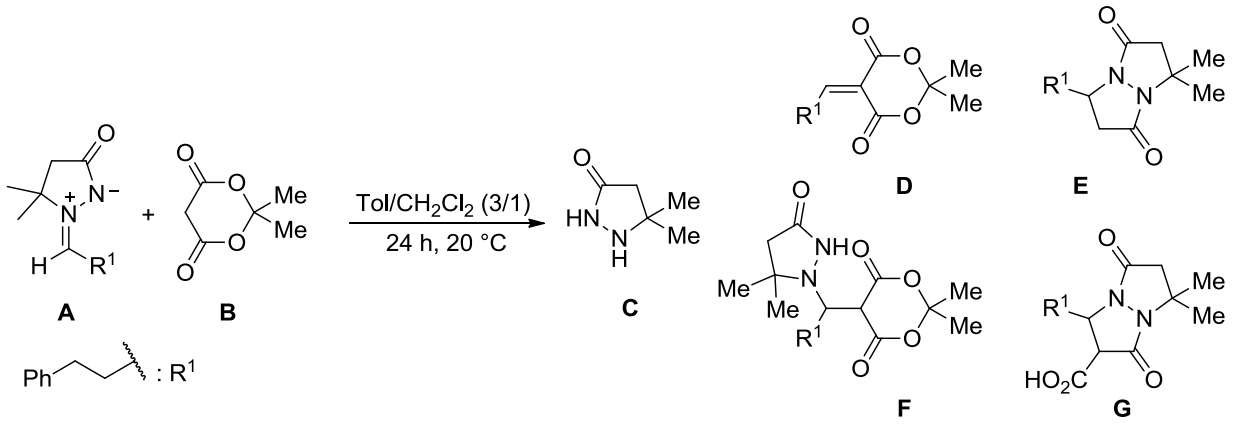
[5] For the synthesis of benzylidene Meldrum's acid, see: A. M. Dumas, A. Seed, A. K. Zorzitto and E. Fillion, *Tetrahedron Lett.*, 2007, **48**, 7072.

The formation of alkylidene Meldrum's acid **D** might also proceed simply by mixing the three components **A**, **B** and **C** whereby the pyrazolidinone **C** could act as an iminium catalyst following a regular Knoevenagel reaction mechanism through **F**.[6] Although the product **E** was hardly formed, we could also detect the formation of the non-decarboxylated precursor **G**. The structures of products **F** and **G** were proposed from the analyses of the crude mixture by means of both ESI/MS spectrometry and ^{1}H NMR.



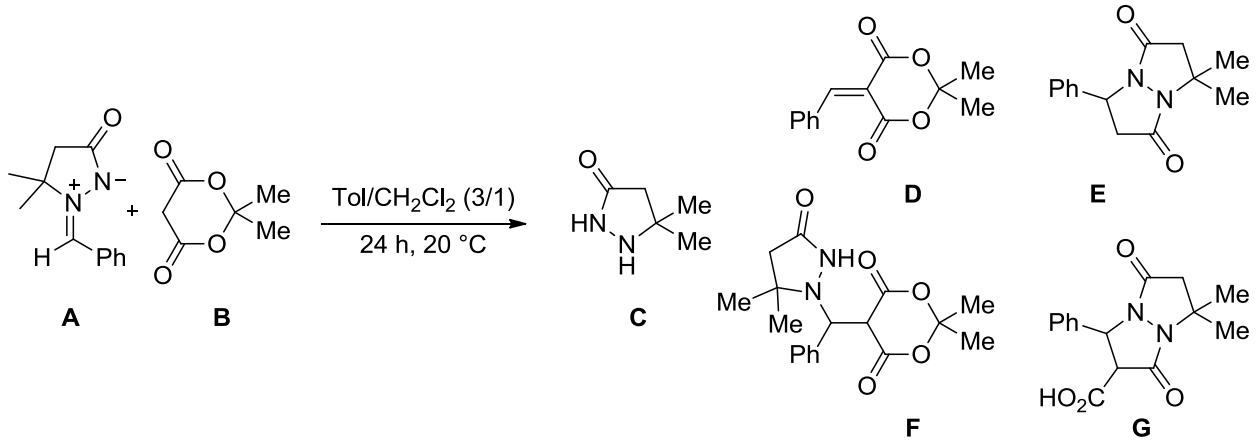
In line of the aforementioned study, the possibility to conduct this reaction from the azomethine imines **A** flanked either by a CH_2-CH_2Ph alkyl chain or a phenyl moiety was also validated:

[6] The formation of the aza-Michael adduct analogue of **F** but having a covalent bond with the amide nitrogen atom cannot be ruled out from our analyses.



% determined by NMR with an internal standard after evaporation

2% (**A**) 9% (**B**) 53% (**C**) 20 %(**D**) 0 %(**E**) 29 %(**F**) 15 %(**G**)

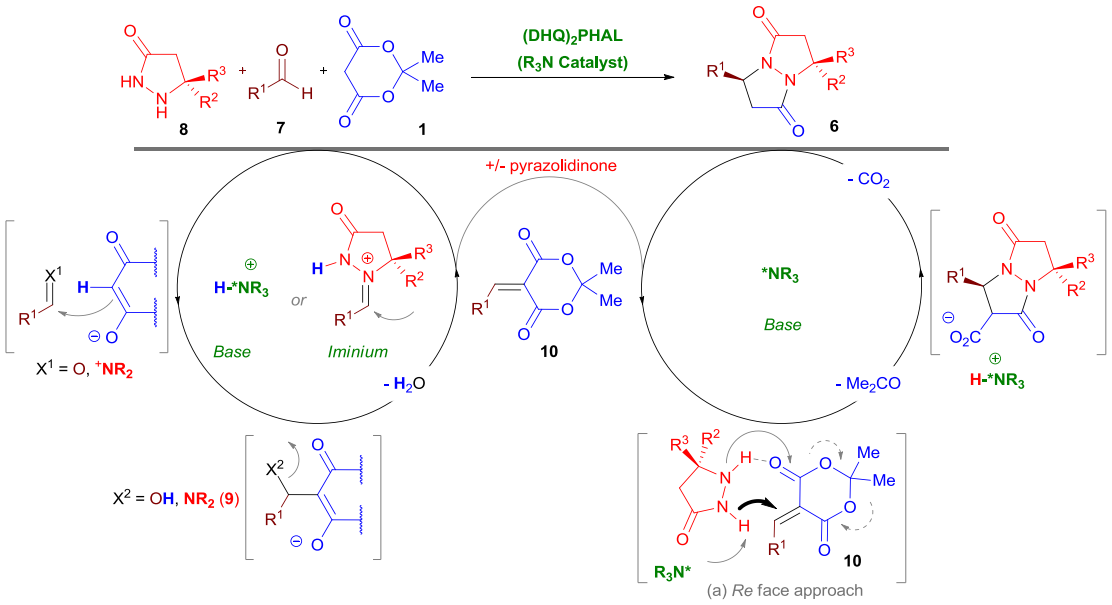


% determined by NMR with an internal standard after evaporation

34% (**A**) 41% (**B**) 28% (**C**) 23% (**D**) traces (**E**) 16% (**F**) 23% (**G**)

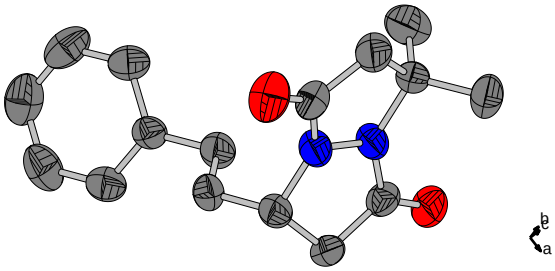
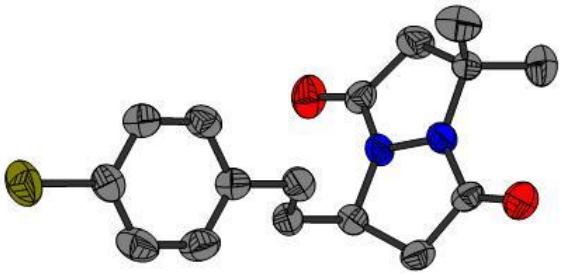
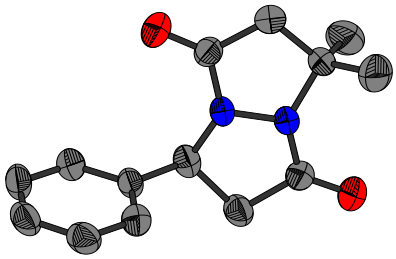
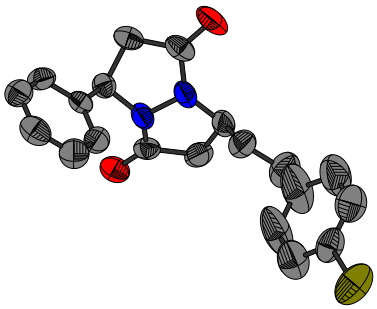
II-6 Proposed catalytic cycle

Based on the preliminary mechanistic investigation (Cf. § II-5), we propose a tandem catalytic cycle in action, upon either a Brønsted base catalytic regime or an iminium regime for the first cycle.



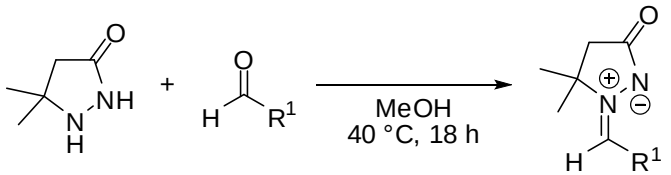
II-7 Structure determination and X-Ray diffraction analyses

The structure determination of bicyclic pyrazolidinones **6** by NMR was not straightforward due to the small size of long range carbon-proton coupling constants though nitrogen atoms by HMQC experiments, namely between C-**H** and C=**O** atoms. Then, the structure determination was achieved by a HMBC $^{1}H/^{15}N$ NMR spectra on compound **6b** and with a series of X-Ray structures; with ORTEP depicted below.

Compound **6a** 	Compound **6b** 
Compound **6l** 	Compound **6q** 

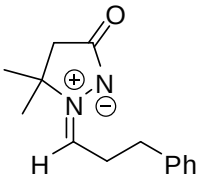
III Experimental procedures

III-1 Azomethine imine synthesis



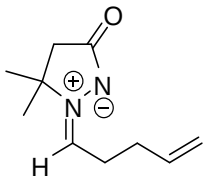
8a (1 equiv) **7a,e** (1.05 equiv) **4a,e**

Representative procedure for the preparation of 5,5-dimethylpyrazolidin-3-one derived azomethine imines 4a and 4e. To a stirred solution of 5,5-dimethylpyrazolidin-3-one (1.00 equiv) in methanol was added the aldehyde (1.05 equiv) at room temperature. After stirring at 40 °C for 18 hours, the mixture was concentrated under reduced pressure and the crude residue was purified by silica gel column chromatography (AcOEt to AcOEt/MeOH: 8/2). The product was then dissolved in CH_2Cl_2, filtered on Celite and evaporated under reduced pressure to afford the desired azomethine imine. Azomethine imines **4f**,[7] **4m-n**[8] and pyrazolidinone **8a**[7] were synthesized according to the literature.



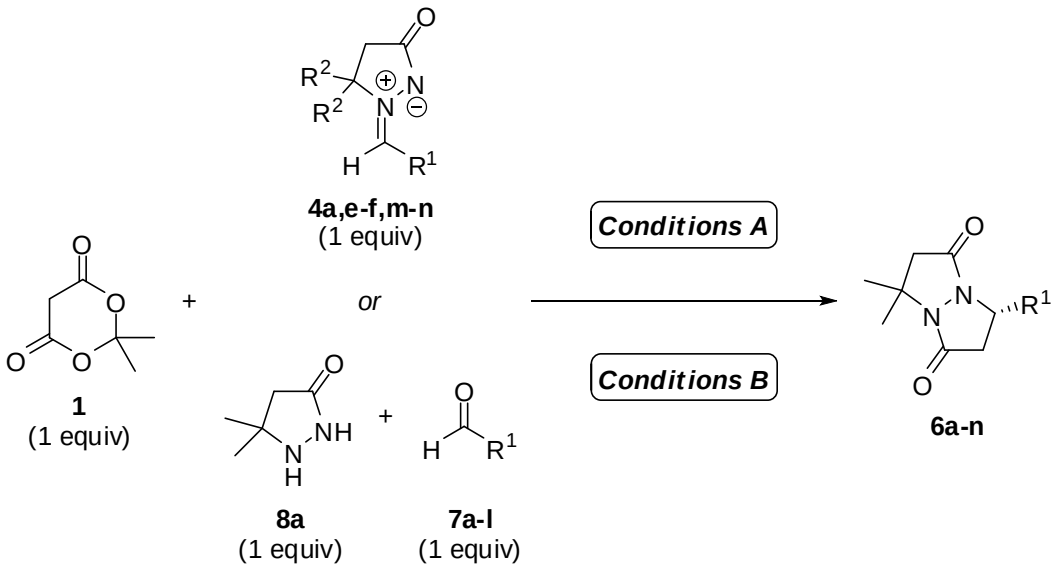
1-Phenylpropylidene-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (4a). Following the general procedure with 5,5-dimethylpyrazolidin-3-one **8a** (571 mg, 5.00 mmol) and 3-phenylpropionaldehyde **7a** (720 µL, 5.50 mmol) in methanol (5.0 mL), the title compound was obtained as a yellow solid (1.03 g, 4.47 mmol, 89%). R_f = 0.26 (AcOEt/MeOH: 8/2). m.p. 50-51 °C. IR (neat) ν_{max} 3210, 3028, 2971, 2932, 1666, 1587, 1323, 1282, 1100, 746, 699 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.32-7.18 (5H, m), 6.39 (1H, t, J = 5.9 Hz), 3.05-2.98 (4H, m), 2.69 (2H, s), 1.50 (3H, s), 1.30 (3H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 180.8 (C=O), 139.6 (C), 135.9 (CH), 128.8 (CH), 128.3 (CH), 126.8 (CH), 72.2 (C), 45.4 (CH_2), 31.2 (CH_2), 30.7 (CH_2), 28.9 (CH_3). HRMS (ESI^+): calcd for $C_{14}H_{19}N_2O$ [$(M+H)^+$]: 231.1492; Found: 231.1497. Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.97; H, 7.99; N, 11.88.

[7] M. Keller, A. S. Sido, P. Pale, J. Sommer, *Chem. Eur. J.* **2009**, *15*, 2810-2817.
[8] R. Shintani, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 10778-10779.



1-(Pent-4'en-1'-ylidene)-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (4e). Following the general procedure with 5,5-dimethylpyrazolidin-3-one **8a** (459 mg, 4.00 mmol) and pent-4-enal **7e** (0.43 mL, 4.25 mmol), the title compound was obtained as a yellow oil (551 mg, 3.06 mmol, 76%). R_f = 0.17 (AcOEt/MeOH: 8/2). IR (neat) ν_{max} 3404, 3076, 2974, 2932, 1665, 1588, 1327, 1135, 1054, 999, 913, 674, 645, 582, 556 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 6.50 (1H, t, J = 6.0 Hz), 5.83-5.70 (1H, m), 5.06-4.99 (2H, m), 2.79-2.72 (2H, m), 2.65 (2H, s), 2.38-2.31 (2H, m), 1.54 (6H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 180.7 (C=O), 136.5 (CH), 136.1 (CH), 116.4 (CH_2), 72.1 (C), 45.4 (CH_2), 29.4 (CH_2), 28.9 (CH_3), 28.4 (CH_2). HRMS (ESI^+): calcd for $C_{10}H_{17}N_2O$ [$(M+H)^+$]: 181.1335; Found: 181.1336.

III-2 Enantioselective synthesis of pyrazolidinones

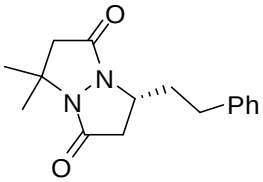


Representative general procedures for the enantioselective synthesis of pyrazolidinones 6a-n.

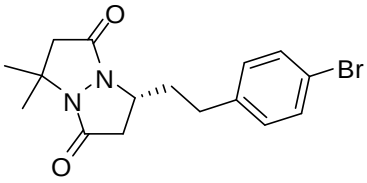
Conditions A: Azomethine imine **4** (0.25 mmol, 1.0 equiv), Meldrum's acid **1** (36.0 mg, 0.25 mmol, 1.0 equiv) and $(DHQ)_2PHAL$ (19.5 mg, 0.025 mmol, 0.1 equiv) were dissolved in a mixture of toluene/CH_2Cl_2 (3/1, 2.5 mL) and the reaction mixture was stirred at 20 °C for 24 hours. The crude mixture was then washed with Na_2CO_3 solution (10% w/w) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (AcOEt) to afford product **6**.

Conditions B: Pyrazolidinone **8a** (28.5 mg, 0.25 mmol, 1.0 equiv), Meldrum's acid **1** (36.0 mg, 0.25 mmol, 1.0 equiv) and $(DHQ)_2PHAL$ (29.2 mg, 0.038 mmol, 0.15 equiv) were dissolved in a mixture of toluene/CH_2Cl_2 (3/1, 2.5 mL) or CH_2Cl_2 (1.25 mL). The appropriate aldehyde **7** (0.25 mmol, 1.0 equiv) was then added and the reaction mixture was stirred at 20 °C for 24 hours. The crude mixture was then washed with Na_2CO_3 solution (10% w/w) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (AcOEt) to afford product **6**.

Remark: all major ennatiomers turned out to be levo (-) isomers with regard to the chiral detector (polarimeter) during HPLC analyses.

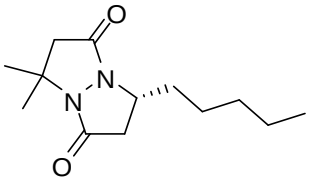


(*R*)-3,3-Dimethyl-7-phenethyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6a). The title compound was prepared according to the above general procedures as a grey solid (53.8 mg, 0.20 mmol, 79% in 7.5:92.5 *er*) using conditions A from azomethine imine **4a** (57.6 mg, 0.25 mmol) and (50.3 mg, 0.19 mmol, 74% in 9:91 *er*) using conditions B from 3-phenylpropionaldehyde **7a** (35 μL, 0.25 mmol). Recrystallization in Et_2O increased the optical purity to 1:99 (38.7 mg, 0.14 mmol, 72%). R_f = 0.24 (AcOEt). m.p. 97-100 °C (Et_2O). $[\alpha]_D^{20}$ −112.7 (*c* 1.00, $CHCl_3$). IR (neat) ν_{max} 2926, 1661, 1287, 752, 701 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.32-7.27 (2H, m), 7.22-7.20 (3H, m), 4.27 (1H, ddt, *J* = 10.3, 7.5, 5.3 Hz), 3.07 (1H, dd, *J* = 17.3, 10.0 Hz), 2.75-2.70 (4H, m), 2.59 (1H, dd, *J* = 17.3, 5.0 Hz), 2.40-2.28 (1H, m), 2.04-1.90 (1H, m), 1.64 (3H, s), 1.56 (3H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.4 (C=O), 164.1 (C=O), 140.4 (C), 128.7 (CH), 128.5 (CH), 126.5 (CH), 59.0 (C), 51.4 (CH), 50.1 (CH_2), 40.8 (CH_2), 35.3 (CH_2), 31.5 (CH_2), 26.6 (CH_3), 25.2 (CH_3). HRMS (ESI^+): calcd for $C_{16}H_{21}N_2O_2$ [$(M+H)^+$]: 273.1598; Found: 273.1592. HPLC analysis: chiral column AD-H (heptane/*i*-PrOH: 90/10, flow rate 1 mL/min, UV 254 nm, t_{mino} = 11.2 min for *S* enantiomer; t_{major} = 12.5 min for *R* enantiomer).

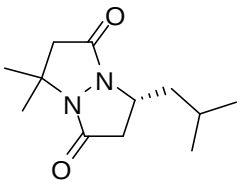


(*R*)-3,3-Dimethyl-7-(2'-(*p*-bromophenyl)ethyl)tetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6b). The title compound was prepared according to the above general procedures as a white solid (70.2 mg, 0.20 mmol, 80% in 10:90 *er*) using conditions B from 3-(4-bromophenyl)propanal **7b** (53.3 mg, 0.25 mmol). Recrystallization in *i*-PrOH afforded an enantiopur sample (35.0 mg, 0.10 mmol, 50%). m.p. 140-141 °C (*i*-PrOH). R_f = 0.15 (AcOEt/MeOH, 95/5). $[\alpha]_D^{20}$ −82.3 (*c* 1.04, $CHCl_3$). IR (neat) ν_{max} 2977, 2927, 1670, 1347, 1321, 1285, 820, 537 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$) δ_H 7.41 (2H, d, *J* = 8.3 Hz), 7.09 (2H, d, *J* = 8.3 Hz), 4.25 (1H, dt, *J* = 11.6, 5.9 Hz), 3.07 (1H, dd, *J* = 17.2, 10.0 Hz), 2.75 (2H, s), 2.68 (2H, t, *J* = 7.93 Hz), 2.57 (1H, dd, *J* = 17.3, 4.9 Hz), 2.34-2.23 (1H, m),

1.98-1.86 (1H, m), 1.64 (3H, s), 1.55 (3H, s). ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 164.4 (C=O), 163.9 (C=O), 139.2 (C), 131.6 (CH), 130.1 (CH), 120.1 (C), 58.9 (C), 51.0 (CH), 49.9 (CH_2), 40.6 (CH_2), 35.1 (CH_2), 30.8 (CH_2), 26.5 (CH_3), 25.0 (CH_3). MS (ESI^+): *m/z* 351.1 and 353.1 [$(M+H)^+$]. HRMS (ESI^+): calcd for $C_{16}H_{20}N_2O_2Br$ [$(M+H)^+$]: 351.0708 and 353.0688; Found: 351.0701 and 353.0684. HPLC analysis: chiral column AD-H (heptane/*i*-PrOH: 90/10, flow rate 1 mL/min, UV 254 nm, t_{mino} = 13.8 min for *S* enantiomer; t_{major} = 15.8 min for *R* enantiomer).

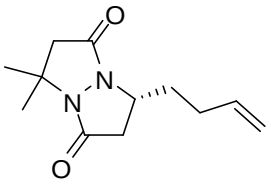


(*R*)-3,3-Dimethyl-7-pentyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6c). The title compound was prepared according to the above general procedures as a colorless oil (42.9 mg, 0.18 mmol, 72% in 6.5:93.5 *er*) using conditions B from hexanal **7c** (31 μL, 0.25 mmol). R_f = 0.20 (AcOEt). IR (neat) ν_{max} 2929, 2860, 1678, 1459, 1315, 1290, 539 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.25-4.16 (1H, m), 3.04 (1H, dd, *J* = 17.2, 10.0 Hz), 2.75 (2H, s), 2.54 (1H, dd, *J* = 17.2, 4.9 Hz), 1.97-1.90 (1H, m), 1.64-1.54 (1H, m), 1.61 (3H, s), 1.54 (3H, s), 1.30-1.22 (6H, m), 0.88-0.84 (3H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.0 (C=O), 163.9 (C=O), 58.8 (C), 51.7 (CH), 50.1 (CH_2), 40.6 (CH_2), 33.4 (CH_2), 31.5 (CH_2), 26.5 (CH_3), 25.2 (CH_3), 24.5 (CH_2), 22.5 (CH_2), 14.0 (CH_3). HRMS (ESI^+): calcd for $C_{13}H_{23}N_2O_2$ [$(M+H)^+$]: 239.1754; Found: 239.1760. HPLC analysis: chiral column AD-H (heptane/*i*-PrOH: 95:5, flow rate 1 mL/min, UV 254 nm, t_{mino} = 11.8 min for *S* enantiomer; t_{majo} = 13.1 min for *R* enantiomer).

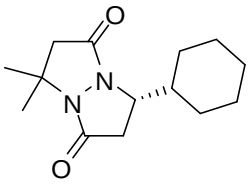


(*R*)-3,3-Dimethyl-7-isobutyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6d). The title compound was prepared according to the above general procedures as a white solid (38.7 mg, 0.17 mmol, 69% in 96:4 *er*) using conditions B from isovaleraldehyde **7d** (27 μL, 0.25 mmol). R_f = 0.25 (AcOEt). m.p. 72-76 °C. IR (neat) ν_{max} 2957, 2930, 2871, 1670, 1334, 1290 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.34-4.24 (1H, m), 3.06 (1H, dd, *J* = 17.1,

9.9 Hz), 2.76 (2H, s), 2.54 (1H, dd, J = 17.2, 4.8 Hz), 2.01-1.92 (1H, m), 1.74-1.64 (4H, m), 1.56 (3H, s), 1.48-1.25 (1H, m), 0.99 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.4 (C=O), 164.3 (C=O), 59.0 (C), 50.5 (CH), 50.2 (CH_2), 42.7 (CH_2), 41.1 (CH_2), 26.6 (CH_3), 25.2 (CH_3), 25.0 (CH), 23.0 (CH_3), 22.2 (CH_3). HRMS (ESI^+): calcd for $C_{12}H_{21}N_2O_2$ [$(M+H)^+$]: 225.1598; Found: 225.1603. HPLC analysis: chiral column AD-H (heptane/*i*-PrOH 95/5, flow rate 1 mL/min, UV 254 nm, t_{majo} = 12.4 min for *R* enantiomer; t_{mino} = 13.4 min for *S* enantiomer).

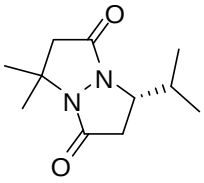


(*R*)-3,3-Dimethyl-7-(but-3'-en-1'-yl)-tetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6e). The title compound was prepared according to the above general procedures as a colorless oil (64.0 mg, 0.29 mmol, 72% in 91.5:8.5 *er*) using conditions A from azomethine imine **4e** (72.1 mg, 0.40 mmol) and (28.9 mg, 0.13 mmol, 52% in 91:9 *er*) using conditions B from 4-pentenal **7a** (25 μL, 0.25 mmol). R_f = 0.17 (AcOEt). IR (neat) ν_{max} 3528, 2976, 2932, 1675, 1315, 1288, 911, 539 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 5.85-5.72 (1H, m), 5.09-4.98 (2H, m), 4.29-4.20 (1H, m), 3.05 (1H, dd, J = 17.3, 10.0 Hz), 2.75 (2H, s), 2.56 (1H, dd, J = 17.3, 5.0 Hz), 2.18-2.03 (3H, m), 1.78-1.66 (1H, m), 1.62 (3H, s), 1.55 (3H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.2 (C=O), 164.0 (C=O), 136.7 (CH), 116.0 (CH_2), 58.9 (C), 51.2 (CH), 50.1 (CH_2), 40.6 (CH_2), 32.7 (CH_2), 29.3 (CH_2), 26.6 (CH_3), 25.1 (CH_3). HRMS (ESI^+): calcd for $C_{12}H_{19}N_2O_2$ [$(M+H)^+$]: 223.1441; Found: 223.1447. HPLC analysis: chiral column IC (heptane/*i*-PrOH: 70/30, flow rate 1 mL/min, UV 254 nm, t_{majo} = 11.9 min for *R* enantiomer; t_{mino} = 43.1 min for *S* enantiomer).

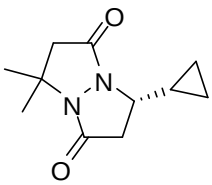


(*R*)-3,3-Dimethyl-7-cyclohexyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6f). The title compound was prepared according to the above general procedures as a pale yellow oil (75.1 mg, 0.30 mmol, 75% in 89:11 *er*) using conditions A from azomethine imine **4f** (83.3 mg, 0.40 mmol) and (30.0 mg, 0.12 mmol, 48% in 87:13 *er*) using conditions B from

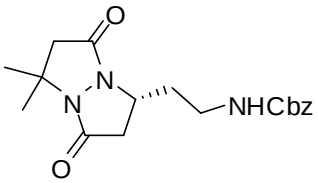
cyclohexanecarboxaldehyde **7f** (30 μL, 0.25 mmol). R_f = 0.17 (AcOEt). IR (neat) ν_{max} 3488, 2925, 2853, 1677, 1449, 1318, 539 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 4.15-4.09 (1H, m), 2.95 (1H, dd, *J* = 17.5, 10.5 Hz), 2.78 (2H, s), 2.64 (1H, dd, *J* = 17.5, 4.3 Hz), 1.81-1.56 (5H, m), 1.65 (3H, s), 1.56 (3H, s), 1.28-1.08 (6H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.9 (C=O), 164.5 (C=O), 58.9 (C), 55.8 (CH), 49.9 (CH_2), 40.8 (CH), 37.4 (CH_2), 28.4 (CH_2), 27.2 (CH_2), 27.1 (CH_3), 26.2 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 25.0 (CH_3). HRMS (ESI^+): calcd for $C_{14}H_{23}N_2O_2$ [$(M+H)^+$]: 251.1754; Found: 251.1760. HPLC analysis: chiral column AD-H (heptane/*i*-PrOH: 90/10, flow rate 1 mL/min, UV 254 nm, t_{majo} = 10.1 min for *R* enantiomer; t_{mino} = 11.4 min for *S* enantiomer).



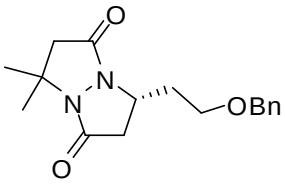
(*R*)-3,3-Dimethyl-7-isopropyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6g). The title compound was prepared according to the above general procedures as a white solid (35.2 mg, 0.17 mmol, 67% in 11.5:88.5 *er*) using conditions B from isobutyraldehyde **7g** (23 μL, 0.25 mmol). Recrystallization in AcOEt/heptane afforded an enantiopur sample (24.6 mg, 0.12 mmol, 70%). R_f = 0.30 (AcOEt). m.p. 130-131 °C (AcOEt/Hept). $[\alpha]_D^{20}$ –182.3 (*c* 0.92, $CHCl_3$). IR (neat) ν_{max} 2971, 2927, 2882, 1667, 1380, 1332, 786 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 4.14-4.07 (1H, m), 2.91 (1H, dd, *J* = 10.7, 4.8 Hz), 2.74 (2H, s), 2.57 (1H, dd, *J* = 10.7, 4.8 Hz), 2.29-2.18 (1H, m), 1.62 (3H, s), 1.52 (3H, s), 0.93 (3H, d, *J* = 4.8 Hz), 0.90 (3H, d, *J* = 4.8 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.8 (C=O), 164.2 (C=O), 58.7 (C), 56.2 (CH), 49.8 (CH_2), 36.7 (CH_2), 30.7 (CH), 26.9 (CH_3), 24.9 (CH_3), 17.8 (CH_3), 16.5 (CH_3). HRMS (ESI^+): calcd for $C_{11}H_{19}N_2O_2$ [$(M+H)^+$]: 211.1441; Found: 211.1441. Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.69; H, 8.66; N, 13.13. HPLC analysis: chiral column IB (heptane/*i*-PrOH: 80/20, flow rate 1 mL/min, UV 254 nm, t_{majo} = 8.9 min for *R* enantiomer; t_{mino} = 22.6 min for *S* enantiomer).



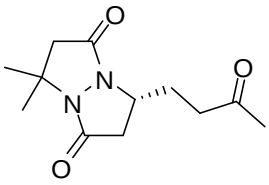
(*R*)-3,3-Dimethyl-7-cyclopropyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6h). The title compound was prepared according to the above general procedures as a colorless oil (30.1 mg, 0.14 mmol, 58% in 92:8 *er*) using conditions B from cyclopropanecarboxaldehyde **7h** (19 μL, 0.25 mmol). R_f = 0.30 (AcOEt). IR (neat) ν_{max} 3552, 2977, 2934, 1674, 1312, 1021, 539 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 3.80 (1H, ddd, *J* = 10.1, 7.7, 4.3 Hz), 3.09 (1H, dd, *J* = 17.3, 10.1 Hz), 2.75 (2H, s), 2.64 (1H, dd, *J* = 17.3, 4.3 Hz), 1.62 (3H, s), 1.56 (3H, s), 1.17-1.09 (1H, m), 0.69-0.51 (3H, m), 0.35-0.27 (1H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.5 (C=O), 164.3 (C=O), 59.1 (C), 55.4 (CH), 50.1 (CH_2), 40.9 (CH_2), 26.8 (CH_3), 25.0 (CH_3), 15.1 (CH), 3.8 (CH_2), 2.1 (CH_2). HRMS (ESI^+): calcd for $C_{11}H_{17}N_2O_2$ [$(M+H)^+$] 209.1285; Found: 209.1289. HPLC analysis: chiral column IB (heptane/*i*-PrOH: 80/20, flow rate 1 mL/min, UV 254 nm, t_{majo} = 10.5 min for *R* enantiomer; t_{mino} = 20.6 min for *S* enantiomer).



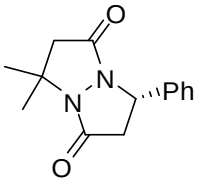
(*R*)-3,3-Dimethyl-7-(2'-((benzyloxycarbonyl)amino)ethyl)-tetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6i). The title compound was prepared according to the above general procedures as a pale yellow oil (52.6 mg, 0.15 mmol, 61% in 91:9 *er*) using conditions B from 3-((benzyloxycarbonyl)amino)propionaldehyde **7i** (51.8 mg, 0.25 mmol). R_f = 0.10 (AcOEt). IR (neat) ν_{max} 3328, 2935, 1668, 1529, 1322, 1246, 1135, 1014, 730, 598, 538 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.35-7.29 (5H, m), 5.78-5.74 (1H, m), 5.08 (2H, m), 4.34-4.28 (1H, m), 3.55-3.44 (1H, m), 3.17-3.05 (2H, m), 2.74 (2H, s), 2.51 (1H, dd, *J* = 17.4, 4.3 Hz), 1.93-1.86 (2H, m), 1.63 (3H, s), 1.52 (3H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 165.5 (C=O), 164.5 (C=O), 156.6 (C=O), 136.6 (C), 128.6 (CH), 128.2 (CH), 128.2 (CH), 66.7 (CH_2), 59.3 (C), 49.8 (CH_2), 49.0 (CH), 41.0 (CH_2), 37.6 (CH_2), 35.0 (CH_2), 27.0 (CH_3), 24.8 (CH_3). HRMS (ESI^+): calcd for $C_{18}H_{24}N_3O_4$ [$(M+H)^+$]: 346.1761; Found: 346.1768. HPLC analysis: chiral column IC (heptane/*i*-PrOH: 50/50, flow rate 1 mL/min, UV 254 nm, t_{majo} = 26.2 min for *R* enantiomer; t_{mino} = 57.4 min for *S* enantiomer).



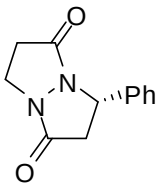
(*R*)-3,3-Dimethyl-7-(2'-(benzyloxy)ethyl)-tetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6j). The title compound was prepared according to the above general procedures as a pale yellow oil (19.5 mg, 0.06 mmol, 26% in 8.5:91.5 *er*) using conditions B from 3-benzyloxy)propanal **7j** (41.1 mg, 0.25 mmol). R_f = 0.19 (AcOEt). IR (neat) ν_{max} 3110, 3080, 3028, 2971, 2930, 2864, 1680, 1317, 1100, 740, 700 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.39-7.28 (5H, m), 4.54-4.36 (3H, m) , 3.65-3.58 (2H, m), 3.06 (1H, dd, J = 17.3, 10.1 Hz), 2.74 (2H, s), 2.73 (1H, dd, J = 17.3, 5.2 Hz), 2.34-2.24 (1H, m), 2.03-1.90 (1H, m), 1.63 (3H, s), 1.54 (3H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.4 (C=O), 164.3 (C=O), 138.1 (C), 128.6 (CH), 127.9 (CH), 127.9 (CH), 73.4 (CH_2), 66.6 (CH_2), 58.9 (C), 50.2 (CH), 50.1 (CH_2), 41.1 (CH_2), 33.7 (CH_2), 26.6 (CH_3), 25.2 (CH_3). HRMS (ESI^+): calcd for $C_{17}H_{23}N_2O_3$ [$(M+H)^+$]: 303.1703; Found: 303.1710. HPLC analysis: chiral column IB (heptane/*i*-PrOH: 80/20, flow rate 1 mL/min, UV 254 nm, t_{majo} = 13.0 min for *R* enantiomer; t_{mino} = 31.8 min for *S* enantiomer).



(*R*)-3,3-Dimethyl-7-(3'-oxobutyl)-tetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6k). The title compound was prepared according to the above general procedures as a colorless oil (20.8 mg, 0.09 mmol, 35% in 92:8 *er*) using conditions B from 4-oxopentanal **7k** (25.0 mg, 0.25 mmol). R_f = 0.07 (AcOEt). IR (neat) ν_{max} 2973, 2934, 2864, 1674, 1320, 1289, 1167, 540 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 4.30-4.21 (1H, m), 3.09 (1H, dd, J = 17.3, 10.1 Hz), 2.72 (2H, s), 2.69-2.61 (2H, m), 2.48 (1H, dd, J = 17.3, 4.4 Hz), 2.16 (3H, s), 2.08-1.85 (2H, m), 1.63 (3H, s), 1.55 (3H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 207.3 (C=O), 165.2 (C=O), 164.4 (C=O), 59.1 (C), 50.9 (CH), 49.9 (CH_2), 41.2 (CH_2), 39.5 (CH_2), 30.1 (CH_3), 28.8 (CH_2), 27.0 (CH_3), 24.9 (CH_3). HRMS (ESI^+): calcd for $C_{12}H_{19}N_2O_3$ [$(M+H)^+$]: 239.1390; Found: 239.1388. HPLC analysis: chiral column AD-H (heptane/*i*-PrOH: 95/5, flow rate 1 mL/min, UV 254 nm, t_{majo} = 35.5 min for *R* enantiomer; t_{mino} = 39.3 min for *S* enantiomer).

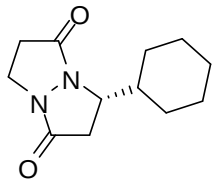


(*R*)-3,3-Dimethyl-7-phenyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6l). The title compound was prepared according to the above general procedures as a white solid (37.8 mg, 0.15 mol, 62% in 8.5:91.5 *er*) using conditions B at 0 °C for 4 days from benzaldehyde **7l** (25 μL, 0.25 mmol) and $(DHQ)_2PHAL$ (19.5 mg, 0.025 mmol, 0.1 equiv) in CH_2Cl_2 (1.25 mL). Recrystallization in MTBE afforded an enantiopur sample (19.6 mg, 0.08 mmol, 53%). m.p. 130-131 °C (MTBE). R_f = 0.33 (AcOEt). $[\alpha]_D^{20}$ −181.8 (*c* 1.00, $CHCl_3$). IR (neat) ν_{max}, 3050, 2977, 2932, 1669, 1327, 1309, 774, 771, 694 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.42-7.31 (5H, m), 5.27 (1H, dd, *J* = 10.7, 4.8 Hz), 3.45 (1H, dd, *J* = 17.4, 10.7 Hz), 2.87 (1H, dd, *J* = 17.4, 4.8 Hz), 2.82 (2H, s), 1.71 (3H, s), 1.65 (3H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 164.4 (C=O), 163.7 (C=O), 138.8 (C), 129.3 (CH), 128.7 (CH), 125.8 (CH), 59.2 (C), 54.1 (CH), 49.9 (CH_2), 44.0 (CH_2), 27.0 (CH_3), 25.2 (CH_3). HRMS (ESI^+): calcd for $C_{14}H_{17}N_2O_2$ $[(M+H)^+]$: 245.1285; Found: 245.1283. HPLC analysis: chiral column AD-H (heptane/*i*-PrOH: 85/15, flow rate 1 mL/min, UV 254 nm, t_{mino} = 10.7 min for *S* enantiomer; t_{majo} = 14.7 min for *R* enantiomer).



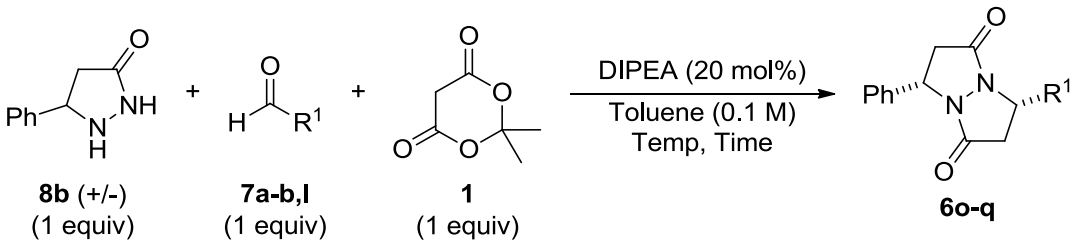
(*R*)-3-Phenyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6m). The title compound was prepared according to the above general procedures as a white solid (51.0 mg, 0.24 mmol, 59% in 55.5:44.5 *er*) using conditions A from azomethine imine **4m** (69.8 mg, 0.40 mmol). R_f = 0.40 (AcOEt). IR (neat) ν_{max} 3110, 3080, 3028, 2971, 2930, 2864, 1684, 1314, 1263, 770, 699 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.42-7.30 (5H, m), 5.37 (1H, dd, *J* = 10.5, 4.2 Hz), 4.23 (1H, dt, *J* = 11.9, 7.5 Hz), 3.83-3.72 (1H, m), 3.33 (1H, dd, *J* = 17.7, 10.5 Hz), 2.92-2.86 (3H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.1 (C=O), 170.3 (C=O), 139.4 (C), 129.3 (CH), 128.5 (CH), 125.8 (CH), 55.3 (CH), 41.7 (CH_2), 39.8 (CH_2), 33.0 (CH_2). HRMS (ESI^+): calcd for $C_{12}H_{13}N_2O_2$ $[(M+H)^+]$: 217.0972; Found: 217.0974. HPLC analysis: chiral column OJ-H

(heptane/*i*-PrOH: 70/30, flow rate 1 mL/min, UV 254 nm, t_{majo} = 49.4 min for *R* enantiomer; t_{mino} = 82.8 min for *S* enantiomer).

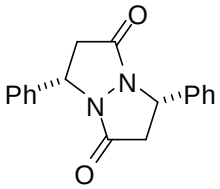


(*R*)-3-Cyclohexyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6n). The title compound was prepared according to the above general procedures as a white solide (49.8 mg, 0.22 mmol, 56% in 55.5:44.5 *er*) using conditions A from azomethine imine **4n** (72.1 mg, 0.40 mmol). R_f = 0.18 (AcOEt). IR (neat) ν_{max} 2922, 2852, 1691, 1325, 1295, 1272, 1221, 972, 712, 547 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 4.19-4.04 (2H, m), 3.71-3.60 (1H, m), 2.92-2.79 (3H, m), 2.63 (1H, dd, *J* = 17.8, 3.8 Hz), 1.80-1.59 (5H, m), 1.33-1.05 (6H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.4 (C=O), 171.0 (C=O), 57.8 (CH), 42.1 (CH), 39.5 (CH_2), 36.5 (CH_2), 33.1 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 25.8 (CH_2). HRMS (ESI^+): calcd for $C_{12}H_{19}N_2O_2$ [$(M+H)^+$]: 223.1441; Found: 223.1448. HPLC analysis: chiral column IB (heptane/*i*-PrOH: 60/40, flow rate 1 mL/min, UV 254 nm, t_{majo} = 9.3 min for *R* enantiomer; t_{mino} = 71.8 min for *S* enantiomer).

III-3 Diastereoselective synthesis of pyrazolidinones

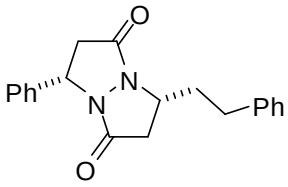


Representative general procedure for the diastereoselective synthesis of pyrazolidinones 6o-q. Pyrazolidinone **8b**[9] (40.5 mg, 0.25 mmol, 1.0 equiv), Meldrum's acid **1** (36.0 mg, 0.25 mmol, 1.0 equiv), DIPEA (9 μL, 0.05 mmol, 0.2 equiv), the appropriate aldehyde **7** (0.25 mmol, 1.0 equiv) were dissolved in toluene (2.5 mL) and the reaction mixture was stirred at the appropriate temperature during the required time. The crude mixture was then concentrated under reduced pressure and purified by column chromatography on silica gel (AcOEt to AcOEt/MeOH: 95/5) to afford product **6**. The major diastereoisomer could be easily separated during the purification step. The diastereoisomeric ratio (dr) was determined by ^{1}H NMR of the crude reaction mixture.

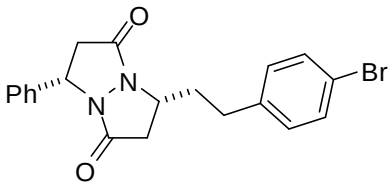


***cis*-3,7-Diphenyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6o).** The title compound was prepared according to the above general procedure as a white solid after 48 hours stirring at 20 °C (60.5 mg, 0.21 mmol, 83% in 93:7 *dr*) from benzaldehyde **7l** (25 μL, 0.25 mmol). R_f = 0.20 (AcOEt). m.p. 88-89 °C. IR (neat) ν_{max} 3100, 3050, 3028, 2971, 2932, 1679, 1304, 775, 713, 695 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.31-7.43 (10H, m), 5.45 (2H, dd, J = 10.6, 4.2 Hz), 3.38 (2H, dd, J = 17.7, 10.6 Hz), 2.92 (2H, dd, J = 17.7, 4.3 Hz). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 170.7 (C=O), 139.5 (C), 129.0 (CH), 128.1 (CH), 125.4 (CH), 55.0 (CH_2), 41.2 (CH_2). HRMS (ESI$^+$): calcd for $C_{18}H_{17}N_2O_2$ [$(M+H)^+$]: 293.1290; Found: 293.1282.

[9] Shintani, R.; Soh, Y.-T.; Hayashi, T. *Org. Lett.* **2010**, *12*, 4106-4109.



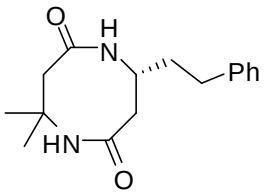
***cis*-3-Phenethyl-7-phenyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6p).** The title compound was prepared according to the above general procedure as a white solid after 14 hours stirring at 40 °C (70.5 mg, 0.22 mmol, 89% in >98:2 *dr*) from 3-phenylpropionaldehyde **7a** (35 μL, 0.25 mmol). R_f = 0.15 (AcOEt/MeOH, 95/5). m.p. 109-110 °C. IR (neat) ν_{max} 2926, 1687, 1660, 1330, 1313, 726, 700, 548 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.43-7.20 (10H, m), 5.39 (1H, dd, *J* = 10.5, 3.9 Hz), 4.47-4.39 (1H, m), 3.34 (1H, dd, *J* = 17.7, 10.5 Hz), 3.03 (1H, dd, *J* = 17.7, 9.8 Hz), 2.90-2.78 (3H, m), 2.57 (1H, dd, *J* = 17.7, 3.6 Hz), 2.27-2.17 (1H, m), 2.03-1.91 (1H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.1 (C=O), 170.7 (C=O), 140.5 (C), 139.6 (C), 129.1 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 126.2 (CH), 125.4 (CH), 54.7 (CH), 52.4 (CH), 41.6 (CH_2), 38.9 (CH_2), 37.1 (CH_2), 32.0 (CH_2). HRMS (ESI^+): calcd for $C_{20}H_{21}N_2O_2$ [$(M+H)^+$]: 321.1603; Found: 321.1607.



***cis*-3-(4-Bromophenethyl)-7-phenyltetrahydropyrazolo[1,2-*a*]pyrazole-1,5-dione (6q).** The title compound was prepared according to the above general procedure as a white solid after 14 hours stirring at 40 °C (95.5 mg, 0.24 mmol, 96% in >98:2 *dr*) from 3-(4-bromophenyl)propanal **7b** (53.3 mg, 0.25 mmol). R_f = 0.10 (AcOEt). m.p. 139-140 °C. IR (neat) ν_{max} 2926, 1688, 1659, 1496, 1356, 1318, 701, 550 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.43-7.28 (7H, m), 7.12 (2H, d, *J* = 8.3 Hz), 5.39 (1H, dd, *J* = 10.5, 3.9 Hz), 4.44-4.34 (1H, m), 3.33 (1H, dd, *J* = 17.7, 10.5 Hz), 3.03 (1H, dd, *J* = 17.7, 9.8 Hz), 2.86 (1H, dd, *J* = 17.9, 3.9 Hz), 2.75 (2H, dd, *J* = 7.4 Hz), 2.55 (1H, dd, *J* = 17.8, 3.6 Hz), 2.23-2.10 (1H, m), 1.97-1.86 (1H, m). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.2 (C=O), 170.9 (C=O), 139.5 (C), 139.5 (C), 131.5 (CH), 130.2 (CH), 129.1 (CH), 128.3 (CH), 125.4 (CH), 120.0 (C), 54.7 (CH), 52.2 (CH), 41.5 (CH_2), 38.8 (CH_2), 37.0 (CH_2), 31.5 (CH_2). MS (ESI^+): *m/z* 399.7 and

401.7 [$(M+H)^+$]. Anal. Calcd for $C_{20}H_{19}BrN_2O_2$: C, 60.16; H, 4.80; N, 7.02. Found: C, 59.99; H, 4.92; N, 6.80.

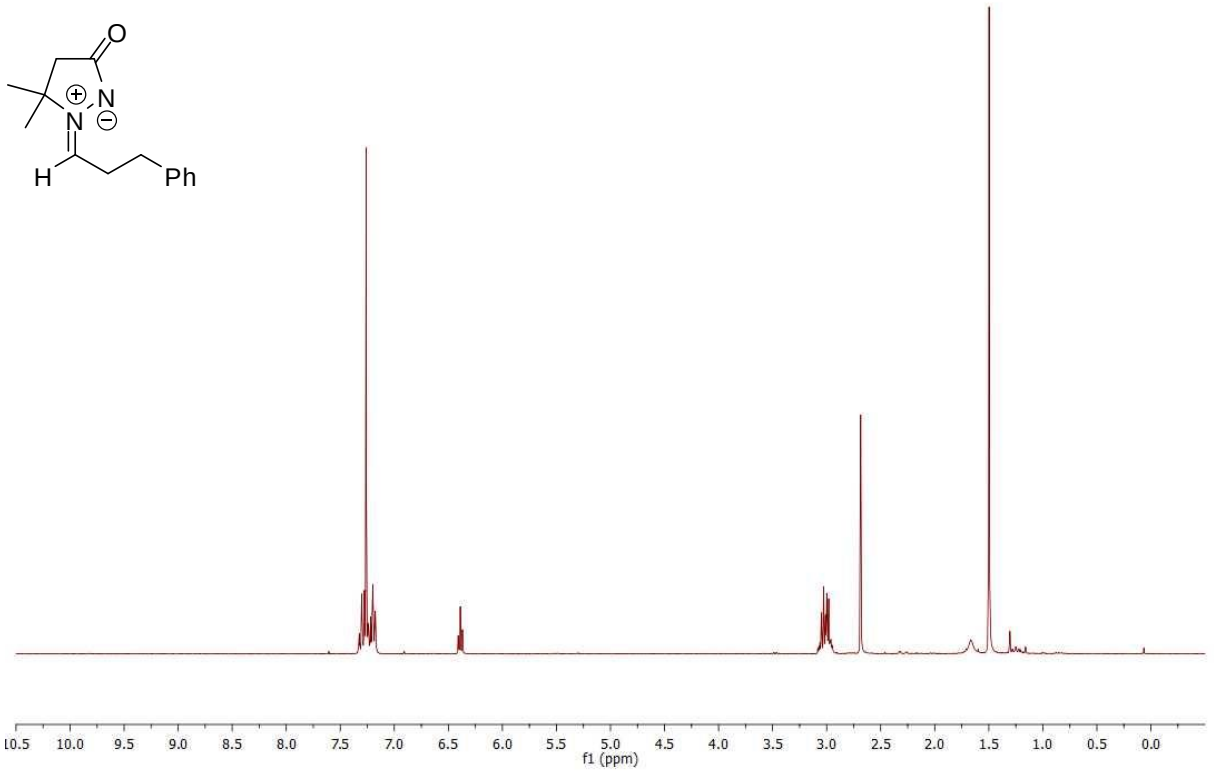
III-4 Reductive cleavage of bicyclopyrazolidinone N-N bond

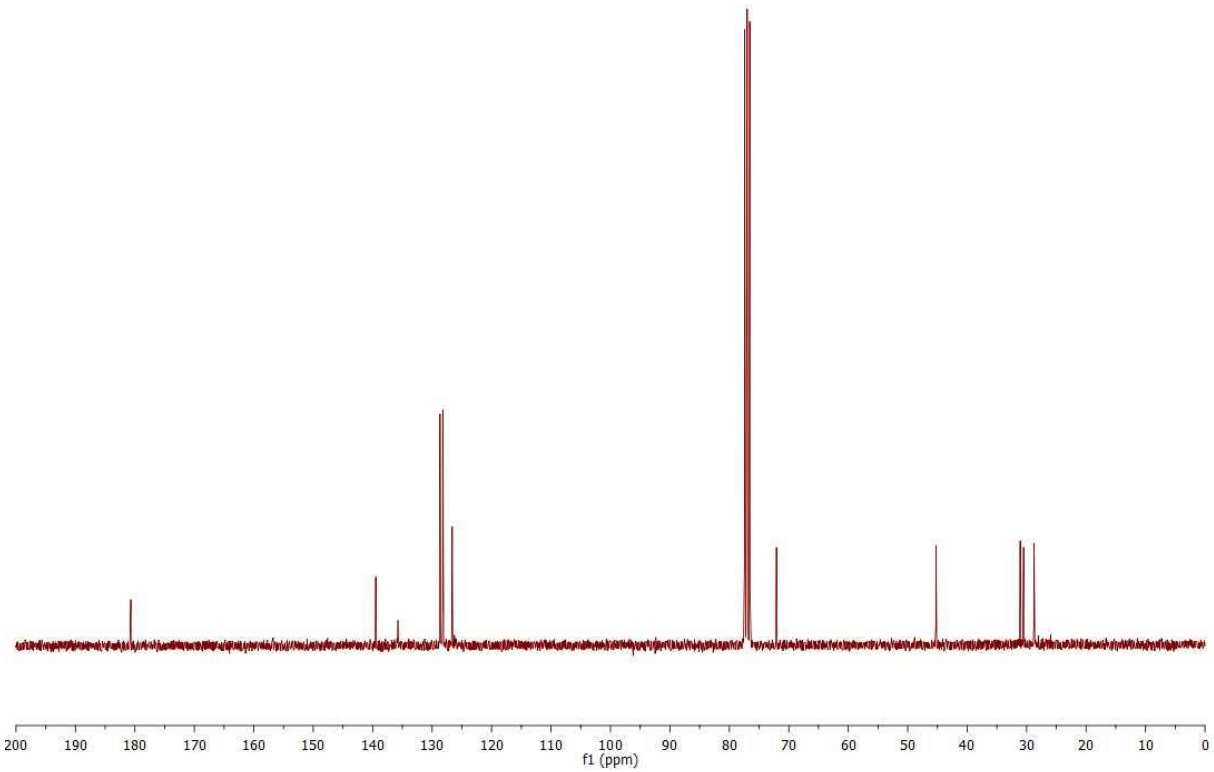


(*R*)-4,4-Dimethyl-8-phenethyl-1,5-diazocane-2,6-dione (11). Dry liquid ammonia was condensed at –78 °C in a three-necked round bottom flask equipped with a Dewar condenser cooled with solid CO_2 in acetone. A solution of bicyclopyrazolidinone **6a** (58.0 mg, 0.21 mmol, 7.5:92.5 *er*) in dry degassed THF (10 mL) was added followed by sodium metal (14.7 mg, 0.64 mmol). The solution became blue in 5 minutes and then discolored to a white cloudy solution. The resulting mixture was stirred for 1 hour at −78 °C before an excess of solid NH_4Cl was added. The reaction mixture was slowly warmed to room temperature until NH_3 has been distilled off. Water was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (AcOEt to AcOEt/MeOH: 95/5) to afford product **11** (33.0 mg, 0.12 mmol, 57% in 9.5:90.5 *er*). R_f = 0.10 (AcOEt/MeOH, 95/5). IR (neat) ν_{max}, 3210, 3067, 2971, 2926, 1651, 1453, 1411, 1244, 750, 700 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.96 (1H, br s), 7.4 (1H, s), 7.31-7.17 (5H, m), 3.56-3.44 (m, 1H), 2.89-2.56 (m, 6H), 2.13-2.01 (1H, m), 1.96-1.84 (1H, m), 1.44 (6H, s). ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 173.6 (C=O), 173.3 (C=O), 141.0 (C), 128.8 (CH), 128.7 (CH), 126.4 (CH), 51.5 (C), 49.1 (CH), 46.4 (CH_2), 40.1 (CH_2), 38.0 (CH_2), 32.1 (CH_2), 30.6 (CH_3), 30.2 (CH_3). HRMS (ESI^+): calcd for $C_{16}H_{23}N_2O_2$ [$(M+H)^+$]: 275.1754; Found: 275.1758. HPLC analysis: chiral column AD-H (heptane/*i*-PrOH: 70/30, flow rate 1 mL/min, UV 230 nm, t_{mino} = 15.5 min for *S* enantiomer; t_{majo} = 31.4 min for *R* enantiomer).

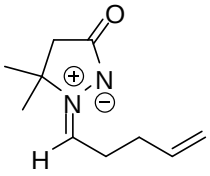
IV NMR spectra

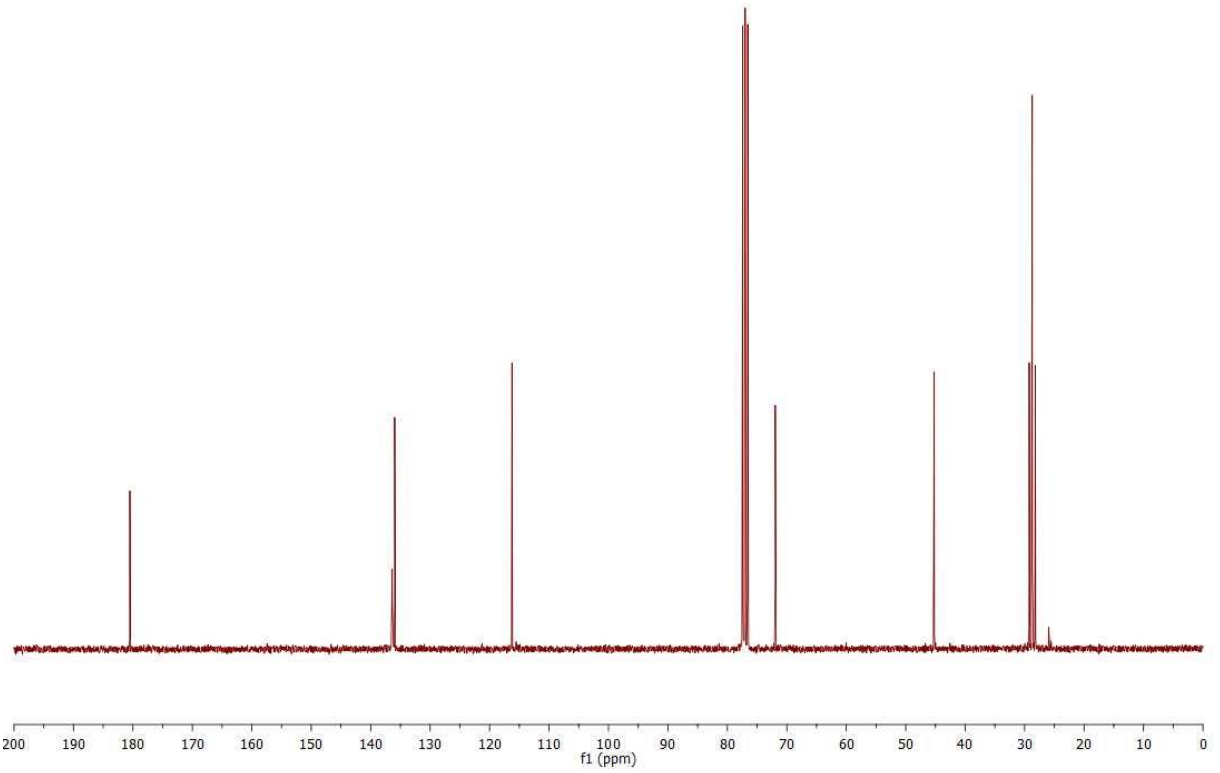
IV.1 1-Phenylpropylidene-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (4a)



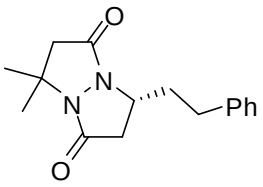


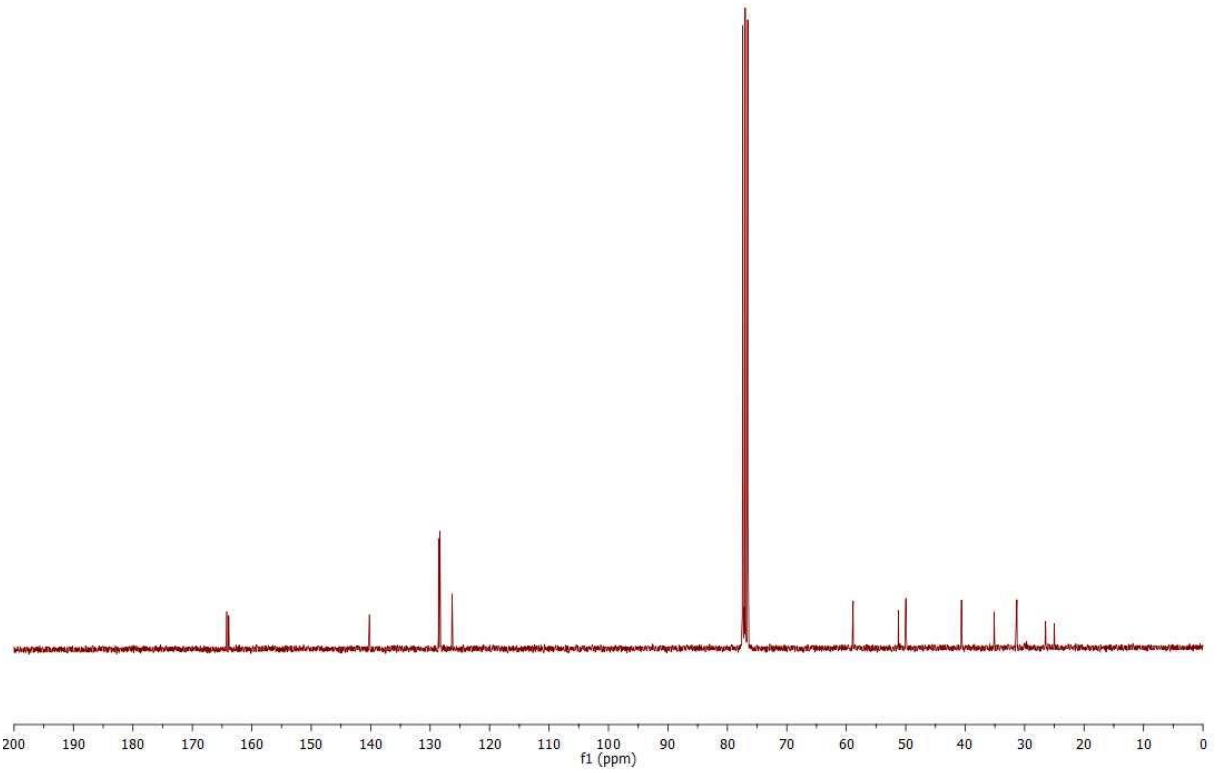
IV.2 1-(Pent-4'en-1'-ylidene)-5,5-dimethyl-3-oxopyrazolidin-1-ium-2-ide (4e)



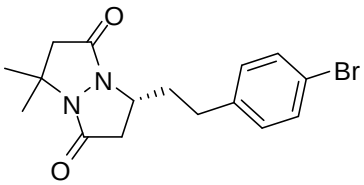


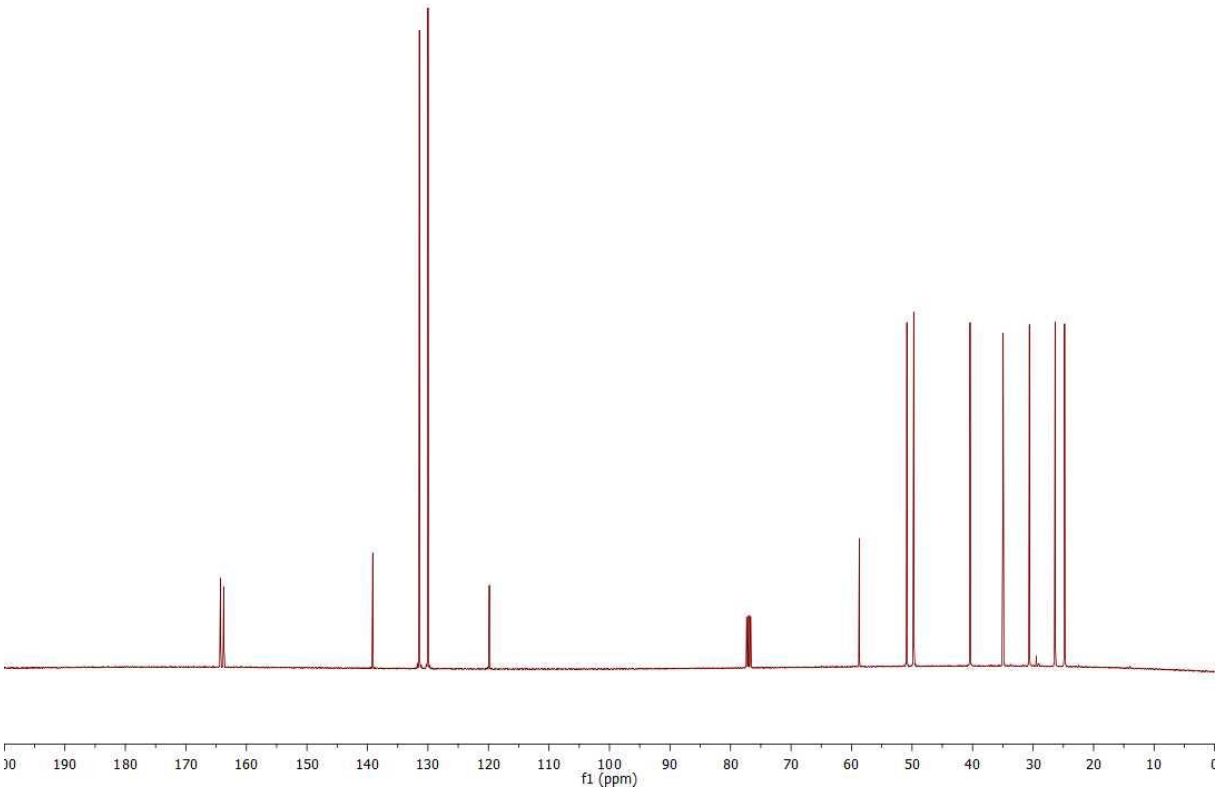
IV.3 (R)-3,3-Dimethyl-7-phenethyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6a)



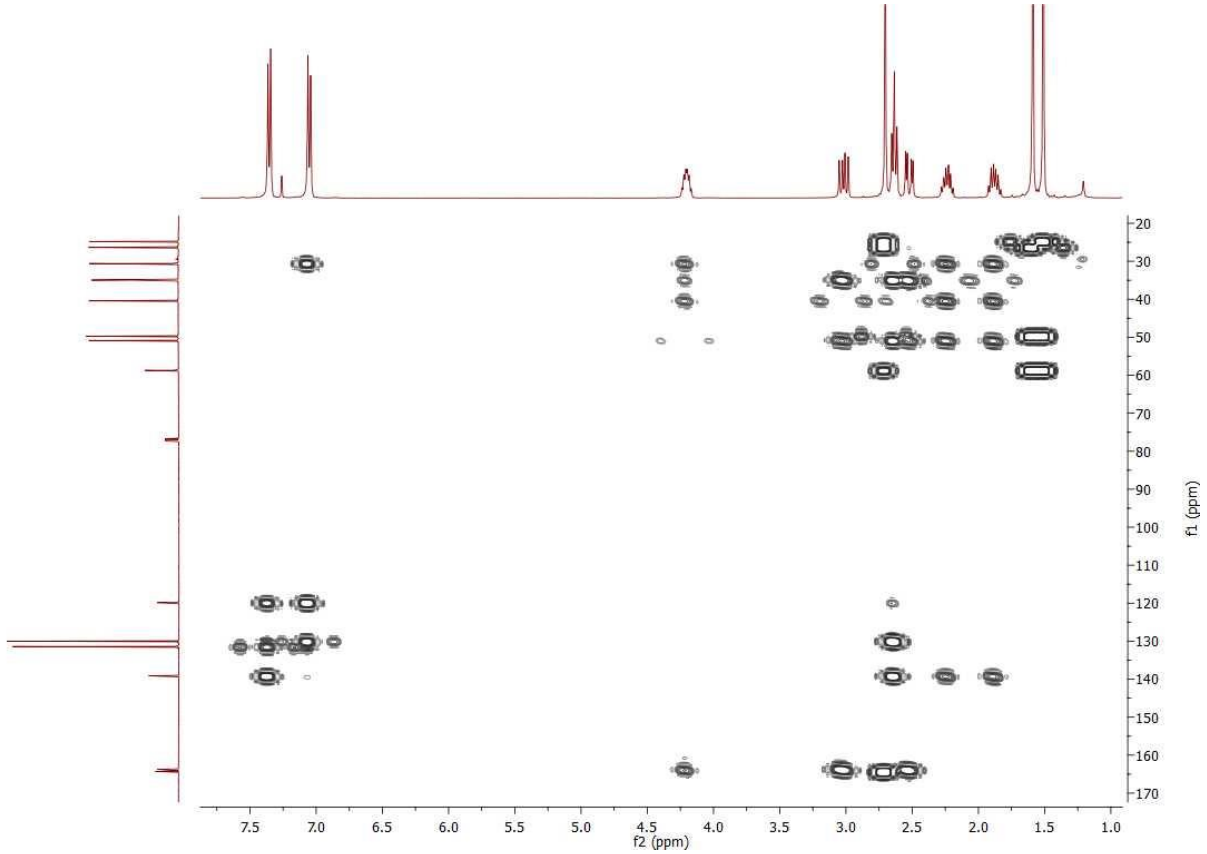


IV.4 (R)-3,3-Dimethyl-7-(2'-(p-bromophenyl)ethyl)tetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6b)

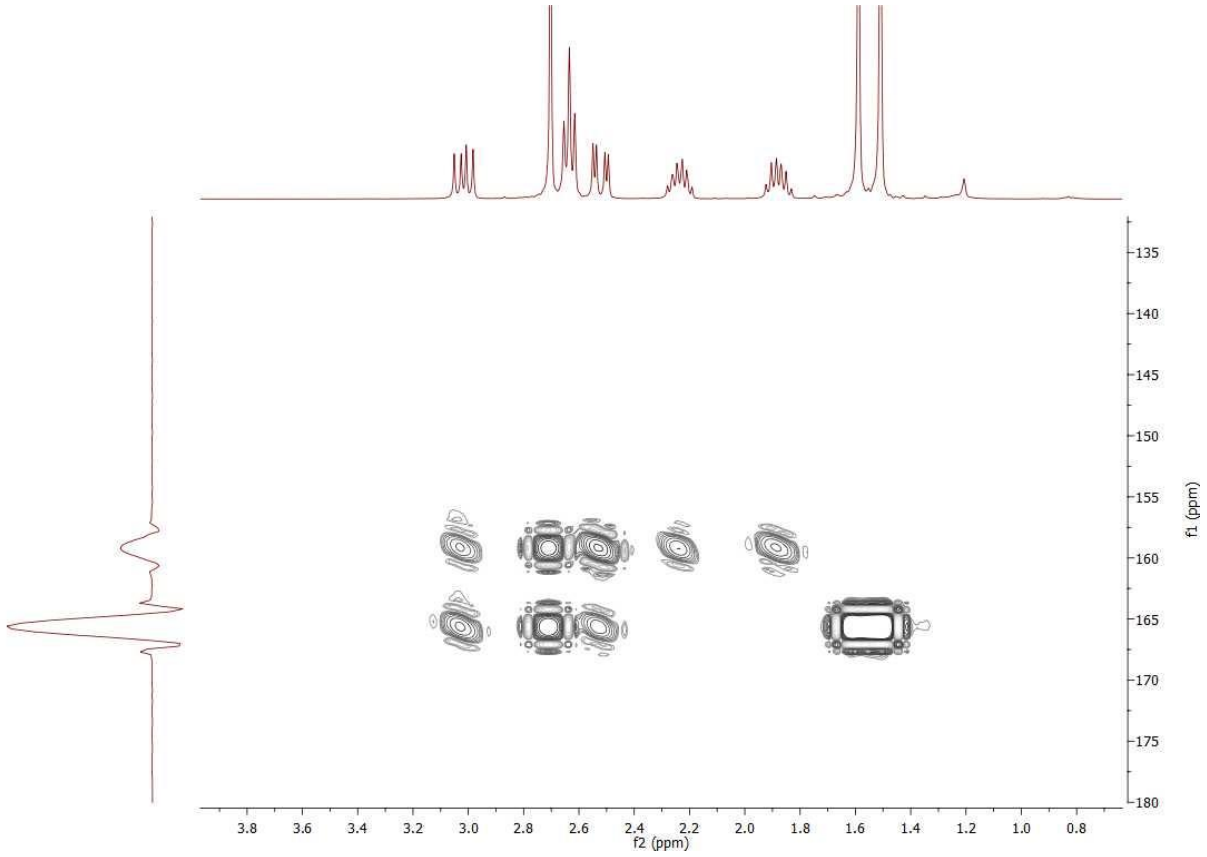




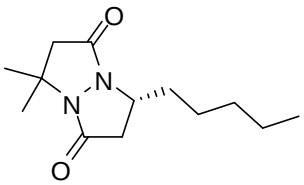
HMBC $^{1}H/^{13}C$ NMR (400 MHz)

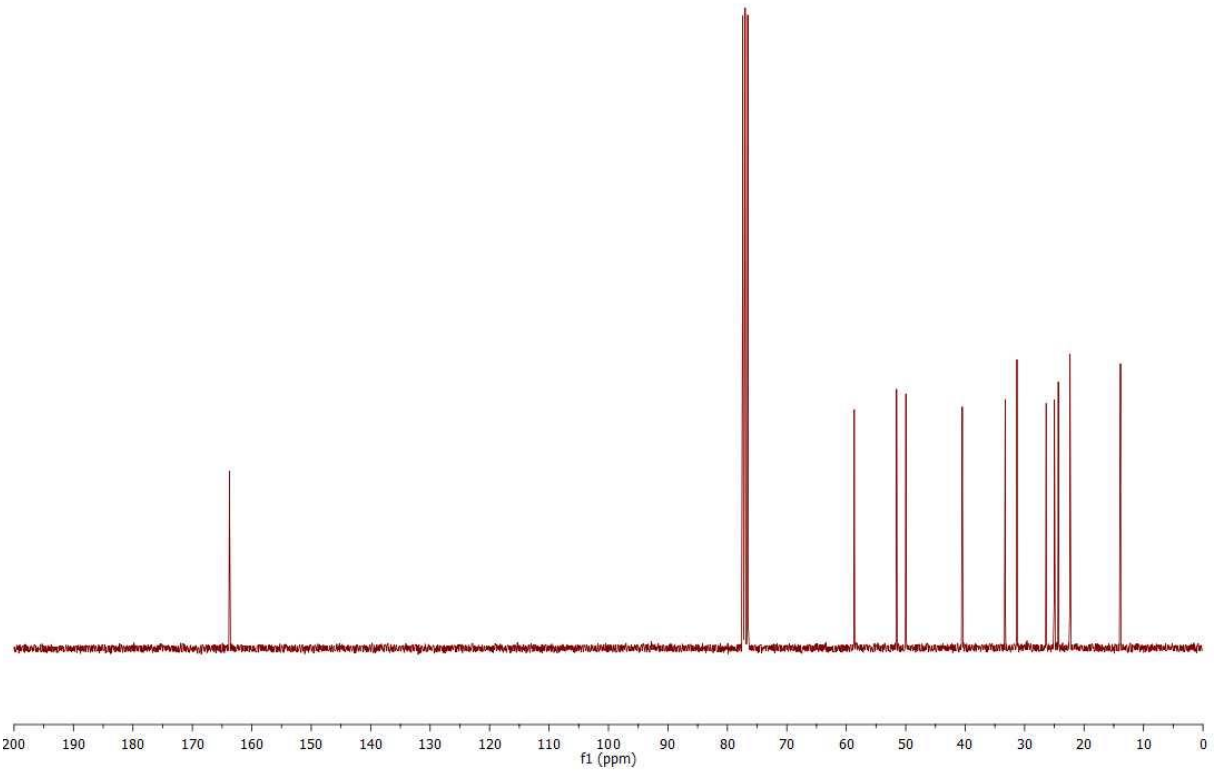


HMBC $^{1}H/^{15}N$ NMR (400 MHz) displaying ^{3}J coupling constant

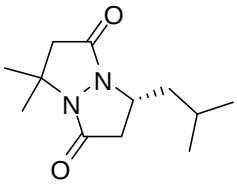


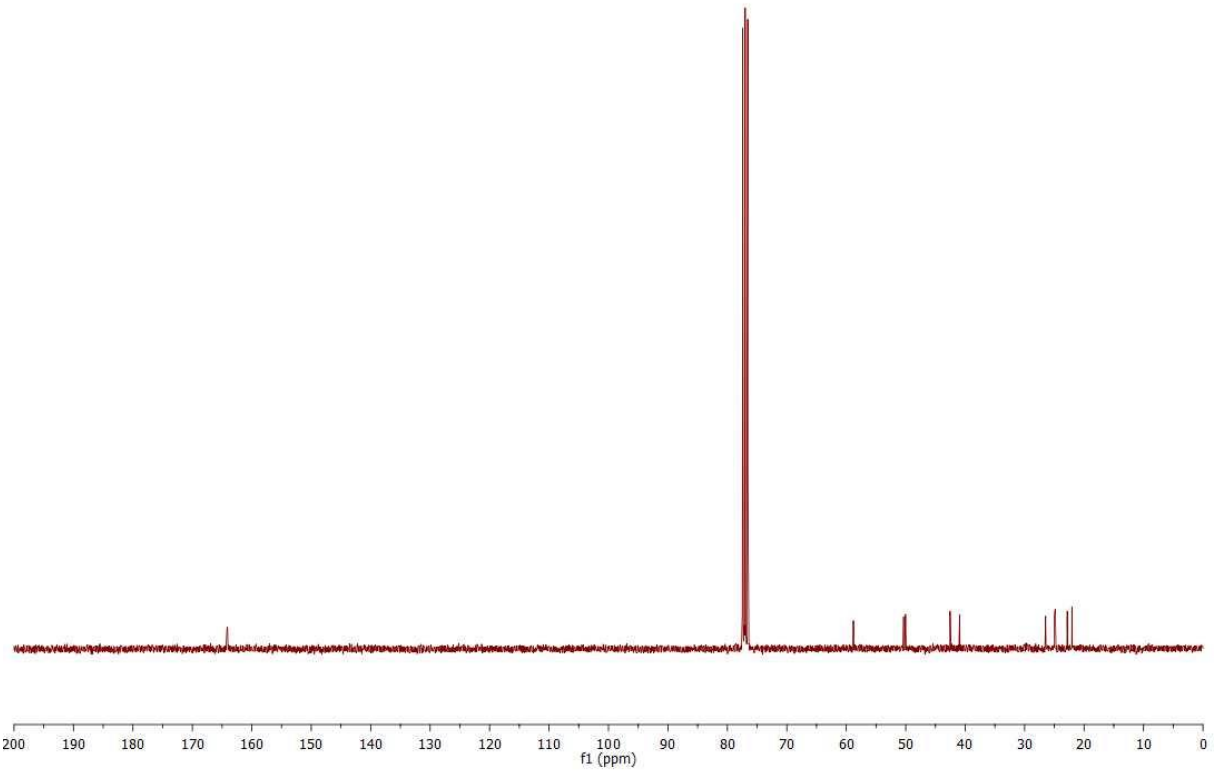
IV.5 (R)-3,3-Dimethyl-7-pentyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6c)



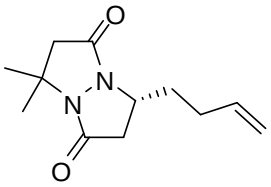


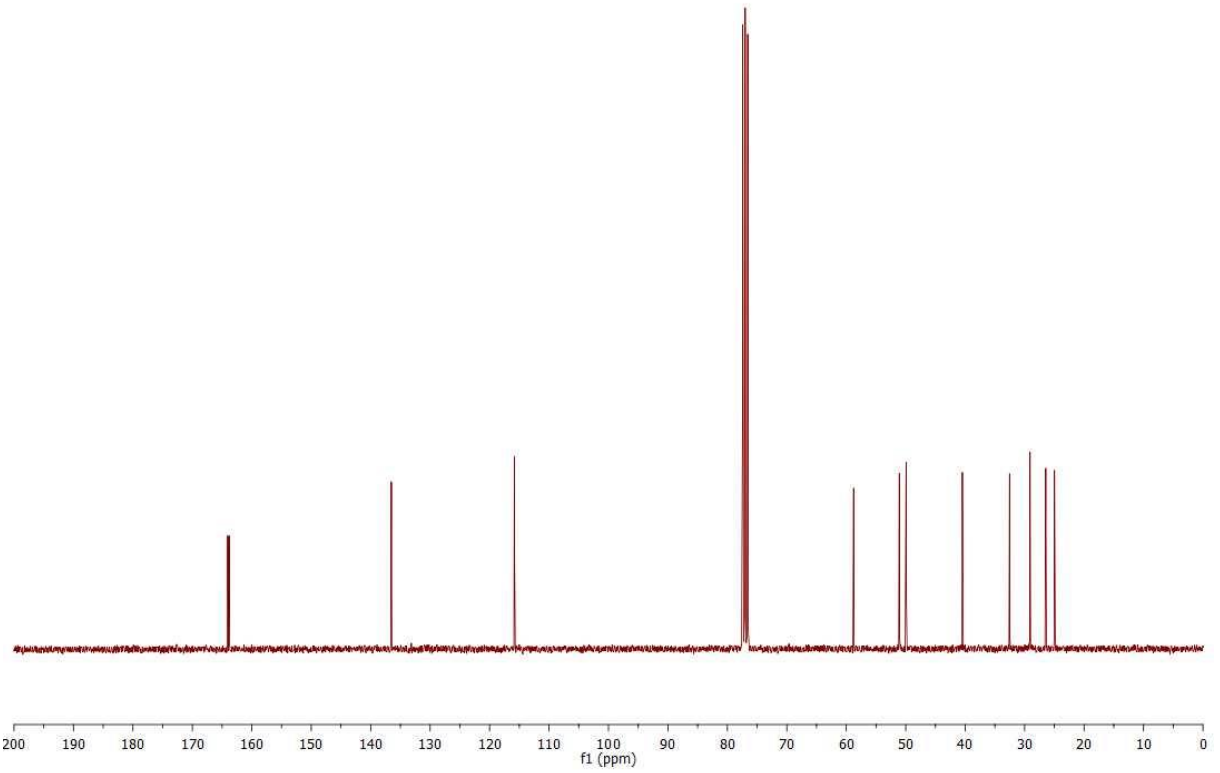
IV.6 (R)-3,3-Dimethyl-7-isobutyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6d)



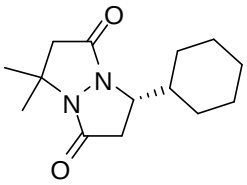


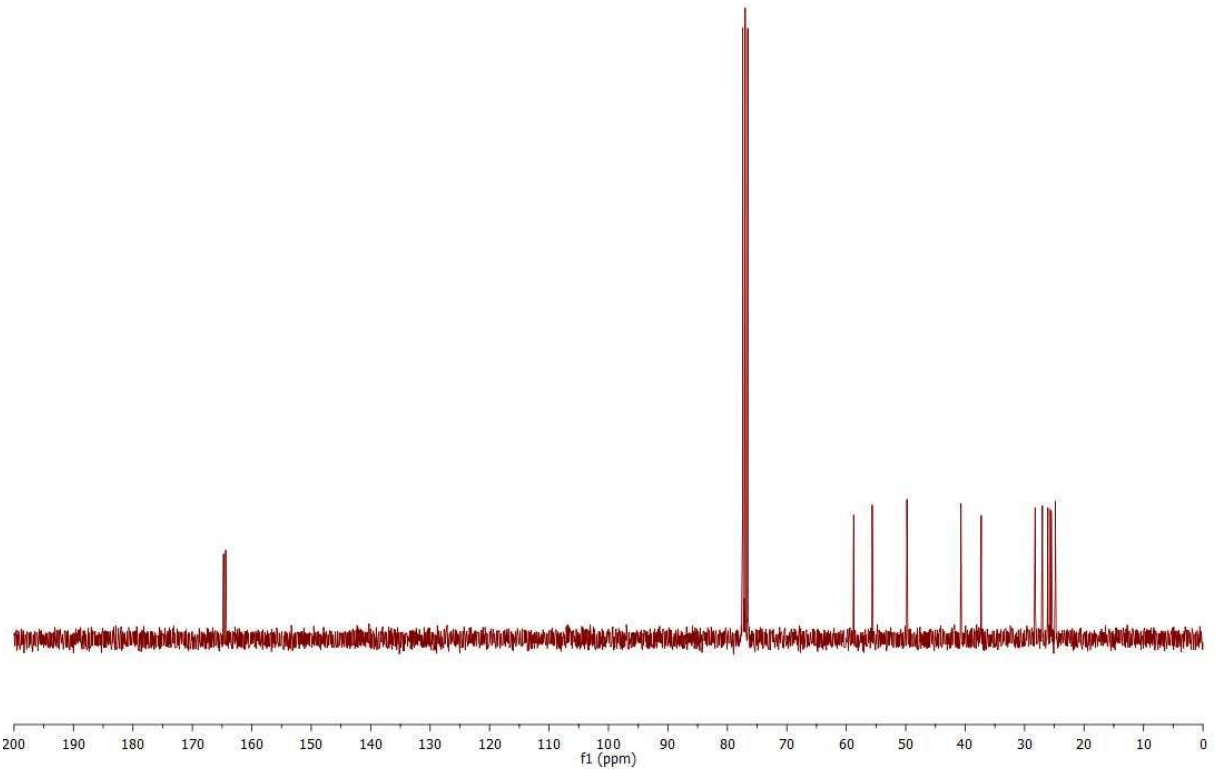
IV.7 (R)-3,3-Dimethyl-7-(but-3'-en-1'-yl)-tetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6e)



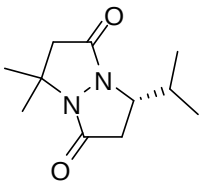


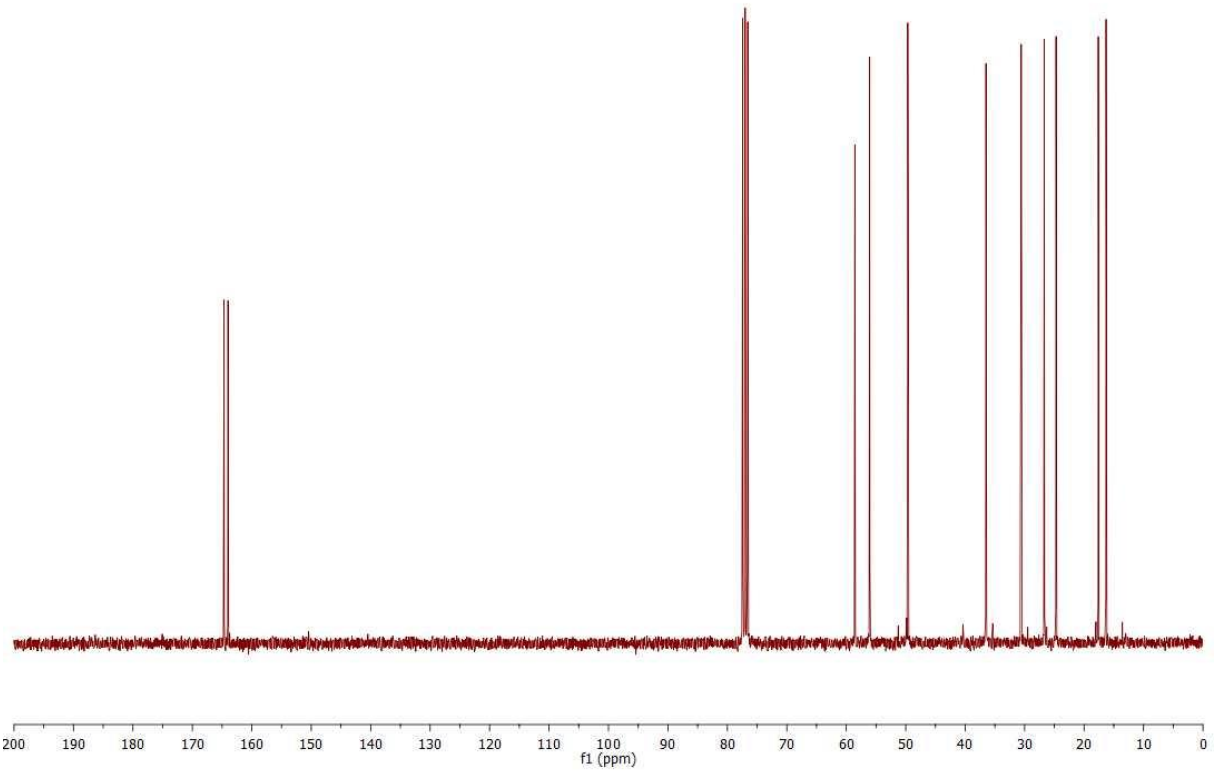
IV.8 (R)-3,3-Dimethyl-7-cyclohexyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6f)



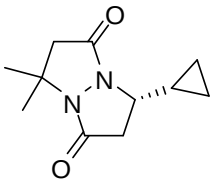


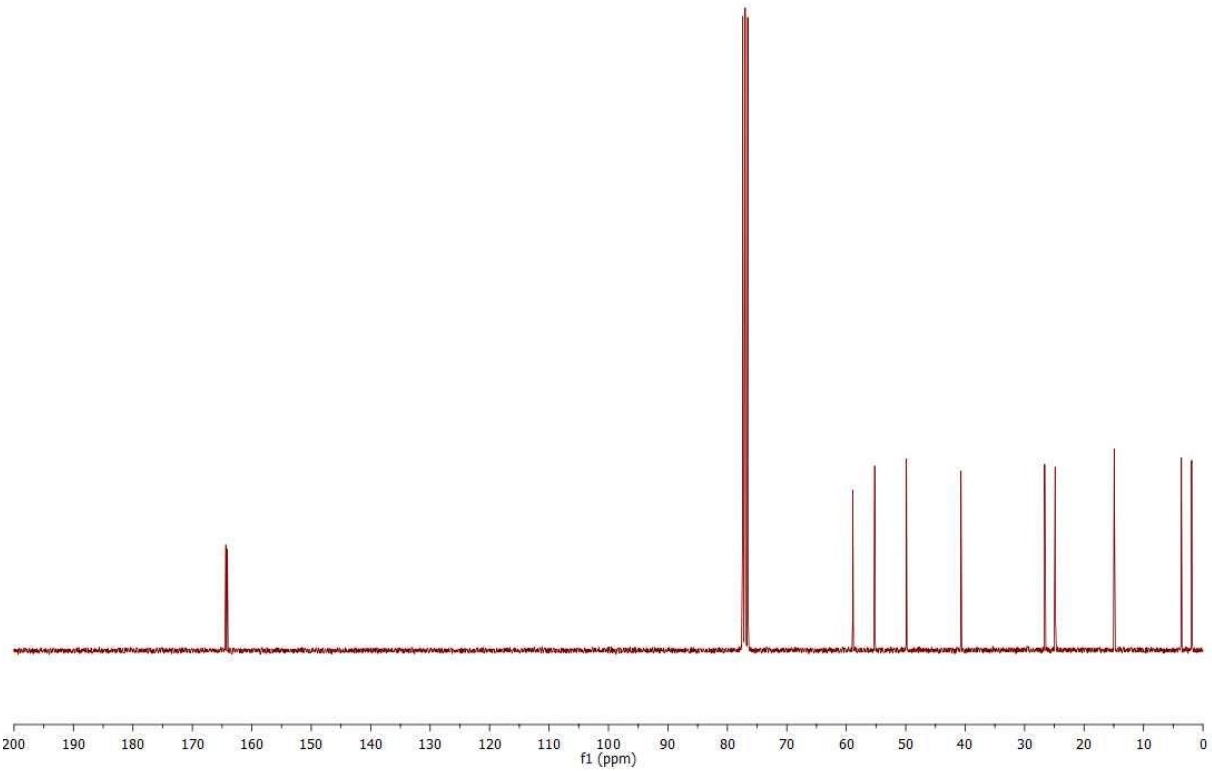
IV.9 (R)-3,3-Dimethyl-7-isopropyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6g)



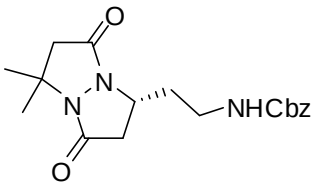


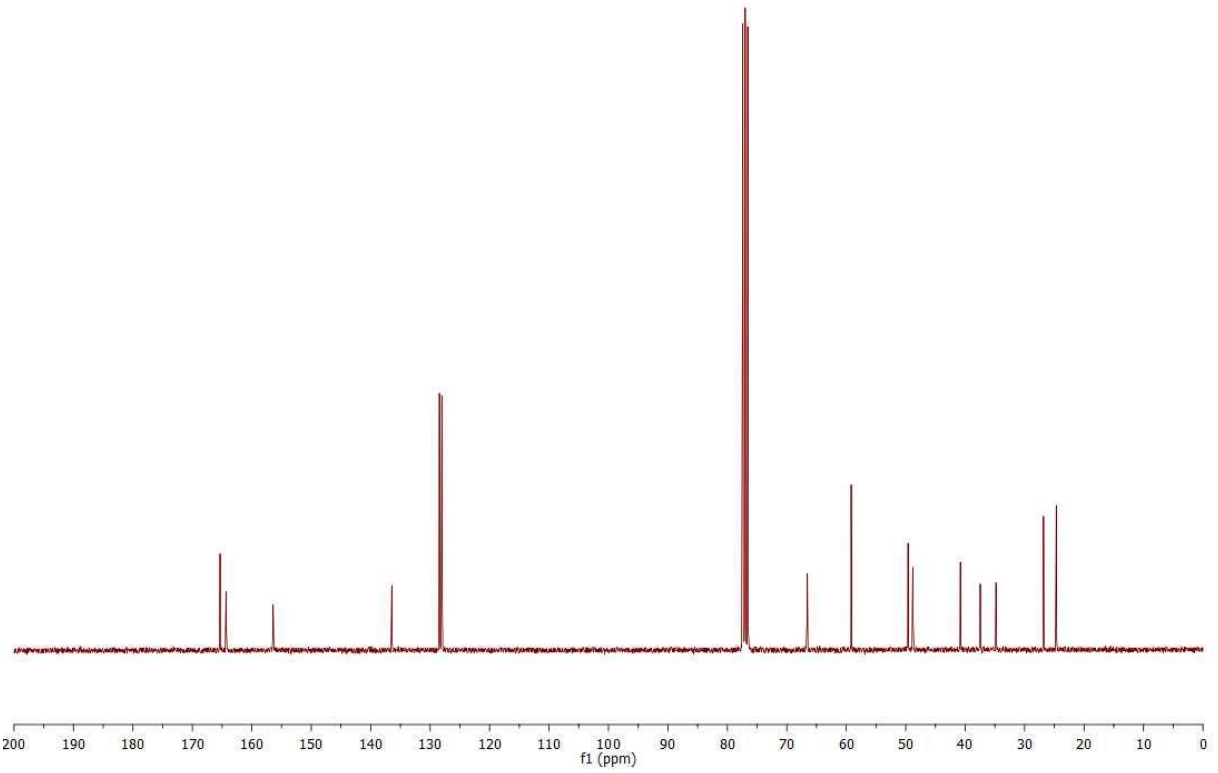
IV.10 (R)-3,3-Dimethyl-7-cyclopropyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6h)



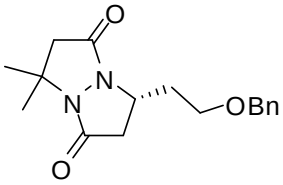


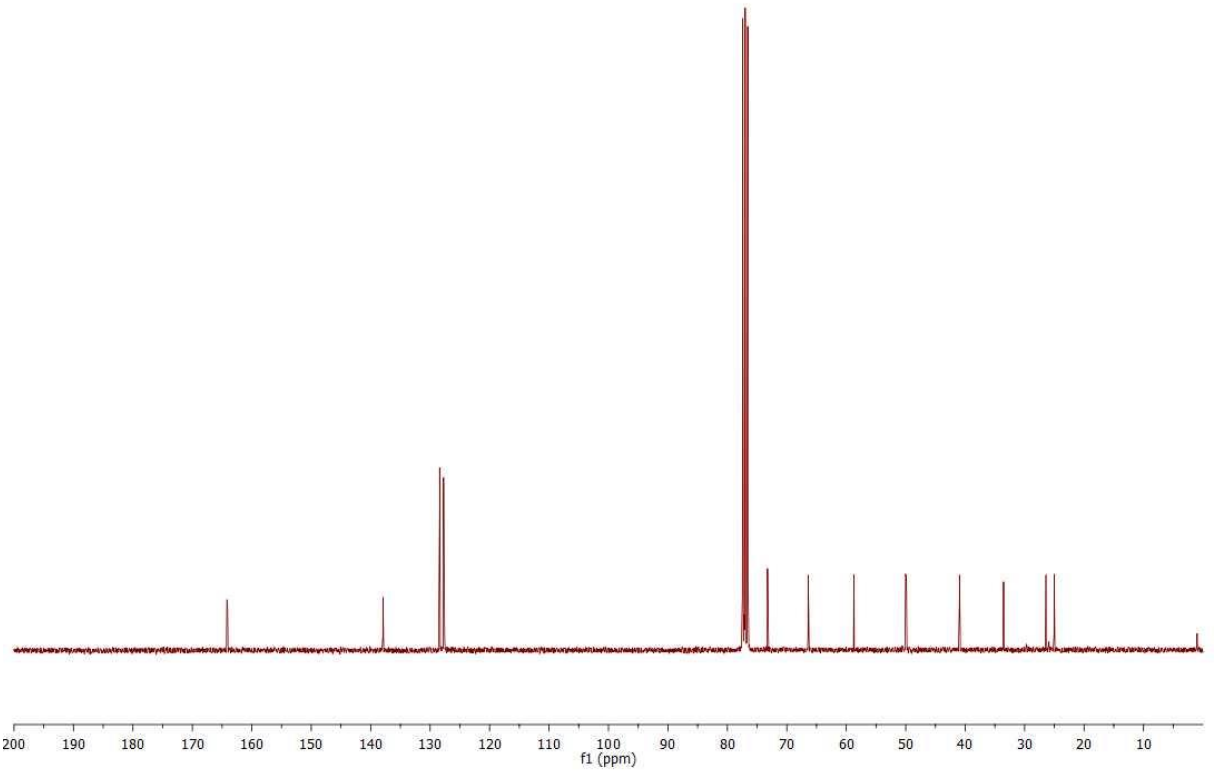
IV.11 (R)-3,3-Dimethyl-7-(2'-((benzyloxycarbonyl)amino)ethyl)-tetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6i)



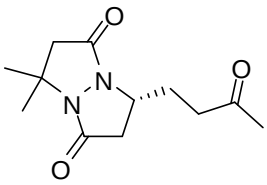


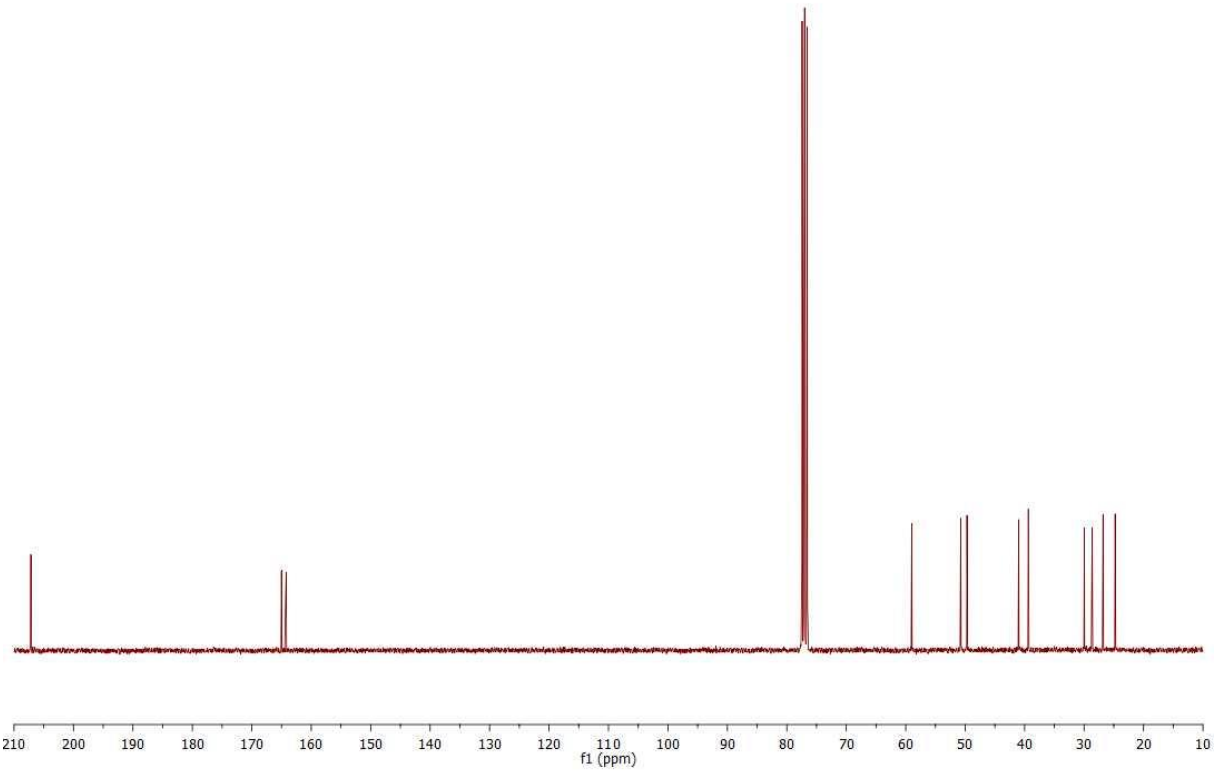
IV.12 (R)-3,3-Dimethyl-7-(2'-(benzyloxy)ehtyl)-tetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6j)



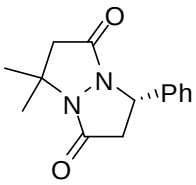


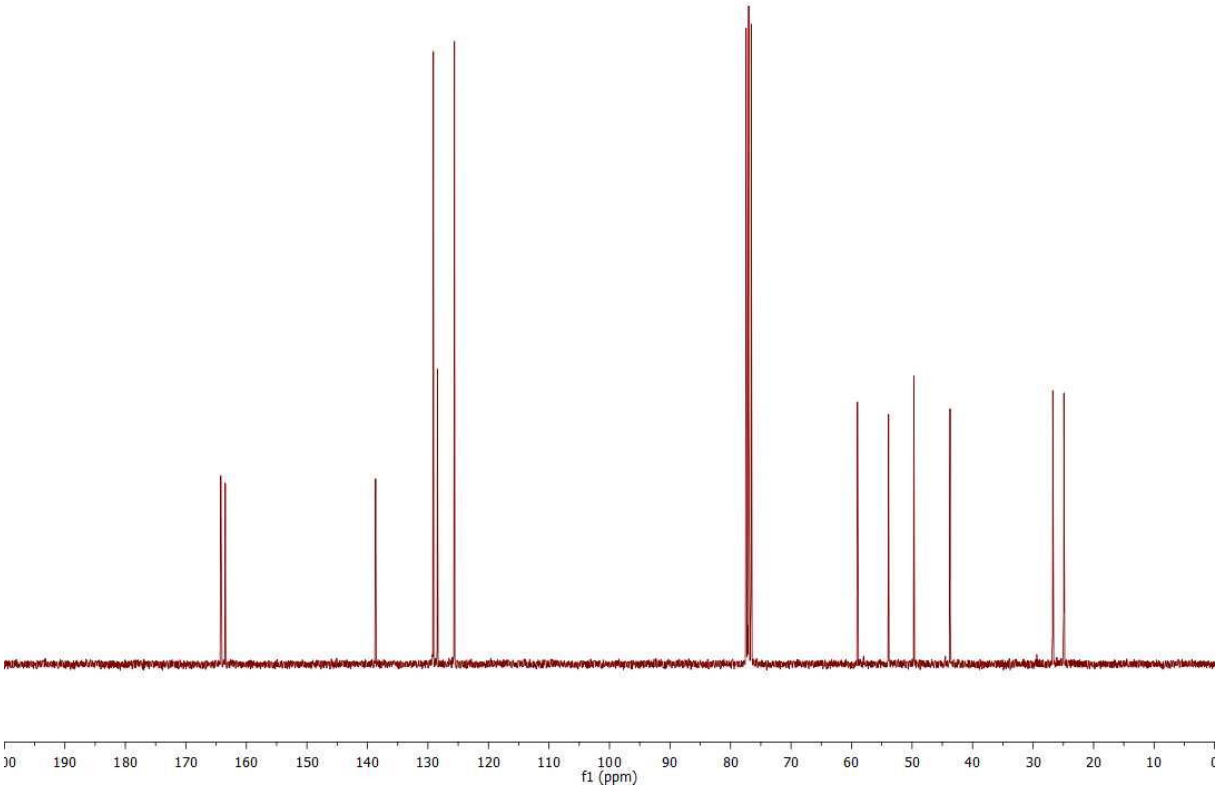
IV.13 (R)-3,3-Dimethyl-7-(3'-oxobutyl)-tetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6k)



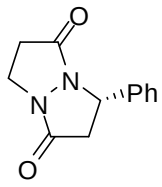


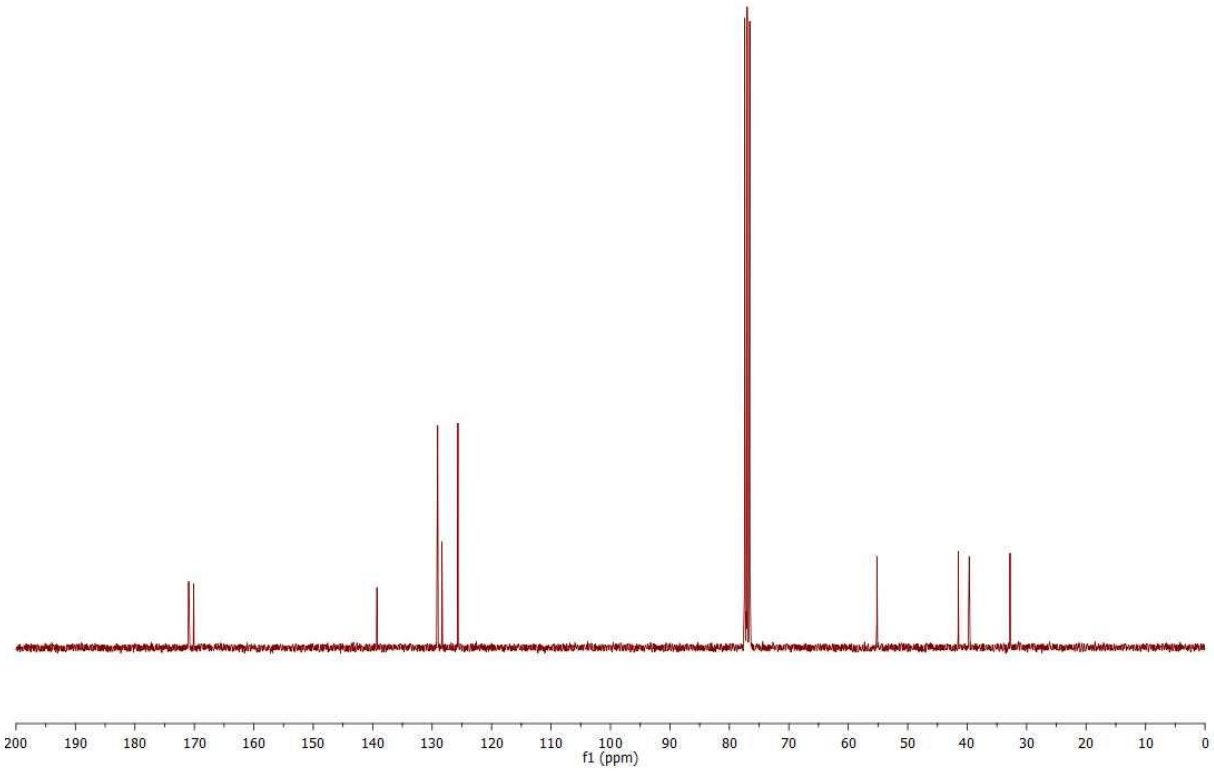
IV.14 (R)-3,3-Dimethyl-7-phenyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6l)



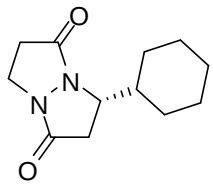


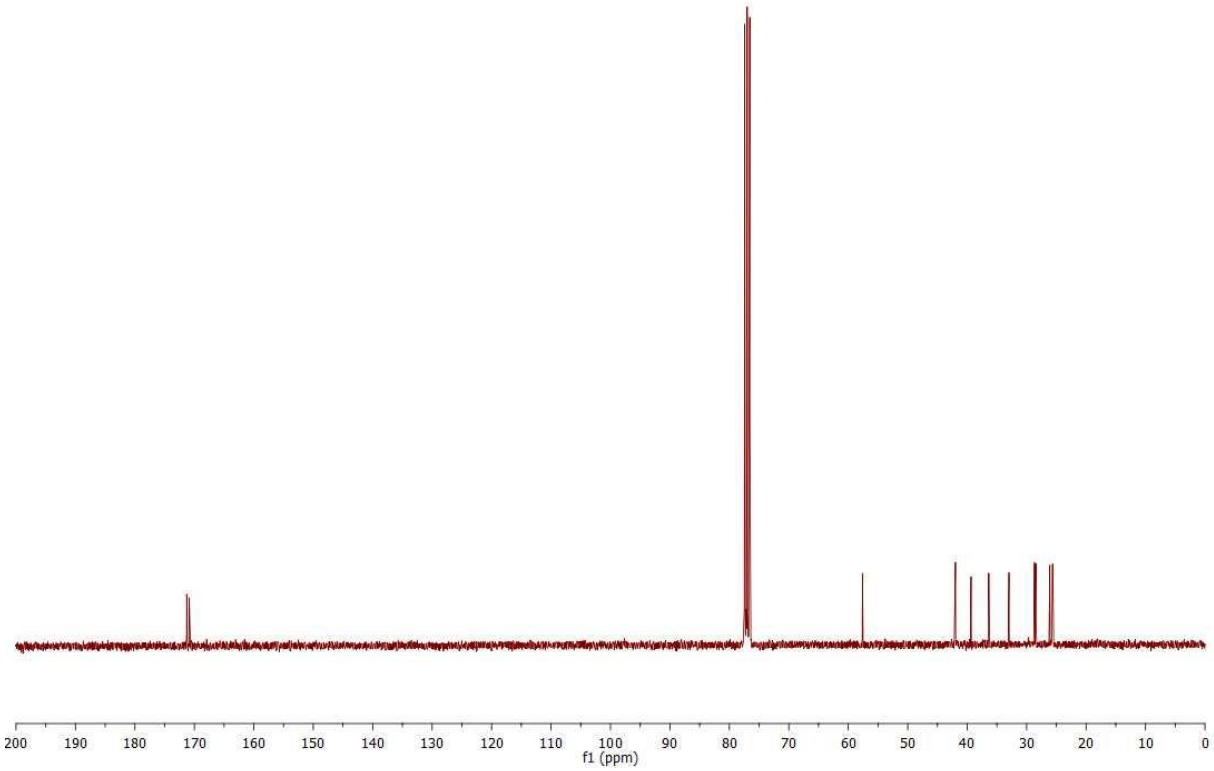
IV.15 (R)-3-Phenyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6m)



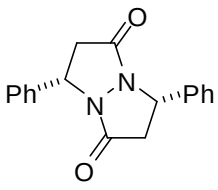


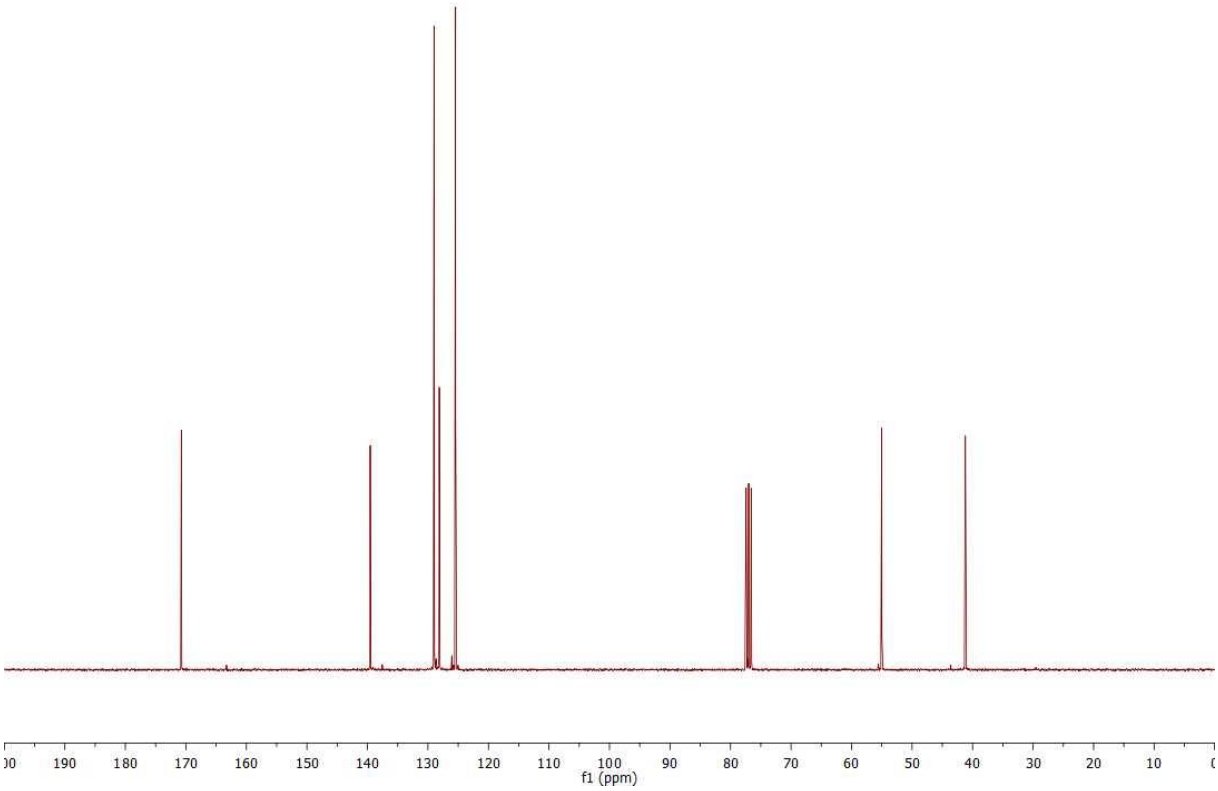
IV.16 (R)-3-Cyclohexyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6n)



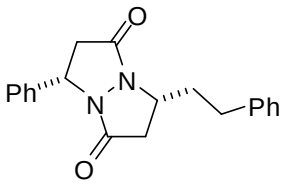


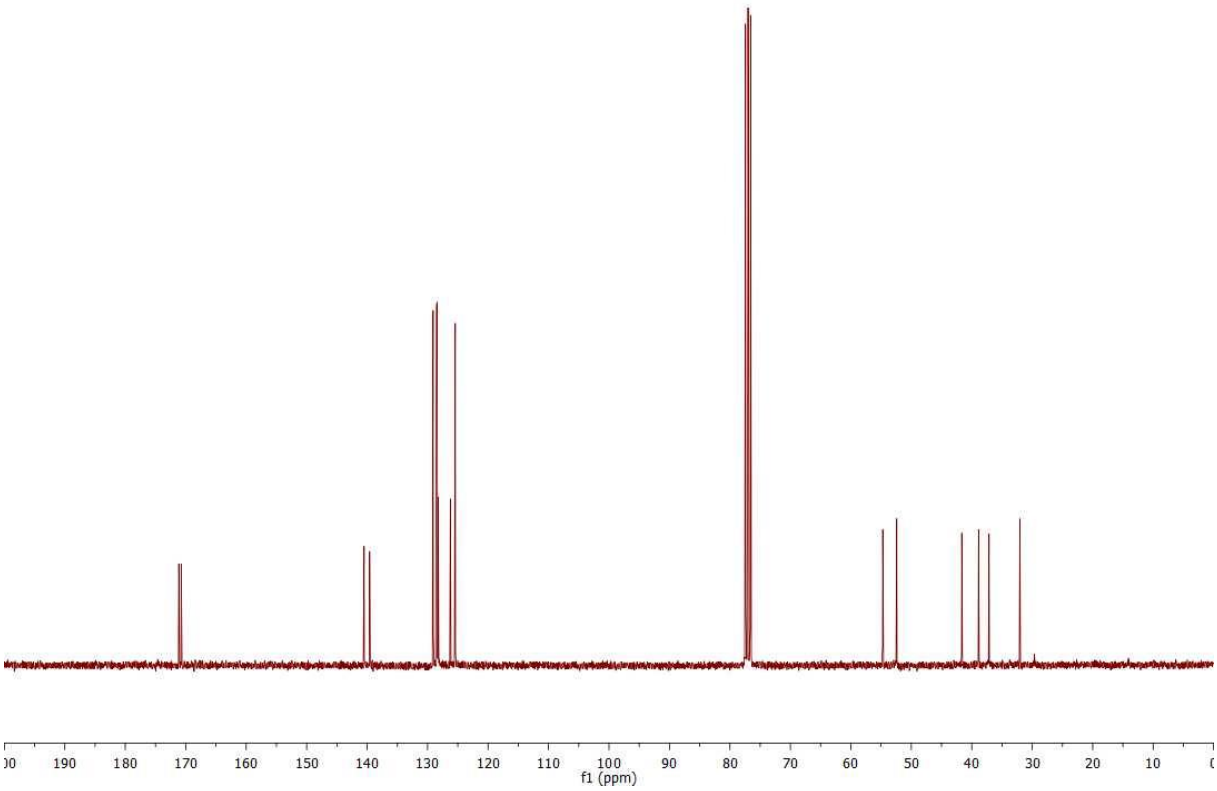
IV.17 cis-3,7-Diphenyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6o)



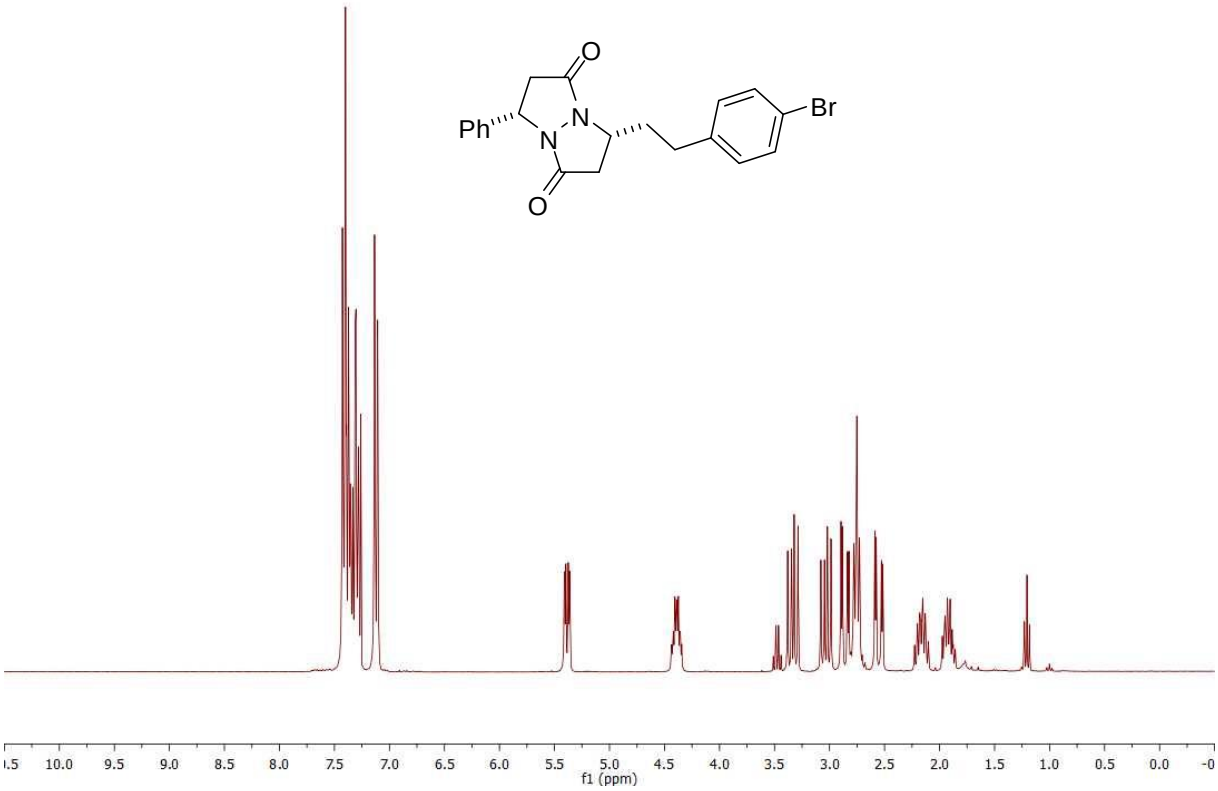


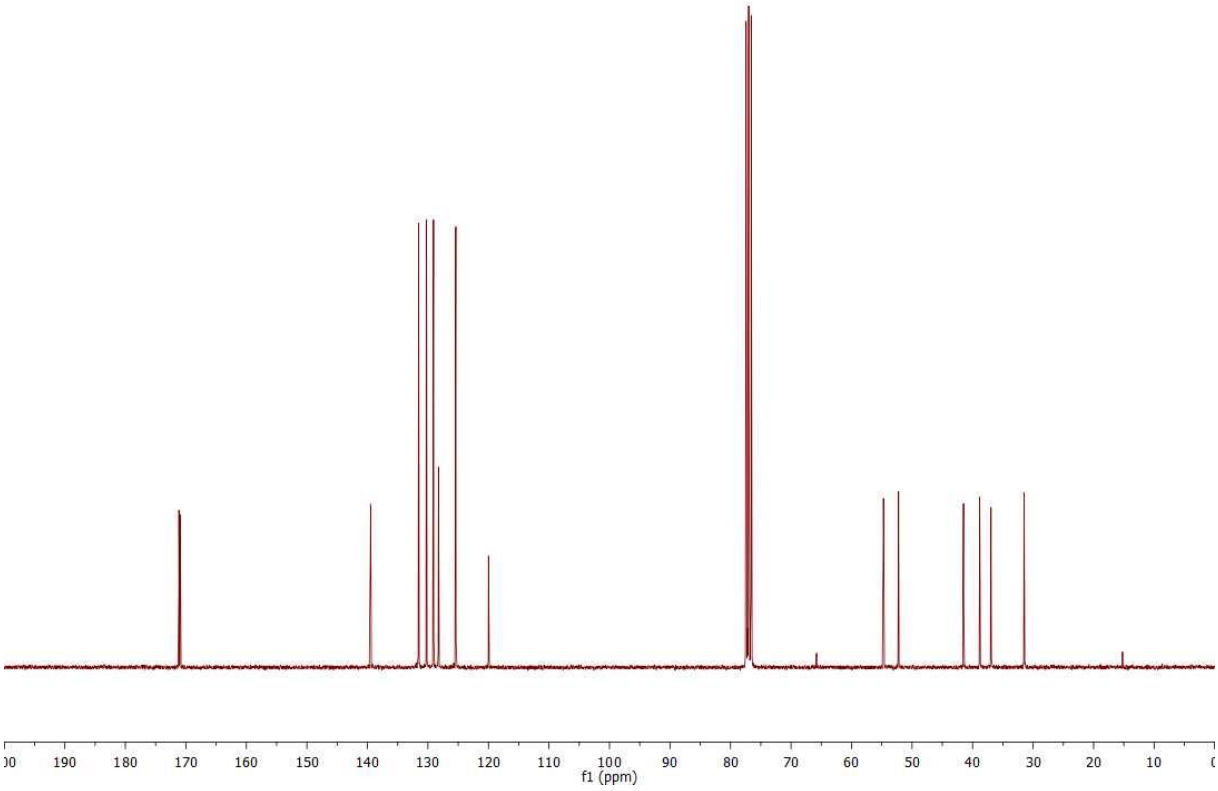
IV.18 cis-3-Phenethyl-7-phenyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6p)





IV.19 cis-3-(4-Bromophenethyl)-7-phenyltetrahydropyrazolo[1,2-a]pyrazole-1,5-dione (6q)





IV.20 (R)-4,4-Dimethyl-8-phenethyl-1,5-diazocane-2,6-dione (11)