Supporting Information

Design and Scale-Up of a Practical Enantioselective Route to 5-Phenylbicyclo[2.2.2]oct-5-en-2-one

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Content:

General:

Unless otherwise stated the ^{1}H, ^{13}C NMR, GC-MS, LC-MS, and chiral HPLC data are presented for the crude intermediates of the runs described in the experimental part on kilogram scale.

Parameters for the GC-MS, LC-MS and chiral HPLC method

GC-MS:

Thermo Trace GC Ultra, Thermo DSQ II MS detector, Thermo TriPlus Autosampler

Injection volume:	1 μL
Column:	Zebron ZB-5-MS, 15 m x 0.25 mm ID, 0.25 mm film
Column flow:	2 ml/min
Carrier gas:	Helium
Split ratio:	20
SSL inlet temp.:	200 °C
Temp. gradient:	60-300 °C from 0 to 4.0 min, 300 °C isotherm from 4.0 to 5.0 min
Ionization:	Chemical ionization with CH_4 as reagent gas

LC-MS method 1:

Agilent G1956B (MS, Ionisation: ESI+, APCI), Agilent G1312B Bin Pump, Agilent G1315C DAD, Agilent G1316B (thermostated column compartment), Agilent G1367C (auto sampler)

Injection volume:	2 μL	
Column:	Kinetex C18, 2.6 μm, 2.1 x 50 mm	
Column flow:	1 ml/min	
Eluent:	Eluent A: Water, 0.08% TFA (trifluoroacetic acid)	
	Eluent B: Acetonitrile, 0.012% TFA	
Gradient:	2.0 min	95% B
	2.8 min	95% B
	3.0 min	5% B
Pressure:	380 bar	
Temperature:	40 °C	
Detection wavelength:	210 nm	

LC-MS method 2:

Same hardware as LC-method 1

Injection volume:	2 μL	
Column:	Eclipse Plus C18, 1.8 μm, 2.1 x 50 mm	
Column flow:	1 ml/min	
Eluent:	Eluent A: Water, 0.08% TFA (trifluoroacetic acid)	
	Eluent B: Acetonitrile, 0.012% TFA	
Gradient:	2.0 min	95% B
	2.8 min	95% B
	3.0 min	5% B
Pressure:	480 bar	
Temperature:	50 °C	
Detection wavelength:	210 nm	

Chiral HPLC method:

Dionex HPG-3400SD Bin pump, Dionex DAD-3000

Injection volume:	2 μL
Column:	ChiralPak AS-H, 4.6 x 250 mm, 5 μm
Column flow:	0.8 ml/min
Eluent:	Heptane (60%) / 2-propanol (40%)
Concentration:	4 mg / mL heptane / 2-propanol 1 : 1
Detection:	210 nm
Temperature:	25 °C

Experimental data for the reactions as depicted in Scheme 4

2-Phenyl-2-(1,4-dioxaspiro[4.5]decan-7-yl)acetonitrile (rac. 11, 1:1 mixture of stereoisomers). Ethylene glycol (26 mL) and pTsOH·H_2O (0.5 g), were added to a soln. of 2-(3-oxocyclohexyl)-2-phenylacetonitrile **20** (10 g, 1:1 mixture of diastereoisomers) in toluene (40 mL). The mixture was heated to reflux for 1.5 h with azeotropic removal of water. After cooling to 20-25 °C, a 1M aqu. NaOH-soln. (0.15 mL) and water were added (40 mL). After phase separation the org. layer was washed with water (40 mL) and concentrated to dryness at 45 °C under reduced pressure to yield rac. **11** as an orange oil containing residual toluene. This crude material was used in the next step without further purification. Yield: 11.9 g (99 %). LC-MS method 2: 67% a/a (toluene substracted), R_t 1.50 min, $[M+1]^+$ = 258; GC-MS: 98% a/a, R_t 3.52 min, $[M+1]^+$ = 258; ^{1}H NMR (MeOD): δ 7.32-7.45 (m, 5H), 7.10-7.26 (m, 1H), 3.84-4.01 (m, 4H), 2.03-2.18 (m, 1H), 1.62-1.85 (m, 4H), 1.30-1.56 (m, 3H), 1.07-1.21 (m, 1 H).

2-Phenyl-2-(1,4-dioxaspiro[4.5]decan-7-yl)acetaldehyde (rac. 21, 1.1 mixture of stereoisomers). A soln. of nitrile rac. **11** (82 g, 1:1 mixture of diastereoisomers) in THF (82 mL) was added drop-wise at 20-25 °C to a 1M soln. of DIBALH in heptane (542 mL) (*exothermic reaction*). After stirring at 20-25 °C for 1 h, TBME (575 mL) was added at 5 °C, followed by the slow addition of a mixture of water (23 mL) in THF (115 mL) (*exothermic reaction*). A soln. of citric acid monohydrate (134 g) in water (246 mL) was added drop-wise (*exothermic reaction*) and the mixture was stirred for 1 h. The layers were separated and the aqu. phase was extracted with TBME (575 mL). The combined org. extracts were concentrated to dryness at 45 °C under reduced pressure to afford rac. **21** as a yellow oil which was used in the next step without further purification. Yield: 49 g (59 %). LC-MS method 2: 84% a/a, R_t 1.24 min, 1.29, $[M-18]^+$ = 242; ^{1}H NMR (CD_3OD): δ 9.67 (s, 0.5H), 9.66 (s, 0.5H), 7.44-7.16 (m, 5H), 3.37-4.07 (m, 4 H), 2.41-2.65 (m, 1H), 0.77-1.92 (m, 9H).

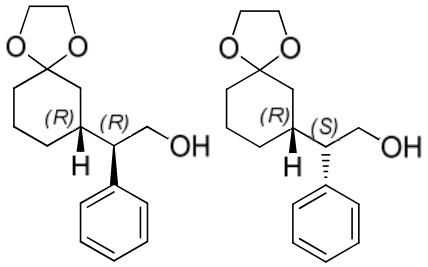
(1R*,4R*,5S*,6S*)-6-Hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (rac. 9). A 5M aqu. phosphoric acid (930 mL) was added at 20-25 °C to a soln. aldehyde rac. **21** (186 g, 1:1 mixture of diastereomers) in THF (930 mL). The mixture was heated to 80 °C for 5 h. Solvent was removed under reduced pressure at 45 °C. iPrOAc (1300 mL) and water (1300 mL) were added. The layers were separated and the org. layer was washed with water (930 mL). The combined org. extracts were concentrated at 45 °C under reduced pressure to afford rac. **9** as an orange solid which was used in the next step without further purification. Yield: 155 g (crude yield), 101%. LC-MS method 2: 83% a/a, R_t 0.96 min. ^{1}H NMR ($CDCl_3$): corresponds to **9**. The crude product can be subjected to the crystallization procedure as depicted below to obtain pure rac. **9a** as colorless crystalline solid with diastereomeric purity > 99.5%.

(1R*,2S*,3S*,4R*)-6-Oxo-3-phenylbicyclo[2.2.2]octan-2-yl methanesulfonate (rac. 22). Et_3N (221 mL) was added to a soln. of rac. **9** (171 g) in DCM (1200 mL). MsCl (11.6 mL) was added at 10-20 °C. After 1 h, the mixture was concentrated to dryness. The residue was taken up in iPrOAc (1 L) and water (1 L). The layers were separated and the aqu. phase was extracted with iPrOAc (500 mL). The combined org. extracts were concentrated under reduced pressure to yield rac. **22** as a brown oil which was used in the next step without further purification. Yield: 208 g (89 %). LC-MS method 2: 70% a/a, R_t 1.1 min. ^{1}H NMR ($CDCl_3$): corresponds to **22**.

(1R*,4R*)-5-phenylbicyclo[2.2.2]oct-5-en-2-one (rac. 1). A soln. of rac. **22** (190 g) in DMF (380 mL) was added at r.t. to a suspension of LiBr (56 g) and Li_2CO_3 (48 g) in DMF (570 mL). The resulting mixture was heated to 150 °C for 1 h. Water (1300 mL) and iPrOAc (1300 mL) were added at r.t. and the layers were separated. The organic layer was washed with brine (1300 mL), water (1300 mL) and concentrated to dryness at 50 °C under reduced pressure to yield rac. **1**as brown oil. Yield: 117 g (91%). 108 g of this crude product was purified by short-path distillation at 120 °C and 0.001 mbar to yield 47 g (37%) of rac. **1** as yellow oil. LC-MS method 2: 97% a/a, R_t 1.26 min. ^{1}H NMR (CD_3OD): corresponds to **1**.

(R*)-2-phenyl-2-((R*)-1,4-dioxaspiro[4.5]decan-7-yl)ethanol (25a) and (R*)-2-phenyl-2-((S*)-1,4-dioxaspiro[4.5]decan-7-yl)ethanol (25b).

Analytical reference samples of rac. **25a** and rac. **25b** were obtained from a racemic run by chromatography on silica gel with heptane/EtOAc (8:2) as eluent. The more polar isomer 1 (TLC) was labelled rac. **25a**. The relative configuration is only tentatively assigned based on correlation of R_f values (TLC) and R_t of GC-MS with rac. **24a**/**24b**.



rac. **25a** rac. **25b**

Rac. **25a**, colourless oil; TLC: R_f 0.23 (toluene/EtOAc 7:3); GC-MS: 98% a/a, R_t 3.44 min, $[M-18+1]^+$ = 245; LC-MS method 1: 98% a/a, $[M-61]^+$ = 201; ^{1}H NMR ($CDCl_3$): δ 7.16-7.44 (m, 5H), 3.77-4.05 (m, 6H), 2.58-2.73 (m, 1H), 1.88-2.11 (m, 2H), 1.16-1.85 (m, 7H), 0.63-1.03 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 141.1, 128.8, 128.6, 126.8, 109.3, 64.7, 64.4, 64.2, 54.3, 40.1, 37.6, 34.7, 29.6, 23.0.

Rac. **25b**, colourless oil; TLC: R_f 0.32 (toluene/EtOAc 7:3); GC-MS: 99% a/a, R_t 3.41 min, $[M-18+1]^+$ = 245; LC-MS method 1: 100% a/a, R_t 1.36 min, $[M-61]^+$ = 201; ^{1}H NMR ($CDCl_3$): δ 7.14-7.41 (m, 5H), 3.72-4.04 (m, 6H), 2.59-2.77 (m, 1H), 0.91-2.12 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 140.9, 128.8, 128.7, 126.8, 109.2, 64.8, 64.2, 64.1, 54.3, 39.3, 37.4, 34.7, 30.0, 23.1.

Cyclization:

Presentation of additional conditions tried for the cyclization of **21** to **9a**.

IPC sample preparation:
Withdraw a sample from the reaction mixture, dilute with EtOAc and extracted with aqu. sat. $NaHCO_3$-soln. (pH 9-10), evaporate the org. phase at r.t. under reduced pressure and weigh in sample for dilution with heptane/isopropanol (1:1, 4 mg/mL) for injection in chiral HPLC.

Table 1. Optimization of cyclization conditions (with rac. **21**)

entry	solvent	acid	temp.	time	rac. **9a**[(a)]	rac. **9b**[(a)]	rac. **9c**[(a)]
1	2 vol. EtOAc	1 eq. 32% HCl	20 °C	2 h	76%	16%	8%
2	2 vol. EtOAc	1 eq. 32% HCl	50 °C	2 h	88%	12%	0%
3	2 vol. EtOAc	1 eq. 1N HCl	20 °C	2 h	46%	27%	27%
4	5 vol. acetone	1.1 eq. 32% HCl	50 °C	7 h	60%	20%	20%
5	2 vol. toluene	1 eq. 32% HCl	20 °C	16 h	61%	34%	5%
6	2 vol. iPrOH	1 eq. 32% HCl	20 °C	16 h	76%	15%	9%
7	2 vol. THF	1 eq. 32% HCl	20 °C	16 h	81%	14%	5%
8	2 vol. TBME	1 eq. 32% HCl	20 °C	16 h	67%	20%	13%
9[(b)]	2 vol. EtOAc	0.3 eq. 32% HCl	50 °C	18 h	100%	0%	0%
10[(c)]	2 vol. EtOAc	0.3 eq. 32% HCl	50 °C	18 h	30%	67%	2%
11[(d)]	2 vol. EtOAc	0.3 eq. 32% HCl	50 °C	18 h	59%	41%	0%

(a) 0.5 g scale, ratio of each isomer normalized to the sum of rac. **9a**, rac. **9b**, and rac. **9c** in the reaction mixture, by % a/a (chiral HPLC). (b) Started with pure rac. **9a**. (c) Started with pure rac. **9b**. (d) Started with pure rac. **9c**; d.r. > 99:1.

Table 2. Optimization of cyclization conditions (with enantiopure **21**)

entry	solvent	temp.	time	**9a**[(a)]	**9b**[(a)]	**9c**[(a)]
1	2 vol. EtOAc	50 °C	2 h	85%	15%	0%
2	5 vol. EtOAc	50 °C	2 h	68%	25%	7%
3	1 vol. EtOAc	50 °C	20 min	78%	13%	9%
4	1 vol. EtOAc	50 °C	100 min	86%	14%	0%
5	1 vol. EtOAc	70 °C	20 min	80%	15%	5%

(a) 5-45 g scale, 32% HCl (0.3 eq.), ratio of each isomer normalized to the sum of **9a**, **9b**, and **9c** in the reaction mixture, by % a/a (chiral HPLC). (b) Started with pure **##a**.

Elimination:

Presentation of additional conditions tried for the elimination of **22a** to **1**.

IPC sample preparation:

Withdraw a sample (ca. 5 μL), evaporate to dryness and dissolve residue in 1 mL acetonitril/water (1:1).

Table 3. Eliminations in presence of amidine bases with **22a**[(a)(b)]

entry	base	solvent	temp.[(c)]	IPC % a/a	comments
1	2 eq. DBU	THF	66 °C	0%	No reaction
2	2 eq. DBU	DMF	150 °C	85-90%	Slow conversion at 100 °C
3	2 eq. DBU	Toluene	140 °C	93%	1 h, product separated as oil
4	2 eq. DBU	Diglyme	150 °C	68%	
5	2 eq. DBU	Butyronitrile	120 °C	79%	
6	10 eq. DBU	-	20 °C	40%	40 h, 72% conversion
7	10 eq. DBU	-	100 °C	76%	35 min, aldol by-products
8	10 eq. DBN	-	100 °C	63%	25 min, ring-opened DBN
9	2 eq. MTBD	DMF	150 °C	45%	Many by-products
10	2 eq. TMPDA	DMF	150 °C	78%	
11	2 eq. DABCO	Acetonitrile	85 °C	8%	Slow, many by-products

(a) 0.1-5 g scale, 5-15 vol. solvent or none, reaction time 2 h, full conversion unless otherwise stated, IPC a/a of desired product **1** (LC-method 1). (b) DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; DBN: 1,5-diazabicyclo[4.3.0]non-5-ene; MTBD: 7-methyl-1,5,7-triazabicyclo[4,4,0]dec-5-ene; TMPDA: N,N,N',N'-tetramethylpropane-1,3-diamine; DABCO: 1,4-diazabicyclo[2.2.2]octane. (c) External temp.

Table 4. Eliminations in presence of alternative bases with **22a**[(a)]

entry	base	solvent	temp.[(b)]	time	IPC % a/a
1	2 eq. Li_2CO_3	NMP or DMF	120 °C	180 min	22-26%
2	2 eq. Li_2CO_3	o-Xylene	100 °C	90 min	8%
3	1.5 eq. Li_2CO_3	DBU	100 °C	25 min	97%
4	1.5 eq. Li_2CO_3	DBU	100 °C	35 min	69%
5	1.5 eq. Li_2CO_3 1 eq. LiBr	NMP or DMF	150 °C	30 min	74%
7	1.5 eq. K_2CO_3	DMSO	150 °C	120 min	60%
8	0.3 eq. NaI	Toluene	140 °C	120 min	16%
9	2 eq. NaOMe or NaO*t*Bu	Diglyme	120 °C	60 min	53%
10	3 eq. KO*t*Bu	THF	20 °C	20 min	40%
11	0.6 wt. SiO_2	DMSO	150 °C	60 min	89%
12	Montmorillonite K-10	Toluene	110 °C	60 min	trace

(a) 0.1-5 g scale, 5-10 vol. solvent, full conversion, IPC a/a of desired product **1** (LC-method 1). (b) External temp.

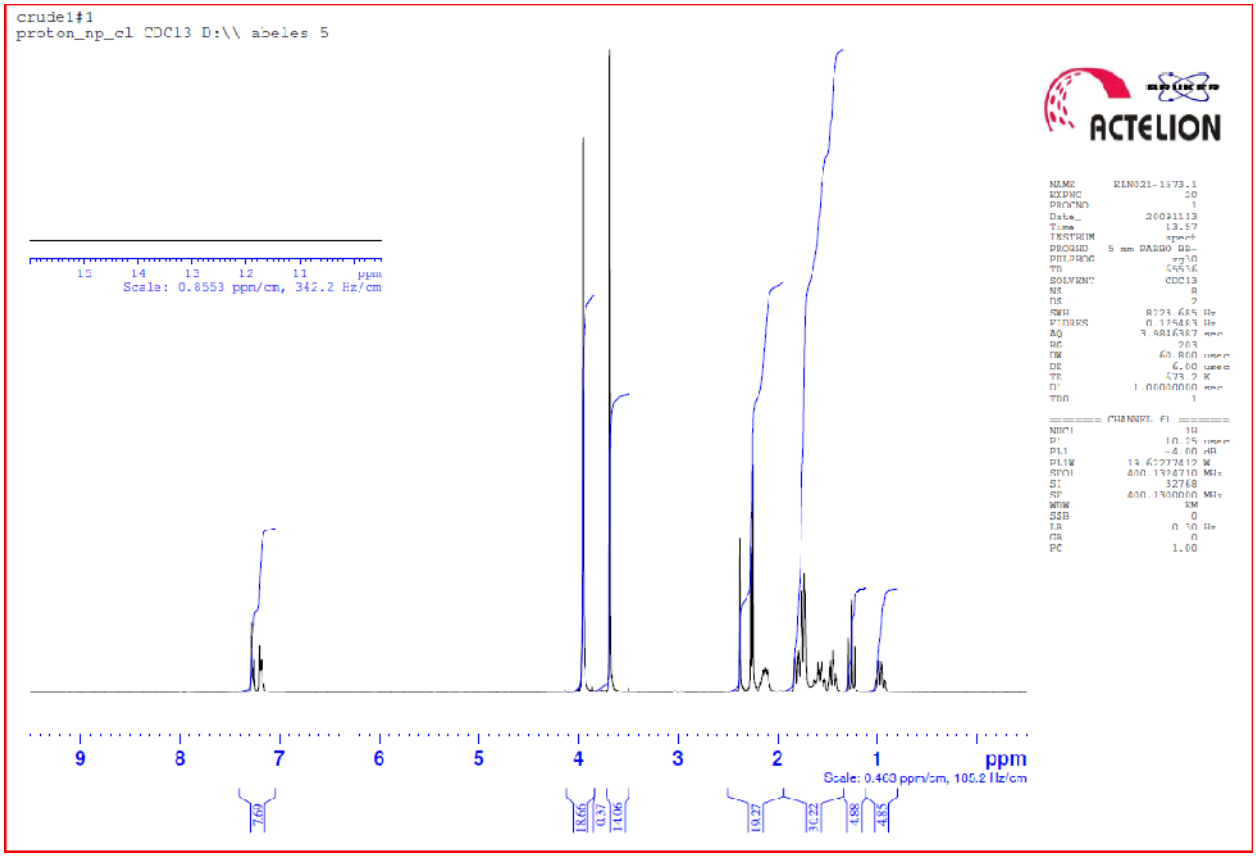
Table 5. Eliminations of **22a** to **1** in the absence of base[(a)(b)]

entry	solvent	temp.[(c)]	time	IPC % a/a
1	Toluene	110 °C	3 h	13%
2	o-Xylene	150 °C	1 h	10%
3	Chlorobenzene	150 °C	1 h	40%
4	DMPU	150 °C	2 h	87%
5	DMF	150 °C	1 h	79%
6	NMP	150 °C	2 h	92%
7	DMSO	150 °C	2 h	79%
8	Sulfolane	150 °C	1 h	99%
9	No solvent (melt)	150 °C	1 h	26%

(a) 0.2 g scale, 5-10 vol. solvent, full conversion, IPC a/a of desired product **1** (LC-method 1). (b) DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone. (c) External temp.

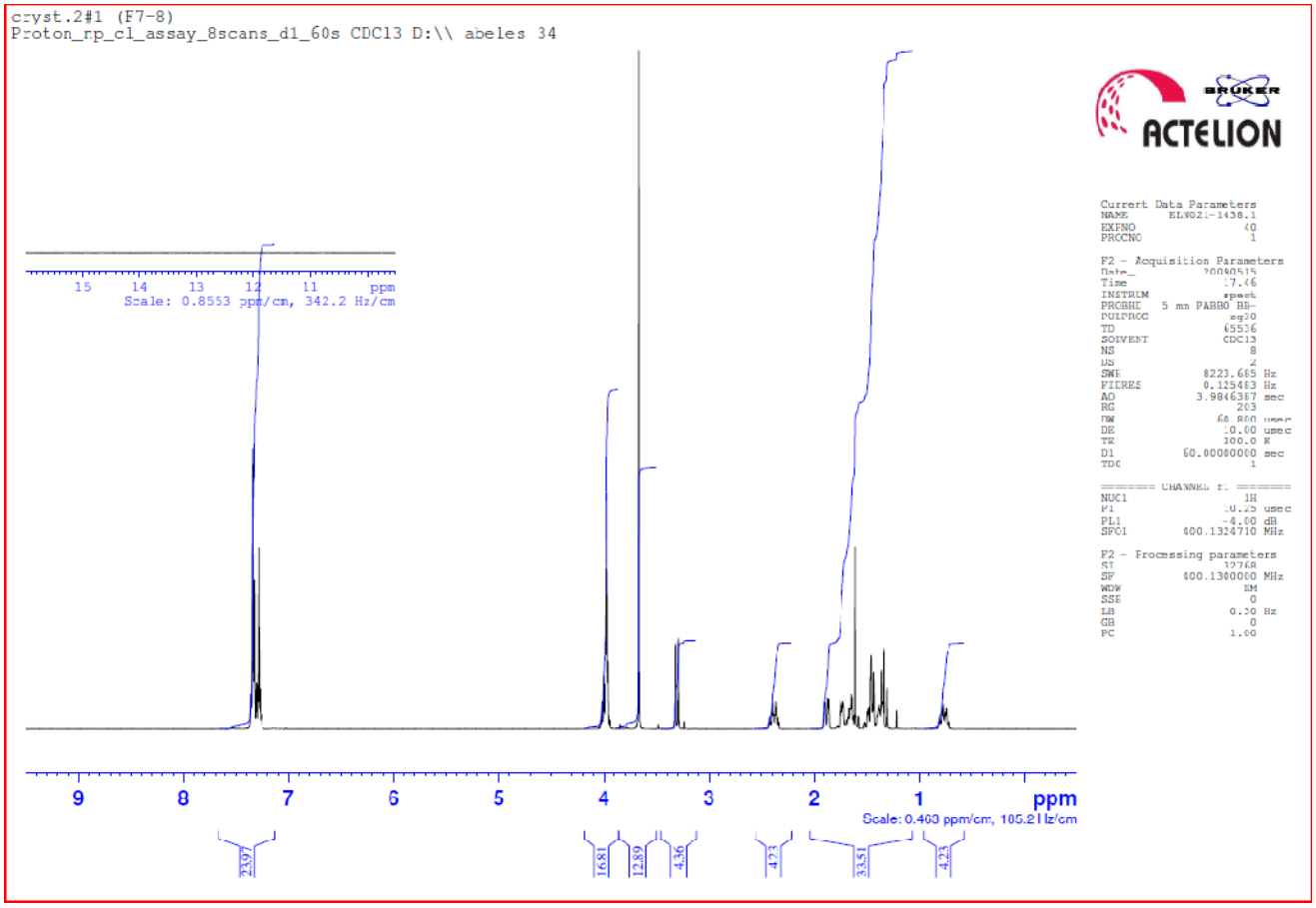
NMR data

Methyl 2-((*R*)-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (12)



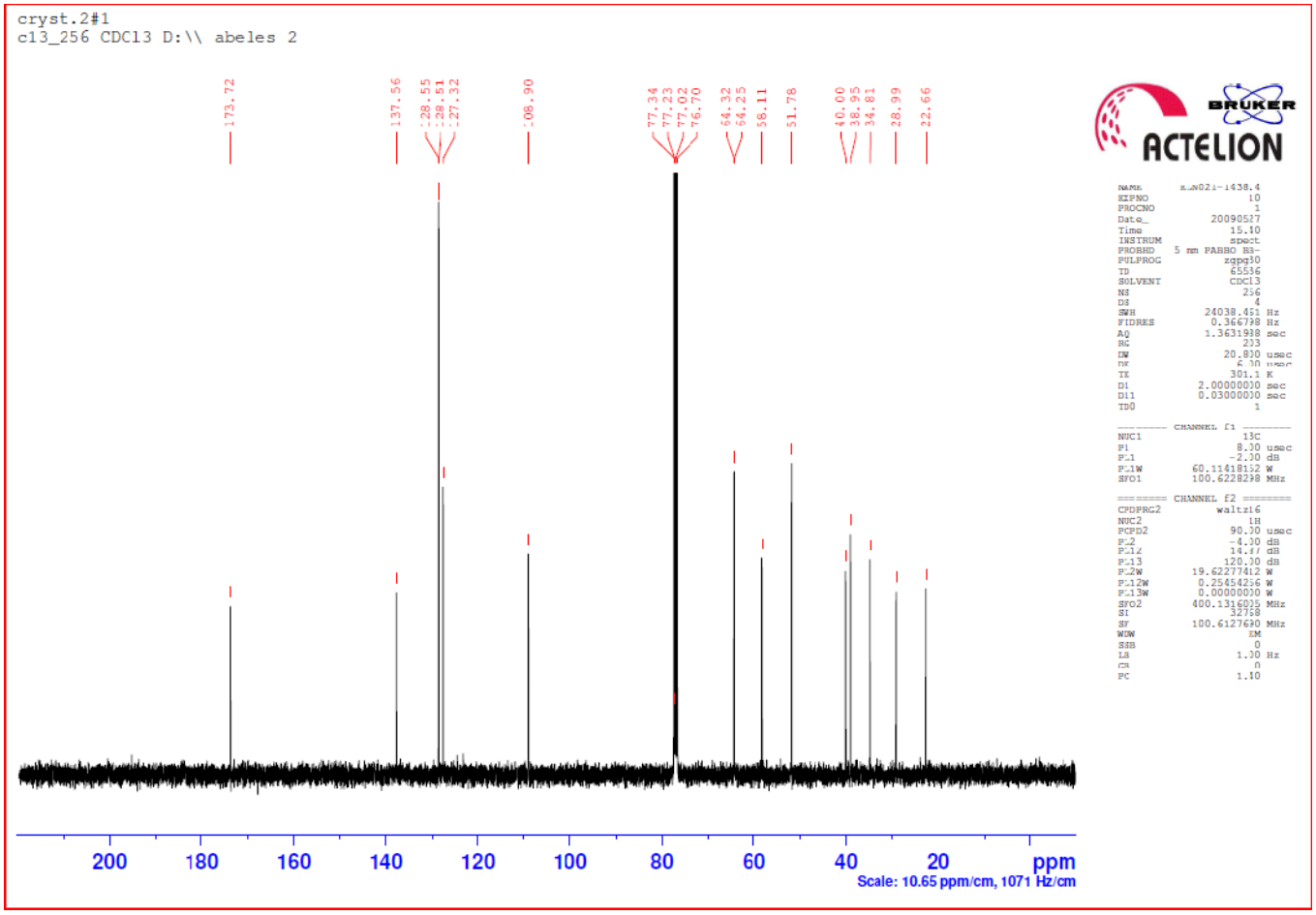
^{1}H NMR ($CDCl_3$) of crude **12**

(*R)-Methyl 2-phenyl-2-((*R**)-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (rac. 24a)**



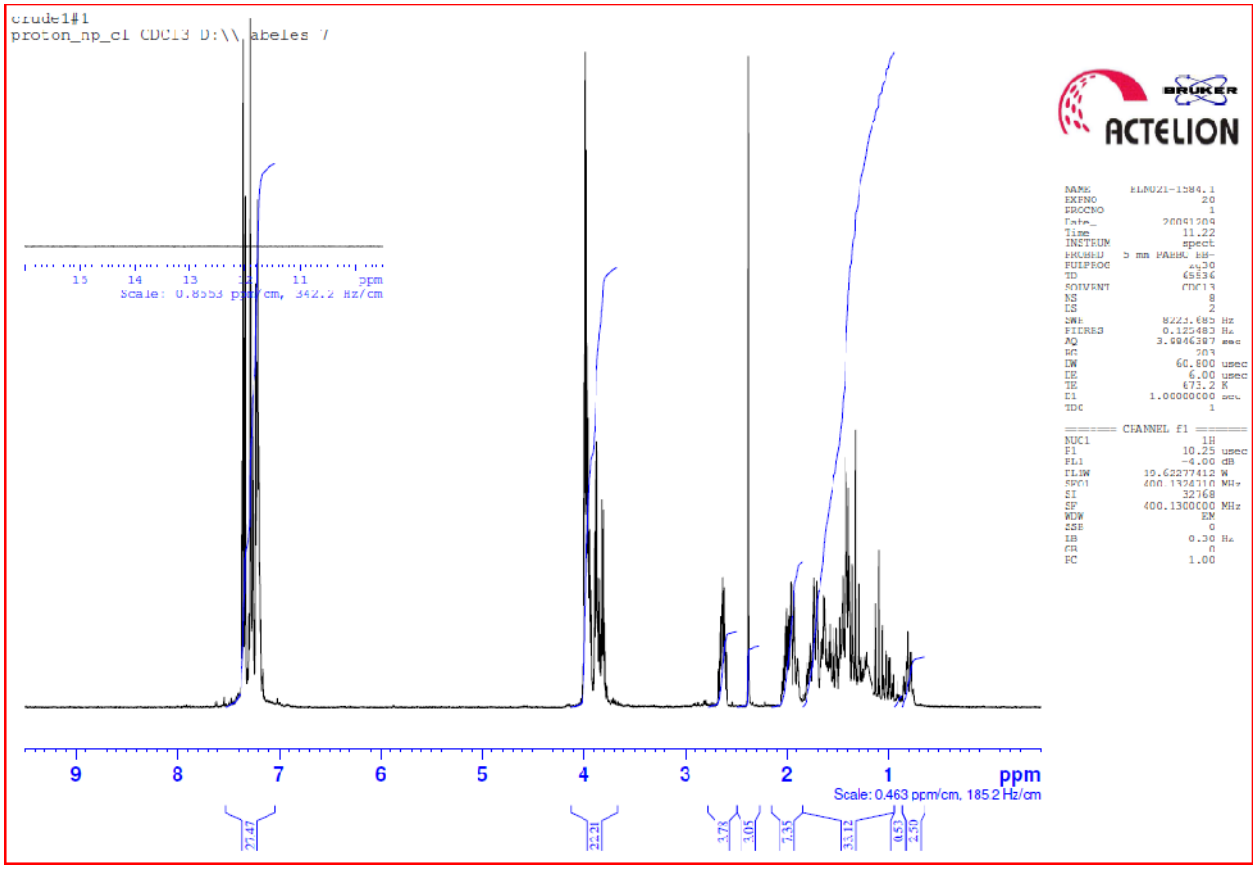
^{1}H NMR ($CDCl_3$) of rac. **24a**

(*R)-Methyl 2-phenyl-2-((*R**)-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (rac. 24a)**



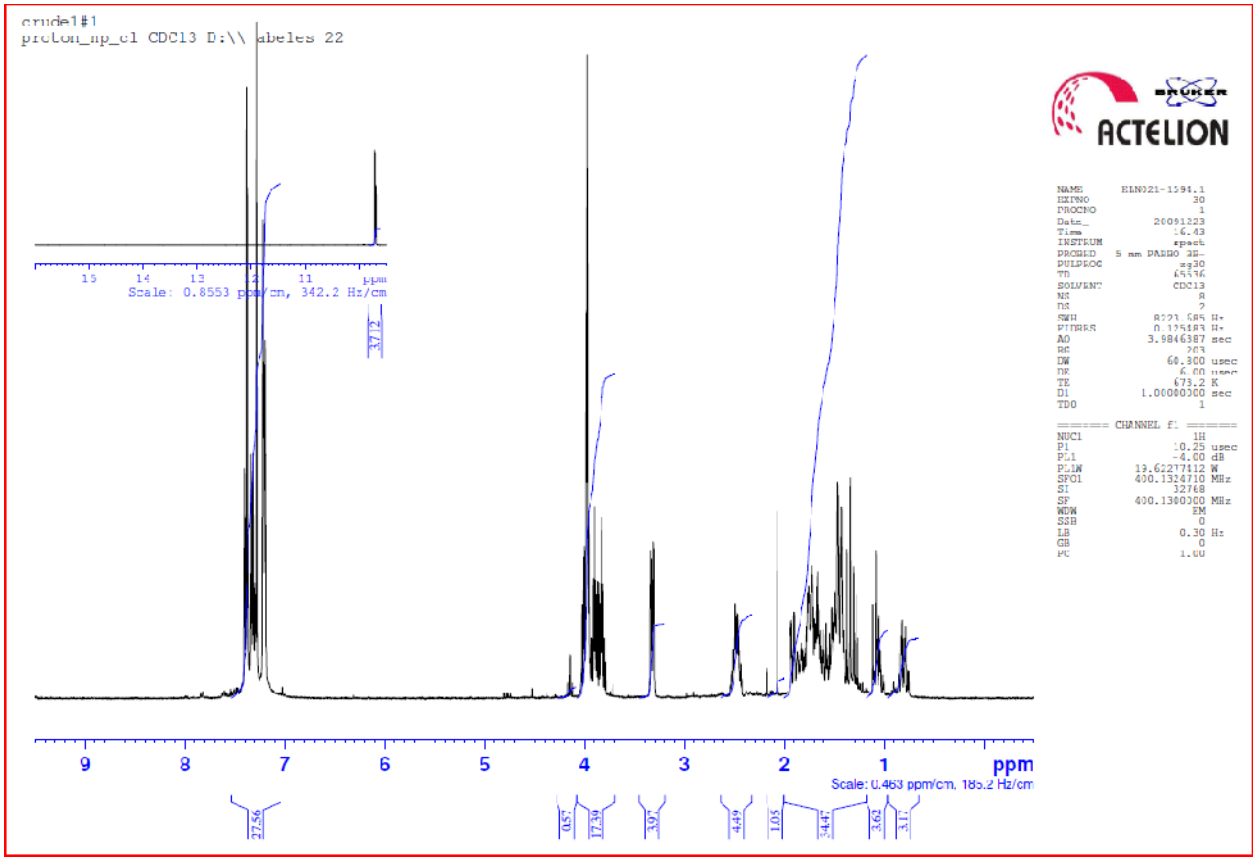
^{13}C NMR ($CDCl_3$) of rac. **24a**

2-Phenyl-2-((R)-1,4-dioxaspiro[4.5]decan-7-yl)-ethanol (25, mixture of diastereoisomers)



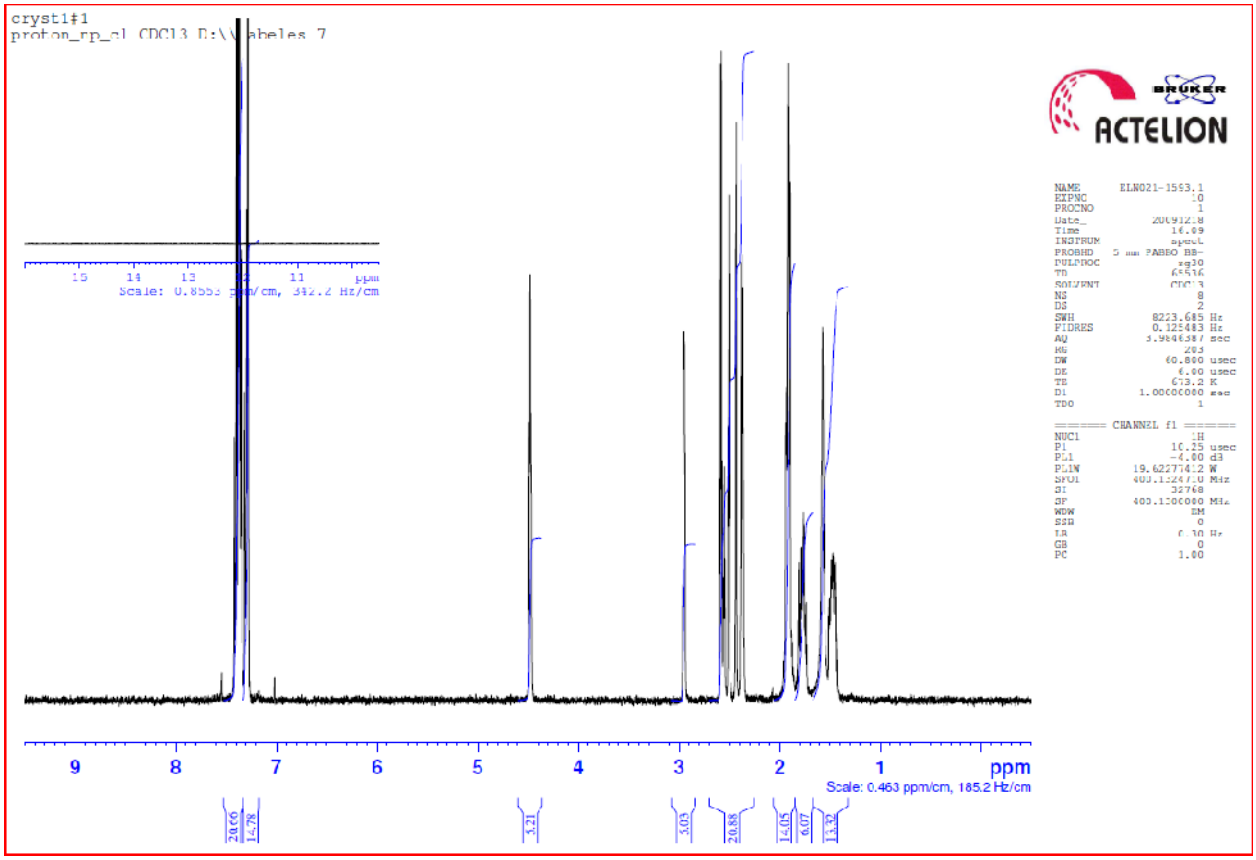
^{1}H NMR ($CDCl_3$) of crude **25**

2-Phenyl-2-((R)-1,4-dioxaspiro[4.5]decan-7-yl)-acetaldehyde (21)

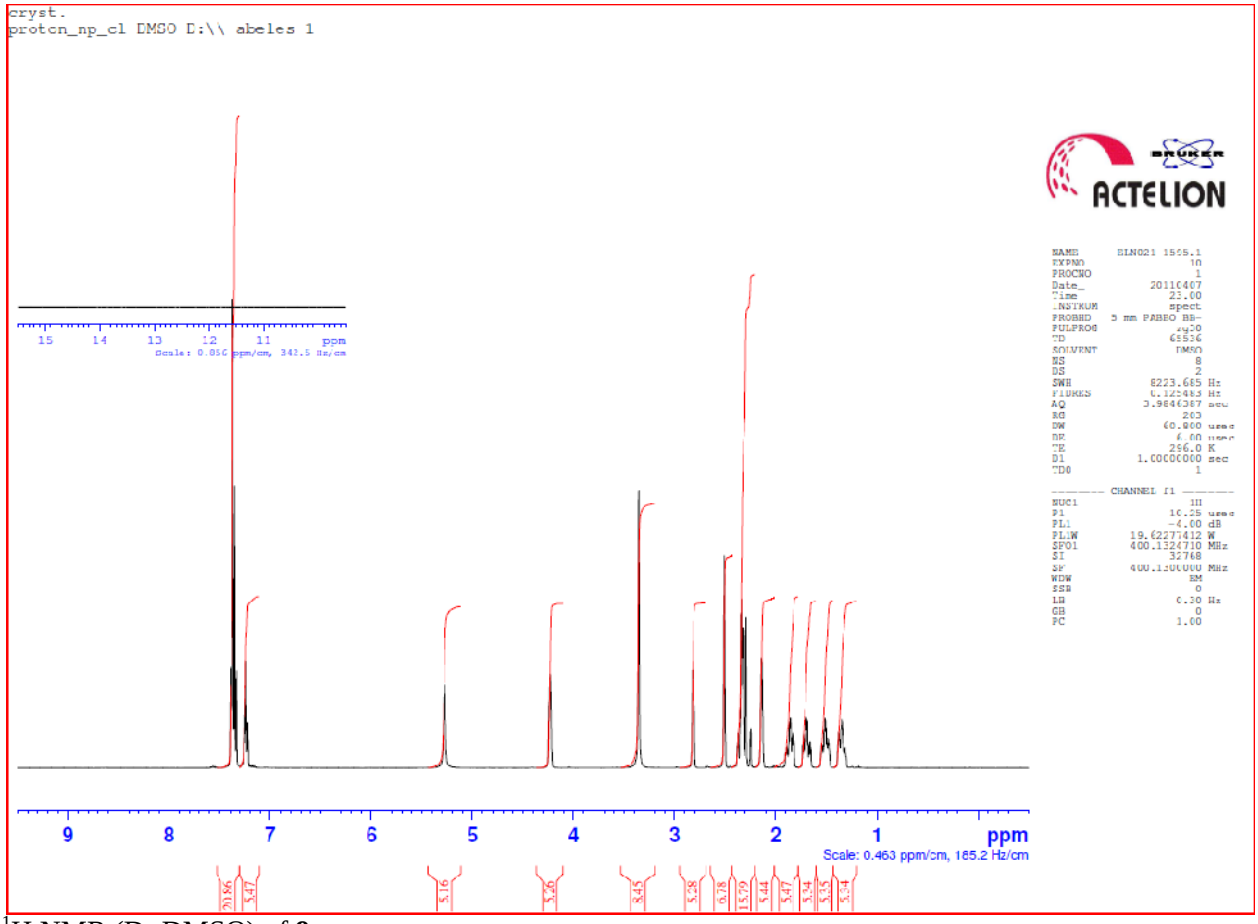


^{1}H NMR ($CDCl_3$) of crude **21** (28.9 g scale with isolation of **21**)

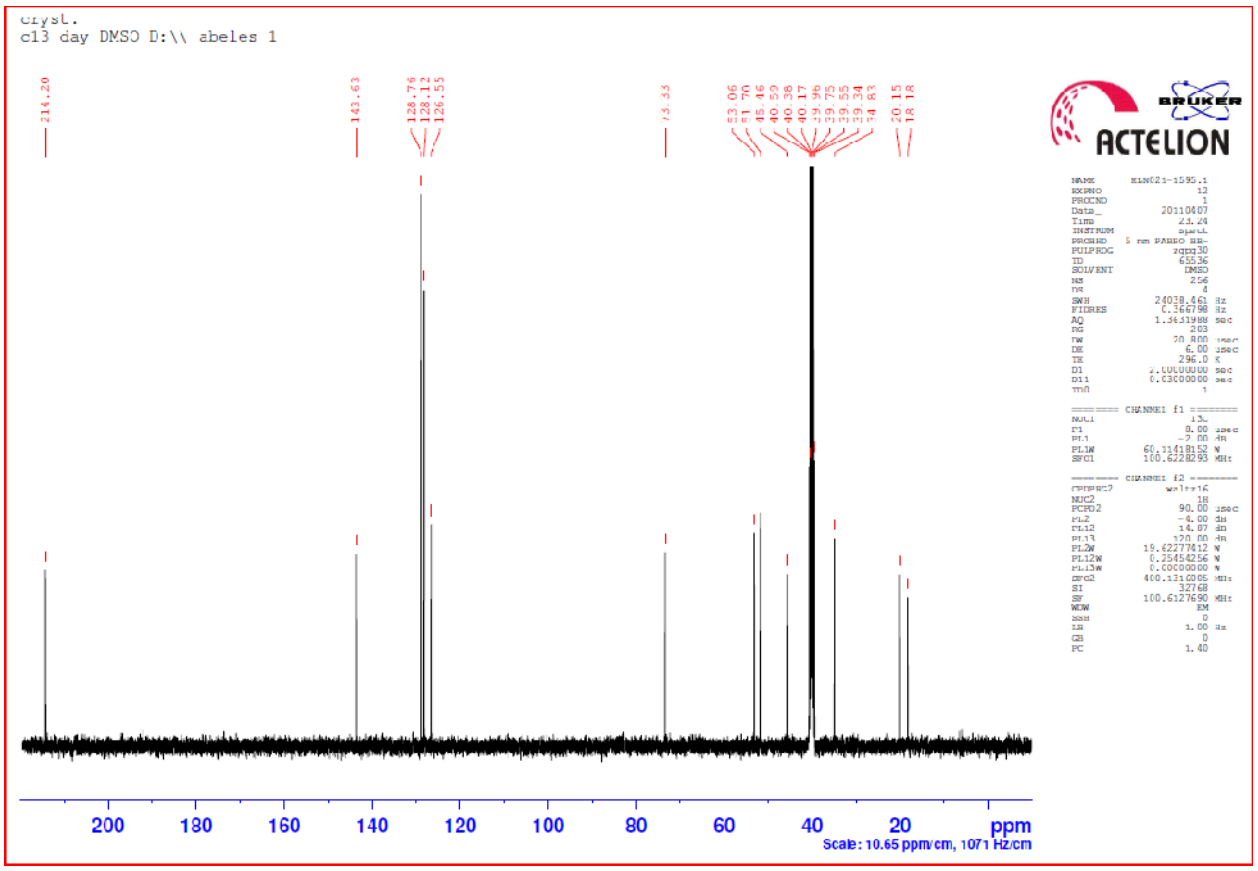
(1R,4R,5S,6S)-6-hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (9a)



^{1}H NMR ($CDCl_3$) of **9a**

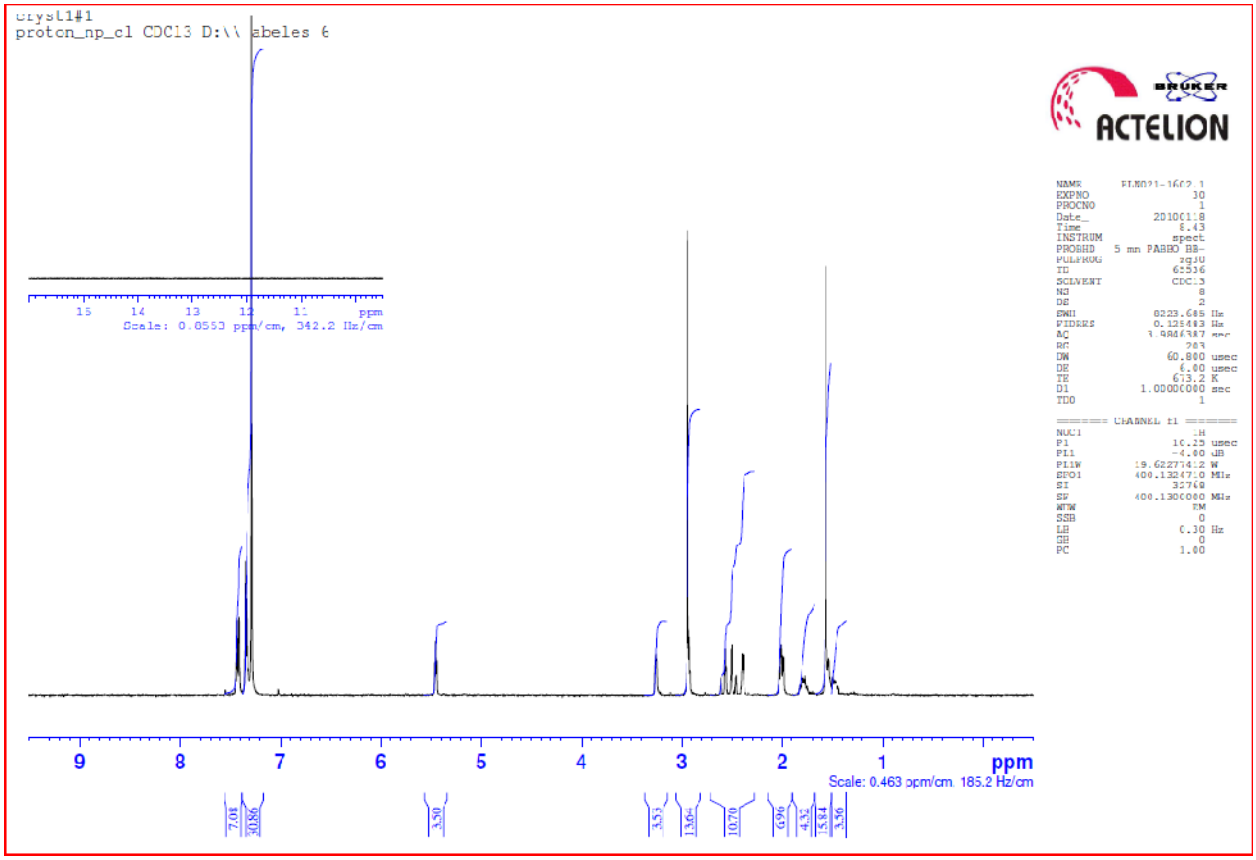


^{1}H NMR (D_6 DMSO) of **9a**

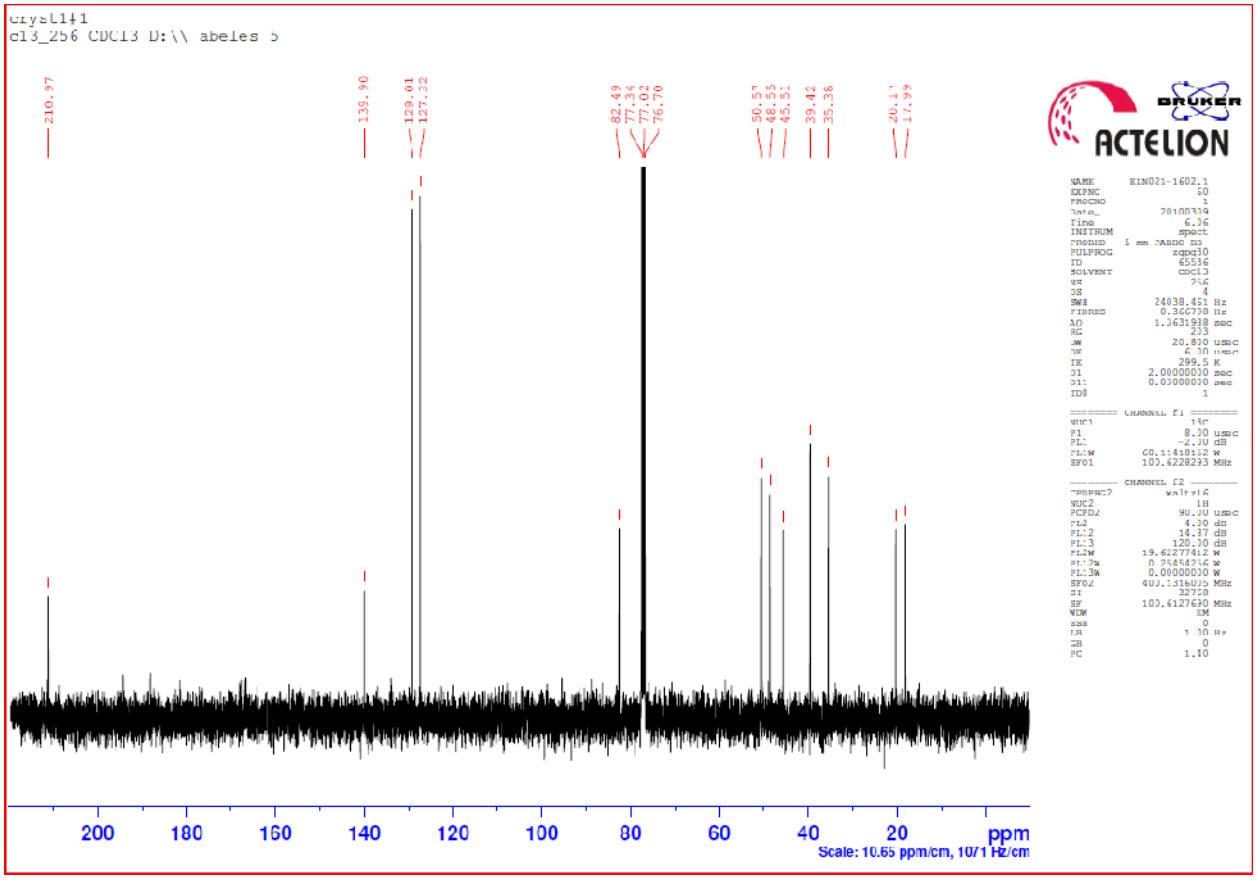


^{13}C NMR (D_6 DMSO) of **9a**

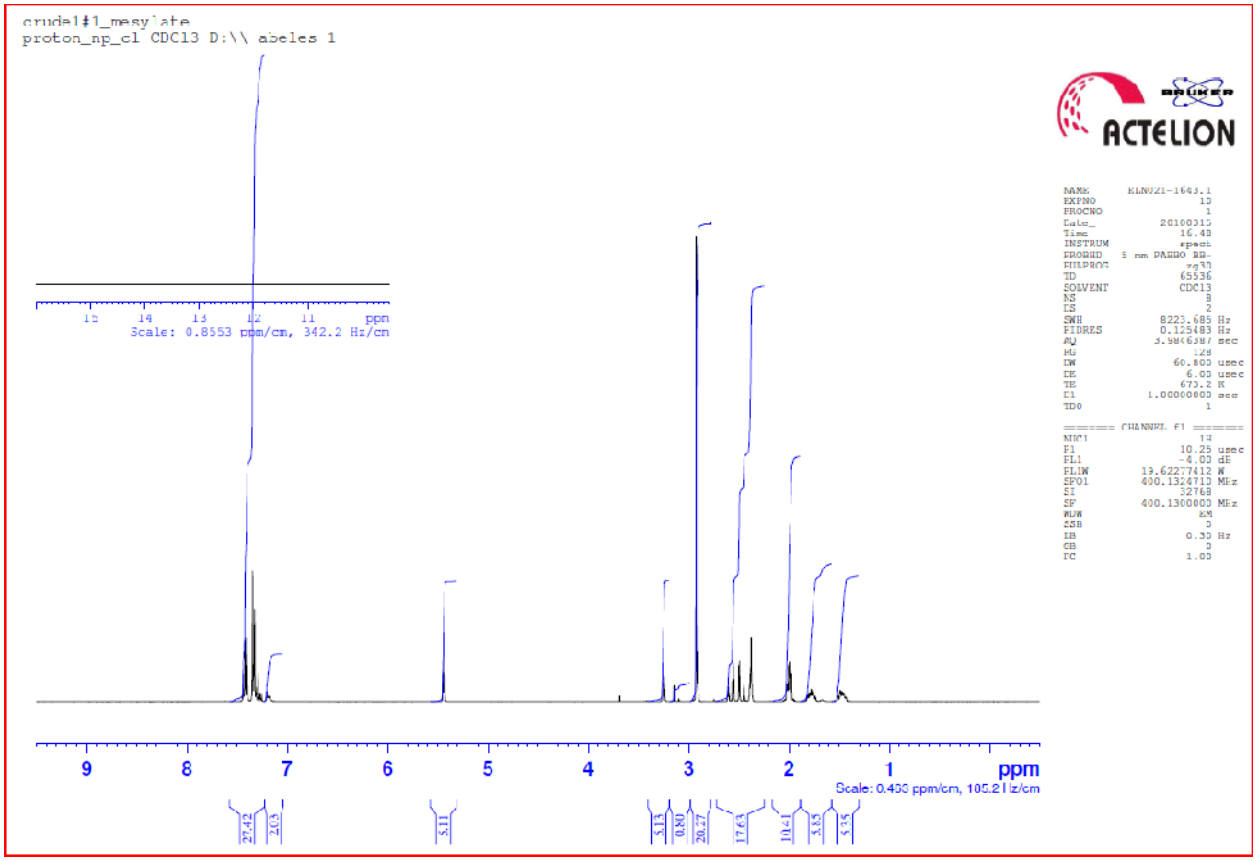
(1R,2S,3S,4R)-6-oxo-3-phenylbicyclo[2.2.2]octan-2-yl methanesulfonate (22a)



^{1}H NMR ($CDCl_3$) of **22a** (25 g scale with isolation of **22a**)

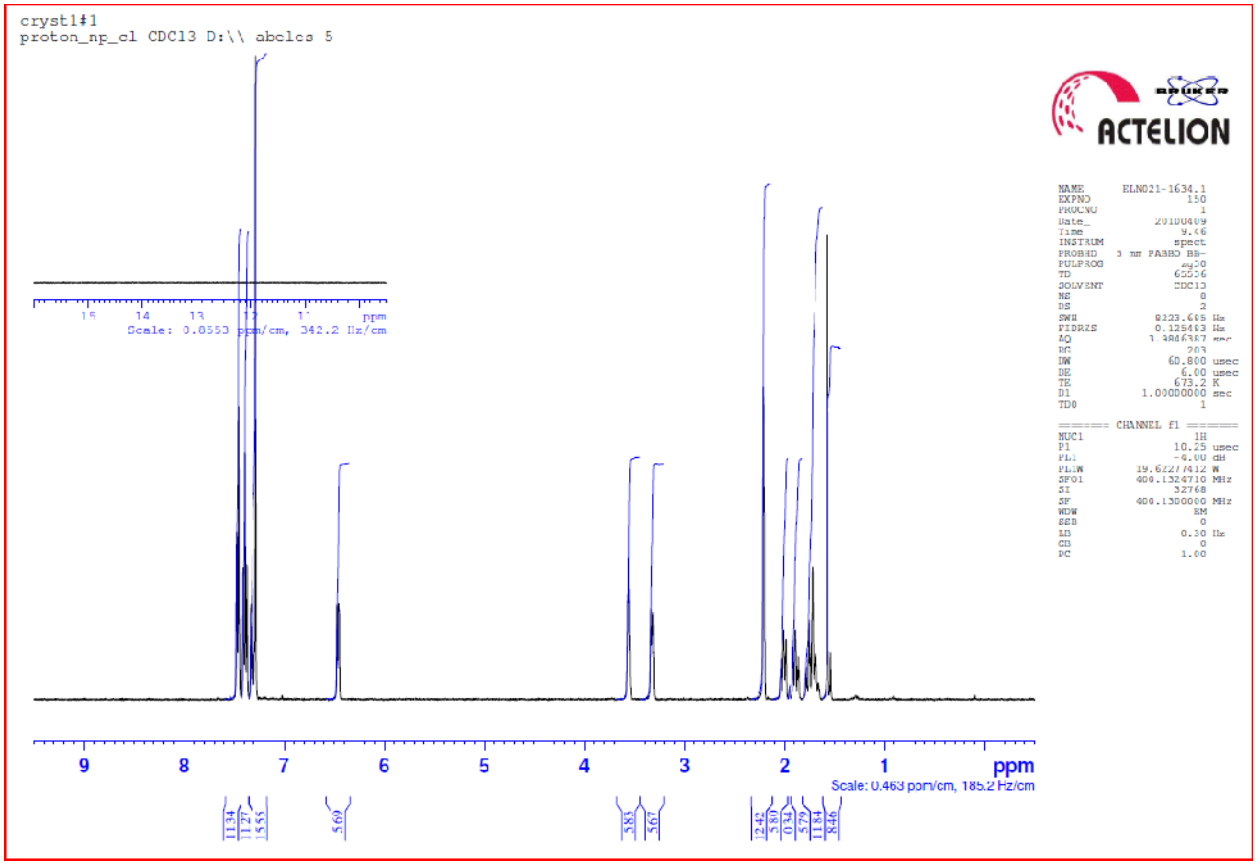


^{13}C NMR ($CDCl_3$) of **22a** (25 g scale with isolation of **22a**)

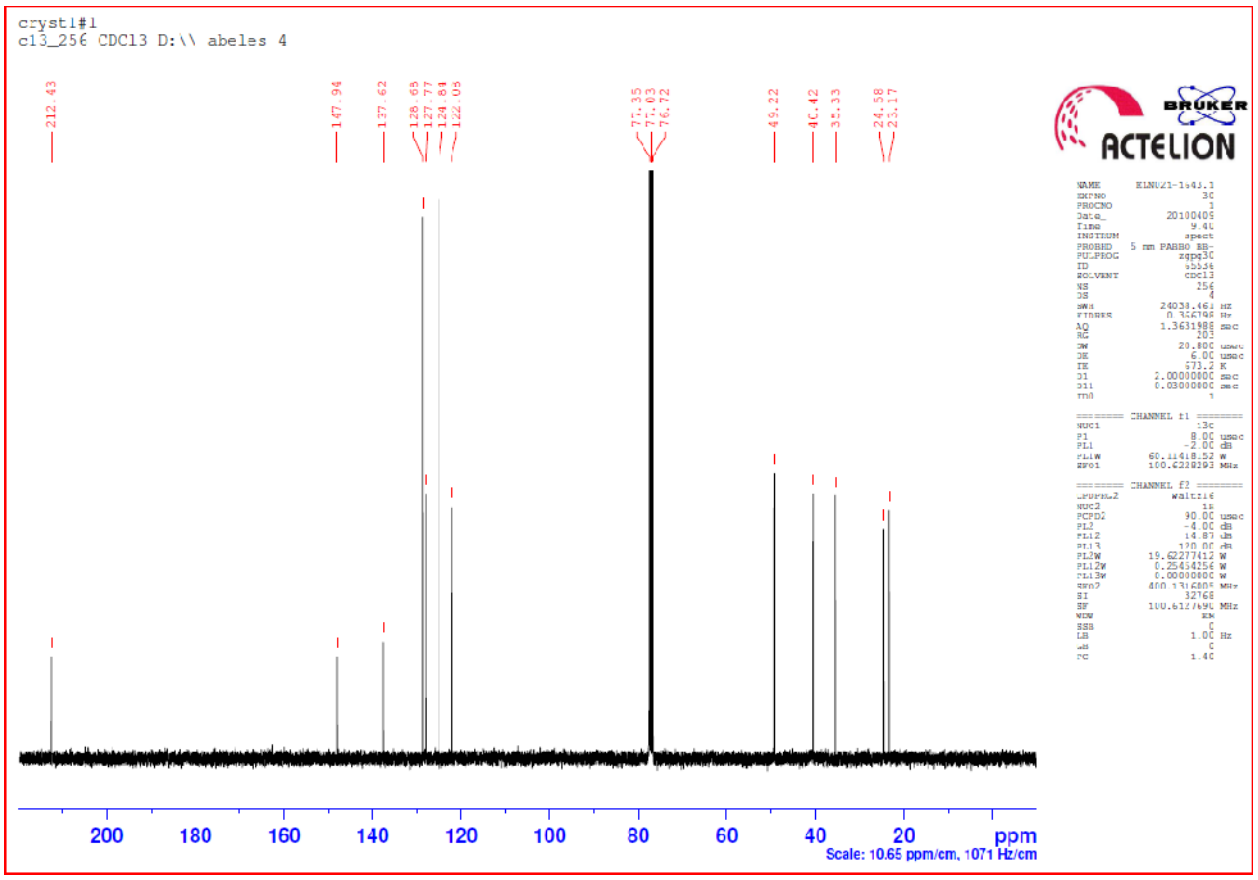


^{1}H NMR ($CDCl_3$) of crude **22a**, telescoped into the elimination.

(1R,4R)-5-phenylbicyclo[2.2.2]oct-5-en-2-one (1)



^{1}H NMR ($CDCl_3$) of **1**



^{13}C NMR ($CDCl_3$) of **1**

GC-MS data

Methyl 2-((*R*)-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (12)

Sample: **ELN021-1573_crude1#1**

Data File:	ELN021-1573_crude1#111130154_140517
Acquisition Date:	11/13/09 02:05:24 PM
Injection Volume(µl):	1.00
Vial:	5
Coulmn:	Zebron ZB-5 MS, 15m x 0.25mm ID, 0.25 um film
Column Flow:	2.0 ml/min
Carrier Gas:	Helium
Split Ratio:	20
SSL Inlet Temp:	200 C
Instrument Method:	C:\Xcalibur\OA Methode & Processing Files\SSL_ZB5_PCI_V03.meth
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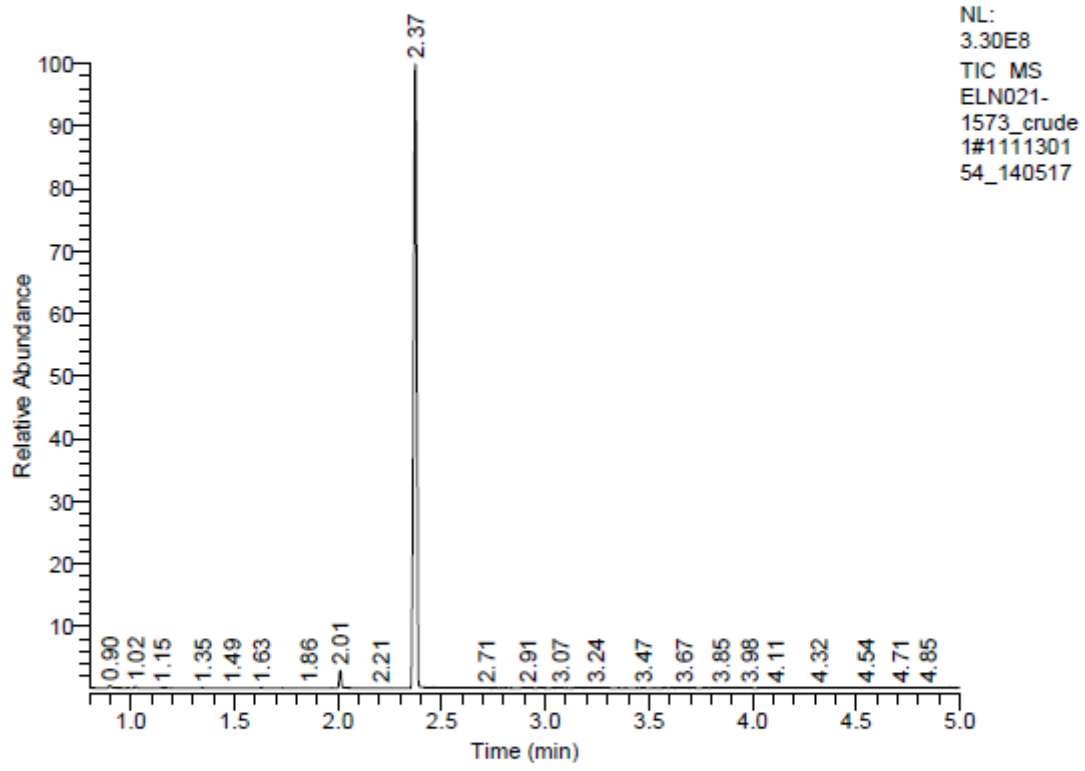
RT: 0.80 - 5.00 SM: 7B



RT	Area %	Peak Area	Peak Height	Peak Width
0.83	0.11	410431.3	503359.7	0.02
0.84	0.03	114473.9	309640.8	0.01
0.85	0.12	434925.3	345340.1	0.03
0.90	0.52	1907094.5	1886793.2	0.07
1.02	0.12	445523.8	1127855.1	0.02
1.15	0.04	160688.8	441385.5	0.01
2.01	1.86	6782687.2	15500587.5	0.04
2.38	97.10	355005376.5	377074447.2	0.09
2.46	0.10	349047.9	390197.6	0.04

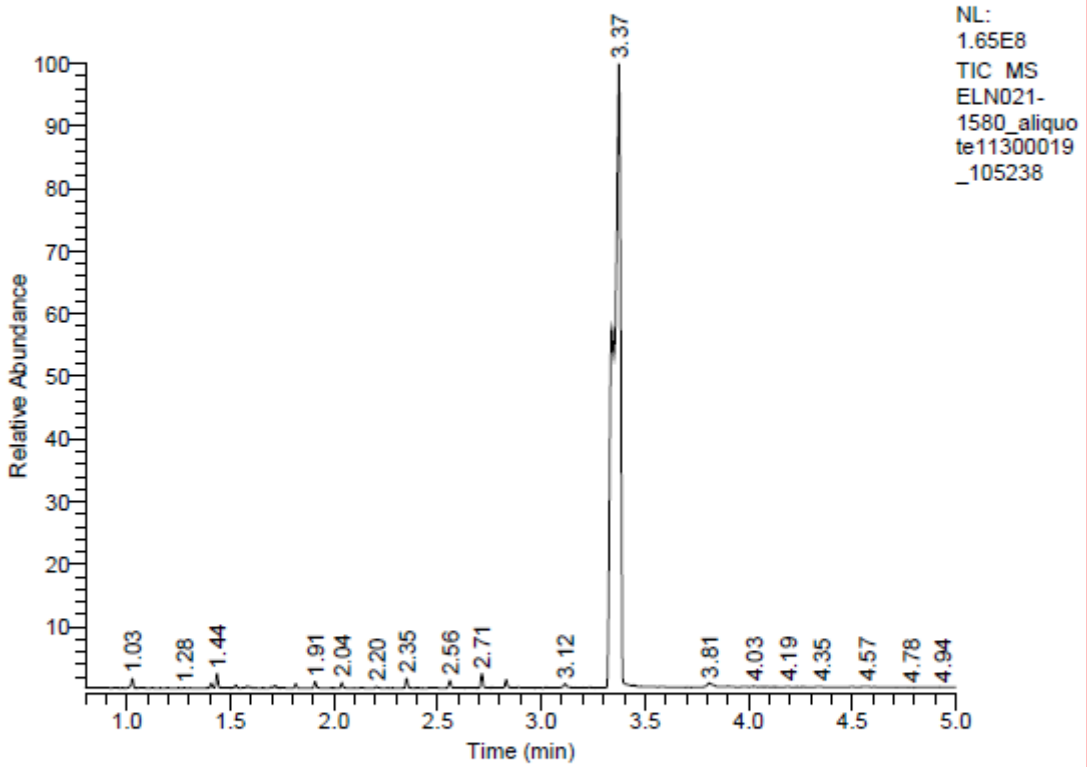
GC-MS trace of crude **12**

Methyl 2-phenyl-2-((*R*)-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (24, mixture of diastereoisomers)

Sample: **ELN021-1580_aliquote**

Data File:	ELN021-1580_aliquote11300019_105238
Acquisition Date:	11/30/09 10:52:47 AM
Injection Volume(µl):	1.00
Vial:	19
Coulmn:	Zebron ZB-5 MS, 15m x 0.25mm ID, 0.25 um film
Column Flow:	2.0 ml/min
Carrier Gas:	Helium
Split Ratio:	20
SSL Inlet Temp:	200 C
Instrument Method:	C:\Xcalibur\OA Methode & Processing Files\SSL_ZB5_PCI_V03.meth
Data Path:	C:\Data01\inauenr

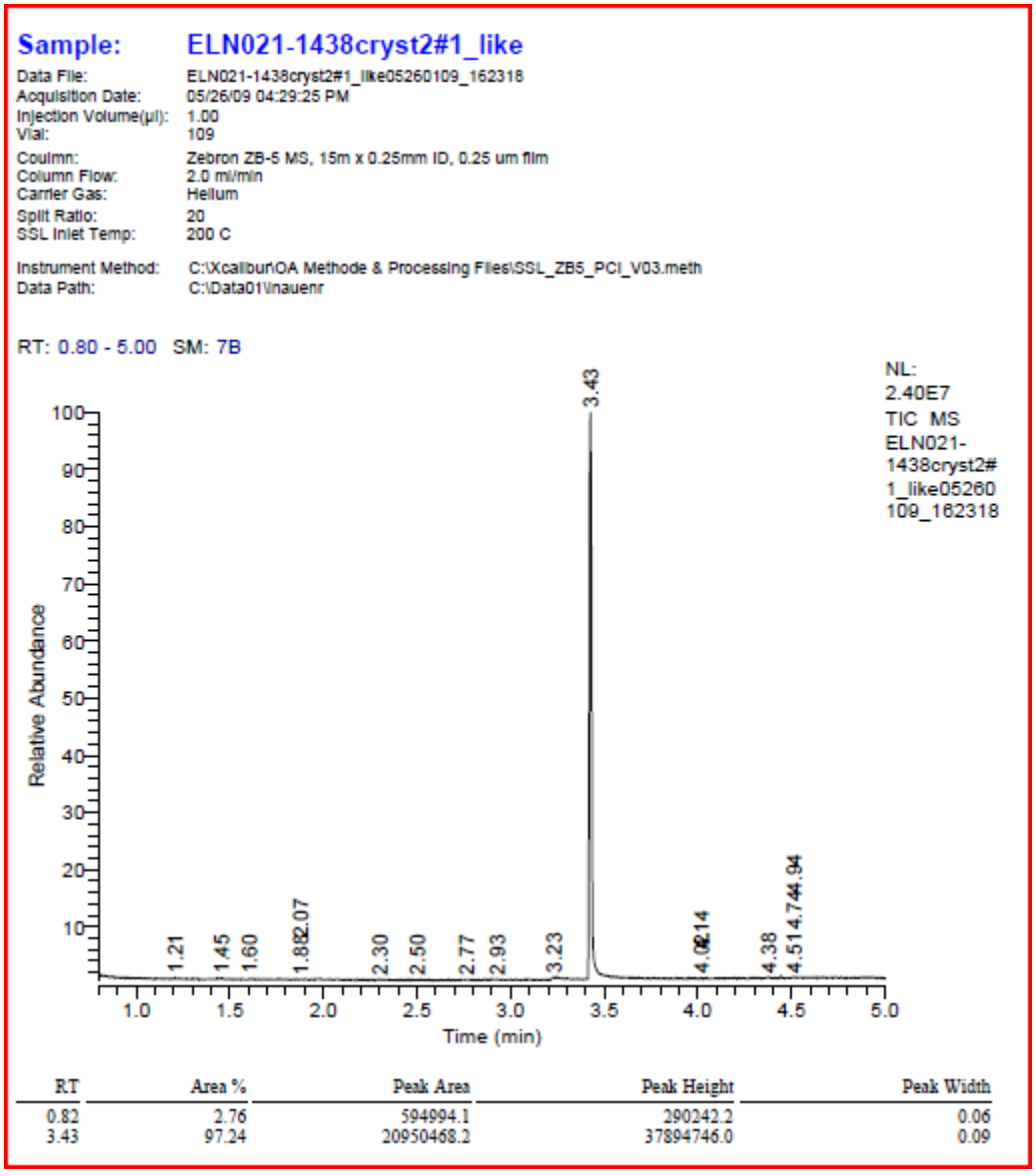
RT: 0.80 - 5.00 SM: 7B



RT	Area %	Peak Area	Peak Height	Peak Width
1.03	0.44	1809505.5	3626064.4	0.03
1.44	0.64	2618094.5	5488828.1	0.02
1.91	0.28	1157548.3	2497841.3	0.02
2.35	0.42	1726148.9	4212058.6	0.03
2.56	0.33	1374800.1	2912423.1	0.02
2.71	0.67	2734670.3	5809435.5	0.03
2.83	0.38	1551426.1	3143177.6	0.03
3.34	33.16	136102712.4	101646881.0	0.04
3.38	63.18	259332310.3	188559837.6	0.08
3.81	0.50	2032434.7	1131087.3	0.07

GC-MS of crude **24**

(*R)-Methyl 2-phenyl-2-((*R**)-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (rac. 24a)**



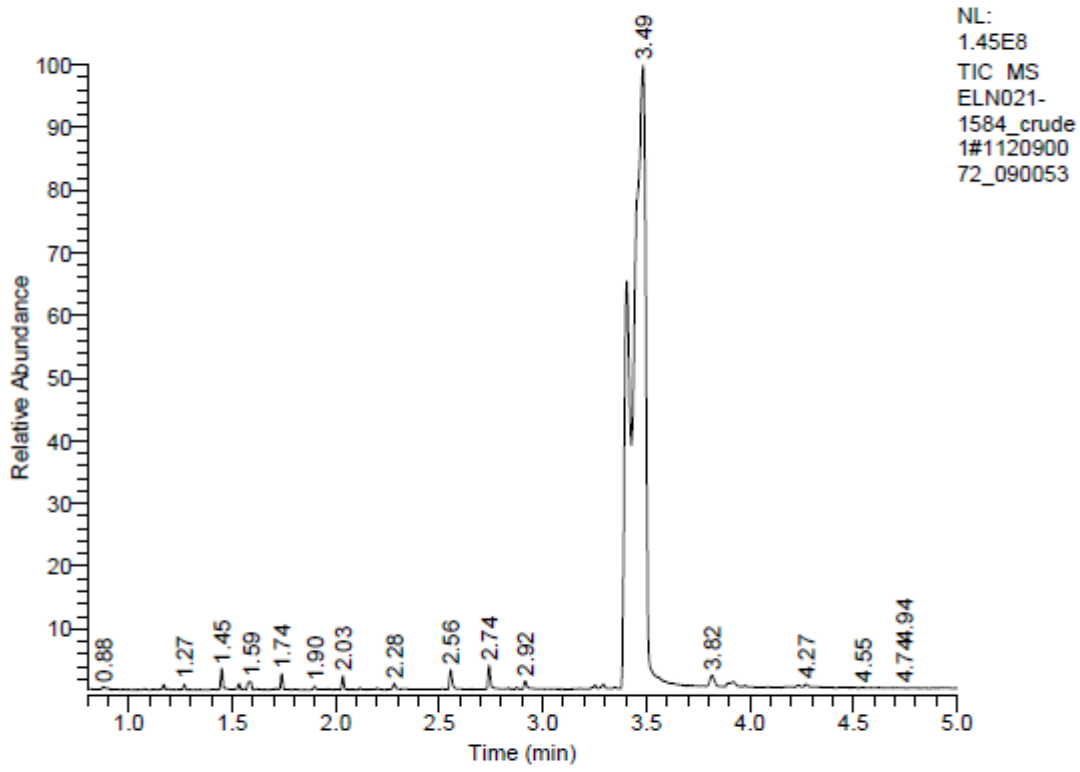
GC-MS of **24a**

2-Phenyl-2-((R)-1,4-dioxaspiro[4.5]decan-7-yl)-ethanol (25, mixture of diastereoisomers)

Sample: **ELN021-1584_crude1#1**

Data File:	ELN021-1584_crude1#112090072_090053
Acquisition Date:	12/09/09 09:01:02 AM
Injection Volume(µl):	1.00
Vial:	72
Coulmn:	Zebron ZB-5 MS, 15m x 0.25mm ID, 0.25 um film
Column Flow:	2.0 ml/min
Carrier Gas:	Helium
Split Ratio:	20
SSL Inlet Temp:	200 C
Instrument Method:	C:\Xcalibur\OA Methode & Processing Files\SSL_ZB5_PCI_V03.meth
Data Path:	C:\Data01\inauenr

RT: 0.80 - 5.00 SM: 7B



RT	Area %	Peak Area	Peak Height	Peak Width
1.45	0.49	3322473.4	7685770.6	0.03
1.59	0.33	2240415.5	2916022.8	0.03
1.74	0.36	2428719.8	5316845.9	0.02
2.03	0.30	2057151.5	4688709.1	0.02
2.55	0.61	4135892.1	6084598.1	0.04
2.74	0.70	4749671.0	8468765.7	0.07
3.40	27.74	187532639.3	97964100.7	0.05
3.49	68.46	462857465.3	148588091.7	0.09
3.81	0.59	3978595.4	3062416.1	0.05
3.92	0.41	2783800.5	1339233.2	0.07

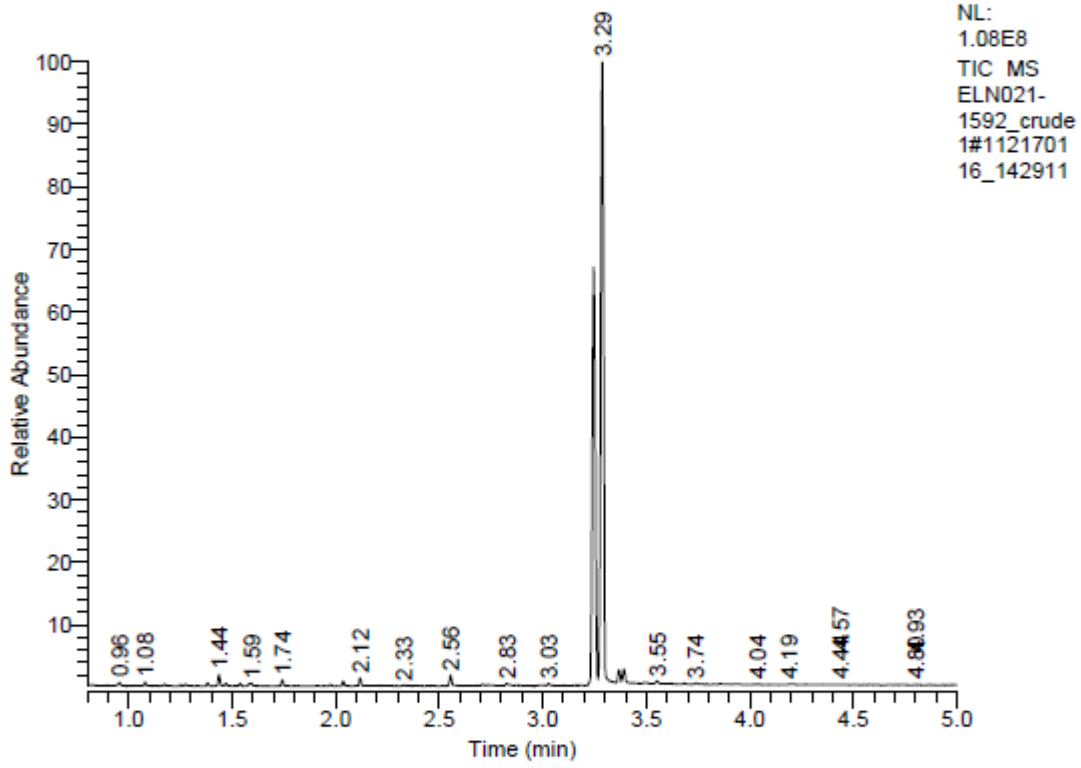
GC-MS of crude **25**

2-Phenyl-2-((R)-1,4-dioxaspiro[4.5]decan-7-yl)-acetaldehyde (21)

Sample: **ELN021-1592_crude1#1**

Data File:	ELN021-1592_crude1#112170116_142911
Acquisition Date:	12/17/09 02:31:26 PM
Injection Volume(µl):	1.00
Vial:	116
Coulmn:	Zebron ZB-5 MS, 15m x 0.25mm ID, 0.25 um film
Column Flow:	2.0 ml/min
Carrier Gas:	Helium
Split Ratio:	20
SSL Inlet Temp:	200 C
Instrument Method:	C:\Xcalibur\OA Methode & Processing Files\SSL_ZB5_PCI_V03.meth
Data Path:	C:\Data01\inauenr

RT: 0.80 - 5.00 SM: 7B



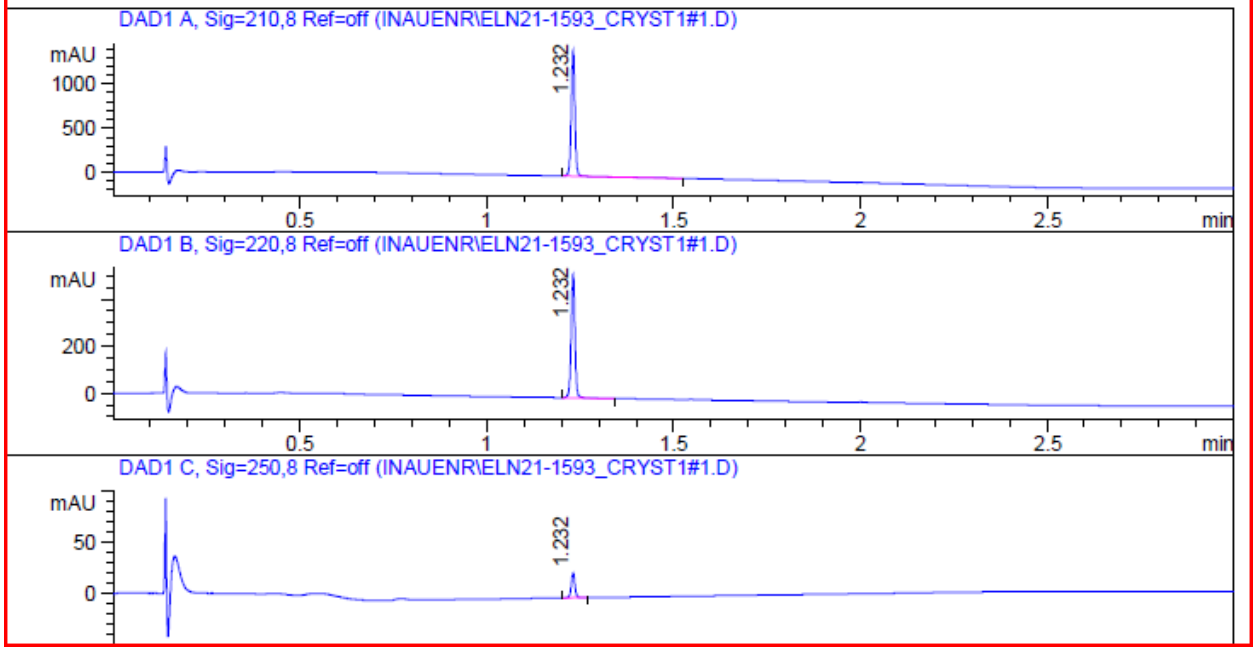
RT	Area %	Peak Area	Peak Height	Peak Width
0.82	0.81	1515717.4	467465.0	0.13
0.96	0.33	616293.3	798894.6	0.03
1.44	0.63	1178972.0	2824267.3	0.02
1.74	0.32	601896.4	1399583.1	0.02
2.12	0.45	848708.1	2094419.7	0.02
2.56	0.70	1308473.2	2542986.8	0.03
3.25	38.54	72281886.2	92913810.5	0.05
3.29	56.24	105467258.7	148221095.1	0.07
3.37	0.94	1754583.7	3551763.6	0.02
3.39	1.04	1958577.9	3382947.5	0.03

GC trace of crude **21**

LC-MS data

(1R,4R,5S,6S)-6-hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (9a)

```
Injection Date   : Fri, 18. Dec. 2009          Seq Line    :          0
Sample Name      : ELN21-1593_cryst1#1         Location    :    P1-D-03
Acq Operator     : inauenr                     Inj. No.    :          0
                                               Inj. Vol.   :       2 µl

Acq. Method      : D:\METHODS\PRMETHOD1.M
Analysis Method  : D:\METHODS\PRMETHOD1.M
PR Method1, 3 min
kinetex 2.6 micron C18,  2.1 x 50 mm, Flow 1 ml, T = 40°C
Eluent A: Water, 0.08 % TFA
Eluent B: Acetonitrile, 0.012% TFA
Gradient:
2.0 min  95% B
2.8 min  95% B
3.0 min   5% B
```



Sample Name: ELN21-1593_crystl#1

DAD1 A, Sig=210,8 Ref=off

Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.232	1433.651	974.197	100.000

DAD1 B, Sig=220,8 Ref=off

Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.232	527.792	366.519	100.000

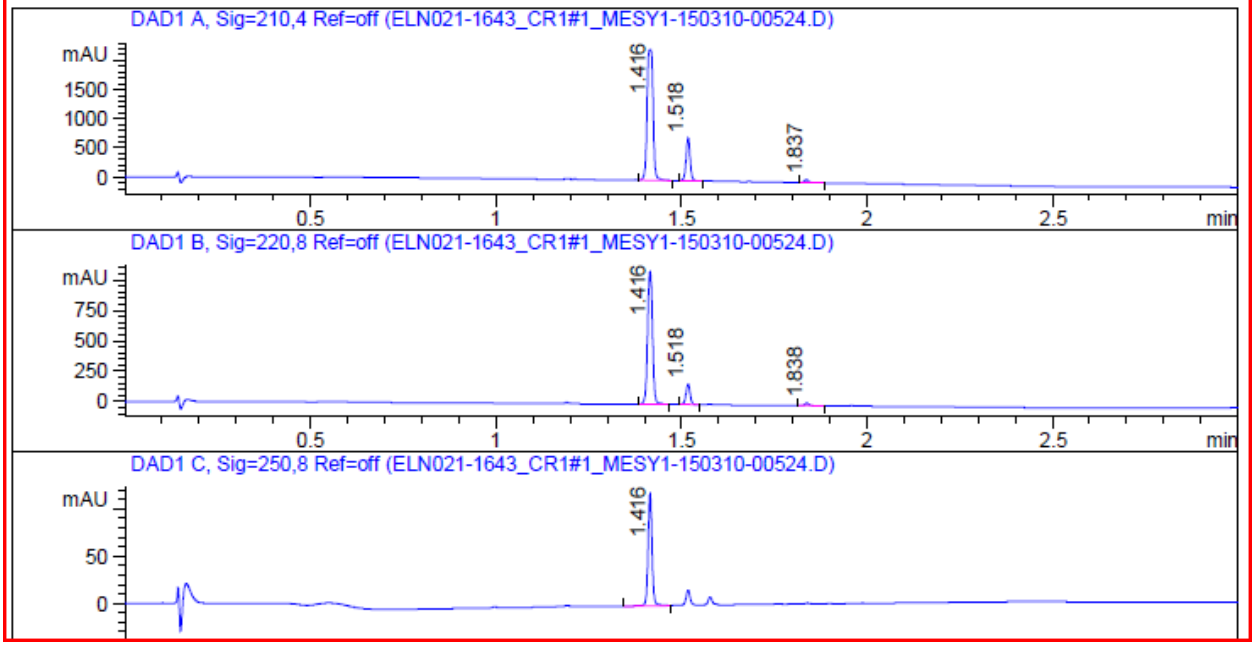
DAD1 C, Sig=250,8 Ref=off

Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.232	24.047	16.257	100.000

LC-MS (LC-MS method 1) of **9a**

(1R,2S,3S,4R)-6-oxo-3-phenylbicyclo[2.2.2]octan-2-yl methanesulfonate (22a)

```
Injection Date  : Mon, 15. Mar. 2010          Seq Line   :          0
Sample Name     : ELN021-1643_cr1#1_mesy      Location   :    P1-D-04
Acq Operator    : inauen                      Inj. No.   :          0
                                              Inj. Vol.  :       2 µl

Acq. Method     : D:\METHODS\PRMETHOD1.M
Analysis Method : D:\METHODS\PRMETHOD1.M
PRMethod1, 3 min
Kinetex C18, 2.6 micron, 2.1 x 50 mm, Flow 1 ml, T = 40°C
Eluent A: Water, 0.08 % TFA
Eluent B: Acetonitrile, 0.012% TFA
Gradient:
2.0 min  95% B
2.8 min  95% B
3.0 min   5% B
```



Sample Name: ELN021-1643_crl#1_mesy

DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.416	2240.750	2508.087	80.925
2	1.518	735.384	552.754	17.835
3	1.837	53.569	38.447	1.241

DAD1 B, Sig=220,8 Ref=off

Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.416	1086.155	1004.695	87.377
2	1.518	167.914	129.353	11.250
3	1.838	21.139	15.788	1.373

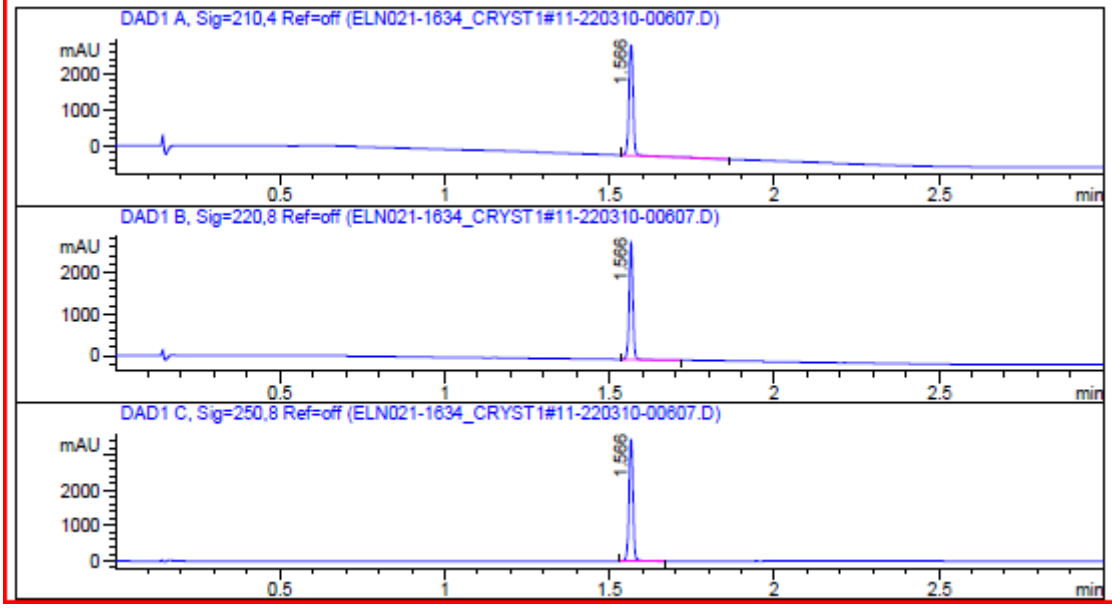
DAD1 C, Sig=250,8 Ref=off

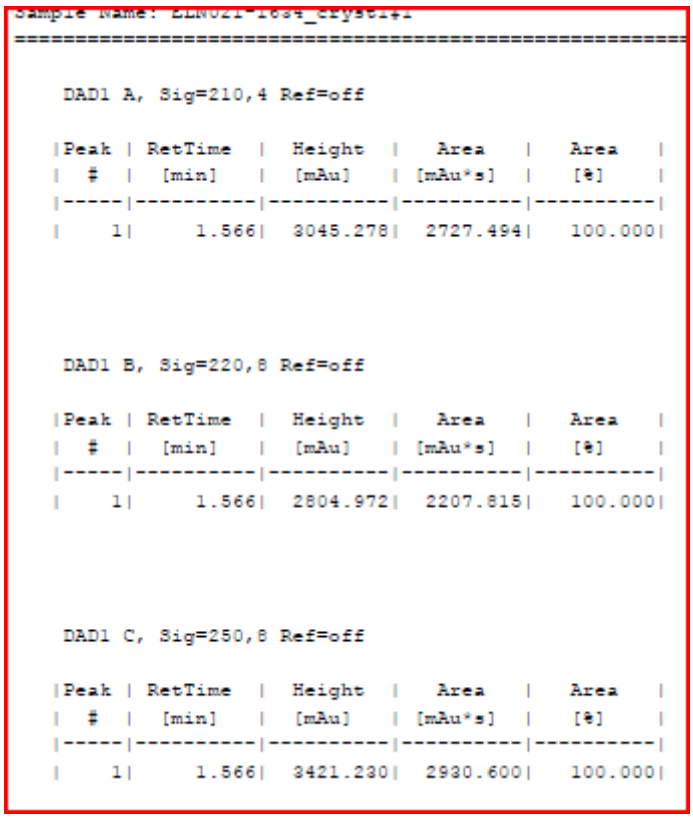
Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.416	118.897	88.724	100.000

LC-MS (LC-MS method 1) of crude **22a**, toluene (R_t 1.518 min)

(1R,4R)-5-phenylbicyclo[2.2.2]oct-5-en-2-one (1)

```
Injection Date  : Mon, 22. Mar. 2010          Seq Line   :          0
Sample Name     : ELN021-1634_cryst1#1        Location   :    P2-A-01
Acq Operator    : inauen                      Inj. No.   :          0
                                              Inj. Vol.  :       2 µl

Acq. Method     : D:\METHODS\PRMETHOD1.M
Analysis Method : D:\METHODS\PRMETHOD1.M
PRMethod1, 3 min
Kinetex C18, 2.6 micron, 2.1 x 50 mm, Flow 1 ml, T = 40°C
Eluent A: Water, 0.08 % TFA
Eluent B: Acetonitrile, 0.012% TFA
Gradient:
2.0 min  95% B
2.8 min  95% B
3.0 min   5% B
```





Sample Name: ELN021-1634_cryst1#1

DAD1 A, Sig=210,4 Ref=off

Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.566	3045.278	2727.494	100.000

DAD1 B, Sig=220,8 Ref=off

Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.566	2804.972	2207.815	100.000

DAD1 C, Sig=250,8 Ref=off

Peak #	RetTime [min]	Height [mAu]	Area [mAu*s]	Area [%]
1	1.566	3421.230	2930.600	100.000

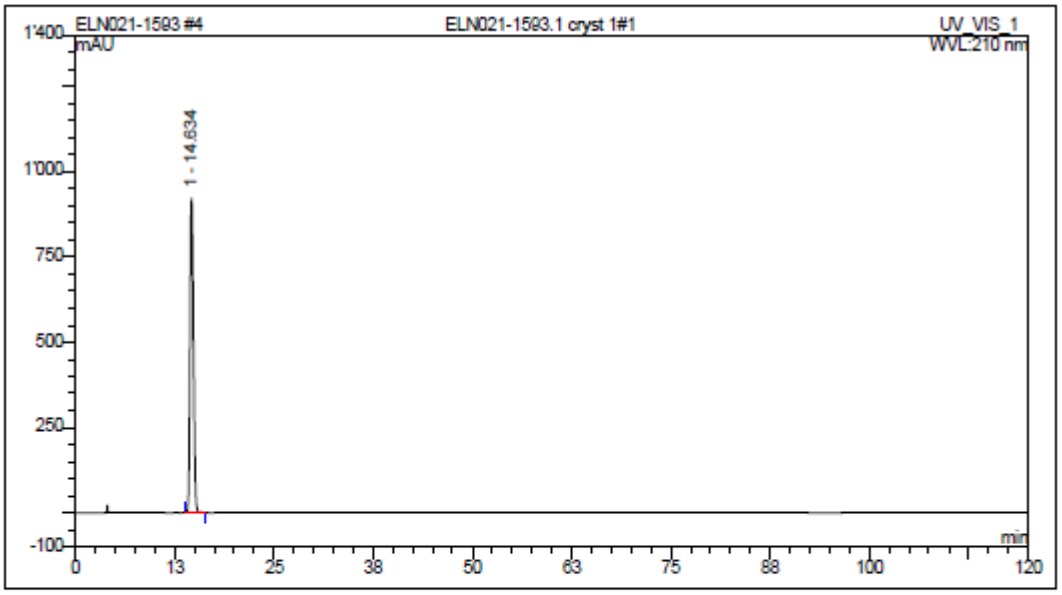
LC-MS (LC-MS method 1) of **1**

Chiral HPLC data

(1R,4R,5S,6S)-6-hydroxy-5-phenylbicyclo[2.2.2]octan-2-one (9a)

ELN021-1593.1 cryst 1#1

Sample ID:	5481dce7-ee63-11de-bf8b-0022191d883c		
Sample Name:	ELN021-1593.1 cryst 1#1	*Date:*	21.12.09
Sample Number:	4		
Time Base:	CHIRALLC02		
Sequence Name:	ELN021-1593		
Sequence Dir:	Data\CHIRALLC02\vogelsr\gemessene Proben\T-Channel		
Inject Volume [ul]:	5	*Comment:*	5.0mg/ml Heptane:2-Propanol 1:1
Quantif. Method:	default		
Eluent A:	60.0 % Heptane		
Eluent B:	40.0 % 2-Propanol		
Flow:	0.800 ml/min		
Column:	ChiralPak AS-H 4.6 x 250 mm, 5um		
Serial number:	ASH0CE-NA013		
Temperature:	25.0 °C		
Detection [nm]:	210		

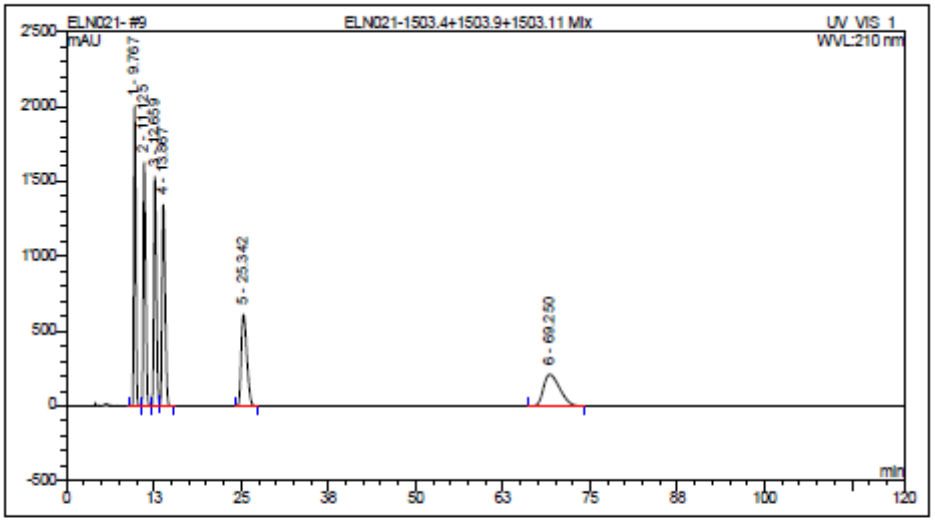


Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	K' UV_VIS_1	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	14.6	2.03	100.0	463.665	n.a.	1.2	5306.0
Total:			100.0	463.7			

Chiral HPLC data of **9a**

ELN021-1503.4+1503.9+1503.11 Mix

Sample ID:	d93a0a8a-c46b-11de-bf8b-0022191d883c
Sample Name:	ELN021-1503.4+1503.9+1503.11 Mix *Date:* 29.10.09
Sample Number:	9
Time Base:	CHIRALLC02
Sequence Name:	ELN021-
Sequence Dir:	Data\CHIRALLC02\vogelsr\gemessene Proben\T-Channel
Inject Volume [ul]:	5 *Comment:* 15.0 mg/ml Heptan:2-Propanol 1:1
Quantif. Method:	default
Eluent A:	60.0 % Heptane
Eluent B:	40.0 % 2-Propanol
Flow:	0.800 ml/min
Column:	ChiralPak AS-H 4.6 x 250 mm, 5um
Serial number:	ASH0CE-NA013
Temperature:	25.0 °C
Detection [nm]:	210



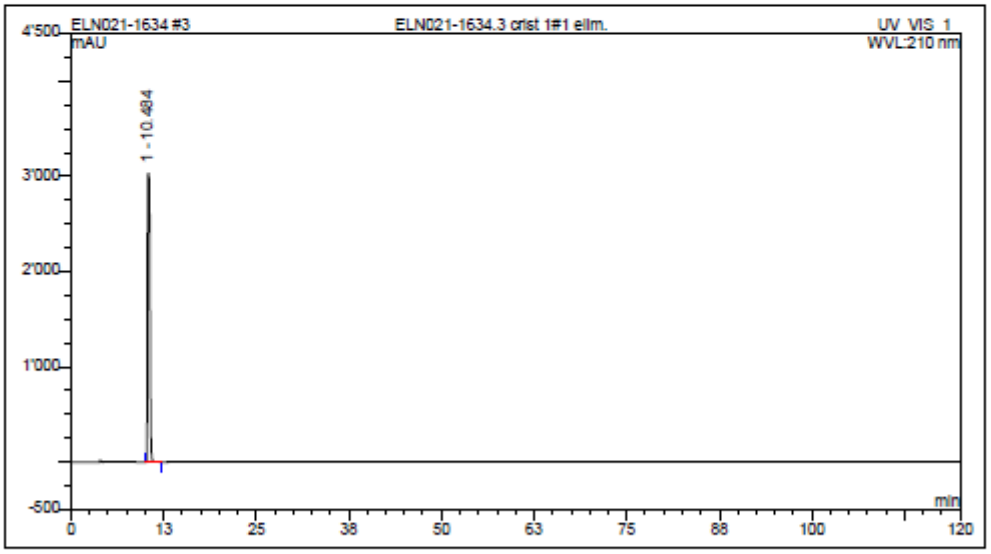
Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	K' UV_VIS_1	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	9.8	1.02	17.2	649.820	2.3	1.2	5595.0
2	11.1	1.30	17.2	650.359	2.3	1.4	4803.0
3	12.7	1.62	17.3	653.009	1.6	1.2	5457.0
4	13.9	1.87	18.1	684.167	9.9	1.3	4601.0
5	25.3	4.24	15.1	572.318	14.9	1.4	4490.0
6	69.3	13.33	15.2	573.381	n.a.	1.4	3992.0
Total:			100.0	3783.1			

Chiral HPLC data of a mixture of rac. **9a** (R_t 11.1, 12.7 min), rac. **9b** (R_t 9.8, 13.9 min), **and** rac. **9c** (R_t 25.3, 69.3 min).

(1R,4R)-5-phenylbicyclo[2.2.2]oct-5-en-2-one (1)

ELN021-1634.3 crist 1#1 elim.

Sample ID:	7b69b6fc-3696-11df-bf8c-0022191d883c		
Sample Name:	ELN021-1634.3 crist 1#1 elim.	*Date:*	23.03.10
Sample Number:	3		
Time Base:	CHIRALLC02		
Sequence Name:	ELN021-1634		
Sequence Dir:	Data\CHIRALLC02\vogelsr\gemessene Proben\T-Channel		
Inject Volume [ul]:	5	*Comment:*	4.0mg/ml Heptane:2-Propanol 1:1
Quantif. Method:	default		
Eluent A:	60.0 %	Heptane	
Eluent B:	40.0 %	2-Propanol	
Flow:	0.800 ml/min		
Column:	ChiralPak AS-H 4.6 x 250 mm, 5um		
Serial number:	ASH0CE-NA013		
Temperature:	25.0 °C		
Detection [nm]:	210		

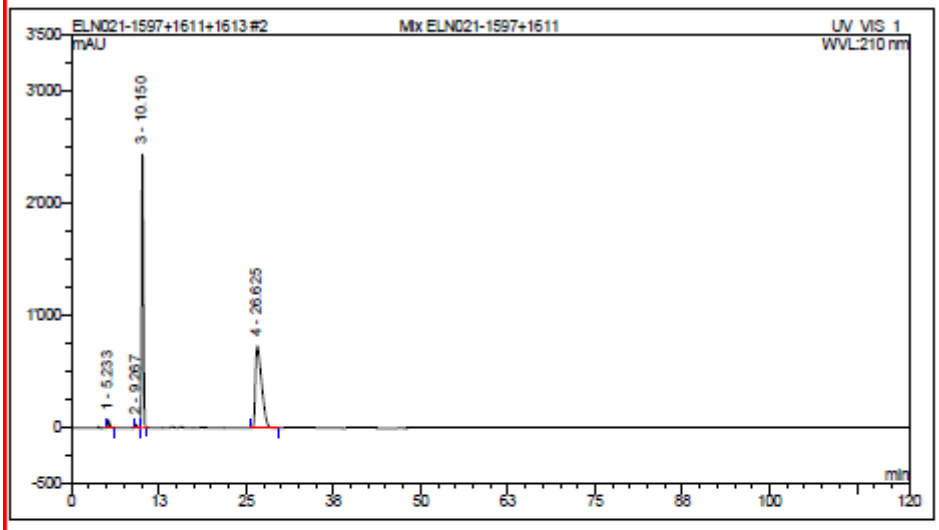


Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	K' UV_VIS_1	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	10.5	1.17	100.0	1194.382	n.a.	1.3	4291.0
Total:			100.0	1194.4			

Chiral HPLC data of **1**

Mix ELN021-1597+1611

Sample ID:	**36a97c53-0019-11df-bf8b-0022191d883c**
Sample Name:	**Mix ELN021-1597+1611** *Date:* **13.01.10**
Sample Number:	**2**
Time Base:	**CHIRALLC02**
Sequence Name:	**ELN021-1597+1611+1613**
Sequence Dir:	**Data\CHIRALLC02\vogelsr\gemessene Proben\T-Channel**
Inject Volume [ul]:	**5** *Comment:* **4.0mg/ml Heptane:2-Propanol 1:1**
Quantif. Method:	**default**
Eluent A:	**60.0 % Heptane**
Eluent B:	**40.0 % 2-Propanol**
Flow:	**0.800 ml/min**
Column:	**ChiralPak AS-H 4.6 x 250 mm, 5um**
Serial number:	**ASH0CE-NA013**
Temperature:	**25.0 °C**
Detection [nm]:	**210**



Peak No. UV_VIS_1	Ret.Time UV_VIS_1 min	K' UV_VIS_1	Rel.Area UV_VIS_1 %	Area UV_VIS_1 mAU*min	Resolution UV_VIS_1	Asymmetry UV_VIS_1	Plates UV_VIS_1
1	5.2	0.08	1.5	21.852	8.9	2.1	1416.0
2	9.3	0.92	0.5	7.432	2.2	1.4	11049.0
3	10.2	1.10	45.8	665.884	15.6	1.2	8574.0
4	26.6	4.51	52.2	758.325	n.a.	1.9	4045.0
Total:			100.0	1453.5			

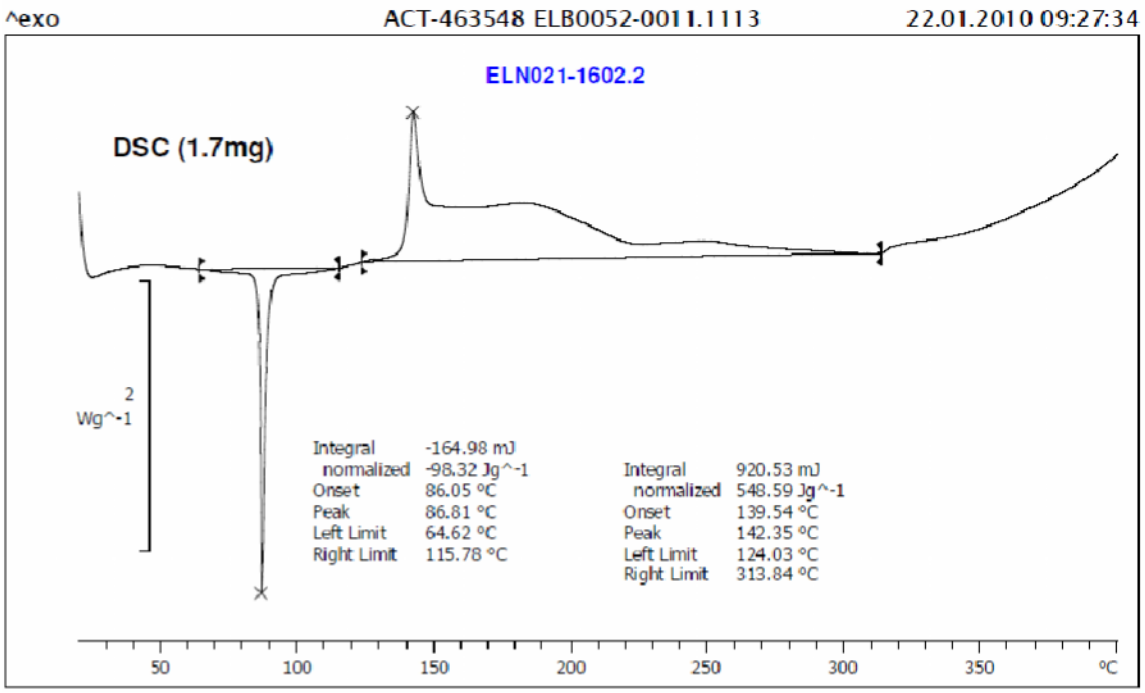
Chiral HPLC data of a mixture of **1** and ent. **1** (obtained via chiral separation of rac. **1**)

DSC data

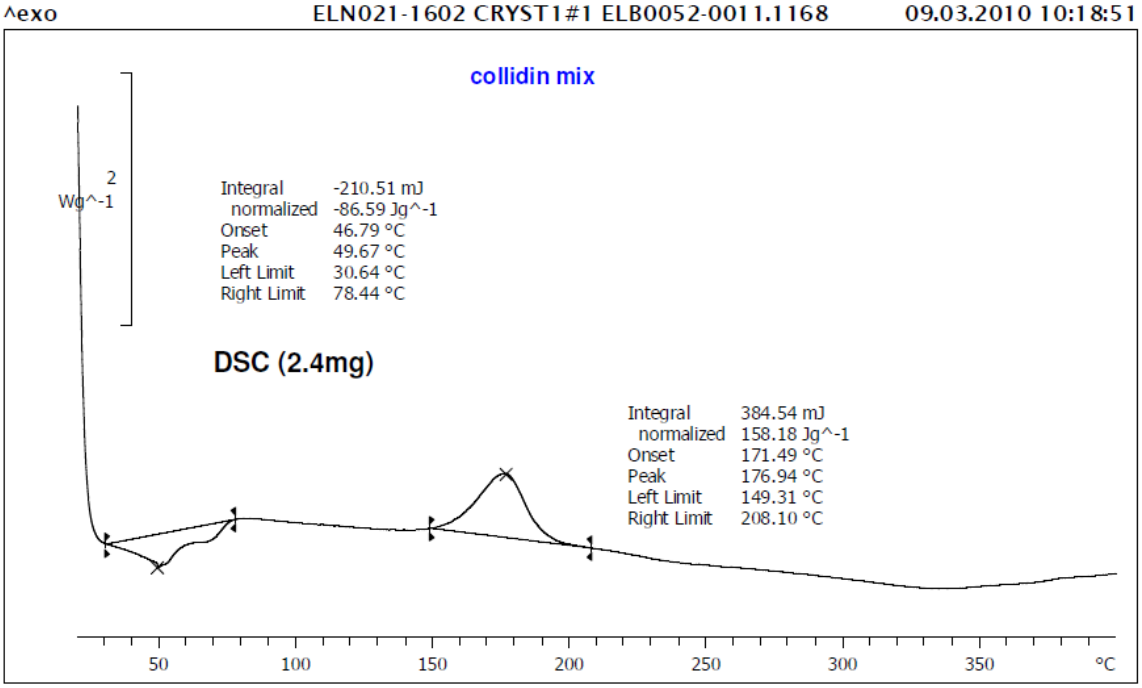
Conditions: DSC822^e/400 instrument and HSS7 sensor from Mettler-Toledo. The sample is weighed in a high pressure gold plated crucible (ref M20, inner volume 20 μL, sample occupies ca. 25% of total volume, Swiss Safety Institute, Basel) which is closed with a flow of 15 mL/min of N_2 during the experiment. The scan goes from 20 °C to 400 °C at a rate of 4 °C/min. The STARe software enables the interpretation of the obtained curve (no baseline correction).

Figure 1. DSC traces of:
(a) **22a**
(b) **22a** 2,4,6-collidine
(c) **22a** in NMP
(d) rac. **22a** in DMSO
(e) NMP
(f) DMSO
(g) Compound **1** ((*R*,*R*)-phenylketone)

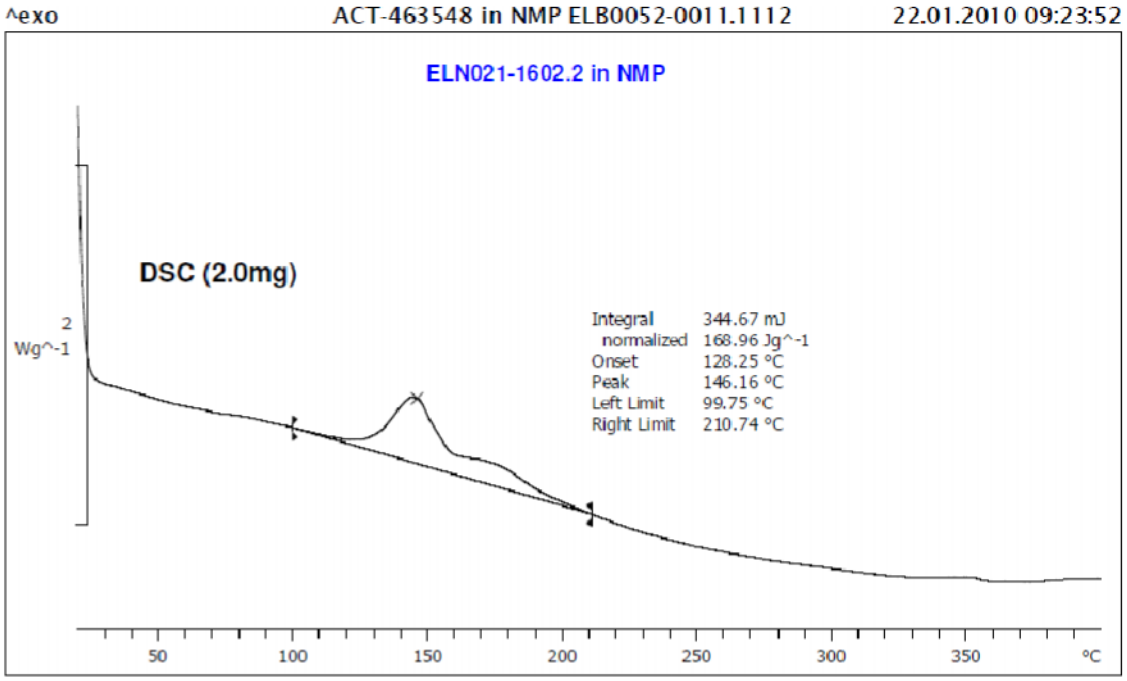
Neat **22a** displayed a left limit for exothermic event at 124 °C with – 549 KJ/Kg. The exothermic event in 2,4,6-collidine starting at 150 °C with peak at 177 °C (- 158 KJ/Kg) might represent the desired reaction; the energy mirroring the dilution factor for this measurement, *i.e.* ca. 4 fold decrease in ΔH by a dilution with 4 vol. In NMP, two kinetic events overlap, starting at 100 °C (- 169 KJ/Kg) whereas the DSC trace of the DMSO soln. indicates overlap of decomposition of the solvent, with a left limit of 176 °C and ΔH = - 739 KJ/Kg.



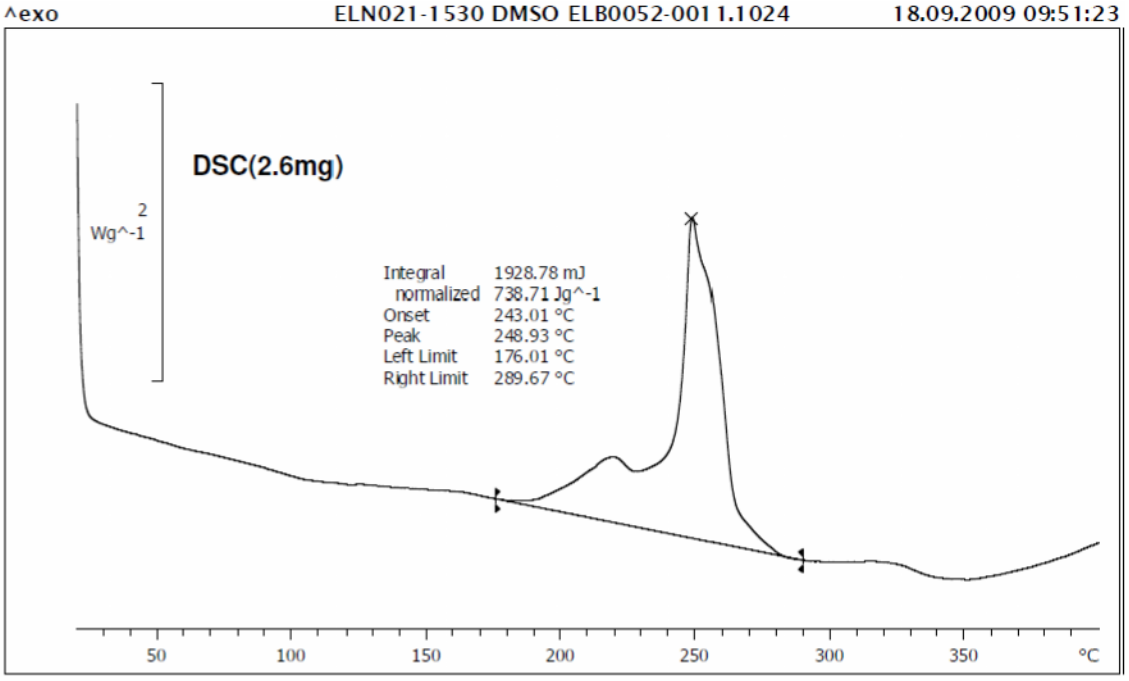
(a) **22a** (pure compound)



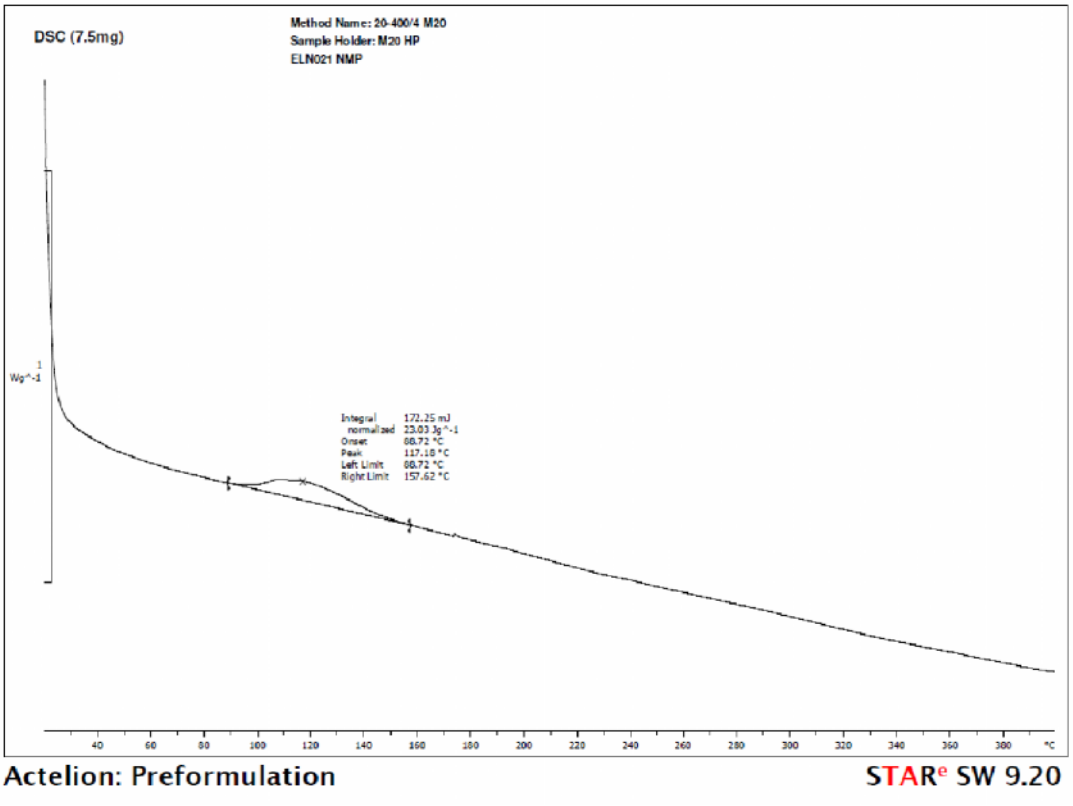
(b) **22a** in 2,4,6-collidine



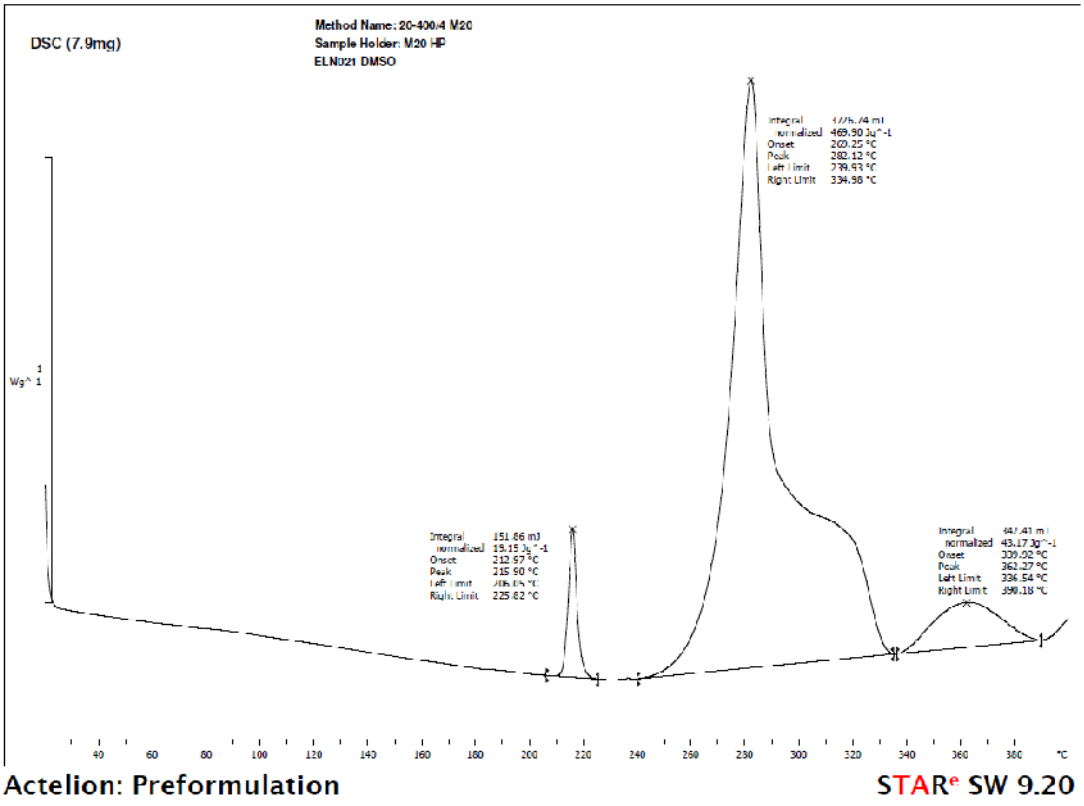
(c) **22a** in NMP



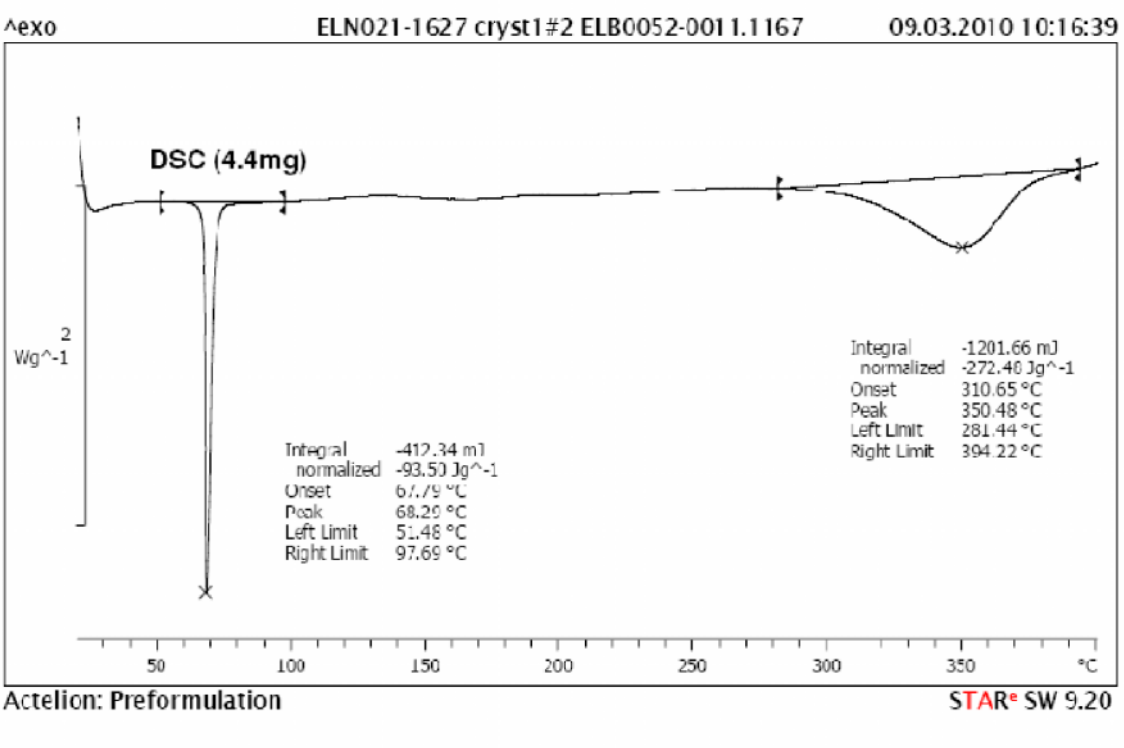
(d) rac. **22a** in DMSO


DSC (7.5mg)
Method Name: 20-400/4 M20
Sample Holder: M20 HP
ELN021 NMP
Integral 172.25 mJ
normalized 23.03 Jg^-1
Onset 88.72 °C
Peak 117.18 °C
Left Limit 88.72 °C
Right Limit 157.62 °C
Wg^-1
°C
Actelion: Preformulation
STARe SW 9.20

(e) NMP


DSC (7.9mg)
Method Name: 20-400/4 M20
Sample Holder: M20 HP
ELN021 DMSO
Integral 1776.74 mJ
normalized 469.90 Jg^-1
Onset 269.25 °C
Peak 282.12 °C
Left Limit 259.93 °C
Right Limit 334.98 °C
Integral 151.66 mJ
normalized 19.15 Jg^-1
Onset 212.67 °C
Peak 215.50 °C
Left Limit 206.05 °C
Right Limit 225.62 °C
Integral 447.41 mJ
normalized 43.17 Jg^-1
Onset 309.02 °C
Peak 362.27 °C
Left Limit 336.54 °C
Right Limit 390.18 °C
Wg^-1
°C
Actelion: Preformulation
STARe SW 9.20

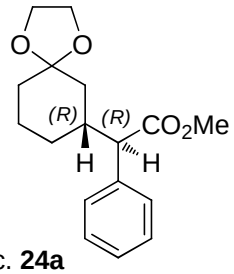
(f) DMSO



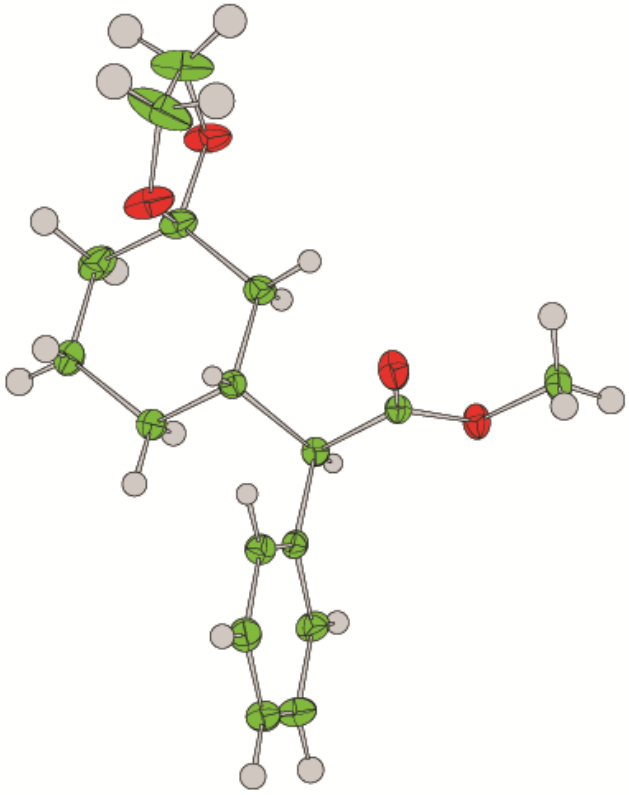
(g) Compound **1** ((*R*,*R*)-phenylketone)

X-ray data

Figure 2. X-ray structure of rac. **24a** (major racemic *like*-isomer)



rac. **24a**

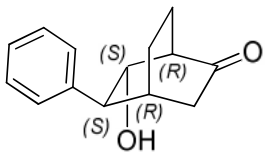


Crystal structure information of **24a**:

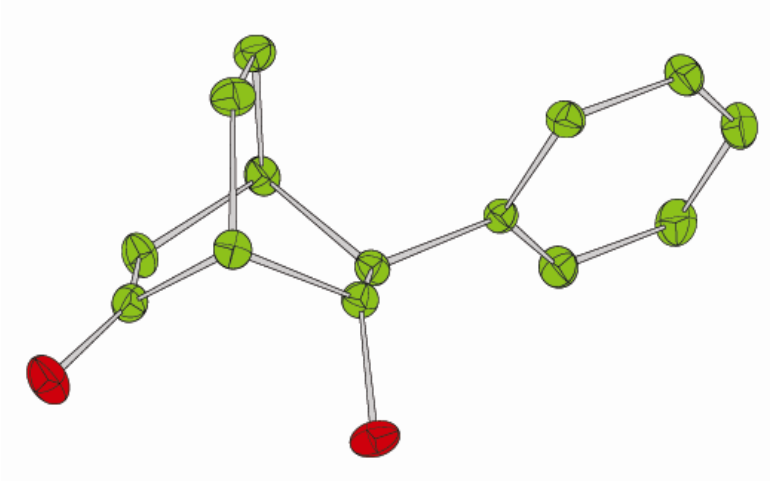
ELN021-1438.4

```
ACT-378546  in P-1 09-05-20
Formula  C17 H22 O4

Crystal Class      Triclinic         Space Group P -1
a                  5.6959(3)         alpha                70.760(3)
b                  10.9414(7)        beta                 86.370(3)
c                  13.2893(8)        gamma                79.409(3)
Volume           768.62(8)           Z                    2

Radiation type     Mo K\a            Wavelength       0.710730
Dx                   1.25            Mr                    290.36
Mu                  0.088            Temperature (K)        293
Size               0.00x 0.00x 0.00
Colour     ?                         Shape      ?
Cell from           0 Reflections    Theta range           0 to   0
Standard Interval         0          Standard Count           0
Diffractometer type UNKNOWN         Scan type      2THETA/OMEG
Absorption type      none           Transmission range   1.00 1.00
Reflections measured     35546      Independent reflections   6569
Rint                    0.0004      Theta max                34.76
Hmin, Hmax               -9     9
Kmin, Kmax              -17    17
Lmin, Lmax              -21    21

Refinement on F
R-factor                0.051       Weighted R-factor        0.055
                                    Max shift/su            0.0009
Delta Rho min           -0.64       Delta Rho max             0.54
Reflections used         5564       sigma(I) limit            3.00
Number of parameters      190       Goodness of fit          1.070
```

Figure 3. X-ray structure of rac. **9a** (major isomer)



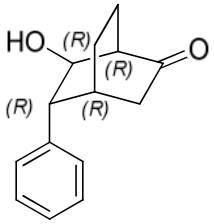
9a



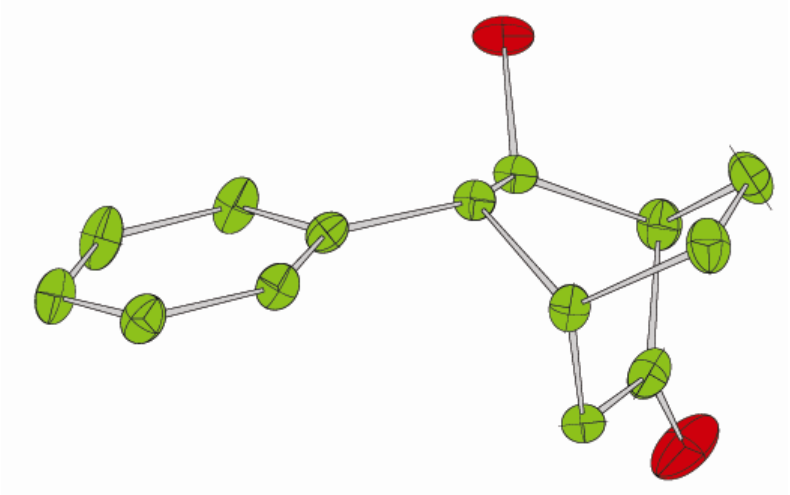
Crystal structure information of rac. **9a**:

```
Crystal structure information:
==============================

eln021_1503.4 in P2(1)/n 09-10-12
Formula  C14 H16 O2
Crystal Class      Monoclinic        Space Group P    1    21/n 1
a                  6.4126(5)         alpha                  90
b                  6.4794(5)         beta                   92.235(4)
c                  26.6854(18)       gamma                  90
Volume           1107.93(14)         Z                      4
Radiation type     Mo K\a            Wavelength         0.710730
Dx                   1.30            Mr                   216.28
Mu                  0.085            Temperature (K)       293
Size               0.00x 0.00x 0.00
Colour     ?                         Shape      ?
Cell from           0 Reflections    Theta range          0 to   0
Standard Interval         0          Standard Count          0
Diffractometer type UNKNOWN         Scan type      2THETA/OMEG
Absorption type      none           Transmission range   1.00 1.00
Reflections measured    19296       Independent reflections   3698
Rint                   0.0005       Theta max              31.51
Hmin, Hmax               -9     9
Kmin, Kmax               -9     9
Lmin, Lmax              -39    39

Refinement on F
R-factor                0.040       Weighted R-factor        0.044
                                    Max shift/su            0.0004
Delta Rho min           -0.21       Delta Rho max            0.40
Reflections used         2741       sigma(I) limit           3.00
Number of parameters      145       Goodness of fit         1.117
```

Figure 4. X-ray structure of rac. **9b**



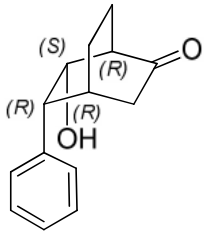
9b



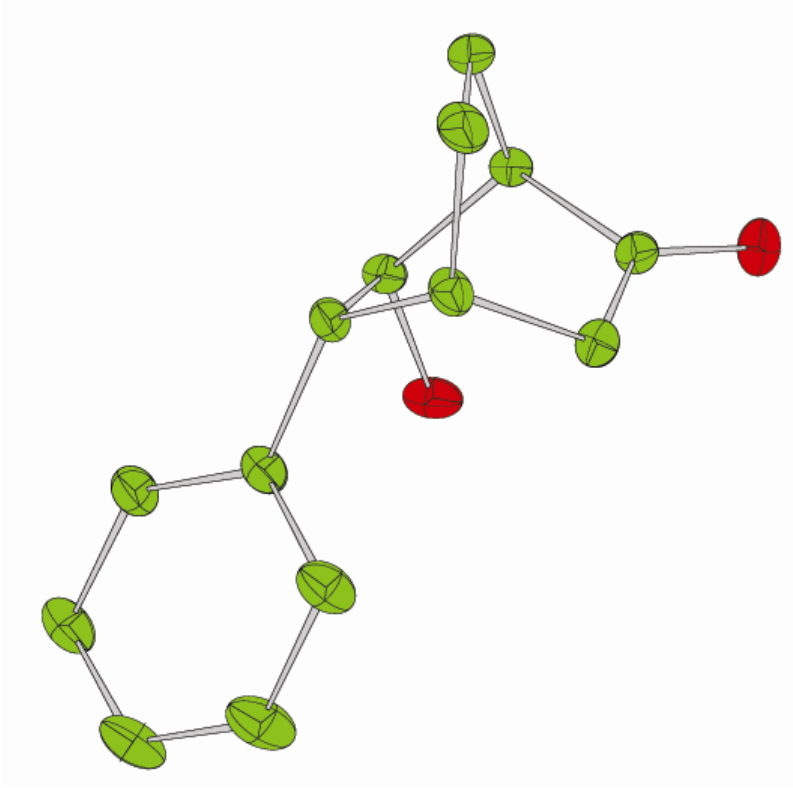
Crystal structure information rac. **9b**:

```
Crystal structure information:
==============================


eln021_1503_9   ACT-453815   in P2(1) 09-09-24

Formula  C14 H16 O2
Crystal Class      Monoclinic        Space Group P    1    21   1
a                  6.2170(4)         alpha                90
b                  8.8214(5)         beta                 101.591(3)
c                  10.2464(6)        gamma                90
Volume           550.48(6)           Z                    2
Radiation type     Mo K\a            Wavelength       0.710730
Dx                   1.30            Mr                   216.28
Mu                  0.086            Temperature (K)       293
Size               0.00x 0.00x 0.00
Colour     ?                         Shape      ?
Cell from           0 Reflections    Theta range          0 to   0
Standard Interval        0           Standard Count           0
Diffractometer type UNKNOWN         Scan type      2THETA/OMEG
Absorption type      none           Transmission range   1.00 1.00
Reflections measured    10045       Independent reflections   1784
Rint                   0.0003       Theta max                30.53
Hmin, Hmax               -8     8
Kmin, Kmax              -12    12
Lmin, Lmax              -14    14

Refinement on F
R-factor                0.031       Weighted R-factor        0.037
                                    Max shift/su            0.0003
Delta Rho min           -0.16       Delta Rho max            0.29
Reflections used         1599       sigma(I) limit           3.00
Number of parameters      145       Goodness of fit          1.101
```

Figure 5. X-ray structure of rac. **9**c



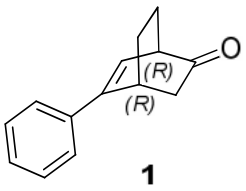
9c



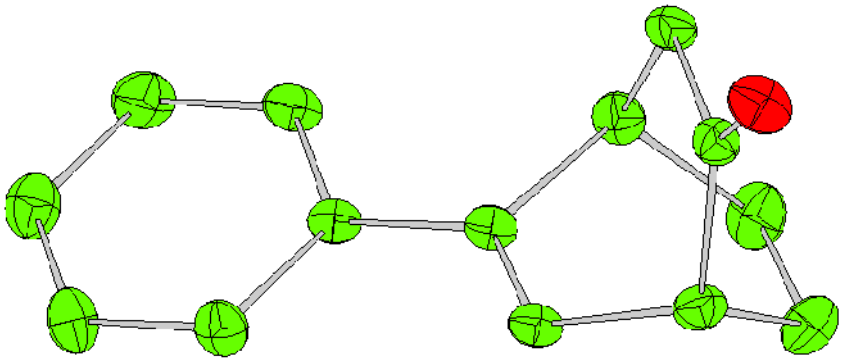
Crystal structure information rac. **9c**:

```
Crystal structure information:
==============================


eln021_1503_11   ACT-453814    in P2(1)/n    09-09-24

Formula  C14 H16 O2
Crystal Class      Monoclinic        Space Group P    1    21/n 1
a                  8.6687(6)         alpha                90
b                  6.3812(5)         beta                 99.963(4)
c                  20.5439(15)       gamma                90
Volume          1119.28(14)          Z                    4
Radiation type     Mo K\a            Wavelength       0.710730
Dx                   1.28            Mr                   216.28
Mu                  0.084            Temperature (K)       293
Size               0.00x 0.00x 0.00
Colour    ?                          Shape     ?
Cell from           0 Reflections    Theta range          0 to   0
Standard Interval         0          Standard Count           0
Diffractometer type UNKNOWN          Scan type      2THETA/OMEG
Absorption type     none             Transmission range   1.00 1.00
Reflections measured     63732       Independent reflections   3412
Rint                    0.0005       Theta max                30.50
Hmin, Hmax               -12    12
Kmin, Kmax                -9     9
Lmin, Lmax               -29    29

Refinement on F
R-factor                 0.040       Weighted R-factor        0.045
                                     Max shift/su            0.0010
Delta Rho min            -0.20       Delta Rho max            0.39
Reflections used          3173       sigma(I) limit           3.00
Number of parameters       145       Goodness of fit         1.098
```

Figure 6. X-ray structure of **1**



1



Crystal structure information of **1**:

eln021_1627_3_123k_0m ACT-291739 in P2(1)2(1)2(1) 10-04-16			
Formula	C14 H14 O1		
Crystal Class	Orthorhombic	Space Group P	21 21 21
a	8.4901(3)	alpha	90
b	10.2635(4)	beta	90
c	12.1116(5)	gamma	90
Volume	1055.38(7)	Z	4
Radiation type	Mo K\a	Wavelength	0.710730
Dx	1.25	Mr	198.26
Mu	0.077	Temperature (K)	293
Size	0.00x 0.00x 0.00		
Colour	cl	Shape	?
Cell from	0 Reflections	Theta range	0 to 0
Standard Interval	0	Standard Count	0
Diffractometer type	UNKNOWN	Scan type	2THETA/OMEG
Absorption type	none	Transmission range	1.00 1.00
Reflections measured	11265	Independent reflections	2292
Rint	0.0003	Theta max	33.13
Hmin, Hmax	-13 11		
Kmin, Kmax	-15 11		
Lmin, Lmax	-18 14		
Refinement on F			
R-factor	0.038	Weighted R-factor	0.040
		Max shift/su	0.0003
Delta Rho min	-0.31	Delta Rho max	0.27
Reflections used	1799	sigma(I) limit	3.00
Number of parameters	136	Goodness of fit	1.129