

Supporting Information

Synthesis of Akt Inhibitor (Ipatasertib). Part 1. Route Scouting and Early Process Development of a Challenging Cyclopentylpyrimidine Intermediate

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1.0. General Information

NMR measurements were carried out on a Bruker, 300 MHz spectrometer equipped with a 5 mm, BBO, Z-gradient probe with TMS internal standard. Data for ^1H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; h, heptet; dd, doublet of doublet; m, multiplet), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (ppm). Trace metal analysis was performed by Intertek Pharmaceutical services using inductively coupled plasma atomic emission spectroscopy (ICP-AES). Melting points were measured by differential scanning calorimetry (DSC). All reactions were performed under an inert atmosphere. Unless otherwise noted, all chemicals were commercially available and used as is. SiliaMetS® thiol (40–63 μm , 60Å) was purchased from Silicycle® and activated carbon was Darco® G60, 100 mesh. (*R*)-(+)-pulegone was sourced from Anthem BioSciences, India.

2.0. Analytical Methods

Method 2.1. HSGC Column: Agilent J&W DB-1, 60 m x 0.53 mm, 3 μm ; Inlet Temperature: 200 °C; Split Ratio: 0.9:1; Column: Flow Nitrogen at 8 mL/min; Oven Temperature: Hold time 2 min (60 °C), ramp 12 °C / min to 250 °C (hold 10 min); Total Run Time: 26 minutes; Detector Type: FID; Detector Temperature: 250 °C.

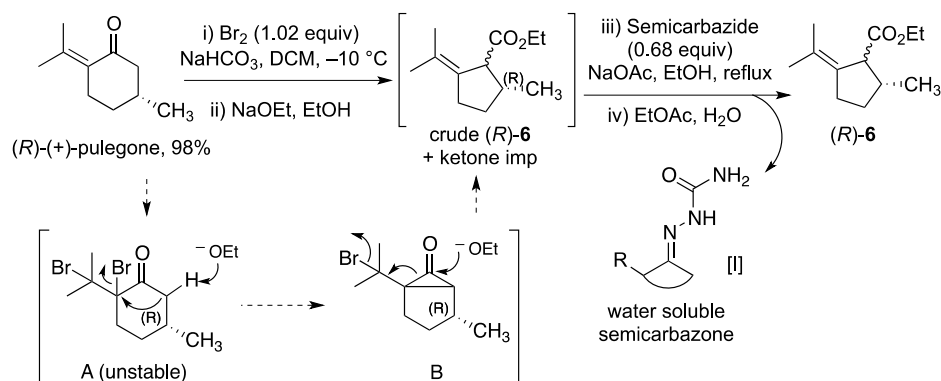
Method 2.2. Chiral HPLC column: Chiralcel AD-H, 4.6 x 250 mm, 5 μm ; Mobile Phase A: n-hexane; Mobile Phase B: MeOH/*i*-PrOH (75:25); A:B = 95:5; A; Flow Rate: 0.8 mL/min; Column Temperature: 40 °C; Detector Wavelength: 254 nm.

Method 2.3. LCMS Column: Atlantis Express C18, 75 mm x 4.6 mm; Mobile Phase A: 0.1% Formic acid in purified water; B: ACN; Gradient: 0.0–1.0 min 70% B, 1.0-1.5 min 95% B, 1.5–2.5 min 95% B, 2.5–3.0 min 70% B, 3.0–5.0 min 70% B; Flow Rate: 0.8 mL/min; Injection Volume: 5 μL ; Detector Wavelength: 254 nm.

Method 2.4. HPLC Column: ZORBAX C18, 150 mm x 4.6 mm; Mobile Phase A: 20mM NH_4OAc in purified water; B: ACN; Gradient: 0.0–4.0 min 40% B, 4.0-8.0 min 90% B, 8.0–12.0 min 90% B, 12.0–15.0 min 40% B, 15.0–20.0 min 40% B; Flow Rate: 0.8 mL/min; Detector Wavelength: 254 nm.

3.0. Experimental Section for (*R*)-(+)-Pulegone Route to Ketone (*R*)-3

3.1. Preparation of cyclopentyl ethyl ester (*R*)-6.

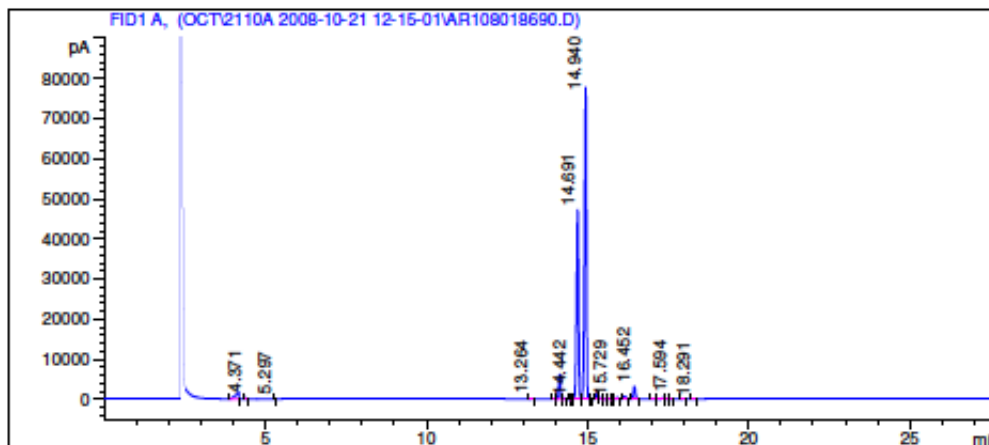


(*R*)-Ethyl 2-methyl-5-(propan-2-ylidene)cyclopentanecarboxylate, 6. Anhydrous sodium hydrogen carbonate (138 g, 0.5 equiv) was charged to a solution of (*R*)-(+)-pulegone (0.5 kg, 1 equiv) in CH_2Cl_2 (2 L). The agitated mixture was cooled to $\leq -10^\circ\text{C}$ and then bromine (0.54 kg, 1.02 equiv) was added drop-wise over ~3 h. The resultant mixture was stirred for 1 h at the same temperature and the reaction was deemed complete by TLC analysis: **pulegone**: Rf. 0.85 and **Int A**: Rf. 0.9; eluent = 100% DCM . The reaction mixture was filtered and the filter cake was washed with CH_2Cl_2 (0.25 L). The combined filtrate was cooled to -40°C and to this, a solution of NaOEt (0.49 kg, 2.2 equiv) in EtOH (1.66 L) was charged. The reaction mixture was agitated for 16 h and was deemed complete by TLC analysis: **Int A**: Rf. 0.9 and product: Rf. 0.95; eluent = 100% DCM . The reaction mixture was quenched with aqueous 1N HCl (840 mL), diluted with CH_2Cl_2 (0.5 L) and then the layers were separated. The aqueous layer was re-extracted using CH_2Cl_2 (3 x 0.5 L) and the combined organic layers were then washed with brine (0.5 L) and finally concentrated under vacuum to a brown oil. The oil was then dissolved in EtOH (1.5 L) and charged with semicarbazide hydrochloride (0.25 kg, 0.68 equiv), NaOAc (0.25 kg, 0.93 equiv) and water (2.5 L). The mixture was heated to reflux for 3 h and then cooled to $\sim 25^\circ\text{C}$ and maintained for 20 h. The reaction mixture was diluted with water (0.5 L) and EtOAc (0.5 L) and the layers separated. The aqueous layer was extracted using EtOAc (2 x 0.5 L) and the combined organic layers were washed with brine (0.5 L) and then concentrated under reduced pressure to afford ester (*R*)-6 (0.40 kg, 89 A% purity by GC as ~2:3 mixture of *cis/trans* isomers (Figure 1.1) in 62% yield as a brown oil. Two additional batches of (*R*)-(+)-pulegone were processed under similar reaction conditions starting with (1) 4.5 kg and (2) 5.0 kg (*R*)-(+)-pulegone and gave: (1) 2.5 kg, 88 A% purity and (2) 3.9 kg, 85 A% purity of cyclopentyl ethyl ester (*R*)-6

respectively. The ^1H NMR (CDCl_3) spectrum conforms to structure (Figure 1.2). No further purification was required and the product was used directly in the next step.¹

Figure 1.1. GC chromatogram of cyclopentyl ethyl ester (*R*)-6.

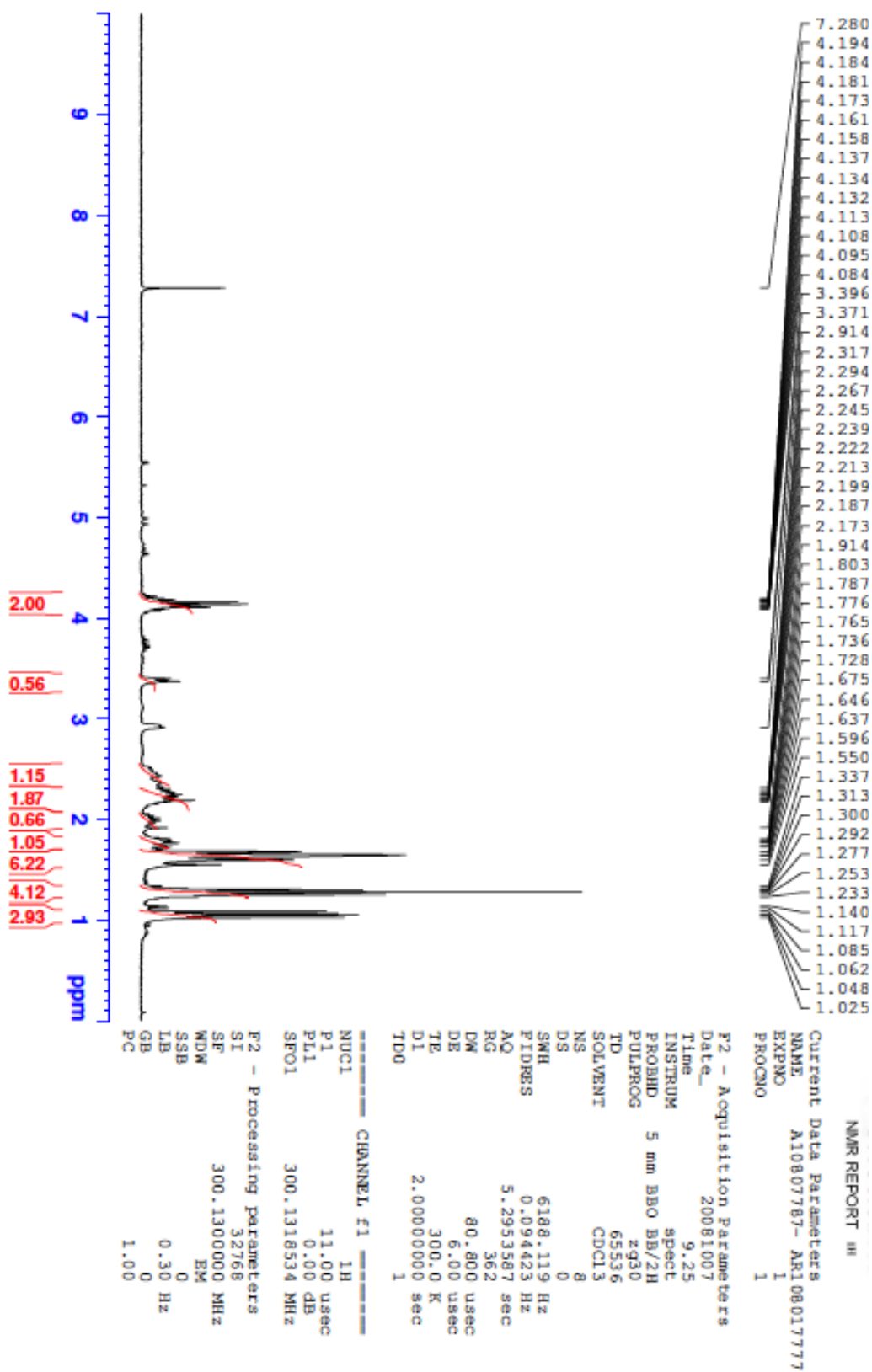
Column- DB-1: 60m X 0.530mm , 3 μm
 Flow- 8.0 ml/min , Carrier gas- Nitrogen , Inlet temp- 200° C , Detector temp - 250° C
 Oven temp- 60° C (Hold-2min), temperature ramp -12° C/min , 250° C (hold -10 min)
 Run time-26.17 minutes, Injection mode- Split (0.9:1) ; Split flow- 7.4ml/min



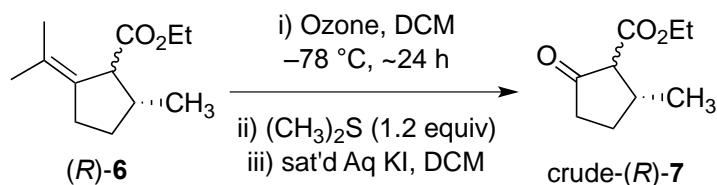
Peak #	RT [min]	Area	Area %
1	4.168	13566.572	2.263
2	4.371	1240.647	0.207
3	5.297	238.905	0.040
4	13.264	1220.189	0.204
5	13.923	805.016	0.134
6	14.132	22607.334	3.771
7	14.289	986.409	0.165
8	14.442	67.577	0.011
9	14.523	19.722	0.003
10	14.691	207075.406	34.545
11	14.940	321896.469	53.700
12	15.113	333.078	0.056
13	15.290	5357.064	0.894
14	15.365	1366.074	0.228
15	15.516	111.041	0.019
16	15.644	826.691	0.138
17	15.729	75.187	0.013
18	15.911	1578.826	0.263
19	16.151	3131.406	0.522

¹In a separate experiment starting with 2.7 kg scale of (*R*)-(+)-pulegone, the concentrated crude product was collected by vacuum distillation at 75–80 °C (1 mm Hg) and gave cyclopentyl ethyl ester (*R*)-6 (2.16 kg) in 67% yield as a 36:43 mixture of *cis/trans* isomers.

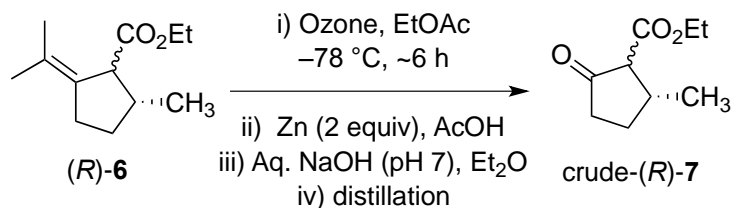
Figure 1.2. ^1H NMR (CDCl_3) spectrum of cyclopentyl ethyl ester (*R*)-6.



3.2. Ozonolysis reaction for preparation of β -keto ester (*R*)-7.



Procedure A: (*R*)-Ethyl 2-methyl-5-oxocyclopentanecarboxylate, 7. Cyclopentyl ethyl ester (*R*)-6 (0.50 kg, 1 equiv) was dissolved in CH_2Cl_2 (5 L) and cooled to $\leq -78\text{ }^\circ\text{C}$. Ozone gas was sparged through the solution until the reaction mixture turned blue in color. The reaction was deemed complete by TLC analysis (100% DCM) after ~ 24 h with consumption of starting material.² The excess ozone was removed by sparging with argon at $\leq -78\text{ }^\circ\text{C}$ for several minutes and then the reaction mixture charged with a solution of dimethylsulfide (DMS) (194 g, 1.2 equiv) in CH_2Cl_2 (1 L) while maintaining the internal temperature $\sim -70\text{ }^\circ\text{C}$. [CAUTION: STENCH — a bleach trap should be used to scrub DMS]. The reaction mixture was gradually warmed to $\sim 25\text{ }^\circ\text{C}$ over 4 h, agitated for 16 h and then quenched with saturated aqueous potassium iodide solution (0.25 L). The layers were separated and then the aqueous layer extracted with CH_2Cl_2 (3 x 0.5 L) followed by washing the combined organic layers with wash brine (0.5 L). The organic layer was concentrated under vacuum to dryness to afford crude (*R*)-7 (0.33 kg, 85 A% purity by GC [Figure 1.3]) in $\sim 75\%$ yield as yellow liquid. No further purification was required and the product was used directly in the next step. Using this procedure, a total of 5.9 kg cyclopentyl ethyl ester (*R*)-6 was converted into 4.68 kg of β -keto ester (*R*)-7 in 15 batches with GC purity ranging between 77–94 A%. The $^1\text{H NMR}$ (CDCl_3) spectrum was consistent with the reported literature.³



² The ozonolysis of cyclopentyl ethyl ester (*R*)-6 was also reported to work well in 5% H_2O / acetone at $0\text{ }^\circ\text{C}$, see: Taber, D. F.; Bai, S.; Tian, W. *J. Org. Chem.* **2011**, *76*, 9733–9737, and reference 5 therein.

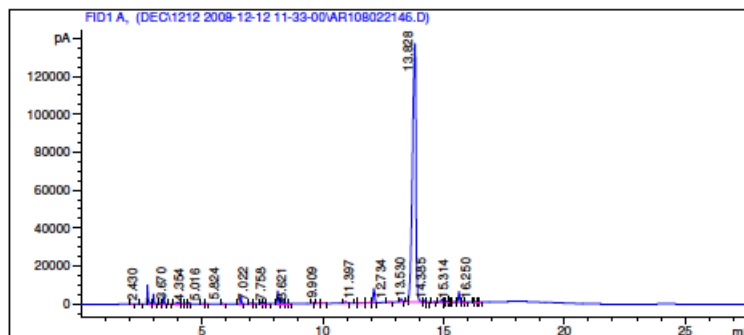
³ Urban, E.; Knühl, G.; Helmchen, G. *Tetrahedron* **1996**, *52*, 971–986.

Procedure B: (*R*)-Ethyl 2-methyl-5-oxocyclopentanecarboxylate, 7. Cyclopentyl ethyl ester (*R*)-6 (0.50 kg, 1 equiv) was dissolved in EtOAc (3 L) and cooled to $-78\text{ }^{\circ}\text{C}$. To this solution, ozone gas was sparged until the reaction mixture turned blue in color (~ 6 h). The reaction was deemed complete as determined by TLC analysis (100% DCM). The solution was concentrated under reduced pressure to give a green, glassy ozonide mixture [CAUTION: potentially explosive intermediate!]⁴ that was then diluted with AcOH (1.5 L) and cooled to $0\text{ }^{\circ}\text{C}$. The reaction mixture was quenched with Zn dust (335 g, 2.0 equiv) portionwise over 30 min (CAUTION: exothermic!) while maintaining the internal temperature $<50\text{ }^{\circ}\text{C}$. The reaction mixture was agitated at $\sim 23\text{ }^{\circ}\text{C}$ overnight and the quench deemed complete when starting material was consumed by TLC analysis: (*R*)-6: Rf. 0.8; (*R*)-7: Rf. 0.5; eluent = 100% DCM). The mixture was filtered to remove excess zinc and then neutralized to pH ~ 7 with 50% aqueous NaOH (0.5 L) and saturated aqueous NaHCO_3 (2 L). The aqueous mixture was extracted with Et_2O (3 x 3 L) and the combined organic layer washed with brine (3 L), dried over MgSO_4 and then concentrated under reduced pressure to brown oil. The product was collected by distillation between $72\text{--}75\text{ }^{\circ}\text{C}$ (1 mm Hg) to give β -keto ester (*R*)-7 (0.34 kg, 74 A% purity by GC) in 78% yield as a colorless oil.

⁴ For a relevant reference to the risk assessment and safety evaluation of an ozonolysis reaction of β -pinene, see: Hida, T.; Kikuchi, J.; Kakinuma, M.; Nogusa, H. *Org. Process Res. Dev.* **2010**, *14*, 1485–1489.

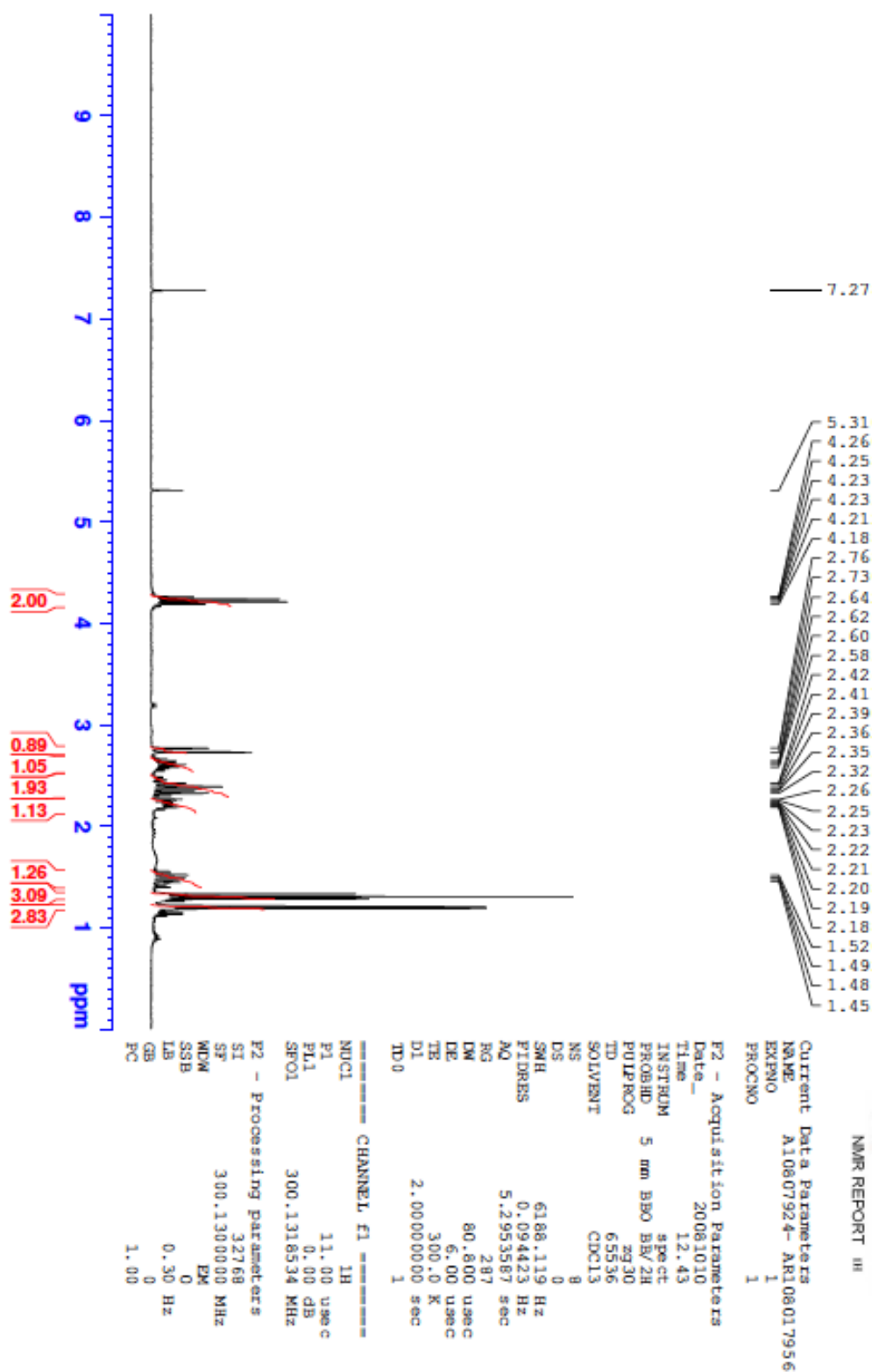
Figure 1.3. GC chromatogram of crude β -keto ester (*R*)-7 (Procedure A).

Column- DB-1: 60m X 0.530mm, 3 μ m
 Flow- 8.0 ml/min, Carrier gas- Nitrogen, Inlet temp- 200° C, Detector temp - 250° C
 Oven temp- 60° C (Hold-2min), temperature ramp -12° C/min, 250° C (hold -10 min)
 Run time-26.17 minutes, Injection mode- Split (0.9:1); Split flow- 7.4ml/min

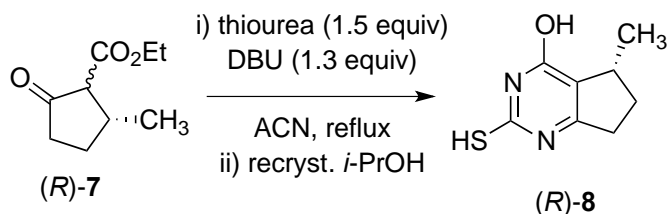


Peak #	RT [min]	Area	Area %
1	2.077	325.399	0.020
2	2.430	121.805	0.008
3	2.746	27860.453	1.736
4	2.991	12299.748	0.767
5	3.259	242.820	0.015
6	3.418	11911.139	0.742
7	3.670	75.155	0.005
8	4.032	5314.136	0.331
9	4.175	84.912	0.005
10	4.354	1065.576	0.066
11	4.477	1963.733	0.122
12	5.016	240.096	0.015
13	5.197	230.706	0.014
14	5.824	356.443	0.022
15	6.601	15249.709	0.950
16	7.022	2005.953	0.125
17	7.207	1033.166	0.064
18	7.463	3296.894	0.205
19	7.566	2353.341	0.147
20	7.758	449.308	0.028
21	8.133	25990.990	1.620
22	8.326	9476.679	0.603
23	8.507	437.687	0.027
24	8.621	407.829	0.025
25	9.588	2217.549	0.138
26	9.816	1953.391	0.122
27	9.909	2108.381	0.131
28	10.955	5032.560	0.314
29	11.397	646.644	0.040
30	11.603	1259.823	0.079
31	11.940	801.494	0.050
32	12.126	35028.680	2.183
33	12.734	1502.361	0.094
34	13.256	7008.643	0.437
35	13.530	2587.109	0.161
36	13.828	1370070.250	85.381
37	14.187	4566.148	0.285
38	14.385	931.243	0.058
39	14.626	2134.562	0.133
40	14.935	7819.737	0.487
41	15.078	1676.614	0.104
42	15.149	3348.535	0.209
43	15.204	1869.235	0.116
44	15.314	326.800	0.020
45	15.444	1590.160	0.099
46	15.649	21054.316	1.312
47	15.795	1399.242	0.087
48	15.905	674.353	0.042
49	16.250	487.992	0.030
50	16.338	788.066	0.049
51	16.431	1852.148	0.115
52	16.459	922.912	0.058

Figure 1.4. ¹H NMR (CDCl₃) spectrum of crude β-keto ester (*R*)-7 (Procedure A).



3.3. Thiourea reaction for preparation of thiopyrimidine (*R*)-8.



(*R*)-2-Mercapto-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-ol, 8. Thiourea (0.24 kg, 1.5 equiv) was charged to a solution of β -keto ester (*R*)-7 (0.35 kg, 1 equiv) in acetonitrile (4.2 L) and to suspension was then added DBU (0.40 L, 1.3 equiv) dropwise ((Exothermic) over ~2 h at ≤ 25 °C The reaction mixture was heated to reflux for 20 h and was deemed complete by TLC analysis (100% DCM) with consumption of starting material. The acetonitrile was removed under reduced pressure to obtain a gummy liquid. The residue was cooled to ≤ -5 °C and then charged with 12N HCl (0.8 L) to obtain pH 1. The suspension was then added to ice (0.41 kg) and the mixture agitated at ~ 20 °C for 1 h. The solids were collected by filtration and the wet cake was washed with H₂O (1.25 L) followed by heptane (1.25 L). The wet-cake was then purified by crystallization from *i*-PrOH (1 L) by heating to 85 °C and then slowly cooling to -5 °C over ~3 h. The solids were collected by filtration, dried under reduced pressure (50 °C, 12 h) to afford thiopyrimidine (*R*)-8 (0.19 kg) in 50% yield as a beige solid. Using this procedure, a total of 5.03 kg β -keto ester (*R*)-7 was converted into ~ 1.8 kg of thiopyrimidine (*R*)-8 with 99 A% purity by HPLC. The ¹H NMR (MeOD) spectrum conformed to the product (Figure 1.5).

Figure 1.5. ¹H NMR (MeOD) spectrum of thiopyrimidine (*R*)-**8**.

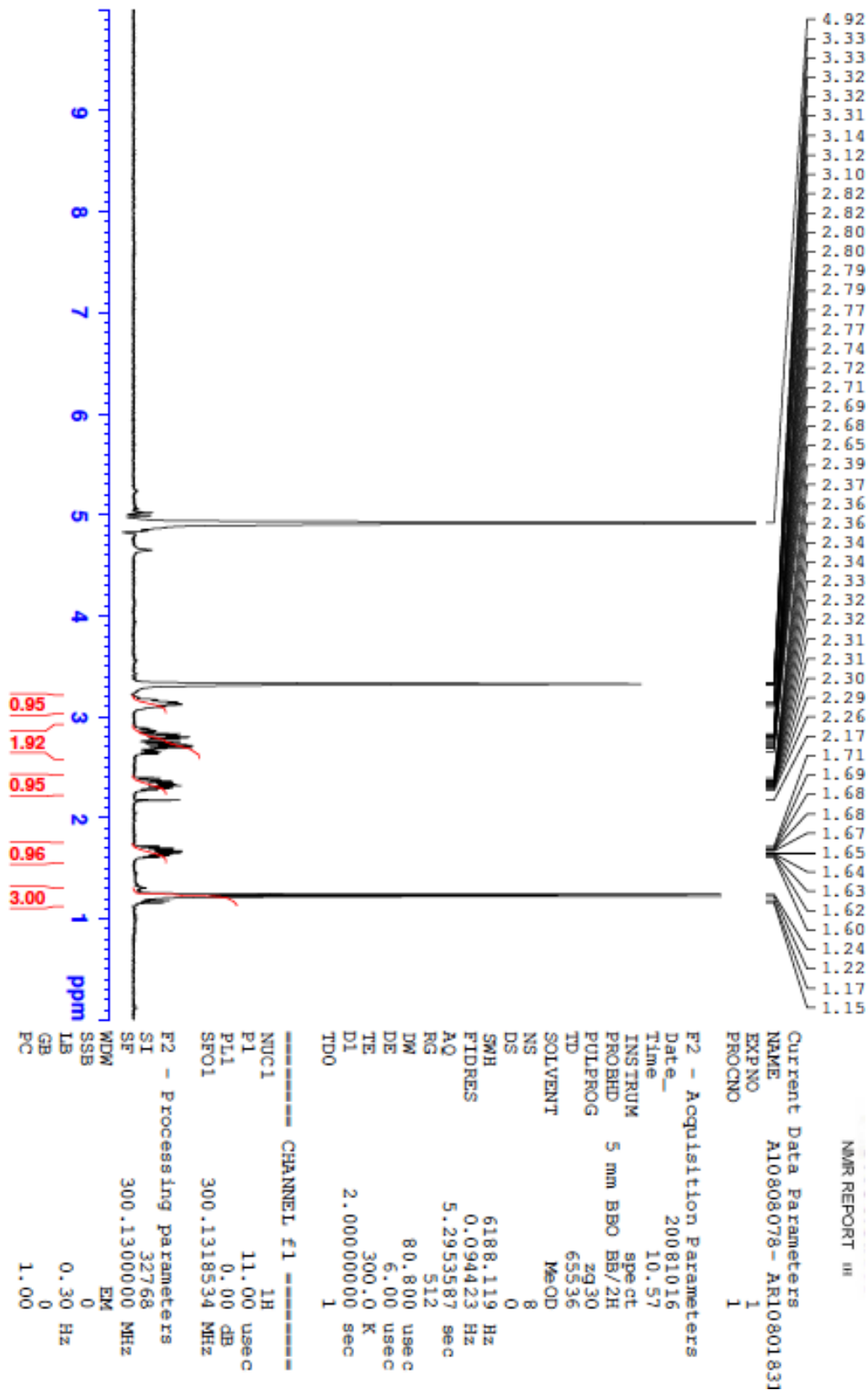
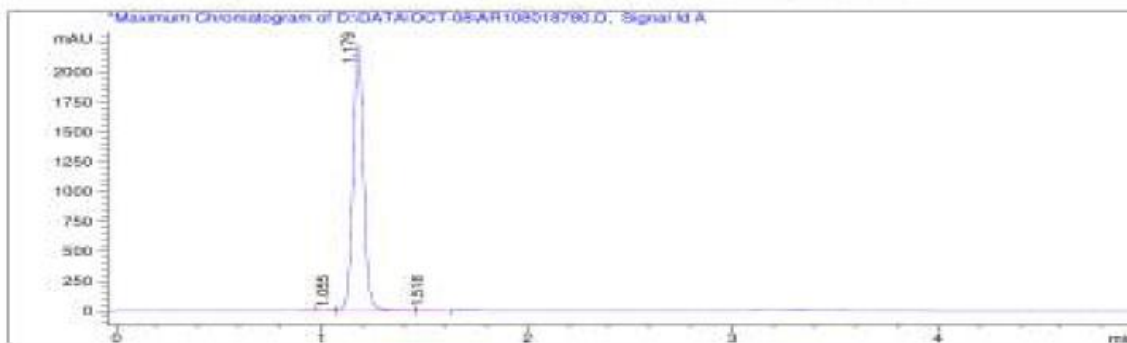
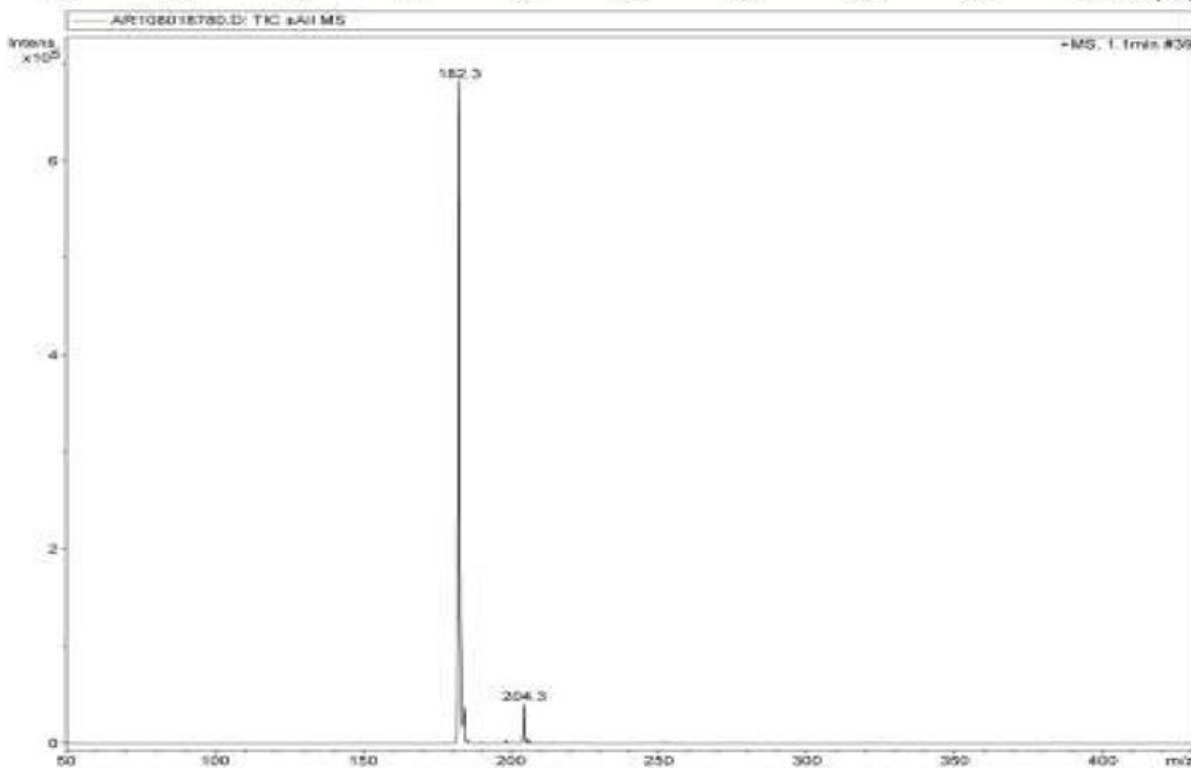


Figure 1.6. LCMS of thiopyrimidine (*R*)-**8**.

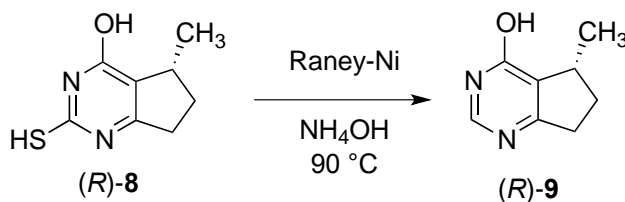
Method info :Atlantis Expressa C18, 75 X4.6mm, 5µm, 0.8ml/min
 MP A- 0.1%COOH, MP B- ACN
 Time(in min) 0 0--1 1--1.5 1.5--2.5 2.5--3 3--5
 KB 70 70 70--95 95--95 95--70 70



#	Meas. Ret.	Area	Area %
1	1.055	16.350	0.205
2	1.179	7,857.63	99.627
3	1.518	13.479	0.168



3.4. Raney-Ni reaction for preparation of pyrimidine (*R*)-9.⁵



(*R*)-5-Methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-ol, 9. To an autoclave containing a solution of thiopyrimidine (*R*)-8 (190 g, 1 equiv) in MeOH (2.85 L) was charged Raney® nickel (0.4 kg, ~2 wt equiv) and NH₄OH (0.58 L) at room temperature. The reaction mixture was slowly heated to 90 °C and after ~6 h, the reaction was deemed complete by TLC analysis (1:1 EtOAc/hexanes) with complete consumption of starting material. The reaction mixture was cooled to ≤30 °C and filtered under nitrogen to remove excess Raney® nickel. The filtrate was concentrated to dryness and the wet-cake was dried under reduced pressure (40 °C for 20 h) to afford hydroxypyrimidine (*R*)-9 (0.13 kg, 83%) as a blue-green solid.⁶ Using this procedure, a total of 1.14 kg thiopyrimidine (*R*)-8 was converted into ~0.98 kg of hydroxypyrimidine (*R*)-9 with ~99 A% purity by HPLC. The ¹H NMR (MeOD) spectrum conformed to the product (Figure 1.7).

Procedure B. An autoclave was charged with thiopyrimidine (*R*)-8 (0.655 kg, 1 equiv), water (10 L), Raney® nickel (1.3 kg) and NH₄OH (2 L) and the mixture was heated to reflux for 3 h (deemed complete by TLC analysis: 1:1 EtOAc/heptane). The reaction mixture was cooled to ≤50 °C and filtered under nitrogen to remove excess Raney® nickel. The filtrate was concentrated to dryness and the wet-cake was dried in a vacuum oven overnight at 35 °C to afford hydroxypyrimidine (*R*)-9 (0.50 kg, 99.9 A% purity by HPLC) in 93% yield as a blue-green solid.

⁵ Synthesis of compound (*R*)-9 was first reported by Array: Mitchell, I. S.; Blake, J. F.; Xu, R.; Kallan, N. C.; Xiao, D.; Spencer, K. L.; Bencsik, J. R.; Liang, J.; Safina, B.; Li, J.; Chabot, C. PCT Int. Appl., (2008) WO2008006032 A1.

⁶ For a related procedure for desulfurization of thiopyrimidine, see: *Organic Syntheses*, Coll. Vol. 4, p.638 (1963); Vol. 35, p.80 (1955).

Figure 1.7. ^1H NMR (MeOD) spectrum of hydroxypyrimidine (*R*)-9.

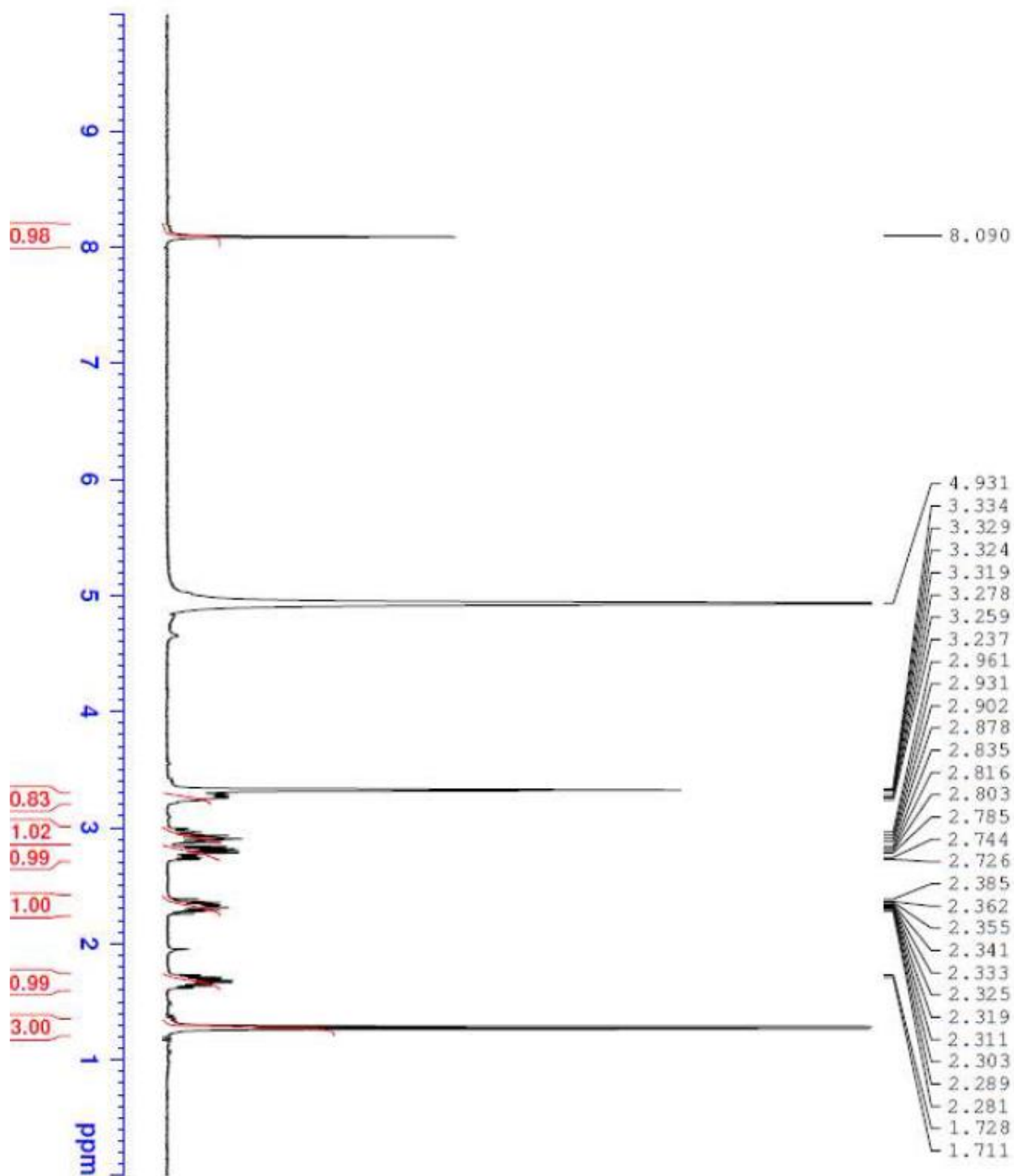


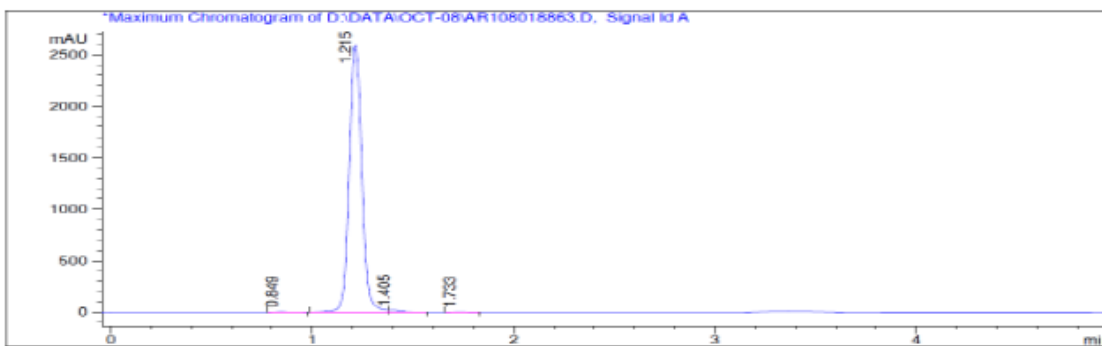
Figure 1.8. LCMS of hydroxypyrimidine (*R*)-9.

Method info :Atlantis Express C10, 75 X4.6mm, 5µm, 0.8ml/min

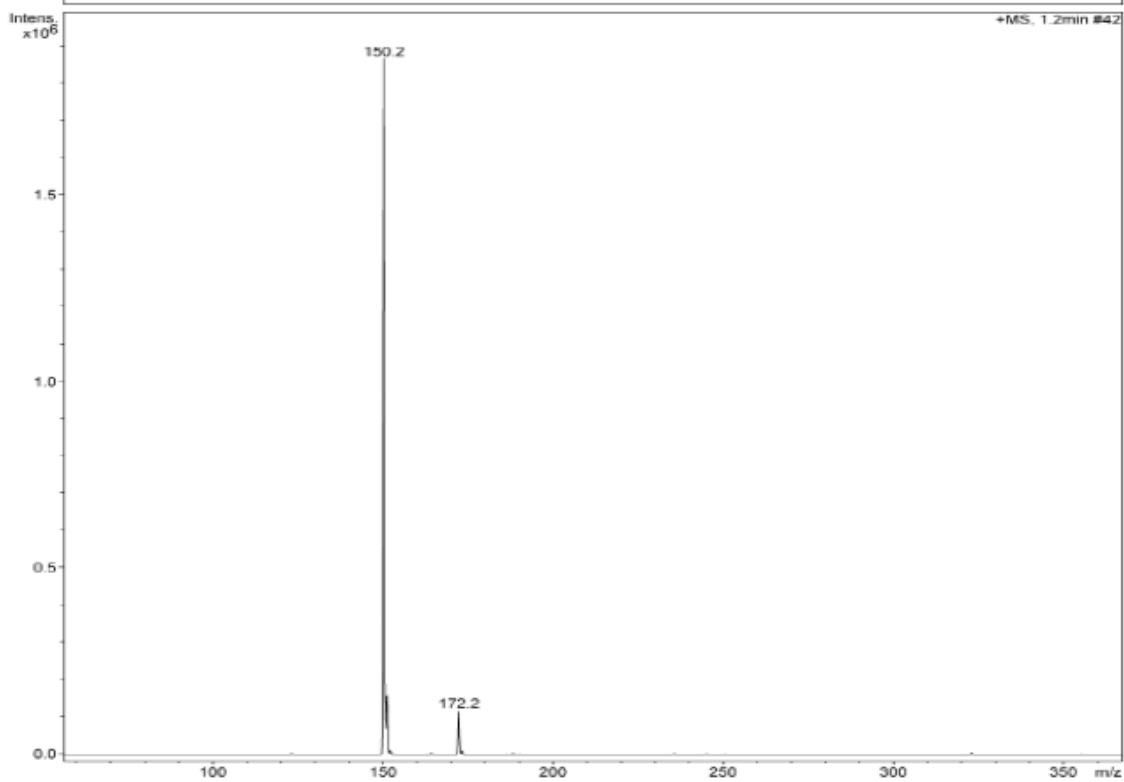
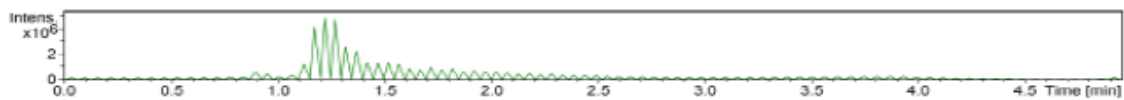
MP A- 0.1%HCOOH, MP B- ACN

Time (in min) 0 0--1 1--1.5 1.5--2.5 2.5--3 3--5

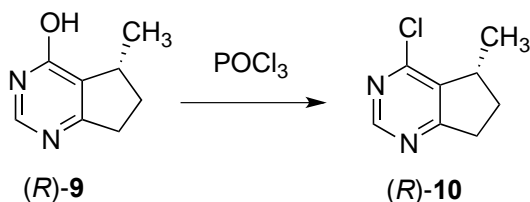
%B 70 70 70--95 95--95 95--70 70



#	Meas. Ret	Area	Area %
1	0.849	32.382	0.286
2	1.215	1,120,941	98.875
3	1.405	76.542	0.676
4	1.733	18.438	0.163



3.5. Chlorination reaction for preparation of chloropyrimidine (*R*)-10.



(*R*)-4-Chloro-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine, 10.

Procedure A: To a 12-L flask containing POCl₃ (2 L, 22 mol, 5 equiv) was charged hydroxypyrimidine (*R*)-9 (0.66 kg, 1 equiv) portionwise with agitation while maintaining the internal temperature <50 °C. The reaction mixture was heated to 100 °C and after ~3 h, the reaction was deemed complete by TLC analysis ((*R*)-9: Rf. 0.1; (*R*)-10: Rf. 0.8; eluent = EtOAc/heptane (1:1)). The excess POCl₃ was removed under high vacuum and the reaction mixture was then poured onto ice (10 kg) and neutralized to pH ~7 with 50% aqueous NaOH (~1.5 L). The aqueous mixture was extracted with CH₂Cl₂ (3 x 5 L), and the combined organic layers washed with brine (10 L), dried over MgSO₄ and then filtered. The solution was concentrated under reduced pressure, passed through a plug of silica gel eluting with CH₂Cl₂ and then concentrated to give chloropyrimidine (*R*)-10 (0.51 kg, 99.9 A% purity by HPLC) in 91% yield as a brown liquid.

Procedure B: To a solution of hydroxypyrimidine (*R*)-9 (0.45 kg, 1 equiv) and CH₂Cl₂ (4.5 L), was charged POCl₃ (0.54 L, 2 equiv) (Caution: Exothermic!) and slowly heated to reflux and then maintained for ~4 h. The reaction was deemed complete by TLC analysis and the mixture was then concentrated via distillation to ~1 vol and poured onto ice (7 kg) followed by neutralization to pH ~7 with 50% NaOH solution (~1.1 L). The aqueous mixture was extracted with CH₂Cl₂ (3 x 3 L) and the combined organic layers washed with brine (7 L) and then concentrated under reduced pressure to afford a residue that was further purified over a plug of silica gel eluting with a gradient mixture of EtOAc/hexanes. The filtrates were concentrated to give chloropyrimidine (*R*)-10 (0.36 kg, >98 A% purity by HPLC) in 71% yield as a brown liquid.

Figure 1.9. ¹H NMR (CDCl₃) spectrum of chloropyrimidine (*R*)-**10** (Procedure B).

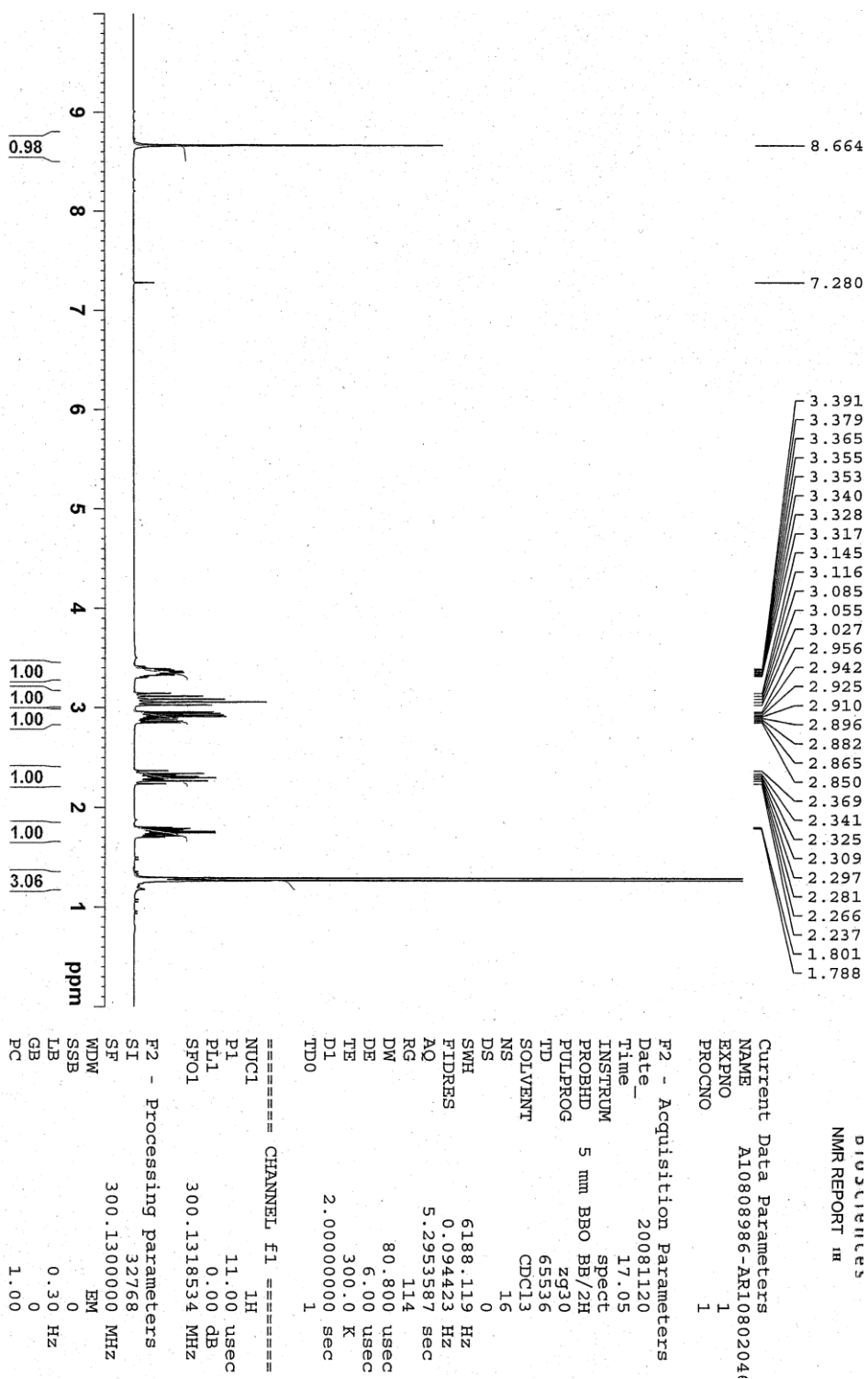


Figure 1.10. ¹³C NMR (CDCl₃) spectrum of chloropyrimidine (*R*)-**10** (Procedure B).

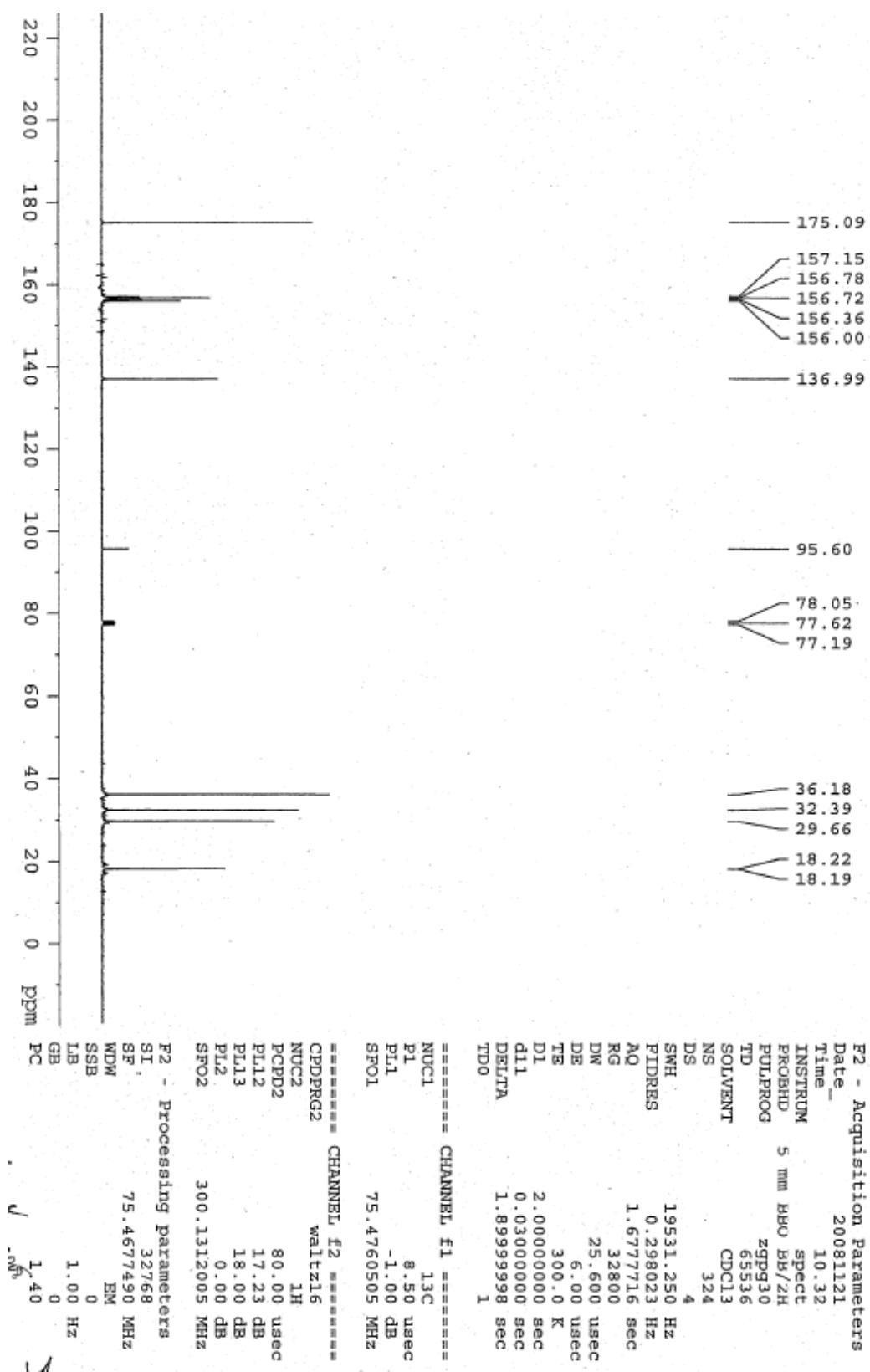
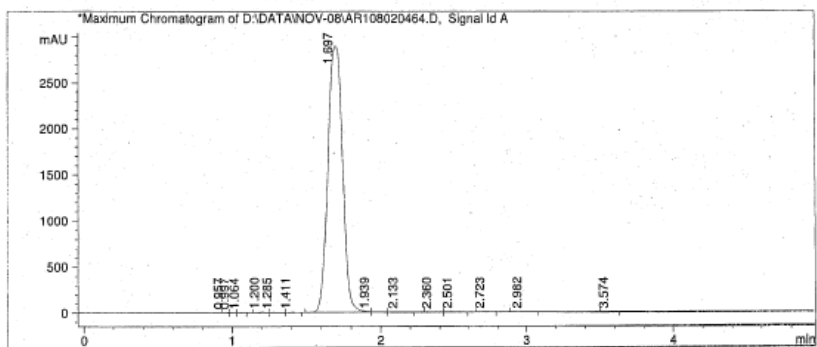


Figure 1.11. LCMS chromatogram of chloropyrimidine (*R*)-**10** (Procedure B).

Method info :Atlantis Express C18, 75 X4.6mm, 5µm, 0.8ml/min
 MP A- 0.1%*HCOOH*, MP B- *ACN*
 Time(in min) 0 0--1 1--1.5 1.5--2.5 2.5--3 3--5
 %B 70 70 70--95 95--95 95--70 70



#	Meas. Ret	Area	Area %
1	0.957	5.873	0.030
2	0.997	9.274	0.047
3	1.064	9.647	0.049
4	1.200	22.239	0.112
5	1.285	13.922	0.070
6	1.411	5.581	0.028
7	1.697	1.970e4	99.343
8	1.939	10.117	0.051
9	2.133	11.041	0.056
10	2.360	2.431	0.012
11	2.501	6.794	0.034
12	2.723	9.726	0.049
13	2.982	17.568	0.089
14	3.574	6.001	0.030

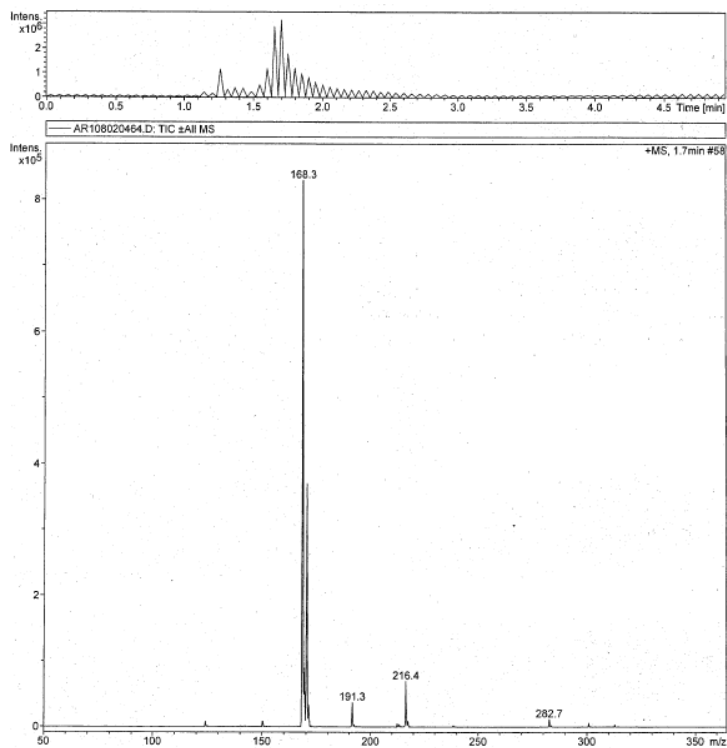
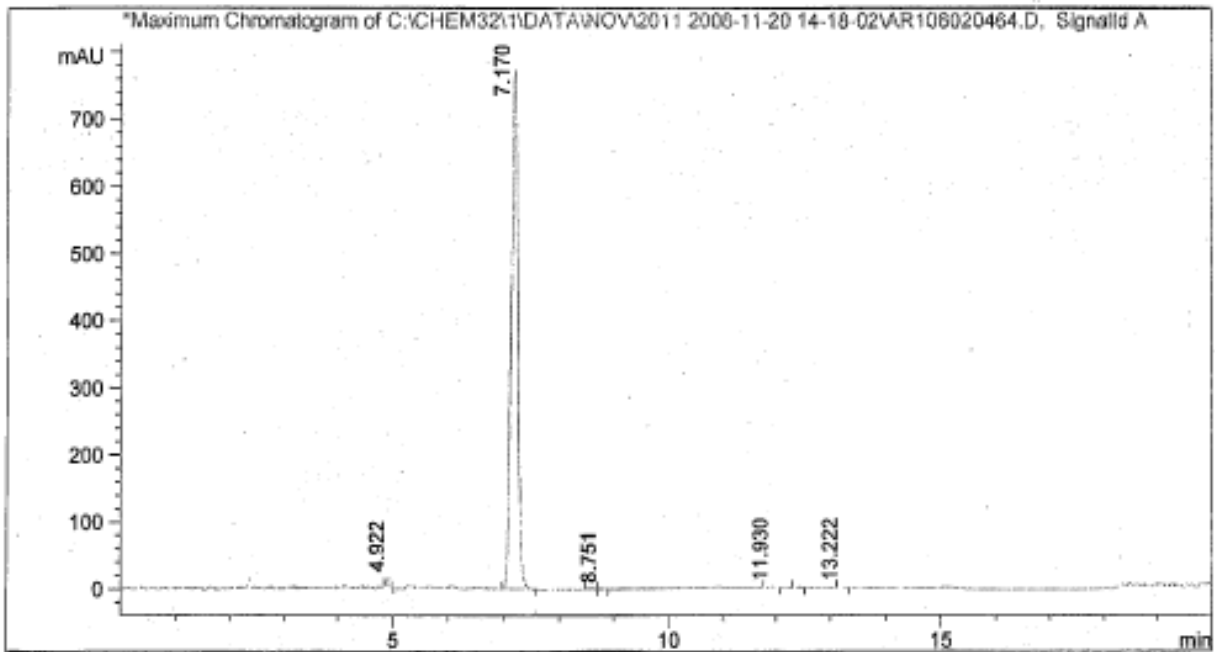


Figure 1.12. HPLC chromatogram of chloropyrimidine (*R*)-**10** (Procedure B).

Column-ZORBAX C18 150mm X 4.6mm, 5 μ m, Flow; 0.8ml/min,
wavelength:Max Chrmo,

A : 20mM NH₄OAC B: ACN

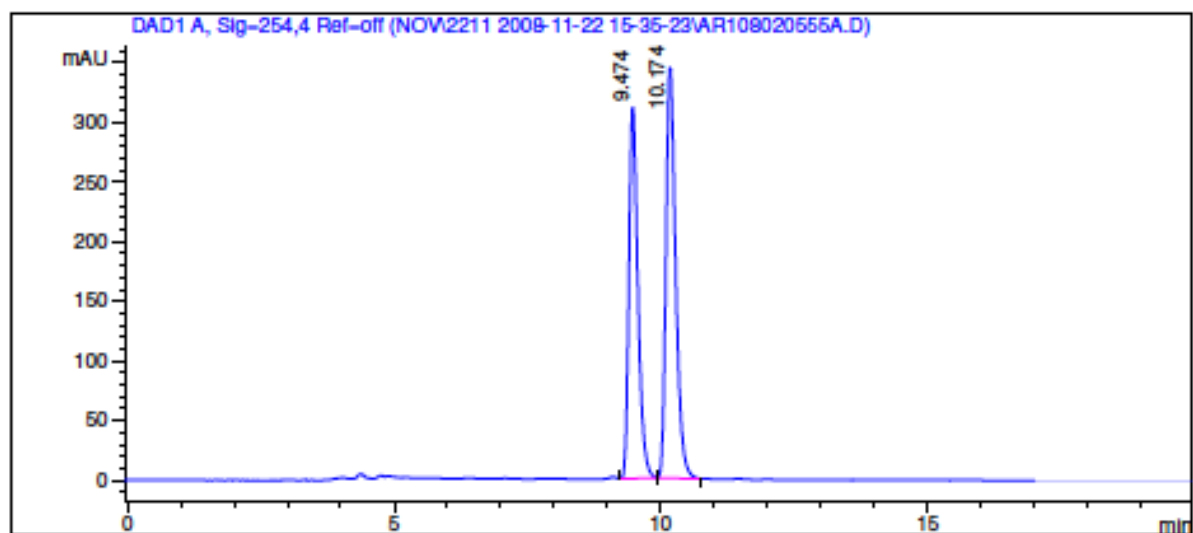
Time (min)	0	4	8	12	15	20
%B	40	40	90	90	40	40



Peak #	RT [min]	Area	Area %
1	4.922	59.565	0.915
2	7.170	6420.121	98.655
3	8.582	7.643	0.117
4	8.751	1.507	0.023
5	11.930	6.407	0.098
6	12.403	7.486	0.115
7	13.222	4.940	0.076

Figure 1.13. Chiral HPLC chromatogram of chloropyrimidine *rac*-10.

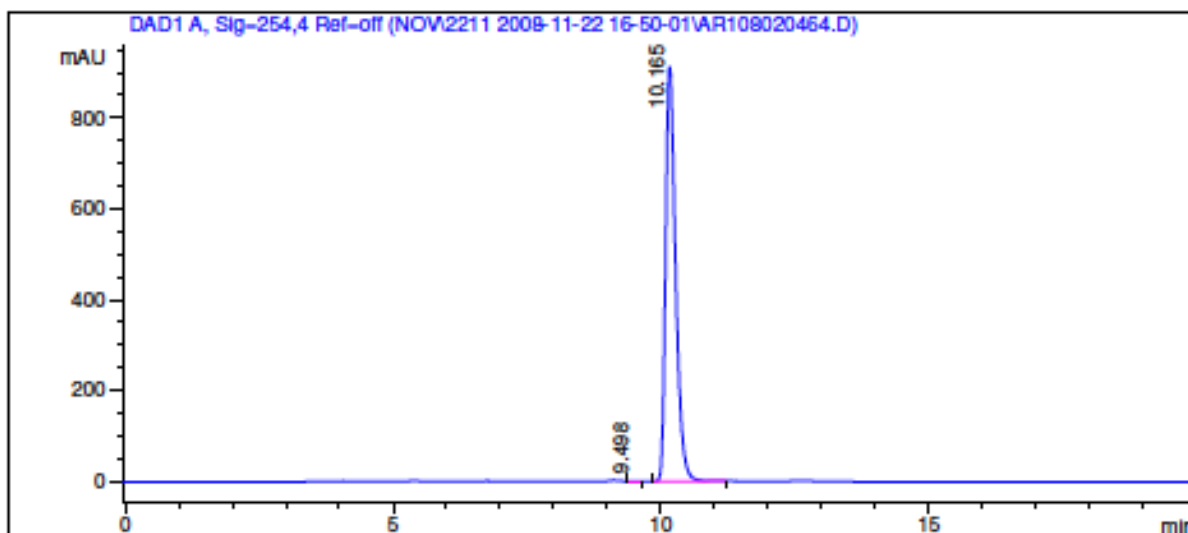
Column-Chiralcel AD-H 4.6 x 250 mm , 5 μ m, Flow-0.8ml/min, Wavelength-254nm
A-n-Hexane ; B- (Methanol:IPA ::75:25), A:B :: 95:5 , Column Temp-40°C



Peak #	RT [min]	Area	Area %
1	9.474	3649.229	45.729
2	10.174	4330.832	54.271

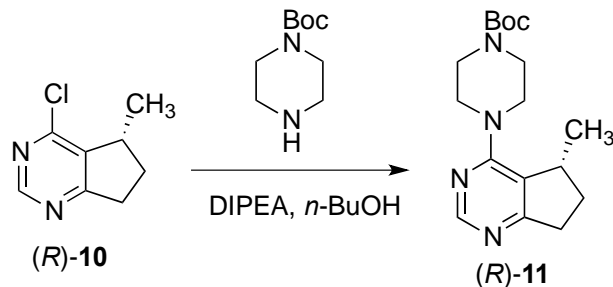
Figure 1.14. Chiral HPLC chromatogram of chloropyrimidine (*R*)-**10** (Procedure B).

Column-Chiralcel AD-H 4.6 x 250 mm , 5µm, Flow-0.8ml/min, Wavelength-254nm
A-n-Hexane ; B- (Methanol:IPA ::75:25), A:B :: 95:5 , Column Temp-40°C



Peak #	RT [min]	Area	Area %
1	9.498	1.737	0.015
2	10.165	11831.053	99.985

3.6. S_NAr reaction with *N*-Boc-piperazine for preparation of (*R*)-**11**.

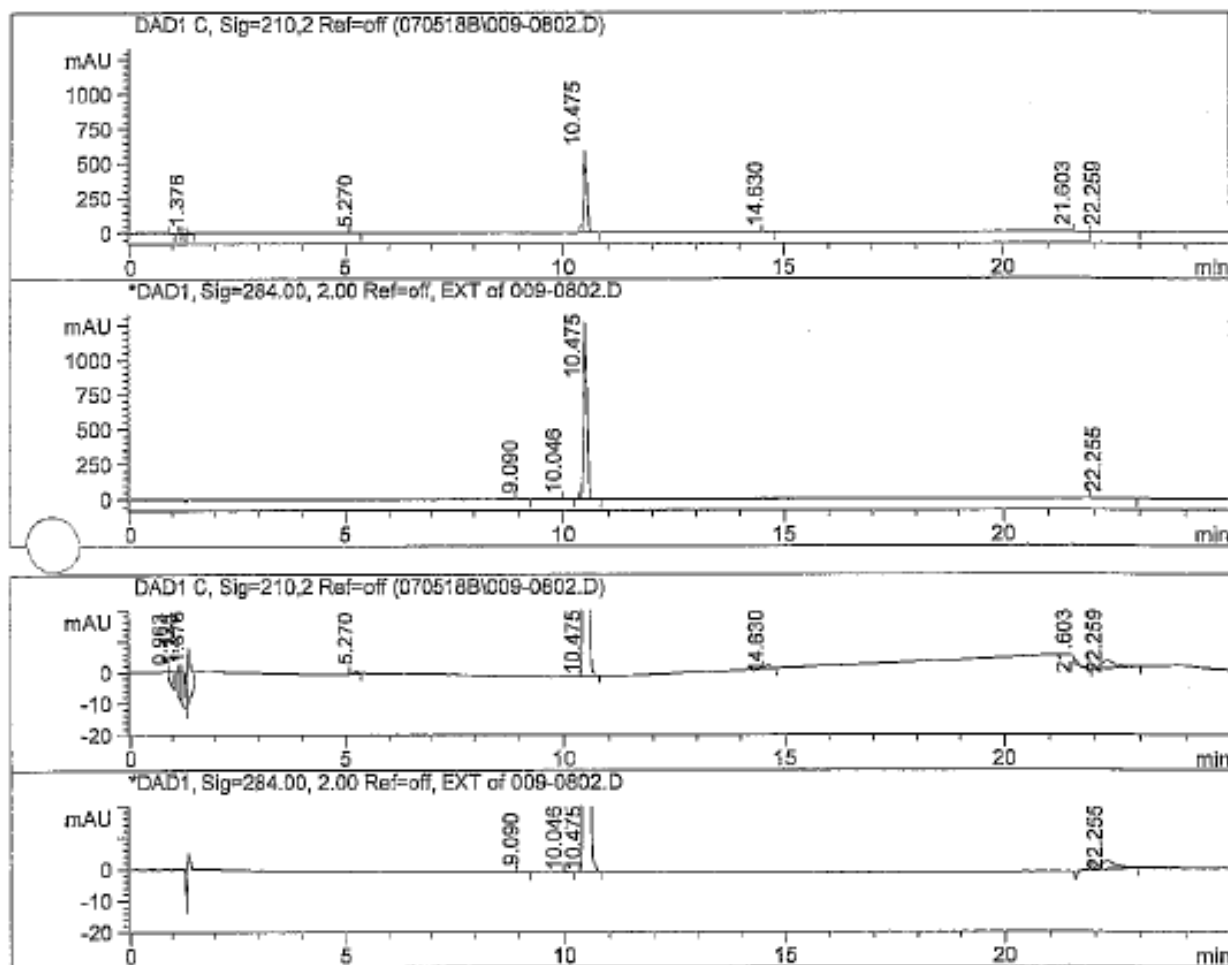


(*R*)-*Tert*-butyl 4-(5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazine-1-carboxylate, **11.**

To a reactor was charged chloropyrimidine (*R*)-**10** (0.46 kg, 2.74 mol, 1 equiv), *N*-Boc piperazine (0.535 kg, 2.87 mol, 1.05 equiv), diisopropylethylamine (1.50 L, 8.39 mol, 3 equiv) and *n*-butanol (4.2 L) at 23 °C. The agitated mixture was heated to reflux for 20 h and deemed complete by consumption of starting material [TLC analysis: (*R*)-**10** R_f = 0.8; (*R*)-**11** R_f = 0.2; eluent = EtOAc/heptane (1:1)]. The reaction mixture was concentrated under reduced pressure and the residue diluted with H₂O (10 L) and CH₂Cl₂ (10 L). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 5 L). The combined organic layers were washed with water (5 L), brine (5 L), dried over MgSO₄, filtered and then concentrated under reduced pressure. The residue was loaded on a plug of silica gel and eluted with EtOAc to afford crude (*R*)-**11** that was then crystallized from heptane (~3 mL/g) while cooling to ~ -20 °C. After warming to room temperature, the solids were filtered to give *N*-Boc pyrimidine (*R*)-**11** (0.69 kg, 99.9 A% purity by HPLC) in 79% yield as an off-white solid. A second batch of *N*-Boc pyrimidine (*R*)-**11** (0.31 kg, 99.9 A% purity by HPLC at 284 nm) was obtained resulting in a total of 1.01 kg of *N*-Boc pyrimidine (*R*)-**11**.

Figure 1.15. HPLC chromatogram of *N*-Boc pyrimidine (*R*)-11.

ACE C18, 4.6 *150 mm



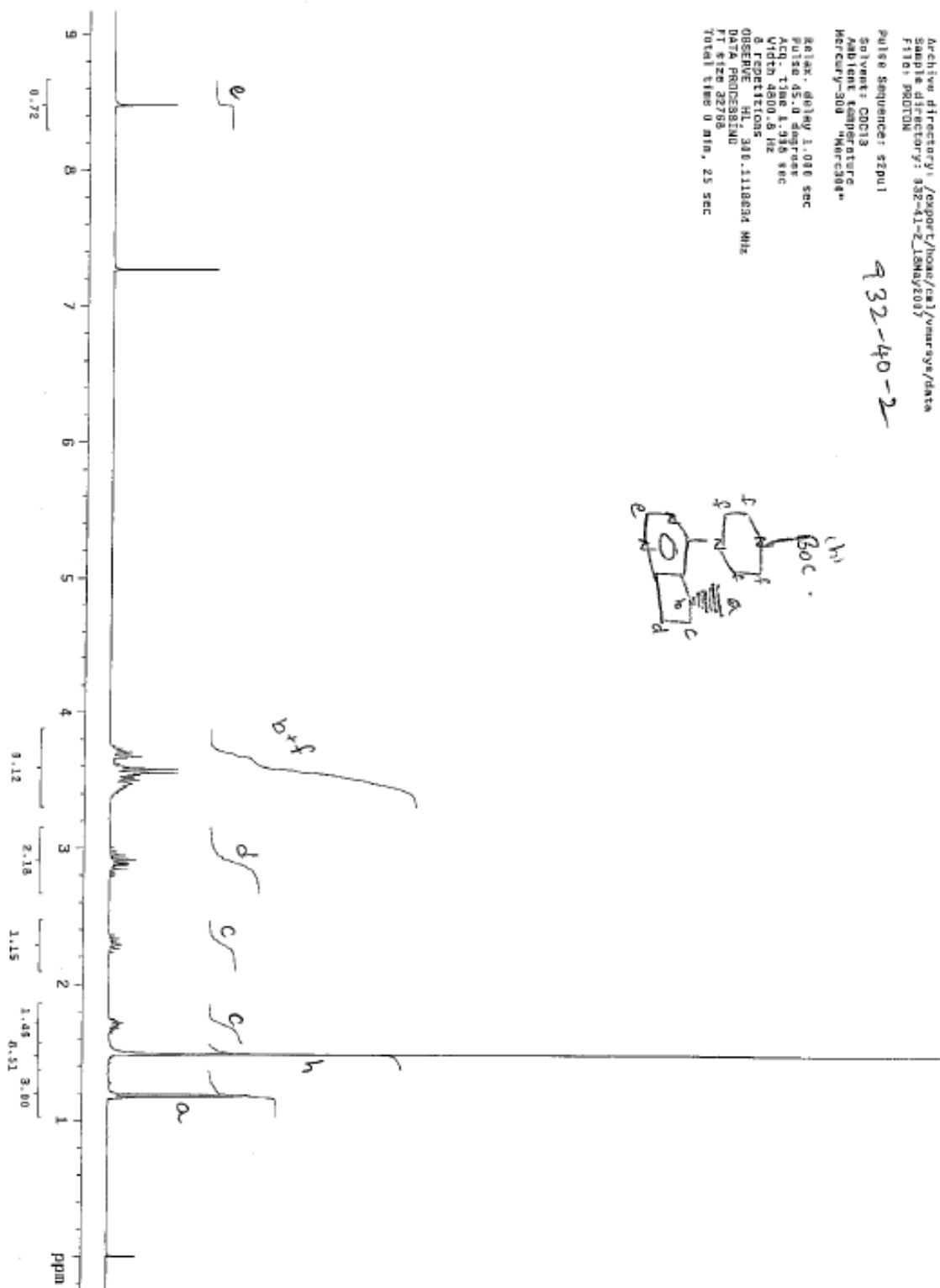
Instrument 1
Data File : C:\HPCHEM\1\DATA\070518B\009-0802.D

Signal 2: DAD1, Sig=284.00, 2.00 Ref=off, EXT

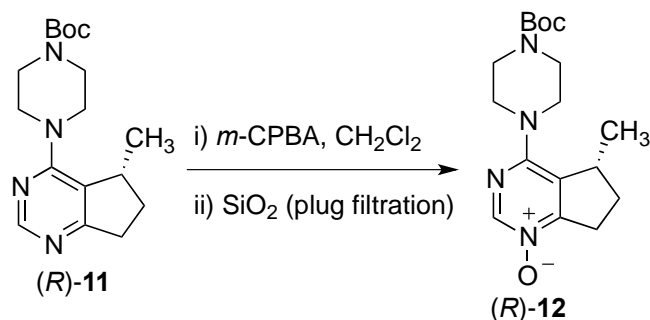
#	Type	RT [min]	Height	Area	Area %	Name
1	MM	9.09	0.3	1.52	0.023	
2	MM	10.05	0.5	2.42	0.036	
3	BB	10.48	1271.5	6563.43	98.944	
4	BB	22.26	2.7	66.13	0.997	

99.9%
from Stzolo7

Figure 1.16. ^1H NMR (CDCl_3) of *N*-Boc pyrimidine (*R*)-11.



3.7. *m*-CPBA reaction to prepare pyrimidine *N*-oxide (*R*)-12.



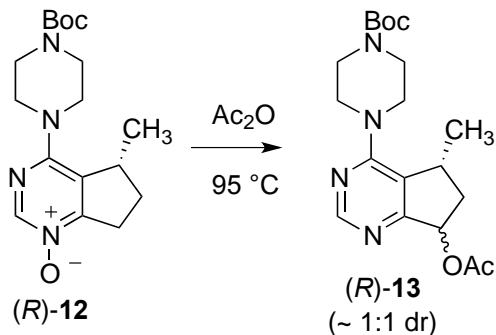
(*R*)-4-(4-(*Tert*-butoxycarbonyl)piperazin-1-yl)-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]-pyrimidine 1-oxide, 12.

To a 22-L 3-neck round bottom flask containing *N*-Boc pyrimidine (*R*)-11 (0.48 kg, 1.49 mol, 1.0 equiv) and CH₂Cl₂ (8 L) was charged *m*-CPBA (0.77 kg, 4.46 mol, 77% by wt) portionwise over 45 min (exothermed to ~32 °C). The agitated reaction mixture was maintained at room temperature for 16 h and analysis by TLC: R_f (*R*)-12 = 0.1, R_f (*R*)-11 = 0.4; eluent = EtOAc/MeOH (9:1) indicated starting material remained. Another portion of *m*-CPBA (0.26 kg, 1.51 mol, 77% by wt) was added and after 3 h, TLC analysis indicated complete consumption of starting material. The reaction mixture was cooled to ~ -10 °C using ice/MeOH bath and then filtered through a glass fiber filter to remove the solid benzoic acid. The filtrate was concentrated under reduced pressure, passed through a plug of silica gel (D x H, 8 x 14 in.) and eluted with 20-30% MeOH/EtOAc. The filtrate containing product was concentrated to give pyrimidine *N*-oxide (*R*)-12 (0.37 kg) in 74% yield as a brown residue. A total of 0.82 kg of pyrimidine *N*-oxide (*R*)-12 was produced and carried directly into the next step.

Safety Note: At this stage of development a safety risk assessment for the *m*-CPBA reaction and for the stability of *N*-oxide 12 were not performed; however, it is highly recommended to do so in light of a recent reported explosion involving an *N*-oxide intermediate.⁷

⁷ (a) Barbas, R.; Botija, M.; Camps, H.; Portell, A.; Prohens, R.; Puigjaner, C. *Org. Process Res. Dev.* **2007**, *11*, 1131–1134. (b) For additional insight into unstable compounds and unexpected reactions, refer to: *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Urben, P. G., Ed.; Elsevier; 2007; Vols. 1–2.

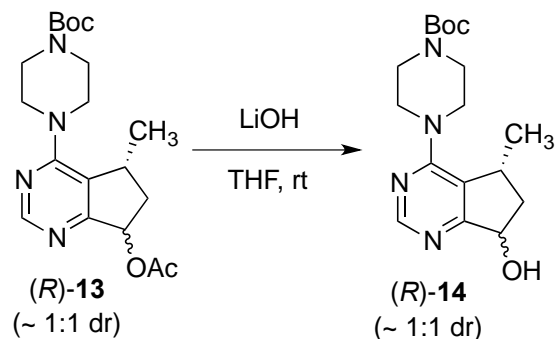
3.8. Step 8: Boekelheide-type oxidation-rearrangement to prepare acetate (*R*)-**13**.



(R)-Tert-butyl 4-(7-acetoxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-piperazine-1-carboxylate, 13.

A 12 L, 3-neck round bottom flask containing pyrimidine *N*-oxide (*R*)-**12** (0.67 kg, 2.0 mol) and acetic anhydride (5.3 L, 56 mol, 28 equiv) was heated to 95 °C with agitation. After 3 h, analysis by TLC [R_f ((*R*)-**13**) = 0.6, R_f ((*R*)-**12**) = 0.1; eluent = EtOAc/MeOH (9:1)] indicated the reaction was complete and the mixture was then concentrated to dryness under reduced pressure. The residue was dissolved in EtOAc (2 L) and the solution charged with aqueous saturated NaHCO_3 (7 L) to give pH ~7. An additional 7 L of EtOAc was added, the layers separated, and the aqueous layer extracted with EtOAc (2 x 6 L). The combined organic layers were washed with brine (8 L), dried (MgSO_4) and then filtered over a plug of silica gel eluting with EtOAc. The filtrates were concentrated to give acetate (*R*)-**13** (0.54 kg) as a 1:1 mixture of diastereomers that was used without further purification. A total of 0.963 kg of *N*-oxide (*R*)-**12** was converted into acetate (*R*)-**13** (0.80 kg).

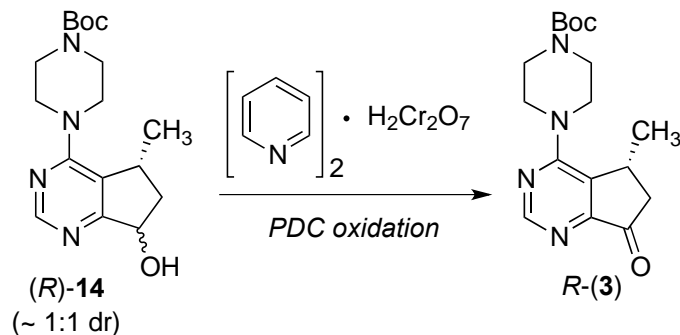
3.9. Acetate hydrolysis to prepare alcohol (*R*)-14.



(*R*)-*Tert*-butyl 4-(7-hydroxy-5-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazine-1-carboxylate, 14.

A 12 L flask containing a solution of acetate (*R*)-**13** (0.54 kg, 1.43 mol) and THF (5.5 L) was charged with H₂O (5.5 L) followed with LiOH hydrate (0.18 kg, 4.30 mol, 3 equiv) (slightly exothermic to ~35 °C). After agitation for 12 h, TLC [*R*_f (**14**) = 0.3, *R*_f (*R*)-**13** = 0.6; eluent = EtOAc/MeOH (9:1)] indicated the hydrolysis was complete and the reaction mixture was diluted with brine (10 L) followed by EtOAc (10 L). The layers were separated and the aqueous layer extracted with EtOAc (2 x 8 L) and the combined organic layers dried (MgSO₄), filtered, and concentrated under reduced pressure to ~one-third volume. The residue was passed through a plug of silica gel (D x H, 8 x 14 in.) eluting with 2-5% MeOH/EtOAc and then concentrated to give alcohol (*R*)-**14** as brown oil. The crude product was dissolved in Et₂O (0.7 L, 1.5 vol), diluted with heptane (5 L) and agitated overnight at room temperature. The solids were filtered, dried under vacuum at 30 °C for 6 h to give alcohol (*R*)-**14** as a 1:1 mixture of diastereomers and a beige solid. A total of 1.23 kg of acetate (*R*)-**15** was converted into alcohol (*R*)-**14** (0.56 kg, ~99 A% purity) in 4 batches with yields ranging from 41–54% over the three steps from *N*-Boc pyrimidine (*R*)-**11**.

3.10. PDC oxidation to prepare ketone (*R*)-3.



(*R*)-*Tert*-butyl 4-(5-methyl-7-oxo-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)piperazine-1-carboxylate, 3.

Pyridinium dichromate (PDC) (0.3 kg, 0.80 mol, 1.3 equiv) was charged in one portion [exothermed to ~40 °C] to a solution of alcohol (*R*)-14 (0.2 kg, 0.60 mol) and CH₂Cl₂ (3.2 L). The reaction mixture was agitated at room temperature and after 2 h TLC analysis [(*R*)-3 R_f = 0.5; (*R*)-14 R_f = 0.3; eluent = EtOAc/MeOH (9:1)] indicated that the reaction was not complete. Another portion of PDC (0.038 kg, 0.10 mol, 0.17 equiv) was charged and after 2 h TLC analysis indicated starting material was still present. Another portion of PDC (0.038 kg, 0.10 mol, 0.17 equiv) was charged and then the reaction mixture was agitated overnight at room temperature. The reaction mixture was poured onto a plug of silica gel (D x H, 8 x 14 in.) and eluted with EtOAc until no product remained as determined by TLC analysis. The fractions were concentrated to obtain the crude product that was then suspended in Et₂O (4 vol) and diluted with heptane (10 vol) with good agitation. The solids were collected by filtration and dried under vacuum at 30 °C for 6 h to give ketone (*R*)-3 (0.072 kg, 96.9 A% purity) in 36% yield. A total of 0.52 kg of hydroxyl (*R*)-14 was converted to ketone (*R*)-3 in three batches and gave a total of 0.21 kg having between 96.9–97.3 A% with yields between 36–43%.

Safety Note: Chromium reagents such as PCC and PDC are known to be toxic to the environment (refer to the MSDS). The fire hazards of PDC have also been reported, and we had no intention of using it beyond the scope of this initial scale-up to ketone (*R*)-3.⁸

⁸ (a) Letter to the editor: *Org. Process. Res. Dev.*, **2003**, 7, 446. (b) *Chemical & Engineering News* (21 Apr 2003) Vol. 81, No. 16, pp. 4).

Figure 1.19. 2D NMR (DMSO-d₆) of β-keto ester *rac*-**24** (Scheme 6 of manuscript).

