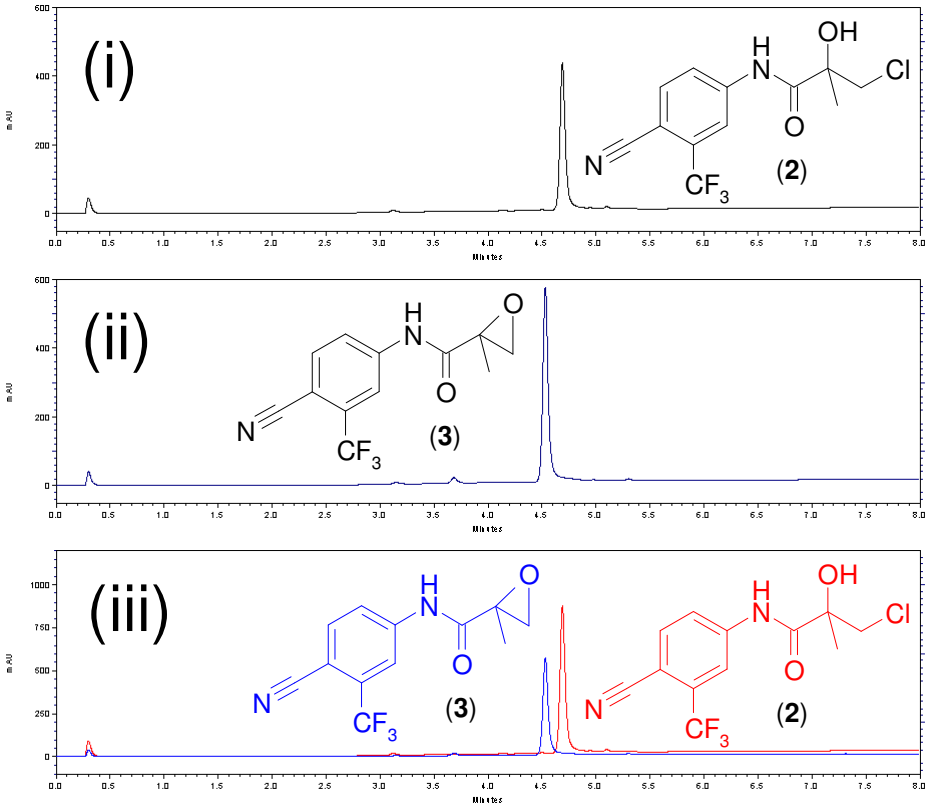
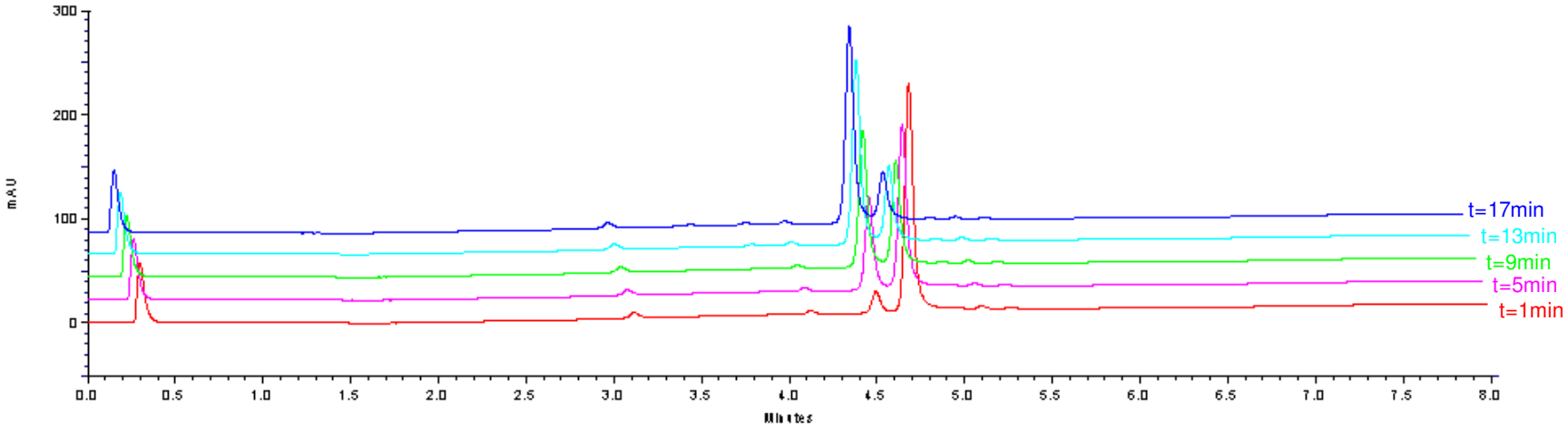
HPLC traces of authentic samples from the AstraZeneca compound collection (i) the chlorohydrin (**2**) (ii) the epoxide (**3**) overlayed traces of the chlorohydrin (**2**) and the epoxide (**3**).



Stacked HPLC traces showing the conversion of the chlorohydrin (**2**) to the epoxide (**3**) over time at pH 9 and 55 ºC.



Data table showing the dependence of rate of formation of epoxide (**3**) on reaction pH at 30 ºC.

pH	Temperature	Method	Log(k.s)	Half-life
9.0	30 ºC	Real-time	-4.56	420.4 min
9.5	30 ºC	Real-time	-4.31	235.5 min
10.0	30 ºC	Real-time	-3.45	32.6 min
10.5	30 ºC	Quenching	-3.03	12.3 min
11.0	30 ºC	Quenching	-2.54	4.0 min

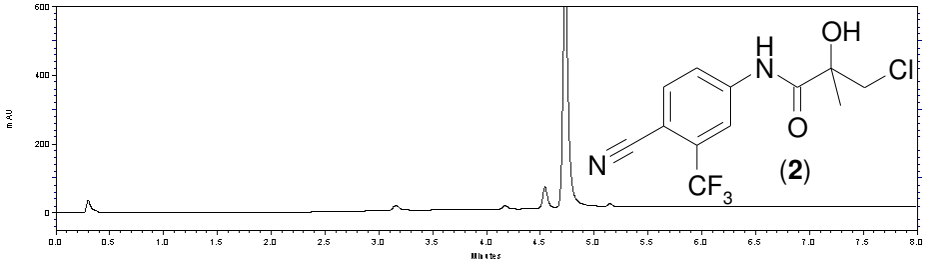
Data table showing the dependence of rate of formation of epoxide (**3**) on reaction temperature at pH 9.

pH	Temperature	Method	Log(k.s)	Half-life
9.0	35 ºC	Real-time	-4.14	160.2 min
9.0	40 ºC	Real-time	-3.77	68.6 min
9.0	45 ºC	Real-time	-3.44	32.0 min
9.0	50 ºC	Quenching	-3.13	15.5 min
9.0	55 ºC	Quenching	-2.84	7.9 min

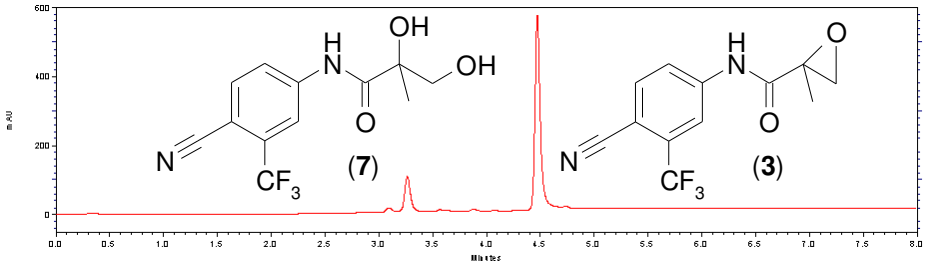
Data table showing the rate of formation of the diol (**9**) from the epoxide (**3**), starting from either the chlorohydrin (**2**) or the epoxide (**3**).

pH,T	method	t(0.5) / min	log(k/s-1)
11,30	real time diol formation from chlorohydrin start	**280.40**	**-4.39**
11,30	real time diol formation from epoxide start	**279.49**	**-4.38**

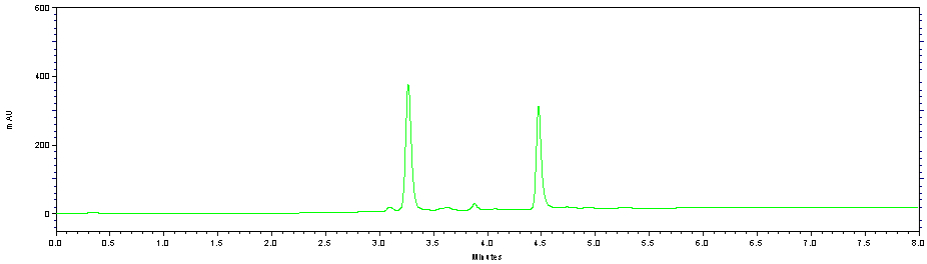
HPLC Traces showing reaction of the chlorohydrin (**2**) at pH 11 and 30 ºC to form the epoxide (**3**) and subsequently the diol (**7**) along with a reference spectrum of the starting material.



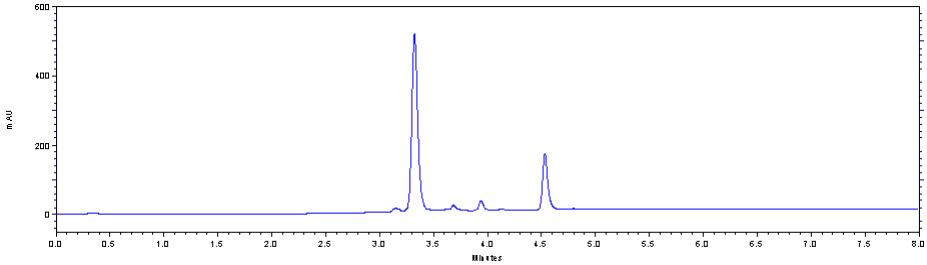
Reference chromatogram of chlorohydrin (**2**) at pH 8.5 showing a trace of the epoxide (**3**)



Chromatogram of chlorohydrin (**2**) at pH 11 and 30 ºC at t = 83 min showing complete conversion of chlorohydrin (II) into Product A and beginning of slow conversion of the epoxide (**3**) into the diol (**7**).



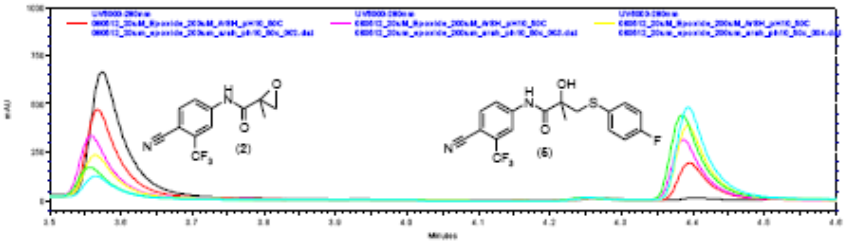
Chromatogram of chlorohydrin (**2**) at pH 11 and 30 ºC at t = 331 min showing further conversion of the epoxide (**3**) into the diol (**7**).



Chromatogram of chlorohydrin (**2**) at pH 11 and 30 ºC at t = 579 min showing further conversion of the epoxide (**3**) into the diol (**7**).

Overlaid HPLC Traces showing reaction of the epoxide (**3**) with 4-flurorbenzenethiol (**4**).

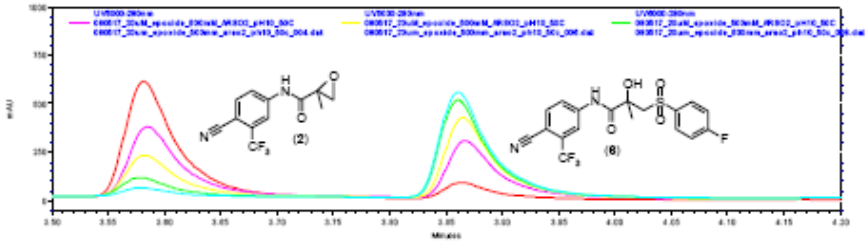
[Please disregard numbering in figure].



Traces: black (t=0), red (t=16 min), magenta (t=32 min), yellow (t=48 min), green (t=64 min), cyan (t=80 min).

Overlaid HPLC Traces showing reaction of the epoxide (**3**) with 4-flurorbenzenesulfinate (**5**).

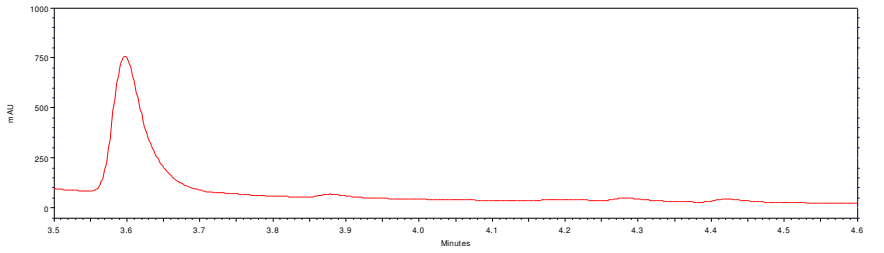
[Please disregard numbering in figure].



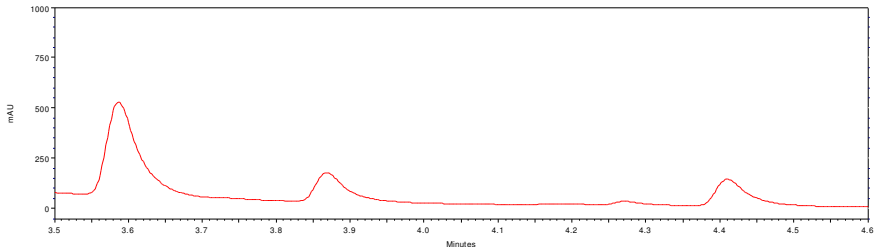
Traces: red (t=0), magenta (t=62 min), yellow (t=124 min), green (t=216 min), cyan (t=308 min).

HPLC traces of the simultaneous reaction of Epoxide (**3**) with 4-fluorobenzenethiolate (**4**) and 4-fluorobenzenesulfinate (**5**), showing both reactions occurring under exactly the same conditions.

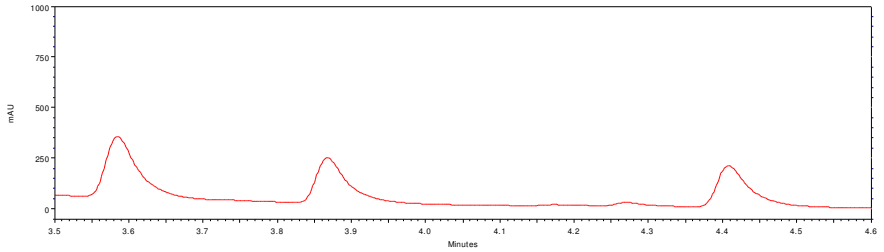
[Please disregard numbering in figure].



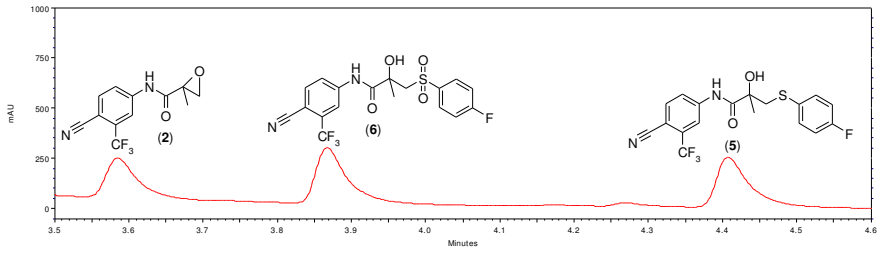
t=0



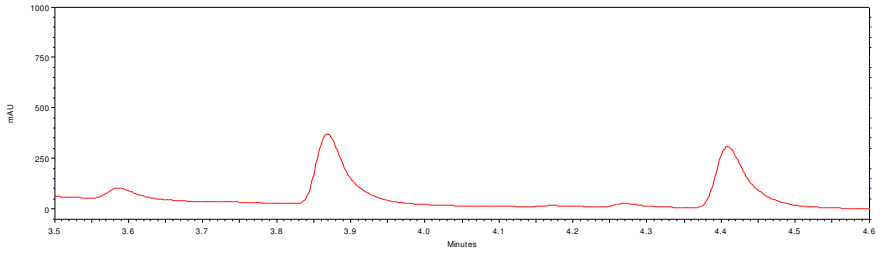
t=16 min



t=32 min



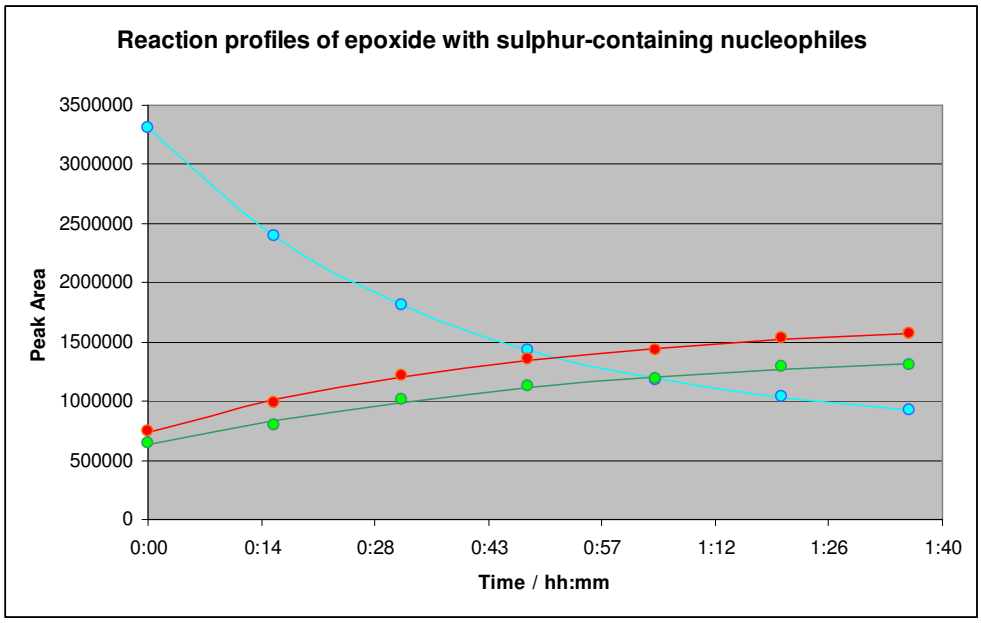
t=48 min



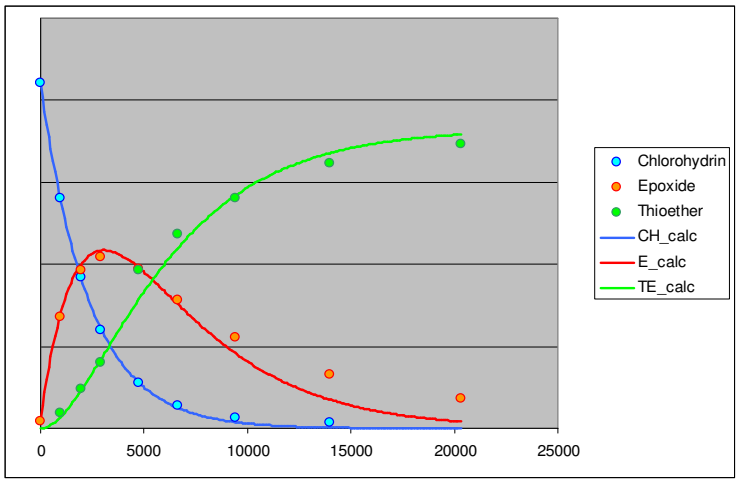
t=96 min

Graph showing integrals of the three species in the above HPLC traces of the simultaneous reaction of Epoxide (**3**) (blue line) with 4-fluorobenzenethiolate (**4**) to give thioether (**6**) (green line) and with 4-fluorobenzenesulfinate (**5**) to give Bicalutamide (**1**) (red line).

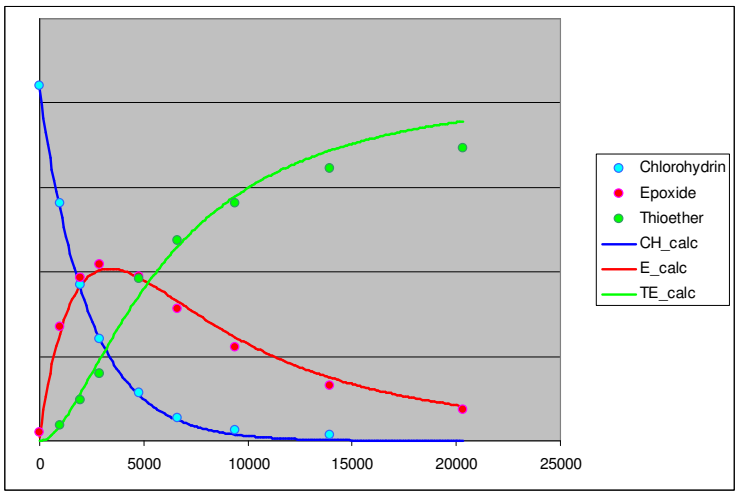
[Data-points are experimental values, lines are exponential fits].



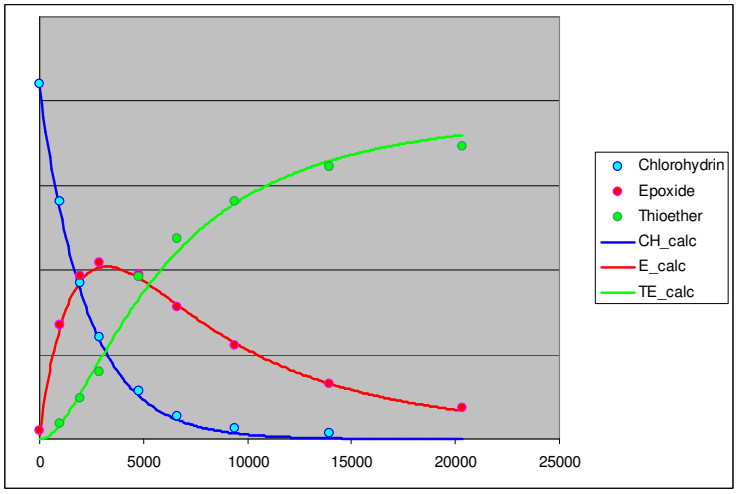
Initial attempts at fitting sequential reaction kinetics.



k_1, k_2, ε_3, ε_6, $[\mathbf{2}]_0$, $[\mathbf{3}]_0$



k_1, k_2, k_{dim}, $[\mathbf{2}]_0$, $[\mathbf{3}]_0$



k_1, k_2, k_{dim}, ε_6, $[\mathbf{2}]_0$, $[\mathbf{3}]_0$

Satisfactory fitting of the kinetics was only achieved when the parallel competing dimerisation reaction of the thiolate nucleophile (**4**) and the different LC-response of the final product (**6**) were taken into account.

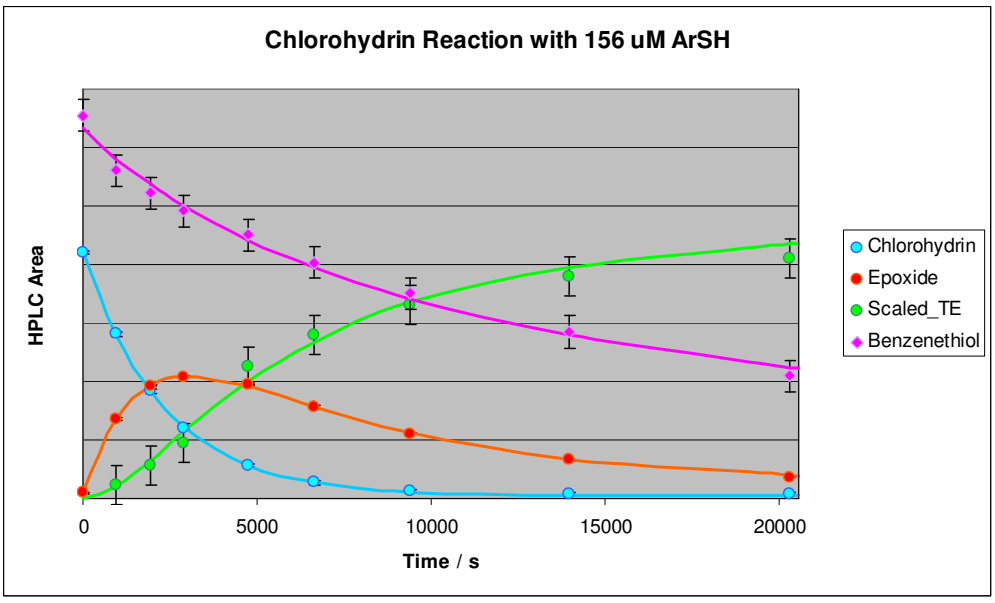
Results of mass balance calculation used to determine the relative extinction co-efficient of the thioether product (**6**).

[Concentrations are molar].

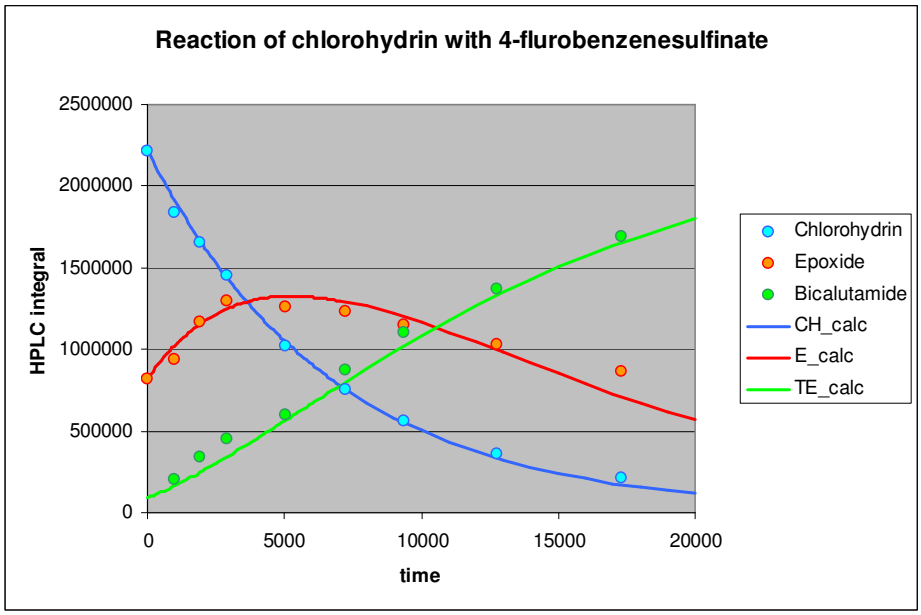
time / s	[4]	[2]	[3]	[6]	[2]+[3]+[6]
966	1.34E-04	1.25E-05	6.02E-06	9.908E-07	2.0E-05
1932	1.24E-04	8.18E-06	8.60E-06	2.497E-06	1.9E-05
2898	1.17E-04	5.34E-06	9.28E-06	4.21E-06	1.9E-05
4764	1.07E-04	2.50E-06	8.64E-06	1.009E-05	2.1E-05
6630	9.62E-05	1.22E-06	6.96E-06	1.244E-05	2.1E-05
9396	8.35E-05	5.81E-07	4.93E-06	1.475E-05	2.0E-05
13962	6.77E-05	3.44E-07	2.92E-06	1.692E-05	2.0E-05
20328	4.99E-05	3.33E-07	1.65E-06	1.82E-05	2.0E-05

HPLC peak area integral-time profile showing consumption of the thiolate (**4**, magenta) in parallel to the desired reaction of the chlorohydrin (**2**, cyan) to the epoxide (**3**, orange) and thioether product (**6**, green).

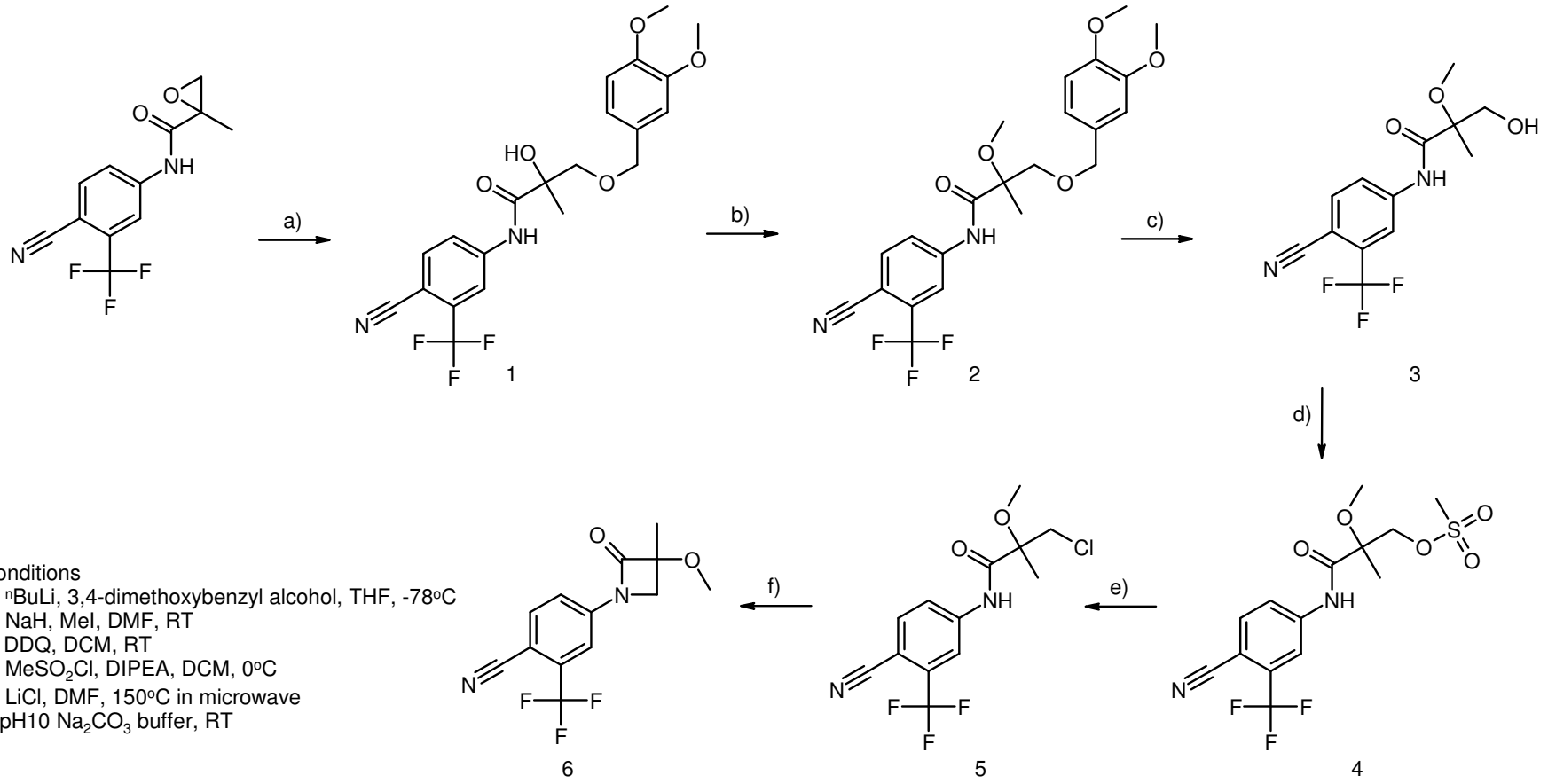
[The thioether product trace (**6**, green) has been scaled to the same HPLC response as the chlorohydrin (**2**, cyan) and epoxide (**3**, orange). The thiolate (**4**, magenta) at time zero is 7.8-fold more concentrated than the sum of the other three species and therefore is not shown on the same scale].



HPLC peak area integral-time profile showing the reaction of the chlorohydrin (**2**, cyan) *via* the epoxide (**3**, orange) with 4-flurorbenzensulfinate (**5**) to give Bicalutamide (**1**, green).

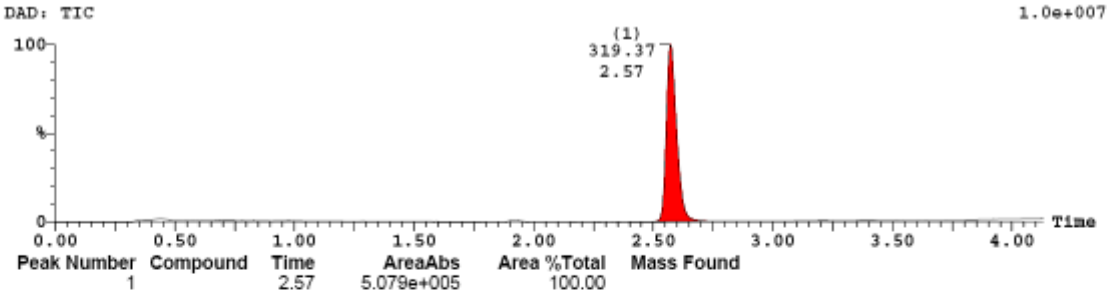


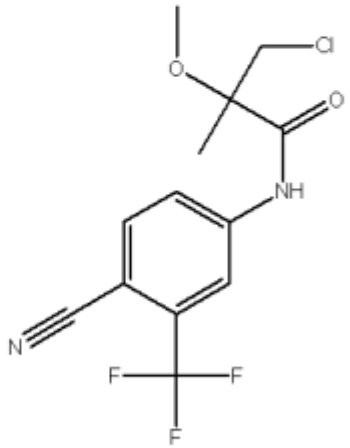
Synthetic Reaction Scheme.



Conditions
a) ^{n}BuLi, 3,4-dimethoxybenzyl alcohol, THF, -78^{o}C
b) NaH, MeI, DMF, RT
c) DDQ, DCM, RT
d) $MeSO_2Cl$, DIPEA, DCM, 0^{o}C
e) LiCl, DMF, 150^{o}C in microwave
f) pH10 Na_2CO_3 buffer, RT

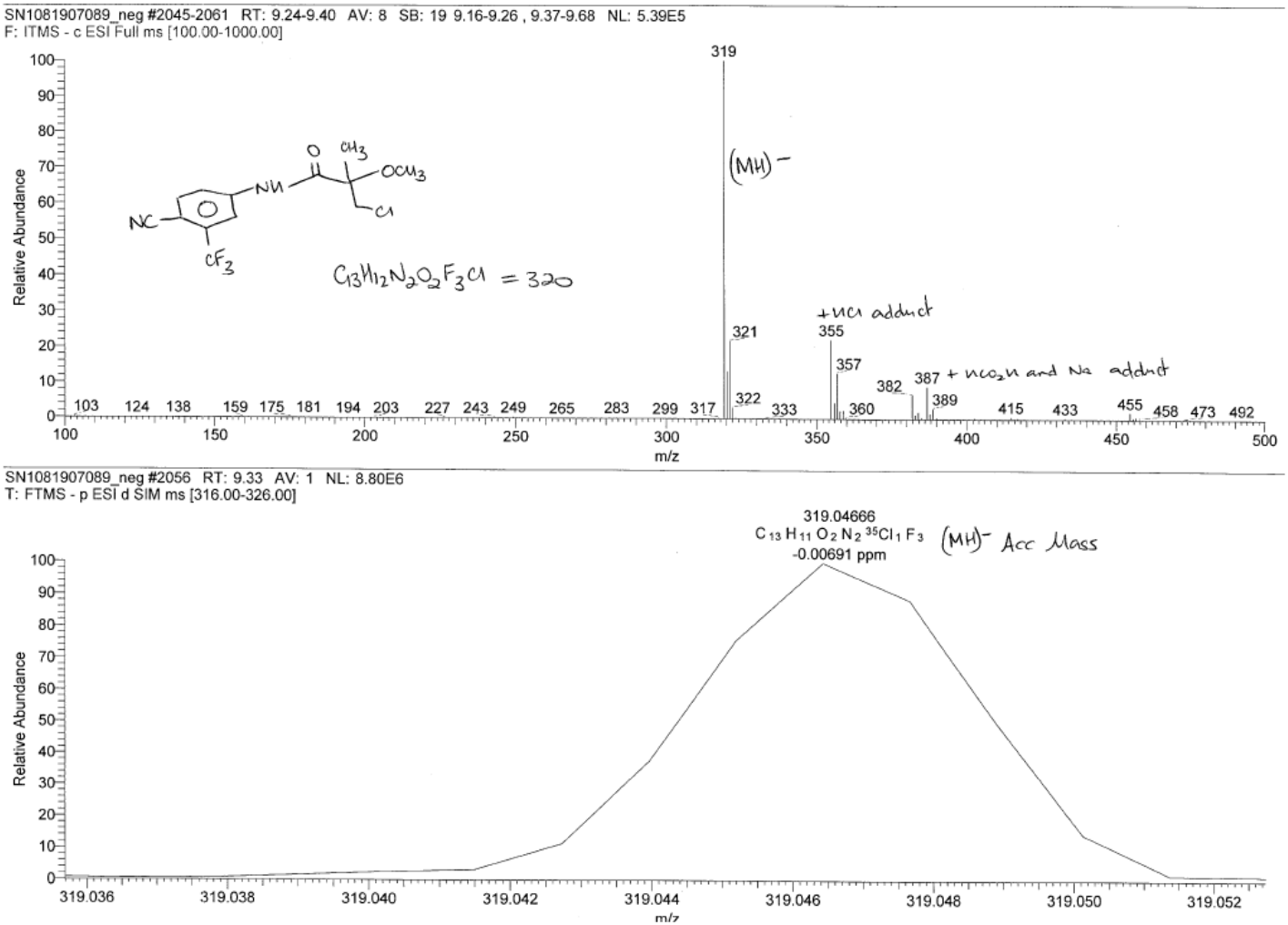
LC-MS Trace for *O*-Methyl Chlorohydrin (8)



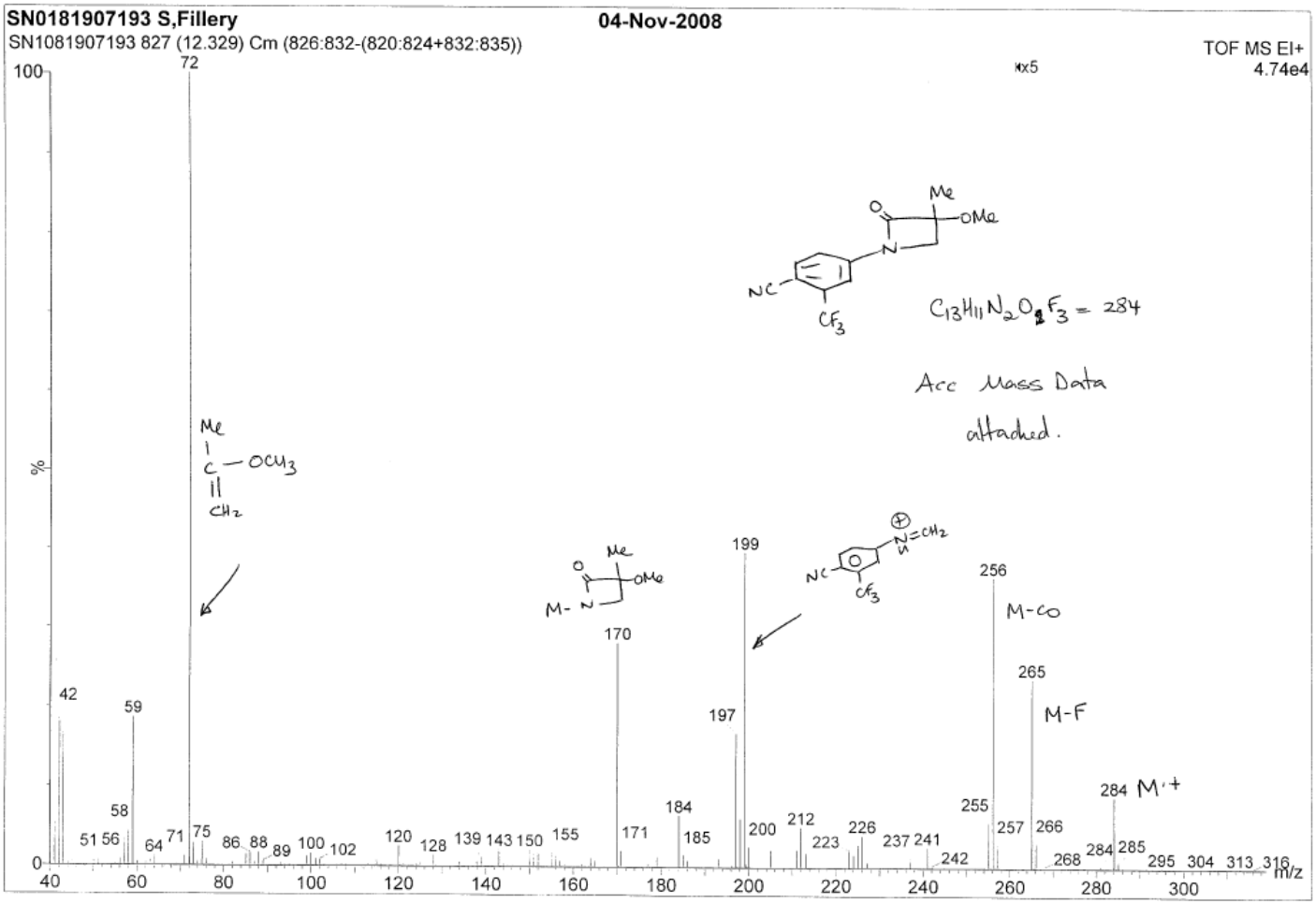


LCMS trace for compound (8)
m/z (ES-) 319.37 $[M-H]^-$

High Resolution MS for *O*-Methyl Chlorohydrin (8): $[M-H]^-$ 319.04666



MS Fragmentation for β-Lactam (9)



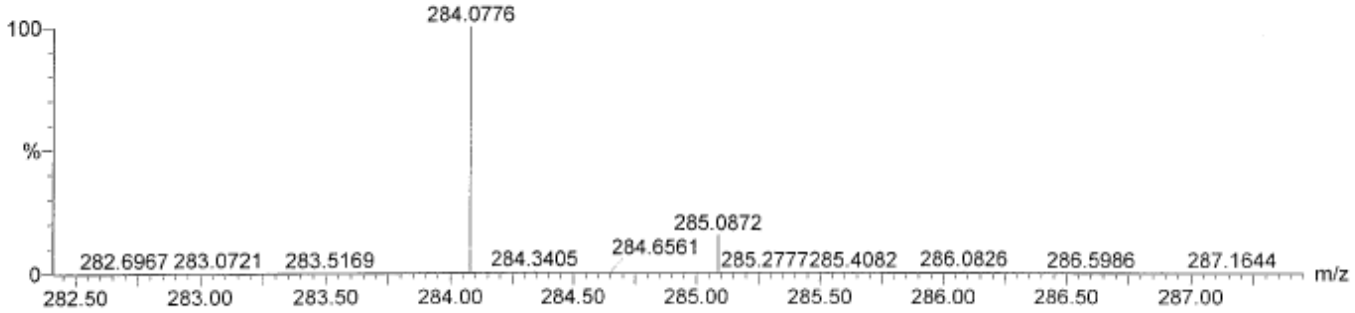
High Resolution MS for β-Lactam (9): $[M\bullet]^+$ 284.0776

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 100.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
10 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-13 H: 0-80 N: 0-2 O: 0-2 F: 3-3

SN0181907193 S,Fillery 04-Nov-2008
SN1081907193_Conc 827 (12.329) Cm (827) TOF MS EI+
1.39e+003



Minimum:				-1.5		
Maximum:		30.0	100.0	50.0		
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
284.0776	284.0773	0.3	1.1	8.0	7.9	C13 H11 N2 O2 F3

$M^{\cdot+}$ Acc Mass