

Synthesis of *trans*-2-(trifluoromethyl)cyclopropanes via Suzuki reactions with an *N*-methyliminodiacetic acid (MIDA) boronate

Matthew A. J. Duncton and Rajinder Singh*

Rigel, Inc., 1180 Veteran's Boulevard, South San Francisco, CA 94080, United States

E.mail: mattduncton@yahoo.com

Supporting Information

CONTENTS

PAGE

LITERATURE 2-(TRIFLUOROMETHYL)CYCLOPROPYL DERIVATIVES ATTACHED TO CYCLIC STRUCTURES.....	S4-S11
DISCUSSION OF CALCULATED LOG P VALUES WITH <i>TRANS</i> -(2-TRIFLUOROMETHYL) CYCLOPROPANES.....	S12-S21
GENERAL EXPERIMENTAL.....	S22-S23
SYNTHESIS OF <i>TRANS</i> -2-(TRIFLUOROMETHYL)CYCLOPROPYLBORONIC ACID	
<i>N</i> -METHYLIminodiacetic acid (MIDA) ESTER (COMPOUND 5).....	S24-S25
PREPARATION OF <i>TRANS</i> -2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)NAPHTHALENE 7	S26-S30
PREPARATION OF <i>TRANS</i> -1-(4-FLUORO-2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-5-NITROPHENYL)-4-METHYL-1 <i>H</i> -TETRAZOL-5(<i>H</i>)-ONE 9A	S31-S32
PREPARATION OF <i>TRANS</i> -1-TERT-BUTYL-4-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE 9B	S33-S34
PREPARATION OF <i>TRANS</i> -4-FLUORO-5-NITRO-2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-ANILINE 9C	S35-S36
PREPARATION OF <i>TRANS</i> -6-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-2,3-DIHYDRO-1 <i>H</i> -INDEN-1-ONE 9D	S37-S38
PREPARATION OF <i>TRANS</i> -3-(TRIFLUOROMETHYL)CYCLOPROPYL)-5-(PENTAFLUOROSULFUR)ANILINE 9E	S39-S40
PREPARATION OF <i>TRANS</i> -1-METHOXY-4-(2-(TRIFLUOROMETHYL)	

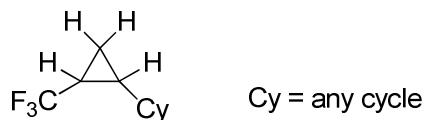
CYCLOPROPYL)BENZENE 9F	S41-S43
PREPARATION OF <i>TRANS</i> - <i>TERT</i> -BUTYL 3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZOATE 9G S44-S45	
PREPARATION OF <i>TRANS</i> -1-(DIETHOXYMETHYL)-3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE 9H S46-S47	
PREPARATION OF <i>TRANS</i> -3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZALDEHYDE 9H(2) S47-S48	
PREPARATION OF <i>TRANS</i> -5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)PYRIMIDINE 9I S49-S50	
PREPARATION OF <i>TRANS</i> -7-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-3,4-DIHYDRO-2 <i>H</i> -PYRIDO[3,2- <i>B</i>][1,4]OXAZINE 9J S51-S52	
PREPARATION OF <i>TRANS</i> -6-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-[1,2,4]TRIAZOLO[1,5- <i>A</i>]PYRIDINE 9K S53-S54	
PREPARATION OF <i>TRANS</i> -5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZO[<i>D</i>]THIAZOLE 9L S55-S56	
PREPARATION OF <i>TRANS</i> -1-METHYL-5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-1 <i>H</i> -INDAZOLE 9M S57-S58	
PREPARATION OF <i>TRANS</i> -2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)THIAZOLE 9N S59-S60	
PREPARATION OF <i>TRANS</i> 4-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)PHTHALAZIN-1(2 <i>H</i>)-ONE 9O S61-S62	
ANALYTICAL DATA FOR <i>TRANS</i> -2-(TRIFLUOROMETHYL)CYCLOPROPYLBORONIC ACID <i>N</i> -METHYLLIMINODIACETIC ACID (MIDA) ESTER (COMPOUND 5)..... S63-S66	
ANALYTICAL DATA FOR <i>TRANS</i> -2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)NAPHTHALENE 7 S67-S70	
ANALYTICAL DATA FOR <i>TRANS</i> -1-(4-FLUORO-2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-5-NITROPHENYL)-4-METHYL-1 <i>H</i> -TETRAZOL-5(4 <i>H</i>)-ONE 9A S71-S73	
ANALYTICAL DATA FOR <i>TRANS</i> -1- <i>TERT</i> -BUTYL-4-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE 9B S74-S77	
ANALYTICAL DATA FOR <i>TRANS</i> -4-FLUORO-5-NITRO-2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-ANILINE 9C S78-S80	
ANALYTICAL DATA FOR <i>TRANS</i> -6-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-2,3-	

DIHYDRO-1H-INDEN-1-ONE 9D	S81-S84
ANALYTICAL DATA FOR <i>TRANS</i> -3-(TRIFLUOROMETHYL)CYCLOPROPYL)-5-(PENTAFLUOROSULFUR)ANILINE 9E	S85-S88
ANALYTICAL DATA FOR <i>TRANS</i> -1-METHOXY-4-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE 9F	S89-S92
ANALYTICAL DATA FOR <i>TRANS</i> - <i>TERT</i> -BUTYL 3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZOATE 9G	S93-S96
ANALYTICAL DATA FOR <i>TRANS</i> -1-(DIETHOXYMETHYL)-3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE 9H	S97-S98
ANALYTICAL DATA FOR <i>TRANS</i> -3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZALDEHYDE 9H(2)	S99-S102
ANALYTICAL DATA FOR <i>TRANS</i> -5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)PYRIMIDINE 9I	S103-S106
ANALYTICAL DATA FOR <i>TRANS</i> -7-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-3,4-DIHYDRO-2 <i>H</i> -PYRIDO[3,2- <i>B</i>][1,4]OXAZINE 9J	S107-S110
ANALYTICAL DATA FOR <i>TRANS</i> -6-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-[1,2,4]TRIAZOLO[1,5- <i>A</i>]PYRIDINE 9K	S111-S114
ANALYTICAL DATA FOR <i>TRANS</i> -5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZO[<i>D</i>]THIAZOLE 9L	S115-S118
ANALYTICAL DATA FOR <i>TRANS</i> -1-METHYL-5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-1H-INDAZOLE 9M	S119-S122
ANALYTICAL DATA FOR <i>TRANS</i> -2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)THIAZOLE 9N	S123-S126
ANALYTICAL DATA FOR <i>TRANS</i> 4-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)PHTHALAZIN-1(2 <i>H</i>)-ONE 9O	S127-S130

LITERATURE 2-(TRIFLUOROMETHYL)CYCLOPROPYL DERIVATIVES ATTACHED TO CYCLIC STRUCTURES

The following sub-structure search was conducted within SciFinder® between 28th February and 16th March 2013 to ascertain the number of 2-(trifluoromethyl)cyclopropyl derivatives attached to cyclic structures that are described in the literature.

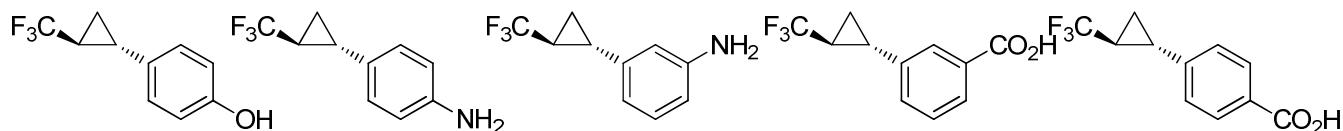
Substructure searched



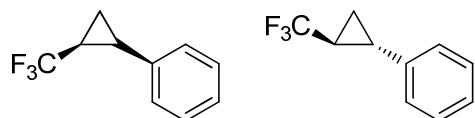
Cy = any cycle

This resulted in the following substances

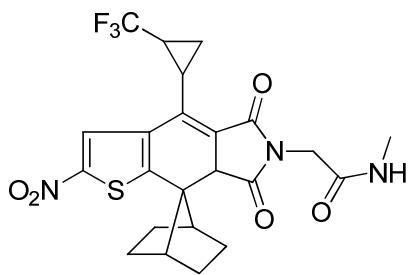
1. Substances registered in SciFinder, but with no citation (some are listed as commercially-available)



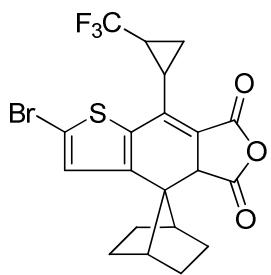
2. Substances detailed in Altman, L. J.; Bramwell, M. R.; Vederas, J. C. Synthesis and stereochemical assignments of some trifluoromethylphenylcyclopropanes. *Can. J. Chem.* **1971**, *49*, 968-971.



3. Substances detailed in Imura, S.; Tanizawa, T.; Kobayakawa, T. Preparation of spirofulgide and - fulgimide analogs as photochromic compounds. European Patent Application 629626, 1994; *Chem. Abstr.* **1994**, *122*, 265237.

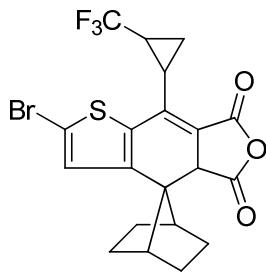
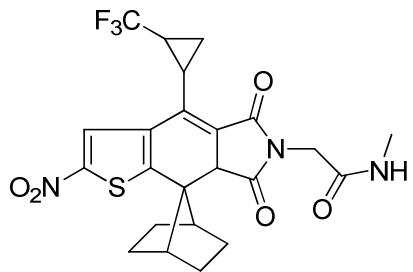


product
(Table 2; page 32)

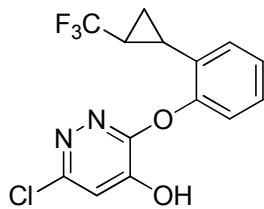


product
(Table 15; page 45)

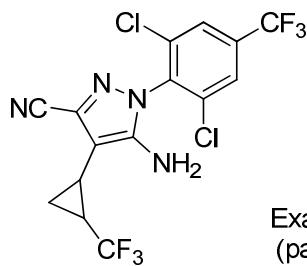
4. Substances detailed in Imura, S.; Tanizawa, T.; Kobayakawa, T. Preparation of fulgide and fulgimide photochromic compounds. Japanese Patent Application 06345772, 1994; *Chem. Abstr.* **1994**, *122*, 265356 (same substances as reference 3 above).



5. Substances detailed in Tsukamoto, Y.; Komai, H.; Kadotani, J.; Koi, K.; Mio, S.; Takeshiba, H. Preparation of 3-phenoxy-4-pyridazinol derivatives as herbicides. WO 2003016286, 2003; *Chem. Abstr.* **2003**, *138*, 187781.

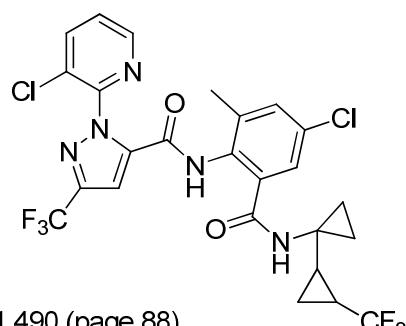


6. Substances detailed in Gladwell, I. R.; Matthews, J. G.; Pettman, A. J. Process for the preparation of substituted pyrazoles via cyclization of diazo compounds with 2,3-dicyanopropionates and related derivatives. WO 2005023773, 2005; *Chem. Abstr.* **2005**, *142*, 316832.



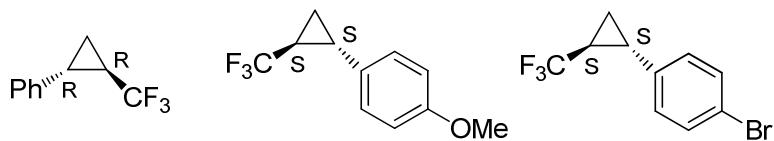
Example 2
(page 34)

7. Substances detailed in O'Sullivan, A. C.; Hughes, D.; eangueat, A.; Muehlebacj, M.; Loiseleur, O. Preparation of anthranilamide derivative acaricides and insectisides. WO 2006040113, 2006; *Chem. Abstr. 2006, 144, 364548.*

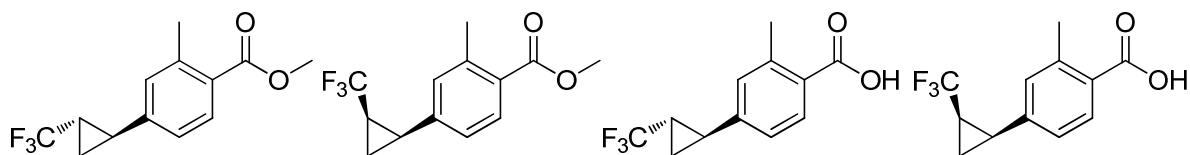


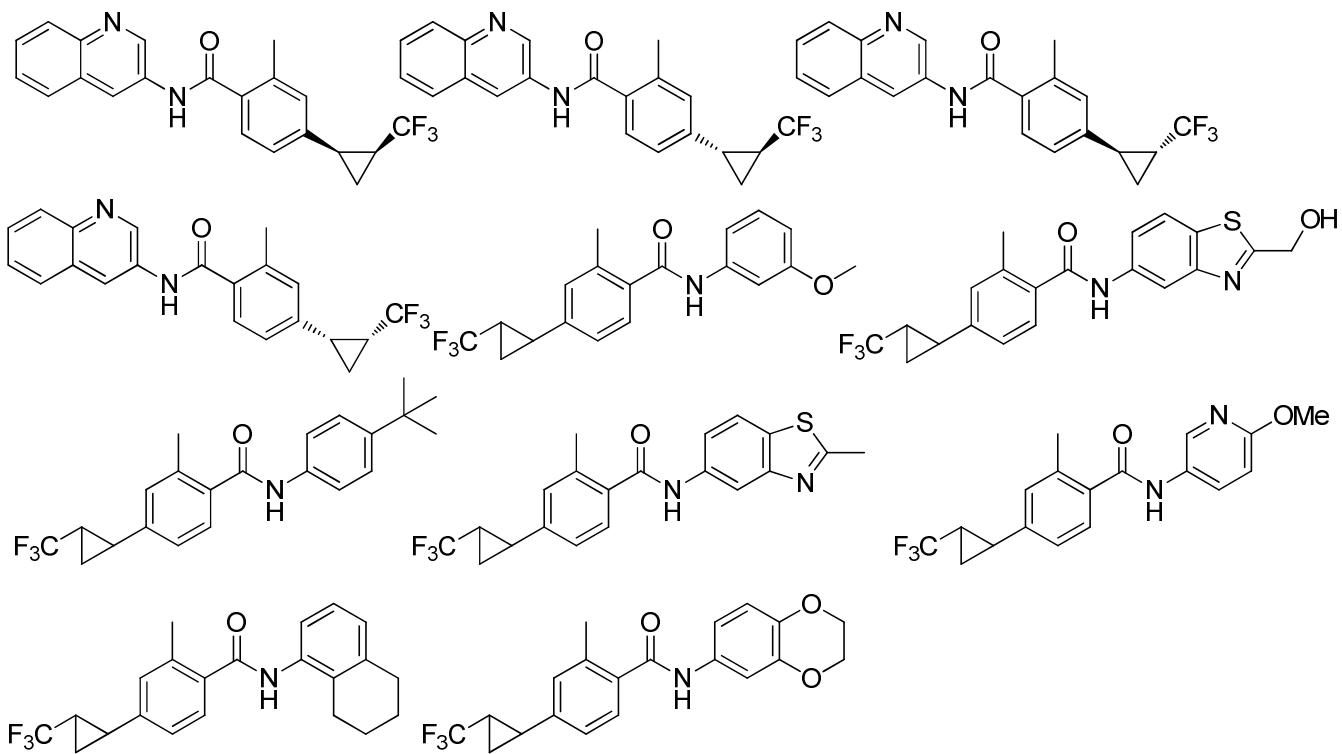
Compound A.1.490 (page 88)

8. Substances detailed in LeMaux, P.; Juillard, S.; Simonneaux, G. Asymmetric synthesis of (trifluoromethyl)phenylcyclopropanes catalysed by chiral metalloporphyrins. *Synthesis 2006, 1701-1704.* (see reference 12(a) in manuscript)

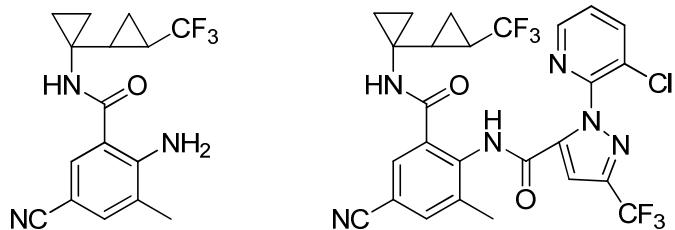


9. Substances detailed in Kelly, M. G.; Kincaid, J.; Janagani, S.; Duncton, M. Preparation of cyclopropyl(hetero)arylamides as vanilloid VR1 receptor antagonists. US Patent 0205773, 2006; *Chem. Abstr. 2006, 145, 336048.* (see reference 5 in manuscript and discussion in introduction)

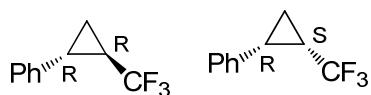




10. Substances detailed in Jeangenat, A.; O'Sullivan, A.; Muehlebach, M.; Trah, S.; Hall, R. G. Preparation of cyanoanthranilamides as insecticides and acaricides. WO2006111341, 2006; *Chem. Abstr.* **2006**, 145, 455006.

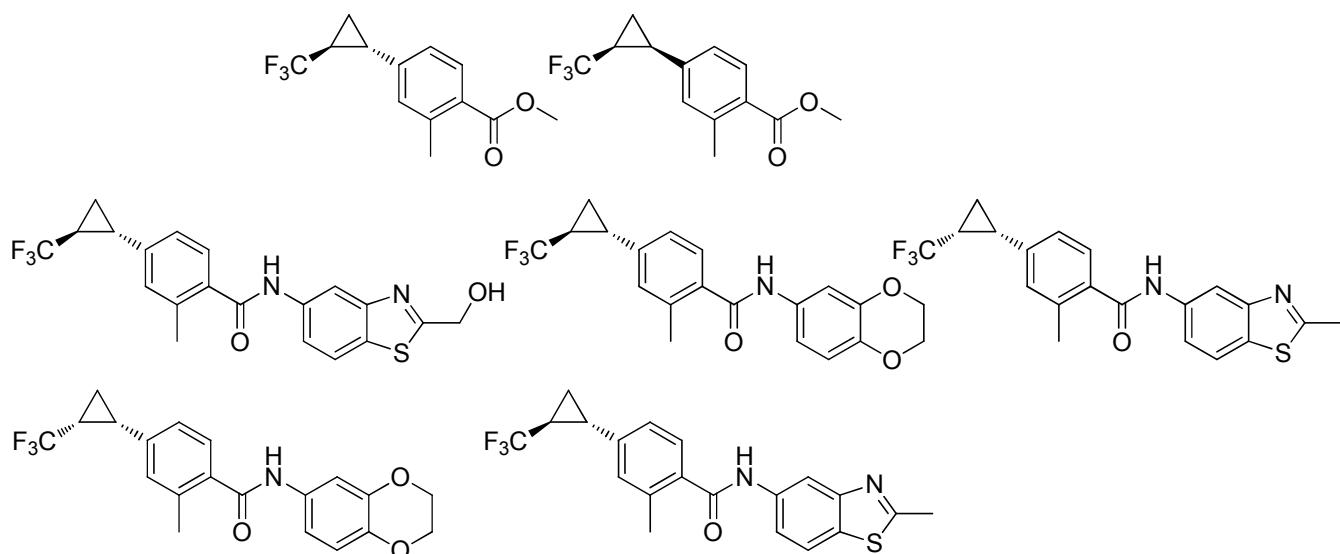


11. Substances detailed in Mykhailiuk, P. K.; Afonin, S.; Ulrich, A. S.; Komarov, I. V. A convenient route to trifluoromethyl-substituted cyclopropane derivatives. *Synthesis* **2008**, 1757-1760. (see reference 12(b) in manuscript)

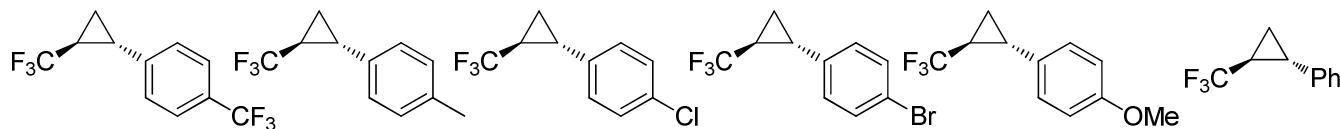


12. Substances detailed in Duncton, M. A. J.; Ayala, L.; Kaub, C.; Janagani, S.; Edwards, W. T.; Orike, N.; Ramamoorthy, K.; Kincaid, J.; Kelly, M. G. Dibutyl 2-(trifluoromethyl)cyclopropylboronate as a

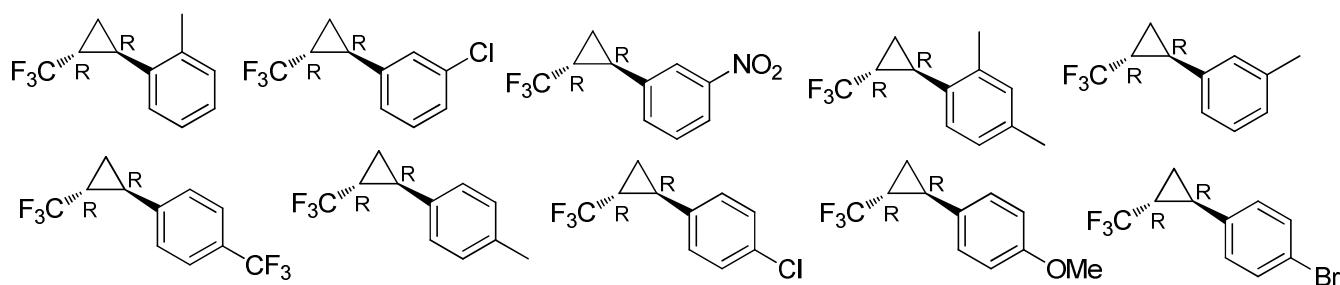
useful (trifluoromethyl)cyclopropyl donor: application to antagonists of TRPV1. *Tetrahedron Lett.* **2010**, *51*, 1009-1011. (see reference 6 in manuscript; See also reference 5 in manuscript and reference 9 above)

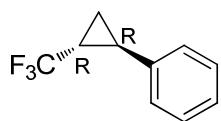


13. Substances detailed in Morandi, B.; Carreira, E. M. Iron-catalysed cyclopropanation with trifluoroethylamine hydrochloride and olefins in aqueous media: in-situ generation of trifluorodiazomethane. *Angew. Chem. Int. Ed.* **2010**, *49*, 938-941. (see reference 13 in manuscript)

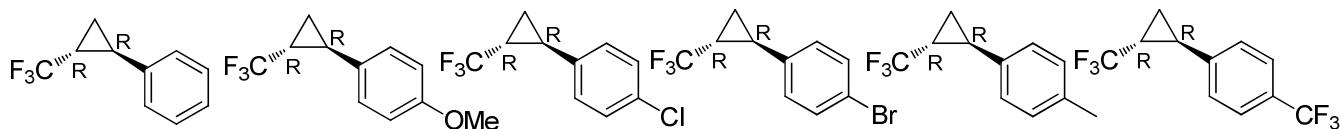


14. Substances detailed in Morandi, B.; Mariampillai, B.; Carreira, E. M. Enantioselective cobalt-catalysed preparation of trifluoromethyl-substituted cyclopropanes. *Angew. Chem. Int. Ed.* **2011**, *50*, 1101-1104. (see reference 28 in manuscript)

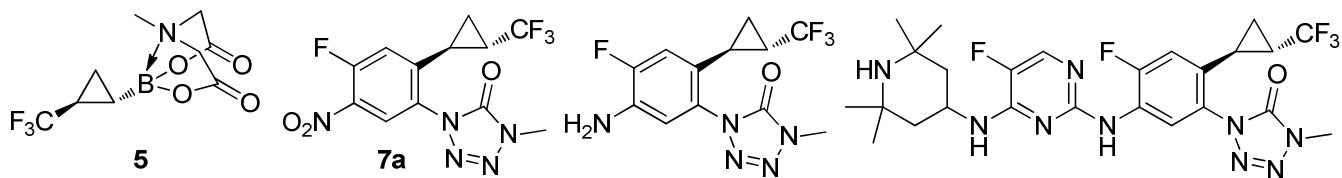




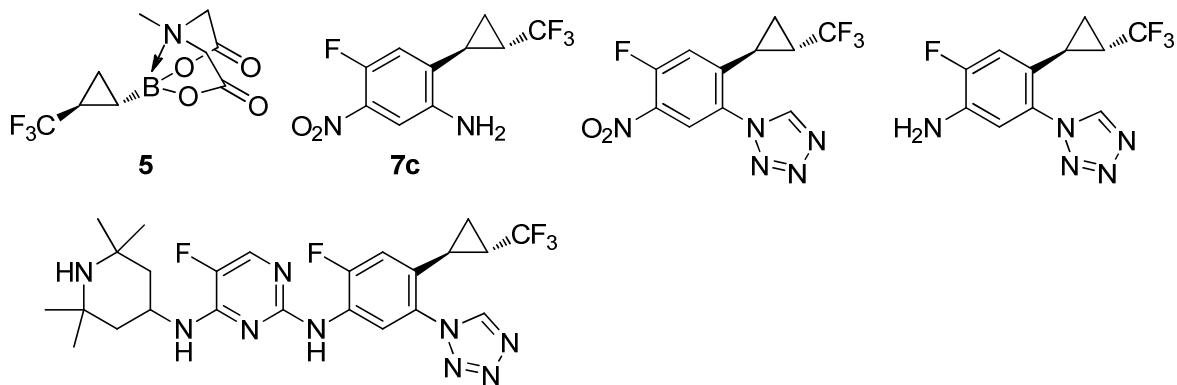
15. Substances detailed in Carreira, E. M. Preparation of trifluoromethylcyclopropanes by catalyzed cyclopropanation of olefins with trifluoroethylamines. Japanese Patent Application JP2011105691, 2011; *Chem. Abstr.* **2011**, *155*, 11475.



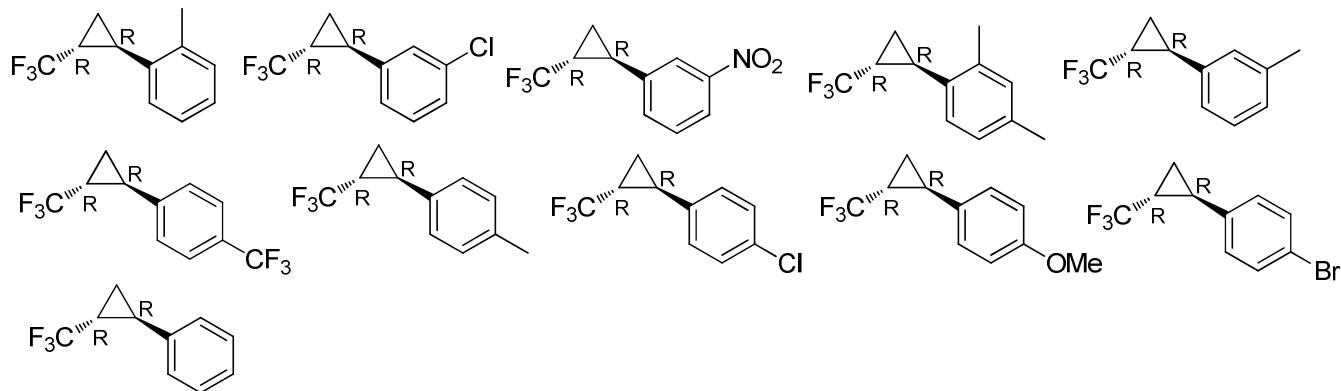
16. Substances detailed in Singh, R.; Tso, K.; Zhang, J.; Duncton, M.; Alvarez, S.; Kolluri, R.; Ramphal, J.; Holland, S. Preparation of N4-(piperidin-4-yl)-2,4-pyrimidinediamine derivatives as protein kinase C inhibitors and uses thereof. US Patent Application 20110130415, 2011; *Chem. Abstr.* **2011**, *155*, 40991. (see example 203, page 94-95)



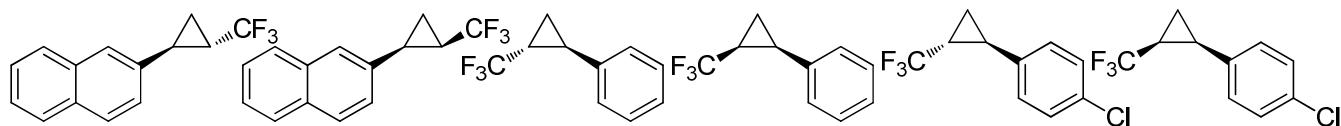
17. Examples detailed in Holland, S.; Kolluri, R.; Alvarez, S.; Duncton, M.; Singh, R.; Zhang, J.; Masuda, E. Preparation of pyrimidinediamine compounds as protein kinase C inhibitors. WO2012012619, 2012; *Chem. Abstr.* **2012**, *156*, 203309. (see example 65, pages 105-110)



18. Substances detailed in Carreira, E. M. Preparation of optically-active trifluoromethylcyclopropanes using optically-active cobalt complex catalysts, and preparation of the cobalt complexes. Japanese Patent Application JP2012036161; *Chem. Abstr.* **2012**, *156*, 336944. (see also reference 28 in manuscript and reference 14 above)

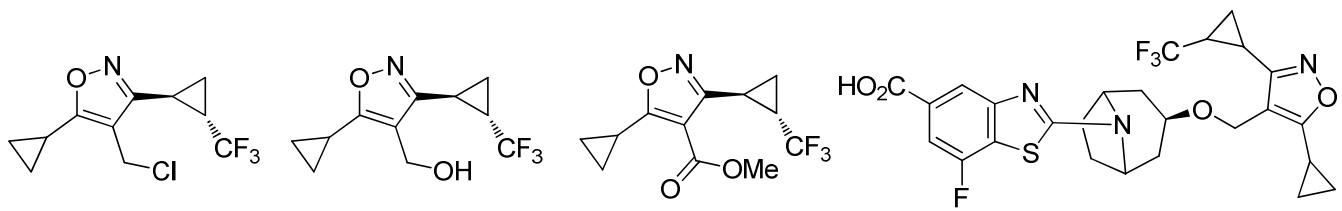


19. Substances detailed in Risse, J.; Fernández-Zúmel, M. A.; Cudré, Y.; Severin, K. Synthesis of trifluoromethyl-substituted cyclopropanes via sequential Karasch-dehalogenation reactions. *Org. Lett.* **2012**, *14*, 3060-3063. (see reference 14 in manuscript)



20. Substances detailed in Dunction, M.; Singh, R. Preparation of cyclopropylboronic acid N-methyliminodiacetic acid (MIDA) ester. Patent WO 075316, 2012; *Chem. Abstr.* **2012**, *157*, 76933. (See reference 16 in manuscript). This patent application contains all the substances detailed in this manuscript.

21. Substances detailed in Tully, D. C.; Rucker, P. V.; Alper, P. B.; Mutnick, D.; Chianelli, D. Nortropine derivatives as farnesoid X receptor modulators and their preparation and use for treatment of farnesoid X receptor-mediated diseases. WO 2012087519, 2012; *Chem. Abstr.* **2012**, *157*, 165713. (see example 11, page 141-142)



DISCUSSION OF CACULATED LOG P VALUES WITH TRANS-2-(TRIFLUOROMETHYL)CYCLOPROPANES

The following discussion is included for the benefit of medicinal chemists, who may be interested to note the effect of a *trans*-2-(trifluoromethyl)cyclopropyl group on the calculated octanol / water partition coefficient (cLog P), in two commonly-used software packages.

After demonstrating that *trans*-2-(trifluoromethyl)cyclopropyl products could be successfully synthesized (see manuscript), we sought to quantify the effect of a *trans*-2-(trifluoromethyl)cyclopropyl group on the octanol-water partition coefficient (Log P). In recent years, inflation in Log P, as estimated by calculated values (cLog P), has been postulated to result in increased attrition of drug candidates through the discovery and development cascade.²² Additionally, an increase in cLog P has been noted to result in an increased risk of failure in toxicological studies,²³ which may be related to an increase in off-target activity (“promiscuity”) as cLog P inflates.²²⁻²⁴ In order to address any concern about a large increase in cLog P with *trans*-2-(trifluoromethyl)cyclopropyl products, we sought to determine a cLog P value using ACD/Log P, a well-known calculator used by both industrial and academic medicinal chemists.²⁵ We chose to report calculated Log P values from ACD Laboratories for three main reasons.

- i. ACD/Log P is an accepted industry-standard software package for calculating cLog P, being used by a number of large pharmaceutical companies
- ii. Over 18,000 compounds with measured Log P values are used as the basis of the training set in ACD Log P. We were able to search this training set, as we use ACD software internally at Rigel, Inc.
- iii. A large body of literature correlates cLog P values (rather than measured values) to observed outcomes (e.g. DMPK characteristics, safety profile, etc.)

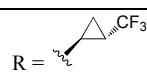
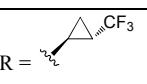
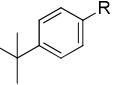
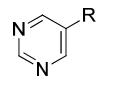
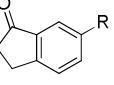
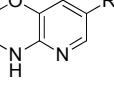
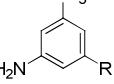
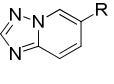
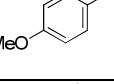
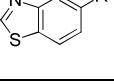
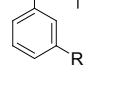
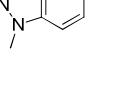
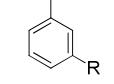
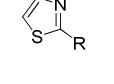
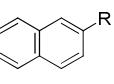
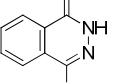
To provide some comparison as to the magnitude of increase in cLog P upon introduction of a *trans*-2-(trifluoromethyl)cyclopropyl group, the cLog P for nonsubstituted and cyclopropyl congeners were also calculated in ACD/Log P. The results from this evaluation are shown in Supplemental Table 1. Significantly, the results suggest that only a modest increase in cLog P may be expected when introducing a *trans*-2-(trifluoromethyl)cyclopropyl group in to an aryl or heteroaryl ring. For example, the increase of cLog P in progressing from an unsubstituted analogue to a *trans*-2-(trifluoromethyl)cyclopropyl counterpart was typically 0.5-1.0 Log units (Supplemental Table 1, entries 1-14). Interestingly, there appeared to be a slight reduction in cLog P when progressing from cyclopropyl examples to *trans*-2-(trifluoromethyl)cyclopropyl congeners. However, considering the variance associated with the calculation, this apparent reduction in cLog P may not be particularly significant. Overall, the results would indicate that a *trans*-2-(trifluoromethyl)cyclopropyl group results in a modest change in cLog P when compared to a non-substituted counterpart.

Supplemental Table 1. Calculated Log P values for representative *trans*-2-(trifluoromethyl)cyclopropanes using ACD/Log P.

Another industry-standard database for calculating Log P values is from Biobyte, Inc. Calculated Log P values are designated as Clog P using this software (either in Bio-Loom or ChemBioDraw Ultra 13.0). About 60,000 compounds are used in the training set for software from Biobyte, Inc. Therefore, after observing the calculated results obtained with ACD/Log P, we also determined Clog P values using Bio-Loom from Biobyte, Inc. or ChemBioDraw Ultra 13.0 using the Clog P plugin (Supplemental Table 2). The calculation in either BioLoom or ChemBioDraw Ultra 13.0 gave identical results. As can be seen

from Supplemental Table 2, Clog P values for *trans*-2-(trifluoromethyl)cyclopropanes appear to be about 1 Log unit higher than non-substituted counterparts, and about the same as cyclopropyl congeners.

Supplemental Table 2. Calculated Log P (Clog P) values for representative *trans*-2-(trifluoromethyl)cyclopropanes using Biobyte software within Bio-Loom or ChemBioDraw Ultra 13.0.

Entry	Compound	Clog P ^a			Entry	Compound	Clog P ^a		
		R = H	R = \triangle	R = 			R = H	R = \triangle	R = 
1		3.97	4.91	4.93	8		-0.31	0.63	0.65
2		1.72	2.66	2.68	9		1.48	2.42	2.45
3		2.15	3.09	3.11	10		0.51	1.45	1.47
4		2.06	3.00	3.03	11		2.08	3.02	3.05
5		3.35	4.29	4.31	12		1.58	2.52	2.55
6		2.54	3.49	3.51	13		0.49	1.43	1.45
7		3.30	4.26	4.28	14		0.16	1.10	1.12

^aClog P values calculated using Biobyte software within Bio-Loom or ChemBioDraw Ultra 13.0.

The observation that *trans*-2-(trifluoromethyl)cyclopropyl products had slightly lower, or equivalent, cLog P values to their cyclopropyl congeners (see Supplemental Tables 1 and 2), could be rather counter-intuitive, since most medicinal chemists presume that adding a trifluoromethyl group will increase Log P (and therefore, its calculated counterpart, cLog P). However, there are some exceptions to this observation, and a few points of fluorine chemistry that are worth discussing in greater detail in this Supporting Information.

Addition of fluorine to saturated alkyl systems reduces Log P, due to the polar character of the carbon-fluorine bond.²⁶ This can be illustrated by considering the Log P reported for propylbenzene (Log P = 3.57-3.72)²⁷⁻³¹ compared with the Log P reported for 3,3,3-trifluoropropylbenzene (Log P = 3.31; Supplemental Figure 1).³² Therefore, it may be that the software used for calculating Log P considers that the fluorine from the (trifluoromethyl)cyclopropyl group is analogous to adding fluorine in to a saturated system, resulting in a slight reduction / little change to cLog P when compared with a cyclopropyl counterpart, due to an increase in polarity.



Supplemental Figure 1. Log P values with propylbenzene and 3,3,3-trifluoropropylbenzene.²⁷⁻³²

However, it is also possible that the Log P software is not fully taking in to account that a cyclopropyl group has a degree of pi-character, and that fluorination adjacent to atoms with pi-bonds increases Log P.²⁶ Of course, the degree to which the fluorine atom of a (trifluoromethyl)cyclopropyl group could

interact with the pi-system of the cyclopropane moiety may determine any magnitude of increase in Log P if such a situation were operating.

In summary, it should be noted that calculated Log P values (cLog P) are routinely used in the medicinal chemistry community as a surrogate for measured values. We accept that without measurements of compounds containing a *trans*-2-(trifluoromethyl)cyclopropyl fragment, the software used for calculations of cLog P may be somewhat inaccurate. Thus, we believe it will be attractive to measure the Log P values for a number of compounds containing a *trans*-2-(trifluoromethyl)cyclopropyl group and compare them to calculated values determined within industry-standard Log P software packages. In the interim, we would treat cLog P values with *trans*-2-(trifluoromethyl)cyclopropyl products with an appropriate degree of caution, due to the lack of measurements of Log P values with compounds containing this fragment.³³

22. Leeson, P. D.; Springthorpe, B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discov.* **2007**, *6*, 881-890.

23. Hughes, J. D.; Blagg, J.; Price, D. A.; Bailey, S.; DeCrescenzo, G. A.; Devraj, R. V. Ellsworth, E.; Fobain, Y. M.; Gibbs, M. E.; Gilles, R. W.; Greene, M.; Huang, E.; Krieger,-Burke, T.; Loesel, J.; Wager, T.; Whiteley, L.; Zhang, Y. Physiochemical drug properties associated with toxicological outcomes. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4872-4875.

24. Also note that ionization class is an important determinant of off-target activity. See ref. 22-23 and Azzaoui, K.; Hamon, J.; Faller, B.; Whitebread, S.; Jacoby, E.; Bender, A.; Jenkins, J. L.; Urban, L. Modeling promiscuity based on in vitro safety pharmacology profiling data. *ChemMedChem* **2007**, *6*, 874-880.

25. Petrauskas, A.; Kolovanov, E. ACD/Log P method description. *Persp. Drug Design* **2000**, *19*, 99-116.

26. Smart, B. E. Fluorine substituent effects (on bioactivity). *J. Fluor. Chem.* **2001**, *109*, 3-11.

27. Sangster, J. Octanol-water partition coefficients of simple organic compounds. *J. Phys. Chem. Ref. Data* **1989**, *18*, 1111-1229. (Log P of propylbenzene = 3.69)

28. Iwasa, J.; Fujita, T.; Hansch, C. Substituent constants for aliphatic functions obtained from partition coefficients. *J. Med. Chem.* **1965**, *8*, 150-153. (Log P of propylbenzene = 3.68)

29. Hansch, C.; Leo, A. J. Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York (1979). (Log P of propylbenzene = 3.57)

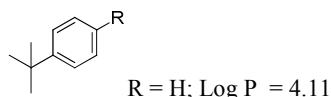
30. Camilleri, P.; Watts, S. A.; Boraston, J. A. A surface area approach to determination of partition coefficients. *J. Chem. Soc. Perkin Trans. II* **1988**, 1699-1707. (Log P of propylbenzene = 3.72)

31. DeVoe, H.; Miller, M. M.; Wasik, S. P. Generator columns and high pressure liquid chromatography for determining aqueous solubilities and octanol-water partition coefficients of hydrophobic substances. *J. Res. Natl. Bur. Stds.* **1981**, *86*, 361-366. (Log P of propylbenzene = 3.72)

32. Akamatsu, M. (Kyoto Univ.) private communication as presented in BioByte Star List (Log P of 3,3,3-trifluoropropylbenzene = 3.31)

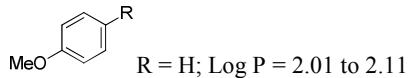
33. For reflections on some limitations when using calculated Log P values, see Lowe, D. Watch that little letter 'c'. http://pipeline.corante.com/archives/2012/08/22/watch_that_little_letter_c.php. We share many of the sentiments expressed in this article.

For reference purposes, the following compounds described in Supplemental Tables 1 and 2 have a measured octanol-water partition coefficient value (Log P) described in the literature.



27. Sangster, J. Octanol-water partition coefficients of simple organic compounds. *J. Phys. Chem. Ref. Data* **1989**, *18*, 1111-1229.

29. Hansch, C.; Leo, A. J. Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York (1979).



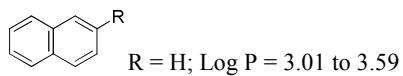
27. Sangster, J. Octanol-water partition coefficients of simple organic compounds. *J. Phys. Chem. Ref. Data* **1989**, *18*, 1111-1229. (Log P of anisole = 2.01)

29. Hansch, C.; Leo, A. J. Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York (1979). (Log P of anisole = 2.10)

34. Fujita, T.; Iwasa, J.; Hansch, C. A new substituent constant, π , derived from partition coefficients. *J. Am. Chem. Soc.* **1964**, *86*, 5175-5180. (Log P of anisole = 2.11)

35. Rogers, K.; Cammarata, A. Superdelocalizability and charge density. A correlation to partition coefficients. *J. Med. Chem.* **1969**, *10*, 692-693. (Log P of anisole = 2.04)

36. Lu, P. Y.; Metcalf, R. Environmental fate and biodegradability of benzene derivatives as studies in a model aquatic ecosystem. *Environ. Health Perspect.* **1975**, *10*, 269-284. (Log P of anisole = 2.08)

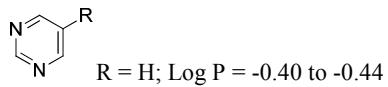


27. Sangster, J. Octanol-water partition coefficients of simple organic compounds. *J. Phys. Chem. Ref. Data* **1989**, *18*, 1111-1229. (Log P of naphthalene = 3.35)

29. Hansch, C.; Leo, A. J. Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York (1979). (Log P of naphthalene = 3.30, 3.45, 3.59)

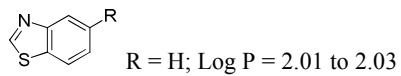
35. Rogers, K.; Cammarata, A. Superdelocalizability and charge density. A correlation to partition coefficients. *J. Med. Chem.* **1969**, *10*, 692-693. (Log P of naphthalene = 3.01)

37. Hansch, C.; Fujita, T. ρ, σ, π Analysis; method for the correlation of biological activity and chemical structure. *J. Am. Chem. Soc.* **1964**, *86*, 1616-1626. (Log P of naphthalene = 3.37)



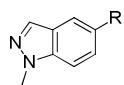
29. Hansch, C.; Leo, A. J. Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York (1979). (Log P of pyrimidine = -0.40)

38. Yamagami, C.; Takao, N.; Fujita, T. Hydrophobicity parameter of diazines. 1. Analysis and prediction of partition coefficients of monosubstituted diazines. *Quant. St.-Act. Rel.* **1990**, *9*, 313-320. (Log P of pyrimidine = -0.44)



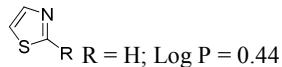
35. Rogers, K.; Cammarata, A. Superdelocalizability and charge density. A correlation to partition coefficients. *J. Med. Chem.* **1969**, *10*, 692-693. (Log P of benzothiazole = 2.03)

39. Hansch, C.; Anderson, S. M. The effect of intramolecular hydrogen bonding on partition coefficients. *J. Org. Chem.* **1967**, *32*, 2583-2586. (Log P of benzothiazole = 2.01)

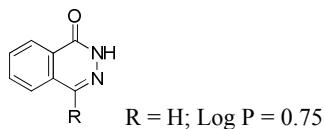


R = H; Log P = 1.34 (note octanol-phosphate buffer partition coefficient measured)

40. Toulmin, A; Wood, M. J.; Kenny, P. W. Towards prediction of alkane/water coefficients. *J. Med. Chem.* **2008**, *51*, 3720-3730.



29. Hansch, C.; Leo, A. J. Substituent constants for correlation analysis in chemistry and biology. John Wiley & Sons, New York (1979).



41. Lewis, S. J.; Mirrless, M. S.; Taylor, P. J. Rationalizations among heterocyclic partition coefficients. Part 2: the azines. *Quant. St.-Act. Rel.* **1983**, *2*, 100-111.

GENERAL EXPERIMENTAL

All reagents and solvents were purchased from commercial suppliers and used without further purification. Starting materials **8a** and **8c** were prepared according to literature methods referenced in the individual experimental section below. Reactions were monitored by thin-layer chromatography or high-performance liquid chromatography. NMR was performed on a 300 MHz NMR spectrometer and all chemical shifts are reported relative to a tetramethylsilane internal standard, or by referencing on the deuterated solvent. Reverse-phase high-performance liquid chromatography was performed on standard equipment and was coupled to diode array and mass spectra detectors – the mass-spectra detector operating under the electrospray ionization (ESI) mode. The column-gradient system was as follows

Column: Phenomenex Gemini 4.6 x 100 mm, C18, 5 μ m, 110 \AA

Column temperature 30°C

Sample temperature 15°C

Solvent A – 0.05% Formic acid in Water

Solvent B – 0.05% Formic acid in Acetonitrile

Flow rate – 1.5 mL/min

Gradient:

Time	A%	B%
0	95	5
10	0	100 (curve=6)
11.1	0	100
11.2	95	5
12.1	95	5

High resolution mass spectrometry were obtained on a LCT Premier XE mass spectrometer (time-of-flight) operating under the electrospray ionization mode. Mass analysis was performed in extended W-mode using leucine enkephalin as reference lock mass (556.2771 Da for positive ion & 554.2615 Da for negative ion).

Physicochemical characteristics (cLog P, freely rotatable bonds, H-bond donors / acceptors, molecular weight and polar surface area) were calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2012 ACD/Labs). Values were determined in October 2012. Calculated Log P values (Clog P) were determined in Bio-Loom from Biobyte, Inc. or ChemBioDraw Ultra 13.0 (see Supplemental Table 1). Calculations were performed on 15th March 2013 and 19th April 2013, respectively.

‘Rule-of-three’ criteria are described in

43. Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. A. A ‘rule of three’ for fragment-based lead discovery? *Drug Discov. Today* **2003**, 8, 876-877 (reference 27 in manuscript).

Molecular weight <300

Number of H-Bond donors ≤ 3

Number of H-Bond acceptors ≤ 3

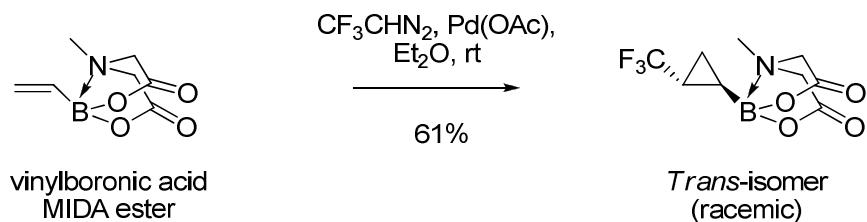
cLog P ≤ 3

Additionally, it is suggested

Number of rotatable bonds ≤ 3

Polar surface area ≤ 60

METHYLMINODIACETIC (MIDA) ACID ESTER (COMPOUND 5)



Step 1: Preparation of trifluoromethyl diazomethane (reference for the procedure is made to *J. Am. Chem. Soc.* **1943**, *65*, 1458)

A safety notice for the procedure: Diazo compounds are potentially explosive. This reaction was performed behind a blast shield in glassware free from cracks or prominent scratches (glassware was inspected prior to use).

Sodium nitrite (4.6 g, 66 mmol) in water (10 mL) was added in one portion to a stirred solution of 2,2,2-trifluoroethylamine hydrochloride (8.1 g, 60 mmol) in water (25 mL) and ether (45 mL) at 0 °C. The reaction vessel was sealed with a teflon stopper and the mixture stirred from 0 °C to room temperature and stirred at room temperature for approximately 3 hours. The mixture was then partitioned in a separating funnel and the ether layer containing the product was used directly in the next step without further purification. The yield of the trifluoromethyl diazomethane product was assumed to be approximately 50% based on literature citation herein (= 3.32 g).

Step 2: Preparation of *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (reference for the procedure is made to *Tetrahedron Letters* **2010**, *51*, 1009-1011)

A safety notice for the procedure: Diazo compounds are potentially explosive. This reaction was performed behind a blast shield in glassware free from cracks or prominent scratches (glassware was inspected prior to use).

A mixture of trifluoromethyl diazomethane (3.32 g, 30 mmol) in Et₂O (45 mL) was added dropwise to a stirred suspension of vinylboronic acid MIDA ester (Sigma-Aldrich, St. Louis, MO; 1.65 g, 9.0 mmol) and Pd(OAc)₂ (50 mg) in Et₂O at room temperature. After adding for 10 minutes (about a quarter of the

trifluoromethyl diazomethane had been added at this stage), more Pd(OAc)₂ (50 mg) and Et₂O (100 mL) was added, and trifluoromethyl diazomethane was added dropwise for another 20 minutes (approximately three quarters added after this time). EtOAc (50 mL) and Pd(OAc)₂ (50 mg) were added at this point and the remaining trifluoromethyl diazomethane was added dropwise over 10 minutes. After complete addition of the trifluoromethyl diazomethane the mixture was analysed by TLC which indicated complete reaction. The solvent was removed under vacuum and the residue was dry-loaded on to silica gel and purified by column chromatography on silica gel using EtOAc as eluent to give the product (1.45 g, 61%) as a solid.

¹H NMR (DMSO-*d*₆, 300MHz): δ 3.99-3.72 (m, 4H), 2.70 (s, 3H), 1.28 (m, 1H), 0.53 (m, 1H), 0.31 (m, 1H), 0.00 (m, 1H)

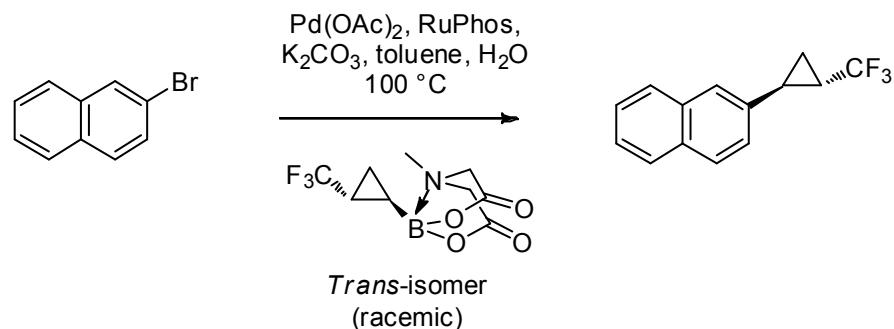
¹⁹F NMR (DMSO-*d*₆, 282 MHz): -65.4 (d, *J* = 7.1 Hz)

¹³C NMR (DMSO, 75MHz): δ 167.9, 169.7, 128.2 (q, *J* = 269 Hz), 61.2, 61.1, 45.3, 14.9 (q, *J* = 35 Hz), 3.5 (q, *J* = 2.6 Hz), 3.5.

A sample was recrystallised from EtOAc, and then a small sample recrystallized again from 1,2-dichloroethane, to give crystals suitable for analysis by x-ray crystallography. X-ray studies confirmed the material to be the *trans*-isomer.

Note: the above reaction could also be repeated on a larger scale using 4.5g of vinylboronic acid MIDA ester, and scaling other reagents as appropriate, to give the product (5.65g, 87%) as a solid.

PREPARATION OF *TRANS* -2-(TRIFLUOROMETHYL)CYCLOPROPYL)NAPHTHALENE **7**



In an open ChemGlass vial with pressure-release top, a stirred mixture of 2-bromonaphthalene **6c** (Aldrich) (52 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (2 prep. TLC plates used) using EtOAc / hexane (1:99) as eluent to give the product (38.1 mg, 65%) as a solid.

^1H NMR (CDCl_3 , 300MHz): δ 7.81-7.75 (m, 3H), 7.57 (s, 1H), 7.50-7.41 (m, 2H), 7.21 (d, J = 1.7 Hz, 1H), 2.56-2.49 (m, 1H), 1.97-1.84 (m, 1H), 1.47-1.40 (m, 1H), 1.31-1.25 (m, 1H)

^{13}C NMR (CDCl_3 , 75MHz): δ 136.7, 133.7, 132.7, 128.7, 128.1 (q, J = 269 Hz), 128.0, 127.8, 126.7, 126.1, 125.4, 124.5, 23.5 (q, J = 36.6 Hz), 20.2 (q, J = 2.6 Hz), 11.1 (q, J = 2.6 Hz)

^{19}F NMR (CDCl_3 , 282 MHz): -66.7 (d, J = 7.1 Hz)

m/z = no mass ion detected by either LC/MS or HRMS

Data in agreement with Risse, J.; Fernández-Zúmel, M. A.; Cudré, Y.; Severin, K. Synthesis of trifluoromethyl-substituted cyclopropanes via sequential Karasch-dehalogenation reactions. *Org. Lett.* **2012**, *14*, 3060-3063 (see reference 14 in manuscript) [note: CD₂Cl₂ was used for NMR analysis in this paper]

Calculated physicochemical characteristics for compound 7:

clog P: 3.96 ± 0.39

Freely rotatable bonds: 1

H-bond acceptors: 0

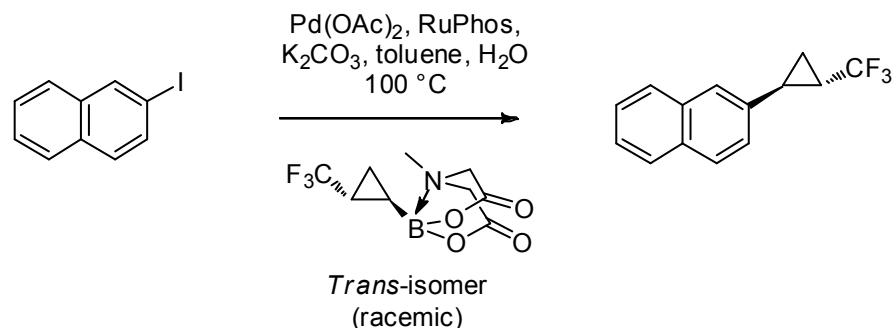
H-bond donors: 0

Sum H-bond donors + acceptors: 0

Molecular weight: 236.23

Polar surface area: 0.0 Å²

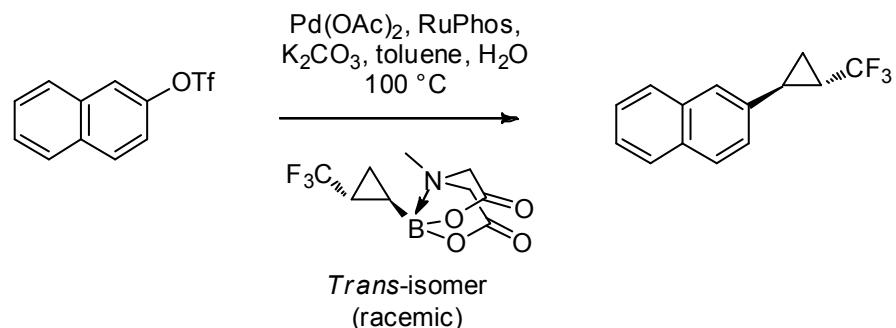
PREPARATION OF *TRANS* -2-(TRIFLUOROMETHYL)CYCLOPROPYL)NAPHTHALENE **7**



In an open ChemGlass vial with pressure-release top, a stirred mixture of 2-iodonaphthylene **6a** (Aldrich) (64 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (2 prep. TLC plates used) using EtOAc / hexane (1:99) as eluent to give the product (46.2 mg, 78%) as a solid.

Data identical to above.

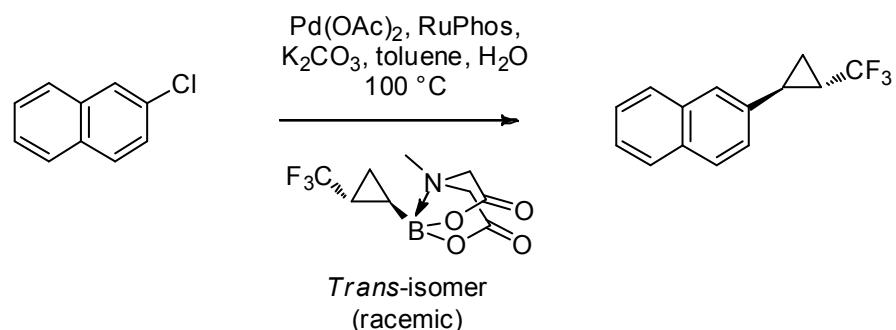
PREPARATION OF *TRANS* -2-(TRIFLUOROMETHYL)CYCLOPROPYL)NAPHTHALENE **7**



In an open ChemGlass vial with pressure-release top, a stirred mixture of 2-naphthyltrifluoromethanesulfonate **6b** (Aldrich) (69 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (2 prep. TLC plates used) using EtOAc / hexane (1:99) as eluent to give the product (45.9 mg, 78%) as a solid.

Data identical to above.

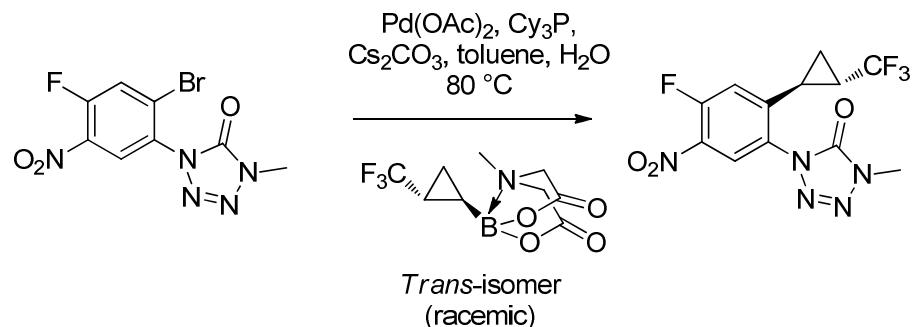
PREPARATION OF *TRANS* -2-(TRIFLUOROMETHYL)CYCLOPROPYL)NAPHTHALENE **7**



In an open ChemGlass vial with pressure-release top, a stirred mixture of 2-chloronaphthylene (TCI America) **6d** (41 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (2 prep. TLC plates used) using EtOAc / hexane (1:99) as eluent to give the product (31.7 mg, 54%) as a solid.

Data identical to above.

PREPARATION OF *TRANS*-1-(4-FLUORO-2-(TRIFLUOROMETHYL)CYCLOPROPYL)-5-NITROPHENYL)-4-METHYL-1*H*-TETRAZOL-5(*4H*)-ONE **9A**



A mixture of 1-(2-bromo-4-fluoro-5-nitrophenyl)-4-methyl-1*H*-tetrazol-5(*4H*)-one (see US20110130415) **8a** (145 mg, 0.46 mmol), *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (240 mg, 0.91 mmol), Pd(OAc)₂ (20 mg, 0.09 mmol), Cy₃P (50 mg, 0.18 mmol) and Cs₂CO₃ (593 mg, 1.82 mmol) in toluene (6 mL) and H₂O (2 mL) was de-gassed with N₂ for 10 mins, then placed under a nitrogen atmosphere and heated to 80 °C overnight (a reflux condenser was used in the apparatus). After completion of the reaction (Note: TLC showed product and starting material to be very close), the mixture was cooled and partitioned between EtOAc (50 mL) and H₂O (50 mL). The aqueous and organic layers were partitioned and the organic layer was washed with brine (1 x 20 mL), dried (MgSO₄), filtered and the solvent removed under vacuum to leave a crude residue. The residue was dry-loaded on to silica gel and purified by column chromatography on silica gel using EtOAc / hexane (3:7 to 4:6) as eluent to give the product (107 mg, 67%).

¹H NMR (CDCl₃, 300MHz): δ 8.19 (dd, 1H), 7.22 (d, 1H), 3.74 (s, 3H), 2.69-2.62 (m, 1H), 1.78-1.69 (m, 1H), 1.50-1.43 (m, 1H), 1.29-1.22 (m, 1H)

¹⁹F NMR (CDCl₃, 282 MHz): -112.9 (dd, *J* = 7.1, 7.1 Hz), -67.6 (d, *J* = 6.2 Hz)

m/z = 389.2 (M+MeCN+H)⁺

Note: Procedure originally part of US20110130415

Calculated physicochemical characteristics for compound **9a**:

cLog P: 0.90 ± 0.59

Freely rotatable bonds: 3

H-bond acceptors: 8

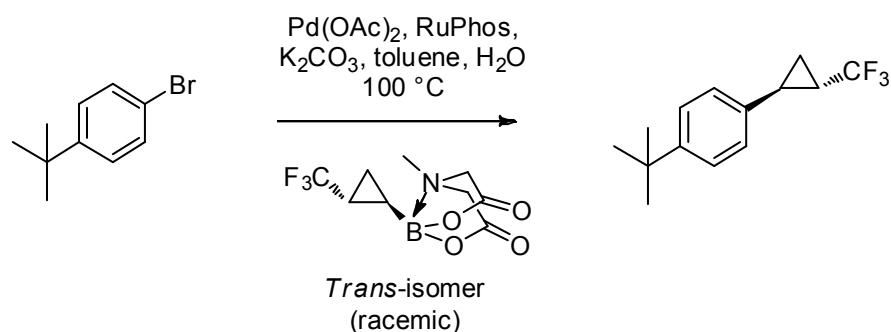
H-bond donors: 0

Sum H-bond donors + acceptors: 8

Molecular weight: 347.23

Polar surface area: 94.1 \AA^2

PREPARATION OF *TRANS*-1-*TERT*-BUTYL-4-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE **9B**



In an open ChemGlass vial with pressure-release top, a stirred mixture of 4-*tert*-butylbromobenzene (Oakwood) **8b** (53 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K₂CO₃ (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H₂O (0.5 mL) was de-gassed with N₂ for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H₂O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (3 prep. TLC plates used) using EtOAc / hexane (1:4) as eluent to give the product (49.1 mg, 81%) as an oil.

¹H NMR (CDCl₃, 300MHz): δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 2.38-2.32 (m, 1H), 1.87-1.74 (m, 1H), 1.39-1.33 (m, 1H), 1.32 (s, 9H), 1.20-1.11 (m, 1H)

¹³C NMR (CDCl₃, 75MHz): δ 150.1, 136.4, 128.1 (q, *J* = 268 Hz), 126.5, 125.9, 34.8, 31.7, 23.9 (q, *J* = 36.8 Hz), 19.5 (q, *J* = 2.7 Hz), 11.1 (q, *J* = 2.6 Hz)

¹⁹F NMR (CDCl₃, 282 MHz): -66.7 (d, *J* = 7.1 Hz)

m/z = no mass-ion by LC/MS or HRMS

Calculated physicochemical characteristics for compound **9b**:

cLog P: 4.86 ± 0.40

Freely rotatable bonds: 2

H-bond acceptors: 0

H-bond donors: 0

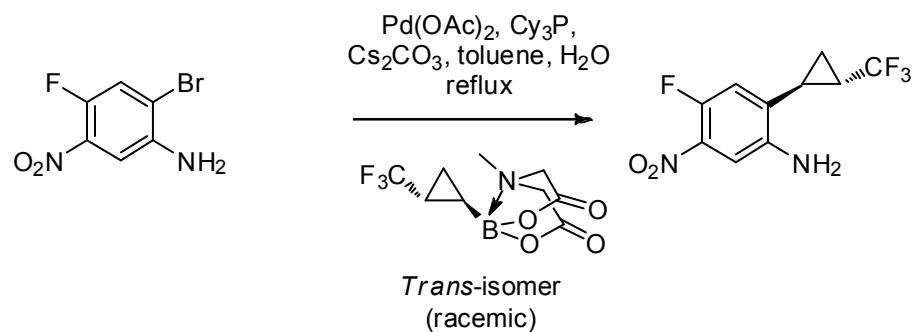
Sum H-bond donors + acceptors: 0

Molecular weight: 242.28

Polar surface area: 0.0 Å²

PREPARATION OF *TRANS*-4-FLUORO-5-NITRO-2-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-ANILINE

9C



A mixture of 2-bromo-4-fluoro-5-nitroaniline (see US2012012619) **8c** (353 mg, 1.5 mmol), *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (477 mg, 1.8 mmol), Pd(OAc)₂ (51 mg, 0.23 mmol), Cy₃P (126 mg, 0.45 mmol) and Cs₂CO₃ (2.93 g, 9.0 mmol) in toluene (5 mL) and H₂O (1.5 mL) was de-gassed with N₂ for 15 minutes, then placed under a nitrogen atmosphere and heated to reflux for 3hr. The temperature of the mixture was reduced to 100 °C (block temperature) and the mixture stirred overnight. After completion of the reaction, the mixture was cooled and EtOAc (100 mL) and H₂O (100 mL) were added. The mixture was filtered through celite and the filter cake washed with H₂O (50 mL) and EtOAc (50 mL). The aqueous and organic layers of the filtrate were partitioned, and the aqueous layer was extracted with EtOAc (1 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried (MgSO₄), filtered and the solvent removed under vacuum to leave a crude residue. The residue was dry-loaded on to silica gel and purified by column chromatography on silica gel using EtOAc / hexane (2:8 to 3:7) as eluent to give the product (214 mg, 54%).

¹H NMR (300MHz, *d*₆-DMSO): δ 7.32 (dd, *J* = 6.8, 2.3 Hz, 1H), 7.03 (dd, *J* = 12.6, 2.0 Hz, 1H), 5.60 (br. s, 2H), 2.49-2.41 (m, 1H), 2.36-2.29 (m, 1H), 1.42-1.35 (m, 1H), 1.16-1.11 (m, 1H)

¹⁹F NMR (282MHz, *d*₆-DMSO): δ -135.7 (dd, *J* = 6.9, 6.8 Hz), -64.8 (d, *J* = 7.0 Hz)
m/z = 265.87 (M+H)⁺; *m/z* = 263.00 (M-H)⁺.

Note: Procedure originally part of US2012012619

Calculated physicochemical characteristics for compound **9c**:

clog P: 1.38 ± 0.48

Freely rotatable bonds: 3

H-bond acceptors: 4

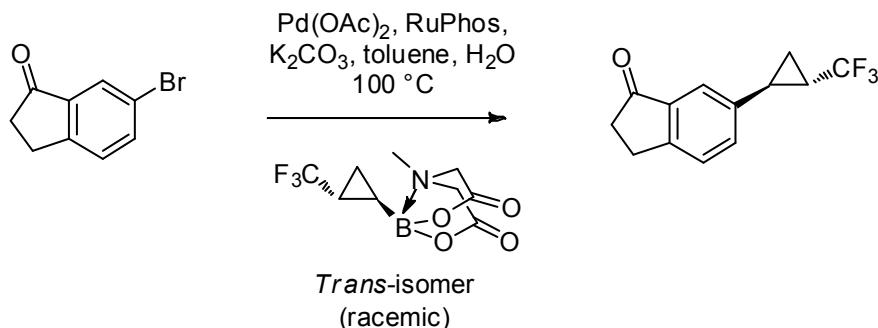
H-bond donors: 2

Sum H-bond donors + acceptors: 6

Molecular weight: 264.18

Polar surface area: 71.8 \AA^2

PREPARATION OF *TRANS* -6-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-2,3-DIHYDRO-1H-INDEN-1-ONE **9D**



In an open ChemGlass vial with pressure-release top, a stirred mixture of 6-bromo-1-indanone (Aldrich) **8d** (53 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (3 prep. TLC plates used) using EtOAc / hexane (1:4) as eluent to give the product (53.8 mg, 90%) as an oil.

^1H NMR (CDCl_3 , 300MHz): δ 7.46 (s, 1H), 7.43 (m, 2H), 3.14-3.10 (m, 2H), 2.73-2.68 (m, 2H), 2.45-2.38 (m, 1H), 1.87-1.76 (m, 1H), 1.45-1.38 (m, 1H), 1.25-1.18 (m, 1H)

^{13}C NMR (CDCl_3 , 75MHz): δ 207.0, 154.1, 139.0, 137.8, 134.2, 127.8 (q, $J = 271$ Hz), 127.2, 121.0, 36.9, 25.8, 23.7 (q, $J = 36.8$ Hz), 19.5 (q, $J = 2.7$ Hz), 11.1 (q, $J = 2.6$ Hz)

^{19}F NMR (CDCl_3 , 282 MHz): -66.9 (d, $J = 5.9$ Hz)

$m/z = 282.05 [\text{M}+\text{MeCN}+\text{H}]^+$

HRMS (EI): $[M+MeCN+H]^+$ calc'd for $C_{13}H_{11}F_3O+MeCN$ m/z 282.1106, found 282.1100.

Calculated physicochemical characteristics for compound **9d**:

clog P: 1.91 ± 0.47

Freely rotatable bonds: 1

H-bond acceptors: 1

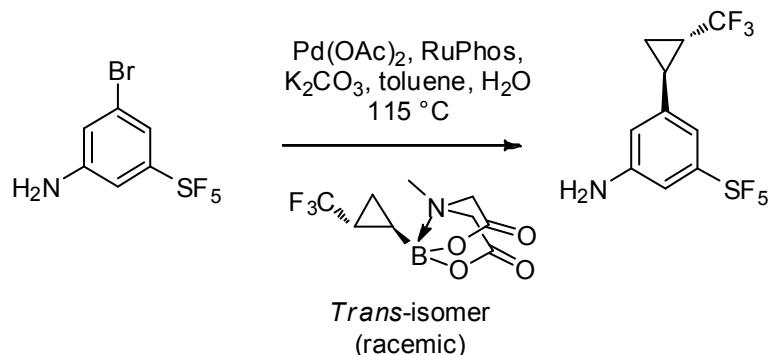
H-bond donors: 0

Sum H-bond donors + acceptors: 1

Molecular weight: 240.22

Polar surface area: 17.1 \AA^2

PREPARATION OF *TRANS*-3-(TRIFLUOROMETHYL)CYCLOPROPYL-5-(PENTAFLUOROSULFUR)ANILINE **9E**



In an open sealed tube, a stirred mixture of 3-bromo-5-(pentafluorosulfur)aniline (JRD Fluorochemicals Ltd.) **8e** (75 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 115°C and stirred overnight. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (4 prep. TLC plates used) using EtOAc / hexane (1:4) as eluent to give the product (62.4 mg, 76%) as a solid.

1H NMR ($CDCl_3$, 300MHz): δ 6.91 (t, J = 2.0 Hz, 1H), 6.85 (t, J = 1.7 Hz, 1H), 6.54 (s, 1H), 3.87 (br. s, 2H), 2.35-2.28 (m, 1H), 1.87-1.74 (m, 1H), 1.42-1.35 (m, 1H), 1.21-1.14 (m, 1H)

^{13}C NMR ($CDCl_3$, 75MHz): δ 147.2, 141.3, 127.7 (q, J = 270 Hz), 116.0, 114.2 (t, J = 4.7 Hz), 111.2 (t, J = 4.7 Hz), 23.5 (q, J = 37.3 Hz), 19.9 (q, J = 2.7 Hz), 11.1 (q, J = 2.5 Hz)

^{19}F NMR ($CDCl_3$, 282 MHz): -66.9 (d, J = 7.1 Hz), -114.2 (m), -137.4 (s), -138.0 (s)

m/z = 369.00 ($M+MeCN+H$)⁺

HRMS (EI): $[M+MeCN+H]^+$ calc'd for $C_{10}H_9F_8NS+MeCN$ m/z 369.0672, found 369.0624.

Calculated physicochemical characteristics for compound **9e**:

clog P: 2.84 ± 1.09

Freely rotatable bonds: 3

H-bond acceptors: 1

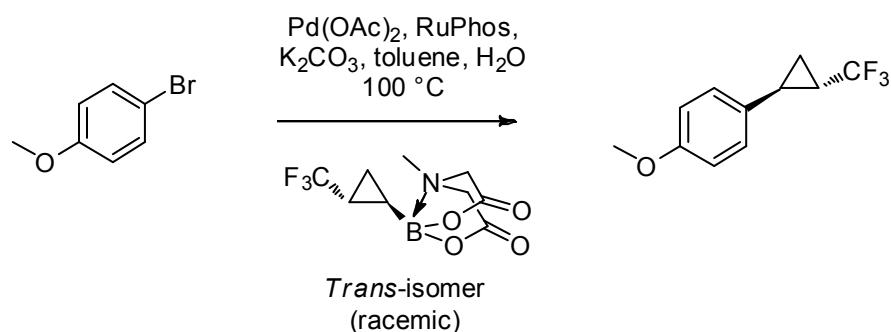
H-bond donors: 2

Sum H-bond donors + acceptors: 3

Molecular weight: 327.24

Polar surface area: 26.0 \AA^2

PREPARATION OF *TRANS*-1-METHOXY-4-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE **9F**



In an open ChemGlass vial with pressure-release top, a stirred mixture of 3-bromoanisole (Aldrich) **8f** (47 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (3 prep. TLC plates used) using EtOAc / hexane (1:4) as eluent to give the product (20.4 mg, 24% - yield adjusted for purity) as an oil (*ca.* 60% pure contaminated with starting material).

^1H NMR (CDCl_3 , 300MHz): δ 7.08 (m, 2H), 6.81 (m, 2H), 3.79 (s, 3H), 2.35-2.28 (m, 1H), 1.76-1.66 (m, 1H), 1.35-1.26 (m, 1H), 1.15-1.07 (m, 1H)

^{19}F NMR (CDCl_3 , 282 MHz): -66.7 (d, $J = 7.1$ Hz)

m/z = no mass-ion by LC/MS

Data in accordance with LeMaux, P.; Juillard, S.; Simonneaux, G. Asymmetric synthesis of (trifluoromethyl)phenylcyclopropanes catalysed by chiral metalloporphyrins. *Synthesis* **2006**, 1701-1704 and Morandi, B.; Carreira, E. M. Iron-catalysed cyclopropanation with trifluoroethylamine

hydrochloride and olefins in aqueous media: in-situ generation of trifluoro diazomethane. *Angew. Chem. Int. Ed.* **2010**, *49*, 938-941 (see references 12(a) and 13 in manuscript)

After review of this manuscript, another series of reactions on the above substrate were performed.

Reaction under the above conditions, but using 3-bromoanisole (94 mg, 0.5 mmol), palladium(II) acetate (11 mg, 0.05 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (46 mg, 0.1 mmol), K_2CO_3 (276 mg, 2.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (198 mg, 0.75 mmol) in toluene (6 mL) and H_2O (1 mL) and heating the reaction to 100 °C and stirring overnight (instead of 6 hours as above), gave the pure product (63.4 mg, 58%) after column chromatography on silica gel (40g CombiFlash Gold column) [note: after workup the mixture was dry-loaded on to silica gel (1g). Hexane / EtOAc (1:0 to 9:1) was used as eluent for the column]. Data for the pure product is shown on pages S89-S92.

1H NMR ($CDCl_3$, 300MHz): δ 7.08 (m, 2H), 6.86 (m, 2H), 3.80 (s, 3H), 2.36-2.30 (m, 1H), 1.78-1.68 (m, 1H), 1.36-1.27 (m, 1H), 1.15-1.08 (m, 1H)

^{19}F NMR ($CDCl_3$, 282 MHz): -66.7 (d, J = 6.8 Hz)

^{13}C NMR ($CDCl_3$, 75MHz): δ 158.7, 131.1, 128.0 (q, J = 269 Hz), 127.9, 114.2, 55.4, 22.5 (q, J = 37 Hz), 19.0 (q, J = 2.7 Hz), 10.6 (q, J = 2.7 Hz)

m/z = no mass-ion by LC/MS

In addition to pure product, an unidentified minor by-product was also isolated from the column as a mixture with the product (elutes before pure product).

Reaction with the original conditions above, but heating at 85 °C for 6 hours (instead of 100 °C) gave mainly starting material, and a little product (impure) after column chromatography.

Reaction using Pd(OAc)₂ and Cy₃P as ligand in toluene and water at 110 °C overnight (Condition A from Table 2 in the manuscript) gave a very small quantity of bi-aryl product (homo-coupling). No other product was isolated from the column.

Calculated physicochemical characteristics for compound **9f**:

clog P: 2.91 ± 0.39

Freely rotatable bonds: 2

H-bond acceptors: 1

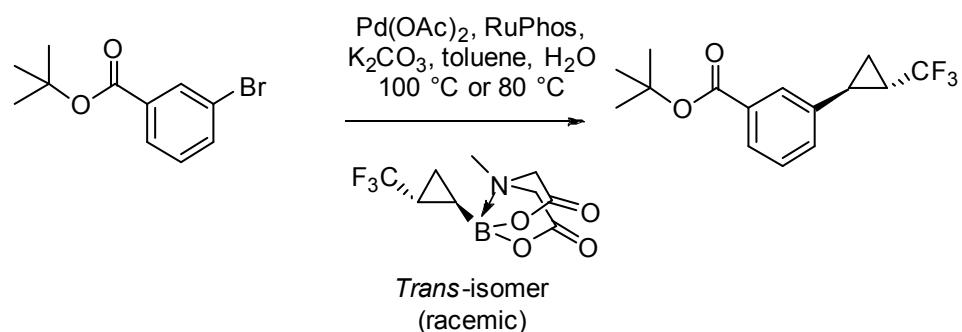
H-bond donors: 0

Sum H-bond donors + acceptors: 1

Molecular weight: 216.20

Polar surface area: 9.2 Å²

PREPARATION OF *TRANS*-*TERT*-BUTYL 3-(TRIFLUOROMETHYL)CYCLOPROPYL BENZOATE **9G**



In an open ChemGlass vial with pressure-release top, a stirred mixture of 3-bromobenzoic acid *tert*-butyl ester (Combi-Blocks) **8g** (64 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (3 prep. TLC plates used) using EtOAc / hexane (1:4) as eluent to give the product (23.3 mg, 23% - yield adjusted for purity) as an oil. [note: product contaminated with by-product – approximately 70% pure by ^1H NMR].

A separate reaction was repeated on the above scale, but with heating at 80 °C overnight. Workup as above, then purification by column chromatography on silica gel using hexane / EtOAc (1:0 to 9:1) as eluent gave the desired compound (31.4 mg, 44%) as an oil and as pure material. Data for this pure material quoted below.

^1H NMR (CDCl_3 , 300MHz): δ 7.86-7.82 (m, 1H), 7.73-7.71 (m, 1H), 7.38-7.25 (m, 2H), 2.43-2.36 (m, 1H), 1.89-1.79 (m, 1H), 1.60 (s, 9H), 1.44-1.36 (m, 1H), 1.26-1.17 (m, 1H)

¹³C NMR (CDCl₃, 75MHz): δ 165.6, 139.4, 132.6, 130.9, 128.6, 128.0, 127.7 (q, J = 269 Hz), 127.3, 81.4, 28.3, 22.9 (q, J = 38 Hz), 19.5 (q, J = 2.8 Hz), 11.1 (q, J = 2.2 Hz)

¹⁹F NMR (CDCl₃, 282 MHz): -66.8 (d, J = 6.8 Hz)

m/z = 229.12 [M-^tBu-H]⁺

HRMS (EI): [M-^tBu-H]⁺ calc'd for C₁₁H₈F₃O₂ *m/z* 229.0432, found 229.0485.

HRMS (EI): [M-^tBu-H+MeCN]⁺ calc'd for C₁₂H₈F₃NO₂ *m/z* 271.0820, found 271.1668.

Calculated physicochemical characteristics for compound **2g**:

clog P: 4.01 ± 0.40

Freely rotatable bonds: 4

H-bond acceptors: 2

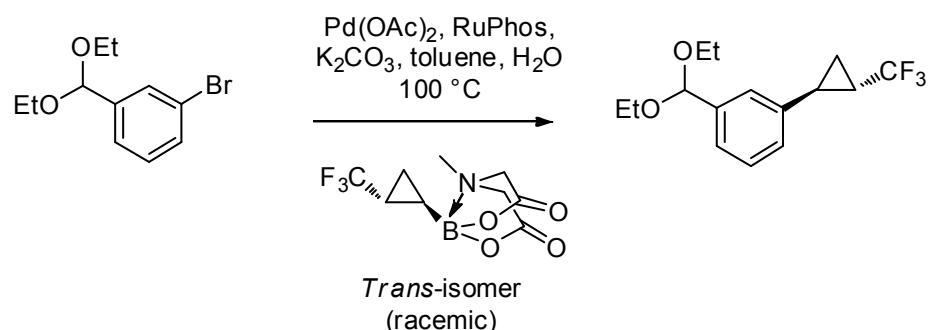
H-bond donors: 0

Sum H-bond donors + acceptors: 2

Molecular weight: 286.29

Polar surface area: 26.3 Å²

PREPARATION OF 1-(DIETHOXYMETHYL)-3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE 9H



In an open ChemGlass vial with pressure-release top, a stirred mixture of 3-bromobenzaldehyde diethylacetal (Aldrich) **8h** (65 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 100°C and stirred for 6 hours. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (3 prep. TLC plates used) using EtOAc / hexane (1:4) as eluent to give the product (58.6 mg, 69% - yield adjusted for 85% purity) as an oil.

Note: desired product is contaminated with the aldehyde version of the product after prep TLC – approximately 85% pure by ^1H NMR. If the yield is calculated on the basis of the isolated material containing a derivative of the desired product, then 58.6mg of an 85:15 mixture of desired product : aldehyde actually represents an 84% yield of the desired transformation occurring (*i.e.* arylbromide to aryl(trifluoromethyl)cyclopropyl).

¹H NMR (CDCl₃, 300MHz): δ 7.34-7.24 (m, 3H), 7.08 (dt, J = 7.1, 1.7 Hz, 1H), 5.46 (s, 1H), 3.67-3.48 (m, 4H), 2.40-2.34 (m, 1H), 1.88-1.75 (m, 1H), 1.40-1.31 (m, 1H), 1.24 (t, J = 7.1 Hz, 6H), 1.20-1.14 (m, 1H)

¹⁹F NMR (CDCl₃, 282 MHz): -66.8 (d, J = 6.8 Hz)

m/z = no mass-ion by LC/MS or HRMS

Calculated physicochemical characteristics for **9h**:

clog P: 2.73 ± 0.52

Freely rotatable bonds: 6

H-bond acceptors: 2

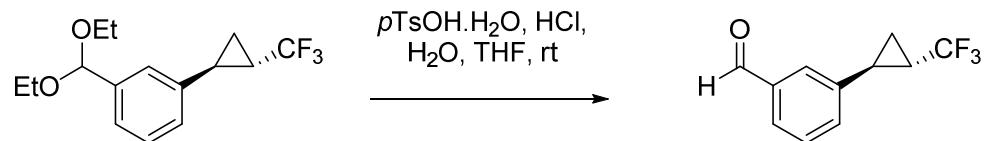
H-bond donors: 0

Sum H-bond donors + acceptors: 2

Molecular weight: 288.31

Polar surface area: 18.5 Å²

PREPARATION OF *TRANS* -3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZALDEHYDE **9h(2) FROM 1-(DIETHOXYMETHYL)-3-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZENE **9h****



The aldehyde product **9h(2)** could be synthesized from diethyl acetal **9h** (from Suzuki coupling above: contains a small portion of aldehyde product already) by reaction with pTsOH.H₂O and HCl(aq) in THF. LC/MS indicates no change in retention time, so mixture left for 1 week. The mixture was worked-up by adding EtOAc (20 mL) and saturated NaHCO₃ (20 mL). The aqueous and organic layers were partitioned and the aqueous layer extracted with EtOAc (20 mL). The combined organic extracts were

dried (Na_2SO_4), filtered and the solvent removed under vacuum to leave a crude residue. The residue was dry-loaded on to silica gel and purified by column chromatography on silica gel using hexane / EtOAc (1:0 to 9:1) as eluent to give *trans*-3-(2-(trifluoromethyl)cyclopropyl)benzaldehyde as an oil.

^1H NMR (CDCl_3 , 300MHz): δ 10.00 (s, 1H), 7.75 (dt, J = 7.5, 1.5 Hz, 1H), 7.64-7.62 (m, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.44 (dt, J = 8.2, 1.7 Hz, 1H), 2.48-2.41 (m, 1H), 1.94-1.81 (m, 1H), 1.49-1.42 (m, 1H), 1.29-1.21 (m, 1H)

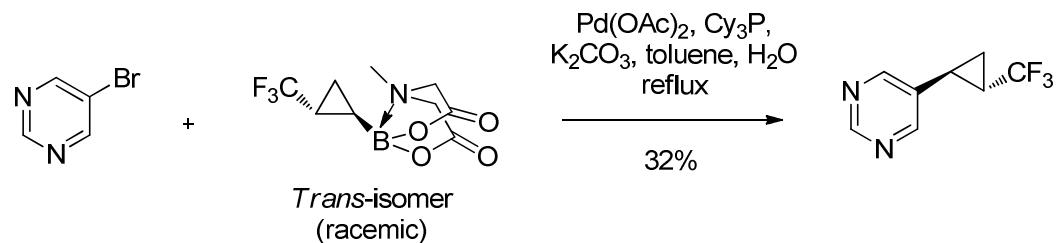
^{13}C NMR (CDCl_3 , 75MHz): δ 192.1, 140.4, 136.9, 133.1, 129.5, 128.9, 127.6 (J = 269 Hz), 126.9, 23.6 (J = 37 Hz), 19.4 (J = 2.6 Hz), 11.4 (J = 2.6 Hz)

^{19}F NMR (CDCl_3 , 282 MHz): -66.9 (d, J = 6.6 Hz)

m/z = 256.21 [M+H+MeCN]+

HRMS (EI): [M+H+MeCN]⁺ calc'd for $\text{C}_{13}\text{H}_{12}\text{F}_3\text{NO}$ m/z 256.0949, found 256.0964.

PREPARATION OF *TRANS* -5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)PYRIMIDINE **9I**



A stirred mixture of 5-bromopyrimidine (Aldrich) **8i** (80 mg, 0.5 mmol), palladium(II) acetate (11 mg, 0.05 mmol), tricyclohexylphosphine (28 mg, 0.1 mmol), K_2CO_3 (276 mg, 2.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (146 mg, 0.55 mmol) in toluene (3 mL) and H_2O (1 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, heated to reflux and stirred overnight. After allowing to cool, the mixture was filtered through celite and the filter cake washed with EtOAc (3 x 10 mL). The filtrate was concentrated under vacuum and the residue purified by preparative thin-layer chromatography (4 prep. TLC plates used) using EtOAc / hexane (1:1) as eluent to give the product (30 mg, 32%) as a solid.

^1H NMR (CDCl_3 , 300MHz): δ 9.12 (s, 1H), 8.57 (s, 2H), 2.40-2.33 (m, 1H), 1.98-1.87 (m, 1H), 1.57-1.50 (m, 1H), 1.32-1.25 (m, 1H)

^{13}C NMR (CDCl_3 , 75MHz): δ 157.7, 155.7, 132.8, 127.4 (q, $J = 269$ Hz), 23.1 (q, $J = 37.4$ Hz), 15.3 (q, $J = 2.9$ Hz), 10.6 (q, $J = 2.6$ Hz)

^{19}F NMR (CDCl_3 , 282 MHz): -67.2 (d, $J = 7.1$ Hz)

$m/z = 188.98 (\text{M}+\text{H})^+$

HRMS (EI): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_8\text{H}_7\text{F}_3\text{N}_2$ m/z 189.0640, found 189.0659.

Also obtained from the preparative thin-layer chromatography plates was an unidentified mixture of products (13 mg).

Calculated physicochemical characteristics for compound **9i**:

clog P: 0.42 ± 0.41

Freely rotatable bonds: 1

H-bond acceptors: 2

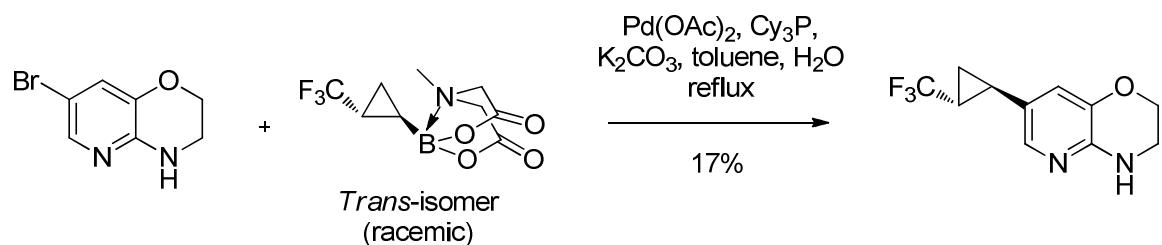
H-bond donors: 0

Sum H-bond donors + acceptors: 2

Molecular weight: 188.15

Polar surface area: 25.8 \AA^2

PREPARATION OF *TRANS*-7-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-3,4-DIHYDRO-2*H*-PYRIDO[3,2-*B*][1,4]OXAZINE 9J



In an open sealed tube, a stirred mixture of 7-bromo-3,4-dihydro-2-pyrido[3,2-*B*][1,4]oxazoline (Maybridge) **8i** (108 mg, 0.5 mmol), palladium(II) acetate (11 mg, 0.05 mmol), tricyclohexylphosphine (28 mg, 0.1 mmol), K_2CO_3 (276 mg, 2.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (159 mg, 0.6 mmol) in toluene (3 mL) and H_2O (1 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, heated to 115°C and stirred for 4 days. After allowing to cool, the mixture was filtered through celite and the filter cake washed with EtOAc (3 x 20 mL), H_2O (10 mL) and EtOAc (20 mL). The aqueous and organic layers of the filtrate were partitioned and the aqueous layer extracted with EtOAc (1 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent removed under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (4 prep. TLC plates used) using EtOAc as eluent to give the product (21 mg, 17%) as a solid.

^1H NMR (CDCl_3 , 300MHz): δ 7.54 (s, 1H), 6.70 (d, J = 1.6 Hz, 1H), 4.99 (br. s, 1H), 4.21 (dt, J = 4.4, 0.7 Hz, 2H), 3.53 (t, J = 4.4 Hz, 2H), 2.26-2.19 (m, 1H), 1.74-1.61 (m, 1H), 1.33-1.26 (m, 1H), 1.10-1.03 (m, 1H)

^{13}C NMR (CDCl_3 , 75MHz): δ 146.6, 139.8, 138.8, 128.0 (q, J = 269 Hz), 125.4, 120.7, 65.0, 40.8, 22.7 (q, J = 36.7 Hz), 17.0 (q, J = 2.8 Hz), 10.2 (q, J = 2.2 Hz)

^{19}F NMR (CDCl_3 , 282 MHz): -66.8 (d, J = 6.8 Hz)

m/z = 245.09 ($\text{M}+\text{H}$)⁺

HRMS (EI): $[M+H]^+$ calc'd for $C_{11}H_{11}F_3N_2O$ m/z 245.0902, found 245.0909.

Also obtained from the preparative thin-layer chromatography plates was recovered 7-bromo-3,4-dihydro-2-pyrido[3,2-*b*][1,4]oxazoline (18 mg, 17%) and reduced starting material, 3,4-dihydro-2-pyrido[3,2-*b*][1,4]oxazoline (9.4 mg, 14%).

Calculated physicochemical characteristics for compound **9i**:

clog P: 1.14 ± 0.61

Freely rotatable bonds: 1

H-bond acceptors: 3

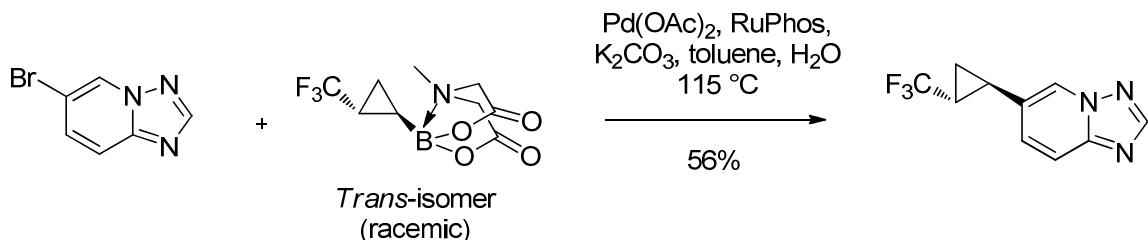
H-bond donors: 1

Sum H-bond donors + acceptors: 4

Molecular weight: 244.21

Polar surface area: 34.2 \AA^2

PREPARATION OF *TRANS*-6-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-[1,2,4]TRIAZOLE[1,5-*A*]PYRIDINE **9k**



In an open sealed tube, a stirred mixture of 6-bromo[1,2,4]triazolo[4,3-a]pyridine (Ark Pharm, Inc) **8k** (50 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (1.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, heated to 115°C and stirred overnight. After allowing to cool, the mixture was diluted with EtOAc (30 mL) and H_2O (30 mL), then filtered through celite and the filter cake washed with EtOAc (3 x 10 mL). The aqueous and organic layers of the filtrate were partitioned and the aqueous extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and the solvent concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (4 prep. TLC plates used) using CH_2Cl_2 / MeOH (95:5) as eluent to give the product (31.8 mg, 56%) as a solid.

^1H NMR (CDCl_3 , 300MHz): δ 8.82 (s, 1H), 8.08 (s, 1H), 7.76 (d, J = 9.5 Hz, 1H), 7.09 (dd, J = 9.5, 1.4 Hz, 1H), 2.43-2.36 (m, 1H), 1.95-1.82 (m, 1H), 1.51-1.44 (m, 1H), 1.30-1.22 (m, 1H)

^{13}C NMR (CDCl_3 , 75MHz): δ 149.1, 135.8, 127.5 (q, J = 269 Hz), 126.1, 121.3, 116.7, 22.5 (q, J = 37.3 Hz), 17.1 (q, J = 2.9 Hz), 9.9 (q, J = 2.5 Hz)

^{19}F NMR (CDCl_3 , 282 MHz): -66.9 (d, J = 6.2 Hz)

m/z = 228.01 ($\text{M}+\text{H}$)⁺

HRMS (EI): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{10}\text{H}_8\text{F}_3\text{N}_3$ m/z 228.0749, found 228.0721.

Calculated physicochemical characteristics for compound **9k**:

clog P: -0.25 ± 0.73

Freely rotatable bonds: 1

H-bond acceptors: 3

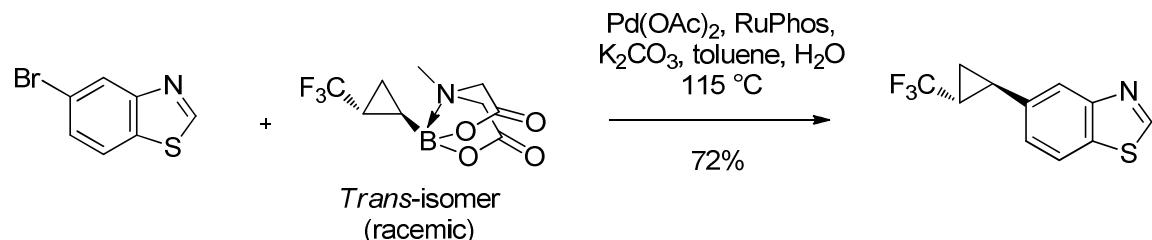
H-bond donors: 0

Sum H-bond donors + acceptors: 3

Molecular weight: 227.19

Polar surface area: 30.2 \AA^2

PREPARATION OF *TRANS* -5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)BENZO[D]THIAZOLE **9L**



In an open sealed tube, a stirred mixture of 5-bromobenzothiazole (Combi-Blocks, Inc.) **8I** (54 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 115°C and stirred overnight. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (4 prep. TLC plates used) using EtOAc / hexane (1:9) as eluent to give the product (43.7 mg, 72%) as an oil.

^1H NMR (CDCl_3 , 300MHz): δ 8.99 (s, 1H), 7.89-7.86 (m, 2H), 7.28-7.24 (m, 1H), 2.57-2.50 (m, 1H), 1.95-1.82 (m, 1H), 1.49-1.42 (m, 1H), 1.31-1.24 (m, 1H)

^{13}C NMR (CDCl_3 , 75MHz): δ 155.0, 154.0, 138.0, 132.4, 127.9 ($J = 269$ Hz), 125.2, 122.2, 121.4, 23.9 (q, $J = 36.8$ Hz), 19.9 (q, $J = 2.7$ Hz), 11.4 (q, $J = 2.6$ Hz)

^{19}F NMR (CDCl_3 , 282 MHz): -66.8 (d, $J = 6.8$ Hz)

$m/z = 243.98 (\text{M}+\text{H})^+$

HRMS (EI): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{11}\text{H}_8\text{F}_3\text{NS}$ m/z 244.0408, found 244.0406.

Calculated physicochemical characteristics for compound **9l**:

clog P: 2.34 ± 0.45

Freely rotatable bonds: 1

H-bond acceptors: 1

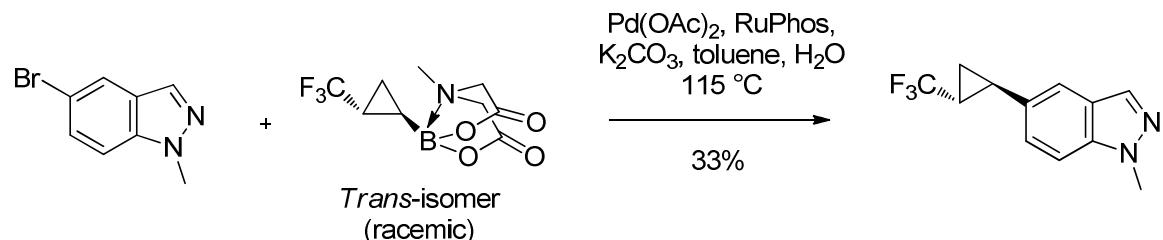
H-bond donors: 0

Sum H-bond donors + acceptors: 1

Molecular weight: 243.25

Polar surface area: 41.1 \AA^2

PREPARATION OF *TRANS*-1-METHYL-5-(2-(TRIFLUOROMETHYL)CYCLOPROPYL)-1*H*-INDAZOLE **9M**



In an open sealed tube, a stirred mixture of 5-bromo-1-methyl-1*H*-indazole (Combi-Blocks, Inc.) **8m** (53 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 115°C and stirred overnight. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (4 prep. TLC plates used) using EtOAc / hexane (2:8) as eluent to give the product (20 mg, 33%) as a solid.

^1H NMR (d_6 -DMSO, 300MHz): δ 7.94 (d, J = 0.8 Hz, 1H), 7.56-7.52 (m, 2H), 7.23 (dd, J = 8.7, 1.7 Hz, 1H), 4.00 (s, 3H), 2.51-2.46 (m, 1H), 2.29-2.17 (m, 1H), 1.37-1.24 (m, 2H)

^{13}C NMR (d_6 -DMSO, 75MHz): δ 139.7, 132.8, 131.8, 129.1 (q, J = 269 Hz), 126.1, 124.5, 118.2, 110.6, 36.3, 23.1 (q, J = 35.6 Hz), 20.1 (q, J = 2.7 Hz), 11.9 (q, J = 2.5 Hz)

^{19}F NMR (d_6 -DMSO, 282 MHz): -64.9 (d, J = 7.6 Hz)

m/z = 241.05 ($\text{M}+\text{H}$)⁺

HRMS (EI): $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{N}_2$ m/z 241.0953, found 241.0948.

Calculated physicochemical characteristics for compound **9m**:

clog P: 2.52 ± 0.83

Freely rotatable bonds: 1

H-bond acceptors: 2

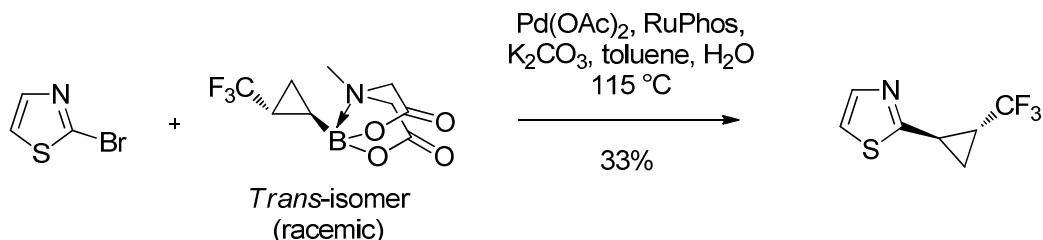
H-bond donors: 0

Sum H-bond donors + acceptors: 2

Molecular weight: 240.22

Polar surface area: 17.8 \AA^2

PREPARATION OF *TRANS* -2-(TRIFLUOROMETHYL)CYCLOPROPYLTHIAZOLE **9N**



In an open, sealed tube a stirred mixture of 2-bromothiazole (Aldrich) **8n** (41 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 115°C and stirred overnight. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue [Note: not completely concentrated as product is volatile]. The residue was purified by preparative thin-layer chromatography (4 prep. TLC plates used) using EtOAc / hexane (5:95) as eluent to give the product (23 mg, 33%; sample contains an equivalent mole of EtOAc – yield adjusted for EtOAc content).

Note: the ^1H and ^{13}C NMR contains *ca.* 1 mole equivalent of EtOAc – after NMRs were obtained, the sample was concentrated and placed on a high vacuum. However, the sample disappeared, indicating the product may be volatile.

^1H NMR (CDCl_3 , 300MHz): δ 7.65 (d, $J = 4.6$ Hz, 1H), 7.19 (d, $J = 4.6$ Hz, 1H), 2.76-2.67 (m, 1H), 2.39-2.26 (m, 1H), 1.57-1.47 (m, 2H)

^{13}C NMR (CDCl_3 , 75MHz): δ 171.5, 142.8, 127.3 (q, $J = 266$ Hz), 118.3, 24.7 (q, $J = 36.8$ Hz), 17.8 (q, $J = 2.7$ Hz), 13.1 (q, $J = 2.8$ Hz)

¹⁹F NMR (CDCl₃, 282 MHz): -67.2 (d, *J* = 5.9 Hz)

m/z = 234.99 (M+MeCN+H)⁺

HRMS (EI): [M+H]⁺ calc'd for C₇H₆F₃NS *m/z* 194.0251, found 194.0251.

Calculated physicochemical characteristics for compound **9n**:

clog P: 1.73 ± 0.40

Freely rotatable bonds: 1

H-bond acceptors: 1

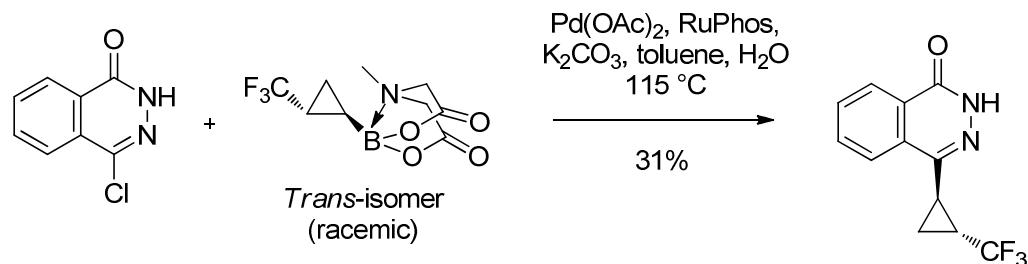
H-bond donors: 0

Sum H-bond donors + acceptors: 1

Molecular weight: 193.19

Polar surface area: 41.1 Å²

PREPARATION OF *TRANS* 4-(TRIFLUOROMETHYL)CYCLOPROPYLPHTHALAZIN-1(2*H*)-ONE **9O**



In an open, sealed tube a stirred mixture of 1-chloro-4-phthalazinone (Maybridge) **8O** (45 mg, 0.25 mmol), palladium(II) acetate (5.5 mg, 0.025 mmol), 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (23 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol) and *trans*-2-(trifluoromethyl)cyclopropylboronic acid MIDA ester (99 mg, 0.38 mmol) in toluene (2.5 mL) and H_2O (0.5 mL) was de-gassed with N_2 for 15 min, then the mixture placed under nitrogen, sealed and heated to 115°C and stirred overnight. After allowing to cool, the mixture was diluted with H_2O (15 mL) and EtOAc (20 mL), then 1N HCl was added until pH 6-7. The mixture was filtered through celite and the filter cake washed with EtOAc (2 x 20 mL). The filtrate was partitioned and the aqueous layer extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to leave a crude residue. The residue was purified by preparative thin-layer chromatography (4 prep. TLC plates used) using EtOAc / hexane (1:1) as eluent to give a mixture of the product and starting 1-chloro-4-phthalazinone (35 mg). The mixture was separated by high-performance liquid chromatography to give the product (20 mg, 31%) as a solid.

^1H NMR (d_6 -DMSO, 300MHz): δ 12.54 (br. s, 1H), 8.26 (d, $J = 7.9$ Hz, 1H), 8.17 (d, $J = 7.7$ Hz, 1H), 8.00 (t, $J = 7.6$ Hz, 1H), 7.86 (t, $J = 7.6$ Hz, 1H), 2.95-2.88 (m, 1H), 2.42-2.28 (m, 1H), 1.45-1.37 (m, 2H)

^{13}C NMR (d_6 -DMSO, 75MHz): δ 160.3, 143.3, 134.6, 132.7, 131.5, 129.0 (q, $J = 270$ Hz), 128.3, 126.9, 125.7, 20.9 (q, $J = 36.0$ Hz), 16.5 (q, $J = 2.8$ Hz), 9.6 (q, $J = 2.4$ Hz)

^{19}F NMR (d_6 -DMSO, 282 MHz): -64.8 (d, $J = 7.6$ Hz)

m/z = 255.02 (M+H)⁺; 253.05 (M-H)⁺

HRMS (EI): [M+H]⁺ calc'd for C₁₂H₉F₃NO *m/z* 255.0745, found 255.0744.

Calculated physicochemical characteristics for compound **9o**:

clog P: 1.69 ± 0.50

Freely rotatable bonds: 1

H-bond acceptors: 3

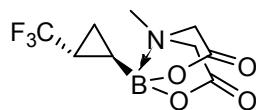
H-bond donors: 1

Sum H-bond donors + acceptors: 4

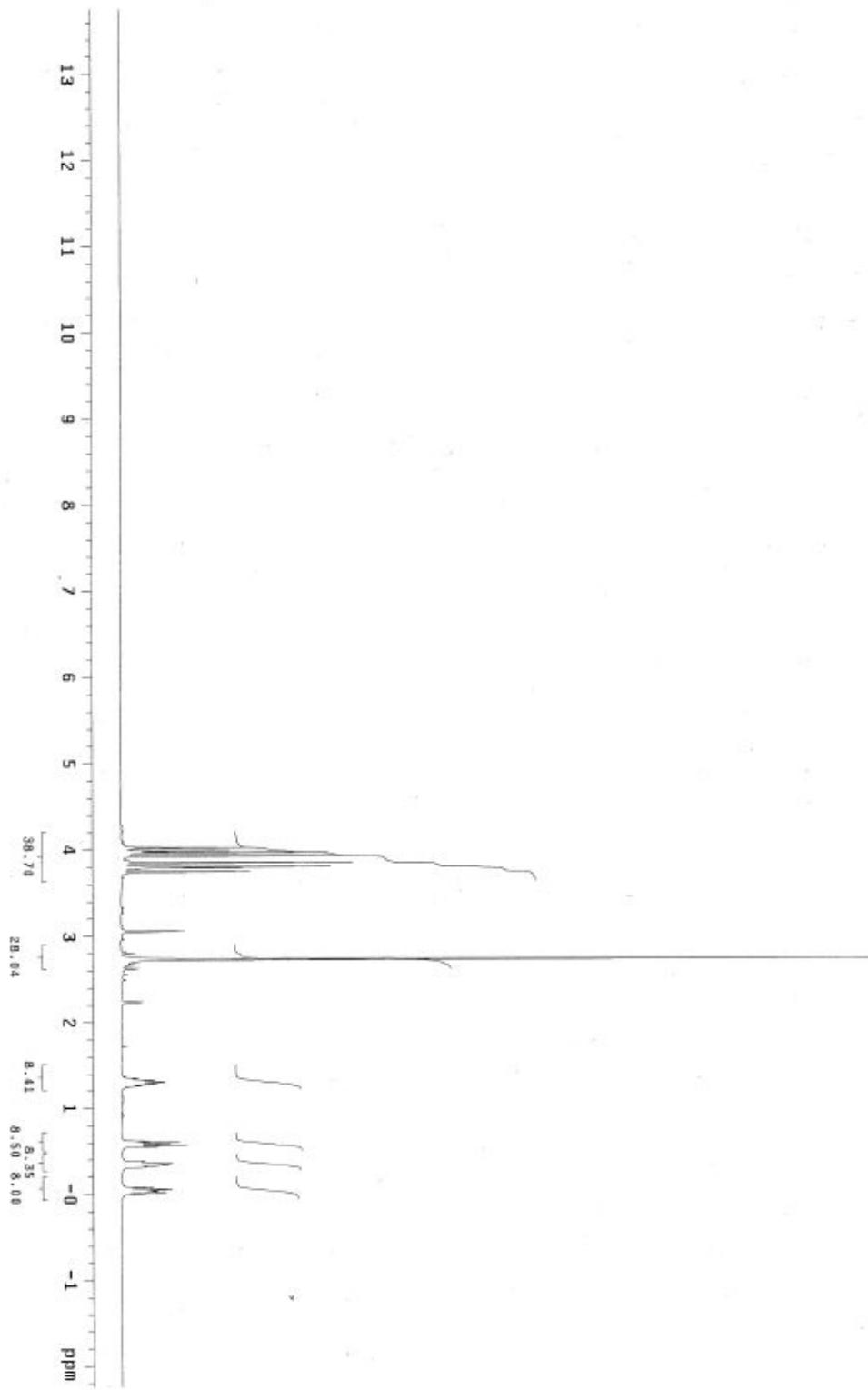
Molecular weight: 254.21

Polar surface area: 41.5 Å²

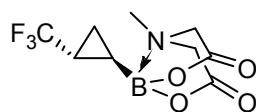
¹H NMR DATA FOR COMPOUND 5



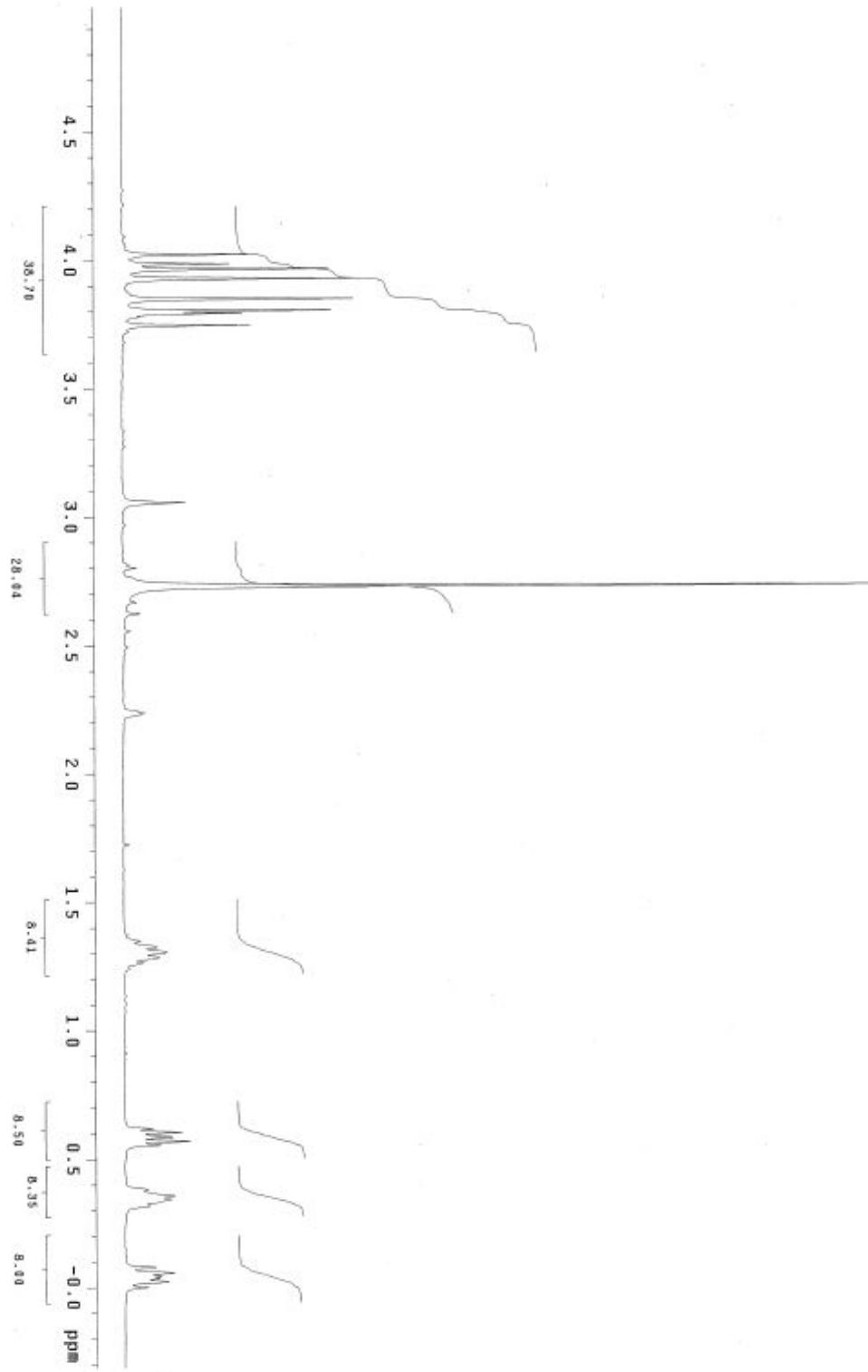
5 *Trans*-isomer
(racemic)



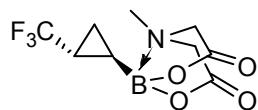
¹H NMR DATA FOR COMPOUND **5 (EXPANSION)**



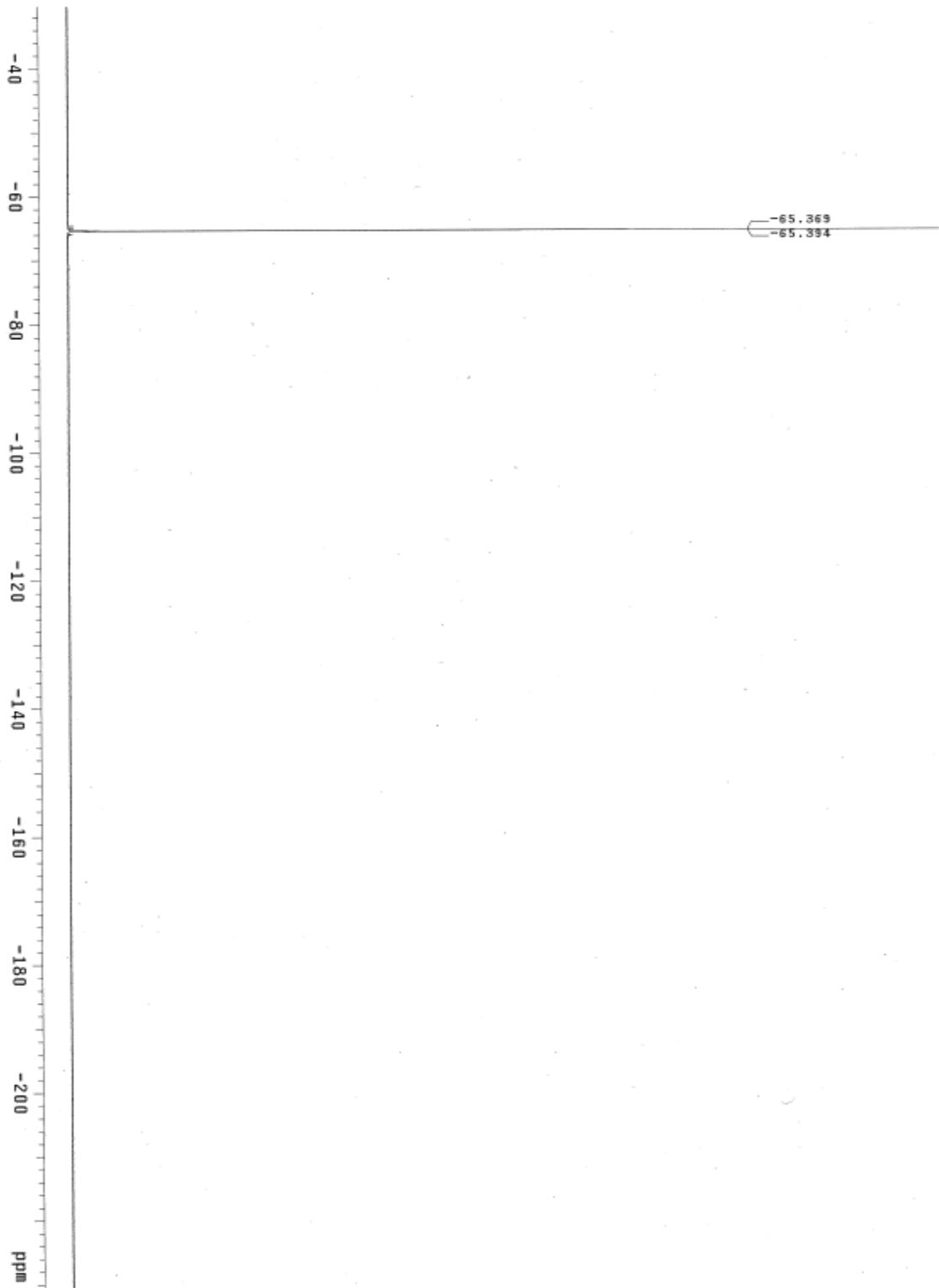
5 Trans-isomer
(racemic)



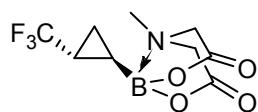
¹⁹F NMR DATA FOR COMPOUND 5



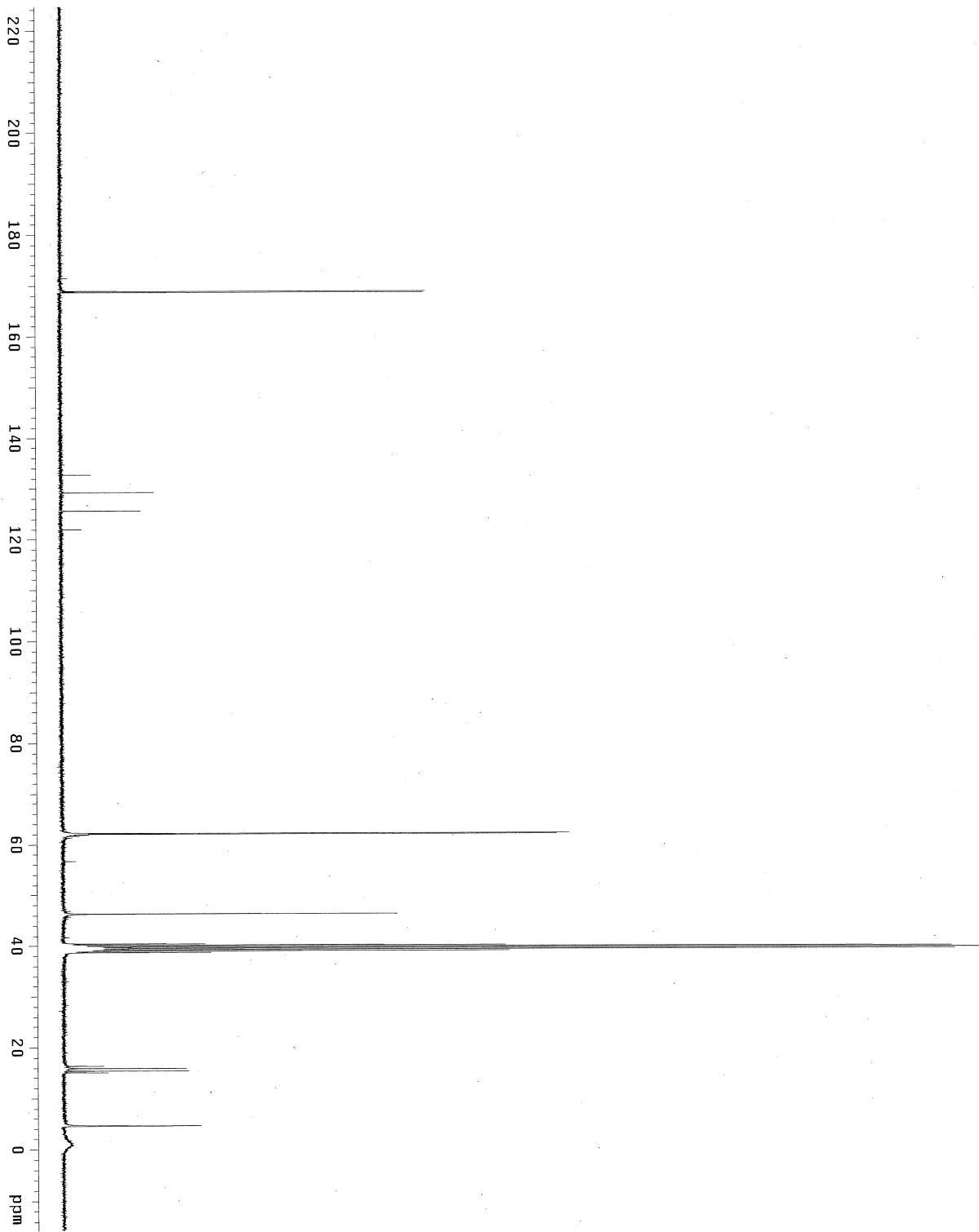
5 Trans-isomer
(racemic)



¹³C NMR DATA FOR COMPOUND 5



5 Trans-isomer
(racemic)



LC DATA FOR COMPOUND 7

Openlynx Report -Yoyo

Sample: 1
File:MD1662-138D
Description:10min

Vial:1:H,5
Date:18-Nov-2011

ID:
Time:13:39:55

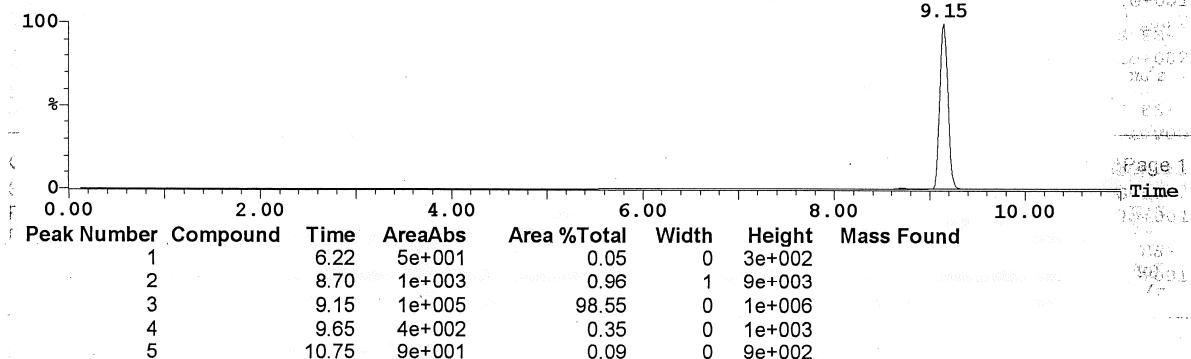
Page 1

Printed: Fri Nov 18 13:52:36 2011

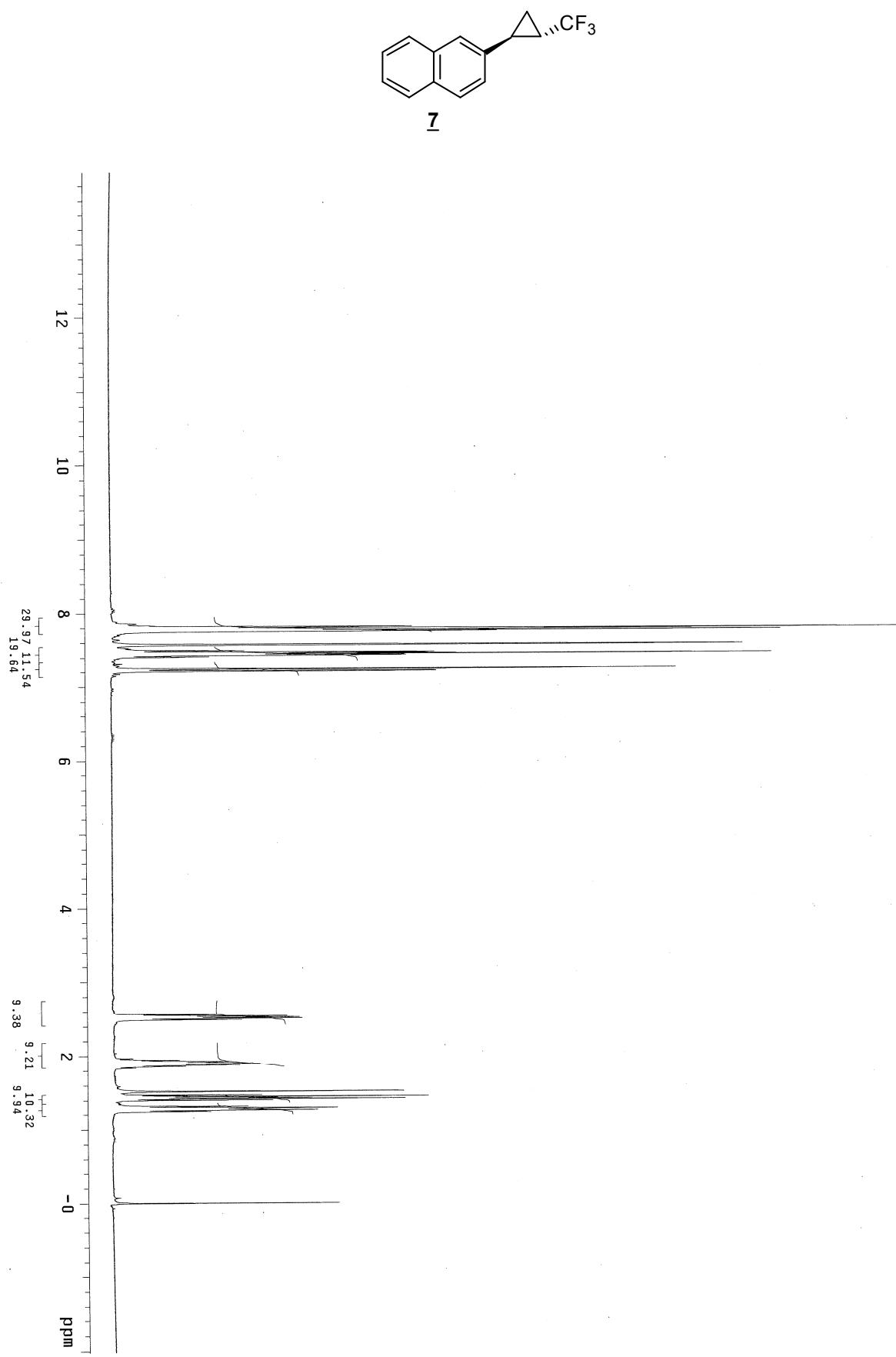
Sample Report:

Sample 1 Vial 1:H,5 ID File MD1662-138D Date 18-Nov-2011 Time 13:39:55 Description 10min

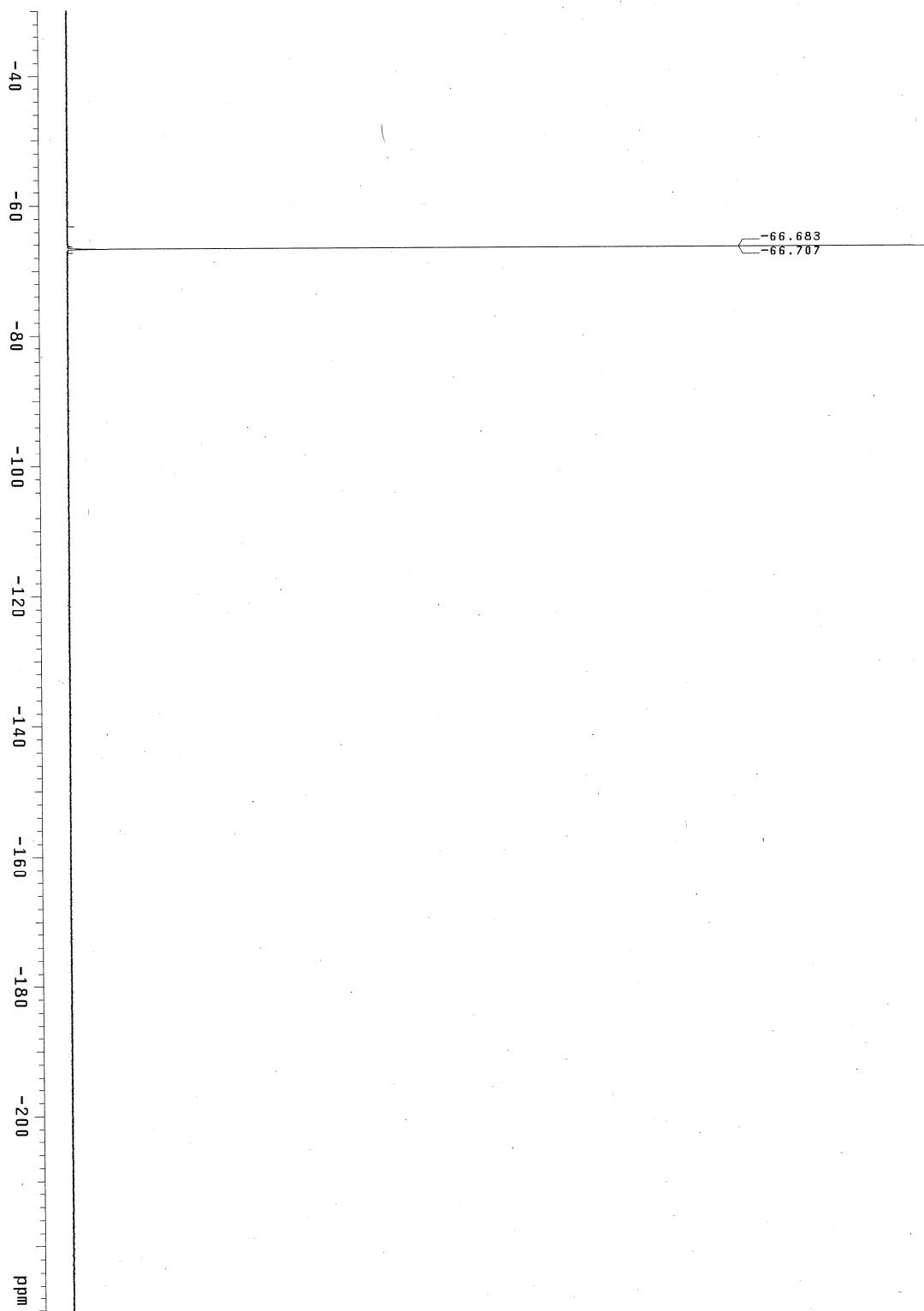
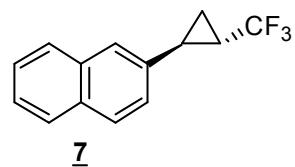
DAD: 254 Smooth (Mn, 1x2)



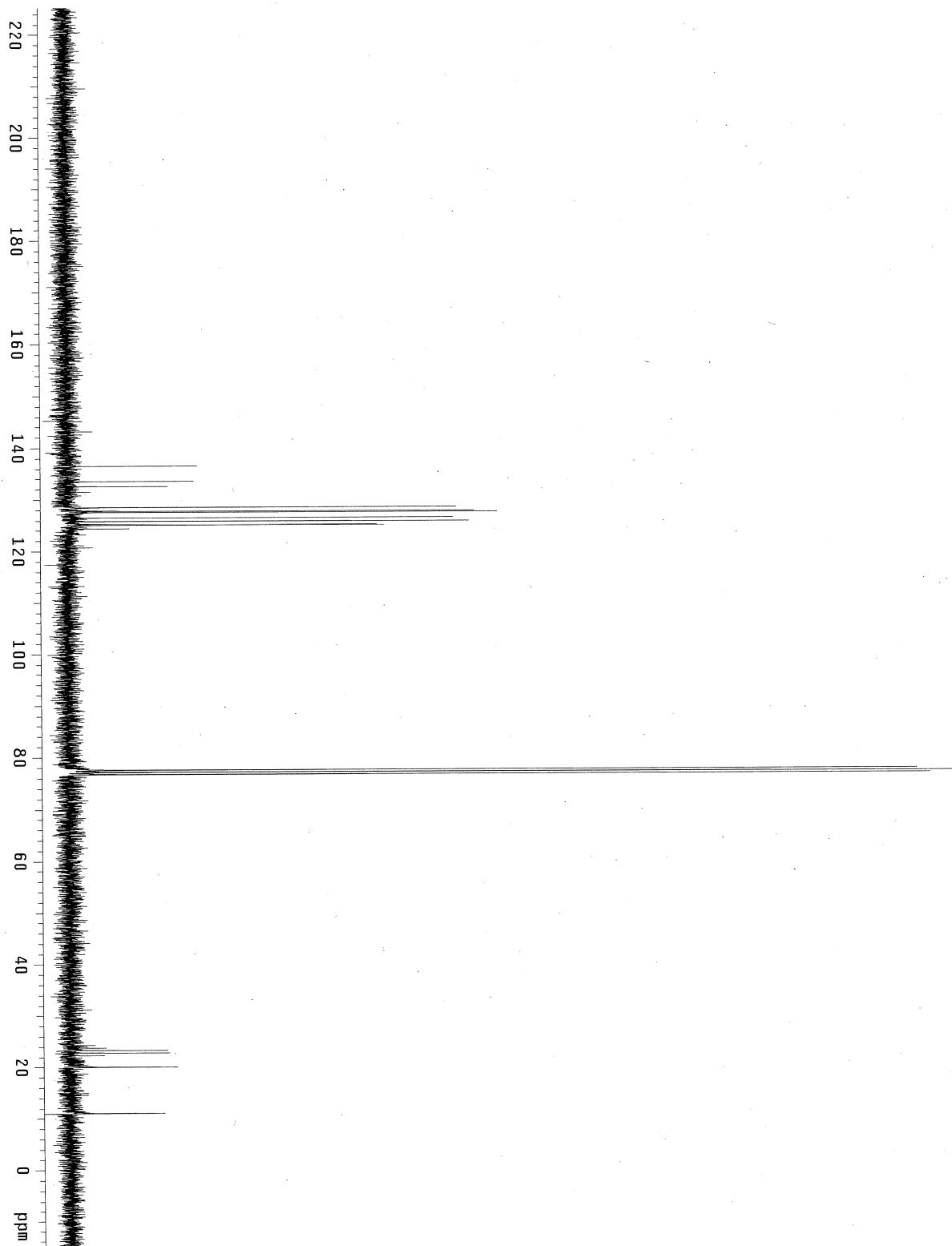
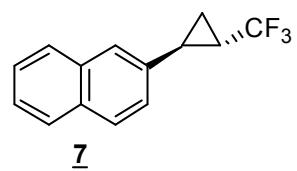
¹H NMR DATA FOR COMPOUND 7



¹⁹F NMR DATA FOR COMPOUND 7



¹³C NMR DATA FOR COMPOUND 7



LC DATA FOR COMPOUND 9A

Openlynx Report -Yoyo

Sample: 1
File:MD1569-084
Description:10min

Vial:1:E,11
Date:06-Oct-2010

ID:
Time:17:56:18

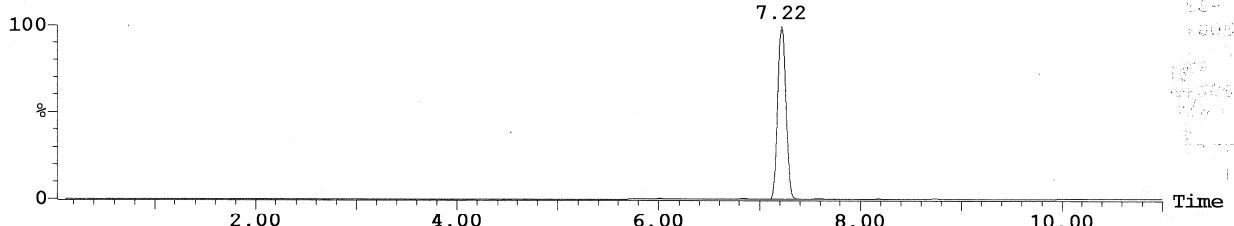
Page 1

Printed: Wed Oct 06 18:08:52 2010

Sample Report:

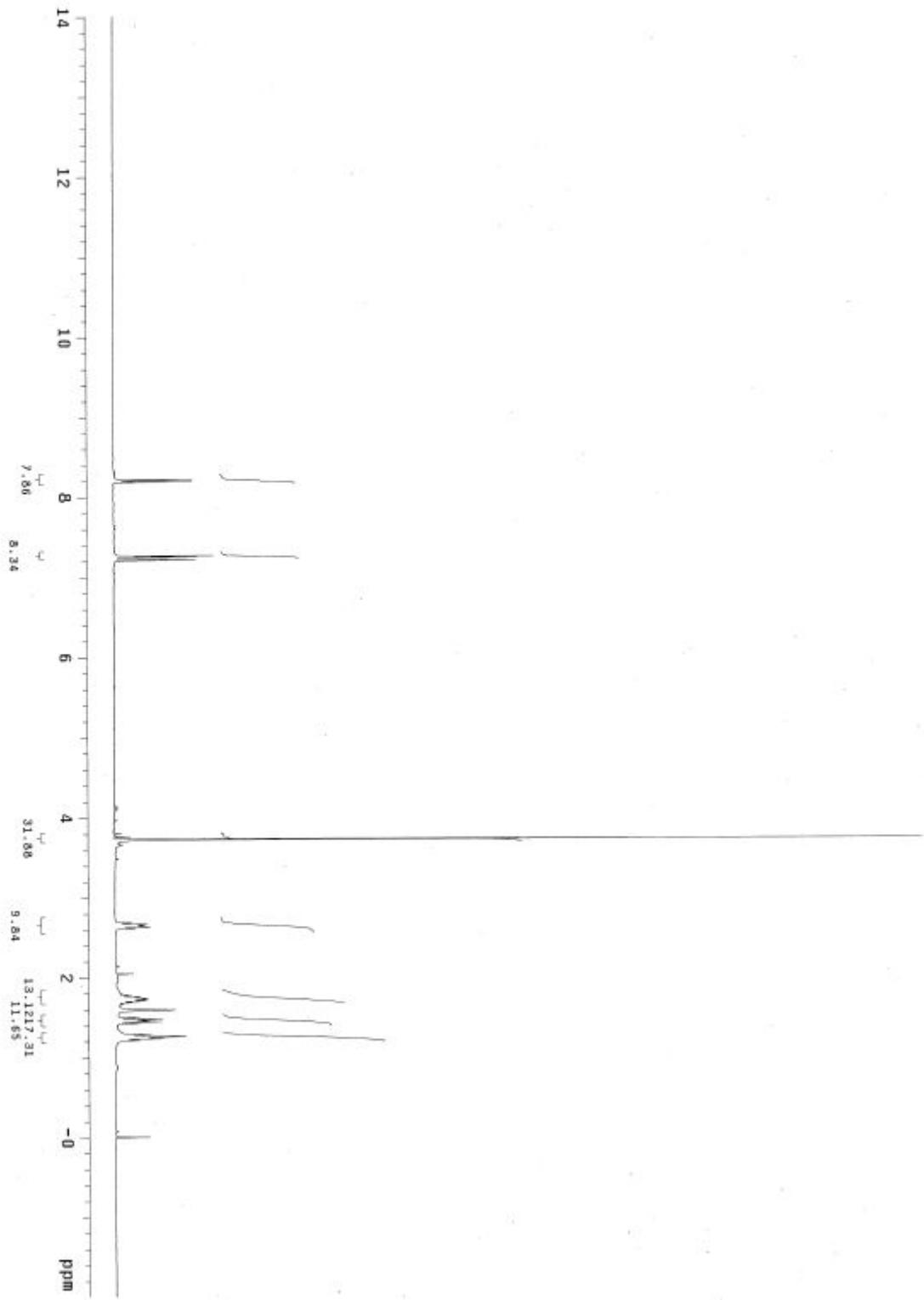
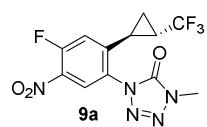
Sample 1 Vial 1:E,11 ID File MD1569-084 Date 06-Oct-2010 Time 17:56:18 Description 10min

DAD: 254 Smooth (Mn, 1x2)

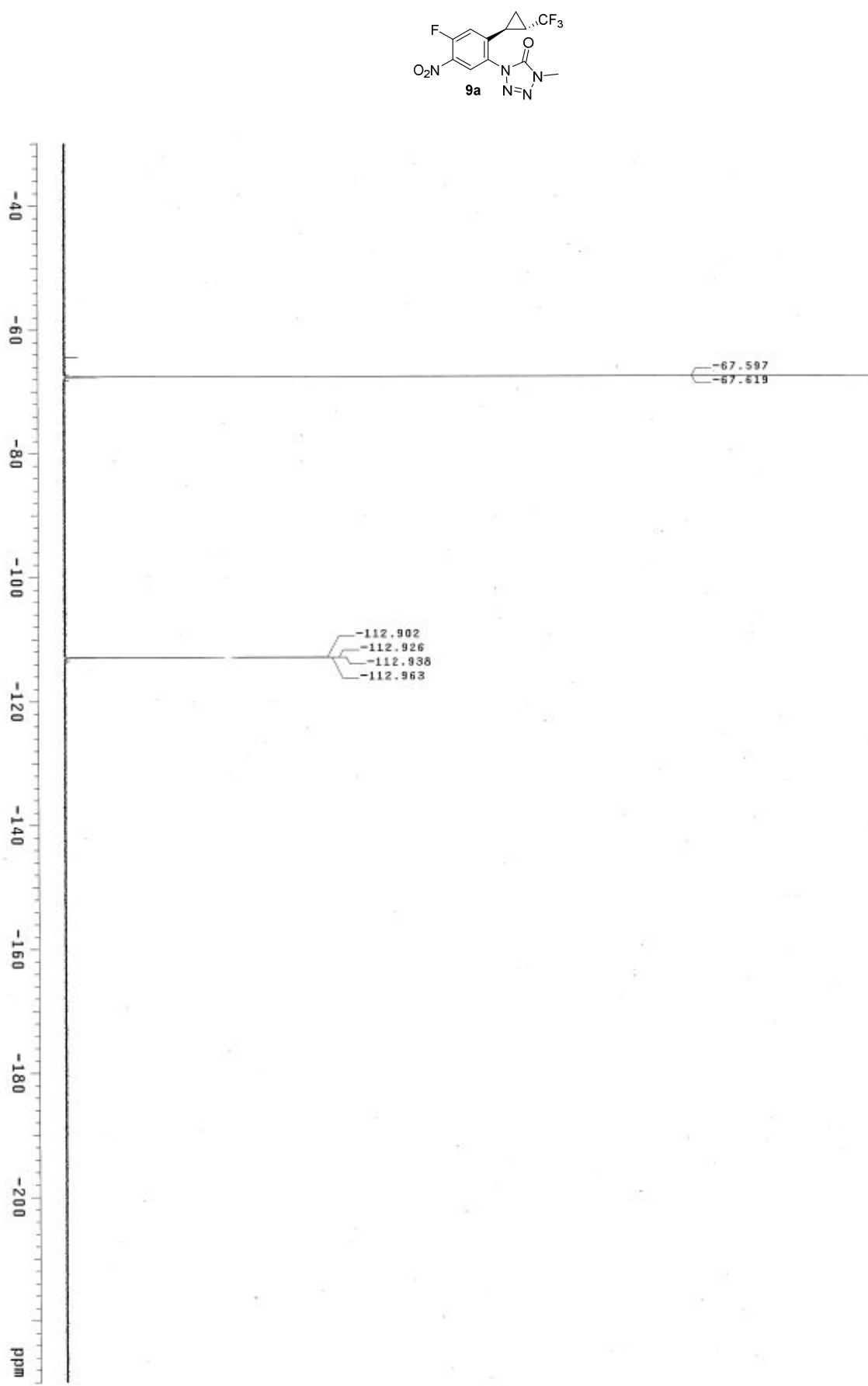


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
3		6.02	6e+002	0.45	0	5e+003	
5		6.84	8e+002	0.61	0	8e+003	
9		7.22	1e+005	97.99	0	1e+006	
10		7.59	3e+002	0.26	0	3e+003	
13		8.19	3e+002	0.20	0	2e+003	

¹H NMR DATA FOR COMPOUND 9A



¹⁹F NMR DATA FOR COMPOUND 9A



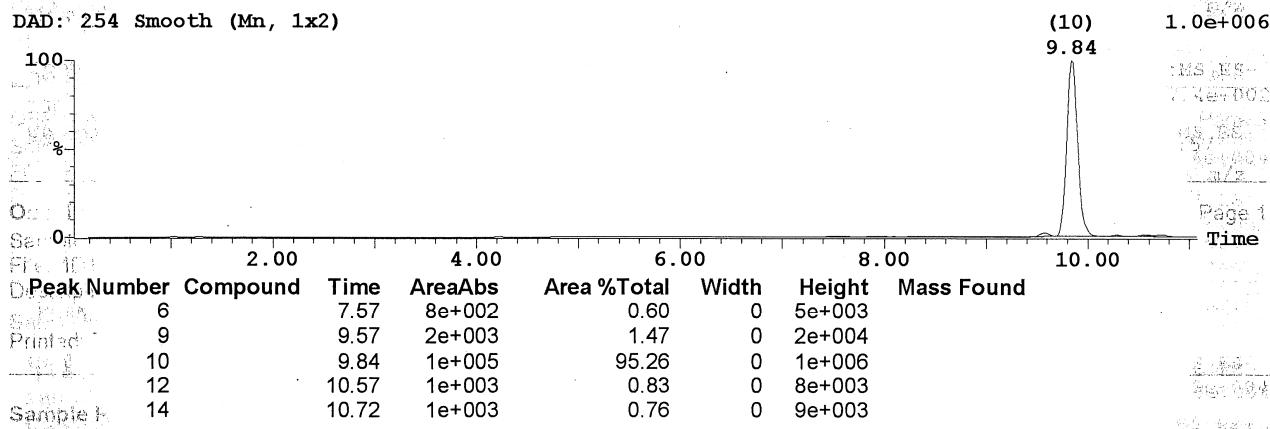
LC DATA FOR COMPOUND 9B

Openlynx Report -Yoyo
Sample: 1 Vial:2:F,2 ID:
File:MD1662-127B Date:04-Apr-2013 Time:17:59:03
Description:10min
Printed: Thu Apr 04 18:11:49 2013

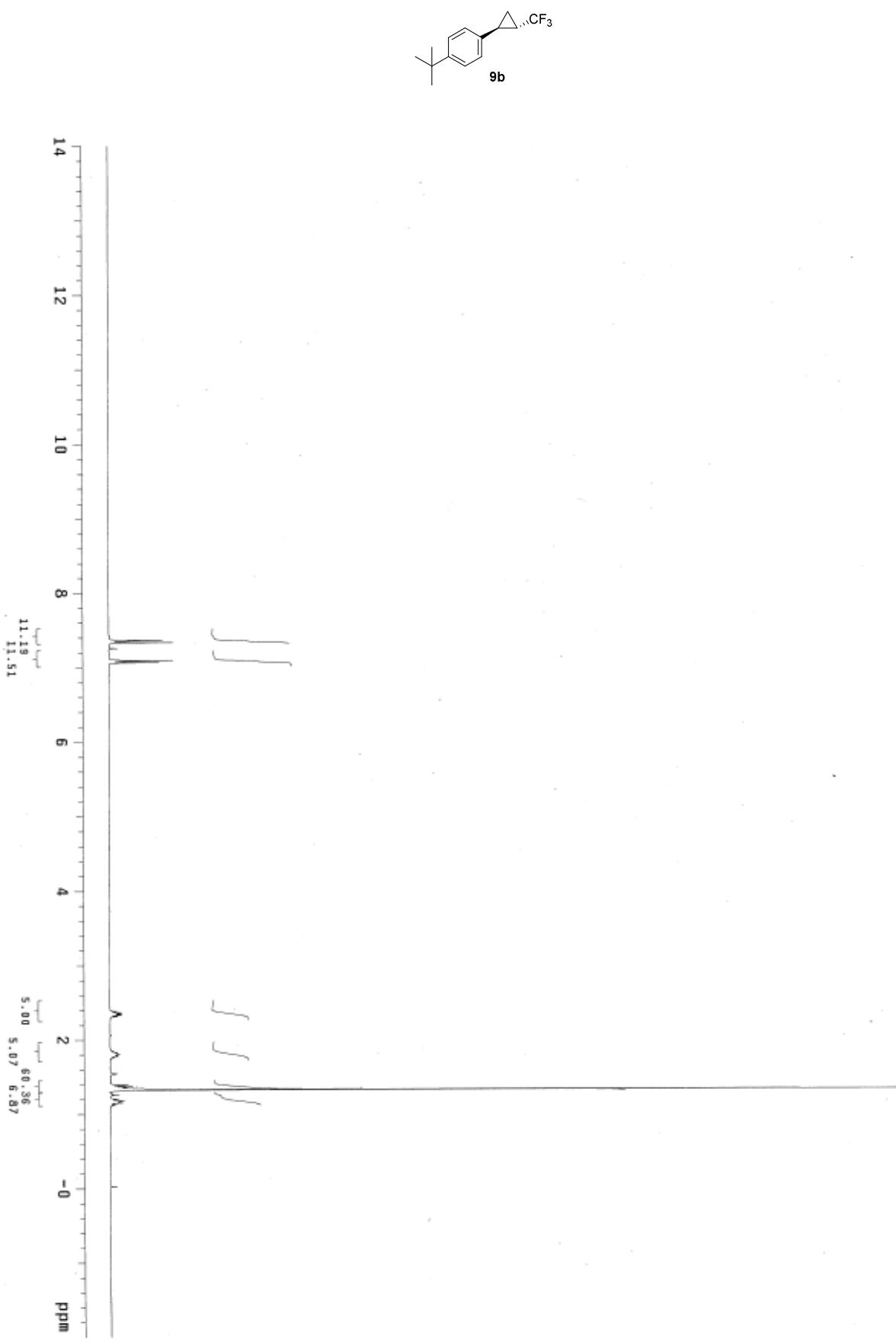
Sample Report:

Sample 1 Vial 2:F,2 ID File MD1662-127B Date 04-Apr-2013 Time 17:59:03 Description 10min

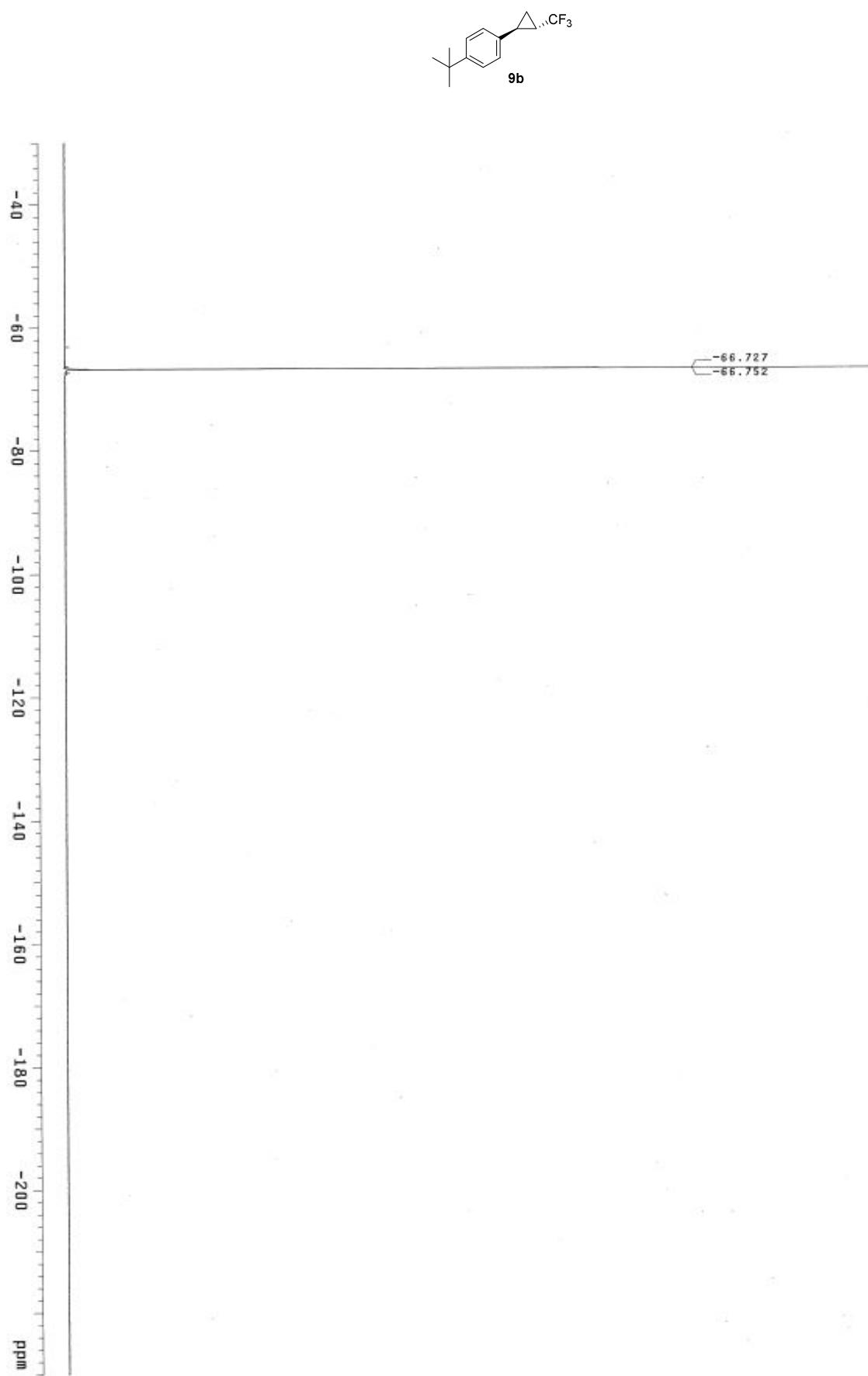
DAD: 254 Smooth (Mn, 1x2)



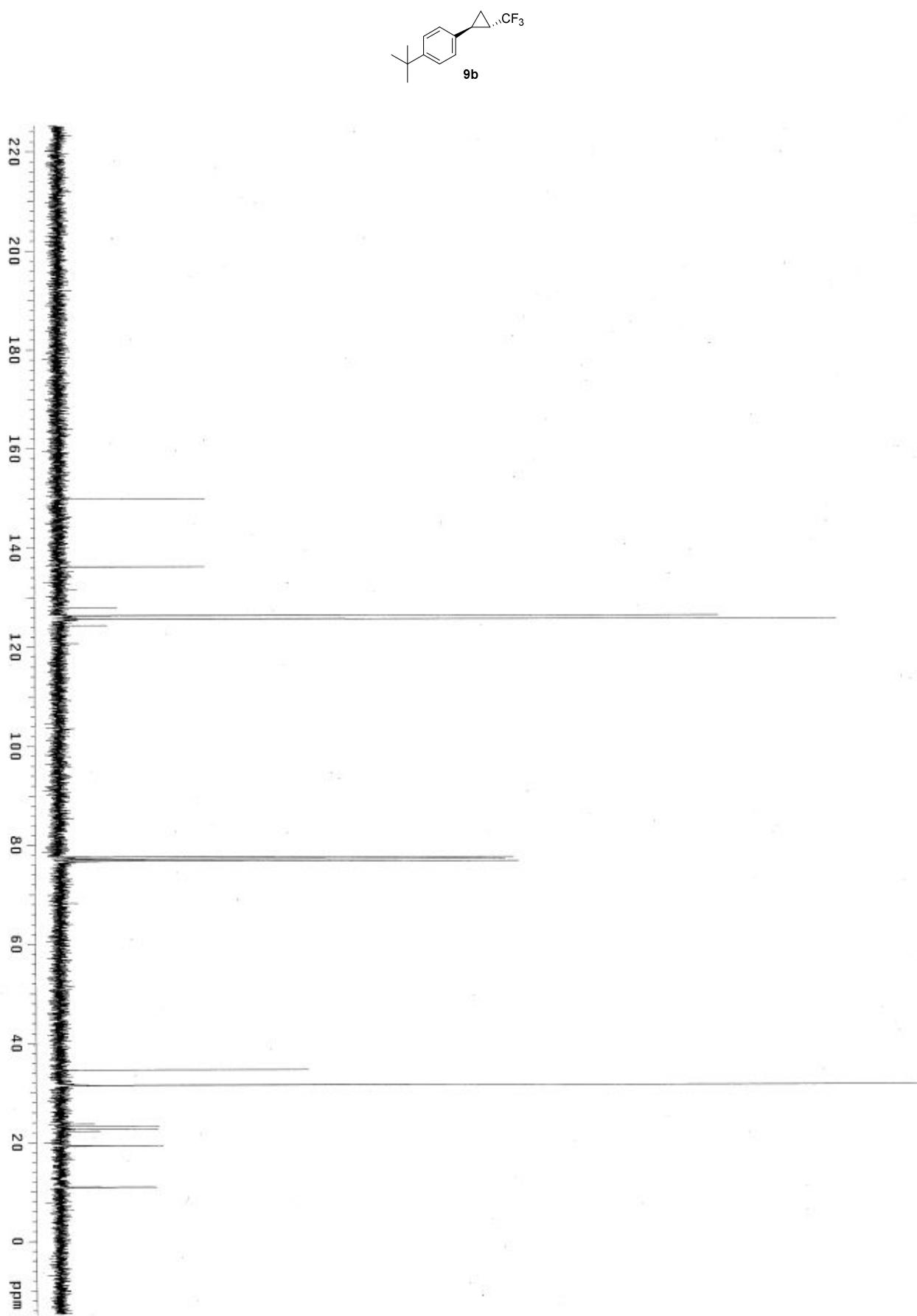
¹H NMR DATA FOR COMPOUND 9B



¹⁹F NMR DATA FOR COMPOUND 9B



¹³C NMR DATA FOR COMPOUND 9B



LC DATA FOR COMPOUND 9C

Openlynx Report -Yoyo

Sample: 1
File:MD1569-055
Description:10min

Vial:1:A,5
Date:18-Aug-2010

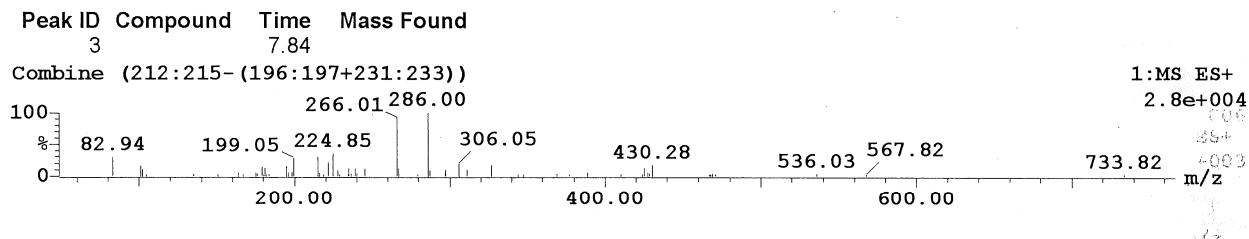
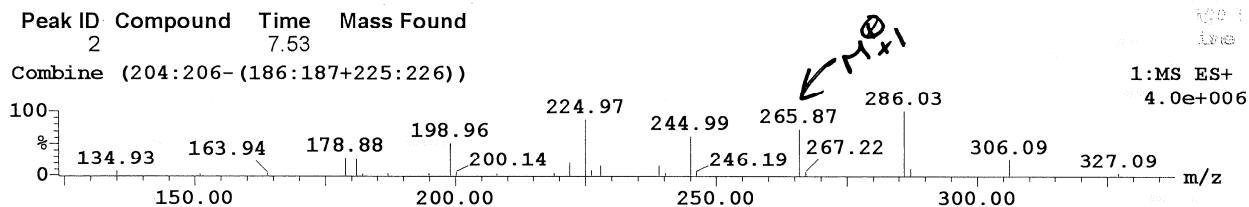
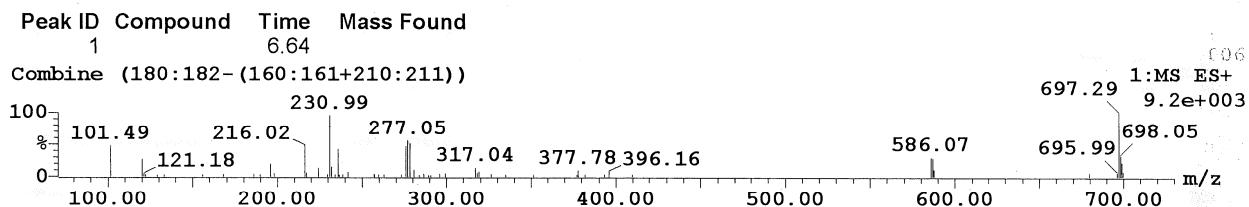
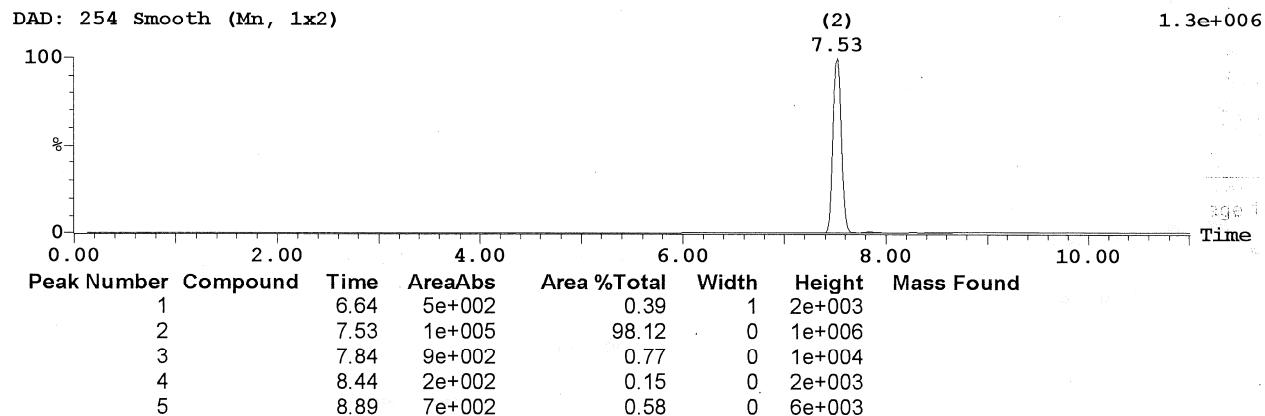
ID:
Time:14:17:08

Page 1

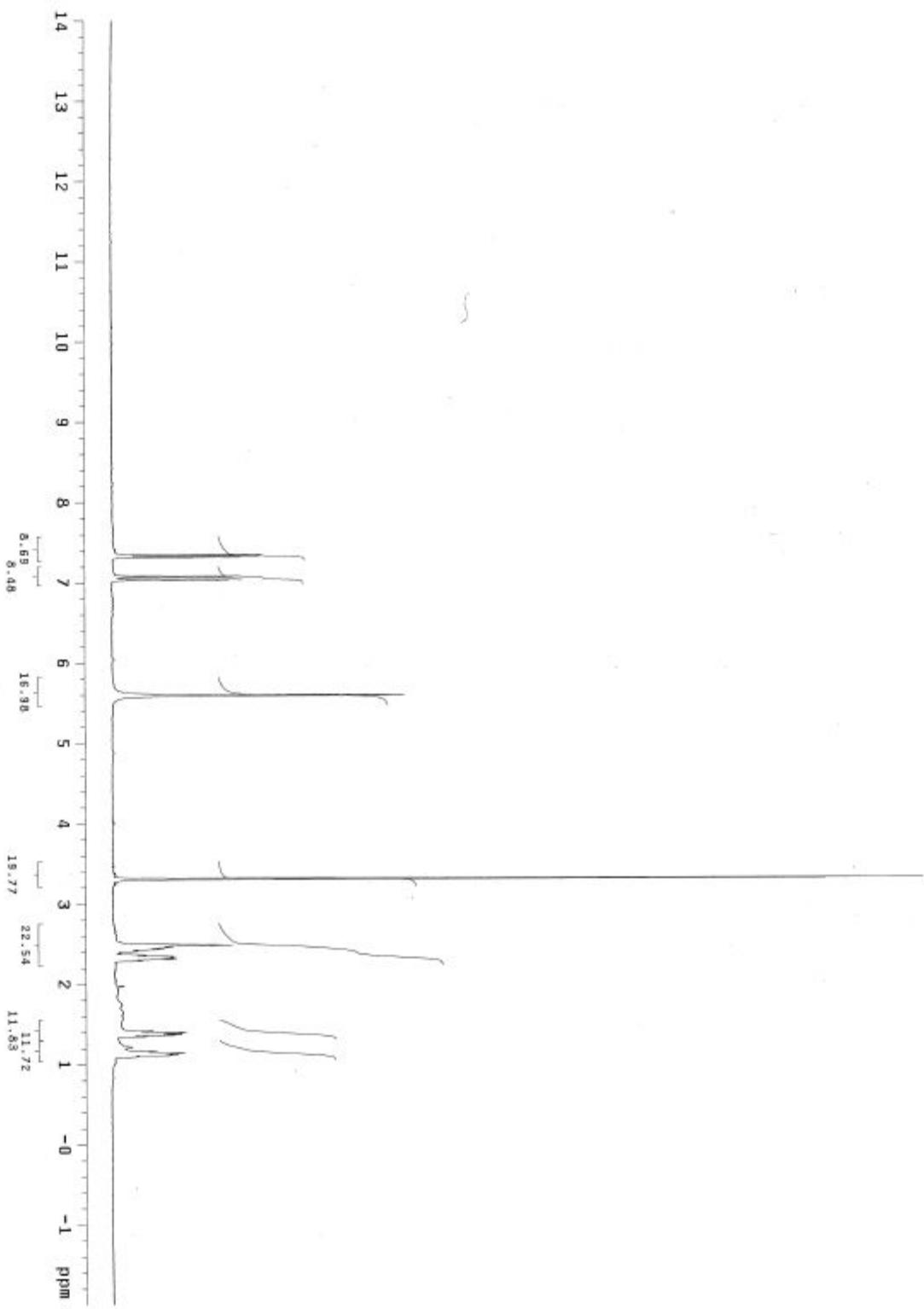
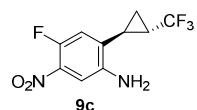
Printed: Wed Aug 18 14:29:56 2010

Sample Report:

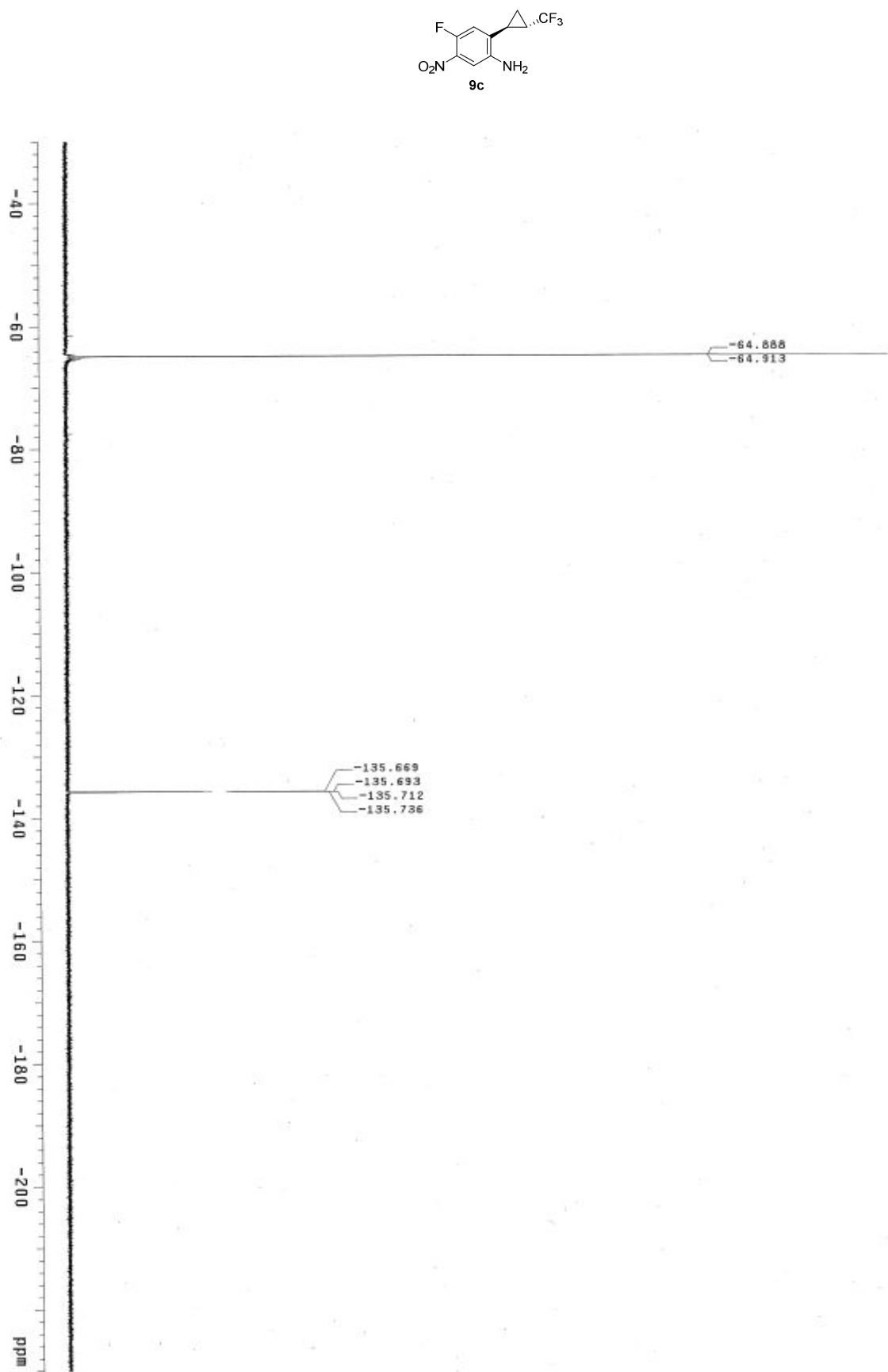
Sample 1 Vial 1:A,5 ID File MD1569-055 Date 18-Aug-2010 Time 14:17:08 Description 10min



¹H NMR DATA FOR COMPOUND 9C



¹⁹F NMR DATA FOR COMPOUND 9C



LC DATA FOR COMPOUND 9D

Openlynx Report -Yoyo

Sample: 1
File:MD1662-137C
Description:10min

Vial:1:F,12
Date:29-Nov-2011

ID:
Time:17:11:06

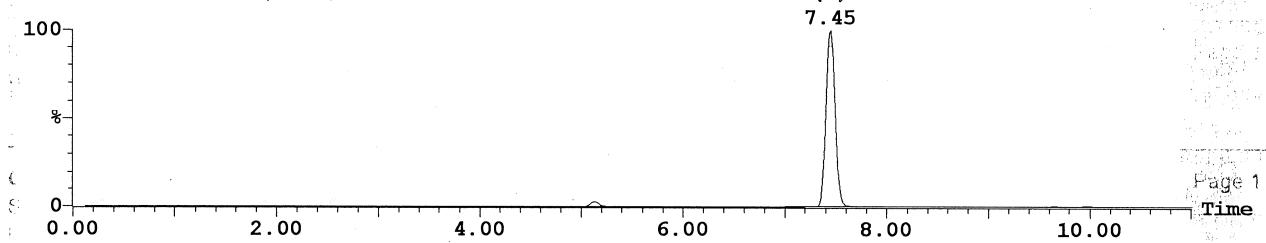
Page 1

Printed: Tue Nov 29 17:24:02 2011

Sample Report:

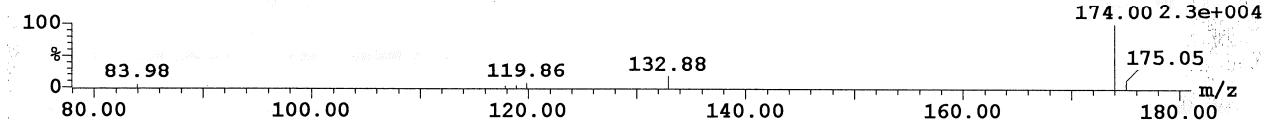
Sample 1 Vial 1:F,12 ID File MD1662-137C Date 29-Nov-2011 Time 17:11:06 Description 10min

DAD: 254 Smooth (Mn, 1x2)

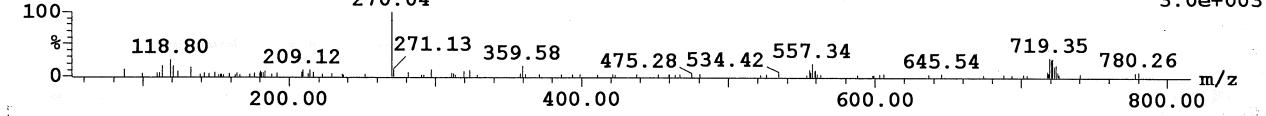


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.14	6e+003	2.40	0	6e+004	
2		7.19	2e+002	0.10	0	2e+003	
3		7.45	2e+005	96.61	1	2e+006	
4		9.65	7e+002	0.30	0	7e+003	
5		9.97	1e+003	0.52	0	1e+004	

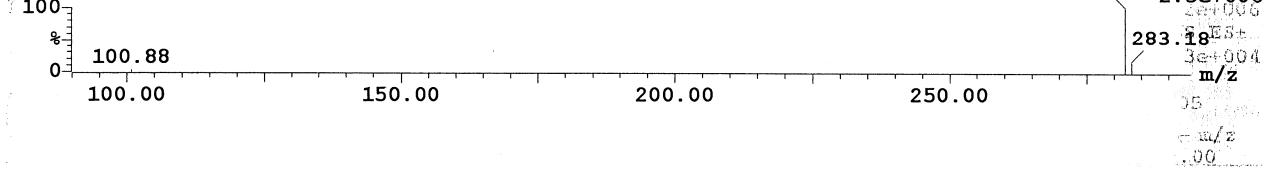
Peak ID Compound Time Mass Found
1 5.14
Combine (139:141- (121:122+161:163))



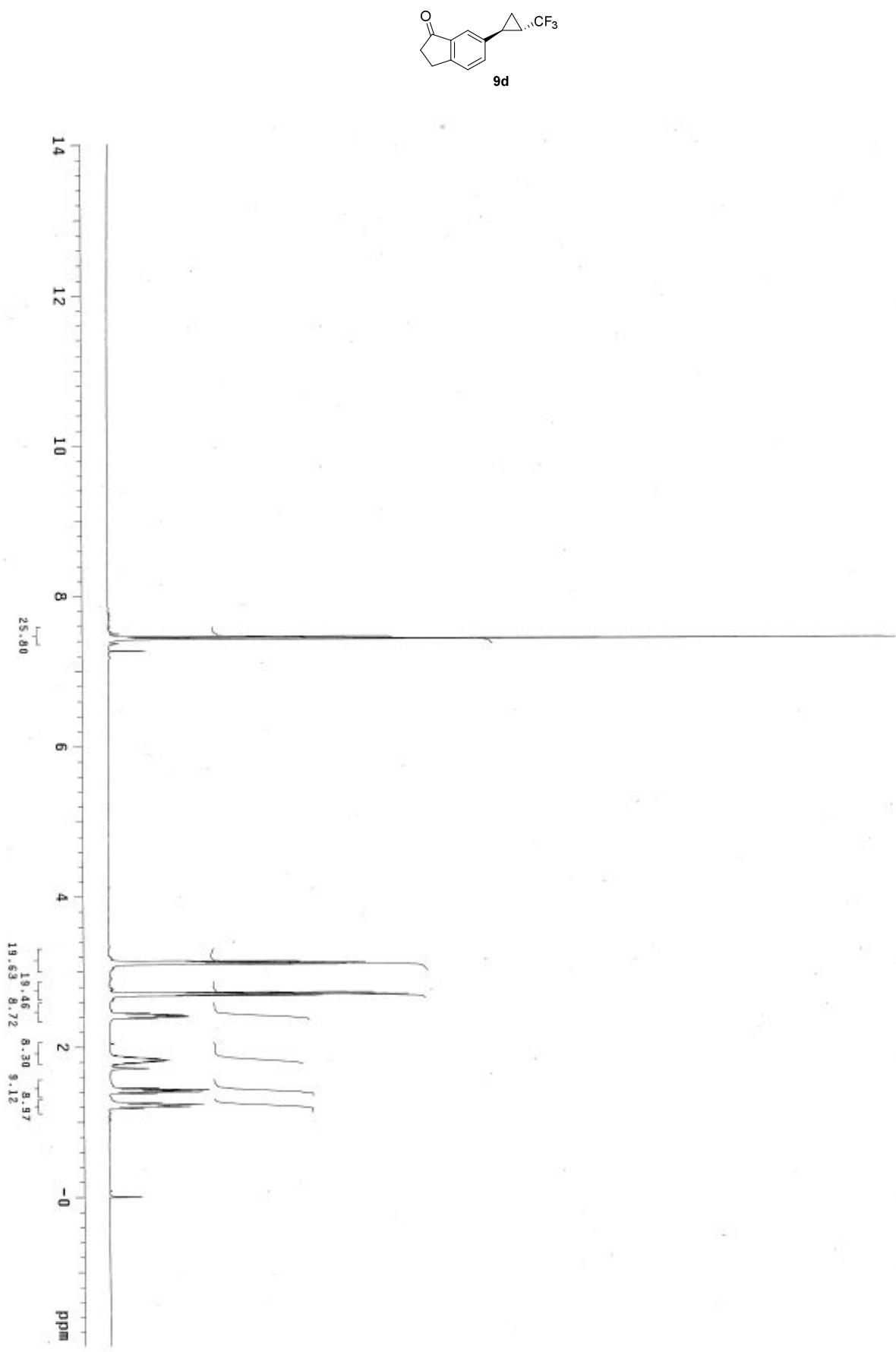
Peak ID Compound Time Mass Found
2 7.19
Combine (194:197- (174:175+211:212))



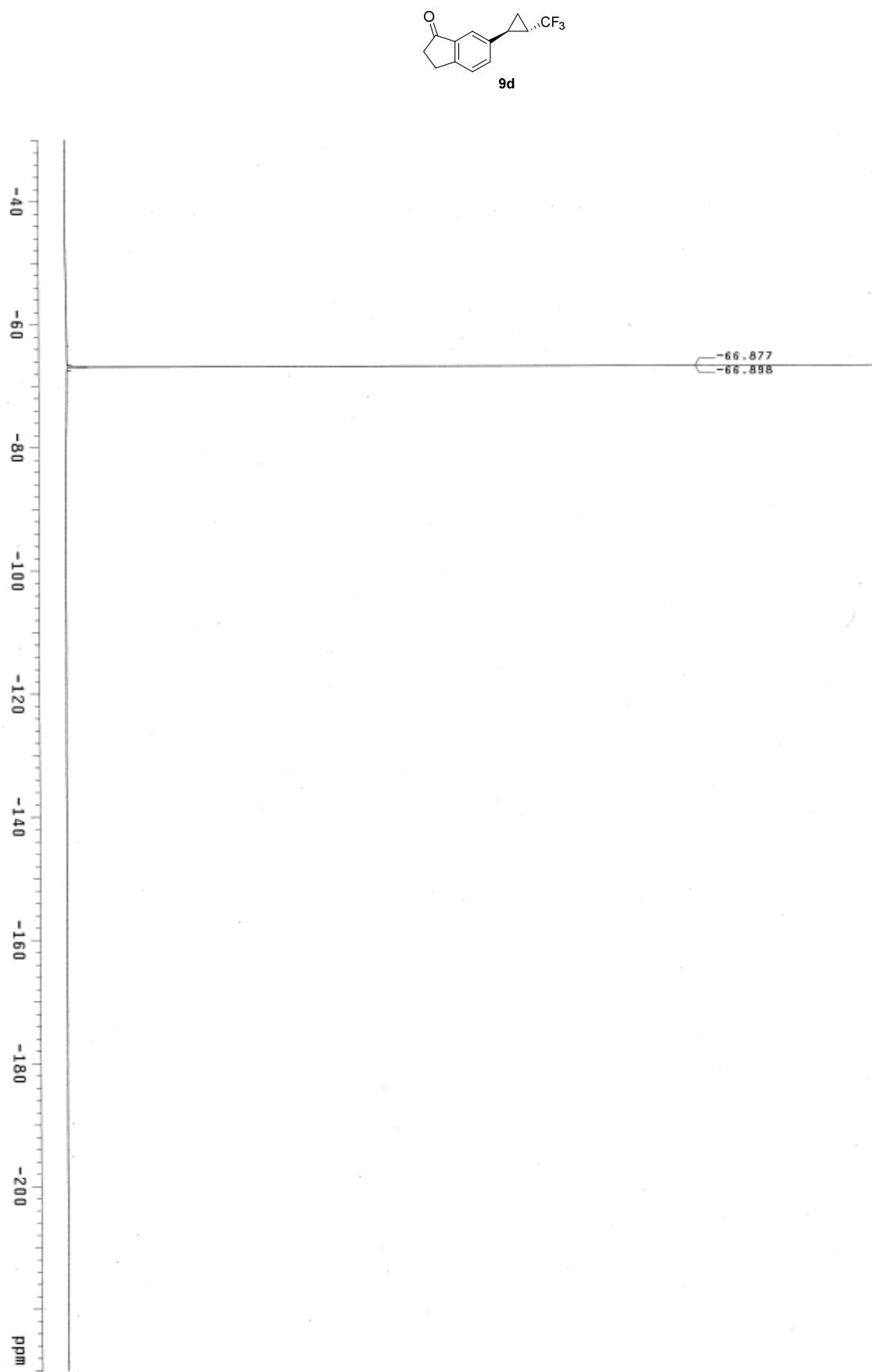
Peak ID Compound Time Mass Found
3 7.45
Combine (202:204- (182:184+227:229))



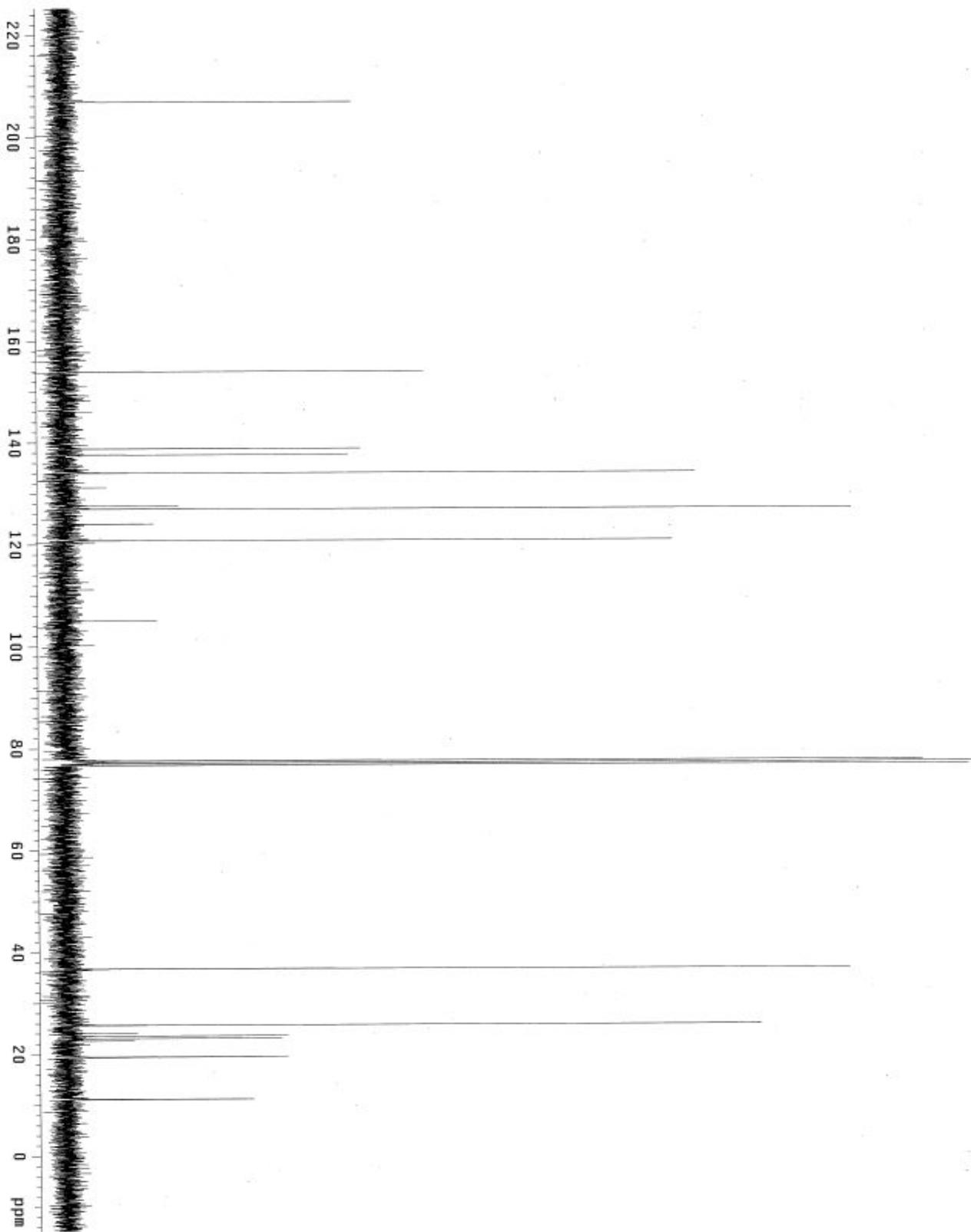
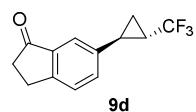
¹H NMR DATA FOR COMPOUND 9D



¹⁹F NMR DATA FOR COMPOUND 9D



¹³C NMR DATA FOR COMPOUND 9D



LC DATA FOR COMPOUND 9E

Openlynx Report -Yoyo

Sample: 1
File:MD1662-137A
Description:10min

Vial:2:G,1
Date:15-Nov-2011

ID:
Time:17:30:52

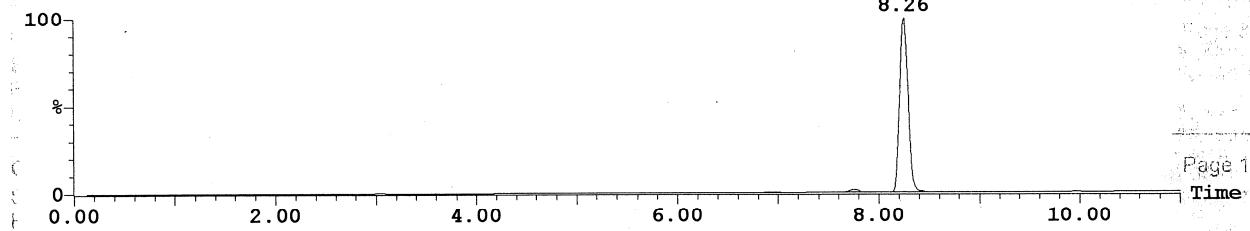
Page 1

Printed: Tue Nov 15 17:43:46 2011

Sample Report:

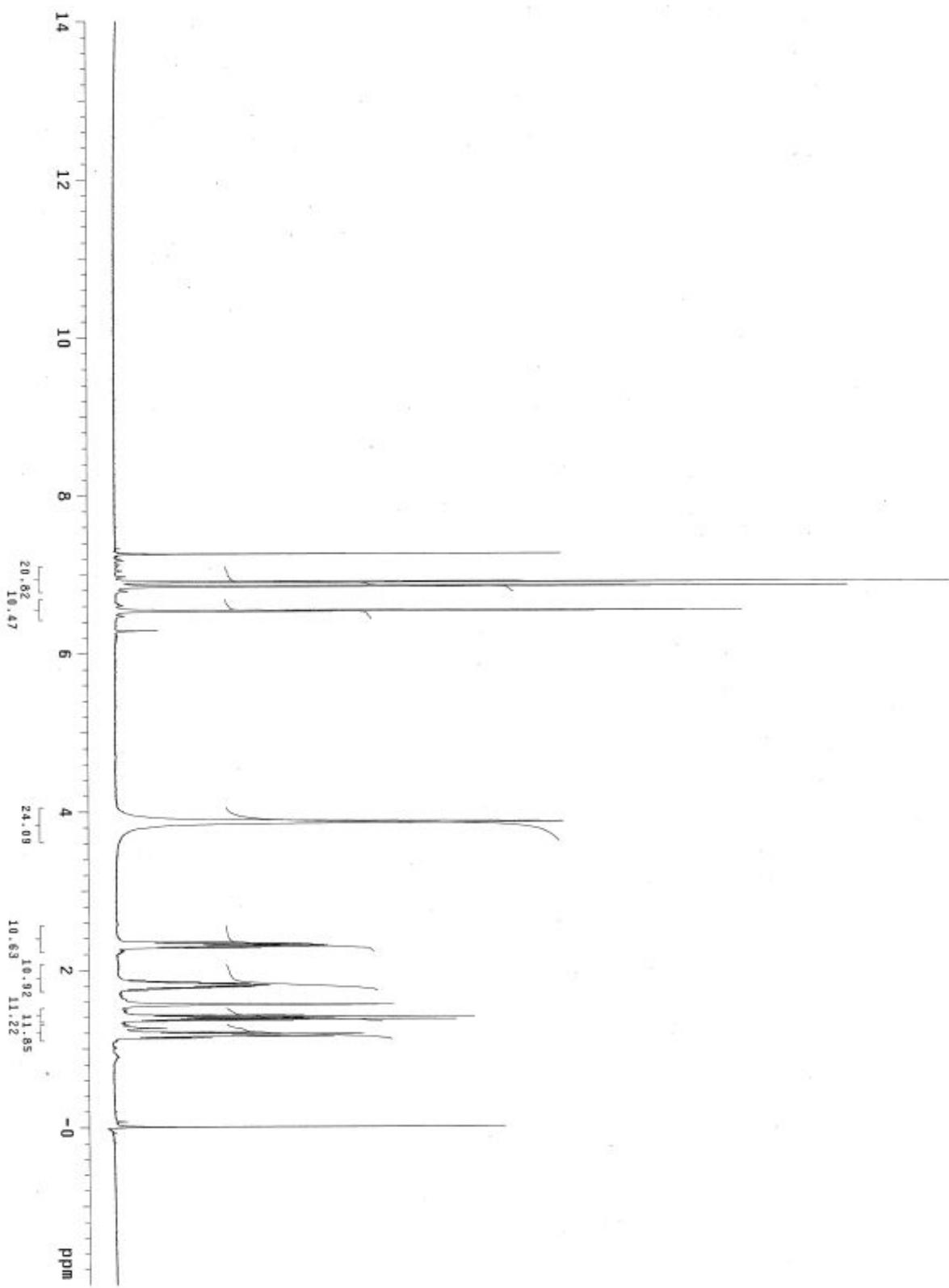
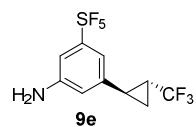
Sample 1 Vial 2:G,1 ID File MD1662-137A Date 15-Nov-2011 Time 17:30:52 Description 10min

DAD: 254 Smooth (Mn, 1x2)

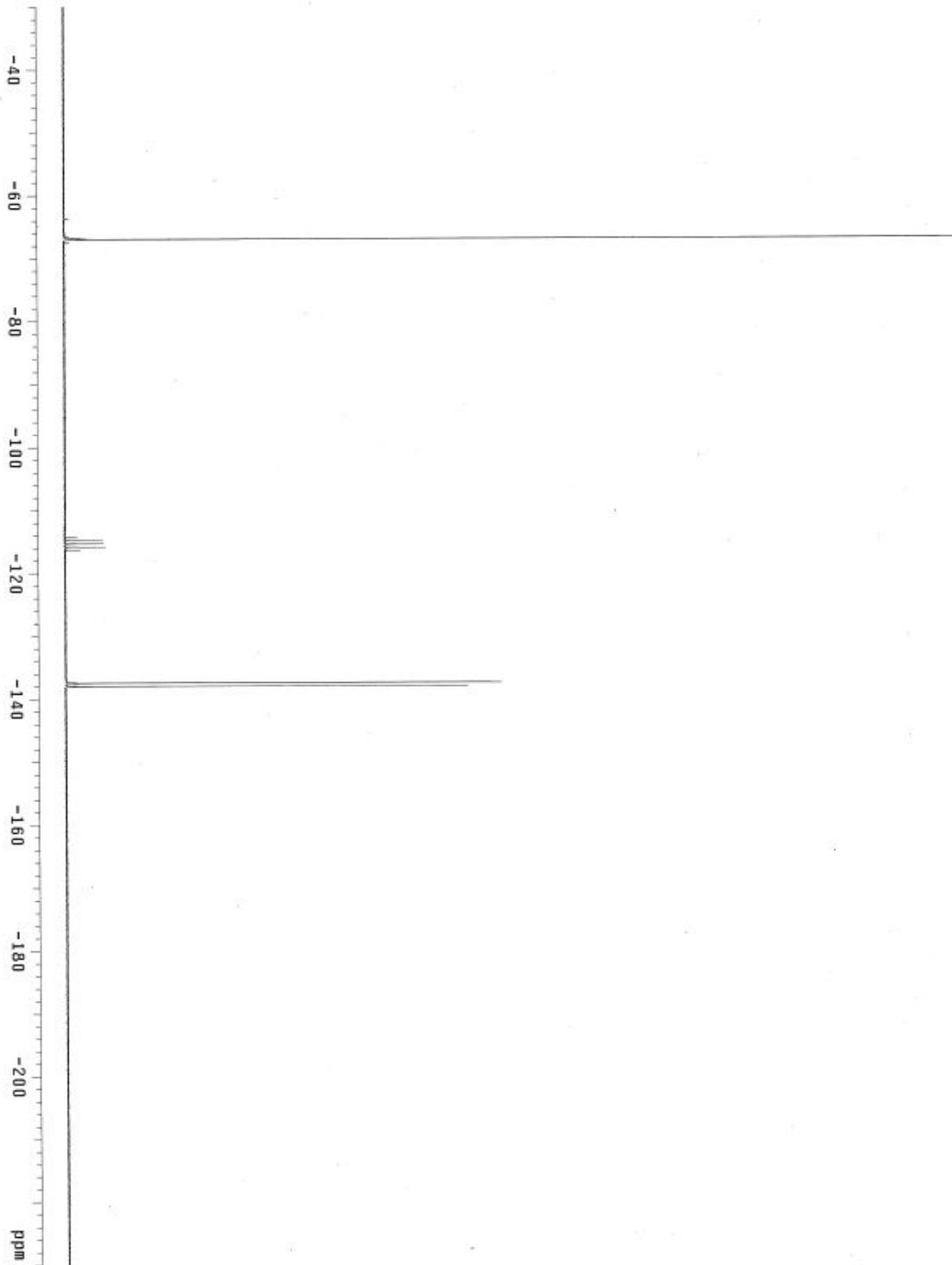
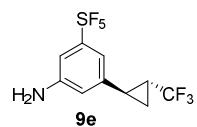


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		6.92	3e+002	0.47	0	3e+003	
2		7.42	1e+002	0.14	0	1e+003	
3		7.76	1e+003	1.85	0	1e+004	
4		8.26	7e+004	97.54	0	7e+005	

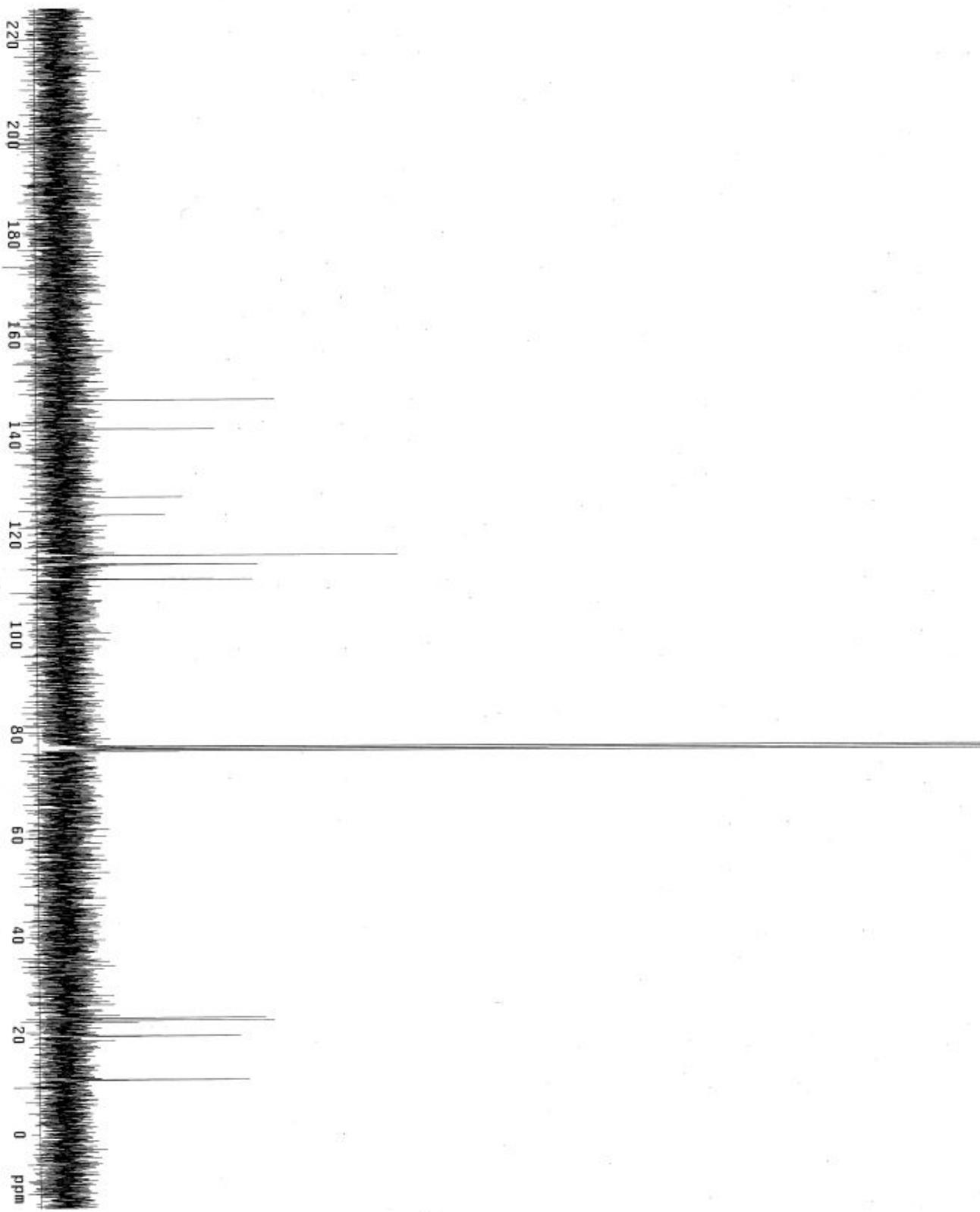
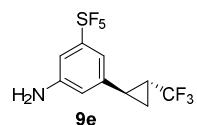
¹H NMR DATA FOR COMPOUND 9E



¹⁹F NMR DATA FOR COMPOUND 9E



¹³C NMR DATA FOR COMPOUND 9E



LC DATA FOR COMPOUND 9F

Openlynx Report -

Vial:1:H,6

Time:14:34:20

File:1740-187

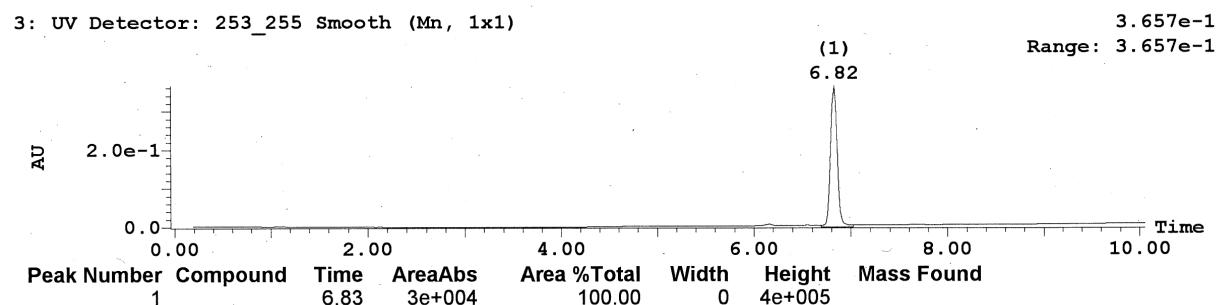
Zed:

Date:07-Aug-2013

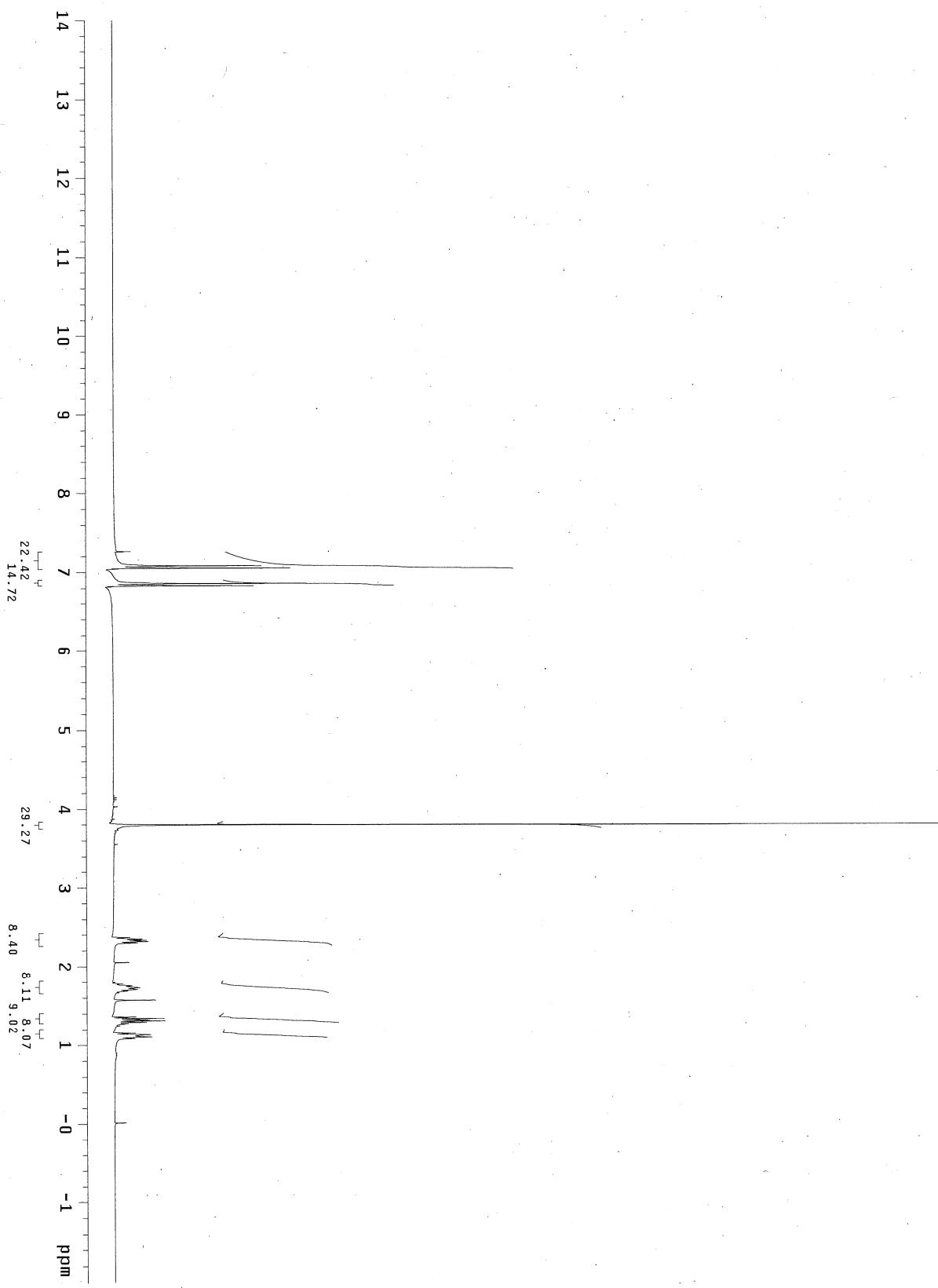
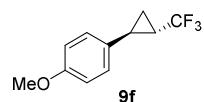
Method:10min

Page 1

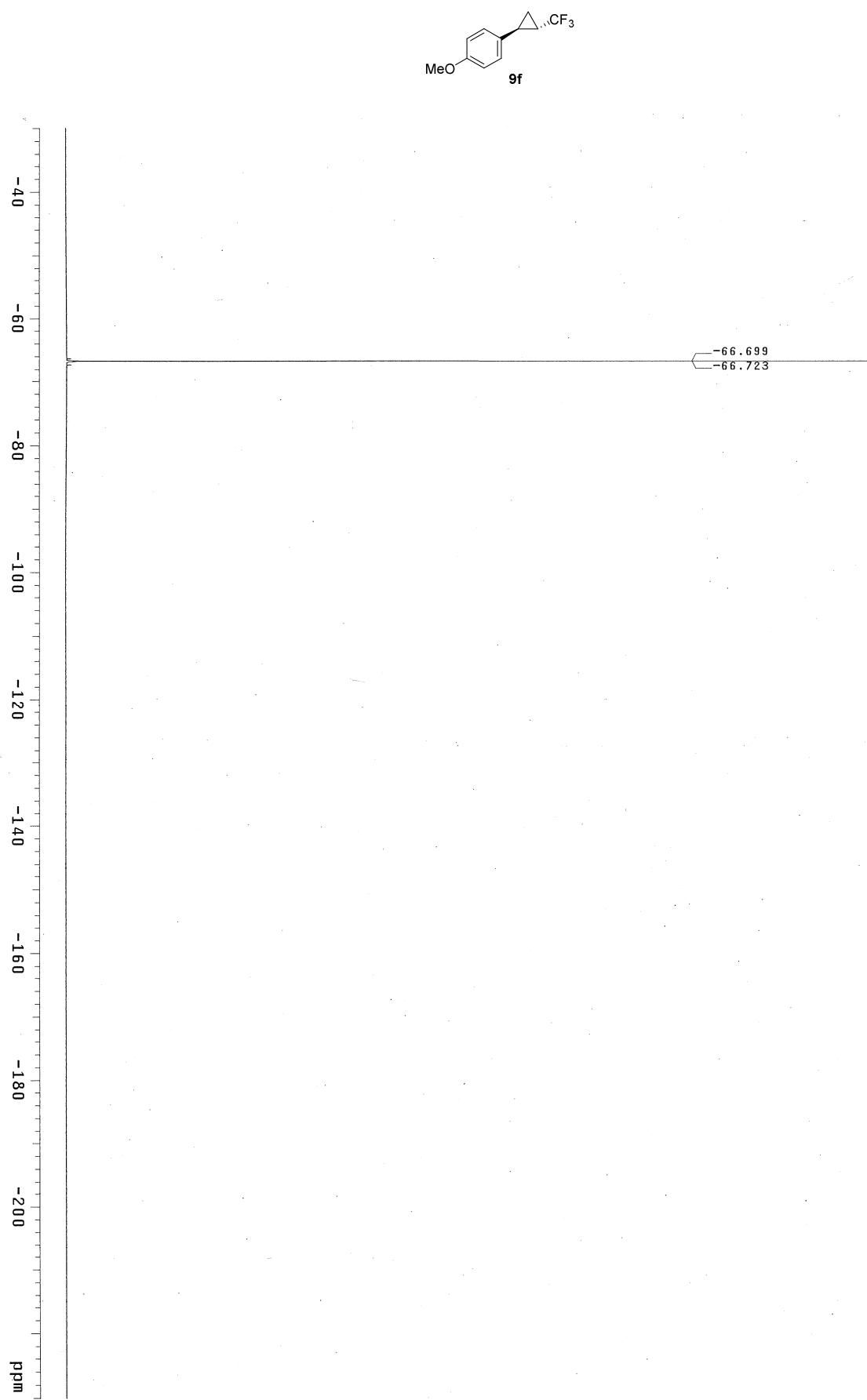
Printed: Wed Aug 07 14:47:42 2013



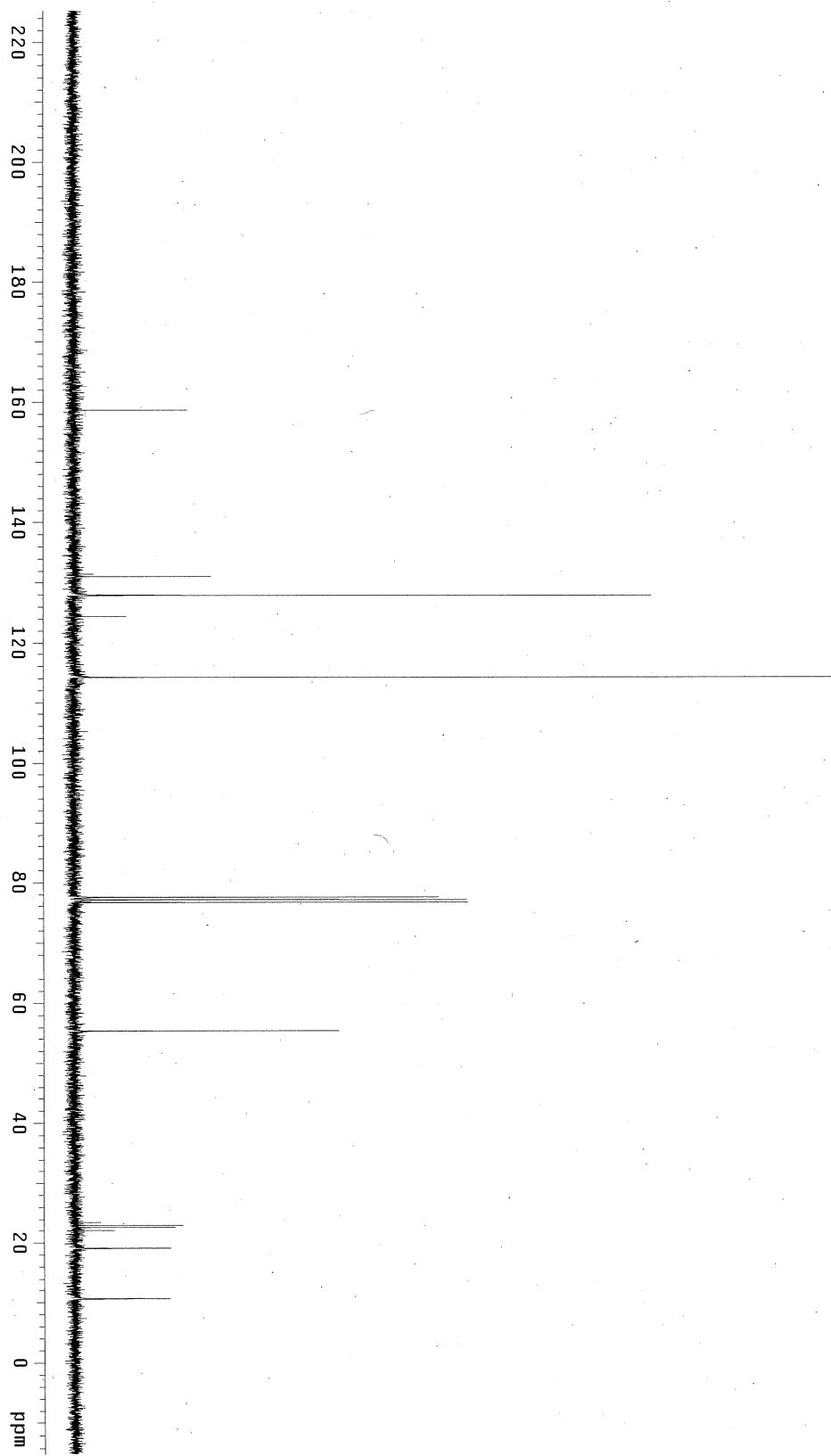
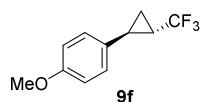
¹H NMR DATA FOR COMPOUND 9F



¹⁹F NMR DATA FOR COMPOUND 9F



¹³C NMR DATA FOR COMPOUND 9F



LC DATA FOR COMPOUND 9G

Openlynx Report -

File:MD1740-156
Xena:Inst

Date:19-Apr-2013
Method:10min

Time:10:50:00
Vial:1:A,4

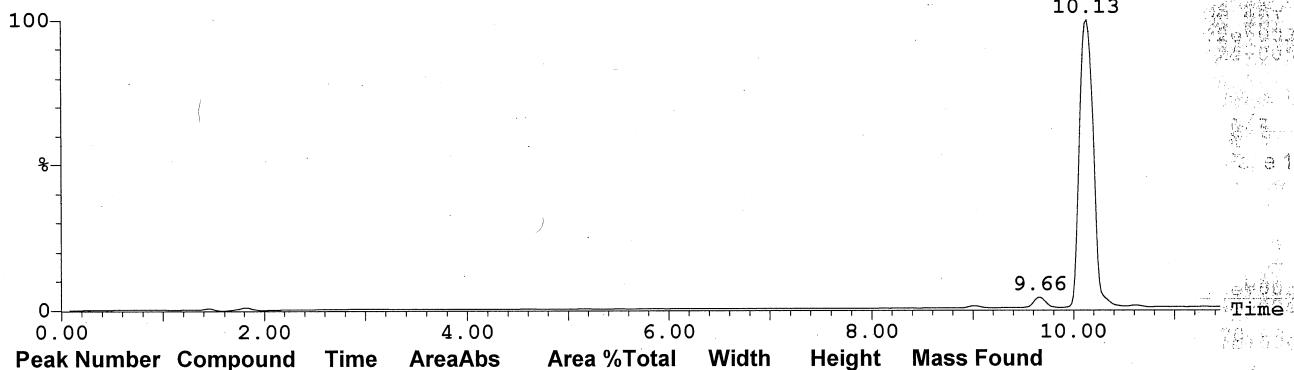
Page 1

Printed: Fri Apr 19 11:02:35 2013

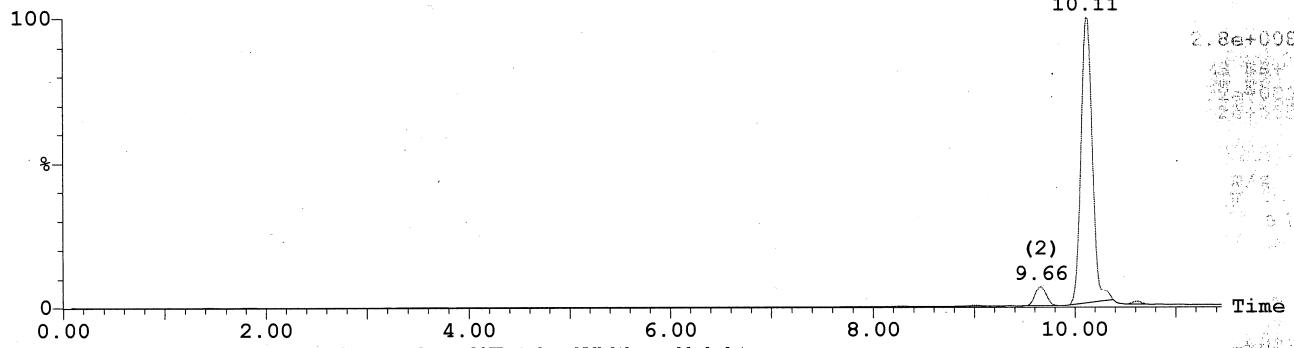
Sample Report:

File MD1740-156 Date 19-Apr-2013 Time 10:50:00 ID Vial 1:A,4

DAD: TIC Smooth (Mn, 1x1)



DAD: 254 Smooth (Mn, 1x1)

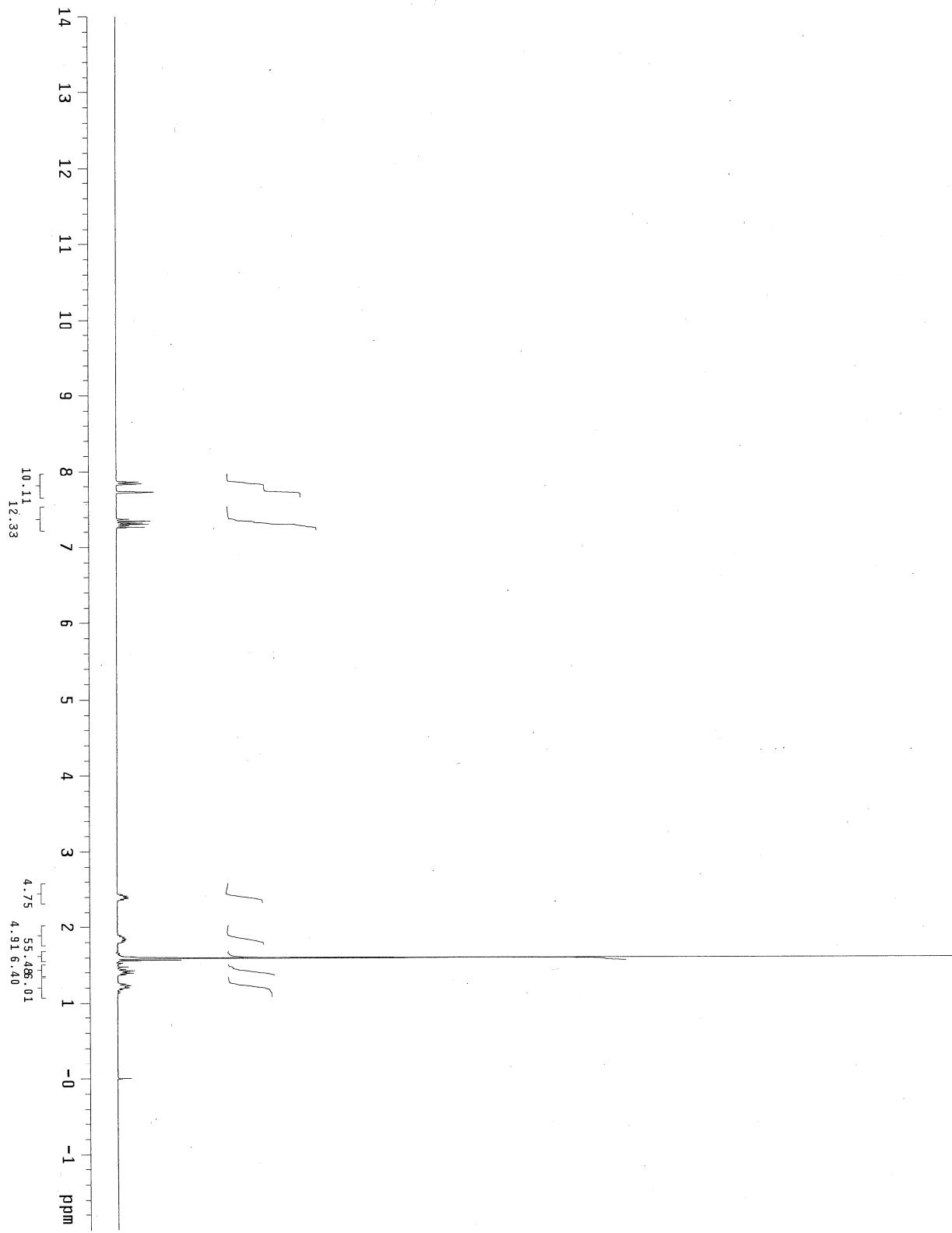
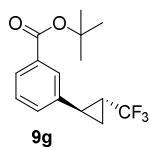


Peak Number	Time	AreaAbs	Area %Total	Width	Height
1	9.01	6e+002	0.33	0	5e+003
2	9.66	1e+004	6.18	0	8e+004
3	10.11	2e+005	92.65	0	1e+006
4	10.61	1e+003	0.69	0	1e+004
5	11.28	2e+002	0.10	0	1e+003

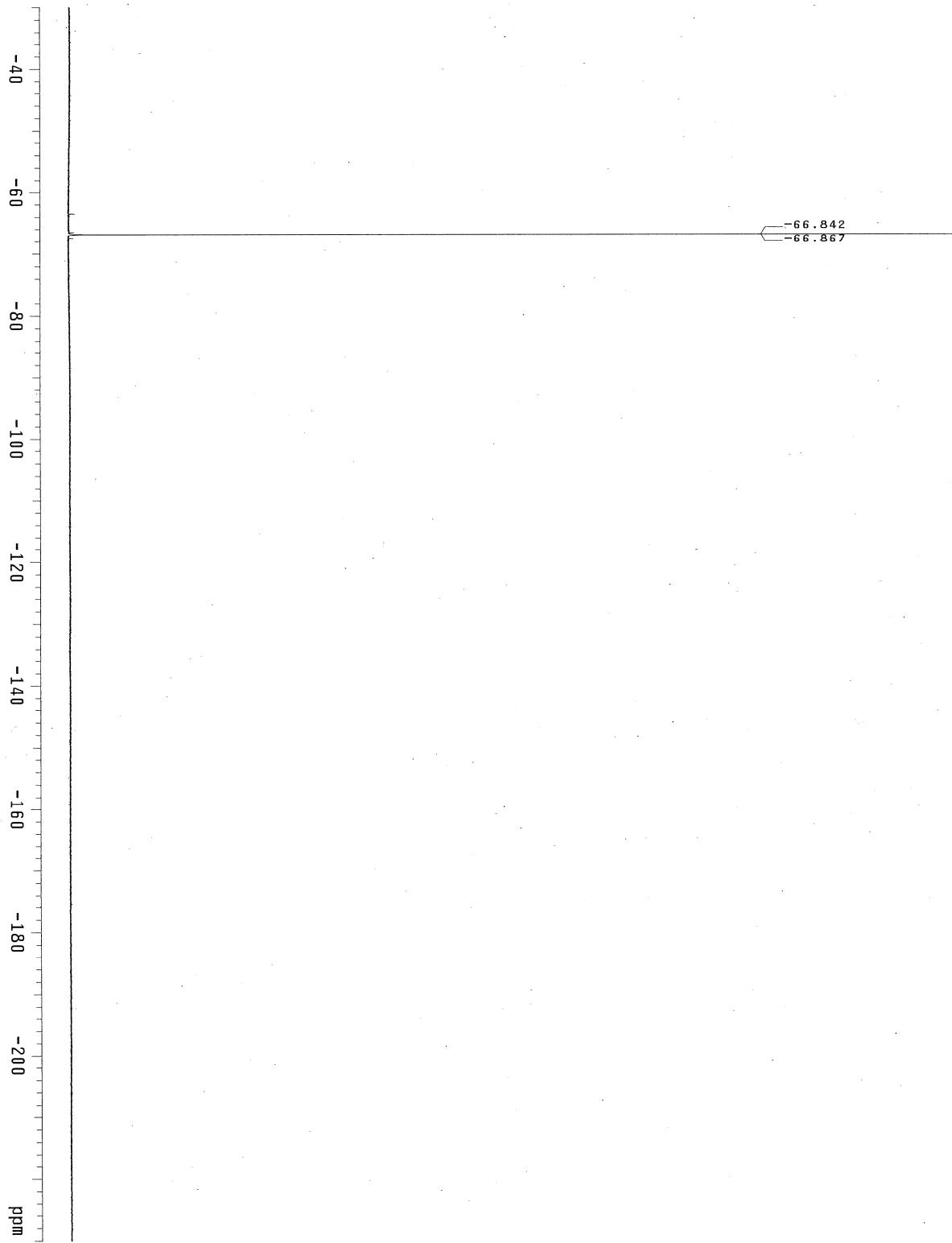
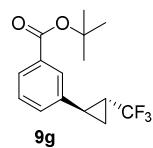
NOTE: NO IMPURITIES BY ^1H & ^{13}C NMR (OTHER THAN RESIDUAL SOLVENT - VERY SMALL TRACE

QUANTITIES)

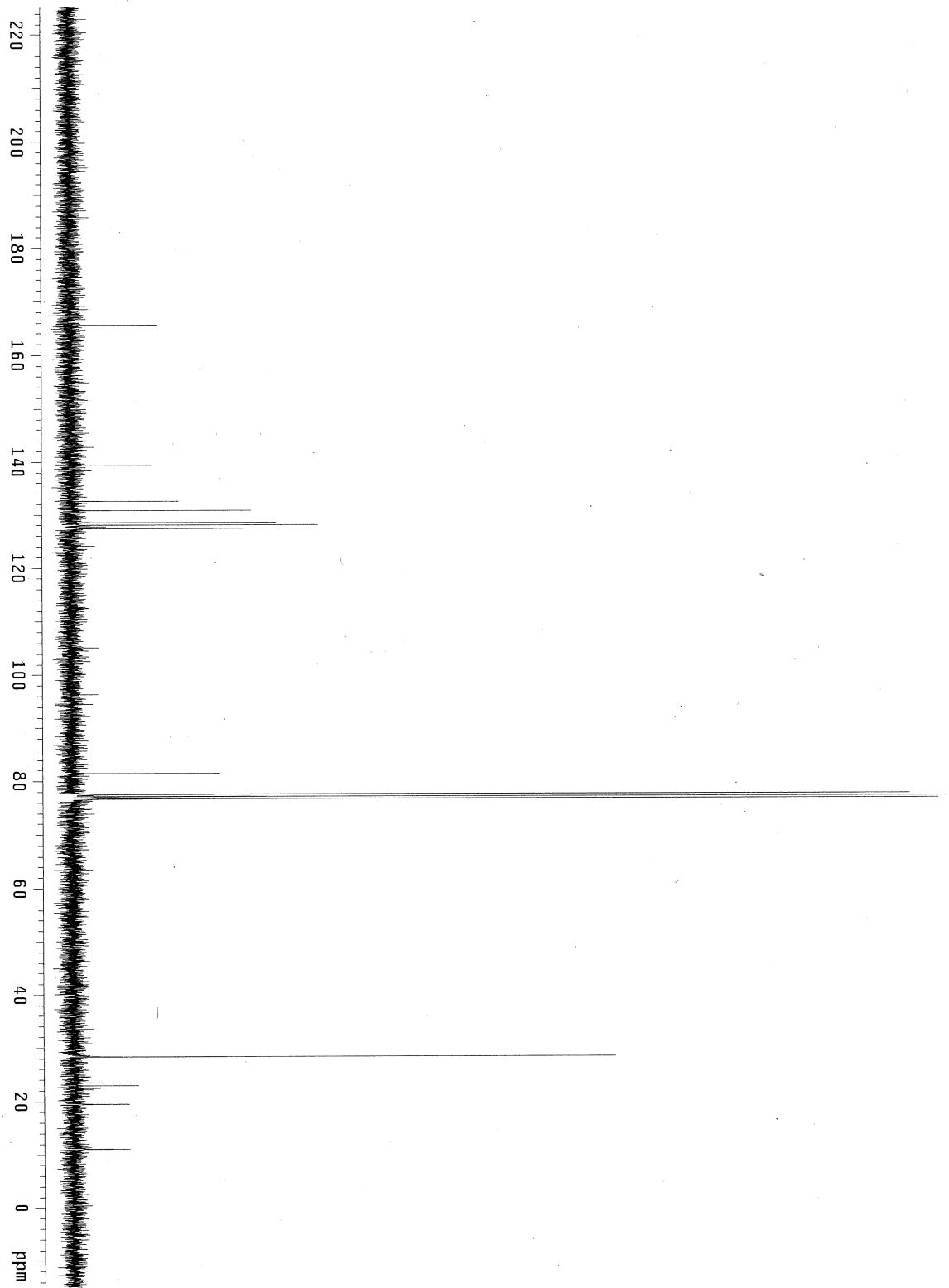
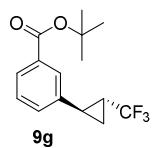
¹H NMR DATA FOR COMPOUND 9G



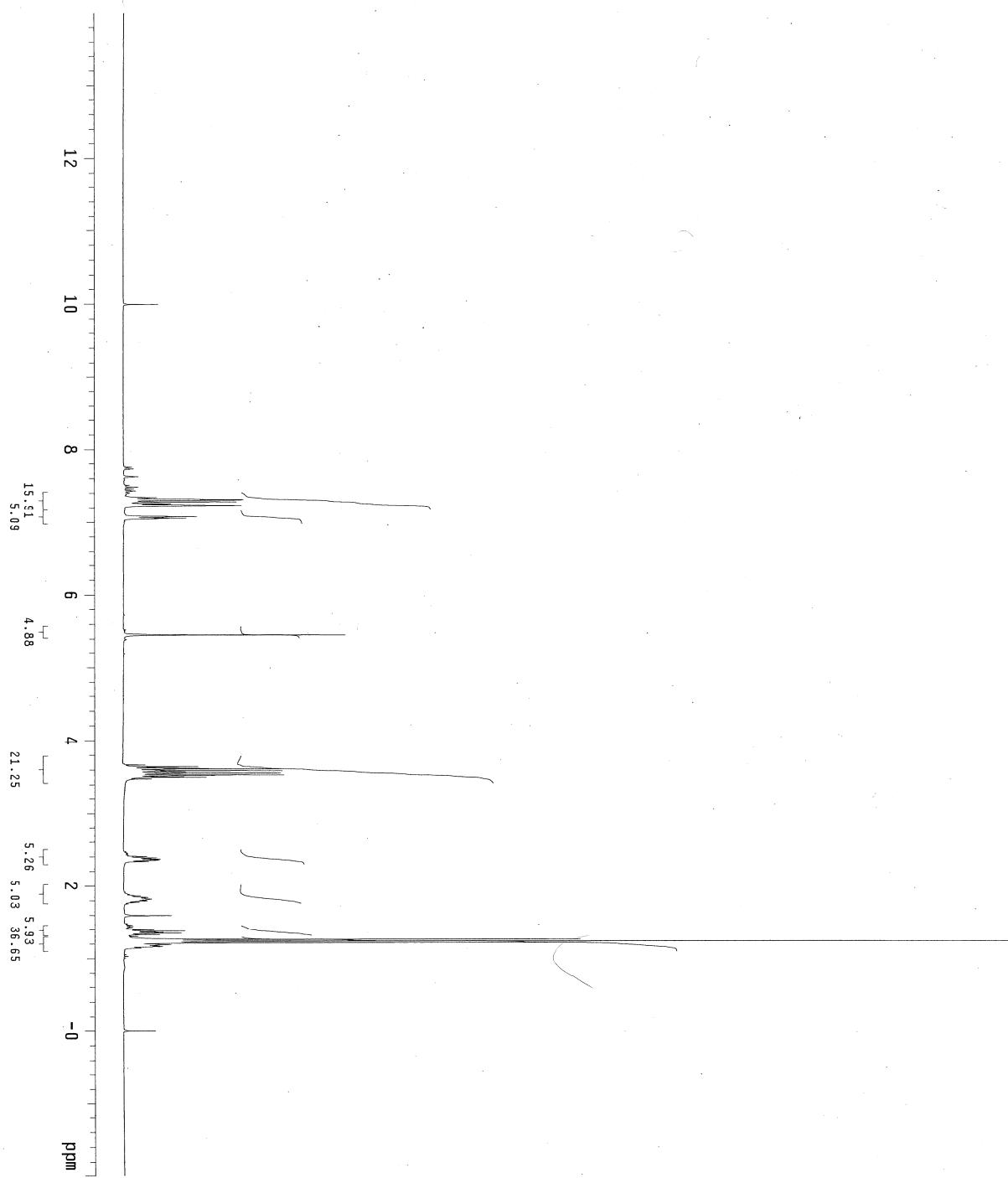
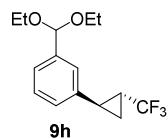
¹⁹F NMR DATA FOR COMPOUND 9G



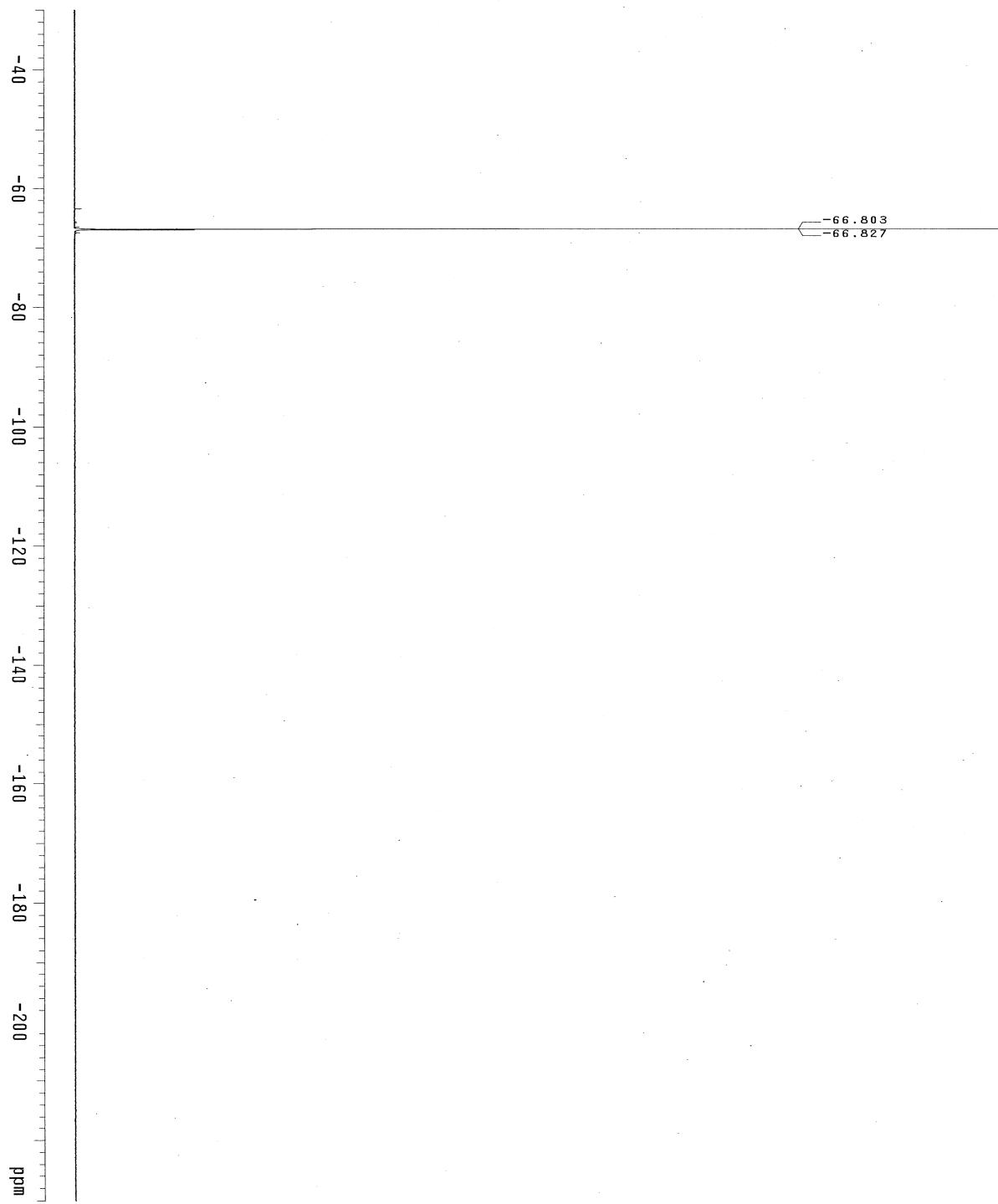
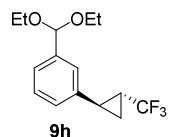
¹³C NMR DATA FOR COMPOUND 9G



¹H NMR DATA FOR COMPOUND 9H: CONTAINS CA. 15% OF ALDEHYDE – COMPOUND 9H(2) (SEE PAGES S99-S102 FOR SPECTRA OF PURE ALDEHYDE 9H(2). ALDEHYDE 9H(2) IS DEPROTECTED FORM OF PRODUCT 9H)

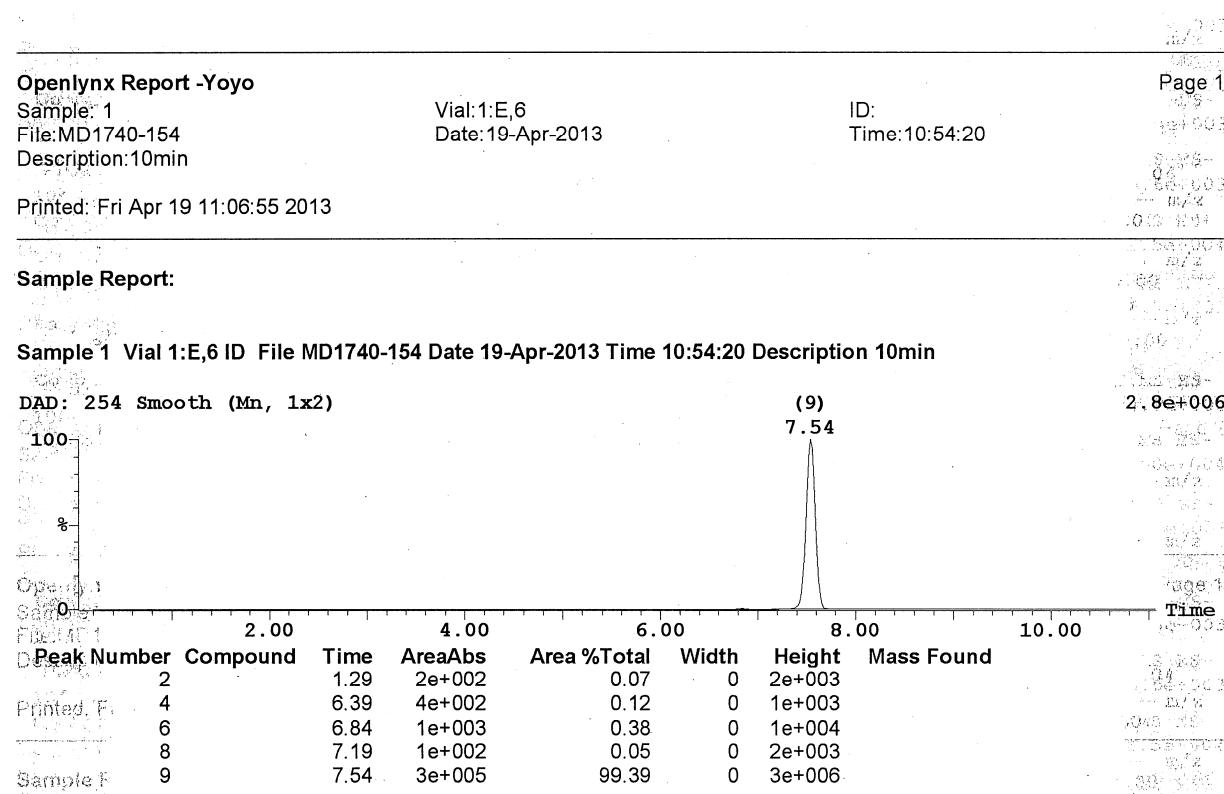


¹⁹F NMR DATA FOR COMPOUND 9H: CONTAINS CA. 15% OF ALDEHYDE – COMPOUND 9H(2) (SEE PAGES S99-S102 FOR SPECTRA OF PURE ALDEHYDE 9H(2). ALDEHYDE IS DEPROTECTED FORM OF PRODUCT 9H)

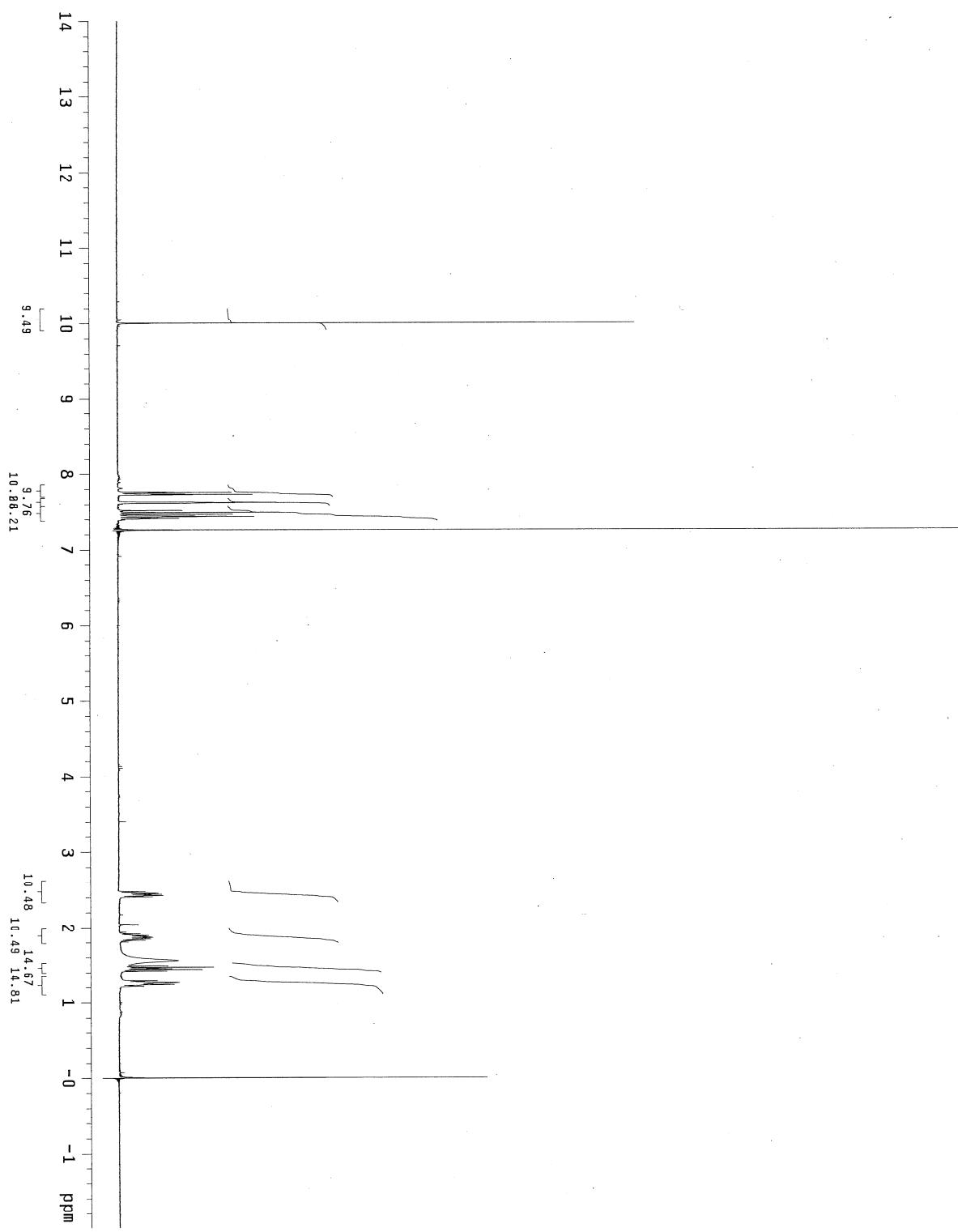
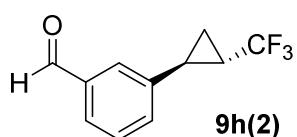


LC DATA FOR COMPOUND 9H(2): ALDEHYDE DERIVED FROM ACETAL 9H BY REACTION WITH ACID

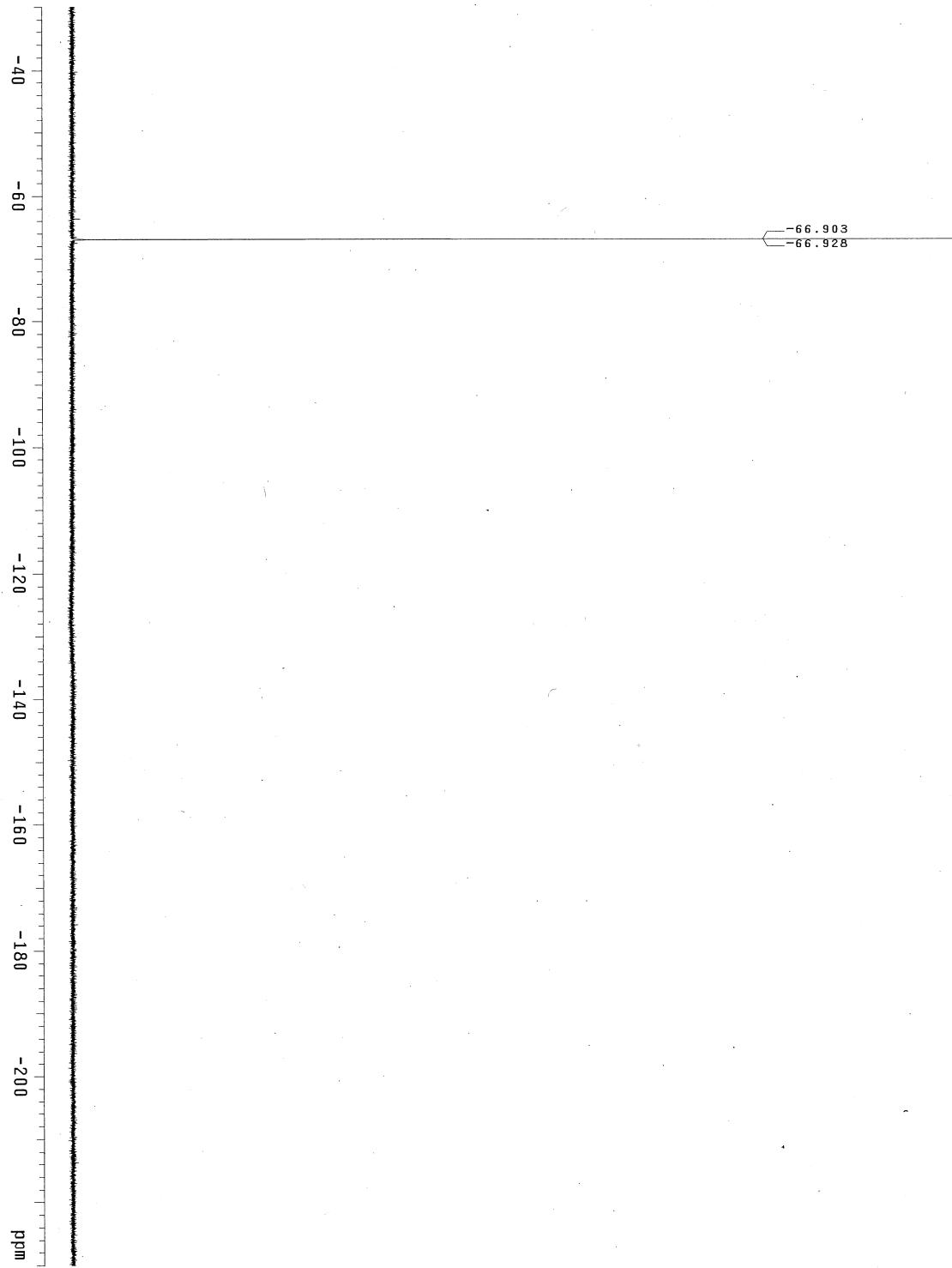
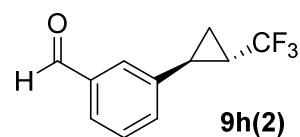
(SEE PAGES S47-S48 FOR EXPERIMENTAL PROCEDURE FOR THIS TRANSFORMATION)



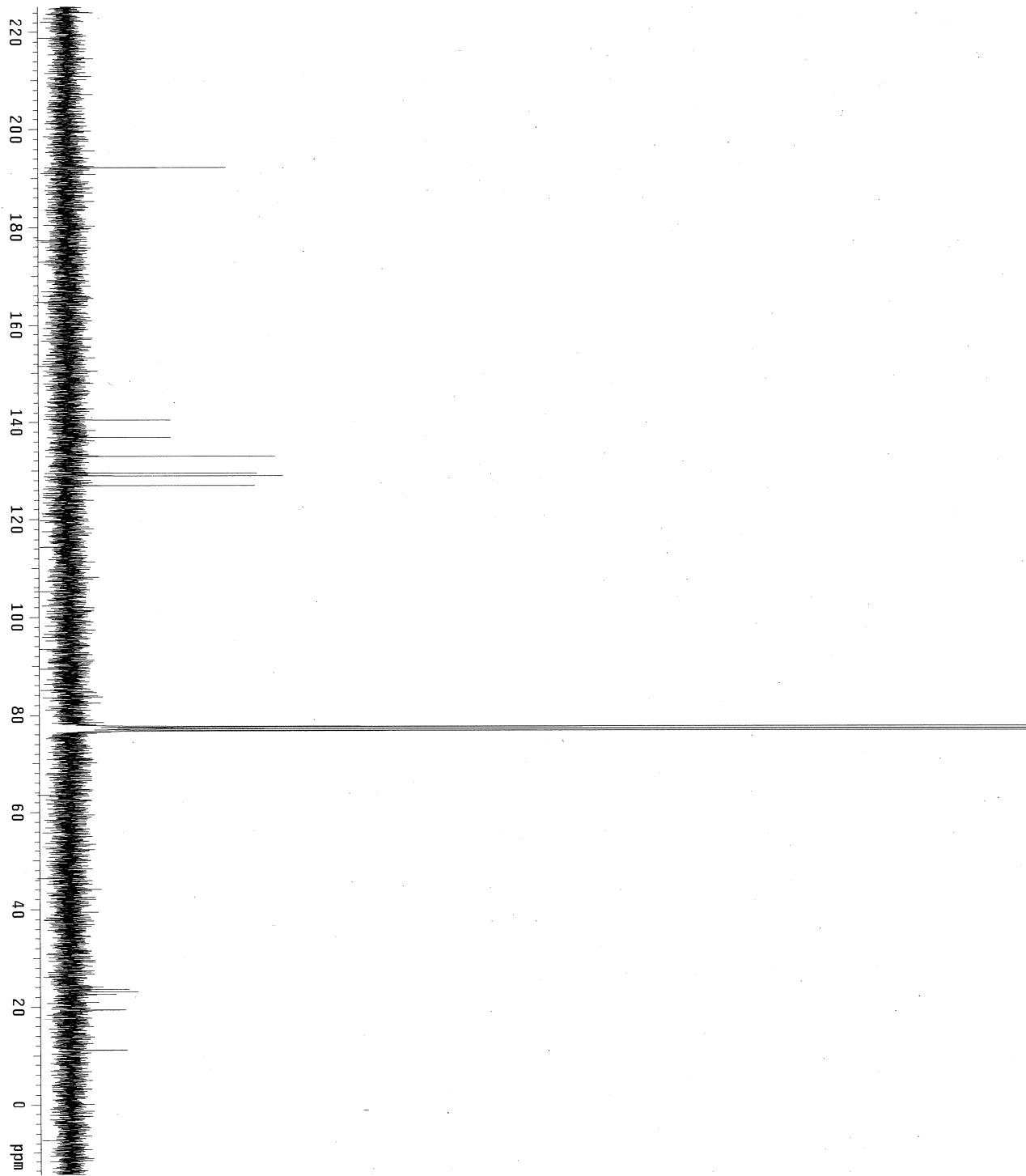
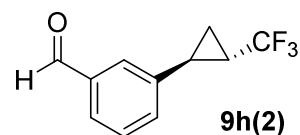
**¹H NMR DATA FOR COMPOUND 9H(2): ALDEHYDE 9H(2) DERIVED FROM ACETAL 9H BY REACTION
WITH ACID. (SEE PAGES S47-S48 FOR EXPERIMENTAL PROCEDURE FOR THIS TRANSFORMATION)**



¹⁹F NMR DATA FOR COMPOUND 9H(2): ALDEHYDE 9H(2) DERIVED FROM ACETAL 9H BY REACTION WITH ACID (SEE PAGES S47-S48 FOR EXPERIMENTAL PROCEDURE FOR THIS TRANSFORMATION)



¹³C NMR DATA FOR COMPOUND 9H(2): ALDEHYDE 9H(2) DERIVED FROM ACETAL 9H BY
REACTION WITH ACID (SEE PAGES S47-S48 FOR EXPERIMENTAL PROCEDURE FOR THIS
TRANSFORMATION)



LC DATA FOR COMPOUND 9I

Openlynx Report -Yoyo

Sample: 1
File:MD1569-185
Description:10min

Vial:1:H,10
Date:25-Apr-2011

ID:
Time:17:18:13

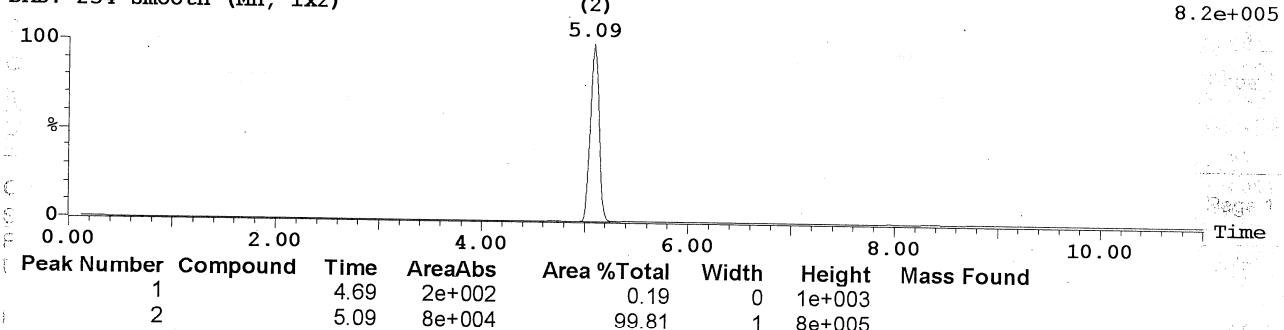
Page 1

Printed: Mon Apr 25 17:31:01 2011

Sample Report:

Sample 1 Vial 1:H,10 ID File MD1569-185 Date 25-Apr-2011 Time 17:18:13 Description 10min

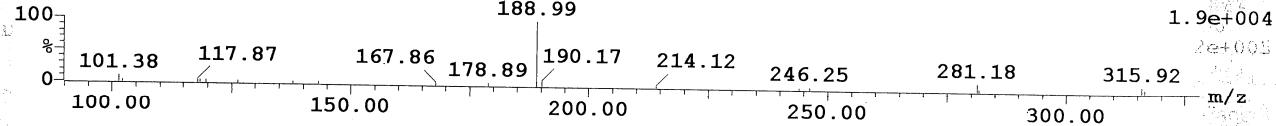
DAD: 254 Smooth (Mn, 1x2)



Peak ID Compound Time Mass Found

1 4.69

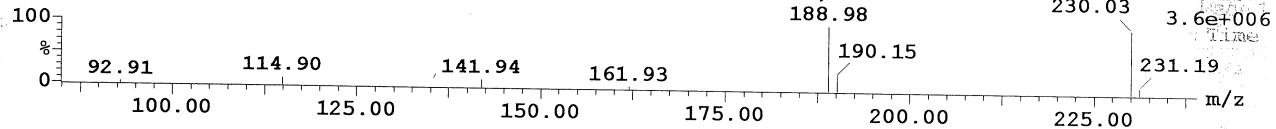
Combine (126:129-(107:109+146:148))



Peak ID Compound Time Mass Found

2 5.09

Combine (137:140-(118:119+161:163))

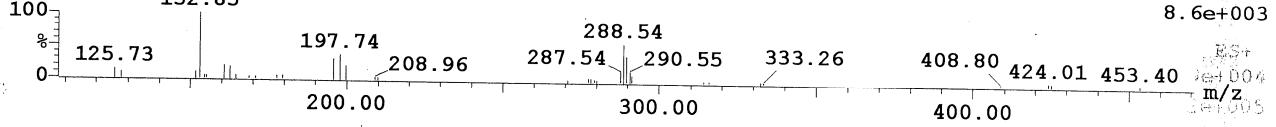


Peak ID Compound Time Mass Found

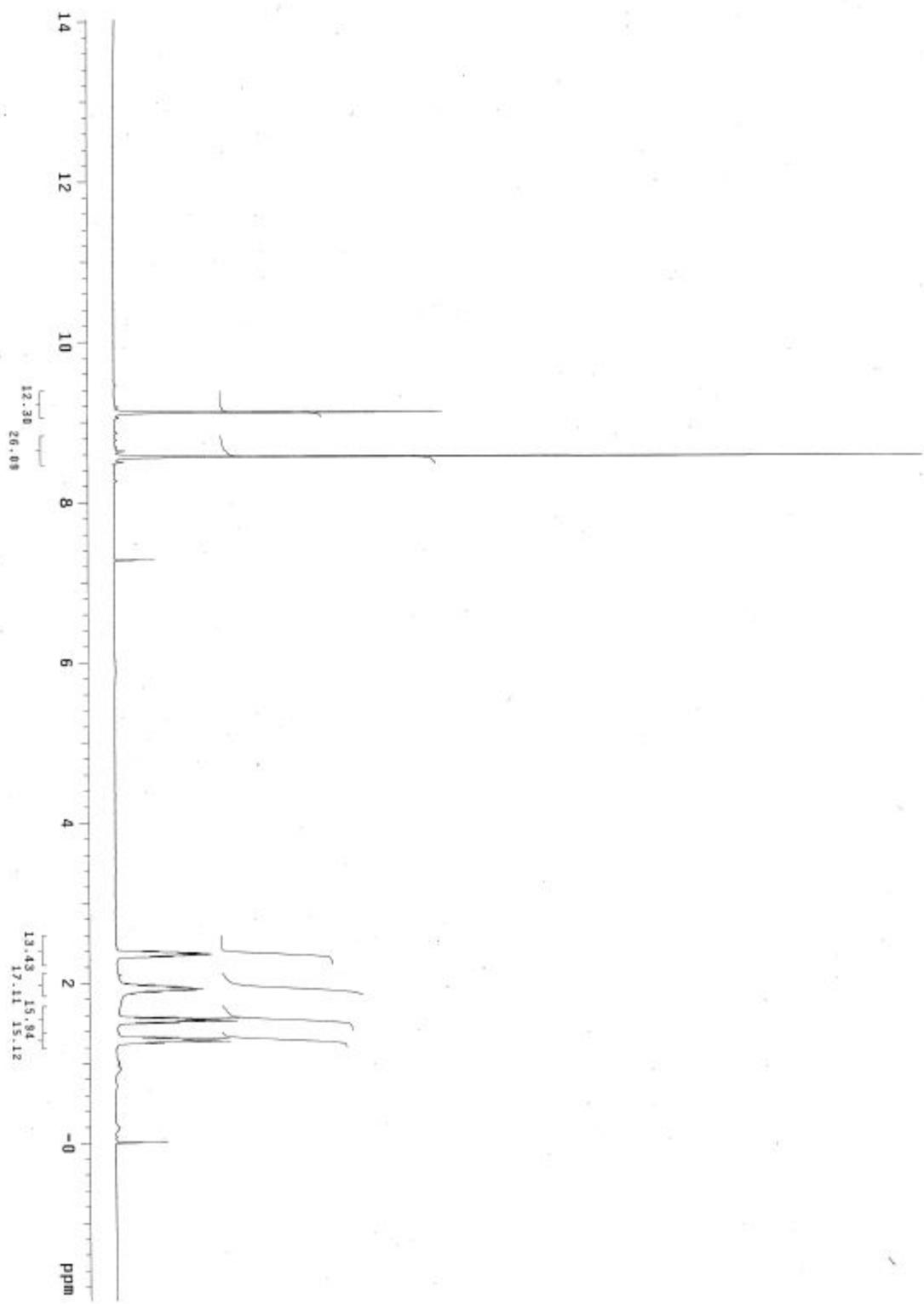
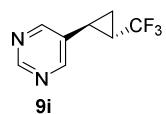
1 4.69

Combine (126:129-(107:108+146:147))

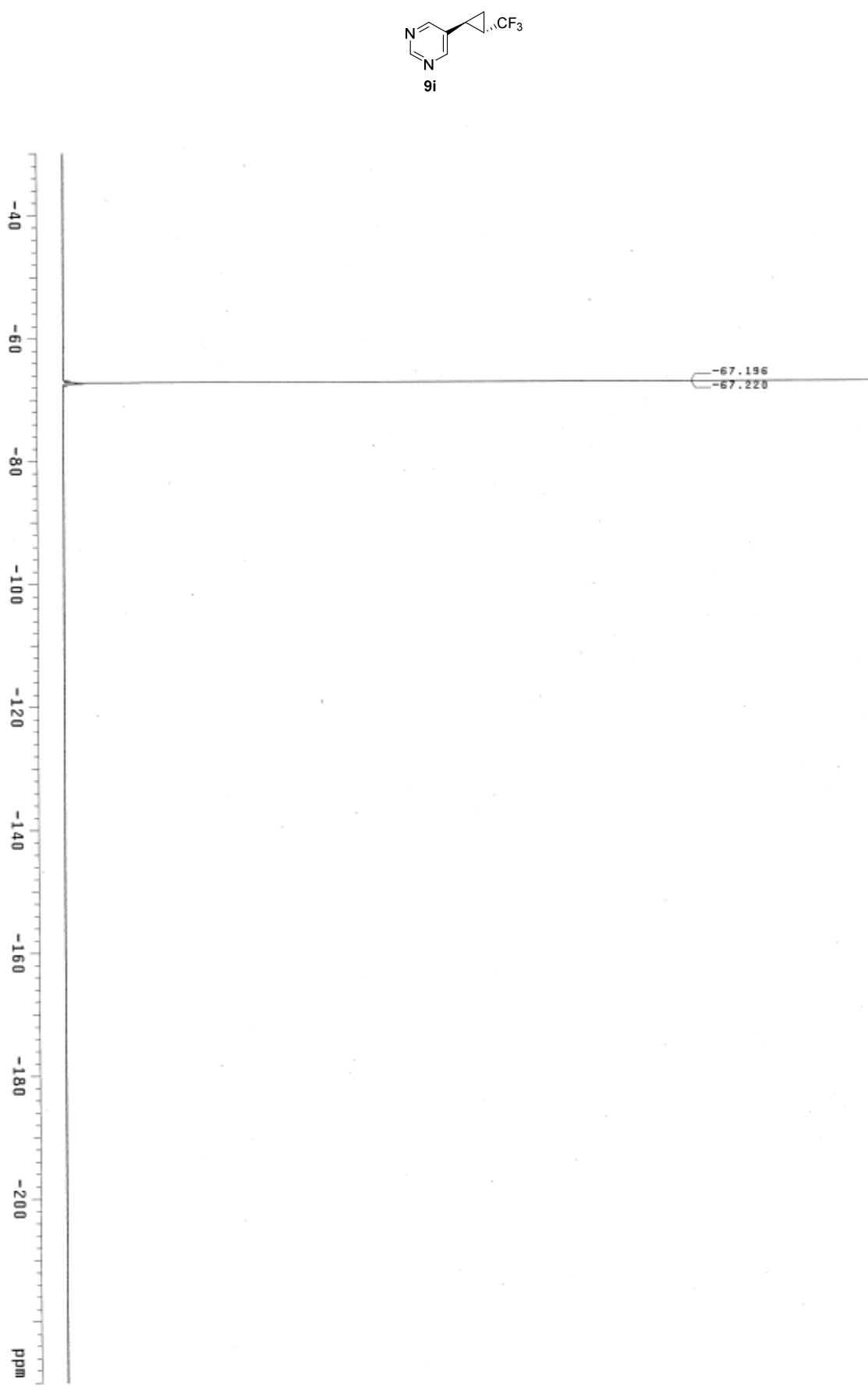
152.85



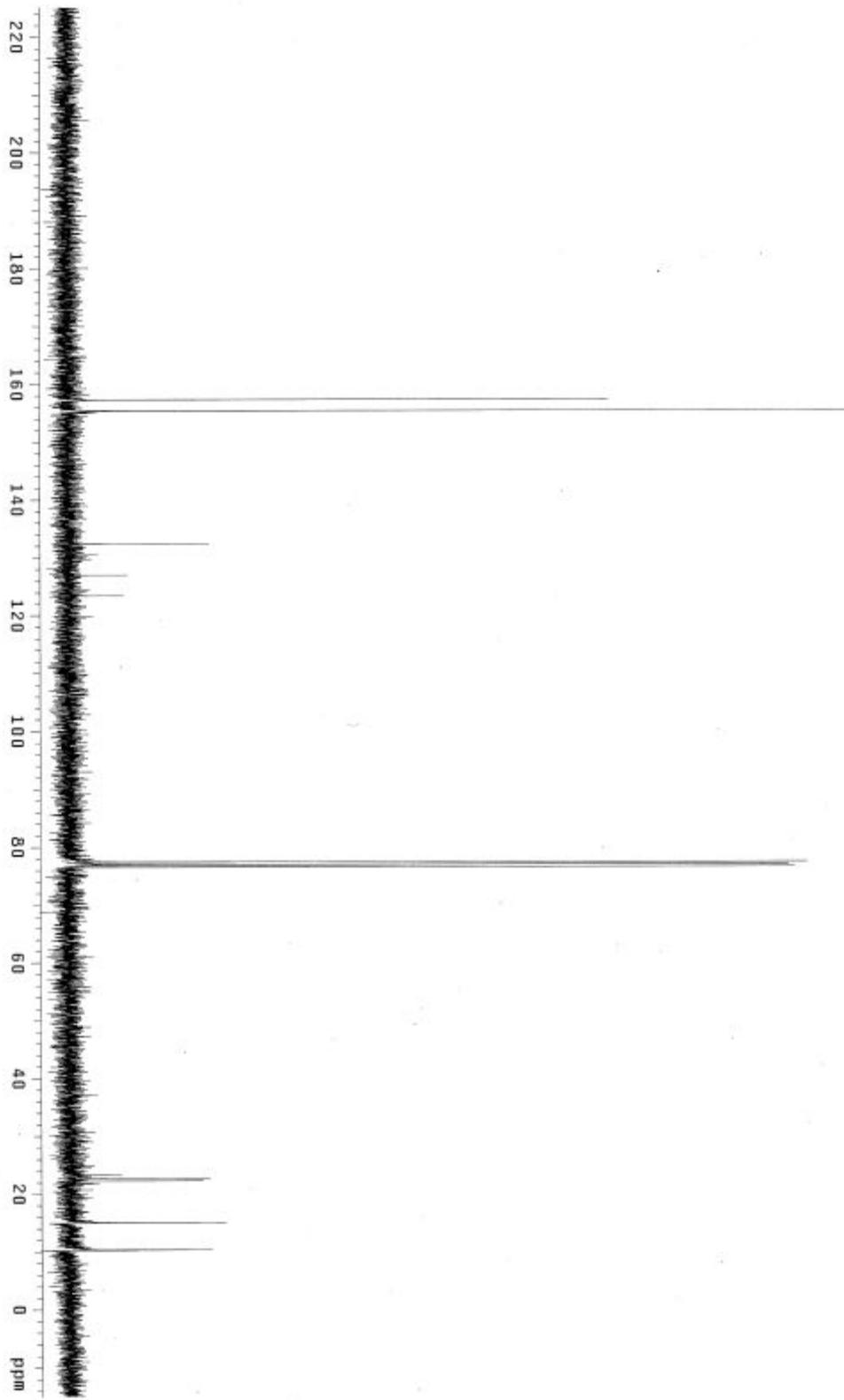
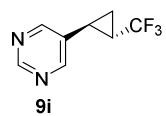
¹H NMR DATA FOR COMPOUND 7I



¹⁹F NMR DATA FOR COMPOUND 7I



¹³C NMR DATA FOR COMPOUND 7I



LC DATA FOR COMPOUND 9J

Openlynx Report -Yoyo

Sample: 1
File:MD1662-089B
Description:10min

Vial:2:G,2
Date:30-Aug-2011

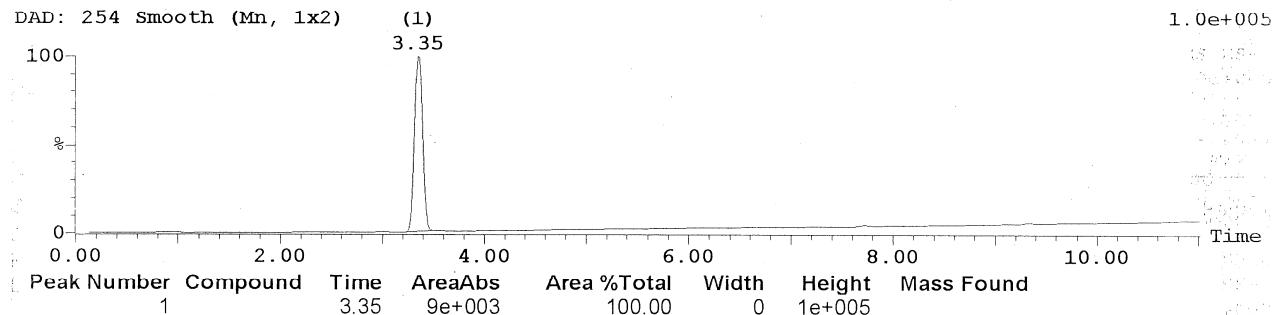
ID:
Time:13:40:30

Page 1

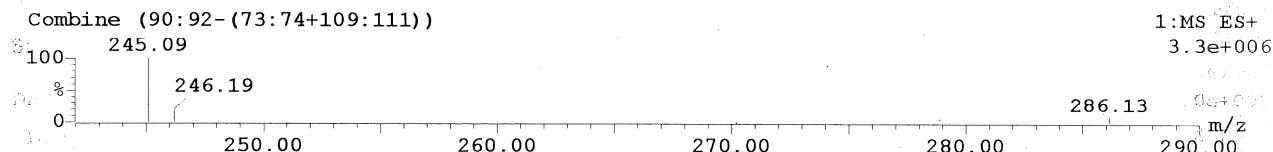
Printed: Tue Aug 30 13:52:30 2011

Sample Report:

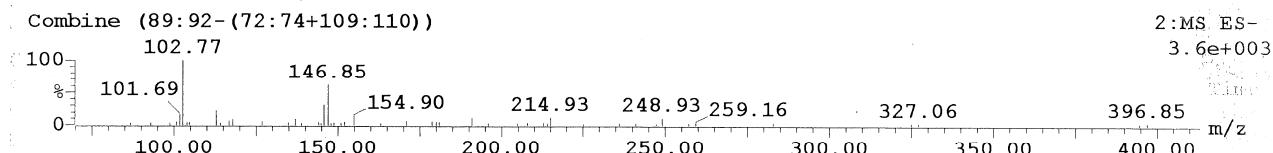
Sample 1 Vial 2:G,2 ID File MD1662-089B Date 30-Aug-2011 Time 13:40:30 Description 10min



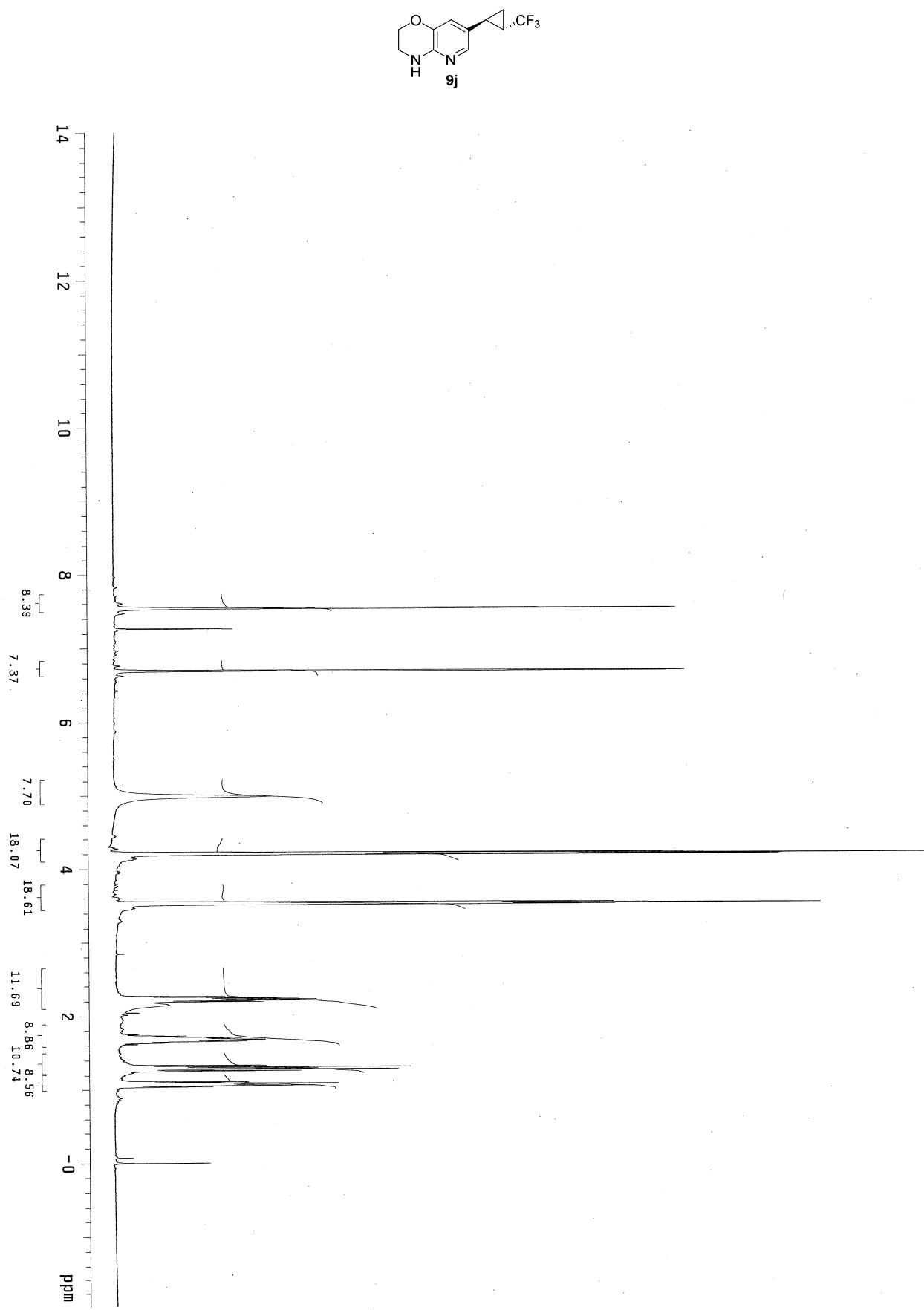
Peak ID Compound Time Mass Found
1 3.35



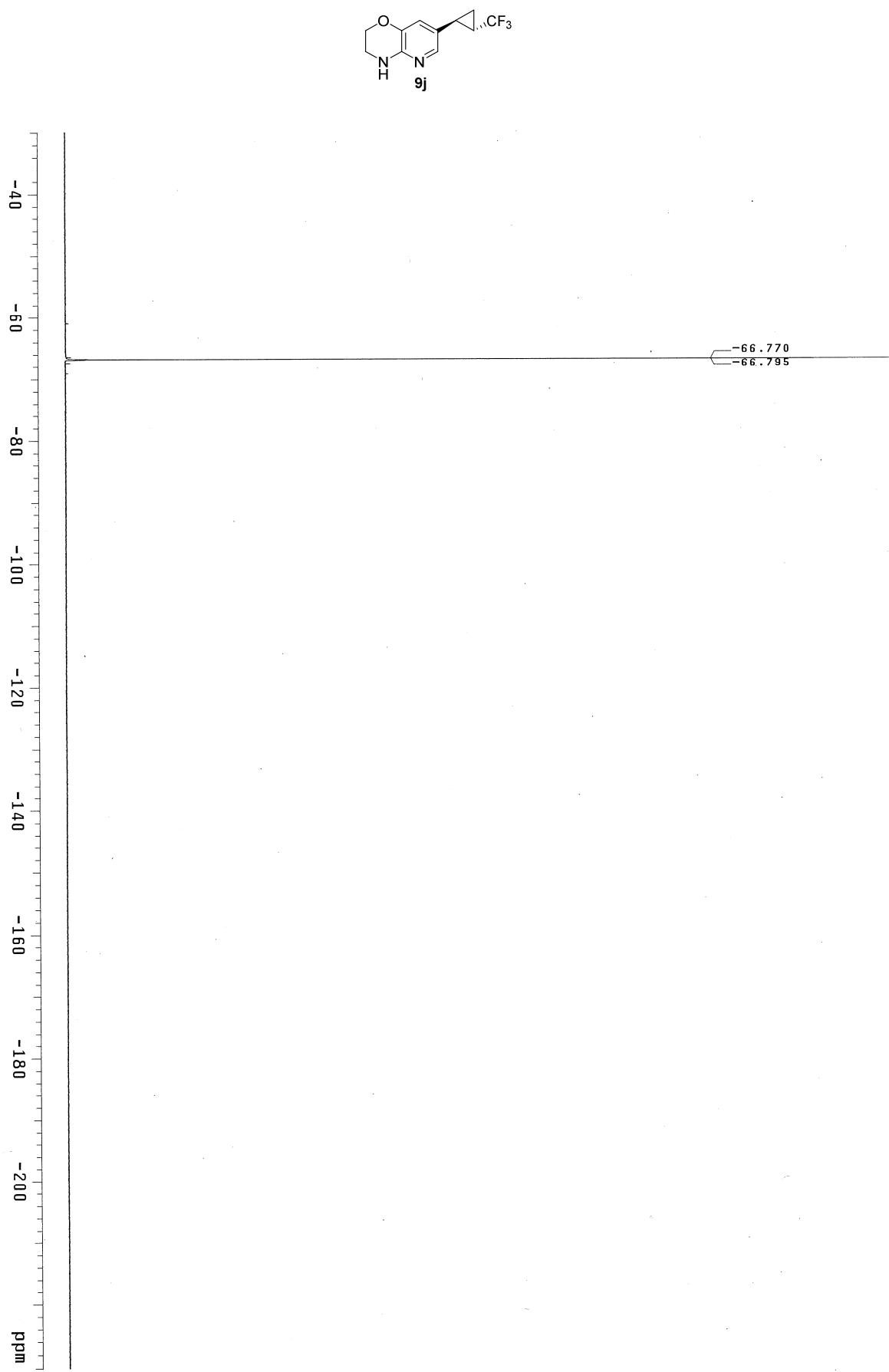
Peak ID Compound Time Mass Found
1 3.35



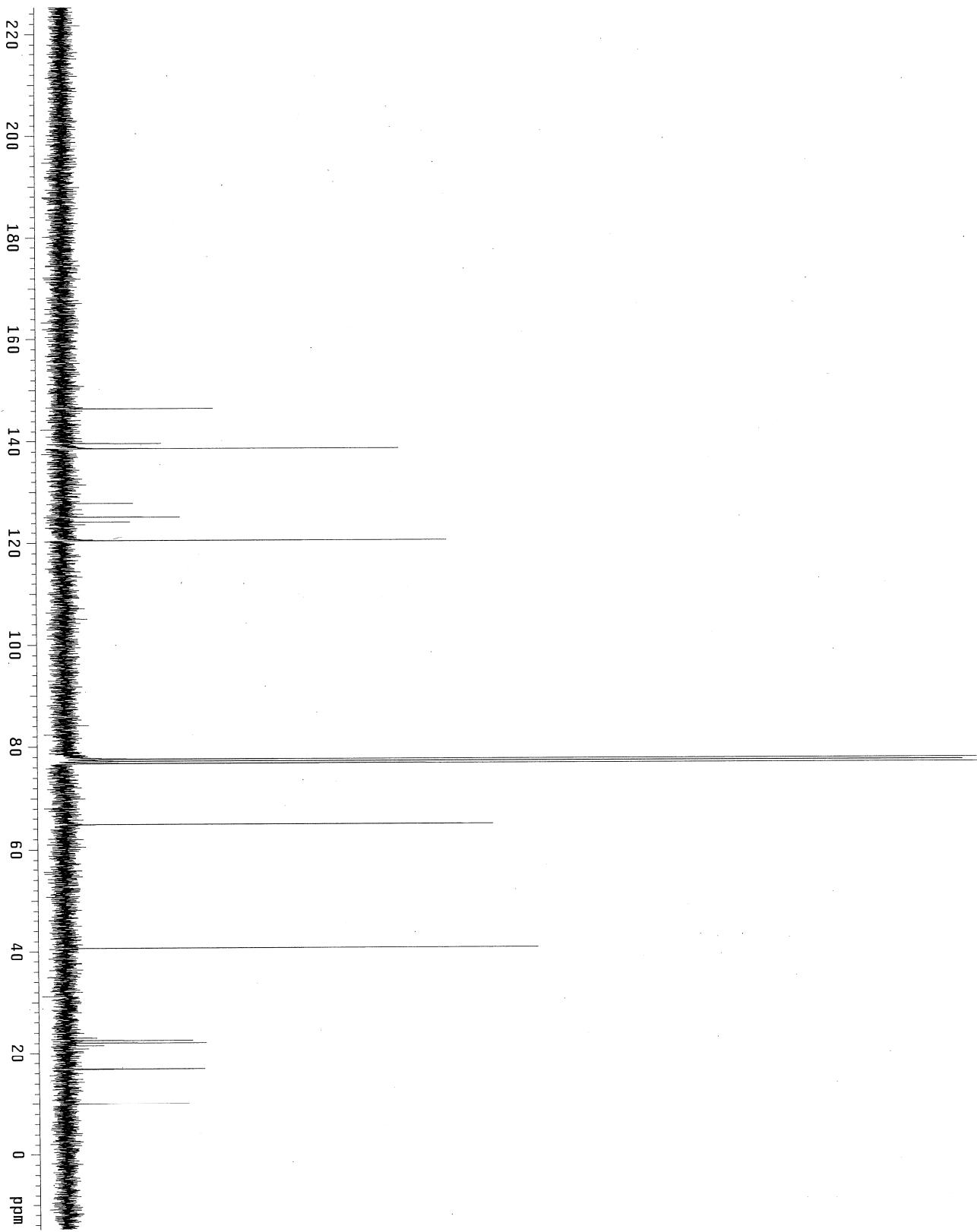
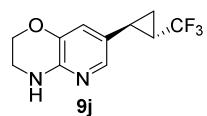
¹H NMR DATA FOR COMPOUND 9J



¹⁹F NMR DATA FOR COMPOUND 9J



¹³C NMR DATA FOR COMPOUND 9J



LC DATA FOR COMPOUND 9K

Openlynx Report -Yoyo

Sample: 1
File:MD1662-113
Description:10min

Vial:1:G,2
Date:13-Oct-2011

ID:
Time:14:21:31

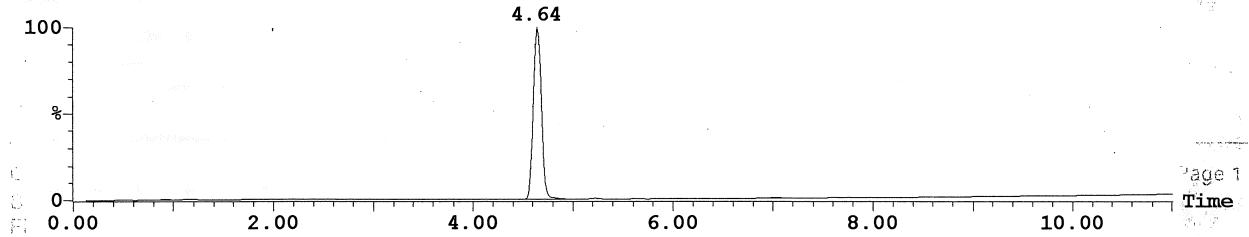
Page 1

Printed: Thu Oct 13 14:34:02 2011

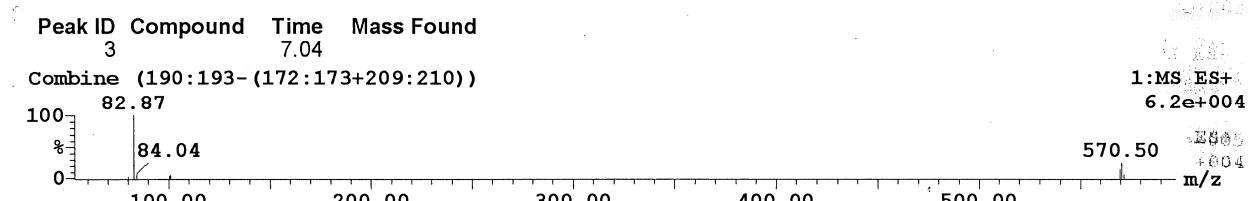
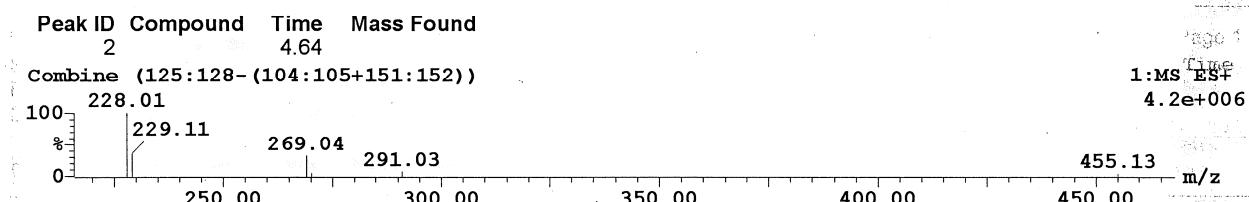
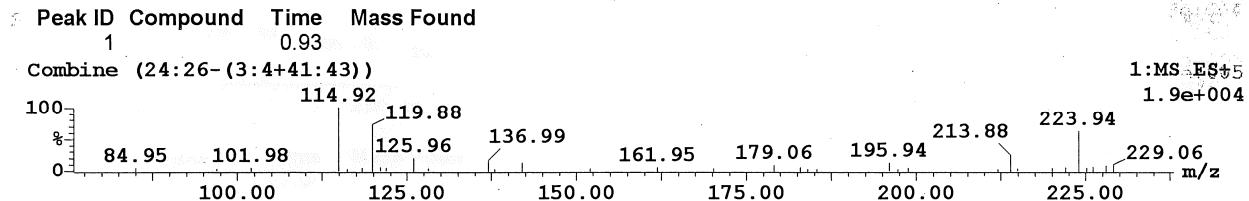
Sample Report:

Sample 1 Vial 1:G,2 ID File MD1662-113 Date 13-Oct-2011 Time 14:21:31 Description 10min

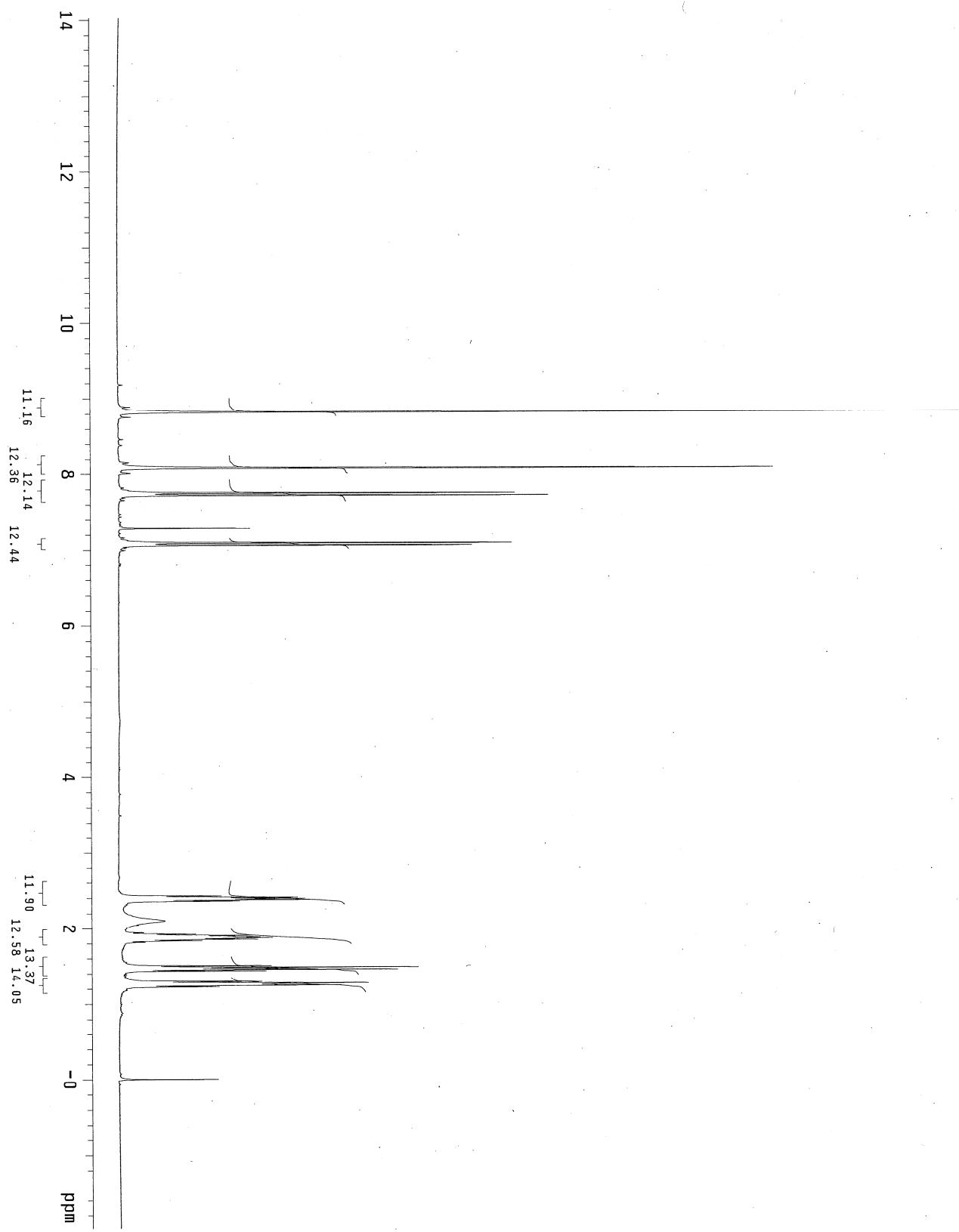
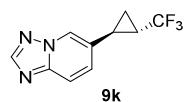
DAD: 254 Smooth (Mn, 1x2) 2.3e+005



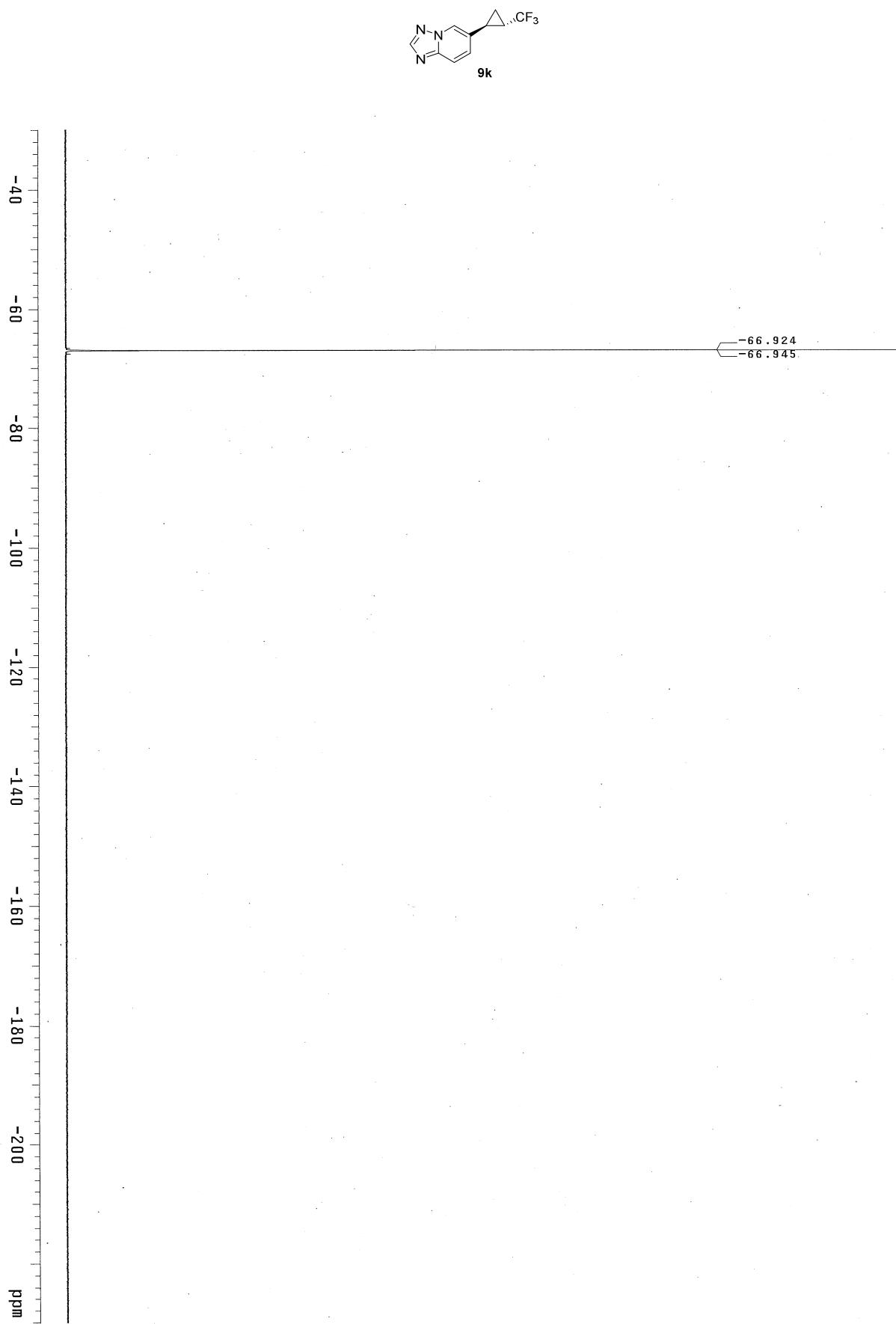
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		0.93	2e+002	0.90	0	1e+003	
2		4.64	2e+004	98.61	1	2e+005	
3		7.04	1e+002	0.46	0	1e+003	
4		9.18	8e+000	0.04	0	8e+001	



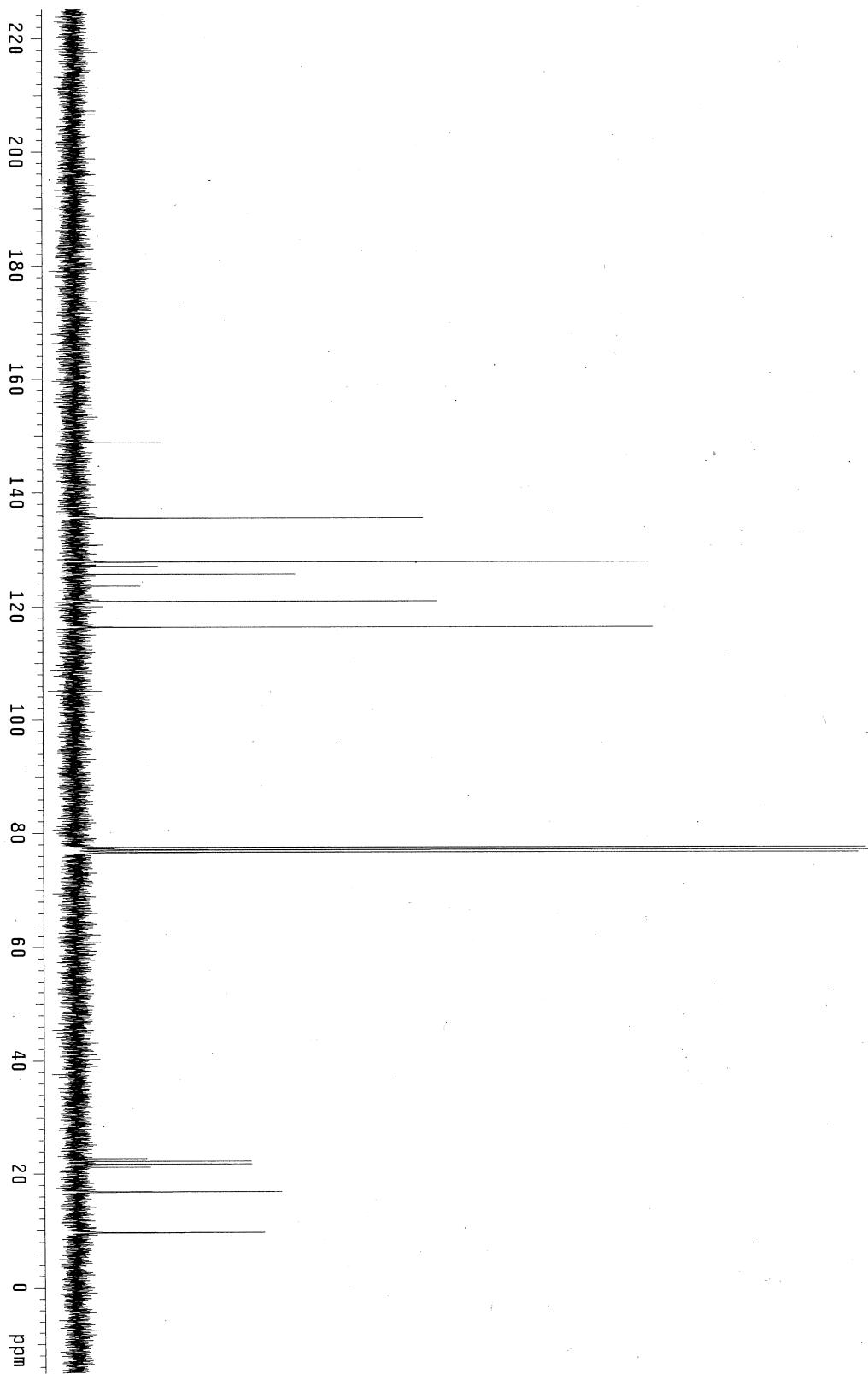
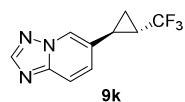
¹H NMR DATA FOR COMPOUND 9K



¹⁹F NMR DATA FOR COMPOUND 9K



¹³C NMR DATA FOR COMPOUND 9K



LC DATA FOR COMPOUND 9L

Openlynx Report -Yoyo

Sample: 1
File:MD1662-116
Description:10min

Vial:1:F,9
Date:18-Oct-2011

ID:
Time:11:49:06

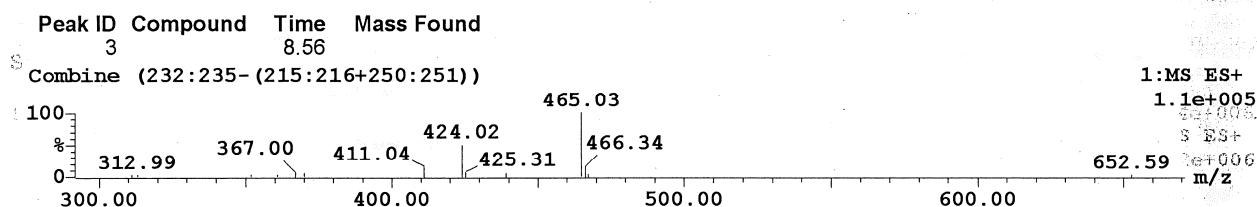
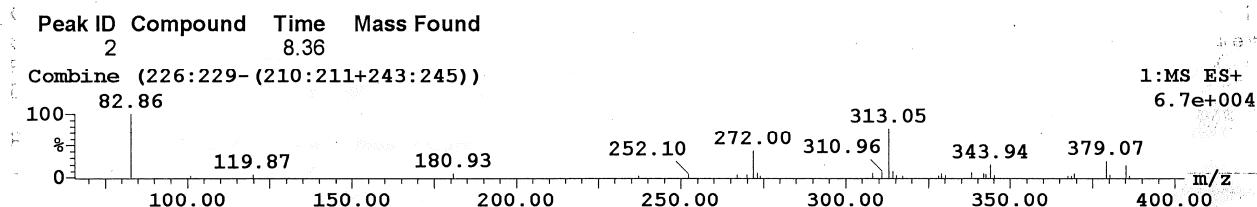
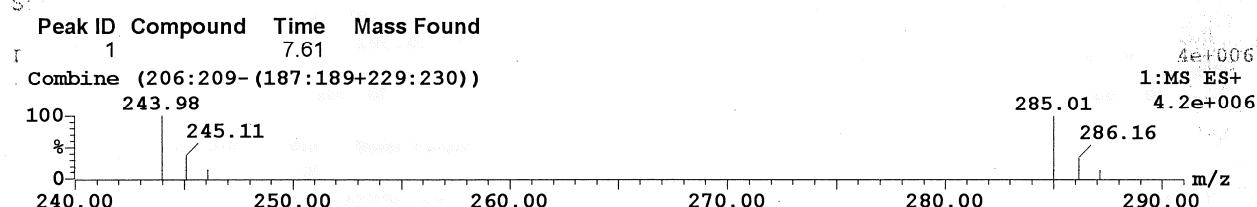
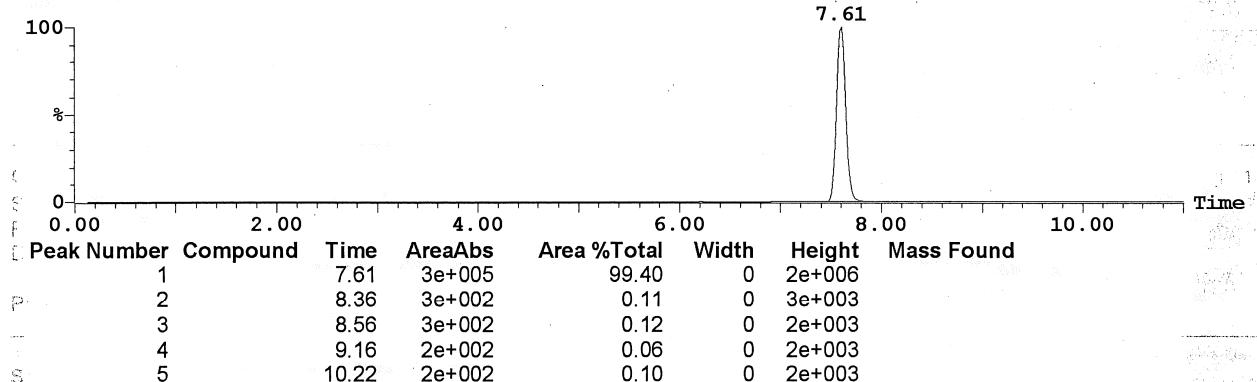
Page 1

Printed: Tue Oct 18 12:01:09 2011

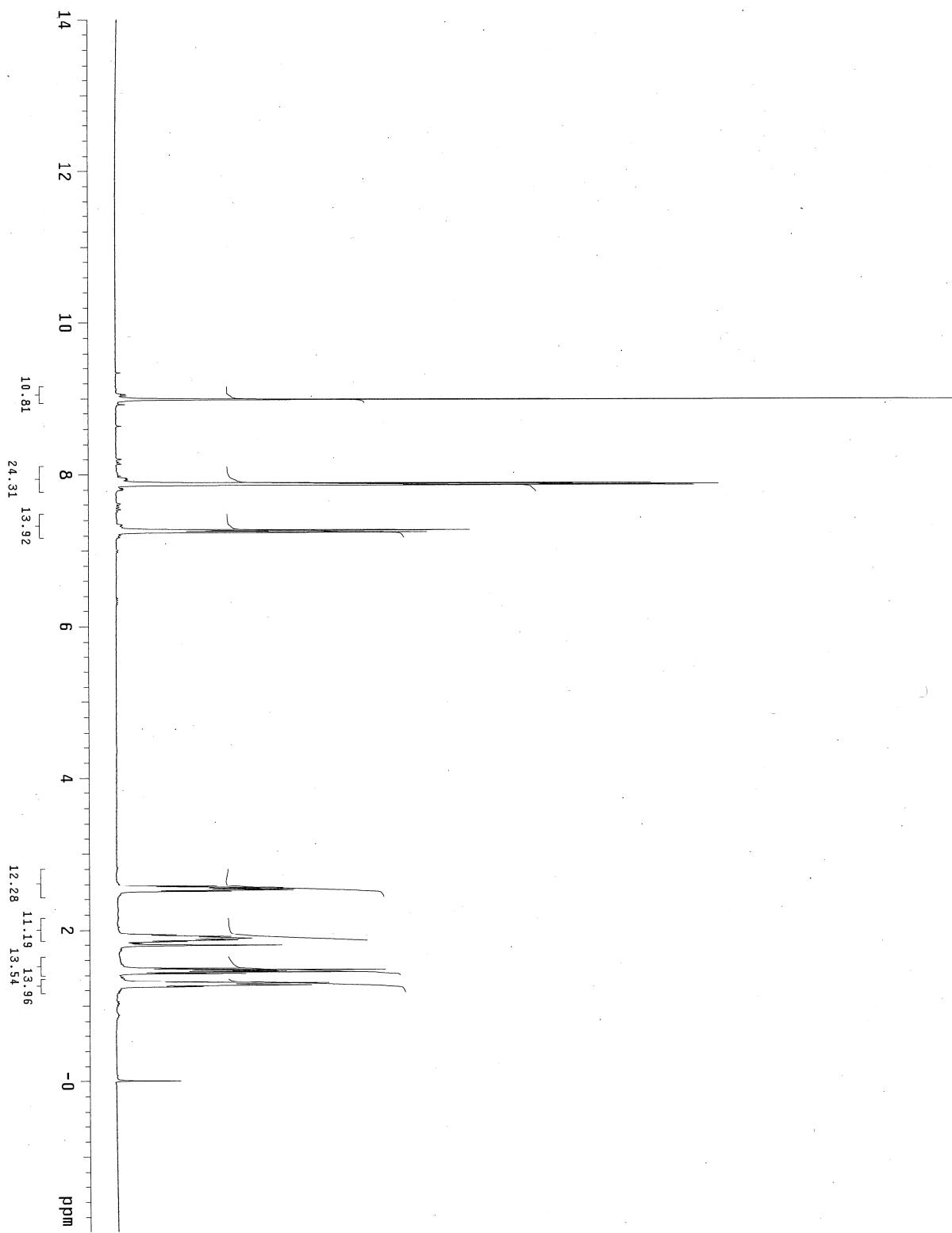
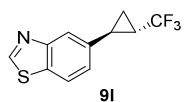
Sample Report:

Sample 1 Vial 1:F,9 ID File MD1662-116 Date 18-Oct-2011 Time 11:49:06 Description 10min

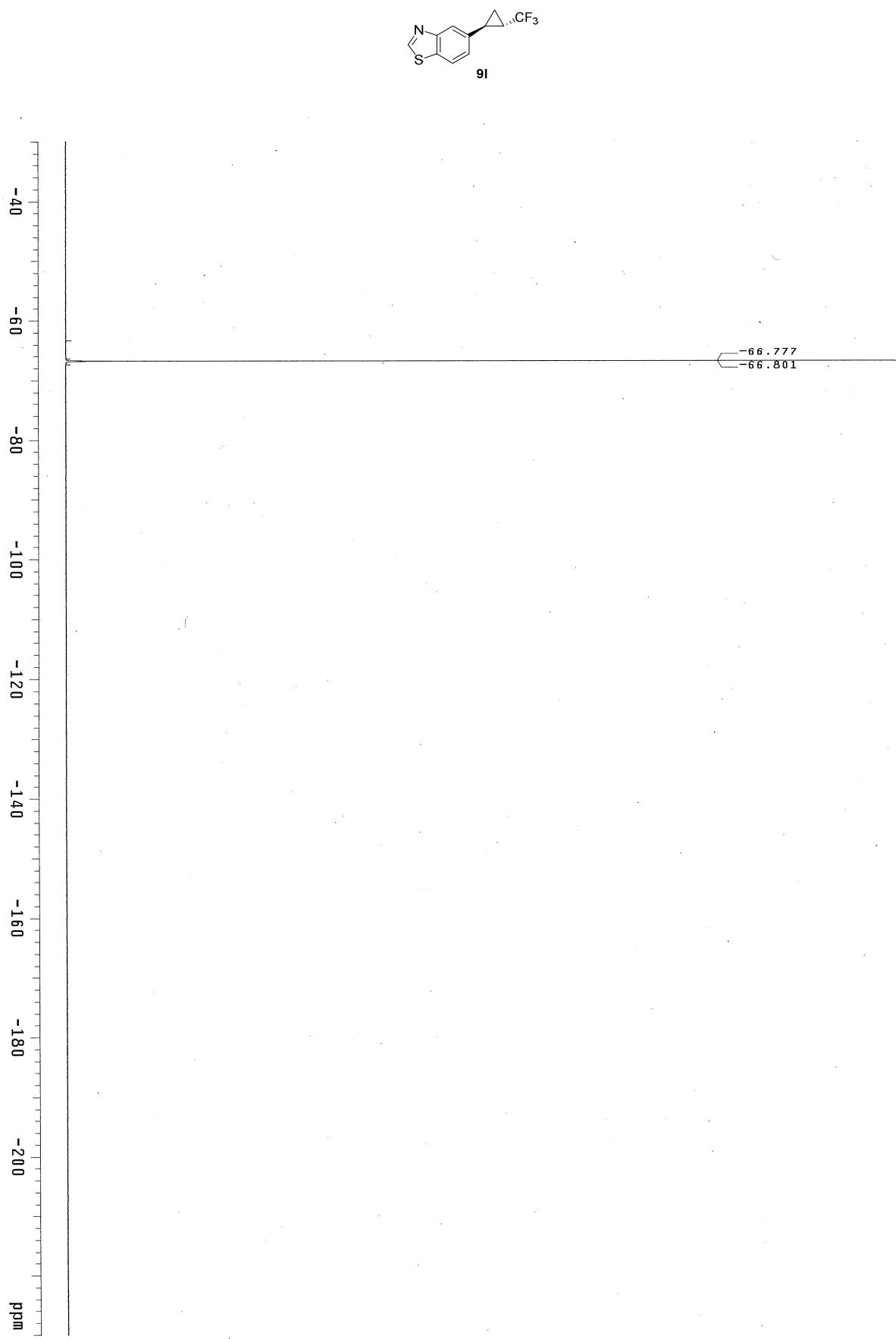
DAD: 254 Smooth (Mn, 1x2)



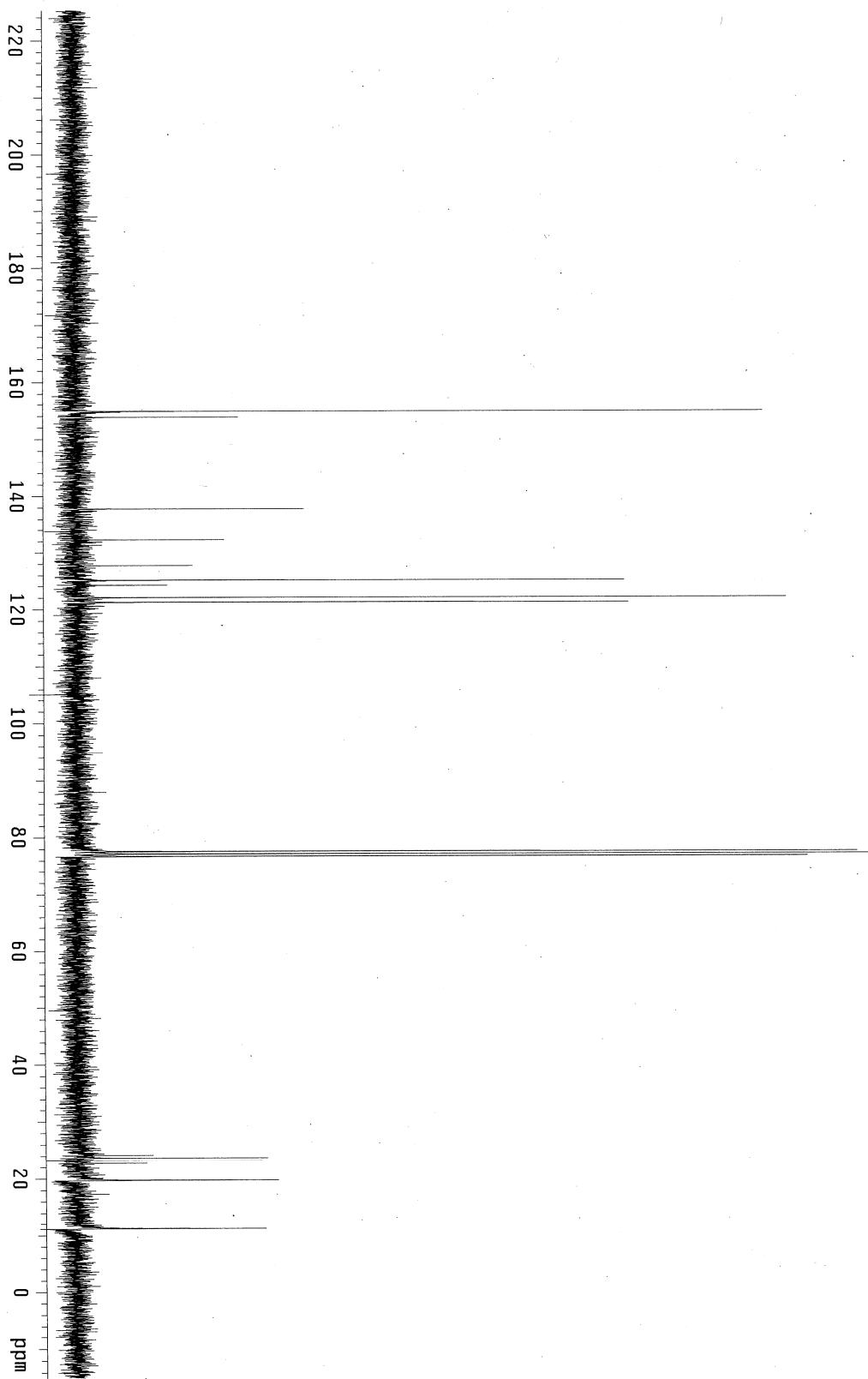
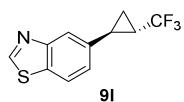
¹H NMR DATA FOR COMPOUND 9L



¹⁹F NMR DATA FOR COMPOUND 9L



¹³C NMR DATA FOR COMPOUND 9L



LC DATA FOR COMPOUND 9M

Openlynx Report -Yoyo

Sample: 1
File:MD1662-118
Description:10min

Vial:1:F,9
Date:26-Oct-2011

ID:
Time:10:48:47

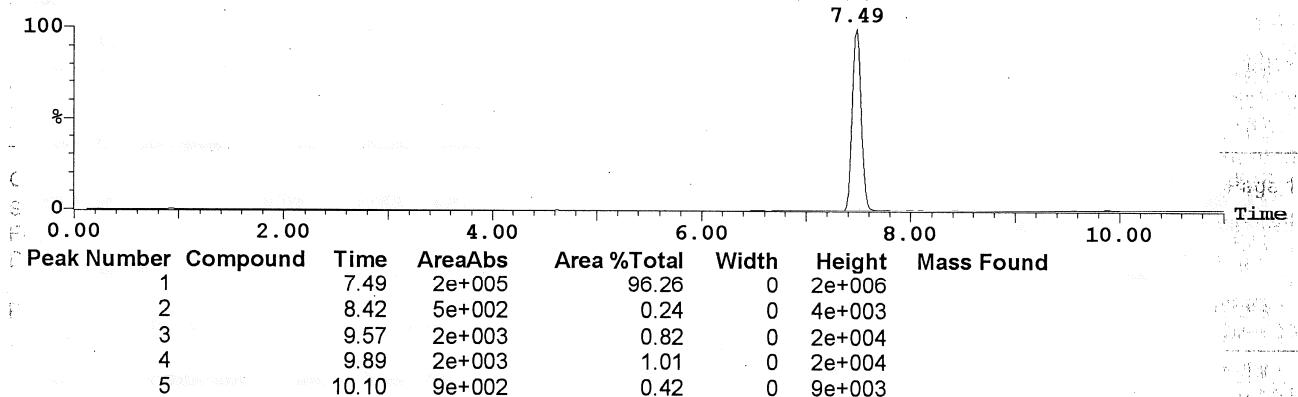
Page 1

Printed: Wed Oct 26 11:01:48 2011

Sample Report:

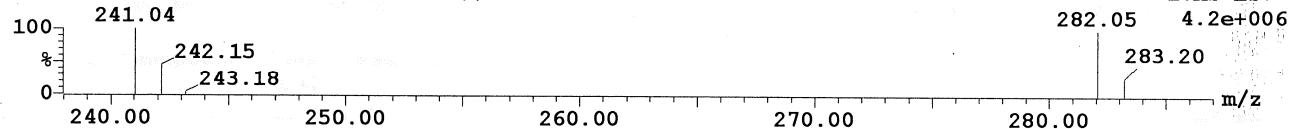
Sample 1 Vial 1:F,9 ID File MD1662-118 Date 26-Oct-2011 Time 10:48:47 Description 10min

DAD: 254 Smooth (Mn, 1x2)



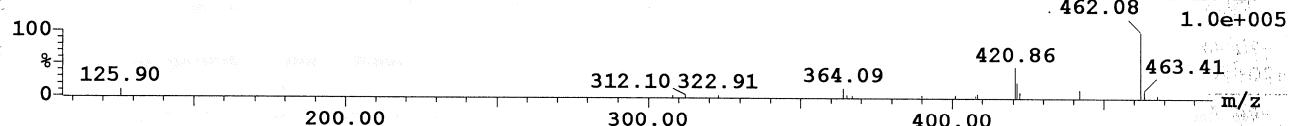
Peak ID Compound Time Mass Found
1 7.49

Combine (203:205- (185:186+224:226))



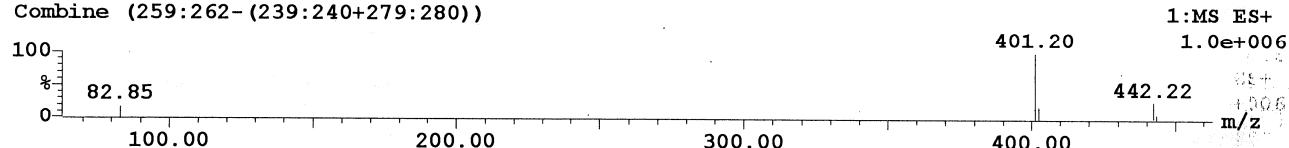
Peak ID Compound Time Mass Found
2 8.42

Combine (228:231- (211:213+246:247))

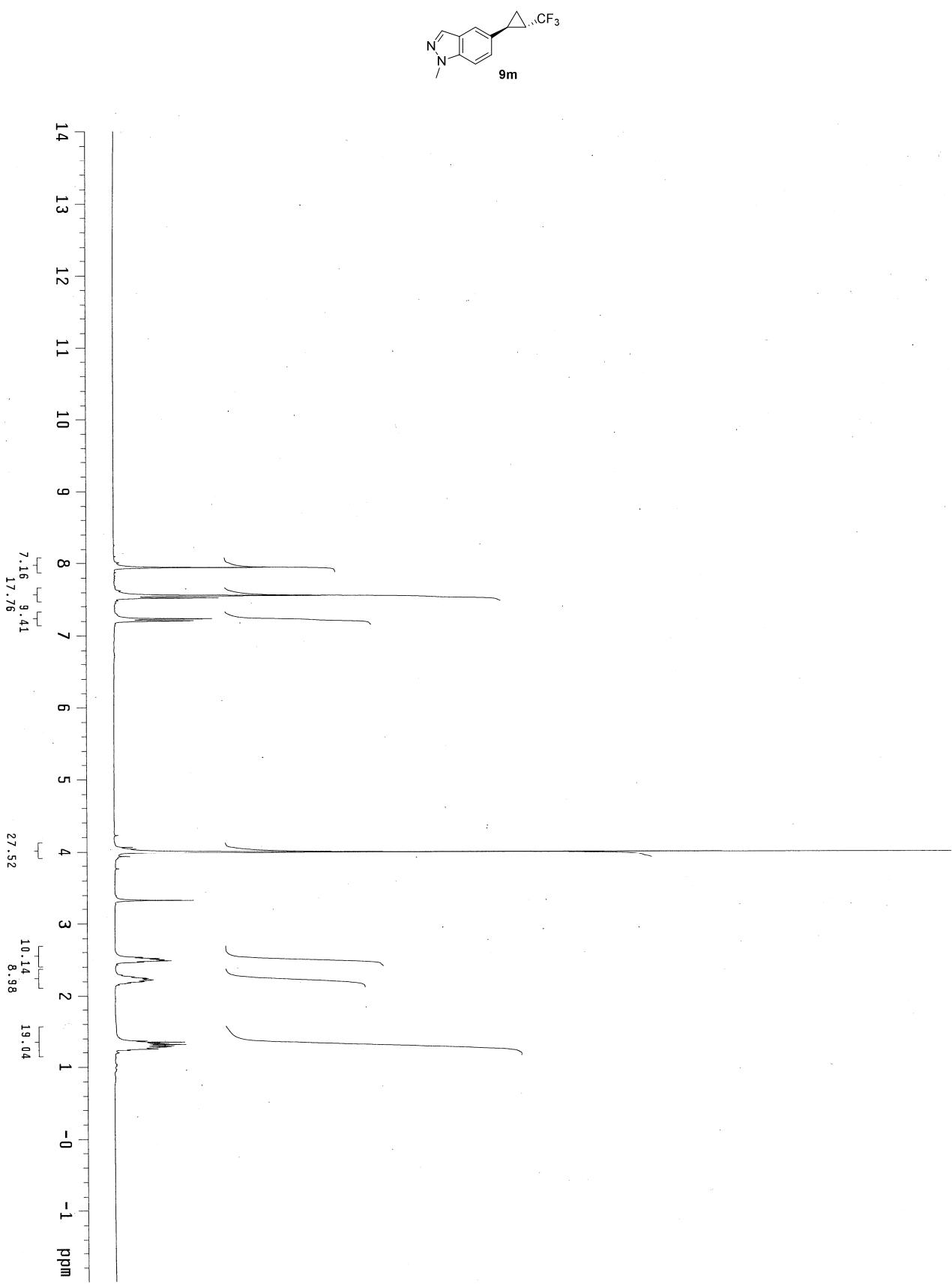


Peak ID Compound Time Mass Found
3 9.57

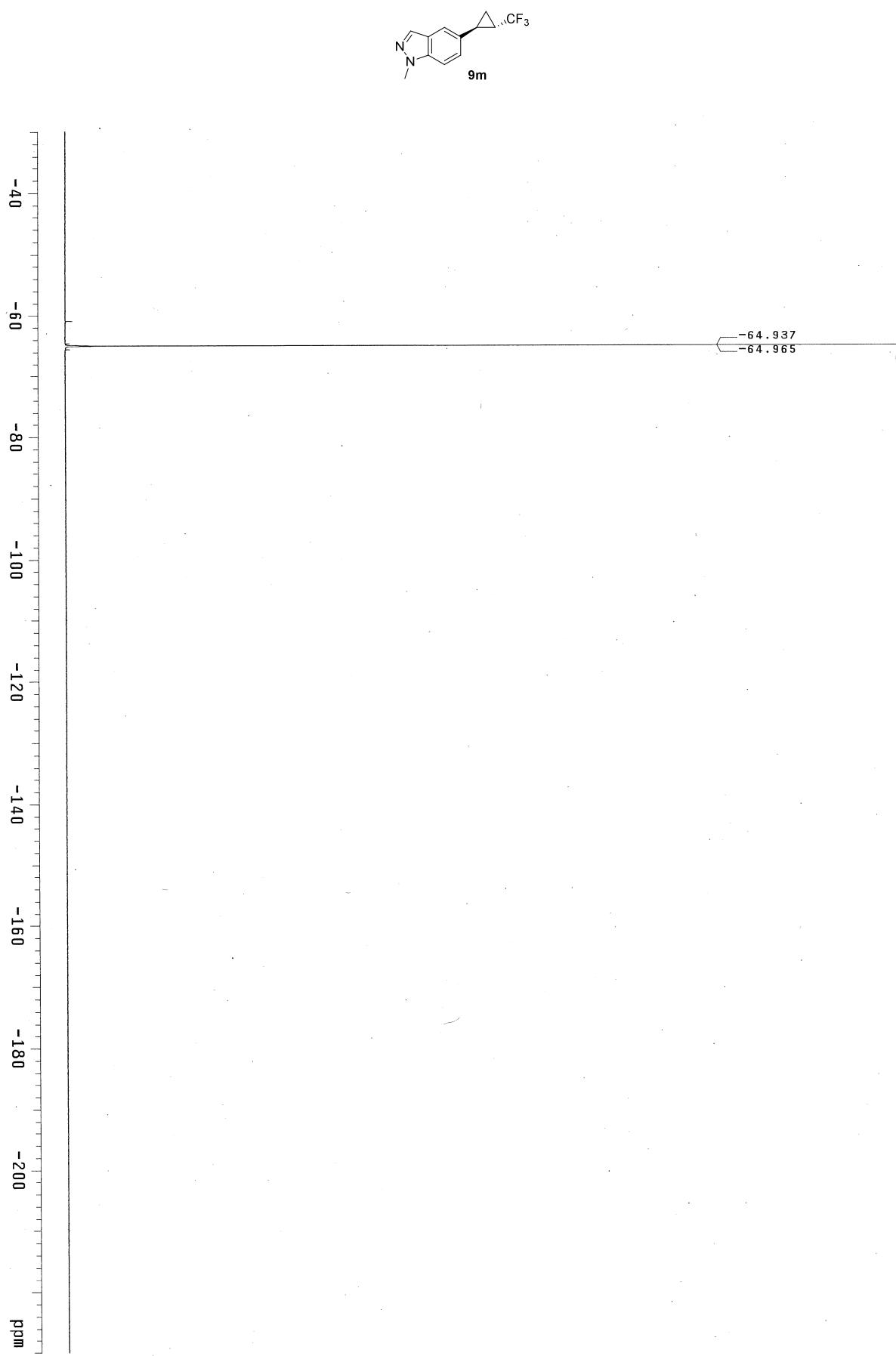
Combine (259:262- (239:240+279:280))



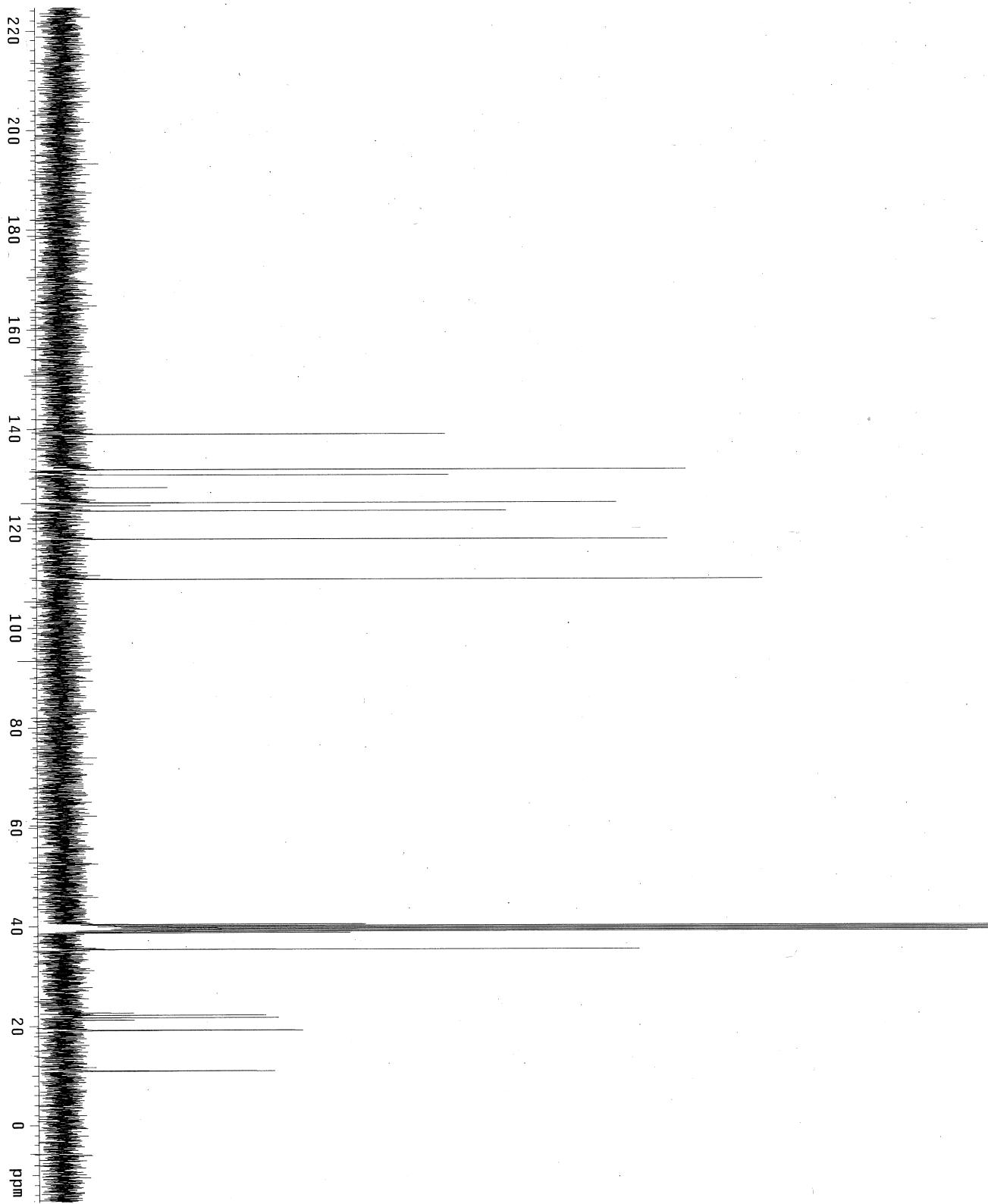
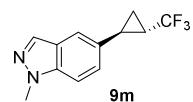
¹H NMR DATA FOR COMPOUND 9M



¹⁹F NMR DATA FOR COMPOUND 9M



¹³C NMR DATA FOR COMPOUND 9M



LC DATA FOR COMPOUND 9N

Openlynx Report -Yoyo

Sample: 1
File:MD1662-117
Description:10min

Vial:1:F,9
Date:25-Oct-2011

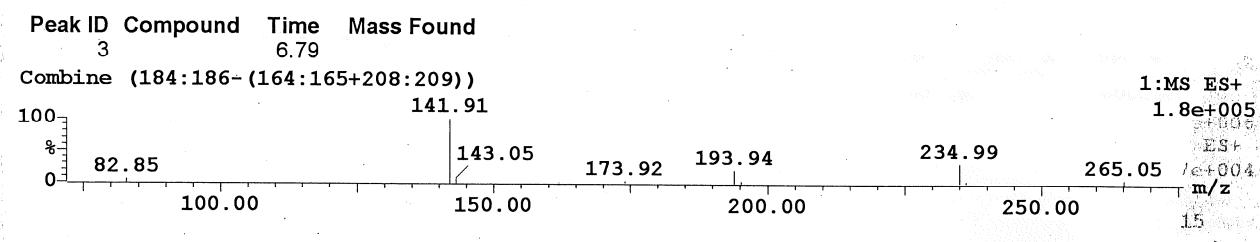
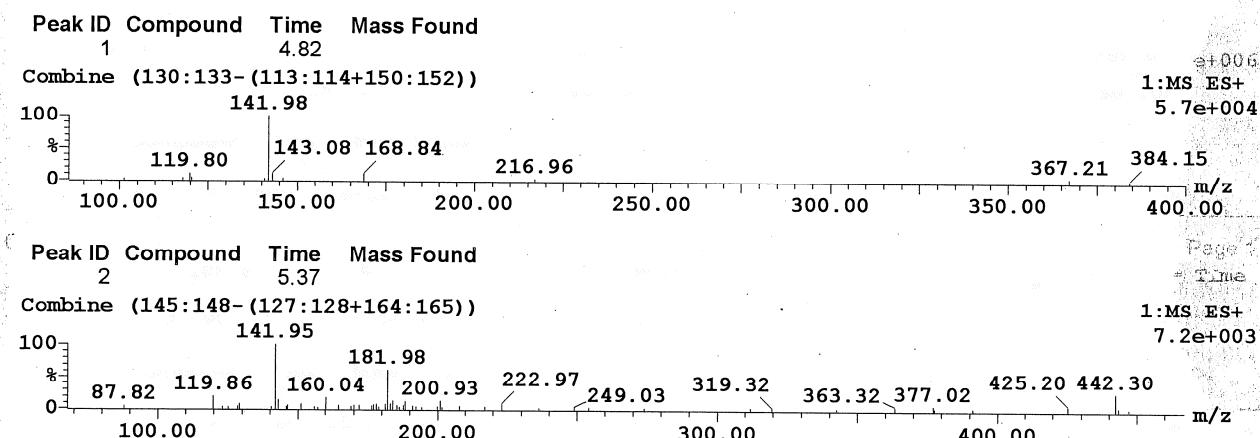
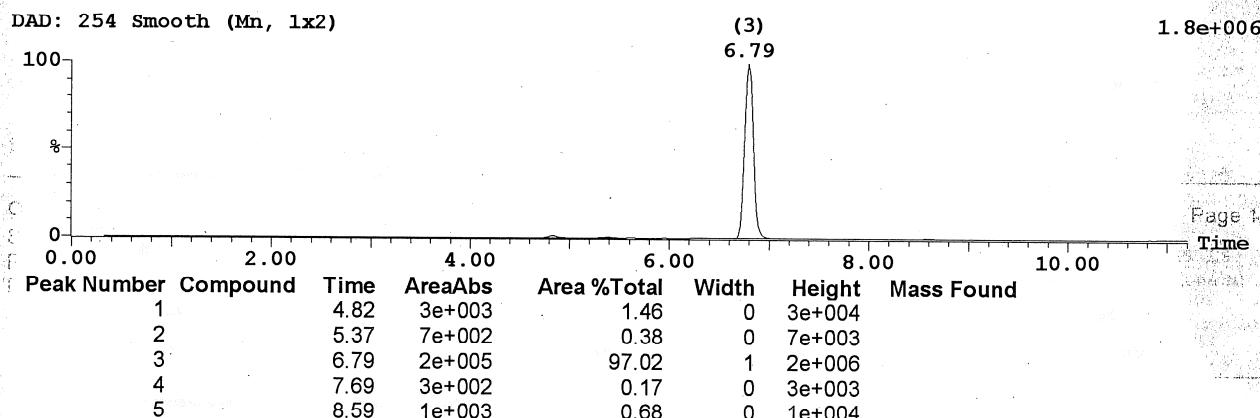
ID:
Time:12:11:21

Page 1

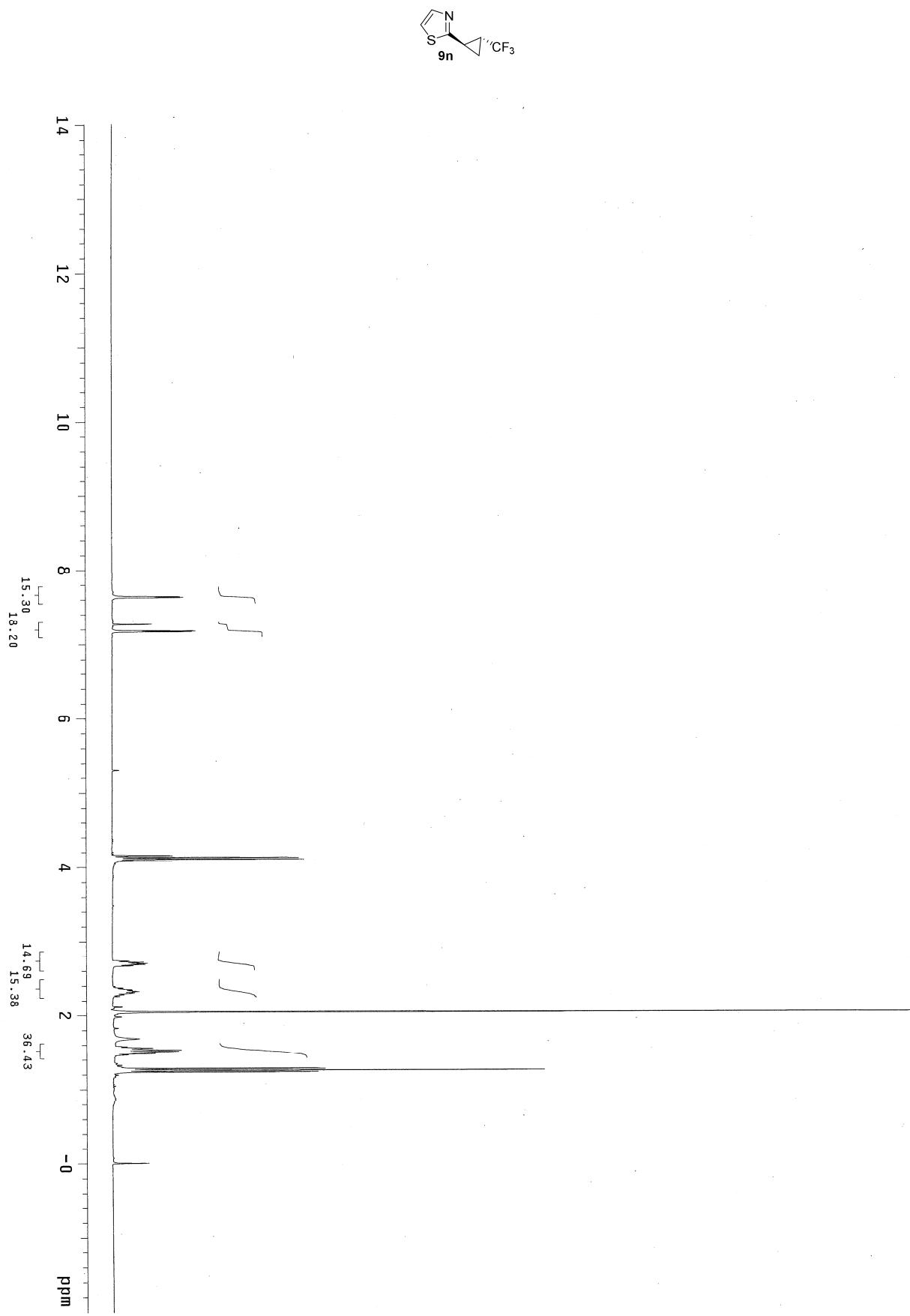
Printed: Tue Oct 25 12:26:02 2011

Sample Report:

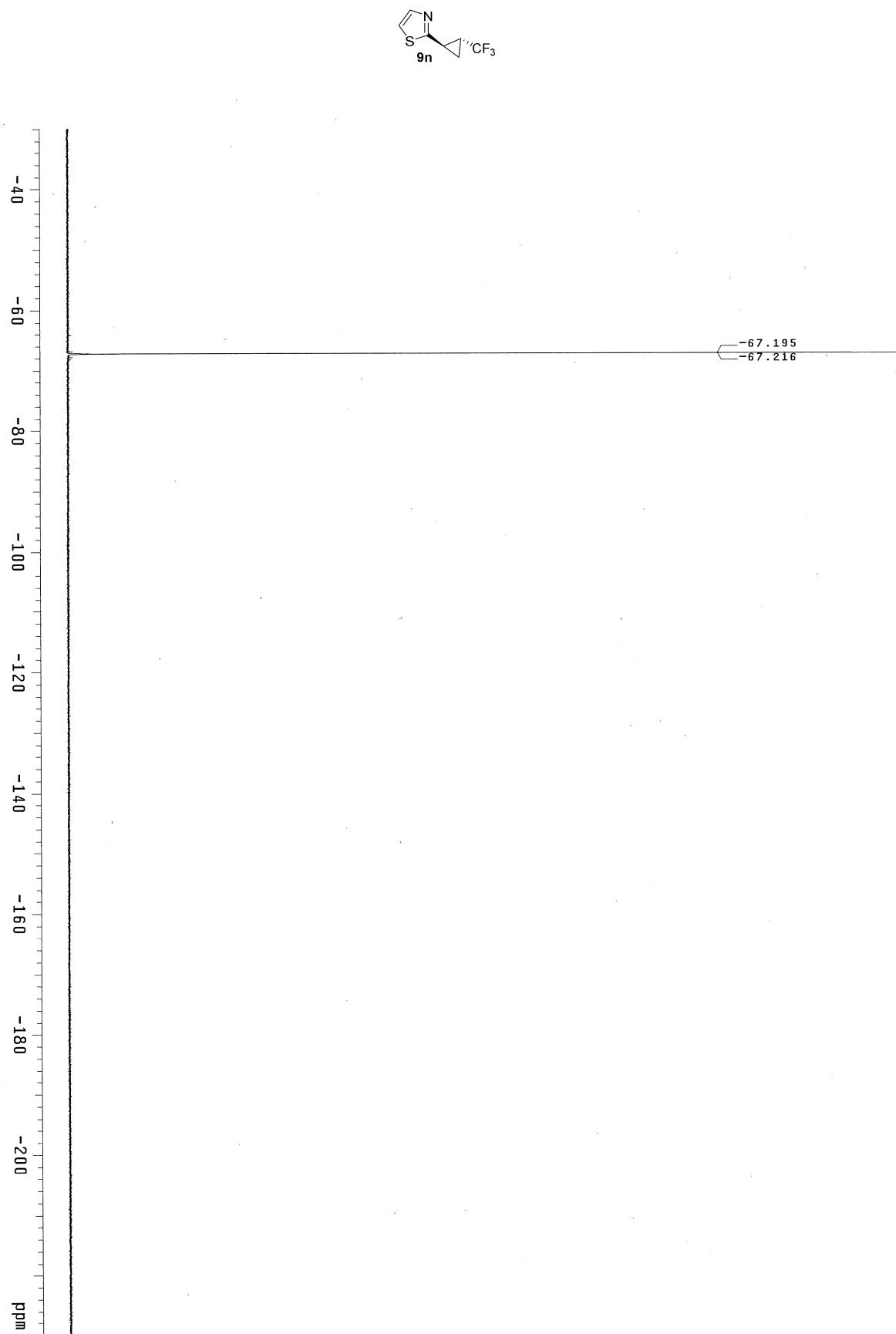
Sample 1 Vial 1:F,9 ID File MD1662-117 Date 25-Oct-2011 Time 12:11:21 Description 10min



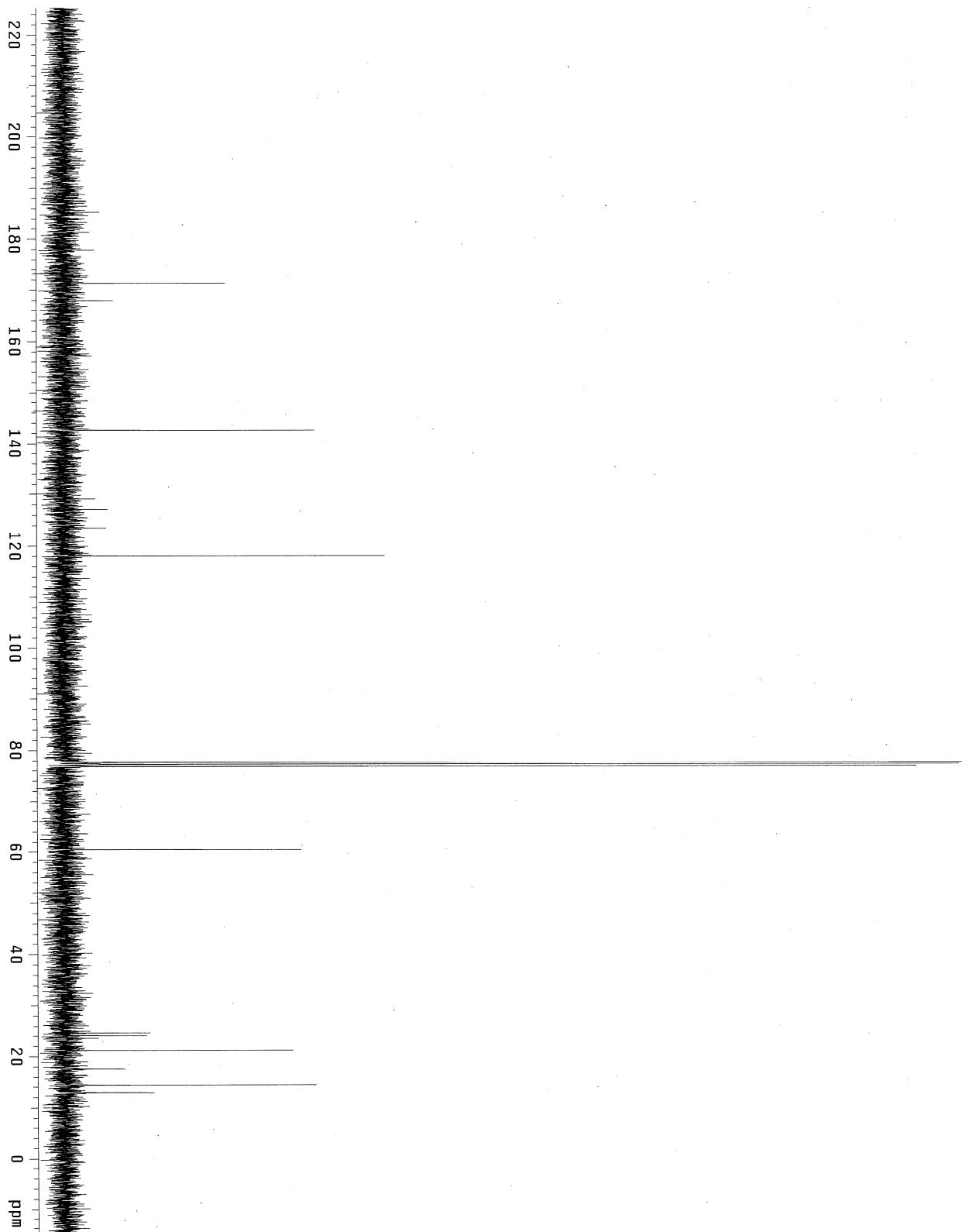
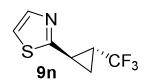
¹H NMR DATA FOR COMPOUND 9N (+ RESIDUAL ETHYL ACETATE)



¹⁹F NMR DATA FOR COMPOUND 9N (RESIDUAL ETHYL ACETATE DOES NOT SHOW ON ¹⁹F NMR)



¹³C NMR DATA FOR COMPOUND 9N (+ RESIDUAL ETHYL ACETATE)



LC DATA FOR COMPOUND 9O

Openlynx Report -Yoyo

Sample: 1
File:MD1662-115afterprepHPL
Description:10min

Vial:1:F,9
Date:24-Oct-2011

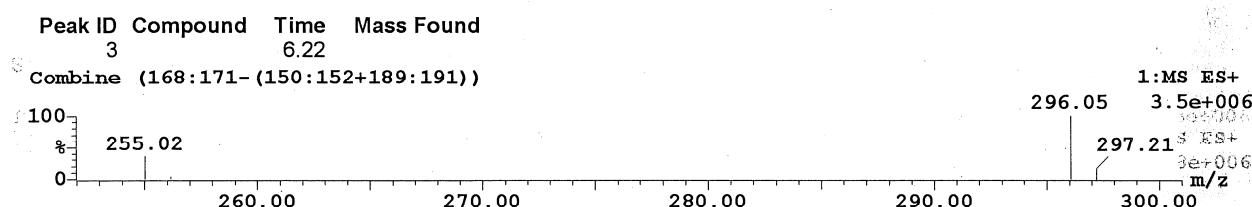
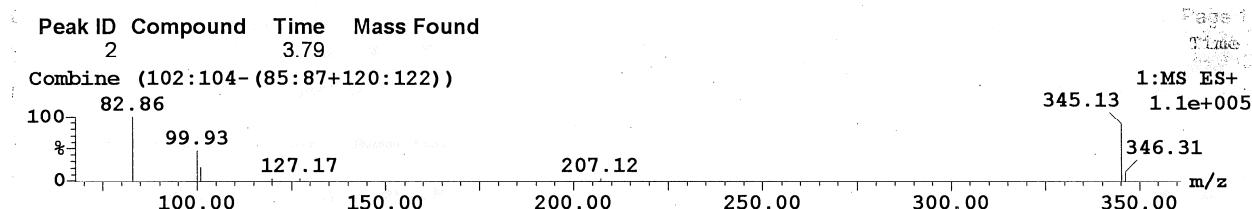
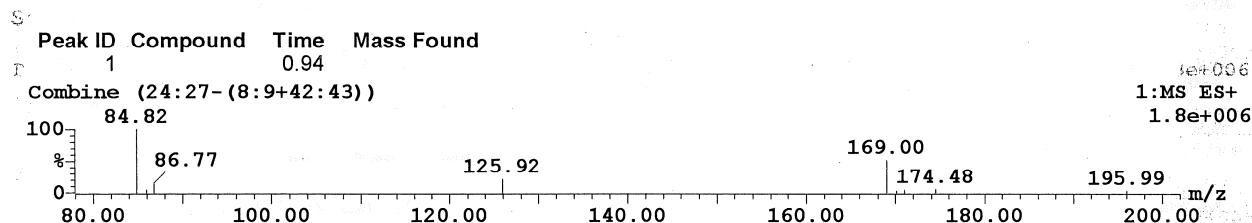
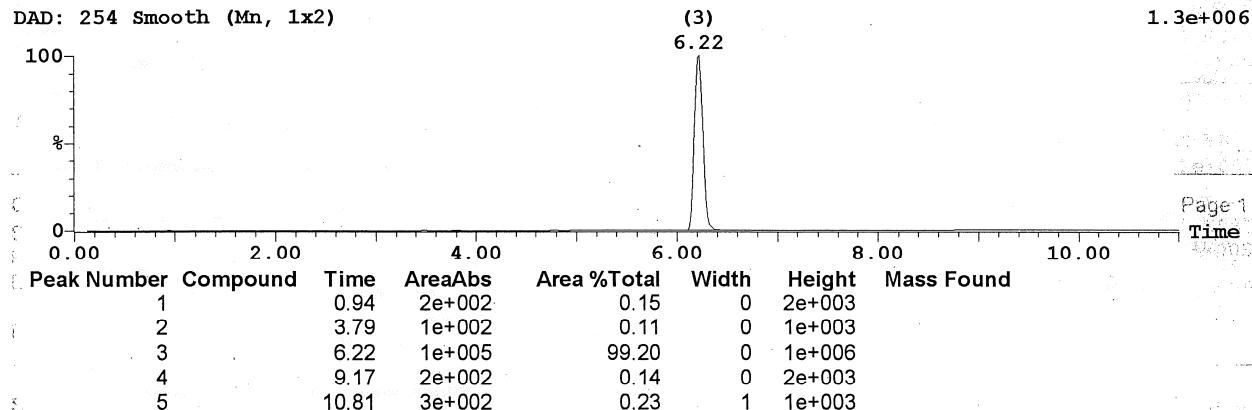
ID:
Time:12:24:37

Page 1

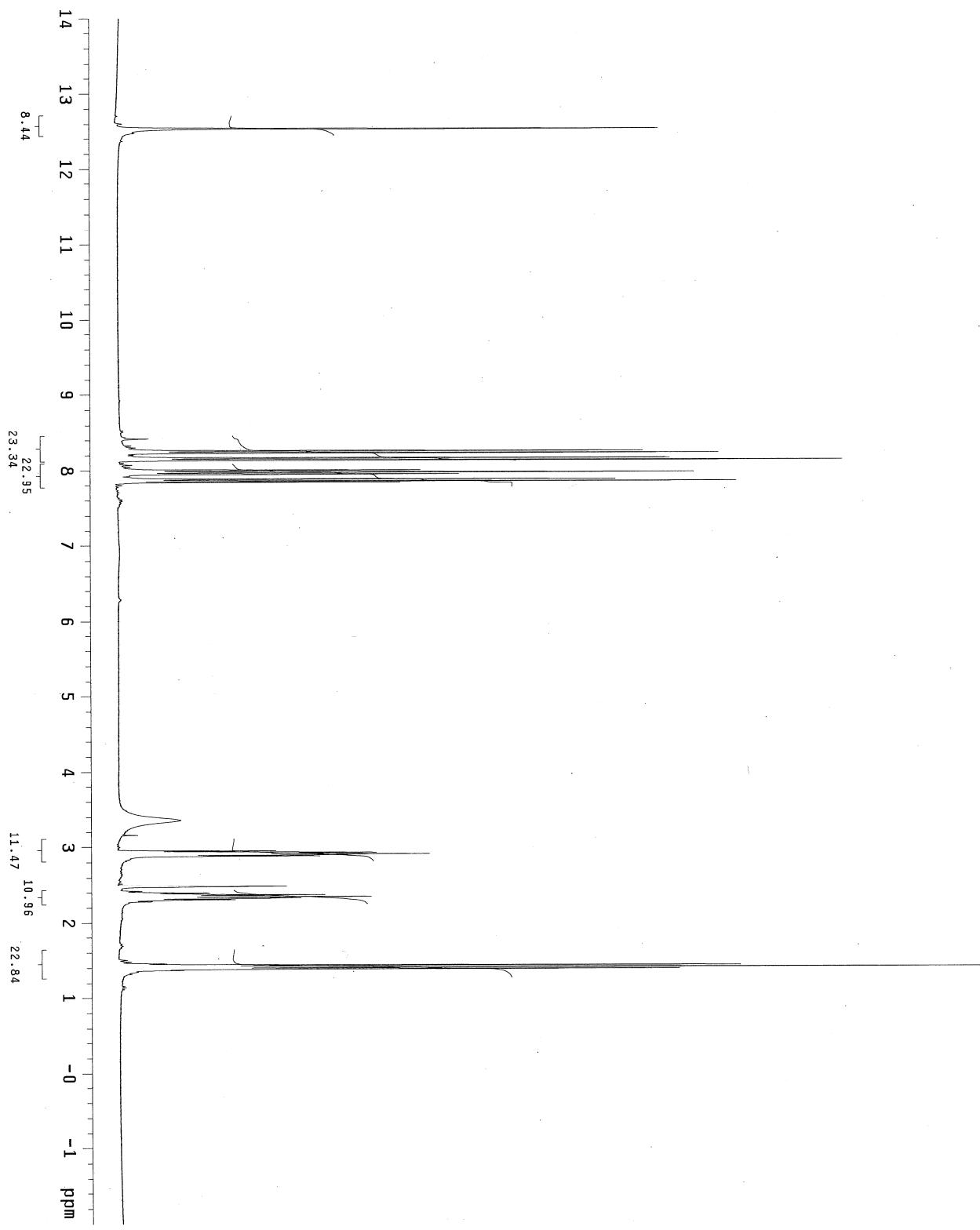
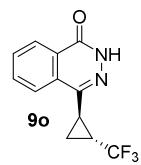
Printed: Mon Oct 24 12:36:41 2011

Sample Report:

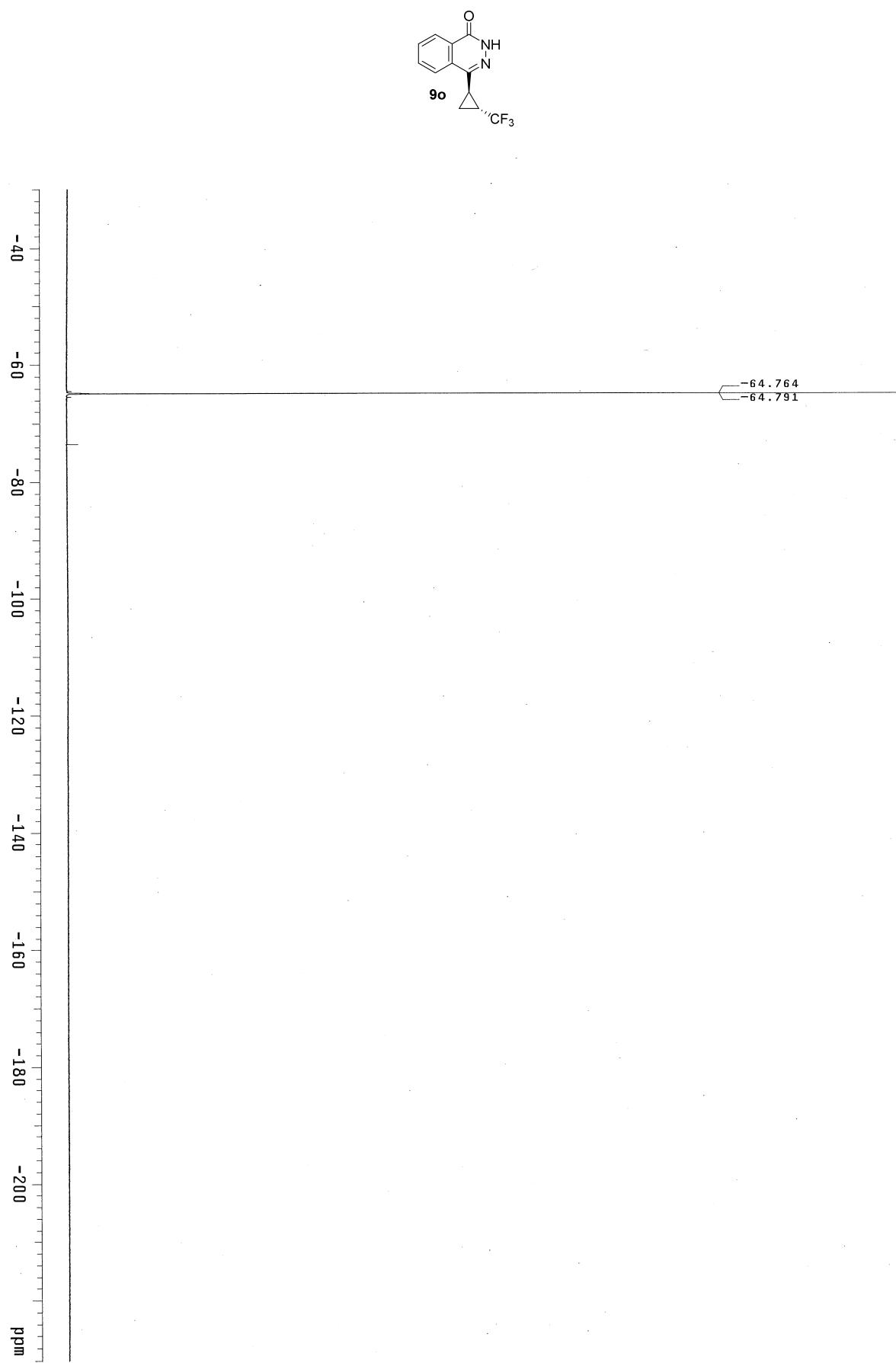
Sample 1 Vial 1:F,9 ID File MD1662-115afterprepHPL Date 24-Oct-2011 Time 12:24:37 Description 10min



¹H NMR DATA FOR COMPOUND 9O



¹⁹F NMR DATA FOR COMPOUND 9O



¹³C NMR DATA FOR COMPOUND 9O

