Paths of analysis*

C121

Synthia

March 3, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: FGI, FGI with protections

Max. paths returned: 5

Max. iterations: 300

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1000 $/g

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 10

My Stockroom:

1. Max. molecular weight - 1000 g/mol

Reaction scoring formula: TUNNEL_COEF*FGI_COEF*STEP*20+1000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)

Chemical scoring formula: SMALLER^ 3,SMALLER^ 1.5

Min. search width: 400

Max. reactions per product: 60

Strategies: none selected

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FGI Coeff: 0

JSON Parameters: {}

2 Paths

3 paths found. *Paths are sorted by score. Reactions are sorted in appearance order for each path.*

2.1 Path 1

Score: 126.45

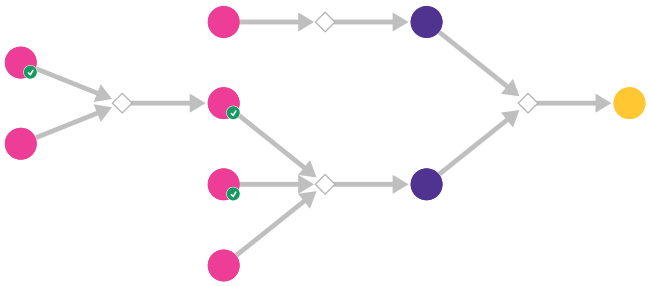
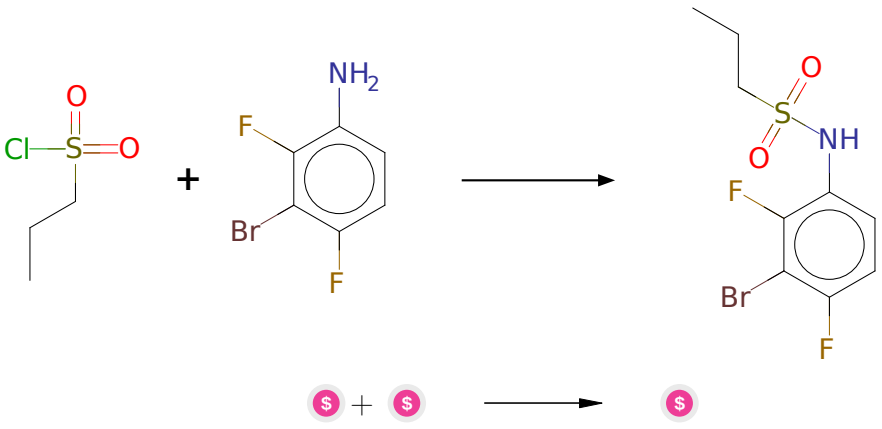


Figure 1: Outline of path 1

2.1.1 N-Sulfonylation



Substrates:

1. 1-Propanesulfonyl chloride - *available at Sigma-Aldrich*
2. 3-Bromo-2,4-difluoroaniline - *AstaTech*

Products:

1. N-(3-Bromo-2,4-difluorophenyl)-1-propanesulfonamide - *available at Sigma-Aldrich*

Typical conditions: THF.rt

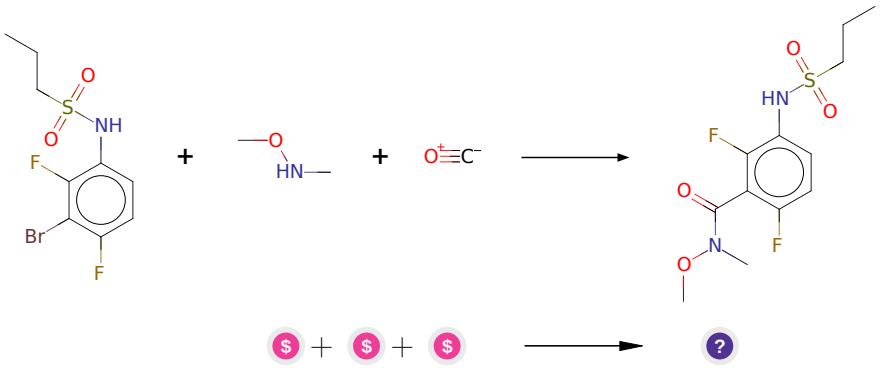
Protections: none

Yield: good

Reference: *10.1055/s-0029-1217565* and *10.1002/(SICI)1099-0690(199806)1998:6<945::AID-EJOC945>3.0.CO;2-3* and *10.1055/s-2001-14567* and *10.1016/j.bmc.2014.07.022*

Retrosynthesis ID: 14717

2.1.2 Pd-catalyzed conversion of aryl bromides to Weinreb amides



Substrates:

1. N-(3-Bromo-2,4-difluorophenyl)-1-propanesulfonamide - *available at Sigma-Aldrich*
2. Carbon monoxide - *available at Sigma-Aldrich*
3. n-methoxymethylamine - *ChemImpexInternational*

Products:

1. CCCS(=O)(=O)Nc1ccc(F)c(C(=O)N(C)OC)c1F

Typical conditions: Pd(OAc)2.Xantphos.CO(1 atm).Na2CO3.toluene.80C

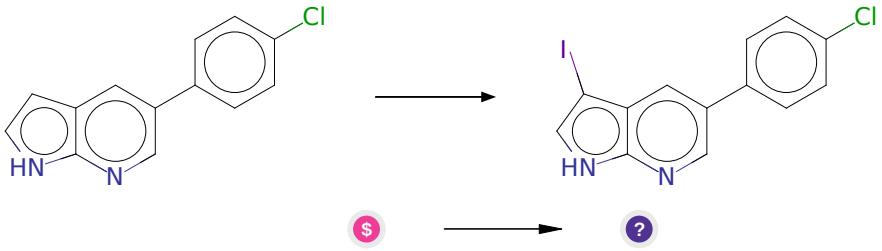
Protections: none

Yield: moderate

Reference: DOI: *10.1021/ol061902t*

Retrosynthesis ID: 1688

2.1.3 Iodination of aromatic compounds



Substrates:

1. 5-(4-Chlorophenyl)-1H-pyrrolo[2,3-b]pyridine - *Combi-Blocks*

Products:

1. Clc1ccc(-c2cnc3[nH]cc(I)c3c2)cc1

Typical conditions: I2 or other iodinating agent e.g. NIS

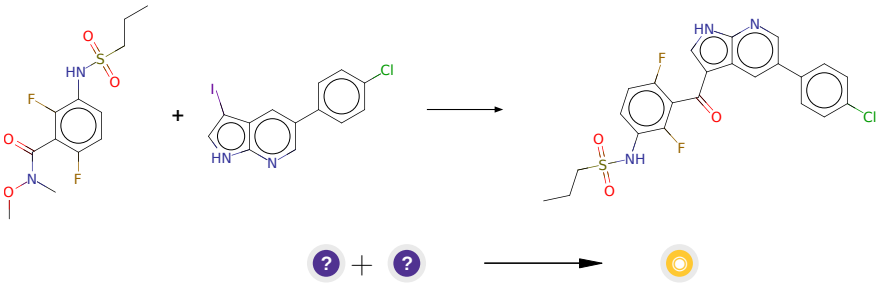
Protections: none

Yield: good

Reference: DOI: *10.1039/C5SC00964B* and *10.1016/j.tetlet.2005.05.117* and *10.1007/s11178-005-0256-1*

Retrosynthesis ID: 10697

2.1.4 Synthesis of ketones from Weinreb amides



Substrates:

1. Clc1ccc(-c2cnc3[nH]cc(I)c3c2)cc1
2. CCCS(=O)(=O)Nc1ccc(F)c(C(=O)N(C)OC)c1F

Products:

1. PLX-4032 - *AstaTech*

Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Yield: good

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 5060

2.2 Path 2

Score: `166.08`

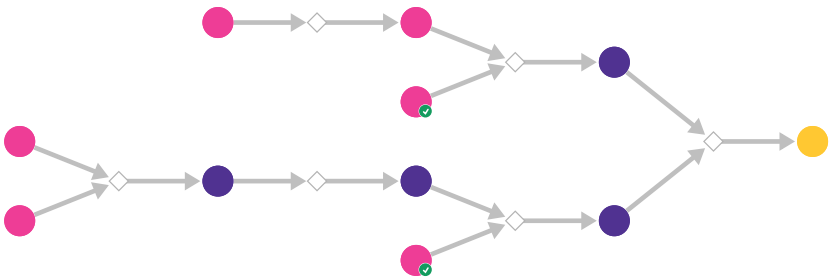
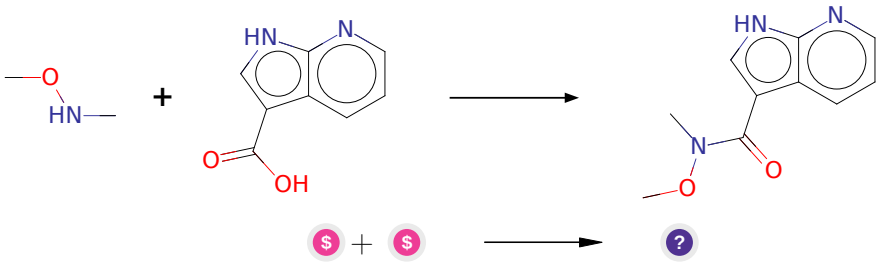


Figure 2: Outline of path 2

2.2.1 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

1. n-methoxymethylamine - *ChemImpexInternational*
2. 7-Azaindole-3-carboxylic acid - *Combi-Blocks*

Products:

1. CON(C)C(=O)c1c[nH]c2ncccc12

Typical conditions: DCC.DMAP or CDI.TEA.DCM

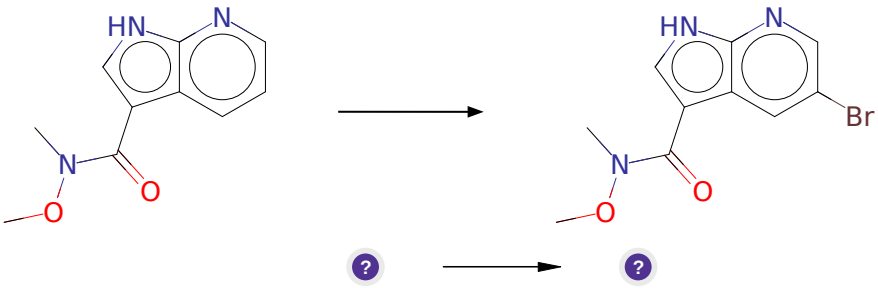
Protections: none

Yield: good

Reference: Patent: WO2007/67333A2, 2007 & *10.1016/j.bmcl.2008.09.100*

Retrosynthesis ID: 1152

2.2.2 Bromination of aromatic compounds



Substrates:

1. CON(C)C(=O)c1c[nH]c2ncccc12

Products:

1. CON(C)C(=O)c1c[nH]c2ncc(Br)cc12

Typical conditions: Br2.Fe

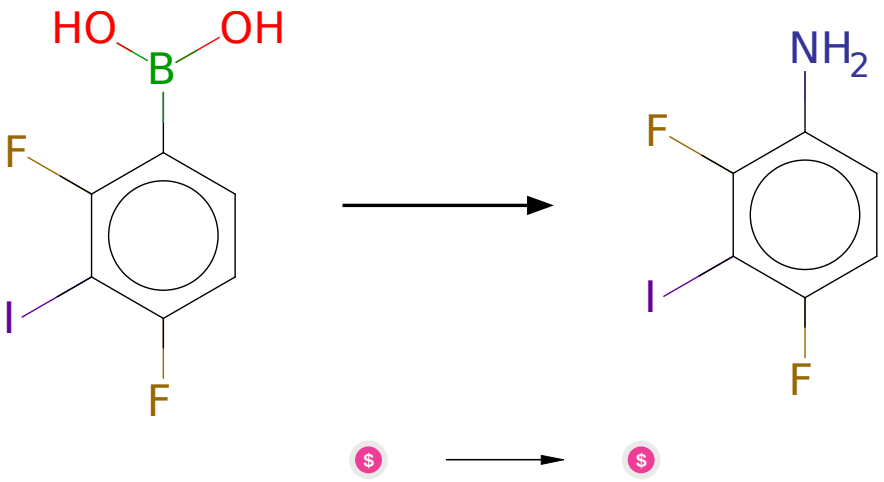
Protections: none

Yield: good

Reference: *10.1021/acs.accounts.6b00120*

Retrosynthesis ID: 7777000

2.2.3 Synthesis of anilines from aryl boronic acids



Substrates:

1. 2,4-Difluoro-3-iodophenylboronic acid - *AOBChem*

Products:

1. 2,4-Difluoro-3-iodoaniline - *Enamine*

Typical conditions: Cu2O.NH3.H2O.air.rt

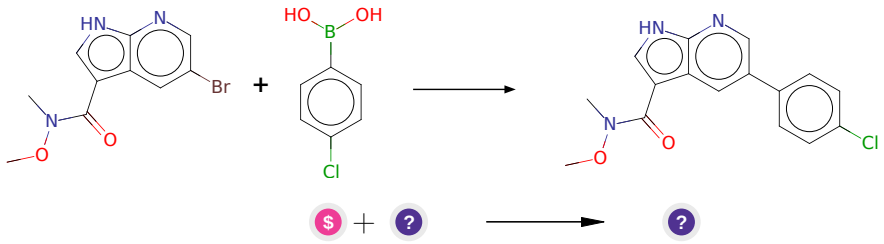
Protections: none

Yield: moderate

Reference: DOI: *10.1002/chem.201003711*

Retrosynthesis ID: 2265

2.2.4 Suzuki coupling of arylboronic acids with aryl bromides



Substrates:

1. 4-Chlorophenylboronic acid - *available at Sigma-Aldrich*

2. CON(C)C(=O)c1c[nH]c2ncc(Br)cc12

Products:

1. CON(C)C(=O)c1c[nH]c2ncc(-c3ccc(Cl)cc3)cc12

Typical conditions: Pd catalyst.base.solvent

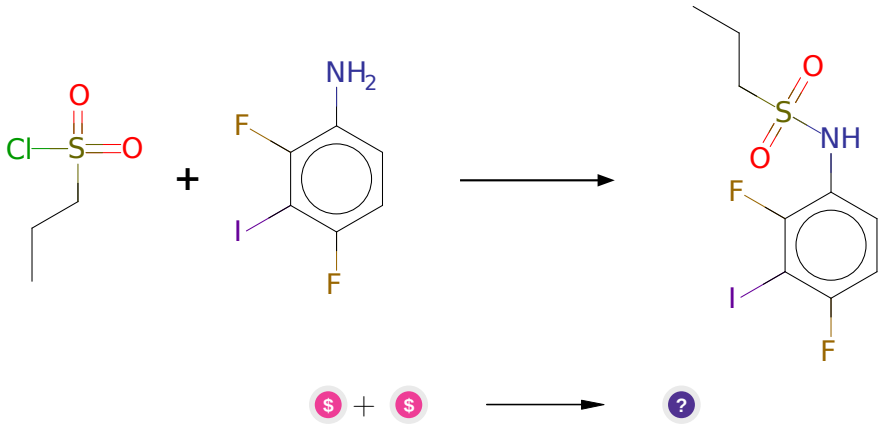
Protections: none

Yield: good

Reference: *10.1021/cr00039a007* and *10.1007/3418_2012_32* and *10.1021/cr0505268* and *10.1016/j.jfluchem.2016.01.018* and *10.1039/C3CS60197H* and *10.1016/j.ejmech.2018.08.092* and *10.1038/s41929-020-00564-z* (metal-free coupling)

Retrosynthesis ID: 25150

2.2.5 N-Sulfonylation



Substrates:

1. 2,4-Difluoro-3-iodoaniline - *Enamine*
2. 1-Propanesulfonyl chloride - *available at Sigma-Aldrich*

Products:

1. CCCS(=O)(=O)Nc1ccc(F)c(I)c1F

Typical conditions: THF.rt

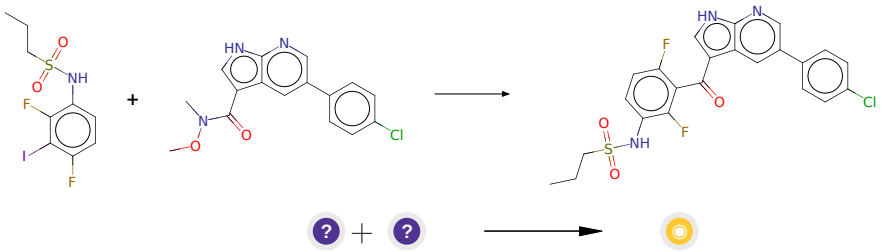
Protections: none

Yield: good

Reference: *10.1055/s-0029-1217565* and *10.1002/(SICI)1099-0690(199806)1998:6<945::AID-EJOC945>3.0.CO;2-3* and *10.1055/s-2001-14567* and *10.1016/j.bmc.2014.07.022*

Retrosynthesis ID: 14717

2.2.6 Synthesis of ketones from Weinreb amides



Substrates:

1. CCCS(=O)(=O)Nc1ccc(F)c(I)c1F
2. CON(C)C(=O)c1c[nH]c2ncc(-c3ccc(Cl)cc3)cc12

Products:

1. PLX-4032 - *AstaTech*

Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Yield: good

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 5060

2.3 Path 3

Score: 229.33

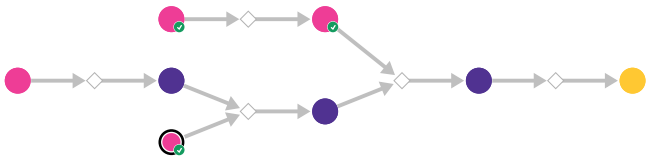
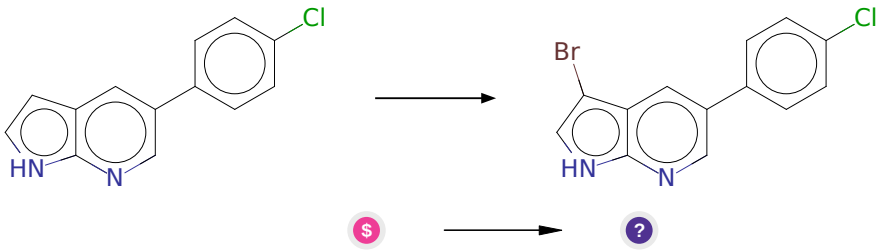


Figure 3: Outline of path 3

2.3.1 Bromination of aromatic compounds



Substrates:

1. 5-(4-Chlorophenyl)-1H-pyrrolo[2,3-b]pyridine - *Combi-Blocks*

Products:

1. Clc1ccc(-c2cnc3[nH]cc(Br)c3c2)cc1

Typical conditions: Br2.Fe

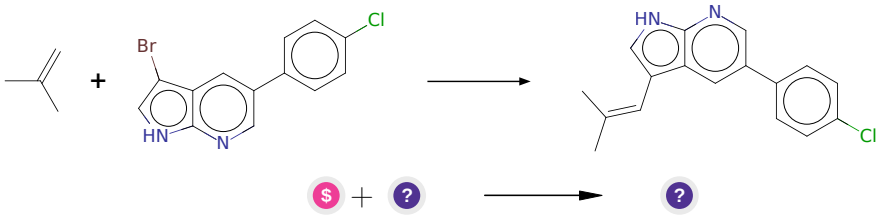
Protections: none

Yield: good

Reference: *10.1021/acs.accounts.6b00120*

Retrosynthesis ID: 7777000

2.3.2 Heck Reaction



Substrates:

1. Isobutylene - *available at Sigma-Aldrich*

2. Clc1ccc(-c2cnc3[nH]cc(Br)c3c2)cc1

Products:

1. CC(C)=Cc1c[nH]c2ncc(-c3ccc(Cl)cc3)cc12

Typical conditions: Pd (cat). Ligand e.g. TXPTS. Base. Temp

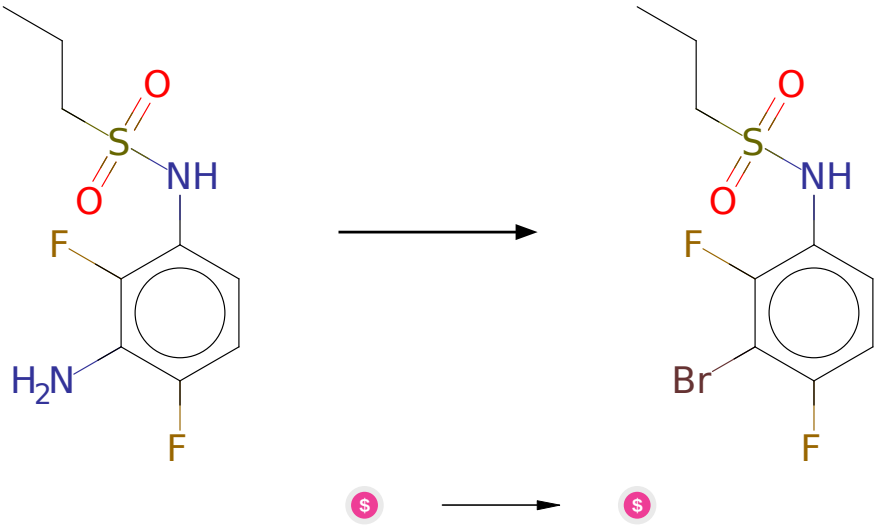
Protections: none

Yield: moderate

Reference: *10.1039/C3GC40493E* *10.1021/ol0360288* or *10.1021/ol702755g* or *10.1055/s-0033-1340319* or *10.1016/j.tet.2004.10.049*

Retrosynthesis ID: 9177

2.3.3 Sandmeyer Reaction



Substrates:

1. N-(3-amino-2,4-difluorophenyl)propane-1-sulfonamide - *available at Sigma-Aldrich*

Products:

1. N-(3-Bromo-2,4-difluorophenyl)-1-propanesulfonamide - *available at Sigma-Aldrich*

Typical conditions: IsoAmONO or t-BuONO.CuBr2.MeCN or HBr.CuBr2.NaNO2

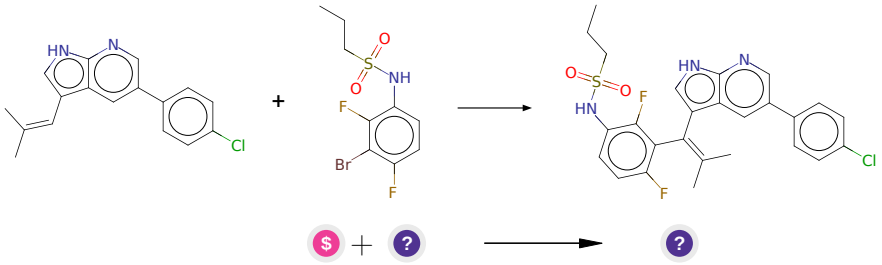
Protections: none

Yield: moderate

Reference: *10.1002/chem.201600278* and *10.1016/j.bmcl.2011.12.131* and *10.1016/j.ejmech.2013.01.046* and *10.1021/jm0002782* and *10.1002/ejoc.201300443* and *10.1021/jo052589w*(SI,page S3) and *10.1021/jm800527x* and *10.1016/j.bmcl.2015.04.098* and *10.1021/ja034563x*

Retrosynthesis ID: 29904

2.3.4 Heck Reaction



Substrates:

1. N-(3-Bromo-2,4-difluorophenyl)-1-propanesulfonamide - *available at Sigma-Aldrich*
2. CC(C)=Cc1c[nH]c2ncc(-c3ccc(Cl)cc3)cc12

Products:

1. CCCS(=O)(=O)Nc1ccc(F)c(C(=C(C)C)c2c[nH]c3ncc(-c4ccc(Cl)cc4)cc23)c1F

Typical conditions: Pd (cat). Ligand e.g. TXPTS. Base. Temp

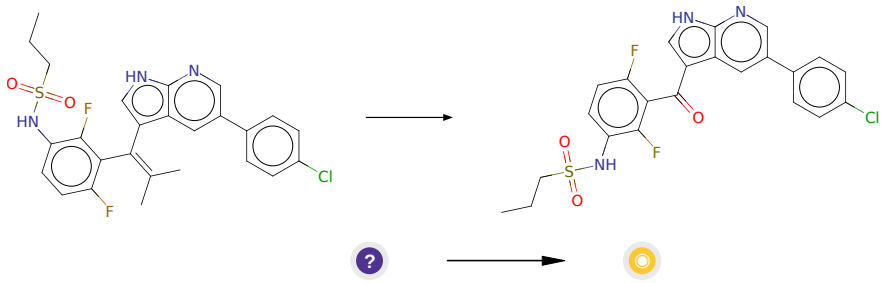
Protections: none

Yield: good

Reference: *10.1016/j.tetlet.2013.01.077* or *10.1021/ja508165a* *10.3390/molecules16108353* or *10.1039/C3GC40493E* *10.1021/ol0360288* or *10.1021/ol702755g* or *10.1055/s-0033-1340319* or *10.1016/j.tet.2004.10.049*

Retrosynthesis ID: 9174

2.3.5 Ozonolysis



Substrates:

1. CCCS(=O)(=O)Nc1ccc(F)c(C(=C(C)C)c2c[nH]c3ncc(-c4ccc(Cl)cc4)cc23)c1F

Products:

1. PLX-4032 - *AstaTech*

Typical conditions: O3.MeOH.CH2Cl2.PPh3 or Me2S.low temperature

Protections: none

Yield: good

Reference: *10.1016/j.tet.2017.03.039*

Retrosynthesis ID: 5079