Paths of analysis*

Analysis 2

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

*The results stated herein were generated using the proprietary platform owned and maintained by Grzybowski Scientific Inventions, Inc., a subsidiary of Merck KGaA, Darmstadt Germany. The results are provided on an as is basis, and shall be used solely in connection with the rights afforded in the license agreement and for no other purpose.

FGI Coeff: 0

JSON Parameters: {}

2 Paths

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

2.1 Path 1

Score: 430.36

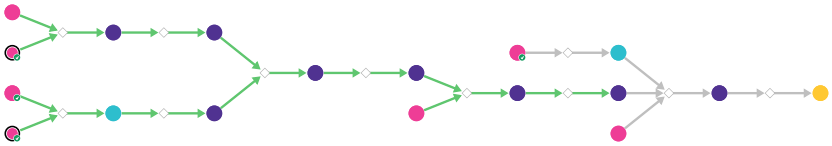
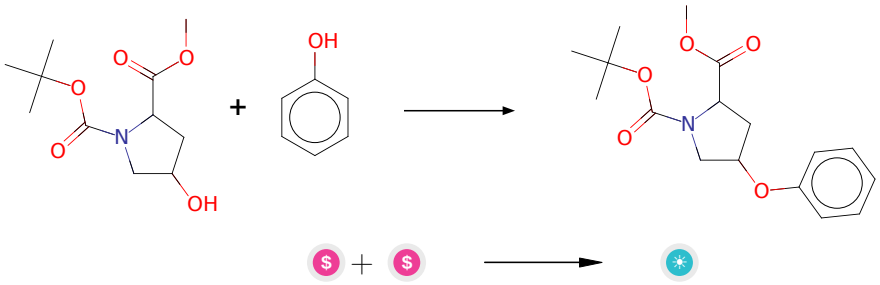


Figure 1: Outline of path 1

2.1.1 Mitsunobu reaction



Substrates:

1. 1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate - *available at Sigma-Aldrich*
2. C6H6O - *available at Sigma-Aldrich*

Products:

1. n-tert-butoxycarbonyl-4-phenoxyproline methyl ester

Typical conditions: DEAD.or.DCAD.or.DIAD.PPh3

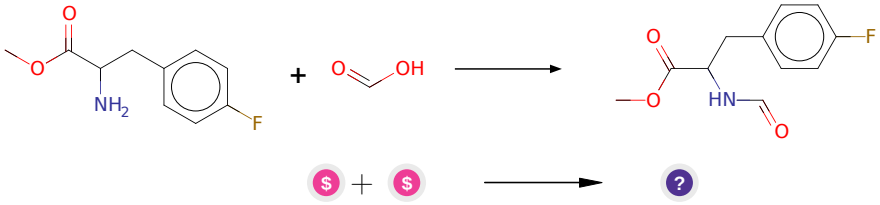
Protections: none

Yield: good

Reference: DOI: *10.1021/jo0345751* AND *10.1021/ol0618757*

Retrosynthesis ID: 7562

2.1.2 amine formylation



Substrates:

1. d,l-p-fluorphenylalanin-methylester - *Combi-Blocks*
2. Formic acid - *available at Sigma-Aldrich*

Products:

1. COC(=O)C(Cc1ccc(F)cc1)NC=O

Typical conditions: HEU(zeolite).RT.no solvent

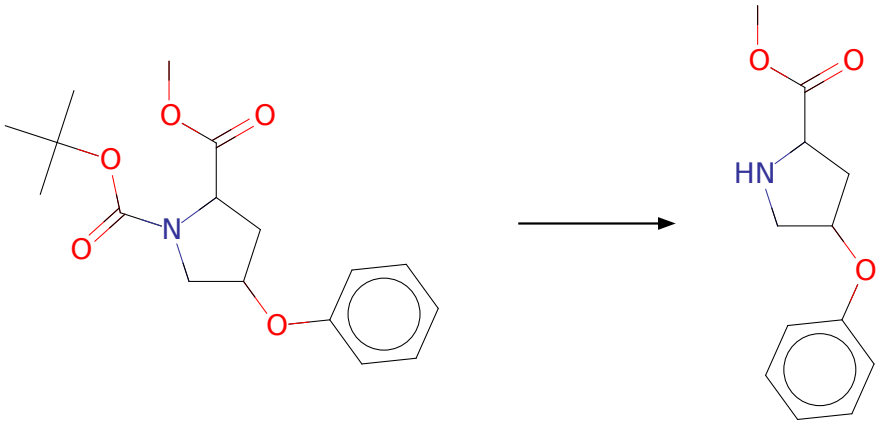
Protections: none

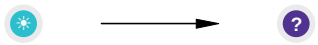
Yield: good

Reference: *10.5012/bkcs.2012.33.7.2251*

Retrosynthesis ID: 6000040

2.1.3 Boc removal





Substrates:

1. n-tert-butoxycarbonyl-4-phenoxyproline methyl ester

Products:

1. COC(=O)C1CC(Oc2ccccc2)CN1

Typical conditions: TFA.DCM or HCl.EtOH

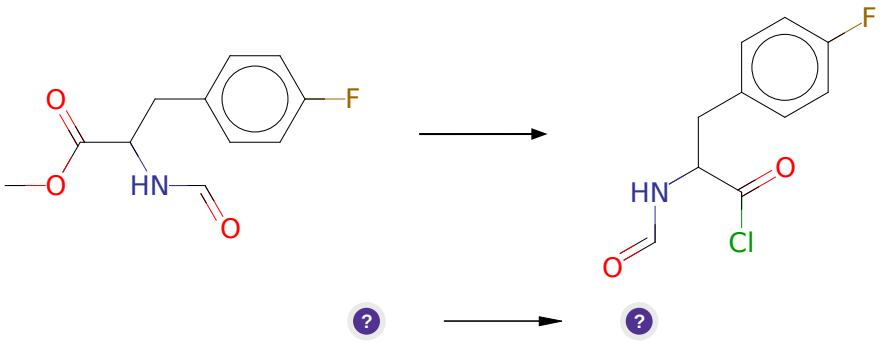
Protections: none

Yield: good

Reference: *10.1021/jm070794t* and *10.1021/jm020598g* and *10.1021/acs.oprd.5b00144* and *10.1016/j.bmc.2003.08.022*

Retrosynthesis ID: 10025810

2.1.4 Synthesis of acid chlorides from esters



Substrates:

1. COC(=O)C(Cc1ccc(F)cc1)NC=O

Products:

1. O=CNC(Cc1ccc(F)cc1)C(=O)Cl

Typical conditions: 1. LiOH.H2O.THF.2. evaporate.3.SOCl2.or.oxalyl.chloride

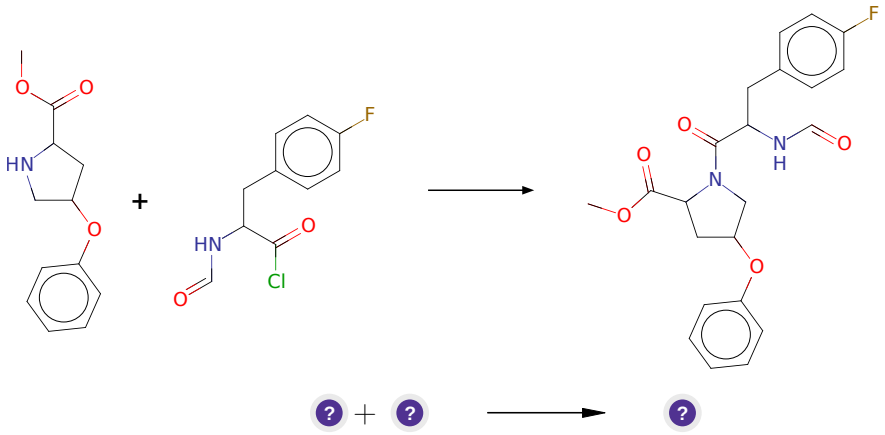
Protections: none

Yield: moderate

Reference: *10.1021/ja073476s* and *10.1016/j.tet.2007.04.043* and *10.1002/adsc.200303011* and *10.3390/50500714*

Retrosynthesis ID: 24406

2.1.5 Synthesis of tertiary amides from acid chlorides



Substrates:

1. O=CNC(Cc1ccc(F)cc1)C(=O)Cl
2. COC(=O)C1CC(Oc2ccccc2)CN1

Products:

1. COC(=O)C1CC(Oc2ccccc2)CN1C(=O)C(Cc1ccc(F)cc1)NC=O

Typical conditions: TEA.DCM.rt

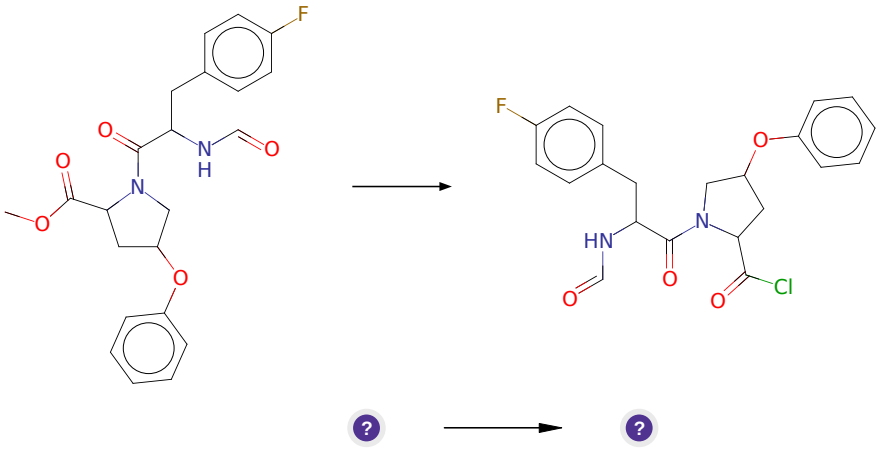
Protections: none

Yield: good

Reference: DOI: *10.1016/j.bmcl.2008.08.004* and *10.1016/j.tetlet.2008.05.010*

Retrosynthesis ID: 9146

2.1.6 Synthesis of acid chlorides from esters



Substrates:

1. COC(=O)C1CC(Oc2ccccc2)CN1C(=O)C(Cc1ccc(F)cc1)NC=O

Products:

1. O=CNC(Cc1ccc(F)cc1)C(=O)N1CC(Oc2ccccc2)CC1C(=O)Cl

Typical conditions: 1. LiOH.H2O.THF.2. evaporate.3.SOCl2.or.oxalyl.chloride

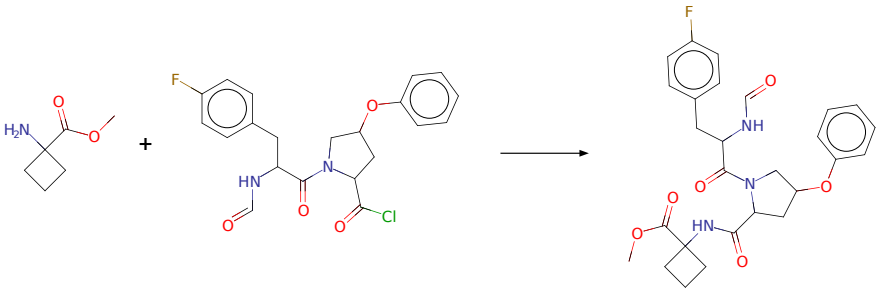
Protections: none

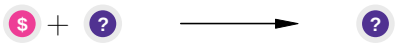
Yield: moderate

Reference: *10.1021/ja073476s* and *10.1016/j.tet.2007.04.043* and *10.1002/adsc.200303011* and *10.3390/50500714*

Retrosynthesis ID: 24406

2.1.7 Reaction of acyl chlorides with amines





Substrates:

1. methyl 1-aminocyclobutane-1-carboxylate - *Combi-Blocks*
2. O=CNC(Cc1ccc(F)cc1)C(=O)N1CC(Oc2ccccc2)CC1C(=O)Cl

Products:

1. COC(=O)C1(NC(=O)C2CC(Oc3ccccc3)CN2C(=O)C(Cc2ccc(F)cc2)NC=O)CCC1

Typical conditions: Net3 or pyridine.DCM

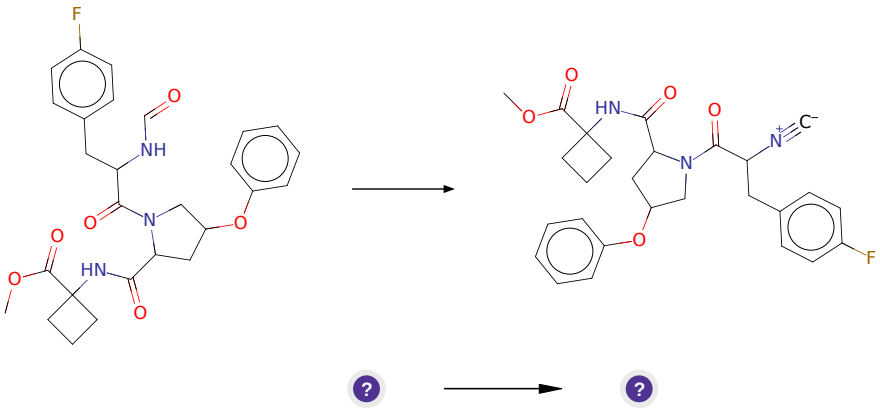
Protections: none

Yield: good

Reference: *10.1016/j.ejmech.2016.03.047* AND *10.1016/j.bmcl.2008.08.004* AND *10.1016/j.bmc.2011.03.002* AND *10.1021/ja077463q* (SI) AND *10.1016/j.tetlet.2014.10.006* (SI) AND *10.1016/j.bmcl.2008.04.018* AND *10.1021/jm980712o* AND *10.1021/jo9906173* AND *10.1021/jf9607371* AND

Retrosynthesis ID: 28547

2.1.8 Synthesis of isocyanides from formamides



Substrates:

1. COC(=O)C1(NC(=O)C2CC(Oc3ccccc3)CN2C(=O)C(Cc2ccc(F)cc2)NC=O)CCC1

Products:

1. [C-]#[N+]C(Cc1ccc(F)cc1)C(=O)N1CC(Oc2ccccc2)CC1C(=O)NC1(C(=O)OC)CCC1

Typical conditions: TCT.DCM.TEA.MW.50-100C

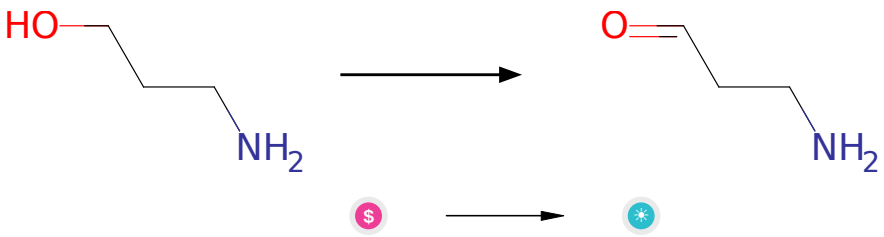
Protections: none

Yield: moderate

Reference: DOI: *10.1021/jo047924f*

Retrosynthesis ID: 245867

2.1.9 Parikh-Doering Oxidation



Substrates:

1. Propanolamine - *available at Sigma-Aldrich*

Products:

1. 3-amino-propionaldehyde

Typical conditions: DMSO. sulfur trioxide pyridine complex. NEt3

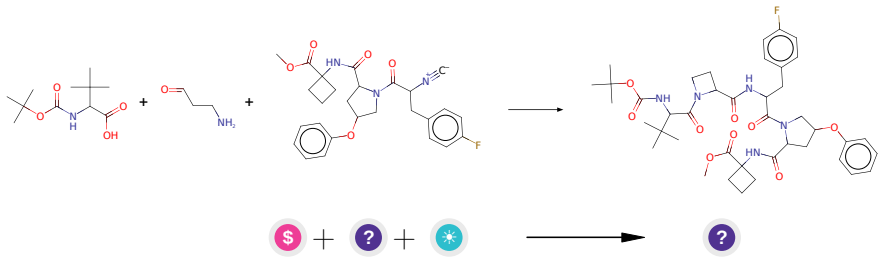
Protections: none

Yield: good

Reference: *10.1021/ja00997a067*

Retrosynthesis ID: 10255

2.1.10 Ugi reaction



Substrates:

1. 2-[(tert-butoxy)carbonyl]amino-3,3-dimethylbutanoic acid - *Enamine*

2. [C-]#[N+]C(Cc1ccc(F)cc1)C(=O)N1CC(Oc2ccccc2)CC1C(=O)NC1(C(=O)OC)CCC1

3. 3-amino-propionaldehyde

Products:

1. COC(=O)C1(NC(=O)C2CC(Oc3ccccc3)CN2C(=O)C(Cc2ccc(F)cc2)NC(=O)C2CCN2C(=O)C(NC(=O

Typical conditions: MeOH

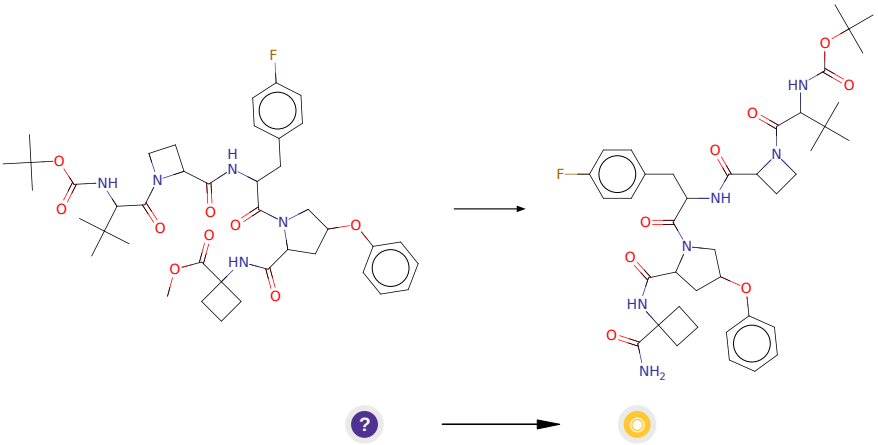
Protections: none

Yield: good

Reference: DOI: *10.1002/ange.19590711110*

Retrosynthesis ID: 222

2.1.11 Aminolysis of esters to primary amides



Substrates:

1. COC(=O)C1(NC(=O)C2CC(Oc3ccccc3)CN2C(=O)C(Cc2ccc(F)cc2)NC(=O)C2CCN2C(=O)C(NC(=O

Products:

1. CC(C)(C)OC(=O)NC(C(=O)N1CCC1C(=O)NC(Cc1ccc(F)cc1)C(=O)N1CC(Oc2ccccc2)CC1C(=O)NC

Typical conditions: NH3.MeOH.50C or NH3.H2O or NH3.THF.H2O

Protections: none

Yield: moderate

Reference: *10.1021/jacs.6b02276* and WO2016114668 p.36 and *10.1016/j.bmc.2008.10.057* and *10.1016/j.bmc.2014.01.030*

Retrosynthesis ID: 31015629

2.2 Path 2

Score: 833.05

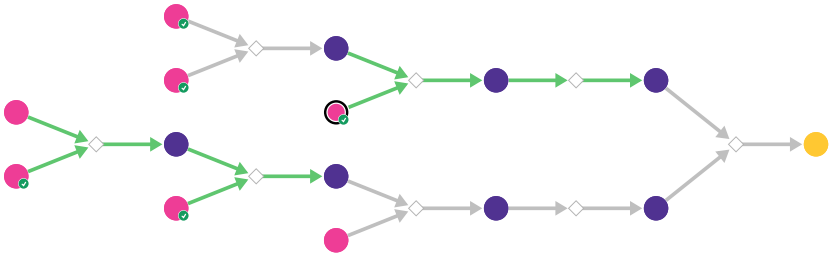
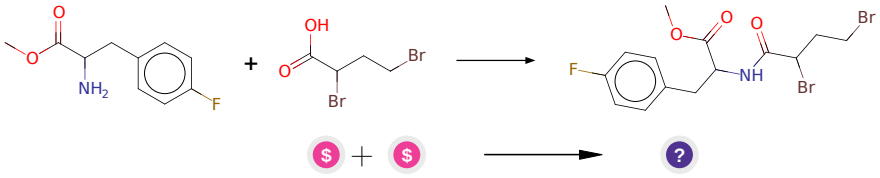


Figure 2: Outline of path 2

2.2.1 Amide coupling



Substrates:

1. d,l-p-fluorphenylalanin-methylester - *Combi-Blocks*
2. 2,4-Dibromo-butyric acid - *available at Sigma-Aldrich*

Products:

1. COC(=O)C(Cc1ccc(F)cc1)NC(=O)C(Br)CCBr

Typical conditions: DCC.DCM or EDC.DCM or SOCl2.DCM

Protections: none

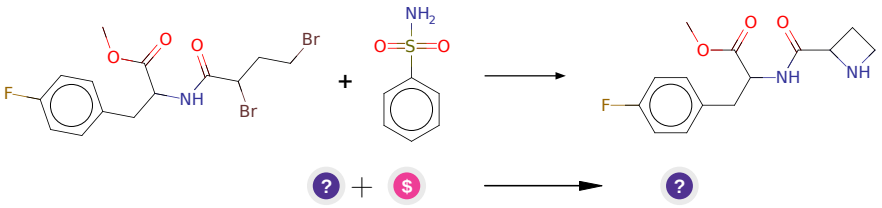
Yield: good

Reference: *10.1021/cr100048w* and *10.1039/B701677H* and *10.1039/C5RA24527C* and *10.3727/000000006783981206* and *10.1021/np060007f* and *10.1021/jo00012a058* and *10.1016/j.bmcl.2007.08.037*

and *10.1039/C0OB00355G* and *10.1021/jm500031w* (p.3056) and *10.1016/j.tet.2011.03.046*

Retrosynthesis ID: 10087

2.2.2 Synthesis of Azetidines from Dihalides followed by N-Tosyl Deprotection



Substrates:

1. COC(=O)C(Cc1ccc(F)cc1)NC(=O)C(Br)CCBr
2. Benzenesulfonamide - *available at Sigma-Aldrich*

Products:

1. COC(=O)C(Cc1ccc(F)cc1)NC(=O)C1CCN1

Typical conditions: 1) K2CO3. CH3CN. Reflux. 2) Na. Napthalene. DME. -78C

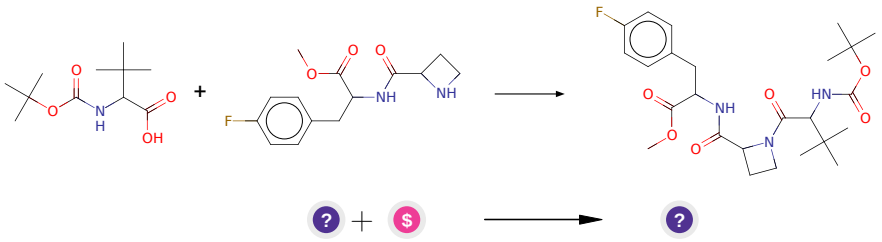
Protections: none

Yield: moderate

Reference: DOI: *10.1021/jo00112a014* or DOI: *10.1016/j.tetlet.2004.03.036* (deprotection)

Retrosynthesis ID: 21047

2.2.3 Amide coupling



Substrates:

1. COC(=O)C(Cc1ccc(F)cc1)NC(=O)C1CCN1

2. 2-[(tert-butoxy)carbonyl]amino-3,3-dimethylbutanoic acid - *Enamine*

Products:

1. COC(=O)C(Cc1ccc(F)cc1)NC(=O)C1CCN1C(=O)C(NC(=O)OC(C)(C)C)C(C)(C)C

Typical conditions: DCC.DCM or EDC.DCM or SOCl2.DCM

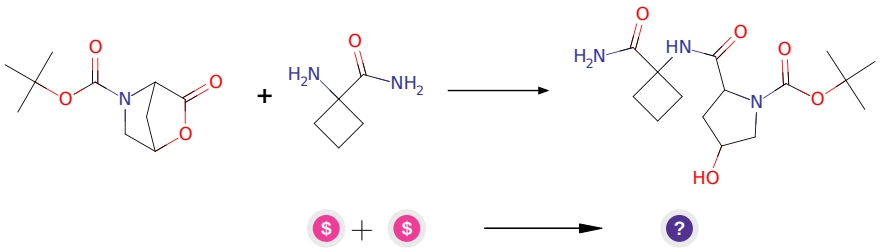
Protections: none

Yield: good

Reference: *10.1021/ol400686f* and *10.1021/jo00200a057* and *10.1021/cr100048w* and *10.1039/B701677H* and *10.1039/C5RA24527C* and *10.3727/000000006783981206* and *10.1021/np060007f* and *10.1021/jo00012a058* and *10.1016/j.bmcl.2007.08.037* and *10.1039/C0OB00355G* and *10.1021/jm500031w* (p.3056) and *10.1016/j.tet.2011.03.046*

Retrosynthesis ID: 9147

2.2.4 Intramolecular amidation of esters



Substrates:

1. tert-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate - *available at Sigma-Aldrich*
2. 1-aminocyclobutane-1-carboxamide - *available at Sigma-Aldrich*

Products:

1. CC(C)(C)OC(=O)N1CC(O)CC1C(=O)NC1(C(N)=O)CCC1

Typical conditions: DABAL-(Me)3.THF.cooling

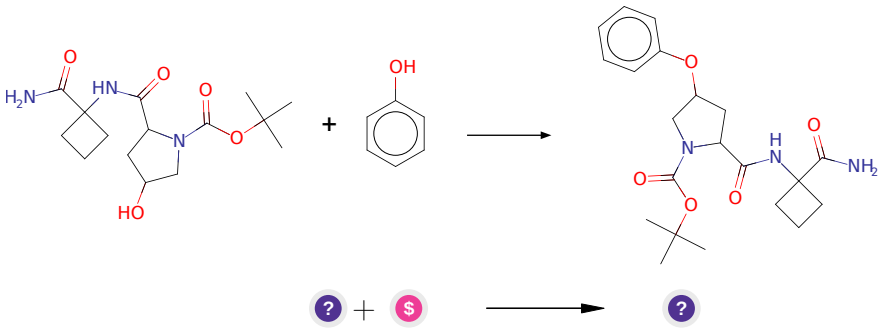
Protections: none

Yield: good

Reference: *10.1016/j.tetlet.2006.06.004* and *10.1246/cl.1987.803* and *10.1016/j.polymer.2013.01.040* and *10.1016/j.tetasy.2003.11.026* and *10.1021/ol050773y*

Retrosynthesis ID: 5035

2.2.5 Mitsunobu reaction



Substrates:

1. CC(C)(C)OC(=O)N1CC(O)CC1C(=O)NC1(C(N)=O)CCC1
2. C6H6O - *available at Sigma-Aldrich*

Products:

1. CC(C)(C)OC(=O)N1CC(Oc2ccccc2)CC1C(=O)NC1(C(N)=O)CCC1

Typical conditions: DEAD.or.DCAD.or.DIAD.PPh3

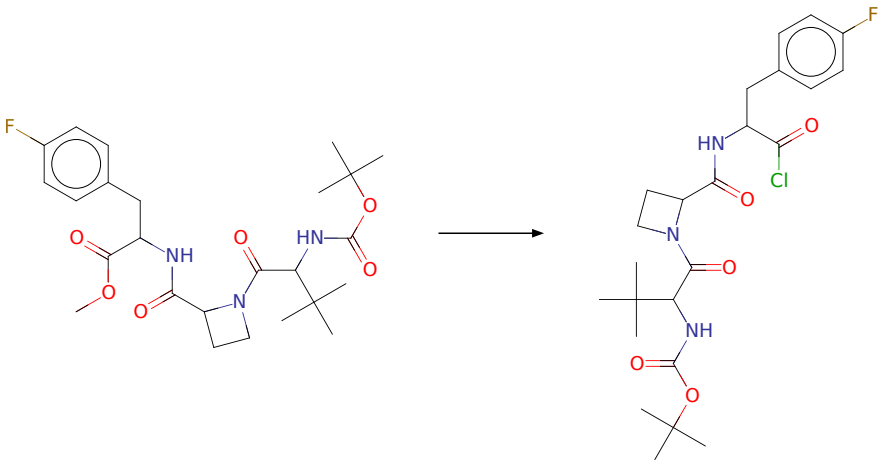
Protections: none

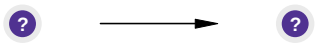
Yield: good

Reference: DOI: *10.1021/jo0345751* AND *10.1021/ol0618757*

Retrosynthesis ID: 7562

2.2.6 Synthesis of acid chlorides from esters





Substrates:

1. COC(=O)C(Cc1ccc(F)cc1)NC(=O)C1CCN1C(=O)C(NC(=O)OC(C)(C)C)C(C)(C)C

Products:

1. CC(C)(C)OC(=O)NC(C(=O)N1CCC1C(=O)NC(Cc1ccc(F)cc1)C(=O)Cl)C(C)(C)C

Typical conditions: 1. LiOH.H2O.THF.2. evaporate.3.SOCl2.or.oxalyl.chloride

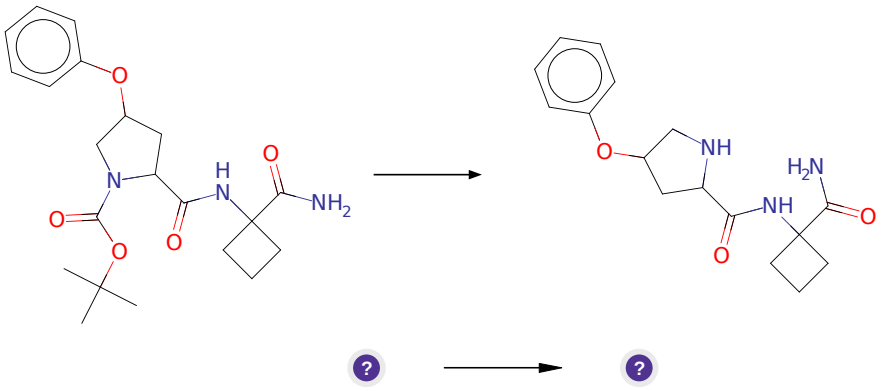
Protections: none

Yield: moderate

Reference: *10.1021/ja073476s* and *10.1016/j.tet.2007.04.043* and *10.1002/adsc.200303011* and *10.3390/50500714*

Retrosynthesis ID: 24406

2.2.7 Boc removal



Substrates:

1. CC(C)(C)OC(=O)N1CC(Oc2ccccc2)CC1C(=O)NC1(C(N)=O)CCC1

Products:

1. NC(=O)C1(NC(=O)C2CC(Oc3ccccc3)CN2)CCC1

Typical conditions: TFA.DCM or HCl.EtOH

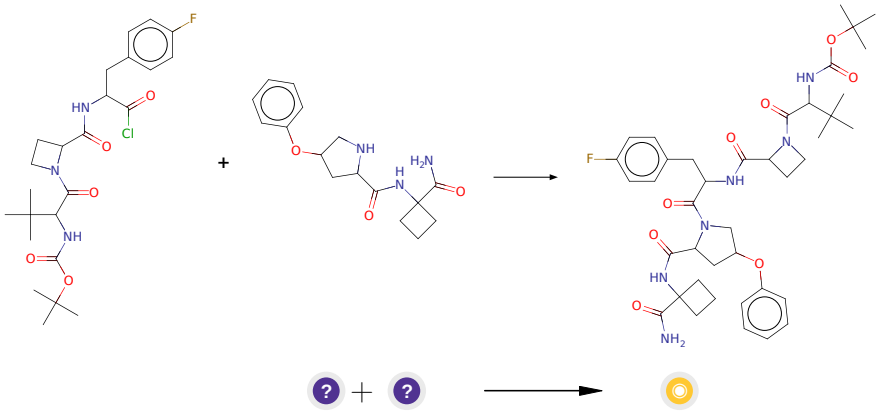
Protections: none

Yield: good

Reference: *10.1021/jm070794t* and *10.1021/jm020598g* and *10.1021/acs.oprd.5b00144* and *10.1016/j.bmc.2003.08.022*

Retrosynthesis ID: 10025810

2.2.8 Synthesis of tertiary amides from acid chlorides



Substrates:

1. CC(C)(C)OC(=O)NC(C(=O)N1CCC1C(=O)NC(Cc1ccc(F)cc1)C(=O)Cl)C(C)(C)C
2. NC(=O)C1(NC(=O)C2CC(Oc3ccccc3)CN2)CCC1

Products:

1. CC(C)(C)OC(=O)NC(C(=O)N1CCC1C(=O)NC(Cc1ccc(F)cc1)C(=O)N1CC(Oc2ccccc2)CC1C(=O)NC

Typical conditions: TEA.DCM.rt

Protections: none

Yield: moderate

Reference: DOI: *10.1016/j.bmcl.2008.08.004* and *10.1016/j.tetlet.2008.05.010*

Retrosynthesis ID: 9146