# Paths of analysis*

Analysis 7

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

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

## 2.1 Path 1

**Score:** 459.93

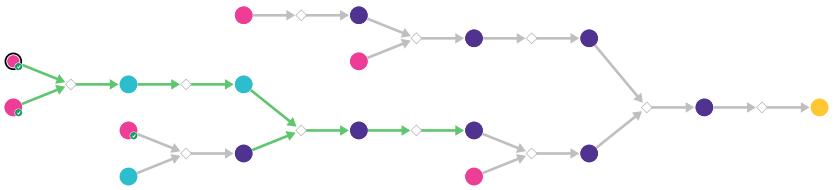
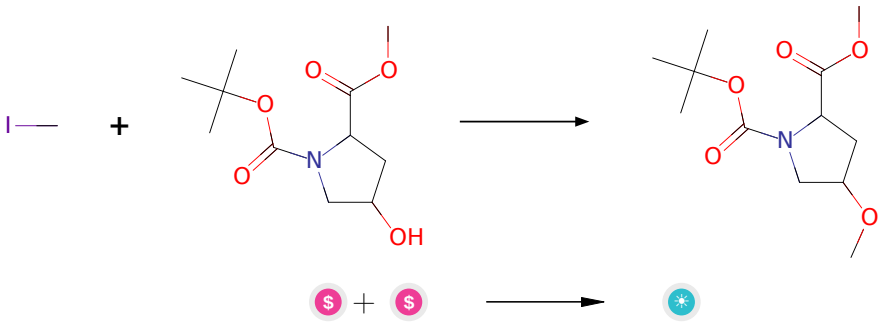


Figure 1: Outline of path 1

### 2.1.1 Methylation of secondary unhindered alcohols




**Substrates:**

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

**Products:**

1. C12H21NO5

**Typical conditions:** NaH.MeI.THF

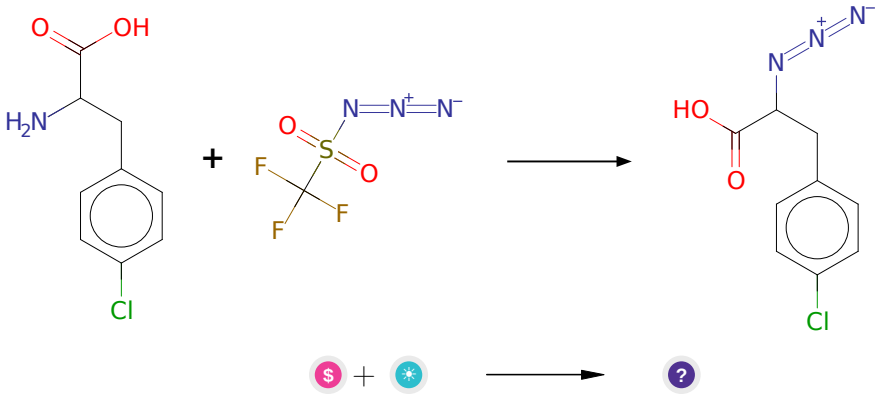
**Protections:** none

**Yield:** good

**Reference:** *10.1016/j.bmc.2010.02.061* and *10.1016/j.tetasy.2010.01.014* and *10.1007/BF02977665* and *10.1002/ejoc.201101635* and *10.1021/ol0064664* and *10.1021/ol035227o*

**Retrosynthesis ID:** 31014843

### 2.1.2 Synthesis of alkyl azides from alkyl amines and TfN3



**Substrates:**

1. 4-Chloro-DL-phenylalanine - *available at Sigma-Aldrich*
2. trifluoromethanesulfonyl azide

**Products:**

1. [N-]=[N+]=NC(Cc1ccc(Cl)cc1)C(=O)O

**Typical conditions:** H2O.K2CO3.CH2Cl2.CuSO4.MeOH

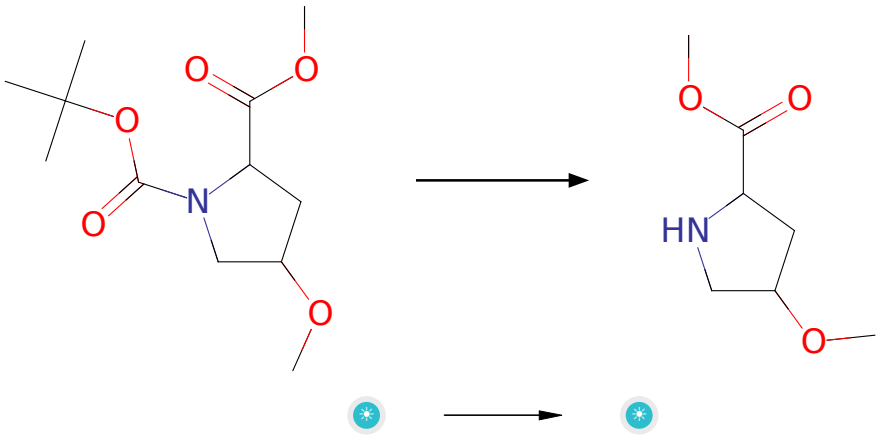
**Protections:** none

**Yield:** moderate

**Reference:** DOI: *10.1016/0040-4039(96)01307-X*

**Retrosynthesis ID:** 9920002

### 2.1.3 Boc removal



**Substrates:**

1. C12H21NO5

**Products:**

1. methyl 4-methoxy-2-pyrrolidinecarboxylate hydrochloride

**Typical conditions:** TFA.DCM or HCl.EtOH

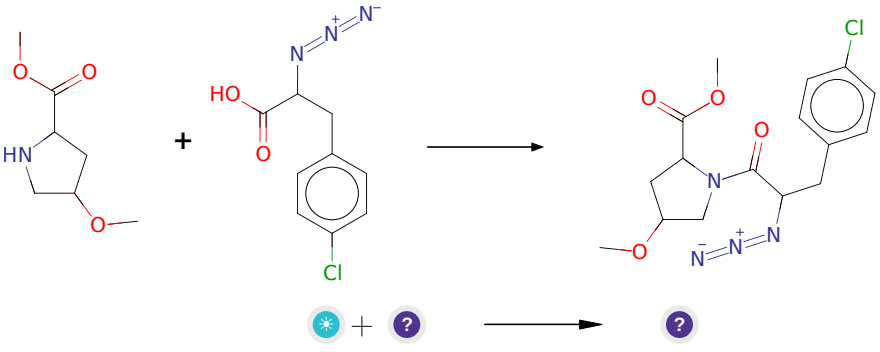
**Protections:** none

**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 Amide coupling



**Substrates:**

1. methyl 4-methoxy-2-pyrrolidinecarboxylate hydrochloride
2. [N-]=[N+]=NC(Cc1ccc(Cl)cc1)C(=O)O

**Products:**

1. COC(=O)C1CC(OC)CN1C(=O)C(Cc1ccc(Cl)cc1)N=[N+]=[N-]

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

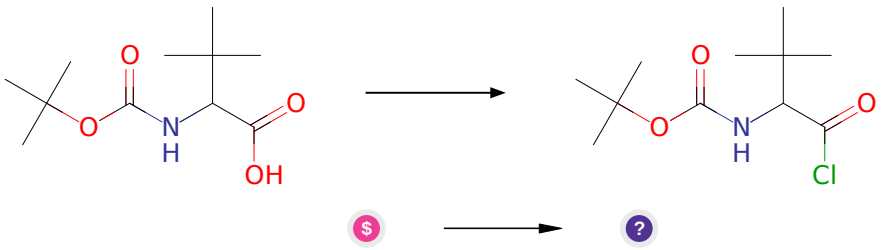
**Protections:** none

**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:** 10091

### 2.1.5 Synthesis of acid chlorides from carboxylic acids




**Substrates:**

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

**Products:**

1. CC(C)(C)OC(=O)NC(C(=O)Cl)C(C)(C)C

**Typical conditions:** oxalyl.chloride.or.SOCl2

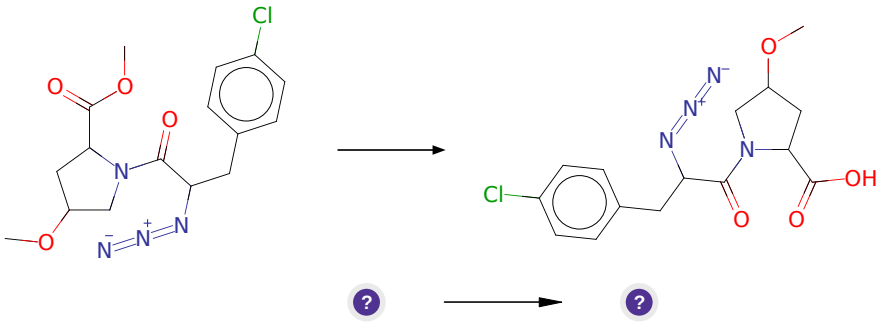
**Protections:** none

**Yield:** good

**Reference:** *10.1002/adsc.200303011* and *10.3390/50500714*

**Retrosynthesis ID:** 24405

### 2.1.6 Synthesis of Carboxylic Acids via Ester Hydrolysis



**Substrates:**

1. COC(=O)C1CC(OC)CN1C(=O)C(Cc1ccc(Cl)cc1)N=[N+]=[N-]

**Products:**

1. COC1CC(C(=O)O)N(C(=O)C(Cc2ccc(Cl)cc2)N=[N+]=[N-])C1

**Typical conditions:** water.base

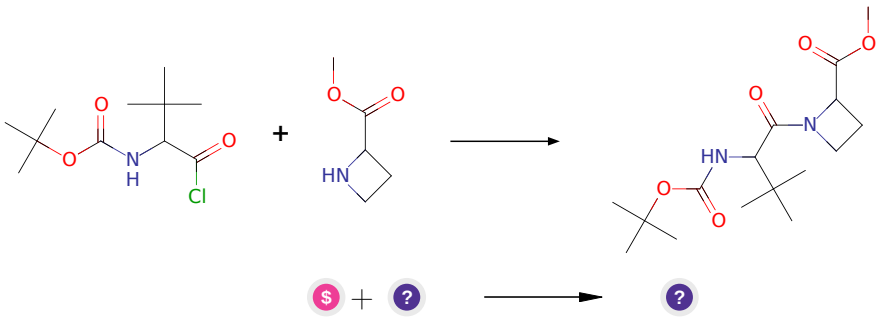
**Protections:** none

**Yield:** moderate

**Reference:** DOI: *10.1016/j.phytochem.2012.08.001* and *10.1021/jm900803q* and *10.1002/anie.201303108* (SI page S14) and *10.1016/j.ejmech.2010.09.003*

**Retrosynthesis ID:** 9224

### 2.1.7 Synthesis of tertiary amides from acid chlorides



**Substrates:**

1. azetidine-2-carboxylic acid methyl ester - *JWPharmlab*
2. CC(C)(C)OC(=O)NC(C(=O)Cl)C(C)(C)C

**Products:**

1. COC(=O)C1CCN1C(=O)C(NC(=O)OC(C)(C)C)C(C)(C)C

**Typical conditions:** TEA.DCM.rt

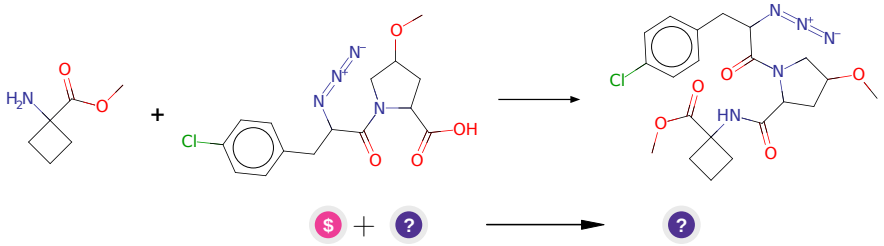
**Protections:** none

**Yield:** good

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

**Retrosynthesis ID:** 9146

### 2.1.8 Amide coupling



**Substrates:**

1. methyl 1-aminocyclobutane-1-carboxylate - *Combi-Blocks*
2. COC1CC(C(=O)O)N(C(=O)C(Cc2ccc(Cl)cc2)N=[N+]=[N-])C1

**Products:**

1. COC(=O)C1(NC(=O)C2CC(OC)CN2C(=O)C(Cc2ccc(Cl)cc2)N=[N+]=[N-])CCC1

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

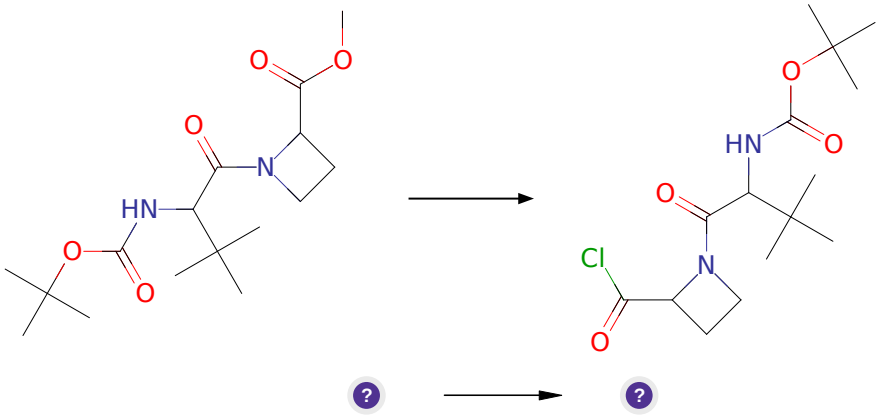
**Protections:** none

**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

### 2.1.9 Synthesis of acid chlorides from esters



**Substrates:**

1. COC(=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)Cl)C(C)(C)C

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

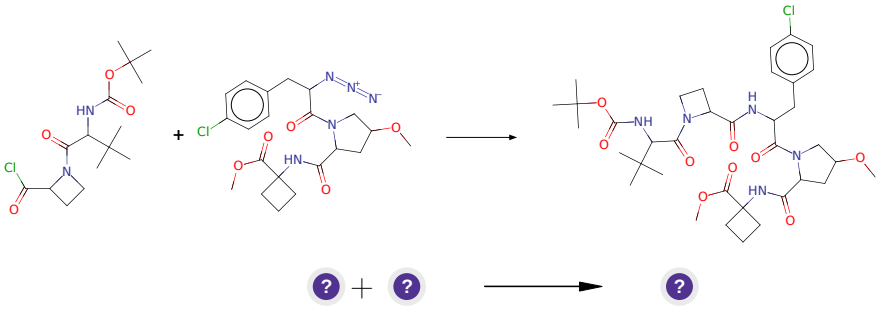
**Protections:** none

**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

### 2.1.10 Synthesis of amides from azides



**Substrates:**

1. CC(C)(C)OC(=O)NC(C(=O)N1CCC1C(=O)Cl)C(C)(C)C
2. COC(=O)C1(NC(=O)C2CC(OC)CN2C(=O)C(Cc2ccc(Cl)cc2)N=[N+]=[N-])CCC1

**Products:**

1. COC(=O)C1(NC(=O)C2CC(OC)CN2C(=O)C(Cc2ccc(Cl)cc2)NC(=O)C2CCN2C(=O)C(NC(=O)OC(C

**Typical conditions:** PPh3.DCM

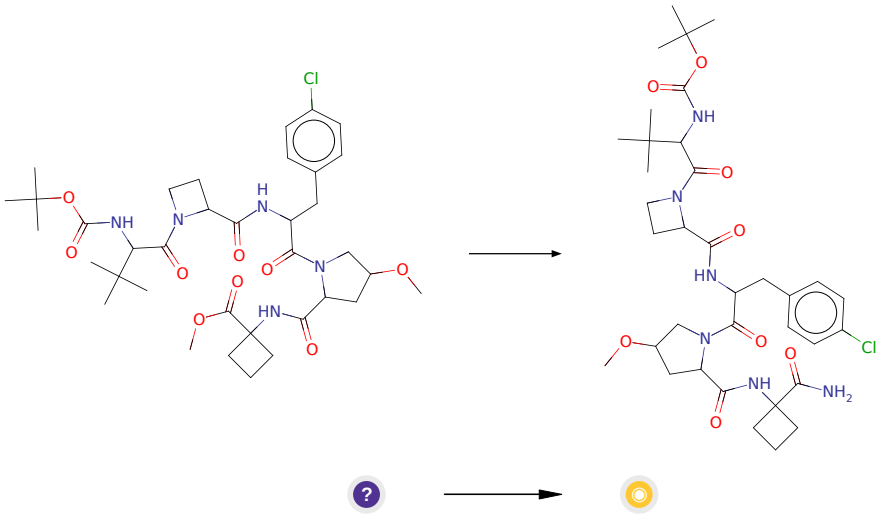
**Protections:** none

**Yield:** moderate

**Reference:** *10.1021/jo026687i* AND *10.1002/cbic.200900617* AND *10.1016/j.carres.2013.03.028*

**Retrosynthesis ID:** 15318

### 2.1.11 Aminolysis of esters to primary amides



**Substrates:**

1. COC(=O)C1(NC(=O)C2CC(OC)CN2C(=O)C(Cc2ccc(Cl)cc2)NC(=O)C2CCN2C(=O)C(NC(=O)OC(C

**Products:**

1. COC1CC(C(=O)NC2(C(N)=O)CCC2)N(C(=O)C(Cc2ccc(Cl)cc2)NC(=O)C2CCN2C(=O)C(NC(=O)O

**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