

# Paths of analysis\*

C23

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:**  $\text{TUNNEL\_COEF} * \text{FGI\_COEF} * \text{STEP} * 20 + 1000000 * (\text{CONFLICT} + \text{NON\_SELECTIVITY} + \text{FILTERS} + \text{PROTECT})$

**Chemical scoring formula:**  $\text{SMALLER}^3, \text{SMALLER}^{1.5}$

**Min. search width:** 400

**Max. reactions per product:** 60

**Strategies:** none selected

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\*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

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

### 2.1 Path 1

Score: 626.83

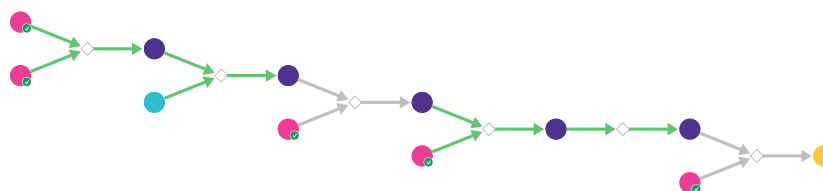
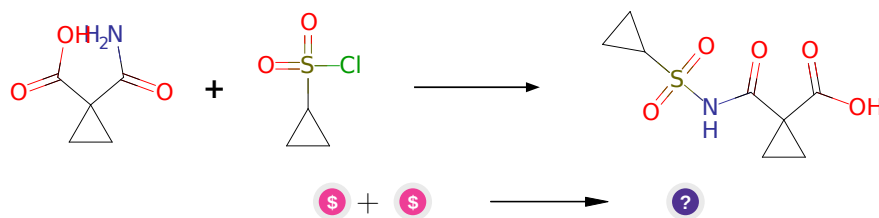


Figure 1: Outline of path 1

#### 2.1.1 Sulfonylation of amides



**Substrates:**

- 1-(Aminocarbonyl)-1-cyclopropanecarboxylic acid - *available at Sigma-Aldrich*
- Cyclopropanesulfonyl chloride - *available at Sigma-Aldrich*

**Products:**

- O=C(O)C1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** Py.RSO<sub>2</sub>Cl

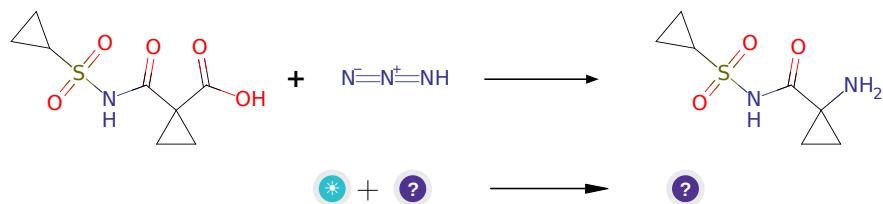
**Protections:** none

**Yield:** good

**Reference:** [10.1021/ja9945313](#) AND [10.1016/j.ejmech.2013.04.028](#)  
AND [10.1039/c5ra14001c](#) AND [10.1016/j.bmcl.2013.12.043](#) AND  
[10.1016/j.tetasy.2012.08.013](#)

**Retrosynthesis ID:** 14787

### 2.1.2 Schmidt Reaction



**Substrates:**

1. hydrazoic acid
2. O=C(O)C1(C(=O)NS(=O)(=O)C2CC2)CC1

**Products:**

1. NC1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** azide.H+.40C

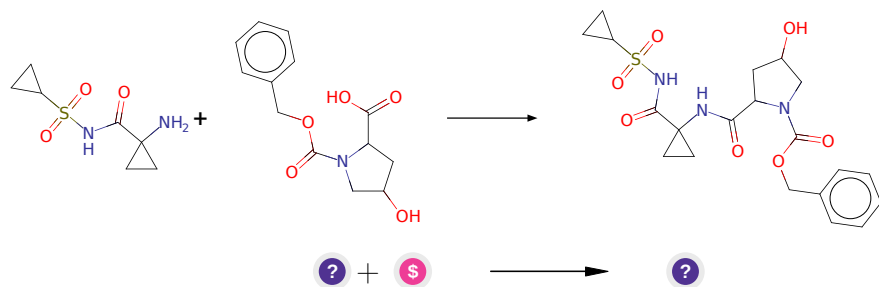
**Protections:** none

**Yield:** moderate

**Reference:** [10.1039/B505080D](#)

**Retrosynthesis ID:** 11704

### 2.1.3 Amide coupling



**Substrates:**

1. NC1(C(=O)NS(=O)(=O)C2CC2)CC1
2. Z-Hyp-OH - *available at Sigma-Aldrich*

**Products:**

1. O=C(NC1(C(=O)NS(=O)(=O)C2CC2)CC1)C1CC(O)CN1C(=O)OCc1ccccc1

**Typical conditions:** DCC.DCM or EDC.DCM or SOCl<sub>2</sub>.DCM

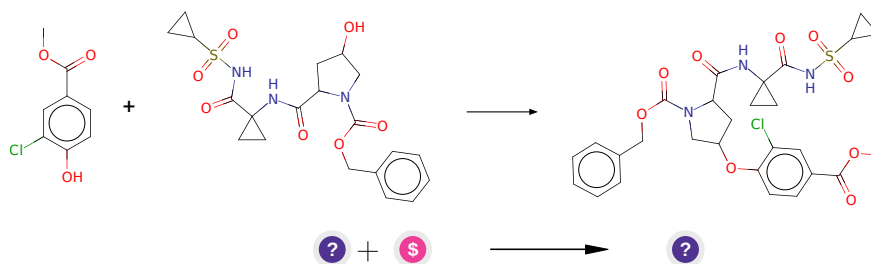
**Protections:** none

**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

#### 2.1.4 Mitsunobu reaction



**Substrates:**

1. O=C(NC1(C(=O)NS(=O)(=O)C2CC2)CC1)C1CC(O)CN1C(=O)OCc1ccccc1
2. Methyl 3-chloro-4-hydroxybenzoate - *available at Sigma-Aldrich*

**Products:**

1. COC(=O)c1ccc(OC2CC(C(=O)NC3(C(=O)NS(=O)(=O)C4CC4)CC3)N(C(=O)OCc3ccccc3)C2)c(Cl)c1

**Typical conditions:** DEAD.or.DCAD.or.DIAD.PPh<sub>3</sub>

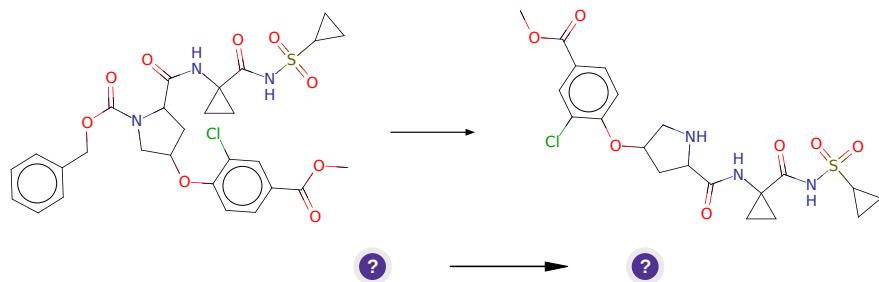
**Protections:** none

**Yield:** good

**Reference:** DOI: [10.1021/jo0345751](#) AND [10.1021/ol0618757](#)

**Retrosynthesis ID:** 7562

### 2.1.5 Cleavage of benzyloxycarbamates



**Substrates:**

1. COC(=O)c1ccc(OC2CC(C(=O)NC3(C(=O)NS(=O)(=O)C4CC4)CC3)N(C(=O)OCc3ccccc3)C2)c(Cl)c1

**Products:**

1. COC(=O)c1ccc(OC2CNC(C(=O)NC3(C(=O)NS(=O)(=O)C4CC4)CC3)C2)c(Cl)c1

**Typical conditions:** H<sub>2</sub>.Pd/C

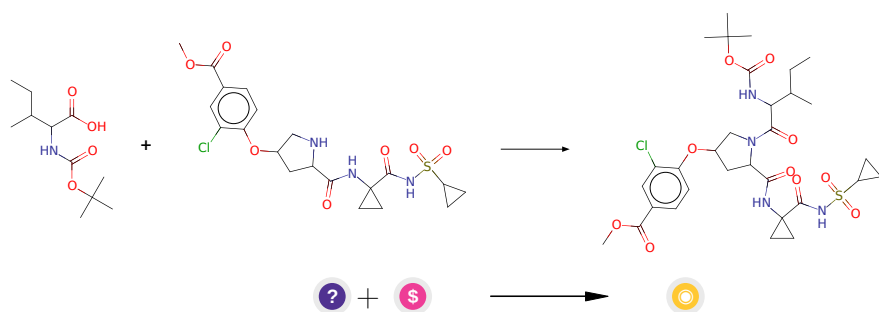
**Protections:** none

**Yield:** good

**Reference:** [10.1021/jm070755h](#) and [10.1021/jm2016057](#) and [10.1055/s-0033-1340215](#) and [10.1016/S0040-4039\(03\)01181-X](#)

**Retrosynthesis ID:** 9990024

### 2.1.6 Amide coupling



**Substrates:**

1. COC(=O)c1ccc(OC2CNC(C(=O)NC3(C(=O)NS(=O)(=O)C4CC4)CC3)C2)c(Cl)c1
2. 2-[(tert-butoxy)carbonyl]amino-3-methylpentanoic acid - *available at Sigma-Aldrich*

**Products:**

1. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC(Oc2ccc(C(=O)OC)cc2Cl)CC1C(=O)NC1(C(=O)NS(=O)=O)

**Typical conditions:** DCC.DCM or EDC.DCM or SOCl<sub>2</sub>.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 Path 2

**Score:** 657.80

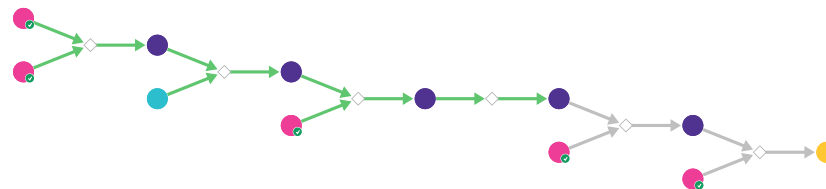
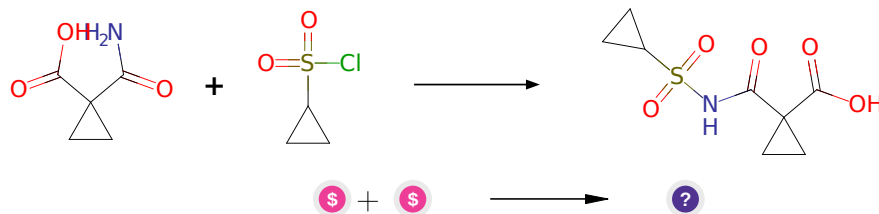


Figure 2: Outline of path 2

### 2.2.1 Sulfonylation of amides



**Substrates:**

1. 1-(Aminocarbonyl)-1-cyclopropanecarboxylic acid - *available at Sigma-Aldrich*

2. Cyclopropanesulfonyl chloride - *available at Sigma-Aldrich*

**Products:**

1. O=C(O)C1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** Py.RSO<sub>2</sub>Cl

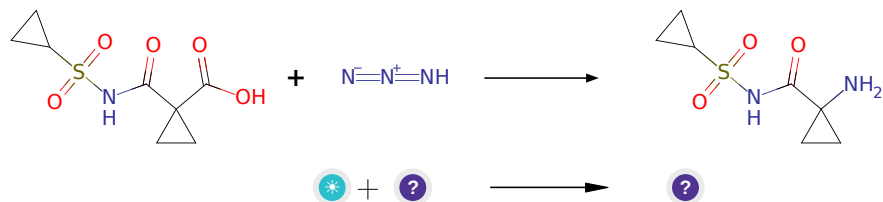
**Protections:** none

**Yield:** good

**Reference:** [10.1021/ja9945313](#) AND [10.1016/j.ejmech.2013.04.028](#)  
AND [10.1039/c5ra14001c](#) AND [10.1016/j.bmcl.2013.12.043](#) AND  
[10.1016/j.tetasy.2012.08.013](#)

**Retrosynthesis ID:** 14787

**2.2.2 Schmidt Reaction**



**Substrates:**

1. hydrazoic acid  
2. O=C(O)C1(C(=O)NS(=O)(=O)C2CC2)CC1

**Products:**

1. NC1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** azide.H<sup>+</sup>.40C

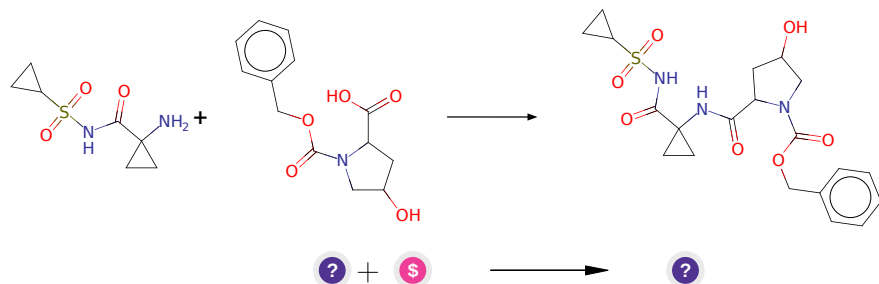
**Protections:** none

**Yield:** moderate

**Reference:** [10.1039/B505080D](#)

**Retrosynthesis ID:** 11704

### 2.2.3 Amide coupling



**Substrates:**

1. NC1(C(=O)NS(=O)(=O)C2CC2)CC1
2. Z-Hyp-OH - *available at Sigma-Aldrich*

**Products:**

1. O=C(NC1(C(=O)NS(=O)(=O)C2CC2)CC1)C1CC(O)CN1C(=O)OCc1ccccc1

**Typical conditions:** DCC.DCM or EDC.DCM or SOCl<sub>2</sub>.DCM

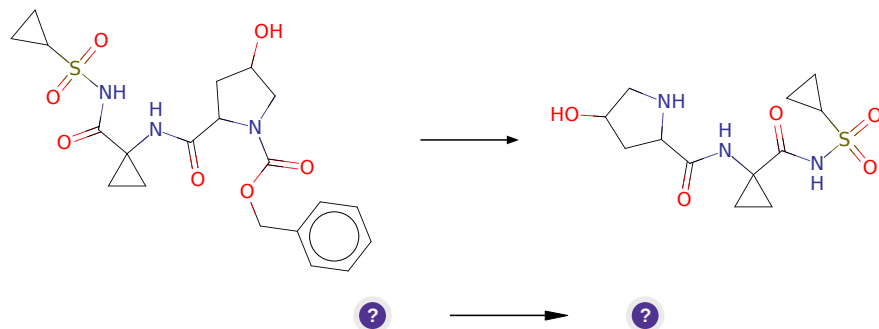
**Protections:** none

**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

### 2.2.4 Cleavage of benzyloxycarbamates



**Substrates:**



1. O=C(NC1(C(=O)NS(=O)(=O)C2CC2)CC1)C1CC(O)CN1C(=O)OCc1ccccc1

**Products:**

1. O=C(NC1(C(=O)NS(=O)(=O)C2CC2)CC1)C1CC(O)CN1

**Typical conditions:** H<sub>2</sub>.Pd/C

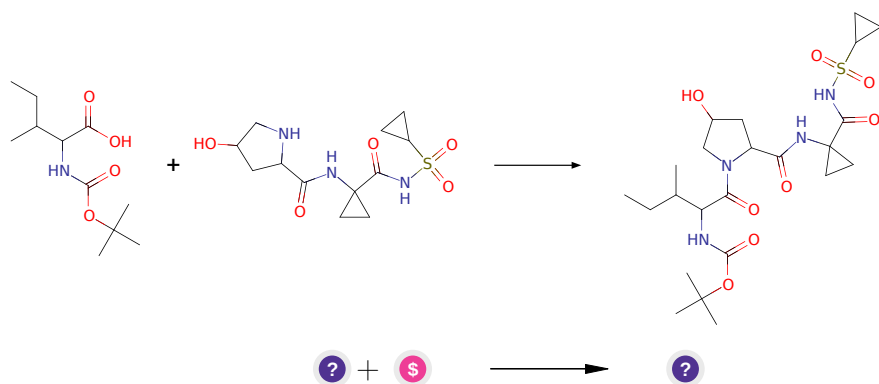
**Protections:** none

**Yield:** good

**Reference:** [10.1021/jm070755h](#) and [10.1021/jm2016057](#) and [10.1055/s-0033-1340215](#) and [10.1016/S0040-4039\(03\)01181-X](#)

**Retrosynthesis ID:** 9990024

## 2.2.5 Amide coupling



**Substrates:**

1. O=C(NC1(C(=O)NS(=O)(=O)C2CC2)CC1)C1CC(O)CN1

2. 2-[(tert-butoxy)carbonyl]amino-3-methylpentanoic acid - *available at Sigma-Aldrich*

**Products:**

1. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC(O)CC1C(=O)NC1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** DCC.DCM or EDC.DCM or SOCl<sub>2</sub>.DCM

**Protections:** none

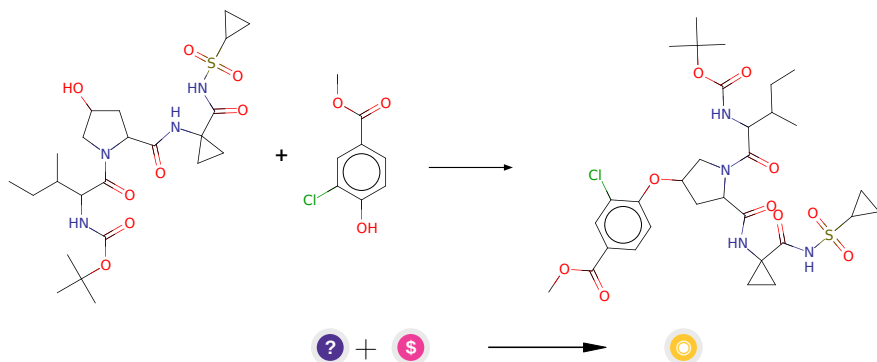
**Yield:** good

**Reference:** [10.1021/ol400686f](#) and [10.1021/jo00200a057](#) and [10.1021/cr100048w](#) and [10.1039/B701677H](#) and [10.1039/C5RA24527C](#) and

[10.3727/00000006783981206](#) 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

### 2.2.6 Mitsunobu reaction



**Substrates:**

1. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC(O)CC1C(=O)NC1(C(=O)NS(=O)(=O)C2CC2)CC1
2. Methyl 3-chloro-4-hydroxybenzoate - *available at Sigma-Aldrich*

**Products:**

1. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC(Oc2ccc(C(=O)OC)cc2Cl)CC1C(=O)NC1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** DEAD.or.DCAD.or.DIAD.PPh<sub>3</sub>

**Protections:** none

**Yield:** good

**Reference:** DOI: [10.1021/jo0345751](#) AND [10.1021/ol0618757](#)

**Retrosynthesis ID:** 7562

## 2.3 Path 3

**Score:** 750.01

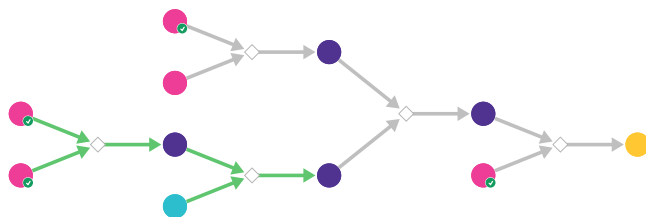
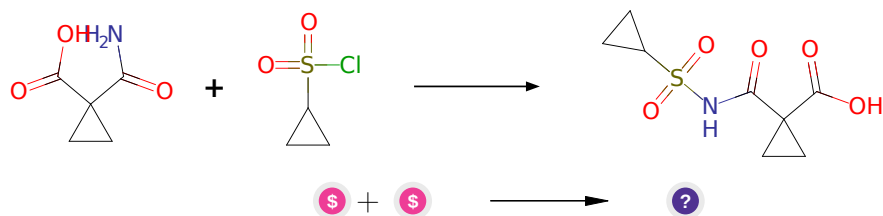


Figure 3: Outline of path 3

### 2.3.1 Sulfonylation of amides



#### Substrates:

- 1-(Aminocarbonyl)-1-cyclopropanecarboxylic acid - *available at Sigma-Aldrich*
- Cyclopropanesulfonyl chloride - *available at Sigma-Aldrich*

#### Products:

- O=C(O)C1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** Py.RSO<sub>2</sub>Cl

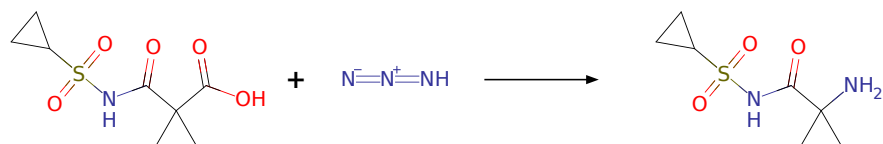
**Protections:** none

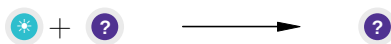
**Yield:** good

**Reference:** [10.1021/ja9945313](https://doi.org/10.1021/ja9945313) AND [10.1016/j.ejmech.2013.04.028](https://doi.org/10.1016/j.ejmech.2013.04.028)  
 AND [10.1039/c5ra14001c](https://doi.org/10.1039/c5ra14001c) AND [10.1016/j.bmcl.2013.12.043](https://doi.org/10.1016/j.bmcl.2013.12.043) AND [10.1016/j.tetasy.2012.08.013](https://doi.org/10.1016/j.tetasy.2012.08.013)

**Retrosynthesis ID:** 14787

### 2.3.2 Schmidt Reaction





**Substrates:**

1. hydrazoic acid
2. O=C(O)C1(C(=O)NS(=O)(=O)C2CC2)CC1

**Products:**

1. NC1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** azide.H+.40C

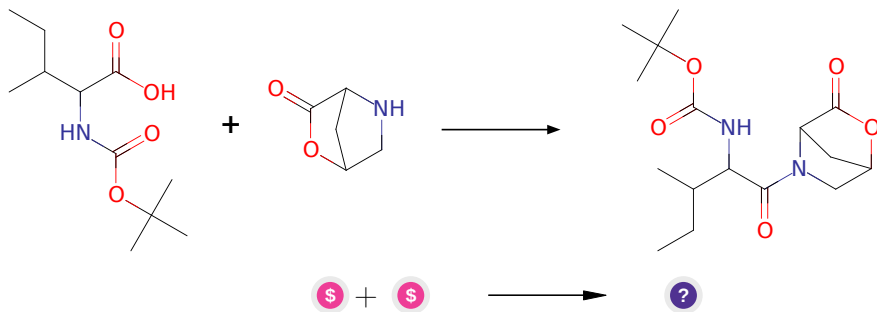
**Protections:** none

**Yield:** moderate

**Reference:** [10.1039/B505080D](#)

**Retrosynthesis ID:** 11704

### 2.3.3 Amide coupling



**Substrates:**

1. 2-[(tert-butoxy)carbonyl]amino-3-methylpentanoic acid - *available at Sigma-Aldrich*
2. cis-4-hydroxy-proline lactone - *Enamine*

**Products:**

1. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC2CC1C(=O)O2

**Typical conditions:** DCC.DCM or EDC.DCM or SOCl<sub>2</sub>.DCM

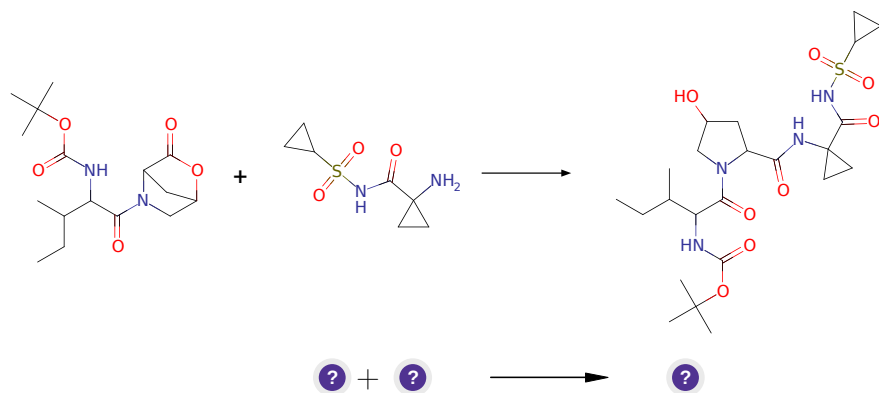
**Protections:** none

**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

### 2.3.4 Intramolecular amidation of esters



**Substrates:**

1. NC1(C(=O)NS(=O)(=O)C2CC2)CC1
2. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC2CC1C(=O)O2

**Products:**

1. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC(O)CC1C(=O)NC1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** DABAL-(Me)<sub>3</sub>.THF.cooling

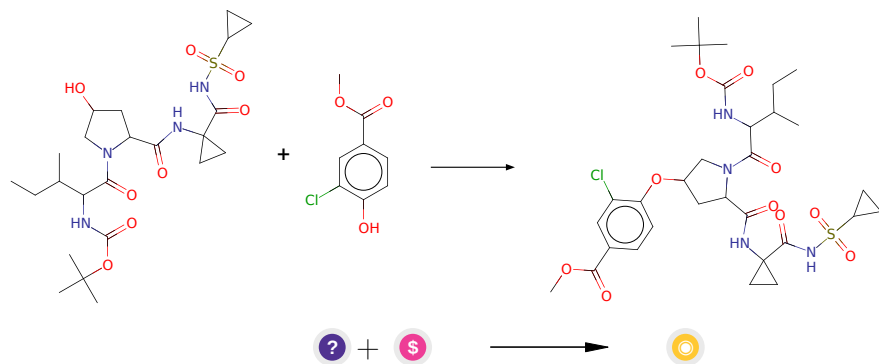
**Protections:** none

**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

### 2.3.5 Mitsunobu reaction



#### Substrates:

1. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC(O)CC1C(=O)NC1(C(=O)NS(=O)(=O)C2CC2)CC1
2. Methyl 3-chloro-4-hydroxybenzoate - *available at Sigma-Aldrich*

#### Products:

1. CCC(C)C(NC(=O)OC(C)(C)C)C(=O)N1CC(Oc2ccc(C(=O)OC)cc2Cl)CC1C(=O)NC1(C(=O)NS(=O)(=O)C2CC2)CC1

**Typical conditions:** DEAD.or.DCAD.or.DIAD.PPh<sub>3</sub>

**Protections:** none

**Yield:** good

**Reference:** DOI: [10.1021/jo0345751](https://doi.org/10.1021/jo0345751) AND [10.1021/ol0618757](https://doi.org/10.1021/ol0618757)

**Retrosynthesis ID:** 7562