

# Paths of analysis\*

AS2

Synthia

October 10, 2022

## 1 Analysis parameters

**Analysis type:** Automatic Retrosynthesis

**Rules:** none selected

**Filters:** Exclude Diastereoselective reactions, Tunnels, FGI, FGI with protections

**Max. paths returned:** 50

**Max. iterations:** 2000

**Commercial:**

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1500 \$/g

**Published:**

1. Max. molecular weight - 1000 g/mol
2. Popularity - 5

**My Stockroom:**

1. Max. molecular weight - 1000 g/mol

**Reaction scoring formula:**  $\text{TUNNEL\_COEF} * \text{FGI\_COEF} * \text{STEP} * 20 + 1000 * (\text{CONFLICT} + \text{NON\_SELECTIVITY} + \text{FILTERS} + \text{PROTECT})$

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

**Min. search width:** 400

**Max. reactions per product:** 60

---

\*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.

**Strategies:** none selected

**FGI Coeff:** 0

**Tunnels 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:** 161.11

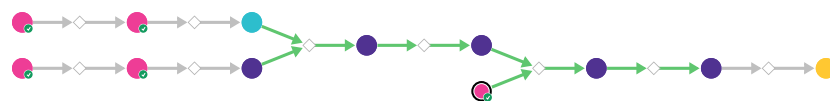
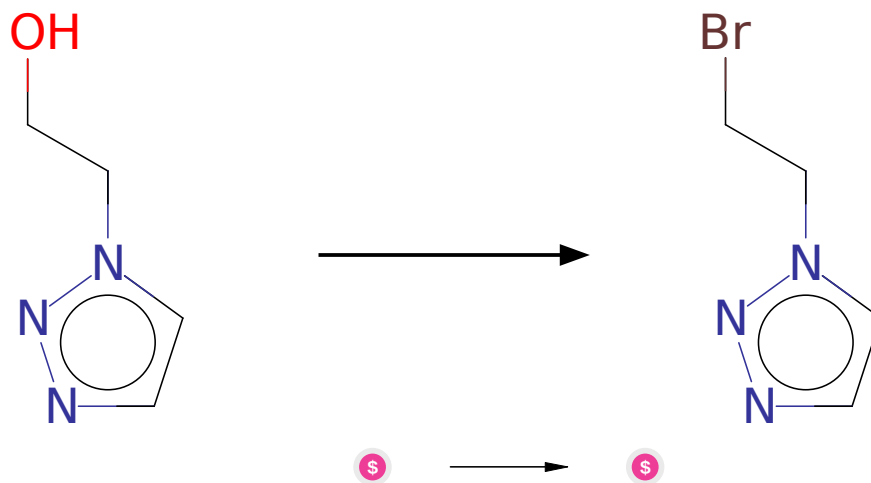


Figure 1: Outline of path 1

#### 2.1.1 Appel Reaction



**Substrates:**

- 2-(1H-1,2,3-triazol-1-yl)ethanol - *available at Sigma-Aldrich*

**Products:**

1. 1-(2-bromoethyl)-1H-1,2,3-triazole - *available at Sigma-Aldrich*

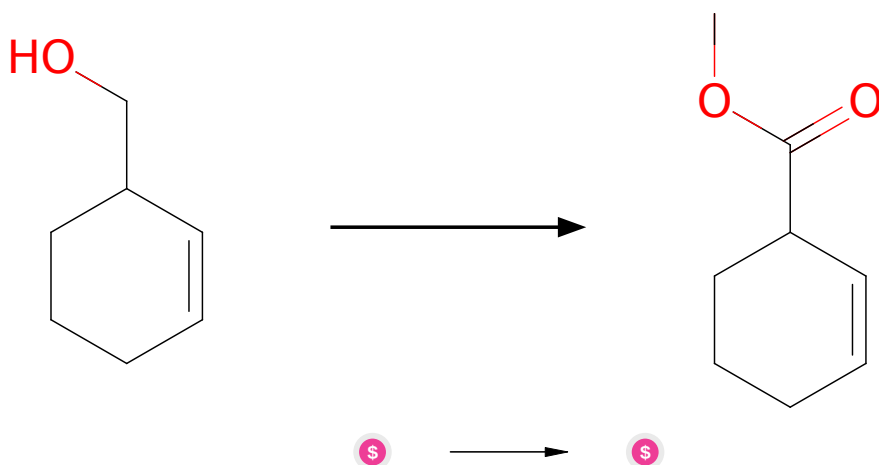
**Typical conditions:** PPh<sub>3</sub>.CBr<sub>4</sub>

**Protections:** none

**Reference:** [10.1021/ja800574m](#) and [10.1016/j.tet.2012.05.010](#) and [10.1016/j.tet.2004.09.021](#) (experimental)

**Retrosynthesis ID:** 9990037

### 2.1.2 Tandem oxidation-esterification



**Substrates:**

1. (cyclohex-2-en-1-yl)methanol - *available at Sigma-Aldrich*

**Products:**

1. methyl cyclohex-2-ene-1-carboxylate - *available at Sigma-Aldrich*

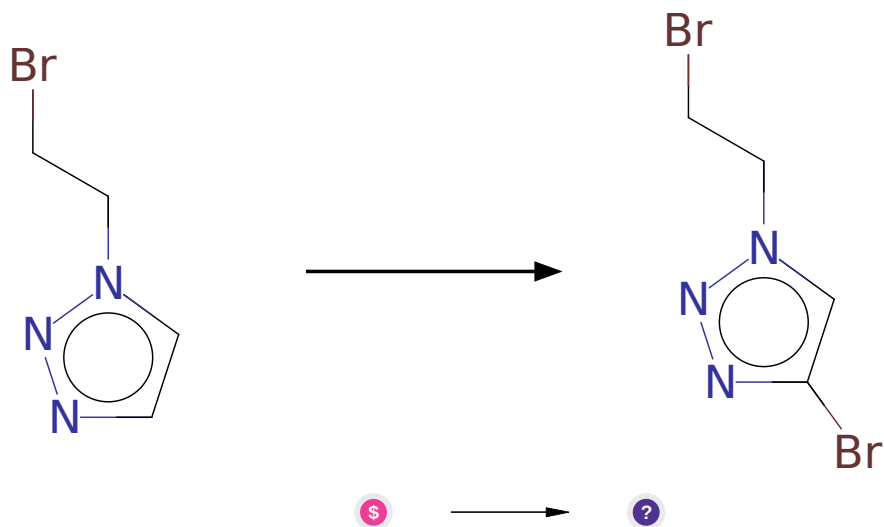
**Typical conditions:** Oxidant (eg. I<sub>2</sub>.K<sub>2</sub>CO<sub>3</sub> or Ca(OCl)<sub>2</sub>).MeOH

**Protections:** none

**Reference:** [10.1016/S0040-4039\(00\)73550-7](#) and [10.1016/j.tet.2005.03.097](#) and [10.1021/ol062940f](#)

**Retrosynthesis ID:** 25234

### 2.1.3 Bromination of aromatic compounds



#### Substrates:

- 1-(2-bromoethyl)-1H-1,2,3-triazole - *available at Sigma-Aldrich*

#### Products:

- BrCCn1cc(Br)nn1

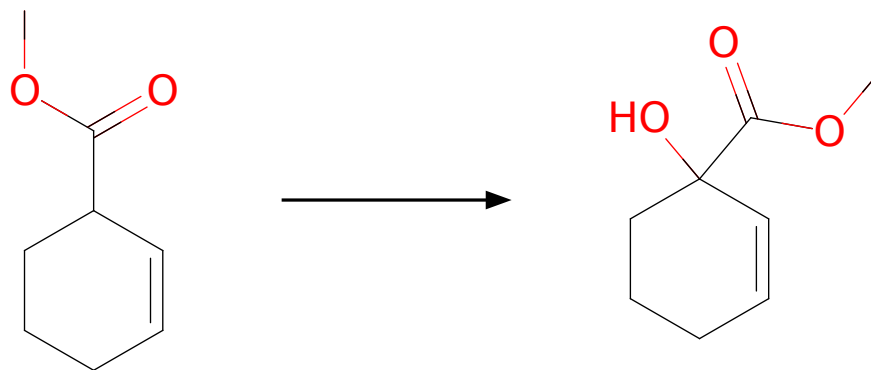
Typical conditions: Br2.Fe

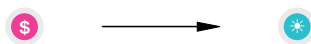
Protections: none

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

Retrosynthesis ID: 7777000

### 2.1.4 Hydroxylation of enolates





**Substrates:**

1. methyl cyclohex-2-ene-1-carboxylate - *available at Sigma-Aldrich*

**Products:**

1. methyl 1-hydroxy-2-cyclohexenoate

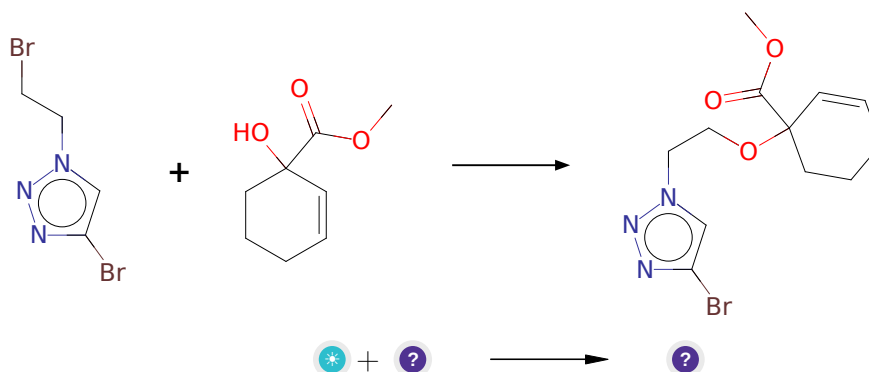
**Typical conditions:** Cs<sub>2</sub>CO<sub>3</sub>.P(OEt)<sub>3</sub>.DMSO.rt.O<sub>2</sub>

**Protections:** none

**Reference:** [10.1002/anie.201308698](#) and [10.1016/j.tetlet.2012.11.083](#)  
and [10.1016/j.tetlet.2012.11.135](#) and [10.1002/ejoc.200390075](#) and  
[10.1016/j.crci.2014.08.003](#)

**Retrosynthesis ID:** 25192

### 2.1.5 Alkylation of tertiary alcohols



**Substrates:**

1. methyl 1-hydroxy-2-cyclohexenoate
2. BrCCn1cc(Br)nn1

**Products:**

1. COC(=O)C1(OCCn2cc(Br)nn2)C=CCCC1

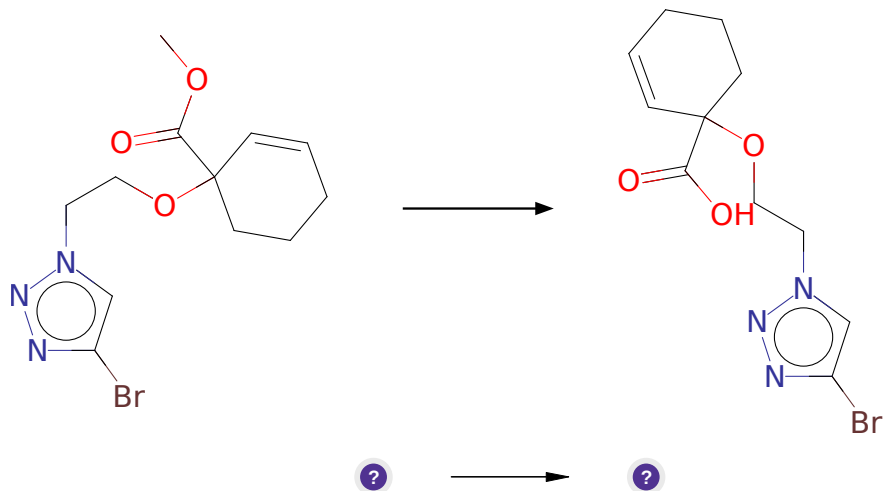
**Typical conditions:** K<sub>2</sub>CO<sub>3</sub>.acetone.heat

**Protections:** none

**Reference:** [10.1038/s41467-018-06099-z](#) and [10.1039/A808980I](#)

**Retrosynthesis ID:** 31010950

### 2.1.6 Synthesis of Carboxylic Acids via Ester Hydrolysis



**Substrates:**

1. COC(=O)C1(OCCn2cc(Br)nn2)C=CCCC1

**Products:**

1. O=C(O)C1(OCCn2cc(Br)nn2)C=CCCC1

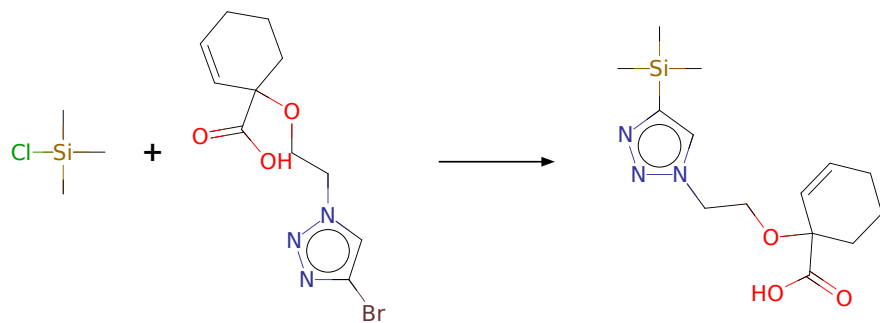
**Typical conditions:** water.base

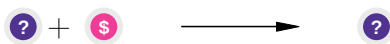
**Protections:** none

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

**Retrosynthesis ID:** 9224

### 2.1.7 Synthesis of silanes, stannanes and germanes from Grignard reagents





**Substrates:**

1. O=C(O)C1(OCCn2cc(Br)nn2)C=CCCC1
2. TMSCl - *available at Sigma-Aldrich*

**Products:**

1. C[Si](C)(C)c1cn(CCOC2(C(=O)O)C=CCCC2)nn1

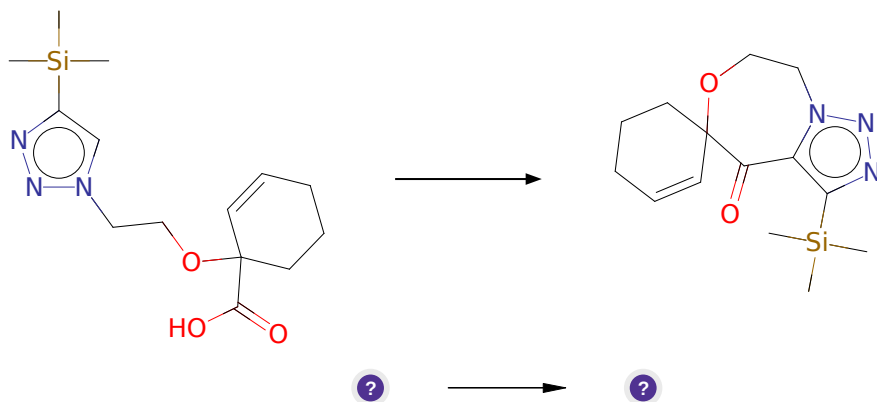
**Typical conditions:** 1.nBuLi.or.Mg.THF.-78C.2.Si-Cl.to.rt

**Protections:** none

**Reference:** [10.1021/jo802433t](#) AND [10.1021/ja01108a009](#)

**Retrosynthesis ID:** 5402

### 2.1.8 Friedel-Crafts Acylation



**Substrates:**

1. C[Si](C)(C)c1cn(CCOC2(C(=O)O)C=CCCC2)nn1

**Products:**

1. C[Si](C)(C)c1nnn2c1C(=O)C1(C=CCCC1)OCC2

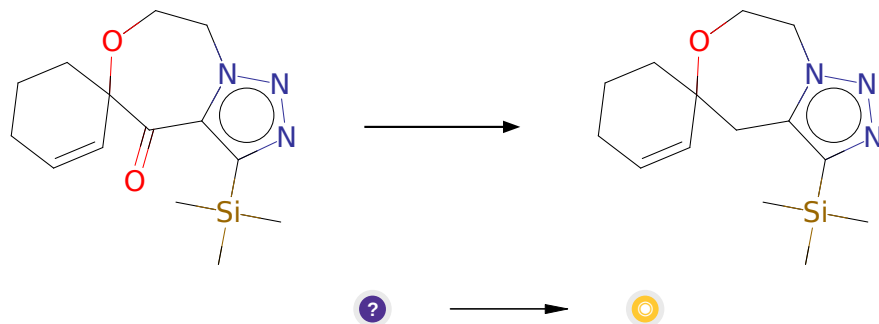
**Typical conditions:** 1(COCl)2.Lewis Acid.solvent

**Protections:** none

**Reference:** [10.1021/ol800752v](#)

**Retrosynthesis ID:** 13729

### 2.1.9 Wolff-Kishner Reduction



**Substrates:**

1. C[Si](C)(C)c1nnn2c1C(=O)C1(C=CCCC1)OCC2

**Products:**

1. C[Si](C)(C)c1nnn2c1CC1(C=CCCC1)OCC2

**Typical conditions:** hydrazine.ethylene glycol.KOH.180-200 C

**Protections:** none

**Reference:** [10.1007/s00044-016-1528-8](#) p. 1116, 1110 and [10.1021/acs.jmedchem.7b01363](#) p. 9408, 9411 and [10.1016/j.tetasy.2006.11.005](#) and [10.1023/A:1024124411892](#)

**Retrosynthesis ID:** 243

### 2.2 Path 2

**Score:** 182.33

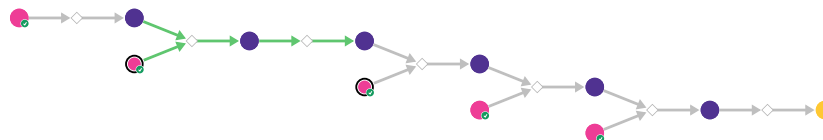
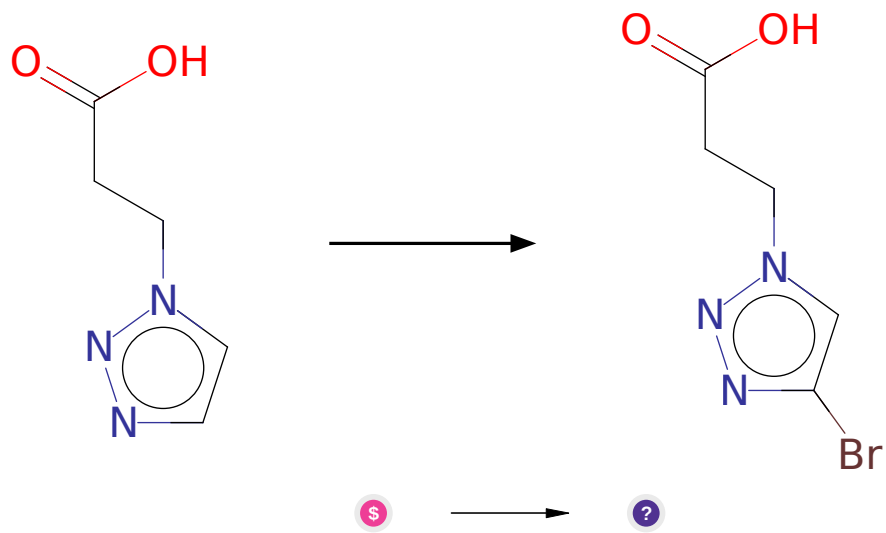


Figure 2: Outline of path 2



### 2.2.1 Bromination of aromatic compounds



**Substrates:**

1. 3-(1H-1,2,3-triazol-1-yl)propanoic acid hydrochloride - *available at Sigma-Aldrich*

**Products:**

1. O=C(O)CCn1cc(Br)nn1

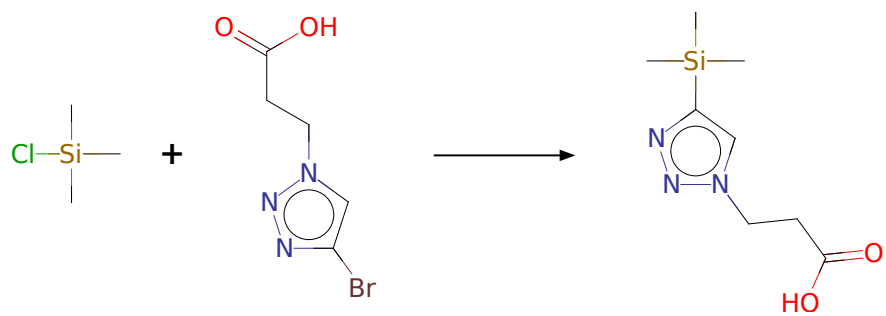
**Typical conditions:** Br<sub>2</sub>.Fe

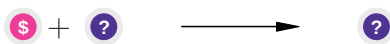
**Protections:** none

**Reference:** [10.1021/acs.accounts.6b00120](#)

**Retrosynthesis ID:** 7777000

### 2.2.2 Synthesis of silanes, stannanes and germanes from Grignard reagents





**Substrates:**

1. TMSCl - *available at Sigma-Aldrich*
2. O=C(O)CCn1cc(Br)nn1

**Products:**

1. C[Si](C)(C)c1cn(CCC(=O)O)nn1

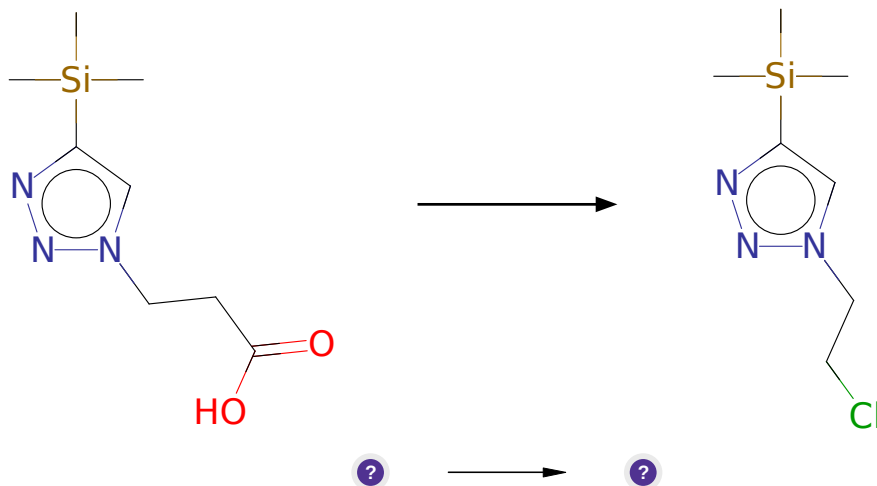
**Typical conditions:** 1.nBuLi.or.Mg.THF.-78C.2.Si-Cl.to.rt

**Protections:** none

**Reference:** *10.1021/jo802433t* AND *10.1021/ja01108a009*

**Retrosynthesis ID:** 5402

### 2.2.3 Synthesis of alkyl chlorides from carboxylic acids



**Substrates:**

1. C[Si](C)(C)c1cn(CCC(=O)O)nn1

**Products:**

1. C[Si](C)(C)c1cn(CCCl)nn1

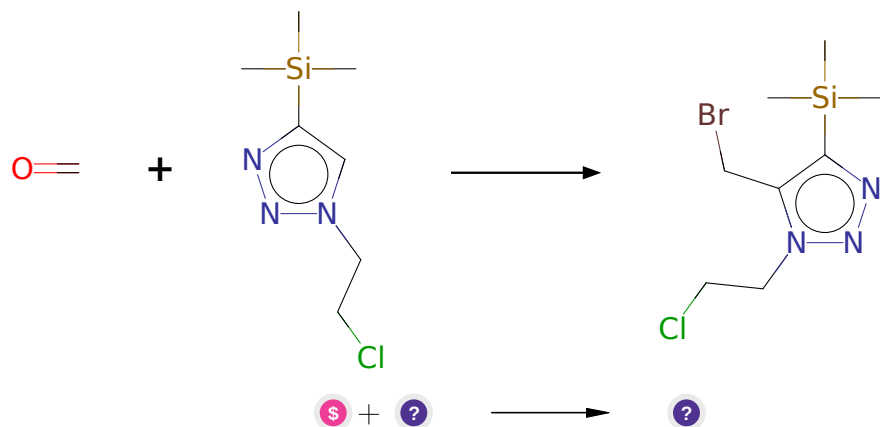
**Typical conditions:** Ag(Phen)2OTf.OtBu.Cl.acetonitrile.RT

**Protections:** none

**Reference:** DOI: *10.1021/ja210361z*

**Retrosynthesis ID:** 11619

### 2.2.4 Blanc bromomethylation



**Substrates:**

1. Formalin - *available at Sigma-Aldrich*
2. C[Si](C)(C)c1cn(CCCl)nn1

**Products:**

1. C[Si](C)(C)c1nn(CCCl)c1CBr

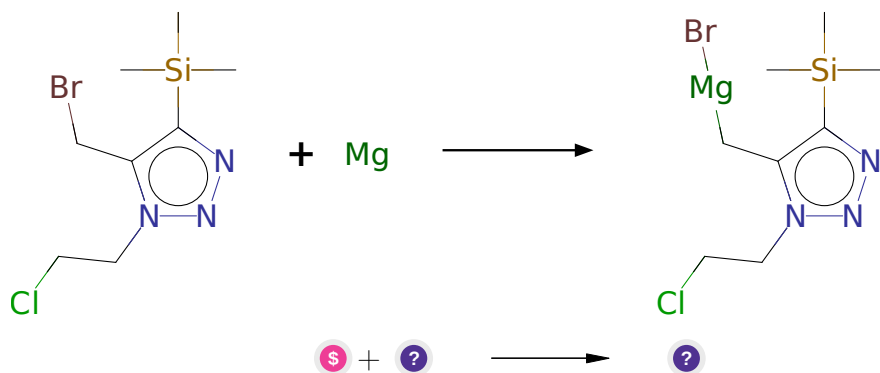
**Typical conditions:** HBr.heat

**Protections:** none

**Reference:** [10.1021/ja011493q](#) and [10.1021/ma012195g](#) and [10.1016/S0040-4039\(02\)01769-0](#) and [10.1021/ja002069c](#)

**Retrosynthesis ID:** 31010730

### 2.2.5 Synthesis of alkyl Grignard reagents



**Substrates:**

1. Magnesium - *available at Sigma-Aldrich*
2. C[Si](C)(C)c1nnn(CCCl)c1CBr

**Products:**

1. C[Si](C)(C)c1nnn(CCCl)c1C[Mg]Br

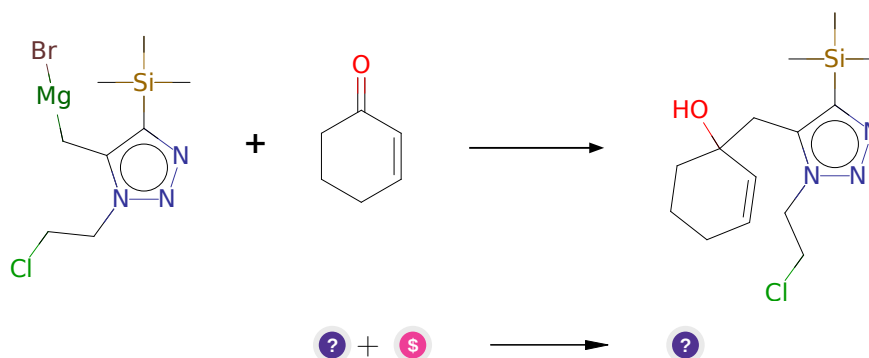
**Typical conditions:** Mg.THF or iPrMgBr

**Protections:** none

**Reference:** DOI: [10.1021/jo00002a039](https://doi.org/10.1021/jo00002a039) and [10.1021/jo047877r](https://doi.org/10.1021/jo047877r) and [10.1021/ol006618v](https://doi.org/10.1021/ol006618v)

**Retrosynthesis ID:** 10011828

**2.2.6 Grignard-Type Reaction**



**Substrates:**

1. C[Si](C)(C)c1nnn(CCCl)c1C[Mg]Br
2. 2-Cyclohexen-1-one - *available at Sigma-Aldrich*

**Products:**

1. C[Si](C)(C)c1nnn(CCCl)c1CC1(O)C=CCCC1

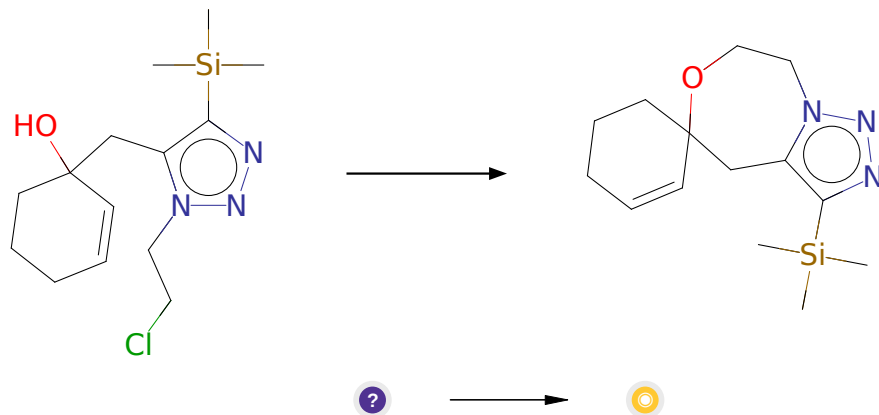
**Typical conditions:** Mg or Li.ether

**Protections:** none

**Reference:** [10.1021/jo010494y](https://doi.org/10.1021/jo010494y) or [10.1016/j.steroids.2015.09.009](https://doi.org/10.1016/j.steroids.2015.09.009) or [10.1021/jo061349t](https://doi.org/10.1021/jo061349t) or [10.1021/ja056165v](https://doi.org/10.1021/ja056165v) (SI page 19)

**Retrosynthesis ID:** 25134

### 2.2.7 Alkylation of tertiary alcohols



**Substrates:**

1. C[Si](C)(C)c1nnn(CCCl)c1CC1(O)C=CCCC1

**Products:**

1. C[Si](C)(C)c1nnn2c1CC1(C=CCCC1)OCC2

**Typical conditions:** K<sub>2</sub>CO<sub>3</sub>.acetone.heat

**Protections:** none

**Reference:** [10.1016/S0040-4020\(01\)90106-1](#) and [10.1021/acs.analchem.5b04461](#) and [10.3390/molecules24091643](#)

**Retrosynthesis ID:** 31010930

## 2.3 Path 3

**Score:** 271.75

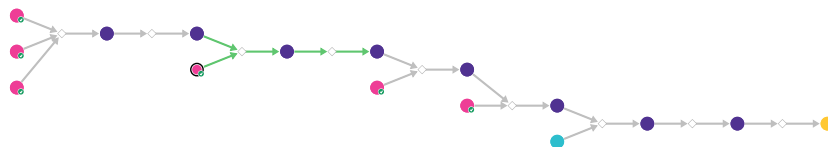
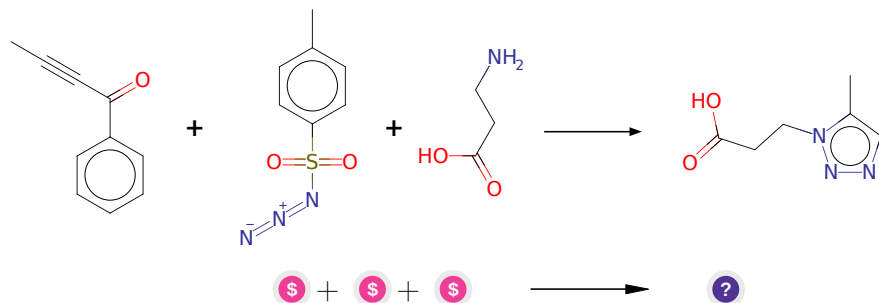


Figure 3: Outline of path 3

### 2.3.1 Metal-free multicomponent synthesis of triazoles



#### Substrates:

1. Tosyl azide solution - *available at Sigma-Aldrich*
2. b-Ala - *available at Sigma-Aldrich*
3. 1-phenyl-but-2-in-1-on - *available at Sigma-Aldrich*

#### Products:

1. Cc1cn[n1]CCC(=O)O

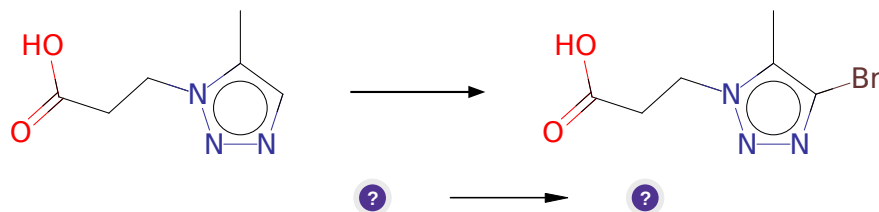
**Typical conditions:** 1. toluene.80C 2. LiOtBu.RT

**Protections:** none

**Reference:** DOI: [10.1002/anie.201307499](https://doi.org/10.1002/anie.201307499)

**Retrosynthesis ID:** 6001

### 2.3.2 Bromination of aromatic compounds



#### Substrates:

1. Cc1cn[n1]CCC(=O)O

#### Products:

1. Cc1c(Br)[n1]n[n1]CCC(=O)O

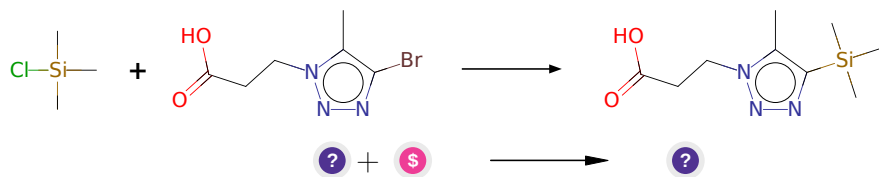
**Typical conditions:** Br<sub>2</sub>.Fe

**Protections:** none

**Reference:** [10.1021/acs.accounts.6b00120](https://doi.org/10.1021/acs.accounts.6b00120)

**Retrosynthesis ID:** 7777000

### 2.3.3 Synthesis of silanes, stannanes and germanes from Grignard reagents



**Substrates:**

1. Cc1c(Br)nn1CCC(=O)O
2. TMSCl - [available at Sigma-Aldrich](#)

**Products:**

1. Cc1c([Si](C)(C)C)nn1CCC(=O)O

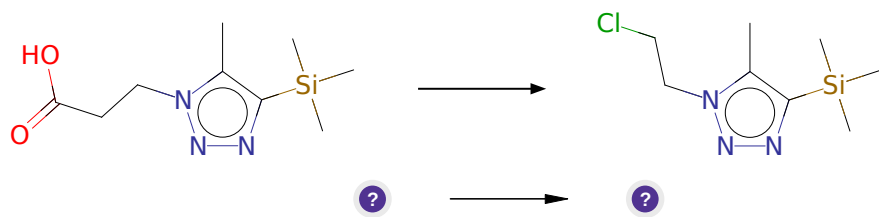
**Typical conditions:** 1. nBuLi. or. Mg. THF. -78C. 2. Si-Cl. to. rt

**Protections:** none

**Reference:** [10.1021/jo802433t](https://doi.org/10.1021/jo802433t) AND [10.1021/ja01108a009](https://doi.org/10.1021/ja01108a009)

**Retrosynthesis ID:** 5402

### 2.3.4 Synthesis of alkyl chlorides from carboxylic acids



**Substrates:**

1. Cc1c([Si](C)(C)C)nn1CCC(=O)O

**Products:**

1. Cc1c([Si](C)(C)C)nnn1CCCCl

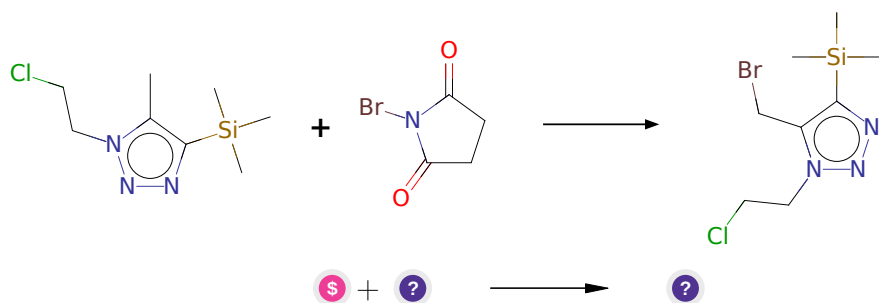
**Typical conditions:** Ag(Phen)2OTf.OtBu.Cl.acetonitrile.RT

**Protections:** none

**Reference:** DOI: [10.1021/ja210361z](https://doi.org/10.1021/ja210361z)

**Retrosynthesis ID:** 11619

### 2.3.5 Wohl-Ziegler Bromination



**Substrates:**

1. N-Bromosuccinimide - [available at Sigma-Aldrich](#)
2. Cc1c([Si](C)(C)C)nnn1CCCCl

**Products:**

1. C[Si](C)(C)c1nnn(CCCl)c1CBr

**Typical conditions:** NBS.AIBN or (BzO)<sub>2</sub> or heat

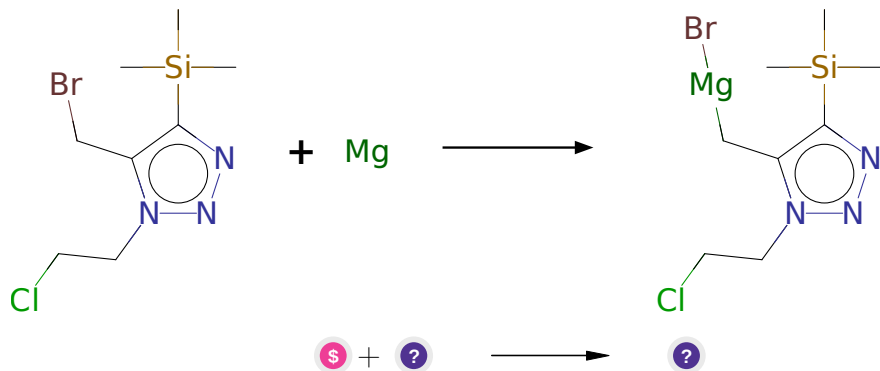
**Protections:** none

**Reference:** [10.1021/acs.organomet.2c00053](https://doi.org/10.1021/acs.organomet.2c00053) (Scheme S1 p. S4) and [10.1021/acs.jafc.0c07237](https://doi.org/10.1021/acs.jafc.0c07237) (Scheme 1) and [10.1002/cbic.201402000](https://doi.org/10.1002/cbic.201402000)

**Retrosynthesis ID:** 245552



### 2.3.6 Synthesis of alkyl Grignard reagents



#### Substrates:

1. Magnesium - *available at Sigma-Aldrich*
2. C[Si](C)(C)c1nnn(CCCl)c1CBr

#### Products:

1. C[Si](C)(C)c1nnn(CCCl)c1C[Mg]Br

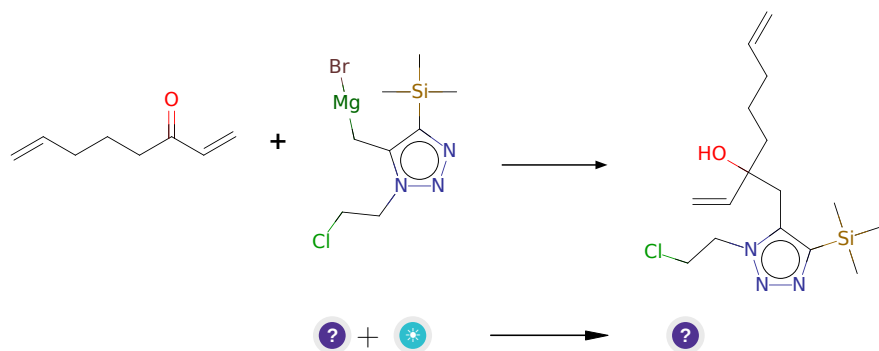
**Typical conditions:** Mg.THF or iPrMgBr

**Protections:** none

**Reference:** DOI: [10.1021/jo00002a039](https://doi.org/10.1021/jo00002a039) and [10.1021/jo047877r](https://doi.org/10.1021/jo047877r) and [10.1021/ol006618v](https://doi.org/10.1021/ol006618v)

**Retrosynthesis ID:** 10011828

### 2.3.7 Grignard-Type Reaction



#### Substrates:

1. C[Si](C)(C)c1nnn(CCCl)c1C[Mg]Br
2. octa-1,7-dien-3-one

**Products:**

1. C=CCCCC(O)(C=C)Cc1c([Si](C)(C)C)nnn1CCCl

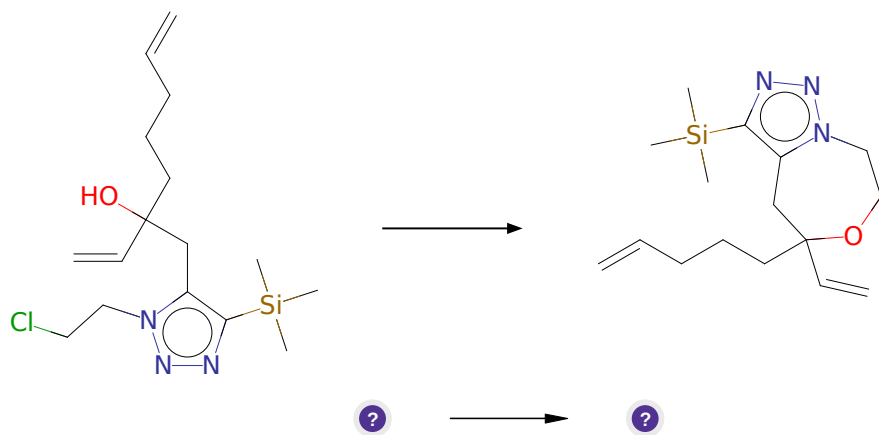
**Typical conditions:** Mg or Li.ether

**Protections:** none

**Reference:** [10.1021/jo010494y](#) or [10.1016/j.steroids.2015.09.009](#) or [10.1021/jo061349t](#) or [10.1021/ja056165v](#) (SI page 19)

**Retrosynthesis ID:** 25134

### 2.3.8 Alkylation of tertiary alcohols



**Substrates:**

1. C=CCCCC(O)(C=C)Cc1c([Si](C)(C)C)nnn1CCCl

**Products:**

1. C=CCCC1(C=C)Cc2c([Si](C)(C)C)nnn2CCO1

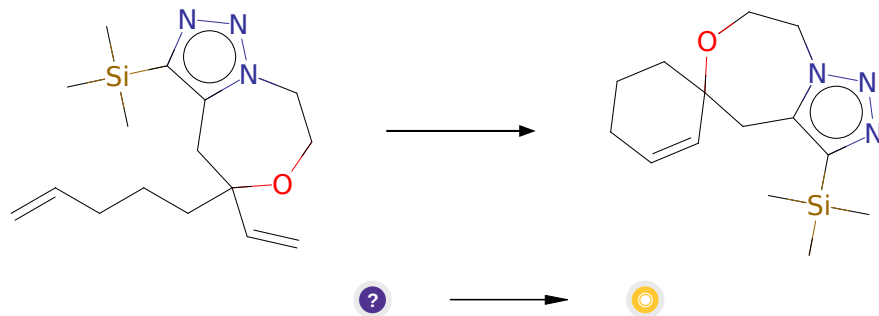
**Typical conditions:** K<sub>2</sub>CO<sub>3</sub>.acetone.heat

**Protections:** none

**Reference:** [10.1016/S0040-4020\(01\)90106-1](#) and [10.1021/acs.analchem.5b04461](#) and [10.3390/molecules24091643](#)

**Retrosynthesis ID:** 31010930

### 2.3.9 Ring-Closing Metathesis



**Substrates:**

1. C=CCCC1(C=C)Cc2c([Si](C)(C)C)nnn2CCO1

**Products:**

1. C[Si](C)(C)c1nnn2c1CC1(C=CCCC1)OCC2

**Typical conditions:** catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH<sub>2</sub>Cl<sub>2</sub>

**Protections:** none

**Reference:** DOI: [10.1002/anie.200800693](https://doi.org/10.1002/anie.200800693) and [10.1021/acs.orglett.8b04003](https://doi.org/10.1021/acs.orglett.8b04003) and [10.1021/jo0264729](https://doi.org/10.1021/jo0264729) and [10.1021/ja072334v](https://doi.org/10.1021/ja072334v) and [10.1002/ejoc.201001102](https://doi.org/10.1002/ejoc.201001102)

**Retrosynthesis ID:** 31014187