Paths of analysis*
AS7

Synthia

October 10, 2022

1   Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: Exclude Diastereoselecitve 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: TUNNEL_COEF*FGI_COEF*STEP*20+1000 000*(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

FGI Coeff: 0

Tunnels Coeff: 0

JSON Parameters: {}

2 Paths

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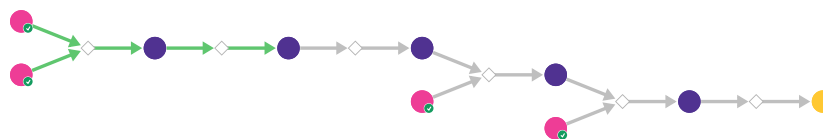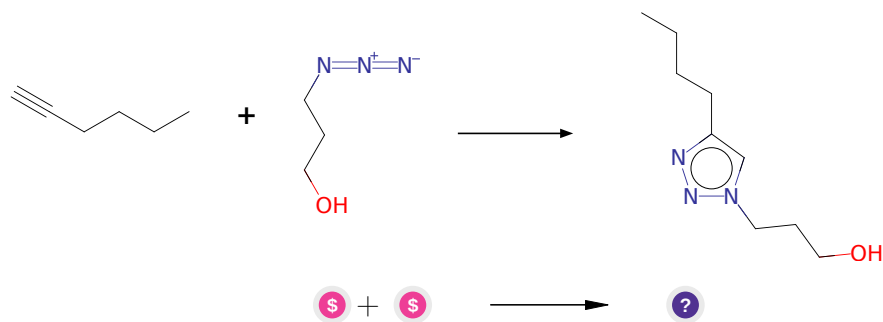
2.1 Path 1

Score: 106.04

Figure 1: Outline of path 1

2.1.1 Huisgen Cycloaddition

Substrates:

1. 3-Azido-1-propanol - *available at Sigma-Aldrich*

2. 1-Hexyne - *available at Sigma-Aldrich*
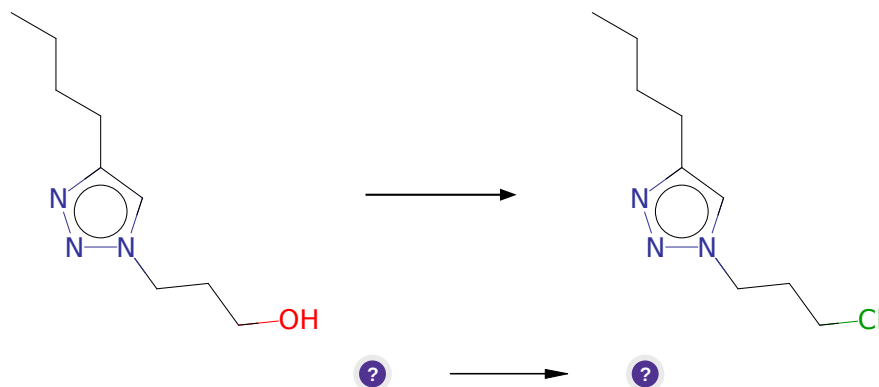
Products:

1. CCCCc1cn(CCCO)nn1

Typical conditions: Cu(I).H2O

Protections: none

Reference: *10.1039/PS9610000357* and *10.1016/S1359-6446(03)02933-7* and *10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5*

Retrosynthesis ID: 10268

2.1.2 Synthesis of alkyl chlorides from alcohols

Substrates:

1. CCCCc1cn(CCCO)nn1
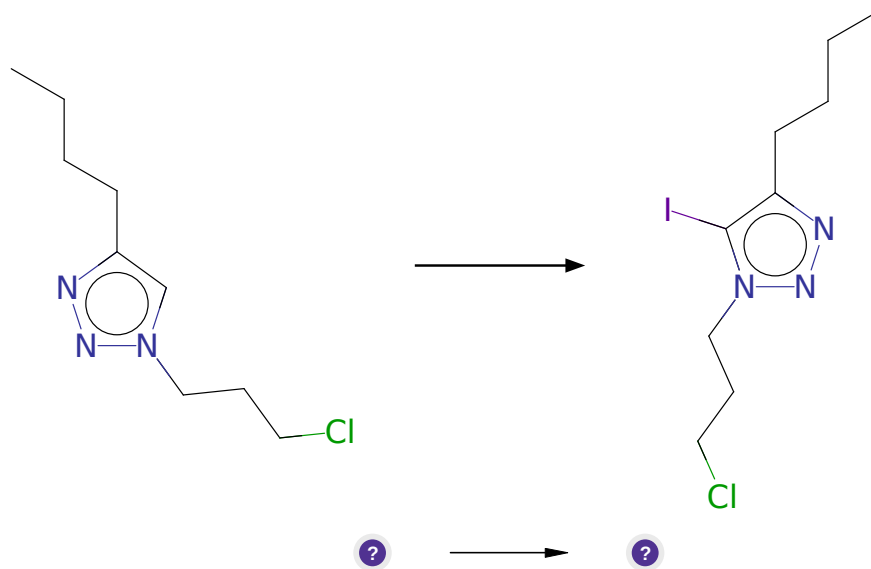
Products:

1. CCCCc1cn(CCCCl)nn1

Typical conditions: cyanuric chloride.DMF.DCM.RT

Protections: none

Reference: DOI: *10.1021/ol017168p*

Retrosynthesis ID: 11617

2.1.3 Iodination of aromatic compounds

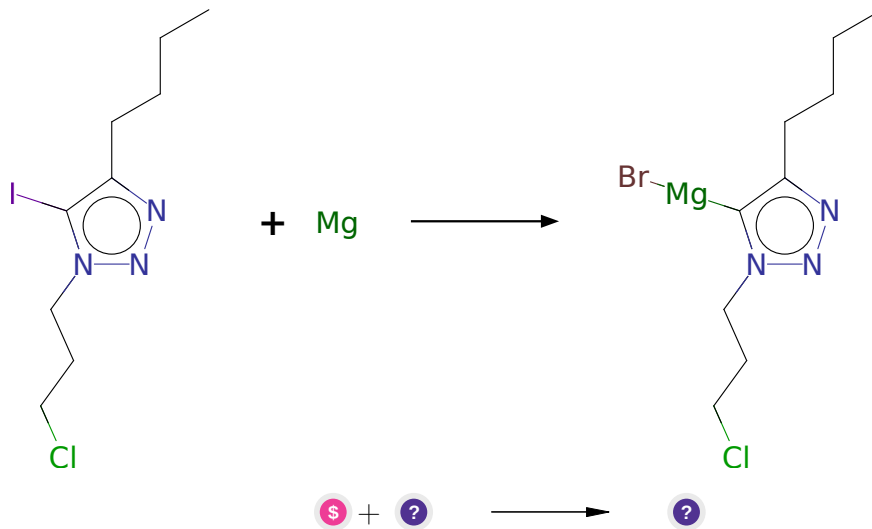**Substrates:**

1. CCCCc1cn(CCCCl)nn1

Products:

1. CCCCc1nnn(CCCCl)c1I

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

Protections: none

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 aryl Grignard reagents

Substrates:

1. Magnesium - *available at Sigma-Aldrich*

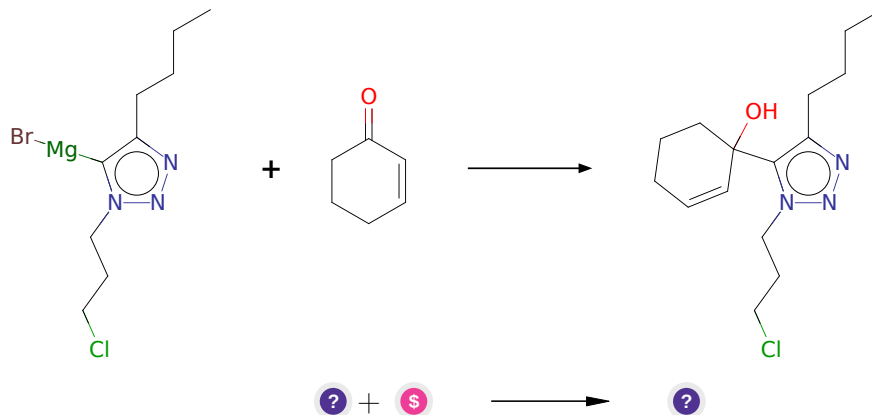2. CCCCc1nnn(CCCCl)c1I

Products:

1. CCCCc1nnn(CCCCl)c1[Mg]Br

Typical conditions: iPrMgCl.LiCl.THF or other conditions Mg.THF or tBuLi.MgBr2

Protections: none

Reference: DOI: *10.1016/S0040-4039(99)01404-5* and *10.1021/jo0000574* and WO2014123793 p.137 and *10.1021/jm400491x* and *10.3762/bjoc.12.36*

Retrosynthesis ID: 10011460

2.1.5 Grignard-Type Reaction

Substrates:

1. CCCCc1nnn(CCCCl)c1[Mg]Br

2. 2-Cyclohexen-1-one - *available at Sigma-Aldrich*

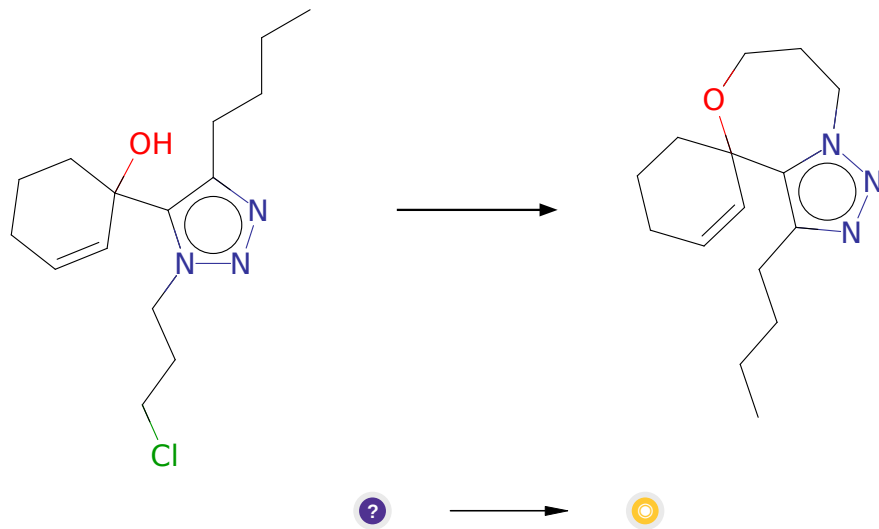**Products:**

1. CCCCc1nnn(CCCCl)c1C1(O)C=CCCC1

Typical conditions: Mg or Li.ether

Protections: none

Reference: *10.1021/jm061429p* or *10.1016/j.bmc.2012.11.015* or *10.1016/j.tetasy.2012.05.024*

Retrosynthesis ID: 25133

2.1.6 Alkylation of tertiary alcohols

Substrates:

1. CCCCc1nnn(CCCCl)c1C1(O)C=CCCC1

Products:

1. CCCCc1nnn2c1C1(C=CCCC1)OCCC2

Typical conditions: K2CO3.acetone.heat
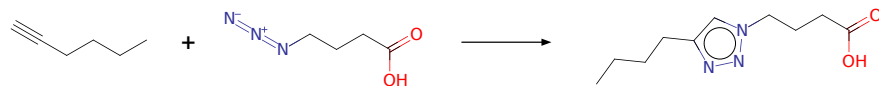
Protections: none

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

Retrosynthesis ID: 31010930

2.2 Path 2

Score: 176.35

2.2.1 Huisgen Cycloaddition
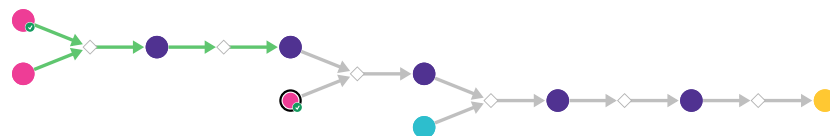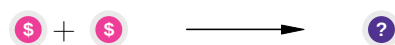
Figure 2: Outline of path 2

Substrates:

1. 1-Hexyne -   *available at Sigma-Aldrich*

2. 4-azido-butyric acid -   *SynthonixCorporation*
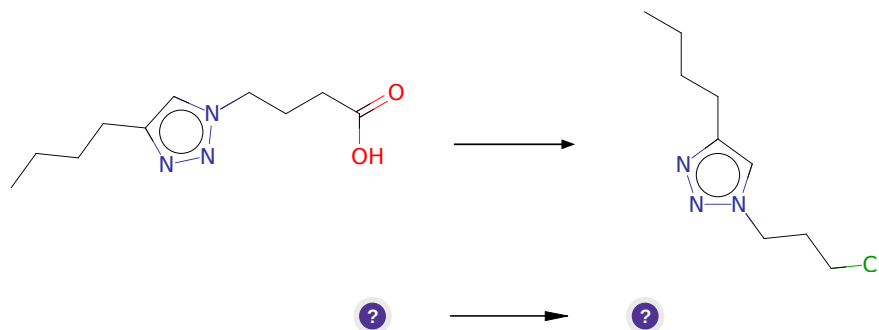
Products:

1. CCCCc1cn(CCCC(=O)O)nn1

Typical conditions: Cu(I).H2O

Protections: none

Reference: *10.1039/PS9610000357*   and   *10.1016/S1359-6446(03)02933-7*   and
10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5

Retrosynthesis ID: 10268

2.2.2 Synthesis of alkyl chlorides from carboxylic acids

Substrates:

1. CCCCc1cn(CCCC(=O)O)nn1
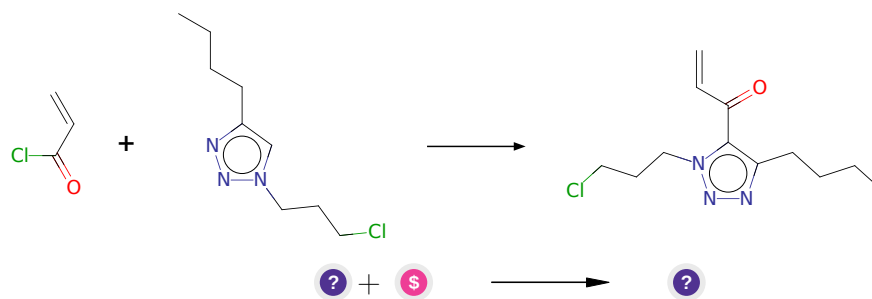
Products:

1. CCCCc1cn(CCCCl)nn1

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

Protections: none

Retrosynthesis ID: 11619

2.2.3 Friedel-Crafts Acylation

Substrates:

1. CCCCc1cn(CCCCl)nn1
2. Acryloyl chloride - *available at Sigma-Aldrich*
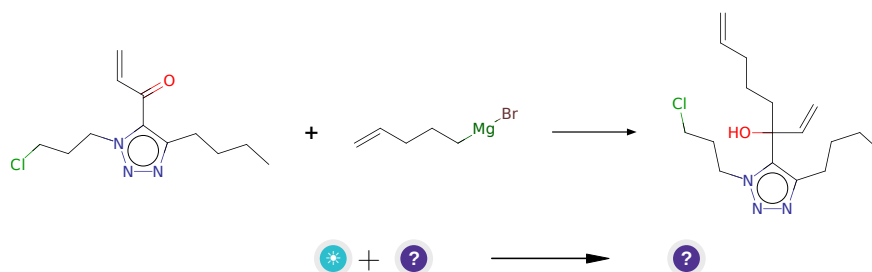
Products:

1. C=CC(=O)c1c(CCCC)nnn1CCCCl

Typical conditions: Lewis Acid.solvent

Protections: none

Retrosynthesis ID: 8722

2.2.4 Grignard-Type Reaction

Substrates:

1. pent-4-enylmagnesiumbromid

2. C=CC(=O)c1c(CCCC)nnn1CCCCl
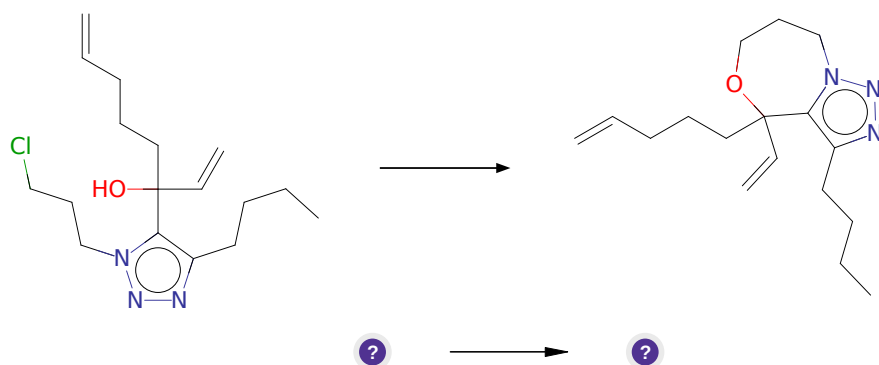
Products:

1. C=CCCCC(O)(C=C)c1c(CCCC)nnn1CCCCl

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

2.2.5 Alkylation of tertiary alcohols

Substrates:

1. C=CCCCC(O)(C=C)c1c(CCCC)nnn1CCCCl

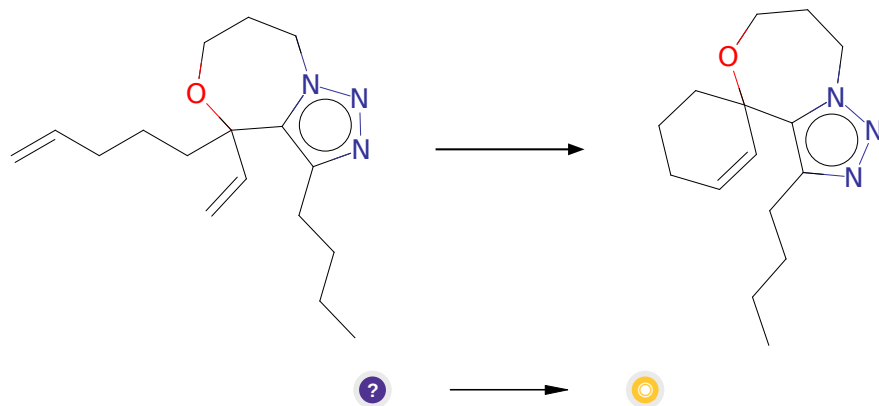**Products:**

1. C=CCCCC1(C=C)OCCCn2nnc(CCCC)c21

Typical conditions: K2CO3.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

2.2.6 Ring-Closing Metathesis

Substrates:

1. C=CCCCC1(C=C)OCCCn2nnc(CCCC)c21

Products:

1. CCCCc1nnn2c1C1(C=CCCC1)OCCC2

Typical conditions: catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH2Cl2

Protections: none

Reference: DOI: *10.1002/anie.200800693* and *10.1021/acs.orglett.8b04003* and *10.1021/jo0264729* and *10.1021/ja072334v* and *10.1002/ejoc.201001102*

Retrosynthesis ID: 31014187
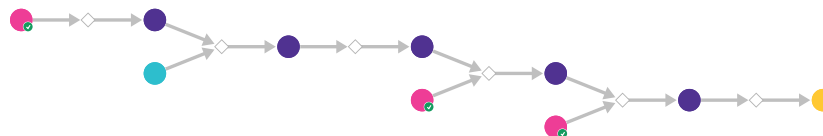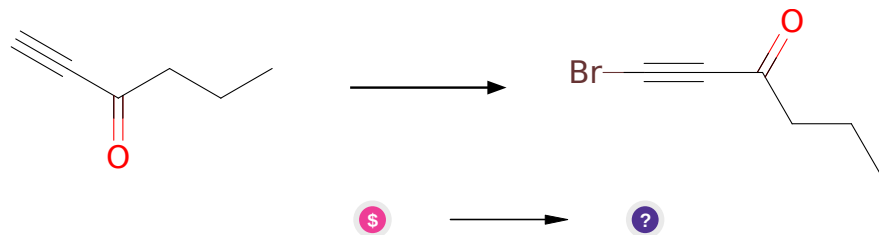
2.3 Path 3

Score: 193.93

Figure 3: Outline of path 3

2.3.1 Synthesis of bromoacetylenes

Substrates:

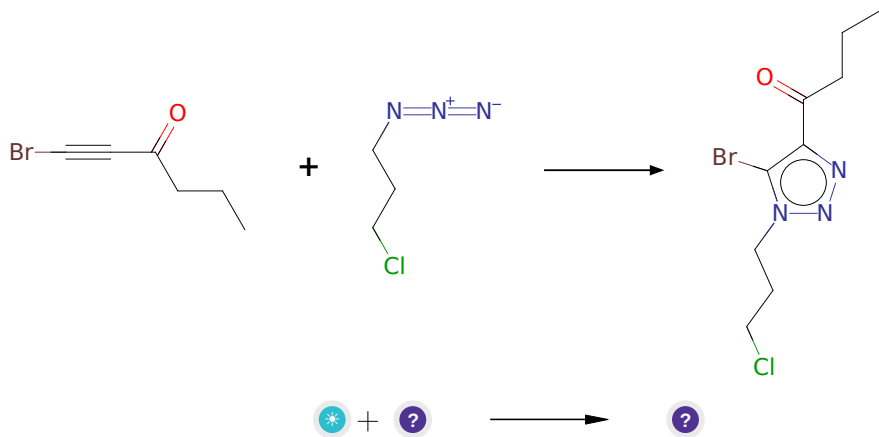1. hex-1-yn-3-one - *available at Sigma-Aldrich*

Products:

1. CCCC(=O)C#CBr

Typical conditions: NBS.acetone

Protections: none

Reference: *10.1021/ja5004747*

Retrosynthesis ID: 5325

2.3.2 Synthesis of triazoles from azides and haloalkynes

Substrates:

1. 1-azido-3-chlor-propan
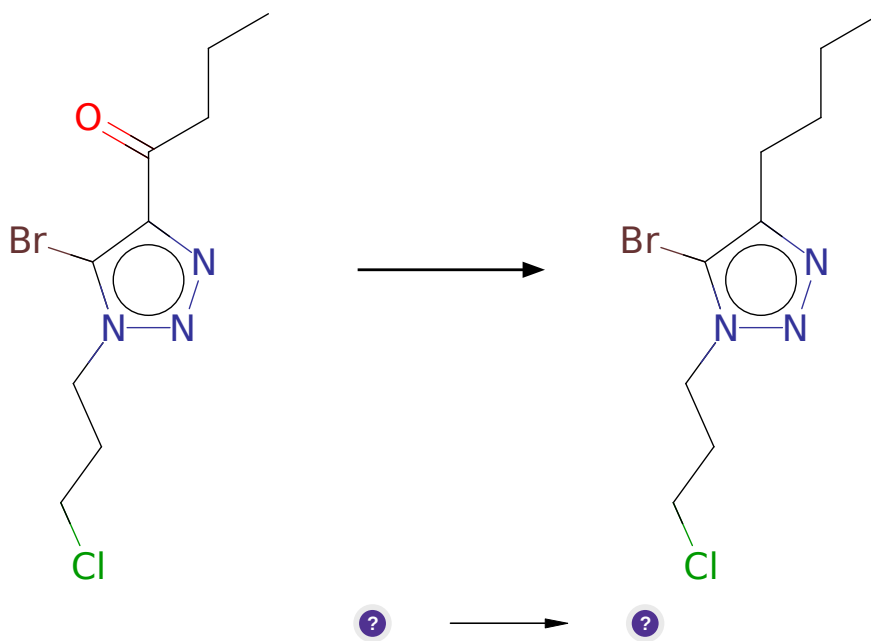2. CCCC(=O)C#CBr

Products:

1. CCCC(=O)c1nnn(CCCCl)c1Br

Typical conditions: CpRuCl(cod).ACN

Protections: none

Reference: *10.1002/chem.201402559*

Retrosynthesis ID: 31456

2.3.3 Clemmensen Reduction

Substrates:

1. CCCC(=O)c1nnn(CCCCl)c1Br
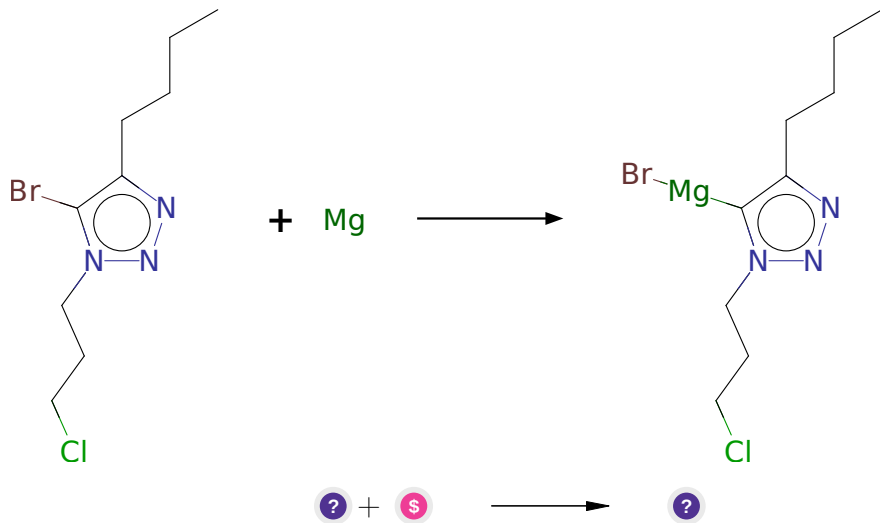
Products:

1. CCCCc1nnn(CCCCl)c1Br

Typical conditions: Zn(Hg).HCl.H2O.EtOH.65 C

Protections: none

Reference: *10.1016/j.bmc.2014.09.022* p. 5873, 5879 and *10.1007/s00044-017-2105-5* p. 828, 819

Retrosynthesis ID: 245

2.3.4 Synthesis of aryl Grignard reagents

Substrates:

1. CCCCc1nnn(CCCCl)c1Br

2. Magnesium -   *available at Sigma-Aldrich*

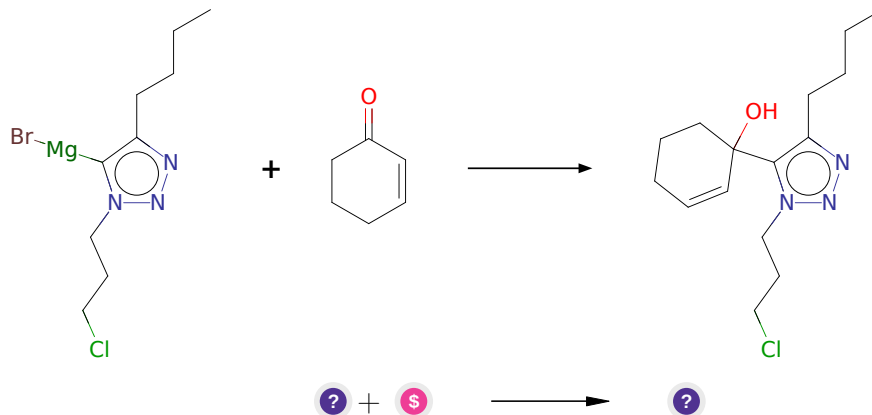**Products:**

1. CCCCc1nnn(CCCCl)c1[Mg]Br

Typical conditions: iPrMgCl.THF or other conditions like BuLi.MgBr2 or Mg.THF

Protections: none

Reference: DOI: *10.1016/S0040-4039(99)01404-5* and *10.1021/jo0000574* and *10.1002/anie.200454084* and *10.1021/ol400150z*

Retrosynthesis ID: 10011461

2.3.5 Grignard-Type Reaction

Substrates:

1. CCCCc1nnn(CCCCl)c1[Mg]Br

2. 2-Cyclohexen-1-one - *available at Sigma-Aldrich*

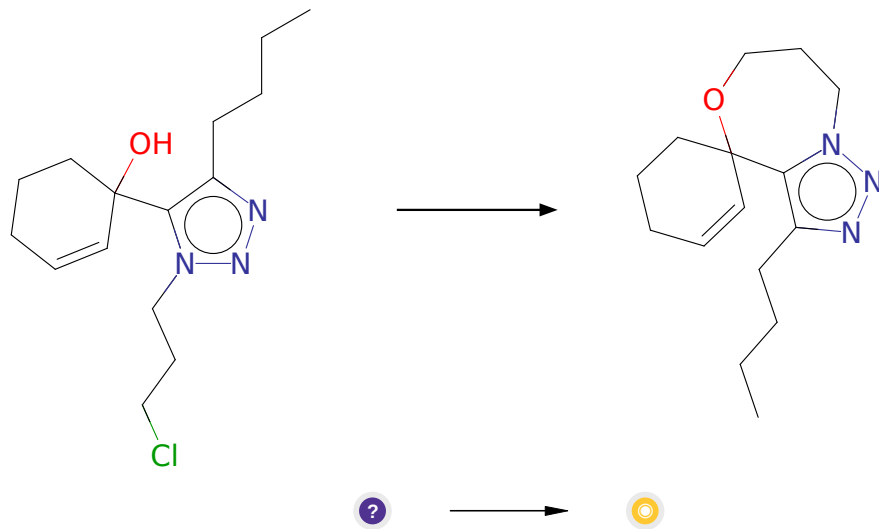**Products:**

1. CCCCc1nnn(CCCCl)c1C1(O)C=CCCC1

Typical conditions: Mg or Li.ether

Protections: none

Reference: *10.1021/jm061429p* or *10.1016/j.bmc.2012.11.015* or *10.1016/j.tetasy.2012.05.024*

Retrosynthesis ID: 25133

2.3.6 Alkylation of tertiary alcohols

Substrates:

1. CCCCc1nnn(CCCCl)c1C1(O)C=CCCC1

Products:

1. CCCCc1nnn2c1C1(C=CCCC1)OCCC2

Typical conditions: K2CO3.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
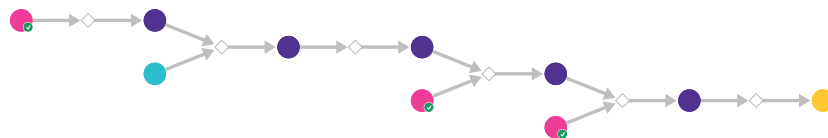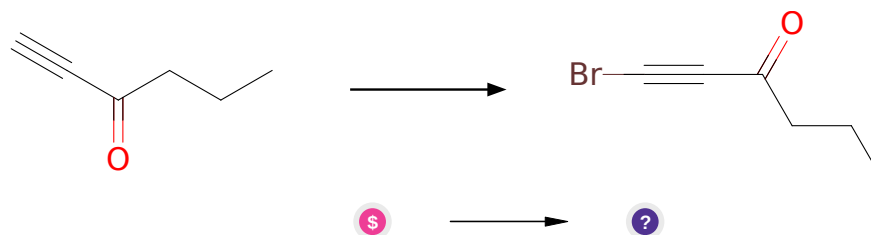
2.4 Path 4

Score: 225.18

Figure 4: Outline of path 4

2.4.1 Synthesis of bromoacetylenes

Substrates:

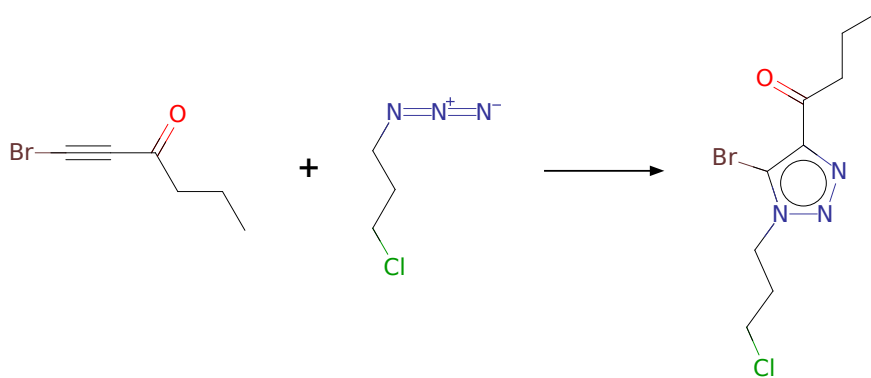1. hex-1-yn-3-one - *available at Sigma-Aldrich*
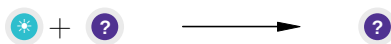
Products:

1. CCCC(=O)C#CBr

Typical conditions: NBS.acetone

Protections: none

Reference: *10.1021/ja5004747*

Retrosynthesis ID: 5325

2.4.2 Synthesis of triazoles from azides and haloalkynes

Substrates:

1. 1-azido-3-chlor-propan

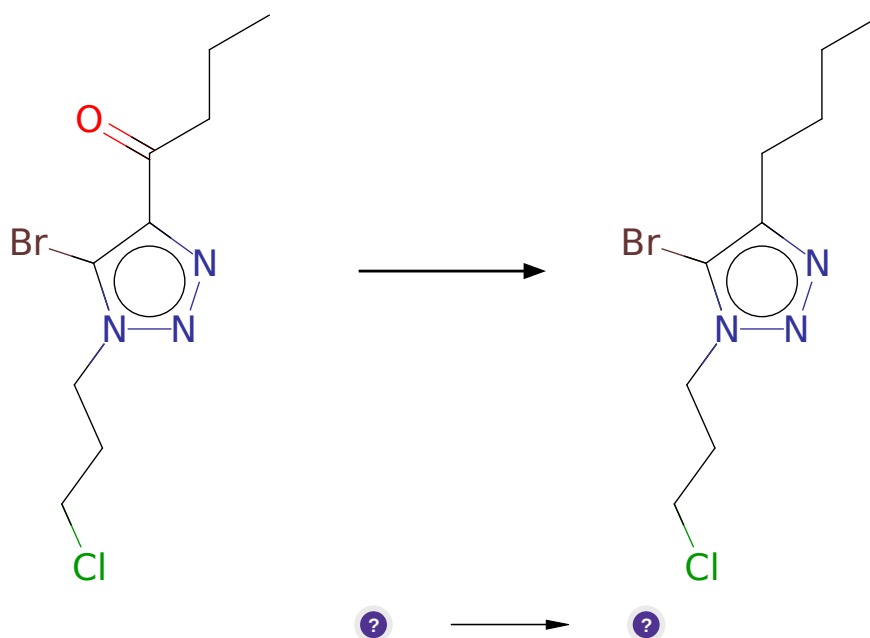2. CCCC(=O)C#CBr

Products:

1. CCCC(=O)c1nnn(CCCCl)c1Br

Typical conditions: CpRuCl(cod).ACN

Protections: none

Reference: *10.1002/chem.201402559*

Retrosynthesis ID: 31456

2.4.3   Clemmensen Reduction

Substrates:

1. CCCC(=O)c1nnn(CCCCl)c1Br

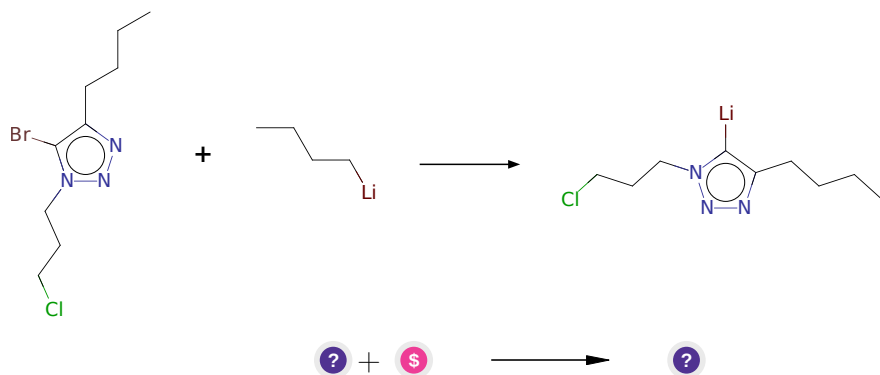**Products:**

1. CCCCc1nnn(CCCCl)c1Br

Typical conditions: Zn(Hg).HCl.H2O.EtOH.65 C

Protections: none

Reference: *10.1016/j.bmc.2014.09.022* p. 5873, 5879 and *10.1007/s00044-017-2105-5* p. 828, 819

Retrosynthesis ID: 245

2.4.4 Br/Li exchange

Substrates:

1. CCCCc1nnn(CCCCl)c1Br

2. n-BuLi - *available at Sigma-Aldrich*

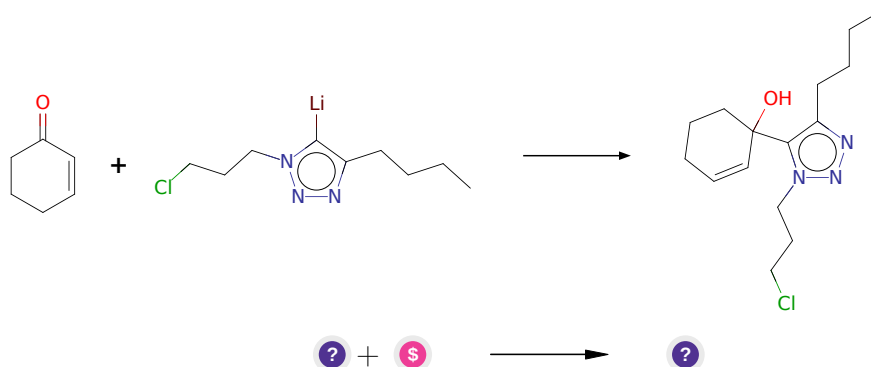**Products:**

1. [Li]c1c(CCCC)nnn1CCCCl

Typical conditions: nBuLi.or.tBuLi.THF.-78C

Protections: none

Reference: *10.1002/ejoc.201101490* and *10.1016/j.tet.2012.03.058* and *10.1016/j.tetlet.2015.01.032* and *10.1021/ja0541175* and *10.1016/j.tetlet.2016.06.123*

Retrosynthesis ID: 30672

2.4.5 Addition of electrophiles to lithiated arenes/heteroarenes

Substrates:

1. [Li]c1c(CCCC)nnn1CCCCl

2. 2-Cyclohexen-1-one - *available at Sigma-Aldrich*

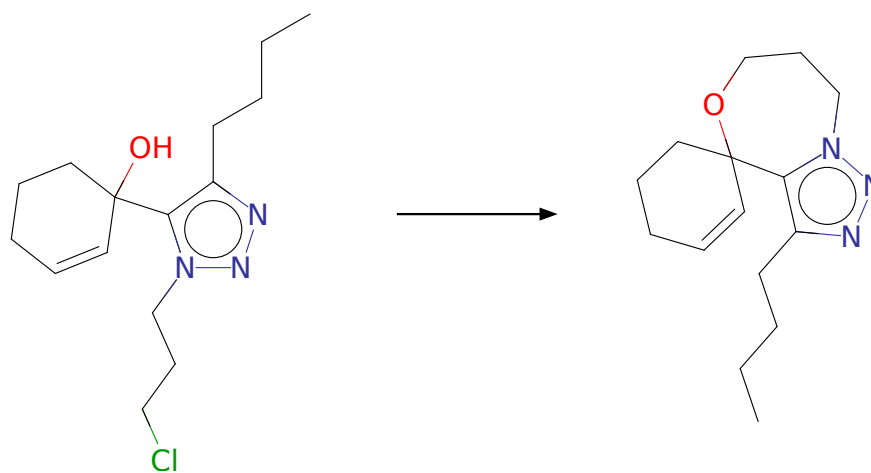**Products:**

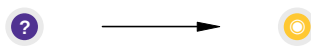1. CCCCc1nnn(CCCCl)c1C1(O)C=CCCC1

Typical conditions: THF.-78 deg C

Protections: none

Reference: *10.1021/ml300335r* and *10.1021/acs.jmedchem.6b00866*

Retrosynthesis ID: 31008139

2.4.6 Alkylation of tertiary alcohols

Substrates:

1. CCCCc1nnn(CCCCl)c1C1(O)C=CCCC1

Products:

1. CCCCc1nnn2c1C1(C=CCCC1)OCCC2

Typical conditions: K2CO3.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