# Paths of analysis\*

## Synthia

October 10, 2022

# 1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: Exclude Diastereoselecitve reactions, Tunnels, FGI, FGI with protec-

tions

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

<sup>\*</sup>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

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

#### 2.1 Path 1

Score: 125.08



Figure 1: Outline of path 1

## 2.1.1 Synthesis of alkyl Grignard reagents



#### Substrates:

- 1. Magnesium available at Sigma-Aldrich
- 2. 4-Bromo-1,1,1-trimethoxybutane available at Sigma-Aldrich

## **Products:**

1. COC(CCC[Mg]Br)(OC)OC

Typical conditions: Mg.THF or iPrMgBr

Protections: none

**Reference:** DOI: 10.1021/jo00002a039 and 10.1021/jo047877r and

10.1021/ol006618v

Retrosynthesis ID: 10011828

# 2.1.2 Grignard-Type Reaction

#### Substrates:

1. 1-Phenylprop-2-en-1-one - available at Sigma-Aldrich

2. COC(CCC[Mg]Br)(OC)OC

#### **Products:**

1. C=CC(O)(CCCC(OC)(OC)OC)c1ccccc1

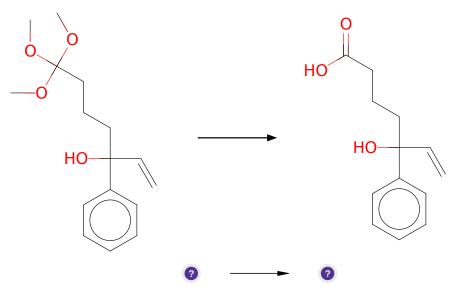
Typical conditions: Mg or Li.ether

Protections: none

**Reference:** 10.1021/j0010494y or 10.1016/j.steroids.2015.09.009 or

10.1021/jo061349t or 10.1021/ja056165v (SI page 19)

# 2.1.3 Synthesis of carboxylic acids from acetals



## Substrates:

 $1. \ C{=}CC(O)(CCCC(OC)(OC)OC)c1ccccc1\\$ 

# Products:

 $1. \ C{=}CC(O)(CCCC(=O)O)c1ccccc1$ 

Typical conditions: HCl.H2O

Protections: none

**Reference:** 10.1016/j.tetasy.2010.12.014

# 2.1.4 Intramolecular Nucleophilic Acyl Addition

## Substrates:

1. C=CC(O)(CCCC(=O)O)c1ccccc1

#### **Products:**

 $1. \ C{=}CC1(c2cccc2)CCCC({=}O)O1$ 

Typical conditions: DCC.4-PPY.DCM or HCl.THF

Protections: none

**Reference:** 10.1016/80040-4020(01)85848-8 p. 613, 615 and

10.1021/jm00046a007 p. 3243, 3244

Retrosynthesis ID: 10161

# 2.1.5 Fosforylation of ketones



#### Substrates:

1. Diethyl chlorophosphate - available at Sigma-Aldrich

 $2. \ C{=}CC1(c2cccc2)CCCC(=O)O1$ 

#### **Products:**

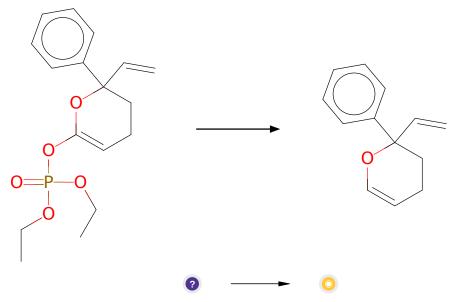
1. C=CC1(c2cccc2)CCC=C(OP(=O)(OCC)OCC)O1

 $\textbf{Typical conditions:} \ \text{KHMDS.HMPA.THF.} cooling$ 

Protections: none

Reference: 10.1021/ja970619+ Retrosynthesis ID: 23009

# 2.1.6 Reduction of enol phosphonates



#### Substrates:

 $1. \ C=CC1(c2cccc2)CCC=C(OP(=O)(OCC)OCC)O1$ 

#### **Products:**

1. C=CC1(c2cccc2)CCC=CO1

Typical conditions: Et3Al.Pd(PPh3)4

Protections: none

**Reference:** 10.1021/jo00387a038 AND 10.1021/jo00292a049 AND

10.1039/C1CS15100B

Retrosynthesis ID: 23046

## 2.2 Path 2

Score: 125.08

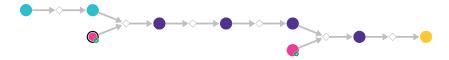
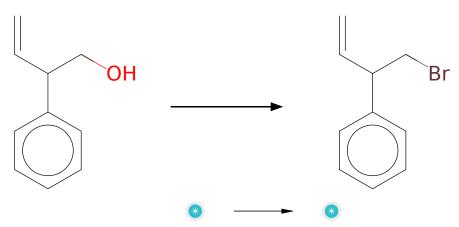


Figure 2: Outline of path 2

# 2.2.1 Appel Reaction



#### Substrates:

1. 2-phenylbut-3-en-1-ol

#### **Products:**

1. 2-phenyl-1-bromo-3-buten

Typical conditions: PPh3.CBr4

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

## 2.2.2 Suzuki alkyl-alkyl coupling

#### Substrates:

1. Methyl acrylate - available at Sigma-Aldrich

2. 2-phenyl-1-bromo-3-buten

#### **Products:**

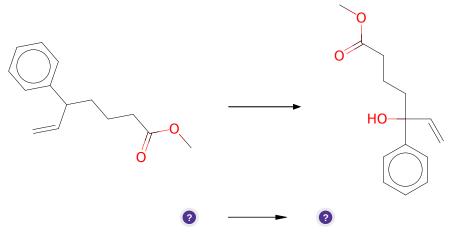
1. C=CC(CCCC(=O)OC)c1ccccc1

Typical conditions: 1.9BBN-H or pinB-Bpin.Cu 2.[Pd].ligand.base

Protections: none

**Reference:** 10.1021/ja074008l and 10.1021/ja011306o and 10.1002/1521-3773(20011217)40:24<4544::AID-ANIE4544>3.0.CO;2-N and <math>10.1021/ol300575d

# 2.2.3 Allylic oxidation to alcohol



## Substrates:

 $1. \ C{=}CC(CCCC(=O)OC)c1ccccc1$ 

## **Products:**

1. C=CC(O)(CCCC(=O)OC)c1ccccc1

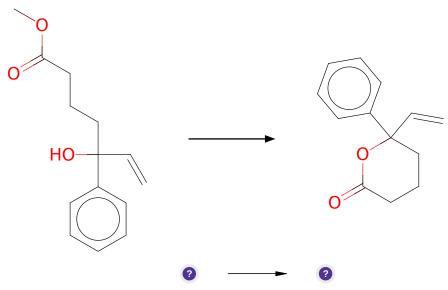
Typical conditions: ArCOOOH or t-BuOOOH

Protections: none

**Reference:** DOI: 10.1021/ja00458a072 AND 10.1016/j.tetlet.2013.03.046 AND

10.1039/b612423b

# 2.2.4 Acid catalyzed transesterification



# Substrates:

 $1. \ C{=}CC(O)(CCCC(=O)OC)c1ccccc1$ 

# Products:

 $1. \ C{=}CC1(c2cccc2)CCCC({=}O)O1$ 

Typical conditions: H+

Protections: none

**Reference:** 10.1021/cr00020a004

## 2.2.5 Synthesis of sulfonylated enol ethers

#### Substrates:

- 1. Triflyl chloride available at Sigma-Aldrich
- 2. C=CC1(c2cccc2)CCCC(=O)O1

## **Products:**

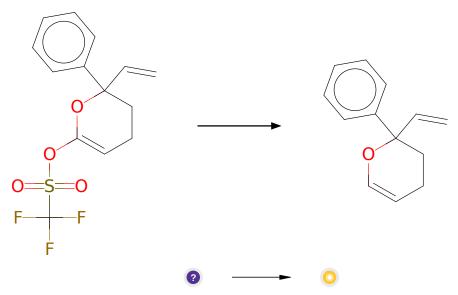
 $1. \ C{=}CC1(c2cccc2)CCC{=}C(OS({=}O)({=}O)C(F)(F)F)O1 \\$ 

 ${\bf Typical\ conditions:}\ {\bf LiHMDS.then.RSO2Cl.or.Tf2O}$ 

Protections: none

**Reference:** 10.1021/o10002370 and 10.1016/j.tetlet.2013.04.038 and 10.1016/S0040-4039(96)02253-8 and 10.1021/jo200271s and 10.1039/B401435A and 10.1021/ja038547b and 10.1021/o1702509a and 10.1016/j.tet.2013.04.039 and 10.1021/jo050995+ and 10.1016/j.tetlet.2013.04.038

#### 2.2.6 Reduction of enol sulfonates



#### Substrates:

1. C=CC1(c2cccc2)CCC=C(OS(=O)(=O)C(F)(F)F)O1

#### **Products:**

1. C=CC1(c2cccc2)CCC=CO1

 $\textbf{Typical conditions:} \ Et3Al.Pd(PPh3)4 \ or \ Bu3SnH.LiCl.Pd(PPh3)4$ 

Protections: none

**Reference:** 10.1021/ol060233g and 10.1021/ja055220x and 10.1021/ja029382u and 10.1021/ja9925958 and 10.1021/jacs.6b03373 and 10.1016/j.tet.2016.03.101

Retrosynthesis ID: 31014801

## 2.3 Path 3

Score: 125.08

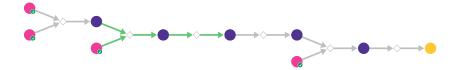


Figure 3: Outline of path 3

# 2.3.1 Synthesis of alkyl Grignard reagents

#### Substrates:

1. Magnesium - available at Sigma-Aldrich

2. 4-Bromo-1,1,1-trimethoxybutane - available at Sigma-Aldrich

#### **Products:**

 $1. \ \mathrm{COC}(\mathrm{CCC}[\mathrm{Mg}]\mathrm{Br})(\mathrm{OC})\mathrm{OC}$ 

 $\textbf{Typical conditions:} \ \mathrm{Mg.THF} \ \mathrm{or} \ \mathrm{iPrMgBr}$ 

Protections: none

**Reference:** DOI: 10.1021/jo00002a039 and 10.1021/jo047877r and

10.1021/ol006618v

Retrosynthesis ID: 10011828

# 2.3.2 Grignard-Type Reaction



#### Substrates:

1. 1-Phenylprop-2-en-1-one - available at Sigma-Aldrich

 $2. \ COC(CCC[Mg]Br)(OC)OC \\$ 

#### **Products:**

1. C=CC(O)(CCCC(OC)(OC)OC)c1ccccc1

 $\textbf{Typical conditions:} \ \operatorname{Mg} \ \mathrm{or} \ \operatorname{Li.ether}$ 

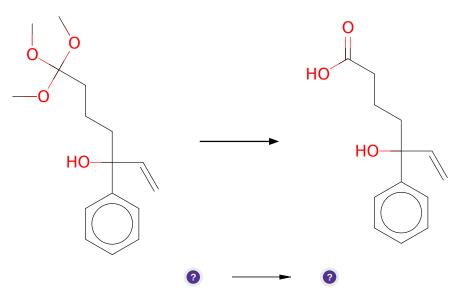
Protections: none

**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

## 2.3.3 Synthesis of carboxylic acids from acetals



#### Substrates:

1. C=CC(O)(CCCC(OC)(OC)OC)c1ccccc1

#### **Products:**

1. C=CC(O)(CCCC(=O)O)c1ccccc1

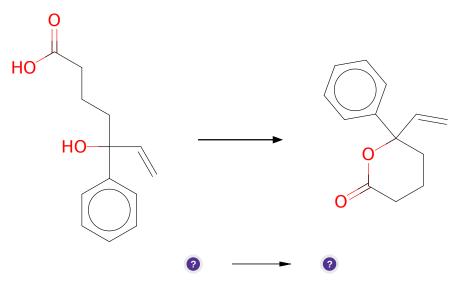
Typical conditions: HCl.H2O

Protections: none

**Reference:** 10.1016/j.tetasy.2010.12.014

Retrosynthesis ID: 25207

## 2.3.4 Intramolecular Nucleophilic Acyl Addition



#### Substrates:

1. C=CC(O)(CCCC(=O)O)c1ccccc1

#### **Products:**

1. C=CC1(c2cccc2)CCCC(=O)O1

 $\textbf{Typical conditions:} \ \, \text{DCC.4-PPY.DCM or HCl.THF}$ 

Protections: none

**Reference:** 10.1016/S0040-4020(01)85848-8 p. 613, 615 and

10.1021/jm00046a007 p. 3243, 3244

## 2.3.5 Synthesis of sulfonylated enol ethers

#### Substrates:

- 1. Triflyl chloride available at Sigma-Aldrich
- 2. C=CC1(c2cccc2)CCCC(=O)O1

## **Products:**

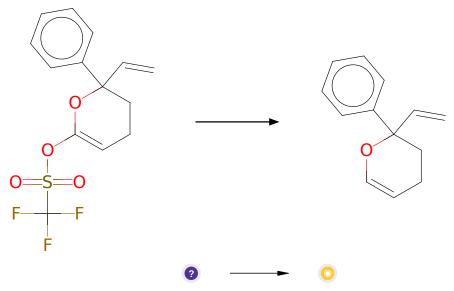
 $1. \ C{=}CC1(c2cccc2)CCC{=}C(OS({=}O)({=}O)C(F)(F)F)O1 \\$ 

 ${\bf Typical\ conditions:}\ {\bf LiHMDS.then.RSO2Cl.or.Tf2O}$ 

Protections: none

**Reference:** 10.1021/o100002370 and 10.1016/j.tetlet.2013.04.038 and 10.1016/S0040-4039(96)02253-8 and 10.1021/jo200271s and 10.1039/B401435A and 10.1021/ja038547b and 10.1021/o1702509a and 10.1016/j.tet.2013.04.039 and 10.1021/jo050995+ and 10.1016/j.tetlet.2013.04.038

#### 2.3.6 Reduction of enol sulfonates



#### Substrates:

1. C=CC1(c2cccc2)CCC=C(OS(=O)(=O)C(F)(F)F)O1

#### **Products:**

1. C=CC1(c2cccc2)CCC=CO1

 $\textbf{Typical conditions:} \ \, \text{Et3Al.Pd(PPh3)4 or Bu3SnH.LiCl.Pd(PPh3)4}$ 

Protections: none

**Reference:** 10.1021/ol060233g and 10.1021/ja055220x and 10.1021/ja029382u and 10.1021/ja9925958 and 10.1021/jacs.6b03373 and 10.1016/j.tet.2016.03.101

Retrosynthesis ID: 31014801

## 2.4 Path 4

Score: 125.08

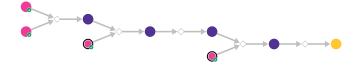


Figure 4: Outline of path 4

## 2.4.1 Synthesis of epoxides under Simmons-Smith conditions

#### Substrates:

1. Chloroiodomethane - available at Sigma-Aldrich

2. Methyl 4-Benzoylbutyrate - available at Sigma-Aldrich

## **Products:**

1. COC(=O)CCCC1(c2cccc2)CO1

Typical conditions: Et2Zn.tetrahydrothiophene or MeLi.LiBr.Et2O.-78 deg  $^{\rm C}$ 

Protections: none

**Reference:** 10.1016/S0040-4039(00)84103-9 and 10.1016/S0040-4039(97)10675-X and 10.1246/bcsj.70.707 and 10.1021/jo971773h

Retrosynthesis ID: 31019397

## 2.4.2 Synthesis of allylic alcohols from epoxides



#### Substrates:

1. Iodomethane - available at Sigma-Aldrich

 $2. \ \mathrm{COC}(=\mathrm{O})\mathrm{CCC1}(\mathrm{c2cccc2})\mathrm{CO1}$ 

#### **Products:**

1. C=CC(O)(CCCC(=O)OC)c1ccccc1

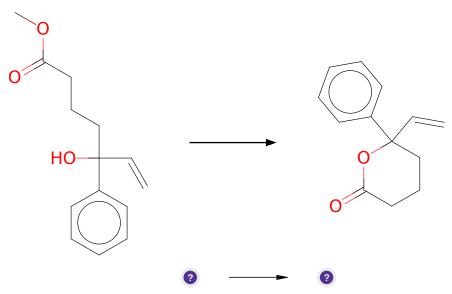
 $\textbf{Typical conditions:}\ 1. DMS. 2. nBuLi. THF. 3. epoxide$ 

Protections: none

**Reference:** 10.1016/S0040-4039(00)73522-2

Retrosynthesis ID: 28068

# 2.4.3 Acid catalyzed transesterification



## Substrates:

1. C=CC(O)(CCCC(=O)OC)c1ccccc1

# Products:

 $1. \ C{=}CC1(c2cccc2)CCCC(=O)O1$ 

Typical conditions: H+

Protections: none

**Reference:** 10.1021/cr00020a004

Retrosynthesis ID: 50438

# 2.4.4 Fosforylation of ketones

#### Substrates:

1. Diethyl chlorophosphate - available at Sigma-Aldrich

 $2. \ C{=}CC1(c2cccc2)CCCC({=}O)O1$ 

## **Products:**

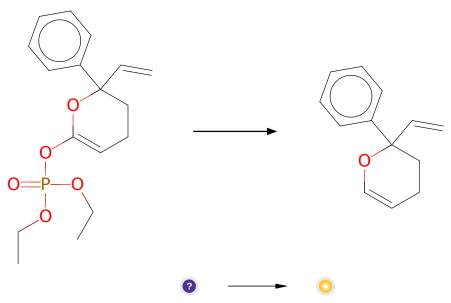
 $1. \ C{=}CC1(c2cccc2)CCC{=}C(OP(=O)(OCC)OCC)O1$ 

 ${\bf Typical\ conditions:}\ {\bf KHMDS.HMPA.THF.cooling}$ 

Protections: none

Reference: 10.1021/ja970619+Retrosynthesis ID: 23009

# 2.4.5 Reduction of enol phosphonates



#### Substrates:

 $1. \ C{=}CC1(c2cccc2)CCC{=}C(OP(=O)(OCC)OCC)O1$ 

## Products:

 $1. \ C{=}CC1(c2cccc2)CCC{=}CO1$ 

Typical conditions: Et3Al.Pd(PPh3)4

Protections: none

**Reference:** 10.1021/jo00387a038 AND 10.1021/jo00292a049 AND

10.1039/C1CS15100B

Retrosynthesis ID: 23046

## 2.5 Path 5

Score: 137.29



Figure 5: Outline of path 5

## 2.5.1 Appel Reaction

#### Substrates:

1. 4-hydroxy-N,N-dimethylbutanamide - available at Sigma-Aldrich

## **Products:**

1. 4-bromobutanoic acid dimethylamide

Typical conditions: PPh3.CBr4

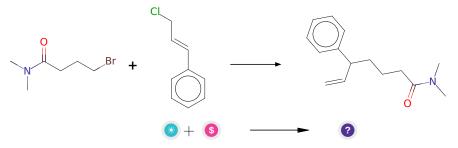
Protections: none

**Reference:** 10.1021/ja800574m and 10.1016/j.tet.2012.05.010 and

10.1016/j.tet.2004.09.021 (experimental)

Retrosynthesis ID: 9990037

# 2.5.2 Asymmetric allylic alkylation



## ${\bf Substrates:}$

- 1. 4-bromobutanoic acid dimethylamide
- 2. Cinnamyl chloride available at Sigma-Aldrich

#### **Products:**

1. C=CC(CCCC(=O)N(C)C)c1ccccc1

Typical conditions: 1.Mg.2.Chiral.[Cu].catalyst.

Protections: none

**Reference:** 10.1351/pac200880051025

Retrosynthesis ID: 7454

# 2.5.3 Hydrolysis of amides

#### Substrates:

 $1. \ C{=}CC(CCCC({=}O)N(C)C)c1ccccc1$ 

## **Products:**

1. C=CC(CCCC(=O)O)c1ccccc1

Typical conditions: NaOH.H2O.EtOH.80  $\rm C$ 

Protections: none

**Reference:** 10.1021/jm020329q p. 2112, 2114 and 10.1021/ja905908z SI p. S4

# 2.5.4 Allylic oxidation to alcohol

## Substrates:

 $1. \ C{=}CC(CCCC(=O)O)c1ccccc1$ 

## **Products:**

 $1. \ C{=}CC(O)(CCCC(=O)O)c1ccccc1$ 

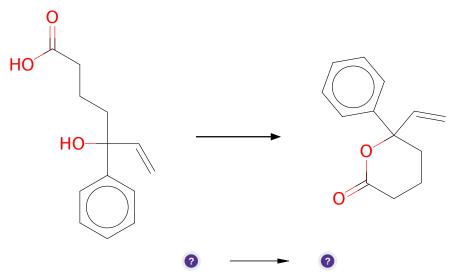
Typical conditions: ArCOOOH or t-BuOOOH

Protections: none

**Reference:** DOI: 10.1021/ja00458a072 AND 10.1016/j.tetlet.2013.03.046 AND

10.1039/b612423b

# 2.5.5 Intramolecular Nucleophilic Acyl Addition



## Substrates:

1. C=CC(O)(CCCC(=O)O)c1ccccc1

#### **Products:**

 $1. \ C{=}CC1(c2cccc2)CCCC({=}O)O1$ 

Typical conditions: DCC.4-PPY.DCM or HCl.THF

Protections: none

**Reference:** 10.1016/S0040-4020(01)85848-8 p. 613, 615 and

10.1021/jm00046a007 p. 3243, 3244

Retrosynthesis ID: 10161

# 2.5.6 Fosforylation of ketones



#### Substrates:

1. Diethyl chlorophosphate - available at Sigma-Aldrich

 $2. \ C{=}CC1(c2cccc2)CCCC(=O)O1$ 

#### **Products:**

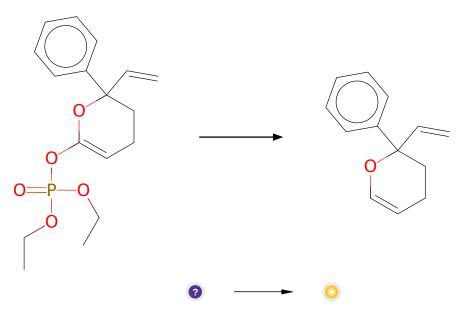
1. C=CC1(c2cccc2)CCC=C(OP(=O)(OCC)OCC)O1

 $\textbf{Typical conditions:} \ \text{KHMDS.HMPA.THF.} cooling$ 

Protections: none

Reference: 10.1021/ja970619+ Retrosynthesis ID: 23009

# 2.5.7 Reduction of enol phosphonates



#### Substrates:

 $1. \ C=CC1(c2cccc2)CCC=C(OP(=O)(OCC)OCC)O1$ 

#### **Products:**

1. C=CC1(c2cccc2)CCC=CO1

Typical conditions: Et3Al.Pd(PPh3)4

Protections: none

**Reference:** 10.1021/jo00387a038 AND 10.1021/jo00292a049 AND

10.1039/C1CS15100B