Paths of analysis*

L1_DIA

Synthia

October 11, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: 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+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

*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

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: 76.25

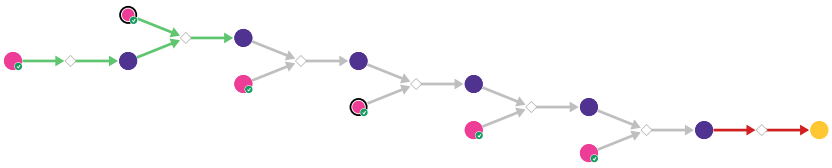
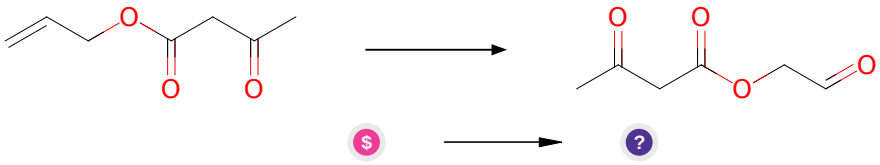


Figure 1: Outline of path 1

2.1.1 Ozonolysis



Substrates:

1. Allyl Acetoacetate - *available at Sigma-Aldrich*

Products:

1. CC(=O)CC(=O)OCC=O

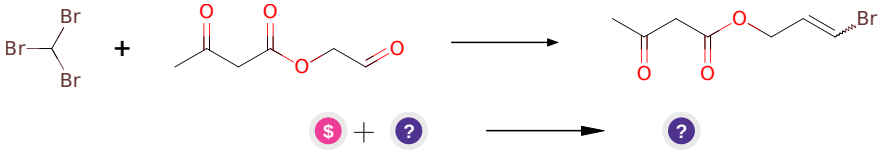
Typical conditions: O3.MeOH.CH2Cl2.PPh3 or Me2S.low temperature

Protections: none

Reference: *10.1016/j.tet.2017.03.039*

Retrosynthesis ID: 5074

2.1.2 Takai olefination



Substrates:

1. Bromoform - *available at Sigma-Aldrich*
2. CC(=O)CC(=O)OCC=O

Products:

1. CC(=O)CC(=O)OCC=CBr

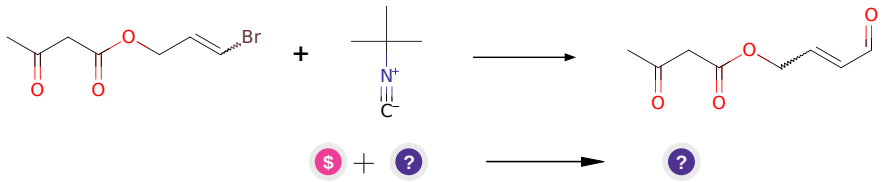
Typical conditions: CrCl2.THF

Protections: none

Reference: *10.1021/ja00283a046* and *10.1021/ja00237a081*

Retrosynthesis ID: 11463

2.1.3 Pd-catalyzed formylation of vinyl halides



Substrates:

1. tert-Butyl isocyanide - *available at Sigma-Aldrich*
2. CC(=O)CC(=O)OCC=CBr

Products:

1. CC(=O)CC(=O)OCC=CC=O

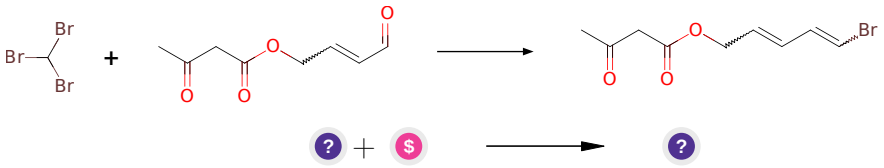
Typical conditions: Pd(OAc)2.JohnPhos.Na2CO3.H2O.Et3SiH.DMF.65C

Protections: none

Reference: DOI: *10.1021/ol5014262*

Retrosynthesis ID: 3104

2.1.4 Takai olefination



Substrates:

1. CC(=O)CC(=O)OCC=CC=O
2. Bromoform - *available at Sigma-Aldrich*

Products:

1. CC(=O)CC(=O)OCC=CC=CBr

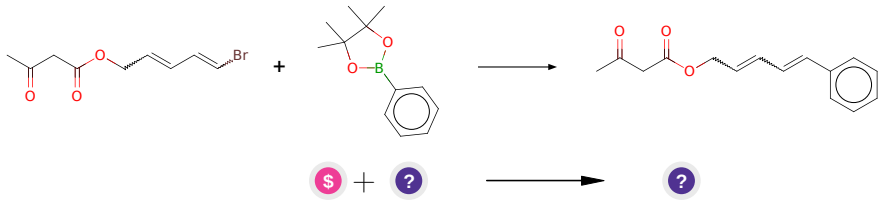
Typical conditions: CrCl2.THF

Protections: none

Reference: *10.1021/ja00283a046* and *10.1021/ja00237a081*

Retrosynthesis ID: 11463

2.1.5 Suzuki coupling of arylboronic pinacol esters with vinyl Bromides



Substrates:

1. (Pinacolboryl)benzene - *available at Sigma-Aldrich*
2. CC(=O)CC(=O)OCC=CC=CBr

Products:

1. CC(=O)CC(=O)OCC=CC=Cc1ccccc1

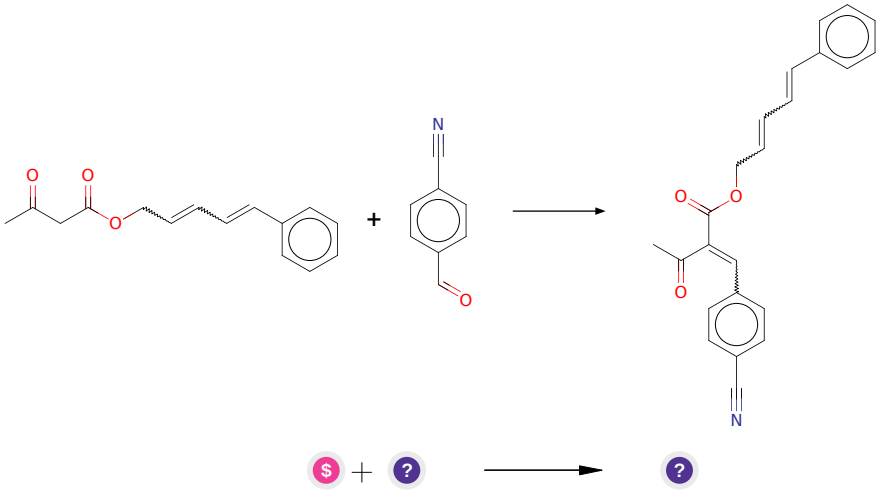
Typical conditions: Pd catalyst.base.solvent

Protections: none

Reference: *10.1021/cr00039a007* and *10.1007/3418_2012_32* and *10.1021/cr0505268* and *10.1016/j.jfluchem.2016.01.018* and *10.1039/C3CS60197H*

Retrosynthesis ID: 10355

2.1.6 Knoevenagel Condensation



Substrates:

1. 4-Cyanobenzaldehyde - *available at Sigma-Aldrich*
2. CC(=O)CC(=O)OCC=CC=Cc1ccccc1

Products:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CC=Cc1ccccc1

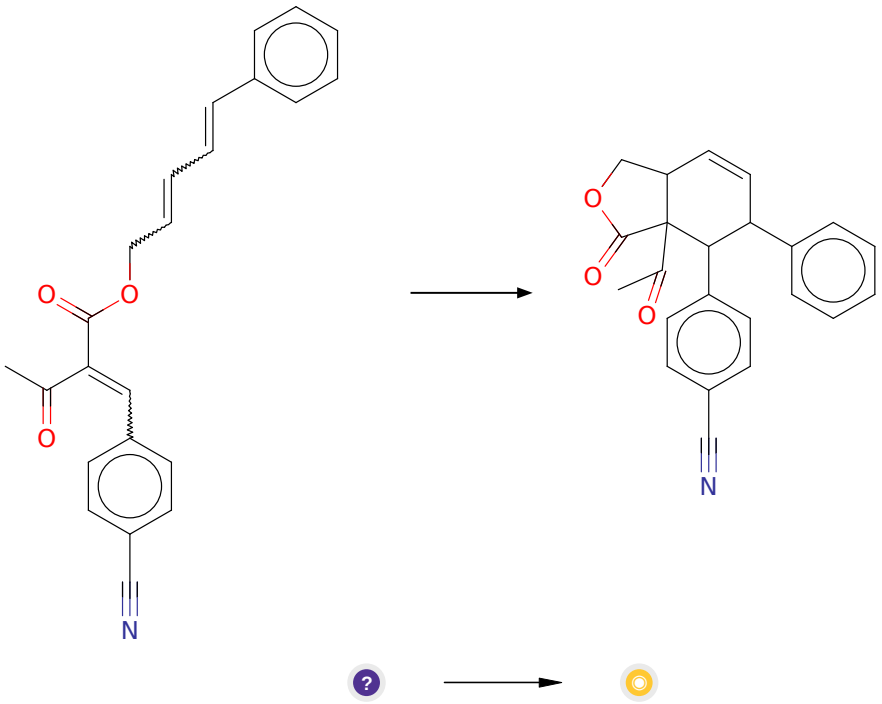
Typical conditions: base e.g.piperidine. solvent

Protections: none

Reference: *10.1002/0471264180.or015.02* and *10.13005/ojc/350154*

Retrosynthesis ID: 252

2.1.7 Diels-Alder



Substrates:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CC=Cc1ccccc1

Products:

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

Typical conditions: Lewis acid or chiral Lewis acid. Solvent.

Protections: none

Reference: DOI: *10.1002/1521-3773(20020517)41:10<1668::AID-ANIE1668>3.0.CO;2-Z* AND *10.1021/ja062508t*

Retrosynthesis ID: 18116

2.2 Path 2

Score: 76.25

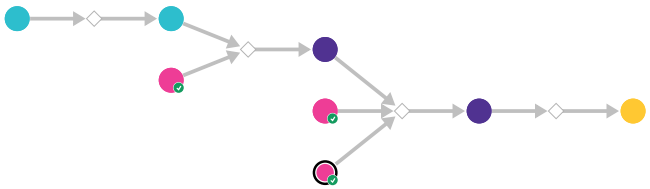
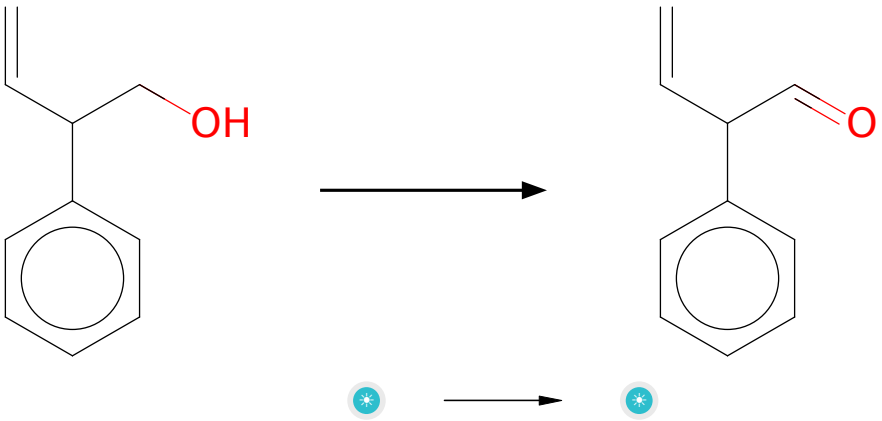


Figure 2: Outline of path 2

2.2.1 Oxidation of primary alcohols with DMP



Substrates:

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

Products:

1. 2-phenyl-but-3-enal

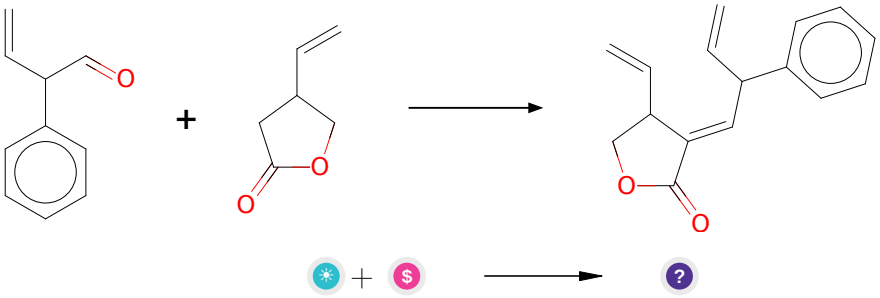
Typical conditions: DMP.DCM.0-25 C

Protections: none

Reference: *10.1016/j.bmc.2020.115469* p. 3, 9 and *10.1021/acs.jmedchem.8b01878* SI p. S43

Retrosynthesis ID: 50426

2.2.2 Condensation of esters with aldehydes



Substrates:

1. 2-phenyl-but-3-enal
2. 4-ethenyloxolan-2-one - *available at Sigma-Aldrich*

Products:

1. C=CC1COC(=O)/C1=C/C(C=C)c1ccccc1

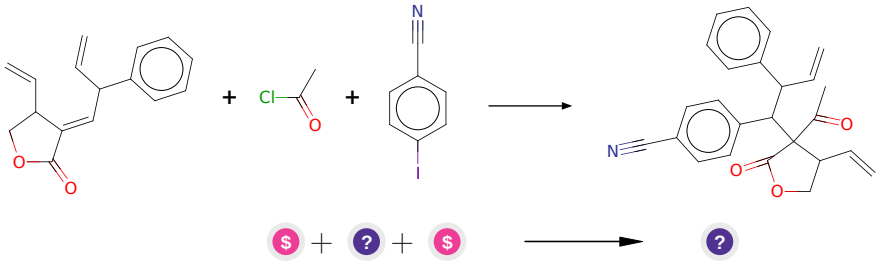
Typical conditions: 1.LDA.2RCHO

Protections: none

Reference: *10.1021/jo970387x* AND *10.1021/jo00076a051* AND *10.1016/S0040-4039(97)10827-9* AND *10.1055/s-2002-25767* AND *10.1039/P19920003277*

Retrosynthesis ID: 14981

2.2.3 Conjugated addition of organocuprate-acylation of enones and enoate esters



Substrates:

1. 4-Iodobenzonitrile - *available at Sigma-Aldrich*
2. C=CC1COC(=O)/C1=C/C(C=C)c1ccccc1
3. Acetyl chloride - *available at Sigma-Aldrich*

Products:

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

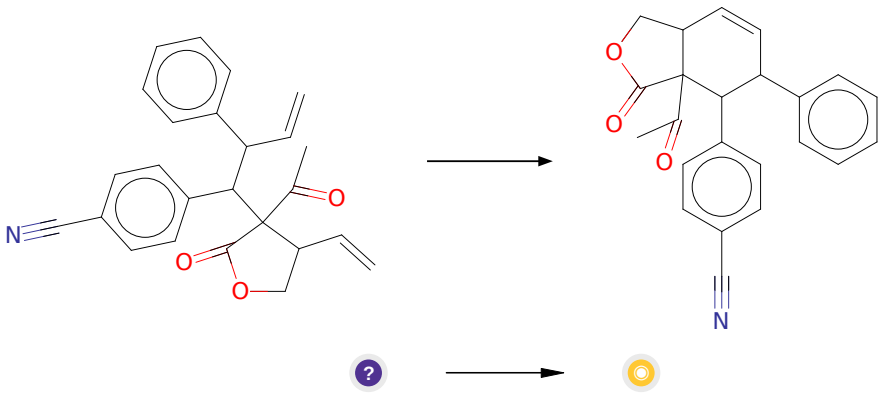
Typical conditions: 1.RCuLi.2.AcCl.HMPA

Protections: none

Reference: *10.3987/COM-99-S143* AND *10.1021/ja00148a023* AND *10.1016/S0040-4039(01)80891-1*

Retrosynthesis ID: 20524

2.2.4 Ring-Closing Metathesis



Substrates:

1. C=CC(c1ccccc1)C(c1ccc(C#N)cc1)C1(C(C)=O)C(=O)OCC1C=C

Products:

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

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: 76.25

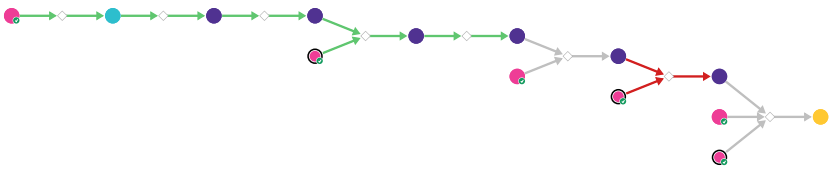
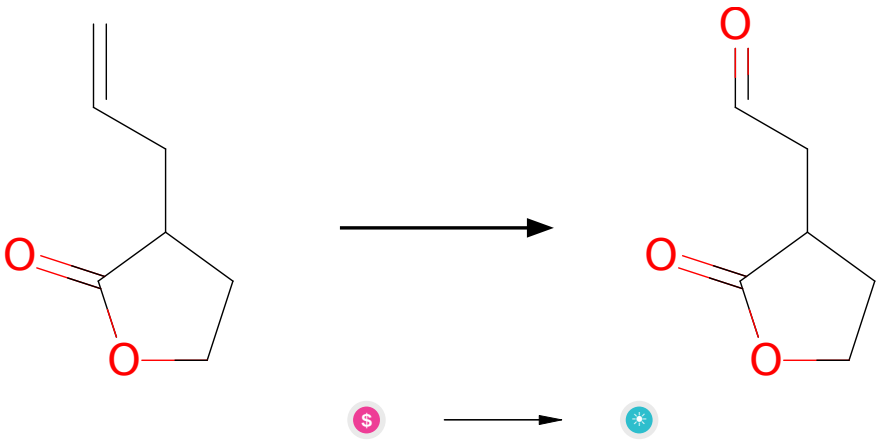


Figure 3: Outline of path 3

2.3.1 Ozonolysis



Substrates:

1. 3-allyl-dihydro-furan-2-one - *available at Sigma-Aldrich*

Products:

1. 2-(2-oxoethyl)-g-butyrolactone

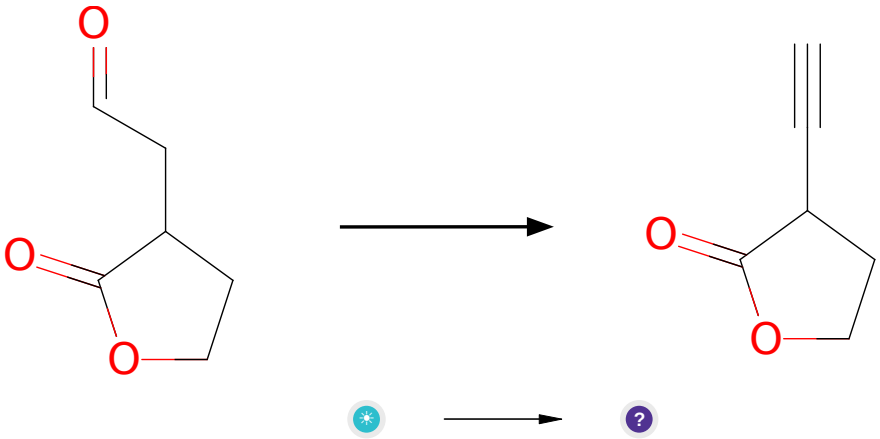
Typical conditions: O3.MeOH.CH2Cl2.PPh3 or Me2S.low temperature

Protections: none

Reference: *10.1016/j.tet.2017.03.039*

Retrosynthesis ID: 5074

2.3.2 Synthesis of alkynes from aldehydes



Substrates:

1. 2-(2-oxoethyl)-g-butyrolactone

Products:

1. C#CC1CCOC1=O

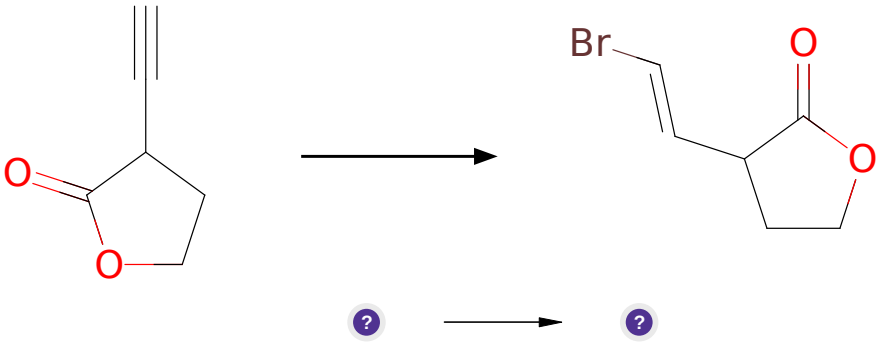
Typical conditions: P1-base.DMF

Protections: none

Reference: *10.1055/s-0028-1087919*

Retrosynthesis ID: 15028

2.3.3 Bromination of vinylalanes



Substrates:

1. C#CC1CCOC1=O

Products:

1. O=C1OCCC1/C=C/Br

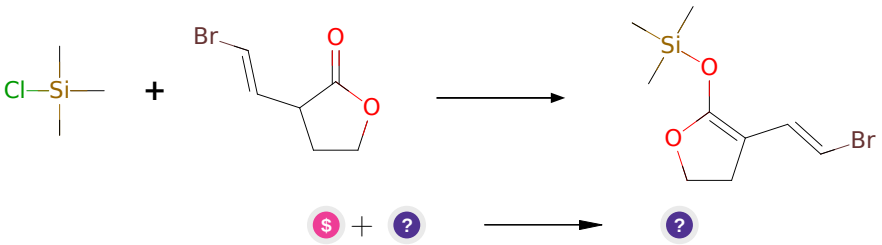
Typical conditions: Schwartz's reagent.then.Br2

Protections: none

Reference: DOI: *10.1039/C2CC36604E* (SI, page S18) AND DOI: *10.1080/00397910008087318*

Retrosynthesis ID: 7405

2.3.4 Enol esters and ethers synthesis



Substrates:

1. TMSCl - *available at Sigma-Aldrich*
2. O=C1OCCC1/C=C/Br

Products:

1. C[Si](C)(C)OC1=C(/C=C/Br)CCO1

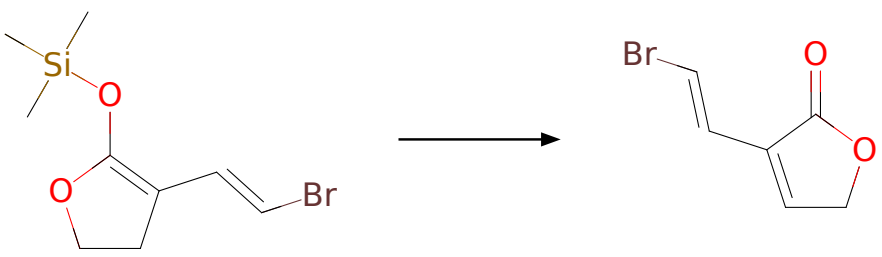
Typical conditions: 1. Et3N.Electrophile

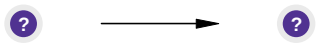
Protections: none

Reference: *10.1016/S0040-4020(03)00977-3* AND *10.1021/ja00056a002*

Retrosynthesis ID: 7799

2.3.5 Dehydrogenation of silyl enol ethers





Substrates:

1. C[Si](C)(C)OC1=C(/C=C/Br)CCO1

Products:

1. O=C1OCC=C1/C=C/Br

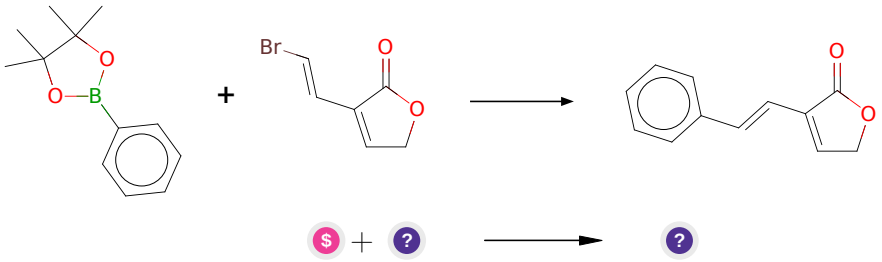
Typical conditions: Pd(OAc)2.Cu(OAc)2.O2.MeCN

Protections: none

Reference: *10.1271/bbb.60.405* and *10.1039/C3CC46778C* and US2015284405 p.40 and *10.1016/S0040-4039(01)81518-5* and US2010204477 p. 15-16 and *10.1016/0040-4039(95)00694-8* and *10.1021/jo00089a034* and *10.1016/S0040-4020(01)90587-3* and *10.1080/00397919008052802* and *10.1021/ja00218a060*

Retrosynthesis ID: 9999877

2.3.6 Suzuki coupling of arylboronic pinacol esters with vinyl Bromides



Substrates:

1. (Pinacolboryl)benzene - *available at Sigma-Aldrich*
2. O=C1OCC=C1/C=C/Br

Products:

1. O=C1OCC=C1/C=C/c1ccccc1

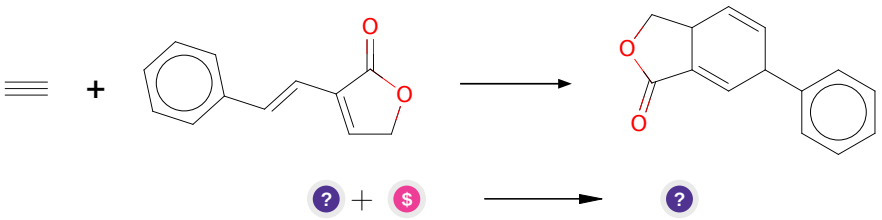
Typical conditions: Pd catalyst.base.solvent

Protections: none

Reference: *10.1021/cr00039a007* and *10.1007/3418_2012_32* and *10.1021/cr0505268* and *10.1016/j.jfluchem.2016.01.018* and *10.1039/C3CS60197H*

Retrosynthesis ID: 10355

2.3.7 Diels-Alder



Substrates:

1. O=C1OCC=C1/C=C/c1ccccc1
2. Calcium carbide - *available at Sigma-Aldrich*

Products:

1. O=C1OCC2C=CC(c3ccccc3)C=C12

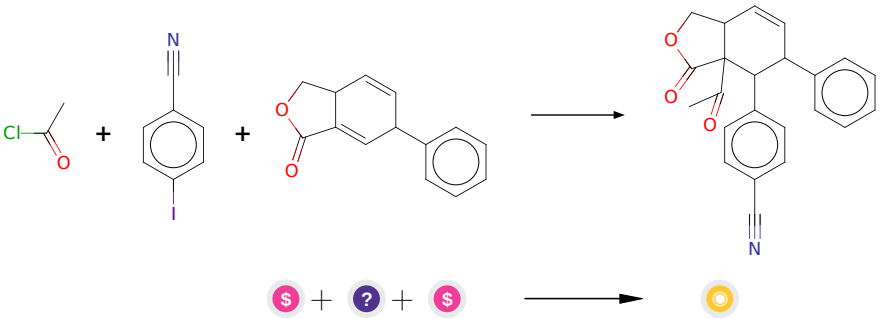
Typical conditions: H2O.MeOH.EtOH.isooctane

Protections: none

Reference: *10.1002/1521-3773(20020517)41:10<1668::AID-ANIE1668>3.0.CO;2-Z*

Retrosynthesis ID: 10557

2.3.8 Conjugated addition of organocuprate-acylation of enones and enoate esters



Substrates:

1. 4-Iodobenzonitrile - *available at Sigma-Aldrich*
2. O=C1OCC2C=CC(c3ccccc3)C=C12
3. Acetyl chloride - *available at Sigma-Aldrich*

Products:

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

Typical conditions: 1.RCuLi.2.AcCl.HMPA

Protections: none

Reference: *10.3987/COM-99-S143* AND *10.1021/ja00148a023* AND *10.1016/S0040-4039(01)80891-1*

Retrosynthesis ID: 12521

2.4 Path 4

Score: 76.25

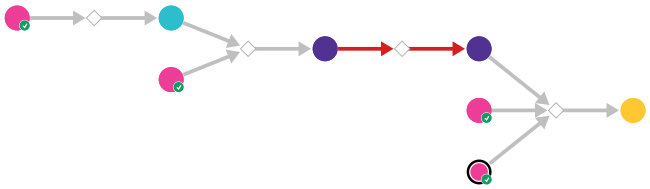
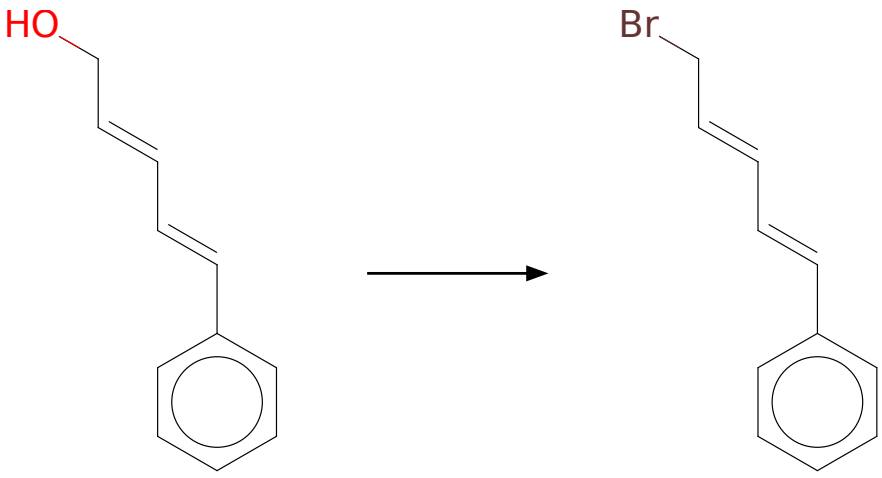
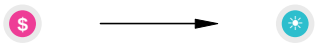


Figure 4: Outline of path 4

2.4.1 Appel Reaction





Substrates:

1. (2E,4E)-5-phenylpenta-2,4-dien-1-ol - *available at Sigma-Aldrich*

Products:

1. 1-bromo-5-phenyl-2,4-pentadiene

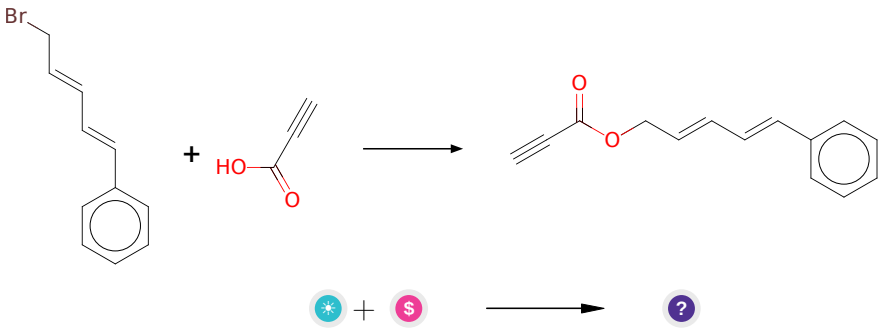
Typical conditions: PPh3.CBr4

Protections: none

Reference: *10.1021/ja800574m* and *10.1016/j.tet.2012.05.010* and *10.1016/j.tet.2004.09.021* (experimantal)

Retrosynthesis ID: 9990037

2.4.2 Synthesis of esters from alkyl chlorides and carboxylic acids or thioacids



Substrates:

1. 1-bromo-5-phenyl-2,4-pentadiene
2. Propynoic acid - *available at Sigma-Aldrich*

Products:

1. C#CC(=O)OC/C=C/C=C/c1ccccc1

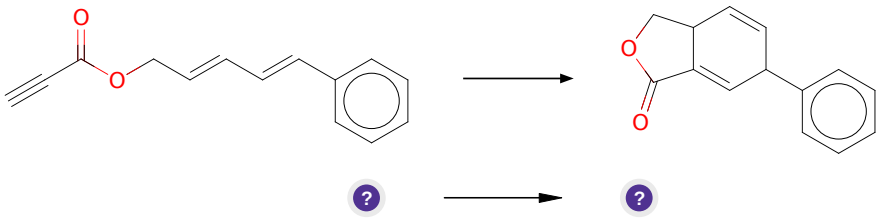
Typical conditions: K2CO3.DMF

Protections: none

Reference: *10.1016/j.bmcl.2005.08.026* AND *10.1021/ol034655r* (SI) AND *10.1039/C3RA41967C* AND *10.1016/j.bmcl.2012.03.093*

Retrosynthesis ID: 14685

2.4.3 Diels-Alder



Substrates:

1. C#CC(=O)OC/C=C/C=C/c1ccccc1

Products:

1. O=C1OCC2C=CC(c3ccccc3)C=C12

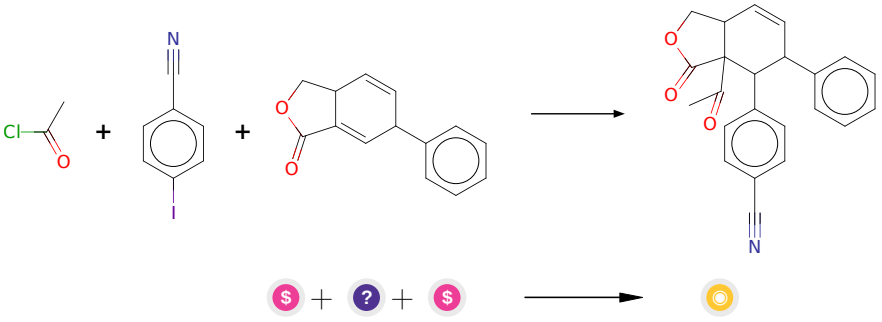
Typical conditions: H2O.MeOH.EtOH.isooctane

Protections: none

Reference: *10.1002/1521-3773(20020517)41:10<1668::AID-ANIE1668>3.0.CO;2-Z*

Retrosynthesis ID: 10557

2.4.4 Conjugated addition of organocuprate-acylation of enones and enoate esters



Substrates:

1. 4-Iodobenzonitrile - *available at Sigma-Aldrich*
2. O=C1OCC2C=CC(c3ccccc3)C=C12
3. Acetyl chloride - *available at Sigma-Aldrich*

Products:

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

Typical conditions: 1.RCuLi.2.AcCl.HMPA

Protections: none

Reference: *10.3987/COM-99-S143* AND *10.1021/ja00148a023* AND *10.1016/S0040-4039(01)80891-1*

Retrosynthesis ID: 12521

2.5 Path 5

Score: 84.06

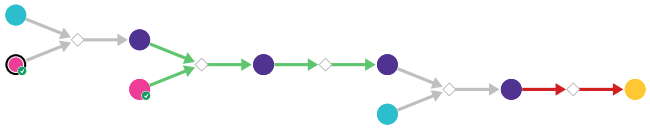
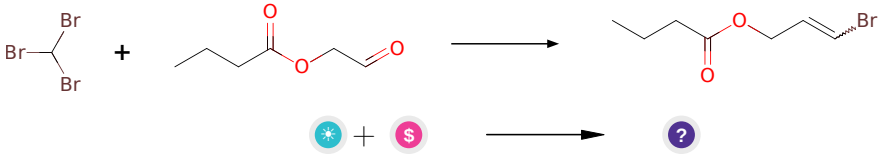


Figure 5: Outline of path 5

2.5.1 Takai olefination



Substrates:

1. butyryloxy-acetaldehyde
2. Bromoform - *available at Sigma-Aldrich*

Products:

1. CCCC(=O)OCC=CBr

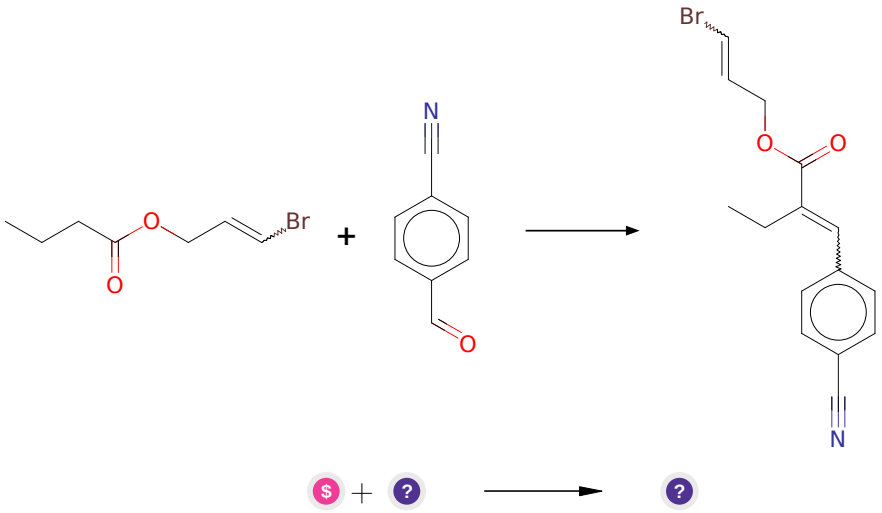
Typical conditions: CrCl2.THF

Protections: none

Reference: *10.1021/ja00283a046* and *10.1021/ja00237a081*

Retrosynthesis ID: 11463

2.5.2 Condensation of esters with aldehydes/ketones



Substrates:

1. 4-Cyanobenzaldehyde - *available at Sigma-Aldrich*
2. CCCC(=O)OCC=CBr

Products:

1. CCC(=Cc1ccc(C#N)cc1)C(=O)OCC=CBr

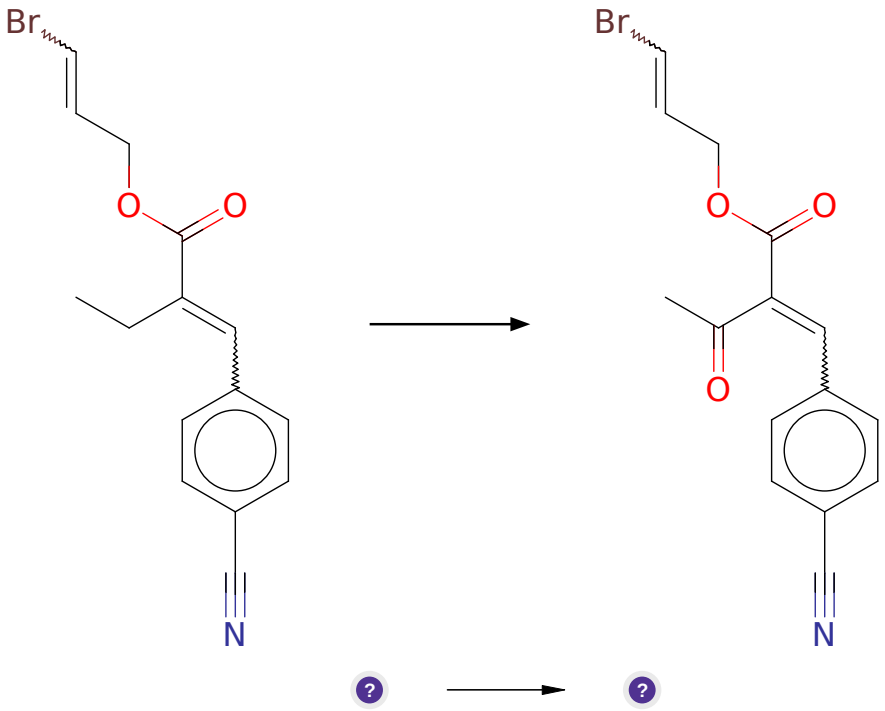
Typical conditions: LDA.THF

Protections: none

Reference: *10.1021/op040006z* AND *10.1016/j.bmcl.2005.10.104* AND

Retrosynthesis ID: 14983

2.5.3 Allylic Oxidation of Alkenes



Substrates:

1. CCC(=Cc1ccc(C#N)cc1)C(=O)OCC=CBr

Products:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CBr

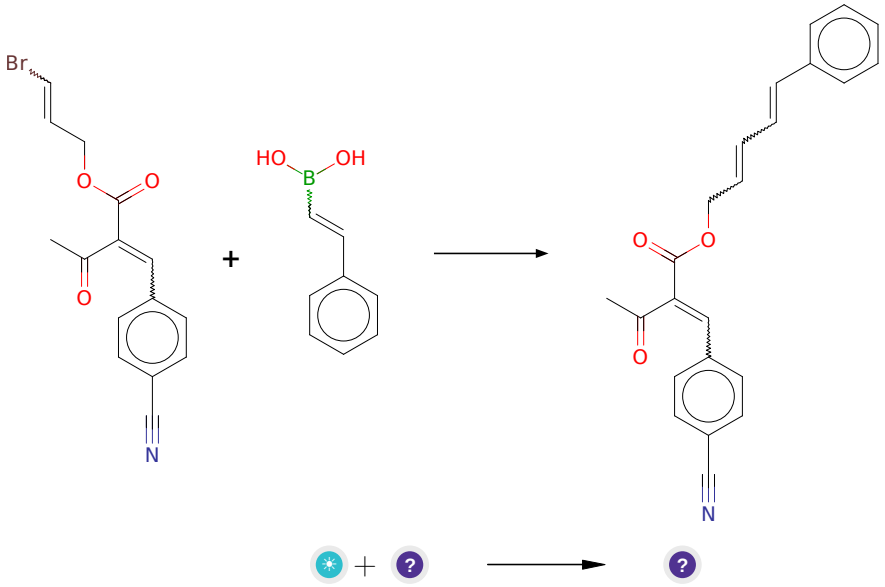
Typical conditions: tBuOOH.Pd(OH)2/C or PhI(OAc)2 or SeO2

Protections: none

Reference: *10.1021/ja0340735* and *10.1021/ol100603q* and *10.1016/j.tetlet.2016.05.063* (Scheme 2)

Retrosynthesis ID: 2583

2.5.4 Suzuki coupling of vinyl bromides with alkenyl boronic acids



Substrates:

1. styrylboronic acid
2. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CBr

Products:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CC=Cc1ccccc1

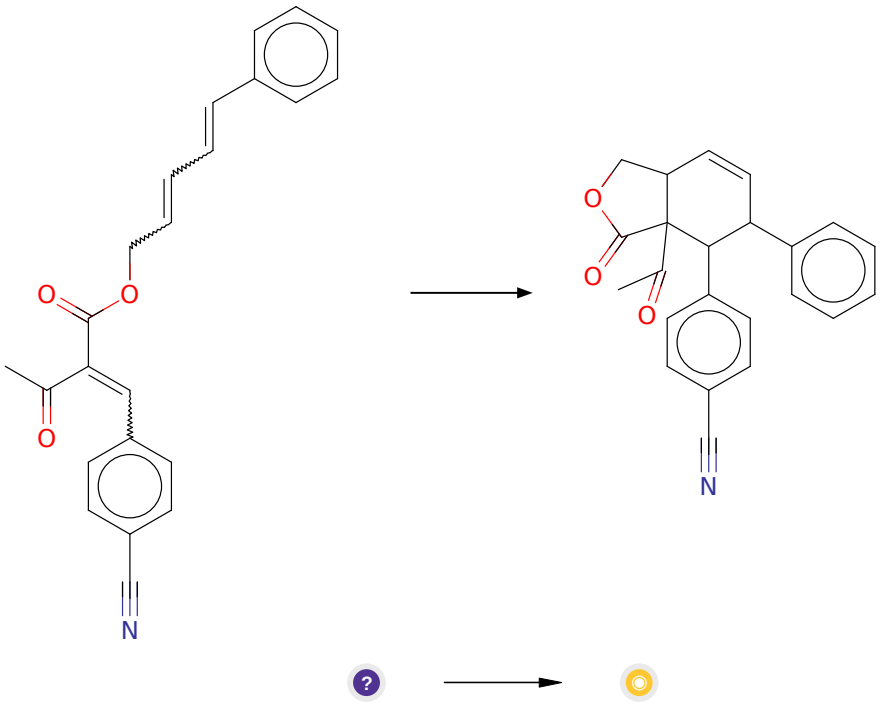
Typical conditions: Pd catalyst.base.solvent

Protections: none

Reference: *10.1021/cr00039a007* and *10.1007/3418_2012_32* and *10.1021/cr0505268* and *10.1016/j.jfluchem.2016.01.018* and *10.1039/C3CS60197H*

Retrosynthesis ID: 24931

2.5.5 Diels-Alder



Substrates:

1. CC(=O)C(=Cc1ccc(C#N)cc1)C(=O)OCC=CC=Cc1ccccc1

Products:

1. CC(=O)C12C(=O)OCC1C=CC(c1ccccc1)C2c1ccc(C#N)cc1

Typical conditions: Lewis acid or chiral Lewis acid. Solvent.

Protections: none

Reference: DOI: *10.1002/1521-3773(20020517)41:10<1668::AID-ANIE1668>3.0.CO;2-Z* AND *10.1021/ja062508t*

Retrosynthesis ID: 18116