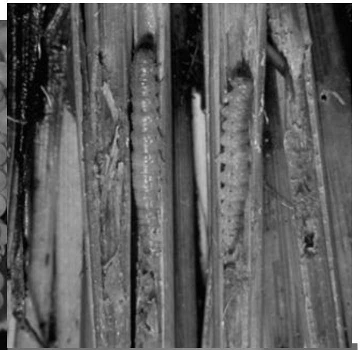
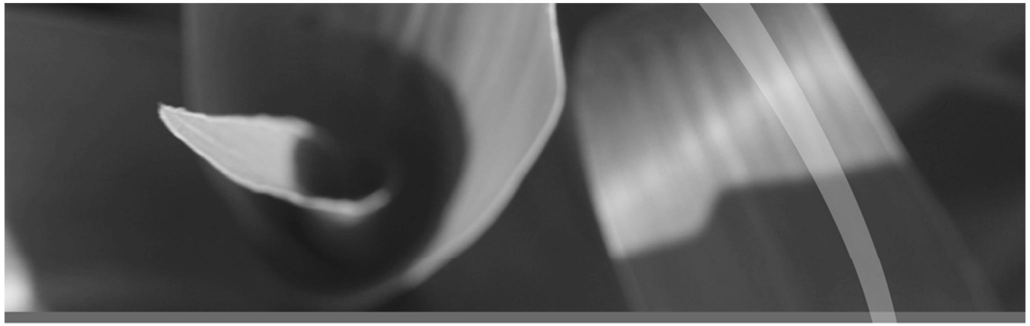
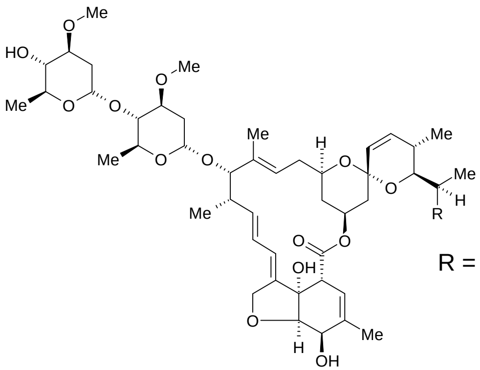
Crop Protection Targets





Discovery of New Mectins as Insecticides-Acaricides

Syngenta Mectins as Insecticides-Acaricides



R = Me 10%, Et 90%

Abamectin

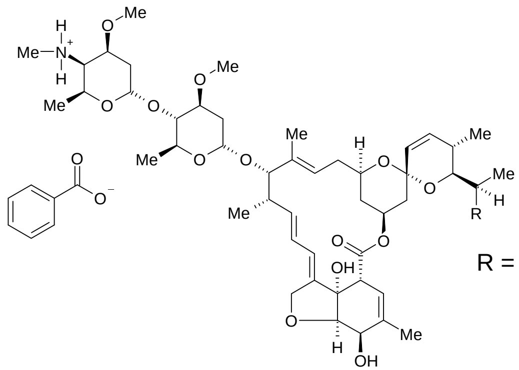
Insecticide, Acaricide, Nematicide; strength on mites

Produced by fermentation

Mode of action ; Stimulates the release of γ–aminobutyric acid (inhibitory neurotransmitter), activates Cl^- channels

Application rates: 5-20g/ha UV sensitive

Syngenta Mectins as Insecticides-Acaricides



R = Me 10%, Et 90%

Emamectin benzoate

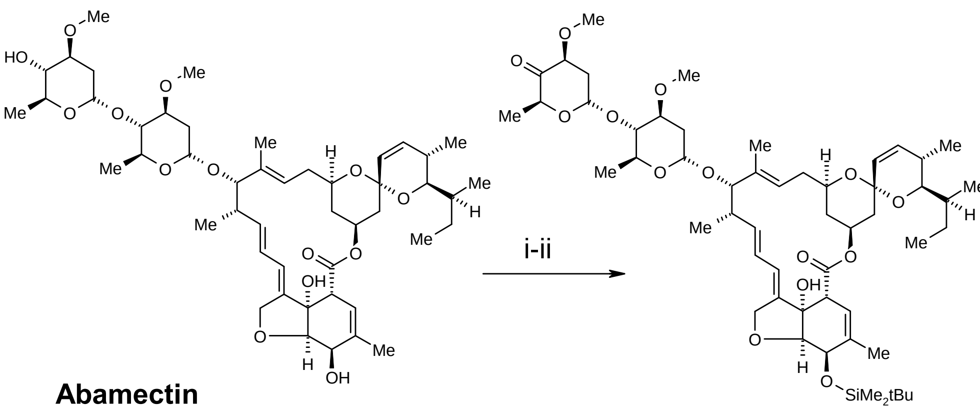
Insecticide; strength on chewing insects Lepidoptera

Produced in 5 chemical steps from Abamectin

Mode of action ; Stimulates the release of γ–aminobutyric acid (inhibitory neurotransmitter), activates Cl^- channels

Application rates: 5-20g/ha UV sensitive

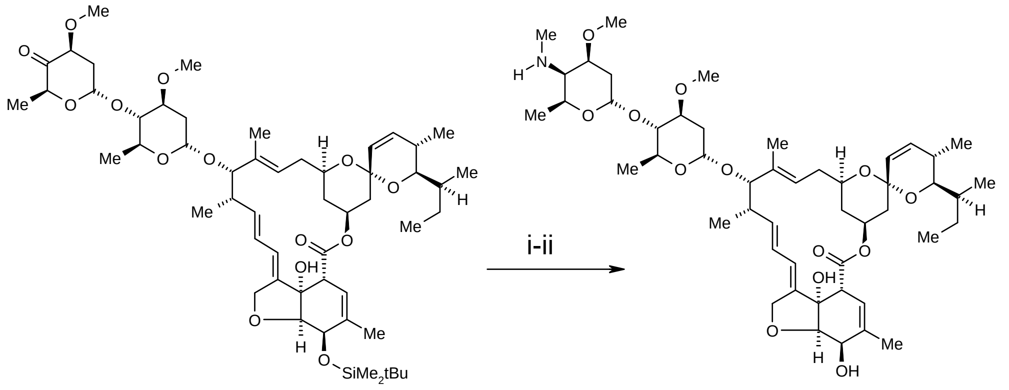
Production Synthesis of Emamectin from Abamectin



Abamectin

i = t-BuMe$_2$Si-Cl , toluene , DMAP , ii = DMSO , NEt$_3$, Ph-POCl$_2$, > 90% 2 steps

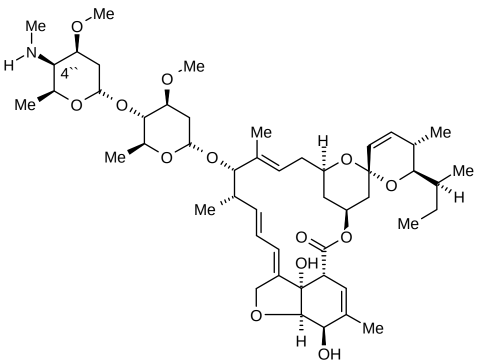
Production Synthesis of Emamectin from Abamectin



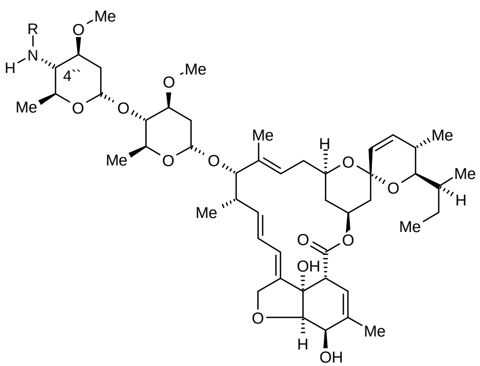
Emamectin

i = Me-N-(SiMe$_3$)$_2$, ZnBr$_2$, EtOH , NaBH$_4$, RT , single isomer
ii = MeOH , MeSO$_3$H , > 90% 2 steps

4“α Amino Mectins: Epi Emamectin

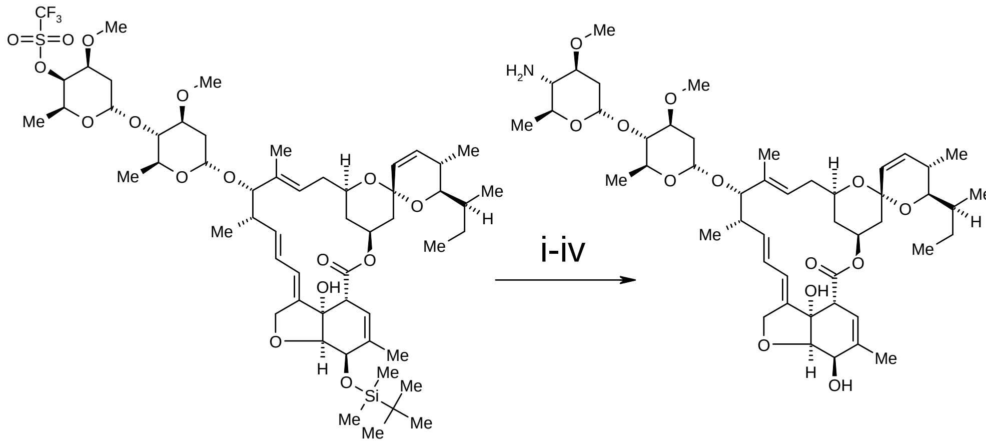


Emamectin



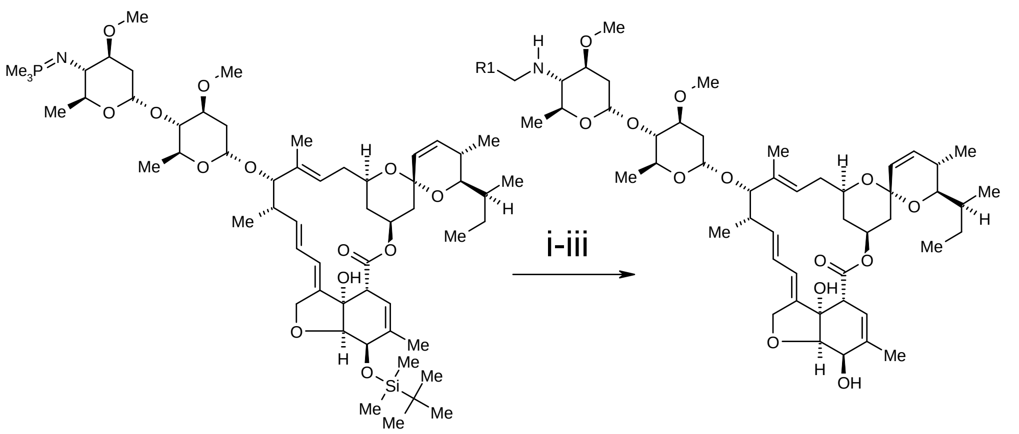
Novel 4" Epi-Amino Mectins

Synthesis of 4“ Epi-Amines



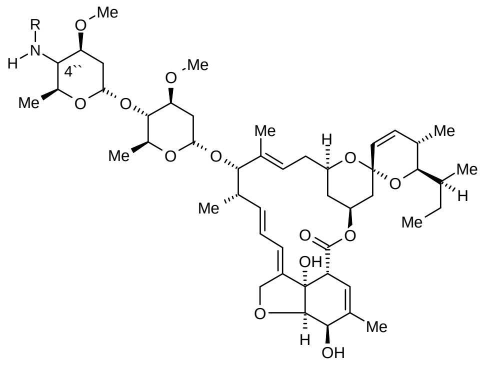
i = NaN$_3$, DMF, 76%, ii = Me$_3$P, THF, iii = NaOH dil., THF, iv = MeSO$_3$H, MeOH, 65%

Synthesis of 4“-Epi Amines

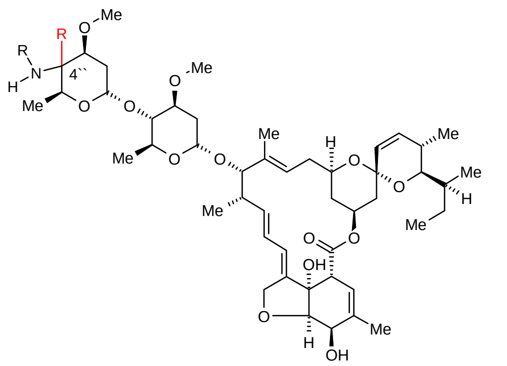


i = R_1-COH, THF, ii = $NaBH_4$, MeOH, pivalic acid cat., iii = $MeSO_3H$, MeOH, 45-67%

C-C Bond Formation at 4“ of α,β- Amino Mectins

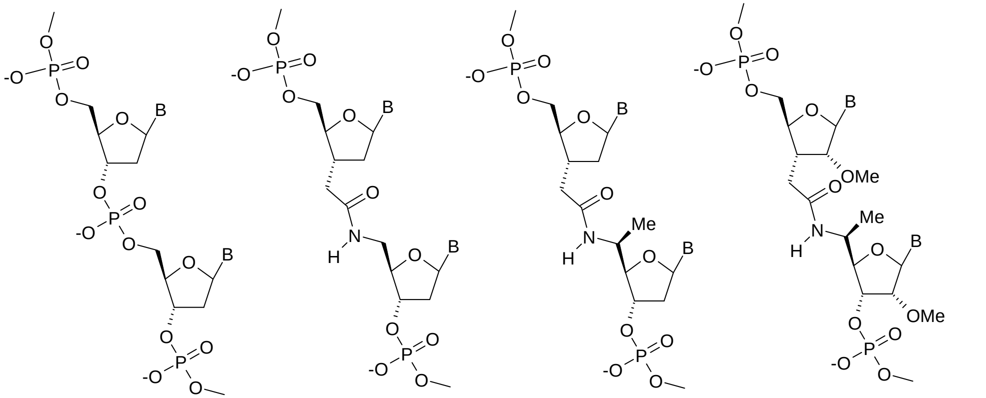


α-Amino Mectins are biologically even more active than the corresponding β isomers



α,β-Amino Mectins having an additional C-substituent at 4“are the most promising derivatives

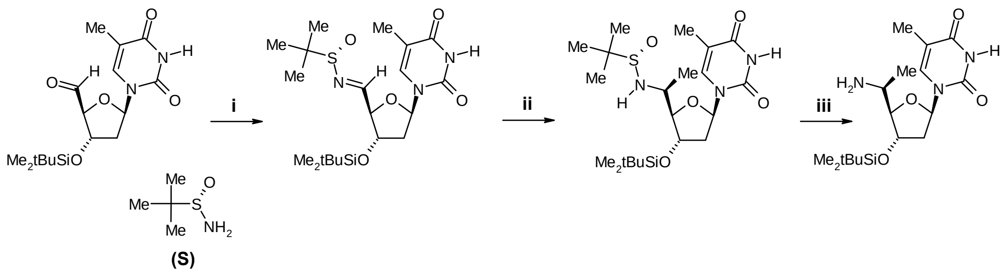
Modified Antisense and Antigene Oligonucleotides



DNA | Amide-3 | 5‘-(S) Methyl Amide-3 | 5‘-(S) Methyl Di-Methoxy Amide-3

A. De Mesmaeker *et al*., Synlett, 1287, (1997)

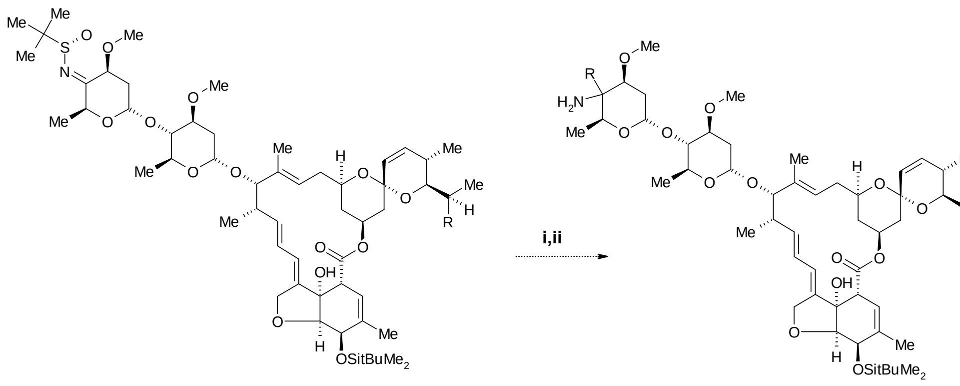
Improved Synthesis of 5‘ (S) Me Amide-3



i = benzene, reflux, 74% , ii = 3 eq. MeMgBr, ether, -48°C to RT, 76%, HCl aq. (4M), dioxane, MeOH, RT, 92%

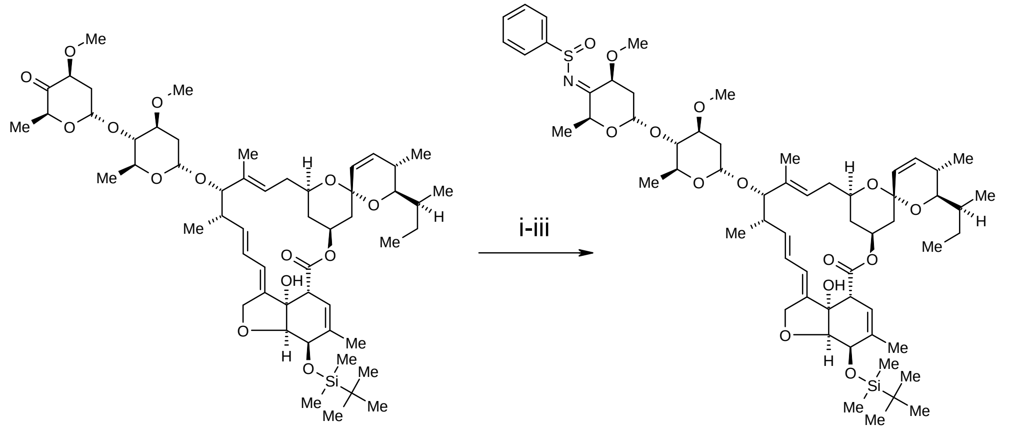
P. Jung, A. De Mesmaeker *et al*., Tetrahedron Letters,44, 293, (2003)

C-C Bond Formation at 4“



ii = RMgX, ii = Selective Hydrolysis

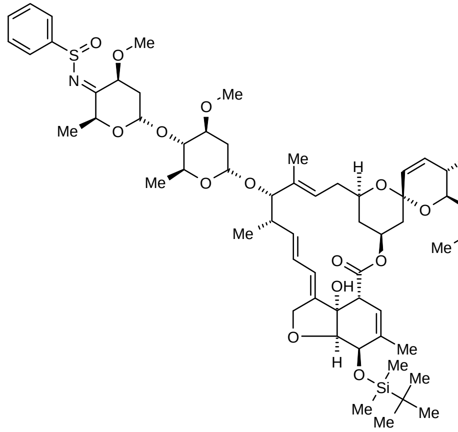
C-C Bond Formation at 4“



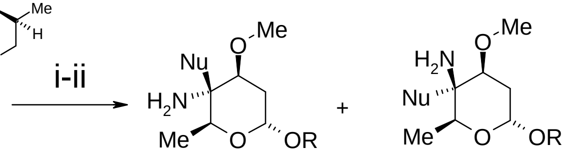
2 diastereomers 1:1

i = NH_2-OH. HCl, pyridine, MeOH, RT, 99% ; ii = n-Bu_3P, PhS-SPh, THF, 0°C, 80% ; iii = m-CPBA, $NaHCO_3$, $CHCl_3$, H_2O, RT, 43%

C-C Bond Formation at 4“



2 diastereomers 1:1

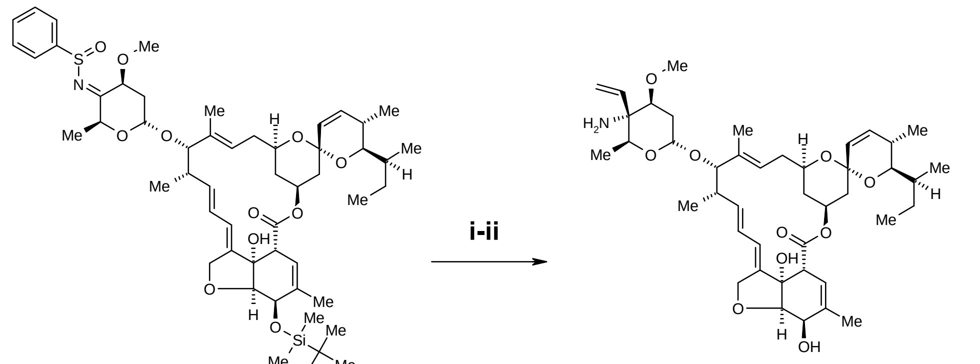


Nu = Allyl 31%	**3**	**7**
Nu = Methyl 19%	**1**	**1**
Nu = Vinyl 43%	**4**	**7**

i = Grignard, ether, 0°C, ii = i-propanol, CH_2Cl_2, CF_3 COOH, 0°C

P. Jung et al. Tetrahedron Letters, <u>47</u>, 5657 (2006)

C-C Bond Formation at 4‘



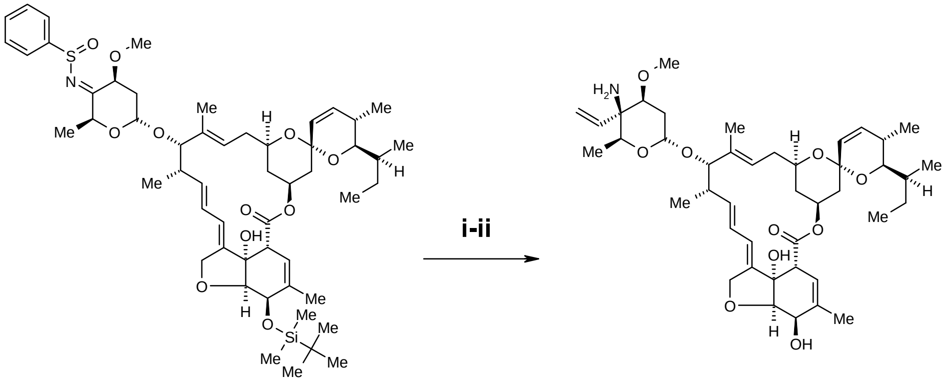
Less polar diastereomer

Single isomer, 2 steps 65%

i = Vinyl Magnesium Bromide, ether, 0°C, ii = MeOH, $MeSO_3$H 0°C

P. Jung et al. Tetrahedron Letters, <u>47</u>, 5657 (2006)

C-C Bond Formation at 4'



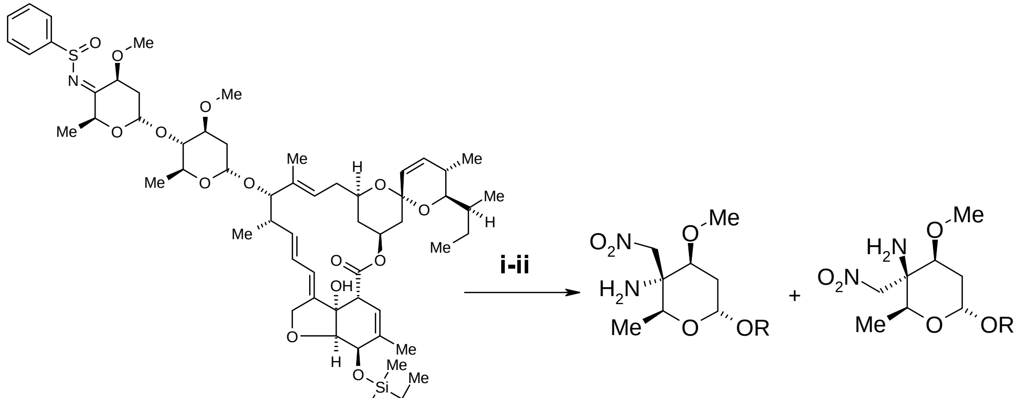
More polar diastereomer

Single isomer, 2 steps 59%

i = Vinyl Magnesium Bromide, ether, 0°C, ii = MeOH, $MeSO_3H$ 0°C

P. Jung et al. Tetrahedron Letters, <u>47</u>, 5657 (2006)

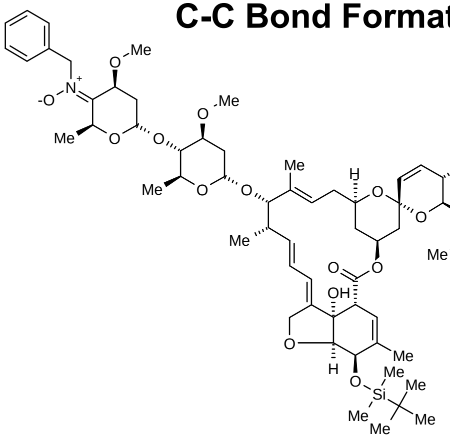
C-C Bond Formation at 4"

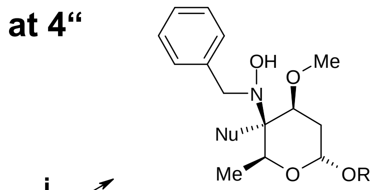


20% **38%**

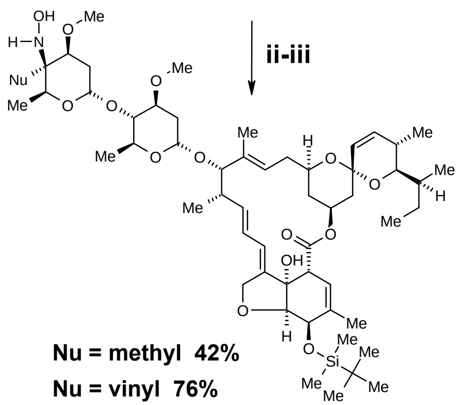
i = $Me\text{-}NO_2$, piperidine, ii = i-propanol, CH_2Cl_2, CF_3COOH, 0°C

C-C Bond Formation at 4"





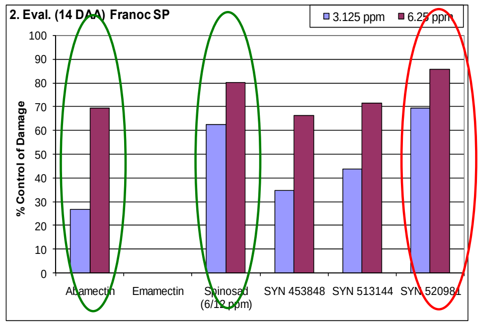
Nu = methyl 47%
Nu = vinyl 44%



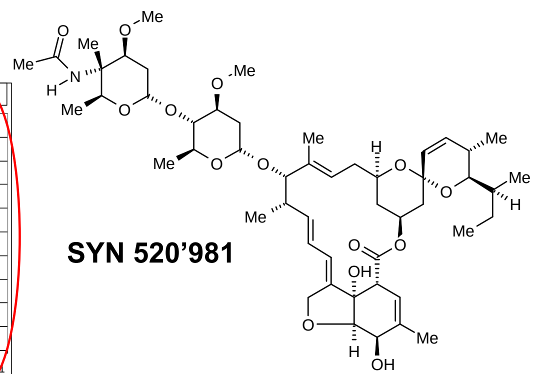
i = Grignard, ether, 0°C, ii = DDQ, CH_2Cl_2, RT,
iii = $NH_2\text{-}OH$. HCl excess, pyridine, MeOH, RT

Nu = methyl 42%
Nu = vinyl 76%

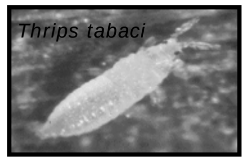
Thripicide – SYN 520981

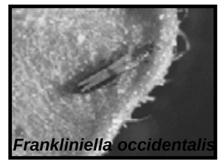


SYN 520'981



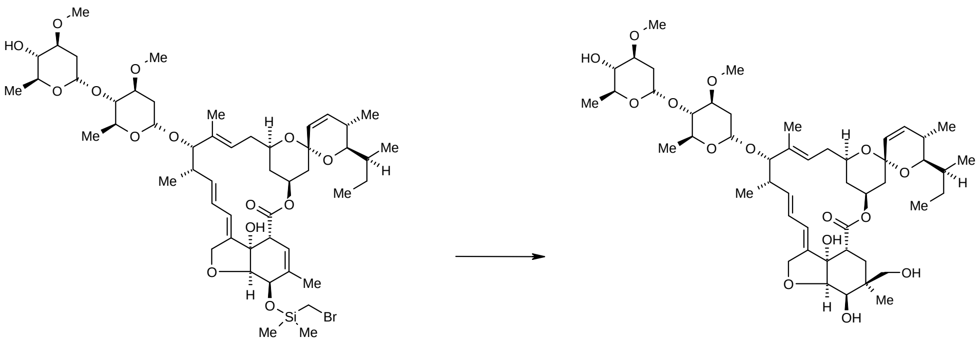
Frankliniella and Thrips
SYN 520981 > Abamectin



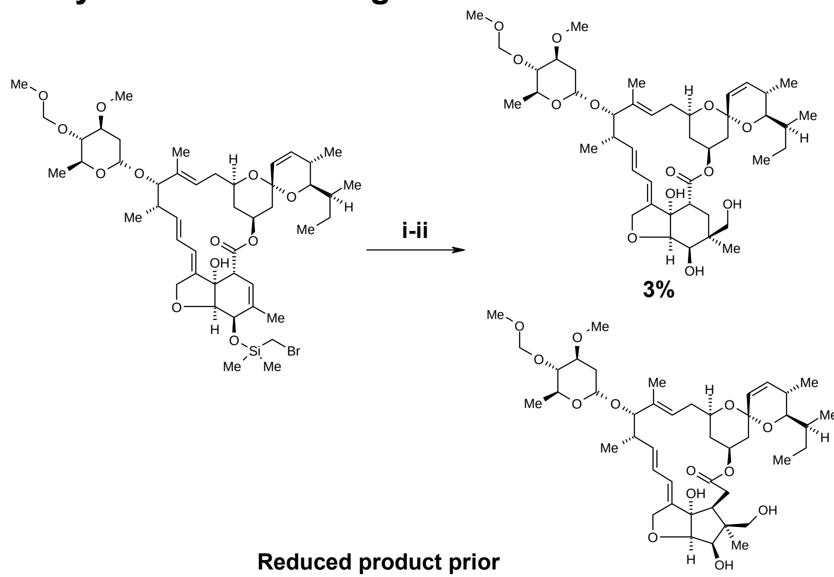


Frankliniella

Core Modifications of Mectins through Radical Cyclization



Radical Cyclization-Rearrangement



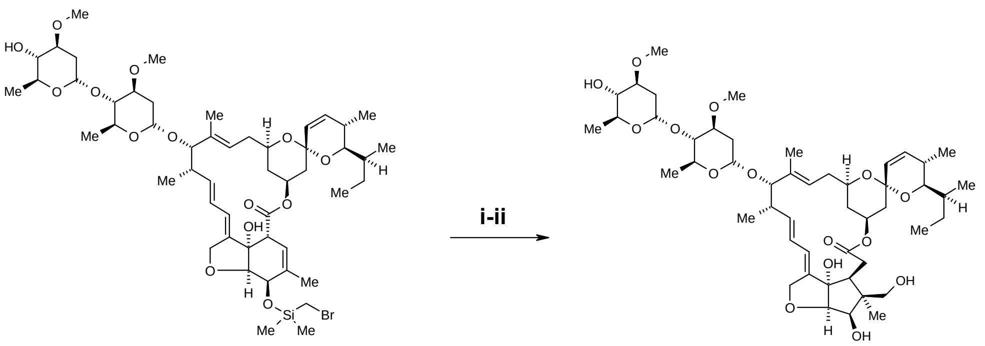
3%

Reduced product prior
to cyclization 12%

46%

i = $NaCNBH_3$, nBu_3SnCl cat., AIBN, t-BuOH, reflux, ii = KF, H_2O_2, $KHCO_3$, THF, MeOH

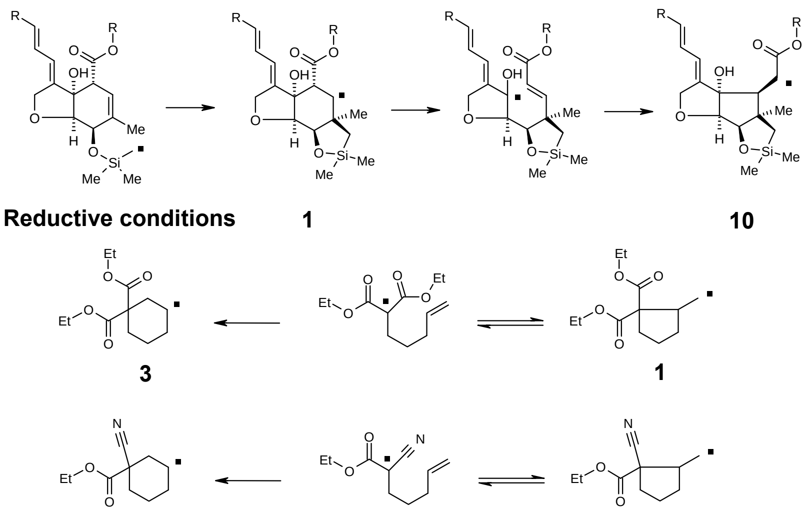
Radical Cyclization-Rearrangement



34%

i = $NaCNBH_3$, nBu_3SnCl cat., AIBN, t-BuOH, reflux, ii = KF, H_2O_2, $KHCO_3$, THF, MeOH

Radical Cyclization-Rearrangement



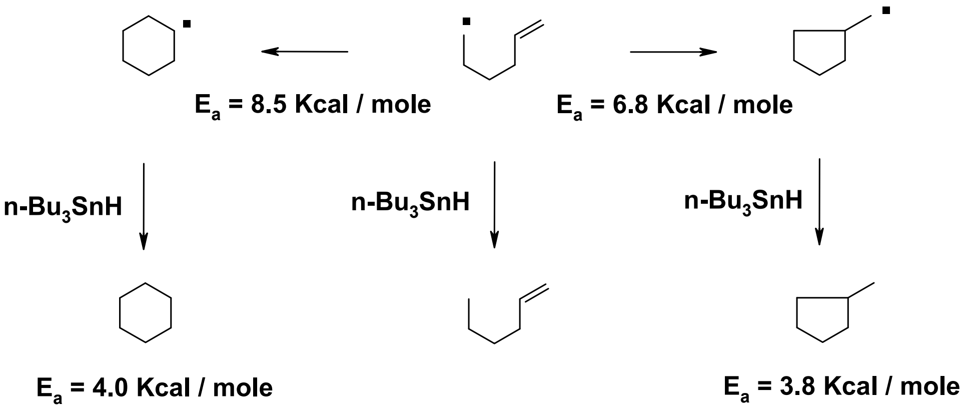
Reductive conditions 1 10

3 1

> 10 1 <

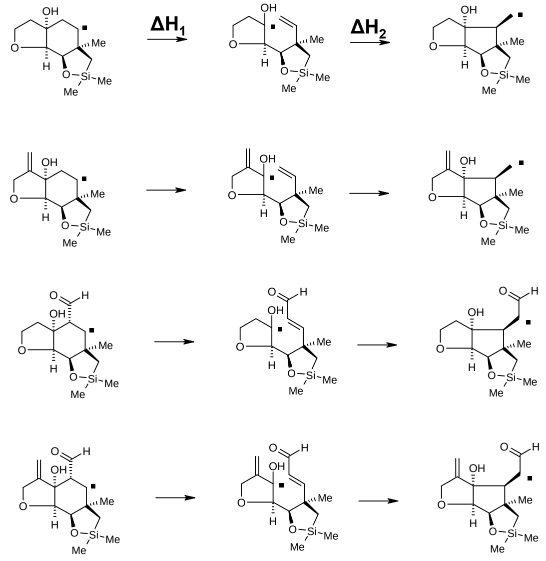
Oxidative conditions Julia et al. 1969

Radical Cyclization Reactions



C. Chatgilialoglu, K. U. Ingold, J. C. Scaiano, J. Am. Chem. Soc., 103, 7739, (1981)

Radical Cyclization-Rearrangement



$\Delta H_1^{\pm}$ = 29.4 Kcal/mole
ΔH_1 = 15.5
$\Delta H_2^{\pm}$ = 6.3
$\Delta H_1 + \Delta H_2$ = 9.3

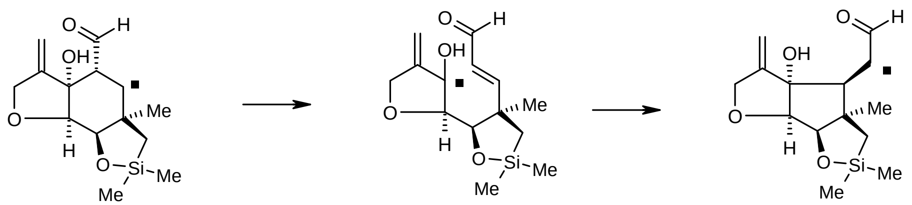
$\Delta H_1^{\pm}$ = 20.1
ΔH_1 = 5.2
$\Delta H_2^{\pm}$ = 13.9
$\Delta H_1 + \Delta H_2$ = 8.5

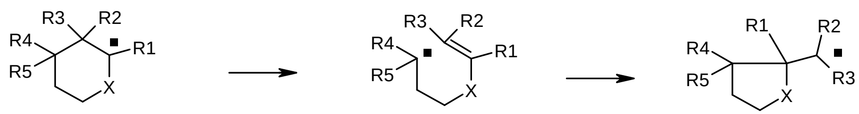
$\Delta H_1^{\pm}$ = 24.0
ΔH_1 = 11.7
$\Delta H_2^{\pm}$ = 2.3
$\Delta H_1 + \Delta H_2$ = -5.1

$\Delta H_1^{\pm}$ = 15.8
ΔH_1 = -1.7
$\Delta H_2^{\pm}$ = 8.0
$\Delta H_1 + \Delta H_2$ = -6.2

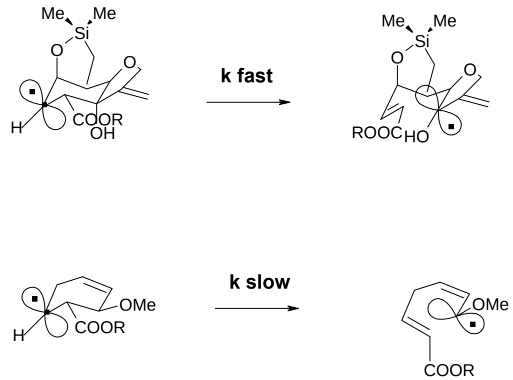
Fiona Murphy Kessabi, K.N. Houk et al., Organic Letters, 10 , 2255 , (2008)

Substituent Effect on Radical Cyclization-Rearrangement



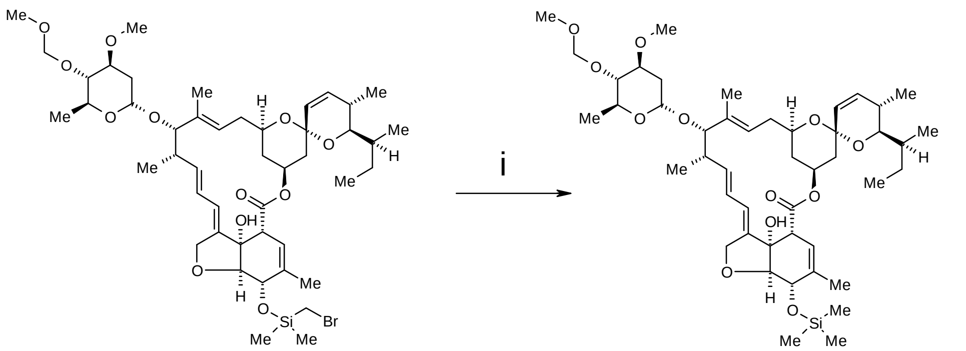


Stereoelectronic Effects on Radical Rearrangement



- In the tricyclic derivative stereoelectronic effects are all favouring C-C bond cleavage : p-σ overlap in the initial radical and p-π overlap in the incipient radical
- In contrast, in the monocyclic radical, only p-σ overlap contributes to the weakening of the C-C bond. However, the incipient radical has its p orbital almost orthogonal to the π orbital of the C=C bond
- Both stereoelectronic effects are required for a fast C-C bond cleavage

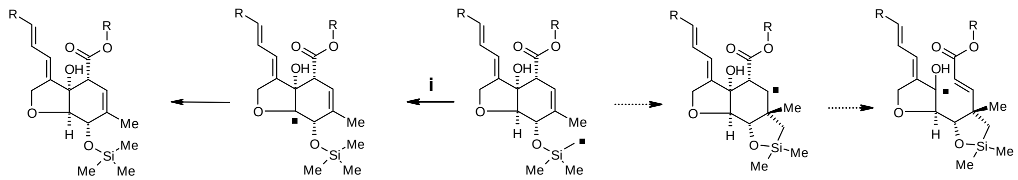
1-5 Hydrogen AtomTransfer Reaction



i = $NaCNBH_3$, n-Bu_3SnCl cat., AIBN, t-BuOH, reflux

syngenta

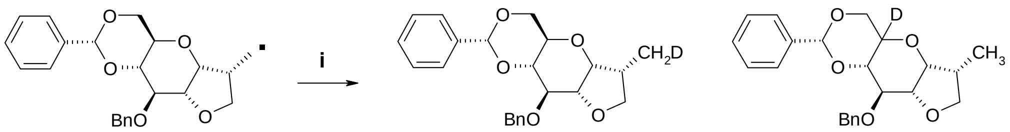
1-5 Hydrogen AtomTransfer Reaction



i = $NaCNBH_3$, n-Bu_3SnCl cat., AIBN, t-BuOH, reflux

syngenta

1-5 Hydrogen AtomTransfer Reaction

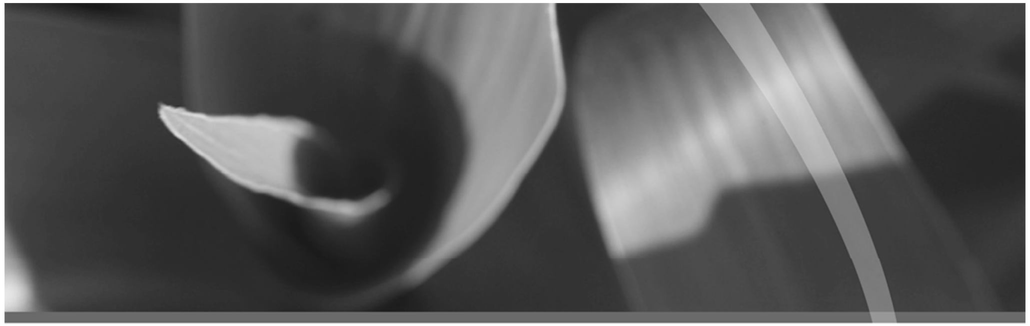


0.01M	**21%**	**79%**
0.001M	**3%**	**97% α:β = 1:3**

i = n-Bu_3SnD, AIBN, benzene, reflux

A. De Mesmaeker *et al*., Synlett, 330, (1994)

syngenta

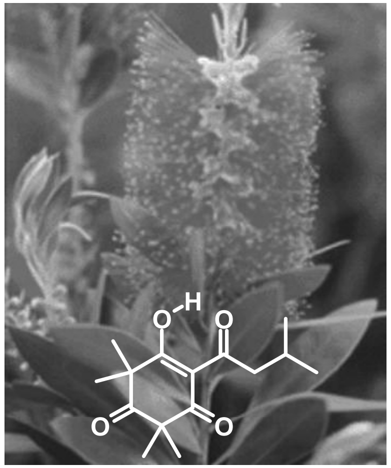


syngenta

New Generation of 1,3-diones in HPPD Inhibitor Chemistry

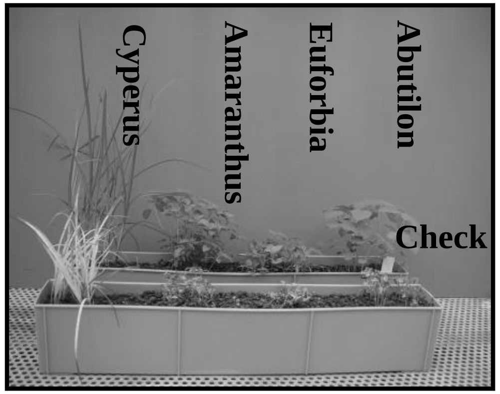
Origin of the Project

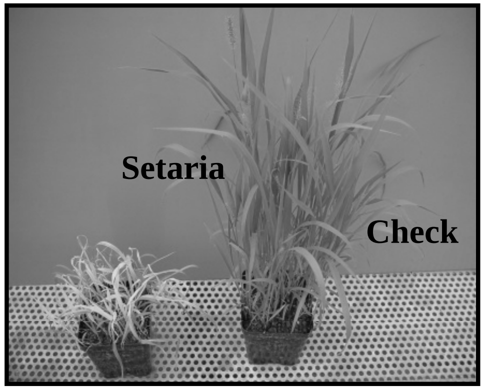
Callistemon Citrinus



Leptospermone

Herbicidal Activity of Leptospermone

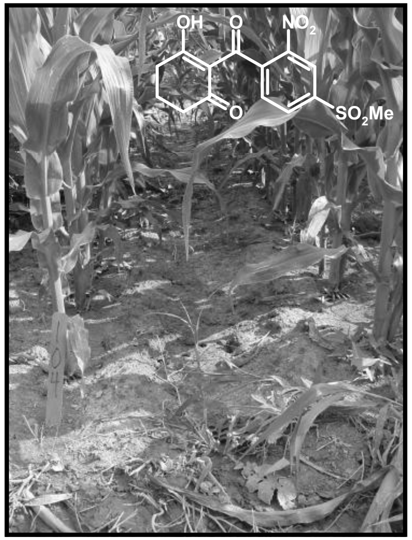




1000 g a.i. / ha post; 10 days after application

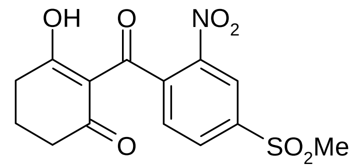
Typical Selective Herbicide: Mesotrione

Untreated

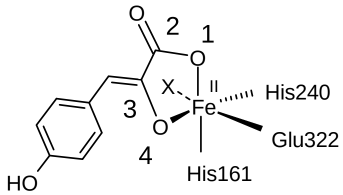


Mesotrione 150 g / ha post

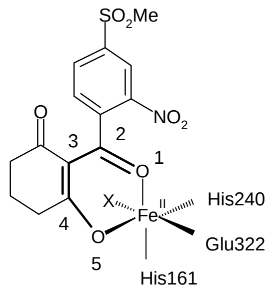
Inhibitor Binding to the HPPD Enzyme



Mesotrione inhibits p-hydroxyphenyl pyruvate dioxigenase in carotenoids biosynthesis

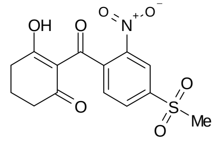


Natural substrate binding to HPPD

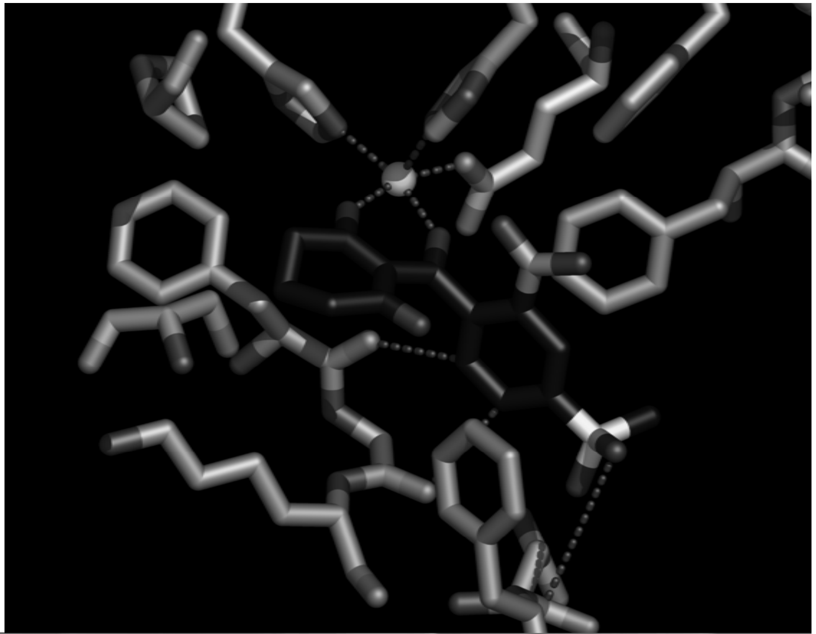


Inhibitor binding to HPPD

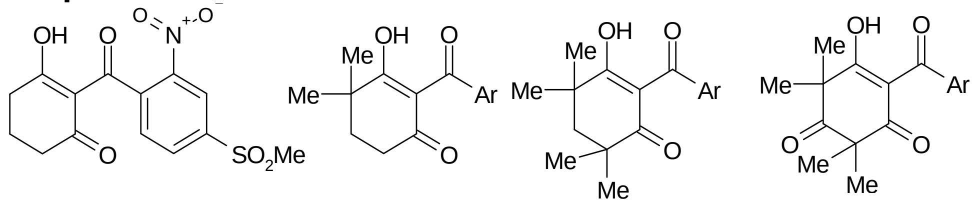
X-Ray Structure of Mesotrione in HPPD Binding Site



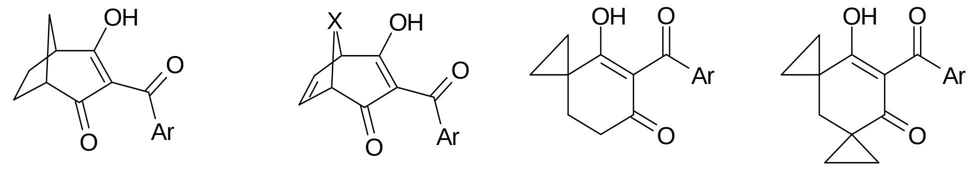
Mesotrione



Optimization of the Dione Scaffold

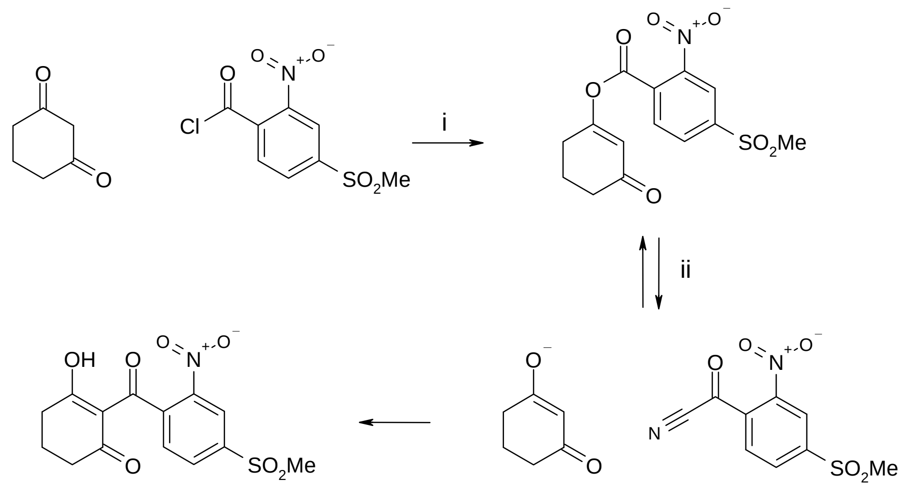


First generation diones



Second generation diones

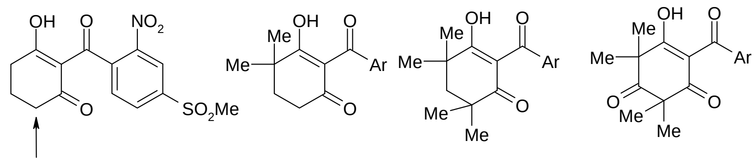
Coupling of diones with Acid Chlorides



pK_a = 2.92 logP = 0.82

i = NEt_3 , MeCN , RT , ii = Acetone cyanohydrin cat. , RT , 95%

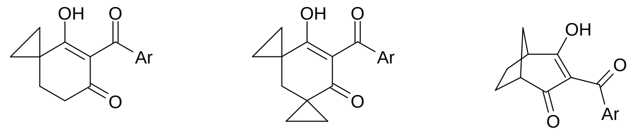
Optimization of the Dione Scaffold



Major site of metabolism
Hydroxylation by Cyt-P-450

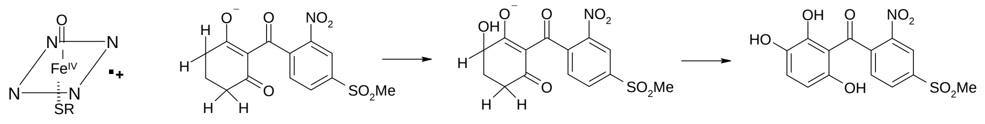
Increasing Herbicidal Activity →

← **Increasing Corn Selectivity**

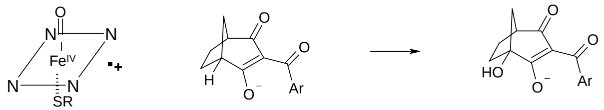


Optimal Activity/Corn Selectivity

Cytochrome P450 Mediated Metabolism of Triones



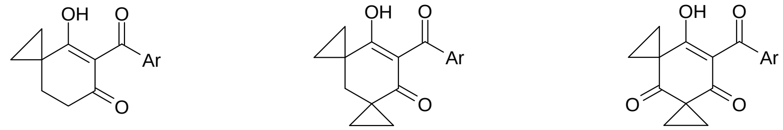
Compound I P450



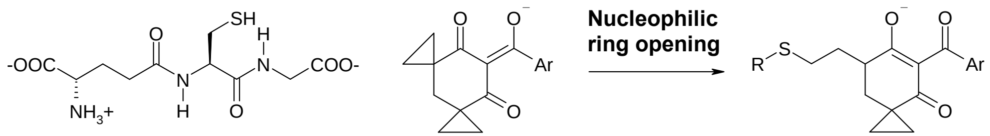
Compound I P450

Less favourable pathway
Sterically , electronically
and stereoelectronically

Dione Optimization for Corn Selectivity through Metabolism

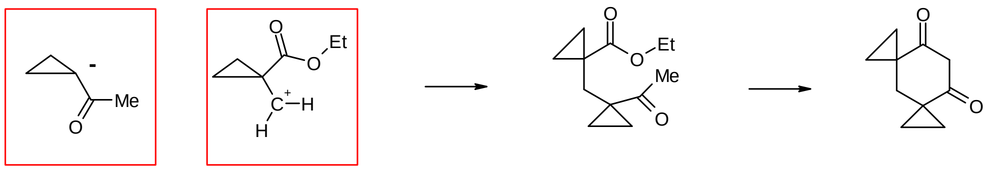


Potentially as active as Di-,Tetra-Methyl diones and more corn selective due to metabolism/detoxification through ring opening with Glutathione

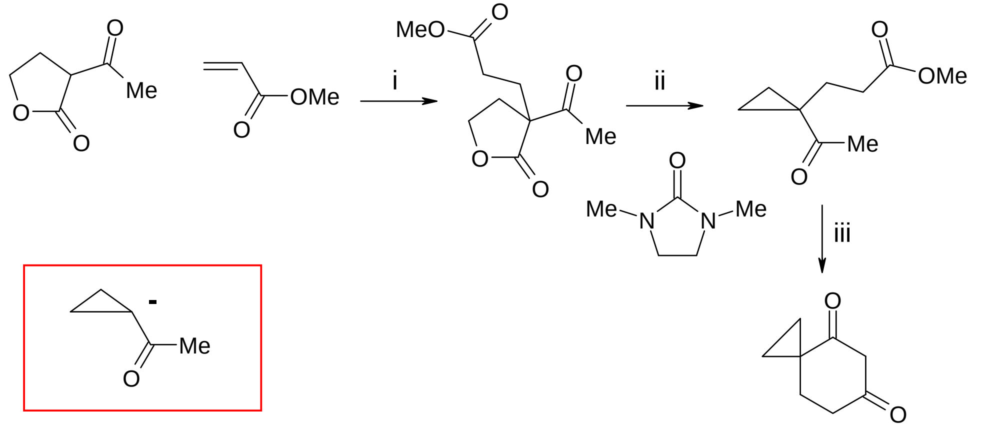


Glutathione

Synthesis of Dispirocyclopropyl Dione

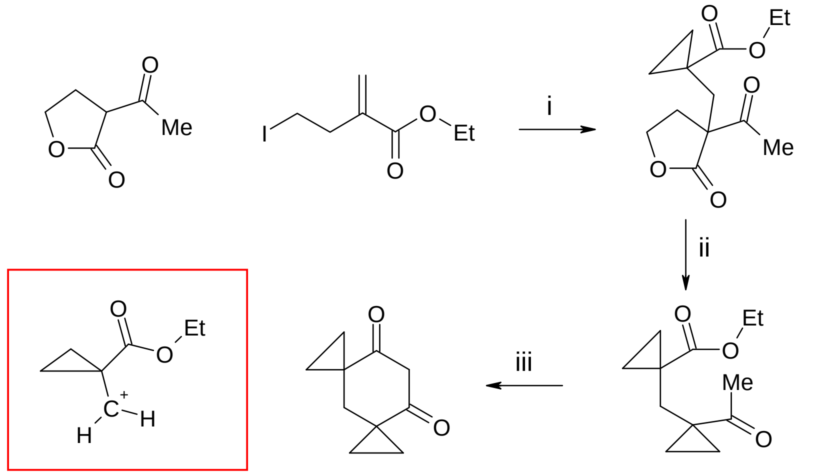


Synthesis of Spirocyclopropyl Dione



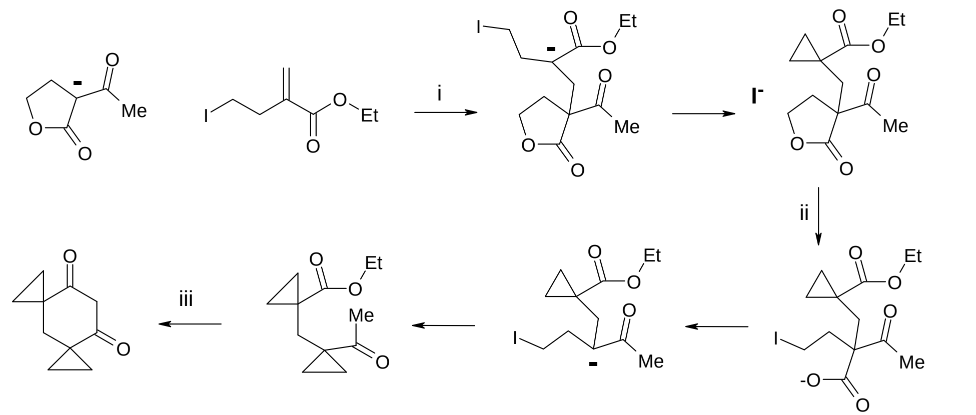
i = t BuONa, tBuOH, RT, 96%, ii = NaI, 190°C , 98%, iii = NaH, DMF:THF, RT , 50%

Synthesis of Dispirocyclopropyl Dione



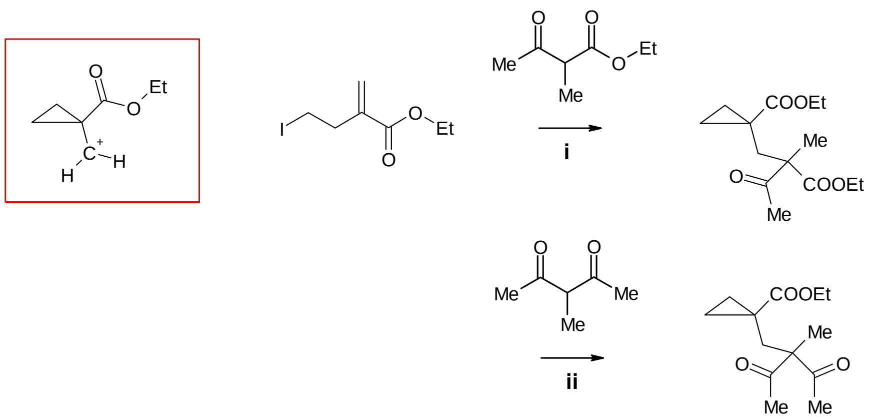
i = NaH , DMF, RT , 77%, ii = NaI , DMF, micro-wave, iii = NaH , DMF, RT , 3 steps one-pot 30%

Synthesis of Dispirocyclopropyl Dione



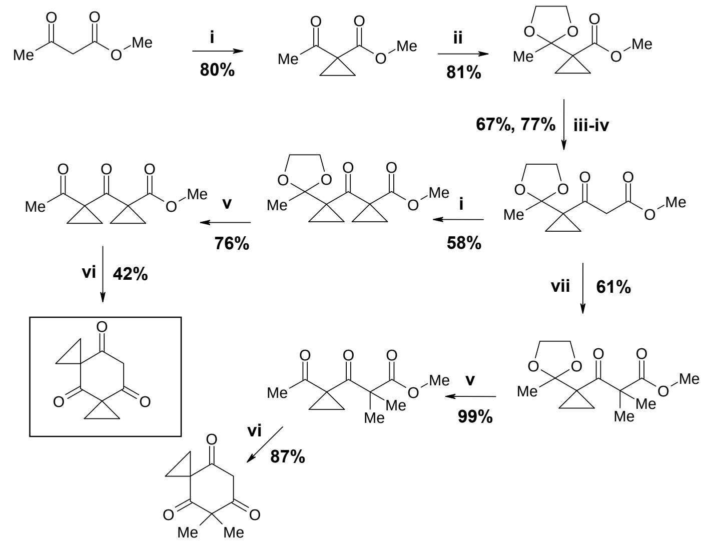
i = NaH , DMF, RT , 77%, ii = NaI , DMF, micro-wave, iii = NaH , DMF, RT , 3 steps one-pot 30%

Synthesis of Cyclopropyl Esters



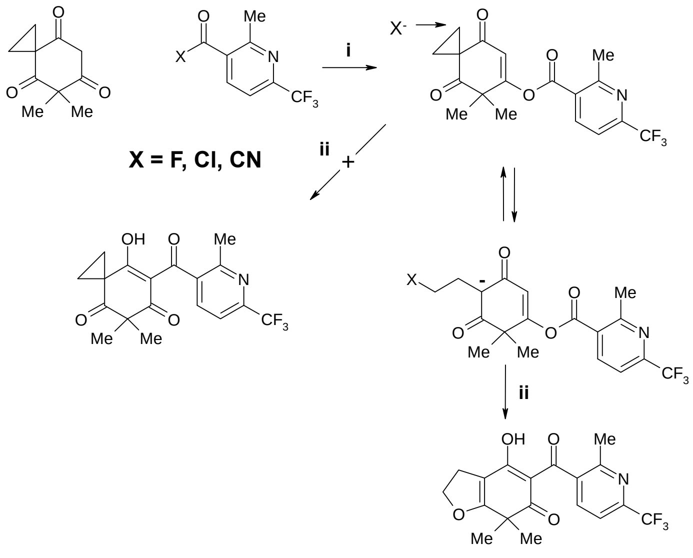
i = NaH , DMF, RT , 62%, ii = NaH , DMF, RT , 76%

Synthesis of Di-Sprirocyclopropyl Trione



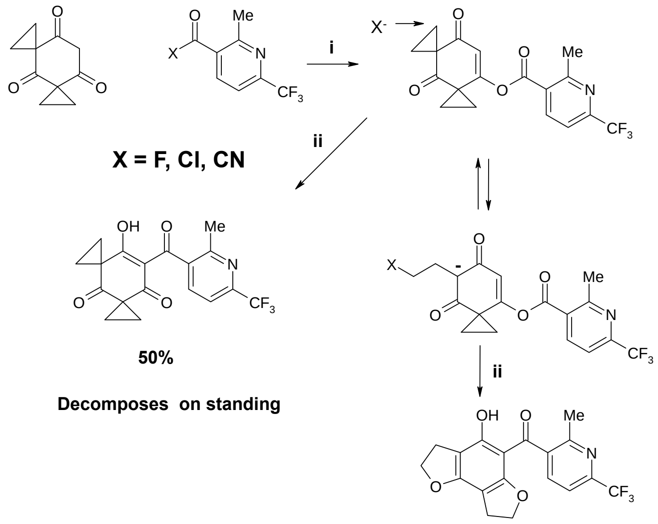
i = Br-CH_2-CH_2-Br, K_2CO_3, acetone, reflux, ii = HO-CH_2-CH_2-OH, TsOH.pyridine, toluene, reflux, iii = NaOHaq., EtOH, RT, iv = $SOCl_2$, $MeCO_2Me$, LiHMDS, THF, -78°C, v = TsOH.pyridine, acetone:H_2O, reflux, vi = MeONa, toluene:DMF, reflux, vii = NaH, MeI, THF, RT

Coupling of Spirocyclopropyl Trione



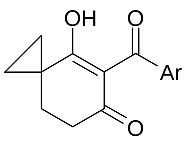
i = NEt_3 , CH_2Cl_2, RT, ii = NEt_3, Acetone Cyanohydrin cat. , MeCN, RT, 29%

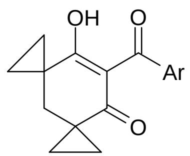
Coupling of Di-Spirocyclopropyl Trione

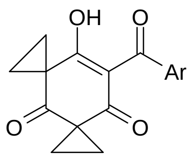


i = NEt_3 , CH_2Cl_2, RT, ii = NEt_3, Acetone Cyanohydrin cat. , MeCN, RT, 29%

Dione Optimization for Corn Selectivity through Metabolism







Among the most promising diones for

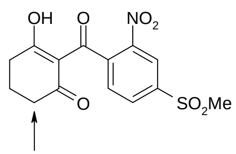
weed control and corn selectivity

Comparable to bicyclic diones

Too labile to be used

in the field

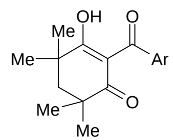
Optimization of the Dione Scaffold



Major site of metabolism

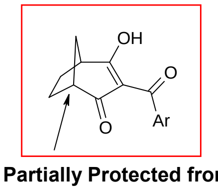
Hydroxylation by Cyt-P45O

in Corn



Improved Herbicidal Activity

Lower Corn Selectivity



Syngenta Bicyclic Dione

Optimal Activity/Corn Selectivity

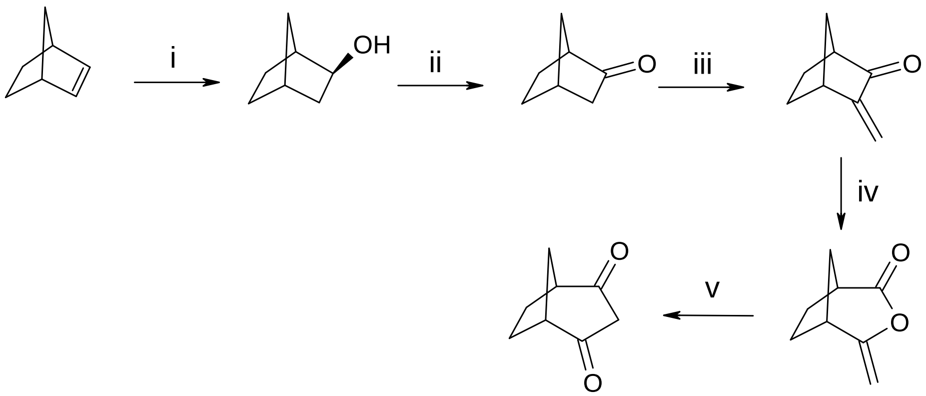
Improved Residual Activity in Soil

Partially Protected from

Cyt-P450 Metabolism in

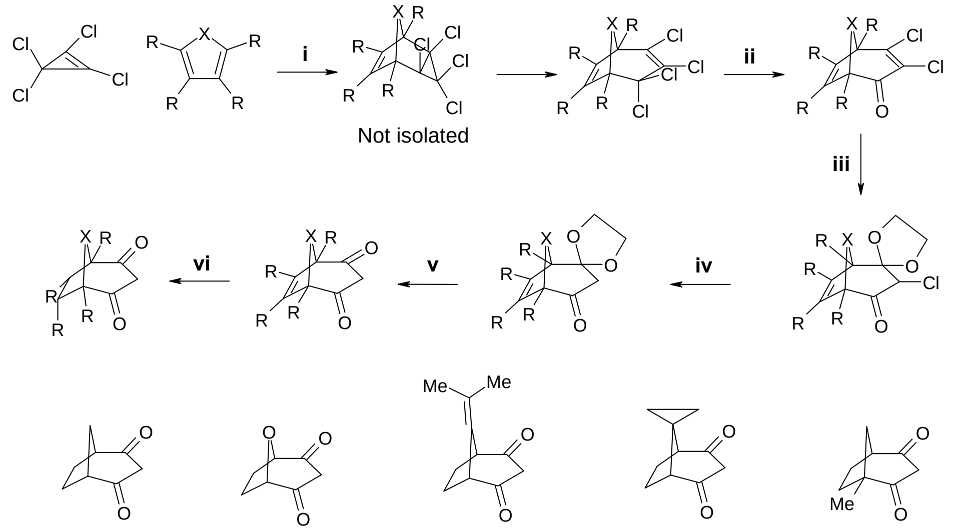
Corn

Synthesis of Bicyclic Dione



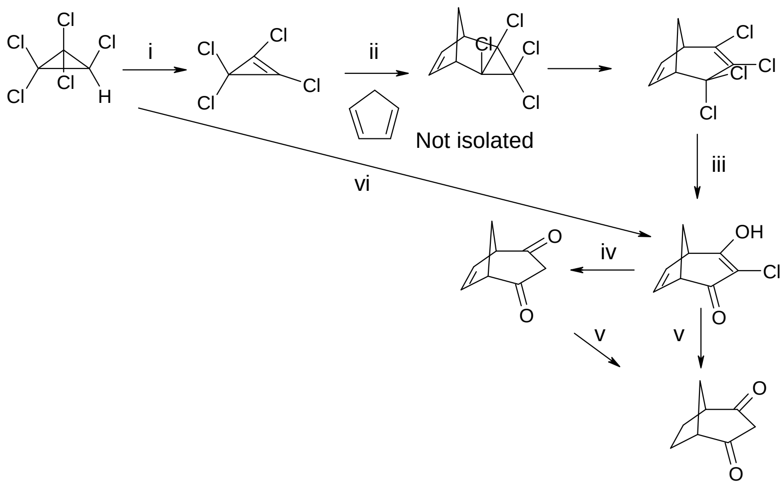
i = H_2SO_4 aq., 80°C, ii = NaOCl, 30°C, 2 steps 95%, iii = CH_2=O , H_2O , $HNEt_2$, AcOH , 100°C , iv = Me-CO_3H , Na_2CO_3 , RT, 2 steps = 68% , V = NaOMe, toluene: DMF, 110°C , 85%

Synthesis of Novel Bicyclic Dione



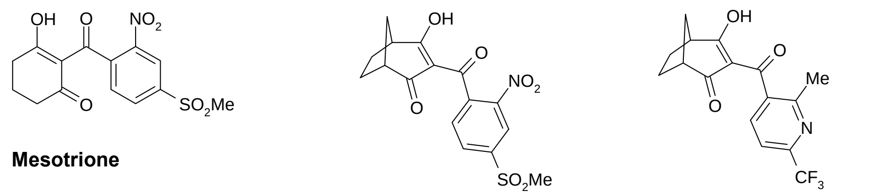
i = toluene, 50-100°C, ii = $AgNO_3$, acetone:H_2O, 70°C, iii = NaH, ethylene glycol, THF, RT, iv = Bu_3SnH, AIBN, toluene, reflux, v = TsOH.pyridine, acetone:H_2O, reflux, vi = H_2, Pd-C, AcOEt, RT

Improved One-Pot Synthesis of Bicyclic Diones



i = KOH, toluene, RT, quantitative, ii = toluene , reflux, 95 % , iii = NaOH, dioxane, reflux, 92 %, iv = Zn , AcOH , 60°C , 85 % , v = H_2 , Pd/C , AcOH, RT, 97% , vi = KOH anhydrous , vi = KOH, toluene, reflux, one-pot 68 %

Optimization of the Benzoic Acid Scaffold



Mesotrione

Syngenta Selective Herbicide

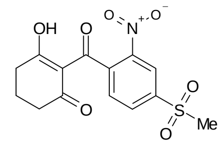
in Corn

Novel Nicotinic Triones

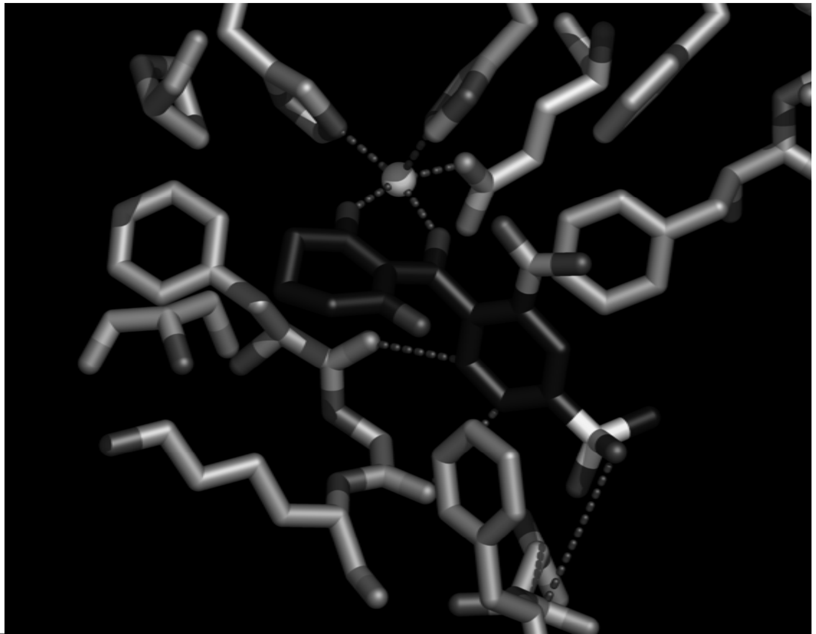
Selective Herbicides in Corn

Increasing Herbicidal Activity
On Monocots and Dicots Weeds

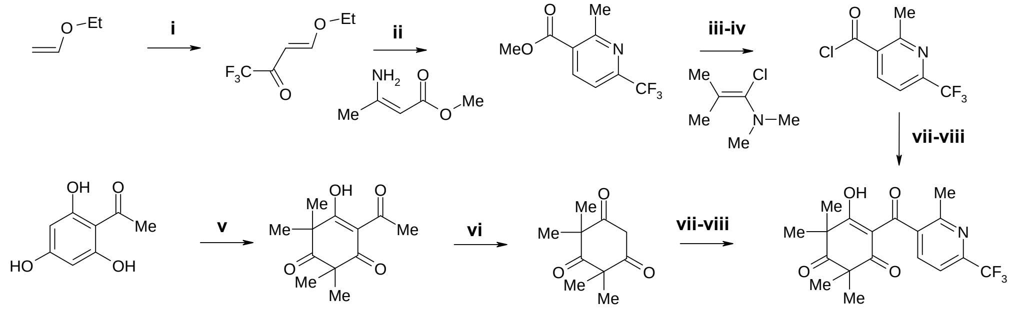
X-Ray Structure of Mesotrione in HPPD Binding Site



Mesotrione

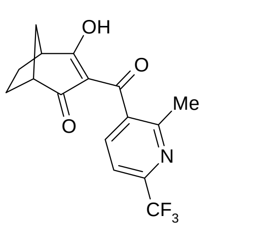


Synthesis of Pyridines as Benzoic Acids Replacement

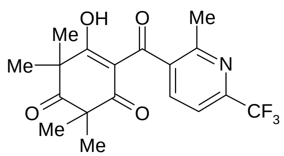


i = CF_3-CO-O-CO-CF_3 , pyridine, CH_2Cl_2 , 97%, ii = CF_3COOH cat., toluene, reflux, 75%, iii = LiOH, H_2O, MeOH, 98%, iv = chlorenamine, CH_2Cl_2 , 99%, v = NaOH, Me_2SO_4, vi = HCl aq., 50% 2 steps, vii = NEt_3, MeCN, RT, viii = acetone cyanohydrine cat., RT, 72% 2 steps

Optimized Diones and Nicotinic Acids for Selective and Non-Selective Applications

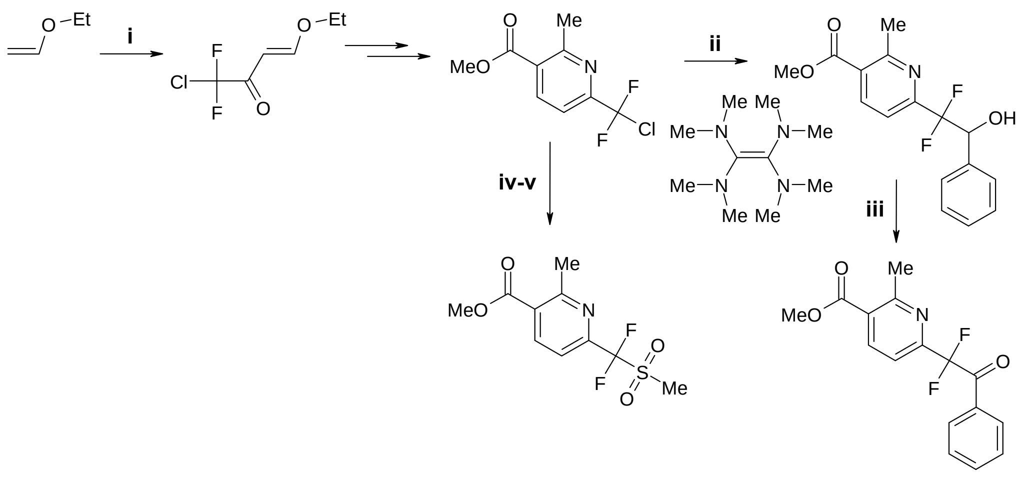


Optimal Activity/Corn Selectivity



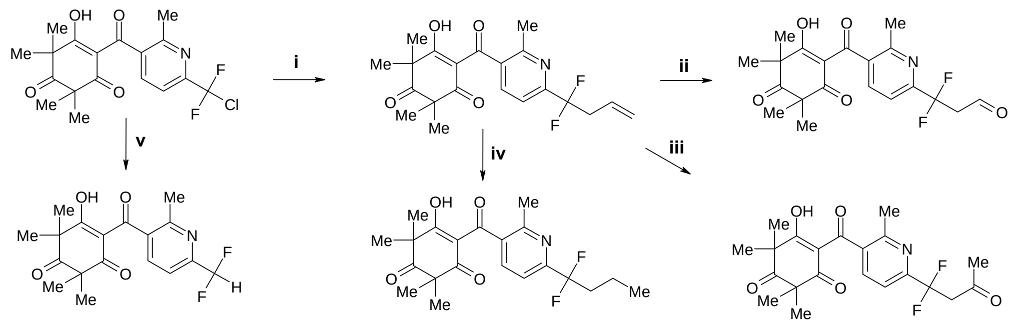
Optimal Non-Selective Activity

Synthesis of Pyridines as Benzoic Acids Replacement



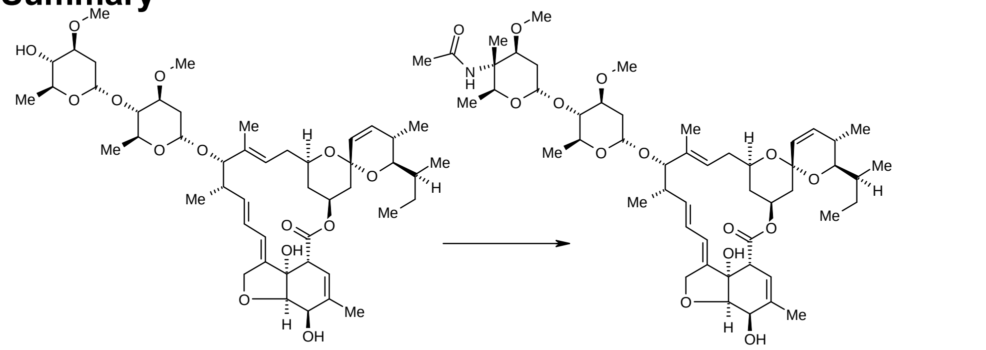
i = $ClCF_2$-CO-O-CO-CF_2Cl, pyridine, CH_2Cl_2, 97%, ii = Ph-CHO, DMF, RT, 75%,
iii = n-PropNRuO_4 cat., N-methylmorpholine oxide, CH_2Cl_2, 4Å, RT, 70%, iv = MeSNa, DMF, RT, 82% , v = $MeCO_3H$, CH_2Cl_2 , 86%

Synthesis of Pyridines as Benzoic Acids Replacement

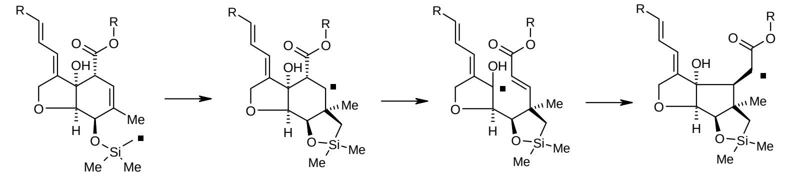


i = CH_2=CH-CH_2-$SnBu_3$, toluene, AIBN cat., 80°C, 65%, ii = OsO_4 cat., $NaIO_4$, H_2O:dioxane, 60% , iii = CuCl, $PdCl_2$ cat., O_2, DMF, H_2O, 71%, iv = H_2, Pd/C, MeOH, 95%, v = $(Me_3Si)_3SiH$, toluene, AIBN cat., 80°C, 85%

Summary

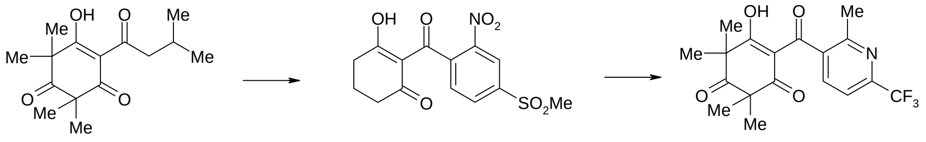


Abamectin **Highly Active Mectin**



New Radical Rearrengement

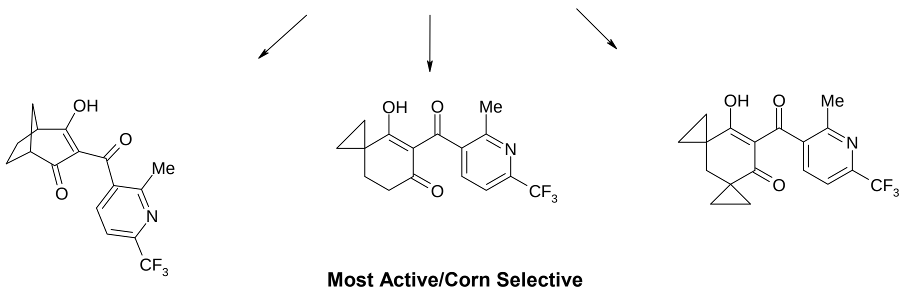
Summary



Leptospermone Lead

Mesotrione
Syngenta Corn Selective Herbicide

Most Active Non-Selective



Most Active/Corn Selective

Acknowledgements

Mectins Chemistry
Hans Tobler
Pierre Jung
Fiona Murphy Kessabi
Mathilde Lachia

X- Rays Structures
Jane Wibley

HPPD Inhibitors Chemistry
Renaud Beaudegnies
Andrew Edmunds