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Synthetic studies toward an analog of Glycinoeclepin A

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Synthetic studies toward an analog of Glycinoeclepin A

by

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Chauncey Dale Jones

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Signatures have been redacted for privacy

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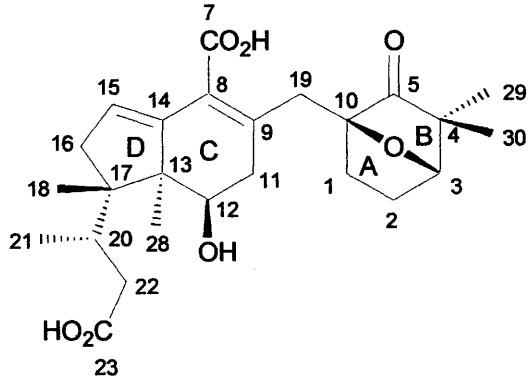
INTRODUCTION

The synthesis of glycinoeclepin A is of economic value to the soybean industry. Glycinoeclepin A is a natural hatch stimulus of soybean cyst nematodes (SCN, *Heterodera glycines*).[1] Soybean cyst nematodes are parasitic worms that bind to the host bean root and deprive the plant host of nutrition, eventually starving and killing the host plant. SCN was first reported by Hori of Japan in 1915 and first appeared in the United States in North Carolina in 1954.[1] Niblack et al. found that SCN population densities of 50-100 eggs/100cm^3 of soil would significantly suppress yields of soybean production.[2] Nematicides, host resistant soybeans, and crop rotation have been used to alleviate the problem. The problem with nematicides are they must be biodegradable in order not to affect the environment. Host resistant soybean use is the most feasible and environmentally safe, but SCN races will evolve over time and will reproduce on resistant soybeans. Crop rotation is another alternative to combat SCN (use of 1-year SCN-resistant soybeans followed by a 2-year period of non-host crop use). This method is effective, but is unattractive to market providers. Glycinoeclepin A offers another alternative.



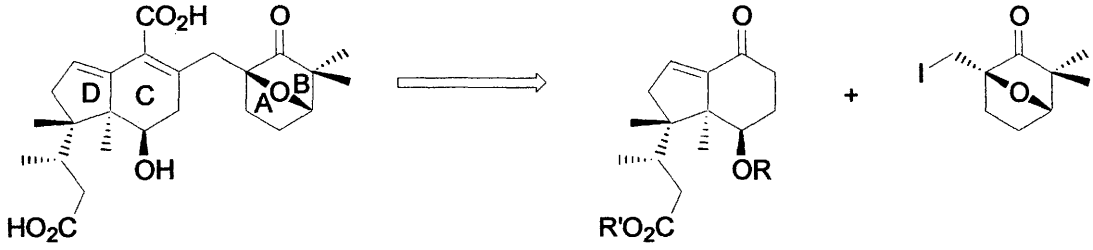
Glycinoeclepin A (1)

Glycinoeclepin A is a natural hatch stimulus of SCN which can induce premature hatch of SCN at concentration levels at 10^{-12} g/ml.[1] The isolation[1] and structural elucidation[3] of glycinoeclepin A **(1)** was carried out by Masamune et al. Of significance is the fact that milligram quantities of **1** were obtained from kilogram amounts of kidney beans.

With such small amounts of **1** available, synthetic chemists began to take the challenge of making a **1**.

The first total synthesis of glycinoeclepin A was done by Murai in 32 steps.[4] Murai's synthesis used convergent chemistry by connecting an isomeric (2R)–alcohol with acetoxycyclohexanone trityl ether via intramolecular coupling. The retrosynthesis below in Scheme I shows the two fragments Murai was targeting. They were made from commercial 2,2-dimethylcyclohexane-1,3-dione and (R)-(-)–carvone.

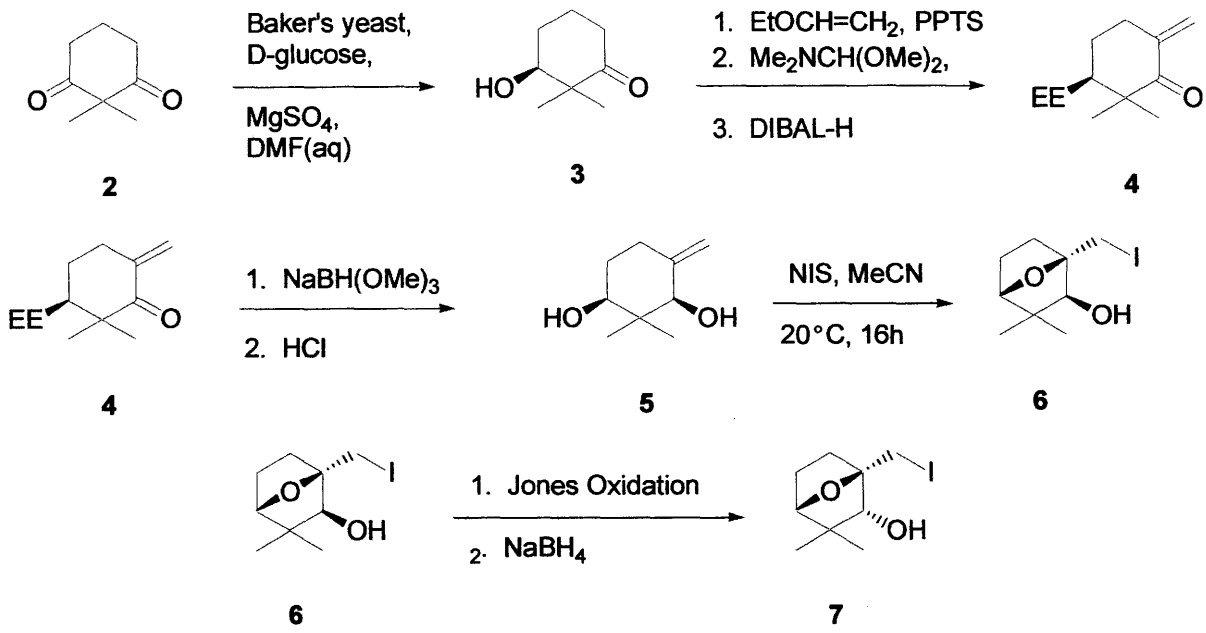
Scheme I



Glycinoeclepin A (1)

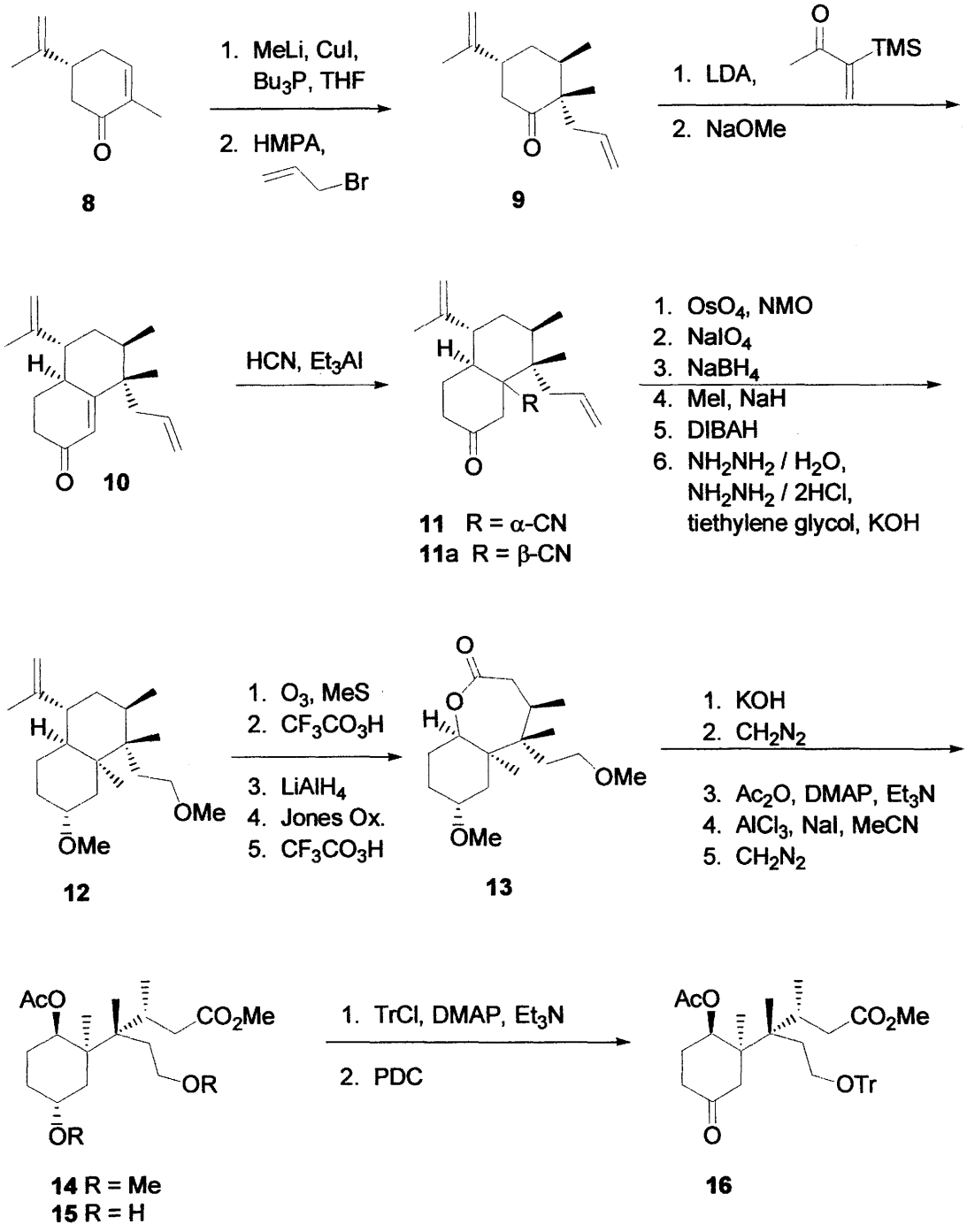
The first step was to synthesis the (2R)-alcohol using 2,2-dimethylcyclohexane-1,3-dione as starting material (Scheme II). An enzymatic reduction with Bakers' yeast[5] of the 2,2-dimethylcyclohexane-1,3-dione **2** afforded the (S)-2,2-dimethyl-3-hydroxycyclohexan-1-one **3**. The hydroxy ketone **3** was then protected using PPTS and ethyl vinyl ether to give the protected alcohol. The protected alcohol was converted to the α,β-unsaturated ketone **4** by Bredereck's reagent[6], followed by treatment with DIBAL-H. Reduction of the unsaturated ketone **4** with $NaBH(OMe)_3$, followed by acid hydrolysis with HCl afforded diol **5**. Compound **5**, when subjected to N-iodosuccinimide in the dark, underwent halocyclization to give the oxabicyclic alcohol **6**. Recrystalization of the oxabicyclic alcohol gave optically pure compound **6** in 79% yield. Compound **6** was oxidized via Jones oxidation followed by reduction of the ketone to give the desired (2R)-alcohol **7**.

Sheme II



Murai's second task was to make the C/D ring moiety, which would incorporate 4 chiral centers (Scheme III). To begin, (R)-(-)-carvone **8** underwent a Michael addition followed by trapping the enolate with allyl bromide to give the dialkylated compound **9**. Compound **9** was then annulated using lithium diisopropylamide, 2-(trimethylsilyl)-3-buten-2-one and sodium methoxide to yield the α,β-unsaturated octalone **10**. The octalone **10** was hydrocyanated under kinetic conditions to yield the cis and trans-cyanoketones **11** and **11a** in 63% and 30% yields, respectively.[7] Mixture **11** was treated with catalytic osmium tetraoxide and NMO to afford the diol which was then oxidized, reduced, and methylated. The methylated intermediate **12** was converted into a decalone through a multi-step process, followed by oxidation with peroxytrifluoroacetic acid to give ε-lactone **13** in 72% yield. Ring opening of lactone **13** was achieved by saponifaction and methylation followed by acetylation of the secondary alcohol to give acetate **14**. Then using Fuji's procedure[8] cleavage of the methoxy groups afforded triol acetate **15** in 85% yield. Compound **15** was treated with trityl chloride, DMAP, and triethyl amine to afford a protected ketol alcohol which was oxidized with pyridinium dichromate to give cyclohexanone **16** in 91% yield.

Scheme III

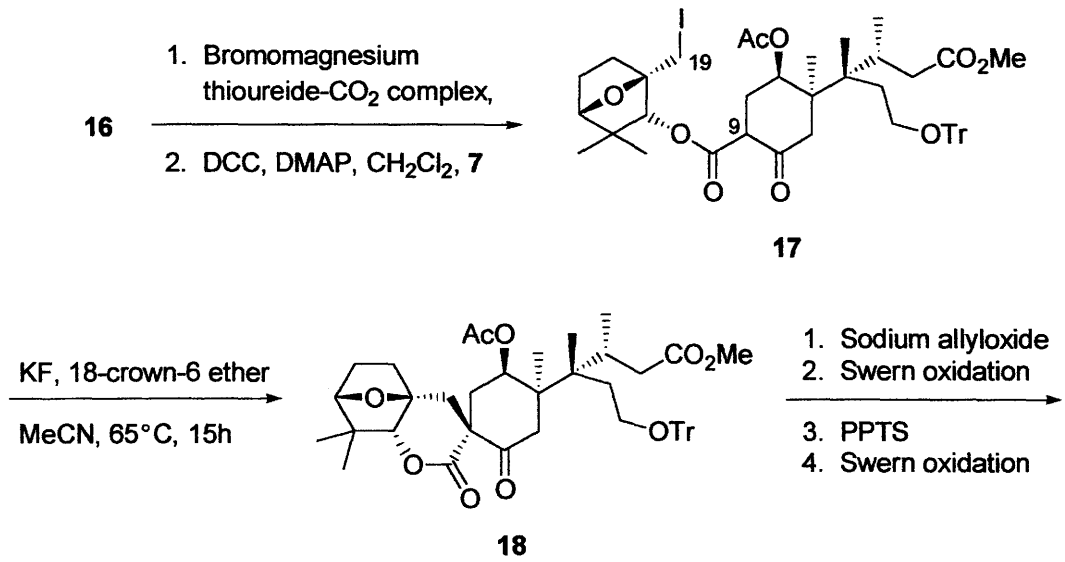


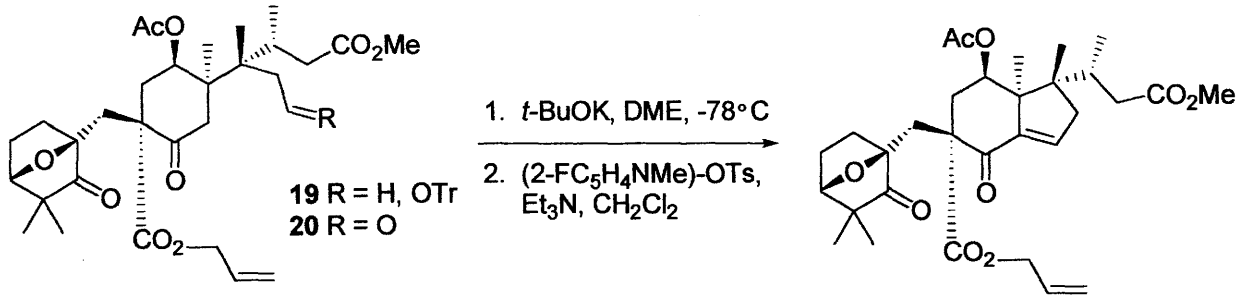
After developing fragments **7** and **16** the next step was to couple the fragments. In Scheme IV compound **16** was treated with bromomagnesium thioureide-carbon dioxide

complex affording the β-ketocarboxylic acid via α- carboxylation, which was reacted with **7** in the presence of dicyclohexyl carbodiimide to afford β-keto ester **17**.[9] The δ-lactone **18** was synthesized by reacting **17** with potassium fluoride in acetonitrile in the presence of 18-crown-6 at 65°C.[10] Lactone **18** was converted to compound **19** by treatment of **18** with sodium allyloxide followed by Swern oxidation[11] to give **19** in 73% yield. Compound **19** was subjected to acidic conditions, followed by Swern oxidation to afford the keto aldehyde **20**.[11] Intramolecular cyclization was achieved by adding **20** to potassium t-butoxide in DME. Treating the aldol product with 2-fluoropyridinium tosylate and triethyl amine afforded the dehydrated enone **21** in 54% yield.[12]

Using Tsuji's procedure[13] the allyloxycarbonyl group of **21** was removed which gave rise to a dienol. It was immediately treated with sodium hydride and phenyl triflimide[14] to afford dienyl triflate **22** in 76% yield. Using a modification of the Ortar method[15] introduction of a 1-carbon unit at C(8) was achieved. Compound **22** was treated with tributylamine, palladium acetate, and 1,1'-bis(diphenylphosphino) ferrocene in DMF/water mixture under a carbon monoxide atmosphere at 95°C to afford a dicarboxylic acid which was saponified with sodium methoxide to yield **1**.

Scheme IV





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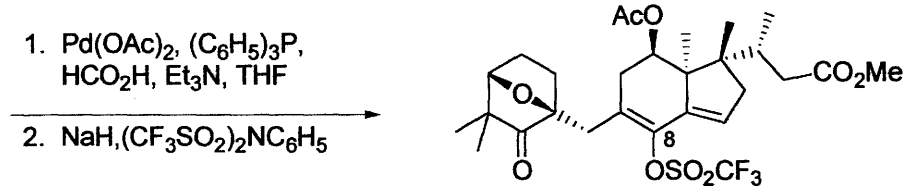

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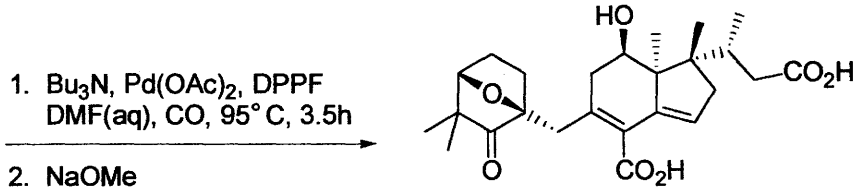


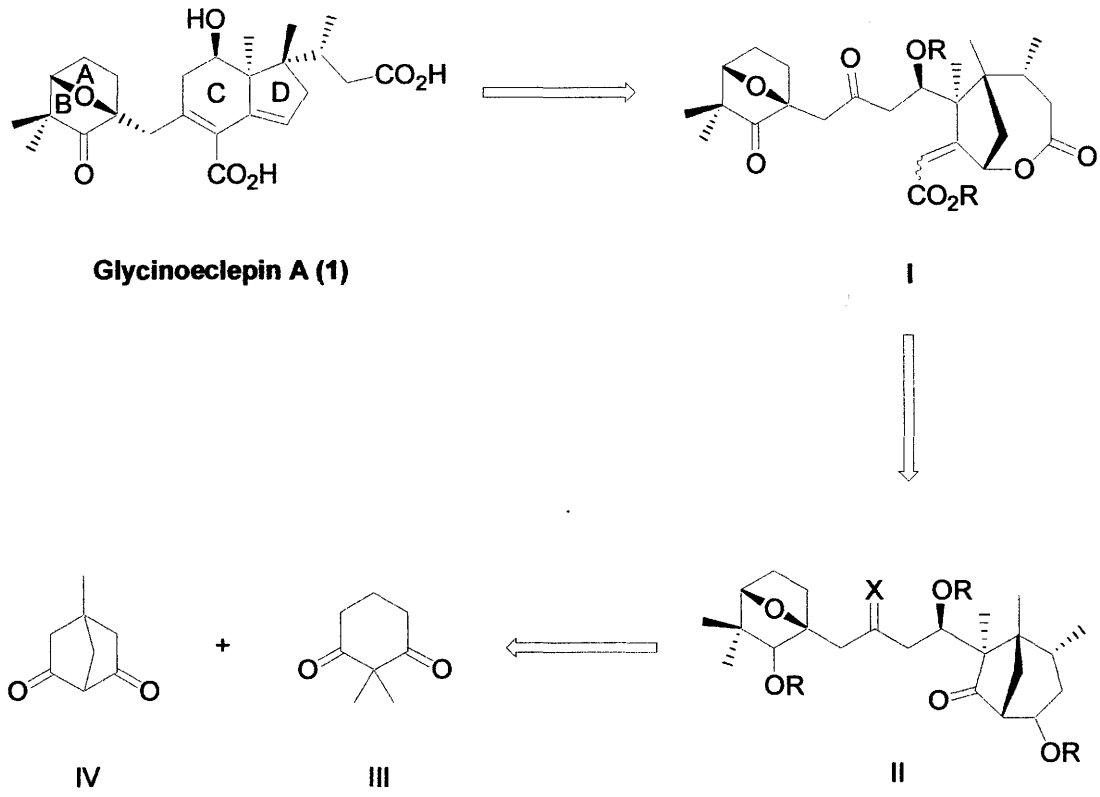
Glycinoeclepin A (1)

The first total synthesis of glycinoeclepin A by Murai was done in 32 steps. The overall yield was 0.4%.[16] With 32 steps in the synthesis and an overall yield of 0.4% there is much room for improvement.

The second total synthesis of glycinoeclepin A was done by Mori in 32 steps.[17] Mori's synthesis was convergent. The three key steps in the synthesis were an asymmetric reduction, a stereoselective aldol condensation, and a reductive lactone cleavage followed by aldol condensation.[17] Mori's retrosynthetic analysis is shown in Scheme V.

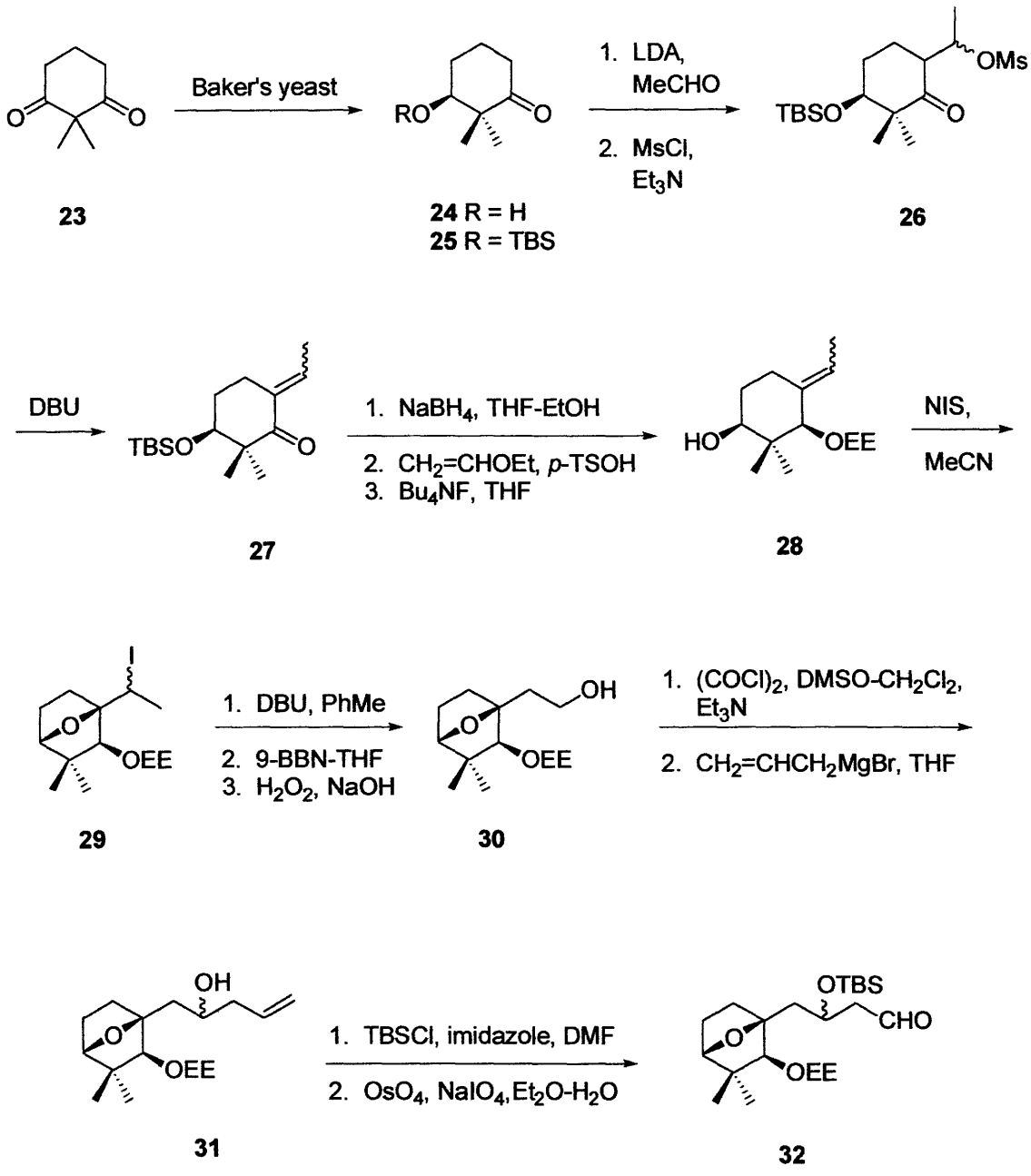
The first step in the synthesis was to asymmetrically reduce the 1,3-diketone **23** by Baker's yeast. The (S)-hydroxy ketone **24** was protected with a TBS group affording protected ketone **25** in 97% ee.[18] The ketone **25** was treated with LDA and acetaldehyde to afford an alcohol, which was mesylated to give **26**. Compound **26** was treated with DBU to

Scheme V



afford the enone **27**, which was reduced with sodium borohydride to afford an alcohol. The alcohol was protected under acidic conditions with *p*-toluenesulfonic acid and ethyl vinyl ether to give the protected alcohol. The TBS group was removed using TBAF to afford the alcohol **28**. Alcohol **28** underwent iodotheration to afford the iodo compound **29**. Treatment of **29** with DBU in toluene under reflux conditions afforded an olefin, which was hydroborated and oxidized to yield alcohol **30** in quantitative yield. Alcohol **30** was converted into an aldehyde through Swern oxidation.[19] The aldehyde treated with allylmagnesium bromide to give secondary alcohol **31**. The alcohol **31** was protected as its TBS ether by imidazole and TBSCl in DMF. One carbon shortening of the side chain was achieved through Lemieux-Johnson oxidation[20] affording aldehyde **32** in 32% overall yield from **24**[4] (Scheme VI).

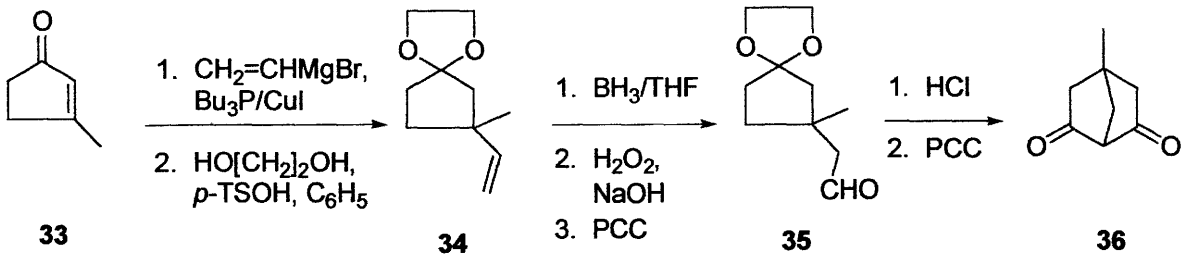
Scheme VI



23 **24** R = H, **25** R = TBS **26** **27** **28** **29** **30** **31** **32**

The second step in the synthesis was to synthesis ketone **III**. This process took a number of steps to complete starting with the synthesis of the diketone **36**. Diketone **36** was synthesized in 40% yield in 6 steps as shown in Scheme VII.

Scheme VII

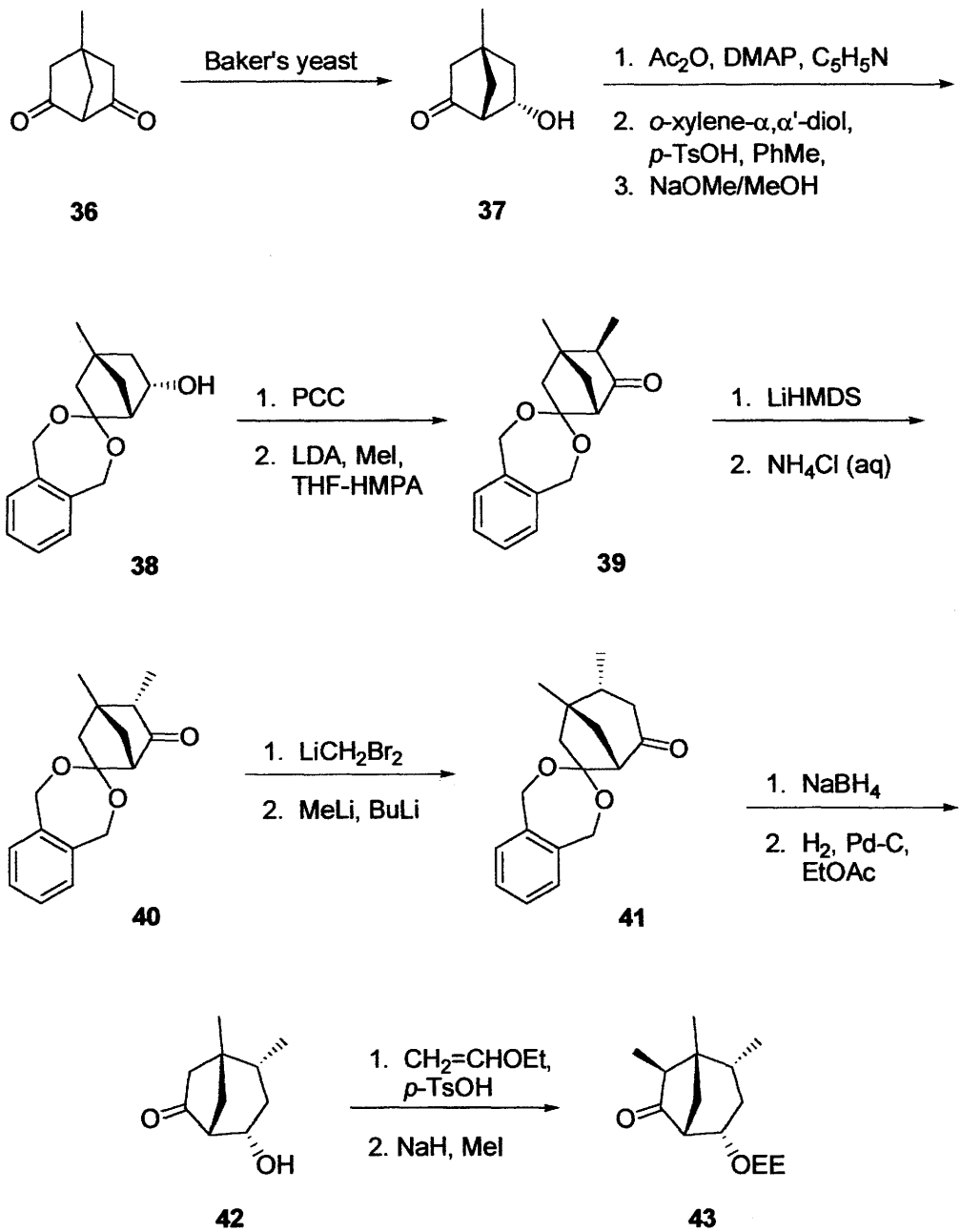


Starting with 3-methyl-2-cyclopentanone **33,** conjugate addition using vinylmagnesium bromide in the presence of tributylphosphine-copper (I) iodide[21,22] afforded an acetal. The acetal was treated with ethylene glycol and *p*-TsOH in benzene to afford the protected ketone **34**. Compound **34** underwent hydroboration-oxidation to give an alcohol, which was oxidized to the aldehyde **35** using pyridinium chlorochromate. Compound **35** was subjected to aldol conditions which afforded a condensation product, which upon oxidation with PCC gave the diketone **36**.

Reduction by Baker's yeast at pH 7 gave **37** in 55% yield and 80% ee. Subsequent protection, followed by deprotection of the acetate and recrystalization, afforded acetal **38** in 100% ee. Oxidation of **38** afforded a ketone which was methylated by LDA, iodomethane and hexamethylphosphoric triamide to afford ketone **39** in 97% yield. Enolization of ketone **39** with lithium hexamethyldisilazide (LiHMDS) followed by protonation afforded epimer **40** in 98% yield. Using a modified Nozaki method[23] ring expansion of epimer **40** to the octanone **41** was achieved. Treatment of **40** with lithium dibromomethide, followed by one equivalent of methyl lithium and one equivalent of butyl lithium yielded **41** in 50% yield. Reduction of ketone **41** with sodium borohydride, followed by deprotection and hydrogenolysis afforded the hydroxyl ketone **42** in quantitative yield. Protection of the secondary alcohol with ethyl vinyl ether followed by methylation with sodium hydride and iodomethane afforded **43** in 97% yield (Scheme VIII).

With the key fragments **32** and **43** successfully synthesized, aldol condensation was tried to no avail. However, when **43** was enolized with sodium hydride and trapped with chlorotrimethylsilane (TMSCl) the enol silyl ether **44** was obtained. Compound **44** was then converted into an enolate according to House's method[24] and treated with aldehyde to afford

Scheme VIII

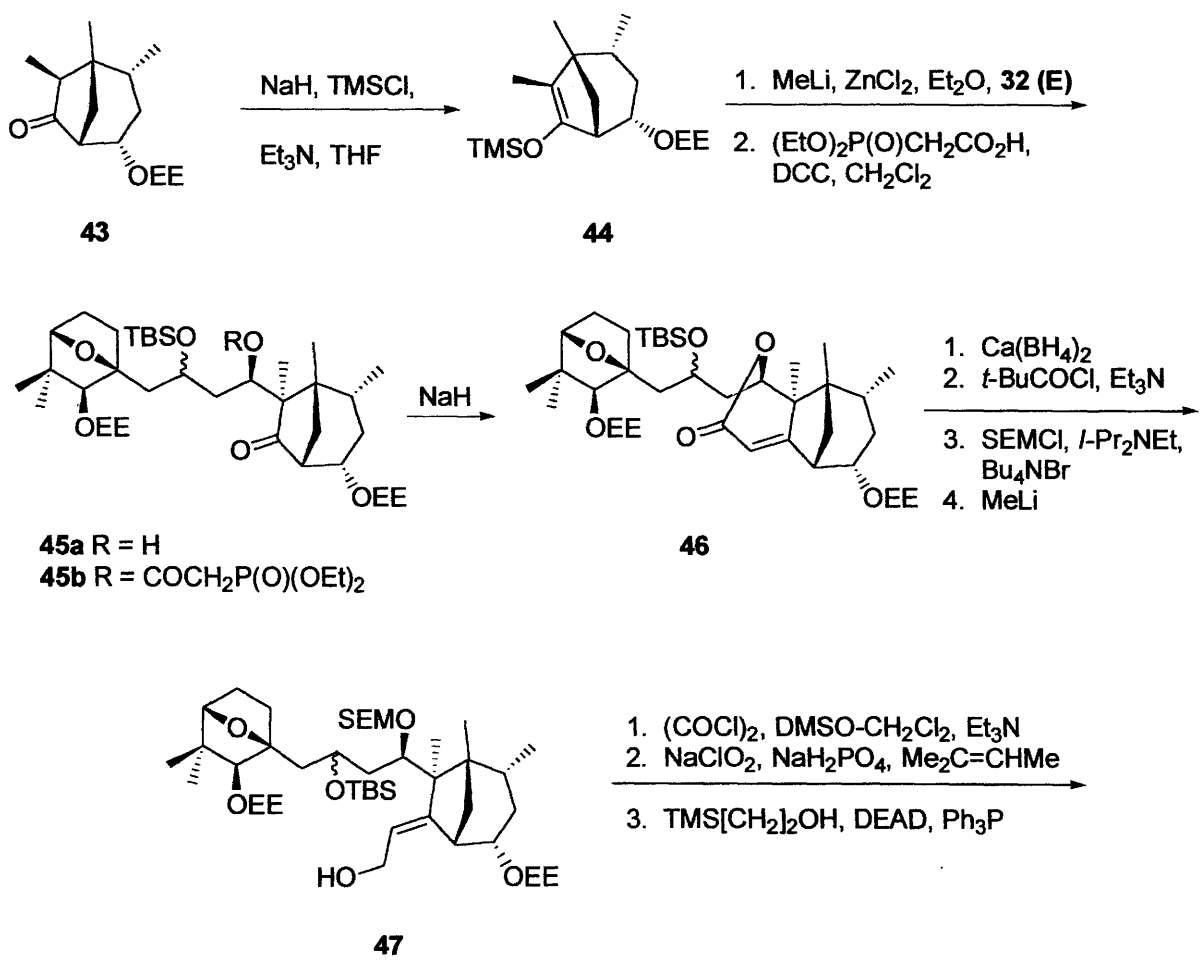


36 37 38 39 40 41 42 43

the unstable **45a**, which was converted to phosphonoacetate **45b**. The phosphonoacetate **45b** underwent an intramolecular olefination reaction by treatment with sodium hydride to give lactone **46**. Lactone **46** was reduced with calcium borohydride to give a diol. The primary hydroxyl group was acylated followed by protection of the secondary alcohol. Then,

deprotection of the acetate afforded the allylic alcohol **47**. Subsequent oxidation followed by esterification by Mitsunobu conditions[25] afforded ester **48**. The two ethoxyethyl and *tert*-butyldimethylsilyl protecting groups were removed to give a triol, which was subjected to Swern oxidation to afford the triketone **49**. Bayer-Villager oxidation of **49** afforded the diketo lactone, which underwent cyclization by treatment with lithium dimethyl cuprate.[26] Methylation using diazomethane afforded **50** in 73% yield. Dehydration of **50** followed by a 3 step deprotection process which included removal of the methyl ester by saponification, removal of [2-(trimethylsilyl)ethoxy]methyl (SEM) by lithium tetrafluoroborate[27], followed by deprotection of the TMS group by tris (dimethylamine)-sulphonium diflurotrimethylsiliconate[28] afforded synthetic glycinoeclepin A **(1)** (Scheme IX).

Scheme IX

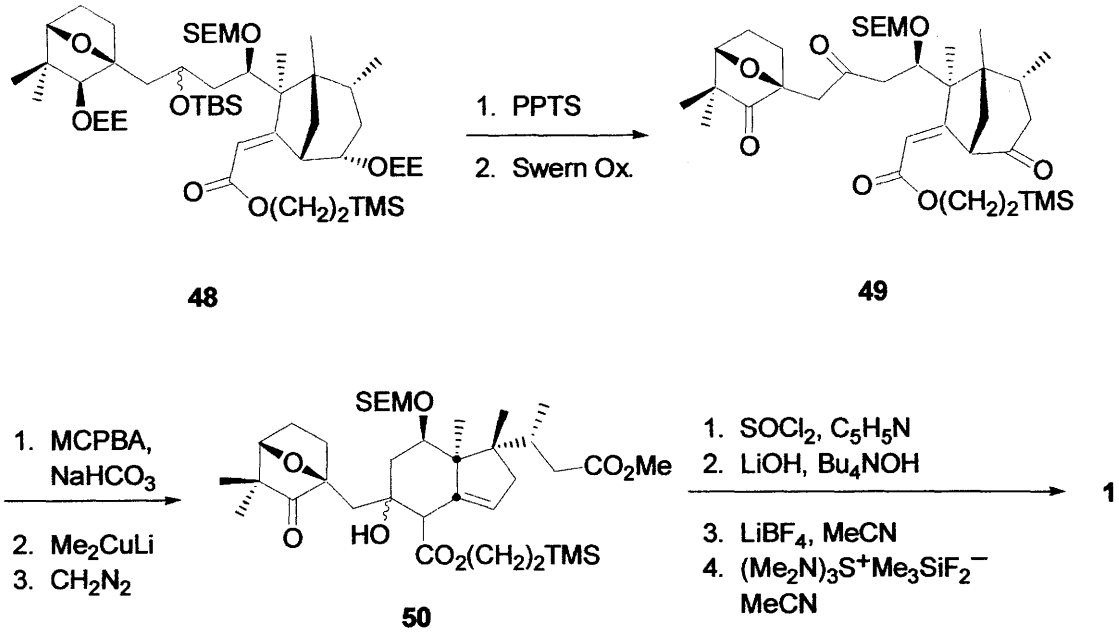


43 **44**

45a R = H
45b R = $COCH_2P(O)(OEt)_2$

46

47

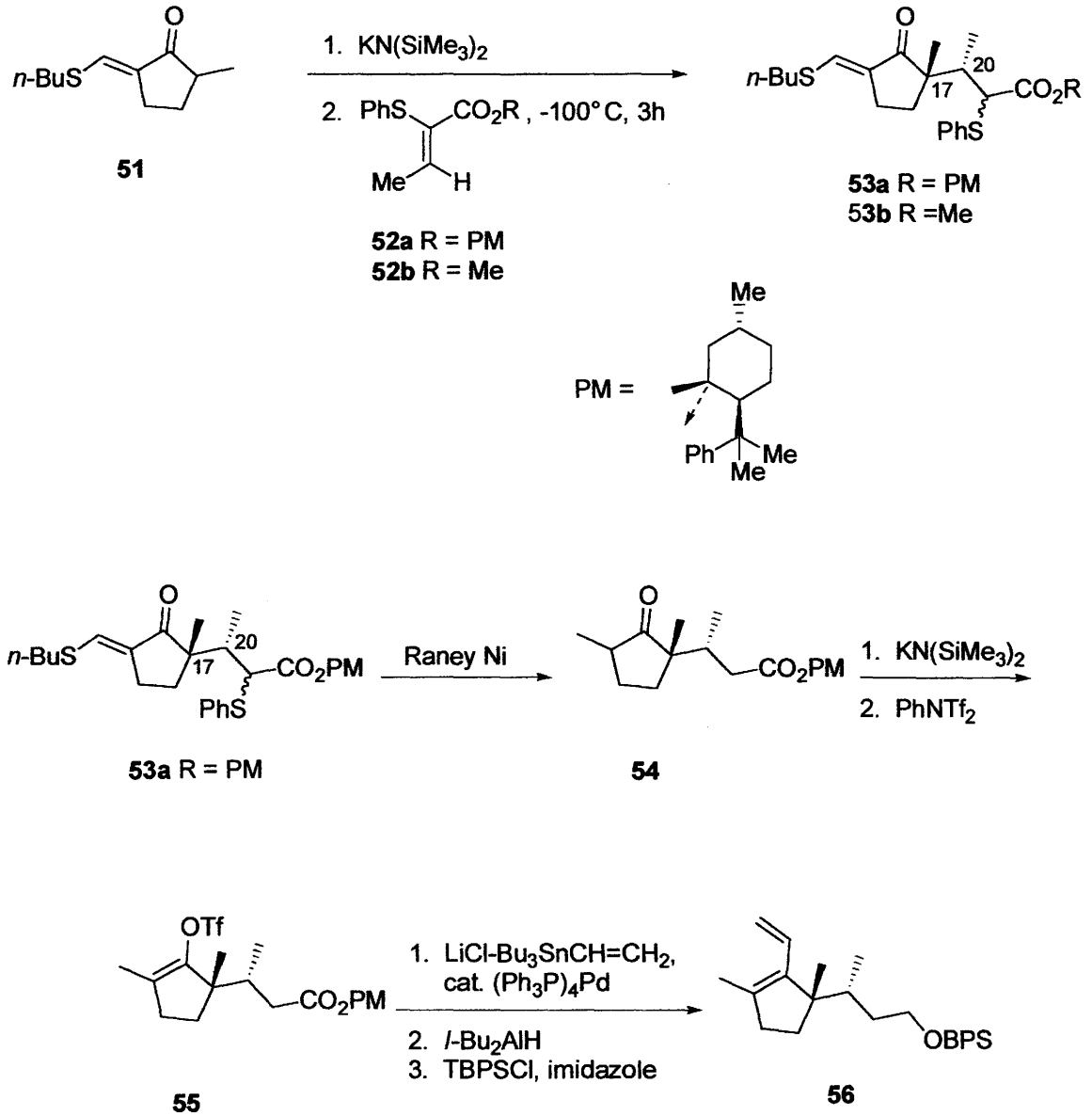


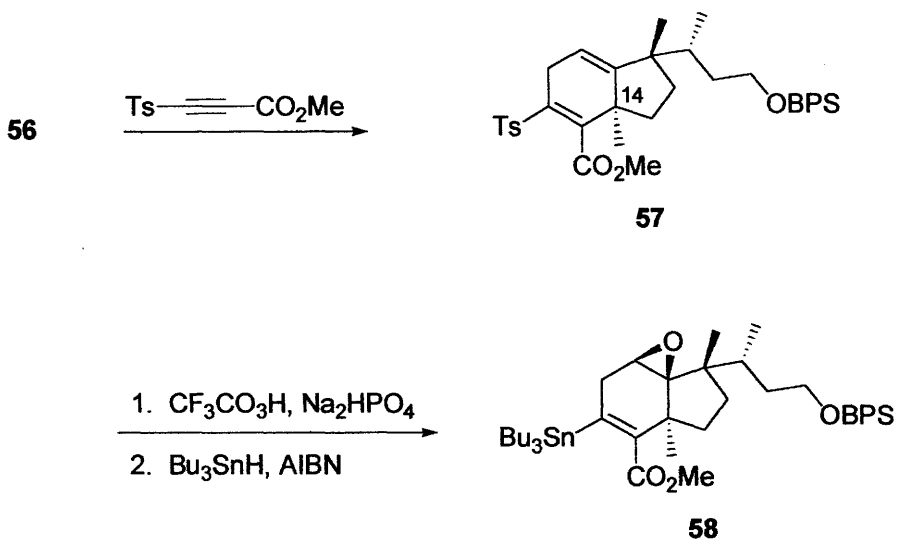
As in Murai's synthesis of glycinoeclepin A, Mori's synthesis took 32 steps. In Mori's synthesis a 3.0% overall yield of synthetic glycinoeclepin A was achieved from intermediate **24**. This was slightly better than Murai's overall yield. With the length and relatively low yield obtained in the above synthesis, there is room for improvement.

Corey achieved the third total synthesis of glycinoeclepin A in 1990.[29] Corey's approach focused on 4 key steps: enantioselective Michael reaction, Diels-Alder reaction, epoxidation and a 1,2-methyl shift.[29] To begin the synthesis, cyclopentanone **51**[30] was converted to the potassium enolate using potassium hexamethyldisilazane. The enolate was allowed to react at -100°C with ester **52a** to afford enone **53a** with 95:5 enantioselectivity and 5:1 C(17) – C(20) diastereoselectivity. Ester **52a** was made from (Z)-2-(phenylthio)crotonic acid[31] and (-)-8-phenylmenthol (PM).[32] The potassium enolate **51** was also allowed to react with methyl ester **52b** to afford (±) **52b** in 82% yield with 97:3 C(17) – C(20) diastereoselectivity. Enone **53a** was treated with Raney nickel to afford the keto ester **54**, which was enolized and trapped by N-phenylbistrifluoromethanesulfonamide to afford the enol triflate **55** in 84% yield. Vinylation[33] of enol triflate **55** with vinyl tributlytin and LiCl in the presence of 0.07 equivalents of $(Ph_3P)_4Pd$ gave a diene ester, which was reduced with DIBAL-H and protected with *tert*-butyldiphenylsilyl chloride (BPSCl) to give diene **56**.

Diene **56** reacted with 3-(*p*-toluenesulfonyl) propiolic acid[34] to afford adduct **57** and the C(14) diastereomer in a 3:1 ratio. The diastereomeric mixture was then treated with anhydrous trifluoroacetic acid in dichloromethane containing Na_2HPO_4 to give an epoxide which was converted to compound **58** through radical chemistry using catalytic AIBN and tri-n-butyltin hydride (Scheme X).

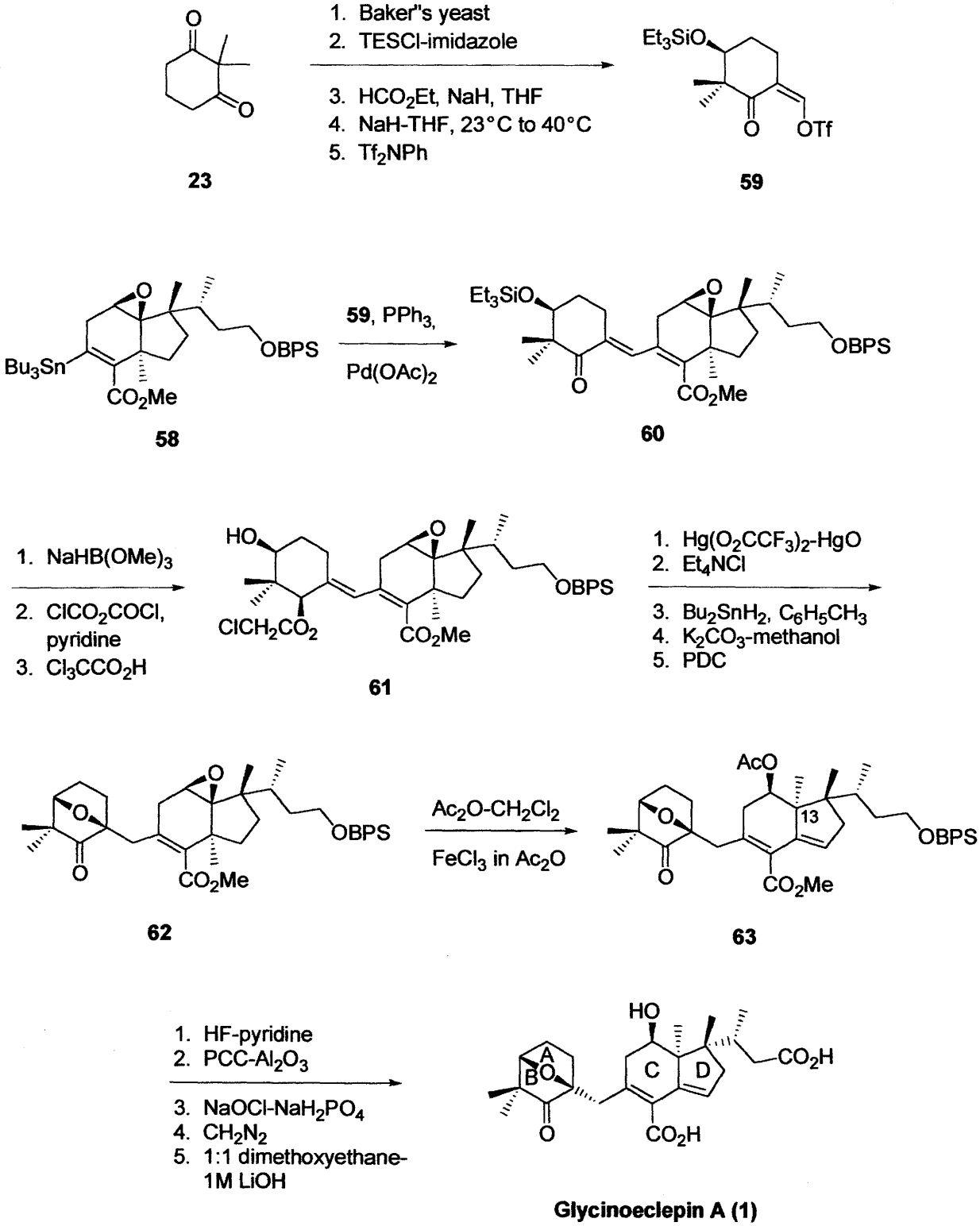
Scheme X





The enol triflate **59** was made by treatment of **23** with Baker's yeast, silylation, formylation, and formation of the triflate with NaH to afford **59** (Scheme XI). Then 0.07 equivalents of $Pd(OAc)_2$ and 0.14 equivalents of triphenylphosphine catalyzed coupling of **58** with triflate **59** to give adduct **60**. Adduct **60** underwent carbonyl reduction with $NaHB(OMe)_3$, followed by chloroacetylation of the secondary alcohol with chloroacetic anhydride, and desilylation with trichloroacetic acid to afford the diene **61** in 82% overall yield. Diene **61** was treated with mercuric trifluoroacetate and HgO in acetonitrile, followed by tetraethylammonium chloride which gave a single bridged ether in 78% yield. Demecuration with Bu_2SnH_2, followed by chloroacetate cleavage with potassium carbonate, and oxidation of the alcohol with PDC provided ether **62**. Corey's next key step was to incorporate the methyl substituent C(13). To achieve this, **62** was treated with acetic anhydride and $FeCl_3$ (1.1 equiv.) at -78°C for 12h to provide rearranged acetate **63** in 83% yield. The Lewis acid was the determining factor for successful rearrangement. When $EtAlCl_2$, Et_2AlCl or $BF_3{\cdot}Et_2O$ were used, **62** was converted to the isomeric ketone by way of hydrogen rearrangement. To complete the synthesis, acetate **63** was desilylated with HF in pyridine, followed by oxidation of the primary alcohol with PCC-Al_2O_3. The newly formed formyl group then was oxidized by sodium chlorite-NaH_2PO_4 and esterified. Hydrolysis of the ester and acetyl groups with lithium hydroxide afforded synthetic glycinoeclepin A **(1)**.

Scheme XI


1. Baker"s yeast
2. TESCl-imidazole
3. HCO2Et, NaH, THF
4. NaH-THF, 23°C to 40°C
5. Tf2NPh
Et3SiO
OTf
23
59
Bu3Sn
OBPS
CO2Me
59, PPh3,
Pd(OAc)2
58
60
1. NaHB(OMe)3
2. ClCO2COCl, pyridine
3. Cl3CCO2H
HO
ClCH2CO2
61
1. Hg(O2CCF3)2-HgO
2. Et4NCl
3. Bu2SnH2, C6H5CH3
4. K2CO3-methanol
5. PDC
62
Ac2O-CH2Cl2
FeCl3 in Ac2O
AcO
13
63
1. HF-pyridine
2. PCC-Al2O3
3. NaOCl-NaH2PO4
4. CH2N2
5. 1:1 dimethoxyethane-1M LiOH
A
B
C
D
CO2H
Glycinoeclepin A (1)

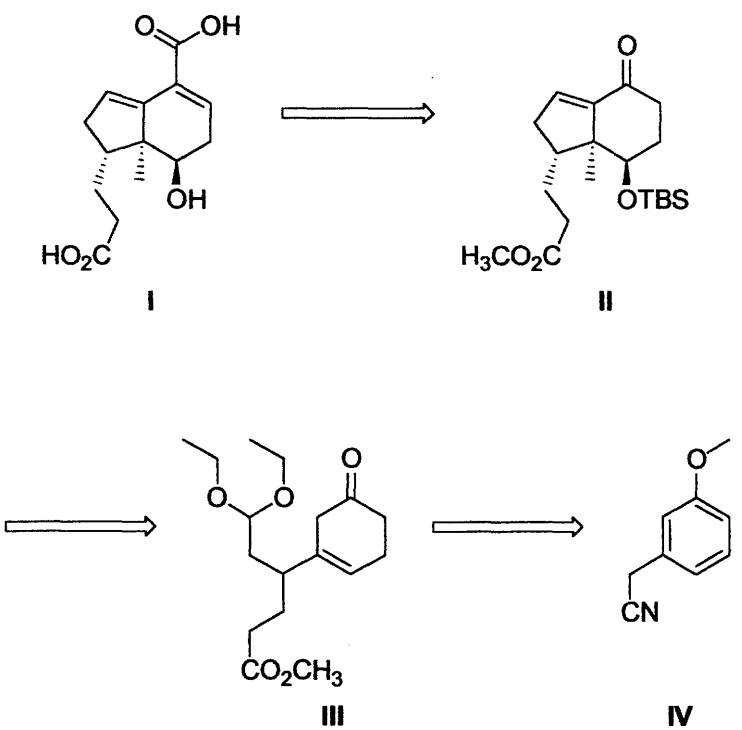
Of the three total syntheses of glycinoeclepin A, Corey's synthesis of 22 steps is by far the shortest route. Worth highlighting is the use of the enantioselective Michael reaction, Diels-Alder reaction, and the 1,2-methyl shift that was incorporated in Corey's synthesis. Still, there is room for improvement. That is where our research begins. We set out to provide a direct synthesis of an analog of glycinoeclepin A.

RESULTS AND DISCUSSION

In a study done by Murai[35] it was determined the carboxyl group and hydroxyl group on the C ring and the carboxyl group on the D ring are essential for hatching activity. The oxabicyclic ring system A contributes minimal activity.[36] The cross-conjugated system in the C ring is not critical for activity. With the above syntheses, Murai's activity studies and Kraus' analog studies[37] in mind, we set out to develop a synthesis that would be cost effective, short, and hold the key components for activity.

The retrosynthetic analysis started with the diacid **I**, which might be made from a Shapiro reaction followed by deprotection and hydrolysis of **II** (Scheme XII).

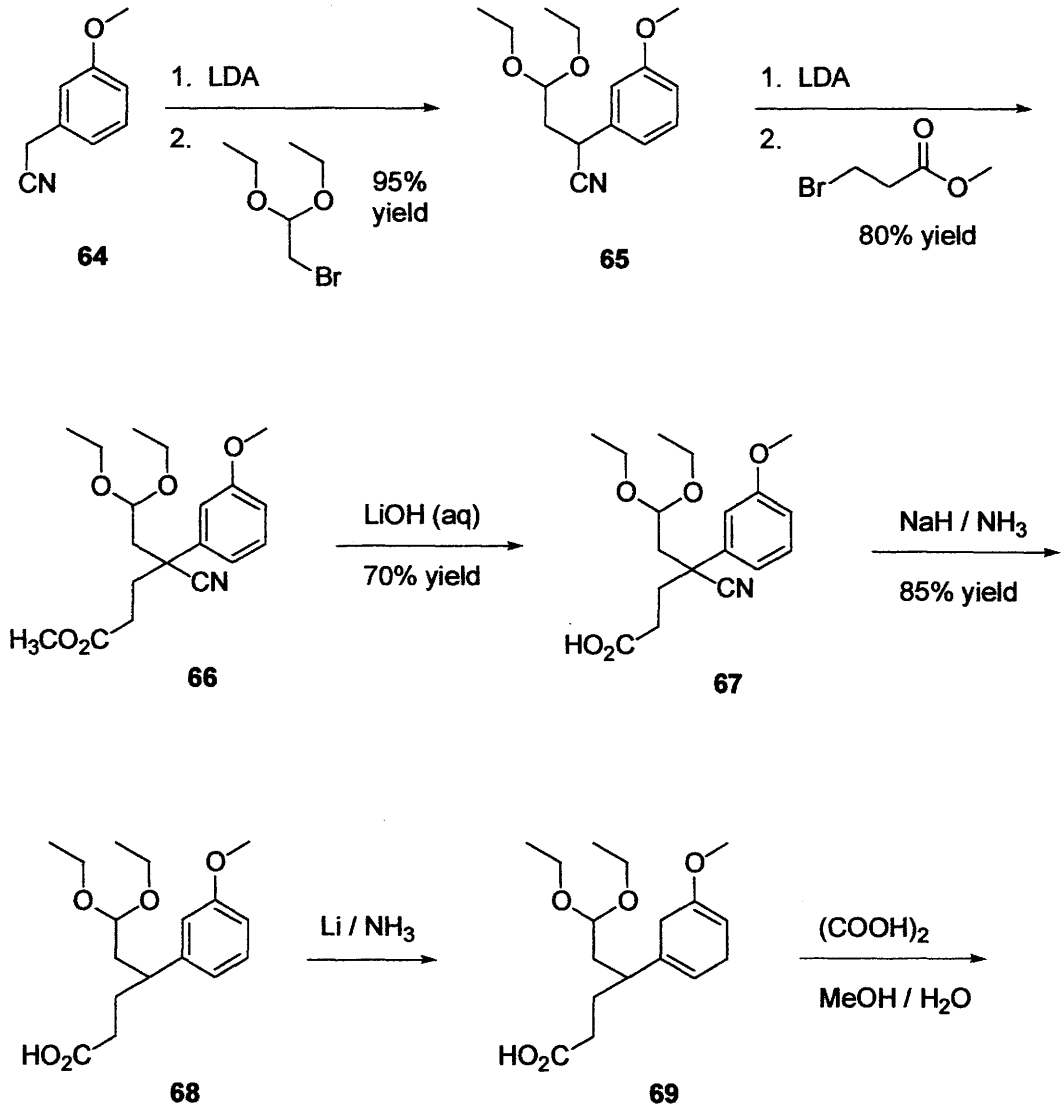
Scheme XII

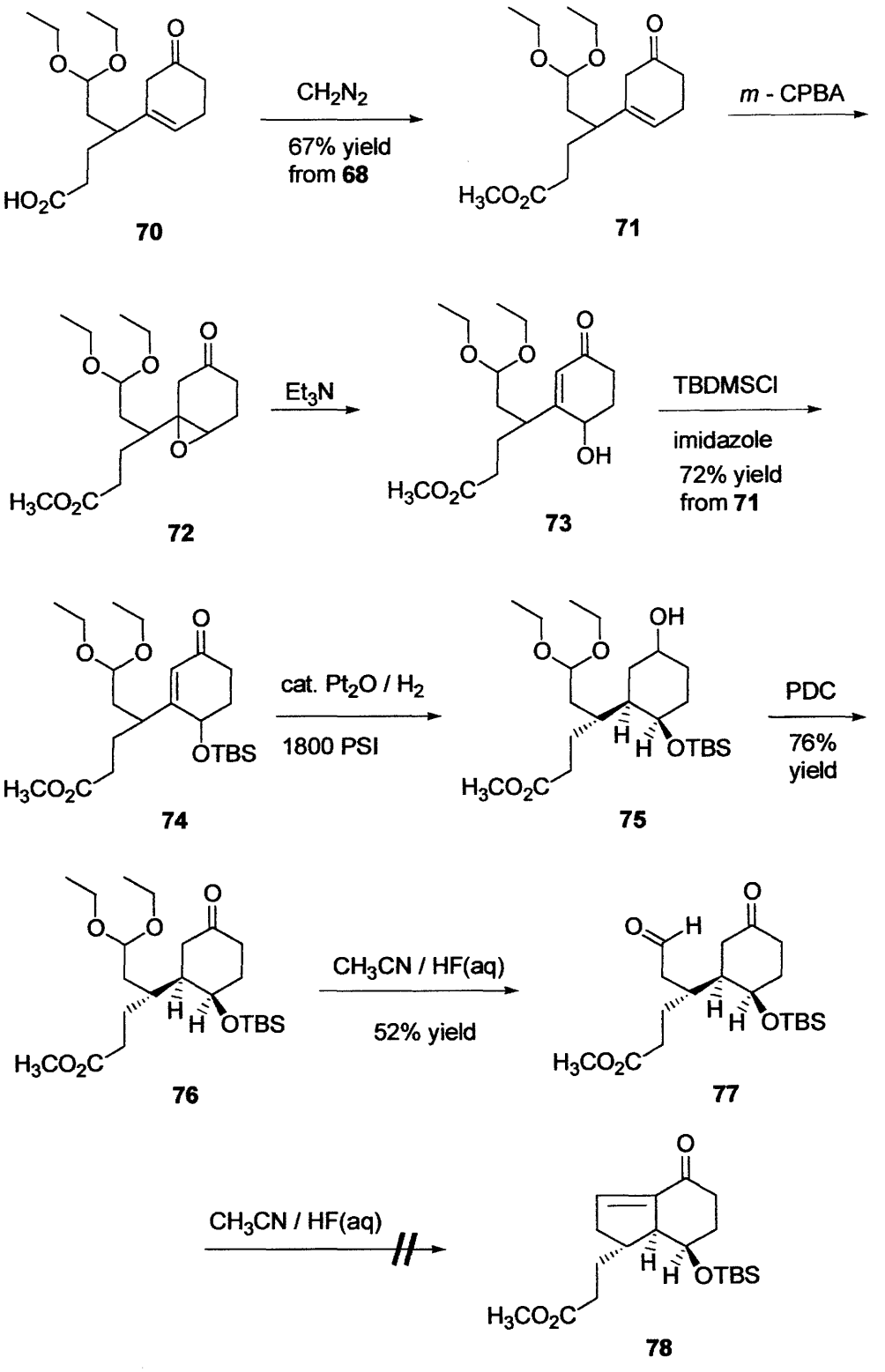


Compound **II** might be made from **III** by epoxidation, followed by elimination to introduce the α,β-unsaturated ketol alcohol. The ketone **III** could come from 3-methoxyphenylacetonitrile.

Our synthesis began with 3-methoxyphenylacetonitrile **64**. Deprotonation using LDA and bromoacetaldehyde diethyl acetal afforded **65** in 95% yield after Kugelrohr distillation (Scheme XIII). Compound **65** reacted with LDA and methyl-3-bromopropionate to afford the tetra-substituted compound **66**. Hydrolysis of **66** with aqueous lithium hydroxide gave **67**. A Birch reduction would have reduced the ester in compound **66**.

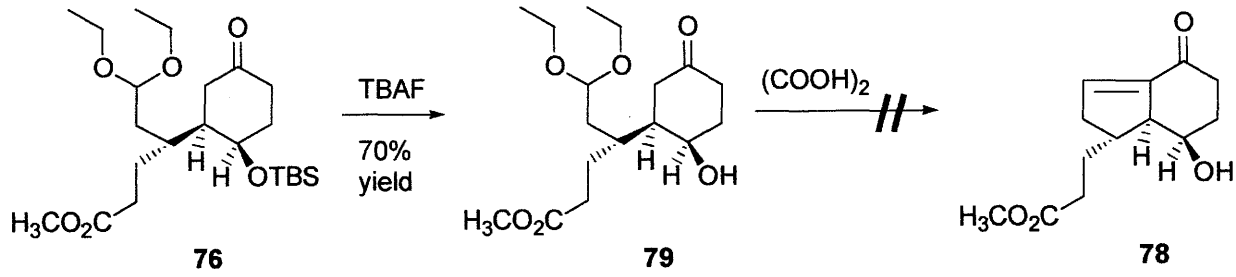
Scheme XIII



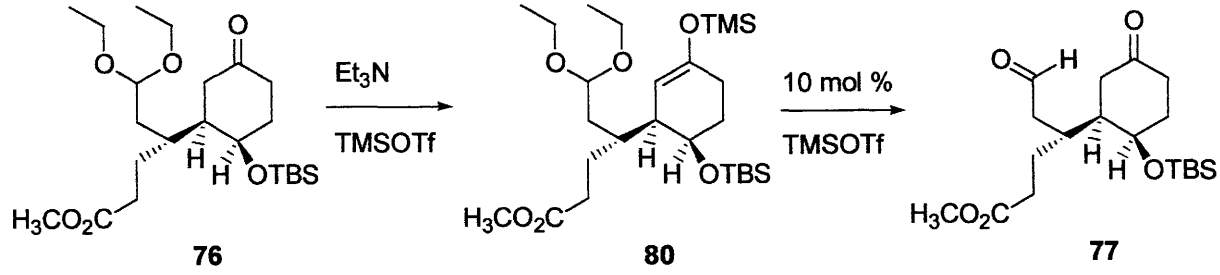

CH2N2
67% yield
from 68
m - CPBA
Et3N
TBDMSCl
imidazole
72% yield
from 71
cat. Pt2O / H2
1800 PSI
PDC
76%
yield
CH3CN / HF(aq)
52% yield
CH3CN / HF(aq)
70
71
72
73
74
75
76
77
78

Compound **67** was reacted with sodium and liquid ammonia at reflux for 10 minutes, quenching with ice to afford **68** in 85% yield.[38] Compound **68** was then submitted to Birch conditions to afford **69**. However, reduction of the benzene ring was incomplete. Using Li in place of Na resulted in reduction of the benzene ring. Also, the use of lithium was better for safety reasons. Dissolving **69** in a 3:1 mixture of methanol:water, followed by treatment with saturated oxalic acid afforded the crude hydrolyzed keto acetal **70** in 91% yield over 2 steps.[39] A mild acid was used to hydrolyze crude **69** to prevent isomerization. If isomerization had occurred, the alcohol introduction at C(12) would have been more difficult. Esterification of **70** with diazomethane-ether solution afforded the methylated **71** in 60% yield from **68**. Epoxidation of **71** with *m*-CPBA afforded epoxide **72**. Epoxide **72** was treated with triethylamine to make α,β-unsaturated ketone **73**, which was immediately dissolved in acetonitrile and treated with imidazole and TBDMSCl to afford ketone **74** in 67% yield from **71**. Next, reduction of the olefin with platinum oxide and hydrogen under 1800 psi for 47 hours afforded crude **75** in 95% yield. The use of the OTBS group in the previous step allowed for hydrogen addition on the opposite face of the OTBS group due to the bulkiness of the OTBS protecting group.[40] The alcohol **75** was oxidized with pyridinium dichromate and an equal amount of silica gel in methylene chloride for 22 hours to give ketone **76** in 76% yield from **74**. Ketone **76** was then deprotected. Aqueous HF[41] reacted with **76** to afford hydrolyzed ketol aldehyde **77** instead of the expected alcohol. Aldehyde **77** was resubmitted to the acidic conditions to make the desired enone **78**. Compound **76** was treated with TBAF[42] to afford **79** in 70% yield (Scheme XIV). Compound **79** failed to cyclize under acidic conditions. Our focus then turned toward enol silyl ether and acetal intramolecular cyclization[43] (Scheme XV). Ketone **76** was treated with triethylamine and trimethylsilyltrifluoromethanesulfonate (TMSOTf) to afford crude **80**, which was treated with 10 mol percent TMSOTf to give keto aldehyde **77** instead of **78**. Our concern at this point was the stereoselectivity of enol silyl ether formation. To circumvent the selectivity problem, we envisioned making enol silyl ethers and an enolate from compound **74** (Scheme XVI). Compound **74** did not react with Wilkinson's catalyst and triethylsilane. Treatment of **74** with *tert*-butyl peroxide and triethylsilane failed to produce **81**. Lastly, **74** was treated with Li, liquid ammonia, and *tert*-butanol. This also failed.

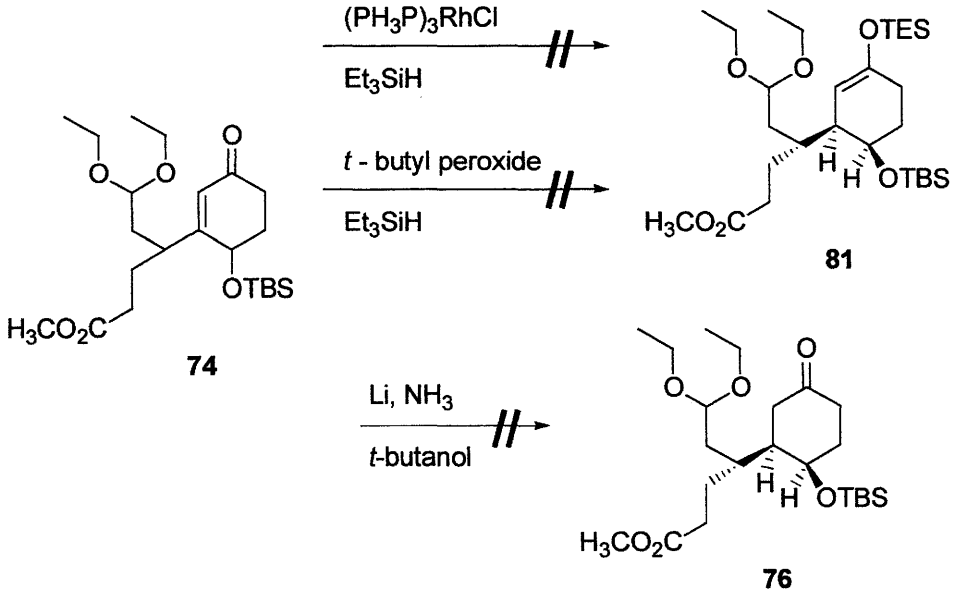
Scheme XIV



Scheme XV



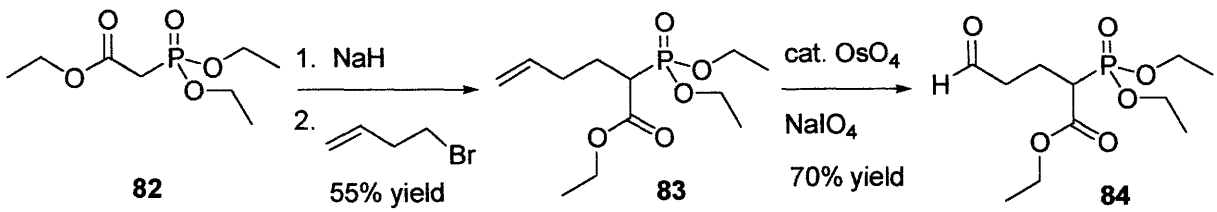
Scheme XVI



At this point, failure of the cyclization step and the length of the synthesis lead us to envision a new synthetic approach. Our first approach was linear. In our new approach we will append a 6-membered functionalized ring to a 5-membered ring ketone through an aldol reaction followed by an intramolecular Wadsworth-Emmons reaction.

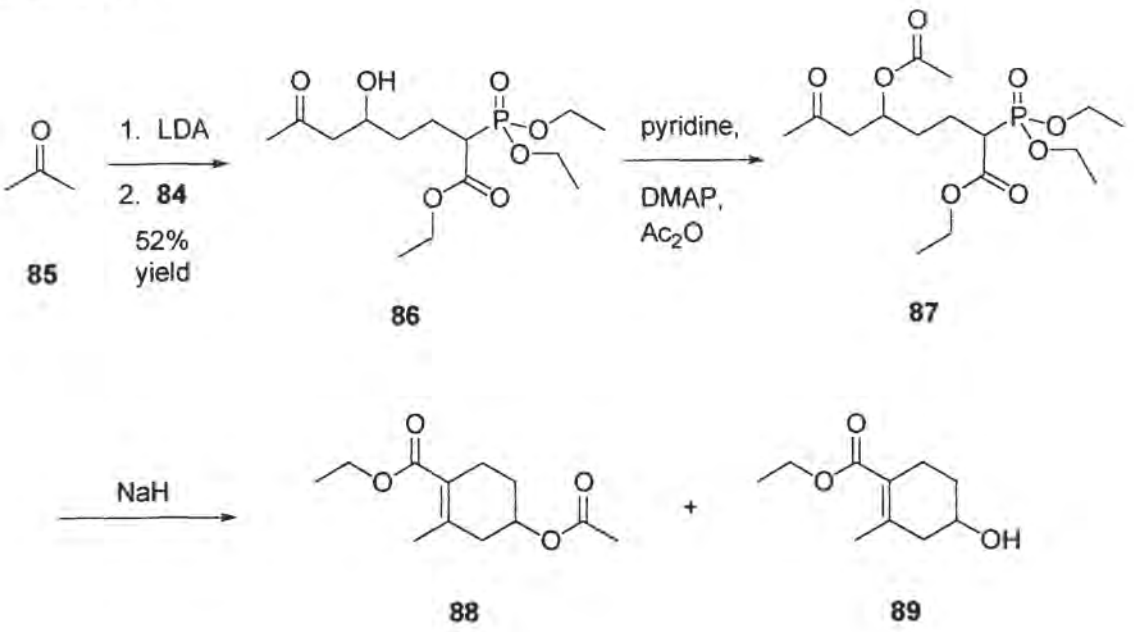
To test our annulation, a model system was done. First, the phosphonate aldehyde was made. Treatment of triethyl phosphonoacetate **82** with NaH, followed by 4-bromo-1-butene[44] afforded the phosphonate olefin[45] **83**. Compound **83** was oxidized through Lemieux-Johnson oxidation[20,46] to give the phosphonate aldehyde **84** in 70% yield (Scheme XVII).

Scheme XVII



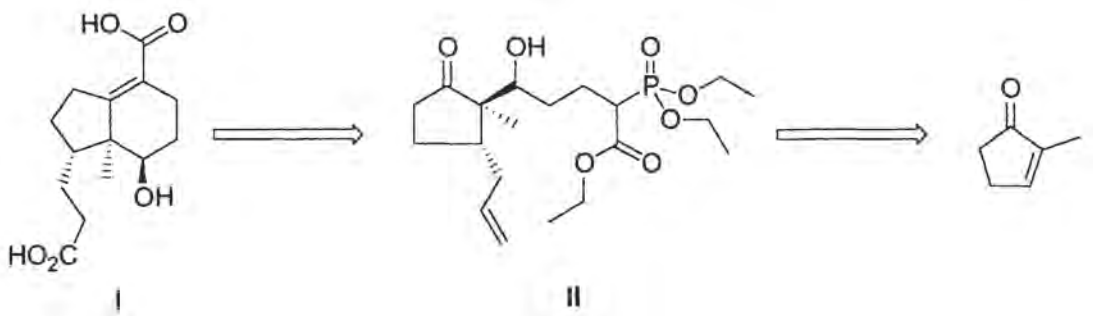
Second, acetone **85** was treated with LDA to form an enolate, which was immediately trapped by **84** resulting in the aldol product **86** in 52% yield. One concern was the ketone enolate might abstract the acidic methane proton of the ester phosphonate rather than react with the aldehyde. However, no products derived from the intramolecular Wadsworth – Emmons cyclization were detected. Attempts to force the cyclization by additional equivalents of base, extended exposure of **84** to the enolate, or heat led to the destruction of the aldol product **86**. Attempts to protect the secondary alcohol as the THP ether produced some protected alcohol plus dehydrated product. The use of pyridine, DMAP, and acetic anhydride led to the acetylated product **87** in quantitative yield. Treatment of **87** with NaH afforded the acetoxy ester **88** (R=Ac) and hydroxy ester **89** (R=H) in 37% and 16% yields, respectively (Scheme XVIII).

Scheme XVIII



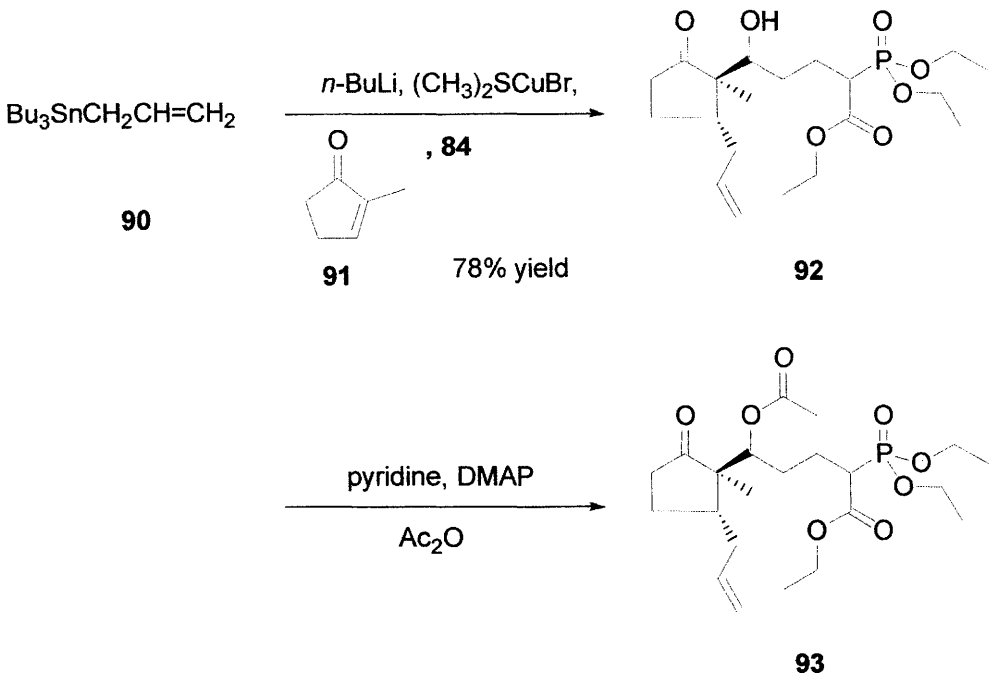
After completion of the model system, we returned to the synthesis an analog of glycinoeclepin A. Our focus was on synthesizing an analog that would contain the minimum functionality necessary for mimicking glycinoeclepin A activity. The retrosynthetic analysis is shown below in Scheme XIX.

Scheme XIX



The target analog **I** could be made by oxidation and hydrolysis of the bicyclic compound which might be made by protection of the secondary alcohol, followed by base cyclization of the aldol product **II**. Compound **II** could come from 2-methyl-2-cyclopentenone by a 1,4-addition followed by aldol chemistry.

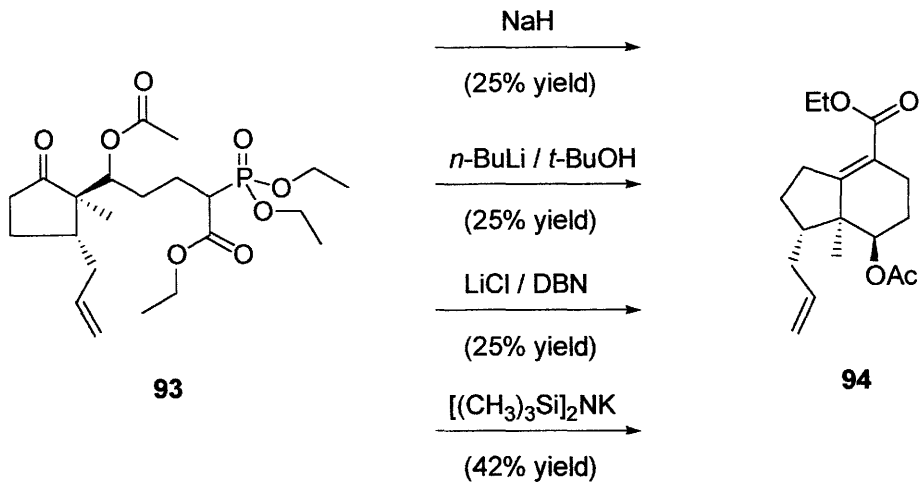
Scheme XX



To begin the synthesis, allyltributyl tin **90** was transmetallated with *n*-butyl lithium, followed by formation of a cuprate reagent. Introduction of 2-methyl-2-cyclopentenone **91** to the cuprate reagent[47] followed by trapping the enolate with **84** afforded a diastereomeric mixture of aldol product **92**in 78% yield. Acetylation of the secondary alcohol with pyridine, DMAP, and acetic anhydride afforded protected alcohol **93** in quantitative yield (Scheme XX). Treatment of **93** with NaH afforded cyclized product **94** in 25% isolated yield. Further attempts to cyclize **93** with *n*-butyl lithium/*tert*-butanol, LiCl/DBN[48] or potassium hexamethyldisilazane afforded **94** in 25-42% yield (Scheme XXI).

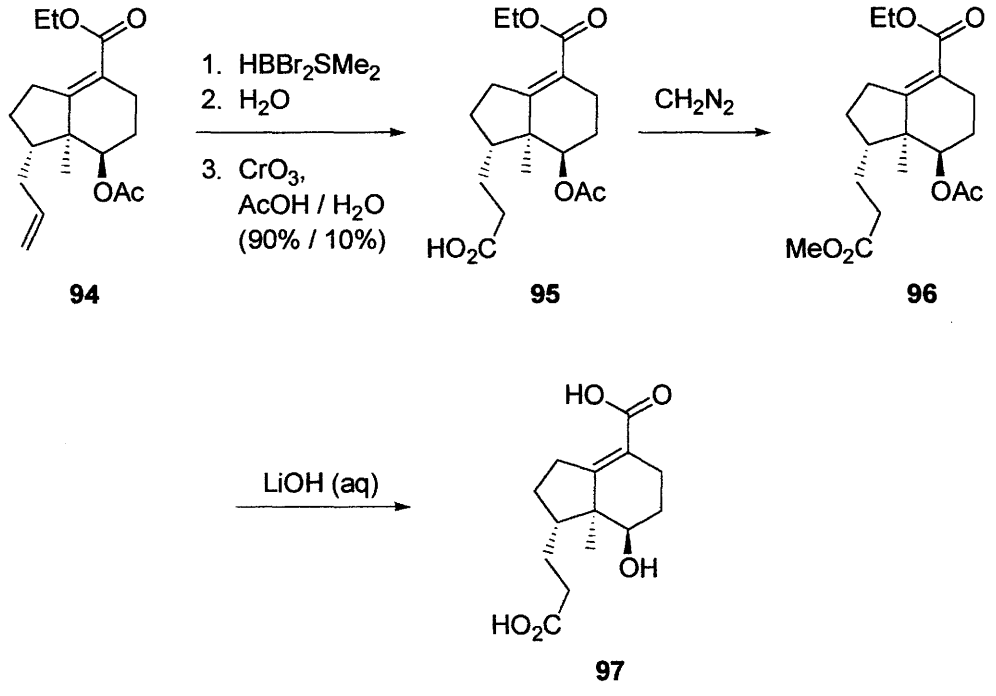
The poor yields could be attributed to the protecting group, or the stereochemistry of the alkoxide and phosphonate in intermediate **93**. Compound **94** was treated with dibromoborane-methylsulfide complex to give a boron adduct, which was treated with water to afford a boronic acid[49]. Oxidation of the boronic acid with chromium (VI) oxide[50] and acetic acid – water lead to the bicyclic acid **95**. Compound **95** was methylated with diazomethane to give **96** in 24% yield from **94**. Hydrolysis of the esters was achieved by treatment of **96** with LiOH at 70°C to afford the desired analog **97** (Scheme XXII).

Scheme XXI



93 **94**

Scheme XXII



94 **95** **96**

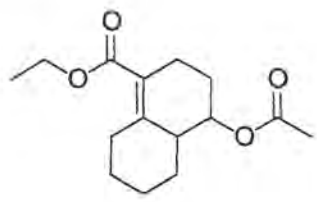
97

Compound **97** has been submitted for testing with Dr. Tylka's lab. At this time we have not received word if compound **97** is a hatch stimulus or not.

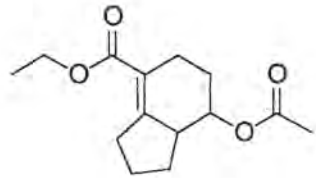
Using procedures for the synthesis of compounds **88**, **89**, and **94** we were able to synthesize six different analogs. Starting from commercially available cyclohexanone,

cyclopentanone, 3-pentanone, 3-methyl-2-butanone, and allyltributyltin. Phosphonate annulation was done to afford the cyclized analogs (Scheme XXIII).

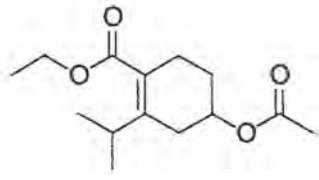
Scheme XXIII



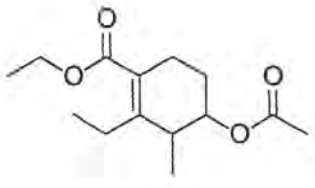
98
80% yield



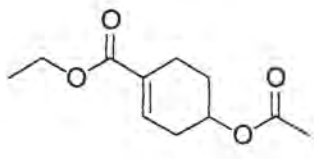
99
81% yield



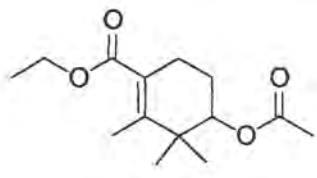
100
20% yield



101
79% yield



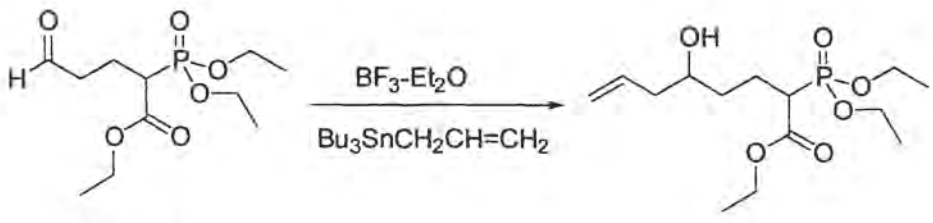
102
12% yield
from **104**



103
37% yield

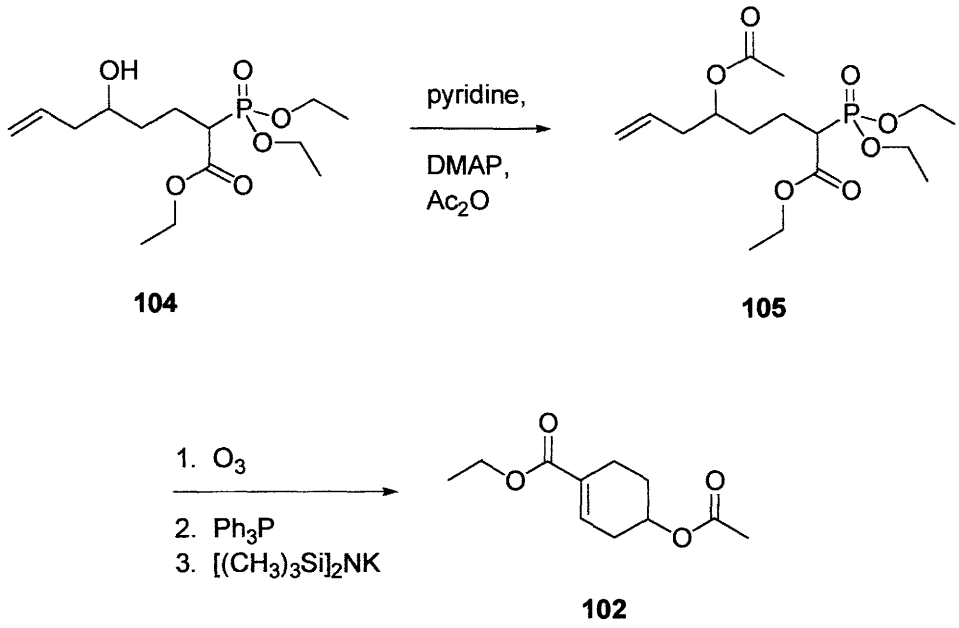
For the allyltributyl tin the aldol chemistry went via a Lewis Acid, not enolate chemistry. Also, after protection of the secondary alcohol the olefin intermediate was treated with ozone and triphenylphosphine to afford an aldehyde. The aldehyde intermediate was then cyclized to the α,β-unsaturated ester (Scheme XXIV).

Scheme XXIV



84 **104**

Scheme XXIV cont.



104 **105**

102

Another problem we faced was the 3-methyl-2-butanone intermediate would eliminate preferentially over cyclization to **100**. We attribute this to steric bulk of the isopropyl group limiting attack of the carbonyl by the phosphonate anion. Overall, 8 analogs were synthesized using the annulation process which will be applicable to other natural product systems.

CONCLUSION

In our attempts to synthesize analogs that would mimic glycinoeclepin A, a new carbanion-based strategy for appendage of a functionalized six-membered ring onto a ketone or aldehyde was developed. Using commercially available reagents we were able to synthesize **97** in 8 steps in an overall yield of 3%. The poor yield can be attributed to conversion of **93** to **96**. The new annulation method presented will be applicable to other natural product systems.

EXPERIMENTAL

All materials were obtained from commercial sources and used without purification unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2) and acetonitrile were distilled from calcium hydride. NaH in 60% mineral oil was purified by washing with pentane, removal of the pentane, and drying with argon. All reactions were conducted under argon atmosphere and extracts were dried over anhydrous magnesium sulfate or sodium sulfate. For anhydrous conditions the glassware was flame-dried under argon or dried in a 150°C oven for 12 hours and cooled under argon flow. Silica gel chromatography (sgc) was performed on Scientific Absorbence Silica gel 60 (mesh 230-400) or Natland International Corporation Silica gel (200-400 mesh). Thin layer chromatography (tlc) was performed using polyester backed silica gel plates purchased from Aldrich Chemical Company with a thickness of 250 μm, particle size 5 to 17 μm, pore size 60 Å and fluorescent indicator. Preparative tlc plates were purchased from Aldrich Chemical Company containing 1000 μm thickness and a fluorescent indicator. The solvent systems used for purification and development were mixtures of hexanes (H) and ethyl acetate (EA). UV-Vis spectra were obtained on a SHIMADZU UV-2101PC and are reported in nm. Infrared spectra were obtained on a Perkin-Elmer 1320 spectrophotometer and are reported in cm^{-1}. Proton nuclear magnetic resonance spectra (300Hz or 400Hz) were obtained using a Varian 300 or 400 Spectrometer. All chemical shifts are reported in δ relative to $CDCl_3$ (7.26 ppm) as an internal standard. Splitting patterns are denoted as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), and m (multiplet); the use of b means a broadened pattern. Carbon-13 spectra (75.46 Hz) were obtained on a Varian 300 or 400 Spectrometer. All chemical shifts are reported in δ relative to $CDCl_3$ (77.00 ppm) as the internal standard. Low resolution mass spectra (MS) were obtained on a Finnigan TSQ700 mass spectrometer. High resolution mass spectra (HRMS) were obtained on a Kratos model MS-50 spectrometer.

4,4-Diethoxy-2-(3-methoxyphenyl)butanenitrile (65): To a 1000 mL round bottom flask containing 600 mL of dry THF at 0°C was added 18.74 g (185.19 mmol)

diisopropylamine and 74.00 mL (185.19 mmol) of a 2.5 M solution of *n*-butyl lithium in hexane. The solution was stirred for 30 minutes at which time the solution was cooled to -78°C. At -78°C, 25 g (169.86 mmol) of 3-methoxyphenylacetonitrile was added dropwise. After 30 minutes 36.82 g (186.82 mmol) of bromoacetaldehyde diethyl acetal was added dropwise. The solution was allowed to warm to room temperature and stirred for an additional 24 hours. The solution was quenched with saturated ammonium chloride and extracted three times with diethyl ether. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo leaving crude **65**, which was purified by Kugelrohr distillation to afford 42.22 g (95%) of purified **65** as a clear colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.18-1.25 (m, 6H), 2.05-2.27 (m, 2H), 3.45-3.75 (m, 4H), 3.80 (s, 3H), 3.88-3.94 (m, 1H), 4.56-4.60 (m, 1H), 6.84-6.92 (m, 3H), 7.28 (t, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 15.4, 33.3, 39.6, 55.4, 62.1, 62.6, 100.2, 113.1, 113.7, 119.6, 120.6, 130.3, 137.0, 160.2. IR (neat) 3055, 2975, 2879, 2240, 1602, 1587 cm^{-1}. MS (CI, m/z) 263 (M+), 217, 172. HRMS (EI) m/z calculated for $C_{15}H_{21}O_3N$: 263.1521, found 263.1523.

Methyl 4-cyano-6,6-diethoxy-4-(3-methoxyphenyl)hexanoate (66): To a 500 mL round bottom flask containing 250 mL of dry THF at 0°C was added 7.03 g (71.97 mmol) of diisopropylamine and 28.79 mL (71.97 mmol) of a 2.5 M solution of *n*-butyl lithium in hexane. The solution was stirred for 30 minutes at which time the solution was cooled to -78°C. At -78°C, 18.93 g (71.97 mmol) of **65** was added dropwise. After 30 minutes, 12.02 g (71.97 mmol) of methyl-3-bromopropionate was added dropwise at -78°C and continued stirring under the same conditions for 30 more minutes. The solution was quenched with saturated ammonium chloride and allowed to warm to room temperature. The solution was extracted with diethyl ether three times and the organic layers were combined and dried over anhydrous magnesium sulfate. The mixture was concentrated in vacuo affording 20.09 g (80% yield) of **66** after sgc (4:1 H:EA) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 1.90-2.39 (m, 6H), 3.17-3.55 (m, 4H), 3.43 (s, 3H), 3.66 (s, 3H), 4.20-4.23 (m, 1H), 6.67-6.70 (m, 1H), 6.84-6.88 (m, 2H), 7.16 (t, J = 8.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 14.8, 29.5, 35.8, 43.9, 44.2, 51.3, 54.9, 61.1, 62.1, 76.8, 77.2, 77.7,

99.9, 112.1, 112.7, 117.8, 120.9, 129.9, 138.4, 159.8, 172.2. IR (neat) 3055, 2975, 2899, 2238, 1739, 1602, 1584 cm^{-1}. MS (CI, m/z) 349 (M+), 304. HRMS (EI) m/z calculated for $C_{19}H_{27}O_5N$: 349.1889, found 349.1891.

4-Cyano-6,6-diethoxy-4-(3-methoxyphenyl)hexanoic acid (67): To a 1000 mL round bottom flask containing 248 mL of methanol at room temperature was added 25.12 g (71.97 mmol) of **66** and 4.53 g (107.99 mmol) of lithium hydroxide dissolved in water. The solution was allowed to stir overnight at which time the reaction was diluted with water. Methylene chloride was added to the mixture and the mixture was acidified with 10% HCl. The layers were separated and the aqueous layer was extracted two more times with methylene chloride. The organic layers were combined, washed with brine, and dried with anhydrous magnesium sulfate. The solution was concentrated in vacuo to afford 16.88 g (70%) of **67** as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 7.2 Hz, 3H), 2.00 (t, J = 6.9 Hz, 3H), 2.08-2.52 (m, 6H), 3.30-3.70 (m, 4H), 3.81 (s, 1H), 4.35-4.39 (m, 1H), 6.82-6.86 (m, 1H), 6.94-7.00 (m, 2H), 7.30 (t, J = 7.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 15.1, 15.2, 29.9, 35.9, 44.3, 44.5, 55.5, 61.6, 62.7, 67.8, 77.2, 77.6, 100.3, 112.4, 113.3, 118.2, 121.2, 130.4, 138.6, 160.2, 177.9. Anal. Calcd. for $C_{18}H_{25}O_5N$: C 64.46, H 7.51, N 4.18. Found: C 64.50, H 7.76, N 4.15.

6,6-Diethoxy-4-(3-methoxyphenyl)hexanoic acid (68): In a 500 mL 3-neck round bottom flask 300 mL of anhydrous ammonia was collected at -33°C. To the liquid ammonia 8.45 g (367.73 mmol) of sodium metal was added slowly. To the solution was added 24.57 g (73.35 mmol) of **67** dropwise and stirred at -33°C for 10 minutes, at which time the solution was poured onto ice-cold diethyl ether and quenched with ice. Removal of the remaining ammonia through an argon flow, addition of methylene chloride, acidification with 10% HCl, extraction with methylene chloride, extraction of the aqueous layer two more times with methylene chloride, drying over anhydrous magnesium sulfate, filtration and concentration in vacuo afforded 19.33 g (85%) of **68** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.6 Hz, 3H), 1.86-2.18 (m, 6H), 2.61-2.80 (m, 1H), 3.36-3.51 (m, 4H), 3.79

(s, 3H), 4.18-4.22 (m, 1H), 6.69-6.76 (m, 3H), 7.23 (t, J = 7.2 Hz, 1H). IR (neat) 3434, 3042, 2974, 2885, 1758, 1616, 1455 cm^{-1}. MS (CI, m/z) (M+), 310, 252, 220.

6,6-Diethoxy-4-(5-methoxy-1,4-cyclohexadienyl)hexanoic acid (69): In a 500 mL 3-neck round bottom flask equipped with a Dewer condenser 13.44 g (43.36 mmol) of **68** was dissolved in 10 equivalents of ethanol. Collection of 175 mL of anhydrous ammonia at -33°C followed by piece-by-piece addition of 2.12 g (304.80 mmol) of lithium metal produced a dark blue colored solution. Stirring at -33°C for 2 hours produced the disappearance of the blue color. The reaction flask was warmed to room temperature, flushed with argon to remove ammonia, and cooled to 0°C while being dissolved in a 3:1 mixture of methanol and water. The solution was acidified with saturated oxalic acid and extracted three times with methylene chloride. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and solvent removed in vacuo to afford crude **69**, which was taken on to **70** without purification.

6,6-Diethoxy-4-(3-oxocyclohex-1(6)-enyl)hexanoic acid (70): In a 250 mL round bottom flask 5.72 g (28.33 mmol) of **69** was dissolved in 120 mL of a 3:1 mixture of methanol and water. Saturated oxalic acid was added until the solution tested red on litmus paper. Once acidic, the solution was stirred for 1.5 hours and extracted three times with methylene chloride. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford crude **70**, which was taken on to **71** without purification.

Methyl 6,6-diethoxy-4-(3-cyclohex-1(6)-enyl)hexanoate (71): In a 50 mL round bottom flask 3.00 g (10.07 mmol) of **70** was dissolved in diethyl ether. Using caution, diazomethane/ether solution was added until a yellow color persisted. The solution was stirred at room temperature for 25 minutes or until evolution of nitrogen gas ceased. The solution was flushed with a stream of argon for 1 hour and the solvent removed in vacuo to afford crude **71**. Purification by sgc (4:1 H:EA) afforded **71** in 60% yield from **68**. ^1H NMR ($CDCl_3$) δ 1.15-1.21 (m, 6H), 1.57-1.80 (m, 4H), 2.23 (t, J = 8.1 Hz, 1H), 2.44 (s, 4H), 2.75

(s, 2H), 3.41-3.63 (m, 4H), 3.67 (s, 3H), 4.42 (t, J = 5.1 Hz, 1H), 5.70 (s, 1H). IR (neat) 3009, 2952, 2859, 1738. MS (CI, m/z) 312 (M+), 283, 254.

Methyl 6,6-diethoxy-4-(7-oxa-3-oxobicyclo[4.1.0]hept-1-yl)hexanoate (72): In a 50 mL round bottom flask 0.88 g (2.83 mmol) of **71** was dissolved in 27 mL of dry methylene chloride. The flask was cooled to 0°C at which time 0.79 g (3.12 mmol) of 68% pure *m*-CPBA was added. The mixture was stirred at 0°C under argon atmosphere for 2.5 hours. The mixture was washed with saturated sodium bicarbonate three times to neutralize the acid and extracted with methylene chloride. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford crude **72** as a white solid which was taken to **73** without purification.

Methyl 6,6-diethoxy-4-(6-hydroxy-3-oxocyclohex-1-enyl)hexanoate (73): In a 50 mL round bottom flask 0.92 g (2.82 mmol) of crude **72** was dissolved in 27 mL of dry methylene chloride. To the solution 1.09 g (10.78 mmol) of triethylamine was added at room temperature under argon atmosphere. The reaction was allowed to react for 1 hour, washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford crude **73**, which was taken to **74** without purification.

Methyl 6,6-diethoxy-4-[3-oxo-6-*tert*-butyldimethylsilyloxy-cyclohex-1-enyl]hexanoate (74): In a 25 mL round bottom flask 0.92 g (2.82 mmol) of crude **73** was dissolved in 11 mL of dry acetonitrile. To the solution 1.62 g (10.77 mmol) of TBSCl and 0.73 g (10.78 mmol) of imidazole was added. The reaction mixture was stirred overnight at room temperature under argon atmosphere. The mixture was washed three times with 20 mL portions of water, extracted, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by sgc (4:1 H:EA) to afford 0.83 g (67% yield from **71**) of **74**. ^{1}H NMR ($CDCl_3$) δ 0.084 (s, 6H), 0.087 (s, 9H), 1.18 (t, J = 8.1 Hz, 6H), 1.30 (s, 2H), 1.48-2.49 (m, 9H), 3.33-6.65 (m, 4H), 3.64 (s, 3H), 4.12 (bs, 1H), 4.45-4.47 (m, 1H), 5.34 (s, 1H). IR (neat) 3006, 2985, 2867, 1738, 1715, 1668. MS (CI, m/z) 430 (M+), 401, 372.

Methyl 6,6-diethoxy-4-[3-hydroxy-6-(*tert*-butyldimethylsilyloxy)-cyclohexyl]hexanoate (75): In a Parr Instruments hydrogen apparatus capable of sustaining 1800 psi was added 0.80 g (1.81 mmol) of **74**, followed by 10 mL of dry ethanol and 0.05 equivalents of platinum (IV) oxide. The hydrogenation apparatus was flushed with hydrogen, sealed and purged with 1800 psi. The solution was stirred 47 hours after which time the solution was carefully filtered through a bed of Celite and dried with anhydrous magnesium sulfate. Removal of the solvent in vacuo left crude **75** in 95% yield which was taken to **76** without further purification.

Methyl 6,6-diethoxy-4-[3-oxo-6-(*tert*-butyldimethylsilyloxy)-cyclohexyl]hexanoate (76): In a 100 mL round bottom flask was dissolved 0.8062 g (1.8077 mmol) of **75** in 20 mL of dry methylene chloride. Then of 2.92 g (7.76 mmol) of pyridinium dichromate and 2.9203 g of silica gel were added to the flask. It was stirred at room temperature for 22 hours after which time the solution was filtered through a bed of Celite while rinsing with ether. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by sgc (4:1 H:EA) afforded 0.6085 g (75% yield from **74**) of **76** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.01-0.03 (m, 6H), 0.81 (s, 9H), 1.06 (t, J = 9 Hz, 6H), 1.26-2.54 (m, 14H), 3.25-3.57 (m, 4H), 3.55 (s, 3H), 4.20 (bs, 1H), 4.45-4.50 (m, 1H). IR (neat) 2972, 2936, 2858, 1738, 1713, 1676.

Methyl 6-oxo-4-[3-oxo-6-(*tert*-butyldimethylsilyloxy)-cyclohexyl]hexanoate (77): To a 30 mL Nalgene beaker containing 10 mL acetonitrile:aqueous HF (85%:15%) mixture was added 0.088 g (0.20 mmol) of **76** dropwise. The solution was stirred for 1 hour at room temperature. After 1 hour, the solution was quenched with saturated sodium bicarbonate and extracted with methylene chloride. The organic layers dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by sgc (4:1 H:EA) afforded 0.038 g (52% yield) of **77** as a clear colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 1.44-2.61 (m, 14H), 3.58 (s, 3H), 4.06 (s, 1H), 9.70 (t, J = 3.1 Hz, 1H). Compound **77** was also obtained by dissolving 0.29 g (0.57 mmol) of **80** in 5 mL of dry methylene

chloride. The flask was cooled to -78°C under argon. To the flask was added 0.013 g (10 mol %) of TMSOTf at -78°C and continued stirring for 7.5 hours. After 7.5 hours the solution was neutralized with saturated sodium bicarbonate at -78°C, extracted with CH_2CH_2 and washed with brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford the undesired product **77**.

Methyl 6,6-diethoxy-4-(2-hydroxy-5-oxocyclohexyl)-hexanoate (79): To a 25 mL round bottom flask containing 6.60 mL of dry THF was added 0.078 g (0.18 mmol) of **76** dropwise. The system was cooled to 0°C at which time 0.20mL (0.20 mmol) of a 0.1M solution of *tetra*-butylammonium fluoride in THF was added. The reaction mixture was stirred until room temperature was attained. Once at room temperature the solution was neutralized with saturated ammonium chloride and extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford 0.0410 g (71%) of crude **79**. Crude **79** was taken onto the next step without purification.

Methyl 4-[6-*tert*-butyldimethylsilyloxy)-3-(trimethylsilyloxy)-cyclohex-2-enyl]-6,6-diethoxyhexanoate (80): In a 25 mL round bottom flask containing 10 mL of dry ether was added 0.25 g (0.57 mmol) of **76** and 0.069 g (0.69 mmol) of triethylamine. The solution was cooled to 0°C at which time 0.14 g (0.63 mmol) of TMSOTf was added. After stirring at 0°C for 5 min, the solution was warmed to room temperature for 1 hour. After 1 hour the solution was diluted with hexane and the liquid decanted off. The solvent was removed in vacuo giving crude **80** which was taken onto the next step without purification.

Triethyl-2-phosphonopentan-5-al (84): To a 500 mL round bottom flask containing 344 mL of a 3:1 mixture of dioxane:water was added 3.69 g (14.24 mmol) of **82**. To the solution was added 0.018 g (0.071 mmol) of osmium tetraoxide (osmium tetraoxide in *t*-butanol 5mg / 1ml) dropwise and stirred 10 minutes. After 10 minutes time 7.62g (35.61 mmol) of powdered sodium periodate was added. It was stirred at room temperature for 20 hours. The mixture was diluted with 500 mL of ethyl acetate, filtered, and washed with 20

mL of water followed by two ethyl acetate washings. The filtrate was transferred to a separatory funnel and water was removed. The organic layer was washed with brine, dried with sodium sulfate, filtered and concentrated in vacuo. Purification of the residue by sgc (1:2 H:EA) afforded **84** in 70% yield as a clear, tint of yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.23-1.34 (m, 9H), 2.16-2.29 (m, 2H), 2.47-2.69 (m, 2H), 2.93-3.06 (m, 1H), 4.10-4.30 (m, 6H), 9.74 (s, 1H). . ^{13}C NMR ($CDCl_3$) δ 14.3, 16.4, 19.6, 41.8, 43.6, 45.3, 61.6, 62.8, 168.8, 200.6. IR (neat) 2983, 2729, 1738, 1727, 1254. MS (EI, m/z) 280 (M-), 260, 246, 235, 224, 205, 197, 179. HRMS (EI) m/z calculated $C_{11}H_{21}O_6P$: 280.1076, found 280.1080

Ethyl 2-(diethoxyphosphoryl)-5-hydroxy-7-oxo-octanoate (86): To a 25 mL round bottom flask containing 4.7 mL dry THF at 0°C was added 0.12 g (1.18 mmol) diisopropylamine and 0.075 g (1.18 mmol) of 2.5M n-butyl lithium solution in hexane. The solution was stirred for 30 minutes at which time the solution was cooled to -78°C. At -78°C, 0.065g (1.12 mmol) of **85** in THF was added dropwise. After 30 minutes 0.31 g (1.12 mmol) of **84** in THF was added dropwise at -78°C. It was stirred at –78°C for 30 minutes. The solution was quenched with acetic acid/THF mixture at -78°C until neutral. Once neutral, 10 mL of brine was added and the mixture was extracted with ethyl acetate. The aqueous layer was extracted two more times with ethyl acetate and all the organic layers combined. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. Purification of the residue by sgc (1:1 H:EA) afforded 0.1995g (52%) of **86** as a clear colorless liquid. ^{1}H NMR ($CDCl_3$) δ 1.25-1.35 (m, 9H), 1.45-1.55 (m, 2H), 1.85-2.10 (m, 2H), 2.17 (s, 3H), 2.48-2.60 (m, 2H), 2.91-3.04 (m, 1H), 3.11 (bs, 1H), 3.89-4.07 (m, 1H), 4.12-4.25 (m, 6H). MS (CI, m/z) 338 (M+), 321, 310, 293.

Ethyl 5-acetoxy-2-(diethoxyphosphoryl)-7-oxo-octanoate (87): To a 10 mL round bottom flask containing 3 mL of dry methylene chloride was added 0.081 g (0.24 mmol) of **86**, 0.038 g (0.48 mmol) of pyridine and 0.0083 g (0.067 mmol) of powdered 4-(dimethylamino)pyridine. The solution was stirred 5 minutes under argon at room temperature after which time 0.049 g (0.48 mmol) acetic anhydride was added dropwise. It was stirred 2 hours. The reaction was quenched with 10 mL of water and extracted with

methylene chloride. The organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by sgc (1:1 H:EA) to afford **87** in quantitative yield as a clear colorless liquid. ^{1}H NMR ($CDCl_3$) δ 1.25-1.39 (m, 9H), 1.61-1.69 (m, 2H), 1.80-2.00 (m, 2H), 2.02 (s, 3H), 2.15 (s, 3H), 2.56-2.64 (m, 2H), 2.71-3.00 (m, 2H), 4.11-4.18 (m, 6H), 5.17-5.30 (m, 1H). MS (EI, m/z) 380 (M-) 381, 337, 321, 295, 278, 237, 224.

Ethyl 4-acteoxy-2-methylcylcohex-1-enecarboxylate (88): A 60% dispersion of NaH in mineral oil (0.015 g, 0.38 mmol) was washed with pentane and suspended in dry THF (5mL/mmol) under an argon atmosphere. A 0.1M solution of **87** (0.064 g, 0.17 mmol) in THF was added dropwise at room temperature. The mixture was stirred at room temperature for 5 hours, quenched with saturated ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by sgc (2:1 H:EA) to afford **88** in 37% yield. ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 1.69-1.89 (m, 2H), 1.99 (s, 3H), 2.04 (s, 3H), 2.16-2.52 (m, 4H), 4.19 (q, J = 7.2 Hz, 2H), 4.95-5.03 (m, 1H). ^{13}C NMR δ 14.3, 21.4, 21.6, 23.7, 26.8, 38.5, 60.1, 68.8, 123.9, 142.4, 168.3, 170.7. UV 209 nm.

Ethyl 4-hydroxy-2-methylcyclohexenecarboxylate (89): Compound **89** was obtained in 16% yield using the above procedure for **88**. ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 5.4 Hz, 3H), 1.60-1.67 (m, 1H), 1.83-1.88 (m, 1H), 2.00 (s, 3H), 2.15 (dd, J = 13.5 Hz, J = 5.1 Hz, 1H), 2.28-2.55 (m, 3H), 3.98 (bs, 1H), 4.19 (q, J = 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 24.6, 30.9, 42.6, 60.4, 66.6, 124.1, 143.4, 169.0. MS (EI, m/z) 184 (M-), 166, 138, 121, 88, 84, 51, 49. HRMS (EI) m/z calculated for $C_{10}H_{16}O_3$: 184.1099, found 184.1102.

Ethyl 5-(2-allyl-1-methyl-5-oxocyclopentyl)-2-diethoxyphosphoryl-5-hydroxypentanoate (92): To a 25 mL round bottom flask containing 10 mL of dry THF was added 1.5 g (4.50 mmol) of allyltributyl tin and 1.99 mL (4.98 mmol) of a 2.5M n-butyl lithium in hexane. The solution was stirred at room temperature for 1 hour. To a separate 100 mL round bottom flask containing 18 mL of dry THF was added 0.47 g (2.28 mmol) of

copper (I) bromide-dimethyl sulfide complex and the flask was cooled -78°C under argon atmosphere. To the copper solution was added allyl lithium dropwise via a syringe. It was stirred 30 minutes at -78°C. After 30 minutes 0.21 g (2.21 mmol) of 2-methyl-2-cylcopentenone **91** was added dropwise. Stirring at -78°C for 40 more minutes generated the lithium enolate of 3-allyl-2-methylcylcopentanone, which was trapped by dropwise addition of 0.63 g (2.21 mmol) of **84** over a 5-minute period. After 30 minutes of stirring at -78°C the reaction mixture was neutralized with an acetic acid/THF (1:3) mixture at -78°C. Brine was added to separate the two layers and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford crude **92**. Purification by sgc (1:1 H:EA) afforded **92** as a diastereomeric mixture in 78% yield. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3H), 1.23-1.36 (m, 9H), 1.49-2.40 (m, 12H), 2.92-3.04 (m, 1H), 3.51-3.60 (m, 1H), 4.10-4.25 (m, 6H), 5.02-5.10 (m, 2H), 5.75-5.86 (m, 1H). MS (EI, m/z) 418 (M-), 400, 358, 322, 281, 235, 207. HRMS (EI) m/z calculated for $C_{20}H_{35}O_7P$: 418.2120, found 418.2127.

Ethyl 5-acetoxy-5-(2-allyl-1-methyl-5-oxocyclopentyl)-2-(diethoxyphosphoryl)-pentanoate (93): To a 25 mL round bottom flask containing 5 mL of dry methylene chloride was added 0.17 g (0.42 mmol) of **92**, 0.066 g (0.83 mmol) of pyridine and 0.051 g (0.41 mmol) of 4-dimethylaminopyridine. The solution was stirred 5 minutes under argon at room temperature at which time 0.085 g (0.83 mmol) of acetic anhydride was added and stirring was continued for 2 hours. The solution was quenched with 20 mL of water and extracted with 20 mL of methylene chloride. The organic layer was dried with sodium sulfate, filtered and concentrated in vacuo. Purification by sgc (2:1 H:EA) afforded the diastereomeric mixture **93** in quantitative yield. ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H), 1.26-1.36 (m, 9H), 1.55-2.41 (m, 14H), 2.87-3.03 (m, 1H), 4.10-4.23 (m, 6H), 4.85-4.95 (m, 1H), 5.04-5.10 (m, 2H), 5.65-5.84 (m, 1H). IR (neat) 3066, 2968, 2859, 1746, 1724, 1632, 1366, 1225, 1024. MS (EI, m/z) 460 (M-), 415, 400, 359, 313, 281. HRMS (EI) m/z calculated for $C_{22}H_{37}O_8P$: 460.2226, found 460.2235.

Ethyl 7-acetoxy-1-allyl-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-indene-4-carboxylate (94): To a 50 mL round bottom flask was added 4.78 mL (23.91 mmol) of a 0.5M potassium bis(trimethylsilyl) amide solution in toluene, followed by addition of 10 mL of dry THF. To the solution was added 0.55 g (11.96 mmol) of **93** dropwise at room temperature. The solution was stirred at room temperature for 5 hours, neutralized with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried, over sodium sulfate, filtered and concentrated in vacuo. Purification of the residue by sgc (3:1 H:EA) afforded 0.1552 g (42%) of mixture **94**. ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 1H), 1.25-1.32 (m, 4H), 1.41-1.47 (m, 1H), 1.80-1.99 (m, 4H), 2.02 (s, 3H), 2.12-2.23 (m, 1H), 2.26-2.35 (m, 2H), 2.71-2.84 (m, 2H), 4.09-4.24 (m, 2H), 4.92-5.07 (m, 3H), 5.65-5.76 (m, 1H). IR (neat) 3071, 2967, 1734, 1708, 1645, 1364, 1244, 1036. MS (EI, m/z) 306 (M-) 281, 260, 246, 205. HRMS (EI) m/z calculated for $C_{18}H_{26}O_4$: 306.1831, found 306.1836.

Ethyl 7-acetoxy-1-(3-hydroxy-3-oxopropyl)-methyl-2,3,5,6,7,7a-hexahydro-1H-indene-4-carboxylate (95): To a 50 mL conical vial was added 0.40 g (0.13 mmol) of a 0.1M solution of **94**. The vial was sealed with a septum and flushed with argon. To the solution was added 0.13 mL (0.13 mmol) of a 1M dibromoborane-methylsulfide complex in methylene chloride. The septum was removed and immediately replaced with a water condenser while flushing with argon. The solution was heated to reflux 3 hours at which time the heat source was removed. The vial was allowed to cool to room temperature then cooled to 0°C. To the borane complex was added 0.75 mL (1:2) water:ether mixture dropwise at 0°C and stirring was continued for 20 minutes. The solution was quenched with 10 mL of cold water and extracted with 20 mL of ether. The aqueous layer was extracted two more times with 10 mL portions of ether and the organic layers combined. The organic layer washed with brine (3 x 4 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to afford a boronic acid compound. The boronic acid compound was then dissolved in 0.50 mL of dry methylene chloride. In a 5 mL conical vial a chromium (VI) oxide solution was prepared by adding 0.0791 g (6.05 mmol) of chromium (VI) oxide and 0.90 mL (9:1) acetic acid:water mixture. The chromium solution was flushed with argon and stirred 5 minutes. After 5 minutes of stirring the prepared boronic acid was added

dropwise to the chromium (VI) oxide solution and stirred for 12.5 hours at room temperature. The solution was diluted with 10 mL of water and extracted with two 20 mL portions of methylene chloride. The organic layers were combined, washed with brine and neutralized with saturated sodium bicarbonate. The aqueous layer was acidified with concentrated HCl until acidic (monitored by pH paper; violent bubbling will occur). The solution was extracted with methylene chloride (3 x 40 mL), dried over sodium sulfate, filtered and concentrated in vacuo to afford crude **95**. Crude **95** was taken onto the methylation step without purification.

Ethyl 7-acetoxy-1-(3-methoxy-3-oxopropyl)-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-indene-4-carboxylate (96): In a 25 mL round bottom flask containing 3 mL of ether was added 0.044 g (0.13 mmol) of **95**. Using caution, diazomethane:ether was added until a yellow color persisted. The solution was stirred at room temperature for 25 minutes after which time the system was flushed with argon to remove unreacted diazomethane. The residue was concentrated in vacuo and purified by sgc (4:1 H:EA) to afford 0.011 g of **96** in 24% yield from **94**. ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H), 1.24-1.32 (m, 4H), 1.36-1.53 (m, 2H), 1.72-2.00 (m, 5H), 2.03 (s, 3H), 2.26-2.36 (m, 3H), 2.76-2.79 (m, 2H), 3.65 (s, 3H), 4.10-4.26 (m, 2H), 5.05 (dt, J = 3 Hz, J = 0.6 Hz, 1H). MS (EI, m/z) 352 (M-), 308, 292, 279, 246, 231. HRMS (EI) m/z calculated for $C_{19}H_{28}O_6$: 352.1886, found 352. 1891.

7-Hydroxy-1-(3-hydroxy-3-oxopropyl)-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-indene-4-carboxylic acid (97): To a 10 mL round bottom flask containing 2 mL of methanol was added 0.011 g (0.031 mmol) of **96** and 0.0083 g (0.20 mmol) of lithium hydroxide dissolved in water. The solution was boiled for 17.5 hours at which time the flask was allowed to cool to room temperature. The solution was neutralized with acetic acid and concentrated in vacuo.

For compounds **98**, **99**, **100**, **101**, and **103** procedures used in the synthesis of **88** and **97** were used.

Ethyl 4-acetoxy-2,3,4,4a,5,6,7,8-octahydronaphthalene-1-carboxylate (98): ^{1}H NMR ($CDCl_3$) δ (1.25-1.45 (m, 4H), 1.64-1.72 (m, 1H), 1.74-1.89 (m, 6H), 2.97 (s, 3H), 2.25-2.25 (m, 4H), 3.25-3.30 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.98-5.50 (m, 1H). MS (EI, m/z) 266 (M-), 221, 206, 177, 160, 133, 91. (80% yield).

Ethyl 7-acetoxy-2,3,5,6,7,7a-hexahydro-1H-indene-4-carboxylate (99): ^{1}H NMR ($CDCl_3$) δ 1.25-1.33 (m, 4H), 1.45-1.91 (m, 4H), 2.04 (s, 3H), 2.06-2.83 (m, 6H), 4.12-4.25 (m, 2H), 5.30 (bs, 1H). MS (EI, m/z) 252 (M-), 206, 192, 163. (81% yield).

Ethyl 4-acetoxy-2-isopropylcyclohex-1-enecarboxylate (100): ^{1}H NMR ($CDCl_3$) δ 0.97 –1.01 (t, J = 5.4 Hz, 3H), 1.25-1.32 (m, 6H), 1.67-1.91 (m, 3H), 2.05 (s, 3H), 2.36-2.50 (m, 3H), 3.21-3.30 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.94-4.99 (m, 1H). MS (EI, m/z) 254 (M-), 208, 194, 179, 166, 149, 120. HRMS (EI) m/z calculated for $C_{14}H_{22}O_4$: 254.1518, found 254.1523. (20% yield).

Ethyl 4-acetoxy-2-ethyl-3-methylcyclohex-1-enecarboxylate (101): ^{1}H NMR ($CDCl_3$) δ 0.99-1.12 (m, 6H), 1.23-1.33 (m, 3H), 1.78-1.84 (m, 2H), 2.04 (s, 3H), 2.30-2.35 (m, 3H) 2.52-2.73 (m, 2H), 4.15-4.23 (m, 2H), 4.82-4.85 (m, 1H). MS (EI, m/z) 254 (M-) 208, 194, 179, 169, 121, 93, 43. (79% yield).

Ethyl 4-acetoxycyclohex-1-enecarboxylate (102): To a 50 mL round flask containing 9 mL of dry methylene chloride was added 0.096 g (0.26 mmol) of **105**. The solution was cooled to -78°C and ozone was added (mmol/min) for 40 minutes to insure the ozonide formation. After 40 minutes, the solution was flushed with argon for 30 minutes. The solvent was removed in vacuo to afford the crude ozonide. The crude mixture was dissolved in 5 mL of methylene chloride. To the solution was added 0.070 (0.27 mmol) of triphenylphosphine. After 30 minutes the solvent was removed under reduced pressure to afford crude phosphonate aldehyde, which was taken on to the next step without purification. To a 25 mL round bottom flask containing 6 mL of dry THF was added a crude phosphonate aldehyde solution in 3 mL of THF. The solution was stirred for 5 hours. After 5 hours the

solution was neutralized with saturated ammonium chloride and extracted with ethyl acetate. The aqueous layer was extracted two times with ethyl acetate. The organic layers combined, dried over sodium sulfate, filtered and concentrated in vacuo. Purification by preparative tlc (2:1 H:EA) afforded **102** in 12% yield from **104** as a clear, yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.27-1.32 (t, J = 7.2 Hz, 3H), 1.81-1.88 (m, 2H), 2.04 (2, 3H), 2.24-2.59 (m, 4H), 4.20 (q, J = 7.2 Hz, 2H), 5.02-5.05 (m, 1H), 6.85 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.25, 21.30, 21.59, 26.60, 31.09, 60.44, 68.20, 130.22, 135.49, 166.82, 170.65. MS (EI, m/z) 212 (M-), 183, 153, 107, 77. HRMS (EI) m/z calculated for $C_{11}H_{16}O_4$: 212.1049, found 212.1052.

Ethyl-4-acetoxy-2,3,3-trimethylcyclohex-1-enecarboxylate (103): ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J = 1.5 Hz, 6H), 1.29 (t, J = 7.2 Hz, 3H), 1.74-1.87 (m, 2H), 1.90 (t, J = 2.1 Hz, 3H), 2.06 (s, 3H), 2.32-2.40 (m, 2H), 4.18 (q, J = 7.2 Hz, 2H), 4.78 (dd, J = 7.8 Hz, J = 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.8, 15.8, 21.2, 21.7, 22.9, 24.2, 25.5, 39.3, 60.2, 76.8, 124.4, 146.7, 169.5, 170.8. MS (EI, m/z) 254 (M-), 209, 194, 179, 151, 121. HRMS (EI) m/z calculated for $C_{14}H_{22}O_4$: 254.1518, found 254.1523. (37% yield).

Ethyl-2-(diethoxyphosphoryl)-5-hydroxyoct-7-enoate (104): To a 10 mL round bottom flask containing 2.5 mL of dry methylene chloride was added 0.20 g (0.71 mmol) of **84**. The solution cooled to -78°C at which time 0.17 g (1.12 mmol) boron trifluoride was added and stirred 10 minutes. After 10 minutes, 0.24 g (0.71 mmol) allyltributyl tin was added dropwise. After 3.5 hours at -78°C the reaction was allowed to warm to room temperature. The solution was neutralized with saturated sodium bicarbonate and extracted with methylene chloride two times. The organic layers were combined, dried over sodium sulfate, filtered and concentrated in vacuo. Purification by sgc (1:1 H:EA) afforded 0.19 g (83%) of **104**. ^{1}H NMR ($CDCl_3$) δ 1.24-1.36 (m, 9H), 1.45-1.57 (m, 2H), 1.76 (bs, 1H), 1.95-2.31 (m, 4H), 2.91-3.04 (m, 1H), 3.61-3.67 (m, 1H) 4.10-4.25 (m, 6H), 5.10-5.15 (m, 2H), 5.73-5.87 (m, 1H). MS (EI, m/z) 322 (M-), 305, 281, 235, 207, 179. HRMS (EI) m/z calculated for $C_{14}H_{27}O_6P$: 322.1545, found 322.1550.

Ethyl-5-acetoxy-2-(diethoxyphosphoryl)-oct-7-enoate (105): To a 50 mL round bottom flask containing 6.70 mL of methylene chloride was added 0.18 g (0.57 mmol) of **104**, 0.090 g (1.14 mmol) of pyridine, and 0.070g (0.57 mmol) of 4-dimethylaminopyridine. The solution was stirred for 5 minutes and 0.12 g (1.14 mmol) of acetic anhydride was added. After 2 hours the solution was diluted with 20 mL of water and extracted with methylene chloride. The aqueous layer was extracted two times with methylene chloride. The organic layers combined, dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by sgc (2:1 H:EA) to afford 0.19 g (93%) of **105** as a clear liquid. ^{1}H NMR ($CDCl_3$) δ 1.26-1.36 (m, 9H), 1.55-1.65 (m, 3H), 1.81-2.03 (m, 1H), 2.04 (s, 3H), 2.30 (t, J = 6.9 Hz, 2H), 2.88-2.99 (m, 1H), 4.09-4.23 (m, 6H), 4.89-4.93 (m, 1H), 5.04-5.10 (m, 2H), 5.68-5.76 (m, 1H). MS (EI, m/z) 364 (M-) 322, 304, 281, 259, 179. HRMS (EI) m/z calculated for $C_{16}H_{29}O_7P$: 364.1651, found 364.1656.

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