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Synthesis of Resveratrol and Its Analogs, Phase-Transfer Catalyzed Asymmetric Glycolate Aldol Reaction, and Total Synthesis of 8,9-Methylamido-Geldanamycin

Jing Liu
Brigham Young University - Provo

SYNTHESIS OF RESVERATROL AND ITS ANALOGS, PHASE-TRANSFER CATALYZED ASYMMETRIC GLYCOLATE ALDOL REACTIONS, AND TOTAL SYNTHESIS OF 8,9-METHYLAMIDO-GELDANAMYCIN

by

Jing Liu

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GRADUATE COMMITTEE APPROVAL

of a thesis submitted by

Jing Liu

This thesis has been read by each member of the following graduate committee and by majority vote has been found to be satisfactory.

Date	Merritt B. Andrus, Chair
Date	Paul B. Savage
Date	Matt A. Peterson
Date	Young Wan Ham
Date	Roger G. Harrison

BRIGHAM YOUNG UNIVERSITY

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Date

Merritt B. Andrus
Chair, Graduate Committee

Accepted for the Department

David V. Dearden
Graduate Coordinator

Accepted for the College

Thomas W. Sederberg, Associate Dean
College of Physical and Mathematical Sciences

ABSTRACT

SYNTHESIS OF RESVERATROL AND ITS ANALOGS, PHASE-TRANSFER CATALYZED ASYMMETRIC GLYCOLATE ALDOL REACTIONS, AND TOTAL SYNTHESIS OF 8,9-METHYLAMIDO-GELDANAMYCIN

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Department of Chemistry and Biochemistry

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The phytoalexin resveratrol and its acetyl analogs have been made using a decarbonylative Heck reaction. The acid chloride derived from 3,5-dihydroxybenzoic acid was coupled with suitable protected 4-hydroxystyrene in the presence of palladium acetate and *N*,*N*-bis-(2,6-diisopropylphenyl)-4,5-dihydro imidazolium chloride to give the substituted stilbene in good yield as the key step. Human HL-60 cell assays showed the 4'-acetyl resveratrol variant improved activity (ED_{50} 17 μM) relative to resveratrol (24 μM).

Cinchona phase-transfer catalysts (PTC) were developed for glycolate aldol reactions to give differentially protected 1,2-diol products. Silyl enol ether of diphenylmethoxy-2,5-dimethoxyacetophenone reacted to generate benzhydryl-protected products. *O*-Allyl trifluorobenzyl cinchonium hydrodifluoride (20 mol %) catalyzed the addition of the silyl enol ether to benzaldehyde to give aldol product as a single *syn*-product in 76% yield and 80% ee. Recrystallization enriched the product to 95% ee, and a Baeyer-Villiger reaction transformed the product into useful ester intermediates.

A novel unnatural product, 8,9-Methylamido-Geldanamycin, has been designed and synthesized. Using a convergent route, the total synthesis of the molecule involved only 27 longest linear steps. New synthesis methodologies, including auxiliary controlled asymmetric *anti*-glycolate aldol, *syn*-norephedrine aldol, and selective *p*-quinone formation, were used.

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List of Abbreviations and Acronyms

Alloc	Allyloxycarbonyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bop-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BTPP	*tert*-Butylimino-tri(pyrrolidino)phosphorane
CAN	Ammonium cerium(IV) nitrate
CDI	1,1'-Carbonyldiimidazole
Cy	Cyclohexyl
DAIB	Diacetoxyiodobenzene
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	(*N*,*N'*-Dicyclohexylcarbodiimide)
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxyIate
DEPC	Diethyl cyanophosphonate
DHP	Dihydropyranyl
DIBAL-H	Diisobutylaluminum hydride
DIEA	*N*,*N*-Diisopropylethylamine; Hünig’s base
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide

DMP	Triacetoxyperiodinane; Dess-Martin periodinane
DPM	Diphenylmethyl
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
H_2IPr	*N*,*N*-Bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N'N'*-tetramethyluranium hexafluorophosphate
HOBt	1-Hydroxybenzotriazole
imid	Imidazole
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
Lev	Levulinyl
Meerwein salt	Trimethyloxonium tetrafluoroborate
Mes	Mesityl
MOM	Methoxymethyl
morph	Morpholine
Ms	Methanesulfonyl
NEM	*N*-Ethylmorpholine
NHMDS	Sodium bis(trimethylsilyl)amide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidinone
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate

PMB	*p*-Methoxybenzyl
Proton-sponge	*N*,*N*,*N'*,*N'*-Tetramethyl-1,8-naphthalenediamine
*p*TsOH	*p*-Toluenesulfonic acid
PyBrop	Bromo-tris-pyrrolidino phosphoniumhexafluorophosphate
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl free radical
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMG	*N*,*N*,*N'*,*N'*-Tetramethyl guanidine
TMS	Trimethylsilyl
tol	Toluene
TPAP	Tetrapropylammonium perruthenate
xyl	Xylene

Chapter 1. Synthesis of Resveratrol and Its Acetyl and Fluoro Analogs Using Decarbonylative Heck Reaction

1.1. Introduction

1.1.1. Discovery

Resveratrol (3,4',5-trihydroxystilbene) **1**, a naturally occurring phytoalexin, was first identified in 1940 as an off-white powder from the extractions of roots of white hellebore lily (*Veratrum grandiflorum* O. Loes).[1] Since that time, it has been detected in more than seventy plant species, including grapes, blueberries, cranberries, mulberries, peanuts, jackfruit, scots pine, corn lilies, etc. The richest natural source is the root of *Polygonum cuspidatum* and the extract of the root of *Polygonium cuspidatum* is the source of most of the marketed resveratrol-containing supplements in the U.S. Plants are induced to produce higher levels of the phytoalexin resveratrol under stress from injury, ultraviolet irradiation, or fungal infection as a defense mechanism.

The use of resveratrol to treat human disease can be tracked back to 600 B.C. Grapes are the principal ingredient of Darakchasava (fermented juice of red grapes), an ayurvedic herbal remedy, which is mainly used in ayurvedic medicine as a cardiotonic.[2] The dried root and stem of *Polygonium cuspidatum* is used in traditional Chinese and Japanese medicine as a circulatory tonic, among other things.[3] This traditional Chinese and Japanese remedy is also known as Hu Zhang and ko-jo-kon.

1.1.2. Biological Activity

Most diseases are caused by dysregulation of multiple genes instead of a single gene. Recent studies have shown that drugs targeted to a specific gene are not likely to cure a disease.[4] Resveratrol can modulate multiple cellular targets and thus it may prove suitable for the prevention and treatment of a wide variety of diseases.

Extensive research work has been carried out with resveratrol after it was discovered to be a causative agent of the "French paradox", the molecule most responsible for the Mediterranean diet effect where high fat intake coupled with moderate wine consumption leads to abnormally low rates of heart disease and cancer.[5] Growing evidence has demonstrated that resveratrol at reasonable dietary concentrations plays an important role in mitigating numerous and diverse human pathological processes including inflammation, atherosclerosis, and carcinogenesis. Specific properties of resveratrol include antioxidant; radical scavenging activity;[6] cyclooxygenase inhibition; lipid modification;[7] platelet aggregation inhibition and vasodilation;[8] inhibition of tumor initiation, promotion, and progression;[9] neuroprotection;[10] and antiviral activity.[11] While various biological targets have been implicated and identified, the mechanism of resveratrol's integrated effect on various cellular pathways remains unclear.[12] Many studies have shown its ability in modulation of gene expression, signal transduction, cell cycle progression, prostaglandin biosynthesis, and angiogenesis.

Recently, resveratrol has also been shown to extend the lifespan of yeast

Saccharomyces cerevisiae, worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, a short-lived fish *Nothobranchius furzeri*, and obese mice.[13] Lifespan extension is believed to arise through activation of sirtuin (SIRT-1, 2), an NAD dependent histone deacetylase that has been shown to directly correlate with cellular longevity. Another research study shows that mice fed resveratrol demonstrated enhanced treadmill endurance compared with controls. This study also supports the effects of resveratrol via activation of SIRT1.[14]

1.1.3. Synthesis of Resveratrol

Although resveratrol's natural sources are abundant, isolation from plant sources in pure form is not efficient, as reported from dried *Cassia q.* Rich (30 mg/kg)[9] or from dried grape skins (92 mg/kg).[15]

The first synthesis of resveratrol was reported by Takaoka using a Perkin condensation of sodium 3,5-dihydroxyphenylacetate **2** with 4-hydroxybenzaldehyde **3** in acetic anhydride (Figure 1.1).[16] The resulting 3,5,4'-triacetoxystillbene-α-carboxylic acid **4** was converted to triacetoxystillbene by decarboxylation and then to resveratrol **1** by hydrolysis. Unfortunately, no yield was reported for any step.

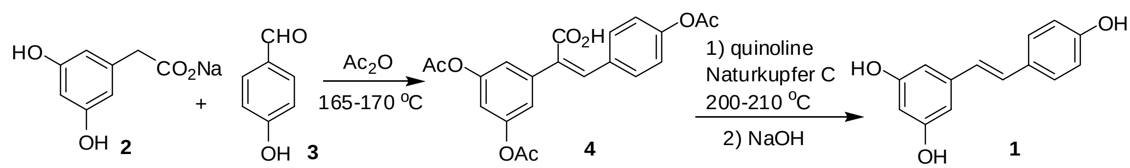


Figure 1.1 The first resveratrol synthesis using a Perkin condensation.

The majority of the recent published synthetic routes rely on Wittig and Horner–Emmons couplings that give mixtures of olefin isomers and require 7–8 steps. Most routes use methyl or benzyl ether protecting groups that require the use of boron tribromide or other inconvenient reagents for removal.[17] Recently, a palladium catalyzed isomerization of *cis*-alkenes to *trans*-alkenes was used to convert a mixture of *trans* and *cis* 3,5,4'-trimethoxystillbene **5** to the corresponding *trans* form **6** (Figure 1.2).[17a]

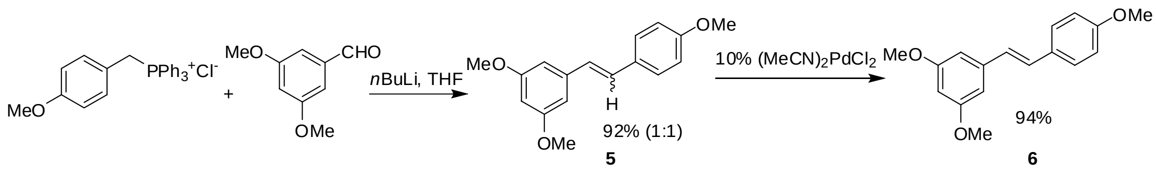


Figure 1.2 Resveratrol synthsis using a Wittig reaction.

A palladium catalyzed Heck reaction route has been reported that utilized a costly starting material, 3,5-dihydroxybenzaldehyde **7**, together with a Wittig reaction to form the styrene coupling partner **8** (Figure 1.3).[18] Heck coupling of this styrene with 4-iodophenylacetate **9** gave 3,5,4'-triacetoxystillbene **10**, which was converted to resveratrol **1** by treatment with sodium methoxide.

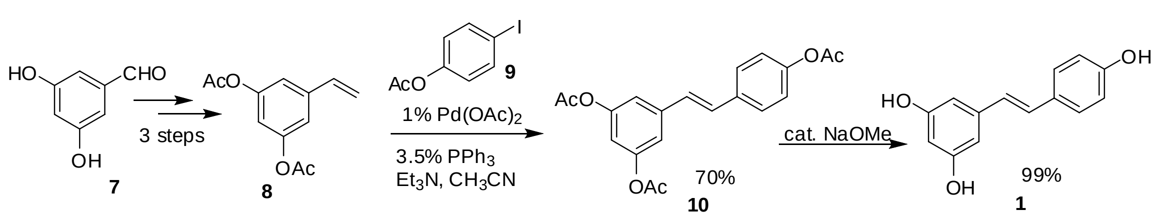


Figure 1.3 Resveratrol synthesis using a Heck reaction.

Recently, a vinylsilane Heck based coupling route using 4-methoxyiodobenzene has been reported that uses methyl ether protecting groups (Figure 1.4).[19] Arylation of vinyltrimethylsilane **12** with 4-methoxyiodobenzene **11** gave the 4-methoxystyrene intermediate. After removal of an excess amount of vinyltrimethylsilane **12**, Heck coupling of the 4-methoxystyrene with 3,5-dimethoxyiodobenzene yielded methyl ether protected resveratrol **6**. The methyl ether protecting groups were removed by boron trichloride.

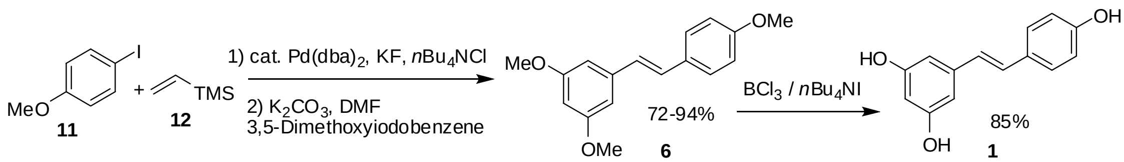


Figure 1.4 Resveratrol synthesis using a one-pot vinylsilane Heck coupling.

1.1.4. Decarbonylative Heck Reactions

Carbon-carbon bond formation is a fundamental goal in organic synthesis. The palladium catalyzed Mizoroki-Heck reaction using aryl halides and olefins has become a powerful and versatile means to accomplish this demand.[20] Besides the commonly used aryl halides, other arylating reagents have been developed,[21] including aryl triflates,[22] aryl sulfonyl halides,[23] aryl diazonium salts,[24] aroyl halids,[25] aryl anhydrides,[26] aryl esters,[27] arenecarboxylates,[28] arylboronic acids,[29] arylsilanols ,[30] arylstannanes,[31] organic tellurides and tellurium salts, [32] organoantimony compounds, [33] and organolead(IV) compounds.[34] Among these arylating reagents, aroyl halides, aryl anhydrides, aryl esters, and arenecarboxylates are readily available from commercial sources or are particularly easy and inexpensive to make.

Blaser and Spencer reported that with catalytic palladium acetate, aroyl chlorides reacted with activated alkenes to give (*E*)-arylation products at 130 ^{o}C in *p*-xylene (Figure 1.5).[25a-d] *N*-Benzyldimethylamine was used as base for most of the substrates, except when strongly electron-withdrawing groups were present in the aroyl chlorides. In these cases, *N*-ethylmorpholine was alternatively used. Although *N*-ethylmorpholine led to a much slower coupling reaction, it did not react with the aroyl chlorides. The reaction tolerated various substituents on the aroyl chloride. In general electron-withdrawing groups on the aroyl chloride hindered the reaction and electron-donating groups favored the reaction. Aliphatic acid chlorides and vinylic acid chlorides did not show reactivity. Aroyl bromides and iodides did not improve reactivity. Activated alkenes gave good reactivity whereas non-activated alkenes, except ethylene, gave none or poor reactivity. A reaction mechanism was also proposed. Palladium acetate is reduced to palladium(0) species by alkene or base. After oxidative addition of the aroyl chloride and aryl group migration to palladium, the carbonyl forms an η^2 complex with palladium. Carbon monoxide release is favored at high temperature. After alkene coordination with the resulting palladium intermediate, alkene insertion, β-hydride elimination and palladium(0) regeneration are followed as proposed by Heck.

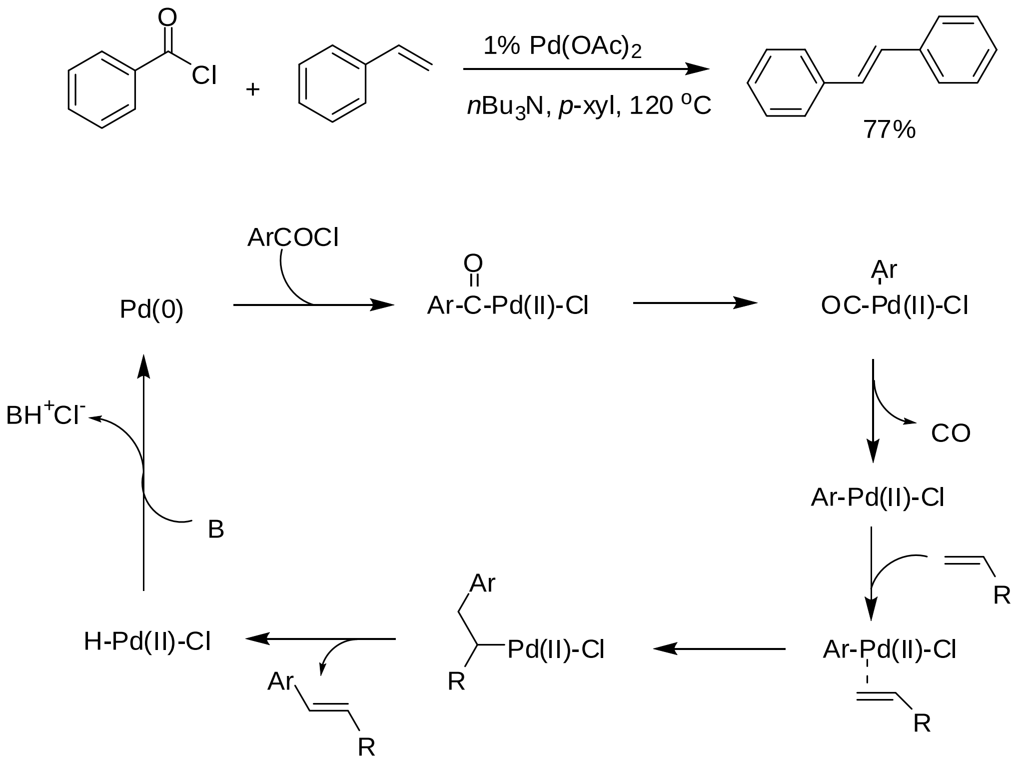


Figure 1.5 Palladium catalyzed decarbonylative Heck reaction with aroyl chloride.

Miura and coworkers reported a $[RhCl(C_2H_4)_2]_2$ catalyzed decarbonylative Heck coupling of aroyl chlorides with styrene or *n*-butyl acrylate in refluxing *o*-xylene at 145 ^{o}C (Figure 1.6).[25e,f] Without phosphine ligand and base, the reaction preceded more smoothly. A slow stream of nitrogen was used to remove generated hydrogen chloride and carbon monoxide. The purification procedure involved filtration, evaporation, and washing with methanol or ethyl acetate. The initial step of the mechanism is oxidative addition of the Rh(I)Cl to the aryl acid chloride. Aryl group migration and decarbonylation give $ArRh(III)Cl_2$. Alkene coordination, 1,2-insertion, and β-hydride elimination give product and $Rh(III)(H)Cl_2$. The last step was conversion to Rh(I)Cl by reductive elimination with release of HCl.

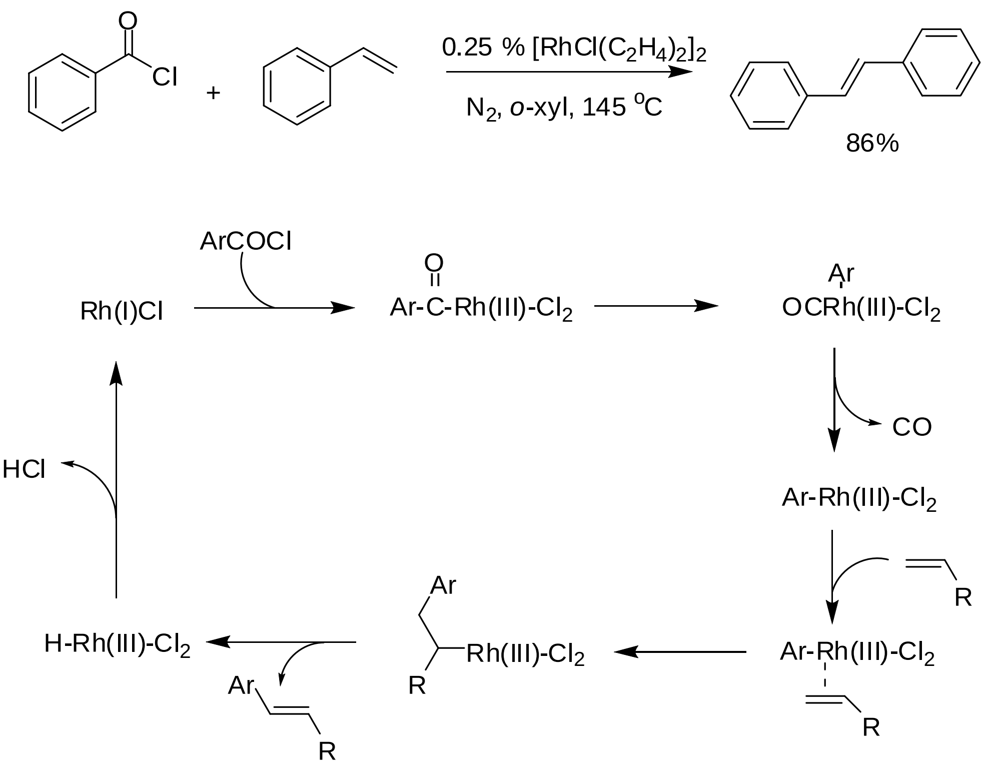


Figure 1.6 Rhodium catalyzed decarbonylative Heck reaction with aroyl chloride.

A base-free decarbonylative Heck reaction was developed by de Vries and coworkers with aromatic carboxylic anhydrides as arylating agents (Figure 1.7).[26a] Under a catalytic amount of palladium chloride and sodium bromide, aromatic carboxylic anhydrides coupled with alkenes at 140-190 ^{o}C in *N*-methylpyrrolidinone (NMP). Aromatic carboxylic acid and carbon monoxide were by-products. Although a catalytic amount of sodium chloride salt was needed, phosphine ligands were not required in this reaction. Aromatic carboxylic anhydrides, such as benzoic anhydrides, *p*-methoxybenzoic anhydride and furanoic anhydride, reacted similarly. Olefins with electron-withdrawing groups showed higher reactivity than olefins with electron-donating groups. However, at this relatively high temperature, double bond isomerization and internal arylation occurred for some substrates.

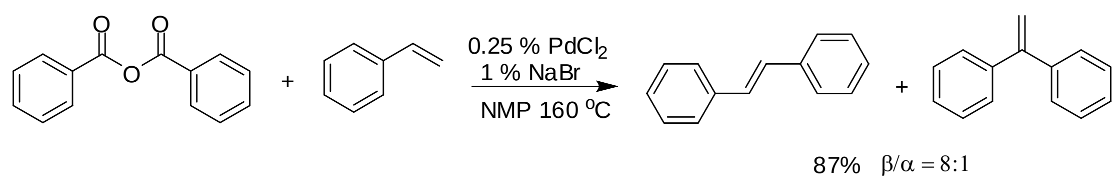


Figure 1.7 Palladium catalyzed decarbonylative Heck reaction with aromatic carboxylic anhydide.

Further investigation of this reaction by Shmidt and Smirnov showed that the nature of the catalytic amount of salt had an important effect on the reactivity and regioselectivity (Figure 1.8).[26b] Lithium chloride was found to be superior to other alkaline halide salts and ammonium halide salts. The effect of lithium chloride is due to carboxylate ligand substitution for a halide anion. Palladium chloride is initially reduced to palladium(0). Oxidative addition of benzoic anhydride to the palladium(0) give an aroyl palladium benzoate complex. Benzoate ligand subsitution for the halide anion give an aroyl palladium halide complex, which is the same oxidative addition complex for aroyl halides substrates. The cation of the salt showed an important effect on the reactivity in water free NMP as solvent. And the anion of the salt showed an important effect on regioselectivity. Aryl group migration, decarbonylation, olefin coordination, 1,2-insertion, and β-hydride elimination give the coupling product. The catalyst was again regenerated by reductive elimination of hydrogen halide.

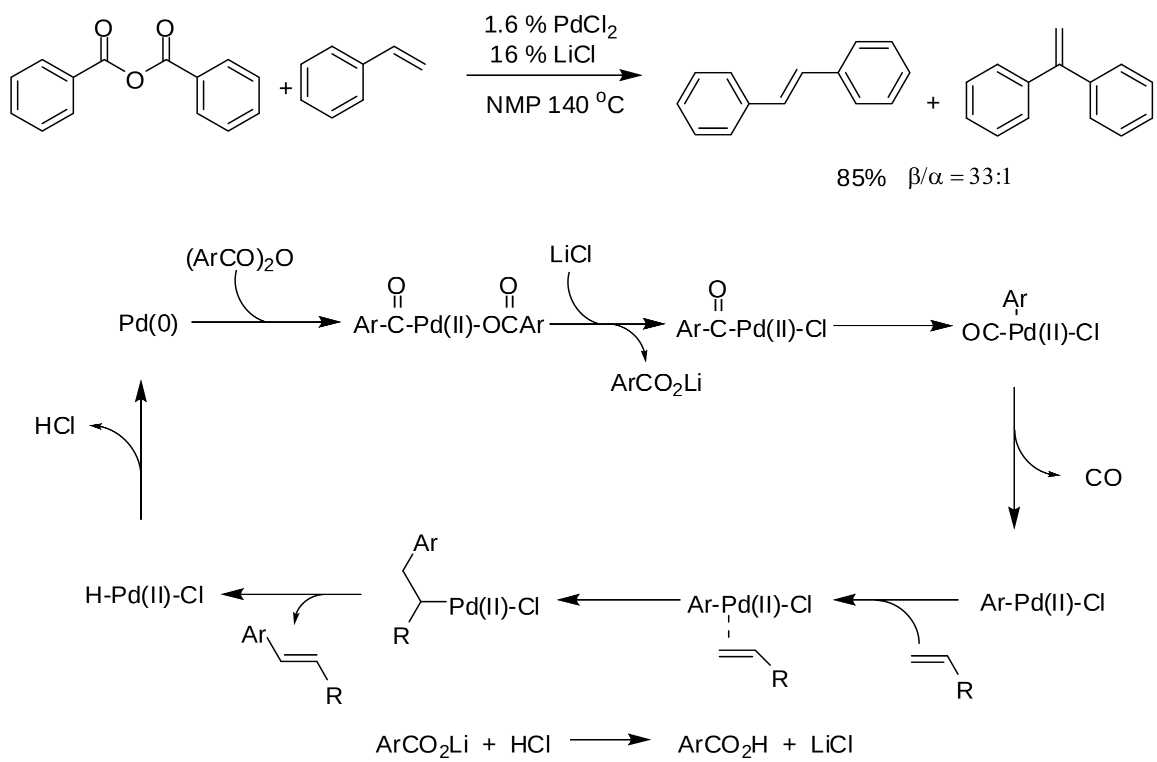


Figure 1.8 The effect of the halide salt on the palladium catalyzed decarbonylative Heck reaction with aromatic carboxylic anhydride.

Gooβen and coworkers reported a palladium catalyzed decarbonylative Heck reaction with an in situ generated mixed anhydride (Figure 1.9).[26d] Aromatic carboxylic acid was activated with Boc_2O to form a mixed anhydride, which coupled with the olefin via catalytic palladium chloride, lithium chloride, and *γ*-picoline at 120 °C in NMP. The byproducts of the reaction were carbon monoxide, carbon dioxide and *tert*-butanol.

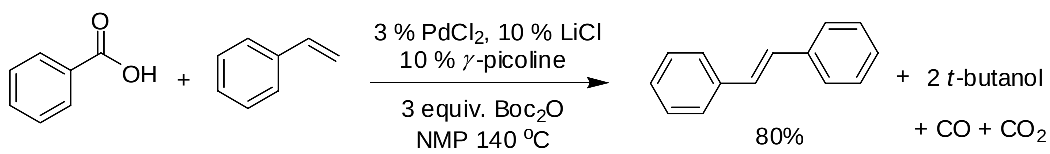


Figure 1.9 Palladium catalyzed decarbonylative Heck reaction with an in situ generated mixed anhydride.

Gooβen and coworkers also developed a Heck reaction with aryl esters as arylating agents at 160 °C (figure 1.10).[27a] Palladium chloride was found to be the best precatalyst. The addition of lithium chloride and isoquinoline improved the reactivity. Phosphine is not a suitable ligand due to its strong coordination with the catalyst. Benzoates of electron-deficient phenols gave good reactivity. Electron-deficient carboxylic esters also gave better yields than the electron-rich derivatives. Both electron-rich and electron-poor olefins gave similar yields. The palladium (0) inserts to the ester carbon-oxygen bond and enters a catalytic cycle similar to the decarbonylative Heck reaction with carboxylic anhydride as the arylating agent.

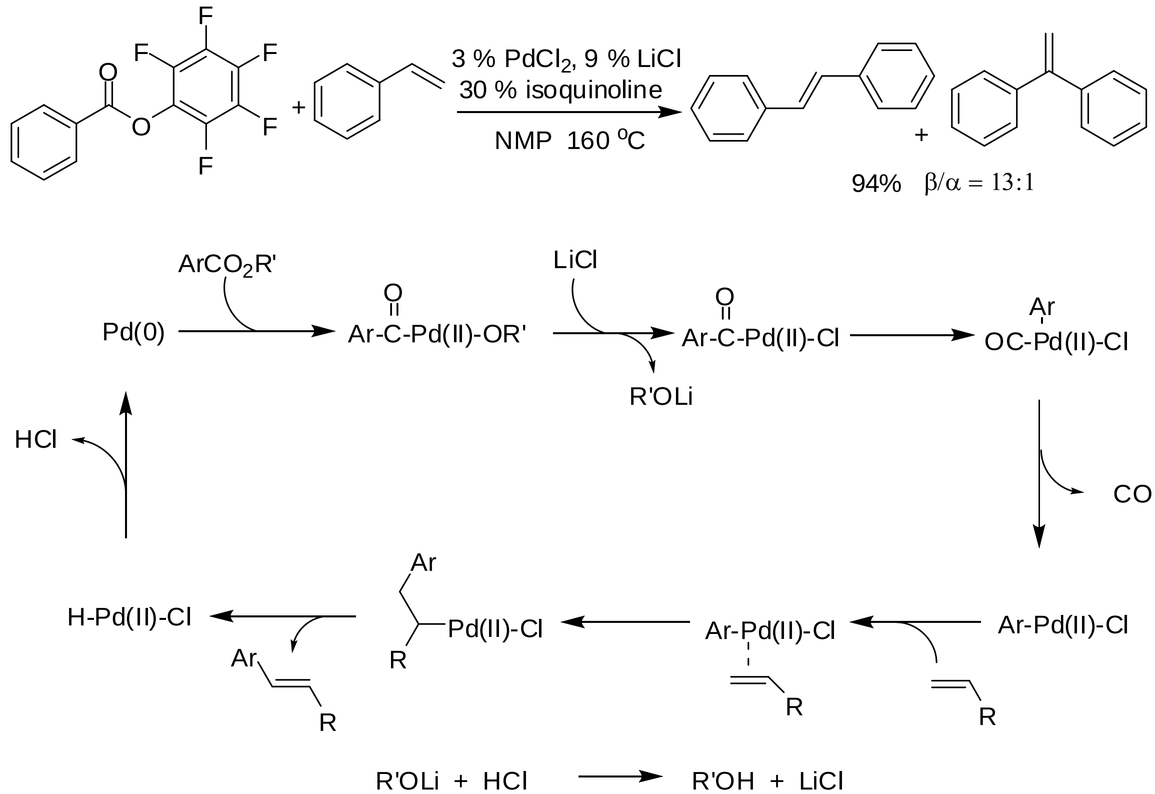


Figure 1.10 Palladium catalyzed decarbonylative Heck reaction with ester.

Further studies by Gooβen and coworkers extended the reaction to the use of isopropenyl arenecarboxylates at 160 °C (Figure 1.11).[27b] Isopropenyl arenecarboxylates were synthesized by a ruthenium catalyzed addition of the carboxylic acids to propyne or allene. Tri-*n*-butyl(2-hydroxyethyl)ammonium bromide additive was found to stabilize the palladium catalyst and gave better yields. Strong coordination ligands such as phosphines and amines decreased the reactivity. By adding celite, the reduced palladium(0) was precipitated on the celite. After the reaction, Pd(0) on celite was filtered and converted back to palladium bromide with bromine. The recycled $PdBr_2$ showed similar reactivity for this coupling. NMP was the best solvent for this reaction. The high reactivity of the reaction allowed coupling of electron-rich and electron-deficient aryl, heteroaryl, and vinyl carboxylic acid esters with various olefins in good yields. The reaction tolerated esters, ethers, nitro, keto, trifluoromethyl, and formyl functional groups. The workup procedure was convenient because the only side products were carbon monoxide and acetone.

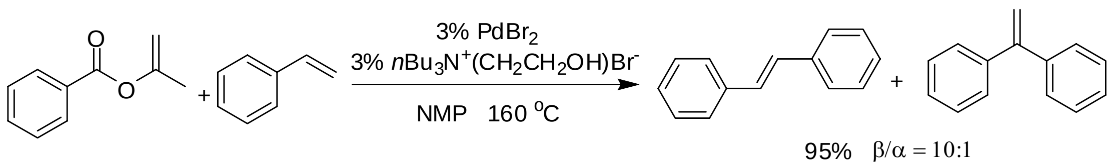


Figure 1.11 Palladium catalyzed decarbonylative Heck reaction with isopropenyl arenecarboxylic acid.

Myers and coworkers reported a palladium catalyzed decarboxylative Heck olefination of arene carboxylic acids (Figure 1.12).[28] With three equivalent of silver carbonate additive, 20% palladium trifluoroacetate catalyzed the olefin coupling reaction of a variety of *ortho*-substituted arene carboxylates with alkenes between 80 and 120 ^{o}C in a short period of time (0.5-3 hours). The silver carbonate salt was believed to function as both a base to deprotonate the carboxylic acid and a stoichiometric oxidant and was believed to extend the catalyst lifetime. Both electron-rich and electron-deficient arene carboxylic acids gave good yields. However, at least one *ortho* substituent was necessary for a successful decarboxylative Heck reaction and to avoid apparent C-H insertion at the *ortho* position (*ortho*-palladation). Styrene, acrylates, (E)-ethyl crotonate, and cyclohexenone were all successful alkene partners. With a stoichiometric amount of palladium trifluoroacetate, the mechanism of generation of the arylpalladium(II) species is different from the standard Heck reaction, which involves oxidative addition of palladium(0) into the carbon-halide bond. The mechanism is initiated with a carboxyl exchange between palladium(II) trifluoroacete and the arene carboxylic acid substrate to form a trifluoroacetato palladium(II) benzoate complex. Intramolecular coordination of the electron-deficient palladium(II) to the *ipso*-carbon of the arene forms a four membered palladacyclic species, which is converted to an arylpalladium(II) trifluoroacetate intermediate by releasing carbon dioxide. After olefin coordination, insertion and β-hydride elimination, the Heck coupling product is generated. Although these steps are common in all Heck reactions, the decarboxylative pathway generated arylpalladium(II) trifluoroacetate coupled preferentially with electron-rich olefins, whereas the standard Heck pathway caused the arylpalladium(II) species to couple preferentially with electron-deficient olefins. The σ-aralkylpalladium(II) trifluoroacetate intermediates also are relativity more stable than the corresponding intermediate produced in the normal Heck reaction. These differences are due to the electron-deficient nature of the palladium(II) intermediates.

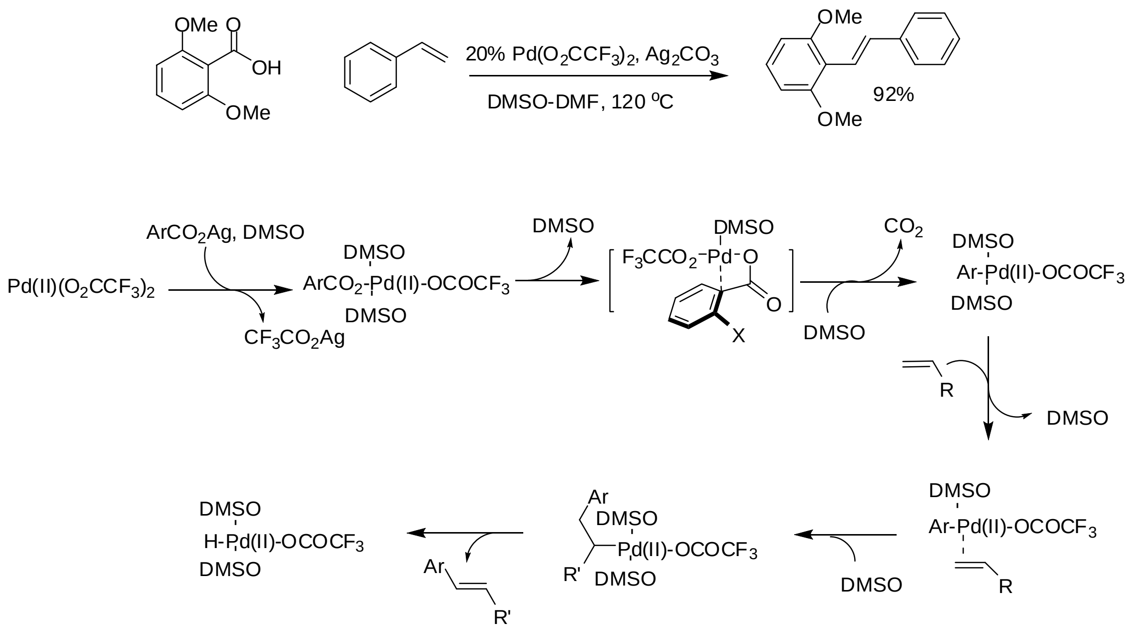


Figure 1.12 Palladium catalyzed decarbonylative Heck reaction with arene carboxylate and mechanism study with stoichiometric amount of catalyst.

1.2. Results and Discussions

1.2.1. Synthesis of Resveratrol Using a Direct Decarbonylative Heck Approach

The novel resveratrol synthesis route involved only four steps from inexpensive resorcylic acid **15**, converted to its acid chloride **13**, and 4-acetoxystyrene **14** (Figure 1.13). A decarbonylative Heck reaction catalyzed by palladium acetate with an imidazolium carbene ligand **16** was used for stilbene formation. The hydroxyls were conveniently protected as acetate esters which were easily removed with hydroxide.[35]

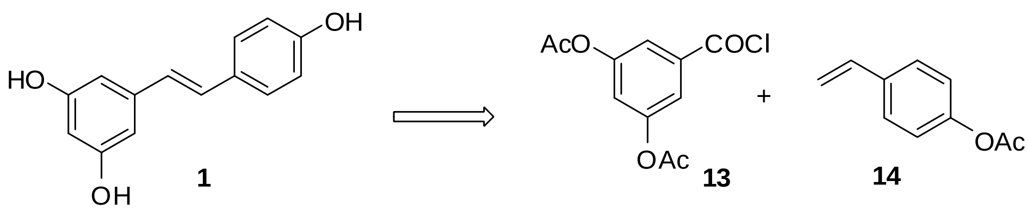


Figure 1.13 Retrosynthetic analysis of resveratrol.

3,5-Dihydroxybenzoic acid **15** (~$25/100 g) was reacted with 5 equiv. of acetic anhydride in the presence of pyridine to give the protected acid, following treatment with aqueous formic acid and recrystallization, in 90% isolated yield (Figure 1.14). Use of 2.6 equiv. of acetic anhydride gave a reduced yield of 75%. Thionyl chloride at 80 °C was then used to convert the protected acid to the acid chloride **13**.[36] The product was recrystallized from hexane in 91% isolated yield. Alternatively, oxalyl chloride could be used with catalytic DMF to give 3,5-diacetoxybenzoyl chloride **13** in 94% isolated yield. Spencer and coworkers reported that aryl acid chlorides react with styrene under palladium(II) acetate catalysis with added base to give styrenes in good yield via a decarbonylative Heck type process.[25a] This approach held particular promise in this case, since the acid chloride was readily made and the styrene coupling partner is readily available and inexpensive. It was shown that the nature of the added base was critical for the success of the transformation. Added phosphine ligand inhibited the reaction, giving greatly lowered yields. Non-coordinating amine bases, *N*-ethylmorpholine (NEM) and *N*,*N*-dimethylbenzylamine, proved optimal. Smaller amines capable of palladium coordination retarded the release of carbon monoxide leading to lower stilbene formation.[37] 3,5-Diacetoxy benzoyl chlorides **13** were not explored previously. We reported the use of *N*,*N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride (H_2IPr) **16** as a carbene-type ligand with palladium(II) acetate for efficient catalysis of Suzuki and Heck couplings with aryl diazonium ions.[38] Using palladium(II) acetate catalyst (1 mol%) and ligand **16**, acid chloride **13** was coupled with styrene **14** (1.2 equiv.) with added *N*-ethylmorpholine in *p*-xylene at 120 °C for 3.5 h. Following standard workup and silica gel chromatography, resveratrol triacetate **10** was obtained in 73% yield. Resveratrol **1** was then obtained in pure form following basic hydrolysis in THF and acidification in 88% yield. The total overall yield was 53%, requiring only four steps from resorcylic acid performed on multigram scale.

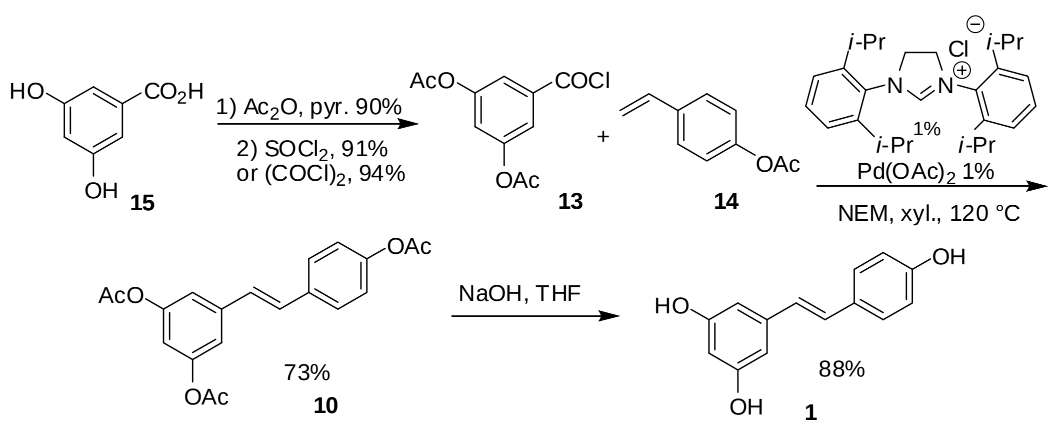
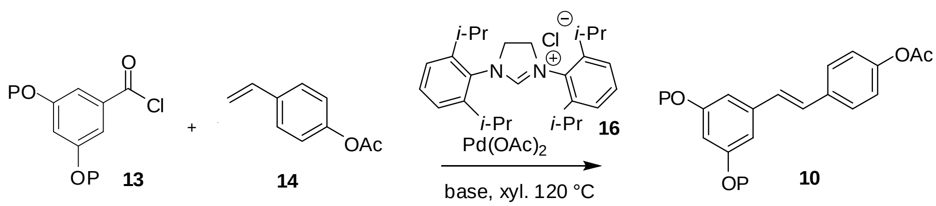


Figure 1.14 Synthesis of resveratrol using decarbonylative Heck reaction.

Variations were explored using the methyl ether protected version of **13**, together with changes in the amount of palladium(II) acetate catalyst, ligand **16**, and the use of other bases to form stilbene **10** (Table 1.1). With dimethyl ether benzoyl chloride **13**

(P=Me) and 5 mol% palladium(II) acetate, an extended reaction time of 18 h was needed to achieve a yield of 75%. *N*,*N*-Dimethylbenzylamine and Hünig's base gave lower yields. Diacetate acid chloride **13** (P=Ac) coupled with good reactivity using one mol% catalyst in less time, 3.5 h. When ligand **16** was left out, the product was obtained in lower yield, 63%. When the catalyst loading was lowered to 0.1 mol%, the yield again dropped to 57%. Use of *N*-methylmorpholine (NMM) was only slightly less effective, while added triethylamine gave product with lowered 57% yield.

Table 1.1 Decarbonylative Heck coupling.



P	mol% Pd	mol% ligand	base	time (h)	yield%
Me	5	0	NEM	18	75
Me	5	0	$BnNMe_2$	18	52
Me	5	0	$EtN(i\text{-}Pr)_2$	18	35
Ac	1	1	NEM	3.5	73
Ac	1	0	NEM	3.5	63
Ac	0.1	0.1	NEM	3.5	57
Ac	1	1	NMM	3.5	70
Ac	1	1	Et_3N	3.5	57

The efficiency of the decarbonylative Heck approach was compared to an aryl diazonium ion approach. Phloroglucinol **17** was converted to 5-azido-1,3-resorcinol **18** using a three-step sequence (Figure 1.15).[39] Acetate protection, aniline formation, and diazotization using *tert*-butyl nitrite, according to the procedure of Doyle, generated the aryl diazonium salt **19**. [40] Coupling of 4-acetoxystyrene with the palladium acetate–imidazolium catalyst gave stilbene **10** product in very low 12% isolated yield. The low efficiency of this coupling and the lengthy route to the aryldiazonium ion illustrated the superiority of the decarbonylative route.

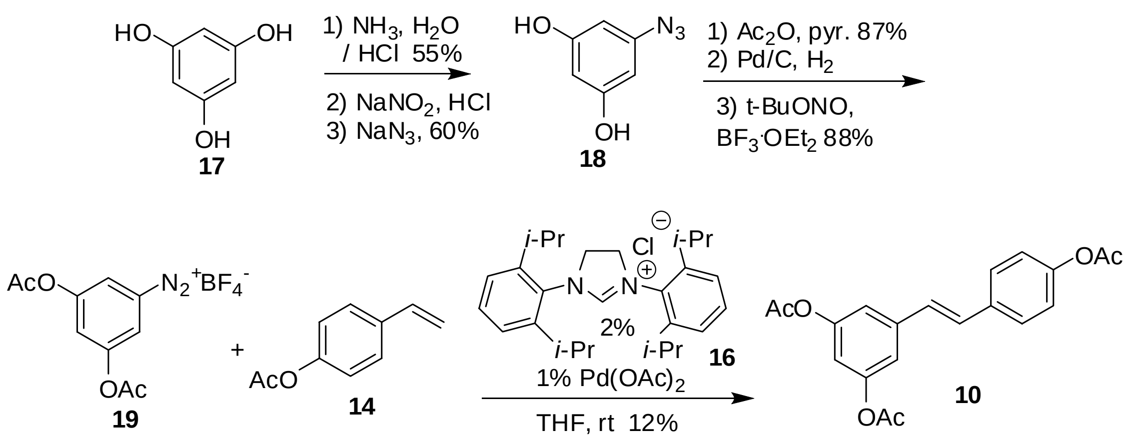


Figure 1.15 Synthesis of resveratrol using aryl diazonium ion approach.

Recently the decarbonylative Heck-type coupling was extended to mixed anhydrides.[26] To explore this option, mixed anhydride **21** was formed from the protected acid using pivaloyl chloride and triethylamine in 92% yield. Reaction under the coupling conditions with styrene **14** again gave a low 20% yield of stilbene product **10** (Figure

1.16).

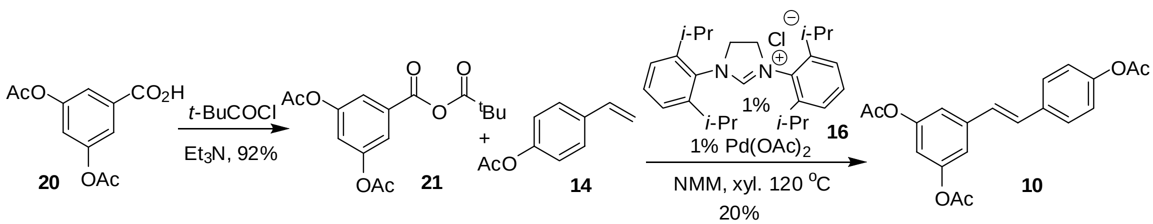


Figure 1.16 Synthesis of resveratrol using decarbonylative Heck coupling with mixed anhydride.

The decarbonylative route was also compared to an optimized Horner–Emmons based route using a diisopropyl phosphonate **24** (Figure 1.17).[41] Resorcylic acid **15** was benzylated and hydrolyzed to give 3,5-dibenzyloxybenzoic acid **22** in good yield. Treatment with lithium aluminum hydride gave a benzyl alcohol that was then converted to benzyl bromide **23** using phosphorous tribromide. Arbuzov reaction with neat isopropyl phosphate produced phosphonate **24** in high yield. Coupling with 4-benzyloxybenzaldehyde **25** using sodium methoxide as base in DMF gave the protected stilbene in 80% yield. Boron tribromide was then used to give resveratrol **1**. The Horner–Emmons step using the diisopropyl phosphonate in this case gave only the *E*-stilbene in contrast to previous phosphonate routes that have produced mixtures.[14] This route required seven steps and gave product in 36% overall yield.

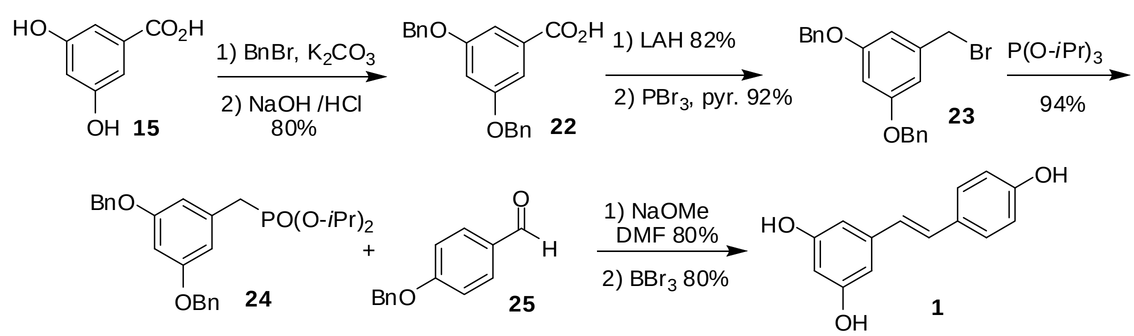


Figure 1.17 Synthesis of resveratrol using an optimized Horner–Emmons approach.

The decarbonylative Heck approach required only four steps from inexpensive resorcylic acid and gave resveratrol in excellent 53% overall yield. The palladium catalyzed coupling allowed for the use of acetate esters, which were easily removed. Aryl diazonium and mixed anhydride based routes were far less efficient. An improved Horner–Emmons synthesis was lower in overall yield and required more steps.

1.2.2. Synthesis of Ester and Fluoro Analogs of Resveratrol Using Decarbonylative Heck Couplings

Numerous closely related resveratrol analogs, derivatives and conjugates have been found from natural sources.[42] In addition, due to its simple structure and broad bioactivity, various resveratrol analogs have been designed to study the structure-activity relationships and to improve its therapeutic activity.[43]

We developed systematic, selective syntheses of acetate and fluoro analogs of resveratrol using decarbonylative Heck couplings[25] with protected resorcylic acid derivatives and styrenes under palladium-*N*-heterocyclic carbene conditions. Suitable protecting groups were employed that allow for efficient cross-couplings with appropriate partners for the selective synthesis of specific resveratrol analogs.

4'-Acetylresveratrol was synthesized in five steps beginning with resorcylic acid **15** (Figure 1.18). Treatment with sodium hydride followed by MOMCl (methoxymethyl chloride) and exposure to sodium hydroxide gave MOM protected resorcylic acid in 91% isolated yield. A stock solution of thionyl chloride and benzotriazole in CH_2Cl_2 was slowly added to a solution of MOM protected resorcylic acid. After filtration of the benzotriazolium chloride by-product and evaporation of solvents, acid chloride **26** was generated.[44] Thionyl chloride on its own, without adding benzotriazole, was found to be ineffective for this transformation, and multiple products were formed. Decarbonylative Heck coupling with 4-acetoxy styrene **14** was performed using palladium(II) acetate (1 mol %) and H_2IPr **16** with *N*-ethylmorpholine as base in *p*-xylene at 120 ^oC following the previous decarbonylative Heck route.[35] The di-MOM stilbene **27** was isolated in 56% yield for the two steps, from MOM protected resorcylic acid. The MOM groups were removed using TMSI, generated from TMSCl and sodium iodide, to give 4'-acetylresveratrol **28**.

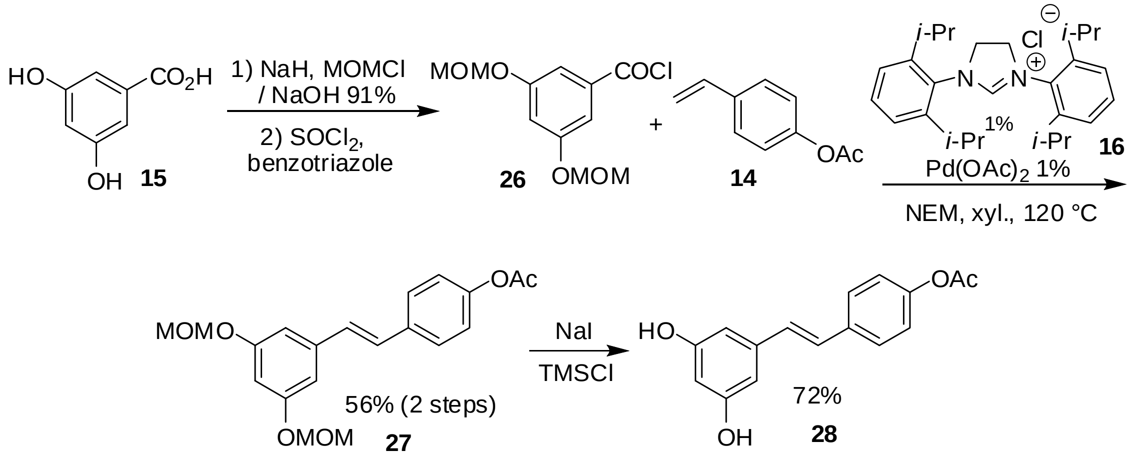


Figure 1.18 Synthesis of 4-acetylresveratrol.

The 3,5-diacetyl analog was generated from the unstable intermediate, 4-vinylphenol,[45] which was accessed from 4-acetoxystyrene **14** (Figure 1.19). To differentiate between the 3,5 and 4'-hydroxyls in this case, the chloroacetate protecting group[46] was found to be superior to the MOM ether. Chloroacetate **29** was formed in high yield using chloroacetyl chloride. 3,5-Diacetoxybenzoyl chloride **13** was reacted under palladium–NHC conditions to give stilbene **30** (70%). Efficient removal of the chloroacetate, in the presence of the 3,5-diacetates, was performed using 50% aqueous pyridine (pH 6.7) to give 3,5-acetylresveratrol **31** in 90% isolated yield.

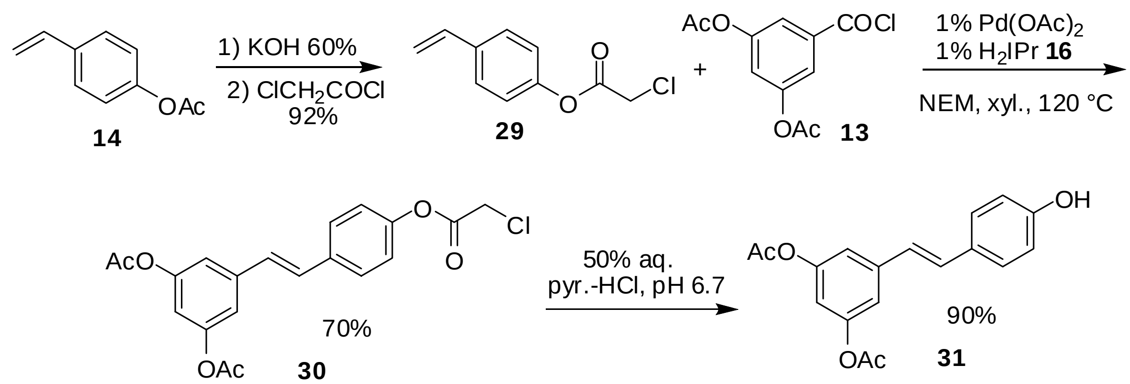


Figure 1.19 Synthesis of 3,5-diacetylresveratrol.

To begin the synthesis of 3,4'-diacetylresveratrol **36**, resorcylic acid **15** was mono-acetylated in 60% yield using acetic anhydride (1 equiv) and sodium hydroxide (3 equiv) to give mono-acetyl protected resorcylic acid (Figure 1.20).[47] Protection of the 5-hydroxyl was found to be most efficient using the seldomly employed levulinate (Lev, 4-oxopentanoate) group.[48] This group was found to be stable to various reaction conditions, including acid chloride formation and the palladium coupling step, and is readily removed using sodium sulfite via the hydroxysulfite adduct. Mono-acetyl resorcylic acid was treated with levulinic anhydride in the presence of pyridine to give differentially protected resorcylic acid **33** in 96% isolated yield. Formation of the acid chloride **34** was then performed using thionyl chloride again with added benzotriazole. Coupling under palladium–NHC conditions, as before, generated levulinic ester **35** (70%). The Lev group was then removed by sodium sulfite and thiosulfate to access the desired 3,4'-diacetylresveratrol analog **36**.

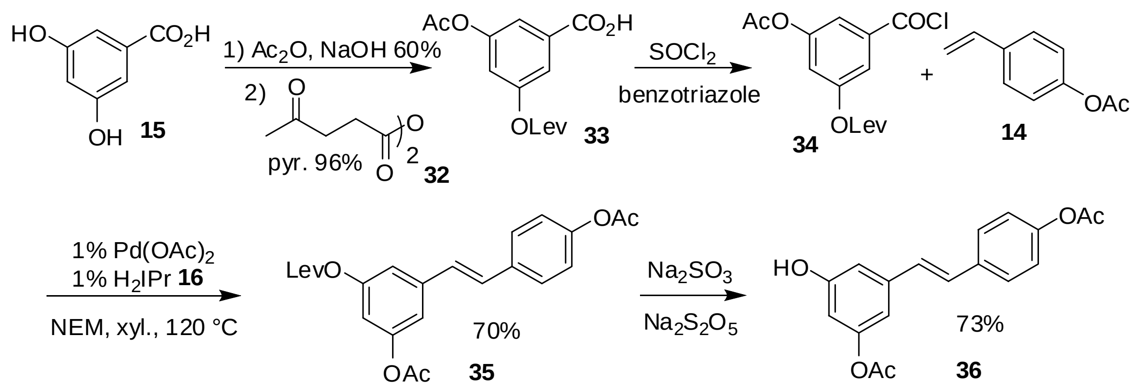


Figure 1.20 Synthesis of 3,4'-diacetylresveratrol.

The levulinate strategy also proved to be most effective for the synthesis of the 3-acetyl analog **39** (Figure 1.21). 4-Hydroxystyrene was treated with levulinic acid under DCC, DMAP coupling conditions to give the Lev-protected hydroxystyrene **37**. Coupling with differentially protected resorcylic acid chloride **34** under the decarbonylative Heck conditions gave the protected stilbene **38** in 72% yield. Removal of the two Lev groups gave 3-acetylresveratrol **39**.

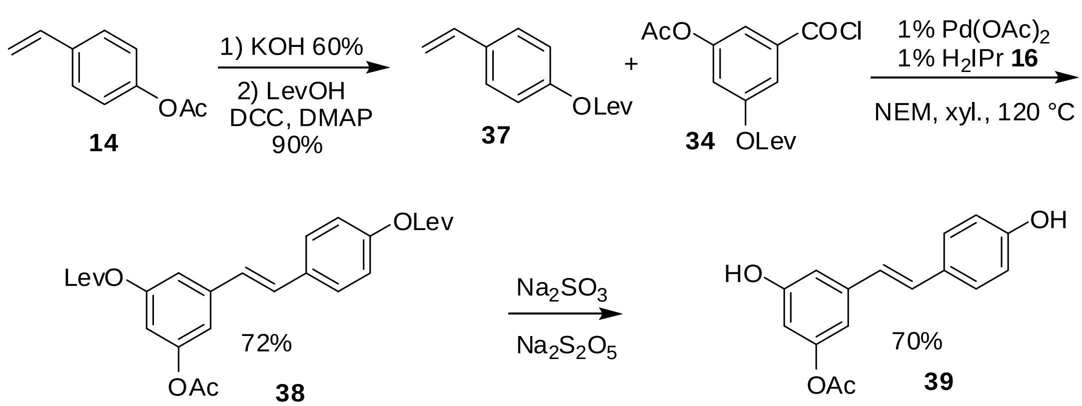


Figure 1.21 Synthesis of 3-acetylresveratrol.

Fluoro analogs were also produced using the decarbonylative coupling reaction. Resveratrol has been found to have a limited cellular lifetime.[49] Fluoride is isosteric with hydroxyl and the stability of the substituted C–F bond can lead to improved activity and resistance to metabolism.[50] 3,5-Difluorobenzoyl chloride **40** reacted with 4-fluorostyrene **41** to give 3,4',5-trifluorostillbene **42** in 80% yield. Coupling of 3,5-Difluorobenzoyl chloride **40** with 4-acetoxystyrene **14** occurred in 74% yield and the difluoro analog **43** was generated in 88% isolated yield (Figure 1.22). 3,5-Diacetoxybenzoyl chloride **13** was also coupled using 4-fluorostyrene **41** to generate 4'-fluoro analog **44** in good overall yield (Figure 1.23).

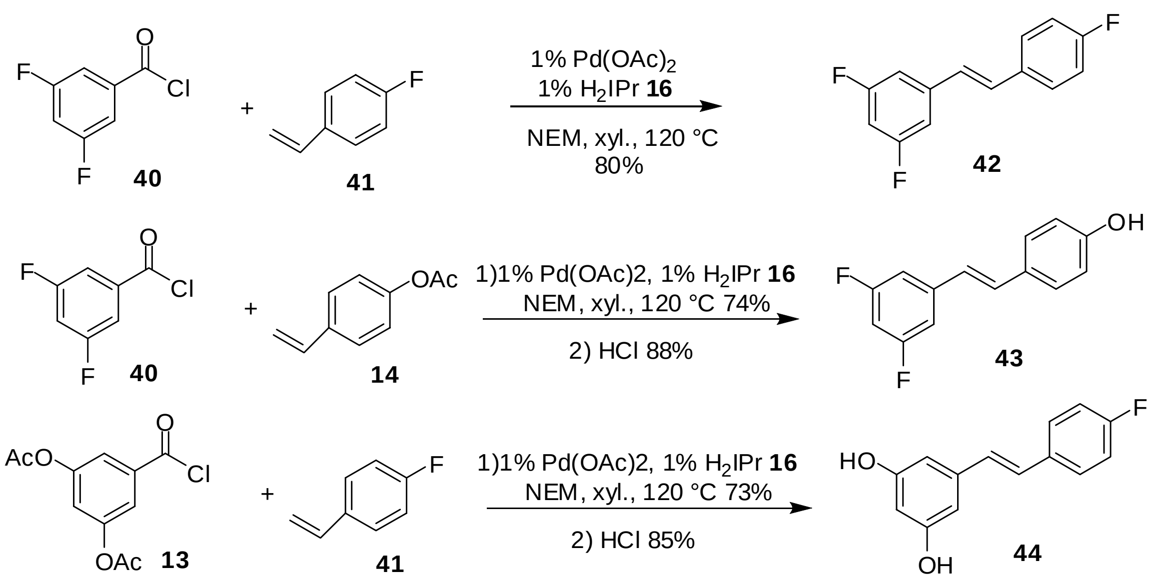


Figure 1.22 Synthesis of fluoro analogs using decarbonylative Heck reaction.

To complete the synthesis of the fluoro analog series, it was found that use of bromobenzene substrates under standard Heck coupling conditions known to produce stilbenes[51] was superior to the previous decarbonylative conditions (Figure 1.23). 1-Bromo-3,5-difluorobenzene **45** was reacted with benzyl alcohol under sodium hydride conditions to give the benzyloxy substituted product **46**.[52] Heck coupling with 4-fluorostyrene **41** and catalytic palladium acetate with tri-*o*-toluylphosphine gave benzyloxy stilbene. Boron tribromide mediated removal of the benzyl ether generated the 3,4'-difluoro analog **47**. Treatment of the benzyloxy adduct **46**, formed from 1-Bromo-3,5-difluorobenzene **45**, with 4-acetoxystyrene **14** gave substituted stilbene which was converted to the 3-fluoro analog **48** following protecting group removal.

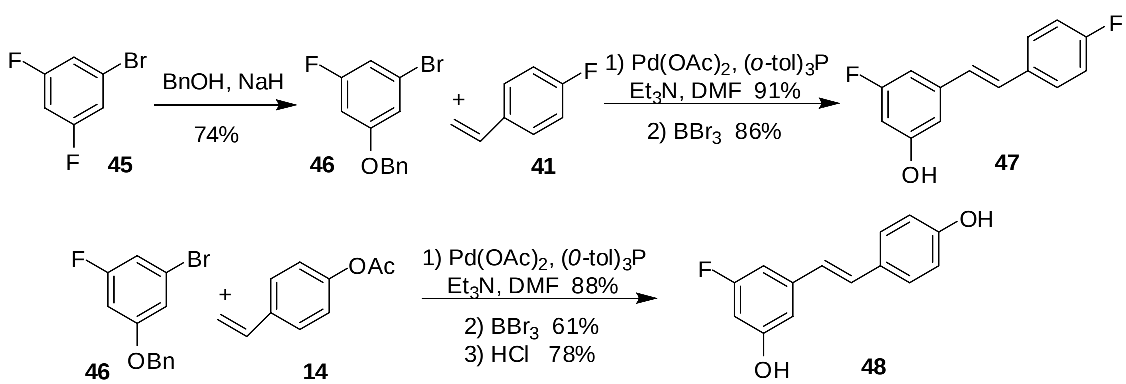
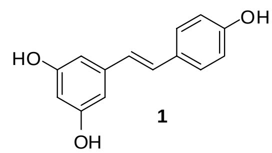
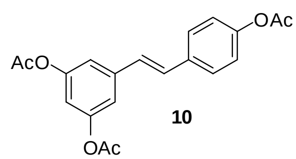
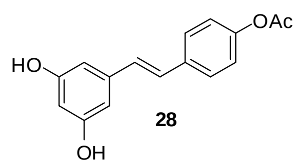
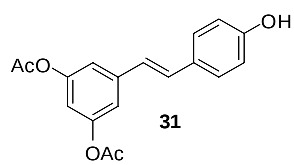
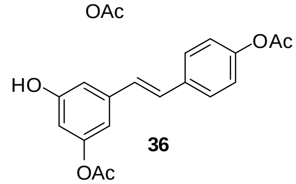
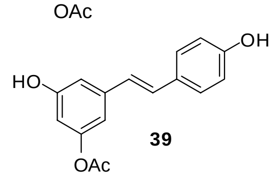


Figure 1.23 Synthesis of fluoro analogs using Heck coupling.

The analogs were tested with human leukemia HL-60 cells to determine anti-cancer potential related to resveratrol. The cells were cultured over various times (24, 48, and 72 h) exposed to compounds (5–100 μM), and ED_{50} values were determined using an established protocol.[53] Triacetyl **10** and 3-acetyl **39** were found to be comparable to resveratrol (23 μM), while the 3,5- and 3,4'-diacetyl analogs, **31** and **36**, were less potent.

Only the 4'-acetyl variant **28** showed somewhat improved anti-cancer activity at 17 μM. In general, the fluoro analogs were found to be toxic to this and other cell lines, limiting their potential for future investigations.

Table 1.2 Bioactivity of the acetate analogs with leukemia HL-60 cells.

X	Y	Z	Analogs	ED_{50} (μM)
OH	OH	OH	 **1**	23
OAc	OAc	OAc	 **10**	27
OH	OH	OAc	 **28**	17
OAc	OAc	OH	 **31**	33
OH	OAc	OAc	 **36**	30
OH	OAc	OH	 **39**	24

1.3. Conclusion and Future Work

The decarbonylative Heck approach required only four steps from inexpensive resorcylic acid and gave resveratrol in excellent 53% overall yield. The palladium catalyzed coupling allowed for the use of acetate esters, which are easily removed. The same coupling approach was applied to the synthesis of resveratrol analogs from substituted acid chlorides and styrenes. Chloro acetate and levulinate protecting groups have been shown to be suitable for this transformation, facilitating selective routes to mono- and di-acetoxy analogs. Heck coupling conditions were found to be more effective for 3-fluoro and 3,4'-difluoro resveratrol synthesis. The 4'-acetoxy variant was found to be more potent than resveratrol using an HL-60 cell assay. Further investigations of the biological activities of these compounds, together with the synthesis of a range of 4'-analogs, can now be pursued using this approach.

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Chapter 2. Asymmetric Glycolate Aldol Reactions Using Cinchonium Phase-Transfer Catalysts

2.1. Introduction

Phase transfer catalysts (PTC) are chemical agents that accelerate reaction rates through transferring a reagent or substrate ion from one phase to another. Anion transfer agents have been used in organic transformation as early as the 1950s.[1] Phase transfer catalyzed reactions have undergone great developments since the 1970s, when the foundations of PTC were laid by Starks,[2] Makosza,[3] and Brandstrom.[4] The most common phase transfer process is the "normal" biphasic phase transfer reaction, in which the phase transfer catalyst coordinates with a reagent or substrate ion and transports the ion into the organic phase. Depending on the reaction conditions, the ion exchange process can occur in the aqueous phase, the interfacial region, or in the organic phase.[5] Despite these mechanism variations, phase transfer catalyzed reactions have many advantages, including operational simplicity, mild reaction conditions with aqueous media, environmental consciousness, and suitability for large-scale production.

The great demand for non-racemic chemicals in both industrial and academic laboratories has led to the rapid development of enantioselective processes using enantiopure phase transfer catalysts, such as chiral quaternary ammonium salts and chiral crown ethers. Crown ethers are usually less favorable as a chemical reagent due to their toxicity and synthetic complexity. Instead, chiral quaternary ammonium salts, derived from the naturally occurring chiral pool, have been widely used because of their low cost and synthetic simplicity. Chiral quaternary ammonium catalysts have also been successfully designed from non-natural substrates. While these catalysts are expensive, they have been effective in a large variety of reactions. Since the pioneering work of the Merk research group[6] and O'Donnell[7] in the 1980s (Figure 2.1), catalytic asymmetric phase transfer reactions have been applied in alkylations, aldol and Mannich reactions, Michael additions, Darzens condensations, Horner-Wadsworth-Emmons reactions, epoxidations, reductions, Robinson annulations, fluorinations, cyclopropanations, aziridinations, Strecker reactions, and esterifications.[5,8]

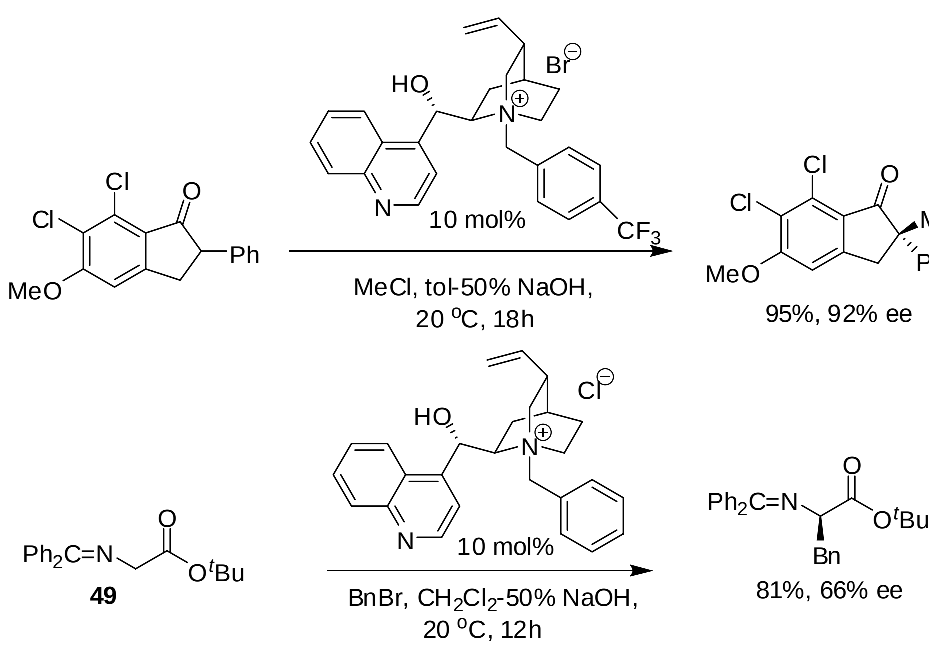


Figure 2.1 Pioneering works in PTC catalyzed asymmetric alkylation.

PTC alkylation, aldol, and Michael additions have mainly focused on the benzophenone imine *t*-butyl glycine substrate **49,** due to its *t*-butyl ester stability, extended enolate delocalization (p*K*a 18, DMSO), and aromatic π-π interaction with the catalyst. Inexpensive cinchona alkaloid derived catalysts are most commonly employed. Variation of the catalyst and conditions has shown steady improvement in selectivity and efficiency.

Although there are numerous reports in asymmetric phase transfer alkylation of the prochiral glycine derivative **49**, reports for aldol reactions are limited. The first catalytic asymmetric aldol condensation of the glycine Schiff base **49** under phase transfer condition was described by Miller (Figure 2.2). [9] Under catalyst *N*-benzyl-cinchonium chloride **50**, benzophenone imine *t*-butyl glycine **49** reacted with heptanal at ambient temperature in a biphasic mixture of CH_2Cl_2 and 5% aqueous NaOH to give 81% product **51**. With hydrocinnamaldehyde as substrate, the yield was 76%. Unfortunately, the diastereoselectivities and enantioselectivities were poor.

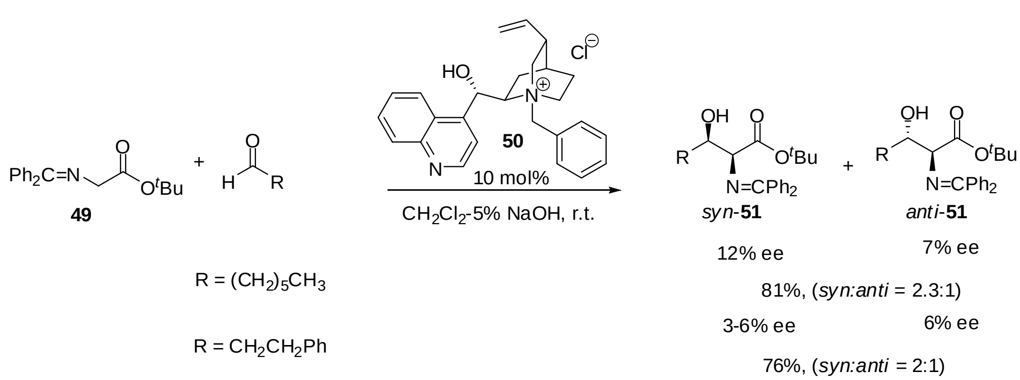
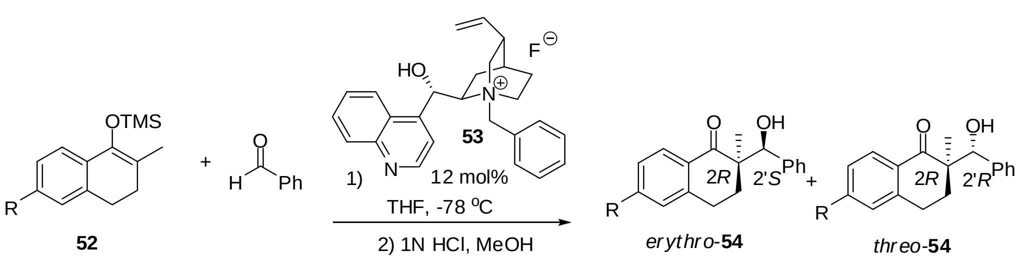


Figure 2.2 Miller's PTC catalyzed aldol reaction.

Shioiri and co-workers reported an *N*-benzyl-cinchonium fluoride **53** catalyzed aldol reaction between silyl enol ether **52** and aldehydes (Table 2.1).[10] The *N*-benzyl-cinchonium chloride was first converted to its corresponding hydroxide by passing through an Amberlyst A-26 OH^- ion exchange column. Then the hydroxide was neutralized with aqueous hydrofluoric acid. In the present of this fluoride catalyst, the silyl enol ethers of 2-methyl-1-tetralone derivatives **52** reacted with benzaldehydes in THF at -78 ^oC to give asymmetric aldol products **54** in good yield and stereoselectivity. The same conditions were also applied to the silyl enol ethers **55** of acetophenone and pinacolone to give aldol products **56** in 65% yield, 39% ee and 62% yield, 62% ee, respectivity (Figure 2.3).

Table 2.1 Shioiri's Mukaiyama-type PTC catalyzed aldol reaction.



R	% yield	*erythro/threo*	% ee (*erythro*)	% ee (*threo*)
H	74	3.5/1	70	22
MeO	73	3.2/1	68	30
Cl	73	4.6/1	66	21
Br	67	4.3/1	66	15

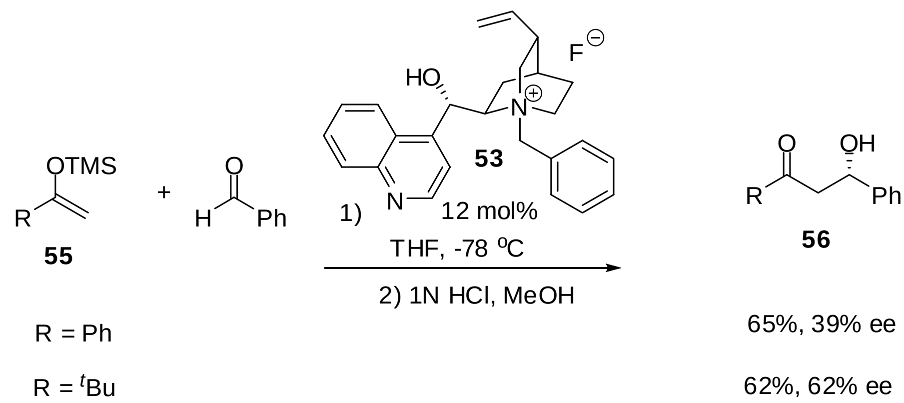


Figure 2.3 Shioiri's Mukaiyama-type cinchonium PTC catalyzed aldol reaction.

Further studies by the same group showed that the stereochemical results of the aldol reaction mainly depended on the hydroxymethyl-quinuclidine fragment.[11] Usually, the cinchonium fluorides were more efficient than cinchonidinium fluorides. In the reactions of silyl enol ethers of 2-methyl-1-tetralone derivatives **52** with benzaldehyde, cinchonium and quinidium fluorides gave *erythro* isomers **54** with (2*R*, 2'*S*)-configuration as major products and *threo* isomers **54** with (2*R*, 2'*R*)-configuration as minor products. Interestingly cinchonidinium and quininium fluorides gave *erythro* isomers **54** with (2*R*, 2'*S*)-configuration as minor products and *threo* isomers **54** with (2*S*, 2'*S*)-configuration as major products. With silyl enol ethers of acetophenone and pinacolone as substrates, *N*-benzyl-cinchonidinium fluoride **53**-CN gave aldol products with the opposite absolute configuration compared with the products from *N*-benzyl-cinchonium fluoride **53**-CD (Figure 2.4).

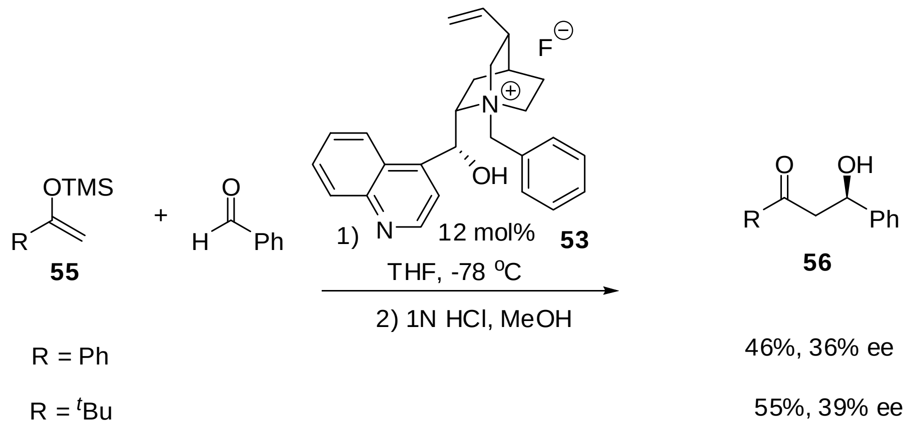


Figure 2.4 Shioiri's Mukaiyama-type cinchonidinium PTC catalyzed aldol reaction.

To facilitate a stereoselective synthesis of the HIV protease inhibitor amprenavir, Corey and Zhang developed a nitroaldol reaction with *N*-anthracenylmethyl-*O*-benzylcinchonidinium fluoride catalyst **58** (Figure 2.5).[12] Since the reaction only needed a catalytic amount of base, a catalytic amount of ammonium fluoride was basic enough to fulfill this requirement. *N*,*N*-dibenzyl-(*S*)-phenylalaninal **57** reacted with nitromethane with a catalytic amount of cinchonium fluoride **58** and 12.5 equivalents of potassium fluoride in THF at -10 °C to give 86% of the desired *syn*-nitro alcohol **59** and 5% of its diastereomer. The diastereoselectivity was about 17:1. When achiral phase transfer catalyst, tetra-*n*-butylammonium fluoride, was used, only 4:1 diastereoselectivity was obtained. The C-2 diastereomer of amprenavir was also synthesized using *N*-tert-butoxycarbonyl-(*S*)-phenylalaninal **60** as a substrate. The fluoride catalyst was generated in situ from its corresponding bromide **61**. The nitroaldol product **62** was obtained in an 88% yield with a 9:1 diasteromeric ratio. In the presence of tetra-*n*-butylammonium fluoride as catalyst, the diasteromeric ratio of the reaction was 1:1.

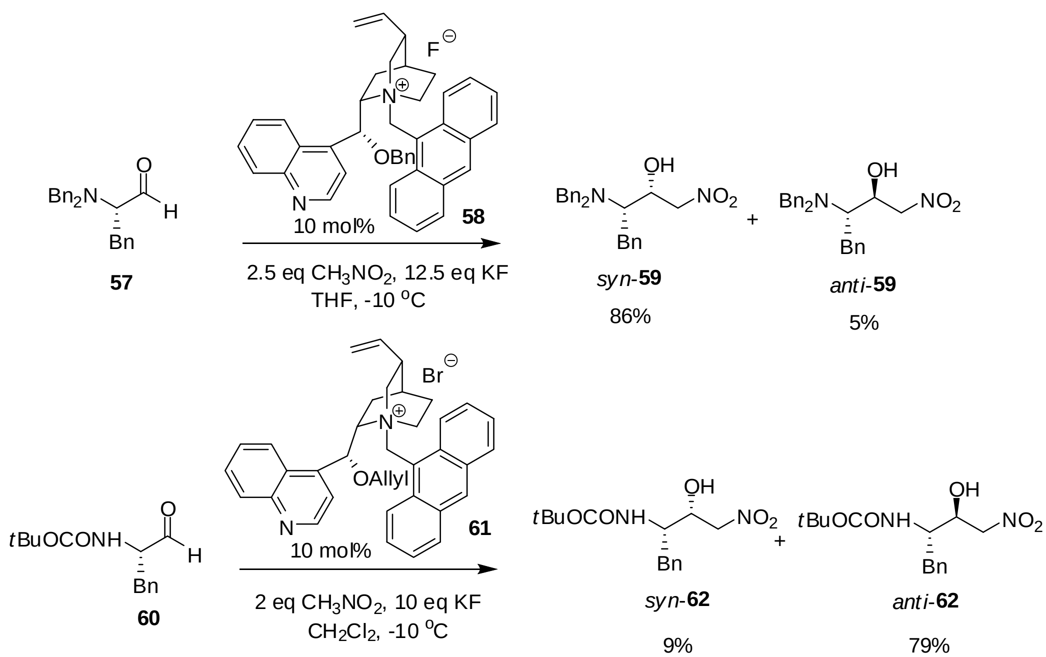
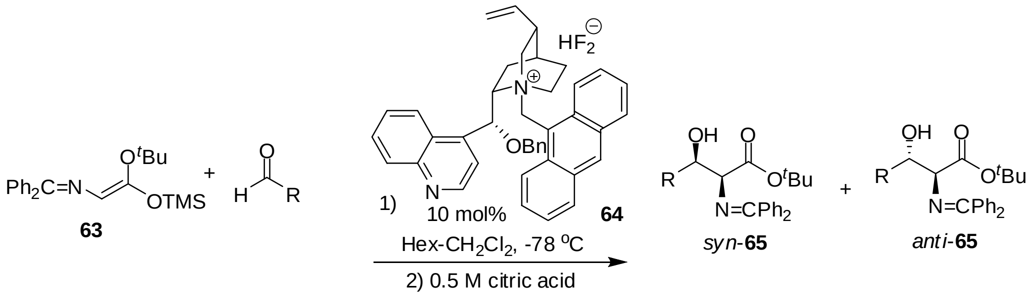


Figure 2.5 Corey's PTC catalyzed nitroaldol reaction.

Later, Corey and coworkers developed a Mukaiyama-type aldol reaction to synthesize chiral *β*-hydroxy-*α*-amino acids in a homogenous organic solution (Table 2.2).[13] Using the cinchonidine derived ammonium bifluoride catalyst **64**, the trimethylsilyl ketene acetal derivative of benzophenone imine *t*-butyl glycine **63** reacted with aliphatic aldehydes at -78 °C in a mixed solvent of hexanes and methylene chloride. The yields and enantioselectivity were good to excellent. The diastereoselectivity depended on the aldehyde substrate. Branched aldehydes gave better diastereoselectivity than unbranched aldehydes.

Table 2.2 Corey's PTC catalyzed Mukaiyama-type aldol reaction.



R	Hex.-CH_2Cl_2	temp (°C)	% yield	*syn/anti*	% ee (*syn*)	% ee (*anti*)
i-Pr	3:1	-78	70	6/1	95	83
c-Hex	5:1	-50	81	13/1	88	46
n-Hex	3:1	-78	79	3/1	89	91
$Cl(CH_2)_3$	5:1	-78	48	1/1	82	86
$Ph(CH_2)_2$	3:1	-78	64	1/1	72	86
i-Bu	5:1	-45	61	3/1	76	70

Cinchona alkaloids and brucine derived chiral ammonium fluorides were used in catalytic asymmetric vinylogous Mukaiyama aldol reactions. Campagne and Bluet reported that sily dienolate **66** reacted with isobutyraldehyde in the presence of 10 mol% of chiral ammonium fluoride **53** to give the vinylogous aldol product **67** in 70% yield with unsatisfactory enantioselectivity (Figure 2.6).[14]

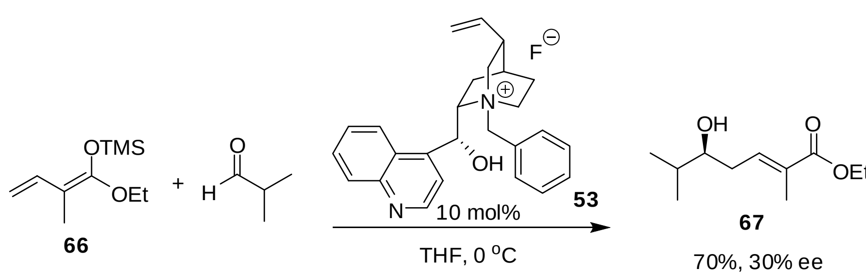
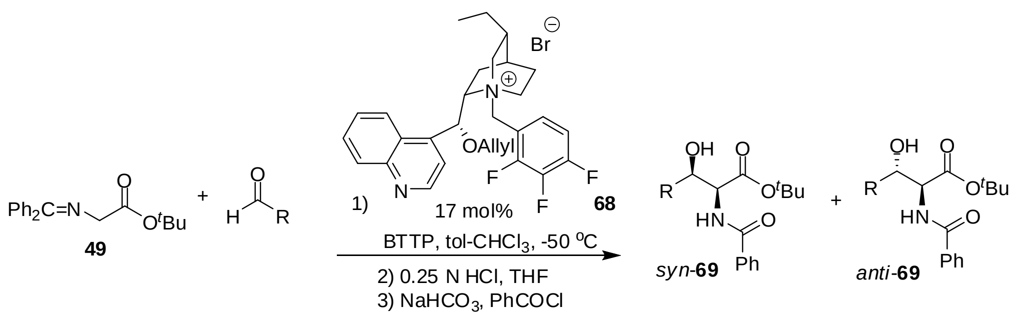


Figure 2.6 Campagne's PTC catalyzed vinylogous Mukaiyama-type aldol reaction.

Castle and coworkers developed an effective direct aldol reaction between benzophenone imine *t*-butyl glycine **49** and aliphatic aldehydes with an *N*-trifluorobenzyl-cinchonidinium bromide catalyst **68** (Table 2.3).[15] Phosphazene base, BTTP, was used under homogeneous conditions. Although the diastereoselectivity was still unsatisfying, the enantioselectivity was much better than Miller's results. Due to a facile retro-aldol process, benzaldehyde was not a suitable substrate. With the pseudoenantiomeric catalyst derived from cinchonine, reversed enantioselectivity was obtained with lower stereoselectivity.

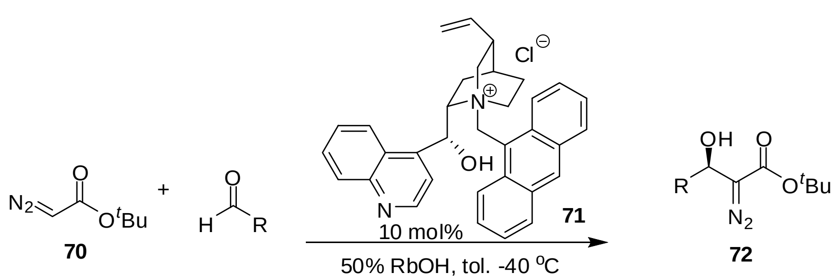
Table 2.3 Castle's PTC catalyzed direct aldol reaction.



R	%yield	*syn/anti*	%ee (*syn*)	%ee (*anti*)
$PhCH_2CH_2$	64	1.3/1	80	33
$BnOCH_2$	70	1/1	83	45
p-$NO_2PhCH_2CH_2$	74	1.3/1	75	60
p-$OMePhCH_2CH_2$	78	1.2/1	50	10
CH_2=$CHCH_2CH_2$	46	1.2/1	60	19
$CH_3(CH_2)_4CH_2$	34	1.2/1	52	6.5

Arai and coworkers investigated asymmetric aldol reactions between tert-butyl diazoacetate **70** and aldehydes using *N*-anthracenylmethyl-cinchonidinium chloride **71** as a catalyst at -40 °C (Table 2.4).[16] The substituents on the benzene ring of benzaldehydes had an important electronic effect. Electron-withdrawing groups increased the reactivity and enantioselectivity, and electron-donating groups decreased the reactivity and enantioselectivity. The substituents on aliphatic aldehydes had a strong steric effect. With a bulky substituent, the yield and enantioselectivity was improved. Since the enantioselectivity of the aldol reaction kept increasing for the first several hours, it was believed that the asymmetric induction was enhanced from both the C-C formation process and the retroaldol step.

Table 2.4 Arai's PTC catalyzed aldol reaction.

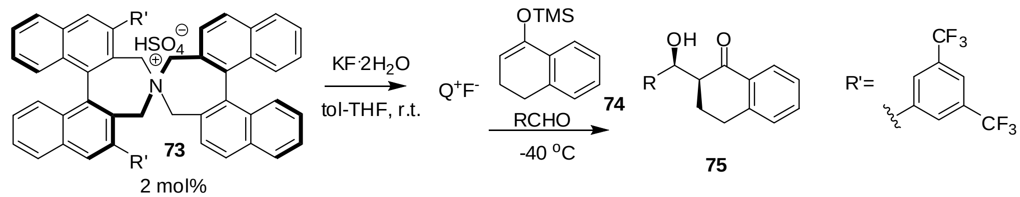


R	time (h)	%yield	%ee	R	time (h)	%yield	%ee
Ph	12	91	56	Ph(CH_2CH_2)$_2$	72	32	31
p-MePh	66	66	39	*i*-Bu	72	85	20
p-MeOPh	120	56	0	*i*-Pr	20	45	40
p-CF_3Ph	140	81	73	*ci*-Hex	10	88	33
1-naphthyl	94	86	79	*t*-Bu	72	83	78

Maruoka and coworkers designed a novel type of *N*-spiro C_2-symmetric chiral phase transfer catalyst derived from (*S*)- or (*R*)-1,1'-bi-2-naphthol. Without β-hydrogens, these catalysts were more stable than the cinchona derived quaternary ammonium catalysts, which degrade under basic condition through Hofmann elimination. Consequently, less than 1 mol% catalyst loading was required. Although they required 12 steps to be synthesized from expensive substrates, these catalysts have been applied in a wide variety of transformations.

Maruoka and coworkers successfully used an in situ generated C2-symmetic chiral quaternary ammonium fluoride salt from the corresponding hydrogen sulfate **73** to catalyze aldol reactions between tetralone-derived trimethyl silyl enol ether **74** and aromatic aldehydes (Table 2.5).[17] The electron-withdrawing effect of the trifluoromethyl groups on the 3,3'-aryl substituents of the catalyst helped form a tight contact ion pairing with the ammonium enolate, thus providing excellent stereoselectivity.

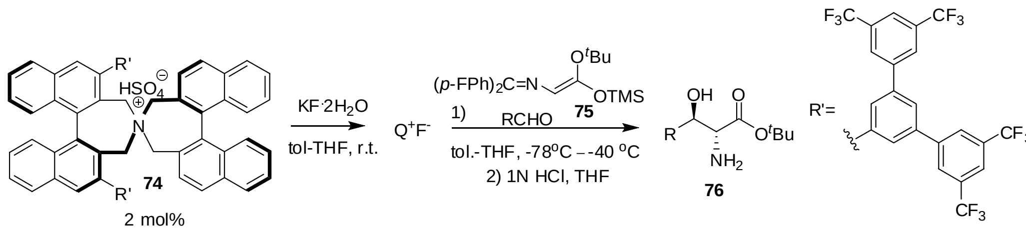
Table 2.5 Maruoka's PTC catalyzed Mukaiyama-type aldol reaction with tetralone derived silyl enol ethers.



R	% yield	*erythro/threo*	% ee (*erythro*)
Ph	90	83/17	84
α-Naph	90	94/6	91
9-phenanthryl	88	95/5	90

The same in situ fluoride catalyst generation strategy was applied to aldol couplings with glycine-derived silyl ketene acetal **75** and aliphatic aldehydes (Table 2.6). [18] With 3,5-bis(3,5-bis(trifluoromethyl)phenyl)phenyl substituents at the 3,3'-postion of the catalyst **74**, both the diastereo- and enantioselectivities were enhanced.

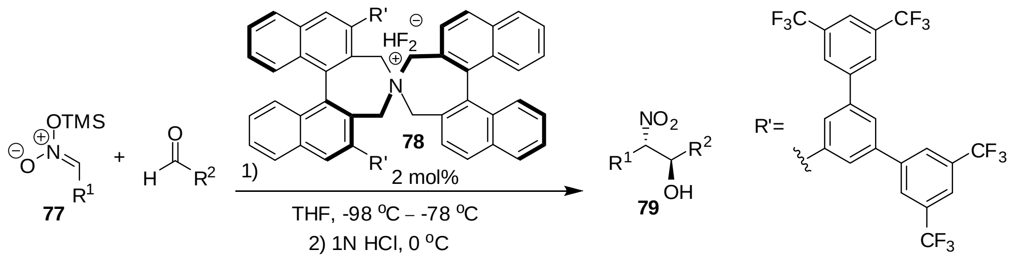
Table 2.6 Maruoka's PTC catalyzed Mukaiyama-type aldol reaction with glycine derived silyl ketene acetal.



R	% yield	*anti/syn*	% ee (*anti*)	R	% yield	*anti/syn*	% ee (*anti*)
$Ph(CH_2)_2$	77	8.3/1	92	*i*-Bu	70	7.2/1	90
$CH_3(CH_2)_4$	58	8.4/1	91	*i*-Pr	65	6.7/1	97
$CH_3(CH_2)_5$	72	11/1	90				

An asymmetric nitro aldol reaction was also investigated by Maruoka's group, using their *N*-spiro C_2-symmetric ammonium bifluoride catalyst **78** (Table 2.7).[19] Silyl nitronates **77** reacted with aromatic aldehydes to give the corresponding nitoalkanol products **79** with excellent stereoselectivities at low temperature (-98 ^{o}C to -78 ^{o}C) in THF (m.p. -108.5 ^{o}C).

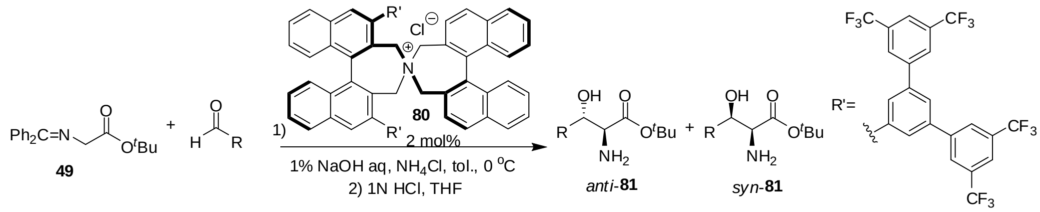
Table 2.7 Maruoka's PTC catalyzed Mukaiyama-type nitroaldol reaction.



R^1	R^2	% yield	*anti/syn*	% ee (*anti)*
CH_3	Ph	92	12/1	95
CH_3	*p*-FPh	94	5/1	90
CH_3	*β*-Np	88	12/1	93
Et	Ph	94	9/1	91
$BnO(CH_2)_2$	Ph	70	7/1	91

A direct aldol reaction was also developed with catalyst **80** (Table 2.8).[20,21] With benzophenone imine *t*-butyl glycine **49** as the substrate, a variety of aliphatic aldehydes gave excellent enantioselectity at 0 °C in a biphasic system, where toluene and 1% aqueous NaOH served as solvents.[20] Further mechanistic studies regarding this aldol process revealed an unfavorable yet inevitable retro aldol reaction under this basic asymmetric condition.[21] By reducing the addition of aqueous base to a catalytic amount of 15 mol% NaOH, with addition of NH_4Cl (10 mol%) to control the pH of the reaction, a wider aliphatic aldehyde scope was obtained with better diastereo- and enantioselectivity. Unfortunately, aromatic aldehydes gave poor yields and poor stereoselectivities.

Table 2.8 Maruoka's PTC catalyzed direct aldol reaction.



R	% yield	*anti/syn*	% ee (*anti)*	R	% yield	*anti/syn*	% ee (*anti)*
$Ph(CH_2)_2$	82	24/1	98	*i*-$PrCH_2$	64	>24/1	96
$CH_3(CH_2)_4$	79	>24/1	97	$AllylCH_2$	82	24/1	98
$CH_3(CH_2)_5$	80	16/1	97	CH_3	54	>24/1	99
$TIPSOCH_2$	73	>24/1	98	*i*-Pr	39	>24/1	98
$BnO(CH_2)_3$	83	24/1	96	Ph	58	1/1.1	25

Similar to aldol reactions, direct Mannich reactions of benzophenone imine *t*-butyl glycine **49** with imine derivative **82** were accomplished with high enantioselectivity using *N*-spiro C_2-symmetric ammonium bromide **83** as the catalyst to give differentially protected 3-aminoaspartate **84** (Figure 2.7).[22] The catalyst with a 3,4,5-trifluorophenyl group at the 3,3'-position gave enhanced enantioselectivity. Switching solvent from toluene to mesitylene further improved the yield and the diastereo- and enantioselectivity.

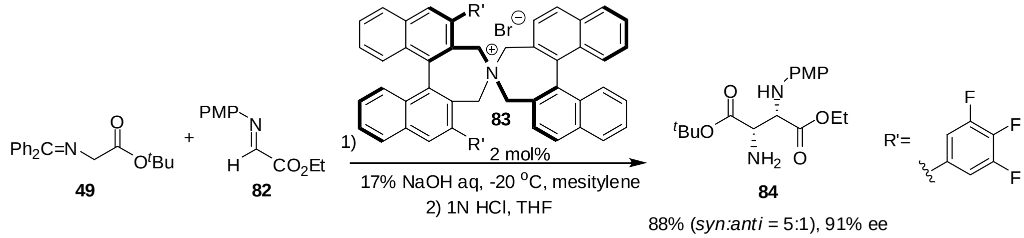
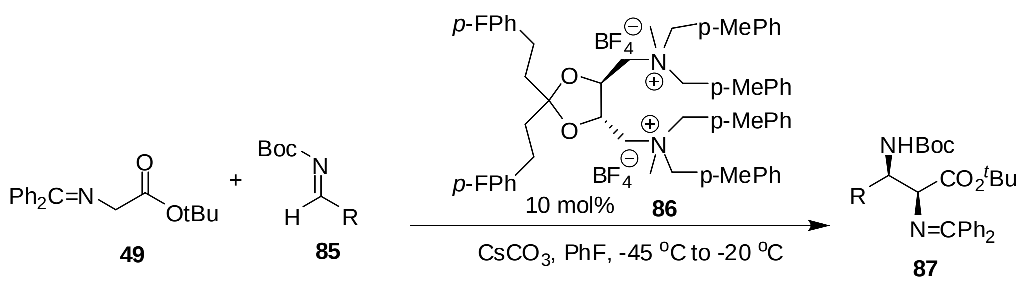


Figure 2.7 Maruoka's PTC catalyzed direct Mannich reaction.

Shibasaki reported another successful phase transfer catalyzed Mannich reaction using a tartrate-derived diammonium salt (TaDiAS) **86** (Table 2.9).[23] Fluorobenzene and cesium carbonate were the best solvent and base, respectively. The electron-withdrawing imine-protecting group, Boc, gave excellent reactivity and diastereoselectivity. Both aromatic and acetal moieties on the catalyst strongly affected the enantioselectivity. Placing a 4-fluorophenyl group at the C2 position of the acetal side chain improved enantioselectivity. A variety of aromatic and α,β-unsaturated imines **85** were suitable substrates. Because of the synthetic difficulty, *N*-Boc C-aliphatic imines were not applied.

Table 2.9 Shibasaki's PTC catalyzed direct Mannich reaction.



R	% yield	*syn/anti*	% ee (*syn*)	R	% yield	*syn/anti*	% ee (*syn*)
Ph	98	99:1	70	*p*-FPh	99	49:1	72
p-MeOPh	95	19:1	82	*p*-ClPh	87	49:1	58
p-MePh	98	49:1	80	*o*-Np	87	>19:1	60
m-MePh	96	19:1	70	*o*-HSPh	98	19:1	80
o-MePh	99	32:1	68	(*E*)-PhCH=CH	86	19:1	66

2.2. Results and Discussions

In an effort to extend the PTC process to oxygenated glycolate products, we previously reported asymmetric PTC-catalyzed alkylations with oxygenated substrates using the novel alkoxyacetophenone **88** (Figure 2.8).[24] The nature of the protecting group and substitution pattern on the aryl ketone proved to be critical for high selectivity and good reaction rates. This method provides a convenient route to a variety of alkylated hydroxy products with high selectivity. Previous to this work, asymmetric glycolate alkylation was limited to chiral auxiliaries.[25]

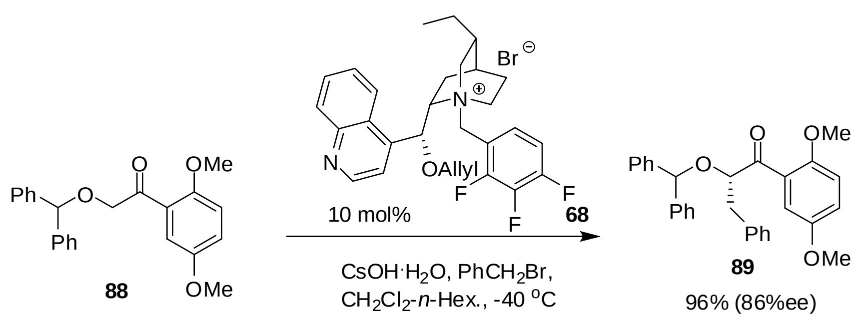
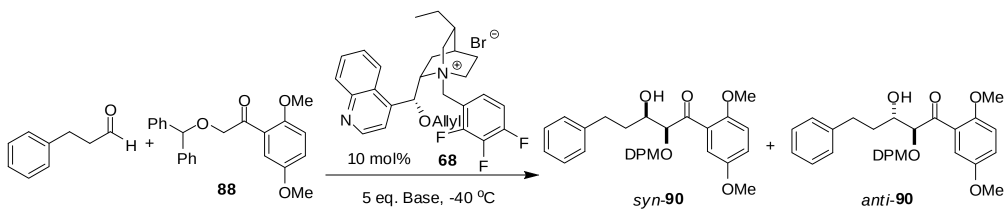


Figure 2.8 PTC-catalyzed glycolate alkylation.

2.2.1. Direct PTC Catalyzed Glycolate Aldol Reactions

Initially the direct aldol reaction of DPM (diphenylmethyl)-protected 2,5-dimethoxyacetophenone derivative **88** was explored using the *N*-trifluorobenzyl cinchonidinium catalyst of Park and Jew **68**-CD^+Br^-.[26] Solid-liquid-phase conditions with either cesium hydroxide or sodium methoxide in THF gave product **90** from dihydrocinnamaldehyde with poor diastereoselectivity and no enantioselectivity at -40 °C (Table 2.10). In toluene, the yield was decreased. Relatively weaker bases such as sodium hydroxide and sodium carbonate did not give any product at this temperature. The phosphazine base, BTPP, also failed to give desired product.

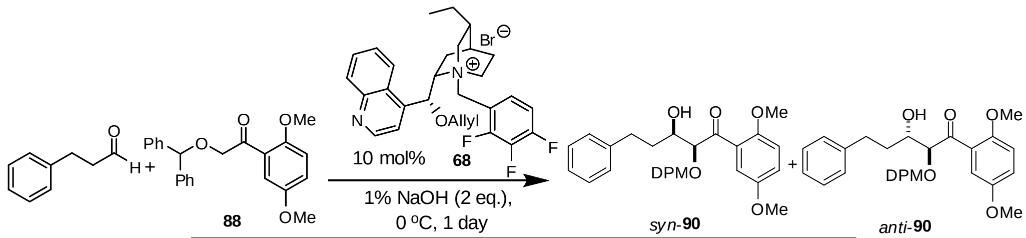
Table 2.10 PTC catalyzed solid-liquid-phase glycolate aldol reaction.



base	solvent	time	yield%	*syn*:*anti*	ee% *syn*
$CsOH\cdot H_2O$	THF	1 day	45	3:1	0
NaOMe	THF	1 day	83	2.5:1	0
NaOMe	Tol.	1 day	61	3:1	0
NaOH	THF	1 day	N. R.		
Na_2CO_3	THF	1 day	N. R.		
BTPP	THF	1 day	No desired prod.		

Liquid-liquid conditions with 1% aqueous sodium hydroxide showed slight improvement in enantioselectivity at 0 °C (Table 2.11). THF solvent gave the best syn/anti selectivity (3.9:1) and 1,2-dimethoxyethane gave the best yield (66%). Benzaldehyde gave a very low yield (15%) in toluene under these conditions.

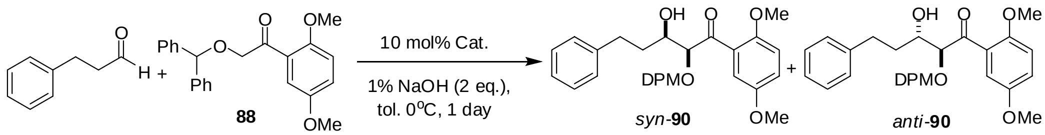
Table 2.11 PTC catalyzed liquid-liquid-phase glycolate aldol reaction.



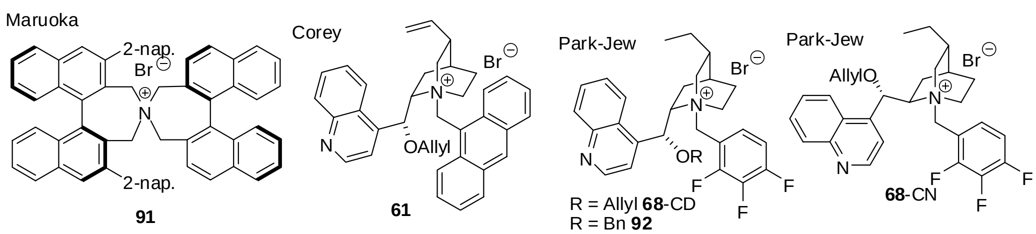
solvent	yield%	*syn*:*anti*	ee% *syn*
Tol.	53	3.7:1	7
CH_2Cl_2+Hexanes (1:5)	40	3.9:1	
THF	63	2:1	
CH_2Cl_2	8.4	3.5:1	
DME	66	2.5:1	
Dioxanes	51	2:1	

The catalyst was then changed to the pseudo-enantiomeric **68**-CN^+Br^- with only slight improvement in the enantioselectivity, 22% ee for the *syn*-product (Table 2.12). Surprisingly, this change to the cinchonium catalyst **68** resulted in production of the same enantiomeric product. Use of Maruoka's bis-binaphthyl catalyst **91** gave only trace product with little selectivity (7%, 6% ee). Corey's catalyst **61**-CD gave opposite stereoselectivity. Self condensation products were not observed under any conditions with dihydrocinnamaldehyde as substrate.

Table 2.12 Different PTCs catalyzed liquid-liquid-phase glycolate aldol reaction.

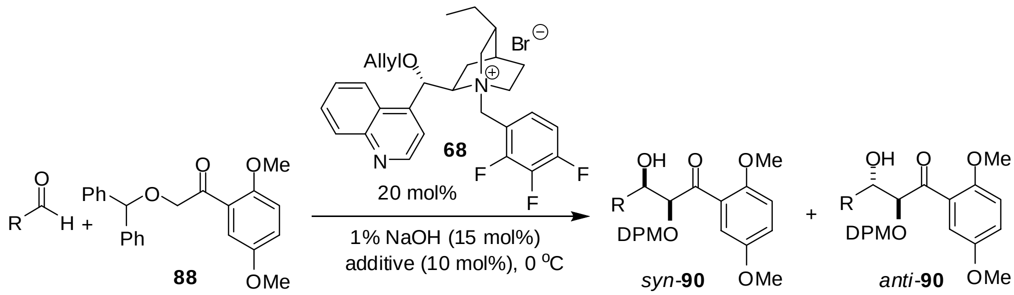


PTC		yield%	syn:anti	ee% syn
Maruoka **91**		7	4.1:1	6
Corey (CD) **61**		15	5.7:1	-20
Park-Jew (CD)	R= Allyl **68**	50	4.9:1	8
	R= Bn **92**	53	4.9:1	7
Park-Jew (CN) **68**		45	3.8:1	22



With Park-Jew's cinchonium bromide catalyst **68**-CN, use of catalytic amount of aqueous NaOH as base and ammonium chloride as an additive in toluene did not improve the yield or selectivity (Table 2.13). Decreasing the reaction time (2 h) lowered the yield. Switching the solvent to THF induced no enantioselectivity. Benzaldehyde did not show enantioselectivity under these conditions.

Table 2.13 Effect of NH_4Cl on PTC catalyzed liquid-liquid-phase glycolate aldol.



R	additive	solvent	time (h)	% yield	*syn*:*anti*	ee% *syn*
$Ph(CH_2)_2$	none	tol.	24	51	3.9:1	25
$Ph(CH_2)_2$	NH_4Cl	tol.	24	55	3.8:1	25
$Ph(CH_2)_2$	NH_4Cl	tol.	2	9	3.6:1	21
$Ph(CH_2)_2$	NH_4Cl	THF	2	10	1:1	0
Ph	NH_4Cl	tol.	24	35	7:1	0

2.2.2. PTC Catalyzed Mukaiyama-Type Glycolate Aldol Reactions

The silyl enol ether of **88** was then made and explored under Corey's cinchonium fluoride catalyst conditions.[13] Compound **88** was treated with LDA and trapped with TMSCl to give **93** as a stable white solid, which is simply purified by filtration and crystallization (Figure 2.9). Fortunately, as a silyl enol ether, **93** is easily manipulated, unlike the corresponding silyl ketene acetal of the protected glycine used in previous PTC aldol studies, which is easily hydrolyzed. The difluoride catalyst **94**-$CN^+HF_2^-$ was easily made from its corresponding bromide salt **68** by passing it through an Amberlyst A-26 (OH^-) ion exchange column, followed by acidification (Figure 2.9).[13]

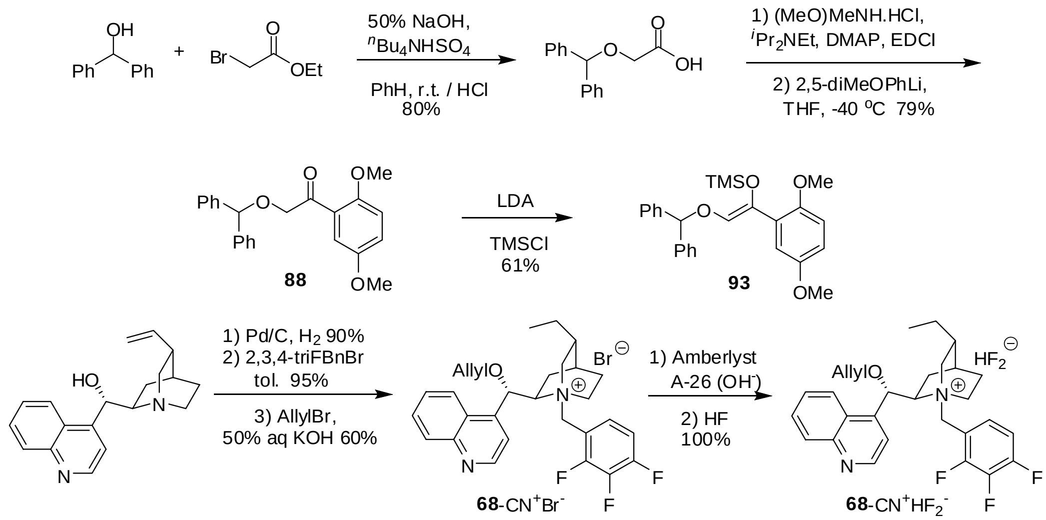
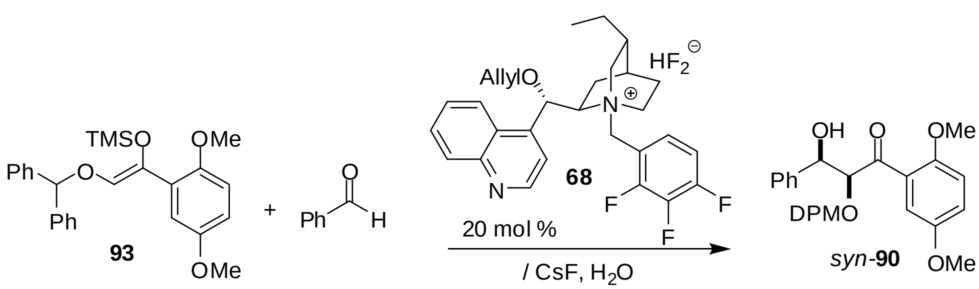


Figure 2.9 Preparation of substrate and catalyst.

Reaction of **93** with benzaldehyde under PTC conditions gave the differentially protected aldol product **90** following treatment with cesium fluoride and water (Table 2.14). In dry THF with the hydrogen difluoride catalyst **68**-$CN^+HF_2^-$ at -45 °C, the yield of **90** was low (35%); however, the selectivity was dramatically improved to 75% ee. In all cases with this substrate, a single *syn*-diastereomer was obtained. Protected glycine PTC aldol reactions typically give a mixture of diastereomers. Various solvents and combinations were also explored under these aldol conditions. Use of toluene, a mixture of dichloromethane and hexanes, and DME did not improve the yield. Surprisingly, use of reagent grade THF with **68**-$CN^+HF_2^-$ improved the rate of the reaction, requiring 1.5 h for completion, and the yield and selectivity also increased (78%, 75% ee). Trace water in this case appears to improve the catalyst turnover and the selectivity. Use of a 1/1 reagent THF/ DMF solvent mixture with

68-CN$^+$HF$_2^-$ proved to be superior, with an 87% yield and an 80% ee for the *syn*-product **90**. Reagent grade THF used alone proved to be the most practical and general solvent for the other aldehyde substrates.

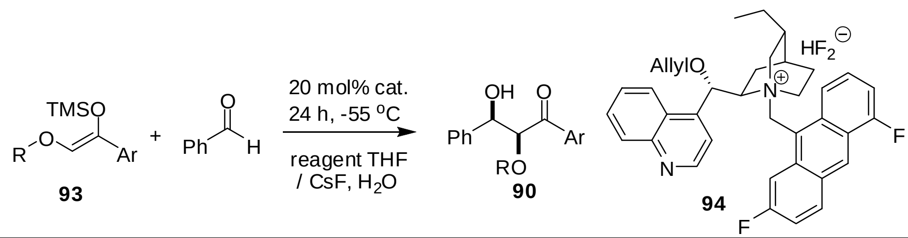
Table 2.14 Effect of solvents on the PTC catalyzed glycolate aldol reaction.



solvent	aldehyde load.	time	temp. (°C)	yield%	ee%
Tol.	8 eq.	> 1day	-45	Trace	
DCM:Hex (3:1)	8 eq.	> 1 day	-45	Trace	
THF	8 eq.	1 day	-45	35	75
THF	8 eq.	2 days	-45	49	67
THF (MS 4Å)	8 eq.	1 day	-45	41	0
reagent THF	2 eq.	1.5 h	-45	78	75
reagent DME	8 eq.	1 day	-45	62	78
DME	8 eq.	1 day	-45	19	37
reagent DME + 3% H_2O	8 eq.	1 day	-45	TMS removal	
reagent THF	2 eq	1 day	-55	76	80
THF/DMF	8 eq.	19 h	-78	87	80

Using the corresponding cinchonidinium catalyst **68-**$CD^+HF_2^-$, the isolated yield increased to 52%; however the selectivity dropped to 41% ee (Table 2.15). Use of the Corey-Lygo catalyst **61**-$CN^+HF_2^-$ extended the reaction time and improved the selectivity (78% ee), but gave a lower yield (52%). Using the optimal catalyst **68**-$CN^+HF_2^-$, the temperature was lowered to -55 °C, to give **90** in 76% yield and 80% ee. Use of the novel difluoroanthracenyl catalyst **94**-F_2-$CN^+HF_2^-$, recently found in the bromide form to give highly selective glycine alkylations,[27] improved the aldol reaction in **90** with an 83% ee. Unfortunately, the isolated yield dropped to 40% in this case.

Table 2.15 Effect of silyl enol ether substrates and catalysts on the PTC aldol.

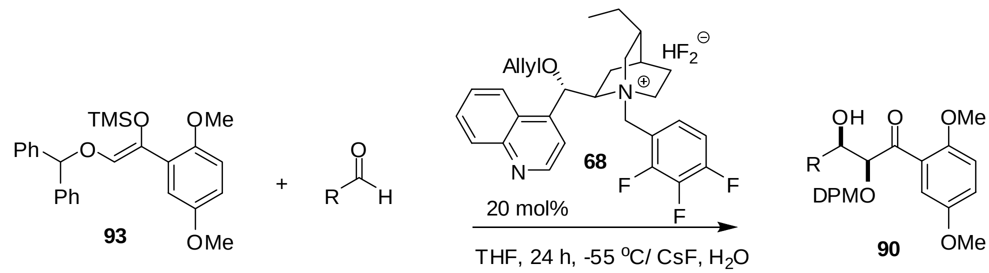


Ar	R	catalyst	% yield	*syn*:*anti*	ee% *syn*
2,5-diMeOPh	DPM	**68**-$CN^+HF_2^-$	76	> 99:1	80
2,5-diMeOPh	DPM	**68**-$CD^+HF_2^-$	52	> 99:1	41
2,5-diMeOPh	DPM	**61**-$CN^+HF_2^-$	52	> 99:1	78
2,5-diMeOPh	DPM	**94**-F_2-$CN^+HF_2^-$	40	> 99:1	83
2,5-diMeOPh	Bn	**68**-$CN^+HF_2^-$	41	>99:1	86
Ph	DPM	**68**-$CN^+HF_2^-$	58	6.3:1	15
2-MeOPh	DPM	**68**-$CN^+HF_2^-$	23	>99:1	52
4-MeOPh	DPM	**68**-$CN^+HF_2^-$	18	3:1	6
2,4-diMeOPh	DPM	**68**-$CN^+HF_2^-$	16	>99:1	60

Variations of the aryl group of the silyl enol ether **93** were also explored. With phenyl in place of the 2,5-dimethoxyphenyl group, the aldol product with benzaldehyde was obtained in a 58% yield with a greatly reduced enatiomeric excess of 15%. With the 2-methoxyphenyl substrate variation, a 52% ee was obtained with a 23% yield. 4-Methoxy- and 2,4-methoxy variants gave only trace aldol product (18%) with poor diastereoselectivity (*syn/anti* = 3:1) (Table 2.15).

Optimized conditions with **68**-$CN^+HF_2^-$ in reagent grade THF were used with a wide range of aldehydes (Table 2.16). In most cases, a single *syn*-diastereomer **90** was again produced. Aromatic aldehydes all reacted with good to excellent results. 4-Biphenylcarboxaldehyde and *o*-methoxybenzaldehyde with yields and selectivities from 70% to 80% were typical. 2-Naphthaldehyde was also efficient again, with a single *syn*-diastereomer in 79% ee. Unfortunately, alkyl and *α,β*-unsaturated aldehydes reacted with lower yield and selectivity. Although conclusions concerning mechanistic details are premature at this time, it can be pointed out that the C2 stereocenter in the product **90** is *S* using either the cinchonine catalyst **68**-CN or cinchonidine **68**-CD as demonstrated below. This is consistent with the major *S*-isomer obtained previously for alkylation of **88** using **68**-CD.

Table 2.16 The scope of the PTC catalyzed glycolate aldol reaction.



RCHO	% yield	*syn*:*anti*	ee% *syn*	RCHO	% yield	*syn*:*anti*	ee% *syn*
Ph	76	>99:1	80	Napth	69	>99:1	79
4-MeOPh	30	>99:1	78	2-MeOPh	70	>99:1	77
4-MePh	58	>99:1	78	2-MePh	57	>99:1	75
4-PhPh	77	>99:1	75	2-PhPh	45	20:1	83
4-ClPh	85	10:1	65	4-NO_2Ph	20	4:1	35
3-furyl	33	>99:1	62	2-furyl	86	6:1	53
$Ph(CH)_2$	36	>99:1	44	$Ph(CH_2)_2$	23	2:1	45
^{i}Pr	11	2:1	43	$BnOCH_2$	25	1:1	33
^{c}Hex	11	5:1	39				

Fortunately, the enantioselectivity of the aldol product was significantly increased on crystallization (Figure 2.10). The major (2*S*,3*R*) *syn*-diastereomer **90**, obtained from addition to benzaldehyde originally at 80% ee, was enriched to 95% ee (65%) following crystallization and filtration of a racemic, conglomerant solid. Elaboration to differentially protected products and proof of the absolute stereochemistry were carried out from this intermediate. Treatement with acetyl chloride and pyridine gave an acetate intermediate, which was unambiguously confirmed by single-crystal X-ray analysis (Figure 2.11). This intermediate was then subjected to titanium chloride at low temperature to effect removal of the diphenylmethyl (DPM) group. The resultant hydroxy ketone **95** (Ar = 2,5-dimethoxyphenyl) was subjected to Shibizaki modified Baeyer-Villiger conditions,[28] involving stiochiometric TMS peroxide, catalytic tin tetrachloride, and (±)-cyclohexyl bis-sulfonamide, to give aryl ester **96** with a 79% isolated yield. Transesterification, with concomitant acetate hydrolysis, gave the known (*S*,*R*)-diol methyl ester **97**.[29]

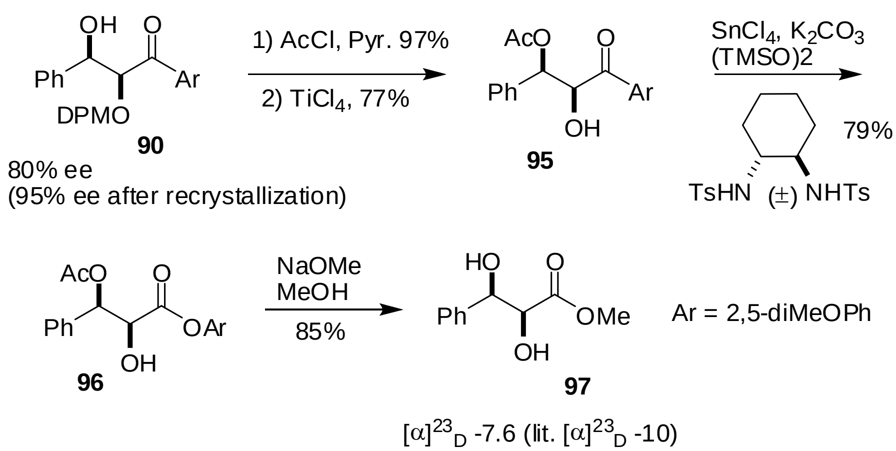


Figure 2.10 Structural proof and elaboration.

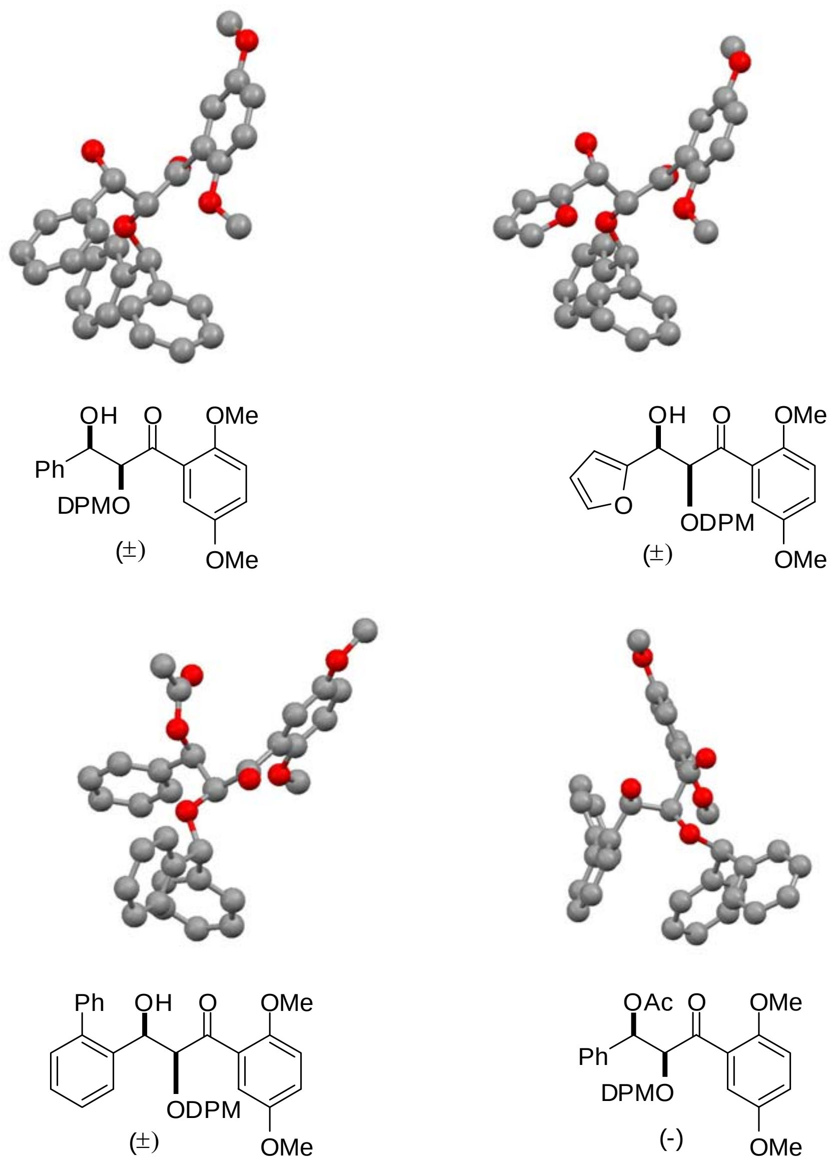


Figure 2.11 X-ray structures of aldol products.

2.3. Conclusion

In summary, a new approach to asymmetric glycolate aldol additions has been developed using readily available catalysts under mild PTC conditions. Differentially protected *syn*-1,2-diols are produced with very high diastereoselectivity and good enantioselectivity. Simple recrystallization and Baeyer-Villiger oxidation generate highly enantioenriched ester diol products. Refinements to the substrate and catalyst are anticipated to lead to further improvements and synthetic applications.

2.4. References

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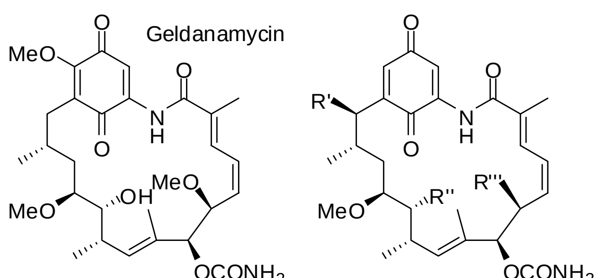
Chapter 3. Design and Synthesis of 8,9-Methylamido-Geldanamycin, an Amide Isostere for a Macrolide Antitumor Antibiotic

3.1. Introduction

3.1.1. Isolation and Bioactivity

Geldanamycin **98**, an anti-tumor Hsp90 inhibitor, was isolated from *Streptomyces hygroscopicus* var. *geldanus var. nova* (UC5208) in 1970 by researchers at Upjohn.[1] Its structure was determined by Rinehart and coworkers shortly thereafter.[2] Different from previously discovered anasamycin antibiotics [3] (e.g. rifamycins, [4] streptovaricins,[5] tolypomycins[6]), which have napthoquinone nuclei, it is the first member containing a benzoquinone nucleus. Other benzoquinone anasamycin antibiotics **99**, such as macbecin[7] and herbimycin[8], were disclosed later (Figure 3.1).



98 **99**

	R'	R''	R'''
Herbimycin A	-OMe	-OMe	-OMe
B	-H	-OH	-OMe
C	-OMe	OH	-OMe
Macbecin I	-OMe	-OMe	-Me

Figure 3.1 Benzoquinone anasamycins.

Geldanamycin demonstrated moderate activity in vitro against protozoa, bacteria, and fungi (MIC: 2-100 μM/ml), and extreme activity against KB cells (<0.001 μM/ml) and L1210 (<0.002 μM/ml). In vivo, geldanamycin was found to be orally active against the parasite *syphacia oblevata* at 0.5 mg/mouse/day for 4 days.[1] Later studies have found that geldanamycin was the most potent member of the ansamycin family, showing broad activity against the NCI 60 cell-line panel (13 nM avg., 70nM SKBr-3 cells).[9] 17-Allylamino-geldanamycin, a semi-synthetic compound, is currently in phase-III clinical trials.[10]

While initially thought to be a tyrosine kinase inhibitor, Neckers and coworkers showed that geldanamycin binds to Hsp90, an abundant cytosolic heat shock chaperone protein that regulates cell signaling.[11] Subsequent studies showed that geldanamycin binds to the ATP binding site (775 nM) of the 25 kD N-terminal domain of Hsp90, leading to inhibition of its protein folding and ATPase activities, which causes client protein degradation and cell death.[12] Hsp90's ATPase activity is essential for function in vivo, which includes complex formation with many other cofactor proteins such as Hsp70, Hsp40, and FKBP53.[13] Although Hsp90 is abundantly present in both tumor and normal cells, recent studies have confirmed that nearly all Hsp90 in cancer cells is found in multi-chaperone complexes.[14] In contrast, Hsp90 in normal cells primarily exists in free, uncomplexed form. A complexed form of Hsp90, consisting of the proteins Hsp70, Hsp40, Hop, and p23, is bound by geldanamycin with high affinity (12 nM), while Hsp90, isolated from normal cells, is bound by geldanamycin much less tightly (2-6 μM). It is believed that a conformational change, imposed by the other chaperone complex members, occurs in Hsp90 to cause to tighter geldanamycin binding.

3.1.2. Design of Geldanamycin Diamide Analog

X-ray crystal structures of the Hsp90-geldanamycin complex show that geldanamycin adopts a "C-clamp" shaped conformation that is higher in energy (+14.9 kcal/mol) than its free, unbound solution conformation (Figure 3.2).[9,15] The bound conformation possesses an *s-cis* amide with a dihydral angle (C22-N-C-O) of -165^{o} while the free conformation possesses a more stable *s-trans* arrangement (8^{o}). It was proposed that the Ser113 residue of Hsp90 catalyzed this conformational change, breeching the amide rotation barrier (>20 kcals) through an enol-keto tautomerism pathway.[16] It may be that the chaperone-complexed Hsp90 is a better catalyst for this conformation change process than the free form of Hsp90.

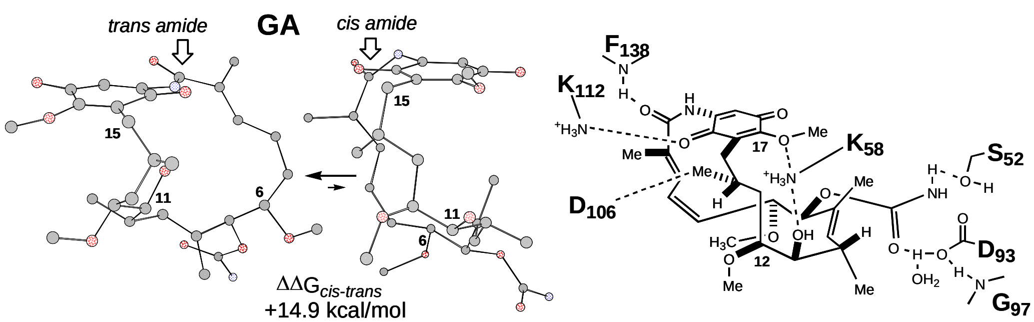


Figure 3.2 Structure of geldanamycin-Hsp90 binding complex.

Our plan is to create and test compounds that are biased toward the chaperone complexed form of Hsp90. Analogs that favor the *s-cis* "C-clamp" conformation should show improved activity and selectivity for binding complexed Hsp90. Targeted high affinity binding for complexed Hsp90 will allow for lower dosage levels and possess lower activity in normal cells, leading to lowered toxicity.[17]

The CLogP of geldanamycin at 2.06 is well below the Lipinski "rule of five" limit of 5 and it might be considered ideal, yet water solubility (0.05 mg/mL) and bioavailability present significant problems with assays and in clinical work.[17] Pharmokinetics, tissue distribution, and metabolism studies have shown that injected geldanamycin and 17-Allylamino-geldanamycin have moderate to good bioavailability (50-100%), from monitoring plasma levels following a subtoxic dosage (5 min, 10 mg/kg), while oral administration is poor (<24%).[17, 18] Hepatic, gastrointestinal, and nephrotoxicity have been noted in these studies with intravenous injection (2-60 mg/kg) in animals, showing poor to moderate tolerance. Studies with cytochrome P-450 reductase and super oxide formation suggest that most cellular geldanamycin toxicity is independent of Hsp90 kinase complex inhibition.[19] The hypothesis is that a more potent, water soluble analog of geldanamycin, constrained to the bound "C-clamp" conformation, can bind selectively to the kinase complexed form of Hsp90 with higher affinity, allowing for lower dosage levels.

Based on both the binding mechanism and an energetics bias, the C8,9 olefin is substituted by an *N*-methylamide surrogate. Conformational analysis and ab-initio quantum chemical calculations have been performed to assess the suitability of this amide substitution. The geometry of geldanamycin and the analog were optimized with density functional theory at the B3LYP/6-31G* level by Dr. Y. S. Lee (NIH, NCI). The Hsp90 bound amide *s-cis* "C-clamp" conformation of geldanamycin is 14 kcals/mol higher in energy than the unbound *s-trans* conformation ($K_{eq}>10^{11}$). The C8

Methyl occupies an axial position with the double bond adopting a typical sp^2 edgewise orientation. The C8,9-*trans* amide will enforce the bound conformation with the carbonyl and the C10 hydrogen coplanar and the *N*-methyl and C7-H coplanar.[20] We were pleased to find that the energy difference between the bound *s-cis* amide conformation and the free form dramatically reduces to +6.3 kcal/mol. This amide substitution also services to both simplify the synthesis and to create a more polar, water soluble template. The C8,9 amide analog shows a CLog P of 1.07. The analog synthesis is convergent with the additional amide, allowing for intermolecular amide formation, followed by macrolactam formation.

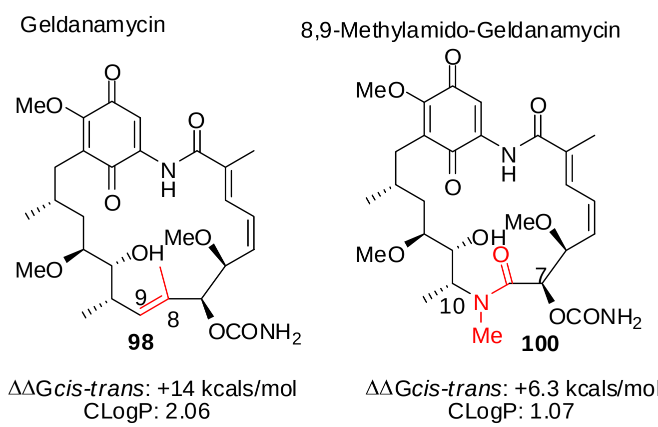


Figure 3.3 Geldanamycin and geldanamycin diamide anolog.

3.1.3. Synthesis of Geldanamycin

As a most potent antitumor antibiotic ansamycin family member, geldanamycin has ironically received less synthetic attention than the closely related macbecin and herbimycin, for which four total syntheses have been done.[21] The first and only total synthesis of geldanamycin was accomplished by Andrus' group using a 41-step linear route from 1,2,4-trimethoxybenzene **101**.[22] The key steps involved a chiral dioxanone auxiliary (**102**)-controlled asymmetric *anti*-glycolate aldol reaction[23] to set the C11,12 hydroxyl-methoxyl stereochemistry; also a chiral norephendrine auxiliary (**103**)- controlled *syn*-aldol[24] to set the methoxy-urethane stereochemistry at C6,7. The macrolactam ring was formed by amide coupling reagent Bop-Cl. Using the previously reported oxidative demethylation with simpler trimethoxybenzene,[25] azaquinone was obtained instead of the desired *p*-quinone. Finally, nitric acid[26] was able to form *o*-quinone geldanamycin as the major product 10:1 over the desired *p*-quinone geldanamycin **98**.

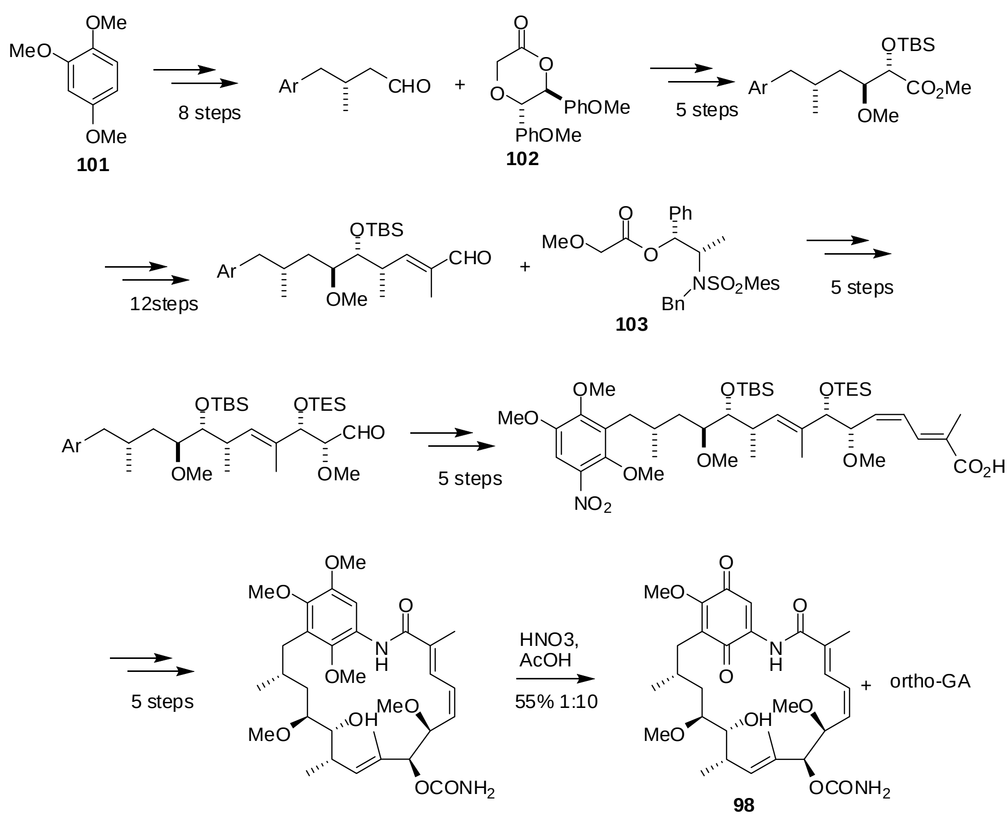


Figure 3.4 Total synthesis of geldanamycin.

A ring-closing metathesis[27] strategy was also explored to develop a more efficient and convergent synthetic route. The Grubbs imidazolium benzylidene ruthenium catalyst failed to give the ring closing product under various solvents, concentrations, modes of addition, and additives. Although this strategy has been successfully applied to close medium and large rings, the combination of the ring size of geldanamycin and a bulky trisubstituted olefin substrate **104** led to an unsuccessful result.[22]

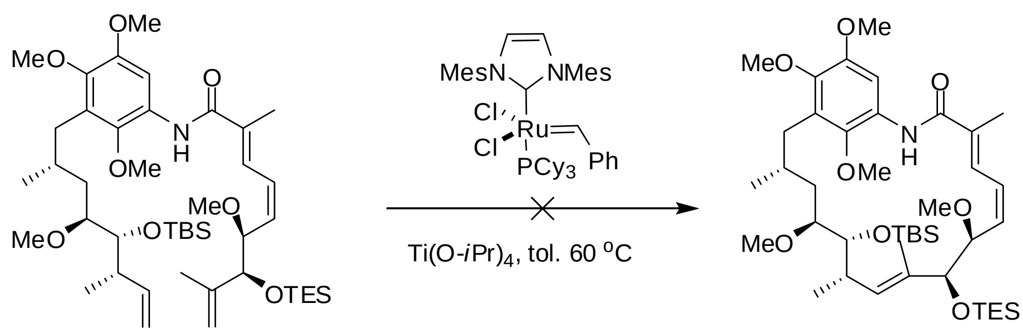


Figure 3.5 Ring-closing metathesis strategy.

A solution to the problem of selective *p*-quinone formation was developed using a 1,4-di-MOM protected model substrate **105**.[28] The MOM protecting groups were selectively removed with in situ generated TMSI. The resulting hydroquinone intermediate was oxidized to *p*-quinone **106** using mild Rapoport conditions[29] with Pd/C in the presence of air.

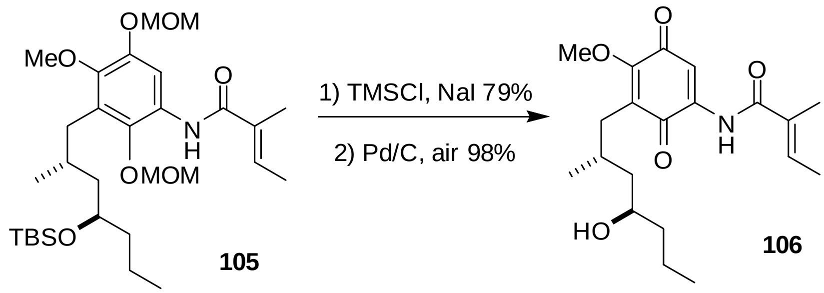


Figure 3.6 Model study of the selective *p*-quinone formation.

3.2. Results and Discussions

3.2.1. Retro-Synthesis of 8,9-Methylamido-Geldanamycin Analog

With our newly developed selective *para*-quinone formation strategy,[28] the desired diamide product **100** was planned from di-MOM precursor **107** (Figure 3.7). With the introduction of the new amide bond, an efficient and convergent route was successfully used to assemble the precursor **107** from diamine **108** and diacid **109**. The 8,9-methylamide bond was formed first to couple these two pieces together, followed by deprotection of the aniline and acid and another amide coupling to form the macrolactam **107**. The right-hand piece **108** was synthesized using Evans oxazolidinone auxiliary-controlled alkylation, [30] dioxanone auxiliary-controlled *anti*-glycolate aldol reaction,[23] and substrate controlled asymmetric reductive amination. [31] The left-hand piece **109** was assembled with Horner-Wadsworth-Emmons olefin coupling, [32] Ando olefin coupling, [33] and norephendrine auxiliary controlled *syn*-glycolate aldol.[24]

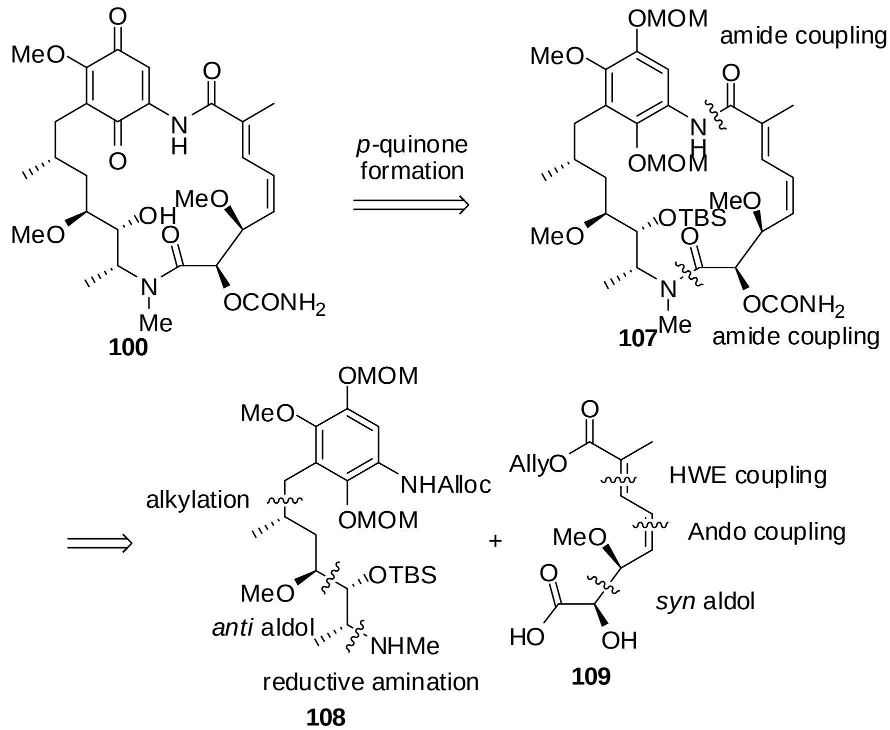


Figure 3.7 Retrosynthetic analysis of 8,9-methylamido-geldanamycin analog.

3.2.2 Synthesis of the Left Hand Piece of the 8,9-Methylamido-Geldanamycin

The anti-glycolate aldol substrate **114** was made from methoxy hydroquinone **110** according to our previously published procedure (Figure 3.8).[28] A variety of reaction conditions for the nitration and MOM reprotection were also explored to improve yields. Because of the strong acidic condition in the nitration step, removal of one MOM protecting group was inevitable. Recently, Blagg and Shen used a nitration reaction to synthesize an unnatural Hsp90 binding compound, radester, a hybrid of radicicol and geldanamycin.[34] The di-MOM protecting group on their substrate was intact under ammonium nitrate and trifluoroacetic anhydride conditions (Figure 3.9). A very similar nitration substrate **117** was obtained from benzaldehyde **111** by reduction with $NaBH_4$. Subjecting benzyl alcohol **117** to the same reaction condition, only a small amount of desired product **118** was formed, together with the benzyl alcohol recovered (Figure 3.9). Extended reaction time, higher nitration reagent loading, and various temperature ranges did not result in a higher yield. Other mild nitration conditions, such as $Cu(NO_3)_2/Ac_2O$ and NO_2BF_4/DMF, produced multiple products or decomposition.

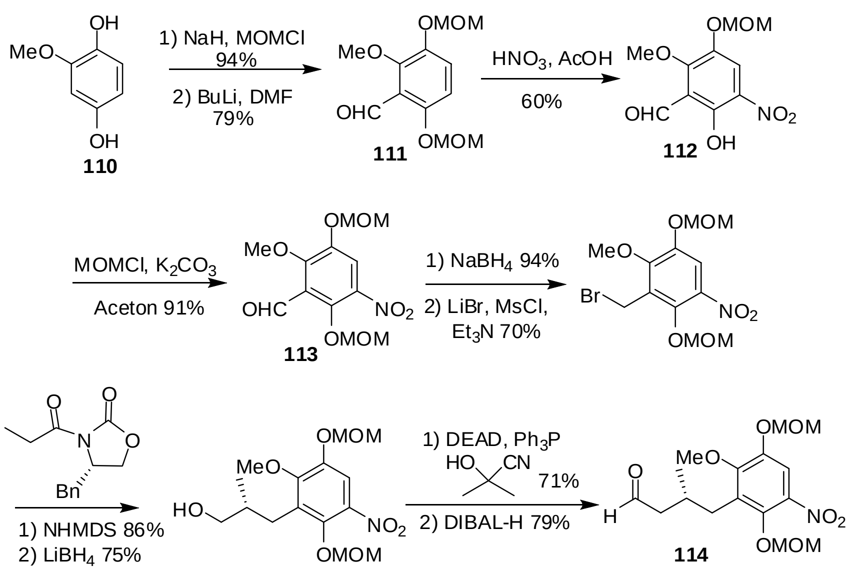


Figure 3.8 Synthesis of the *anti*-aldol aldehyde substrate.

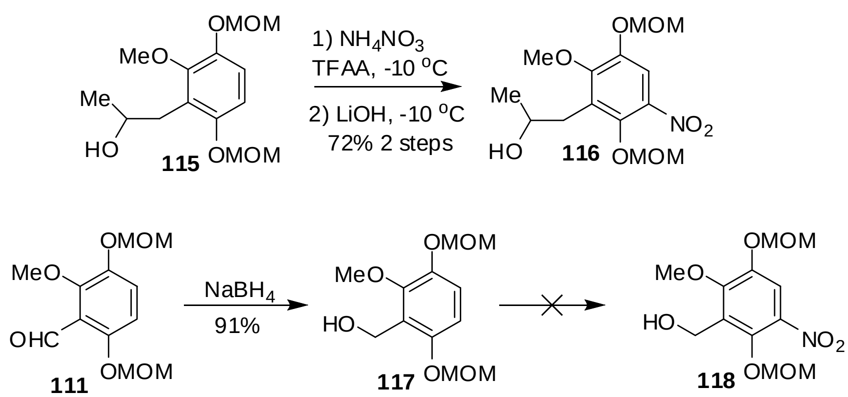


Figure 3.9 Nitration of the aromatic core.

Using excess amount of KH in THF with phase transfer catalyst $n\mathrm{Bu_4N^+I^-}$ as indicated in our previous publication,[28] we were not be able to achieve a good yield. After extended reaction time (two days), a significant amount of decarbonylative product **119** was isolated, and the structure was confirmed by NMR and X-ray analysis (Figure 3.10). With a milder organic base (Et_3N) and a shorter time period (one hour), the di-MOM protected product **113** was obtained with an 81% yield. Switching the triethylamine to inorganic base potassium carbonate further increased the yield to 91% (Figure 3.8).

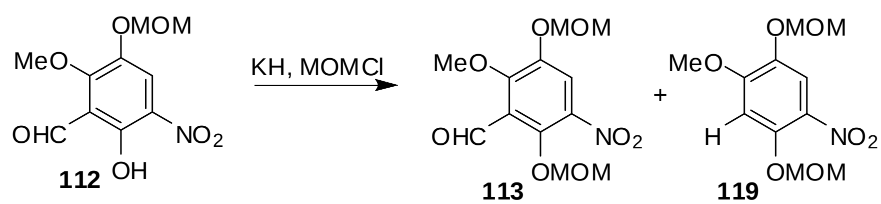


Figure 3.10 MOM ether reinstallation.

S,S-Bis-4-methoxyphenyldioxanone **102** was treated with 2 equiv of dicyclohexylboron triflate and 2.5 equiv of Et_3N to give the locked *E*-boron enolate (Figure 3.11). Aldehyde **114** was then added to the enolate solution to generate the *anti*-glycolate aldol adduct **120** in 70% yield with 8:1 selectivity.[23] The attack of the aldehyde is constrained to a closed Zimmerman-Traxler chair arrangement on the *si*-enolate face away from the C5 methoxyphenyl. The amount of the boron triflate and triethylamine is critical. Too much boron triflate (3 equiv) led to very poor reactivity and only a tiny amount of aldol product. Converting the newly generated secondary alcohol as a methoxy group with Meerwein salt gave **121** with quantitative yield. NaOMe (1 mol%) catalyzed lactone-ester exchange provided methylester **122**. A higher amount of NaOMe (10 mol%) generated multiple products. The benzyl ether was then oxidatively removed using CAN and the resulting alcohol was protected with TBSCl to give **123**. Other benzyl ether protecting group cleavage methods, such as DDQ or Pd/C catalyzed hydrogenation, gave multiple products.

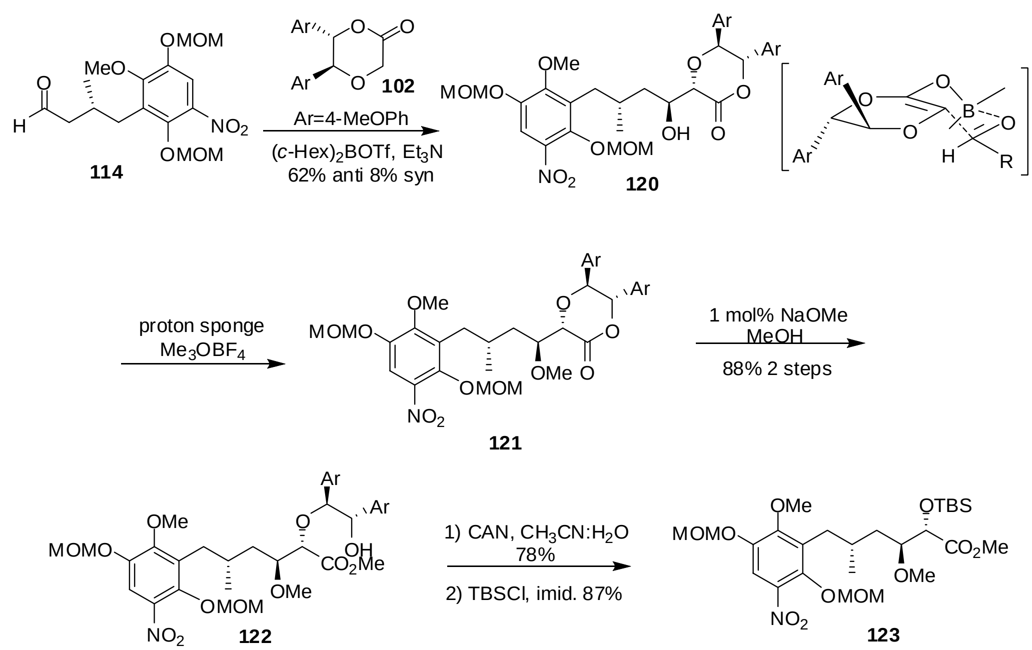


Figure 3.11 Application of the *anti*-glycolate aldol reaction.

The methyl ketone intermediate **125** was obtained through a three-step sequence from ester **123**. DIBAL-H reduced the ester **123** to aldehyde **124** at low temperature (-78 ^{o}C) in CH_2Cl_2. A 1.5 M DIBAL-H toluene solution was added to the reaction along the flask's inside wall to prevent formation of the over-reduced alcohol product.

Methylation with trimethylaluminum to the aldehyde **124** gave a pair of secondary alcohol diastereomers, which were oxidized to methyl ketone **125** by Dess-Martin periodinane.[35] The success of the reduction of nitrobenzene **125** to aniline **126** using Pd/C catalyzed hydrogenation depended on the nature of the alcohol solvent. Primary alcohols, such as methanol or ethanol, gave *N*-methyl or *N*-ethyl anilines in quantitative yield. With isopropyl alcohol as the solvent, the desired aniline **126** was obtained. The nitro reduction *N*-alkylation cascade process was unprecedented with methyl and ethyl alcohol. It is believed that primary alcohols were oxidized to aldehydes through a palladium catalyzed oxidation reaction. The resulting aldehydes reacted with aniline **126** to give imine intermediates, which were then reduced to the *N*-alkyl aniline under hydrogenation conditions. Bulkier alcohols, however, may be more slowly oxidized to ketones. Or, the resulting ketones were not as favorable as aldehydes to form imine intermediates. Aniline **126** was protected as the allylcarbamate **127**. The ketone group was converted to secondary amine **108** through a titanium(IV) isopropoxide mediated asymmetric reductive amination using the modified conditions of Bhattacharyya.[31] The diastereoselectivity was high (>20:1), and the absolute configuration of the newly generated C10 stereocenter was assumed to be *syn* in accord with a chelation controlled model. This assignment is tentative, awaiting an unambiguous X-ray crystal structure of derivatives of this intermediate. Magnesium perchlorate was also tried in this amination transformation[36] as a chelation metal reagent in the presence of methylamine and sodium borohydride or sodium cyanoborohydride; however, poor yield and selectivity were obtained.

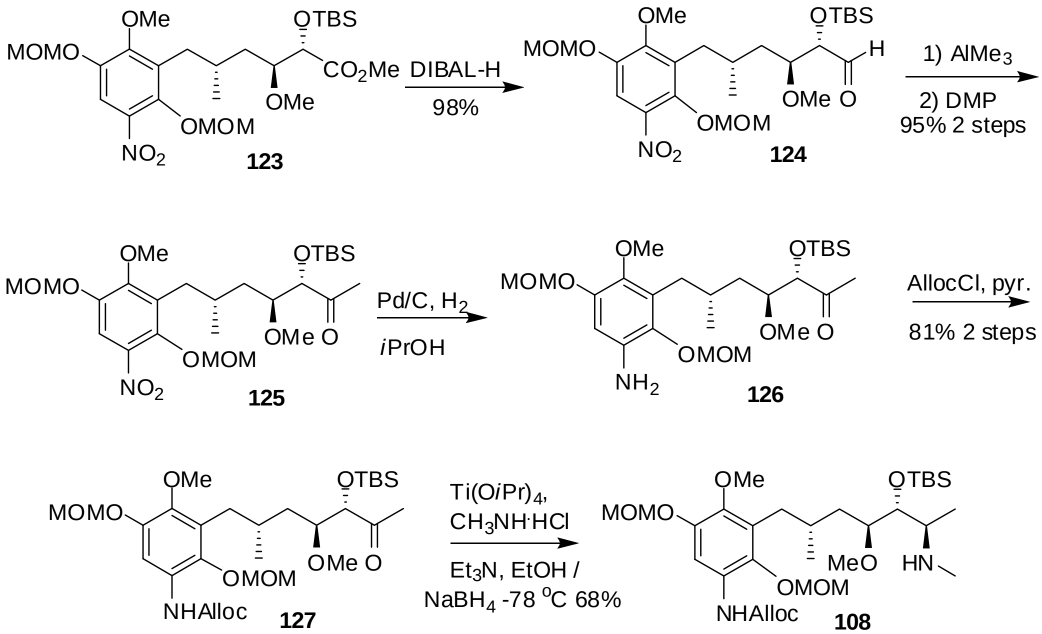


Figure 3.12 Completion of the left-hand piece of the geldanamycin diamide analog.

A Weinreb amide[37] approach was also explored to access the methyl ketone **125**. Attempts to synthesize Weinreb amides through trimethylaluminum or Grignard reagents following one-step ester-amide exchange have failed with intermediates **121**, **123**, and **128** (Figure 3.13). Finally, ester **123** was hydrolyzed to acid **129** in the presence of potassium trimethylsilanolate (Figure 3.14).[38] Other bases, such as LiOH , NaOH or KOH were not able to hydrolyze this ester in dioxane-H_2O, with or without H_2O_2. Weinreb amide **130** was then successfully prepared from acid **129** with 1,1'-carbonyldiimidazole (CDI) as the amide coupling reagent. Surprisingly, EDCI was not be able to produce the desired amide product, and multiple products were generated. Attempts to convert the Weinreb amide **130** to methyl ketone were unsuccessful with Grignard reagent or methyl lithium. It is known that nitro aryl compounds are able to react with Grignard reagents.

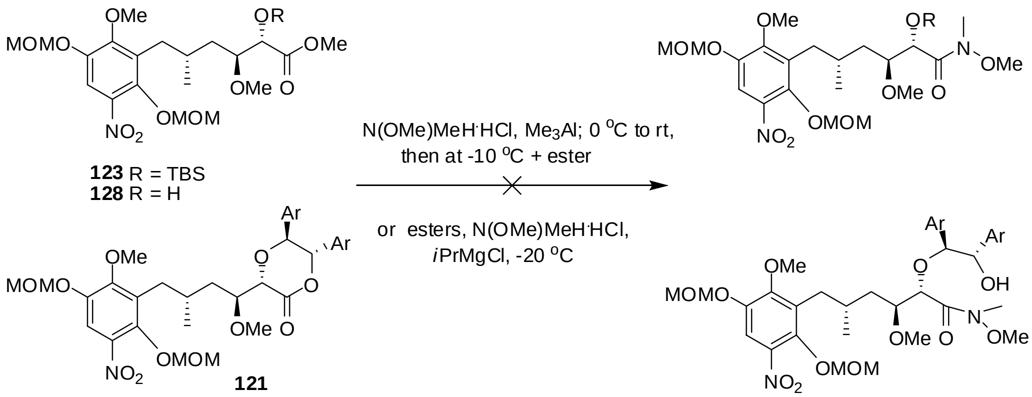


Figure 3.13 Weinreb amide synthesis using one-step ester-amide exchange strategy.

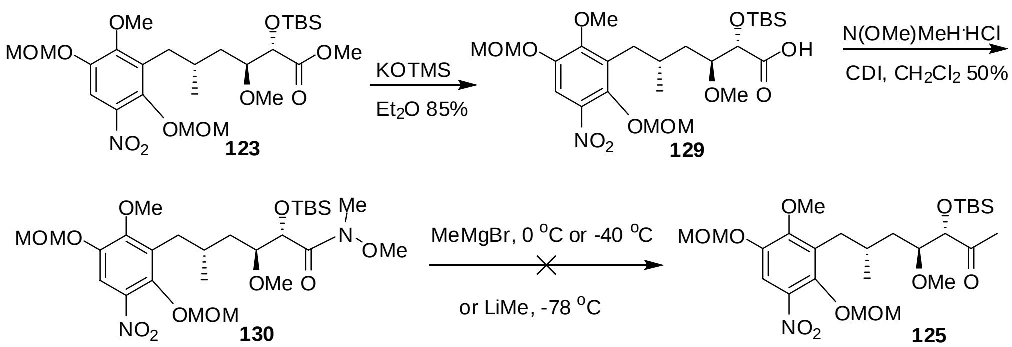


Figure 3.14 Weinreb amide approach to synthesis the methyl ketone intermediate.

3.2.3. Synthesis of the Right Hand Piece of the 8,9-Methylamido-Geldanamycin

4-Methoxybenzyl protected α-hydroxyacetaldehyde **131** was prepared according to Smith's procedure (Figure 3.15).[39] Using flash chromatography instead of distillation to purify the ozonolysis product greatly improved the yield to 93% from 53%. Our previously developed (-)-norephedrine-derived glycolate **103** reacted with dicyclohexyl boron triflate and triethylamine, followed by addition of aldehyde **131**, to generate *syn* aldol product **132** in 91% yield and >20:1 selectivity (Figure 3.15).[24] The resulting free alcohol was then protected by TMSCl. The norephedrine auxiliary was removed by DIBAL-H mediated half-reduction, and aldehyde **134** was obtained. Although the yield of the half-reduction step was high enough, it took an extremely long time to purify the product by flash chromatography because the unreacted substrate, desired product, and norephedrine have similar R_f values and coelute. A two-step process was also developed by reducing the ester **133** into a primary alcohol intermediate and then oxidizing the alcohol to aldehyde **134**. While lithium borohydride in THF did not provide a good yield (56%), addition of 3 equiv of methanol in the presence of 3 equiv of lithium borohydride in refluxing diethyl ether resulted in an 82% yield.[40] It was believed that methanol was a good proton source for this reduction through hydrogen-bonding. Another possibility was that methoxy-substituted lithium borohydrides formed in situ were the actual reducing species. The alcohol was conveniently separated from the unreacted substrate and norephedrine. Dess-Martin periodinane successfully oxidized the alcohol to aldehyde **134** with a 90% yield. The combination of TPAP and NMO gave a much lower 67% yield.[41]

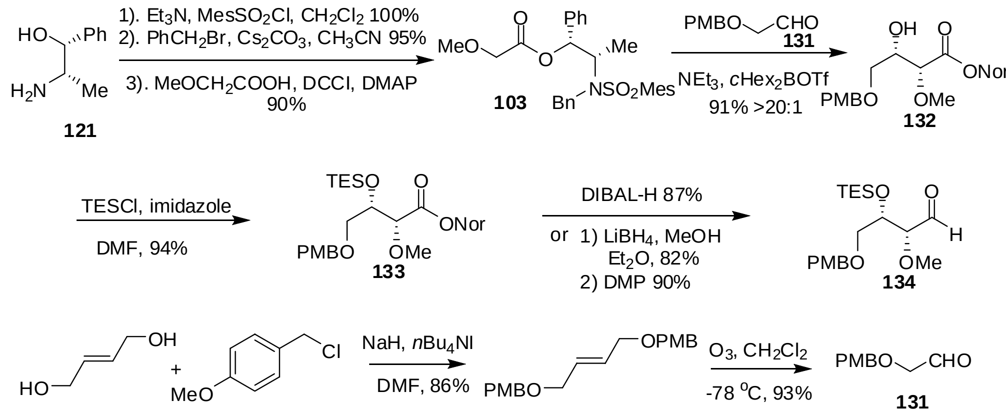


Figure 3.15 Application of the *syni*-glycolate aldol reaction.

To synthesize the *Z*-olefin intermediate **137**, a Touchard modified Ando reagent **135** was successfully performed with aldehyde **134** in the presence of TMG and sodium iodide additive at -78 °C (Figure 3.16).[33] Excellent yield (98%) and *Z/E* selectivity (>20:1) were obtained. For comparison, 2 equiv of the common Still-Gennari hexafluorophosphonate[42] in the presence of KHMDS and 18-crown-6 did not completely convert the aldehyde **134** to olefin **136** after extended time. The ester **136** was reduced to a primary alcohol by DIBAL-H in diethyl ether at low temperature (-78 °C). Dess-Martin periodinane then oxidized the resulting alcohol to the enal **137**.

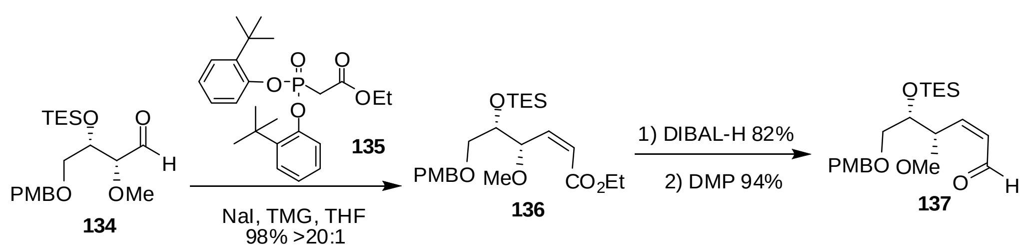


Figure 3.16 *Z*-Olefination using Ando phosphonate.

Following Roush's procedure,[32] enal **137** was reacted with allyl ester phosphonate **138** together with lithium chloride and DBU at 0 °C to give the desired *E,Z* diene ester **139** with excellent yield (98%) and selectivity (>20:1) (Figure 3.17). The PMB protecting group on diene ester **139** was oxidatively cleaved by DDQ in a mixed solvent of methylene chloride and water. CAN in acetonitrile and water was not a good alternative reagent for this deprotection, as the TES protecting group was removed before the PMB group. The newly generated alcohol **140** was oxidized to acid **142** through a two-step oxidation procedure. DMP oxidized the alcohol to aldehyde **141**, which was further oxidized to acid **142** by sodium chlorite and sodium dihydrogen phosphate in a mixture of *t*-butanol, water, and 2-methyl-2-butene. One-step oxidation from alcohol **140** to acid **142** using PDC in DMF, or the combination of diacetoxyiodobenzene and TEMPO[43] were futile. Other oxidation reagents, such as AgO or H_2O_2, were also tried in various solvents and temperatures; however, decomposition was observed.

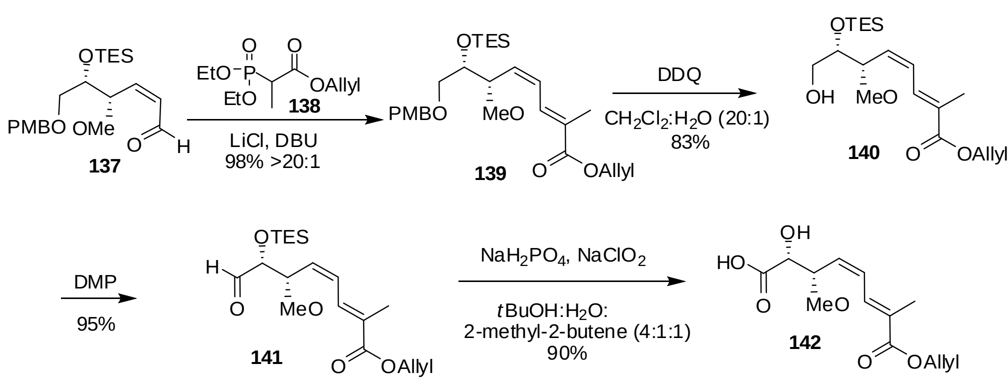
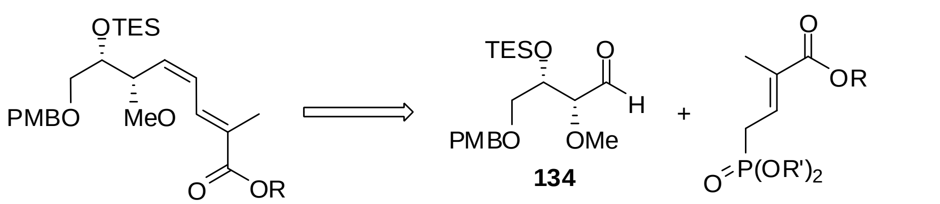


Figure 3.17 Completion of the left-hand piece of the geldanamycin diamide analog.

A more convergent route was also explored to synthesize the *E*,*Z*-dienoate **139** by a Horner-Wadsworth-Emmons reaction of the aldehyde **134** with unsaturated Still-Gennari[42] or Touchard modified Ando phosphonates **144-146** (Figure 3.18).[33] This strategy was recently applied in the total synthesis of (+)-macbecin[21c] and (+)-damavaricin D[44] with low selectivities (2.7:1, and 4:1, respectively) using the unsaturated Still-Gennari hexafluorophosphonates.



139 R = Allyl
143 R = Et

144 R = Allyl, R' = CH_2CF_3
145 R = Allyl, R' = *o*-*t*BuPh
146 R = Et, R' = CH_2CF_3

Figure 3.18 Retrosynthetic analysis of the olefin coupling with unsaturated phosphonates.

According to Nicolaou's procedure,[45] intermediate **149** was synthesized from (*Z*)-but-2-ene-1,4-diol through THP protection, Wittig reaction and THP deprotection (Figure 3.19). The bromination of the allyl alcohol **149** was accomplished by slowly adding methanesulfonyl chloride into a mixture of **149**, lithium bromide and triethylamine in THF.[46] The resulting bromide **150** was then submitted to Arbuzov conditions with 2,2,2-trifluoroethyl phosphite in the presence of a catalytic amount of tetrabutylammonium iodide to provide the unsaturated ethyl phosphonate **151** in 45%

yield.[47]

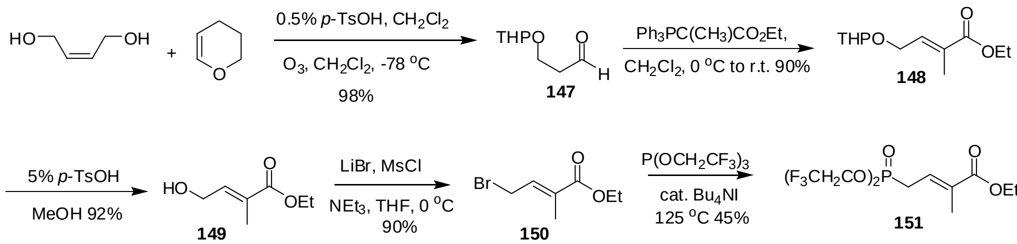


Figure 3.19 Synthesis o f the Still-Gennari ethyl phosphonate.

To synthesize the unsaturated allyl phosphonates **144** and **145**, ethyl ester **148** was converted to allyl ester **152** in the presence of lithium bromide, DBU, and allyl alcohol, to give an 88% yield (Figure 3.20).[48] Deprotection, bromination and Arbuzov reaction with tris(2,2,2-trifluoroethyl) phosphite and bis(2-*tert*-butylphenyl) ethyl phosphite[33] provided unsaturated allyl phosphonates **144** and **145**, respectively. Olefination between aldehyde **147** or **154** and Horner-Wadsworth-Emmons reagent **138**,[21c] unfortunately, gave poor *E*/*Z* selectivity (4:1 or 1.2:1).

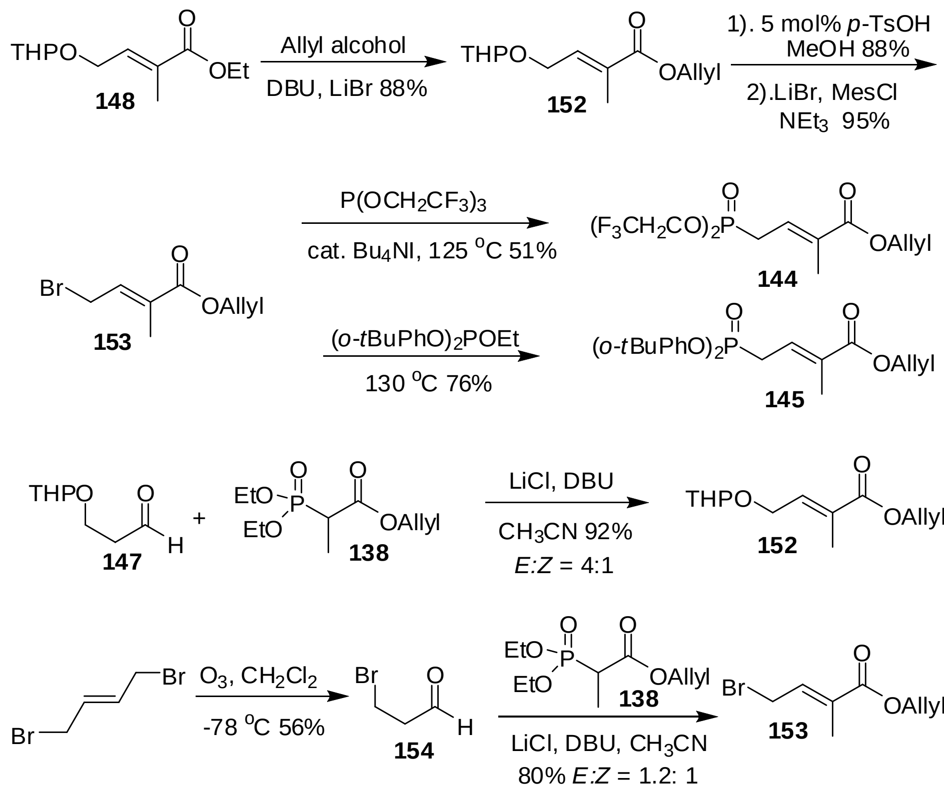
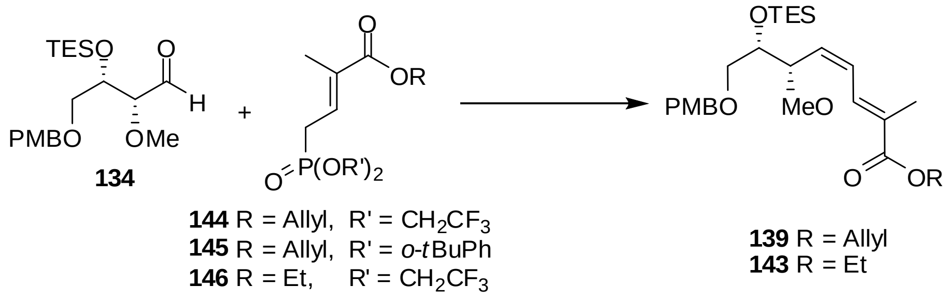


Figure 3.20 Synthesis of allyl phosphonates.

Aldehyde **134** was slowly added to an ether solution of Still-Gennari phosphonate anion, which was generated by deprotonation of the corresponding phosphonate in the presence of KHMDS or *n*-BuLi, at -78 ^{o}C, over one hour (Figure 3.21).[44] When KHMDS was used as base, 1.4 equivalents of allyl phosphonate **146** gave a better yield than ethyl phosphonate **144** with the same *E*,*Z*-selectivity. Switching the base to *n*-BuLi, eight equivalents of allyl phosphonate **146** gave better selectivity (4:1) but lower yield (50%). Deprotonation of Ando phosphonate **145** by TMG in THF at 0 ^{o}C gave a solution of the corresponding phosphonate anion.[33] Aldehyde **134** was slowly added to this anion solution at -78 ^{o}C to generate the dienoate **139** with a 61% yield devoid of selectivity.

Table 3.1 Olefin coupling with unsaturated phosphonates.



R	R'	conditions	% yield	(*E*,*Z*): (*E*,*E*)
Et	CH_2CF_3	KHMDS, Et_2O, -78 °C	30	2:1
Allyl	CH_2CF_3	KHMDS, Et_2O, -78 °C	76	2:1
Allyl	CH_2CF_3	*n*-BuLi, Et_2O, -78 °C	50	4:1
Allyl	*o*-*t*BuPh	NaI, THF, TMG (0 °C), aldehyde (-78 °C)	61	1:1

3.2.4. Coupling, Cyclization, and Completion of Geldanamycin Diamide

Initially, methyl ketone **125** was converted to secondary amine **155** with 85% yield by titanium(IV) isopropoxide mediated reductive amination.[31] HATU and *N*,*N*-diisopropylethylamine coupled the resulting amine **155** and acid **109** to give intermediate **156**. Other amide coupling reagents, such as PyBrop, BOP-Cl, and DEPC, did not give good reactivity.[49] A variety of reductive reagents, such as $NaBH_4{\cdot}S$, $Zn/NH_4Cl/MeOH$, $SnCl_2$, and $Pd/C/(NH_4)O_2CH$, failed to convert the nitrobenzene **156** to aniline **157**. Allyl ester **156** was then removed using palladium tetrakistriphenylphosphine and morpholine to generate the acid **158**.[50] Unfortunately, under all reductive conditions attempted, the aniline **159** was not obtained.

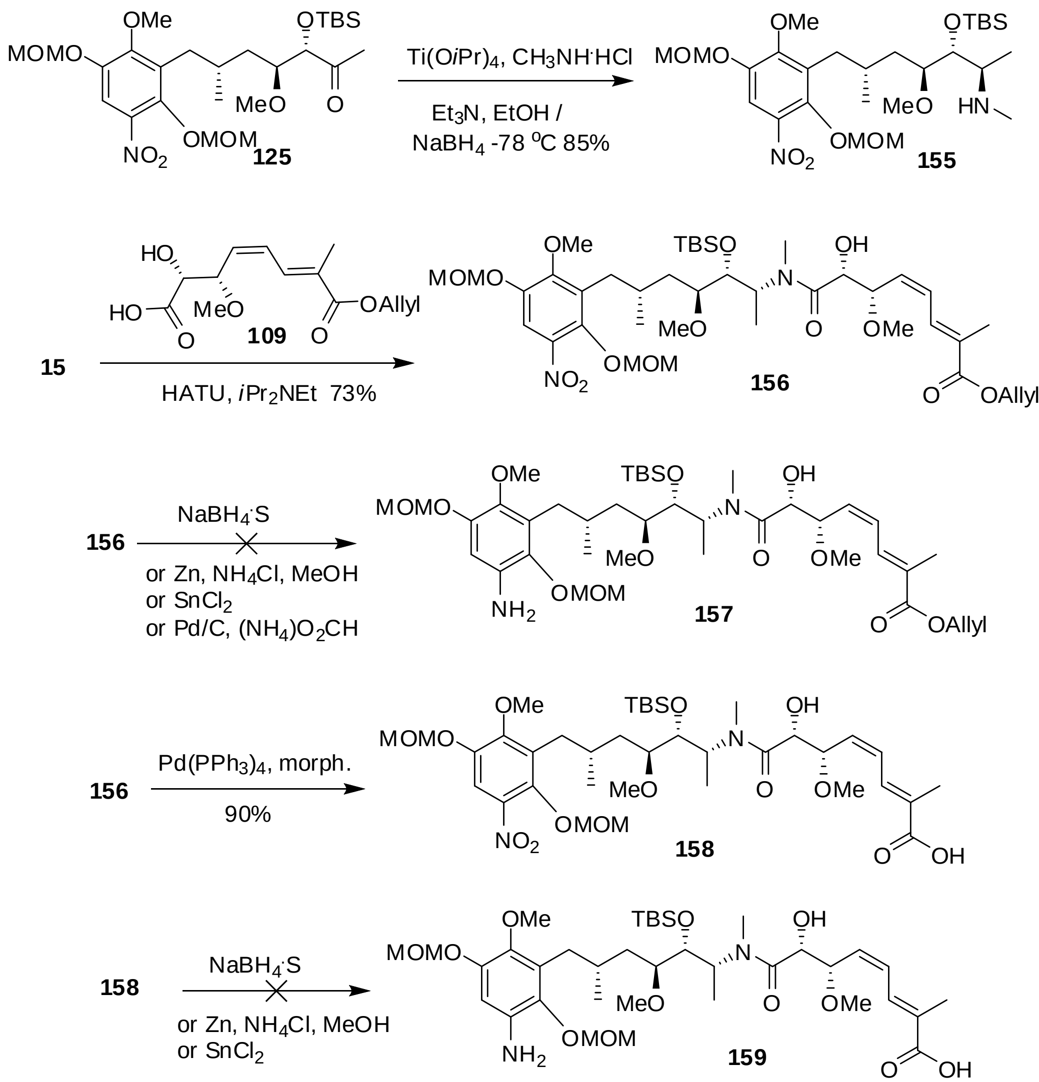


Figure 3.21 Reduction of the nitro benzene after 8,9-amide bond formation.

Amine **108** was then successfully coupled with acid **109** through an amide bond formation under HATU and DIPEA at 0 °C to generate the protected amino acid **160** as a pair of rotamers, which complicated the NMR analysis. Simultaneously removing both allyl ester and allylcarbomate protecting groups by $Pd(PPh_3)_4$ and morpholine produced an amino acid intermediate.[50] Use of HATU with DIPEA and catalytic amount of DMAP in methylene chloride (0.0005M) provided the macrolactam **161**. Following Kocovsky's procedure,[51] trichloroacetyl isocyanate was employed to form the protected carbamate. Deprotection with potassium carbonate produced the C7 urethane **107** in 86% yield. Deprotection of both MOM and TBS ether protecting groups with in situ generated TMSI provided the dihydroxyquinone, which was oxidized to the desired *p*-quinone macrolactam **100** by a catalytic amount of palladium on carbon and with the flask open to air.[28,29]

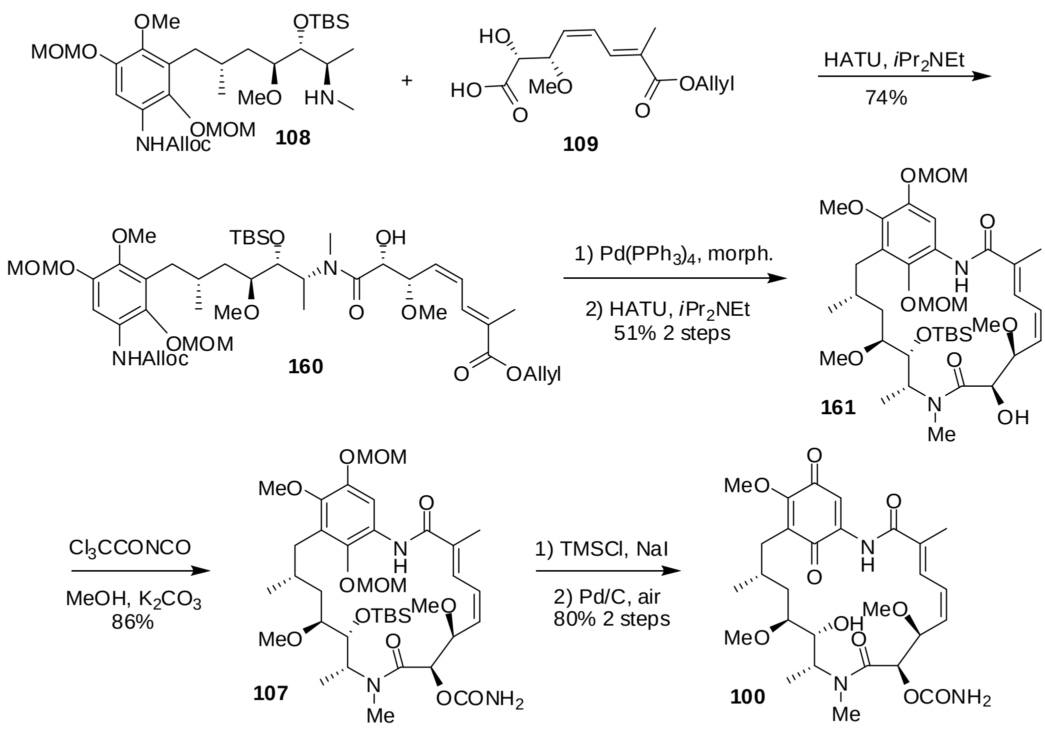


Figure 3.22 coupling, cyclization, and completion of Geldanamycin diamide.

3.3. Conclusion and Future Work

In summary, the first geldanamycin diamide analog has been made through a convergent route, involving 27 greatly simplified steps in its longest linear sequence. New synthesis methodologies, including auxiliary controlled asymmetric *anti*-glycolate aldol, *syn*-norephedrine aldol, and selective *p*-quinone formation, were used. This route can be applied to the synthesis of other GA-diamide analogs. Preliminary bioactivity assessment of this analog showed 100 times less potency than the geldanamycin natural product in cell and Hsp90 assays. This may due to the newly introduced 8,9-methylamido group, or the configuration of the C10 stereocenter. More analogs can be designed and synthesized to improve the bioactivity and further simplify the synthesis. Such might include inverting the C14 stereocenter, removing the C10 methyl group, removing the *N*-methyl group, and substitution of the *Z*, *E* diene by benzene.

3.4. References

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Chapter 4. Experimental Details and Data

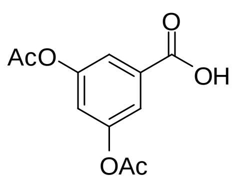
4.1. General Method and Materials

Air and water sensitive reactions were performed in flame-dried glassware under a nitrogen atmosphere. Water sensitive reagents were introduced via dry syringe or cannula. Methylene chloride, toluene, benzene, THF, diethyl ether, acetonitrile, DMSO, DMF, methanol, triethylamine and pyridine were dried by passing through columns of activated alumina. Hexanes, 1,2-dimethoxyethane, *p*-xylene were distilled with CaH_2. Other solvents, such as ethanol, isopropyl alcohol, acetone, and chloroform, were stored over molecular sieves. Reagents were purchased from Aldrich and Lancaster. Flash chromatography was carried out using 60-230 mesh silica gel. Radial chromatography was performed using 1, and 2 mm plates loaded with 230-400 mesh PF-254 gypsum bound silica. Analytical thin-layer chromatography (TLC) was performed with Merck silica gel 60 F_{254}, 0.25 mm pre-coated TLC plates. TLC plates were visualized using UV_{254} and cerium molybdate with charring. All ^1H NMR spectra were obtained with either 300 or 500 MHz Varian spectrometers using TMS (0.0 ppm) or chloroform (7.27 ppm) as an internal reference. Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), and dd (doublet doublet); and coupling constants are reported in Hertz (Hz). ^{13}C NMR spectra were obtained with either 75 or 125 MHz Varian spectrometers using chloroform (77.23 ppm) as the internal standard. Mass spectral data (HRMS, CI, EI, FAB) were obtained from the Brigham Young

University mass spectrometry facility. Optical rotations were obtained on a Perkin Elmer 241 polarimeter using the sodium D line at ambient temperature. Low temperatures were maintained using an immersion cooler with a cooling probe placed in an acetone bath. Combustion analysis was performed by M-H-W Laboratories, Phoenix, AZ.

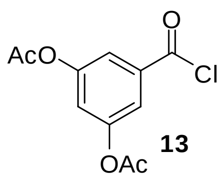
4.2. Synthesis of Resveratrol and Its Acetyl and Fluoro Analogs

4.2.1. Synthesis of Resveratrol



Preparation of 3,5-diacetoxybenzoic acid

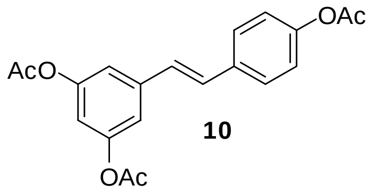
To a stirred solution of 3,5-dihydroxybenzoic acid (7.71 g, 50 mmol) in EtOAc (110 mL) were added acetic anhydride (12.25 mL, 130 mmol) and pyridine (8.08 mL, 100mmol) in an ice-water bath under a nitrogen atmosphere. The mixture was stirred at 0 °C for 40 min and then stirred at ambient temperature for 4 h. 98% Formic acid (2.36 mL, 60 mmol) was added and the resulting mixture was stirred for 1 h. Then, the mixture was poured into water and extracted with EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification of the residue via recrystallization from *n*-heptane/EtOAc provided 3,5-diacetoxybenzoic acid (8.97 g, 75%) as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.1 (bs, 1H), 7.73 (d, *J* = 2.1 Hz, 2H), 7.21 (t, *J* = 2.1 Hz, 1H), 2.32 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 169.0, 151.2, 131.5, 121.3, 121.0, 21.2; mp = 161–162 °C; HRMS (EI^+) found 238.0475 M^+, calcd 238.0477 for $C_{11}H_{10}O_6$; Anal. Calcd for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23. Found: C, 55.62; H, 4.37.



13

Preparation of 3,5-diacetoxybenzoyl chloride (13)

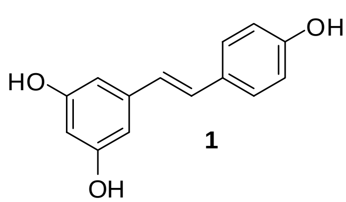
To a mixture of 3,5-diacetoxybenzoic acid (8.00 g, 33.59 mmol) and DMF (5 drops) added fresh distilled thionyl chloride (16 mL). The mixture was stirred for 15 min under nitrogen atmosphere at ambient temperature. Then it was refluxed for 2 h at 80 °C in a hot water bath. The excess thionyl chloride was evaporated under vacuum and toluene was added. Insoluble yellow solid was discarded. Toluene was evaporated under reduced pressure to give 3,5-diacetoxybenzoyl chloride **13** (8.23g, 96%) as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, *J* = 2.1 Hz, 2H), 7.29 (t, *J* = 2.1 Hz, 1H), 2.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 167.0, 151.4, 135.3, 122.8, 122.0, 21.2; mp = 89.5–91 °C; HRMS (EI^+) found 256.0130 M^+, calcd 256.0139 for $C_{11}H_9O_5Cl$; Anal. Calcd for $C_{11}H_9O_5Cl$: C, 51.48; H, 3.53. Found: C, 51.60; H, 3.68.



10

Preparation of resveratrol triacetate (10)

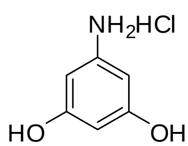
A 100 mL round bottom flask was charged with *p*-xylene (56 mL), $Pd(OAc)_2$ (62.86 mg, 0.28 mmol), *N,N*-bis-(2,6-diisopropylphenyl)-4,5-dihydro imidazolium chloride **16** (119.53 mg, 0.28 mmol), 3,5-diacetoxybenzoyl chloride **13** (7.19 g, 28 mmol), 4-acetoxystyrene **14** (5.35 mL, 33.6 mmol), and *N*-ethyl morpholine (4.2 mL, 33.6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. And the whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give resveratrol triacetate **10** (6.95g, 70%) as a white solid. Data are: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50 (d, J = 9.0 Hz, 2H), 7.12-6.94 (m, 6H), 6.82 (t, J = 2.1 Hz, 1H), 2.31(s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 169.2, 151.5, 150.6, 139.7, 134.7, 129.9, 127.9, 127.4, 122.1, 117.1, 114.6, 21.4; mp = 116-118 °C; HRMS (EI^+) found 354.1118 M^+, calcd 354.1103 for $C_{20}H_{18}O_6$; Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79, H, 5.12. Found: C, 67.93, H, 5.26.



1

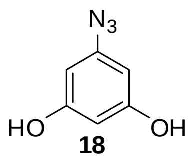
Preparation of resveratrol (1)

To a stirred solution of resveratrol triacetate **10** (6.02g, 17 mmol) in THF (170 mL) added a solution of NaOH (4.67g, 119 mmol) in water (170 mL). The mixture was stirred at ambient temperature for 2 h. Then 5 N HCl was added until the pH is 4. The solution is evaporated in vacuo to remove THF. Then it was extracted with EtOAc. The organic phase was washed with water and brine and dried over Na_2SO_4. The dried solution was filtered and evaporated. Purification via flash chromatography (35% EtOAc/hexane) gave resveratrol **1** (3.43 g, 88%) as a pale yellow solid. Data are: ^{1}H NMR (aceton-d_6, 300 MHz) δ 8.45 (s, 1H), 8.18 (s, 2H), 7.41 (d, J = 12.6 Hz, 3H), 7.05-6.82 (m, 6H), 6.53 (d, J = 3.3 Hz, 3H), 6.27 (t, J = 3.3 Hz, 1H); ^{13}C NMR (aceton-d_6, 75 MHz) δ 159.8, 158.4, 140.7, 129.8, 129.0, 128.7, 126.8, 116.5, 105.5, 102.7; mp = 259-261 °C; HRMS (EI$^+$) found 228.0780 M$^+$, calcd 228.0786 for $C_{14}H_{12}O_3$; Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67, H, 5.30. Found: C, 73.67, H, 5.52.



Preparation of 5-aminobenzene-1,3-diol hydrochloride

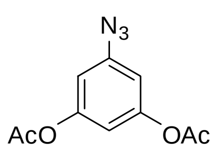
Ammonium hydroxide (30%, 30 mL) was added to phloroglucinol dihydrate (5.18 g, 31 mmol) at 0 °C over 3 min. Ammonia gas was bubbled in for 30 min. Then the mixture was allowed to warm to ambient temperatures and stirred for 2 days, at which time it was concentrated under vacuum at 50 °C. The resulting solid was dissolved in 5 N HCl (10 mL). After evaporation, the crude product was obtained as a yellow solid. Purification by crystallized in acetone to gave 5-aminobenzene-1,3-diol hydrochloride (2.77 g, 55%). Data are: ^{1}H NMR (acetone-d_6, 300 MHz) δ 7.71 (s, 2H), 5.71 (d, J = 1.8 Hz, 2H), 5.67 (t, J = 1.8 Hz, 1H), 4.39 (bs, 2H); HRMS (EI$^+$) found 125.0476 M$^+$, calcd 125.0477 for $C_6H_7NO_2$.



18

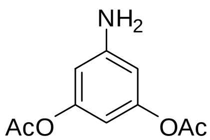
Preparation of 5-azidobenzene-1,3-diol (18)

To a stirred solution of 5-aminobenzene-1,3-diol hydrochloride (1.00 g, 6.19 mmol) and concentrated HCl (2.5 mL) in water (25 mL) was added a solution of $NaNO_2$ (0.39 g, 5.71 mmol) in water (2.5 mL) over 5 min at 0 ^oC. The mixture was stirred for 10 min before a solution of NaN_3 (0.41 g, 6.25 mmol) in water (2.5 mL) was added. After 1 h, the reaction was extracted 3 times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. Purification with flash chromatography (30% EtOAc/hexanes) gave 0.52 g (60%) desired product. Data are: HRMS (EI^+) found 151.0378 M^+, calcd 151.0382 for $C_6H_5N_3O_2$.



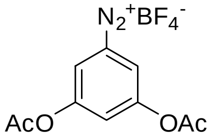
Preparation of 5-azido-1,3-phenylene diacetate

To a stirred solution of 5-azidobenzene-1,3-diol **18** (0.52 g, 3.43 mmol) in EtOAc (7 mL) were added acetic anhydride (1.05 g, 10.29 mmol) and pyridine (0.54 g, 6.86 mmol) at 0 ^oC under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min and then warmed to ambient temperature and stirred for 3 h. The reaction mixture was poured in to water and extracted 3 times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (30% EtOAc/hexanes) gave 0.70 g (87%) desired product. Data are: ^{1}H NMR (acetone-d_6, 300 MHz) δ 6.80 (m, 3H), 2.26 (s, 6H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 169.3, 153.4, 142.7, 113.6, 111.2, 21.0; HRMS (EI$^+$) found 235.0584 M$^+$, calcd 235.0593 for $C_{10}H_9N_3O_4$.



Preparation of 5-amino-1,3-phenylene diacetate

In a Parr hydrogenation tube filled with Ar were charged with 5-azido-1,3-phenylene diacetate (0.63 g, 2.66 mmol), EtOAc (30 mL), and Pd/C (10%, 0.17 g). The tube was sealed, vacuumed and purged with H_2. The reaction was carried out at 50 psi of hydrogen atmosphere for 17 h, at which time the solution was passed through a celite cup and eluted with MeOH. After solvent evaporation, 5-amino-1,3-phenylene diacetate (0.56 g, 100%) was obtained. Data are: ^{1}H NMR (acetone-d_6, 300 MHz) δ 6.29 (d, J = 2.1 Hz, 2H), 6.12 (t, J = 2.1 Hz, 1H), 4.98 (bs, 2H), 2.19 (s, 6H); HRMS (EI$^+$) found 209.0675 M$^+$, calcd 209.0688 for $C_{10}H_{11}NO_4$.

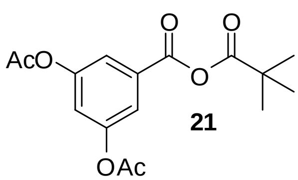


19

Preparation of 3,5-diacetoxybenzenediazonium borotetrafluoride (19)

A flame dried flask was charged with $BF_3{\cdot}Et_2O$ (0.54 g, 3.80 mmol). A solution of

5-amino-1,3-phenylene diacetate (0.53 g, 2.53 mmol) in THF (5 mL) was added at -15 ^{o}C. More THF was needed if solid precipitated. *Tert*-butyl nitrite (0.36 mL, 3.04 mmol) was dropwisely added over 10 min as a THF (2.5 mL) solution. The mixture was stirred at -15 ^{o}C for 10 min, at which time it was warmed to 5 ^{o}C over 20 min. Pentane was added to precipitate the diazonium product. Filtration, wash with cold ether, and air-dry generated desired product **19** 0.68 g (88%). Data are: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.57 (d, *J* = 2.1 Hz, 2H), 8.07 (t, *J* = 2.1 Hz, 1H), 2.37 (s, 6H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 168.4, 151.0, 129.8, 123.6, 117.7, 20.7.

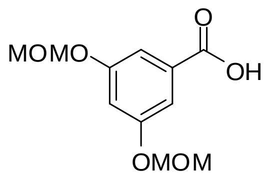


21

Preparation of 3,5-diacetoxybenzoic pivalic anhydride (21)

To a mixture of 3,5-diacetoxybenzoic acid (0.238 g, 1 mmol) and pivaloyl chloride (0.145 g, 1.2 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.152 g, 1.5 mmol). The resulting solution was stirred for 30 min at ambient temperature and then the solvent was evaporated in vacuo. The concentrated crude product was dissolved in benzene and filtrated. After evaporation, the desired product was obtained in 92% yield (0.296 g). Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, *J* = 2.4 Hz, 2H), 7.23(t, *J* = 2.4 Hz, 1H), 2.33 (s, 6H), 1.36 (s, 9H); HRMS (EI^+) found 322.1036 M^+, calcd 322.1053 for $C_{16}H_{18}O_7$.

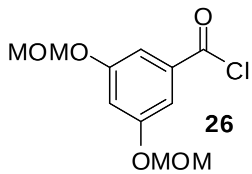
4.2.2. Synthesis of Resveratrol Acetyl Analogs



Preparation of 3,5-bis(methoxymethoxy)benzoic acid

A flame dried flask was charged with dry DMF (75 mL) and 60% oil dispersion NaH (3.8 g, 95 mmol). The mixture was cooled to 0 ^{o}C before a solution of 3,5-dihydroxybenzoic acid **5** (4.6 g, 30 mmol) in DMF (25 mL) was added dropwisely over 20 min. The mixture was allowed to stir for 1 h under N_2. MOMCl (7.5 mL, 100 mmol) was added slowly at 0 ^{o}C. The mixture was then slowly warmed to ambient temperature. After 30 h, the insoluble material was filtered and the filtrate was concentrated to an oil residue, which was partitioned between benzene and water. The water layer was extracted 3 times with benzene. The combined benzene extracts were dried by Na_2SO_4 and concentrated to pale yellow oil, which was dissolved in 50 mL methanol. And 2 N aqueous NaOH (25 mL, 50 mmol) was added. The solution was stirred for 3 h before it was concentrated and dissolved in 30 mL water. The aqueous solution was washed with benzene and acidified with 10% aqueous HCl. The white solid precipitate was filtered and washed with water and dried to give 6.6 g (91%) of product **6**, which can be further purified by recrystallization from EtOAc-hexanes. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (d, 2H), 6.98 (t, 1H), 5.21 (s, 4H), 3.50 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 158.4, 131.4, 111.5, 110.7, 94.7, 56.4;

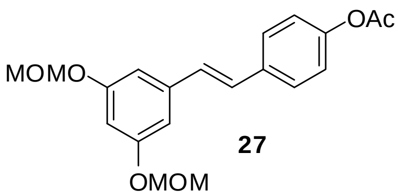
mp = 129-130 °C; HRMS (EI$^+$) found 242.0796 M$^+$, calcd 242.0790 for $C_{11}H_{14}O_6$.



26

Preparation of 3,5-bis(methoxymethoxy)benzoic chloride (26)

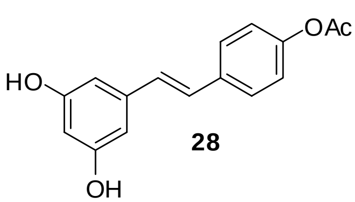
A stock solution was prepared by dissolving benzotriazol (1.49 g, 12.5 mmol), thionyl chloride (0.91 mL, 12.5 mmol) in 8.0 mL CH_2Cl_2. The reaction was carried out by adding the stock solution into a stirred solution of 3,5-bis(methoxymethoxy) benzoic acid (2.60 g, 10 mmol) in 200 mL CH_2Cl_2. Before the addition was complete, benzotriazole hydrochloride started to precipitate out as a white solid. The mixture was stirred for another 12 min. After filtration, the filtrate was stirred with $MgSO_4 \cdot 7H_2O$ (5 g) to destroy excess thionyl chloride. The white solid was filtered and the filtrate was concentrated, at which time more white solid was generated. The mixture was redissloved in benzene, filtrated and concentrated to give 2.5 g (97%) crude product **26**. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44 (d, *J* = 2.4 Hz, 2H), 7.04 (t, *J* = 2.4 Hz, 1H), 5.20 (s, 4H), 3.49 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 158.5, 135.3, 112.6, 111.9, 94.7, 56.4; HRMS (EI$^+$) found 260.0465 M$^+$, calcd 260.0452 for $C_{11}H_{13}O_5Cl$.



27

Preparation of 3,5-bis(methoxymethoxy)-4'-acetoxy stillbene (**27**)

A 50 mL round bottom flask was charged with *p*-xylene (20 mL), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), *N,N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride **16** (42.7 mg, 0.1 mmol), 3,5-bis(methoxymethoxy)benzoic chloride **26** (2.42 g, 10 mmol), 4-acetoxystyrene **14** (1.94 g, 12 mmol),and *N*-ethyl morpholine (1.38 g, 12 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. And the whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product **27** (2.1 g, 59%) as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.08-6.93 (m, 4H), 6.86 (d, *J* = 2.1 Hz, 2H), 6.66 (t, *J* = 2.1 Hz, 1H), 5.19 (s, 4H), 3.50 (s, 6H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 158.7, 150.3, 139.5, 135.0, 128.7, 128.5, 127.6, 121.9, 108.0, 104.5, 94.6, 56.2, 21.2; HRMS (EI^+) found 358.1409 M^+, calcd 358.1416 for $C_{20}H_{22}O_6$.

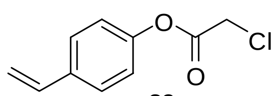


28

Preparation of 3,5-dihydroxy-4'-acetoxy stillbene (28)

To a stirred solution of 3,5-bis(methoxymethoxy)-4'-acetoxy stillbene **27** (0.358 g, 1 mmol) in dry CH_2Cl_2 (50 mL) and dry CH_3CN (50 mL) was added NaI (0.18 g, 2.4

mmol) and freshly distilled trimethylsilyl chloride (0.15 g, 2.4 mmol) at 0 ^{o}C. The mixture was stirred under argon for 15 min. The solution was diluted with CH_2Cl_2 (50 mL) and washed with a freshly prepared saturated $Na_2S_2O_4$ (3 x 40mL) solution, saturated $NaHCO_3$, and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column and gave 0.20 g product **28** (72%). Data are: ^{1}H NMR (Aceton-d$_6$, 300 MHz) δ 8.25 (s, 1H), 7.60 (m, 2H), 7.13-7.08 (m, 4H), 6.59 (d, *J* = 2.1 Hz, 2H), 6.32 (t, *J* = 2.1 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (Aceton-d$_6$, 75 MHz) δ 169.7, 159.7, 151.4, 140.4, 136.0, 130.0, 128.3, 128.3, 123.0, 106.1, 103.3, 21.1; HRMS (EI$^+$) found 270.0889 M$^+$, calcd 270.0892 for $C_{16}H_{16}O_4$.

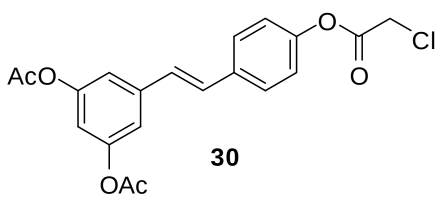


29

Preparation of 4-chloroacetoxystyrene (29)

To a round bottom flask was charged 4-acetoxystyrene **14** (10.00 g, 61.73 mmol), methanol (30 mL), and KOH (0.13 g, 2.23mmol), and 1 drop of water. After the mixture was stirred for 5 min under N_2, the temperature was raised to 65 °C. The mixture was stirred for 1.5 h and then cooled to ambient temperature. Acetic acid (0.14 g, 2.44 mmol) in methanol (0.5 mL) was added slowly over 5 min. The mixture was stirred for another 5 min and then concentrated. The residue was dissolved in toluene and filtered. The filtrate was cooled to -78 °C and the 4-hydroxystyrene was precipitated, filtered and dried to give 4.5 g product (60%).

To a stirred solution of 4-hydroxystyrene (1.22 g, 10 mmol) in ethyl ether (140 mL) was added chloroacetyl chloride (2.26 g, 20 mmol) and Et_3N (1.62 g, 16 mmol). After 2 h, the mixture was washed with $NaHCO_3$ and water. The ether solution was dried by Na_2SO_4 and concentrated. After purification by flash column, 4-chloroacetoxystyrene **29** (1.8 g, 92%) was obtained. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (d, , *J* = 8.4 Hz, 2H), 7.11 (d, 2H, *J* = 8.4 Hz), 6.73 (dd, *J* = 11.1, 18 Hz, 1H), 5.74 (d, *J* = 18 Hz, 1H), 5.29 (d, *J* = 11.1 Hz, 1H), 4.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.0, 150.0, 136.0, 135.8, 127.4, 121.3, 114.6, 41.0.

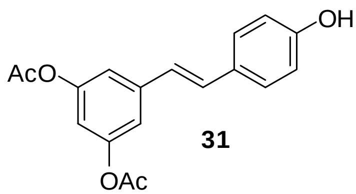


30

Preparation of 3,5-diacetoxy-4'-chloroacetoxy stillbene (30)

A 10 mL round bottom flask was charged with *p*-xylene (4 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), *N,N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride **16** (8.6 mg, 0.02 mmol), 3,5-diacetoxybenzoyl chloride **13** (0.77 g, 3.0 mmol), 4-chloroacetoxystyrene **29** (0.393 g, 2.0 mmol), and *N*-ethyl morpholine (0.28 g, 2.4 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to giveto give the product **30** (0.54 g, 70%) as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, *J* = 8.7 Hz, 2H), 7.14-6.89 (m, 6H), 6.83 (t, *J* = 2.1 Hz , 1H), 4.29 (s, 2H), 2.29 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 165.9, 151.4, 150.1, 139.5, 135.1, 129.5, 127.9, 127.7, 121.6, 117.1, 114.7, 41.0, 21.2; HRMS (EI^+) found 388.0710 M^+, calcd 388.0714 for

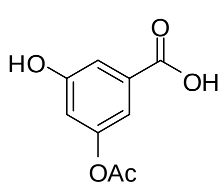
$C_{20}H_{17}ClO_6$.



31

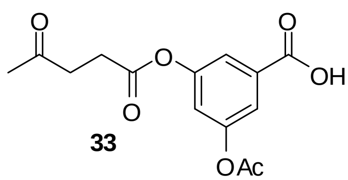
Preparation of 3,5-diacetoxy-4'-hydroxy stillbene (31)

A solution of 3,5-diacetoxy-4'-chloroacetoxy stillbene **30** (0.388 g, 1 mmol) in 50% aqueous pyridine, which was adjusted to pH 6.7 with hydrochloric acid, was stirred for 6 h at ambient temperature. The mixture was concentrated and diluted with EtOAc. The mixture was washed with 1 N aqueous HCl, saturated $NaHCO_3$ and water. The EtOAc layer was dried and concentrated. After purification by radial chromatography, the product **31** (0.28 g, 90%) was obtained. Data are: ^{1}H NMR (Aceton-d_6, 300 MHz) δ 8.55 (bs, 1H), 7.47 (m, 2H), 7.25-7.00 (m, 4H), 6.86 (m, 2H), 6.82 (t, J = 2.1Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (Aceton-d_6, 75 MHz) δ169.5, 158.7,152.7, 141.2, 131.4, 129.5, 129.2, 124.8, 117.5, 116.6, 115.1, 21.0; HRMS (EI$^+$) found 312.0993 M$^+$, calcd 312.0998 for $C_{18}H_{16}O_5$.



Preparation of 3-acetoxy-5-hydroxybenzoic acid

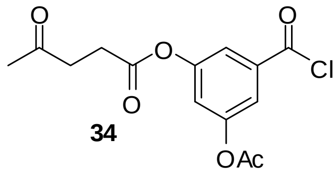
To 3,5-dihydroxybenzoic acid **15** (20 g, 129 mmol) added NaOH (15.6 g, 390 mmol) in 100 mL water. After the mixture was cooled to 0 °C, Ac_2O (13.2 g, 129 mmol) was added. The solution was stirred for 40 min and then acidified with 10% H_2SO_4 at 0 °C. The precipitate was filtered and washed with cold water. The crude product was recrystallized from water to give 3-acetoxy-5-hydroxybenzoic acid (15.2 g, 60%). Data are: ^{1}H NMR (Aceton-d_6, 300 MHz) δ 8.96 (s, 1H), 7.40 (dd, J = 1.5Hz, 1H), 7.26 (dd, J = 1.5Hz, 1H), 6.86 (t, J = 2.1H, 1H), 2.27 (s, 3H); HRMS (EI$^+$) found 196.0380 M$^+$, calcd 196.0372 for $C_9H_8O_5$.



33

Preparation of 3-acetoxy-5-levulinoxy-benzoic acid (33)

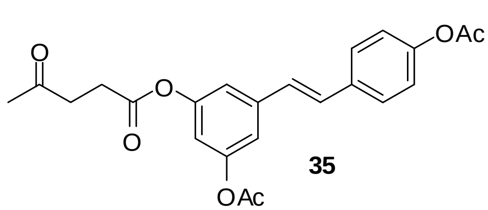
To a stirred solution of 3-acetoxy-5-hydroxybenzoic acid (2.45 g, 12.5 mmol) in CH_2Cl_2 (25 mL) were added levulinic anhydride (5.4 g, 25 mmol) and pyridine (1.22 mL, 15 mmol) at 0 °C. The mixture was stirred at 0 °C for another 0.5 h, at which time it was warmed to ambient temperature. After 3 h, 98% formic acid was added and stirred for 1 h. The mixture was washed with 1 N HCl, saturated $NaHCO_3$ and water. Then it was dried with Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography to give 3-acetoxy-5-levulinoxy-benzoic acid **33** (3.52 g, 96%). Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, J = 1.2Hz, 2H), 7.20 (t, J = 1.2Hz, 1H), 2.85 (m, 4H), 2.32 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.6, 177.6, 171.0, 170.0, 169.0, 151.2, 131.7, 121.1, 121.1, 121.0, 38.1, 30.0, 28.3, 21.2; HRMS (EI$^+$) found 294.0741 M$^+$, calcd 294.0740 for $C_{14}H_{14}O_7$.



34

Preparation of 3-acetoxy-5-levulinoxy-benzoic chloride (34)

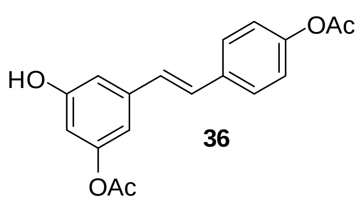
A stock solution was prepared by dissolving benzotriazole (1.49 g, 12.5 mmol), thionyl chloride (0.91 mL, 12.5 mmol) in 8.0 mL CH_2Cl_2. The reaction was carried out by adding the stock solution intermittently into a stirred solution of 3-acetoxy-5-levulinoxy-benzoic acid **33** (2.94 g, 10 mmol) in 200 mL CH_2Cl_2. Before the addition was complete, benzotriazole hydrochloride started to precipitate out as a white solid. The mixture was stirred for another ten min. After filtration, the filtrate was stirred with $MgSO_4{\cdot}7H_2O$ (5 g) to destroy excess thionyl chloride. After concentration, the residue was extracted several times with hot dry hexane and recrystallized from hexanes to give 3-acetoxy-5-levulinoxy-benzoic chloride **34** (1.4 g, 45%). Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (d, *J* = 2.1Hz, 2H), 7.28 (t, *J* = 2.1Hz, 1H), 2.86 (m, 4H), 2.33 (s, 3H), 1.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.3, 170.9, 168.7, 167.1, 151.42, 151.38, 135.3, 122.8, 122.1, 121.9, 38.0, 30.0, 28.3, 21.2; HRMS (EI^+) found 312.0390 M^+, calcd 312.0401for $C_{14}H_{13}O_6Cl$.



35

Preparation of 3,4'-diacetoxy-5-levulinoxystillbene (35)

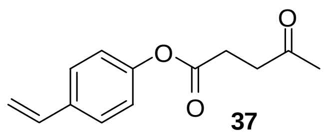
A 25 mL round bottom flask was charged with *p*-xylene (6 mL), $Pd(OAc)_2$ (6.9 mg, 0.03 mmol), *N,N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride **16** (12.9 mg, 0.03 mmol), 3-acetoxy-5-levulinoxy-benzoic chloride **34** (0.94 g, 3.0 mmol), 4-acetoxystyrene **14** (0.58 g, 3.6 mmol), and *N*-ethyl morpholine (0.42 g, 3.6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product **35** (0.86 g, 70%) as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (m, 2H), 7.12 (m, 6H), 6.81 (t, *J* = 1.2Hz, 1H), 2.85 (m, 4H), 2.31 (s, 1H), 2.30 (s, 1H), 2.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.4, 171.2, 169.5, 169.1, 151.5, 150.6, 140.0, 134.7, 129.8, 127.8, 127.4, 122.1, 117.14, 117.09, 114.6, 38.1, 30.0, 28.4, 21.32, 21.29.



36

Preparation of 3,4'-diacetoxy-5-hydroxystillbene (36)

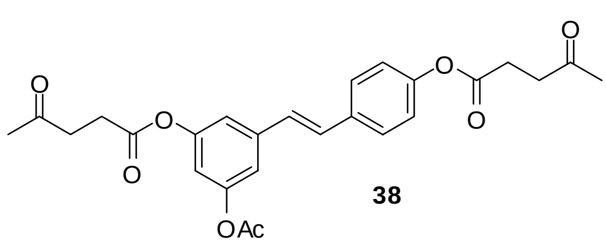
To a stirred solution of 3,4'-diacetoxy-5-levulinoxystillbene **35** (0.72 g, 1.75mmol) in THF (5 mL) was added a solution of Na_2SO_3 (0.26 g, 2.1 mmol) and $Na_2S_2O_5$ (0.1 g, 0.53 mmol) in water (5 mL). The reaction mixture was stirred for 9 h at ambient temperature under N_2. Then the mixture was poured into water and extracted 3 times with EtOAc and dried over Na_2SO_4. The solvent was removed under reduced pressure and purified by radial chromatography to give 3,4'-diacetoxy-5- hydroxystillbene **36** (0.40 g, 73%). Data are: ^{1}H NMR (Aceton-d_6, 300 MHz) δ 8.66 (bs, 1H), 7.63 (m, 2H), 7.25 (m, 4H), 6.94 (t, *J* = 1.8Hz, 1H), 6.86 (t, *J* = 1.8Hz, 1H), 6.54 (t, *J* = 2.1Hz, 1H), 2.26 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (Aceton-d_6, 75 MHz) δ 169.7, 169.6, 159.2, 153.2, 151.6, 140.4, 135.6, 129.4, 128.8, 128.3, 122.9, 111.85, 111.79, 109.4, 21.07, 21.02; HRMS (EI^+) found 312.0996 M^+, calcd 312.0998 for $C_{18}H_{16}O_5$.



37

Preparation of 4-levulinoxystyrene (37)

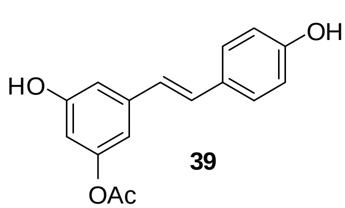
A flame dried flask was charged with dioxane (120 mL), 4-hydroxystyrene (3.66 g, 30 mmol), levulinic acid (6.97 g, 60 mmol), DCC (12.39 g, 60 mmol), and DMAP (300 mg). The mixture was stirred under N_2 for 3.5 h. and the mixture was washed with water, dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column to give 4-levulinoxystyrene **37** (5.9 g, 90%). Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 2H), 7.04 (m, 2H), 6.68 (dd, *J* = 10.8, 17.7 Hz, 1H), 5.69 (d, *J* =17.7 Hz, 1H), 5.69 (d, *J* = 10.8Hz, 1H), 2.82 (m, 4H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.5, 171.5, 150.4, 136.0, 135.5, 127.3, 121.7, 114.1, 38.0, 30.0, 28.3; HRMS (EI^+) found 218.0955 M^+, calcd 218.0943 for $C_{13}H_{14}O_3$.



38

Preparation of 3-acetoxy-4',5-dilevulinoxystillbene (38)

A 25 mL round bottom flask was charged with *p*-xylene (6 mL), $Pd(OAc)_2$ (6.9 mg, 0.03 mmol), *N,N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride **16** (12.9 mg, 0.03 mmol), 3-acetoxy-5-levulinoxy-benzoic chloride **34** (0.936 g, 3.0 mmol), 4-levulinoxystyrene **37** (0.786 g, 3.6 mmol),and *N*-ethyl morpholine (0.42 g, 3.6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product **38** (1.0 g, 72%) as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (m, 2H), 7.11-6.92 (m, 6H), 6.81 (t, *J* = 2.1Hz, 1H), 2.89-2.80 (m, 8H), 2.29 (s, 3H), 2.224 (s, 3H), 2.221 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.6, 206.5, 171.5, 171.2, 169.1, 151.4, 151.5, 150.6, 139.7, 134.6, 129.8, 127.8, 127.3, 122.0, 117.10, 117.05, 114.5, 38.07, 38.02, 30.01, 30.00, 28.32, 28.30, 21.3; HRMS (EI$^+$) found 466.1636 M$^+$, calcd 466.1628 for $C_{26}H_{26}O_8$.

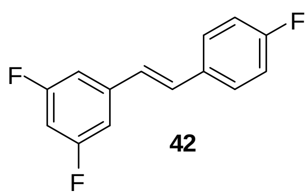


39

Preparation of 3-acetoxy-4',5-dihydroxystillbene (39)

To a stirred solution of 3-acetoxy-4',5-dilevulinoxystillbene **38** (0.47 g, 1.0 mmol) in THF (3 mL) was added a solution of Na_2SO_3 (0.30 g, 2.4 mmol)and $Na_2S_2O_5$ (0.11 g, 0.6 mmol) in water (3 mL). The reaction mixture was stirred for 7 h at ambient temperature under N_2. Then the mixture was poured into water and extracted 3 times with EtOAc and dried over Na_2SO_4. The solvent was removed under reduced pressure and purified by radial chromatography to give 3-acetoxy-4',5- dihydroxystillbene **39** (0.19 g, 70%). Data are: ^{1}H NMR (Aceton-d_6, 300 MHz) δ 8.56 (s, 1H), 8.48 (s, 1H), 7.45 (m, 2H), 7.04 (m, 2H), 6.90-6.80 (m, 4H), 6.50 (t, *J* = 2.1Hz, 1H), 2.24 (s, 1H); ^{13}C NMR (Aceton-d_6, 75 MHz) δ 169.6, 159.2, 158.5, 153.3, 141.1, 129.8, 130.3, 129.0, 116.5, 111.5, 111.4, 108.8, 21.1; HRMS (EI$^+$) found 270.0896 M$^+$, calcd 270.0892 for $C_{16}H_{16}O_4$.

4.2.3. Synthesis of Resveratrol Fluoro Analogs

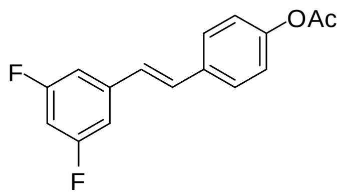


42

Preparation of 3,5,4'-trifluorostillbene (42)

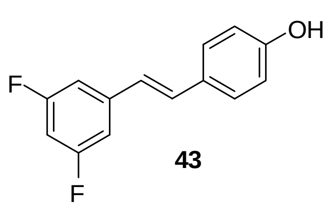
A 25 mL round bottom flask was charged with *p*-xylene (10 mL), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), *N,N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride **16** (21.4 mg, 0.05 mmol), 3,5-difluorobenzoyl chloride **40** (0.89 g, 5 mmol), 4-fluorostyrene **41** (0.74 g, 6 mmol), and *N*-ethyl morpholine (0.69 g, 6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product **42** (0.94g, 80%) as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (m, 2H), 7.08-6.88 (m, 6H), 6.70 (tt, *J* = 2.4, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.52 (dd), 162.98 (d), 140.82 (t), 132.77, 130.26, 128.58 (d), 126.53, 116.03 (d), 109.20 (q), 102.98(t); ^{19}F NMR ($CDCl_3$, 282

MHz) δ -31207.2 (q, J = 2580.3 Hz, 2F), -31965.6 (q, J = 1723.02 Hz, 1F); HRMS (EI^+) found 234.0645 M^+, calcd 234.0656 for $C_{14}H_9F_3$.



Preparation of 4'-acetoxy-3,5-difluorostilbene

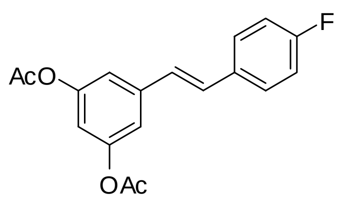
A 25 mL round bottom flask was charged with *p*-xylene (10 mL), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), *N,N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride **16** (21.4 mg, 0.05 mmol), 3,5-difluorobenzoyl chloride **40** (0.89 g, 5 mmol), 4-acetoxystyrene **14** (0.97 g, 6 mmol), and *N*-ethyl morpholine (0.69 g, 6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was purified by a flash chromatography (20% EtOAc/hexanes) to give the product (1.02 g, 74%) as a white solid. Data are: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, J = 8.4 Hz, 2H), 7.12-6.97 (m, 6H), 6.70 (t, 1H), 2.31(s, 3H).



43

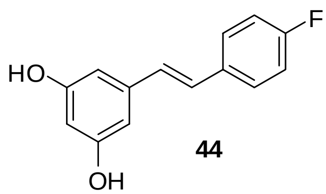
Preparation of 3,5-difluoro-4'-hydroxystilbene (43)

To a stirred solution of 3,5-difluoro-4'-acetoxy-stillbene (0.69 g, 2.5 mmol) in MeOH (10 mL) were added 5 mL 4 N HCl in 1,4-dioxane. The mixture was stirred for 20 min at ambient temperature. After purification by flash chromatography, 3,5-difluoro-4'- hydroxystillbene **43** (0.51g, 88%) was obtained. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 (m, 2H), 7.05-6.83 (m, 6H), 6.67 (tt, *J* = 2.1, 8.7 Hz, 1H), 4.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.49(d), 162.47, 156.01, 141.29, 130.90, 128.53, 124.74, 115.96, 109.03 (t), 102.53 (t); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -31278.95 (t, *J* = 1720.2Hz, 2F); HRMS (EI^+) found 232.0715 M^+, calcd 232.0700 for $C_{14}H_{10}F_2O$.



Preparation of 3,5-diacetoxy-4'-fluorostilbene

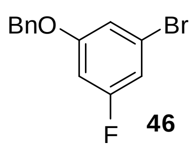
A 25 mL round bottom flask was charged with *p*-xylene (10 mL), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), *N,N*-bis-2,6-diisopropylphenyl-4,5-dihydro imidazolium chloride **16** (21.4 mg, 0.05 mmol), 3,5-diacetoxybenzoyl chloride **13** (1.28 g, 5 mmol), 4-fluorostyrene **41** (0.73 g, 6 mmol), and *N*-ethyl morpholine (0.69 g, 6 mmol). The mixture was heated at 120 °C for 3.5 h under nitrogen atmosphere. Then it was cooled to ambient temperature. The whole mixture was transferred to a flash chromatography (20% EtOAc/hexanes) to give the product (1.15 g, 73%) as a white solid. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (m, 2H), 7.11-6.91 (m, 6H), 6.82 (t, *J* = 1.95 Hz, 1H), 2.31 (s, 6H).



44

Preparation of 4'-fluoro-3,5-dihydroxystilbene (44)

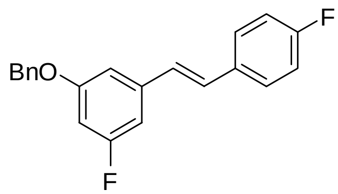
To a stirred solution of 3,5-diacetoxy-4'-fluoro-stillbene (0.79 g ,2.5 mmol) in MeOH (10mL) was added 10 mL 4 N HCl in 1,4-dioxane. The mixture was stirred for 30 min at ambient temperature. After purification by flash chromatography, 3,5-difluoro-4'-hydroxystillbene **44** (0.49g, 85%) was obtained. Data are: ^{1}H NMR (Aceton-d_6, 300 MHz) δ 8.25 (s, 1H), 7.61 (m, 2H), 7.16-7.00 (m, 4H), 6.58 (d, J = 2.4 Hz), 6.31 (t, *J* = 2.4 Hz); ^{13}C NMR (Aceton-d_6, 75 MHz) δ; ^{19}F NMR (Aceton-d_6, 282 MHz) δ -32881.41 (m); HRMS (EI^+) found 230.0737 M^+, calcd 230.0743 for $C_{14}H_{11}FO_2$.



46

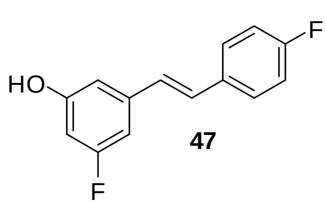
Preparation of 3-benzyloxy-5-fluorophenyl Bromide (46)

To a stirred solution of benzyl alcohol (3.86 g, 20 mmol) in DMA (30 mL), NaH (0.80 g, 20 mmol, 60% dispersion in oil) was dropwisely added. After 1 h, 1-bromo-3,5-difluorobenzene **45** (3.86 g, 20 mmol) was added at such a rate to maintain the temperature no higher than 40 ^{o}C. The mixture was stirred at ambient temperature overnight. The reaction was quenched with water and extracted with EtOAc. Purification by flash chromatography gave the product **46** (4.17g, 74%) as colorless oil. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41-7.43 (m, 5H), 6.94 (m, 1H), 6.86 (dt, *J* = 2.1, 8.1 Hz, 1H), 6.63 (dt, *J* = 2.4, 8.1 Hz, 1H), 5.02 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.20, 161.89, 160.72, 160.56, 136.01, 128.94, 128.57, 127.77, 127.73, 122.99, 122.83, 114.58, 114.53, 112.18, 111.84, 102.29, 101.96, 70.76; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -31129.40 (t, *J* = 2583.12Hz, 1F).



Preparation of 3-benzyloxy-5, 4'-difluorostillbene

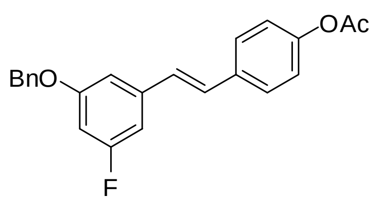
A mixture of 3-benzyloxy-5-fluorophenyl bromide **46** (2.81 g, 10 mmol), $Pd(OAc)_2$ (0.067 g, 0.3 mmol), tri-*o*-tolylphosphine (0.18g, 0.6mmol), 4-fluorostyrene **41** (1.53 g, 12.5 mmol), and Et_3N (1.26 g, 12.5 mmol) in 20 mL dry DMF was stirred under N_2 at 100 ^oC for 24 h. The dark mixture was distributed between EtOAc and 1 N HCl. The organic layer was separated and washed with water and brine, dried over Na_2SO_4, filtered, and evaporated. After flash chromatography, the desired product (2.93g, 91%) was obtained. Data are: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49-7.34 (m, 7H), 7.08-6.81 (m, 6H), 6.60 (dt, *J* = 2.4, 10.5 Hz, 1H), 5.08 (s, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -31666.54 (t, *J* = 2583.12, 1F), -32136.54 (t, *J* = 2580.3 Hz, 1F). HRMS (EI^+) found 322.1169 M^+, calcd 322.1169 for $C_{21}H_{16}F_2O$.



47

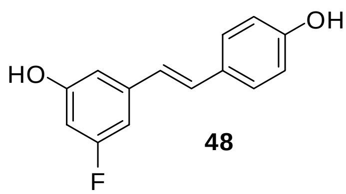
Preparation of 3, 4'-difluoro-5-hydroxystillbene (47)

A solution of BBr_3 (9 ml, 9 mmol, 1 M in CH_2Cl_2) was added to a well-stirred solution of 5-benzyloxy-3, 4'-difluorostillbene (0.97g, 3 mmol) in dry CH_2Cl_2 (120 mL) at –78 ^oC. The mixture was warmed to –20 ^oC and stirred for 10 min. Then MeOH was added at –78 ^oC. The mixture was washed with saturated $NaHCO_3$, and water. Flash chromatography gave 5-hydroxy-3, 4'-difluorostillbene **47** (0.60 g, 86%) as white solid. Data are: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46 (m, 2H), 7.08-6.73 (m, 6H), 6.48 (dt, J = 2.4, 9.6 Hz, 1H), 4.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.05 (d), 161.78 (d), 157.06 (d), 140.43 (d), 133.06 (d), 129.40 (s), 128.45 (d), 127.25 (t), 115.95 (d), 109.42 (d), 105.91 (d), 102.60 (d); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -31703.17 (t, J = 2583.12 Hz, 1F), -32099.92 (t, J = 2583.12, 1F); HRMS (EI^+) found 232.0714 M^+, calcd 232.0700 for $C_{14}H_{10}F_2O$.



Preparation of 4'-acetoxy-3-benzyloxy-5-fluorostillbene

A mixture of 3-benzyloxy-5-fluorophenyl bromide **46** (2.81 g, 10 mmol), $Pd(OAc)_2$ (0.067 g, 0.3 mmol), tri-*o*-tolylphosphine (0.18 g, 0.6 mmol), 4-acetoxystyrene **14** (2.03 g, 12.5 mmol), and Et_3N (1.26 g, 12.5 mmol) in 20mL dry DMF, was stirred under N_2 at 100 ^oC for 24 h. The dark mixture was distributed between EtOAc and 1 N HCl. The organic layer was separated and washed with water and brine, dried over Na_2SO_4, filtered, and evaporated. After flash chromatography, the desired product (3.19 g, 88%) was obtained. Data are: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51-7.34 (m, 7H), 7.11-6.82 (m, 6H), 6.60 (dt, J = 2.1, 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.66, 165.64, 162.40, 160.47, 150.58, 140.07 (d), 136.59, 134.76, 129.41, 128.91, 128.41, 128.04 (d), 127.79 (d), 122.11, 109.36 (d), 105.86 (d), 101.91 (d), 70.57, 21.37; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -31675.70 (t, J = 3011.76 Hz, 1F); HRMS (EI^+) found 362.1302 M^+, calcd 362.1318 for $C_{23}H_{19}FO_3$.



48

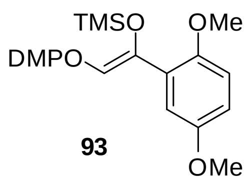
Preparation of 3-fluoro-5,4'-dihydroxystillbene (48)

A solution of BBr_3 (9 mL, 9 mmol,1 M in CH_2Cl_2) was added to a well-stirred solution of 5-benzyloxy-3-fluoro-4'-acetoxystillbene (1.09 g, 3mmol) in dry CH_2Cl_2 (120 mL) at -78 °C. The mixture was warmed to –20 °C and stirred for 10 min. Then MeOH was added at –78 °C. The mixture was washed with saturated $NaHCO_3$, and water, dried over Na_2SO_4, and evaporated. The intermediate 4'-acetoxy-3-fluoro-5-hydroxystillbene (0.50g, 61%) was obtained as a white solid. To a stirred solution of the crude 4'-acetoxy-3-fluoro-5-hydroxystillbene (0.50g ,1.8mmol) in MeOH (7.5 mL) was added HCl (3.7 mL, 4 M in 1,4-dioxane). The mixture was stirred for 20 min at ambient temperature. After purification by flash chromatography, 3-fluoro-5,4'-dihydroxystillbene **48** (0.33g, 78%) was obtained. Data are: ^{1}H NMR (Aceton-d_6, 300 MHz) δ 8.624 (s, 2H), 7.46 (m, 2H), 7.06 (q, 2H), 6.84 (m, 4H), 6.66 (dt, J = 2.1, 10.5 Hz, 1H); ^{13}C NMR (Aceton-d_6, 75 MHz) δ 164.90 (d), 159.96 (d), 158.57, 142.02 (d), 130.84, 129.63, 129.10, 125.55 (d), 116.53, 110.28 (d), 104.44 (d), 102.00

(d); ^{19}F NMR (Aceton-d_6, 282 MHz) δ -32429.72 (t, *J* = 2583.12, 1F); HRMS (EI^+) found 230.0738 M^+, calcd 230.0743 for $C_{14}H_{11}FO_2$.

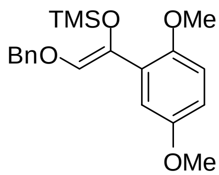
4.3. Asymmetric Phase-Transfer-Catalyzed Glycolate Aldol Reaction

4.3.1. Substrate Preparation



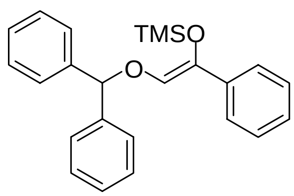
93

(*Z*)-(2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)ethenyloxy)trimethyl silane (93). To a stirred solution of 2-Benzhydryloxy-1-(2,5-dimethoxy-phenyl)-ethanone **88** (3 mmol, 1.09 g) in 10 ml dry THF was dropwisely added LDA (2.5 mL) at -78 °C. After 1 h, TMSCl (2.5 mL) was added slowly. The mixture was stirred for another 1 h and the color was changed to pale yellow from orange. The reaction was warmed to ambient temperature. After THF was removed under reduced pressure, dry hexanes were added. The resulting white precipitates were removed by filtration. After concentration, the residue was purified by recrystallization with hexanes to give **2** as white solid (0.80 g, 61%). Data are: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 (d, *J* = 7.5 Hz, 4 H), 7.34 (t, *J* = 7.5 Hz, 4 H), 7.26-7.28 (m, 2 H), 7.07 (d, *J* = 0.3 Hz, 1 H), 6.72 (d, *J* = 9.0 Hz, 1 H), 6.63 (dd, *J* = 3.0, 9.0 Hz, 1 H), 5.79 (s, 1 H), 3.75 (s, 3 H), 3.61 (s, 3 H), 0.17 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.8, 150.1, 141.5, 135.4, 131.0, 128.6, 127.9, 127.5, 126.9, 112.94, 112.91, 112.1, 85.7, 56.2, 55.8, 0.8; HRMS (FAB^+) found 457.1806, calcd 457.1811 for $C_{26}H_{30}O_4SiNa$.



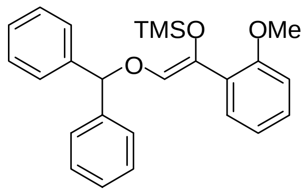
(*Z*)-(2-(Benzyloxy)-1-(2,5-dimethoxyphenyl)vinyloxy)trimethylsilane

Data are: [1]H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.29 (m, 5H), 7.11 (d, *J* = 3.5 Hz, 1H), 6.94 (s, 1H), 6.76 (d, *J* = 9 Hz, 1H), 6.66 (dd, *J* = 3.5, 9 Hz, 1H), 4.88 (s, 2H), 3.76 (s, 3H), 3.74 (s, 3H), 0.18 (s, 9H); [13]C NMR ($CDCl_3$, 125 MHz): δ 153.9, 150.1, 137.6, 136.1, 131.1, 128.6, 128.5, 128.4, 128.22, 128.19, 126.7, 113.0, 112.6, 112.0, 77.5, 77.3, 77.0, 74.5, 56.3, 55.8, 0.80; HRMS (FAB^+) found 358.1591, calcd 358.1600 for $C_{20}H_{26}O_4Si$.



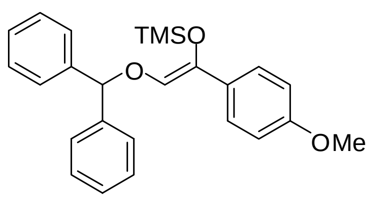
(*Z*)-(2-(Benzhydryloxy)-1-phenylvinyloxy)trimethylsilane

Data are: [1]H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.40 (m, 4H), 7.36-7.32 (m, 6H), 7.29-7.21 (m, 4H), 7.16-7.11 (m, 1H), 6.41 (s, 1H), 5.77 (s, 1H), 0.18 (s, 9H); [13]C NMR ($CDCl_3$, 125 MHz): δ 141.3, 137.2, 134.9, 130.2, 128.7, 128.3, 128.0, 127.3, 126.8, 123.8, 85.9, 0.84; HRMS (FAB^+) found 397.1597, calcd 397.1600 for $C_{24}H_{26}O_2SiNa$.



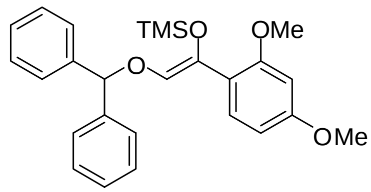
(*Z*)-(2-(Benzhydryloxy)-1-(2-methoxyphenyl)vinyloxy)trimethylsilane

Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.40 (m, 4H), 7.34-7.31 (m, 4H), 7.28-7.24 (m, 3H), 7.13-7.09 (m, 1H), 6.90-6.87 (m, 1H), 6.80-6.78 (m, 1H), 6.74 (s, 1H), 5.77 (s, 3H), 3.68 (s, 3H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.1, 141.6, 134.6, 131.5, 128.5, 128.41, 128.36, 128.3, 128.1, 127.9, 127.6, 127.4, 127.3, 126.0, 120.7, 111.3, 85.7, 55.5, 0.84; HRMS (FAB$^+$) found 427.1714, calcd 427.1705 for $C_{25}H_{28}O_3SiNa$.



(*Z*)-(2-(Benzhydryloxy)-1-(4-methoxyphenyl)vinyloxy)trimethylsilane

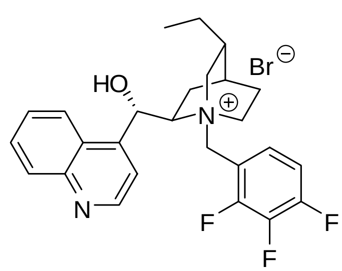
Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40-7.38 (m, 2H), 7.34-7.30 (m, 4H), 7.27-7.23 (m, 5H), 6.78-6.76 (m, 3H), 6.27 (s, 1H), 3.75 (s, 3H), 0.17 (s, 9 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.9, 141.5, 135.1, 130.6, 130.0, 128.9, 128.6, 128.5, 128.0, 127.8, 127.7, 127.6, 127.4, 127.2, 125.3, 113.8, 85.8, 55.5, 0.85; HRMS (FAB$^+$) found 427.1697, calcd 427.1705 for $C_{25}H_{28}O_3SiNa$.



(*Z*)-(2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)vinyloxy)trimethylsilane

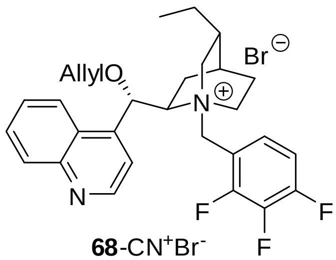
Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.42 (m, 4H), 7,36-7.33 (m, 4H), 7.32-7.26 (m, 3H), 6.57 (s, 1H), 6.44 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.40 (d, *J* = 2.5 Hz, 1H), 5.76 (s, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 0.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6, 157.3, 141.7, 133.1, 131.6, 129.0, 128.5, 128.3, 127.8, 127.7, 127.6, 127.5, 127.2, 118.9, 104.1, 99.1, 85.5, 55.5, 55.4, 0.8; HRMS (FAB$^+$) found 434.1902, calcd 434.1913 for $C_{26}H_{30}O_4Si$.

4.3.2. Bifluoride Salt Preparation



***N*-2',3',4'-trifluorobenzylhydrocinchonium bromide.**

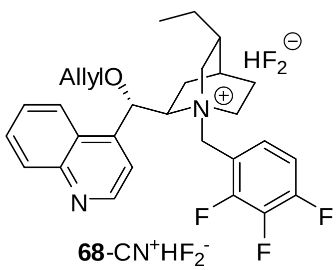
To a flame dried 50 mL round bottom flask was added hydrocinchonine (5.0 g, 16.81 mmol) and 35 mL toluene. Then 2,3,4-trifluorobenzylbromide (2.25 mL, 17.11 mmol) was dropwisely added. The resulting mixture was stirred at 100 °C for 7 h. After cooling to ambient temperature, the product was precipitated out. Filtration and wash 3 times with Et_2O gave desired title compound (8.49 g, 97%).



68-CN$^+$Br$^-$

Park & Jew – ***O*(9)-allyl-*N*-2',3',4'-trifluorobenzylhydrocinchonium bromide (68-CN$^+$Br$^-$).**

The catalyst was prepared according to the published procedure with the exceptions that the product was purified by flash column instead of recrystallization.



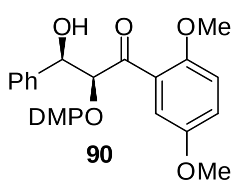
68-CN$^+$HF$_2^-$

***O*(9)-Allyl-*N*-2',3',4'-trifluorobenzylhydrocinchonium hydrodifluoride (68-CN$^+$HF$_2^-$).**

Amberlyst A-26 (Br$^-$ form, 1.6 g, 9.6 meq) column was flushed with 1 N aqueous NaOH until all of the Br$^-$ was exchanged by OH$^-$. The column was washed with H_2O until it was neutral. Then it was flushed with MeOH. A solution of Cinchonium bromide **68**-CN$^+$Br$^-$ (0.5 mmol) in 10 mL MeOH was slowly passed through the column and eluted with MeOH. The eluent was neutralized with 1 N HF (1 mL). The solvents were removed under reduced pressure to provide the title product in quantitative yield. Data for **68**-CN$^+$HF$_2^-$ are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.98 (d, *J*

= 4.5, 1H), 8.59 (d, *J* = 8 Hz), 8.15 (d, *J* = 9 Hz, 1H), 8.02 (m, 1H), 7.90 (bs, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.61 (bs, 1H), 7.21 (m, 1H), 6.22 (bs, 1H), 6.07 (m, 1H), 5.82 (d, *J* = 12 Hz, 1H), 5.42 (d, *J* = 1.5 Hz, 1H), 5.39 (d, *J* = 1 Hz, 1H), 4.78 (d, *J* = 12.5 Hz, 1H), 4.55 (t, *J* = 11 Hz, 1H), 4.49 (m, 1H), 4.26 (m, 1H), 4.04 (m. 1H), 4.00 (m, 1H), 3.22 (t, *J* = 10.5 Hz, 1H), 2.88 (q, *J* = 10 Hz, 1H), 2.31(t, *J* =11.5 Hz, 1H), 2.01 (m, 1H), 1.94 (m, 1H), 1.76 (m, 2H), 1.58 (m, 2H), 1.11(m, 1H), 0.94 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.9, 152.3, 152.2, 151.9, 150.3, 150.2, 149.7, 148.7, 141.0, 140.0, 139.1, 139.0, 132.4, 131.3, 130.4, 130.1, 129.2, 129.0, 128.4, 125.7, 125.4, 124.2, 120.3, 119.8, 119.1, 114.1, 113.9, 113.1, 74.2, 70.7, 70.5, 66.8, 57.5, 56.7, 54.6, 36.2, 24.7, 24.5, 24.3, 22.1,11.5; HRMS (FAB^+) found 504.2364, calcd 504.2359 for $C_{29}H_{32}F_3N_2NaO$.

4.3.3. Asymmetric Aldol Reaction

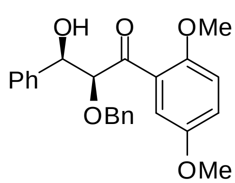


90

2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-phenylpropan-1-one (90).

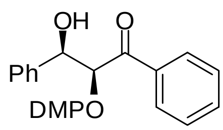
O(9)-Allyl-*N*-2',3',4'-triflurorbenzylhydrocinchonium bifluoride salt **68-CN$^+$HF$_2^-$** (15 mg, 0.003 mmol) was dissolved in reagent grade 1.5 mL THF. Benzaldehyde (0.3 mmol, 0.0318g) was added and the mixture was cooled to -55 ^{o}C. (*Z*)-(2-(benzhydryloxy)-1-(2,5-dimethoxyphenyl)ethenyloxy)trimethyl silane (0.15

mmol, 0.0652g) **93** was added. After 24 h, the reaction was quenched with CsF and H_2O. The solution was extracted 5 times with CH_2Cl_2. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. The mixture was filtered and concentrated *in vacuo*. Radial chromatography afforded the desired compound **90** (0.054 g, 76%). Its enantioselectivity can be enriched by recrystallization with EtOH and hexanes. The crystals were racemic and the residue was the enantio-enriched product. Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10-7.31 (m, 14 H), 6.98-7.00 (m, 1 H), 6.78-6.85 (m, 3 H), 5.48 (s, 1 H), 5.28 (d, *J* = 2.5 Hz, 1 H), 5.03 (s, 1 H), 3.77 (s, 3 H), 3.55 (s, 3 H), 3.13 (b, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.1, 154.0, 152.5, 142.2, 141. 2, 140.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 126.2, 121.1, 114.3, 113.3, 84.7, 82.5, 73.9, 55.99, 55.97; HRMS (FAB^+) found 491.1844, calcd 491.1834 for $C_{30}H_{28}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 23.1 (minor). t_R = 33.0 (major).



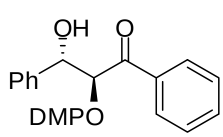
2-(Benzyloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-phenylpropan-1-one

Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33-7.22 (m, 8H), 7.19 (d, *J* = 3.0 Hz, 1H), 7.08 (m, 2H), 7.00 (dd, *J* = 3.5, 9.0 Hz, 1H), 6.83 (d, *J* = 9.0 Hz), 5.26 (d, *J* = 3.0 Hz, 1H), 5.01 (dd, *J* = 3.0, 7.5 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.04 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.1, 154.0, 152.6, 141.0, 137.7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.13, 127.06, 126.5, 121.4, 121.0, 114.4, 113.2, 113.1, 86.6, 74.0, 72.8, 56.1, 56.0; HRMS (FAB$^+$) found 415.1538, calcd 415.1521 for $C_{24}H_{24}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 51.1 (minor). t_R = 60.1 (major).



2-(Benzhydryloxy)-3-hydroxy-1,3-diphenylpropan-1-one

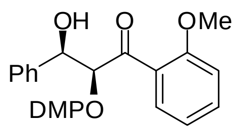
Data (major) are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68-7.66 (m, 2H), 7.49-7.45 (m, 1H), 7.32-7.15 (m, 15H), 7.05-7.03 (m, 2H), 5.41 (s, 1H), 5.01 (t, 1H), 4.88 (d, *J* = 5.0 Hz, 1H), 3.15 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.1, 141.6, 140.2, 139.6, 136.4, 133.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.20, 128.17, 127.8, 127.7, 127.4, 126.7, 83.2, 75.2; HRMS (FAB$^+$) found 431.1636, calcd 431.1623 for $C_{28}H_{24}O_3Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 12.8 (major). t_R = 14.6 (minor).



2-(Benzhydryloxy)-3-hydroxy-1,3-diphenylpropan-1-one

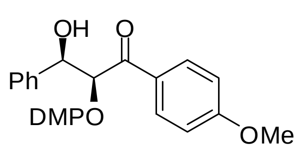
Data (minor) are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76-7.74 (m, 2H), 7.50-7.47 (m, 1H), 7.35-7.17 (m, 15H), 6.98-6.96 (m, 2H), 5.27 (s, 1H), 5.18 (dd, *J* = 3.0, 7.0 Hz, 1H), 4.83 (d, *J* = 7.0 Hz, 1H), 2.51 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz):

δ 200.1, 141.7, 140.7, 140.5, 137.1, 130.33, 128.8, 128.64, 128.55, 128.5, 128.4, 128.0, 127.73, 127.68, 127.4, 127.3, 127.2, 83.2, 75.7; HRMS (FAB^+) found 431.1624, calcd 431.1623 for $C_{28}H_{24}O_3Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 12.6 (major). t_R = 14.8 (minor).



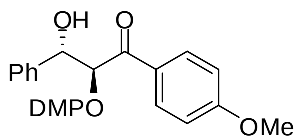
2-(Benzhydryloxy)-3-hydroxy-1-(2-methoxyphenyl)-3-phenylpropan-1-one

Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.44-7.40 (m, 1H), 7.31-7.23 (m, 9 H), 7.21-7.17 (m, 2H), 7.15-7.12 (m, 2H), 6.99 (dt, *J* = 1.5, 7.5 Hz, 1H), 6.87-6.83 (m, 3H), 5.50 (s, 1H), 5.26 (d, *J* = 3.0 Hz, 1H), 5.01 (dd, *J* = 3.0, 7.5 Hz, 1H), 3.60 (s, 3H), 3.11 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.7, 158.0, 142.2, 141.1, 140.5, 134.1, 131.1, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.3, 127.1, 126.3, 121.4, 111.6, 84.8, 82.6, 73.9, 55.4; HRMS (FAB^+) found 461.1729, calcd 461.1729 for $C_{29}H_{26}O_4Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 52.3 (major). t_R = 57.5 (minor).



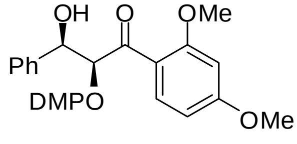
2-(Benzhydryloxy)-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one

Data (major) are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72-7.70 (m, 2H), 7.28-7.19 (m. 13H), 7.07-7.04 (m, 2H), 6.81-6.78 (m, 2H), 5.39 (s, 1H), 5.09 (t, *J* = 3.5 Hz, 1H), 4.82 (d, J = 5.5 Hz, 1H), 3.83 (s, 3H), 3.20 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.2, 163.9, 141.7, 140.3, 139.7, 131.1, 129.4, 128.8, 128.4, 128.18, 128.15, 127.8, 127.7, 126.8, 113.9, 83.0, 82.9, 75.4, 55.7; HRMS (FAB^+) found 461.1728, calcd 461.1729 for $C_{29}H_{26}O_4Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 22.0 (major). t_R = 26.9 (minor).



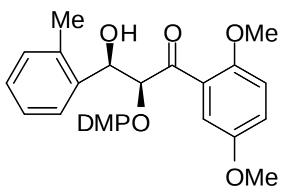
2-(Benzhydryloxy)-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one

Data (minor) are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80-7.78 (m, 2H), 7.36-7.34 (m, 2H), 7.31-7.28 (m, 3H), 7.23-7.17 (m, 8H), 6.96-6.94 (m, 2H), 6.81-6.79 (m, 2H), 5.27 (s, 1H), 5.17 (m, 1H), 4.77 (d, J = 6.5 Hz, 1H), 3.84 (s, 3H), 2.58 (d, J = 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.3, 163.9, 141.8, 140.8, 140.6, 131.3, 130.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.71, 127.68, 127.2, 113.8, 82.8, 81.8, 75.7, 55.7; HRMS (FAB^+) found 461.1728, calcd 461.1729 for $C_{29}H_{26}O_4Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 22.3 (major). t_R = 32.3 (minor).

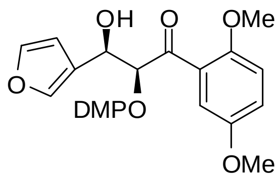


2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxy-3-phenylpropan-1-one

Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (d, J = 8.5 Hz, 1H), 7.33-7.24 (m, 9H), 7.21-7.17 (m, 2H), 7.14-7.11 (m, 2H), 6.85 (d, *J* = 7.5 Hz, 2H), 6.53 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.32 (d, *J* = 2.5 Hz, 1H), 3.84 (s, 3H), 3.59 (s, 3H), 3.16 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.3, 165.0, 160.3, 142.3, 141.3, 140.7, 133.6, 128.4, 128.3, 128.2, 127.9, 127.7, 127.51, 127.45, 127.3, 126.3, 120.0, 106.0, 98.5, 84.3, 82.3, 74.1, 55.8, 55.4; HRMS (FAB$^+$) found 491.1843, calcd 491.1834 for $C_{30}H_{28}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 31.8 (minor). t_R = 34.6 (major).

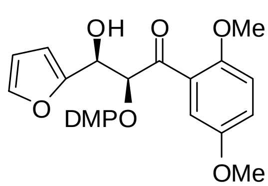


2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-*o*-tolylpropan-1-one. Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51 (m, 1 H), 7.12-7.32 (m, 10 H), 7.00 (m, 2 H), 6.93 (m, 1 H), 6.84 (m, 2 H), 6.71 (d, *J* = 9.5 Hz, 1 H), 5.47 (s, 1 H), 5.28 (d, *J* = 3.5 Hz, 1 H), 5.12 (dd, *J* = 3.5, 7.0 Hz, 1 H), 3.75 (s, 3 H), 3.41 (s, 3 H), 3.07 (d, *J* = 7.0 Hz, 1 H),1.94 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.0, 153.8, 151.8, 142.2, 140.8, 138.3, 134.3, 130.3, 128.44, 128.35, 128.1, 127.73, 127.65, 127.62, 127.57, 127.3, 127.2, 125.8, 120.0, 114.1, 112.5, 82.7, 82.6, 71.3, 56.0, 55.5, 18.6; HRMS (FAB$^+$) found 505.1986, calcd 505.1991 for $C_{31}H_{30}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 12.2 (minor). t_R = 21.3 (major).



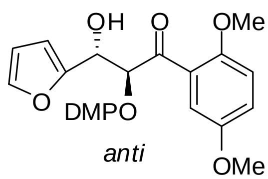
2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-(furan-3-yl)-3-hydroxypropan-1-one.

Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.15-7.36 (m, 15 H), 7.00 (q, *J* = 2.5Hz, 1 H), 6.79 (d, *J* = 9.5 Hz,1 H), 6.21 (s,1 H), 5.60 (s, 1 H), 5.23 (d, *J* = 2.5 Hz, 1 H), 4.96 (dd, *J* = 2.5, 8.5 Hz, 1 H), 3.77 (s, 3 H), 3.56 (s, 3 H), 2.95 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.7, 154.0, 152.6, 143.0, 142.1, 140.6, 140.0, 128.5, 128.3, 128.2, 128.0, 127.6, 127.3, 126.9, 126.3, 121.2, 114.1, 113.3, 109.2, 83.8, 82.6, 68.1, 56.0; HRMS (M^+) found 458.1723, calcd 458.1729 for $C_{28}H_{26}O_6$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 43.0 (minor). t_R = 47.7 (major).



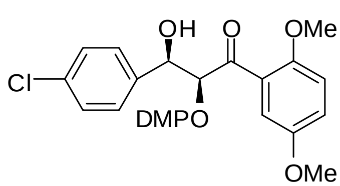
2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-(furan-2-yl)-3-hydroxypropan-1-one.

Data (major) are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21-7.37 (m, 10 H), 7.00-7.05 (m, 3 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 6.29-6.35 (m, 2 H), 5.53 (s, 1 H), 5.42 (d, *J* = 2.5 Hz, 1 H), 5.04 (dd, *J* = 2.5, 9.0 Hz, 1 H), 3.78 (s, 3 H), 3.62 (s, 3 H), 3.09 (d, *J* = 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.9, 154.1, 153.9, 153.0, 142.1, 141.8, 140.6, 128.5, 128.3, 127.9, 127.7, 127.4, 126.3, 121.5, 114.1, 113.3, 110.6, 107.2, 82.7, 82.6, 69.2, 56.0, 55.9; HRMS (FAB^+) found 481.1637, calcd 481.1627 for $C_{28}H_{26}O_6Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 21.4 (minor). t_R = 38.3 (major).



2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-(furan-2-yl)-3-hydroxypropan-1-one.

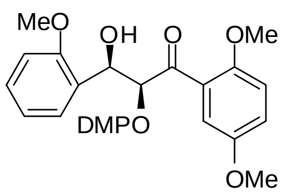
Data (minor) are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17-7.30 (m, 11 H), 6.95-6.99 (m, 2 H), 6.76 (d, *J* = 9.5 Hz, 1 H), 6.32 (s, 1 H), 6.28 (s, 1 H), 5.47 (s, 1 H), 5.43 (d, *J* = 5.5 Hz, 1 H), 5.04 (dd, *J* = 5.5, 8.5 Hz, 1 H), 3.73 (s, 3 H), 3.58 (s, 3 H), 2.94 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 200.6, 153.9, 153.2, 152.5, 142.04, 142.0, 141.0, 128.6, 128.3, 128.1, 128.0, 127.96, 127.6, 127.4, 120.8, 113.8, 113.4, 110.6, 108.5, 82.9, 82.0, 69.1, 56.2, 56.0; HRMS (FAB^+) found 481.1624, calcd 481.1627 for $C_{28}H_{26}O_6Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 27.5 (minor). t_R = 31.0 (major).



2-(Benzhydryloxy)-3-(4-chlorophenyl)-1-(2,5-dimethoxyphenyl)-3-hydroxypropa

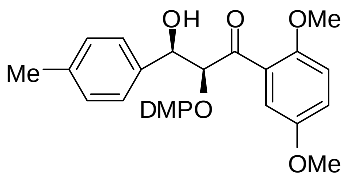
n-1-one.

Data are: major: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13-7.32 (m, 13 H), 7.00-7.02 (m, 1 H), 6.79-6.86 (m, 3 H), 5.47 (s, 1 H), 5.22 (dd, *J* = 1.0 Hz), 4.99 (s, 1 H), 3.77 (s, 3 H), 3.56 (s, 3 H), 3.20 (bs, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.8, 154.0, 152.5, 142.0, 140.2, 139.8, 133.1, 128.4, 128.3, 128.2, 127.9, 127.6, 127.2, 121.1, 114.3, 113.4, 84.5, 82.6, 73.3, 56.0, 55.9; HRMS (FAB$^+$) found 525.1457, calcd 525.1445 for $C_{30}H_{27}O_5ClNa$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 23.2 (minor). t_R = 28.9 (major).



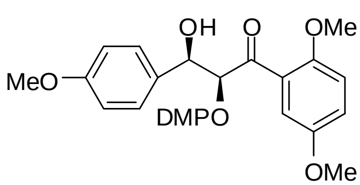
2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-(2-methoxyphenyl) propan-1-one.

Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.45 (m, 1 H), 7.09-7.31 (m, 9 H), 6.92-7.02 (m, 3 H), 6.68-6.81 (m, 4 H), 5.45 (s, 1 H), 5.35 (d, *J* = 2.0 Hz, 1 H), 5.19 (dd, *J* = 2.0, 9.0 Hz, 1 H), 3.74 (s, 1 H), 3.47 (s, 1 H), 3.465 (s, 1 H), 3.23 (d, *J* = 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.3, 156.0, 153.7, 152.0, 142.4, 141.0, 129.0, 128.5, 128.4, 128.3, 128.2, 127.7, 127.5, 127.4, 127.2, 120.5, 119.3, 114.2, 112.6, 110.0, 82.8, 82.3, 70.2, 55.9, 55.7, 54.9; HRMS (FAB$^+$) found 521.1954, calcd 521.1940for $C_{31}H_{30}O_6Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 19.0 (minor). t_R = 31.8 (major).



2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-p-tolylpropan-1-one.

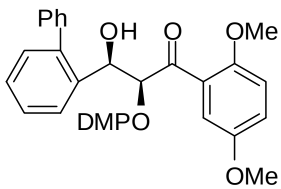
Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.07-7.32 (m, 13 H), 6.96-6.99 (m, 1 H), 6.88-6.90 (m, 2 H), 6.78 (d, J = 9 Hz, 1 H), 5.48 (s, 1 H), 5.26 (d, J =3.0 Hz, 1 H), 4.99 (dd, J = 3.0, 7.5 Hz, 1 H), 3.76 (s, 3 H), 3.54 (s, 3 H), 3.05 (d, J = 7.5 Hz, 1 H), 2.35 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.3, 154.0, 152.5, 142.3, 140.7, 138.1, 137.1, 128.9, 128.7, 128.4, 128.3, 127.9, 127.7, 127.5, 127.3, 126.2, 120.9, 114.3, 113.3, 84.9, 82.6, 73.9, 56.0, 21.3; HRMS (M^+) found 482.1078, calcd 482.2093 for $C_{31}H_{30}O_5$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 21.0 (minor). t_R = 32.3 (major).



2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-(4-methoxyphenyl) propan-1-one.

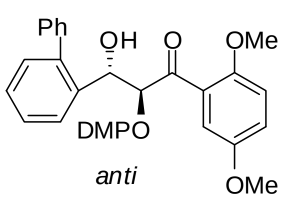
Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.14-7.33 (m, 11 H), 6.93-6.99 (m, 3 H), 6.76-6.81 (m, 3 H), 5.26 (d, J = 3.5 Hz, 1 H), 4.97 (dd, J = 3.5, 7.5Hz, 1 H), 3.81 (s, 3 H), 3.76 (s, 3 H), 3.54 (s, 3 H), 3.06 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.4, 159.2, 154.0, 152.5, 142.3, 140.7, 133.1, 128.7, 128.5, 128.3, 128.0, 127.8, 127.6, 127.4, 120.9, 114.3, 113.6, 113.3, 84.9, 82.6, 73.8, 56.0, 55.5; HRMS

(FAB$^+$) found 521.1940, calcd 521.1940 for $C_{31}H_{30}O_6Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 36.1 (minor). t_R = 49.8 (major).



2-(Benzhydryloxy)-3-(biphenyl-2-yl)-1-(2,5-dimethoxyphenyl)-3-hydroxypropan-1-one.

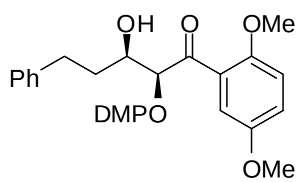
Data (major) are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.73 (d, *J* = 8.0 Hz, 1 H), 7.02-7.42 (m, 14 H), 6.80-6.82 (m, 1 H), 6.74-6.78 (m, 4 H), 6.64 (d, *J* = 3.0 Hz, 1 H), 6.50 (d, *J* = 9 Hz, 1 H), 5.38 (s, 1 H), 5.26 (dd, *J* = 2.5, 7.5 Hz, 1 H), 4.76 (d, *J* = 2.5 Hz, 1 H), 3.71 (s, 3 H), 3.29 (s, 3 H),, 3.06 (d, *J* =7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.9, 153.5, 151.0, 142.3, 140.9, 140.44, 140.37, 137.7, 130.3, 128.9, 128.5, 128.3, 128.2, 128.1, 127.8, 127.71, 127.68, 127.55, 127.49, 127.3, 126.9, 118.5, 113.2, 112.3, 83.1, 82.4, 70.4, 56.0, 55.5 ; HRMS (FAB$^+$) found 567.2161, calcd 567.2147 for $C_{36}H_{32}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 16.8 (minor). t_R = 21.0 (major).



2-(Benzhydryloxy)-3-(biphenyl-2-yl)-1-(2,5-dimethoxyphenyl)-3-hydroxypropan-

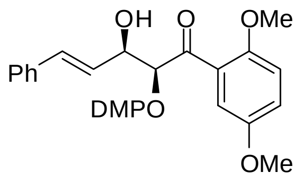
1-one.

Data (minor) are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.07-7.49 (m, 18 H), 6.97-7.00 (dd, *J* = 3.5, 9.0 Hz, 1 H), 6.86-6.89 (m, 2 H), 6.78 (d, *J* = 9.0 Hz, 1 H), 5.51 (s, 1 H), 5.34 (d, *J* = 3.0 Hz, 1 H), 5.09 (dd, *J* = 3.0, 8.5 Hz, 1 H), 3.75(s, 3 H), 3.55 (s, 3 H), 3.14 (d, *J* = 8.5 Hz, 1 H); HRMS (FAB^+) found 567.2158, calcd 567.2147 for $C_{36}H_{32}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 33.8 (major). t_R = 44.3 (minor).



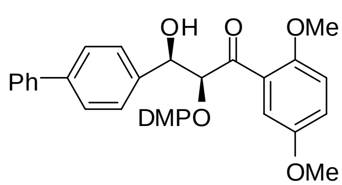
2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-5-phenylpentan-1-one.

Data are: major ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.43 (d, *J* = 7.5 Hz, 2 H), 7.15-7.36 (m, 12 H), 7.07 (d, *J* = 7.0 Hz, 2 H), 6.99 (dd, *J* = 3.5, 8.5 Hz, 1 H), 6.76 (d, *J* = 9.5 Hz, 1 H), 5.64 (s, 1 H), 5.01 (d, *J* = 1.5 Hz, 1 H), 3.84 (dd, *J* = 1.5, 10 Hz, 1 H), 3.76 (s, 3 H), 3.46 (s, 3 H), 2.63 (m, 1 H), 2.44 (m, 1 H), 2.35 (d, *J* = 10 Hz, 1 H), 2.00 (m, 1 H), 1.78 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.6, 154.0, 152.5, 142.3, 142.0, 141.0, 128.7, 128.60, 128.57, 128.5, 128.30, 128.27, 127.6, 127.3, 127.2, 126.0, 120.9, 114.2, 113.2, 83.0, 82.2, 71.6, 56.0, 55.8, 36.5, 32.0; HRMS (FAB^+) found 519.2149, calcd 519.2147 for $C_{32}H_{32}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 38.0 (minor). t_R = 51.0 (major).



(*E*)-2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-5-phenylpent-4-en-1-one.

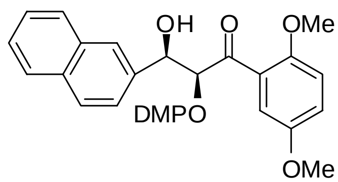
Data are: major ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.15-7.41 (m, 16 H), 6.98 (dd, *J* = 3.0, 8.5 Hz, 1 H), 6.79 (d, *J* = 9.5 Hz, 1 H), 6.56 (d, *J* = 16 Hz, 1 H), 6.13 (dd, *J* = 5.5, 16 Hz, 1 H), 5.62 (s, 1 H), 5.12 (d, *J* = 3.0 Hz, 1 H), 4.56 (bs, 1 H), 3.72 (s, 3 H), 3.56 (s, 3 H), 2.73 (d, *J* = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.0, 154.1, 152.6, 142.1, 140.8, 136.8, 131.2, 129.4, 128.7, 128.6, 128.4, 128.3, 128.2, 127.8, 127.6, 127.5, 127.2, 126.7, 121.0, 114.2, 113.3, 84.1, 82.8, 73.0, 56.05, 55.96; HRMS (M^+) found 494.2091, calcd 494.2093 for $C_{32}H_{30}O_5$; HPLC (DAICEL Chiralpack AD, 10% IPA/hexane, flow rate 1.0 mL/min): t_R = 30.8 (minor). t_R = 35.7 (major).



2-(Benzhydryloxy)-3-(biphenyl-4-yl)-1-(2,5-dimethoxyphenyl)-3-hydroxypropan-1-one.

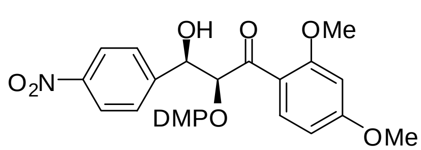
Data are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.45-7.52 (m, 4 H), 7.10-7.38 (m, 12 H), 7.00 (dd, *J* = 3.0, 9.0 Hz, 1 H), 6.88-6.90 (m, 2 H), 6.80 (d, *J* = 9.0 Hz, 1 H), 5.50 (s, 1 H), 5.31 (d, *J* = 3.0 Hz, 1 H), 5.07 (dd, *J* = 3.0, 8.0 Hz, 1 H), 3.77 (s, 3 H), 3.60 (s, 3 H), 3.14 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ

200.2, 154.0, 152.6, 142.2, 141.2, 140.5, 140.2, 129.0, 128.43, 128.36, 127.9, 127.8, 127.6, 127.5, 127.32, 127.27, 127.1, 126.9, 126.7, 121.0, 114.4, 113.3, 84.9, 82.6, 73.8, 56.1, 56.0; HRMS (FAB^+) found 567.2141, calcd 567.2147 for $C_{36}H_{32}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 33.6 (minor). t_R = 38.2 (major).



2-(Benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-(naphthalen-2-yl)propan-1-one.

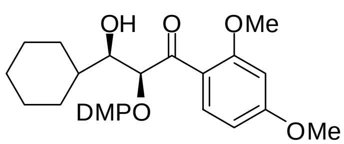
Data are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.80-7.82 (m, 1 H), 7.71-7.76 (m, 3 H), 7.45-7.48 (m, 2 H), 7.09-7.35 (m, 8 H), 6.92-6.96 (m, 3 H), 6.74-6.80 (m, 3 H), 5.48 (s, 1 H), 5.39 (d, *J* = 2.5 Hz, 1 H), 5.18 (bs, 1 H), 3.71 (s, 3 H), 3.57 (s, 3 H), 3.23 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.2, 154.0, 152.5, 142.1, 140.4, 138.6, 133.3, 133.1, 128.3, 128.2, 127.9, 127.84, 127.75, 127.5, 127.3, 127.2, 126.2, 126.0, 125.3, 124.3, 120.9, 114.3, 113.3, 84.7, 82.7, 74.1, 56.0, 55.9; HRMS (FAB^+) found 541.1998, calcd 541.1991 for $C_{34}H_{30}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 31.8 (minor). t_R = 41.4 (major).



2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxy-3-(4-nitrophenyl)propan-

1-one

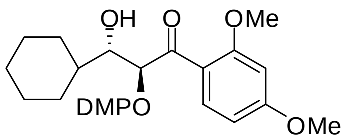
Data are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 8.14 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.29-7.25 (m, 5H), 7.24-7.20 (m, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 7.06 (dd, *J* = 4.0 Hz, 9.0 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 2H), 5.46 (s, 1H), 5.29 (d, *J* = 2.0 Hz, 1H), 5.11 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 3.22 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.1, 154.3, 152.7, 149.1, 147.4, 141.7, 140.0, 128.5, 128.4, 128.2, 128.1, 127.8, 127.2, 127.1, 126.6, 123.5, 121.6, 114.4, 113.7, 83.9, 82.7, 73.2, 56.3, 56.1; HRMS (FAB$^+$) found 536.1679, calcd 536.1685 for $C_{30}H_{27}NO_7Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 45.2 (minor). t_R = 49.9 (major).



2-(Benzhydryloxy)-3-cyclohexyl-1-(2,4-dimethoxyphenyl)-3-hydroxypropan-1-one

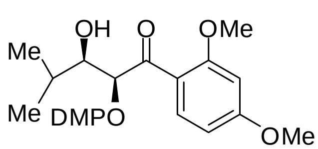
Data (major) are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.50-7.47 (m, 2H), 7.39-7.31 (m, 7H), 7.27-7.24 (m, 2H), 7.01 (dd, *J* = 3.0, 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.61 (s, 1H), 5.21 (d, *J* = 1.5 Hz, 1H), 3.78 (s, 3H), 3.59 (s, 3H), 3.33 (t, *J* = 10 Hz, 1H), 2.06 (m, 1H), 1.73-1.50 (m, 4H), 1.19-0.96 (m, 4H), 0.82-0.79 (m, 1H), 0.61-0.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.6, 154.1, 152.3, 142.4, 141.1, 129.1, 128.5, 128.34. 128.27, 127.5, 127.3, 127.2, 120.8, 114.2, 113.0, 82.0, 80.8, 76.6, 56.0, 55.8, 40.8, 29.9, 29.7, 29.0, 26.5, 26.2, 26.1; HRMS (FAB$^+$) found 497.2297, calcd

497.2304 for $C_{30}H_{34}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 10.5 (minor). t_R = 23.6 (major).



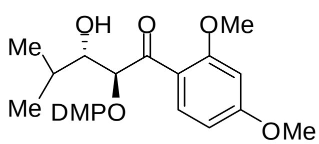
2-(Benzhydryloxy)-3-cyclohexyl-1-(2,4-dimethoxyphenyl)-3-hydroxypropan-1-one

Data (minor) are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.37-7.29 (m, 8H), 7.28-7.26 (m, 1H), 7.22-7.19 (m, 1H), 7.13 (d, *J* = 3.5 Hz, 1H), 7.00 (dd, *J* = 3.5, 9.0 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 5.45 (s, 1H), 5.16 (d, *J* = 6.0 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H), 2.27 (d, *J* = 7.0 Hz, 1H), 1.64-0.87 (m, 11H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.8, 153.9, 152.4, 142.2, 141.4, 129.0, 128.6, 128.3, 128.2, 128.1, 127.6, 127.4, 120.5, 113.9, 113.3, 96.4, 82.6, 81.2, 77.7, 56.1, 40.0, 30.0, 27.0, 26.6, 26.5, 26.2; HRMS (FAB^+) found 497.2300, calcd 497.2304 for $C_{30}H_{34}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 12.7 (minor). t_R = 21.4 (major).



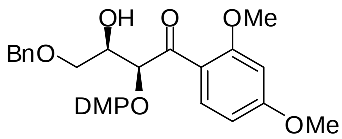
2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxy-4-methylpentan-1-one

Data (major) are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.48-7.46 (m, 2H), 7.37-7.31 (m, 7H), 7.26-7.25 (m, 2H), 7.01 (dd, *J* = 3.5, 9.0 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 3.27 (t, *J* = 10.5 Hz, 1H), 2.18 (d, *J* = 10.5 Hz, 1H), 1.92 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.51 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.3, 154.1, 152.3, 142.4, 141.0, 129.1, 128.6, 128.35, 128.28, 127.6, 127.5, 127.2, 127.1, 120.9, 114.3, 113.0, 81.8, 81.0, 77.8, 56.0, 55.7, 31.5, 19.6, 18.8; HRMS (FAB^+) found 457.1974, calcd 457.1991 for $C_{27}H_{30}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 13.6 (minor). t_R = 39.8 (major).



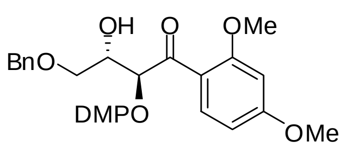
2-(Benzhydryloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxy-4-methylpentan-1-one

Data (minor) are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.36-7.29 (m, 7H), 7.27-7.24 (m, 2H), 7.21-7.18 (m, 1H), 7.13 (d, J = 3.0 Hz, 1H), 7.00 (dd, J = 3.0, 9.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 5.46 (s, 1H), 5.17 (d, J = 6.0 Hz, 1H), 3.77 (s, 3H), 3.76-3.73 (m, 1H), 3.56 (s, 3H), 2.28 (d, J = 8.0 Hz, 1H), 1.85 (m, 1H), 0.83 (apparent t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.5, 153.9, 152.5, 142.2, 141.3, 128.8, 128.7, 128.3, 128.2, 128.1, 127.5, 127.3, 120.6, 113.9, 113.4, 95.0, 82.5, 81.7, 78.2, 56.0, 30.2, 30.0, 19.8, 16.8; HRMS (FAB^+) found 457.1989, calcd 457.1991 for $C_{27}H_{30}O_5Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 11.0 (minor). t_R = 12.2 (major).



2-(Benzhydryloxy)-4-(benzyloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxybutan-1-one

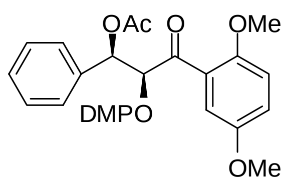
Data are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.41 (d, *J* = 7.0 Hz, 2H), 7.34-7.32 (m, 4H), 7.31-7.23 (m, 7H), 7.20-7.17 (m, 3H), 6.98 (dd, *J* = 3.0, 8.5 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 5.64 (s, 1H), 5.26 (d, *J* = 2.0 Hz, 1H), 4.42 (ABq, *J* = 11.5 Hz, 1H), 4.38 (ABq, *J* = 11.5 Hz, 1H), 4.09-4.04 (m, 1H), 3.75 (s, 3H), 3.62-3.54 (m, 2H), 3.44 (s, 3H), 2.48 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 200.6, 153.9, 152.7, 142.3, 141.0, 138.2, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.4, 127.0, 120.9, 114.0, 113.2, 82.3, 80.8, 73.4, 71.4, 70.8, 56.0, 55.8; HRMS (FAB^+) found 535.2114, calcd 535.2097 for $C_{32}H_{32}O_6Na$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 35.9 (minor). t_R = 45.2 (major).



2-(Benzhydryloxy)-4-(benzyloxy)-1-(2,4-dimethoxyphenyl)-3-hydroxybutan-1-one

Data are: ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.33-7.17 (m, 15H), 7.10 (d, *J* = 3.5 Hz, 1H), 6.97 (dd, *J* = 3.5, 9.0 Hz, 1H), 6.77 (d, *J* = 9.0 Hz, 1H), 5.52 (s, 1H), 5.29 (d, *J* = 5.5 Hz, 1H), 4.43 (s, 2H), 4.16-4.14 (m, 1H), 3.70 (s, 3H), 3.70-3.60 (m, 2H), 3.46 (s, 3H), 2.61 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 201.0, 153.8, 152.8, 142.2, 141.3, 138.2, 128.7, 128.5, 128.3, 128.1, 127.9, 127.6, 127.5, 120.8, 113.9, 113.5, 82.7, 81.1, 73.6, 72.1, 70.8, 56.0, 55.9; HRMS (EI^+) found 535.2203, calcd 512.2199 for $C_{32}H_{32}O_6$; HPLC (DAICEL Chiralpack AD, 10% EtOH/hexane, flow rate 1.0 mL/min): t_R = 84.4 (minor). t_R = 95.1 (major).

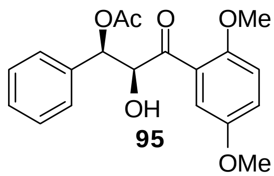
4.3.4. Product Elaboration and Absolute Configuration Determination



2-(Benzhydryloxy)-3-(2,5-dimethoxyphenyl)-3-oxo-1-phenylpropyl acetate

To a stirred solution of 2-(benzhydryloxy)-1-(2,5-dimethoxyphenyl)-3-hydroxy-3-phenylpropan-1-one **90** (0.6 g, 1.28 mmol) in EtOAc (3 mL) were added pyridine (0.31 mL, 3.84 mmol), DMAP (20 mg), and acetyl chloride (0.27 mL, 3.84 mmol)at 0 ^{o}C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min and then stirred at ambient temperature for overnight. The reaction was quenched by 1 N HCl. The resulting mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The product (0.64 g, 97%) was used for the next step without further purification, although it can be recrystallized with ethyl acetate and hexanes. Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10-7.32 (m, 13 H), 7.03 (d, *J* = 3.0 Hz, 1 H), 6.96-6.99 (m, 1 H), 6.79-6.85 (m, 3 H), 6.14 (d, *J* = 3.5 Hz, 1 H), 5.48 (s, 1 H), 5.26 (d, *J* = 3.5 Hz, 1 H), 3.74 (s, 3 H), 3.59 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75

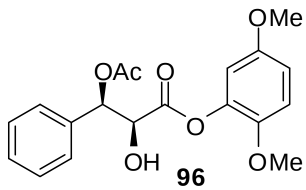
MHz): δ 198.9, 170.0, 154.1, 152.4, 142.6, 141.1, 137.6, 128.5, 128.38, 128.36, 128.2, 128.0, 127.8, 127.4, 127.2, 127.1, 120.6, 114.5, 113.4, 83.5, 83.1, 75.5, 56.1, 56.0, 21.2; HRMS (FAB$^+$) found 533.1953, calcd 533.1940 for $C_{32}H_{30}O_6Na$.



95

3-(2,5-Dimethoxyphenyl)-2-hydroxy-3-oxo-1-phenylpropyl acetate (95)

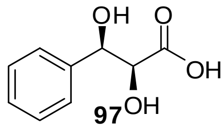
A solution of 2-(benzhydryloxy)-3-(2,5-dimethoxyphenyl)-3-oxo-1-phenylpropyl acetate (0.51 g, 1 mmole) in 25 mL CH_2Cl_2 was cooled to –78 °C. And $TiCl_4$ (1.1 mL, 1.0 M CH_2Cl_2) was added dropwisely. The resulting dark red solution was stirred at -78 °C for 2 h, at which time the reaction was quenched by saturated $NaHCO_3$ solution. The aqueous layer was extracted 3 times with ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$. The solution was then filtered and concentrated *in vacuo*. Radial chromatography afforded the desired compound **95** (0.27 g, 77%). Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27-7.44 (m, 6 H), 7.13 (dd, *J* = 3.0, 9.0 Hz, 1 H), 6.98 (d, *J* = 9.0 Hz, 1 H), 6.13 (d, *J* = 1.5 Hz, 1 H), 5.44 (dd, *J* = 1.5, 7.0 Hz, 1 H), 3.97 (d, *J* = 7.0 Hz, 1 H), 3.95 (s, 3 H), 3.81 (s, 3 H), 1.99 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.2, 169.8, 154.1, 153.6, 137.9, 128.6, 128.3, 127.0, 122.3, 114.8, 113.5, 79.3, 75.0, 56.3, 56.1, 20.9; HRMS (FAB$^+$) found 367.1156, calcd 367.1158 for $C_{19}H_{20}O_6Na$.



96

2,5-Dimethoxyphenyl 3-acetoxy-2-hydroxy-3-phenylpropanoate (96)

To a flame dried round bottom flask was added activated 4 angstrom molecular sieves (1.0 g), K_2CO_3 (0.2142 g, 1.55 mmol), trans-*N,N*-bis(p-toluenesulfonyl)-1,2-cyclohexanediamine (0.3275 g, 0.775 mmol) and 10 mL of CH_2Cl_2. The mixture was cooled to 0 °C and $SnCl_4$ (0.78 mL, 1 M in CH_2Cl_2) was added followed by bis(trimethylsilyl) peroxide (0.33 mL, 1.55 mmol). The mixture was stirred at 0 °C for 15 min, then 3-(2,5-dimethoxyphenyl) -2-hydroxy-3-oxo-1-phenylpropyl acetate **95** (0.2669 g, 0.775 mmol) was added as a CH_2Cl_2 solution (7.5 mL). The reaction stirred at 0 °C for 50 min, at which time the reaction was quenched by the addition of a saturated $NaHCO_3$ followed by a saturated $Na_2S_2O_3$ solution. The mixture was stirred at ambient temperature for 30 min then diluted with EtOAc and the layers separated. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with H_2O and brine. The mixture was then filtered, concentrated and purified by radial chromatography to provide the desired product **96** (0.22 g, 79%). Data are: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.48 (m, 5 H), 6.90 (d, *J* = 8.5 Hz, 1 H), 6.76 (dd, *J* = 3.0, 9.5 Hz, 1H), 6.59 (d, *J* = 3.0 Hz, 1H), 6.30 (d, *J* = 3.0 Hz, 1H), 4.70 (dd, *J* = 3.0, 8.5 Hz, 1H), 3.752 (s, 3 H), 3.747 (s, 3 H), 3.05 (d, *J* = 8.5 Hz, 1 H), 2.15 (s, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0, 169.8, 153.9, 145.3, 139.5, 136.6, 128.8, 128.7, 127.2,113.6, 112.3, 109.3, 75.7, 73.9, 56.6, 56.0, 21.1; HRMS (M^+) found 360.1223, calcd 360.1209 for $C_{19}H_{20}O_7$.

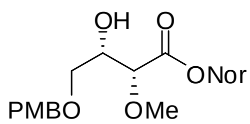

97

Methyl 2,3-dihydroxy-3-phenylpropanoate (97).

To a flame dried round bottom flask containing 2,5-dimethoxyphenyl-3-acetoxy-2-hydroxy-3-phenylpropanoate **96** (0.1 g, 0.28 mmol) was added 2.8 mL of MeOH and 2.8 mL of THF. The solution was cooled to 0 °C and then a freshly prepared NaOMe solution (5.8 mL, 0.1 M in MeOH) was added. The solution was stirred at 0 °C for 1 h then at ambient temperature for 17 h, at which time the reaction was quenched by the addition of a saturated NH_4Cl solution. The resulting solution was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash column chromatography to provide the title compound **97** (0.0182 g, 85%). Data are: $[\alpha]^{23}_{D}$ -7.6 (c 0.3, $CHCl_3$); [Lit. -10.7 (c 1.0, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30-7.41 (m, 5 H), 5.01 (dd, *J* = 3.0, 6.5 Hz, 1 H), 4.37 (dd, *J* = 3.0, 6.5 Hz, 1 H), 3.80 (s, 3 H), 3.17 (d, *J* = 5.5 Hz, 1 H), 2.83 (d, *J* = 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 140.1, 128.7, 128.3, 126.4, 74.9, 74.6, 53.1; HRMS (FAB^+) found 219.0635, calcd 219.0633 for $C_{10}H_{12}O_4Na$.

4.4. Total Synthesis of 8,9-Methylamido-Geldanamycin

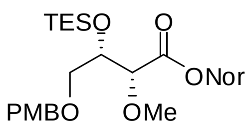
4.4.1. Preparation of Intermediates for Successful Route



132

(2*R*,3*S*)-((1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 3-hydroxy-2-methoxy-4-(4-methoxybenzyloxy)butanoate (132)

A 500 mL flame dried flask was charge with auxiliary **103** (4.957 g, 10 mmol) and 300 mL dry CH_2Cl_2. The solution was cooled to -78 ^oC under N_2 atmosphere. NEt_3 (3.4 mL, 25 mmol) was added dropwisely over 5 min, followed by slow addition of *c*-Hex_2BOTf (20 mL, 1 M hexanes) over 30 min. The resulting mixture was stirred at -78 ^oC for 2.5 h at which time aldehyde **131** (2.7 g, 15 mmol) was added as a CH_2Cl_2 (5 mL) solution over 5 min. The mixture was stirred for another 2 h, at which time it was quenched with pH 7 buffer (10 mL), MeOH (10 mL) and 30% H_2O_2 (2 mL). The mixture was warmed to ambient temperature and $NaHCO_3$ aqueous solution was added. The layers were separated and aqueous layer was extracted 3 times with CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4, filtered and concentrated. Chromatograph (20-30% EtOAc/hexanes) provides the desired product **132** (6.14 g, 91%). Data are: TLC R_f = 0.3 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ = +39.2^o (c 3.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 (d, *J* = 7.0 Hz, 2H), 7.23-7.13 (m, 8H), 6.88-6.83 (m, 6H), 5.87 (d, *J* = 5.0 Hz, 1H), 4.75 (A of AB q, *J* = 16.5 Hz, 1H), 4.51 (B of AB q, *J* = 16.5 Hz, 1H), 4.42 (apparent q, *J* = 11.5 Hz, 2H), 4.15 (m, 2H), 3.83 (d, *J* = 3.5 Hz, 1H), 3.77 (s, 3H), 3.47 (d, *J* = 7.0 Hz, 2H), 3.35 (s, 3H), 2.56 (d, *J* = 7.5 Hz, 1H), 2.47 (s, 6H), 2.27 (s, 3H), 1.21 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 159.4, 142.7, 140.4, 138.5, 138.0, 133.3, 132.3, 129.9, 129.5, 128.4, 128.1, 127.9, 127.3, 126.4, 113.9, 80.4, 78.7, 77.5, 77.2, 77.0, 73.2, 70.8, 69.7, 59.5, 56.9, 55.3, 48.3, 23.0, 21.0, 14.0; HRMS (FAB+) found 675.3533 M+ , calcd 675.2866 for $C_{38}H_{45}NO_8S$.

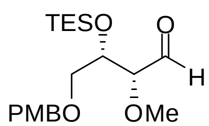


133

(2*R*,3*S*)-((1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl) 2-methoxy-4-(4-methoxybenzyloxy)-3-(triethylsilyloxy)butanoate 133

A 100 mL dry flask was charged with the aldol product **132** (6.24 g, 9.1 mmol) and DMF (50 mL). To the stirring solution was added imidazole (1.86 g, 27.3 mmol) followed by TESCl (3.1 mL, 18.2 mmol). The mixture was stirred for 4 h at ambient temperature and then quenched with H_2O (200 mL). The layers were separated and aqueous layer was extracted 3 times with Et_2O. The organic layers were combined, dried and concentrated. Chromatograph (20% EtOAc/hexanes) provided the desired product **133** (6.75 g, 94%). Data are: TLC R_f = 0.6 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.32 (d, *J* = 6.5 Hz, 2H), 7.26-7.18 (m, 6H), 7.10 (t, *J* = 7.5 Hz, 2H), 6.85-6.83 (m, 6H), 5.81 (d, *J* = 5 Hz, 1H), 4.77 (A of AB q, *J* = 16 Hz, 1H), 4.51 (B of AB q, *J* = 16 Hz, 1H), 4.35 (m, 2H), 4.13-4.11 (m, 2H), 3.79 (s, 3H), 3.73 (d, *J* = 5 Hz, 1H), 3.51-3.48 (m, 1H), 3.33 (m, 4H), 2.41 (s, 6H), 2.29 (s, 3H), 1.18 (d, *J* =

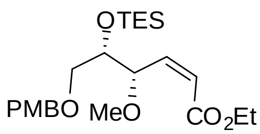
7 Hz, 3H), 0.81 (t, *J* = 7 Hz, 9H), 0.48-0.43 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 159.4, 142.7, 140.5, 138.7, 138.0, 138.3, 132.3, 130.3, 129.5, 128.6, 128.4, 128.2, 128.1, 127.5, 126.9, 82.5, 78.8, 73.1, 72.1, 70.6, 59.8, 56.9, 55.5, 48.2, 23.1, 21.1, 14.7, 6.9, 5.0; HRMS (FAB+) found 812.3633 [M+Na]+ , calcd 816.3628 for $C_{44}H_{59}NO_8SSiNa$.



134

(2*R*,3*S*)-2-Methoxy-4-(4-methoxybenzyloxy)-3-(triethylsilyloxy)butanal (134)

A flame dried 250 mL round bottom flask was charged with the TES protected aldol product **133** (2.25 g, 2.8 mmol) and 80 mL dry CH_2Cl_2. The resulting solution was cooled to -78 °C under nitrogen atmosphere. DIBAL-H (4.7 mL, 1.5 M in toluene) was added along the inner wall of the flask over 20 min. The mixture was stirred for 3 h before being quenched with 4 mL MeOH and 12 mL Na/K tartrate aqueous solution at -78 °C. The mixture was allowed to warm to ambient temperature and stirred for another 1.5 h, at which time it was diluted with 80 mL Na/K tartrate salt solution and extracted 4 times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed (10% acetone/hexanes) to give the title compound **134** (0.86 g, 87%). Data are: TLC R_f = 0.6 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ = +31.7° (c 3.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.76 (d, *J* = 1.5 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.45 (A of AB q, *J* = 11.5 Hz, 1H), 4.41 (b of AB q, *J* = 11.5 Hz, 1H), 4.20-4.17 (m, 1H), 3.81 (s, 3H), 3.69-3.68 (m, 1H), 3.59-3.56 (m, 1H), 3.48 (s, 3H), 3.45-3.43 (m, 1H), 0.93-0.89 (m, 9H), 0.61-0.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.6, 159.4, 130.2, 129.6, 113.9, 87.0, 73.2, 72.1, 70.1, 59.6, 55.5, 6.9. 4.9; HRMS (FAB+) found 391.1916 [M+Na]+ , calcd 391.1917 for $C_{19}H_{32}O_5SiNa$.

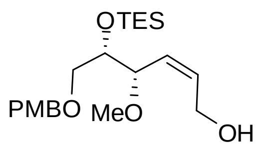


136

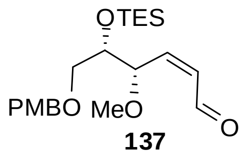
(4*S*,5*S*,*Z*)-Ethyl 4-methoxy-6-(4-methoxybenzyloxy)-5-(triethylsilyloxy)hex-2-enoate (136)

To a mixture of phosphonate **135** (1.17 g, 2.71 mmol) and NaI (1.69 g, 11.3 mmol) in 20 mL THF was slowly added tetramethylguanidine (0.37 mL, 2.94 mmol) at -78 ^{o}C. After the mixture was stirred for 30 min, aldehyde **134** (0.83 g, 2.26 mmol) was added as a THF (3 mL) solution. The mixture was stirred for another 5 h and then quenched with NH_4Cl aqueous solution. The layers were separated. Aqueous layer was extracted 3 times with Et_2O. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by chromatograph (5% EtOAc/hexanes) and provided **136** (0.97 g, 98%, 16:1–28:1 selectivity). Data are: TLC R_f = 0.6 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.25 (dd, *J* = 8.3 and 12 Hz, 1H), 5.97 (d, *J* = 12 Hz, 1H), 4.92 (m, 1H), 4.50 (A of AB q, *J* = 12 Hz, 1H), 4.42 (B of AB q, *J* = 12 Hz, 1H), 4.21- 4.15 (m, 2H), 4.03-4.00 (m, 1H), 3.80 (s, 3H), 3.62 (dd, *J* = 6 and 10 Hz, 1H), 3.43 (dd, *J* = 6 and 10 Hz, 1H), 3.29 (s, 3H), 1.28 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J*

= 8 Hz, 9H), 0.60-0.55 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.0, 159.2, 149.0, 130.7, 129.4, 122.5, 113.7, 77.8, 73.9, 73.0, 71.5, 60.4, 57.7, 55.4, 14.3, 7.0, 5.0; HRMS (FAB+) found 461.2330 [M+Na]+ , calcd 461.2335 for $C_{23}H_{38}O_6SiNa$.



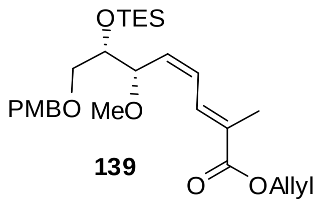
(4*S*,5*S*,*Z*)-4-Methoxy-6-(4-methoxybenzyloxy)-5-(triethylsilyloxy)hex-2-en-1-ol. A solution of ester **136** (0.814 g, 1.86 mmol) in 30 mL Et_2O was cooled to -78 ^{o}C. DIBAL-H (3.1 mL, 1.5 M in toluene) was added dropwisely. Afer the mixture was stirred for 30 min, it was quenched with Na/K tartrate aqueous solution. The mixture was warmed to ambient temperature and stirred for 15 min, at which time the two layers were clear. The two layers were separated and aqueous layer was extracted 5 times with Et_2O. The combined Et_2O solution was dried over Na_2SO_4, filtered and concentrated. Chromatograph column (10-20% EtOAc/hexanes) provided the title compound (0.6 g, 82%). Data are: TLC R_f = 0.2 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.96 (m, 1H), 5.4 (t, *J* = 10 Hz, 1H), 4.48 (q, *J* = 11.5 Hz, 2H), 4.21-4.17 (m, 1H), 4.13-4.10 (m, 1H), 4.09-4.05 (m, 1H), 3.82-3.80 (m, 1H), 3.80 (s, 3H), 3.53 (dd, *J* = 7 and 10.5 Hz, 1H), 3.43 (dd, *J* = 5 and 10.5 Hz, 1H), 3.28 (s, 3H), 2.58 (bs, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.3, 133.6, 130.3, 130.2, 129.6, 113.9, 78.6, 74.6, 73.6, 71.7, 58.5, 56.9, 55.4, 7.0, 5.0; HRMS (+TOF MS) found 419.1859 [M+Na]+ , calcd 419.22130 for $C_{21}H_{36}O_5SiNa$.



137

(4*S*,5*S*,*Z*)-4-Methoxy-6-(4-methoxybenzyloxy)-5-(triethylsilyloxy)hex-2-enal (137).

To a stirred solution of the above alcohol (1.05 g, 2.65 mmol) in 20 mL CH_2Cl_2 was added Dess-Martin periodinane (1.68 g, 3.97 mmol) in one portion at ambient temperature. The solution was stirred for 45 min, at which time it was diluted with Et_2O and quenched with $Na_2S_2O_3$ (6.58 g, 26.5 mmol) aqueous solution. The resulting mixture was stirred for another 20 min. The layers were separated and organic layer was washed 3 times with $Na_2S_2O_3$ and $NaHCO_3$ aqueous solution. Chromatograph (10% EtOAc/hexanes) provided **137** (0.98 g, 94%). Data are: TLC R_f = 0.6 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.11 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.47 (m, 1H), 6.11 (m, 1H), 4.56 (m, 1H), 4.43 (A and B of AB q, *J* = 11.5 Hz, 2H), 3.91 (dd, *J* = 5.5 and 7.8 Hz, 1H), 3.80 (s, 3H), 3.58 (m, 1H), 3.77 (m, 1H), 3.34 (s, 3H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.60 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.0, 159.4, 148.6, 132.8, 130.2, 129.6, 113.9, 78.8, 73.7, 73.3, 71.0, 57.7, 55.4, 7.0, 5.0; HRMS (+TOF MS) found 412.2631 [M+NH_4]+ , calcd 412.2514 for $C_{21}H_{38}NO_5Si$.

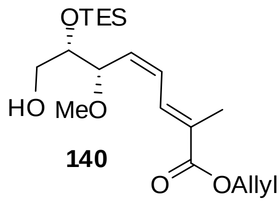


139

(2*E*,4*Z*,6*S*,7*S*)-Allyl 6-methoxy-8-(4-methoxybenzyloxy)-2-methyl-7-(triethylsilyl-oxy)octa -2,4-Dienoate (139)

To a stirred solution of phosphonate **138** (0.83 g, 3.32 mmol) in 25 mL CH_3CN was added LiCl (0.14 g, 3.32 mmol) at ambient temperature. The mixture was stirred for 15 min before it was cooled to 0 ^oC. After it was stirred for another 10 min, DBU (0.45 mL, 2.98 mmol) was added slowly. The mixture was stirred for 15 min and aldehyde **137** (0.65 g, 1.66 mmol) was added as a CH_3CN (3 mL) solution. After 2 h at 0 ^oC, the reaction was quenched with NH_4Cl aqueous solution. These two layers were separated and the aqueous layer was extracted 3 times with Et_2O. The combined ether layers was dried over Na_2SO_4, filtered and concentrated. Chromatograph (5% EtOAc/hexanes) provided **139** (0.80 g, 98%, 25:1 selectivity) product. Data are: TLC R_f = 0.6 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, ***J*** **=** 12 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.55 (t, *J* = 11.5 Hz, 1H), 5.96 (m, 1H), 5.72 (t, 10.5 Hz, 1H), 5.34 (d, *J* = 10.5 Hz, 1H), 5.23 (d, *J* = 9.0 Hz, 1H), 4.67 (m, 2H), 4.45 (q, *J* = 12 Hz, 2H), 4.26 (m, 1H), 3.83 (q, *J* = 5.5 Hz, 1H), 3.80 (s, 3H), 3.56 (m, 1H), 3.36 (m, 1H), 3.27 (s, 3H), 1.99 (s, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.60 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 159.2, 136.1, 132.7, 132.6, 130.5, 129.5, 129.2, 127.6, 118.1, 113.8, 78.2, 74.3, 73.2, 71.5, 65.5, 57.1, 55.4, 12.7, 7.0, 5.0; HRMS (+TOF MS) found 513.2649 [M+Na]+ , calcd 513.2643 for

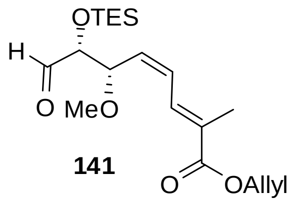
$C_{27}H_{42}O_6SiNa$.



140

(2*E*,4*Z*,6*S*,7*S*)-Allyl 8-hydroxy-6-methoxy-2-methyl-7-(triethylsilyloxy)octa-2,4-dienoate (140)

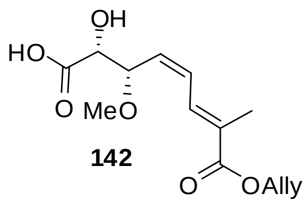
To a stirred solution of allyl ester **139** (0.39 g, 0.8 mmol) in 16 mL CH_2Cl_2 and 0.8 mL H_2O was added DDQ at ambient temperature. The resulting green colored mixture was stirred for 1.5 h before being quenched with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted 3 times with CH_2Cl_2. And the combined organic layers were washed 3 times with aqueous $NaHCO_3$. The resulting organic layer was dried over Na_2SO_4, filtered and concentrated. Chromatograph (10% EtOAc/hexanes) provided **140** (0.25 g, 84%). Data are: TLC R_f = 0.2 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, *J* = 12 Hz, 1H), 6.61 (t, *J* = 11.0 Hz, 1H), 5.96 (m, 1H), 5.68 (t, *J* = 11.0 Hz, 1H), 5.35 (d, *J* = 17 Hz, 5.25 (d, *J* = 12 Hz, 1H), 4.69-4.67 (m, 2H), 4.24 (m, 1H), 3.82 (m, 1H), 3.63 (m, 1H), 3.53 (m, 1H), 3.28 (s, 3H), 2.16 (m, 1H), 1.99 (s, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.64 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 135.0, 132.6, 132.5, 129.7, 128.6, 118.1, 79.2, 74.5, 65.6, 64.0, 56.9, 12.7, 7.0, 5.1; HRMS (+TOF MS) found 371.2255 [M+H]+ , calcd 371.2248 for $C_{19}H_{35}O_5Si$..



141

(2*E*,4*Z*,6*S*,7*R*)-Allyl 6-methoxy-2-methyl-8-oxo-7-(triethylsilyloxy)octa-2,4-dienoate (141)

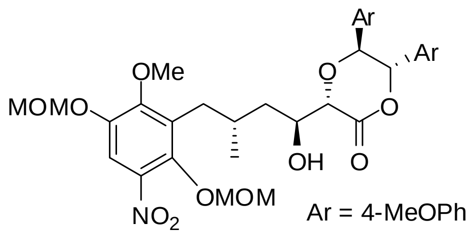
A flame dried flask was charged with alcohol **140** (0.8 g, 2.16 mmol) and 10 mL CH_2Cl_2. Dess-Martin periodinane (1.37 g, 3.24 mmol) was added in one portion at ambient temperature. The solution was stirred for 1 h and diluted with Et_2O and quenched with $Na_2S_2O_3$ (5.36 g, 21.6 mmol) aqueous solution. The mixture was stirred for 15 min before the layers were separated and organic layer was washed 3 times with $Na_2S_2O_3$ and $NaHCO_3$ aqueous solution. Chromatograph (10% EtOAc/hexanes) provided **141** (0.76 g, 95%). Data are: TLC R_f = 0.5 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300MHz) δ 9.69 (d, *J* = 1.5 Hz, 1H), 7.49 (d, *J* = 12.0 Hz, 1H), 6.62 (t, *J* = 12.0 Hz, 1H), 5.96 (m, 1H), 5.77 (t, *J* = 10.2 Hz, 1H), 5.33 (m, 2H), 4.69 (d, *J* = 6.0 Hz, 2 H), 4.53 (m, 1H), 3.27 (s, 3H), 1.99 (s, 3H), 0.95 (t, *J* = 8.1 Hz, 9H), 0.62 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.0, 168.0, 133.8, 132.5, 131.8, 130.4, 128.6, 118.3, 79.9, 78.4, 65.7, 57.3, 12.8, 6.9, 4.9; HRMS (+TOF MS) found 391.1897 [M+Na]+, calcd 391.1911 for $C_{19}H_{32}O_5SiNa$.



142

(2*R*,3*S*,4*Z*,6*E*)-8-(Allyloxy)-2-hydroxy-3-methoxy-7-methyl-8-oxoocta-4,6-dienoic acid (142)

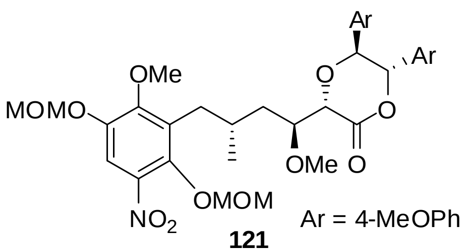
A 50 mL flask was charged with aldehyde **141** (0.68 g, 1.85 mmol), $NaH_2PO_4{\cdot}H_2O$ (0.61 g, 4.44 mmol), 16 mL *t*-BuOH, 4 mL H_2O, and 4 mL 2-methyl-2-butene. $NaClO_2$ (0.52 g, 5.74 mmol) was added at 0 ^{o}C. The resulting mixture was warmed to ambient temperature and allowed to stir for 2 h. The reaction was quenched with aqueous NH_4Cl and extracted 10 times with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The crude product was passed through a silicon plug eluting with 30% EtOAc/hexanes to get rid of some yellow impurities, and then eluting with MeOH to get the product. After MeOH solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2. The insoluble silicon was removed by filtration. The product **142** (0.45 g, 90% yield) was recovered after CH_2Cl_2 removal. Data are: TLC Rf = 0.2 (20% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = -33.7^{o} (c 4.2, $CHCl_3$); ^{1}H NMR (CD_3OD, 300MHz) δ 7.64 (d, *J* = 12.0 Hz, 1H), 6.69 (t, *J* = 11.4 Hz), 6.06-5.89 (m, 2H), 5.37-5.21 (m, 2H), 4.69-4.67 (m, 2H), 4.64 (bs, 1H), 4.00 (bs, 1H), 3.28 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (CD_3OD, 75 MHz) δ 178.1, 169.4, 136.3, 134.0, 133.5, 130.9, 128.6, 118.4, 79.4, 76.2, 66.6, 57.5, 12.8; HRMS (+TOF MS) found 293.0996 [M+Na]+, calcd 293.0996 for $C_{13}H_{18}O_6Na$.



120

(3*S*,5*S*,6*S*)-3-((1*S*,3*R*)-1-Hydroxy-4-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitro phenyl)-3-methylbutyl)-5,6-bis(4-methoxyphenyl)-1,4-dioxan-2-one (120)

A flame dried flask was charge with dioxanon **102** (0.93 g, 2.97 mmol) and 80 mL CH_2Cl_2. The solution was cooled to -78 °C under nitrogen atmosphere. Et_3N (1.03 mL, 7.43 mmol) was added dropwisely, followed by *c*-hex$_2$BOTf (6 mL, 1M in hexanes) over 0.5 h. The resulting mixture was stirred at -78 °C for 3 h, at which time aldehyde **114** (1.2 g, 3.56 mmol) was added in 3 mL CH_2Cl_2 dropwisely over 10 min. The reaction was stirred for another 3 h at -78 °C and then quenched with pH 7 buffer (10 mL), MeOH (10 mL) and 30% aqueous H_2O_2 (3 mL). The mixture was warmed to ambient temperature and $NaHCO_3$ aqueous solution was added. The layers were separated and aqueous layer was extracted 3 times with CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4, filtered and concentrated. Chromatograph (30-40% EtOAc/hexanes) provided the desired product **120** (1.26 g, 63%) and an isomer (0.16 g, 8%). Data are: TLC R_f = 0.2 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ = -103.7° (c 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (s, 1H), 7.00-6.94 (m, 4H), 6.78-6.74 (m, 4H), 5.37 (d, *J* = 9.0 Hz, 1H), 5.19 (s, 2H), 5.00 (q, *J* = 6.0 Hz, 2H), 4.93 (d, *J* = 9.0 Hz, 1H), 4.54 (d, *J* = 5.5 Hz, 1H), 4.26 (m, 1H), 3.93 (s, 3H), 3.757 (s, 3H), 3.756 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H), 2.88 (d, *J* = 5.5 Hz, 1H), 2.71 (m, 2H), 2.13 (m, 1H), 1.75 (m, 1H), 1.65 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 160.2, 159.9, 153.3, 146.2, 145.8, 139.6, 131.5, 129.0, 128.7, 128.1, 126.8, 113.9, 111.1, 101.8, 95.6, 85.2, 78.2, 76.8, 71.5, 61.2, 57.9, 56.6, 55.3, 40.4, 32.9, 30.2, 19.2; HRMS (FAB+) found 694.2474 [M+Na]+, calcd 694.2476 for $C_{34}H_{41}NO_{13}Na$.

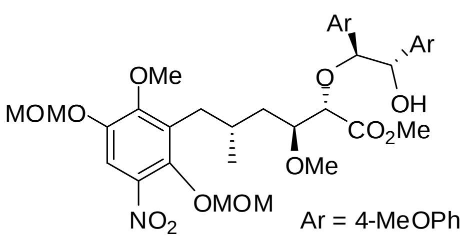


121

(3*S*,5*S*,6*S*)-3-((1*S*,3*R*)-1-Methoxy-4-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitro phenyl)-3-methylbutyl)-5,6-bis(4-methoxyphenyl)-1,4-dioxan-2-one (121)

A flame dried 100 mL flask was charged with the aldol product **120** (1.7 g, 2.53 mmol) and 40 mL CH_2Cl_2. The solution was cooled to 0 ^oC before proton sponge (1.09 g, 5.06 mmol) was added, followed by Me_3OBF_4 (0.75 g, 5.06 mmol). The resulting mixture was warmed to ambient temperature and stirred for 5 h, at which time another portion of proton sponge (0.54 g, 2.53 mmol) and Me_3OBF_4 (0.37 g, 2.53 mmol) was added. The reaction was stirred for overnight, at which time it was filtered through a silicon plug eluting with Et_2O and concentrated. Chromatograph (20-30% EtOAc/hexanes) provided **121** (1.73 g, 100%). Data are: TLC R_f = 0.5 (30% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.57 (s, 1H), 6.99 (t, *J* = 9.0 Hz, 4H), 6.75 (q, *J* = 9.0 Hz, 4H), 5.38 (d, *J* = 9.0 Hz, 1H), 5.17 (s, 2H), 5.01 (s, 2H), 4.97 (d, *J* = 9.0 Hz, 1H), 4.87 (d, *J* = 2.5 Hz, 1H), 3.93 (s, 3H), 3.91 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.54 (s, 3H), 3.48 (s, 3H), 3.44 (s, 3H), 2.71 (m, 2H), 2.08 (m, 1H), 1.92

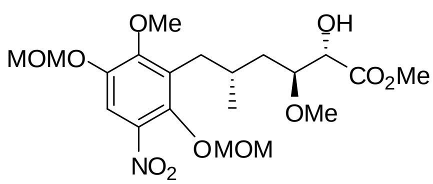
(m, 1H), 1.58 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.1, 160.0, 159.8, 153.2, 146.2, 145.6, 139.6, 131.2, 128.9, 128.8, 128.1, 127.3, 113.81, 113.77, 111.0, 101.8, 95.4, 85.5, 82.7, 77.9, 74.4, 61.1, 57.9, 57.6, 56.6, 55.3, 37.9, 32.7, 30.4, 19.7; HRMS (FAB+) found 708.2637 [M+Na]+, calcd 708.2632 for $C_{35}H_{43}NO_{13}Na$.



122

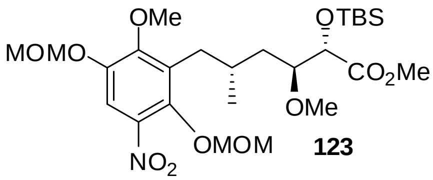
(2*S*,3*S*,5*R*)-Methyl 2-((1S,2S)-2-hydroxy-1,2-bis(4-methoxyphenyl)ethoxy) -3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-5-methylhexanoate (122)

A solution of the protected aldol product **121** (1.73 g, 2.53 mmol) in 20 mL dry THF and 20 mL dry MeOH was cooled to 0 °C. A freshly prepared NaOMe (0.25 mL, 0.1 M in MeOH) was added. The resulting mixture was stirred at 0 °C for 3 h, at which time it was quenched with NH_4Cl solution. The mixture was extracted 5 times with Et_2O. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. Chromatograph (30% EtOAc/hexanes) provided desired product **122** (1.60 g, 88%). Data are: TLC R_f = 0.4 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (s, 1H), 6.94 (apparent q, *J* = 8.5 Hz, 4H), 6.70 (t, *J* = 8.5 Hz, 4H), 5.22 (s, 2H), 5.03 (q, *J* = 6.5 Hz, 2H), 4.71 (d, *J* = 9.0 Hz, 1H), 4.31 (d, *J* = 8.0 Hz, 1H), 4.23 (d, *J* = 3.5 Hz, 1H), 3.99 (s, 1H), 3.95 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.65 (m, 1H), 3.59 (s, 3H), 3.52 (s, 3H), 3.50 (s, 3H), 3.40 (s, 3H), 2.76 (m, 1H), 2.66 (m, 1H), 2.12 (m, 1H), 1.92 (m, 1H), 1.32 (m, 1H), 0.86 (d, J = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.2, 159.4, 159.1, 153.3, 146.3, 145.9, 139.7, 131.5, 129.6, 129.4, 128.5, 113.4, 113.3, 111.2, 101.8, 95.6, 90.1, 81.0, 79.1, 78.6, 61.2, 58.2, 57.9, 56.6, 55.2, 51.9, 38.3, 33.0, 30.2, 19.0; HRMS (+TOF MS) found 740.2888 [M+Na]+ , calcd 740.2889 for $C_{36}H_{47}O_{14}Na$.



(2*S*,3*S*,5*R*)-Methyl 2-hydroxy-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy) -5- nitrophenyl)-5-methylhexanoate

To a stirred solution of the methyl ester **122** (1.36 g, 1.89 mmol) in 25 mL CH_3CN and 2.7 mL H_2O was added ceric ammonium nitrate (2.59 g, 4.72 mmol) at 0 ^oC. The resulting mixture was stirred at 0 ^oC for 30 min, at which time the reaction was diluted with H_2O and Et_2O. The two layers were separated and aqueous layer was extracted 5 times with Et_2O. The Et_2O layers were combined, dried, filtered, concentrated, and chromatographed (30% EtOAc/hexanes) to provide the title compound (0.68 g, 78%). Data are: TLC R_f = 0.3 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (s, 1H), 5.22 (s, 2H), 5.00 (s, 2H), 4.45 (m, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.60-3.57 (m, 1H), 3.56 (s, 3H), 3.52 (s, 3H), 3.42 (s, 3H), 2.87 (d, J = 5.5 Hz, 1H), 2.72-2.69 (m, 1H), 2.63-2.59 (m, 1H), 2.05 (m, 1H), 1.76 (m, 1H), 1.12 (m, 1H), 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 153.3, 146.3, 145.8, 139.7, 131.4, 111.1, 101.8, 95.6, 80.9, 72.0, 61.2, 58.3, 57.9, 56.7, 52.7, 37.4, 32.7, 30.1, 19.3; HRMS (+TOF MS) found 484.1797 [M+Na]+ , calcd 484.1789 for $C_{20}H_{31}NO_{11}Na$.

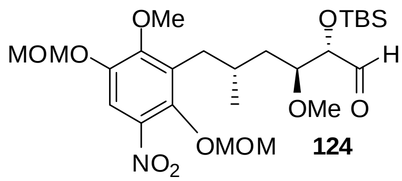


123

(2*S*,3*S*,5*R*)-Methyl 2-(tert-butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis (methoxymethoxy)-5-nitrophenyl)-5-methylhexanoate (123)

A flame dried 25 mL flask was charge with the previous α-hydroxyl ester (0.33 g, 0.72 mmol), 5 mL DMF, and imidazole (0.25 g, 3.61 mmol). The resulting solution was cooled to 0 ^{o}C before TBSCl (0.22 g, 1.44 mmol) was added in portions. The reaction was stirred for overnight, at which time it was quenched with NH_4Cl and diluted with Et_2O. The two layers were separated and aqueous layer was extracted 3 times with ether. Ether layers were combined, dried, filtered, concentrated, and chromatographed (10% EtOAc/hexanes) to give desired product **123** (0.36 g, 87%). Data are: TLC R_f = 0.7 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ = -22.0^{o} (c 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60 (s, 1H), 5.22 (s, 2H), 5.00 (q, *J* = 6.0 Hz, 2H), 4.28 (d, *J* = 4.5 Hz, 1H), 3.93 (s, 3H), 3.73 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H), 3.51-3.48 (m, 1H), 3.45 (s, 3H), 2.72- 2.60 (m, 2H), 2.05 (m, 1H), 1.70-1.65 (m, 1H), 1.26-1.19 (m, 1H), 0.89 (s, 9H), 0.86 (d, *J* = 6.0 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 153.4, 146.3, 146.0, 139.6, 131.7, 111.1, 101.8, 95.6, 81.5, 73.8, 61.2, 58.3, 57.9, 56.7, 52.0, 38.2, 33.1, 30.0, 25.8, 19.3, 18.4, -5.0, -5.1; HRMS

(+TOF MS) found 593.3101 [M+NH_4]+ , calcd 593.3100 for $C_{26}H_{49}N_2O_{11}Si$.

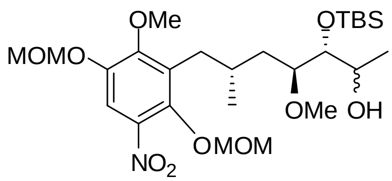


124

(2*S*,3*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-5-methylhexanal (124)

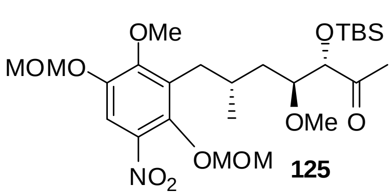
A flame dried flask was charged with ester **123** (0.82 g, 1.42 mmol) and 25 mL CH_2Cl_2. The solution was cooled to -78 ^oC. DIBAL-H (1 mL, 1.5 M in toluene) was added slowly along the flask inside wall. After 2 h, another portion of DIBAL-H (1 mL, 1.5 M in toluene) was added slowly. The mixture was stirred for another 2 h at which time it was quenched with 1 mL MeOH and aqueous Na/K tartrate. The mixture was warmed to ambient temperature and stirred until the layers became clear. The two layers were separated and the aqueous layer was extracted 5 times with Et_2O. The combined ether layers were dried, filtered, concentrated and chromatographed (10% EtOAc/hexanes) to provide aldehyde **124** (0.76 g, 98%). Data are: TLC R_f = 0.5 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.66 (s, 1H), 7.61 (s, 1H), 5.22 (s, 2H), 5.00 (q, *J* = 6.0 Hz, 2H), 4.10 (s, 1H), 3.92 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H), 3.49-3.46 (m, 1H), 3.37 (s, 3H), 2.71-2.60 (m, 2H), 2.05 (m, 1H), 1.78-1.72 (m, 1H), 1.14-1.11 (m, 1H), 0.90 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.7, 153.4, 146.3, 146.0, 139.6, 131.6, 111.1, 101.9, 95.6, 81.5, 79.2, 61.2, 58.4, 57.9, 56.7, 38.2, 33.0, 29.9, 38.1, 33.0, 29.9, 25.9, 19.3, 18.4, -4.7; HRMS (+TOF MS) found 568.2552 [M+Na]+ , calcd 568.2548 for

$C_{25}H_{43}NO_{10}SiNa$.



(3*R*,4*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-methoxy-7-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-6-methylheptan-2-ol

A flame dried 50 mL flask was charged with aldehyde **124** (0.77 g, 1.41 mmol) and 20 mL CH_2Cl_2. The resulting solution was cooled to -78 ^{o}C before $AlMe_3$ (2.1 mL, 2 M in hexanes) was slowly added. After 1.5 h, another portion of $AlMe_3$ (2.1 mL, 2 M in hexanes) was added and the mixture was allowed to stir for 6 h, at which time the reaction was quenched with aqueous NH_4Cl and was warmed to ambient temperature. Aqueous Na/K tartrate was added and the resulting mixture was stirred for another 20 min. The layers were separated and aqueous layer was extracted 5 times with CH_2Cl_2. The combined organic layers were dried, filtered, concentrated, and filtered through a silica plug (20% EtOAc/hexanes) to provide 0.79 g products (100%) as a pair of diastereomers. Data are: TLC R_f = 0.3 and 0.4 (30% EtOAc/hexanes); HRMS (+TOF MS) found 584.2861 [M+Na]+ , calcd 584.2861 for $C_{26}H_{47}NO_{10}SiNa$.

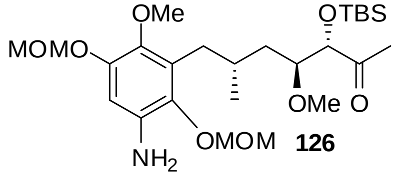


125

(3*S*,4*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-methoxy-7-(2-methoxy-3,6-bis(metho

xymethoxy)-5-nitrophenyl)-6-methylheptan-2-one (125)

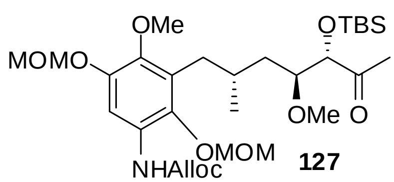
To a stirred solution of the previous alcohol (0.79 g, 1.41 mmol) in 20 mL CH_2Cl_2 was added Dess-Martin periodinane (0.90 g, 2.12 mmol) at 0 ^oC. The resulting mixture was warmed to ambient temperature and stirred for 1 h. It was diluted with ether and quenched with saturated $NaHCO_3$ and $Na_2S_2O_3$ (5.26 g, 21.2 mmol). The mixture was stirred for 20 min at which time the layers were separated. The organic layer was washed 3 times with aqueous $NaHCO_3$ and $Na_2S_2O_3$. The organic layer was dried, filtered, concentrated, and chromatographed (10% EtOAc/hexanes) to provide desired methyl ketone product **125** (0.75 g, 95%). Data are: TLC R_f = 0.7 (30% EtOAc/hexanes); $[\alpha]_D^{23}$ = -36.2^o (c 3.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.60 (s, 1H), 5.21 (s, 2 H), 5.00 (q, *J* = 6.5 Hz, 2H), 4.14 (d, *J* = 3.0 Hz, 1H), 3.92 (s, 3H), 3.55 (s, 3H), 3.52 (s, 3H), 3.44-3.40 (m, 1H), 3.35 (s, 3H), 2.67-2.60 (m, 2H), 2.22 (s, 3H), 2.05-2.02 (m, 1H), 1.72-1.67 (m, 1H), 1.00-0.95 (m, 1H), 0.89 (s, 9H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.7, 153.4, 146.3, 146.0, 139.6, 131.7, 111.1, 101.8, 95.6, 81.9, 80.0, 61.2, 58.2, 57.9, 56.7, 37.3, 33.1, 29.8, 27.7, 25.9, 19.3, 18.3, -4.6, -5.1; HRMS (+TOF MS) found 582.2716 [M+Na]+ , calcd 582.2705 for $C_{26}H_{45}NO_{10}SiNa$.



126

(3*S*,4*S*,6*R*)-7-(3-Amino-6-methoxy-2,5-bis(methoxymethoxy)phenyl)-3-(tert-butyl dimethylsilyloxy)-4-methoxy-6-methylheptan-2-one (126)

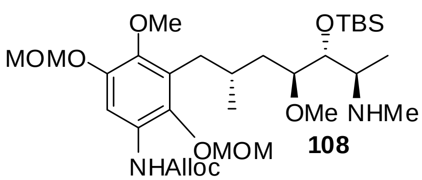
To a stirred solution of previous prepared methyl ketone **125** (0.25 g, 0.45 mmol) in 20 mL *i*-PrOH was added Pd/C (0.1 g, 10 wt%). The reaction was put under high vacuum and then purged with H_2. After the reaction was stirred for 5 h under H_2 balloon, the mixture was filtered through a celite plug eluting with MeOH. The solvent was evaporated to provide the aniline product **126** (0.24 g, 100%). Data are: TLC R_f = 0.2 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.47 (s, 1H), 5.13 (s, 2H), 4.91 (m, 2H), 4.12 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 2H), 3.74 (s, 3H), 3.59 (s, 3H), 3.50 (s, 3H), 3.45-3.40 (m, 1H), 3.35 (s, 3H), 2.56-2.48 (m, 2H), 2.22 (s, 3H), 2.02 (m, 1H), 1.77-1.68 (m, 1H), 1.04-0.97 (m, 1H), 0.91 (s, 9H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); HRMS (+TOF MS) found 552.2947 [M+Na]+ , calcd 552.2963 for $C_{26}H_{47}NO_8SiNa$.



127

Allyl 3-((2*R*,4*S*,5*S*)-5-(tert-butyldimethylsilyloxy)-4-methoxy-2-methyl-6-oxoheptyl)-4- methoxy-2,5-bis(methoxymethoxy)phenylcarbamate (127)

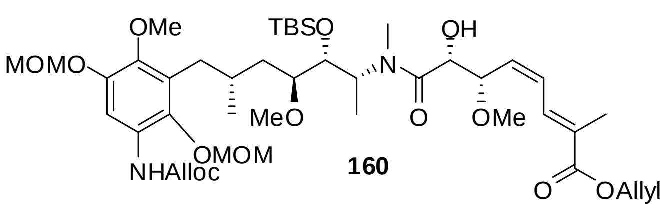
A flame dried 50 mL flask was charged with aniline **126** (0.24 g, 0.45 mmol) and 10 mL CH_2Cl_2. The solution was cooled to 0 ^oC before pyridine (0.11 mL, 1.35 mmol) was added dropwisely, followed by AllocCl (0.14 mL, 1.35 mmol) and DMAP (0.02g). The mixture was stirred at 0 ^oC for 2 h, at which time it was warmed to ambient temperature. After another 3 h, the reaction was quenched with diluted HCl, and extracted 3 times with EtOAc. The combined organic layers were dried, filtered, concentrated and chromatographed (20% EtOAc/hexanes) to provide product **127** (0.23g, 83%). Data are: TLC R_f = 0.4 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ = -26.2^o (c 3.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (bs, 2H), 5.97-5.92 (m, 1H), 5.33 (d, *J* = 19 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 5.17 (s, 2H), 4.88 (s, 2H), 4.64 (d, *J* = 6.0 Hz, 2H), 4.10 (d, *J* = 2.5 Hz, 1H), 3.78 (s, 3H), 3.58 (s, 3H), 3.50 (s, 3H), 3.41-3.38 (m, 1H), 3.33 (s, 3H), 2.51-2.46 (m, 2H), 2.19 (s, 3H), 1.97-1.94 (m, 1H), 1.70-1.64 (m, 1H), 0.98-0.93 (m, 1H), 0.87 (s, 9H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.01 (s, 3H), 0.00(s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.4, 153.4, 147.0, 144.2, 141.0, 132.8, 128.5, 127.7, 117.7, 106.3, 100.6, 95.6, 82.0, 80.1, 65.6, 60.9, 58.1, 57.4, 56.5, 37.5, 33.1, 29.9, 27.6, 25.8, 19.3, 18.2, -4.7, -5.2; HRMS (+TOF MS) found 636.3157 [M+Na]+ , calcd 636.3174 for $C_{30}H_{51}NO_{10}SiNa$.



108

Allyl 3-((2*R*,4*S*,5*R*,6*R*)-5-(*tert*-butyldimethylsilyloxy)-4-methoxy-2-methyl-6-(methyllamino)heptyl)-4-methoxy-2,5-bis(methoxymethoxy)phenylcarbamate (108)

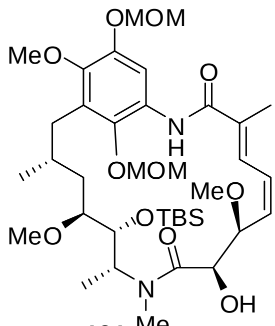
A flam dried 25 mL flask was charged with the Alloc protected aniline **127** (0.178 g, 0.29 mmol) and 5 mL dry ethanol. To this stirred solution was added $CH_3NH{\cdot}HCl$ (0.077g, 1.16 mmol), Et_3N (0.16 mL, 1.16 mmol), and Ti(O-*i*Pr)$_4$ (0.35 mL, 1.16 mmol). The mixture was stirred overnight at ambient temperature before being cooled to -78 ^{o}C. $NaBH_4$ (0.033g, 0.87 mmol) was added and the resulting mixture was stirred for 8 h. The reaction was diluted with Et_2O and quenched with saturated Na/K tartrate and 10% ammonium aqueous solution. The mixture was separated and the aqueous layer was extracted 3 times with Et_2O and 5 times with EtOAc. The combined organic layers were dried over Na_2SO4, filtered, concentrated and chromatographed (2% $MeOH/CH_2Cl_2$ and 6 drops of $NH_3 \cdot H_2O$) to provide **108** (0.1249 g, 68%). Data are: TLC R_f = 0.7 (10% $MeOH/CH_2Cl_2$); $[\alpha]_D^{23}$ = -9.8° (c 3.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (bs, 1H), 7.78 (bs, 1H), 5.98-5.91 (m, 1H), 5.32 (d, *J* = 17 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 5.18 (s, 2H), 4.90 (s, 2H), 4.64 (d, *J* = 5.5 Hz, 2H), 3.79 (s, 3H), 3.61-3.59 (m, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 3.35-3.31 (m, 1H), 3.28 (s, 3H), 2.56-2.46 (m, 3H), 2.36 (s, 3H), 2.01-1.97 (m, 1H), 1.58-1.53 (m, 1H), 1.29-1.24 (m, 1H), 1.22 (bs, 1H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.85 (s, 9H), 0.84 (d, *J* = 7.5 Hz, 3H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.5, 147.0, 144.2, 141.1, 132.9, 128.9, 127.7, 117.7, 106.3, 100.7, 95.6, 80.7, 76.3, 65.6, 60.9, 57.6, 57.4, 56.5, 38.1, 34.4, 33.3, 30.4, 26.2, 19.4, 18.4, 16.3, -4.1, -4.5; HRMS (+TOF MS) found 651.3639 [M+Na]+ , calcd 651.3647 for $C_{31}H_{56}N_2O_9SiNa$.



160

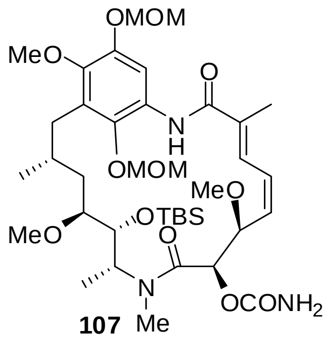
(2*E*,4*Z*,6*S*,7*R*)-Allyl 8-(((2*R*,3*R*,4*S*,6*R*)-7-(3-(allyloxycarbonylamino)-6-methoxy-2,5-bis(methoxymethoxy)phenyl)-3-(tert-butyldimethylsilyloxy)-4-methoxy-6-methylheptan-2-yl)(methyl)amino)-7-hydroxy-6-methoxy-2-methyl-8-oxoocta-2,4-dienoate (160)

A solution of acid **109** (0.054 g, 0.20 mmol) and amine **108** (0.125 g, 0.20 mmol) in 4 mL CH_2Cl_2 was cooled to 0 ^oC. HATU (0.091 g, 0.24 mmol) was added followed by *i*Pr_2NEt (0.077 g, 0.1 ml). After 3 h, acid **109** (0.011 g, 0.04 mmol) and HATU (0.015 g, 0.04 mmol) were added. After another 2 h, more acid **109** (0.011 g, 0.04 mmol) and HATU (0.015 g, 0.04 mmol) were added. After another 3 h, the reaction mixture was passed through a silica plug eluting with EtOAc. The filtrate was concentrated and purified with radial chromatograph (20% EtOAc/hexanes + 1% MeOH) to provide amide products **160** (0.13 g, 74%) as a pair of rotamers (2:1). Data are: TLC R_f = 0.7 (50% EtOAc/hexanes); $[\alpha]_D^{23}$ = +4.5^o (c 3.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.85 (bs, 1H), 7.77 (bs, 1H), 7.55 (d, *J* = 12.0 Hz, 1/3H), 7.53 (d, *J* = 12.0 Hz, 2/3H), 6.67-6.61 (m, 1H), 5.98-5.91 (m, 2H), 5.68 (t, *J* = 10.0 Hz, 2/3H), 5.62 (t, *J* = 10.0 Hz, 1/3H), 5.32 (apparent d, *J* = 17.0 Hz, 2H), 5.22 (apparent t, *J* = 10.5 Hz, 2H), 5.17 (s, 2H), 4.90 (s, 2H), 4.73-4.41 (m, 7H), 3.97-3.92 (m, 1H), 3.79 (s, 2/3 x 3H), 3.77 (s, 1/3 x 3H), 3.74-3.71 (m, 1H), 3.59 (s, 2/3 x 3H), 3.57 (s, 1/3 x 3H), 3.50 (s, 3H), 3.29-3.23 (m, 6H), 3.10 (d, *J* = 11.0 Hz, 1H), 2.98 (s, 2/3 x 3H), 2.84 (s, 1/3 x 3H), 2.51-2.47 (m, 2H), 2.02 (m, 1H), 1.97 (s, 3H), 1.69-1.65 (m, 2/3H), 1.54-1.50 (m, 1/3H), 1.29 (d, *J* = 6.0 Hz, 1/3 x 3H), 1.18 (d, *J* = 6.0 Hz, 2/3 x 3H), 1.14-1.12 (m, 2/3H), 0.95-0.89 (m, 1/3H), 0.84-0.78 (m, 12 H), 0.02- -0.06 (m, 6H); HRMS (+TOF MS) found 903.4647 [M+Na]+ , calcd 903.4645 for $C_{44}H_{72}N_2O_{14}SiNa$.



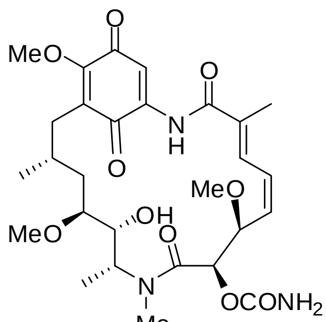
161

To a stirred solution of previous amide **160** (0.13 g, 0.15 mmol) in 4 mL dry THF was added morpholine (0.26 mL, 2.92 mmol) and $Pd(PPh_3)_4$ (0.068 g, 0.058 mmol). The resulting solution was stirred 4 h at ambient temperature before being diluted with Et_2O and queched with NaH_2PO_4 and water. The mixture was separated and aqueous layer was extracted twice with Et_2O and 8 times with EtOAc. The combined organic layers were dried, filtered, concentrated and radial chromatographed (50% EtOAc/hexanes + 10 drops AcOH) to get crude amino acid product. This crude amino acid was dissolved in 300 mL CH_2Cl_2 (0.0005M). HATU (0.13 g, 0.35 mmol), DIPEA (0.16 mL, 0.88 mmol) and DMAP (0.010 g) were added at ambient temperature. The resulting mixture was stirred for 2 days, at which time the mixture was concentrated and passed through a silica plug eluting with EtOAc. The concentrated crude product was purified with radial chromatograph (50% EtOAc/hexanes) to provide desired product **161** (0.056 g, 51%). Data are: TLC R_f = 0.2 (50% EtOAc/hexanes); $[\alpha]_D^{23}$ = -7.3^o (c 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.62 (bs, 1H), 7.98 (bs, 1H), 6.84 (bs, 1H), 6.46 (t, *J* = 11.0 Hz, 1H), 5.86 (m, 1H), 5.19 (m, 4H), 4.96 (bs, 1H), 4.66 (d, *J* = 5.5 Hz, 2H), 4.46 (bs, 1H), 3.84 (s, 4H), 3.52 (s, 3H), 3.42-3.31 (m, 12H), 2.89 (m, 2H), 2.69 (bs, 1H), 2.03 (s, 3H), 1.76 (bs, 1H), 1.45-1.37 (m, 1H), 1.32 (bs, 3H), 1.20-1.16 (m, 1H), 1.06 (m, 3H), 0.89 (s, 9H), 0.13-0.00 (m, 6H); HRMS (+TOF MS) found 761.4017 [M+Na]+ , calcd 761.4015 for $C_{37}H_{62}N_2O_{11}SiNa$.



107

A 25 mL round bottom flask was charged with the previous diamide **161** (0.044 g, 0.06 mmol) trichloroacetyl isocyanate (0.014 mL, 0.12 mmol) and 4 mL CH_2Cl_2. The mixture was allowed to stir for 30 min before MeOH (6 mL) and K_2CO_3 (0.041g, 0.30 mmol) was added. The mixture was stirred for 2 h before it was quenched with water and 3 drops of 1 N HCl aqueous solution. The mixture was extracted 5 times with CH_2Cl_2 and 5 times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by radial chromatograph (50% EtOAc/hexanes + 1% MeOH) to provide desired product **107** (0.04 g, 86%). Data are: TLC R_f = 0.7 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = -4.4^o (c 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.78 (bs, 1H), 7.67 (bs, 1H), 7.12 (bs, 1H), 6.46 (t, *J* = 11.0 Hz, 1H), 5.81 (bs, 1H), 5.19 (s, 4H), 5.07-4.76 (m, 3H), 4.75 (d, *J* = 4.5 Hz, 2H), 4.67 (s, 1H), 3.83 (s, 3H), 3.53 (s, 3H), 3.43-3.32 (m, 11H), 3.00 (s, 3H), 2.73 (bs, 1H), 2.35 (bs, 1H), 2.03 (s, 3H), 1.81 (bs, 1H), 1.60 (bs, 1H), 1.19 (s, 4H), 1.01 (bs, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); HRMS (+TOF MS) found 804.4071 [M+Na]+ , calcd 804.4073 for $C_{38}H_{63}N_3O_{12}SiNa$.



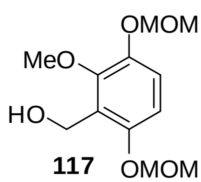
100

(4*E*,6*Z*,8*S*,9*R*,12*R*,13*R*,14*S*,16*R*)-13-Hydroxy-8,14,19-trimethoxy-4,11,12,16-tetramethyl-3,10,20,22-tetraoxo-2,11-diazabicyclo[16.3.1]docosa-1(21),4,6,18-tetraen-9-yl carbamate (100)

To a stirred solution of compound **107** (0.011 g, 0.014 mmol) in 2 mL CH_2Cl_2 and 2 mL CH_3CN was added NaI (0.021 g, 0.14 mmol) and TMSCl (0.18 mL, 0.14 mmol). The resulting mixture was stirred 1 h before being quenched with saturated $Na_2S_2O_3$ solution. The organic layer was washed 3 times with $Na_2S_2O_3$ solution. And the combine aqueous layers were extracted 3 times with CH_2Cl_2 and 5 times with EtOAc. The combined organic layers were dried, filtered, concentrated and radial chromatographed (7% MeOH/CH_2Cl_2) to provide deprotected product. This intermediate was dissolved in 3 mL EtOAc. And Pd/C (0.012 g, 10 wt%) was added. The mixture was stirred at ambient temperature, open to the air for 45 min. The mixture was then filtered through a celite plug eluting with EtOAc. The crude product was further purified by radial chromatograph (5% MeOH/CH_2Cl_2) to provide desired product **100** (0.0065 g, 80%). Data are: TLC R_f = 0.4 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{23}$ = +8.3^o (c 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.82 (s, 1H), 7.38 (d, *J* = 10.8 Hz, 1H), 7.27 (s, 1H), 6.56 (t, *J* = 11.1 Hz, 1H), 5.79 (t, *J* = 11.1 Hz, 1H), 5.53 (d, *J* = 4.5

Hz, 1H), 4.87 (m, 3H), 4.31 (m, 1H), 4.08 (s, 3H), 3.96 (m, 1H), 3.66 (bs, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 3.32 (m, 1H), 3.07 (s, 3H), 2.52-2.46 (m, 1H), 2.36-2.29 (m, 1H), 2.01 (s, 3H), 1.98 (m, 1H), 1.62 (m, 1H), 1.26 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 184.5, 184.4, 168.4, 168.1, 157.3, 155.8, 138.9, 136.1, 133.8, 129.9, 127.9, 127.4, 111.3, 81.3, 76.6, 73.8, 73.1, 68.6, 61.7, 57.9, 57.2, 55.0, 31.3, 29.9, 27.4, 22.7, 12.4, 11.4; HRMS (+TOF MS) found 578.2708 [M+H]+ , calcd 578.2708 for $C_{28}H_{40}N_3O_{10}$.

4.4.2. Preparation of Intermediates for Unsuccessful Routes

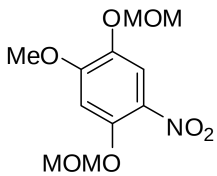


117

(2-Methoxy-3,6-bis(methoxymethoxy)phenyl)methanol

To a stirred solution of 2-methoxy-3,6-bis(methoxymethoxy)benzaldehyde **111** (0.51 g, 2 mmol) in THF (10 mL) was added $NaBH_4$ (0.23 g, 6 mmol) in portions. The resulting mixture was stirred at ambient temperature for 3.5 h, at which time the reaction was quenched with H_2O. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were dried over Na2SO4 and concentrated. Chromatography (30% EtOAc/hexanes) provided **117** (0.47 g, 91%). Data are: TLC R_f = 0.2 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (d, *J* = 9.0 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 5.17 (s, 2H), 5.15 (s, 2H), 4.77 (d, *J* = 4.0 Hz, 2 H), 3.91 (s, 3H), 3.51 (s, 3H), 3.49 (s, 3H), 2.56 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

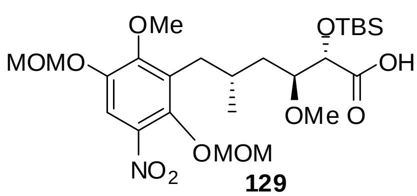
171.3, 151.2, 149.3, 145.6, 125.0, 117.4, 110.8, 96.1, 95.8, 61.9, 56.5, 56.4, 55.6; HRMS (+TOF MS) found 259.1185 [M+H]+ , calcd 259.1182 for $C_{12}H_{19}O_6$.



119

1-Methoxy-2,5-bis(methoxymethoxy)-4-nitrobenzene (119)

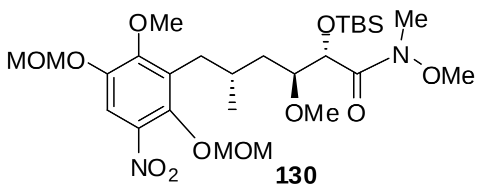
It is the byproduct from MOM reprotection step. Data are: TLC R_f = 0.3 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (s, 1H), 6.84 (s, 1H), 5.27 (s, 2H), 5.20 (s, 2H), 3.95 (s, 3H), 3.56 (s, 3H), 3.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.3, 148.5, 140.7, 132.8, 114.3, 101.8, 107.8, 96.6, 96.3, 56.9, 56.6; HRMS (+TOF MS) found 274.0910 [M+H]+ , calcd 274.0921 for $C_{11}H_{16}NO_7$.



129

(2*S*,3*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-5-methylhexanoic acid (129)

A flame dried flask was charged with methyl ester 123 (0.05 g, 0.087 mmol) and Et_2O (2 mL). After TMSOK (0.025 g, 0.19 mmol) was added, the color changed to orange. The resulting mixture was stirred at ambient temperature for overnight. Then it was diluted with EtOAc and quenched with 1 N HCl. The mixture was washed 3 times with water and the organic layer was dried over Na_2SO_4 and concentrated. The concentrated solution was passed through a silica cup elutingwith EtOAc. After solvent evaporation, the desired acid **129** was obtained (0.042, 85%). Data are: TLC R_f = 0.1 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 1H), 5.21 (s, 1H), 5.00 (m, 1H), 4.44 (d, *J* = 1.8 Hz, 3.92 (s, 3H), 3.55 (s, 3H), 3.52 (s, 3H), 3.45-3.40 (m, 1H), 3.39 (s, 3H), 2.65 (dd, *J* = 3.0, 7.5 Hz, 2H), 2.05 (m, 1H), 1.70 (m, 1H), 1.08-1.01 (m, 1H), 0.95-0.82 (m, 12 H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.67, 153.4, 146.3, 146.0, 139.6, 131.6, 111.2, 101.8, 95.7, 81.2, 73.8, 61.2, 58.4, 57.9, 56.7, 36.7, 33.0, 29.7, 25.8, 19.3, 18.3, -4.6, -5.4; HRMS (+TOF MS) found 584.2488 [M+H]+ , calcd 584.2498 for $C_{25}H_{43}NO_{11}SiNa$.

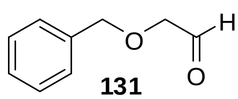


130

(2*S*,3*S*,5*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxy-6-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-5-methylhexanoic acid (130)

A flame dried round bottom flask was charged with acid **129** (0.03 g, 0.053 mmol) and CH_2Cl_2 (1 mL). 1,1'-Carbonyldiimidazole (0.014 g, 0.086 mmol) was then added slowly. The resulting solution was stirred for 25 min at ambient temperature before *N,O*-dimethylhydroxylamine hydrochloride (0.013 g, 0.13 mmol) was added. After the mixture was stirred for overmight, it was diluted with ether and washed with 5% citric acid aqueous solution. The organic layer was dried over $MgSO_4$ and concentrated. Radial chromatography (20% EtOAc/hexanes) provided **130** (0.016 g, 50%). Data are: TLC R_f = 0.5 (40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ

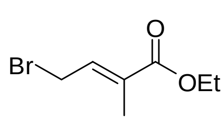
7.60 (s, 1H), 5.22 (s, 2H), 5.00 (A and B of ABq, *J* = 6.5 Hz, 2H), 4.55 (bs, 1H), 3.93 (s, 3H), 3.72 (s, 3H), 3.54 (s, 3H), 3.51 (s, 3H), 3.50-3.47 (m, 1H), 3.32 (s, 3H), 3.22 (bs, 3H), 2.71-2.63 (m, 2H), 2.09-2.03 (m, 1H), 1.57-1.45 (m, 2H), 0.89 (s, 9H), 0.89-0.88 (m, 3H), 0.060 (s, 3H), 0.057 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.4, 146.3, 146.1, 139.7, 131.9, 111.1, 101.9, 95.6, 80.8, 70.5, 61.2, 58.7, 57.9, 56.7, 39.0, 33.4, 30.2, 26.0, 19.4, -4.7, -4.9; HRMS (+TOF MS) found 627.2897 [M+H]+ , calcd 627.2920 for $C_{27}H_{48}N_2O_{11}SiNa$.



131

2-(Benzyloxy)acetaldehyde (131)

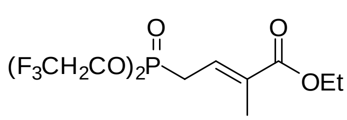
A round bottom flask was charged with 1,4-bis(benzyloxy)but-2-ene (3.54 g, 10.8 mmol) and 110 mL CH_2Cl_2. The resulting solution was cooled to -78 °C before ozone was bubbled in until the color changed to blue. After purging with argon, PPh_3 (4.24 g, 16 mmol) was added slowly. The solution was warmed to ambient temperature. After it was stirred for 7 h, the solution was concentrated in vacuo and purified by silica chromatography (20% EtOAc/hexanes) to give **131** (3.62 g, 93%). Data are: TLC R_f = 0.2 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.71 (s, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 4.57 (s, 2H), 4.07 (s, 2H), 3.82 (s, 3H).



150

(*E*)-Ethyl 4-bromo-2-methylbut-2-enoate (150)

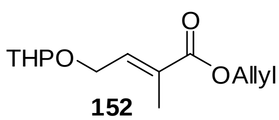
A flame dried round bottom flask was charged with LiBr (4.34 g, 50 mmol) and THF (14 mL). The solution was stirred until LiBr dissolved, at which time Et_3N (1.74 mL, 12.5 mmol) was added. To this stirred solution was added a solution of (*E*)-ethyl 4-hydroxy-2-methylbut-2-enoate **149** (0.72 g, 5 mmol) in 14 mL THF. The resulting solution was cooled to 0 °C, and MsCl (0.81 mL, 10.5 mmol) was dropwisely added. The reaction was stirred at 0 °C for 2 h, at which time it was quenched by water. The mixture was extracted 3 times with ether. And the combined ether solution was washed with a saturated $NaHCO_3$ solution, followed with a saturated NaCl solution. The ether solution was then dried over $MgSO_4$ and concentrated in vacuo. Purification with column chromatography (10% EtOAc/hexanes) provided **150** (0.94 g, 90%). Data are: TLC R_f = 0.7 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.93 (t, *J* = 8.0 Hz, 1H), 4.20 (q, *J* = 7.5 Hz, 2 H), 4.04 (d, *J* = 8.0 Hz, 2H), 1.93 (s, 3H), 1.31 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3, 134.9, 132.3, 61.1, 26.2, 14.3, 12.3; HRMS (FAB+) found 228.9834 [M+Na]+ , calcd 228.9840 for $C_7H_{11}BrO_2Na$.



151

(*E*)-Ethyl 4-(bis(2,2,2-trifluoroethoxy)phosphoryl)-2-methylbut-2-enoate (151)

To a mixture of (*E*)-ethyl 4-bromo-2-methylbut-2-enoate **150** (0.41 g, 2 mmol) and tris(2,2,2-trifluoroethyl) phosphate (6.56 g, 20 mmol) was added catalytic amount of tetra-*n*-butylammonium iodide (0.074 g, 0.2 mmol). The resulting mixture was stirred for 1 day at 125 °C. The whole mixture was purified by a column chromatography (10% EtOAc/hexanes) to give the title compound **151** (0.34 g, 45%). Data are: TLC R_f = 0.7 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.69 (dd, *J* = 1.5, 7.5 Hz, 1H), 4.44-4.37 (m 4H), 4.24-4.20 (q, *J* = 7.0 Hz, 2H), 2.93 (dd, *J* = 7.5, 24.5 Hz, 2H), 1.91 (d, *J* = 5.0 Hz, 3H), 1.31 (t, *J* = 7.0, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.1, 134.2 (d), 126.9 (d), 123.7 (d), 121.5 (d), 62.6 (dq), 61.2, 27.9, 26.8, 14.3, 12.7; HRMS (FAB+) found 395.0448 [M+Na]+ , calcd 395.0459 for $C_{11}H_{15}F_6PO_5Na$.

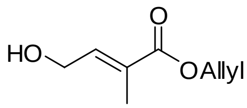


152

(*E*)-Allyl 2-methyl-4-(tetrahydro-2H-pyran-2-yloxy)but-2-enoate (152)

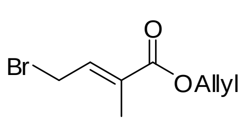
To a stirred solution of (*E*)-ethyl 2-methyl-4-(tetrahydro-2H-pyran-2-yloxy)but-2-enoate **148** (1.14 g, 5 mmol) in allyl alcohol (5 mL) was added LiBr (2.17 g, 25 mmol). DBU (1.12 mL, 7.5 mmol) was dropwisely added and the resulting mixture was stirred for 9 h at ambient temperature. After evaporation of the allyl alcohol solvent under reduced pressure, a saturated NH_4Cl solution was added. The resulting mixture was extracted 3 times with Et_2O. The combined ether solution was condensed *in vacuo* and purified by column chromatography (3% EtOAc/hexanes) to give product **152** (1.06 g, 88%). Data are: TLC R_f = 0.3 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.89 (m, 1H), 5.95 (m, 1H), 5.34 (m, 1H), 5.24 (m, 1H), 4.65 (m, 3H), 4.40 (m, 1H), 4.19 (m, 1H), 3.87 (m, 1H), 3.52 (m, 1H), 1.87 (s, 3H), 1.86-1.53 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.4, 138.6, 132.6, 129.2, 118.2, 98.5, 65.5, 64.1, 62.3, 30.7, 25.6, 19.4, 13.0; HRMS (FAB+) found 241.1425 [M+H]+ , calcd

241.1400 for $C_{13}H_{21}O_4$.



(*E*)-Allyl 4-hydroxy-2-methylbut-2-enoate

To a stirred solution of THP ether **152** (0.90 g, 3.74 mmol) in MeOH (15 mL) was added catalytic amount of *p*-TsOH (0.036 g, 0.187 mmol). The resulting solution was stirred at ambient temperature for 3 h, at which time 0.3 mL Et_3N was added to quench the reaction. After concentration in vacuo, the residue was dissolved in EtOAc and washed with a saturated $NaHCO_3$ solution. The aqueous layer was extracted 3 times with EtOAc. The combined organic layers were dried and concentrated. Column chromatography (10-20% EtOAc/hexanes) provided the title compound (0.51 g, 88%). Data are: TLC R_f = 0.2 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.87 (m, 1H), 5.96-5.92 (m, 1H), 5.36-5.32 (m, 1H), 5.26-5.23 (m, 1H), 4.65 (m, 2H), 4.35 (s, 2H), 2.52 (bs, 1H), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.6, 140.9, 132.3, 128.4, 118.2, 65.6, 59.8, 12.8; HRMS (FAB+) found 157.0863 [M+H]+ , calcd 157.0865 for $C_8H_{13}O_3$.

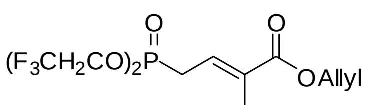


153

(*E*)-Allyl 4-bromo-2-methylbut-2-enoate (153)

A flame dried rounf bottom flask was charged with LiBr (9.26 g, 106.67 mmol) and THF (35 mL). The solution was stirred until LiBr dissolved, at which time Et_3N (3.72

mL, 26.67 mmol) was added. To this stirred solution was added a solution of (*E*)-Allyl 4-hydroxy-2-methylbut-2-enoate (1.67 g, 10.67 mmol) in 35 mL THF. The resulting solution was cooled to 0 ^{o}C before MsCl (1.73 mL, 22.4 mmol) was dropwisely added over 5 min. After the mixture was stirred at 0 ^{o}C for 2 h, it was quenched by water and extracted 3 times with ether. The combined ether solution was washed with a saturated $NaHCO_3$ solution and then a saturated NaCl solution. The ether solution was then dried over $MgSO_4$ and concentrated in vacuo. Purification with column chromatography (10% EtOAc/hexanes) provided **153** (2.18 g, 99%). Data are: TLC R_f = 0.7 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (t, *J* = 9.0 Hz, 1H), 5.99-5.92 (m, 1H), 5.34 (m, 1H), 5.25 (m, 1H), 4.67 (m, 2H), 4.04 (d, *J* = 9.0 Hz, 2H), 1.94 (s, *J* = 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 135.4, 132.3, 132.2, 118.4, 65.8, 26.1, 12.4; HRMS (EI+) found 217.9941 [M]+ , calcd 217.9942 for $C_8H_{11}O_2Br$.

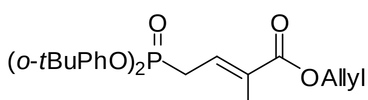


144

(*E*)-Allyl 4-(bis(2,2,2-trifluoroethoxy)phosphoryl)-2-methylbut-2-enoate (144)

To a mixture of (*E*)-Allyl 4-bromo-2-methylbut-2-enoate **153** (1.10 g, 5 mmol) and tris(2,2,2-trifluoroethyl) phosphate (8.20 g, 25 mmol) was added catalytic amount of tetra-*n*-butylammonium iodide (0.18 g, 0.5 mmol). The resulting mixture was stirred at 125 ^{o}C for 1 day, at which time the whole mixture was purified by a column chromatography (10% EtOAc/hexanes) to give the title compound **144** (0.97 g, 51%). Data are: TLC R_f = 0.7 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ

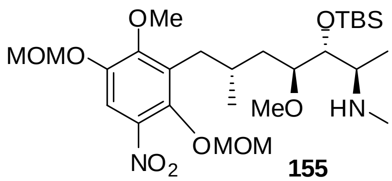
6.75-6.71 (m, 1H), 5.98-5.93 (m, 1H), 5.33 (dd, *J* = 1.5, 17 Hz, 1H), 5.25 (dd, *J* = 1.5 Hz, 5.0 Hz, 1H), 4.67 (d, *J* = 6.0 Hz, 2H), 4.45-4.37 (m, 4H), 2.98-2.90 (m, 2H), 1.93 (d, *J* = 5.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.6 (d), 133.9 (d), 132.2, 127.5 (d), 126.9 (d), 125.9 (d), 123.7 (d), 121.5 (d), 118.2, 65.7, 62.4 (dq), 61.1, 27.9, 26.7, 14.2, 12.7; HRMS (FAB+) found 385.0642 [M+H]+ , calcd 385.0640 for $C_{12}H_{16}F_6O_5P$.



145

(*E*)-Allyl 4-(bis(2-tert-butylphenoxy)phosphoryl)-2-methylbut-2-enoate (145)

A mixture of (*E*)-Allyl 4-bromo-2-methylbut-2-enoate **153** (0.22 g, 1 mmol) and bis(2-*tert*-butylphenyl) ethyl phosphite (0.75 g, 2 mmol) was stirred at 130 °C for 9 h. The whole mixture was purified by column chromatography to give the title compound **145** (0.37 g, 76%). Data are: TLC R_f = 0.3 (20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.16-7.13 (m, 2H), 7.10-7.07 (m, 2H), 6.98-6.95 (m, 1H), 5.93-5.87 (m, 1H), 5.31-5.21 (m, 2H), 4.61 (d, *J* = 6.0 Hz, 2H), 3.22-3.16 (m, 2H), 1.79 (d, *J* = 4.0 Hz, 3H), 1.36 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7, 150.2, 150.1, 139.3, 139.3, 132.9, 132.8, 132.3, 129.2, 129.1,127.9, 127.6, 124.7, 119.7, 118.4, 65.7, 34.9, 30.2, 29.1, 28.0, 12.9; HRMS (FAB+) found 485.2459 [M+H]+ , calcd 485.2379 for $C_{28}H_{38}O_5P$.



155

(2*R*,3*R*,4*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-methoxy-7-(2-methoxy-3,6-bis(methoxymethoxy)-5-nitrophenyl)-*N*,6-dimethylheptan-2-amine (155)

A flame dried 25 mL flask was charged with the methyl ketone **125** (0.10 g, 0.18 mmol) and 5 mL dry ethanol. To this stirred solution was added $CH_3NH\cdot HCl$ (0.048g, 0.72 mmol), Et_3N (0.10 mL, 0.72 mmol), and Ti(O-*i*Pr)$_4$ (0.22 mL, 0.72 mmol). The mixture was stirred overnight at ambient temperature before being cooled to -78 ^oC. $NaBH_4$ (0.02g, 0.54 mmol) was added and the resulting mixture was stirred for 8 h at -78 ^oC. The reaction was diluted with Et_2O and quenched with saturated Na/K tartrate and 10% ammonium aqueous solution. The mixture was separated and the aqueous layer was extracted 3 times with Et_2O and 5 times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and chromatographed (2% MeOH/CH_2Cl_2 and 6 drops of $NH_3\cdot H_2O$) to provide **155** (0.088 g, 85%). Data are: TLC R_f = 0.6 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (s, 1H), 5.2 (s, 2H), 4.98 (m, 2H), 3.91 (s, 3H), 3.60 (m, 1H), 3.54 (s, 3H), 3.50 (s, 3H), 3.33 (m, 1H), 3.28 (s, 3H), 2.7-2.60 (m, 2H), 2.54-2.51 (m, 1H), 2.37 (s, 3H), 2.07-2.04 (m, 1H), 1.57-1.53 (m, 1H), 1.31-1.26 (m, 2H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 3H), -0.018 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ153.4, 146.3, 146.0, 139.7, 131.9, 111.0, 101.8, 95.6, 95.0, 80.2, 76.5, 61.1, 57.9, 57.6, 57.3, 56.7, 36.5, 33.8, 33.3, 29.9, 26.3, 26.1, 19.6, 18.6, 15.6, -3.9, -5.0; HRMS (+TOF MS) found 575.3358 [M+H]+ , calcd 575.3364 for $C_{27}H_{51}N_2O_9Si$.