Studies Toward the Total Synthesis of (-)-Zampanolide

Dawn Troast
Advisor: John A. Porco, Jr.

1.0 Background and Significance: The unique 20-membered macrolide (-)-zampanolide (1, Figure 1) was isolated in 1996 by Tanaka and Higa from the sponge Fasciospongia rimosa, collected near Okinawa, Japan. This structurally interesting molecule has a high degree of unsaturation and an unusual N-acyl hemiaminal side chain. In addition to its unique structure, zampanolide displays potent cytotoxic activity (1-5 ng/mL) against P388, A549, HT29, and MEL28 tumor cell lines. Recently, Smith et. al. reported the total synthesis and tentative stereochemical assignment of the antipode (+)-zampanolide as 11R, 15R, 19R, and 20R. Our initial studies on zampanolide have focused on the synthesis of the unusual and unstable N-acyl hemiaminal side chain. Preliminary results in the total synthesis have focused on the synthesis of the 2,6-syn-disubstituted exo-methylene pyran subunit via an intramolecular silyl-modified Sakurai cyclization (ISMS). Currently, work on C18-C19 bond construction using sp2-sp3 cross-coupling is being investigated.

Figure 1: zampanolide

In addition to being a biologically interesting and challenging synthetic target, the macrolactone and the unsaturated side chain of zampanolide are reminiscent of the enamide natural products also being studied in our lab (oximidine II and lobatamide C, Figure 2). Other natural products similar to zampanolide include the mycalamides (4), pederin (5), the theopederins (6), spergualin (7a), and 15-deoxyspergualin (7b). These compounds contain an N-acyl amino moiety (4, 5, and 6) or an N-acyl hemiaminal (7a and 7b), which has been proven essential for their biological activity.

1.1 Background of N-Acyl Hemiaminal Synthesis: The most common method used to install the N-acyl aminal in these molecules is reduction of an N-acyl imidate (inset, Figure 2), but this produces a mixture of epimers with moderate to poor selectivity.

There are relatively few synthetic methods available for the preparation of N-acyl hemiaminals. Smith et. al. installed the N-acyl hemiaminal of (+)-zampanolide using a
stereospecific Curtius rearrangement as a key step. Direct condensation of amides and aldehydes has been reported, but is generally limited to very electron-poor aldehydes or unsubstituted amides and typically affords $N,N'$-alkylidene bisamides via acyl iminium intermediates. $N$-Acyl hemiaminals were also reported as undesired products in an attempted DABCO-mediated Baylis-Hillman reaction of acrylamide and protected amino aldehydes. Recently, reduction of an $N$-acyl imidate was used to prepare an $N$-acyl hemiaminal en route to a glycosylcarbinolamide.

1.2 Smith’s Synthesis of (+)-Zampanolide: The recent synthesis of the antipode (+)-zampanolide by Smith et al. was highlighted by methylenation of dioxanone with Petasis-Tebbe reagent followed by a Petasis-Ferrier rearrangement to construct the cis-pyranone followed by ketone methylenation to afford the 2,6-syn-disubstituted exo methylene pyran. A higher order cuprate derived from vinyl bromide was used to open epoxide to furnish a Curtius rearrangement of followed by thermal rearrangement and trapping of the isocyanate, gave which upon acylation with afforded the PMB protected $N$-acyl hemiaminal. This occurs with complete transfer of the C20 stereochemistry, however the stereocenter was later epimerized in the final deprotection, illustrating the instability of this functionality as well as the advantage to installing it in the late stages of the synthesis.

2.0 Research Design and Methods
2.1 Retrosynthetic Analysis: In planning a retrosynthesis of zampanolide, a few key issues had to be kept in mind: the instability of the $N$-acyl hemiaminal, the acid labile exo cyclic methylene
Figure 4: Retrosynthetic Analysis

masked as a 2,2-dimethyloxazolidine, and (Z,E)-sorbic acid 19. Compound 18 may be derived from an intramolecular Stork-Takahashi alkylation\(^\text{15}\) of the trimethylsilyl cyanohydrin ketone which results from xxx of 20. Due to the instability of the $\beta,\gamma$-unsaturated ketone, reduction and protection as a silyl ether until the final steps of the synthesis may be required. Esterification of 21 with 22 followed by PMB removal, oxidation, and Wittig reaction gives enal 20. The key C9-C20 fragment (21) may be prepared by lithiation then lithium-zinc exchange of vinyl iodide 23 followed by a nickel catalyzed $sp^2$-$sp^3$ cross-coupling with serine-derived alkyl iodide (24).\(^\text{16}\) Compound (23) will be obtained from allyl silane 25 and iodoenal 26 employing an intramolecular silyl-modified Sakurai cyclization (ISMS) reaction\(^\text{17}\) to construct the 2,6-syn-disubstituted exo methylene pyran subunit. This route allows flexibility for fragment coupling, as well as for the oxidation state of the N-acyl hemiaminal precursor, without losing the highly convergent nature of the synthesis.

Another approach being considered for the construction of the C19-C20 bond, which is more closely related to a model study done on the side chain (cf. section 2.2), would involve an asymmetric aldol reaction between glycine equivalent 30 and aldehyde 31 (inset, Figure 4). Possible conditions for this reaction will be discussed in section 2.6. Synthetically, only protecting group strategy would change between the two approaches to obtain the C9-C20 fragment. The aldol approach would result in the presence of a free NH and a t-butyler ester, which would have to both be considered further in the synthesis.

2.2 Model Studies on the N-Acyl Hemiaminal Side Chain.\(^\text{18}\) Initial studies focused on the preparation of an N-acyl hemiaminal model system in order to evaluate methods that may be applicable to the synthesis of the natural product. Studies were initiated to determine if N,O-acetals derived from oxidative decarboxylation of N,O-acylamino acids,\(^\text{19}\) may be hydrolyzed under acidic conditions to afford N-acyl hemiaminals (Scheme 1). L-Threonine was chosen as a model $\beta$-hydroxy-$\alpha$-amino acid, and 2,3-hexadienoic (sorbic) acid as a surrogate for the unsaturated lactone segment of the natural product. Commercially available L-threonine derivative 32 was acylated with sorbic acid to afford hydroxyamide 33 which was further
esterified with sorbic acid using Keck conditions\textsuperscript{20} to furnish 34. tert-Butyl ester removal was accomplished using TFA/Et\textsubscript{3}SiH to afford acid 35.

**Scheme 1: Synthesis of model N-acyl hemiaminals**

Since we were unable to achieve direct conversion of the carboxylic acid to the N-acyl hemiaminal,\textsuperscript{21} we focused on development of conditions to produce the acetate cleanly. N-Acyl-\(\alpha\)-amino acid 35 was subjected to oxidative decarboxylation to afford pure N,O-acetal 36 after extractive workup, with no evidence of N-acyl hemiaminal formation. A number of Lewis acid catalysts were then screened for the solvolysis of 36→37. After considerable experimentation, we found that Yb(OTf)\textsubscript{3} (20 mol %, \textit{aq}. THF), followed by purification through a neutral alumina cartridge,\textsuperscript{22} gave optimal results to afford N-acyl hemiaminal 37 (88 %). Other acid catalysts either led to no reaction (LiClO\textsubscript{4}), intolerably slow reactions (Mg(ClO\textsubscript{4})\textsubscript{2}) or destruction of the compound (TMSOTf/CH\textsubscript{2}Cl\textsubscript{2} or BF\textsubscript{3}-Et\textsubscript{2}O/\textit{aq}. CH\textsubscript{3}CN), the latter conditions affording considerable amounts of an aldehyde product by \textit{\textsuperscript{1}H} NMR. The Z,E sorbamide-based N-acyl hemiaminal (38, \textit{inset, Scheme 1}) was made through a series of analogous transformations, employing (2Z,4E)-sorbic acid\textsuperscript{24} in the initial acylation step. In the latter transformation, isomerization of the (Z,E)-diene was a significant concern, but fortunately the (Z)-olefin configuration was maintained throughout the synthesis without difficulty.

Substrates lacking either one or both of the sorbic side chains were also evaluated in the hydrolysis protocol, but these gave poor results. The surprising stability of model compounds such 37 and 38 in comparison to other N-acyl hemiaminals may be due to stabilization resulting from a hydrogen bonding network as well as the electron-withdrawing effects of the unsaturated ester in 37 and 38, which would stabilize the tetrahedral N-acyl hemiaminal and discourage formation of the transient iminium ion species. For model compound 37, the stabilization through a hydrogen bonding network has been shown by \textit{\textsuperscript{1}H} NMR experiments. Evaluation of coupling constants, H-D exchange, and chemical shift of the amide proton all support the formation of a hydrogen bond network. These studies indicate that a hydrogen bond network could also stabilize and provide structural rigidity of the N-acyl hemiaminal side chain of zampanolide. Similar \textit{\textsuperscript{1}H} NMR studies will be performed on the natural product to determine if a hydrogen bonding network exists and understand its importance in the potent cytotoxicity of zampanolide.

**2.3 Synthesis of the C9-C17 Fragment:** Preliminary studies have established methodology for preparation of the 2,6-syn-disubstituted \textit{exo}-methylene pyran portion (23) of zampanolide using the ISMS reaction. Such reactions have been found to afford 2,6 syn-disubstituted \textit{exo} methylene pyrans with high levels of stereocontrol.\textsuperscript{17} We have prepared the allyl silane \textit{via} two different routes,
ene reaction, which occurred with very low yields. This reaction initially offered an opportunity to develop an asymmetric ene reaction, but poor initial results and literature precedent led us to explore a third route to prepare 25. The current approach (route 3) begins with (+)-epoxide, which is prepared from an m-CPBA epoxidation followed by a hydrolytic kinetic resolution.

Scheme 4: ISMS cyclization reaction

Use of Grignard reagent in a copper(I)-mediated epoxide opening of should give secondary alcohol 25. Preliminary results did provide some product in the opening of the racemic epoxide (% yield), but generation of the Grignard reagent on small scale was problematic. Due to the cost of the vinyl bromide precursor of ($65.20/g) efforts to synthesize it from 2,3-dibromopropene on larger (10–20g) scale are underway.

2.4 Synthesis of C9-C20 Fragment 21: Fragment 40 was derived from the serine-derived Garner aldehyde by stereoselective epoxidation using dimethylsulfonium methylide. The coupling of 40 with model compound 41 was studied extensively, focusing mainly on the use of Lipshutz’s higher order cuprate, (2-th)Cu(CN)Li (Table 1). There was some difficulty in generation of the reactive cuprate in this reaction due to its extreme air sensitivity. In these reactions, mostly starting material was recovered, along with a complex mixture of products. There are examples where a Lewis acid is used to activate the epoxide, but even with a large excess of Lewis acid (3.0 equiv. BF3·Et2O) no product was formed. In some cases, it appeared that some epoxide had been opened, by a halogen to form a halohydrin side-product.

Table 1: Cuprate Opening of an Epoxide
Precedent for opening this serine-derived epoxide with an acetylide anion,\(^{34}\) led us to try this transformation, which was successful, but the subsequent hydridoracination, transmetallation to aluminum, and quenching with paraformaldehyde\(^{35}\) produced mostly starting material and the protonate alkene. The epoxide has a lot of steric bulk, which could be preventing attack on the epoxide, so ring opening of an epoxide without the acetonide (43, Figure 5) was also attempted, hoping that this would make the epoxide more accessible to the nucleophile. Attempted copper(I)-mediated ring opening with isopropenyl magnesium bromide gave a small amount of product, but mostly starting material was recovered. Without any promising results for this type of epoxide opening, we have looked for alternate routes to make this fragment.

2.5 \(sp^2\)-\(sp^3\) Coupling for C9-C20 Fragment 21: The next plan for the synthesis of fragment 21 involves metal catalyzed \(sp^2\)-\(sp^3\) cross-coupling. The most common method for this type of coupling is palladium-mediated coupling using an alkyl boron and a vinyl halide.\(^{36}\) There are some examples where yields of \(sp^2\)-\(sp^3\) coupling were improved using an alkyl zinc reagent due to its higher reactivity in the transmetallation step.\(^{37}\) Initially, zinc insertion into a model alkyl iodide containing a \(\beta\)-hydroxy group was attempted. The zinc inserted compound was prepared using zinc dust,\(^{38}\) zinc/copper couple,\(^{39}\) and lithium-zinc exchange.\(^{40}\) The zinc insertion on its own was a difficult task. The lithium-zinc exchange seemed to work best, but complete consumption of the starting material was not seen in any attempt. A concern with a substrate such as 24 was the \(\beta\)-elimination once the zinc inserted. Experiments on model compound 44\(^{41}\) showed that this would likely be a problem (Table 2). The hydroxyl protecting group was initially TIPS, hoping that the bulkiness of this group would prevent it from eliminating, but this did not show promise. A THP group was also employed thinking that the pyran oxygen could chelate to the zinc and stabilize the intermediate, but this also produced a significant amount of eliminated product (and starting material). The use of an alkyl boron reagent was predicted to give similar difficulties and was not attempted. Considering these negative results, attention was turned to the cross coupling with a reversal in the reactivity. The vinyl iodide 43 was lithiated\(^{42}\) then a lithium-zinc exchange afforded the vinyl zinc, which

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Additive</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(2-th)Cu(CN)Li, 'BuLi</td>
<td>----</td>
<td>Starting material</td>
</tr>
<tr>
<td>2</td>
<td>(2-th)Cu(CN)Li, 'BuLi</td>
<td>BF(_3)Et(_2)O</td>
<td>Starting material and complex mixt.</td>
</tr>
<tr>
<td>3</td>
<td>CuCn, 'BuLi</td>
<td>----</td>
<td>Starting material and protonated 41</td>
</tr>
<tr>
<td>4</td>
<td>'BuLi</td>
<td>BF(_3)Et(_2)O</td>
<td>Starting material</td>
</tr>
<tr>
<td>5</td>
<td>'Pr'Bu(_2)MgLi</td>
<td>----</td>
<td>Starting material</td>
</tr>
<tr>
<td>6</td>
<td>'BuLi, Me(_3)Al</td>
<td>BF(_3)Et(_2)O</td>
<td>Starting material and complex mixt.</td>
</tr>
<tr>
<td>7</td>
<td>(2-th)Cu(CN)Li, 'BuLi (purchased)</td>
<td>BF(_3)Et(_2)O</td>
<td>Starting material</td>
</tr>
</tbody>
</table>

Table 2: Zn insertion on model compound 44

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>Zn source</th>
<th>Results (44:45:46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TIPS</td>
<td>Zn(^0)/TMSCl</td>
<td>12:trace:1</td>
</tr>
<tr>
<td>2</td>
<td>THP</td>
<td>Zn(^0)/TMSCl</td>
<td>1.3:0:1</td>
</tr>
<tr>
<td>3</td>
<td>TIPS</td>
<td>Zn/Cu couple</td>
<td>only 44</td>
</tr>
<tr>
<td>4</td>
<td>TIPS</td>
<td>Li-Zn exchange</td>
<td>1:trace:1.2</td>
</tr>
</tbody>
</table>
Scheme 5:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(acac)$_2$, THF:NMP (2:1), ligand 48</td>
</tr>
<tr>
<td>2</td>
<td>Ni(acac)$_2$, THF:NMP (2:1), ligand 48</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh$_3$)$_4$, DMF</td>
</tr>
<tr>
<td>4</td>
<td>CuCN ·2LiCl, THF</td>
</tr>
</tbody>
</table>

entry 3, has been used in the alkylation of dihydropranyl acetates with vinyl zinc compounds. The copper zinc reagent (entry 4) is another possible condition, which has been used to couple alkyl zinc reagents with a variety of electrophiles. These conditions will all be used on a model system with alkyl iodide 44 and vinyl iodide 41. The promising conditions will then be applied to the real system in order to optimize the conditions.

2.6 Asymmetric Aldol to Construct the C19-C20 Bond: An alternative route in the synthesis of fragment 29, would involve an asymmetric aldol reaction between glycine equivalent 30 and aldehyde 31. β-Hydroxy-α-amino acids are important building blocks in organic synthesis, but the asymmetric synthesis of these compounds is still limited. There are fewer examples of the use of aldol reactions to make β-hydroxy-α-amino acids. These methods tend to give moderate selectivity or depend greatly on the substrates. Glycine equivalent 30 is well known in literature, mainly involving alkylation reactions. Asymmetric alkylation reactions with this substrate have shown very high selectivity in many cases, but this selectivity has yet to be carried over to aldol reactions. Cinchonidine-derived catalyst have been employed for aldol reactions, which give moderate selectivity with certain substrates, but it drops quickly with other substrates, limiting the utility of this system. Titanium enolates of N-alkylideneglycinates have been used in direct aldol reactions with simple aliphatic aldehydes to give anti-selectivity, but poor selectivity was seen with vinylic or aromatic aldehydes. A Ni(II) complex which contains homochiral Schiff base ligands has also been used in asymmetric aldol reactions to yield β-hydroxy-α-amino acids in high enantiomeric excess. Unfortunately, this procedure requires one equivalent of catalyst and two equivalents of the aldehyde, which makes this approach not as attractive as a catalytic reaction. Another approach uses acylation of t-butyl-N,N-dibenzylglycinate with an acid chloride followed by NaBH$_4$ reduction to produce β-hydroxy-α-amino acids with high selectivity in two steps, but only moderate selectivity was reported for the direct aldol reaction using lithium enolates. From these examples, it is apparent that there is still a need for a general, highly selective method for the synthesis of β-hydroxy-α-amino acids using catalytic asymmetric methods.

Lanthanides have become very important reagents in organic synthesis and are especially effective in stereo-controlled reactions. There are many examples in literature for use of lanthanides in asymmetric aldol reaction, but none for the synthesis of β-hydroxy-α-amino acids. We would like to employ a lanthanide metal with a chiral ligand to catalyze this reaction. The first step in developing this reaction will be to screen ligands which have been reported in lanthanide catalyzed aldol reactions. Some of the more common chiral ligands used in reactions was directly added to a solution of alkyl iodide (44) and nickel(II) catalyst. In the absence of the styrene ligand 48, no product formed (Scheme 5). Knochel has reported that styrene ligand 48 can be used to facilitate the reductive elimination of the product (entry 1). Bu$_4$NI has also been used as an additive in sp$^3$-sp$^3$ coupling of alkyl zinc reagents and alkyl halides. It is thought that the I- could coordinate to the alkyl zinc complex to form a more reactive zincate species. The palladium(0) system,
with lanthanides, include the pybox class of ligands and chiral crown ethers. As a model system, ethyl ester will be used as the glycine equivalent and phenylacetaldehyde will be used as a model β,γ-unsaturated aldehyde. Preliminary work on an asymmetric aldol will involve screening of chiral ligands with various lanthanides to look for reactivity. Once a few sets of good reaction conditions are found, a screen for enantiomeric excess will be done based on these results. Catalysts will be tested in an arrayed catalyst evaluation protocol performed in 96 well plates or in block synthesizers such as Radley’s Greenhouse (24 reactors). These are multi-variable reactions, therefore the outcome will depend on; lanthanide metal, chiral ligand, solvent, additives, and counter ion (Figure 8). Ideally all possible combinations will be tried, but initial tests for reactivity will only involve a lanthanide triflate and a chiral ligand in CH₂Cl₂. The progress of the reactions will be monitored by TLC and the enantiomeric excess will be determined using chiral HPLC. The second phase of screening will look at other variables such as solvent and counter ion effects to optimize the reaction conditions and examine the selectivity. The exact conditions used will probably be changed based on the results of the first screen. The lanthanide metals tested will be based on performance in the first screen and on availability (an x-ed out box indicates that the catalyst is unavailable). The Z and E-enolate can both be accessed for this glycine equivalent, which will provide access to another variable to examine in the later stages of development. Using this method, we expect to uncover a reactive catalyst which may be used to prepare β-hydroxy-α-amino acids with high selectivity. It is expected that particular catalyst systems may be uncovered which afford either high syn or anti selectivity. Screening reactions conditions in parallel should lead to an effective catalyst-ligand system for asymmetric aldol reactions in a very quick and efficient manner.

2.7 Completion of the Synthesis: The initial approach to the completion of the macrolide involves esterification of with E,E-dienoic acid to afford (Scheme 6). will be derived from a Stille coupling between cis-2-methyl-3-trimethylstannanyl-2-propen-1-ol and trans-3-iodo acrylic acid ethyl ester. Removal of the PMB protecting group and subsequent oxidation followed by a Wittig reaction will afford the precursor for the Stork-Takahashi cyanohydrin alkylation. Due to the instability of the β,γ-unsaturated ketone, reduction and protection of the hydroxyl group may be necessary for the remaining steps in the synthesis. Initial experiments will be done with the β,γ-unsaturated ketone, but we will be looking for migration of the double bond. A benefit of this approach is that if there is a problem with the intramolecular Stork-Takahashi cyanohydrin alkylation reaction, this can also be performed intermolecularly followed by a more common intramolecular esterification to close the macrolactone.
of a trityl group with p-TsOH resulted in transesterification\textsuperscript{64} of the sorbic chain (Scheme 7). Hopefully, the constraints from the macrolide will prevent this, but it will be a concern. The resulting amino alcohol hydrochloride 54 will be acylated with \(Z,E\)-sorbic acid 19 to afford \(N\)-acylamino alcohol 54. It should be noted that at this stage alternate acids may be coupled to prepare analogues or probe reagents derived from the zampanolide core. Removal of the C7 hydroxyl and oxidation of the allylic alcohol will yield the \(\beta,\gamma\)-unsaturated ketone 56. This represents a C20 methylene-inserted zampanolide analogue which will also be tested for biological activity. The identification of stable and bioactive analogues of 1 which lack the \(N\)-acyl hemiaminal would be extremely advantageous from the point of view of shelf-stability and further mechanism of action studies. Among these lines, methylene-inserted analogues of the \(\alpha\)-hydroxyglycine of spergualin (cf. 7a, Figure 2) have been shown to retain the antitumor activity of the parent compound, demonstrating the possibility that the \(N\)-acyl hemiaminal of 1 could conceivably be replaced.\textsuperscript{65} Final oxidation of 56 with Pd(OAc)\(_4\) or the derived carboxylic acid (PDC/DMF) should form \(N,O\)-acetal intermediates which will be hydrolyzed with aqueous Yb(OTf)\(_3\) to form zampanolide 1 and its C20 epimer. It has been shown that these compounds can be separated to produce pure(\(-\))-zampanolide 1.\textsuperscript{ref-smith}

Scheme 8: Final Transformations for Aldol Pathway

The final transformation if the aldol pathway is used are shown in Scheme 8. Although this pathway is more closely related to the model study (cf. section 2.2), it does not provide access to the methylene inserted compound 56. The aldol adduct 29, after protection of the amine, will undergo the same transformations as 21 (Scheme 6) to yield the macrolactone 58. Removal of the amine protecting group will afford
59, which will be acylated with 19 to give 54. TBAF deprotection, oxidation of the allylic alcohol (again, only if necessary to reduce the β,γ-unsaturated ketone), and removal of the tert-butyl group will afford N-acyl-α-amino acid 61. Finally, oxidative decarboxylation followed by hydrolysis will yield (±)-zampanolide 1.

2.8 Pyran Ring as a Scaffold for Diversity Oriented Synthesis: Diversity oriented synthesis is a new and useful strategy to synthesize large numbers of complex molecules based on natural products. Natural product-like compounds can be used as scaffolds to create new, highly functionalized structures. The ISMS reaction provides an efficient, stereoselective route to 2,6-syn-disubstituted exo methylene pyran rings. Using an allyl silane such as 39 and aromatic aldehydes such as p-bromobenzaldehyde 62, this reaction can provide a template such as 63 for metal-catalyzed, cross-coupling reactions (Scheme 7). The right side chain alcohol could be used to attach a solid support, or it can be oxidized to an aldehyde and further functionalized. Scheme 7: Pyran Ring as a Scaffold

The aromatic portion can be functionalized using Stille, Suzuki, or Sonogashira couplings. Finally, the exo methylene provides a position for intermolecular Pauson-Khand reactions. The stereoselectivity at the emerging spiro stereocenter will also be investigated and determined by the appropriate NMR techniques such as NOE. These reactions will provide densely functionalized spiro compounds with two functionalized arms on the pyran ring. This could create an interesting library of complex compounds that could be screened for biological activity.

3.0 Summary: This proposal discusses the planned total synthesis of antitumor macrolide (-)-zampanolide. This synthesis will include a nickel(II) catalyzed sp²-sp³ coupling reaction to make fragment X, an ISMS cyclization reaction to create the pyran ring moiety Y, and a intramolecular Stork-Takahashi cyanohydrin alkylation to close the macrolactone. A model study on the side chain of zampanolide has established an oxidative-decarboxylation/hydrolysis protocol to install the N-acyl hemiaminal. This study also showed evidence for a hydrogen-bonding network in the side chain model, which could have some effect on the biological activity of zampanolide. Plans to create a library of highly functionalized spiro-ketal compounds base on the pyran moiety of zampanolide has also been discussed as an extension this project. ……

References Cited:
(22) A Waters Sep-Pak® neutral alumina cartridge (12 cc, 2 g) was utilized. Attempted purification of hemiaminal and acetate products, in low (10-20 %) yields.
(21) Oxidative decarboxylation with Pb(OAc)4, Cu(OAc)2 with iPr2EtN in THF afforded a mixture of N-acyl hemiaminal and acetate products, in low (10-20 %) yields.
(22) A Waters Sep-Pak® neutral alumina cartridge (12 cc, 2 g) was utilized. Attempted purification of N-acyl hemiaminal products such as using silica gel chromatography led to low recoveries of product.
(26) Ref for ene rxn w/ electron poor aldehydes
(41) Jackson ref on elimination
(42) Earlier experiments showed that this compound could be lithiated cleanly, 'BuLi (2 equiv.) in Et2O.
(58) greenhouse
(60) syn of vinyl stannane
(69) Use of NOE to determine stereochemistry of the pauson khand product: