



Trip Report:
39th National Organic Chemistry Symposium
The University of Utah,
Salt Lake City, Utah
June 12 – 16, 2005

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***Abstract:** The 39th National Organic Chemistry Symposium was held June 12-16, 2005 at the University of Utah in Salt Lake City, Utah. The symposium included 14 lectures in several different areas of organic chemistry and four evening poster sessions. Presenters included Prof. Amos B. Smith III, Prof. M. Reza Ghadiri, Prof. Stephen L. Buchwald and Prof. K. C. Nicolaou, among others. Poster presentations included work from academic groups as well as pharmaceutical and chemical companies. A broad range of topics were covered, with a focus on organic chemistry and its applications.*

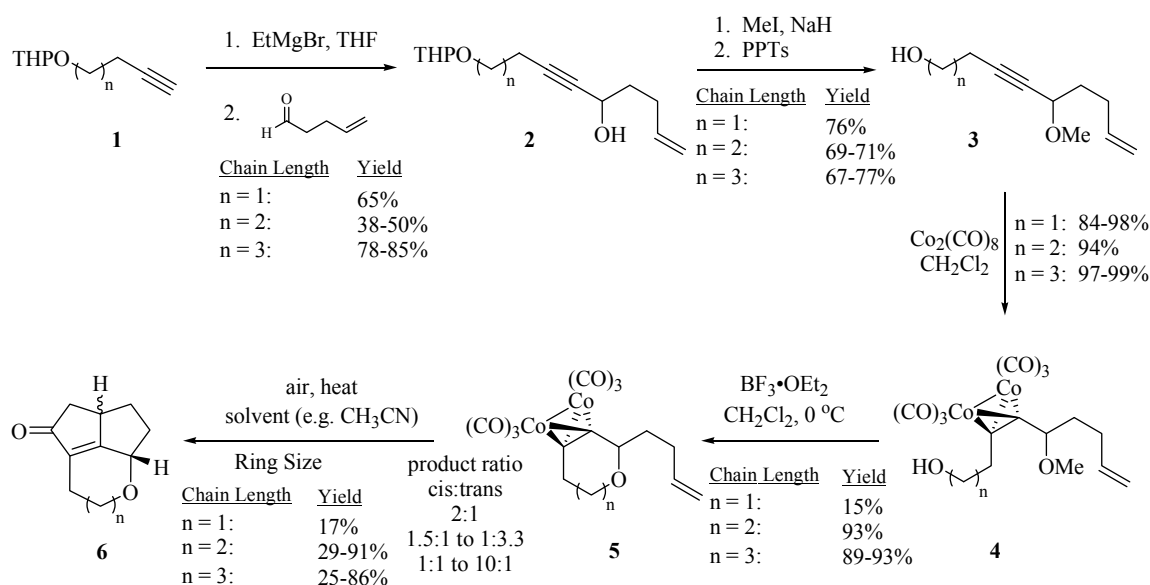
Poster: "Tandem Intramolecular Nicholas and Pauson-Khand Reactions for the Synthesis of Tricyclic Heterocycles,"

Closser, K. D.; Quintal, M. M.; Shea, K. M. (Smith College), Northampton, MA.

Although both the Nicholas reaction and the Pauson-Khand reaction employ cobalt-complexed alkynes, only a few examples exist in which these transformations are used sequentially to provide a tricyclic ring system. The research summarized here uses the Nicholas reaction and the Pauson-Khand reaction sequentially to provide a variety of tricyclic heterocycles. For a literature reference related to this work, see: Quintal, M. M.; Closser, K. D.; Shea, K. M. *Organic Letters*, **2004**, *6*, 4949.

An example is shown in Scheme 1. Deprotonation of alkyne **1** using ethylmagnesium bromide, followed by reaction with 4-pentenal, provided secondary alcohol **2**. Compound **2** was transformed into the corresponding methyl ether and the primary hydroxyl was deprotected to give compound **3**. This alkyne was reacted with dicobalt octacarbonyl to afford complexation product **4**. Next, the Nicholas reaction was performed. Compound **4** was reacted with boron trifluoride diethyl etherate, producing the cobalt-catalyzed cation, which reacted with the primary internal alcohol to provide the cyclic ether **5**. Heating compound **5** in solvents such as acetonitrile provided tricyclic Pauson-Khand products such as **6**. The ratio of the possible relative stereoisomers in the products appears to be dependent on the solvent used. Other solvents used in this transformation include cyclohexylamine and NMO.

Scheme 1



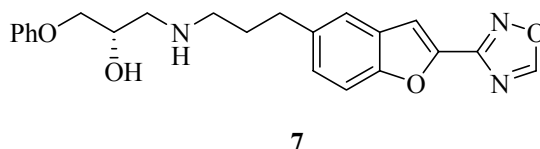
Similar procedures were used to prepare tricyclic amine analogues as well as lactones.

Poster: "Preparation of 1-(2-[2-Oxadiazol-3-ylbenzofuran-5-yloxy]ethylamino)-3-phenoxy-2(S)-ol,"

Fox, D. E.; DeVries, K.; Snyder, W. M.; Reynolds, S.; Watson, H. (Pfizer Global Research & Development, Groton/New London Laboratories, Pfizer Inc.), Groton, CT.

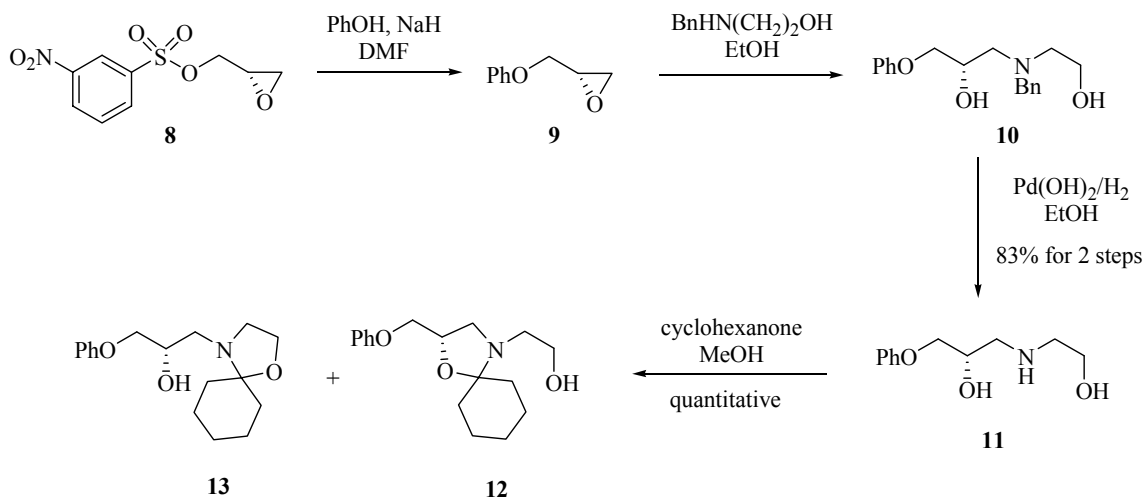
Compound **7** (Figure 1) is a selective beta-3 receptor agonist. The synthesis of **7** required the use of a suitably protected aminoalcohol intermediate and a benzofuran.

Figure 1



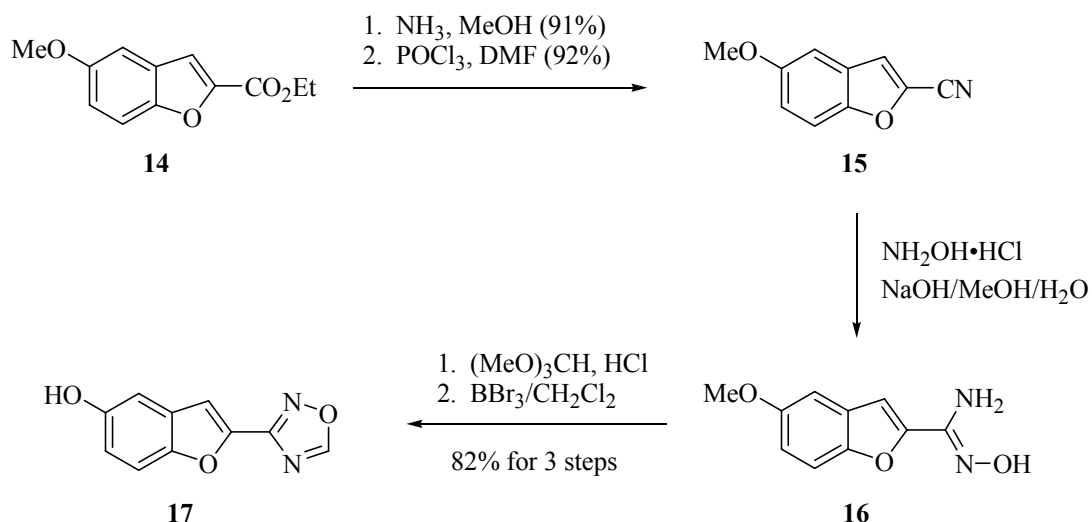
Scheme 2 shows the preparation of the requisite protected aminoalcohol. Addition of phenoxide into nosylate **8** provided phenyl ether **9**. This epoxide was reacted with *N*-benzylethanolamine to give protected aminoalcohol **10**. The *N*-benzyl group was removed and intermediate **11** was reacted with cyclohexanone to give a mixture of regioisomers **12** and **13**.

Scheme 2



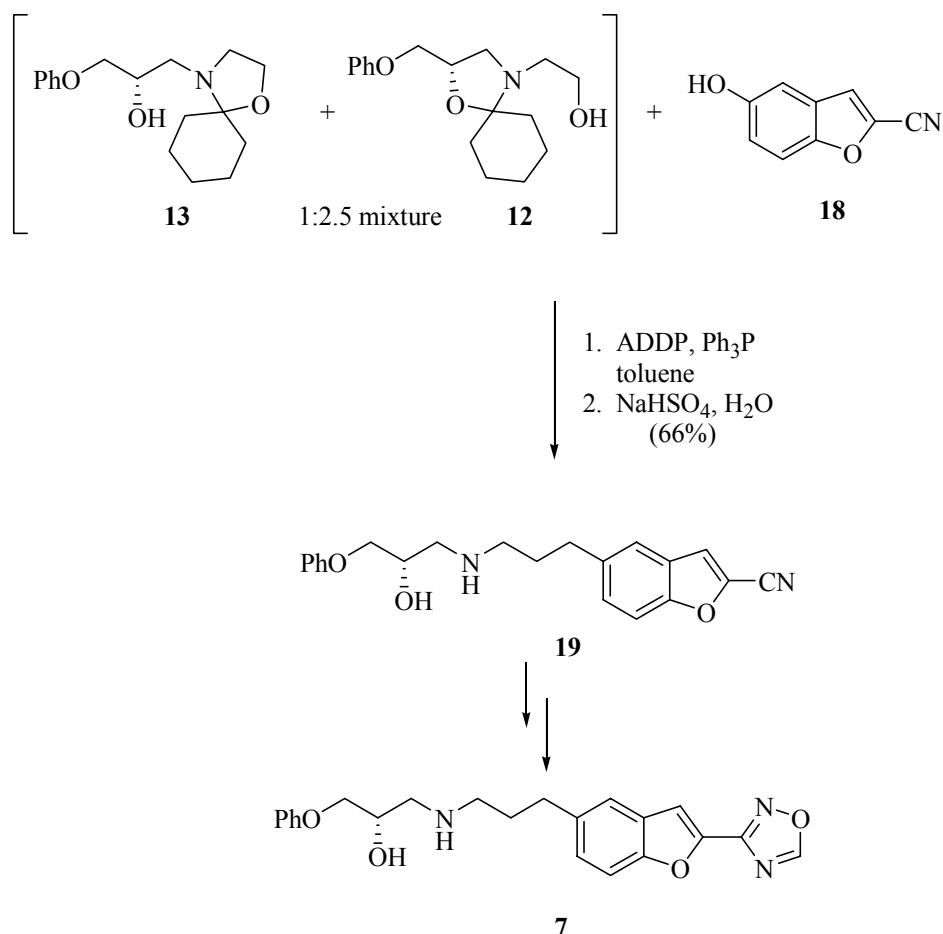
Scheme 3 shows the preparation of the substituted benzofuran. 2-Carboethoxybenzofuran **14** was transformed into nitrile **15**. Transformation of compound **15** into oxadiazole **17** was performed in two steps.

Scheme 3



In the key reaction of the sequence, the protected amino alcohol (structures **12** + **13**) was reacted with OH-substituted benzofuran under Mitsunobu conditions to provide intermediate **19** in 66% yield (Scheme 4). Compound **19** was transformed into the desired product **7**.

Scheme 4

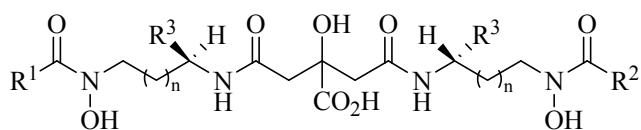


Seminar: “The Chemical Biology of Iron,”

Groves, J. T.; Luo, M.; Fadeev, E.; Shimanovich, R. (Department of Chemistry, Princeton University), Princeton, NJ.

Iron plays a critical role in biology, but is not always readily abundant in the environment. In such situations, bacteria secrete siderophores to sequester the available iron. Siderophores are highly selective iron chelating agents.

Compounds such as schizokinen and acinetoferrin (Figure 2) are a subset of siderophores that are citrate-based and amphiphilic. These compounds possess hydrophilic iron-chelating moieties as well as lipophilic hydrocarbon chains. The amphiphilic characteristics allow for both iron acquisition and membrane interaction.

Figure 2

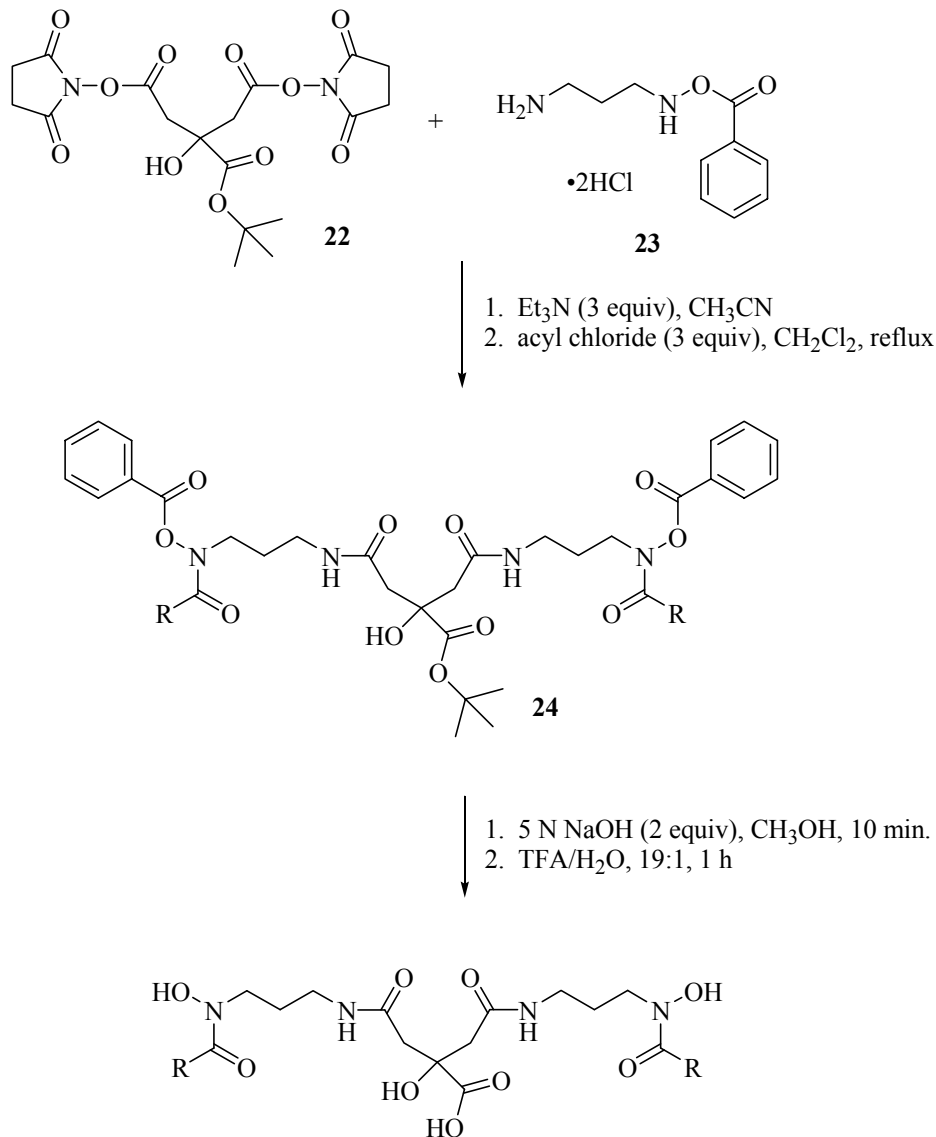
20: Schizokinen: $n = 1$, $R^3 = H$, $R^1 = R^2 = CH_3$

21: Acinetoferrin: $n = 1$, $R^3 = H$, $R^1 = R^2 =$

The 3-D structure and membrane properties of acinetoferrin show that the two hydroxamate-conjugated octenoyl chains play important roles in membrane partitioning and trans-membrane permeability. This amphiphile may be able to access host intracellular iron pool upon diffusion. The high iron-chelating ability for acinetoferrin must be attributed to its hydroxamate-conjugated double bonds, since schizokinen, a less-bulky siderophore analogue without such electron-donating moieties, shows a much weaker ability to mobilize transferring iron.

The syntheses of schizokinen and acinetoferrin have been reported previously by different research groups. Scheme 5 shows a general procedure developed by this group for the preparation of schizokinen. This route allows for the easy preparation of acinetoferrin, as well as analogues (see also Fadeev, E. A., et al. *J. Am. Chem. Soc.* **2004**, *126*, 12065). Citrate analogue **22** was coupled with amine **23**, and then the intermediate amine was acylated to provide intermediate **24**. Deprotection of **24** was achieved by treatment with NaOH/MeOH, followed by TFA.

Scheme 5



20: Schizokinen

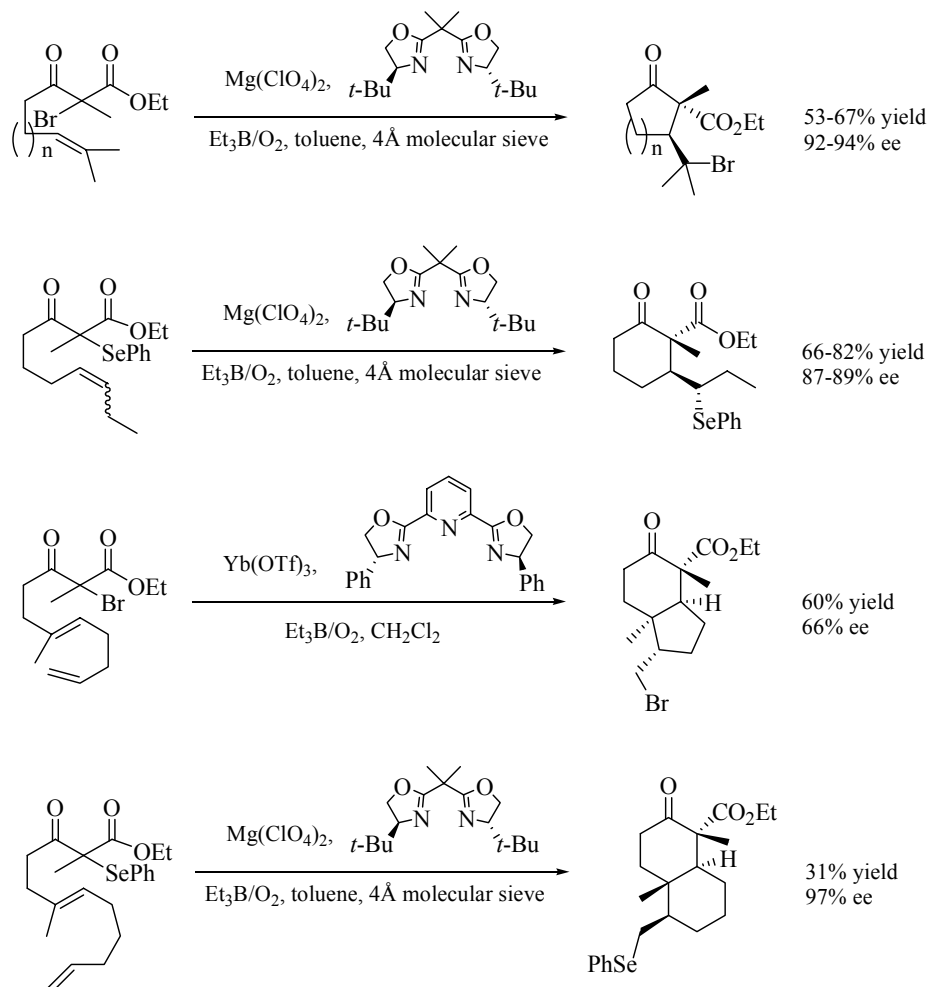
Seminar: "Catalytic Asymmetric Cyclization Reactions for Natural Product Synthesis,"

Yang, D. (Dept. of Chemistry, The University of Hong Kong).

Professor Yang's group developed a series of oxidation methods (ketone-catalyzed epoxidation, C-H bond oxidation and peroxynitric decomposition) and cyclization methods in her group's program on chemistry and biology of natural products. Professor Yang presented their recent results on catalytic asymmetric cyclization reactions, which range from atom and group transfer radical cyclization to transition metal-catalyzed cyclization, and their applications in the construction of various carbocycles and heterocycles found in many bioactive natural products.

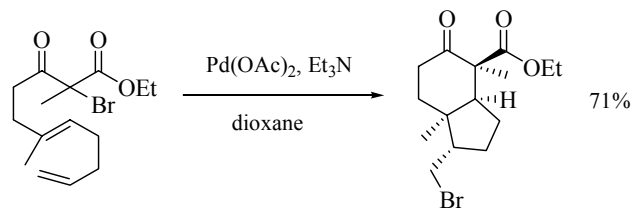
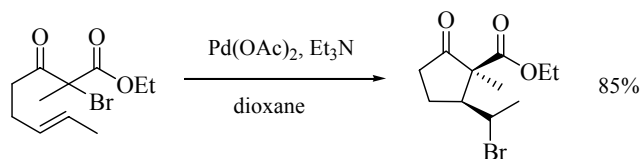
It was found that catalytic amounts of Lewis acid $\text{Mg}(\text{ClO}_4)_2$, combined with a chiral bis(oxazoline) ligand, could promote atom or group transfer radical cyclization reactions of unsaturated keto esters resulting in 2,3-disubstituted ketones in excellent enantioselectivity (up to 94% ee) (Scheme 1). The group also found that Lewis acids effectively catalyzed atom or group transfer tandem radical cyclization of a series of unsaturated β -keto esters to provide various polycyclic ring skeletons with moderate to good yields and excellent stereoselectivities. The first enantioselective tandem radical cyclization promoted by chiral Lewis acids has been achieved in both atom transfer and group transfer reactions with up to 97% ee (Scheme 1).

Scheme 1



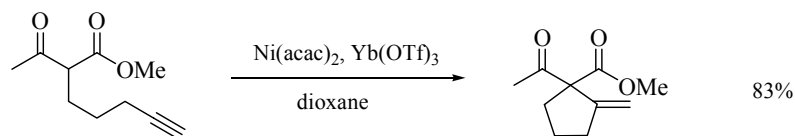
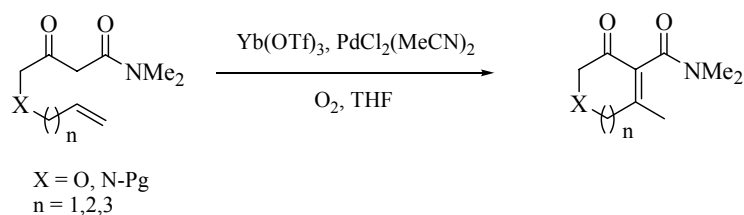
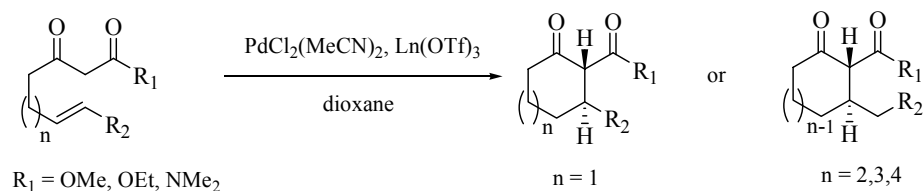
In addition, the group has found $\text{Pd}(\text{OAc})_2$ can catalyze bromo atom transfer cyclization reaction in the presence of Et_3N , and this reaction was also applicable to the tandem cyclization reactions (Scheme 2). Preliminary mechanistic studies indicate that these Pd-catalyzed atom transfer reactions may not proceed via a radical pathway.

Scheme 2



More recently, they have investigated several transition metal-catalyzed cyclization reactions, including lanthanide triflates-promoted Pd-catalyzed intramolecular hydroalkylation reaction and oxidative cyclization reaction under aerobic conditions, as well as lanthanide triflates-promoted Ni-catalyzed Conia-ene reaction of β -dicarbonyl compounds with alkynes (Scheme 3).

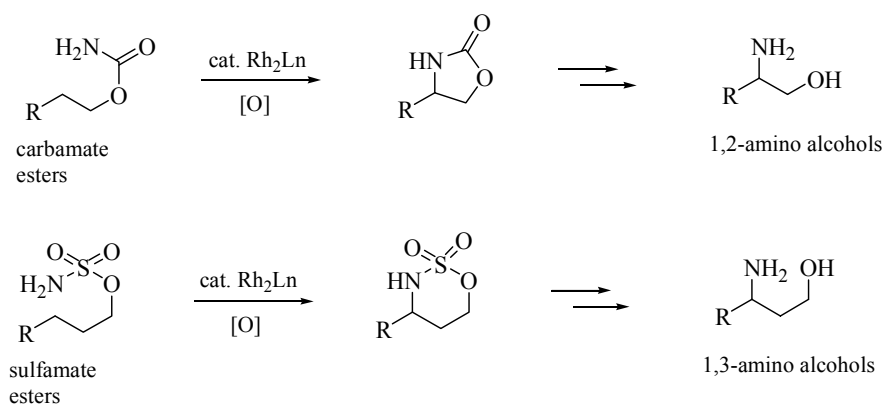
Scheme 3



Seminar: “C-H Oxidation Reactions as Enabling Methodologies for Organic Synthesis,”
Du Bois, J. (Dept. of Chemistry, Stanford University).

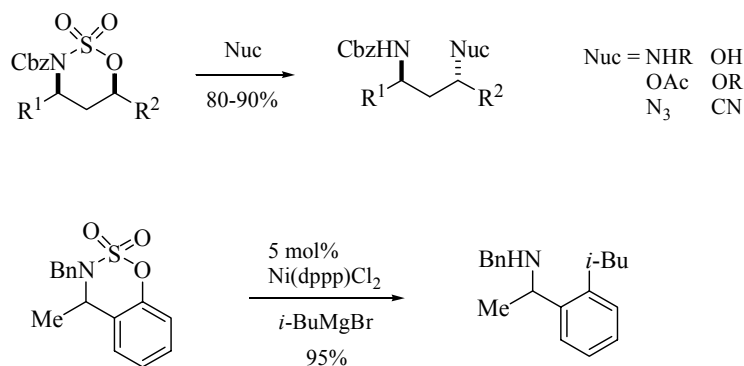
Professor Du Bois showed new strategies for the selective conversion of saturated C-H bonds to carbinolamine stereocenters. The methods have general utility and make available large numbers of amine derivatives from inexpensive and easily prepared primary carbamate and sulfamate ester starting materials (Scheme 4).

Scheme 4



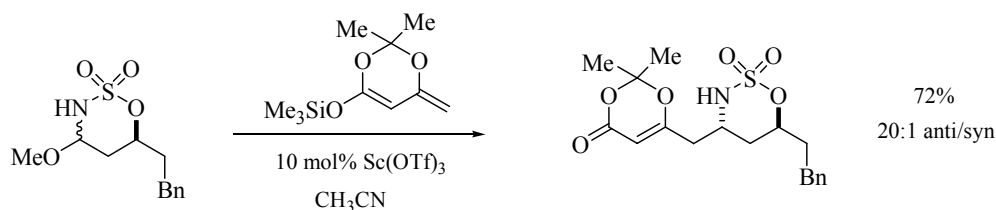
Products from C-H insertion of sulfamate esters serve as useful precursors to β -amino alcohols and acids, as well as other 1,3-difunctionalized amine derivatives. Such structural types are found commonly in naturally occurring compounds and therapeutic agents. The group has identified conditions for conducting Ni-catalyzed cross-coupling reactions between N-alkyloxathiazinane derivatives and Grignard reagents (Scheme 5).

Scheme 5



The rate of C-H bond insertion can be influenced by steric and electronic effects, and such differences are sufficient to offer reasonable levels of product regiocontrol. The α -C-H positions of etheral groups are particularly active substrates for this oxidation process. These finding has been exploited in order to generate a series of N,O-acetal oxathiazinanes for use as iminium ion equivalents. The coupling of allylsilane, silyl enol ether, silyl ketene acetal, and alkynylzinc nucleophiles to such compounds occurs smoothly with Lewis acid promoters and furnishes products rich in structural complexity.

Scheme 6

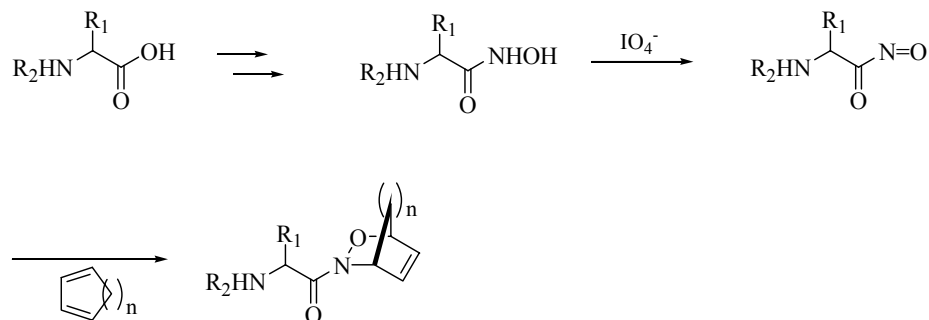


Poster: “The Design and Synthesis of Structurally Novel Antibacterial Compounds Related to β -Lactam Antibiotics,”

Nora, G. and Miller, M. (Department of Chemistry and Biochemistry, University of Notre Dame).

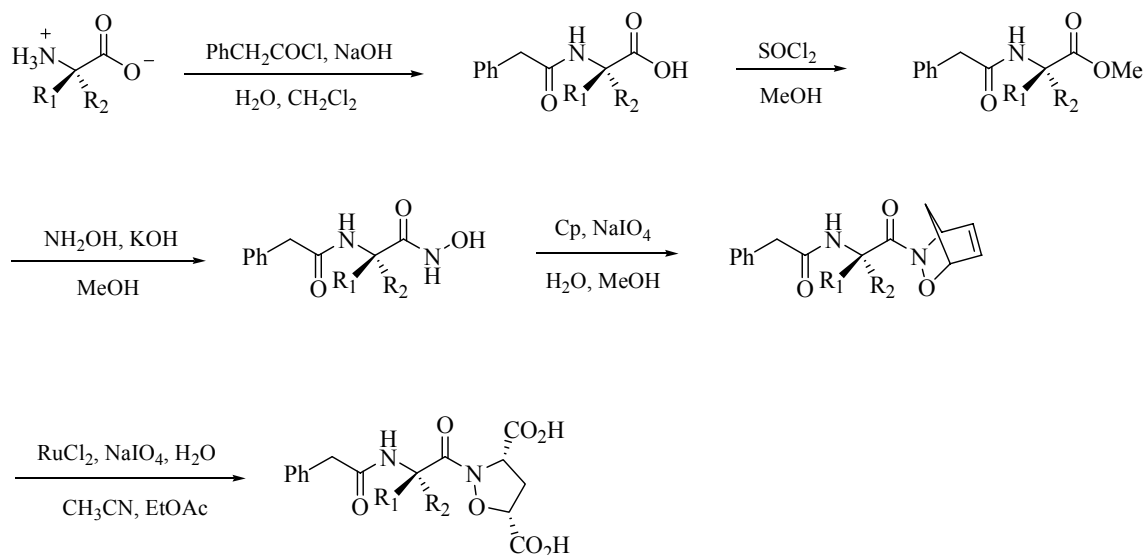
Professor Miller's group recently found that amino acid based acyl nitroso derivatives can be generated by oxidation of the corresponding hydroxamic acids and trapped with dienes to give cycloadducts (Scheme 7). These optically pure Diels-Alder products are functionally rich and serve as precursors of a number of types of compounds of biological interest.

Scheme 7



Oxidative cleavage of the carbon-carbon double bond of the cycloadduct produces a diacid which is a peptide containing a novel carboxy terminal amino acid. Thus, in unprecedented fashion, the carbon framework for the new amino acid was derived from the original diene. The new C-terminal amino acid can be considered to be an analog of proline or a conformationally restricted analog of glutamic acid which may be useful for the preparation of peptide mimetics or novel CNS agents. The group used this methodology to synthesize isoxazolidines as novel antibacterial compounds related to β -lactam antibiotics.

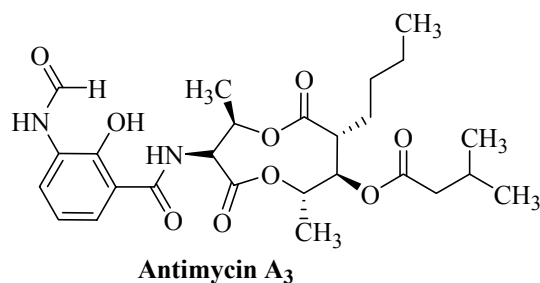
Scheme 8



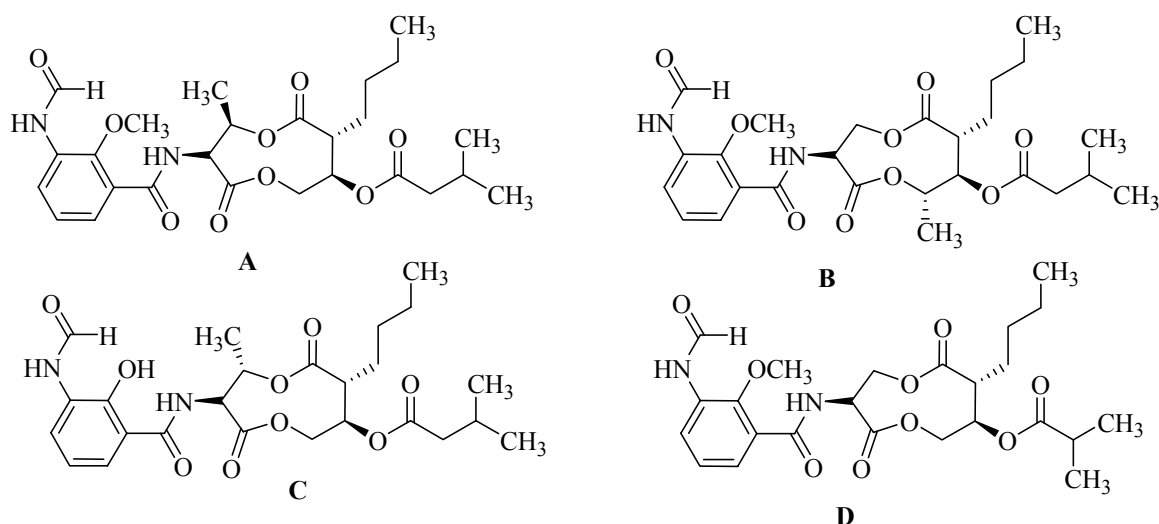
Poster: “Synthesis of Novel Analogues of Antimycin A₃”

Hu, Z.; Jiang, X.J. and Han, W. (Department of Discovery Chemistry, Pharmaceutical Research Institute, Bristol-Myers Squibb Company), Princeton, NJ.

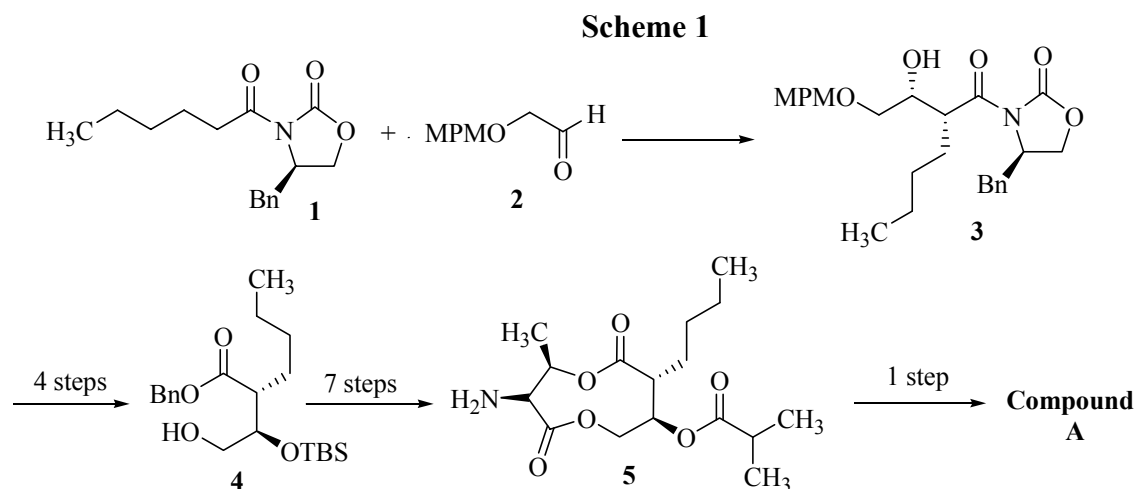
Antimycin A₃ is a natural product isolated from the *streptomyces* species. First investigated for its antifungal activities it was also found to inhibit the electron transfer



activity of ubiquinol-cytochrome *c* oxidoreductase. While analogs varying the aromatic side chain were known in the literature, little was reported on variation of the dilactone core. A series of four analogs (A, B, C, and D) were designed to examine the effects on variation of this core structure. Variations include converting the phenol to a methyl

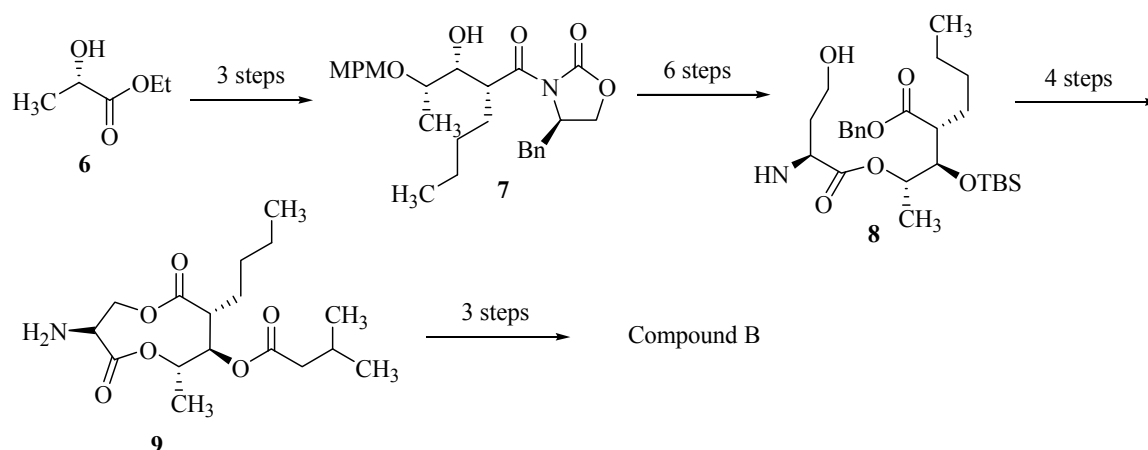


ether (**A**, **B**, and **D**) and removal of one or both of the methyl groups attached at the core. Synthesis of analog **A** is outlined in Scheme 1. The stereochemistry is set by an aldol reaction between the Evan's chiral auxiliary **1** and the aldehyde **2**. Subsequent removal of the auxiliary, protection of the resulting acid, TBS protection of the secondary alcohol and removal of the MPM protecting group affords **4**. Transformation of **4** into **5** is accomplished in a seven step sequence that includes EDCI coupling of an amino acid and Cyclolactonization. Conversion of **5** to **A** is completed with an EDCI coupling of the appropriate aromatic acid.



Synthesis of analog **B** was via a different route, outlined in Scheme 2. Protection of the alcohol **6** was followed by reduction of the ester and coupling with the Evan's auxiliary **1** to afford **7**. Transformation of **7** into **8** followed a six step sequence, the first four steps being protections and deprotections of hydroxyls, while the last two were EDCI coupling of Boc-serine and liberation of the acid to provide **8**. Next, lactonization was followed by removal of the TBS group, alkylation of the resulting free hydroxyl, and loss of the *N*-Boc protecting group to yield **9**. Final conversion of **9** into **B** was accomplished with the coupling of the appropriate aromatic acid and formylation of the amino group to afford **B**.

Scheme 2



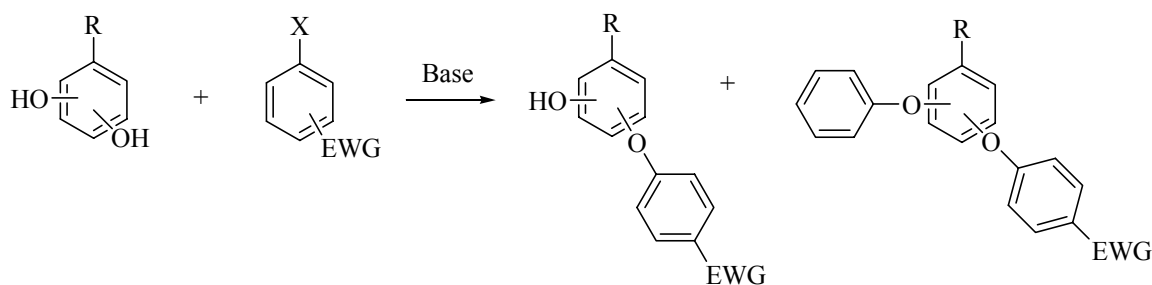
Similar chemistry and some common intermediates were used in the successful construction of compounds C and D. Presented also was early efforts towards lactam analogues in which one of the lactone oxygen atoms was replaced by a nitrogen.

Poster: "S_NAR Reaction on Biphenols: Mono vs. Bis Selectivity as a Function of Base Equivalents,"

Sullivan, K.; Xie, C.; Lauria, M.; Pu, J. and Mitchell, D. (Lilly Research Labs, Chemical Product and Research Development), Indianapolis, IN.

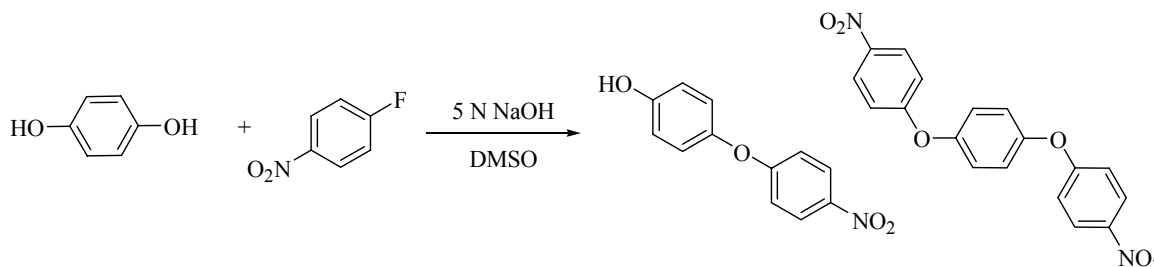
Monoalkylation and monoarylation of biphenols has historically been difficult to achieve selectively. Lilly has an interest in molecules such as these for use as intermediates in the construction of molecules of biological interest. Traditional methods using either one or two equivalents of base usually result in mixtures of mono- and di-substituted products, and in low yields (Scheme 1). Work presented in this poster outlines Lilly's efforts to achieve monoarylations of hydroquinone, resorcinol, 2-methylresorcinol, and orcinol.

Scheme 1



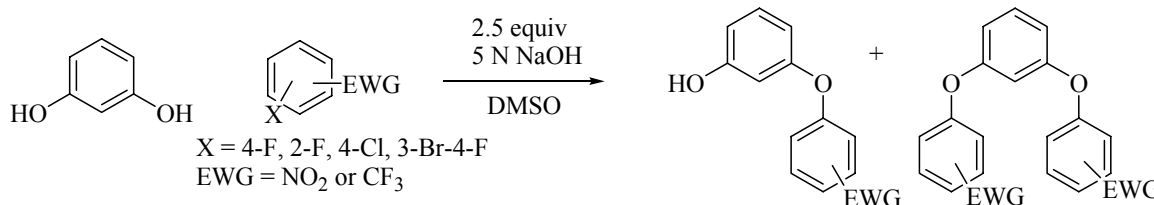
Initial efforts examined reaction of hydroquinone with 4-fluoronitrobenzene (Scheme 2). Several sets of reactions conditions were examined, varying the number of equivalents of 5 N NaOH from 1.0 to 3.0. Yields and selectivity increased with increasing equivalents of base. In the initial runs of the reaction the base solution was

Scheme 2



added in one portion, but upon further investigation it was determined that slow addition of base to the reaction solution enhanced selectivity of mono over bis products, such that under optimized conditions an 87% yield of 22:1 mono to bis ratio was achieved. Efforts then shifted to arylation of resorcinol, 2-methylresorcinol, and orcinol. Results using 5 N NaOH mirrored those found for hydroquinone, with increased base leading to increased yields and selectivity. A series of electrophiles was then examined for reactivity and selectivity (Scheme 3). Different substitution patterns of the halogen as well as different halogens were investigated. Exchange of the nitro group with a trifluoromethyl group as the electron withdrawing functionality was investigated concurrently. From these studies

Scheme 3



it was determined that fluorides combined with either a nitro or trifluoromethyl group worked well, whereas chlorides did not work for either electron withdrawing group examined.

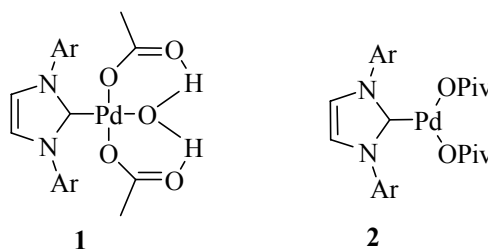
The final variable examined was the base used. All studies discussed thus far employed aqueous 5 N NaOH solution. Three additional bases, namely sodium hydride, cesium carbonate, and potassium carbonate were investigated in the arylation of resorcinol with 4-fluoronitrobenzene. The best result was obtained when 2.5 equivalents of cesium carbonate was used and the reaction allowed to proceed for 24 h. These conditions provided a 93% yield in a >100:1 ratio of mono:bis. Investigations into the application of this method to unsymmetrical phenols is currently in progress.

Seminar: “Design and Mechanistic Studies of Palladium-Catalyzed Oxidations for Organic Synthesis,”

Sigman, M. (Department of Chemistry, University of Utah), Salt Lake City, UT.

Prof. Sigman presented recent results from his lab detailing efforts to achieve palladium mediated air-oxidation of alcohols to aldehydes and ketones. Prof. Sigman and his group have found optimal catalysts and conditions to carry out these oxidations at low temperatures (rt to 60 °C) often with ambient air as the oxidant. His group has carried out extensive mechanistic studies which he presented, a full discussion of which can be found in a recent publication¹. A summary of the applications and scope of the transformation is included here.

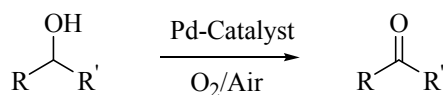
Three catalyst systems were investigated, palladium acetate and triethylamine and two systems where slightly differing N-heterocyclic carbene ligands (**1** and **2**) were employed. A variety of substrates and reactions conditions were examined to determine the extent of usefulness of the reaction as well as optimal conditions for each substrate class. The first group of substrates discussed were benzylic alcohols. It was found that



Ar = 2,6-di^tPr-Phenyl

primary, secondary, and cyclic benzylic alcohols were easily oxidized with any of the three catalyst systems examined (Table 1). The exceptions to this were some electron-

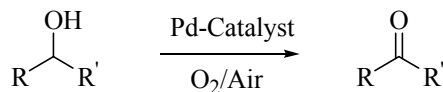
Table 1



R =	R' =	Optimized conditions
Phenyl	Methyl	1 mol% 2 , air, rt, 14 h, 0.5 mol% PivOH
4-OMe-C ₆ H ₄	Methyl	0.5 mol% 1 , air, 60 °C, 14 h, 4 mol% AcOH
4-OMe-C ₆ H ₄	H	1 mol% 2 , air, rt, 14 h, 0.5 mol% PivOH
4-NO ₂ -C ₆ H ₄	Methyl	3 mol% Pd(OAc) ₂ , 6 mol% Et ₃ N, O ₂ , rt, 12 h
3-CF ₃ -C ₆ H ₄	Methyl	0.5 mol% 1 , air, 60 °C, 12 h, 2 mol% AcOH
Phenyl	C(CH ₃) ₃	0.75 mol% 1 , O ₂ , 60 °C, 14 h, 5 mol% Bu ₄ NOAc

¹ Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.*, **2004**, *126*, 9724-9734.

deficient alcohols, such as (4-trifluoromethylphenyl)methanol. A series of aliphatic and allylic alcohols were also explored (Table 2). Again, the three catalyst systems were employed, using either oxygen or air as the oxidant, at either room temperature or 60 °C.

Table 2

R =	R' =	Optimized conditions
C ₈ H ₁₇	Methyl	1 mol% 2 , air, rt, 14 h, 0.5 mol% PivOH
2-methylcyclohexanol		3 mol% Pd(OAc) ₂ , 6 mol% Et ₃ N, O ₂ , rt, 12 h
Cyclohexyl	Methyl	1 mol% 2 , air, rt, 14 h, 0.5 mol% PivOH
3-Methyl-cyclohex-2-enol		1 mol% 2 , air, rt, 14 h, 0.5 mol% PivOH
C ₁₁ H ₂₃	H	0.5 mol% 1 , O ₂ , 60 °C, 10 h, 5 mol% Bu ₄ NOAc
1-Cyclohexene	Methyl	1 mol% 2 , air, rt, 14 h, 0.5 mol% PivOH

Many secondary alcohols readily oxidized under mild conditions, with air at room temperature. Oxidation of primary alcohols was more challenging but it was found that addition of Bu₄NOAc instead of acetic acid resulted in successful oxidation to the desired aldehydes. Also, catalyst **2** was found to be a poor catalyst for the oxidation of primary aliphatic alcohols. The concentration of acetic acid used was also important to optimization of the above reactions.

Also examined was oxidation of more functionalized alcohol, including 1,2- and 1,3-monoprotected alcohols and 1,2-amino alcohols. Protecting groups examined included TBS, acetyl, trityl, and benzyl. In the case of 1,3-monoprotected diols it was determined that the nature of the protecting group does not effect the success rate of the oxidation, but rather the substrate itself determines the ease of oxidation. More generality was found for 1,2-monoprotected diols, with high yields obtained in many cases. For specific examples, see ref 1.

Prof. Sigman is continuing to explore the application of his catalysts **1** and **2** to oxidation reactions, including extension to olefin oxidations similar to the Wacker oxidation. Publication of the results of these efforts is forthcoming.

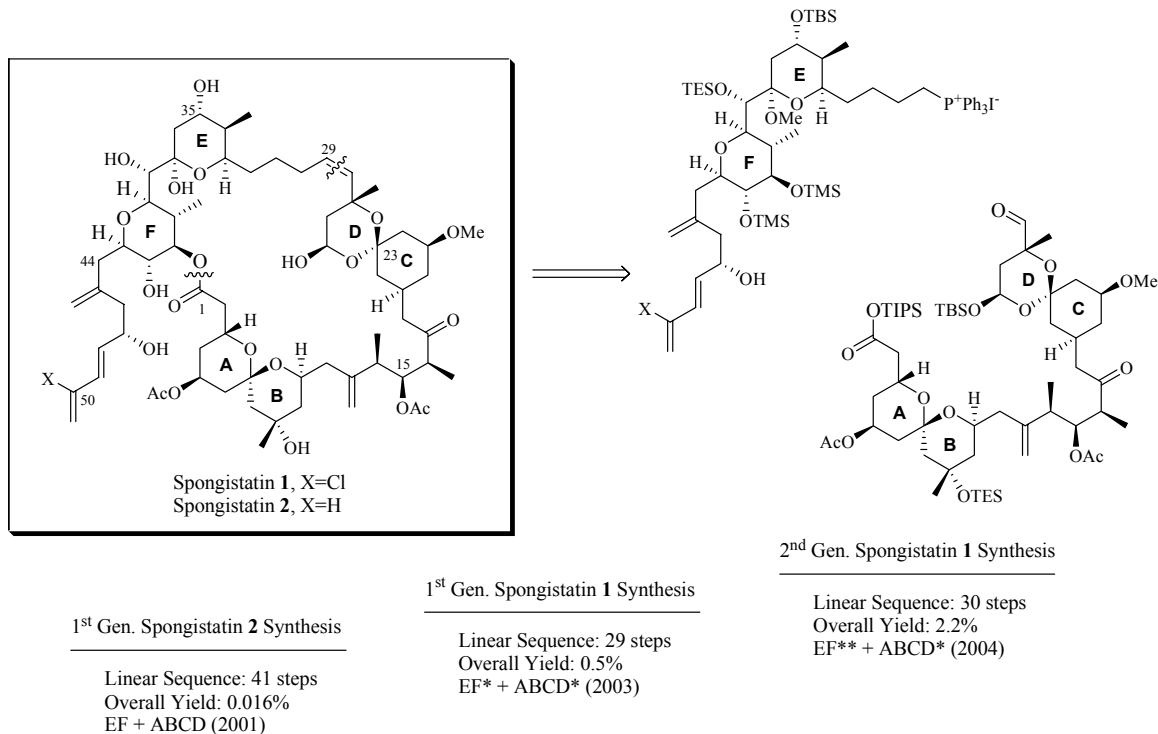
Seminar: “Evolution of a Gram-Scale Total Synthesis of the Antitumor Agent (+)-Spongistatin 1: Challenges, Excitement and Frustrations,”

Smith, A.B., III (University of Pennsylvania).

Prof. Smith’s seminar described the status of their current efforts to develop a scalable (ca. one-gram) synthesis of (+)-Spongistatin **1** (1). Three total synthesis of the spongistatin antitumor agents have been achieved to date (Figure 1), the first in 2001 of (+)-Spongistatin **2** (2), a second in 2003 of (+)-Spongistatin **1**, and a third in 2004, again of (+)-Spongistatin **1** (1) (Figure 1). It is the latter synthesis which they believe holds the promise of providing material sufficient for preclinical evaluation.

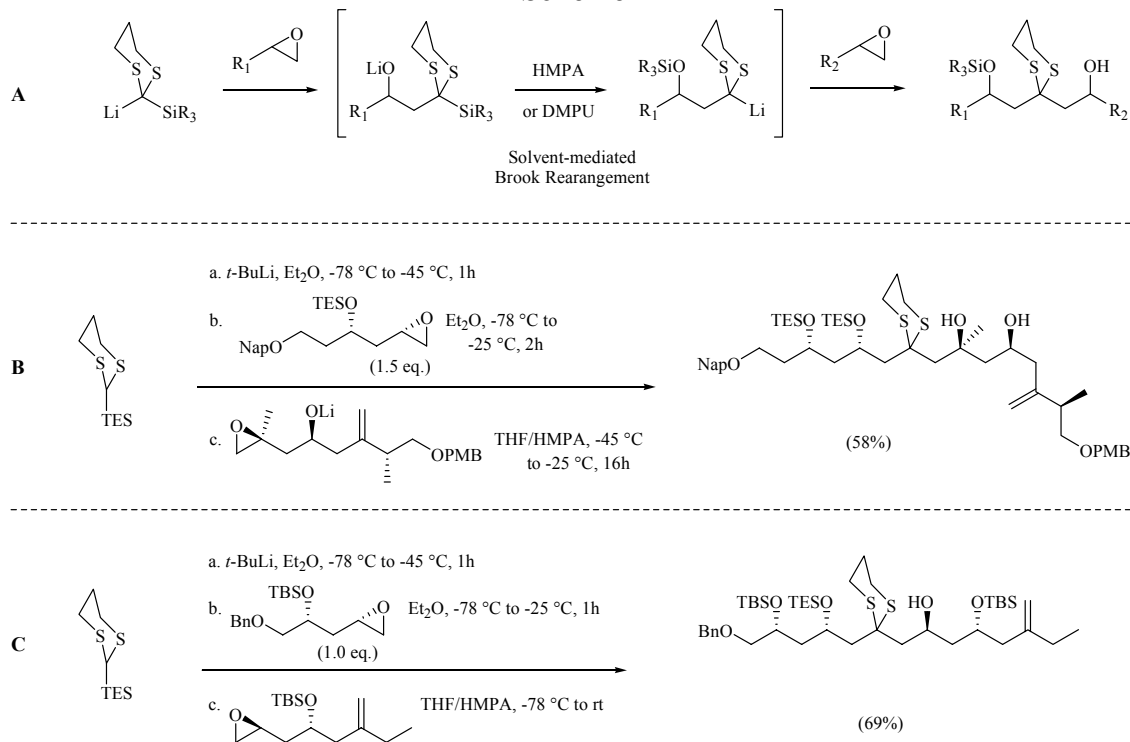
Figure 1

Evolution of the Penn Spongistatin Synthesis



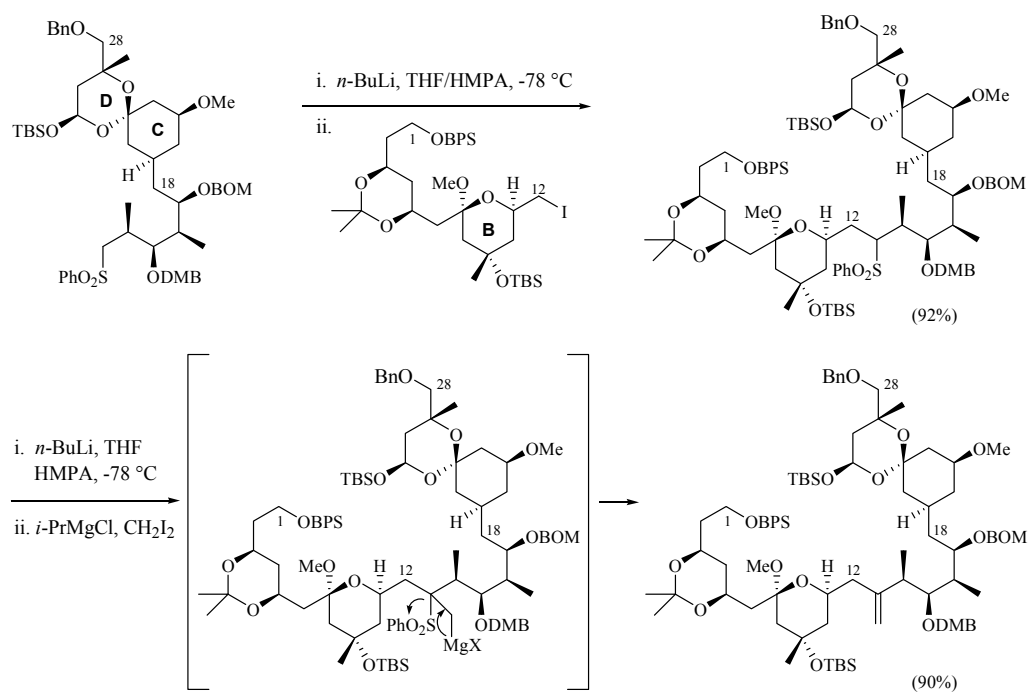
The utility of dithiane nucleophiles as acyl anion equivalents has led to numerous applications in the Smith group total synthesis. More specifically, the multicomponent dithiane/epoxide linchpin coupling tactic (Scheme 1A) enables the rapid, stereoselective construction of orthogonally functionalized 1,5-diols, which are a common feature in advanced intermediates *en route* to Spongistatin 1 (Scheme 1B, C).

Scheme 1



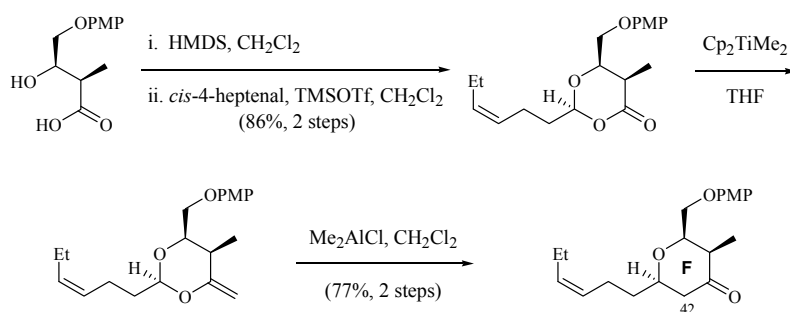
The Julia olefination/methylenation sequence has enabled a strategic fragment union in the context of the efforts toward the spongistatin (Scheme 2). Of note is the overall efficiency of the two-step protocol (83%), during which a key C-C bond is formed between the CD-spiroketal sulfone and the B-ring alkyl iodide.

Scheme 2



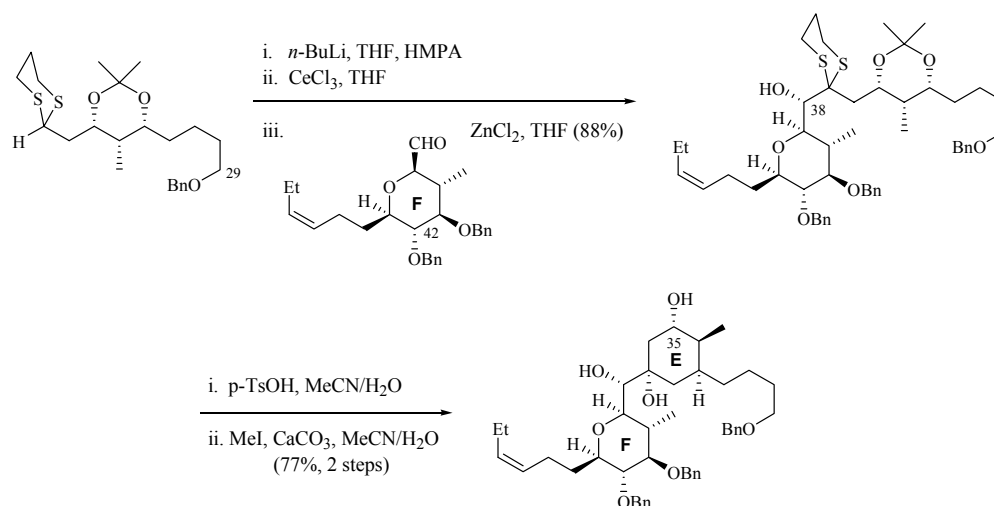
A third transformation that is exploited with great success is the Petasis-Ferrier union/rearrangement, which enables the facile elaboration of 2,6-*cis*-disubstituted tetrahydropyran ring systems. Here, condensation of a β -hydroxy acid and an aldehyde, followed by methylenation of the resultant dioxanone, affords an enol acetal (Scheme 3). Treatment with Me_2AlCl then prompts a rearrangement to afford the desired tetrahydropyran intermediate.

Scheme 3



Efficient EF fragment union was achieved via treatment of the cerium anion generated from dithiane with a premixed solution of aldehyde and zinc chloride to afford a single isomer (Scheme 4). Acidic removal of acetonide, followed by dethioketalization with *in situ* formation of the E-ring hemiketal, afforded the EF bis-pyran.

Scheme 4



The synthesis of the EF Wittig salt achieved with a longest linear sequence of 26 steps (8.3% overall yield), represents a dramatic improvement in yield compared to the first-generation total synthesis of Spongistatin **1** (24 steps, 1.8% overall yield). Completion of a second-generation synthesis of Spongistatin **1** was achieved in a fashion similar to the first-generation approach [i.e., EF Wittig salt with ABCD fragment, followed by desilylation, regioselective Yamaguchi cyclization and global deprotection].

Poster: "Synthesis of Functionalized Thiophene Derivatives,"

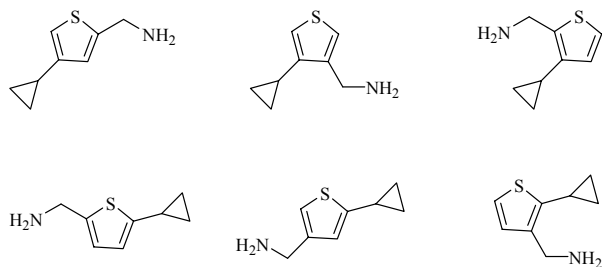
Manikowski, J.J.; Bungard, C.J. (Merck & Co., Inc).

Thiophene-containing molecules have proven efficacious in a wide range of medicinal treatments. The incorporation of thiophene moieties into therapeutic agents can afford several benefits over other aromatic systems. The ring system serves as a more electron-rich surrogate than bioisosteres such as benzene, and the low lying d-orbitals of the sulfur heteroatom can enhance receptor binding affinity. Also, thiophene analogs may provide structural novelty and thus, potential patentability over more common aromatic moieties. For these reasons, the synthesis of functionalized thiophenes is of particular interest.

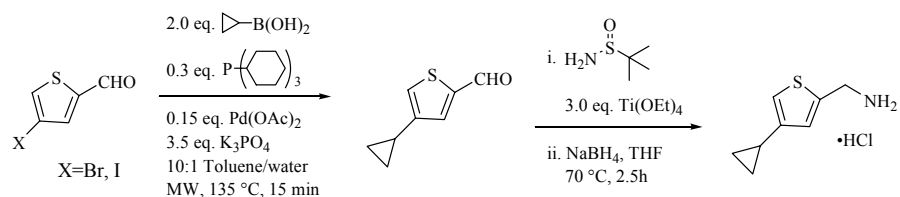
Manikowski described the work performed at Merck involving the synthesis of a library of multi-substituted thiophene derivatives. Where applicable, microwave synthesis was employed, which led to considerably shorter reaction times and often, increased yields and cleaner workups.

Figure 2

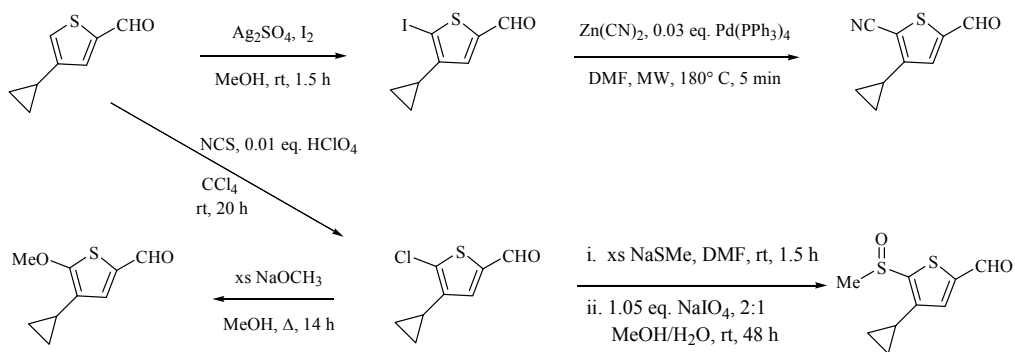
Initial Targets



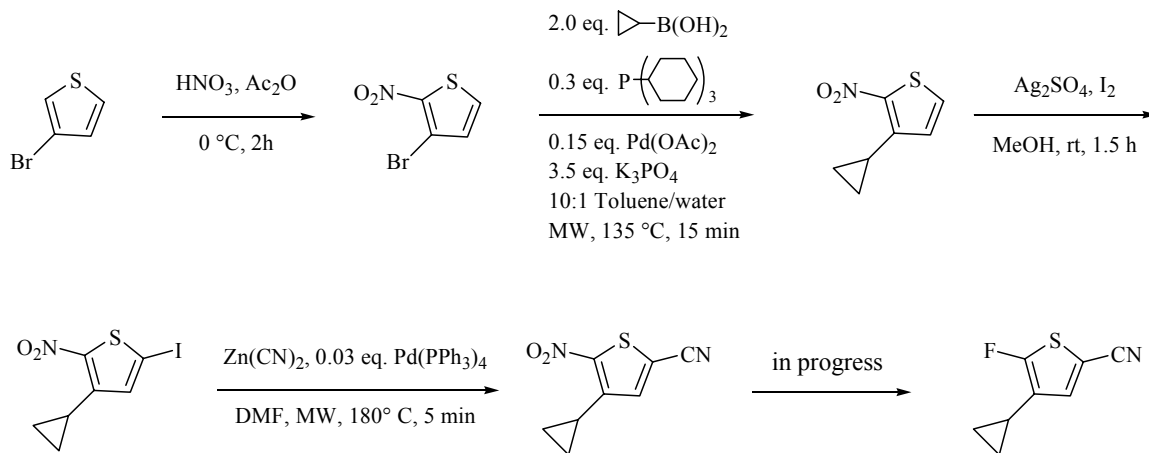
Typical Procedure



Further Functionalization



Introduction of Fluorine



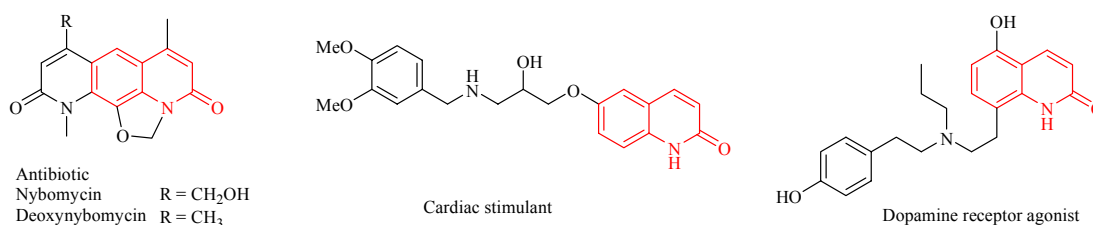
Poster: “Application of Ring-Closing Metathesis to the Synthesis of Substituted Quinolin-2(1H)-Ones,”

Dufresne, C.; Minville, J.; Sturino, C. (Merck Frosst Centre).

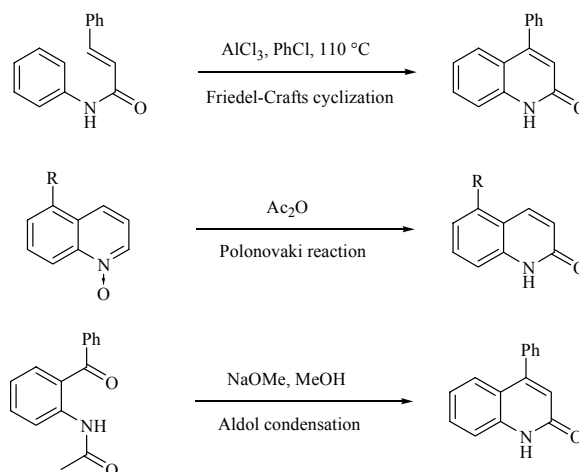
The quinolin-2(1H)-ones motif has been found in a lot of therapeutic agents (Figure 3). There are some usual ways to prepare quinolin-2(1H)-ones derivatives. The chemist at Merck Frosst Centre developed a ring-closing metathesis method to prepare substituted quinolin-2(1H)-ones derivatives.

Figure 3

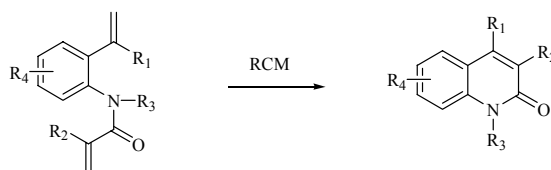
Quinolin-2(1H)-Ones in Medicinal Chemistry



Usual Ways to Prepare Quinolin-2(1H)-Ones

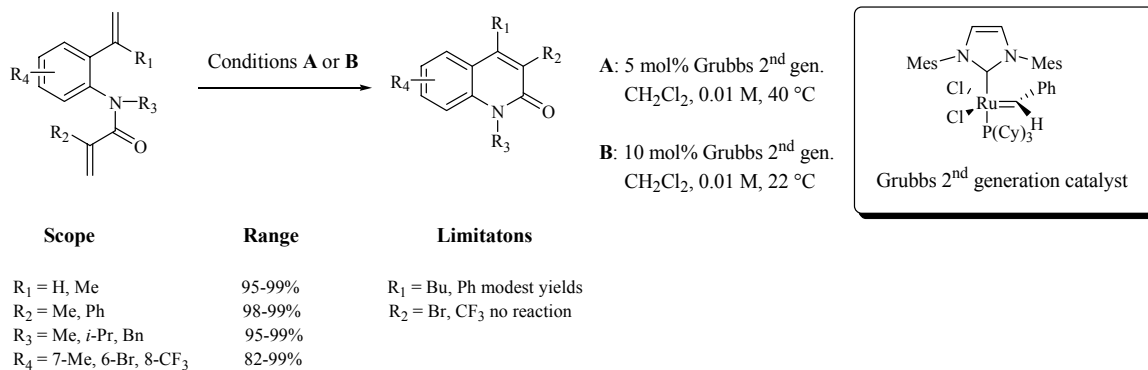


Target Quinolin-2(1H)-Ones



R₁ = H, Me, Bu, Ph, 4-Fluorophenyl
R₂ = H, Me, CF₃, Ph
R₃ = H, Me, *i*-Pr, Bn
R₄ = H, Me, Br, CF₃

Ring-Closing Metathesis Results

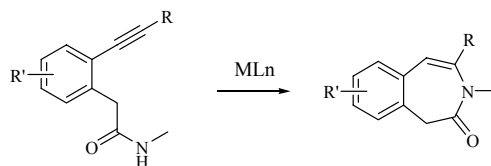


Poster: “Synthesis of Benzoazepinones and Isoquinolinones via Palladium-Catalyzed Addition of Tethered Amides to Phenyl Acetylenes,”

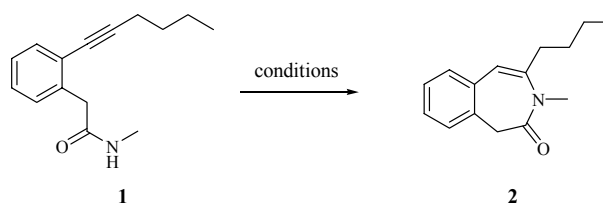
Yu, Y.; Mitchell, D. (*Eli Lilly & Co*).

Benzoazepinones are interesting structural motifs presented in some biologically active molecules. Yu and Mitchell of Eli Lilly demonstrated a general synthetic method *via* transition metal-catalyzed cyclization of alkynes (Figure 4).

Figure 4



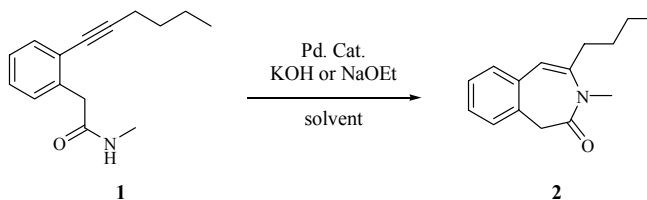
Demonstration of the Concept



Conditions	1	2	Other observation
10% Cu(OTf) ₂ , ClCH ₂ CH ₂ Cl, reflux, overnight	100%	0	
10% Cu(OAc) ₂ , ClCH ₂ CH ₂ Cl, reflux, overnight	>95%	0	Trace unidentified products
10% Cu(OAc) ₂ , K ₂ CO ₃ , THF, 55 °C, 6 h	100%	0	
5% Pd(OAc) ₂ (PPh ₃) ₂ , 1 eq. <i>t</i> -BuOK, THF, 55 °C, 5 h	0	65%	One major byproduct
5% Pd(OAc) ₂ (PPh ₃) ₂ , 2 eq. KOH, DMF, 55 °C, 16 h	Trace	82%	Trace byproducts

5% Pd(OAc) ₂ (PPh ₃) ₂ , 2 eq. NaOEt, THF, 55 °C, 3 h	0	80%	Trace byproducts
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Optimizing Conditions



Pd Catalysts:

Pd(PPh₃)₂(OAc)₂, Pd(PPh₃)₂Cl₂ and Pd(PhCN)₂Cl₂ are good (~80%);

Pd₂(dba)₃/*t*-Bu₃P and Pd₂(dba)₃/dppb are fair;

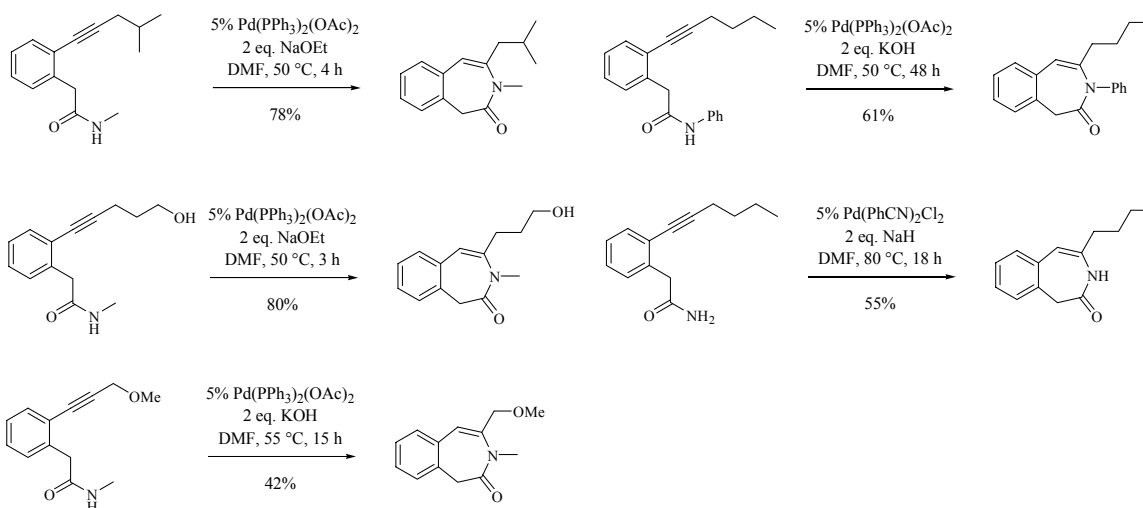
Pd₂(dba)₃/*o*-tolyl)₃P and Pd₂(dba)₃/P(OPh)₃, Pd₂(dba)₃, Pd(OAc)₂ and Pd(dppf)Cl₂ are not efficient (<50%).

Solvents:

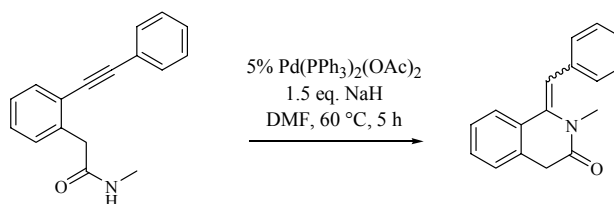
DMF and DMA are good (~10 mL/g); THF, DMSO, AcCN and toluene are not.

Heat at 50–60 °C, higher temperature led to decomposition.

Cyclization of Other *o*-Alkynyl Benzeneacetamides

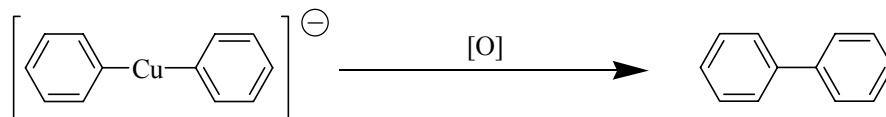


Cyclization of *o*-Phenylethynyl N-Methyl Benzeneacetamide: 6-Membered Ring Formation



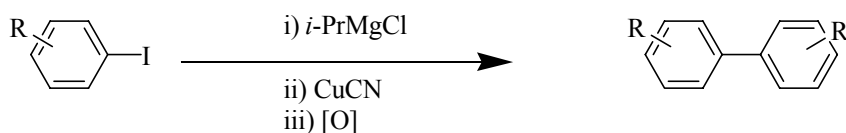
Poster: "Oxidation of Organocuprates with "Sub-Stoichiometric" Oxidant and the Synthesis of Strained Medium Rings,"*Surry, D. S.; Su, X.; Spring, D. R. (University of Cambridge).*

The oxidation of an aryl cuprate results in the formation of a biaryl bond. This reaction has been reported in the formation of both intermolecular and intramolecular biaryl bonds.



The major limitations of this reaction are poor functional group tolerance and harsh reaction conditions. The purpose of this research was the optimization of organocuprate oxidation that was achieved by employing the iodine-magnesium exchange procedure and the design of a new oxidant. Thus organocuprates are obtained by transmetalation of aryl Grignard compounds and then they are oxidised to obtain biaryl products.

The procedure proposed requires low temperature and a significant range of functional groups can be tolerated.



The oxidant appears to be crucial to the success of the reaction. A range of oxidants were examined and the best reagent was found to be the dinitrobenzene derivative **1** (Table 1). One advantage of **1** is that it can be removed easily during work-up by an aqueous acid wash and that it can be synthesised on large scale in a single step from commercially available starting materials (D. S. Surry, X. Su, D. J. Fox, V. Franckevicius, D. R. Spring, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1870).

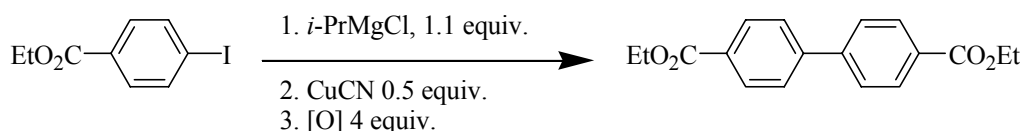
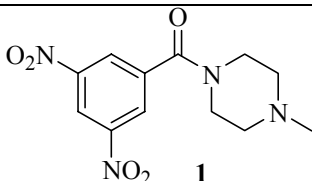
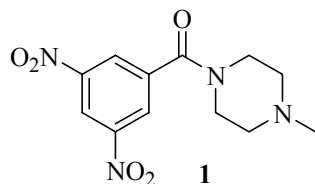


Table 1: Oxidants used in biaryl formation

Oxidant	Yield (%)
FeCl ₃	66
O ₂	48
CuCl ₂	44
CeSO ₄	26
<i>m</i> -dinitrobenzene	80
 1	79

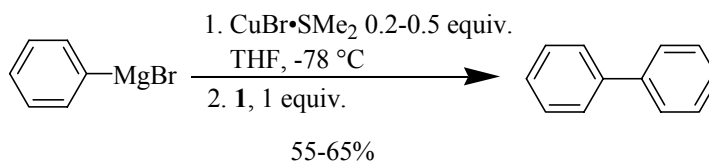
Sub-stoichiometric oxidant may be used without significant depreciation of yield:

Table 2

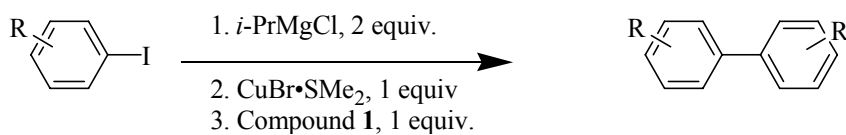
Equivalents of oxidant 1	Yield
1	79
0.2	62
0.1	31

A possible explanation of this sub-stoichiometric effect may be that the dinitroarene **1** can accept more than one electron during the oxidation process.

Also, sub-stoichiometric copper may be used in the transmetalation. No significant variation of yield was observed when CuBr•SMe₂ was used in the range between 0.2 and 0.5 equiv.



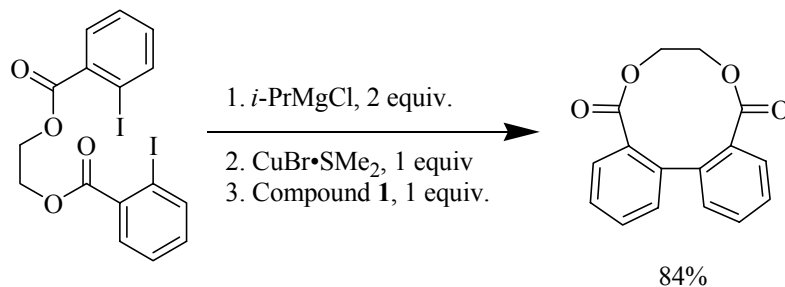
This methodology was used to the synthesis of a wide range of functionalized biaryls (Table 3).

Table 3: Biaryl formation

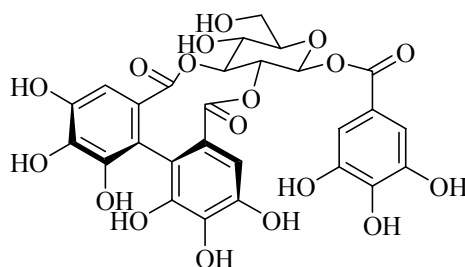
Entry	Substrate	Product	Yield
1			88
2			88
3			85
4			67
5			82
6			72
7			66
8			75

A range of substitution patterns is tolerated. This reaction can be used with iodinated heterocycles (entry 5, Table 3) and it does not seem to be influenced by steric effects (entries 1 and 2). Diiodinated aryls undergo a single iodine-magnesium exchange and this permits the preparation of iodinated biaryls (entry 6 – 8). Also, brominated biaryls can be prepared by iodine-magnesium exchange of iodo-bromo-aryls (entry 4).

This reaction can be successfully employed in the synthesis of strained medium ring compounds in good yields:



This methodology will be applied to the synthesis of the natural product sanguiin H-5.

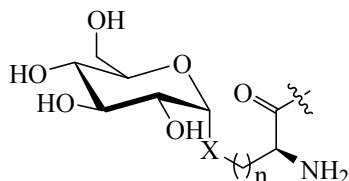


Sanguiin H-5

Poster: "Synthesis of C-Glycosyl- α -Serine and Alanine by a Cross Methathesis / Cyclization Strategy,"

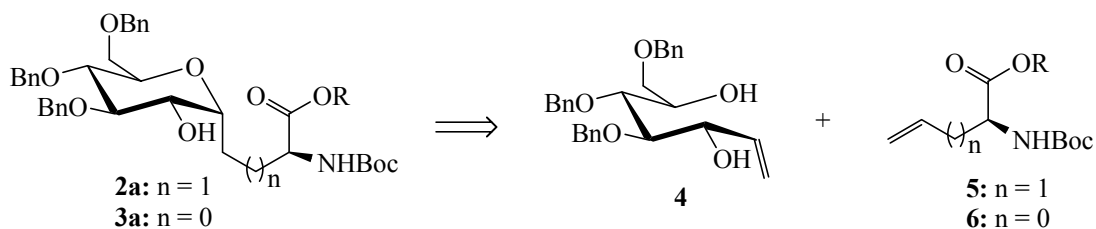
Nolen, E. G.; Kurish, A. J.; Donahue, L. (Colgate University).

C-glycosides occur when the *exo*-oxygen atom at the anomeric position is replaced by a carbon. Glycosylated proteins are of interest because the physico-chemical properties and activity of proteins are altered and the carbohydrate moiety can bind to the cell surface. The *O*-glycosylated proteins **1** have been investigated by many groups as potential therapeutic agents. The authors of this paper describe the syntheses of *C*-glycosyl amino acid mimics **2** and **3**.

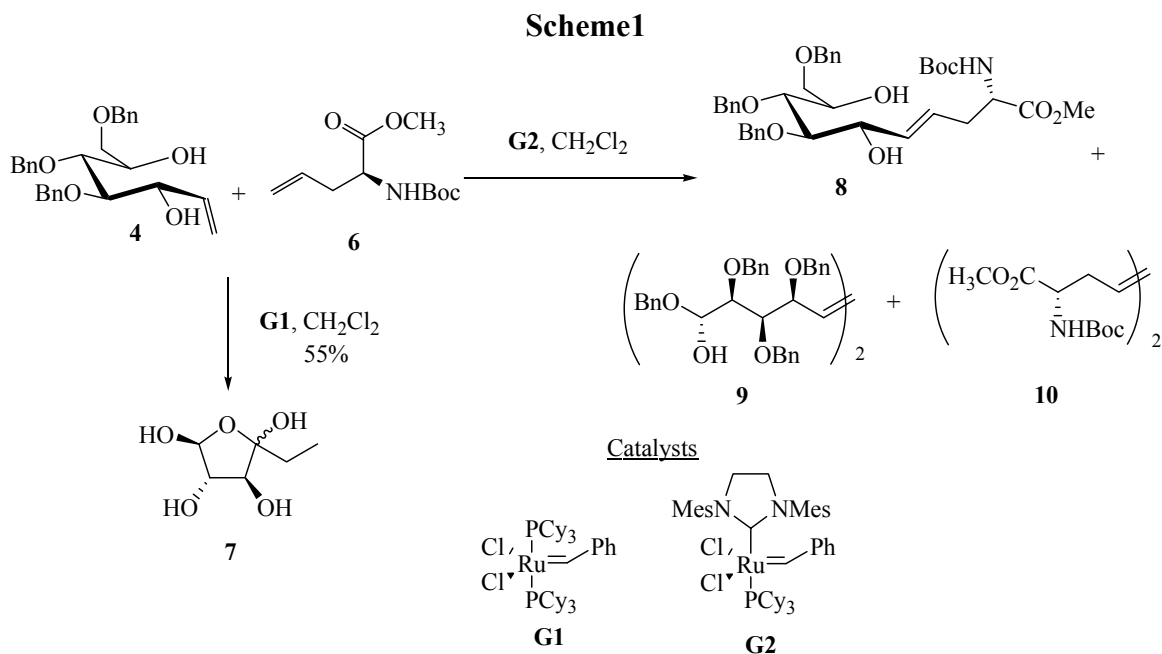


- 1:** X = O
2: X = CH₂, n = 1
3: X = CH₂, n = 0

The synthetic approach to compounds **2** and **3** is based on a cross-methathesis / cyclization strategy, inspired by earlier work by Nicotra and co-workers (Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, 53, 4181 – 4185).

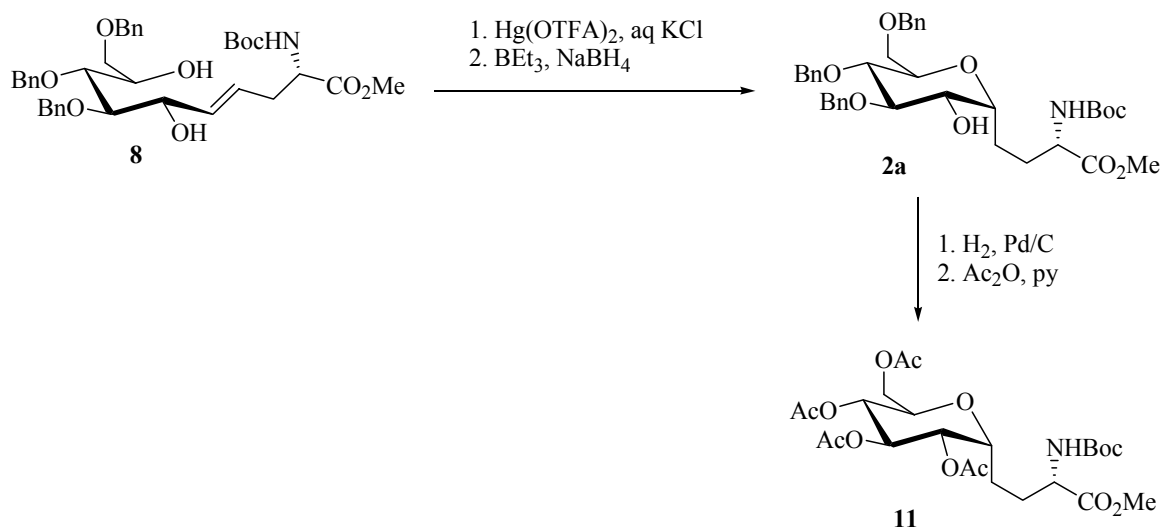


Attempts at cross metathesis of **4** with **6** (Scheme 1) using the catalyst **G1** afforded the product **7**. When the catalyst **G2** was used the result was a mixture consisting of the desired product **8** along with **9** and **10**. The dimers **9** and **10** could be recycled to the desired product **8** by treatment with the catalyst **G2**.



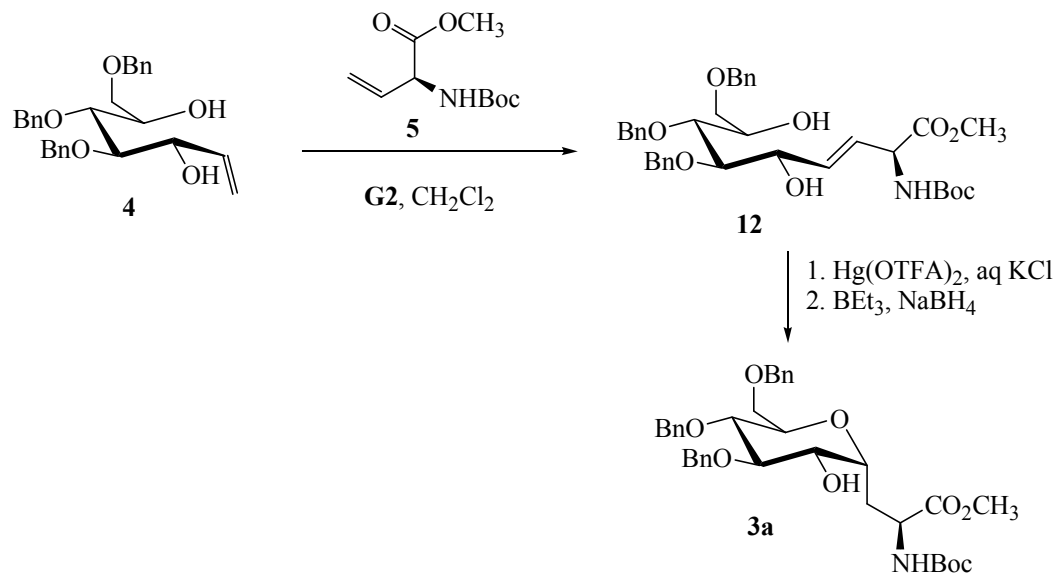
Cyclization of **8** (Scheme 2) was achieved using $Hg(OTFA)_2$ (Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59-62). Only the α -anomer was obtained, with no trace of the β isomer. The compound **11** was then obtained via hydrogenolysis of **2a** followed by acetylation. Comparison of the NMR of **11** with the data of the same compound previously reported (Nolen, E. G.; Watts, M. M.; Fowler, D. J. *Org. Lett.* **2002**, *4*, 3963-3965) confirmed the assignment of the α -configuration at the anomeric center.

Scheme 2



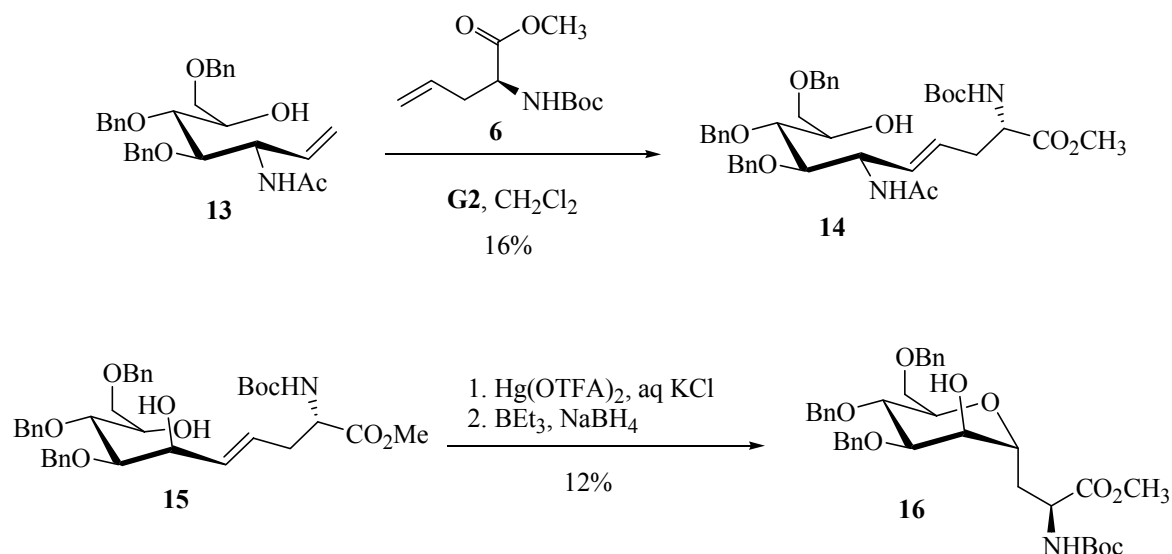
The same procedure was applied to the synthesis of the chain-shortened α -C-glycosyl alanine **3a** (scheme 3) via cross metathesis between **4** and **5** followed by cyclization of **12**. In this case the product **3a** was a 7.5:1 mixture of α and β anomers.

Scheme 3



When this procedure was applied to *N*-acetyl glucose **13** (Scheme 4) the cross metathesis reaction gave **14** with only 16% yield. The cyclization reaction in the mannose series also proceeded with an unsatisfactory yield (12%) for the cyclization of **15** to **16**.

Scheme 4

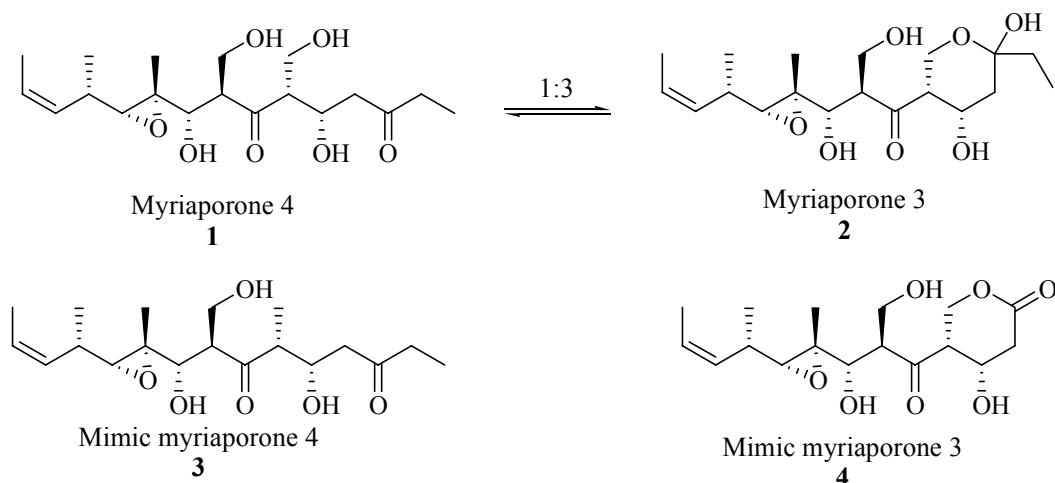
**Poster: "Structure-Activity Relationship Study of Myriaporones,"**

Roy, M.; Cheng, H.; Taylor, R. E. (University of Notre Dame).

Myriaporones are natural products isolated in 1995 and closely related to tedanolide, a cytotoxic compound that displays high potency against lymphocytic leukemia and human nasopharynx carcinoma. Myriaporones also exhibit interesting cytotoxicities with IC_{50} in the nanomolar range for several cancer lines.

These compounds exist as an equilibrium of an open form (myriaporone **4**, **1**) and a closed form (myriaporone **3**, **2**).

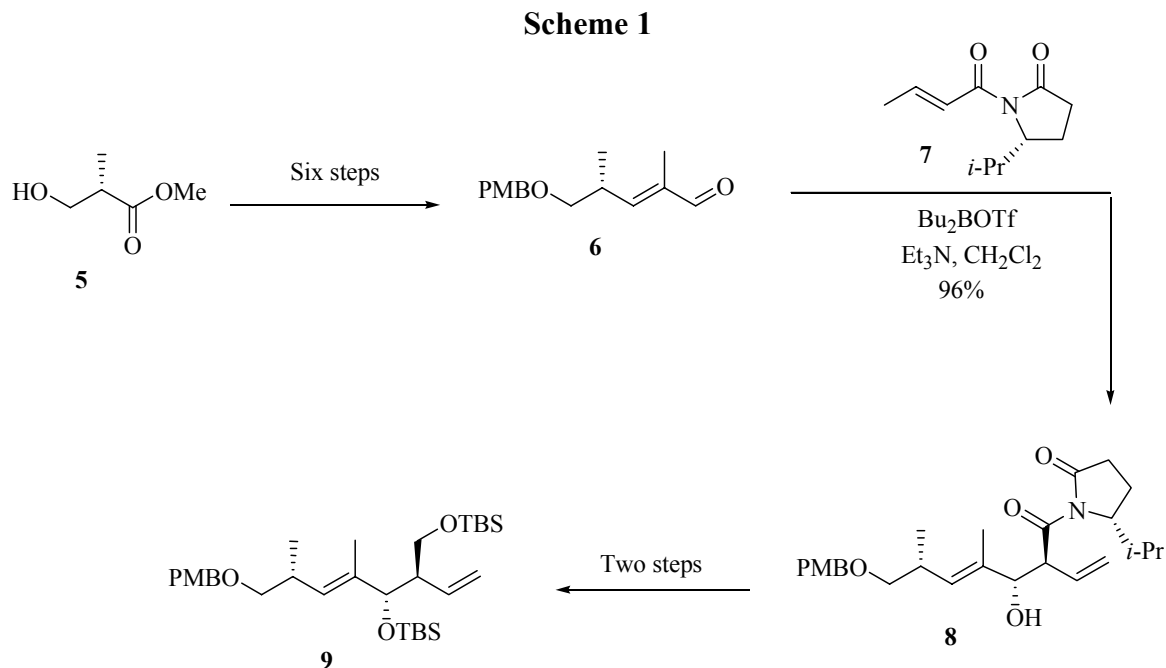
The purpose of this research project was to identify the role of each form of the equilibrium by synthesizing the two analogues **3** and **4** with locked conformation. Other analogues were also prepared to extend the SAR.



In compound **3** one of the primary hydroxyl groups present in compound **1** was removed in order to prevent the formation of the hemiacetal **2** and to lock the mimic myriaporone in the open form.

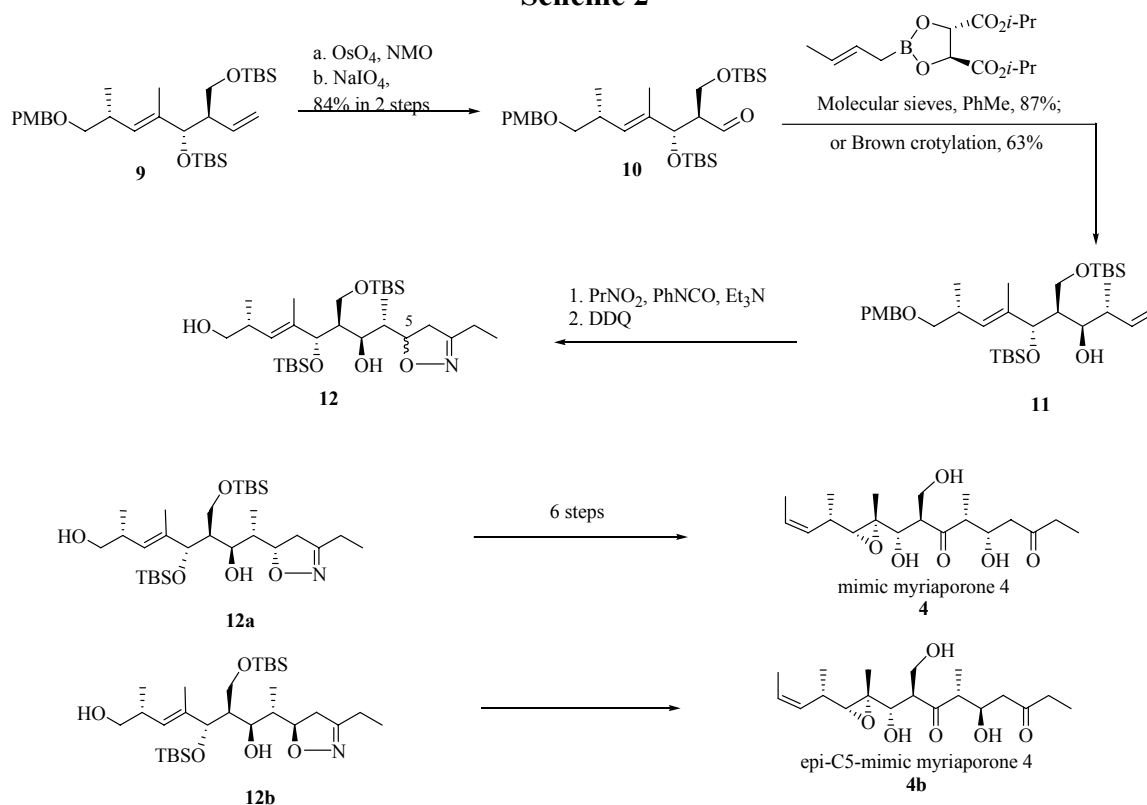
To lock the myriaporone in the closed form the hemiacetal in **3** was replaced by a lactone in **4**.

The starting material **5** was converted to **6** in six steps (Scheme 1). Evans' aldol condensation of the aldehyde **6** with **7** led to the formation of a single diastereomer **8** that was converted to **9** in two steps.



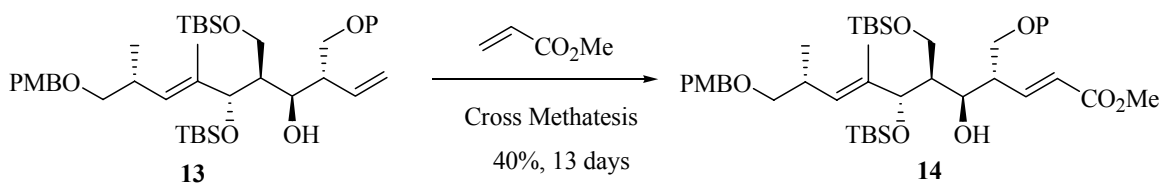
The completion of the synthesis involved the Roush crotylation to obtain **11** and the separation of the two diastereomers **12** that were carried on separately to obtain the mimic myriaporone **4**, **4** and its epimer at C-5 **4b** (Scheme 2).

Scheme 2



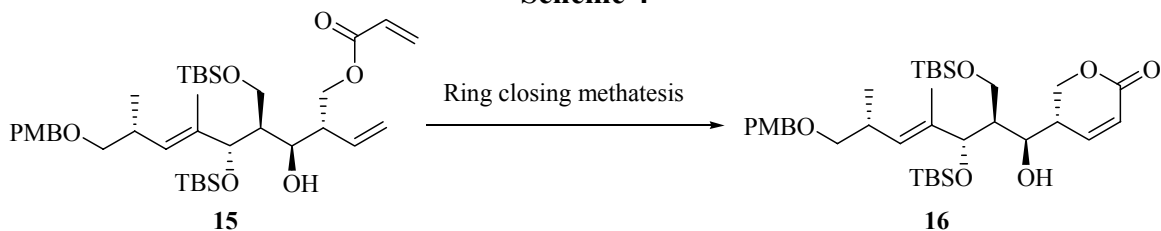
The synthesis of the closed form of mimic myriaporone 3 is currently under investigation. The key step, involving a cross metathesis of **13** (Scheme 3), was sluggish and with low yield, so alternative approaches are being explored.

Scheme 3



A promising result was achieved via ring closing metathesis of the advanced intermediate **15** (Scheme 4). The completion of the synthesis of the mimic myriaporone 3 is in progress.

Scheme 4



The compounds prepared, along with other analogues of myriaporone, were tested against several cancer cell lines. The natural myriaporone was the most active. The unnatural epimers at C5 were

inactive. Analogs that are missing the epoxide function were found to be inactive. This supports the hypothesis that the biological activity of these compounds depends on the binding to the receptor via a covalent bond formed by the epoxide. The reduced activity of mimic myriaporone 4 suggests that the active form of the myriaporone is the closed form.