Senior Scientist Mentor Program

Institution	Awardee	Department	Area of Interest
2008			
California Institute of Technology	John D. Roberts	Chemistry and Chemical Engineering	Our studies of conformational analysis, mostly involve 1,2-disubstitued ethanes, with the aid of NMR spectroscopy. In a departure from the past, we have investigated a wide range of protic and aprotic solvents. The emphasis has been on the interplay of different kinds of substituents between steric hindrance, polar, electrostatic, hydrogen bonding, solvent, and â≠œgauche" effects. Planned work is a deep study of histidine, histamine, (4-imidazole)-3-propanoic acid, the cis-and transurocanic acids.
Columbia University in the City of New York	Koji Nakanishi	Chemistry	Half the drugs handled by the pharmaceutical industry exert their activities through G-protein coupled receptor (GPCR). Upon light activation, the visual pigment rhodopsin, a protopypcial GPCR, undergoes changes through batho-, lumi-, meta-I and meta-II rhodopsin. Using a photoaffinity labeled undecapeptidic fragment of the G-protein, we recently clarified the contact point between this peptide and meta-II rhodopsin, in which the pigment has just left the lipid bilayer. We plan to clarify contact points in other intermediates.
James Madison University	Benjamin A. DeGraff	Chemistry	The project involves the design, synthesis, characterization, and evaluation of luminescent transition metal complexes which can serve as molecular reporters. The luminescent behavior of suitable complexes can be altered by interaction with the local microenvironment and "reported" by changes in luminescent intensity, color distribution, and/or lifetime. Applications range from detecting lead in drinking water to monitoring oxygen levels and pH in growing tumors. Mentored students receive training in synthesis, molecular structure determination using multiple techniques, and evaluation of reporter characteristics using modern photophysics.
Michigan State University	James L. Dye	Chemistry	Alkali metals and alloys added to silica gel or alumina gel form powders that retain the reducing ability of the parent metals. Some can be made non-pyrophoric by appropriate heat treatment. These materials permit a wide variety of batch or column reduction reactions such a Birch reductions, Wurtz coupling, desulfurization, deprotection, etc. Undergraduates learn various inert atmosphere synthesis and characterization techniques, while producing cutting-edge, publishable research that is of significant interest to industry.

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New York University	Jules W. Moskowitz	Chemistry	We propose a rigorous theoretical study of the quantum translation-rotation (T-R) dynamics of a methane molecule confined inside both the small and medium cages of the sII clathrate hydrate. All three translational and the three rotational degrees of freedom of the methane molecule will be included explicitly, as fully coupled, while the cage is treated as rigid. The energy levels will be assigned translational and rotational quantum numbers and compared to experimental spectroscopic (INS and IXS) results.
Purdue University	Ronald P. Andres	Chemical Engineering	The aim of this project is to develop a nanoparticle based technology for fabrication of low cost, low volume, low weight capacitors for electric energy storage.
Seattle University	John E. Meany	Chemistry	The project director proposes to mentor approximately 4 undergraduate research students per year in the chemistry department at Seattle University. The group of research projects chosen for the present proposal includes kinetic and thermodynamic studies of important chemical and biochemical reactions. Some of the enzymes chosen for study are involved in certain disease states such as glaucoma, epilepsy and cancer (carbonic anhydrase), Alzheimerâ≠™s (acetylcholinesterase) and fetal alcohol syndrome (alcohol dehydrogenase), while the studies proposed for other chemical and enzymatic reactions are aimed at delineating the steric and electronic characteristics of enzyme active sites.
Syracuse University	Donald C. Dittmer	Chemistry	Non-toxic, recoverable elemental tellurium is used in a new variation of the synthesis of the biologically important tetramic acids and also in expediting the anionic oxy-Cope rearrangement. Advantages of the tellurium procedure are (1) minimization of racemization of the key stereogenic center in tetramic acids derived from an Î±-amino acid and (2) the streamlining of the anionic oxy-Cope rearrangement to a one-step process from telluride ion and a p-toluenesulfonate ester of a chiral oxiranemethanol.

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Texas A&M University	John P. Fackler, Jr.	Chemistry	Over the past few years our work with gold and other Group 11 compounds has focused on the synthesis, structural characterization and physical properties of new materials. Ligands with nitrogen coordination have been found to lead to excellent precursors for the formation of catalytically active nanoparticle for oxidation of CO at room temperature and atmospheric pressure. The photophysical and oxidative properties of these complexes also have produced unique results. The shortest Au-Au bonds have been observed with guanidinate complexes produced upon oxidation to Au(II). This project attempts to generalize the synthetic and physical properties of nitrogen ligand complexes of gold, expanding on the knowledge gained from amidinate and guanidinate studies to date. New luminescent materials will be synthesized and characterized. Further expansion of our knowledge regarding the formation of mixed metal clusters will be developed.
The University of Vermont	A. Paul Krapcho	Chemistry	Telomerase is an enzyme found in many tumor cells and is necessary to restore telomeres (chromosome ends) to promote the uncontrolled growth and immortality of these cells. Telomeres are guanine (G) rich and fold to form G-quadruplexes. Telomerase can only replicate the DNA strand in its open form. The goal of the research is a continuation of a study to synthesize molecules related to macrocyclic bis-1,10-phenanthrolines which will stabilize the G-quadruplexes by binding and inhibit the function of telomerase. This should lead to the suppression of the tumor growth and hopefully eradicate the cancer.
University of California, Berkeley	Andrew Streitwieser	Chemistry	My experimental research has provided aggregation equilibrium constants and reactivities of a number of lithium and cesium enolates and related polymetallated species in ethereal solvents. The present project is to develop quantitative computational models of these results that can be extrapolated generally to other compounds. The role of solvation will be explored by continuum models as well as by coordination of solvent with the alkali cation.
University of California Los Angeles	Verne N. Schumaker	Chemistry and Biochemistry	We believe that we have developed a series of methods to analyze human and mouse HDL into discrete components, and to analyze these in detail to yield two to six human components, including the prebeta HDL. Moreover, we can isolate the "Heinecke" proteins (the 48 protein which are bound to the HDL. J Clin Invest 117:746-756 2007.) And we can resolve the pressure problem, which confuses the centrifugal isolation of HDL.

Senior Scientist Mentor Program

Institution	Awardee	Department	Area of Interest
University of Florida	David A. Micha	Chemistry	Undergraduate students will apply practical computational approaches to the calculation of optical properties of semiconductor surfaces, including nanostructured adsorbates, needed for identification of materials useful in the capture of solar energy. Research work will be based on available computational chemistry software including semiempirical electronic structure programs and density functional methods suitable for solid state chemistry applications, to be used to identify the conformations of structures of interest, and to calculate their excitation energies in the range of visible light as well as oscillator strengths and transition dipoles. Systems of interest are surfaces of Si and SiO2 semiconductors, first with adsorbed H for comparisons with experimental data, and next with adsorbed lattices of metal clusters on the surfaces, to discover novel properties. A study will also be initiated of p- and n-doped Si compounds. The subject is very relevant to development of photovoltaic solar cells and production of fuels by hotoelectrochemical means. Computational treatments are missing in these very important
2007			
Clemson University	John W. Huffman	Chemistry	The research is a continuation of our program that has developed a number of indole based cannabinoid receptor ligands. The compounds are synthesized from commercially available indoles, an acid chloride and an alkyl halide using established synthetic procedures. Pharmacology is be carried out by our collaborators at the Virginia Commonwealth University.
Cornell University	Jerrold Meinwald	Chemistry & Chemical Biology	There are ~ 40,000 described spider species, and it is thought that they all produce venoms capable of paralyzing their prey. Although many venoms have been studied chemically, it was only during our Cornell research that a neuroactive sulfated nucleoside derivative was characterized and synthesized. Direct NMR-analysis of spider venoms now reveals that sulfated nucleosides, previously undetected, occur frequently. We will use NMR techniques to characterize new venom constituents, and synthesize the most important compounds for biological study.
Duquesne University	Omar Steward	Chemistry & Biochemistry	The resources from this grant will enable undergraduate students to study in the area of structural inorganic chemistry under my direction. The research project is designed to introduce undergraduate students to the challenge of tailoring the synthesis and determining the structures of coordination polymers. Extensive use of X-ray diffraction techniques are required to investigate the use of ligand steric effects to control the polymer geometry and the arrangement of metal centers in bimetallic coordination polymers.

Senior Scientist Mentor Program

Institution	Awardee	Department	Area of Interest
Lafayette College	Joseph A. Sherma	Chemistry	The Senior Scientist Mentor and his students will use high performance thin-layer chromatography (HPTLC) techniques to determine the differences in the amounts of various compound classes in the feces and urine of mice experimentally infected with the intestinal trematode Echinostoma caproni. The HPTLC method, which could be easily adapted for use with humans, would be simpler and faster than the cumbersome technique of fecal examination presently used to detect trematode eggs in host stool.
New York University	David Schuster	Chemistry	For the past ten years, the Schuster lab has studied the synthesis and photophysics of [60]fullerene-porphyrin hybrid materials which function as artificial photosynthetic reaction centers. Upon exposure to light in the visible region, these materials undergo extremely rapid intramolecular energy and electron transfer processes to produce very long lived charge separated states. New examples of such materials with unusual molecular architectures are envisaged, building on work carried out with the participation of undergraduate research students. The photophysical studies on very short time scales are done in collaboration with scientists at other institution. A second set of studies involved fullerene derivatives which act as nontoxic inhibitors of HIV protease, again building on prior studies with strong undergraduate participation.
Oberlin College	Norman Craig	Department of Chemistry and Biochemistry	A combined spectroscopic-quantum chemical method is used to determine equilibrium structures accurate to 0.001 ‡ for small molecules. The high accuracy of these structures reveals for the first time subtle structural consequences of electronic effect. A recent example is the demonstration that pi-electron delocalization in butadiene is evident in legthened “double” bonds and a shortened “single” bond. New systems proposed for study are cis- and trans-hexatriene, the three isomers of 1,4-difluorobutadiene, 1,1-difluorocyclopropane, and 1,1-difluorothylene. In the hexatrienes we expect to find bigger structural effects of pi-electron delocalization than in butadiene. the other systems will show the impact of fluorine substitution on structures.
San Jose State University	Juana Acrivos	Chemistry	The structural chemistry involved in the insulator to metal phase transitions in low dimensional solids is investigated by spectroscopic and computational methods. Presence of transverse periodic lattice distortions in YBa2Cu3O7-d, YBCO along the a-b plane diagonal and the effect of X-ray flux on the phases in YBCO 50nm films gives evidence for excitations leading to activated state complex: X-Ray photoms(hv)+YBCO =>Xfi and YBCO(metal) <=>Xfi<=>YBCO(insulator), promising to explain the details of the phase transition to superconductivity.

Senior Scientist Mentor Program

Institution	Awardee	Department	Area of Interest
University of Pittsburgh	Theodore Cohen	Chemistry	The project involves undergraduate participation in exploiting recently discovered techniques of greatly generalizing cyclizations by intramolecular carbometallations of unactivated or weakly activated alkenes. Key features are the ability to convert readily available alkyl or allyl phenyl sulfides or sulfones into alkyllithiums or allylzincs and the highly diastereoselective reduction of esters by DIBAL. Biologically important natural products are being synthesized. The senior mentor will be heavily involved, on a daily basis, with the undergraduate researchers.
2006			
California Institute of Technology	John D. Roberts	Chemistry and Chemical Engineering	Support is sought for continuation of research involving a summer program of ten weeks involving 4-7 undergraduates on conformational analysis by NMR of 1,2-substituted ethanes and 1,3-disubstituted propanes. The program involves undergraduate students from the United States and abroad. Each student is assigned an individual compound for study, chosen to give previously unknown and unpredictable results. Throughout the years of our study in this arena, new and surprising results are very often encountered.
James Madison University	Benjamin A. DeGraff	Chemistry	The project involves the design, synthesis, characterization, and evaluation of luminescent transition metal complexes which can serve as molecular reporters. The luminescent behavior of suitable complexes is altered by interaction with the microenvironment and "reported" by changes in luminescent intensity, color distribution, and/or lifetime. These materials find applications as diverse as monitoring the blood oxygen level in cardiac care patients to tracking the pH of the water in fish farms. The students involved receive training in synthesis, establishing molecular structure by several types of spectroscopy, and evaluation of reporter suitablity using a variety of modern techniques.
Michigan State University	James L. Dye	Chemistry	Alkali metals added to silica gel or other nanoporous oxides form "sequestered alkali metals" that are as reducing as the parent metals or alloys, but much safer and easier to handle. Undergraduates would work with the Senior Scientist to prepare and study these materials. Techniques would include glovebox and vacuum line use, NMR analysis, DSC and computer graphics. Other possible methods include magnetic susceptibility, solid state NMR and EPR, electron microscopy, conductivity, XPS and XRD.

Senior Scientist Mentor Program

Institution	Awardee	Department	Area of Interest
Oregon State University	Joseph W. Nibler	Chemistry	This project will involve student participation in the synthesis and spectroscopic analysis of several unusual molecules. These are the quasi-linear molecule C3O2, the reactive molecule SO3, and the "pinwheel" molecule B(OH)3. Students will obtain laboratory experience with gas phase vibrational-rotational spectroscopy at state-of-the-art resolution (0.0015 cm-1). The molecules to be studied have sufficiently high symmetry that detailed theoretical analysis will be feasible, leading to accurate molecular parameters such as bond lengths and vibrational frequencies.
Purdue University	Jurgen M. Honig	Chemistry	Proposed to investigate consequences of building into current thermodynamic theory of phase transitions the effects of assigning two comonents of a binary mixture two different interaction energies. Also, x-ray investigations are planned to study vanadium sequioxide.
Rice University	Robert Curl	Chemistry	Exploratory research aimed at developing a method for simultaneously determining many genetic anomalies, primarily SNPs, without amplification of the genetic material through whole-chip imaging. The chip is to be covered with thousands of primer features with each feature containing ~100000 primers complementary to the region just before a SNP location. Terminating bases labeled with four different dyes and polymerase add a single labeled base to the primer. Four lasers of different wavelengths matching the dyes read the whole chip's fluorescence at once.
Stanford University	James Collman	Chemistry	Using self-assembled monolayers (SAMs) and covalently attached functional-synthetic models of the active site in cytochrome c oxidase (CcO) the catalytic reduction of dioxygen will be studied under conditions of rate-limiting electron transfer. These conditions are involved in the steady-state turnover of CcO during respiration. The selectivity and turnover number will be evaluated as a function of the rate of electron transfer.
The University of Chicago	Stuart A. Rice	Chemistry/PSD	Support is requested for experimental studies of confined quasi-one-dimensional (q-1D) and quasi-two-dimensional (q-2D) colloid suspensions. The research proposed will examine several structural and dynamic properties of q-2D and q-1D systems, and the nature of the changes in those properties as the degree of confinement of the system changes, thereby testing some of the many predictions that, as a generic class of materials, two-dimensional and one-dimensional matter have unusual properties.

Senior Scientist Mentor Program

Institution	Awardee	Department	Area of Interest
The University of Chicago	R. Stephen Berry	Chemistry	Atomic valence electrons correlate so strongly that, in alkaline earth atoms, their properties are better described by a molecule-like, rotor-vibrator model than by the traditional independent-particle orbital model. This project has two goals: quantifying the validity of various models from the variances, from accurate calculations, of quantities that are precise constants of motion in specific simple models, and determining the extent and nature of valence shell correlation in atoms with three and four valence electrons.
The University of Wisconsin-Madison	Julius Adler	Biochemistry	Undergraduates will contribute to Julius Adler's further research on the biochemistry of the Drosophila brain. How vision and smell are integrated is the primary subject. This will be studied by biochemical methods, along with molecular genetics. The outcome will provide new information about the mechanism of an animal's response to stimuli.
University of Arizona	Michael A. Wells	Biochemistry & Molecular Biophysics	We will investigate the use of stable isotopes and mass spectrometry to study carbohydrate metabolic rates in mosquitoes. Trehalose containing 13C in specific carbons will be prepared biologically. These molecules will be used to determine the fragmentation patterns of trehalose in order to find the most useful ions to characterize metabolism. Then mosquitoes will be fed [2-13C] - glucose and the labeling pattern in trehalose will be used to measure the rate of the pentose phosphate pathway.
University of Washington, Seattle	Bruce A. Finlayson	Chemical Engineering	Undergraduates will perform research in computational fluid dynamics on problems of interest in microfluidics, problems with graduate students in bioengineering, and problems jointly with industrial firms. The computer program FEMLAB (now Comsol Multiphysics) will be used to solve two- and three-dimensional flow and diffusion problems. This computer program has allowed undergraduates to be creative and solve problems much more difficult than those in their textbooks. Students who perform these projects gain a deeper understanding of transport processes and confidence as problem-solving engineers, but they also receive cross cutting experiences in important professional skills like teamwork and communication. The Senior Scientist Mentor Program would continue the success in which students bring enthusiasm and energy to problems they don't know 'can't be solved'.
Wake Forest University	George Holzwarth	Physics	The maximum force generated by 1 kinesin motor protein molecule in vitro is 7 pN. There is indirect evidence that in cells, several kinesin motors need to cooperate to move a single vesicle, because the drag force that must be overcome is 5-40 pN. We will measure velocity-force curves for 2, 3, or 4 kinesin motors pulling a single load in vitro against a carefully measured viscous or magnetic force.

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Institution	Awardee	Department	Area of Interest
2005			
Cornell University	Harold A. Scheraga	Chemistry and Chemical Biology	We will determine the intramolecular interactions that dictate the regeneration of RNase A from the reduced form. Mutants of RNase A will be used to investigate the interaction between residues in the native state, and to develop a general model to explain the oxidative folding of multi-disulfide-containing proteins. Furthermore, in vivo protein folding will be addressed by investigating the mechanism by which the oxidoreductase protein disulfide isomerase catalyzes the formation of native disulfide bonds in the protein.
Oberlin College	Norman C. Craig	Chemistry	A combined spectroscopic-quantum chemical method is used to obtain equilibrium structures for interesting small molecules, such as butadiene, the three isomers of 1,4-difluorobutadiene, and the two isomers of hexatriene. Ground state rotational constants for a variety of isotopomers are obtained from microwave spectroscopy for polar molecules or from the rotational structure in high-resolution infrared spectra for nonpolar molecules. The ground state rotational constants are "corrected" to vibration-free equilibrium rotational constants with vibration-rotation constants computed with high-level quantum chemical methods. Equilibrium structures are then fit to the equilibrium rotational constants. These combined spectroscopic-QC equilibrium structures reveal fine adjustments in bond lengths and bond angles, which should correlate with electronic effects such as partial pi-electron delocalization and the effects of fluorine substitution. Equilibrium structures may be used to evaluate structures computed by QC methods alone.
Purdue University	Ronald P. Andres	Chemical Engineering	The aims of this project are to: 1) attach folic acid to novel magnetic nanoparticles synthesized for the first time at Purdue University, 2) measure the uptake of these particles by cancer cells via folate receptor-mediated endocytosis, 3) determine the optimum conditions for MRI imaging of cancer cells that have been exposed to folate conjugated magnetic nanoparticles, and 4) determine the time-dependent viability of cancer cells treated with resonant microwave radiation after exposure to folate conjugated magnetic nanoparticles.
The University of Texas at Austin	James E. Boggs	Chemistry and Biochemistry	Support will be used to enable two undergraduate students per year to join an active research program and become involved in computational chemistry directed either toward predicting the thermochemistry of free radical intermediates in atmospheric and combustion chemistry or toward understanding the role of vibronic interactions in determining the chemistry of transition metal compounds. Students will be directed from simple systems into the complexities at the forefront of modern theoretical research.

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Institution	Awardee	Department	Area of Interest
University of Pittsburgh	Theodore Cohen	Chemistry	The project will involve undergraduate participation in the exploitation of recently discovered techniques of greatly generalizing cyclizations by intramolecular carbometallations of unactivated or weakly activated alkenes or of carbonyl groups. A key feature is the ability to convert readily available allyl phenyl sulfides or sulfones to allylmetals. Biologically important natural products will be synthesized. The senior mentor will be heavily involved, on a daily basis, with the undergraduate researcher.
University of Rochester	Esther M. Conwell	Chemistry	A basic question still undecided is whether the wavefunction of an exciton or excess electron or hole on the base stack of DNA is localized on a single base or delocalized over a number of bases. The argument vs. delocalization is that the bases are weakly coupled and subject to strong thermal vibrations. To aid in resolving this question we propose further calculations of the delocalized wavefunctions and comparison with experiment.
University of Vermont	A. Paul Krapcho	Chemistry	Telomerase is an enzyme which is able to restore telomeres and has been found in over 90% of tumor cell lines. Telomerase in tumors promotes the uncontrolled growth and immortality of these cells. Telomers are rich in guanine(G) and fold back on themselves to form G-tetrads. We wish to design and synthesize molecules that will stabilize the G-quadruplex and inhibit the function of telomerase.
2004			
California Institute of Technology	John D. Roberts	Chemistry and Chemical Engineering	Even after some 20 years of investigations, involving some 86 undergraduate summer students, on hydrogen bonding, electrostatic, polar "gauche" effects, we are still finding very unexpected perturbations of conformational equilibria of 1,2-disubstituted ethanes and 1,2, 3-trisubstituted propanes. The results are most interesting in non-polar solvents and we now have multiple examples where two negative substituents prefer to be close together, rather than assuming positions as far apart as possible. Naturally, we wish to continue this research.
Harvard University	Dudley R. Herschbach	Chemistry and Chemical Biology	Undergraduates may chose to pursue either of two projects, both striving to develop and exemplify new research tools that will have broad application: (1) Experimental means to generate beams of ultracold molecules and manipulate their trajectories, in order to study collision dynamics of "nanomatter waves" having deBroglie wavelengths of 1 to 100 nm; or (2) A computer model for enzyme catalysis of DNA replication, including response to tension applied to the DNA template strand.

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Institution	Awardee	Department	Area of Interest
Harvard University	William Klemperer	Chemistry and Chemical Biology	The determination of intermolecular interactions is made quantitative by the spectroscopic measurement of the structure of molecular complexes.. We study hydrogen bonding by laser induced fluorescence of the v=3 and 4 levels of hydrogen fluoride in complexes previously characterized at the v=1 level complexes. The research provides the vibrational dependence of interaction energy and predissociation lifetime. This may be analyzed in terms of the dependence of hydrogen bonding upon the H-F internuclear distance.
Lafayette College	Joseph A. Sherma	Chemistry	Neutral lipids and phospholipids will be analyzed in Helix pomatia, the edible terrestrial snail used for escargot, and the medically important leech Hirudo medicinalis. The data obtained will be of value in assessing the nutritive value of H. pomatia and in better understanding the chemical composition of the active anticoagulant (hirudin) present in the saliva of the leech. Sample preparation and quantitative high performance thin layer chromatography (HPTLC) methods we have previously developed for identification and quantification of lipids in Biomphalaria glabrata and Helisoma trivolvis snails will be modified and validated in order to carry out analyses of these invertebrates. As time permits after completing the lipid studies, the following additional research will be carried out on these samples: (1) HPTLC methods will be developed and used to qualitatively and quantitatively characterize the fat-soluble chloroplast pigments, amino acids, and carbohydrates, and (2) inductively coupled plasma-atomic emission spectrometry and atomic absorption spectrometry methods will be developed and
San Jose State University	Juana V. Acrivos	Chemistry	Research on the solid state properties and the possible applications of layer materials, especially organic conductors, superconducting cuprates and nano-films of the latter are to be carried out by two undergraduates working at San José State University and traveling to synchrotron sources to measure their X-Ray diffraction and absorption spectra with the PI. The work will involve molecular orbital computations to understand the effects discovered under the support of the 2002 grant.
University of Wisconsin-Madison	Julius Adler	Biochemistry	Undergraduates will contribute to Julius Adler's research on the roles of calcium ions, sodium ions, and potassium ions in the chemotaxis of Escherichia coli bacteria. This will be studied by biochemical methods, and molecular genetics will also be used. The outcome will provide new information about the mechanism of bacterial chemotaxis. In addition, undergraduates will contribute to Adler's research on the biochemistry of the Drosophila brain.

Senior Scientist Mentor Program

Institution	Awardee	Department	Area of Interest
Washington State University	Roger D. Willett	Chemistry	The synthesis, crystal growth and characterization of novel low dimensional magnetic systems will be pursued. Emphasis will predominantly be placed on chain systems with competing ferromagnetic and antiferromagnetic interactions. Techniques employed will include single crystal diffraction, spectroscopic techniques and magnetic studies.
Williams College	J. Hodge Markgraf	Chemistry	A new synthetic route to sampangine alkaloids is proposed that affords these tetracyclic structures in three steps from 2,7-naphthyridine via formation and rearrangement of Reissert compounds, followed by radical aryl-aryl coupling. The incorporation of a variety of ring-D components is readily accommodated. This pathway avoids the regioselective ambiguities associated with the cycloaddition step in all previous methods.