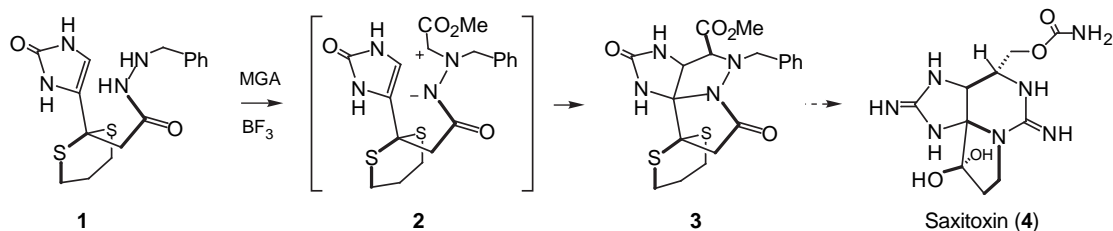


Jacobi Group Projects

I. Cycloaddition Reactions. Cycloaddition chemistry is an area of longstanding interest in the group, especially as applied to natural product synthesis. A number of examples are summarized below.

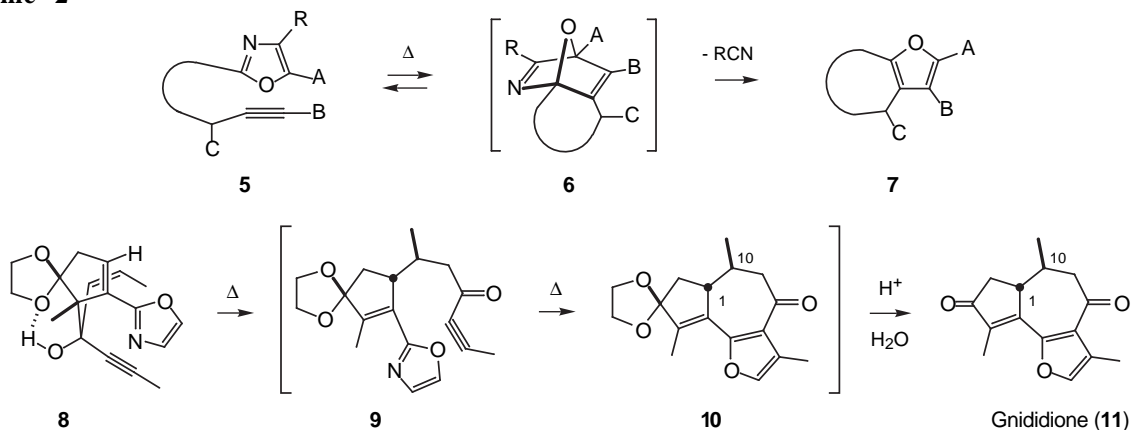
For a synthesis of Saxitoxin (**4**) we employed an azomethine imine cyclization in the pivotal ring-forming step (Scheme 1).¹ The reactive 1,3-dipolar species **2** was generated *in situ* by condensation of hydrazide **1** with methyl glyoxalate hemiacetal (MGA). Without isolation, **2** underwent ($4\pi + 2\pi$)-cycloaddition to afford the tricyclic pyrazoline **3**, which contains many of the structural features found in **4**. After functional group elaboration, the perhydropurine skeleton of **4** was completed by reductive cleavage of the pyrazoline N-N bond followed by pyrimidine ring cyclization.

Scheme 1



In carbocyclic chemistry we have made extensive use of intramolecular alkyne-oxazole cycloadditions of type **5** \rightarrow **6** (Scheme 2).² Diels-Alder adducts **6** are generally not stable and suffer rapid loss of RCN to give furans **7**. This methodology is well suited for synthesizing fused-ring furan derivatives and it can frequently be employed as part of a reaction "cascade." An interesting example is provided in our synthesis of Gnididione (**11**), where the stereochemical relationship between C-1 and C-10 was established by a chemoselective oxy-Cope rearrangement (**8** \rightarrow **9**). Once formed, alkyne-oxazole **9** underwent spontaneous Diels-Alder cyclization and loss of HCN to give furanoguaiane **10** in a single step. Simple ketal hydrolysis then afforded **11** in >60% overall yield.²

Scheme 2



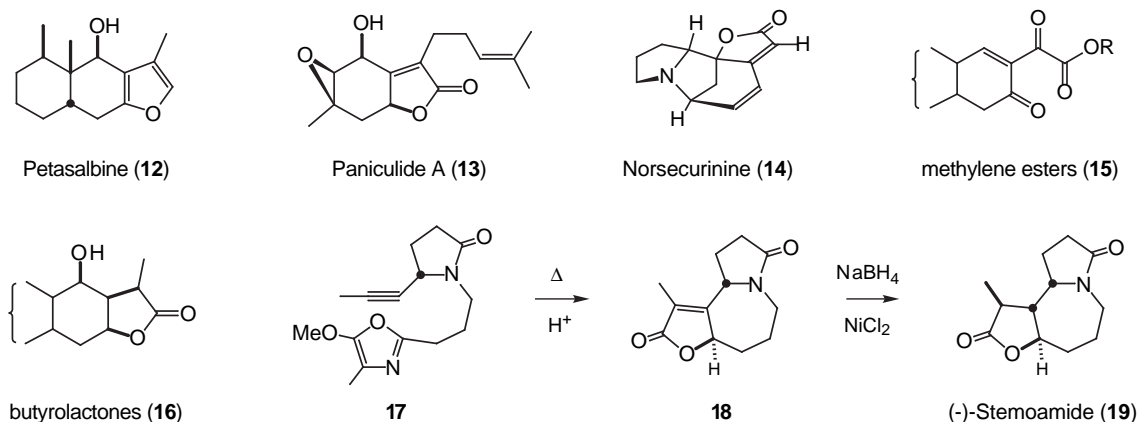
In similar fashion we synthesized Petasalbine (**12**) and a number of related furanoeremophilanes (Scheme 3). Also, we have adapted this methodology to prepare naturally occurring butenolides such as Paniculide A (**13**) and Norsecurinine (**14**), methylene esters of type **15**, and highly substituted butyrolactones of type **16**.² This last ring system is found in many terpenes as well as in alkaloids of the *Stemona* class. In this context we recently synthesized (-)-Stemoamide (**19**) from the alkyne-oxazole **17**, itself readily derived from L-pyroglutamic acid (Scheme 3).³ Thermolysis of **17** with concomitant hydrolysis gave a 55% yield of butenolide **18**, which upon reduction with $\text{NaBH}_4/\text{NiCl}_2$ afforded **19** in two steps and with excellent stereochemical control. These transformations were guided by MM2 calculations, which showed that at each step the desired isomer was thermodynamically favored.

¹ Jacobi, P.A. in *Strategies and Tactics in Organic Synthesis*, Volume II, Thomas Lindberg, Ed., Academic Press, Inc., New York, New York, 1989, and references therein.

² Jacobi, P.A. in *Advances in Heterocyclic Natural Product Synthesis*, Volume II, William H. Pearson, Ed., Jai Press Inc., Greenwich, Connecticut, 1992, and references therein.

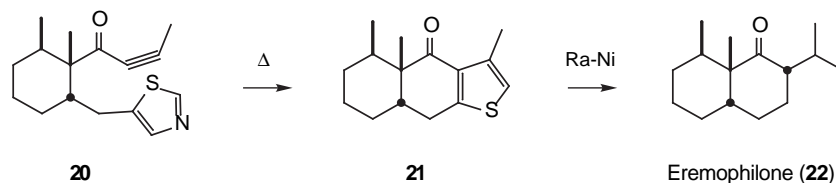
³ Jacobi, P.A.; Lee, K., *J. Am. Chem. Soc.* 2000, 122, 4295.

Scheme 3



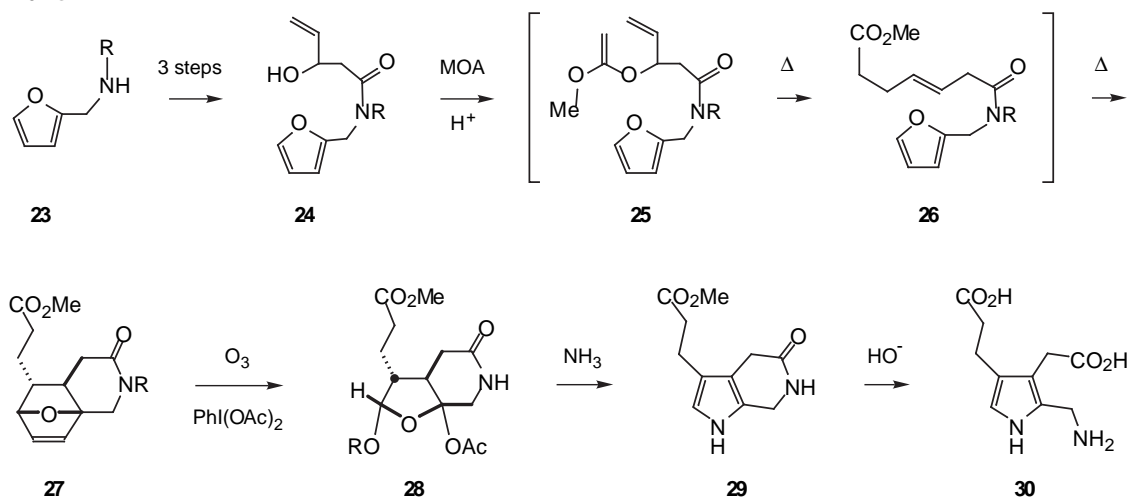
Although less reactive, intramolecular Diels-Alder cyclizations can also be effected with alkyne-thiazoles, and the resultant thiophenes are useful synthons. For example, thermolysis of **20** produced the keto-thiophene derivative **21**, which upon Ra-Ni reduction was transformed directly to 7*S*-eremophilone (**22**) (Scheme 4).²

Scheme 4



Finally, in related studies we have utilized Diels-Alder chemistry in a very efficient synthesis of Porphobilinogen (**30**) (Scheme 5).⁴ This deceptively simple-appearing pyrrole is the biological precursor to nearly all naturally occurring tetrapyrroles, and it is also of interest as a pro-drug in tumor photodynamic therapy (PDT). Our synthesis of **30** began with furfurylamine (**23**, R = H), which was converted to the allylic alcohol **24** by a three-step sequence involving alkylation (R = suberyl), *in situ* acylation, and aldol condensation with acrolein. Upon heating with methyl orthoacetate (MOA) **24** gave a 72% yield of the 7-oxonorbornene derivative **27**, by initial Johnson orthoester Claisen rearrangement (**24** → **26**), followed by intramolecular Diels-Alder cyclization. Compound **27** was then subjected to a novel ozonide cleavage/oxidation reaction, which generated tetrahydrofurans **28** in the proper oxidation state for direct aminolysis to pyrrole **29**. Hydrolysis of **29** following the literature procedure then gave Porphobilinogen (**30**) in seven steps, and ~20-30% overall yield, from **23**.

Scheme 5

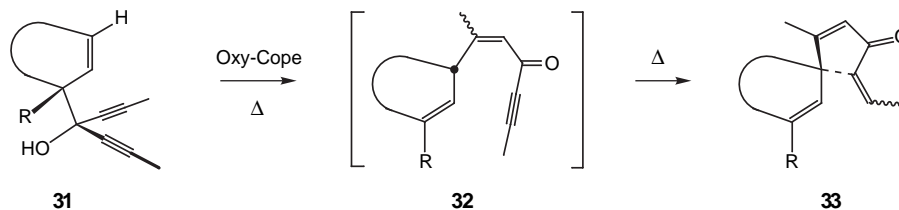


⁴ Jacobi, P.A.; Li, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9307.

II. Electrocyclic Chemistry.

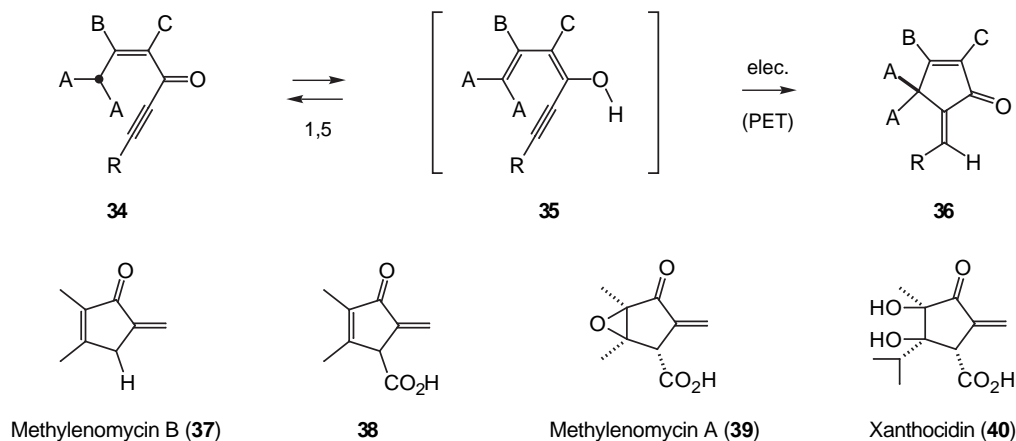
Our interest in electrocyclic chemistry stems from an observation made during our synthesis of Gnidione (**11**) (cf. Scheme 2).² In these studies we found that *bis*-alkyne alcohols of general structure **31** undergo facile 3,3-sigmatropic rearrangement, affording high yields of enynones **32** upon heating in benzene (Scheme 6). Unexpectedly, however, in some cases **32** underwent further reaction to produce spirocyclic methylenecyclopentenones of type **33**. At the time, cyclizations of this nature were unprecedented.

Scheme 6



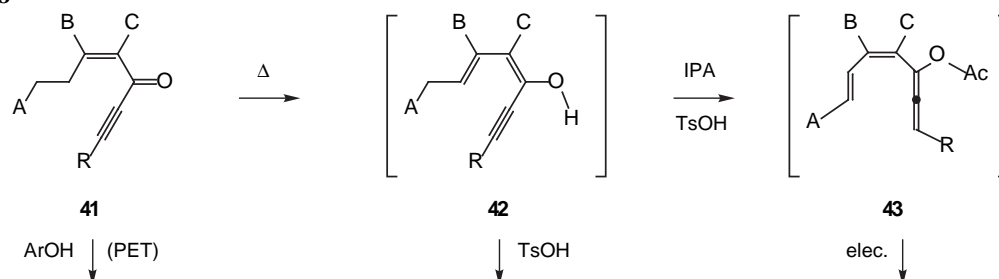
To explore this reaction we prepared a large number of model compounds **34** for mechanistic studies (Scheme 7). Based upon geometry requirements we concluded that the initial step in this process is enolization by 1,5-hydrogen transfer to afford dienol **35**. In favorable cases this step is followed by a symmetry allowed ($\pi^4s + \sigma^2s + \pi^2a$)-electrocyclization to give **36**. However, the efficiency of this transformation depends strongly upon the nature of substituents A-C and R, being particularly accelerated by extended conjugation (A,B,C = Ph or $-\text{CH}=\text{CH}-$; R = CO_2R). For less activated substrates (A,B,C,R = alkyl or H), the conversion of **35** to **36** is sluggish under thermal conditions but it can be catalyzed by both thermal and photoassisted single electron transfer (PET). Phenols of low oxidation potential are effective electron donors. This transformation was put to practical use in the syntheses of a number of methylenecyclopentenone antibiotics, including Methylenomycin B (**37**), Desepoxy-4,5-didehydromethylenomycin A (**38**), Methylenomycin A (**39**) and Xanthocidin (**40**).⁵

Scheme 7

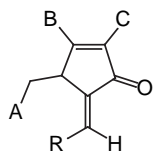


In the absence of suitable electron donors the reactivity pattern of enynones of general structure **41** is quite different (Scheme 8). For example, under conditions of simple acid catalysis **41** are converted to highly substituted phenols of type **45** in 80-90% yield and with >90% selectivity (*path b*). Alternatively,

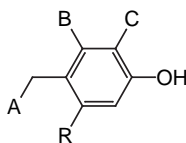
Scheme 8



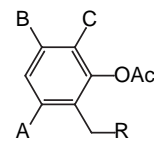
⁵ Jacobi, P.A.; Briemann, H.L.; Cann, R.O. *J. Org. Chem.* **1994**, *59*, 5305, and references therein.



44 (path a)



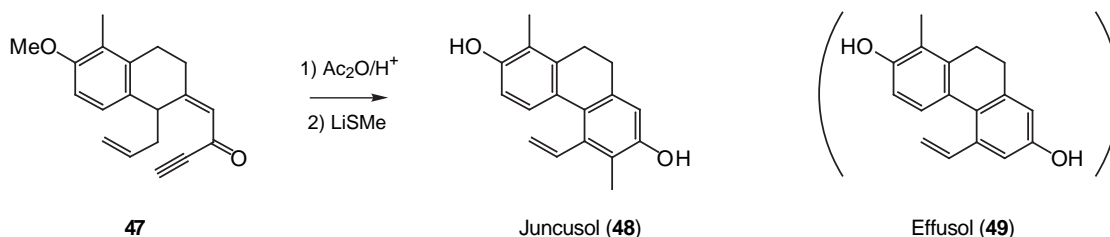
45 (path b)



46 (path c)

with isopropenyl acetate (IPA)/TsOH enynones **41** are converted to the isomeric phenol acetate derivatives **46**, again in high yield and with excellent selectivity (*path c*). *Path c* involves the intermediate formation of conjugated allene derivatives of type **43**, which upon electrocyclic ring closure and tautomerization afford **46**. In addition to antibiotics **37-40** cited above (cf. Scheme 7), this selectivity was exploited in a highly efficient synthesis of the antimicrobial-cytotoxic agent Juncusol (**48**) and in preparing a number of analogs of Effusol (**49**) (Scheme 9).⁶

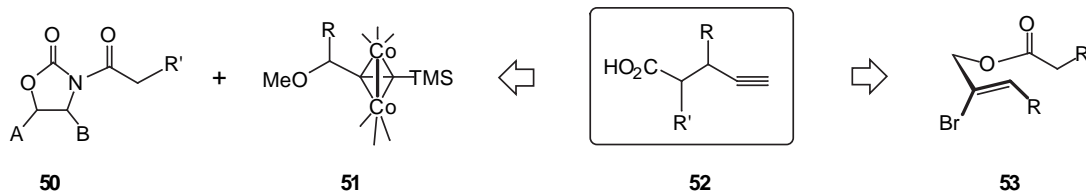
Scheme 9



III. β -Amino Acids and Paraconic Acids.

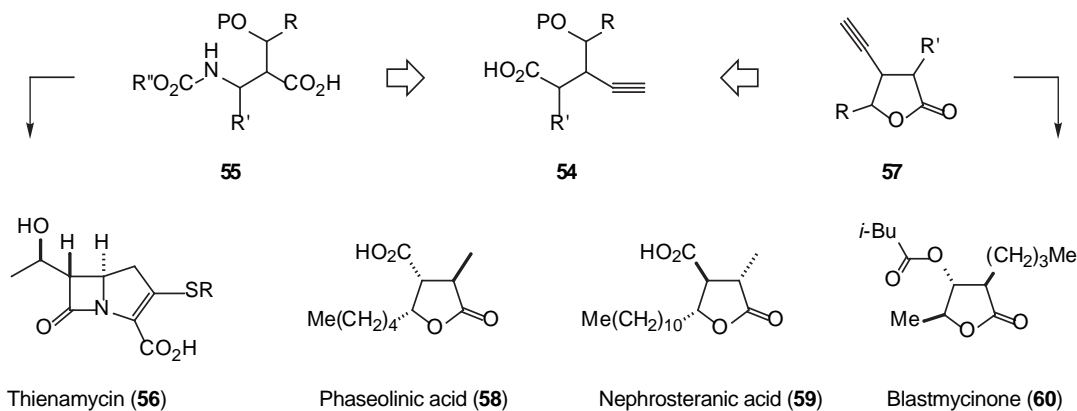
We have devoted considerable effort to synthesizing homochiral alkyne acids of type **52**, which are very versatile synthons (Scheme 10). In our early work acids **52** were prepared using a Nicholas-Schreiber reaction (**50 + 51** \rightarrow **52**), but more recently we have employed an asymmetric Ireland-Claisen reaction (**53** \rightarrow **52**, reagent control). A third method involving substrate control is discussed below.

Scheme 10



In one investigation, alcohol acids **54** were transformed to β -amino acids of type **55** via a two-step sequence involving Curtius rearrangement followed by oxidative cleavage of the alkyne bond (Scheme 11). Cyclization of **55** then gave the corresponding β -lactams, which were utilized in formal syntheses of Thienamycin (**56**) and other carbapenem antibiotics.⁷ In another study lactonization of **54** gave excellent

Scheme 11



⁶ Jacobi, P.A.; J.I. Kravitz, J.I.; Zheng, W. *J. Org. Chem.* **1995**, *60*, 376, and references therein.

⁷ Jacobi, P.A. in *Enantioselective Synthesis of β -Amino Acids*, Eusebio Juaristi, Ed., VCH Publishers, Inc., New York, **1997**, and references therein.

yields of alkyne-lactones **57**, which are appropriately functionalized for conversion to members of the Paraconic acid class of antibiotics. For example, oxidative cleavage of alkynes **57** with $\text{RuCl}_3/\text{NaIO}_4$ affords the corresponding carboxylic acids, a transformation we employed in enantioselective syntheses of Phaeolinic acid (**58**) and Nephrosteranic acid (**59**).⁸ Alternatively, acid catalyzed hydration of **57** followed by Bayer-Villiger reaction was a key step in our enantioselective synthesis of Blastmycinone (**60**).⁸

IV. Linear and Macrocyclic Tetrapyrroles.

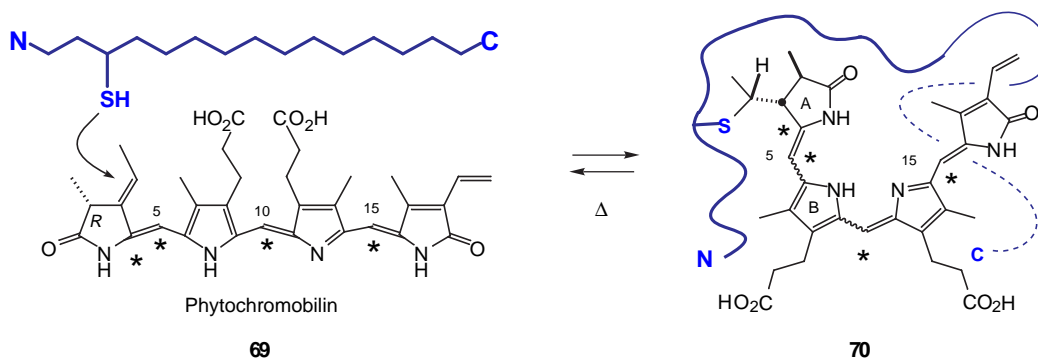
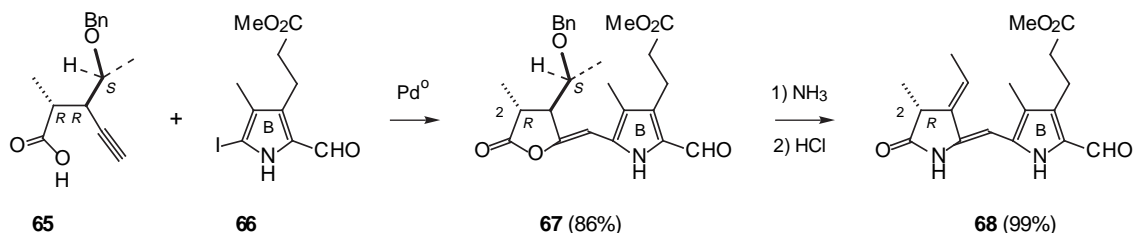
Alkyne acids **61** undergo a variety of transition metal-mediated reactions, the end result of which is often lactonization (Scheme 12). For example, Pd(0)-mediated coupling/cyclization of **61** with iodopyrrole **62** affords excellent yields of enelactones **64**, probably via the intermediacy of vinyl-Pd species **63**. In such reactions the thermodynamic driving force for Pd-reductive elimination overcomes any steric hindrance to enelactone formation. Four projects that exploit this reaction are described below.

Scheme 12



A. Phytochrome. This methodology was first employed in an enantioselective synthesis of Phytochromobilin (**69**), the linear tetrapyrrole chromophore of Phytochrome (**70**) (Scheme 13).⁹ Phytochrome is a protein-bound tetrapyrrole that regulates photomorphogenesis in plants, although its mechanism of action remains unclear. In the key bond forming step, Pd(0)-mediated coupling/cyclization of alkyne acid **65** and iodopyrrole **66** gave an 86% yield of the enelactone **67**. Brief exposure of **67** to NH_3 , followed by acid catalyzed elimination, then gave an essentially quantitative yield of the dihydropyrromethene **68**. In analogous fashion we prepared the C,D-ring component of **69**, which was readily joined with **68** to afford enantiomerically pure **69**. Tetrapyrrole **69** was identical to that derived by thermolysis of naturally occurring Phytochrome (**70**), which established the absolute stereochemistry of this material for the first time. Finally, in collaboration with Professor J. Clark Lagarias (UCal Davis), **69** was reconstituted with phytochrome apoprotein **N-C** to generate **70** in its photochemically active form. ¹³C-labeled (*) derivatives of **69** are currently being incorporated with **N-C** for *in vivo* mechanistic studies.

Scheme 13

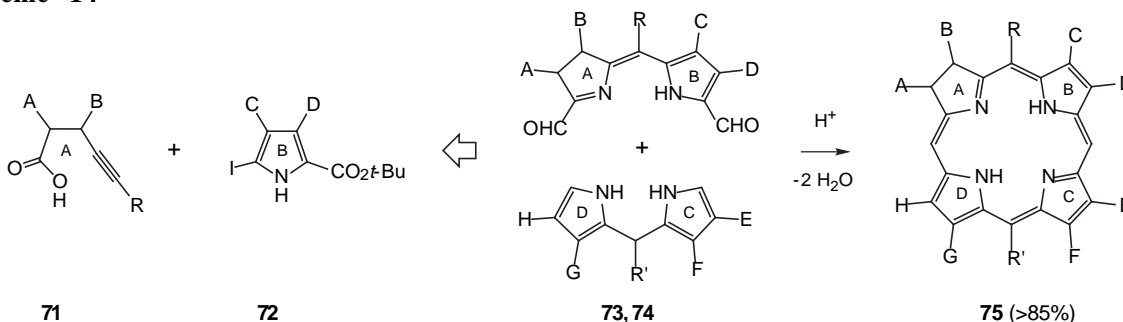


⁸ Jacobi, P.A.; Herradura, P. *J. Can. Chem. Soc.* **2001**, 1727, and references therein.

⁹ Jacobi, P.A.; Pippin, D. *Organic Letters* **2001**, 3, 827, and references therein.

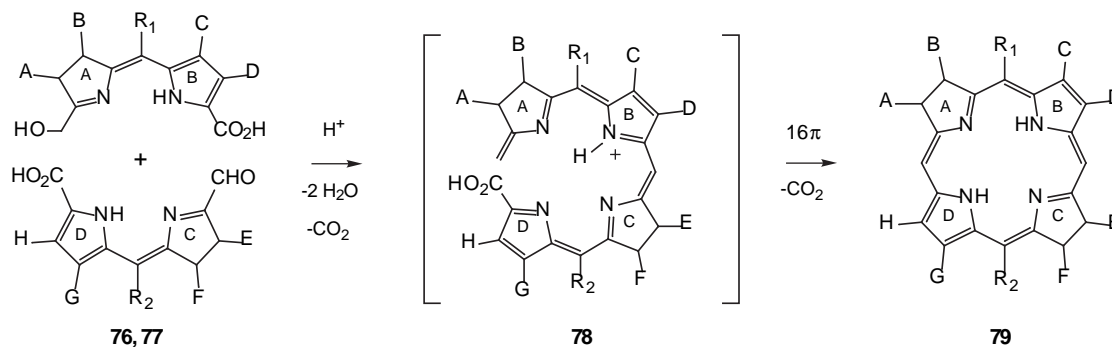
B. Chlorins. The Pd(0)-mediated coupling/cyclization strategy also served well in a new synthesis of chlorins (Scheme 14).¹⁰ The requisite dihydrodipyrriins **73** were prepared in five steps, and excellent overall yield, from alkyne acids **71** and iodopyrroles **72**. As above, the key bond forming step involved enolactone formation, which was followed by methylation (Tebbe's reagent), aminolysis, and SeO₂ oxidation of the resultant methyl-substituted dihydrodipyrriin. Once in hand, acid-catalyzed condensation of **73** with dipyrromethanes **74** afforded chlorins **75** in >85% yield. A significant advantage to this methodology is that **75** are formed directly in the proper oxidation state and with no requirement for metal templates.

Scheme 14



C. Bacteriochlorins. In analogous fashion we prepared the dihydrodipyrriins **76** and **77** for a planned synthesis of bacteriochlorins (Scheme 15). The substitution patterns of **76** and **77** were chosen to facilitate acid-catalyzed condensation to give linear tetrapyrrole derivatives of type **78**, which we hoped might undergo 16 π -electrocyclic ring closure to give bacteriochlorins **79** directly. Our initial experiments in this area have been very promising. Although not yet optimized, combination of **76** and **77** in TFA initiated the desired series of transformations, which culminated in isolated yields of **79** in excess of 40%.¹¹ Chlorins **75** and bacteriochlorins **79** are undergoing testing at the Dartmouth Medical School for activity in tumor photodynamic therapy (PDT).

Scheme 15



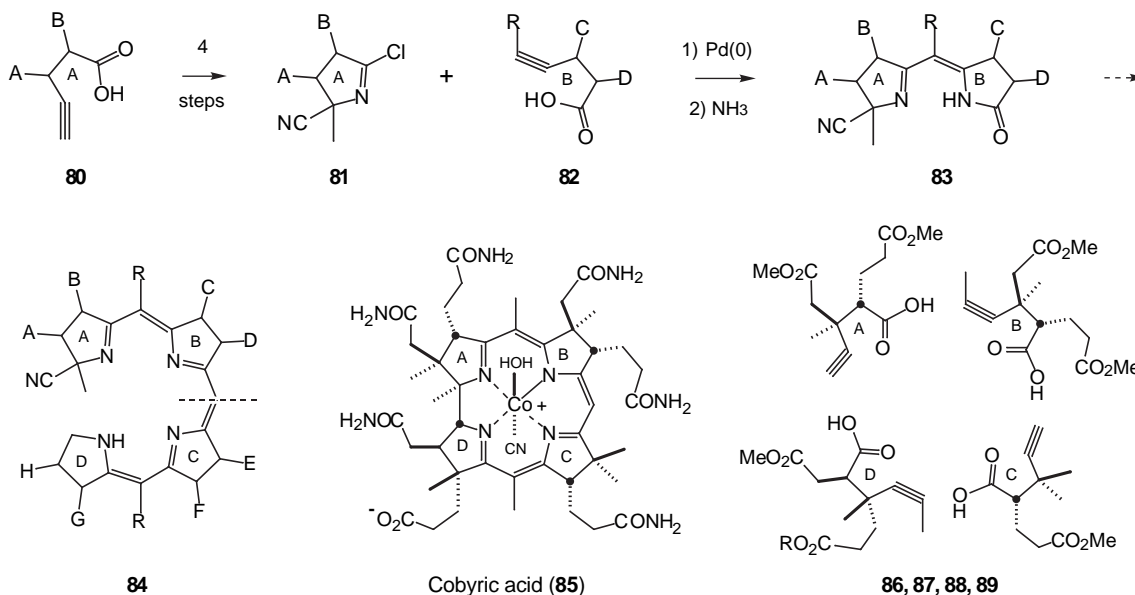
D. Corrins. Corrins are the most complicated of the naturally occurring tetrapyrroles in that each ring has at least two stereocenters. In principle the alkyne acid methodology is well suited to synthesis in this area, since the key building blocks can be prepared in enantioselective fashion. This strategy is illustrated in Scheme 16 for syntheses of semicorrins **83** and *seco*-corrins **84**. Alkyne acids **80** were first converted to imidoyl chlorides **81** by a four step sequence involving Pd(II)-catalyzed cyclization, aminolysis of the resultant enolactone, enamide protection (KCN), and chlorination. Imidoyl chlorides **81** were then transformed to semicorrins **83** by Pd(0)-mediated coupling/cyclization with alkyne acids **82** followed by aminolysis. From this point two pathways are available leading to **84**. Repetition of the sequence of enamide activation and Pd(0)-mediated coupling/cyclization affords tripyrrolines and higher analogues in an iterative fashion. Alternatively, condensation of **83** with a similarly derived C,D-ring semicorrin provides direct access to *seco*-corrins **84**, which are properly functionalized for photochemical ring closure to produce corrins.¹² Eschenmoser pioneered this photochemical route to corrins in his extraordinary synthesis of Cobyric acid (**85**), a known precursor to Vitamin B₁₂.

¹⁰ Jacobi, P.A.; Ghosh, I.; Lanz, S.; Pippin, D. *Organic Letters* **2001**, 3, 831, and unpublished results.

¹¹ Jacobi, P.A.; Roberts, F. unpublished results.

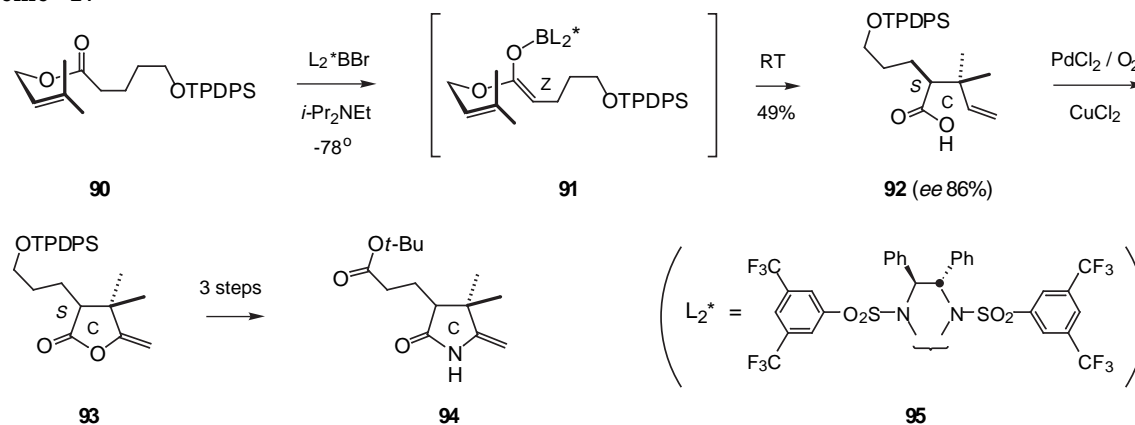
¹² (a) Jacobi, P.A.; Liu, H. *J. Am. Chem. Soc.* **1999**, 121, 1958. (b) Jacobi, P.A.; Liu, H. *J. Org. Chem.* **1999**, 64, 1778. (c) Jacobi, P.A.; Liu, H. *Organic Letters* **1999**, 1, 341.

Scheme 16



Currently we are engaged in a synthesis of Cobyric acid (**85**) using the methodology described above. Our first objective is to develop enantioselective syntheses of alkyne acids **86-89** or closely related synthons. Thus far we have carried out two syntheses of ring-C analogues, both of which have the capability of providing high enantiomeric excesses. One approach began with the allylic ester **90** and made use of a "reagent controlled" asymmetric Ireland-Claisen rearrangement (Scheme 17). Thus far, the best results for this step were obtained using the Corey reagent **95**, which gave a 49% yield of the carboxylic acid **92** with *ee* = 86%. For characterization purposes, **92** was converted to the known ring-C derivative **94** by a four step sequence involving Pd(II)-catalyzed oxidative cyclization (**92** → **93**), followed by deprotection, oxidation (CrO₃/DMF/*t*-BuOH), and aminolysis.¹³

Scheme 17

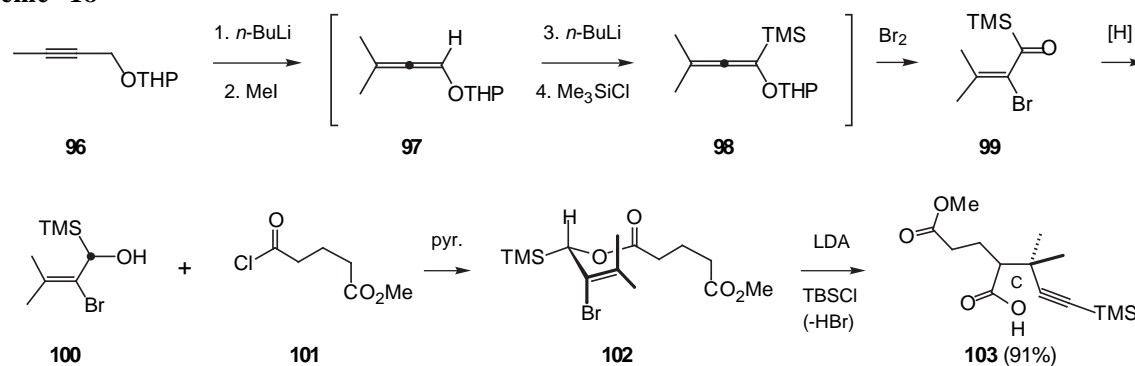


Our second synthesis also employed an Ireland-Claisen rearrangement, but in this case using substrate control (Scheme 18). A key intermediate in this approach was the silyl ketone **99**, which was prepared in a "one-pot" transformation beginning with the propargyl ether **96**. Many examples of chiral reductions of such species are known, and the absolute configuration of alcohols **100** controls the stereochemical outcome of subsequent Claisen rearrangements. Thus far we have optimized this route with racemic **100**, which upon condensation with the commercially available acid chloride **101** was smoothly converted to the allylic ester **102**. The Ireland-Claisen rearrangement of **102** was remarkably clean, and occurred with concomitant HBr elimination to afford the alkyne acid **103**. Conversion of **103** to the target alkyne-acid **88** was then accomplished in quantitative yield with Na₂CO₃/MeOH. At present we are repeating this sequence with homochiral **100**. With suitable modification this strategy should also be applicable to the synthesis of alkyne acids **86**, **87** and **89**.¹⁴

¹³ Jacobi, P.A.; Li, Y., *Organic Letters* **2002** (submitted).

¹⁴ Jacobi, P.A.; Tassa, C. manuscript in preparation.

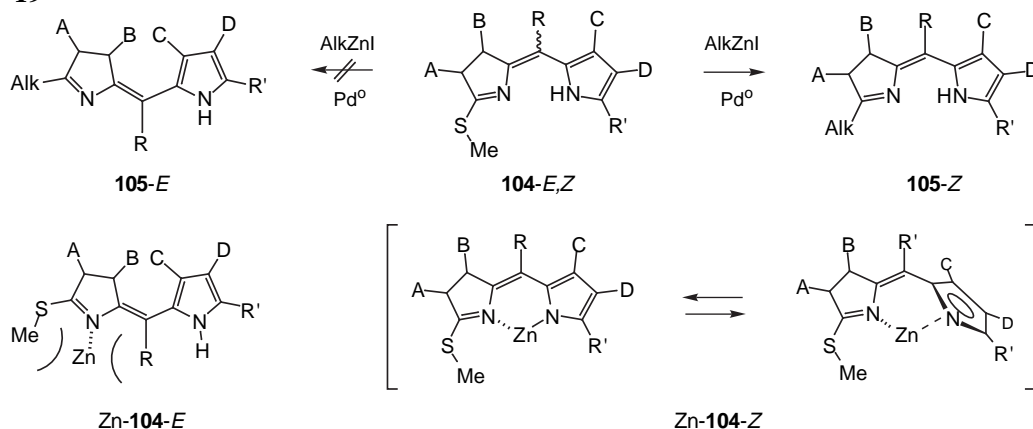
Scheme 18



V. Mechanistic Studies of Transition Metal Mediated Processes. Much of our synthetic work in this area has required supporting mechanistic studies. Two examples are described below.

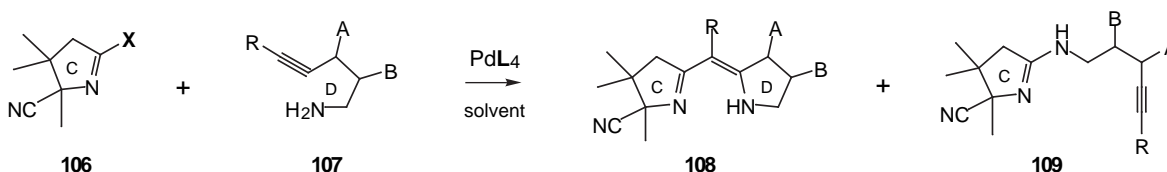
In early cross-coupling studies we observed a marked difference in reactivity between the isomeric thioimidates **104-Z** and **104-E** (Scheme 19). Thioimidates **104-Z** were readily converted to imines **105-Z** employing Pd(0)/AlkZnI, while the geometric isomers **104-E** were inert. This difference was eventually traced to an activating effect of Lewis acids, which function to polarize the thioimide C-S bond prior to oxidative addition. Complexation with AlkZnI is facile with **104-Z**, which can accommodate Zn in either of two chelated forms (Zn-**104-Z**). In contrast, activation of this type is not possible with **104-E**. Moreover, NOE and X-ray studies showed that simple imine complexes of type Zn-**104-E** are sterically unfavorable. One practical consequence of these studies is that many systems previously regarded as unreactive can be induced to undergo cross-coupling reactions. With **104-E**, for example, addition of the smaller (and harder) Lewis acid BF₃ efficiently catalyzed its conversion to **105-E**.^{15a}

Scheme 19



Finally, dipyrins **108** are important C,D-ring precursors to corrins that present special synthetic challenges (Scheme 20). Ideally these materials would be derived by Pd(0)-mediated coupling/cyclization of imino-derivatives **106** and alkyne amines **107**. However, in most cases amidine formation, by direct nucleophilic substitution, competes effectively with the desired Pd(0)-mediated process. Typical ratios for **108**:**109** ranged from 1:5 to 2:1 under standard conditions. From mechanistic studies we postulated that dipyrin formation occurs via a cationic, dissociative mechanism, which should be favored by both "hard" leaving groups **X** and poor Pd-ligands **L** in weakly coordinating solvents. Building on this premise we found that the combination of X=OTf, "ligandless-Pd" (Pd₂dba₃), and MeCN as solvent gave **108** and **109** in the much improved ratio of ~8:1.^{15b}

Scheme 20



¹⁵ (a) Ghosh, I.; Jacobi, P.A. *J. Org. Chem.* **2002** (in press, Web ASAP 11/02). (b) Jacobi, P.A.; Liu, H. *J. Org. Chem.* **2000**, *65*, 7676.