We approach chemical synthesis by identifying biomedically interesting natural products that offer an opportunity for methodology development. Thus, a potential target is subject to extensive retrosynthetic analysis to evaluate possible routes. This may reveal that a yet unknown reaction would facilitate the synthetic problem. Suitable methodology is then developed and ultimately applied to the molecule in question. Indeed, every total synthesis completed in this group has introduced new techniques. A selection of the methods developed in this laboratory, and of the target molecules for which they were devised, is provided below, together with relevant literature references.

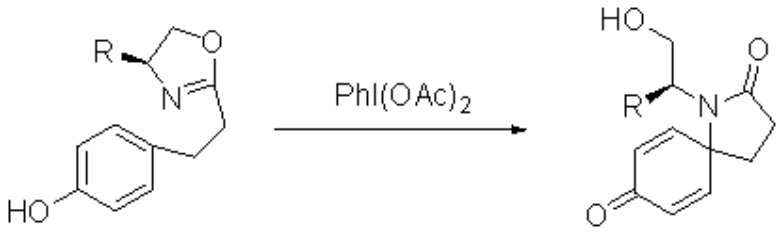
Table of Content

SYNTHETIC METHODS AND METHODOLOGY

1. New Oxidative Amidation of Phenols

1.1 Oxidative Transformations of Phenolic and Indolic Oxzolines

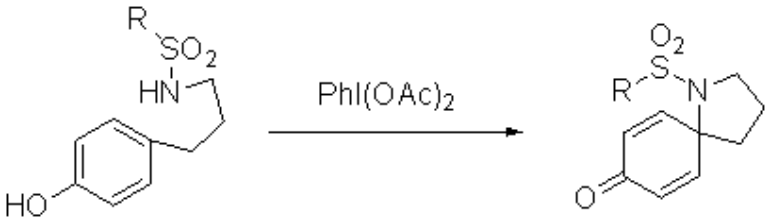
The oxidative cyclization of a phenolic amide to a spirolactam had long been regarded as an "impossible" reaction, because attempts in that direction result only in formation of spirolactones and consequent loss of the amine segment. We determined that this transformation may be achieved if an oxazoline is utilized as a surrogate of an amide. Thus, phenolic and indolic oxazolines are converted to spirolactams in moderate yield upon exposure to iodobenzene diacetate.



J. Org. Chem. **2000**, *65*, 4397

1.2 Efficient Oxidative Spirocyclization of Phenolic Sulfonamides

The analogous oxidative cyclization of free phenolic primary amines is problematic. A technique to achieve the equivalent of such a transformation has been developed in the form of the oxidative spirocyclization of homotyramine sulfonamides, reaction of which with iodobenzene diacetate in hexafluoroisopropanol produces the desired spirocycles in high yield.

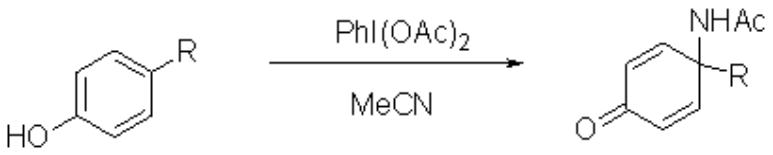


Tetrahedron Lett. **2002**, *43*, 5193.

1.3 Nitrogenous Educts through Oxidative Amidation of Phenols: The Bimolecular Reaction

A major limitation of above technology is that it works well for the formation of 2-azaspiro[5.4]decanes, but it is inefficient for the preparation of 2-azaspiro[5.5]undecanes and of larger ring systems of the type found in many synthetically appealing natural products. A bimolecular version of the process circumvents such difficulties and provides new strategic

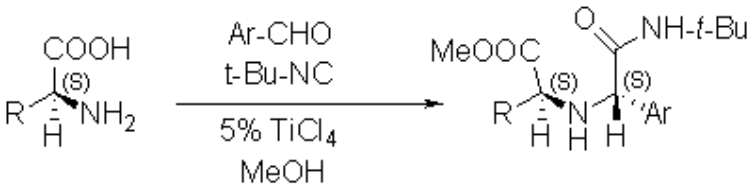
opportunities in the chemical synthesis of nitrogenous substances.



Org. Lett. **2005**, *7*, 175.

2. Titanium Catalysis in the Ugi Reaction of -Amino Acids with Aromatic Aldehydes

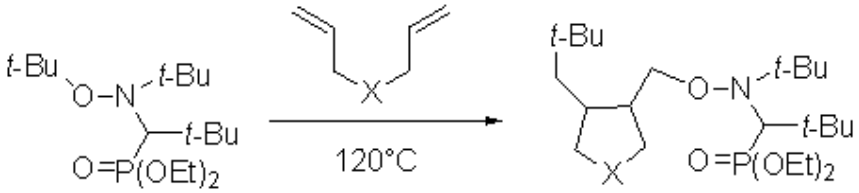
Ugi reactions of α-amino acids are documented in pioneering reports by Ugi himself, but they have received only sporadic attention, and their sense of diastereoinduction has been the subject of conflicting reports. Moreover, the literature records only instances of such reactions with aliphatic aldehydes. Ongoing synthetic work prompted us to investigate the analogous reaction of aromatic aldehydes, which proved to be poor substrates for this transformation. We found that such Ugi reactions proceed in good yield and with good diastereoselectivity under catalysis by $TiCl_4$ in MeOH. The sense of diastereoinduction is *lk*.



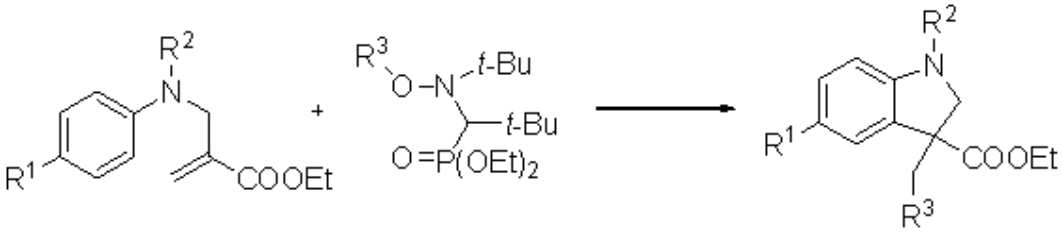
Org. Lett. **2004**, *6*, 3281.

3. Alkoxyamine-Mediated Radical Cyclizations

A new "conjunctive" radical cyclization process was devised, which involves the reaction of a 1,6-diene with the Tordo alkoxyamine, an agent originally developed for the radical polymerization of certain olefins through the "persistent radical effect". The methodology has been applied to the synthesis of indolinones and indolines.



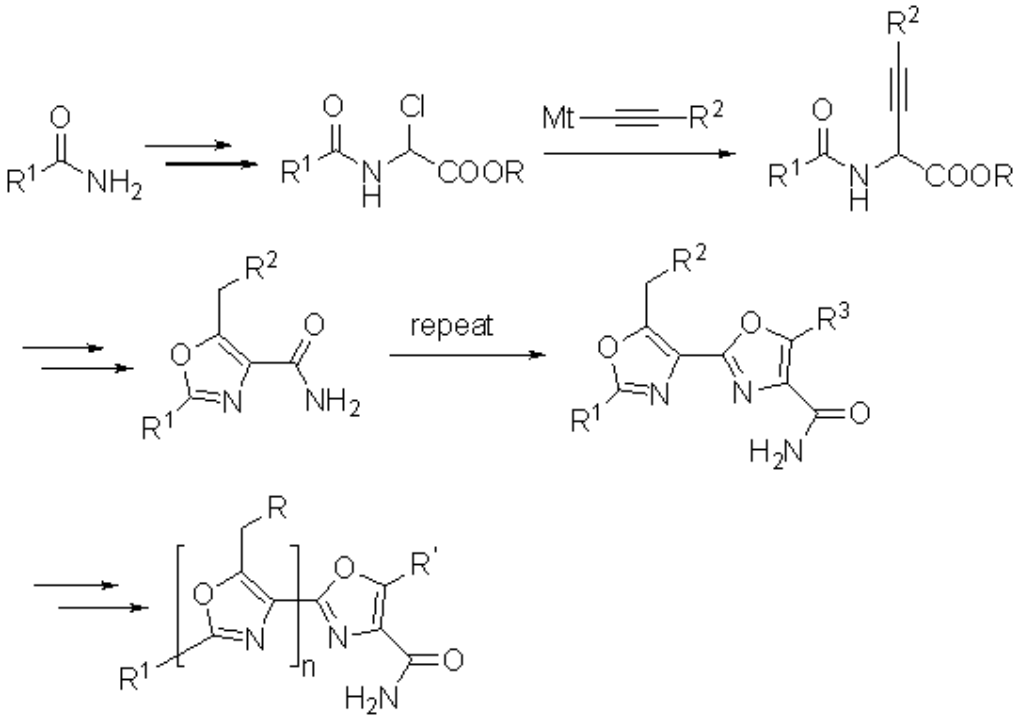
Org. Lett. **2003**, *5*, 1079.



Org. Lett. **2003**, *5*, 4943.

4. Iterative Oxazole Synthesis via α-Chloroglycinates

A new route to oxazole-4-carboxylic esters proceeds through the base-promoted cyclization of alkynylglycinates, readily prepared by the action of alkynylaluminum reagents on α-chloroglycinate esters. The resultant oxazole ester may be converted to an amide and subjected to the same reaction sequence, leading to a bisoxazole. Generic polyoxazoles emerge after *n* such iterations.

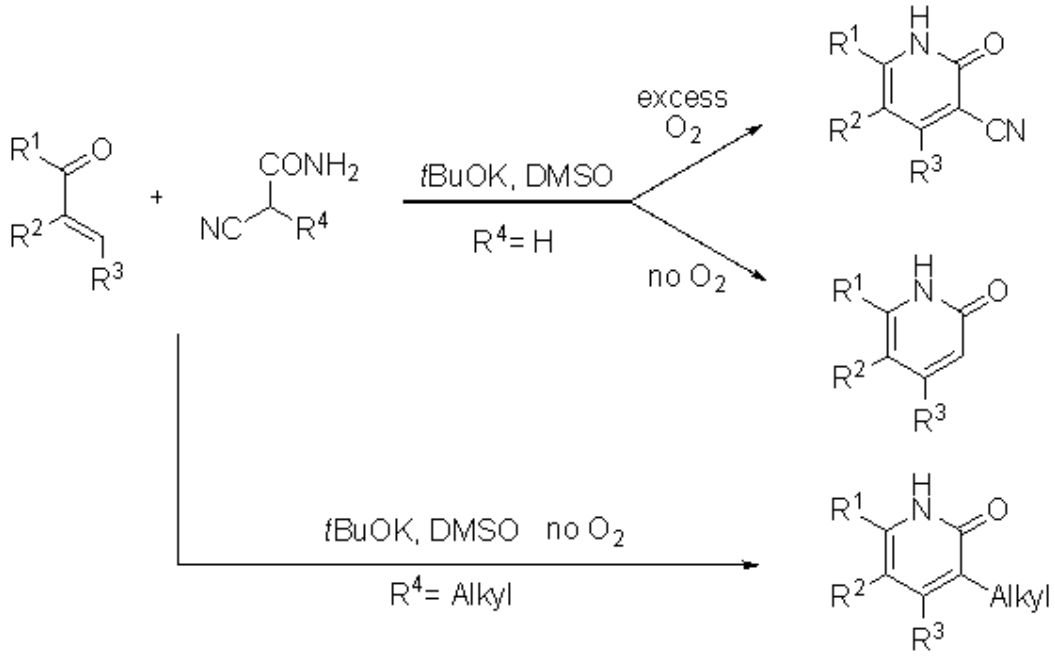


Angew. Chem. Int. Ed. **2003**, *42*, 1411; *Angew. Chem.* **2003**, *115*, 1454.

5. 2-Pyridones from Cyanoacetamides and Enecarbonyl Compounds

The condensation of an enone or enal with cyanoacetamide derivatives and t-BuOK furnishes either 3-cyano-2-pyridones or 3-unsubstituted-2-pyridones, depending on whether the reaction is carried out in the presence or in the absence of O_2. In the first case, in situ oxidation of Michael-type intermediates takes place; in the second case, a "decyanidative aromatization" of such

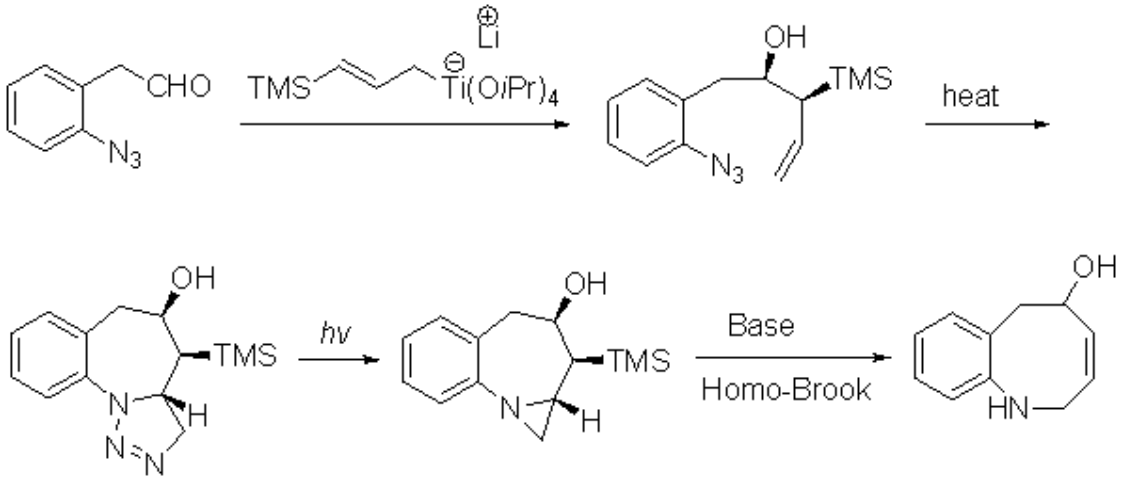
intermediates occurs.



J. Org. Chem. **2002**, *67*, 4304; *Tetrahedron Lett.* **1995**, *36*, 3307.

6. Homo-Brook route to Benzazocenols and Congeners via Allylsilane-derived Aziridines

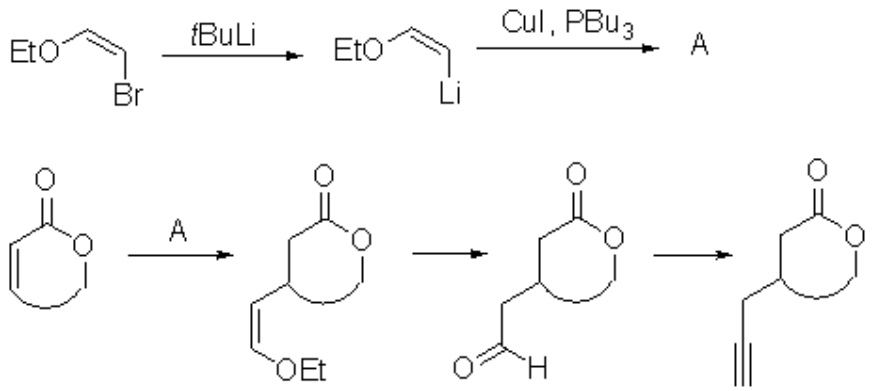
A concise entry to benzazocenols intermediates for mitomycinoids proceeds via a homo-Brook rearrangement–ring opening sequence of a silylated aziridine. The latter is obtained by intramolecular 1,3-dipolar cycloaddition of an azide with an allylsilane, followed by irradiation of the resulting triazoline.



Tetrahedron Lett. **2001**,*42*, 9175.

7. Conjugate Propargylation of α, β-Unsaturated Lactones: a Solution via 1,4-Addition of (Z)-2-Ethoxyvinyl Anion

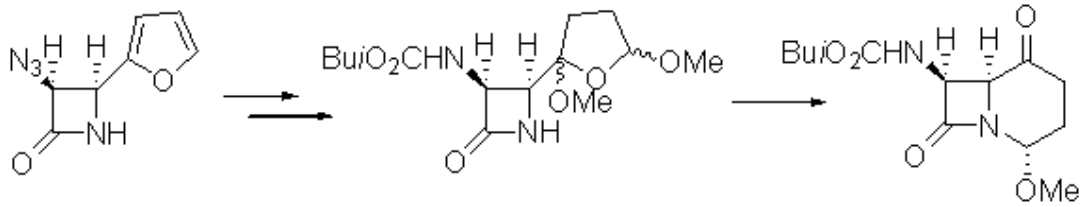
Conjugate addition of (Z)-2-ethoxyvinyl anion to α,β-unsaturated lactones is best effected via Noyori type organocopper reagents. The resulting adducts may be advanced to β-propargyllactones or utilized in the preparation of functionalized pyridines.



Tetrahedron Lett. **2000**, *41*, 8873.

8. Aza-Achmatowicz Rearrangement

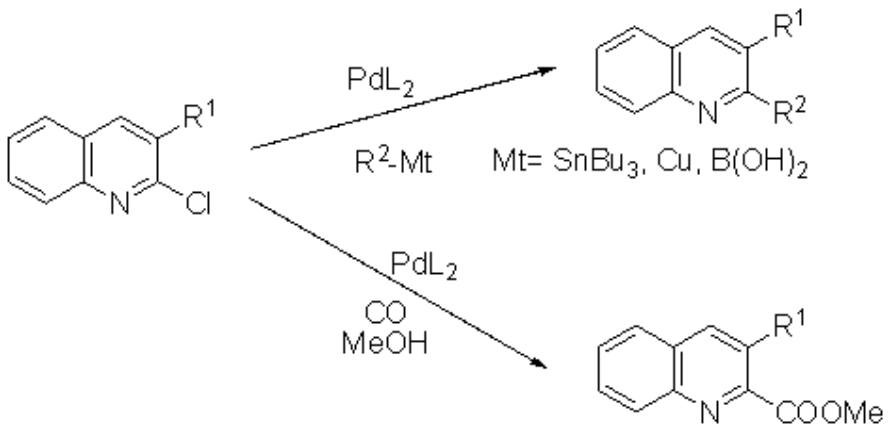
Aza-achmatowicz rearrangement is defined as the conversion of furylamides to heterocycles. The rearranged products are useful building blocks for the total synthesis of alkaloids, carbacephems, and unusual aminoacids.



Synlett **1998**, 105; *J. Chem. Soc., Chem. Commun*. **1996**, 881; *Tetrahedron Lett.* **1986**, *27*, 5085.

9. Facile Palladium-Mediated Substitution of Chlorine in 2-Chloroquinolines

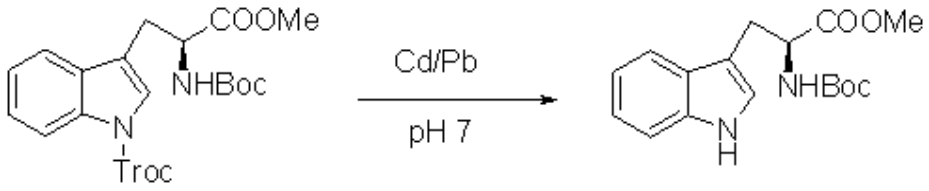
In response to a need to prepare 2,3-dialkyl quinolines, we studied Pd-mediated substitution reactions of readily accessible 2-chloro-3-alkyl quinolines, available in quantity through the Meth-Cohn quinoline synthesis. This approach offers significant advantages over classical Friedländer reactions because it suppresses the need for sensitive/costly 2-aminobenzaldehydes and it greatly improves overall efficiency.



Tetrahedron Lett. **1996**, *37*, 8281.

10. Reductive Cleavage of TROC Groups under Neutral Conditions with Cadmium-Lead Couple

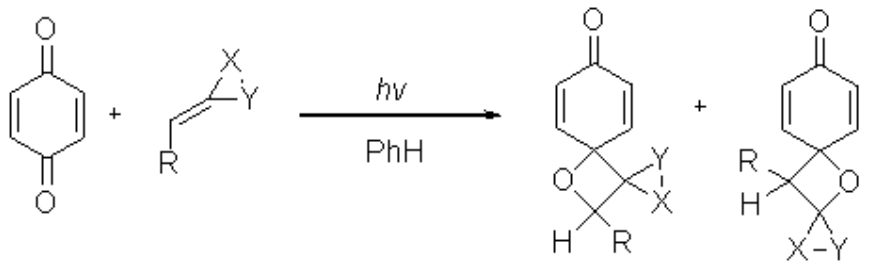
Cadmium-lead couple induces rapid and efficient reductive cleavage of TROC groups under extremely mild conditions. The couple is readily prepared and it is not pyrophoric. An example is given below.



Tetrahedron Lett. **1995**, *36*, 5681.

11. Origin of Regioselectivity in Paternò-Büchi Reactions of Benzoquinones with Alkylidenecycloalkanes

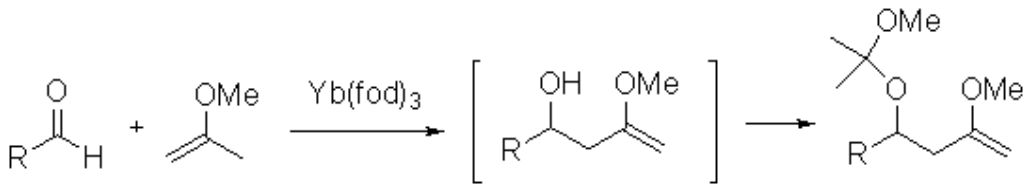
Paternò-Büchi reactions of benzoquinones with alkylidenecycloalkanes proceed regioselectively. The sense of regioselectivity is determined by the ring size of the olefin, and it appears to be controlled by the conformational properties of the substrate. Oxetane formation is likely to occur through concerted collapse of an exciplex that possesses considerable charge-transfer character.



J. Am. Chem. Soc. **1994**, *116*, 1272; *Tetrahedron Lett.* **1993**, *34*, 3505.

12. $Yb(fod)_3$-Promoted Ene Reaction of Aldehydes with Vinyl Ethers

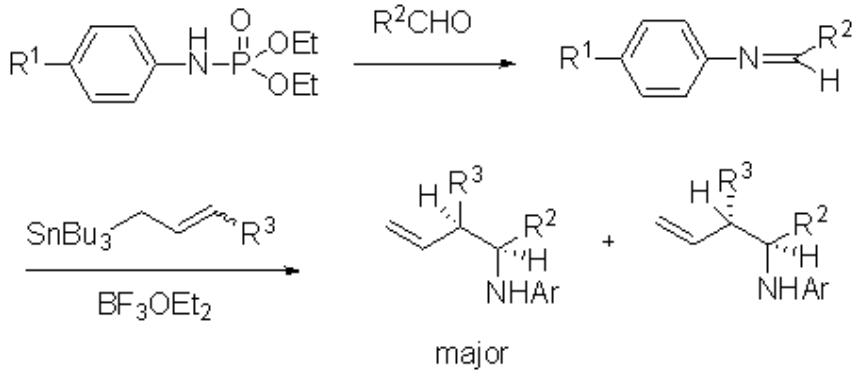
Catalytic amounts of $Yb(fod)_3$ catalyze a bimolecular ene-like reaction between ordinary aldehydes and vinyl ethers in which the oxygen functionality is located at the central carbon of an allylic system. These reactions proceed at room temperature in high yield.



Tetrahedron Lett. **1993**, *34*, 2409.

13. The Preparation of Activated Imines and Their Condensation with Allylstannanes: Stereoselective Synthesis of 1,2-Amino Alcohols

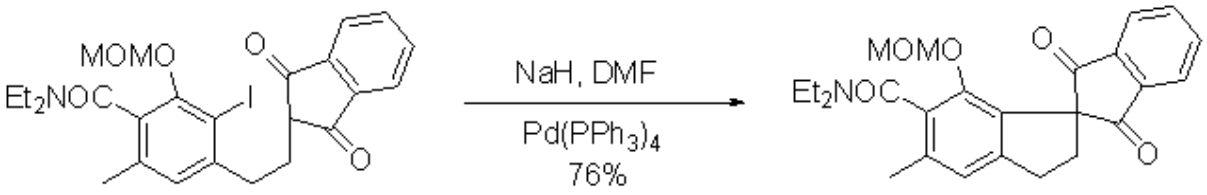
A modified Wadsworth-Emmons reaction affords hitherto inaccessible imines derived from aliphatic or aromatic aldehydes and aromatic amines carrying electron-withdrawing substituents. The resulting imines condense rapidly and stereoselectively with oxygenated allylstannanes under the influence of $BF_3{\bullet}OEt_2$, thus establishing a new avenue to *erythro* 1,2-amino alchols.



J. Org. Chem. **1989**, *54*, 4739.

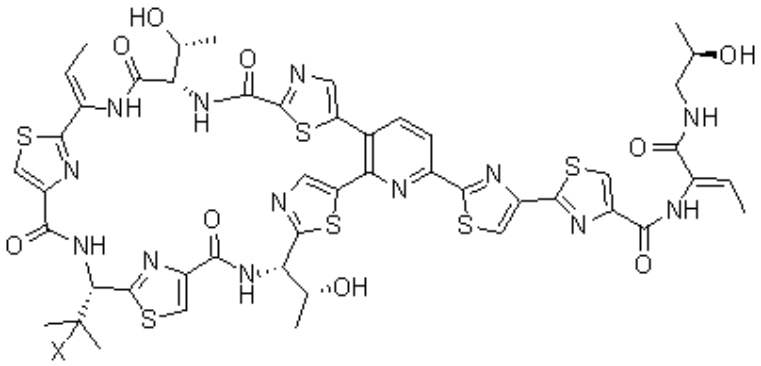
14. Intramolecular Arylations of Soft Enolates Catalyzed By Zerovalent Palladium

A new method of ring formation involving palladium-catalyzed displacement of halide from aromatic substrates by stabilized enolates is described. The new reaction permits creation of benzo-fused, five- or six-membered rings, in the homocyclic or in the heterocyclic mode. An example is given below.

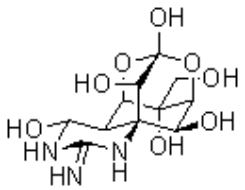


J. Org. Chem. **1988**, *53*, 4149.

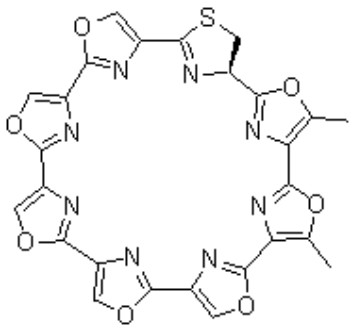
ONGOING NATURAL PRODUCT & ANALOG SYNTHESIS



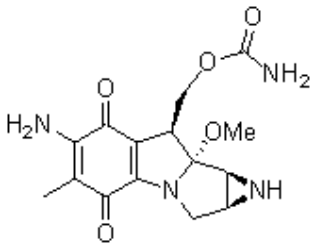
MICROCOCCIN P1 (X=H)(newly completed); YM 266184 (X=OH)



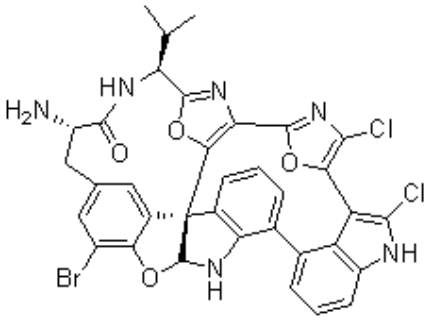
TETRODOTOXIN



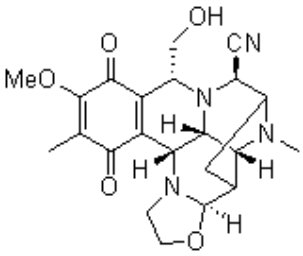
TELOMESTATIN



MITOMYCIN C

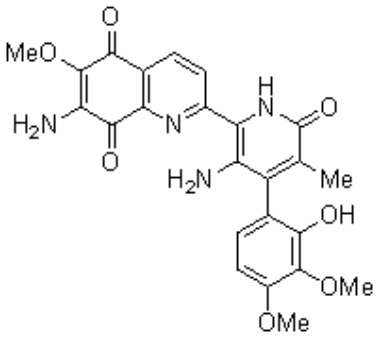


DIAZONAMIDE B



CYANOCYCLIN C

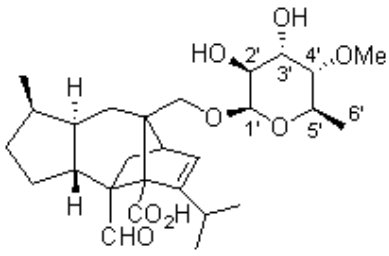
HALL OF FAME- SELECTED NATURAL PRODUCT & ANALOG SYNTHESIS



STREPTONIGRONE

total synthesis

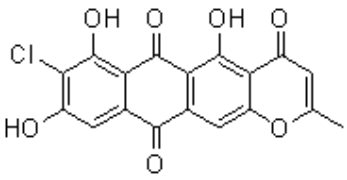
J. Org. Chem. **2007**, *72*, 8489.



SORDARIN

analog synthesis

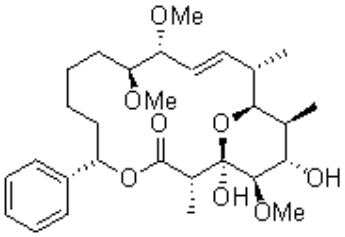
Org. Lett. **2007**, *9*, 4119.



TOPOPYRONE B&D

total synthesis

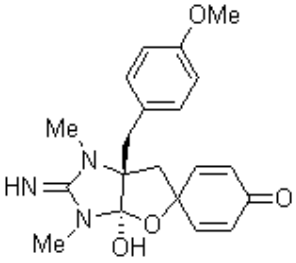
Org. Lett. **2006**, *8*, 4771.



SORAPHEN A

synthetic study

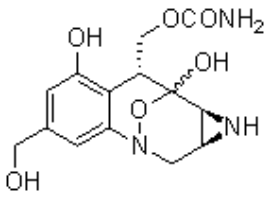
Org. Lett. **2006**, *8*, 2791.



SPIROLEUCETTADINE

synthetic study

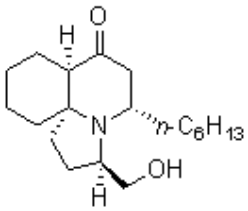
Tetrahedron Lett. **2006**, *47*, 3599.

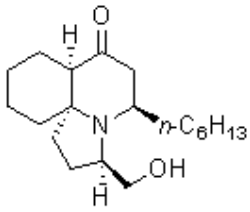


(±)-FR66979

total synthesis

Angew. Chem. Int. Ed. **2002**, *41*, 4688.

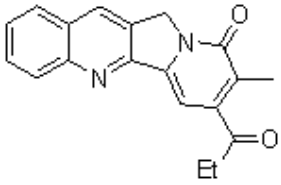




(-)-CYLINDRICINE C & (-)-2-EPICYLINDRICINE C

total synthesis

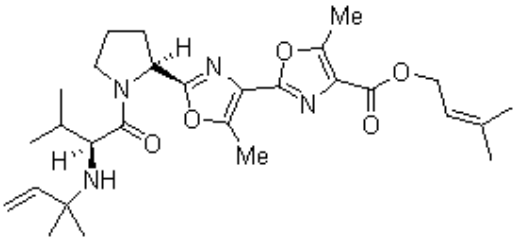
Angew. Chem. Int. Ed. **2004**, *43*, 4336.



NOTHAPODYTINE B

total synthesis

J. Org. Chem. **2002**, *67*, 4304.

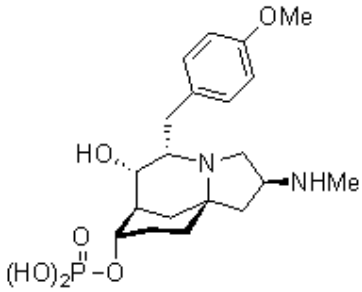


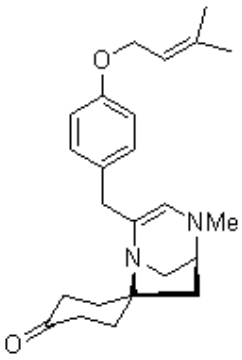
(-)-MUSCORIDE A

total synthesis

Angew. Chem. Int. Ed. **2003**, *42*, 1411.

Angew. Chem. **2003**, *115*, 1454.



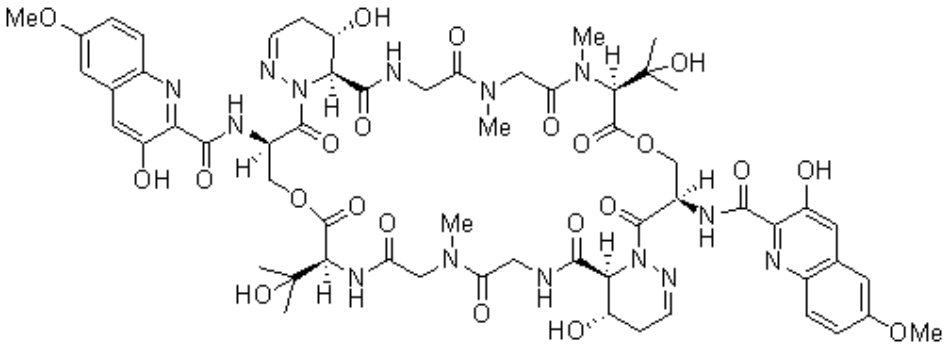


FR901483 **TAN1251C**

total synthesis

Org. Lett. **2001**, *3*, 765.

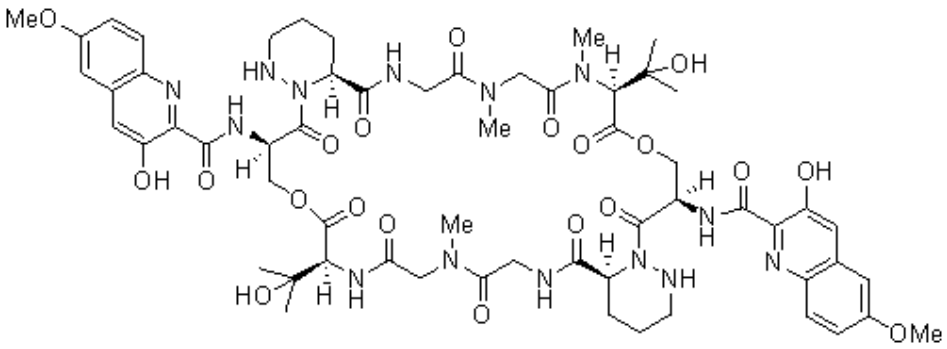
J. Am. Chem. Soc. **2001**, *123*, 7534.



LUZOPEPTIN C

total synthesis

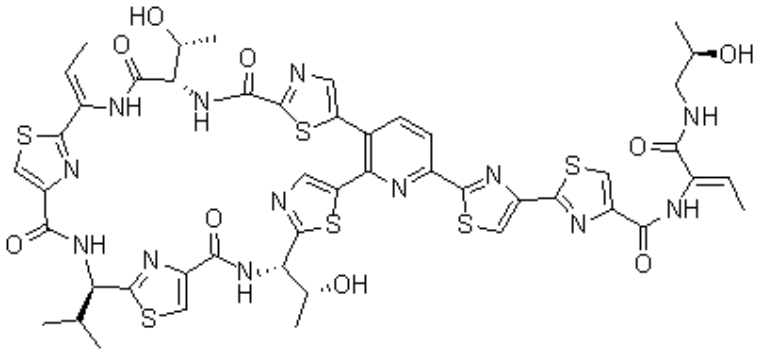
Tetrahedron Lett. **2001**, *42*, 1907.



LUZOPEPTIN E2

total synthesis

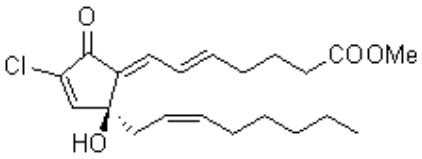
Angew. Chem. Int. Ed. **2000**, *39*, 2493



MICROCOCCIN P1 BYCROFT-GOWLAND STRUCTURE

total synthesis

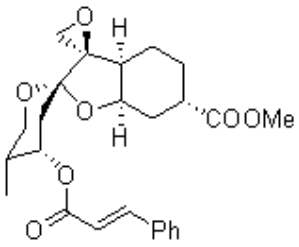
Org. Lett. **1999**, *1*, 1843.



(±)-CHLOROVULONE II

total synthesis

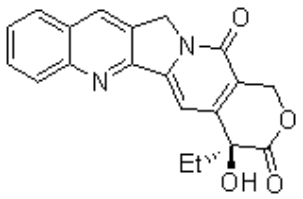
J. Org. Chem. **1998**, *63*, 1668.



(±)-PHYLLANTHOCIN

total synthesis

J. Org. Chem. **1997**, *62*, 7806.



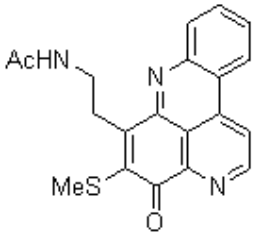
(+)-CAMPTOTHECIN

total synthesis

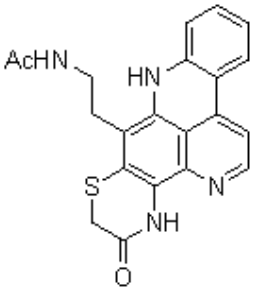
Angew. Chem. **1996**, *108*, 1789.

Angew. Chem. Int. Ed. **1996**, *35*, 1692.

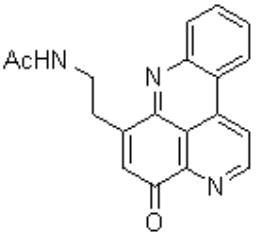
Tetrahedron **1997**, *53*, 11049.



CYSTODYTIN J



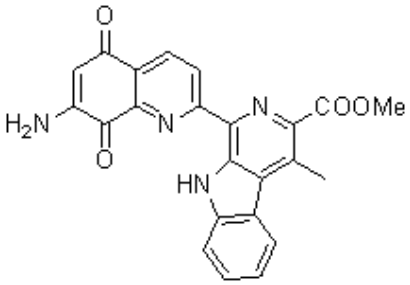
DIPLAMINE



SHERMILAMINE B

total synthesis

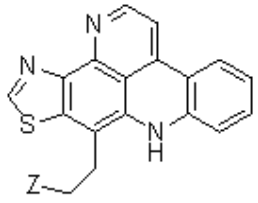
Tetrahedron Lett. **1995**, *36*, 4709.

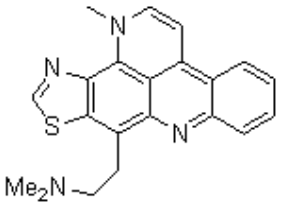


LAVENDAMYCIN METHYL ESTER

formal synthesis

J. Chem. Soc., Chem. Commun. **1993**, 1463.

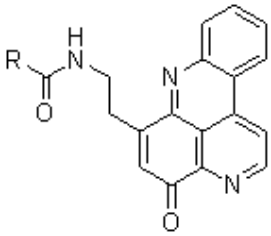




KUANONIAMINE B-D **DERCITINS**

total synthesis

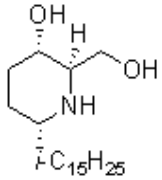
J. Am. Chem. Soc. **1992**, *114*, 10081.



CYSTODYTINS A-C

total synthesis

J. Am. Chem. Soc. **1991**, *113*, 8016.



(+) Desoxoprosopinine

total synthesis

J. Am. Chem. Soc. **1989**, *111*, 3473.