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Recent Advances in the Use of Tandem Reactions for Organic Synthesis

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1. Introduction

The development of tandem reaction processes is a rapidly growing area of synthetic organic chemistry. It is virtually impossible to pick up a current journal without seeing several papers describing new methods in this domain or to find a total synthesis that does not incorporate a one-flask multistep reaction. Though hundreds of examples have been known and used for many years, only recently has a focused effort been made to expand their use in organic synthesis.

Tandem reactions, sometimes also called domino, sequential, cascade, consecutive, iterative, zipper, and one-pot (one-flask) reactions, link several transformations together in a single synthetic step. Typically, an initial reaction produces an intermediate that undergoes further transformations with strategically positioned reactive centers in the same molecule, with other compounds in the reaction mixture, or with additional reagents

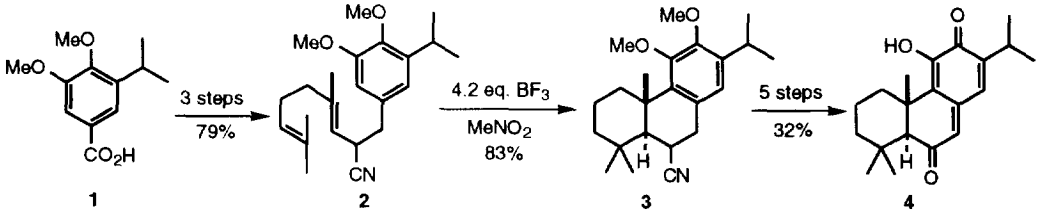
introduced after the initial transformation takes place. Over the past decade, tandem reactions have gained wide acceptance because they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used. Furthermore, they frequently permit efficient access to unique chemical structures and occasionally result in greater reaction selectivity.

The proliferation of tandem reactions is evidenced by the number of recent reviews covering this topic. One book and three review articles have presented excellent overviews of the field covering the literature through 1992.[1-4] Other articles have presented summaries of individual reaction types.[5-8] The purpose of this review is to update the entire field with coverage extending from late 1991 to early 1995. It is, of course, impossible to locate all of the published examples of tandem reactions, since many are incorporated in total syntheses advertised under different keywords. The cases cited in this Report have been selected to highlight the most promising applications of tandem reactions to organic synthesis.

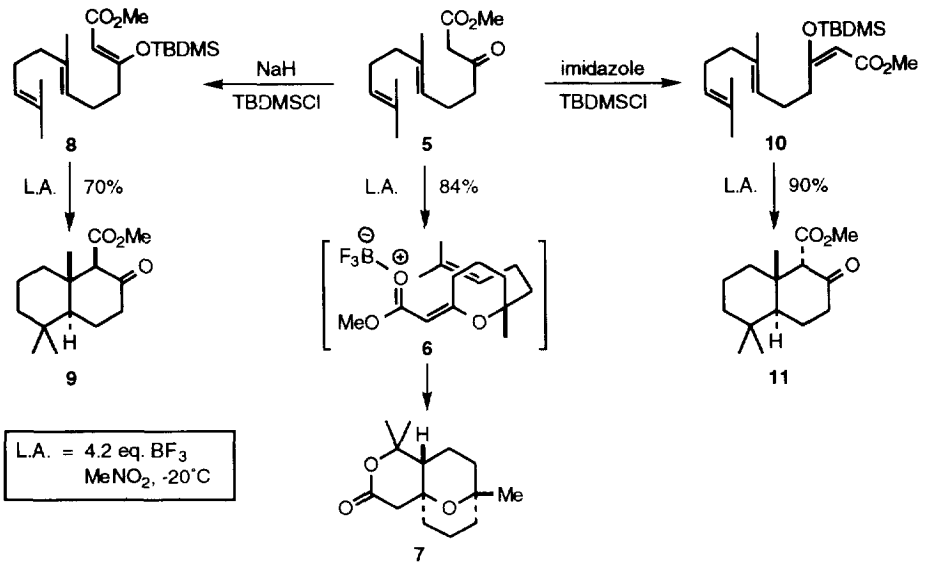
It is difficult to organize a review that covers such a diverse array of transformations. Fortunately, one of the earlier reviews[3a] presented an excellent system: it catalogued the reactions on the basis of the reaction intermediates or, in some cases, the reaction types involved in the first two synthetic steps. A similar organization has been adopted in this Report. As the period covered by this survey is limited, several of the possible classifications have been left out due to a lack of suitable new examples to report.

2. Cationic Sequences

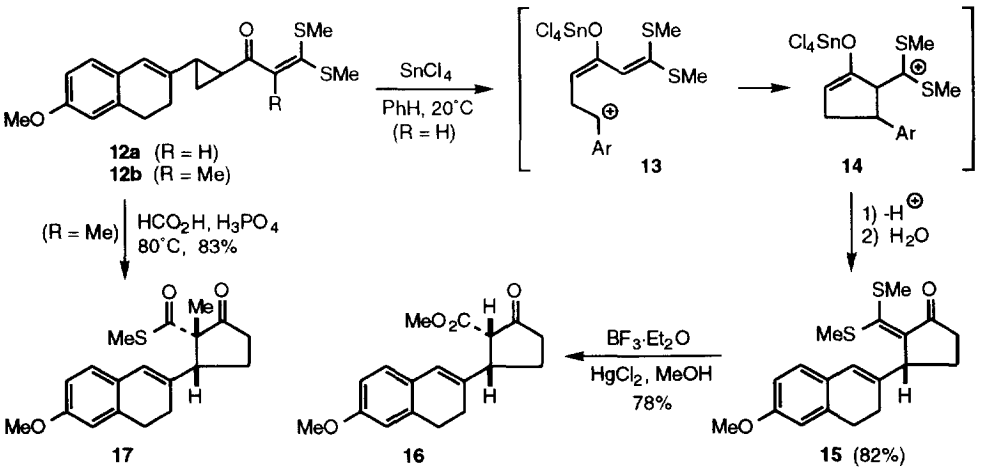
Cation-mediated reactions constitute one of the oldest known subsets of tandem reactions. Recent examples include a number of cationic-cationic processes that have been used to "zip" together potentially useful ring structures. Livinghouse and Harring[9] have recently applied Lewis acid-promoted biomimetic polyene cyclizations to diterpene synthesis. In this work, BF_3 in $MeNO_2$ was found to provide an efficient means of initiating the cyclization. Thus, aromatic diene **2**, prepared in three steps from 3-isopropyl-4,5-dimethoxybenzoic acid (**1**), was treated with BF_3 in $MeNO_2$ to afford an 83% yield of the tricyclic intermediate **3**. A five-step sequence then provided (±)-taxodione (**4**) in a 32% overall yield.



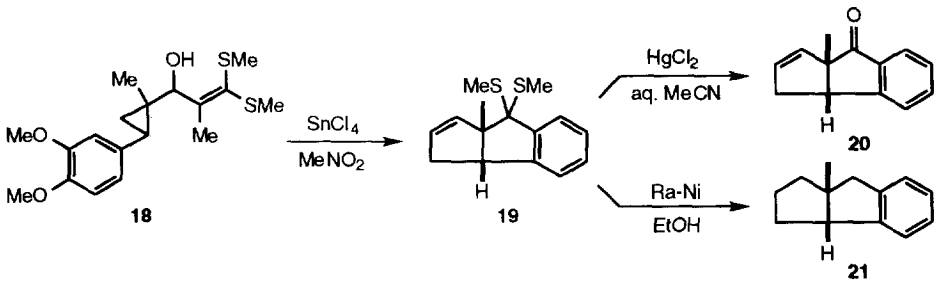
These same authors further demonstrated[10] that the outcome of BF_3-$MeNO_2$ polyene cyclizations is sensitive to the terminating moiety. Direct cyclization of β-ketoester **5** furnished the unexpected tricyclic lactone **7** in 84% yield by a process that can be formulated as either an inverse electron demand [4+2] cycloaddition via **6** or a stepwise cationic process. On the other hand, cyclization of the (*Z*)- and (*E*)-silyloxyenoates (**8** and **10**) provided the equatorial and axial β-ketoesters **9** and **11** in 70% and 90% yield, respectively.



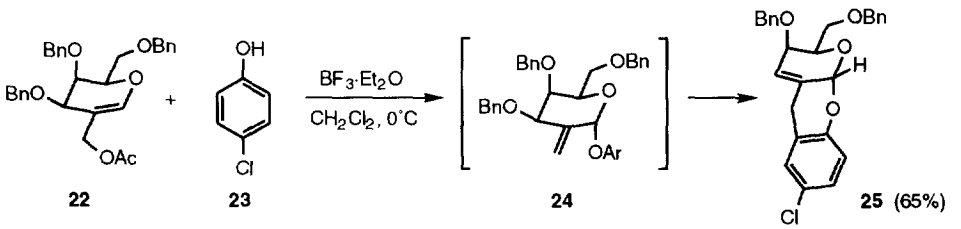
Another example of a tandem cationic-cationic process utilized α-[bis(methylthio)methylene]alkyl cyclopropyl ketones in a general synthesis of cyclopentanone derivatives.[11] One striking example was explored as a potential entry to the 11-oxosteroid framework. Treatment of **12a** with $SnCl_4$ in benzene furnished cyclopentanone **15** in 82% yield. This transformation involved coordination of the $SnCl_4$ to the carbonyl, three-ring opening to give the aryl-stabilized carbocation **13**, cyclization to the sulfur-stabilized carbocation **14**, and loss of a proton to give, after workup, the ketene thioacetal **15**. Further treatment with $BF_3{\cdot}Et_2O$ and $HgCl_2$ in MeOH effected conversion of **15** to **16** in 78% yield. A similar reaction on **12b** was carried out in HCO_2H / H_3PO_4 to generate 11-oxosteroid precursor **17** in 83% yield.



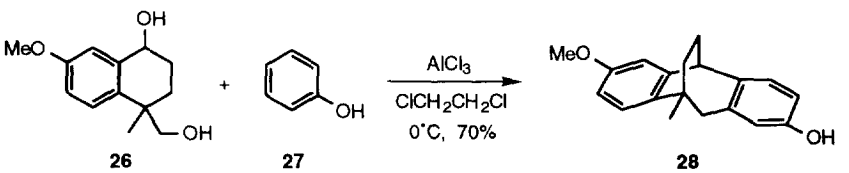
A second application of this rearrangement strategy provided rapid access to the cyclopent[*a*]indene ring skeleton.[12] Treatment of alcohol **18** with $SnCl_4$ in $MeNO_2$ converted it to the bis(methylthio) ketal **19**. The thioketal was then treated with either $HgCl_2$ in aqueous MeCN to produce ketone **20** or Raney nickel in EtOH to give cyclopent[*a*]indene **21**. Both products were reportedly isolated in "good yield."



A novel tandem Ferrier rearrangement / cyclization has been used to prepare chiral pyrano[2,3-*b*][1]benzopyrans by a one-flask cation-mediated process.[13] Reaction of 2-C-acetoxymethylgalactal **22** with *p*-chlorophenol (**23**) in the presence of $BF_3{\cdot}Et_2O$ resulted in an exocyclic Ferrier rearrangement to give **24**, followed by an intramolecular cyclization to the chiral pyrano[2,3-*b*][1]benzopyran **25** in 65% yield. Other phenols were also successfully converted making this an efficient and general approach to this ring system.



Finally, a double Friedel-Crafts reaction has been described for the synthesis of benzo-annulated bicyclo[3.2.2]nonane systems.[14] Treatment of diol **26** with phenol (**27**) in the presence of catalytic $AlCl_3$ afforded **28** in 70% yield. Since phenol should undergo initial substitution in the para position, it appears that the benzylic alcohol reacts first followed by the unactivated primary alcohol. Yields for five examples reported were in the 50-75% range.



3. Anionic Sequences

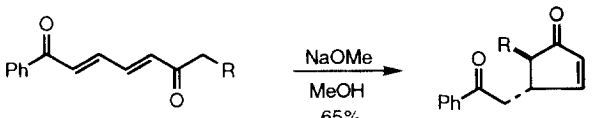
The largest family of tandem reactions involves anionic intermediates. Some of the more established tandem processes (i.e., Robinson annulation, double Michael reactions, reduction / lactonization of γ-ketoacids, etc.) fall into this category. Consequently, this family of transformations has been used extensively

in total syntheses and has been adapted to the preparation of a broad range of target compounds. Efforts in this area have provided some very elegant and selective approaches to polycyclic structures.

3a. Anionic-Anionic Reactions

A large fraction of anionic-anionic processes involve either a Michael-initiated or a Michael-terminated process and generate a cyclic structure. The Michael-Michael tandem reaction is a powerful tool in forging ring systems common to many natural products. In this sequence, a nucleophilic species adds to an activated alkene to produce a stabilized anion, which then adds to a second activated alkene positioned so as to close a five- or six-membered ring. The sequence is terminated by reaction with an electrophile, most often a proton, an alkylating agent, or yet another alkene. The recent examples that appear below have considerable potential in organic synthesis.

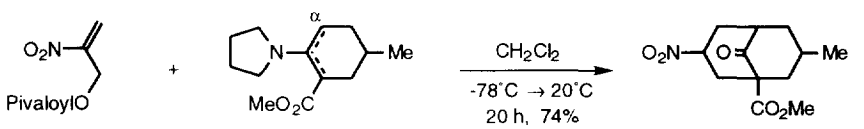
An interesting approach to cyclopentenones was observed upon treatment of 1,6-dioxo 2,4-dienes such as **29** with sodium methoxide.[15] The process involved 1,4-addition of methoxide to the unsaturated alkyl ketone, anion exchange, and closure on the unsaturated aryl ketone. Finally, base-induced elimination of methoxide introduced the double bond to give cyclopentenone **30**. The reaction succeeded in cases where R was alkyl (60-65% yield), but the methyl ketone (R = H) failed to give a cyclopentenone derivative.



29 **30**

Similar compounds have been prepared in 35-82% yields by use of a novel base-catalyzed "pseudo-cine" substitution reaction between diketene and 4-hydroxy-2-cyclopenten-1-one.[16]

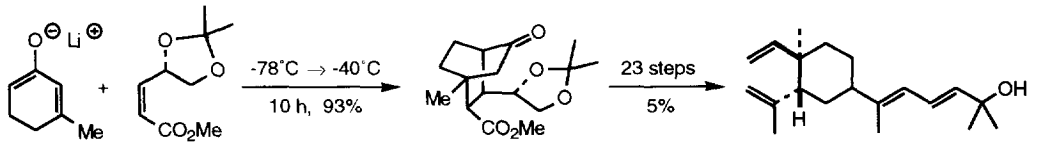
Enamines derived from β-ketoesters undergo bicycloannulation with masked double Michael acceptors such as 2-nitro-3-pivaloyloxypropene (**31**).[17] Reaction of the six-membered cyclic enamine **32** with **31** in CH_2Cl_2 at -78 °C → 20 °C gave **33** in 74% yield. The mechanism has been shown to involve initial S_N2' displacement of the pivaloyloxy group by the α carbon of the enamine. In further experiments, this reactivity was exploited to achieve essentially complete regioselectivity in cyclizations of unsymmetrically functionalized double Michael acceptors, though only modest yields of 29-49% were achieved.



31 **32** **33**

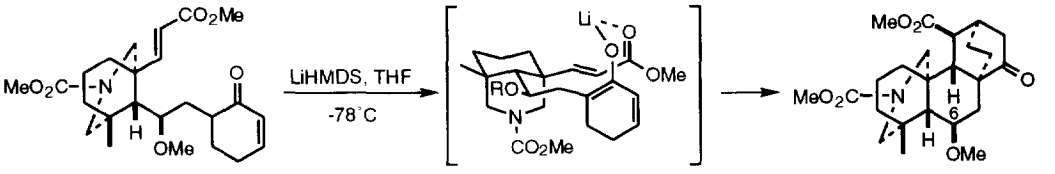
Excellent selectivities have been observed in double Michael additions of cyclohexenone lithium enolates with acrylate esters.[18-23] Recent examples include an approach to a key intermediate for the synthesis of the sesquiterpene 2-isocyanatopupukeanane[20] and an intramolecular variant that provided the tricyclo-[5.3.1.$0^{3,8}$]undecane ring system common to patchouli alcohol and seychellene.[21] In a beautiful example, this procedure was used as the first step of an enantioselective synthesis of the diterpene fuscol (**37**).[22] Addition of the kinetic enolate of 3-methyl-2-cyclohexenone (**34**) to α,β-unsaturated ester **35** afforded ketoester **36** as a

single isomer in 93% yield. This compound was converted to the natural product **37** in 23 steps with a 5% overall yield.



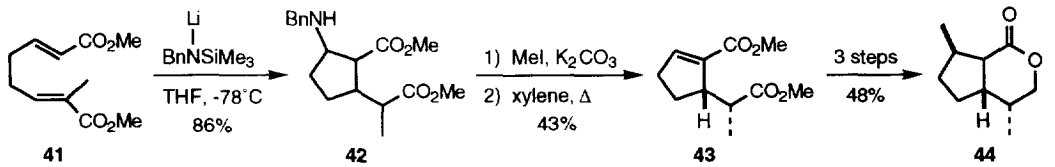
34 **35** **36** **37**

A second elegant application of the intramolecular double Michael addition has been described by Fukumoto and co-workers in the synthesis of oxygenated derivatives of the diterpene alkaloid atisine.[23] Chiral cyclization substrate **38** was prepared in six steps by adaptation of methods previously reported by the authors. This compound was treated with LiHMDS to afford a 62% yield of the double Michael product **40** as a single stereoisomer, presumably through the lithium chelated species **39**. Hydrolysis and (radical) decarboxylation of the carbon-bound ester in **40** subsequently delivered the C(6)-oxygenated atisine derivative.



38 **39** **40** (62%)

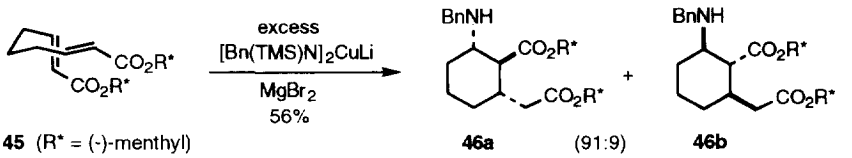
Further applications of tandem conjugate additions involving (2*E*,6*E*)-2,6-octadienedioate and (2*E*,7*E*)-2,7-nonadienedioate esters have been reported.[24] In a synthesis of (±)-dihydronepatalactone (**44**),[24a] lithium *N*-benzyl-*N*-(trimethylsilyl)amide (LSA) was added to dimethyl (2*E*,6*E*)-2-methyl-2,6-octadienedioate (**41**) to afford a complex mixture of ring-closed diesters **42** in 86% yield. Quaternization and elimination of the amine group from **42** provided a 7:3 mixture of unsaturated esters, from which the major isomer **43** was isolated in 43% yield. A three-step sequence involving (1) reduction of both esters, (2) selective oxidation of the allylic alcohol with spontaneous lactonization, and (3) addition of lithium dimethylcuprate furnished the natural product. The regioselective addition to the unsubstituted acrylate moiety in the first step was rationalized in terms of the increased electron density at the β carbon of the methyl substituted alkene, which would tend to deactivate it toward attack by LSA.



41 **42** **43** **44**

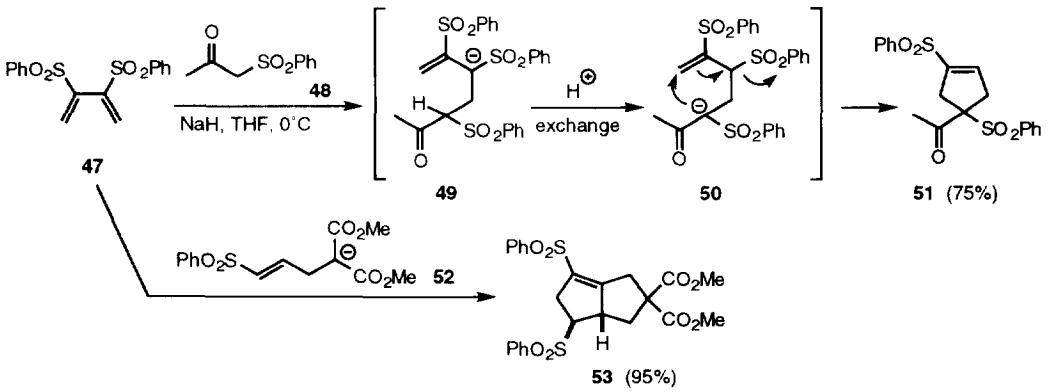
In the cyclohexane series, double conjugate additions showed a high preference for the all-equatorial product. For example, addition of the LSA "cuprate" to the di-(-)-menthyl (2*E*,7*E*)-2,7-nonadienedioate (**45**) exhibited high diastereo- and enantioselectivity when the addition was carried out in the presence of a bidentate

chelating Lewis acid such as $MgBr_2$.[24b] The Lewis acid was thought to favor the intermediacy of the folded conformation of the diene (indicated) which led to high asymmetric induction in the formation of product **46**.

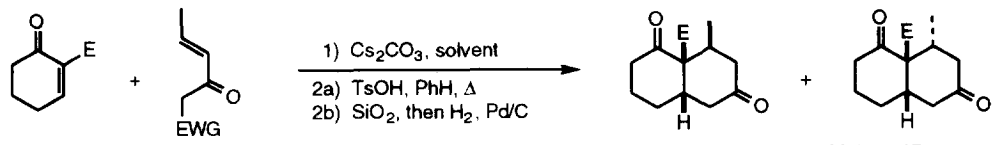


45 (R* = (-)-menthyl) **46a** (91:9) **46b**

Padwa and co-workers have explored an interesting Michael / Michael / elimination sequence as a [4+1] annulation approach to cyclopentenes from 2,3-bis(phenylsulfonyl)-1,3-butadiene (**47**).[25a] Treatment of **47** with phenylsulfonyl acetone (**48**) in the presence of a slight excess of NaH, afforded the cyclopentene **51** in 75% yield. The reaction involved Michael addition of the active methylene compound to give **49**, proton exchange to give the more stable anion **50**, and Michael ring closure with elimination of the allylic sulfone. This procedure was further extended to develop a Michael / [3+2] approach to bicyclo[3.3.0]octenes.[25b] Reaction of **47** with the donor-acceptor reagent **52** afforded the bicyclic compound **53** by consecutive Michael, anion exchange, Michael, Michael, and elimination reactions. The final Michael addition in both sequences appears to be a disfavored 5-*endo-trig* cyclization, but such reactions are known to proceed when elimination can occur from the anion produced.[25c]



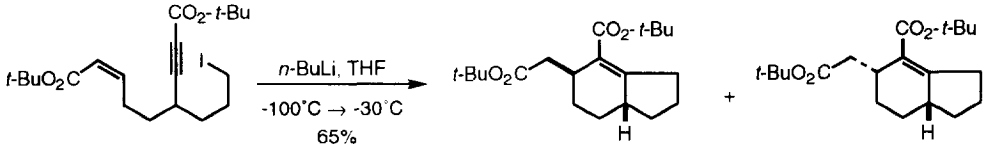
Several groups have explored the use of Nazarov reagents as donor-acceptor reagents for double Michael reactions. Albertini et al.[26] have employed this strategy to assemble a key intermediate in the synthesis of (±)-epibatidine. Additionally, Deslongchamps and co-workers[27] have thoroughly studied this process in a general approach to *cis*-decalins. The annulation of **54** by **55** was observed to proceed by either a [4+2] cycloaddition or a double Michael addition, the preferred pathway being determined by solvent polarity and by substitution on the Nazarov reagent. Sequential treatment of **55** with Cs_2CO_3 followed by cyclohexenone **54** produced a mixture of **56** (cycloaddition product) and **57** (double Michael product) after cleavage of the electron withdrawing group (EWG). Annulation with **55a** was most sensitive to solvent polarity, giving a 1:1 ratio of the two products in polar solvent and a large preference for the cycloaddition product (i.e. **56**) in nonpolar solvent. Keto sulfoxide **55b** favored the double Michael route to give **57** regardless of solvent.



54 **56** (E = CO_2Me) **57**

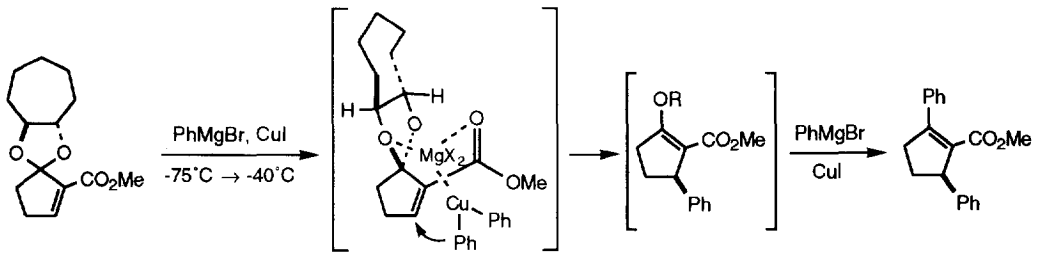
	Solvent		
55a (EWG = CO_2-*t*-Bu)	DMF	54	46
	$CHCl_3$	≥ 99	1
55b (EWG = SOPh)	DMF	1	99
	CH_2Cl_2	1	99

Tandem conjugate additions have also been observed in reactions of organolithium and organocopper reagents. Metal-halogen exchange[28] in compounds such as the iodo diester **58** led to consecutive intramolecular conjugate additions and the formation of bicyclic compounds **59** (major) and **60** (minor). Interestingly, the preference for **59** was greater from closure on the *Z* alkene (3.5:1) than the *E* alkene (1.1:1). Chelation and conformational effects were invoked to rationalize this enhanced selectivity, but it was suggested that further work would be necessary to substantiate these claims.



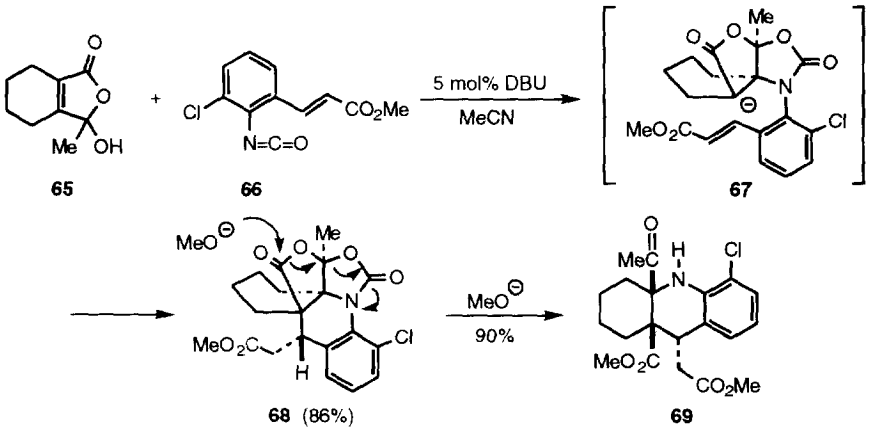
58 **59** (3.5:1) **60**

Although multiple additions of cuprates have been reported,[29] one of the more intriguing tandem reactions initiated by an organometallic species involved a diastereoselective conjugate addition / elimination / conjugate addition / elimination from reaction of PhMgBr/CuI (2:1) with chiral ketal **61**.[30] Following addition of the first phenyl group to **61**, elimination of one ketal oxygen gave enol ether **63**, which underwent a second addition-elimination sequence to produce the 2,5-diphenyl-1-cyclopentenecarboxylic ester **64** with high enantioselectivity. It was tentatively proposed that steric control of chelation in **62** was responsible for selective delivery of the phenyl group from the *si* face of the double bond.

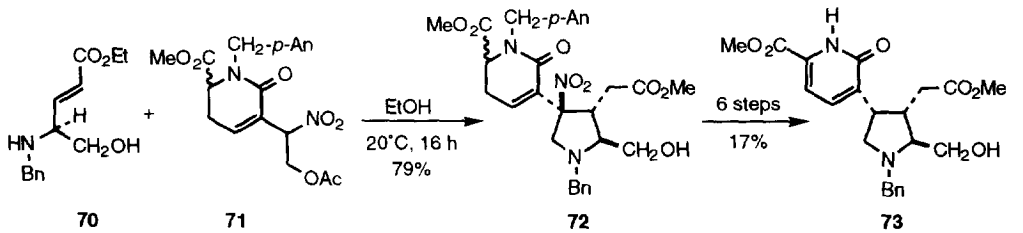


61 **62** **63** **64** (69%) [93% ee]

Heterocycles are also available through the use of tandem reaction strategies. A novel construction of the octahydroacridine skeleton has been reported from reaction of hydroxylactone **65** with isocyanate **66** in the presence of DBU.[31] The transformation involved addition of the alcohol to the isocyanate and Michael addition of the resulting amide anion to the unsaturated lactone to give **67**, followed by a second Michael addition to give pentacycle **68** in 86% yield. The key to the sequence was the use of the relatively strong amidine base, which permitted rotamer equilibration in the reversible closure leading to **67**. Treatment of **68** with methoxide then resulted in fragmentation-decarboxylation to afford the highly functionalized octahydroacridine **69** in 90% yield.

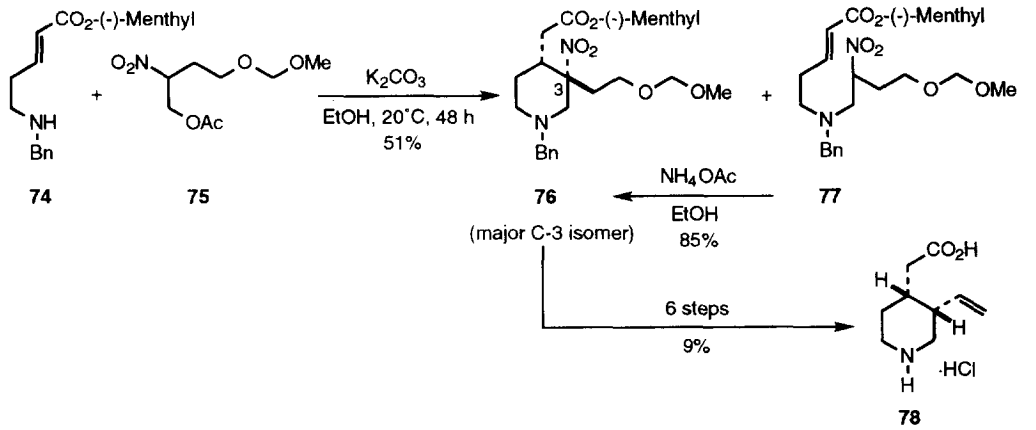


Double Michael reactions involving nitroalkene acceptors have been used by Benetti and co-workers in syntheses of acromelic acid A and (-)-meroquinene·HCl. In a formal synthesis of acromelic acid A,[32] the β,γ-unsaturated glutamic acid derivative **70** was used as the donor-acceptor reagent with β-acetoxynitro compound **71**. Reaction in EtOH resulted in elimination of HOAc from **71** to generate the unsaturated nitro compound, which underwent tandem Michael addition with **70** to give pyrrolidine **72** as a mixture of diastereomers in 79% yield. A six-step sequence converted this mixture to **73**, an intermediate in an earlier synthesis of acromelic acid A.

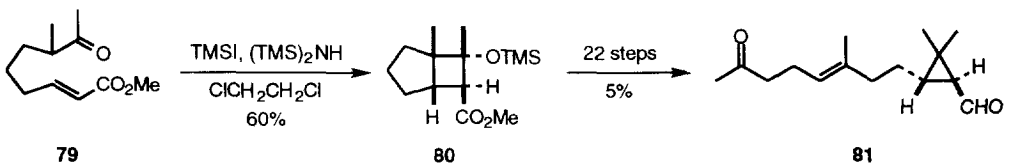


(-)-Meroquinene·HCl (**78**)[33] was prepared by use of (-)-menthyl (*E*)-5-(*N*-benzylamino)-2-pentenoate (**74**) as the donor-acceptor reagent. Reaction of **74** with the masked 2-nitro-1,3-butadiene **75** in the presence of K_2CO_3, afforded adduct **76** in 51% yield as a 4:1 mixture of diastereomers along with 36% of the simple Michael adduct **77**. The latter product could be cyclized to **76** (85%, 4:1 diastereomeric mixture) by separate

treatment with NH_4OAc in EtOH, effectively raising the yield for this process to 81%. The remainder of the synthesis required six steps from **76** and gave the target structure in 9% overall yield.

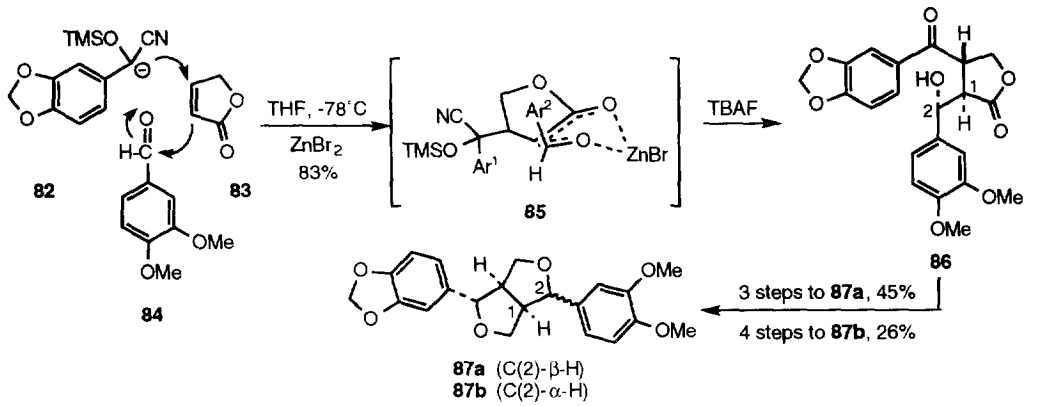


Several new methods linking one or more Michael additions with the aldol condensation have been delineated, many in the context of total synthesis work.[34-39] Fukumoto and co-workers[37] have developed a protocol for the preparation of polycyclic cyclobutanols by an intramolecular Michael / aldol tandem. Treatment of keto acrylate **79** with TMSI / $(TMS)_2NH$ produced the protected cyclobutanol **80** in 60% yield. This compound was subsequently converted in 22 steps (5% overall yield) to the natural product (±)-anthoplalone (**81**).

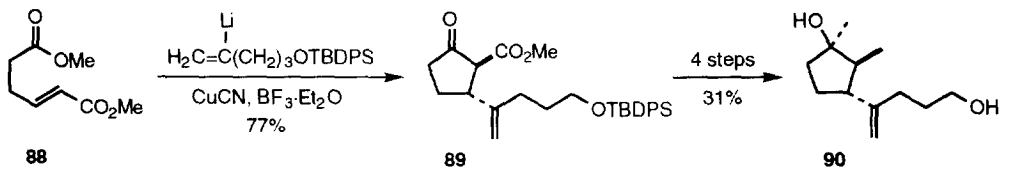


This same group also reported[38] a synthesis of (±)-ricciocarpin A by cyclization of dimethyl (2*E*,9*E*)-4,4-dimethyl-2,9-undecadienedioate using TBDMSOTf / Et_3N. In this case, ring closure formally involved Michael addition of the unsubstituted γ-carbon of the dienoate anion (C(8)) to the second acrylate moiety.

An intermolecular Michael / aldol sequence has been used for the synthesis of two epimeric furofuran lignans, methyl piperitol (**87a**) and fargesin (**87b**), from a common intermediate.[39] Deprotonation of the trimethylsilyl cyanohydrin of piperonal (**82**) with LDA and sequential addition of 2-butenolide (**83**), zinc bromide, and 3,4-dimethoxybenzaldehyde (**84**) afforded, after desilylation, adduct **86** with a 98:2 preference for the syn orientation of the C(1)-H and the C(2)-OH. In the key cyclization, it was proposed that exchange of the lithium counterion by zinc stabilized the required twist-boat transition state (**85**) essential for high stereoselectivity. Ketol **86** was carried on, in separate syntheses, to methyl piperitol (three steps, 45%) and to its C(2) epimer fargesin (four steps, 26%).

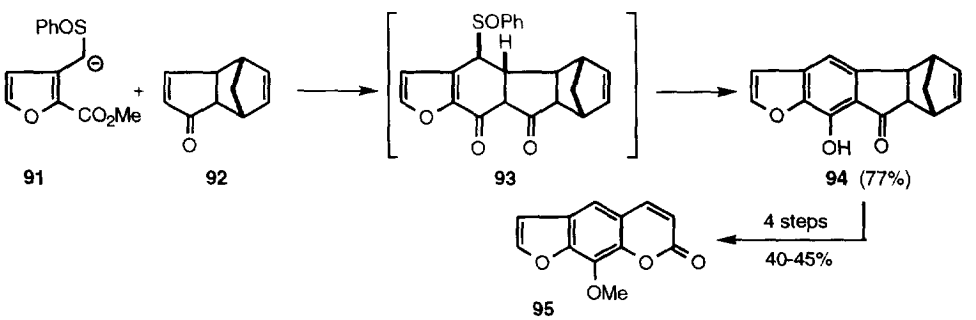


Tandem reactions combining a Michael addition with a Claisen condensation or another acylation process are also well represented in the recent literature.[40-46] In one report,[43] a conjugate addition / Dieckmann cyclization of the vinyl cuprate derived from 2-lithio-5-(*tert*-butyldiphenylsilyloxy)-1-pentene to dimethyl (*E*)-2-hexenedioate (**88**) was used to produce the five-membered cyclic keto ester **89**. This product was carried on to the fungitoxic modified sesquiterpene (±)-chokol A (**90**) in four steps with an overall yield of 31%.



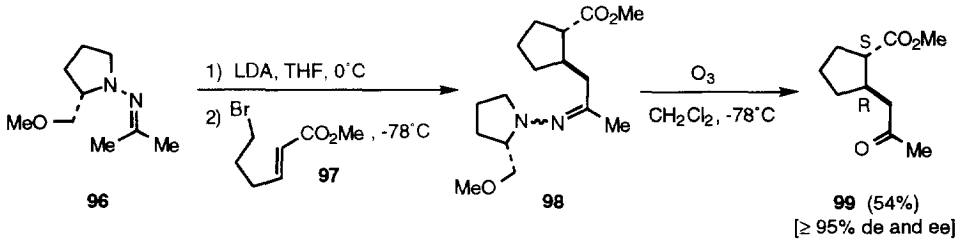
Work by other researchers[44] has extended the conjugate addition / Dieckmann cyclization protocol to the preparation of six-membered cyclic β-keto esters, but no total syntheses have yet appeared based on this methodology.

Michael addition / acylation processes have been further employed in the synthesis of carbazole and furocoumarin ring structures.[45,46] In the latter case,[46] the anion derived from furosulfoxide **91** was added to the masked cyclopentadienone **92**. This resulted in Michael addition / acylation to give **93**, and spontaneous loss of the sulfoxide group by a syn elimination to give the rearomatized structure **94** in 77% yield. A short synthetic sequence then converted this compound to methoxsalen (**95**). Interestingly, when the reaction was



performed with the analogous sulfone, rearomatization did not occur since an antiperiplanar E2 transition state would be required for elimination.

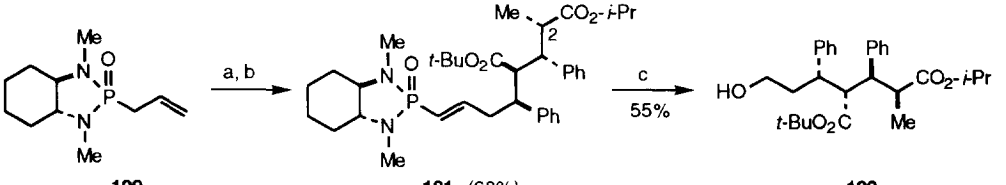
Two investigations of the tandem Michael addition / S_N2 reaction, also known as the Michael initiated ring closure (MIRC) reaction, have explored the possibility of achieving useful asymmetric induction. Enders and co-workers[47] have recorded excellent diastereo- and enantioselectivities in Michael / S_N2 reactions of SAMP- and RAMP-hydrazones. For example, deprotonation of SAMP-hydrazone **96** followed by reaction with methyl (*E*)-6-bromo-2-hexenoate (**97**) afforded the MIRC product **98**. Oxidative removal of the SAMP group afforded keto ester **99** in 54% overall yield with ≥ 95% diastereomeric and enantiomeric excess.



96 **97** **98** **99** (54%) [≥ 95% de and ee]

The second study, by Little and co-workers,[48] evaluated the Michael / S_N2 reaction using a series of chiral esters of ω-bromo-2-alkenoic acids. The best results were obtained for the addition of LDA to 10-dicyclo-hexylsulfamoyl-D-isobornyl (*E*)-7-bromo-2-heptenoate in THF at -72 °C → 0 °C. This gave a 78% yield of the 2-(diisopropylamino)-1-cyclohexanecarboxylic ester with a respectable 95% de. Use of other chiral ester groups and closure of smaller rings, however, showed only modest asymmetric inductions.

Hanessian and Gomtsyan[49] have developed a highly controlled asymmetric Michael / Michael / alkylation using a chiral phosphonamide anion with cinnamate esters to generate acyclic molecules with three and four contiguous stereogenic centers. Deprotonation of the phosphonamide **100** and sequential addition of *tert*-butyl cinnamate and *iso*-propyl cinnamate followed by quenching with methyl triflate afforded a 60% yield of **101** along with 7% of the C(2) epimer. Ozonolysis and reductive workup then provided the alcohol **102** in 55% yield.



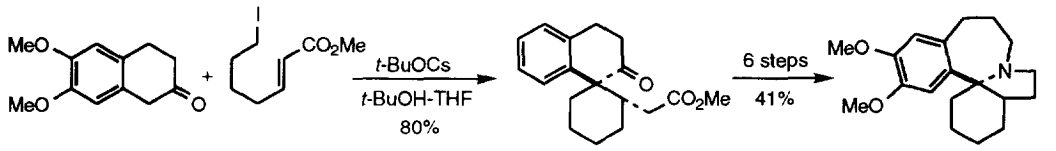
100 **101** (60%) **102**

a) *n*-BuLi, THF, -78°C, 1 min; b) (i) PhCH=CHCO$_2$-*t*-Bu, -78°C, (ii) PhCH=CHCO$_2$-*i*-Pr, -78°C, (iii) MeOTf, pyridine, -78°C; c) O_3, CH_2Cl_2-MeOH, -78°C; $NaBH_4$

Several other notable conjugate addition / S_N2 reactions included a formal [3+2] annulation procedure to generate nitrocyclopentanes,[50] a synthesis of 3-azabicyclo[3.1.0]hexanes,[51] a novel approach to cephalosporins,[52] and several ring-forming reactions involving organolithium[53] and organocopper[54] reagents.

Finally, a Michael addition / bromination sequence provided an asymmetric synthesis of precursors to a number of unusual amino acids.[55]

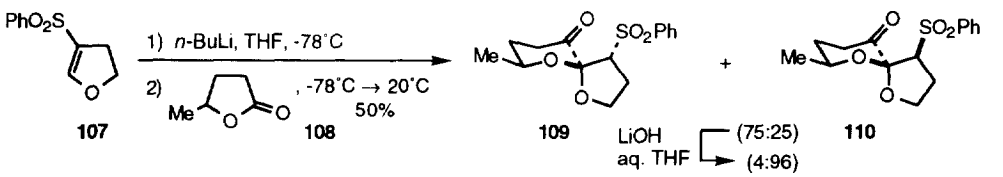
d'Angelo and co-workers[56] have used an S_N2 / Michael addition reaction to assemble the molecular skeleton of the Homoerythrina alkaloids. Reaction of β-tetralone **103** with iodo acrylate **104** using Cs_2CO_3 in DMF resulted in alkylation / Michael addition to give the spirane **105** as a single isomer in 48% yield. The selectivity of the reaction was thought to arise from kinetic control directed by chelation of the side chain ester group by the cesium counterion of the tetralone enolate. A later paper by Desmaële and Louvet[57a] reported an 80% yield for this reaction when cesium *tert*-butoxide was used as the base. This adduct was then efficiently converted to (±)-3-demethoxy-1,2-dihydrocomosidine (**106**) in six steps with an overall yield of 41%.



103 **104** **105** **106**

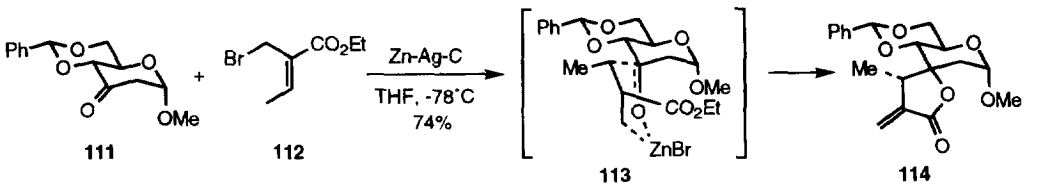
Interestingly, this second paper[57] offers some insight into one of the controlling factors in the chronology of tandem processes involving Michael additions and S_N2 reactions. The authors demonstrated that the pKa of the nucleophile in large part determines which reaction occurs first; nucleophiles with a pKa > 16 were observed to undergo Michael addition first whereas those with a pKa < 16 proceeded by an initial S_N2 attack. In addition to examples presented by the authors, a recent synthetic approach to nitrogen and sulfur heterocycles[58] lends further support to these findings.

Tandem reactions involving alkoxide addition to activated alkenes have also shown promise in organic synthesis.[59-65] For example, treatment of the anion derived from β-phenylsulfonyl dihydrofuran **107** with butyrolactone **108** resulted in acylation followed by Michael addition of the resulting alkoxide to the unsaturated sulfone to give 1,6-dioxaspiro[4.5]decanes **109** and **110**.[64] At low temperature, the reaction produced a kinetic adduct bearing a cis relationship between the carbonyl and the phenylsulfonyl group. Equilibration with base, however, afforded the more stable trans product.

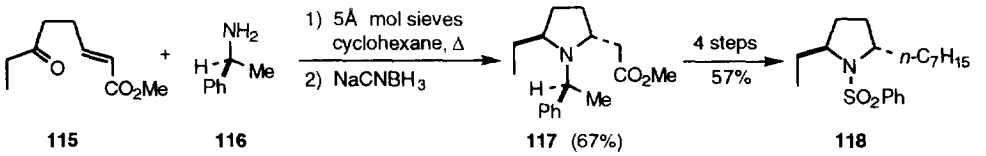


107 **108** **109** **110**

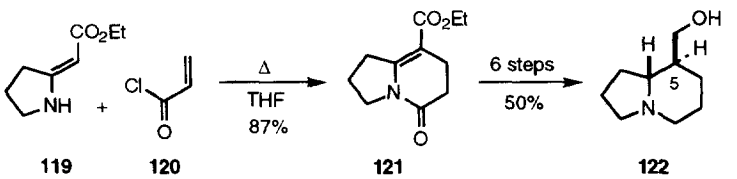
Double stereodifferentiating Dreiding-Schmidt reactions have been employed in a synthesis of spiroannulated carbohydrate-derived α-methylene-γ-butyrolactones.[65] Reaction of methyl-4,6-O-benzylidene-2-deoxy-α-D-erythro-hex-3-ulopyranoside (**111**) with the organozinc reagent derived from ethyl (*E*)-2-bromomethyl-2-butenoate (**112**) and zinc-silver / graphite at -30 °C afforded **114** in 74% yield after chromatographic workup. Selectivity for *re-re* attack in this reaction was attributed to transition state **113**, which minimizes steric interactions.



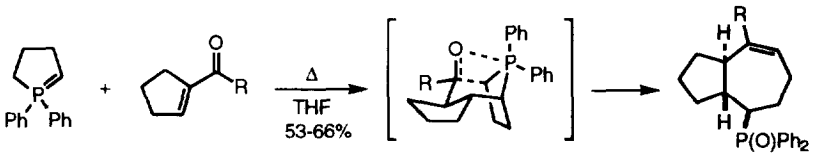
Nitrogen heterocycles are also accessible by tandem reaction processes.[66-71] Pyrrolidines have been prepared by a novel procedure involving sequential reductive amination / Michael addition.[70] Condensation of keto acrylate **115** with (*S*)-1-phenylethylamine (**116**) followed by imine reduction with $NaCNBH_3$ afforded a 67% yield of the racemic *trans*-2,5-disubstituted pyrrolidine **117** along with 8% of the cis isomer. Surprisingly, the greatest selectivity was achieved through the use of more hindered amines; the use of chiral amines did not result in significant asymmetric induction. Thus, while benzylamine produced a 2.6:1 ratio of trans:cis pyrrolidines, the use of α-isopropylbenzylamine afforded essentially 100% of the trans 2,5-disubstituted product. The utility of this method was validated in a synthesis of (±)-*trans*-5-ethyl-2-heptyl-1-pyrrolidine (as its *N*-phenylsulfonyl derivative **118**), a central nervous system-active constituent of fire ant venom.



A novel acylation / Michael reaction has been used by Paulvannan and Stille[71] to synthesize (±)-tashiromine (**122**). Reaction of β-enamino ester **119** with acryloyl chloride (**120**) furnished the aza-annulation product **121** via an acylation / Michael sequence. The indolizidine product was then converted to the alkaloid in six steps with an overall yield of 50%. Control in the double bond reduction of **121** was best achieved by hydrogenation in the presence of Na_2CO_3, which provided a > 95:5 cis:trans preference in the product. Thus, an epimerization at C(5) was necessary in the latter stages of the synthesis to secure the target alkaloid with the correct relative stereochemistry.



The Michael reaction has been coupled with the Wittig olefination to produce several attractive sequences. A stereoselective synthesis of the *trans*-hydroazulene ring system has been developed based on the reaction of ylide **123** with 1-acylcyclopentene derivatives **124**.[72] In each case, the hydroazulene **126** was produced as a single stereoisomer in 53-66% yield. The high diastereoselectivity was attributed to the equatorial-equatorial ring fusion in phosphabicyclic transition state **125**, which minimizes 1,3-diaxial interactions.

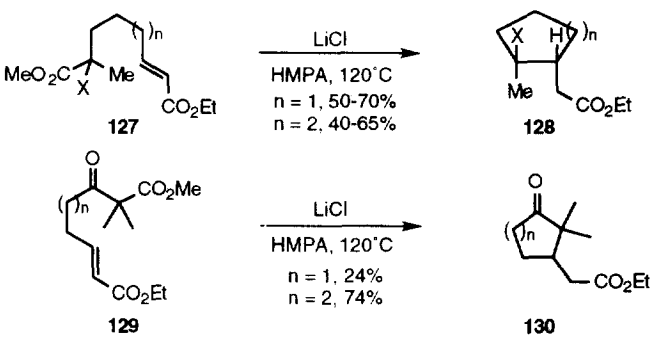


123 **124** **125** **126**

Other processes incorporating Wittig procedures included a Wittig / Michael synthesis of C-furanosyl α-hydroxy propanals and propanoic acids,[73] a Horner-Emmons / Michael route to 5-hydroxy prolinates,[74] a DIBALH reduction / Wittig-Horner reaction to prepare *N*-protected γ-amino-α,β-unsaturated dicarboxylate esters,[75] and multiple aza-Wittig-type reactions to generate indoles and 1,3-benzodiazepines.[76] Additionally, an unexpected synthesis of spirobicyclo[3.1.0]hexanes was achieved through a tandem acetylene addition / Michael cyclization between pinacolone-type ketones and 4-pentynyltriphenylphosphonium bromide.[77]

Several interesting rearrangements have been observed in the formation of naphthols and indanes from reaction of dilithiated 2-butenoic acid derivatives with 3,6-dimethylbenzyne.[78] Additionally, lithiated aromatic and heteroaromatic acetonitriles have been added to substituted benzynes to give 2-benzylbenzo-nitriles.[79,80] In this reaction, addition of the organolithium species to the benzyne followed by migration of the nitrile to the ortho aromatic position by an addition-elimination process accounted for the observed products.

One final entry utilized a demethoxycarbonylation / Michael addition reaction to generate highly functionalized carbocycles.[81,82] Two examples of this reaction type are illustrated for the conversion of **127** to **128** and **129** to **130**. Substrates were designed to be activated toward decarboxylation once the methyl ester was cleaved (i.e., X = EWG for **127**). Selective nucleophilic attack at the methyl ester (by chloride) initiated demethoxycarbonylation to produce a stabilized anion which then cyclized in Michael fashion on the tethered acrylate ester. Selectivity in the ring closure led to a preponderance of the product having the X group and the acetate side chain oriented trans in product **128**, even when the donor moiety was further substituted with an alkyl group. Early work on carbocycles required the use of HMPA as a solvent, but recent studies aimed at heterocycle syntheses have shown that DMEU and DMPU are reasonable substitutes in these cases.



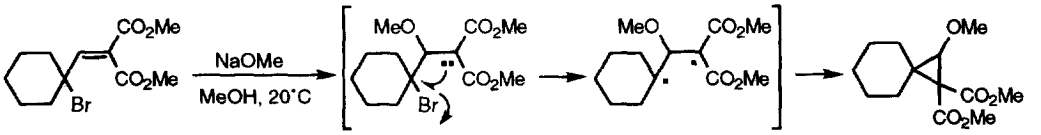
127 **128** **129** **130**

3b. Anionic-Radical and Anionic-Carbene Sequences

Anionic-radical and anionic-carbene sequences are two new classifications added only recently to the growing list of tandem processes. Thus far, only one example of each has been chronicled, and these are

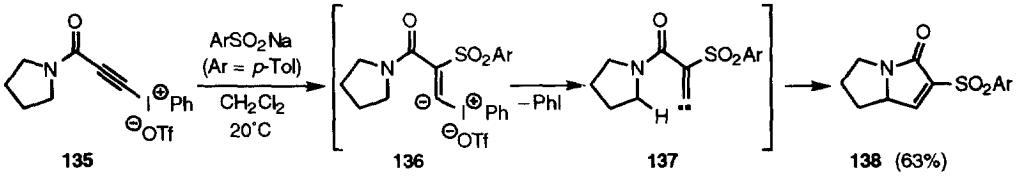
outlined below. Since both reactions generate unique ring structures, further work in this area is warranted and should prove fruitful.

One report[83] has detailed the intervention of a single electron transfer mechanism in the Michael / S_N2 (MIRC) reaction of tertiary allylic bromide **131** doubly activated by electron withdrawing substitution at C(1) of the allylic moiety. Addition of methoxide to the acceptor gave the stabilized malonate anion **132**. To explain displacement of the tertiary bromide, closure was thought to involve single electron transfer from the anionic center to the carbon-bromine antibonding orbital to produce the carbon radical and bromide anion. Closure of the resulting 1,3-diradical **133** then gave cyclopropane **134**.



131 **132** **133** **134** (79%)

A second new process involving a Michael addition / carbene insertion sequence has been investigated by Stang and co-workers.[84] In this reaction, sodium *p*-toluenesulfinate was added in a Michael reaction to β-ketoethynyl(phenyl)iodonium triflates such as **135**. Loss of iodobenzene from the intermediate anion **136** produced the alkylidene carbene **137**, which underwent 1,5-C-H insertion to the fused-ring γ-lactam **138**. The preference for C-H insertion from the carbene intermediate was reported to derive from the low migratory aptitude of the β-carbonyl and β-sulfonyl functions.



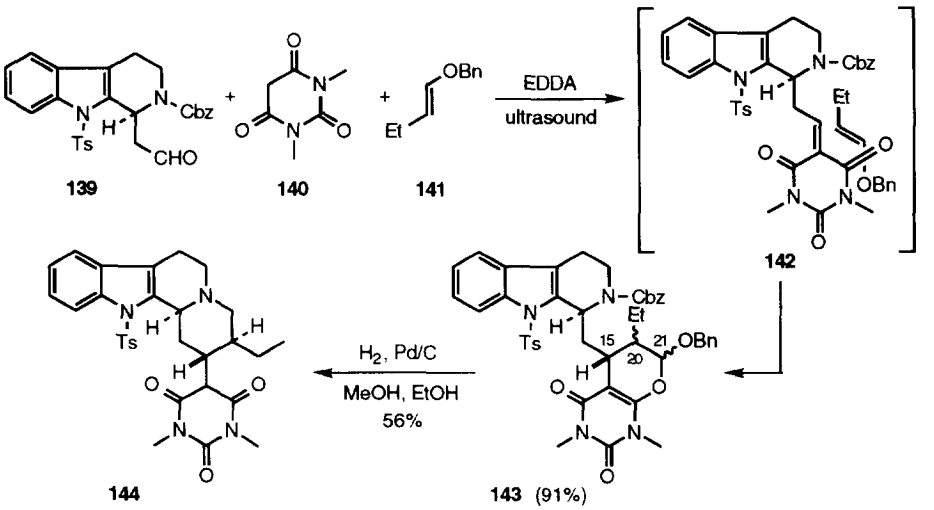
135 **136** **137** **138** (63%)

3c. Anionic-Pericyclic Sequences

Several sequential anionic-pericyclic processes have also been documented in the recent literature.[85-94] In these reactions, an initial addition or elimination reaction leads to a reactive intermediate capable of further pericyclic reactions with inter- or intramolecular functionality. Anionic reactions have been coupled with the Diels-Alder and [3+2] cycloadditions, Claisen rearrangements, electrocyclizations, and [2,3]-sigmatropic shifts. This area also appears to offer considerable opportunity for further work.

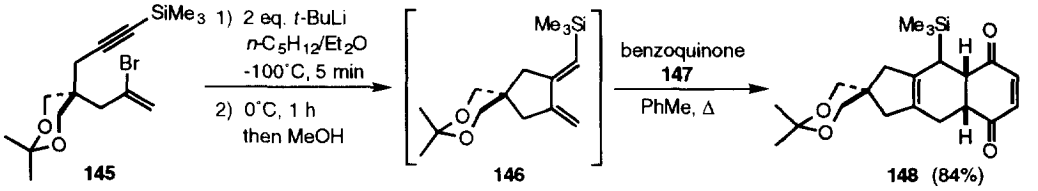
One of the most elegant applications of this technology is exemplified by the synthesis of normal, *pseudo*, and *allo* type indole alkaloid derivatives by a highly efficient three-component tandem Knoevenagel / hetero-Diels-Alder / hydrogenation sequence.[88] For example, reaction of the tetrahydro-β-carboline aldehyde **139**, *N,N'*-dimethylbarbituric acid (**140**), and (*Z*)-1-benzyloxy-1-butene (**141**) under ultrasound conditions with catalytic ethylenediammonium diacetate (EDDA) afforded the strictosidine analogue **143** as a mixture of isomers at C(20) and C(21) but with a > 20:1 preference for the *R* configuration at C(15). The reaction essentially follows a biomimetic pathway and can be used to generate enantiomerically pure products by

starting with a chiral aldehyde. Hydrogenation of **143** cleaved both benzyl protecting groups liberating the ring nitrogen and the protected aldehyde. Cyclization to the iminium ion and reduction under the hydrogenation conditions then gave the *pseudo* type indole alkaloid derivative **144**.



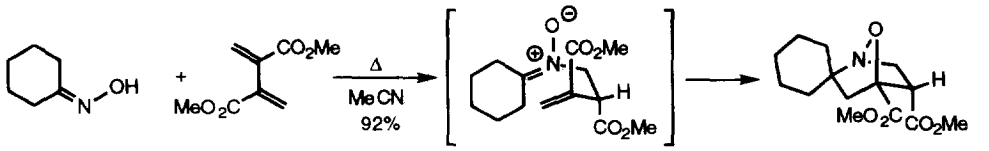
139 **140** **141** **142** **143** (91%) **144**

Several tandem processes have exploited rearrangements of organolithium compounds. Bailey and co-workers have investigated a number of interesting cycloisomerization reactions initiated by metal-halogen exchange of δ- and ε-unsaturated iodides with *tert*-butyllithium.[89,90] Beyond simple cycloisomerizations, a one-flask sequential anionic cyclization / cycloaddition route to linear fused-ring systems has been developed.[91] Lithium-halogen exchange of the acetylenic vinyl bromide **145** with *tert*-butyllithium followed by ring closure gave the 1,2-bis-exocyclic diene **146**. This diene was further treated with benzoquinone (**147**) in a Diels-Alder reaction to produce the isomerically pure fused-ring adduct **148** in 84% overall yield.



145 **146** **148** (84%)

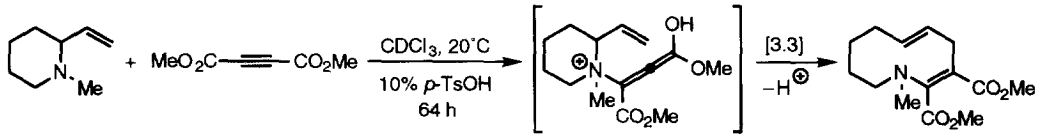
Two groups have incorporated 1,3-dipolar cycloadditions into tandem reaction schemes. Grigg and co-workers[92] have developed a general and versatile method for generating nitrones that involves Michael addition of oximes to activated alkenes followed by intramolecular cycloaddition to a second double bond. For example, addition of cyclohexanone oxime (**149**) to 2,3-di(methoxycarbonyl)-1,3-butadiene (**150**) afforded nitrone **151**, which underwent 1,3-dipolar cycloaddition from the indicated conformation to produce the bicyclic adduct **152**.



149 150 151 152

In a second paper, Yokoyama et al.[93] described a similar Michael addition / [3+2] cycloaddition starting from sugar oximes. This reaction exploited the natural chirality of the sugar to induce asymmetry in the final heterocyclic products.

A tandem Michael / aza-Claisen sequence has been presented[94] as a means of generating ring-expanded nitrogen heterocycles from 1-methyl-2-vinyl pyrrolidines and piperidines. For example, treatment of **153** with dimethyl acetylenedicarboxylate (**154**) in the presence of *p*-TsOH afforded a 71% yield of the 1-azacyclodeca-2,5-diene derivative **156**. The reaction presumably proceeded through the protonated allenic intermediate **155** under the catalytic acid conditions.



153 154 155 156 (71%)

4. Radical Primary Step

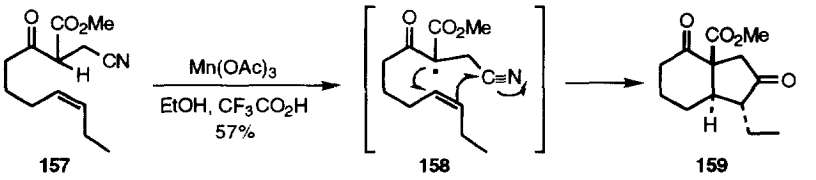
The past decade has seen explosive growth in the use of radicals, especially carbon-centered radicals, in organic synthesis. During the past three years, tremendous strides have been made in the use of tandem radical reactions, and it is currently one of the most active areas in the field. The potential of these reactions is very high due to the mild conditions under which radicals are generated. These gentle reaction conditions tolerate a wide range of functionality in the substrates; thus, complex synthetic targets can be prepared with minimum use of protecting groups. An additional advantage to the use of radicals is that they add to unactivated double and triple bonds as well as to those bearing polarizing groups. The majority of transformations in this category involve radical-radical tandem processes but recently several new variations have appeared.

4a. Radical-Radical Sequences

Tandem radical-radical reactions have become ubiquitous in organic synthesis. Radicals are routinely generated from readily available halides (Br or I) or from less available, nitro, phenylthio and phenylselenyl compounds by use of *n*-Bu_3SnH with a radical initiator (i.e., AIBN) in aromatic solvents. Additionally, redox procedures involving Mn(III) or Sm(II) can be employed to initiate tandem radical processes. As the following examples will attest, synthesis using odd-electron species has virtually unlimited potential for generating complex ring structures.

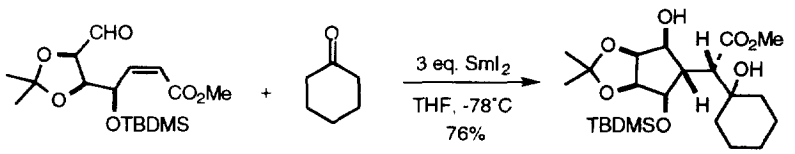
In the area of redox reactions, Snider and co-workers have continued to develop the use of $Mn(OAc)_3$ in tandem radical reactions. Recently, a synthesis of cyclopentanones and cyclohexanones involving a Mn(III)-

based oxidative free-radical tandem cyclization terminated by addition to a nitrile has been reported.[95] Treatment of the acetoacetic ester derivative **157** with two equivalents of $Mn(OAc)_3$ afforded the bicyclic diketone **159** in 57% yield. Since the acidity of the proton α to the cyano group is enhanced in radical intermediate **158**, the reaction proceeded best when five equivalents of CF_3CO_2H were added to suppress deprotonation. Without added acid, radical anion formation and subsequent oxidation by Mn(III) gave the unsaturated nitrile, which was subject to polymerization and nucleophilic addition.



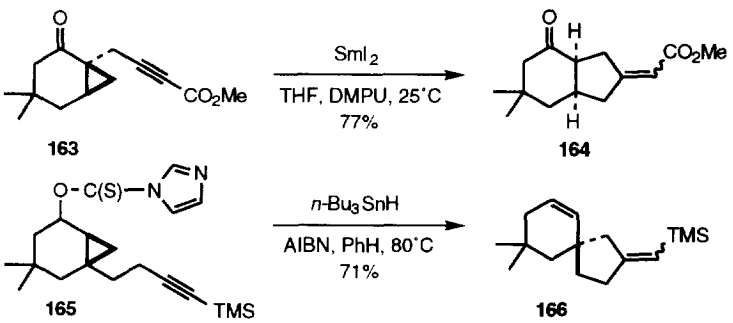
157 **158** **159**

One-electron reductions of carbonyl compounds with SmI_2 have also received considerable attention in the recent literature. Enholm and Trivellas[96] have described a sequential intramolecular one-electron cyclization of a samarium ketyl to an unsaturated ester followed by a two-electron intermolecular carbonyl addition to generate highly oxygenated bicyclic products. Addition of a solution of **160** and two equivalents of cyclohexanone (**161**) to a solution of three equivalents of SmI_2 afforded **162** in 76% yield as the only stereoisomeric product.



160 **161** (2 eq.) **162**

A second report[97] detailed an interesting ring opening / cyclization process initiated by exposure of α-cyclopropyl ketones to SmI_2. Treatment of **163** with SmI_2 in 9:1 THF:DMPU at 20°C afforded the rearranged bicyclic compound **164** in 77% yield. In a related reaction, treatment of thiocarbonyl imidazolide derivative **165** with *n*-Bu_3SnH and AIBN in benzene delivered the spiroalkene **166** in 71% yield.[98]

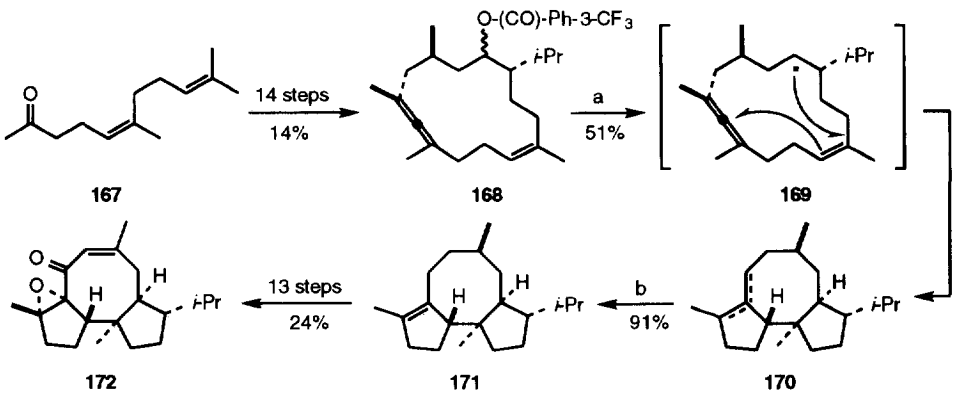


163 **164** **165** **166**

Analogous processes have been observed in the treatment of α,β-epoxy ketones[99a] and α,β-epoxy thiocarbonyl imidazolides[99b] with *n*-Bu_3SnH under radical conditions. Following generation of an initial odd-

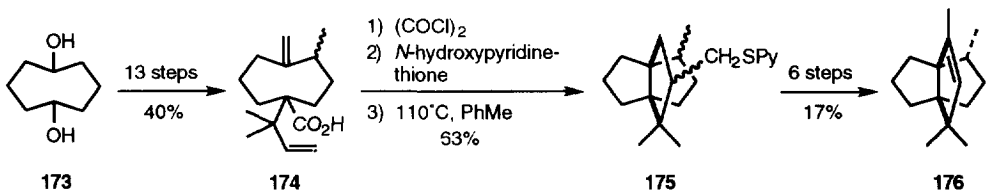
electron species (a tin ketyl from the ketone; an oxiranyl carbinyl radical from the thiocarbonyl imidazolide), epoxide ring opening, 1,5-H transfer, and ring closure gave fused-ring keto alcohols in 50-70% yield. Several additional tandem reactions involving epoxide fragmentation have also been reported.[99c,d]

Tandem cyclization of a saturated carbon radical has been the key step in a number of natural product syntheses.[100-114] Myers and Condroski[109] have employed a novel radical cyclization in an impressive synthesis of the diterpenoid (±)-7,8-epoxy-4-basmen-6-one (**172**). From neryl acetone (**167**), a 14-step sequence was used to prepare the cyclization substrate **168** in 14% overall yield. Irradiation of **168** in the presence of *N*-methylcarbazole (sensitizer) and 1,4-cyclohexadiene (H donor) in 10:1 THF:H_2O afforded a 51% yield of the tricyclic product **170** via a double transannular radical cyclization illustrated in **169**. Treatment of **170** with catalytic AIBN in 1:3 v/v thiophenol:heptane isomerized the product mixture to a single double bond isomer **171**. This ring-closed product was converted in 13 steps to the target natural product in 24% overall yield.



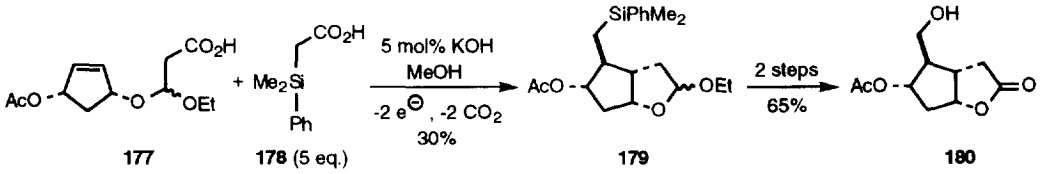
a) hv, Pyrex, *N*-methylcarbazole, 1,4-cyclohexadiene, 10:1 THF:H_2O, 55°C, 5 h
b) cat. AIBN, 1:3 v/v PhSH:heptane, 50°C, 30 min

A second transannular tandem radical cyclization has been utilized in a synthesis of (±)-modhephene (**176**).[110] Carboxylic acid **174** was prepared in 13 steps (40% overall yield) from 1,5-cyclooctanediol (**173**). Conversion to the thiohydroxamate ester and heating in refluxing toluene resulted in homolytic cleavage of the 2-thiopyridyl group, spontaneous loss of CO_2, tandem cyclization to afford the [3.3.3]propellane, and capture by 2-thiopyridyl radical to give triquinane **175** as a 4:1 mixture of diastereomers in 63% yield. The mixture was then elaborated to **176** through a relatively short series of interconversions.



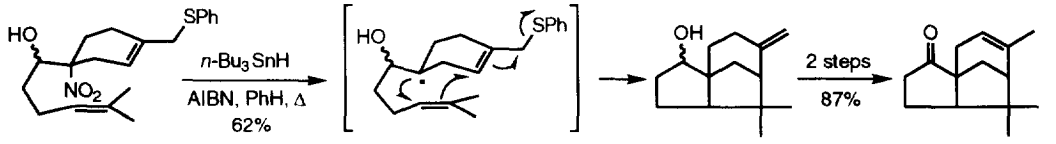
The Kolbe electrolysis (anodic oxidation / decarboxylation) of readily available carboxylate salts permits the generation of radicals without the need for toxic tin reagents. Weiguny and Schäfer[111] have explored a

radical addition / radical coupling strategy for the preparation of advanced prostaglandin precursors. Co-electrolysis of substrate acid **177** with five equivalents of (dimethylphenylsilyl)acetic acid (**178**) and 5 mol% of KOH in MeOH resulted in decarboxylation of both acids, 5-*exo-trig* closure of the side chain odd-electron center to the cyclopentene double bond, and capture of the cyclopentyl radical by the (dimethylphenylsilyl)methyl radical to give **179**. A two-step sequence converted the bicyclo[3.3.0] ether **179** to the Corey lactone (**180**). The overall yield for the three-step synthesis was 19.5%.



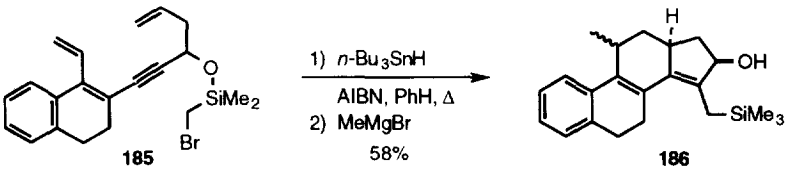
177 **178** (5 eq.) **179** **180**

Chen and co-workers[112] have reported a formal total synthesis of α-cedrene using a tandem radical cyclization initiated from nitro alcohol **181**. Treatment of **181** with *n*-Bu_3SnH / AIBN produced tertiary radical **182**, which closed to the tricyclic alcohol **183** by addition to the side chain double bond and allylic displacement of the thiophenoxy radical. Oxidation of the alcohol and isomerization of the double bond then gave norcedrenone (**184**) in 87% overall yield. Norcedrenone has been previously converted to α-cedrene.



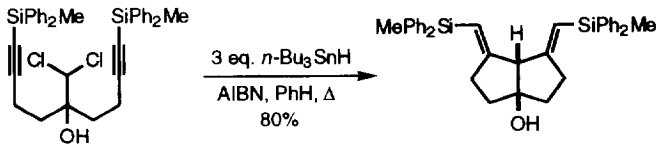
181 **182** **183** **184**

The steroid nucleus has also been efficiently stitched together through the use of a radical-mediated polycyclization.[113] (Bromomethyl)dimethylsilyl ether **185** was synthesized by standard methods from 3-tetrahydropyranyloxy-1-hexen-5-yne in three steps (46% overall yield). Treatment of **185** with *n*-Bu_3SnH / AIBN in benzene gave the tetracyclic product **186** as the major product in 58% yield after silyl ether cleavage with methylmagnesium bromide.



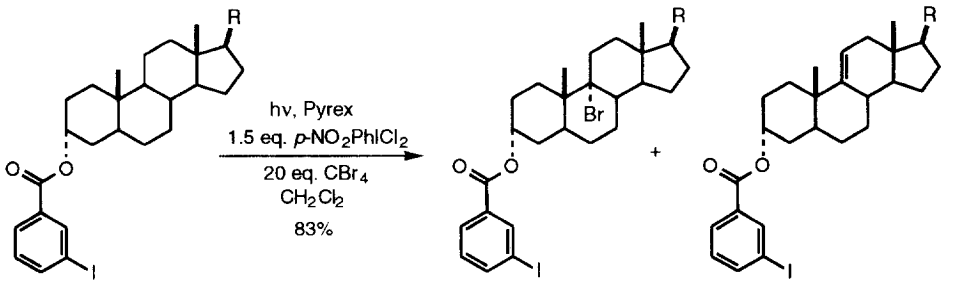
185 **186**

Clive and Cole have further reported[114] a practical method for generating polycyclic structures from geminal radical precursors. Substrate **187** was prepared straightforwardly in three steps (47% overall yield) from 4-bromo-1-*tert*-butyldiphenylsilyl-1-butyne. Treatment of **187** with three equivalents of *n*-Bu_3SnH and catalytic AIBN afforded the double cyclization product **188** in 80% yield. Bromides and phenylselenyl groups were also found to be usable as geminal radical precursors.



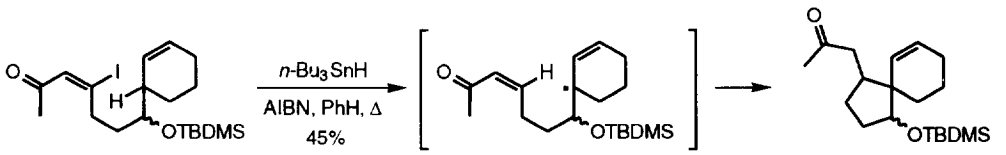
187 188

During the past several years, further progress has been made in the development of tandem radical reactions initiated by H-abstraction processes. Wiedenfeld and Breslow[115] have continued investigations on remote functionalization of the steroid skeleton by H-abstraction / halogenation / elimination. Irradiation of the 3-iodobenzoate ester of 3α-cholestanol **189** with p-NO_2PhICl_2 and CBr_4 in CH_2Cl_2 afforded, after chromatographic workup, 31% of the 9-bromosteroid **190** and 51% of the 9,11-dehydrosteroid **191** from spontaneous elimination of HBr. This route to the dehydrosteroid is reportedly superior to the analogous chlorination / dehydrochlorination sequence.



189 (R = $CH(CH_3)$-$(CH_2)_3$-$CH(CH_3)_2$) **190** **191**

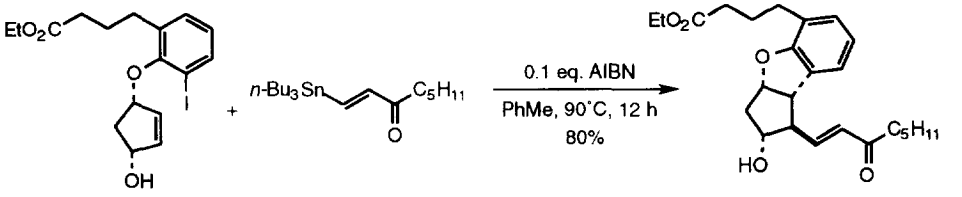
Radical H-abstraction / addition processes have also been advanced as an entry to fused-ring carbocyclic,[116] heterocyclic,[117] and most recently spirocyclic compounds.[118] In the last case, the odd-electron intermediate generated from vinyl iodide **192** abstracted a hydrogen from the tertiary cyclohexenyl allylic center to give **193**. The resulting allylic radical then added to the activated alkene to furnish the spirocyclic compound **194** as a mixture of stereoisomers in 45% yield.



192 **193** **194**

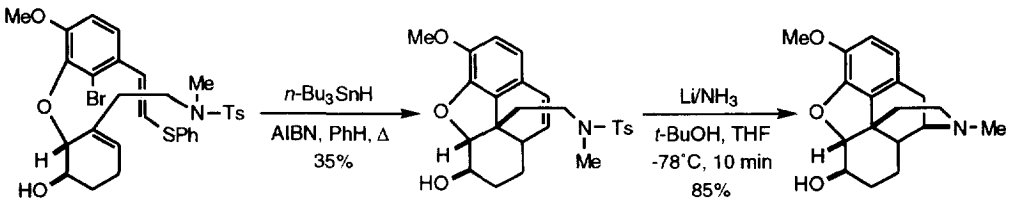
Several interesting papers have been published describing tandem cyclizations of aryl radicals.[119-129] An approach to benzoprostacyclins[119] involved sequential intramolecular addition of an aryl radical to a cyclopentene double bond and intermolecular addition-elimination of the resulting cyclopentyl radical to a β-stannyl enone terminator. Optimum results were obtained by treating iodide **195** with four equivalents of the

trapping agent **196** and 0.1 equivalents of AIBN in toluene at 90 °C. This procedure afforded an 80% yield of the benzoprostacyclin precursor **197**.



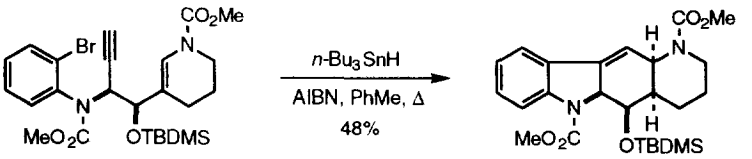
195 **196** (4 eq.) **197**

Tandem cyclization of aryl radicals has also been applied to a formal total synthesis of (±)-morphine.[120] Substrate **198** was prepared from 2-(3-methoxyphenyl)ethylamine in nine steps with an overall yield of 38%. Treatment of **198** with n-Bu_3SnH / AIBN produced the aryl radical, which underwent sequential addition across the cyclohexene double bond and addition-elimination to the styryl double bond to afford the tetracyclic structure **199** in 35% yield. Cleavage of the *N*-tosyl group under dissolving metal conditions (Li/NH_3, *t*-BuOH) afforded the deprotected, ring-closed (±)-dihydroisocodeine (**200**) in 85% yield. Swern oxidation of **200** provided (±)-dihydroisocodeinone, which had been previously converted to (±)-morphine.



198 **199** **200**

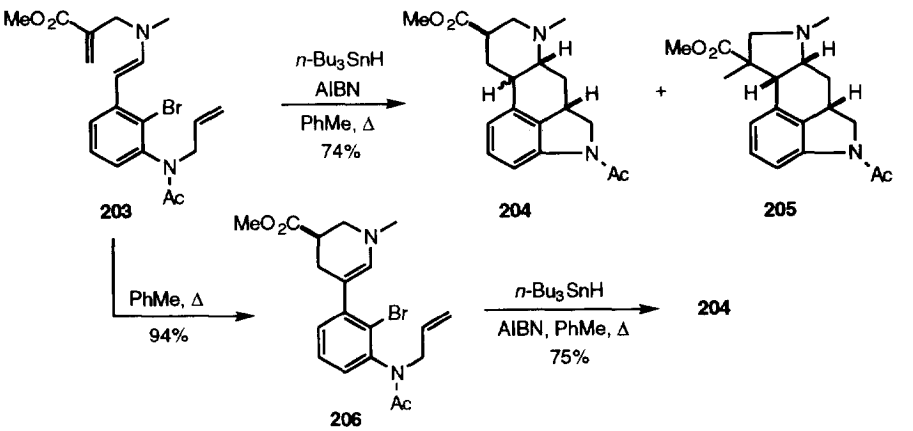
Parsons et. al.[121] have reported two additional applications of sequential cyclizations initiated from aryl radicals. Their first paper described an approach to the quebrachidine indole alkaloids in which the protected enamine **201** was converted to **202** in 48% yield by reaction with n-Bu_3SnH / AIBN. Interestingly, this tandem radical cyclization was observed only from the erythro isomer of the substrate; the threo isomer reportedly formed a transoid silicon ate complex, which positioned the enamine double bond unfavorably for cyclization. In contrast to pilot studies on an all-carbon model compound where the final ring closure afforded predominantly trans-fused rings, reaction of the protected enamine produced only the cis-fused product.



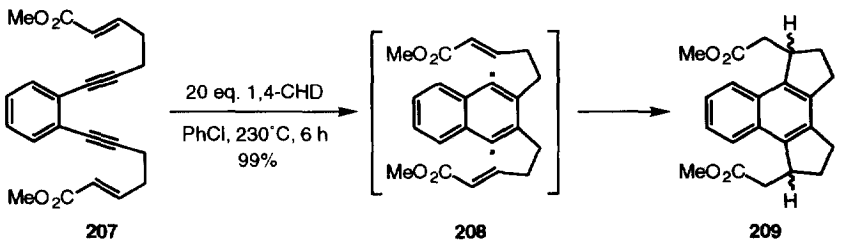
201 **202**

Their second paper described the synthesis of lysergic acid derivatives through a tandem radical cyclization procedure.[122] The enamine cyclization substrate **203** was prepared in 12 steps (30% overall yield)

from 3-nitrophthalic acid. Treatment of **203** with *n*-Bu_3SnH / AIBN afforded a 74% yield of a 2:1 mixture of tetrahydrolysergate **204** and tetracycle **205**, believed to be the kinetic cyclization product. A more satisfactory yield of **204** (75% of a 3:1 mixture of epimers) was obtained when **203** was thermally cyclized to **206** prior to radical closure.

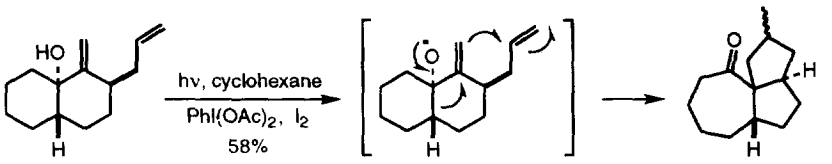


A novel Bergman cyclization has been exploited to close enediynes to polycyclic ring systems.[123-129] Cyclization of 1,2-bis(enyne) **207** at 230 °C in PhCl in the presence of 20 equivalents of 1,4-cyclohexadiene (1,4-CHD) gave a 99% yield of the cyclopentannulated naphthalene **209** as an inseparable 1:1 mixture of diastereomers. Initial ring closure afforded a reactive aromatic 1,4-diyl species **208**, which immediately cyclized on the pendant acrylate groups; H-donation from 1,4-CHD terminated the reaction. The conversion proceeded best for the production of 5-membered rings. Attempts to close 6-membered rings were complicated by 1,5-H abstraction from the side chain allylic methylene positions and gave rise to significant quantities of uncyclized α,β- and β,γ-unsaturated esters.



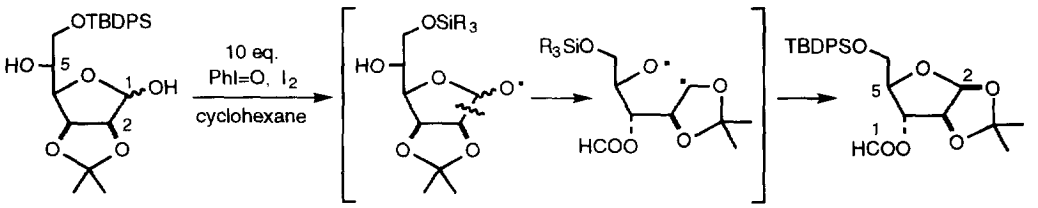
The development of reactions based upon heteroatom-centered radicals has also become an active area of research during the past few years. Several new transformations have been reported involving the intermediacy of alkoxy radicals.[130-133] Mowbray and Pattenden[132] have presented an intriguing fragmentation / transannulation / cyclization reaction for the synthesis of polycyclic ketones that should find use in natural products synthesis. Treatment of dienol **210** in deoxygenated cyclohexane with diacetoxyiodobenzene and iodine under sunlamp irradiation provided the 7,5,5-tricyclic ketone **212** in 58% yield. The process involves

generation of the tertiary alkoxy radical **211**, fragmentation of the central bicyclic bond, and sequential closure of the resulting radical across the two strategically positioned double bonds.



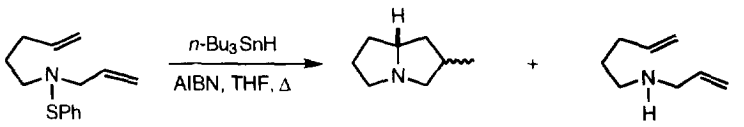
210 **211** **212**

Carbohydrates have been converted to the next lower homologues by a tandem β-fragmentation / cyclization sequence.[133] Treatment of mannofuranose **213** with 10 equivalents of iodosylbenzene and three equivalents of iodine in cyclohexane at 20°C afforded the fully-protected arabinofuranose **216** in 89% yield. As the reaction proceeds, C(2) becomes C(1) and the anomeric carbon of the starting sugar becomes the formyl protecting group in the product via radicals **214** and **215**. The high selectivity of the reaction together with the natural chirality of the sugars makes this procedure highly valuable as a source of chiral building blocks for organic synthesis.



213 **214** **215** **216** (89%)

A pioneering study has addressed the use of nitrogen-centered radicals in a synthesis of pyrrolizidines.[134] Treatment of sulfenamide **217** with *n*-Bu_3SnH / AIBN in deoxygenated THF afforded a 72% yield of the 2-methylpyrrolizidine **218** as a 5.5:1 mixture of isomers along with 28% of the unclosed *N*-allyl-4-pentenylamine **219**. Citing previous findings, the authors pointed out that multiple cyclizations gave better results than monocyclizations since trapping the initial cyclization product in a second ring-forming reaction prevented the monocyclic radical from ring opening, which occurred at a rate comparable to closure.

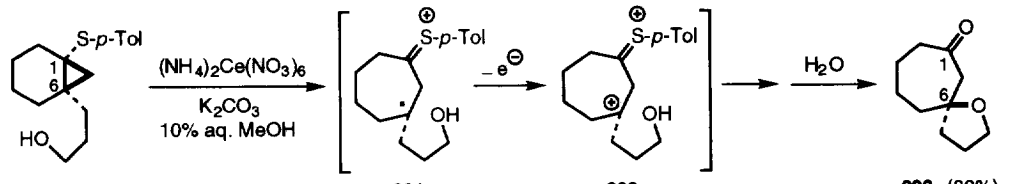


217 **218** (72%) **219** (28%)

4b. Radical-Cationic Sequences

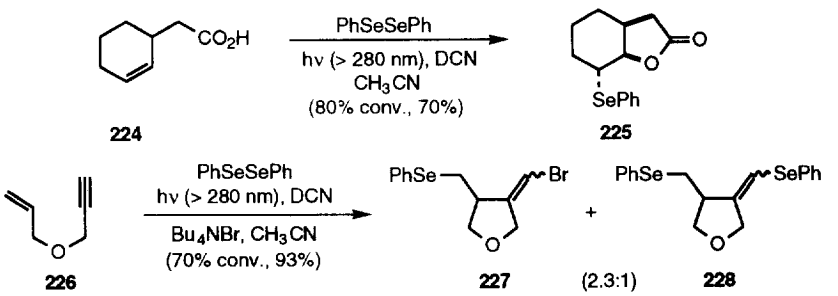
Several recent papers have described radical-cationic processes for the synthesis of ring compounds from sulfur and selenium containing substrates.[135-137] Iwata and co-workers[136] have detailed an oxidative ring

expansion involving radical-cation intermediates that preserved chirality built into the substrate. In this work, optically active 1-arylthiobicyclo[4.1.0]heptane **220**, substituted at C(6) by a side chain bearing a nucleophilic functional group, was subjected to single electron transfer with ceric ammonium nitrate. The resulting radical cation underwent three-ring fission to afford radical cation **221**, loss of an electron to give carbocation **222**, and attack by the side chain nucleophile to produce spiro ether **223** after aqueous workup. Side chain oxygen and carbon nucleophiles (i.e. enol ethers) were found to work well, and chirality was largely retained at C(6).



220 **221** **222** **223** (88%) [> 90% ee]

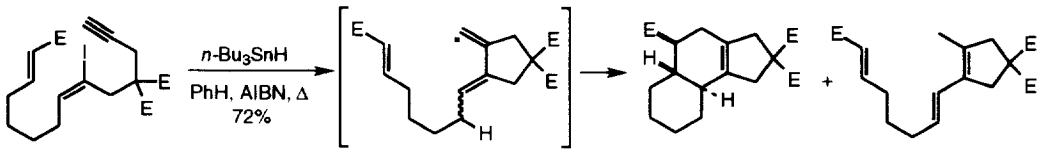
Finally, a series of reports have described cyclizations initiated by an electrophilic selenium species generated by photoelectron transfer from diphenyl diselenide to dicyanonaphthalene (DCN). For example, reaction of 2-cyclohexenylacetic acid (**224**) afforded the ring-closed phenylselenyl lactone **225**.[137] Similarly, enyne **226** under this regime cyclized to afford a 2.3:1 ratio of **227** and **228**.[138]



224 **225** **226** **227** (2.3:1) **228**

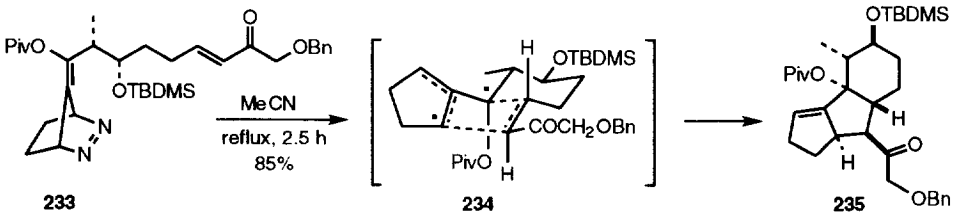
4c. Radical-Pericyclic Sequences

One example of a tandem radical cyclization-Diels Alder reaction has been reported[139] and this case appears to be the first reported to date. Compound **229** was treated with 1.5 equivalents of *n*-Bu_3SnH and 0.1 equivalents of AIBN over a period of 16 h. The initially generated vinyl radical cyclized to provide dienic radical intermediate **230**. Reduction of (*E*)-**230** by the tin hydride reagent and intramolecular [4+2] cycloaddition then afforded the tricyclic adduct **231** as a single stereoisomer in 58% yield along with 14% of **232** (from 1,5-H transfer in (*Z*)-**230**). Importantly, the *E*:*Z* ratio in recovered starting material was unchanged, indicating that the initial stereochemistry of the starting compound was of no consequence to the outcome.



229 (E = CO_2Me) **230** **231** (4:1) **232**

In a final example of a radical-pericyclic process, Little and co-workers[140] have used an elegant diyl trapping reaction to set four contiguous stereocenters in an approach to potential precursors of the phorbol nucleus. Treatment of azo substrate **233** in MeCN formed the tricyclic product **235** in 85% yield. Nitrogen disengagement resulted in diyl **234**, which underwent cycloaddition with the side chain enone. Stereospecificity presumably derived from pseudo-equatorial positioning of the methyl, silyl ether, and diyl ring about the periphery of the six-membered ring being produced.



233 **234** **235**

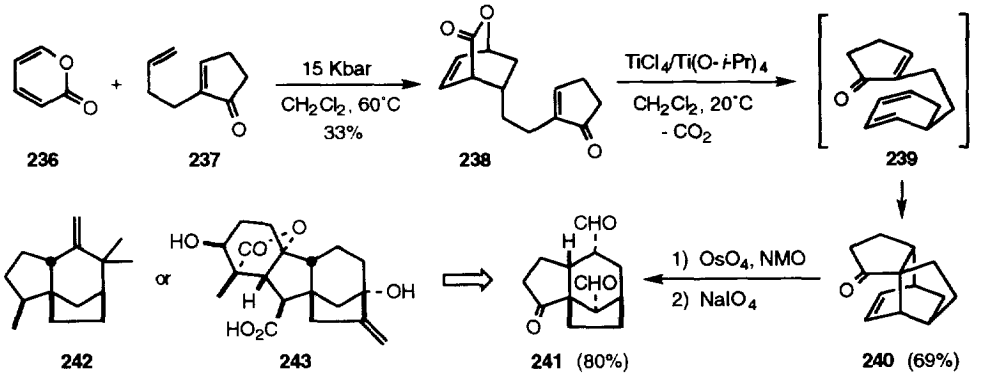
5. Pericyclic Primary Step

There have been considerable advances in the use of pericyclic processes to initiate both inter- and intramolecular sequences. Pericyclic reactions can be easily coupled with other pericyclic or anionic processes to yield complex natural products often with highly predictable stereoselectivity. Though an *in situ* elimination or deprotonation is sometimes required prior to the reaction cascade, these processes are included in this category because the major skeletal change involves a pericyclic process.

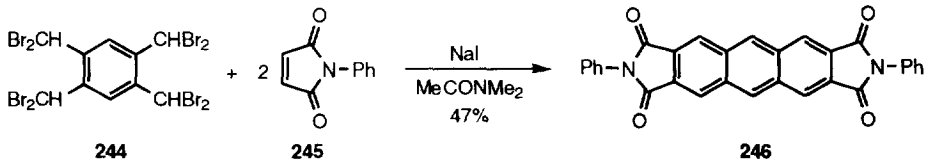
5a. Pericyclic-Pericyclic Sequences

This section starts with cycloadditions, such as the Diels-Alder reaction, the retro-Diels-Alder reaction, 1,3-dipolar cycloadditions, and chelotropic reactions. Subsequent sections deal with sigmatropic rearrangements and other miscellaneous transformations that proceed via cyclic transition states. This is clearly a broad area where new schemes will continue to appear at a rapid rate.

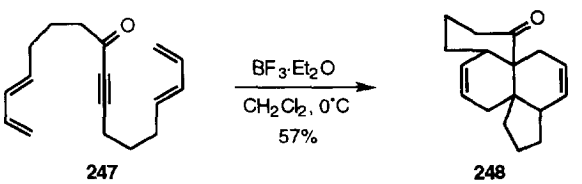
A Diels-Alder / retro-Diels Alder sequence has been routinely used for the rapid construction of a variety of common ring systems.[141-144] One report detailed a synthesis of the core skeleton of zizaene (**242**) and of gibberellic acid (**243**).[144] The pressure-induced Diels-Alder reaction of 2-pyrone (**236**) with the unactivated double bond of 2-(3-butenyl)-2-cyclopenten-1-one (**237**) afforded a modest yield of adduct **238**. Exposure to $TiCl_4/Ti(O\text{-}i\text{-}Pr)_4$ promoted sequential loss of CO_2 and a second Diels-Alder cycloaddition to give tetracycle **240**. *cis*-Hydroxylation of the double bond and oxidation of the resulting 1,2-diol furnished the tricyclic dialdehyde **241**, which possessed the core skeleton of the two natural products.



A number of research groups have used domino Diels-Alder reactions to fuse several new rings onto a pre-existing ring.[145,146] When these reactions involve unstable dienes and dienophiles, it is often necessary to run the reaction under conditions that generate the reactive species *in situ*.[147,148] For example, a synthesis of linear aromatics through a 1,4-elimination / Diels-Alder / 1,4-elimination scheme has been described from 1,2,4,5-tetrakis(dibromomethyl)benzene (**244**). Treatment of this compound with sodium iodide in *N*,*N*-dimethylacetamide in the presence of *N*-phenylmaleimide (**245**) delivered the 2,3,6,7-tetrasubstituted anthracene **246** in 47% yield.

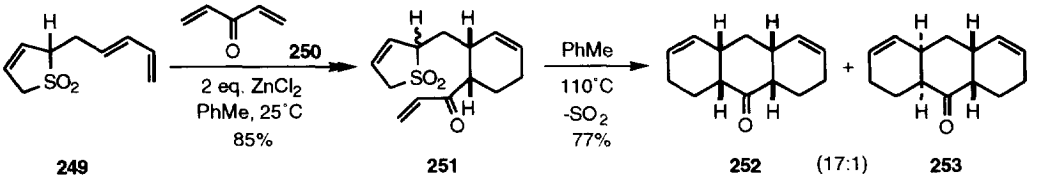


Domino Diels-Alder reactions of activated alkynes have also been reported. Exposure of ketone **247** to $BF_3{\cdot}Et_2O$ in CH_2Cl_2 under high dilution resulted in a tandem intramolecular Diels-Alder reaction to afford the tetracyclic ketone **248** as a mixture of two isomers in 57% yield.[149] Although the authors were unable to assign the structure of the major isomer, spectral data were consistent with the atom connectivity of the tetracyclic product. Future work in this area should lead to compounds more amenable to structure elucidation.



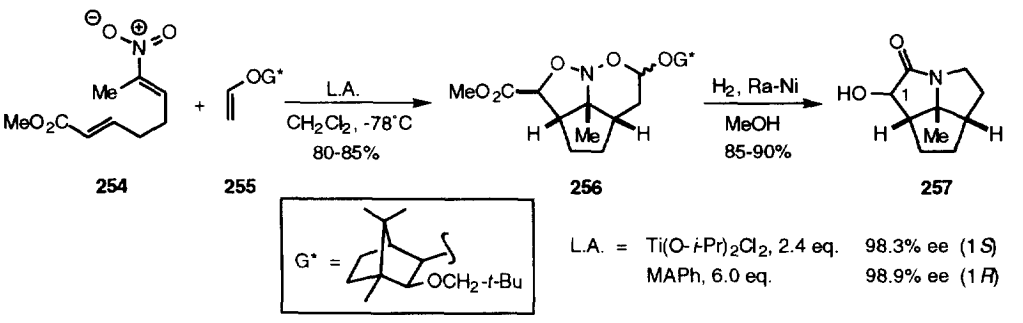
Finally, a Diels-Alder / chelotropic elimination / Diels-Alder sequence has been used to assemble linear polycyclic ketones with high selectivity.[150a] When a mixture of sulfolene diene **249** and divinyl ketone (**250**) was treated with $ZnCl_2$ at 25 °C, cycloaddition occurred to give **251** as a 1.1:1 mixture of isomers in 85% yield. Subsequent heating of **251** expelled SO_2 from the butadiene sulfone moiety to give the diene, which reacted with the remaining enone double bond to give a 17:1 ratio of the tricyclic ketodienes **252** and **253** in

77% yield. Recently, a similar tandem Diels-Alder procedure has been applied to the synthesis of the taxane nucleus.[150b]

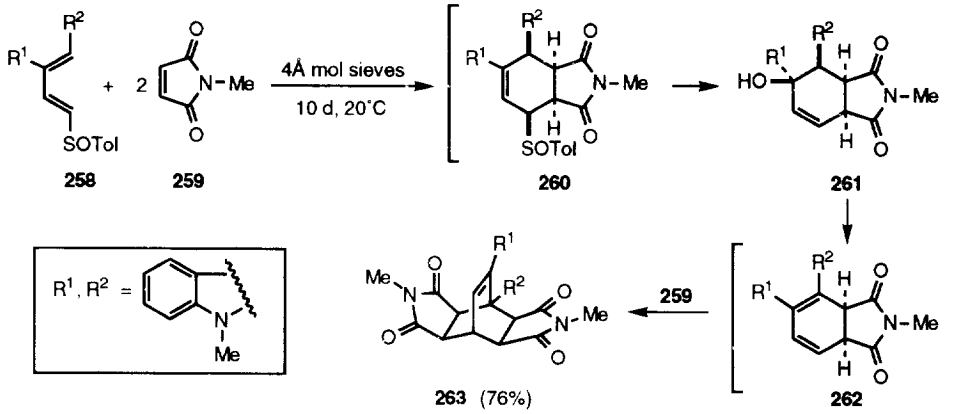


The Diels-Alder reaction has been coupled with several other transformations to produce versatile synthetic approaches to novel ring structures. One report described the use of a cobalt-catalyzed acetylene trimerization / electrocyclic benzocyclobutene opening / Diels-Alder to prepare the carbon backbones of aphidicolan and stemodan.[151] Another sequence involving an electrocyclic ring opening / Diels-Alder / [2+2] process starting with 2*H*-benzo[*b*]thiete and methoxyallene produced a mixture of spiro[2*H*-1-benzothiopyran-3(4*H*),1'-cyclobutane] derivatives.[152]

Denmark and co-workers have explored the sequential intermolecular [4+2] / intramolecular [3+2] cycloaddition chemistry of nitroalkenes for the synthesis of fused,[153] spiro,[154] and bridged[155] ring systems. Though not all of these transformations classify as tandem reactions, the following example[153d] illustrates the use of this elegant technology for asymmetric synthesis of fused-ring α-hydroxylactams. Treatment of nitroalkene **254** with the camphor-derived enol ether **255** in the presence of dichlorotitanium diisopropoxide afforded adduct **256** which, after hydrogenation, furnished the (1*S*)-hydroxylactam **257**. The reaction can be fine-tuned to give the (1*R*)-hydroxylactam by use of methyl aluminum bis(2,6-diphenylphenoxide) (MAPh), a sterically more demanding Lewis acid catalyst.

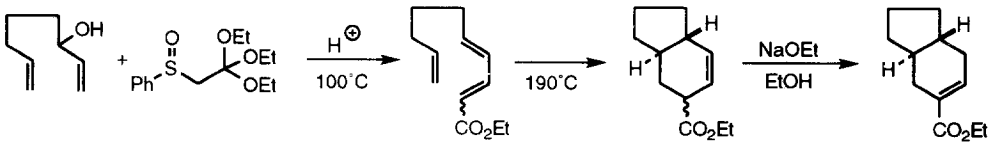


The Diels-Alder reaction can also be run in series with sigmatropic rearrangements.[156-160] In a recent report,[158] diene **258** and *N*-methylmaleimide (**259**) underwent a novel Diels-Alder / [2,3] sulfoxide-sulfenate sigmatropic shift / dehydration / Diels-Alder sequence in high yield with excellent selectivity for the all-cis adduct **263**. The reaction proceeded best at 20 °C with $SnCl_4$ or 4Å molecular sieves as a catalyst.



258 259 260 261 262 263 (76%)

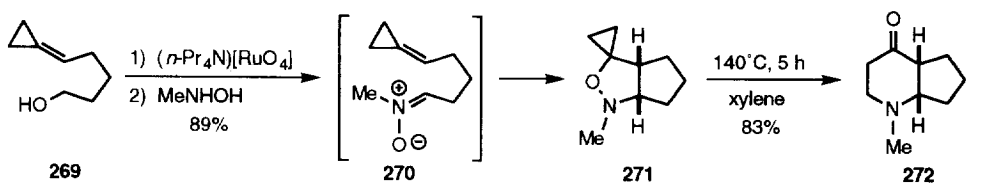
Posner and co-workers[159] have reported the use of a sulfinyl orthoester reagent in a one-flask, four step conversion of allylic alcohols into bicyclic cyclohexenes. Treatment of allylic alcohol **264** with orthoester **265** afforded bicyclic product **268** as a single stereoisomer after base-promoted double bond isomerization. The sequence involves orthoester Claisen rearrangement and sulfoxide elimination to generate dienoate **266** followed by intramolecular Diels-Alder cycloaddition to give adduct **267**. Treatment with ethanolic sodium ethoxide isomerized this compound to the α,β-unsaturated ester in an overall 24% yield.



264 265 266 267 **268** (24%)

An analogous transformation, with 1-chloro-1-ethoxy-2-sulfinylethylene, has been developed by these same authors[160] to convert propargyl alcohols to 4-oxo-2-alkenoate esters in 55-80% yields.

One-flask sequential transformations involving [3+2]-cycloadditions are less common, but several examples have appeared in the recent literature.[161-163] A rearrangement of tricyclic isoxazolidines isolated from intramolecular [3+2] cycloaddition of cyclopropylidene nitrones has been found to give good conversion to fused-ring nitrogen heterocycles.[163] Though the intermediate isoxazolidines were isolated and characterized, this sequence appears to have potential as a tandem reaction candidate. Nitrone **270** was generated *in situ* from alcohol **269** by a simple two step procedure involving oxidation to the aldehyde and condensation with methylhydroxylamine. Cycloaddition of the nitrone in benzene at 20 °C afforded the fused-ring adduct **271** in

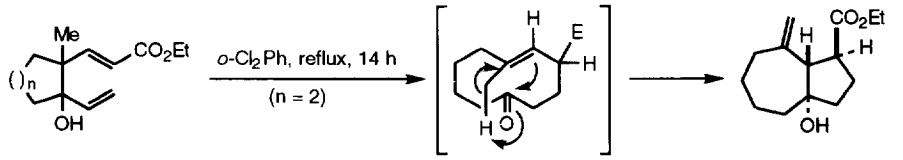


269 270 271 272

89% yield. Heating **271** in xylene resulted in N-O bond cleavage and rearrangement to **272**, which was isolated as a 7:1 cis:trans mixture in 83% yield.

Serial sigmatropic rearrangements have also been exploited for synthetic purposes. A thermal Claisen / Cope sequence has been applied to the synthesis of a large family of natural coumarin derivatives.[164] Double Ireland-Claisen rearrangements have been reported as an approach to the C(1)-C(13) fragment of erythronolide[165] and the C(22)-C(34) segment of the polyether macrolide halichondrin.[166] A similar strategy has been devised to provide a stereocontrolled, two-directional chain synthesis which sets stereochemistry at four chiral centers and two trisubstituted double bonds.[167]

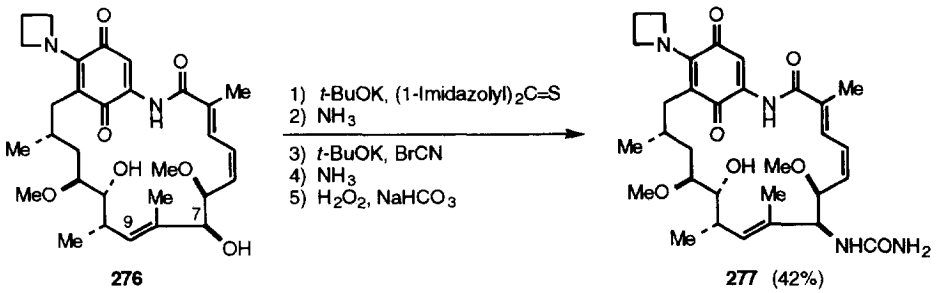
A ring enlargement / annulation procedure has been described that involves a thermal oxy-Cope / ene reaction of 1,2-divinyl alcohols such as **273**.[168] Upon thermolysis, an oxy-Cope rearrangement produced the ring-expanded product **274**, which underwent ring closure by a transannular ene reaction to give hydroazulenol **275** in 90% yield. The final product was isolated as a single stereoisomer regardless of the geometry of the acrylate moiety in the starting dienol. The reaction was versatile and allowed construction of 6-5 and 7-5 fused-ring motifs from **273** where n = 1 or 2, respectively. Larger ring systems (i.e. **273** with n = 3) led only to the ring-expanded product, presumably because the greater transannular distance precluded the final ene reaction.



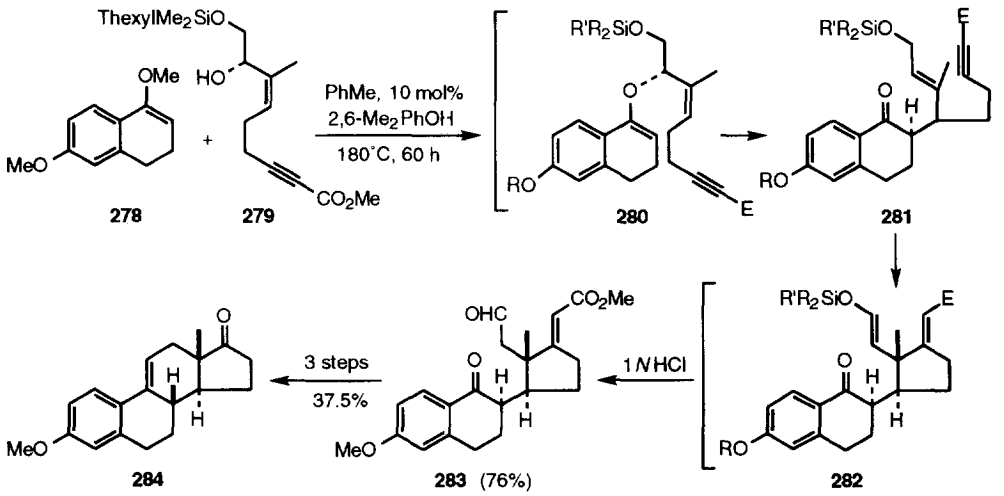
273 (n = 1, 2, 3) **274** **275** (90%)

Greeves and Vines have presented a detailed evaluation of acyclic stereocontrol in the tandem [2,3]-Wittig / anionic oxy-Cope sequence.[169] Their study demonstrated that while product stereochemistry in the Wittig rearrangement depended on alkene geometry, the anionic oxy-Cope was stereoconvergent, and produced the same major stereoisomeric product regardless of reactant geometry. Thus, reaction of a stereoisomeric mixture of bis-allylic ethers afforded the same *E syn* δ,ε-unsaturated aldehyde. These results were reportedly consistent with transition states predicted from literature.

A novel stereospecific alcohol-to-amine interchange has been reported for functional group adjustment in ansamycin, an analogue of the geldanamycin oncogene inhibitors.[170] Conversion of (7*S*)-alcohol **276** to the (7*S*)-thiocarbonyl imidazolide gave spontaneous [3,3]-sigmatropic rearrangement to the (9*S*)-thiocarbamate, and cleavage with NH_3 gave the (9*S*)-thiol. Treatment of the (9*S*)-thiol with *t*-BuOK / BrCN gave the (9*S*)-thiocyanate, which underwent spontaneous [3,3]-sigmatropic rearrangement to the (7*S*)-isothiocyanate. Reaction of the (7*S*)-isothiocyanate with NH_3 produced the (7*S*)-thiourea, and treatment with basic H_2O_2 delivered the (7*S*)-urea **277** in 42% overall yield. Though this interconversion was carried out as a series of steps, several tandem processes were embedded in this ring modification sequence.

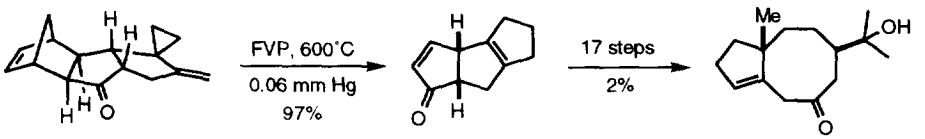


Two research groups have documented a Claisen / ene approach to the synthesis of the steroid nucleus. The first group described the synthesis of (+)-13-ethyl-3-methoxygona-1,3,5,9(11)-tetraen-17-one, a potential precursor to the progestagens desogestrel and 3-ketodesogestrel.[171] In the second report, Mikami and co-workers[172] incorporated a Claisen / ene sequence as part of a total synthesis of (+)-9(11)-dehydroestrone methyl ether (**284**). Sealed tube reaction of enol ether **278** with the monoprotected diol **279** in toluene containing 2,6-dimethylphenol afforded aldehyde **283** in 76% yield after acid hydrolysis of the initial Claisen / ene product **282**. This product was converted to the target compound in three steps with an overall yield of 37.5%.



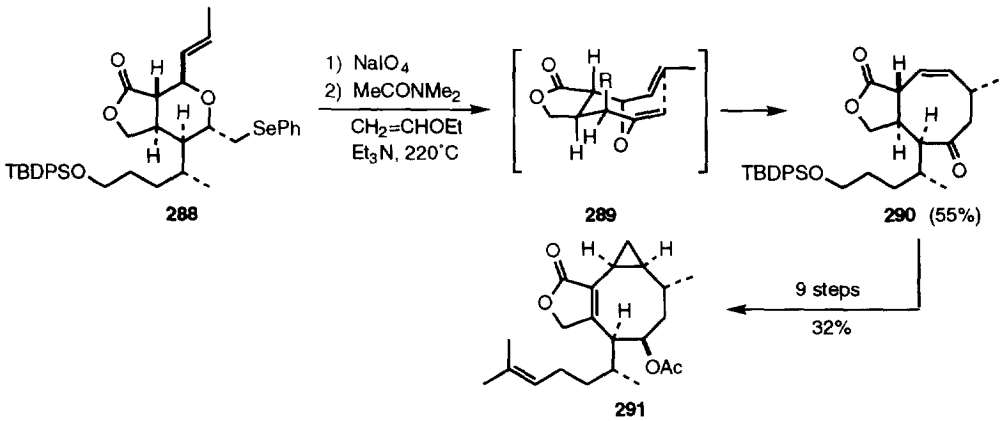
Two additional transformations have been successfully incorporated into total syntheses. In the first, a retro-Diels-Alder cycloaddition / vinylcyclopropane rearrangement was used to generate triquinacene **286**, which was carried on to (±)-11-hydroxyjasionone (**287**).[173] Polycyclic spirane **285** was prepared in 60% yield by palladium-catalyzed trimethylenemethane-type cycloaddition of 2-(1-(trimethylsilyl)-1-cyclopropyl)-allyl pivalate and tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one (**92**). Flash vacuum pyrolysis of this compound effected a retro-Diels-Alder reaction to unmask the cyclopentenone followed by a vinylcyclopropane

rearrangement to produce cyclopentannulation product **286** in 97% overall yield. Further elaboration to the natural product required 17 steps and proceeded in 2% overall yield.



285 **286** **287**

Finally, a selenoxide elimination has been linked with a Claisen rearrangement in a synthesis of (+)-acetoxycrenulide (**291**).[174] Substrate **288** was prepared in 25 steps from (*R*)-citronellol in 6.5% overall yield. Oxidation to the selenoxide and tandem elimination / Claisen rearrangement (via **289**) at 220 °C in *N*,*N*-dimethylacetamide containing ethyl vinyl ether and triethylamine to scavenge acidic by-products delivered a 55% yield of **290** incorporating the 5-8 fused-ring framework of the target molecule. Completion of the synthesis was accomplished in nine steps with a 32% overall yield.



288 **289** **290** (55%)

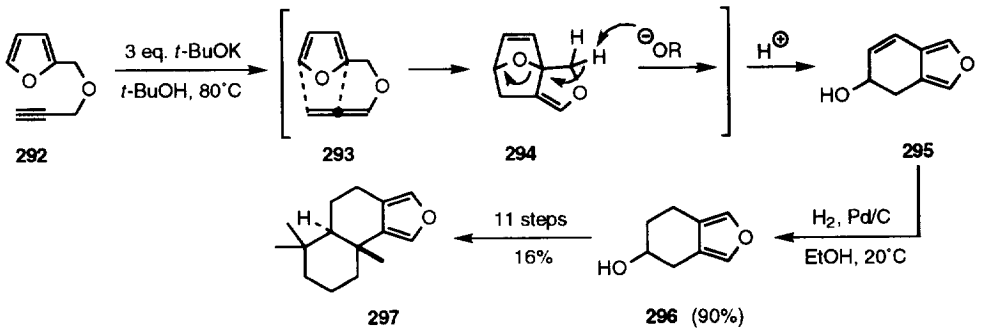
291

5b. Pericyclic-Anionic Sequences

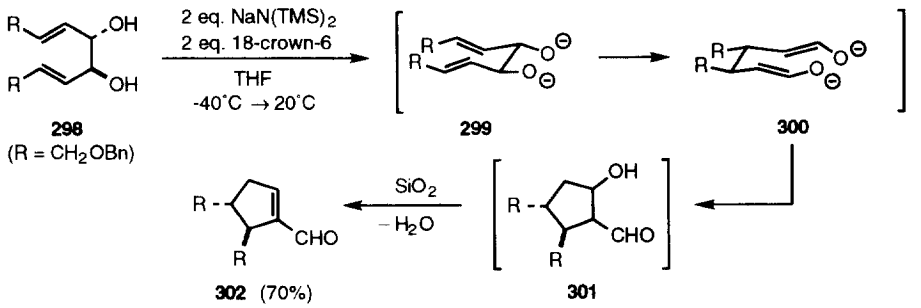
Pericyclic processes are most easily coupled to anionic processes since many rearrangements require deprotonation prior to reaction. The products of these sequences frequently incorporate enolates or other nucleophilic groups that can further react with electrophilic reagents. An important consideration in these cases is that most pericyclic reactions afford products significantly enriched in one stereoisomer. Thus, careful design of substrates can take advantage of predictable pericyclic processes to install functionality in a highly controlled way. The following examples illustrate recent applications of this strategy and suggest that many other useful transformations should be possible.

Pericyclic reactions followed by eliminations, additions to π bonds, or alkylations have been used by several research groups to efficiently prepare fused- and spirocyclic systems.[175-185] Kanematsu et al.[178] have employed an interesting "furan ring transfer" for the synthesis of (±)-euryfuran (**297**). The propargyl furfuryl ether **292** was readily obtained from propargyl bromide and furfuryl alcohol under phase transfer conditions. Treatment of **292** with *t*-BuOK in *t*-BuOH eventuated a sequence involving prototropic rearrangement to the allenic ether **293**, Diels-Alder reaction to produce **294**, and base-promoted rearomatization / fragmentation to

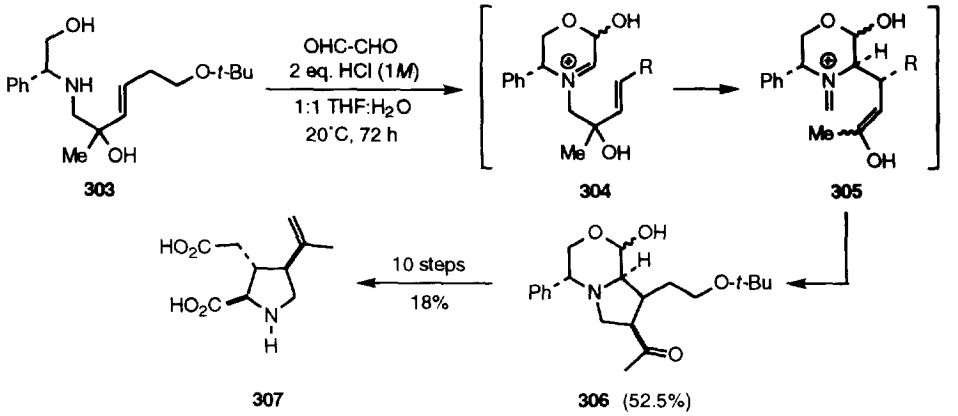
give the unstable fused-ring allylic alcohol **295**, which was reduced to **296** in 90% overall yield. Compound **296** was then converted to the natural product **297** in 11 steps with a 16% overall yield.



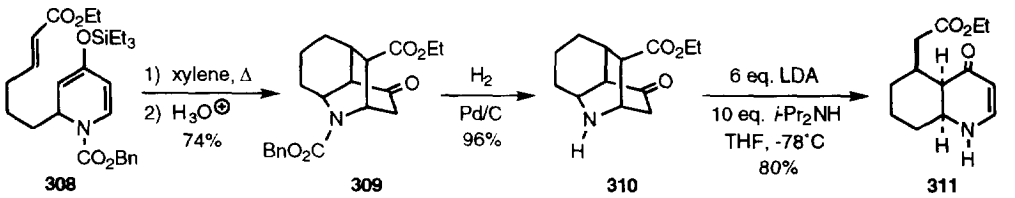
An interesting dianionic oxy-Cope / aldol sequence has been advanced as an efficient route to chiral 1-cyclopentenecarboxaldehyde building blocks for natural product synthesis.[179] Treatment of the acyclic (*E,E*)-bis-allylic diol **298** with $NaN(TMS)_2$ and 18-crown-6 gave the initial aldol product **301**, which underwent spontaneous dehydration during chromatographic purification to furnish (-)-**302** with high optical purity. Though it was suggested that selectivity derived from sodium chelation of the equatorially disposed oxygens in cyclohexane chair-like intermediate **299**, this is unlikely since 18-crown-6 should coordinate most of the sodium ion. The reaction proved to be quite versatile producing enantiomerically pure (+)-**302** starting from the (*Z,Z*)-bis-allylic substrate.



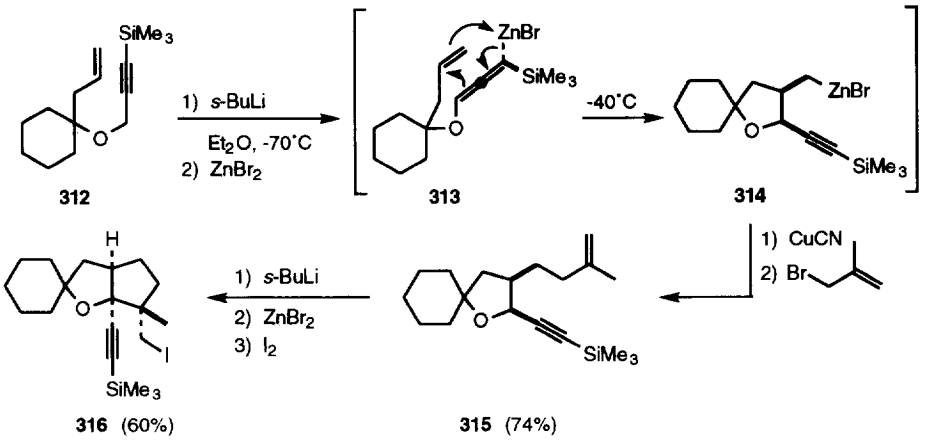
An aza-Cope / Mannich sequence has been used by Couty and co-workers for the asymmetric synthesis of several nitrogen-containing ring structures including a homochiral proline derivative[180] and the non-proteinogenic amino acid (-)-α-allokainic acid (**307**).[181] In the latter case, aminodiol **303** was treated with glyoxal at pH 4-5 in aqueous THF to give a three-reaction sequence involving (1) formation of iminium ion **304**, (2) aza-Cope rearrangement to **305**, and (3) Mannich ring closure to hemiacetal **306** in 45% yield along with 20% of a 2:1 adduct. Re-exposure of the 2:1 adduct to the same acid conditions afforded additional **306**, effectively increasing the yield to 52.5%. Final conversion to **307** was accomplished in 10 steps with an overall yield of 18%.



Comins and Al-awar have reported[182] an interesting sequence that involves a tandem intramolecular Diels-Alder / retro-Mannich reaction for the synthesis of the *cis*-perhydroquinoline ring system found in the *Lycopodium* alkaloids. Since the intermediate Diels-Alder product was isolated prior to the retro-Mannich, this sequence is not formally a tandem reaction, but it is nevertheless a useful approach to this family of compounds. Intramolecular cycloaddition of **308** with hydrolytic workup afforded adduct **309**. Hydrogenolysis of the benzyl carbamate group then gave tricyclic amine **310** in 71% overall yield from **308**. Retro-Mannich ring-opening of **310** was effected with six equivalents of LDA and 10 equivalents of diisopropylamine to furnish enamine **311** in 80% yield. These conditions promoted slow protonation α to the ester in the trianion of **310** and ring-opening to give the 6-6 fused-ring framework. Despite the large excess of base, the *cis*-perhydroquinoline precursor **311** was isolated with no epimerization at any of the stereogenic centers.



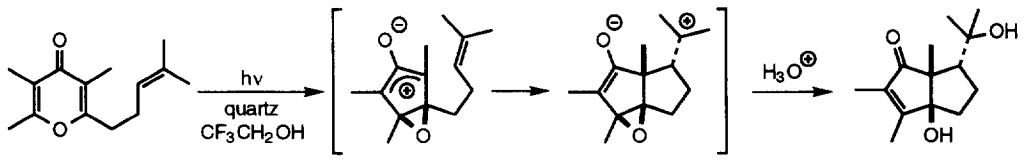
A metalla-Claisen / 1,3-elimination sequence from allyl vinyl zinc reagents has been reported to give cyclopropane derivatives in a highly stereoselective manner.[183] A more recent adaptation of this technology has utilized a "zinca-en-allene" cyclization for the selective preparation of substituted tetrahydrofurans.[184] Metallation of substrate **312** with *sec*-BuLi followed by addition of $ZnBr_2$ led to the α-silyl allenylzinc bromide **313**, which underwent a highly diastereoselective cyclization at -40 °C to **314**. Transmetallation of **314** to the organocopper reagent followed by reaction with methallyl bromide afforded the spirocyclic tetrahydrofuran **315**. This tetrahydrofuran derivative was further cyclized to **316** by repetition of the cyclization procedure and a quench with iodine.

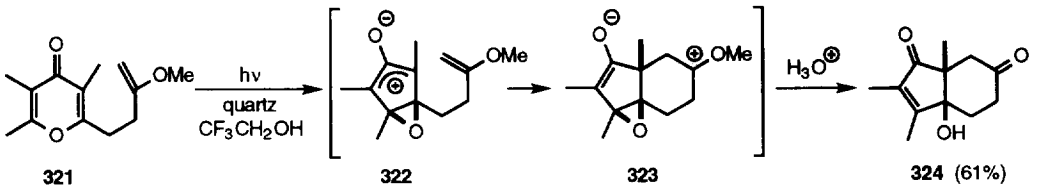


6. Photochemical Sequences

Photochemistry represents a potentially rich area for new tandem reactions, though relatively few developments have been reported during the past several years. The advantage of using light to drive reactions lies in the fact that it is an environmentally safe "reagent" that tolerates many functional groups. Since photochemical reactions usually proceed from an excited electronic state, reactions often produce unique products that are not available from ground state reactants. On the other hand, reactions involving excited states do not always meet the selectivity requirements needed for organic synthesis, and the chromophores required for light absorption generally leave unwanted functionality in the product.

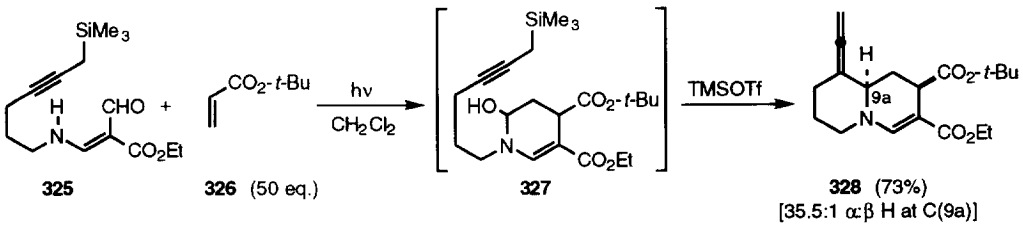
West and co-workers[185] have developed several useful transformations based on intramolecular trapping of zwitterions formed during irradiation of 4-pyranone derivatives. Irradiation of 4-pyranone **317** in 2,2,2-trifluoroethanol through quartz generated zwitterion **318**, which was captured by the side chain alkene to give the ring closed zwitterion **319**. To avoid isolation of a complex mixture of trifluoroethyl ketals, the photolysate was subjected to mild acid workup that gave the keto diol **320** in 69% yield. A similar series of events presumably took place for substrate **321**. As might be expected, regioselectivity in the trapping reaction was governed by the stability of the carbocation produced upon ring closure.





In another variant of this reaction, oxyallyl zwitterionic intermediates derived from irradiation of 4-pyranones were trapped in electrophilic aromatic substitution reactions to produce tetrahydrobenz[*e*]inden-1-ones in 20-75% yields.[186]

A second photochemical process to receive attention was a novel sequential cycloaddition / iminium ion formation / propargylsilane cyclization to generate quinolizidines and pyrido[1,2-*a*]azepins.[187] As an example, enamino aldehyde **325** was irradiated in the presence of 50 equivalents of *tert*-butyl acrylate (**326**) to afford 2-hydroxytetrahydropyridine **327**. Cyclization with TMSOTf then gave the quinolizidine **328** in 73% overall yield as a 35.5:1 mixture of α:β epimers at C(9a). In a formal sense, product **327** could arise from an initial [2+2] reaction to the imino enol form of **325** followed by a ring expansion, but the authors point out that the initial photochemical step is not yet fully understood.

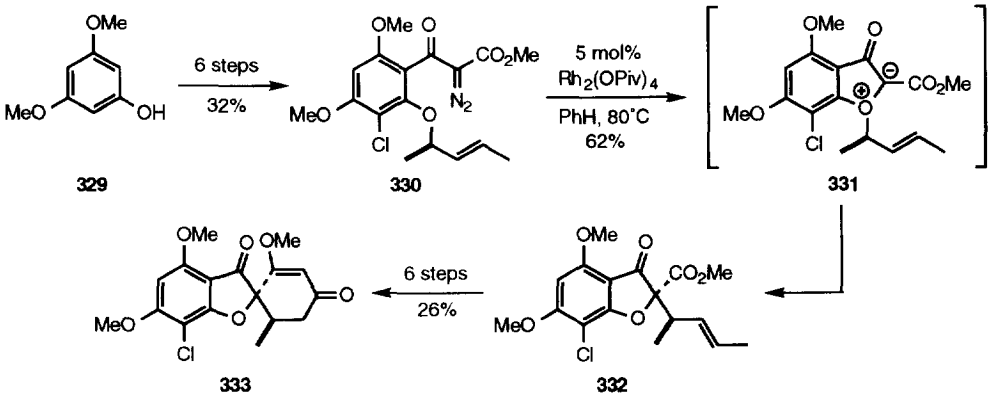


7. Carbene Sequences

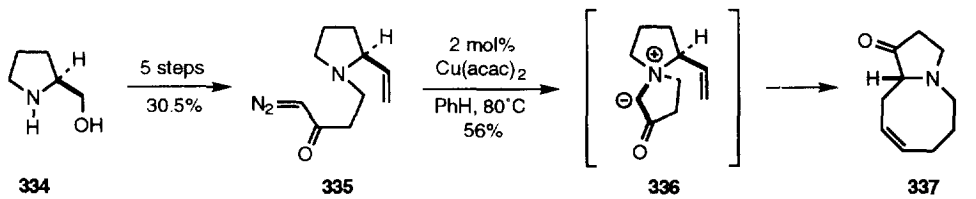
Cascade reactions initiated from carbene intermediates have been a productive area of discovery during the past several years. The central theme of these processes revolves around the observation that electrophilic carbenes and carbenoids formed in the vicinity of heteroatom-containing functional groups (especially ethers, amines, and carbonyls) react to form ylides capable of undergoing further transformations. Processes initiated by heteroatom addition to a carbene center include [2,3]-sigmatropic rearrangements,[188-190] Stevens [1,2]-alkyl shifts,[191-196] and 1,3-dipolar cycloaddition of carbonyl ylides.[197-201] Oxygen-containing chiral auxiliaries have also induced modest enantioselectivity in cyclopropanation / Cope reactions by blocking reaction at one face of a rhodium carbenoid through intramolecular coordination.[202] Finally, work has started to appear using metal carbene complexes in tandem reaction sequences.[203,204] All of these methods generate structure motifs having potential value in organic synthesis.

Two syntheses based on [2,3]-sigmatropic rearrangement of carbene-derived ylides have been reported. In an extension of earlier work,[188] Pirrung and co-workers[189] have utilized a carbene-based tandem reaction in an enantioselective synthesis of the antifungal agent (+)-griseofulvin (**333**). The diazoketoester **330** was prepared from 3,5-dimethoxyphenol (**329**) in six steps with an overall yield of 32%. Decomposition of **330**

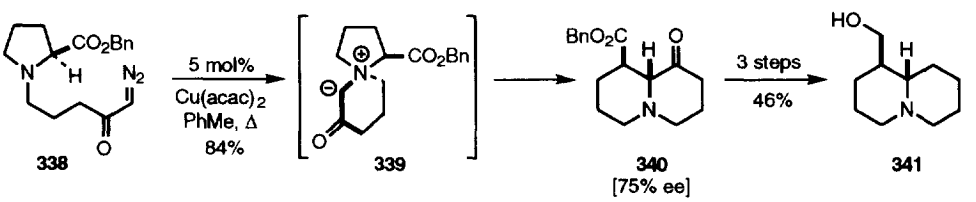
in the presence of $Rh_2(OPiv)_4$ produced oxonium ylide **331**, which underwent [2,3]-sigmatropic rearrangement to afford a 62% yield of **332** as a single stereoisomer. A six-step sequence converted **332** to the natural product in 26% overall yield.



A related process was employed in an approach to the CE ring system of the manzamine and ircinal alkaloids.[190] (*S*)-Prolinol (**334**) was converted to diazoketone **335** in five steps with an overall yield of 30.5%. Thermolysis of **335** in the presence of $Cu(acac)_2$ resulted in carbenoid formation, cyclization to the ammonium ylide **336**, and [2,3]-sigmatropic rearrangement to give the azabicyclo[6.3.0]undecanone **337** in 56% yield. The 8-5 fused heterocycle **337** constitutes the CE ring framework of the complex target alkaloids.

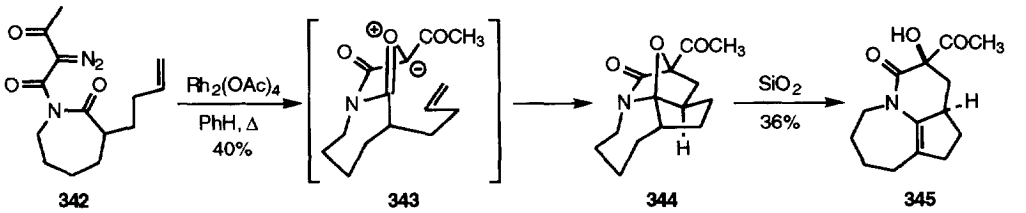


In a series of papers, West and co-workers have reported Stevens [1,2]-alkyl shifts in oxonium and ammonium ylides generated by carbene interaction with ether[191] and amine[192-196] functional groups. For example, thermolysis of the diazoketone **338** in the presence of $Cu(acac)_2$ afforded quinolizidine **340** and its bridgehead epimer in a 95:5 ratio in 84% yield with a 75% ee.[195] The catalyst used in these transformations proved critical to optimizing the yield.[196] The observed enantioselectivity suggested that the reaction proceeded



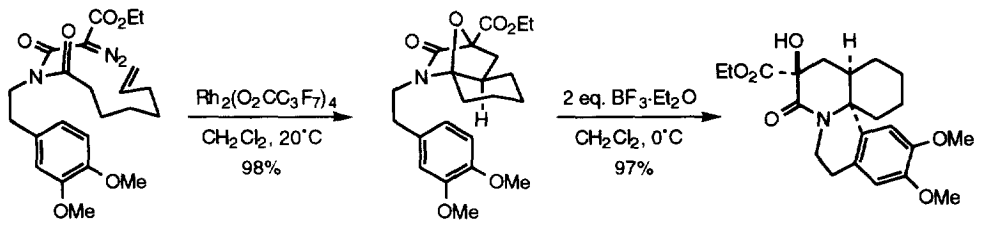
via ylide **339**, but radical intermediates could also be possible. The rearrangement product **340** was finally converted to (-)-epilupinine (**341**) in three steps with an overall yield of 46%.

Padwa and co-workers have reported several applications of intramolecular cycloadditions of carbonyl ylides generated by reaction of rhodium carbenoids with γ or δ carbonyl groups tethered to π bonds that can serve as 1,3-dipolarophiles.[197-200] When the readily available diazoimide **342** was treated with a catalytic quantity of $Rh_2(OAc)_4$, the rhodium carbenoid cyclized on the γ carbonyl to give the carbonyl ylide **343**, which in turn added across the pendant alkene to give the tetracyclic adduct **344**. Purification by silica gel chromatography resulted in ring opening to give the interesting tricyclic enamide **345**.[199]



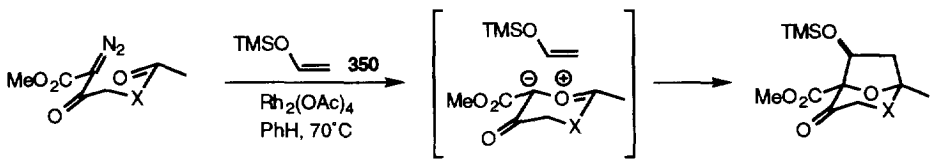
342 **343** **344** **345**

In another application of this technology,[200] exposure of diazoimide **346** to catalytic $Rh_2(O_2CC_3F_7)_4$ [rhodium(II) perfluorobutyrate] produced adduct **347**. Further treatment of **347** with $BF_3{\cdot}Et_2O$ gave tetracycle **348**, a B-ring homologue of the erythrinane alkaloids. This rearrangement involves Lewis acid-assisted opening of the oxygen bridge and attack by the activated aromatic ring on the resulting *N*-acyliminium ion.



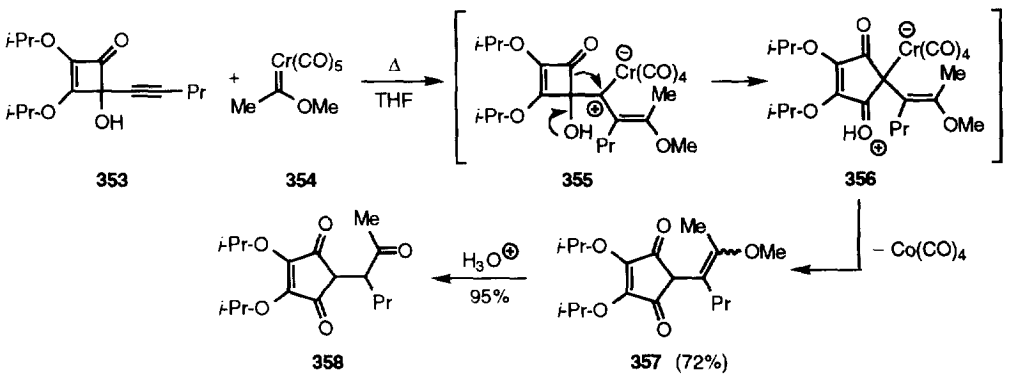
346 **347** **348**

Carbene-derived carbonyl ylides have also been used in an approach to the core structure of zaragozic acid.[201] Thermolysis of diazoketoester **349** in the presence of trimethylsilyloxyethene (**350**) and catalytic $Rh_2(OAc)_4$ resulted in the formation of carbonyl ylide **351**, which underwent cycloaddition to give **352**. While the reaction proceeded in a respectable 66% yield for the formation of the carbon analogue **352a**, the cyclization resulted in a disappointing 16% yield for the oxygen-containing system **352b** found in the natural product.



349a (X = CH_2) **351a** (X = CH_2) **352a** (X = CH_2) (66%)
b (X = O) **b** (X = O) **b** (X = O) (16%)

Finally, semipinacol-type ring expansions have been reported with 1-(1-alkynyl)cyclobutenols under palladium-mercury co-catalytic conditions[203] and from reaction with metal-carbene complexes.[204] In the latter case, treatment of alkynylcyclobutenol **353** with chromium carbene complex **354** resulted in alkyne insertion to generate electrophilic carbene complex **355**, ring expansion to **356**, and loss of chromium tetracarbonyl to give enol ether **357**. Hydrolysis of **357** then produced triketone **358** as the only product in 95% yield.



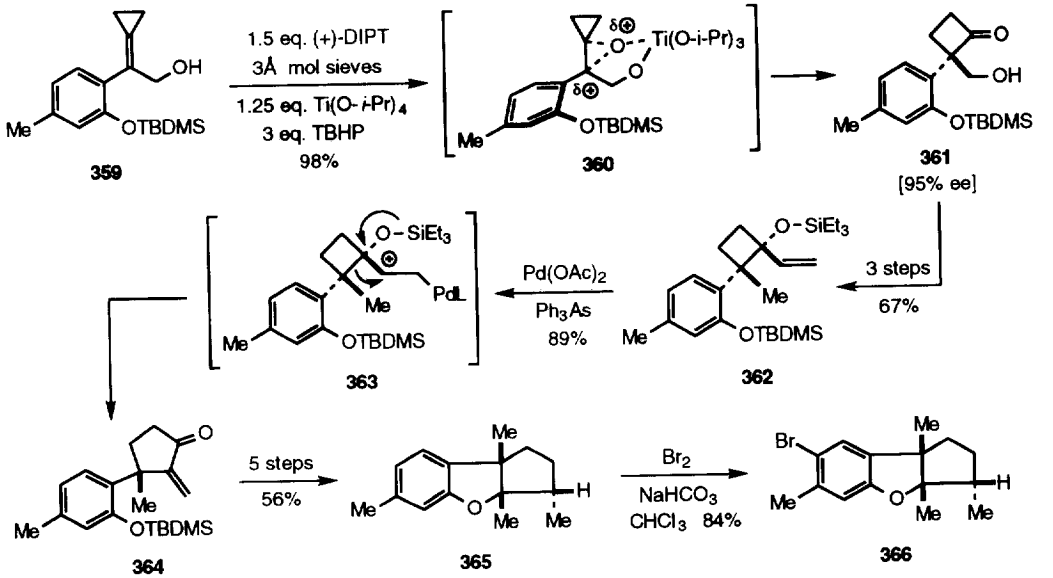
8. Transition Metal-Catalyzed Sequences

Organic chemistry has witnessed a tremendous surge in the study of transition metal-catalyzed reactions. Hardly a synthesis is reported that does not include an elegant display of the power of these catalysts. Many of these transformations involve one-flask multistep processes that involve major skeletal reorganization and thus qualify as tandem reactions. Though research on the use of transition metals in organic synthesis is a hot area that has attracted many investigators, a wealth of undiscovered synthetic possibilities clearly remains.

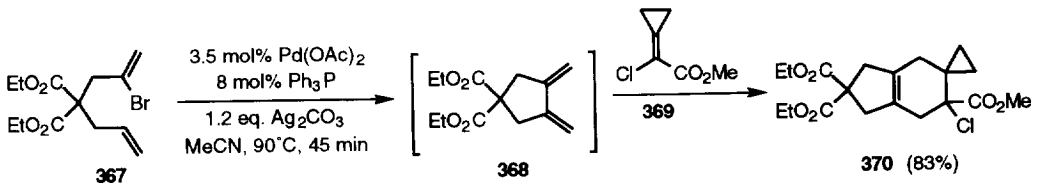
One of the most heavily studied families of transition metal catalysts are those based on palladium. Over the past 20 years, many new reactions have been uncovered, and activity in this area has remained high. This section begins with several new applications of palladium catalysis then moves on to other transition metals that have shown promise in synthetic applications.

Fukumoto and co-workers have devised a general approach to *cis*-hydrindanes[205] as well as total syntheses of (-)-debromoaplysin and (-)-aplysin[206] employing two novel transition metal-mediated processes. For the synthesis of the natural products, cyclopropylidene alcohol **359** was prepared from methyl glycolate in nine steps with an overall yield of 48%. Treatment of **359** under Katsuki-Sharpless conditions with (+)-DIPT, 3Å molecular sieves, $Ti(O\text{-}i\text{-}Pr)_4$, and *t*-BuOOH effected an epoxidation / 1,2-rearrangement sequence to afford the 2-(hydroxymethyl)cyclobutanone **361** in 98% with a 95% ee. While high asymmetric induction was expected in the epoxidation, the high enantioselectivity in the 1,2-rearrangement was somewhat surprising. The latter was attributed to the steric effect of the *tert*-butyldimethylsilyl ether, which would force the phenyl to rotate out of conjugation with the developing benzylic positive charge (as in **360**) thus precluding epimerization from a stabilized carbocation intermediate. A three-step sequence converted **361** to the protected vinylcyclobutanol **362**, which upon exposure to $Pd(OAc)_2$ and Ph_3As ring expanded via **363** to the 2-

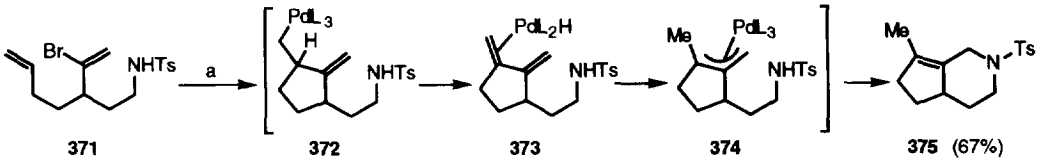
methylenecyclopentanone **364** in 67% overall yield. This ketone was converted to (-)-debromoaplysin (**365**) in five steps with an overall 56% yield. Subsequent treatment of **365** with Br_2 in $CHCl_3$ containing $NaHCO_3$ provided (-)-aplysin (**366**) in 84% yield.



The Heck reaction is an important way to couple aryl and vinyl systems in the presence of palladium, and it forms the keystone of many tandem reaction processes.[207-212] Pursuant to a strategy for the synthesis of illudin M, a Heck vinylation / Diels-Alder reaction has been investigated as a route to fused-ring bicyclic systems.[211] Heck cyclization of 2-bromo-1,6-diene **367** afforded the bis(exomethylene)cyclopentane **368** which, in the presence of methyl 2-chloro-2-cyclopropylideneacetate **369**, afforded an 83% yield of bicyclic spirane **370**. The reaction proceeded best when the entire transformation was carried out without isolation of the intermediate diene **368**.



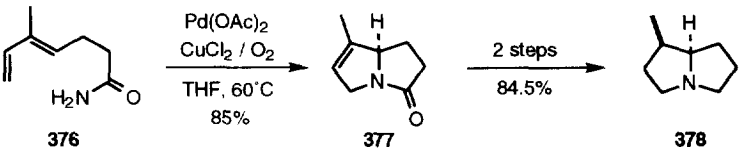
Weinreb and co-workers[212] have described a tandem Heck cyclization / nucleophilic trapping procedure for the preparation of spiro, bicyclic, and fused nitrogen heterocycles. Reaction of diene sulfonamide **371** with Pd(0) resulted in 5-*exo-trig* closure by a Heck reaction to give **372**, followed by β-hydride elimination to give the η^2-complex **373**. Rearrangement to the π-allylpalladium species **374** and nucleophilic closure then gave the bicyclic sulfonamide **375**.



371 372 373 374 375 (67%)

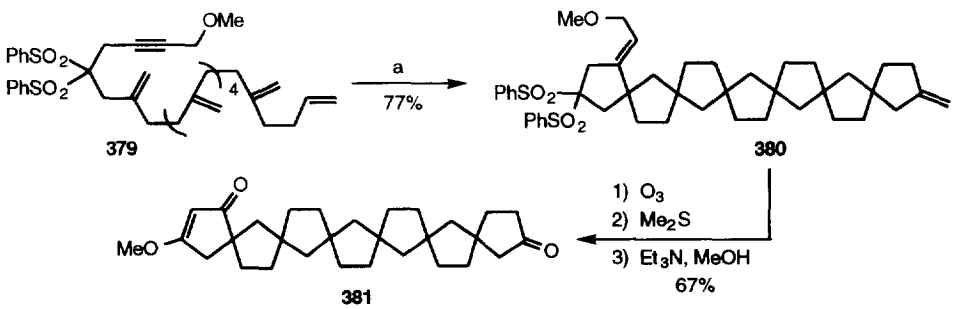
a) 5 mol% $Pd(OAc)_2$, 10 mol% (*o*-Tol)$_3$P, 3.5 eq. Na_2CO_3, 2 eq. *n*-Bu_4NCl, DMF, 65°C, 48 h

Many other reactions involving nucleophilic trapping of π-allylpalladium intermediates or alkene-palladium π complexes have been communicated.[213-216] Andersson and Bäckvall[216] have developed an efficient Pd(II)-promoted tandem cyclization protocol for the preparation of pyrrolizidines and indolizidines from 4,6- and 5,7-diene amides. For example, 4,6-diene amide **376** was cyclized in the presence of $Pd(OAc)_2$ with $CuCl_2$ / O_2 as a reoxidant (Pd(0) → Pd(II)) to form pyrrolizidinone **377** in 85% yield. Compound **377** was further converted to (±)-heliotropane (**378**) in two steps with an overall yield of 84.5%.



376 377 378

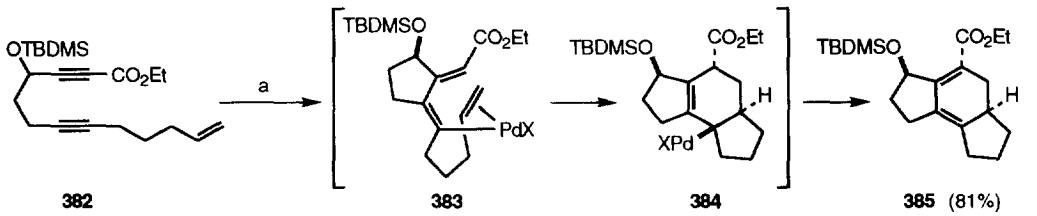
Several Pd(0)-catalyzed cycloisomerization procedures have appeared that show great promise for the rapid assembly of complex molecular architectures. Meyer and de Meijere[217] have described the domino cyclization of 2-bromododeca-1,11-dien-6-ynes to form angularly bisannulated cyclohexadienes. A "palladium ene" process has been reported by Oppolzer and co-workers[218] as a procedure for highly selective polycyclizations of 2,7,12-trienyl acetates via π-allylpalladium intermediates. More recently, Trost and Shi[219] have advanced several spectacular cascade cyclizations involving polyenyne substrates without the need for a vinyl halide or an allylic acetate in the substrate. For example, treatment of **379** with Pd_2(dibenzylideneacetone)$_3$·$CHCl_3$ [$Pd_2(dba)_3$·$CHCl_3$], Ph_3Sb, and HOAc in benzene produced the heptacyclic spirane **380** in 86% yield. Further treatment with O_3, followed sequentially by Me_2S and Et_3N in MeOH provided keto enone **381** in 67% yield.



379 380 381

a) 2.5 mol% $Pd_2(dba)_3$·$CHCl_3$, 10 mol% Ph_3Sb, 1 eq. HOAc, PhH, 50-65°C, 12 h

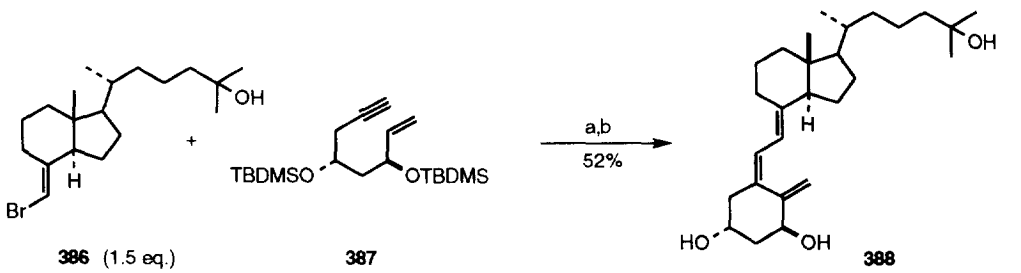
In a similar process,[220] enediyne **382** was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ and HOAc in benzene to afford an 81% yield of the tricyclic diene **385** as a single diastereomer. To account for the high diastereoselectivity, a novel Diels-Alder cycloaddition of palladadiene **383** was proposed with cyclization guided by minimization of steric interaction between the bulky silyl ether and the dienophilic side chain. The initial adduct **384** underwent 1,4-elimination of HPdX to afford the tricyclic product **385**.



382 **383** **384** **385** (81%)

a) 2.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 30 mol% HOAc, PhH, 20°C, 28 h

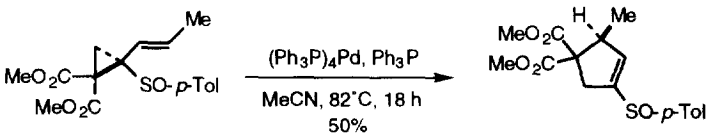
A further exhibition of this methodology[221] has utilized a Pd(0)-catalyzed alkylative cyclization of enyne substrates to produce vitamin D_3 metabolites. To a mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ and Ph_3P in toluene containing Et_3N was added a solution of vinyl bromide **386** and enyne **387**. The reaction was refluxed, then directly desilylated to afford a 52% yield of calcitriol (**388**) after chromatography.



386 (1.5 eq.) **387** **388**

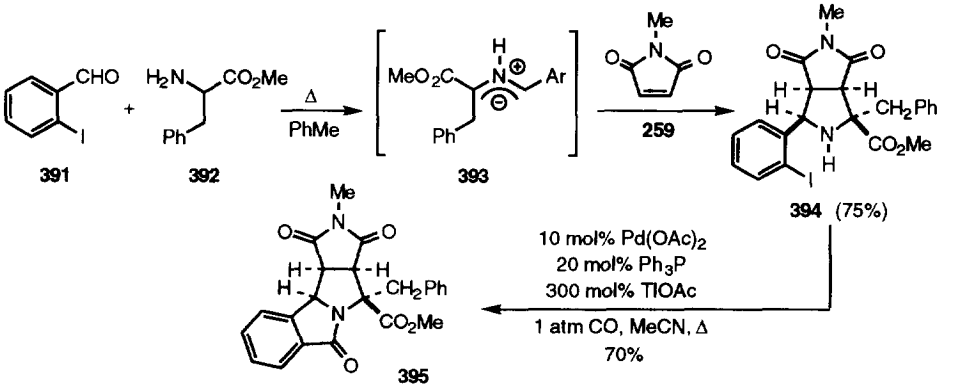
a) 3 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 30 mol% Ph_3P, 3.5 mol% Et_3N, PhMe, 110°C, 2 h; b) Bu_4NF, THF

Studies have demonstrated that high stereoselectivity in vinylcyclopropane rearrangements can be achieved in the presence of transition metal catalysts.[222,223] For example, treatment of the chiral cyclopropane sulfoxide **389** with Pd(0) in MeCN gave cyclopentene **390** in 50% chemical yield with an 89% ee.[223] Similar stereospecificity observed from the analogous sulfone indicated that asymmetry in the cyclopentene product derived primarily from the chirality of the cyclopropane ring rather than from the chiral sulfinyl group. Larger alkyl groups on C(2) of the vinyl moiety had an adverse affect on the stereospecificity.

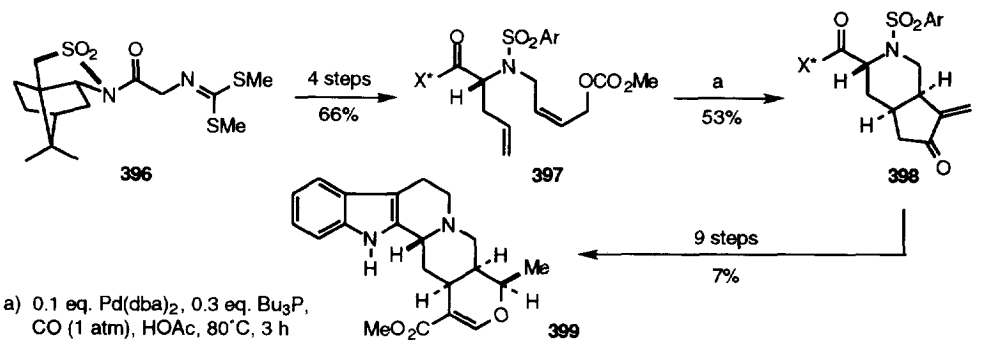


389 **390** (89% ee)

Another valuable reaction promoted by palladium and other transition metal catalysts is carbonyl insertion.[224-229] Grigg and co-workers[227] have employed a 1,3-dipolar cycloaddition / palladium-catalyzed carbonylation / cyclization to prepare five- and six-membered lactams with high diastereospecificity. Diazabicyclo[3.3.0]octane **394** was prepared in 75% yield by cycloaddition of azomethine ylide **393**, derived from *o*-iodobenzaldehyde (**391**) and methyl phenylalaninate (**392**), with *N*-methylmaleimide (**259**). Treatment of **394** with $Pd(OAc)_2$, Ph_3P, and TlOAc in dry MeCN under 1 atm of CO resulted in carbonylation / cyclization to afford **395** in 70% yield.

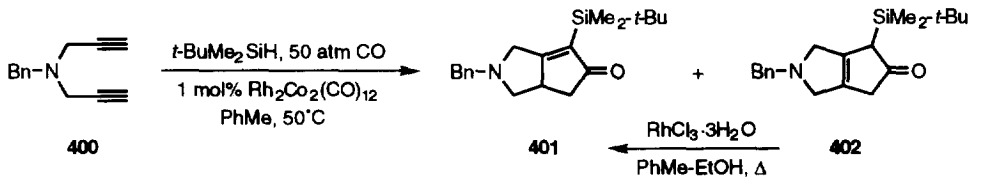


A catalytic "palladium ene" / carbonylation reaction has been developed and applied to the synthesis of a heteroyohimbine alkaloid.[228] The chiral glycinate equivalent **396** was converted in four steps to the dienyl carbonate **397**. Upon exposure to $Pd(dba)_2$ and Bu_3P in HOAc under 1 atm of CO, compound **397** underwent cyclization / carbonylation to give three stereoisomeric products, of which **398** comprised the major isomer. A series of nine synthetic steps transformed **398** to the alkaloid (+)-3-isorauniticine (**399**) in 7% overall yield.

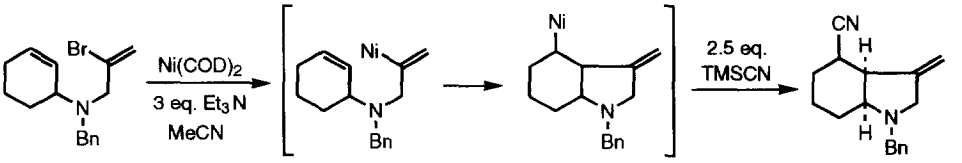


A novel silylcarbocyclization reaction of 1,6-diynes catalyzed by mixed metal carbonyls has been exploited as a route to bicyclo[3.3.0]octenones.[229] Reaction of the benzyldipropargylamine **400** with *tert*-butyldimethylsilane under 50 atm of CO in the presence of $Rh_2Co_2(CO)_{12}$ in toluene afforded a 6:1 mixture of

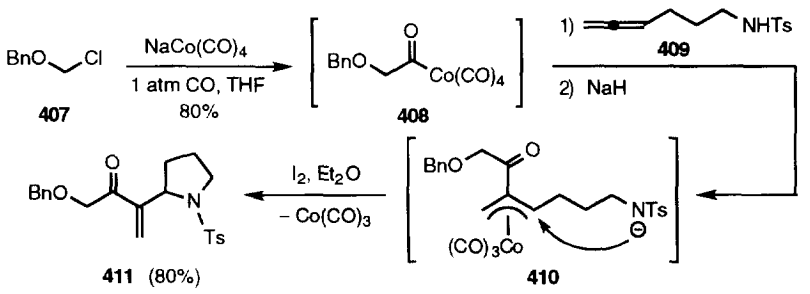
the two 7-azabicyclo[3.3.0]octenes, **401** and **402**. Quantitative isomerization of **402** to the conjugated product isomer with $RhCl_3 \cdot 3H_2O$ resulted in an overall 70% yield of **401**.



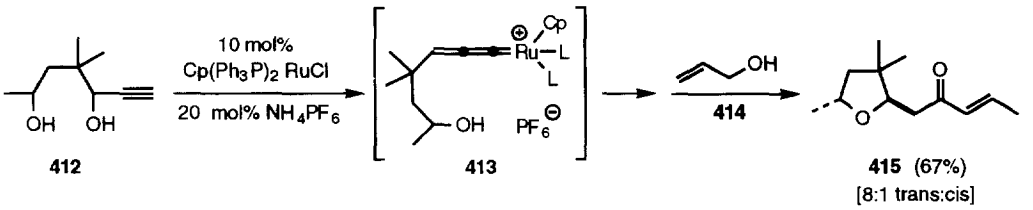
Nickel has also proven to be an effective catalyst for cyclizations. In a tandem cyclization / electrophilic capture procedure, Ni(0) promoted the cyclization of vinyl bromides and alkenes tethered by ether[230] or amine[231] linkages. Treatment of the 2-bromo-4-aza-1,6-diene **403** with a slight excess of $Ni(COD)_2$ in dry MeCN containing Et_3N followed by quenching with TMSCN afforded the octahydroindole **406** in 99% overall yield. The reaction presumably generated the vinylnickel species **404**, which closed to give the alkylnickel intermediate **405**. Electrophilic capture of this species prior to workup then permitted installation of the nitrile (or other) functional group.



A communication detailing an acylation / cyclization reaction of π-allylcobalt complexes has also appeared.[232] Treatment of reactive methyl halides such as benzyloxymethyl chloride (**407**) with sodium tetracarbonylcobaltate under 1 atm of CO generated the acyltetracarbonylcobalt species **408**. Addition of allenic sulfonamide **409** under CO produced the π-allylcobalt complex **410**, and subsequent treatment with NaH resulted in deprotonation of the sulfonamide and five-membered ring-closure by nucleophilic attack on the cobalt-complexed allyl fragment. Treatment with ethereal iodine decomposed the cobalt carbonyl complex to furnish the vinyl-substituted pyrrolidine **411**.



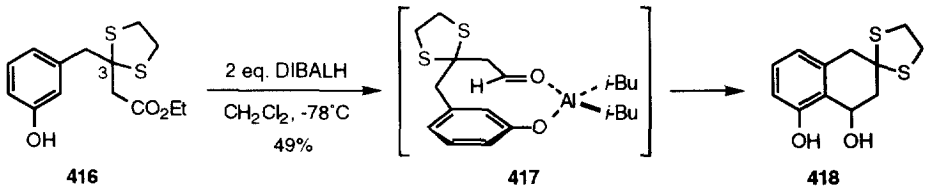
Finally, an intriguing ruthenium-catalyzed process involving cyclization of propargyl alcohols followed by addition of allylic alcohols has been reported for the synthesis of five- and six-membered oxygen heterocycles.[233] Treatment of a neat mixture of propargyl alcohol **412** and allyl alcohol (**414**) with $Cp(Ph_3P)_2RuCl$ and NH_4PF_6 afforded a 67% yield of tetrahydrofuran **415** as an 8:1 mixture of trans:cis 2,5-disubstituted isomers. The reaction was proposed to proceed through the allenylidene complex **413**, but a detailed mechanism has not been firmly established.



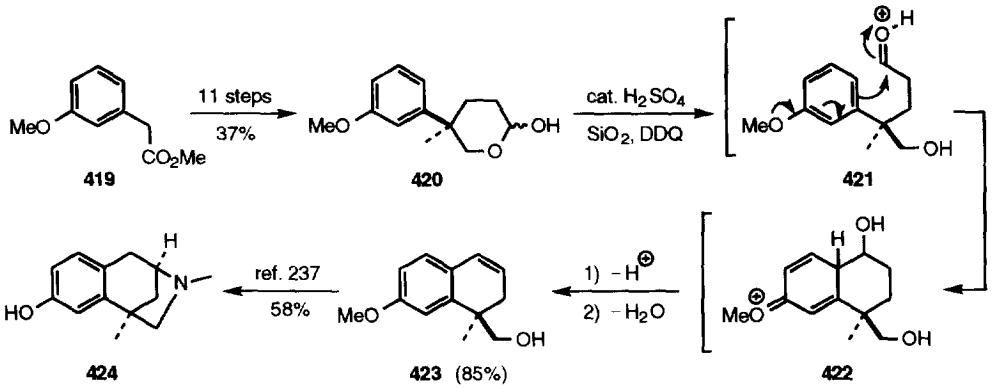
9. Miscellaneous Sequences

Some procedures defy classification according to the schemes outlined above. This last section describes a series of unrelated reactions for which mechanistic details at some stage of the reaction are obscure. It also includes several late entries to this review. Many interesting and novel transformations have been reported, and several of them will likely lead to valuable and general synthetic methodologies.

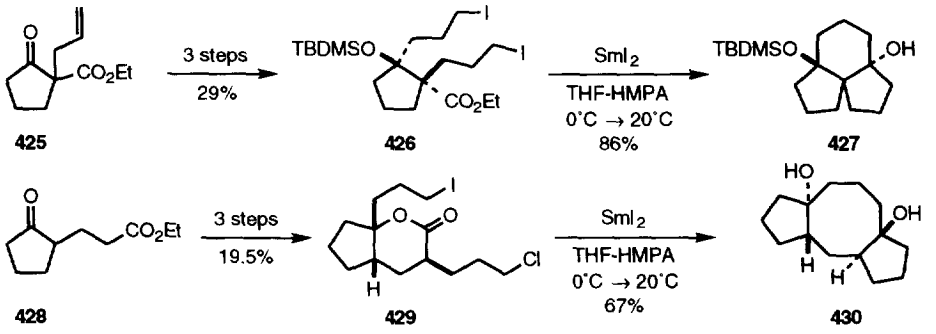
A tandem reduction / intramolecular hydroxyalkylation of 4-(3-hydroxyphenyl)alkanoates has resulted in a regioselective synthesis of 1,8-dihydroxytetralins.[234] Treatment of ester **416** with DIBALH produced the dihydroxytetralin **418** as the major product in 49% yield. The mechanism proposed involved initial formation of a diisobutylaluminum phenolate and partial reduction of the ester to give the aluminum chelate **417**. Upon workup, the liberated aldehyde carbonyl was attacked by the position ortho to the aluminum phenolate to give **418**. The observation that geminal substitution at C(3) was paramount to the success of the reaction is possibly a manifestation of the Thorpe-Ingold effect[235] where these substituents would assist in aligning the reactive centers for cyclization.



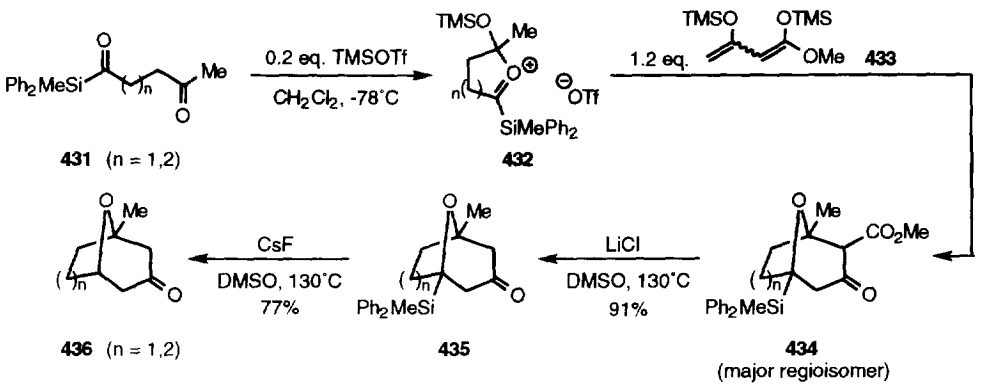
A cationic cyclization / oxidation sequence has been employed in a formal synthesis of (-)-aphanorphine (**424**).[236] Chiral lactol **420** was prepared from methyl 3-methoxyphenylacetate (**419**) in 11 steps with an overall yield of 37%. Exposure of **420** to catalytic sulfuric acid and 2,3-dichloro-5,6-dicyanoquinone (DDQ) on silica gel resulted in cyclization of the electron rich aromatic ring on the protonated aldehyde, rearomatization, and oxidation to alcohol **423** in an overall yield of 85%. The remainder of the synthesis was carried out as previously described by other researchers.[237]



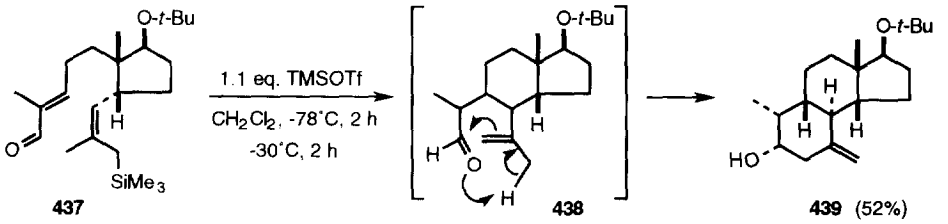
Samarium iodide has recently been employed in a tandem intramolecular nucleophilic acylation / Barbier cyclization to prepare fused bicyclic and tricyclic rings with high diastereoselectivity.[238] Protected hydroxyester **426**, prepared in three steps (29% overall yield) from ketoester **425**, was treated with SmI_2 in THF-HMPA at 0 °C → 20 °C for 5-6 h to afford the monoprotected tricyclic diol **427** in 86% yield. Similar treatment of lactone **429**, prepared from **428** in three steps (19.5% overall yield), generated the 5-8-5 tricyclic diol **430** in 67% yield. Following generation of the bis(organosamarium) species, attack by one metalated center at the ester in an acylation reaction followed by cyclization of the second organosamarium group on the resulting ketone afforded the observed products.



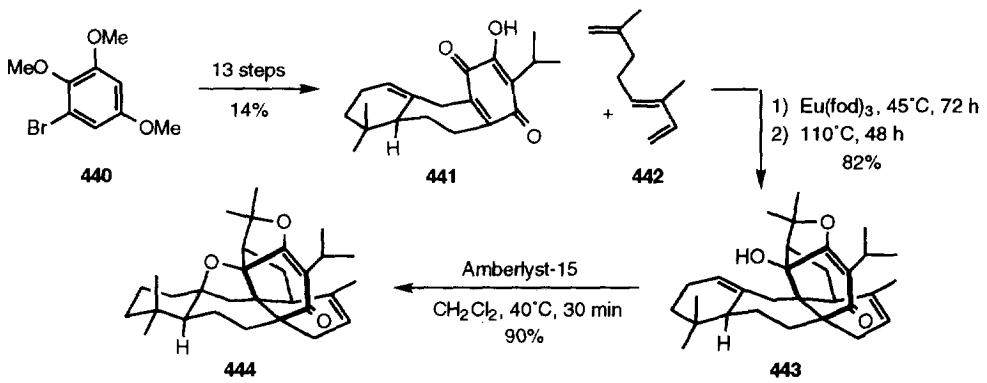
Novel [3+4] and [3+5] annulations involving Lewis acid-catalyzed reaction of 1,4- and 1,5-acylsilane dicarbonyl dielectrophiles with bis(trimethylsilyl) enol ethers have been used in the construction of oxabicyclo[3.*n*.1]alkan-3-ones.[239] Treatment of a mixture of acylsilane **431** and 1-methoxy-1,3-bis-(trimethylsilyloxy)-1,3-butadiene (**433**) with catalytic TMSOTf resulted in regioselective (generally ≥ 20 : 1) formation of the bicyclic ether **434** via oxocarbenium ion **432**. Following standard demethoxycarbonylation to **435**, the bridgehead silane was best removed using CsF in DMSO at 130 °C to afford keto ethers **436** in overall yields of 50-58% from the acylsilane dicarbonyl substrates.



Tietze and Rischer[240] have applied a tandem Sakurai / carbonyl ene reaction to the construction of the steroidal BCD ring architecture. Enone **437** was prepared from (+)-(1*S*,7a*S*)-1-*tert*-butoxy-7,7a-dihydro-7a-methyl-5(6*H*)-indanone by a relatively short synthetic scheme. Treatment with TMSOTf at -78°C followed by warming to -30 °C resulted in a Sakurai reaction to give **438**, followed by an intramolecular ene process to give the tricyclic alcohol **439**. The overall yield for the transformation was 52%.

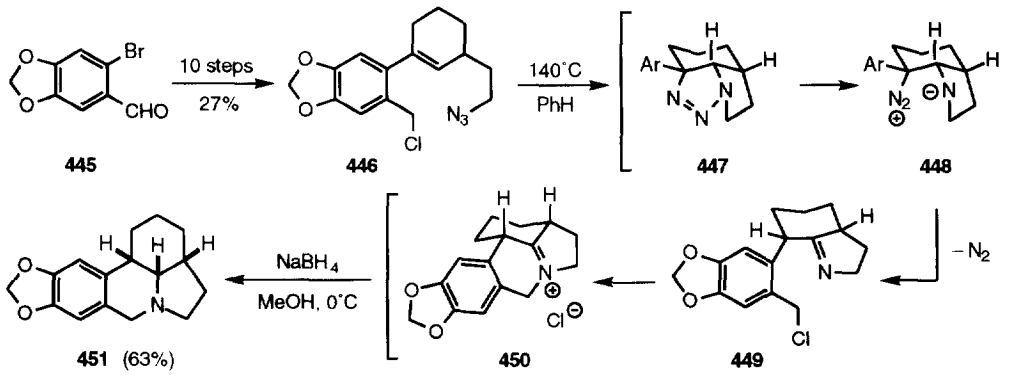


A one-flask polycyclization sequence has been employed by Majetich and Zhang[241] in an elegant synthesis of the complex triterpene (±)-perovskone (**444**). Synthesis of tandem reaction substrate **441** was accomplished in 13 steps from 1-bromo-2,3,5-trimethoxybenzene (**440**) in 14% overall yield. Treatment of **441** and *trans*-α-ocimene (**442**) with $Eu(fod)_3$ at 45 °C for 72 h followed by 110 °C for 48 h resulted in Diels-

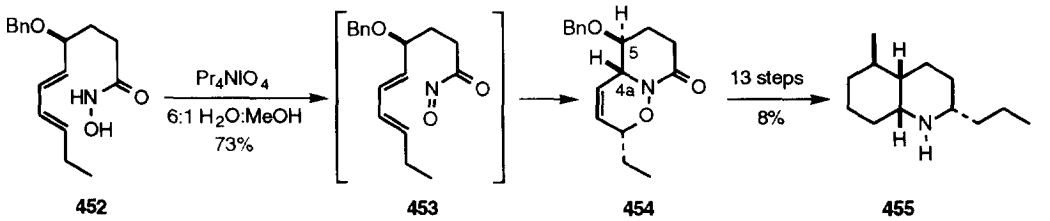


Alder cycloaddition, side chain double bond isomerization, Prins reaction, and tetrahydrofuran ring closure to give **443**. Subsequent reaction of **443** with Amberlyst-15 resulted in closure of the final tetrahydrofuran ring to give **444** in 74% yield from **441**.

Pearson and Schkeryantz[242] have exploited a novel tandem process in a beautiful synthesis of the alkaloid (±)-γ-lycorane (**451**). Substrate **446** was prepared from bromopiperonal **445** in 10 steps with an overall yield of 27%. Heating **446** at 140 °C promoted a sequence involving (1) intramolecular 1,3-dipolar azide cycloaddition, (2) fragmentation of the triazoline with concomitant hydride migration, and (3) intramolecular *N*-alkylation via intermediates **447-449** to give the iminium salt **450**. Direct treatment of **450** with $NaBH_4$ resulted in selective reduction of the iminium ion from the convex face of the molecule to give the target alkaloid **451** in 62% overall yield. These same researchers have employed a similar strategy for the preparation of (-)-slaframine.[243]

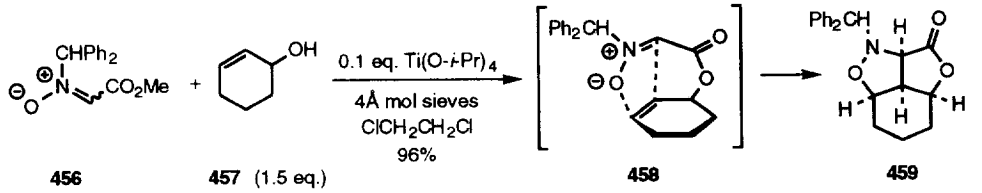


A synthesis of (-)-pumiliotoxin C (**455**) includes a tandem oxidation / Diels-Alder sequence.[244] Treatment of hydroxamic acid **452** with Pr_4NIO_4 in 6:1 H_2O:MeOH oxidized it to the acylnitroso diene **453**, which spontaneously underwent intramolecular Diels-Alder cycloaddition to adduct **454** with a 4.5:1 preference for the isomer bearing trans hydrogens at C(4a) and C(5). Compound **454** was then converted to the target alkaloid in 13 steps with an 8% overall yield. A similar procedure has been used by Keck and Romer[245] in a synthesis of highly oxygenated indolizidine alkaloids related to swainsonine.

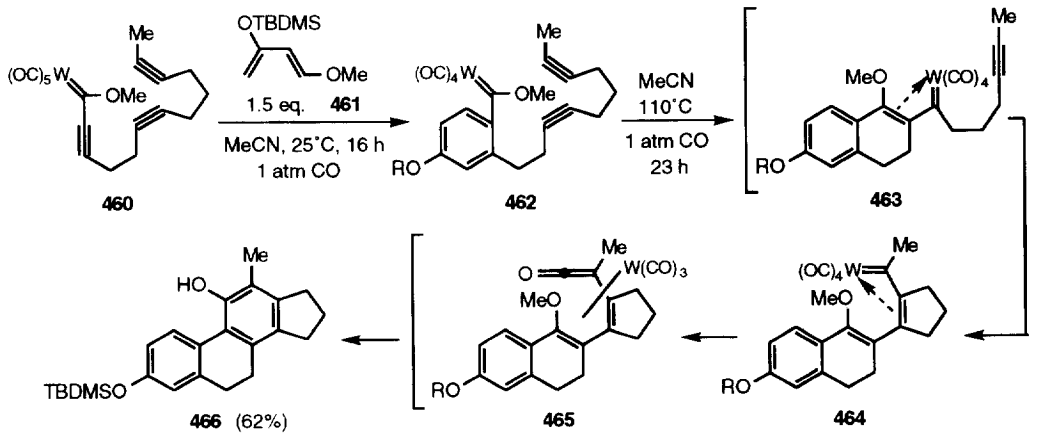


A sequential transesterification / intramolecular 1,3-dipolar cycloaddition of nitrones has furnished densely functionalized synthetic intermediates with high selectivity.[246] Exposure of nitrone **456** and 2-cyclohexen-1-ol (**457**) to catalytic $Ti(O\text{-}i\text{-}Pr)_4$ and 4Å molecular sieves resulted in sequential transesterification,

E,Z-isomerization of the nitrone, and [3+2] cycloaddition (via **458**) to give the tricyclic heterocycle **459** in 96% yield. The tandem process was extended to geometry-differentiated cycloaddition of *E*:*Z* mixtures of allylic alcohols.

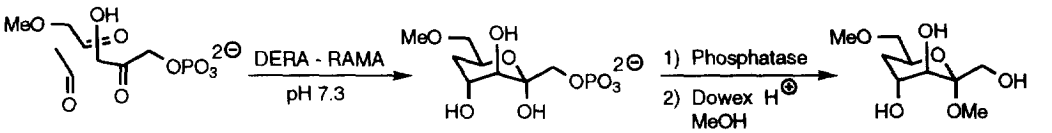


A one-flask Diels-Alder / double intramolecular alkyne annulation procedure involving metal carbene complexes has been applied to the construction of the steroid ring skeleton.[247] Tungsten carbene complex **460** was available in two steps (29% overall yield) from 1,5-hexadiyne and 4-pentynyl triflate. Treatment of **460** with Danishefsky's diene (**461**, TBDMS derivative) in MeCN under 1 atm of CO resulted in Diels-Alder reaction and spontaneous aromatization to give **462**. The reaction mixture was diluted 10-fold, degassed, sealed under 1 atm of CO, and heated to afford a 62% overall yield of the tetracyclic product **466** via cyclization intermediates **463-465**. This process is only the second case of a 0 → ABCD strategy[248] for the synthesis of steroidal ring systems.



Finally, Gijsen and Wong have reported the use of enzymes in tandem aldol reactions. The enzyme 2-deoxyribose-5-phosphate aldolase (DERA, EC 4.1.2.4) has been used to asymmetrically couple three acetaldehyde molecules to give a trideoxyhexose.[249] More dramatically, a multi-enzyme system of DERA and fructose-1,6-diphosphate aldolase (RAMA, EC 4.1.2.13) was used to catalyze a ternary crossed aldol between an α-substituted acetaldehyde derivative (acceptor aldehyde), acetaldehyde, and dihydroxyacetone phosphate.[250] For success in this process, a ratio of acceptor aldehyde : acetaldehyde : DHAP of 2:3:1 was used and substrates were selected such that formation of a stable hemiketal was not possible after the first aldol. To cite a specific example, methoxyacetaldehyde (**467**), acetaldehyde (**468**), and DHAP (**469**) were combined in the presence of DERA and RAMA at pH 7.3 to afford a 45% yield of the 5-deoxyketose **470**, which was

assayed as the methyl glycoside **471** after dephosphorylation and acetal formation. The final product was formed along with several minor side-products, which were easily removed by flash chromatography.



467 468 469 **470** **471 (45%)**

This methodology appears to be a powerful new way to generate deoxysugars. Though further work is necessary, this approach to chiral molecular building blocks should gain increased importance as knowledge of enzymes in organic synthesis becomes more widespread.[251,252]

10. Conclusion

The present compilation clearly demonstrates the diversity and power of tandem reactions in the field of synthetic organic chemistry. As sights are set on more complex target compounds, new methodology will be required for the rapid construction of molecules bearing unusual substitution patterns, and tandem reactions will play a very important role in accessing these new structures. Thus, work continues in an effort to elucidate innovative new processes, and organic chemists can expect a wealth of highly efficient and selective transformations to be reported in the coming years.

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