The Vinylogous Aldol Reaction: A Valuable, Yet Understated Carbon−Carbon Bond-Forming Maneuver

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I. Introduction

The aldol reaction is a cornerstone of synthetic organic chemistry and has been the subject of considerable optimization, especially in terms of diastereo- and enantiocontrol.[1] The wealth of imaginative reagents, catalysts, and protocols that have been devised to this purpose cogently testifies the amount of work dedicated to the area and reflects the importance of aldols as synthetic intermediates as well as ultimate targets. In the aldol reaction, a carbonyl electrophile interacts with an enol nucleophile under the agency of acid or base catalysis and formation of a β-hydroxy carbonyl derivative (aldol) ensues. The intrinsic polar nature of the mechanism qualifies the aldol reaction as a prime candidate for vinylogous extension. Vinylogy can be defined as the transmission of electronic effects through a conjugate system,[2] a concept traditionally credited to Claisen, who clearly formulated it in 1926 to explain the acidic properties of formylacetone and related β-keto aldehydes.[3] The principle of vinylogy has proved to be useful to rationalize the behavior of combinations of functional groups and to expand the scope of reactions where interacting functional groups can be coupled efficiently through the π-system of a C−C double bond. The SN′ is probably the best known example of reactions where a double bond acts as an electron-conducting channel between two reacting termini.[4] Many other polar reactions have, however, been modified in vinylogous terms, including the Claisen and benzoin condensations,[5] the bimolecular elimination, and the electrophilic addition to double bonds.[2] Vinylogy has also guided drug design,[6] as testified by the current intense interest in vinylogous peptides.[7]

The aldol reaction can be extended in vinylogous terms employing an α,β-unsaturated carbonyl compound either as the electrophilic component or as the dienol (dienolate) source (Scheme 1). While α,β-unsaturated carbonyl compounds are firmly enshrined in the mainstream of organic chemistry as electrophilic components in Michael reactions,[8] their alternative use as dienol precursors has surprisingly

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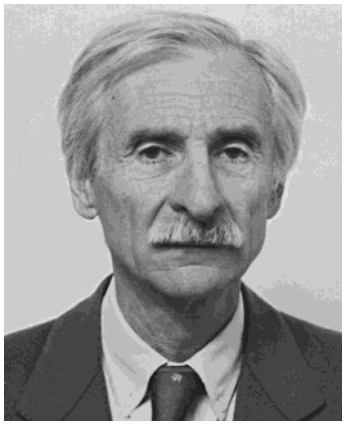


Giovanni Casiraghi was born and raised in Monza, Italy. He received his graduate education at the University of Pavia, where he received his Laurea degree in Chemistry in 1964. He pursued his research as a Shell-sponsored postdoctoral fellow in the laboratories of Professor S. Pietra at University of Pavia. In 1968 he joined Professor G. Casnati's group at the University of Parma, where he rose through the ranks to become Full Professor of Organic Chemistry in 1985. From 1986 to 1991 he served at the Department of Chemistry of the University of Sassari, and in 1992 he accepted an appointment at the Faculty of Pharmacy of the University of Parma, Chair in Organic Chemistry, establishing a laboratory engaged in both synthetic organic and bio-organic chemistry. G. Casiraghi's research interests focus on method- and target-oriented synthesis, molecular design and recognition, and the biological actions of organic molecules.

Franca Zanardi was born in S. Secondo, Parma, Italy, in 1968. She studied Chemistry at the University of Parma where she received her Laurea degree in 1993. In 1997 she received her D.Phil. degree in Bioorganic Chemistry from University of Parma under the direction of Professor G. Casiraghi. At present she is a Researcher at the Pharmaceutical Department of the University of Parma. Her research interests are in the areas of synthetic organic chemistry, medicinal, and bioorganic chemistry.

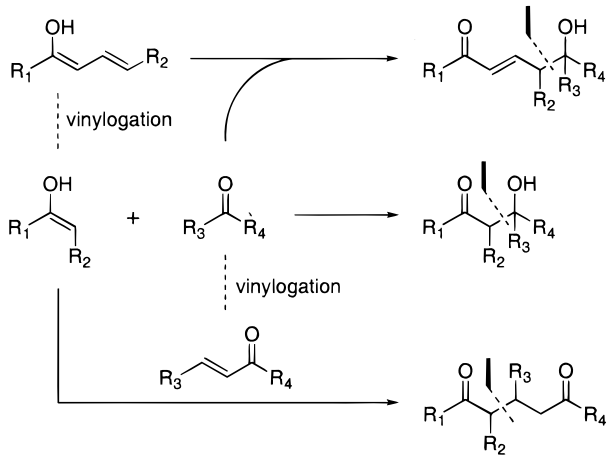
Giovanni Appendino was born in 1955 in Carmagnola, Torino, Italy, and in 1979 earned his Laurea degree from the University of Torino, to whom he has been associated since 1983. In 1985 he spent one year at the University of Ghent, Belgium, where he joined the group of Professor J. De Clercq, working on the total synthesis of gibberellins. He is currently an Associated Professor at the Faculty of Pharmacy, University of Torino. His major field of research is the isolation, chemical modification, and total synthesis of biologically active isoprenoids (phorboids, taxoids, vanilloids, meroterpenoids). His studies on medium-sized isoprenoids earned him in 1991 the Rhone-Poulenc-Rorer Award of the Phytochemical Society of Europe.

Gloria Rassu is a Researcher at the Consiglio Nazionale delle Ricerche (CNR), Area della Ricerca di Sassari. She was born and raised in Sassari, Italy, and earned her Laurea degree in Chemistry at the University of Sassari. After five years of postdoctoral work, in 1984 she joined the Istituto per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici del CNR, Sassari, where she assumed her current position. In 1987 she joined the research group of Professor G. Casiraghi working on the development of a novel vinylogous aldol methodology and its exploitation in the total synthesis of densely functionalized chiral compounds. In 1991 she began her independent research, focusing upon the design and application of new stereoselective methods with great predilection toward the synthesis of biologically active molecules and variants of them.

received only scanty systematic attention. This paradoxical situation is even more surprising in the light of the early interest and recognition of the synthetic potential of vinylogous reactions[2] and of the higher structural complexity of vinylogous aldols as compared to Michael adducts. The vinylogous aldol reaction has the potential of generating three elements of stereogenicity (two carbons and one double bond), while the Michael reaction is limited to two. The vinylogous aldol motif (δ-hydroxy-α,β-unsaturated carbonyl structure, Scheme 1) is also structurally more complex than its Michael counterpart, a 1,5-dicarbonyl moiety, and can provide a framework for further modification. In this context, the presence of an oxygenated function adjacent to the double bond is an additional asset, which can be harnessed for the regio-, diastereo-, and enantioselective functionalization of the olefin system of vinylogous aldols. Alternatively, vinylogous aldols can be dehydrated to polyenic compounds, a sometimes useful alternative to Wittig-type olefination strategies.

The remarkable increase in educt complexity qualifies the vinylogous aldol reaction as a strategy-level maneuver for multistep syntheses, while the occurrence of a vinylogous aldol motif in many natural products and the involvement of vinylogous aldol chemistry in their reactivity and/or biogenesis are further elements of interest in the reaction. The aldol chemistry of vinylogous carbonyl acceptors has tra-

Scheme 1



ditionally been included in the realm of Michael reactions.[8] It seems, therefore, convenient to limit the term "vinylogous aldol reactions" to processes where a vinylogous enol or enolate adds in a 1,2-fashion to a carbonyl or a surrogate thereof. Vinylogous aldol reactions which are nucleophilic additions to a carbon−carbon double bond conjugated to a carbonyl are better described as Michael reactions, and there is ample historical precedent for this distinction.[2]

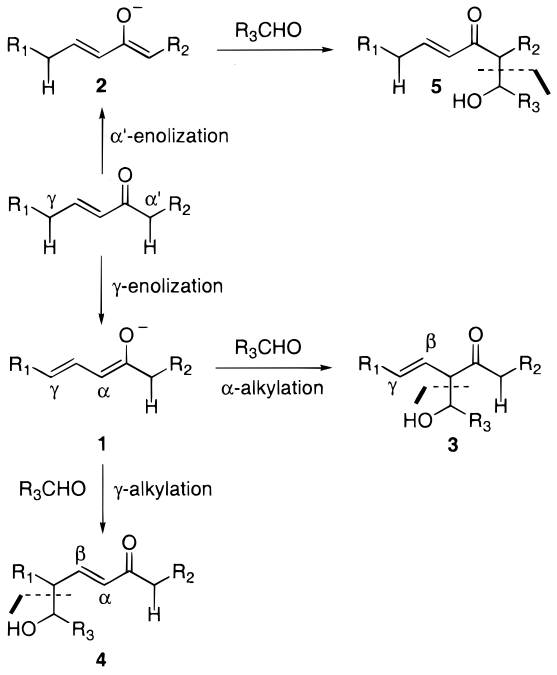
While partial accounts on the development of a specific entry to vinylogous aldols—namely, the heterocyclic silyloxy diene strategy—have been published,[9] no general coverage of the vinylogous aldol reaction is otherwise available, and our article seeks to fill this void. Rather than being an encyclopedic coverage of a subject wildly scattered and difficult to search, this review will highlight relevant applications of the vinylogous aldol reaction in synthesis and in natural product chemistry. Mannich-type reactions, basically isosteric modifications of the aldol theme, will also be included.

II. Regiochemical Issues

The structural complexity achieved in a vinylogous aldol reaction is somewhat compensated for by the need to address critical regiochemical issues at the stage of dienolate formation and alkylation. The most critical situation is with α,*β*-unsaturated ketones, imines, and hydrazones. Owing to the presence of two potential sites of enolization (*γ* and α′), both a through-conjugated (thermodynamic, **1**) and a cross-conjugated dienolate (kinetic, **2**) can originate from the deprotonation step (Scheme 2).[10] Through-conjugated dienolates can be alkylated at the α- or *γ*-position, behaving as d^2- or d^4-reagents[11] and affording *β*,*γ*- (**3**) or α,*β*-unsaturated (**4**) adducts, respectively. In principle, three distinct types of adducts, **3**, **4**, and **5**, can thus be obtained from the alkylation of α,*β*-unsaturated ketones, imines, and hydrazones (Scheme 2), while with other carbonyl-stabilized (COOR, CONHR, etc.) vinylogous carbanions, only the issue of α- vs *γ*-alkylation needs to be considered.

For α,*β*-unsaturated ketones, the formation of cross-conjugated dienolates is overwhelmingly favored under standard kinetic conditions of enolization

Scheme 2

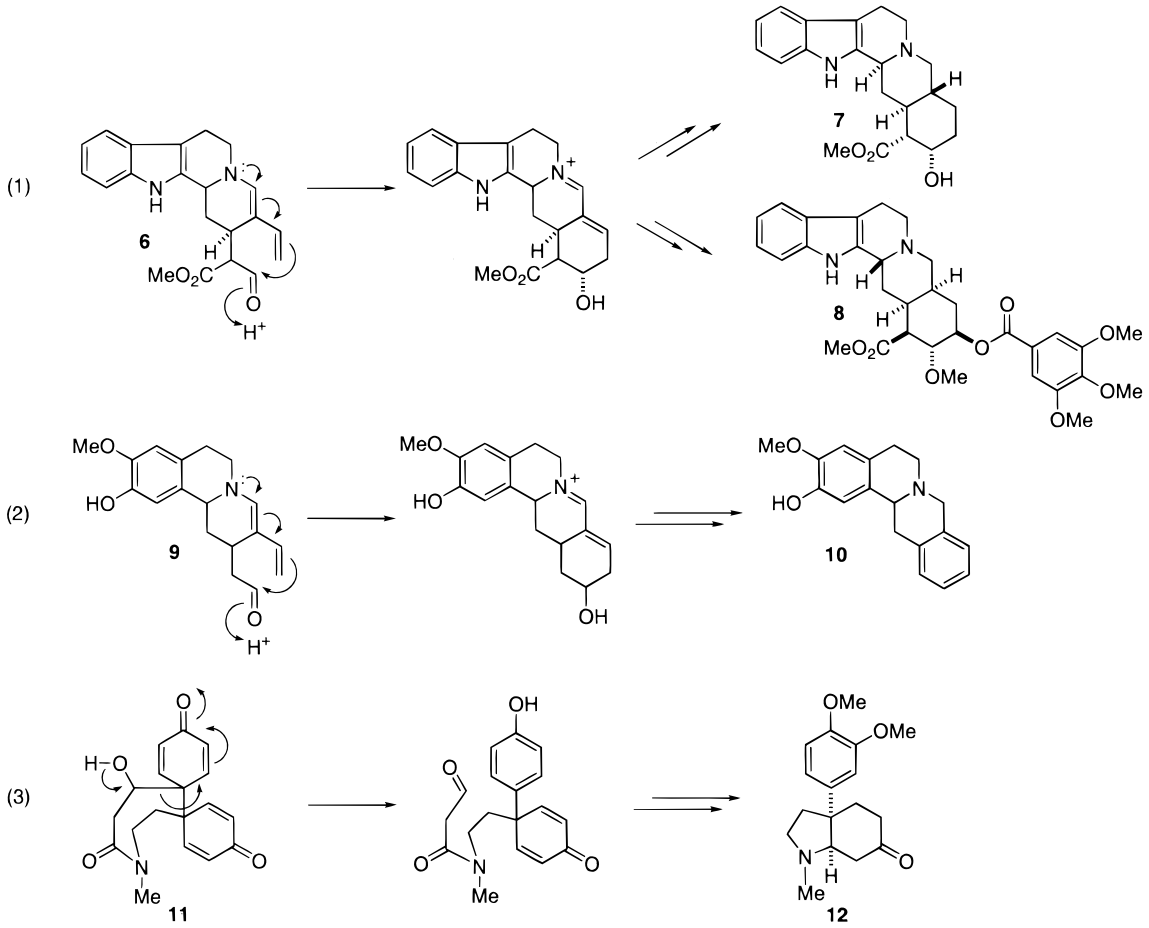


(lithium base, THF, low temperature).[12,13] Under these conditions, a "normal" aldol course is followed and adducts such as **5** (Scheme 2) are obtained also with ketones capable of undergoing enolate equilibration.[13] Fully conjugated dienolates of α,*β*-unsaturated ketones are difficult to obtain,[13] and the early recognition of this troublesome problem led Stork to develop an ingenious entry into vinylogous aldols which does not rely on vinylogous aldol chemistry but on the kinetic deprotonation of enol ethers of symmetric 1,3-diketones.[14] To coax enolization of α,*β*-unsaturated ketones toward the formation of thermodynamic dienolates, special protocols and/or suitable catalysts are in fact necessary (see section V.A).

The reaction of metal dienolates with hard electrophiles such as carbonyl compounds gives a mixture of α- and *γ*- alkylated products, in a ratio dependent on the nature of the dienolate precursor, the pattern of substitution at the α- and *γ*-position, the nature of the associated cation(s), the structure of the carbonyl compound, and reaction parameters such as temperature, solvent, and time. In general,[13] unconjugated α-adducts are obtained under conditions of kinetic control (low temperature, short reaction time, stoichiometric amounts of bases) while conjugated *γ*-adducts are produced under conditions favoring thermodynamic control (room or higher temperatures, longer reaction times, substoichiometric amounts of bases). The α-adducts can be equilibrated to the more stable *γ*-adducts, and a high *Z*/*E* stereoselectivity is generally observed in the latters. Interestingly, trapping of dienolates and metallodienamines with alkyl halides mainly gives, instead, α-alkylated unconjugated adducts,[13,15] a reaction extensively employed to introduce angular methyls in steroid chemistry.[16]

It should be pointed out, however, that little systematic work has been done on the complex

Scheme 3



regiochemical issues involved in the vinylogous aldol reactions, and critical parameters which could potentially affect the course of the reaction, like enolate counterion, solvent, temperature, and additives, are still largely unexplored for many types of dienolates. The regiochemical problems associated to metal dienolates can be overcome using their silyl derivatives, whose generation and alkylation can be disciplined by the judicious choice of catalysts (promoters) and additives (see section VI). In this context, silyloxy dienes have emerged as superb surrogates of metal dienolates for the vinylogous aldol reaction. Thanks mainly to this development, the reaction has now grown into a reliable methodology, testified by its inclusion in complex multistep syntheses and by the numerous studies aimed at its mechanistic rationalization.

III. Relevance of Vinylogous Aldol Additions in Natural Products Chemistry

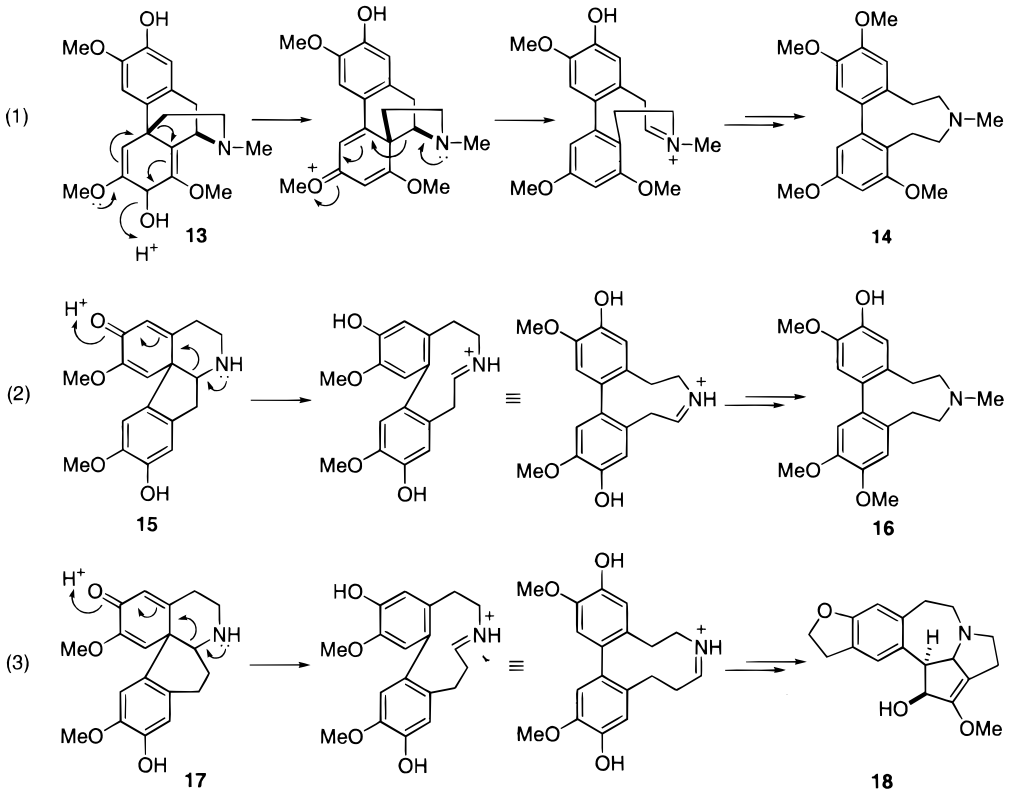
The potential of the vinylogous aldol reaction to build complex molecular constructs did not go unnoticed in nature, and the assembly or the fragmentation of a vinylogous aldol motif is involved in the formation of the carbon skeleton of important secondary metabolites. Many examples come from the field of alkaloids, where the Mannich reaction is extensively employed to join building blocks of different biogenetic origin. Examples of the vinylogous version of the reaction are encountered in the further elaboration of these adducts. The assembly of the yohimbane skeleton from a corynanthe-type dienaminoaldehyde **6** is a preeminent example en route to the α_2-adrenergic (and, therefore, sympatholytic) agent yohimbine (**7**) and the antihypertensive drug reserpine (**8**) (Scheme 3, eq 1).[17]

Yohimbine has recently made headline news in the mainstream press for its alleged, and not yet conclusively proved, aphrodisiac and lipolytic properties. The biogenesis of the monoterpene isoquinoline alkaloids resembles that of the monoterpene indole alkaloids. It is not, therefore, surprising that a process related to the one involved in the formation of the yohimbane skeleton has also been postulated for the biogenesis of the ipecac-type alkaloid bharanamine (**10**) from the phenantridine **9** (eq 2).[18] Attempts to mimic the vinylogous Mannich reaction involved in the formation of **10** have failed.[18]

The key step in the assembly of *Sceletium* alkaloids such as mesembrine (**12**) (eq 3), a compound with cocaine-type activity,[19] is a vinylogous retro-aldol fragmentation of the bis-spirodienone **11**,[20] and two distinct vinylogous retro-Mannich fragmentations have been postulated in the biogenesis of the structurally related dibenzazonine alkaloids protostephanine (**14**) and erybidine (**16**) (Scheme 4, eqs 1 and 2).[21]

The relatively simple skeleton of these compounds has a rather complex biosynthesis, involving morphinane **13** and neoproaporphine **15** precursors. This

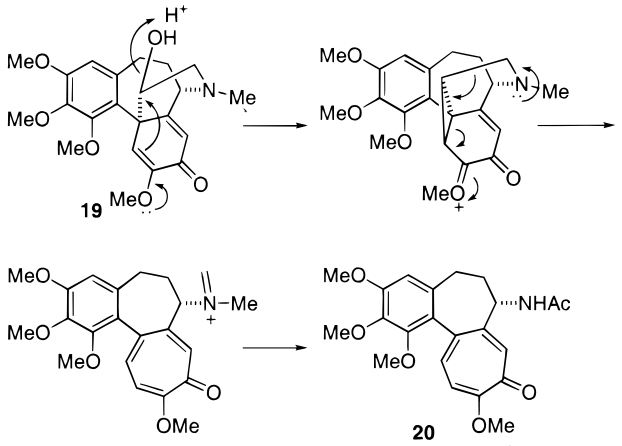
Scheme 4



is a curious example of how nature sometimes defies the Ockham principle and chooses apparently roundabout routes to build secondary metabolites. Dibenzazonines are in turn the precursors of the toxic and curare-like *Erythrina* alkaloids, though the involvement of a neoproporphine intermediate in the biosynthesis of these compounds has recently been questioned.[22] The vinylogous retro-Mannich fragmentation of **17** (eq 3), the homologue of **15**, is a key step in the biogenesis of the homoerythrina and the *Cephalotaxus* alkaloids.[23] Esters of cephalotaxine (**18**) have attracted considerable attention on account of their powerful anticancer activity.[24]

Finally, the "cyclopropylogous" version of a vinylogous retro-Mannich fragmentation is featured in the final steps of the biogenesis of the known antimitotic agent colchicine (**20**) from hydroxyandrocymbine (**19**) (Scheme 5).[25] The biosynthesis of colchicine,

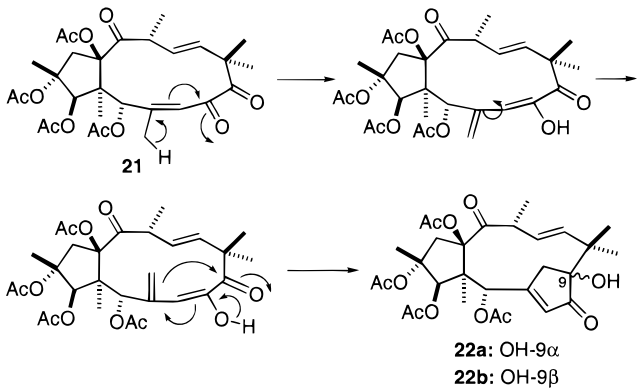
Scheme 5



the main alkaloid of the autumn crocus (*Colchicum autumnale* L.), is not at all obvious from the nature of the starting compounds (two molecules of phenylalanine), and its rationalization was guided by the isolation of precursors of the tropolone ring from plants related to the autumn crocus.[25]

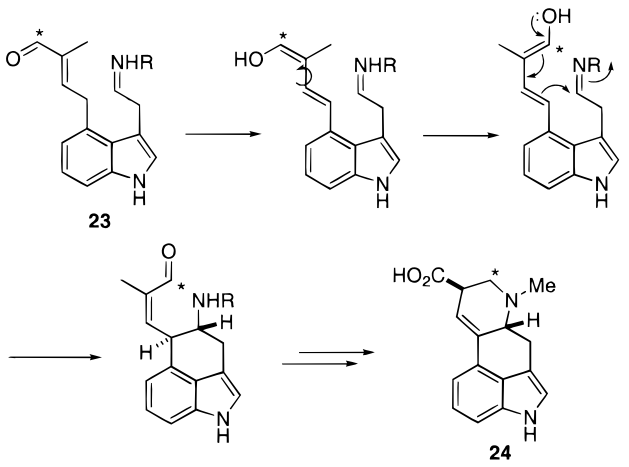
In the field of isoprenoids, an intramolecular vinylogous aldol reaction has been postulated to rationalize, in biogenetic terms, the unusual carbon−carbon connectivity of the euphoperfoliane skeleton of the complex diterpenoids **22a** and **22b**.[26] These compounds were isolated from *Euphorbia semiperfoliata* Viv., a spurge endemic to Sardinia, and a macrocyclic jatrophane structure **21** was proposed as their precursor (Scheme 6). A vinylogous Mannich

Scheme 6



reaction might also be involved in the assembly of ring C of lysergic acid **24** from a 4-prenylated indole like **23**. Formation of a dienol or a dienolate (Scheme 7) could provide a mechanism for the puzzling

Scheme 7



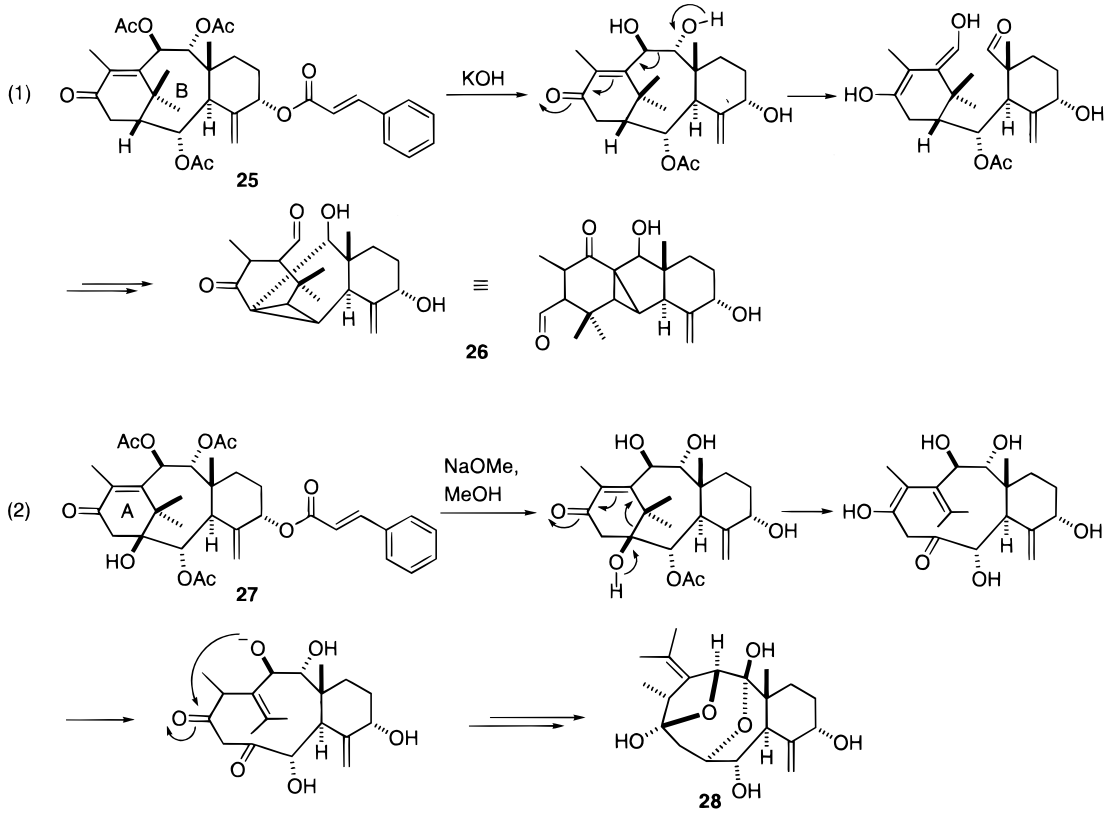
isomerization of the double bond of the isoprenoid moiety observed in feeding experiments with C-2-labeled mevalonate. This possibility was, however, apparently overlooked.[27]

The vinylogous aldol motif occurs in many secondary metabolites, and its fragmentation is at the basis of a series of long-standing skeletal rearrangements and isomerizations observed during the structure elucidation of important natural products. The rearrangement of taxinine (**25**), the first taxane to be obtained in pure form, to anhydrotaxininol (**26**) was discovered as early as in 1931, long before the constitution of the taxane skeleton was elucidated.[28] This remarkable transformation (Scheme 8, eq 1) is triggered by the base-induced vinylogous retro-aldol fragmentation of ring B and played a key role in the structure elucidation of taxinine.[29] It also inspired a total synthesis of Taxol (vide infra). Interestingly, the basic degradation of 1-hydroxyderivatives of taxinine (e.g., **27**) is triggered by a different vinylogous retro-aldol fragmentation, leading to the breakage of ring A and the eventual formation of the A-*seco* bisacetal **28** (Scheme 8, eq 2).[30] A similar fragmentation was reported for the 13-dehydroderivatives of baccatin VI[31] and baccatin III.[32]

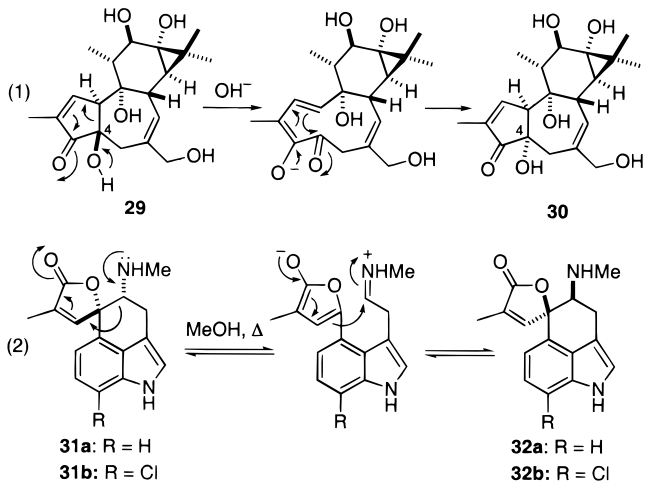
Phorbol esters are very important investigational tools in cell biology and in pharmacology. In basic medium, phorbol (**29**) is quantitatively epimerized to 4α-phorbol (**30**) through a vinylogous retro-aldol reaction (Scheme 9, eq 1).[33] This epimerization causes complete loss of activity and was important to rationalize the reactivity of the natural product and its lability to basic conditions.[34] A related retro-Mannich reaction was invoked to explain the interconversion of the ergot alkaloids rugulovasines A (**31a**) and B (**32a**). Warming in polar solvents was sufficient to affect the isomerization (eq 2), and their toxic 8-chloro derivatives (**31b** and **32b**) behaved similarly.[35] This reaction is presumably responsible for the isolation of these chiral compounds in racemic form.[35]

Vinylogous aldol-type reactions were also discovered, often serendipitously, in the course of projects aimed at the chemical modification of natural products. Scheme 10 depicts an example taken from an attempt of biomimetic assembly of the cage skeleton of the so-called CP compounds, a series of microbial inhibitors of cholesterol biosynthesis.[36] Dimerization of the anion of anhydride **33** afforded a dienolate which then collapsed in a Michael fashion to the

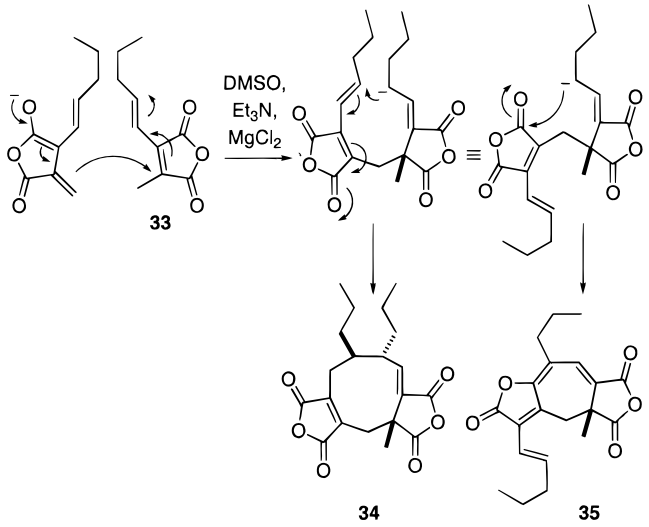
Scheme 8



Scheme 9



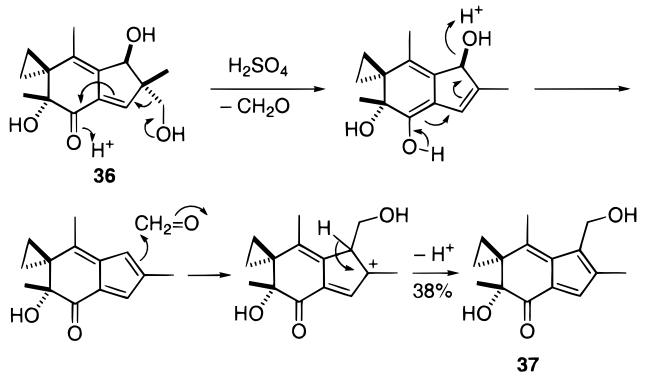
Scheme 10



isoglaucanic acid derivative **34**. The cycloheptadiene derivative **35**, the result of an intramolecular vinylogous aldol reaction, was obtained as a side product.[36]

Finally, a vinylogous retro-aldol reaction is involved in the semisynthesis of the anticancer agent hydroxymethylacylfulvene (HMAF, **37**) from illudin S (**36**) (Scheme 11).[37] Treatment with diluted acids causes the elimination of formaldehyde, which then re-adds in a Prins fashion to the fulvene moiety.

Scheme 11



HMAF is being investigated in phase II human clinical trials against solid tumors[38] and shows a better profile than its precursor **36**, a sesquiterpene obtained from the luminescent mushroom jack o'lantern (*Omphalotus illudens*).[39]

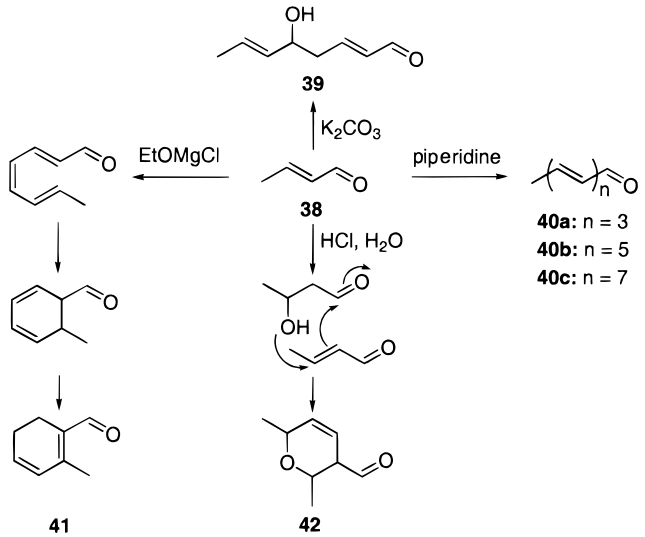
Taken together, these observations show an interesting connection between the vinylogous aldol reaction and some important medicinal agents of natural origin, either at the level of biogenesis (yohimbine, reserpine, colchicine, cephalotaxine, possibly lysergic acid) or reactivity (taxanes, phorbol) and semisynthesis (HMAF). It is not, therefore, surprising that some of the most spectacular and modern applications of the reaction are in the realm of natural product synthesis (see section VI).

IV. Nondirected Vinylogous Aldol Additions

In a nondirected aldol reaction, the nucleophilic species (enolate or enol) is generated in a substoichiometric way in situ, namely, in the presence of its complementary electrophilic carbonyl partner. Acid or base catalysis is necessary to trigger the reaction, and vinylogous aldol adducts rarely survive these conditions, since their higher conjugation favors crotonization and polymerization. For reactions carried out in nucleophilic solvents (water, alcohol), Michael addition prior to the aldolization step can further complicate the scenario and, except for special cases, poor yields are obtained.

The self- and crossed condensation of α,β-unsaturated aldehydes was an important synthetic route to polyenals before the advent of the Wittig reaction. However, a large body of the literature on this subject does not report yields and, being old, has not been validated by studies employing modern techniques of structure elucidation. The data on crotonic aldehyde (2-butenal, **38**) are exemplificative of this situation (Scheme 12).

Scheme 12

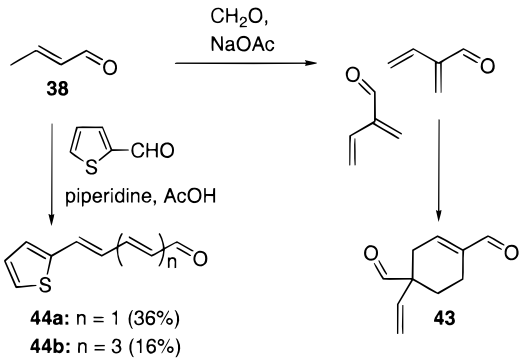


Self-condensation of **38** has been reported to afford different compounds according to the conditions employed, all in unreported yield. With K_2CO_3, formation of the vinylogous aldol **39** was claimed,[40]

while in the presence of piperidine or other amines, the corresponding crotonized adduct **40a** was obtained, accompanied by the corresponding trimer **40b**.[41] When EtOMgCl was employed, the crotonized adduct underwent an electrocyclic reaction, affording, after double-bond migration, the cyclohexadiene **41**.[42] Under acidic conditions (HCl), the pyrane **42** was obtained instead.[43] Compound **42** is presumably the result of Michael addition of water to the starting enal, followed by dimerization in a Michael fashion, and eventual intramolecular aldolization/dehydration.

Crossed condensation of **38** with formaldehyde afforded only polymeric material with K_2CO_3[44] and the cyclohexene **43** (unreported yield) with NaOAc (Scheme 13).[44] Compound **43** is formed from the

Scheme 13

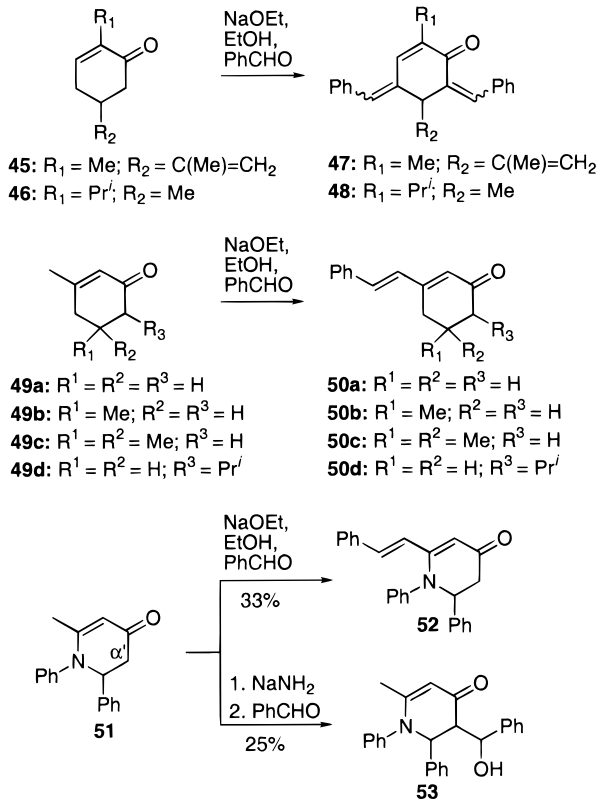


α-methylenated adduct via a Diels−Alder reaction. In acidic medium, only the crotonized vinylogous adduct of type **40a** was obtained.[45] With aliphatic aldehydes (acetaldehyde, undecanal) and aromatic aldehydes as the a[1]-component, crotonized vinylogous adducts were obtained, in some cases in reported yields (e.g., 36% for **44a**, starting from thiophenecarbaldehyde).[46] However, the reaction was plagued by the formation of higher homologues, like the tetraenal **44b**.[46]

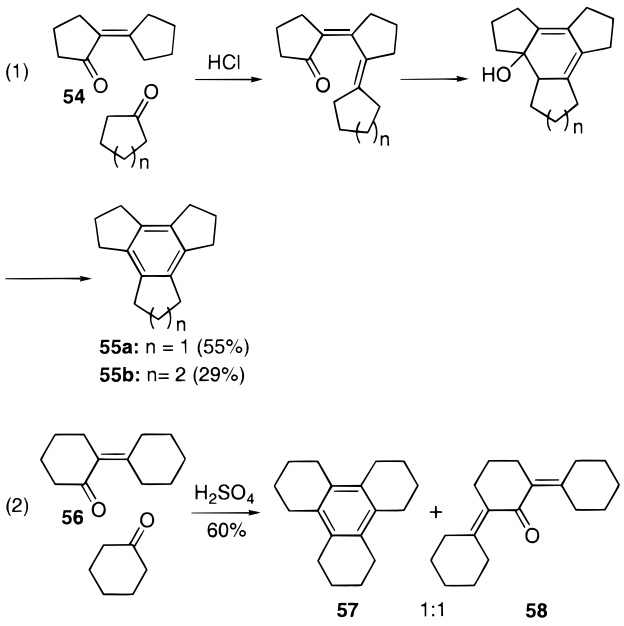
The self-condensation of α,*β*-unsaturated ketones follows, at least in acidic medium, a Michael course, as exemplified by the formation of isophorone (3,5,5-trimethyl-2-cyclohexenone) from phorone (bis-isopropylidene acetone). Cyclic α,*β*-unsaturated ketones can, however, be condensed with aromatic aldehydes. The reaction has been investigated with benzaldehyde and cyclic enones bearing a *γ*-methylene or a *β*-methyl group. The terpenoids carvone (**45**) and menthenone (**46**) gave bis-benzylidene adducts **47** and **48**, respectively,[47] while cyclic enones with a *β*-methyl group, **49a**−**d**, gave selectively *γ*-monobenzylidene adducts **50a**−**d** (Scheme 14).[48] A similar reaction was reported for the vinylogous amide **51**, which afforded the benzylidene adduct **52**.[49] Interestingly, the preformed enolate of **51** reacted instead at the α′-position to give **53**, since formation of the more conjugated adduct is presumably favored under conditions of enolate equilibration.[49,50]

An interesting reaction of cycloaromatization has been reported for 2-cyclopentylidenecyclopentanone (**54**). Treatment with simple cyclic ketones (cyclopentanone, cyclohexanone) gave the tetracyclic benzene

Scheme 14



Scheme 15

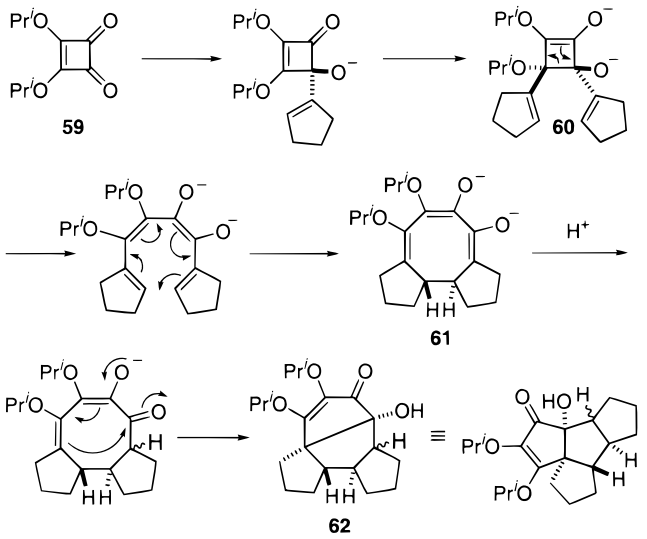


derivatives **55a** and **55b** (Scheme 15, eq 1).[51] These compounds are the result of a 2-fold vinylogous crotonic condensation. The first one leads to a dienone, which then undergoes a formal intramolecular vinylogous aldolization to a cyclohexadienol, eventually aromatized by dehydration. Alternatively, the saturated ketone adds to the enone in a 1,2-fashion and the vinylogous self-crotonization then ensues. Though the yield was modest, the simplicity of the conditions, the availability of the starting materials, and the complexity of the formed adducts make this

reaction one of the few nondirected vinylogous aldol reactions of current synthetic utility. 2-Cyclohexylidenecyclohexanone (**56**) behaved in a similar way, but the cycloaromatized vinylogous aldol adduct **57** was obtained as an equimolecular mixture with the α′-crotonized aldol adduct **58** (eq 2).[52]

A self-condensation somewhat similar to that involved in the formation of **55a**,**b** and **57** was observed by Paquette in the course of studies on the cascade rearrangements following the 2-fold addition of alkenyl anions (e.g., cyclopentenyl anion) to squarate esters (e.g., **59**) (Scheme 16). Both nucleophilic ad-

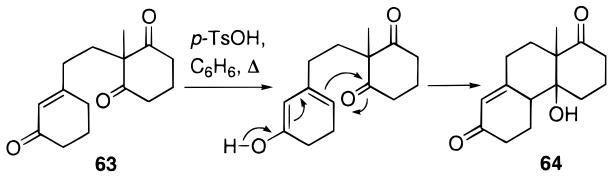
Scheme 16



ditions normally follow a 1,2-pattern, but occasionally the second addition proceeded in a 1,4-manner, giving *trans*-1,2-cyclobutenes such as **60**. After disrotatory opening of the cyclobutene ring and conrotatory closure of the resulting tetraene, a doubly charged triene **61** was obtained. Protonation of the latter triggered a vinylogous aldol cyclization to the polyquinane **62**.[53]

Very few examples of successful nondirected intramolecular vinylogous aldolizations have been reported. Of special relevance is a reaction described by Torgov in 1964,[54] where the tricyclic D-homosteroid precursor **64** was assembled from the C-*seco* compound **63** by refluxing with *p*-toluenesulfonic acid in benzene (Scheme 17). This reaction represents the

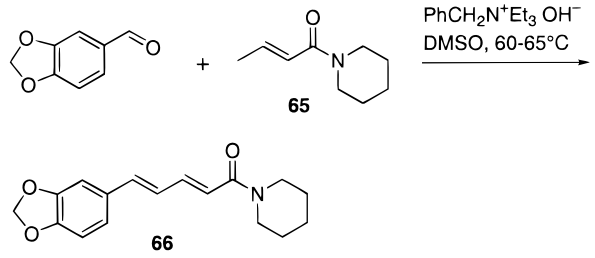
Scheme 17



first intramolecular vinylogous aldol reaction, and it is, therefore, an unfortunate case that the yield was not given.

Since aldehydes and ketones are stronger acids than α,β-unsaturated esters and amides, nondirected crossed condensations are only feasible with carbonyl compound lacking α-hydrogens. The synthesis of piperine **66**, the pungent principle of black pepper, from the piperide of crotonic acid **65** is an interesting case (Scheme 18).[55]

Scheme 18



In conclusion, except for special cases, the nondirected vinylogous aldol reaction lacks general applicability and, as an entry to polyenals, has been subsided by the Wittig and related reactions. From the mechanistic point of view, the data available in the literature show a definite tendency for γ- vs α-alkylation for dienolates generated under equilibrating conditions, at least when aldehydes different from acetaldehyde are employed. Under conditions of thermodynamic control, the higher stability of the more conjugated crotonized adducts seemingly drives the reaction toward γ-attack.

V. Vinylogous Aldol Additions Using Metal Di- and Higher Enolates

The availability of strong bases of low nucleophilicity and the wide repertoire of chelating or basifying solvents have made the stoichiometric generation of enolates possible, allowing an unprecedented expansion of our arsenal of carbon−carbon bond-forming reactions.[56] Vinylogous dienolates are basically carbonyl-stabilized allylic carbanions, and their generation and reactivity has attracted considerable attention. The development of alternatives to deprotonation for the generation of metal dienolates has further fuelled interest in this class of anions, whose reactivity has been exploited in elegant syntheses of natural products with a remarkable regio-, diastereo-, and enantiocontrol.

A. Dienolates from Unsaturated Aldehydes and Ketones

Direct enolization of saturated aldehydes by treatment with strong bases of low nucleophilicity is plagued by polymerization and is unrewarding from a synthetic standpoint.[57] α,β-Unsaturated aldehydes show a similar behavior, while the enolization of enones under standard conditions (LDA, THF, low temperature) is overwhelmingly biased toward α′-deprotonation.[13] Alternative procedures or indirect methods have, therefore, been used to generate dienolates of aldehydes and ketones. Interest in the chemistry of these dienolates is testified by the host of methods developed for their generation from both carbonyl and non-carbonyl precursors. Regrettably, trapping with electrophiles different from carbonyl compounds was generally reported and aldol chemistry was not investigated. The recent breakthrough

discovery that in the presence of a bulky Lewis acid dienolates of aldehydes and ketones can be generated by direct deprotonation and coupled in situ to saturated aldehydes rekindled interest in the field.[58]

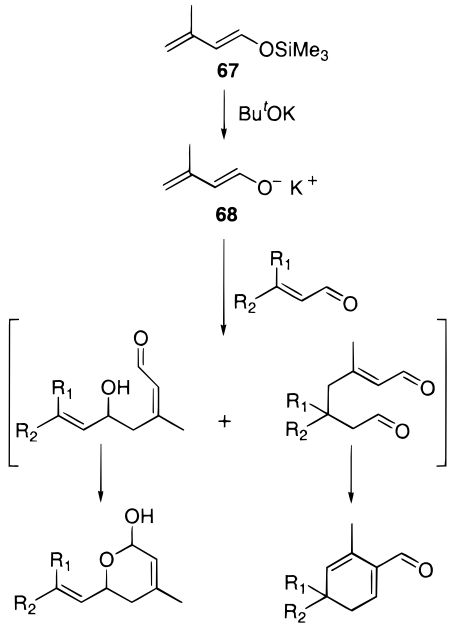
Dienolates of α,β-unsaturated aldehydes can be generated with systems such as KH in THF and KNH_2 in liquid ammonia,[59] where they show a surprising stability.[60] However, their reactivity with carbonyl compounds was not systematically investigated. Formation of imine derivatives allowed formation of dienolates by deprotonation with lithium bases, but the method turned out to lack general applicability.[61] Many protocols were also developed to prepare extended dienolates from specific α,β-unsaturated ketones, but none has gained widespread use.[62] The method based on methyllithium-assisted cleavage of silyl enol ethers (Stork)[63] and enol acetates (House)[64] showed more synthetic latitude. Two equivalents of methyllithium was originally reported to be necessary for the cleavage of dienol acetates,[64] but 1 equiv was then proved to suffice, since lithium *tert*-butoxide (generated from the reaction of acetone with methyllithium) turned out to be able to cleave enol acetates.[65] Alkali alkoxides (especially potassium *tert*-butylate) proved to be the reagents of choice to cleave silyl dienol ethers obtained from α,β-unsaturated aldehydes and could be used in substoichiometric way, since aldol anions could cleave silyl enol ethers.[66]

The reaction of the dienolate of prenal with polyenaldehydes is an attractive strategy for the synthesis of retinoids and polyprenols and was investigated in detail by the group of Duhamel in Rouen to define the factors which control the regiochemistry of alkylation.[67] When stoichiometric amounts of potassium *tert*-butylate were employed to generate **68** from its corresponding dienoxysilane **67**, mixtures of γ-1,2- (**69a**−**c**) and γ-1,4- (**70a**−**c**) adducts were obtained, in a ratio dependent on the reaction conditions (time, temperature) (Scheme 19). At low temperature (−78 °C) and for short reaction times (<3 h), the major reaction products were the γ-1,2-addition products **69a**−**c**, accompanied by minor amounts of the cyclohexadienals **70a**−**c**, formed by a tandem 1,4-addition/intramolecular crotonization.

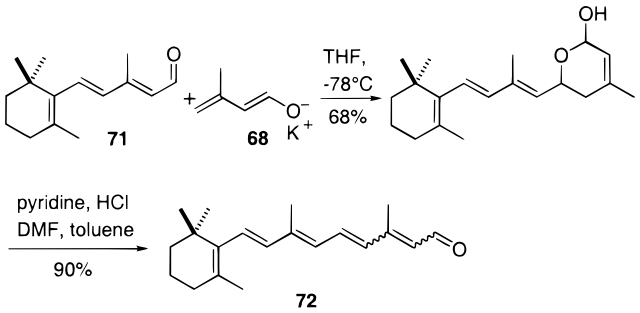
Interestingly, the γ-1,2-adducts were isolated exclusively as their lactolized *Z* isomers (**69a**−**c**). The increase of temperature and/or reaction time also increased the proportion of the γ-1,4-adducts, which for reaction times >3 h and at 0 °C became the exclusive reaction products. These results were rationalized in terms of kinetic control to γ-1,2-adducts and thermodynamic shift to γ-1,4-adducts. The dihydropyrane adducts **69a**−**c** could be converted into polyenals by simple treatment with pyridinium chloride. Mixtures of double-bond isomers were, however, obtained with a prevalence of 2*E* isomers.

This strategy was applied to a short synthesis of retinal (**72**) from β-ionylidene acetaldehyde **71** (Scheme 20). The target was obtained as a mixture of four isomers, which could be easily isomerized to the all-trans form.[67] A different scenario emerged when catalytic amounts of alkali alkoxides such as potassium *tert*-butylate were employed.[66] Cleavage of the

Scheme 19

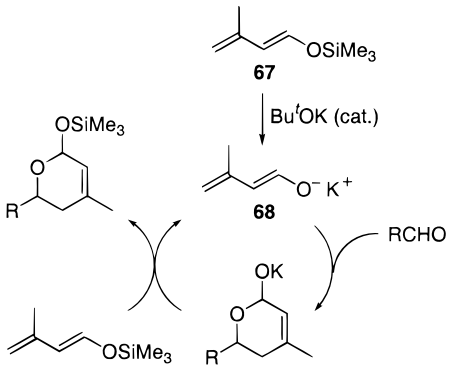


Scheme 20



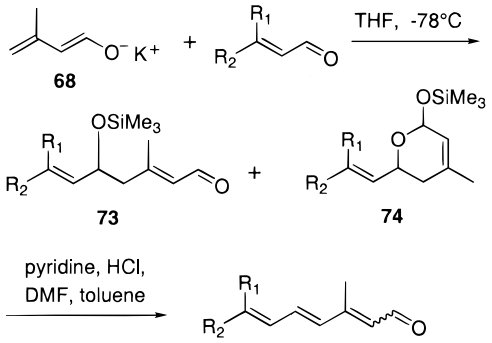
oxygen−silicon bond of the enoxy silane by the hemiacetalic hydroxyl of the 1,2-γ-adduct made the reaction catalytic (Scheme 21) and prevented the

Scheme 21



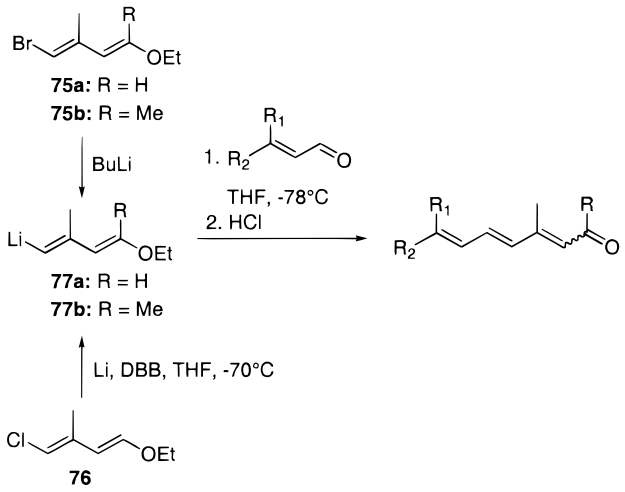
retro-aldol isomerization to γ-1,4-adducts. The primary γ-1,2-reaction product was obtained as a mixture of silylated δ-hydroxy enal **73** and dihydropyran hemiacetal **74** in a ratio dependent on the starting aldehyde (Scheme 22).[66] Both isomers could be converted to the same mixture of polyenals by treatment with acids.

Scheme 22



Another prenyl synthon is the δ-lithio dienyl ether **77a**, which can be prepared from the corresponding bromide **75a** by bromine−lithium exchange or, more conveniently, from the corresponding chloride **76** by di-*tert*-butyldiphenyl- (DBB) catalyzed lithium−chlorine exchange.[68] When treated with α,β-unsaturated aldehydes, the lithio dienyl ether **77a** gave exclusively γ-1,2-attack. After acidic hydrolysis (1 N HCl), polyenals were directly obtained as a mixture of *E*/*Z* diastereisomers (Scheme 23).[68] The lithio

Scheme 23

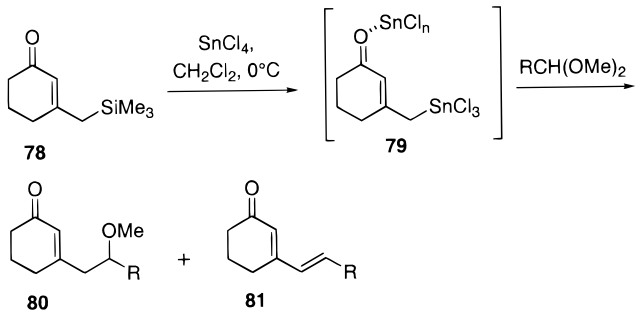


dienyl ether **77b** was generated in a similar way from the bromide **75b** and behaved as a synthon of the dienolate of pent-3-en-2-one, giving adducts similar to those obtained from **77a**.[68]

Taken together, these studies show that the prenal metal dienolates **68** and **77a** add to unsaturated aldehydes with a remarkable γ-1,2-stereoselectivity, though a poor *E*/*Z* stereoselection was observed when **68** was generated in a catalytic way. The same prenylation reaction can also be done, in a more direct way and with an excellent regio- and stereocontrol, by condensation of the dienoxysilane **67** with an aldehyde under Mukaiyama conditions, and this reaction has found application in the total synthesis of natural products.[69]

A different strategy was developed by Kuwajima, who exploited the regioselective condensation of γ-(trimethylsilyl)methylcyclohexenone (**78**) with acetals and aldehydes to build vinylogous aldols and their crotonization products.[70] Under the agency of stannic chloride, the reaction occurred exclusively at the

Scheme 24

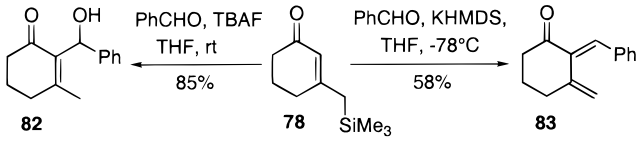


carbon bearing the silyl group (Scheme 24). The observation is surprising in light of the behavior of allyl silanes which react with electrophiles at their γ-carbon[71] and suggests that an adjacent carbonyl can override the β-effect of silicon on carbocations.

The regiochemical course was rationalized in terms of formation of an intermediate tin-chelated γ-stannyl species **79**, for which spectroscopic evidence was obtained. The reaction gave a mixture of vinylogous aldol ethers **80** and their crotonization products **81**, in a ratio depending on the structure of the starting enone and acetal. Aldehydes could not be used for the reaction unless trimethylsilyl iodide was substituted for stannic chloride, while titanium tetrachloride and boron trifluoride etherate were not effective catalysts, at least for the intermolecular version of the reaction.

The fluorine-catalyzed condensation of **78** with aldehydes gave exclusively α-addition, double-bond-isomerized products (e.g., **82**), as expected from the generation of a naked dienolate and a charge-controlled addition, while with potassium hexamethyldisilazide crotonized adducts (e.g., **83**) were obtained (Scheme 25).[70] In sharp contrast to these

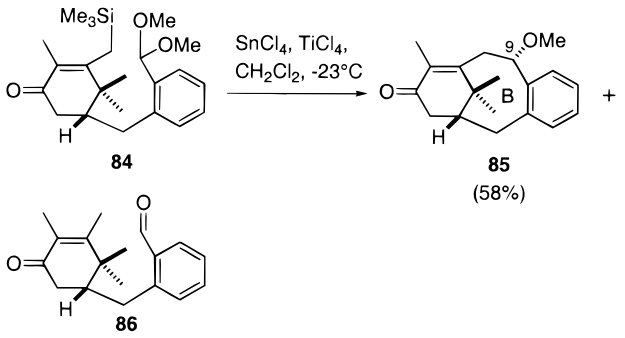
Scheme 25



results, ω-silylated crotonaldimines and sorbaldimines gave exclusively vinylogous aldols and their crotonized products upon treatment with CsF.[72] This observation was developed by Bellassoued into a valuable protocol for the di- and tri-vinylogation of aldehydes.[72]

The γ-silyl strategy turned out to be powerful enough to be employed, in an intramolecular version, for the closure of the B-ring of the taxane skeleton,[73] a daunting synthetic challenge on account of the compact shape of this framework, which leads to severe steric interactions between the substituents around the central ring B. The reaction required a considerable optimization of the conditions, with a protocol eventually emerging capable of maximizing the conversion of the B-*seco*-taxane **84** to the *C*-aromatic taxane **85** and limiting the retro-aldol conversion of the latter to the desilylated aldehyde **86** (Scheme 26). The taxane **85** was obtained as a single isomer, with the methoxyl at C-9 (taxane

Scheme 26



numbering) in the equatorial (α) orientation favored by both thermodynamic and kinetic considerations.[73] This biogenetic-type approach (see section III) to the taxane skeleton was later included, with a dienoxy silane precursor, in the total synthesis of taxusin and Taxol (see section VI.D).

An entirely different and revolutionary strategy for the vinylogous aldol reaction was devised by Yamamoto, who built a library of vinylogous and "phenylogous" aldols exploiting the host properties of the bulky Lewis acid aluminum tris(2,6-diphenyl)phenoxide (ATPH, **87**) for carbonyl guests.[58] ATPH and carbonyl compounds self-assemble to form complexes where the carbonyl can either be protected toward nucleophilic addition or activated toward selective transformations unattainable under normal conditions.[74] Thus, complexation of an equimolecular mixture of an unsaturated enolizable aldehyde (**88a**−**e**) and a saturated aldehyde (**89a**−**d**) with ATPH encapsulated the carbonyl substrates in the cavity of the Lewis acid, shielding their α-carbons. Though the α-position of a carbonyl compound is more acidic than the γ-position of its α,β-unsaturated counterpart, only the latter was sterically accessible for deprotonation by a bulky base like LDA. A counter-thermodynamic and regioselective deprotonation took, therefore, place, affording a dienolate which then added in a γ-1,2-fashion to the nondeprotonated carbonyl substrate (Scheme 27).

Since ATPH-encapsulated carbonyls do not react with nucleophiles, even as strong as methyllithium,[74] the vinylogous aldol reaction presumably took place between the encapsulated dienolate and the free aldehyde in equilibrium with its encapsulated form. No crotonization of the adducts was observed, while with all-trans polyenal systems [2,4-hexadienal (**88d**) and sorbaldehyde (**88e**)], ω-deprotonation and retention of configuration of the olefinic double bonds were observed. When a nonenolizable α,β-unsaturated aldehyde was used as dienolate acceptor **89d**, only 1,4-attack took place. The reaction was also applied to cyclic enones [cyclohexenone (**90**) and 3-methylcyclohexenone (**91**)] and to *p*-methylacetophenone (**92**), obtaining the corresponding vinylogous (phenylogous) aldols (Scheme 28). With 3-methylcyclohexenone (**91**), deprotonation and condensation occurred selectively at the γ-*exo* position.

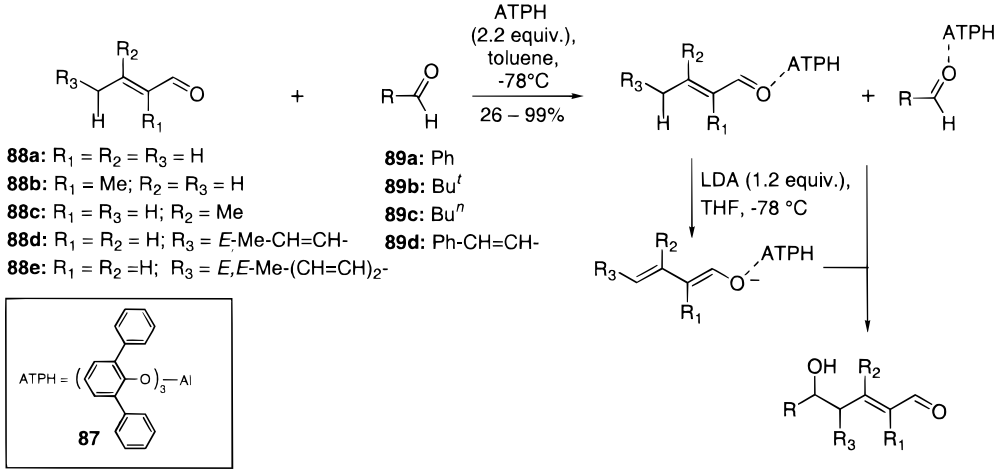
This revolutionary approach to direct (in terms of chemoselectivity) and discipline (in terms of regiochemistry of dienolate formation and attack) the course of the vinylogous aldol reaction is undoubtedly a prime achievement in the aldol field. The observed regioselectivity is in fact unattainable under normal conditions, and the role of ATPH in the reaction is somewhat a reminder of enzymes in biological systems.

B. Dienolates from Unsaturated Carboxylic Acids

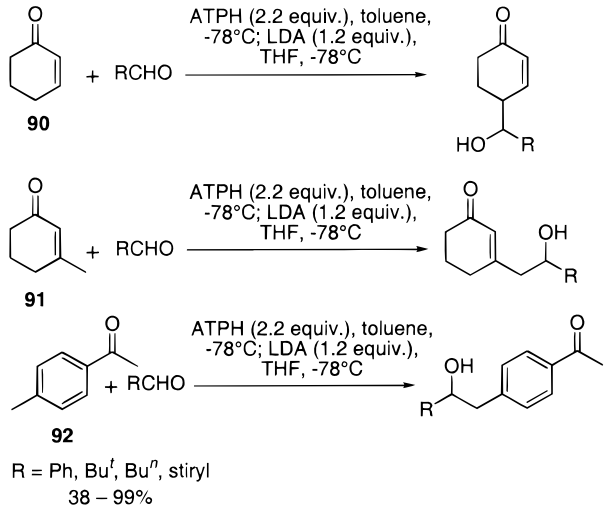
The chemistry of dimetalated carboxylic acids has a long history, dating back to their early recognition by Grignard in 1904,[75] and has had a considerable impact in the synthetic practice.[76] The vinylogous version of the reaction of dimetalated carboxylic acids with carbonyl compounds is also useful. It has found use in natural product synthesis, mainly as part of addition−elimination sequences to isoprenoids, with early applications to the preparation of insect juvenile hormone analogues,[77] terpene alcohols,[78] and retinoids.[79] A short synthesis of vitamin A (**95**) from the C_{15}-aldehyde β-ionylidene acetaldehyde (**93**) and the dianion **94** exemplifies the potential of the reaction (Scheme 29).[79]

Owing to the negative charge of the carboxylate, the dienolates of carboxylic acids are less prone to self-condensation via Michael addition than those of esters. Dienolates can be prepared from α,β- or β,γ-unsaturated acids by direct deprotonation with 2

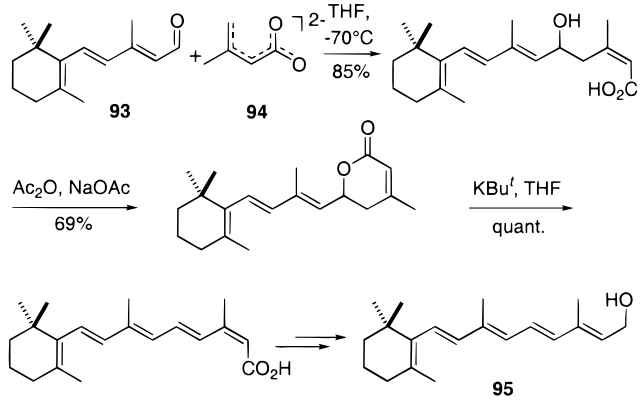
Scheme 27



Scheme 28



Scheme 29

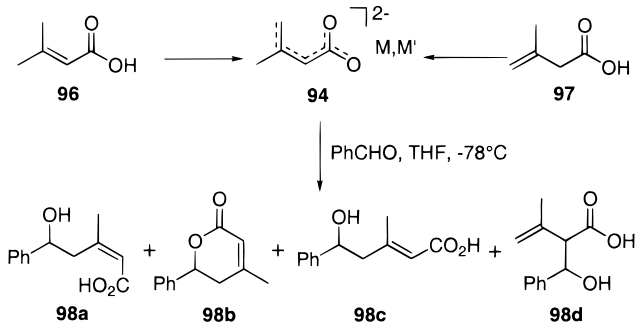


equiv of lithium bases such as LDA[78] or, alternatively, by stepwise deprotonation using alkali hydrides to ionize the carboxyl group and lithium bases to generate the carbonyl-stabilized allyl anion (Creger's procedure).[80] Dienolates derived from acids are versatile reagents whose reactivity strongly depends on the nature of the counterion(s) and the temperature of the reaction. The possibility to modulate reactivity by changing the ionic character of the organometallic bond and by varying the reaction conditions is a remarkable asset of this type of dienolates.

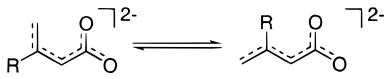
The dianion **94**, obtained by the deprotonation of senecioic acid (**96**) or its β,γ-isomer **97**, is an important prenyl synthon, suitable for iterative prenylation, a strategy where C_5-units are added in a stepwise head-to-tail manner to a growing chain, somewhat mimicking a biological process.[79] The reaction of **94** with carbonyl compounds has, therefore, been investigated in detail.[81,82] The regioselectivity of the alkylation turned out to be dependent on many factors, the most important being the nature of the counterion and the temperature. Thus, the lithium tributyltin salt gave exclusively α-attack, while with the strongly ionic dipotassium salt only γ-attack was observed (Scheme 30).[81]

With other salts, the product distribution was qualitatively proportional to the ionic character of the organometallic bond. The composition of the reaction mixture was not affected by the nature of the starting

Scheme 30



M	M'	relative yield (%)			
		98a	**98b**	**98c**	**98d**
Li	$SnBu_3$	-	-	-	100
Li	Li	19	27	-	54
Na	Li	5	44	5	46
K	Li	54	24	-	22
K	K	100	-	-	-

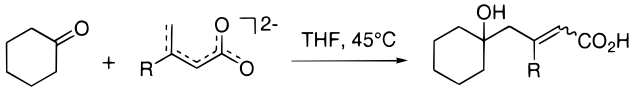


99a: R = Me **100a:** R = Me
99b: R = H **100b:** R = H

acid, but higher chemical yields were obtained when **97** rather than **96** was employed as a dienolate source, presumably because of the higher acidity of the α-hydrogen of **97** compared to the γ-hydrogen atom of **96**.[81] γ-Alkylation was favored by the addition of HMPA and employment of α,β-unsaturated aliphatic aldehydes,[78,79] but the *E*/*Z* ratio observed in the γ-adducts was relatively insensitive to changes of counterions and to the use of additives. The *Z* regioselectivity observed in the products of γ-attack was rationalized in terms of an higher stability[83] of the *s-cis* conformation of the dianion **94** (U form, **99a**) compared to the *s-trans* geometry (sickle form, **100a**). The latter is in fact destabilized by allylic strain between the γ-methyl and the oxygen atom of the carboxyl.[81] Competitive deprotonation of one of the two γ-methyls was ruled out by the obtainment of the same *Z*/*E* mixture from both **96** and **97**.[81]

When quenched with cyclohexanone, the dianions of senecic (**96**) and crotonic (**101**) acids gave γ-adducts **102a**,**b** with opposite stereoselectivity (Scheme 31),[82]

Scheme 31



96: R = Me **102a:** R = Me (*Z*/*E* = 9:1)
101: R = H **102b:** R = H (*Z*/*E* = 1:9)

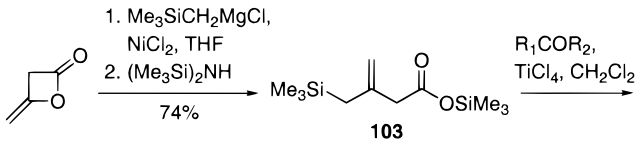
presumably because the lack of a γ-substituent shifts the equilibration of the dienolate **101** toward the *s-trans* (sickle) conformation **100b**.[84] The reversible nature of the addition was also evidenced, showing the possibility of equilibrating the kinetic α-adducts to the thermodynamic γ-adducts by simple heating

of the reaction mixture at room or higher temperature.[82] In this way, γ-adducts could be obtained also from dilithiated dienolates.[78] Similar results were achieved with tiglic acid, another prenyl building block.[85]

When lithium bases are used in the deprotonation step, the unconjugation of α,β-unsaturated acids takes place to a much higher extent than deuterium incorporation,[82] suggesting that, in these conditions, dianions are formed only in equilibrium concentration.[86] Since unsaturated acids are only partially ionized during the reaction, both the ionization and the addition step are better carried out at low temperature (−70 °C). Strong temperature dependence for the Michael self-condensation and a fast addition/slow retro-addition process to carbonyl compounds are seemingly responsible for the limited self-condensation at low temperature.[82]

The allylsilane **103**—a surrogate of the dianion **94**—is useful in prenylation reactions and is conveniently prepared from diketene by nickel-catalyzed addition of Me_3SiCH_2MgCl.[87] Under Lewis acid catalysis ($TiCl_4$), **103** adds to carbonyl compounds to give δ-hydroxy acids, which are isolated, after acidic treatment, as their corresponding α,β-unsaturated δ-lactones (Scheme 32).[87] This is similar to the

Scheme 32



R_1	R_2	yield (%)
H	Pr^n	81
H	Pr^i	79
H	Bu^t	78
Me	Me	80
-(CH_2-CH_2)$_2$-		78

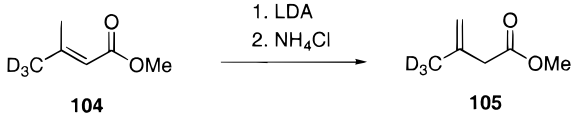
strategy developed by Kuwajima for the regioselective γ-alkylation of enones, using γ-trimethylsilyl enones as dienolate synthons (vide supra).[73]

C. Dienolates from Unsaturated Esters

The reaction of ester enolates with carbonyl compounds is a standard synthetic procedure whose stereochemical course can be predicted, with a certain degree of confidence, in light of the enolate *Z*/*E* geometry.[88] The vinylogous version of the reaction has also been investigated for mechanistic and synthetic purposes.[89] Since α,β-unsaturated esters are more prone to conjugate addition than other classes of unsaturated carbonyls, highly hindered bases should be used for deprotonation purposes. In general, LDA can be used only when two γ-substituents are present and Michael addition of the base is consequently slowed.[90] In the other cases, the LDA−HMPA (hexamethylphosphoramide) adduct is employed (Schlessinger procedure).[91] The seminal discovery that HMPA renders LDA essentially nonnucleophilic was reported as early as in 1973,[91] but the nature of the seemingly 1:1 adduct formed in the reaction is still unknown.

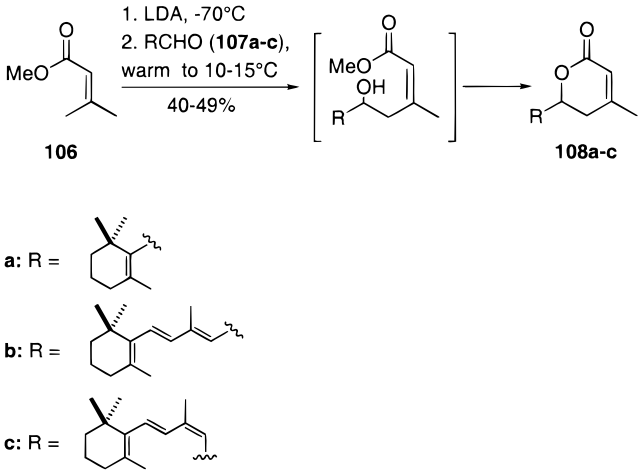
The reactivity of ester dienolates with carbonyl compounds closely parallels that of the dianions of α,β-unsaturated acids, with unconjugated α-adducts favored over conjugated γ-adducts under kinetic conditions and γ-adducts prevailing under thermodynamic conditions. Higher ester enolates show a similar reactivity.[92] The preferential kinetic deprotonation of the γ-*Z*-alkyl group was evidenced with d_3-labeled methylsenecioate (**104**), which maintained all three of its deuterium atoms in experiments of base-induced unconjugation (Scheme 33).[93] *Z*-γ-Ad-

Scheme 33



ducts are generally isolated as their corresponding δ-lactones, and the reaction of β,β-disubstituted acrylates with aldehydes is a general entry into 4-substituted dihydro α-pyrones (Scheme 34).[94]

Scheme 34

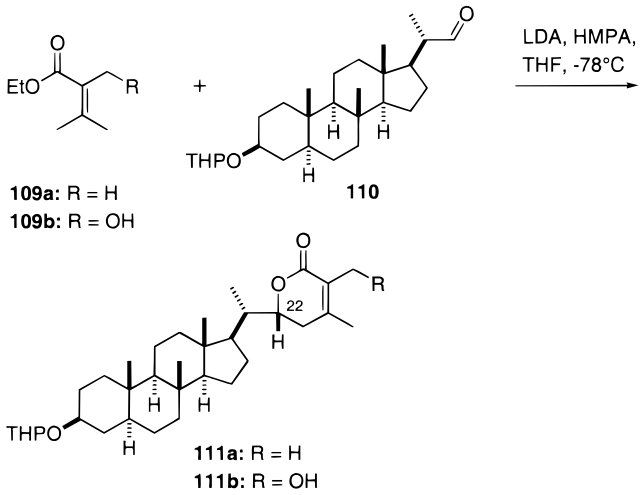


In acrylate esters, a 2-fold β-substitution facilitates the generation of the dienolate and secures the formation of the double bond in a *Z* configuration by destabilization of the *s-trans* conformation of the dienolate by $A^{1,3}$ strain.[94] Interesting applications of the reaction are the preparation of a series of retinoid lactones **108a**−**c** of potential antineoplastic activity by condensation of methyl senecioate (**106**) and carotenoid aldehydes **107a**−**c** (Scheme 34)[94] and the synthesis of steroids having a side chain of withanolides **111a**,**b** from the homopregnane aldehyde **110** and the α-substituted senecioates **109a**,**b** (Scheme 35).[95]

Compared to natural withanolides, these steroid−withanolides hybrids have an unnatural configuration at C-22 and their biological activity was not seemingly investigated.[95] The diastereoselection observed in the reaction was, however, excellent, and the system is well worth further investigation.

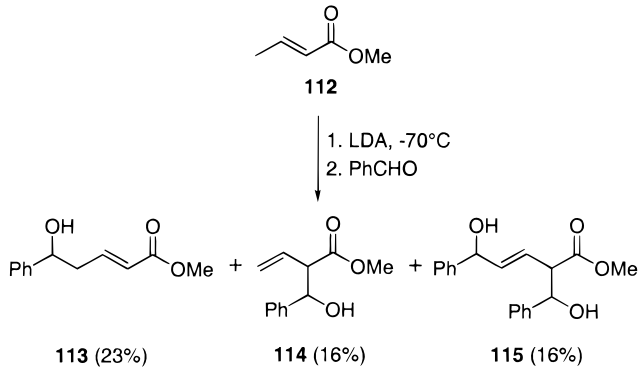
α-Pyrones lacking a substituent at C4 cannot be prepared with this strategy, since the reaction of

Scheme 35



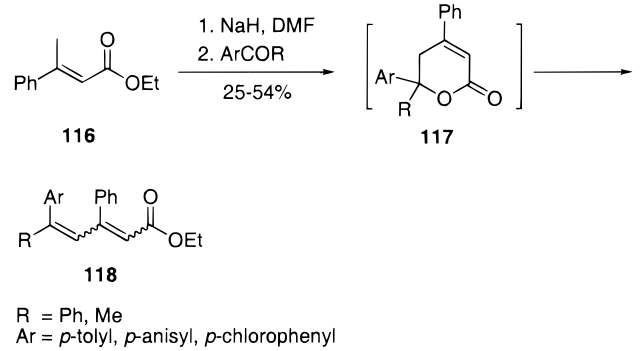
methyl crotonate (**112**) with aldehydes gives a mixture of γ-*E* adducts **113**, α-adducts **114**, and α,γ-dialkylated products **115** (Scheme 36).[94] Reaction of

Scheme 36



ethyl 3-phenylcrotonate (**116**) with aromatic ketones directly afforded dienoic esters **118** of unreported configuration, presumably via unstable 6,6-disubstituted α-pyrones **117** (Scheme 37).[96] Interestingly, the

Scheme 37

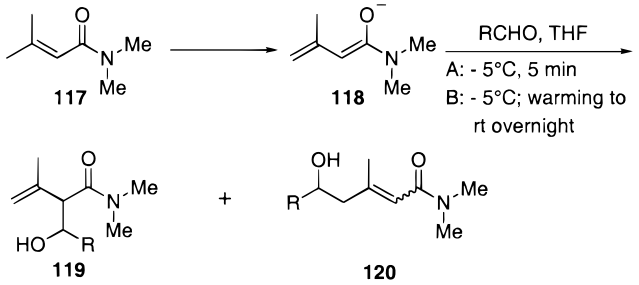


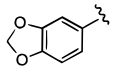
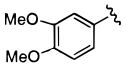
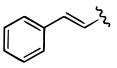
E isomer of **116** reacted much faster than its *Z* counterpart,[96] in accordance with the results observed with labeled senecioates.[91] For the use of butenolides, see section V.E.

D. Dienolates from Unsaturated Amides and Imides

The reaction of dienolates of α,β-unsaturated amides with carbonyl compounds was extensively investigated by Snieckus, who evidenced a surprising dependence of the reaction course not only from the reaction conditions, but also from the structure of the reacting partners.[97] The results obtained in the aldol coupling between *N,N*-dimethylsenecioamide (**117**) and some aromatic and aliphatic aldehydes are interesting in order to compare them with the results obtained with the corresponding acid. When benzaldehyde was reacted with the lithium dienolate of **117** at low temperature (−78 °C) and the reaction was quenched 10 s after the addition of the aldehyde, the α-adduct **119** was obtained as the only reaction product as a *syn,anti* mixture (Scheme 38).

Scheme 38



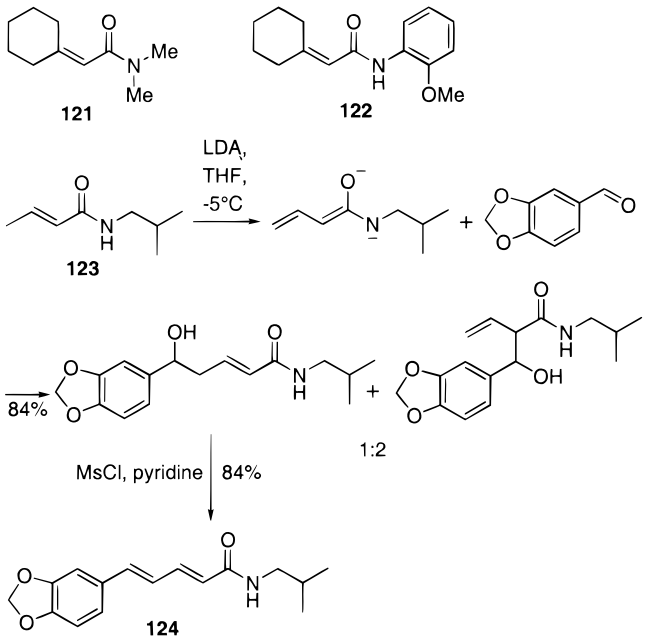
R	**119/120** ratio method A	method B
Ph	80:20	0:100
	88:12	0:100
	82:18	0:100
Pr^n	100:0	13:87
	100:0	15:85
	100:0	100:0
	100:0	100:0
	100:0	100:0

At higher temperature and for longer reaction times, the α-adduct **119** was irreversibly transformed into the *Z* γ-adduct **120**, according to a trend already observed with senecioic acid.[82] Similar results were obtained with piperonal, veratraldehyde, pyridine-3-carbaldehyde, and butanal. A surprising reversal of configuration was observed with the latter, which gave an *E* γ-adduct. Pyridine 2- and 4-carbaldehydes as well as cinnamaldehyde gave, instead, a mixture of *syn,anti* α-adducts which did not equilibrate to their corresponding γ-isomers at room temperature. Resonance effects,[98] stabilizing the products of nucleophilic attack on pyridine 2- and 4-carbaldehyde more than that obtained from their 3-isomer, might be responsible for this puzzling observation.[97] Ben-

zophenone and cyclohexanone gave products of α-attack which were extensively degraded under the conditions of thermodynamic equilibration.

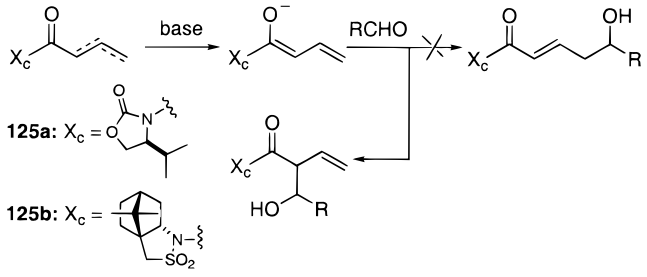
The reaction was extended to the cyclic analogues of senecioamide **121** and **122**, which gave exclusively α-adducts under conditions of both kinetic and thermodynamic control, and to *N*-isobutyl crotonamide (**123**). The *N*-isobutylamide group is the hallmark of *Piper* alkaloids, a class of compounds of considerable biological interest,[99] and the reaction of the dianion of **123** with aromatic aldehydes represents an expeditious entry into these amides. A relatively low level of regioselectivity was unfortunately observed, even under conditions favoring thermodynamic control.[97] The reaction was applied to the synthesis of piperlonguminine (**124**),[100] which gave one of the best γ- vs α-alkylation ratios (ca. 1:2) (Scheme 39).[97]

Scheme 39



Chiral imide dienolates can easily be prepared from α,β- or β,γ-unsaturated precursors such as **125a** and **125b**, obtained by reacting the corresponding acids with proper chiral auxiliaries such as Evans' oxazoline or Oppolzer's sultame, respectively. Their γ-alkylation with carbonyl compounds represents a general enantioselective version of the vinylogous aldol reaction (Scheme 40). The strategy is highly attractive,

Scheme 40



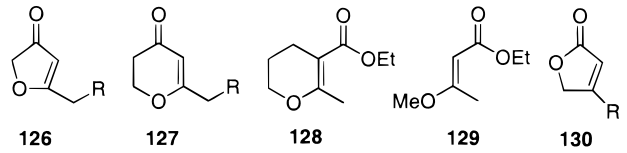
since, in accordance with the higher functionalization of vinylogous aldols, the chiral auxiliary could be further used to direct the additional selective elaboration of the unsaturated system via Michael addition or Diels−Alder reactions. This challenge is, however, still unmet since boron[101] and tin dienolates[102] of crotyl imides such as **125a** and **125b** give exclusively α-addition with carbonyl compounds with high ee.

In conclusion, compared to other types of dienolates, those derived from unsaturated amides show a less predictable behavior in their reaction with carbonyl compounds. Though undoubtedly a drawback for synthetic applications, this puzzling reactivity should foster mechanistic studies aimed at their rationalization.

E. Dienolates from β-Heterosubstituted α,β-Unsaturated Carbonyls and Butenolides

β-Oxygen-, nitrogen-, and thio-substituted α,β-unsaturated carbonyls can be viewed as the vinylogous version of heteroatom-substituted carbonyls such as esters, carbonates, carbamates, amides, ureas, and thioesters. Compounds of this type have proved to be useful as dienolate precursors for aldol chemistry, especially when the carbonyl and one of the substituents on the β-carbon are part of a ring [3(2*H*)-furanones **126**, γ-pyrones **127**, Scheme 41] and

Scheme 41



when substitution on the heteroatom makes the dienolate chiral, as in the vinylogous uretane strategy developed by Schlessinger. Butenolides **130** are also discussed here, because they too give oxygen-substituted dienolates.

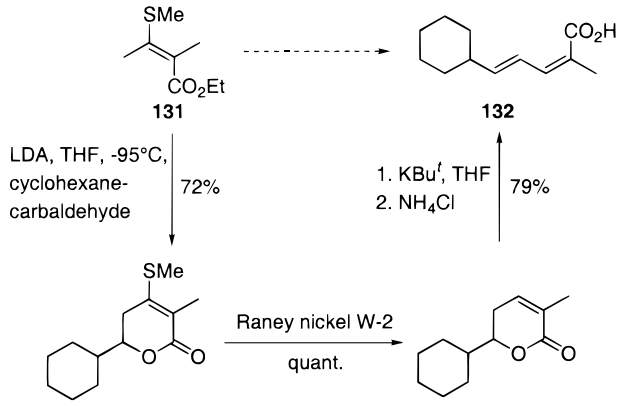
Interest in the synthetic potential of these compounds was fuelled by the discovery that β-enaminoketones derived from secondary amines can be selectively γ-alkylated with a variety of electrophiles,[103] and by the isolation of fungal metabolites based on a methoxybutenolide structure (*O*-methyl tetronic acid derivatives).[104]

The selective γ-alkylation of enaminoketones with alkyl halides stands in sharp contrast with the behavior of analogous oxygen, sulfur, and carbon systems, where α′- and α-alkylations prevail.[105] When aldehydes are employed as electrophiles, β-heterosubstitution favors γ- vs α-alkylation not only with nitrogen, but also with oxygen and sulfur. Thus, compared to their corresponding crotonates, cyclic and acyclic β-alkoxycrotonates such as **128** and **129** (Scheme 41) reacted with aldehydes with excellent γ-selectivity, directly affording 3-alkoxy-2,4-dienoic acids.[106]

This strategy was employed by Corey to build, in a stereospecific way, the 1,3-diene unit of the *ansa*-bridge of rifamycins, condensing ethyl β-methylthiocrotonate (**131**) with various aldehydes. In situ lactonization of the γ-hydroxyalkylation product se-

cured the 2*Z* configuration of **132**, while generation of the 4*E* double bond was affected, after desulfurization, with an E_2-type elimination (Scheme 42).[107]

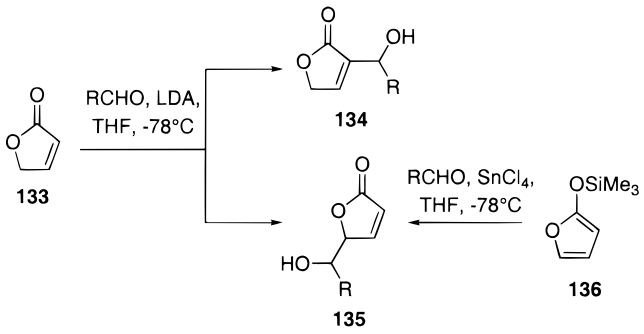
Scheme 42



Synthesis of 2-methyl-5-alkyldienoates using Wittig-type strategies afforded the more stable 2*E*,4*E* isomers, instead.[107]

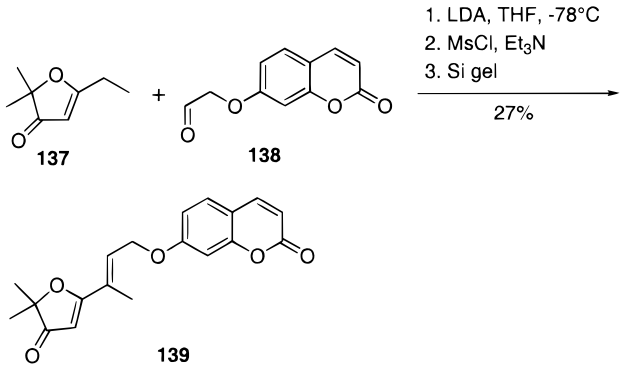
Dienolates of heterocylic systems have been extensively employed in synthesis. Reaction of the dienolate of butenolide **133** [alias 2(5*H*)-furanone] with a series of aliphatic aldehydes gave mixtures (ca. 3:1) of conjugated α- and γ-adducts **134** and **135**, with essentially no *threo*/*erythro* diastereoselection (Scheme 43).[108] The same reaction carried out under Mukaiyama conditions using the silyloxyfuran **136** as a dienolate synthon had a more disciplined course, affording ca. 9:1 *threo*/*erythro* mixtures of γ-adducts **135** as the only reaction products.[108] This result highlights the advantages often offered by silyloxy dienes as compared to metal dienolates (vide infra).

Scheme 43



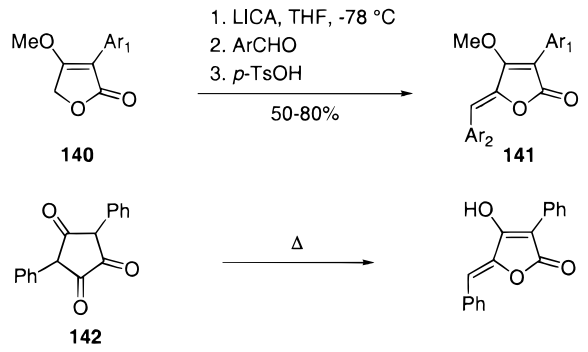
The aldol condensation of the lithium dienolate of the 3(2*H*)-furanone **137** was investigated by Smith in the context of studies aimed at the total synthesis of the antitumor prenylated coumarin geiparvarin (**139**), a compound isolated from the rutaceous Australian plant *Geijera parviflora*.[109] Only γ-aldol condensation was generally observed both at −78 and 0 °C, with benzaldehyde being an exception and affording, instead, a 2:3 mixture of α- and γ-adducts at 0 °C. The umbelliferone-derived aldehyde **138** was used as a dienolate trap in the eventual synthesis of the natural product (Scheme 44).[110]

Scheme 44



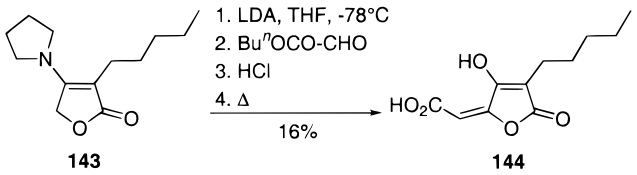
The vinylogous aldol condensation of metalated 2-aryl *O*-methyltetronic acids **140** proved to be superior to Wittig-type approaches for the synthesis of pulvinones **141**, a group of 4-benzylidene-2-phenyl tetronates from mushrooms and moulds. These pigments were isolated in the 1970s,[111] but the basic pulvinone skeleton has been known since 1895, when Claisen obtained it by thermal rearrangement of 2,5-diphenylcyclopentane-1,3,4-trione (**142**).[112] Since natural pulvinones are unsymmetrically substituted, a general synthetic route alternative to that devised by Claisen was developed by Pattenden to confirm (and in some cases to revise) the structure of the natural products (Scheme 45).[113]

Scheme 45



Thus, **140** was metalated by treatment with lithium isopropylcyclohexylamide (LICA) and then treated with various aldehydes. The resulting γ-aldols were then dehydrated with *p*-TsOH, affording exclusively *Z* stereoisomers **141**. 4-Alkylidene tetronates were prepared with a similar strategy from 3-pyrrolidino derivatives of tetronic acid. After alkylation, the pyrrolidine group was converted into a hydroxyl by a nucleophilic vinyl substitution.[114] The synthesis of multicolanic acid (**144**) from the pyrrolidine derivative of 2-pentyltetronic acid **143** exemplifies this strategy (Scheme 46).[114] The exomethylene bond was generated in a *E* configuration, stabilized by the

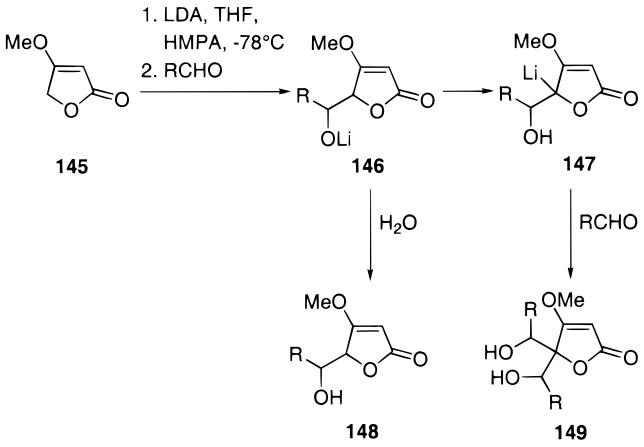
Scheme 46



formation of an intermolecular hydrogen bonding between the carboxyl and the enolic hydroxyl.

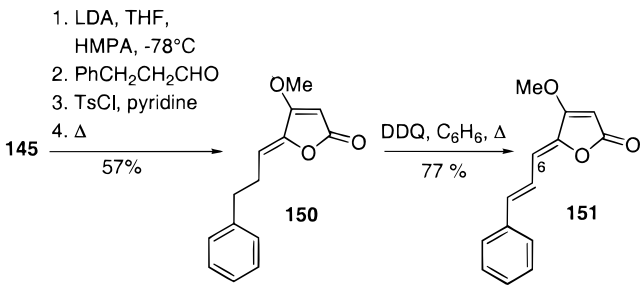
Tetronates are typical microbial and fungal metabolites,[114] but a structurally unique class of tetronates was isolated from *Piper sanctum*[115] and *Piper fadyenolii*,[116] two species of *Piper* from the New World. These compounds have an interesting pharmacology and show strong sedative properties similar to those of kawalactones.[117] The synthesis of these compounds turned out to be more difficult than that of pulvinones, since the reaction of metalated *O*-methyl tetronic acid (**145**) with aldehydes was troubled by the formation of substantial amounts of γ,γ-dialkylated products **149** (Scheme 47).

Scheme 47



An apparently paradoxical procedure was devised to overcome these difficulties. Thus, dialkylation was completely suppressed when the aldehyde was added to the dienolate as a 1:1 mixture with water. The authors reasoned that since the reaction of organometallics with water can be slower as compared to their reaction with carbonyl compounds,[118] formation of the vinylogous aldol should then be faster than the protonation of the dienolate. Successive quenching of the oxyanion **146** with water should thus proceed much faster than its rearrangement to the carbanion **147**, affording the vinylogous monoaldol **148** as the only reaction product. In this way, 6-demethoxypiperolide (**151**) was synthesized from the crotonized aldol adduct **150** by dehydration and oxidation with DDQ (Scheme 48).[117] An aldol reaction of the lithium

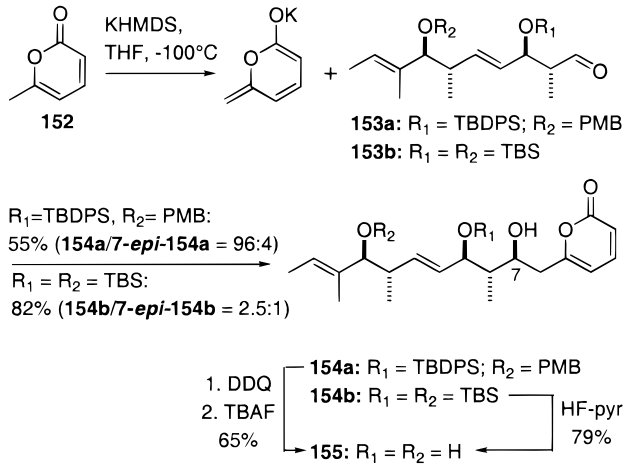
Scheme 48



salt of 3-methyl *O*-tetronate was employed by Kende in the synthesis of the complex piperidine alkaloid isostemofoline.[119]

The ω-alkylation of the achiral α-pyrone **152** with the enantiomerically pure aldehydes **153a**,**b** is a key step in the synthesis of the ACRL Toxin IIIB (**155**), a mould polyketide produced by *Alternaria citri*, the causative agent of the brown spot disease of certain types of *Citrus*.[120] The regiochemistry of the alkylation of the anion of **152** depends critically on the reaction temperature and the nature of the counterion. Low temperatures and the use of KHMDS were found to suppress γ-alkylation and promote ω-attack.[121] The synthesis by Paterson employs the aldehyde **153b** and afforded a ca. 2.5:1 mixture of diastereomers (Scheme 49).[122] Using aldehyde **153a**,

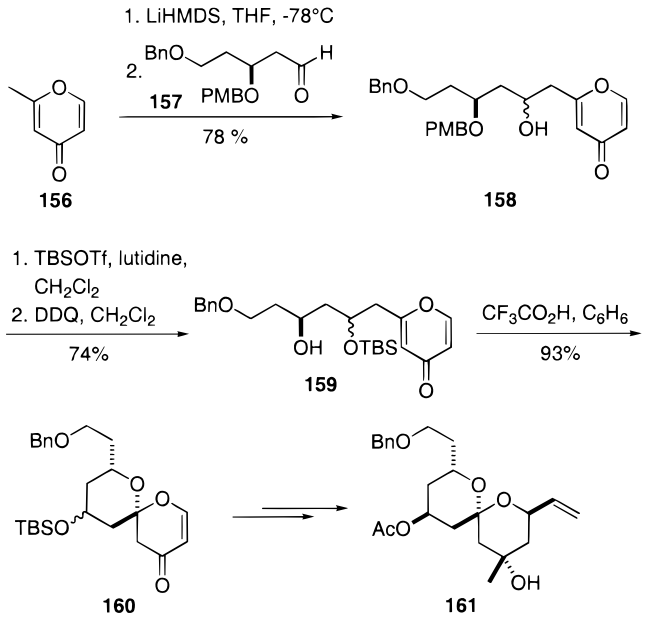
Scheme 49



Mulzer previously reported a remarkable diastereoselectivity (96:4) under apparently similar conditions.[121]

The addition of alkyl-substituted metalated γ-pyrones to β-alkoxyaldehydes was exploited by Crimmins for the preparation of 6,6-spiroketals (Scheme 50).[123] This moiety is an important template for

Scheme 50



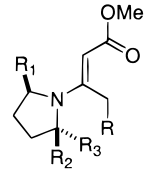
stereocontrol[124] and occurs in important natural products such as spongiastatin 1, an extraordinarily

powerful anticancer marine compound of very limited availability by isolation.[125]

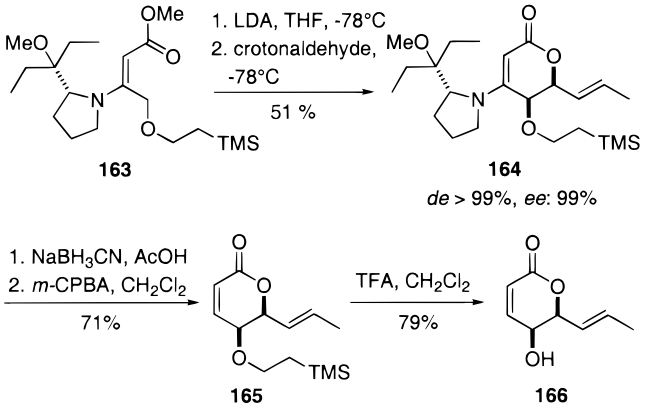
The spiroketalization protocol to the AB spiroketal moiety of spongiastatin 1 commences with the metalation reaction of 2-methyl γ-pyrone (**156**), which is then condensed with the orthogonally protected β-hydroxy aldehyde **157**, affording in good yield the vinylogous aldol **158**. The aldol hydroxyl is next protected as a silyl ether, and the PMP group is removed by oxidation with DDQ, affording the alcohol **159**. Treatment with CF_3COOH triggers then the spiroketalization to **160**. This compound was then further elaborated into **161**, a fragment of spongiastatin 1.[123b]

C4-Substituted vinylogous uretanes of general formula **162a**,**b**, derived from chiral nonracemic secondary amines, were developed by Schlessinger and systematically employed in the synthesis of a variety of natural products containing a 4,5-dihydro-1-pyrone motif or a structural element derived thereof. The vinylogous uretanes **162a**,**b** behave as chiral crotonate dienolates, and much of their very interesting chemistry was published posthumous in a series of preliminary notes. Condensation of the lithium dienolate (LDA, THF, −78 °C) of these compounds with aldehydes affords *syn*-vinylogous aldols in the form of 5,6-substituted α-pyrones (e.g., **164**, Scheme 51) with extremely high diastereoselectivity (up to

Scheme 51



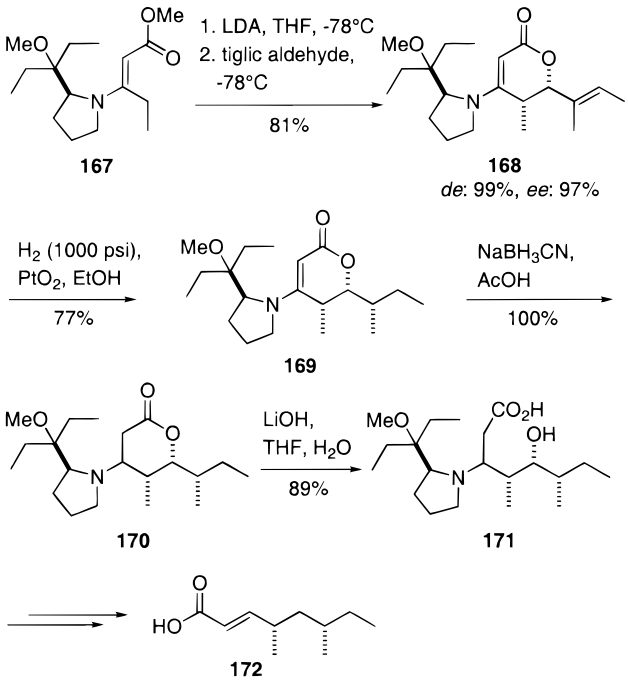
162a: $R_1 = R_3 = Me$; $R_2 = H$
162b: $R_1 = Et_2C(OMe)$-; $R_2 = R_3 = H$
ent-**162b:** $R_1 = R_3 = H$; $R_2 = Et_2C(OMe)$-



>99%).[126] The chemical auxiliary could then be directly removed by a two-step Borch reduction/Cope elimination protocol, affording dihydropyrones, a strategy exemplified by the synthesis of (+)-phomalactone (**166**).[127] Alternatively, the aldolization product was further elaborated into various targets exploiting the rigid backbone of the α-pyrone ring, whose axial C4 substituent serves to direct the formation of additional stereocenters.

The synthesis of the side chain of zaragozic acid A **172** exemplifies the use of this strategy to build "skip" 1,3-dimethyl fragments (Scheme 52)[128] and com-

Scheme 52

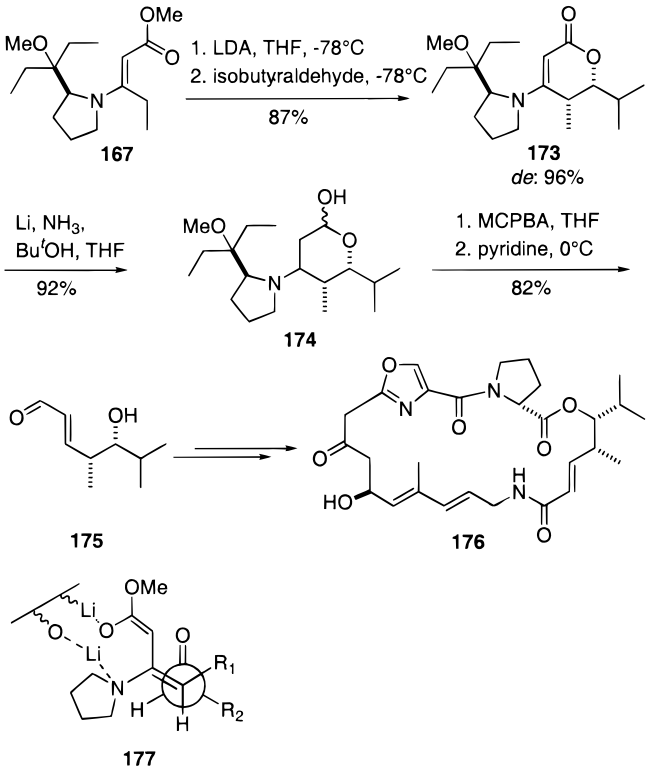


mences with the condensation of the vinylogous uretane **167** and tiglic aldehyde. Adduct **168** was then catalytically reduced with good diastereoselectivity (10:1 in favor of the desidered isomer), capitalizing on the steric bias of the axial 4α-methyl. The pyrone double bond was next reduced with $NaBH_3CN$ and the lactone ring was opened with LiOH, affording the β-amino-δ-hydroxy acid **171**. Removal of the amino and the hydroxy functions eventually yielded the target acid **172**.

In another somewhat different application, the α-pyrone adduct **173** was reduced with lithium and *tert*-butyl alcohol in liquid ammonia, and the β-amino lactol obtained in this way, **174**, was subjected to Cope elimination, affording an α,β-unsaturated δ-hydroxyenal **175** (Scheme 53). The latter was eventually incorporated into the depsipepdide antibiotic virginiamicin M_2 (**176**).[129] The vinylogous uretane strategy was further applied by Schlessinger to the asymmetric synthesis of various other natural products targets, like the complex sugar KDO,[130] and various fragments of the marine ionophore okadaic acid.[131]

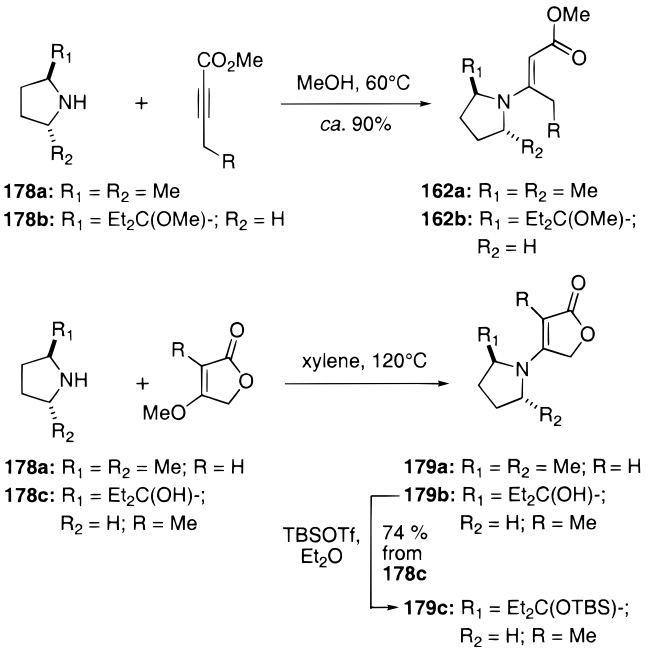
The remarkable stereoselectivity of the reaction was rationalized in terms of the involvement of a rigid dimeric dienolate of *Z* geometry around the ketene acetal moiety and *E* enamine geometry, a proposal backed up by X-ray data.[132] A twisted diene structure with each lithium atom bound to the nitrogen of the chiral auxiliary and the oxygen of the dienolate of type **177** was found.[132] The observed regiochemistry of addition to aldehydes implies a dipole-stabilized "closed" transition state, as depicted in **177**.[133]

Scheme 53



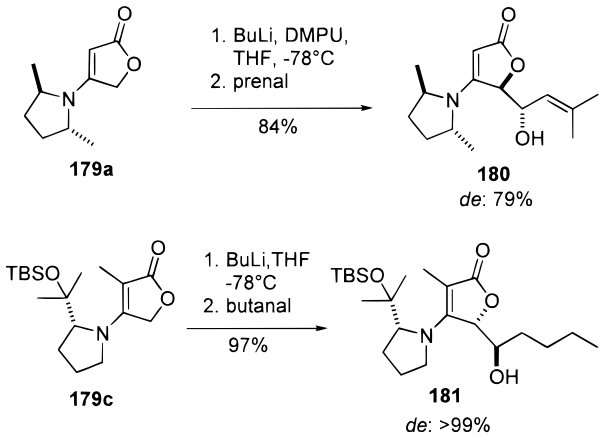
The first chiral auxiliary employed was the C_2-symmetric dimethylpyrrolidine **178a**,[134] later replaced by the prolinol derivative **178b**, a simpler and more readily prepared nonracemic auxiliary.[135] The synthesis of the dienolate precursors is based on the Michael addition of the secondary amino group of the chiral auxiliary on a propargyl ester (Scheme 54).

Scheme 54



Predominant *anti*-selectivity was observed with vinylogous uretanes derived from *tert*-butylamine or diisopropylamine.[130] A chiral version of the reaction was developed with the vinylogous uretane lactones **179a** and **179c**. These compounds also proved to be useful for the enantioselective γ-alkylation with alkyl halides[129,131a] and could be prepared from the chiral amines **178a**,**c** and (di)methyltetronic acid through an alkenyl nucleophilic substitution. Compounds **179a** and **179c** were employed for the synthesis of **180**[131] and **181**,[136] en route to fragments of okadaic acid and erythronolide, respectively (Scheme 55).

Scheme 55



VI. Vinylogous Enoxy Silane Synthons

The exploitation of the aldol addition to form carbon−carbon bonds en route to both simple and complex molecular constructs has taken enormous benefit from the development of new variants and techniques for the creation of confined and stereodefined enolate synthons. Dramatic evolution in this field has been pioneered by Mukaiyama, who first found, in a series of seminal papers, that enoxy silane compounds easily react with carbonyl acceptors in the presence of Lewis acids to give aldol and aldol-related products.[137]

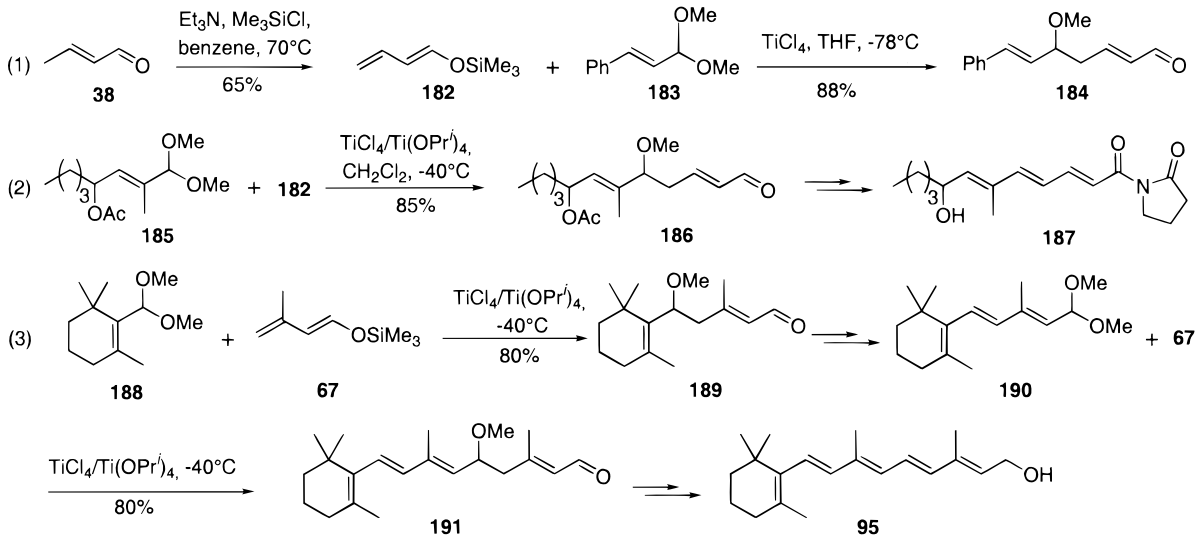
Since the mid-1970s, the Lewis acid-promoted or -catalyzed addition of enoxy silanes to carbonyl electrophiles (alias the Mukaiyama reaction) has become a fundamental maneuver with which a huge number of molecular frameworks and targets have been implemented.[138] The aim of this section is to highlight the merits of the vinylogous version of this process, that is the synthetic achievements sprung from the application of the reaction involving vinylogous variants of enoxy silane synthons and carbonyl and carbonyl-related electrophilic acceptors. Here, reactions involving open-chain and alicyclic silyloxy dienes as well as vinylogous silyl ketene acetals will be covered in detail, while only a selection of synthetically relevant applications exploiting heterocyclic silyloxy dienes—a theme recently surveyed in a few specific accounts[9]—will be presented to provide the readers with a more complete insight into the subject matter.

A. Additions of Enoxy Silanes to Carbonyl and Carbonyl-Related Electrophiles

1. Additions to Aldehydes, Ketones, Acetals, and Orthoesters

Not surprisingly, the Mukaiyama group, who first launched and rendered the enoxy silane aldolization

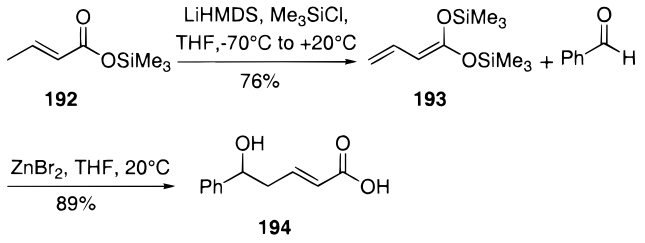
Scheme 56



chemistry a popular maneuver, was among the pioneers of the vinylogous version of this reaction. It was found[139] that dienoxy silane **182**, easily produced from crotonaldehyde (**38**) and trimethylchlorosilane under basic conditions, promptly reacted with acetal **183** under the agency of Ti(IV)-based Lewis acids to give the corresponding δ-alkoxy-α,β-unsaturated aldehyde **184**, with no detectable amount of the corresponding β-alkoxy congeners (Scheme 56, eq 1). As an extension of this chemistry directed toward the synthesis of biologically relevant substances, the same researchers succeeded in the preparation of racemic variotin (**187**) (eq 2)[140] and vitamin A (**95**)[141] (eq 3) by starting with dienoxy silanes **182** and **67**, respectively. Of note, during the synthesis of vitamin A (**95**), the vinylogous silane **67** served as a four-carbon synthon in two sequential vinylogous aldol maneuvers, allowing rapid implementation of the entire conjugated polyenic frame of **95**.

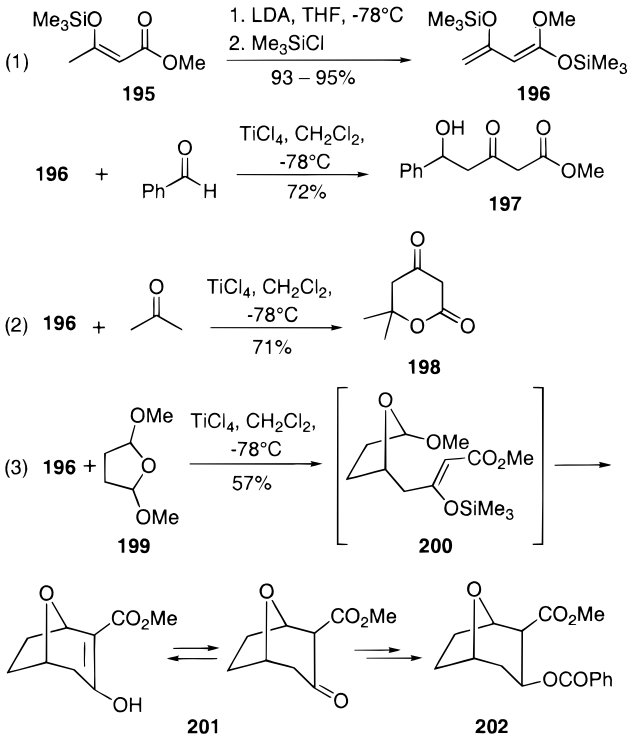
The preparation of 1,1-bis(trimethylsilyloxy)-1,3-butadiene (**193**) from trimethylsilyl ester **192** and its reaction with benzaldehyde was thoroughly investigated by Bellassoued et al.,[142] under a wide panel of conditions and procedures (Scheme 57). Under optimal circumstances ($ZnBr_2$ as the catalyst in THF at room temperature), exclusive formation of δ-hydroxylated α,β-unsaturated carboxylic acid **194** formed in excellent yield. A variety of reaction conditions were also employed, encompassing fluoride ion systems and titanium(IV) promoters. Remarkably, substantial amounts of adducts resulting from competitive α-attack were obtained, with both catalytic systems.

Scheme 57



In a series of papers[143] that appeared during the period 1979−1984, Chan and colleagues extensively investigated the preparation and use of 1,3-bis-(trimethylsiloxy)-1-methoxybuta-1,3-diene synthons of type **196** as dianion equivalents of methyl acetoacetate compounds. Representative examples of this chemistry are portrayed in Scheme 58. Equation 1 deals with the preparation of **196** by starting with 3-trimethylsiloxy crotonate **195** and its reaction with benzaldehyde. In the event, using $TiCl_4$ as the Lewis acid promoter, a good yield of the expected δ-hydroxy-β-keto ester **197** was obtained.[143a,b] Similarly (eq 2), the same reaction with acetone led to β-keto lactone **198** directly. The key virtue of **196**, which resides in its ambident nucleophilic nature, was strikingly

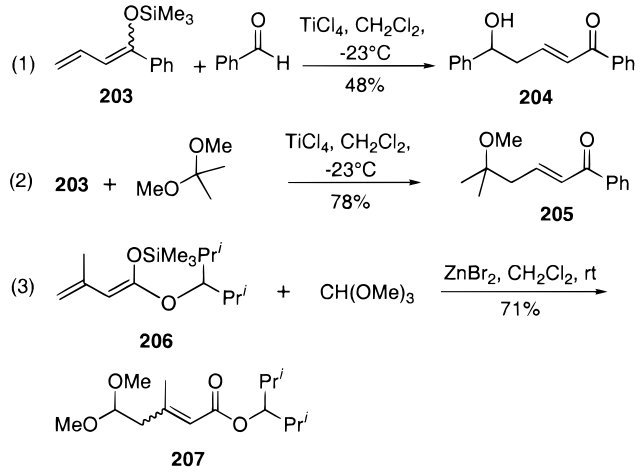
Scheme 58



manifested in the reaction sequence of eq 3.[143c,d] Thus, the reaction with 2,5-dimethoxytetrahydrofuran (**199**), a fragment embodying two electrophilic sites, straightforwardly gave bicyclic adduct **201** via the intermediacy of vinylogous aldol adduct **200**. Interestingly, **201** was then utilized to approach racemic compound **202**, the 8-oxa analogue of cocaine. In a related paper,[144] the same group synthesized sclerin, a metabolite isolated from *Sclerotinia* fungi, by a biomimetic multistep sequence featuring, as the key reaction, the vinylogous cross aldolization between a 4-methyl homologue of **196** and methyl orthoformate.

Trimethylsilyl dienol ether **203** and ketene acetal congener **206** also react with a variety of electrophiles to give a high proportion of products resulting from a vinylogous attack (d^4-reactivity).[145] Thus, as shown in Scheme 59, aldehydes, ketals, and orthoesters

Scheme 59

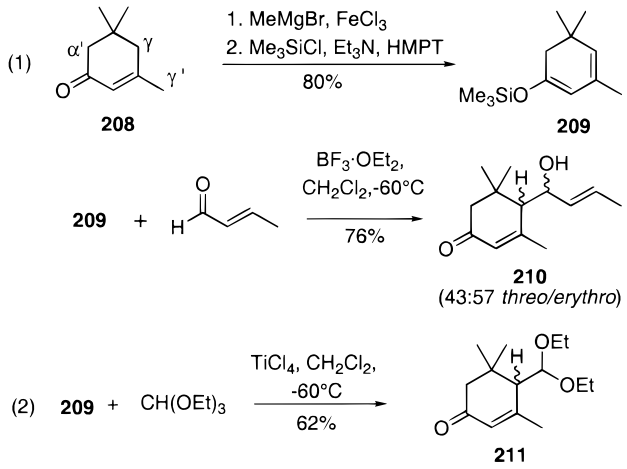


were uneventfully joined at the γ-carbon of the dienoxy silanes **203** or **206**, giving rise to the expected adducts **204**, **205**, and **207** predominantly.

When this investigation was performed, the major emphasis was paid to chemical and regiochemical aspects of the carbon−carbon bond-forming reaction (aldol vs vinylogous aldol), thus squandering the relevant synthetic opportunities of the functionality-rich addition constructs. Cleverly, this issue was addressed a decade later by Paterson, who exploited certain chiral nonracemic vinylogous aldol templates to forge complex targets of biological interest (vide infra).

Naturally occurring cyclohexanoid structures, such as isophorone and carvone, embodying enolizable γ-positions were largely used to access cyclic dienoxy silane nucleophiles[146] to be, in turn, employed in vinylogous aldol processes with aldehyde and orthoester acceptors. Along this line, Takazawa et al.[147] prepared isophorone-based silyloxy diene **209** according to a regioselective protocol involving the conjugated *endo* γ-methylene site. Under the employed conditions (Scheme 60, eq 1), neither the *exo* γ'-methyl group nor the α'-methylene were affected and silyl dienolate **209** solely formed in 80% yield. Boron trifluoride-mediated vinylogous 1,2-addition of **209** to crotonaldehyde then provided a mixture of *threo* and *erythro* isomers **210** in good yield. Similarly, **209**

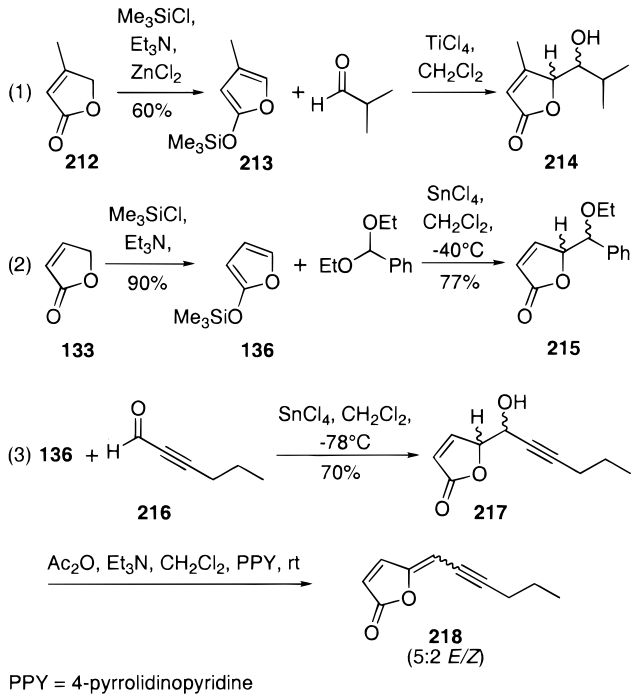
Scheme 60



reacted with a variety of electrophiles, including ethyl orthoformate (eq 2), giving rise to the expected vinylogous addition product **211**.

In a pioneering work, Yoshii[148] first reported the preparation of furan-based 2-silyloxy diene synthons and employed them to synthesize a variety of butenolide-like compounds. As an example, eq 1 in Scheme 61 illustrates a prototypical reaction where 4-methyl-

Scheme 61

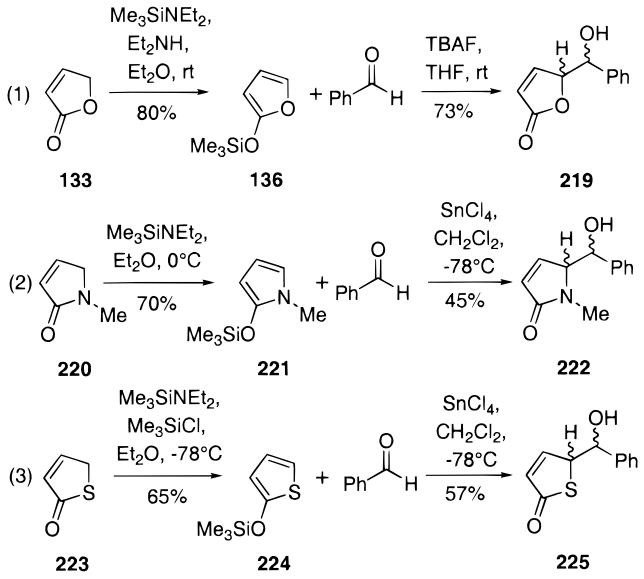


2-[(trimethylsilyl)oxy]furan (**213**) was added to isobutyraldehyde to form butenolide **214**, which was isolated as a mixture of racemic stereoisomers. With parallel chemistry, the Asaoka group[149] expanded this approach to various electrophiles (eqs 2 and 3) and synthesized a number of α,β-unsaturated lactones (e.g., **215** and **217**). The utilization of the aldol products was limited to dehydration processes, giving rise to γ-alkylidene butenolide compounds (e.g., **218**).[149c,150]

The heterocyclic triad, 2-[(trimethylsilyl)oxy]furan (**136**), and previously unknown 1-methyl-2-[(trimeth-

ylsilyl)oxy]pyrrole (**221**) and 2-[(trimethylsilyl)oxy]-thiophene (**224**), almost uniformly obtainable from the respective α,β-unsaturated heterocycles **133**, **220**, and **223**, was introduced by Ricci et al.,[151] who investigated the regiochemical behavior of these reagents toward aldehydes and ketones. As shown in Scheme 62, the three silyloxy dienes uneventfully

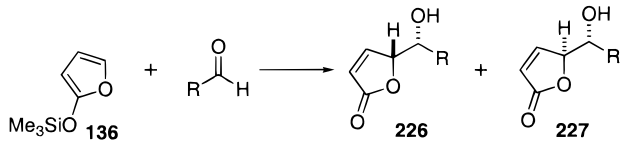
Scheme 62



reacted with benzaldehyde under fluoride ion or $SnCl_4$ catalysis, giving rise to the corresponding vinylogous adducts **219**, **222**, and **225**, which were invariably obtained as *threo*/*erythro* isomer mixtures. No attempts were made to ascertain and rationalize the basic stereochemical outcome of the processes, namely, the control of simple diastereoselection during the key carbon−carbon bond formation between the prochiral donor and acceptor sites.

This issue was first addressed by the Jefford[152] and Brown[108] groups during a series of investigations in 1987. These authors found that in Lewis acid-guided reactions of 2-[(trimethylsilyl)oxy]furan (**136**) with aldehyde acceptors (Scheme 63, entries 1, 2, 4−7),

Scheme 63



entry	R	conditions	yield (%)	**226/227**	Ref.
1	Pr^i	$TiCl_4$, THF	~50	90:10	108
2	Pr^i	TESOTf, CH_2Cl_2, -78°C	88	81:19	152a
3	Pr^i	TBAF, THF, -78°C	77	13:87	152a
4	$PhCH_2$	$TiCl_4$, THF	~50	90:10	108
5	$PhCH_2$	TESOTf, CH_2Cl_2, -78°C	92	82:18	152a
6	$C_5H_{11}{}^n$	$BF_3{\cdot}OEt_2$, CH_2Cl_2, -78°C	95	81:19	152a
7	$C_5H_{11}{}^n$	$SnCl_4$, CH_2Cl_2, -78°C	88	76:24	152a

threo-configured aldol adducts of type **226** invariably predominated over their *erythro* counterparts **227**. In fluoride ion-promoted vinylogous aldol additions (entry 3), instead, reverted stereochemical outcome favoring *erythro* compounds **227** was observed.

To shed light into the diastereoselective behavior of the reaction, it was postulated that under the Lewis acid catalysis, either a Diels−Alder-like transition-state model **TS1** or an open-chain transition-state **TS3** could be operative, accounting for the formation of *threo* or *erythro* compounds (Scheme 64). The favorable orbital interactions within **TS1** would explain the predominance of *threo* isomers. On the other hand, under fluoride ion catalysis, open-chain models **TS2** (for *threo* aldols) and **TS4** (for *erythro* aldols) have been invoked, where the negative charge is well dispersed. Here, the *erythro* prevalence could be due to favorable steric interactions within **TS4**.

After these pioneering works, along the years, the synthetic utility of the vinylogous aldol reaction involving variously substituted furan-based silyloxy diene synthons has been explored, utilizing a variety of achiral aldehydes and acetals.[117,153−159] These efforts culminated in numerous total syntheses of achiral, chiral racemic, and chiral nonracemic target compounds as, for example, the antibiotic patulin,[153] neopatulin,[154] nostoclides I and II,[155] rubrolides C and E,[156] goniobutenolides A and B,[157] *Z* and *E* freelingyne,[158] and fadyenolides and relatives.[117]

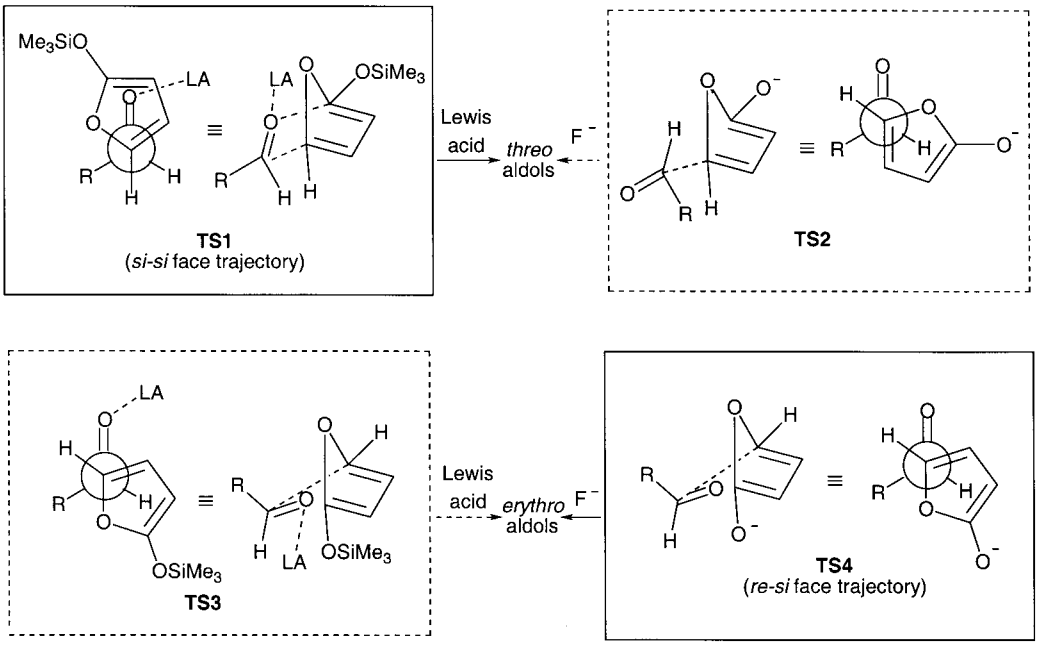
2. Additions to Imines, Nitrones, and Iminium Ions (Mannich-Type Reactions)

The Mannich-type additions of silyl enolate d^2-synthons to iminium ions, imines, and nitrone compounds (Mukaiyama−Mannich reaction) constitutes an efficient method for the preparation of β-amino carbonyl compounds, finding fertile field in the synthesis of alkaloids and other biologically relevant nitrogen-containing heterocycles.[160] The vinylogous variant of this carbon−carbon bond construction might be attractive, since δ-amino α,β-unsaturated carbonyl synthons—the products of such a vinylogous process—could admirably serve to implement very complex constructs.[160]

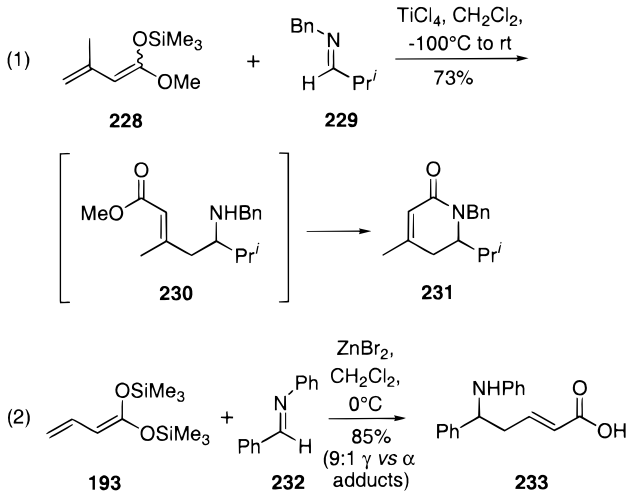
One of the first applications of this maneuver[161] in a racemic domain involved vinylketene silyl acetals of type **228** and various aldimines including *N*-benzyl imine **229** (Scheme 65, eq 1). In the event, unsaturated δ-lactams of type **231** regioselectively formed, through the intermediacy of open-chain adducts, i.e., **230**. No products arising from α-addition of vinylketene silyl acetals were obtained in all the experienced cases. An alternative Diels−Alder cycloadditive mechanism was ruled out, based on the observation that intermediates such as compound **230** truly disappeared during the process leading to annulated products such as **231**. In about the same manner,[162] 1,1-bis(trimethylsilyloxy)buta-1,3-diene (**193**) reacted with aryl imines (e.g., **232**) to afford δ-amino acids (e.g., **233**) predominantly (Scheme 65, eq 2).

In connection with a concise synthesis of the optically inactive alkaloid karachine (**238**), Stevens

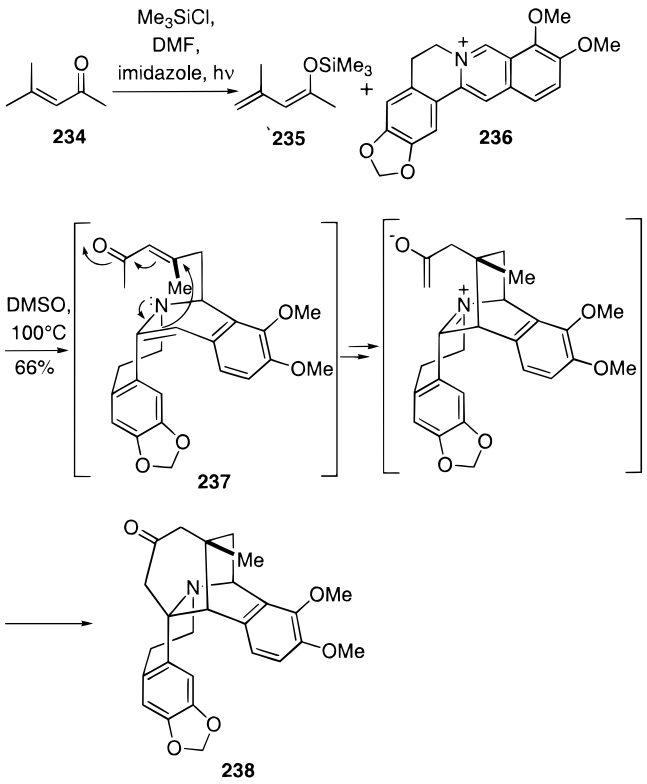
Scheme 64



Scheme 65



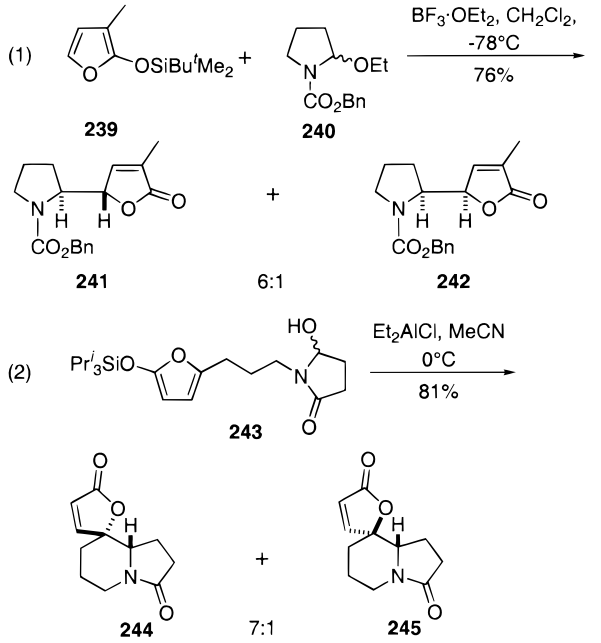
Scheme 66



and Pruitt[163] exploited the potentiality of silyl dienolate synthon **235**, easily obtained from ketone **234**, to implement the core ring portion of the alkaloid (Scheme 66). The key operation was, indeed, an intermolecular vinylogous Mannich reaction between berberine (**236**) and dienolate **235**, giving rise, initially, to ketone intermediate **237**. According to a domino process, an intramolecular Michael addition followed by an intramolecular Mannich annulation straightforwardly completed the construction of karachine (**238**), with a 66% isolated yield, based on **236**.

Properly substituted furan-based 2-silyloxy dienes have been admirably utilized by Martin as the constitutive elements of important polycyclic alkaloidal structures in a variety of synthetic ventures featuring inter- and intramolecular vinylogous Mannich reactions with cyclic iminium ions and imines. In preparatory works[164] directed toward the total synthesis of *Stemona* alkaloid croomine (*vide infra*), it was found that cyclic *N*-acyliminium ions diastereoselectively add, both inter- and intramolecularly, at the γ-position of 2-silyloxyfuran moieties, affording adjacently linked binuclear adducts (Scheme 67, eq 1) or more complex trinuclear structures (eq 2). In particular, dienoxy silane **239** reacted with the iminium ion generated from **240** (BF_3·OEt_2) leading to *threo*-configured butenolide adduct **241** predominantly, along with a minor amount of its *erythro* counterpart **242**.[165] In an analogous manner, the intramolecular version of the reaction using dienoxy silane **243**, embodying the Mannich acceptor component, directly afforded spirocyclic trinuclear *threo* butenolide construct **244** with a good margin of diastereoselection. The viability of this chemistry and

Scheme 67



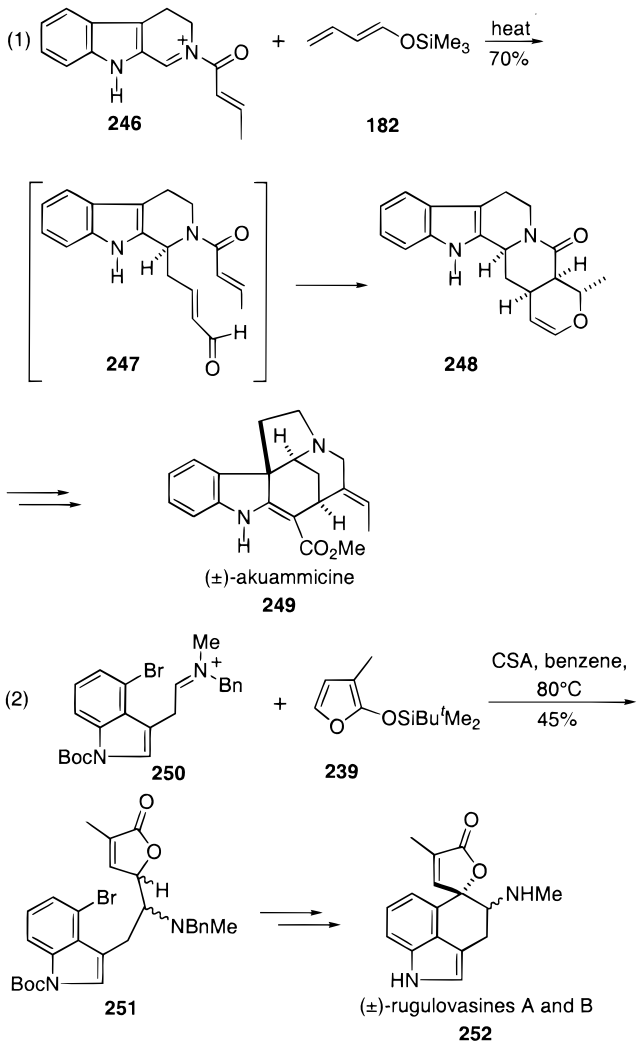
the related stereochemical implications paved the way for the brilliant studies by the same author in the chiral nonracemic domain (section VI.B.2).

Also, application of the vinylogous Mannich reaction using open-chain and cyclic dienoxy silane reagents allowed Martin to succeed in total syntheses of important alkaloid representatives, (±)-akuammicine (**249**) and (±)-rugulovasines A and B (**252**) (Scheme 68).[166,167] To access akuammicine (**249**) (eq 1), tryptamine-derived iminium ion **246** was elongated with **182** giving rise to the expected addition product **247**, which underwent an intramolecular hetero-Diels−Alder reaction upon heating to give **248**, the key precursor of the alkaloid target. According to the same concept, a remarkable route to *Strichnos* alkaloids rugulovasines A and B (**252**) (eq 2) commenced with the vinylogous Mannich addition between silyloxy furan **239** and iminium ion **250**, giving rise to the addition mixture **251**, the immediate precursor of epimeric rugulovasines.

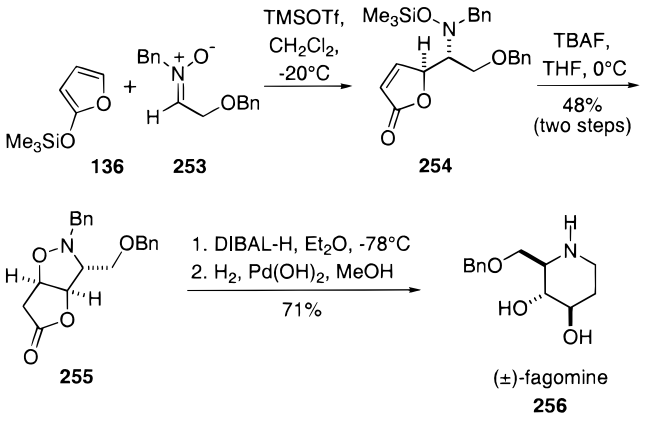
The utility of nitrone compounds as Mannich-type acceptors in vinylogous additions to cyclic and acyclic enoxy silanes was largely experienced by Trombini in the mid-1990s.[168,169] As shown in Scheme 69, the assemblage of racemic fagomine (**256**)[168] was ensured by the TMSOTf-catalyzed addition of nitrone **253** to d^4-donor silyloxy furan **136**. In the event, *erythro*-configured butenolide **254** initially formed (*erythro*/*threo* 6:4), which was then exposed to TBAF to afford bicyclic furanone **255**. Simple reductive workup finally allowed ring expansion to fagomine (**256**).

The addition of nitrone derivatives to a series of open-chain vinylogous silyl ketene acetals was pursued by the same author[169] aiming at exploring the regiochemistry of the event. It was shown that while enoxy silanes lacking a γ-substituent regioselectively gave γ-addition products (60−90% yields), γ-substituted derivatives mainly afforded adducts arising from an α-alkylation process (64−87% yields).

Scheme 68



Scheme 69



B. Additions of Enoxy Silanes to Chiral Carbonyl and Carbonyl-Related Electrophiles

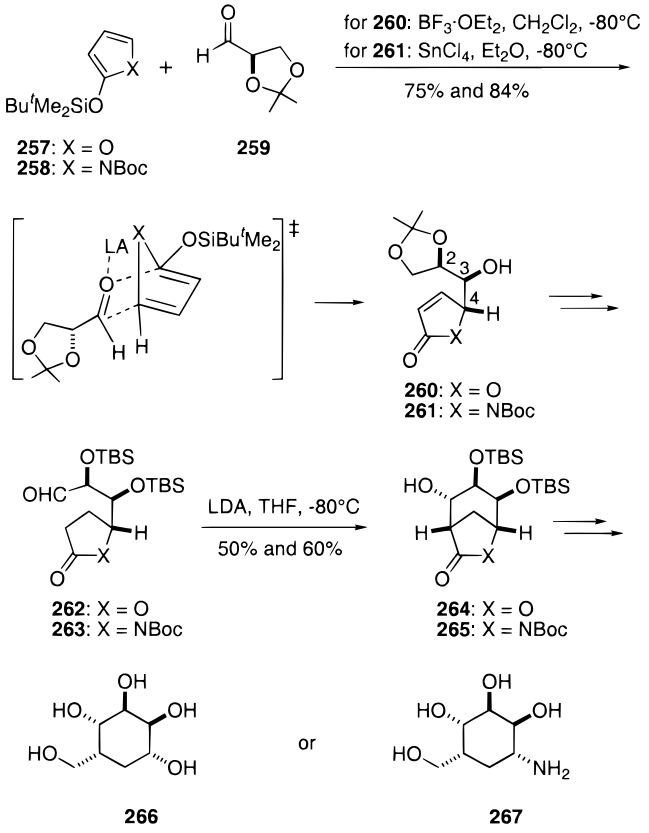
1. Additions to Aldehydes

The diastereoselective vinylogous aldol reactions involving chirality transmittal from a chiral (racemic or nonracemic) carbonyl a[1]-acceptor provides useful routes for the asymmetric synthesis of chiral δ-hydroxy α,β-unsaturated carbonyl compounds, which are versatile building blocks in the preparation of a

vast array of important molecules.[170] A large body of work sprang from the Casiraghi and Rassu laboratories that exploited, during the past decade, the addition of furan-, pyrrole-, and thiophene-based 2-silyloxy dienes with a variety of chiral pool-derived aldehyde synthons. While the reader is addressed to some recent accounts[9] for a detailed insight into the heterocyclic 2-silyloxy dienes realm, here the discussion is restricted to a few emblematic applications that resulted in total synthesis of biologically relevant constructs.

A recent example[171] of this chemistry is the diastereoselective synthesis of chiral nonracemic pseudo-β-D-gulopyranose (**266**) and 1-deoxy-1-amino-pseudo-β-D-gulopyranose (**267**) (1,2,4-tri-*epi*-validamine), by starting with furan- and pyrrole-based 2-silyloxy dienes **257** and **258** and utilizing 2,3-*O*-isopropylidene-D-glyceraldehyde (**259**) as the common chiral source (Scheme 70). To arrive at these cyclohexanoid

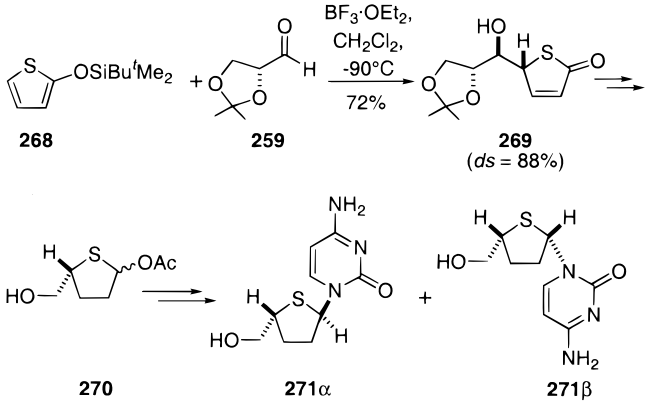
Scheme 70



constructs in a nonracemic format, two parallel sequences were undertaken in which the opening moves were the highly regio- and diastereoselective vinylogous aldolizations between d[4]-donor **257** or **258** and a[1]-acceptor **259**. There, a couple of aldols, **260** and **261**, formed, which were then elaborated into seven-carbon aldehydes **262** and **263**, ready for the crucial intramolecular aldolization. This maneuver directly installed the cyclohexanoid moiety of the pseudo-sugars with a high level of diastereocontrol. Reductive opening of the five-membered rings at the lactone/lactam linkage finally afforded the two carbasugars **266** and **267**. The highly diastereoselective character of the vinylogous aldolization, strongly favoring 2,3-*erythro*-3,4-*threo*-configured isomers **260** and **261**, may be rationalized based on a Diels−Alder-like transition state (in square brackets), where the bulky dioxolane moiety of **259** is arranged *exo* with respect to the silyloxy diene ring. Likely, the facial selectivity may be dictated by a Felkin-type approach of the nucleophiles on the less encumbered *si*-face of the α-alkoxy aldehyde **259**.

By changing 2-[(*tert*-butyldimethylsilyl)oxy]thiophene (**268**) for the previously mentioned oxygen and nitrogen analogues **257** and **258**, preparation of thiolactone **269** was easily secured.[172] As shown in Scheme 71, this reaction variant allowed for a facile

Scheme 71

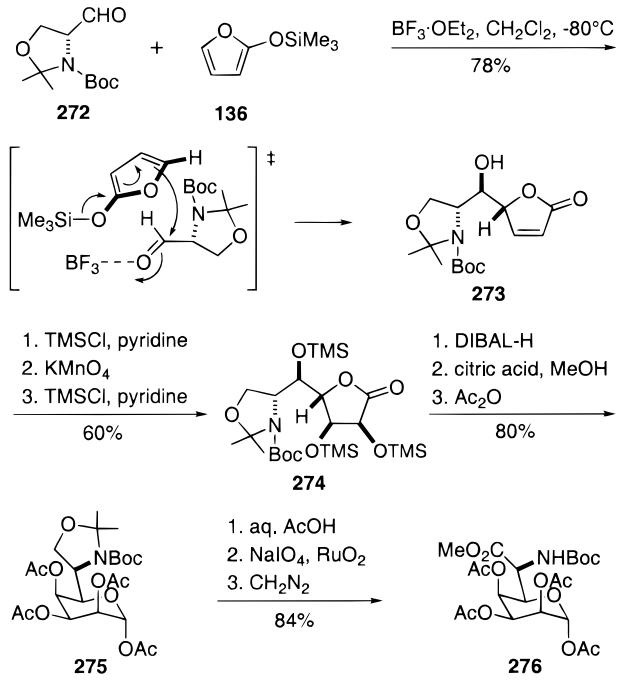


entry to α- and β-2′,3′-dideoxy-4′-thiocytidines **271**α and **271**β. Apart from the initial vinylogous aldolization reaction leading to **269**, the overall sequence encompassed two further operations, namely, two-carbon shortening of the triol arm within **269** and Vorbrüggen-type coupling of thiosugar **270** to activated cytosine.

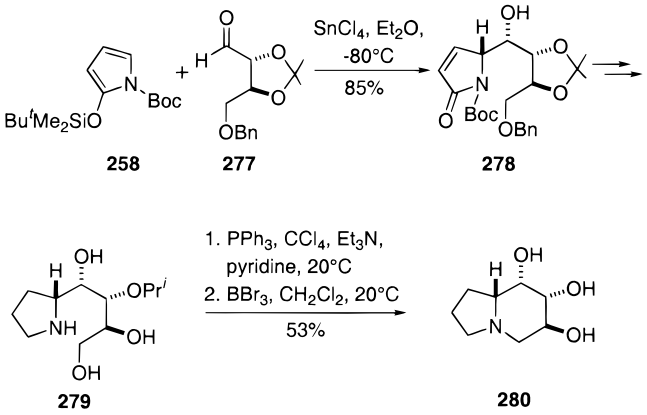
An important sugar amino acid ensemble whose synthetic access can be planned by using the vinylogous aldolization between furan-based dienoxy silanes and aldehyde chirons is related to the *C*-glycopyranosyl glycine compounds of the amipurimycin and the miharamycin family.[173] As portrayed in Scheme 72, central to the success of a versatile synthesis of one representative of this rare compound class was the vinylogous aldol addition between 2-[(trimethylsilyl)oxy]furan (**136**) and protected D-serinal **272**. Under BF_3 etherate assistance, the coupling proved to be highly diastereoselective, leading to *threo*,*erythro*-configured butenolide **273** in a 78% yield and 94% de. Mechanistically, a Felkin/Diels−Alder-like transition state may be invoked to account for the observed behavior. Moving from **273**, a set of operations encompassing (1) double-bond dihydroxylation to **274**, (2) reduction of the lactone carbonyl to a lactol, (3) furanose to pyranose ring expansion to **275**, and (4) oxidation of the hydroxymethyl terminus to a carboxylic function completed the synthesis of sugar amino acid **276**.

A short access to a densely hydroxylated indolizidine derivative of the castanospermine family, compound **280**, was also pursued, by utilizing the vinylogous aldol addition between pyrrole-based dienoxy silane **258** and protected L-threose **277** (Scheme 73).[174] In the event, employing $SnCl_4$ as the promoter,

Scheme 72



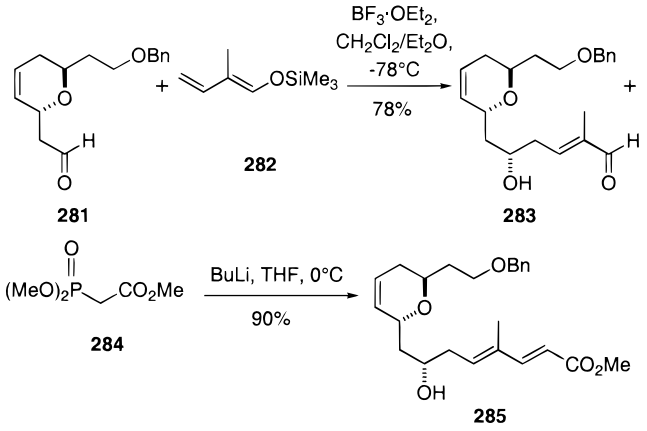
Scheme 73



an excellent level of diastereoselection was attained and lactam **278** was formed in 85% yield. Simple chemistry then furnished pyrrolidine **279**, which was subjected to a Mitsunobu-type six-membered ring closure ($PPh_3/CCl_4/Et_3N$), thus providing (+)-1-deoxy-8-*epi*-castanospermine (**280**).

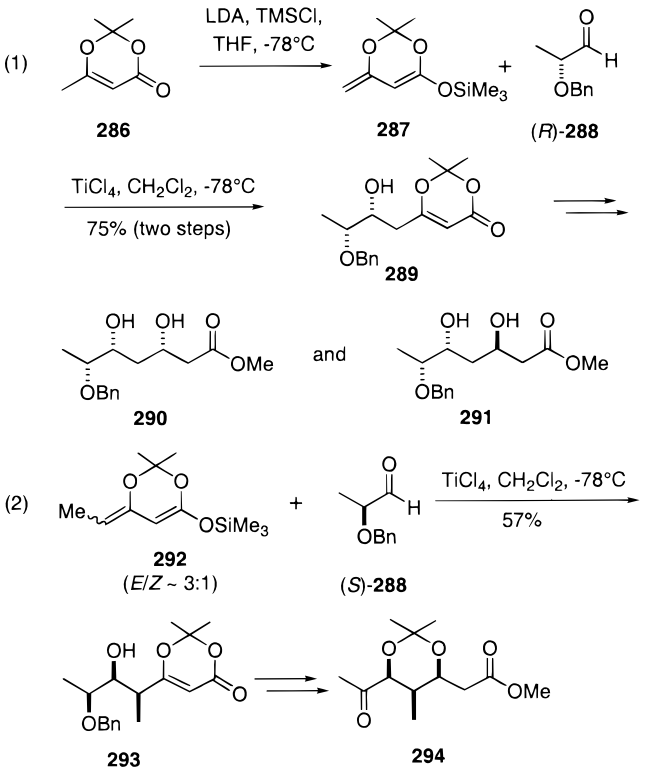
A vinylogous Mukaiyama aldol reaction was also adopted in a chiral racemic domain by Paterson and Smith[69] in a study directed toward the preparation of a segment for the cytotoxic marine macrolide swinholide A (Scheme 74). The BF_3-mediated addition of the silyl dienol ether **282** to racemic aldehyde **281** only gave products of γ-attack on **282**, resulting in formation of the enal product **283** in a 9:1 diastereomeric ratio and exclusive *E* configuration of the trisubstituted double bond. Substrate-controlled installation of the carbinol stereocenter in a 1,3-anti sense possibly resulted from β-chelation between the aldehyde and pyrane oxygens. The aldol adduct was finally converted into the corresponding *E*,*E* unsaturated ester **285** (the C_1-C_{15} segment of swinholide A) in 90% yield by a Horner−Emmons reaction using phosphonoacetate **284**.

Scheme 74



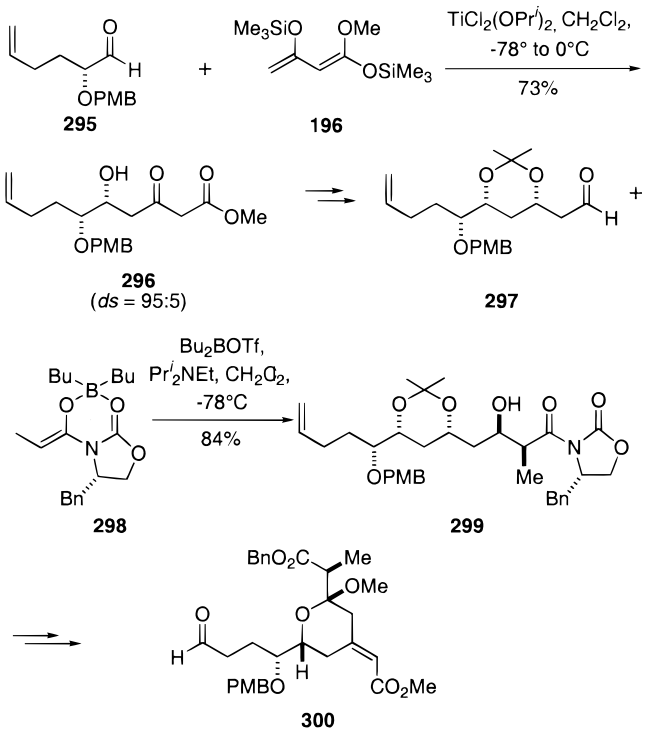
The potential of 4-trimethylsilyloxy-6-methylene-1,3-dioxines of type **287** and **292** (Scheme 75) has

Scheme 75



been demonstrated by Sato and Kaneko,[175] who first exploited these acetoacetate-synthon equivalents in diastereoselective aldol additions to enantiopure aldehydes. As an example (eq 1), when vinylogous silyl ketene acetal **287**, derived from 6-methyldioxinone **286**, reacted with lactaldehyde (*R*)-**288** in the presence of $TiCl_4$, the sole syn product **289** emerged, as expected for a chelation-controlled mechanism. The enantiopure seven-carbon aldol product thus obtained could be converted to both heptanoates **290** and **291**, which represent useful building blocks for the diastereoselective synthesis of amphotericin B and bryostatins. In an analogous manner (eq 2), methyl-substituted silyl enol derivative **292** reacted in a vinylogous sense with protected (*S*)-lactaldehyde (*S*)-**288**, giving rise to *syn*,*syn*-aldol **293** (57%) along

Scheme 76



with minor amounts of its *anti,syn*-epimer (9%, not shown). By simple chemistry, **293** was then elaborated into keto ester **294**, the $C_{22}-C_{27}$ segment of FK 506.

In a brilliant, recent synthesis of the marine macrolide (+)-miyakolide, D. A. Evans[176] benefited from the potentiality of the vinylogous aldolization during the assemblage of the C_1-C_{11} subunit of the macrolide. As displayed in Scheme 76, the four-carbon elongation of chiral nonracemic α-alkoxy aldehyde synthon **295** was effected by using acetoacetate-derived dienoxy silane **196** (Chan's diene). By using $TiCl_2(OPr^i)_2$ in CH_2Cl_2, keto ester **296** was obtained in 73% yield, with excellent diastereoselectivity (20:1 isomeric ratio). The syn stereodisposition of the two hydroxyl substituents within **296** was presumed to have arisen from chelation control between the aldehyde carbonyl and the α-alkoxy group of **295** by means of the complexing Ti(IV) promoter. A multistep sequence including, inter alia, a further propionate aldol elongation (**297** + **298** → **299**) then furnished the proper C_1-C_{11} fragment of miyakolide **300** in 17 steps and with a 15% overall yield.

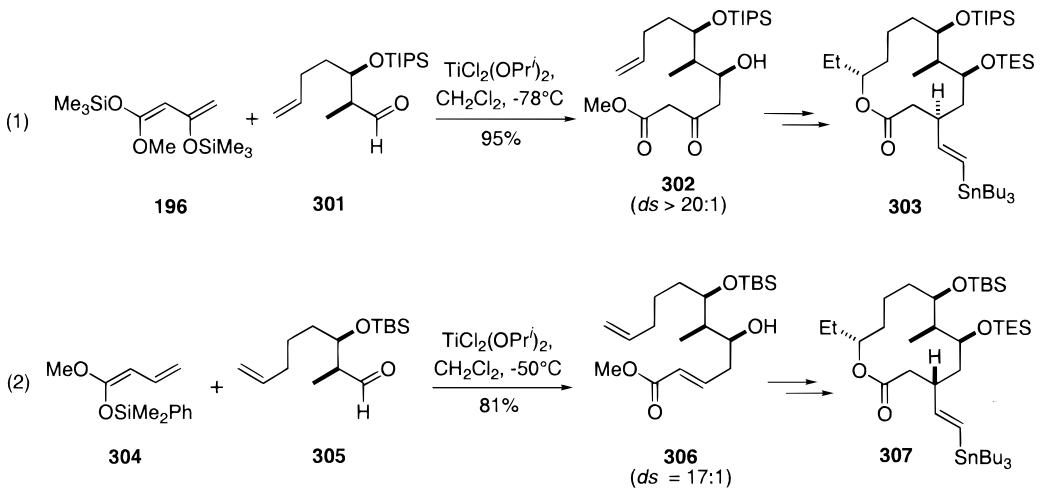
Similar chemistry has been recently applied by Evans to assemble the C_1-C_9 subunit of bryostatin 2, exploiting silyl ketene acetal **196** and a proper chiral *β*-hydroxy aldehyde synthon. As observed in the above vinylogous aldolization leading to **296**, a high level of diastereoselection was reached.[177]

In planning and executing the first total synthesis of the tetracyclic macrolide lepicidin A, Evans and Black[178] applied a highly diastereoselective version of the acetoacetate vinylogous aldolization to construct the 12-membered macrocycle **303**, the core segment of the title lepicidin. As shown in Scheme 77 (eq 1), the $TiCl_2(OPr^i)_2$-promoted reaction of aldehyde **301** with dienoxy silane **196** proved to be highly diastereoselective (>20:1 ds), affording the desired Felkin adduct **302** in high isolated yield. During an earlier attempt to implement the same macrocyclic fragment, vinylogous aldolization between ketene acetal **304** and aldehyde **305** was also investigated (eq 2), resulting in the formation of unsaturated ester **306** with excellent diastereoselection. Unfortunately, subsequent manipulation of this adduct to the desired macrocycle was frustrated, the epimer **307** being obtained en lieu of **303**.

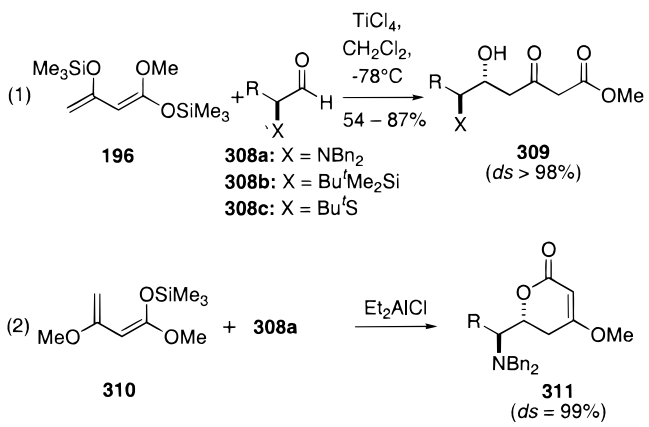
The diastereoselective addition of 1,3-bis(trimethylsilyloxy)-1-methoxybutadiene (**196**) to chiral nonracemic aldehydes was also investigated by Enders[179] as the fundamental maneuver during a process directed toward the preparation of a HMG−CoA−reductase inhibitor. As indicated in Scheme 78 (eq 1), the Mukaiyama-type aldol addition of **196** to aldehydes **308a**−**c** proceeded with complete nonchelation control and without any appreciable racemization to furnish 6-heterosubstituted 5-hydroxy-3-oxoesters **309** as single diastereoisomers in moderate-to-good yields. Analogously (eq 2), aldehyde **308a** reacted with **310** in the presence of Et_2AlCl to provide unsaturated lactone **311** with virtually complete diastereselection.

The potentiality of the vinylogous aldolization using the bis(trimethylsilyl)enol ether of methyl

Scheme 77

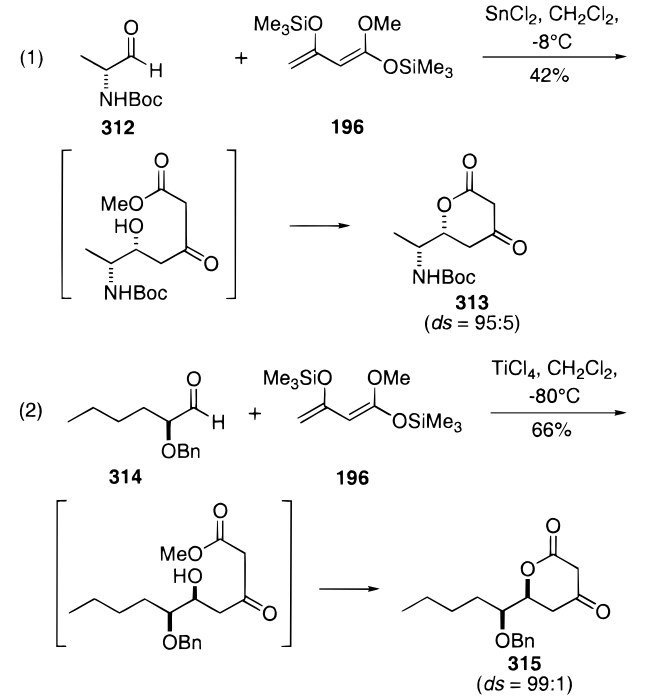


Scheme 78



acetoacetate was independently tested by two Japanese teams in the context of total synthesis of naturally occurring sperabillins[180] (Scheme 79, eq 1)

Scheme 79

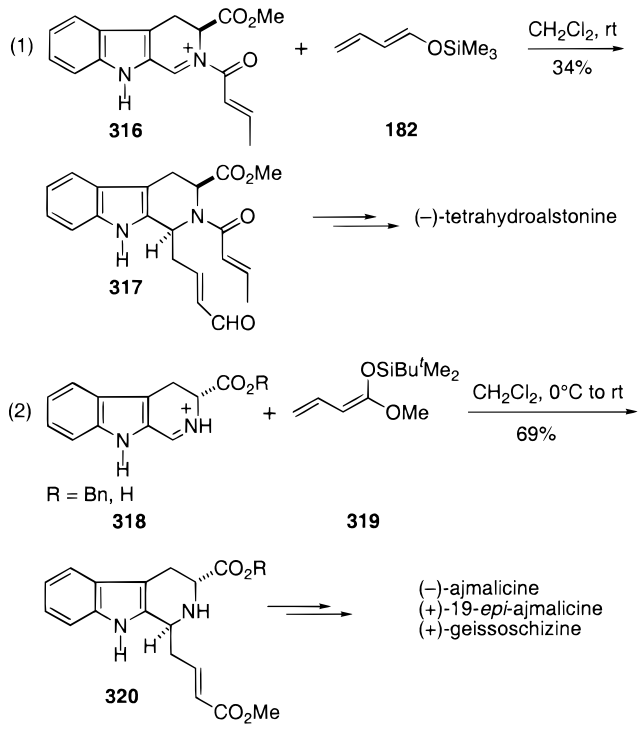


and (−)-pestalotin (eq 2).[181] In both instances, the Lewis acid-promoted reactions with proper α-amino- and α-alkoxy aldehydes (e.g., **312** and **314**) behaved cleanly to afford acceptable yields of the cycloadducts **313** and **315**. The observed diastereoselectivity, favoring *syn*-configured aldols, is likely indicative of a chelate mechanism involving the metal promoter and the α-located heterosubstituent.

2. Additions to Imines and Iminium Ions (Mannich-Type Reactions) and Oxonium and Thionium Species

Strictly speaking, the vinylogous Mukaiyama−Mannich reaction involves the Lewis acid-catalyzed (promoted) addition of nitrogen-stabilized a^1-carbenium ions to d^4-dienoxy silane compounds (or higher homologues). In a broader sense, however, nitrones and imines may be also considered as Mannich acceptors. This section is further expanded to embody oxygen- and sulfur-stabilized carbenium species, due to close reactivity resemblance. The use of such electrophilic compounds in a chiral nonracemic field has received a great deal of interest, this maneuver being the route of choice with which a number of alkaloidal targets or other important heterocycles have been constructed. As a first example,[182] the application of the vinylogous Mannich reaction to enter diverse members of the indole alkaloid family has been addressed by Martin and colleagues (Scheme 80). By starting with enantiomerically pure carboline

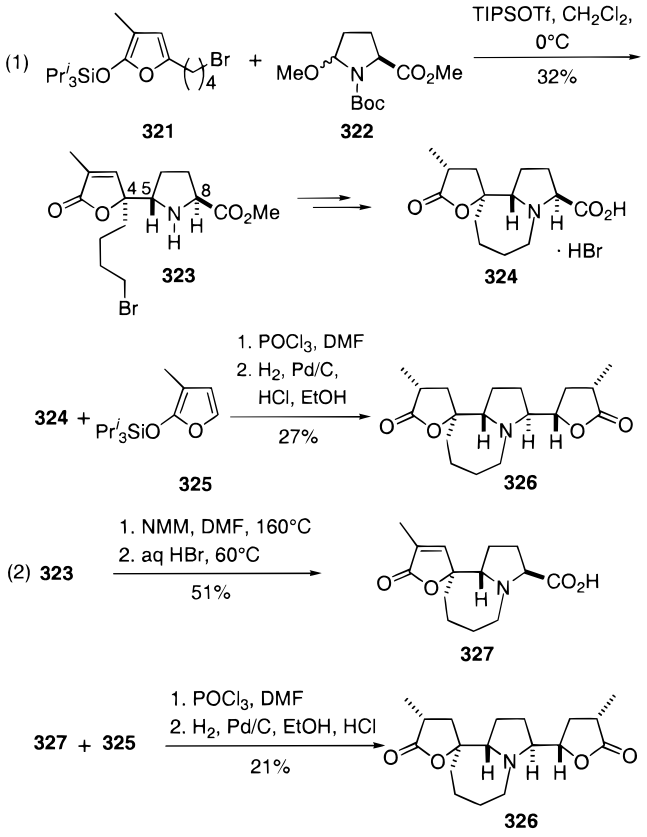
Scheme 80



iminium scaffolds of type **316** and **318** and utilizing dienoxy silanes (e.g., **182**) or vinylogous ketene acetals (e.g., **319**), a number of complex alkaloidal structures, including (−)-tetrahydroalstonine, (−)-ajmalicine, (+)-19-*epi*-ajmalicine, and (+)-geissoschizine, have been assembled. The opposite stereochemical behavior of the two reactions giving rise to *cis*-adducts (eq 1) or *trans*-adducts (eq 2) is noteworthy and merits comment. With less reactive dienoxy silane **182**, activation of the carboline system as a *N*-acyl iminium ion **316** was necessary before the vinylogous coupling, while for the more nucleophilic vinyl ketene acetal **319**, the coupling could be effected on unsubstituted iminium **318** directly. Thus, the *β*-trajectory of the incoming nucleophile in **316** could be dictated by the location of the proximal *N*-acyl substituent, which is pushed trans (α) with respect to the carboxylate moiety. On the other hand, with **318**, lacking a *N*-substituent, the nucleophile would preferentially enter the *β* face of the carboline, trans to the carboxylate moiety, for steric reasons.

A nice synthetic achievement has been recently accomplished by the same group,[183] who exploited two sequential vinylogous additions involving methyl-substituted silyloxy furans and five-membered iminium species to assemble the *Stemona* alkaloid (+)-

Scheme 81

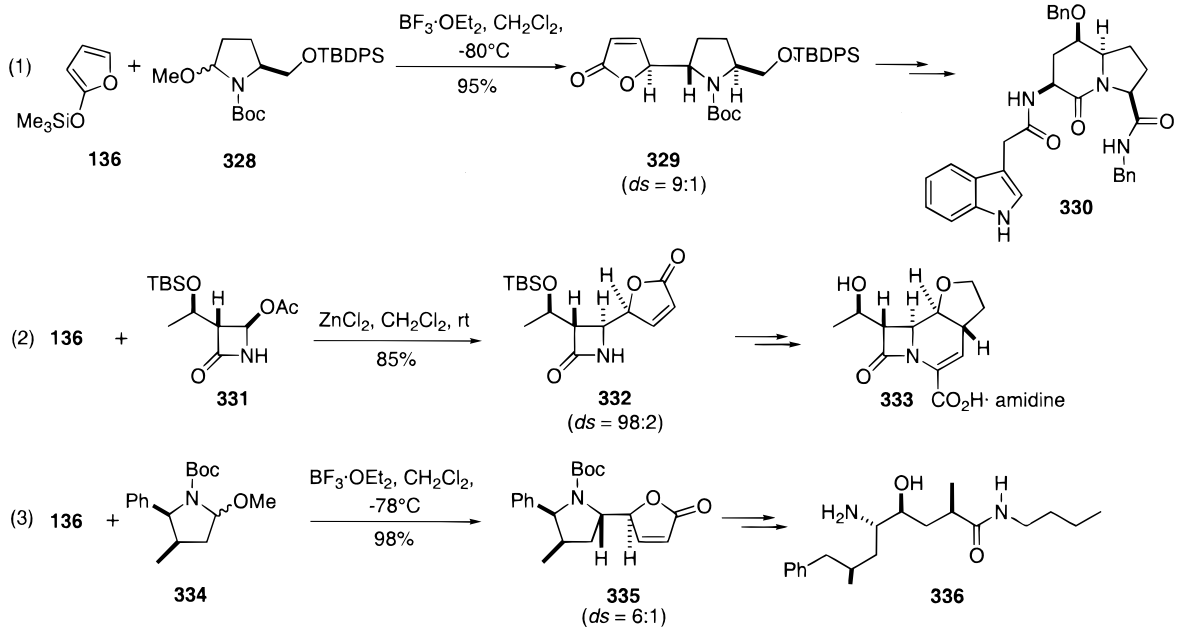


croomine. As shown in Scheme 81 (eq 1), the synthesis adopted a first coupling between γ-substituted silyloxy furan **321** and the iminium acceptor derived from **322**. There, adjacently linked binuclear adduct **323** solely formed, equipped with the requisite 4,5-*threo*-5,8-trans relative stereochemistry. A second vinylogous Mannich coupling between silyloxy diene **325** and the trinuclear iminium species from **324**, in turn derived from the first adduct **323**, nicely resulted in completion of the tetranuclear scaffold of croomine (**326**). In a second, more convenient approach (eq 2),[183b] the initial Mannich adduct **323** was transformed into the unsaturated tricyclic intermediate **327**, which was directly coupled to **325**, as previously described, to afford, after hydrogenation, the target croomine (**326**).

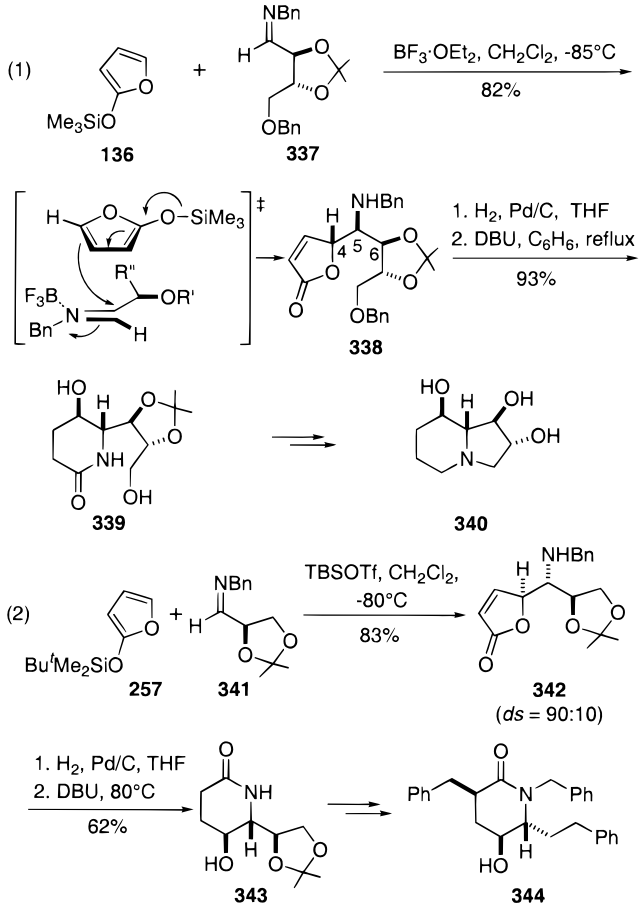
Total asymmetric syntheses of chiral nonracemic, pharmaceutically interesting prototypes, including the β-turn peptidomimetic scaffold **330**, the tricyclic carbacephem **333**, and the nonpeptidic renin inhibitor **336**, have been executed by Hanessian,[184−186] again highlighting the merits of dienoxy silane **136** in Mukaiyama−Mannich reactions with in-situ-generated cyclic iminium ions derived from **328**, **331**, and **334** (Scheme 82). In all cases, the Lewis acid-assisted vinylogous couplings behaved similarly, resulting in almost exclusive formation of the expected *threo,trans*-configured binuclear adducts **329**, **332**, and **335**. The precious functionalities and chirality within these butenolide precursors ensured ample malleability, allowing for rapid access to the title targets.

Chiral nitrogen-containing compounds are largely encountered in nature, and some of them are known to display important bioactivities. The use of chiral imines as electrophilic units in a coupling reaction to dienoxy silane matrices can offer a promising entry into this compound class. For example, syntheses of (−)-1-*epi*-swainsonine (**340**) and novel lactam peptidomimetic **344** have been completed by Casiraghi et al.,[187,188] adopting, as pivotal carbon−carbon bond-forming process, the vinylogous Mannich-type addition of silyloxy furan reagents **136** and **257** to threose imine **337** and glyceraldehyde **341**, respectively. For the swainsonine analogue **340** (Scheme 83, eq 1),[187] the vinylogous addition of 2-[(trimethylsilyl)oxy]furan (**136**) to D-tartrate-derived imine **337** (BF_3·OEt_2 as the promoter) afforded 4,5-*erythro*-5,6-*erythro* butenolide **338** with no stereoisomeric contamination. The addition regiosense (attack at the remote γ-position of furan **136**), the simple diastereoselection (4,5-anti),

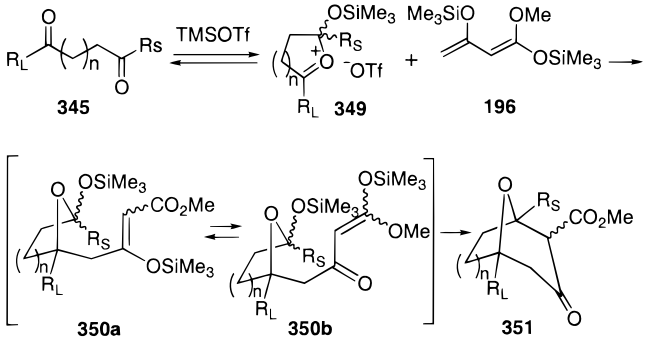
Scheme 82



Scheme 83



Scheme 84



as well as the induced (facial) diastereoselection (5,6-anti) may possibly be governed by the transition state shown, where an open-chain/Felkin-type model favorably applies.

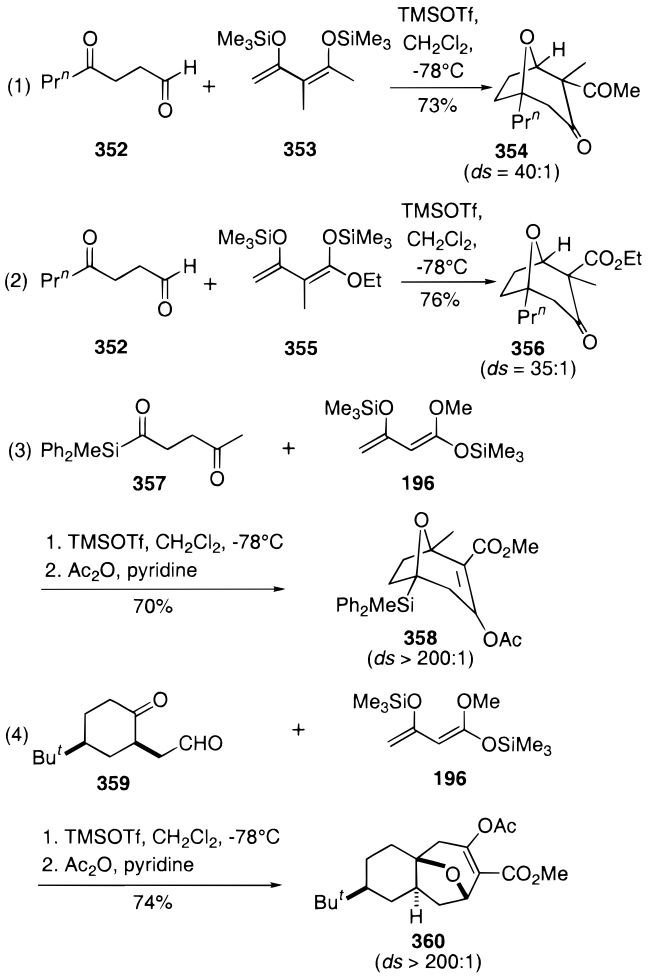
For piperidinone **344** (eq 2),[188] the starting move was similar, with 2-[(*tert*-butyldimethylsilyl)oxy]furan (**257**) and glyceraldehyde imine **341** as the reaction components. Here, the vinylogous Mannich reaction was carried out in the presence of 0.6 equiv of TBSOTf and led to seven-carbon butenolide **342** with a good 9:1 diastereomeric ratio. In both syntheses, the furanone moieties within adducts **338** and **342** were then saturated and expanded to piperidinone structures (e.g., **339** and **343**), which served as the basic scaffolds to access swainsonine and piperidinone targets **340** and **344**.

A coherent body of work centered upon the preparation and synthetic exploitation of both acyclic and cyclic bis(trimethylsilyl)enol ethers was assembled by Molander and his associates,[189,190] comprising a number of clever entries to seven- and eight-membered ring structures. As portrayed in Scheme 84, the basic idea entails a sort of nonsynchronous Lewis acid-promoted [3 + 4] and [3 + 5] cycloadditive operations between 1,4- and 1,5-dicarbonyl substrates and bis(trimethylsilyl)enol ethers to gain access to seven- and eight-membered carbocycles. A unique mechanism involving an intermediary oxocarbenium ion (e.g., **349**) permits excellent regio- and stereocontrol during the annulation process. A number of 1,4- and 1,5-dicarbonyl bis-electrophiles **345** and varied dienoxy silane reagents (e.g., **196**) have been used as complementary substrates in these annulations, some of which were employed toward the synthesis of important natural products. During the key aldolization, intermediary equilibrium adducts of type **350a** and **350b** plausibly formed, arising from initial attack of the electrophile **349** to the more nucleophilic carbon of the dienoxy silane **196**. The final ring closure to bicyclic compounds **351** emerged from a further, intramolecular aldolization involving a second oxocarbenium ion in situ generated from silyl ketal **350a**,**b**. As for the regiocontrol of the process, it might be thought that preferential coordination of the Lewis acid to the less hindered carbonyl within **345** exclusively leads to oxonium ion **349**, thus dictating the site to which the nucleophile attacks.

In a continuing evolution of this chemistry, a vast repertoire of experiments has been executed in order for this approach to highlight its virtue and applicability. As shown in Scheme 85,[189] dienol ether **353**, methyl-substituted ketene acetal **355**, and unsubstituted ketene acetal **196** were subjected to annulation with acyclic and cyclic γ-dicarbonyl compounds **352**, **357**, and **359**, giving rise to seven-membered bicyclic or tricyclic adducts **354**, **356**, **358**, and **360**. Of note, products derived from the reaction of 3-substituted bis(trimethylsilyl)enol ethers derived from β-diketones (eq 1) displayed opposite relative stereochemistry to those obtained by reaction of analogous 2-substituted bis(trimethylsilyl)enol ethers derived from β-keto esters (eq 2). Furthermore, reverted regiochemistry was observed (eq 3) when a masked keto-aldehyde synthon, e.g. **357**, was employed, where the bulky silyl group hampers Lewis acid coordination to the proximal carbonyl function, ultimately forcing diene **196** to enter the masked aldehyde site, in accordance with the previously disclosed reaction mechanism (Scheme 84). With chiral racemic cyclohexanone-derived aldehyde **359**, highly functionalized tricyclic ethers of type **360** were straightforwardly generated, with the bis(trimethylsilyl)enol ether entering the activated ketone carbonyl group first.

The heights of this chemistry were reached by Molander himself with total syntheses of sesquiterpene cyclooctanoid (+)-dactylol (**363**) (Scheme 86, eq 1), the ingenol B,C ring-related systems **366** (eq 2), and racemic *Artemisa* sesquiterpene (±)-davanone (**369**) (eq 3).[190] To enter chiral nonracemic (+)-dactylol (**363**), aldehyde **361** was first prepared from commercial (+)-pulegone. Then, treatment of this precur-

Scheme 85

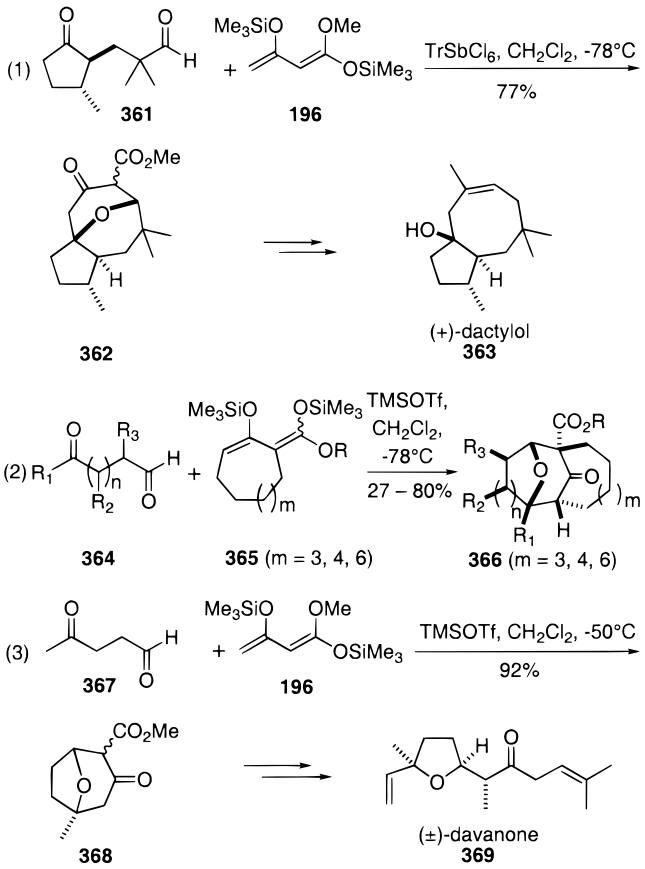


sor with dienoxy silane **196** in the presence of $TrSbCl_6$ led to a mixture of keto−enol tautomers of **362** in 77% yield. Decarboxylation, Tebbe's methylenation, double-bond *endo* isomerization, and reductive opening of the ether bridge provided, albeit in a rather low yield, the sesquiterpene **363**. For complex trans intrabridgehead keto esters **366**, structures reminiscent of the ingenol B,C-subunit, macrocyclic dienoxy silanes of type **365** were employed. The annulations with various keto−aldehyde synthons were totally regioselective, with the nucleophilic attack occurring at the more congested ketone carbonyl, as usual.

Oxabicyclo[3.2.1]heptanone **368**, easily obtained by TMSOTf-catalyzed annulation of **196** to **367**, was the key intermediate with which the plant metabolite davanone (**369**) was synthesized in a racemic format. Here, the chemistry linking **368** to **369** did not involve complex manipulations, highlighting once more the utility of the Molander's vinylogous aldol addition/annulation strategy.

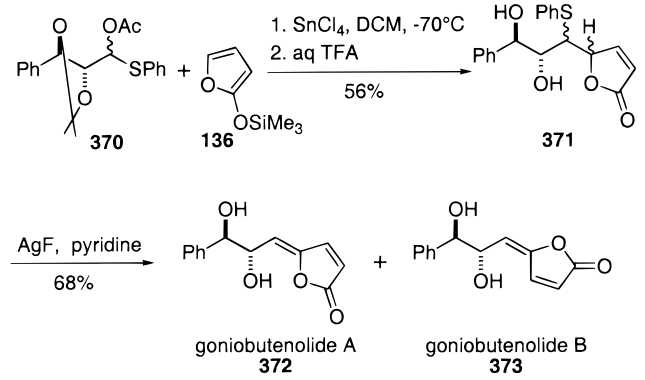
Cyclic thionium ions, in situ generated from *O,S*-mixed acetals, may be envisioned as efficient electrophilic synthons—a sort of Mannich acceptors, in an extended sense—to be used in Mukaiyama−Mannich vinylogous reactions with proper dienoxy silanes. Along this concept, Ko and Lerpiniere[191] utilized chiral nonracemic *O,S*-acetal **370**, obtained by enantioselective functionalization of (*E*)-cinnamyl

Scheme 86



alcohol, in the $SnCl_4$-promoted vinylogous aldol addition to 2-[(trimethylsilyl)oxy]furan (**136**) (Scheme 87). After acidic workup, an isomeric mixture of

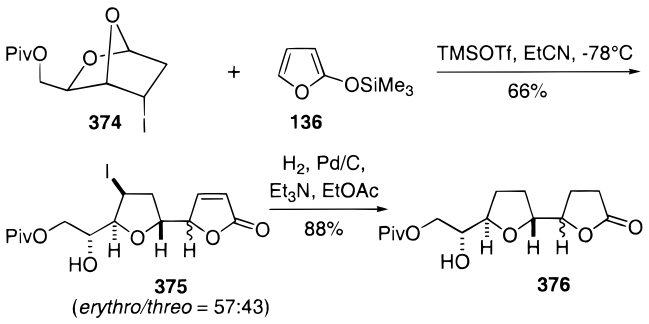
Scheme 87



butenolides **371** was recovered, which was converted to naturally occurring goniobutenolides A (**372**) and B (**373**) by benzenethiol elimination (AgF, pyridine).

The same procedure has been recently paralleled by Solladié et al.,[192] in order to chemically correlate a couple of oxalic acid-derived *syn*- and *anti*-configured 1,2-diols to goniobutenolides A and B. As a route to adjacently linked bis-tetrahydrofuranic segments related to the core substructure of annonaceous acetogenins, Veyriéres and colleagues[193] devised a strategy wherein silyloxy furan **136** regioselectively reacted with the cyclic oxycarbenium species in situ generated from *endo*-iodide **374** (Scheme 88). Disappointingly, a mixture of inseparable *erythro,trans* and

Scheme 88

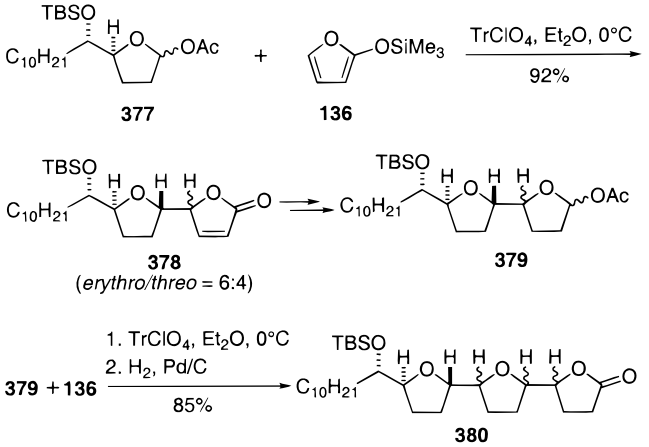


threo,trans butenolides **375** formed, which was subjected to catalytic hydrogenation to form a 1:1 mixture of saturated units **376**.[194]

In the important field of annonaceous acetogenin synthesis, several research groups have been recently challenged, mainly stimulated by the strikingly cytotoxic and antitumoral potency of this compound class, as well as by the charming architecture of these constructs.[195] Owing to the bis-tetrahydrofuranic nature of the core segments of the majority of bioactive acetogenins, it is not surprising that an appealing construction of these scaffolds has entailed the use of furan-based 2-silyloxy diene modules as the basic building blocks.[196−198] By analogy, related heterocyclic synthons such as pyrrole- and thiophene-based silyloxy dienes could pave the way to a number of deeply modified, isosteric components.[197] This theme has been independently addressed by the Figadère and Casiraghi groups, who exploited reiterative vinylogous aldol additions to implement diverse oligotetrahydrofuranic core motives of annonaceous acetogenins,[196,197] as well as varied oligopyrrolidinic, oligothiolanic, and mixed heterocyclic variants.[197]

As shown in Scheme 89, the modular construction introduced by Figadère[196a,b] moved from chiral nonracemic 2,5-disubstituted acetoxy synthon **377** which was coupled in a vinylogous sense with 2-silyloxy furan **136** ($TrClO_4$). The reaction displayed only partial diastereoselection, giving rise to a mixture of two separable butenolide adducts **378** (out of four) to which *erythro,trans*- and *threo,trans*-configurations were assigned. Conventional chemistry then allowed transformation of individual butenolides **378** to the

Scheme 89

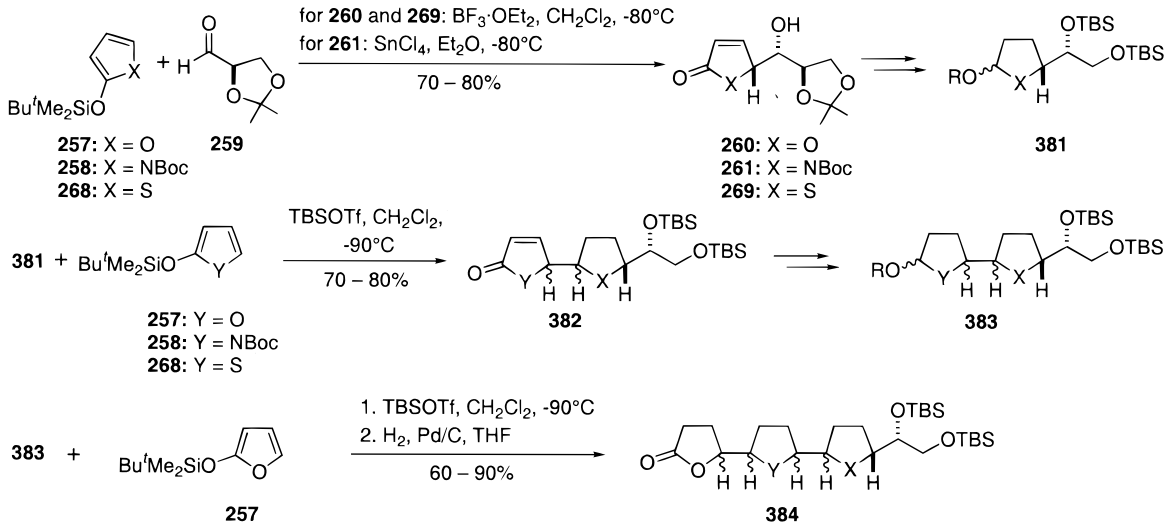


corresponding bis-tetrahydrofuranic acceptors **379**. A second vinylogous coupling of **379** to the same donor module **136** finally provided trinuclear constructs **380** possessing diverse stereochemical arrangements. Due to the scantily selective character of both of the vinylogous aldol processes, the reaction scheme renders the synthesis of a useful collection of acetogenin-related scaffolds feasible, though separation of isomeric products at each stage of the synthesis cannot be avoided.

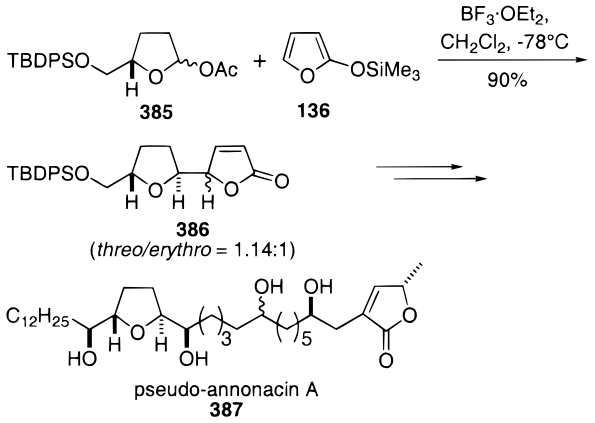
A conceptually similar approach has been applied by Casiraghi[197a,b] in a wider context, where a triad of heterocyclic dienoxy silanes based on furan, pyrrole, and thiophene was employed. The reiterative construction in Scheme 90 is oversimplified in order for the reader to savor the overall strategy, neglecting the many stereochemical implications. Starting from D-glyceraldehyde chiron **259**, a first vinylogous coupling to each of the dienoxy silanes **257**, **258**, or **268** led to butenolide intermediates **260**, **261**, or **269**, which invariably possess a *threo,erythro* configuration. These adducts were then independently converted to lactol-type compounds **381** that represent the acceptor scaffolds on which further vinylogous aldolizations were performed. Depending upon the nature of the heteroatom composition of the planned binuclear adducts **382**, the electrophilic (**381**) and nucleophilic (**257**, **258**, or **268**) components had to be properly combined. Here, the stereochemical diversity of adducts of general formula **382** is strongly dictated by the chosen heteroatom composition. As an example, when tetrahydrofuran **381** (X = O) was coupled to 2-silyloxyfuran **257** (Y = O), a 1:1 mixture of *erythro,trans*- and *threo,trans*-butenolide isomers **382** (X = Y = O) formed, while when pyrrolidinose **381** (X = NBoc) reacted with **258** (Y = NBoc), a 1:1 separable mixture of *erythro,cis*- and *erythro,trans*-configured isomers **382** (X = Y = NBoc) was recovered. Adjacently linked binuclear adducts **382** were then uneventfully converted to the corresponding activated electrophiles **383**, setting the stage for the third vinylogous aldol coupling. In the event, each individual component of general formula **383** reacted, under TBSOTf catalysis, with 2-silyloxyfuran **257**, eventually producing a collection of isosterically and stereochemically diverse trinuclear adducts **384**, the core units of natural annonaceous acetogenins and analogues thereof.

In a recent paper[198] focused on the concise, stereocontrolled total synthesis of an annonacin A-type acetogenin, Hanessian and Grillo exploited the vinylogous aldol chemistry as the key constructive maneuver to forge the hydroxylated tetrahydrofuran core of the target biomolecule (Scheme 91). Once again, according to the chiron approach, the Lewis acid-promoted Mukaiyama aldolization involving dienoxy silane **136** and L-glutamic acid-derived tetrahydrofuran **385** proceeded in a vinylogous sense, giving rise to an almost equimolar mixture of separable *threo,trans* and *erythro,trans* epimers **386**.[196c] Hydrogenation of the carbon−carbon double bond within **386** and stereochemical adjustment of the *threo,trans* component into the required *erythro,trans* isomer provided the chiral nonracemic $C_{12}-C_{20}$ het-

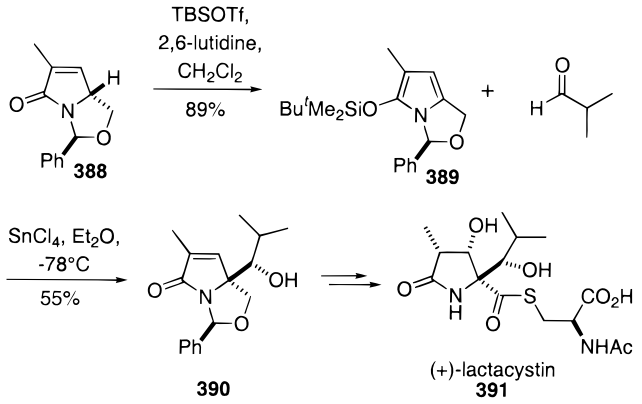
Scheme 90



Scheme 91



Scheme 92



erocyclic core portion with which monotetrahydrofuranic annonaceous acetogenin **387** was conveniently implemented.

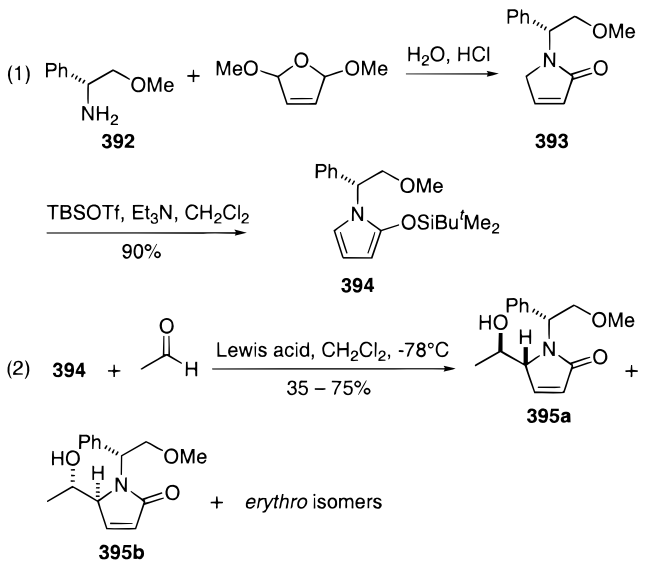
C. Additions of Chiral Enoxy Silanes to Carbonyl and Carbonyl-Related Electrophiles

Sporadic examples of vinylogous aldol or Mannich-type additions between intrinsically chiral or auxiliary-chiralized silyl dienolates and achiral eletrophiles have been reported, and only a few applications culminated in total synthesis of relevant constructs. The most salient contribution dealt with the synthesis of (+)-lactacystin,[199] a microbial product showing selective and irreversible inhibition of proteasome-mediated peptidase activity.[200] The route Baldwin planned to access this molecule features a vinylogous aldol reaction between (*R*)-glutamate-derived chiral nonracemic α,γ-disubstituted silyloxy pyrrole **389** and isobutyraldehyde to construct the quaternary carbon center of the target (Scheme 92). Thus, γ-enolization of lactam **388** and subsequent silylation led to diene **389**, where the original pyroglutamate chirality was lost. Since the chirality was transferred to the nitrogen substituent in advance, vinylogous aldolization of **389** with isobutyraldehyde occurred diastereo- and enantioselectively, producing **390** in a reasonable yield. A multistep sequence comprising proper installation of the methyl and hydroxyl substituents within the pyrrolidinone ring, removal of the auxiliary, oxidation to a carboxylic acid, and coupling to cysteine ultimately completed the synthesis.

Starting from *O*-protected (*R*)-(−)-phenylglycinol **392**, chiral silyloxypyrrole **394** was prepared by Royer[201] (Scheme 93, eq 1), and its reaction with achiral aldehyde acceptors under Mukaiyama conditions was thoroughly investigated. The reaction of **394** with acetaldehyde in the presence of various Lewis acid promoters was first studied (eq 2), and this reaction was then extended to a variety of saturated and α,β-unsaturated carbonyl compounds. In any case, a high margin of simple diastereoselection was observed, favoring a *threo* arrangement of the two newly generated stereogenic centers (e.g., **395a** and **395b**). The facial stereoselection was, instead, lower due to a mediocre induction of the auxiliary appendage.

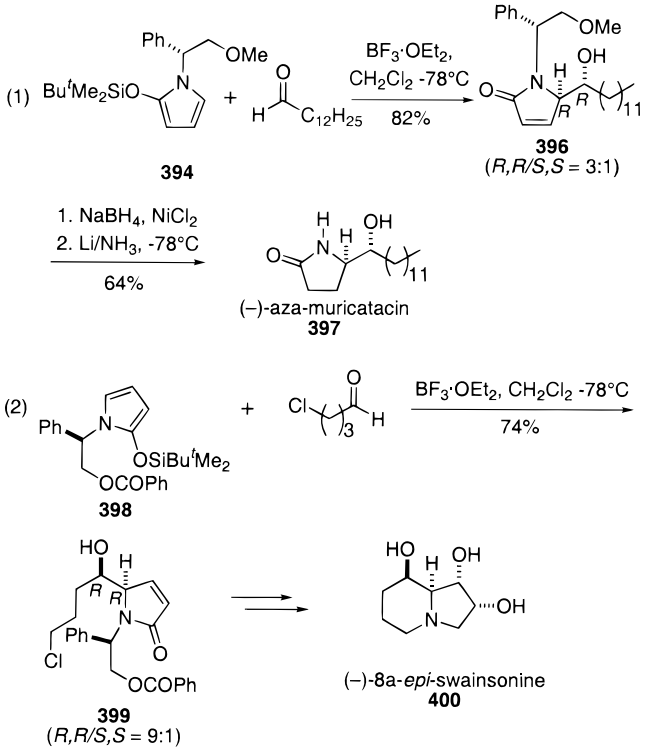
As an application, the same author adapted this strategic move to access aza-muricatacin (**397**)[202] (Scheme 94, eq 1), an analogue of the naturally occurring muricatacin, and hydroxylated indolizidine compound **400**[203] of the swainsonine family (eq 2). In both instances, the key vinylogous aldol adducts (e.g., **396** and **399**) were obtained with excellent *threo* preference and acceptable-to-good induced diastereoselection.

Scheme 93



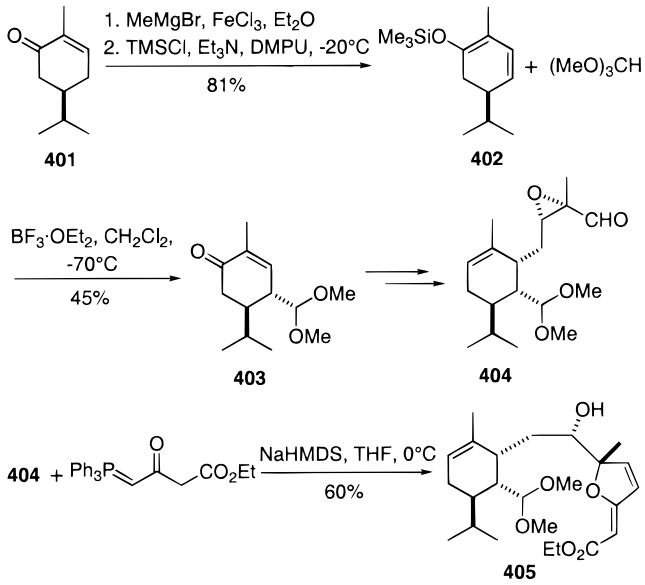
L.A.	395a/395b	*threo/erythro*
$TiCl_4$	74:18	92:8
$SnCl_4$	66:27	93:7
$BF_3{\cdot}OEt_2$	53:31	84:16

Scheme 94



A very close technique has been independently utilized by Poli,[204] moving from analogous chiralized silyloxy pyrrole nucleophiles. This researcher investigated their reactivity toward achiral and chiral acetal systems and rationalized the stereochemical behavior of the vinylogous aldolization process based on proper predictive models. In an interesting approach to the synthesis of sarcodictyns and eleutherobin, potent cytotoxic agents against a variety of tumor cell lines, Gennari[205] adopted, as the opening reaction, a vinylogous aldolization between (−)-carvone-derived chiral dienoxy silane **402** and methyl orthoformate, leading to *trans*-configured aldehyde acetal **403** (Scheme 95).

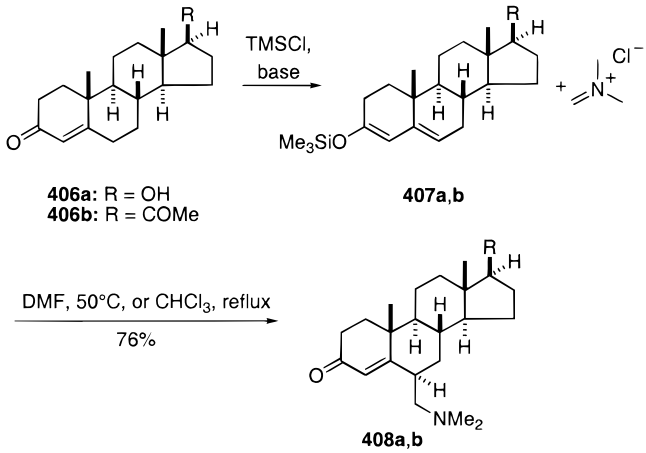
Scheme 95



During the multistep sequence, **403** was then elaborated to epoxy aldehyde **404**, an advanced intermediate on which the furanic moiety corresponding to the C ring of the target sarcodictyin and eleutherobin natural constructs was implemented.

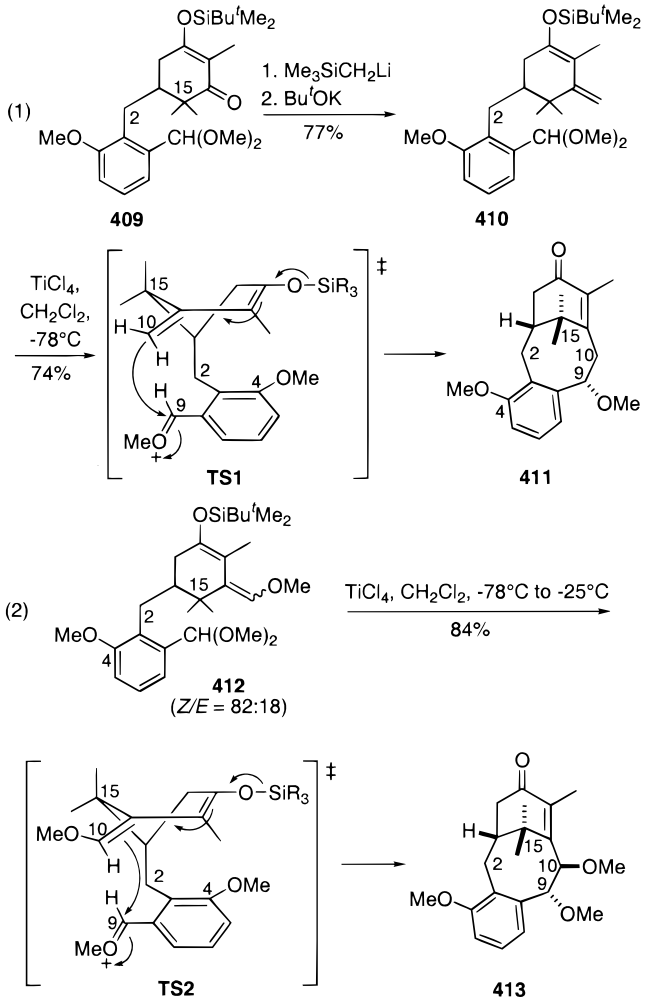
Site-specific vinylogous Mannich reactions have been independently applied in the steroid series by Danishefsky[206] and Caputo,[207] as an entry to γ-aminomethyl derivatives of type **408a** or **408b** (Scheme 96).

Scheme 96



Under the usual conditions, the enolization/silylation sequence regioselectively occurred at the γ-carbon of the enone portion of steroids **406a** and **406b**, giving rise to dienoxy silanes **407a**,**b**. Subsequent coupling of **407a**,**b** to formaldehyde *N*,*N*-dimethyliminium chloride occurred in a vinylogous sense, producing the expected Mannich adducts **408a**,**b** in a satisfactory yield and excellent margin of diastereocontrol.

Scheme 97



D. Additions of Chiral Enoxy Silanes to Chiral Carbonyl and Carbonyl-Related Electrophiles (Intramolecular Processes)

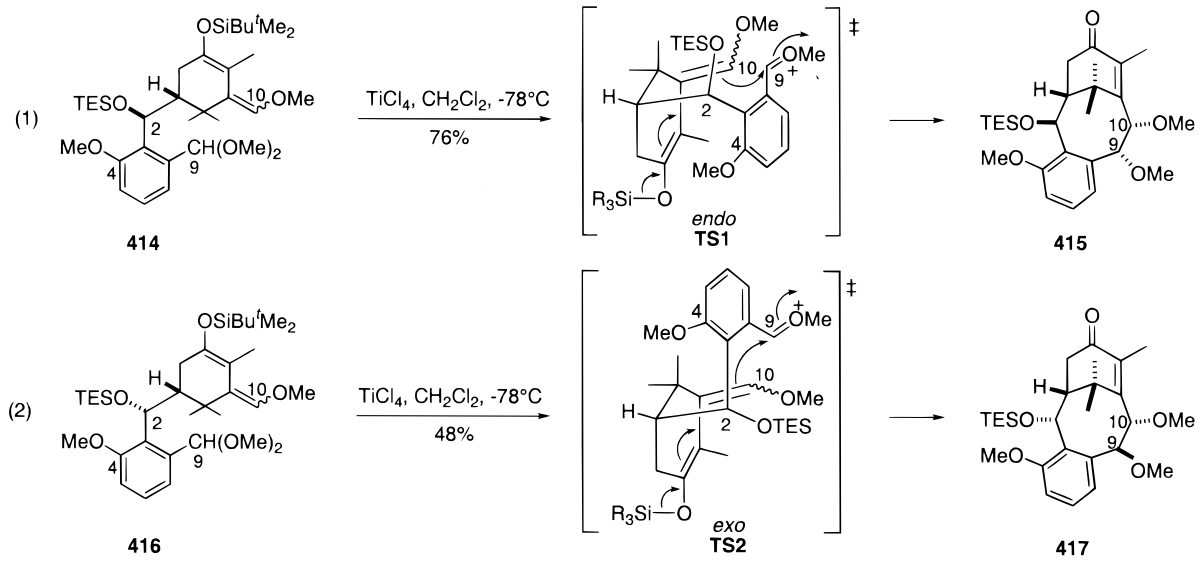
To our knowledge, no intermolecular aldol processes involving chiral dienoxy silanes and chiral electrophiles appeared in the literature until July 1999, although a vast repertoire of intramolecular variants of this chemistry is documented. In these intramolecular ring-forming processes, the two reaction components, that is the silyloxy diene donor and the carbonyl-related acceptor, are embodied in the same scaffold, so that all the chiral information within the molecule can govern the stereochemical outcome of the carbon−carbon bond formation between the donor and the acceptor sites. Excellent achievements in this field sprang from the work of the Kuwajima group,[73,208−215] interested in the use of intramolecular vinylogous Mukaiyama aldol reaction for the synthesis of taxane-related medium-sized ring systems. The viability of the strategy has been ascertained in model systems involving dienoxy silane and acetal frames.[73,208−212] Illustrative examples of this preparatory work are grouped in Schemes 97 and 98. The first reaction (Scheme 97, eq 1) deals with $TiCl_4$-mediated intramolecular vinylogous aldolization involving γ-unsubstituted dienoxy silane **410** derived from α,β-unsaturated ketone **409** via Peterson olefination. The aldol process proved to be highly diastereoselective, producing eight-membered ring compound **411** with an *endo*-9α configuration. A transition state **TS1** can explain the *endo* preference during the intramolecular carbon−carbon bond-forming reaction, as well as the stereocontrol at C9.

When a γ-substituted dienoxy silane moiety such as **412** is involved (eq 2), the two newly formed stereocenters at C9 and C10 preferentially emerge in a *trans*-relationship, likely due to thermodynamic control. Here, a transition state **TS2** was postulated to account for the *endo*-9α,10β arrangement in the cyclized adduct **413**. In contrast to the strong *endo* preference observed in the previously disclosed cyclizations of 2-unsubstituted substrates **410** and **412**, it was found that the *endo* vs *exo* conformation of the cyclization product critically depends on the stereochemistry of the 2-substituent (Scheme 98). While a 2β-configured structure **414** (eq 1) exclusively formed the *endo* cyclization product **415** with a 9α-substituent, 2α-isomer **416** (eq 2) afforded the *exo* cyclization product **417** preferentially (2:1 *exo*/*endo* ratio) with a 9β-methoxy substituent. Transition states **TS1** and **TS2** have been proposed for these cyclizations to shed light into the observed annulation behavior. The remarkable directing effect of the C2-silyloxy group is probably due to steric and/or electrostatic repulsion between the silyl group and the C4 methoxy substituent. Furthermore, an electrostatic attraction between the C2 moiety and the intermediate oxonium ion species may act in a cooperative fashion.

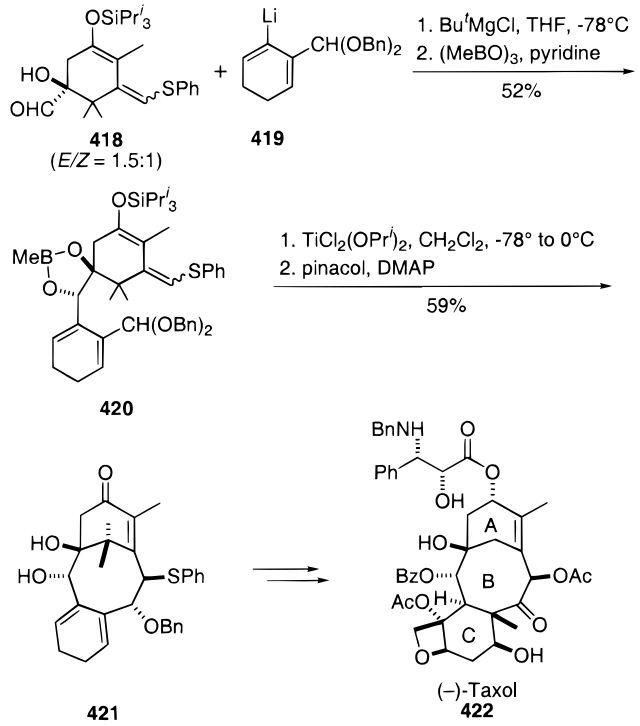
Having thus demonstrated the reliability of the intramolecular vinylogous Mukaiyama-aldol reaction with a variety of model systems, the Kuwajima group took on the more demanding task of applying this strategic technique to the synthesis of important taxane diterpenes, such as Taxol (**422**),[213] as well as racemic[214] and enantiopure taxusin (**427**).[215] The overall synthetic strategy to Taxol (**422**) started with a preformed dienoxy silane aldehyde **418** (Scheme 99) bearing a stereogenic quaternary carbon atom, whose absolute configuration corresponds to that of C1 within the Taxol target. During the crucial move, the cyclooctanoid B-ring was formed via a vinylogous Mukaiyama aldol reaction involving the appendages belonging to the A and C rings. Thus, reaction of aldehyde **418** with the C-ring fragment **419**, under chelation control [Mg(II) ion], gave the corresponding coupling product with complete stereocontrol in the desired manner. Protection of the vicinal diol as a boronate then provided the cyclization precursor **420**, on which the crucial B-ring implementation was performed. Among the several Lewis acids examined, $TiCl_2(OPr^i)_2$ proved to be the most efficient one to induce the intramolecular vinylogous aldolization. Subsequent removal of boronate thus produced the corresponding 9α,10β-disubstituted tricarbocycle **421**, embodying the A,B,C-ring structure of Taxol (**422**).

To approach (+)-taxusin (**427**) in an enantioselective manner, the strategy utilized chiral nonracemic enone precursor **423** incorporating the A and C rings of the target (Scheme 100). Treatment of **423** with Bu^{t}OK then generated the thermodynamically fa-

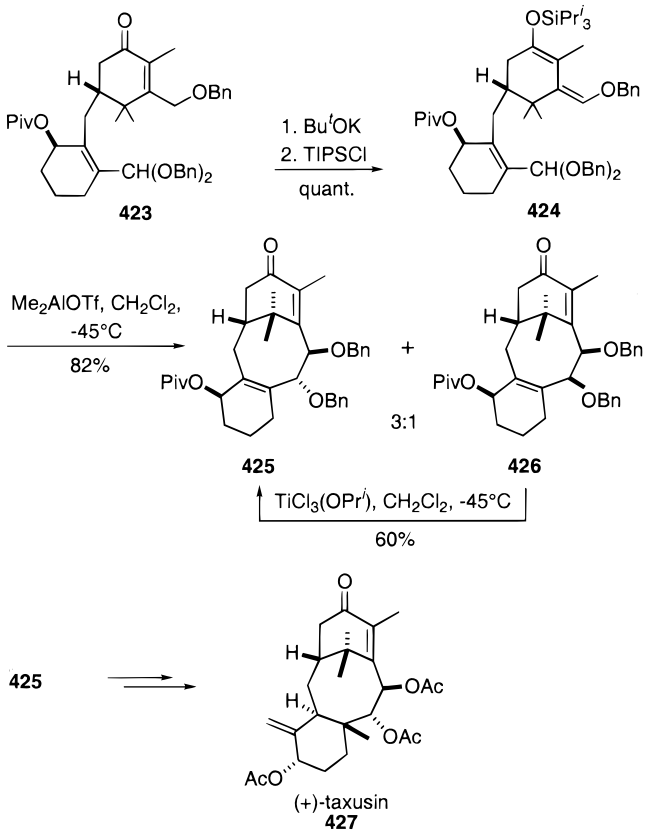
Scheme 98



Scheme 99



Scheme 100



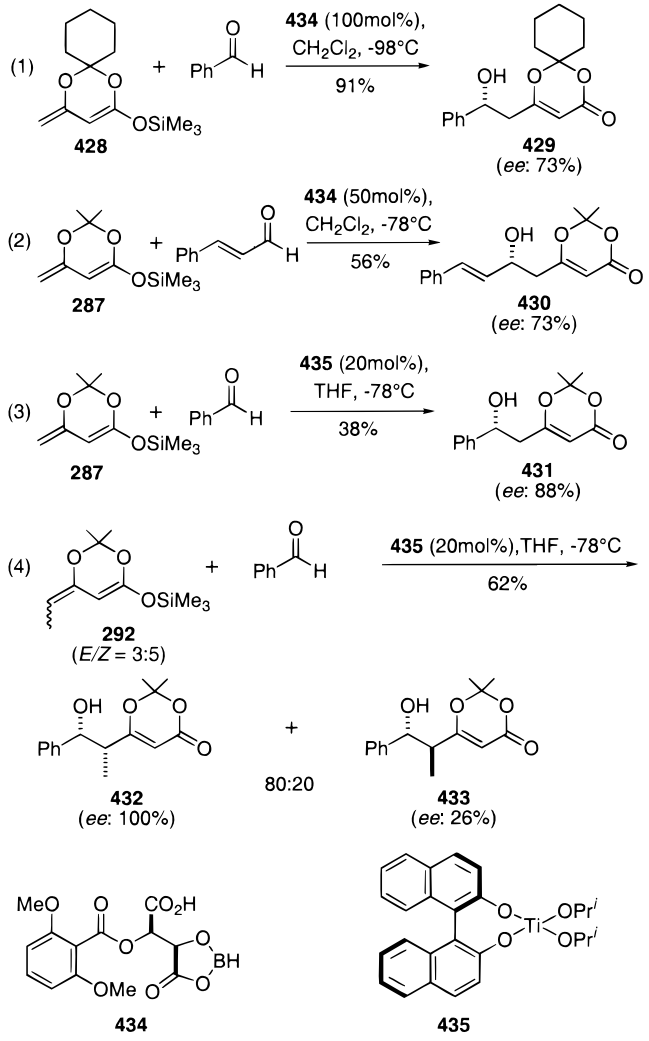
vored dienolate, via γ-deprotonation, on which subsequent silylation afforded dienoxy silane **424** as a single *Z* isomer. The crucial eight-membered B-ring formation (vinylogous Mukaiyama-aldol reaction) was optimized employing various Lewis acids, among which Me_2AlOTf was found to be the best choice. Under these conditions, the aldolization proceeded nicely, giving rise to *endo*-9α,10β tricyclic cyclooctanoid **425** (62%) along with a minor amount of its stereoisomer **426** (*exo*-9β,10β). Compound **425** was assumed to be the thermodynamically most favored isomer; hence, exposure of the less favored epimer **426** to a proper Lewis acid [$TiCl_3(OPr^i)$] isomerized this byproduct into the desired compound **425**. Exploiting the basic tricarbocyclic scaffold **425**, (+)-taxusin (**427**) was then cleverly synthesized.

E. Catalytic Enantioselective Versions

Enantioselection in Lewis acid-catalyzed aldol additions is one of the most salient issues of the organic synthesis repertoire. The use of chiral nonracemic catalysts in these and related reactions undoubtedly constitutes a prime resource with which large quantities of chiral nonracemic compounds can hopefully be prepared by employing only a limited amount of chiral sources.[216] The vinylogous Mukaiyama aldolization can be adapted to a catalytic, enantioselective execution, remarkably extending its synthetic scope.[170] The first attempts to control a vinylogous

crossed addition between achiral (prochiral or not) dienoxy silanes and achiral prochiral aldehydes through the use of chiral Lewis acids (catalysts or stoichiometric promoters) were made by Sato et al. in 1994−1995.[217,218] Representative reactions with ketene acetals **428**, **287**, and **292** are collected in Scheme 101. Among several chiral borane catalysts,

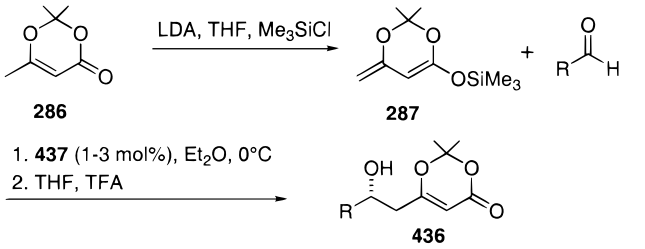
Scheme 101



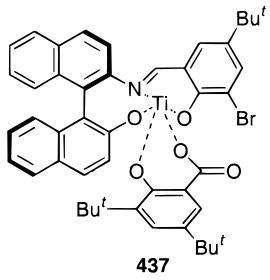
tartaric acid-derived acyl borane **434** gave the best results with aromatic, aliphatic (not shown), and α,β-unsaturated aldehydes (eqs 1 and 2). There, the corresponding vinylogous aldol products formed in high yields and satisfactory enantiomeric excesses. Disappointingly, a low turnover number was experienced by this borane catalyst and at least a 50% molar loading was required. Substantial improvement was subsequently done by the same author[218] by employing Ti(IV)-based binaphthol **435**, with which a 20 mol % catalyst loading was requested to reach good enantioselection (eqs 3 and 4). Noteworthy, when prochiral silyl ketene acetal **292** was employed under Ti(IV)-BINOL catalysis in a reaction with benzaldehyde (eq 4), good margins of both simple and induced stereoselection were reached, with the syn isomer **432** being preferentially obtained.

During a study carried out independently from the above Sato work, Carreira and Singer[219] developed an extremely efficient Ti(IV)−salicylidene binaphthyl catalyst, **437**, for the asymmetric aldol addition of silyl dienolate **287**—directly obtained by deprotonation/silylation of commercially available dioxinone **286**—with a number of saturated and unsaturated aldehydes (Scheme 102). After surveying a number

Scheme 102



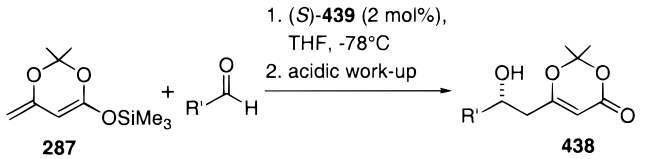
aldehyde	yield (%)	*ee* (%)
Pr^i_3Si—≡—CHO	86	91
Ph—CHO	88	92
—CHO	95	92
PhCHO	83	84
Ph—CHO	97	80

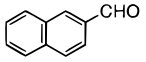
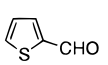
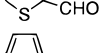
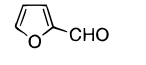
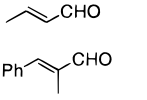


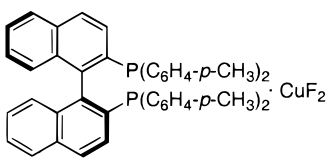
of acetoacetate derivatives, the authors showed that the use of isopropylidene-blocked dienolate **287** is optimal and, when applied in conjunction with chiral salicylidene/Ti(IV) complex **437**, produced varied protected δ-hydroxy acetoacetate adducts **436** in high yields and very good extent of asymmetric induction. Remarkably, dioxinones of type **436** proved to be flexible chiral synthons to be used in a variety of synthetic transformations.[220]

In more recent studies, an even more potent binaphthyl-based system was developed by Carreira[221] to catalyze the vinylogous aldolization process of acetoacetate synthon **287** with aldehyde derivatives. The most salient results are grouped in Scheme 103,

Scheme 103

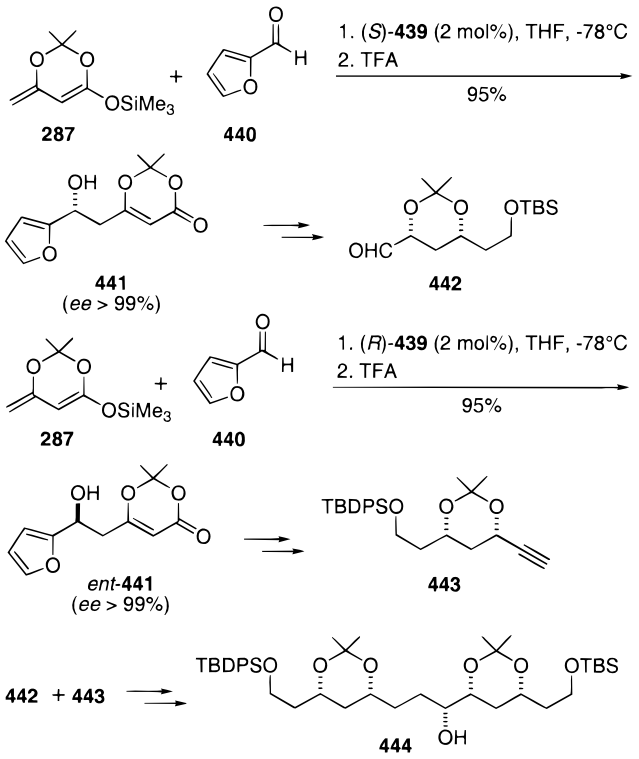


aldehyde	yield (%)	*ee* (%)
PhCHO	92	94
	86	93
	98	95
	91	94
	48	91
	74	65



(*S*)-(−)-tol-BINAP·CuF_2
(*S*)-**439**

Scheme 104

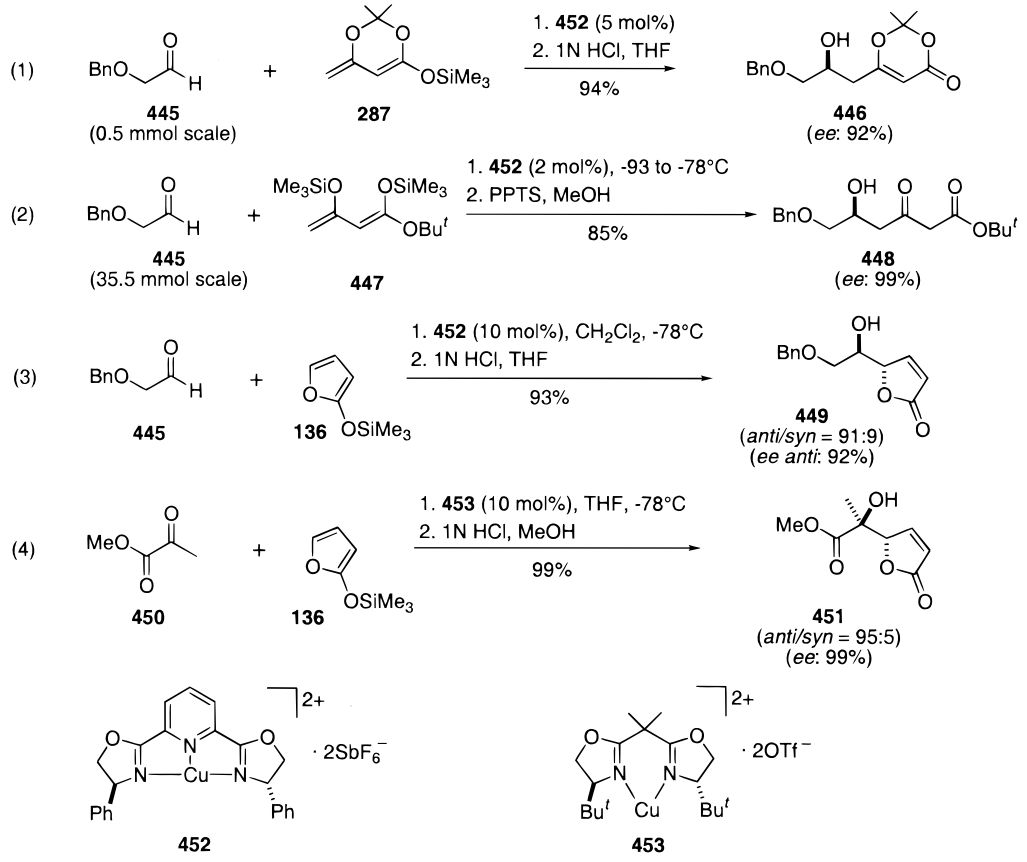


showing reactions with aromatic, heteroaromatic, and α,β-unsaturated aldehydes. The catalyst, the bisphosphoranyl−Cu(II) fluoride complex (*S*)-**439**, is readily available from commercial sources and has demonstrated its utility in providing a wide variety of chiral nonracemic adducts **438** in excellent yields and useful levels of enantioselectivity.

This latter chiral catalyst (*S*)-**439** along with its (*R*)-(+)-tol-BINAP·CuF_2 enantiomer, (*R*)-**439**, admirably served to forge two complementary fragments, i.e., **442** and **443**, in a convergent synthesis of the amphotericin polyol C_1-C_{13} subunit, **444** (Scheme 104).[222] Both processes, leading to **442** and **443**, started with an enantioselective vinylogous cross aldolization between dienoxy silane **287** and furfural (**440**), giving rise to adducts **441** and *ent*-**441** according to the chirality of the employed catalyst. Only slightly different chemistry then allowed elaboration of the enantiomeric couple **441**/*ent*-**441** into advanced intermediates **442** and **443**. The completion of the C_1-C_{13} polyol chain **444** was then effected by conjoining the two complementary fragments.[223]

During a thorough investigation on the scope and mechanism of the catalytic enantioselective aldol additions of enol silanes to benzyloxy acetaldehyde[224] and pyruvate esters,[225] Evans and colleagues introduced C_2-symmetric copper(II) complexes as chiral Lewis acid catalysts. As part of this study, it was found that acyclic and heterocyclic dienoxy silanes could be exploited in enantioselective vinylogous Mukaiyama aldol additions to the same carbonyl acceptors. As portrayed in Scheme 105, under optimal conditions, tridentate bis(oxazolinyl)pyridine−Cu(II) complex **452** or bidentate bis(oxazolinyl) analogue **453** served to catalyze the asymmetric vinylogous coupling of acetoacetate-derived silyl ketene acetals **287** and **447** as well as furan-based silyloxy diene **136** to benzyloxy acetaldehyde (**445**) (eqs 1−3)

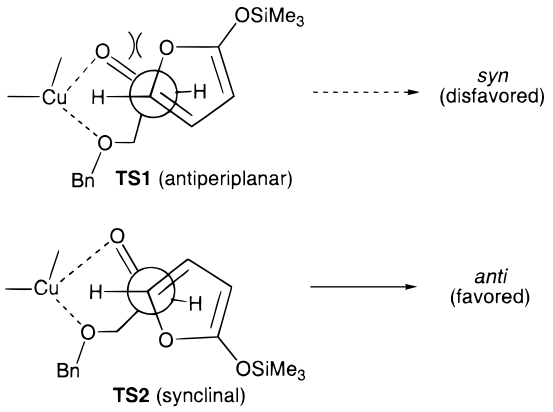
Scheme 105



or pyruvate ester **450** (eq 4). Invariably, the expected aldols **446**, **448**, **449**, and **451** were formed in high yields and excellent ee's.

It should be pointed out that when silyloxyfuran **136** was employed (eqs 3 and 4), the relative *erythro* stereochemistry of the two newly created centers within the formed aldol adducts (**449** and **451**) was reverted vis-à-vis the usual *threo* stereochemical outcome for similar reactions promoted by achiral Lewis acids (vide supra). Here, the *erythro* diastereoselectivity observed in the aldol addition of **136** to **445** (or **450**) may be rationalized through the inspection of each of the acyclic transition states **TS1** and **TS2**, shown in Scheme 106. Synclinal transition

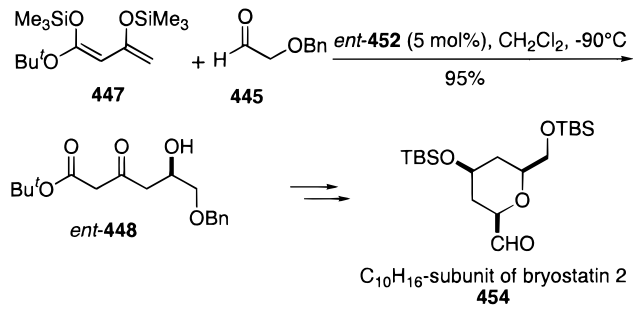
Scheme 106



state **TS2** seems to be favored with respect to the antiperiplanar transition state **TS1** due to the electrostatic repulsion between the two aldehyde and furan oxygens.

This exciting chemistry was nicely adopted by the same author[177] to implement the $C_{10}-C_{16}$ subunit of bryostatin 2, a complex macrolide first isolated in 1968 from the bryozoan *Bugula neritina*. As a key step along this venture, the copper-catalyzed asymmetric vinylogous aldolization between **445** and **447** was employed, producing the six-carbon acetoacetate *ent*-**448** with an excellent level of enantio- and diastereoselection (Scheme 107). It should be noted

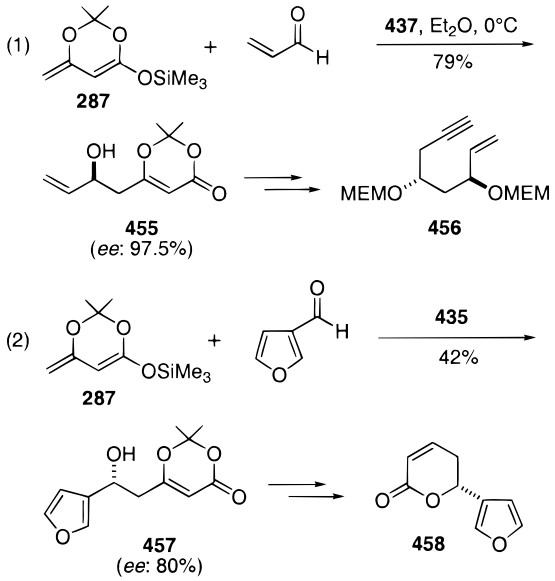
Scheme 107



that in the course of the study, a second diastereoselective vinylogous aldol reaction was utilized to complete the construction of the C_1-C_9 subunit of the same target.

The catalytic enantioselective vinylogous aldol reactions of *O*-TMS dienolate **287** with acrolein (Scheme 108, eq 1) and 3-furyl aldehyde (eq 2) were adopted by Vandewalle[226] and Scettri,[227] respectively,

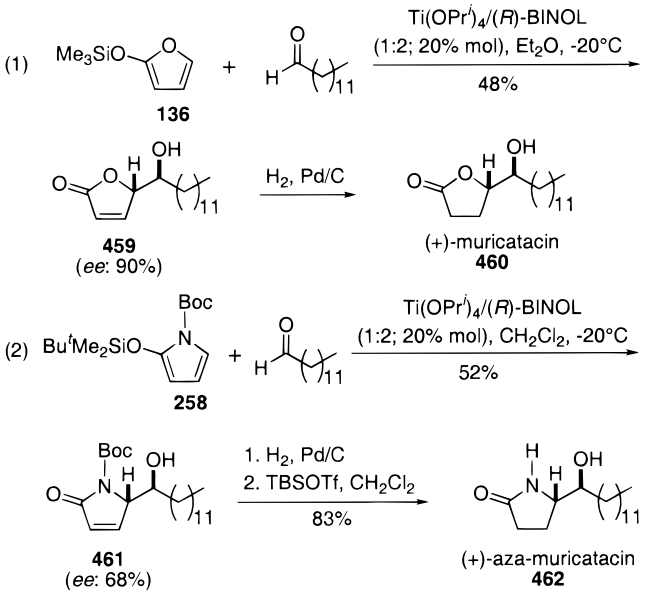
Scheme 108



to access certain fragments of natural constructs (e.g., **456** and **458**). Both approaches exploited the potentiality of chiral binaphthol-based titanium complexes **437** and **435** to direct the vinylogous coupling enantioselectively, with aldol products **455** and **457** being obtained in moderate-to-good yields and good-to-excellent ee's.

Chiral (*R*)-BINOL$_2$Ti complex was used by Figadère[228,229] to enter naturally occurring (+)-muricatacin (**460**) and synthetic (+)-aza-muricatacin (**462**). As depicted in Scheme 109, the key moves of both

Scheme 109



syntheses were the enantioselective vinylogous aldolizations between furan-based or pyrrole-based 2-silyloxy dienes **136** or **258** and tridecanal. Irrespective of the nature of the d^4-nucleophile, both processes displayed high levels of regio-, diastereo-, and enantioselectivity, affording the respective γ-homologated (4*S*,5*S*)-*syn*-adducts **459** and **461** in about 50% yield and 68−90% ee's. Subsequent saturation of the

double bond within **459** and **461** and deprotection (for **461**) finally completed the syntheses.

VII. Closing Remarks

The vinylogous aldol reaction provides access to a range of structurally diverse targets but has long remained a marginally explored area of organic synthesis. In the past few years, however, its applications have burgeoned, especially in the silyloxy diene version, earning the reaction a secure place in the repertoire of organic chemists. The examples we have provided show that vinylogous dienolates and their synthons have a sumptuos aldol chemistry, which nature has deftly exploited in a variety of structurally complex molecular environments. Recent exciting and unexpected developments in chemo-, diastereo-, and enantiocontrol like those achieved by Yamamoto, Evans, Carreira, and Kuwajima will undoubtedly focus the attention of the future generations of synthetic chemists on the still largely untapped potential of this reaction.

The achievements of synthetic organic chemistry during the 20th century were nothing short of spectacular. However, as the age of molecular sciences and genomics dawns, organic synthesis is faced with unprecedented challenges in terms of efficiency and throughput in the generation of diversity. Vinylogy, namely, the cross-talk of functional groups through a π-system, could undoubtedly contribute to meet these challenges, providing, as the aldol reaction cogently demonstrates, new fundamentals for the design of reactions efficient in terms of control, atom economy, and versatility.

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