JOC The Journal of Organic Chemistry

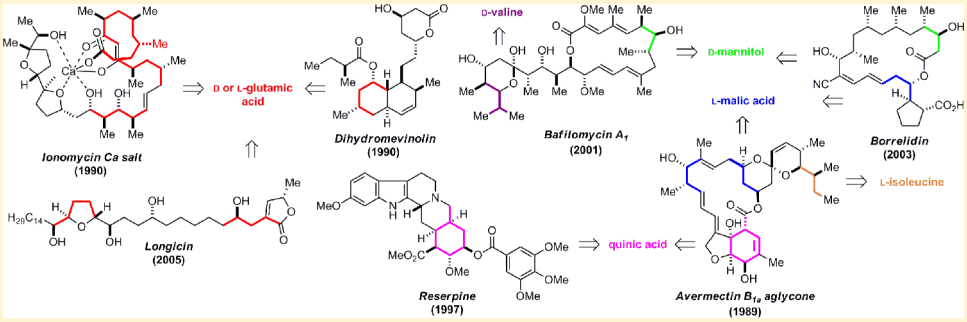
Perspective

pubs.acs.org/joc

The Enterprise of Synthesis: From Concept to Practice

Stephen Hanessian*

Department of Chemistry, Université de Montréal, C.P. 6128, Succursale Centre-Ville Montréal, Québec H3C 3J7, Canada



ABSTRACT: A retrospective account of natural products synthesis adopting the *Chi*ral Synth*on* (Chiron) Approach and spanning nearly 50 years of personal research activity is presented highlighting the interplay between the eye and the mind's eye. Synthesis planning is discussed in terms of *visual relational* and *visual reflexive* thinking modalities relying on the recognition of naturally occurring nonracemic starting materials such as amino acids, carbohydrates, hydroxy acids, and terpenes in the carbon framework of target molecules. Lessons learned and synthetic methods developed are discussed in the context of selected natural products covered in this Perspective.

INTRODUCTION

I was asked to write a Perspective article on the occasion of the ACS 2012 Ernest Guenther Award in Natural Products Chemistry. I am honored to have been the recipient of this prestigious award, and I salute the many highly deserving nominees whose seminal contributions will no doubt be recognized in the context of natural products chemistry in the years to come. In spite of a career starting as an industrial research chemist for seven years, and continuing as a still-active academic 45 years later, I remain an ardent student of our profession. I am motivated by the exhilaration of discovery and the creative possibilities that organic synthesis offers.

With merely a decade into the third millennium, the present-day level of achievements in organic synthesis in general, and natural products in particular, is the highest ever compared to as recently as a generation ago.[1] Building on the monumental discoveries and the fundamentally important concepts that have been the foundations of the discipline of organic chemistry over the last century, we are in an unprecedented period of evolution in the science of chemical synthesis. Aided by powerful instrumental techniques and ingenious methods for stereocontrolled and site-selective bond forming reactions, the enabling aspect of organic synthesis has manifested itself in many areas that contribute directly to the well-being of humankind. Consider, among others, the impact of life-sustaining drugs derived from purely synthetic efforts on the one hand and natural products on the other. In this context, we are in a position as synthetic chemists to engage in exciting research projects that aim at solving important unmet medical needs especially in conjunction with great advances in the biological sciences.[2]

My move to academia after seven years in the pharmaceutical industry allowed me to pursue projects where practicality and innovation could be combined to the best of my ability. Besides the purely academic projects involving organic synthesis and methodology, I was privileged to come in contact with many pharmaceutical and agrochemical research laboratories worldwide with whom I have had very productive and long-lasting collaborations especially with regard to having compounds synthesized in my own laboratories tested.[3] In the following pages, I provide a retrospective of a selection of projects focusing primarily on natural product synthesis, which I present in a chronological order starting in 1966 when I was a bench chemist.

THE CONCEPT OF SYNTHESIS

As synthetic chemists, our vocation is to "make molecules" either from basic components or by chemical modification of existing ones. Once such an objective is defined, the synthetic chemist invariably begins by asking the following three questions: (1) How can I synthesize my molecule efficiently? (2) How can I make sure that I have come up with a viable strategy? and (3) How and where do I begin? Added to these questions is a long list of "wishes", not the least of which is the desire to innovate, to be competitive, and to contribute to co-worker training, thus rendering service to humankind through chemistry.

Faced with a challenging target molecule to synthesize, our first contact is visual. What follows, once the adrenaline rush caused by its structural complexity has subsided, is a subliminal interplay between the eye and the mind's eye, triggering a complex yet quasi-instantaneous series of *visual relational* and *visual reflexive* chemical and mental thought-processing events that are a part of

Received: May 3, 2012
Published: July 11, 2012

   dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

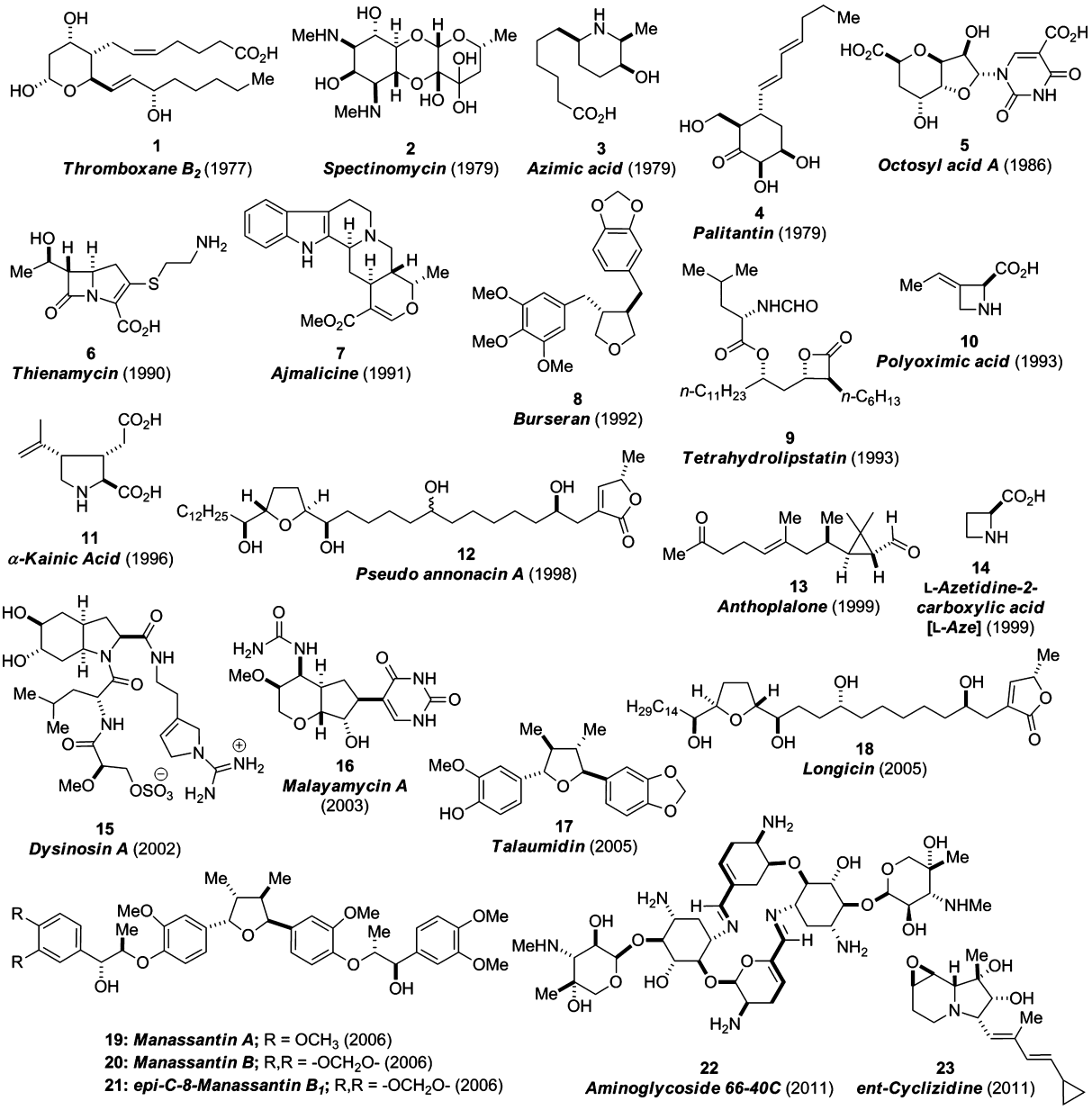


Figure 1. Selected syntheses of natural products using the *chiron approach* (1977–2011).

the psychobiological basis of generating a synthesis plan.[1a,4] This heuristic aspect of design and strategy that starts with a visual dialogue between the molecule and the mind's eye is a fundamentally human and personalized tenet of synthesis. It demonstrates the strength (and limitations) of our powers of perception and creativity when planning a synthetic strategy.

The *visual relational* thought process is the basis of the *chiron approach*,[1a,4,5] where segments of a target molecule can be related in shape, structure, and stereochemistry to native *chiral* synth*ons* (chirons) derived from small natural compounds such as amino acids, carbohydrates, hydroxy acids, terpenes, and some lactones. The *chiron approach* has an aesthetic appeal and offers a high level of predictability. The *visual reflexive* thought process involves the stereocontrolled formation of one or more bonds pertaining to a substructure of the intended molecule relying on asymmetric processes whereby racemic or achiral entities may be engaged in asymmetric bond-forming steps using chiral auxiliaries or chiral catalysts originally derived from native chirons. This strategy is generally applicable in cases where one or two stereogenic centers are generated per reaction. Many innovations have been introduced in asymmetric reactions, especially involving catalytic variants in recent years.[6] Whereas the *chiron approach* has the attributes of predictive power and general utility in total synthesis, the *asymmetric synthesis* approach offers intellectual stimulation and practical advantages in many cases especially through ligand design in catalytic systems. Although the two approaches are philosophically different, they share the same objective of synthesizing segments of a given target molecule with a high level of stereochemical purity. Whenever applicable, chirons can also be the starting points as substrates for catalytic reactions en route to more elaborate intermediates, provided that the resident inherent chirality reinforces the stereodifferentiating event. Thus, the combined perceptive and knowledge-based thinking modalities when planning the synthesis of a molecule related to a natural product in particular, or a molecule of general interest, allows for a great deal of innovation and ingenuity.

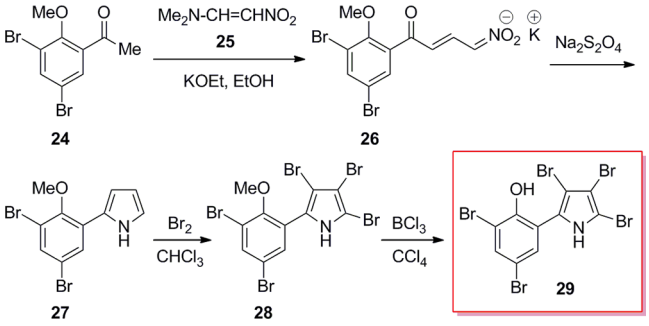
dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

A very large number of natural products of diverse complexities have been synthesized adopting the *chiron approach* in conjunction with other strategies.[1a] Structures of selected natural products synthesized in my laboratory over the years are shown in Figure 1.[7] Others will be discussed in more detail in this Perspective with an emphasis on the use of the *chiron approach* while delineating the incentives, challenges, and most of all, lessons learned.

A BROMINE-RICH MARINE ANTIBIOTIC

My first experience with total synthesis occurred while I was employed as a Ph.D. chemist at the Parke-Davis Research Laboratories in Ann Arbor, MI. I was contacted by scientists in the microbiology department who, in turn, had received a small amount of a substance isolated from a marine bacterium by Dr. P. R. Burkholder. After exhausting most of the material while conducting biological testing and performing routine analytical studies, I was given less than 2 mg of material for which a preliminary structure had been assigned by X-ray crystallography (Scheme 1).[8] The mass spectrum suggested a molecular weight

Scheme 1. Total Synthesis of a Bromine-Rich Marine Antibiotic



of 553.5 amu and the presence of five bromine atoms, corresponding to 70% of the weight! At the time, the presence of so much bromine had cast some uncertainty about the definitive structure by X-ray analysis. The only way to validate the proposed structure was by a total synthesis. In collaboration with another colleague, Dr. J. S. Kaltenbronn, we embarked on a short synthesis that led to a product that was identical to the natural material, showing a rare example where synthesis confirmed the proposed structure by X-ray.[9]

AVERMECTIN B_{1A}

In considering various synthetic approaches toward the potent anthelmintic natural product avermectin B_{1a} (**30**),[10] it was very appealing to adopt a strategy in which several chirons derived from Nature could be used as starting materials.[11] As shown in Figure 2, L-isoleucine, two molecules of L-malic acid, the dioxaspiroacetal **34**, and an oxahydrindene (**35**) obtained by controlled ozonolysis of avermectin B_{1a} (or by semisynthesis from quinic acid (**36**)) were used to assemble the aglycone in conjunction with other subunits (Figure 2). Critical olefinic linkages were introduced through Julia (olefination) coupling reactions (see disconnections in Figure 2). In particular, coupling of **37** with **38** eventually gave **39**, which was transformed to the macrolactone **40** (Scheme 2). Glycoside formation by a method developed in our laboratory[12] using an anomeric 2-thiopyridyl donor such as **41** led to **42**, which was deprotected to give avermectin B_{1a} (**30**). Soon after the publication of this work,[11] it became evident that as a result of subsequent studies in our

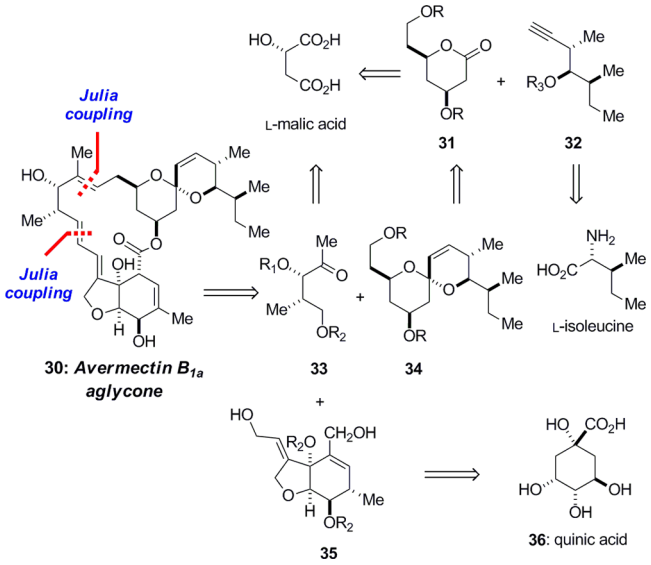


Figure 2. Disconnections of avermectin B_{1a} aglycone to L-isoleucine, L-malic acid, and quinic acid as chirons.

laboratory and elsewhere[13] the major product initially obtained was in fact the 2-*epi*-isomer **43** (Scheme 3).

To rectify this discrepancy, we hypothesized that treatment of the 2-*epi* intermediate **43**, with imidazole as a mild base and proton source, could establish an equilibrium in which the natural deconjugated olefin corresponding to the *O*-TBS avermectin B_{1a} derivative (**46**) could be obtained.[14] Indeed, refluxing a solution of the **43** (R = TBS) in benzene, containing excess imidazole, provided a mixture of the starting **43** and the desired natural isomer **46** presumably by a relay proton transfer mechanism involving the hemiketene acetal **45**.

The discrepancy regarding the identity of the synthetic product could have been resolved in a collegial manner through personal communication rather than in print.[13a] Nevertheless, such episodes are incentives toward creative solutions, as was found with the use of imidazole as a mild base and proton source.

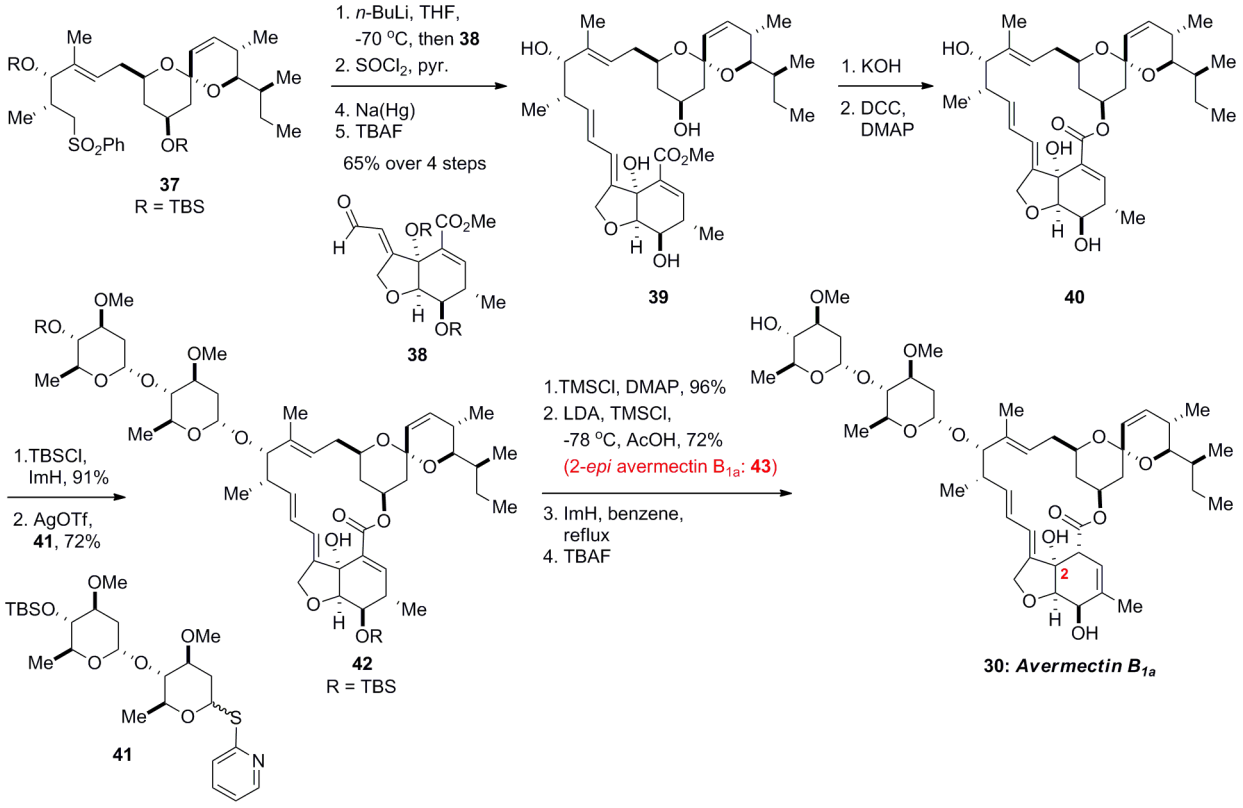
Our interest in the avermectins led us to prepare a bis-homoavermectin B_{1a} analogue (**47**) and 19-*epi*-avermectin A_{1a} (**48**)[15] in which the hydroxyl group at C_{19} was inverted,[16] as well as through controlled cleavage of the C_{11}–C_{12} double bond and insertion of an olefinic appendage, affording a ring-expanded version harboring a *trans*-diene. Unfortunately, neither analogue showed any anthelmintic activity (Figure 3).

IONOMYCIN

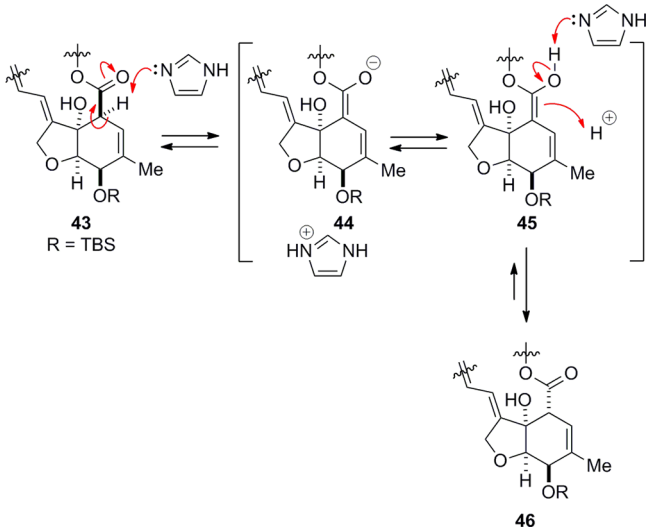
Our second foray into complex molecule synthesis involved the ionophore ionomycin.[17] The incentive for this synthesis came from our studies in the construction of polypropionate subunits by an iterative process, which will be discussed below. A cursory look at the structure of ionomycin Ca salt (**49**) presents the daunting task of analyzing stereochemical relationships between the many stereogenic centers (Figure 4). Not until one is presented with the "stretched out" perspective drawing of the free acid (**50**) does one realize that the challenge resides in developing methods for generating deoxyproprionate and propionate triads of specified relative and absolute configurations spanning C_1–C_{22} of the acyclic chain. Our stereochemical decoding strategy culminated with aldol, Wittig, and Julia coupling reactions.[18] The required building blocks for the various segments are shown in Figure 4. Precursors **51** and **52** originated

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Scheme 2. Assembly of Subunits and Glycoside Formation in the Total Synthesis of Avermectin B_{1a}



Scheme 3. Deconjugation and Epimerization by a Relay Proton Transfer Mechanism



from **53**–**56**, which were synthesized from epoxide **57**, geraniol, and four molecules of L-glutamic acid as a common chiron for the C_1–C_{22} segment of ionomycin.[18] Unlike the tetrahydrofuran (subunit **53**), which can be visually related to an appropriate oxacyclic precursor, such as the known epoxide **57** (*visual relational* thinking), it is not evident how L-glutamic acid can be related to precursors harboring deoxypropionate and propionate motifs as found in subunits **52**, **54**, and **55**.

Concurrent studies in our group had led to a general protocol for the synthesis of all possible diastereomeric propionate motifs by adopting an iterative process shown in Scheme 4.[5a,19]

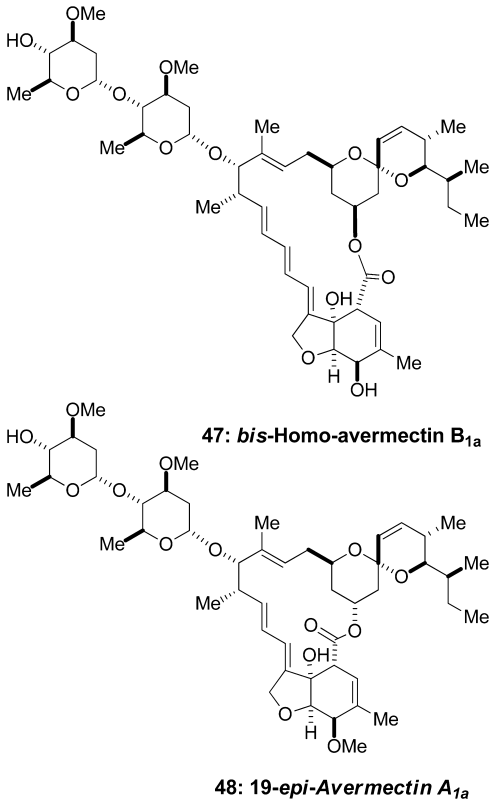


Figure 3. Biologically inactive congeners of avermectin B_{1a} and avermectin A_{1a}.

Thus, a butenolide template such as **58** could be elaborated in a linear array involving 1,4-conjugate additions of lithium

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

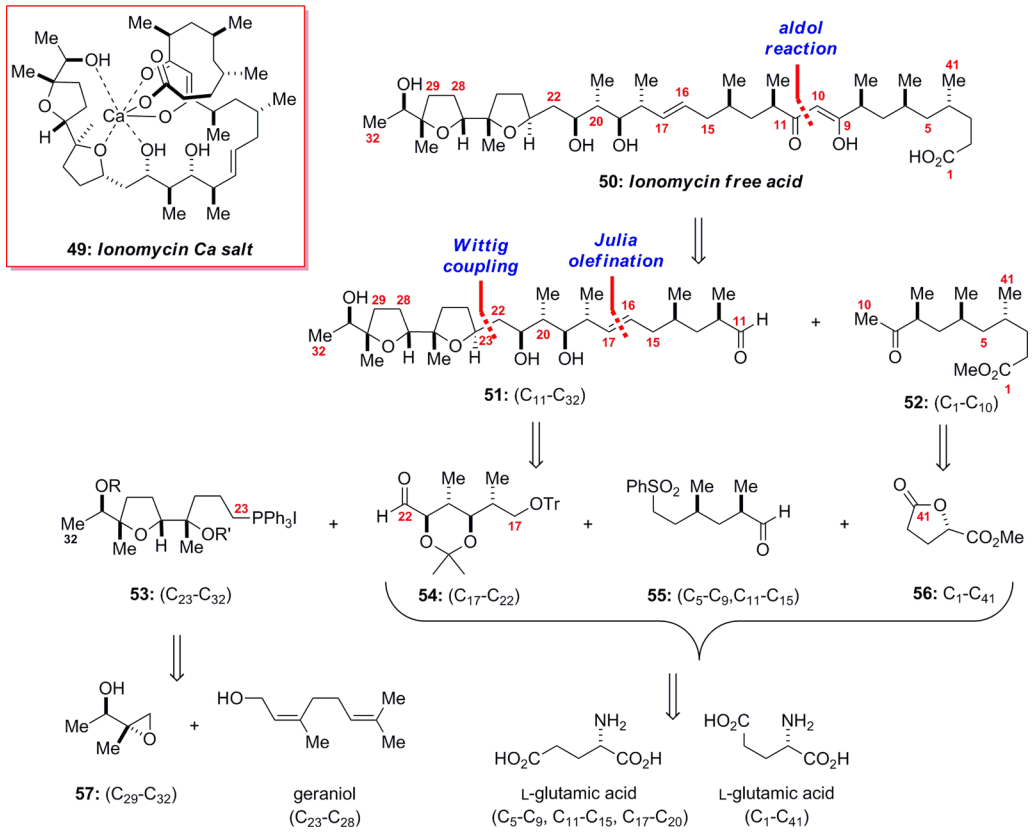
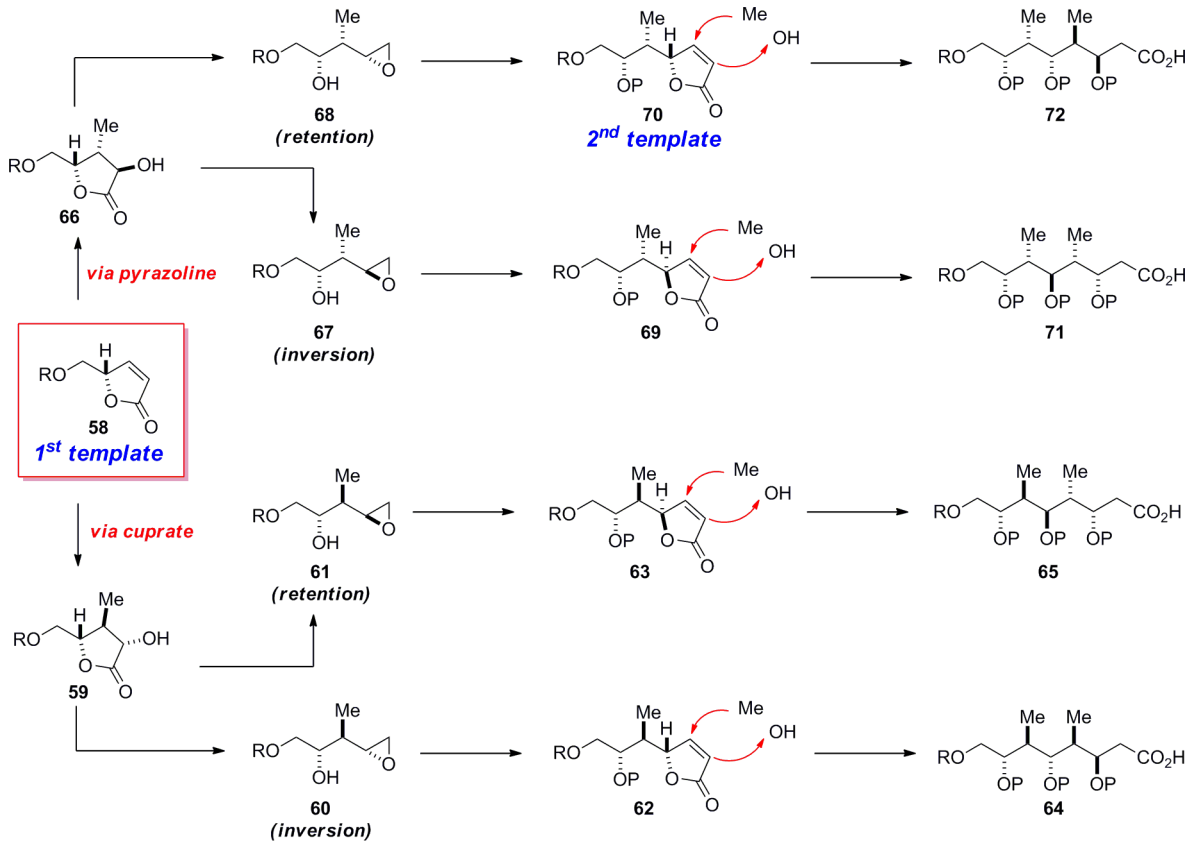


Figure 4. Stereochemical decoding of ionomycin and the emergence of L-glutamic acid as a common progenitor via butenolide templates.

Scheme 4. Replicating Lactone Strategy for Propionate Subunits

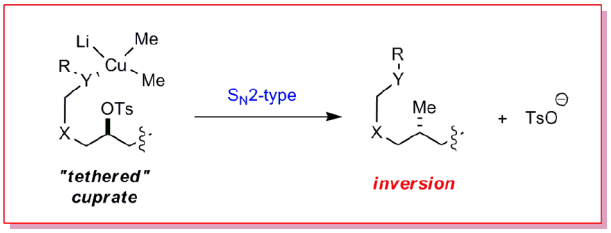


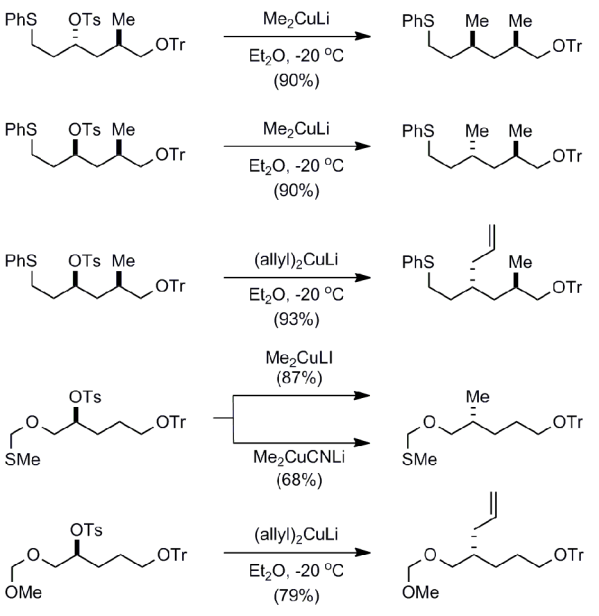
dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657−6688

dimethylcuprate, followed by enolate hydroxylation to give the *anti*/*anti* lactone **59**. Conversion to the terminal epoxides **60** and **61** could be accomplished so as to give two diastereomers via inversion or retention of the α-hydroxyl groups, respectively. A two-carbon extension with phenylselenoacetic acid dianion, lactonization, and elimination would lead to butenolide templates **62** and **63**. A second iteration of the sequence used as for **58** could then be repeated with stereochemical diversification to give **64** and **65**. Treatment of **58** with diazomethane would give a Δ^2-pyrazoline (not shown). Thermal extrusion of nitrogen from the Δ^2-pyrazoline affords a 3-methyl butenolide, which upon catalytic hydrogenation and enolate hydroxylation affords **66**, a diastereomer of **59**. Application of the same sequence of synthetic operations as described for **60** and **61** leads to diastereomeric polypropionate units **71** and **72**. At the time of this study over 25 years ago, this replicating lactone strategy offered a viable route to polypropionates of diverse stereochemical nature, thus complementing the then emerging asymmetric aldol routes pioneered by Evans, in particular,[20] and utilized in an independent total synthesis of ionomycin.[21]

Although it was possible to also access deoxypropionate triads by avoiding the enolate hydroxylation in the above protocol, we found an expedient method that exploited a new concept in S_N2 displacements of tosylates using organocuprates.[22] It was thought that placing a coordinating functional group within geometrically proximal positions relative to a nucleofugal tosylate would favor the anchoring of a cuprate reagent and effect an S_N2-type displacement resulting in inversion of configuration as evidenced in **74**, **76**, **78**, **80**, and **82**. This conceptually novel idea was indeed realized in practice as illustrated in Scheme 5.

Scheme 5. Heteroatom-Assisted S_N2-Type Displacement of Secondary Tosylates with Dialkyl Cuprates





DIHYDROMEVINOLIN

Emerging interest in the family of mevinic acids as potential cholesterol lowering drugs[23] led us to explore another application of the *chiron approach* utilizing L-glutamic acid as a native chiron. Once again, analysis of the structure of dihydromevinolin (**83**) reveals no direct progeny with an amino acid such as L-glutamic acid (Figure 5). Our disconnective analysis reveals several challenges, not the least of which is the stereocontrolled construction of the tricyclic core structure **86**, and its further elaboration to the target molecule.[24]

Access to **86** was envisaged to occur through a key intramolecular Diels–Alder reaction involving the tethered butenolide diene **85**, which would be obtained from **84**. In considering L-glutamic acid as a native starting chiron, it was necessary to formally replace the amino group with a hydroxyl group and to introduce a *C*-methyl substituent via enolate alkylation. Our prior experience with such systems[19] made it possible to convert L-glutamic acid to a lactone that led to **84** as the major product relying on resident chirality-induced *C*-methylation of the lactone enolate. The rationale for an *endo*-transition state (**90**) in the Diels–Alder reaction is shown in Figure 5 and experimentally substantiated with the isolation of **86** as the sole cycloaddition product. Key reactions for the completion of the synthesis are shown in Scheme 6. A nitroalkane anion conjugate addition of **91** onto the enone **92** led to **93**, in which the nitro group was reductively eliminated to give **94**.

Adjustment of functional groups allowed a seldom-used Baeyer–Villiger reaction[25] to transform **95** into lactone **96**. Having reached the penultimate stage in the synthesis, we were frustrated with the difficulties encountered during the removal of the *O*-benzyl ether protecting group in **96**. Finally, it succumbed to a Lewis acid-mediated cleavage, albeit requiring HPLC purification. Such is the enterprise of synthesis, allowing relatively complex transformations to occur without difficulty, only to present technical issues in the least expected and somewhat trivial steps.

RESERPINE

The first total synthesis of reserpine by Woodward and coworkers in 1956 exemplifies his prowess for tactical elegance and timely achievement.[26] Other than the challenge of assembling the complete pentacyclic structure of reserpine, a major hurdle was to secure the 3β-H configuration rather than epimeric 3α-H, which corresponds to the thermodynamically more stable isoreserpine. This feature has been the Achilles heel in most of the synthetic efforts directed toward reserpine. Analysis of the fused pentacyclic structure of reserpine led us to consider quinic acid (**36**) as a precursor to ring *E*,[27] which is elaborated to the pentasubstituted cyclohexane **100**, to be coupled with 6-methoxytryptamine (**99**) in a Pictet–Spengler reaction leading to **98** (Figure 6).

The stereocontrolled functionalization of quinic acid (**36**) presented the opportunity to apply an interesting conjugate addition involving an α-ester radical intermediate[28] (Scheme 7). Formation of the iodoacetate **105** from **104**, followed by treatment with Ph_3SnH under standard conditions, led to bicyclic lactone **106**. Further manipulations afforded **101**, which was then engaged in a Pictet–Spengler reaction with 6-methoxytryptamine (**99**) to give the pentacyclic lactam **98** and its C-3 epimer (**98a**, see Figure 7). A series of functional group transformations led to reserpine (**97**) and isoreserpine in a 1.4:1 ratio. Although we developed a different approach toward reserpine, the stereochemical issue at C_3 was not altogether

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

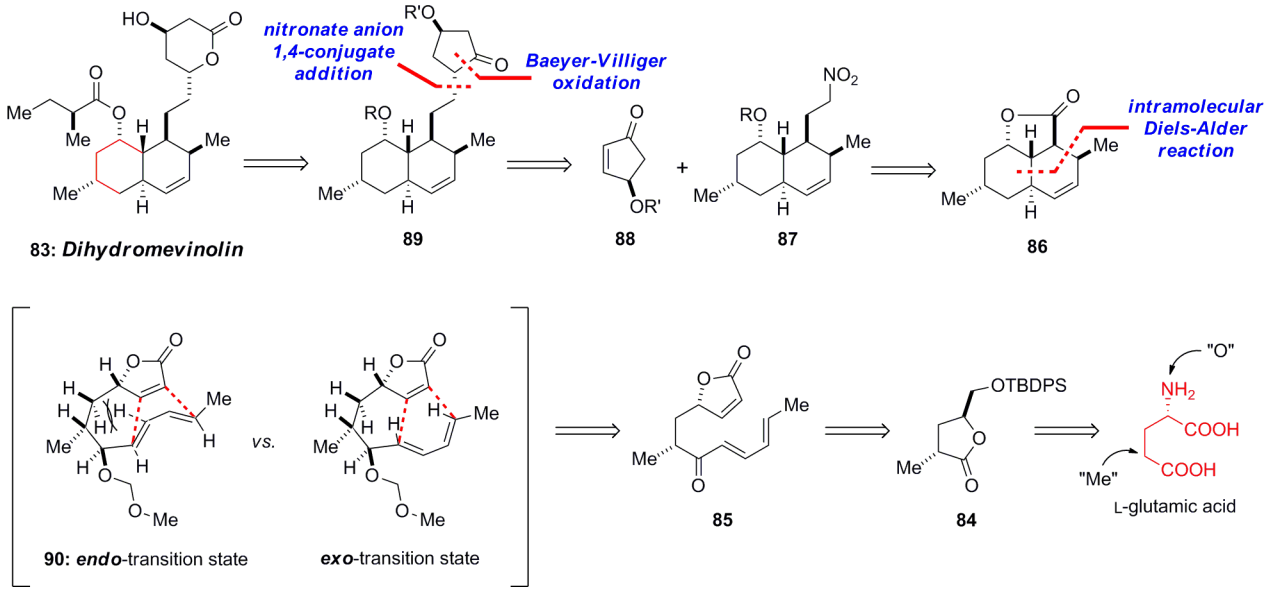
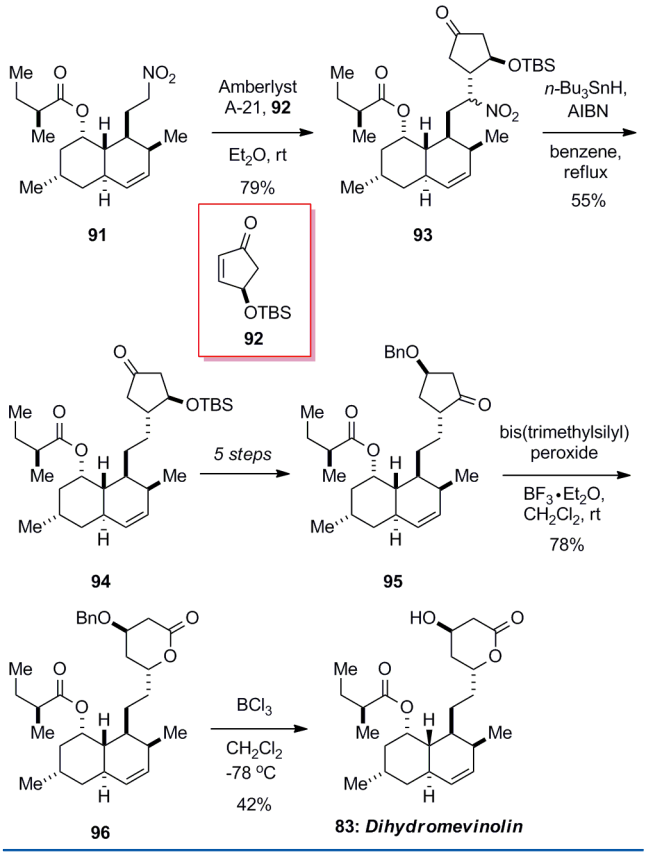


Figure 5. Disconnection of dihydromevinolin to an intramolecular Diels–Alder butenolide precursor derived from L-glutamic acid and pictorial representation of *endo*- and *exo*-transition states.

Scheme 6. Elaboration of the Lactone Subunit and Completion of the Synthesis of Dihydromevinolin



resolved, even if the natural isomer was slightly more favored. The mechanistic interpretation of the pivalic acid induced Pictet–Spengler reaction is shown in Figure 7.

The key α-ester radical cyclization to **106** deserves comment. Because of their stabilized nature, α-ester radical species have been considered unsuitable for C–C bond formation in the presence of tin hydrides. This dogma had instigated the search for alternative methods involving α-bromoacetals for example.[29]

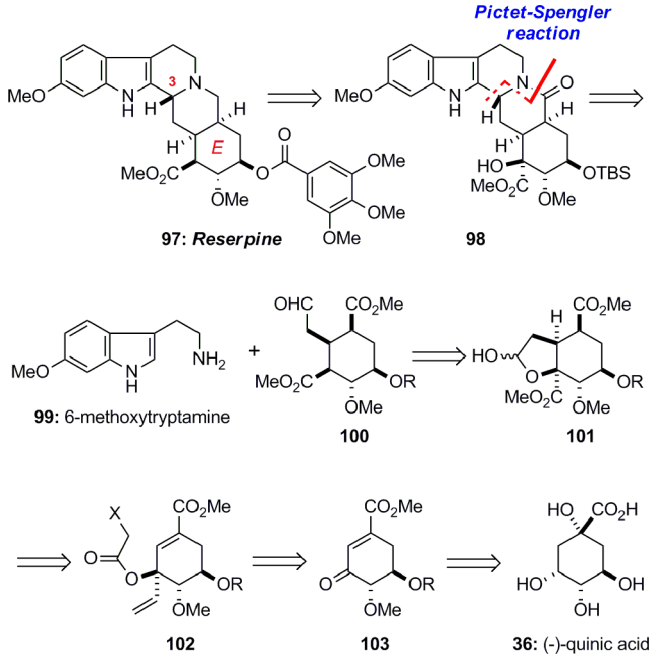
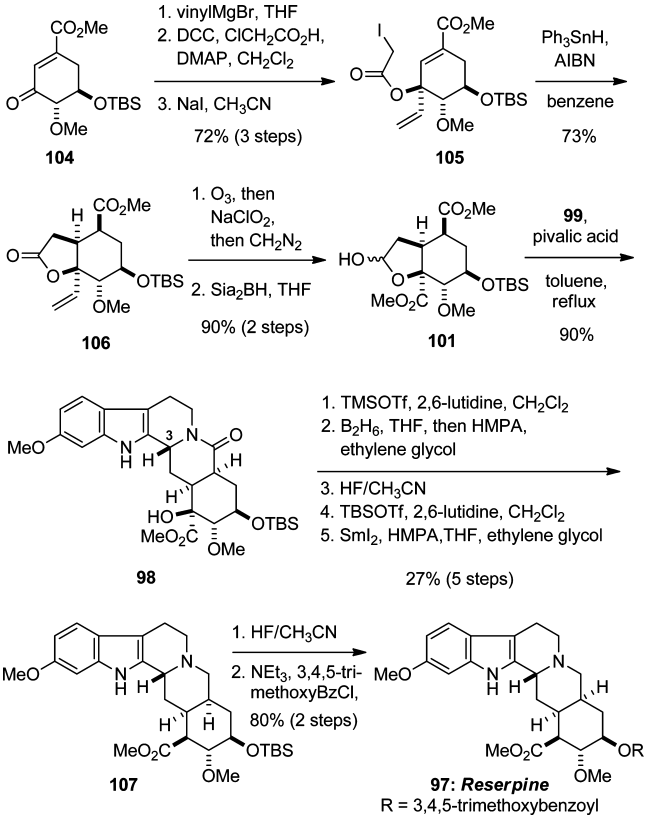


Figure 6. Disconnection of reserpine to 6-methoxytryptamine and a chiron derived from quinic acid.

Our studies demonstrated the suitability of α-ester radicals to engage in C–C bond-forming reactions with a number of practical advantages (Scheme 8).[28] Thus, primary and secondary radicals generated from α-haloesters undergo smooth intramolecular cyclization with activated and unactiveated olefins to give γ- and δ-lactones having an *anti*-stereochemical preference. Two new contiguous stereogenic centers can be generated even when the propionate ester originates from a racemic 2-halopropionic acid. It is possible that the radical species adopts a preferred orientation (a stereodifferentiating "chirad") in the transition state just prior to the formation of the new sp^3–sp^3 C–C bond, thereby effecting chirality transfer. Representative lactones prepared using this strategy are shown in Scheme 8.

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Scheme 7. Synthesis of Reserpine from (−)-Quinic Acid



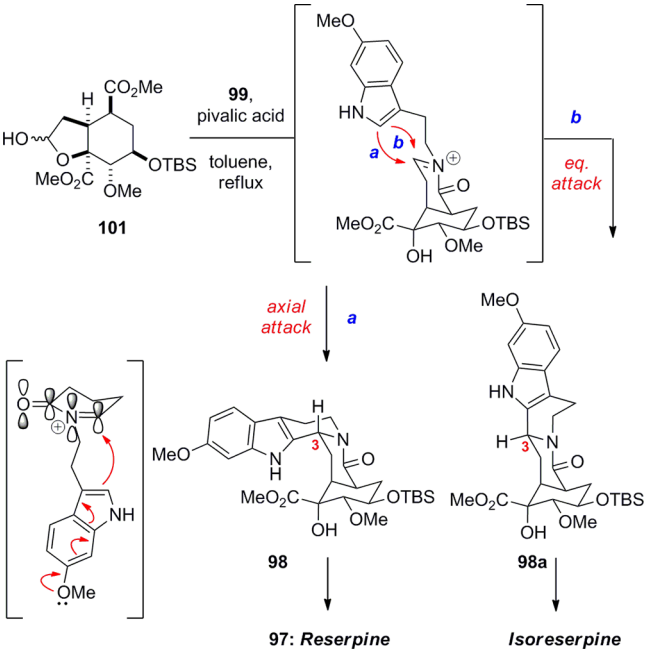
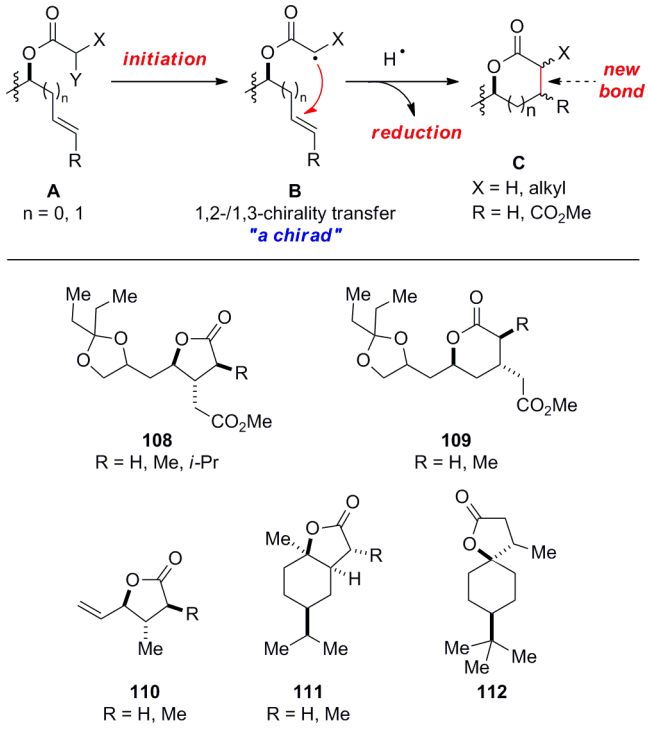


Figure 7. Axial and equatorial modes of attack on an iminium intermediate during the Pictet−Spengler condensation.

THE QUEST FOR ITERATIVE 1,2-INDUCTION FOR POLYPROPIONATE MOTIFS: RIFAMYCIN S AS A MODEL

The C_{19}−C_{28} segment of rifamycin S (**113**) contains the longest sequence of contiguous propionate-derived units among the macrolide and ansa antibiotics (Figure 8).[30] Our interest in exploring stereochemical studies in acyclic systems relying on 1,2-inductions from a resident stereogenic center led us to consider the elaboration of the polypropionate segment of rifamycin S (**113**) and bafilomycin A_1 (**114**) from a common chiron **115**. The strategy was based on initial studies involving a 1,4-conjugate addition of lithium dimethylcuprate to an α,β-unsaturated ester bearing a γ-alkoxy group, represented by **116**.[31] It was of interest to see whether a series of 1,2-inductions involving cuprate addition and enolate hydroxylation could be rendered iterative as illustrated in Scheme 9. In practice, except for motif **D**, the three combinations of propionate motifs represented by **A**−**C** could be accessed by this protocol from a single chiral progenitor such as D-mannitol.[32] Thus, enoate **116**, readily available from D-glyceraldehyde acetonide, afforded **118** as the preponderant conjugate addition product (Scheme 10).

Scheme 8. Ester Radical Cyclization on Activated and Unactivated Olefins



Formation of the potassium enolate of **117** followed by hydroxylation with the Davis oxaziridine reagent[33] led to **118**. A series of extensions and reiteration of the same process led to **121**, **125**, and **130** with excellent stereochemical control. What was remarkable in this protocol was the fidelity of sequential 1,2-inductions regardless of the length of the growing chain bearing multiple coordinating functional groups, such as MOM and BOM ethers. The stereoselective cuprate additions and enolate hydroxylations could be rationalized on the basis of established stereoelectronic concepts.[34]

The iterative assembly of polypropionate subunits could also be done on solid support using a modified Wang-type resin.[35] The generality of the approach and the fidelity of 1,2-induction in linear, as well as two directional modes, was demonstrated in the synthesis of phenyl acetate stereotriads along with mixed propionate and phenyl acetate triads as detailed in Scheme 11.[36]

High diastereoselectivity was observed during each iteration leading to phenylacetate triads, which after deprotection could have interesting properties as amphiphilic hydrocarbon chains.

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657−6688

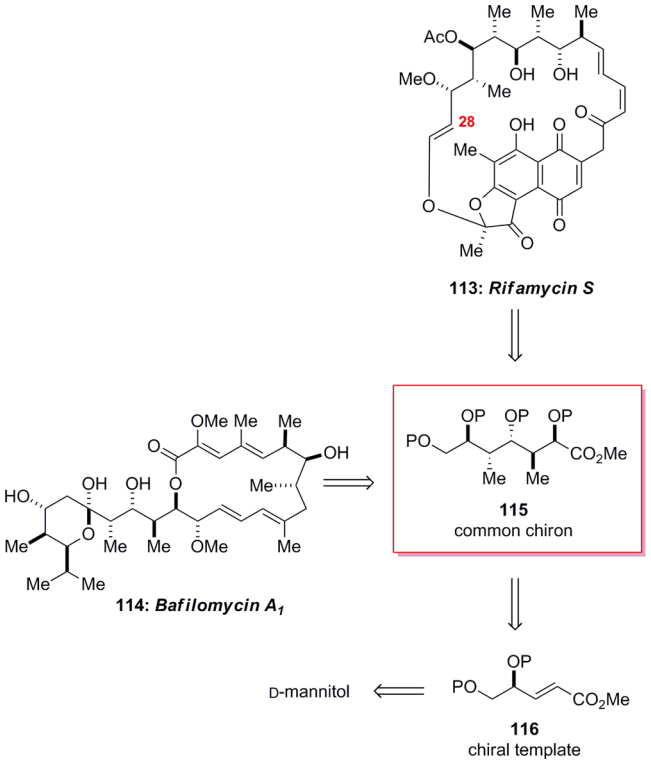
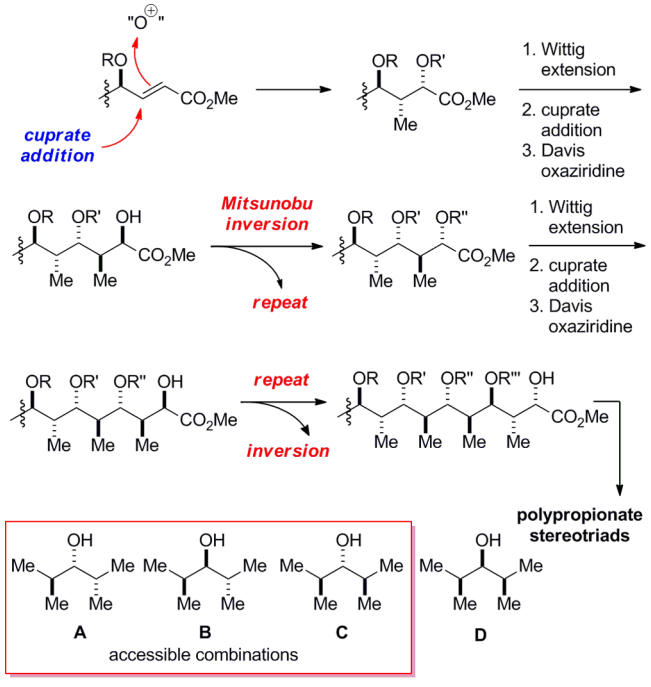


Figure 8. Disconnections of polypropionate-containing segments in macrolide and ansa natural products to a common chiron.

Scheme 9. General Stereocontrolled Strategy for the Iterative Elaboration of Polypropionate Subunits from a Single Acyclic Chiron



Finally, our initial studies involving 1,4-conjugate additions to γ-ureido-α,β-unsaturated esters[31] could be extended to enolate hydroxylations and azidations affording precursors to polyamino alcohols, such as **150**, with predisposed stereochemistry (Scheme 12).[37]

BAFILOMYCIN A_1

Analysis of the stereochemical arrangement of propionate subunits in bafilomycin A_1 (**114**)[38] offered yet another opportunity to apply the iterative 1,2-induction protocol (Figure 9).[39] A logical disconnection led to *seco*-acid **151**, which would be assembled via a Stille coupling between vinylstannane **152** and vinyl iodide **153**. These advanced intermediates could be prepared from protected D-glyceraldehyde and D-valine precursors through a series of stereocontrolled lithium dimethyl cuprate additions and α-enolate hydroxylations, proceeding through intermediates **154**–**156** and **157**–**159** for the C_{13}–C_{24} subunit. Intermediate **153** would be obtained via a two-directional protocol, first installing the *C*-methyl group by a lithium dimethyl cuprate addition to an α,β-unsaturated ester (**116**, Scheme 10), transformation to an extended α,β-unsaturated ester **160**, and then introducing the second methyl group relying on 1,2-induction from the resident ether group at C_7 (bafilomycin A_1 numbering) to give **161**, and finally elaborating both extremities to reach **153**.

One of the major hurdles in the total synthesis of highly functionalized natural products is the necessity to choose the appropriate protecting groups so that the deprotection steps may proceed to deliver the intact final product. In this regard, the use of silyl ether groups was found to be compatible with the projected steps in the synthesis of bafilomycin A_1. However, having assembled the Stille cross-coupling partners **162** and **153** (R = TES) with appropriate silyl protecting groups, numerous attempts, which had succeeded in model studies, failed in the intended reaction to give **163** (Scheme 13). Eventually, it was discovered that the use of $Pd(dppf)Cl_2$ and $AsPh_3$ in the presence of Hünig's base afforded the desired coupled product **163** in 60% yield. Subsequent steps proceeded uneventfully to yield **164** and eventually to crystalline bafilomycin A_1 (**114**).[40] It is noteworthy that the macrolactonization was successfully accomplished using the traditional carbodiimide method in 65% yield without contamination from the larger 18-membered lactone (see Scheme 14).

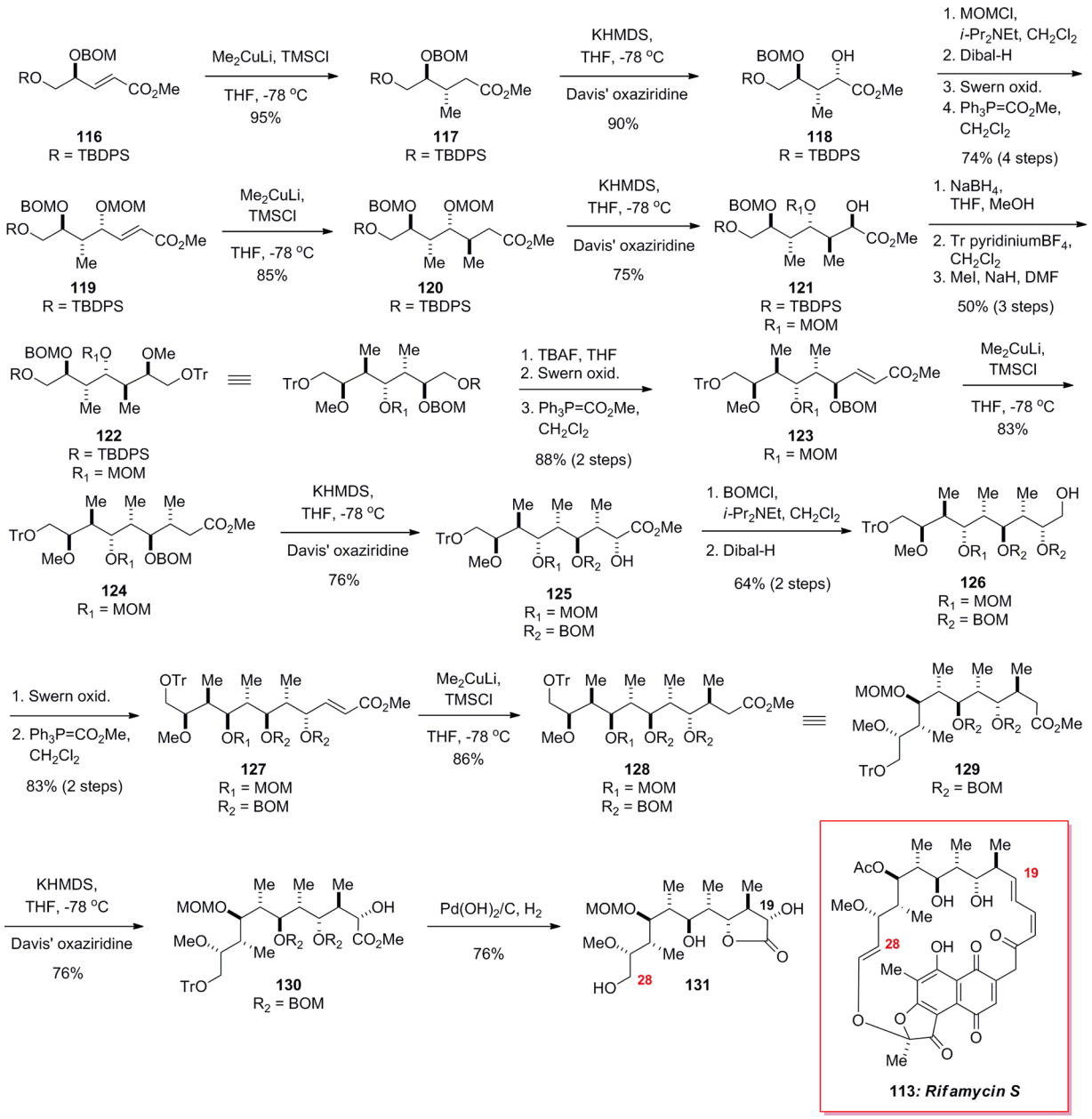
One of the objectives of the bafilomycin A_1 (**114**) synthesis project, which was done in collaboration with AstraZeneca scientists in Mölndal, Sweden, was to study the biological activity of analogues and congeners. Treatment of the 7,21-di-*O*-trimethylsilyl derivative of bafilomycin A_2 (**165**), the methyl glycoside of bafilomycin A_1, with an organocopper reagent, resulted, after deprotection of the silyl ethers, in the formation of a ring-expanded 18-membered lactone homologue, *iso*-bafilomycin A_2 (**166**), which was characterized by X-ray crystallography after deprotection (Scheme 14).[41] The process can be rationalized by the presence of alkoxide species such as **A** and **C** that can form an ortho acid salt intermediate **B** reversibly.

Curiously, when the deprotection was performed in a 0.2 M solution of TBAF (instead of 0.05 M), the product obtained was bafilomycin A_2 as a result of a ring contraction. Interestingly, *iso*-bafilomycin A_1 (**167**) did not show biological activity reflecting on the importance of maintaining the 16-membered ring, and possibly the need for an H-bonding network involving the lactone carbonyl group and the adjacent C_{17} hydroxyl group.

Attempts to perform a Mitsunobu reaction to functionalize one of the secondary hydroxyl groups in bafilomycin A_1 resulted in another unexpected transformation (Scheme 15).[42] Thus, treatment with Ph_3P and DEAD in the absence of a carboxylic acid nucleophile afforded the fragmentation product **168** in 86% yield, whose structure was ascertained by X-ray crystallography. Remarkably, it maintained the same overall shape as bafilomycin A_1 (**114**) in the solid state, including an intramolecular H-bond

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Scheme 10. Elaboration of C19−C28 Segment of Rifamycin S from a Single Chiron by Iterative Cuprate Conjugate Additions and Enolate Hydroxylations



involving the lactone carbonyl group and the C_{17} hydroxyl group. Although bafilomycin A_1 is rapidly dehydrated in acid media, compound **168** was stable even in 6 N HCl. Its formation can be rationalized on the basis of a C_{21}-alkoxyphosphonium salt **B**, which undergoes a stereocontrolled Grob-type fragmentation reaction involving the antiparallel C_{19}−C_{20} bond (Scheme 15).

BORRELIDIN

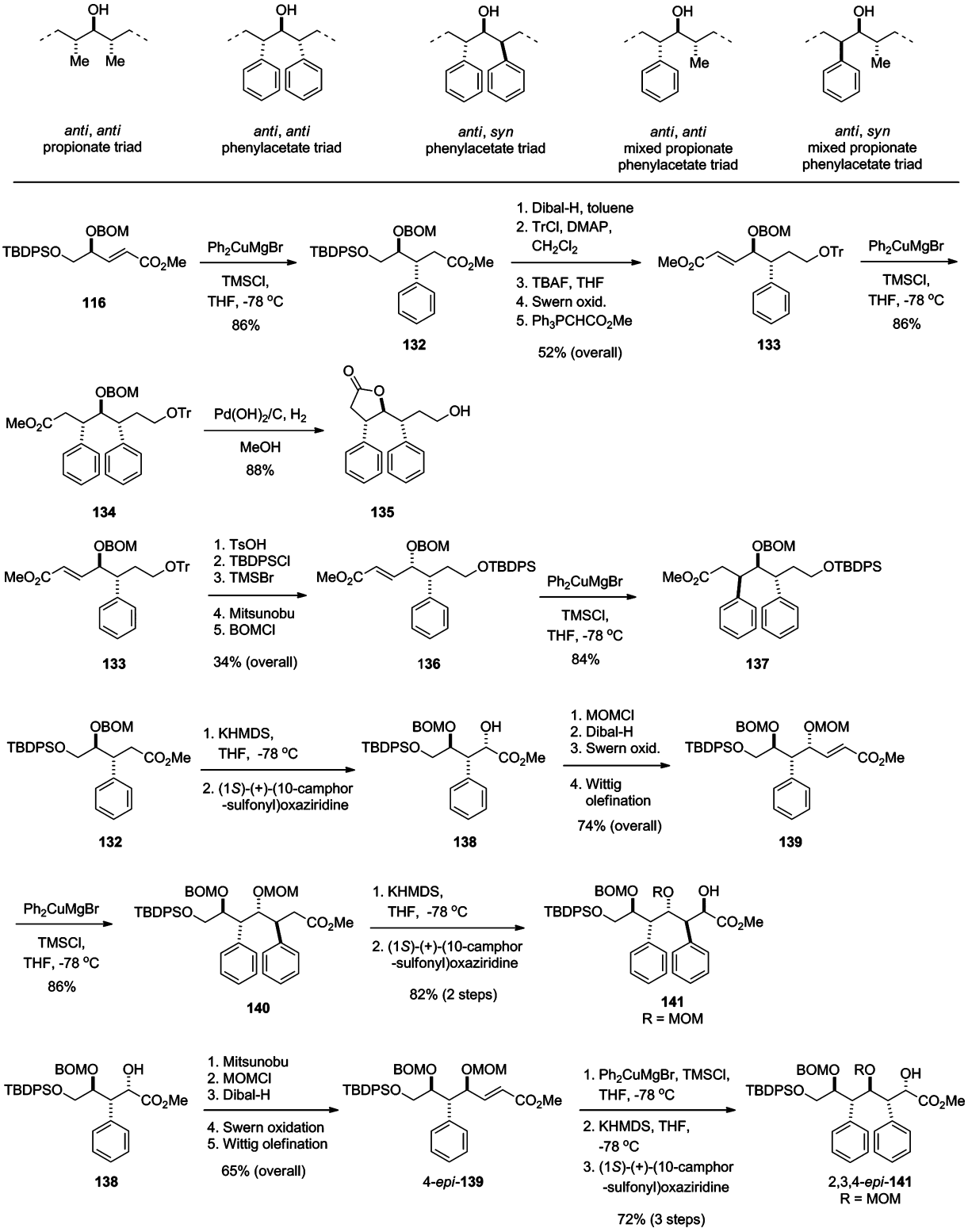
Deoxypropionate motifs are ubiquitous components of a number of natural products derived from polyketide pathways.[43] Our successful strategy toward iterative 1,2-induction, in the synthesis of polypropionate motifs, led us to study a similar approach toward deoxypropionates, wherein a 1,3-asymmetric induction paradigm would be explored. Preliminary and encouraging studies (see below) led us to borrelidin (**169**) as a synthetic target (Figure 10). This structurally unique macrolide antibiotic[44] harbors three *syn*-disposed deoxypropionate subunits comprising the C_4−C_9 framework of the 18-membered macrolactone.

Disconnective analysis of borrelidin led to subunits **170** and **171** as coupling partners that would originate from L-malic acid and D-glyceraldehyde, respectively.[45] Subunit **171** would result from **172**, which would come from an iterative 1,3-induction sequence, that involved the addition of lithium dimethylcuprate to *α,β*-unsaturated ester **173** (harboring two deoxypropionate triads) and **174**. This hypothetical plan was indeed realized in practice as shown in Scheme 16.

Three cycles of cuprate 1,4-conjugate additions to respective *α,β*-unsaturated esters **116**, **177**, and **179** with high 1,2- and 1,3-stereoinduction, considering the acyclic nature of the growing chain, led to **180**. Incorporation of the fourth *C*-methyl group constituting a single propionate unit at C_{10}−C_{11} was achieved via a Sharpless asymmetric epoxidation reaction of an olefin

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657−6688

Scheme 11. Elaboration of Phenyl Acetate Stereotriads by Iterative, Two-Directional Conjugate Addition and Enolate Hydroxylation



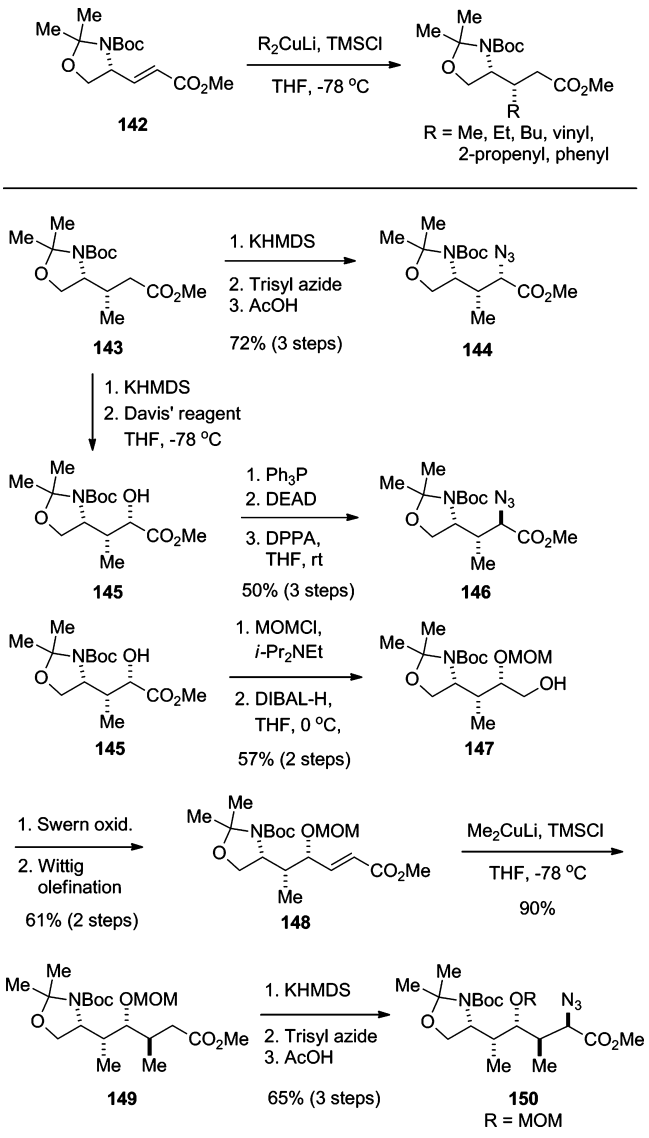
precursor, followed by a Lewis acid-catalyzed reductive opening of the epoxide to give **181**. Chain extension to the cyanohydrin **182** and elaboration to the *cis*-cyano alkylidene group gave **183** using a Still–Gennari olefination reaction. Conversion to the aldehyde **184** followed by a Julia–Kocienski sulfone anion coupling with **170** gave **185**. Assembly of subunits and macrolactonization completed the first total synthesis of crystalline borrelidin (as the benzene solvate)[45,46] (Figure 10).

■ DOLICULIDE

The cytotoxic cyclodepsipeptide doliclide (**188**) harbors two *syn*-oriented deoxypropionate subunits on the C_2–C_5 macrocyclic

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Scheme 12. Elaboration of Polyamino Alcohol Stereotriads by Iterative Conjugate Addition and Enolate Hydroxylation



framework (Figure 11). The initiating chiron in this case was L-ascorbic acid (**189**), which provided the α,β-unsaturated ester **190** possessing the *S*-configured γ-alkoxy group required for the first cuprate addition to give **191**.[47] Elaboration of the acyclic enolate through a second 1,4-conjugate addition led to **192**, which underwent a third cycle to afford an diastereomerically enriched ester **193** after elaboration of the end groups. Addition of the dithiane anion of **194** led to **195**, which was eventually converted to doliculide (**188**) in 14 linear steps.[48]

CONFORMATIONAL DESIGN IN ACYCLIC STEREOSELECTION

At first glance, the *syn*-selective stereochemical control in the assembly of deoxypropionate subunits by iterative 1,3-inductions via the 1,4-conjugate addition of cuprates to enoates containing a δ-*C*-methyl group may appear to be unusual (Scheme 16). How could such control be achieved in a seemingly flexible acyclic system? A closer look reveals that two deoxypropionate motifs are a part of an isolated 2,4-dimethylpentane hydrocarbon unit. Three deoxypropionates would correspond to a 2,4,6-trimethylalkane system. Despite the many degrees of rotational freedom, such systems can be made monoconformational by anchoring an inducting group so as to avoid *syn*-pentane interactions.[49] Nature relies on the same principles in the biosynthesis of metabolites in which stereoregular single, double, or triple *syn*-deoxypropionate triads are created. This preference is nicely corroborated in the X-ray crystal structure of borrelidin[45] and acyclic metabolites like TMC-151.[50] In fact, the ^{1}H NMR spectrum of intermediate **179** is remarkably well resolved and easily distinguishable from its diasteriomeric counterparts.[45] In considering the synthesis of *syn*-deoxypropionate subunits by iterative 1,4-conjugate addition of cuprates to α,β-unsaturated esters containing a δ-*C*-methyl group as in **177** (Scheme 17), we relied on the basic notion that transition state conformations leading to intermediates in which *syn*-pentane interactions are minimized, would be favored. To visualize the process, we used a virtual diamond lattice[51] as a hypothetical template, upon which we superimposed the carbon backbone of the acyclic intermediates **177** and **179**. It can be seen that the *C*-methyl groups in the respective cuprate addition products **178** and **180** are staggered in a gauche orientation, which is also corroborated from X-ray structural data.[46,45] During the course of our studies, we also found an "ester effect" wherein increasing bulk changed the 50:50 *syn*/*anti* ratio of a methyl ester to 80:20 for the *tert*-butyl ester, to 82:18 for the neopentyl ester, and to 89:1 for the methylcyclopentyl ester.[52]

We can conclude that there are three "effects" that contribute to the preponderance of *syn*-oriented deoxypropionates in these iterative inductions:

(a) The alkoxy effect regulates 1,2-induction in the 1,4-conjugate addition of a cuprate to an α,β-unsaturated ester.
(b) Subsequent 1,3-induction relies on a combination of the anchoring group of the chain extremity and the increasing bulk of the ester moiety.
(c) An isotactic-type folding of the growing chain is transmitted from adjacent resident stereocenters to the newly created *C*-methyl center, thus avoiding *syn*-pentane interactions toward stereoregular deoxypropionate motifs (Scheme 17).[53] Elegant catalytic methods have also been developed by Negishi,[54a] Feringa,[54b] Schneider,[54c] and their respective groups.

THE AERUGINOSINS

My many years of consulting at AstraZeneca in Sweden had a number of redeeming benefits. Among these was the opportunity to explore synthetic approaches to two families of natural products, namely bafilomycin A_1 (**114**), a member of the hydrolide group (Figure 9), and the aeruginosins, a class of cyanobacterial metabolites isolated from diverse aquatic regions (Figure 12) and exhibiting serine protease activity.[55] The structure of dysinosin A (**198**)[7o] had been proposed by Quinn and co-workers[56] based on spectroscopic studies and a cocrystal structure with the enzyme thrombin (Factor IIa). The in vitro inhibitory activity of dysinosin A (IC_{50} = 46 nM) showed it to be the most potent among other members of the aeruginosin family. Soon after completion of the synthesis of dysinosin A we became aware of a second member of these linear peptides harboring an 1-amidino-Δ^3-pyrroline as an arginine mimetic. Our total synthesis of oscillarin (**199**) also allowed for the revision of its structure due to an incorrect depiction of the 1-amidino-Δ^3-pyrroline in the original patent.[57] Oscillarin showed an IC_{50} = 28 nM, thus surpassing dysinosin A against thrombin. However, a third member, which we called chlorodysinosin A (**200**), revealed a record-holding IC_{50} = 6 nM activity against the same

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

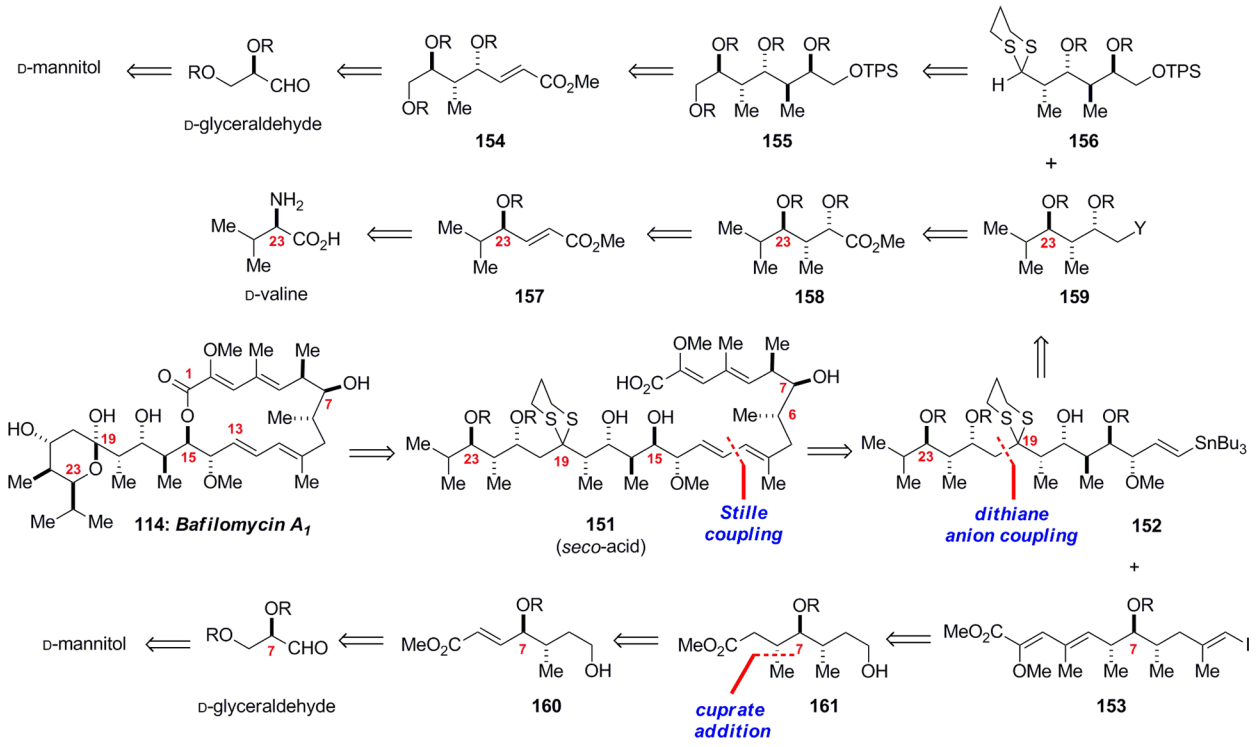
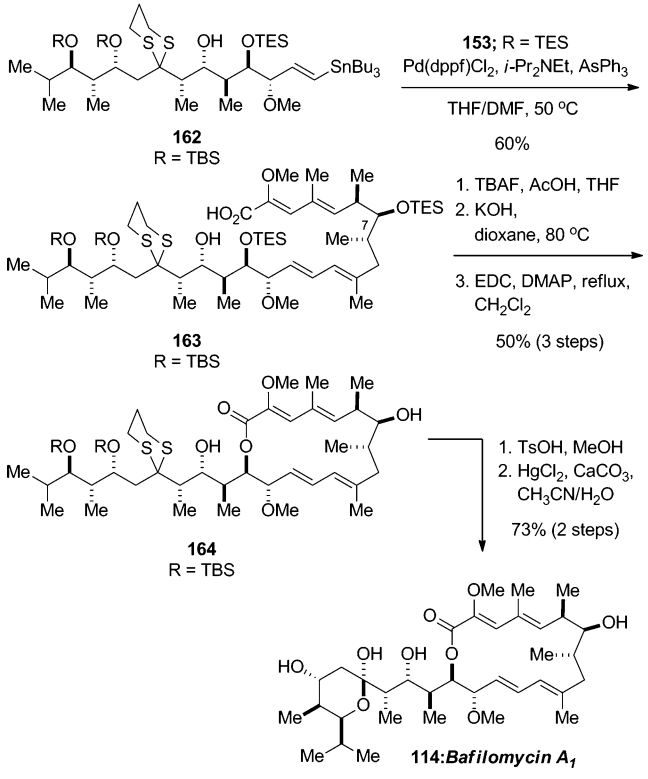


Figure 9. Disconnection of bafilomycin A_1 to D-glyceraldehyde and D-valine as chirons. Application of iterative propionate synthesis relying on 1,2-induction and a two-directional protocol.

Scheme 13. Assembly of Subunits and Completion of the Synthesis



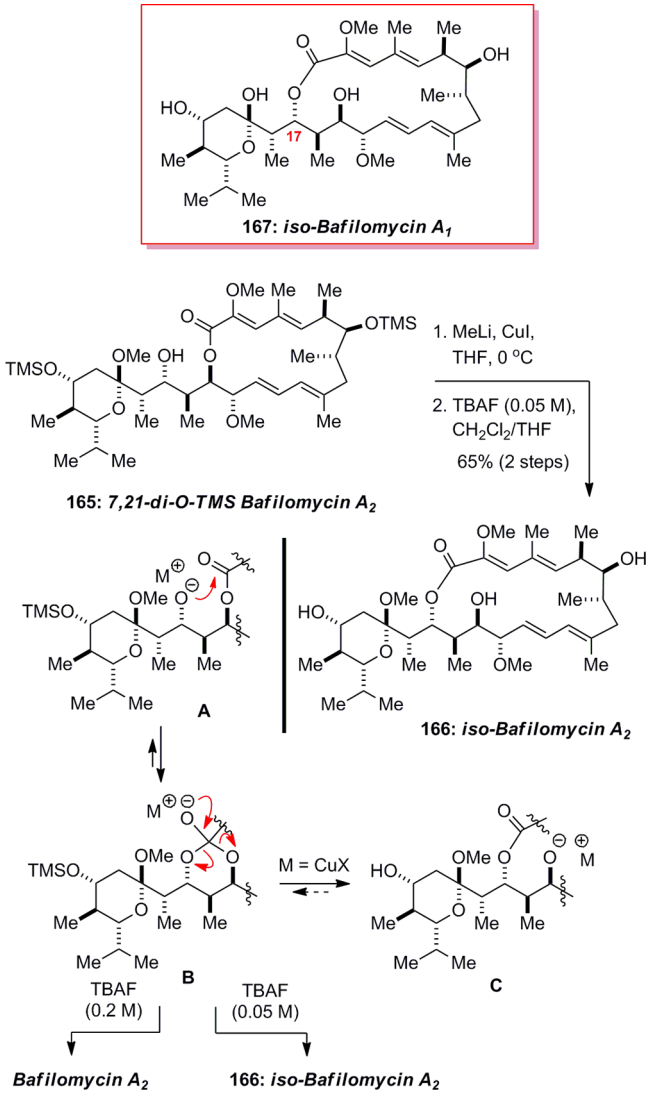
enzyme following our total synthesis and structural confirmation.[58] The striking improvement in in vitro activity against thrombin (as well as other factors involved in the blood coagulation process) was remarkable (Figure 12). A rationalization of this effect was based on the crystal structures of dysinosin A (**198**) and chlorodysinosin A (**200**). Thus, the space-filling structural comparison shows that the S3 hydrophobic active site cavity is better occupied by the 3-chloro-D-leucyl moiety in chlordysinosin A compared to dysinosin A. Molecular dynamics calculations revealed that the χ' angle of the 3-chloro amino acid is more restricted in chlorodysinosin A, providing better hydrophobic interaction with the S3 side, releasing water and also gaining in entropy. This rationale was also corroborated with semisynthetic analogues showing potent in vitro thrombin-inhibiting activity (see below, Figure 14).

Chlorodysinosin A. Like other members of the aeruginosin family, dysinosin A (**198**), chlorodysinosin A (**200**), and oscillarin (**199**) contain a central 2-carboxylperhydroindole core subunit (Figure 12). However, the above three natural products distinguish themselves by the presence of a 1-amidino-Δ^3-pyrroline representing the P3 subunit, which interacts with Asp189 in the S3 site. Chlorodysinosin A and dysinosin A possess a *trans*-diol in the perhydroindole subunit, which interestingly does not interact with the enzyme as deduced from X-ray cocrystal structures.[58]

A disconnection of the three natural aeruginosins reveals the logical subunits **201**, **202**, and **203**, which can be synthesized and assembled to the respective target compounds (Figure 12). For the synthesis of subunit **201** (X = H), we chose a seldom exploited azonia-Prins reaction[59] involving a tethered olefinic appendage (rather than an RCM strategy as used for dysinosin A,[7o] Scheme 18). In order to secure the *syn*-orientation of the ring junction and the methoxycarbonyl group, we started with **204**, which was alkylated to **205** via its dianion.[60] Conversion to the lactam **206** and the corresponding 2-acetoxy hemiaminal **207** led to a smooth $SnBr_4$-mediated carbocyclization via an iminium ion intermediate to give the bromo derivative **208**. Inversion of configuration led to the enantiopure acetoxy perhydroindole

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Scheme 14. Ring Expansion and Contraction Reactions in the Bafilomycin A_2 Series



209, which is present in oscillarin (**199**). The likely involvement of an antiperiplanar rather than a synclinal attack was supported by subsequent studies (see below). DBU-mediated elimination from **208**, followed by epoxidation and treatment with TFA afforded the *trans*-diol **210**.

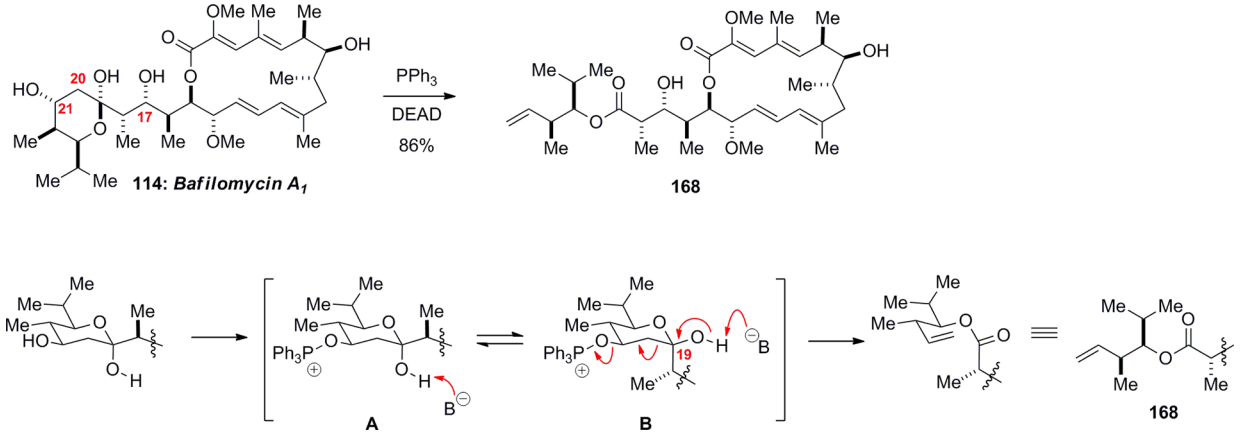
The unprecedented occurrence of a (3*R*)-3-chloro-D-leucine (**202**) as an amino acid residue in chlorodysinosin A (**200**) presented a challenge for its stereocontrolled synthesis (Scheme 19). Several attempts at regioselective opening of *N*-sulfonyl derivatives of aziridine **213** with various sources of chloride ion afforded mixtures of regioisomers. However, using the *N*-*tert*-butylsulfonyl (*N*-Bus) protecting group[61] as in **214**, in conjunction with $CeCl_3$, led to virtually a single isomer **215** as required for the natural product. Great care was taken in the elaboration to the peptide **216** in order to avoid β-elimination.

The final assembly of the subunits presented two major obstacles (Scheme 20). In the first of these, we had underestimated the difficulty in amide coupling between subunit **219** and **218**. After exploring a variety of conditions, we were successful in using DEBPT, the Goodman reagent,[62] to give **220** in 55−60% yields reproducibly. The second hurdle to overcome was to hydrolyze the methyl ester of **220** (not shown) for the final amide coupling with **203**. Many attempts led to undesired products including elimination. Eventually, we benefited from our prior experience with organotin chemistry[63] and cleanly achieved hydrolysis employing excess Me_3SnOH in refluxing toluene.[64] Final coupling, sulfation, and deprotection gave chlorodysinosin A (**200**), which was cocrystallized with thrombin[58] and used for in vitro testing against several serine proteases. Our studies also led to the synthesis of aeruginosins 205A (**222**) and B (**223**),[65] also containing a (3*R*)-chloro-D-leucine residue, thus correcting the previously misassigned structures with regard to the positions of the chlorine atoms, the sulfate group, and the α-D-xylopyranosyl moiety (Figure 13).[66]

From Natural Products to Peptidomimetics and to Achiral Inhibitors. The structure-based rationalization of improved in vitro antithrombin activity of chlorodysinosin A[58] was further validated with the synthesis and testing of hybrid and truncated molecules in which one or more original functional groups were removed (Figure 14). Thus, the benzamide derivatives in which the diol unit in the octahydroindole portion was absent and the amino acid residue was modified with an oscillarin-type phenyllactic acid amide appendage, represented by analogues **224**−**227**, were found to be potent inhibitors of thrombin.[67]

The well-known chloromethylketone tripeptide PPAK (**228**)[68] was used as a starting point for the synthesis of constrained analogues as potential inhibitors (**229** and **230**).[69] Using the

Scheme 15. Stereochemically Controlled Fragmentation Reaction of Bafilomycin A_1: Mechanistic Rationale for the Fragmentation Reaction



dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657−6688

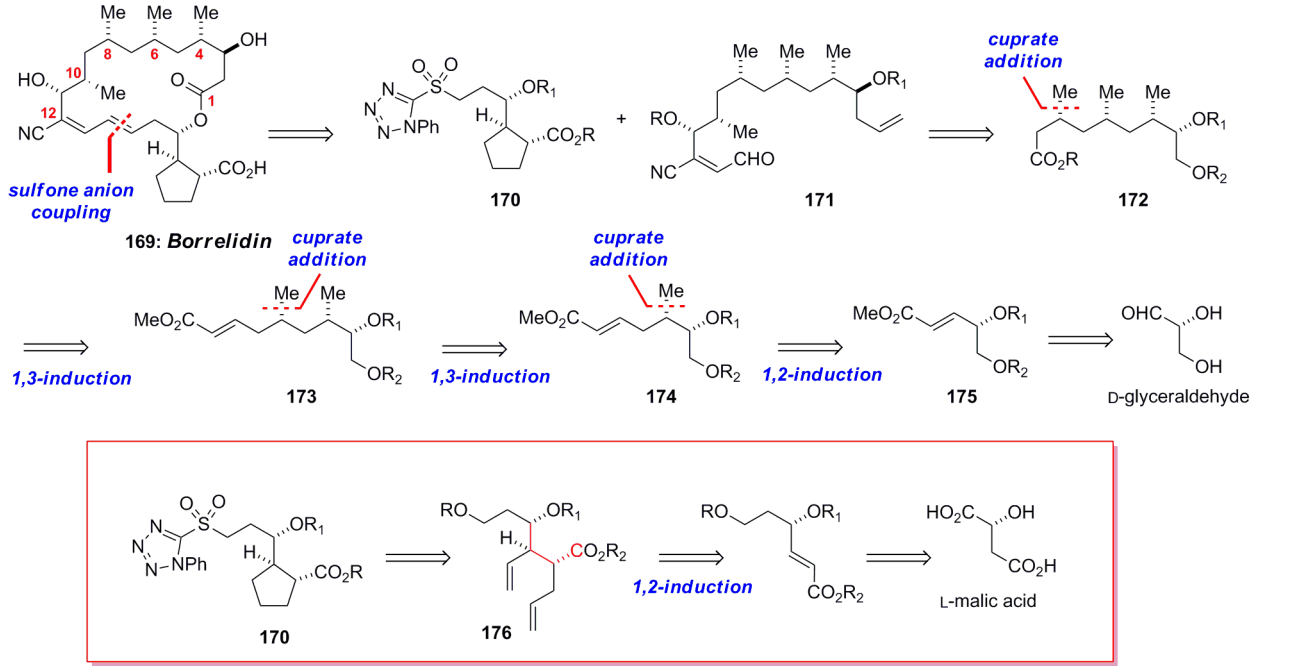


Figure 10. Disconnection of borrelidin to D-glyceraldehyde and L-malic acid as native chirons. Application of iterative conjugate additions toward 1,3-asymmetric induction.

same structure-based design paradigm, in conjunction with AstraZeneca scientists, we proposed and synthesized a number of indolizidinones and showed that the antiparallel Gly216 interaction, also present in the aeruginosins, can be reproduced in peptidomimetics involving a tertiary hydroxyl or amino group as substantiated by X-ray cocrystal structures with the enzyme. However, unlike PPAK, which reacts irreversibly with the catalytic Ser195, the indolizidinones were reversible inhibitors (Figure 15).

Finally, the collaborative project with AstraZeneca scientists in Mölndal, Sweden was diverted to the design and synthesis of achiral inhibitors. The core subunit was the 2-aminophenol moiety (Figure 16), which after appropriate substitution would also engage in the requisite interactions with the enzyme, especially with the proper choice of *N*-substituents such as sulfonamides, and amidino benzamides as arginine mimetics. A series of such analogues represented by **231** were synthesized and tested, and the relevant interactions were validated by X-ray cocrystal structures with thrombin.[70]

In a final study, we synthesized novel cores corresponding to *N*-aminopyridones and *N*-aminodihydropyridones represented by **232** and **233** (Figure 17).[71,72] There was a remarkable drop in in vitro thrombin inhibitory activity in going from a dihydropyridone to a pyridone, which was rationalized on the basis of an X-ray cocrystal structure with the enzyme. At physiological pH (~7.4), the pyridone analogue **232** and related systems are deprotonated with a delocalized negative charge on the sulphonamide nitrogen (and possibly also when complexed to thrombin), thus preventing the interaction with Gly216. On the other hand, the nonionized and highly active dihydropyridones, such as **233**, still retain the ability to interact with this residue (Figure 18).

The "medicinal chemistry" part of my collaboration with AstraZeneca in Sweden was concluded with the exciting journey that took us from total synthesis and structural confirmation of three novel aeruginosins, to peptidomimetics and hybrids, and finally to potentially "druglike" molecules represented by achiral *N*-amino dihydropyridones such as **233**.[55,73] In the process, my group benefitted enormously from the rich chemistry and biology associated with antithrombin compounds. As in other instances, it is difficult to predict if the potent *N*-amino dihydropyridones would be promising drug candidates without further pharmacological and related studies, which would arguably involve costly and time-consuming efforts. As such, our obligations as academic collaborators were fulfilled since the "risks" we took were not at the expense of the otherwise valuable time had the projects been done internally. The discovery and development of antithrombotics remains, by and large, as an unmet medical need.[74]

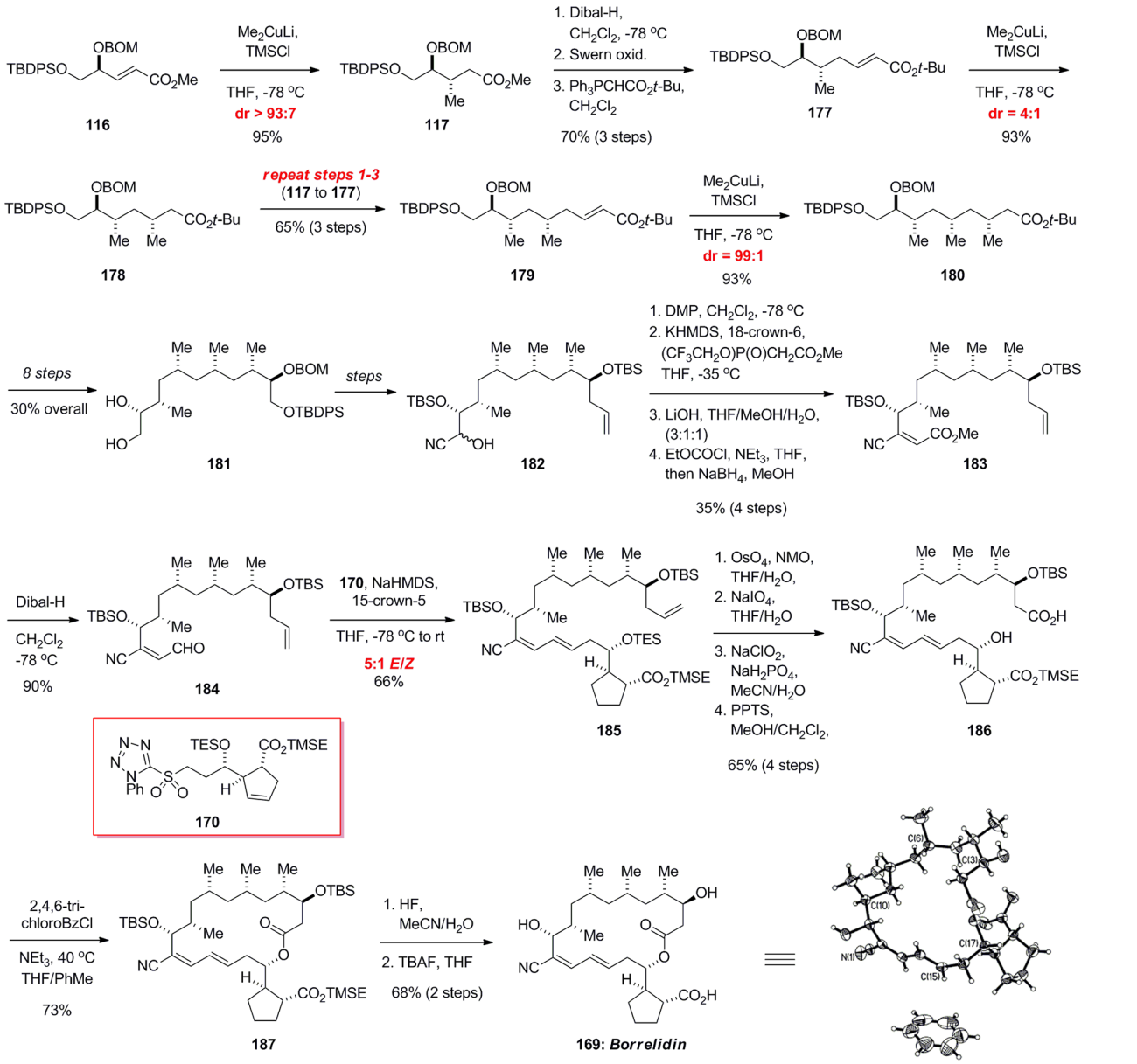
Incentives for New Methodology. The need to synthesize the 2-carboxyperhydroindole core of the aeruginosins in enantiopure form led us to explore aspects of the azonia–Prins reaction.[75] We initially rationalized the stereocontrolled formation of the 6-substituted intermediate **208** (Scheme 21) based on a stereoelectronically controlled attack of bromide ion on an iminium ion bearing a terminal butenyl tether via an antiperiplanar approach and proceeding through a carbocation. The corresponding synclinal approach would not be favored especially on account of the pseudoaxial ester group due to $A^{1,3}$ strain in such systems. When the butynyl tether was used, the product was vinylbromide **236**, which presumably arose from trapping of a vinyl cation.

In an effort to substantiate the antiperiplanar approach idea, we subjected acetoxy hemiaminal **237**, harboring two terminal butenyl appendages, to the azonia–Prins cyclization (Scheme 22). In this instance, either chain could engage in the cyclization. However, only the product **240** was formed in the alkene and alkyne series presumably through the more favored antiperiplanar approach of the blue alkenyl/alkynyl tethers onto the iminium ion intermediate **238** rather than **239**, which would have led to **241**.[75]

An unexpected reaction occurs when the corresponding propenyl and allenyl appendages in acetoxy hemiaminals **242** and **243**[75] were subjected to the azonia-Prins reaction. In both cases, the products were the corresponding dihydrooxazinones **244** and **245**, respectively (Scheme 23). These structurally

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Scheme 16. Assembly of Subunits and Completion of the Total Synthesis of Borrelidin as a Crystalline Benzene Solvate



compact, multifunctional scaffolds are of interest as core structures for diversification at more than one site. Interestingly, the ester group in **244** can be hydrolyzed to the acid in the presence of the cyclic carbamate.

Having access to the vinyl bromide **236**, a series of well-known transformations involving the venerable Suzuki, Heck, and Stille cross-coupling reactions led to the scaffolds **246**–**248** (Scheme 24).[76]

Oidiodendrolides. Another highly rewarding consulting activity was my long-standing association with the agrochemical giant ex-Ciba-Geigy Agro, which became Syngenta after a mega merger over a decade ago. In a period spanning some 25 years, a number of collaborative projects were initiated and successfully completed with the Basel, Switzerland, and Jealott's Hill, UK groups in my laboratory at the University of Montreal. Among these, were the design and synthesis of natural inhibitors of adenylosuccinate synthetase and hybrids thereof,[77] the synthesis and structural confirmation of malayamycin A[79] (Figure 1), as well as unnatural analogues as potent fungicides.[78]

Interest in the family of norterpenoid dilactones, known as podolactones, arose because of their activities as antifeedants, as fungicial, insecticidal, and plant growth regulatory properties.[79] In view of the paucity of material from natural sources for certain oidiodendrolides, we undertook a study of their synthesis.[80] Analysis of the intended structures **249**–**255** revealed a common precursor which could be functionalized in a diverse set of transformations, as shown in structure **256** (Figure 19).

Although the utilization of the Wieland–Miescher ketone (**257**) as a starting carbocyclic chiron was visually evident, it was not clear how intermediate **258** could be transformed to the triyclic lactone that is present in the intended target compounds (Scheme 25). A Baylis–Hillman hydroxymethylation of **258** led to **259**, which upon treatment with bromine in $CHCl_3$ afforded **260**. Treatment with base led to the desired trilactone **262**, presumably via the formation of spiroepoxide **261**. Another critical transformation was accomplished in the Ni-catalyzed Reformatsky reaction[81] of **262** to give the branched tertiary alcohol **263**. This core intermediate was systematically transformed

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

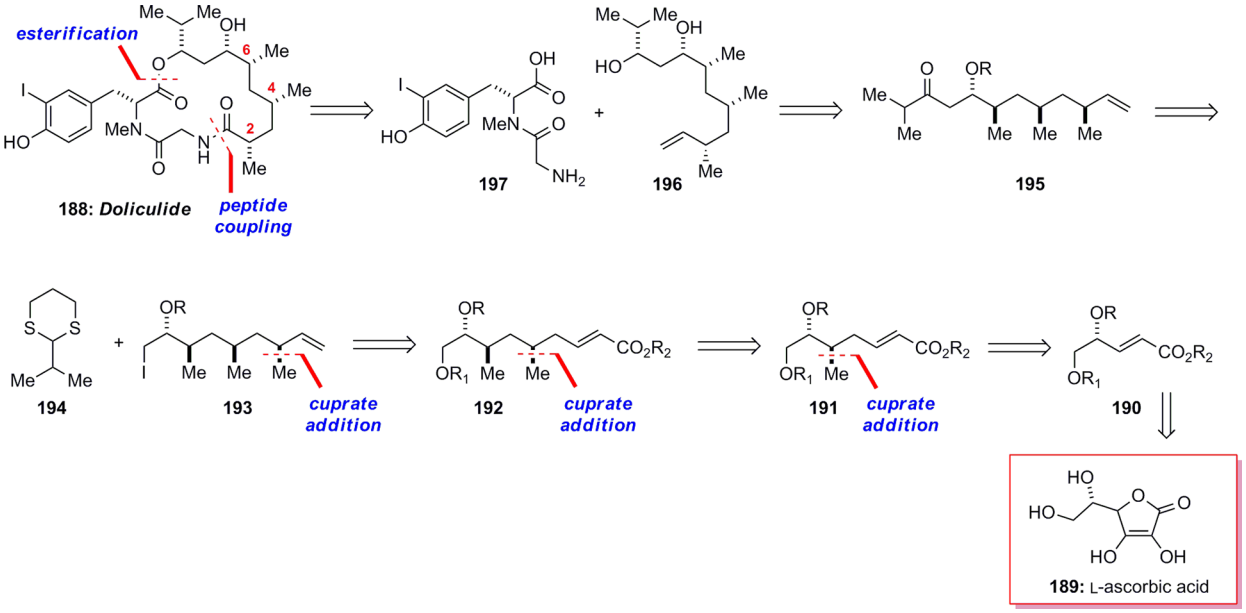
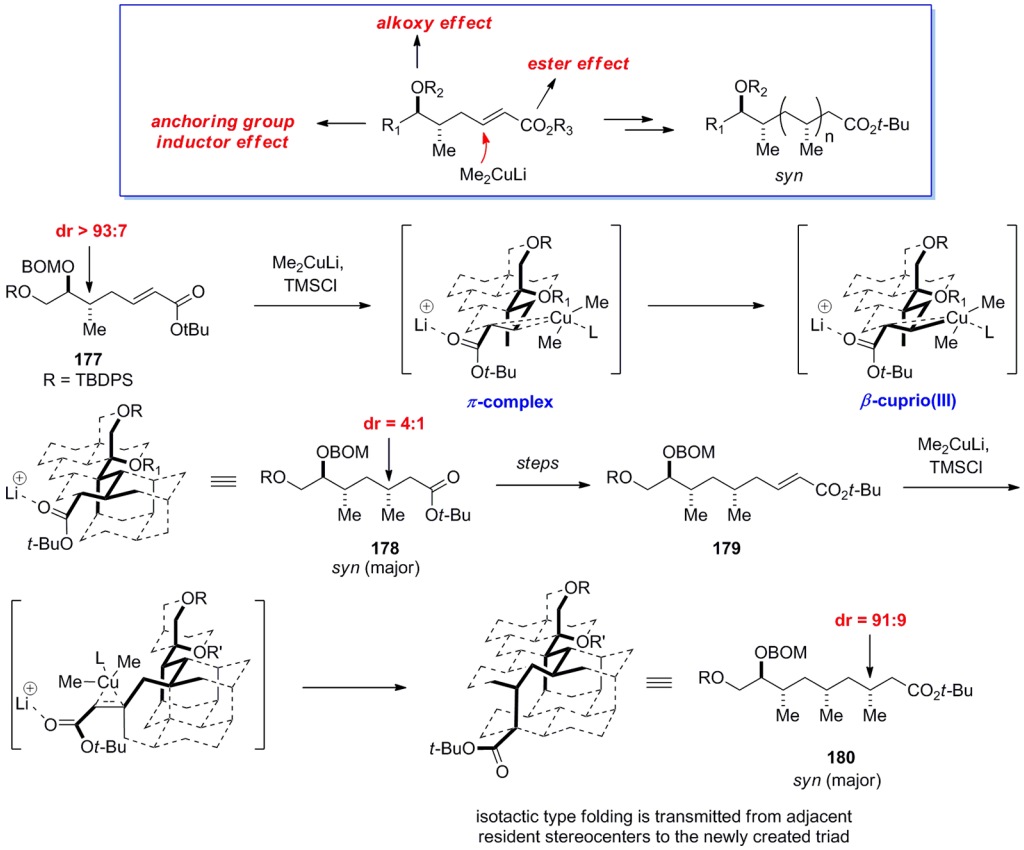


Figure 11. Disconnection of doliculide to L-ascorbic acid as a chiron. Application of iterative conjugate additions toward 1,3-asymmettric induction.

Scheme 17. Mechanistic Rationale for the Iterative *Syn*-Selective Conjugate Addition of Cuprates to Enoates



to give six naturally occurring oidiodendrolides (**249**-**251** and **253**-**255**), as well as nagilactone F (**252**) in excellent yields and high stereoselectivity.

Applications of Chiral Phosphonamide Anion Chemistry to Natural Product Synthesis. The versatility of organophosphorus compounds and their reactivity through various electronic states in ionic and neutral forms was a source of inspiration to me early in my academic career. I was also impressed by the principles of "hard and soft acids and bases" pioneered by Ralph Pearson.[82] I still teach aspects of this fundamental concept to this day, and I continue to use trivalent phosphorus compounds as marquis examples of soft bases. This led me to study the bromination of polyhydroxy compounds such as carbohydrates with the combination of triphenylphosphine and *N*-bromosuccinimide.[83] Further studies into the properties of trivalent organophosphorus compounds led us to

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657−6688

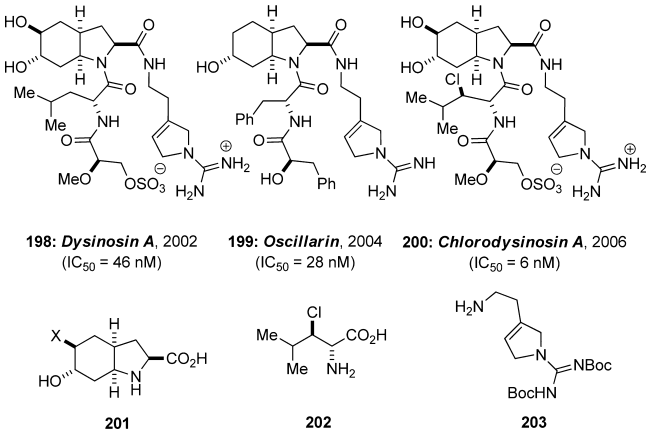
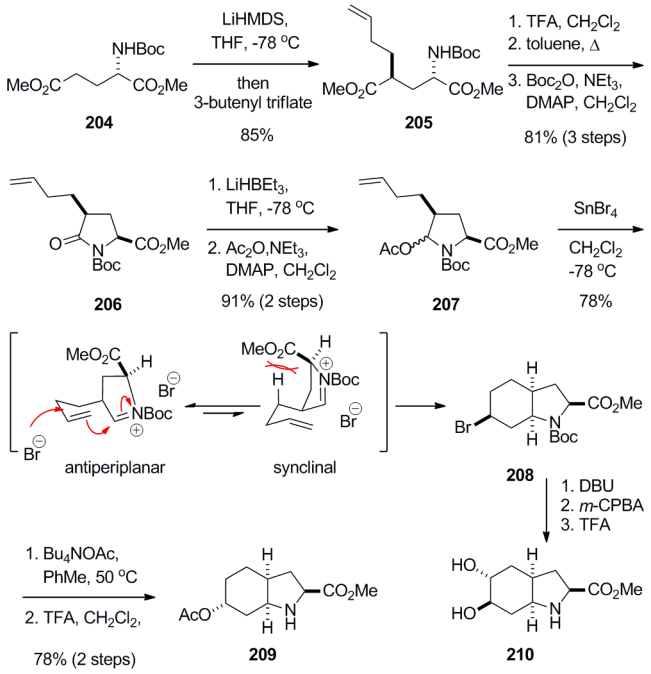


Figure 12. Structures of dysinosin A, chlorodysinosin A, and oscillarin octahydroindole carboxylic acid, (3*R*)-3-chloro-L-leucine, and Δ^3-pyrroline segments. In vitro activities against thrombin (factor IIa).

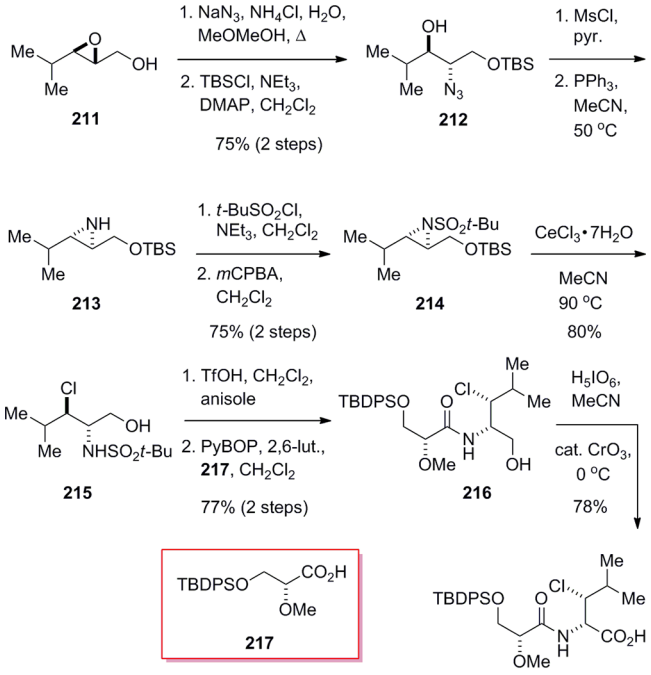
Scheme 18. Synthesis of the Octahydroindole Subunit in Oscillarin, Dysinosin A, and Cholordysinosin A via an Azonia–Prins Key Reaction



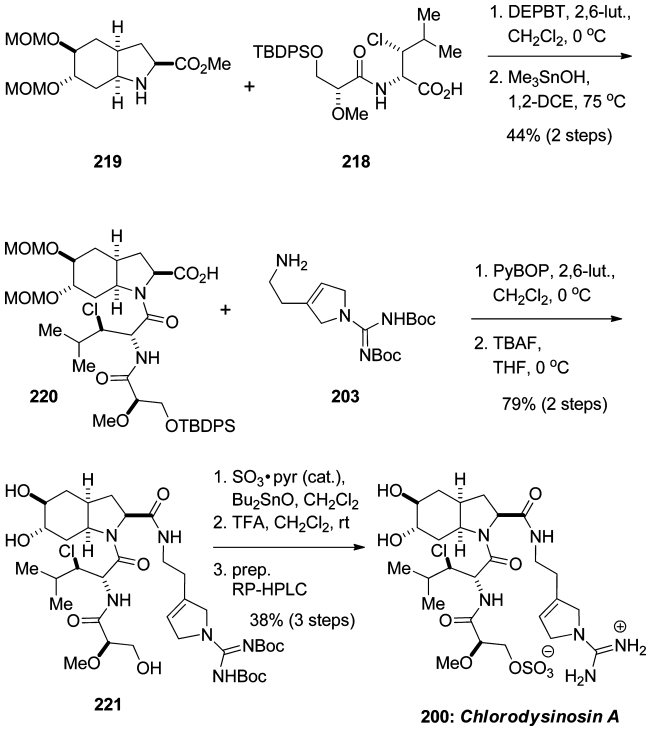
the use of 2-dimethylamino-*N*,*N*-diphenyl-1,3,2-diazaphospholidine as reagents for the derivatization of alcohols to give the alkoxyphospholidine counterparts, which were highly crystalline (Scheme 26).[84] Furthermore, treatment of these derivatives with halide sources, such as methyl iodide, led to the corresponding iodides with inversion of configuration.

Interest in the stereoelectronic properties of oxaphosphetanes in Wittig and Horner–Wadsworth–Emmons-type olefination reactions led us to study cyclic phosphonamides **264** in olefination reactions[85] (Scheme 27). Although weakly basic, the corresponding anions were excellent reagents for the olefination of aldehydes and ketones to give the corresponding alkylidene counterparts (**265**). Moreover, contrary to phosphorus ylides, the olefination of Δ^5-cholestenone[86] led to the corresponding unconjugated olefin **266** with recovery of unreacted enone. Thus, attack of the "soft" phosphonamide anion on the carbonyl group

Scheme 19. Synthesis of the (3*R*)-3-Chloro-D-leucine Subunit



Scheme 20. Assembly of Chlorodysinosin A



was favored over enolization and double bond conjugation to the Δ^4-enone isomer of **266**. It should be noted that the cyclic oxaphosphetane oxide (**268**) undergoes rapid fragmentation even in presence of cold acetic acid. The corresponding acyclic *N*,*N*-diethylphosphonamides require refluxing in methyl iodide or silica to release the corresponding olefins.[87] We then focused on exploring the reactivity of chiral, nonracemic phosphonamides in the hope of achieving asymmetric olefination reactions.

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

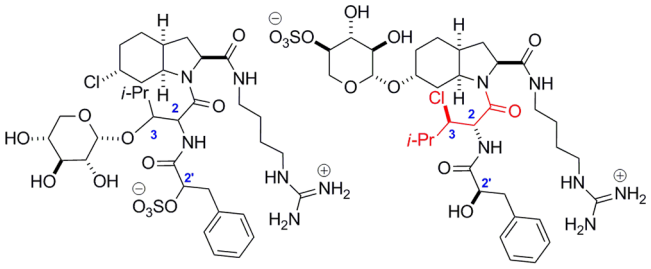


Figure 13. Proposed and revised structures of aeruginosins 205A and 205B.

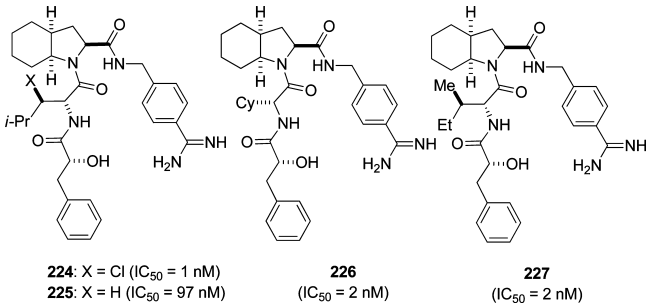


Figure 14. Octahydroindole analogues incorporating a D-leucyl C-3 substituent and their inhibitory in vitro activity against thrombin.

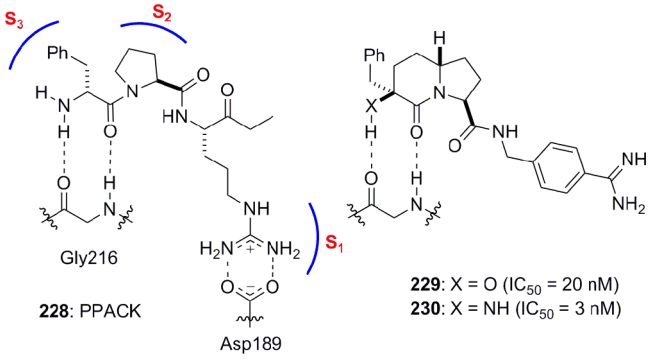


Figure 15. Structure of PPACK. Constrained indolizidinone analogues and their in vitro inhibitory activity against thrombin.

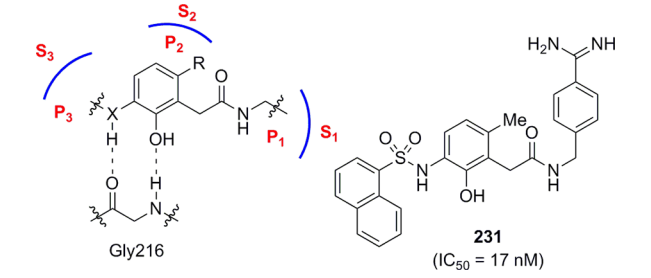


Figure 16. Left: model for binding of a P_2/P_3 phenolic core. Right: thrombin inhibitory activity of an achiral naphthylsulfonamide phenol analogue.

To this end we conceived of C_2-symmetric phosphonamide **270**, readily prepared from *trans*-(*R*,*R*)-1,2-diaminocyclohexane (**269**) as a chiral version of the monocyclic variants shown above (Scheme 28).[88] By virtue of its C_2-symmetry, phosphonamide **270** exists in a single diastereomeric form, in

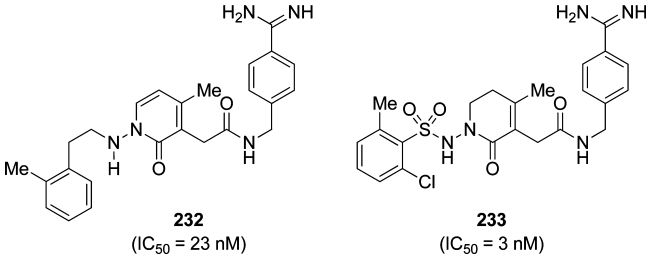


Figure 17. *N*-Aminopyridin-2-one, *N*-aminodihydropyridin-2-one core motifs, and their in vitro thrombin inhibitory activity.

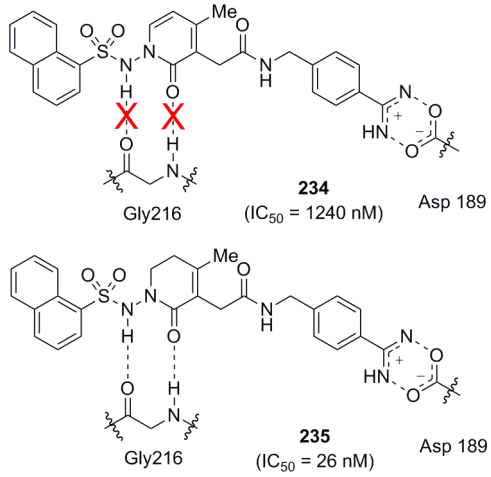
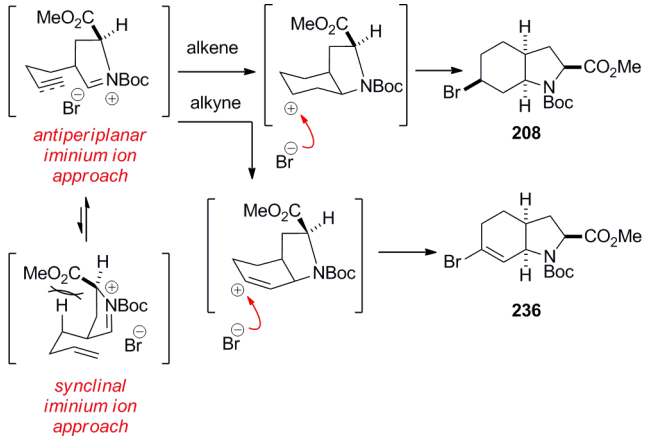


Figure 18. Comparative in vitro activity against thrombin for pyridone and dihydropyridone-based inhibitors.

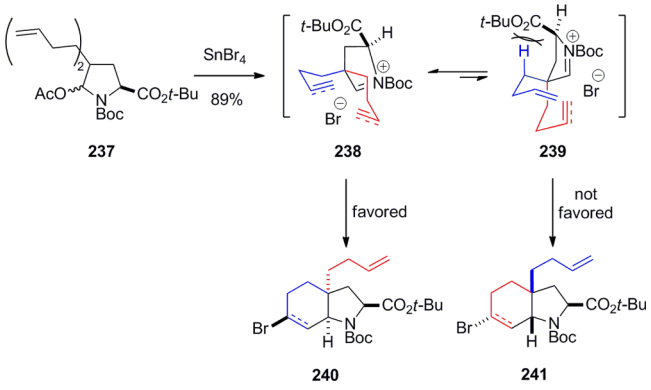
Scheme 21. Proposed Reactive Intermediates in the *N*-Acyloxyiminium Ion Azonia–prins Halocarbocyclization to Octahydroindoles and Hexahydroindoles



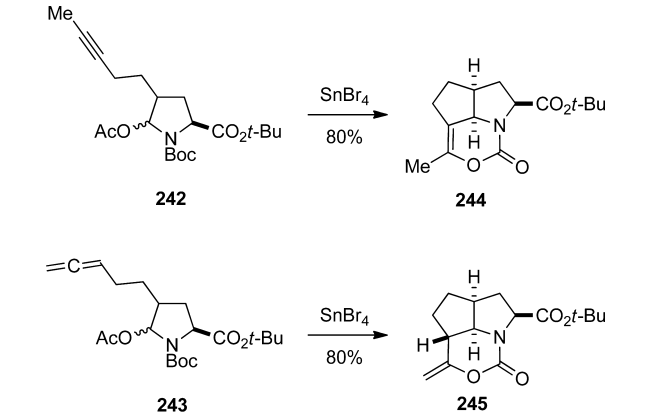
which steric and stereoelectronic effects would favor the attack of an electrophile from the "left cleft" side of the anion in the (*R*,*R*)-isomer (**A**). Thus, *α*-substituted phosphonamides of high enantiopurity represented by **271** could be obtained by this method and further hydrolyzed to the corresponding phosphonic acids. In practice, olefin formation could be achieved from axially symmetrical 4-*tert*-butylcyclohexanone and **272** in 90% ee. That the enantiofacial equatorial approach was favored, was later supported by the X-ray crystal structures of intermediates *β*-hydroxyphosphonamides such as **275** prior to their fragmentation.[89]

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

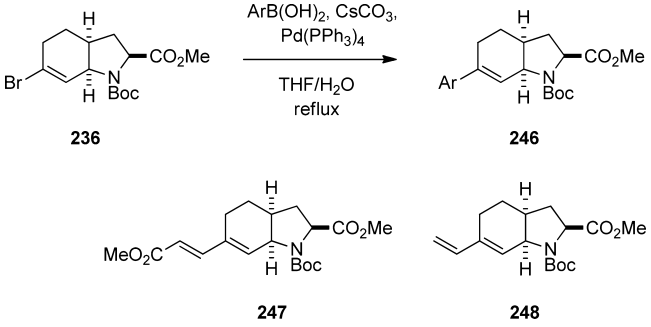
Scheme 22. Proposed Mechanism for the Diastereoselective Azonia–Prins Cyclization of Bis Alkene and Alkyne Tethers



Scheme 23. Synthesis of Functionalized Dihydrooxazinones



Scheme 24. Synthesis of 6-Substituted Hydroindole-2-carboxylic Acids Exploiting Suzuki, Heck, and Stille Pd-Catalyzed Functionalizations



This result, already reported in 1984, was the first example of a rationally designed asymmetric olefination reagent[88] and demonstrated the conceptual utility of *trans*-(*R*,*R*)- or (*S*,*S*)-1,2-diaminocyclohexanes as a versatile chiral template in asymmetric synthesis. Elegant applications can now be found in the Jacobsen[90] and Trost[91] catalysts for asymmetric epoxidation and allylation reactions.

Other applications of phosphonamide anions in asymmetric C–C bond formation include single-stage Michael addition to enones, lactones, lactams, and α,β-unsaturated esters followed by enolate alkylation to generate vicinal and quartenary carbon centers in high diasteromeric purity.[92] These reactions are likely to proceed via lithium-coordinated intermediates **279** and **280** (Scheme 29). Oxidative cleavage of the resulting

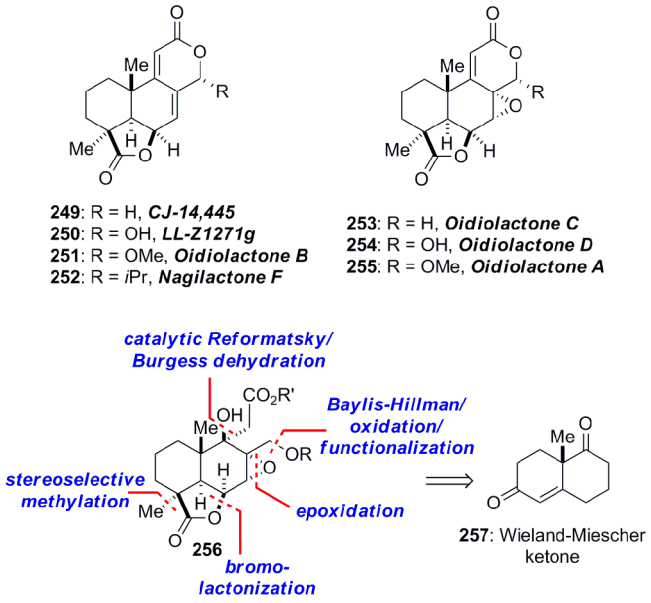
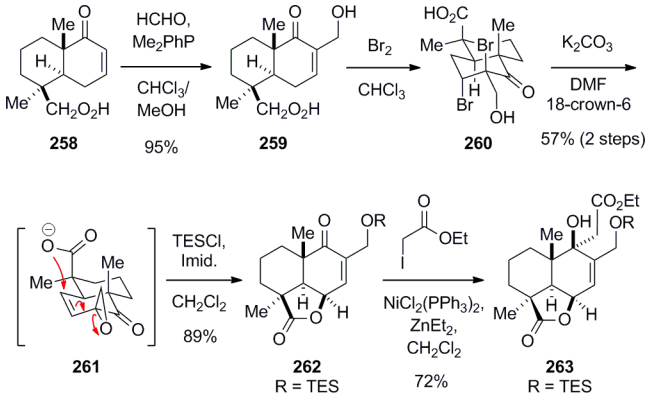
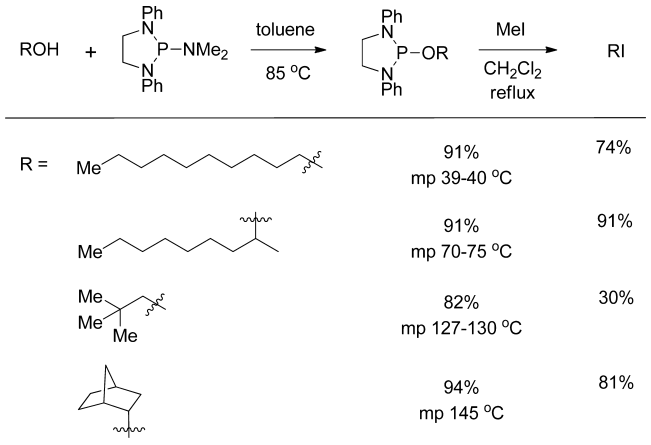


Figure 19. Structures and total synthesis of naturally occurring norditerpene dilactones and strategic transformations toward a common precursor.

Scheme 25. Ni-Catalyzed Reformatsky Reaction



Scheme 26. Synthesis of Crystalline Alkoxy *N,N*-Diphenyl-1,3,2-diazaphospholidines and Their Conversion to Iodides



vinyl phosphonamide appendages affords the corresponding aldehydes **281**–**284** or alcohols **285**–**288** after reduction (Scheme 29).

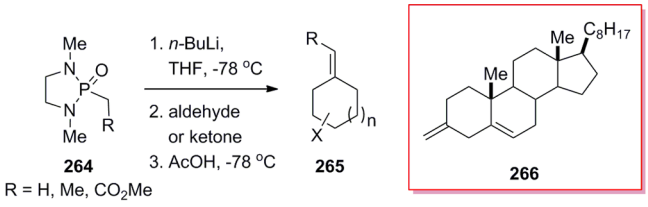
dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Sequential 1,4-conjugate additions to two different cinnamate esters leads to seven-carbon acyclic diesters **290**–**292** with predisposed phenyl and methyl substituents as illustrated in Scheme 30.[93] Oxidative cleavage and reduction afford **293** and **294**. The reactions proceed most likely via lithium-cordinated intermediates such as **295**, **296**, and **297**.

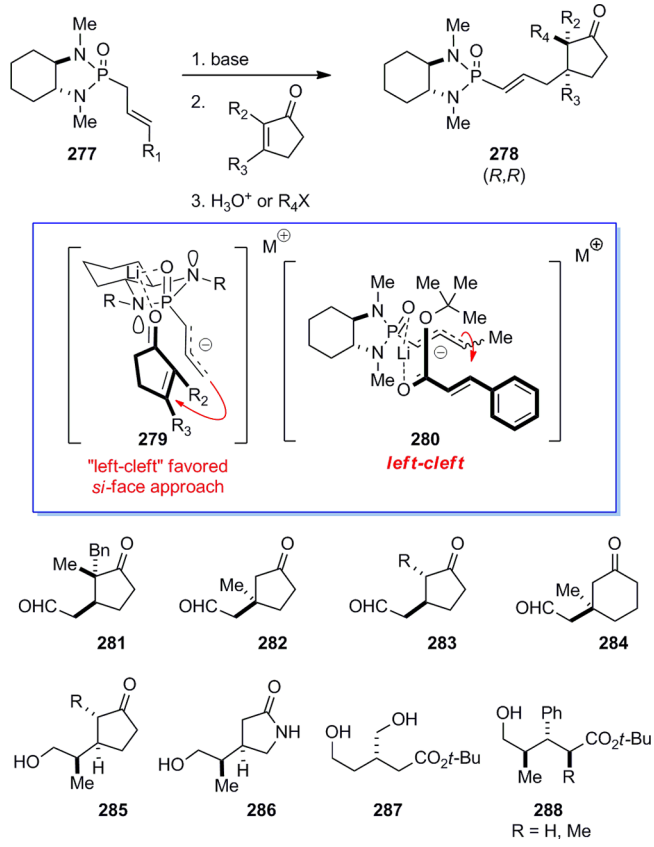
Utilization of chloroallyl phosphonamides, such as **298**, results in 1,4-conjugate addition to enones, followed by stereocontrolled attack of the resulting enolate with elimination of chloride via **299** and **300** to give fused the cyclopropane **301**, which can be cleaved to the corresponding aldehyde and further epimerized if needed. The cyclopropanation reaction is applicable to enones, lactones, lactams, and acyclic α,β-unsaturated esters (Scheme 31).[94]

The design and reactivity of the bicyclic phosphonamides such as **277** (Scheme 29) was also validated in the synthesis of

Scheme 27. Olefination with Cyclic Phosphonamide Anions and Mechanistic Rationale

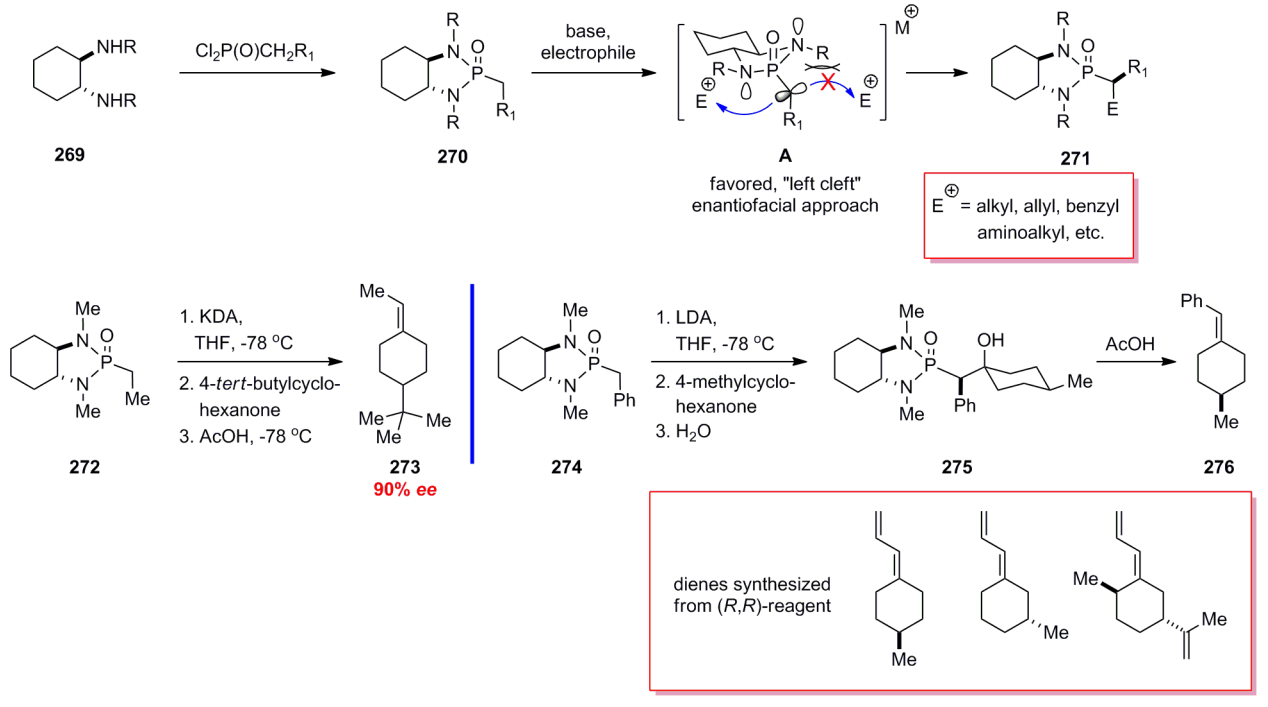


Scheme 29. Asymmetric Conjugate Additions in Cyclic Enones, Lactones, Lactams, and α,β-Unsaturated Esters with Optional Enolate Alkylation[a]



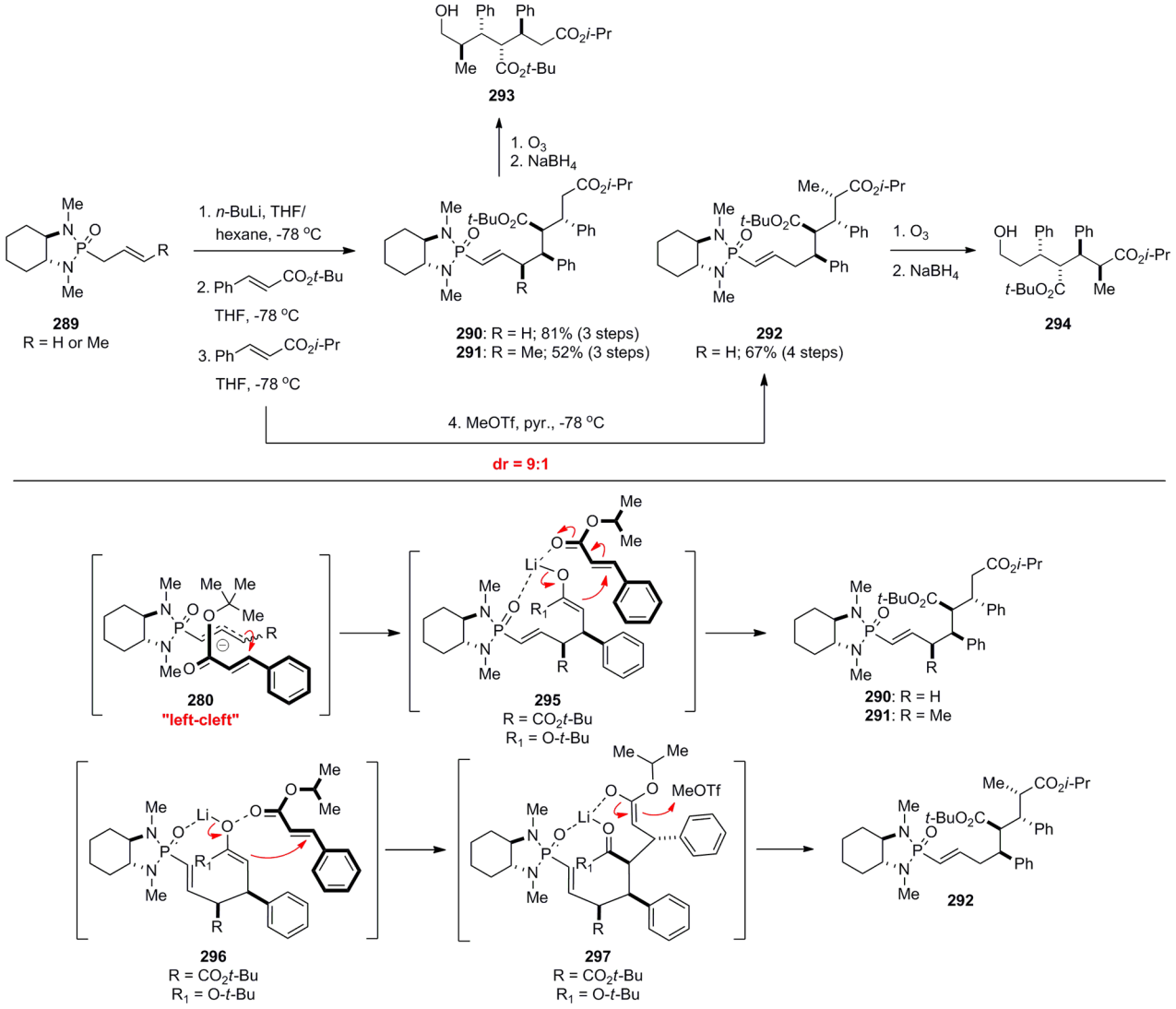
[a]Products are shown after oxidative cleavage of the corresponding vinylic phosphonamides or after reduction.

Scheme 28. Stereodifferentiating Phosphonamide Anions, Mechanistic Rationale, and Asymmetric Olefinations

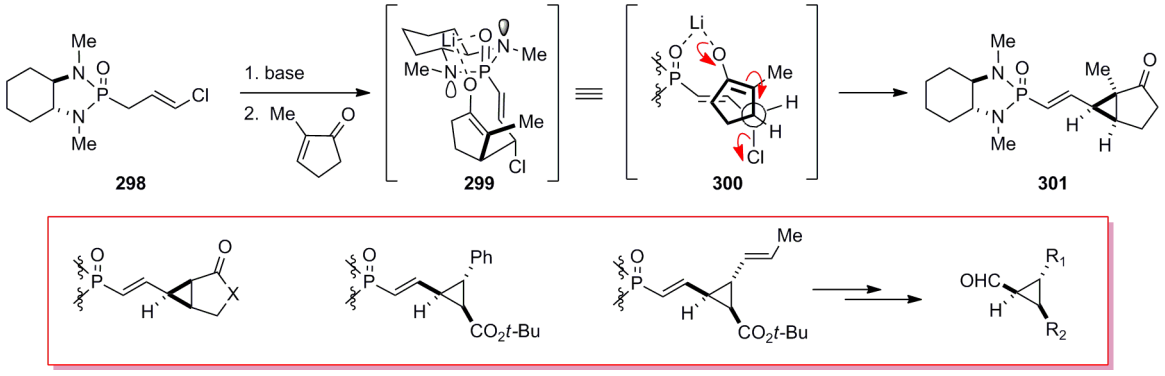


dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Scheme 30. Sequential 1,4-Conjugate Additions and Mechanistic Rationales and Products of Oxidative Cleavage and Reduction



Scheme 31. Asymmetric cyclopropanation of Cyclic Enones, Lactones, Lactams and α,β-Unsaturated Esters with Chloroallyl Phosphonamides



enantiopure α-alkyl[95] and α-amino[96] phosphonic acids as well as enantiopure cyclopropane phosphonic acids.[97]

Nudiflosides A and D. The iridoid glycosides represented by nudiflosides A (**302**) and D (**303**)[98] contain a pentasubstituted cyclopentane core unit, in which one of the appendages also harbors a stereogenic *C*-methyl group (Figure 20). We envisaged a strategy wherein subunits **304** and **305** would be coupled to give the mono- or diester natural products. The sequence of bond-forming reactions toward the cyclopentane core unit **304**, schematically depicted in the Figure 20, relied on the stereocontrolled Michael addition of a crotyl phosphonamide anion derived from **289**.[99]

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

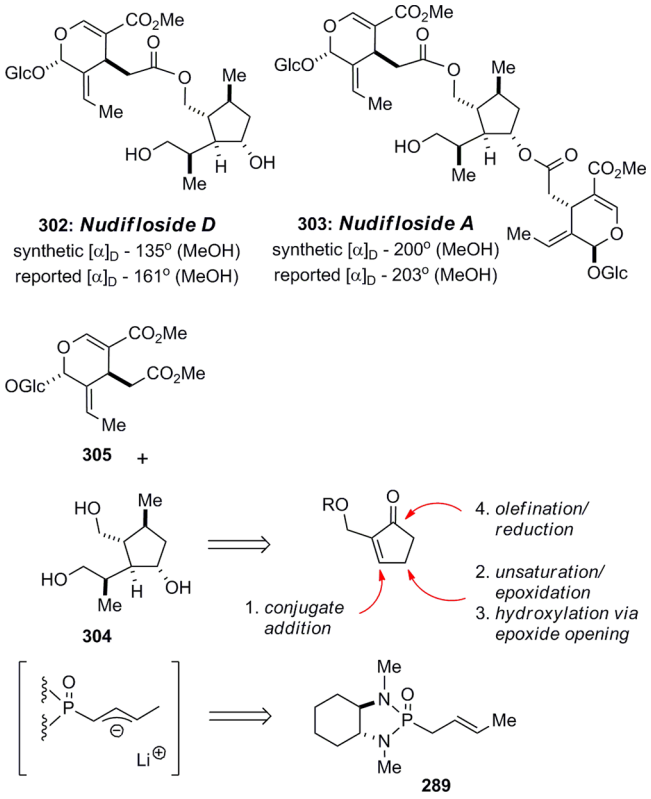


Figure 20. Structures of nudiflosides A and D and disconnection to a substituted cyclopentane core subunit.

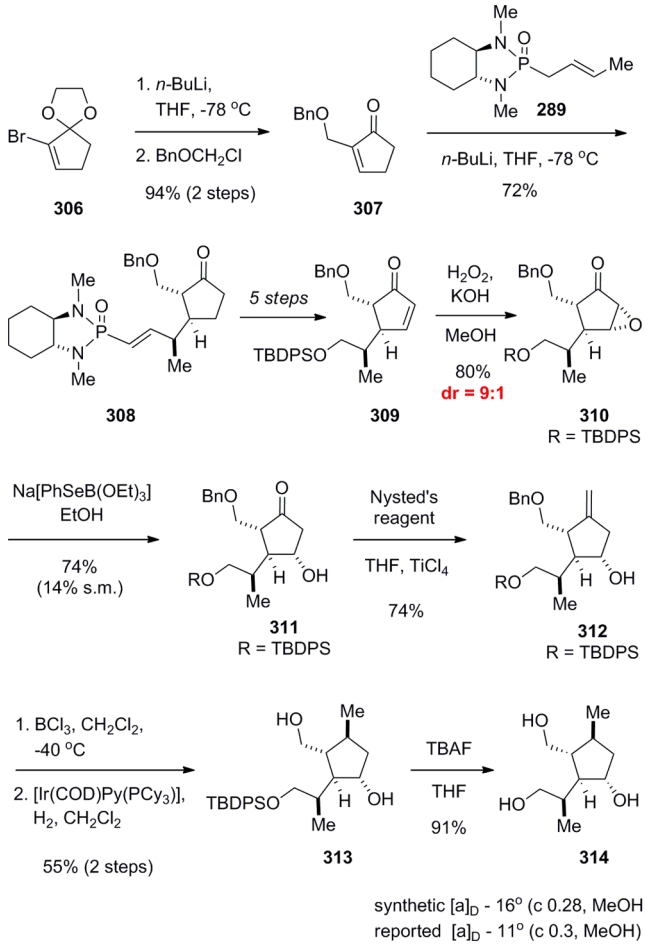
The systematic functionalization of the bromocyclopentanone **306** led to **307**, which upon reaction with the anion of **289** gave **308** (Scheme 32). Further manipulation by application of known chemical transformations afforded the cyclopentane triol **314**, which was esterified with **305** (Figure 20) to give nudiflosides A (**303**) and D (**302**), thereby completing their synthesis and confirming their proposed stereochemistry.

Jerangolid A and Ambruticin S. A variety of myxobacteria produce two families of linear polyketides having potent antifungal properties. Among the five members of the jerangolide family[100] jerangolid A (**315**) is reported to be the most active. Our strategy for the first synthesis of jerangolid A is depicted in retrosynthetic form leading to dihydropyran (**318**) and lactone (**319**) subunits (Figure 21).[101] The key assembly strategy to generate the *trans*-double bonds would rely on phosphonamide and sulfone anion coupling reactions. Glycidol **316** and Roche ester **317** were the starting chirons for the elaboration of the dihydropyran unit **318** and the isolated stereogenic center flanked by the two double bonds. The elaboration of lactone **319** proved to be particularly challenging with regard to the I−Mg exchange to install the requisite hydroxymethyl group.

Ambruticin S. The antifungal natural polyketide ambruticin S (**320**) belongs to a more populated family that comprises about a dozen members (Figure 22).[102] Of the four published total syntheses of ambruticin S,[103] that of Liu and Jacobsen is the most innovative in terms of its conceptual design and utilization of catalytic methods.[103d] Due to their close resemblance in the "eastern" segment of jerangolid A (**315**) and ambruticin S (**320**), a common synthetic strategy was considered.[104] Disconnection of ambruticin S at logical sites led to **321** and **322** as intermediates, which would be derived from D-glucose and *O*-benzyl (*R*)-glycidol derivative (**323**) respectively. Phosphonamide-mediated olefination and cyclopropanation reactions would feature prominently in the synthesis of **324**. Thus, utilizing the chlorallyl phosphonamide anion of **298** led to a stereocontrolled 1,4-conjugate addition to *tert*-butyl cinnamate to give cyclopropane **325** with the desired relative and absolute stereochemistry. Oxidative cleavage of the olefin furnished aldehyde **326** (Scheme 33).

The elaboration of olefin linkages is shown in Scheme 34, where monocyclic phosphonamides anions were utilized. Trisubstituted olefin **329** was obtained as a 6:1 mixture of *E*/*Z*-isomers, whereas **331** was obtained as a single *E*-isomer.

Scheme 32. Synthesis of the Pentasubstituted Cyclopentane Core of Nudiflosides A and D



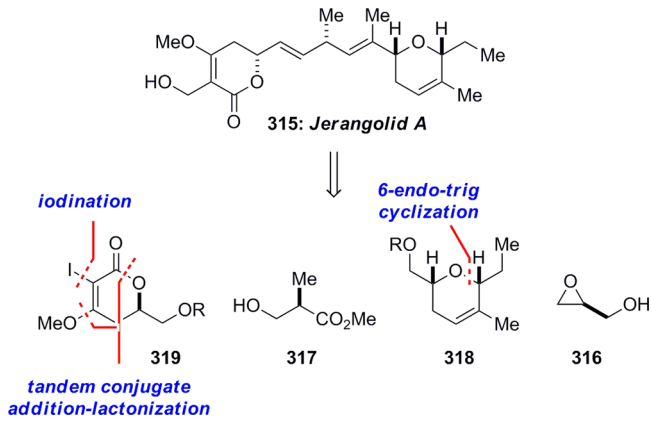


Figure 21. Disconnection of jerangolid A to various chirons and key assembly strategies.

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657−6688

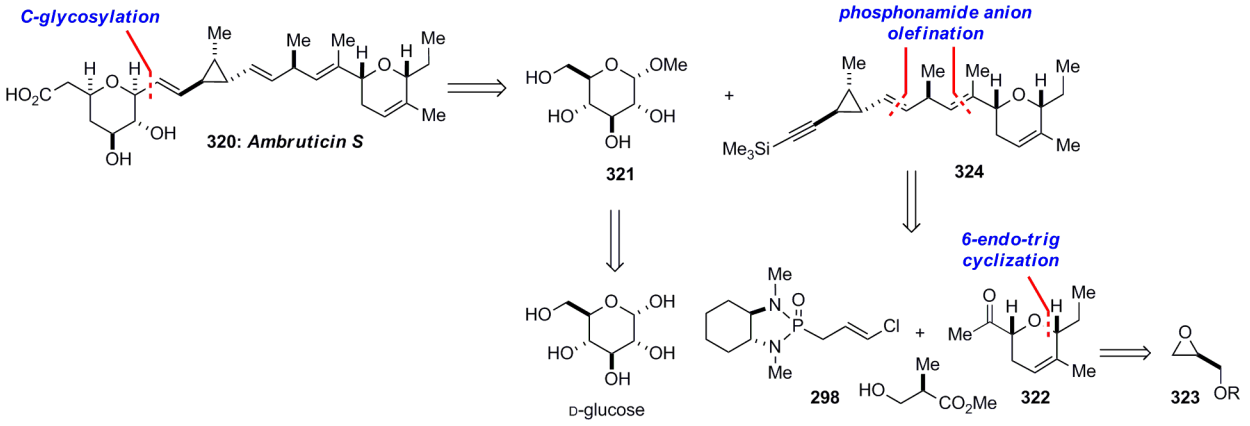
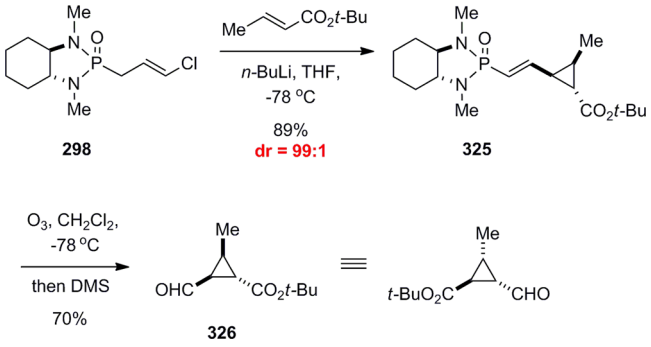


Figure 22. Disconnection of ambruticin S to various chirons and key assembly strategies.

Scheme 33. Asymmetric Synthesis of the Trisubstituted Cyclopropane Core Subunit



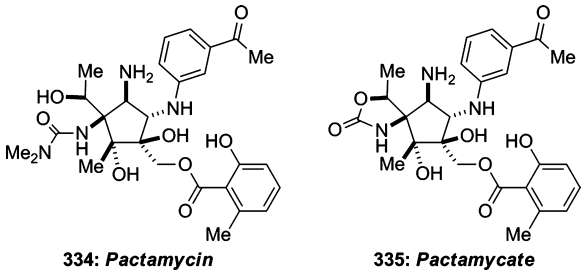
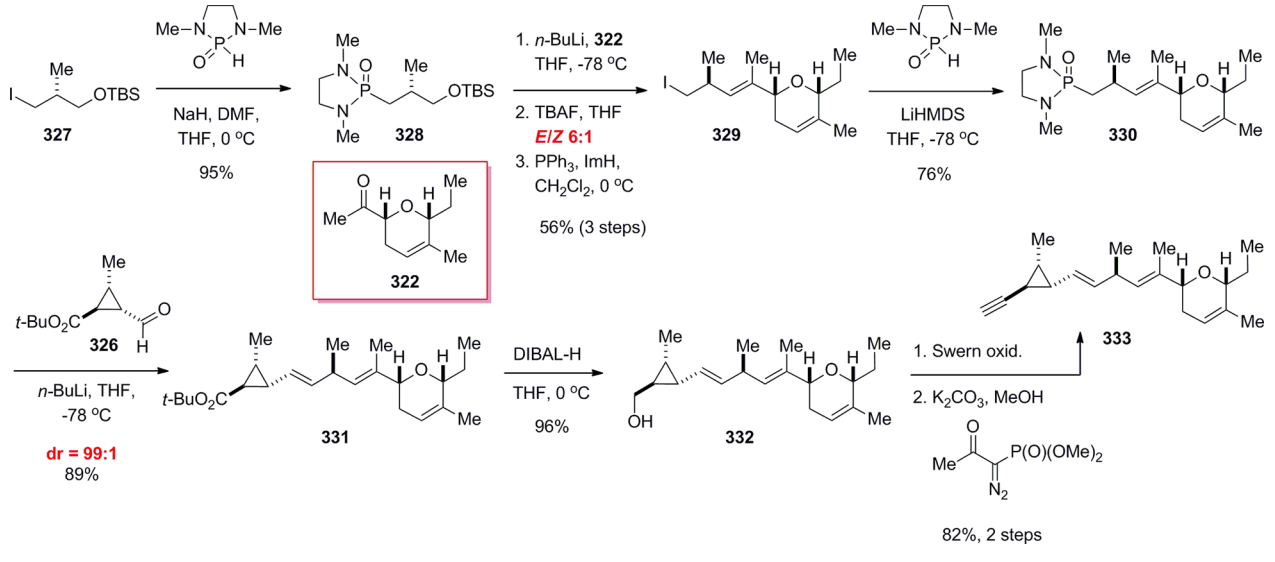


Figure 23. Structures of pactamycin and pactamycate.

Further elaboration led to the acetylenic subunit **333**, which was used for the final assembly to ambruticin S (**320**). This fifth total synthesis of ambruticin S was primarily undertaken to develop methodology toward truncated analogues to be tested as antifungal agents. Our productive collaboration with Syngenta in Basel, Switzerland, led us to probe the pharmacophoric subunit in ambruticin S believed to be associated with the olefinic system in conjunction with the dihydropyran ring C. Thus, a library of analogues was synthesized from a truncated portion of ambruticin S and tested at Syngenta.[104] We were also successful in obtaining an X-ray structure of the triformate ester of ambruticin S, in which the carboxyl group was reduced to the primary alcohol. Thus, the unique topology of the middle segment of ambruticin S in the solid state was unveiled for the first time.[103]

Pactamycin. Our molecule of the year for 2011! As in some of the above-illustrated syntheses, we as a community of synthetic chemists are indebted to many pharmaceutical companies, as well as to academic groups, for their efforts in isolating structurally intriguing and often biologically relevant natural products. These "gifts" from nature have provided great incentives to pursue challenging projects toward the total synthesis of complex natural products with great rewards, not the least of which is

Scheme 34. Key Steps in the Phosphonamide Anion-Mediated Olefination



dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657−6688

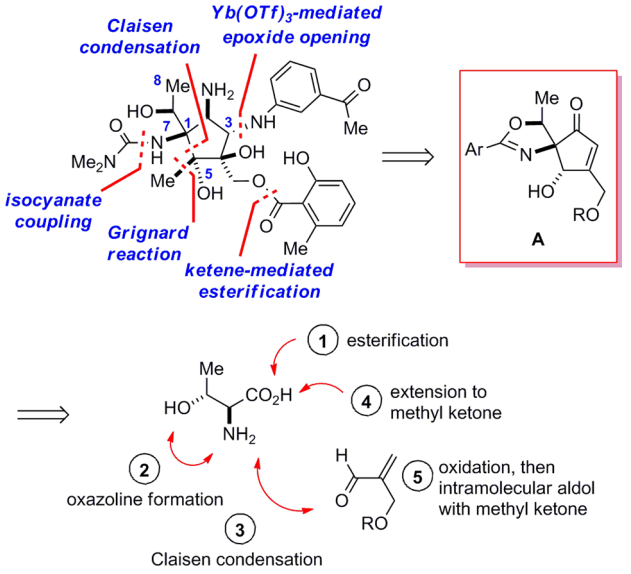
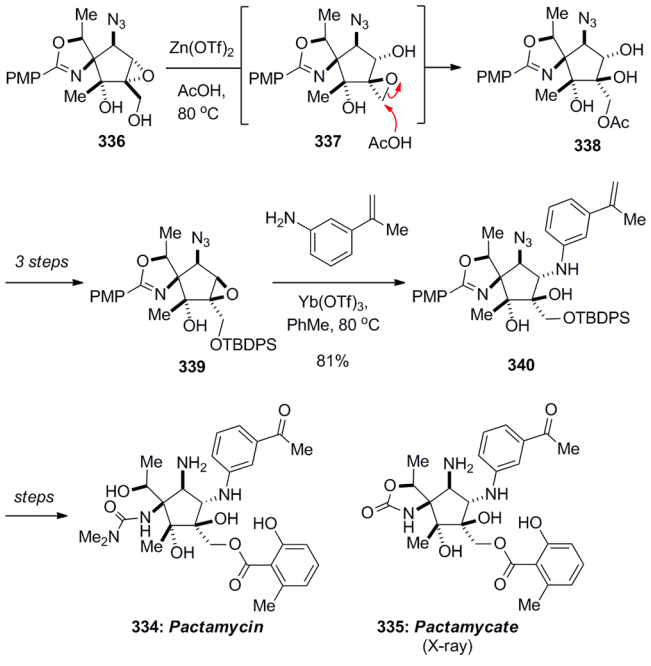


Figure 24. Strategic bond disconnections and key transformations shown in their order of execution. **A** = core cyclopentenone intermediate.

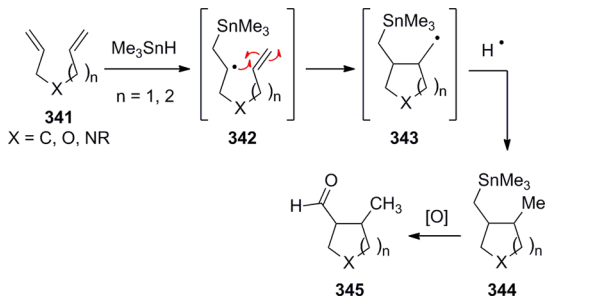
Scheme 35. Key "Epoxide Inversion" Sequence



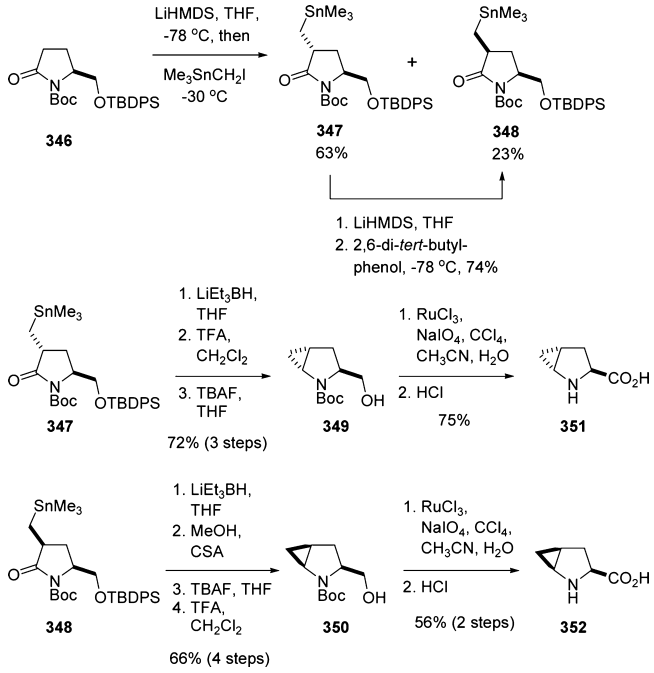
co-worker training. A proposed structure for pactamycin (**334**) was reported in 1970 by Upjohn Company scientists as a result of seminal studies involving chemical degradation.[105] The structure was subsequently corrected in 1972 based on X-ray crystallographic studies of derivatives.[106] The interaction of pactamycin with the 30S RNA site in *Thermus thermophylus* was reported in pioneering X-ray studies by Ramakrishnan and co-workers.[107] Its diverse biological activities, unique mode of binding, as well as its challenging structure incited us to attempt its first total synthesis, which was completed in 2011[108] (Figure 23).

Analysis of the structure of pactamycin (**334**) and that of a congener pactamycate (**335**) presents a daunting task of introducing densely packed functionality on an aminocyclopentanol core motif (Figure 23). Added to the challenge was the order in which functional groups would be introduced and the reactions of choice. A synopsis of this strategy is shown in Figure 24 starting with L-threonine as a partially hidden chiron.

Scheme 36. Trimethylstannyl Radical Addition to Dienes and Oxidative Cleavage



Scheme 37. Synthesis of *cis*- and *trans*-4,5-Methano-L-prolines via Intramolecular Destannylative Iminium Ion Cyclization



An undertaking of this complexity cannot be completed without its trials and tribulations, particularly as more and more functionality was introduced by systematic elaboration of the cyclopentenone core motif **A** (Figure 24). An apparent setback early in the synthesis was encountered with the "wrong" "down" epoxide **336**, which we believed to be the correct "up" epoxide for several steps beyond this stage (Scheme 35). It became imperative to either change our strategy or to find a way to "invert" the epoxide to its "up" diastereomer in order to introduce the aniline moiety. After many attempts, it was found that solvolysis in the presence of $Zn(OTf)_2$ and AcOH led to the desired triol **338**, presumably via formation of a spiro epoxide **337** and subsequent opening with AcOH to give **338**. An $Yb(OTf)_3$-mediated epoxide opening with 3-(2-propenyl)aniline led to **340** in 81% yield.

Having reached advanced intermediate **340**, there remained to cleave the PMP oxazoline and to introduce peripheral functional groups such as the *N*,*N*-dimethylurea. Once again, the curse of extreme proximity effects led to many frustrated attempts at appending an *N*,*N*-dimethylamino carbonyl group onto an

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657−6688

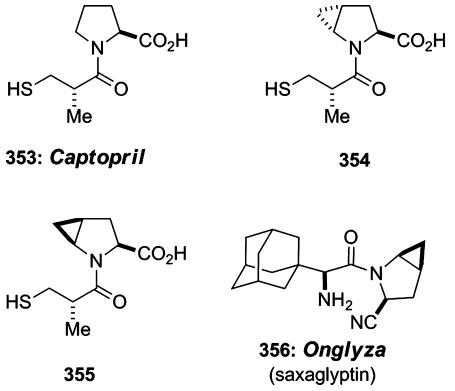


Figure 25. Structure of captopril and 4,5-methano congeners. Structure of Onglyza.

intermediate aminotriol. Surprisingly, all attempts led to *O*-substitution and cyclic carbamate formation involving the tertiary hydroxyl group. Finally, neutralizing the undesirable participating effect of this hydroxyl group by temporary protection as the acetonide, we were able to introduce the dimethylaminocarbonyl group via the intermediacy of a stable isocyanate. Further steps led to pactamycin (**334**) and pactamycate (**335**).[108] Having reached our goal, a quote from Kipling would be appropriate:

"If you could meet with Triumph and Disaster and treat those two imposters just the same"

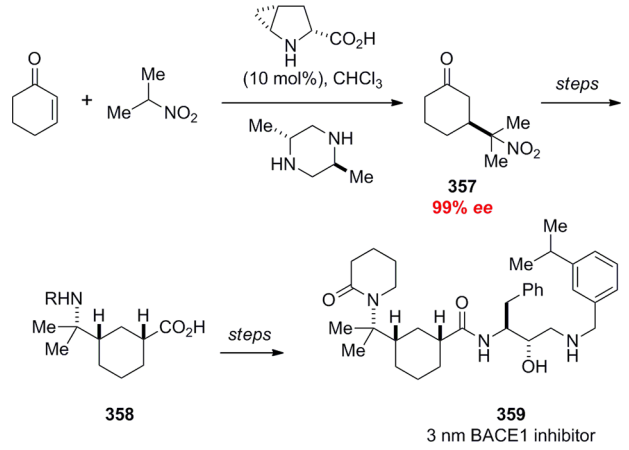
From Concept to Market. Our studies on free-radical tin-mediated additions to terminal dienes, such as **341**,[109] led to formation of five- and 6-membered carbo- and heterocycles (Scheme 36). It was previously assumed that adducts would undergo heterolytic cleavage to the primary free radicals, which would then be reduced.[110] Furthermore, we discovered that the resulting Me_3Sn group in **344** could be oxidatively cleaved to the corresponding aldehydes **345** with ceric ammonium nitrate. This new method of radical-induced carbo- and heterocycle formation from tethered dienes and extended dienes was used toward the synthesis of lignans[7j] and kainoids[7k] (see Figure 1).

An alternative access to trimethylstannylmethyl groups as appendages to core heterocycles was reported based on enolate alkylation chemistry (Scheme 37).[111] Thus, the enolate derived from the lactam **346** led to the *anti*-product **347** as the major isomer and the **348** as the minor. Enolate formation and protonation with a bulky acid source allowed for the conversion of the *anti*-isomer to the *syn*-isomer (Scheme 37).

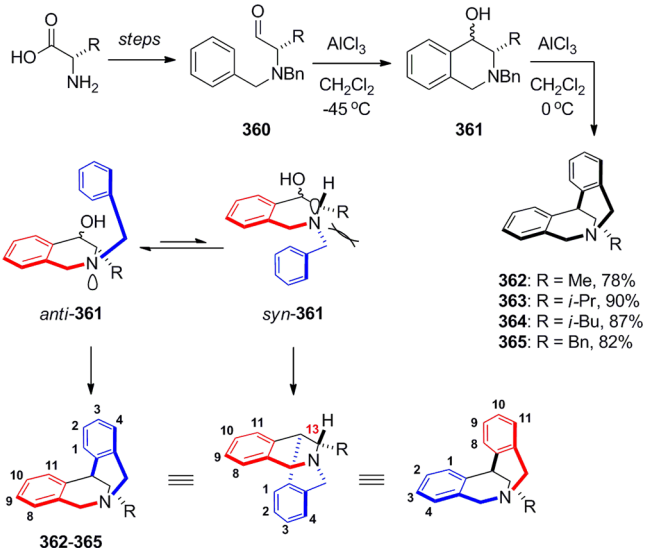
Each isomer was then converted to the hemiaminal or the methoxyhemiaminal, then treated with a protic acid to give the corresponding 4,5-*trans*-methano-*N*-Boc-L-prolinol (**349**) and 4,5-*cis*-methano-*N*-Boc-L-prolinol (**350**), respectively. Oxidation to the corresponding acids gave 4,5-*trans*-methano-L-proline (**351**) and 4,5-*cis*-methano-L-proline (**352**). We were intrigued at the time that the free amino acids **351** and **352** as well as their *N*-Boc derivatives were considerably "flatter" compared to *N*-Boc-L-proline or L-proline itself.

We surmised that the exchange of L-proline by its 4,5-methano counterparts in drug substances or as peptidomimetics would have interesting consequences because of the altered conformation and possibly the pyramidal or planar nature of the nitrogen atoms especially as amides. Captopril (**353**) was the first example of a rationally designed inhibitor of the angiotensin converting enzyme (ACE).[112] Subsequent structural variants showed that bicyclic analogues such as ramipril were susceptible

Scheme 38. Catalytic Asymmetric Michael Addition and Synthesis of a Potent Enzyme Inhibitor



Scheme 39. Synthesis and Perspective Drawings of C_{13}-Substituted Dihydromethanodiarylazocines and Possible Friedel–Crafts Cyclization Models

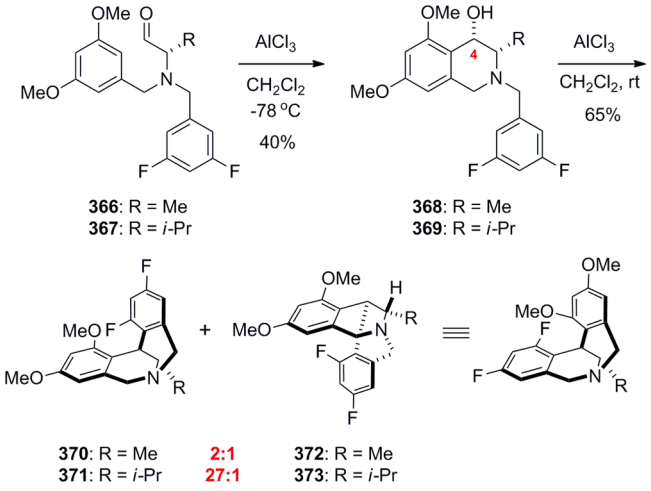


to the stereochemistry of the ring function. We reasoned that the smaller size of the fused methano group in synthetic variants of captopril represented by **354** and **355** could be tolerated in the enzyme active site (Figure 25).[113] Indeed, they showed excellent in vitro inhibitory activity against ACE, which was equal or superior to captopril. The concept of conformational change through ring flattening of pyrrolidines was used in the development of Onglyza (saxaglyptin) (**356**), a DDP-inhibitor, presently marketed for the treatment of type II diabetes by Bristol-Myers-Squibb.[114] In the absence of the 4,5-methano constraint, the half-life of the drug is considerably shorter due to a facile intramolecular attack of the amino group on the nitrile function. It is interesting that unbeknownst to an investigator, curiosity-driven research can find its way to the development of a drug substance exploiting the concepts discovered during original research efforts.

The enormous recent interest in proline and related compounds as so-called organocatalysts[115] prompted our interest in the use of 4,5-methanoprolines in 1,4-conjugate addition reaction.[116] In the presence of 2,5-dimethyl piperazine as an additive *trans*-4,5-methano-L-proline is an excellent catalyst

dx.doi.org/10.1021/jo300902m | J. Org. Chem. 2012, 77, 6657–6688

Scheme 40. Desymmetrization of Dihydromethanodiarylazocines

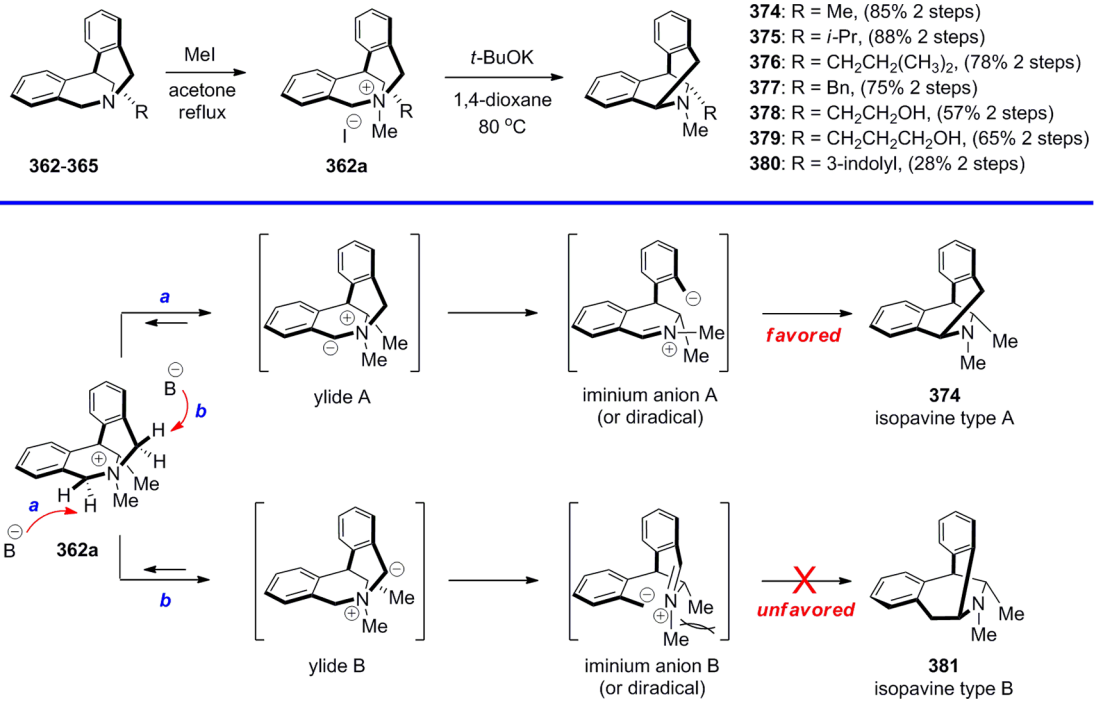


in the addition of 2-nitropropane, and other nitroalkanes, to 2-cyclohexenone. The >99% enantiomerically pure (3*R*)-nitro-2-propyl cyclohexanone **357** was converted to the γ-amino acid **358**, and ultimately elaborated to the potent inhibitor of β-amyloid cleaving enzyme (BACE1) (Scheme 38).[117]

Beauty Is in the Eyes of the Beholder. Eye-Teasing Molecules. Small compact molecules with interesting topologies often present intriguing kaleidoscopic shapes. Consider such "gems" as cubane, twistane, and bulvallene as molecules with rich legacies and beautiful symmetries.[118] Our first contact with molecules is visual. What follows is a fascinating series of eye to the mind's eye signaling events that manifest themselves in many ways depending on the task at hand. For the purposes of total synthesis, two chemists may see totally different connectivities resulting in different approaches, a subject that can be discussed at length.[1a] To a medicinal chemist, the shape and topology of a potential drug illicits images of molecular recognition and structure-based design of analogues. During a study of alkaloid synthesis from *N*,*N*-dibenzylamino acid aldehydes **360**, we prepared a series of "dihydroazocines" as functionalized tetrahydroisoquinolines (Scheme 39).[119] Viewed in a three-dimensional perspective, these molecules portray an interesting topology, wherein the aryl rings adopt a structurally orthogonal orientation, comprising two tetrahydroisoquinoline motifs with a common nitrogen atom. The presence of the C_{13} appendage from the original amino acid, effectively desymmetrizes the molecule compared to achiral and symmetrical counterparts.

A cursory look at the perspective structures **362**−**365** is misleading, since the rigid topology does not truly reflect the enantiotopic pathways of ring closure from the initially formed *N*-benzyl-4-hydroxytetrahydroisoquinoline **361**. In fact, two *ortho*-cyclization modes are possible in the Friedel−Crafts reaction, rapidly involving equilibrating *N*-benzyl invertomers of **361** (*anti*-**361** and *syn*-**361**). The putative *anti*-**361** representing the "blue" *anti*-benzyl group relative to R, effectively cyclizes to produce the (13*S*)-isomer shown as **362**-**365**. However the *syn*-**361** invertomer would also lead to the same (13*S*) product **362**-**365**. This topological eye-teaser can be better appreciated by numbering and color-coding the phenyl rings. Based on this tenet, one would intuitively conclude that the steric encumberment in the "*syn*" isomer resulting from **361** should favor the closure of the "*anti*" isomer of **361** with an unimpeded trajectory of attack of the "blue" benzyl group on the incipient benzylic carbocation. Although such a trend may indeed be operative, it is not possible to validate it in the case of the unsubstituted dihydro-methano-dibenzoazocines, because both pathways of cyclization lead to the same product (Scheme 39). In order to resolve this issue, we carried out the ring closure from a

Scheme 41. [1,2]-Stevens Rearrangement, which Leads to Isopavine Type A via Dianion (or Diradical) Intermediates



dx.doi.org/10.1021/jo300902m | *J. Org. Chem.* 2012, 77, 6657−6688

dissymmetric *N*-benzyltetrahydroisoquinoline with a "small" (methyl) and a "large" (isopropyl) side chain (Scheme 40).

Reaction of *N*-3,5-dimethoxybenzyl-*N*′-3,5-difluorobenzyl-2-amino-L-propionaldehyde (**366**) with $AlCl_3$ at −45 °C led, as expected, to the corresponding 3,5-dimethoxy-*N*′-3,5-difluorobenzyltetrahydroisoquinoline **368**. Upon ring closure at room temperature, we obtained a mixture of inseparable products assumed to consist of **370** and **372** (R = Me) in a ratio of 2:1 as estimated by ^{1}H NMR. However, when the bulk of the C_3 side-chain was increased to an isopropyl group, as in **367**, the quasi-exclusive product arising from the cyclization of the intermediate **369**, which was obtained as a single diastereomer, was found to be **371**. This would result from an "*anti*" attack of the *N*′-3,5-difluorobenzyl group on the incipient carbocation at C_4 of the 3,5-dimethoxytetrahydroisoquinoline **369** from the side opposite to the bulky isopropyl group. In this manner, we could show indirectly the influence of the C_3 substituent (tetrahydroisoquinoline numbering) on the mode of cyclization, which also leads to differentially functionalized aryl rings in this series.[120,121]

From the Eye Teasing to Eye-Opening Molecules: Morphinomimetics. Isopavines and pavines have long been associated with various pharmacological properties in the CNS area. With a method to access C_{13}-substituted enantiopure dihydromethanodiarylazocines in hand, we studied their transformation to 6-substituted isopavines utilizing a [1,2]-Stevens rearrangement.[122] Highly diastereoselective intramolecular cyclizations took place to give the corresponding isopavines with appropriate appendages. (Scheme 41).[120,121] Mechanistic rationales suggested that the intermediate *N*-methylazocinium ion **362a** undergoes site-selective benzylic H-abstraction to afford an ylide anion or diradical and then closure to the isopavine (Scheme 41).

Manual inspection of molecular models and computer-aided visualization of ORTEP structures from X-rays revealed an eye-opening feature of these isopavines. Viewed as constrained piperidines, and focusing on the lone pair of electrons on the nitrogen atom, an inescapable spacial relationship with morphine (**382**) became evident from a quasi-ideal convergence of their rigid carbon framework and the strategic location of the tertiary nitrogen atom (Figure 26). However, when isopavine **364** prepared from

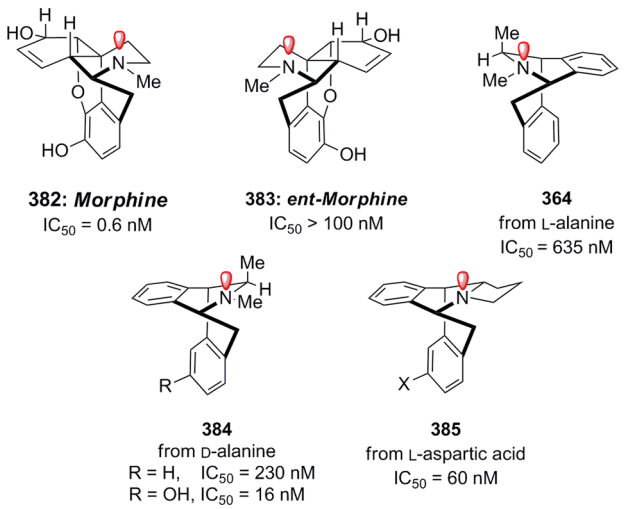


Figure 26. Spacial relationships of isopavines with morphine.

L-alanine was tested against the human μ-opioid receptor, the value of IC_{50} = 635 nM compared to 1 nM for morphine was not encouraging.[123] Upon further visual scrutiny, it became clear that the problem resided in the incorrect orientation of the nitrogen lone pair since the tested isopavine from L-alanine actually corresponded to the enantiomer of L-morphine (**383**), which is considerably less active. This proposal was put to the test by synthesizing the enantiomeric isopavine from D-alanine (**384**). Indeed, the activity was vastly improved, especially after some SAR studies involving substituents on the aryl rings.[124] Another way to properly orient the lone pair was to stay in the L-amino acid series but constrain the fused isopavine in a pentacyclic structure as in **385**.

CONCLUSION

In spite of its labor intensive nature, the enterprise of total synthesis can be a highly rewarding activity with many benefits, not the least of which is co-worker training. We are at an exciting crossroads in organic synthesis, where aspects of innovative methodology, function (biological or otherwise), and practical utility, manifest themselves in the structures of fascinating molecules that can be synthesized. In the realm of natural products, there appears to be no boundaries to the structural complexities that have been conquered by synthesis. Conceptually different approaches to one and the same molecule showcase the creative flair of the modern-day synthetic chemist in the planning phases. The two principal modalities of achieving stereocontrolled syntheses of molecules (as an entity, or of a segment thereof) continue to rely to a larger part on the recognition of chiral nonracemic precursors (chirons) as starting materials, and on bond-by-bond forming reactions, which can now be achieved with high levels of enantioselectivity in catalytic or stoichiometric fashion.

As long as the enterprise of synthesis remains as a reagent- and reaction-based operational activity, the above-mentioned modalities (in combination with biocatalytic methods) will continue to be the way in which molecules are synthesized in the laboratory. There is no shortage of generating creative ideas toward the synthesis of complex (or not so complex) target molecules on paper. We are, however, not as directly successful in the execution or such well-laid plans, in spite of the advent of sophisticated instrumentation and advanced synthetic methodologies. Issues related to reaction efficiency, repeated manipulation of functional groups, unexpected results, and recalcitrant chemistry combine to lengthen sequences with impractical consequences. These problems are all the more important in a Process Development group working toward an economical synthesis of a potential drug substance. However, synthetic chemists can also be at their best under duresse, rising to the challenge and succeeding against all odds. In reality, the prowess of the modern-day synthetic chemist, whether in academia or industry, is undeniably evident. As a result, the discipline of organic synthesis, particularly when directed at natural products and related bioactive molecules, will continue to evolve as newer and more efficient methodologies are developed. It is also hoped that the combined efforts of synthetic chemists and biologists will lead to highly stimulating discoveries leading eventually to life-saving medicines for the benefit of humankind.

AUTHOR INFORMATION

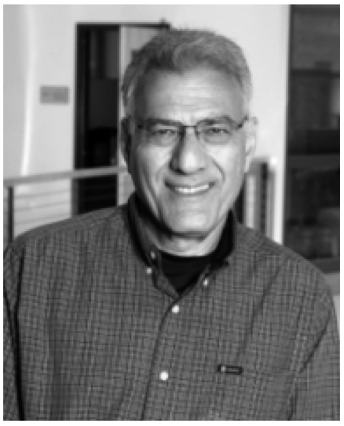
Corresponding Author

*E-mail: stephen.hanessian@umontreal.ca.

Notes

The authors declare no competing financial interest.

Biography



Stephen Hanessian obtained his Ph.D. degree at the Ohio State University in 1960. After seven years at the Parke-Davis Research Laboratories in Ann Arbor, MI, he accepted a faculty position at the University of Montreal in 1968 as Associate Professor. A year later he was promoted to Full Professor and currently holds the Isis Pharmaceutical Research Chair. He is also on the Faculty of the Departments of Chemistry, Pharmaceutical Sciences, and Pharmacology at the University of California, Irvine.

■ ACKNOWLEDGMENTS

I am grateful for generous funding from NSERC and FQRNT throughout my academic career. Collaborative projects with dozens of pharmaceutical research laboratories worldwide have been a quasicontinuous and highly appreciated source of financial contributions. Finally, I thank the over 300 past and present co-workers for their dedication and productivity. Special thanks go to Benoît Deschênes-Simard for his services as the group X-ray crystallographer and computer go-to person and for rendering the artwork on the cover of this issue. The assistance of Brad Merner and Stephane Dorich in the preparation of the final version of this manuscript is highly appreciated.

■ REFERENCES

(1) For examples, see: (a) Hanessian, S.; Giroux, S.; Merner, B. L.; *Design and Strategy in Organic Synthesis: From the Chiron Approach to Catalysis*; Wiley-VCH: Weinheim, 2012. (b) Nicolaou, K. C.; Chen, J. S. *Classics in Total Synthesis III: Further Targets, Strategies, Methods*; Wiley-VCH, Weinheim, 2011. (c) Corey, E. J.; Kürti, L. *Enantioselective Chemical Synthesis: Methods, Logic, and Practice*; Direct Book Publishing: Dallas, 2010.

(2) For a historical perspective, see: Nicolaou, K. C.; Montagnon, T. *Molecules that Changed the World,* Wiley-VCH: Weinheim, 2008. See also: Corey, E. J.; Kürti, L.; Czakó, B. *Molecules and Medicine*; Wiley: New York, 2007.

(3) Hanessian, S. *ChemMedChem* **2006**, *1*, 1300.

(4) Hanessian, S.; Franco, J.; Larouche, B. *Pure Appl. Chem.* **1990**, *62*, 1887.

(5) For selected reviews, see: (a) Hanessian, S. Reflections on the Total Synthesis of Natural Products: Art, Craft, Logic, and the Chiron Approach. *Pure Appl. Chem.* **1993**, *65*, 1189. (b) Hanessian, S. Design and Implementation of Tactically Novel Strategies for Stereochemical Control Using the Chiron Approach. *Aldrichimica Acta* **1989**, *22*, 3. See also: Hanessian, S. *Total Synthesis of Natural Products: The "Chiron Approach"*; Pergamon: Oxford, 1984.

(6) For examples, see: (a) Gawley, R.; Aubé, J. *Principles of Asymmetric Synthesis*, 2nd ed.; Pergamon: New York, 2012. (b) *Fundamentals of Asymmetric Catalysis*; Walsh, P. J., Kozlowski, M., Eds.; University Science Books: Sausalito, 2008. (c) *Catalysis of Organic Reactions*; Schmidt, S. R., Ed.; CRC Press: Boca Raton, 2007.

(7) (a) Thromboxane B_2 (**1**): Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1977**, *55*, 562. Hanessian, S.; Lavallée, P. *Can. J. Chem.* **1981**, *59*, 870. (b) Spectinomycin (**2**): Hanessian, S.; Roy, R. *J. Am. Chem. Soc.* **1979**, *101*, 5839. Hanessian, S.; Roy, R. *J. Antibiot.* **1979**, *32*, S-73. (c) Azimic acid (**3**): Hanessian, S.; Frenette, R. *Tetrahedron Lett.* **1979**, *36*, 3391. (d) Palitantin (**4**): Hanessian, S.; Sakito, Y.; Dhanoa, D.; Baptistella, L. *Tetrahedron* **1989**, *45*, 6623. (e) Octosyl acid A (**5**): Hanessian, S.; Kloss, J. *J. Am. Chem. Soc.* **1986**, *108*, 2758. Hanessian, S.; Kloss, J.; Sugawara, T. *ACS Symp. Ser.* **1988**, 64. (f) Thienamycin (**6**): Hanessian, S.; Desilets, D.; Bennani, Y. *J. Org. Chem.* **1990**, *55*, 3098. (g) Ajmalicine (**7**): Hanessian, S.; Faucher, A.-M. *J. Org. Chem.* **1991**, *56*, 2947. (h) Burseran (**8**): Hanessian, S.; Léger, R. *Synlett* **1992**, 402. (i) Tetrahydrolipstatin (**9**): Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768. (j) Polyoximic acid (**10**): Hanessian, S.; Fu, J.-M.; Chiara, J.; DiFabio, R. *Tetrahedron Lett.* **1993**, *34*, 41557. Hanessian, S.; Fu, J.-M. *Can. J. Chem.* **2001**, *79*, 1812. (k) Kainic acid (**11**): Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (l) Pseudoannonacin A (**12**): Hanessian, S.; Abad-Grillo, T. *J. Org. Chem.* **1998**, *63*, 1049. (m) Anthoplalone (**13**): Hanessian, S.; Cantin, L.-D.; Andreotti, D.; Gomtsyan, A. *J. Org. Chem.* **1999**, *64*, 4893. (n) Azetidinecarboxylic acid (**14**): Hanessian, S.; Bernstein, S.; Yang, R.-Y.; Maguire, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1437. (o) Dysinosin A (**15**): Hanessian, S.; Margarita, R.; Hall, A.; Johnstone, S.; Tremblay, M.; Parlanti, L. *J. Am. Chem. Soc.* **2002**, *124*, 13342. (p) Malayamycin A (**16**): Hanessian, S.; Marcotte, S.; Machaalani, R.; Huang, G. *Org. Lett.* **2003**, *5*, 4277. Hanessian, S.; Marcotte, S.; Machaalani, R.; Huang, G.; Perron, J.; Loiseleur, O. *Tetrahedron* **2006**, *62*, 5201. (q) Talaumidin (**17**): Hanessian, S.; Reddy, G. I. *Synlett* **2007**, 475. (r) Longicin (**18**): Hanessian, S.; Giroux, S.; Buffat, M. *Org. Lett.* **2005**, *7*, 3989. (s) Manassantin A (**19**), B (**20**), B_1 (**21**): Hanessian, S.; Reddy, G. J.; Chahal, N. *Org. Lett.* **2006**, *8*, 5477. (t) Aminoglycoside 66-40C (**22**): Hanessian, S.; Maianti, P. *Chem. Commun.* **2010**, *46*, 2013. Hanessian, S.; Maianti, P.; Ly, V. L.; Deschênes-Simard, B. *Chem. Sci.* **2012**, *3*, 249. (u) *ent*-Cyclizidine (**23**): Hanessian, S.; Soma, U.; Dorich, S.; Deschênes-Simard, B. *Org. Lett.* **2011**, *13*, 1048.

(8) Lovell, F. M. *J. Am. Chem. Soc.* **1996**, *88*, 4510.

(9) Hanessian, S.; Kaltenbronn, J. S. *J. Am. Chem. Soc.* **1966**, *88*, 4509.

(10) Chabala, J. C.; Mrozik, H.; Tolman, R. L.; Eskola, P.; Lusi, A.; Peterson, L. H.; Woods, M. F.; Fisher, M. H.; Campbell, W. C.; Egerton, J. R.; Ostlind, D. A. *J. Med. Chem.* **1980**, *23*, 1134.

(11) Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; André, C. *J. Am. Chem. Soc.* **1986**, *108*, 2276. See also: Hanessian, S.; Ugolini, U.; Hodges, P.; Beaulieu, P.; Dubé, D.; André, C. *Pure Appl. Chem.* **1987**, *59*, 299. Hanessian, S.; Beaulieu, P.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 5071.

(12) Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17. See also: Hanessian, S. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.: Dekker: New York, 1996; Chapter 16, p 381. Hanessian, S.; Lou, B. *Chem. Rev.* **2000**, *100*, 4443.

(13) (a) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933. See also: (b) Pivichny, J. V.; Shim, J.-S.; Simmerman, L. A. *J. Pharm. Sci.* **1983**, 733.

(14) Hanessian, S.; Dubé, D.; Hodges, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 7063.

(15) Hanessian, S.; Chemla, P.; Tu, Y. *Tetrahedron Lett.* **1993**, *34*, 1407.

(16) Hanessian, S.; Chemla, P. *Tetrahedron Lett.* **1991**, *32*, 2719.

(17) Toeplitz, B. K.; Cohen, A. I.; Funke, P. T.; Parker, W. L.; Gougoutas, J. Z. *J. Am. Chem. Soc.* **1979**, *101*, 3344 and references cited therein.

(18) Hanessian, S.; Dehoff, B.; Cooke, N.; Sakito, N. *J. Am. Chem. Soc.* **1990**, *112*, 5276.

(19) (a) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055. (b) Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1171.

(20) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Eliel, E., Allinger, N., Eds.; Wiley-Interscience: New York, 1982; Vol. *13*, p 1. Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 1.

(21) Evans, D. A.; Dow, R. L.; Shih, J. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5276. See also: Lautens, M.; Colucci, J. J.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879.
(22) Hanessian, S.; Thavonekham, B.; Dehoff, B. *J. Org. Chem.* **1989**, *54*, 5831.
(23) Albers-Schönberg, G.; Joshua, M.; Lopez, M. B.; Hensens, O. D.; Springer, J. P.; Chen, J.; Ostrove, S.; Huffman, C. H.; Alberte, A. W.; Patchett, A. A. *J. Antibiot.* **1981**, *34*, 507. See also: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4209.
(24) Hanessian, S.; Roy, P. J.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Garganico, G. *J. Org. Chem.* **1990**, *55*, 5766.
(25) (a) Matsubara, S.; Takai, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029. (b) Suzuki, M.; Takeda, H.; Noyori, R. *J. Org. Chem.* **1982**, *47*, 902.
(26) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023. For other significant contributions, see: (a) Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439. (b) Wender, D. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157. (c) Martin, S. F.; Rueger, H.; Williamson, S. A.; Grzejszak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124. For a review, see: Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671.
(27) Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465.
(28) Hanessian, S.; Di Fabio, R.; Marcoux, J.-F.; Prud'homme, M. *J. Org. Chem.* **1990**, *55*, 3436.
(29) For examples, see: (a) Heno, Y.; Chimo, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (c) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140.
(30) For a total synthesis, see: (a) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. P.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. (b) Iio, H.; Nagaoka, H.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7965.
(31) Hanessian, S.; Sumi, K. *Synthesis* **1991**, *12*, 1083.
(32) Hanessian, S.; Gai, Y.; Wang, W.; Olivier, E. *J. Am. Chem. Soc.* **1997**, *119*, 10034.
(33) (a) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919. (b) Vishwa Karma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1987**, *66*, 203.
(34) For examples, see: (a) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524. (b) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (c) Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951.
(35) (a) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4631. (b) Hanessian, S.; Gai, Y.; Wang, W. G. *Tetrahedron Lett.* **1996**, *37*, 7473.
(36) Hanessian, S.; Ma, J.; Wang, W. *Tetrahedron Lett.* **1999**, *40*, 4631.
(37) Hanessian, S.; Gai, Y.; Wang, W. G. *Tetrahedron Lett.* **1996**, *37*, 7477.
(38) Werner, G.; Hagenmaier, H.; Drautz, H.; Baumgartner, A.; Zähner, H. *J. Antibiot.* **1984**, *37*, 110. See also: Everett, J. R.; Baker, G. H.; Dorgau, R. J. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 717. Corey, E. J.; Ponder, J. W. *Tetrahedron Lett.* **1984**, *25*, 4325.
(39) Hanessian, S.; Ma, J.; Wang, W.; Gai, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10200.
(40) For other total syntheses, see: (a) Evans, D. A.; Calter., M. A. *Tetrahedron Lett.* **1993**, *34*, 6871. (b) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Noguchi, Y.; Yoshida, T.; Murase, H.; Nakata, M.; Matsumara, S. *J. Org. Chem.* **1997**, *62*, 3271. (c) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed.* **1999**, *38*, 1692. See also: Marshall, J. A.; Adams, N. A. *Org. Lett.* **2000**, *2*, 2897.
(41) Hanessian, S.; Meng, Q.; Olivier, E. *Tetrahedron Lett.* **1994**, *35*, 5393.
(42) Hanessian, S.; Tehim, A.; Meng, Q.; Granberg, K. *Tetrahedron Lett.* **1996**, *37*, 9001.
(43) For examples, see: (a) Khosla, C. *Chem. Rev.* **1997**, *97*, 2577. (b) Katz, L. *Chem. Rev.* **1997**, *97*, 2557.
(44) Berger, J.; Jampolsky, L. M.; Goldberg, M. W. *Arch. Biochem.* **1949**, *22*, 476. See also: Keller-Schierlein, W. *Helv. Chim. Acta* **1967**, *50*, 731. Anderson, B. F.; Herlt, A. J.; Rickards, R. W.; Robertson, G. B. *Aust. J. Chem.* **1989**, *42*, 717.
(45) Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F. *J. Am. Chem. Soc.* **2003**, *125*, 13784.
(46) For other total syntheses, see: (a) Duffey, M. O.; Le Tiran, A.; Morken, J. D. *J. Am. Chem. Soc.* **2003**, *125*, 1458. (b) Vong, B. G.; Kim, S. H.; Abraham, S.; Theodorakis, E. A. *Angew, Chem. Int. Ed.* **2004**, *43*, 3947. (c) Nagamitsu, T.; Takano, D.; Fukuda, T.; Otoguro, K.; Kuwajima, I.; Harigaya, Y.; Õmura, S. *Org. Lett.* **2004**, *6*, 1865.
(47) Hanessian, S.; Giroux, S.; Mascitti, V. *Proc. Nat. Acad. of Sci. U.S.A.* **2004**, *101*, 11996.
(48) For other syntheses, see: (a) Ishiwata, H.; Nemoto, M.; Ojka, M.; Yamada, K. *J. Org. Chem.* **1994**, *59*, 4710. (b) Ghosh, K. K.; Liu, C. *Org. Lett.* **2001**, *3*, 635.
(49) For examples, see: (a) Hoffman, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2094. (b) Hoffman, R. W.; Gottlich, R.; Schöpfer, U. *Eur. J. Org. Chem.* **2001**, 1865.
(50) Kohno, J.; Nishio, M.; Sakurai, M.; Kawano, K.; Hajime, H.; Kameda, N.; Kishi, N.; Yamashita, T.; Okuda, J.; Komatsubara, S. *Tetrahedron* **1999**, *55*, 7771.
(51) For examples, see: (a) Dale, J. *J. Chem. Soc.* **1963**, 93. (b) Dale, J. *Angew, Chem. Int. Ed.* **1966**, *5*, 1000. (c) Celmer, W. D. *Symposium on Antibiotics*; Ste. Marguerite, Québec, Canada, Mar 1−3, 1971; Butterworths: London, 1971; pp 413−453.
(52) Hanessian, S.; Chahal, N.; Giroux, S. *J. Org. Chem.* **2006**, *71*, 7403.
(53) For reviews, see: (a) Hanessian, S.; Giroux, S.; Mascitti, V. *Synthesis* **2006**, *7*, 1057. (b) ter Horst, B.; Feringa, B. L.; Minaard, A. J. *Chem. Commun.* **2010**, *46*, 2535.
(54) (a) Novak, T.; Tan, Z.; Liang, B.; Negishi, E.-I. *J. Am. Chem. Soc.* **2009**, *127*, 2838. (b) Lopez, F.; Harutyunian, S. R.; Meetsma, A.; Minaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2752. (c) Weise, C.; Pischl, M. C.; Pfaltz, A.; Schneider. *J. Org. Chem.* **2012**, *77*, 1477.
(55) For a review, see: Ersmark, K.; DelValle, J. R.; Hanessian, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2.
(56) Carroll, A. R.; Pierens, G.; Fechner, G.; de Almeida Leone, P.; Ngo, A.; Simpson, M.; Hooper, J. N. A.; Boström, S.-L.; Musil, D.; Quinn, R. J. *J. Am. Chem. Soc.* **2002**, *124*, 13340.
(57) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064.
(58) Hanessian, S.; Del Valle, J. R.; Xue, Y.; Blomberg, N. *J. Am. Chem. Soc.* **2006**, *128*, 10491.
(59) For reviews on *N*-acyliminium chemistry, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, J., Heathcock, C. H., Eds.; Pergamon: New York, 1991, Vol. 2, p 1047.
(60) Hanessian, S.; Margarita, R. *Tetrahedron Lett.* **1998**, *39*, 5887.
(61) Sun, P.; Weinreb, S. *J. Org. Chem.* **1997**, *62*, 8604. See also: Hanessian, S.; Wang, X. *Synlett* **2009**, 2803.
(62) Li, H.-T.; Jiang, X.-H.; Ye, Y.-H.; Fan, C.-Y.; Roncoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91.
(63) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(64) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S.-H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378.
(65) Hanessian, S.; Wang, X.; Ersmark, K.; Klegraf, E. *Org. Lett.* **2009**, *11*, 4232.
(66) (a) Shin, H. J.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *J. Org. Chem.* **1997**, *62*, 1810. (b) Toyooka, N.; Nakazawa, A.; Himiyama, T.; Nemoto, H. *Heterocycles* **2003**, *59*, 75. see also: Valls, N.; Vallribera, M.; Font-Bardia, M.; Solans, X.; Bonjoch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1241.
(67) (a) Hanessian, S.; Ersmark, K.; Wang, X; Del Valle, R. R.; Blomberg, N.; Xue, Y.; Fjellström, O. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3480. (b) Hanessian, S.; Guillemette, S.; Ersmark, K. *Chimia* **2007**, *61*, 361.
(68) Banner, D. W.; D'Arcy, A.; Chene, C.; Winkler, F. K.; Guha, A.; Konigsberg, W. H.; Nemerson, Y.; Kirchhofer, D. *Nature* **1996**, *380*, 41.
(69) (a) S. Hanessian, S.; Balaux, E.; Musil, D.; Olsson, L.-L.; Nilsson, I. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 243. (b) Hanessian, S.; Therrien, E.; Granberg, K.; Nilsson, I. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2907. (c) Hanessian, S.; Sailes, H.; Therrien, E. *Tetrahedron* **2003**, *59*, 7047.

(70) Hanessian, S.; van Otterlo, W. A .L; Bayrakdarian, M.; Therrien, E.; Nilsson, I.; Petersen, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1032.
(71) Hanessian, S.; Simard, D.; Bayrakdarian, M.; Therrien, E.; Nilsson, I.; Fjellström, O. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1972.
(72) Hanessian, S.; Therrien, E.; van Otterlo, W.; Xue, Y.; Gustafsson, D.; Nilsson, I.; Fjellström, O. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5429.
(73) Hanessian, S. *Pure Appl. Chem.* **2009**, *81*, 1085.
(74) For example, see: The World Health Organization (WHO) Cardiovascular Disease (CVD) Global Strategy on Diet, Physical Activity and Health, WHO, 2003. See also: Hughes, B. *Nat. Rev. Drug. Discov.* **2010**, *9*, 903.
(75) Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070.
(76) S. Hanessian, S.; Tremblay, M. *Org. Lett.* **2004**, *6*, 4683.
(77) S. Hanessian, S.; Lu, P.-P.; Sancéau, J.-Y.; Chemla, P.; Prade, L.; Gohda, K.; Fonne-Pfister, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3159.
(78) (a) Hanessian, S.; Huang, G.; Chenel, C.; Machaalani, R.; Loiseleur, O. *J. Org. Chem.* **2005**, *70*, 6721. (b) Hanessian, S.; Ritson, D. J. *J. Org. Chem.* **2006**, *71*, 9807. (c) Loiseleur, O.; Hermann, O.; Huang, S.; Machaalani, G.; Sellès, R.; Crowley, P.; Hanessian, P. *S. Org. Proc. Res. Dev.* **2006**, *10*, 518. (d) Loiseleur, O.; Ritson, D.; Nina, M.; Crowley, P.; Wagner, T.; Hanessian, S. *J. Org. Chem.* **2007**, *72*, 6353.
(79) For example, see: (a) Barrero, A. F.; Quílez Del Moral, J. F.; Herrador, M. M. *Stud. Nat. Prod. Chem* **2003**, *28*, 3453. (b) Banerjee, A. K.; Laya, M. S.; Moro, H. R.; Cabrera, E. L. *Curr. Org. Chem.* **2008**, *12*, 1050. See also: John, M.; Krohn, K.; Flörke, U.; Aust, H.-J.; Draeger, S.; Schulz, B. *J. Nat. Prod.* **1999**, *62*, 1218.
(80) S. Hanessian, S.; Boyer, N.; Reddy, G. J.; Deschênes-Simard, B. *Org. Lett.* **2009**, *11*, 4640.
(81) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143.
(82) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Pearson, R. G. *J. Chem. Educ.* **1968**, *45* (581), 643. See also: Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic: New York, 1977.
(83) (a) Ponpipom, M. M.; Hanessian, S. *Carbohydr. Res.* **1971**, *18*, 342. (b) Hanessian, S.; Ponpipom, M. M.; Lavallée, P. *Carbohyd. Res.* **1972**, *24*, 45. (c) Hanessian, S; Lavallée, P. *J. Antibiot. (Japan)* **1973**, *25*, 683.
(84) Hanessian, S.; Leblanc, Y.; Lavallée, P. *Tetrahedron Lett.* **1982**, *23*, 4411.
(85) Hanessian, S.; Bennani, Y. L.; Leblanc, Y. *Heterocycles* **1993**, *35*, 1411.
(86) For example, see: McMurray, J.; von Beroldingen. *Tetrahedron* **1974**, *30*, 2027.
(87) (a) Corey, E. J.; Kwiatkowsky, G. T. *J. Am. Chem. Soc.* **1968**, *90*, 6816. (b) Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1969**, *34*, 3053.
(88) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754. For a review, see: Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.
(89) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655.
(90) For examples, see: (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I, Ed.; VCH: New York, 1993; p 159.
(91) For examples, see: (a) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
(92) Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032. Hanessian, S.; Gomtsyan, A.; Malek, N. *J. Org. Chem.* **2000**, *65*, 5623.
(93) Hanessian, S.; Gomtsyan, A. *Tetrahedron Lett.* **1994**, *35*, 7509.
(94) Hanessian, S.; Andreotti, D.; Gomtsyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393.
(95) Hanessian, S.; Bennani, Y. L. *Tetrahedron* **1996**, *52*, 13847.
(96) (a) Hanessian, S.; Bennani, Y. L.; Hervé, Y. *Synlett* **1993**, 35. (b) Hanessian, S.; Bennani, Y. L. *Synthesis* **1994**, 1272.
(97) Hanessian, S.; Cantin, L. D.; Roy, S.; Andreotti, D.; Gomtsyan, A. *Tetrahedron Lett.* **1997**, *38*, 1103.
(98) For example, see: Tanahashi, T.; Takenada, Y.; Nagakura, N.; Nishi, J. *J. Nat. Prod.* **1998**, *62*, 1311.
(99) Hanessian, S.; Mainetti, E.; Lecomte, F. *Org. Lett.* **2006**, *8*, 4047.
(100) Gerth, K.; Washausen, P.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 71.
(101) Hanessian, S.; Focken, T.; Oza, R. *Org. Lett.* **2010**, *12*, 3172.
(102) Connor, D. T.; Greenough, R. C.; von Strandtmann, M. *J. Org. Chem.* **1977**, *42*, 3664.
(103) (a) Kende, A. S.; Mendoza, J. S.; Fuhii, Y. *Tetrahedron* **1993**, *49*, 8015. (b) Berberich, S. M.; Cherney, R. J.; Colucci, J.; Courillon, C.; Geraci, L. S.; Kirkland, T. A.; Marx, M. A.; Schneider, M. F.; Martin, S. F. *Tetrahedron* **2003**, *59*, 6819. (c) Lee, E.; Choi, S.; Kim, H.; Han, H. O.; Kim, Y. K.; Min, S. J.; Son, S. H.; Lim, S. M.; Jang, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 176. (d) Liu, P.; Jacobsen, E. N. *J. A. Chem. Soc.* **2001**, *123*, 10772.
(104) Hanessian, S.; Focken, T.; Mi, X.; Ritson, D.; Oza, R.; Chen, B.; Beaudegnies, R. *J. Org. Chem.* **2010**, *75*, 5601.
(105) Wiley, P. F.; Janke, H. K.; MacKellar, F.; Kelly, R. B.; Argoudelis, A. D. *J. Org. Chem.* **1970**, *35*, 1420.
(106) Duchamp, D. J. *Abstracts J. Am. Crystal Assoc.* Winter Meeting, Albuquerque, NM, **1972**, April, p 23. See also: Weller, D. D.; Haber, A.; Rinehart, K. L., Jr. *J. Antibiot.* **1978**, *31*, 997.
(107) Brodersen, D. E.; Clemens, W. M.; Carter, A. P., Jr.; Morgan-Warren, R. J.; Wimberley, B. T.; Ramakrishnan, V. *Cell* **2000**, *103*, 1143.
(108) Hanessian, S.; Reddy Vakiti, R.; Dorich, S.; Banerjee, S.; Lecomte, F.; DelValle, J. R.; Zhang, J.; Deschênes-Simard, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 3497.
(109) Hanessian, S.; Léger, S. *J. Am. Chem. Soc.* **1992**, *114*, 3115.
(110) For example, see: Kuivila, H. G.; Sommer, R. *J. Am. Chem. Soc.* **1967**, *89*, 5616.
(111) Hanessian, S.; Reinhold, U.; Gentile, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 1881.
(112) (a) Ondetti, M. A.; Cushman, D. W. *J. Med. Chem.* **1981**, *24*, 355. (b) Cushman, D. W.; Ondetti, M. A. *Prog. Med. Chem.* **1980**, *17*, 41. (c) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *196*, 441.
(113) Hanessian, S.; Reinhold, U.; Saulnier, M.; Claridge, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2123.
(114) Rohl, J. A.; Hamann, L. G. In *Accounts of Drug Discovery*; Barnish, J. C., Carter, P. H., Cheng, P. T. W., Zahler, R., Gwaltney, S. L., II, Stafford, J. A., Eds.; Royal Society of Chemistry: London, 2011; Chapter 1, p 1. See also: *Annu. Rep. Med. Chem.* **2005**, *40*, 156.
(115) For examples, see: (a) *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007. (b) *Asymmetric Organocatalysis: From Biometric Concepts to Asymmetric Synthesis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, 2005. For a recent review, see: Marquez-Lopez, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep.* **2010**, *27*, 1138 and references cited therein.
(116) (a) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8*, 4787. (b) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (c) Hanessian, S.; Govindan, S.; Warrier, J. S. *Chirality* **2005**, *17*, 540.
(117) (a) Hanessian, S.; Shao, Z.; Betschart, C.; Rondeau, J.-M.; Neumann, U.; Tintelnot-Blomley, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1924. (b) Hanessian, S.; Maji, D. K.; Govindan, S.; Matera, R.; Tintelnot-Blomley, M. *J. Org. Chem.* **2010**, *75*, 2861−2876.
(118) For examples, see: (a) *Fascinating Molecules in Organic Chemistry*; Vögtle, F., Ed.; Wiley: New York, 1992. (b) *Organic Chemistry: The Name Game*; Nickon, A., Silversmith, E. F., Eds.; Pergamon: New York, 1987.
(119) Hanessian, S.; Mauduit, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3810.
(120) (a) Hanessian, S.; Mauduit, M.; Demont, E.; Talbot, C. *Tetrahedron* **2002**, *58*, 1485. (b) Hanessian, S.; Talbot, C.; Mauduit, M.; Parthasarathy, S.; Gone, J. R. *Heterocycles* **2006**, *67*, 205.
(121) For examples, see: (a) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903. (b) Shamma, M.; Moniot, J. L.; Chinnasamy, P. *Heterocycles* **1977**, *6*, 399.

(122) Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; Macnicol, M. *J. Chem. Soc.* **1928**, 3193. For a review, see: Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: New York, 1991; Vol. 3, p 913.
(123) Hanessian, S.; Parthasarathy, S.; Mauduit, M.; Payza, K. *J. Med. Chem.* **2003**, *46*, 34.

■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on July 11, 2012. The Table of Contents/Abstract Graphic was replaced. The revised paper was reposted on July 25, 2012.