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Synthetic Strategies Employed for the Construction of Fostriecin and Related Natural Products

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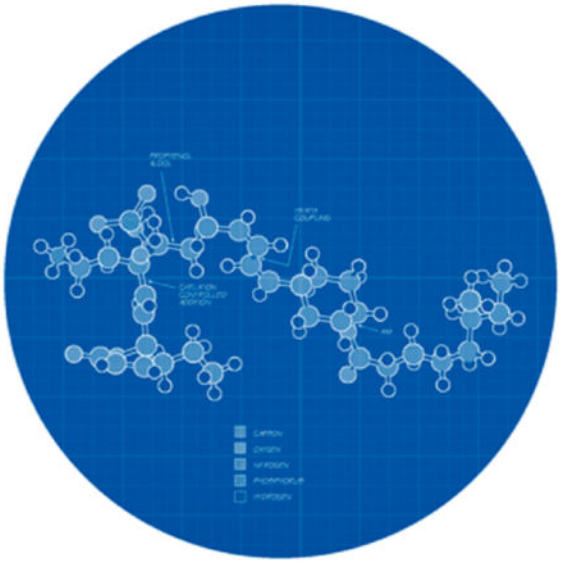
Abstract

Fostriecin and related natural products present a significant challenge for synthetic chemists due to their structural complexity and chemical sensitivity. This review will chronicle the successful efforts of synthetic chemists in the construction of these biologically active molecules. Key carbon–carbon bond forming reactions will be highlighted, as well as the methods used to install the numerous stereocenters present in this class of compounds.

Graphical Abstract



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Notes

The authors declare no competing financial interest.

1. INTRODUCTION

Fostriecin (CI-920) and structurally related natural products constitute an important class of compounds possessing an impressive array of biological activities, ranging from antifungal activity, to cytotoxicity, and to the up-regulation and differentiation of blood cells. The biological activities of this class of compounds have generated a great deal of interest. However, clinical studies have been thwarted because of physicochemical issues, thus creating a need for synthetic access to create analogues that overcome these limitations. Further, only fostriecin is available from commercial sources (via fermentation and isolation). Synthetic strategies toward these molecules will be examined in this review with a special emphasis on key transformations.

Fostriecin (**1**) and its relatives are characterized by an α,β-unsaturated lactone moiety and a polyene portion, connected by a stereodefined polyhydroxylated carbon chain (Figure 1). The members of this class of compounds contain an anionic phosphate group, essential to their bioactivities. Fostriecin (**1**), PD 113,270 (**2**), and PD 113,271 (**3**), which were isolated together from *Streptomyces fostreus*,[1,2] differ only in the oxidation state of the lactone ring and the polyene terminus. The antifungal and antitumor agent sultriecin (**4**), the structure of which has since been revised by Boger and renamed phostriecin (**5**),[3] was isolated from *Streptomyces roseiscleroticus*,[4] and cytostatin (**6**) was isolated from *Streptomyces* sp. MJ654-NF4.[5,6] Both lack the tertiary alcohol at C8 that is characteristic of the rest of the family members. The phosphazomycins, phoslactomycins, and leustroducsins, all isolated from strains of *Streptomyces*,[7–12] are characterized by a cyclohexyl unit and a diene, rather than the triene that the other members possess. These compounds differ in the identity of the acyl group attached to the cyclohexyl ring, except for the less oxidized phoslactomycin B (**7**) and the unacylated leustroducsin H (**8**). These side chains may contain additional stereocenters, as is found in the structure of phoslactomycin F (**13**) and leustroducsin B (**16**). Several members of the family have been described in the patent literature, but are unnamed (**18**–**23**),[13–17] including alcohol **23**, in which the pendant ammonium group has been replaced by a primary alcohol. Another family member has been isolated and named phosphazomycin A; however, the structure has not yet been reported.[12] The geometry of fostriecin's double bonds was disclosed at the time of isolation, but the stereochemistry of the family members was unknown when the initial structures were reported. The C5 stereocenter of fostriecin was assigned shortly after the initial isolation was reported by utilizing chemical degradation to a compound of known configuration.[18] The full stereochemical assignment of fostriecin was determined by Boger, allowing for the assignment of most of the stereocenters of the rest of the family by analogy.[19]

The structural complexity of this class of molecules presents numerous challenges for synthetic endeavors. The multitude of stereocenters and geometrically defined olefins require selective reactions for their introduction. The acid sensitivity of the lactone moiety adds to the challenge of synthesizing this class of compounds. This review will focus on key transformations and the overall efficiency of each reported synthetic strategy for this family of natural products. Each synthesis will be analyzed by step count (longest linear and total number of steps), as well as overall yield from commercially available starting materials. Counting chemical steps is not uniform among the scientific community. For the purposes of

this review, to allow comparison between syntheses, a single chemical step will end when a workup, including concentration, or a purification is performed. Recrystallization will not be counted as a separate step.

2. FOSTRIECIN

Fostriecin is a cytotoxic agent against a broad spectrum of cancer cell lines, including breast cancer, ovarian cancer, and leukemia.[20–23] This activity was formally imputed to fostriecin's inhibition of topoisomerase II catalytic activity with micromolar affinity.[24] Topoisomerase II is essential for regulating DNA conformation, and its inhibition results in impaired DNA and RNA synthesis.[25] However, the potency and cell cycle effects of fostriecin are inconsistent with topoisomerase II as the primary cellular target.[22] Fostriecin also interferes with cellular proliferation and differentiation through inhibition of serine/threonine protein phosphatase type 2A (PP2A), which in turn inhibits the mitotic entry checkpoint. Fostriecin is a much more potent inhibitor of PP2A than of topoisomerase II, and this target is now considered the primary means by which fostriecin imparts its cytotoxicity.[22,26] The selectivity of this inhibition over other phosphatases is remarkable; for example, fostriecin binds protein phosphatase type 1A (PP1A) with 10^4 times lower affinity than type 2A. Fostriecin also inhibits protein phosphatase 4 (PP4) with nanomolar affinity.[27–32] Selective phosphatase inhibitors provide a powerful biological tool and are potentially valuable drug candidates.[33–35] Reversible conjugate addition of an active site cysteine residue, present in PP2A and not in PP1A, to the α,β-unsaturated lactone of fostriecin is conjectured to account for this selectivity.[36] The isolation of a phoslactomycin A/PP2A adduct covalently bound at Cys-269 lends support for this interaction with the related natural product fostriecin.[37] Boger has also shown that fostriecin analogues lacking the α,β-unsaturated lactone are 200-fold less active than the parent molecule, and that conjugate addition of both sulfur and oxygen nucleophiles into the α,β-unsaturated lactone is a facile process.[36]

Fostriecin's impressive anticancer activity has resulted in phase I clinical trials, but the trials were stopped due to the instability of fostriecin, as well as inconsistent purity of the compound from natural sources.[26] Synthetic approaches toward fostriecin are particularly valuable, therefore, as they provide an opportunity for the synthesis of potentially more stable analogues and should provide the desired material in consistently high purity. Synthetic strategies for the construction of fostriecin have been previously reviewed, most recently in 2009.[22,38–41] We will include these previously reviewed contributions in order to better capture the full story of the evolution of synthetic strategies toward this family of natural products. There have also been several reports on synthetic endeavors to create portions of the fostriecin structure or functional analogues,[42–45] which will not be included, but are also noteworthy.

2.1. Just's Synthesis

Just and O'Connor reported the synthesis of an epimer of dephosphofostriecin in 1988.[46] At the outset of their endeavor, only the stereochemistry at C5 was known from the degradation experiments reported by Hokanson and French, a mere three years prior to Just's publication.[18] The remaining three stereocenters were unassigned, resulting in eight

stereoisomeric possibilities for the natural product. Although the odds of guessing correctly in this situation were only 1 in 8, the authors set out to synthesize an isomer in the hopes that it would be the correct one, or, at least, that they could eliminate one of the possible stereoisomers and possibly gain some insight into the stereochemistry of the natural product by comparing the spectral data with their synthetic product. Their synthetic plan took advantage of the chiral pool for the incorporation of three of the four stereocenters, and relied on a Cram chelation[47,48] controlled addition of trimethylaluminum to set the final stereocenter (Figure 2). Sonogashira cross-coupling[49,50] and a Horner–Wadsworth–Emmons[51–54] (HWE) strategy were used to unite the fragments.

Just's synthesis of the lactone portion of fostriecin begins from an acetonide-protected form of 3-deoxyglucose (**24**) (Scheme 1). This compound is currently commercially available, though the authors appear to have synthesized it by radical deoxygenation of a glucose derivative[55] (yields were not provided for this sequence). In a sequence that is not reported in this article, the authors synthesize terminal olefin **25** using the procedure of Cleophax.[56] Though the yield for this sequence is not given, Ziegler has performed this operation in two steps and in 95% yield.[57] A four-step sequence consisting of hydroboration, Jones oxidation, methylation, and ring-opening by ethanethiol gave diol **26** in 60% yield. Cyclization of diol **26** proved challenging, due to side reactions, and lactone **27** was obtained in 35% yield based on recovered starting material. Elimination of the alcohol occurred in 95% yield, and was followed by careful hydrolysis of the thioacetal under oxidative conditions. Aldehyde **28** was unstable to silica gel chromatography, and was therefore used directly in the Horner–Wadsworth–Emmons[51–54] reaction in a later step.

The central portion of fostriecin was constructed from commercially available acetonide-protected glucose derivative **29** (Scheme 2). In five steps this material was transformed into thioacetal **30**. Neither the identity of these transformations nor the yields were reported. Thioacetal **30** was hydrolyzed using a combination of mercuric chloride and mercuric oxide. A Wittig reaction was performed on the crude aldehyde to install the *cis*-vinyl bromide (**31**) in 61% yield over the two steps (the *cis* selectivity was not given). Hydrolysis of the cyclic carbonate, diol cleavage, and chromium oxidation in the presence of methanol[58] yielded ester **32**. Sonagashira cross-coupling[49,50] with alkyne **33** (available in one step and quantitative yield from the commercially available alcohol[59]) proceeded in 88% yield. This was followed by nickel boride reduction[60] that produced a mixture of the product **34**, unreacted starting material, and over-reduced products. After formation of the phosphonate needed for the Horner–Wadsworth–Emmons olefination, the desired product could be isolated away from the other impurities. The yield for these steps was not given. The olefination reaction proceeded in 50% yield to give enone **35**. Addition of trimethylaluminum installed the final stereocenter in 65% yield, which was assigned as the *R* configuration by invoking the Cram chelation[47,61] model. Deprotection yielded dephosphofostriecin epimer **36a** (yield not given), which was not spectroscopically identical to the dephosphorylated product described by Hokanson and French.[18]

Just's synthesis of dephosphofostriecin epimer **36a** was completed in 16 longest linear steps (26 total steps) from protected glucose derivative **29**. The original synthesis involved more steps, but the deoxyglucose derivative **24** is now commercially available. The yield of this

sequence cannot be calculated because the yields of several steps are not given. Just's synthesis demonstrated the utility of a cross-coupling approach for the construction of the triene portion of the molecule. Although this synthesis ruled out one stereochemical possibility for fostriecin, seven other potential isomers remained as viable candidates for the true structure. With the benefit of hindsight, one can examine the ^{1}H NMR data and see that the largest difference in the two spectra (Δ = 0.44 ppm, where Δ_{avg} = 0.13 ppm) is at the C9 stereocenter, which is where the synthesized structure is epimeric to the true natural product. However, at the time of synthesis it was not possible to know how many stereocenters were incorrect, and the ^{13}C NMR does not show a large difference at the C9 position.

2.2. Boger's Synthesis

Boger determined the stereochemistry of fostriecin in 1997 using a combination of spectroscopic and chemical techniques.[19] The stereochemistry at C5 had been determined by chemical degradation of the natural product by Hokanson and French in 1985.[18] This left the C8, C9, and C11 stereocenters undefined. Boger's strategy was to create cyclic structures and look for characteristic nuclear Overhauser effects (NOEs) in order to determine spacial relationships between the substituents that would be unique for the different stereoisomeric possibilities. The location of the stereocenters in 1,2- and 1,3-relationships meant that the cyclic structures could be five- or six-membered rings. Since a great deal is known about the conformations of such rings, the spectroscopic analyses would rely on well-established methods. Chemical degradation would be used to determine the absolute configuration of one of the stereocenters by comparison to a compound of known configuration, since determining a special relationship to the known C5 stereocenter would not be facile.

Cyclization of the C8 and C9 stereocenters was achieved by formation of a cyclic phosphate using *p*-bromobenzoyl chloride and pyridine (Scheme 3). The formation of the five-membered phosphodiester **37** was confirmed by a characteristic chemical shift of 14.69 that is characteristic of a five-membered phosphodiester (10–15 ppm), rather than a six-membered phosphodiester (–0.5 to −5.0 ppm). The cyclic structure displayed NOEs between the alkene proton at C7 and the C9 hydrogen, indicating their *cis* relationship. The C10 hydrogens and the methyl group attached to C8 also display an NOE, confirming this assignment. The C8 and C9 alcohols in fostriecin were therefore determined to be in a 1,2-*syn* relationship.

The relationship between the C9 and C11 stereocenters was determined by selective formation of a six-membered acetonide ring (Scheme 4). This was achieved by carefully limiting the reaction time (10–15 min) in order to favor the kinetically formed six-membered acetonide **38** over the five-membered acetonide. This outcome was confirmed by monoacylation of the primary alcohol, even in the presence of excess acetic anhydride. The five-membered acetonide would possess a more reactive secondary alcohol, rather than a tertiary alcohol, resulting in a bisacylation product. ^{13}C NMR spectroscopy indicated a twist boat conformation (methyl peaks of approximately the same chemical shift, versus distinct axial and equatorial values). Observation of NOEs between different methyl groups for H11 and H9 indicates a 1,3-*anti* relationship, since the 1,3-*syn* relationship places the two hydrogens on the same face as the axial methyl only. With these relationships in hand, it

remained to determine the absolute stereochemistry of these stereocenters. Since determining a relationship to the known, but distal C5 stereocenter could not be achieved easily, chemical degradation was pursued. In six steps fostriecin (**1**) was transformed into tribenzoate **39**, which was also synthesized from enantiopure (*R*)-1,2,4-butanetriol ((*R*)-**40**), as well as (±)-1,2,4-butanetriol (*rac*-**40**). HPLC comparison of the three samples on a chiral OD-H column revealed the C11 stereocenter to be the *R* configuration. Together with the relative stereochemistry and the previously determined C5 stereochemistry, the assignment of fostriecin's structure was complete. Boger also confirmed Hokanson and French's original C5 stereochemical determination by completing an asymmetric synthesis of a reported degradation product and comparing the optical rotation. These efforts successfully defined the stereochemistry of fostriecin and, by analogy, many of the stereocenters of the other family members. This work also confirmed the stereochemical assignments of Shibata, who reported the absolute stereochemistry of the leustroducsins by selective formation and analysis of Mosher esters[62,63] at four of the five alcohol stereocenters of leustroducsin H (**8**).[64]

With a defined stereochemical target now in place, Boger set out to construct fostriecin, and reported the successful completion of the target in 2001.[65] Boger's synthetic strategy was flexible by design, in order to adjust the synthesis in the event of a misassignment of the stereochemistry (including olefin geometry), and to provide access to analogues that might improve bioactivity or physicochemical stability (Figure 3). With that in mind, each stereocenter, except for the stereocenter at C8, was installed using an asymmetric technique that could easily be performed with the opposite enantiomer to provide access to diastereomeric products. Also, the triene was installed one alkene unit at a time to allow for variation of the geometry. Boger planned a Horner–Wadsworth–Emmons reaction[51–54] to unite the core of fostriecin to the lactone fragment.

The lactone portion of fostriecin was synthesized from a straight-chain precursor (Scheme 5). Sharpless asymmetric dihydroxylation[66,67] (SAD) of alkene **41** (created in one step in 89% yield from hex-5-enoic acid[19]) installed the C5 stereo-center in 70% yield and in 88% enantiomeric excess (ee). This selectivity was improved to greater than >98% ee by recrystallization to give diol **42** in 51% yield. Protection and cyclization yielded lactone **43** in 67% yield over two steps. Installation of the alkene was achieved by enolate selenation followed by oxidation and elimination to give α,β-unsaturated lactone **44** in 43% yield. Reduction to the acetal, deprotection, and oxidation yielded aldehyde **45** in 74% yield. This completed the synthesis of the aldehyde component for the planned Horner–Wadsworth–Emmons[51–54] olefination.

The synthesis of the central portion begins with (D)-glutamic acid (**46**), which provides the C9 stereocenter of fostriecin (Scheme 6). The first reaction of the sequence is an interesting van Slyke reaction[68] that preserves the stereochemical information of the amino acid by double inversion.[69] Diazotization, followed by initial formation of α-lactone **47**, is followed by intramolecular attack of the pendant carboxylic acid to form γ-lactone **48**.[70,71] Reduction of the unstable γ-lactone **48** provides alcohol **49**. Protection and a reduction/elimination reaction yields dihydrofuran **50**.

With the C9 stereocenter set, the next task was the installation of the C11 stereocenter (Scheme 7). This was achieved by Sharpless asymmetric dihydroxylation[66,67] of dihydrofuran **50** to provide hemiacetal **51** in 100% yield and in greater than 10:1 diastereomeric ratio (dr). Selective protection of the newly formed C11 stereocenter at low temperature was followed by homologation using a Horner–Wadsworth–Emmons[51–54] olefination with phosphonate **52**. This sequence provides enoate **53** in 79% yield and in 29:1 *Z:E* selectivity. Protection and oxidation state adjustments gave aldehyde **54** in three steps and in 86% yield. Corey–Fuchs olefination[72] installed the second alkene unit (diene **55**) of the triene in 94% yield. Protecting groups adjustments were then performed to generate diene **56**. Selective reduction of the most sterically accessible C–Br bond proceeded in 84% yield to give the *cis*-vinyl bromide **57**. The final unit of the triene was then installed using a Stille cross-coupling[73] with vinyl stannane **58** (available in two steps and in 70% yield from propargyl alcohol[74]) in 82% yield. In four further steps acetate **59** was transformed to phosphonate **60** for the key Horner–Wads-worth–Emmons[51–54] coupling reaction.

The key step uniting the two fragments was achieved in 91% yield, producing enone **61**. The final C8 stereocenter was then installed using a cerium reagent to give tertiary alcohol **62** in 3:1 dr and in 96% yield. The authors invoke Felkin–Anh selectivity to account for the stereochemistry of the addition. In four further steps and in 26% yield, the oxidation state of the lactone was reintroduced and the protecting groups were adjusted to allow for selective phosphorylation at the C9 alcohol of advanced intermediate **63**. Interestingly, Boger noted that a base-catalyzed migration of the C9 silyl group to the C8 tertiary alcohol occurs, allowing for selective protection of the more hindered alcohol. This observation proved useful in later syntheses, aiding in selective phosphate introduction. Phos-phorylation using a modified procedure developed by Evans [PCl_3 and pyridine in DCM, then *p*-methoxylbenzyl alcohol (PMBOH), followed by oxidation with *tert*-butylhydroperoxide][75] installed the C9 phosphate group. Global deprotection under mild conditions gave the natural product fostriecin (**1**), confirming Boger's stereochemical assignment. The yield for this final step was not given. In addition to this proof of structure, Boger also synthesized intermediate **63** by manipulation of the natural product isolate to further support the stereochemical assignment.

Boger's synthesis of fostriecin is completed in 27 longest linear steps (38 total steps) and in 3.5% overall yield from (D)-glutamic acid (not including the final step, for which the yield was not given). This synthesis confirmed Boger's earlier stereochemical assignment using a flexible route that allowed for the correction of stereochemical errors, should the need have arisen.

This synthesis also enabled the evaluation of numerous analogues, which were reported in 2003 (Figure 4).[36] Among those analogues tested, several are of particular interest. Deleting the phosphate group (analogue **36b**) obliterates activity. Other changes to the phosphate group (analogues **64** and **65**) decrease activity by 4 orders of magnitude. Acylation of the C11 hydroxyl group (analogue **66**) also completely destroys activity. Removal of the α,β-unsaturated lactone, either by reduction (analogue **67**) or by prior Michael addition (analogue **68**), reduces activity by 3 orders of magnitude. Analogue **68**, as well as three other conjugate addition analogues, was synthesized directly from the natural product, confirming

the ability of fostriecin to undergo 1,4-addition with both oxygen and sulfur nucleophiles. Interestingly, the α,β-unsaturated lactone imparts a high degree of potency, but is not required for activity. This can be seen in the remarkable activity of simplified analogue **69**, lacking the entire C1–C6 portion of fostriecin. These studies have greatly enhanced our knowledge about the structure–activity relationship of fostriecin. This work also indicates that less complex structures that do not contain the α,β-unsaturated lactone may be good targets for selective PP2A inhibition, though with greatly reduced potency. This modification may impart greater stability to the molecule, which would be highly beneficial in generating a new clinical analogue of fostriecin.

2.3. Jacobsen's Synthesis

In 2001 Chavez and Jacobsen reported a concise synthesis of fostriecin that utilizes several transformations developed in the Jacobsen group (Figure 5).[76] The lactone portion was created using a chromium-catalyzed hetero-Diels–Alder (HDA) reaction.[77] Their strategy centers on the use of a lynchpin, epoxide **70** (Scheme 8), to join two larger fragments together, thereby increasing the convergency of the synthesis. This epoxide was synthesized using Jacobsen's hydrolytic kinetic resolution.[78] Stille cross-coupling[73] was used to create the triene.

Epoxide **70** (made in only one step from methyl vinyl ketone using the highly optimized conditions of Wellman[22]) was rendered enantiopure by utilizing Jacobsen's [Co(salen)]-catalyzed hydrolytic kinetic resolution.[78,79] The authors found that performing the reaction under an oxygen atmosphere prevented catalyst precipitation and allowed the reaction to be carried out with only 2 mol % catalyst to give the desired epoxide **70** in 99% ee. Since the reaction is a kinetic resolution, the maximum theoretical yield is only 50%. The observed yield is 40%, with near perfect enantioselectivity.

The lactone portion of fostriecin is made using an elegant chromium-catalyzed hetero-Diels–Alder reaction developed in the Jacobsen laboratories.[77] With only 3 mol % catalyst, diene **72** and ynal **73** are converted to the protected lactone **74** in 90% yield and in 89% ee, with greater than 95:5 dr. The synthesis of diene **75** was not reported, but this compound has been made in two longest linear (four total) steps from acrolein and benzyloxyacetic acid previously, in 51% yield.[80] Ynal **73** is available in one step from commercially available triisopropylsilylacetylene.[81] Removal of the silyl group and epimerization to the more stable acetal was followed by recrystallization, resulting in enantiopure acetal **75**. Completion of the lactone portion set the stage for investigation of the first coupling reaction with the lynchpin epoxide **70** using the Wipf conditions optimized for a model system.[82–84] The terminal alkyne was hydrozirconated and transmetalated to give a zincate reagent, which was then added to ketone **70** in a highly diastereoselective fashion (greater than 30:1 dr). The hydrozirconation and silyl protection steps proceeded in 45% yield. Without transacetalization to the isopropyl acetal, the yield for this sequence was 33%. The selectivity of this ketone addition is excellent and provides rapid access to the coupled product **76** containing three of the four stereocenters of fostriecin. The second coupling was achieved by lithiating 1,3-dithiane **77** to open the less hindered terminus of epoxide **76**.

Dithiane **77** is available in two steps from 1,3-propanedithiol and propiolaldehyde.[85,86] The acetal was then hydrolyzed and oxidized to lactone **78** in 58% yield from epoxide **76**.

Dithiane removal and PMB protection proceeded in 48% yield over two steps to yield ynone **79** (Scheme 9). The final stereocenter of fostriecin was installed using an asymmetric Noyori transfer hydrogenation[87] to deliver the desired propargyl alcohol **80** in excellent yield and enantioselectivity. The next challenge was the installation of the triene unit of fostriecin. Protecting group manipulations and transformation of the alkynyl silane into the vinyl iodide using a diimide reduction of an iodoalkyne[88,89] gave the desired *Z* olefin geometry selectively, providing vinyl iodide **81** in 65% yield over four steps. A palladium-catalyzed ligand-free Stille reaction[73] was then used to install the triene unit in 85% yield using geometrically defined vinyl stannane **82** (available in three steps from 2-penten-4-yn-1-ol[90]). Phosphorylation of alcohol **83** using the Evans protocol[75] previously employed by Boger,[65] followed by global deprotection, delivered the natural product fostriecin (**1**) in 29% yield over the final two steps.

Jacobsen's synthesis of fostriecin is only 20 steps in the longest linear sequence (30 total steps), with an overall yield of 1.0% from commercially available acrolein and benzyloxyacetic acid. This synthesis is remarkably concise and illustrates the utility of both the [Co(salen)]-catalyzed hydrolytic kinetic resolution and the chromium-catalyzed hetero-Diels–Alder reaction for the rapid construction of complexity. These technologies greatly reduce the number of steps needed for the synthesis by quickly assembling the core of fostriecin.

2.4. Falck's Synthesis

In 2002 Reddy and Falck reported a synthetic approach to fostriecin that features an acylation/ring-closing metathesis[91,92] strategy for the construction of the α,β-unsaturated lactone of the natural product (Figure 6).[93] The synthesis also features a Suzuki–Miyaura[94] cross-coupling to install the triene, avoiding the use of toxic tin-containing coupling partners. Sharpless asymmetric dihydroxylation[66,67] was used to install the C8 and C9 stereocenters.

Falck's synthesis begins with an asymmetric Brown allylation[95,96] of ynal **84**, followed by silyl protection to give alkene **85** in 48% yield and in approximately 98% ee (Scheme 10). Dihydroxylation and cleavage yielded aldehyde **86**, which was then elongated by Wittig olefination[97] in 87% yield (*E:Z* selectivity not given). Sharpless asymmetric dihydroxylation[66,67] of enoate **87** installed the C8 and C9 stereocenters in 3:1 dr after acetonide protection in 73% combined yield. Diastereomers **88** were separable. Bromination of the terminal alkyne, diimide reduction, and oxidation state adjustments yielded aldehyde **89** in 50% yield over four steps. The next task was the construction of the α,β-unsaturated lactone, which was achieved in a very concise manner. Elongation of the carbon chain via Wittig olefination,[97] followed by the use of Brown's chiral allylboration reagent,[95,96] installed the C5 stereocenter in approximately 98% diastereomeric excess (de) and in 72% yield. Acylation of alcohol **90** with acryloyl chloride was followed by ring-closing metathesis[91,92] with Grubbs's second-generation catalyst[98] to give α,β-unsaturated lactone

91 in 74% yield. These four steps rapidly generated the lactone portion of fostriecin with excellent control of the stereoselectivity. Installation of the triene unit was achieved by Suzuki–Miyaura[94] cross-coupling with vinyl boronate **92** (available in two steps and in 63% yield from commercially available 2-(*E*)-penten-4-yn-1-ol), after deprotection of the acetonide with montmorillonite. Boger previously observed that a C9 to C8 base-catalyzed silyl migration occurred on a similarly protected advanced intermediate,[65] and therefore Falck and Reddy similarly took advantage of this chemistry to selectively protect the C8 hydroxyl of diol **93** to allow for installation of the C9 phosphate of advanced intermediate **94**. Global deprotection yielded the natural product (**1**) in 52% yield.

Falck and Reddy completed the synthesis of fostriecin in 20 longest linear steps (22 total steps) and in 0.81% overall yield. This synthesis demonstrated the power of an acylation/ring-closing metathesis[91,92] strategy for the rapid construction of the α,β-unsaturated lactone of fostriecin. This success of this strategy is attested to by its frequent recurrence in later syntheses of this family of natural products. The replacement of a tin-containing coupling partner with a less toxic boron reagent in the cross-coupling reaction is also noteworthy. The endgame strategy for installation of the phosphate group also successfully addresses the problem of selectivity in a concise fashion with an alternate phosphate-protecting group.

2.5. Imanishi's Synthesis

Imanishi disclosed a synthesis of fostriecin in 2002 that features a key Horner–Wadsworth–Emmons olefination[51–54] to unite the lactone portion to the core of the molecule (Figure 7).[40,99,100] The C11 stereocenter is derived from the chiral pool, while the C8 and C9 stereocenters arise from a Sharpless asymmetric dihydroxylation.[66,67] A Stille[73] cross-coupling connects the triene to the core of the molecule.

Imanishi's synthesis begins with alcohol **95** (available in two steps and in 83% yield from (*R*)-malic acid,[101] Scheme 11). Moffatt–Swern oxidation[102] followed by in situ Wittig olefination[97] yields enoate **96** in 86% yield (selectivity not given). Reduction and protection over two steps provides alkene **97** in 84% yield. Sharpless asymmetric dihydroxylation[66,67] installs the C8 and C9 stereocenters of diol **98** in 19:1 dr and in 92% yield. In six further steps, and in 59% yield, the protecting groups were manipulated to reveal primary alcohol **99**, which was then oxidized to the aldehyde and olefinated with phosphonate **100** (synthesized in three steps using Wenkert's procedure[103]). Enone **101** was produced in 79% yield (selectivity not given). The C5 stereocenter was then introduced using chiral reduction reagent (*R*)-BINAl to give allylic alcohol **102** in 73% yield and in greater than 20:1 dr. In seven steps and in 43% yield the lactone was cyclized and the unsaturation was installed, and the PMB-protected primary alcohol was transformed to *cis*-vinyl iodide **103**. Stille cross-coupling[73] with stannane **82** completed the carbon framework of fostriecin, yielding triene **104**. Phosphate installation was achieved by cyclic phosphate formation after silyl protection of the C11 alcohol. Cyclic phosphate **105** was opened with 80% selectivity for the correct C9 phosphate using conditions optimized for a model system. Deallylation of phosphate **105**, followed by global desilylation over two steps, gave fostriecin (**1**) in 63% yield over the final four steps.

Imanishi's synthesis was completed in 28 longest linear steps (31 total steps) and in 3.1% overall yield. The key steps include a Horner–Wadsworth–Emmons olefination[51–54] and a Stille cross-coupling.[73] In previous syntheses the cyclic phosphate had been avoided; however, this synthesis shows that the phosphate can be installed via selective opening of a cyclic phosphate.

2.6. Kobayashi's Synthesis

In 2002 Kobayashi published a formal synthesis of fostriecin that features a diastereoselective Grignard addition to unite two fragments and construct the core of the molecule (Figure 8).[104,105] The synthesis also features an acylation/ring-closing metathesis[91,92] for the construction of the α,β-unsaturated lactone. Three of the four stereocenters are generated using a series of Sharpless asymmetric epoxidations[106–108] (SAEs).

The synthesis begins with a Sharpless asymmetric epoxidation[106–108] that accomplishes a kinetic resolution on the starting allylic alcohol **106** (prepared in one step and in 91% yield from methacrolein, Scheme 12). The resolved alcohol (*R*)-**106** was recovered in 49% yield and in 98% ee. After protection and reduction, primary alcohol **107** was isolated in 86% yield over two steps. Moffatt–Swern oxidation[102] followed by Horner–Wadsworth–Emmons[51–54] olefination gave enone **108** in 99% yield. Ester reduction followed by Sharpless asymmetric epoxidation[106–108] proceeded in 85% yield and in 23:1 dr. Transformation of primary alcohol **109** to propargyl alcohol **110** was achieved using Yadav's[109] procedure, by first transforming the alcohol into a chloride, followed by double elimination with *n*-BuLi. Oxidative cleavage of the alkene was achieved in two steps and in 86% yield to give ketone **111**, one of the fragments for the key diastereoselective coupling reaction.

The Grignard precursor was synthesized from aldehyde **112** (Scheme 13). Addition of allyl magnesium bromide gave racemic alcohol **113**, which was then deracemized using a Sharpless asymmetric epoxidation to give recovered alcohol (*S*)-**113** in 45% yield and in greater than 99% ee, as well as epoxide **114a** in 46% yield and in greater than 99% ee. Both products were processed into vinyl iodide **115** using a procedure previously described by Kobayashi's group.[110] Epoxide **114a** was transformed into vinyl iodide **115** over three steps and in greater than 91% yield. The enantioenriched alcohol (*S*)-**113** was first epoxidized under Sharpless asymmetric epoxidation[106–108] conditions. The alcohol stereo-center was then inverted using a Mitsunobu[111,112] reaction, followed by hydrolysis of the resultant ester to yield epoxide **114b**, a diastereomer of epoxide **114a**. The same three steps used for the diastereomer converted epoxide **114b** to vinyl iodide **115** in greater than 78% yield. This completed the synthesis of the Grignard precursor **115**.

The key coupling step was accomplished by lithium–halogen exchange of vinyl iodide **115**, followed by transmetalation to magnesium (Scheme 14). Chelation-controlled addition to ketone **111** proceeded with greater than 50:1 dr and in 89% yield after deprotection, yielding tertiary alcohol **116**. An acylation/ring-closing metathesis[91,92] sequence completed α,β-unsaturated lactone **117**. In three further steps Jacobsen's[76] and Imanishi's[40,99,100]

intermediate **81** was intercepted, completing the formal synthesis of fostriecin. Later, this intermediate was also made by Hatakeyama.[113] This intermediate can be transformed to fostriecin in two (Jacobsen, 29% yield, Imanishi, 21% yield) or three steps (Hatakeyama, 79% yield).

Kobayashi's synthesis of advanced intermediate **81** was completed in 20 longest linear steps (33 total steps including all steps for the utilization of both products of the Sharpless asymmetric epoxidation[106–108] of alcohol **113**) and in 7.1% overall yield. Using Hatakeyama's high yielding endgame sequence, the synthesis of fostriecin would be completed in 23 longest linear steps (39 total steps), with 5.6% overall yield. The key features of this synthesis are the convergent processing of both products of the Sharpless asymmetric epoxidation[106–108] and the highly selective vinyl metal addition to unite the ketone and vinyl iodide fragments.

2.7. Hatakeyama's Synthesis

In 2002, Hatakeyama's group reported the synthesis of fostriecin.[113,114] Later, Hatakeyama reported a second strategy for fostriecin, as well as the related natural product phoslactomycin B.[115] The first reported strategy envisioned a Sharpless asymmetric dihydroxylation[66,67] to set the C8 and C9 stereocenters and a Brown allylation[95,96] to create the C5 stereocenter (Figure 9). To install the α,β-unsaturated lactone, an acylation/ring-closing metathesis[91,92] sequence was planned.

Hatakeyama's first synthesis in 2002[113,114] begins with an interesting copper-mediated ring-opening reaction, first reported by Kocienski,[116] to create stereochemically defined vinyl stannane **121** from dihydrofuran **118** in a single step (Scheme 15). The toxicity of stannanes and the safety concerns associated with *tert*-butyllithium make this a daunting reaction for the beginning of a synthetic sequence, but the rapid generation of chemical complexity is noteworthy.

Iodination and protection yielded vinyl iodide **122** in 90% yield, setting the stage for a Heck reaction[117] to extend the carbon skeleton. This elongation is accomplished with only 2 mol % palladium acetate to give the desired enal **123** in 73% yield. This type of carbon skeleton elongation is frequently accomplished via Horner–Wadsworth–Emmons olefination[51–54] of an aldehyde, followed by a reduction/oxidation sequence to transform the ester resulting from the Horner–Wadsworth–Emmons reaction into another aldehyde. The Heck reaction provides a succinct catalytic alternative to this type of Horner–Wadsworth–Emmons sequence, provided that the vinyl halide starting material is accessible.

The stereochemistry of the natural product was set using a Brown allylation[95,96] to generate alcohol **124**, which was then subjected to an acylation/ring-closing metathesis[91,92] sequence to install the α,β-unsaturated lactone. The enantioselectivity of the allylation was evaluated at this stage and was found to be 77% ee. Sharpless asymmetric dihydroxylation[66,67] was then used to set the C8 and C9 stereocenters, and fortuitously, the dihydroxylation improved the enantiopurity of diol product **126** relative to the starting material (**125**). This presumably occurred due to the increased reactivity of the major enantiomer with the chiral catalyst, resulting in a kinetic resolution.

Diol **126** was transformed into vinyl iodide **127** in seven steps and in 42% yield (Scheme 16). The vinyl iodide could be prepared with either *E* or *Z* geometry selectively, allowing for the preparation of fostriecin analogues about this double bond. Diastereoselective reduction installed the C11 stereocenter in 99% yield and 84% de. Hatakeyama also demonstrated that the epimer could be formed selectively in order to prepare *epi*-C11 fostriecin analogues. Silylation of diol **128** and cross-coupling with vinyl stannane **82** completed the carbon framework of the natural product. Intermediate **83** was also an intermediate in the Jacobsen synthesis.[76] Hatakeyama installed the phosphate using Bannwarth's phosphoramidite method to create protected phosphate **129**.[118] This required an additional step in the deprotection sequence, but increased the overall yield for the phosphate installation sequence. The final two deprotection steps were deallylation and desilylation to reveal fostriecin (**1**) in 79% yield.

Hatakeyama constructed fostriecin in 21 longest linear steps (24 total steps) and in 4.4% overall yield from dihydrofuran **118**. Rapid construction of the core of the molecule using a copper-mediated ring opening and a Heck reaction contribute to the relatively high yield and short overall step count of this strategy for the synthesis of fostriecin. The stereocenters were set using a Sharpless asymmetric dihydroxylation[66,67] and a Brown allylation,[95,96] and construction of the α,β-unsaturated lactone was carried out using an acylation/cross-metathesis.[91,92]

In 2009 Hatakeyama revealed a second strategy for the synthesis of fostriecin.[115] This strategy intercepts the first, but reenvisions the construction of the core of the molecule. In this new strategy, an epoxide (**135**) was synthesized that could be opened with either a hydride source or cyanide to give access to the C8 methyl of fostriecin, or the aminoethyl side chain of the phoslactomycins, leustroducsins, and phosphazomycins. To generate this epoxide, a catalytic asymmetric Morita–Baylis–Hillman[119,120] (MBH) reaction was planned to install the secondary alcohol at C9, which could then be used to install the epoxide stereoselectively (Figure 10).

Hatakeyama's second fostriecin synthesis begins with a catalytic asymmetric Morita–Baylis–Hillman reaction[119,120] between aldehyde **130** (available in two steps and in 92% yield from 1,3-propanediol) and hexafluoroisopropyl acrylate **131** to give adduct **132** in 58% yield and 99% ee (Scheme 17). Transesterification, reduction, and protection over three steps gave alcohol **133** in 97% yield. Oxidation, Horner–Wadsworth–Emmons olefination,[51–54] and silyl deprotection afforded allyl alcohol **134**, which then underwent directed epoxidation to install the key spiro-epoxide **135**. This advanced intermediate was used to intercept both their previous synthesis of phoslactomycin B (vide infra) and fostriecin.

Reduction with $LiEt_3BH$ reduced the ester and reductively opened the epoxide in 98% yield to give tertiary alcohol **136** (Scheme 18). Dess–Martin oxidation[121] and Brown allylation[95,96] installed the C5 stereocenter of intermediate **137** in greater than 20:1 diastereoselectivity and in 79% yield. An acylation/ring-closing metathesis[91,92] sequence completed the α,β-unsaturated lactone **138**. Six more steps were then needed to intercept

ynone **139** from their previous route in 56% overall yield. A further eight steps (proceeding in 25% yield) are needed to complete the synthesis of fostriecin.

Hatakeyama's second strategy completes the synthesis of fostriecin in 30 longest linear steps (33 total steps) and in 2.1% overall yield from 1,3-propanediol. This strategy demonstrates several novel approaches, such as the catalytic asymmetric Morita–Baylis–Hillman reaction[119,120] that sets the initial stereocenter at C9, which is then used to set the neighboring stereocenter at C8 through directed epoxidation. This key epoxide intermediate will also be used to complete a synthesis of phoslactomycin B (vide infra) by taking advantage of the structural similarities of the family members. The creativity of this strategy, coupled with the relatively high yield of the sequence, make for a very elegant solution to the challenges posed by this complex family of molecules.

2.8. Shibasaki's Synthesis

In 2003 Shibasaki reported a formal synthesis of fostriecin employing several reactions developed in his laboratories.[122,123] Shibasaki's strategy involves construction of the tertiary alcohol stereocenter using his asymmetric cyanosilylation reaction,[124,125] and elaboration of this core (Figure 11). A direct catalytic aldol developed in his laboratories[126–128] served to elongate the structure in one direction, while a catalytic allylation reaction developed by Yamamoto[129] was used to generate the C5 stereocenter and enable the synthesis of the α,β-unsaturated lactone via a ring-closing metathesis strategy.[91,92]

Shibasaki's synthesis began with the cyanosilylation of ketone **140** (available in one step and in 66% yield from commercially available benzyloxyacetaldehyde,[130] Scheme 19). The desired transformation was achieved in 93% yield and 85% ee after tuning both the alcohol-protecting group of ketone **140** and the substituent on the catechol portion of the titanium ligand. The enantioselectivity was improved further by transforming cyanide **141** into the crystalline *p*-nitrophenyl derivative **142** and performing a recrystallization. Protecting group manipulations and oxidation of the primary alcohol delivered the enal **143** over five steps and in 83% yield. The stage was set for implementation of a catalytic asymmetric allylation reaction using a silver–BINAP complex developed by Yamamoto.[129] The reaction proceeded in excellent yield and diastereoselectivity to deliver alcohol **144**. Interestingly, using a titanium catalyst developed by Keck[131] gave 39% yield for this substrate. This difference in reactivity was attributed to the strong chelation of the titanium catalyst to the MOM-protecting group. This catalyst sequestration was mitigated by using the less strongly coordinating silver complex. The chiral ligand in this reaction could be recovered by chromatography. This is an appealing alternative to stoichiometric asymmetric allylations. Installation of the lactone of fostriecin was accomplished by acylation followed by ring-closing metathesis[91,92] employing Grubbs's first generation catalyst[132,133] to give lactone **145** in 71% yield over the two steps. Deprotection and oxidation delivered aldehyde **146**.

Aldehyde **146** was subjected to an aldol reaction with commercially available ynone **147** to deliver the aldol adduct **148** in 65% yield with 3.6:1 dr (Scheme 20). The use of ynones was a novel implementation of the previously developed aldol chemistry developed in the Shibasaki group.[126–128] The MOM group was removed and the resulting diol was ketalized under acidic conditions. The ynone was then reduced using Noyori's transfer

hydrogenation[87] to install the final stereocenter of fostriecin. The desired diastereomer **149** was isolated in 39% yield, along with other diastereomers arising from the prior aldol reaction. These were isolated separately in 14% yield over the two steps. In six steps and in 3% overall yield the propargylic alcohol **149** was transformed into *Z* vinyl iodide **81**. These steps include protecting group interchanges and a diimide reduction.[88,89] The Stille cross-coupling conditions[73] used by Jacobsen[76] were employed to complete the formal synthesis of fostriecin by delivering triene **83**, a common intermediate in the total syntheses of fostriecin completed by Jacobsen,[76] Imanishi,[99,100] and Hatakeyama.[113] This intermediate can be transformed to fostriecin in two (Jacobsen, 29% yield; Imanishi, 21% yield) or three steps (Hatakeyama, 79% yield).

In 2005 Shibasaki reported the synthesis of 8-*epi*-fostriecin (*epi*-**1**) by using a gadolinium-catalyzed cyanosilylation[134,135] employing the parent ligand structure used for the synthesis of fostriecin **1** (Scheme 21).[123] Since the ligand is derived from a naturally occurring sugar, the enantiomer is not readily available. Luckily, switching the metal from titanium to gadolinium changes the identity of the major enantiomer generated in the reaction of enone **140**, allowing access to the opposite enantiomer *epi*-**141**. This complementary reaction allowed Shibasaki to complete the synthesis of 8-*epi*-fostriecin (*epi*-**1**) following the same reaction sequence developed for the natural isomer.

Shibasaki compared the activity of 8-*epi*-fostriecin (*epi*-**1**) with fostriecin **1** in four different biological assays. In three of the four cases, 8-*epi*-fostriecin (*epi*-**1**) had significantly less affinity for PP2A. This lends support to the theory that the C8 hydroxy and methyl group imitates threonine in the binding pocket of PP2A and thus must be present in the correct orientation.[22,36]

Shibasaki completes the synthesis of the common intermediate **84** in 25 steps from benzyloxyacetaldehyde (28 total steps) and in 0.10% overall yield. Overall, using Hatakeyama's higher-yielding endgame strategy, this route delivers fostriecin in 28 steps (31 total steps) and in 0.08% yield. This synthesis illustrates the utility of several asymmetric addition reactions developed in the Shibasaki laboratories for the facile construction of structural complexity, such as the cyanosilylation reaction[124,125] and the lanthanum-catalyzed direct aldol reaction.[126,128] The utility of Yamamoto's silver-catalyzed allylation[129] is also noteworthy. This synthesis highlights the utility of ring-closing metathesis[91,92] for the construction of the α,β-unsaturated lactone, a technique that has proven effective in a number of previously reviewed[22,39] syntheses of fostriecin, including the syntheses of Reddy and Falck,[93] Kobayashi,[104] and Hatakeyama.[113] Finally, Shibasaki's gadolinium-catalyzed hydrocyanation[134,135] provides access to *epi*-**141**, and ultimately to the synthesis and evaluation of the biological activity of 8-*epi*-fostriecin (*epi*-**1**), giving insight into the requirements for binding of fostriecin to PP2A.

2.9. Trost's Synthesis

In 2005 Trost reported the synthesis of dephosphofostriecin, constituting a formal synthesis of fostriecin.[136] Trost's strategy takes advantage of a direct catalytic aldol catalyzed by a dinuclear zinc complex (ProPhenol) developed in his laboratories,[137] and a Hiayama cross-

coupling reaction, also developed by Trost,[138] to unite the side chain to the core of fostriecin (Figure 12). The installation of the lactone was planned via an acylation/ring-closing metathesis,[91,92] a strategy that had been proven successful in previous syntheses.[93,104,113,122,123]

Trost's synthesis begins with a direct catalytic asymmetric aldol reaction between ynone **151** [available in two steps and in 89% yield from benzyldimethylsilyl chloride (BDMSCl)] and aldehyde **150** (available in one step from ethyl pyruvate[137]) (Scheme 22). This reaction proceeds in 58–67% yield and in 99% ee with only 3 mol % catalyst. Ynone **152** is then reduced using Noyori's transfer hydrogenation catalyst[87] to give the desired diol **153** in 88% yield and greater than 10:1 dr. Diol **153** was then differentially protected and the acetal was hydrolyzed to give ketone **154**.

The stage was now set for a diastereoselective addition of vinyl iodide **155** (prepared in five steps and in 36% yield using a Brown allylation[95,96] to set the stereochemistry in 95% ee) to ketone **154**. This was accomplished by generating a magnesium-ate reagent by lithium–halogen exchange, followed by transmetalation to magnesium. Magnesium bromide was used as a chelating additive, delivering the desired tertiary alcohol **156** in 75% yield and in greater than 20:1 dr. Protecting group manipulation and acylation of the C5 alcohol proceeded in three steps and in 89% yield to give diene substrate **157** for ring-closing metathesis.[91,92] Grubbs's first generation catalyst[132,133] delivered the desired lactone **158** in 93% yield.

The protecting group at C9 of compound **158** was removed, and then the alkyne was reduced using diimide[89,139] to give *Z*-vinyl silane **159** in 50% yield (Scheme 23). A silicon cross-coupling reaction[138] using tetrabutylammonium fluoride (TBAF) to initiate the transmetalation from silicon to palladium was then used to couple vinyl BDMS **159** and the *cis*-vinyl iodide **160** (available in four steps from ethyl propiolate). TBAF initiates the process by causing the silicon group to undergo hydrolytic debenzylation, generating the silanol, which then undergoes transmetalation to palladium.[140] The cross-coupling conditions also served to deprotect the silyl groups, delivering dephosphofostriecin **36b** in 54% yield and completing the formal synthesis of fostriecin.

Trost's synthesis of dephosphofostriecin is completed in 15 steps in the longest linear sequence (25 total steps) and in 6.6% overall yield from commercially available BDMSCl. Boger has shown that dephosphofostriecin **36b** can be transformed into fostriecin in four additional steps (less than 45% yield, since the yield for the final step is not given). The overall yield to fostriecin using this route is therefore approximately 3.0% over 19 longest linear steps and 29 total steps.

Trost's synthesis illustrates the utility of the direct catalytic asymmetric aldol reaction[137] for the construction of complex molecules, rapidly delivering the core of fostriecin in fair yield and excellent enantioselectivity. This synthesis also reemphasizes the utility of ring-closing metathesis[91,92] for the construction of α,β-unsaturated lactones. Another remarkable feature of Trost's synthesis is the silicon cross-coupling reaction,[138] which mitigates the need for toxic tin-containing compounds. Trost's synthesis is remarkably concise, illustrating the

utility of the catalytic methodologies developed in his laboratories for the rapid construction of complexity.

2.10. Yadav's Synthesis

Yadav reported a formal synthesis of fostriecin in 2006, based upon a chiral pool approach utilizing the inexpensive and abundant sugar, glucose (Figure 13).[141] This strategy also features an acylation/ring-closing metathesis[91,92] for the construction of the α,β-unsaturated lactone, and relies on a Brown allylation[95,96] to set the stereochemistry at C5. The tertiary alcohol stereocenter at C8 is generated by a Sharpless asymmetric epoxidation.[106–108]

Yadav's synthesis begins with the synthesis of ketone **162** from a commercially available protected form of glucose (**161**) in six steps and in 60% yield (Scheme 24). One of these transformations is the inversion of the C4 stereocenter (sugar numbering) that will become the C9 stereocenter of fostriecin. This is accomplished by elimination of the undesired alcohol at C3 (sugar numbering), followed by diastereoselective hydrogenation. After this six-step sequence, ketone **162** is olefinated to give the desired *E* olefin **163**. DIBAL-H reduction followed by Sharpless asymmetric epoxidation[107,108] sets the C8 stereocenter of fostriecin in good yield and in 10:1 dr. Epoxy alcohol **164** was then transformed to propargylic alcohol **165** using a procedure developed by Yadav[109] that involves formation of an alkyl chloride from the primary alcohol in the first step, and base-catalyzed elimination to give the propargylic alcohol in the second step. This procedure gives a 76% yield of propargylic alcohol **165** in diastereomerically pure form. In three steps and in 68% yield, propargylic alcohol **165** was transformed into enal **166**, which was then subjected to a Brown allylation[95,96] to give allylic alcohol **167**. The authors do not comment on the diastereoselectivity of this transformation.

With the C5 stereocenter installed, Yadav turned to the installation of the α,β-unsaturated lactone (Scheme 25). Acylation followed by ring-closing metathesis[91,92] with 10 mol % of Grubbs's first generation catalyst[132,133] delivered the desired lactone **168** in 92% yield over the two steps. The formal synthesis was then completed by hydrolysis of the acetonide, followed by a Stork–Zhao olefination[142] of the hemiacetal to give vinyl iodide **103** in 58% yield, favoring the desired *Z* isomer in a 3:1 ratio. This completed the formal synthesis of fostriecin, as vinyl iodide **103** is an intermediate in Imanishi's synthesis of fostriecin.[99,100] Imanishi completes the synthesis of fostriecin in five steps (stannane **82** is used, requiring three additional steps) from compound **103** in 7.0% yield (although Imanishi's intermediate had a *Z:E* ratio of 4:1).

Yadav completes the synthesis of advanced intermediate **103** in 19 steps (longest linear and total) from protected glucose derivative **161** in 8.9% yield. The overall yield to fostriecin using this route is approximately 0.62% over 24 longest linear steps (27 total steps) using the final steps from Imanishi's sequence. This strategy relies upon the inexpensive and abundant natural product glucose for the generation of the stereochemistry at C9 and C11 of fostriecin. Well-precedented techniques are used for the installation of the remaining chiral centers, namely a Sharpless asymmetric epoxidation[106–108] and a Brown allylation.[95,96] This strategy is an effective approach to the target molecule **103** that highlights the utility of the

conversion of epoxy alcohol **164** to inverted propargyl alcohol **165** developed in Yadav's laboratories.

2.11. Hayashi's Synthesis

Hayashi reported a formal synthesis of fostriecin in 2008 that focused on the use of diastereoselective reactions for the installation of most of the stereocenters (Figure 14).[143,144] Many of the previous syntheses of fostriecin employed numerous asymmetric catalysts or reagents to carry out diastereoselective reactions. Hayashi planned to set the absolute stereochemistry of C8 and C9 via a Sharpless asymmetric dihydroxylation[66,67] and then induce the distal C5 stereocenter by employing a cobalt–alkyne complex capable of inducing 1,4-stereocontrol, a technique recently developed by Hayashi.[145] The C11 stereocenter would be controlled using a chelation-controlled addition reaction. The α,β-unsaturated lactone was envisioned to occur via an acylation/ring-closing metathesis[91,92] sequence.

Hayashi's synthesis begins with commercially available 1,3-propanediol **169** (Scheme 26). In seven steps and in 68% yield this simple diol is transformed into trisubstituted olefin **170**. Chemoselective Sharpless asymmetric dihydroxylation[66,67] gave the desired diol **171** in 88% yield and in 93% ee. In seven straightforward steps and in 33% yield diol **171** was transformed into ynal **172**. Cobalt complexation was now undertaken in order to alter the geometry about the alkyne, allowing for 1,4-induction from the nearby tertiary alcohol stereocenter. The titanium-catalyzed addition of an allyl tin reagent to aldehyde **173** occurred in excellent diastereoselectivity and in 60% yield to give intermediate **174**. Removal of the cobalt restored the alkyne, which was then selectively reduced to the *E* olefin in 98% yield. Allyl alcohol **175** was transformed into α,β-unsaturated lactone **176** in 82% yield by acylation followed by treatment with Grubbs's second generation catalyst.[98]

A series of protecting group manipulations and oxidations yielded aldehyde **177** over four steps and in 66% yield (Scheme 27). This set the stage for a diastereoselective addition reaction[146] controlled by chelation of the aldehyde and the C9 alkoxy group. After screening a number of conditions, Hayashi found that the conditions developed by Fukuyama,[147] involving a higher order alkynyl zinc reagent, gave the desired propargylic alcohol **179** in 74% yield and in 9:1 dr. The alkyne (**178**) used in this addition reaction was synthesized in five steps and in 65% yield from *cis*-1,2-dichloroethene. Propargylic alcohol **179** was transformed into an intermediate (**104**) in Imanishi's synthesis of fostriecin[99,100] in 52% yield over three steps consisting of protecting group manipulation and a *Z* selective reduction of the alkyne using buffered Rieke zinc.[148,149] Imanishi's synthesis transforms advanced intermediate **104** into fostriecin in five steps and in 45% yield.

Hayashi completes a formal synthesis of fostriecin in 29 longest linear steps (34 total steps) and in 3.7% overall yield from the commercially available diol **169**. To reach the completed fostriecin structure using this sequence together with Imanishi's endgame requires 34 longest linear steps (39 total steps) with an approximate yield of 1.7%. The stereochemistry is set by a single asymmetric transformation, with the subsequent diastereoselective

reactions proceeding in excellent selectivity. This synthesis demonstrates the utility of cobalt–alkyne complexes in achieving diastereoselective induction.

2.12. McDonald's Synthesis

McDonald published a formal synthesis of fostriecin in 2009 that demonstrates the power of cross-coupling in the construction of the natural product (Figure 15).[150] Though cross-coupling has been widely used to install the triene portion of the molecule, McDonald envisioned using this technology to unite a central fragment to the lactone portion of the molecule, as well as the methyl group at C8. These disconnections yield a highly convergent strategy. McDonald planned on using a combination of resolution chemistry[151,152] and asymmetric dihydroxylation to install the stereocenters present in fostriecin.

Mcdonald's synthesis begins with allylation of commercially available ynal **73** to generate racemic propargyl alcohol *rac*-**180** (Scheme 28). Resolution is accomplished with a lipase to generate the resolved alcohol (–)-**180** in 49% yield and acylated **181** in 48% yield, which has the correct stereochemistry for the synthesis of the natural enantiomer of fostriecin. The enantioselectivity of this transformation was not given, but the related TMS-protected ynal gave 98% ee for alcohol **184** and 98% ee for ester **185**, respectively (Scheme 29).[152] Hydrolysis of ester **181** gave enantioenriched propargyl alcohol (+)-**180**. To address the instability of the lactone portion of the molecule under acidic conditions, a lower oxidation state was carried forward by a transacetalation/ring-closing metathesis[91,92] sequence to yield cyclized intermediate **182**. After ring formation, the acetal stereochemistry was set by transacetalation to the isopropyl acetal, and the alkyne was deprotected. This yielded terminal alkyne **183** in 88% yield over four steps.

The core of fostriecin was synthesized using a very similar strategy as the lactone portion (Scheme 29). Allylation of ynal **84** gave racemic propargyl alcohol *rac*-**184**, which was then resolved to give enantioenriched propargyl alcohol (*S*)-**184** and acetate **185**. In this sequence, the alcohol required inversion to generate the proper stereochemistry at the propargylic position. Mitsunobu inversion[111,112] of the propargylic stereocenter, followed by silyl protection, set the correct stereochemistry at C11. Oxidative cleavage of alkene **186** yielded aldehyde **187**, which was transformed to bis-vinyl bromide **188** by using the Corey–Fuchs procedure.[72] The introduction of these two halides set the stage for successive cross-coupling reactions to install the lactone and methyl group of fostriecin.

Alkyne **183** underwent hydrozirconation followed by transmetalation to provide vinyl zinc reagent **189** in situ for Negishi cross-coupling[153] with bis-vinyl bromide **188** (Scheme 30). Cross-coupling at the most sterically accessible site proceeded with complete selectivity to give the adduct **190** in 73% yield from alkyne **183**. Another Negishi cross-coupling[153] installed the methyl group in 98% yield. Deprotection and oxidation of acetal **191** completed the synthesis of the α,β-unsaturated lactone and generated dihydroxylation substrate **192**. This substrate possesses several unsaturations, but the most electron-rich is the desired C8/C9 olefin. Despite this electronic preference, when the standard Sharpless dihydroxylation[66,67] ligand $(DHQD)_2$-PHAL was employed in the asymmetric dihydroxylation, a 1:1 ratio of dihydroxylation of the desired C8/C9 olefin and the undesired

C6/C7 olefin was obtained. McDonald turned to the less sterically hindered DHQD-4-MEQ ligand to improve the selectivity for the C8/C9 dihydroxylation product. This gave a 59% yield of the desired isomer **193** and 13% of the undesired dihydroxylation product resulting from reaction of the C6/C7 olefin. The diaster-eoselectivity of this transformation was not reported. In three steps diol **193** was processed to vinyl iodide **81**, which is an intermediate in the Jacobsen,[76] Imanishi,[100] and Hatakeyama[113] syntheses.

McDonald explored a Suzuki–Miyaura[94] cross-coupling strategy to replace the Stille cross-coupling[73] and therefore avoid the use of toxic stannanes, but found that toxic Tl_2CO_3 was necessary to carry out the transformation in high yield. Vinyl iodide **81** can be transformed to fostriecin (**1**) in four steps and in 62% yield using Hatakeyama's[114] synthetic route. Thus, McDonald has completed a formal synthesis of fostriecin in 19 longest linear steps (29 total steps) and in 2.3% overall yield from ynal **84**. The highlight of this synthetic approach is the use of the central fragment as a lynchpin to append both the triene portion of the molecule and the lactone and methyl fragments. This innovation resulted in a highly convergent synthesis for the construction of fostriecin that illustrates the utility of cross-coupling reactions in the rapid assembly of complexity.

2.13. Zhang's Synthesis

In 2010 Zhang and co-workers published a formal synthesis of fostriecin that relies on a key Julia–Kocienski olefination[116,154,155] to unite two fragments (Figure 16).[156] These two fragments were envisaged as arising from a common intermediate, ultimately derived from the chiral pool. Diastereoselective Sharpless asymmetric dihydroxylation[66,67] was planned for the installation of the C8 and C9 stereocenters.

Zhang's synthesis begins with diethyl D-(+)-malate (**194**), which is transformed to aldehyde **195** in four steps and in approximately 67% yield (Scheme 31). Following the procedure of Dias and Meira,[157] a Horner–Wadsworth–Emmons reaction[51–54] with phosponate **196** is used to install a *Z* enoate in approximately 16:1 dr and in 75% yield. Enoate **197** is elaborated to a protected form of the α,β-unsaturated lactone, and then in nine further steps and in 35% yield sulfonate **198** was completed.

The central fragment is prepared from the same intermediate aldehyde **195** via Wittig olefination,[97] which proceeds with excellent control of the olefin geometry and in 90% yield (Scheme 32). Ester **199** is reduced to the alcohol and then reoxidized to give aldehyde **200** in 94% yield. The key Julia–Kocienski olefination[116,154,155] proceeds smoothly under optimized conditions to give the desired *E* isomer **201** in 15:1 selectivity and with 82% yield. Deprotection and oxidation steps yield lactone **202** in three steps and in 52% yield. Chemo-and diastereoselective dihydroxylation proceeds with good selectively to yield the desired diol **203** in 85% yield together with a small amount of the C6/C7 dihydroxylated isomer (19:1). After protecting group manipulations and installation of the vinyl iodide, advanced intermediate **81** was constructed, which is an intermediate in the Jacobsen,[76] Imanishi,[100] McDonald,[81] and Hatakeyama[113] syntheses. Zhang carries out the Stille reaction[73] to complete the carbon framework of the natural product (triene **83**) in 80% yield.

A further three steps are needed to complete the synthesis using Hatakeyama's[114] sequence, which proceeds in 70% yield. Zhang's synthetic sequence from diethyl D-(+)-malate comprises 28 longest linear steps and 34 total steps and proceeds in 1.3% overall yield. The highlight of this strategy is the utilization of intermediate aldehyde **195** for the construction of both the lactone and core fragments.

2.14. O'Doherty's Synthesis

O'Doherty and Gao published a total synthesis of fostriecin in 2010,[158] featuring Sharpless asymmetric dihydroxylation[66,67] to set three of the four stereocenters, and a Leighton allylation[159] for the construction of the final stereocenter (Figure 17). O'Doherty also replaced the toxic tin-based cross-coupling of former syntheses with a Suzuki–Miyaura cross-coupling[94] strategy. The α,β-unsaturated lactone was installed via an acylation/ring-closing metathesis[91,92] sequence.

O'Doherty's synthesis begins with commercially available allylic alcohol **204** (Scheme 33). In four steps and in 66% yield ynal **205** was produced and the carbon chain was then extended using a Horner–Wadsworth–Emmons olefination[51–54] to yield enoate **206** in 91% yield and in 4:1 selectivity for the desired *E* isomer. Reduction of the ester followed by oxidation yielded ynal **207** in 87% yield. At this point the minor *Z* isomer was separated and equilibrated to give the desired *E* isomer in 86% yield. Another olefination was performed to give enoate **208** in 94% yield and greater than 20:1 *E:Z* selectivity. Despite the many unsaturations present in triene **208,** Sharpless asymmetric dihydroxylation[66,67] proceeded selectively, and after cyclization, carbonate **209** was generated in 80% yield. The enantioselectivity of this reaction was not reported at this stage, and no mention of products arising from reaction at other unsaturation sites was reported. The most distal olefin to the electron-withdrawing ester group reacted preferentially—an excellent example of the chemoselectivity possible using the Sharpless asymmetric dihydroxylation.[66,67] To remove the unwanted stereocenter at C10, palladium-catalyzed allylic reduction was performed, followed by silylation to give protected silyl ether **210**. A second Sharpless asymmetric dihydroxylation[66,67] was performed on diene **210** to set the C8 and C9 stereocenters. After protection, silyl ether **211** was obtained in 62% yield and in greater than 96% ee and de.

Installation of a surprisingly robust vinyl boronate using rhodium-catalyzed hydroboration after alkyne deprotection yielded enoate **212** in 73% yield and in greater than 6:1 selectivity for the desired *Z* geometry (Scheme 34). Enoate **212** was transformed into aldehyde **213** in two steps and in 72% yield. Diastereoselective allylation to produce alcohol **214** was achieved using Leighton's chiral silane.[159] This installed the final stereocenter of fostriecin in 85% yield and in greater than 99% de. The enantioselectivity was also improved to 99% ee. The newly installed stereocenter was then acylated and the α,β-unsaturated lactone **215** was constructed using ring-closing metathesis.[91,92] Remarkably, the vinyl boronate was compatible with all of these transformations. Given this stability, it is unsurprising that the cross-coupling reaction needed optimization in order to achieve the desired coupling reaction of vinyl iodide **216** with the poorly reactive substrate **215**. Fortunately, optimization of the reaction conditions yielded the desired result, an 80% yield of adduct **217**. Five further steps were needed to complete the synthesis, which proceeded in 17% yield.

The completed synthesis was accomplished in 27 longest linear steps and in 0.58% overall yield. The synthetic sequence needed to construct vinyl iodide **216** was not given, so the total number of steps required to complete this synthesis is not clear. The utilization of a highly selective Sharpless asymmetric dihydroxylation,[66,67] coupled with reductive palladium-catalyzed dehydrogenation, was noteworthy, and the use of a Leighton allylation[159] was a novel and very successful approach to the construction of the C5 stereocenter. Another interesting feature of O'Doherty's synthesis is the demonstrated stability of the vinyl boronate group. This remarkable stability allows for flexibility in the introduction of the vinyl metal group needed for cross-coupling, yet despite that stability, conditions were still found to achieve the desired cross-coupling in good yield. This is an excellent demonstration of the benefits associated with using the Suzuki–Miyaura[94] reaction.

3. PD 113,271

The cytotoxic and antifungal agent[21–23] PD 113,271 (**3**) was isolated along with fostriecin (**1**)[1,2,18,160] and PD 113,270 (**2**). It also inhibits the enzyme topoisomerase II.[20,24] Compared to fostriecin (**1**), little effort has been exerted for the synthesis of PD 113,271 (**3**), likely due to its additional complexity. Little was known about PD 113,271 (**3**) at the outset of Sugawara's synthesis in 2006,[161,162] including the relative and absolute configurations of the molecule. This ambiguity is an added challenge for the synthesis, but also illustrates the importance of synthesis in determining chemical structure. Despite powerful spectroscopic techniques, synthesis still plays an important role in structure determination.

3.1. Sugawara's Synthesis

Sugawara hypothesized that PD 113,271 (**3**) is biosynthesized in a similar fashion as fostriecin (**1**), and therefore the relative and absolute configurations of the C5, C8, C9, and C11 stereocenters should be identical.[161,162] This left only the C4 stereocenter unassigned. Comparison of the coupling constants for the α,β-unsaturated lactone of PD 113,271 (**3**), phomalactone (**218a**), and 4-*epi*-phomalactone (**218b**) allowed for the tentative assignment of this final stereocenter, providing a target molecule for their synthetic efforts (Figure 18).

Sugawara's strategy for the synthesis PD 113,271 relied on a chiral pool approach for the installation of the stereocenters (Figure 19). A late stage cross-coupling reaction was envisioned for installation of the triene. A Horner–Wadsworth–Emmons reaction[51–54] was planned for the union of the core with the lactone moiety. This constitutes a highly convergent strategy, requiring the synthesis of three building blocks.

Sugawara's synthesis begins with the transformation of dimethyl L-tartrate **219** into primary alcohol **220** in four steps and in 83% yield (Scheme 35). Oxidation followed by a Horner–Wadsworth–Emmons olefination[51–54] with Ando's reagent[163–167] gave enoate **221** in 93% yield (the olefin geometry selectivity was not given). In four further steps and in 66% yield the synthesis of aldehyde **222** was completed. The phosphonate for the olefination reaction was also made from the chiral pool, D-galactose **223**. In five steps (yield not given), lactone **224** was synthesized. This material was transformed into the desired phosphonate **225** in three steps and in 88% yield.

The coupling of these two fragments was successful, and was followed by a Felkin–Anh addition of methyllithium into the ketone in the presence of $CeCl_3$ (Scheme 36). The selectivity of this addition was 4:1, but the isomers were separable and tertiary alcohol **226** was isolated in 70% yield in pure form. Oxidation of the acetal to the lactone (via a two-step protocol consisting of hydrolysis and treatment with manganese dioxide) and protecting group manipulations deliver diol **227** in four steps and in 36% yield. Oxidative cleavage of diol **227** gave the aldehyde, which was then subjected to a Stork–Zhao olefination,[142] giving the desired *Z* vinyl iodide **228** in 2:1 selectivity. In five protecting group manipulation steps and in 27% yield, the C9 hydroxyl was deprotected and the undesired olefin isomer was separated from the desired *Z* isomer, delivering vinyl iodide **229**. This set the stage for a Stille palladium-catalyzed cross-coupling reaction,[73] which proceeded in 96% yield to give triene **230**. In three additional steps the phosphate was appended to the carbon framework using the phosphoramidite method of Bannwarth[118] and the compound was fully deprotected in 86% yield. The synthetic compound **3** was in good agreement with the reported values for natural PD 113,271 (**3**); however, no authentic sample was available for direct comparison. Global acylation of the synthetic material produced PD 116,251 (**231**), which gave spectral values in excellent agreement with the authentic sample.[168] Sugawara also revised the structure of PD 116,251 (**231**) by using mass spectrometry techniques along with ^{31}P NMR. The structure was revised from an acyclic phosphate attached only at C9 to the cyclic phosphate **231** attached at both C8 and C9. Sugawara completed the synthesis of PD 113,271 (**3**) in 27 longest linear steps (38 total steps) and in 2.4% overall yield. This synthesis confirms the stereochemical assignment proposed by Sugawara and revises the structure of the acylated compound PD 116,251 (**231**). The synthesis illustrates the utility of the Horner–Wadsworth–Emmons olefination reaction for the union of the lactone portion to the central core. Cross-coupling was demonstrated to be an effective strategy for the union of the triene portion to the core of PD 113,271 (**3**). Sugawara's synthesis and stereochemical assignment of PD 113,271 (**3**) should open the door for future biological and chemical investigations of this relatively unstudied natural product.

4. SULTRIECIN AND PHOSTRIECIN

Sultriecin was first isolated and found to be an antifungal and antitumor antibiotic in 1992 from *Streptomyces roseiscleroticus* by a research group at Bristol-Myers Squibb.[4] Sultriecin's reported structure differed from other members of the family by the presence of a sulfate, rather than a phosphate group. This group was proposed based on the natural product's mass spectrum, its reactivity toward a sulfatase, and a negative Hanes test. The stereochemistry was not determined in the initial isolation report.

4.1. Boger's Synthesis and Structural Reassignment

Boger reported a synthesis and structural reassignment of the natural product sultriecin in 2010.[3] Due to the lack of stereochemical information, Boger was guided by the other members of the family and key coupling constants of the natural product to generate the most likely structural target. The core stereotriad of the molecule was proposed to be the same as cytostatin, which was substantiated by key coupling constants characteristic of the internally hydrogen-bonded C11 alcohol and putative C9 sulfate group. The C4 stereocenter

was assigned by comparison to structurally similar lactones phomalactone **218a** and 4-*epi*-phomalactone **218b** (Figure 20).

With a defined target in hand, Boger commenced with the synthesis of the putative structure using a strategy involving oxidative ring expansion to create the α,β-unsaturated lactone (atoms originating from the original furan ring are highlighted in red, Figure 21). The synthesis relies on the chiral pool for the installation of the characteristic C10 methyl group. The triene portion would be appended by a diastereoselective vinyl metal addition, generating the C11 stereocenter simultaneously.

The synthesis begins with alcohol **232**, available in two steps and in 91% yield from the Roche ester, which was oxidized and subjected to allylation at −100 °C using the Brown protocol[95,96] to generate allyl alcohol **233** in 14:1 dr (Scheme 37). Protection and installation of the alkyne was accomplished over four steps to give alkyne **234** in 48% yield from alcohol **232**. Coupling of the alkyne with 2-furoyl chloride was accomplished under palladium-catalyzed conditions.[169] Ketone **235** underwent asymmetric Corey–Bakshi–Shibata (CBS) reduction[170,171] with 12.5:1 selectivity and in 84% yield after alkyne reduction with lithium aluminum hydride. Furan **236** was subjected to an oxidative ring expansion[172,173] to generate the desired ring system with a carbonyl perfectly poised to install the characteristic C4 alcohol of sultriecin. Reduction of lactone **237** did not give the desired stereochemistry for the alcohol, but lithium aluminum hydride reduction gave greater than 30:1 selectivity for the undesired stereochemistry, which was then inverted using a Mitsunobu reaction[111,112] to give pivalate **238** in 38% yield from furan **236**. Deprotection and oxidation proceeded in two steps and in 68% yield to give aldehyde **239**.

Synthesis of fragment **243** was achieved in only three steps and in 66% yield from pyrylium tetrafluoroborate **240** (available in four steps and in 15% yield from pyridine)[174] by an elegant organolithium addition followed by a pericyclic ring opening, originally developed by Taylor,[175] to create aldehyde **242** (Scheme 38). Further functionalization produced the stereodefined triene **243**. This strategy had previously been used for the synthesis of the related triene **288** in Boger's earlier cytostatin synthesis (vide infra, Scheme 44).[176]

With aldehyde **239** and vinyl bromide **243** in hand, the key addition reaction was investigated (Scheme 39). Lithium–halogen exchange of vinyl bromide **243** with *tert*-butyllithium followed by transmetalation to copper and then addition to aldehyde **239** gave the desired product **244** in 85% yield and in greater than 5:1 dr. Protecting group manipulations, oxidation to the lactone, and sulfate installation proceeded over six steps and in 25% yield to give the putative structure of sultriecin (**4**). This material did not match the reported spectral values of the natural product.

Boger first investigated the possibility that the stereochemistry of the central triad was incorrect, but the stereochemistry was confirmed by ^{13}C NMR of the cyclic acetonide. Informed by his surprising prior results of the inactivity of a sulfate analogue of cytostatin (Figure 28, analogue **292**), he suspected that the sulfate group might have been misassigned in the original structure determination. Completion of the phosphate containing analogue **5** was achieved over seven steps and in 31% yield and produced material identical to the

natural product. This misidentification is understandable, given the very similar monoisotopic mass values (492.1889 vs 492.1794) and the results of the chemical tests.

Boger renamed the natural product phostriecin. He tested the original proposed structure, sultriecin, phostriecin, and a number of synthetic analogues to develop a structure–activity relationship (Figure 22). As was found in the cytostatin analogue study, the sulfate-containing analogue **246**, as well as the formerly proposed structure of the natural product, sultriecin (**4**), were completely inactive. The phosphate group is essential for biological activity. Interestingly, the lactone was not entirely necessary for activity (though it was important for potency), which is surprising given the role of the α,β-unsaturated lactone in forming a covalent (though reversible) adduct with PP2A. Also interesting is the importance of the unsaturated carbon chain. While the fully saturated chain maintains activity (though much reduced), the specificity is lost.

Boger's synthesis of phostriecin is completed in 25 longest linear steps and 32 total steps from the Roche ester with an overall yield of 2.2%. The strategy features an elegant synthesis of the triene portion, and a useful oxidative ring expansion reaction to create the lactone portion of the molecule. This synthesis also provides access to numerous analogues, which Boger tested to determine the key features necessary for biological activity. One of the most important benefits of pursuing total synthesis of a natural product is that it allows for the creation and testing of analogues that are not available from natural sources and that provide important insight into the key structural features of the molecule. These insights can lead to the design of simpler compounds with desirable biological properties.

Another important lesson demonstrated by this synthesis is the importance of total synthesis in structure determination. Despite chemical evidence for the presence of a sulfate monoester in the natural product, the true structure was only revealed by synthesis of the putative structure and of the true natural product, phostriecin. The perceived role of synthesis in structure determination has greatly diminished with improved analytical methods; however, the synthesis of putative structures and comparison to the natural product remains the ultimate confirmation of a structural assignment.[177]

5. CYTOSTATIN

Cytostatin (**6**), isolated in 1994 by Ishizuka,[5,6] displays potent and selective inhibition of PP2A,[178,179] though with a lower affinity than fostriecin.[29] Cytostatin inhibits adhesion of B16 melanoma cells to laminin and collagen[180] and induces apoptosis[181] of these cancerous cells.[182] Cytostatin also displays antimetastatic and cytotoxic activity through augmentation of natural killer cells.[183] Though the connectivity of cytostatin was determined by Ishizuka, no stereochemical information was determined.[5,6] This was both an added challenge and an incentive for Bialy and Waldmann's total synthesis of cytostatin in 2002,[184] as it provided an opportunity to verify their hypothesized structural assignment of cytostatin through total synthesis.

5.1. Waldmann's Synthesis

Bialy and Waldmann based their stereochemical assignment of cytostatin on the known configurations of related natural products, such as fostriecin and, in particular, phoslactomycin A (**9**), as it also contains an alkyl substituent at C4 (Figure 23).[184,185] The C10 stereochemistry was assigned using the Karplus relationship as *anti* between H10 and H11 from the coupling constant between them, assuming an internal H-bond between the alcohol at C11 and the phosphate group. The C6 stereocenter was assigned through synthesis of a small molecule (**251**) containing the α,β-unsaturated lactone and C4–C6 stereotriad.[185]

Bialy and Waldmann pursued a strategy that would provide flexibility in the installation of the tentatively assigned stereocenters, centered around the use of Evans's oxazolidinone technology (Figure 24).[186,187] The triene was installed using a Stille reaction.[73]

Waldmann's synthesis begins with alcohol **252**, itself derived from an Evans's procedure in two steps from acylated oxazolidinone **253** in 68% yield (Scheme 40).[187] After Moffatt–Swern oxidation,[102] an Evans's aldol[186,187] provides the *syn* aldol adduct **254** in 68% yield over the two steps. In four steps and 61% yield aldol adduct **254** was transformed into primary alcohol **255**. Another oxidation and Evans's aldol produced *syn* aldol adduct **256**.

In four steps and 75% yield oxazolidinone **256** was transformed into ynone **257** (Scheme 41). Ynone **257** was subjected to a catalyst-controlled reduction using the CBS protocol[170,171] to install the final stereocenter of cytostatin. In nine steps and in 31% yield, propargylic alcohol **258** was transformed into *Z* vinyl iodide **259**. The olefin geometry was set using a diimide reduction of an iodoalkyne. Stille cross-coupling[73] installed the triene unit in 62% yield (the vinyl stannane **260** was made in four steps and in 47% yield from crotonaldehyde). Base-promoted deprotection of the fluorenyl methyl groups of advanced intermediate **261** gave cytostatin **6**, which could not be compared directly to the isolated product using optical rotation, as the natural compound's rotation was not reported. The binding affinity of the synthetic material to PP2A was quantified and found to be an order of magnitude lower than that of cytostatin, but these values have been found to vary substantially depending on the identity of the substrate used for the assay, as shown by Boger.[188] Successive syntheses of cytostatin have lent further support that synthetic product **6** is indeed the natural product and the observed incongruencies have been attributed to impurities in the isolated natural product.

Waldmann used his established synthetic approach to generate a number of synthetic analogues for biological testing and SAR evaluation (Figure 25).[189,190] The inability of truncated analogue **262** to bind PP2A indicates the necessity of the triene unit for binding. Use of partially protected analogue **264** results in poor binding affinity, suggesting close contacts between the phosphate and the protein in the binding pocket. Propargyl alcohol **263** retains most of the binding affinity of cytostatin **6**, indicating that the triene unit can be replaced with a truncated hydrophobic group. Acylated analogue **265** showed no affinity for PP2A, indicating the importance of the free alcohol at C11 for binding. Alkynyl iodide **266**, similar to terminal alkyne **263**, retains most of its binding affinity, as does vinyl iodide **267**. Elimination of the lactone unsaturation results in no detectable binding to PP2A, supporting

the proposed reversible 1,4-addition of an active site cysteine into the α,β-unsaturated lactone.[191]

Waldmann's synthesis of cytostatin is completed in 27 longest linear steps (31 total steps) and in 2.5% yield from oxazolidinone **253**. The synthesis takes advantage of flexible auxiliary- and catalyst-controlled methods for the installation of each of the stereocenters of cytostatin in order to allow for the synthesis of diastereomers in case the original proposed structure was incorrect. This synthetic strategy also allowed for the synthesis and evaluation of a number of analogues that indicated important aspects of cytostatin's structure that impart binding affinity for PP2A.

5.2. Marshall's Synthesis

In 2004 Marshall and Ellis reported a formal synthesis of cytostatin.[192] Their strategy focused on the use of a propargylation developed in the Marshall laboratories[193] and two Noyori reductions to set the C9 and C11 stereocenters.[87] Previous research in the Marshall laboratories indicated that this strategy gave results superior to those of an alternate strategy based on Carreira alkynylation (Figure 26).[194–196]

With this strategy in mind, Marshall began the synthesis using a highly *anti* selective propargylation of chiral aldehyde **269** (available from the Roche ester in three steps and in 95% yield, Scheme 42).[197] This reaction is a modification of the Tamaru reaction,[198] developed by Marshall,[193] that employs chiral propargylic mesylate **270** [synthesized in one step (yield not given) from the commercially available alcohol[199]]. Alkyne **271** was added to a chiral Weinreb amide[200] **272** [made in two steps (yield not given) from commercially available (*R*)(–)-methyl-3-hydroxy-2-propionate][201,202] after MOM protection to give ynone **273**. Noyori reduction[87] followed by alkyne reduction delivered alcohol **274** in 97% yield. After five further transformations and in 79% yield, ynone **275** was synthesized. Reduction with Noyori's chiral catalyst[87] installed the final stereocenter of cytostatin in 62% yield as the only detectable diastereomer. Protecting group manipulations over two steps and in 89% yield intercepted Waldmann's synthesis by converging on terminal alkyne **277**.

Marshall's synthesis of advanced intermediate **277** was completed in 16 longest linear steps (19 total steps) and in 21.6% yield from the Roche ester. Ten further steps are needed to transform intermediate **277** into cytostatin. Combining the Marshall and Waldmann syntheses yields a total of 26 longest linear steps and 33 total steps for the synthesis of cytostatin in approximately 3.5% overall yield. Marshall's synthesis is high yielding and uses effective techniques for the installation of cytostatin's stereocenters. Implementation of the Marshall–Tamaru[193,199] propargylation methodology effectively sets two stereocenters with remarkably high diastereoselectivity. The use of an alkyne as a lynchpin effectively joins the two fragments, first with the diastereoselective propargylation of aldehyde **269**, and then with the Weinreb amide[200] **272**. This strategy rapidly builds complexity, generating the C3–C11 carbon core of cytostatin in only three steps.

5.3. Boger's Synthesis

In 2006, Boger and co-workers reported a new total synthesis of cytostatin.[176,188] Their strategy split the molecule into three pieces, retrosynthetically, to increase the convergency of the sequence. The key coupling steps planned for the synthesis of cytostatin were an epoxide opening reaction to unite the lactone portion to cytostatin's core, and a vinyl metal addition into an aldehyde to set the C11 stereocenter and install the triene unit (Figure 27). An acylation/ring-closing metathesis[91,92] strategy was used to install the α,β-unsaturated lactone.

With this strategy in mind, Boger set out to synthesize the necessary building blocks for this convergent synthesis (Scheme 43). The most complicated fragment was synthesized from chiral aldehyde **278** (available in three steps and in 82% yield from the Roche ester) by first employing a diastereoselective crotylation with a chiral Brown reagent.[95,96,203,204] This gave the desired homoallylic alcohol **279** containing one of cytostatin's stereotriads in 63% yield and in 8:1 dr. Acylation followed by cross-metathesis[91,92] with Grubbs's first generation catalyst[132,133] gave lactone **280** in good yield. In five further steps the lactone was reduced to the cyclic acetal and the protected alcohol was transformed into primary iodide **281** in 60% yield.

The core fragment was made from a Sharpless asymmetric epoxidation[107,108] of commercially available olefin **282**, which yields epoxide **283** in 86% yield and in 89% ee (Scheme 44).[205] The methyl group was then installed by opening the epoxide using the Tius procedure,[206] which resulted in a 3:1 regioisomeric mixture favoring the desired isomer. Periodate cleavage removed the undesired regioisomer to give the desired diol **284** in 50% yield over the two steps. Further transformations gave the desired epoxide **285** for the first key coupling reaction with primary iodide **281**.

The coupling reaction between primary iodide **281** and epoxide **285** was achieved by transforming the primary iodide to a cuprate reagent via lithium–halogen exchange followed by transmetalation (Scheme 45). Addition of the cuprate to epoxide **285** gave the desired coupled product **286** in 84% yield through selective addition to the least hindered side of the epoxide. In three steps and 70% yield the PMB ether **286** was transformed to aldehyde **287**, setting the stage for the next key reaction. Diastereoselective addition of vinyl bromide **288** (synthesized in 7% yield in seven steps from pyridine in an analogous fashion to triene **243**, Scheme 38) into aldehyde **287** was achieved by lithium–halogen exchange followed by transmetalation to copper to give the chelation-controlled addition product **289** in 76% yield and in 7:1 dr.[207] Interestingly, direct addition of the vinyl lithium species without transmetalation to form the cuprate gave a 2:1 dr favoring the opposite and undesired diastereomer. In six steps and in 45% yield intermediate **289** was converted to cytostatin **6** using the fluorenyl methyl protected phosphate seen previously in Waldmann's synthesis.[184,189,190]

Boger completed the synthesis of cytostatin **6** in 22 longest linear steps (37 total steps) and in 1.4% yield from pyridine (the yield of triene **288** is lower than the yield for aldehyde **287**, but the longest linear sequence is from the Roche ester). Boger used a crotylation[95,96,203,204] and ring-closing metathesis[91,92] strategy for the installation of the lactone, a popular and

effective strategy that proves its utility yet again in this synthesis. Boger's use of an electrocyclic ring-opening to control the geometry of the triene unit is an elegant and concise way to access the desired compound. The two coupling reactions were very effective, illustrating the utility of cuprate chemistry for selective transformations, including the use of an unusual diastereoselective carbonyl addition of a cuprate.

Boger used this synthetic strategy to complete the synthesis of several cytostatin analogues that further corroborated the stereochemical assignment that Waldmann proposed by eliminating several other isomeric possibilities.[188] Boger also found that there was a discrepancy between the reported value for the optical rotation and the value for the synthetic product. In addition to helping assign the stereochemistry of cytostatin **6**, these isomers also provided the opportunity to evaluate the importance of stereochemistry on the binding affinity of cytostatin **6** to PP2A.

Boger tested several diastereomers, along with other analogues (made using synthetic routes similar to that used for cytostatin **6**), for their ability to bind PP2A using two different substrates (Figure 28, only phosphohistone substrate data shown).[208] The diastereomeric analogues **6b**–**6d** all possessed at least 2 orders of magnitude lower activity (for the natural substrate phosphohistone) than the natural product, highlighting the importance of the central stereotriad. Analogue **290**, lacking the phosphate group, did not bind PP2A well, as expected from previous results obtained for fostriecin.[36] Interestingly, sulfate analogue **291** inspired by the original proposed structure of sultriecin **4** also did not bind PP2A with any measurable affinity. The authors suggest that this result may indicate that sultriecin **4** derives its cytotoxicity by a different mechanism, despite its structural similarity to fostriecin (**1**) and cytostatin (**6**). Later results from Boger's laboratory would reveal that the originally proposed structure of sultriecin **4** was incorrect, and that the sulfate group was, in fact, a phosphate group. The lack of activity of sulfate **291** would prove pivotal in this discovery (vide supra).

Protected truncated analogue **294** did bind PP2A with moderate affinity, though the affinity was 2 orders of magnitude lower than cytostatin (**6**). This result corresponds well with what Waldmann observed in his analysis of analogues **263**, **266**, and **267** (Figure 25). The deprotected truncated analogue **293** had a slightly higher affinity, though still 2 orders of magnitude lower than cytostatin (**6**). Analogue **292**, lacking the C11 hydroxyl group of cytostatin (**6**) also binds PP2A with 2 orders of magnitude lower affinity than cytostatin (**6**). Boger also compared fostriecin (**1**) and found that it binds PP2A with about an order of magnitude higher affinity.

Boger's synthesis provides valuable information about the binding of cytostatin (**6**) to PP2A and illustrates a number of powerful synthetic reactions. These studies were also accompanied by docking models of both fostriecin (**1**) and cytostatin (**6**) with the binding pocket of PP2A. Additionally, binding studies with analogue **291** provided the first evidence that would later lead to a structural revision of sultriecin.[3]

5.4. Cossy's Synthesis

In 2007 Cossy and co-workers reported a formal synthesis of cytostatin **6**.[209,210] Their strategy relied on a diastereoselective alkylation using a chiral oxazolidinone auxiliary, followed by a crotylation[95,96,203,204]/ring-closing metathesis[91,92] strategy to form the lactone portion of cytostatin (Figure 29). The central portion's stereochemistry was set using an enzymatic reduction. The two fragments were then united using a diastereoselective addition into an aldehyde.

Cossy's synthesis begins with alcohol **295** (available in quantitative yield in one step from butane-1,4-diol),[211] which in two steps is converted into acyl oxazolidinone **296** in 58% yield (Scheme 46). Diastereoselective alkylation[186] delivered oxazolidinone **297** in 80% yield and in greater than 96:4 dr. Removal of the chiral auxiliary, oxidation to the aldehyde, and diastereoselective crotylation using a chiral boronate reagent **298**[198,212] gave homoallylic alcohol **299** containing the stereotriad of the lactone portion of cytostatin. Acylation and ring-closing metathesis[91,92] using Grubbs's second generation catalyst[98] gave α,β-unsaturated lactone **300** in 95% yield over the two steps. In four further steps and in 80% yield, primary iodide **301** was synthesized.

The central portion of cytostatin **6** was synthesized by formation of a β-keto ester in 91% yield from commercially available enoate **302**, followed by an enzymatic reduction[213] to give propargylic alcohol **303** in 72% yield and in 92% ee (Scheme 47). Diastereoselective alkylation gave ester **304** in 94% yield and in 93:7 dr. Three further steps furnished aldehyde **305**.

Lithium–halogen exchange of primary iodide **301** followed by Felkin–Anh addition to aldehyde **305** gave coupled product **306** in 52% yield and 3:1 diastereoselectivity (Scheme 48). In five further steps, protected phosphate **307**, an intermediate in Waldmann's synthesis, was completed.

Cossy completed the formal synthesis of cytostatin in 19 longest linear steps (25 total steps) from butane-1,4-diol. In three more steps Waldmann transformed intermediate **307** into cytostatin **6**. Overall, therefore, the synthetic sequence to cytostatin is 22 longest linear steps and 32 total steps and provides cytostatin in 1.5% overall yield. Cossy's synthesis successfully uses a chiral auxiliary-based alkylation reaction,[186] a crotylation with a chiral tartrate derived reagent,[212,214] coupled with an acylation/ring-closing metathesis[91,92] strategy to generate the lactone portion of cytostatin **6**. The coupling of these two fragments is an effective strategy that gives adduct **306** in 52% yield and in 3:1 dr.

5.5. Curran's Synthesis

In 2008 Curran reported the synthesis of cytostatin **6** using a fluorous mixture strategy to generate four stereoisomers.[215] The discrepancies in the optical rotations of isolated cytostatin **6** and the synthetic material generated by both Waldmann and Boger led Curran to investigate the stereochemical assignment through synthesis of four stereoisomers of the natural product. Curran reasoned that, though spectroscopic techniques had sufficiently determined the configuration of the stereotriads, the relationship between these stereotriads

was less certain. The distance between the stereotriads increases the likelihood that an isomer of cytostatin may appear nearly identical with the authentic compound spectroscopically. Curran set out to synthesize the four possible stereoisomers without depending on its structural similarity to fostriecin (**1**) and other members of the fostriecin family. The synthetic strategy envisioned creation of one stereotriad via Evans's aldol methodology[186,187] and the other using Brown crotylation (Figure 30).[95,96,203,204] The pieces would be united with a Horner–Wadsworth–Emmons olefination.[51–54]

Curran relied on Evans chiral auxiliary aldol methodology[186,187] for the synthesis of the lactone stereotriad (Scheme 49). The known aldol adducts **308** and *ent*-**308** (available in three steps and in 72% yield from the Roche ester)[216–218] were silylated with different fluorinated silyl groups differing in the length of their fluorinated chains, and then the pseudoenantiomers **309** and **310** were mixed together. Four further steps gave the mixed aldehydes **M-311**. Curran begins his synthesis of the phosphonate portion from the known propargylic alcohol **312** and its enantiomer. These arise from a Brown crotylation[95,96,203,204] of commercially available 3-(trimethylsilyl)-2-propynal, providing adduct **312**, containing the first two stereocenters for the second stereotriad in 66% yield and in 90% ee.[219,220] After silylation with differentially fluorinated silyl groups, the pseudoenantiomers **313** and **314** were mixed. Four further steps were required to generate the desired phosphonate **M-315** for a Horner–Wadsworth–Emmons reaction.[51–54] The olefination reaction was accomplished using barium hydroxide to give the mixed ynone products **M-316** in 80% yield.

1,4-Reduction of enones **M-316** followed by diastereoselective reduction of the ketones gave the *syn* alcohols **M-317** via substrate control (Scheme 50). In five further steps alcohols **M-317** were transformed into the fluorenyl methyl protected phosphates **M-318**, which were demixed using preparative fluorous HPLC to give each of the diastereomers containing the same relative stereochemistry for each stereotriad.

The individual quasiisomers were then transformed separately into cytostatin **6** and three other stereoisomers in five steps and in 16% yield (Scheme 51). Interestingly, the spectral data for the two diastereomers were substantially different despite the distance between the stereotriads, particularly at the C8 position. The four isomers were analyzed using optical rotation, NMR spectroscopy, and TLC and compared with a sample of the natural product. Curran found the same discrepancy between the optical rotations as observed by Waldmann and Boger, but was able to rule out diastereomers **319** and *ent*-**319** by TLC and ^{1}H NMR spectroscopy. Curran found that the spectra, even of the enantiomers, were not identical, likely due to small differences in pH and concentration. Curran identifies the same structure as Waldmann and Boger proposed as the correct structure for cytostatin **6**.

In 21 longest linear steps (31 total steps) and in 0.82% yield from the Roche ester, Curran synthesized cytostatin **6** and three other diastereomers by employing a fluorous mixing technique. The key transformations included an Evans aldol,[186,187] a Brown crotylation,[212,214] and a Horner–Wadsworth–Emmons olefination.[51–54] This synthesis provides further evidence that the structure originally proposed and synthesized by Waldmann for cytostatin **6** is indeed the product originally isolated.

6. PHOSLACTOMYCIN B

Phoslactomycin B (**7**) is the simplest member of the cyclohexane-containing members of the fostriecin family of natural products. Like other members of the family, phoslactomycin B (**7**) is known to bind PP2A specifically through interaction with cysteine-269.[37,221] Additionally, the deamino-hydroxy biosynthetic precursor of phoslactomycin B is known to induce myeloid differentiation.[222] Phoslactomycins also possess antifungal activity.[223] The remarkable biological activity of phoslactomycin has inspired genetic engineering of mutant strains for the production of phoslactomycins.[37,183,224–227]

One of the unique challenges for the synthesis of phoslactomycin B and the other cyclohexane-containing members of the family is the ethyl amino substituent at C8. This added challenge, common to the phoslactomycins, phosphazomycins, and leustroducsins, has been met by using a variety of strategies, including installation of an azide using S_N2 chemistry followed by reduction, as well as cross-coupling.

6.1. Kobayashi's Synthesis

Kobayashi reported the first synthesis of phoslactomycin B (**7**) in 2006.[228] The key disconnections used were a Sonogashira cross-coupling[49] and a chelation-controlled addition of a vinyl metal reagent into a ketone (Figure 31). With these reactions in mind, Kobayashi set out to synthesize the fragments needed for these transformations.

Kobayashi's synthesis began with a deracemization of alcohol **320** (available in one step and 96% yield from crotonaldehyde) via a kinetic resolution (Scheme 52). Sharpless asymmetric epoxidation[106–108] using 30 mol % of the chiral ligand left the *R* enantiomer of alcohol **320** in 44% yield and greater than 97% ee. In five steps, including a Horner–Wadsworth–Emmons reaction,[51–54] ester (*R*)-**320** was transformed into primary alcohol **321**. Another Sharpless asymmetric epoxidation[107,108] (this time with 36 mol % of the chiral ligand) gave epoxide **322** in 93% yield and in greater than 20:1 diastereoselectivity. In six steps, including a Yadav elimination[109] to install the alkyne, epoxide **322** was transformed into the diastereomeric secondary alcohols **323**. Selective protection of the primary alcohol followed by oxidation of the secondary alcohol to give the ketone set the stage for a chelation-controlled addition. Grignard addition proceeded in an excellent 87% yield for the three steps giving tertiary alcohol **324** as the sole diastereomer. In three steps, including a Horner–Wads-worth–Emmons olefination,[51–54] terminal olefin **324** was elongated to enoate **325**. Sonogashira cross-coupling[49] with vinyl iodide **326** installed the cyclohexyl group characteristic of phoslactomycin B (intermediate **327**) in 87% yield. Reduction followed by oxidation gave aldehyde **328** in 94% yield. In order to set the stereochemistry about the lactone ring, an aldol reaction was performed using Evans chiral oxazolidinone **329**.[186,187] This reaction proceeded in excellent yield to give the desired *syn* isomer **330**. The chiral auxiliary was then removed in two steps to give the aldehyde, which was olefinated using the Ando reagent[164] to give *Z* olefin **331** selectively.

In three steps the silyl groups were removed and lactone **332** was formed in 71% yield (Scheme 53). A reduction developed by Brandsma[229] was then used to install the *Z* olefin of triol **333** in 83% yield. The triol was differentially protected in three steps and in 73% yield

to give primary alcohol **334**. This set the stage for installation of the primary amine characteristic of the cyclohexane-containing members of the fostriecin family of natural products. This was achieved using a Mitsunobu reaction[111,112,230] giving the bis-Alloc protected amine **335** in 73% yield. Four steps were needed to deprotect the PMB ether, install the phosphate group using the phosphoramidite method of Bannwarth,[118] and globally deprotect the compound, yielding phoslactomycin B (**7**).

Kobayashi completed the synthesis of phoslactomycin B in 40 longest linear steps and total steps with 0.61% yield from crotonaldehyde. In order to improve the yield of this synthesis, Kobayashi reported an improved approach to intermediate **344**.[231] The new strategy installs the C9 stereocenter using a Sharpless asymmetric dihydroxylation[66,67] rather than an epoxidation (Figure 32).[106–108] The C11 stereocenter is created with a Noyori reduction,[87] and the C8 stereocenter is created using a diastereoselective vinyl metal addition.

Starting from commercially available diol **336**, aldehyde **337** was synthesized in two steps with 96% yield (Scheme 54). Aldol condensation followed by decarboxylation gave enoate **338** in 80% yield (the *Z:E* ratio for the olefin geometry was not reported). Sharpless asymmetric dihydroxylation[66,67] furnished lactone **339** in 89% yield and 97.6% ee. Protecting group manipulations and reduction proceeded in three steps and 69% yield to give alcohol **340**. Oxidation to the ketone followed by diastereoselective Grignard addition and protection yielded **341** as the exclusive diastereomer in 82% yield. Further manipulations gave ynone **342** in 75% yield over three steps. Use of Noyori's chiral catalyst for transfer hydrogenation[87] set the C11 stereocenter of propargyl alcohol **343** in 87% yield and in 17:1 dr. Protecting group manipulations completed the synthesis of intermediate **344** in two steps and in 92% yield.

Kobayashi's new synthesis of intermediate **344** proceeds in 16 steps and in 23% yield from commercially available diol **336**, as compared to the 11% yield over 17 steps obtained using the previous strategy. This improves the overall yield of phoslactomycin B from 0.61 to 1.2% over 39 total steps. Kobayashi's synthesis uses a number of reliable reactions for the installation of the stereocenters, such as the Sharpless asymmetric dihydroxylation,[66,67] Noyori's transfer hydrogenation,[87] and an Evans aldol reaction.[186,187] The diastereoselective Grignard addition proceeds in excellent selectivity to install the C8 stereocenter. Finally, the Sonogashira cross-coupling[49] is an effective strategy for the installation of the cyclohexyl moiety.

6.2. Hatakeyama's Synthesis

Hatakeyama reported the synthesis of phoslactomycin B (**7**) in 2008.[114,232] The strategy employed by Hatakeyama relies on Stille cross-coupling[73] for the installation of the cyclohexyl unit and a pentenylation/ring-closing metathesis[91,92,214,233] strategy for the synthesis of the α,β-unsaturated lactone (Figure 33). In order to install the primary amine characteristic of the cyclohexyl-containing fostriecin family members, a Suzuki–Miyaura[94] cross-coupling was envisioned. The stereochemistry of the C8 and C9 stereocenters would be set simultaneously using a Sharpless asymmetric dihydroxylation.[66,67]

Hatakeyama's synthesis begins with protection and oxidation of commercially available diol **169** (Scheme 55). A Horner–Wadsworth–Emmons reaction[51–54] with in situ generated triethyl iodophosphonoacetate[234,235] homologated aldehyde **130** to enoate **345** in 62% yield over the first three steps and in a 4:1 *Z:E* ratio, favoring the desired olefin geometry. Reduction of ester **345** followed by oxidation to aldehyde **346** was accompanied by an increase in the *Z:E* ratio to 20:1, either by selective decomposition or equilibration of the isomers. Interestingly, Moffatt–Swern[102] and Dess–Martin oxidation[121] conditions did not increase the isomeric ratio. In three steps and in 82% yield this compound was transformed via a Wittig reaction into diene **347**. Oxidation state adjustments gave aldehyde **348**. This set the stage for one of the key transformations of the synthesis, an asymmetric pentenylation using a chiral pentenylboron reagent to set both the C4 and C5 stereocenters of alcohol **349**. Hatakeyama found that the reagent derived from 2-pentenylpotassium gave a higher *syn*/*anti* ratio than the Grignard reagent used with the Brown method[95,96,204] and a better ee than the reagent generated with the Roush protocol.[214] At this stage the amine of phoslactomycin B was installed as a Boc-protected amine using a Suzuki–Miyaura[94] cross-coupling reaction. The coupling partner 9-(*N*-Boc-aminoethyl)-9-BBN (**350**) was prepared in one step (yield not given) from *tert*-butyl vinylcarbamate. Amide **351** was obtained in 90% yield under the palladium-catalyzed conditions.

The lactone was formed via an acylation/ring-closing metathesis[91,92] sequence employing Grubbs second-generation catalyst[98] to give the desired α,β-unsaturated lactone **352** in 76% yield over the two steps (Scheme 56). Sharpless dihydroxylation[66,67] gave the desired diol **353** in 68% yield together with the undesired diol resulting from dihydroxylation of the C6/C7 olefin in an 87:13 ratio. Interestingly, diol **353** was obtained in enantiopure form, despite the use of starting olefin **352** with 93% ee. PMB-protected alcohol **353** was transformed in seven steps to iodoenone **354** in 38% yield, including a change in the amine-protecting group from Boc to Alloc. Diastereoselective reduction[236] proceeded in 96% yield to give the desired diol **355** in excellent *anti* selectivity. This set the stage for a Stille cross-coupling reaction[73] with vinyl stannane **356** to install diene **357**, yielding the entire carbon framework of phoslactomycin B (**7**) in 46% yield. This reaction did not go to completion, and 43% of the starting vinyl iodide **355** could be reisolated and recycled in the reaction. The stannane **356** was made in two steps from ethynylcyclohexane in 69% yield. Four further steps gave phoslactomycin B (**7**) in 33% yield, using a diallylphosphoramidite[118] to install the phosphate group.

Hatakeyama completed the synthesis of phoslactomycin B (**7**) in 26 longest linear steps (29 total steps) and in 0.85% yield from commercially available diol **169**. Hatakeyama also synthesized three other isomers of intermediate **355**, differing in the geometry of the vinyl iodide and the C11 stereochemistry. This should provide an opportunity to synthesize several analogues of phoslactomycin B (**7**) in the future. Hatakeyama's synthesis demonstrates the applicability of asymmetric pentenylation for the synthesis of complex natural products, a reaction that was developed for this synthesis inspired by the success of Brown's[95,96,203,204] and Roush's[214] allylation and crotylation reactions. The Suzuki–Miyaura[94] cross-coupling for the installation of the amine group was a highly successful strategy. Sharpless dihydroxylation[66,67] was used effectively to install the C8 and C9 stereocenters. The use of

Evans acetoxyborohydride[236] for the installation of the C11 stereocenter illustrates the utility of this diastereoselective reaction rather than the use of more expensive chiral catalysts, which have frequently been employed in other syntheses of this class of compounds.

Hatakeyama reported a second-generation synthesis of phoslactomycin B (**7**) in 2009 that takes advantage of the structural similarity between fostriecin and phoslactomycin B.[115] The same intermediate used in Hatakeyama's 2009 synthesis of fostriecin (vide supra) was used to complete a synthesis of phoslactomycin B (**7**) as well. The advanced intermediate epoxide **135** was opened with cyanide (rather than hydride) to give a precursor to the C8 aminoethyl group of phoslactomycin B (Figure 34). Hatakeyama then uses an asymmetric pentenylation[95,96,204] and an acylation/ring-closing metathesis strategy[91,92] to install the–unsaturated lactone. This route intercepts Hatakeyama's first generation strategy,[232] completing a formal synthesis of phoslactomycin B (**7**).

Hatakeyama's second-generation strategy for the synthesis of phoslactomycin B (**7**) starts with ester **135** (Scheme 57, see Scheme 17 for the synthesis of this advanced intermediate), which when reduced with DIBAL-H does not open the epoxide, in contrast to opening with lithium triethylborohydride (Scheme 18). The alcohol was then oxidized to give enal **358**. Pentenylation proceeds with 83% yield and in 97:3 dr. Epoxide **359** is then opened with cyanide and then reduced and protected to install the amino ethyl side chain of the phoslactomycins, leustroducsins, and phosphazomycins. This gives Boc-protected **360** in 66% yield. An acylation/ring-closing metathesis[91,92] sequence provides lactone **361** in 62% yield. Six more steps are carried out to transform the protected alcohol into ynone **362** (an intermediate in their previous synthesis) in 31% yield. A further eight steps are required to complete the synthesis of phoslactomycin B (**7**).

This second-generation strategy requires 32 longest linear steps (34 total steps) from 1,3-diol and proceeds in 0.29% overall yield. This synthesis has several noteworthy features, including the asymmetric Morita–Baylis–Hillman reaction[119,120] used to set the C9 stereocenter and the ability to synthesize either the methyl or aminoethyl side chain from a common epoxide, which is an advanced intermediate for both syntheses.

6.3. Cossy's Synthesis

In 2009 Cossy and co-workers reported a formal synthesis of phoslactomycin B (**7**).[237,238] Their strategic plan was to set the C8 stereocenter and unite two smaller fragments by employing a diastereoselective alkyne addition into a ketone (Figure 35). The stereochemistry of the lactone portion would be set by a Noyori reduction.[87] The stereocenter set using this methodology would then be used to generate the C4 and C5 stereocenters of phoslactomycin B (**6**) via a [2,3]-Wittig rearrangement.[239,240] The C9 stereocenter would be set by employing a second Noyori reduction.[87] An acylation/relay ring-closing metathesis[91,92,237] strategy was used to install the α,β-unsaturated lactone.

Cossy's synthesis begins with allyloxyacetic acid **363** (available in one step and quantitative yield from allyl alcohol and bromoacetic acid),[241] which is transformed into ynone **364** in two steps and in 71% yield (Scheme 58). Noyori reduction[87] gave alcohol **365** in 97% yield

and 91% ee. Brandsma reduction[229] followed by propargylation with alkyl bromide **366** gave alkyne **367** in 84% yield. Deprotonation at the propargylic position followed by a [2,3]-Wittig rearrangement[239,240] gave propargyl alcohol **369** in 99% yield with 98:2 dr. The TIPS group was then removed quantitatively to give terminal alkyne **370**.

Cossy synthesized the core of phoslactomycin B (**7**) beginning with 1,3-propanediol (**169**) (Scheme 59).[190,191] In four steps and in 61% yield ynone **371** was constructed. Noyori reduction[87] delivered propargylic alcohol **372** in 89% yield and in 97% ee. Formal hydration of alkyne **372** was accomplished in two steps by utilizing a cyclofunctionalization with TsNCO catalyzed by copper(I) iodide and triethylamine.[242] This key reaction was followed by hydrolysis of cyclic carbamate **373** to give the desired ketone with little to no loss of enantiomeric excess. Protection of the secondary alcohol with a MOM group completed the synthesis of ketone **374**.

With these two fragments in hand, the key coupling reaction was investigated (Scheme 60). Terminal alkyne **370** was deprotonated to generate the dianion with two equivalents of isopropylmagnesium chloride, and the resultant dianion was added to ketone **374** to give tertiary alcohol **375** in 84% yield (based on ketone **374**) and in 92:8 dr. Alkyne **370** was used in a 3.5:1 ratio relative to ketone **374**; however, alkyne **370** was recovered and recycled after the reaction. The authors note that addition of the corresponding alkenyl reagent into ketone **374** gave very little reaction and was accompanied by significant enolization of ketone **374**. Selective *trans* reduction of alkyne **375** followed by acylation gave ester **376** in 62% yield. This set the stage for a relay ring-closing metathesis[243] reaction using 17 mol % Grubbs second generation catalyst,[98] delivering the desired lactone **377** in 62% yield. Lower catalyst loadings were found to give incomplete ring formation—the intermediate diene was also isolated together with the desired product. Two further steps were used to transform the trityl protecting group of compound **377** into the desired mesylate **378**. The mesylate was displaced with sodium azide, and then the resulting azide was reduced using a Staudinger reduction[244,245] and protected in situ to give carbamate **379** in 29% yield over four steps. Two further steps exchanged the protecting groups to give TES ether **380**, an intermediate in Hatakeyama's synthesis of phoslactomycin B (**7**).

Cossy completed the synthesis of advanced intermediate **380** in 18 longest linear steps and in 2.0% yield from 1,3-propanediol (**169**). Hatakeyama transforms this intermediate into phoslactomycin B (**7**) in 11 further transformations. The overall step count using this sequence is therefore 29 longest linear steps (38 total steps) and 0.15% overall yield. Cossy illustrates a number of interesting transformations in this formal synthesis. The use of a [2,3]-Wittig rearrangement[239,240] to set the C4 and C5 stereocenters is a unique and highly successful approach to this family of molecules. This reaction relies on a catalytic enantioselective Noyori reduction[87] to set the absolute stereochemistry rather than a stoichiometric chiral auxiliary. Also noteworthy is the hydration of alkyne **372** to give α-hydroxy ketone **373** with little or no loss of enantiomeric excess. Use of a dianion for the addition into ketone **374** avoids the use of a protecting group for propargylic alcohol **370** and gives the desired tertiary alcohol **375** in good yield and diastereoselectivity.

7. PHOSLACTOMYCIN A

Phoslactomycin A (**9**) contains an added element of complexity over phoslactomycin B (**7**) in that it contains two more stereocenters in the cyclohexyl portion of the structure. This added complexity, common to all the phoslactomycins, phosphazomycins, and leustroducsins, except for phoslactomycin B (**7**), requires enantioselective methods for the construction of the stereocenters about the cyclohexane fragment. This challenge is met by a myriad of different approaches, including asymmetric Michael addition,[202,203] enzymatic acylation,[204] chiral auxiliary directed Diels–Alder cyclization,[205–207] and enantioselective allylic alkylation.[208]

7.1. Koert's Synthesis

In 2009 Koert and co-workers reported the first total synthesis of phoslactomycin A (**9**).[246,247] Their synthesis envisioned a copper-mediated coupling of a vinyl tin reagent with a vinyl iodide derived from the core of the molecule to unite the cyclohexyl portion to the rest of the molecule (Figure 36). The cyclohexyl portion was constructed by employing an enantioselective Michael reaction of a vinyl boronic acid into an enone. The core of the molecule was constructed starting from the chiral pool and includes a Sharpless dihydroxylation[66,67] to control the C8 and C9 stereocenters. An Evans's aldol[186,187] was used for the construction of the C4 and C5 stereocenters. The nitrogen was installed using a Mitsunobu reaction, followed by a Staudinger reduction.

The cyclohexyl fragment synthesis began with cyclohexenone (**381**) (Scheme 61). Rhodium-catalyzed Michael addition using Hayashi's protocol[248,249] delivered the desired coupled product **382** in 96% yield and in 94% ee. Diastereoselective reduction followed by silyl protection gave silyl ether **383** in 88% yield and in 7:1 dr. Vinyl stannane **384** was synthesized in five further steps, including ozonolysis of the styrene, Wittig olefination,[97] and acylation to install the acyl group characteristic of phoslactomycin A (**9**).

Koert synthesized the core of phoslactomycin A (**9**) starting from epoxide **385** (available in one step and 96% yield from (*S*)-glycidol),[250] which was transformed into enoate **386** in seven steps, including a Wittig reaction[97] to extend the carbon chain (Scheme 62). Sharpless asymmetric dihydroxylation[66,67] delivered the desired diol in 9:1 dr, which was then protected as dimethoxyphenyl acetal **388** (diastereoselectivity for this new stereocenter not given). Five further steps were needed to obtain aldehyde **389** in 91% yield. A diastereoselective aldol using Evans chiral oxazolidinone **390**[186,187] gave oxazolidinone **391** in 95% yield and in 95:5 dr. In six steps and in 53% yield oxazolidinone **391** was transformed into lactone **392**. The azide was then installed using a Mitsunobu[111,112] reaction. The acetal was then cleaved to give diol **393** in 76% yield over two steps.

In eight further transformations vinyl iodide **394** was synthesized, using a diallylphosphoramidite[118] to install the phosphate group and a Stork–Zhao olefination[142] to furnish the *Z* vinyl iodide in greater than 20:1 selectivity (Scheme 63). The key cross-coupling event was carried out with a stoichiometric copper-mediated coupling of vinyl iodide **394** and vinyl stannane **384** to give the coupled product **395** in 61% yield without

deallylation of the protected phosphate group. Global deprotection completed the synthesis of phoslactomycin A (**9**).

Koert completed the synthesis of phoslactomycin A (**9**) in 34 longest linear steps (42 total steps) and in 1.3% yield from (*S*)-glycidol. This synthesis features a number of useful transformations including the chemoselective copper-mediated cross-coupling reaction to unite the cyclohexyl fragment to the core of phoslactomycin A (**9**). Another notable transformation is the rhodium-catalyzed Michael addition to set the absolute stereochemistry of the cyclohexyl fragment, which proceeded in 96% yield and in 94% ee. Koert also successfully employed a Sharpless dihydroxylation[66,67] and an Evans's aldol reaction[186,187] to set the C4, C5, C8, and C9 stereocenters. Koert's strategy is the only reported synthesis of phoslactomycin A to date.

8. LEUSTRODUCSIN B

Leustroducsins A–C were originally identified and isolated in a screen for inducers of colony-stimulating factors (CSFs).[9,10,64] CSFs promote the production and differentiation of blood cells, and compounds that up-regulate their production are of interest for the treatment of immunosuppressed states, such as are found in patients undergoing chemotherapy. Leustroducsin B (**16**) is the most potent of the three isolates, and has been found to induce granulocyte-macrophage-CSF (GM-CSF) and granulocyte-CSF (G-CSF) production by KM-102 cells in vitro.[9] Additionally, leustroducsin B (**16**) has been shown to augment host resistance to lethal infection with *Escherichia coli*[251] and induce thrombocytosis when administered to mice in vivo.[252] This activity is speculated to occur via a distinct mechanism from that of interleukin-1β, bacterial lipopolysaccharide, and phorbol 12-myristate 13-acetate.[253] It has been shown that leustroducsin B (**16**) may induce a variety of cytokines in primary human bone marrow stromal cells. In addition to these activities, the leustroducsins possess antifungal and antibiotic activities.[9,10]

This impressive biological activity has inspired the synthetic community to develop new strategies for the synthesis of the most potent member of the leustroducsins, leustroducsin B (**16**). In addition to the challenges associated with the synthesis of phoslactomycin B (**7**), three new stereocenters are present in leustroducsin B (**16**): two on the cyclohexyl ring and a remote stereocenter on the acyl group. As we will see, a variety of methods have been employed to meet these new challenges.

8.1. Matsuhashi's Semisynthesis

In 2002 Matsuhashi and Shimada reported a semisynthesis of leustroducsin B (**16**) from the unacylated compound leustroducsin H (**8**).[254] The leustroducsins are isolated as a mixture, with leustroducsin B (**16**) present as a minor component. Though large-scale fermentation has been achieved on a multi-hundred-gram scale, only 9.83 mg of leustroducsin B (**16**) is obtained from 60 L of culture broth after repeated HPLC purifications.[10] This supply problem prompted Matsuhashi to develop a semisynthesis of leustroducsin B (**16**) from leustroducsin H (**8**), which is available from the mixture by selective ester hydrolysis using pig liver esterase (PLE) (Figure 37).[255] Preliminary studies by Matsuhashi and co-workers indicated that selective protection of the phosphate was impractical, which led them to

pursue a strategy involving phosphate removal and reinstallation at a later point in the synthesis.

After selective hydrolysis using pig liver esterase to convert the mixture of leustroducsins to the unacylated leustroducsin H (**8**), selective Alloc-carbamate formation of the amine was followed by phosphate removal (Scheme 64). Extensive screening identified alkaline phosphatase type-1 (Sigma) as a uniquely effective phosphatase, giving the desired product **396** after cyclic acetal formation in 28% yield over three steps. Selective formation of the 1,3-dioxane was observed to predominate over formation of the 1,2-dioxorane. Installation of the acyl side chain characteristic of leustroducsin B (**16**) was accomplished at this stage using the Yamaguchi protocol.[256]

Protection of the tertiary alcohol of intermediate **399** and hydrolysis of the acetonide was achieved over three steps and in 65% yield, as the free tertiary alcohol had been problematic in their earlier studies due to partial formation of the cyclic phosphate upon phosphorylation conditions. The allylic alcohol was then protected, though the desired protected product **400** was contaminated with protection of the other alcohol and the bisacylated product. These undesired products could be recycled by treatment with ammonium hydroxide. Phosphorylation was then accomplished to give the fully protected compound **401** in 27% yield over the two steps. Deprotection was achieved by deacylation using ammonium hydroxide and then the allyl and TMS groups were removed using catalytic palladium to give the desired natural product, leustroducsin B (**16**).

Matsuhashi's semisynthesis was completed in 11 steps and in 1.8% yield from leustroducsin H (**8**). Matsuhashi's synthesis paves the way for future biological testing of leustroducsin B (**16**). In addition, this work provides useful insight into the late-stage reactions that can be tolerated without significant decomposition, as leustroducsin B (**16**) has been found to be sensitive to both acid and base.

8.2. Fukuyama's Synthesis

Fukuyama reported the first total synthesis of leustroducsin B (**16**) in 2003.[147] The strategy employed by the Fukuyama group includes several new strategies for the synthesis of the fostriecin family of natural products, including an enzymatic desymmetrization and a diastereoselective allylation for the installation of the C9 stereocenter (Figure 38). Fukuyama also employs an Evans aldol reaction[186,187] and a diastereoselective alkynylation to set three further stereocenters. An enzymatic acylation was also utilized to set the stereochemistry about the cyclohexane ring.

Fukuyama's synthesis began with an extremely efficient six-step sequence featuring a Pummerer reaction[257] and an alkylative Cannizzaro reaction,[258] yielding the meso diol **405** in 71% yield from the starting ethyl 4-chloroacetoacetate **402** (Scheme 65). Desymmetrization using Lipase AK[48] and vinyl acetate followed by silylation gave protected tetraol **406** in 86% yield and 90.2% ee. In six steps and 70% yield, acetate **406** was transformed into free alcohol **407**. After oxidation, Grignard addition gave allyl alcohol **408** in 80% yield over the two steps as a single diastereomer. Protecting group manipulations yielded allylic alcohol **409**, which was then protected as an acetal that was specially

designed for this synthesis to allow for facile deprotection under mild conditions at a later stage. The TBS group of this protecting group was removed during a four-step sequence that interchanged the protecting groups and was then reinstalled after oxidation of the primary allylic alcohol to give enal **410**. An Evans aldol[186,187] using chiral acyl oxazolidinone **329** was then employed to give the desired *syn* product **411** (selectivity not reported).

The alkynyl zinc reagent **418** was synthesized in 15 steps from racemic carboxylic acid **412** (Scheme 66). In four steps, including iodolactonization, elimination, lactone opening, and benzylation, racemic alcohol **413** is formed in 86% yield. Enzymatic kinetic resolution returned resolved alcohol **413** in 50% yield and in 83% ee. In four steps the alcohol was protected, the olefin and benzyl groups were removed, and the aldehyde was formed. Stork–Zhao olefination[142] of aldehyde **414** gave the desired *Z* vinyl iodide **415** in 6:1 selectivity. Sonogashira cross-coupling[49] gave TMS alkyne **416**. Protecting group manipulations gave terminal alkyne **417** in 58% yield over three steps. Formation of zinc acetylide **418** was achieved in a straightforward manner for the diastereoselective addition into the central fragment of the molecule.

The main fragment was processed into an appropriate aldehyde for addition by first removing the chiral auxiliary (Scheme 67). Formation of the lactone was achieved using the Ando reagent[164] to selectively give the desired *Z* olefin geometry, which was then cyclized. Six steps were needed to achieve these transformations with an overall yield of 52% (**410** → **411** → **419**). Sharpless asymmetric dihydroxylation,[66,67] followed by lead tetraacetate cleavage to give aldehyde **420**, was used, presumably to impart chemoselectivity not obtained with ligandless oxidation conditions. This set the stage for the key diastereoselective addition reaction with alkynyl zinc reagent **418**. The desired transformation proceeded in 77% yield over two steps to give propargylic alcohol **421** as a single diastereomer. After the alkynylation reaction successfully installed the C11 stereocenter, Brandsma reduction[229] gave the desired *Z* olefin **422**. Protecting group manipulations gave primary alcohol **423** in three steps and in 58% yield from trityl-protected alcohol **422**. At this stage the amine was installed and protected via a Mitsunobu reaction[111,112] using an azide, followed by a Staudinger reduction[244,245] and in situ protection to yield carbamate **424**. Six further transformations were needed to manipulate the various protecting groups and install the phosphate group using Bannwarth's[118] method, yielding protected phosphate **425** in 19% yield. Acylation of alcohol **425** resulted in ester **426** with the side chain characteristic of leustroducsin B (**16**) in 92% yield. Europium triflate was used to remove the phenoxyacetate, and then global deallylation under palladium catalysis delivered the natural product leustroducsin B (**16**) in 35% yield for the two steps.

Fukuyama completed the synthesis of leustroducsin B (**16**) in 47 longest linear steps (61 total steps) with 0.071% yield from commercially available ethyl 4-chloroacetoacetate **402**. This synthesis illustrates the utility of several important methodologies, including enzymatic acylation,[48] and diaster-eoselective addition reactions.

8.3. Imanishi's Synthesis

Imanishi and co-workers reported the synthesis of leustroducsin B (**16**) in 2007 using a highly convergent strategy.[40,259,260] Their strategy envisioned two key disconnections to break the molecule into three pieces of approximately equal complexity (Figure 39). A Julia olefination[154,155] would be used to unite the lactone portion to the core, and a Stille coupling[73] would be used to unite the cyclohexyl fragment. A Sharpless asymmetric epoxidation[107,108] was planned to set the stereochemistry of the lactone portion, while a Sharpless asymmetric dihydroxylation[66,67] was envisioned to set the C8 and C9 stereocenters. The construction of the cyclohexane fragment spurred the development of a chiral auxiliary controlled Diels–Alder reaction,[261] inspired by the work of Raw and Jang.[262]

Imanishi's synthesis began with a Sharpless asymmetric epoxidation[107,108] of commercially available allylic alcohol **427**, giving epoxide **428** in 82% yield and in 95% ee (Scheme 68). Epoxide opening using an aluminum alkyne gave a 39% yield of the desired regioisomer **429** together with 15% of the other regioisomer resulting from epoxide opening at the other side. Five further steps gave the sulfone coupling partner **430** for the Julia olefination[116,154] in 30% yield. Interestingly, Lindlar reduction was unsuccessful, as an inseparable mixture of the desired *Z* olefin and the overreduced product was obtained. Brandsma reduction[229] was used to overcome this problem.

The core of leustroducsin B (**16**) was synthesized using a chiral pool strategy, beginning with acetonide **95**, which was derived from (*R*)-malic acid in two steps and in 83% yield (Scheme 69).[101] In five further steps featuring a Wittig reaction[97] to extend the carbon framework, *E* olefin **431** was obtained in 30% yield. Sharpless asymmetric dihydroxylation[263] proceeded in 91% yield to give diol **432** as a single diastereomer, successfully installing the C8 and C9 stereo-centers of leustroducsin B (**16**). In six further protecting group manipulations and an oxidation, aldehyde **433** was obtained in 58% yield.

The cyclohexane fragment of leustroducsin B (**16**) was made using a chiral-auxiliary-based Diels–Alder[261] strategy (Scheme 70). The reported Diels–Alder methods for the synthesis of similar optically active cyclohexane carboxylic acids relied on expensive chiral auxiliaries (sometimes because they required the unnatural configuration of a chiral pool starting material) in order to obtain the desired absolute configuration needed for the synthesis of leustroducsin B (**16**). Imanishi decided to pursue a modification of a procedure reported by Raw and Jang[262] for the Diels–Alder reaction, based on the easily accessible oxazolidinone chiral auxiliary. Acryloyl oxazolidinone **434** (available in one step and in 79% yield from the commercially available oxazolidinone[263]) reacts with butadiene to give the desired product **435** as a single isomer in 63% yield. Hydrolysis of the chiral auxiliary gave carboxylic acid **436** in 67% yield and 94% ee. Iodolactonization was performed to install the second stereocenter of the cyclohexane ring needed for leustroducsin B (**16**) and then the iodine atom was removed under tin-free radical conditions to give the reduced bicyclic lactone **437** in 76% yield over two steps. Reductive opening of the lactone gave the hemiacetal, which was then olefinated using a Wittig reagent[97] to give dibromide **438** in 71% yield over two steps. Dibromide **438** was transformed into tin alkyne **439** without protection of the free

alcohol group. Reduction of alkynyl tin **439** to *Z* vinyl tin **440** was achieved using the Schwartz reagent in 52% yield over two steps. Acylation with carboxylic acid **398** installed the side chain characteristic of leustroducsin B (**16**) in 84% yield (intermediate **441**).

With each of the fragments in hand, Imanishi set out to join the pieces together to assemble the natural product (Scheme 71). The first strategy was reported in 2007,[259] using a Julia olefination[116,154] for the coupling reaction. Aldehyde **433** was subjected to various olefination conditions. Unfortunately, epimerization at the C5 position was observed when either sodium or potassium hexamethyldisilazide was used. The authors suggest that this epimerization occurs prior to olefination after deprotonation of the sulfone (**430**). The more strongly associated lithium counterion prevented this epimerization, giving the desired product in 14% yield. Deprotection gave primary alcohol **443** in 79% yield from the desired epimer **442**.

In 2008 Imanishi reported an alternate strategy for the coupling of the lactone and core fragments (Scheme 72).[260] This strategy features a Nozaki–Hiyama–Kishi (NHK) coupling reaction.[264–266] Aldehyde **433** was transformed into *E* vinyl iodide **444** in 65% yield using a Takai olefination.[267] The NHK reaction with aldehyde **445** (available in nine steps and in 10.8% yield using a enzymatic kinetic resolution to set the stereochemistry)[268] gave a 19% yield of alcohol **446** and a 56% yield of the C5-epimer of **446**. The mixture of products (**446** and *epi*-**446**) could be transformed to primary alcohol **443** in five steps, through a sequence involving oxidation, selective reduction to *epi*-**446**, inversion using a Mitsunobu reaction,[111,112] and protecting group removal in 56% yield. This procedure was higher yielding than their first generation Julia[154,155] coupling strategy.

At this stage, diol **443** was transformed to the α,β-unsaturated lactone, the *E* vinyl iodide was formed using a Stork–Zhao olefination,[142] and several protecting group manipulations were performed over the course of five steps to give primary alcohol **447** in 31% yield (Scheme 73). The olefination installed the vinyl iodide geometry in 4.3:1 *Z:E* selectivity. The pendant amine group was installed using a two-step protocol involving a Mitsunobu reaction[111,112] with an azide, followed by Staudinger reduction[244,245] and in situ protection with AllocCl to give carbamate **448** in 74% yield. Deprotection of the acetonide and TBS groups was followed by a Stille cross-coupling reaction[73] to give diene **449** in 61% yield. Selective protection of the allylic alcohol allowed for phosphorylation of the C8 and C9 alcohols. The cyclic phosphate was then opened to give monoallylated **450**, together with the C8 regioisomer and the fully deallylated cyclic phosphate in 66% yield from triol **450**. This mixture was desilylated and deallylated to give leustroducsin B (**16**) in 49% yield.

Imanishi completed the synthesis of leustroducsin B (**16**) in 30 longest linear steps (47 total steps) from (*R*)-malic acid using their first-generation strategy featuring a Julia olefination. The overall yield was 0.048% yield from allylic alcohol **427**. The synthesis of sulfone **430**, though shorter in steps, was lower in yield than the synthesis of aldehyde **433**; therefore, the longest linear sequence was not used to calculate the overall yield. Their second-generation strategy employing an NHK reaction gave leustroducsin B (**16**) in 35 longest linear steps (54 total steps) with 0.21% yield. Several interesting methodologies were used in the synthesis,

including a chiral auxiliary directed Diels–Alder reaction.[261] The convergency of Imanishi's synthesis is noteworthy.

8.4. Cossy's Synthesis

Cossy reported a formal synthesis of leustroducsin B (**16**) in 2008.[238,269] The key transformations include a Sharpless asymmetric dihydroxylation[66,67] of a diene, Brown crotylation,[95,96,203,204] and an acylation/ring-closing metathesis[91,92] strategy to install the α,β-unsaturated lactone (Figure 40).

Cossy's synthesis begins with commercially available (*R*)-glycidol **451**, which is converted to terminal olefin **452** in three straightforward steps and in 92% yield (Scheme 74).[270,271] This set the stage for a cross-metathesis[91,92] reaction using conditions developed in the Cossy laboratories that include the use of 5 mol % chlorocatecholborane as an additive.[272] This additive prevents the formation of 3-methyl-2(5*H*)-furanone, a product that is formed under standard cross-metathesis conditions. Under these optimized conditions the desired enoate **454** was obtained in 72% yield. In three further steps the lactone was opened and the system was homologated to give diene **455** in 63% yield. Sharpless dihydroxylation[66,67] gave a 1.7:1 mixture of the unwanted isomeric diol at C6 and C7, to the desired diol **456** in 42% yield. Fortunately diol **456** was obtained as a single diastereomer. The undesired isomer was recycled in three steps and in 74% yield to give the starting diene **455**. Protecting group manipulations gave acetonide **457** in two steps and in 86% yield. Reduction of ester **457** to the alcohol oxidation state, followed by oxidation to the aldehyde, set the stage for a pentenylation using Brown conditions.[95,96,204] This gave the desired *syn* diastereomer **458** in greater than 95:5 diastereoselectivity relative to the C8, C9, and C11 stereocenters and in 67% yield. This was followed by an acylation/ring-closing metathesis[91,92] sequence to give the α,β-unsaturated lactone in 51% yield. Four further transformations gave Imanishi's intermediate **447** in 27% yield, including a Stork–Zhao olefination,[142] which favored the desired *Z* vinyl iodide in a 2.5:1 isomeric ratio.

Cossy completed the synthesis of Imanishi's intermediate in 19 steps and in 1.4% yield from (*R*)-glycidol. Imanishi completed the synthesis of leustroducsin B (**16**) from intermediate **447** in nine further linear steps. Therefore, the Cossy route to create leustroducsin would take 28 longest linear steps and 38 total steps and proceed in 0.20% yield. Cossy's cross-metathesis conditions[272] for the construction of lactone **454** provide a nice alternative to the Wittig reaction[97] used in Imanishi's synthesis of leustroducsin B (**16**) to make a similar intermediate. As seen previously, Brown pentenylation,[95,96,204] acylation, and ring-closing metathesis[91,92] are a successful sequence for the installation of the α,β-unsaturated lactone.

8.5. Johnson's Synthesis

Johnson published a formal synthesis of leustroducsin B in 2011, featuring a novel Reformatsky/Claisen condensation developed in his laboratories (Figure 41).[273] This strategy also features a catalytic asymmetric β-lactone forming reaction originally developed by Nelson,[274] which set the absolute stereochemistry of the molecule. Johnson's strategy also uses a Brown pentenylation,[95,96,204] and a metathesis[91,92] strategy for installation of the α,β-unsaturated lactone.

Johnson's synthesis begins with formation of β-lactone **460** from ynal **84** and acetyl bromide, using a chiral aluminum catalyst developed by Nelson (Scheme 75).[274] This reaction proceeds in 67% yield and in 78–83% ee. This provided the substrate for Johnson's key transformation between silyl glyoxylate **461** (synthesized in two steps and in 82% yield from benzyl diazoacetate[275]), Reformatsky reagent **462**, and β-lactone **460**.[276] This multicomponent reaction begins by addition of Reformatsky reagent **462** to silyl glyoxylate **461**, which then undergoes a [1,2]-Brook rearrangement[277] to give zinc aldolates **463** and **464**. Kinetically formed enolate **463** can be equilibrated to the more stable enolate **464**. Alkylation with β-lactone **460** gives ketone **465** in 61% yield and in greater than 20:1 dr. These two steps rapidly generate molecular complexity and give the leustroducsin core. The stereocenter at C11 is opposite to that needed for the natural product, requiring inversion. Before inversion, however, this stereocenter was used to set the stereochemistry at C9 by utilizing a Prasad reduction.[278] The resulting diol was obtained in greater than 25:1 dr and was then protected as acetal **466**. In three steps and in 55% yield aldehyde **467** was synthesized and subjected to a Horner–Wadsworth–Emmons reaction.[51–54] Reduction gave aldehyde **468**. Use of the cyano-containing reagent facilitated reduction directly to the aldehyde, rather than the more commonly employed ester-containing reagent, which generally requires reduction to the alcohol, followed by oxidation to the aldehyde.

Aldehyde **468** was used in a Brown-type pentenylation[95,96,204] reaction to set the C4 and C5 stereocenters (Scheme 76). The compound was isolated as a mixture of diastereomers, the ratio of which depended on the enantioselectivity of the initial β-lactone **460**. At this stage ring-closing metathesis[91,92] was attempted, but the substrate **469** was found to be unreactive. The authors hypothesized that the terminal alkyne was sequestering the catalyst, and therefore protected the alkyne as dicobalt hexacarbonyl complex **470**. Ring-closing metathesis[91,92] proceeded, and after deprotection of the alkyne, the desired α,β-unsaturated lactone **471** was obtained in 66% yield. At this point, several protecting group interchanges were necessary in order to obtain a suitable substrate (**472**) for inversion of the C11 stereocenter. This required five steps and proceeded in 55% yield. The stereocenter was then inverted and the resulting chloroester was hydrolyzed to give the desired alcohol **473** with the correct stereochemistry at C11. Four further steps installed the vinyl iodide and exchanged protecting groups to intercept Imanishi's intermediate **447**.[259,260] The diastereomers created in the pentenylation step were now separated: a 5:1 diastereomeric mixture was purified by HPLC to give a single isomer. A further nine steps are required to reach leustroducsin B (**16**) using Imanishi's route.

Johnson's formal synthesis of leustroducsin B (**16**), when the steps from Imanishi's sequence are considered, is 35 longest linear steps and 47 total steps with an overall yield of 0.23%. The highlight of this synthesis is the first two reactions: the Reformatsky/Claisen condensation[273] and Nelson's[274] catalytic asymmetric β-lactone formation. These transformations demonstrate the power of addition reactions to quickly assemble molecular complexity.

8.6. Trost's Synthesis

Trost's synthesis of leustroducsin B (**16**) was reported in 2015.[279] This synthesis relies on a highly convergent strategy with two key disconnections to break the molecule into three fragments of approximately equal complexity (Figure 42). The first key disconnection is a diastereoselective addition of a vinyl zincate reagent into a ketone. The second key disconnection is a Hiyama cross-coupling reaction employing a vinyl silane developed in the Trost laboratories.[138] The stereochemistry of each of the fragments were planned via an Evans aldol,[186] an asymmetric direct catalytic aldol reaction using a zinc ProPhenol complex,[137] and an asymmetric allylic alkylation (AAA) reaction.[280]

Trost's synthesis begins with an asymmetric Evans aldol[186] (**329** + **474** → **475**) to set the C4 and C5 stereocenters in greater than 20:1 dr and in 87% yield (Scheme 77). Reduction and Wittig olefination[97] gave a mixture of cyclized **476** and uncyclized **477**. These acetals were then transacetalated and the terminal alkyne was deprotected in a one-pot reaction, followed by installation of the vinyl iodide to yield fragment **478**.

The central fragment was synthesized by a direct catalytic asymmetric aldol developed in the Trost group[137] between aldehyde **479** (available in three steps from ethyl diethoxyacetate) and ynone **151** (available in two steps from benzyldimethylsilyl chloride, Scheme 78). The aldol product **480** is obtained in 78% yield and in 99% ee. Diastereoselective reduction with the Noyori's catalyst[87] gave the desired diol **481** in greater than 20:1 dr and in 80% yield after silylation. Protecting group installation and azide incorporation gave ketone **482** in two steps and in 88% yield.

The cyclohexyl fragment was synthesized by employing an asymmetric allylic alkylation[280] using carboxylic acid **398** as a nucleophile (Scheme 79). Upon formation of the π-allyl palladium complex, the racemic electrophile **483** is rendered pseudomeso, resulting in the transformation of both enantiomers of the starting allyl carbonate **483** (made in four steps from commercially available racemic carboxylic acid **412**) into a single enantiomer of product **484** with 93% yield and greater than 99% ee. Four further transformations, including a Stork–Zhao olefination,[142] gave *Z* vinyl iodide **485** in greater than 20:1 selectivity and in 49% yield.

With these fragments in hand, the key coupling reactions were investigated (Scheme 80). Addition of the zincate reagent derived from *E* vinyl iodide **478** to ketone **482** gave the desired tertiary alcohol **486** in 75% yield and in greater than 20:1 dr. Two further steps oxidized the methyl acetal to the lactone and reduced the silyl alkyne to the vinyl silane **487** in 30% yield. This vinyl silane **487** was cross-coupled to vinyl iodide **485** under buffered TBAF conditions with catalytic palladium.[138] The silicon cross-coupling reaction yielded the entire carbon framework of leustroducsin B (**16**) in 70% yield. Five further steps were needed to install the phosphate, reveal the amino group, and remove the protecting groups to reveal leustroducsin B (**16**).

Trost's synthesis of leustroducsin B (**16**) is achieved in 17 longest linear steps and 32 overall steps in 0.36% overall yield from ethyl diethoxyacetate. This highly convergent approach greatly reduces the linear sequence needed to complete the synthesis. The coupling

strategies result in an extremely concise approach to leustroducsin B (**16**). Several enabling methodologies greatly reduce the number of steps needed to build up molecular complexity. The direct catalytic asymmetric aldol reaction[137] quickly assembles the core of the molecule and incorporates the silyl group needed for the cross-coupling reaction[138] that unites the cyclohexyl group to the core of the molecule. Also remarkable is the asymmetric allylic alkylation reaction[280] for the construction of the cyclohexyl fragment that both unites the acyl side chain of leustroducsin B and sets the absolute configuration of both of the cyclohexyl stereocenters. These addition reactions greatly simplify the synthesis of these fragments, thereby shortening the overall synthesis considerably. The diastereoselective zincate addition was a highly successful and selective strategy for uniting the core fragment to the lactone portion of the molecule.

9. CONCLUSIONS

The reported syntheses of the fostriecin family of natural products highlight a number of different approaches to the various substructures present in the family's architecture. Nearly all of the reported syntheses rely on an acylation/ring-closing metathesis[91,92] approach for the construction of the α,β-unsaturated lactone. This is a high yielding and functional group tolerant strategy that is used effectively by many groups. In several cases, particularly with terminal alkynes, metathesis is unsuccessful until protection of the alkyne is carried out. Strategies that avoid the presence of terminal alkynes at the metathesis stage avoid these unwanted additional steps. The Jacobsen group employs a completely different strategy for the synthesis of the lactone portion by employing their chromium-catalyzed hetero-Diels–Alder reaction.[77] This quickly builds the desired ring system at one oxidation state lower than the lactone, which also serves to protect the acid-sensitive lactone. By using an asymmetric addition reaction, Jacobsen and Chavez are able to quickly assemble the lactone portion of fostriecin, making their synthesis extremely concise.

Another common strategy of these synthetic endeavors is the Brown allylation[95,96,204] or longer chain variants,[203] which is an extremely reliable way of introducing the C5 (and C4) stereocenter. O'Doherty employed a Leighton allylation[159] to achieve a similar transformation in his synthesis of fostriecin. Shibasaki's synthesis nicely highlighted the more recently developed allylation reaction of Yamamoto[129] that can be performed catalytically, even in the presence of heteroatoms that can compete for binding. This strategy should gain in popularity, as it avoids the need for sensitive stoichiometric chiral reagents.

The use of asymmetric addition reactions for rapidly constructing molecular complexity is also nicely displayed in the aldol reactions of both Shibasaki's[126] and Trost's[137] syntheses. These strategies serve to couple larger fragments together, while at the same time controlling the new stereocenter that is formed. This provides a more concise construction of the C9 stereocenter, as it unites the carbon–carbon bond-forming reaction with the installation of the stereocenter. The asymmetric Morita–Baylis–Hillman reaction[119,120] utilized by Hatakeyama and co-workers is another successful addition reaction. The Nelson β-lactone formation[274] is also employed to good effect in the Johnson synthesis, and the diastereoselective Reformatsky/Claisen condensation[276] that follows this step is an excellent example of the power of addition reactions to rapidly increase complexity.

Cross-coupling is another method that is used frequently, and certainly to great effect for the synthesis of the fostriecin family of natural products. Trost's silicon based cross-coupling[138] is particularly noteworthy as it obviates the need to install a vinyl iodide on a complex molecule and avoids the use of toxic tin compounds. Indeed, the silicon group can be carried through the entire synthesis and then can be activated easily and selectively with TBAF. Even base-sensitive compounds are tolerated under these conditions as the basic TBAF can be buffered and the cross-coupling reaction still proceeds. McDonald's synthesis of fostriecin[150] also highlights the way in which cross-coupling can be used to disconnect at positions that are not sp^2-hybridized. This strategy uses a "hidden alkene" in the retrosynthetic analysis to unite both the lactone portion and the C8 methyl group to the fostriecin core, and then a dihydroxylation to functionalize this alkene to the desired set of stereocenters at C8 and C9. This is a very successful strategy that has also proven effective for the installation of the aminoethyl group of the phoslactomycins, phosphazomycins, and leustroducsins, as demonstrated by the successful cross-coupling employed by Hatakeyama in his 2008 synthesis of phoslactomycin B.

The fostriecin family of natural products possesses a variety of different functional groups, providing numerous challenges for the synthetic chemist. The diverse functional groups present in these molecules and the variety of approaches toward their synthesis provide an excellent opportunity to compare the effectiveness of a number of strategies. Among these strategies, addition reactions that quickly assemble molecular complexity stand out as enabling technologies that greatly shorten the synthetic sequences needed to complete the target compounds.

This collection of syntheses also remind us about the importance of total synthesis in structure determination, as seen in Boger's reassignment[3] of the structure (and renaming) of the natural product phostriecin and Curran's fluorous mixture synthesis[215] to synthesize and compare several isomers of cytostatin. Total synthesis also provides valuable insights into the relationship between molecular structure and biological activity by providing a means to test chemical structures that are not available from biological sources. The analogue work of Boger[3,3,188,208] and Waldmann[189,190] is particularly notable in this family of natural products, and will hopefully lead to the identification of a biologically active and phosphatase specific inhibitor that is superior to those available from nature.

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Biographies

Barry M. Trost was born in Philadelphia, PA, in 1941 and studied at the University of Pennsylvania (BA, 1962). He obtained his Ph.D. in 1965 at the Massachusetts Institute of Technology. He moved to the University of Wisconsin, where he was made professor in 1969 and subsequently Vilas Research Professor in 1982. He moved to Stanford University in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition to holding visiting professorships at several universities worldwide, he has been awarded numerous prizes. His interests span the entire field of organic synthesis, particularly in the development of novel methodology and strategy for total synthesis of bioactive complex molecules.

Joshua Knopf is currently in his senior year of undergraduate study at Trinity College and a member of the Beta Beta Beta Biological Honor Society. In May 2017, he will graduate with a degree in biochemistry and plans on attending medical school or an M.D./Ph.D. program. Since May of 2014, Joshua has been a part of the breast medical oncology research team, led by Dr. Lajos Pusztai, at the Yale Cancer Center. Joshua's schooling and prior research has helped him develop interests in oncology research and drug development.

Cheyenne S. Brindle received her B.A. at Reed College, where she began her research in the field of total synthesis. She then earned her doctorate in chemistry at Stanford University under the tutelage of Prof. Barry M. Trost, where she pursued total synthesis and asymmetric catalysis. She then moved east to take a position as an American Cancer Society postdoctoral fellow at Harvard University in the research group of Prof. Eric N. Jacobsen, where she studied hydrogen bond donating asymmetric catalysis. In her current position at Trinity, she investigates novel catalyst designs based on restricting molecular motion in small molecules and the synthesis of bioactive natural products.

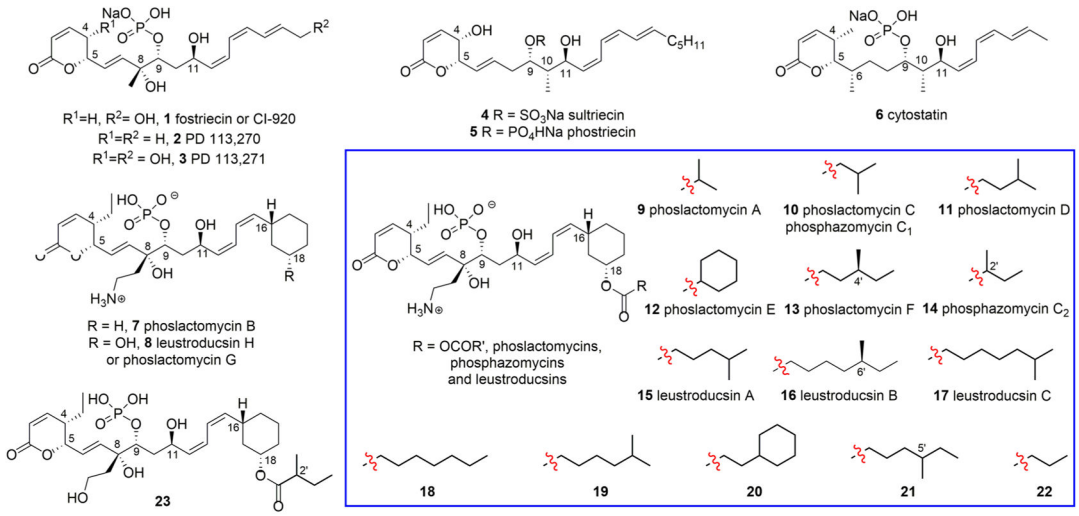


Figure 1.
Fostriecin and related natural products.

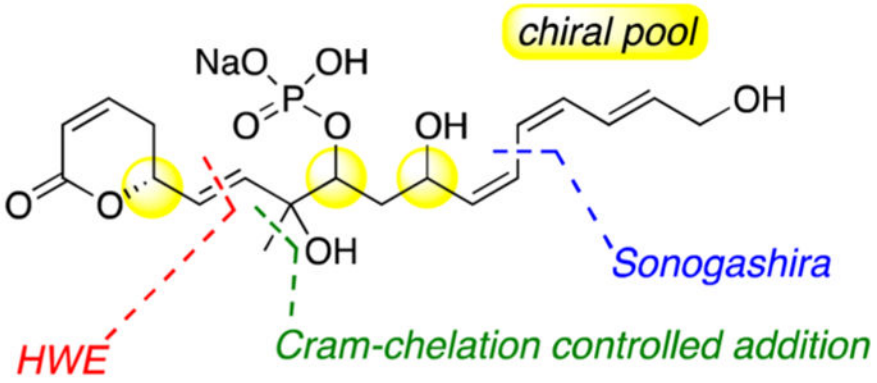


Figure 2.
Just and Reddy's retrosynthetic analysis.

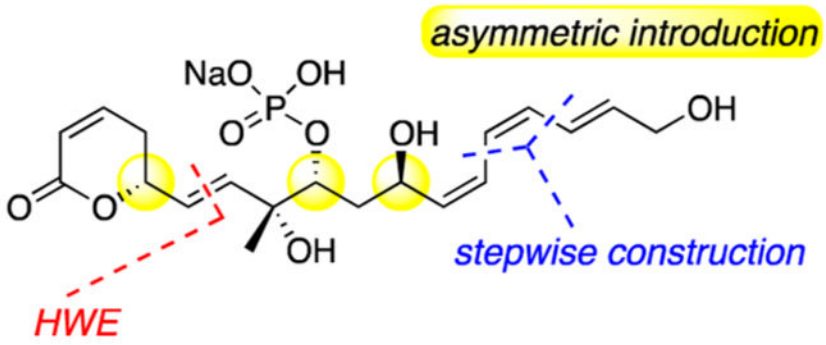


Figure 3.
Boger's retrosynthetic analysis of fostriecin.

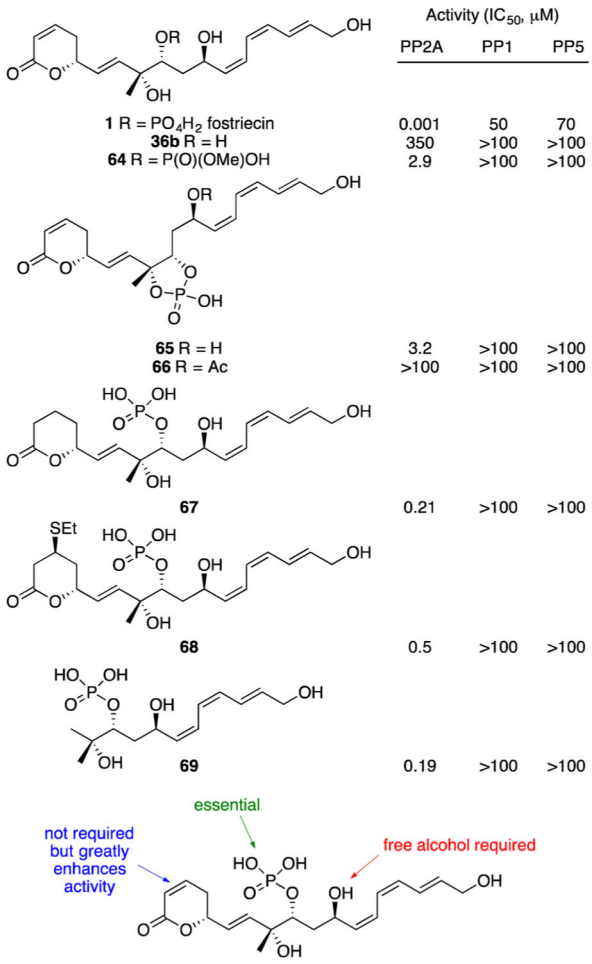


Figure 4.

Evaluation of fostriecin analogues highlights the importance of the unsaturated lactone and phosphate for potency.

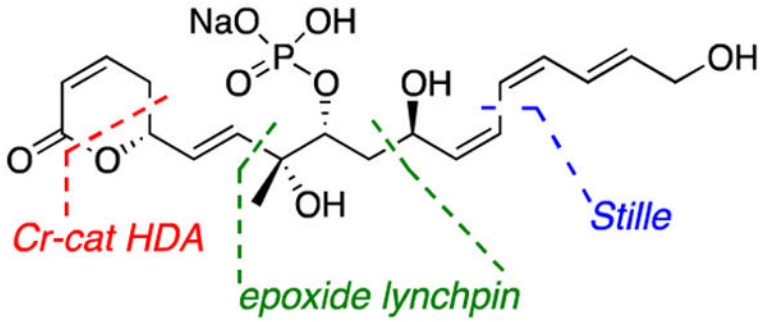


Figure 5.
Jacobsen's retrosynthetic analysis of fostriecin.

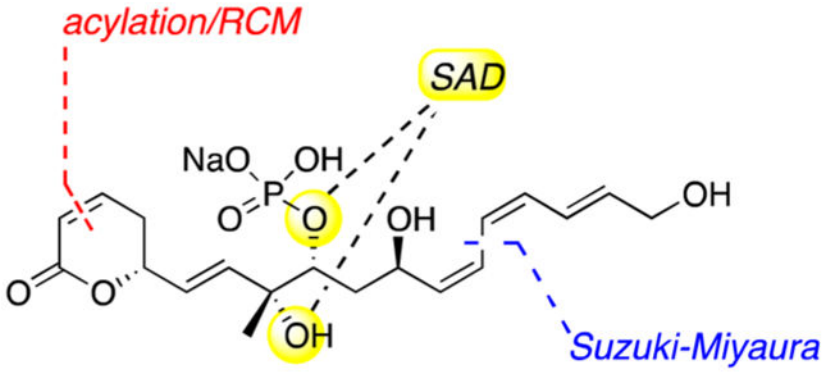


Figure 6.
Falck and Reddy's retrosynthetic analysis of fostriecin.

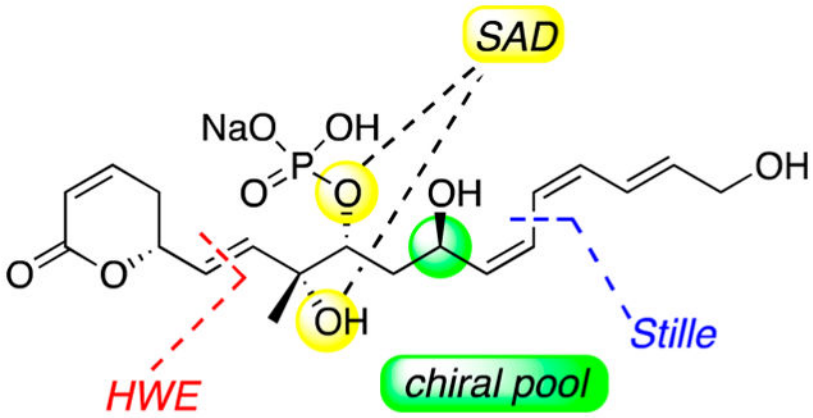


Figure 7.
Imanishi's retrosynthesis of fostriecin.

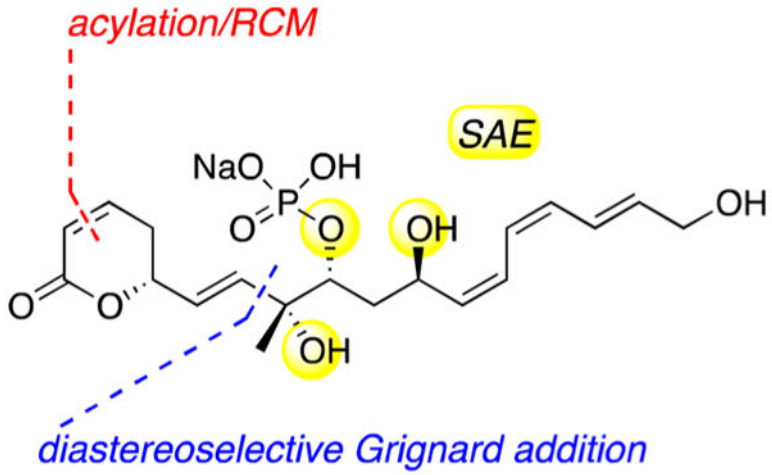


Figure 8.
Kobayashi's retrosynthetic analysis of fostriecin.

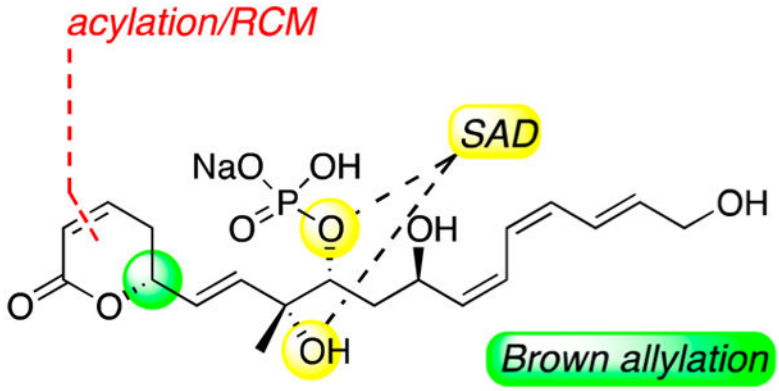


Figure 9.
Hatakeyama's retrosyntheis of fostriecin.

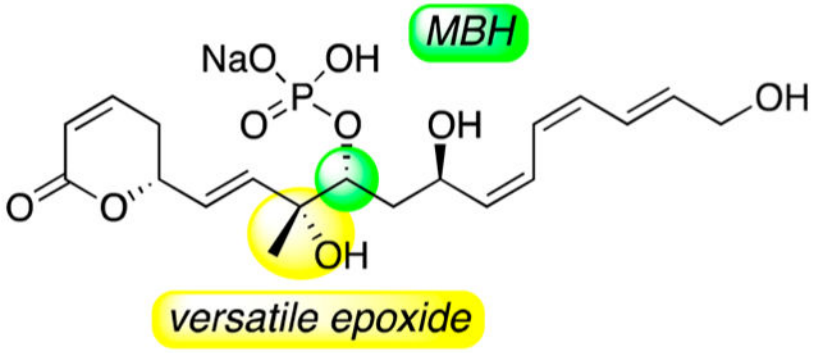


Figure 10.
Hatakeyama's second approach to fostriecin.

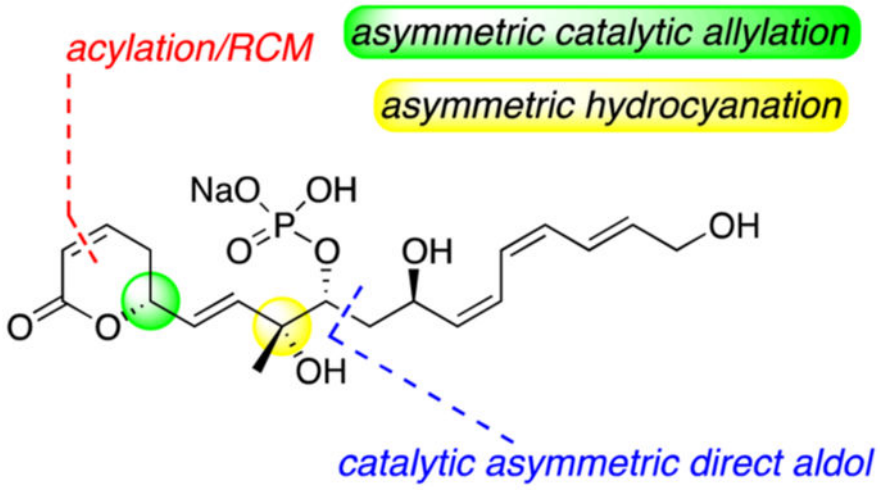


Figure 11.
Shibasaki's retrosynthesis.

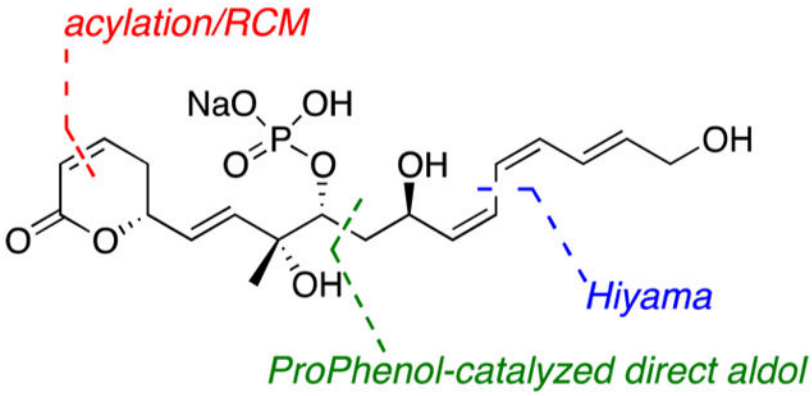


Figure 12.
Trost's retrosynthetic analysis of fostriecin.

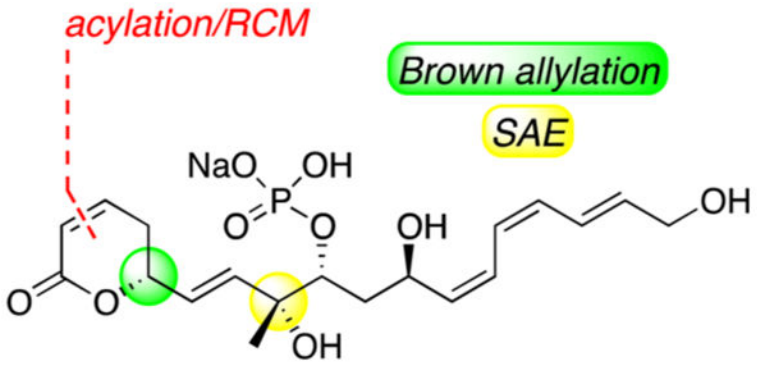


Figure 13.
Yadav's retrosynthesis of fostriecin.

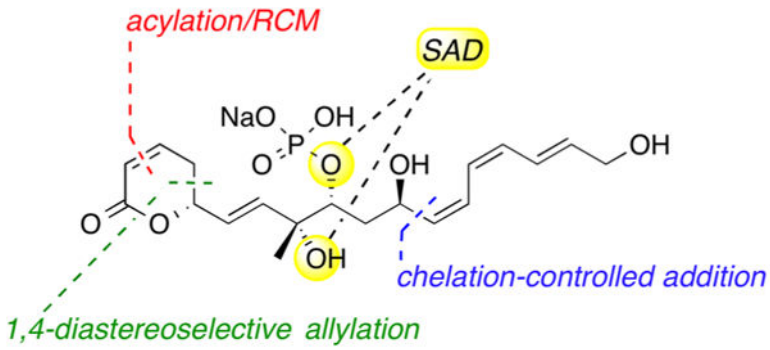


Figure 14.
Hayashi's retrosynthetic analysis of fostriecin.

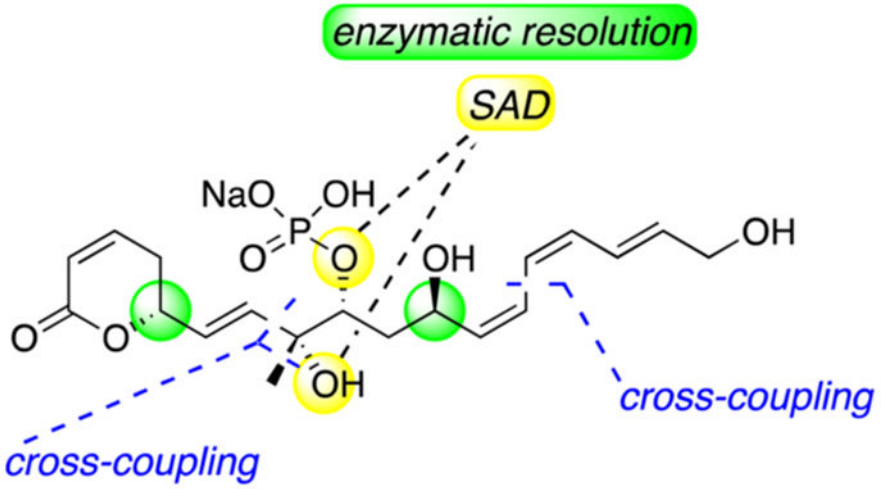


Figure 15.
McDonald's retrosynthesis.

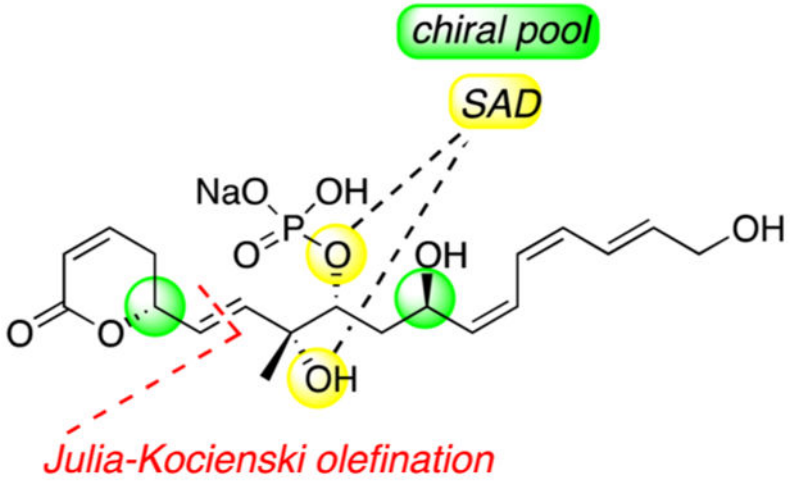


Figure 16.
Zhang's retrosynthesis of fostriecin.

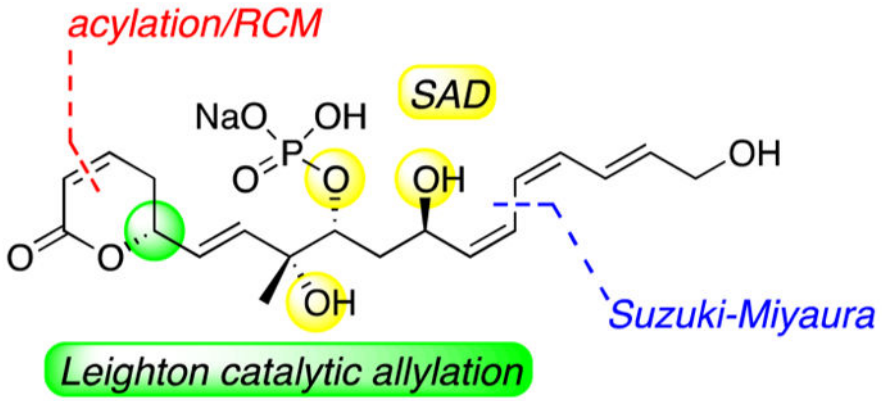


Figure 17.
O'Doherty and Gao's retrosynthesis.

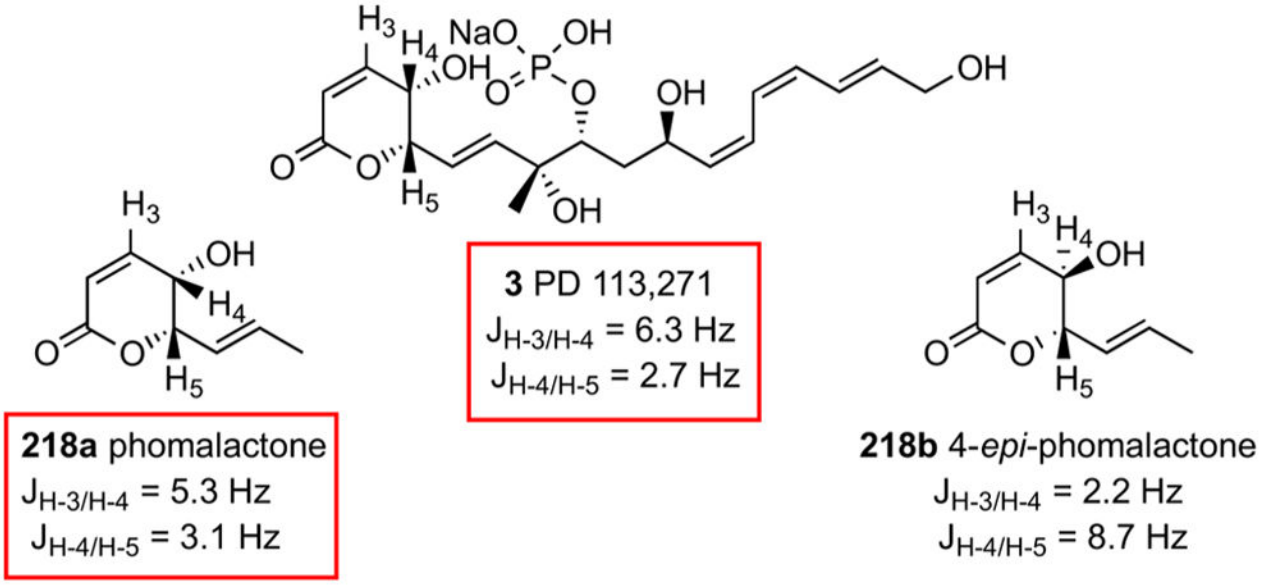


Figure 18.
Sugawara's stereochemical assignment relies on ^{1}H NMR coupling constants.

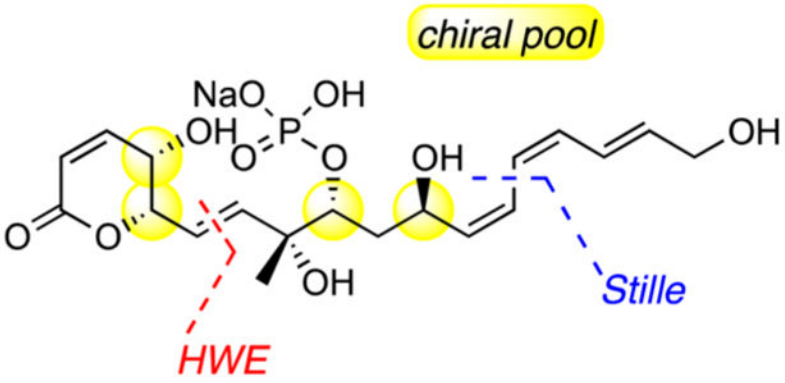


Figure 19.
Sugawara's retrosynthesis of PD 113,271.

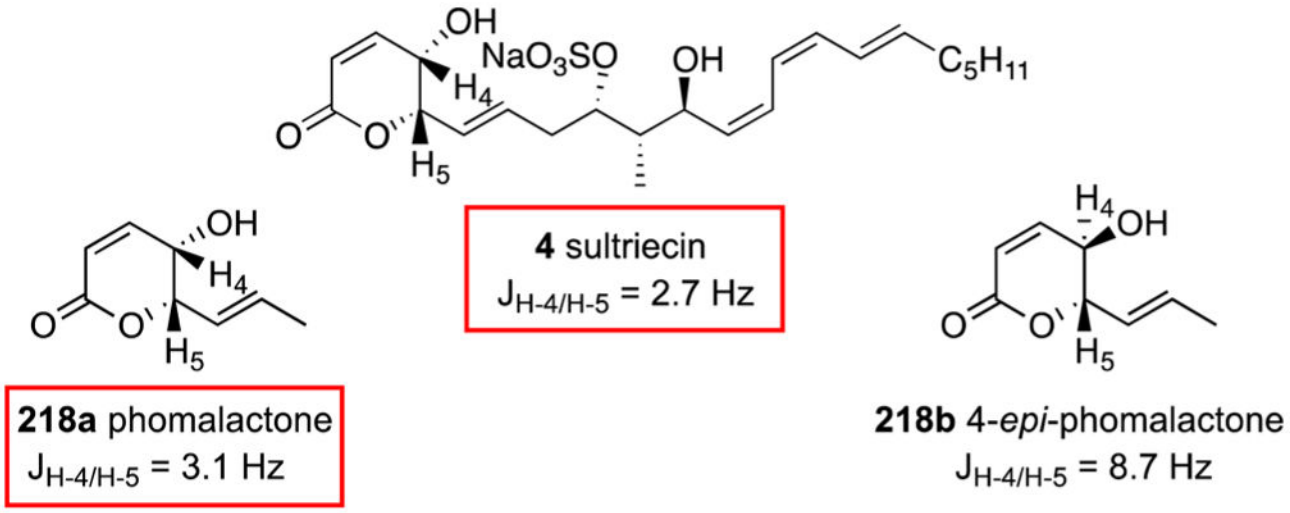


Figure 20.

Boger's stereochemical assignment of sultriecin's C4 stereocenter is based on ^{1}H NMR coupling constants.

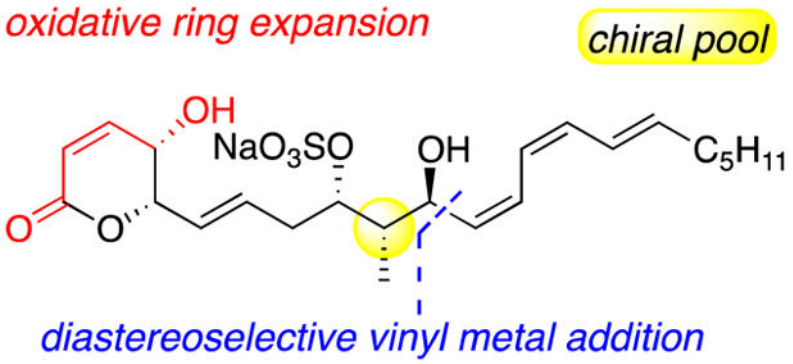


Figure 21.
Boger's retrosynthetic analysis of sultriecin.

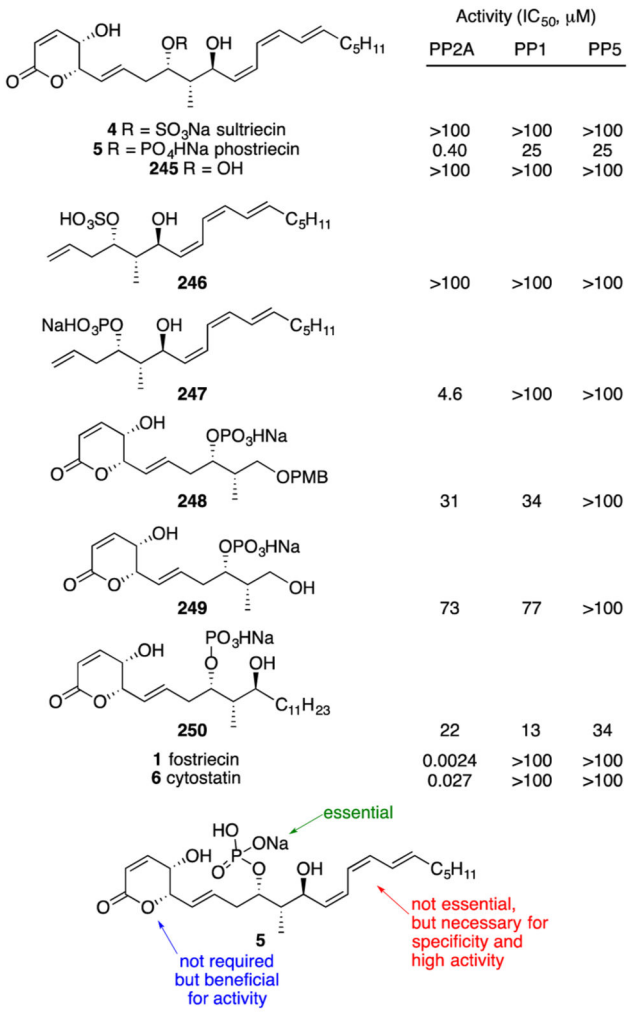


Figure 22.

Phosphatase activity of sultriecin and analogues reveals the importance of the phosphate moiety.

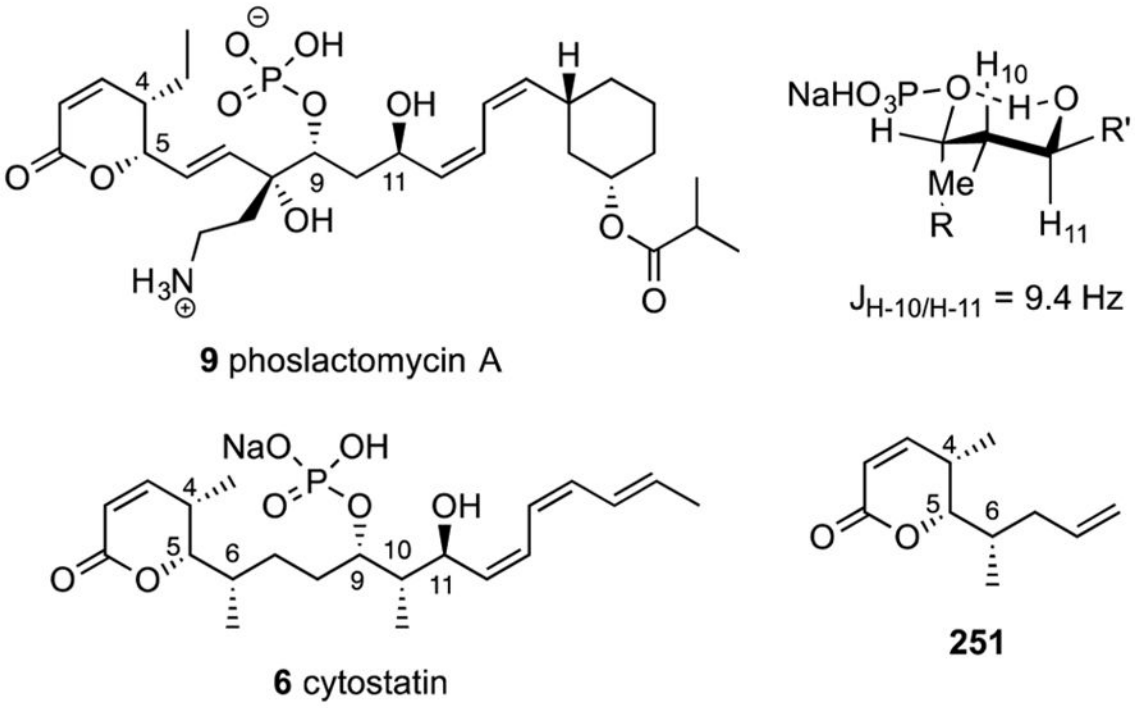


Figure 23.

Waldmann's stereochemical assignment of cytostatin was based on analogy to phoslactomycin A and ^{1}H NMR coupling constants.

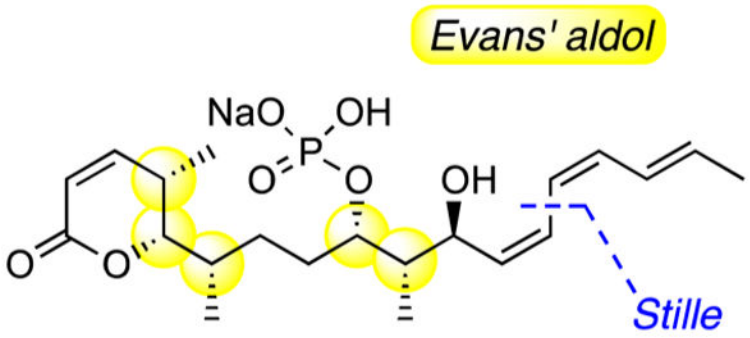


Figure 24.
Bialy and Waldmann's retrosynthetic analysis of cytostatin.

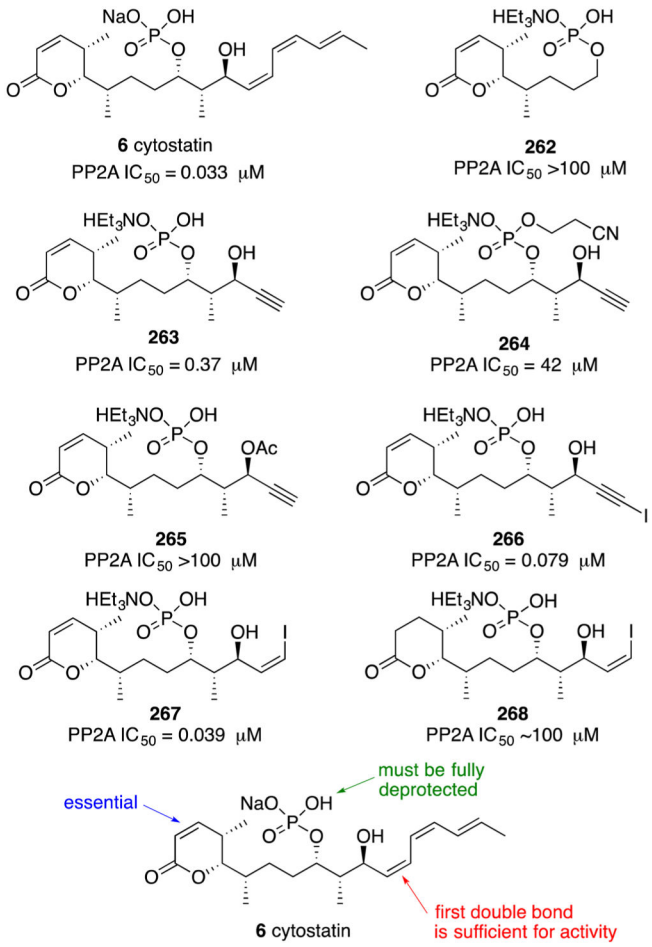


Figure 25.
Waldmann explores the phosphatase activity of several analogues of cytostatin.

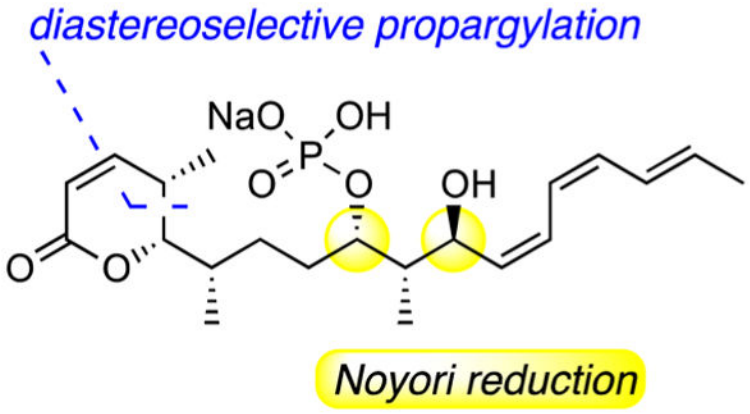


Figure 26.
Marshall's retrosynthetic analysis of cytostatin.

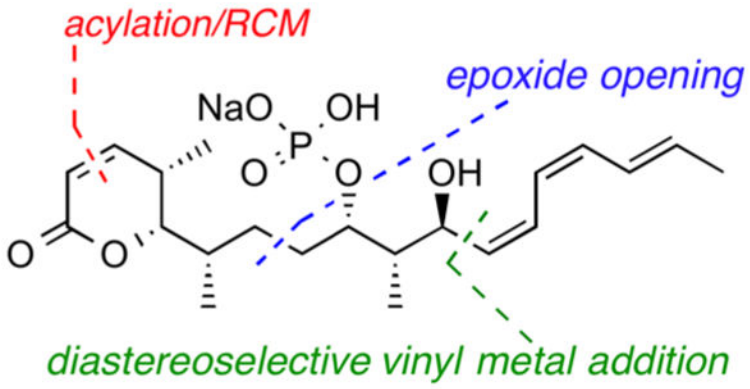


Figure 27.
Boger's retrosynthetic analysis of cytostatin.

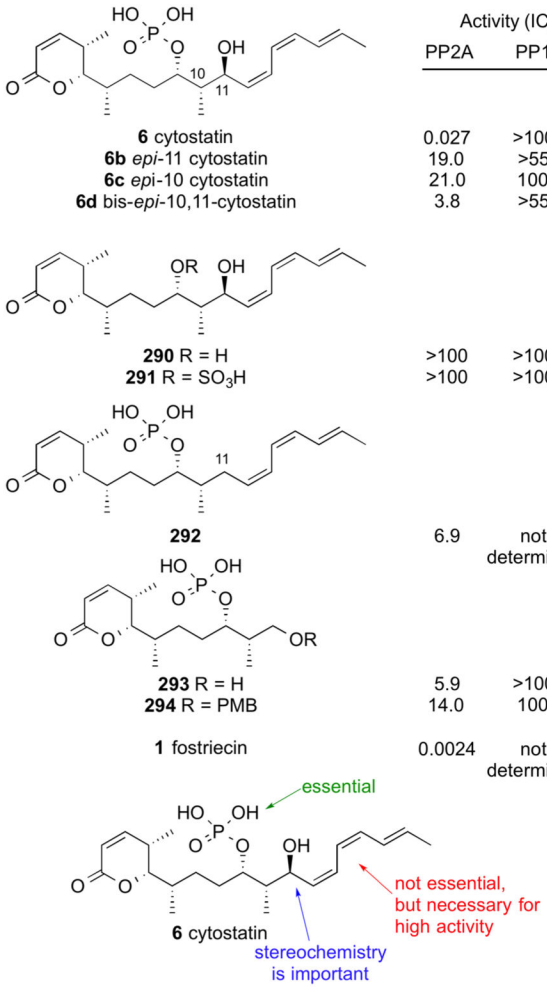


Figure 28.

Boger's analysis of the phosphatase activity of cytostatin analogues reveals the inactivity of the sulfate analogue.

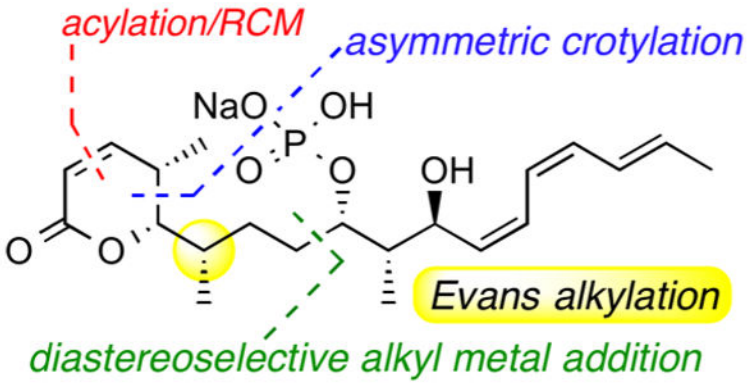


Figure 29.
Cossy's retrosynthetic analysis of cytostatin.

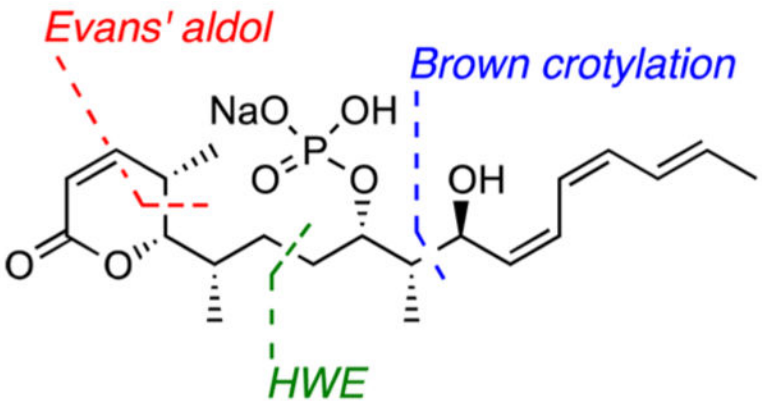


Figure 30.
Curran's retrosynthetic analysis of cytostatin.

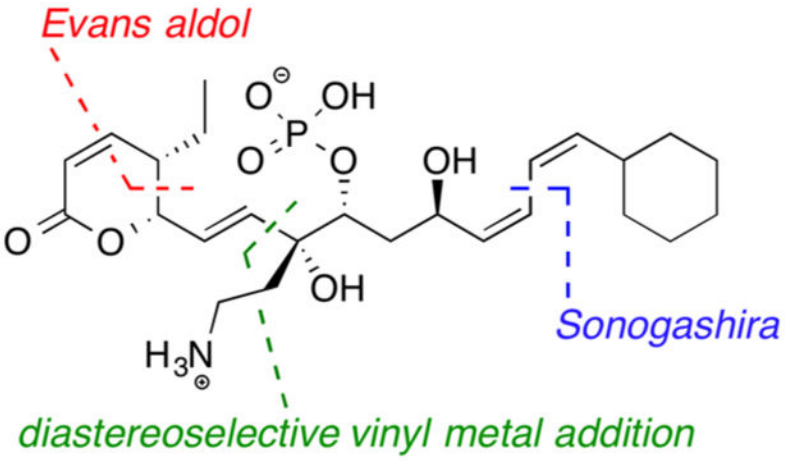


Figure 31.
Kobayashi's first retrosynthetic analysis of phoslactomycin B.

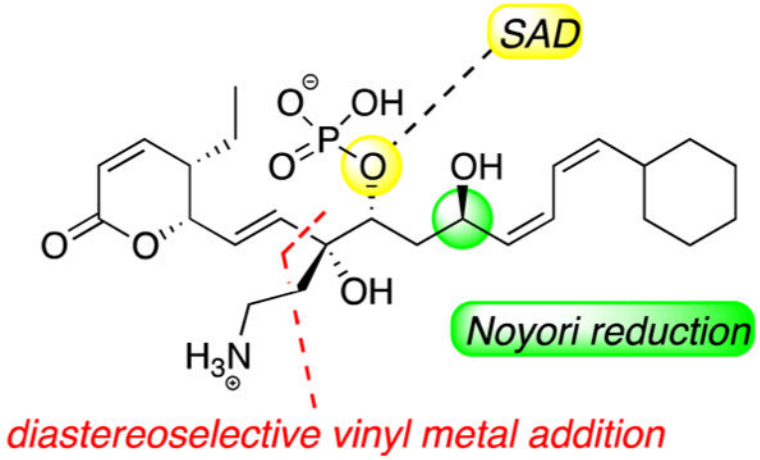


Figure 32.
Kobayashi's revised retrosynthetic analysis of phoslactomycin B.

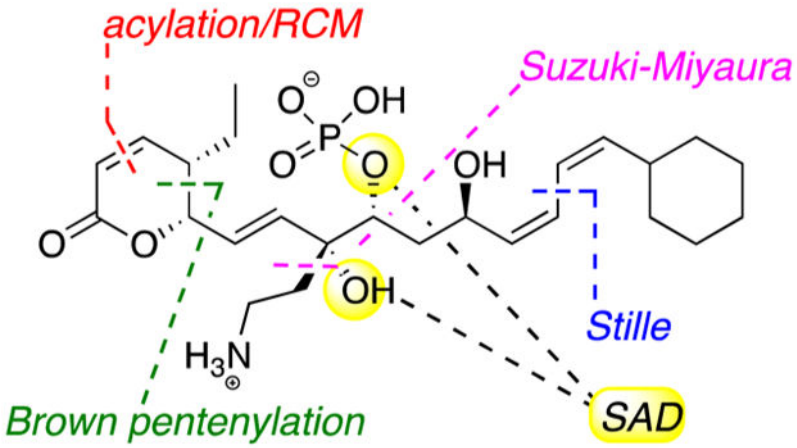


Figure 33.
Hatakeyama's first approach to phoslactomycin B.

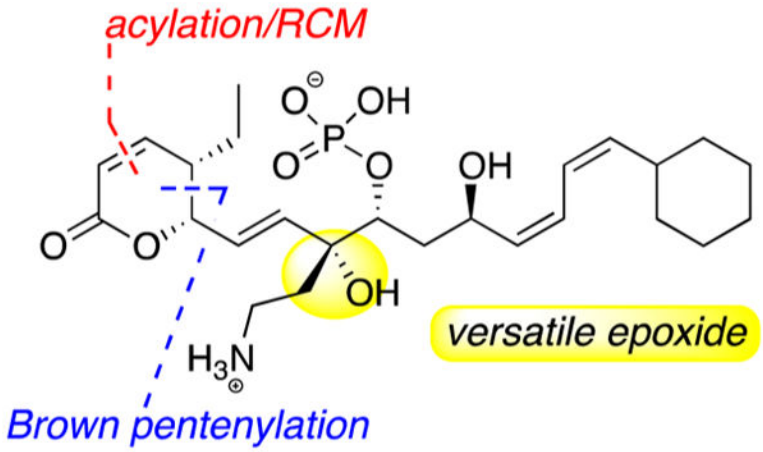


Figure 34.
Hatakeyama's second-generation approach to phoslactomycin B.

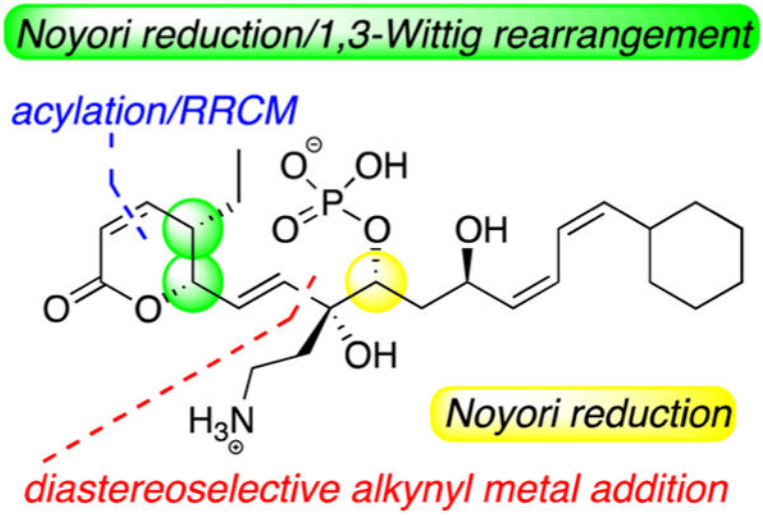


Figure 35.
Cossy's retrosynthesis of phoslactomycin B.

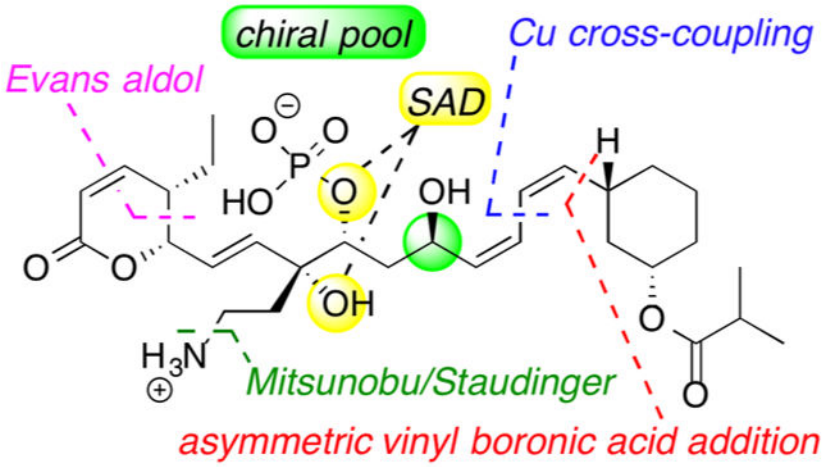


Figure 36.
Koert's retrosynthetic analysis of phoslactomycin A.

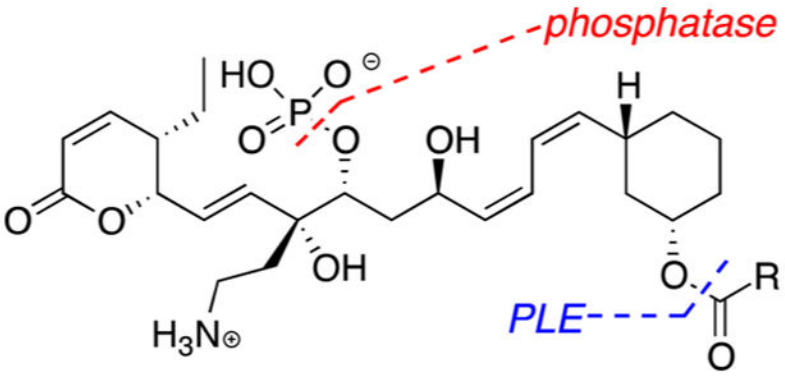


Figure 37.
Masuhashi's approach to the semisynthesis of leustroducsin B.

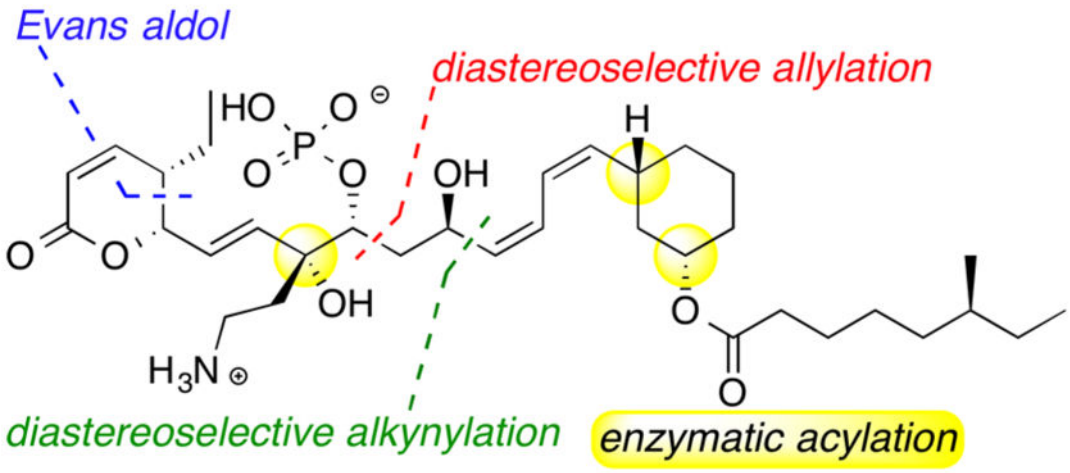


Figure 38.
Fukuyama's retrosynthetic analysis of leustroducsin B.

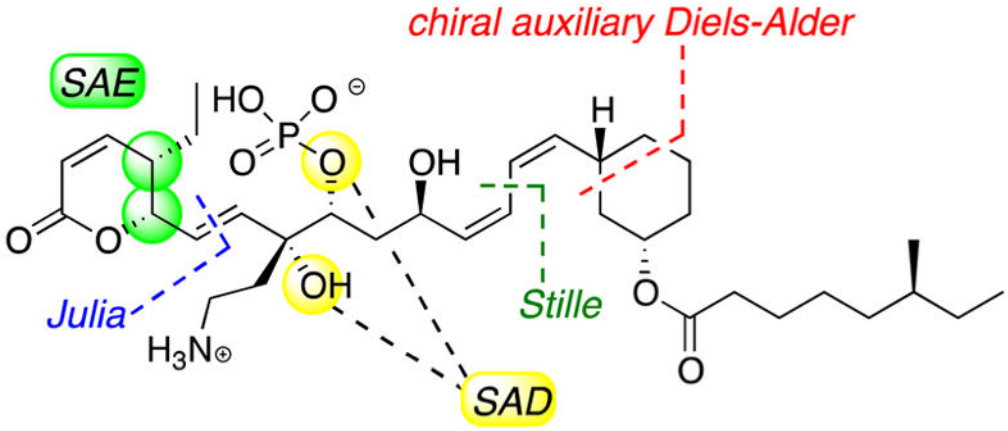


Figure 39.
Imanishi's retrosynthetic analysis of leustroducsin B.

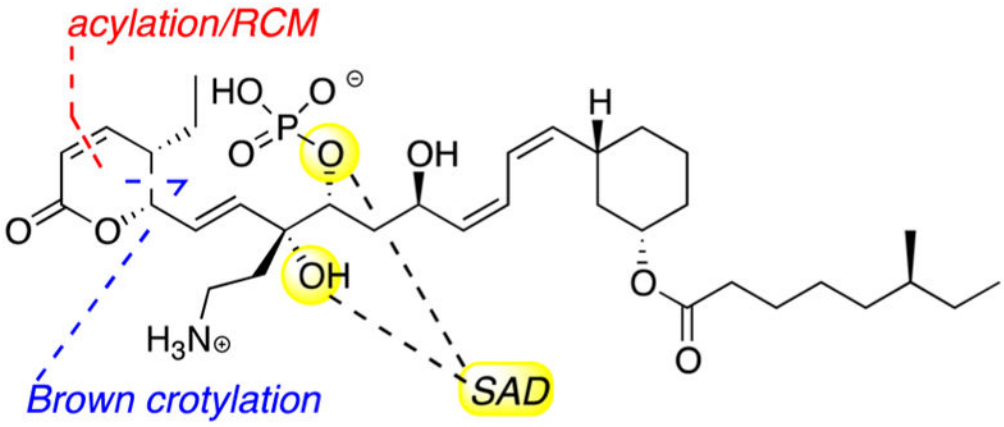


Figure 40.
Cossy's retrosynthetic analysis of leustroducsin B.

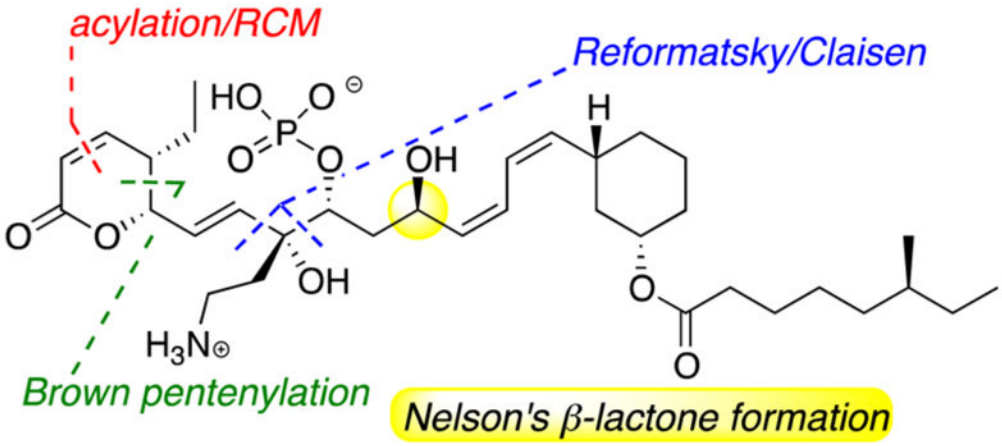


Figure 41.
Johnson's approach to leustroducsin B.

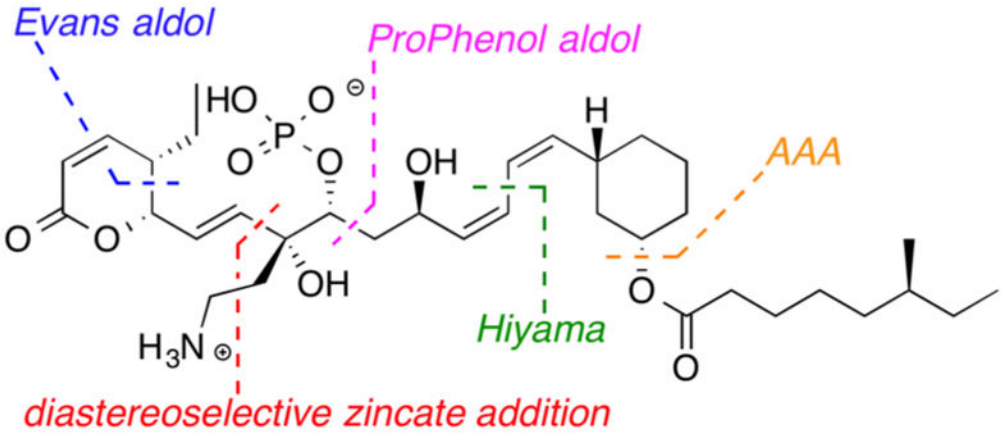
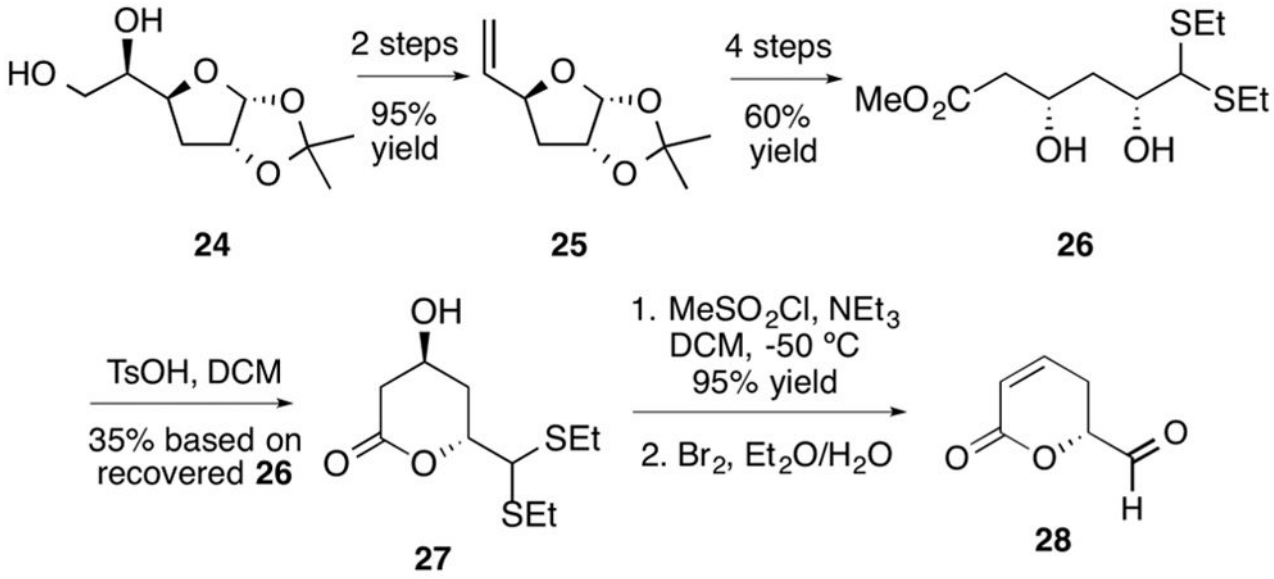
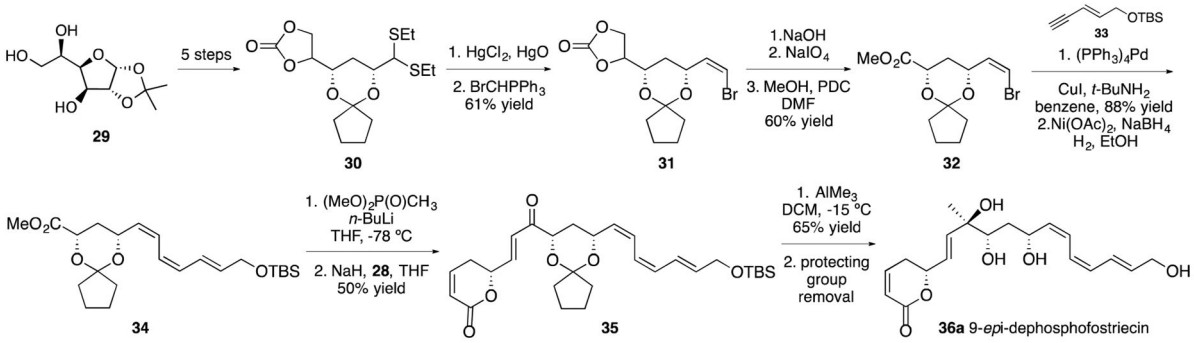


Figure 42.
Trost's retrosynthetic analysis of leustroducsin.



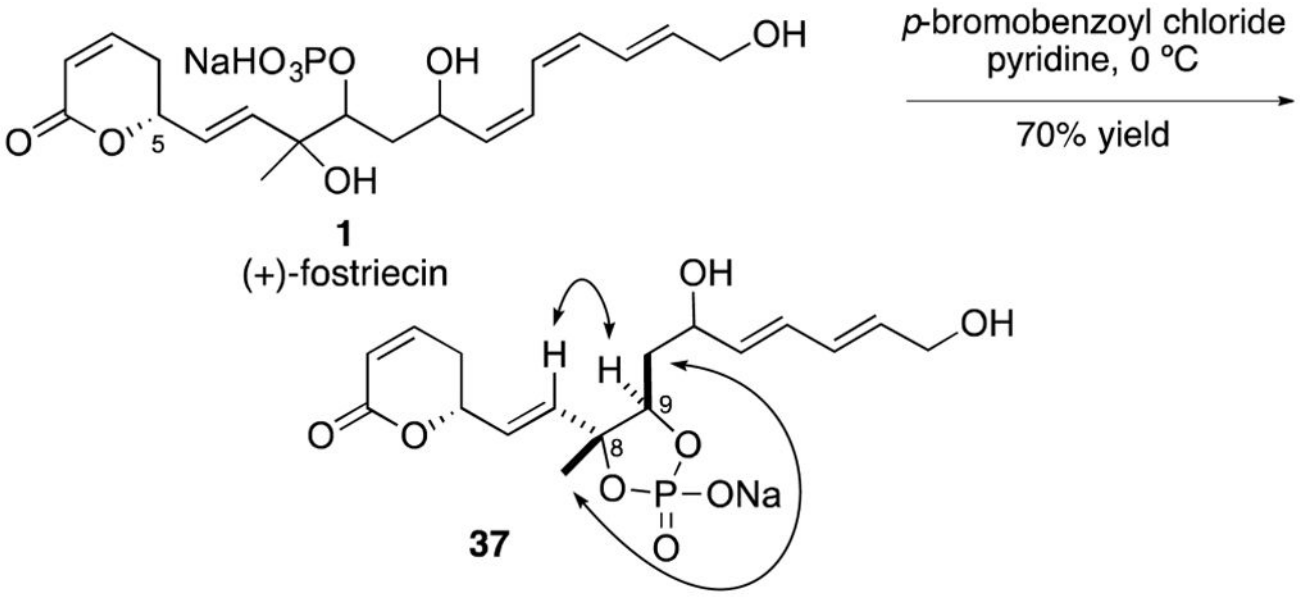
Scheme 1.

Just's Chiral Pool Synthesis of the Lactone Portion of Fostriecin



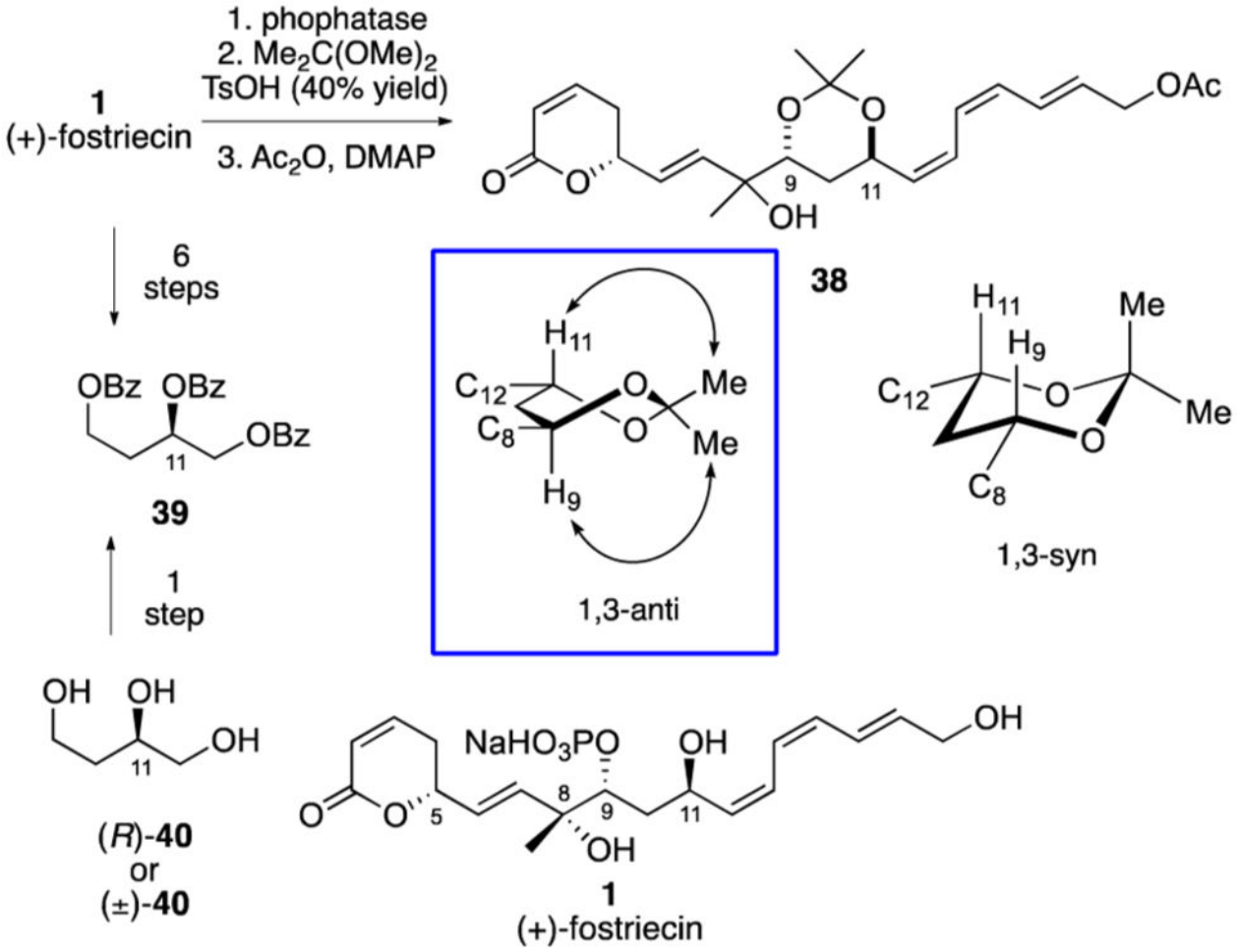
Scheme 2.

Just's Synthesis of a Dephosphofostriecin Epimer Features a Sonogashira Coupling and Horner–Wadsworth–Emmons Olefination



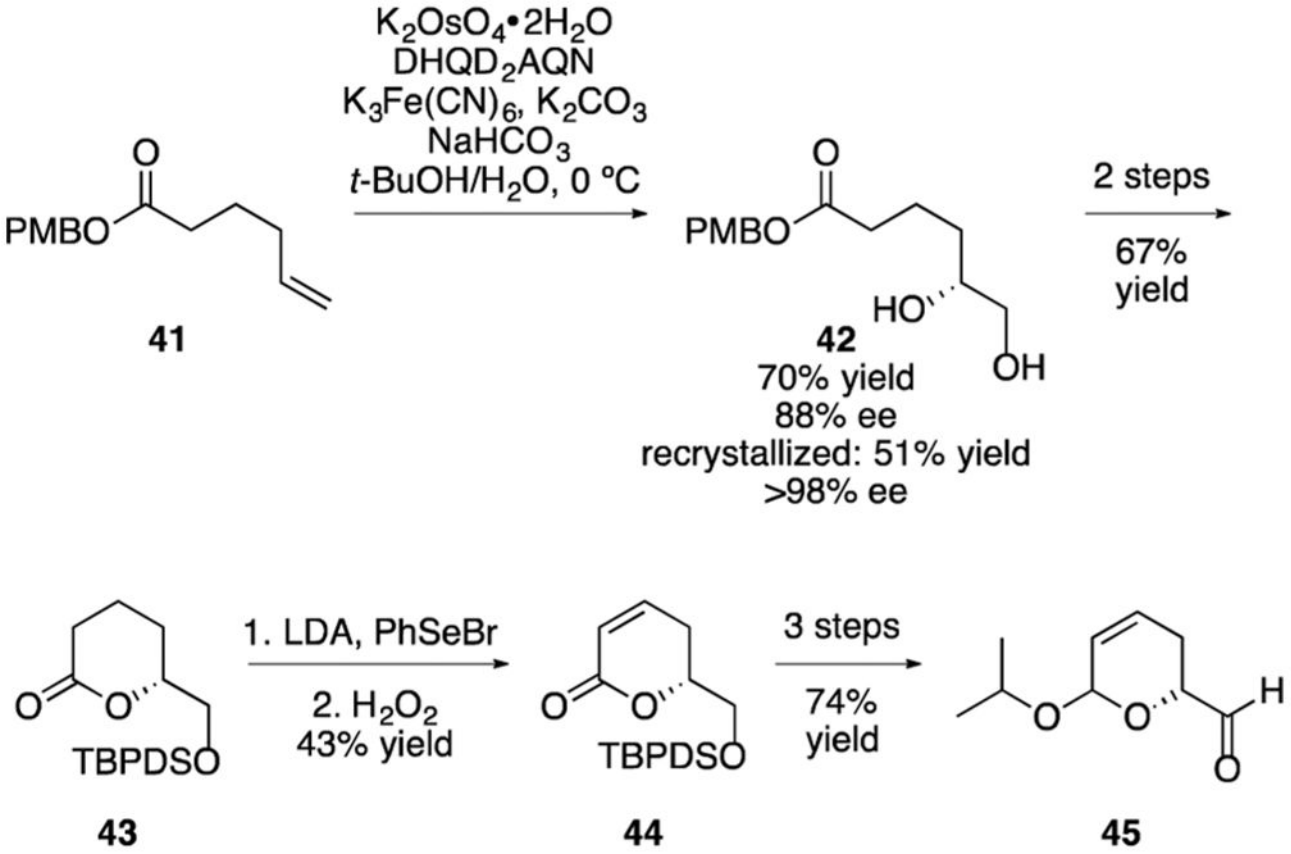
Scheme 3.

Cyclic Phosphate Formation Reveals Key NOEs Establishing a *cis* Relationship between C8 and C9



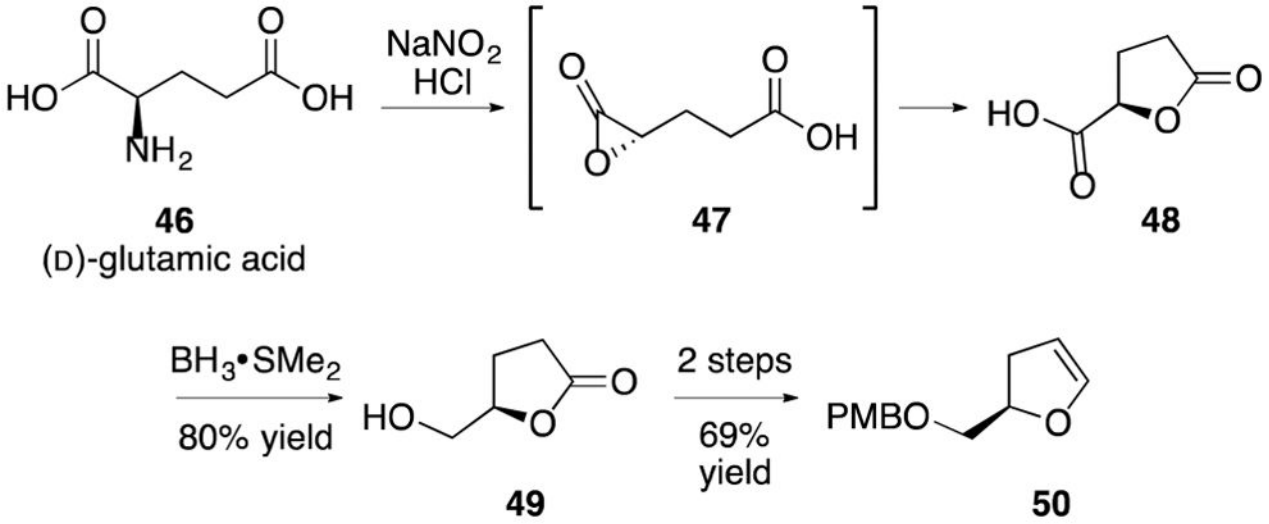
Scheme 4.

Acetonide Formation Reveals 1,3-*anti* Relationship between C9 and C11, While Degradation Determines Absolute Stereochemistry of C11 To Be *R*



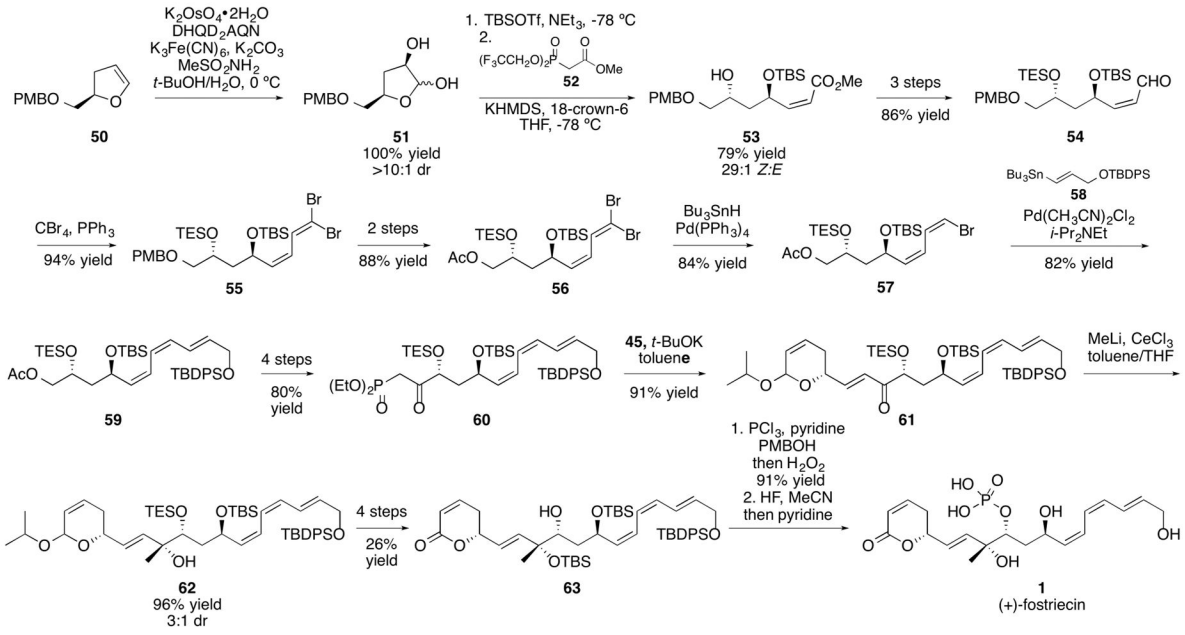
Scheme 5.

Boger's Synthesis of the Lactone Fragment of Fostriecin Sets the C5 Stereocenter with a Sharpless Asymmetric Dihydroxylation



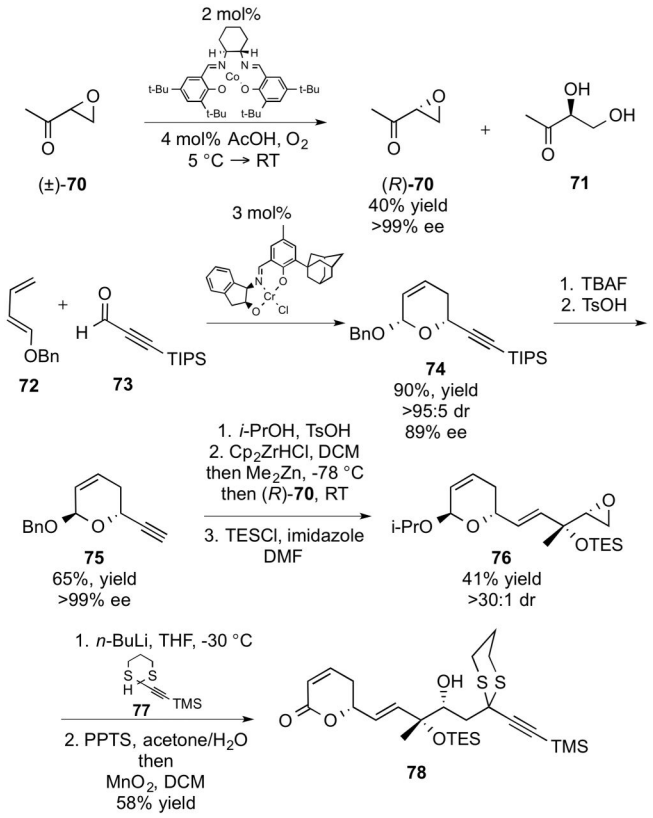
Scheme 6.

Absolute Stereochemistry of the Central Portion Is Set by a Double Inversion, Using a van Slyke Reaction



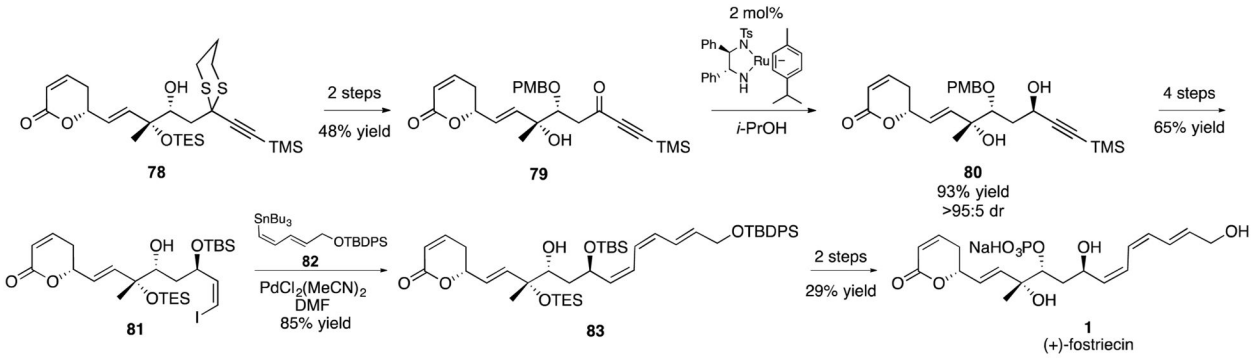
Scheme 7.

Boger's Completion of Fostriecin Features a Stille Cross-Coupling and a Horner–Wadsworth–Emmons Olefination



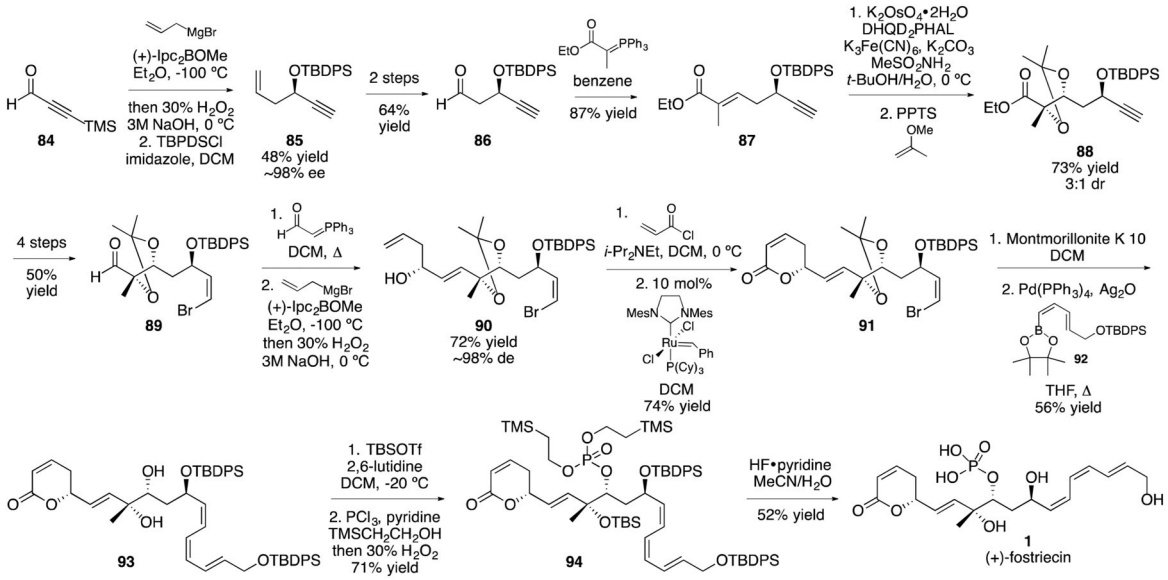
Scheme 8.

Jacobsen's Synthesis of the Core of Fostriecin Features a Hydrolytic Resolution of a Racemic Epoxide Catalyzed by a Cobalt Complex and a Chromium-Catalyzed Hetero-Diels–Alder Reaction



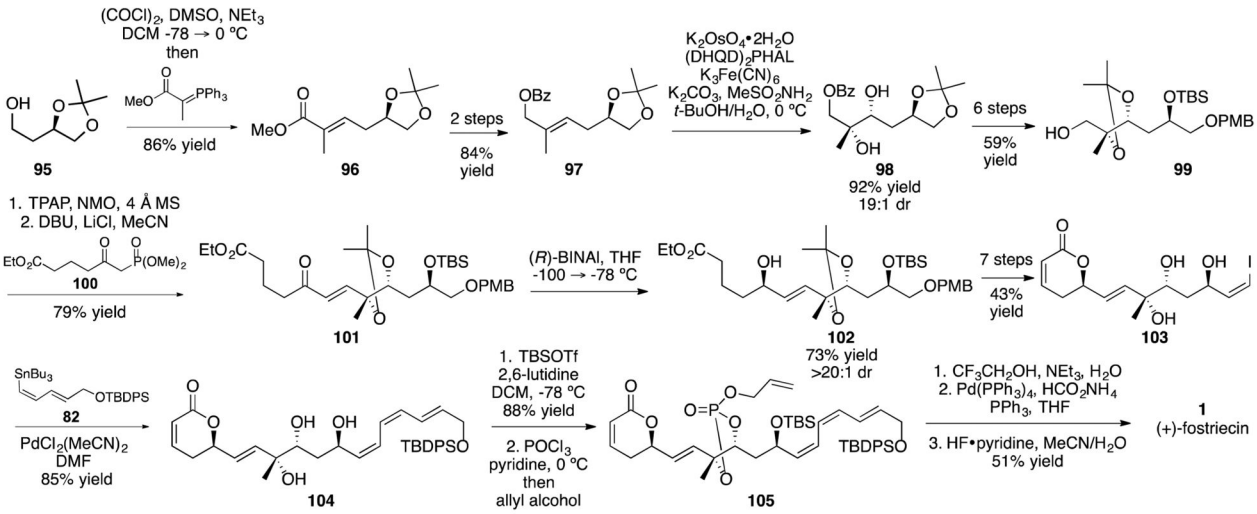
Scheme 9.

Jacobsen's Completion of Fostriecin Utilizes a Noyori Reduction To Set the C11 Stereocenter



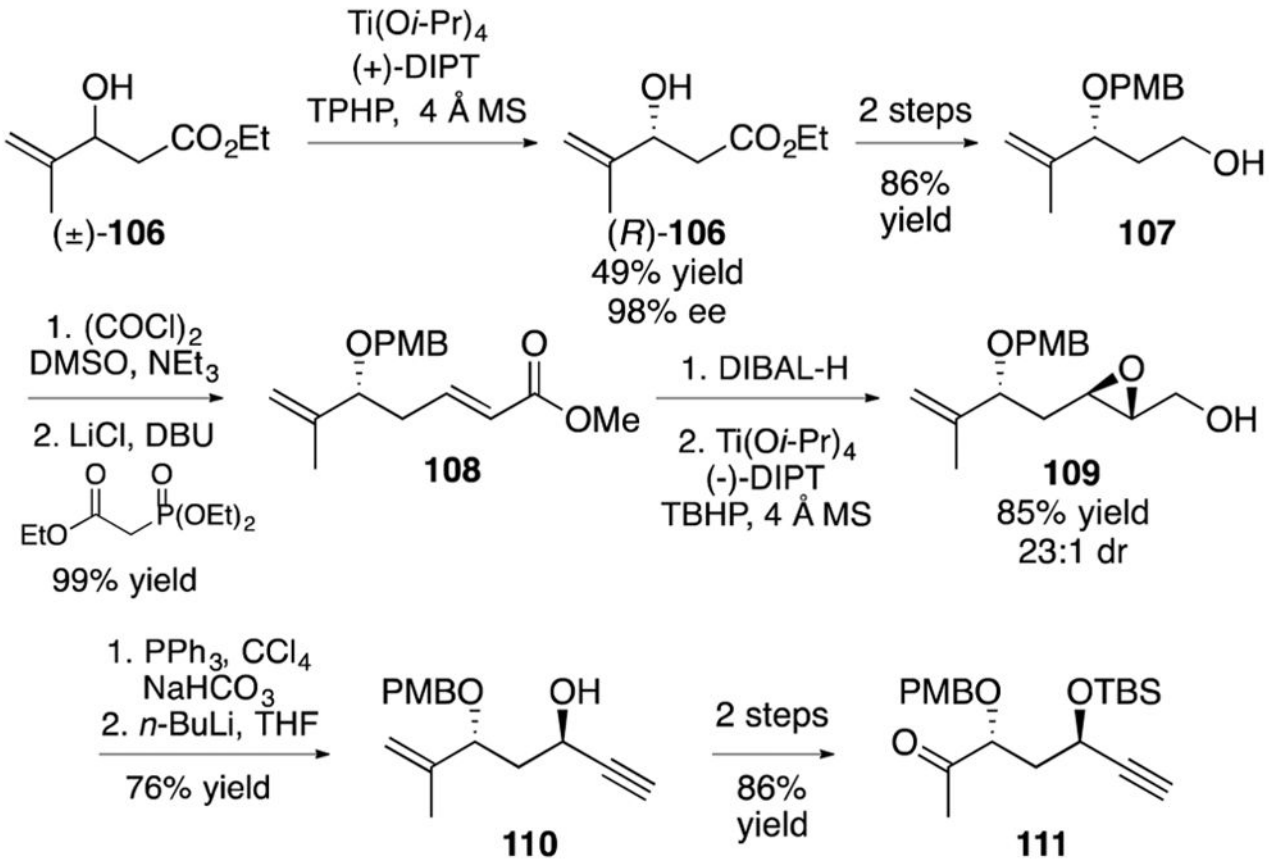
Scheme 10.

Falck's Synthesis Demonstrates the Utility of an Acylation/Metathesis Approach for the Synthesis of the α,β-Unsaturated Lactone of Fostriecin



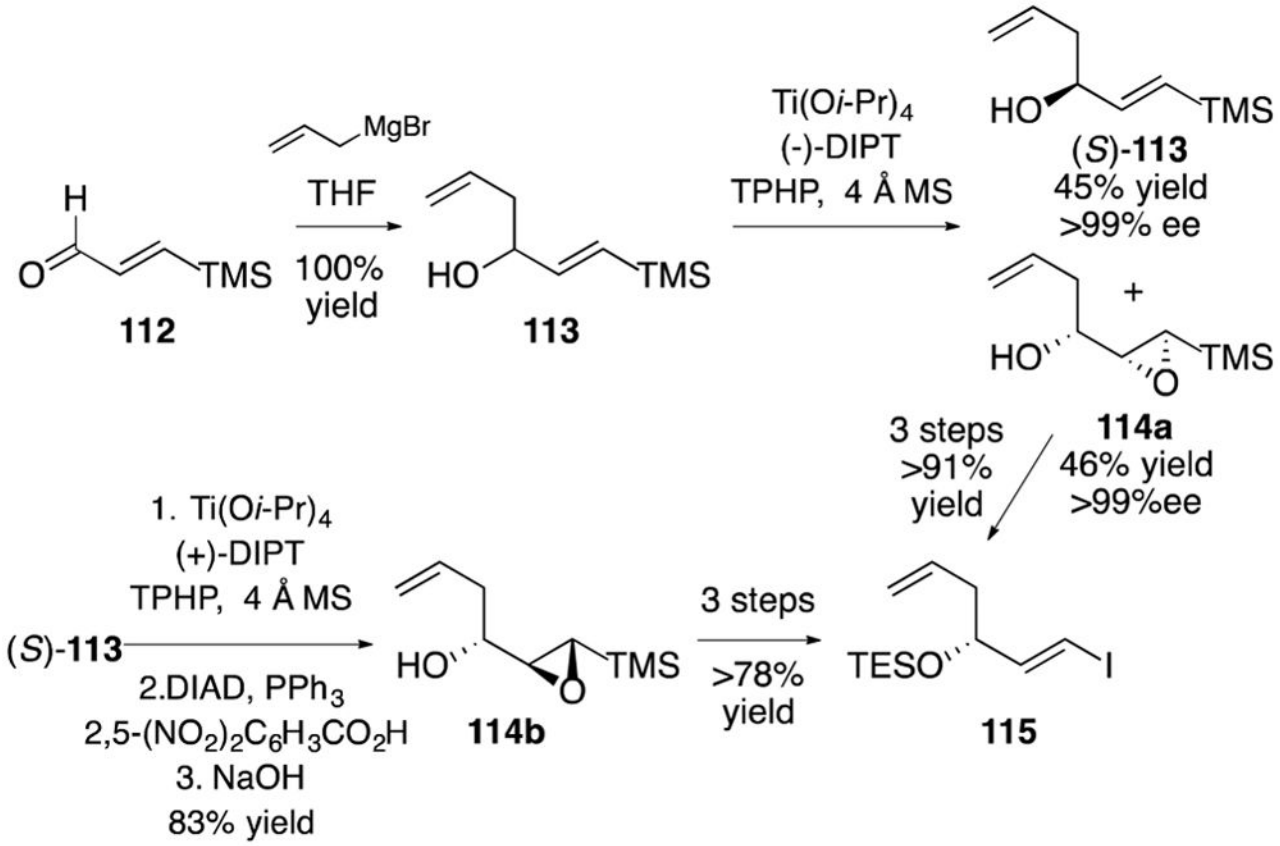
Scheme 11.

Imanishi's Synthesis of Fostriecin Features Installation of the C9 Phosphate via Selective Opening of a Cyclic Phosphate



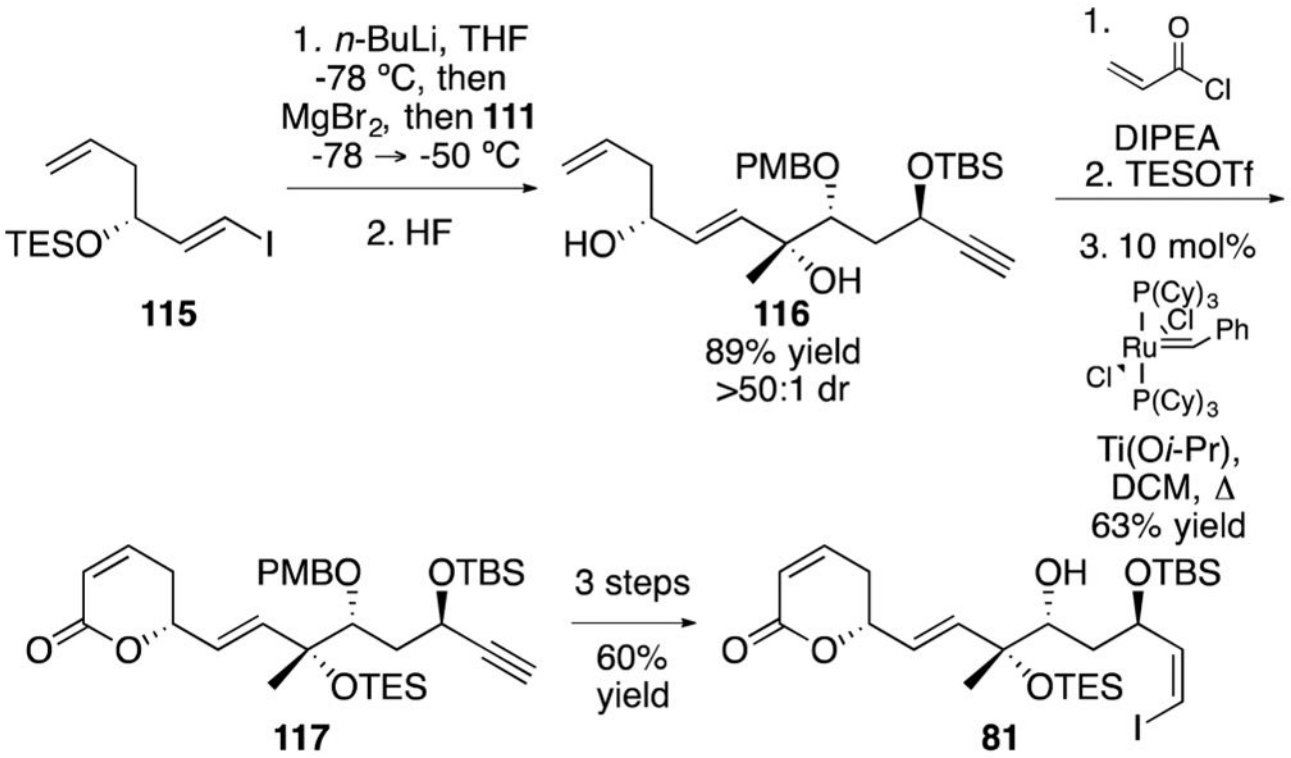
Scheme 12.

Kobayashi's Synthesis of the Central Fragment Features Two Sharpless Asymmetric Epoxidations

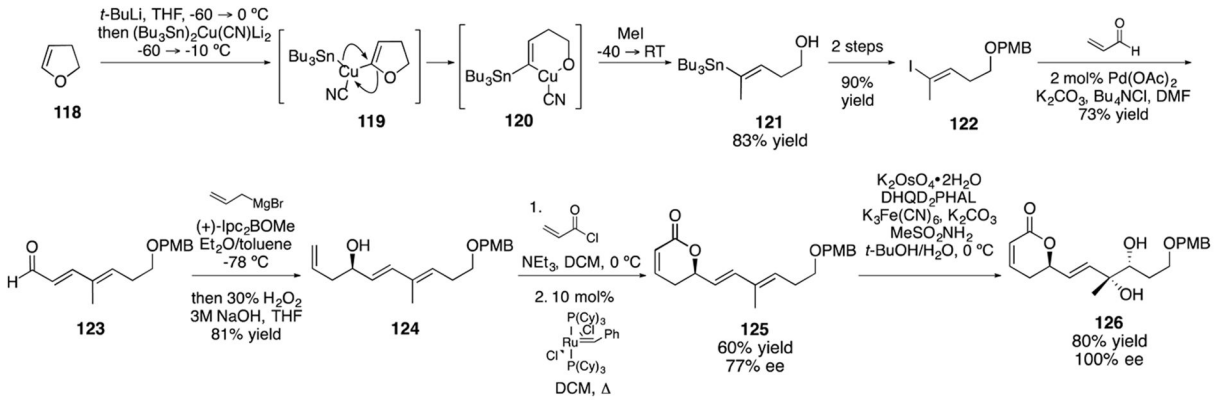


Scheme 13.

Kobayashi's Synthesis of the C3–C7 Fragment Utilizes Both Products of a Kinetic Resolution

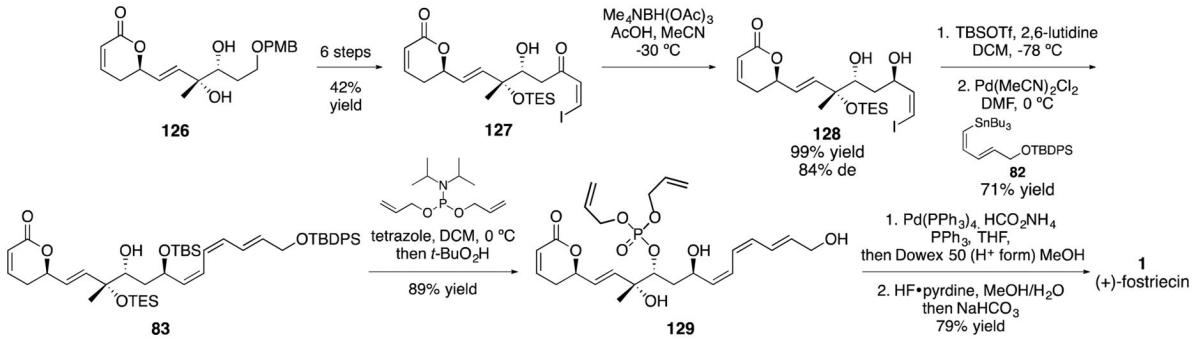


Scheme 14.
Kobayashi Unites the Fragments with a Stereoselective Grignard Addition



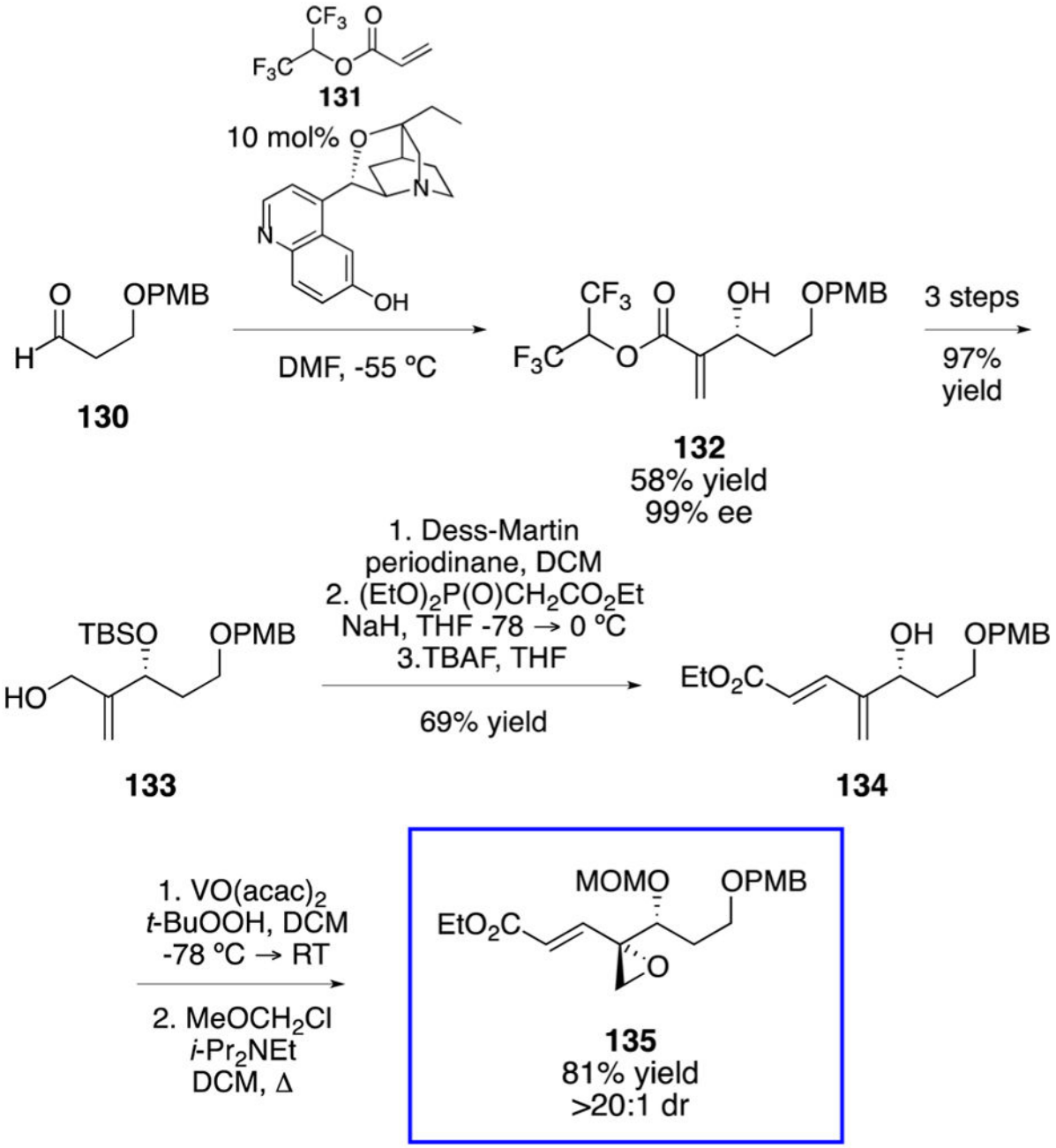
Scheme 15.

Hatakeyama's Synthesis of the Core of Fostriecin Features a Heck Reaction To Elongate the Carbon Chain



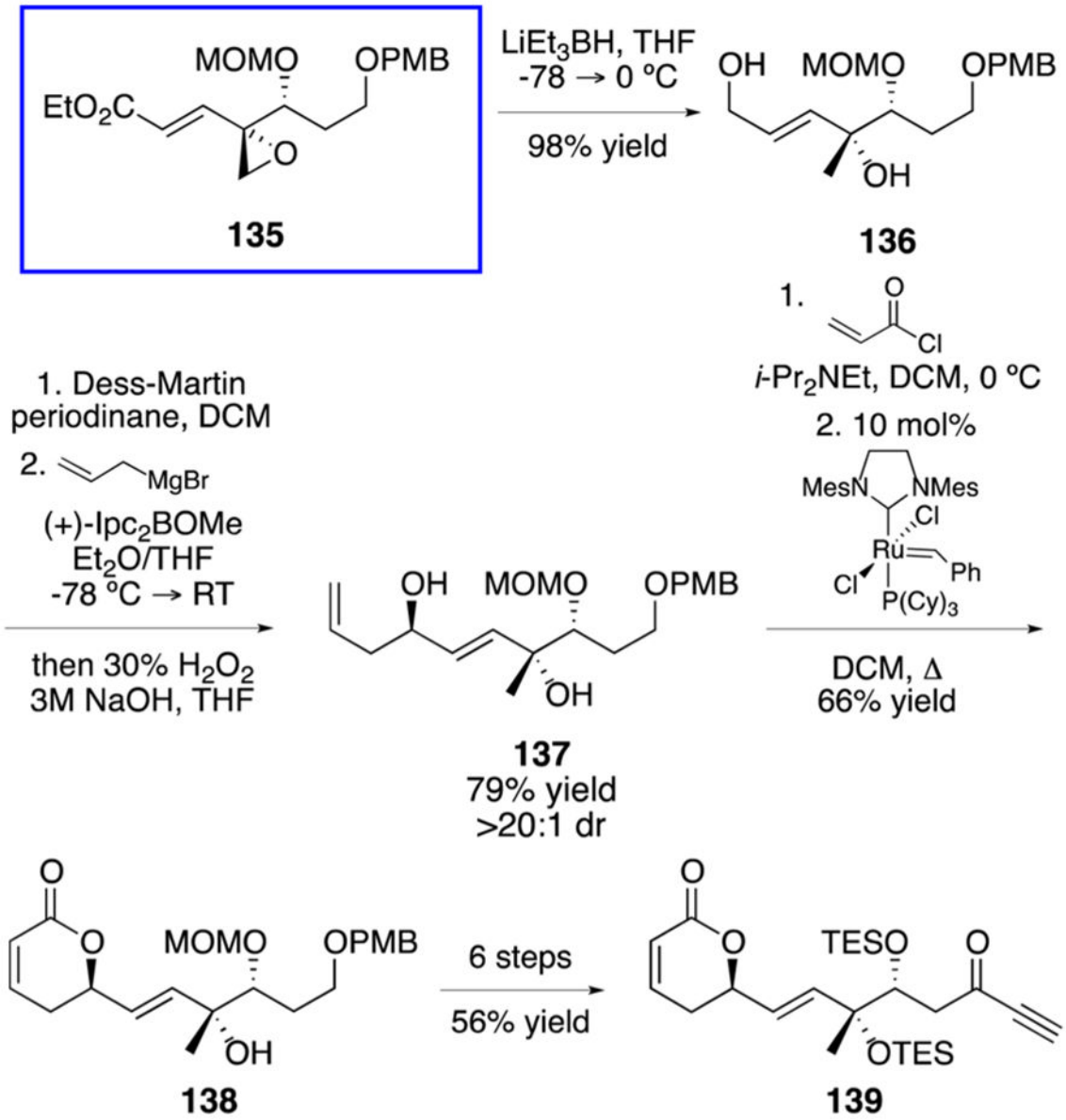
Scheme 16.

Hatakeyama's Completion of Fostriecin Relies on a Diastereoselective Reduction To Set the C11 Stereocenter



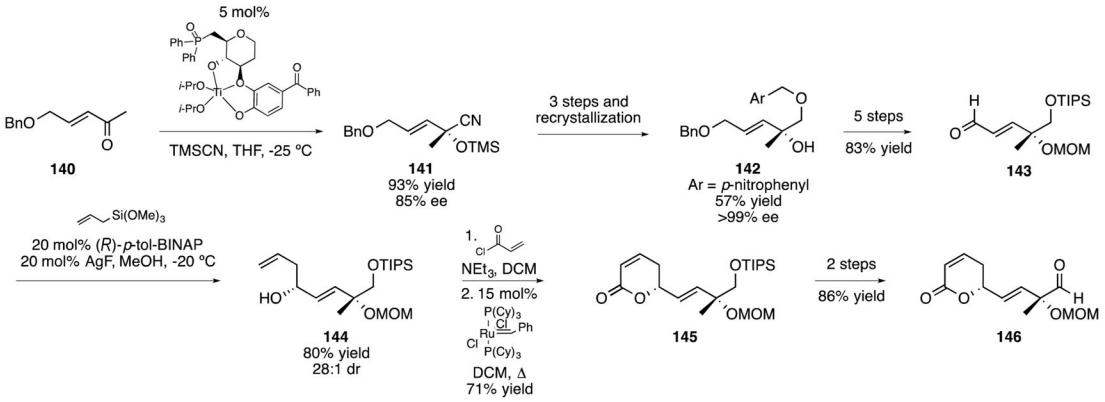
Scheme 17.

Hatakeyama's Second Strategy Pursues the Synthesis of a Key Epoxide Intermediate Allowing Access to Both Fostriecin and the Phoslactomycins



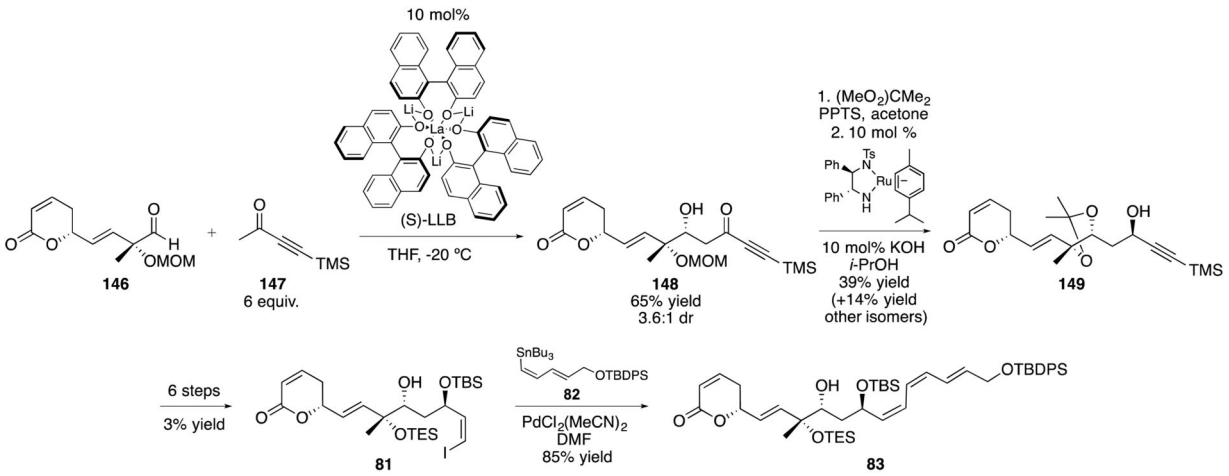
Scheme 18.

Hatakeyama Reductively Opens the Key Epoxide Intermediate and Intercepts His Previous Route to Fostriecin



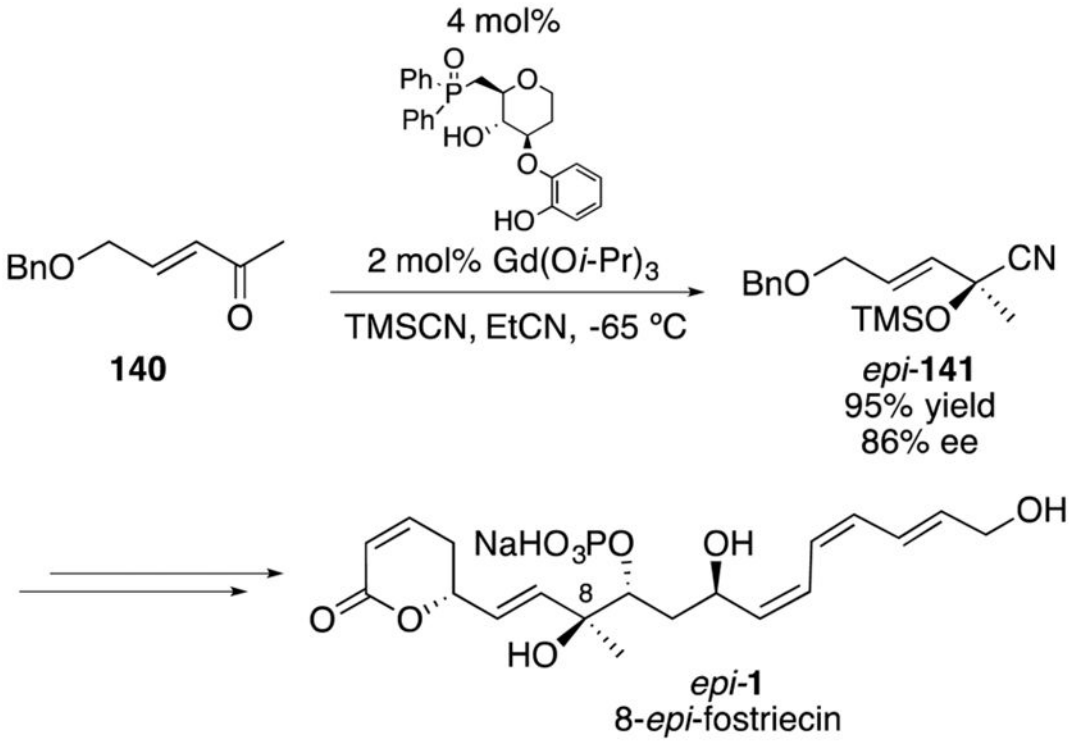
Scheme 19.

Shibasaki's Synthesis of the C1–C9 Portion of Fostriecin Featuring an Enantioselective Cyanosilylation Reaction

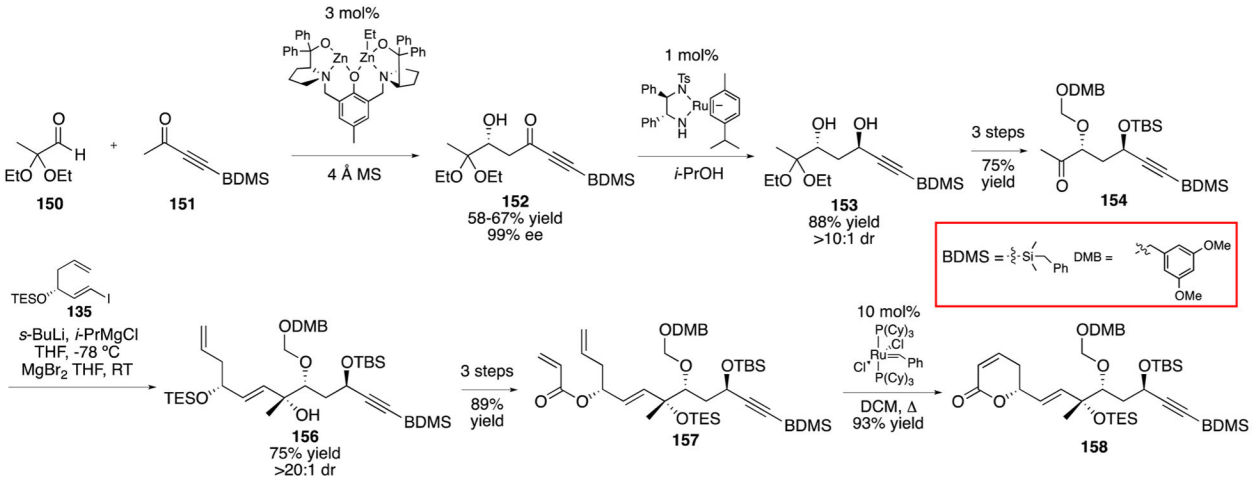


Scheme 20.

Shibasaki's Completion of a Formal Synthesis of Fostriecin Featuring a Key Lanthanum-Catalyzed Enantioselective Direct Catalytic Aldol Reaction

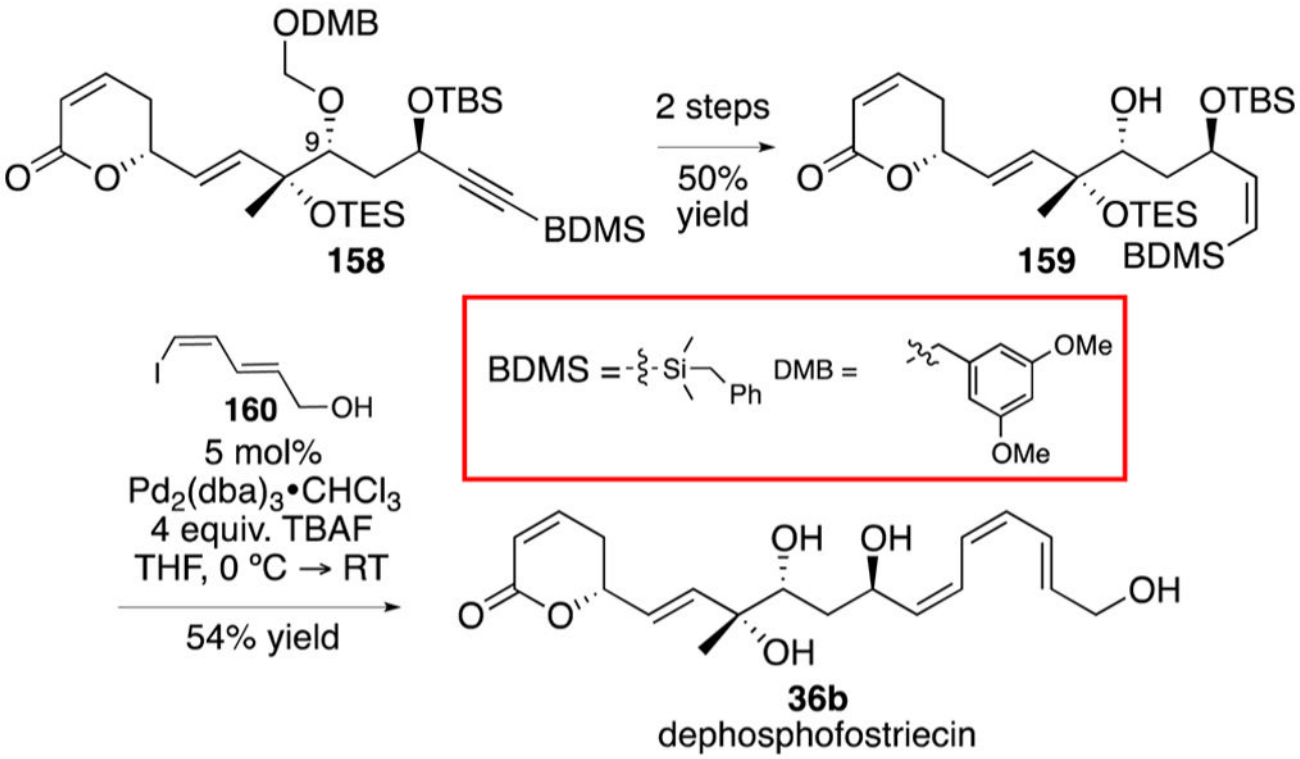


Scheme 21.
Shibasaki's Key Cyanosilylation Leading to the Synthesis of 8-*epi*-Fostriecin



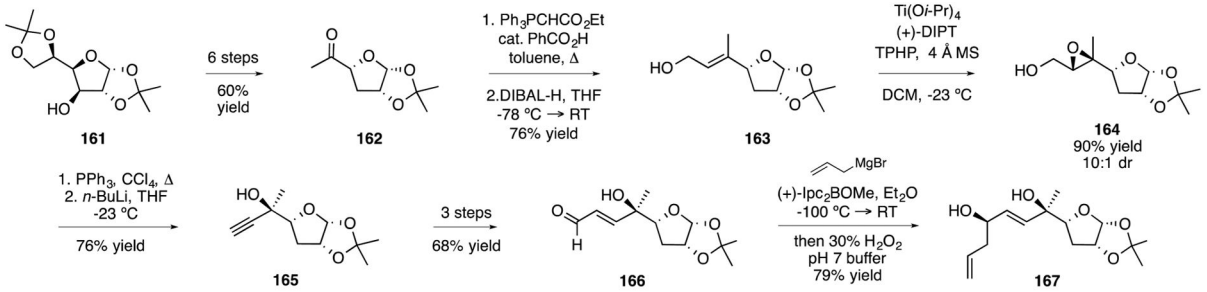
Scheme 22.

Trost's Synthesis of the Core of Fostriecin Featuring a Catalytic Enantioselective Direct Aldol Reaction



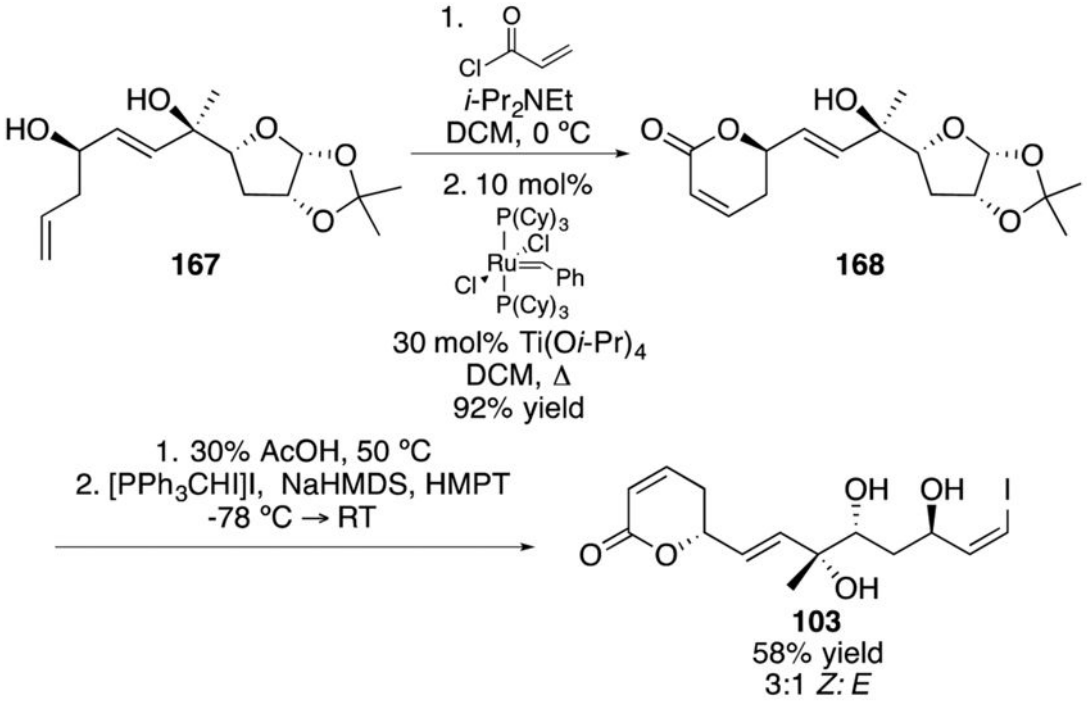
Scheme 23.

Trost's Completion of Dephosphofostriecin Highlights the Utility of Silicon Cross-Coupling Reactions

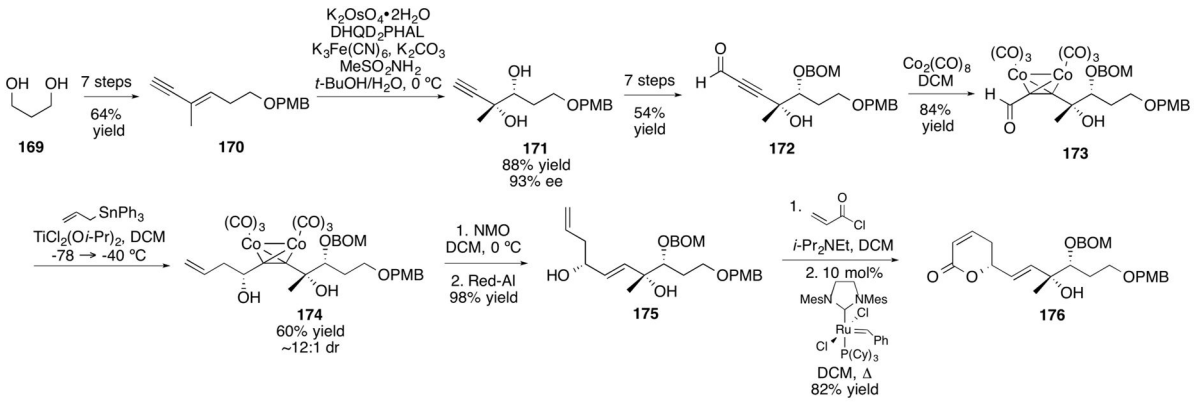


Scheme 24.

Yadav's Chiral Pool Approach to the Synthesis of the Core of Fostriecin

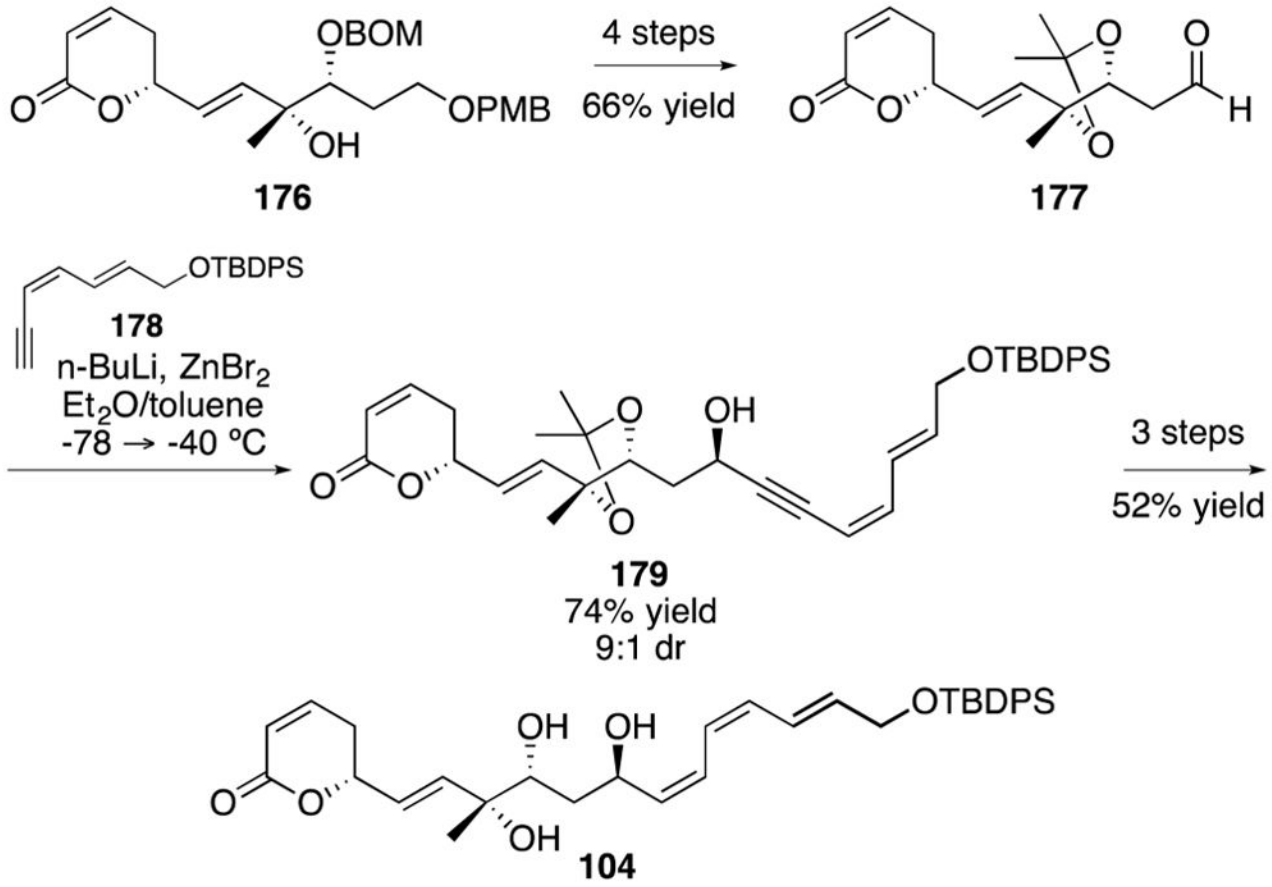


Scheme 25.
Yadav's Completion of a Formal Synthesis of Fostriecin



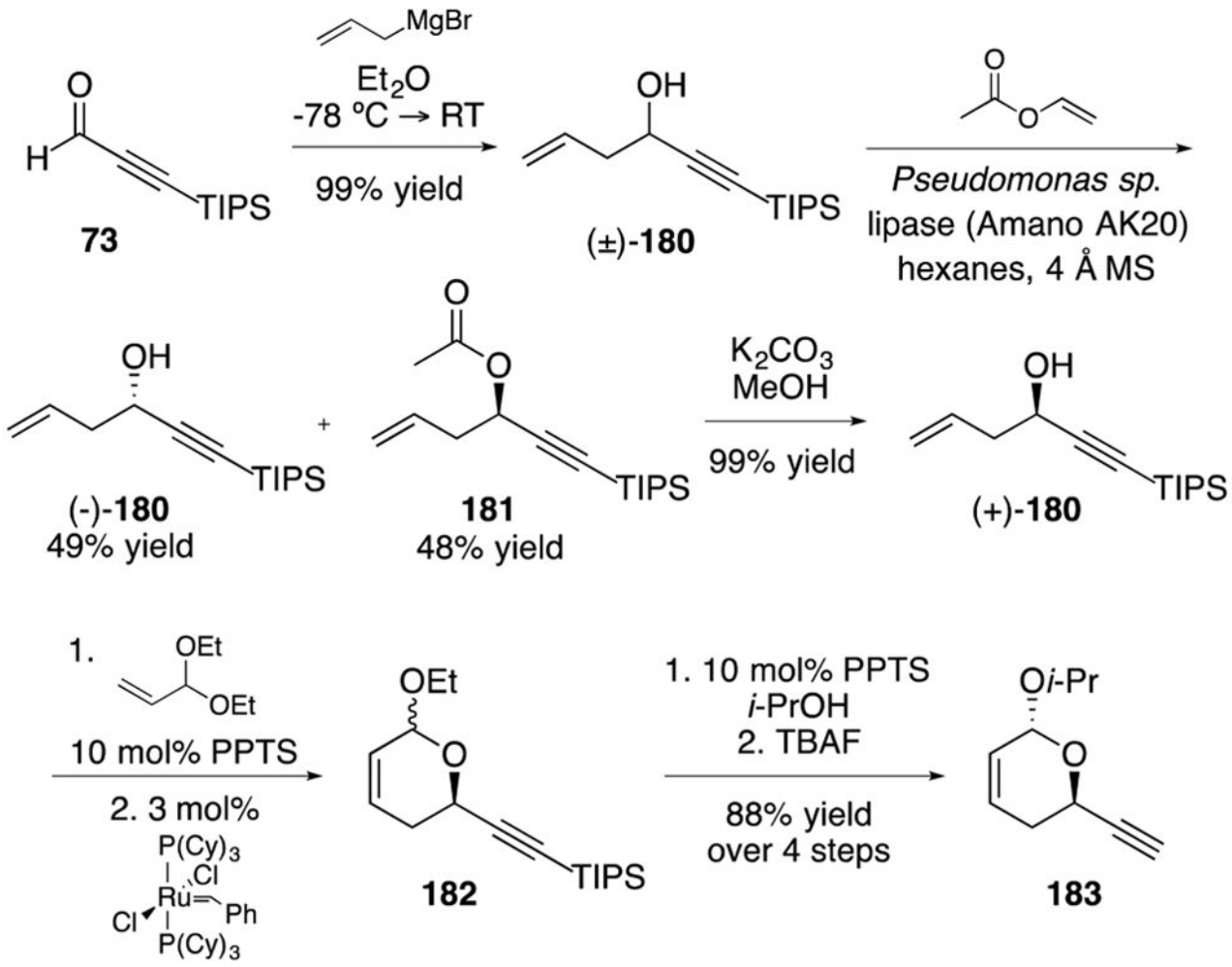
Scheme 26.

Hayashi's Synthesis of the Core of Fostriecin Featuring a Biscobalthexacarbonyl Complex for Stereochemical Induction

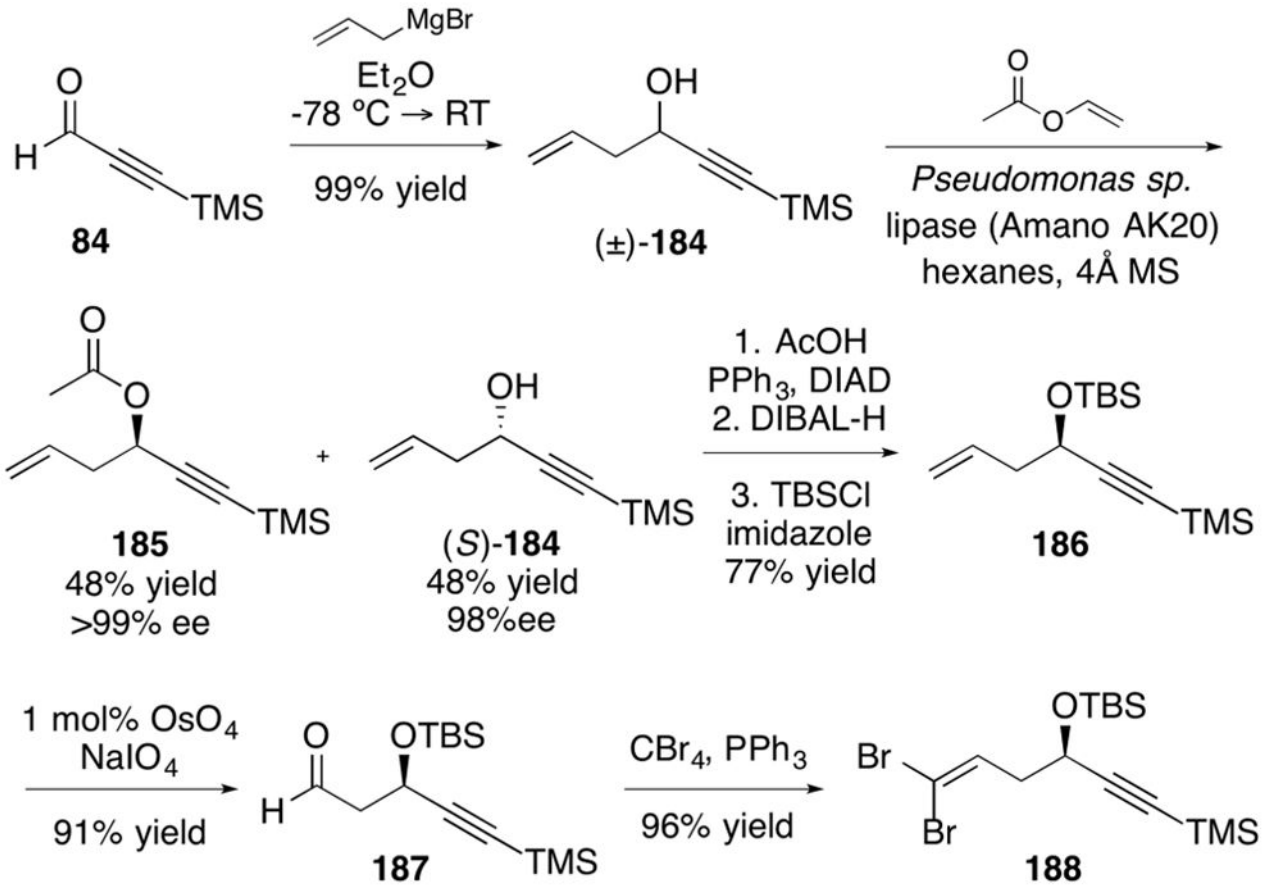


Scheme 27.

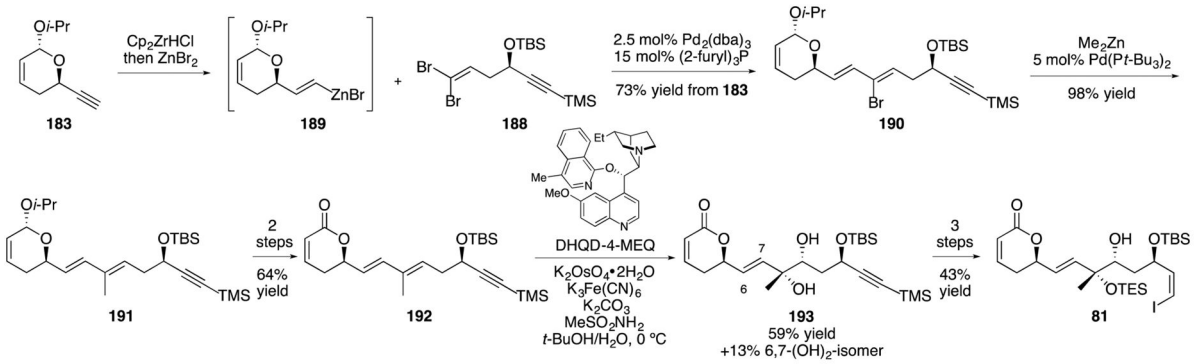
Hayashi's Completion of a Formal Synthesis of Fostriecin Features a Diastereoselective Alkynylzinc Addition into a β-Alkoxy Ketone



Scheme 28.
McDonald's Enzymatic Resolution Strategy Sets the C5 Stereocenter

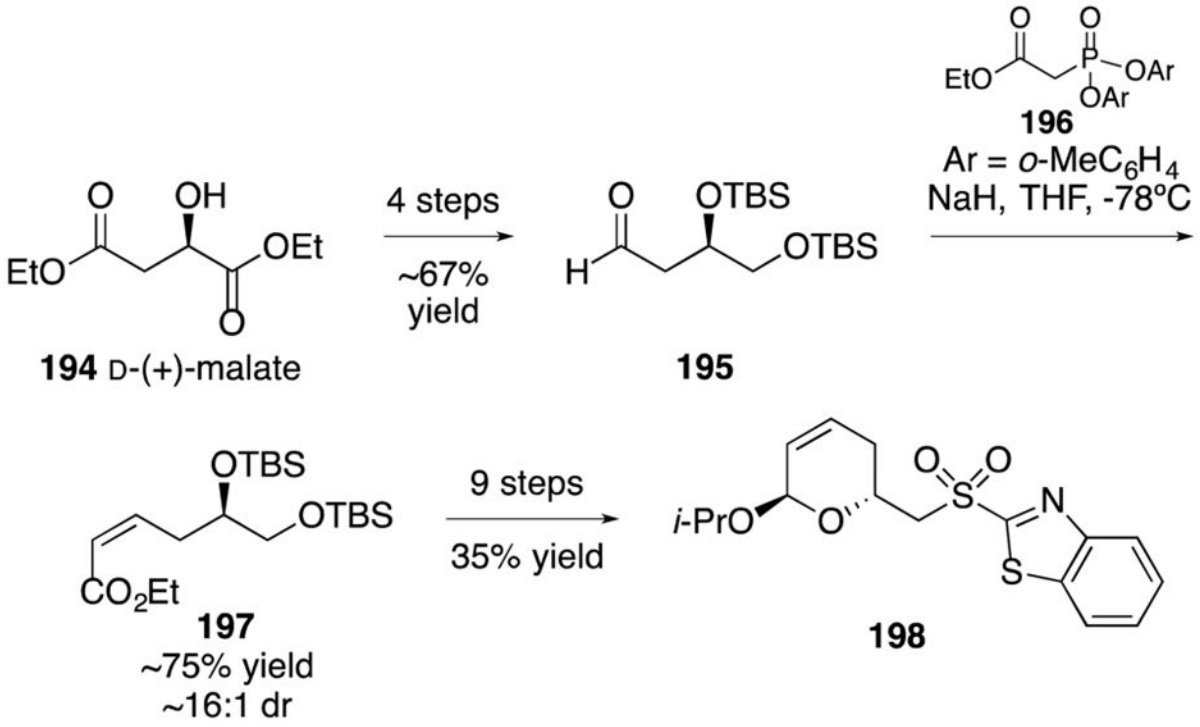


Scheme 29.
Core of Fostriecin Is Synthesized via Enzymatic Resolution

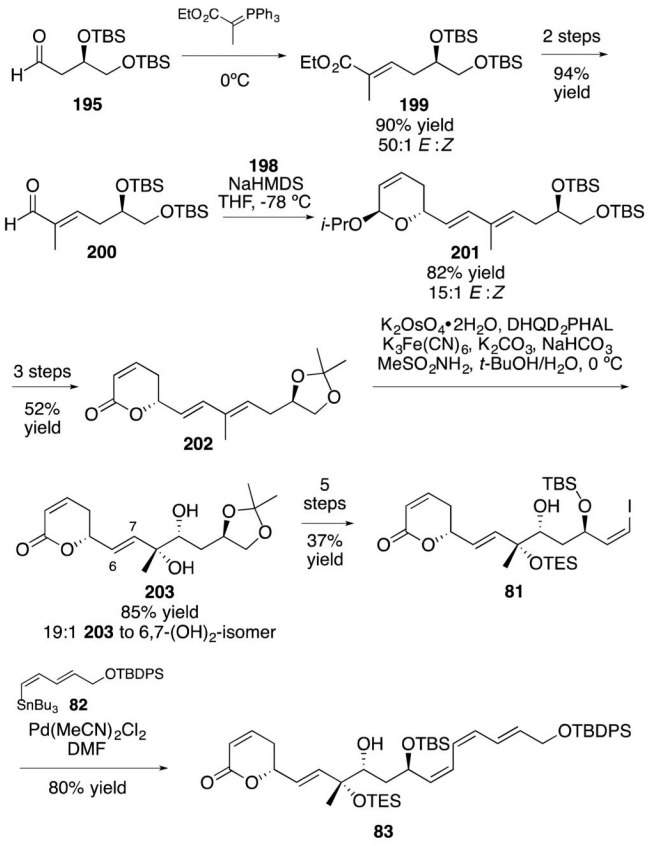


Scheme 30.

McDonald Completes a Convergent Formal Synthesis of Fostriecin by Carrying Out Successive Cross-Couplings To Unite the Three Fragments

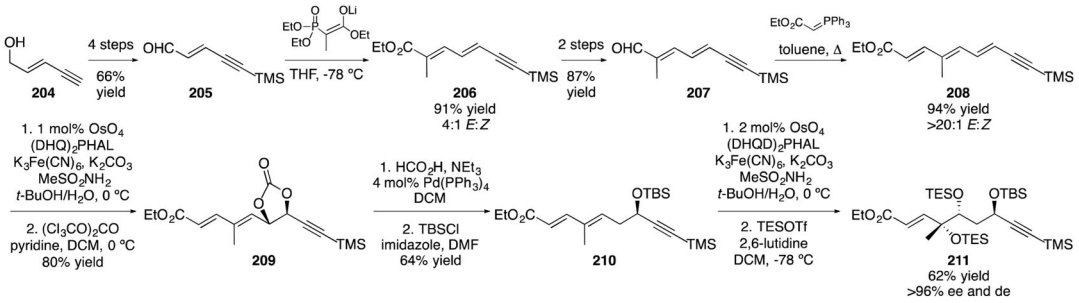


Scheme 31.
Zhang's Chiral Pool Synthesis of a Julia Reagent for the Key Coupling Step



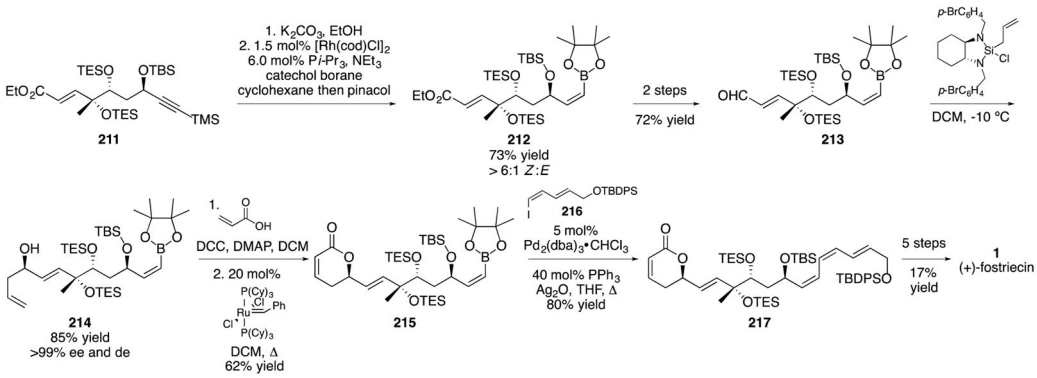
Scheme 32.

Zhang Completes a Formal Synthesis of Fostriecin Using the Same Intermediate Aldehyde As Was Used for Construction of the Julia Coupling Reagent



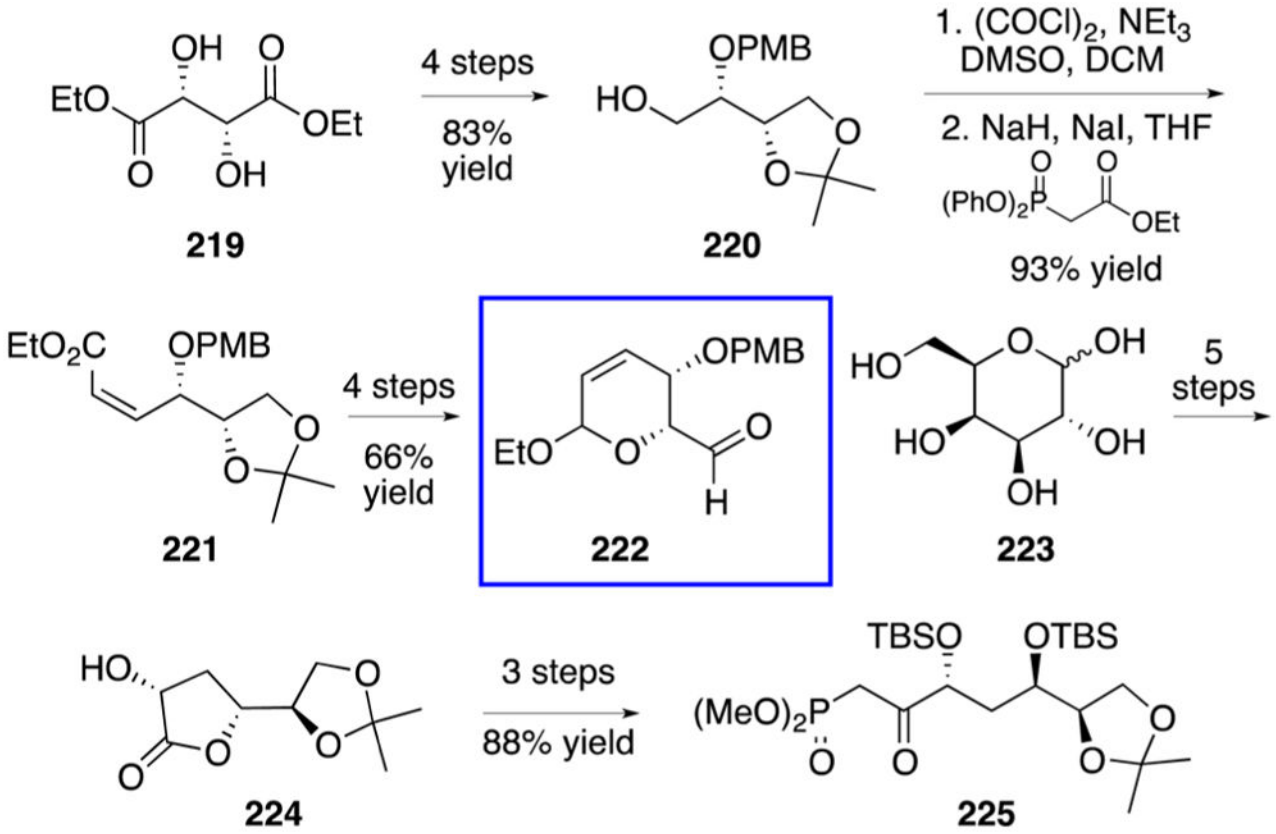
Scheme 33.

O'Doherty's Synthesis of the Core of Fostriecin Features Horner–Wadsworth–Emmons Olefinations and Selective Sharpless Asymmetric Dihydroxylations

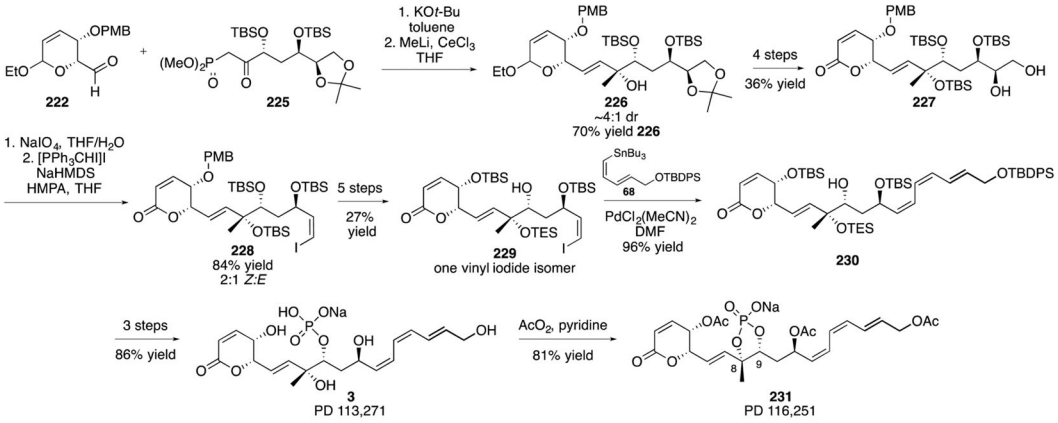


Scheme 34.

O'Doherty's Completion of Fostriecin Features a Leighton Allylation and an Unusually Robust Vinyl Boronate

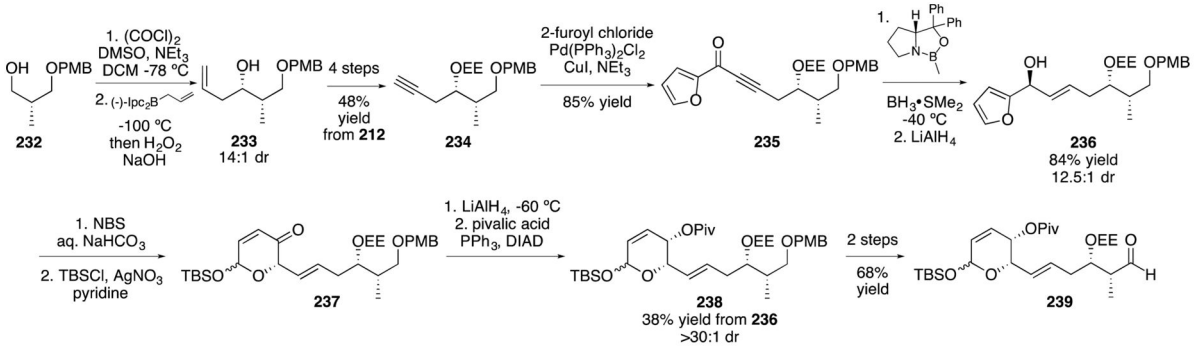


Scheme 35.
Sugawara's Chiral Pool Syntheses of the Olefination Reagents



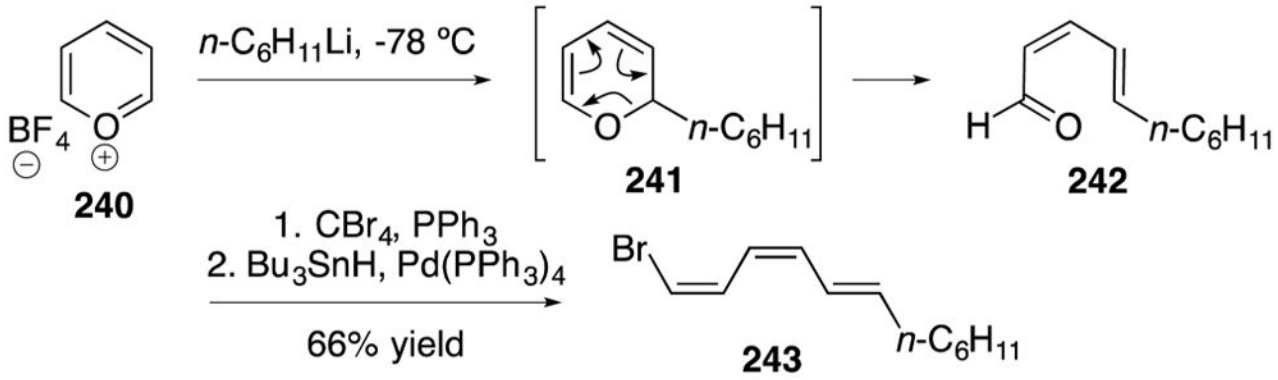
Scheme 36.

Sugawara's Horner–Wadsworth–Emmons Strategy Creates the Core That Is Elaborated to PD 113,271 and PD 116,251



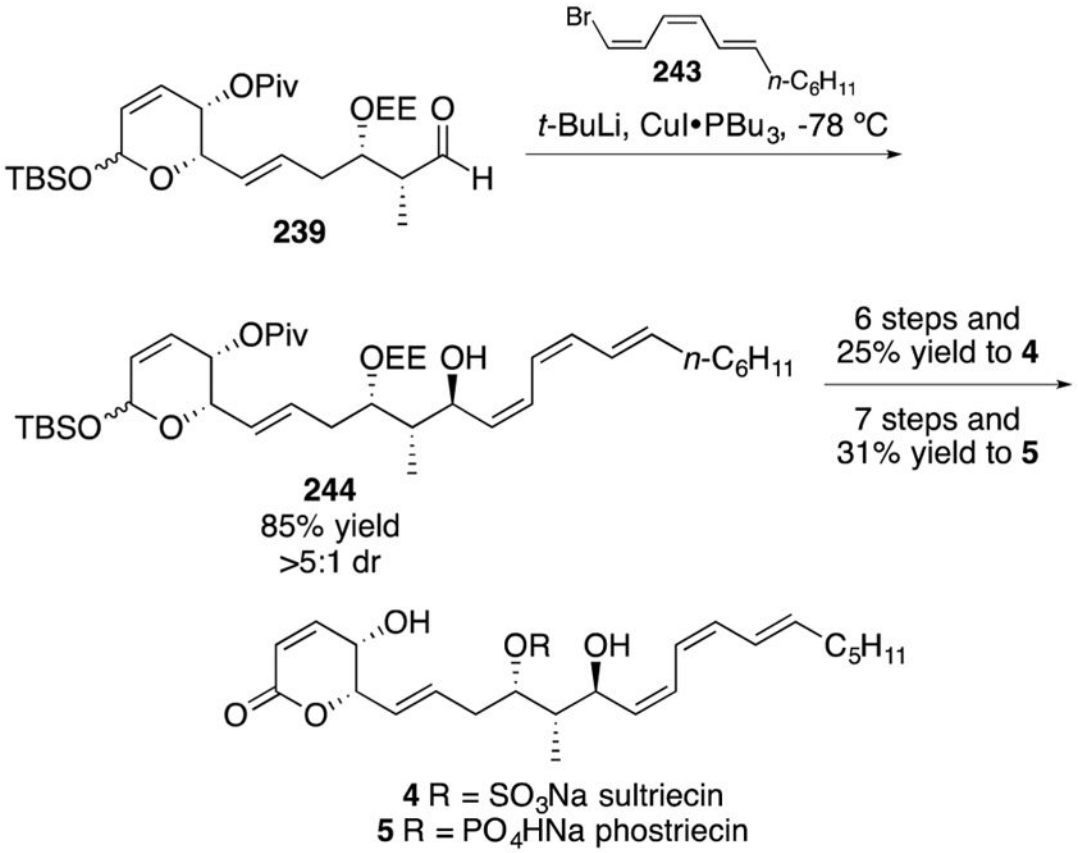
Scheme 37.

Boger's Synthesis of Sultriecin Features a Bromonium-Initiated Ring-Opening To Create the Lactone Portion of the Molecule



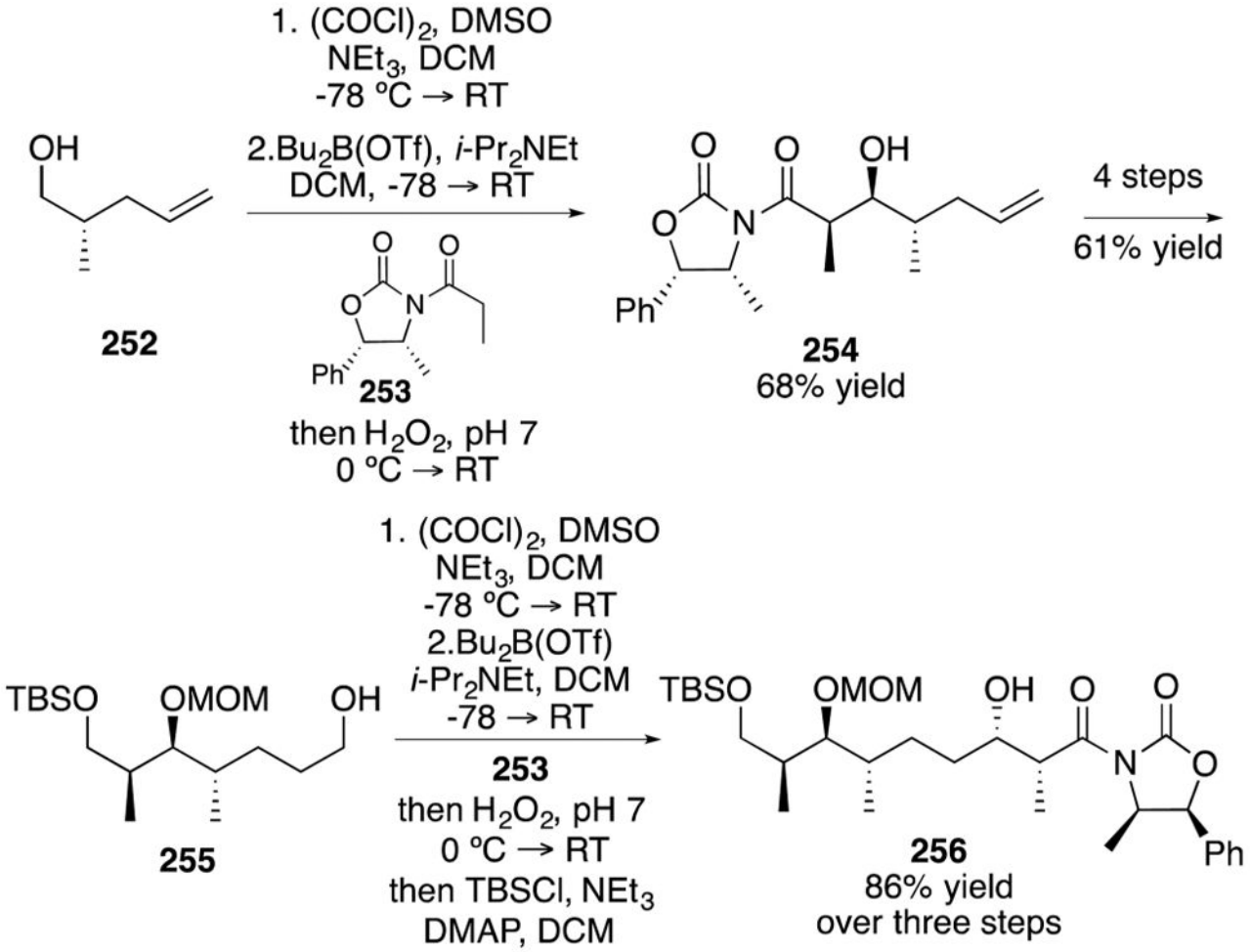
Scheme 38.

Organolithium Addition into a Pyrylium Ion, Followed by Electrocyclic Ring-Opening Sets the Olefin Geometry for the Unsaturated Tail of Sultriecin

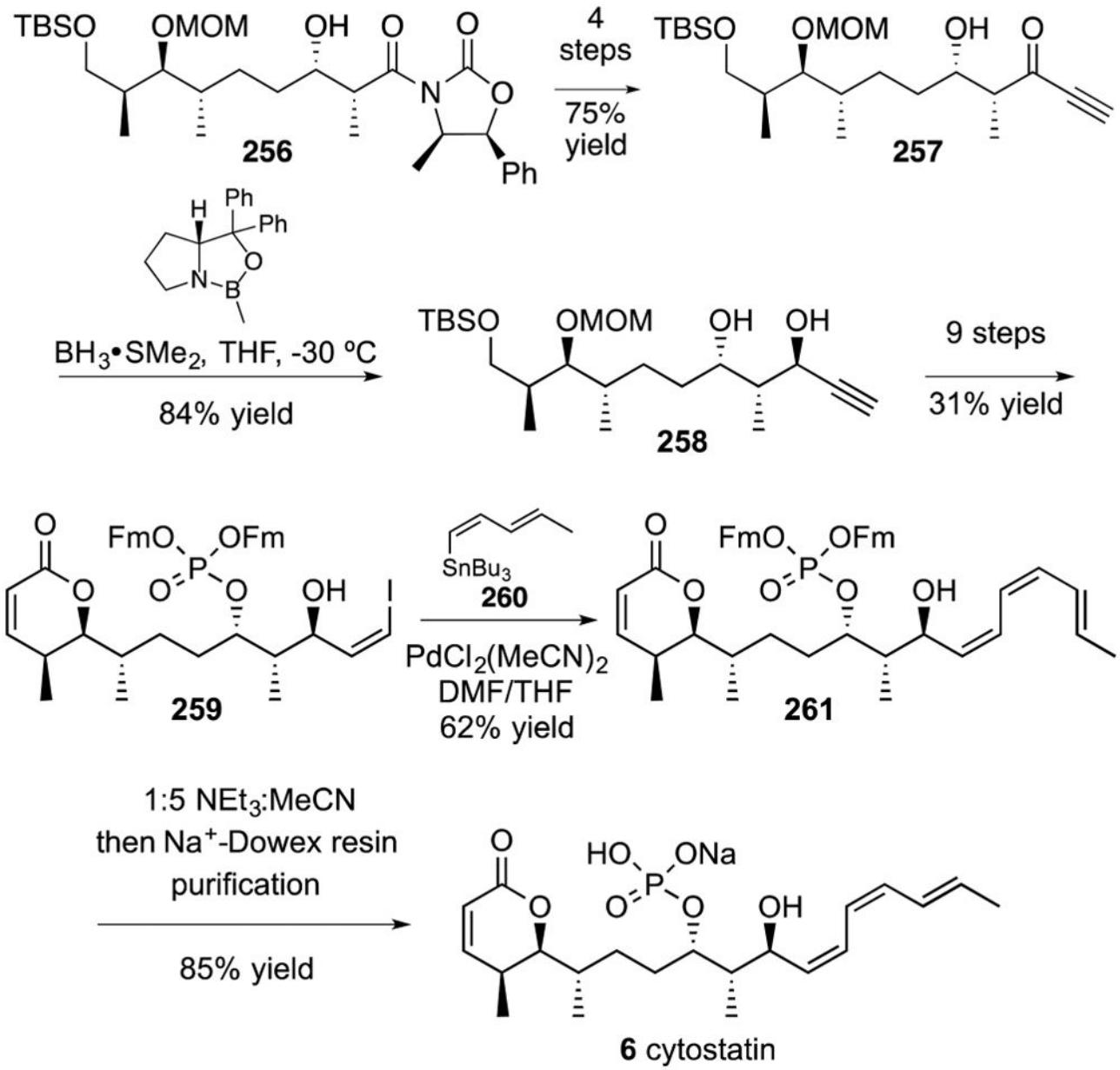


Scheme 39.

A Copper-Mediated Diastereoselective Aldehyde Addition Completes the Carbon Framework for the Synthesis of Sultriecin and Phostriecin

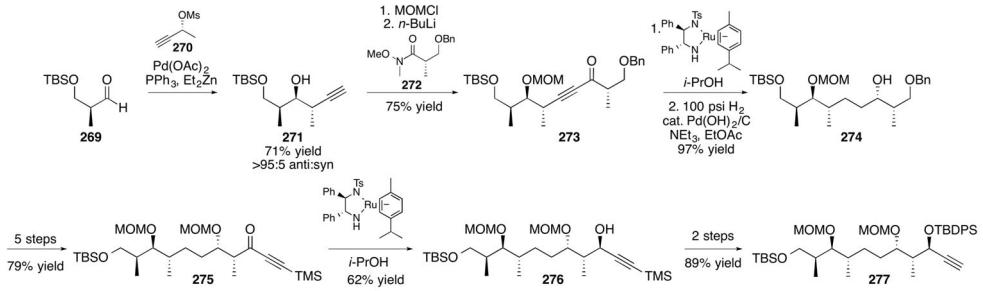


Scheme 40.
Waldmann Uses a Chiral Auxiliary Approach for the Synthesis of the Core of Cytostatin



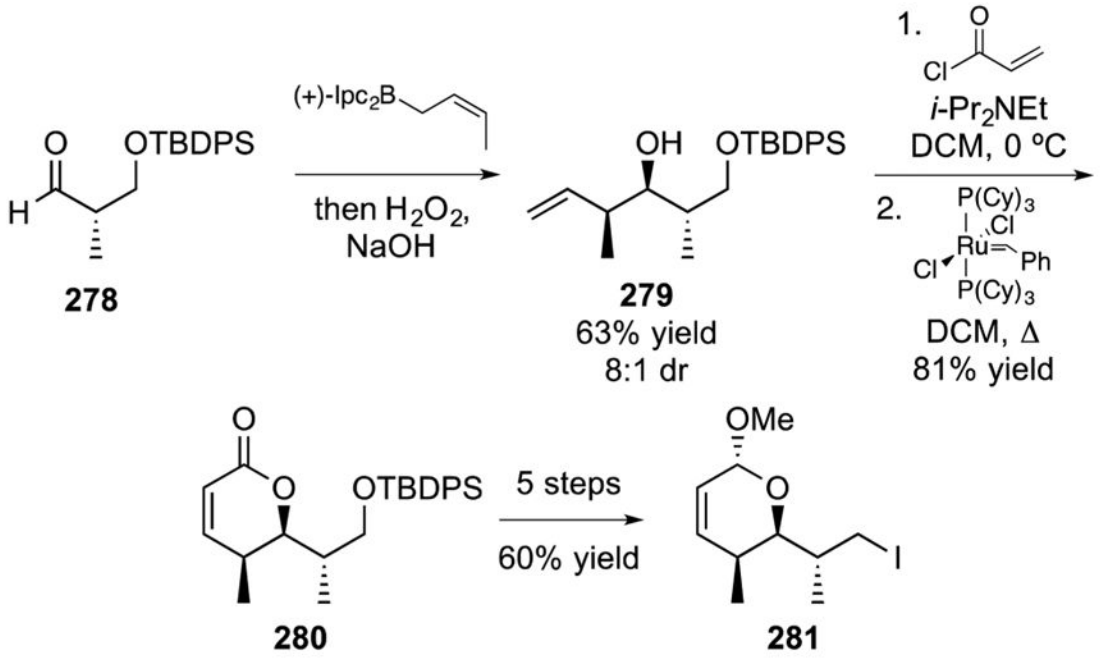
Scheme 41.

Waldmann Completes the Synthesis of Cytostatin Using a CBS Reduction To Set the C11 Stereocenter



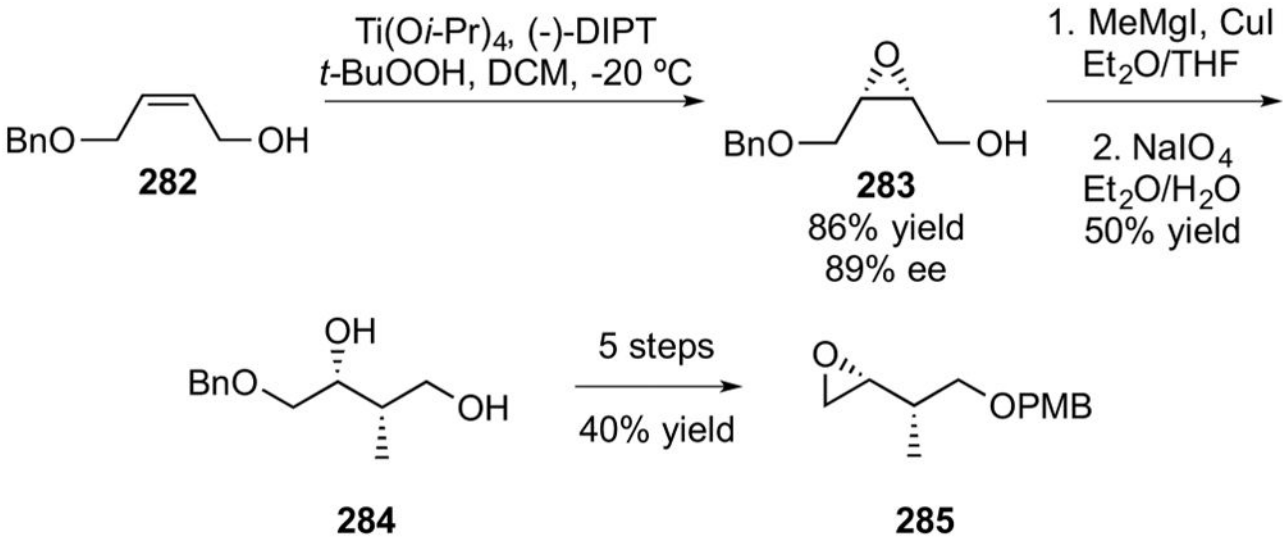
Scheme 42.

Marshall's Synthesis of the Core of Cytostatin Features a Diastereoselective Propargylation



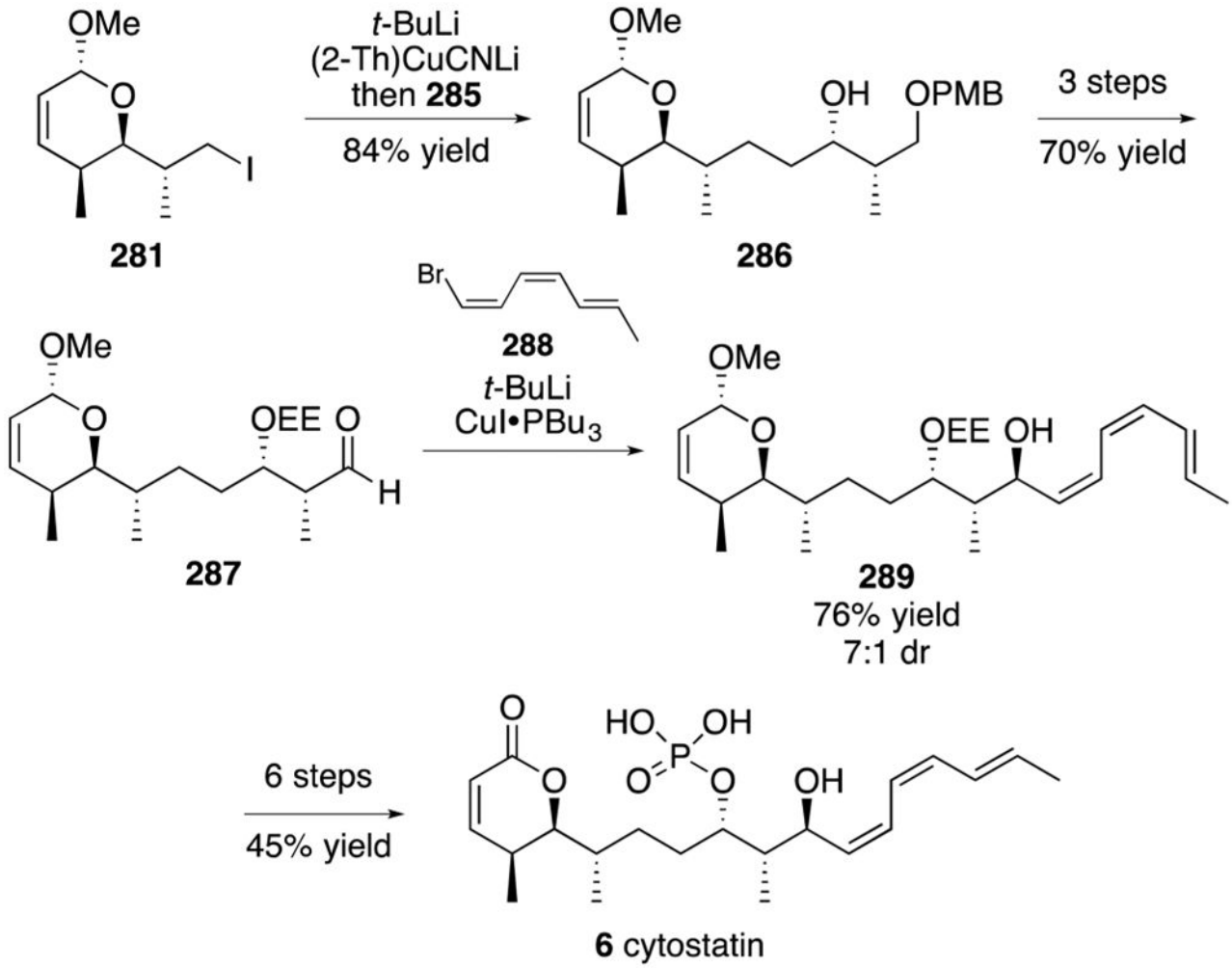
Scheme 43.

Boger Utilizes a Brown Crotylation To Control the Diastereoselectivity of the C4 and C5 Stereocenters of Cytostatin

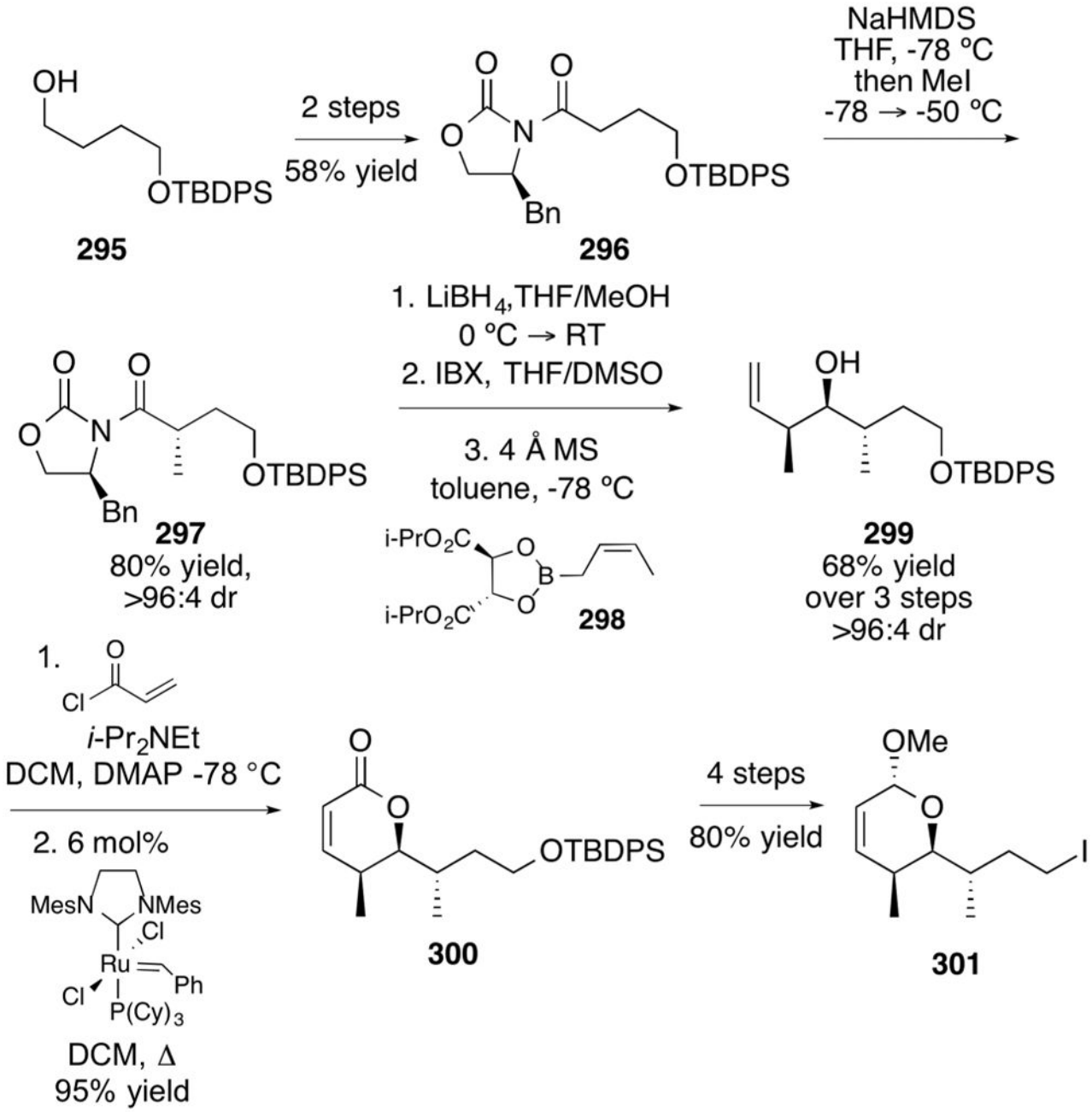


Scheme 44.

Core of Cytostatin Is Constructed by Opening an Epoxide Generated Using a Sharpless Asymmetric Epoxidation

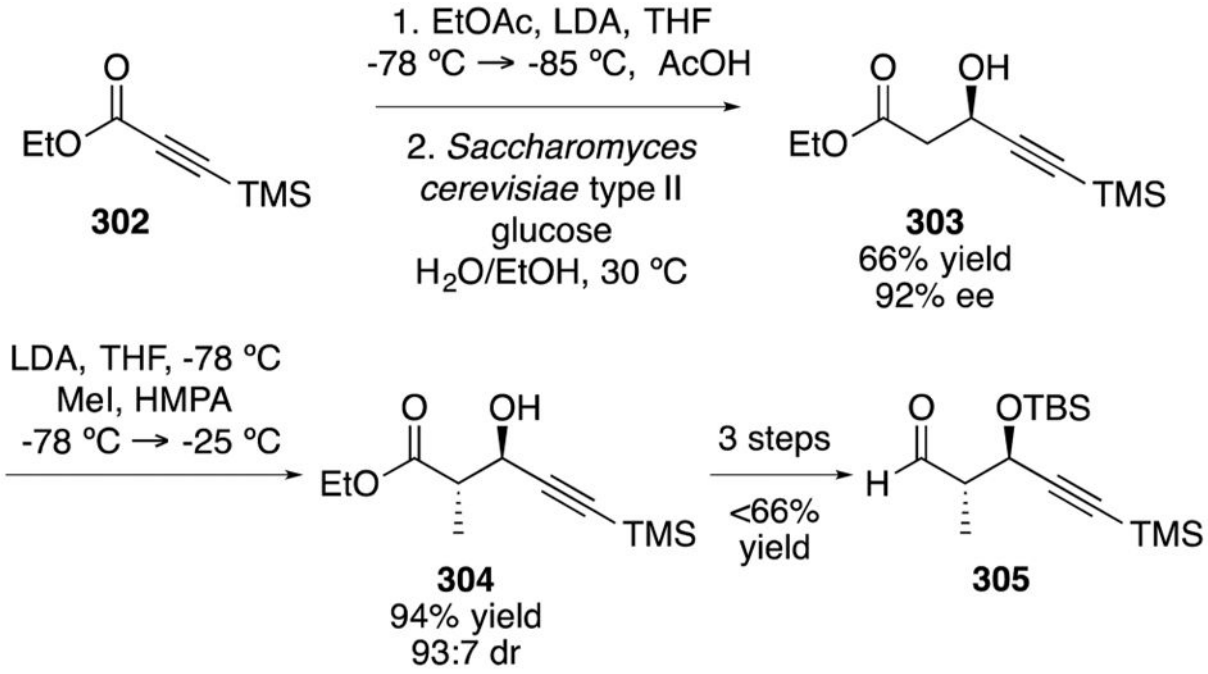


Scheme 45.
Cytostatin Is Completed Using Two Copper-Mediated Addition Reactions



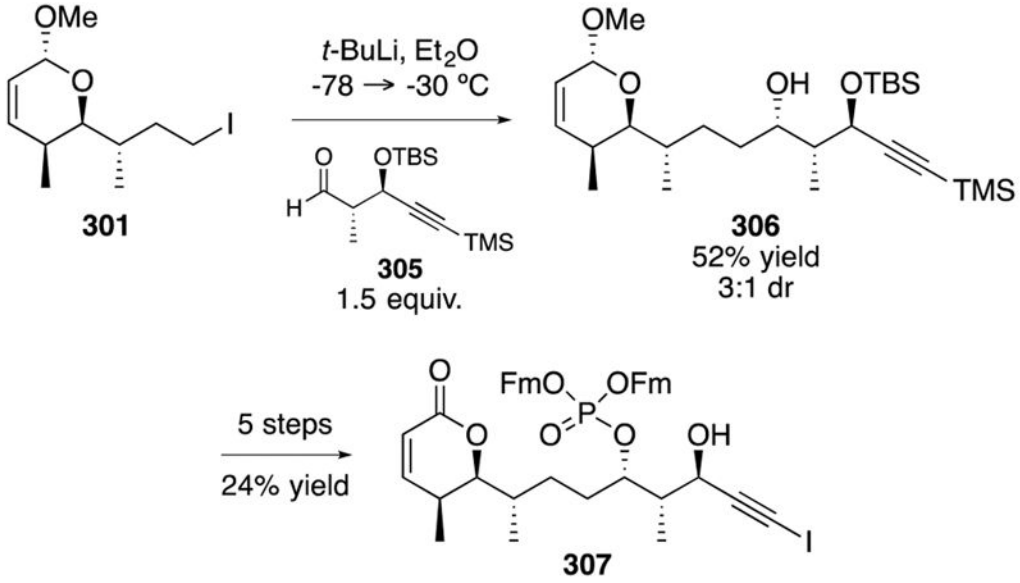
Scheme 46.

Cossy's Construction of the Lactone Portion of Cytostatin Relies on the Use of Evans Chiral Auxiliary Methodology



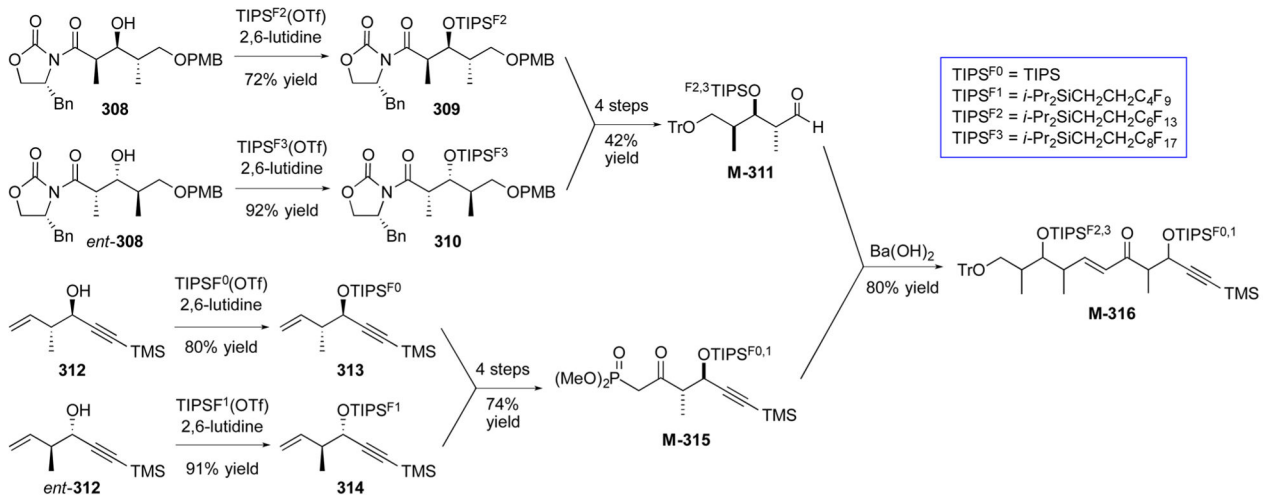
Scheme 47.

Central Portion of Cytostatin Is Constructed Using an Enzymatic Reduction To Set the Absolute Configuration



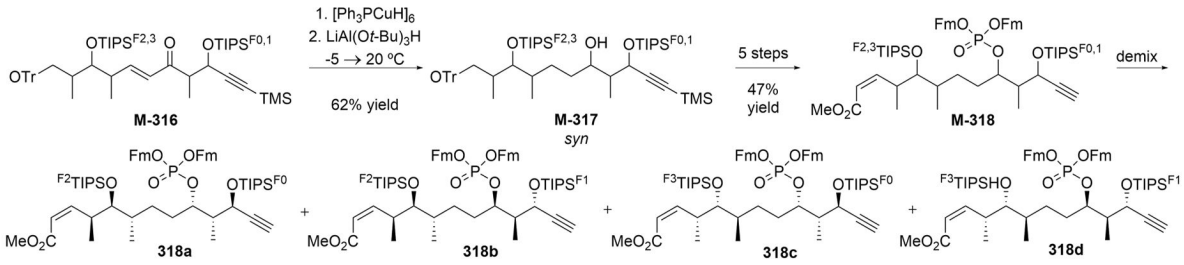
Scheme 48.

Cossy Completes a Formal Synthesis of Cytostatin Using an Alkynyl Lithium Addition into an Aldehyde To Unite the Fragments



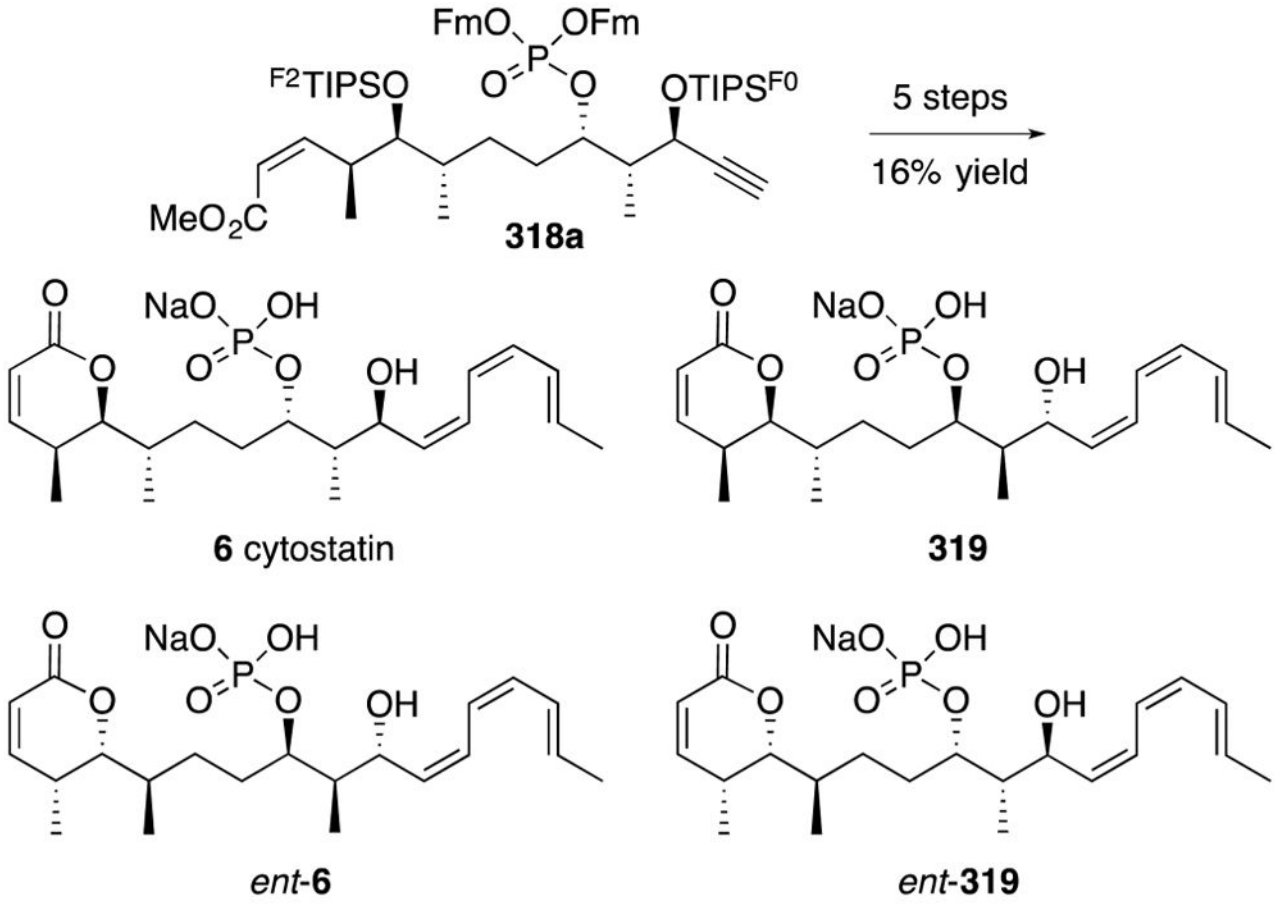
Scheme 49.

Curran Creates a Mixture of Four Possible Stereochemical Possibilities for the Structure of Cytostatin and Tags Them with Fluorous Labels in Order To Aid in the Stereochemical Determination of Cytostatin's Structure

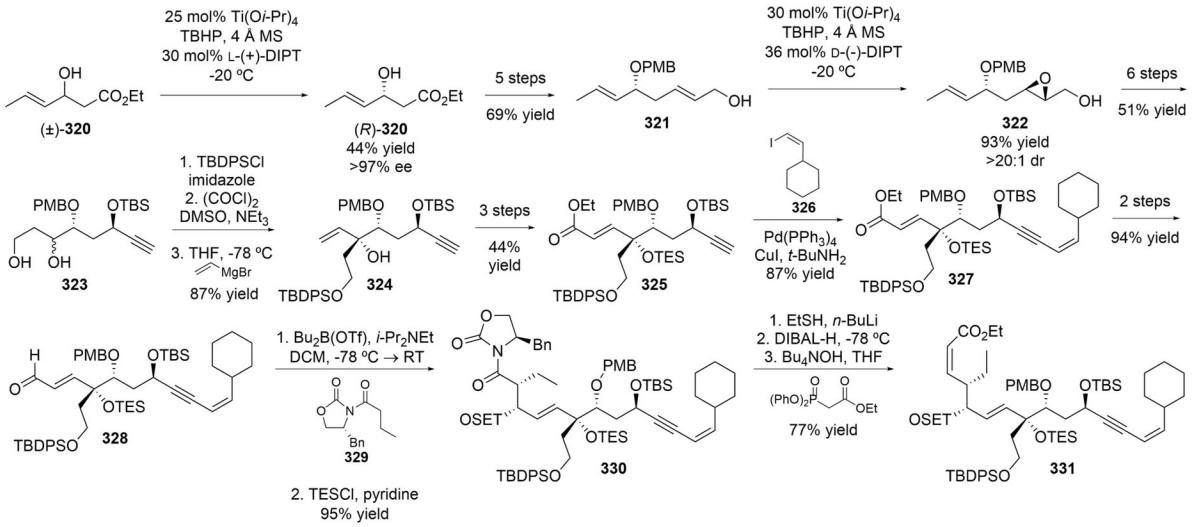


Scheme 50.

Final Stereocenter Is Installed and the Diastereomers Are Separated Using Their Fluorous Tags

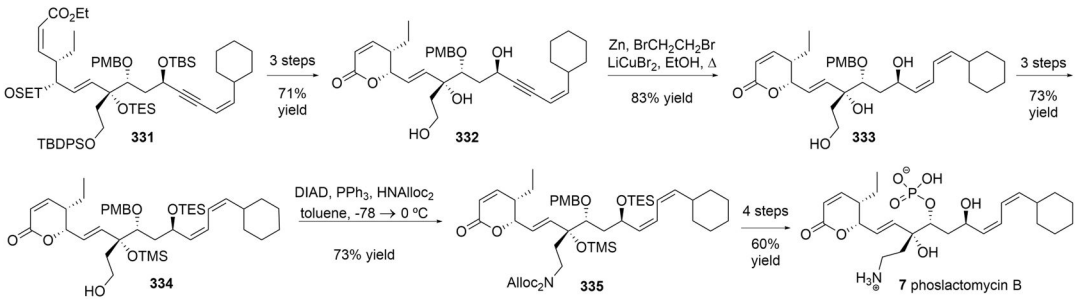


Scheme 51.
Cytostatin and Three Diastereomers Are Completed by Curran



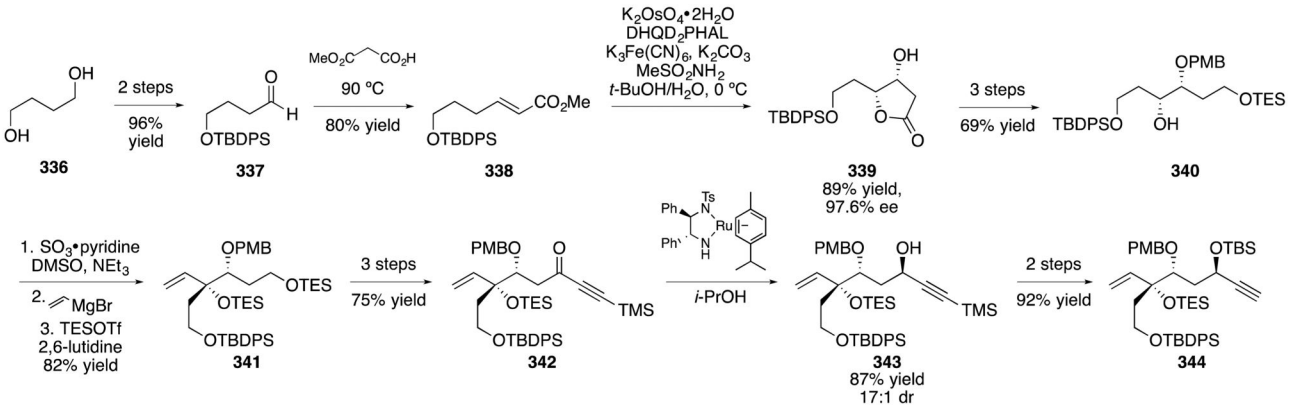
Scheme 52.

Kobayashi's Synthesis Utilizes Sharpless Asymmetric Epoxidations for Kinetic Resolution and Diastereoselective Epoxide Formation



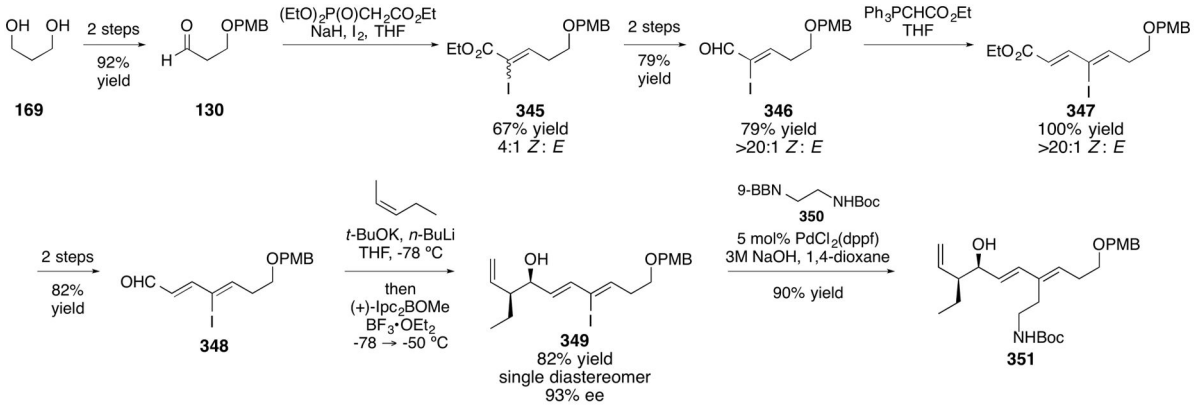
Scheme 53.

Kobayashi Completes the Synthesis of Phoslactomycin B, Installing the Azide Using a Mitsunobu Reaction



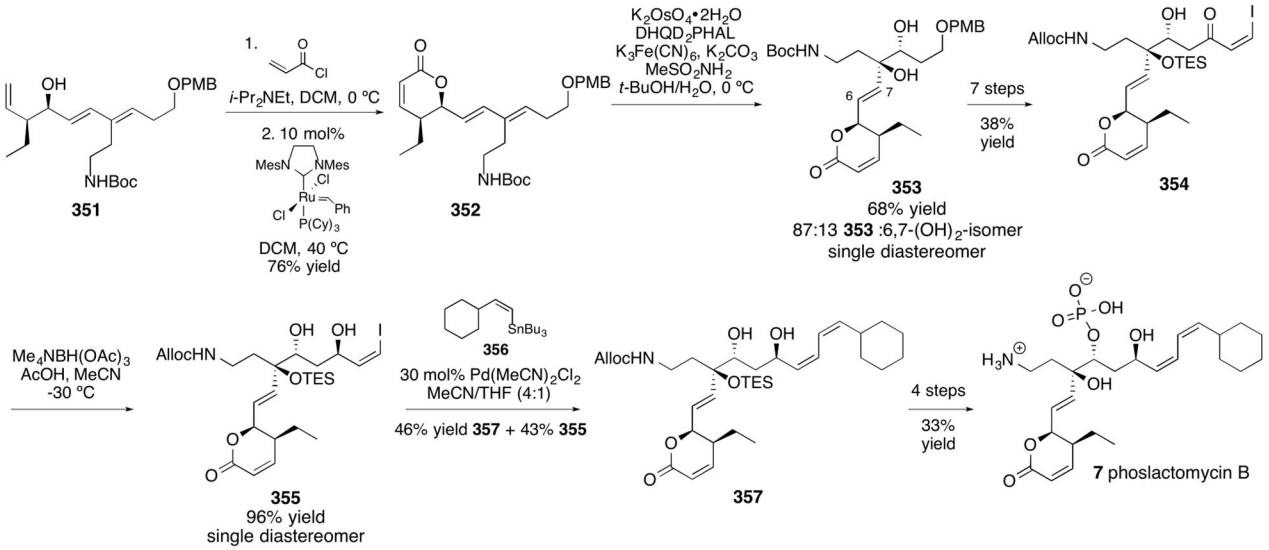
Scheme 54.

Kobayashi's Second-Generation Strategy for the Synthesis of the Core of Phoslactomycin B



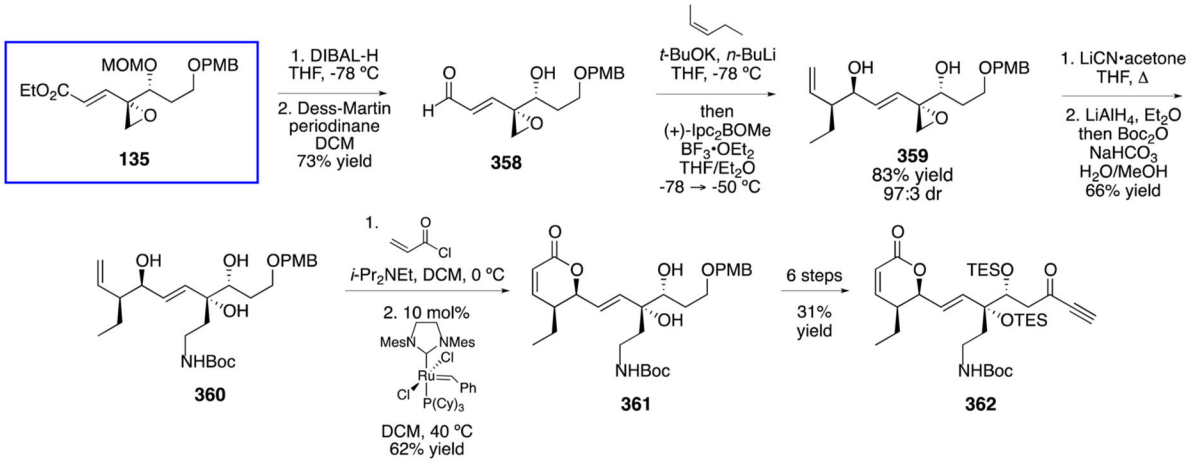
Scheme 55.

Hatakeyama's Synthesis of the Core of Phoslactomycin B Relies on Iterative Horner–Wadsworth–Emmons Olefinations and Installs the Aminoethyl Group via Cross-Coupling



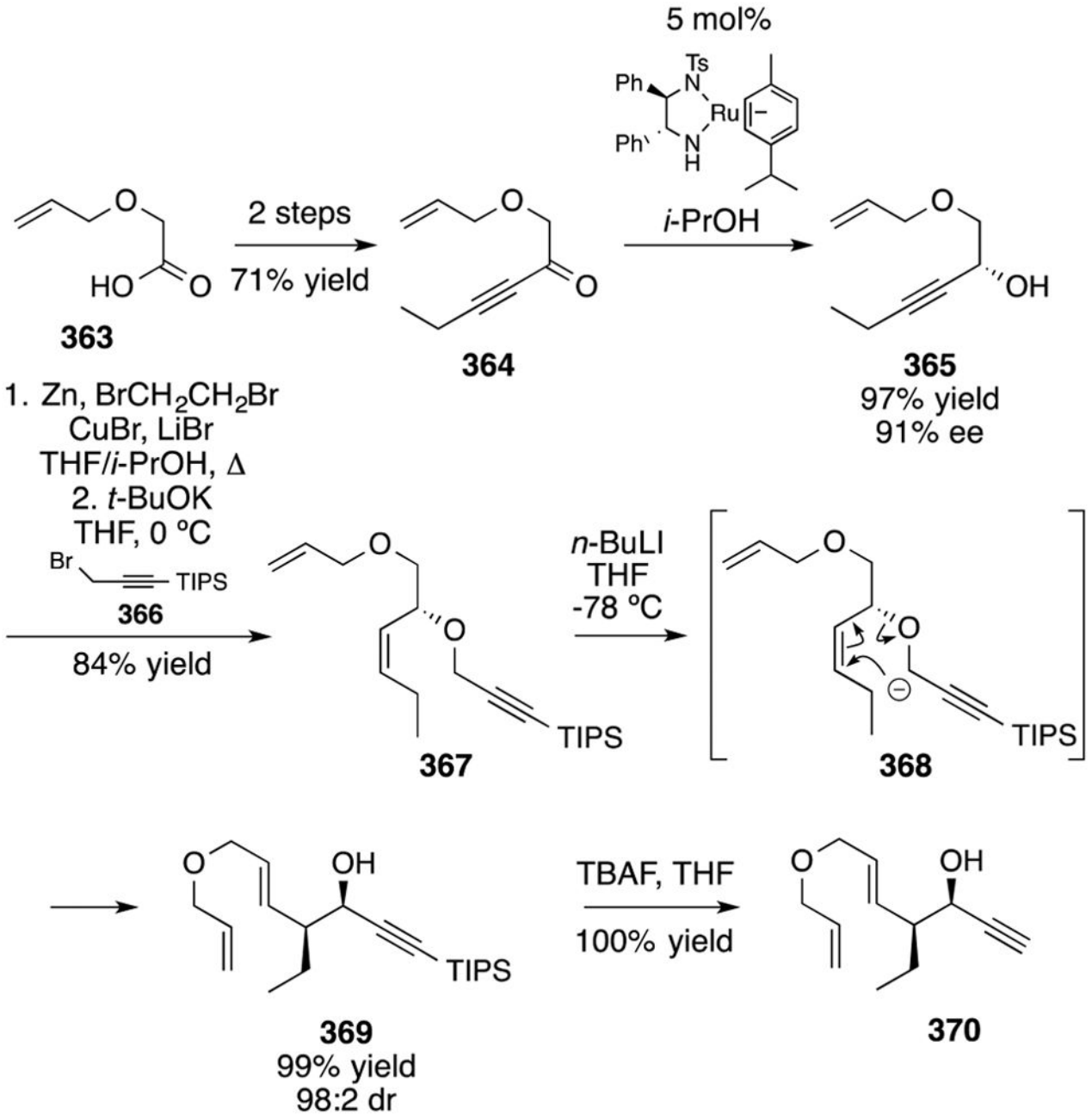
Scheme 56.

Hatakeyama Completes Phoslactomycin B Using a Sharpless Asymmetric Dihydroxylation To Install the C8 and C9 Stereocenters and a Stille Cross-Coupling To Unite the Cyclohexyl Fragment



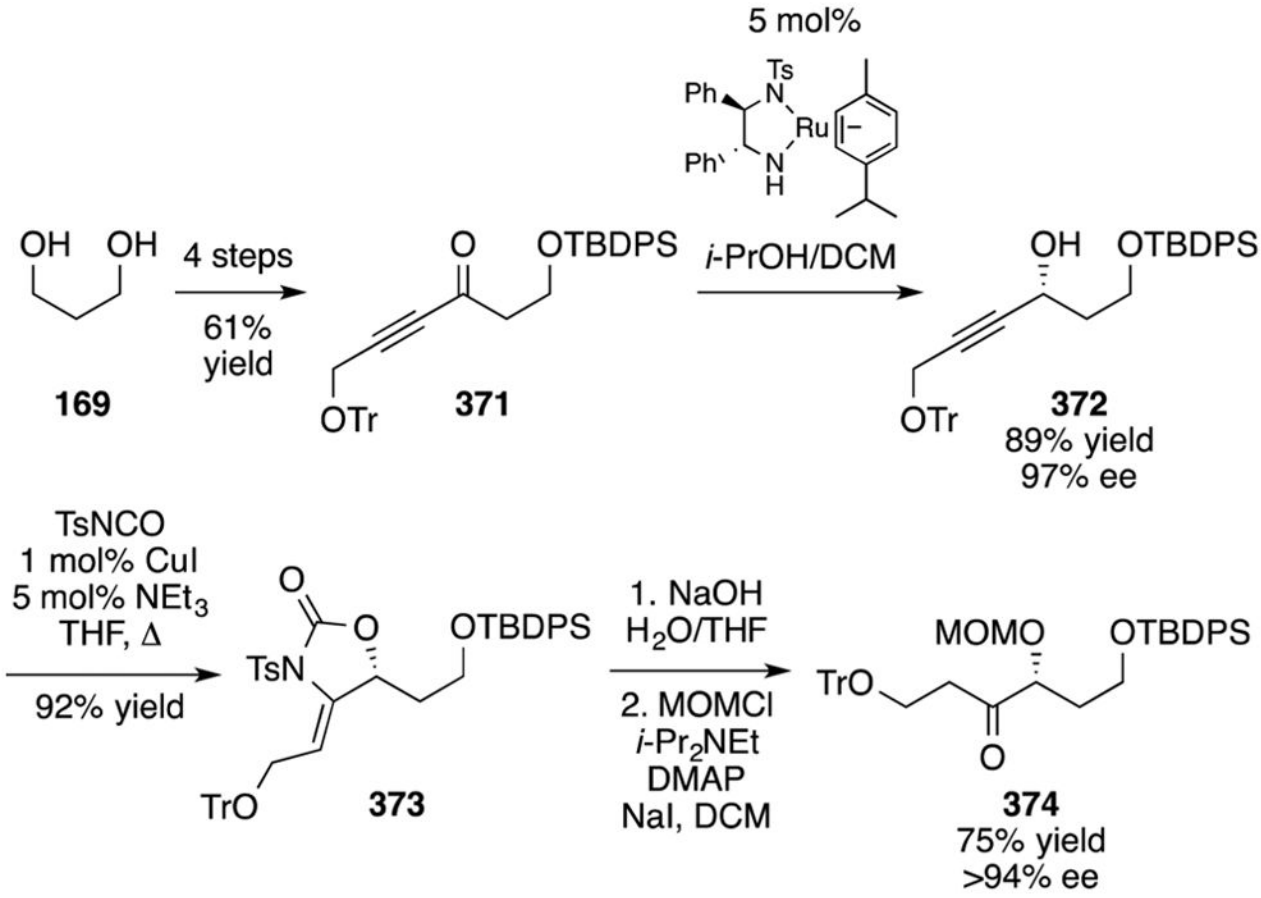
Scheme 57.

Hatakeyama's Second Phoslactomycin Strategy Takes Advantage of a Shared Intermediate Epoxide from His Fostriecin Synthesis

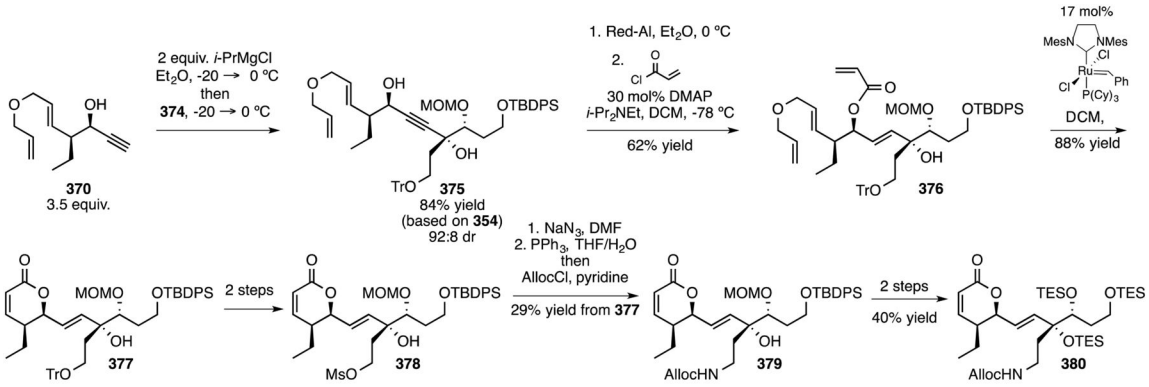


Scheme 58.

Cossy's Synthesis of Phoslactomycin B Features a 1,3-Wittig Rearrangement

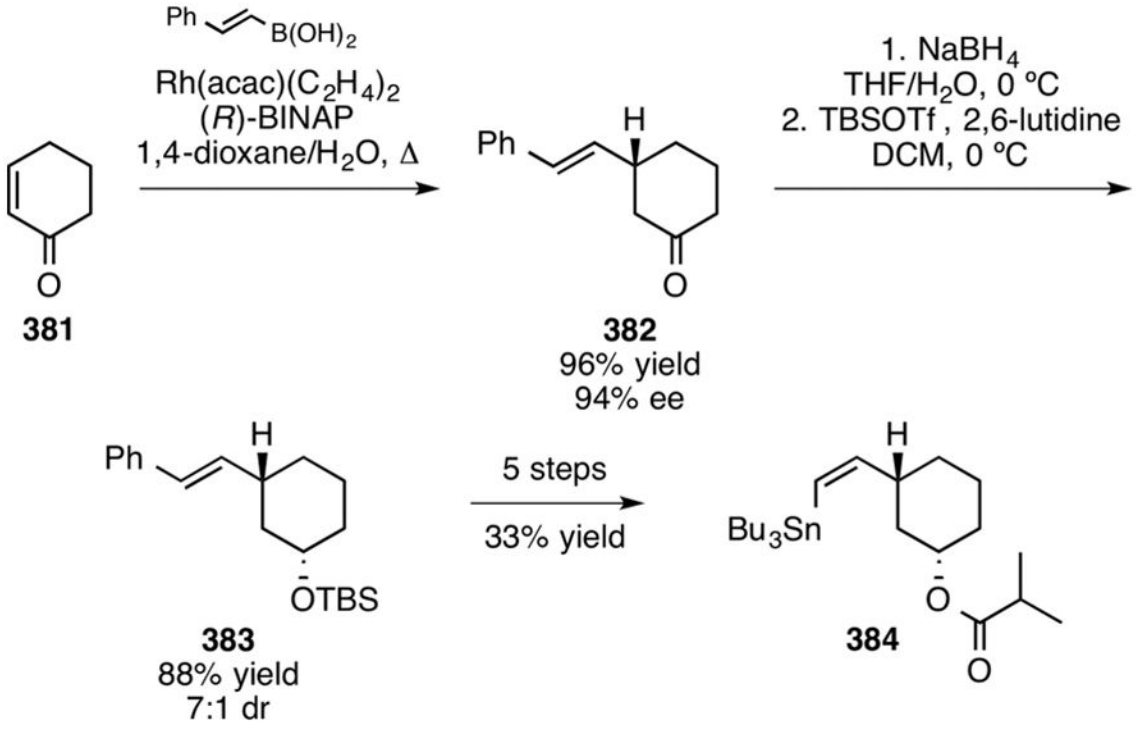


Scheme 59.
Mild Hydration of the Alkyne Creates Cossy's Desired Central Fragment



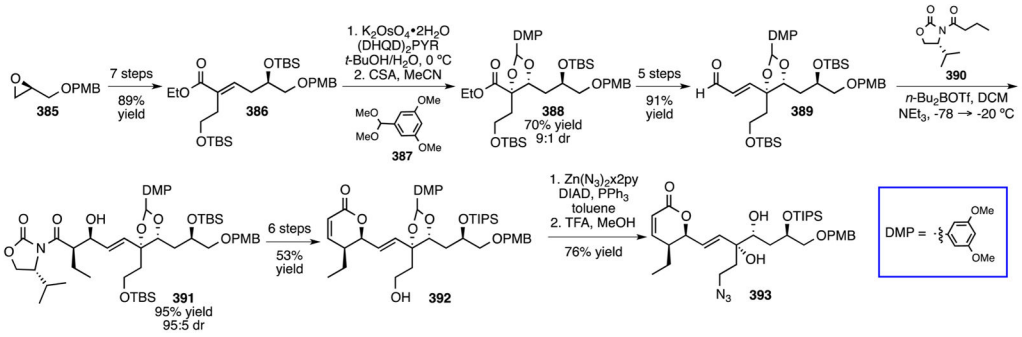
Scheme 60.

Cossy Completes the Formal Synthesis of Phoslactomycin B Using a Relay Ring-Closing Metathesis Strategy To Construct the Lactone and a Mitsunobu Reaction To Install the Amine Group



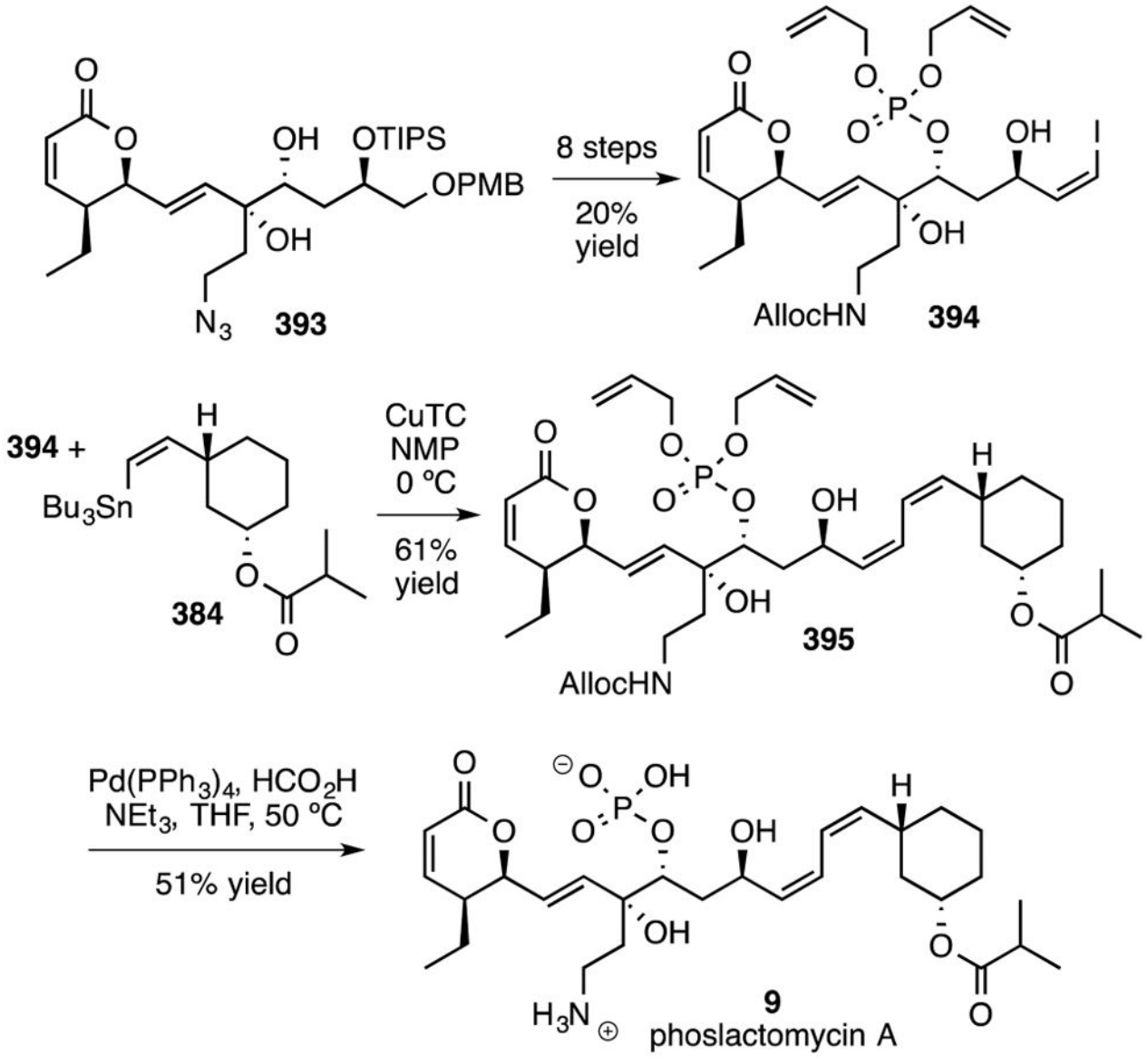
Scheme 61.

Koert's Synthesis of the Stereochemically Defined Cyclohexyl Fragment of Phoslactomycin A

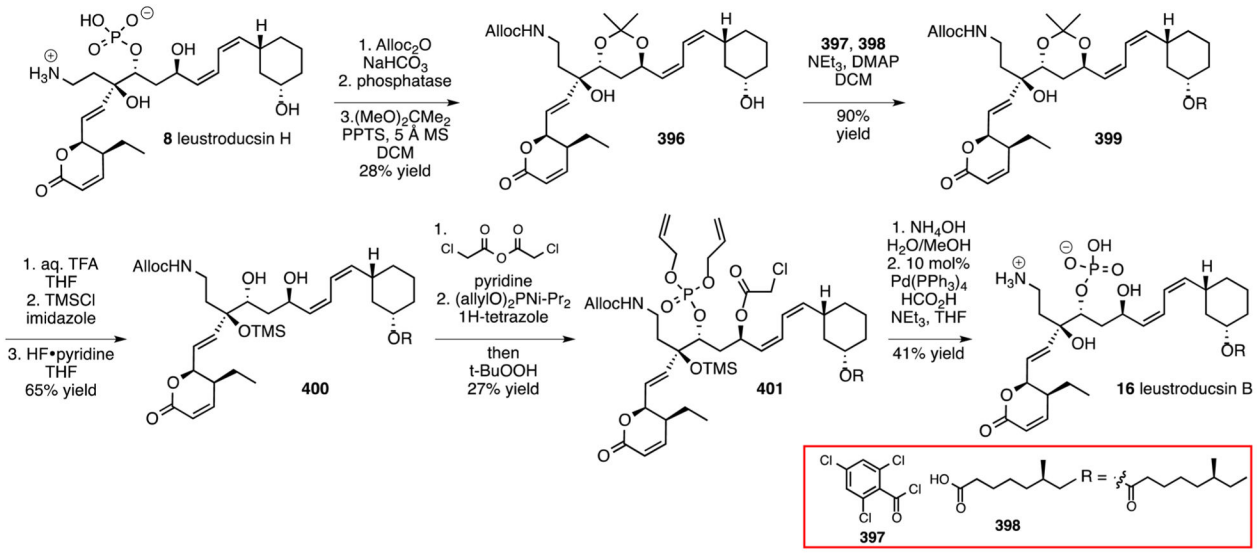


Scheme 62.

Koert's Construction of the Core of Phoslactomycin A Utilizes Sharpless Asymmetric Dihydroxylation and an Evans Aldol Reaction To Set Stereochemistry

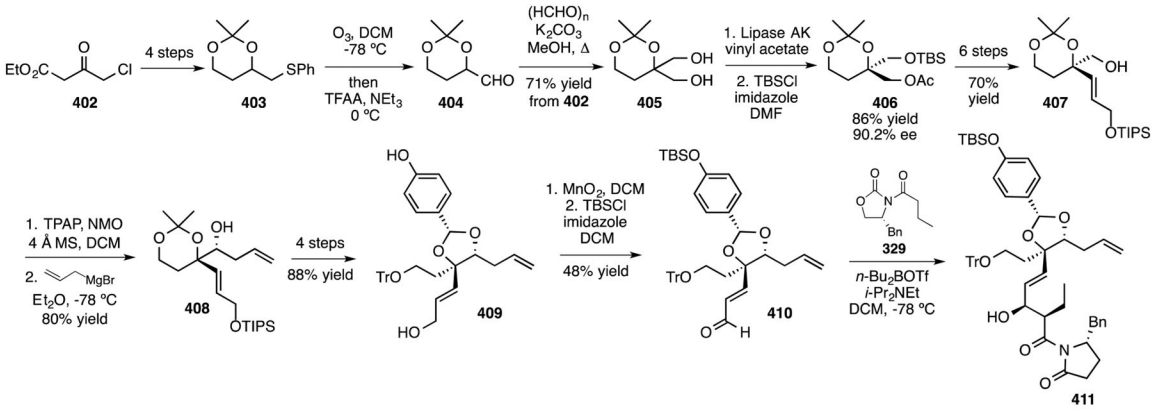


Scheme 63.
Completion of Phoslactomycin a Uses a Copper-Mediated Cross-Coupling Reaction



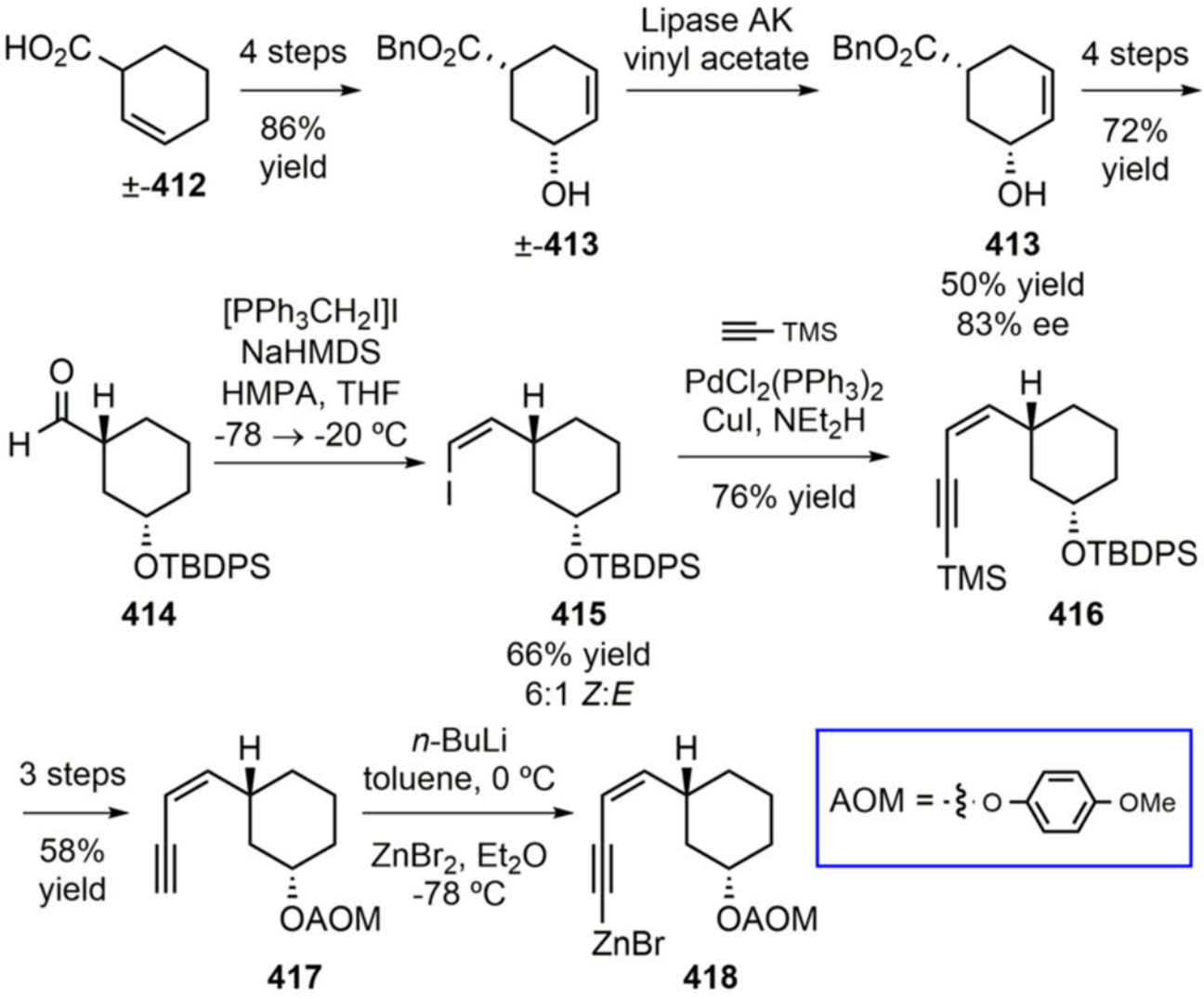
Scheme 64.

Matsuhashi's Semisynthesis of Leustroducsin B Illustrates the Natural Product's Sensitivity and Informs the Endgame Strategies for Future Total Syntheses

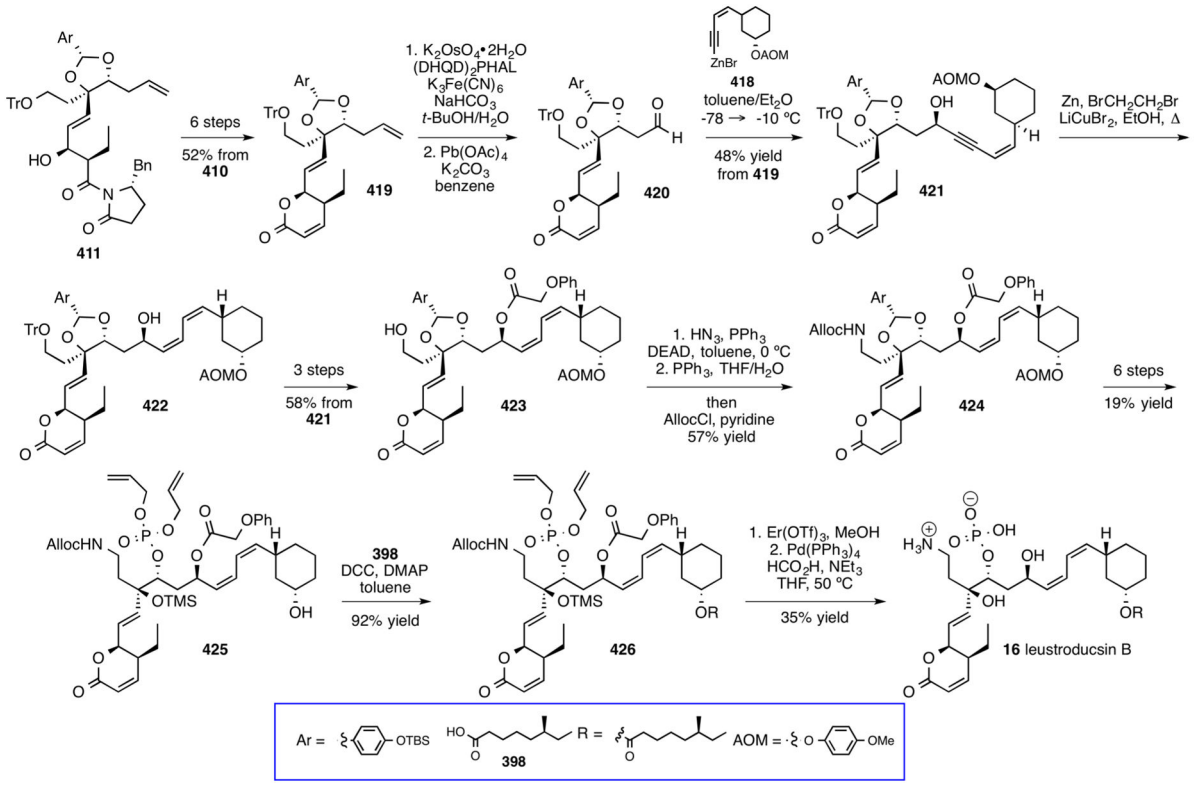


Scheme 65.

Fukuyama's Synthesis of the Core of Leustroducsin B Features an Enzymatic Desymmetrization To Set the Absolute Configuration

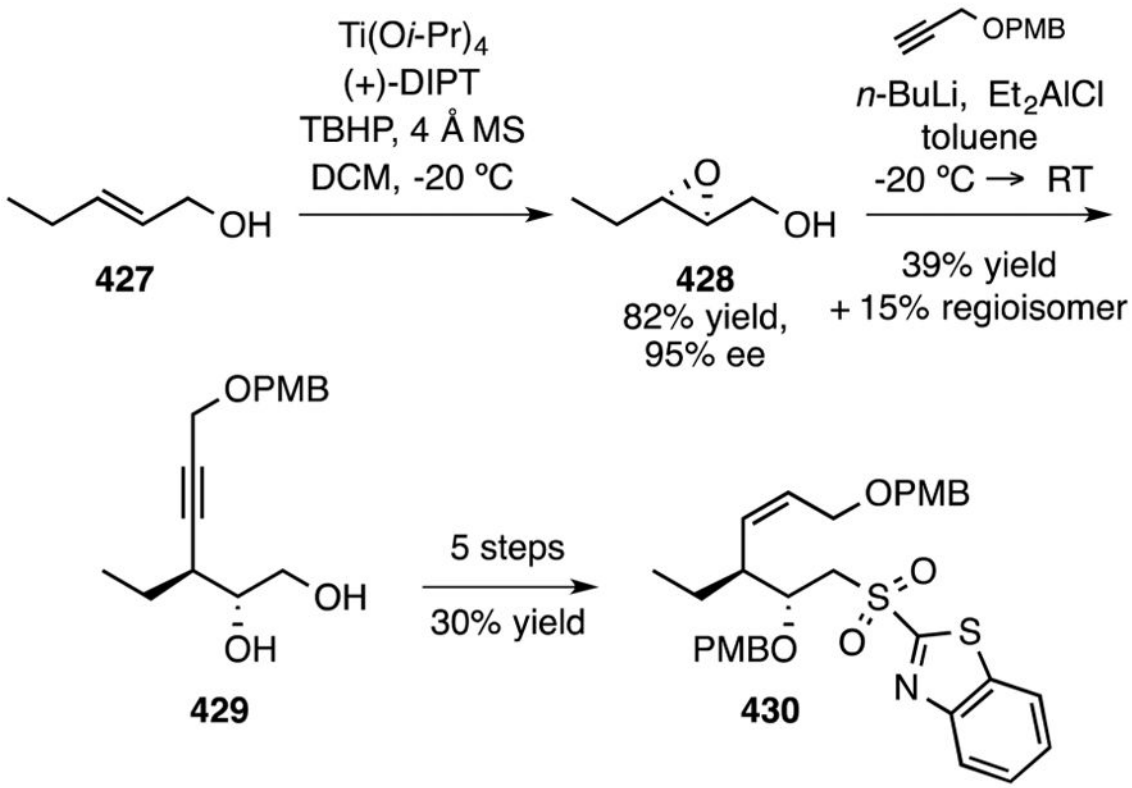


Scheme 66.
Cyclohexyl Fragment Is Constructed Using Enzymatic Resolution

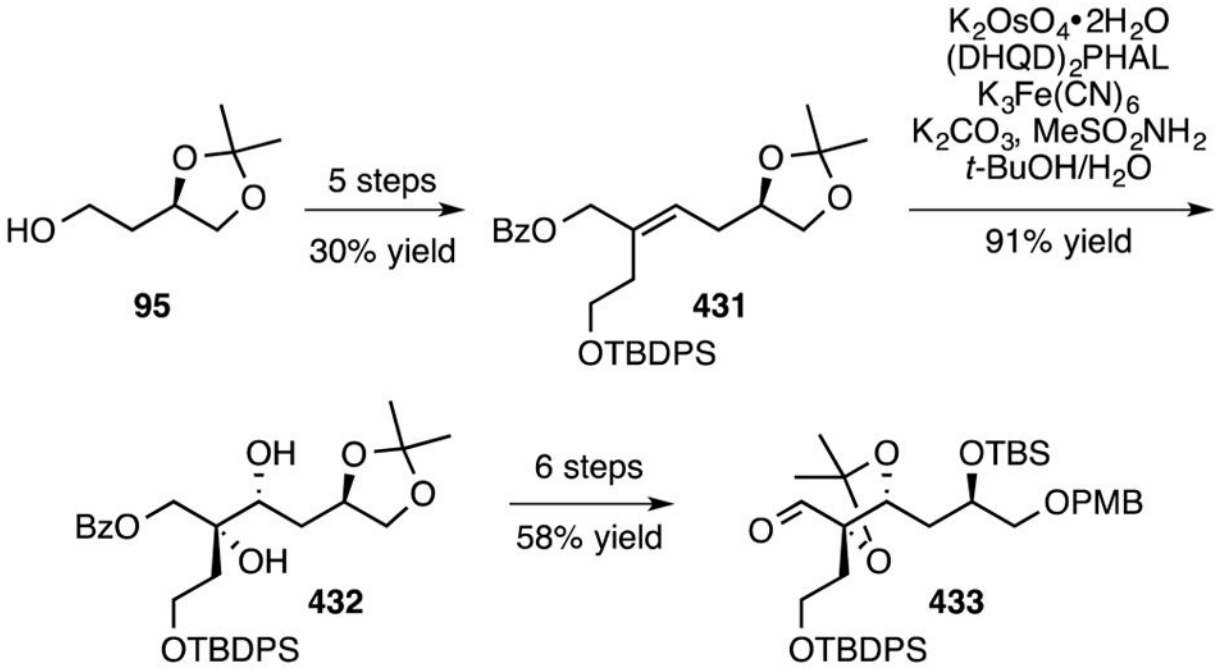


Scheme 67.

Fukuyama's Completion of Leustroducsin B Utilizes an Alkynyl Zincate Addition into an Aldehyde To Unite the Fragments

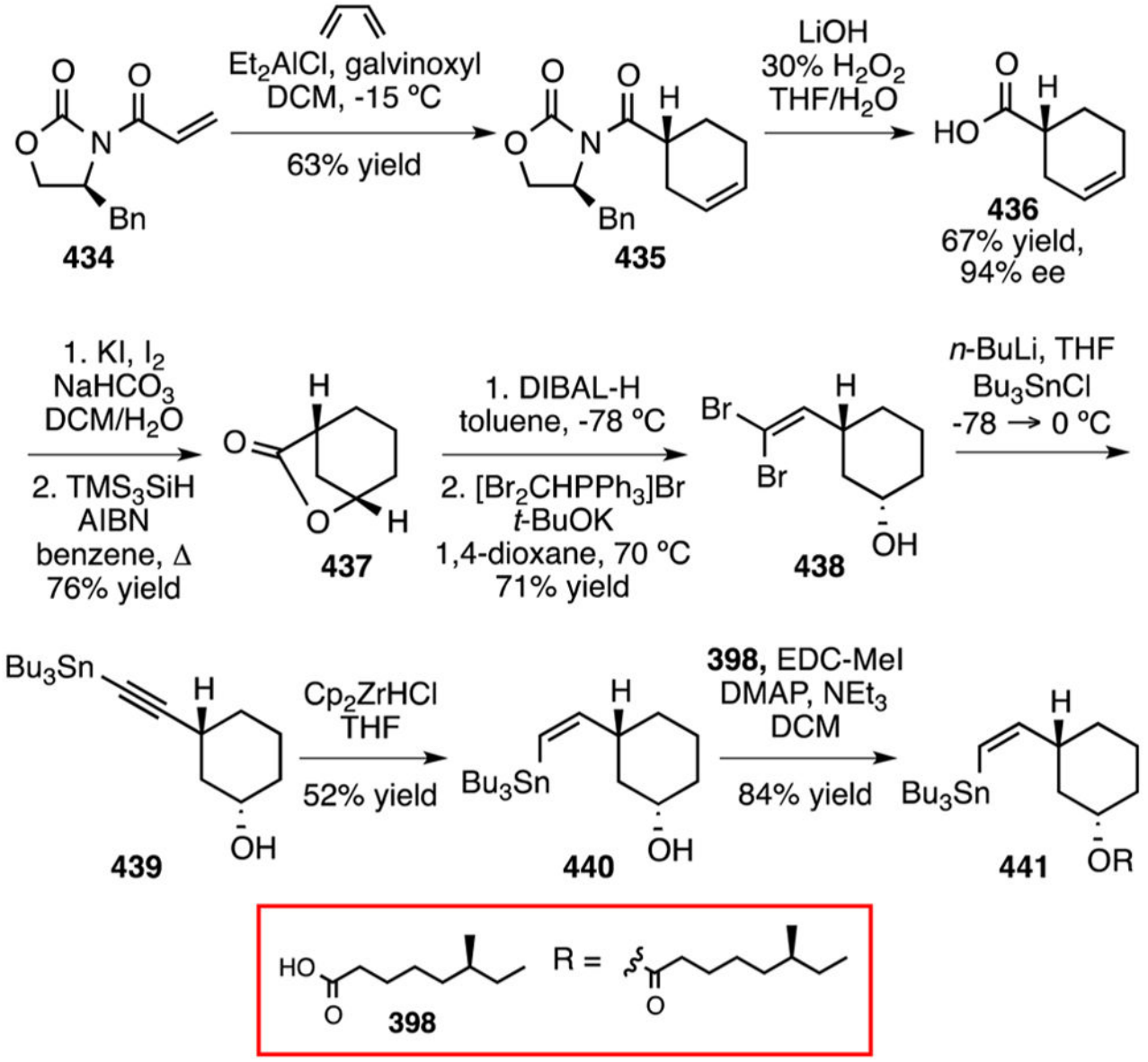


Scheme 68.
Imanishi's Synthesis of a Julia Reagent Begins with a Sharpless Asymmetric Epoxidation



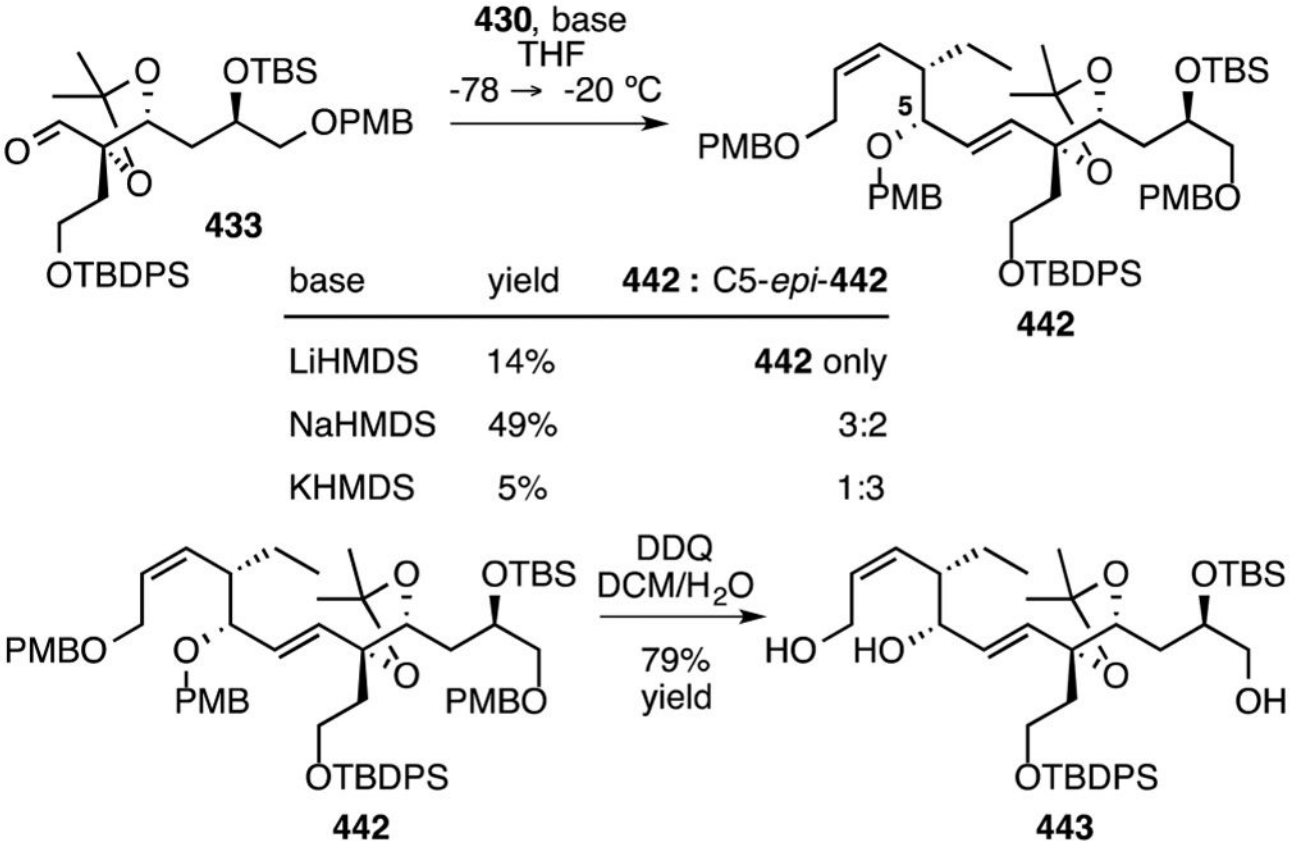
Scheme 69.

Core of Leustrodusin B Was Synthesized Using a Chiral Pool Approach Combined with a Sharpless Asymmetric Dihydroxylation

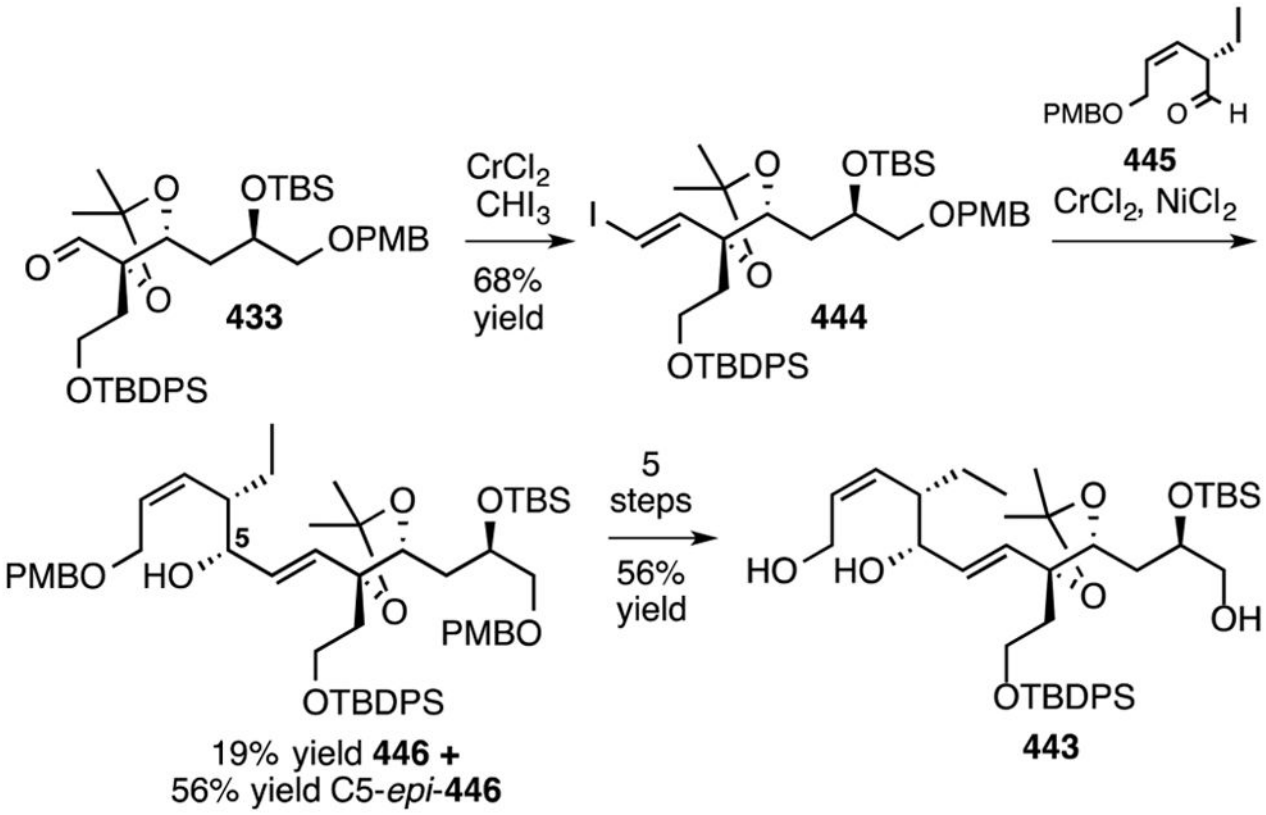


Scheme 70.

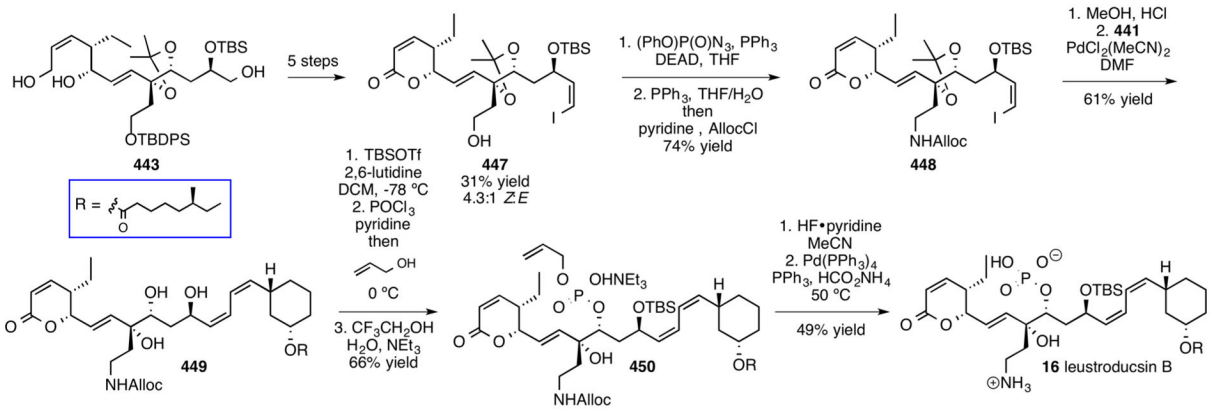
Imanishi Created the Stereochemically Defined Cyclohexyl Fragment by Employing a Chiral Auxiliary Directed Diels–Alder Reaction



Scheme 71.
Imanishi's Key Julia Olefination Is Problematic

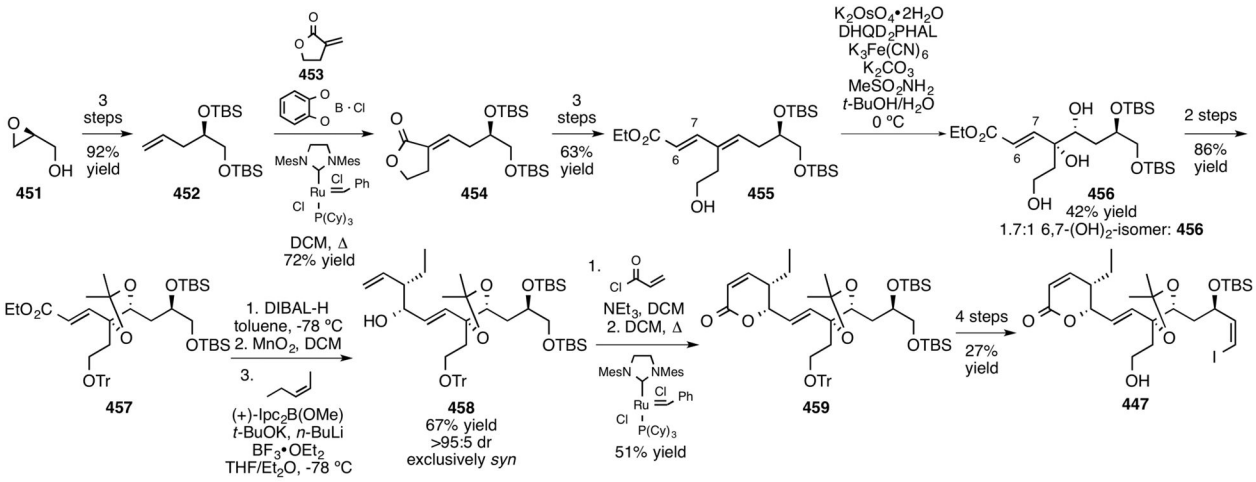


Scheme 72.
Imanishi's Second Generation Strategy Features an NHK Addition



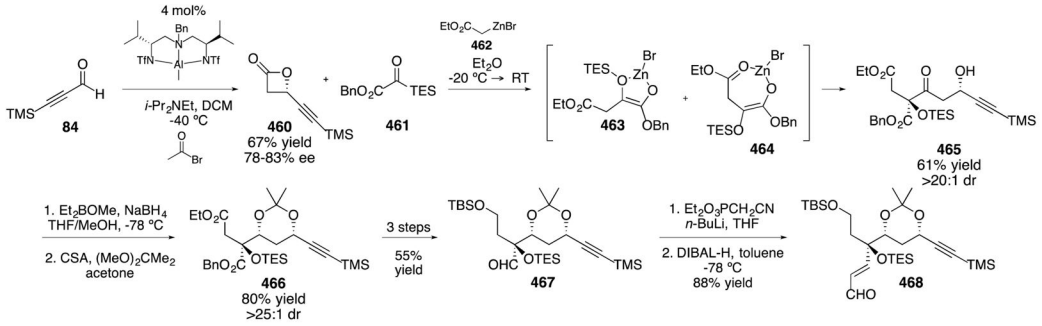
Scheme 73.

Imanishi Completes the Synthesis of Leustroducsin B by Installing the Amine via Mitsunobu Reaction and Appending the Cyclohexyl Fragment with a Stille Cross-Coupling



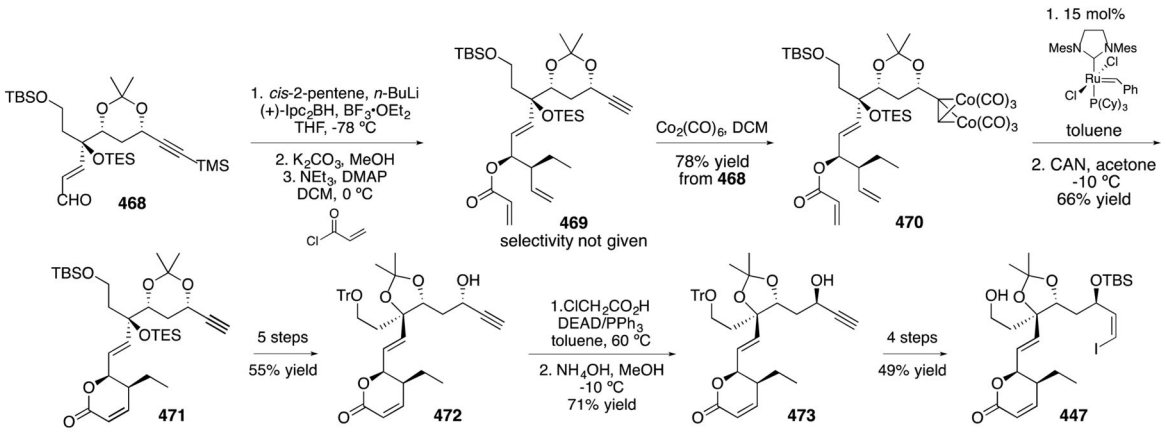
Scheme 74.

Cossy's Formal Synthesis of Leustroducsin B Features a Cross-Metathesis Reaction To Install a Precursor to the Aminoethyl Side Chain



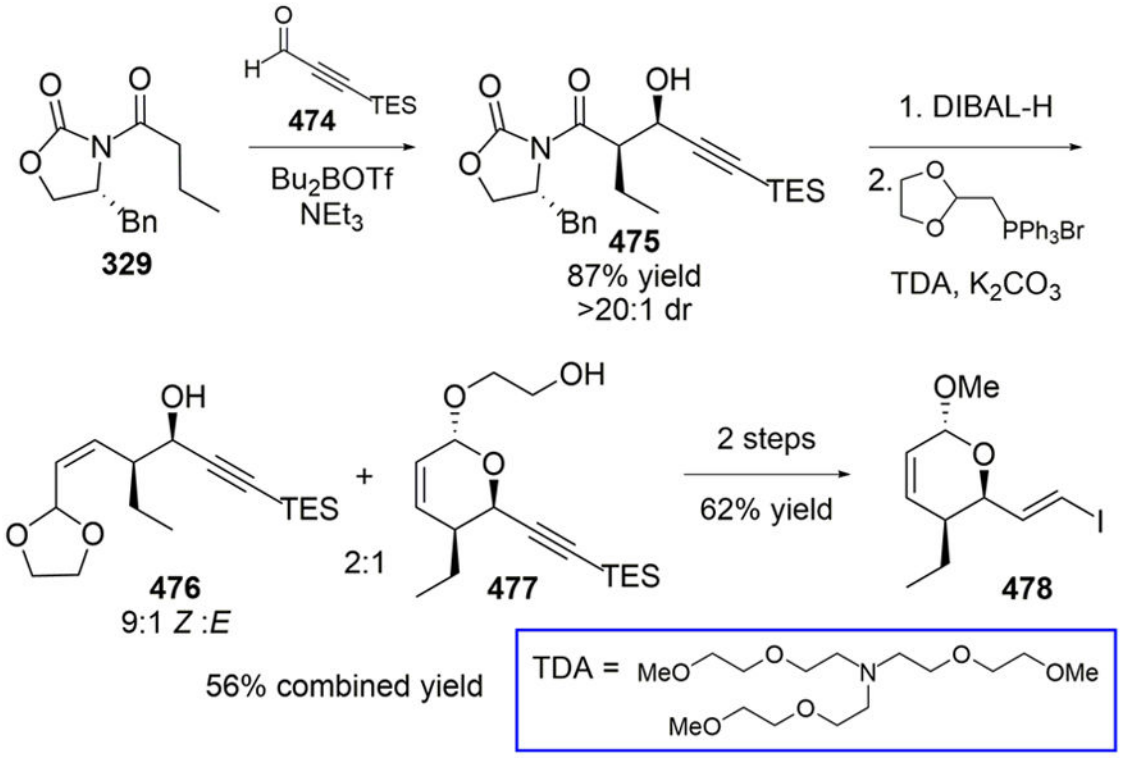
Scheme 75.

Johnson Created a Novel Three-Component Reaction for the Synthesis of the Core of Leustroducsin B



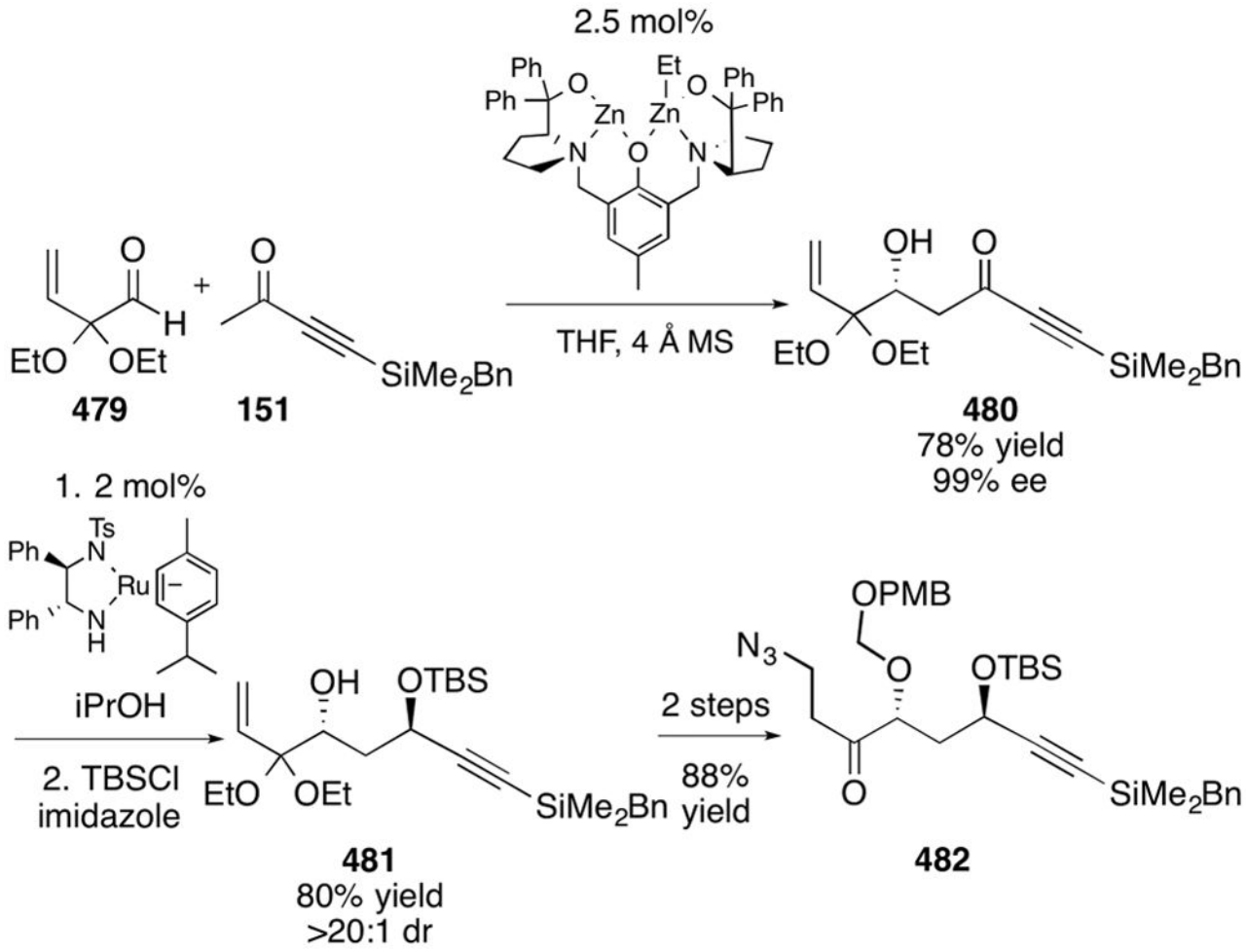
Scheme 76.

Johnson's Formal Synthesis of Leustroducsin B Utilizes a Dicobalt Hexacarbonyl Complex Protection of the Terminal Alkyne To Facilitate Ring-Closing Metathesis



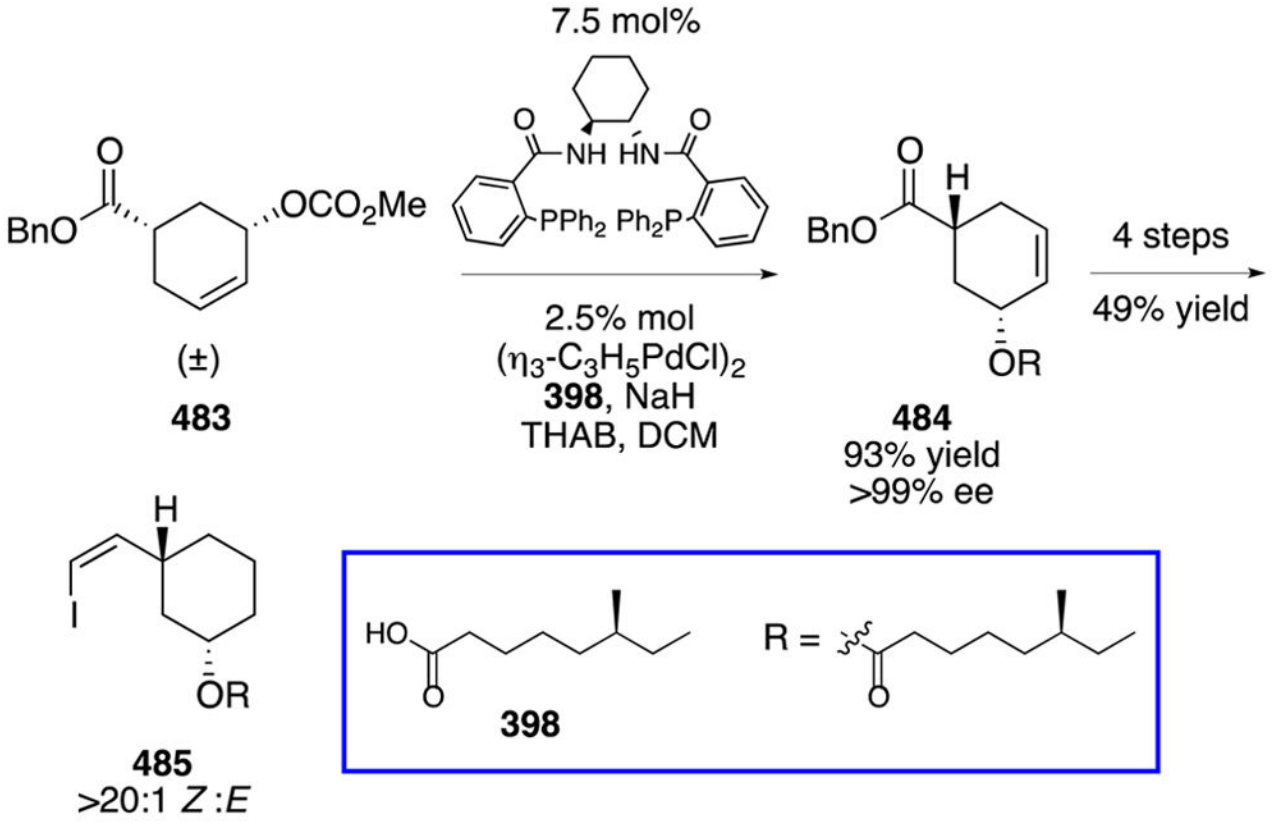
Scheme 77.

Trost's Synthesis of the Lactone Portion of Leustroducsin B Utilizes an Evans Aldol Reaction To Set the Stereochemistry



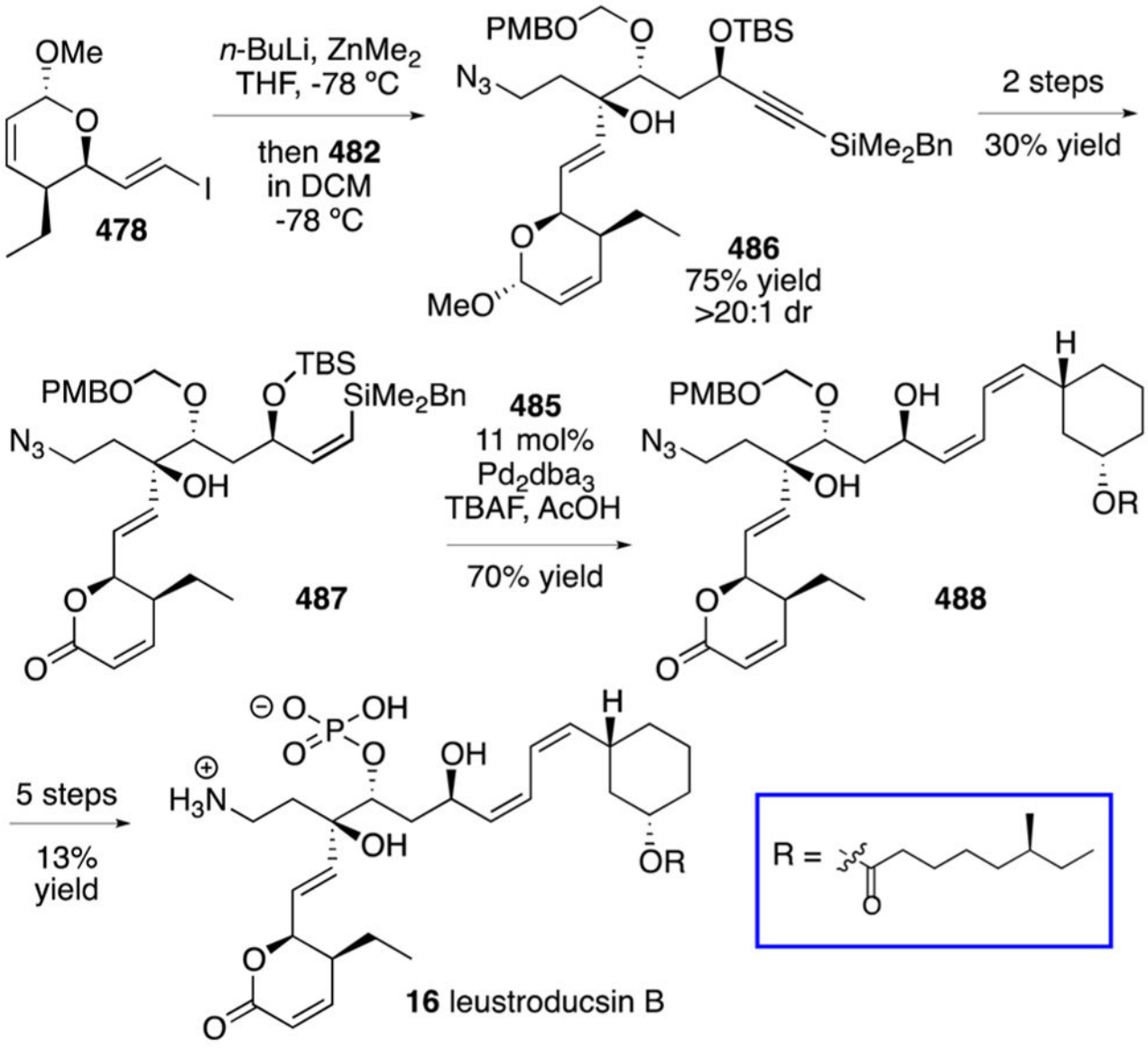
Scheme 78.

A Catalytic Direct Aldol Reaction Sets the Stereochemistry of Trost's Central Fragment



Scheme 79.

Cyclohexyl Fragment Is Constructed Using a Palladium-Catalyzed Allylic Alkylation That Deracemizes the Starting Material



Scheme 80.

Trost Completes the Structure of Leustroducsin B Using a Diastereoselective Vinyl Zincate Addition and a Silicon Cross-Coupling Reaction