Synthesis of Bioactive Natural Products by Asymmetric *syn*- and *anti*-Aldol Reactions

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Abstract: The use of several variants of the asymmetric aldol reaction as key steps in the syntheses of bioactive target molecules is described.

Key words: natural products, asymmetric synthesis, chiral auxiliary, *syn*-aldol, *anti*-aldol, indanolamine

For centuries, natural products have been a major source of inspiration to researchers in the fields of chemistry, biology, and medicine. Numerous natural products and their derivatives have received approval as front-line therapies for the treatment of a variety of human diseases. The seemingly endless structural diversity, complexity, and important biological functions of natural products have provided an impetus for the development of novel methodologies for their synthesis. Furthermore, drug-discovery researchers frequently attempt to reproduce various structural motifs and stereochemically defined functionalities from natural products. This has further stimulated the design and development of new and practical synthetic technologies, and has greatly enhanced medicinal research investigations in academia and industry.

Over the years, we have been involved in the synthesis of a range of structurally diverse natural products with a variety of biological activities. Our objectives have been to synthesize these scarce natural products efficiently, to carry out further biological evaluation, to perform structure–activity studies, and to prepare structural variants for biological studies. In this context, we have developed a variety of methods for asymmetric synthesis, including highly diastereoselective *syn*- and *anti*-aldol reactions that rely on ester-derived titanium enolates.

The aldol reaction is one of the most powerful reactions for forming carbon–carbon bonds that is available in organic synthesis. Asymmetric aldol reactions have proved their versatility and utility in organic synthesis, especially for the construction of architecturally complex natural products. Here we report our attempts to use the asymmetric aldol reaction as a key step in the synthesis of a variety of bioactive target molecules (Figure 1). In these studies, we used several asymmetric aldol reactions, including Evans's *syn*-aldol protocol,[1] Mukaiyama's aldol reaction,[2] our own chiral ester-based asymmetric aldol reaction, and a nitro-aldol reaction.[3] We will also describe a recent asymmetric reductive aldol process developed in our laboratory in the context of the synthesis of peloruside A, a potent anticancer agent with clinical potential.[4,5] Furthermore, we report an asymmetric aldol-based synthesis of a stereochemically defined bis-tetrahydrofuran (bis-THF) scaffold present in ginkolide natural products.[6] This scaffold has been successfully incorporated in the design and development of Darunavir, a HIV-1 protease inhibitor for the treatment of multi-drug-resistant HIV-1 variants that has recently been approved by the US Food and Drug Administration (FDA).

Hapalosin

Multi-drug resistance (MDR) is a phenomenon whereby many cancers develop resistance to chemotherapeutic drugs, and it is a major factor for treatment failure. It appears that MDR is caused by overexpression of P-glycoprotein, a 170–200 kDa transmembrane protein that acts as an ATP-dependent drug efflux pump.[7] Hapalosin (**1**), isolated from the blue-green alga *Hapalosiphon welwitschii*,[8] has shown a reversing effect on MDR in tumor cells.[9] We reported the first total synthesis of hapalosin in 1996. In this synthesis, we used Evans's asymmetric *syn*-aldol reaction to install two key stereocenters.[10] This aldol strategy involved the use of an aminoindanol-based chiral oxazolidinone as the chiral auxiliary. As shown in Scheme 1, the reaction of oxazolidinone **9**[11] and octanal with dibutylboryl triflate and triethylamine at –78 °C gave the aldol adduct **10** in 90% yield. The resulting aldolate was protected as its tetrahydropyranyl ether, and the chiral auxiliary was removed to give the corresponding acid. Coupling of this acid with alcohol **11** gave diester **12**. The tetrahydropyranyl group was removed and the diester was coupled with acid **13** to provide the corresponding ester. Removal of the benzyl and benzyloxycarbonyl protecting groups, followed by cycloamidation of the resulting amino acid **14** with *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide and *N*-hydroxybenzotriazole afforded the corresponding cycloamide. Removal of the methoxymethyl protecting group then gave synthetic hapalosin.

(+)-Cryptophycin B

The synthesis of cryptophycins, which are a group of marine depsipeptides isolated from *Nostoc* sp., has attracted much attention over the years because of the significant clinical potential of these chemicals and their relatively low natural abundance.[12] Members of the cryptophycin

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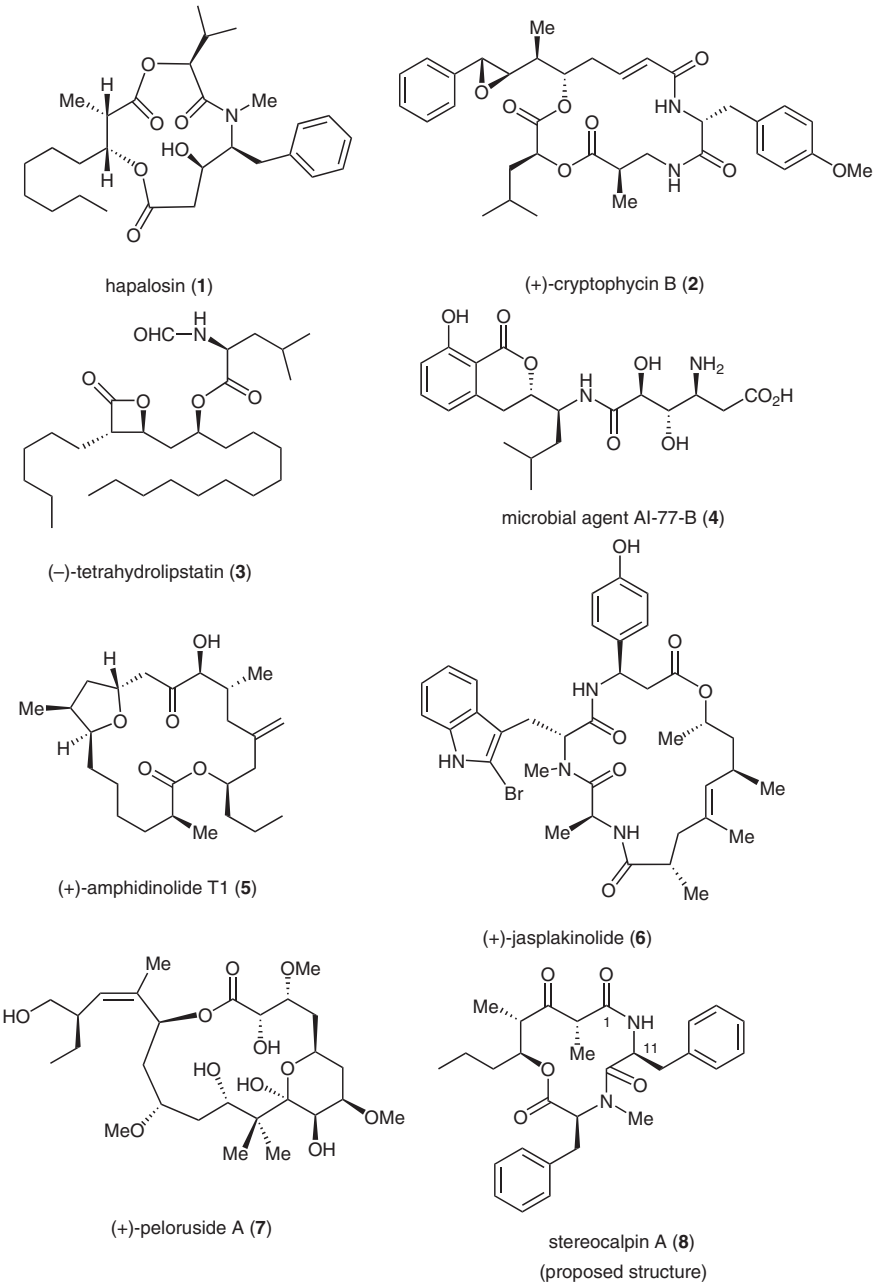
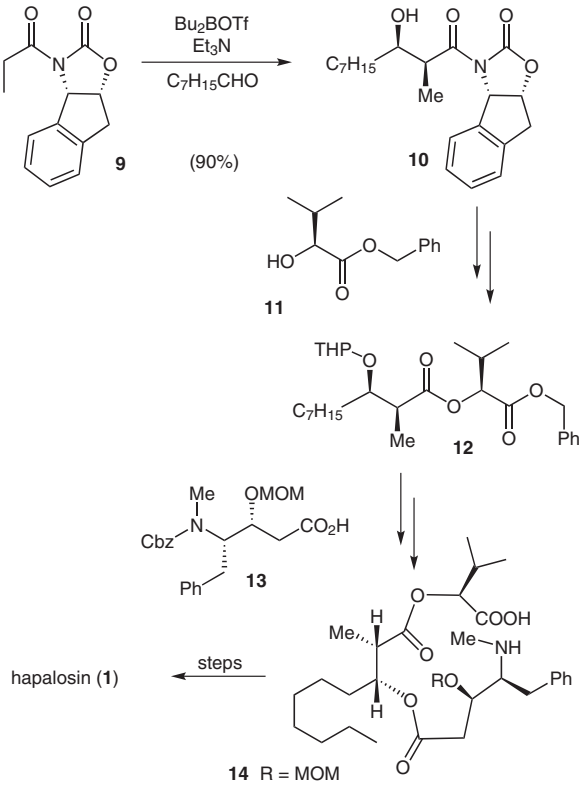


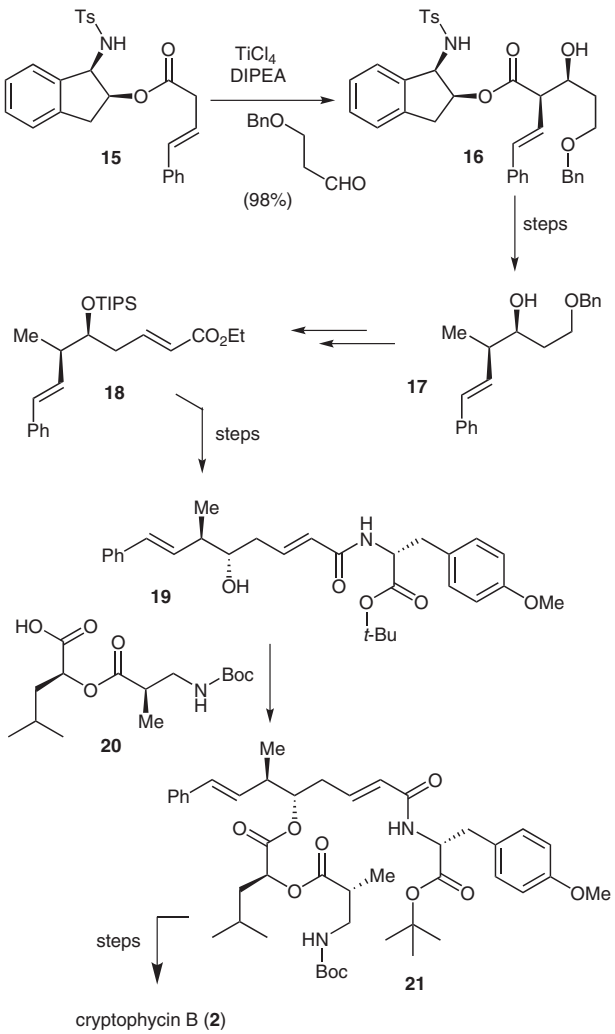
Figure 1 Some natural products synthesized by aldol reaction strategies

family, including arenastatin, inhibit tubulin polymerization in vitro, which may render these compounds or their derivatives important in cancer therapy.[13]

We carried out a convergent synthesis of cryptophycin B (**2**) by using aldol reactions based on asymmetric titanium enolates that we developed in our laboratory.[14] As shown in Scheme 2, ester **15**, obtained by coupling (3*E*)-4-phenylbut-3-enoic acid and 1-(*N*-tosylamino)indan-2-ol, was treated with titanium tetrachloride and *N*,*N*-diisopropylethylamine. The resulting enolate was treated with 3-(benzyloxy)propanal to provide the *syn*-aldol adduct **16** in 98% yield as a single diastereomer. Reduction of the aldol adduct with lithium aluminum hydride and selective conversion of the primary hydroxy group into the corresponding methyl group was accomplished in a one-pot, two-step sequence to give the alcohol intermediate **17**. This was converted into the corresponding aldehyde followed by a Horner–Wadsworth–Emmons reaction with ethyl (diethoxyphosphono)acetate to give ester **18**. This acid was coupled with *tert*-butyl *O*-methyl-D-tyrosinate to afford amide **19**, which was then attached to the protected amino acid **20** by means of Yamaguchi coupling. Macrolactamization of the amino acid derived from the resulting derivative **21** was accomplished by using Yamaguchi's protocol. Epoxidation with dimethyldioxirane gave the title compound as a 3:1 mixture of epoxides. We have since carried out a synthesis of cryptophycin-52 by a non-aldol process.[15]



Scheme 1 Synthesis of hapalosin



Scheme 2 Synthesis of cryptophycin B

(–)-Tetrahydrolipstatin

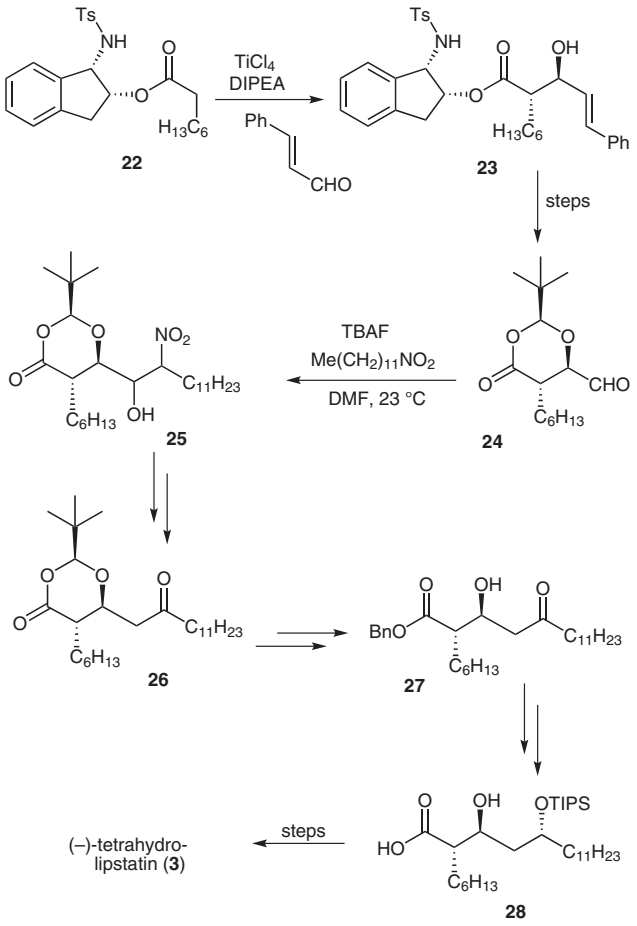
(–)-Tetrahydrolipstatin (**3**), a saturated derivative of lipstatin, was isolated in 1987, from the bacterium *Streptomyces toxytricini*.[16,17] This compound, under the trade name Xenical®, has been approved by the FDA as an anti-obesity agent. It inhibits pancreatic lipase by irreversibly binding to the serine at the active site with its β-lactone moiety.[17] We synthesized tetrahydrolipstatin using an asymmetric ester-derived titanium enolate *anti*-aldol reaction and a nitro-aldol reaction as key steps.[18]

Chiral ester **22**, was treated with titanium tetrachloride and *N*,*N*-diisopropylethylamine in dichloromethane at 0 °C to 23 °C. The resulting enolate was then cooled to –78 °C and *trans*-cinnamaldehyde complexed with dibutylboryl triflate (premixed) was added to give the *anti*-aldol product **23** in 60% yield (6.1:1 *dr*). This aldol product was converted into the aldehyde **24**. A nitro-aldol reaction of aldehyde **24** with nitrododecane in *N*,*N*-dimethylformamide containing a catalytic amount of tetrabutylammonium fluoride provided the nitro-aldol product **25** in 82% yield as a mixture of diastereomers. After dehydration of the nitro-aldolate, the resulting nitrovinyl moiety was converted into the corresponding oxime, which was reduced to give ketone **26** as a single isomer. The dioxanone was hydrolyzed under Seebach's conditions,[19] and the resulting β-hydroxy acid was protected as a benzyl ester. The resulting ketone was reduced by using an *anti*-selective reduction protocol developed by Evans (selectivity 22:1).[20] Selective protection of the less hindered hydroxy group gave the triisopropylsilyl ether **28**. The synthesis of tetrahydrolipstatin was completed by treating acid **28** with benzenesulfonyl chloride in pyridine at 0 °C to give the β-lactone and then removal of the triisopropylsilyl ether and Mitsunobu esterification with *N*-formyl-L-leucine.

Pseudopeptide Microbial Agent AI-77-B

AI-77-B (**4**) was isolated from the fermentation broths of *Bacillus pumilus* AI-77 in 1982.[21] It has unique gastroprotective properties with few side effects; however, its therapeutic potential has been limited because of its poor oral absorption properties.[22] We synthesized the compound by using a titanium enolate-mediated *syn*-aldol reaction to generate the dihydroxyamino acid moiety.[23] Other key reaction steps of our synthesis include a Curtius rearrangement, a regioselective Diels–Alder reaction, and a Dondoni homologation.

Chiral ester **29** was treated with titanium tetrachloride and *N*,*N*-diisopropylethylamine in dichloromethane at room temperature to give the corresponding titanium enolate, which was cooled to –78 °C and treated with (benzyloxy)acetaldehyde. The resulting aldol adduct **30** was isolated as a single diastereomer in 97% yield. The chiral



Scheme 3 Synthesis of tetrahydrolipstatin

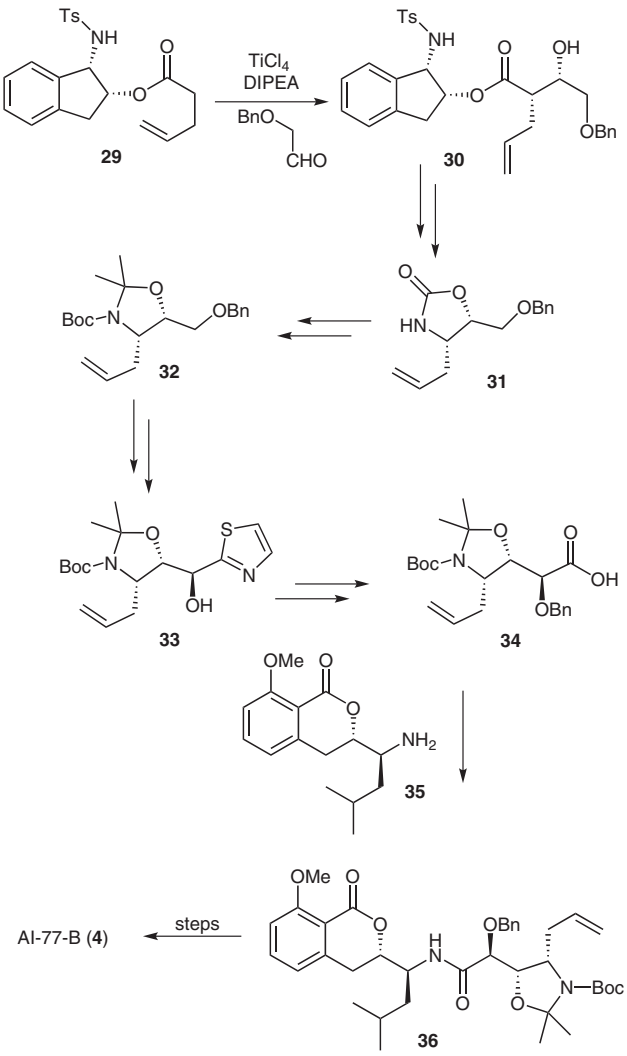
auxiliary was removed and the resulting acid was converted into oxazolidinone **31** by a Curtius rearrangement. Oxazolidinone **31** was converted into the *tert*-butoxycarbonyl-protected acetonide **32**. Benzyl deprotection and Swern oxidation gave an aldehyde that was subjected to stereoselective homologation, as developed by Dondoni and co-workers,[24] to provide thiazole **33**. This thiazole was transformed into the corresponding aldehyde, which was oxidized to give the acid analogue **34**. Coupling of this acid with the isocoumarin fragment **35** provided amide **36**.[25] The terminal alkene group of amide **36** was oxidized to an acid and protected as its benzyl ester, which allowed a clean O-demethylation of the aromatic methoxy group. Removal of the protecting groups gave AI-77-B (**4**).

(+)-Amphidinolide T1

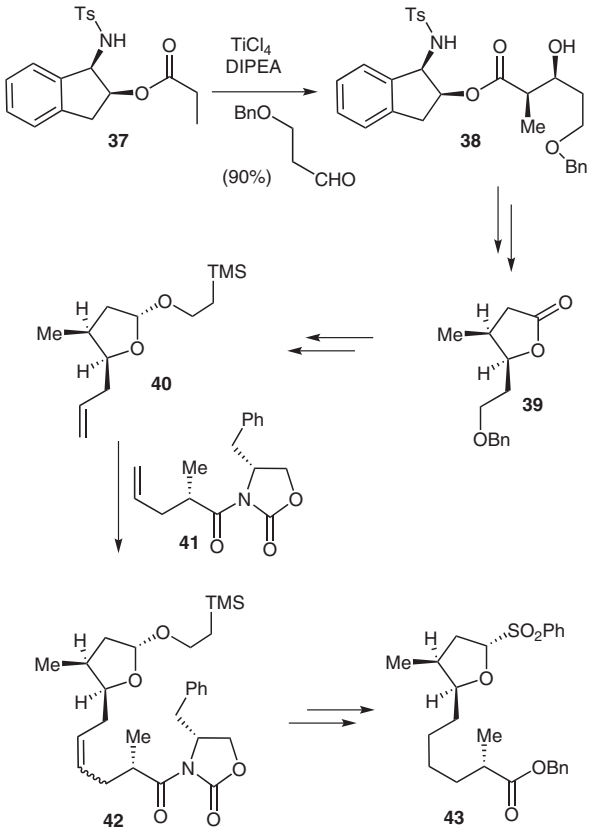
The *Amphidinium* species of marine dinoflagellates have developed metabolites that are quite potent against a variety of cancer cell lines.[26] The 19-membered amphidinolide T1, (**5**) has shown potent activity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines.[27] As a result of their low natural abundance, high biological activity, and unique structural features, the amphidinolides have attracted much attention and have been the subject of many synthetic and biological studies. We accomplished the first total synthesis of amphidinolide T1 utilizing diastereoselective aldol reactions, an oxocarbenium ion-mediated alkylation, cross-metathesis, and a novel *exo*-methylene group protection as the key steps.[28]

Aldol adduct **38** was generated from the condensation of the 1-(*N*-tosylamino)indan-2-ol ester **37** with 3-(benzyloxy)propanal (Scheme 5). The aldol adduct was obtained as a single diastereomer in 90% yield. Removal of the chiral auxiliary with lithium aluminum hydride gave the corresponding diol, which was converted into the γ-lactone **39** in three steps. Lactone **39** was, in turn, transformed into alkene **40**. Cross-metathesis of **40** and oxazolidinone derivative **41** in the presence of Grubbs catalyst gave a 1:1 mixture of the *E*- and *Z*-isomers of the cross-coupled product **42**. Sulfone **43** was obtained by treating the corresponding benzyl ester derivative of **42** with benzenesulfinic acid and calcium chloride.

Scheme 6 outlines the synthesis of the C11–C22 segment and the completion of the synthesis of amphidinolide T1. Ester-enolate aldol reaction of *ent*-**37** with (benzyloxy)acetaldehyde gave the aldolate **44** as a single diastereomer in 95% yield. This was readily converted into



Scheme 4 Synthesis of the pseudopeptide microbial agent AI-77-B



Scheme 5 Synthesis of sulfone fragment **43**

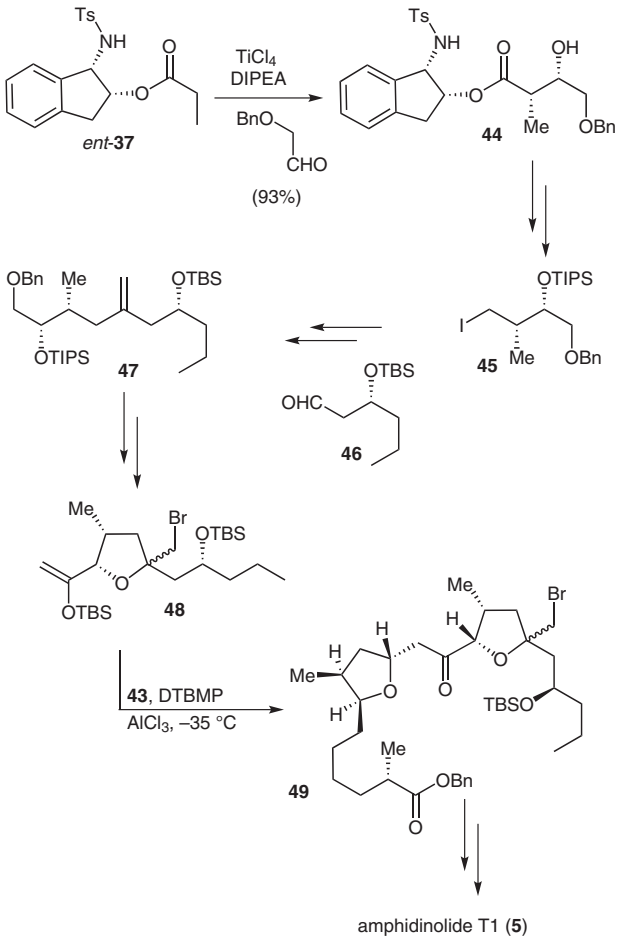
iodide **45** by protecting the alcohol as a triisopropysilyl ether, reduction with diisobutylaluminum hydride, and conversion of the resulting alcohol into an iodide. Lithiation of iodide **45** followed by reaction with aldehyde **46** gave a 1:1 mixture of alcohols, which were oxidized to give a ketone that was converted into olefin **47** under Petasis's conditions.[29] After reductive removal of the triisopropysilyl and benzyl groups, the resulting diol was treated with *N*-bromosuccinimide to give a bromotetrahydrofuran that was subsequently converted into enol ether **48**. A modified procedure, first developed by Ley,[30] was used to carry out the key oxocarbenium ion-mediated alkylation of segments **43** and **48** to give compound **49**. Deprotection of the coupled product **49** and subsequent Yamaguchi macrolactonization gave the macrolactone, which upon reductive unmasking of the bromoether gave amphidinolide T1.

(+)-Jasplakinolide

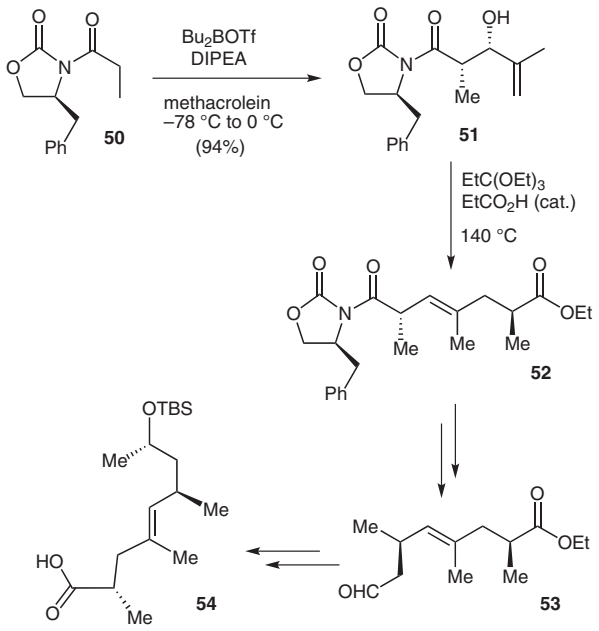
Jasplakinolide (**6**), a 19-membered cyclic depsipeptide, has attracted the attention of many synthesis groups since its isolation from the Fijian marine sponge *Jaspis splendens* in 1986.[31] Jasplakinolide has shown excellent antitumor activity,[32] and was a candidate for clinical development until this was stopped as a result of the compound's toxicity.[33] A number of syntheses of jasplakinolide have been reported.[34] We recently reported a convergent synthesis of this molecule. The polypropionic acid segment was synthesized by using an aldol reaction followed by a Claisen rearrangement as the key steps.[35]

The initial C2-stereocenter was created by an Evans *syn*-aldol reaction, as shown in Scheme 7.[1] The boron-enolate of oxazolidinone **50** was treated with methacrolein at –78 °C to 0 °C to give the aldol condensation product **51** in 94% yield. Allylic alcohol **51** was heated in 1,1,1-triethoxypropane at 140 °C in the presence of a catalytic amount of propionic acid to yield the Claisen rearrangement product, ester **52**.[36] Hydrolysis of the oxazolidinone afforded a primary hydroxy group that was converted into a nitrile group through a Mitsunobu reaction using acetone cyanohydrin. The resulting nitrile was reduced with Raney nickel catalyst to give aldehyde **53**. Methyl Grignard addition to aldehyde **53**, silylation, and ester hydrolysis gave acid **54**. The mixture of diastereomers resulting from the Grignard reaction was readily separated, and the undesired diastereomer was converted into the desired alcohol by a two-step procedure.

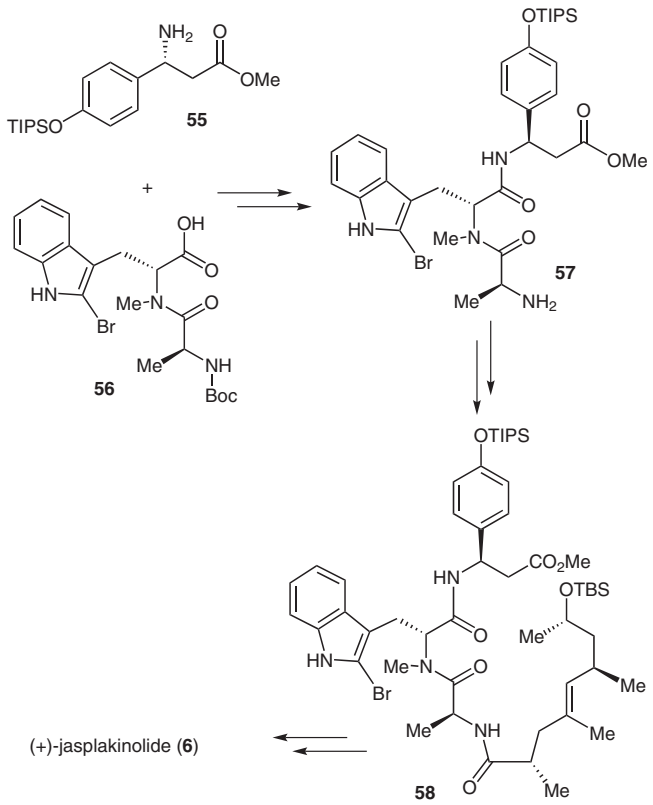
The β-tyrosine moiety was prepared by using chemistry developed by Davis and co-workers.[37] Coupling of amino ester **55** and acid **56** gave the tripeptide **57** (Scheme 8). Further coupling of acid **54** to tripeptide **57** gave ester **58**. Removal of the *tert*-butyl(dimethyl)silyl protecting group and ester hydrolysis followed by Yamaguchi macrolactonization gave the corresponding macrolactone. Subsequent removal of the phenolic triisopropylsilyl group gave



Scheme 6 Completion of the synthesis of amphidinolide T1; DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine



Scheme 7 Synthesis of protected 8-hydroxynonenoic acid **54**



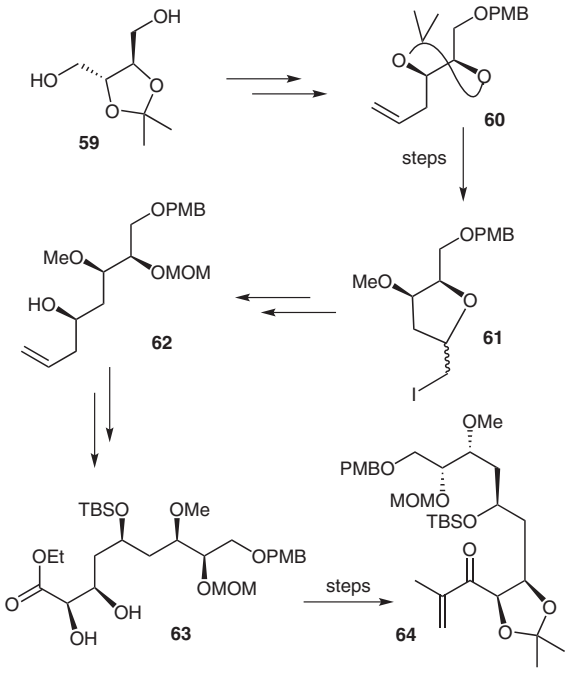
Scheme 8 Completion of (+)-jasplakinolide

synthetic jasplakinolide. Structural modifications with the goal of identifying less toxic and more potent derivatives are currently in progress in our laboratory.

Peloruside A

The microtubule-stabilizing agent peloruside A (**7**) was isolated from the marine sponge *Mycale hentscheli* in 2000.[38] Like laulimalide, peloruside A shows a synergistic effect with taxol, arresting cells undergoing mitosis in the G2-phase by binding to a nontaxoid region of tubulin.[39] Peloruside A represents a new class of antitumor agents, and it has shown excellent potency against P388 murine leukemia cells (IC_{50} = 10 nM).[40] The potency, intriguing structure, and potential clinical applications have attracted much interest. Two total syntheses[41] and several synthetic studies on peloruside have been published.[42,43] We have reported a convergent synthesis of peloruside A that featured a novel aldol reaction mediated by L-Selectride [lithium tri(*sec*-butyl)borohydride] as one of the key steps.[5]

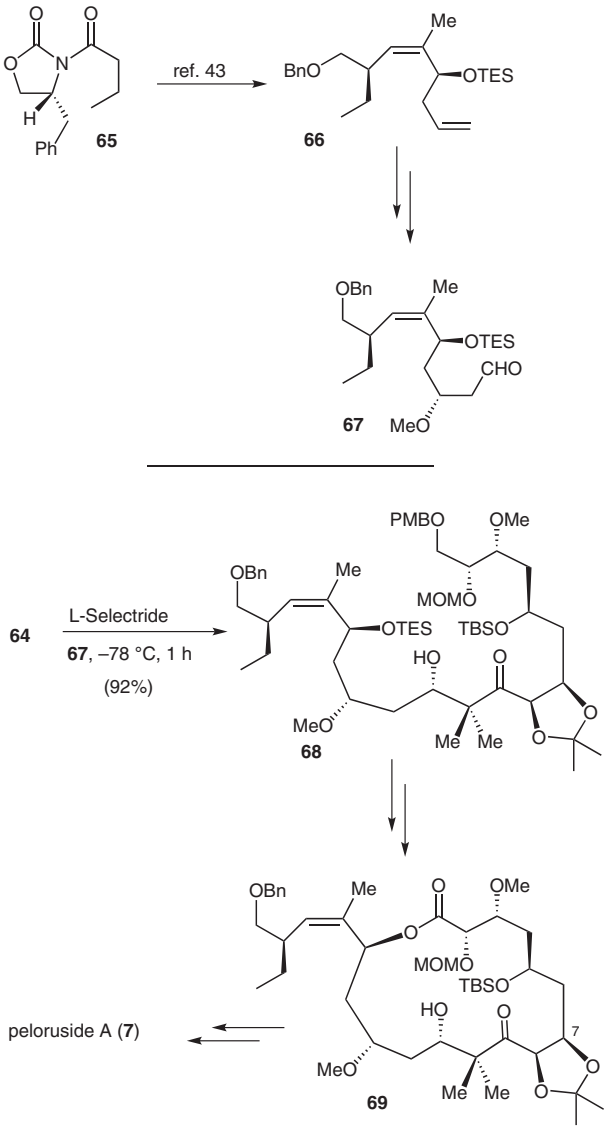
The synthesis of the C1–C10 segment is shown in Scheme 9. Commercially available isopropylidene-D-threitol (**59**) was converted into the isopropylidene product **60**. Acid-catalyzed removal of the isopropylidene group followed by iodoesterification and subsequent O-methylation gave iodide **61**. This was then converted into an aldehyde, which in turn was subjected to Brown's asymmetric allylation to give alcohol **62**.[44] Alcohol **62** was converted into diol **63** by using an Ando *Z*-olefination[45] and a Sharpless asymmetric dihydroxylation[46] as the key steps. The diol was then converted into enone **64** by standard synthetic steps.



Scheme 9 Synthesis of peloruside A intermediate **64**

The completion of the synthesis of peloruside A is shown in Scheme 10. The protected homoallylic alcohol **66** was generated from chiral imide **65**.[43] The terminal olefin was oxidized and exposed to asymmetric allylation conditions to give a 5:1 mixture of diastereomers. The resulting alcohol was converted into a methyl ether, and oxidative cleavage of the terminal alkene gave aldehyde **67**. Treatment of enone **64** with L-Selectride at –78 °C for 10 minutes, followed by addition of aldehyde **67**, gave aldol

adduct **68** as a 4:1 mixture of diastereomers in 92% yield. We recently investigated the scope of this reaction for a variety of chiral and achiral enones and aldehydes. Our exploration of this reductive aldol strategy showed that several representative aldol adducts can be prepared in good yield and high diastereoselectivity when the reactant aldehyde contains an α-chiral center.[4] The synthesis of peloruside A was carried out by removal of the *p*-methoxybenzyl protecting group and oxidation of the primary alcohol to the corresponding acid, followed by Yamaguchi lactonization to provide macrolactone **69**. This was then converted into (+)-peluroside A.

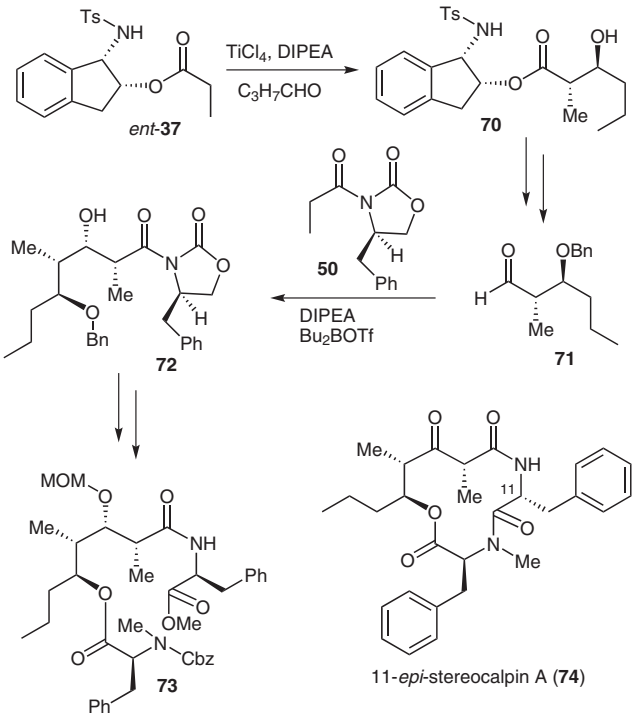


Scheme 10 Synthesis of intermediate **67** and completion of the synthesis of peloruside A

Stereocalpin A

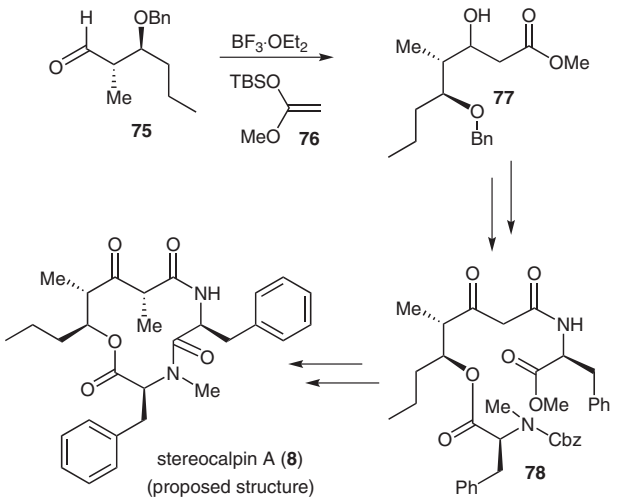
The antitumor depsipeptide stereocalpin A (**8**) was isolated from the dry lichen *Ramalina terebrata* in 2008.[47] This 12-membered cycloamide shows good activity against human colon, skin, and liver solid tumor cell lines. In addition, stereocalpin displays protein tyrosine phosphatase 1B (PTP1B) inhibitory activity.[47] We recently carried out a 14-step synthesis of the proposed structure of stereocalpin A, which involved *syn*- and *anti*-aldol reactions as key steps.[48]

As shown in Scheme 11, in a titanium tetrachloride-promoted *anti*-aldol reaction, the 1-(tosylamino)indan-2-ol ester *ent*-**37** and *N*,*N*-diisopropylethylamine were added to a mixture of butanal (2 equiv), titanium tetrachloride (2 equiv), and acetonitrile (2 equiv) at –78 °C to give *anti*-aldol adduct **70** in 65% yield and excellent diastereoselectivity (37:1 by ^{1}H NMR and ^{13}C NMR spectroscopy). Benzyl protection of aldol adduct **70** followed by lithium aluminum hydride reduction and subsequent oxidation of the resulting alcohol gave aldehyde **71**. The C2- and C3-stereocenters were installed by using an Evans *syn*-aldol procedure.[1] The reaction between the chiral oxazolidinone **50** and aldehyde **71** in *N*,*N*-diisopropylethylamine containing dibutylboryl triflate gave the aldol product **72** in 89% yield (7:1 dr). Aldol product **72** was protected as a methoxymethyl ether, and the chiral auxiliary was removed. The resulting acid was coupled with L-phenylalanine and then esterified with *N*-benzyloxycarbonyl-*N*-methylphenylalanine. This provided the protected amino ester **73**. Interestingly, initial attempts at macrolactamization resulted in complete epimerization at the C11 stereocenter. Other coupling reagents, including *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate and (benzotriazole-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, gave the same epimerized product. To overcome the steric constraints of the 12-membered ring, our strategy was altered to generate the ketone at C3 and install the C2-methyl group after macrolactamization.



Scheme 11 Synthesis of 11-*epi*-stereocalpin A

As shown in Scheme 12, aldehyde **75** was subjected to a Mukaiyama aldol protocol using ketene acetal **76** to give aldol product **77** in 72% yield (5:1 dr).[2,49] Hydrolysis of methyl ester **77** followed by ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide-mediated coupling with L-phenylalanine and subsequent oxidation gave the desired keto amide. Benzyl deprotection and esterification with *N*-benzyloxycarbonyl-*N*-methyl-L-phenylalanine gave ester **78**. This was converted into the corresponding cycloamide in 47% yield, along with 10% of the epimerized product. Methylation from the less-hindered face using cesium carbonate and methyl iodide completed the synthesis of the compound with the proposed structure of stereocalpin A; however, our spectral data for the synthetic stereocalpin did not match those for natural stereocalpin, which led us to believe that the absolute stereochemistry of stereocalpin had been assigned incorrectly.[47]



Scheme 12 Synthesis of the compound with the proposed structure of stereocalpin A

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol Ligand

The development and FDA approval of the first protease inhibitors (PIs) in 1996 marked a new era of HIV/AIDS management. HAART (highly active antiretroviral therapy) drug combinations containing PIs arrested the progression of HIV/AIDS by reducing the viral load and increasing the CD_4^+ lymphocyte cell count in HIV/AIDS patients.[50] Gaining the upper hand in the battle against HIV/AIDS proved bittersweet, as it became apparent that these potent first-generation PIs had several drawbacks, including high toxicity and related side-effects, high therapeutic doses, and expensive treatment costs. The emergence of multi-drug-resistant HIV-1 variants also became a major problem. Drug-resistant HIV is responsible for nearly 40–50% of patients who have previously shown viral suppression to undetectable levels, to rapidly experience treatment failure.[51] In addition, resistant HIV-1 strains have probably been transmitted, as 20–40% of previously untreated HIV-infected individuals have shown continued viral replication despite HAART treatment regimens.

Recently, through a structure-based approach, we have designed a series of exceedingly potent nonpeptidyl HIV PIs.[52] One inhibitor, TMC114 (**79**; Daranuvir) has been approved by the FDA for the treatment of drug-resistant HIV.[53] A key feature of these potent inhibitors is the incorporation of a stereochemically defined bis-THF as the P2-ligand. This ligand was designed to maintain backbone hydrogen-bonding interactions at the active site of the protease. Another inhibitor, GW0385 (**80**, Brecanavir), which also contains the bis-THF ligand, has undergone phase II clinical trials.[54]

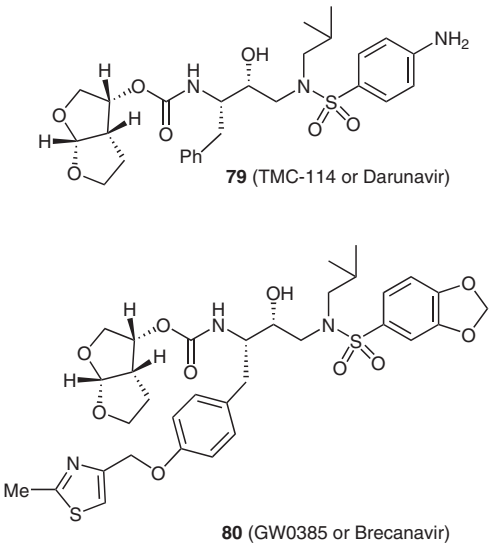
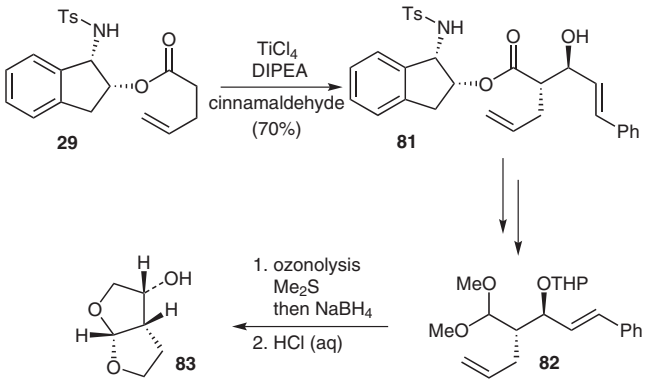


Figure 2 Structure of protease inhibitors **79** and **80**

We have developed a number of synthetic routes for preparing the key bistetrahydrofuran ligand in an optically active form. Our previous method using diethyl (3*R*)-malate as a key starting material was overall not very efficient. We subsequently developed a procedure that required a lipase-catalyzed enzymatic resolution; this, however, resulted in optical purity in the range 92–96% ee.[55] Synthesis of the ligand by means of a diastereoselective Michael addition reaction has been recently reported by Quaedflieg and co-workers.[56] To obtain the bistetrahydrofuran ligand efficiently and in high optical purity, we carried out a synthesis using a titanium-enolate based *anti*-aldol reaction as the key step.[6]

As shown in Scheme 13, aldol condensation product **81** was obtained in 70% yield and a 96:4 *anti*/*syn* ratio by the reaction of ester **29** with cinnamaldehyde. Subsequent manipulations of the aldolate, including protection, reduction, Swern oxidation of the alcohol, and protection of the resulting aldehyde gave the methyl acetal **82**. Ozonolysis of **82**, followed by reduction of the resulting aldehydes, gave the corresponding diol. This diol was treated with aqueous hydrochloric acid, which resulted in deprotection and acid-catalyzed cyclization to provide the desired ligand **83** with a very high optical purity (>99% ee Mosher ester analysis).



Scheme 13 Synthesis of a bistetrahydrofuran ligand

In conclusion, the expansion of aldol methodologies has contributed significantly to advancing the synthesis of natural products. Our titanium enolate mediated *syn*- and *anti*-aldol strategies have been a cornerstone of our syntheses of β-hydroxy α-alkyl carbonyl derivatives. We have incorporated this strategy into an efficient synthesis of an optically pure form of the bistetrahydrofuran ligand, which is a crucial component of potent HIV protease inhibitors. We have also used Evans aldol reactions in the syntheses of a number of natural products. Furthermore, we have recently developed a novel L-Selectride-mediated reductive aldol reaction and have demonstrated its usefulness by synthesizing the anticancer natural product peloruside A.

Natural products will continue to stimulate scientists in all disciplines. These natural masterpieces have been, and will continue to be, mirrored through the art of organic synthesis. The struggles and achievements on the path to the synthesis of bioactive natural products will continue to enrich the ever-expanding tapestry of chemical methodologies.

Example of an Evans *syn*-Aldol Reaction: (4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*S*)-5-(benzyloxy)-3-hydroxy-2,4-dimethyloctanoyl]-1,3-oxazolidin-2-one (72)

A 1 M soln of Bu_2BOTf in CH_2Cl_2 (8.5 mL, 8.5 mmol) and DIPEA (1.6 mL, 9.3 mmol) were added sequentially to a soln of (4*R*)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one (**50**; 1.81 g, 7.74 mmol) in CH_2Cl_2 (30 mL), and the clear soln was stirred at 0 °C for 30 min then cooled to –78 °C. A soln of aldehyde **71** (1.32 g, 5.96 mmol) in CH_2Cl_2 (10 mL) was then slowly added by syringe. The aldehyde flask was washed with CH_2Cl_2 (5 mL) and the remaining soln was also added to the enolate soln. The mixture was stirred at –78 °C for 10 min then warmed to 0 °C over 1 h. The reaction was quenched with pH 7 buffer (10 mL) and MeOH (15 mL). A 30% soln of H_2O_2 (10 mL) and MeOH (20 mL) were slowly added while the internal temperature was kept below 5 °C. The mixture was stirred at 0 °C for an additional 1 h then diluted with CH_2Cl_2 (40 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, hexanes–EtOAc, 85:15); yield: 2.45 g (89%).

Example of a Titanium Enolate *syn*-Aldol Reaction: (1*S*,2*R*)-1-(Tosylamino)indan-2-yl (2*S*,3*R*)-4-(Benzyloxy)-3-hydroxy-2-methylbutanoate (44)

Neat $TiCl_4$ (1.47 mL, 13.4 mmol) and DIPEA (7.75 mL, 44.5 mmol) were added to a soln of propionate *ent*-**37** (4.0 g, 11.1 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The resulting soln was warmed to 23 °C, stirred for 2 h, and then cooled to –78 °C. A mixture of $TiCl_4$ (3.68 mL, 33.4 mmol) and $BzOCH_2CHO$ (3.13 mL, 22.3 mmol) in CH_2Cl_2 (20 mL) was slowly added, and the dark soln was stirred for 2 h at –78 °C. The reaction was quenched with sat. aq NH_4Cl, and the mixture was warmed to 23 °C. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a brown residue that was purified by column chromatography to provide the pure product; yield: 5.27 g (93%).

Examples of Titanium Enolate *anti*-Aldol Reaction: (1*S*,2*R*)-1-(Tosylamino)indan-2-yl(1*S*,2*R*)-3-Hydroxy-2-methylhexanoate (70)

$TiCl_4$ (4.34 mL, 39.6 mmol, 1.1 equiv) was added dropwise to a soln of propionate *ent*-**37** (12.93 g, 36 mmol) in CH_2Cl_2 (180 mL) at 0 °C and the mixture was stirred at 0 °C for 15 min before DIPEA (23.8 mL, 137 mmol, 3.8 equiv) was added slowly. The dark soln was allowed to warm to 23 °C and stirred at 23 °C for 2 h. In a separate flask, $TiCl_4$ (7.9 mL, 2 equiv) was added slowly to PrCHO (6.5 mL, 72 mmol, 2 equiv) in CH_2Cl_2 (180 mL) at –78 °C, followed by addition of anhyd MeCN (3.8 mL, 2 equiv). The mixture was stirred at –78 °C for 5 min while a white precipitate formed. The soln of the titanium enolate prepared from *ent*-**37** was added to this mixture from a cannula, over 15 min. The resulting dark soln was stirred at –78 °C for 2 h, and then the reaction was quenched with sat. aq NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexanes–EtOAc, 9:1); yield: 10.1 g (65%; 37:1 dr).

(1*S*,2*R*)-1-(Tosylamino)indan-2-yl (3*S*,4*E*)-2-Allyl-3-hydroxy-5-phenylpent-4-enoate (81)

A 1.8 M soln of $TiCl_4$ (13.8 mL, 24.8 mmol) was added dropwise to a stirred soln of pent-4-enoate **29** (7.89 g, 20.5 mmol) in CH_2Cl_2 (210 mL) at 0 °C under an inert atmosphere. The resulting soln was stirred for 5 min and then DIPEA (13.9 mL, 79.7 mmol) was added dropwise. The mixture was allowed to warm to 23 °C and stirred for 2 h. In a separate flask, a 1.8 M soln of $TiCl_4$ in CH_2Cl_2 (11.5 mL, 20.7 mmol) was added dropwise to cinnamaldehyde (5.30 mL, 42 mmol) in CH_2Cl_2 (320 mL) at –78 °C, and the soln was stirred for 5 min at –78 °C. DIPEA (7.3 mL, 41.9 mmol) was then added dropwise and the resulting mixture was stirred for an additional 5 min. The titanium enolate soln prepared from pent-4-enoate **29** was added dropwise through an insulated cannula over 30 min, and the mixture was stirred at –78 °C for 3.5 h. The reaction was quenched with sat. aq NH_4Cl and the mixture was allowed to warm to 23 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a crude aldol product that was purified by chromatography (silica gel, 15% then 20% EtOAc–hexanes) to give diastereomerically pure *anti*-aldol product **81** as a gummy solid; yield: 7.43 g (70%).

Example of an L-Selectride-Mediated Reductive Aldol Reaction: Aldol Product 68

A 1.0 M soln of L-Selectride in THF (1.1 mL, 1.1 mmol) was added to a soln of enone **64** (645 mg, 1.06 mmol) in Et_2O (200 mL) at –78 °C, and the mixture was kept at –78 °C for 10–15 min. A soln of aldehyde **67** (520 mg, 1.2 mmol) in Et_2O (20 mL) was added at –78 °C, and the mixture was stirred at –78 °C for 1 h. The reaction

was quenched with sat. aq NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with H_2O and brine then dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography to give the major isomer **68**; yield: 823 mg (92%; dr 4:1).

References

(1) Evans, D. A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454.
(2) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
(3) (a) Ghosh, A. K.; Kim, J. *Org. Lett.* **2003**, *5*, 1063. (b) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527.
(4) Ghosh, A. K.; Kass, J.; Anderson, D. D.; Xu, X.; Marian, C. *Org. Lett.* **2008**, *21*, 4811.
(5) Ghosh, A. K.; Xu, X.; Kim, J.-H.; Xu, C.-X. *Org. Lett.* **2008**, *10*, 1001.
(6) Ghosh, A. K.; Li, J.-F. *Synthesis* **2006**, 3015.
(7) (a) Kartner, N.; Riordan, J. R.; Ling, V. *Science* **1983**, *221*, 1285. (b) Pastan, I.; Gottesman, M. M. *Annu. Rev. Med.* **1991**, *42*, 277.
(8) Stratmann, K.; Burgoyne, D. L.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Org. Chem.* **1994**, *59*, 7219.
(9) Endicott, J. A.; Ling, V. *Annu. Rev. Biochem.* **1989**, *58*, 137.
(10) Ghosh, A. K.; Liu, W.; Xu, Y.; Chen, Z. *Angew. Chem.,Int. Ed. Engl.* **1996**, *35*, 74.
(11) Ghosh, A. K.; Duong, T. T.; McKee, S. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1673.
(12) Schwarz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M.; Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind. Microbiol.* **1990**, *5*, 113.
(13) Smith, C. D.; Zhang, X.; Mooberry, S. L.; Patterson, G. M. L.; Moore, R. E. *Cancer Res.* **1994**, *54*, 3779.
(14) Ghosh, A. K.; Bischoff, A. *Org. Lett.* **2000**, *2*, 1573.
(15) Ghosh, A. K.; Swanson, L. *J. Org. Chem.* **2003**, *68*, 9823.
(16) (a) Hochuli, E.; Kupfer, E.; Maurer, R.; Meiser, W.; Mercadel, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086. (b) Weibel, E. K.; Hadvary, P.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081.
(17) (a) Borgstrom, B. *Biochem. Biophys. Acta.* **1988**, *962*, 308. (b) Hadvary, P.; Sidler, W.; Meiser, W.; Vetter, W.; Wolfer, H. *J. Biol. Chem* **1991**, *266*, 2021.
(18) Ghosh, A. K.; Fidanze, S. *Org. Lett.* **2000**, *2*, 2405.
(19) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017.
(20) (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Org. Chem.* **1988**, *53*, 3560.
(21) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Agric. Biol. Chem.* **1982**, *46*, 1823.
(22) (a) Shimojima, Y.; Hayashi, H. *J. Med. Chem.* **1983**, *26*, 1370. (b) Shimojima, Y.; Shirai, T.; Baba, T.; Hayashi, H. *J. Med. Chem.* **1985**, *28*, 3.
(23) Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Org. Lett.* **2001**, *3*, 2677.
(24) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1988**, 685. (b) Dondoni, A.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron Lett.* **1985**, *26*, 5477. (c) Dondoni, A.; Perrone, D.; Semola, M. T. *J. Org. Chem.* **1995**, *60*, 7927.
(25) (a) Bertelli, L.; Fiaschi, R.; Napolitano, E. *Gazz. Chim. Ital.* **1993**, *123*, 669. (b) Kotsuki, H.; Miyazaki, A.; Ochi, M. *Chem. Lett.* **1992**, 1255. (c) Superchi, S.; Minutolo, F.; Pini, D.; Salvadori, P. *J. Org. Chem.* **1996**, *61*, 3183.
(26) Kobayashi, J. In *Comprehensive Natural Products Chemistry*, Vol. 8; Barton, D. H. R.; Nakanishi, K.; Meth-Cohn, O., Eds.; Elsevier: New York, **1999**, 619.
(27) Tsuda, M.; Endo, T.; Kobayashi, J. *J. Org. Chem.* **2001**, *66*, 134.
(28) Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc.* **2003**, *125*, 2374.
(29) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6394.
(30) Ley, S. V.; Lygo, B.; Wonnacott, A. *Tetrahedron Lett.* **1989**, *26*, 535.
(31) (a) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797. (b) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3123.
(32) Inman, W.; Crews, P. *J. Am. Chem. Soc.* **1986**, *111*, 2822.
(33) Bubb, M. R.; Senderowicz, A. M. J.; Sausville, E. A.; Duncan, K. L. K.; Korn, E. D. *J. Biol. Chem.* **1994**, *269*, 14869.
(34) (a) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196. (b) Grieco, P. A.; Hon, Y. S. *J. Am. Chem. Soc.* **1988**, *110*, 1630. (c) Hanada, Y.; Shioiri, T. *Tetrahedron Lett.* **2004**, *35*, 591. (d) Hirai, Y.; Yokota, K.; Momose, T. *Heterocycles* **1994**, *39*, 603. (e) Imaeda, T.; Rao, A. V.; Gurjar, M. K.; Nallaganchu, B. R.; Bhandari, A. *Tetrahedron Lett.* **1993**, *34*, 7085.
(35) Ghosh, A. K.; Moon, D. K. *Org. Lett.* **2007**, *9*, 2425.
(36) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.
(37) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037.
(38) West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445.
(39) (a) Pryor, D. E.; O'Brate, A.; Bilcer, G.; Diaz, J. F.; Wang, Y.; Kabaki, M.; Jung, M. K.; Andreu, J. M.; Ghosh, A. K.; Giannakakou, P.; Hamel, E. *Biochemistry* **2002**, *41*, 9109. (b) Gaitanos, T. N.; Buey, R. M.; Diaz, J. F.; Northcote, P. T.; Teesdale-Spittle, P.; Andreu, J. M.; Miller, J. H. *Cancer Res.* **2004**, *64*, 5063.
(40) Hood, K. A.; West, L. M.; Rouwe, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, S. J.; Miller, J. H. *Cancer Res.* **2002**, *62*, 3356.
(41) (a) Jin, M.; Taylor, R. E. *Org. Lett.* **2005**, *7*, 1303. (b) Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem. Int. Ed.* **2003**, *42*, 1648.
(42) (a) Chen, Z.-L.; Zhou, W. S. *Tetrahedron Lett.* **2006**, *47*, 5289. (b) Engers, D. W.; Bassindale, M. J.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 663. (c) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967. (d) Gurjar, M. K.; Pedduri, Y.; Ramana, C. V.; Puranik, V. G.; Gonnade, R. G. *Tetrahedron Lett.* **2004**, *45*, 387. (e) Liu, B.; Zhou, W. S. *Org. Lett.* **2004**, *6*, 71. (f) Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941. (g) Paterson, I.; Di Francesco, M. E.; Kuhn, T. *Org. Lett.* **2003**, *5*, 599. (h) Roulland, E.; Ermolenko, M. S. *Org. Lett.* **2005**, *7*, 2225. (i) Taylor, R. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959.
(43) Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 7659.
(44) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.
(45) Ando, K. J. *J. Org. Chem.* **1998**, *63*, 8411.
(46) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(47) Seo, C.; Kim, J. H.; Lee, H. K.; Park, S. M.; Sohn, J.-H.; Oh, H. *Tetrahedron Lett.* **2008**, *49*, 29.
(48) Ghosh, A. K.; Xu, C.-X. *Org. Lett.* **2009**, *11*, 1963.
(49) (a) Mutou, T.; Suenaga, K.; Fujita, T.; Itoh, T.; Takada, N.; Hayamizu, K.; Kigoshi, H.; Yamada, K. *Synlett* **1997**, 199. (b) Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261. (c) Paterson, I.; Smith, J. D. *Tetrahedron* **1995**, *51*, 9413.

(50) Sepkowiz, K. A. *N. Engl. J. Med.* **2001**, *344*, 1764.
(51) (a) Grabar, S.; Pradier, C.; Le Corfec, E.; Lancar, R.; Allavena, C.; Bentata, M.; Berlureau, P.; Dupont, C.; Fabbro-Peray, P.; Poizot-Martin, I.; Costagliola, D. *AIDS* **2000**, *14*, 141. (b) Pillay, D.; Bhaskaran, K.; Jurriaans, S.; Prins, M.; Masquelier, B.; Dabis, F.; Gifford, R.; Nielsen, C.; Pedersen, C.; Balotta, C.; Rezza, G.; Ortiz, M.; de Mendoza, C.; Kucherer, C.; Poggensee, G.; Gill, J.; Porter, K. *AIDS* **2006**, *20*, 21. (c) Wainberg, M. A.; Friedland, G. *J. Am. Med. Assoc.* **1998**, *279*, 1977.
(52) (a) Ghosh, A. K.; Shin, D. W.; Swanson, L.; Krishnan, K.; Cho, H.; Hussain, K. A.; Walters, D. E.; Holland, L.; Buthod, J. *Farmaco* **2001**, *56*, 29. (b) Ghosh, A. K.; Kincaid, J. F.; Cho, W.; Walters, D. E.; Krishnan, K.; Hussain, K. A.; Koo, Y.; Cho, H.; Rudall, C.; Holland, L.; Buthod, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 687. (c) Koh, Y.; Nakata, H.; Maeda, K.; Ogata, H.; Bilcer, G.; Devasamudram, T.; Kincaid, J. F.; Boross, P.; Wang, Y.-F.; Tie, Y.; Volarath, P.; Gaddis, L.; Harrison, R. W.; Weber, I. T.; Ghosh, A. K.; Mitsuya, H. *Antimicrob. Agents Chemother.* **2003**, *47*, 3123. (d) Yoshimura, K.; Kato, R.; Kavlick, M. F.; Nguyen, A.; Maroun, V.; Maeda, K.; Hussain, K. A.; Ghosh, A. K.; Gulnik, S. V.; Erickson, J. W.; Mitsuya, H. *J. Virol.* **2002**, *26*, 1349.
(53) Darunavir received FDA approval on June 23, 2006: see http://www.fda.gov/bbs/topics/NEWS/2006NEW01395.html
(54) Miller, J. F.; Andrews, C. W.; Brieger, M.; Furfine, E. S.; Hale, M. R.; Hanlon, M. H.; Hazen, R. J.; Kaldor, I.; McLean, E. W.; Reynolds, D.; Sammond, D. M.; Spaltenstein, A.; Tung, R.; Turner, E. M.; Xu, R. X.; Sherrill, R. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1788.
(55) (a) Ghosh, A. K.; Kincaid, J. F.; Walters, D. E.; Chen, Y.; Chaudhuri, N. C.; Thompson, W. J.; Culberson, C.; Fitzgerald, P. M. D.; Lee, H. Y.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Darke, P. L.; Zugay, J. A.; Schleif, W. A.; Axel, M. G.; Lin, J.; Huff, J. R. *J. Med. Chem.* **1996**, *39*, 3278. (b) Ghosh, A. K.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 505. (c) Ghosh, A. K.; Leshchenko, S.; Noetzel, M. J. *J. Org. Chem.* **2004**, *69*, 7822.
(56) Quaedflieg, P. J. L. M.; Kesteleyn, B. R. R.; Wigerinck, P. B. T. P.; Goyvaerts, N. M. F.; Vijn, R. J.; Liebregts, C. S. M.; Kooistra, J. H. M. H.; Cusan, C. *Org. Lett.* **2005**, *7*, 5917.