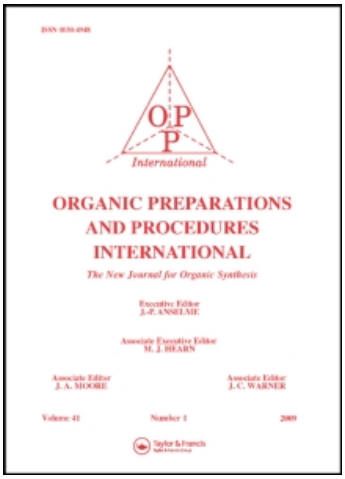

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Syntheses of the Crocacins. A Review

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Introduction and Background of the Crocacins

This review covers the total and formal syntheses of crocacins A-D, a family of biologically active polyketide-derived natural products, reported in the period of 2000–2008. The organization of the review is as follows: total syntheses of each natural product will be discussed first, beginning with the simplest congener crocacin C, followed by formal syntheses. The order of approaches presented is chronological.

In 1994, Jansen and co-workers reported the isolation and structure determination of a group of electron transport inhibitors from the myxobacterium *Chondromyces crocatus* possessing moderate inhibition of Gram-positive bacterial growth, in addition to antifungal and cytotoxic activity.[1] In 1999, they disclosed the relative stereochemistry of parent crocacin C (**1**) and its congeners crocacins A (**2**), B (**3**) and D (**4**) (*Figure 1*).[2]

Recently, the crocacins have been identified as novel agricultural pesticide leads.[3] By inspection, crocacin C (**1**) is composed of a polyketide fragment possessing the challenging *anti-anti-syn* stereotetrad (C16-C19) in addition to a conjugated (*E*,*E*)-dienamide system (C11-C15). Crocacins A (**2**), B (**3**) and D (**4**) are further characterized by an acid-sensitive (*Z*)-*N*-acylenamine motif (C7-C11) tethered to a glycine residue. These structural features coupled with an interesting bioactivity profile have made these natural products attractive targets for synthesis.

I. Total Syntheses of Crocacin C

1. Rizzacasa's Approaches

The first enantioselective total synthesis of (+)-crocacin C was reported in 2000 by Rizzacasa's group (*Scheme 1*).[4] The synthesis commenced with the application of Paterson's dipropionate synthon **5**,[5] which is prepared in three steps from the commercially available Roche ester [Methyl (*S*)-(+)-3-hydroxy-2-methylpropionate].[6] In such a strategy, the homochiral methyl from the propionate reagent **5** enables high π-facial selectivity in the

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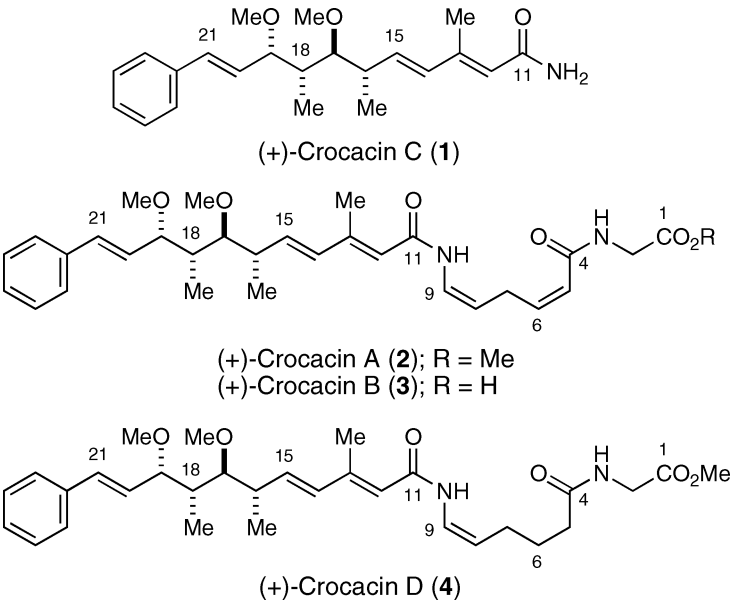


Figure 1
Structures of Crocacins A-D.

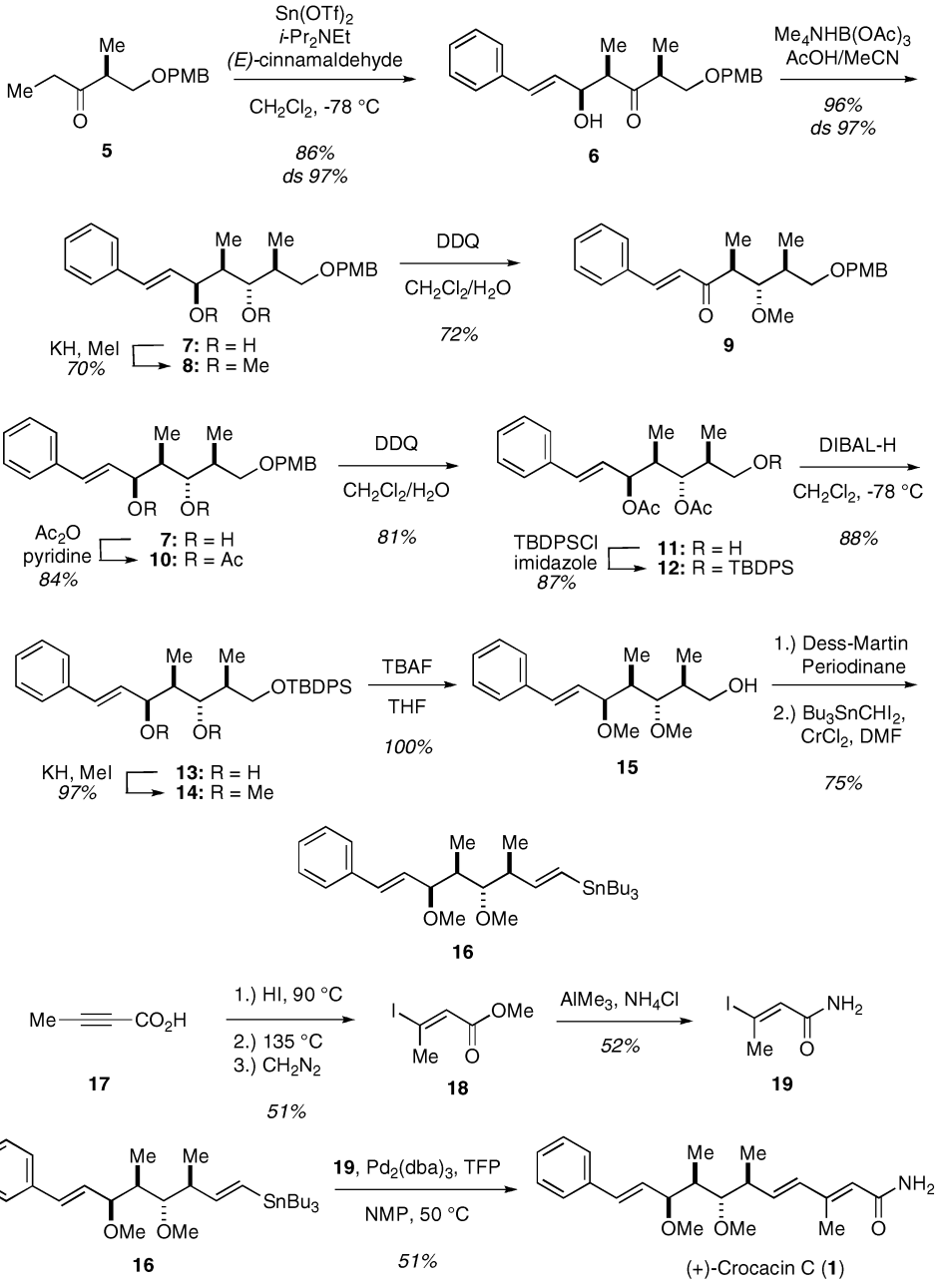
Sn(II) *syn*-aldol manifold and becomes incorporated into the target molecule (*i. e.*, C-16 methyl). The C-18 methyl is derived from the ethyl ketone.

The Sn(II) aldol reaction between ethylketone **5** and (*E*)-cinnamaldehyde furnished *syn*-aldol **6** in 86% yield (97% ds). Substrate-based *anti*-selective hydride delivery was accomplished with $Me_4NHB(OAc)_3$ to access the 1,3-*anti* diol and concisely prepare the challenging *anti-anti-syn* stereotetrad.[7] The relative stereochemistry of the reduction was confirmed by ^{13}C analysis of the acetonide derived from **7**.[8,9]

Methylation of both hydroxy groups (KH, MeI) in **7** delivered **8**. At this point, removal of the *p*-methoxybenzyl (PMB) ether with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was complicated by the unwanted oxidation of the electron-rich allylic ether at C-19 to the enone **9** in 72% yield. To solve this problem, electronically deactivating protecting groups were recruited. In the event, acetylation of diol **7** (Ac_2O, pyridine) furnished diacetate **10** that when treated with DDQ successfully delivered alcohol **11** in 81% yield.

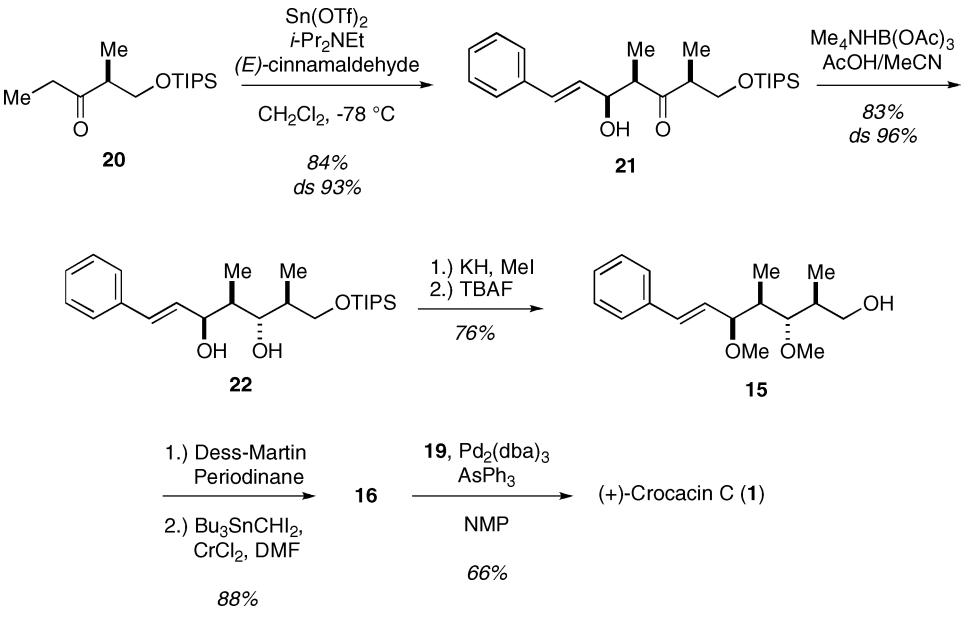
Protection of the primary alcohol as its *tert*-butyldimethylsilyl (TBDMS) ether, reductive removal of the acetates with diisobutylaluminum hydride (DIBAL-H), and methylation of the resulting diol **13** (KH, MeI) provided intermediate **14**. Removal of the silyl-protecting group with tetrabutylammonium fluoride (TBAF) quantitatively furnished alcohol **15**. Oxidation with the Dess-Martin Periodinane[10] and application of Hodgson's Cr-mediated vinylstannation[11,12] delivered **16**, thus completing the synthesis of C14-C21 fragment of the molecule.

The C11-C14 fragment commenced with tetrolic acid (**17**). The addition of HI gave initially mostly the (*Z*)-acid, which upon heating to 135°C for 16 h isomerized to a 70:30 mixture of *E:Z* isomers, respectively.[13] Methylation with diazomethane and chromatographic separation yielded known ester **18**.[14] Weinreb amidation delivered **19**.[15]



Scheme 1
Rizzacasa's 1st Generation Synthesis of (+)-Crocacin C

The synthesis of (+)-crocacin C (**1**) was accomplished by a Stille coupling[16,17] wherein vinylstannane **16** and iodide **19** were heated in *N*-methyl-2-pyrrolidone (NMP) at 50°C with catalytic Pd_2dba_3 and trifurylphosphine (TFP), which proceeded in 51% yield. Due to problems associated with the PMB protecting group and the need for a streamlined route to



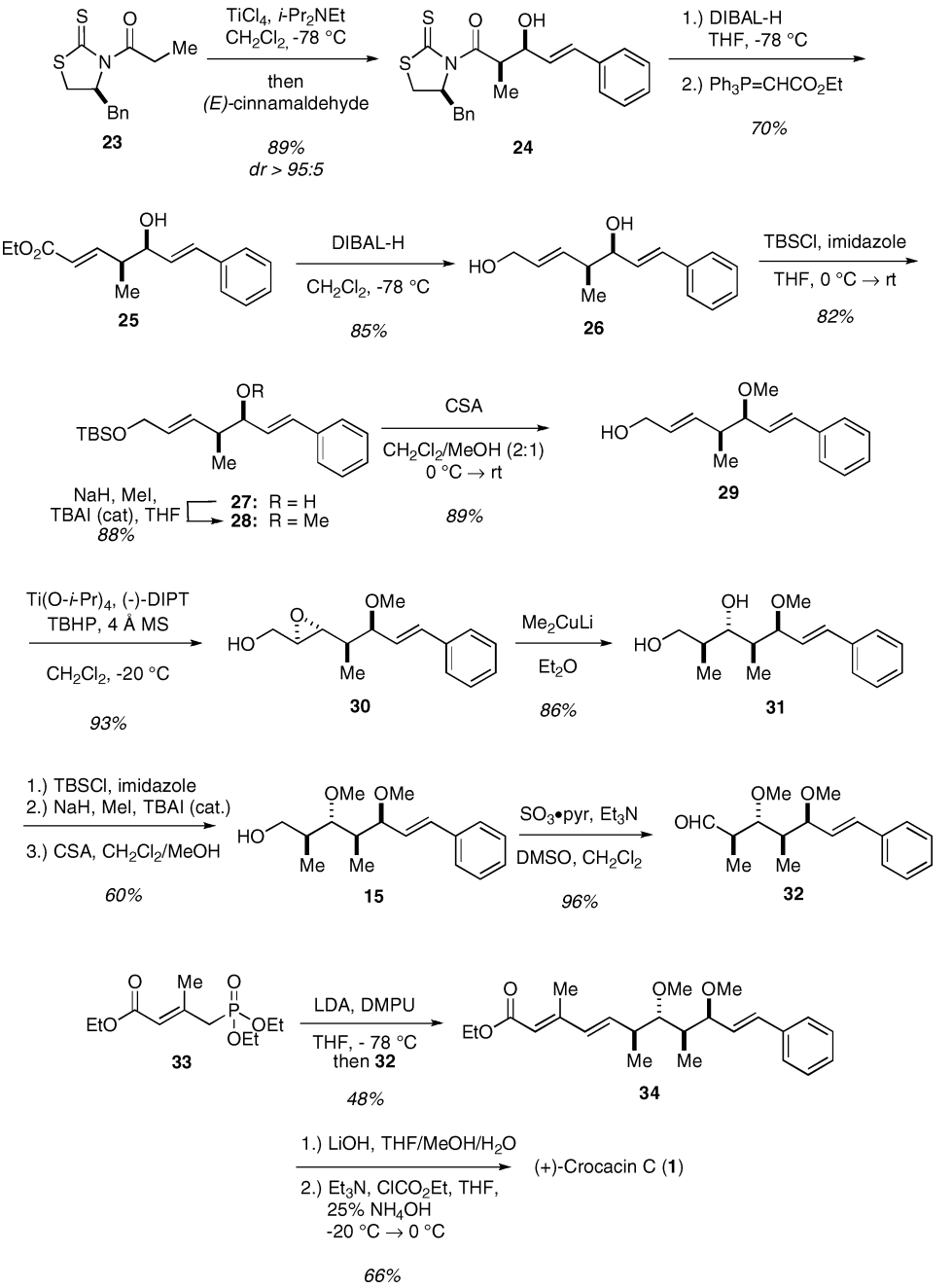
Scheme 2
Rizzacasa's 2nd Generation Synthesis of (+)-Crocacin C (**1**)

advanced material for the synthesis of the crocacins, recourse to the triisopropylsilyl (TIPS) protecting group was made (*Scheme 2*).[4,18] In the Sn(II)-mediated aldol reaction, ethylketone **20** and (*E*)-cinnamaldehyde delivered *syn*-aldol **21** in 84% yield (93% ds). *Anti*-reduction (83% yield, 96% ds), methylation, and TBAF-mediated desilylation (76% for both steps) afforded alcohol **15**, which was transformed into stannane **16** utilized in the 1st generation approach. The coupling of **16** and **19** was optimized by exchanging the ligands on palladium (*i. e.*, trifurylphosphine to triphenylarsine),[19] delivering **1** in 66% yield.

2. Chakraborty's Approach

The asymmetric synthesis of **1** by Chakraborty quickly followed Rizzacasa's (*Scheme 3*).[20] Chakraborty began with a Crimmins aldol reaction[21] between *N*-acylthiazolidinethione **23** and (*E*)-cinnamaldehyde to set the first two stereocenters in **24** (89%, *dr* > *95:5*). Reductive removal of the auxiliary with DIBAL-H and a Wittig olefination furnished enoate **25** in 70% yield. Further reduction of the enoate yielded diol **26** (85%). Regioselective protection of the primary alcohol as its TBS ether **27** (89%) enabled methylation of the remaining secondary alcohol to access **28** (88%).

Removal of the silyl ether (89%) with camphorsulfonic acid (CSA) set the stage for a Sharpless asymmetric epoxidation, which proceeded in 93% yield to produce epoxy alcohol **30**[22] as a single diastereomer. Regioselective ring-opening with Me_2CuLi gave mostly 1,3-diol **31** in 86% yield. Reiteration of the three-step diol differentiation protocol utilized before (regioselective silylation, methylation, desilylation) furnished alcohol **15** in 60% overall yield.



Scheme 3
Chakraborty's Synthesis of (+)-Crocacin C (**1**)

Parikh-Doering oxidation[23] of **15** delivered aldehyde **32**, which set the stage for the key vinylogous Horner-Wadsworth-Emmons reaction[24] with known phosphonate **33**.[25] In the event, deprotonation of **33** with LDA and DMPU followed by the addition of aldehyde **32** at -78°C afforded the *E,E* dienoate **34** in 48% isolated yield. Saponification with LiOH,

activation of the resulting acid with isobutyl chloroformate and amidation with ammonium hydroxide delivered **1** in 66%, thus completing their total synthesis.

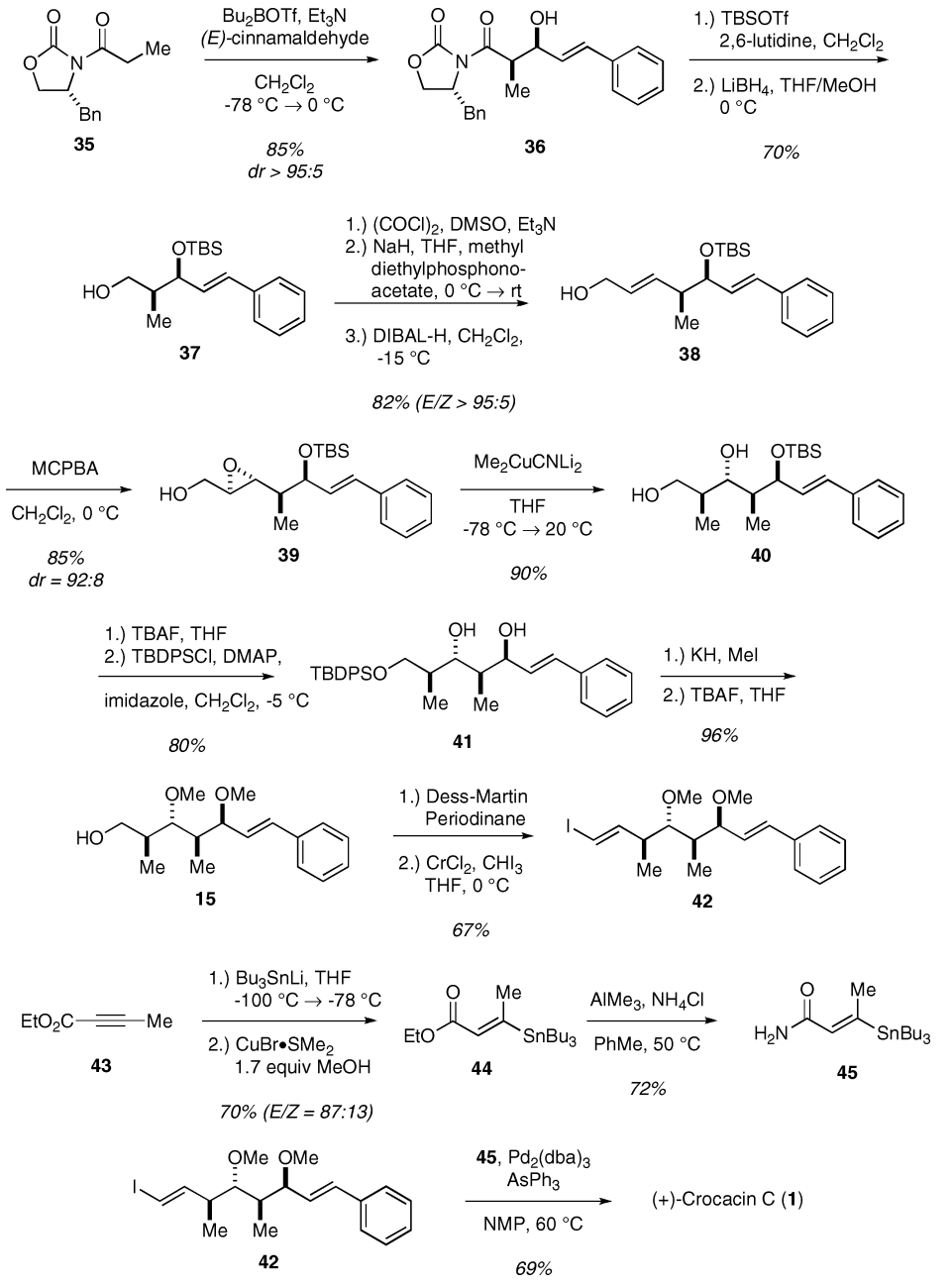
3. Dias's Approach

The synthesis of **1** by the Dias group shortly followed and began with an Evans aldol reaction between commercially available *N*-propionyl oxazolidinone **35** and (*E*)-cinnamaldehyde to access aldol **36** in 85% yield (*dr > 95:5*).[26] Silylation and reductive removal of the auxiliary with $LiBH_4$ afforded alcohol **37** in 70% overall yield. Homologation by the three-step sequence (Swern oxidation,[27,28] Horner-Wadsworth-Emmons olefination,[24] reduction) delivered allylic alcohol **38** in 82% overall yield (*Scheme 4*). Oxidation of **38** with MCPBA proceeded with high regio- and diastereoselectivity (*dr = 92:8*) to furnish *anti*-epoxy alcohol **39** in 94% yield. Ring-opening with $Me_2CuCNLi_2$ yielded diol **40** thus securing the *anti-anti-syn* stereotetrad of target **1**.[29] Removal of the TBS ether with TBAF yielded a triol, which was treated with TBDPSCl to selectively protect the primary alcohol and furnish **41**. Carbon-13 NMR analysis of acetonides derived from both **40** and **41** confirmed the 1,3-*anti* relative stereochemistry.[8] Methylation of both secondary alcohols (KH, MeI) followed by desilylation with TBAF afforded alcohol **15**, converging on an intermediate previously prepared by both Rizzacasa and Chakraborty.

Endgame began with oxidation of **15** and Takai olefination (CHI_3, $CrCl_2$) to afford vinyl iodide **42** (67% over two steps).[30] To forge the dienoate portion of crocacin C (**1**), methodology by Piers[31] was recruited. Ethyl 2-butynoate (**43**) was treated with Bu_3SnLi and $CuBr{\cdot}Me_2S$ to afford vinyl stannane **44** (70% yield, *E/Z* = 87:13). Amidation of **44** under the agency of $AlMe_3$ furnished amide **45** in 72% yield. Stille coupling of vinyl iodide **42** and vinyl stannane **45** in the presence of catalytic Pd_2dba_3 and $AsPh_3$ in NMP at 60°C delivered (+)-crocacin C (**1**) in 69% yield.[16]

4. Andrade's Approach

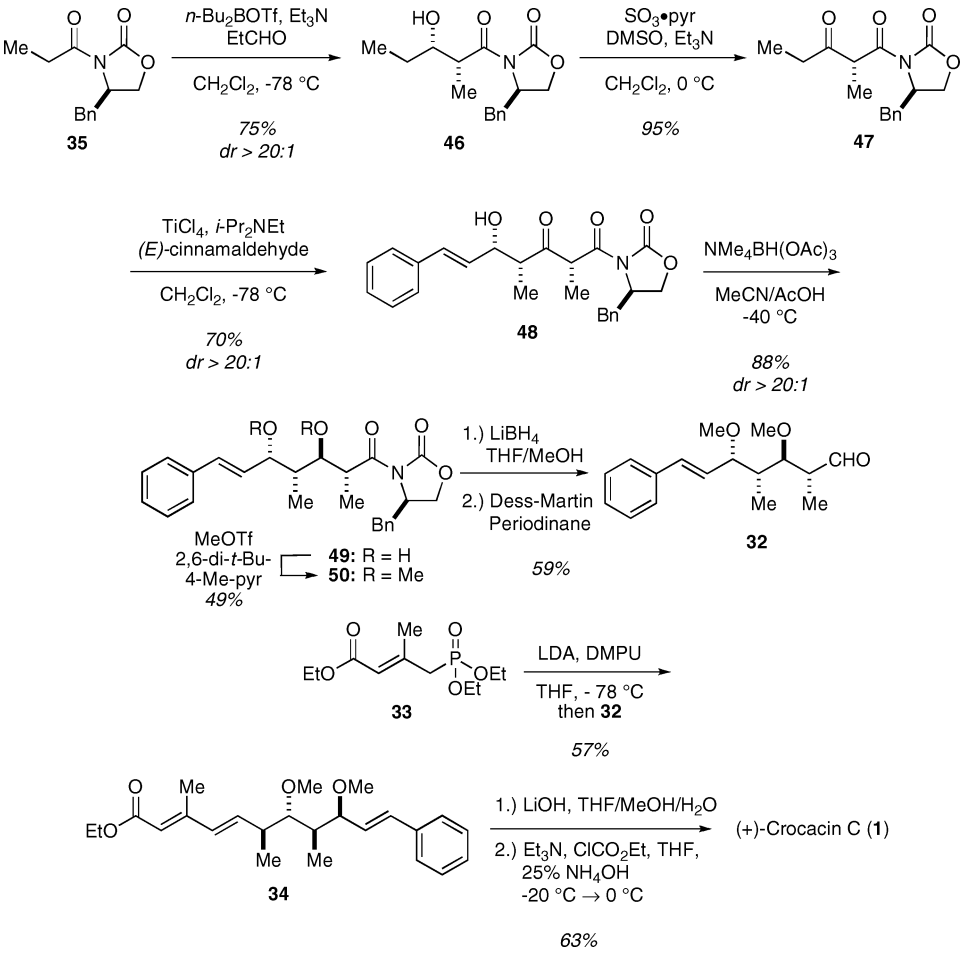
The β-keto imide dipropionate methodology[32] developed by Evans in the early 1990s was recruited by Andrade in his synthesis of **1** (*Scheme 5*).[33] Commercially available propionimide **35** was transformed into the dipropionate synthon **47** in two steps (71% overall yield).[34] Treatment of the titanium enolate of **47** with (*E*)-cinnamaldehyde furnished aldol **48** in 70% (*dr > 20:1*). Substrate-directed *anti*-selective hydride reduction with $Me_4NBH(OAc)_3$ secured diol **49** in 88% (*dr > 20:1*).[7] At this point, various methylation protocols were screened with MeOTf in the presence of 2,6-di-*t*-butyl-4-methylpyridine providing **50** in highest yield (49%).[35] Reductive removal of the auxiliary with $LiBH_4$ and subsequent oxidation using the Dess-Martin Periodinane[10] furnished known aldehyde **32** (59% for two steps). The remainder of the synthesis followed Chakraborty's endgame, which featured a vinylogous Horner-Wadsworth-Emmons olefination[24] to install the diene portion of **1**.[20] Functional group manipulation delivered the target. Andrade's synthesis of **1** was accomplished in 10 steps from commercially available imide **35** (5% overall yield) and avoided protecting groups altogether.



Scheme 4
Dias's Synthesis of (+)-Crocacin C (**1**)

5. Burke's Approach

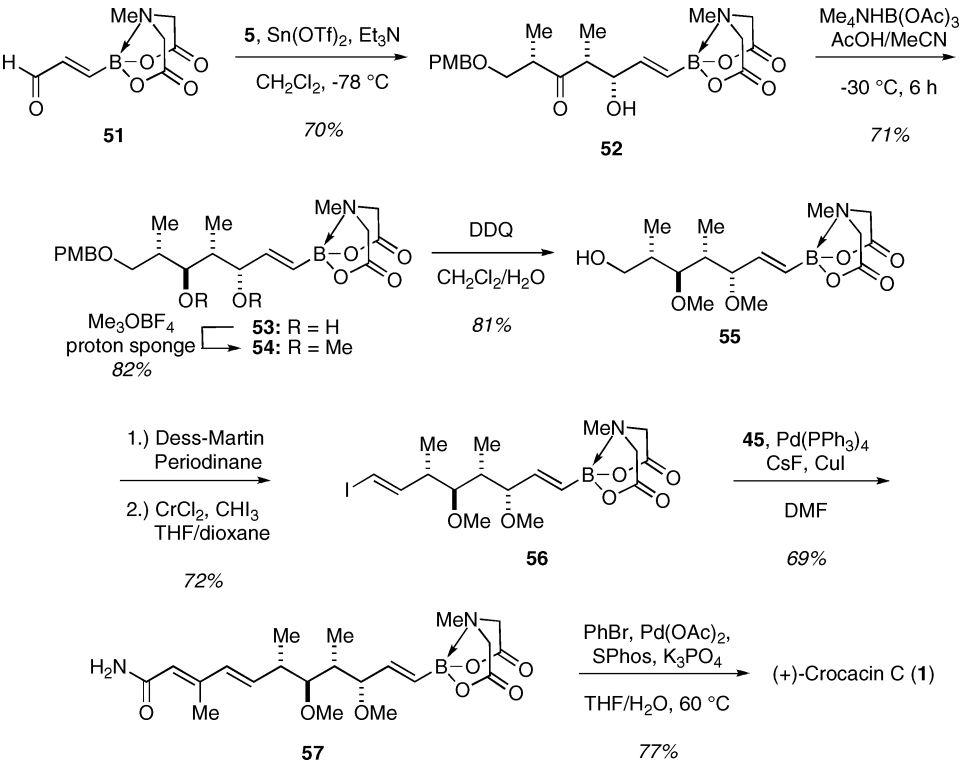
Burke has pioneered the use of *N*-methyliminodiacetic acid (MIDA) boronates as robust vinylboronic acid surrogates.[36] These compounds are bench stable, can withstand a wide range of reaction conditions, and can be purified by standard silica gel chromatography.



Scheme 5
Andrade's Synthesis of (+)-Crocacin C (**1**)

To demonstrate their feasibility in natural product synthesis, the Burke lab employed these MIDA boronates for the synthesis of **1** (*Scheme 6*).[37]

The first portion of the synthesis follows the Rizzacasa protocol.[4] A Paterson aldol reaction with **5** furnished aldol **52** in 70% yield. Selective *anti* reduction furnished diol **53** in 71% yield. Alkylation of both hydroxyls with Meerwein's salt and proton sponge provided intermediate **54** in 82% yield. Removal of the PMB ether with DDQ, oxidation with the Dess-Martin Periodinane,[10] and Takai olefination[30] secured vinyl iodide **56** in 52% over three steps. Stille coupling of **56** with Dias's stannane **45** in the presence of $Pd(PPh_3)_4$, CsF, and CuI furnished dienamide **57** in 69% yield.[38] A final Suzuki coupling of MIDA boronate and bromobenzene in the presence of $Pd(OAc)_2$ and SPhos (Pd/SPhos)[39] furnished Crocacin C (**1**) in 77% yield.



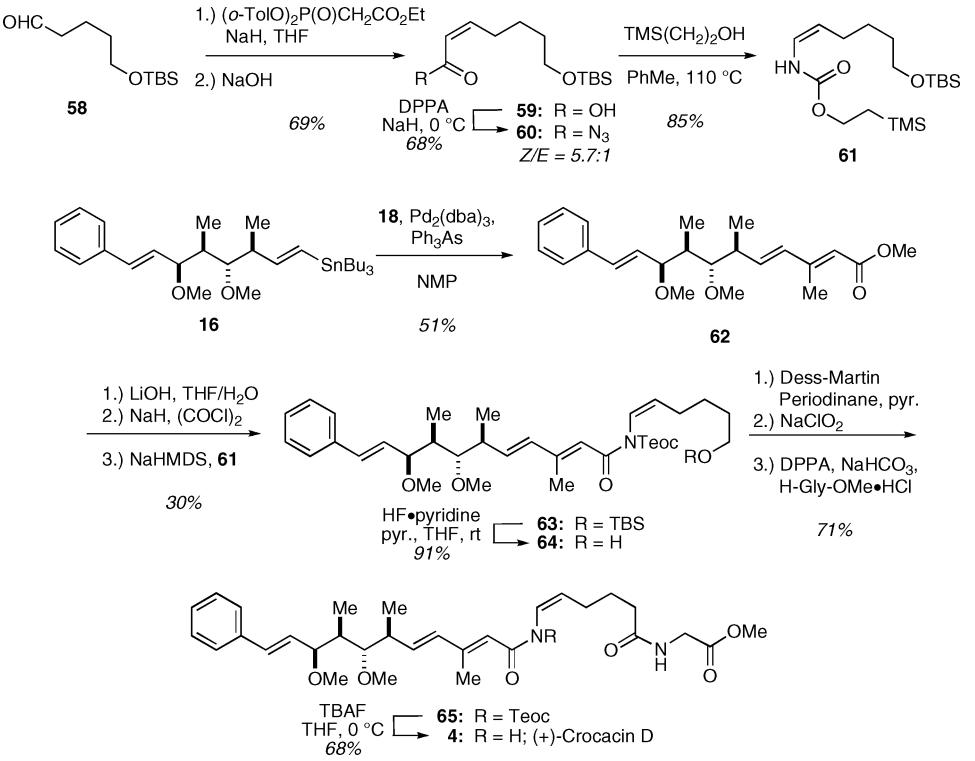
Scheme 6
Burke's Synthesis of (+)-Crocacin C (**1**)

II. Total Syntheses of Crocacin D

1. Rizzacasa's Approach

Rizzacasa and his group were the first to report the asymmetric synthesis of (+)-crocacin D (**4**).[40] This required the synthesis of the side-chain possessing the sensitive (*Z*)-enamide functional group. Toward this goal, aldehyde **58** was subjected to a *Z*-selective Ando olefination reaction.[41] Saponification of the intermediary enoate afforded acid **59** (69% for two steps). A Curtius rearrangement[42,43] was recruited to install the (*Z*)-enamide. Following the Kitahara protocol,[44] the acid was converted to the acyl azide **60** with diphenylphosphoryl azide (DPPA) and NaH at 0°C, thus minimizing isomerization. The ratio of olefin isomers was found to be 5.7:1 (*Z*/*E*). Heating the acyl azide effected the Curtius rearrangement to the vinyl isocyanate, which in the presence of TMS ethanol yielded carbamate **61** (*i. e.*, Teoc protected enamine) in 85% yield (*Scheme 7*).[45]

As crocacin C (**1**) is the common structural component of all crocacins, Rizzacasa selected vinylstannane **16** as a launching point for the synthesis of **4**.[4] A Stille coupling with vinyl iodide **18** furnished dienoate **62**.[16] Saponification and reaction with oxalyl chloride and NaH furnished the acid chloride, which was treated with the sodium anion of **61** to afford imide **63** in 30% overall yield from **62**. Removal of the TBS ether in the presence of the Teoc group was accomplished with HF-pyridine in THF/pyridine (91%).[46] Oxidation



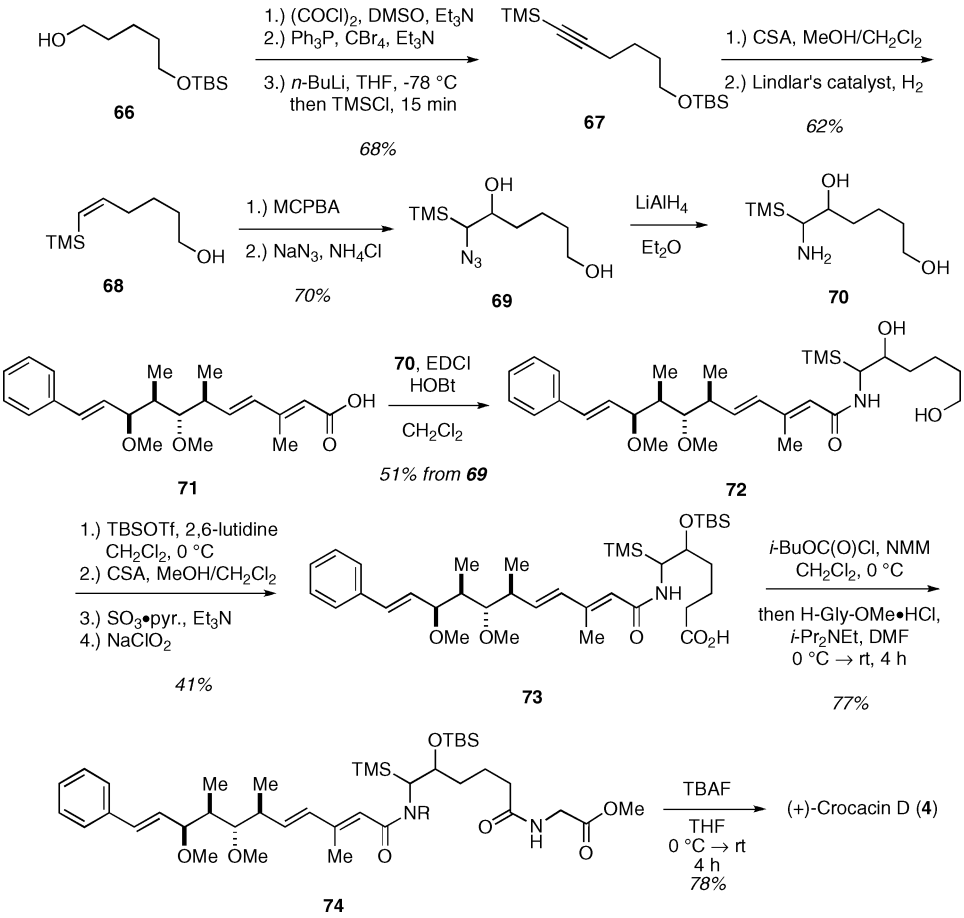
Scheme 7
Rizzacasa's Synthesis of (+)-Crocacin D (**4**)

to the carboxylic acid *via* the intermediary aldehyde and DPPA-mediated coupling [47] with glycine methyl ester successfully installed the entire framework of (+)-crocacin D (**4**). A final Teoc deprotection with TBAF delivered **4** in 68% yield.

2. Chakraborty's Approach

Chakraborty's strategy for the synthesis of (+)-crocacin D (**4**) included a late stage Peterson olefination[48] to install the sensitive *N*-acyl (*Z*)-enamide (*Scheme 8*).[49]

Swern oxidation[27] of alcohol **66** and Corey-Fuchs alkynylation[50] furnished TMS acetylide **67** in 68% yield. Acidic deprotection of the TBS group with CSA and partial reduction of the alkyne to the (*Z*)-vinylsilane proceeded in 62% yield. Epoxidation of the alkene with MCPBA and regioselective ring-opening with NaN_3 furnished racemic diol **69** in 70% yield. Reduction of the azide with LAH afforded the secondary amine **70**.[51] Coupling of **70** to acid **71**, previously employed in the synthesis of **1**,[20] under the agency of EDCI and HOBt delivered dienamide **72** as a mixture of inconsequential diastereomers that was carried forward in 51% from diol **69**. Protection of both alcohols with TBSOTf and 2,6-lutidine followed by CSA deprotection of the primary TBS enabled differentiation of both alcohols. The primary alcohol was thus oxidized under Parikh-Doering conditions[23] and oxidized with $NaClO_2$ to furnish acid **73** in 40% overall yield. Transformation of **73** into a reactive mixed anhydride and treatment with glycine methyl ester furnished

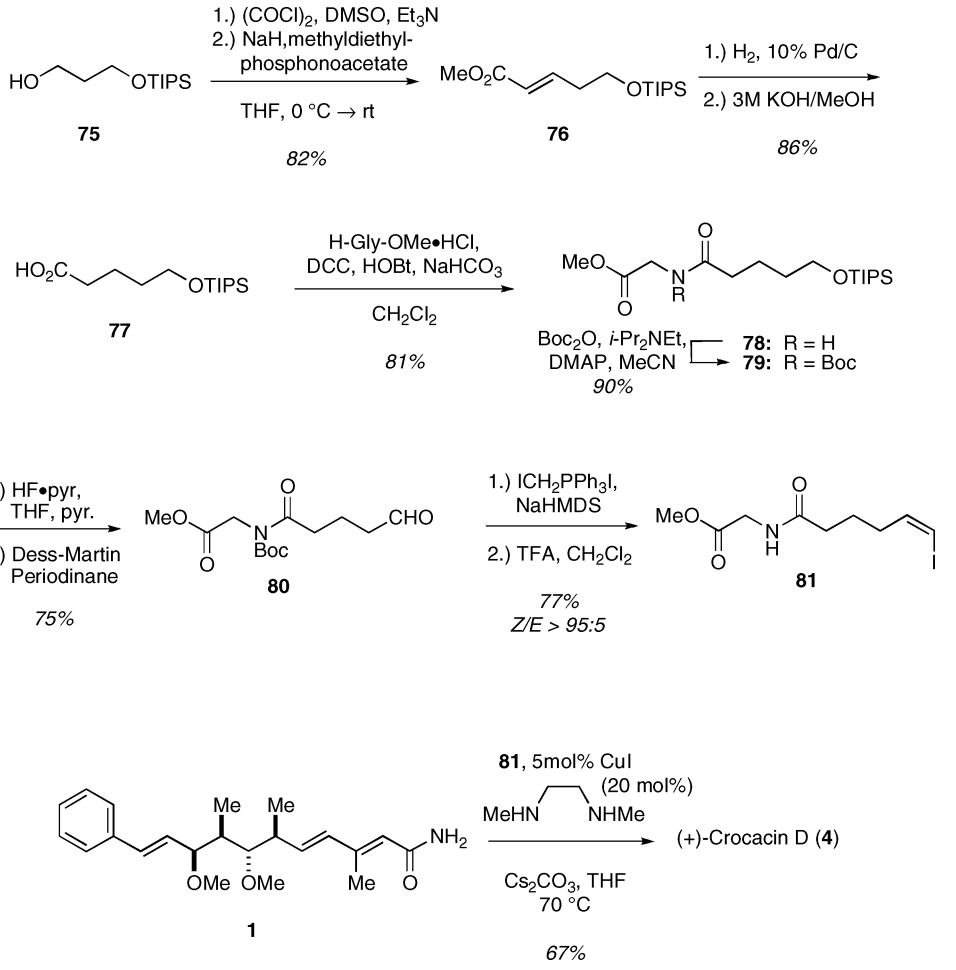


Scheme 8
Chakraborty's Synthesis of (+)-Crocacin D (**4**)

intermediate **74**, establishing the entire framework of **4**. Reaction of **74** with TBAF initiated a tandem desilylation/Peterson olefination to deliver (+)-crocacin (D) **4** in 78% yield.

3. Dias's Approach

Dias's synthesis of (+)-crocacin D (**4**)[52] centered on a copper-catalyzed coupling of amides and vinyl halides, which was developed by Buchwald[53] and made his approach very efficient and concise. To this goal, alcohol **75** was transformed into (*E*)-enoate **76** *via* Swern[27] and Horner-Wadsworth-Emmons protocols[24] in 82% yield. Hydrogenation, saponification and DCC-mediated coupling of glycine methyl ester delivered amide **79** in 70% overall yield. Protection of the secondary amide with Boc afforded imide **79** in 90% yield. Desilylation with buffered HF-pyridine and subsequent Dess-Martin oxidation[10] furnished aldehyde **80** in 75% overall yield. A (*Z*)-selective Wittig olefination accessed the requisite vinyl iodide **81** after removal of the Boc group with TFA (77% yield overall, >95:5 *Z*/*E*). This set the stage for the critical cross-coupling reaction to access the target natural product.[53] In the



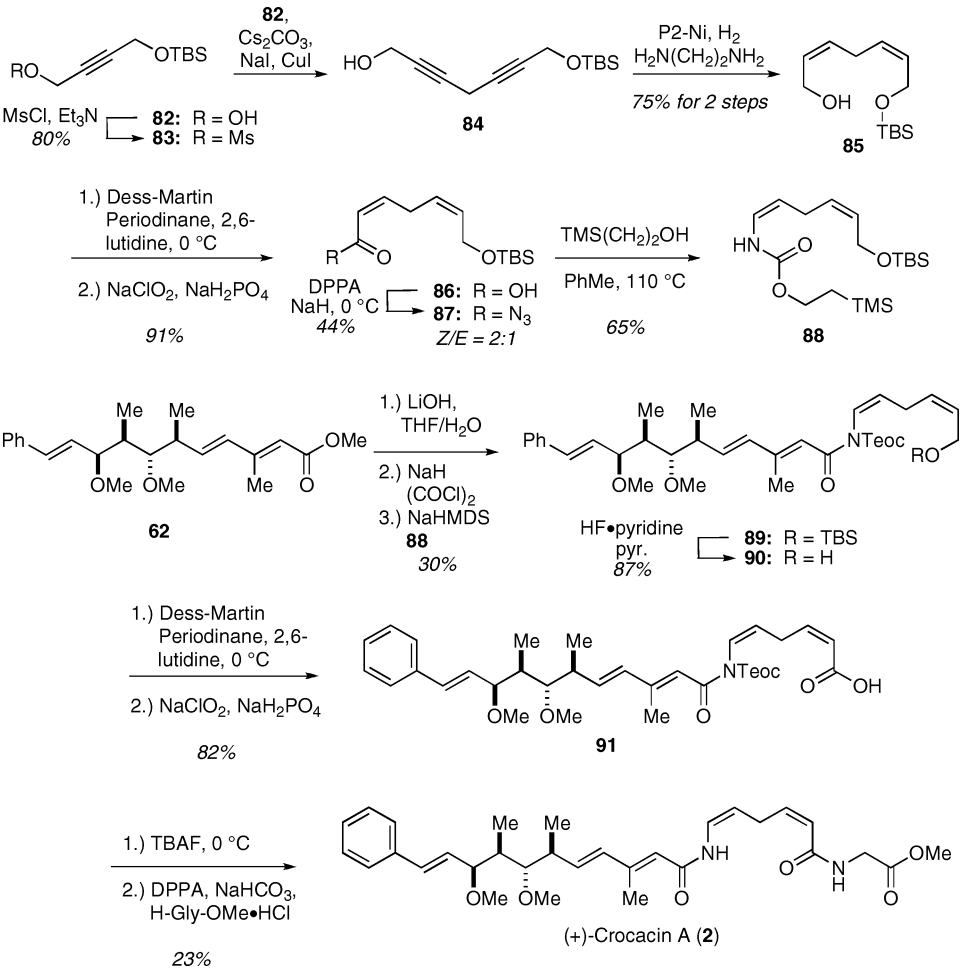
Scheme 9
Dias's Synthesis of (+)-Crocacin D (**4**)

event, (+)-crocacin C (**1**) and vinyl iodide **81** were treated with 5 mol% CuI in the presence of 20 mol% *N,N'*-dimethylethylenediamine and Cs_2CO_3 in THF at 70°C to deliver **4** in 67% yield (*Scheme 9*).

III. Total Syntheses of Crocacin A

1. Rizzacasa's Approach

The first synthesis (+)-crocacin A (**2**) was also reported by the Rizzacasa group.[54] Crocacins A and B differ from D in that they posses a *Z* olefin at the C5-C6 position, adding synthetic challenge (*Scheme 10*). Alcohol **82** was first dimerized by preparing mesylate **83** and effecting a copper-catalyzed coupling with **82** to afford diyne **84**.[55] Selective reduction to the skipped *Z,Z* diene **85** was realized with Brown's procedure of P2-Ni[56] and ethylenediamine under an atmosphere of H_2 in 75% overall yield.[57] Dess-Martin oxidation[10] of the alcohol



Scheme 10
Rizzacasa's Synthesis of (+)-Crocacin A (**2**)

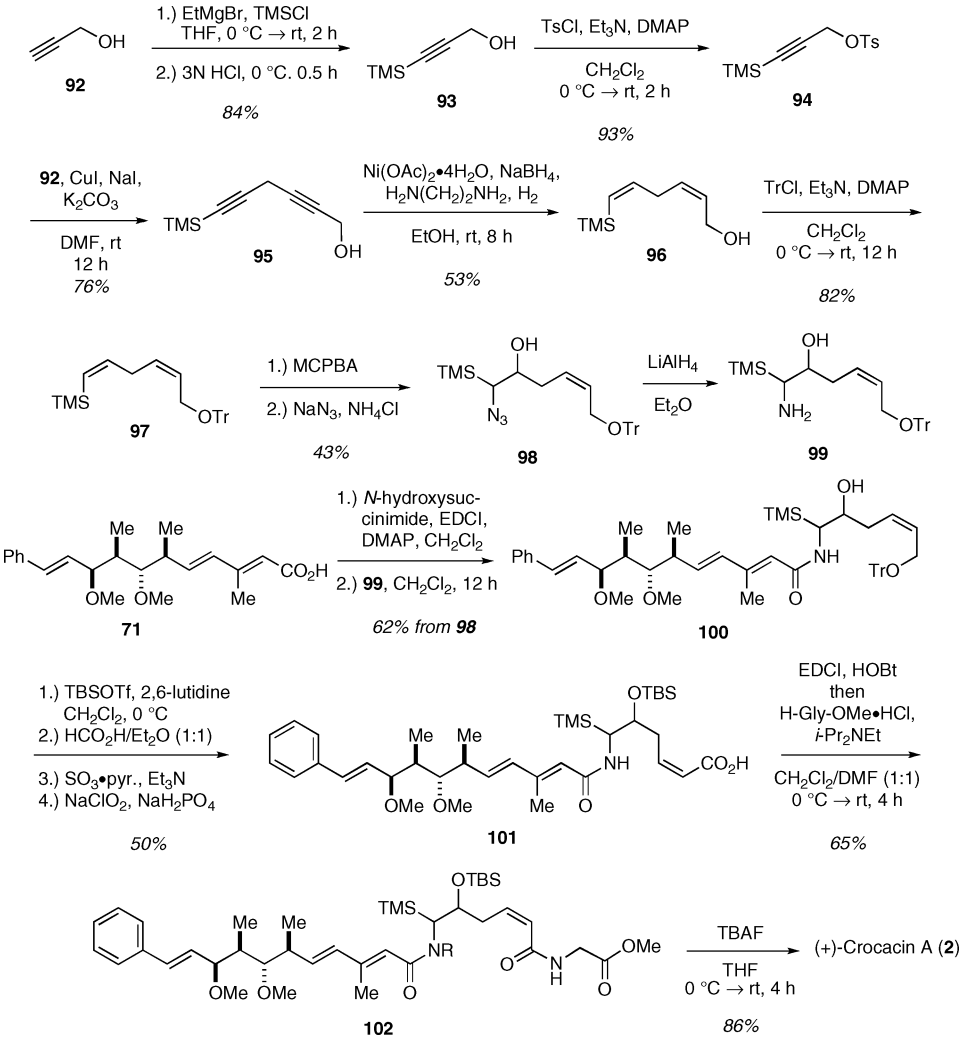
to the aldehyde and $NaClO_2$-mediated oxidation to carboxylic acid **86** proceeded in 91% overall yield. A Curtius rearrangement[42] with the Kitahara protocol,[44] followed by trapping with TMS ethanol, afforded Teoc-protected dienamine **88**. The reaction was accompanied by isomerization such that the best *Z/E* ratios obtained were 2:1, respectively.

Saponification of dienoate **62**, conversion to the corresponding acid chloride and coupling with the sodium anion of dienamide **88** afforded imide **89**. Removal of the TBS ether with HF-pyridine furnished alcohol **90**. Reiteration of the two-step oxidation protocol (Dess-Martin Periodinane,[10] $NaClO_2$) delivered acid **91** in 82% yield. Removal of the Teoc group with TBAF followed by DPPA-mediated peptide coupling with glycine methyl ester afforded (+)-crocacin A (**2**) in 23% yield overall.

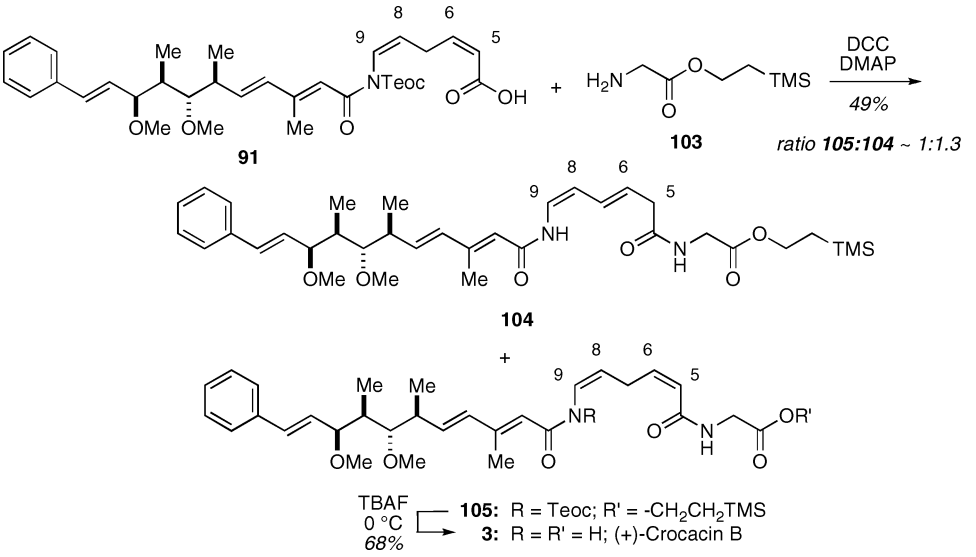
2. Chakraborty's Approach

The synthesis of **2** by Chakraborty shortly followed and took advantage of the Petersen olefination to install the C8-C9 *Z*-enamide moiety.[58] The beginning of the synthesis

tactically parallels Rizzacasa's route. TMS protection of the acetylenic hydrogen of propargyl alcohol (**92**) afforded alcohol **93** in 84% yield. Tosylation of this alcohol gave compound **94** which was subjected to copper-catalyzed coupling with **92** to afford diynyl alcohol **95** in 76% yield (*Scheme 11*). Treatment of **95** with P2-Ni[56] generated *in situ* furnished skipped *Z,Z*-dienenol **96**. Tritylation, oxidation with *m*-CPBA and treatment with NaN_3 proceeded in 35% overall yield to deliver racemic **98**. Conversion from the azide to the amine was realized with $LiAlH_4$. Acid **71** was converted into a *N*-hydrosuccinimidyl ester and treated with amine **99** to afford dienamide **100** in 62% yield from azide **98**. Protection of the secondary alcohol as its TBS ether, Parikh-Doering oxidation[23] and subsequent $NaClO_2$ oxidation furnished acid **101** in 50% overall yield. Peptide coupling with glycine methyl ester was accomplished under the agency of EDCI and HOBt, affording **102** in 65% yield.



Scheme 11
Chakraborty's Synthesis of (+)-Crocacin A (**2**)



Scheme 12
Rizzacasa's Synthesis of (+)-Crocacin B (**3**)

With the framework of the target in place, TBAF-mediated desilylation/Petersen olefination was performed to deliver (+)-crocacin A (**2**) in 86% yield.

IV. Rizzacasa's Total Synthesis of Crocacin B

As the hydrolysis of (+)-crocacin A (**2**) to directly access (+)-crocacin B (**3**) was not successful, the Rizzacasa group replaced glycine methyl ester with glycine Tmse ester **103**.[59] In the event, coupling with acid **91** under the agency of DCC and DMAP afforded both Tmse-protected crocacin B **105** accompanied by the isomerization of the C5-C6 double bond to the C6-C7 position (*i. e.*, **104**) in 49% yield and with a ratio of 1:1.3, respectively (*Scheme 12*). Coupling with EDCI in place of DCC lowered the yield to 32%. Removal of both Teoc and Tmse groups was effected by TBAF at 0°C, delivering (+)-crocacin B (**3**) in 68% yield.

V. Formal Syntheses of Crocacins A-D

Many formal syntheses of the crocacins have appeared, beginning with Gurjar's report in 2003. The final sections of this review will go through each formal synthesis in the order in which they appeared in the literature.

1. Gurjar's Approach

Gurjar's formal synthesis of the crocacins employed a chiral pool strategy,[60] drawing from the rich stereochemical nature of the carbohydrates.[61] Starting with the known dicyclohexylidene of D-glucose **106**,[62] oxidation of the C3 alcohol with PDC and Wittig methylenation afforded **107** in 52% yield for both steps. Stereoselective hydrogenation installed the methyl group in **108**, which maps onto the C18 group of the target, in 97%

yield (*Figure 1*). Site-selective removal of the C5,C6 cyclohexylidene with sulfuric acid in MeOH afforded diol **109** in 83% yield, which was converted to the terminal olefin **110** *via* known methods.[63] A Heck coupling[64] of **110** with iodobenzene afforded styrenyl furanoside **111** in 63% yield as a key step. Treatment of **111** with MeOH and acidic resin (Amberlyst IR-120) converted the 1,2-cyclohexylidene acetal into a mixture of methyl glycosides. Methylation of the remaining C2 hydroxyl with NaH and MeI afforded **112** in 78% over two steps. Hydrolysis of the methyl glycosides and treatment with MeMgCl furnished a mixture of diastereomeric alcohols **113** in 59% overall. Protection of these alcohols as their TBS ethers and a Mitsunobu reaction[65] employing the Martin-Dodge protocol[66] proceeded in 41% yield (including saponification step), inverting the configuration at C19 to match that of **1**. Removal of the TBS groups proceeded in 93% yield. Oxidation to the ketone with the Dess-Martin Periodinane (91%),[10] Wittig methylenation and finally stereoselective hydroboration of the *exo*-methylene moiety (54% for both steps) delivered alcohol **15**,[4] thus completing the formal syntheses of crocacins A-D (*Scheme 13*).

2. Raghavan's Approach to Antipode

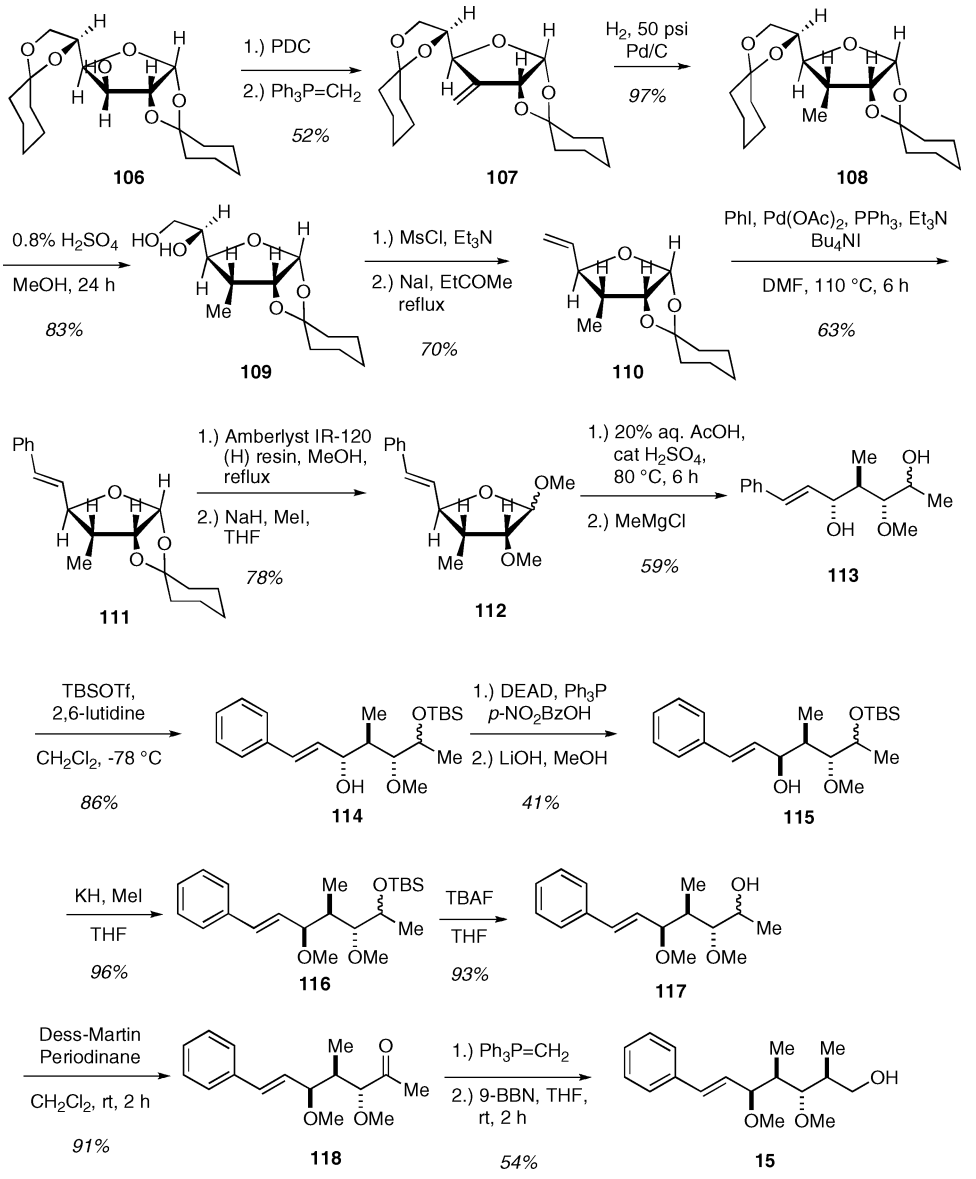
In 2004, Raghavan reported a stereoselective synthesis of *ent*-**15**,[4] which centered around (1) a stereoselective Hg-promoted hydration of an enoate; and (2) a substrate-controlled β-hydroxy ester alkylation (*i. e.*, Frater alkylation) [67] to prepare the *anti*-aldol motif in **15**.[68] Treatment of diastereomeric sulfoxides **119**,[69] prepared from the corresponding homochiral sulfide and MCPBA, with mercuric trifluoroacetate and HgO in PhMe containing water delivered sulfoxides **124** after demercuration in 75% yield (*Scheme 14*).

The mechanistic rationale includes a transfer of oxygen from sulfur to carbon *via* a five-membered ring transition state. The sulfoxide oxygen is derived from water in the reaction mixture; studies using ^{18}O-labelled water confirmed this hypothesis. The diastereomeric sulfoxides **124** were first oxidized to sulfone **125** with MCPBA in 90% yield then reduced with $TiCl_3$[70] to sulfide **126**. At this point, the Frater alkylation[67] was employed to afford *anti*- aldol **127** in 75% yield as a single diastereomer. Saponification of the ester with LiOH and DCC-mediated coupling with morpholine furnished amide **128** in 63% yield. Addition of styrenyl lithium (**17**), which was prepared from the corresponding stannane[71] *via* a metal-halogen exchange reaction with *n*-BuLi, furnished styrenyl ketone **129** in 80% yield. Substrate-directed reduction with $Me_4NBH(OAc)_3$ afforded *anti* diol **130** in 85% yield as a single diastereomer. Methylation of diol **130** with NaHMDS and MeI delivered **131**.

Oxidation of sulfide **131** with $NaIO_4$ to the sulfoxide (80%)[72] and Pummerer rearrangement, [73] followed by treatment with $NaBH_4$ secured *ent*-**15** in 75% yield for the two steps, thus completing Raghavan's formal synthesis of the crocacins.

3. Furstner's Approach

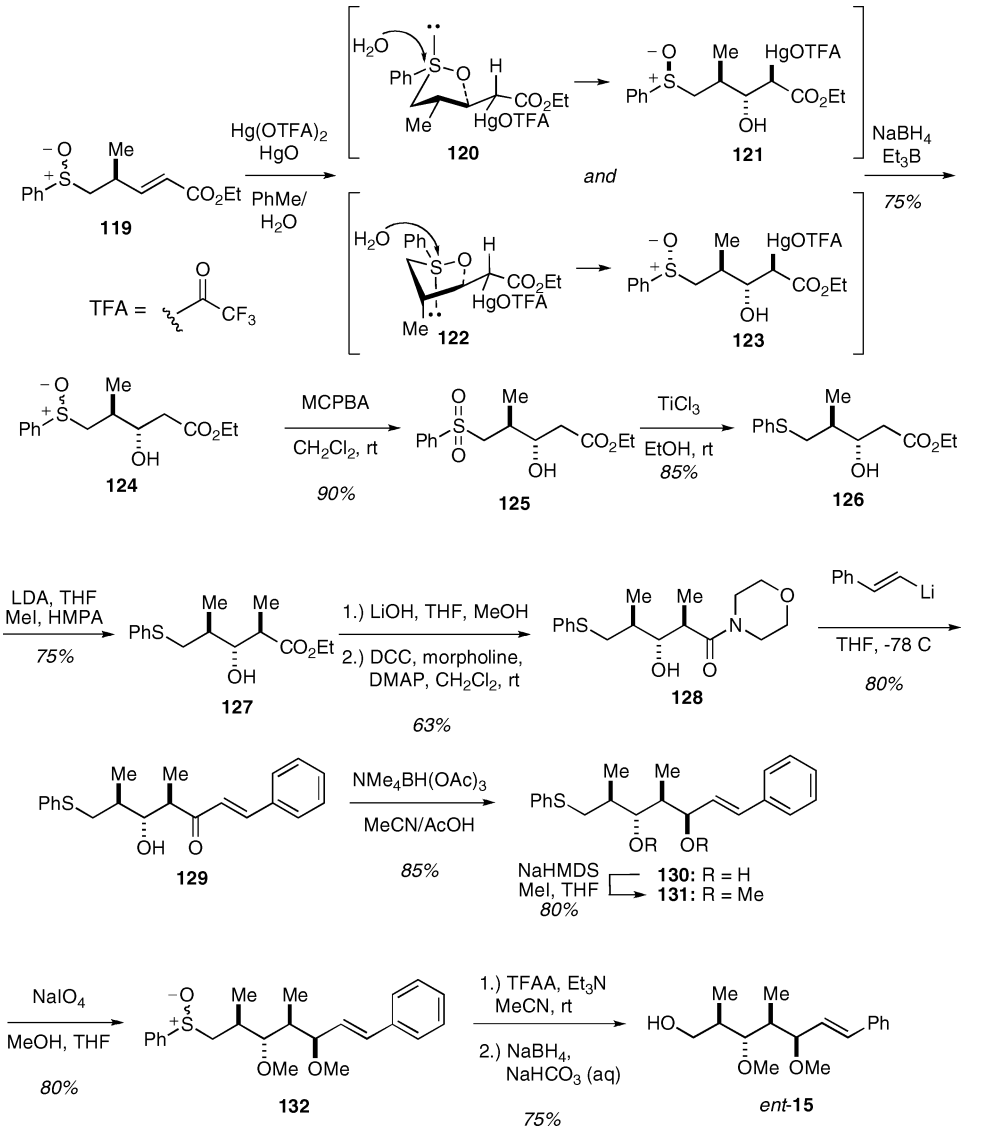
Furstner's formal synthesis[74] began with a titanium-mediated aldol reaction[75] of valinol-derived propionate **133** and *(E)*-cinnamaldeyde to afford aldol **134** in 85% (*dr∼10:1)*. Protection of the hydroxyl group with TBS and removal of the auxiliary with $LiBH_4$ afforded alcohol **136** in 86% overall yield. Dess-Martin oxidation[10] to the aldehyde (87%



Scheme 13
Gurjar's Formal Synthesis

yield) and Zn-mediated, Pd-catalyzed addition of a propargyl mesylate (*i. e.*, Marshall allenylation)[76] yielded alcohol **138** in 72% yield, concisely establishing the stereotetrad of the crocacins (*Scheme 15*). Removal of the TBS ether with TBAF and methylation of both hydroxyls with MeOTf and 2,6-di-*t*-butyl-4-methylpyridine furnished alkyne **139** in 55% overall yield. Hydroboration to the vinyl borane **140** proceeded in 87% yield.

To complete the formal synthesis, hydrostannylation of ester **141** afforded vinyl stannane **142**, which was converted to iodide **143** in one step. With **143** in hand, the key Suzuki

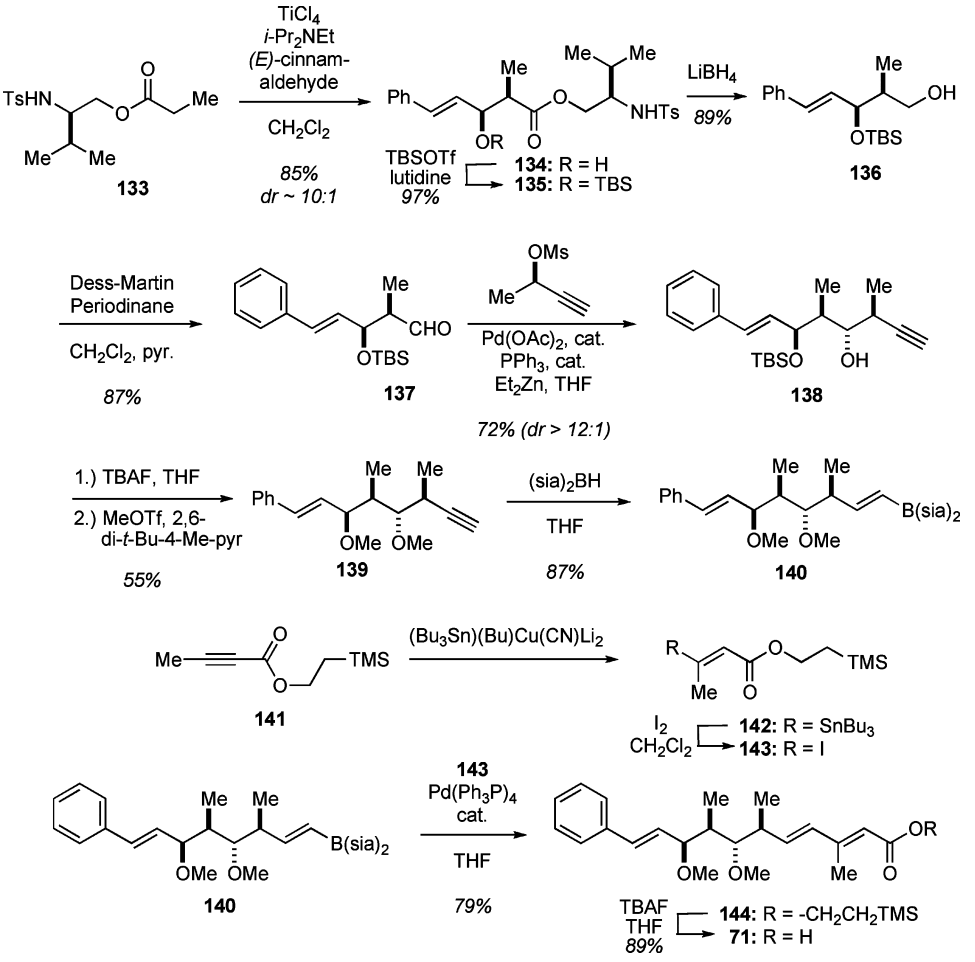


Scheme 14
Raghavan's Formal Synthesis

coupling was realized with catalytic $Pd(PPh_3)_4$ to forge dienoate **144**. Fluoride-mediated removal of the Tmse group liberated acid **71**,[49] thus completing Furstner's formal synthesis.

4. Yadav's 1st and 2nd Generation Approaches

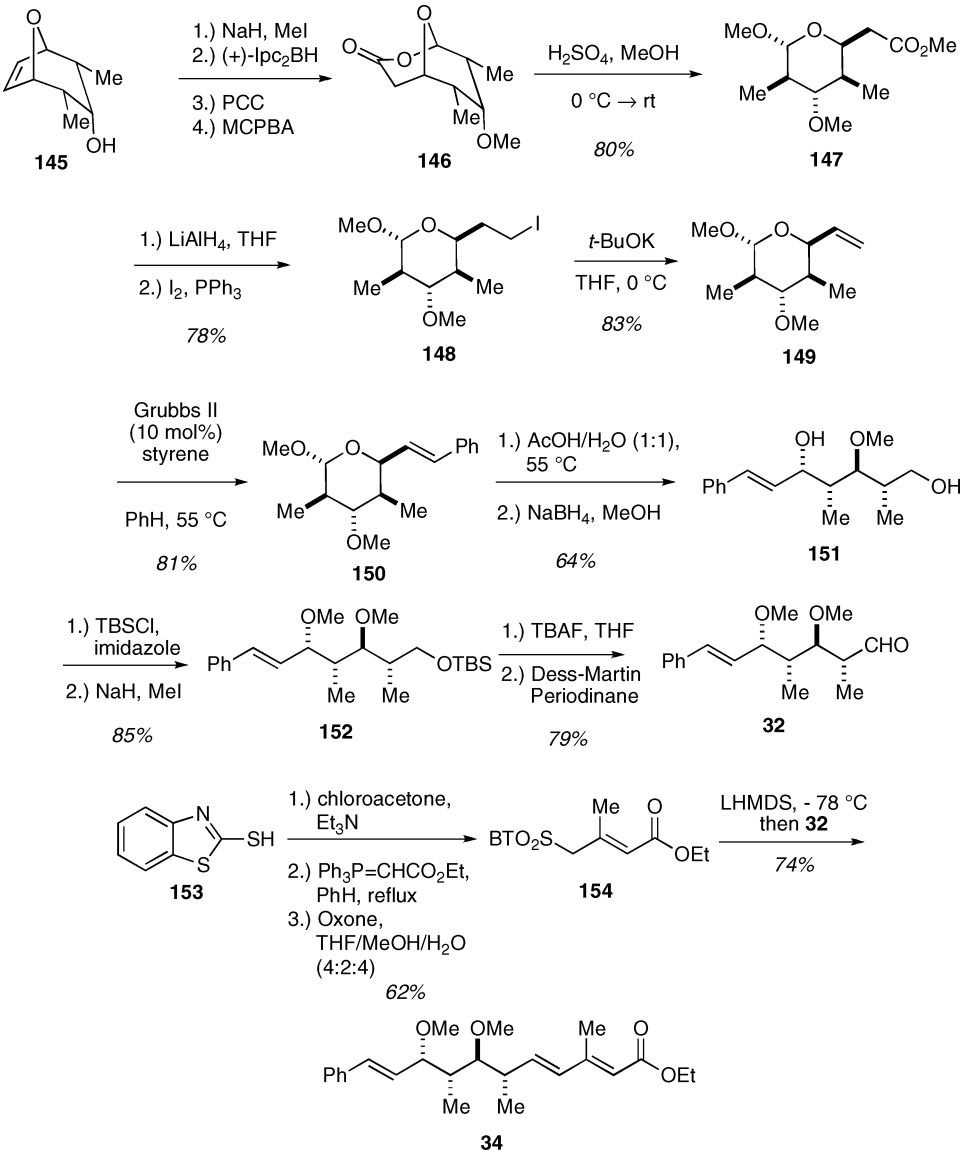
Yadav reported two different formal syntheses of the crocacins in 2007. The first[77] featured the asymmetric hydroboration of *meso* olefin **145** with (+)-Ipc_2BH (*Scheme 16*).[78] Bicyclic lactone **146** was prepared in four steps from **145** and served as the starting point. Acidic methanolysis of the lactone afforded methyl ester **147** in 80% yield. Reduction of the ester



Scheme 15
Furstner's Formal Synthesis

with $LiAlH_4$ and conversion of the alcohol to the iodide with I_2, Ph_3P and imidazole,[79] furnished iodide **148** in 78% yield for the two steps. Elimination with *t*-BuOK secured the terminal olefin in **149** (83%).[80] A cross-metathesis reaction[81] of **149** with 10 mol% Grubbs 2nd generation catalyst[82] and styrene delivered pyranoside **150** in 81% yield. Acetal hydrolysis[83] and reduction of the hemiacetal yielded diol **151** in 64% yield. Selective silylation of the primary hydroxyl with TBS and methylation of the remaining secondary hydroxyl with NaH and MeI delivered **152** in 85% overall yield. Fluoride-mediated removal of the TBS group and oxidation of the alcohol with the Dess-Martin Periodinane[10] provided aldehyde **32**.[20] A vinylogous modified Julia olefination[84] of **32** with lithium anion derived from sulfone **154**, prepared in three steps from **153** in 62% overall yield, furnished dienoate **34**, which Chakraborty had previously carried to crocacins C (**1**),[20] D (**4**)[49] and A (**2**).[58]

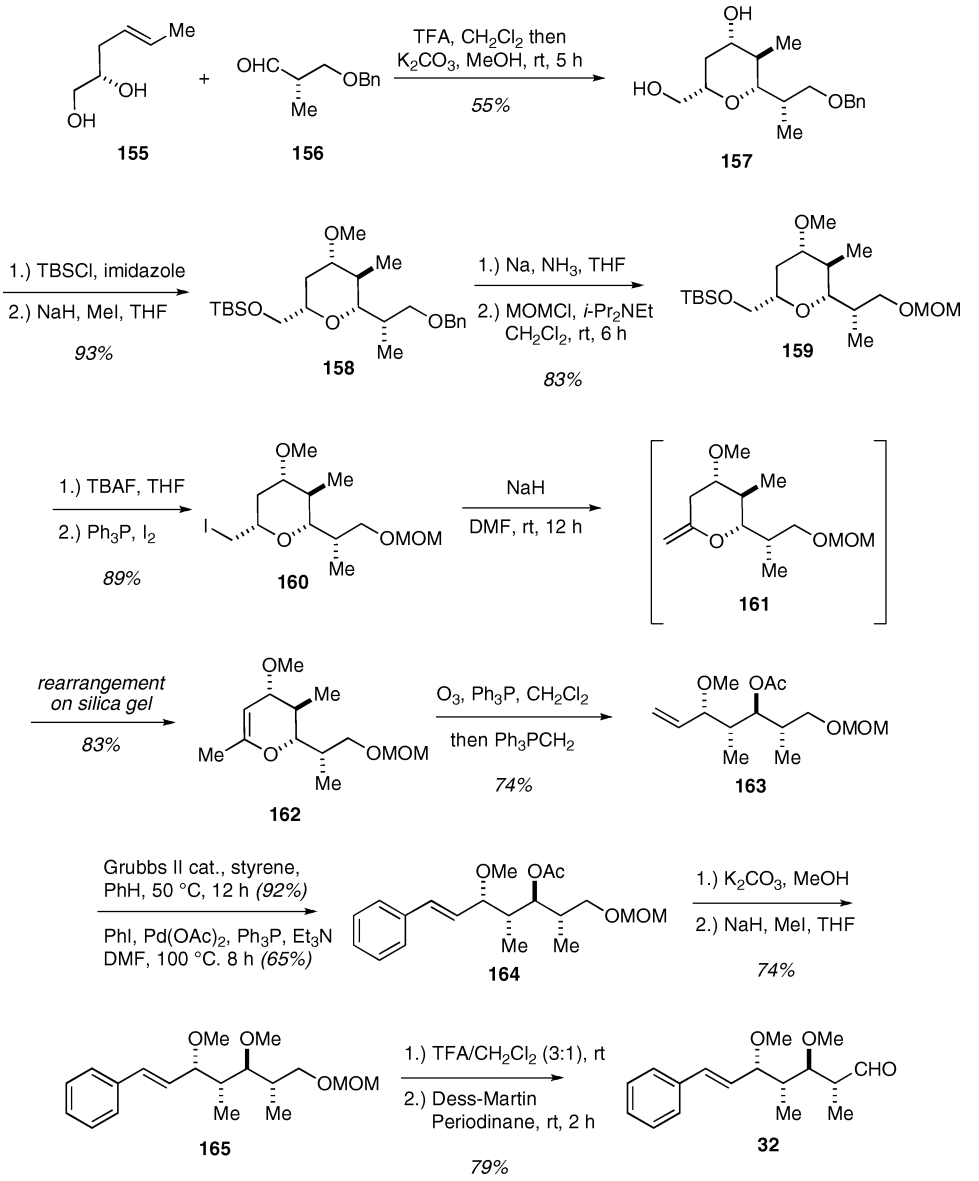
Yadav's second-generation approach had a Prins cyclization[85] as key step, which was performed early in the synthesis.[86] In the event, diol **155** was condensed with aldehyde **156**



Scheme 16
Yadav's 1st Generation Formal Synthesis

in the presence of TFA to afford tetrahydropyran **157** in 55% as the only isolated product after saponification of the TFA ester intermediate (*Scheme 17*).

Selective protection of the primary hydroxyl with TBS and methylation of the remaining alcohol provided **158** in 93% overall yield. At this point, the benzyl ether was replaced with a MOM ether in 83% following standard protocols. Fluoride-mediated removal of the TBS group and replacement with an iodide *via* Appel conditions[87] furnished iodide **160**. Treatment of **160** with NaH in DMF at room temperature for 12 h effected an elimination to form **161**,[88] which rearranged on silica gel to deliver dihydropyran **162**. Ozonolysis



Scheme 17
Yadav's 2nd Generation Formal Synthesis

and subsequent Wittig methylenation proceeded in 74% to access **163**. Cross-metathesis[81] with styrene (92%), or alternatively a Heck coupling[64] with iodobenzene (65%), installed the entire carbon framework of crocacin C. Saponification of the acetate and methylation (NaH, MeI) afforded **165** in 74% over two steps. Removal of the MOM ether with TFA and oxidation of the alcohol to the aldehyde with the Dess-Martin periodinane[10] secured aldehyde **32**[20] which has been carried forward to the crocacins.

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