Account / Revue

Design and synthesis of ansamycin antibiotics

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Abstract

Ansamycin antibiotics are a class of microbial metabolites that exhibit an array of biological activities. This review covers the synthetic chemistry and biological activity of benzenic ansamycins from 1989 to 2007. In the first section, synthetic approaches to the C15-benzene ansamycins (geldanamycin and related) are discussed. Access to the C17-benzene ansamycins (or ansatrienins) is disclosed in the second half of this article. ***To cite this article: Iwona E. Wrona et al., C. R. Chimie 11 (2008).***
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Résumé

Les ansamycines constituent une famille d'antibiotiques d'origine bactérienne possédant un large éventail d'activités biologiques. Cette revue couvre la préparation et l'évaluation biologique des ansamycines dites de type benzénique de 1989 à 2007. Dans une première partie, les approches synthétiques vers les ansamycines benzéniques de type C15 (geldanamycine et apparentées) seront discutées. L'accès aux ansamycines benzéniques de type C17 (ou ansatriénines) sera détaillé dans la seconde partie de cette contribution. ***Pour citer cet article : Iwona E. Wrona et al., C. R. Chimie 11 (2008).***
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1. General introduction

Polyketide natural products are a structurally diverse family of compounds showing a wide range of biological activities. Some examples include antibiotic erythromycin A [1], immunosuppressant rapamycin [2], and antitumor antibiotic doxorubicin [3] (Fig. 1). Specifically, ansamycin antibiotics have become an important class of naturally occurring bioactive compounds with the discovery of the antibacterial properties of rifamycin B in 1959 [4]. Specifically, rifamycins have been used to treat tuberculosis, leprosy and AIDS-associated mycobacterial infections [5]. These macrolactams are named because of their ''basket-like'' structure consisting of an aromatic chromophore connected at nonadjacent positions by an aliphatic chain, like a handle or ansa [6]. The structure of the aromatic moiety distinguishes the two types of these natural products (Fig. 2).

Naphthalenic ansamycins (rifamycin, streptovaricin, naphthomycin) exhibit strong antimicrobial activities [7], whereas benzenic ansamycins (geldanamycin, herbimycin, trienomycins) have demonstrated their potential as antineoplastic agents [8]. An additional mode of differentiation can be made within the ansa chain (C15- and C17-) of the benzene ansamycins (Fig. 3). The geldanamycin type ansamycins **IIa** are comprised of a 19-membered lactam that contains an isolated trisubstituted olefin. Alternatively, the 21-membered macrolactam of mycotrienin type ansamycins **IIb** consists of
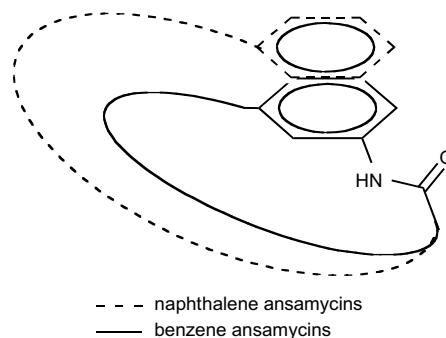
Fig. 2. ''Basket-like'' structure of ansamycins.

an all (*E*)-triene system; this subclass of ansamycins will be subsequently referred to as ansatrienins.

1.1. Biosynthesis of benzenic ansamycins

The biosynthesis of ansamycin natural products occurs *via* the common precursor 3-amino-5-hydroxybenzoic acid (AHBA), Fig. 4 [9]. The ansa chain of geldanamycin is assembled from AHBA by sequential addition of 4 propionate, 2 glycerate/glycolate and 1 acetate groups [10]. These seven chain-elongation steps utilize substrate condensation and various reductions or dehydrations to produce the nascent polyketide framework. The methoxy carbons are derived from methionine while the carbamate carbon comes from the ureido group of citrulline. In a similar fashion, the aliphatic

Fig. 1. Representative structures of erythromycin A, rapamycin, doxorubicin, and rifamycin B.

Fig. 3. Representative structures of naphthalene ansamycins **I** and C15- and C17-benzene ansamycins **II**.
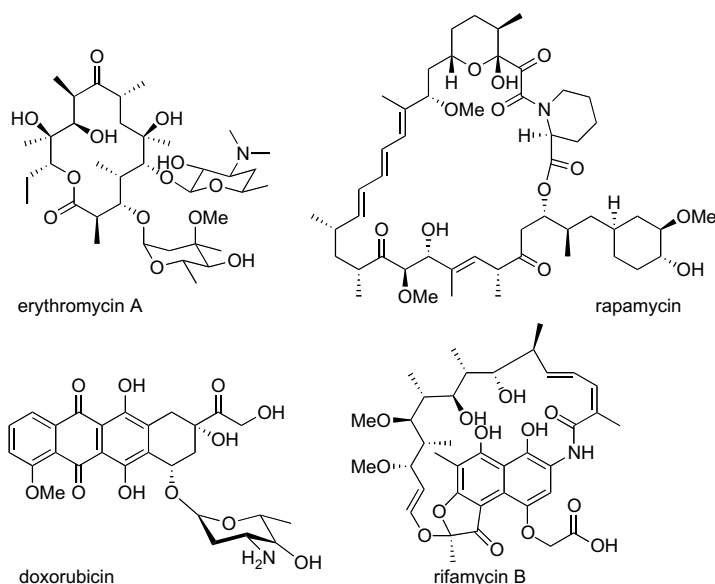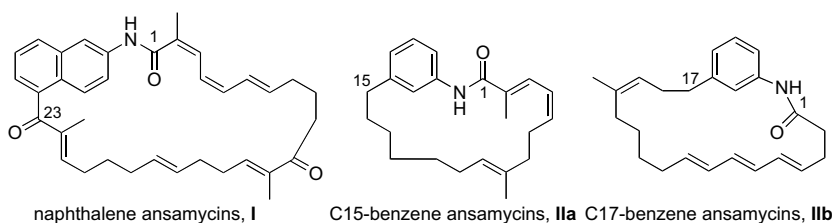
chain of ansatrienins is derived from 6 acetate and 2 propionate subunits [11]. Subsequent formation of a macrolactam between the terminal C1-carboxyl and 3-amino group of AHBA results in characteristic ''basket-like'' molecular conformation of the C15- and C17-benzene ansamycins.

In recent years, the production of novel structural variants of these macrolides has been achieved by genetic manipulation of these biosynthetic pathways [12]. For example, Kosan Biosciences reported that alteration of a gene cluster responsible for the biosynthesis of geldanamycin led to discovery of KOSN1559 with 8-fold greater binding affinity to Hsp90 than natural geldanamycin [13]. Some of these geldanamycin derivatives are currently being evaluated in clinical trials as antitumor agents [14]. Although the biological activity of C15- and C17-benzenic ansamycins have been reviewed [15], there are few reports on their chemical syntheses. Accordingly, the next two

sections will provide a detailed overview of the chemical approaches and associated bioactivities of these 19- and 21-membered macrolactams.

2. C15-Benzoquinone ansamycin antibiotics

2.1. Isolation, structure and biological activity

The C15-benzoquinone ansamycins were discovered between 1970 and 2000 from several strains of *Streptomyces* and *Nocardia* in screens for antibacterial, antifungal, and antiviral compounds (Fig. 5). Structurally, these macrolactams contain six or seven stereogenic centers, a C7-carbamate, a trisubstituted double bond, and a C1−C5 dienoate. The different substitution patterns within the carbon skeleton at C6, C11, C12, C15, and C17 as well as the oxidation state of the aromatic chromophore define this class of polyketide antibiotics.
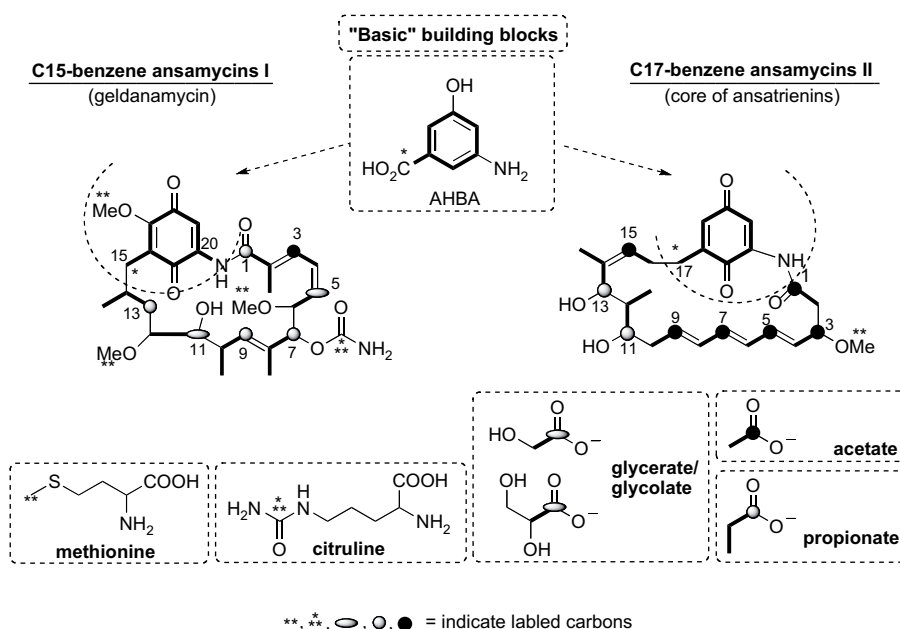

$**, \overset{*}{**}, \ominus, \bigcirc, \bullet$ = indicate labled carbons

Fig. 4. Biosynthesis of geldanamycin and ansatrienins.

R^1	R^2	R^3	R^4	R^5	
-OMe	-OMe	-H	-Me	-H	geldanamycin, **1**
-H	-OMe	-Me	-Me	-OMe	herbimycin A/TAN 420F, **2a**
-H	-OMe	-H	-Me	-H	herbimycin B, **2b**
-H	-OMe	-H	-Me	-OMe	herbimycin C/TAN 420D, **2c**
-H	-Me	-Me	-Me	-OMe	macbecin I, **3a**
-H	-Me	-Me	-Me	-OMe	macbecin II (hydroquinone), **3b**
-H	-OMe	-H	-H	-OMe	TAN 420A (hydroquinone), **4a**
-H	-OMe	-H	-H	-OMe	TAN 420B, **4b**
-H	-OMe	-H	-Me	-OMe	TAN 420C (hydroquinone), **4c**
-H	-OMe	-Me	-Me	-OMe	TAN 420E (hydroquinone), **4d**

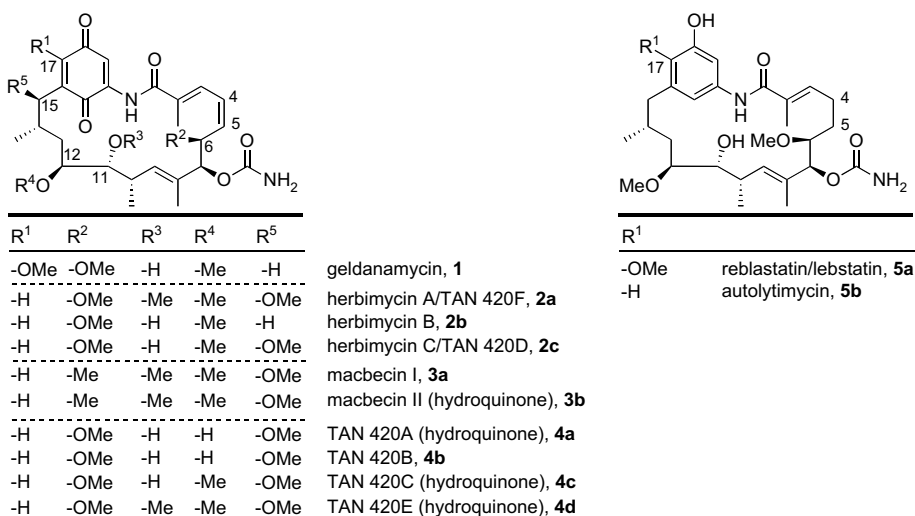| R^1	
-OMe	reblastatin/lebstatin, **5a**
-H	autolytimycin, **5b**

Fig. 5. Molecular architectures of C15-benzene ansamycins.

Geldanamycin **1** was the first member of this family to be isolated from a strain of *Streptomyces hygroscopicus* var *geldanus* [16−18]. Initial screenings showed modest biological activity against Gram-positive bacteria, fungi, and parasites [17]. However, a report by Neckers [19] in 1994 found that geldanamycin was a potent inhibitor of heat shock protein 90 (Hsp90). The molecular chaperone Hsp90 regulates proteins in cell growth and survival as well as assisting the folding and maturation of client proteins such as signaling kinases and transcription factors. The Hsp90 client proteins seem to be involved in all hallmarks of cancer, thus their inhibition is supposed to disrupt multiple oncogenic signaling pathways. This finding initiated considerable interest in this class of natural products and resulted in synthesis of various analogues as potential anticancer agents. Most of these semi-synthetic derivatives are generated from functionalization at the C17-position [20] of the natural product and some have advanced to phase II clinical trials [14].

Herbimycin A **2a** was isolated from the fermentation broth of *S. hygroscopicus* var *geldanus* strain AM-3672 in 1979 [21]. The structure and absolute configuration of herbimycin A were based on ¹H and ¹³C NMR spectroscopic analyses and X-ray crystallographic studies [22]. Not surprisingly, this macrolide is quite similar to geldanamycin with retention of configuration at all shared stereocenters, differing only in the substituents at C11, C15, and C17 (Fig. 5). Along with herbimycin A, two other isomers were resolved, herbimycin B **2b** [23] and herbimycin C **2c**. [24]. These natural products are identical to the parent compound except for functionality at C11 and C15.

Similar to geldanamycin, the herbimycins were shown to have antibacterial, antifungal, herbicidal, anti-angiogenic and antitumor properties, including inhibition of Hsp90 [21,22,25].

Macbecin I **3a**, along with its hydroquinone derivative macbecin II **3b**, was isolated in 1980 from the strain of *Nocardia* sp. [26]. Their structures and absolute configurations were determined from partial degradation studies and X-ray crystal structure analysis [27]. The macrolide ring system and stereochemistry of macbecin I once again resemble the architecture of geldanamycin except for C6, C11, C15, and C17 positions. Interestingly, macbecin I is the only member of the C15-benzoquinone ansamycin family to contain a methyl group instead of a methyl ether at C6. Macbecin I and II were shown to have moderate activity against Gram-positive bacteria and fungi *in vitro* and good antitumor activity *in vivo* [26,27]. Only recently, macbecin I **3a** has been evaluated as an Hsp90 inhibitor [28].

In 1986, TAN 420 series of ansamycins **4a−d** were isolated from a strain of *S. hygroscopicus* [24,25b,29]. Three hydroquinone (A, C and E) and three related quinone (B, D and F) isomers were elucidated; however, only TAN 420A and TAN 420B were structurally different from other ansamycins with the presence of C12-hydroxy group. These natural products displayed biological activity against Gram-positive bacteria and fungi [29].

The most recent additions to the C15-ansamycin class of natural products, isolated from a culture of *Streptomyces*, are reblastatin **5a** [30,31] and autolytimycin **5b** [31,32]. In 2000, Takatsu and co-workers

reported a benzenoid-type antibiotic that was very similar to geldanamycin except for the aromatic moiety (phenol versus quinone) and saturation of C4−C5 olefin within the C1−C5 dienoate. In the original report, reblastatin was shown to exhibit antitumor activity [30]. The related natural product autolytimycin **5b** was isolated in 2001 from a strain of *Streptomyces autolyticus* JX-47 [32]. Autolytimycin differs structurally from reblastatin in the aromatic region, specifically at C17, and was shown to possess activity in a cell based oncostatin M signaling assay [31]. The architectural similarities of reblastatin and autolytimycin to geldanamycin and other members of the ansamycin family have led to exploration of these molecules as potential Hsp90 inhibitors [13].

2.2. Introduction: synthetic approaches toward the C15-ansamycins

This section provides a comprehensive, chronological overview of synthetic approaches developed toward the benzenic ansamycins. Specifically, previous syntheses of geldanamycin **1**, herbimycin A **2a**, (+)-macbecin I **3a**, and reblastatin **5a** are presented. In all, there are 12 reports from nine different groups detailing total and formal syntheses. Reports on advanced fragment syntheses [33] and model studies [34] of these ansamycins will not be discussed in this review.

The first common disconnection of the C15-ansamycins occurred at the C1−N20 amide bond. Macrocyclization of these 19-membered lactams **IIa** was performed on seco-amino acid **IIIa** using BOP−Cl as the coupling reagent (Scheme 1). Baker reported the first use of this approach in 1990 and will be discussed in more detail in the following section (Section 2.3.1) [35]. For redundancy purposes, conversion of these different acyclic frameworks to ansamycins will be omitted after the first total synthesis, with one exception. Panek utilized intramolecular copper-mediated amidation of bromo-amide **IIIb** to form the 19-

membered macrolactam of reblastatin (and later geldanamycin), see Section 2.3.6 for discussion [36]. This is the first example of a Buchwald aryl amidation reaction used for macrocyclization. The following discussion is divided into two distinct parts and is based on a second common disconnection at the C15−C16 benzylic bond or at the C14−C15 aliphatic bond of the ansamycin framework. Of the 12 syntheses, there are seven reports that utilize aromatic aldehyde **IVa** as the starting point for ansa chain construction (i.e. aromatic elongation). The remaining five employ aryl lithium **IVb** to install the C15-alcohol of the ansamycin framework (i.e. late-stage assembly). These two different synthetic pathways allow for direct comparison of methodologies utilized to arrive at similar complex fragments and will be reviewed as such in the following section.

## 2.3. Syntheses of ansamycins utilizing ''aromatic elongation''

2.3.1. First total synthesis of (+)-macbecin I by Baker (1989)

Baker and co-workers reported the first approach to the ansamycin class of natural products in 1989 with their enantioselective synthesis of macbecin I **3a** [35]. Retrosynthetic disconnection at the C1−N20 amide bond reveals the prevalent acyclic framework **6** (Scheme 2). The (*E*,*Z*)-conjugated diene of the seco-amino acid **6** was envisaged to be formed from successive Wittig olefinations, while cuprate-mediated coupling of epoxide **7** with vinyl iodide **8** would afford the crucial C9−C10 bond construction. The *syn*-relationship at C6−C7 and C14−C15 stereocenters was installed using Evans' metal enolate-based aldol strategy [37], while Sharpless asymmetric epoxidation (SAE) was used to install the C10−C11 stereocenters.

Installation of the C6−C7 stereocenters of the vinyl iodide fragment **8** was achieved using Evans' chiral auxiliary [38] (Scheme 3). The vinyl iodide **9** was
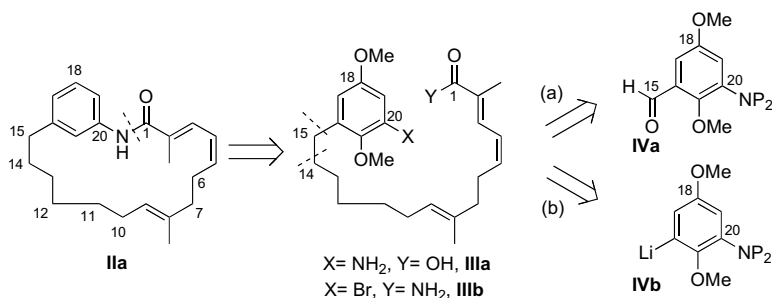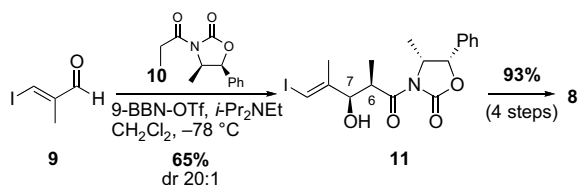

Scheme 1.
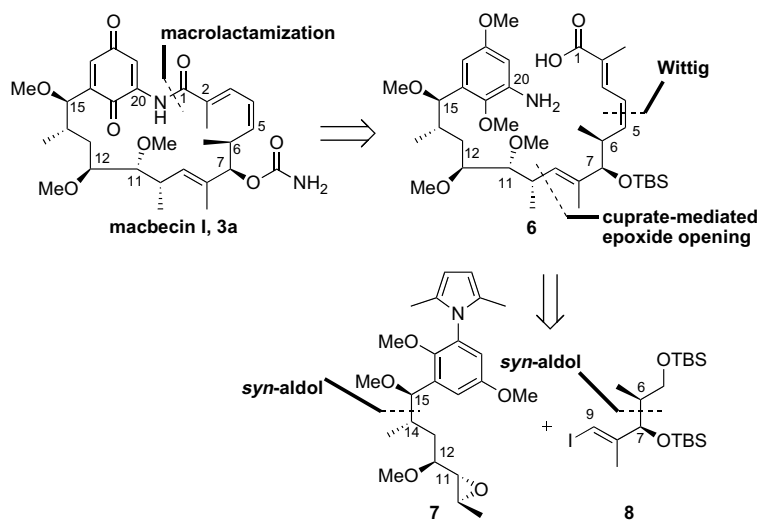
Scheme 2.

prepared in four steps (40% yield) from commercially available diethyl methyl malonate [35d]. Reaction of aldehyde **9** with the Z(O)-boron enolate of chiral propionyl oxazolidinone **10** under soft enolization conditions with 9-BBN-OTf provided the *syn*-C7-allylic alcohol **11** in 65% yield. Removal of the auxiliary and protection of the resulting alcohols as TBS ethers completed the preparation of vinyl iodide **8** in 93% yield.

Synthesis of the advanced intermediate **7** featured asymmetric aldol, enolate hydroxylation, and Sharpless epoxidation reactions (Scheme 4). The benzaldehyde **12** was prepared in three steps starting from *p*-methoxyphenol (33% yield) [35a]. Treatment of 2,5-dimethoxy-3-nitrobenzaldehyde **12** with the Z(O)-boron enolate [37] of **10** afforded the *syn*-aldol adduct **13** in 88% yield and 20:1 diastereoselectivity. The benzylic alcohol **13** was converted to the acyl oxazolidinone **14** in 11 steps (62% yield). The desired C12-alcohol was installed using, at the time, recently developed asymmetric hydroxylation of enolates. Thus, reaction of sodium enolate of **14** with Davis' reagent **15** [39] gave the required alcohol **16** in 83% yield and excellent diastereoselectivity. The oxazolidinone **16** was converted to the C12-allylic alcohol intermediate **17** in five steps (73% yield). Sharpless

asymmetric epoxidation of (E)-allylic olefin with stoichiometric amounts of (+)-DIPT and Ti(O^{i}Pr)$_4$ afforded the required fragment **7** after protection of the alcohol as its methyl ether (88% over two steps).

Fragment coupling, diene insertion and macrocyclization were required for completion of the synthesis. The crucial coupling of cyanocuprate **8** with activated epoxide **7** (BF$_3$·OEt$_2$) yielded the desired homoallylic alcohol (Scheme 5), which was subsequently protected as its methyl ether **18** (81% over two steps). The advanced intermediate **18** was converted to the (Z,E)-conjugated acid **6** *via* sequential Horner–Emmons and Wittig reactions with good selectivities. Macrocyclization of the seco-amino acid **6** with BOP–Cl, followed by CAN oxidation provided macrolactam **19** in 43% yield (two steps). Removal of the C7-TBS ether with TBAF and installation of the carbamate functionality with sodium cyanate completed the total synthesis of macbecin **3a**. The authors also reported that urethane installation can precede the quinone oxidation with a similar yield.

The first synthesis of (+)-macbecin **3a** was achieved in 38 steps with 0.79% overall yield beginning with *p*-methoxyphenol (longest linear sequence). As such, Baker's synthesis of macbecin I generated enormous interest from the synthetic community from this important class of natural products.

2.3.2. Total synthesis of (+)-macbecin I by Evans (1992)

Evans' synthesis of macbecin featured late-stage macrocyclization, Still–Gennari homologation and asymmetric oxazolidinone-based aldol reactions [40].
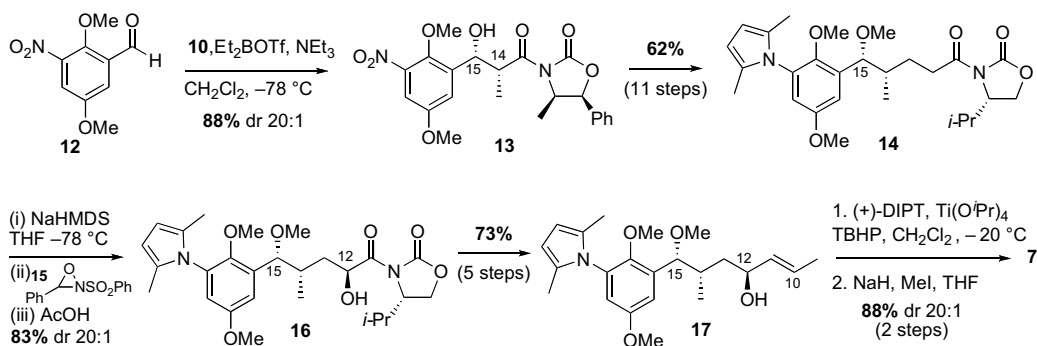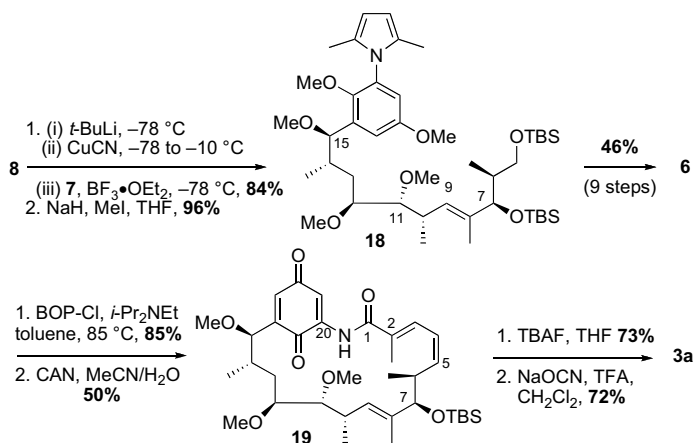

Scheme 3.

Scheme 4.

The retrosynthesis in Scheme 6 began with a disconnection at the C12−C13 bond of the seco-amino acid **6** to reveal two fragments of similar size and complexity. In a forward sense, the union of aromatic **20** and aldehyde **21** fragments was accomplished using a *syn*-aldol reaction. All three *syn* methyl-methoxy group relationships of macbecin (C6−C7, C10−C11 and C14−C15) were introduced using sequential asymmetric boron-mediated aldol processes [37]. The C12-stereocenter was introduced using chelate-controlled reduction of ketone.

The *syn*-stereocenters (C14−C15) of the 2-mercaptothiazoline fragment **20** were generated using previously described sequence (refer to Baker's preparation of aromatic fragment **13** in Scheme 4).

The *syn* methyl-oxygen stereogenic centers (C6−C7 and C11−C10) of complex fragment **21** were installed using sequential Evans' aldol reactions [37] (Scheme 7). Treatment of *trans*-cinnamaldehyde **22** with the boron enolate of imide **10** afforded the aldol adduct **23** in 70% yield (dr 20:1). This allylic *syn*-alcohol **23** was

converted to the (*E*)-α,β-unsaturated aldehyde **24** in six steps (60% overall yield). Second iteration of the aldol reaction with imide **10** furnished the allylic alcohol **25** in 78% yield with 20:1 diastereoselectivity. Protection of C7-alcohol, transamidation, and ozonolysis were necessary to convert adduct **25** to the chiral aldehyde intermediate **21**.

Coupling of thioimide **20** with aldehyde **21** in a double stereodifferentiating aldol reaction was initially problematic (Scheme 8). Complex mixtures of products and low selectivity were obtained using boron and tin enolates. In a clever modification, the authors were able to obtain the desired aldol adduct **26** as a single diastereomer using the titanium enolate of **20**. Intended radical decarboxylation of the carboxylic acid derivative, obtained *via* hydrolysis of thiamide moiety of **26**, resulted in competitive β-lactone formation or reduction of the aromatic nitro group. This required an alternate decarboxylation method at C13 to complete the synthesis. Oxidation of C12-alcohol with Dess−Martin periodinane (90%), followed by lithium

Scheme 5.
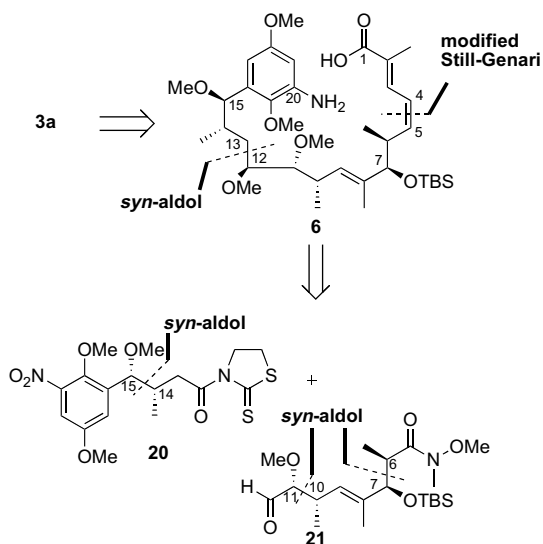
Scheme 6.

hydroxide hydrolysis of the thiazolidinethione and *in situ* formal decarboxylation, afforded the desired ketone **27** in 73% yield. Chelate-controlled reduction of ketone **27** with $Zn(BH_4)_2$ provided the (S)-C12-alcohol as a single diastereomer in 85% yield. Methylation of the resulting secondary alcohol with Meerwein's reagent, followed by DibalH reduction produced aldehyde **28** in 79% yield over two steps. The C2–C5 diene of the seco-amino acid **6** was incorporated using Horner–Emmons olefination of aldehyde **28** with phosphonate reagent **29**. The resulting (E,Z)-conjugated ester was obtained in 70% yield, as a 3.7:1 mixture of olefinic isomers. Reduction of the nitro group with Lindlar's catalyst (94% yield) gave the anilinic ester that was subsequently hydrolyzed with LiOH to give the desired carboxylic acid **6**. The remaining steps in Evans' synthesis of macbecin I **3a** are similar to the reported sequence developed by Baker. This convergent synthetic route toward macbecin was completed in just 25 steps from

trans-cinnamaldehyde (longest linear sequence) and 1.2% overall yield.

2.3.3. Panek's total synthesis of (+)-macbecin I (1995)

While the first two enantioselective syntheses of (+)-macbecin I utilized Evans' chiral metal enolate-based bond construction to introduce stereogenic centers of the ansa chain, the approach by Panek and co-workers featured use of chiral crotylsilane methodology (mechanistically, fundamentally different) (Scheme 9) [41,42]. Homologation of the aromatic acetal **30** to the (E,Z)-dienoate **6** was achieved using crotylsilane reagents **31a–c**. This crotylation approach was used to install six out of seven stereogenic centers of the molecule (C6–C7, C10–C11, and C14–C15). The remaining C12-stereocenter was introduced using an alkoxy-directed hydroboration reaction developed in the Panek laboratory [43].

The synthesis of macbecin I **3a** was initiated with a TMSOTf-catalyzed condensation reaction between 2,5-dimethoxy-3-nitrobenzaldehyde dimethyl acetal **30** and (E)-crotylsilane reagent **31a** (Scheme 10). The homoallylic C15-methyl ether **32** was obtained in 89% yield and with high diastereoselectivity *via in situ*-generated oxocarbenium ion, which is illustrated in the antiperiplanar transition state in Scheme 10. The resulting α-alkoxy-β,γ-unsaturated methyl ester **32** was subjected to a borane-dimethyl sulfide hydroboration reaction [43]. In this intramolecular process, selective reduction of the methyl ester afforded good levels of regio- and diastereoselection in the olefin oxidation (dr 8.5:1) and the desired 1,3-diol **33** was obtained in 85% yield.

The 1,3-diol **33** was initially converted to α-methoxy aldehyde **34** in five steps and 64% yield (Scheme 11, Eq. (1)). Crotylation of aldehyde **34** with silane reagent **31b** installed C10–C11 stereocenters in 80% yield and moderate diastereoselectivity (dr 12:1). This *syn* bond construction reinstalled the C11-alcohol that was removed during preparation of **34**. In this
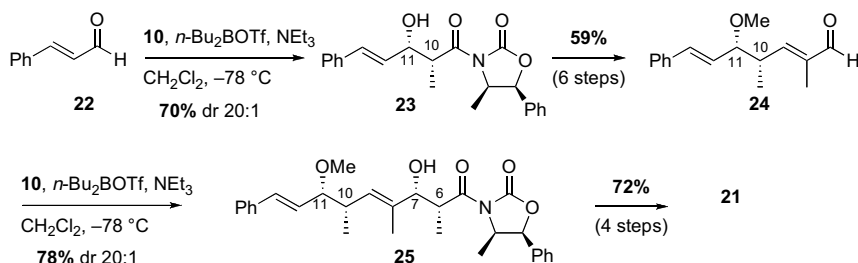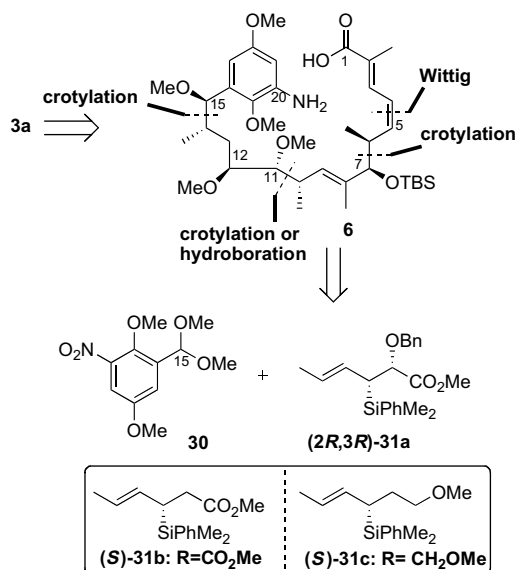

Scheme 7.
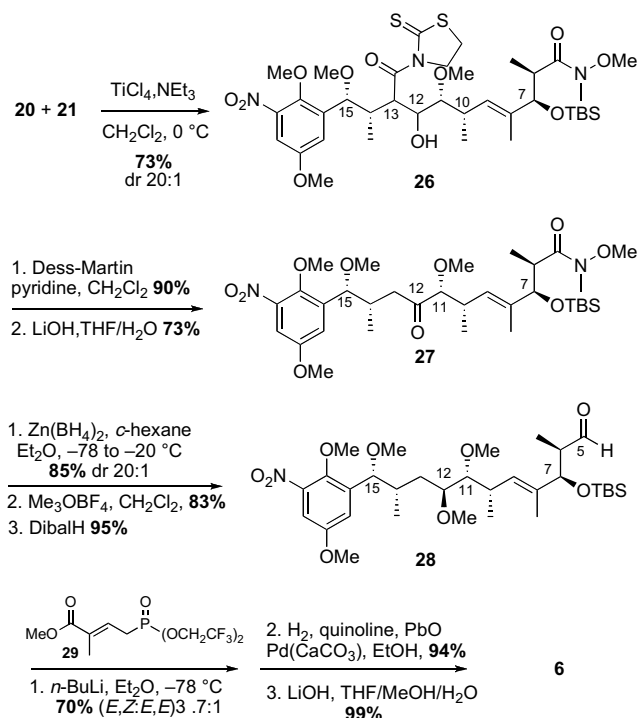
Scheme 8.

double stereodifferentiating reaction, C11–C12 stereocenters emerged *via* an *anti*-Felkin relationship, with crotylsilane **31b** overriding the chirality of aldehyde **34**. Ozonolysis of the aforementioned product gave the desired α-methyl aldehyde **35** in 65% yield.

An alternate route to α-methyl aldehyde **35** is illustrated in Scheme 11, Eq. (2). Conversion of 1,3-diol **33** to aldehyde **36** preserved the previously established C11 stereocenter (Scheme 10). Chiral aldehyde **36** was converted to the 1,1-disubstituted olefin intermediate **37** *via* a four-step sequence (alkylation with AlMe$_3$, oxidation, Wittig homologation, silyl deprotection) in 72% yield. Hydroboration of terminal allylic alcohol **37** with BH$_3$·THF complex afforded the desired 1,3-diol **38** in excellent yield (83%) and moderate diastereoselectivity (dr 5:1) [44]. Protection of the secondary C11-hydroxyl group in **38** and subsequent oxidation of the primary alcohol completed the preparation of the aldehyde **35**. Both reaction pathways produced the desired aldehyde **35** in ~30% yield from 1,3-diol **33** (seven steps for Eq. (1) versus 15 steps for Eq. (2), Scheme 11).

The final two stereocenters (C6–C7) of macbecin I were also introduced using a crotylsilane-based bond construction methodology (Scheme 12). Homologation of α-methyl aldehyde **35** to the α,β-unsaturated aldehyde **39** was accomplished *via* Wittig olefination, subsequent DibalH reduction of the ester and Swern oxidation of the primary alcohol. Condensation of aldehyde **39** with crotylsilane reagent **31c** in the presence of 4-acetoxybenzyl trimethylsilyl ether afforded the protected *syn*-alcohol **40** in 92% yield (dr 20:1). Intermediate **40** was converted to the (*E,Z*)-conjugated acid **6** *via* sequential phosphorus-based olefinations
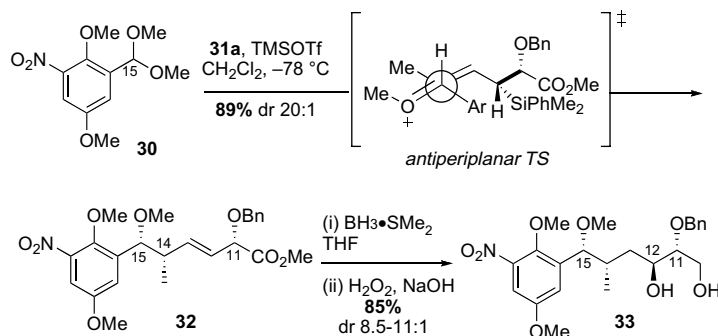
Scheme 9.

Scheme 10.

(Horner–Emmons and Wittig). Similar known methods for macrocyclic ring closure and functional group interconversion completed the synthesis.

Panek's synthesis of (+)-macbecin I **3a** relied on use of chiral (*E*)-crotylsilane methodology to construct six of seven stereogenic centers of the molecule. Macbecin was completed in 29 steps and 0.78% overall yield starting from *p*-methoxyphenol (longest linear sequence). This convergent approach differed from Baker's and Evans' use of metal enolate-based methodology to prepare the ansa chain.

2.3.4. First total synthesis of geldanamycin by Andrus (2002)

Andrus and co-workers accomplished the total synthesis of geldanamycin **1** in 2002 [45]. The long delay between isolation (1970) and synthesis may be attributed to challenges accompanied with the molecular architecture of geldanamycin. Unlike herbimycin A and macbecin I, geldanamycin possesses a C17-

methyl ether on the quinone, but lacks the methoxy group at C15. The latter prevents use of aldol reaction to generate the C14–C15 stereochemistry and represented different synthetic challenges not directly amendable to an alcohol based bond construction (Scheme 13). In addition, the C11 stereocenter is a hydroxyl group as opposed to the methyl ether present in other benzoquinone ansamycins.

A linear approach was undertaken by Andrus to accommodate structural changes present in the ansa chain of geldanamycin (Scheme 13). Assembly of the seco-amino acid **41** was envisioned to come from sequential aldol and olefination reactions starting from aldehyde **42**. Specifically, *anti*-glycolate aldol with an oxapyrone boron enolate was utilized to set the stereochemical relationship between the C11–C12 functionalities [46].

Synthesis of acyclic geldanamycin **41** utilized auxiliary-directed addition reactions to install the stereogenic centers (Scheme 14). The necessary benzyl
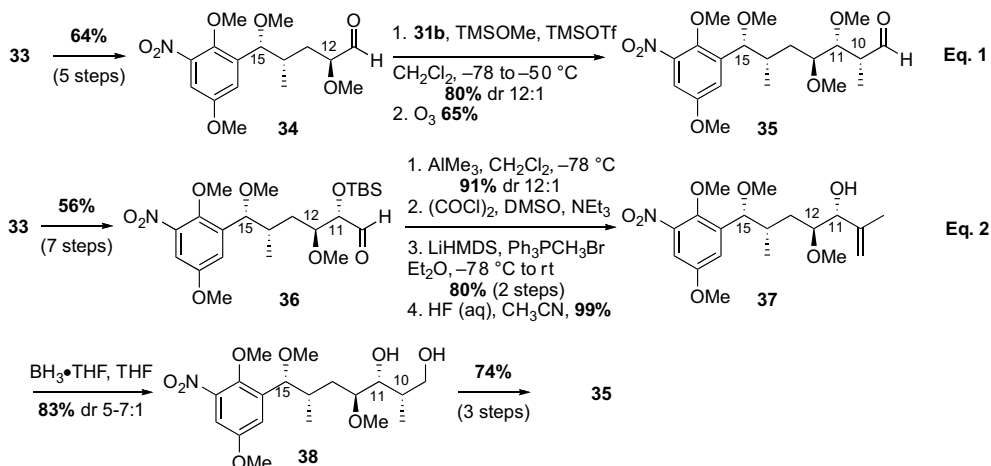
Scheme 11.
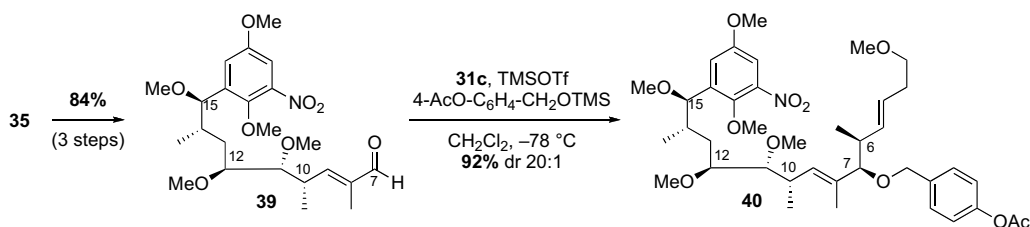
Scheme 12.

bromide **43** was prepared from 1,2,4-trimethoxybenzene in four steps (56% yield). Asymmetric Evans' alkylation [47] was used to introduce the methyl group at C14. Treatment of alkyl bromide **43** with the sodium enolate of (S)-**44** afforded the desired adduct **45** in good yield and selectivity. The auxiliary product **45** was converted to the aldehyde **42** in just three steps. To install the C12-stereocenter, the authors applied an *anti*-glycolate aldol reaction using chiral dioxanone **46** [46]. Condensation of aldehyde **42** with "locked" E(O)-boron enolate of oxapyrone **46** yielded the *anti*-aldol product **47** with 10:1 diastereoselectivity (70% yield). This methodology complements the predominantly *syn*-glycolate adducts obtained from acyclic auxiliaries (Z(O)-enolates) or addition of allylmetal reagents containing (Z)-γ-alkoxy functionality [48]. Removal of the auxiliary and installation of the C10-methyl and trisubstituted alkene were accomplished using known methods [41,44]. The C6–C7 diol was introduced using the *syn*-glycolate aldol reagent **49**, derived from (−)-norephedrine as previously developed by Andrus [49]. Reaction of aldehyde **48** with the Z(O)-enolate of glycolate **49** afforded allylic alcohol **50** in 90% yield and high selectivity. Homologation of alcohol **50** to conjugated acid **41** proceeded smoothly using previously described olefination procedures.

The key steps for completion of the synthesis were macrocyclization, carbamate installation and quinone oxidation. Cyclization of **41** in the presence of BOP–Cl provided the 19-membered core **51** in 76% yield

(Scheme 15). Selective removal of TES ether with TBAF, followed by urethane formation using trichloroacetylisocyanate [50] proceeded in 80% yield over two steps. Removal of C11-TBS ether was achieved using aqueous hydrogen fluoride to furnish geldanamycin precursor **52** in 95% yield. Formation of the *p*-quinone from the trimethoxy precursor **52** proved challenging due to unforeseen conformational and electronic issues of the molecule. Various oxidants such as CAN or AgO/HNO₃ were examined, but the dominant product from these reactions was the aza-quinone **53**. Ultimately, the use of nitric acid permitted formation of the desired *p*-quinone product **1**, albeit as the minor product (1:10, *p*-quinone/*o*-quinone).

The structurally distinct ansa chain of geldanamycin proved to be a challenging molecule for total synthesis. Andrus and co-workers developed two glycolate aldol reactions to introduce the key stereogenic relationships at C11–C12 and C6–C7. The synthetic product **1** was obtained in low overall yield (0.05%, 41 steps, starting from 1,2,4-trimethoxybenzene) due to competitive *o*-quinone formation **54**. Since their initial publication, Andrus and co-workers reported a model study on the *p*-quinone formation, which can be selectively produced from mild oxidation of the 1,4-dihydroquinone precursor [51].

2.3.5. Panek's approach to the synthesis of herbimycin A (2004)

Due to their complex structural architecture and biological properties, the Panek laboratory has
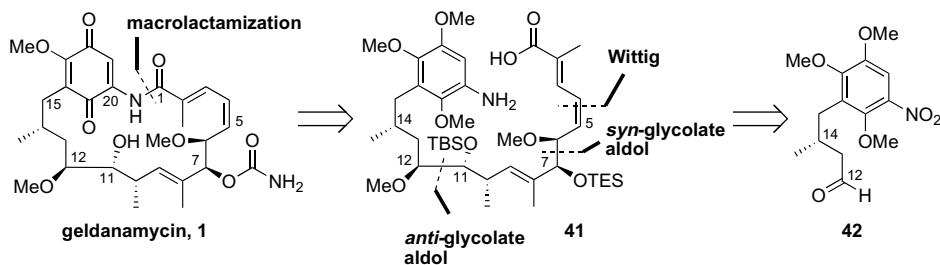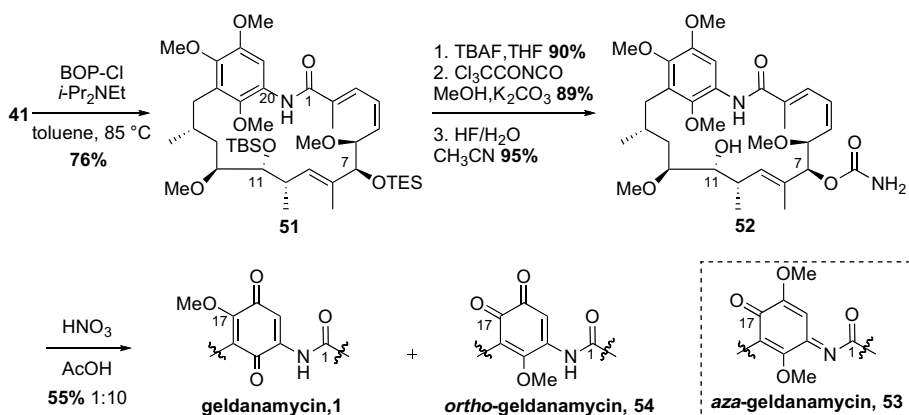

Scheme 13.
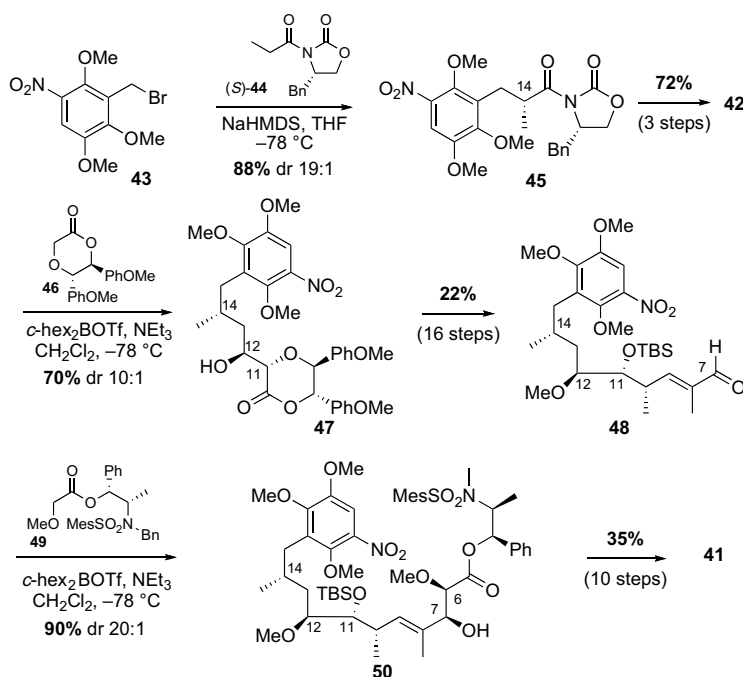
Scheme 14.

maintained an interest in the synthesis of ansamycins for over 15 years. The stereochemistry of the ansa chain inspired development of the crotylsilane-based reagents to construct key fragments of this class of natural products. Prior to this publication [52], the only previous synthesis of herbimycin A **2a** was reported by Tatsuta in 1991 (see Section 2.4.1) [44,53]. This natural product differs from macbecin I **3a** at the C6 position by having a methyl ether instead of a methyl group. The retrosynthesis of herbimycin A begins with the disconnection of the C1–N20 amide bond (Scheme 16). The two *syn*-methoxy-methyl stereocenters at

C10–C11 and C14–C15 were introduced using sequential crotylations with chiral silane reagents **31a–b**. The C6–C7 *syn*-diol of acyclic framework **55** was envisioned to come from Brown's asymmetric allylboration methodology [54].

The common left-hand motif of macbecin and herbimycin, aromatic fragment **39**, was prepared as described previously (Section 2.3.3) [41]. Asymmetric allylboration of aldehyde **39** with γ-methoxyallyl organoborane reagent **56** introduced the desired *syn*-relationship between the C6–C7 stereocenters (Scheme 17). The corresponding allylation adduct **57**

Scheme 15.

Scheme 16.
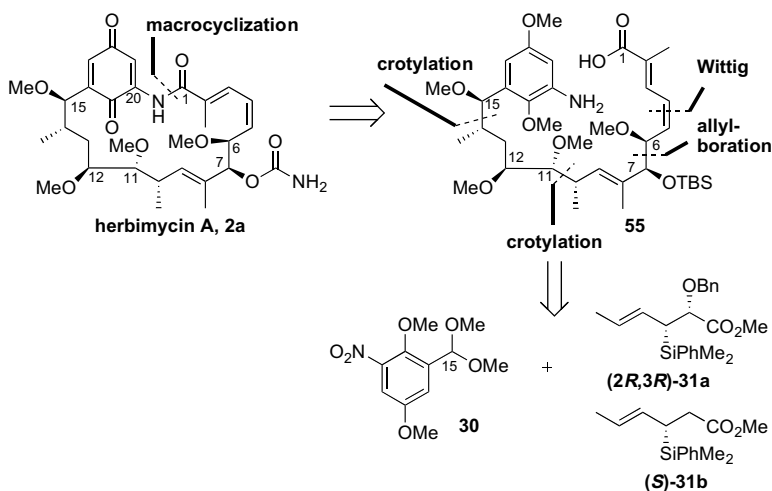
was obtained as one diastereoisomer in 77% yield. Following previously published methodology for the synthesis of macbecin, Panek and co-workers completed the synthesis of herbimycin A **2a**.

This report documents reliability and high levels of stereoselectivity that can be attained using crotylsilane methodology. With that said, synthesis of herbimycin A was realized quickly (31 steps with 0.57% yield beginning with *p*-methoxyphenol) following reported protocols due to structural similarities of these ansamycin natural products.

### 2.3.6. First total synthesis of reblastatin by Panek (2005)

In 2000, Takatsu isolated the benzenoid ansamycin, reblastatin **5a**, possessing structural similarity to geldanamycin [30]. The presence of a phenol and C17-methoxy group, as well as saturation at C4−C5 olefin of the C1−C5 dienoate, presented a new synthetic challenge. Mindful of these subtle architectural differences within the ansa chain the Panek group set out to design a convergent synthesis of the natural product.

Strategy for the synthesis of reblastatin **5a** focused on a late-stage copper-mediated aryl amidation for

macrolide formation (Scheme 18). Intramolecular copper-mediated amidation of acyclic skeleton **58** was anticipated to form the 19-membered macrolactam. A second disconnection was envisaged at the C7-allylic alcohol to give alkyne **59** and aldehyde **60**. Addition of an (*E*)-vinyl zirconium species, derived from **59**, to aldehyde **60** would allow for convergent assembly of the acyclic framework **58**. Sequential crotylation reactions installed the four stereogenic centers of the aromatic intermediate **59**, while the α-methoxy aldehyde **60** was obtained from a readily available compound present in the chiral pool.

The preparation of aldehyde **60** was possible from chiral furanone **61** (Scheme 19). Lactone **61** was prepared from L-glutamic acid in three steps (64% yield) [55]. Protection of the alcohol in **61** as a TBS ether, followed by DibalH reduction of lactone provided the intermediate lactol. Treatment of the resulting lactol with (carbethoxyethylidene)triphenyl phosphorane furnished the desired unsaturated ethyl ester **62** in 73% yield (three steps). The C6-alcohol was converted to the desired aldehyde partner **60** in three steps (93%).

The preparation of the methyl alkyne fragment **59** is shown in Scheme 20. Commercially available
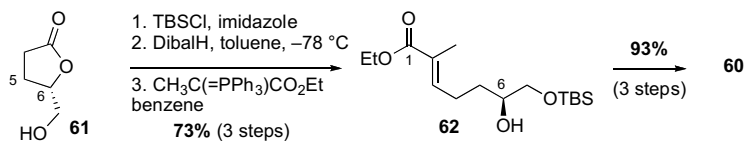

Scheme 17.

Scheme 18.
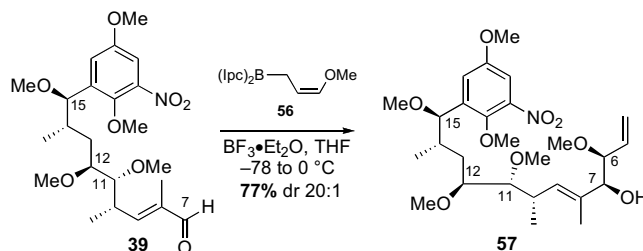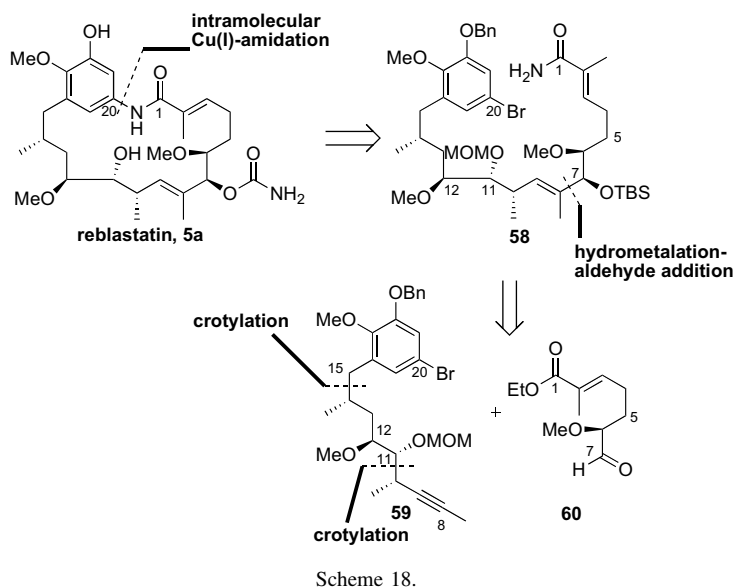
2,3-dihydroxybenzaldehyde was functionalized to 5-bromobenzaldehyde **63** in three steps (57% yield). Crotylation of aldehyde **63** with (*E*)-crotylsilane reagent **31a** provided the desired C15-*syn*-homoallylic alcohol (dr 20:1) that was subsequently removed under ionic conditions (Et₃SiH, BF₃·OEt₂) to afford methyl ester **64** in 60% yield. Conversion of ester **64** to the α-methoxy aldehyde **65** was achieved utilizing a similar six-step sequence reported in Panek's synthesis of macbecin [41] and herbimycin [52] (Sections 2.3.3 and 2.3.5, respectively). A matched crotylation between aldehyde **65** and (*S,S*)-crotylboronate **66** [56] yielded *syn*-homoallylic alcohol as a single diastereomer. The resulting C11-alcohol was protected as a MOM-ether **67** (71% yield, two steps) and converted to the methyl alkyne **59** in a four-step sequence (Scheme 21).

Completion of the synthesis featured an asymmetric coupling of alkyne and aldehyde and an intramolecular aryl amidation reaction. To achieve crucial fragment assembly of advanced intermediates **59** and **60**, hydrometalation-aldehyde addition sequence was explored [57]. Hydrozirconation of **59** followed by transmetalation and addition to aldehyde **60** afforded the desired allylic alcohol **68** as one diastereomer in

55% yield. In order to obtain the desired regioselectivity (dr 20:1) in the hydrozirconation process, elevated temperatures and greater than 2 equiv of Schwartz's reagent were necessary. After protection of the C7-alcohol as a TBS ether, the ethyl ester was converted to the unsaturated amide **58**. The crucial macrocyclization step was attempted using Buchwald's amidation conditions [58]. Although Buchwald demonstrated that his Cu(I) system can generate five-membered heterocycles [58,59], Panek and co-workers wanted to determine if the reaction conditions would transfer to macrocyclic lactams. Accordingly, subjection of the bromo-amide **58** to amidation conditions (CuI, K₂CO₃, diamine ligand) provided the desired 19-membered macrolactam **69** in 83% yield. Following macrolactamization, completion of the first total synthesis of reblastatin **5a** was accomplished in three steps (37% yield). Since the initial publication [36], several examples of intramolecular amidation to form macrolides of 10-membered rings or greater have been reported [60].

The first synthesis of phenol containing ansamycin, reblastatin **5a**, was achieved in just 25 steps and 0.79% overall yield beginning with 2,3-dihydroxybenzaldehyde.
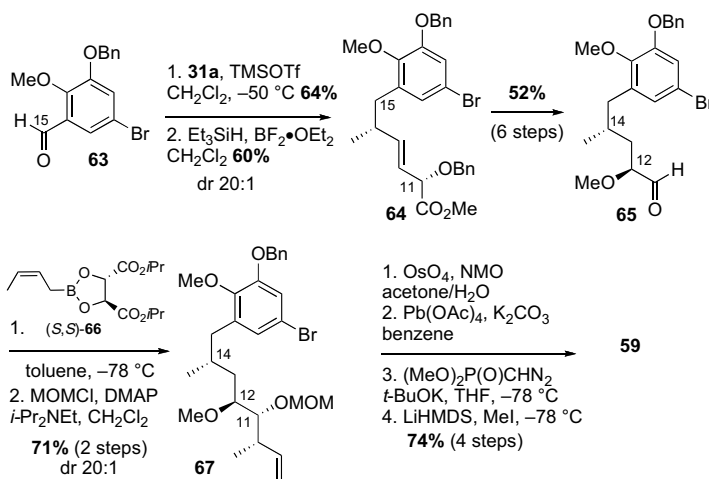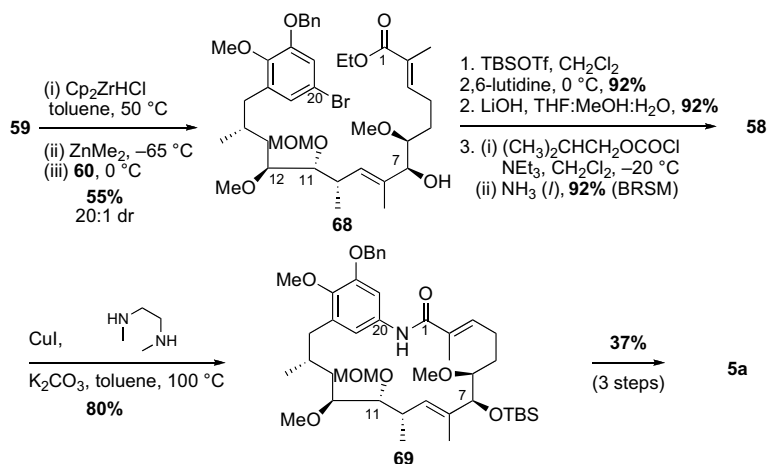

Scheme 19.

Scheme 20.

2.3.7. Panek's total synthesis of geldanamycin (2008)

In 2008, Panek and co-workers reported the second synthesis of the known Hsp90 inhibitor, geldanamycin **1** [61]. The convergent synthesis was highlighted by a scandium triflate pyran-ring opening reaction [62] and an enantioselective crotylation reaction to introduce the (*E*)-trisubstituted double bond and set the *syn*-relationship between the C10–C11 stereocenters of the molecule (Scheme 22). Macrocyclization was effected with an intramolecular copper-mediated amidation reaction of bromo-amide **70**, which was first utilized in the total synthesis of reblastatin **5a** [36]. The geldanamycin aromatic moiety was protected as bis-isoproxy ethers to facilitate late-stage deprotection followed by oxidation to the dihydroquinone, a problem encountered by Andrus and co-workers in their synthesis of geldanamycin [45].

The synthetic strategy for C13–C21 fragment **71** of the ansamycin framework featured a [4 + 2]-annulation followed by ScOTf₃/Et₃SiH mediated opening of an aryl C-glycoside (Scheme 23) [62]. Accordingly, annulation of 3-bromo-2,5-diisopropoxy-6-methoxybenzaldehyde **74** with (*E*)-*anti*-crotylsilane **75** was mediated with trifluoromethanesulfonic acid. The desired 2,6-*trans*-dihydropyran **76** was obtained in 84% yield with moderate diastereoselectivity (dr 4:1). Regio- and diastereoselective hydroboration of the *endo* cyclic olefin followed by methylation of the resulting secondary alcohol yielded the pyran opening substrate **77** in excellent yield. Reduction of the benzylic C–O σ-bond with scandium triflate in the presence of Et₃SiH [62] furnished the stereochemically well-defined acyclic fragment **78** in 72% yield and the de-isopropoxy byproduct **79**. Fortunately, phenol **79**
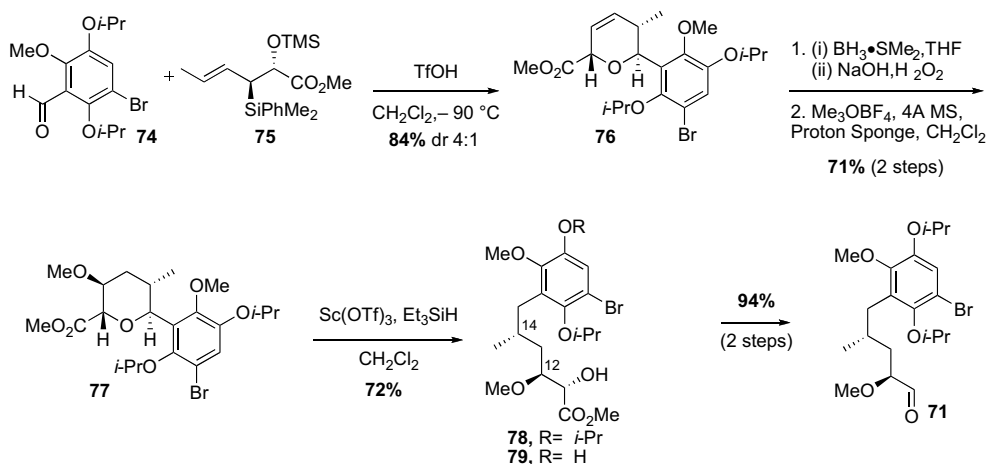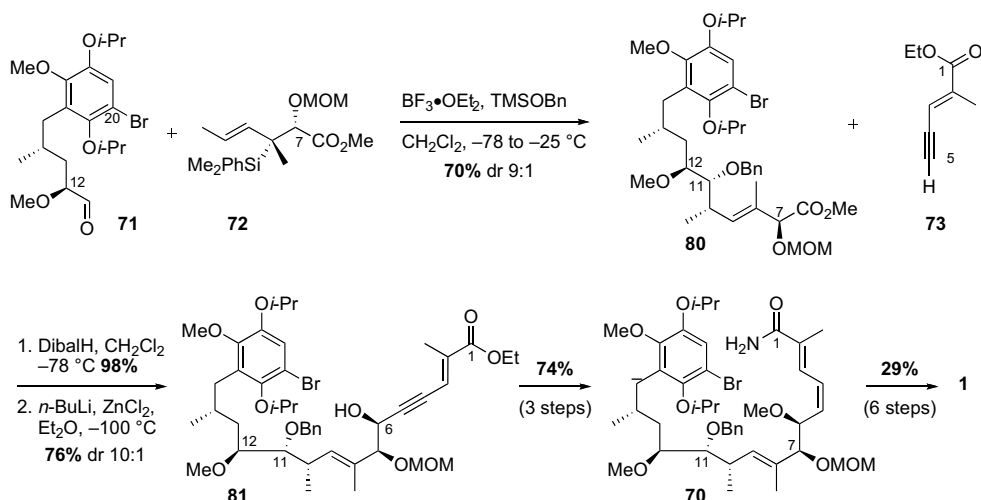

Scheme 21.

Scheme 22.
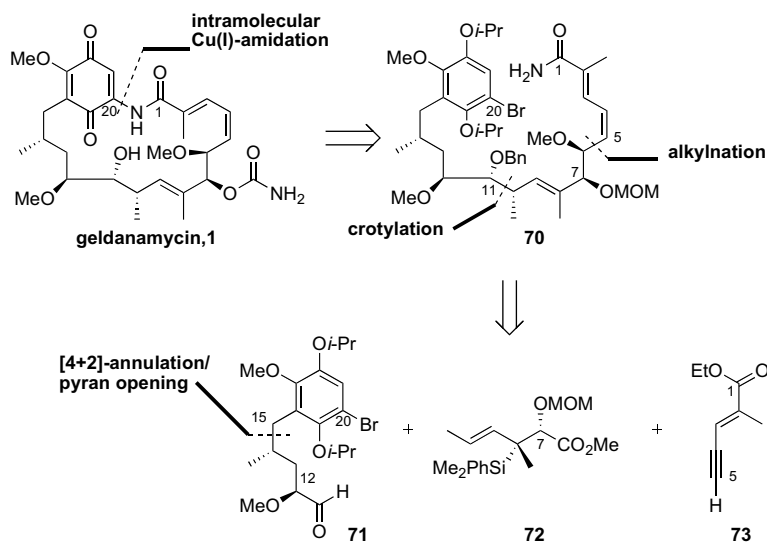
was recycled back to the desired product **78** and two-step functionalization procedure afforded α-methoxy aldehyde **71**.

Having the desired aldehyde **71** in hand, Panek group applied the newly developed crotylsilane reagent **72** [63] for installation of the remaining stereocenters of the C6–C21 fragment of geldanamycin (Scheme 24). Utility of methyl-substituted crotylsilanes was previously exploited in the [4 + 2]-annulation reaction during synthesis of a tetrahydropyran fragment of kendomycin by Panek and co-workers [63]. As anticipated, crotylation of silane **72** with aldehyde **71** in the presence of BF$_3$·OEt$_2$ proceeded to give benzyl protected homoallylic ether **80** in 70% yield with moderate selectivity

(dr 9:1). In a one step fashion, crotylation reaction installed the C10,C11-*syn* stereocenters, the C7-ether and the (*E*)-trisubstituted double bond.

Completion of the fully functionalized acyclic framework of geldanamycin featured a chelation-controlled addition of acetylene, Lindlar's reduction and intramolecular copper-mediated amidation reaction (Scheme 24). Sequential treatment of ester **80** with DibalH and metallated acetylide **73** furnished the propargylic alcohol **81** in 76% yield and good diastereoselectivity (dr 10:1). The Cram-chelate product **81** was further modified with the (*E*,*Z*)-conjugated amide **70** in three steps. Following a reported protocol for copper-mediated ring macrocyclization [36], the

Scheme 23.

Scheme 24.

19-membered core of geldanamycin was observed in 81% yield. Installation of the C7-carbamate moiety as well as bis-isopropoxyether deprotections [61] occurred without complication to provide the synthetic geldanamycin **1** in 2% overall yield (20 linear steps starting from commercially available 2-methoxy hydroquinone).

Panek's synthetic strategy of geldanamycin **1** differed vastly from the linear approach reported by Andrus. Specifically, reductive opening of pyran substrate and subsequent crotylation reaction yielded the functionalized C7–C21 fragment in high yield [61]. Further application of the intramolecular Buchwald amidation to stereochemically similar substrates (19-membered macrolactams) expanded the scope of the useful reaction. Having a short and high-yielding synthetic route toward geldanamycin allows for useful generation of structural derivatives of the natural product which could act as potential Hsp90 inhibitors.

2.4. Syntheses of ansamycins via late-stage union of aromatic moiety and C15-ansa chain

The second strategy employed in the synthesis of ansamycins involved coupling of the aryl lithium fragment with a functionalized C15-aldehyde ansa chain. Tatsuta first described this approach in 1991 in his synthesis of herbimycin A **2a**. A more recent account of this sequence was reported by Cossy in 2007. The two formal syntheses of macbecin by Martin and Kallmerten utilized masked aldehyde (lactol) ansa frameworks for union with the aromatic chromophore.

2.4.1. First total synthesis of herbimycin A by Tatsuta (1991)

The first total synthesis of herbimycin A **2a** by Tatsuta and co-workers featured fragment coupling of an aryl lithium derivative with a polyketide unit [44,53]. Disconnection at the C15–C16 bond of the seco-acid **55** reveals bromobenzene **82** and chiral aldehyde **83** (Scheme 25). In a forward sense, halogen–lithium exchange of **82** and addition to aldehyde **83** would introduce the required C15-hydroxyl group of the natural product. The assembly of fragment **83** was envisioned to come from homologation of methyl α-D-mannopyranoside (C11–C12, C14) and use of a metal-based asymmetric allylation reaction [54] to set the *syn* stereochemistry at C6–C7.
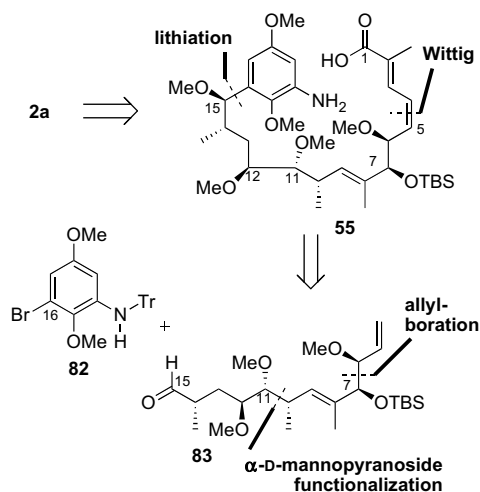
Scheme 25.
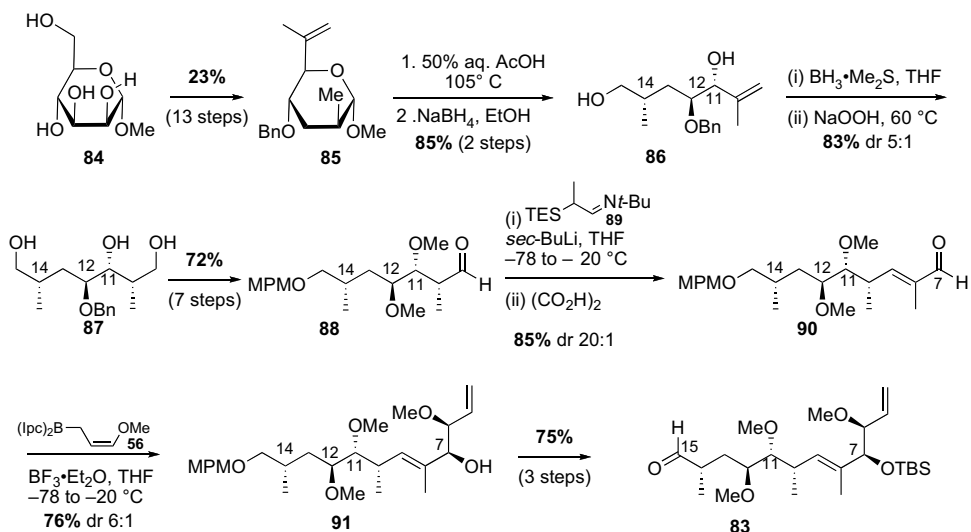
Scheme 26.

Synthesis of C5–C15 aldehyde fragment **83** proceeded in a linear fashion from a natural sugar (Scheme 26). Commercially available methyl-α-D-mannopyranoside **84** was converted to 1,1-disubstituted olefin intermediate **85** [64]. Hydrolysis of **85** was followed by NaBH$_4$ reduction to afford diol **86** with the required C11, C12, and C14 configurations. Asymmetric hydroboration of terminal olefin **86** provided triol **87** with the newly installed stereogenic center at C10 (dr 5:1). The triol **87** was functionalized to α-methyl aldehyde **88** and subjected to Corey–Schlessinger's olefination [65] conditions with imine **89** to provide the α,β-unsaturated aldehyde **90** in 85% yield (E:Z 20:1). Condensation of intermediate **90** with Brown's allylboration reagent **56** [54] afforded the syn-homoallylic alcohol **91** in 76% yield with moderate selectivity (dr 6:1). Protection of the C7-alcohol, MPM deprotection, and subsequent oxidation of the resulting primary alcohol produced aldehyde intermediate **83**.

Completion of herbimycin commenced with the assembly of the acyclic framework **92** (Scheme 27). Subjection of aldehyde **83** to the lithiated aromatic chromophore **82** resulted in formation of the secondary

benzylic alcohol **92** in a combined yield of 80% (dr 1:1). The undesired C15-epimer was conveniently recycled into the natural C15-epimer via a two-step process (56% yield). Following reported protocol for macbecin I **3a** [35], advanced intermediate **92** was converted to herbimycin A **2a** and thus concluded the first enantioselective synthesis of this ansamycin in 41 steps with 1.9% overall yield starting with methyl-α-D-mannopyranoside **84** (longest linear sequence).

2.4.2. Formal synthesis of (±)-macbecin I by Kallmerten (1990)

In 1990, Kallmerten reported a racemic synthesis of the carbon backbone of macbecin I with elegant use of sequential sigmatropic rearrangements (Scheme 28) [66]. Disconnection at the C15–C16 bond of rac-**18** reveals the aromatic bromide **93** and the lactol subunit rac-**94**. The aniline functionality was masked with a 2,5-dimethylpyrrole group. Racemic lactol **94** was envisioned to arise from successive [2,3]-Wittig rearrangements.

The preparation of the required C5–C21 fragment of macbecin I is illustrated in Scheme 29. Racemic diol **95** was transformed to tertiary allylic alcohol rac-**96** in eight steps and 57% overall yield. The alcohol was alkylated with chloromethyl oxazoline **97** and the obtained ether was treated with LDA to trigger [2,3]-Wittig rearrangement to produce rac-**98** in 75% yield with high diastereoselectivity (35:1). The Wittig rearrangement established the syn methyl-oxygen relationship at C10–C11 and simultaneously generated the desired (E)-trisubstituted olefin. A second sigmatropic
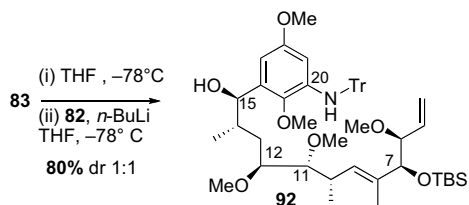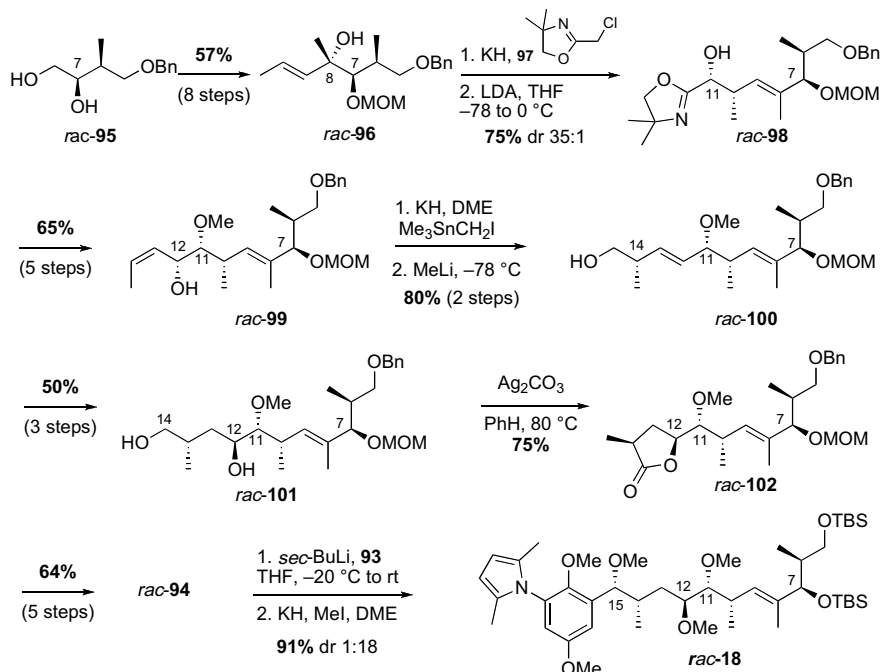

Scheme 27.
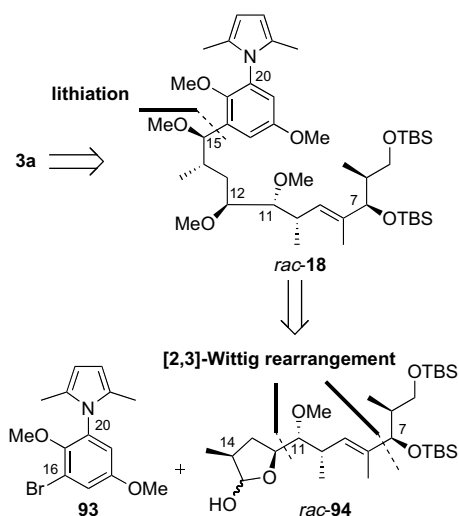
Scheme 28.

rearrangement was exploited to establish the remaining stereocenters of the ansa chain. The desired sigmatropic precursor, (Z)-allylic alcohol *rac*-**99**, was prepared from the Wittig adduct *rac*-**98** in 5 steps. Alkylation of the C12-alcohol *rac*-**99** with iodomethyl trimethylstannane and subsequent treatment with methyl lithium initiated the rearrangement. The resulting [2,3]-Wittig product *rac*-**100** installed the

C14-methyl group in 80% yield and as a single diastereomer. The disubstituted olefin in *rac*-**100** was chemoselectively oxidized to introduce the C12-hydroxyl *rac*-**101** *via* epoxidation and oxirane reduction sequence. Selective oxidation of diol *rac*-**101** with Fetizon's reagent afforded the desired lactone *rac*-**102** in 75% yield. The masked aldehyde *rac*-**94** was prepared from DibalH reduction of lactone *rac*-**102**. Exposing lithiated aryl chromophore **93** to lactol *rac*-**94** gave a mixture of diols that were subsequently alkylated with methyl iodide. Unfortunately, it was the minor product, *rac*-**18**, that contained the C15-methyl ether in the correct configuration. The authors suggested that the addition of anion **93** to lactol *rac*-**94** occurred *via* internal chelation with the C12-alcohol to give the Cram-chelate product as the major isomer.

It is important to note that aryl lithium additions to other ansamycin skeletal frameworks have proceeded in Felkin–Anh additions, resulting in the correct C15-stereochemistry. These experiments were first reported by Tatsuta and will be further discussed in the following two syntheses by Martin and Cossy.

2.4.3. Formal synthesis of (+)-macbecin I by Martin (1992)

In 1992, Martin and co-workers reported an asymmetric synthesis of macbecin I (Scheme 30) [67]. The

Scheme 29.
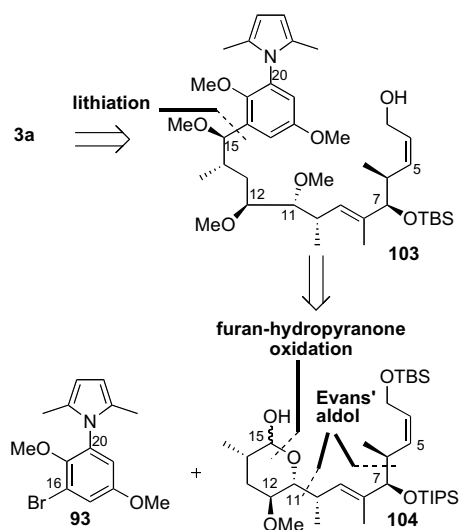
Scheme 30.

assembly of macbecin I precursor **103** would arise from an aryl addition of **93** to lactol **104**. The construction of skeletal framework **104** was expected to come from a furan-hydropyranone transformation adduct *via* functional group manipulation. The tetrahydropyran-ring system in **104** proved to be an excellent template for stereoselective introduction of

C14-methyl and C12-methoxy substituents. The *syn* methyl-oxygen relationships at C6–C7 and C10–C11 were incorporated using Evans' aldol reactions [37].

Martin's synthesis of the ansa chain utilized furan to pyranone oxidation, Evans' aldol and aryl alkylation reactions (Scheme 31). Condensation of 2-furaldehyde **105** with the *Z(O)*-boron enolate of **10** afforded the aldol adduct **106** in 92% yield. Oxidation of the furan **106** to dihydropyranone, followed by TBS protection of the resulting anomeric alcohol furnished a separable mixture of C15-isomers **107** (dr 3:1). Conjugate addition of lithium dimethyl cuprate to enone **107** in the presence of trimethylsilyl chloride yielded C14-methyl pyranone in 97% yield. Reduction of the pyranone with NaBH₄ proceeded stereoselectively with concomitant cyclization to give the γ-lactone **108** in 89% yield. Unfortunately, the various hydride donors examined all produced the undesired C12 axial alcohol. Inversion of the stereocenter to the correct C12-epimer was attained with a Mitsunobu reaction. Accordingly, lactone **108** was reduced to a diol and the primary alcohol was selectively protected as a TBS ether **109** in 58% yield (two steps). Exposure of the secondary alcohol **109** to *p*-nitrobenzoic acid and DEAD in benzene afforded the desired product **110** after hydrolysis (80% yield over two steps). The inverted C-12 alcohol was methylated
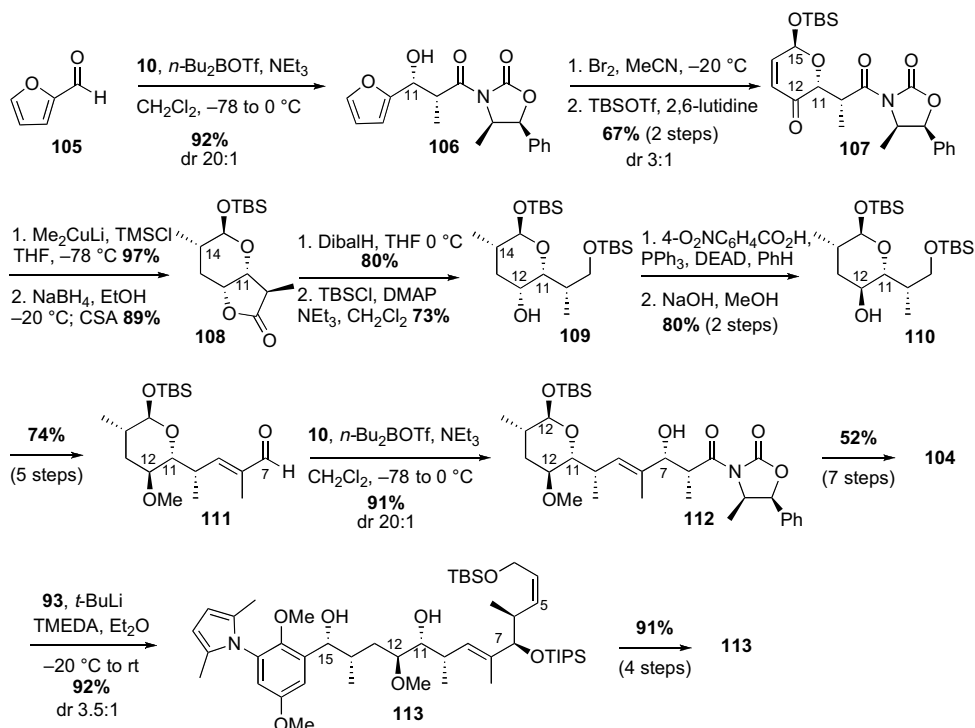
Scheme 31.

and subsequently homologated to α,β-unsaturated aldehyde **111**. Treatment of this aldehyde with the Z(O)-boron enolate of **10** gave the *syn* allylic alcohol **112** in 91% yield with high diastereoselectivity. Imide **112** was further derivatized to compound **104** over a 7-step sequence. Subjection of advanced intermediate **104** to lithium reagent **93** produced benzylic alcohol **113** as the major product (C15, dr 3.5:1). In contrast, addition of five-membered lactol to anion **93** provides the undesired epimer at C15 as the major product (see Section 2.4.2). The major isomer **113** was converted to alcohol **103**, an intermediate in Baker's synthesis of macbecin I (Section 2.3.1) which completed the formal synthesis of this ansamycin.

### 2.4.4. Cossy's synthesis of herbimycin A (2007)

Cossy and co-workers reported the most recent synthesis of herbimycin A. In their publication [68], the authors utilized aryl alkylation reaction of **115** and **83** to provide the seco-amino acid **114** (Scheme 32). The (Z)-olefin of the diene system **114** was envisioned to arise from a ring closing metathesis (RCM) [69]. Assembly of the aldehyde fragment **83** would arise from elongation of Roche ester **116** (16 steps and 25% overall yield) using sequential allylmetal additions to install five of six stereogenic centers (C6−C7 and C10−C12). In comparison, Tatsuta homologated the readily available methyl α-D-mannopyranoside **84** (28 steps and 3.6 overall yield) to establish three of six stereocenters of intermediate **83** (Scheme 26) [64].

The acyclic skeleton of herbimycin A was prepared using sequential allylmetal addition reactions (Scheme 33). Commercially available hydroxy ester **116** was converted to the homo-methyl aldehyde **117** in four steps and 80% yield. Exposing aldehyde

117 to allyltitanium reagent (S,S)-**118** provided the desired C12-homoallylic alcohol **119** with high yield and diastereoselectivity. Methylation of alcohol **119**, followed by olefin isomerization and subsequent oxidative cleavage, afforded α-methoxy aldehyde **120**. The *syn* stereochemical relationship at C10−C11 was constructed using a matched crotylation reaction of aldehyde **120** and (Z)-crotylboronate **66** [56]. The resulting homoallylic alcohol **121** was modified to α,β-unsaturated aldehyde **122** in four steps, including a Corey−Schlessinger olefination [65]. Addition of (Z)-γ-methoxy allylborane **56** [54] to aldehyde **122** afforded the *syn* product **123** in 69% yield after TBS protection of the nascent C-7 alcohol. The low diastereoselectivity (dr 4:1) observed in this oxy-allylboration reaction is consistent with Tatsuta's report on a similar system (Scheme 26). Interestingly, the presence of an aromatic chromophore in the aldehyde electrophile yields higher reaction selectivity (Scheme 17) [52]. Selective deprotection of TBDPS group with ammonium fluoride and oxidation of the resulting primary alcohol afforded the desired C5−C15 fragment **83**.

Completion of the ansa framework of herbimycin A utilized late-stage aromatic alkylation and RCM [69] reactions (Scheme 34). Addition of organolithium reagent **115** to aldehyde **83** gave a separable mixture of benzylic alcohol epimers. The desired Felkin−Anh product **124** was obtained in 54% yield from a 1.6:1 ratio of adducts. Advanced intermediate **124** was further functionalized to provide the RCM precursor **125** in five steps. The C7-acrylate was subjected to metathesis conditions with Grubbs II catalyst **126** to afford unsaturated lactone **127** in 72% yield. Reduction of the lactone **127** with DibalH and treatment of the resulting lactol with a stabilized phosphonate reagent completed the preparation of the (E,Z)-dienoate system **128**. Following reported protocols for macrocyclization and urethane formation, Cossy and co-workers completed the total synthesis of herbimycin A **2a**.

The synthesis of herbimycin A by Cossy is very comparable to the other reports in overall yield (1.5%, longest linear sequence) and number of steps (30, beginning with Roche ester **116**). The authors utilized selective allylmetal additions to install stereochemical relationships within the ansa chain of the natural product. Use of RCM to produce α,β-unsaturated lactone and thus setting the (Z)-olefin of the dienoate is a complimentary approach to the standard olefination procedures.
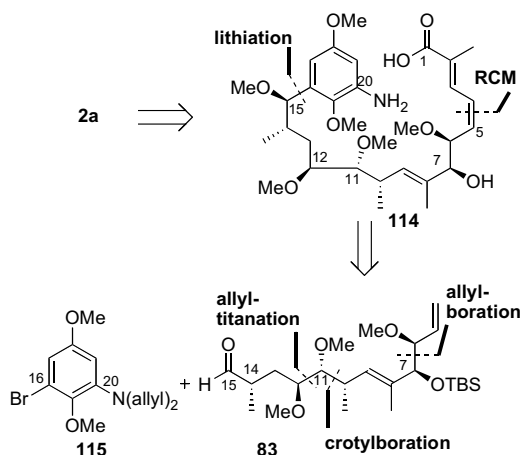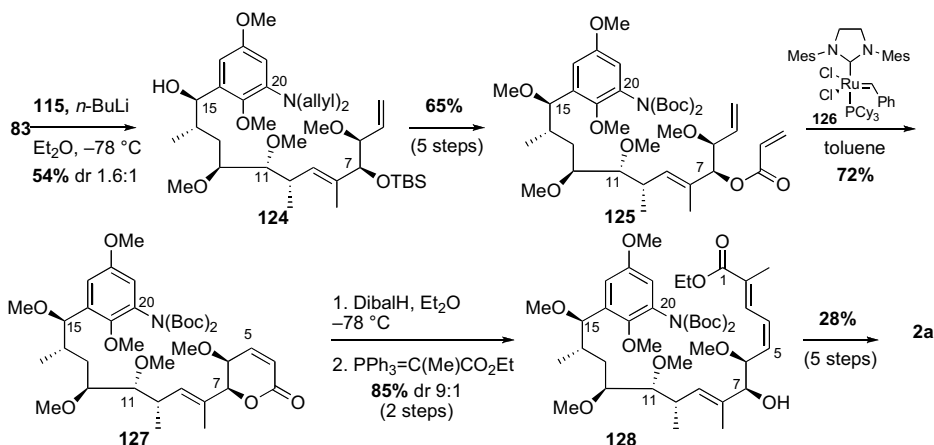

Scheme 32.
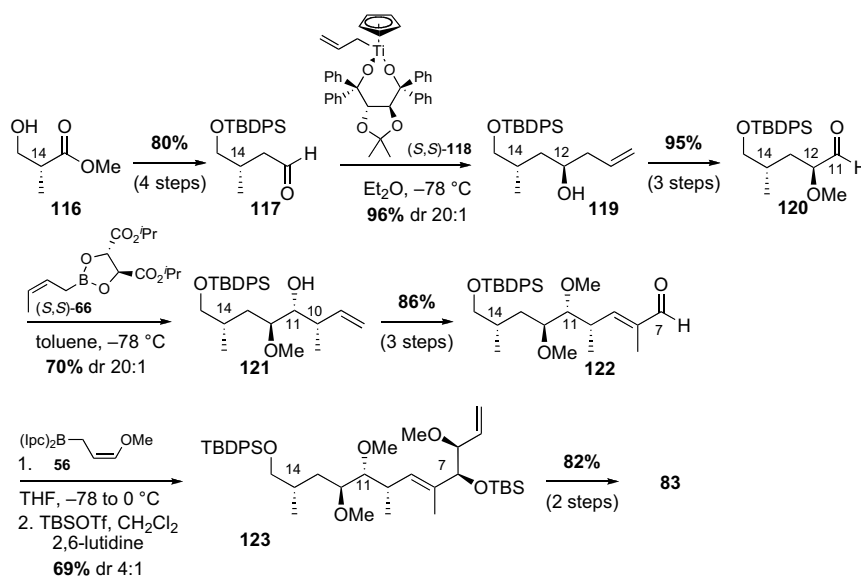
Scheme 33.

2.4.5. Micalizio's synthesis of (+)-macbecin I (2008)

The most recent total synthesis of (+)-macbecin I **3a** was reported by Micalizio and co-workers (Scheme 35) [70]. The preparation of the ansamycin antibiotic precursor **129** was envisioned through a metal-mediated reductive coupling of aniline methyl alkyne fragment **130** with β,σ-unsaturated aldehyde **131**. Nucleophilic addition and substitution as well as propargylation installed the required stereochemical relationships of the alkyne fragment **130**. Conversely, the (E,Z)-diene of the aldehyde fragment **131** was obtained via a palladium cross-coupling strategy.

Preparation of the C8–21 coupling partner **130** of macbecin is depicted in Scheme 36. Subjection of Roche ester derived α-methyl iodide **132** (three steps from Roche ester **116**) to pseudoephedrine based auxiliary **133** triggered formation of the alkylated adduct in moderate selectivity (dr 9:1). Reductive cleavage of the auxiliary and Dess–Martin oxidation of the resulting primary alcohol yielded α-methoxy aldehyde **134** in 70% yield over two steps.

Installation of the C11,C12-anti-stereochemistry of alkyne fragment **130** was triggered with a diastereoselective propargylation utilizing chiral allenyl stannane **135**. The newly emerged C11-homopropargylic alcohol **136** was obtained in modest yield and selectivity (50% yield, dr 4:1); partial epimerization of stannane **135** was responsible for the low

Scheme 34.

Scheme 35.
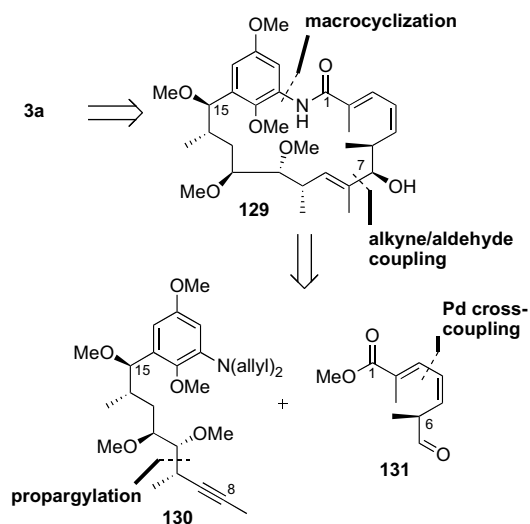
diastereoselection. The C11-alcohol was methylated and subsequently converted to aldehyde **137** in two steps. In analogy to Cossy's method, nucleophilic addition of the aryl lithium reagent derived from **115** to aldehyde **137** proceeded to give C15-benzylic alcohol in 81% yield, albeit low stereoselection (dr 2:1). Fortunately, the minor C15-isomer was recycled to the desired alcohol *via* a two step oxidation/reduction sequence. Methylation of C15-alcohol followed by deallylation furnished the required C8−C21 alkyne fragment **130** of macbecin.

The synthesis of the homoconjugated aldehyde **131** featured two successive Pd(PPh₃)₄ catalyzed reactions (Scheme 37). Accordingly, exposure of α-silyloxy aldehyde **138** with alkyne **139** in the presence of palladium(0) provided the *anti*-homopropargylic alcohol **140** in 82% yield and modest diastereoselectivity (dr 5:1). Sonogashira coupling of **140** with readily available vinyl iodide **141** furnished enyne

142 in high yield. Finally, a three-step derivatization of **142** effected formation of (*E*,*Z*)-diene containing aldehyde **131** in 90% yield.

Completion of the total synthesis of macbecin **3a** was highlighted by the titanium-mediated coupling reaction developed in Micalizio's laboratories (Scheme 37) [70]. Reductive titanium alkoxide mediated cross-coupling of a highly functionalized methyl alkyne **130** with the sensitive polyunsaturated aldehyde **131** provided a mixture of regio- and diastereomers **143** in 74% yield. Sequential exposure of alcohol **143** to LiOH and BOP−Cl afforded the desired macrocycle of macbecin **129** in 44% yield. Gratifyingly, the minor regio- and stereo-isomers obtained from the titanium-mediated coupling reaction were effectively removed. Urethane installation at C7-alcohol and oxidation of the aromatic moiety to quinone with CAN completed the preparation of (+)-macbecin **3a**.

Micalizio's synthesis of macbecin incorporates a more convergent route to the 19-membered macrolactam. The synthesis featured key reaction methodologies which afforded products in moderate yields and selectivities. Overall, the synthesis of macbecin was accomplished in 17 steps (1.3% yield, longest linear sequence) starting from commercially available Roche ester **116**.

2.5. Conclusions

In this account, different approaches toward the synthesis of C15-ansamycin antibiotics were surveyed. Macrocyclization of the ansa chain framework was completed utilizing either BOP−Cl coupling of the seco-amino acid or intramolecular copper-mediated amidation of a bromo-amide. The assembly of these acyclic skeletons relied on the biomimetic elongation of the aromatic moiety through sequential aldol, allylmetal, and/or alkylation reactions. An alternate strategy exploited late-stage union of the aromatic
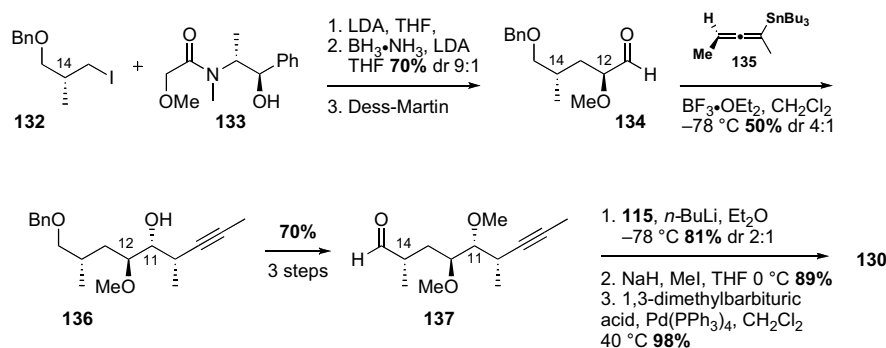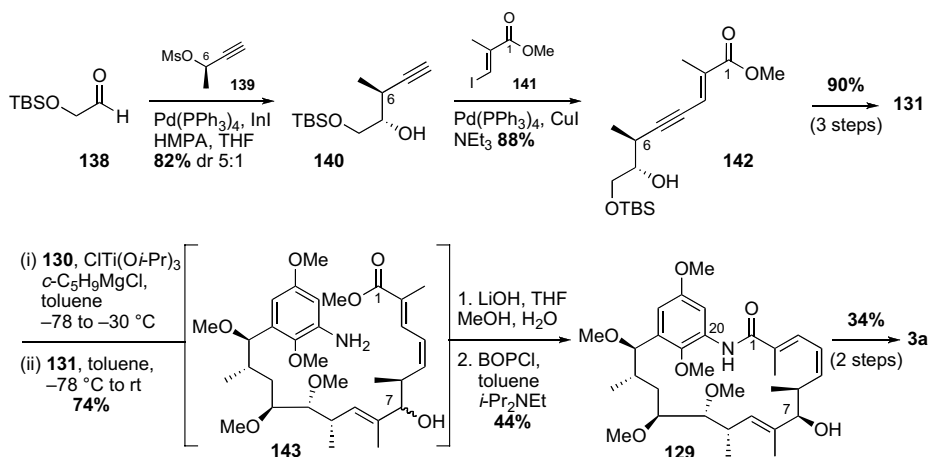
Scheme 36.

Scheme 37.

chromophore to the preformed C15-ansa chain. In this approach, various methodologies were successfully applied to install the required stereocenters of the molecule. Among these, [2,3]-Wittig rearrangement and a furan−pyran oxidation were developed. The C15-ansamycin class of natural products has served to further develop novel macrocyclization and asymmetric C−C bond forming reactions.
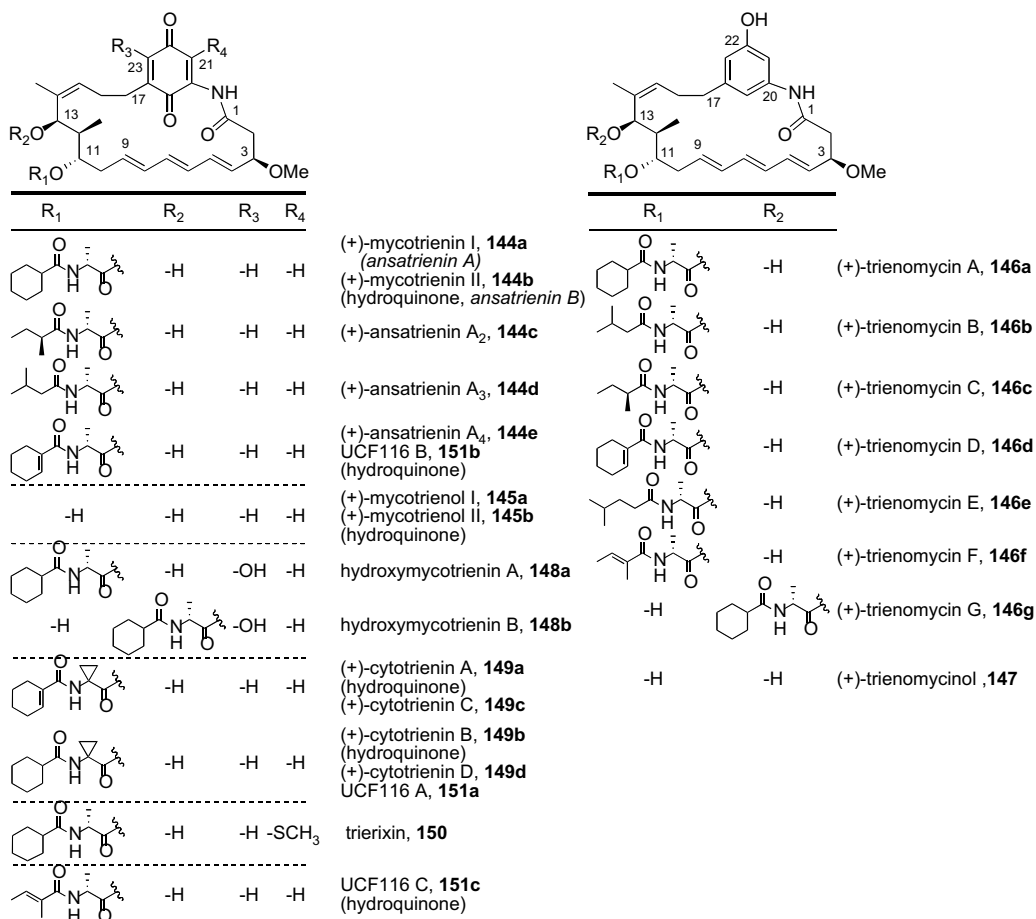

Fig. 6. Triene-ansamycin antibiotics.
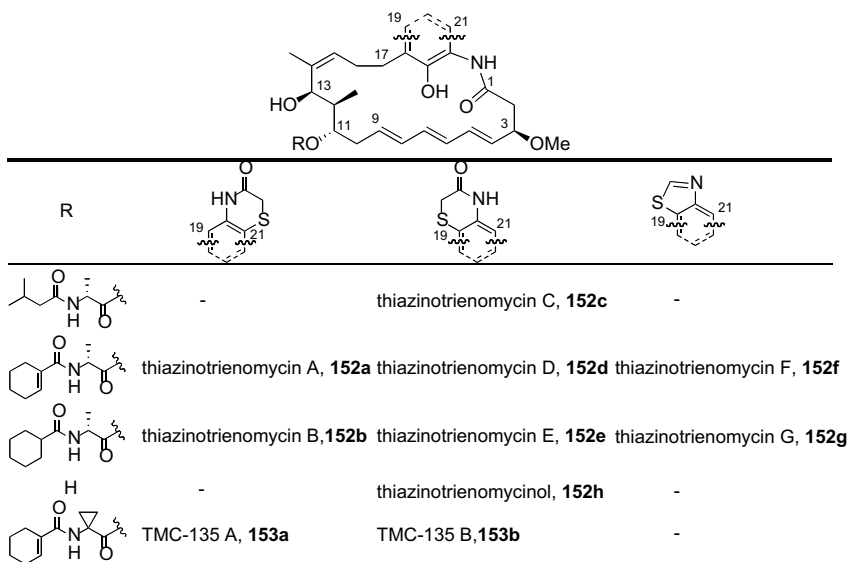
Fig. 7. Triene-ansamycin antibiotics.

3. C17-Benzene ansamycin antibiotics

3.1. Isolation, structure and bioactivity

Similar to the C15-ansamycins, the ansatrienins (or triene-ansamycins) constitute more than 30 members of the benzene ansamycin antibiotics (Figs. 6 and 7). Structurally, the C17-aliphatic ansa chain encompasses a C3-methyl ether and a C11−C13 stereotriad flanked by a (Z)-trisubstituted olefin and a conjugated (E,E,E)-triene. Notably, the ansatrienin biological diversity arises from the structural variations of the aromatic chromophore and the amino acid side chain at C11. The various oxidation states and substitution patterns define the aromatic moiety, whereas the C11 side chain is one of many N-acylated amino acids that are predominately derived from D-alanine or aminocyclopropane. These subtle structural changes originate in wide range of biological activities for ansatrienin ansamycins.

The parent compound of the C17-ansamycins, mycotrienin (renamed mycotrienin II), was first isolated from a strain of Streptomyces in 1967 by Coronelli [71]. Between 1981 and 1983, mycotrienins I and
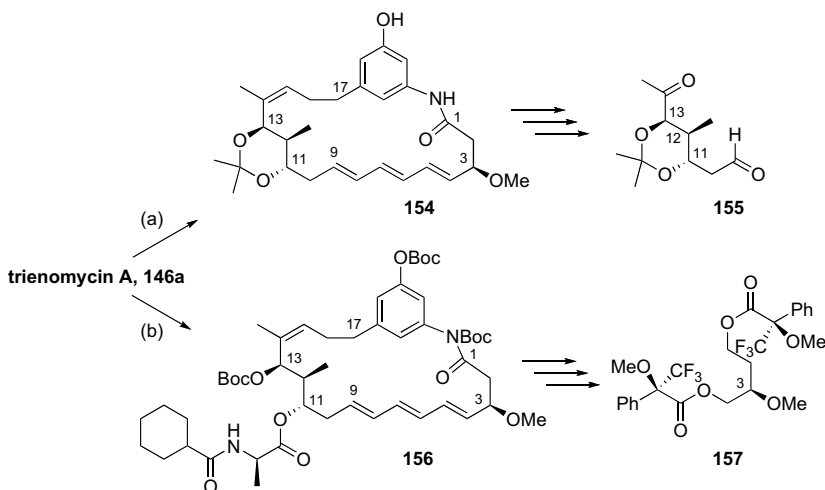
Scheme 38.
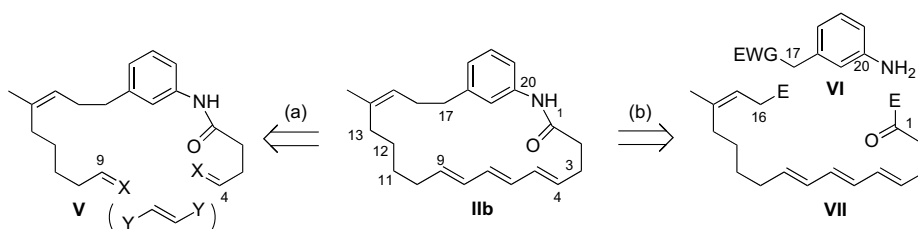
Scheme 39.

II (ansatrienins A and B) **144a–b** were isolated from fermentation broths of *Streptomyces collinus* [72] and *Streptomyces rishiriensis* T-23 [11a,73]. Additional three congeners, ansatrienins A_2–A_4 **144c–e** [11b,74], were elucidated as minor components of these cultures. They differ from the parent at the C11-acyl residue. The mycotrienins were shown to have potent antifungal activity, yet weak antitumor activity [11b,73b]. (+)-Mycotrienol I **145a** and its hydroquinone derivative (+)-mycotrienol II **145b** [75] are the least active natural products of this family, presumably due to lack of alanine-derived side chain at C11.

In 1985, Umezawa and co-workers isolated five new ansamycins, trienomycins A–E **146a–e**, from the culture broth of *Streptomyces* sp. No. 83-16 [76]. Not surprisingly, the trienomycins are very similar to ansatrienins except for the aromatic moiety (phenol versus quinone). In 1991, Smith and co-workers discovered and characterized another congener of the family, trienomycin F **146f** [77]. Although structurally similar to mycotrienins, trienomycins showed very little antimycobacterial properties, but rather exhibited promising *in vitro* cytotoxicity against HeLa-S3, PLC hepatoma and L5178Y murine leukemia cell lines

[76a,78]. The difference in the bioactivity (antibacterial versus antitumor) of the triene-ansamycins was later ascribed to the nature of the benzenoid moiety.

Between 1995 and 2007, distinct members of the C17-ansamycins were isolated possessing various structural modifications. Hydroxymycotrienins A–B **148a–b**, produced by *Bacillus* strains [79], contain hydroxyl groups at C23 of the benzoquinone. On the other hand, cytotrienins A–D **149a–d** [80] possess an unusual aminocyclopropane carboxylic acid side chain. Among these, cytotrienin A notably demonstrated an ability to induce apoptosis in human acute promyelotic leukemia HL-60 cells with an ED_{50} value of 7.7 nM [81]. More recent additions to the ansatrienin family, trierixin **150** [82], UCF-116 A–C **151a–c** [83], and trienomycin G **146g** [84] were obtained from diverse culture broths of *Actinomycete* strains. These natural products were found to inhibit various enzymes and transcription factors involved in carcinogenesis or cellular stress.

A novel class of cytotoxic ansamycin antibiotics, thiazinotrienomycins A–E **152a–e** [85,86], was isolated in 1995 by Hosokawa and co-workers (Fig. 7). Thiazinotrienomycins are distinct from other
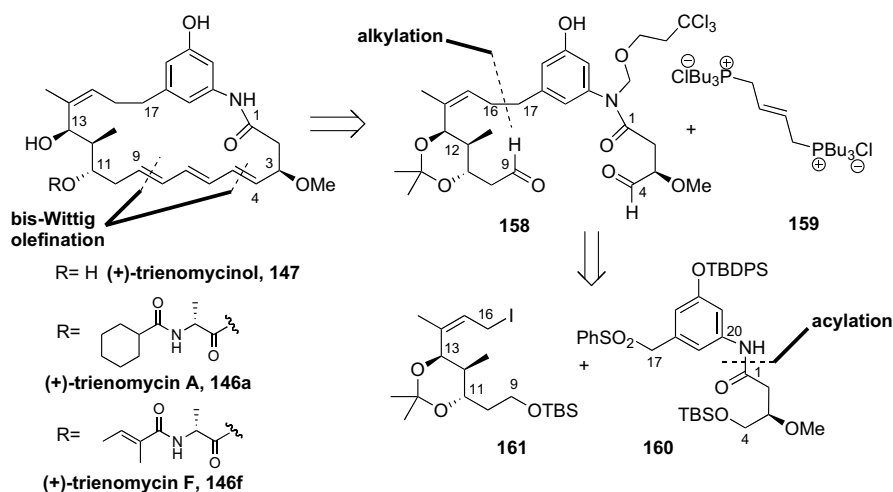
Scheme 40.

ansatrienins with the presence of a benzothiazine ring system. These heterocyclic ansamycins differ in the connectivity of the benzothiazine moiety and the structure of the C11-acyl appendage. Related compounds, thiazinotrienomycins **152f–g** [87], incorporate a benzothiazole ring as the aromatic chromophore. Other *in vitro* cytotoxic members of this family include TMC-135 A–B **153a–b** [88].

Although triene-ansamycin antibiotics displayed promising antitumor properties, they were overshadowed by the C15-ansamycins upon discovery of their effectiveness in disrupting the Hsp90 complex.

3.2. Structure elucidation: determination of absolute and relative stereochemistry of triene-ansamycins

In 1982, Zeeck and co-workers elucidated the molecular structure of triene-ansamycins using extensive NMR analysis [11b,74]. However, it took nearly 10 years before the relative and absolute configurations of the C17-ansamycins were assigned. Toward this end, Smith and co-workers conducted degradative and analytical studies on trienomycins A–C **146a–c** [89]. Deacylation of trienomycin A provided trienomycinol **147** (Fig. 6) that was subsequently converted to acetonide **154** (Scheme 38, path a). Ozonolysis followed by reductive workup furnished ketoaldehyde **155**. Analysis of the ^{1}H coupling constants within the dioxane ring of ketoaldehyde **155** revealed the C11–C12-*anti* and C12–C13-*syn* relative stereochemistry. To elucidate the absolute configuration of the C11–C13 fragment, Smith undertook and reported the enantioselective synthesis of the stereotriad's enantiomer, *ent*-**155**. The C9–C14 fragment synthesis of trienomycins by Fürstner [90] and Yadav [91] later confirmed these findings.

In order to assign the C3-methyl ether configuration of trienomycin A **146a**, the natural product was protected as

the tris-Boc derivative **156** (Scheme 38, path b). Reductive ozonolysis furnished a 1,4-diol that was subsequently derivatized as the bis-Mosher ester **157**. Comparison of spectroscopic data of **157** with authentic samples unequivocally established the (*R*)-configuration at C3. In a similar study, Smith and co-workers established the relative and absolute stereochemistries of mycotrienins I and II *via* chemical correlation of (+)-trienomycin A **146a** [92]. This investigative approach was also applied to the related heterocyclic thiazinotrienomycins [93]. These structure determination–stereochemical correlation studies have allowed for extension of stereochemical assignments (by analogy) to other members of the C17-ansamycin family.

3.3. Introduction: total syntheses of the triene-ansamycin antibiotics

This part of the account will provide a comprehensive overview of the synthetic approaches toward the ansatrienins. Specifically, previous total syntheses of (+)-trienomycins A **146a** and F **146f**, (+)-mycotrienin I **144a**/(+)-mycotrienol I **145a** and thiazinotrienomycin E **152e** are presented. In addition, two approaches for preparation of the macrocyclic cores of cytotrienins **149** and ansatrienins **144** are also depicted. In the course of these contributions, two distinct strategies emerged with regard to the retrosynthetic disconnections. The first approach utilizes a late-stage installation of the (*E,E,E*)-triene system with concomitant macrocyclization (Scheme 39, path a). The macrolactam formation **V → IIb** was achieved through tandem inter/intramolecular reactions (double stitching) or olefin metathesis. An alternative sequence relies on late-stage assembly of the aromatic core **VI** with the fully functionalized ansa chain **VII** (Scheme 39, route b). This second strategy offers more flexibility in the
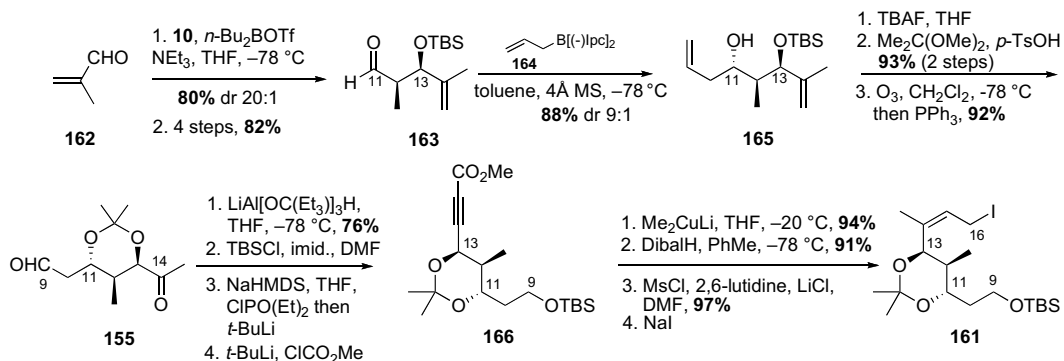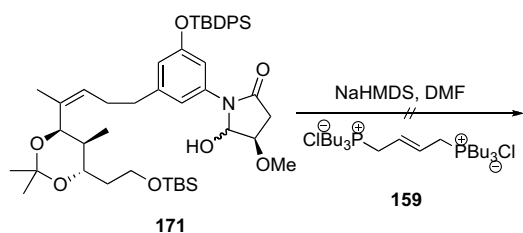

Scheme 41.
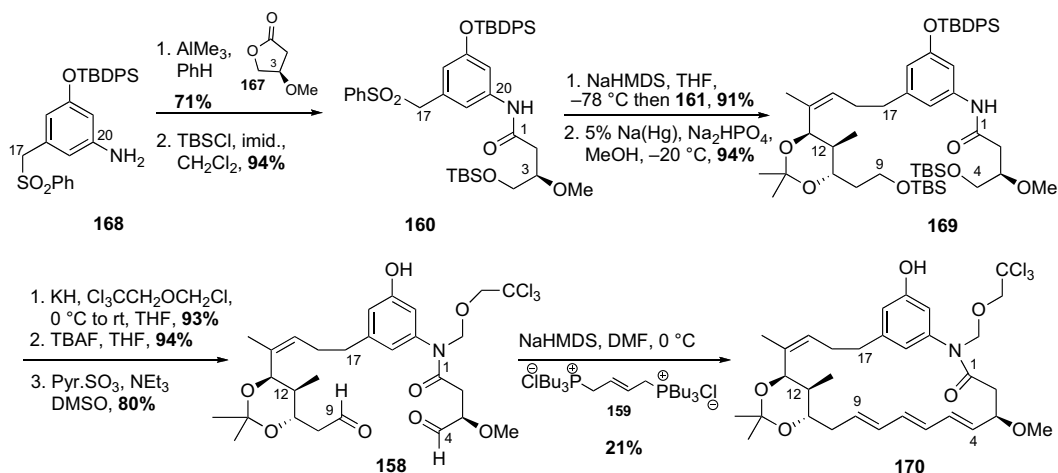
Scheme 42.

choice of the aromatic moiety and thus allows for rapid assembly of the different ansatrienins.

The next two sections will describe the different synthetic pathways, with particular emphasis on the installation of the C11–C13 stereotriad and the all (E)-triene system.

3.4. Approaches involving concomitant installation of the (E,E,E)-triene and macrocyclization

3.4.1. First total syntheses of trienomycins A and F by Smith (1995)

Smith and co-workers were the first to open up the field of the synthesis of triene-ansamycin antibiotics in 1995 [94]. From a retrosynthetic perspective, the trienomycins A **146a** and F **146f** were envisioned to come from a common advanced intermediate, (+)-trienomycinol **147** (Scheme 40). Construction of the (E,E,E)-triene moiety and thus macrocyclization was anticipated from a bis-Wittig olefination reaction of aldehyde **158** and phosphonium salt **159**. The C4–C23 fragment **158** would arise from alkylation of sulfone **160** with allylic iodide **161**. Acylation of aniline provided the aromatic fragment **160**.

Scheme 43.

The C11–C13 stereotriad of the allylic iodide fragment **161** was installed using Evans' aldol and Brown's allylboration reactions. Treatment of meth-acrolein **162** with the Z(O)-boron enolate of oxazoli-dinone **10** [37] afforded the desired *syn*-C13-alcohol in 80% and high diastereoselectivity (Scheme 41). The aldol adduct was then converted to the C11-aldehyde **163** in 82% yield over four steps. The *anti*-stereo-chemical relationship at C10–C11 was installed using Brown's allylboration reagent **164** [95]. The resulting homoallylic alcohol **165** was produced in 88% yield and with good selectivity (dr > 9:1). Removal of the C13-TBS ether with TBAF, followed by acetonide formation and ozonolytic cleavage afforded the ketoaldehyde **155** in 86% yield over three steps. The C9-aldehyde was chemoselectively reduced with lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride to primary alcohol and protected as TBS ether. Following Negishi's protocol [96], the C14-ketone was converted to the α,β-acetylenic ester **166** in 78% yield over two steps. Conjugate addition of lithium dimethyl cuprate to alkyne **166** furnished the required (Z)-trisubstituted olefin as one isomer (94% yield). A three-step trans-formation of methyl ester to allylic iodide completed the preparation of the advanced fragment **161**.

The key steps for formation of the macrocyclic core of trienomycins were aniline acylation, sulfone alkyl-ation and Wittig olefination. The required acylation coupling partners, γ-lactone **167** [97] and aromatic sulfone **168**,[1] were obtained from D-malic and readily available 3-hydroxy-5-nitrobenzoic acids, respectively.

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[1] Aromatic sulfone **168** was obtained from 3-hydroxy-5-nitro-benzoic acid in five steps, see Ref. [87].

Acylation of aniline **168** *via* ring opening of chiral lactone **167** and subsequent protection of the primary alcohol afforded the desired amide fragment **160** in 73% yield (Scheme 42). Sulfone **160** was deprotonated with NaHMDS and treated with allylic iodide **161**. Mercury-mediated desulfonylation furnished the desired Wittig precursor **169**. At this stage, the free amide was protected to prevent competitive formation of an *N*-acylhemiaminal **171**, which did not react under Wittig conditions (Scheme 43). Subjection of amide **169** to chloromethyl 2,2,2-trichloroethyl ether [98] followed by silyl ethers deprotection and Parikh–Doering oxidation delivered the bis-aldehyde **158** (70% yield, three steps). The critical Wittig olefination of **158** with phosphonate salt **159** effected macrocyclization with formation of the (*E,E,E*)-triene **170** (21% yield). A significant amount of other triene isomers (34%) was also detected.

Completion of the synthesis required selective installation of the amino side chains (Scheme 44). As such, phenol **172** was protected as a TBS ether and the amide was deprotected with (Na)Hg in MeOH to reveal intermediate **173**. Exposure of acetonide **173** to CSA unveiled the 1,3-diol at C11–C13. This intermediate was regioselectively esterified at C11 by a symmetrical anhydride of FMOC-D-alanine [89]. Liberation of the primary amine group with diethylamine followed by BOP-mediated coupling with either cyclo-hexenecarboxylic or tiglic acid provided the respective natural product precursors. Removal of the final protecting group ensued synthesis of trienomycin A **146a** and F **146f** in 38% and 23%, respectively, over the last three steps.

Smith and co-workers completed the first total synthesis of trienomycins and provided a viable route

toward the formal synthesis of mycotrienins. Trieno-mycin A was completed in 29 steps with 0.77% overall yield starting from methacrolein (longest linear sequence), while trienomycin F was obtained in 0.47% overall yield. The benzenoid moiety of trienomycins was oxidized to the corresponding quinone using Fre-my's salt [92]. Due to the low-yielding ring closure, alternative approaches were investigated to improve formation of the macrocyclic core of other ansatrienin congeners.

3.4.2. Total synthesis of (+)-mycotrienol I and (+)-mycotrienin I by Panek (1997)

Application of asymmetric crotylsilane bond construction methodology resulted in total syntheses of mycotrienin I **144a** and mycotrienol I **145a** in 1997 [99]. Installation of the triene moiety in mycotrienins was envisioned to come from Stille-type cross-coupling of bis-iodide **174** and enedistannane **175** (Scheme 45). This type of macrocyclization technique was previously applied in the synthesis of both rapa-mycin [100] and dynemycin [101]. Further discon-nection at C16–C17 bond revealed dimethyl acetal containing fragment **176** and sulfone intermediate **177**. The two subunits are closely related to fragments utilized in Smith's synthesis of trienomycins. The stereogenic centers of both the propionate unit **176** and aromatic sulfone **177** were installed using the cro-tylsilane reagent **31b** [41].

The preparation of the C9–C16 fragment **176** relied on use of enantioenriched silicon reagents to introduce the C11–C13 stereotriad (Scheme 46). Condensation of α-keto-dibenzylacetal **178** and (*E*)-crotylsilane reagent (*S*)-**31b** provided the homoallylic benzyl ether **179** in high yield and diastereoselectivity (80%, dr
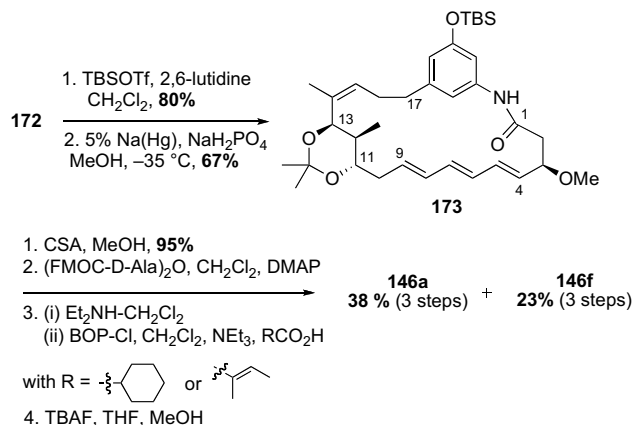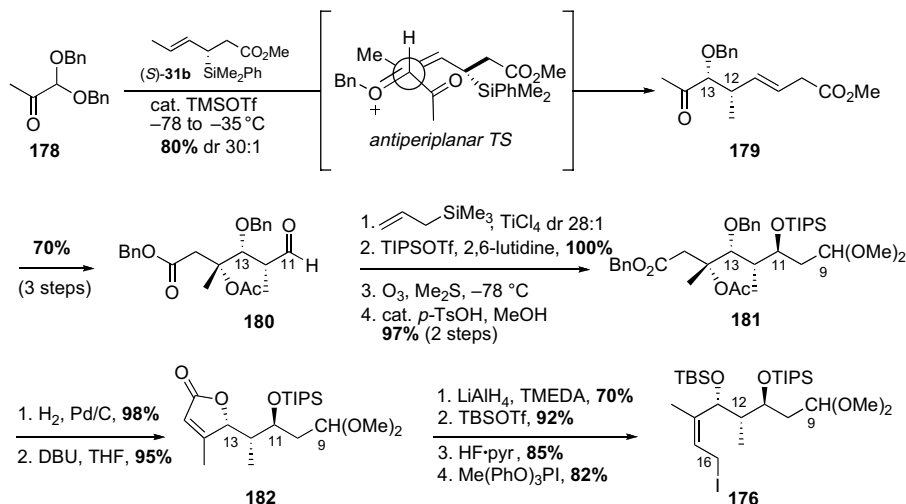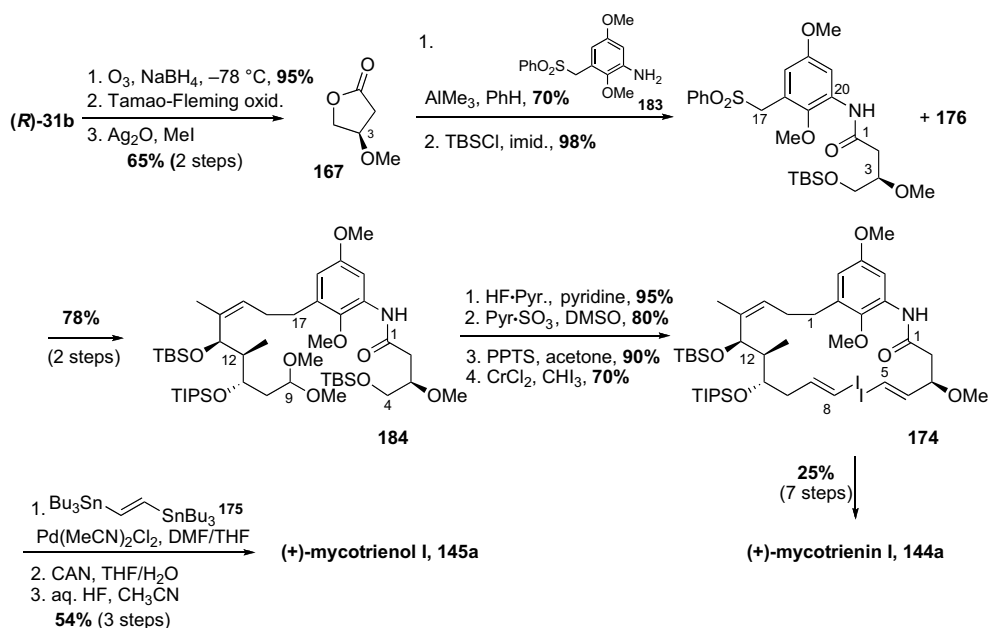

Scheme 44.
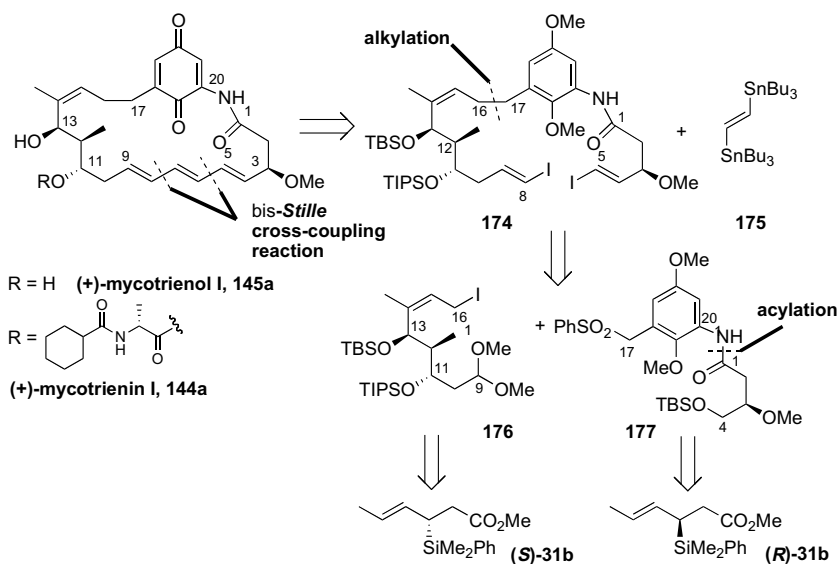
Scheme 45.

30:1). The *anti*-$S_{E'}$ mode of addition, illustrated in the antiperiplanar transition state, accounts for the high levels of relative and absolute stereocontrol. The crotylation product **179** was converted to α-methyl aldehyde **180** in 70% yield over three steps. Hosomi–Sakurai-type allylation [102] of **180** with TMS-allylsilane afforded the C11-alcohol with high diastereoselectivity. The 1,3-*anti*-relationship was rationalized by a nucleophilic addition to a titanium chelate between C13-benzyl ether and C11-aldehyde [103]. The newly emerged C11-alcohol was protected as TIPS ether and converted to dimethyl acetal

containing fragment **181**. Catalytic hydrogenation of benzyl groups effected simultaneous cyclization to γ-lactone. Elimination of the tertiary C14-acetoxy group with DBU afforded α,β-unsaturated lactone **182** in 93% yield over two steps. Reductive opening with LiAlH₄ unveiled the (Z)-olefin and subsequent conversion of the primary alcohol to allylic iodide provided the C9–C16 fragment **176** in 14 steps (21% overall yield).

Completion of mycotrienin I and mycotrienol I relied on construction of the Stille-type precursor **174** utilizing aniline acylation, sulfone alkylation and Takai
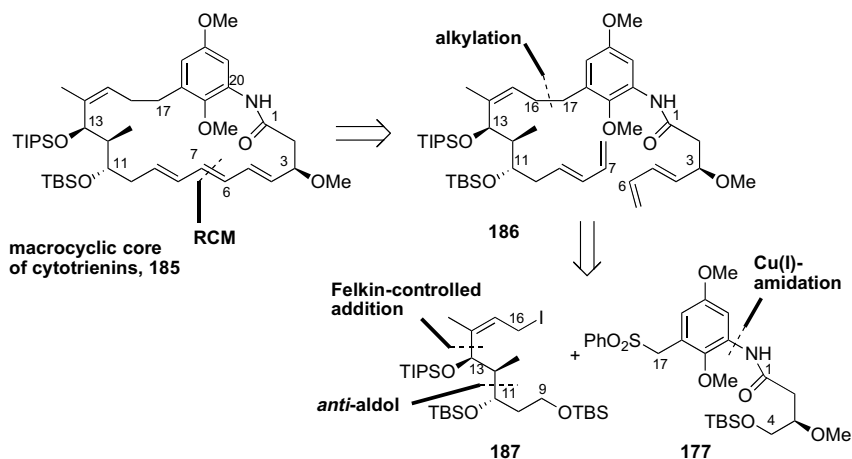

Scheme 46.

Scheme 47.

olefination reactions followed by macrolactamization (Scheme 47). Smith obtained the C3-methyl ether containing γ-lactone **167** from D-malic acid in four steps (refer to Scheme 44). Panek and co-workers modified their enantiopure crotylsilane reagent (*R*)-**31b** to prepare lactone **167** *via* Fleming−Tamao's procedure for silyl to hydroxyl interconversion. Acylation of 2,5-dimethoxy aniline **183** with lactone **167** in the presence of AlMe₃ provided the benzylic sulfone fragment in 70% yield. The resulting primary alcohol was protected as a TBS ether to complete the preparation of C4−C16 fragment **177**. The critical coupling

of benzylic sulfone **177** with allylic iodide **176** followed by reductive desulfonylation afforded the dimethyl acetal containing subunit **184** in 78% yield (two steps). Formation of bis-aldehyde substrate was achieved in three steps (68% yield). Subsequent homologation to the bis-(*E*,*E*)-vinyl iodide **174** was achieved using the Takai olefination protocol [104]. The crucial Stille-type "double stitching" cyclization of **174** with enedistannane **175** successfully installed the desired (*E*,*E*,*E*)-triene of mycotrienins. Oxidation of the aromatic core followed by immediate global deprotection of all masked oxygen atoms furnished

Scheme 48.
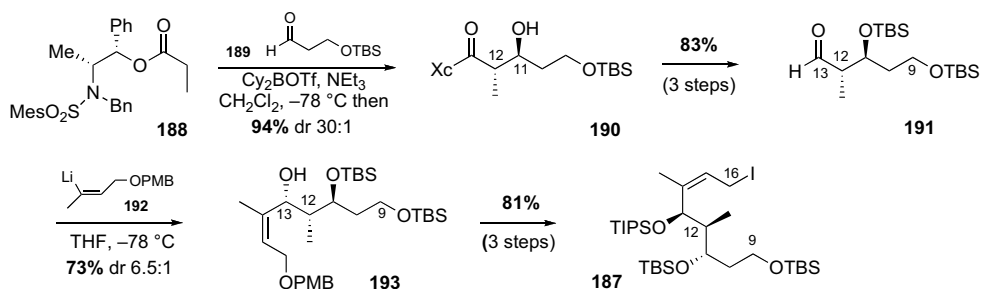
Scheme 49.

mycotrienol I **145a** in 0.86% overall yield over 27 steps (longest linear sequence starting from pyruvate aldehyde dimethyl acetal). In addition, selective deprotection of the C11-secondary TIPS group over the C13-TBS silyl ether permitted regiospecific introduction of the side chain following Smith's precedent [89]. Oxidation of the aromatic core and subsequent removal of the remaining protecting group delivered mycotrienin I **144a** in 0.40% overall yield over 31 steps.

The Stille-type cross-coupling strategy used in preparation of mycotrienins installed the configurationally pure (E,E,E)-triene. Since formation of other triene isomers was not observed, this method underscores the efficacy of this macrocyclization step.

3.4.3. Synthesis of the macrocyclic core of cytotrienins by Panek (2004)

Inspired by recent advances in ring closing metathesis reactions [105], the Panek group initiated a revised route to the macrocyclic core of cytotrienins **185** in 2004 (Scheme 48) [106]. It was predicted that RCM of bis-diene **186** would install the C4−C9

(E,E,E)-triene and simultaneously effect macrocyclization. Disconnection at the C16−C17 bond of the triene precursor **186** revealed the prevalent allylic iodide **187** and sulfone **177** fragments. In contrast to their previous work on the mycotrienins, the stereogenic centers (C11−C13) of the stereotriad fragment **187** were introduced using aldol and Felkin-controlled addition reactions. Alternatively, construction of the aromatic sulfone **177** was attempted using a copper(I)-mediated amidation reaction.

Preparation of the C9−C16 subunit **187** with aldol and anion addition reactions resulted in a more convergent and efficient sequence (46% over eight steps) than their earlier approach (21% yield over 14 steps). The synthesis of the stereotriad commenced with the installation of the *anti*-C11−C12 relationship utilizing Abiko and Masamune's *anti*-aldol methodology (Scheme 49) [107]. Condensation of E(O)-boron enolate of (−)-norephedrine derivative **188** with aldehyde **189** afforded the *anti*-addition adduct **190** in 94% yield and with high selectivity (dr 30:1). The C11-alcohol was protected as a TBS ether and subsequent
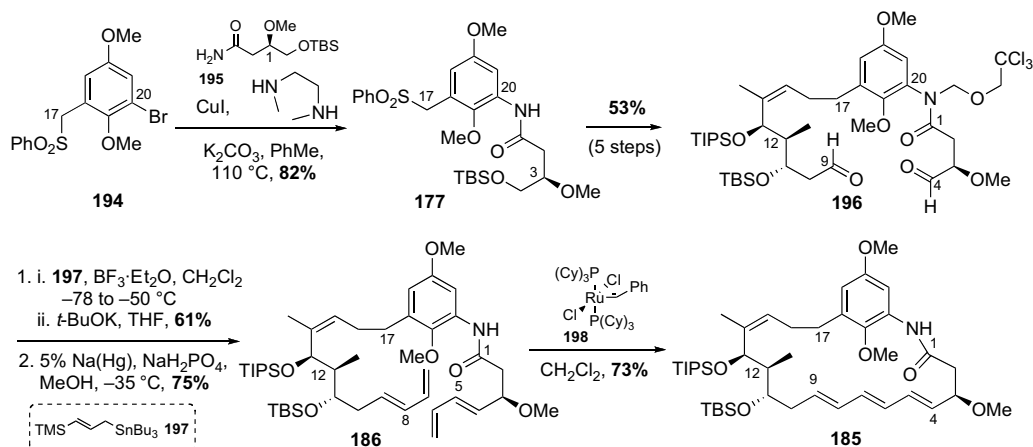
Scheme 50.
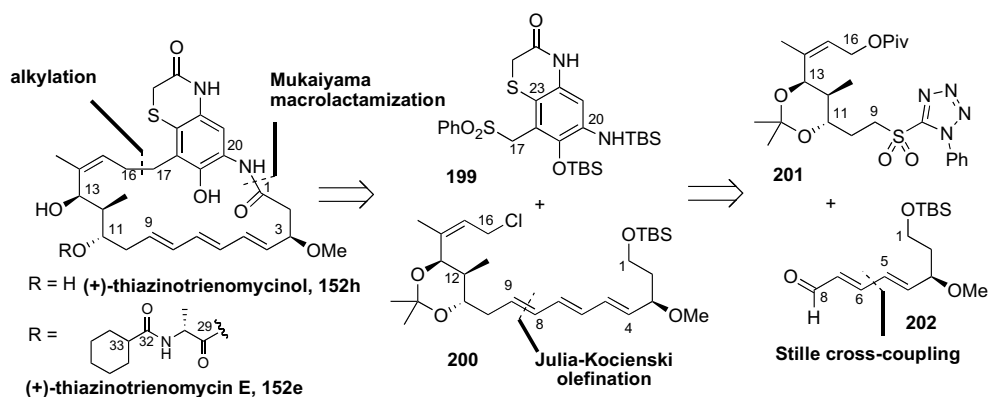
Scheme 51.

auxiliary cleavage yielded α-methyl aldehyde **191**. Treatment of aldehyde **191** with the vinyllithium reagent **192**[2] produced the C13-alcohol as the major Felkin-adduct from a 6.5:1 epimeric mixture. Conversion of the stereotriad **193** to the primary iodide **187** completed the fragment synthesis (three steps, 81% yield).

Fragment coupling, bis-diene installation and RCM were all that remained for completion of the macrocyclic core of cytotrienins (Scheme 50). The aromatic sulfone **177** was obtained utilizing Buchwald copper(I)-amidation [58]. Union of phenylbromide **194** and primary amide **195** in the presence of CuI afforded the desired fragment **177** in 82% yield. Following Smith's reported protocol for formation of bis-aldehyde **196**, sulfone **177** was alkylated with allylic iodide **187** and the product amide was masked as the trichloroethylmethyl ether (five steps, 53%). Exposure of **196** to allyl tin reagent **197** in the presence of BF$_3$·OEt$_2$ and *t*-BuOK resulted in formation of the (*E,E*)-bis-diene product in 61% yield [108]. The desired RCM precursor **186** was obtained after deprotection of the amide protecting group (75% yield). The crucial macrocyclization and (*E,E,E*)-triene formation were accomplished using RCM. Subjection of **186** to Grubbs II catalyst **126** initially afforded the thermodynamically favoured (*E,E*)-diene product in 43% yield [69]. Use of less reactive Grubbs I catalyst **198**, however, granted access to the desired (*E,E,E*)-cytotrienin core **185** in 73% yield. The macrocyclic core of cytotrienins was accomplished in just 18 steps with 6.6% overall yield beginning with 1,3-propane diol (longest linear sequence).

This last work highlights the synthetic utility of olefin metathesis for macrocyclization in contrast to more traditional carbon−carbon double bond construction methodologies [109]. To illustrate the efficiency of the RCM reaction, Blagg and co-workers recently prepared various trienomycin-based scaffolds employing this methodology [110].

3.5. Synthetic approaches involving a late union of the aromatic core and the C17-ansa chain

The second strategy employed for the synthesis of the triene-containing ansamycins involved final coupling of the aromatic fragment with a fully functionalized ansa chain. The advantage of this approach would allow for late-stage insertion of any aromatic fragment, providing facile access to a variety of triene-ansamycin natural products and structural analogues. Natural product synthesis of (+)-thiazinotrienomycin E **152e** by Smith and preparation of the ansatrienol core **213** by Kirschning and co-workers are two successful applications of this synthetic strategy.

3.5.1. Total synthesis of (+)-thiazinotrienomycin E by Smith (1999)

Smith and co-workers reported the first successful execution of this strategy during their synthesis of thiazinotrienomycin E **152e** [111]. Retrosynthetic analysis of this trienomycin planned for late-stage installation of the ester-linked side chain (C29−C38). Key disconnections of the macrocycle at C16−C17 and C1−N20 bonds revealed the aromatic fragment **199** and the aliphatic ansa chain containing fragment **200** (Scheme 51). It was envisioned that the macrocycle would be formed by alkylation of sulfone **199** with triene **200**, followed by a Mukaiyama macrolactamization reaction. Construction of the (*E,E,E*)-

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[2] Addition of such vinyllithium-type reagent has been initially reported by Smith and co-workers in 1999. See paragraph 2.2.1.
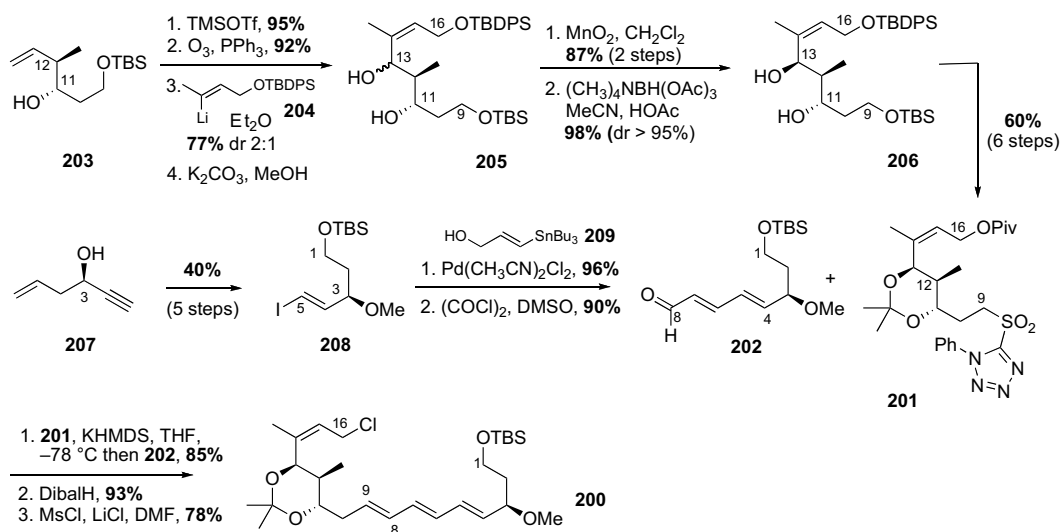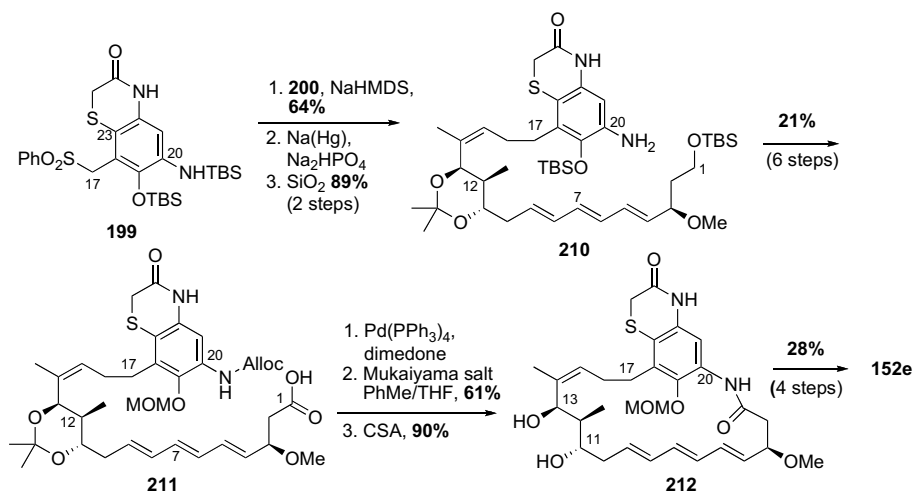
Scheme 52.

triene **199** was achieved using a Kocienski-modified Julia olefination between tetrazole **201** and unsaturated aldehyde **202**. The (*E,E*)-diene containing aldehyde **202** was proposed to arise from a Stille-cross-coupling reaction.

The (*E,E,E*)-triene of the ansa chain fragment **200** was installed using Stille coupling and a Julia olefination reaction. Synthesis of the C16–C9 tetrazole **201** started from readily available chiral homoallylic alcohol **203** (Scheme 52) [112]. After alcohol protection and reductive ozonolysis, the C13-aldehyde was alkylated using the *in situ*-generated vinyllithium species **204**. The resulting diol **205** was obtained in

77% yield with modest diastereocontrol (dr 2:1). Sequential allylic oxidation and 1,3-directed β-hydroxyketone reduction furnished diol **206** with excellent diastereoselectivity (dr > 95%). Protecting group modification and installation of the required sulfone produced the phenyltetrazole **201** over six steps in 60% yield.

The aldehyde coupling partner **202** was accessed from secondary propargylic alcohol **207**. Conversion of this alcohol to the vinyl iodide **208** was accomplished in 40% yield over 5-step sequence. Aldehyde fragment **202** was obtained in 87% yield over two steps *via* Stille coupling of iodide **208** with stannane **209** and

Scheme 53.
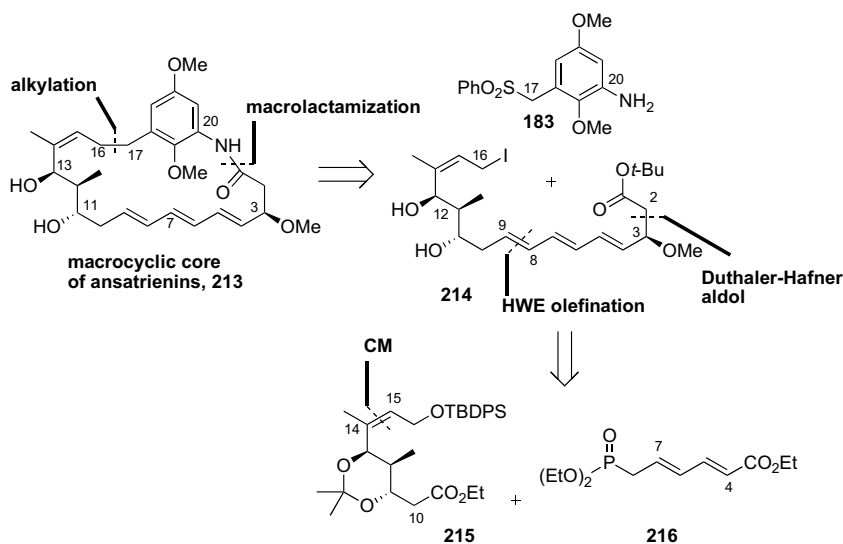
Scheme 54.

subsequent Swern oxidation of the resulting alcohol. A Kocienski-modified Julia olefination reaction between tetrazole **201** and aldehyde **202** afforded the (*E,E,E*)-triene in 85% yield with moderate selectivity (10:1) [113]. The completed ansa chain fragment **200** was obtained after conversion of the protected allylic alcohol to the necessary chloride.

The remaining synthetic hurdles were incorporation of the aromatic ring into the macrocycle and attachment of the amino acid side chain (Scheme 53). The anion of sulfonate **199** was alkylated with allyl chloride **200**. Following sulfonyl decomposition and acid deprotection aniline **210** was produced in 57% yield over three steps. Subsequent protecting group modifications and oxidation of the C1 alcohol provided the free acid **211**. After unmasking of the aniline, a Mukaiyama salt-promoted macrolactamization [114] delivered the MOM-protected thiazinotrienomycinol

derivative **212** in good yield. Smith and co-workers installed the side chain in a fashion reminiscent of their previous syntheses of trienomycin A **146a** and F **146f**. With this said, coupling of diol **212** to FMOC-alanine anhydride produced a 2:1 (C11/C13)-regioisomeric mixture of monoacylated products along with bis-acylated byproduct. Deprotection of the MOM-group and final HPLC purification furnished the natural product thiazinotrienomycin E **152e** in 28% yield over four steps from diol **212**. The first total synthesis of thiazinotrienomycin E was achieved in 35 steps with 0.27% overall yield starting with 3-buten-1-ol (longest linear sequence).

3.5.2. *Kirschning's total synthesis of the ansatrienol Core (2007)*

Kirschning and co-workers reported the second application of late-stage coupling of the aromatic
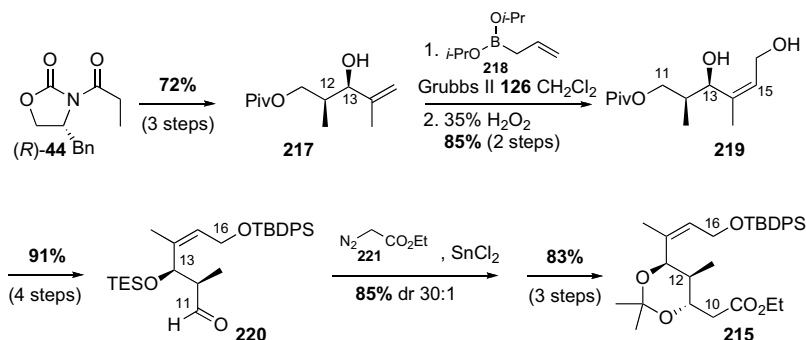
Scheme 55.
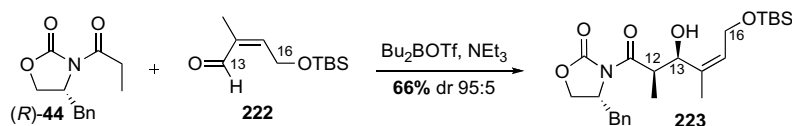
Scheme 56.

fragment with the completed ansa chain in their synthesis of the ansatrienol macrocycle **213** [115]. Retrosynthetic analysis starts with disconnection of the C16–C17 and C1–N20 bonds revealing the aromatic aniline **183** and triene-containing vinyl iodide **214** (Scheme 54). Similar to the approach used by Smith for thiazinotrienomycin E, formation of the macrocycle was proposed to arise from sequential alkylation and macrolactamization reactions. A Duthaler–Hafner acetate aldol reaction was proposed to install the C3-stereocenter of the ansa chain **214**. Disconnection of the C8–C9 olefin revealed the ester-containing fragment **215** and phosphonate **216**. Formation of the (*E,E,E*) triene was to be completed using a Horner–Wadsworth–Emmons (HWE) olefination. The trisubstituted olefin of fragment **215** was planned to arise *via* a cross-metathesis reaction.

The ester-containing fragment **215** was prepared in a sequence that featured a β-chelation-controlled reduction, cross-metathesis and Evans aldol reaction as the key steps (Scheme 55). The C12-methyl stereocenter was installed *via* an Evans aldol reaction of the *Z*(*O*)-boron enolate (*R*)-**44** to methacrolein **162**. Removal of the chiral auxiliary and protection of the primary alcohol with pivaloyl chloride produced the

vinyl alcohol **217** in 72% yield over three steps. Olefin cross-metathesis with allylic boronate **218** using Grubbs II generation catalyst **126**, followed by hydroboration furnished allylic diol **219** in high yield [116].

Protecting group modification and oxidation of the C11-alcohol eventually furnished protected aldehyde **220**. Tin-mediated homologation with diazo ester **221** produced an intermediate β-keto ester in 85% yield with dr 30:1. Triethylsilyl ether deprotection was followed by a selective *anti*-1,3 reduction and subsequent diol protection to produce ester **215** in 83% yield. This sequence to access the C16–C9 fragment **215** proved to be more reliable than an earlier method developed by Kirschning that relied on an Evans aldol reaction to install the C12–C13 stereocenters of **223** using the (*Z*)-configured aldehyde **222** (Scheme 56) [117].

Completion of the ansamycin derivative relied on Horner–Wadsworth–Emmons olefination and Duthaler–Hafner aldol reactions to construct the ansa chain, whereas alkylation and macrolactamization reactions were used to close the 21-membered ring (Scheme 57). Ester **215** was reduced to the necessary aldehyde and combined with phosphonate **216** in an HWE alkenation that produced a 6:1 (*E,E,E*):(*Z,E,E*) triene mixture in
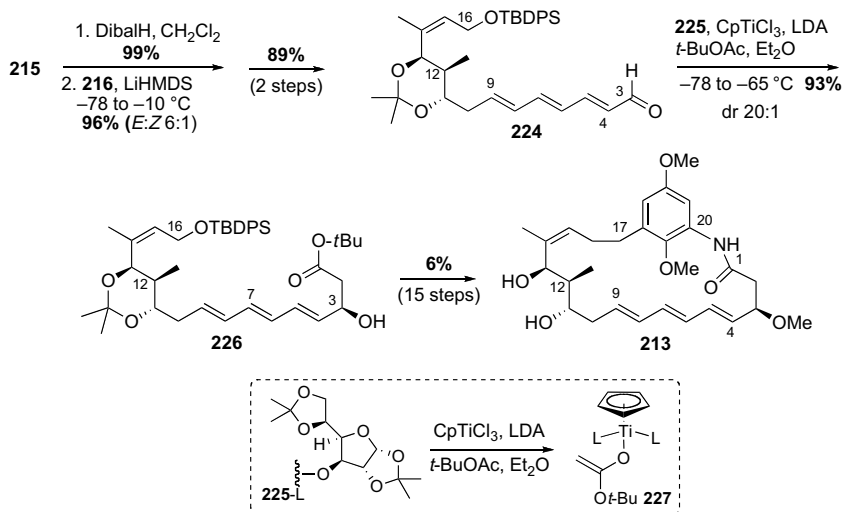
Scheme 57.

96% yield. Subsequent ester reduction and oxidation furnished aldehyde **224** in 89% yield over two steps. The C3-stereocenter was installed using a Duthaler−Hafner acetate aldol reaction [118]. Titanium enolate **227**, derived from D-glucose diacetonide **225**, was condensed with aldehyde **224** to give the corresponding alcohol **226** in 93% yield. This approach provided multigram quantities of pure ansa chain **226** and was transformed into the ansatrienol core **213** in 6% yield (15 steps) using similar alkylation and macro-lactamization protocols employed by Smith during synthesis of (+)-thiazinotrienomycin [94]. Overall, the thiazinotrienomycin core was prepared in 34 linear steps (1.3% yield) beginning with methacrolein.

3.6. Conclusions

Two complementary general strategies have been employed for five successful total syntheses of triene-containing ansamycin antibiotics and derivatives. Introduction of the triene moiety *via* stitching approach to effect macrocyclization was reported by Smith and Panek. In this context, the most recent approach to the ansatrienin core utilized RCM as a high-yielding macrocyclization step. In a different and complementary approach, Smith and Kirschning proposed an easily scalable process to access the fully constructed ansa chain. Late incorporation of the aromatic core and subsequent ring closure by macrolactamization offers a highly convergent route to a variety of trienomycin natural product and structural analogues. This approach could be exploited to probe the structure−activity relationship of triene-ansamycins, allowing for deeper understanding of the associated biology.

Acknowledgments

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