Total Synthesis of Antibiotics: Recent Achievements, Limitations and Perspectives.

Evgeny V. Prusov*

Helmholtz Zentrum für Infektionsforschung, Braunschweig, Germany

Tel +49 531 6181 9407

Fax +49 531 6181 9499

Evgeny.Prusov@helmholtz-hzi.de

Abstract

Several recently accomplished total syntheses of antibiotic natural products were summarized in this review in order to present current trends in this area of research. Compounds from different substance classes, including polyketide, depsipeptide, polyketide-polypeptide hybrid and saccharide, were chosen to demonstrate the advancement in both chemical methodology and corresponding synthetic strategy.

Introduction.

Secondary metabolites produced by various microorganisms have a long standing tradition as a source of biologically active compounds and lead structures for development of novel pharmaceuticals and plant protecting agents.(Jesse, 2009) Especially in such important areas as anti-infectives and cancer treatment, the share of drugs derived from the natural products is extraordinary high.(Ganesan, 2008) Since many natural products are only available in small quantities from their original sources, several complimentary approaches emerged to address the issues of substance supply. Contrary to the *semi*-synthesis,(Hamann, 2003) which utilizes a controlled degradation of natural products to obtain advanced building blocks, and *muta*-synthesis,(Kirschning, 2012) in which genetically modified bacterial strains are forced to accommodate unnatural precursors, the total synthesis relies solely on extracellular chemical transformations. Apart from the scientifically crucial task of providing a final proof of assigned structure,(Maier, 2009; Nicolaou, 2005) total synthesis is often the only feasible way to access such important analogs of natural products as fluorinated derivatives or heterocyclic bioisosters. Below, we summarized several recently accomplished total syntheses of microbial isolates from different structural classes. The substances presented in

this review are neither most complex nor most potent; however, they were selected to give the reader an impression of how various structural elements in the antibiotic natural products can be approached with the modern synthetic methodologies and which strategies are most frequently used to assemble those pieces together.

Etnangien.

Etnangien (**1**, Figure 1) is an inhibitor of bacterial RNA-polymerase isolated from two strains of myxobacterium *Sorangium Cellulosum*, So ce 750 and 1045.(Irschik, 2007) Antibiotic activity of this compound against several bacterial characterized by MIC values in the range from 0.03 ug/ml for *C. glutamicum* DSM 20300 to 1 ug/ml for *Staphylococcus aureus*. A complete assignment of configuration for all stereocenters in the etnangien molecule was accomplished by a combination of high-field NMR experiments, including $^{3}J_{CH}$ coupling constants analysis, molecular modeling and genetic analysis of polyketide synthase cluster.(Menche, 2008) The structure of etnangien features a 22-membered macrolactone with a rather rare tetra-*syn,anti*-stereohexad and an exceptionally long and sensitive polyenic side chain terminated with a carboxylic acid. In their retrosynthetic analysis of etnangien,(Li, 2009) Menche group dissected the target molecule at the C13-C14, C31-C32 double bonds and at the lactone functionality in three fragments of approximately equal complexity.

Construction of the top polyketid fragment **2** was started with a Sn(II)-triflate mediated double diastereoselective aldol reaction (Paterson, 1992) of ethyl ketone **6** and the Roche ester derived aldehyde **5** (Scheme 1, TS1). Subsequent 1,3-*syn*-selective reduction of the β-hydroxyketone using dicyclohexylborane as a chelating Lewis acid (TS2) and protection with dimethoxypropane provided acetonide **13** with excellent selectivity. Introduction of the terminal allylic group was accomplished via nucleophilic substitution of tosylate with sodium acetylide and a late-stage hydrogenation of triple bond over Lindlar catalyst. Deprotection of PMB-group with dichlorodicyanobenzoquinone (DDQ) and two consecutive oxidations with Dess-Martin periodinane (Dess, 1983) and sodium hypochlorite were used to install the carboxylic acid functionality at the right-hand terminus of the C32-C42 fragment **2**.

For the preparation of the bottom subunit, two different Paterson aldol reaction methodologies (Cowden, 1997) were sequentially employed (Scheme 2). At first,

addition of *E*-enolate of ethyl ketone **7** (derived from the L-lactate) to the unsaturated aldehyde **8** led furnished the aldol adduct **15**. Exhaustive reduction and oxidative cleavage of the resulted diol furnished the corresponding aldehyde, which was converted into the methyl ketone **16** through addition of methyllithium and oxidation. This ketone was introduced in (+)-Ipc_2BCl mediated aldol reaction with aldehyde **20**, which was synthesized from chiral epoxide **18** in six simple steps. The last aldol adduct was subjected to the *anti*-selective Evans-Carreira reduction (Evans, 1988) producing the corresponding diol, in which the less hindered hydroxyl function at C-24 was selectively protected as a TBS ether to give directly the desired alcohol **3**.

For the synthesis of the side chain fragment, Brown asymmetric allylation (Brown, 1983) was used to introduce the required stereocenter (Scheme 2, TS3). Then, a terminal ester functionality was secured by two consecutive oxidations with Dess-Martin periodinane and sodium hypochlorite (Pinnick oxidation) (Bal, 1981) followed by esterification with diazomethane. Functionalization of the terminal double bond by a cross-metathesis with crotonaldehyde gave rise to the unsaturated aldehyde **23**, which was subjected to the Horner-Wadsworth-Emmons olefination (Nicolaou, 1997) with vinylogous phosphonate reagent **10** to provide the polyenic stannane **4**.

In the endgame of the synthesis (Scheme 3), the carboxylic acid **2** was first esterified with alcohol **3** according to the Yamaguchi protocol (Inanaga, 1979) to provide the substrate for the macrolactone ring closure. The pivotal intramolecular Heck reaction proceeded smoothly and provided the desired 32-*E* diene **24** with a better than 20:1 ratio of geometrical isomers, whereas intermolecular coupling gave a mixture of *Z* and *E* products. Removal of the primary TBS protecting group by hydrolysis in mild acidic conditions followed by DMP-oxidation and the terminal vinyl iodide was installed by Takai olefination reaction.(Takai, 1986)

It was established that a rather sensitive nature of the conjugated hexaene fragment necessitated removal all TBS-protecting groups from the macrocyclic core before the attachment of the side chain can be done. This was achieved by treatment **25** with TBAF. Exposure of the resulted polyol to stannane **4** in the presence of $PdCl_2$-acetonitrile complex in DMF resulted in a clean conversion to the complete carbon skeleton of etnangien. Removal of the acetonide protection under mild acidic conditions and enzymatic hydrolysis of the methyl ester

concluded the total synthesis of the target molecule, which confirmed the assigned structure and delivered the natural product with 0.25 % yield over a 23 steps longest linear sequence. Owing to its modular nature, the developed approach allows preparation of further etnangien analogs for a comprehensive elucidation of structure-activity relationship. However, two late stage deprotection steps with relatively low yields represent the "bottleneck points" of this synthesis and can be a subject for further improvement.

Virginiamycin M_2

Virginiamycin M_2 (**27**, Figure 2) is a depsipeptide antibiotic, originally isolated in 1966 as ostreogrycin A from *Streptomyces ostreogrisezts*,(Delpierre, 1966) and belongs to the virginiamycin group A group of compounds, of which dalfopristin is approved in a combination with quinupristin as a synergistic antibiotic for the treatment of Gram-positive bacterial infections.(Barrière 1993, 1994) The structure of virginiamycin was established by X-ray crystallography in 1974, however, due to the presence of pH sensitive β-hydroxyketone moiety, the first total synthesis of this natural product was achieved more than twenty year later.(Schlessinger, 1996) Recently, a very concise synthesis of virginiamycin M_2 was accomplished by Panek group.(Wu, 2010) Their strategy relied on the intamolecular Barbier/Reformatsky type reaction and low-valent Ti-mediated reductive alkyne-alkyne coupling as a key steps.

Condensation of serine with dichloroacetonitrile (Hermitage, 2001) followed by saponification, peptide coupling and cationic cleavage of benzyl ester with boron trichloride provided the 2-chlormethyloxazole-N-prolinamide building block **28** (Scheme 4). The second fragment was quickly made by N-methylephedrine-catalyzed asymmetric addition of propyne to a TBS-protected β-hydroxypropanal according to the Carreira protocol.(Frantz, 2000) The third precursor was also easily obtained using asymmetric crotylsilylation methodology developed by the same group.(Wu, 2010)

The reductive alkyne-alkyne coupling (Reichard, 2008) (Scheme SI-1) starts from the deprotonation of propargylic alcohol **30** with *n*-butyllithium to give first lithium alkoxide, which is then treated with chlortriisopropyltitanium to produce a mixed titanium alkoholate. Reaction of this alkoholate with cyclopentylmagnesium chloride generated a so called titancyclopropane intermediate, which undergoes a rapid ligand exchange to form the bicyclic

titanacyclopropene. Finally, intermolecular carbometallation with a molecule of *terminal* alkyne give rise, after hydrolytic workup, to the desired (*E,E*)-diene.

In the present case, the coupling of **30** and **31** under conditions described above provided diene **37** in 58% yield (Scheme 5). A slightly higher yield of the coupling product can be obtained with alkynamide bearing acetyl protecting group on the C-1 hydroxyl. The less stericaly hindered hydroxyl group at C-11 was selectively silylated and the oxazole-proline fragment was appended by Yamaguchi esterification, followed by liberation of terminal alcohol and its oxidation to aldehyde **40**.

Exposure of chloromethyloxazole **40** to Sm(II)-iodide in *benzene* generated a corresponding "benzylic"-organometallic intermediate, which undergoes Barbier/Reformatsky type addition (Edmonds, 2004) to the carbonyl group to give the macrocyclic alcohol **41** in 40% yield (42% for the iodomethyloxazole analogue). Two final steps of the synthesis were the oxidation of alcohol by a modified Swern protocol and removal of the TBDPS protecting group with Olah reagent. Despite a moderate yield of intramolecular Barbier reaction, the longest linear sequence of only nine steps makes this route highly attractive for a rapid generation of libraries of virginiamycin analogs and their development into the clinical candidates. Also, pH-sensitivity problems, associated with dehydration of β-hydroxyketone during the final oxidation step, were nicely resolved in this synthesis.

Branimycin.

Branimycin (**42**, Figure 3) is polycylic antibiotic isolated by Laatsch research group from the actinomycetes strain GW 60/1571.(Speitling, 2000, 2001) Branimycin is characterized by an extreme complex molecular architecture, since all except one carbon atoms in its skeleton are either stereogenic or functionalized. Additionally, the core of the molecule contains an *oxa*-bridged *cis*-octaline motif to which an eight-membered macrolactone ring is attached at the bridgehead position. In the approach to branimycin developed in by Mulzer group,(Marchart, 2010) the target molecule was retrosynthetically disconnected at the bridgehead position and at the lactone group to give the octalin fragment **44** and polyketid unit **46**.

The key intermediate for the construction of the *cis*-fused octalin system was derived from a double Diels-Alder adduct of furane and ethyl propiolate (Scheme

6).(Gromov, 2009) The carboxylic group was removed by saponification followed by a modified Barton-MacCombie reductive decarboxylation. Compound **45** elaborated further by *anti*-S_N' addition of methylsilane anion, Tamao-Fleming oxidation, methylation of the resulted alcohol, chiral HPLC and asymmetric reduction to the alcohol **51**, which after oxidation and double bond isomerization provided enone **52**. The subunit was completed by PMB to TBS protecting group swap and subsequent regioselecteve epoxidation. The polyketide part of the macrolactone ring was constructed by a *syn*-selective Lewis-acid mediated addition of chiral allenylsilane to the aldehyde **47**, which was prepared in four steps from *S*-glycidol.(Felzmann, 2007)

With both fragments in hand, vinyliodide **46** was subjected to the halogen-metal exchange and the resulted vinyllithium species was allowed to react with ketone **44** at low temperature (Scheme SI-2). The following warm-up of the reaction mixture triggered an intramolecular epoxide opening in the intermediate product of addition resulting in the formation of the oxo-bridged *cis*-octalin core of branimycin.

Construction of the macrolactone ring started from the allylic oxidation of **54** to enone **55**, which after conjugated addition of sodium dimethyl malonate was deoxygenated to alkene **56** through formation of enol triflate and subsequent Pd(0)-catalyzed reaction with tributyl stannane (Scheme 7). Both ester groups were reduced with LAH and monomethylation of the corresponding diol (**43** in Figure 3) mediated by silver(I) oxide(Bouzide, 1997) followed by TEMPO-catalyzed chemoselective oxidation(DeMico, 1997) of the residual primary hydroxyl group gave rise to the seco-acid **58**. Application of the Nicolaou macrolactonisation conditions(Corey, 1974) yielded the penultimate intermediate **59**. Final deprotection of all TBS groups with TBAF furnished the natural product along with its C-26 epimer, which were separated by HPLC.

The synthesis, which proceeds in 22 steps over the longest linear sequence and 2% overall yield, confirmed the structure assignment accomplished by NMR-experiments only. A rather straightforward construction of the oxo-bridged *cis*-octalin core from the epoxyketon **44** can be utilized for the preparation of simplified lactone analogs and elucidation of structural requirements for antibiotic activity. Implementation of a stereocontrolled methylation reaction of diol **43**, for example by enzymatic desymmetrization, could, potentially, double the overall

yield of final product and eliminate the need for separation of the diastereomeric compounds in the last step.

Oxazolomycin A.

Oxazolomycins are a family of linear hybrid polyketide-peptide metabolites isolated in 1983 from *Streptomyces sp.* strain KBFP-2025(Mori, 1985; Takahashi, 1985) and later rediscovered in the fermentation broth of *Streptomyces albus* strain JA3453.(Gräfe, 1992) Their molecules characterized by a densely functionalized γ-lactam/β-lactone spirocycle, which is linked through a short polyketide fragment, two polyenic tethers and an amide bond to the unsubstiuted oxazole ring. Oxazolomycin A (**60**, Figure 4) possesses a selective antibiotic activity against *Agrobacterium tumefaciens* with a MIC of 3.4 μg/ml and also inhibits crown gal formation at a dose of 2.5 μg per 1 cm disk.(Kawai, 1989) Other interesting biological properties of oxazolomycins and related compounds were summarized in the review.(Moloney, 2004) Several synthesis of oxazolomycin fragments and a total synthesis of neooxazolomycin were reported.(Kende, 1990; Onyango, 2007) In their approach to the oxazolomycin A,(Eto, 2011) Hatakeyama group naturally opted to divide the target molecule in three fragments: β-hydroxy acid **61**, unsaturated amine **62** and lactam **63**, which can be prepared by a In(III)-catalyzed variant Conia-Ene reaction developed in the same group.(Takahashi, 2008)

Construction of the lactone/lactam bicycle was started form the alkylation of alkyne **67**(Trost, 2004) with triflate **68**,(Abiko, 1995) both available from Roche ester, setting up two stereocenters bearing methyl group (Scheme 8). The resulted alcohol was converted to the amide of dimethyl 2-(methylamino)malonate by Jones oxidation(Ley, 1991) followed by treatment with thionyl chloride and corresponding amine. Intramolecular nucleophilic addition of the malonamide to the triple bond proceeded with high regio- and stereoselectivity and furnished lactam **70** as a sole reaction product in excellent yield. The following *syn*-selective Upjohn dihydroxylation(VanRheenen, 1976) of the double bond by OsO_4/NMO system established a sequence of three contiguous stereocenters in one step. Further elaboration of the intermediate γ-lactone/γ-lactam was somewhat more difficult and demanded temporary reduction of both carboxylic groups and orthogonal protection of the resulted alcohols. Finally, a suitable for coupling

building block, was prepared as a di-*i*-propylsilylenediyl ether protection of hydroxyl groups.

For the synthesis of the oxazole fragment, a catalytic asymmetric cycloaddition of methyl ketene to the unsaturated aldehyde developed by Nelson group (Zhu, 2004) was used to create the stereocenter adjustent to the polyenic moiety (Scheme 9). Opening of the four-membered lactone and following alkylation led to the α,α-dimethyl-β-hydroxy ester **78**. Cleavage of the TMS-protecting group, iodination of the alkyne and *Z*-specific reduction with diimide generated from *o*-nitrotosyldrazide **82** provided the (*Z*,*Z*)-conjugated vinyl iodide **79**. Stille cross-coupling (Farina, 1998) with vinyl stannane afforded intermediate **80**, which after some simple protecting group manipulations was converted to the desired carboxylic acid **61**.

The middle segment of the molecule was prepared from allylamnine in three simple steps and attached to the lactam by Nosaki-Hiyama-Kishi(Takai, 2000) reaction, which in this particular case produced a 3:2 mixture of epimeric alcohols with major diastereomer to be the desired one. The ratio was improved to 4:1 by DMP oxidation/L-Selectride reduction to give after acylation intermediate **84**.

Following the cleavage of the Fmoc protecting group from amine, the left-hand fragment was appended to the rest of the molecule using BOPCl (**86**) mediated peptide coupling. At the last stage of the synthesis, the four-membered β-lactone ring was formed using HATU-mediated esterification. With a total 34 steps in the longest linear sequence, the natural product was obtained in a respectable yield of 1.4%. The route utilizes easily scalable reactions and allows introduction of other heterocyclic substituents at the oxazole terminus of the molecule as well as variations in the lengths of unsaturated chains, however, it would benefit significantly if the preparation of the lactam building block **63** from the key γ-lactone **71**, which currently requires 15 chemical steps, can be shortened to some extent.

Streptolydigin

Streptolydigin (**87**, Figure 5) is a RNA-polymerase inhibitor isolated by De Boer group in 1956 from *Streptomyces lydicus*.(DeBoer, 1956; Eble, 1956; Lewis, 1956) Its molecule features the presence of a bicyclic ketal core with an exocyclic epoxide and a highly substituted acyl tetramic acid. Streptolydigin is structurally related to tirandalydigin **88**(Brill, 1988) and tirandamycin **89**(Carlson, 2009,

Hagenmaier, 1976; Meyer 1971) antibiotics and exhibit activity against several gram-positive bacteria with MIC values of 0.04 mg/ml.(Tuske, 2005) The mode of action of streptolydigin is based on blocking of RNA-polymerase bridge-helix in a straight conformation. Since the binding site of streptolydigin located 20 Å away from that of rifamycin, only minimal cross-resistance is observed between these classes of antibiotics (Artsimovitch, 2005; Campbell, 2001).

Taking advantage of a relatively short polyene system, Kozmin group divided the target molecule into two main fragments: a bicyclic acetal **90** and a diketone precursor of 3-acyltetramic acid **91** (Figure 5). (Pronin, 2010) The acetal core was to be prepared from a stereotetrade **96** and dihydroxyacid **97**. The polyketide fragment of bicyclic ketal was prepared using chelation-controlled aldol reaction followed by 1,3-*anti* Evans-Tischenko(Evans, 1990) reduction (Scheme 10). The second building block was made from α-hydroxymethyl crotonic acid **100** via Sharpless asymmetric dihydroxylation, regioselective formation of acetonide, trifluorosulfonylation/elimination and saponification. A difference in the steric hindrance of two hydroxyl groups in diol **96** allowed a selective acylation of the allylic alcohol with acid **97** using Steglich conditions.(Neises, 1978) After simple protecting group manipulations, the six-membered lactone **92** was formed by a ring-closing methathesis reaction and then opened again to the corresponding Weinreb amide.

Addition of the methyl lithium and subsequent acid-catalyzed acetalization of the resulted methyl ketone **104** furnished the ketal core of the molecule. Removal of the benzyl protecting group by "ammonia free" variant of Birch-reduction(Freeman, 1980; Shimshock, 1991) followed by oxidation and Wittig olefination gave rise to the left-hand fragment of streptolydigin.

Then, the ester group was reduced to the allylic alcohol and silylated with TIPSCl (Scheme 11). Selective cleavage of the TIPS-ether adjustent to the tertiary alcohol with LAH provided diol **107**, which was next cyclized into the epoxide by treatment with triflic anhydride and DBU. The required for the completion of the molecule right-hand fragment was assembled from the α-amino imid **95**, accessible through asymmetric azidation of Evans enolate,(Evans, 1987) a protected L-(-)-rhodinose derivative **94**(Schlessinger, 1987) and a known compound **9**.(Ley, 1992) Combination of the α-amino imid **95** and hemi-acetal **94**

in methanol provided corresponding aminal, which was then acylated with thioester **93** upon silver-salt activation.

Finally, concomitant Dieckmann condensation,(Andrews, 1998) HWE-olefination and TES protecting group removal were used to construct the polyene system and 3-acyl tetramic acid terminus of the molecule in one step. In total, the synthesis counts 24 chemical steps in the longest linear sequence. Using this synthetic strategy, several simplified analogs of streptolydigin were prepared and evaluated for antibacterial activity in RNA-polymerase assays.(Pronin, 2011) It was shown that the presence both spiroacetal and tetramic acid fragments is required for inhibitory activity.

Ripostatins A and B.

Ripostatins A and B (**111**, **112**, Figure 6) are secondary metabolites with moderate antibiotic activity against gram-positive bacteria isolated from the myxobacterium *Sorangium cellulosum* So ce 377.(Irschik, 1995) Much like streptolidigin, they inhibit bacterial RNA-polymerase, though their binding site is the so-called switch region and blocking the enzyme in the opened conformation.(Mukhopadhyay, 2008) Structurally, ripostatins characterized by a highly unsaturated 14-membered lactone ring with a phenylalkyl side chain. Owing to a relatively small number of stereogenic centers in their molecules, the structures of ripostatins were assigned relatively fast;(Augustiniak, 1996) however, first studies towards the total synthesis appeared only ten years later.(Kujat, 2006)

It became quickly apparent that a skipped polyene motif in the macrocyclic ring of ripostatins (C2-C9) represent a significant synthetic challenge due to its instability under moderately basic and acidic conditions and inherent propensity for isomerization into a conjugated diene, which pose significant constrains on the synthesis design. Notwithstanding, underlining the importance of ripostatins as synthetic targets and promising leads for discovery of novel antibiotics, three independent total syntheses of ripostatin B were recently reported.(Winter, 2012; Tang, 2012; Glaus, 2012) Due to some similarities in strategy and tactics, it's reasonable to discuss them in parallel.

In all three syntheses, the macroalctone ring was dissected at C5-C6 double bond to give the RCM-precursor **113**, which was further was traced back to a known iodoacrylic acid **114**(Kanematsu, 2009) and a polyol fragment **115** (Figure 6). The Christmann's route to the polyol fragment is based on the anion relay chemistry

pioneered by Schaumann (Fischer, 1994) and developed by Tietze and Smith and utilizes the "linchpin coupling" of 2-TBS-1,3-dithiane as a masked formyl dianion equivalent with epoxides **116** and **117**, both obtainable from geranyl acetate **118**, whereas approaches of Altmann and Prusov utilize an asymmetric Paterson aldol reaction between appropriate aldehyde and keton to construct the same intermediate.

In the forward direction, geranyl acetate **118** was converted to the epxide **121** and the allylic acetoxy group was displaced by either phenyl or vinyl rest by copper(I)-catalyzed reaction with corresponding Grignard reagent (Scheme 12). In the case epoxide **116**, the synthesis proceeded through Jacobsen hydrolytic kinetic resolution(Schaus, 2002) of racemic epoxide **rac-116**, the diol by-product of this reaction was also converted to the epoxide **116** in three-step sequence, thus raising the overall yield to 79%. The right-hand epoxide **117** was prepared from the intermediate aldehyde **125** by organocatalitic asymmetric α-chlorination,(Brochu, 2004; Halland, 2012; Winter, 2011) reduction and cyclisation in basic conditions.

In the pivotal "linchpin-coupling", the anion obtained by deprotonation of 2-TBS-1,3-dithiane was first allowed to react with the epoxide **117** to give the corresponding lithium alkoxide (Scheme SI-3). Then, dimethoxyethane was put into reaction mixture to trigger a 1,4-Brook rearrangement (*C→O* migration of the TBS-group)(Moser, 2001) and restore the anionic reactivity center at the dithiane position. Addition of this "regenerated" anion to the second epoxide molecule gave rise to the polyol fragment **128** with a dithiane-protected ketone functionality. Interestingly, in this particular case, the overall yield of reaction was affected by the order of in which the epoxides were coupled with the "linchpin".

The Prusov approach to the polyol fragment **133** is outlined in Scheme 13. (±)-Epichlorohydrine was converted into the known homoallylic alcohol **129** in four steps. Installation of the β-methyl vinyl iodide moiety by carboalumination with iodine quench followed by double bond dihydroxylation and cleavage of the diol with sodium periodate furnished aldehyde **120**. The ketone component for the Paterson aldol reaction (Cowden, 1997) was prepared in only two steps from alkynyl iodide **15** via one-pot carboalumination–cross-coupling reaction and acylation of the alkyllithium species derived from iodide **16**. Subsequent addition of Ipc_2B-enolate of **119** to aldehyde **120** gave rise to the β-hydroxyketone **132** with a good yield and selectivity. Evans-Tischenko(Evans, 1990) reduction and

subsequent exchange of acetyl ester to TBS protecting group provided the required 1,3,5-*syn,anti*-triol **133**.

The synthesis of β-silyloxyaldehyde intermediate **140** in Altmann's approach commenced with opening of epoxide **134** with lithium acetylide of ethyl propiolate (Scheme 14). Then, β-methylacrylate ester **135** was by accessed by stereoselective addition of thiophenol followed by displacement of thioether with cuprate reagent derived from methylmagnesium bromide. The terminal allylic group was installed via reduction of ester, conversion of allylic alcohol into bromide **138** by Appel reaction(Appel, 1975) and Stille cross-coupling(Farina, 1998) with vinyltributhyl stannane. Lewis acid mediated deprotection of PMB group and oxidation of the corresponding alcohol to aldehyde. The ketone **119** was made in three steps from phenylacetaldehyde by addition of isopropenylmagnesium bromide, Claisen-Jonson rearrangement(Guthrie, 1982; Johnson, 1970) and one-pot conversion of a methyl ester into the corresponding methyl ketone without isolation of the intermediate Weinreb amide.(Williams, 1995) Execution of the Paterson aldol reaction in *dichloromethane* provided the adduct **132** in 62% yield and 94% *de*.

The end-game of the Christmann's route is shown in Scheme 15. Idoacrylic acid **114** and alcohol **144** were combined in a modified Yamaguchi esterification(Inanaga, 1979) protocol to give the ester **145**. The use of 3,4-Dihydro-2*H*-pyrido[1,2-a]pyrimidin-2-on as a weakly-basic proton trap was important at this step, since elimination of HI from **114** was observed with common bases, such as Et_3N and DIPEA. Subsequent Stille cross-coupling provided the RCM-precursor **146**, which upon exposure to Grela catalyst **149** provided macrolactone **147**. Concomitant cleavage of acid-labile primary TBS-ether and oxidation of the resulted alcohol to the carboxylic acid under Jones conditions followed by deprotection of secondary silyl ether led to the penultimate intermediate **148**, which was converted to ripostatin B by chemoselective reduction of the propionate ester.

Similarly, the final steps in Altmann's synthesis feature the use of a Stille cross-coupling and first generation Grubbs catalyst for the ring-closing metathesis reaction (Scheme 16). The exocyclic carboxylic group was secured by a one-pot Dess-Martin periodidnane/Pinnick oxidation procedure due to a rapid decomposition of intermediate aldehyde upon $Na_2S_2O_3/NaHCO_3$ workup.

The Prusov's synthesis differs from those described above in that two allylic groups were simultaneously introduced in the Stille cross-coupling step and a second generation Grubbs catalyst was employed to promote the ring-closing metathesis reaction.

Utilizing the established route to the ripostatin skeleton, Prusov group completed a short-cut synthesis of 15-deoxyripostatin A (Scheme 17), which could serve as a molecular probe to test the structural requirements for efficient RNAP-binding. The tetrahydropyrane core of the molecule was constructed by means of Prins cyclization of homoallylic alcohol and 4-pentynal. The triple bonds were then separately elaborated to the phenylalkyl side chain and α-methyl vinyliodide group. Since, the opposite configuration of the stereocenter at C-13 was obtained from the Prins reaction, a Mitsunoby esterification with iodoacrylic acid **114** was used to invert it to the correct one. The rest of the sequence is essentially the same as described before; however, a significantly higher yield of the intermediate macrolactone **160** was obtained in the ring-closing metathesis reaction. More recently, a total synthesis of ripostatin A was also completed by Prusov group. (Tang, 2012) A key element of their strategy was to use a cyclic methyl acetal as a protected form of C15 ketone group of ripostatin A (Scheme 17). For this purpose, adducts obtained from aldol reaction with Ipc_2BCl of opposite chirality were cyclized to the separable acetals **163** and **164**, and then converted into the same ester **165** by either Mitsunoby or Yamaguchi esterification, respectively. From here on, the remaining transformations parallel those previously described until the known methyl acetal of ripostatin A.(Augustiniak, 1996) The carbonyl group was liberated by autocatalyzed hydrolysis of acetal **166** in wet dioxane. The identity of obtained material with natural product was confirmed by NMR-spectroscopy, optical rotation and HRMS.

Although, a ring-closing metathesis approach to the construction of macrolactone ring of ripostatins was rather obvious and straightforward, the most crucial step for success of all three syntheses of ripostatin B was the introduction of the skipped dienoate fragment C1-C6 by a Stille cross-coupling of the corresponding β-iodoacrylate ester with allyltributylstannane. All previous attempts to attach such fragment directly using various esterification reactions ultimately failed due to a concomitant isomerization into the conjugated system. It was also demonstrated here that several orthogonal strategies and tactics to the same

molecular architectures can be developed independently in a short time. Combination of the best features from all three syntheses of ripostatins now enables a consistent exploration of biochemical potential of this rather interesting leads. Further work aimed at the synthesis and biological evaluation of stabilized and bioisosteric analogs of ripostatins is currently underway in all three laboratories and may give some interesting results in the near future.

Corallopyronin and myxopyronin.

Corallopyronins and myxopyronins are two families of closely related polyketide natural products isolated from *Corallococcus coralloides* strain Ccc127, DSM2550 and *Myxococcus fulvus* strain Mx f50 (=*M. fulvus* HR4, DSM 2549), respectively.(Irschik,1985; Irschik; 1983, Jansen, 1985; 78) Their common structural motive is a 4-hydroxy-α-pyrone ring with two side chains attached at C3 and C6 positions. A crystal structure of RNA-polymerase-myxopyronin complex was obtained by Ebright and co-workers identified the "switch region" of the RNA-polymerase as a binding site of these compounds.(Mukhopadhyay, 2008) Two racemic total syntheses of myxopyronin B were reported in the past;(Hu, 1998; Lira, 2006) however, the first enantioselective total synthesis of corallopyronin A (**167**, Figure 7) and myxopyronin B was accomplished by Kalesse group only recently.(Rentsch, 2012) In their retrosynthetic analysis, the target molecule was to be assembled from the western side chain aldehyde **168** and appropriately protected 4-hydroxypyranone fragment **169**. Each half of the molecule was to be assembled from simple starting materials, such as geraniol or silyl dienol ether **172**.

The 4-hydroxypyranone core of the molecule with the eastern side chain was prepared from the rather inexpensive β-(–)-citronellene **173**, which provides a good handle for introduction of the stereocenter at C7 (Scheme 18). The terminal hydroxyl function was established by epoxidation of the most substituted double bond with *m*CPBA, cleavage of the in-situ formed diol with periodic acid and reduction with sodium borohydride. Protection of the alcohol and ozonolysis of the residual double bond led to aldehyde **175**, which was elaborated to acetonide **176** by a vinylogous Mukaiyama aldol reaction.(Boulard, 2007; Trost, 2001) Oxidation of alcohol to a ketone followed by a thermal retro-Diels-Alder reaction in boiling toluene generated the acylketene intermediate, which undergoes intramolecular acylation of enol form (Lokot, 1999; Sato, 1991) to give the 4-

hydroxy-pyranonone **176**. Finally, α,β-unsaturated acid **179**, obtained in three simple steps, was treated with ethyl chloroformate and sodium azide to give the corresponding acylazide. Subsequent Curtius rearrangement and trapping of the resulted vinylic isocyante with methanol provided the enamine carbamate **169**.(Chaturvedi, 2012)

The route to the left hand side chain utilizes a general method for the synthesis of α-methyl-*Z*-allylic alcohols from the haloalkynes developed by Walsh.(Chen, 2004) So, hydroboration of the O-TBS protected 1-bromobutynol with dibromoborane followed by treatment with an excess of dimethyl zinc generated a mixed organozinc compound **170** (Scheme 19). Addition of this species to the geraniol derived aldehyde **182** furnished alcohol **183** as a racemate.

In order to install the correct stereocenter at C-24, intermediate **183** was oxidized to the unsaturated ketone **184** and subjected to the enantioselective reduction with isopinocampheylboryl chloride,(Dhar, 1994) providing alcohol **185** in 95% *ee* (Scheme 20). After some trials, it was established that a Julia-Kocienski olefination (Blakemore, 1998) of acetaldehyde with phenyltetrazolylsulfone **187** is the best way to append the skipped diene terminus to the western side chain. Attempted reactions of ethyl phenyltetrazolylsulfone with the aldehyde derived from the alcohol **186** gave substantially lower yields of the desired diene **188**.

Union of two subunits was accomplished by reaction of the 3-lithiated pyrone **189** with aldehyde **188** to give a complete carbon skeleton of corallopyronin (Scheme 21). Oxidation of the resulted allylic alcohol **190** with manganese dioxide and removal of TBS and SOM protecting groups provided the natural product which spectroscopic properties were identical to those reported by Höfle and König.(Erol, 2010)

According to this general synthetic strategy, a suitable left-hand fragment for the synthesis of myxopyronin B was prepared from ester **191** by conjugated addition of lithium dibutyl cuprate, conversion of the resulted ester to the aldehyde **193**, Wittig olefination and reduction/oxidation sequence (Scheme SI-4). Coupling of thus obtained aldehyde with the 3-lithiated pyrone **189** followed by oxidation of the secondary alcohol and global deprotection provided myxopyronin B.

Enantioselective synthesis of corallopyronin and myxopyronin delivered the ultimate proof for the correct assignment of the absolute stereochemistry at C-7. Application of the SOM-protecting group tactics circumvented several problems

associated with the use of sterically hindered silyl ethers, notably, decomposition of the pyrone ring under deprotection conditions. The coupling of lithiated pyrone fragment with other suitable aldehydes allows introduction of various side chains in corallopyronin molecule, thus facilitating further studies of structure-activity relationships.

Herbicidin and aureonuclemycin.

Herbicidin A (**196**) and aureonuclemycin (**197**, Figure 8) were isolated in **1976** from a *Streptomyces* strain No. 4075, designated as *S. saganonensis*, and found to be potent inhibitors of the leaf blight infection bacterium *Xanthomas oryzae* parasiting, a parasite of rice crops. Their protective effect was present at concentrations as low as 3 ppm. Other biological activities of herbicidins include reduction of seed germination of rice and Chinese cabbage, diminishing algal growth and selective toxicity towards dicotyledonous plants.(Arai, 1976; Haneishi, 1976) Structurally, herbicidins belong to the undecose nucleosides substance class and characterized by a fused furano-pyrano-pyran ring system to which the adenosine base is connected at the anomeric center of furan. In their retrosynthetic analysis of herbicidin C,(Hager, 2012) Trauner and co-workers planned to employ a late-stage glycosidation to introduce the adenine base in the tricyclic intermediate **198**. The corresponding acetate was to be constructed by a double acetalization of a properly configured triol **199**, which can be obtained from the unsaturated ester **200** by dihydroxylation and functionalization of carboxylic group. The ester, in turn, can be traced back to the allylic C-glycoside **201**.

The synthesis was started from D-glucose, which was converted to the bicyclic compound **203** by selective tosylation of the primary alcohol, NaOH promoted cyclisation at the anomeric hydroxyl group and exhaustive benzylation (Scheme 22).(Zottola, 1989) Nucleophilic substitution at the anomeric carbon with allyltrimethylsilane led to the C-glycoside product **201** (Lewis, 1982) removal of the benzylic group (Cipolla, 1997) providing orthogonally protected alkene **204**. This was extended to the usaturated ester **200** and subjected to the Sharpless asymmetric dihydroxylation to install two additional hydroxyl groups. The ester was converted into the Weinreb amide and combined with vinylmagnesium bromide to give the unsaturated ketone **206**. As it was later found out by the X-ray analysis of an intermediate, reduction of this ketone to the alcohol with the desired

configuration requires a CBS-catalyst of opposite chirality to what is predicted by the commonly accepted reaction transition-state.(Corey, 1998)

Deprotectection of the acetonide ketal **199** and subsequent ozonolysis of the double bond gave rise to the intermediate aldehyde, which undergoes spontaneous cyclisation to give the undecose skeleton **209** (Scheme 23). It was also established that removal of benzyl protecting groups will not be possible at the end of the synthesis; therefore, an exchange of all benzyl ethers to acetates was performed at this stage. The late-stage glycosylation of acetate was accomplished according to a modified Hilbert–Johnson–Vorbrüggen (Vorbrüggen, 1981) protocol by treatment of **198** with trimethylsilyl triflate and adenine and furnished the penultimate intermediate **210** as a single diastereomer.

Cleavage of acetate and benzoate esters as well as TMS-ether with sodium methylate led to herbicidin C, which was indistinguishable from the authentic sample of natural product by means of NMR-spectroscopy. Saponification of the methyl ester under mild conditions provided additionally aureonuclemycin. The developed synthetic strategy starts from the readily accessible compound and can be utilized for the preparation of other undecose derivatives, such as deoxygenated and amino-saccharides, as well as for the introduction of other suitable nucleobases in the furan ring.

Conclusions and Outlook.

The examples presented in this review make it evident that majority of bacterial isolates can now be synthesized in a 20-25 steps. As it can also be seen, recently achieved total syntheses of bacterial isolates feature a widespread application of highly convergent or bidirectional approaches, which rely on current synthetic tools such as asymmetric aldol reactions with remote stereoinduction, olefin metathesis and cross-coupling reactions. Although, overall yields of such sequences are usually in the range of few percent, they can still provide the target compounds in milligram to tens of milligrams quantities, which is mostly sufficient for complete biological evaluation by *in vivo* and *in vitro* assays. Further advancements in this field of research would be possibly directed towards discovery of even more atom-economic reactions, broader application of enzyme-catalyzed transformations, as well as development of the protecting group-free strategies and methodologies related to the synthesis of polyketide-like natural products.

Figures:

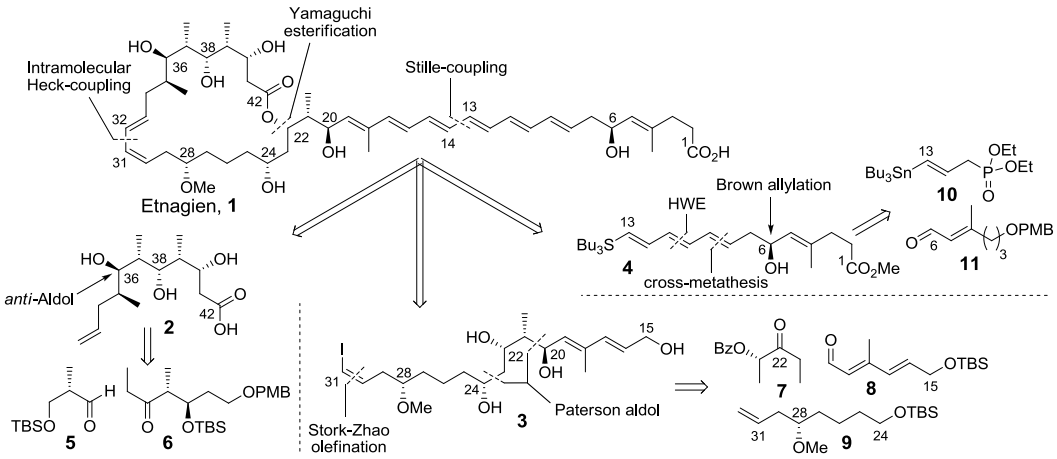


Figure 1. Retrosynthetic analysis of etnangien.

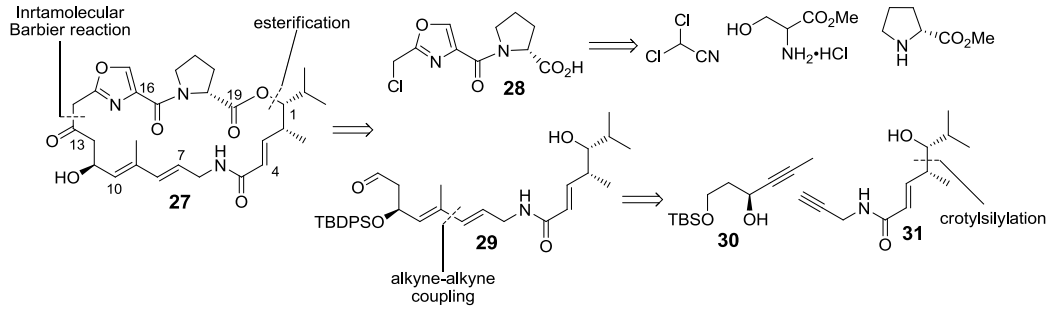


Figure 2. Intramolecular Barbier-reaction approach to the virginiamycin M2

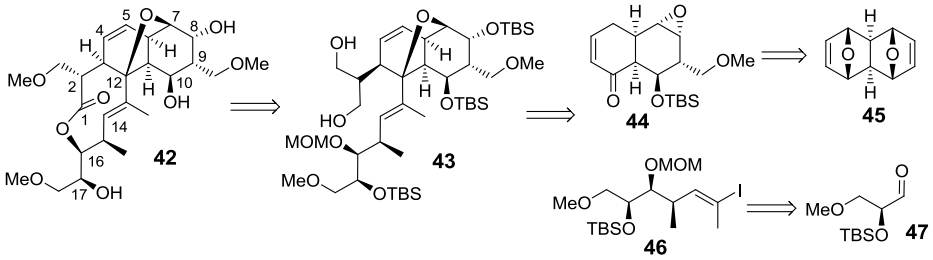


Figure 3. Retrosynthetic analysis of branimycin.

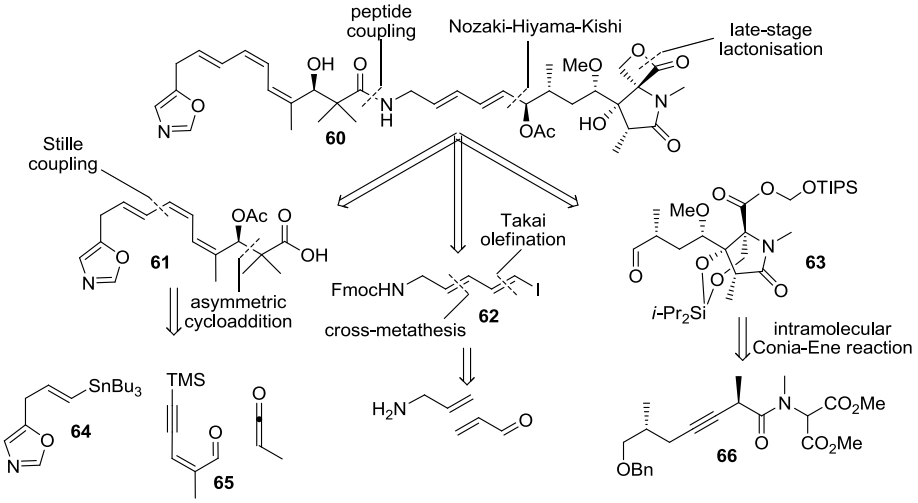


Figure 4. Retrosynthetic analysis of oxazolomycin.

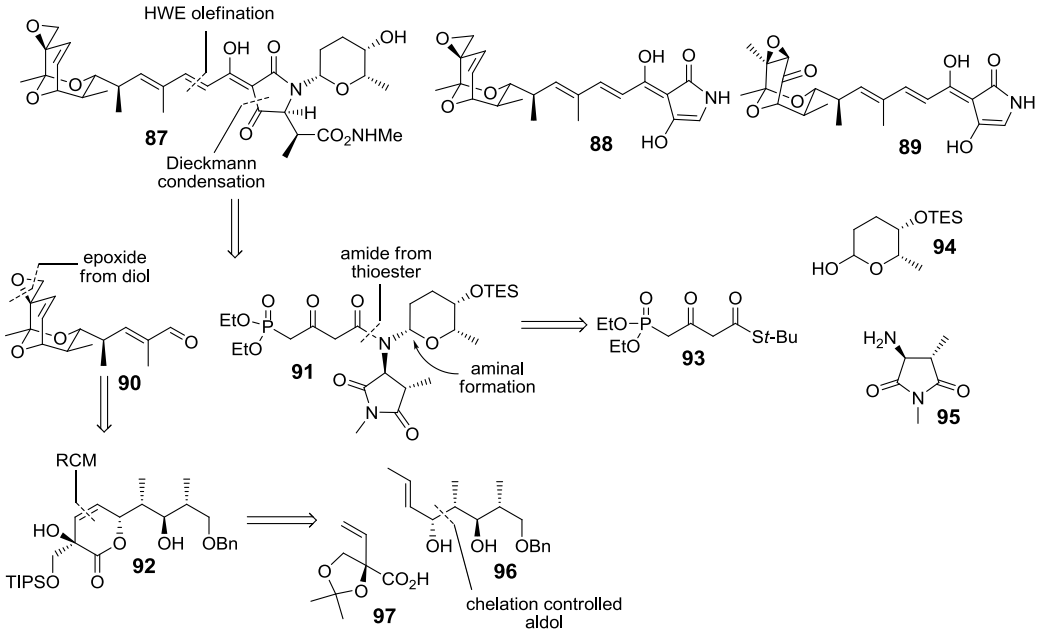


Figure 5. Retrosynthetic analysis of streptolydigin (**87**).

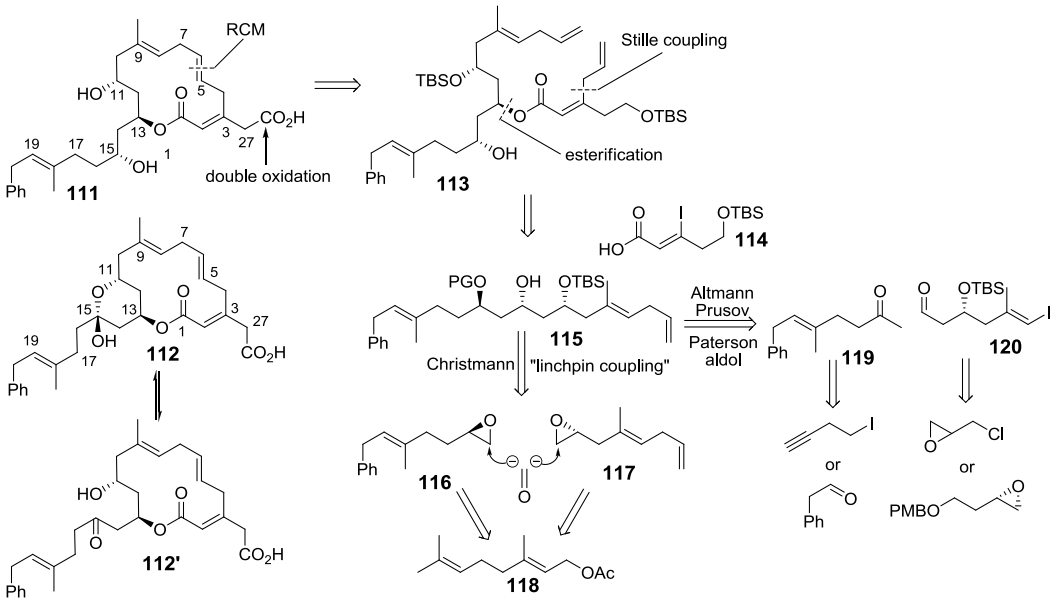


Figure 6. Alternative synthetic pathways to the polyol fragment of ripostatin B

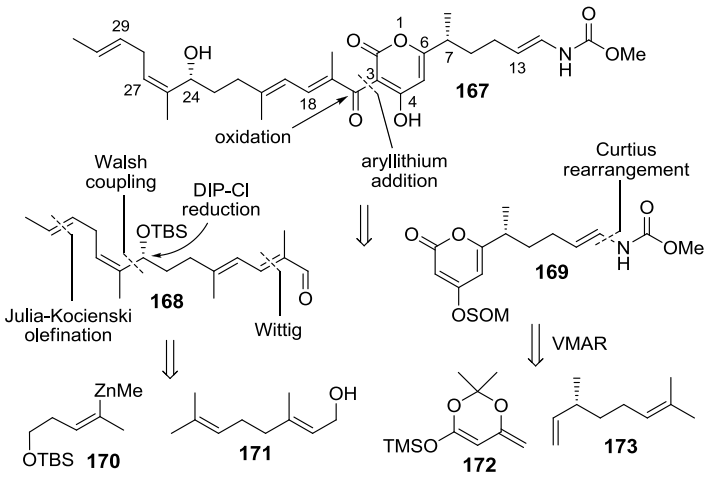


Figure 7. Aryllithium addition/Walsh coupling approach to corallopyronin

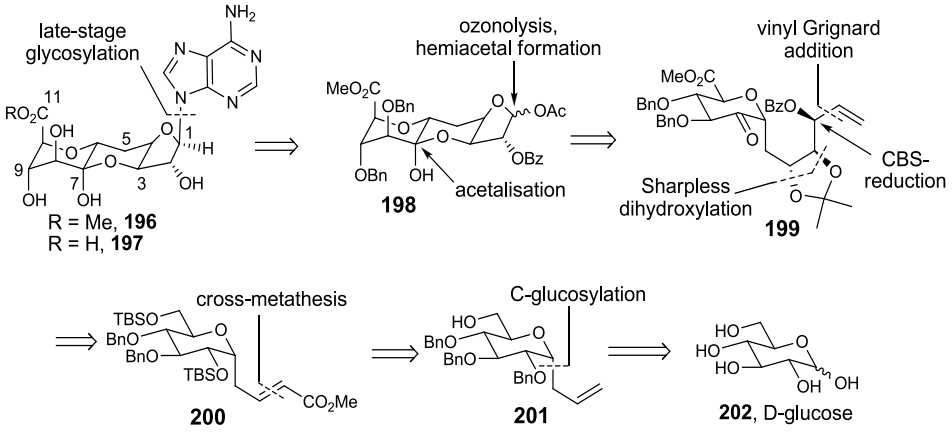
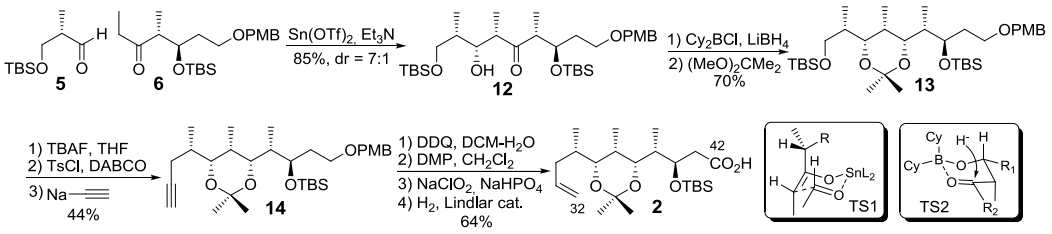
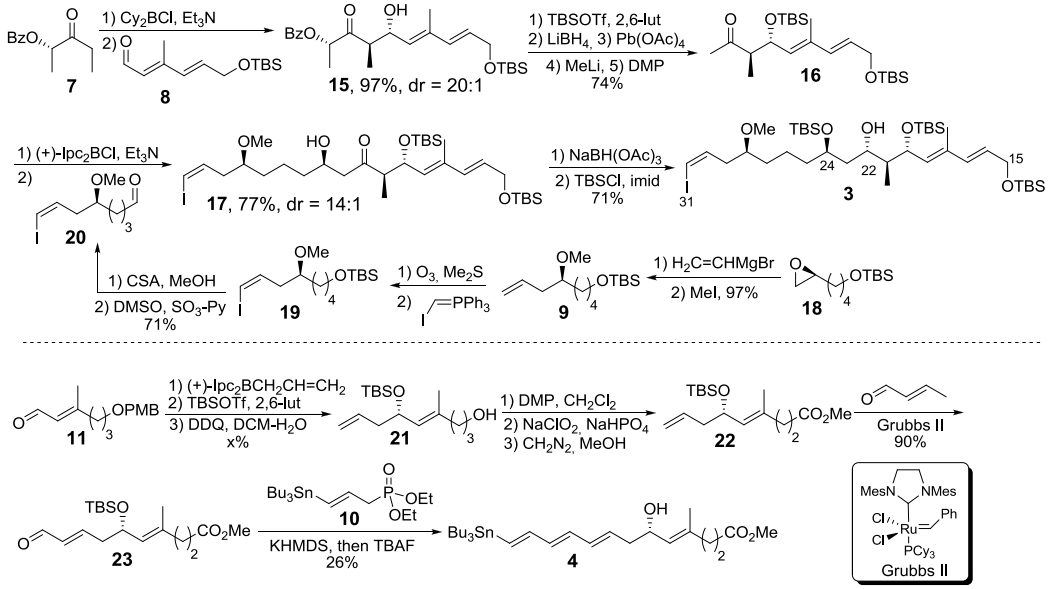


Figure 8. Late-stage glycosylation approach to herbicidin C

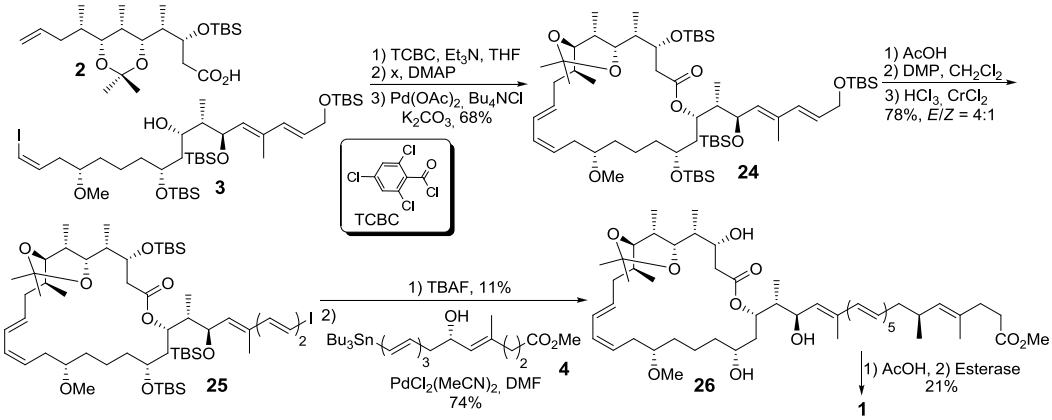
Schemes:



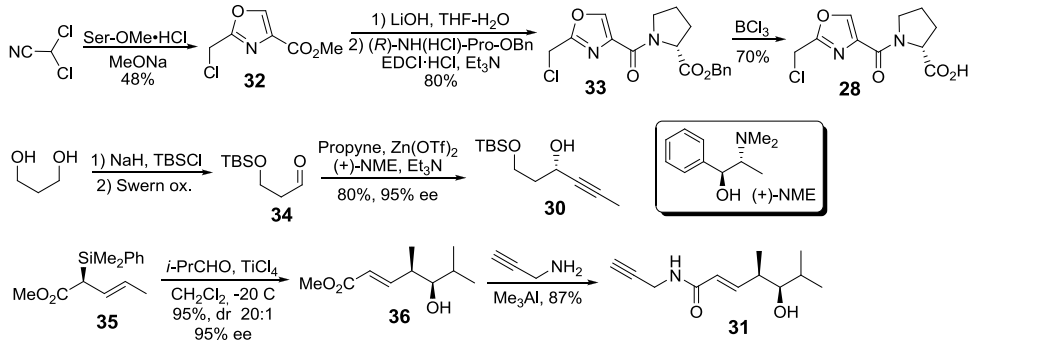
Scheme 1. Synthesis of the top arc of the macrocycle. (For the sake of shortness, throughout this review, a single number below the reaction arrow indicates the overall yield for the steps listed above and/or before, and the usual "for *x* steps" is omitted.)



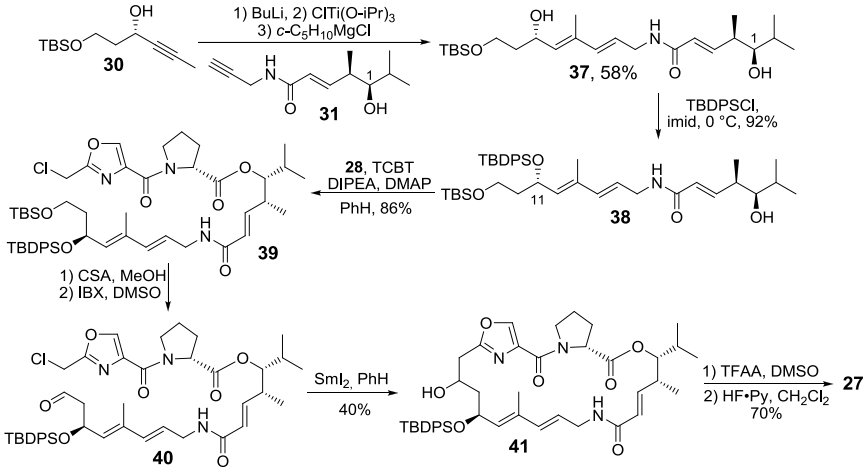
Scheme 2. Preparation of the second partner for the intramolecular Heck cross-coupling and polyenic side chain.



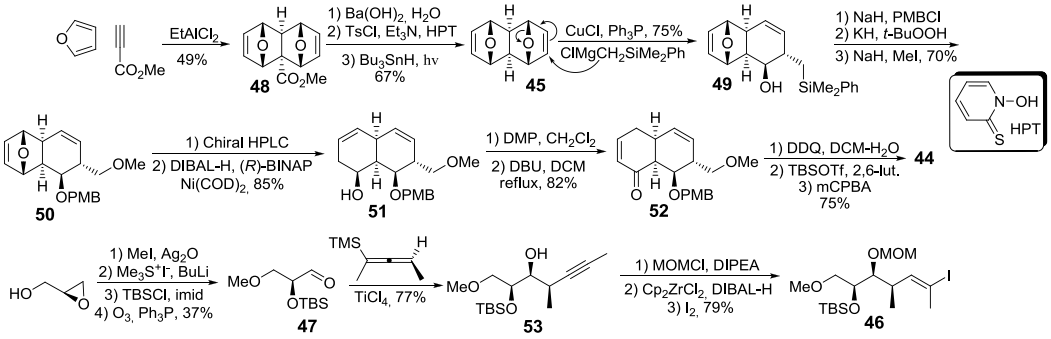
Scheme 3. Endgame of the synthesis.



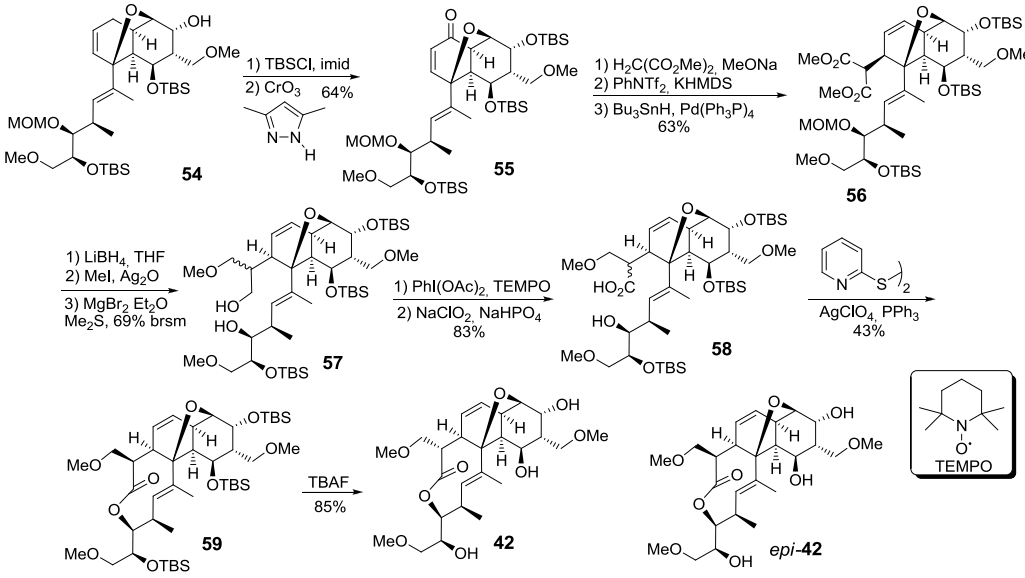
Scheme 4. Synthesis of the building blocks.



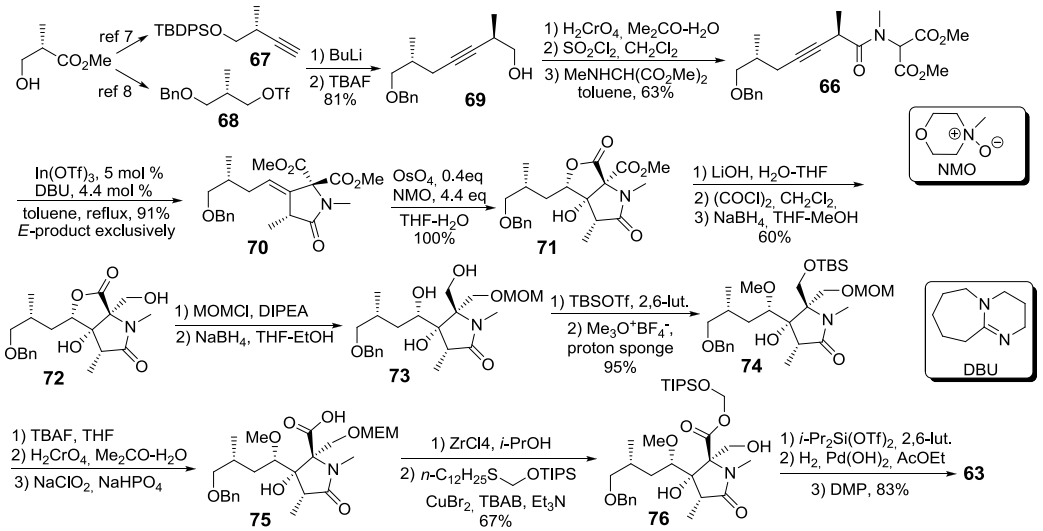
Scheme 5. Alkyne-alkyne coupling and completion of the molecule.



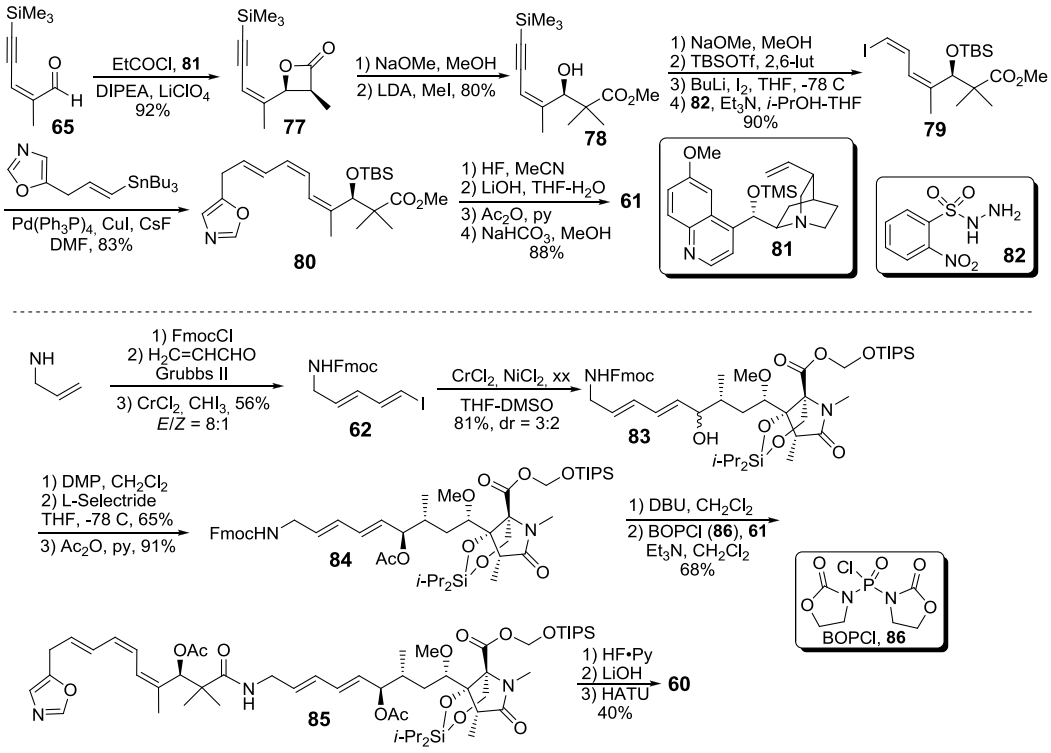
Scheme 6. Synthesis of the branimycin precursors.



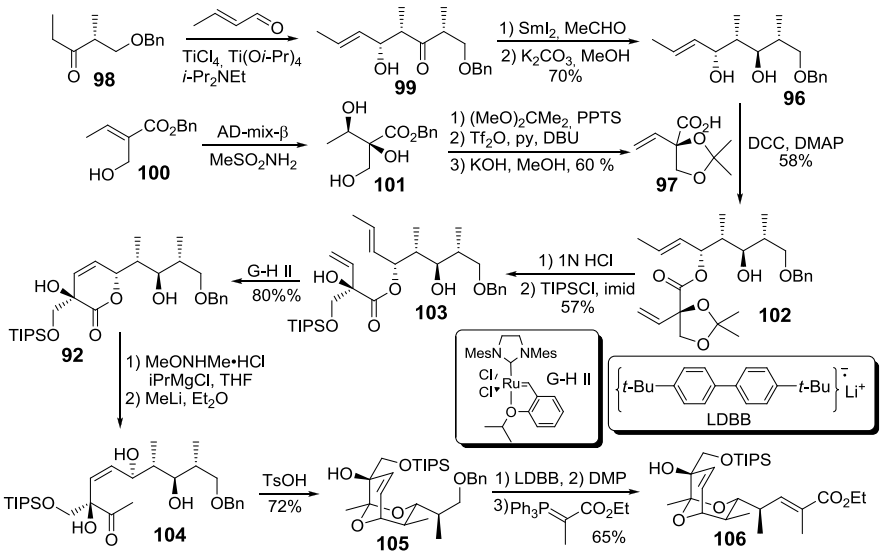
Scheme 7. Engame of the synthesis.



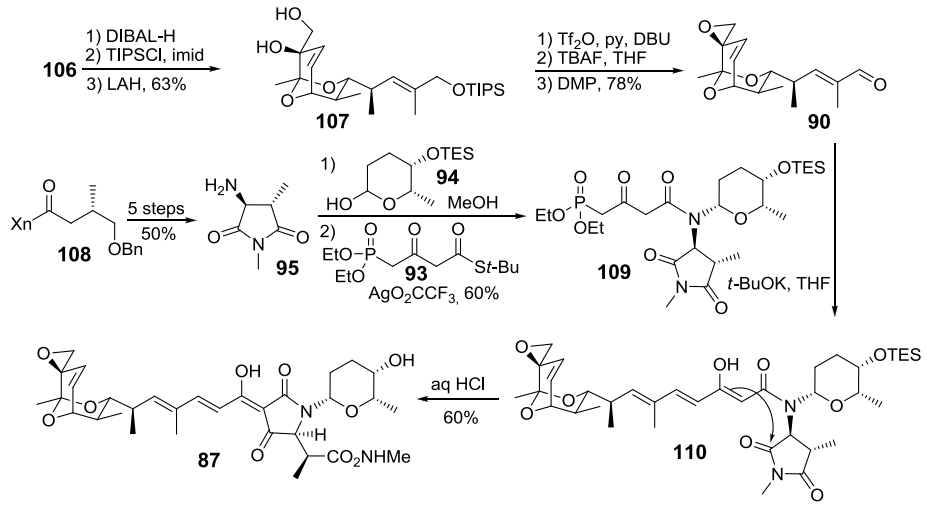
Scheme 8. Preparation of the lactam building block



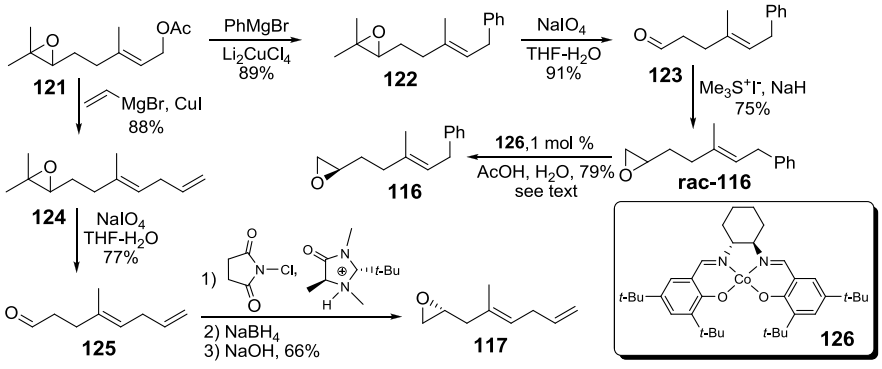
Scheme 9. Synthesis of the polyene-oxazol fragment, amine tether and assembly of the molecule.



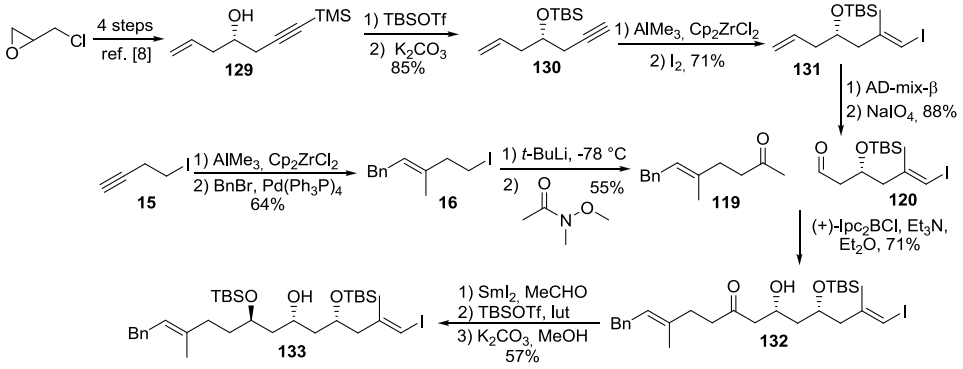
Scheme 10. Construction of bicyclic acetal core of streptolydigin.



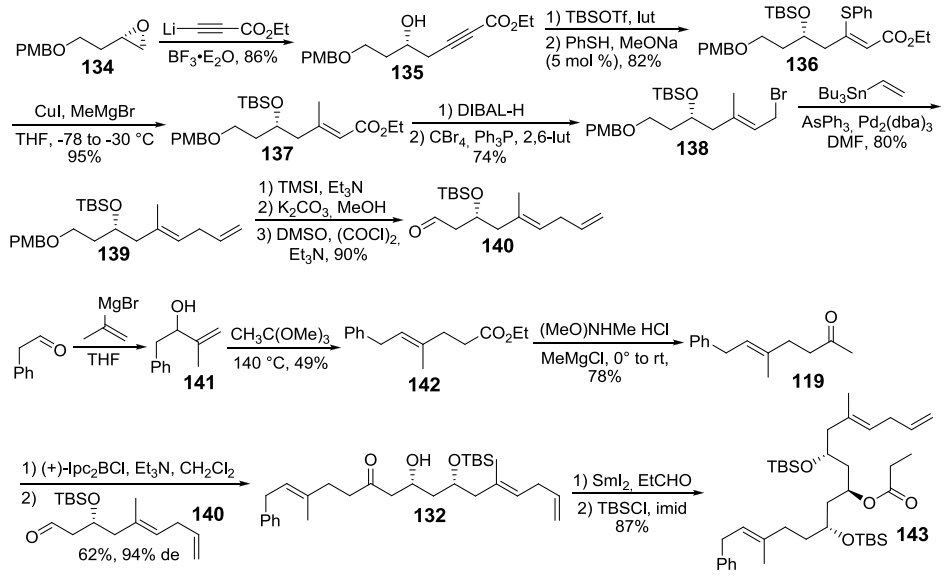
Scheme 11. Synthesis of tetramic acid subunit and completion of the synthesis.



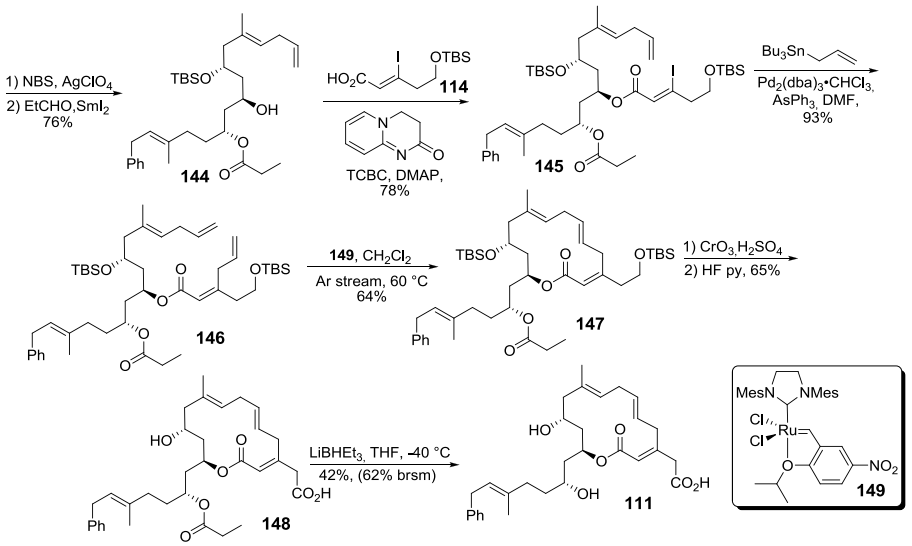
Scheme 12. Bi-directional approach to the epoxide precursors by Christmann



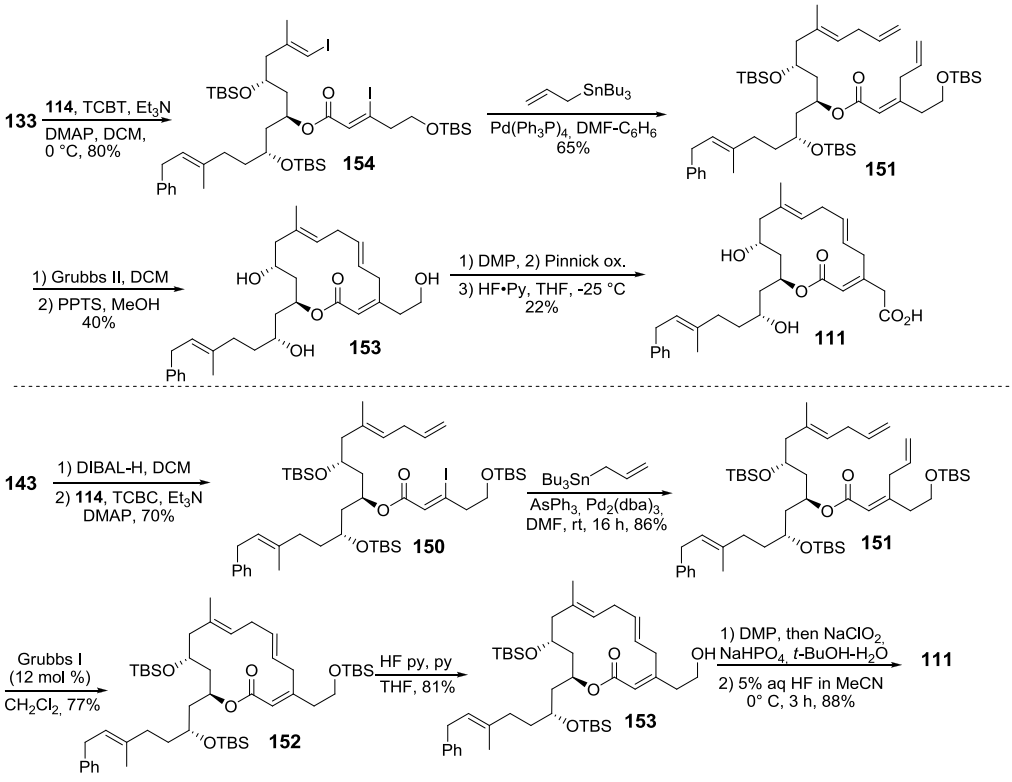
Scheme 13. Prusov synthesis of the polyl fragment.



Scheme 14. Synthesis of the 1,3,5-triol fragment by Altmann.

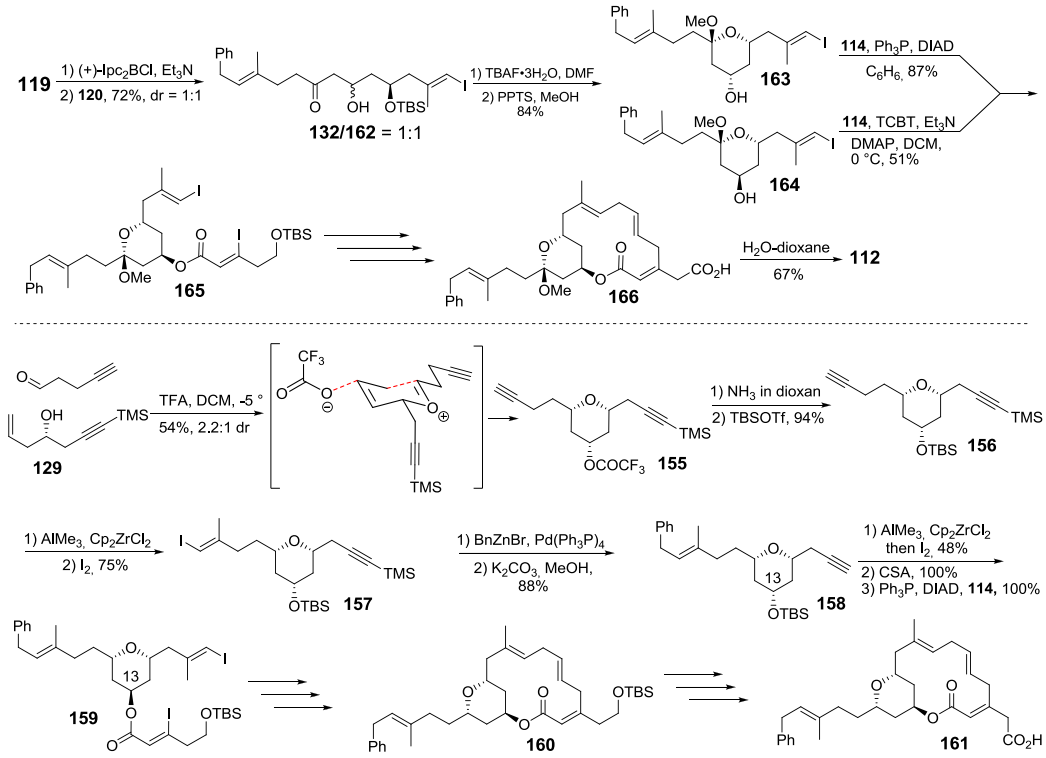


Scheme 15. Completion of the synthesis by Christmann.

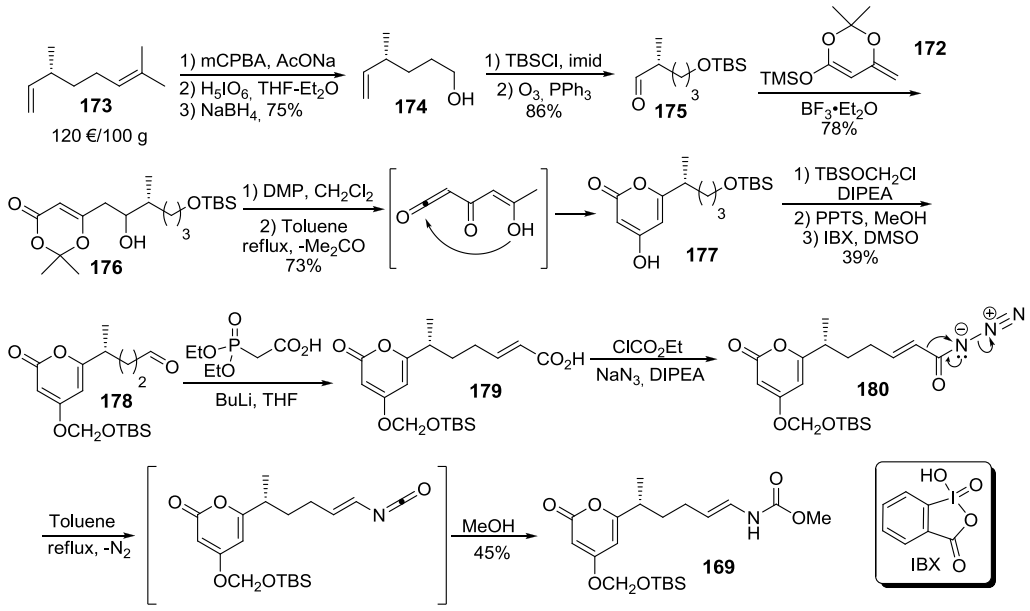


Sc

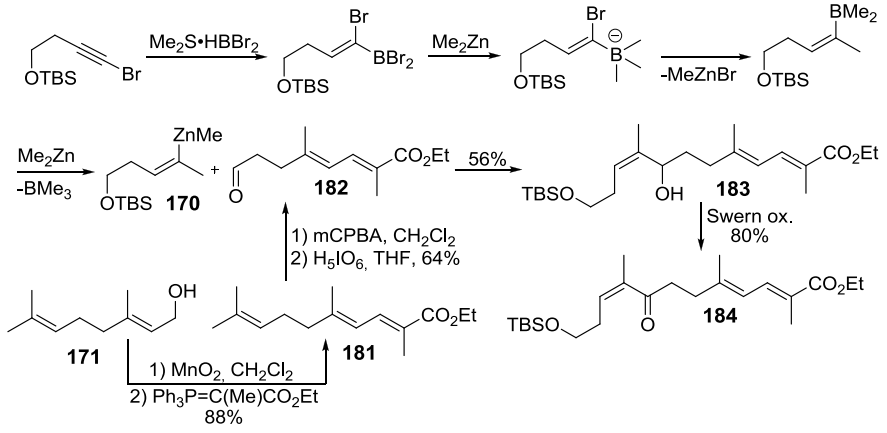
Scheme 16. Completion of the synthesis by prusov and Altmann.



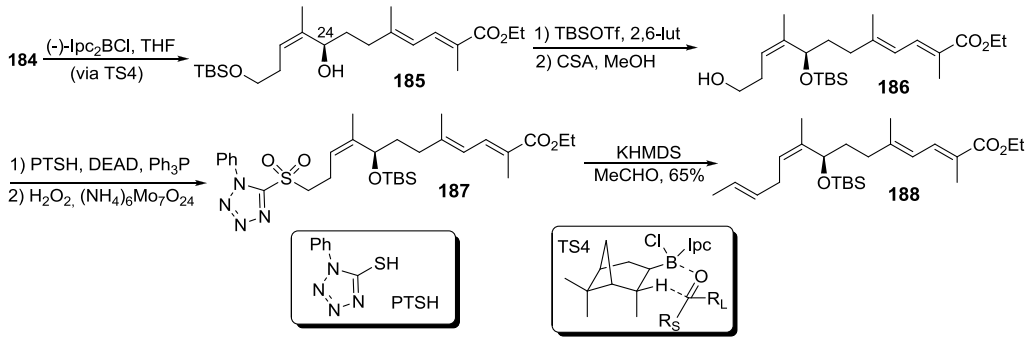
Scheme 17. Synthesis of ripostatin A and 15-deoxyripostatin A.



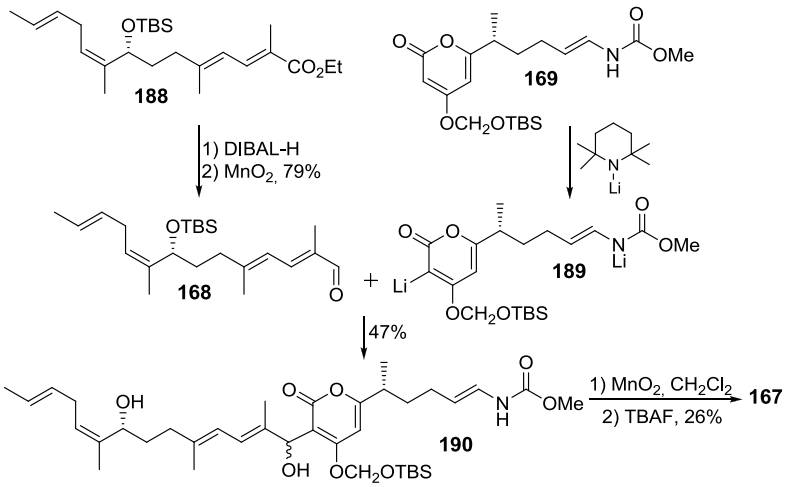
Scheme 18. Acylketene cycloaddition/Curtius rearrangement approach to the corallopyronin core.



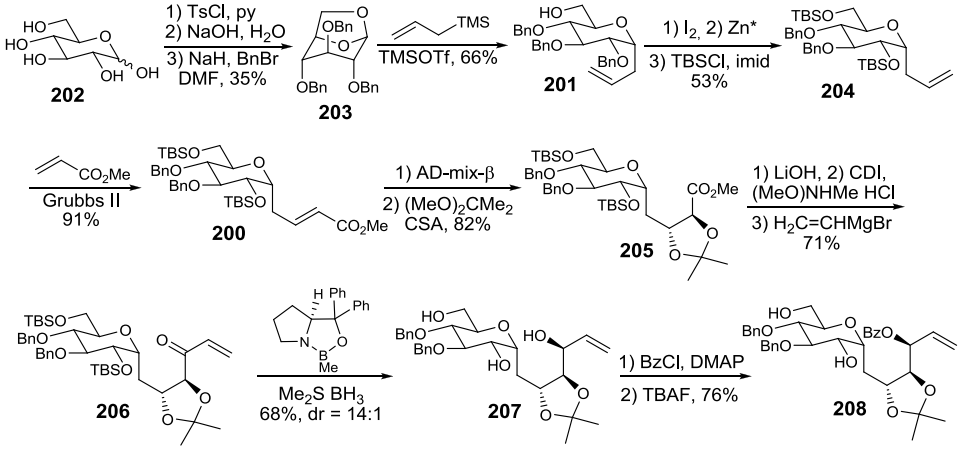
Scheme 19. Sythesis of the left-hand side chain precursor.



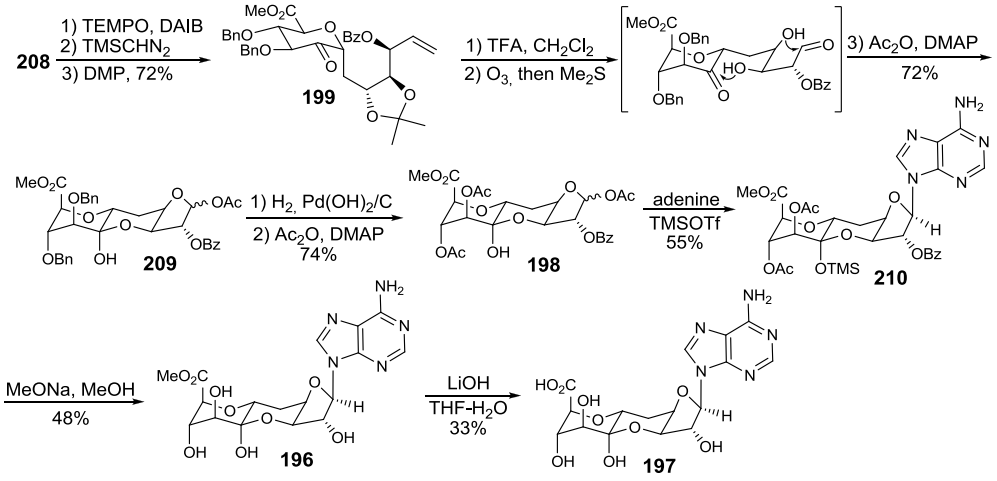
Scheme 20. DIP-Cl reduction and Julia-Kocienski olefination.



Scheme 21. Fragment assembly and completion of the synthesis.



Scheme 22. Synthesis of the undecose precursor from D-glucose.



Scheme 23. Construction of the tricylic undeose system and a completion of the synthesis.

References:

Abiko A, Moriya O, Filla SA, Masamune S (1995) Benzopyranoisoxazolidines as chiral auxiliaries for asymmetric synthesis Angew Chem Int Ed 34:793–795; Angew Chem 107:869–871

Andrews MD, Brewster AG, Crapnell KM, Ibbett AJ, Jones T, Moloney MG, Prout K, Watkin D (1998) Regioselective Dieckmann cyclisations leading to enantiopure highly functionalised tetramic acid derivatives. J Chem Soc Perkin Trans 1: Organic and Bio-Organic Chemistry 223–236

Appel R (1975) Tertiary phosphane/tetrachloromethane, a versatile reagent for chlorination, dehydration, and P-N linkage. Angew Chem Int Ed 14:801–811; Angew Chem 87:863–874

Arai M, Haneishi T, Kitahara N, Enokita R, Kawakubo K, Kondo Y (1976) Herbicidins A and B, two new antibiotics with herbicidal activity. I. Producing organism and biological activities. J Antibiot 29:863–869

Artsimovitch I, Vassylyeva MN, Svetlov D, Svetlov V, Perederina A, Igarashi N, Matsugaki N, Wakatsuki S, Tahirov TH, Vassylyev DG (2005) Allosteric modulation of the RNA polymerase catalytic reaction is an essential component of transcription control by rifamycins. Cell 122:351–363

Augustiniak H, Höfle G, Irschik H, Reichenbach H (1996) Antibiotics from gliding bacteria, LXXVIII. Ripostatin A, B, and C: Isolation and structure elucidation of novel metabolites from *Sorangium cellulosum*. Liebigs Ann 1657–1663

Bal BS, Childers WE, Pinnick HW (1981). Oxidation of α,β-unsaturated aldehydes. Tetrahedron 37:2091–2096

Barrière JC, Bouanchaud D, Desnoottes JF, Paris JM (1994) Streptogramin analogues. Expert Opin Invest Drugs 3:115–131

Barrière JC, Paris JM (1993) RP 59500 and related semisynthetic streptogramins. Drugs of the Future 18:833–845

Blakemore PR, Cole WJ, Kocieński PJ, Morley A (1998) A stereoselective synthesis of trans-1,2-disubstituted alkenes based on the condensation of aldehydes with metallated 1-Phenyl-1H-tetrazol-5-yl sulfones. Synlett 26–28

Bouzide A, Sauve G (1997) Highly selective silver(I) oxide mediated monoprotection of symmetrical diols. Tetrahedron Lett 38:5945–5948

Brill GM, McAlpine JB, Whittern DJ (1988) Tirandalydigin, a novel tetramic acid of the tirandamycin-streptolydigin type. I. Taxonomy of the producing organism, fermentation and biological activity. Antibiot 41:36–44

Brochu MP, Brown SP, MacMillan DWC (2004) Direct and enantioselective organocatalytic α-chlorination of aldehydes. J Am Chem Soc 126:4108–4109

Brown HC, Jadhav PK (1983) Asymmetric carbon-carbon bond formation via β-allyldiisopinocampheylborane. Simple synthesis of secondary homoallylic alcohols with excellent enantiomeric purities. J Am Chem Soc 105:2092–2093

Campbell EA, Korzheva N, Mustaev A, Murakami K, Nair S, Goldfarb A, Darst SA (2001) Structural mechanism for rifampicin inhibition of bacterial RNA Polymerase. Cell 104:901–912

Carlson JC, Li S, Burr DA, Sherman DH (2009) Isolation and characterization of tirandamycins from a marine-derived *Streptomyces sp*. J Nat Prod 72:2076–2079

Chaturvedi D (2012) Perspectives on the synthesis of organic carbamates. Tetrahedron 68: 15-45

Chen YK, Walsh PJ (2004) A one-pot multicomponent coupling reaction for the stereocontrolled synthesis of (Z)-trisubstituted allylic alcohols. J Am Chem Soc 126:3702–3703

Cipolla L, Lay L, Nicotra F (1997) New and easy access to C-glycosides of glucosamine and mannosamine. J Org Chem 62:6678–6681

Corey EJ, Helal CJ (1998) Reduction of carbonyl compounds with chiral oxazaborolidine catalysts: A new paradigm for enantioselective catalysis and a powerful new synthetic method. Angew Chem Int Ed 37:1986–2012; Angew Chem 110:2092–2118

Corey EJ, Nicolaou KC (1974) Efficient and mild lactonization method for the synthesis of macrolides. J Am Chem Soc 96:5614–5616

Cowden CJ, Paterson I (1997) Asymmetric aldol reactions using boron enolates Org React 51:1–200

DeBoer C, Dietz A, Silver WS, Savage GM (1956) Streptolydigin, a new antimicrobial antibiotic. I. Biologic studies of streptolydigin. Antibiot Annu 886–892

Delpierre GR, Eastwood FW, Gream GE, Kingston DGI, Todd ARL, Williams DH (1966) Antibiotics of the ostreogrycin complex. Part II. Structure of ostreogrycin A J Chem So. C 1653–1669

DeMico A, Margarita R, Parlanti L, Vescovi A, Piancatelli G A (1997) Versatile and highly selective hypervalent iodine (III)/2,2,6,6-tetramethyl-1-piperidinyloxyl-mediated oxidation of alcohols to carbonyl compounds. J Org Chem 62:6974–6977

Dess DB, Martin JC (1983) Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. J Org Chem 48:4155–4156

Dhar RK (1994) Diisopinocamphenylchloroborane, (DIP-Chloride), an excellent chiral reducing reagent for the synthesis of secondary alcohols of high enantiomeric purity. Aldrichimica Acta 27: 43–51

Eble TE, Large CM, DeVries WH, Crum GF, Shell JW (1956) Streptolydigin, a new antimicrobial antibiotic. II. Isolation and characterization. Antibiot Annu 893–896

Edmonds DJ, Johnston D, Procter DJ (2004) Samarium(II)-iodide-mediated cyclizations in natural product synthesis. Chem Rev 104:3371–3404

Erol Ö, Schäberle TF, Schmitz A, Rachid S, Gurgui C, El-Omari M, Lohr F, Kehraus S, Piel J, Müller R, König GM (2010) Biosynthesis of the myxobacterial antibiotic corallopyronin A. ChemBioChem 11:1253–1265

Eto K, Yoshino M, Takahashi K, Ishihara J, Hatakeyama S (2011) Total synthesis of oxazolomycin A. Org Lett 13:5398–5401

Evans DA, Britton TC (1987) Electrophilic azide transfer to chiral enolates. A general approach to the asymmetric synthesis of α-amino acids. J Am Chem Soc 109:6881–6883

Evans DA, Chapman KT, Carreira EM (1988) Directed reduction of α-hydroxy ketones employing tetramethylammonium triacetoxyborohydride. J Am Chem Soc 110:3560–3578

Evans DA, Hoveyda AH (1990) Samarium-catalyzed intramolecular Tishchenko reduction of β-hydroxy ketones. A stereoselective approach to the synthesis of differentiated *anti*-1,3-diol monoesters. J Am Chem Soc 112:6447–6449

Farina V, Krishnamurthy V, Scott WJ in "The Stille reaction". *Organic Reactions 50,* 1–652 (1998) ISBN 0471312738

Felzmann W, Castagnolo D, Rosenbeiger D, Mulzer J (2007) Crotylation versus propargylation: two routes for the synthesis of the C13−C18 fragment of the antibiotic branimycin. J Org Chem 72:2182–2186

Fischer M-R, Kirschning A, Michel T, Schaumann E (1994) Syntheses of cyclopentanols by a silicon-induced cascade reaction. Angew Chem Int Ed 33:217-218; Angew Chem 106:220-221

Frantz DE, Fassler R, Carreira EM (2000) Facile enantioselective synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes. J Am Chem Soc, 122:1806–1807

Freeman PK, Hutchinson LL (1980) Alkyllithium reagents from alkyl halides and lithium radical anions. J Org Chem 45:1924–1930

Ganesan A (2008) The impact of natural products upon modern drug discovery. Curr Opin Chem Biol 12:306–317

Glaus F, Altmann KH (2012) Total synthesis of the bacterial RNA polymerase inhibitor ripostatin B. Angew Chem Int Ed 51:3405–3409; Angew Chem 124:3461–3465

Gräfe U, Kluge H, Thiericke R (1992) Biogenetic studies on oxazolomycin, a metabolite of *Streptomyces albus* (strain JA 3453). Liebigs Ann Chem 429–432

Gromov A, Enev VS, Mulzer J, (2009) A desymmetrization approach toward highly oxygenated *cis*-decalins. Org Lett 11:2884–2886

Guthrie AE, Semple JE, Joullié MM (1982) Synthetic studies of fungal metabolites: ascofuranone and colletochlorin D. J Org Chem 47:2369–2376

Hagenmaier H, Jaschke KH, Santo L, Scheer M, Zahner H (1976) Metabiolic products of microorganisms. Tirandamycin B. (in German) Arch Microbiol 109:65–74

Hager D, Mayer P, Paulitz C, Tiebes J, Trauner D (2012) Stereoselective total syntheses of herbicidin C and aureonuclemycin through late-stage glycosylation. Angew Chem Int Ed 51:6525–6528; Angew Chem 124:6631–6634

Halland N, Braunton A, Bachmann S, Marigo M, Jørgensen KA (2004) Direct organocatalytic asymmetric α-chlorination of aldehydes. J Am Chem Soc 126:4790–4791

Hamann MT (2003) Enhancing marine natural product structural diversity and bioactivity through semisynthesis and biocatalysis. Curr Pharm Des 9:879–889

Haneishi T, Terahara A, Kayamori H, Yabe J, Arai M (1976) Herbicidins A and B, two new antibiotics with herbicidal activity II. Fermentation, isolation and physico-chemical characterization. J Antibiot 29:870–875

Hermitage SA, Cardwell KS, T. Chapman, J. W. B. Cooke, R. Newton (2001) An efficient, practical approach to the synthesis of 2,4-disubstituted thiazoles and oxazoles: application to the synthesis of GW475151. Org Process Res Dev 5:37–44

Hu T, Schaus JV, Lam K, Palfreyman MG, Wuonola M, Gustafson G, Panek JS (1998) Total synthesis and preliminary antibacterial evaluation of the RNA polymerase inhibitors (±)-myxopyronin A and B. J Org Chem 63:2401–2406

Hughes DL (1992) "The Mitsunobu Reaction" in Org Reactions 42:335–656 [76]

Inanaga J, Hirata K, Saeki H, Katsuki T, Yamaguchi M (1979) A rapid esterification by means of mixed anhydride and its application to large-ring lactonization. Bull Chem Soc Jpn 52:1989–1993

Irschik H, Augustiniak H, Gerth K, Höfle G, Reichenbach H (1995) The ripostatins, novel inhibitors of eubacterial RNA polymerase isolated from myxobacteria. J Antibiot 48:787–792

Irschik H, Gerth K, Höfle G, Kohl W, Reichenbach H (1983) The myxopyronins, new inhibitors of bacterial RNA synthesis from Myxococcus fulvus (Myxobacterales) J Antibiot 36:1651–1658

Irschik H, Jansen R, Höfle G, Gerth K, Reichenbach H (1985) The corallopyronins, new inhibitors of bacterial RNA synthesis from Myxobacteria. J Antibiot 38:145–152

Irschik H, Schummer D, Höfle G, Reichenbach H, Steinmetz H, Jansen R (2007) Etnangien, a macrolide-polyene antibiotic from Sorangium cellulosum that inhibits nucleic acid polymerases. J Nat Prod 70:1060–1063

Jansen R, Irschik H, Reichenbach H, Höfle G (1985) Corallopyronin A, B, and C: three novel antibiotics from Corallocuccus coralloides Cc c127 (Myxobacterales). (in German) Liebigs Ann Chem 822–836

Jesse WHL, Vederas JC (2009) Drug discovery and natural products: end of an era or an endless frontier? Science 325:161–165

Johnson WS, Gravestock MB, McCarry BE (1970) Simple stereoselective version of the Claisen rearrangement leading to trans-trisubstituted olefinic bonds. Synthesis of squalene. J Am Chem Soc 92:741–743

Kanematsu M, Shindo M, Yoshida M, Shishido K (2009) Total synthesis of bongkrekic acid via sequential Suzuki-Miyaura coupling reactions. Synthesis 2893–2904

Kawai S, Kawabata G, Kobayashi A, Kawazu K (1989) Inhibitory effect of oxazolomycin on crown gall formation. Agric Biol Chem 53:1127–1133
Kende AS, Kawamura K, DeVita RJ (1990) Enantioselective total synthesis of neooxazolomycin. J Am Che. Soc 112:4070–4072
Kirschning A, Hahn F (2012) Merging chemical synthesis and biosynthesis: a new chapter in the total synthesis of natural products and natural product libraries. Angew Chem Int. Ed 51:4012–4022
Kujat C, Bock M, Kirschning A (2006) Synthesis of the the C1-C5 and C6-C24 Fragments of the RNA-polymerase inhibitors Ripostatin A and B. Synlett 419–422
L. Boulard, S. BouzBouz, J. M. Paris, J. Cossy, Synthesis of the C1-C13 Fragment of (+)-Callipeltoside A Synlett 2007, 1461 – 1463. [84] b)
Lewis C, Wilkins JR, Schwartz DF, Nikitas CT (1956) Streptolydigin, a new antimicrobial antibiotic. III. In vitro and in vivo laboratory studies. Antibiot Annu 897–902
Lewis MD, Cha JK, Kishi Y (1982) Highly stereoselective approaches to α-and β-C-glycopyranosides. J Am Chem Soc 104:4976–4978
Ley SV, Madin A, In *Comprehensive Organic Synthesis*, Trost BM (Ed.), I. Fleming (Ed.) vol. 7 pp 253–256 (1991) ISBN ISBN: 978-0-08-052349-1 [42]
Ley SV, Smith SC, Woodward PR (1992) Further reactions of *t*-butyl 3-oxobutanthioate and t-butyl 4-diethyl-phosphono-3-oxobutanthioate: Carbonyl coupling reactions, amination, use in the preparation of 3-acyltetramic acids and application to the total synthesis of fuligorubin A. Tetrahedron 48:1145–1174
Li P, Li J, Arikan F, Ahlbrecht W, Dieckmann M, Menche D (2009) Total synthesis of etnangien. J Am Chem Soc 131:11678–11679
Lira R, Agrios KA, Doundoulakis T, Simonsen KB, Webber SE, Xiang AX (2006) An efficient synthesis of (±)-myxopyronin B via versatile pyridone intermediates. Heterocycles 68:1099–1103
Lokot IP, Pashkovsky FS, Lakhvieh FA (1999) A new approach to the synthesis of 3,6- and 5,6-dialkyl derivatives of 4-hydroxy-2-pyrone. Synthesis of rac-germicidin. Tetrahedron 55:4783–4792
Maier ME (2009) Structural revisions of natural products by total synthesis. Nat Prod Rep 26:1105–1124

Marchart S, Gromov A, Mulzer J (2010) Total synthesis of the antibiotic branimycin. Angew Chem Int Ed 49:2050–2053; Angew Chem 122:2094–2097

Menche D, Arikan F, Perlova O, Horstmann N, Ahlbrecht W, Wenzel SC, Jansen R, Irschik H, Müller R (2008) Stereochemical determination and complex biosynthetic assembly of etnangien, a highly potent RNA polymerase inhibitor from the myxobacterium *Sorangium cellulosum*. J Am Chem Soc 130:14234–14243

Meyer CEJ (1971) Tirandamycin, a new antibiotic isolation and characterization. Antibiot 24:558–560

Moloney MG, Trippier PC, Yaqoob M, Wang Z (2004) The oxazolomycins: a structurally novel class of bioactive compounds. Curr Drug Discovery Technol 1:181–199

Mori T, Takakashi K, Kashiwabara M, Uemura D, Katayama C, Iwadare S, Shizuri Y, Mitomo R, Nakano F, Matsuzaki A (1985) Structure of oxazolomycin, a novel β-lactone antibiotic. Tetrahedron Lett, 26:1073–1076

Moser WH (2001) The Brook rearrangement in tandem bond formation strategies. Tetrahedron 57:2065–2084

Mukhopadhyay J, Das K, Ismail S, Koppstein D, Jang M, Hudson B, Sarafianos S, Tuske S, Patel J, Jansen R, Irschik H, Arnold E, Ebright RH (2008) The RNA polymerase "switch region" is a target for inhibitors. Cell 135:295–307

Neises B, Steglich W (1978) Simple method for the esterification of carboxylic acids. Angew Chem Int. Ed 17:522–524; Angew Chem 90:556–557

Nicolaou KC, Harter MW, Gunzner JL, Nadin A (1997) The Wittig and related reactions in natural product synthesis. Liebigs Ann/Rec 1283–1301

Nicolaou KC, Snyder SA (2005) Chasing molecules that were never there: misassigned natural products and the role of chemical synthesis in modern structure elucidation. Angew Chem Int Ed 44:1012–1044; Angew Chem 117:1036–1069

Onyango E. O, Tsurumoto J, Imai N, Takahashi K, Ishihara J, Hatakeyama S (2007) Total synthesis of neooxazolomycin. Angew Chem Int Ed, 46:6703–6705 Angew Chem 119:6823–6825

Paterson I, Tillyer RD (1992) Studies in polypropionate synthesis: high π-face selectivity in syn aldol reactions of tin(II) enolates from (*R*)- and (*S*)-1-benzyloxy-2-methylpentan-3-one. Tetrahedron Lett 33:4233–4236

Pronin SV, Kozmin SA (2010) Synthesis of streptolydigin, a potent bacterial RNA polymerase inhibitor. J Am Chem Soc 132:14394–14396
Pronin SV, Martinez A, Kuznedelov K, Severinov K, Shuman HA, Kozmin SA (2011) Chemical synthesis enables biochemical and yntibacterial evaluation of streptolydigin antibiotics. J Am Chem Soc 133:12172–12184
Reichard HA, Rieger JC, Micalizio GC (2008) Total synthesis of callystatin-A by titanium-mediated reductive alkyne–alkyne cross-coupling. Angew Chem Int Ed 47:7837–7840; Angew Chem 120:7955–7958
Rentsch A, Kalesse M (2012) The total synthesis of corallopyronin A and myxopyronin B. Angew Chem Int Ed 51:11381–11384; Angew Chem 124:11543–11547
Sato M, Sakakl J, Sugita Y, Yasuda S, Sakoda H, Kaneko C (1991) Two lactone formation reactions from 1,3-dioxin-4-ones having hydroxyalkyl group at the 6-position: Difference in ring opening and closure. Tetrahedron 47:5689–5708
Schaus SE, Brandes BD, Larrow JF, Tokunaga M, Hansen KB, Gould AE, Furrow ME, Jacobsen EN (2002) Highly selective hydrolytic kinetic resolution of terminal epoxides catalyzed by chiral (salen)CoIII complexes. Practical synthesis of enantioenriched terminal epoxides and 1,2-diols. J Am Chem Soc 124:1307–1315
Schlessinger RH, Graves DD (1987) A non-congener based synthesis of L-(-)-rhodinose and of a C4 hydroxyl protected derivative. Tetrahedron Lett 28:4381–4384
Schlessinger RH, Li Y-J (1996) Total synthesis of (–)-Virginiamycin M_2 using 2nd-generation vinylogous urethane chemistry. J Am Chem Soc 118:3301–3302
Shimshock SJ, Waltermire RE, DeShong P (1991) A total synthesis of (+)-tirandamycin B. J Am Chem Soc 113:8791–8796
Speitling M, Grün-Wollny I, Hannske FG, Laatsch H (2000 and 2001) Poster presentations at 12 and 13 IRSEER Naturstofftage der DECHEMA e.V. Irsee
Takahashi K, Kawabata M, Uemura D, Iwadare S, Mitomo R, Nakano F, Matsuzaki A (1985) Structure of neooxazolomycin, an antitumor antibiotic Tetrahedron Lett 26:1077–1078
Takahashi K. Midori M, Kawano K, Ishihara J, Hatakeyama S (2008) Entry to heterocycles based on indium-catalyzed Conia-ene reactions: Asymmetric

synthesis of (−)-salinosporamide A, Angew Chem Int Ed 47:6244–6246; Angew Chem 120:6340–6342
Takai K, Nitta K, Utimoto K (1986) Simple and selective method for aldehydes (RCHO) → (E)-haloalkenes (RCH=CHX) conversion by means of a haloform-chromous chloride system. J Am Chem Soc 108:7408–7410
Takai K, Nozaki H (2000) Nucleophilic addition of organochromium reagents to carbonyl compounds. Proc Japan Acad Ser B 76:123–131
Tang W, Prusov EV (2012) Total synthesis of ripostatin A. Org Lett 14:4690–4693
Tang, WF, Prusov EV (2012) Total synthesis of RNA-polymerase inhibitor ripostatin B and 15-deoxyripostatin A. Angew Chem Int Ed 51:3401–3404; Angew Chem 124:3457–3460
Trost BM, Gunzner JL (2001) Total synthesis of deschlorocallipeltoside A. J Am Chem Soc 123:9449–9450
Trost BM, Papillon JPN (2004) Alkene−alkyne coupling as a linchpin: An efficient and convergent synthesis of amphidinolide P. J Am Chem Soc 126:13618–13619
Tuske S, Sarafianos SG, Wang X, Hudson B, Sineva E, Mukhopadhyay J, Birktoft JJ, Leroy O, Ismail S, Clark AD, Dharia C, Napoli A, Laptenko O, Lee J, Borukhov S, Ebright RH, Arnold E (2005) Inhibition of bacterial RNA polymerase by streptolydigin: stabilization of a straight-bridge-helix active-center conformation. Cell 122:541–552
VanRheenen V, Kelly RC, Cha DY (1976) An improved catalytic OsO_4 oxidation of olefins to cis-1,2-glycols using tertiary amine oxides as the oxidant. Tetrahedron Lett 17:1973–1976
Vorbrüggen H, Bennua B (1981) Nucleoside syntheses, XXV. A new simplified nucleoside synthesis. Chem Ber 114:1279–1286
Williams JM, Jobson RB, Yasuda N, Marchesini G, Dolling UH, Grabowski EJJ (1995) A new general method for preparation of N-methoxy-N-methylamides. Application in direct conversion of an ester to a ketone. Tetrahedron Lett 36:5461–5464
Winter P, Hiller W, Christmann M (2012) Access to skipped polyene macrolides through ring-closing metathesis: Total synthesis of the RNA polymerase inhibitor ripostatin B. Angew Chem Int Ed 51:3396–3400; Angew Chem 124:3452–3456

Winter P, Swatschek J, Willot M, Radtke L, Olbrisch T, Schäfer A, Christmann M (2011) Transforming terpene-derived aldehydes into 1,2-epoxides via asymmetric α-chlorination: subsequent epoxide opening with carbon nucleophiles. Chem Commun 47:12200–12202

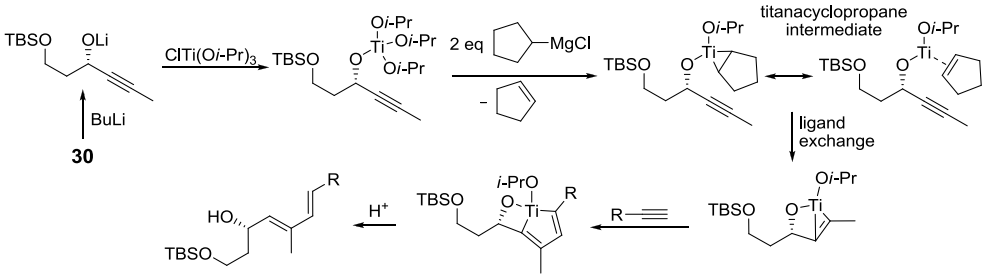
Wu J, Chen Y, Panek JS (2010) Vinylogous aldol products from chiral crotylsilanes obtained by enantioselective Rh(II) and Cu(I) carbenoid Si−H insertion Org Lett 12:2112–2115

Wu J, Panek JS (2010) Total synthesis of (–)-Virginiamycin M_2 Angew Chem Int Ed 49:6165–6168; Angew Chem 122:6301–6304

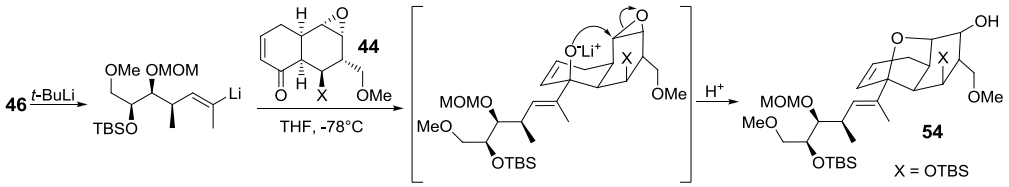
Zhu C, Shen X, Nelson SG (2004) Cinchona alkaloid-Lewis acid catalyst systems for enantioselective ketene−aldehyde cycloadditions. J Am Chem Soc 126:5352–5353

Zottola MA, Alonso R, Vite GD, Fraserreid B (1989) A practical, efficient large-scale synthesis of 1,6-anhydrohexopyranoses. J Org Chem 54:6123–6125

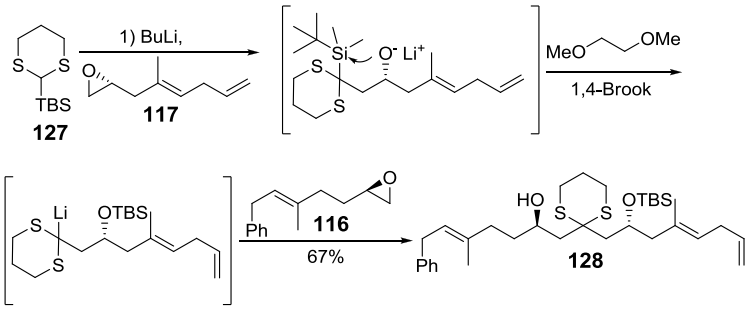
Supplementary Information.



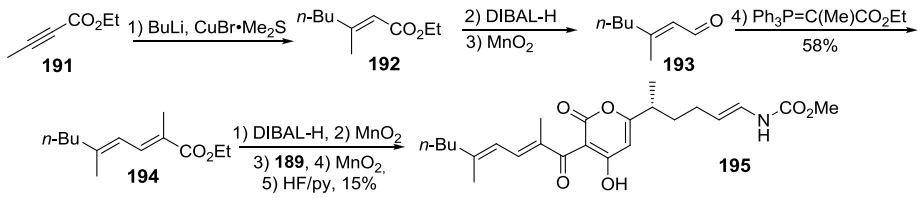
Scheme SI-1. Mechanism of the Ti(II)-mediated alkyne-alkyne coupling.



Scheme SI-2. Cascade carbonyl addition/epoxide opening construction of branimycin core.



Scheme SI-3. Linchpin coupling of 2-TBS-dithiane with epoxides **116** and **117**.



Scheme SI-4. Total synthesis of myxopyronin B