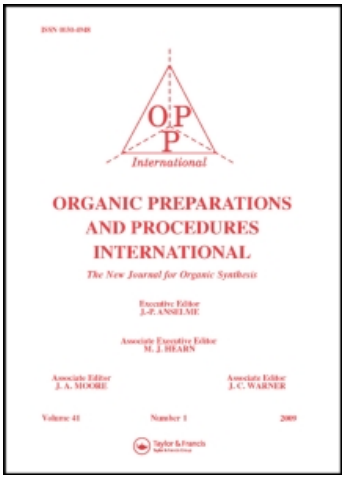

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INTRODUCTION

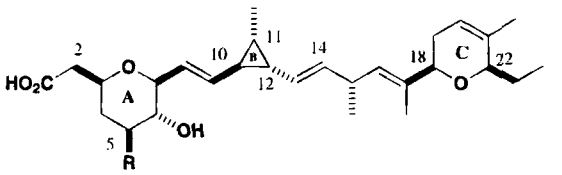
The continued emergence of bacterial resistance to existing drug therapies is a compelling issue. Vancomycin is no longer a last line of defense against microbes that have developed drug resistance *via* mutation or other means. Subsequently, there is a genuine if not urgent need to identify and develop more powerful antibiotics.

Secondary metabolites isolated from various microorganisms have traditionally proven to be a rich source of novel antibiotics. One prominent source of biologically relevant secondary metabolites is the myxobacteria (gliding bacteria), prokaryotes that can move by sliding or creeping across glass and agar surfaces. Largely due to the work of researchers at Gesllschaft für Biotechnologische Forschung (GBF) in Germany, a number of compounds derived from the myxobacteria have been discovered to exhibit biological activity as antibiotic agents.[1] These metabolites, which span a range of approximately 50 structural classes with nearly 300 structural variants, possess a diverse array of functionalities (including *C*-glycosides, polyenes, heterocycles, and macrolides) and are therefore appealing targets for synthetic organic chemists. While the screening, isolation, and biological activities of these metabolites have been well documented in several reviews,[2–5] this account is intended to summarize the efforts devoted to the structure elucidation and synthesis of these novel antibiotics. Important lessons can be learned while applying known methodology to total synthesis. The exercise of total synthesis itself holds particular relevance to the advancement of chemical synthesis for it often spurs further interests in developing new methodology.

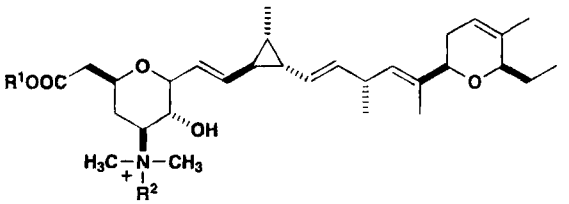
The epothilones (A–E) were isolated from the myxobacterium *Sorangium cellulosum* by the Höfle and Reichenbach group in 1993.[6] Because of their unique cytotoxic activity with the same mechanism of action as that of paclitaxel (by binding to the same microtubule sites), intensive synthetic endeavors have been undertaken to develop these compounds as biological analogs of paclitaxel for cancer therapy. In particular, the Nicolaou, Danishefsky, and Schinzer groups have made great strides in achieving both total syntheses of the natural epothilones and their analogs for the structure–activity relationship studies. Although epothilones are probably the most important secondary metabolites isolated from myxobacteria, their synthetic efforts are not covered here since there have

been three recent reviews on that subject.[7–9]

I. INCORPORATION OF NOVEL *C*-LINKED GLYCOSIDES[10]



	R	Ambruticin
1a	OH	S
1b	NH_3^+	VS-5
1c	$NH_2CH_3^+$	VS-4
1d	$NH(CH_3)_2^+$	VS-3
1e	$N(CH_3)_3^+$	VS-1



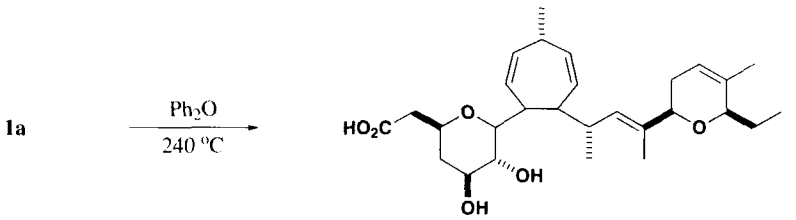
	R^1	R^2	Ambruticin
2a	CH_3	CH_3	VS-2
2b	H	O^-	VS-3 *N*-oxide

Ambruticin S and Ambruticin VS-Variants

Fig. 1.

Ambruticin was the first example and has continued to be one of the most intensively studied antibiotics isolated from the fermentation media of gliding bacteria. In 1977,[11] the Connor group at Parke–Davis disclosed the isolation and structure elucidation of a 5,6-hydroxypolyangioic acid (W-7783, which was later officially renamed as ambruticin S, **1a**) from an ethyl acetate extract of the fermentation medium of the myxobacterium *Sorangium (Polyangium) cellulosum var fulvam.* Although a large number of ambruticin derivatives are oils or gums, the triformate of **1a** was obtained as a crystalline solid. This facilitated the establishment of the structure including the relative stereochemistry by single crystal X-ray crystallography. The absolute configuration of **1a** was subsequently established by Just and Potvin[12] by oxidative degradation of **1a** to tetrahydropyran and cyclopropane fragments by reductive ozonolysis. Comparing their optical rotations with derivatives synthesized from natural *L*-arabinose and (*R*)-Feist's acid led to the stereochemical assignment. The absolute configuration was later confirmed by Davidson and Proctor in the course of their synthetic studies (*vide infra*).[13] Furthermore, in 1991, Höfle's group at GBF reported the isolation and characterization of six additional antifungal metabolites (ambruticins, **1b–2b**, Fig. 1) from *Sorangium cellulosum.*[14]

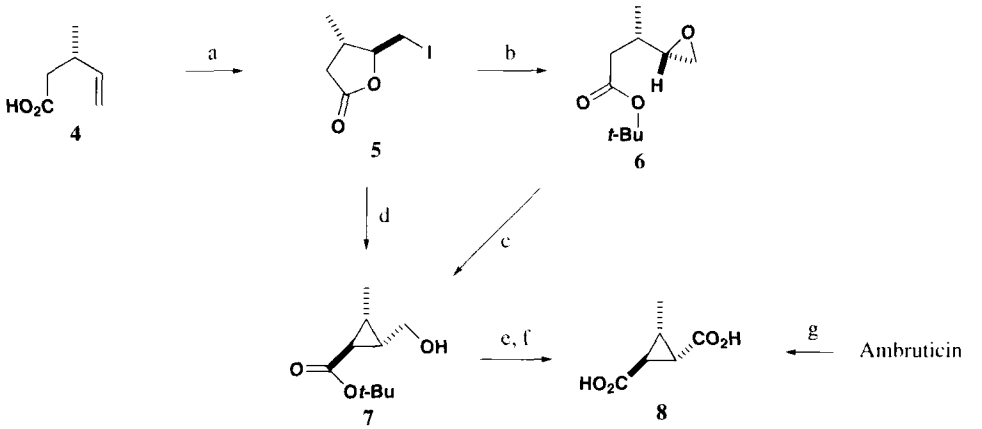
These structures were determined by spectroscopic methods, and the absolute configurations were inferred from the comparison of their optical rotations and CD spectra with those of the parent **1a**.



3

Ambruticin S demonstrates both *in vitro* and *in vivo* activities against a variety of pathogenic fungi and has been the subject of intensive biological studies.[15–24] To gauge the structure–activity relationship profile of ambruticins, many derivatives of **1a** were synthesized and biological activities were evaluated in systemic fungal infections.[21–24] Ambruticin S was found to be thermally labile, demonstrating a formal [3,3] electrocyclic rearrangement of the *trans*-divinyl cyclopropane moiety to the cycloheptadiene **3**.[21] This isomeric compound is devoid of antifungal activity, indicating that these properties may depend on the recognition and electrophilic chemistry emanating from the divinyl cyclopropane unit. In addition, twenty-three esters and amides at C_1 of **1a** were prepared and did not display any improvement in antifungal activity over **1a**[23, 24] indicating the polar functions at C_1, C_5, and C_6 are important for antifungal activity. Despite excellent *in vivo* activity and low toxicity, ambruticin S (**1a**) has not been commercially developed because the spectrum of its antifungal activity is not sufficiently broad to a number of pathogenic fungi in a common treatment protocol.

1.a. Initial Approaches

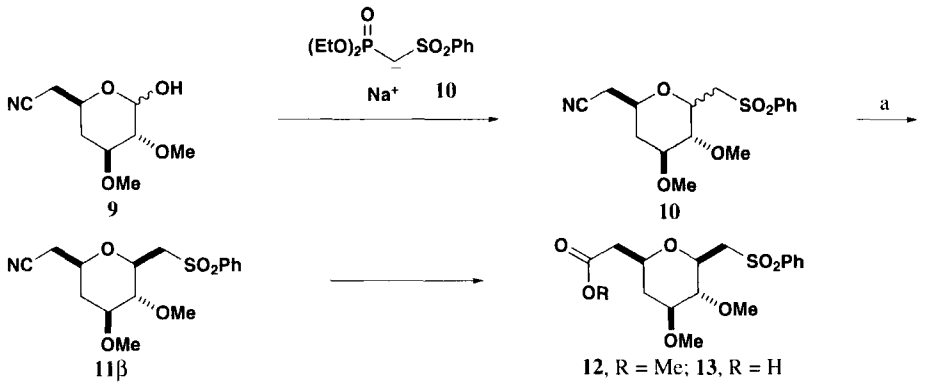


Key: (a) I_2 (3 eq.), CH_3CN, 75%; (b) LiO*t*-Bu, THF, 70%; (c) LDA, THF, 90%; (d) KO*t*-Bu, THF, 20%; (e) Jones reagent, 60%; (f) TFA, 90%; (g) O_3, acetone, then Jones reagent.

Scheme 1

Proctor reported a highly stereoselective synthesis of the cyclopropane moiety of ambruticin S in 1981 (*Scheme 1*).[25] Treatment of enantiopure acid **4**, obtained from (*R*)-(+)-citronellal, with iodine in acetonitrile resulted in preferential formation of the thermodynamically more stable iodolactone **5**, which was converted into epoxide **6** by reaction with lithium *tert*-butoxide in THF. The cyclization of **6** to cyclopropane **7** was carried out using LDA. Alternatively, cyclopropane **7** could be directly obtained by treating iodolactone **5** with potassium *tert*-butoxide. Oxidation of **7** with Jones reagent and subsequent hydrolysis of the *tert*-butyl ester with trifluoroacetic acid led to the dicarboxylic acid **8**. **8** was identical to the degradation product derived from the natural material **1a**, indicating that the absolute stereochemistry of **1a** was the same as that of **8**. This synthesis extends the efforts towards the synthesis of Feist's acid[12] to provide the enantiocontrolled preparation of novel trisubstituted cyclopropanes.

A model study was undertaken to examine an intramolecular conjugate addition route for constructing the *C*-glycoside A ring.[26] The scheme employed a carbohydrate as the chirality source, as diastereomeric lactols **9** were prepared from the readily available methyl-6-chloro-4,6-dideoxy-α-*D*-galactopyronoside (*Scheme 2*). Treatment of **9** with the sodium anion of phosphonate sulfone **10** directly afforded tetrahydropyran **11** as a mixture of α- and β-isomers (ratio = 3:2, yield 60%). The mixture was converted to the more stable β-isomer **11β** by epimerization with NaH in THF. **11β** was then transformed into the ester (**12**) and the acid (**13**).

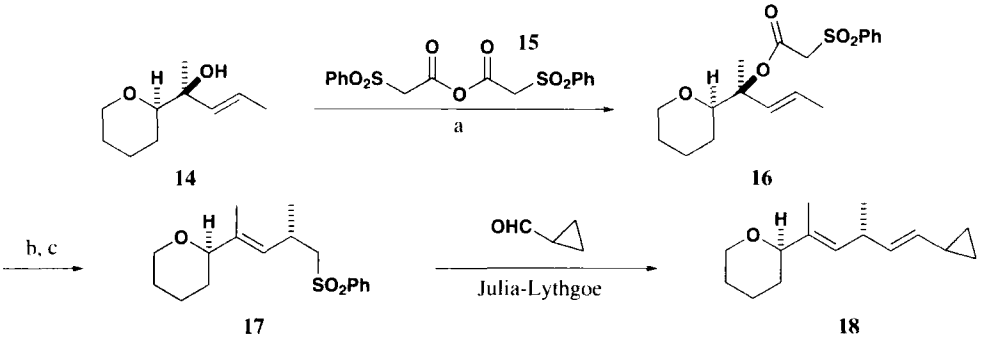


Key: (a) NaH, THF

Scheme 2

Davidson's group subsequently conducted another model study[27] for the synthesis of a fragment which would incorporate the tetrahydropyranyl C ring and the non-conjugated diene with the bis-allylic C_{15} stereogenic center (*Scheme 3*). This provides a clear strategy for chirality transfer from alcohol **14** to sulfone **17**. Thus, allylic alcohol **14** was treated with anhydride **15** to provide the tertiary sulfone ester **16**. Generation and capture of the enolate derived from **16** with TMSCl led to formation of a silyl ketene acetal, which underwent an Ireland–Claisen rearrangement to provide sulfone carboxylic acid. Decarboxylation of the resultant sulfone carboxylic acid furnished the resulting γ,δ-

unsaturated sulfone **17**. The subsequent Julia–Lythgoe coupling of **17** and cyclopropane aldehyde provided 1,4-diene **18** as a model for the right-hand portion with both B and C rings.

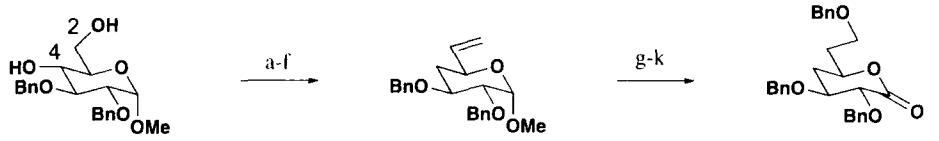


14 **16** **17** **18**

Key: (a) Pyridine, $CHCl_3$, 80%; (b) LDA, Me_3SiCl, 75%; (c) Na_2CO_3, DMF, 100 °C, 95%.

Scheme 3

In 1983, Sinaÿ *et. al.* described synthetic efforts toward the ambruticin system (*Scheme 4*)[28, 30] using methyl 2,3-di-*O*-benzyl-α-*D*-glucopyranside (**19**) as the precursor for the A-ring. Key operations included a Barton deoxygenation at C_4 (ambruticin numbering), and an one-carbon chain homologation using a Wittig reaction at C_2 to produce **20**, which was transformed to lactone **21** using conventional functional group manipulations.

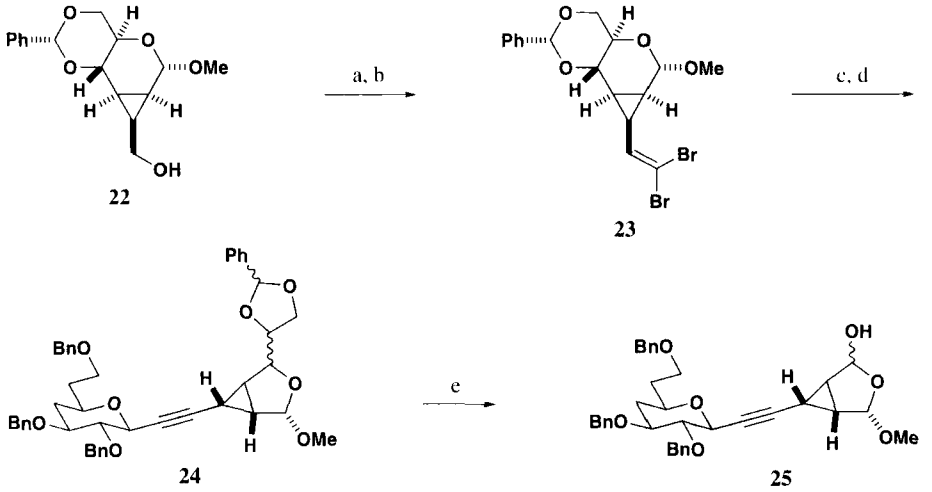


19 **20** **21**

Key: (a) PhCOCN, CH_2Cl_2/pyr, 93%; (b) SO_2Cl_2, CH_2Cl_2/pyr, 67%; (c) Bu_3SnH, toluene, 90°C, 95%; (d) MeOH/MeONa, 85%; (e) Swern, 89%; (f) $Ph_3P^+CH_3Br^-$, $NaNH_2$, toluene, 80%; (g) 9-BBN; (h) NaOH–H_2O_2, 72%; (i) $PhCH_2Br$, NaH, DMF; (j) H_2SO_4–AcOH, 80°C, 45%; (k) Swern, 80%.

Scheme 4

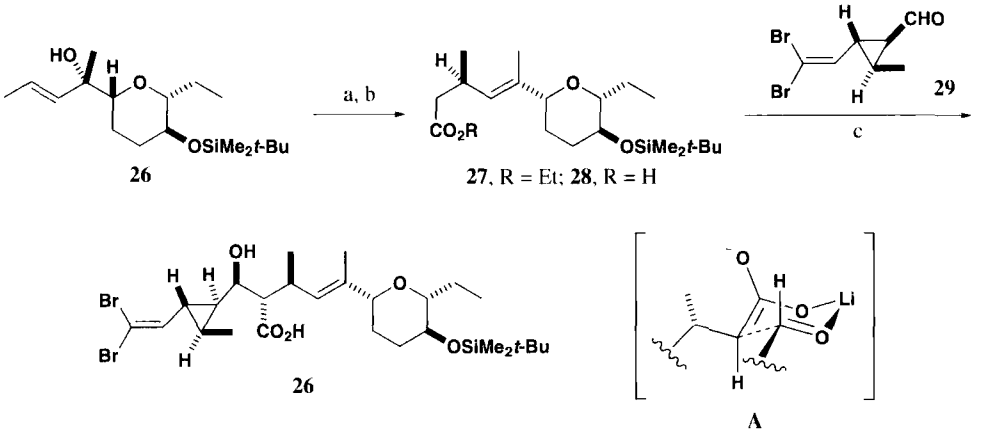
The fragment incorporating C_8–C_{11} was prepared from *D*-glucose *via* methodology explored at the laboratories of Fraser-Reid.[29] Thus, treatment of methyl 2,3-anhydro-*O*-benzylidene-α-*D*-allopyranoside with ethyl diethoxyphosphonyl acetate furnished the enantiopure cyclopropane **22**. Dibromoolefin **23** was obtained from **22** as a masked alkynyl anion. Therefore, coupling of lactone **21** (from *Scheme 4*) with the intermediate alkynyl anion generated from dibromoolefin **23** using *n*-BuLi afforded a mixture of hemiketals. A stereocontrolled reduction with BF_3•OEt_2/Et_3SiH provided axial hydride delivery to yield the *C*-glycoside, and transketalization furnished **24**. Hydrolysis and diol cleavage then produced propargyl cyclopropane **25**.



Key: (a) PCC, 83%; (b) Ph_3P, CBr_4, collidine, 83%; (c) *n*-BuLi, THF, then **21**; (d) Et_3SiH, $BF_3{\cdot}Et_2O$, MeCN, MS 4Å, –40°C; (e) 0.1 M HCl, then $NaBH_4$, MeOH; then $NaIO_4$, MeOH.

Scheme 5

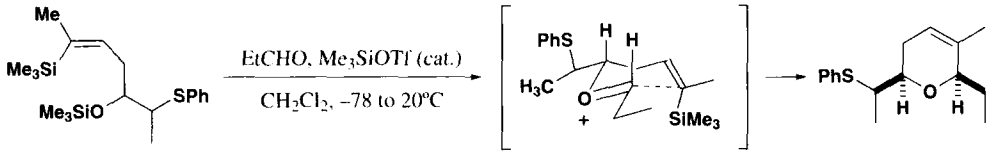
As illustrated in *Scheme 6*, Sinaÿ's efforts toward the C ring[30] used an approach similar to Davidson's Claisen study.[27] In this case, an orthoester Claisen rearrangement of the allylic alcohol **26** was followed by ester hydrolysis to furnish acid **28**. An aldol condensation of **28** with the cyclopropane system **29** established the C_8–C_{25} connection to afford **30**. The adduct provided three contiguous stereogenic centers *via* a Felkin–Ahn addition (**A**) to the chiral aldehyde with the enolate of carboxylate **28**. This is a particularly noteworthy example of early advances in aldol chemistry.



Key: (a) Claisen rearrangement; (b) LiOH; (c) BuLi.

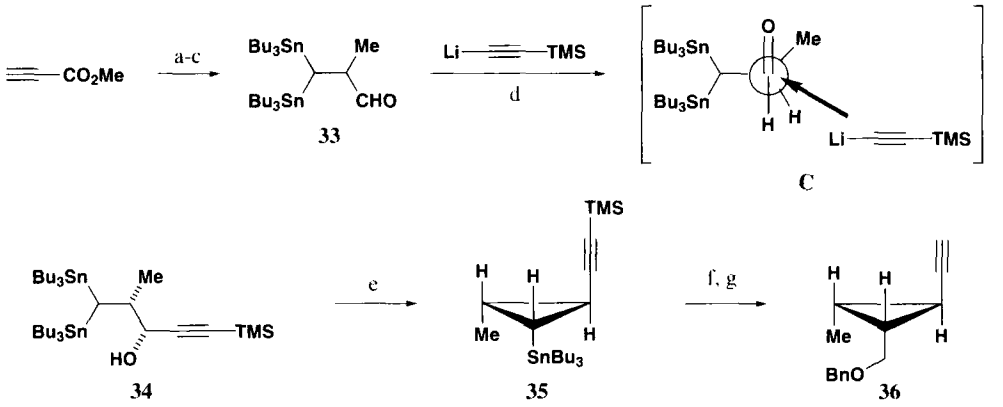
Scheme 6

Other approaches toward ambruticin included Donaldson's synthesis of an A-ring (C_1–C_8) starting from the diethyldithioacetal of *L*-arabinose.[31] Martin's group utilized an intramolecular cyclopropanation of allylic diazoacetate to assemble the B ring moiety of ambruticin S.[32] Using a dirhodium (II) amide complex, $Rh_2(5S\text{-MEPY})_4$, the cyclopropyl lactone intermediate was obtained in 70–94% *ee* and 92% yield. In addition, Markó and coworkers have synthesized a fully functionalized C-ring **32** from vinylsilane silylether **31** in a noteworthy example of an intramolecular silyl-modified Sakurai (ISMS) annulation (via transition state **B**).[33] The cyclization process illustrates the importance of the vinylsilane stereochemistry and ability to transmit stereochemical information from one pre-existing site of chirality. The sulfide is well tolerated in this process.



31 **B** **32**

Making use of their bis-tributylstanne chemistry, Mori and associates accomplished an asymmetric preparation of trisubstituted cyclopropane (B-ring) segment from methyl bis(tributylstannyl)propionate.[34] Therefore, treatment of methyl propiolate with $Bu_3SnSiMe_3$ in the presence of a phase-transfer catalyst ($BnEt_3NCl$) led to methyl bis(tributylstannyl)propionate, which was methylated and reduced to aldehyde **33**. Nucleophilic addition of lithium (trimethylsilyl)acetylide to **33** through the Felkin-Ahn transition state **C** to give propargyl alcohol **34** as the major diastereomer (*cis*:*trans* = 7.5:1). Subsequent cyclopropanation was carried out smoothly *via* the intermediacy of the propargyl mesylate to afford **35**, which was further transformed to cyclopropane **36** as the B ring fragment of ambruticin S *via* a *W*-shaped γ-elimination process. An impressive feature of Mori's approach to cyclopropane **36** is the intermediacy of organostannanes. Contrary to common belief, they have survived many steps including strong base conditions without proto-destannylation.

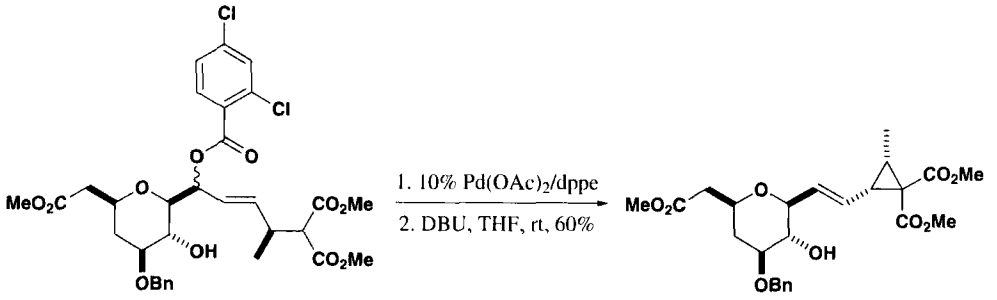


33 **C** **34** **35** **36**

(a) $Bu_3SnSiMe_3$, $BnEt_3NCl$, solvent, 91%; (b) LDA, HMPA, then MeI, 98%; (c) DIBAL, 74%; (d) THF, –78°C, 77%; (e) MsCl, Et_3N, 99%; (f) *n*-BuLi, HMPA then $ClCH_2OBn$, 67%; (g) TBAF, 72%.

Scheme 7

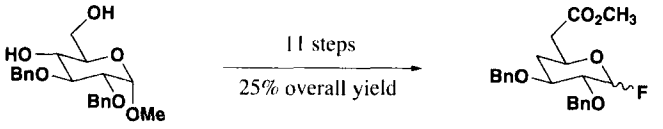
In 1999, Genêt *et al.* prepared a C_{10}–C_{11} *cis*-isomer fragment **38** of ambruticin using a novel asymmetric synthesis of cyclopropane.[35] The mechanism of the cyclopropanation is akin to an intramolecular Tsuji–Trost reaction. Thus, oxidative addition of allylic ester **37** to Pd(0) generates the π-allylpalladium complex which is attacked by the malonate anion. Reductive elimination then leads to cyclopropane **38** in exclusively *cis* configuration. While the intramolecular Tsuji–Trost reaction here did not offer the right configuration as that in ambruticin, this is certainly a unique method for the synthesis of cyclopropanes.



37 **38**

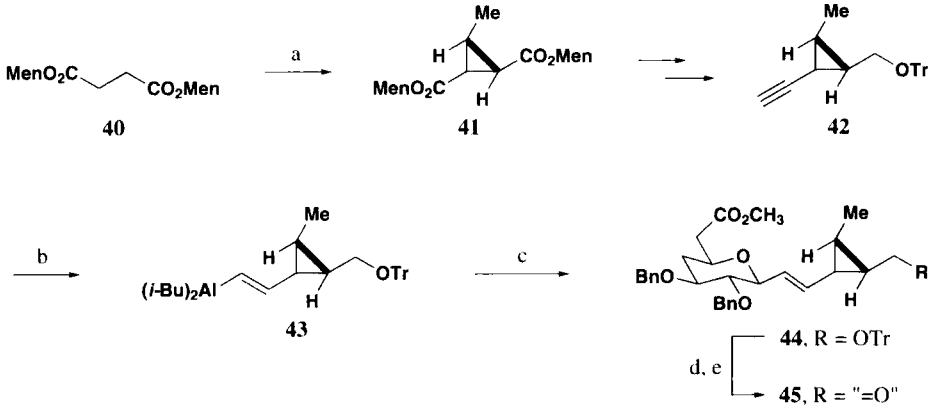
1.b. Total Synthesis of Ambruticin S

In 1990, Kende and coworkers completed the first total synthesis of ambruticin S (**1a**).[36] Kende's construction of the A ring began in a fashion analogous to Sinaÿ's carbohydrate route with the same methyl α-glucopyranoside (**19**) precursor. One-carbon chain homologation at C_6 was achieved by a photochemical Arndt–Eistert reaction in this eleven-step sequence. Glucosyl fluoride **39** (α:β = 27:73) was prepared by treating the corresponding lactol with diethylamine sulfur fluoride (DAST).



19 **39**

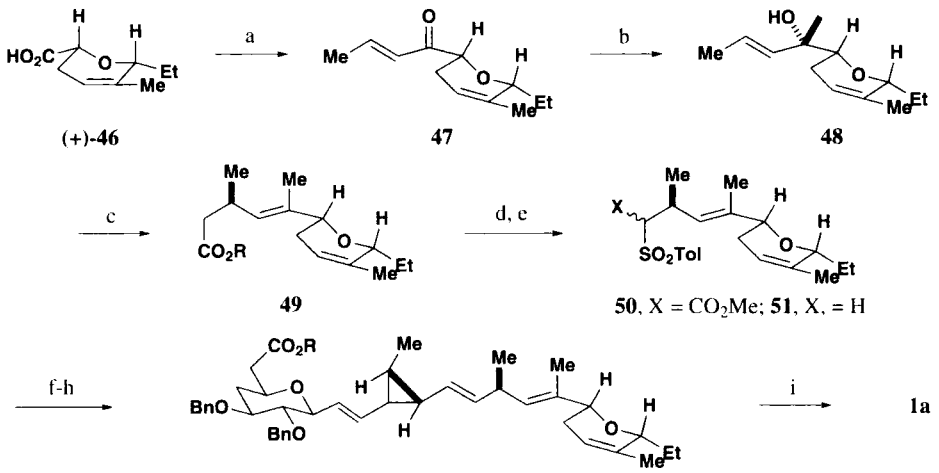
A noteworthy feature of the Kende synthesis was an extension of Yamamoto's dianion chemistry[37] to synthesize the cyclopropane motif (*Scheme 8*). Cyclopropane **41**, whose absolute stereochemistry was controlled using chiral auxiliaries, was isolated in 45% yield from the bis-menthol ester **40** and with excellent stereoselectivity (> 97% homogeneous by NMR). This methodology can be potentially applied to synthesize similar cyclopropanes in an asymmetric fashion. With **41** in hand, selective hydrolysis and a Corey–Fuchs one-carbon chain elongation subsequently established the cyclopropane fragment as vinyl alane **43**. Using methodology developed by Posner,[38] the reaction of **43** and glucosyl fluoride **39** installed the *C*-glycoside connection of **44**. Removal of the trityl protective group and Dess–Martin oxidation then afforded an important intermediate, aldehyde **45**.



Key: (a) Lithium 2,2,6,6-tetramethylpiperidide, THF, –78°C, then 1-bromo-1-chloroethane, 45%; (b) DIBAL, hexane; (c) **39**, toluene, –30°C to rt, 49% 2 steps; (d) PTSA (cat.), MeOH/CH_2Cl_2 (1:1), 92%; (e) Dess–Martin periodinane, 90%.

Scheme 8

The dihydropyranyl ring of ambruticin S was synthesized by the hetero Diels–Alder reaction of (*E*)-3-methyl-1,3-hexadiene with glyoxylic acid, followed by resolution of the enantiomers with (+)-α-phenylethylamine to give carboxylic acid (+)-**46** with an overall yield of 12% (*Scheme 9*). Stille coupling of *E*-propenyltrimethyltin and the acid chloride generated from (+)-**46** afforded enone **47**.



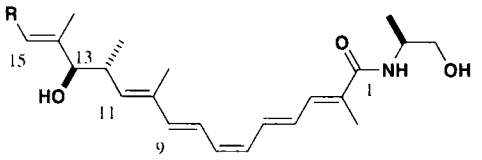
Key: (a) $(COCl)_2$, DMF (cat.), CH_2Cl_2, then *trans*-propenyltrimethyltin, $BnPdCl(PPh_3)_2$ (cat.), HMPA, 70°C, 90%; (b) MeMgBr, THF, 92%; (c) *i.* Ac_2O, DMAP, Et_3N, CH_2Cl_2, 72%; *ii.* LDA, THF, then TBSCl, THF/HMPA, then H_3O^+, 61%; *iii.* CH_2N_2, Et_2O, 92%; (d) LDA, THF, then PTSF, THF, 43%; (e) Me_4NOAc, HMPA, 100°C, 71%; (f) *n*-BuLi, Et_2O/hexane, then **45**; (g) Na(Hg), 6%, MeOH/THF (1:1), 63%; (h) LiOH, THF/H_2O (3:1); (i) Li, liquid NH_3/EtOH (5:1), 63%, 2 steps.

Scheme 9

After chelation-controlled stereoselective addition of MeMgBr, the acetate of the resulting tertiary allylic alcohol underwent an Ireland–Claisen rearrangement to produce the *E* trisubstituted olefin in **49** and transpose the alcohol with high fidelity to establish the critical C_{15} stereochemistry. Transformation into intermediate sulfone **51** provided access to the sulfone anion for a Julia–Lythgoe coupling with the aldehyde **45**, establishing the C_{13}–C_{14} olefin predominantly in the thermodynamically more stable *E* geometry (*E*/*Z* = 92:8). Saponification and deprotection then completed the total synthesis of **1a**.

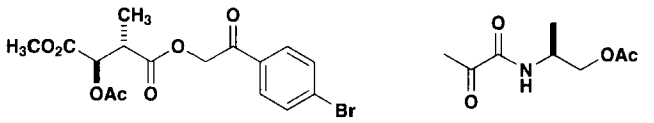
II. STUDIES OF CONJUGATED POLYENES

The myxalamides were isolated from two gliding bacteria, *Myxococcus xanthus* Mk 12[39] and *Stigmatella aurantica* Sg a15.[40] The structure of myxalamide B (**55**, Fig. 2) was elucidated by Höfle *et. al*[41, 42] after extensive spectroscopic study. Myxalamides A (**54**), B (**55**), C (**56**), and D (**57**) are alaninol amides of a hexa-ene branched fatty acid. The absolute configuration was established[39] by the single crystal X-ray analysis of the diester **58** (Fig. 3) derived from ozonolysis of **55**. Thus the *R* configurations of stereocenters C_{12} and C_{13} were unambiguously determined. The configuration of the amide portion was deduced as *S* since a derivative from the ozonolysis was identical to synthetic *O*-acetyl-*N*-pyruvoyl-*L*-alaninol (**59**, Fig. 3).



Myxalamides A **54**: R = (*S*)-*i*-Bu C **56**: R = Et
B **55**: R = *i*-Pr D **57**: R= Me

Fig. 2



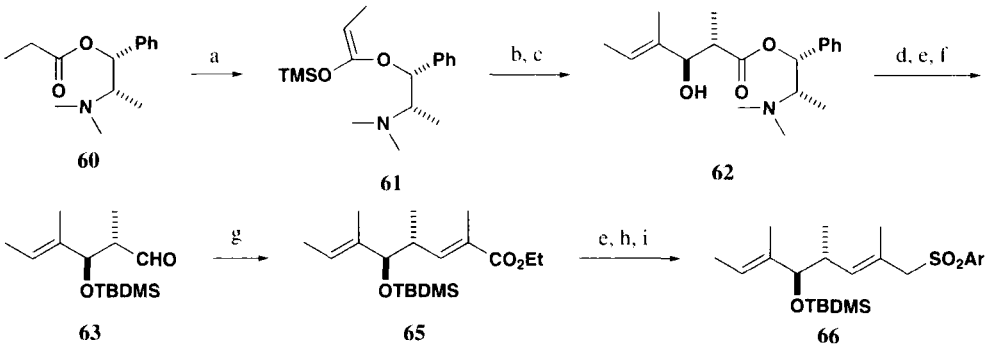
p-Bromophenacyl 3-acetoxy-2-4-oxopentanoate and *O*-acetyl-*N*-pyruvoyl-*L*-alaninol

Fig. 3

Myxalamide B (**55**), the major component isolated from the fermentation mixture, has been the subject of thorough investigations. Myxalamide B (**55**) is an effective electron transport inhibitor, blocking NADH oxidation at Complex I in mitochondria.[39, 40] It was moderately active in some yeast and molds and in several bacteria. However, because of the high toxicity associated with the myxalamides, their limited applications are as insecticides or fungicides.

2.a. An Approach toward Myxalamide D

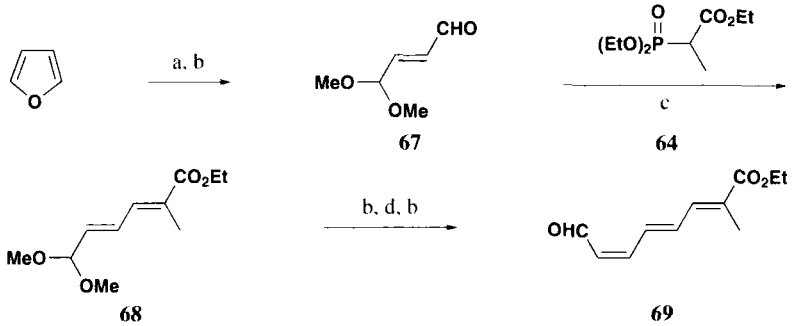
Whiting's group reported a synthetic approach toward myxalamide D (**57**) in 1991.[43-45] As illustrated in *Scheme 10*, this target stimulated studies of the enatioselective anti aldol process as described by the condensation of the homochiral silylketene acetal **61** (from ester **60**), and the *E*-2-methylbut-2-enal under Lewis acid conditions (85% *de*). The second trisubstituted olefin was installed by Horner–Emmons olefination (*E*:*Z* = 7:3) of aldehyde **63**, and elaboration to the allylic sulfone provided the Julia coupling precursor for future chemistry.



Key: (a) LDA, THF, TMSCl; (b) $TiCl_4$; (c) *E*-2-methylbut-2-enal; (d) TBDMSCl; (e) DIBAL; (f) Swern; (g) $(EtO)_2POCH(Me)CO_2Et$ (**64**); then (e); (h) Ph_3P, I_2, imidazole; (i) Tol-SO_2Na.

Scheme 10

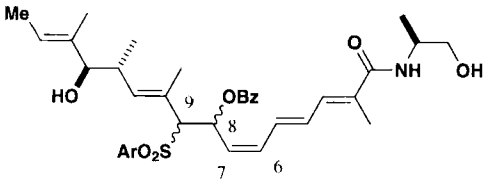
For the synthesis of the C_1–C_8 motif (*Scheme 11*), furan was treated with bromine in methanol, followed by hydrolysis to give *E*-aldehyde **67**. Horner–Emmons reaction with phosphonate **64** resulted in the second *E*-olefin in **68**. However, the most noteworthy formation of the *Z*-olefin **69** (*E,E,Z* : *E,E,E* = 85:15, separable by chromatography) was obtained *via* application of Bestman's ylide **70** followed by careful hydrolysis.



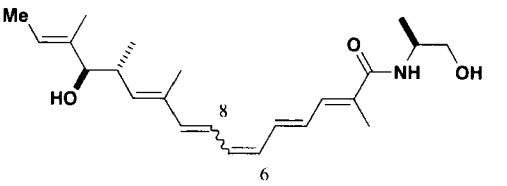
Key: (a) Br_2, MeOH; (b) Amberlyst-15, 69%; (c) NaH, 85%; (d) $Ph_3P{=}CHCH(OEt)_2$ (**70**).

Scheme 11

Unfortunately, the synthesis encountered difficulties in the Julia olefination, producing a 20% yield of **71**. Furthermore, the reductive elimination was problematic, yielding 38% of **72** at 60% conversion, and considerable stereomutation of the C_8–C_9 *Z*-olefin had also occurred.



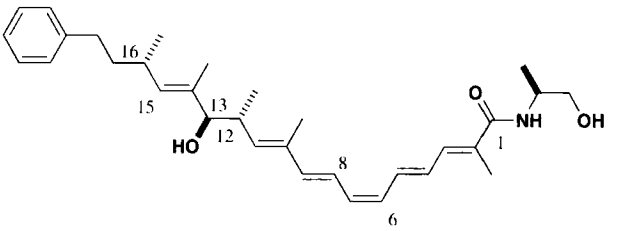
71



72

2.b. Total Synthesis of Stipiamide

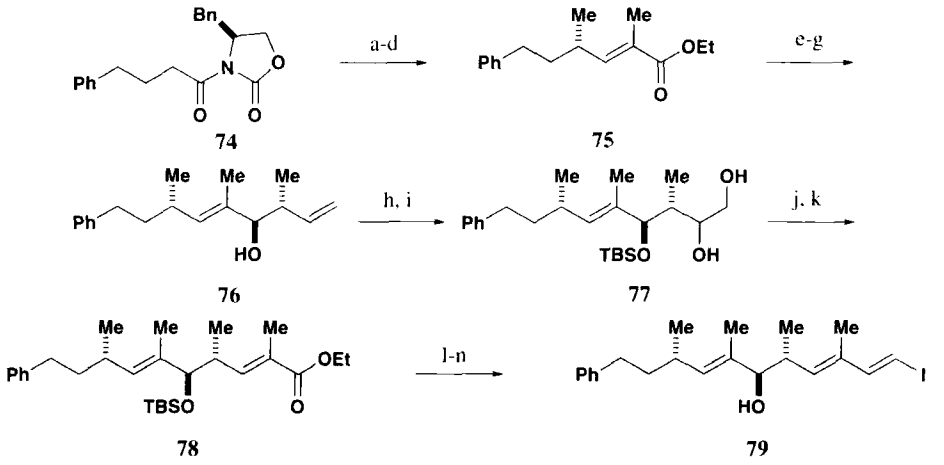
(–)-Stipiamide (**73**, Fig. 4) was initially discovered by Seto[46] from the soil bacterium *Myxococcus stipiatus* and also was later isolated by Höfle.[47] Its structure is closely related to the myxalamide A–D polyenes with a slight increase of complexity in the left-hand terminus. Although stipiamide is only marginally effective as an antimicrobial agent, it has been shown to reverse multidrug resistance (MDR) of human breast cancer cells (MCF-7adrR). Andrus *et. al.* described the total synthesis of stipiamide in 1997[48] employing the Stille cross-coupling of the vinyl iodide **79** and the alkenylstannane **83** as the pivotal convergent step.



(–)-Stipiamide (**73**)

Fig. 4

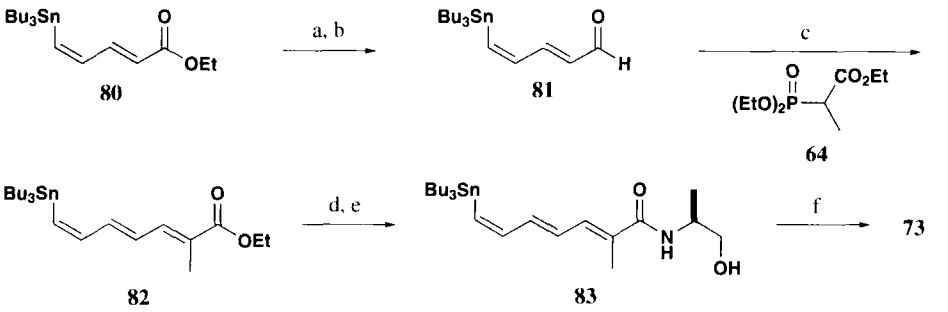
As shown in *Scheme 12*, the assembly of the vinyl iodide fragment **79** began with an Evans alkylation of chiral acyloxazolidinone **74**. Chain homologation with a Wittig olefination using carbethoxyethylidenetriphenylphosphorane afforded the α,β-unsaturated ester **75** in 8:1 (*E/Z*) ratio. A subsequent chain elongation reaction was accomplished using the Brown chiral crotylborane derived from (–)-α-pinene to establish the anti stereochemistry of C_{12}–C_{13} in terminal olefin **76** with 7:1 ratio favoring the desired stereochemistry. Subsequent silylation of the secondary alcohol and a regioselective Sharpless asymmetric dihydroxylation furnished diol **77** without oxidation of the internal olefin. The diol **77** was oxidatively cleaved employing sodium periodate and the resulting aldehyde underwent smooth conversion to the α,β-unsaturated ester **78** in 8:1 (*E/Z*) ratio. The ester was transformed to the vinyl iodide **79** *via* reduction followed by application of the Takai reaction (70% yield, 20:1 *E/Z* selectivity).



Key: (a) NaHMDS, MeI, THF, –78°C, 80% 25:1; (b) LAH, 0°C; (c) TPAP, NMO; (d) (Carbethoxyethylidene)triphenylphosphorane, tol, 90°C, 55%, 3 steps; (e) DIBAL, THF, –40°C; (f) TPAP, NMO; (g) Diisopinocamphenyl-(*E*)-crotylborane, 60% 3 steps; (h) TBSCl, imidazole, 97%; (i) AD-mix-α, 1:1 *t*-BuOH/H_2O, 87%; (j) $NaIO_4$; (k) (Carbethoxyethylidene)triphenylphosphorane, tol, 90°C, 63%, 2 steps; (l) DIBAL, THF, –40°C; (m) TPAP, NMO, 63%, 2 steps; (n) CHI_3, $CrCl_2$, THF, 70%; TBAF, 86%.

Scheme 12

As illustrated in *Scheme 13*, the synthesis of the right-hand fragment of stipiamide commenced with the preparation of the alkenylstannane **80** *via* a unique acetylene-propiolate-cuprate addition reaction. Rather unconventionally, the authors carried the alkenylstannane **80** through an



Key: (a) DIBAL; (b) TPAP, NMO; (c) *n*-BuLi, 73% for 3 steps; (d) LiOH; (e) (*S*)-alaninol, PyBroP, 59% for 2 steps; (f) **79**, $(MeCN)_2PdCl_2$, NMP, 78%.

Scheme 13

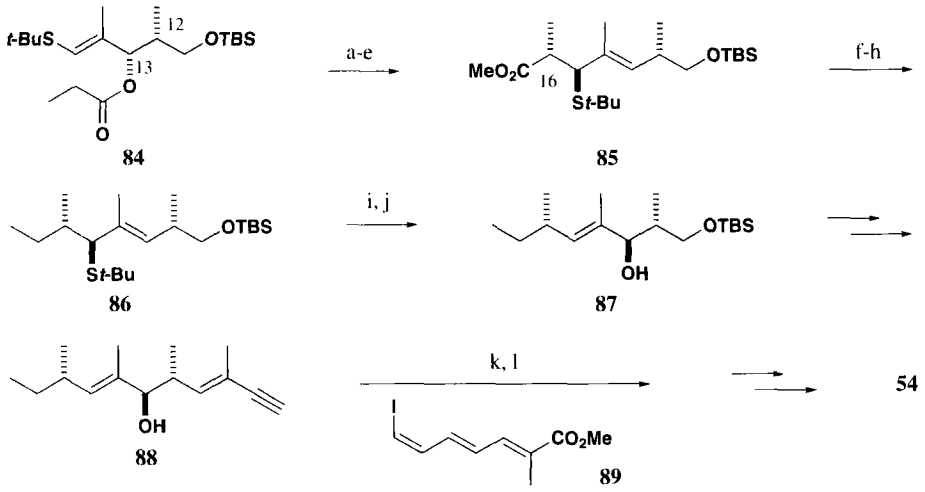
array of manipulations without proto-destannylation. Those steps include a reduction and an oxidation (**80** → **81**), a Horner–Emmons olefination with phosphonate **64** (**81** → **82**), and amide formation (**82** → **83**). Finally, the Stille coupling of alkenylstannane **83** and vinyliodide **79** was conducted at the last

stage of the synthesis to secure (–)-stipiamide (**73**). An NMR analysis of the isolated hexa-ene product revealed that it was a mixture of 4:2:1 mixture of (–)-stipiamide, the all *trans*- and the (4*Z*)-isomers, respectively. The authors speculated that the isomerization occurred during the isolation step owing to the established stereochemical fidelity of the Stille reaction. A similar ratio of isomers was also observed in the authentic sample.

Andrus and coworkers also designed and synthesized two acetylenic analogs of (–)-stipiamide including the 6,7-dehydro-stipiamide (DHS) and 4,5-dihydro-DHS derivative. They were found to be less toxic than stipiamide and were much more effective as MDR reversal agents.

2.c. Total Synthesis of Myxalamide A

In 1999, Mapp and Heathcock disclosed their total synthesis of myxalamide A.[49] Heathcock created the stereochemistry of C_{16} using a unique remote-control technique developed in his laboratories, which parleys the stereochemistry of C_{12}–C_{13} derived from an Evans aldol condensation to C_{16}.



Key: (a) LDA, THF, –78°C; (b) TBS, HMPA; (c) –78°C → rt; (d) aq. K_2CO_3, THF; (e) CH_2N_2, 86%, 5 steps; (f) $LiAlH_4$; (g) *p*-TsCl, Et_3N, DMAP; (h) $Me_2CuCNLi_2$, 0°C, 87%, 3 steps; (i) *m*-CPBA; (j) $(MeO)_3P$, MeOH, 71% 2 steps; (k) catecholborane, *N,N*-diethylaniline; (l) **89**, $Pd(OAc)_2$, TPPTS, *i*-Pr_2NH, CH_3CN/H_2O, 44%.

Scheme 14

Therefore, the *syn* stereochemistry in **84** resulted from the Evans asymmetric aldol condensation using an oxazalidinone chiral auxiliary. A Claisen rearrangement of **84** was carried out *via* the *E*-silyl ketene acetal intermediate to set the configuration of C_{16} in **85** as *S*. Subsequent functional group transformations converted ester **85** to allylic thioether **86**. After oxidation of **86** to its corresponding sulfoxide as a mixture of diastereomers, the Evans–Mislow rearrangement led to allylic alcohol **87** with all three chiral centers established. In Heathcock's aldol–Claisen–Evans–Mislow strategy, allylic alcohol **87** was prepared in 12 steps and 32% overall yield from 1-bromo-2-methylacrylate. Finally, enyne **88**,

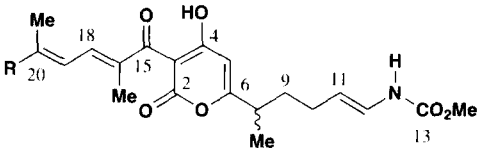
derived from **87** in 9 steps, was treated with 2 equivalents of catecholborane and the resulting *cis* vinylborane was coupled with vinyliodide **89** under the Suzuki coupling conditions to secure the adduct (44% yield) which was easily transformed to myxalamide A (**54**).

In the aforementioned syntheses of conjugated ployenes including myxalamide D, stipiamide, and myxalamide A by Whiting, Andrus, and Heathcock, respectively, three strategies are employed to achieve the convergency. Among the Julia–Lythgoe olefination, Stille coupling, and Suzuki coupling approaches employed, it seems that the Suzuki coupling conditions were most robust in terms of preserving the stereochemical fidelity for these particular substrates.

2.d. Total Syntheses of (±)-Myxopyronin A

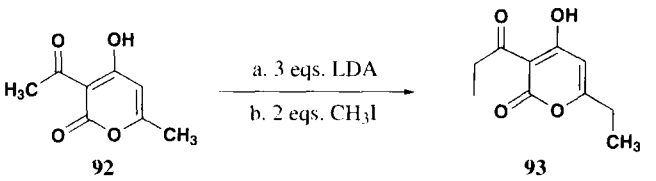
In 1983, Höfle and coworkers reported the isolation and structural elucidation of two antibiotics, myxopyronin A (**90**) and B (**91**, Fig. 5), from the gliding bacterium *Myxococcus fulvus* Strain Mx f 50.[50] Their chemical structures were derived from spectroscopic analysis and chemical degradations and consisted of a highly unsaturated 3-acyl-4-hydroxy-2-pyrone core structure with an *N*-alkenylcarbamate side chain. The absolute configuration of C_7 was deduced as *R* since the derivative, 2-methylglutaric acid, obtained from ozonolysis of myxopyronin A (**90**) and B (**91**), had the opposite optical rotation to that of natural *S*-(+)-2-methylglutaric acid.

A ^{13}C and ^{15}N NMR labeling study[51] showed that myxopyronin A (**90**) is biosynthesized from acetate, glycine and methionine. Myxopyronin A (**90**) and B (**91**) block the growth of many Gram-positive and several Gram-negative bacteria, but do not affect yeasts and fungi.[52] These metabolites selectively block eubacterial RNA-polymerase versus human RNA-polymerase. A structurally related family of antibiotics, corallopyronin A, B, and C, have also been reported.[53]



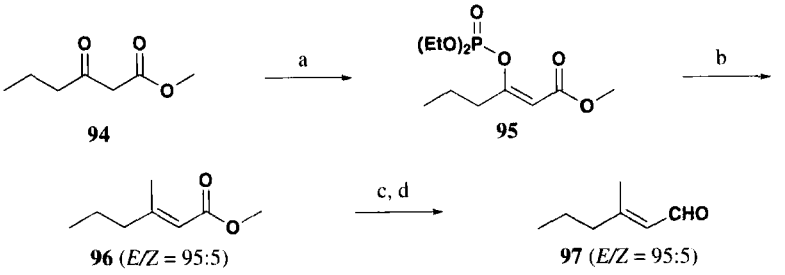
90, (±)-Myxopyronin A; R = n-C_3H_7
91, (±)-Myxopyronin B; R = n-C_4H_9

Fig. 5



In 1986, E. Funk at Technical University Braunschweig in Germany described the first total synthesis of (±)-myxopyronin A (**90**).[54] The core intermediate, 3-acyl-4-hydroxy-α-pyrone (**93**), was directly obtained from alkylation of the known **92**. As shown in *Scheme 15*, phosphate ester **95** was

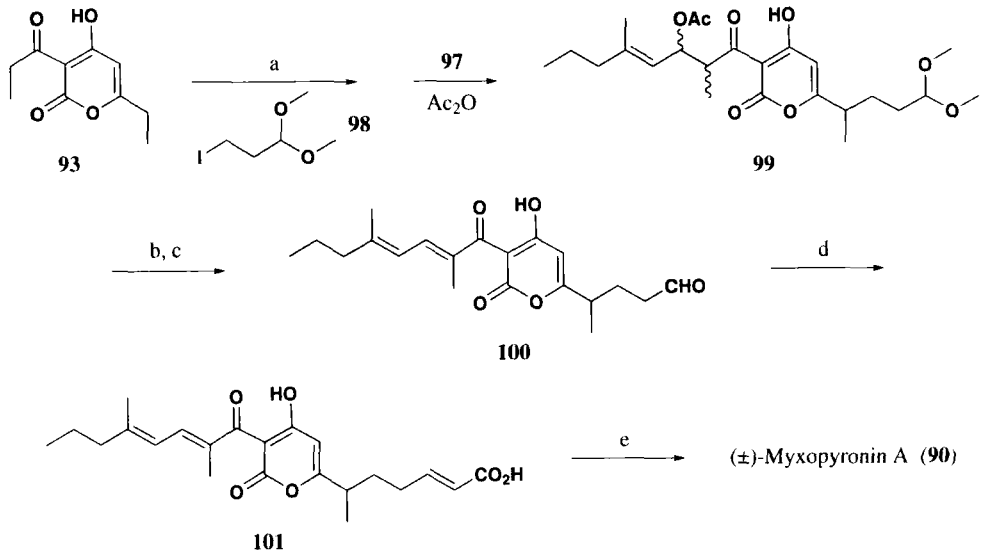
obtained from β-ketoester **94**. A stereoselective conjugate replacement of the phosphate ester **95** with dimethylcuprate installed the trisubstituted olefin **96** in a 95:5 (*E*:Z) ratio. Reduction and oxidation of **96** then furnished the desired α,β-unsaturated aldehyde **97**.



Key: (a) NaH, $(EtO)_2P(O)Cl$, 100%; (b) $LiCuMe_2$, 94%; (c) LAH, 99%; (d) MnO_2, 76%.

Scheme 15

As illustrated in *Scheme 16*, alkylation of the trianion derived from precursor **93** with primary iodide **98** was immediately followed by an aldol condensation with **97**. The alkoxide intermediate of the aldol adduct was trapped as the corresponding acetate by quenching the reaction with acetic anhydride as a one-pot tandem sequence for construction of **99**. The elimination of the acetate in **99** furnished the trisubstituted C_{17}–C_{18} olefin **100**, providing access to the thermodynamically stable *E* isomer. Finally, Horner–Emmons reaction of aldehyde **100** and the dianion generated from diethylphosphonoacetic acid afforded the carboxylic acid **101** and a Curtius reaction with diphenylphosphoryl azide in methanol completed the total synthesis of (±)-**90**.

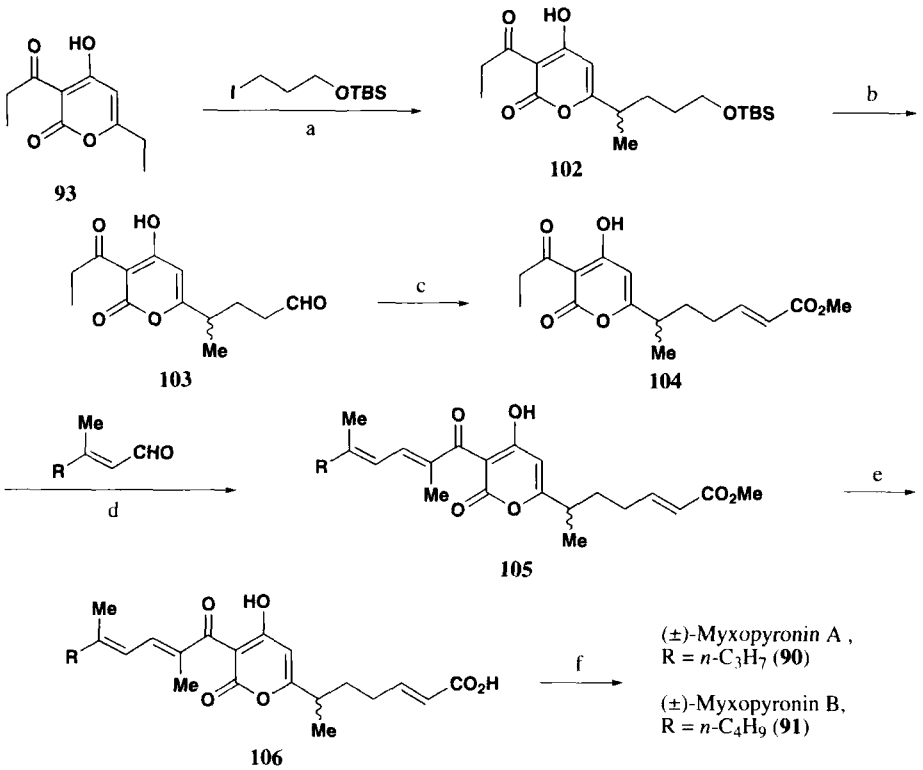


Key: (a) 3 eq. LDA, THF/HMPA, –78°C, then **98**; then **97**, Ac_2O; (b) DBU, 70°C; (c) $HOAc/H_2O$ (1:1); (d) NaH, $(EtO)_2P(O)CH_2CO_2H$, *n*-BuLi; (e) $(PhO)_2P(O)N_3$, Et_3N, MeOH, dioxane.

Scheme 16

A second synthesis of (±)-myxopyronin A and B has been published by Panek and coworkers.[55] The strategic design of this approach follows the general pathway of Funk's efforts. Neither route is adaptable for enantio-controlled development of C_7 stereogenicity. In the Panek synthesis, regioselective alkylation at C_7 was achieved by formation of the trianion of **93** with LDA, and alkylation to yield pyrone **102**. Two-carbon chain extension of **103** proceeded by the Horner–Emmons–Wadsworth olefination to **104**. A pivotal feature of the synthesis involved a titanium(IV)-promoted aldol condensation of the enolate generated by the treatment of ethyl ketone **104** with excess $TiCl_4$ and DIPEA. Condensation with aldehyde **97** directly provided *(E,E)*-dienone **105**. Finally, carboxylic acid **106** was converted to the racemic natural product (±)-**90** using a modified Curtius rearrangement process. (±)-**91** was synthesized in the same fashion.

The Panek group also conducted preliminary antibacterial evaluations of the myxopyronins with an *in vitro* transcription assay employing *E. coli* RNA polymerase. All myxopyronins exhibited comparable micromolar inhibitory activity. Synthetic myxopyronin B was 4-fold more potent against



Key: (a) LDA (3.2 eq.), THF/HMPA, –78°C, 87%; (b) *i.* AcOH/THF/H_2O (3:1:1), > 90%; *ii.* Dess–Martin, 89%; (c) NaH/THF, $(EtO)_2P(O)CH_2CO_2CH_3$, 82%; (d) $TiCl_4$, DIPEA, 58%; (e) LiOH, quant.; (f) EtOCOCl, NaN_3, PhMe/MeOH, 71% for myxopyronin A; 66% for myxopyronin B.

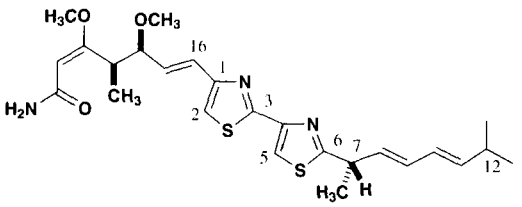
Scheme 17

E. coli RNA polymerase than myxopyronin A, and was also 30-fold more potent than myxopyronin A in cell-based activities for the *S. aureus* Gram-positive strain. This limited structure–activity relationship study provides some insight to the importance of chain length of the dienone moiety.

III. HETEROCYCLIC TARGETS FROM MYXOBACTERIA

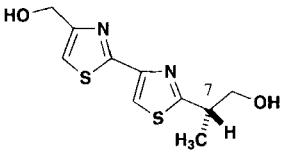
3.a. Myxothiazole

Myxothiazole (**107**, Fig. 6) is one of the ten distinct electron transport inhibitors isolated from myxobacteria.[5] The metabolite was isolated in 1980 from gliding bacterium *Myxococcus fulvus* strain Mx F16[56] and, later from *Angcoccus dixiformis* strain An d30.[57] Extensive biological activity studies[58] have revealed that **107** acts on β-type cytochromes in the respiratory chain and during photosynthesis. Myxothiazole was utilized to elucidate the complicated biochemistry of the complex III and its Q-cycle.[59] After elucidation of the myxothiazole structure using spectroscopic and degradation methods,[60] the absolute configurations of the side chains were determined by X-ray crystallography.[61] Reductive workup ($NaBH_4$ in methanol) of the ozonolysis reaction product furnished a crystalline diol (**108**), and X-ray structural analysis established that the absolute stereochemistry of C_7 was *S*. The absolute configuration of the left-hand fragment was determined by comparing the degradation product (**109**) generated from oxidative workup of ozonolysis of **107** with the same compound made from authentic sample, 2*R*, 3*R-threo*-β-methylmalic acid.

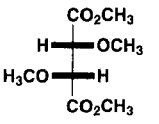


Myxothiazole (**107**)

Fig. 6

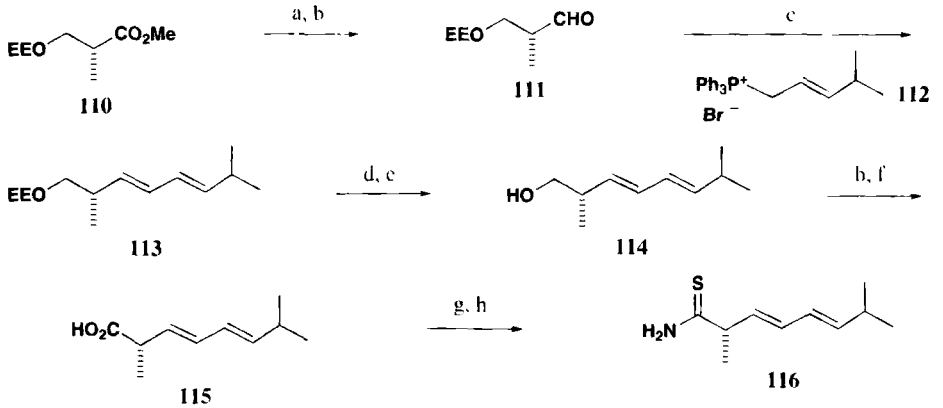


108



109

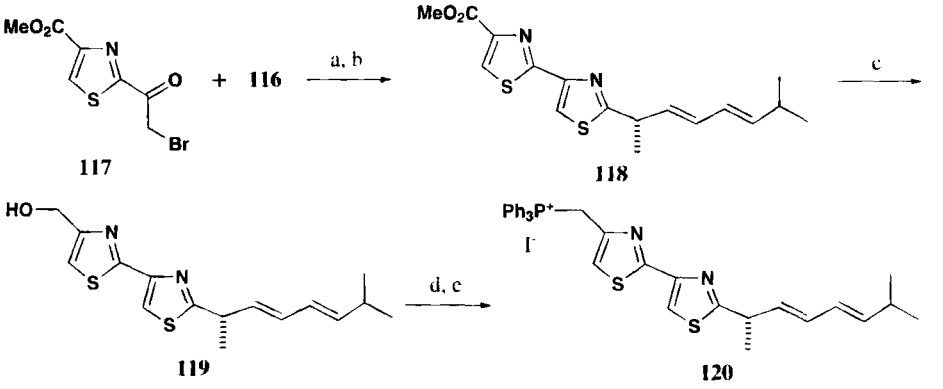
The total synthesis of myxothiazole by Pattenden's group was published in 1993.[62] Commercially available *R*-methyl-3-hydroxy-2-methylpropionate was protected as an ethylethoxyl ether **110**. It was then transformed to the corresponding aldehyde **111**, which underwent a Wittig reaction with phosphonium salt **112** to give a 4:1 mixture of *E,E*- and *Z,E*-geometrical isomers of the diene **113**. After deprotection, the minor *Z,E*- isomer was isomerized to the thermodynamically more stable *E,E*-isomer **114** by irradiation of the dienol in benzene in the presence of iodine. Heptadienyl thioamide **116** was prepared by conventional functional group manipulations from acid **115**.



Key: (a) LAH, 90%; (b) Dess–Martin periodinane; (c) *n*-BuLi, Et_2O, –10°C, 60%; (d) HCl, THF/H_2O, 93%; (e) I_2, (cat.), Et_2O, *hv*, 89%; (f) $NaClO_2$, 60%; (g) $(COCl)_2$, DMF (cat.), CH_2Cl_2, then NH_3, Et_2O, 75%; (h) P_4S10, 49%.

Scheme 18

Two approaches to the substituted *bis*-thiazole **120** were described in Pattenden's synthesis. The more convergent version involves the condensation of **116** and the 2,4-disubstituted thiazole bromoketone **117**. The adduct **118** was subsequently reduced to alcohol **119**, which was converted to Wittig reagent **120**.

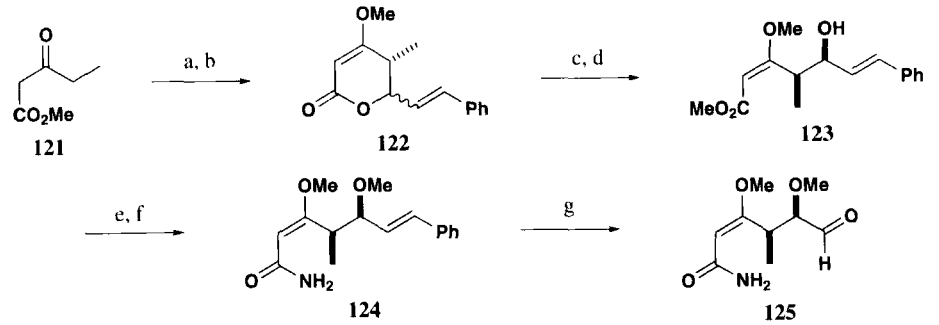


Key: (a) $KHCO_3$, THF, 0°C, 65%; (b) TFAA, pyr, 59%; (c) DIBAL, 80%; (d) PPh_3, imidazole, I_2, 78%; (e) PPh_3, PhH, 80%.

Scheme 19

The β-methoxyacrylamide unit as **125** was prepared in the racemic form. Therefore, a diastereomeric mixture (*syn:anti* = 1:1) of 2*H*-pyran-2-one was produced from the aldol condensation between methyl 3-oxopentanoate **121** and cinnamaldehyde, followed by a methylation to afford methyl ether **122**. **122** was transformed to methyl ester **123** as a mixture of diastereomers that were separated by chromatography. The *syn* (4*RS*, 5*SR*)-diastereomer **123** was converted to amide **124**, which was oxidatively cleaved using a two step protocol to afford the unstable and sensitive amide aldehyde **125**.

Successful Wittig reaction was accomplished between **120** and **125** utilizing lithium hexamethyldisilazide as the base to give the desired myxothiazole **107** as the *E*-olefin. Thus, a mixture of myxothiazole (7*S*, 18*S*, 19*R*) and a diastereomer (7*S*, 18*R*, 19*S*) was synthesized. The spectroscopic data were completely superimposable with the natural product (7*S*, 18*S*, 19*R*) derived from *Myxococcus fulvus*.

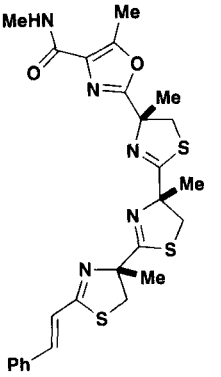


Key: (a) NaH, *n*-BuLi, THF, then PhCH=CHCHO; (b) Me_2SO_4–K_2CO_3, 70%; (c) KOH, H_2O; (d) CH_2N_2; (e) MeI, Ag_2O, 55%; (f) Me_2AlNH_2, 77%; (g) OsO_4, NMO, 49%, then $NaIO_4$, 32%.

Scheme 20

3.b. Thiangazole

Since its isolation and characterization in 1991, (–)-thiangazole (**126**) has elicited interest from synthetic chemists due to its unique structure and potent antiviral activity. In one specific antiviral assay, **126** was found to be at least 100 times more potent than AZT.[63] Three reviews[64–66] have covered recent synthetic efforts.

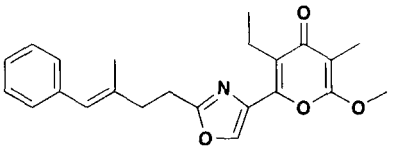


(–)-Thiangazole (**126**)

Fig. 7

3.c. Phenoxan

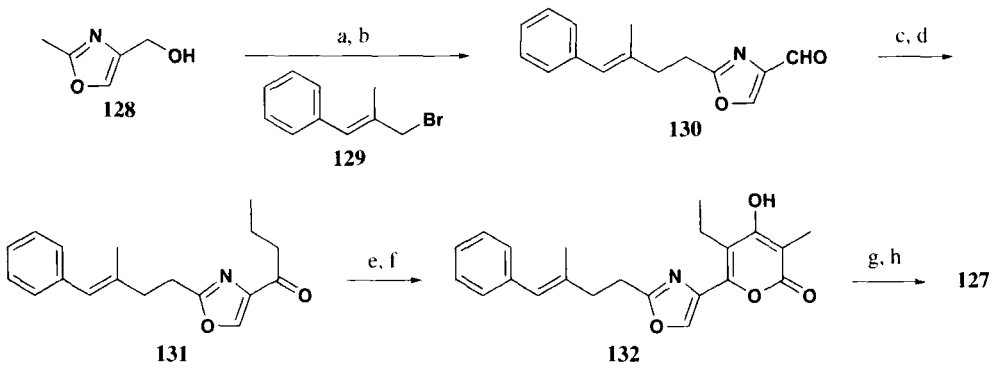
Phenoxan (**127**) was isolated from myxobacterium, *Poliangium spec.*, strain PL VO19.[67, 68] It has been found to have potent anti-HIV activities with low cytotoxicity in some assays. Two total syntheses have emerged with distinctive approaches. In Peña's strategy,[69-71] an oxazole substrate was employed, and the 4-hydroxypyran-2-one moiety was assembled. In the synthesis by Nishiyama coworkers,[72] the 4-hydroxypyran-2-one fragment was used as the starting point, and the oxazole ring was built at the end of the synthesis.



Phenoxan (**127**)

Fig. 8

In a very concise approach, Peña's synthesis[70] commenced with homologation of oxazole alcohol **128** with methyl cinnamylbromide **129** to aldehyde **130**. Ketone **131**, easily derived from **130**, was treated with lithium bis(trimethylsilyl)amide followed by ethyl 2-methylmalonyl chloride. The resulting *bis*-ketoester intermediate was cyclized to pyr-2-one **132** under acidic catalysis. Protection of the enol motif in **132** using TBSOTf was followed by the treatment with Meerwein's reagent (Me_3OBF_4) then delivered the natural product (**127**).

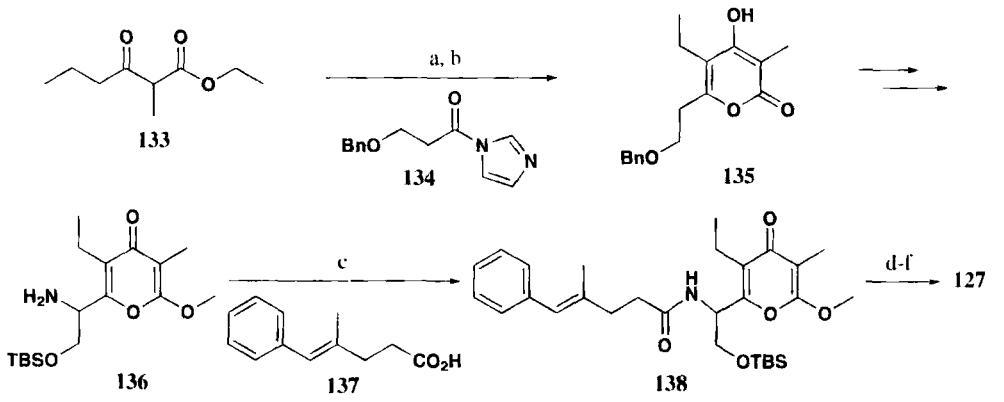


Key: (a) 2 eq. LDA, then **129**, 50%; (b) Swern, 73%; (c) PrMgBr, 81%; (d) Swern, 95%; (e) LiHMDS, then ethyl 2-methylmalonyl chloride, 28%; (f) PTSA, tol., 48%; (g) TBSOTf, pyr.; (h) Me_3OBF_4, CH_2Cl_2, 32%, 2 steps.

Scheme 21

Due to an unexpected enediol-orthoester rearrangement, Nishiyama's initial synthesis of the oxazole ring led to a regioisomer of **127**.[72] As a consequence, they chose to install the nitrogen functionality before the assembly of the oxazole ring. Thus, cyclization of β-ketoester **133** with **134** led to

α-pyrone **135**. After transforming **135** to primary amine **136**, its condensation with pentenoic acid **137** provided amide **138** with the requisite carbon backbone. Subsequent desilylation and mesylation offered the corresponding oxazoline, which upon oxidation secured phenoxan (**127**).



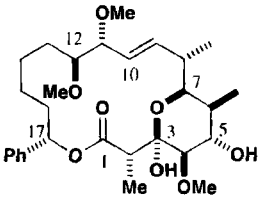
Key: (a) NaH, then LDA (0°C, 30 min.); then **134**, THF, −78°C, 1 h; (b) DBU, PhH, 60°C, 3 h, 68%; (c) DCC, HOBt, Et_3N, THF, rt, 5 h, 93%; (d) TBAF, THF, (0°C, 30 min.), 88%; (e) MsCl, Et_3N, CH_2Cl_2, 77%; (f) MnO_2, $CHCl_3$, reflux, 6 h, 75%.

Scheme 22

IV. MACROLIDE ANTIBIOTICS

4.a. Total Synthesis of Soraphen

Soraphen A (**139**) was isolated by Höfle's group from the myxobacterium *Sorangium cellulosum* in 1995.[73] Its 18-membered macrolide structure was determined by spectroscopic methods and the absolute configuration of the ten stereogenic centers were determined by X-ray crystallography.[74]



Soraphen A1α (**139**)

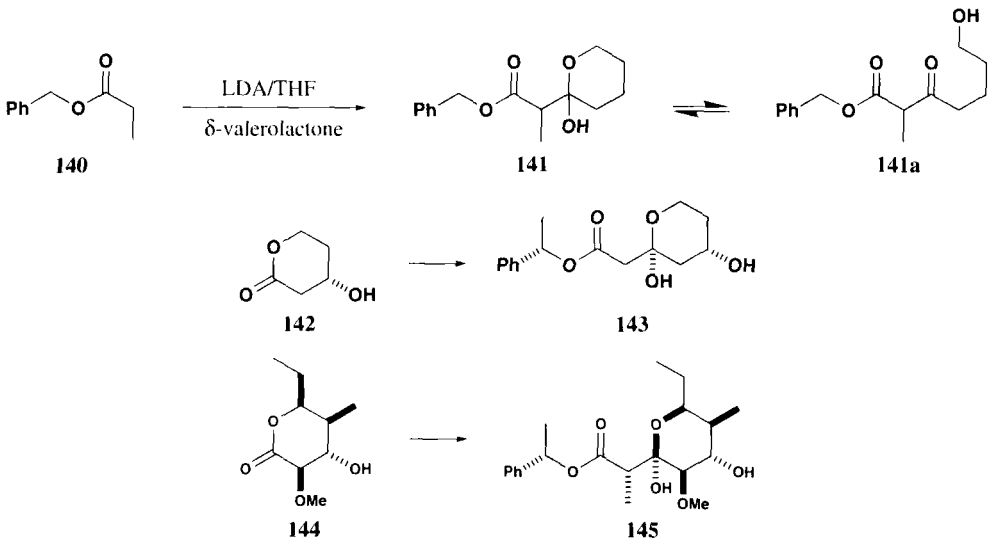
Fig. 9

Screening of **139** as a fungicide revealed that it possesses excellent activities against fungal pathogens on plants. A family of 32 naturally occurring soraphen derivatives were isolated from the fermentation broth. Hundreds of semisynthetic derivatives were prepared using the major metabolite **139**. Even though most derivatives were generated from the macrolide were much weaker fungicides than **139**,[75]

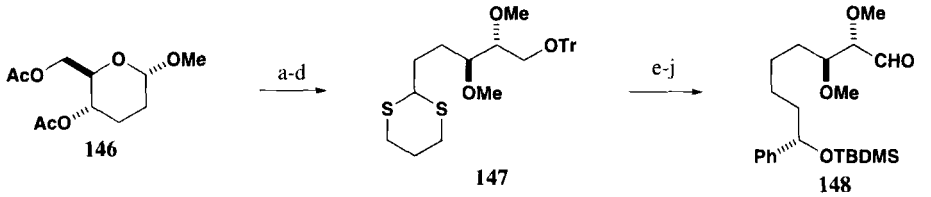
many 5-ester analogs were found to have excellent fungicidal activities, with some more potent than **139** itself.[76] The hydrolytically labile formate, dichloroacetate, and glycinate esters are among the most potent compounds, indicating that some of them may be acting as pro-drugs. Chemical derivatization and fungicidal activity of the derivatives have been reviewed elsewhere.[76] Here, only the chemical synthesis effort will be discussed.

The potent fungicidal activity of soraphen, combined with its intriguing 18-membered macrolide structure compactly housing 10 asymmetric centers has elicited great interest among synthetic chemists. In one attempt by the Sinnes group to retain the biological activity by molecule truncation, a simplified version of the 6-membered hemiacetal portion was prepared.[77] Thus, the enolate of benzyl propionate **140** was quenched with δ-valerolactone to give the desired product as hemiacetal **141**, which slowly interconverted to its tautomer **141a** until a ca. 1:1 ratio was reached at the equilibrium. The hemiacetal **141** and several closely related analogs were all void of the fungicidal activity against a series of plant pathogens. They were also inactive as inhibitors of acetyl coenzyme A carboxylase which soraphen A was believed to inhibit.

The Sinnes group also prepared both the simplified and the exact southern-half fragment[78a] of soraphen A[78b] *via* enantioselective synthesis. The enantiomerically pure starting material, 4*S*-hydroxytetrahydropyran-2-one **142**, was prepared from PLE enzymatic resolution. The more elaborate version of δ-valerolactone **143** was prepared *via* the Evans asymmetric aldol condensation of acylated oxazolidinone and an aldehyde. Thus, treatment of the lactones (**142** and **144**) with the enolate of *S*-benzyl acetate furnished both **143** and **145** (Meinwald reaction). Many analogs with different absolute stereochemistry were prepared. Unfortunately, they were all void of the fungicidal activity that soraphen A possesses. A stereoselective synthesis of C_3–C_9 segment of soraphen A similar to δ-valerolactone **145** was also reported. The stereochemistry of that fragment was installed by a Sharpless asymmetric epoxidation and dihydroxylation.[79]



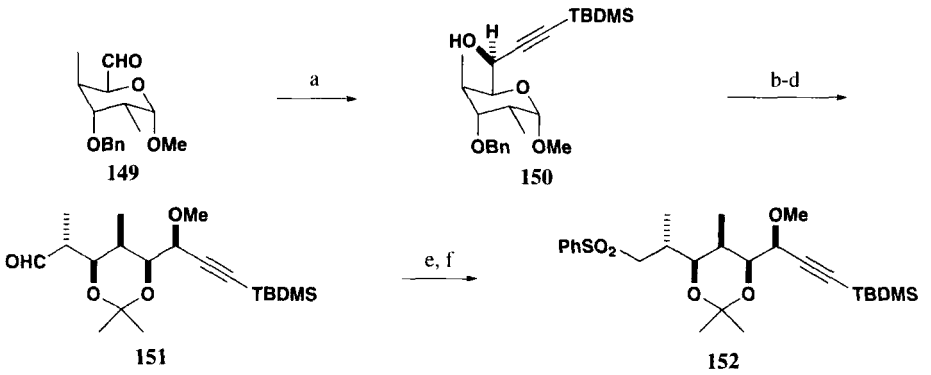
The only total synthesis of soraphen A was reported in 1994 by Giese.[80] The convergent synthesis was realized by a Julia coupling in which both the sulfone and aldehyde fragments were prepared from *D*-glucose. As illustrated in *Scheme 23*, for the aldehyde **148** synthesis, the dideoxy-sugar **146** was transformed to dithiane **147**. Chain elongation was accomplished using the S_N2-ring opening reaction (Corey–Seebach method) between the dithiane anion and (*R*)-phenyloxirane to afford the desired aldehyde **148**.



Key: (a) NaOMe/MeOH, 98%; (b) $HS(CH_2)_3SH$, conc. HCl, 95%; (c) TrCl, pyr, 85%; (d) NaH, Bu_4NI, MeI, 71%; (e) *n*-BuLi, (*R*)-phenyloxirane, 70%; (f) *p*-toluenesulfonic acid, CH_2Cl_2, CH_3OH, 3.5 h, 20°C, 94%; (g) Ni, EtOH, 81%; (h) TBDMSCl, imidazole, DMAP, 95%; (i) TBAF, 86%; (j) Swern, 90%.

Scheme 23

The aldehyde **149** for the preparation of the sulfone fragment **152** was also derived from D-glucose. As depicted in *Scheme 24*, the chain elongation was realized by chelation controlled addition of an alkynyl anion to the aldehyde in the presence of magnesium bromide to give **150**. Concurrent ring-opening and acetonide formation, followed by methylation furnished aldehyde **151**. Ultimately, sulfone **152** was produced by several straight-forward functional group manipulations from **151**.

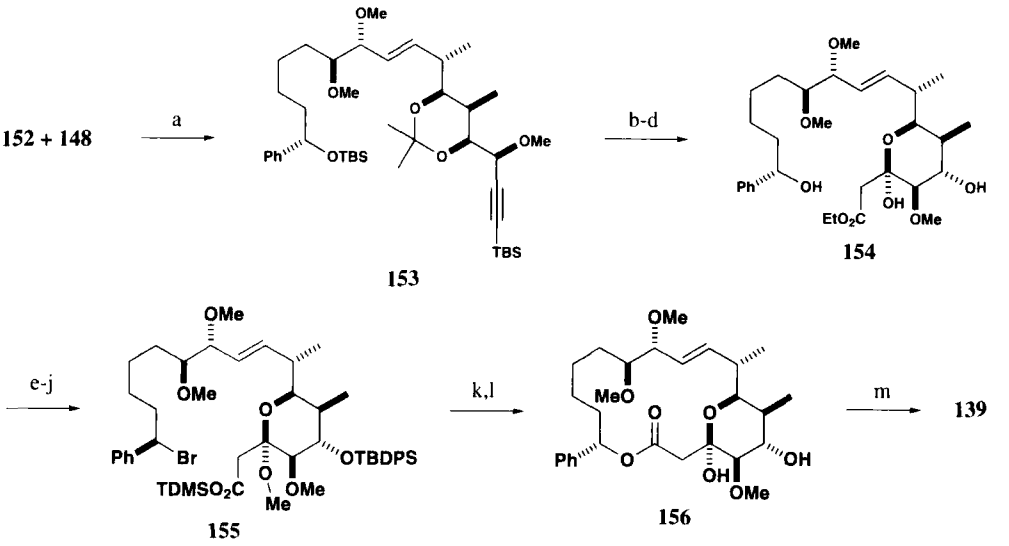


Key: (a) TBDMS–C≡C–H, MeLi, $MgBr_2$, 87%; (b) MeI, AgI, 94%; (c) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, 77%; (d) $Me_2C(OMe)_2$, 10-camphorsulfonic acid, then $CaCO_3$, MeI, 87%; (e) $NaBH_4$, EtOH, then Bu_3P, Ph_2S_2, 81%; (f) MCPBA, $NaHCO_3$, 97%.

Scheme 24

The convergent assembly of sulfone **152** and aldehyde **148** was realized by Julia coupling to give the *trans* olefin **153**. After desilylation of **153**, the carboxylic acid function was introduced with ethyl chloroformate. As a pivotal step, the addition of water across the triple bond *via* an enamine

intermediate followed by cleavage of the protective groups resulted in formation of the tetrahydropyran ring structure of **154**. The benzyl alcohol was allowed to react with the bromoenamine to yield the bromide **155** with an inversion of the configuration. The macrocyclization of the cesium carboxylate of **155** produced the soraphen ring skeleton with an inversion of configuration at the benzyl position. By using 2 equivalents of potassium 2,6-di-*tert*-butylphenoxide, the hemiketal ring of **156** was opened and deprotonated to give the potassium enolate. Quenching with methyl iodide, followed by the hemiketal formation in acidic medium afforded soraphen $A_{1\alpha}$ **139** in 70 % yield.



Key: (a) *t*-BuLi/THF; BzCl, pyr. Then Na(Hg), 35%; (b) TBAF, 85%; (c) *n*-BuLi, $ClCO_2Et$, 85%; (d) morpholine, THF, reflux, 60%; then CH_3CO_2H, 75%; (e) TBDPCl, 96%; (f) Ac_2O, pyr, DMAP, 98%; (g) $HC(OMe)_3$, 99%; (h) $Ti(O\textit{i}\text{-}Pr)_4$, 2-(trimethylsilyl)-ethanol, 90%; (i) CsF, DMF, 98%; (j) thexyldimethylsilyl chloride (TDMSCl), Et_3N, then $(CH_3)_2C{=}CBr(NMe_2)$, Et_3N, 91%; (k) Et_3N, acetone, H_2O; then Cs_2CO_3, DMF, 50%; (l) TBAF, then 1 M HCl, 95%; (m) 2 equiv. of potassium 2,6-di-*tert*-butylphenoxide, then MeI, DMF, 4Å MS, then HCl, 70%.

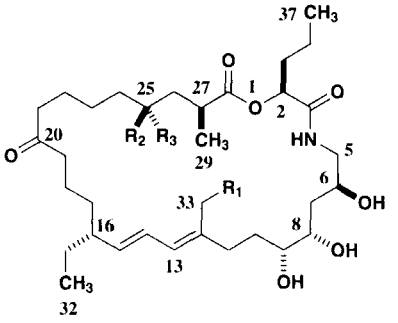
Scheme 25

4.b. Total Syntheses of Myxovirescin B and A_1

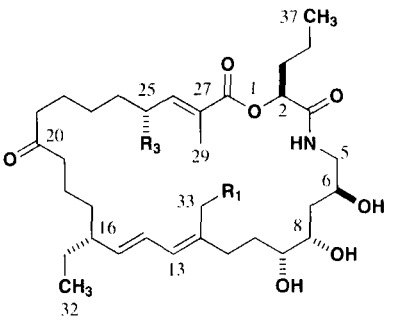
The myxovirescins comprise a family of thirty-one structurally related macrolide antibiotics which were initially isolated in 1982 from *Myxococcus virescens* Mx v48.[81] Several macrolides from this family are active against both gram positive and gram negative bacteria, and these compounds are proposed to exert their biological effect by blocking the incorporation of *N*-acetylglucosamine, thus interfering with bacterial cell wall biosynthesis.

The epimeric myxovirescins A_1 and A_2 (**Fig. 10**) are the most naturally abundant members of the myxovirescin family, and were initially characterized by the research group of Gerhard Höfle at the Gesellschaft fur Biotechnologische Forschung using ^1H and ^{13}C NMR analysis.[82] Subsequent

degradation studies, and X-ray analysis firmly established the structure and absolute stereochemistry of these 28-membered lactam-lactones, and additional studies provided characterization of the related myxovirescins B–T which vary in ring size, oxidation state, and nature of the alkyl group at C_{16}.[83]



157 Myxovirescin A_1; $R_1 = OCH_3$, $R_2 = H$, $R_3 = CH_3$
158 Myxovirescin A_2; $R_1 = OCH_3$, $R_2 = CH_3$, $R_3 = H$
159 Myxovirescin M_2; $R_1 = H$, $R_2 = CH_3$, $R_3 = H$

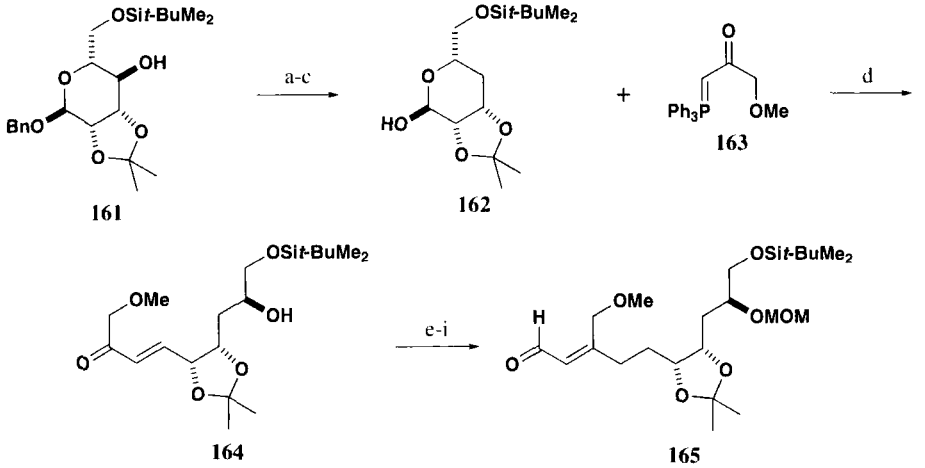


160 Myxovirescin B; $R_1 = OCH_3$, $R_3 = CH_3$

Fig. 10

In 1990 Williams and McGill reported a highly efficient total synthesis of optically active myxovirescin B.[84] The critical convergent step in this work involved construction of a C_5–C_{27} fragment (myxovirescin numbering) using a Julia–Lythgoe type coupling between an optically pure arylsulfone and an α,β-unsaturated aldehyde (*vide infra*).

The synthesis began with construction of a C_5–C_{14} aldehyde building block, **165**, utilizing the protected carbohydrate precursor **161**[85] to supply the correct absolute stereochemistry at C_6–C_9 (*Scheme 26*). Deoxygenation and debenzylation of **161** provided the hemiacetal **162** which served as a

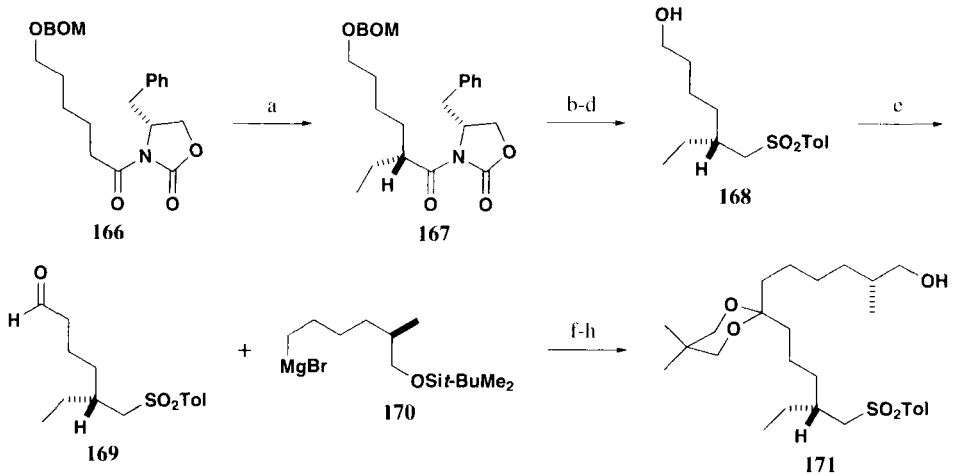


Key: (a) $(imd)_2CS$, dichloroethane, reflux, 82%; (b) n-Bu_3SnH, toluene, reflux, 87%; (c) Na, NH_3, THF, 89%; (d) **163**, propionic acid, THF, reflux, 81%; (e) Rh/Al_2O_3, H_2, THF, 96%; (f) MOMCl, i-$PrNEt_2$, 88%; (g) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, HMPA, 77%; (h) DIBAL, CH_2Cl_2, –78°C, then MeOH, aqueous Rochelle's salt, 88%; (i) excess MnO_2, CH_2Cl_2, 92%.

Scheme 26

substrate for Wittig olefination *via* the phosphine **163**. In this instance, addition of catalytic acid was found to suppress unwanted tetrahydropyran formation resulting from intramolecular alkoxide addition to the initially formed α,β-unsaturated ketone **164**. Finally, the trisubstituted *Z* olefin **165** was obtained in 91% yield *via* a Horner–Emmons condensation with the stabilized anion of triethylphosphonoacetate, affording a separable mixture of *Z*:*E* isomers (5:1).

The northwestern portion (C_{15}–C_{26}) of myxovirescin B was prepared as the optically active sulfone **171** (*Scheme 27*). Initially the tertiary asymmetric center at C_{16} was established *via* an Evans alkylation of the oxazolidinone **166**. Optimized alkylation conditions for this reaction required stirring with excess ethyl triflate at –30° (10 h), and provided **167** as a single isomer. Reductive cleavage of the chiral auxiliary yielded the primary alcohol which was converted, in two steps, to the sulfone **168** and ultimately to the aldehyde **169**. Addition of the Grignard, **170**, derived from (+)-methyl 3-hydroxy-2(*S*)-methylpropionate, oxidation, and ketalization afforded the remaining carbon framework of the northwestern segment **171**.

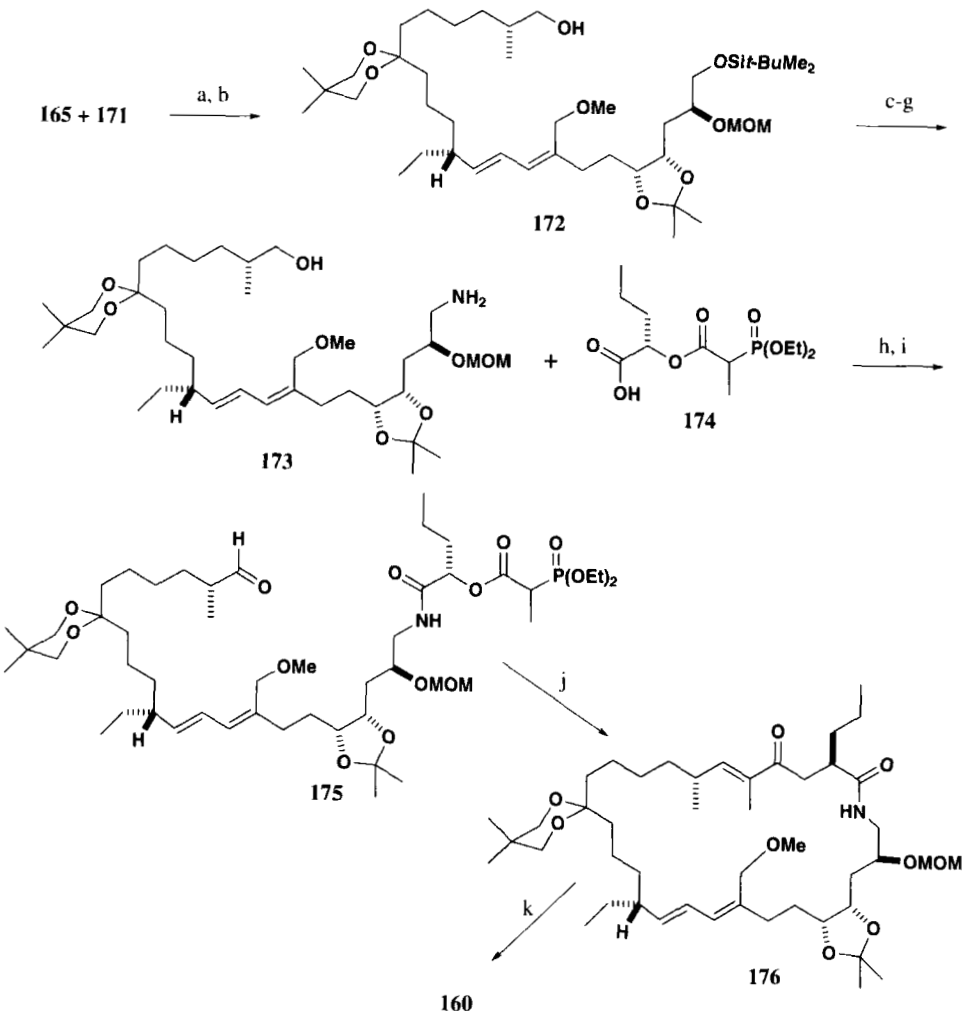


Key: (a) $NaN(TMS)_2$, THF, EtOTf, –78°C, 65 %; (b) $LiAlH_4$, Et_2O, 0°C, 84%; (c) I_2, PPh_3, imidazole, CH_2Cl_2, then $NaSO_2Tol$, DMF, 85%; (d) H_2, Pd black, MeOH, cat. HCl, , 97%; (e) $(COCl)_2$, DMSO, Et_3N, –78°C, 85%; (f) **170**, Et_2O, 83%; (g) PCC on Al_2O_3, CH_2Cl_2, 97%; (h) 2,2-dimethyl-1,3-propanediol, $PhCH_3$, TsOH, 80°C, 86%.

Scheme 27

At this point a Julia–Lythgoe reductive coupling between the optically pure arylsulfone **171** and α,β-unsaturated aldehyde **165** was found to proceed in excellent yield (79%) *via* the expected intermediate β-hydroxysulfone (*Scheme 28*). This reaction required no additional derivitization of the intermediate hydroxyl group prior to reductive elimination and provided the resulting diene, **172**, as a mixture of C_{14}–C_{15} isomers (9:1, *E*:*Z*). This mixture was carried on, in several steps to the amino alcohol **173**. The ketophosphonate **175** was then prepared *via* a carbodiimide-mediated coupling of **173** with the carboxylic acid **174** followed by Swern oxidation of the primary alcohol. Cyclization of

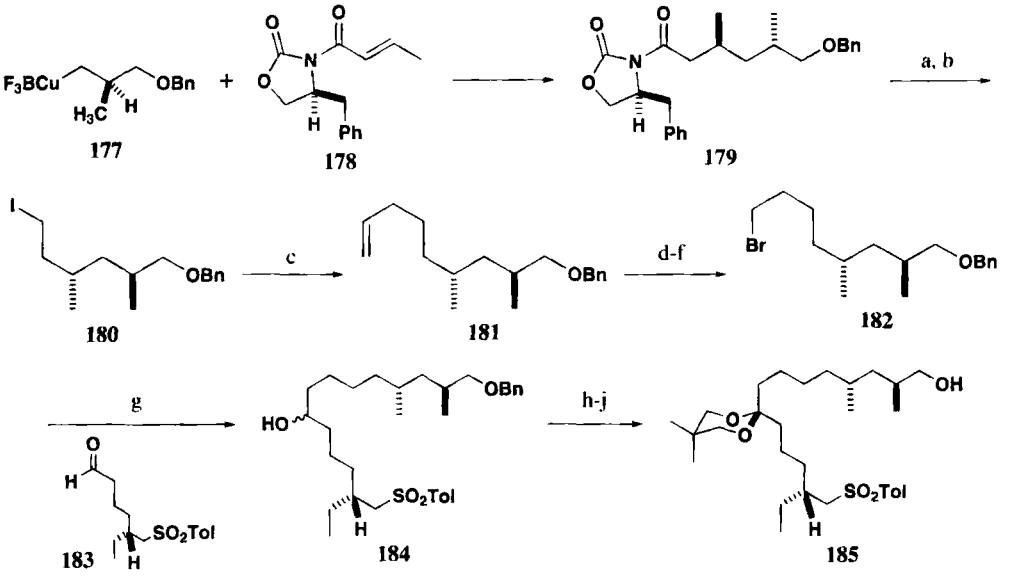
175 *via* an intramolecular Horner–Emmons reaction under Masamune–Roush conditions[86] afforded the desired macrolactone **176** as mixture of C_{26}–C_{27} isomers (7:1, *E*:*Z*). Finally, purification by preparative HPLC and global deprotection provided crystalline myxovirescin B (**160**) which was identical to the natural product in all respects.



Key: (a) **171**, *n*-BuLi (8 equiv), –78°C, then **165**; (b) 6% Na(Hg), THF/MeOH (2:1), KH_2PO_3, 79% (two steps); (c) Ac_2O, Et_3N, DMAP, 98%; (d) TBAF, THF, 94%; (e) MsCl, Et_3N, DMAP, then LiN_3, DMF, 60°C, 95%; (f) K_2CO_3, MeOH, 96%; (g) PPh_3, THF, Δ, then NH_4OH, 93%; (h) 1-cyclohexyl-3-(2morpholinoethyl)carbodiimide methyl-*p*-toluenesulfonate, CH_2Cl_2, 0°C, 92%; (*i*) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, 92%; (j) DBU, CH_3CN, LiCl, 78%; (k) $HClO_4$, MeOH, H_2O, 70%.

Scheme 28

A second entry into the myxovirescin family, involving a total synthesis of myxovirescin A_1, was reported in 1994 by Williams and Li.[87] Relative to previous efforts (*vide supra*), this work defined a viable strategy for obtaining the C_{25}–C_{27} *anti*-1,3-dimethyl substitution pattern common to the myxovirescins. In addition, this synthesis utilized a novel macrolactamization strategy to afford the 28-member macrocyclic ring system. Thus, as illustrated in *Scheme 29*, chelation controlled conjugate addition of the cuprate, **177**, to 4-(*S*)-benzyl-2-oxazolidine **178** occurred with high diastereofacial selectivity providing the Michael adduct **179** as a 9:1 mixture of C_{25} isomers (96%). Reductive cleavage of the chiral auxiliary, and treatment of the resulting primary alcohol with triphenylphosphine-iodine afforded the iodide **180**. The iodide was converted to **181** on treatment with allylmagnesium chloride and ultimately to the bromide **182** under standard conditions. Addition of the Grignard derived from **182** to the aldehyde **183** afforded the hydroxysulfone **184** as a mixture of C_{20} epimers. Finally, oxidation, ketalization, and deprotection of **184** produced the optically pure sulfone **185** in 83% overall yield.



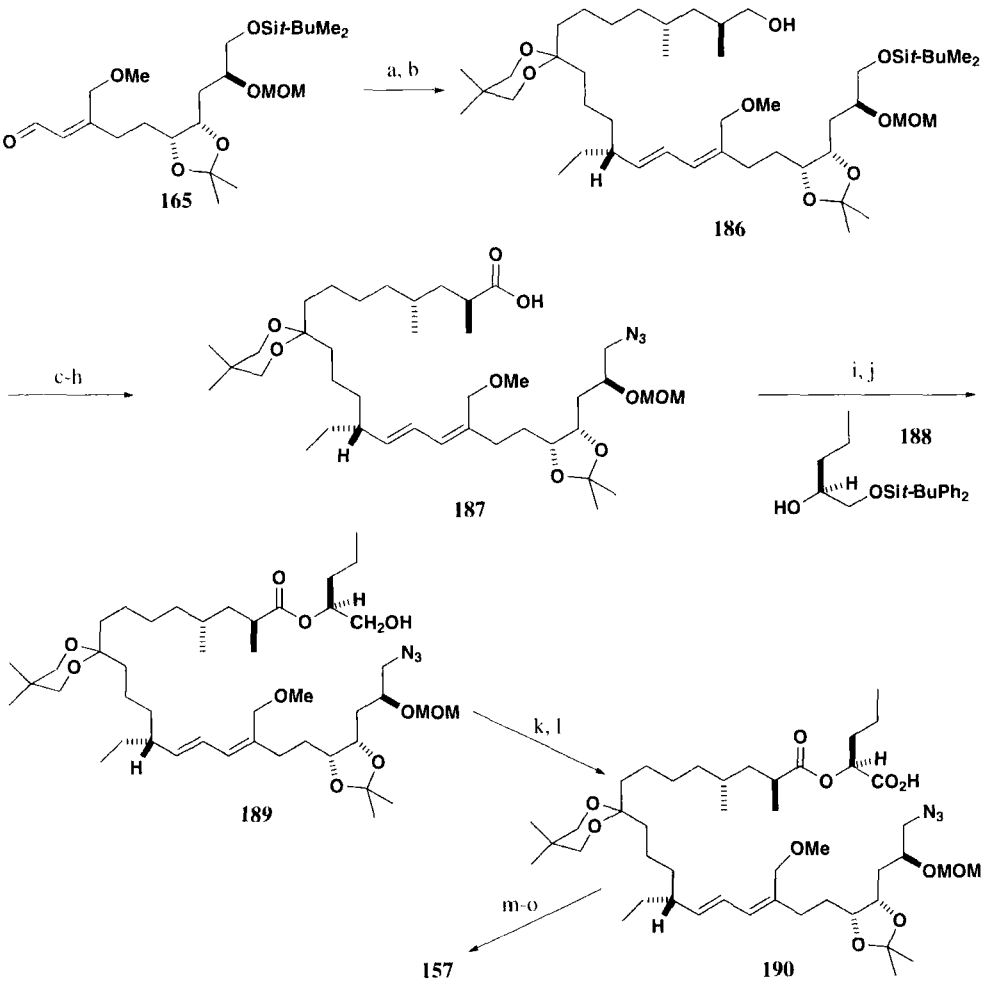
Key: (a) $LiAlH_4$, 87%; (b) I_2, PPh_3, Imidazole; (c) allylmagnesium chloride, 92% (2 steps); (d) O_3, Et_2O, –10°C, then LAH, 73%; (e) MsCl, Et_3N, DMAP; (f) LiBr, 87% (2 steps); (g) **182**, Mg, THF, then **183**, 88%; (h) PCC; (i) 2,2-dimethyl-1,3-propanediol, toluene, Δ; (j) H_2, Pd/C, EtOH, 83% (3 steps).

Scheme 29

Following the precedent established in the myxovirescin B synthesis (*vide supra*), a Julia–Lythgoe coupling between **165** and **185** provided the diene **186** in good yield (69%) as a mixture of C_{14}–C_{15} isomers (*E:Z*, 6.5:1; *Scheme 30*). Conversion of **186** to the C_5 azide and oxidation of the C_{28} alcohol was accomplished in several steps including a mild two-step oxidation *via* the C_{28}

aldehyde. Esterification of **187** with 2(*S*)-*tert*-butyldiphenylsilyloxy-2-pentanol[88] using the Yamaguchi protocol[89] provided the ester **189** in quantitative yield. Selective deprotection and oxidation afforded the acyclic intermediate **190** without epimerization at C_2.

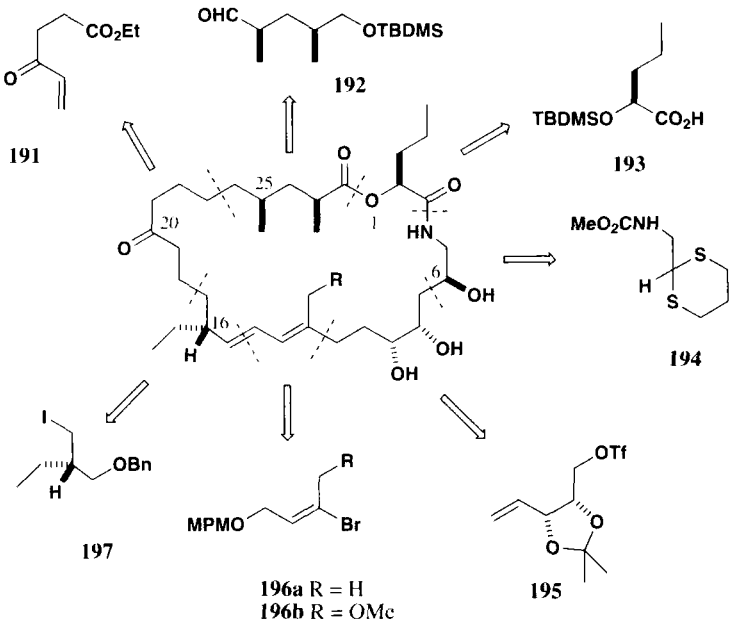
The final macrolactamization step was achieved by quantitative reduction of **190** to the amino acid followed by cyclization using Mukaiyama's reagent. This provided the 28-membered macrocycle in an excellent 59% yield from **190**. Acid-promoted deprotection provided synthetic myxovirescin A_1 which was identical to the natural product in all respects.



Key: (a) **185**, *n*-BuLi (8 equiv), –78°C, then **165**, 79%; (b) Na(Hg) 6%, THF/MeOH (2:1), KH_2PO_4, 86%; (c) Ac_2O, Et_3N, DMAP, 99%; (d) TBAF, THF, 94%; (e) MsCl, Et_3N, DMAP, then LiN_3, DMF, 60°C, 90%; (f) K_2CO_3, MeOH, 99%; (g) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, CH_3CN, *t*-BuOH, 81% (2 steps); (i) $Cl_3PhCOCl$, Et_3N, THF, then **188**, DMAP, $PhCH_3$, Δ, 99%; (*j*) Et_3N•HF, CH_3CN, (95%); (k) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N; (l) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, CH_3CN, *t*-BuOH, 83% (2 steps); (m) PPh_3, THF, H_2O, Δ, 92%; (n) Et_3N, 2-chloro-1-methylpyridinium iodide, CH_2Cl_2, 59%; (o) $HClO_4$, MeOH, H_2O, 70%.

Scheme 30

4.c. Total Syntheses of M_2 and A_1

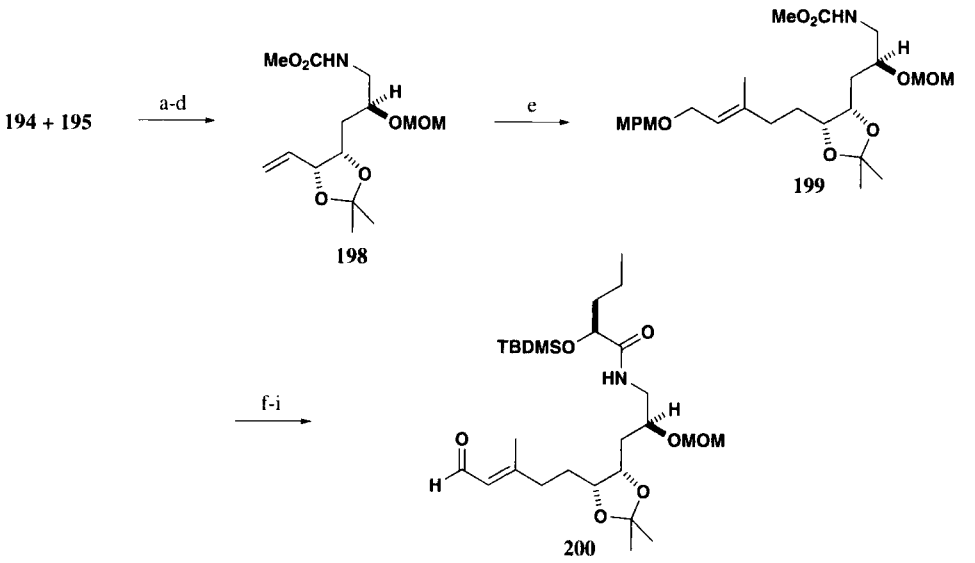


Myxoversin M_2 (**159**, R = H) and A_1 (**157**, R = OMe) Retrosynthetic Analysis

Fig. 11

An alternative synthetic approach to the myxovirescin family of antibiotics was reported by Seebach and co-workers in 1991.[90] This strategy was initially applied to a total synthesis of myxovirescin M_2, and was later extended to a synthesis of myxoviresin A_1.[91] Thus, as illustrated in Figure 11, optically pure myxovirescin M_2 (R = H) or A_1 (R = OCH_3) was prepared from a total of seven building blocks, including the chiral starting materials **192**, **193**, **194**, and **197**. These enantiopure starting materials were ultimately obtained either directly from the chiral pool or indirectly *via* enzymatic and classical resolution techniques. Key steps in this synthesis include a Julia–Lythgoe reductive coupling to build up the C_5–C_{20} skeleton of myxovirescin M_2 and a Yamaguchi macrolactonization which provides the penultimate 28-membered macrocycle.

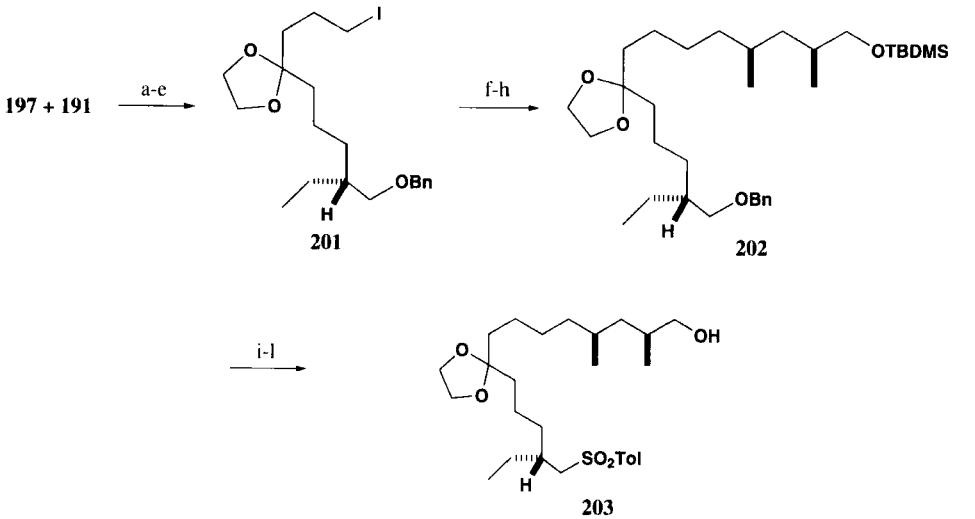
A synthesis of the requisite C_5–C_{14} aldehyde precursor **200**, required for the Julia–Lythgoe coupling, is outlined below (*Scheme 31*). Initially, the dilithio anion of dithiane **194** was alkylated with the triflate **195**, derived from *cis*-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-ol. An NCS-mediated removal of the dithiane moiety followed by reduction of the resulting carbonyl and protection of the hydroxyl group provided the terminal alkene **198**. Finally, a Suzuki type coupling of **198** with the vinyl bromide **196a** gave **199**. Selective deprotection/oxidaton and coupling with **193** yielded the α,β-unsaturated aldehyde **200**.



Key: (a) **194**, *n*-BuLi (2 equiv), DMPU, THF, –78°C, then **195**, 72%; (b) $AgNO_3$, NCS, CH_3CN/H_2O (4:1), 93%; (c) $Li[Al(Ot\text{-}Bu)_3]H$, Et_2O, rt, 94%; (d) MOMCl, DMAP, DIPEA, CH_2Cl_2, 93%; (e) 9-BBN, THF, 0°C, then $PdCl_2(dppf)$, **196a**, NaOH, H_2O_2, 85%; (f) KOH, $MeOH/H_2O$ (4:1), Δ, 95%; (g) DIPEA, BOPCl, **193**, CH_2Cl_2, –20°C, 78%; (h) DDQ, CH_2Cl_2, 22%; (i) PDC, DMF, 94%.

Scheme 31

Preparation of the C_{15}–C_{20} portion of myxovirescine M_2 began with a conversion of the iodide **197** to the corresponding cuprate followed by Michael addition to the enone **191** (*Scheme 32*).

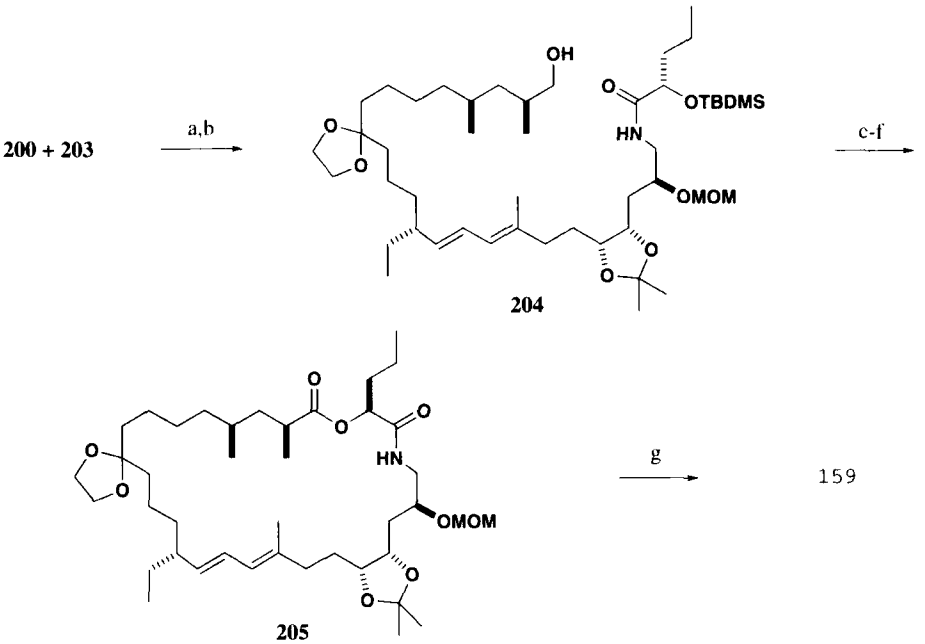


Key: (a) **197**, *t*-BuLi (2 equiv), CuCN, Et_2O, –78°C, then **191**, TMSCl; (b) TBAF, THF, 78% (2 steps); (c) $HO(CH_2)_2OH$, CSA; (d) LAH, Et_2O, 99% (2 steps); (e) PPh_3, imidazole, I_2, CH_2Cl_2, 97%; (f) *t*-BuLi (2 equiv), Et_2O, –78°C, then **192**, 88%; (g) TsCl, pyridine, rt, 82%; (h) $LiBH_4$, $LiBEt_3H$, 95%; (i) H_2, Pd/C, EtOH, 99%; (j) PPh_3, imidazole, I_2, CH_2Cl_2, 97%; (k) $TolSO_2Li$, DMF, 93%; (l) TBAF, THF, 95%.

Scheme 32

Selective protection of the resulting ketone, and elaboration of the pendant ethyl ester provided the iodide **201**. Metalation of **201**, addition to the aldehyde **192**, and deoxygenation *via* the tosylate afforded the unsymmetrically protected dihydroxy-ketal **202** which was transformed to the hydroxy-sulfone **203** through a series of standard functional group manipulations.

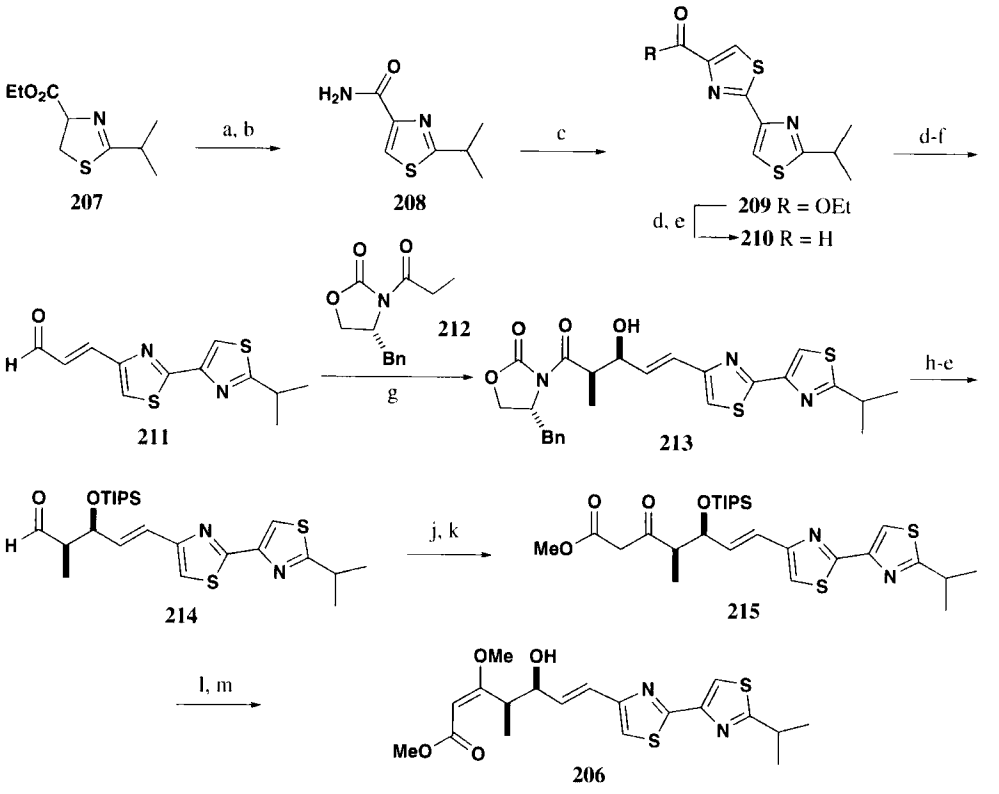
As illustrated in *Scheme 33*, addition of the dilithiated hydroxy-sulfone **203** to the α,β-unsaturated aldehyde **200** and reductive elimination gave the diene **204** as a mixture of C_{14}–C_{15} isomers (4:1, *E*:*Z*). Oxidation of the primary alcohol to the corresponding acid and silyl-ether cleavage gave a precursor which was cyclized (Yamaguchi conditions) to the desired macrolactone **205** in 83% overall yield. Final deprotection under acidic conditions ultimately provided the target molecule (+)-myxovirescin M_2 (from **196a**) which was identical to the natural product in all respects.



Key: (a) **203**, *n*-BuLi (2 equiv), THF, –78°C, then **200**, 96%; (b) Na/Hg, KH_2PO_4, THF/MeOH (4:1), 62%; (c) PDC, DMF; (d) TBAF, THF, 70% (2 steps); (e) 2,4,6-$Cl_3PhCOCl$, Et_3N, THF, 88%; (f) DMAP, toluene, Δ, dilution < 10^{-3} M, 93%; (g) $HClO_4$, MeOH/H_2O, 64%.

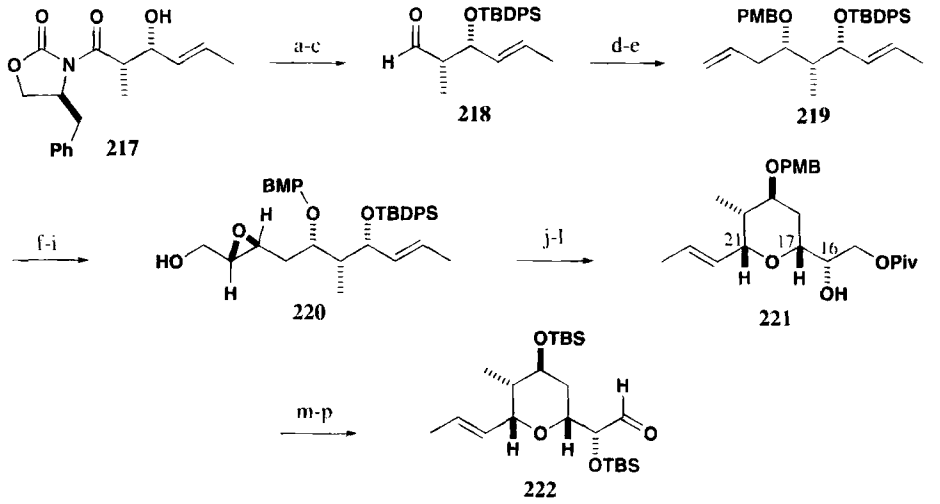
Scheme 33

In addition to the aforementioned syntheses of the antibiotics isolated from myxobacteria, syntheses of a few other natural products in the same category exist. Noticeably, the syntheses of althiomycin have been reported by Shiba[92] and Toogood.[93] The total syntheses of three natural products, tartralon B,[94] phenalamide A_2,[95] and thiangazole[96] have been published by the groups of Muzler, Hoffmann, and Akaji, respectively. Recently, the Williams group has completed the asymmetric total syntheses of two antibiotics from myxobacteria, cystothiazole (**206**, *Scheme 34*)[97] and ratjadon (**225**, *Scheme 35* and *36*).[98]



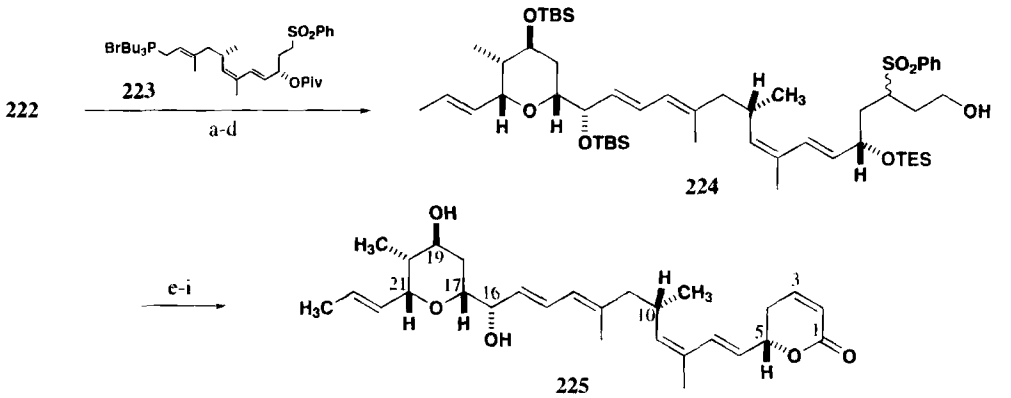
Key: (a) DBU, $BrCCl_3$, CH_2Cl_2, 83%; (b) NH_3, MeOH, 89%; (c) Lawesson's reagent, refluxing xylenes then $BrCH_2COCO_2Et$, EtOH, 95% over 2 steps; (d) DIBAL, 96%; (e) Swern, 86%; (f) $(MeO)_2P(O)CH_2CO_2Et$, NaH, > 95%; (g) **212**, *n*-Bu_2BOTf, Et_3N, 0°C then cool to −78°C add **211**, 74%; (h) MeMgBr, MeOH, 0°C, 83%; (i) TIPSOTf, Collidine, 0°C, quant.; (j) Methyl acetate, LDA, −78°C, then **214**, 80%; (k) Swern, 50%; (l) HMPA, Et_2O, Me_2SO_4, 85%, 4:1; (m) TBAF buffered in NH_4Cl, THF.

Scheme 34



Key: (a) TBDPSCl, imid; (b) $LiBH_4$; (c) Swern; (d) $Ipc_2B(allyl)$; (e) PMB trichloroacetimidate, CSA; (f) AD-mix-α; (g) $NaIO_4$; Ph_3PCHCO_2Me; (h) DIBAL; (i) (+)-DET, $Ti(Oi\text{-}Pr)_4$, TBHP, 4Å MS; (j) PivCl, pyr; (k) TBAF; (l) CSA; (m) CAN; (n) TBSCl, imid, DMAP; (o) DIBAL; (p) Dess–Martin.

Scheme 35



Key: (a) *t*-BuOK, toluene:THF (5:1); (b) DIBAL; (c) TESCl, pyr; (d) *n*-BuLi, THF, HMPA, then ethylene oxide; (e) Dess–Martin; (f) PPTS; (g) TPAP, NMO; (h) DBU; (i) HF, pyr, THF.

Scheme 36

V. CONCLUSION

The myxobacteria are a rich source of novel natural products ranging from polyenes and complex heterocycles to macrolide antibiotics. Many of these unique secondary metabolites possess significant biological activities. It is our expectation that the myxobacteria will continue to serve as

fertile ground for the discovery of novel natural products which will provide interesting opportunities and challenges for synthetic organic chemistry.

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