Microtubule-Stabilizing Marine Metabolite Laulimalide and Its Derivatives: Synthetic Approaches and Antitumor Activity

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I. Introduction

In 1988, *Cacospongia mycofijiensis*, a chocolate sponge collected from Vanuatu, became the object of an intense study at the University of California because the liquid squeezed from freshly collected material killed tropical fish being held in an aquarium within 10 min. This primary effort to protect the sponge against predators originated from two cytotoxic macrolides—fijianolide B (**1**) and fijianolide A (**2**)—whose gross structure was elucidated mostly by NMR analysis.[1b] Independently, the same compounds were isolated by Hawaiian scientists from an Indonesian sponge—*Hyattella sp.*—and given the now commonly used names laulimalide (**1**) and isolaulimalide (**2**),[1a] the names being derived from Hawaiian language ("laulima" = people working together), due to the cooperating research groups. Interestingly, **1** and **2** were also isolated from the extracts of a predator nudibranch, *Chromodoriz lochi*, that was found grazing on the sponge.[1a,b] Later on, **1** and **2** were also isolated from the Okinawan sponge *Fasciospongia rimosa*[1d] and very recently also from a sponge in the genus *Dactylospongia*.[1e] In 1996, the structure of **1** and its absolute configuration was confirmed by Higa et al. through X-ray diffraction studies.[1c] Higa's group also isolated a ring-expanded regioisomer of **1**—neolaulimalide (**3**)—as a minor congener of **1** and **2**.[1d]

Laulimalide (**1**), meanwhile identified as a potent inhibitor of cellular proliferation with IC_{50} values against numerous drug-sensitive cell lines in the low nanomolar range,[1a,d,2] is an 18-membered macrolide (within the inner perimeter) that contains nine chiral carbons (5*R*, 9*S*, 11*S*, 16*S*, 17*S*, 19*S*, 20*S*, 23*S*) and two dihydropyran rings, one (C_5−C_9) annulated to the macrocycle in 2,6-trans fashion and the second one (C_{23}−C_{27}) connected to the macrolide core via an *E*-allylic alcohol. Furthermore, **1** contains a trans-disubstituted epoxide at C_{16} and C_{17} and a 2,3-*Z*-enoate.

Isolaulimalide (**2**) is an isomer of **1** whose tetrahydrofuran ring is formed by an S_N2-type attack of the C_{20} hydroxyl group on C_{17} of the epoxide, the acid-catalyzed isomerization being complete within a few hours.[1b] Isolaulimalide exhibits significantly reduced

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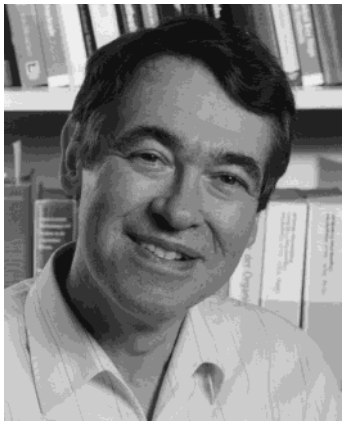


Johann Mulzer was born in 1944 at Prien in Upper Bavaria, Germany. In 1974 he received his Ph.D. degree under the supervision of Rolf Huisgen at the Ludwig-Maximilians University in Munich. Subsequently, he joined the group of E. J. Corey at Harvard as a postdoctoral fellow. From 1982 to 1996 he held professorships at the University of Düsseldorf, the Free University of Berlin, and the Johann-Wolfgang-Goethe University in Frankfurt. Since 1996 he has been a full professor at the Institute of Organic Chemistry of the University of Vienna. His main research interests are focused on the total synthesis of structurally and physiologically interesting natural products.

Elisabeth Öhler was born in Vienna, Austria, and received her Ph.D. degree in Organic Chemistry at the University of Vienna in 1968 for work on reactions with organophosphorus compounds under the guidance of Friedrich Wessely. Afterward, she joined Ulrich Schmidt for work on Reformatsky-type reactions and syntheses of dehydroamino peptides, and in 1978 she joined the team of Erich Zbiral to explore reactions of unsaturated phosphonates. Since 1996, she has been a senior research fellow in the Mulzer group. Apart from laulimalide, she has also contributed to various epothilone syntheses.

activity with IC_{50} values in the low micromolar range, which may indicate that the epoxide function is necessary for high activity.

Neolaulimalide (**3**) is the ring-enlarged regioisomer of **1** with an intact epoxide moiety and was reported to possess high cytotoxicity in the same range as **1**.[1d] It is distinctly more stable than **1**, the acid-promoted rearrangement to **2** being complete only after 2 days.[1d]

In February 1999, **1** and **2** were recognized as new members of the MSAA (microtubule-stabilizing antitumor agents) family of compounds,[2a] which share the same or a similar mechanism of action as the frontline anticancer drugs Taxol (paclitaxel)[3] and Taxotere (docetaxel). Thus, the list of compounds with "taxol-like" activity[4] currently includes the following members: taxanes (isolated from yew trees), marine metabolites (sarcodictyins/eleutherobin, discodermolide, laulimalide, dictyostatin, and peloruside A),[5] microbial metabolites (the epothilones,[6] which are already under clinical investigation and the polycyclic compound FR182877, formerly known as WS9885B[7]), other natural products (taccalonolide,[8a] tryprostatin,[8b] xanthochymol[8c]), and non-natural compounds (for instance, an analogue of estradiol,[9a] a combretastatin D analogue[9b] and GS-164[9c]). Moreover, it was shown that **1**, like the epothilones and discodermolide, is an effective inhibitor of cell growth in paclitaxel-resistant cells.[2] A very recent study revealed that laulimalide, in contrast to the epothilones, discodermolide, and eleutherobin, apparently does not bind at the taxol site to the tubulin polymer and is also active against epothilone-resistant cell lines.[2b]

Apart from the significant clinical potential of **1** and its restricted natural supply, the attraction of laulimalide as a synthetic target originates from its unique and complex molecular architecture. Specifically, its 16,17-epoxide is susceptible to nucleophilic attack from the 20-hydroxy group to form the more stable tetrahydrofuran isomer **2** and the 2,3-*cis*-enoate moiety readily undergoes *Z*/*E*-isomerization. In the following, it will be demonstrated that the principal difficulties during total synthesis of laulimalide arise during or after the introduction of these two functionalities.

To date, the use of ring-closing olefin metathesis (RCM) in laulimalide synthesis[10a] and selected total syntheses of **1**[10b] have been briefly reviewed. The present review will summarize the complete laulimalide-directed synthetic work available up to April 2003, including the syntheses of some non-natural analogues, as well as the biological data available from laulimalide and its natural co-metabolites **2** and **3** and from the few analogues which have been investigated to date.

II. Chronological Evolution of Laulimalide Synthesis

Synthetic work toward laulimalide[11−23] started in 1996, when the absolute configuration of **1** was determined.[1c] These early efforts resulted in three reports on fragment syntheses by the groups of Ghosh[11a] and Nishiyama.[12] However, these primary approaches were not successfully brought to completion. The interest in **1** was distinctly intensified after February 1999, when laulimalide was identified as a new member of the MSAA family.[2a] In September 1999, Mulzer's group reported the synthesis of the "lower" C_1-C_{12} moiety of **1**, utilizing ring-closing olefin metathesis (RCM)[24] for the construction of the dihydropyran subunit.[13a] This communication was followed in close succession by an independent report of Ghosh and Wang, concerning the synthesis of an extended C_2-C_{16} fragment of **1** which used a slightly different RCM methodology for elaboration of the dihydropyran moiety.[11b]

Since these early fragment syntheses, an impressive number of 16 approaches to key fragments of **1** have been contributed by different groups,[11−16] and seven teams have completed as many as 10 total

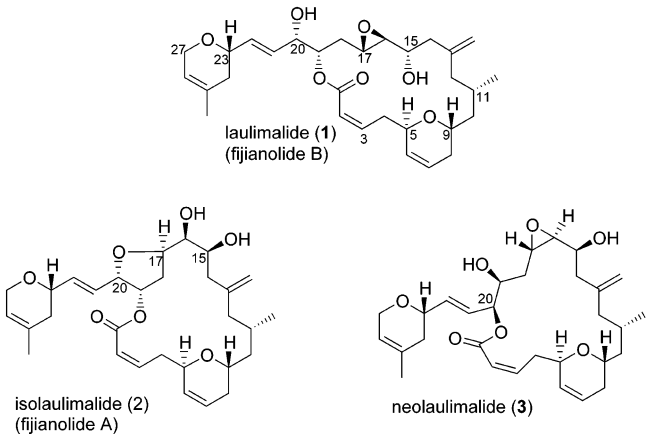


Figure 1. Laulimalide (**1**), isolaulimalide (**2**), and neolaulimalide (**3**).

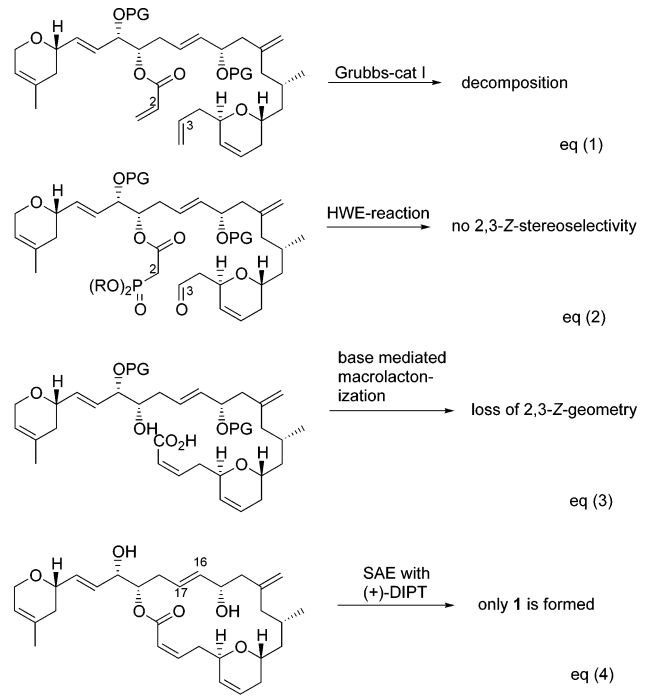


Figure 2. Unsuccessful or nonstereoselective ring closures, and selective epoxidation of unprotected desepoxylaulimalide.

syntheses.[17−23] The first total synthesis of (−)-laulimalide was accomplished in 2000 by Ghosh and Wang,[17a] who later refined their approach by an improved introduction of the 2,3-*cis*-enoate.[17b,c] Almost 1 year later, Ghosh's first report was followed in close succession by three approaches from Mulzer's team,[18a−c] among which one was totally stereoselective, and one from Paterson's group,[19] which before had achieved the synthesis of the fully functionalized macrocyclic core of **1**.[15]

From these early syntheses the following conclusions concerning a successful "endgame" can be drawn.

The macrocycle of **1** cannot be obtained through RCM of a 19-acryloyl 5-allyl-substituted *seco* compound (Figure 2, eq 1).[17c]

Macrocyclization via intramolecular Horner−Wadsworth−Emmons−(HWE) olefination of an aldehyde−phosphonate produces unfavorable 2,3-*E*/*Z*-mixtures (ca. 2:1) in favor of the (*E*)-isomer (Figure 2, eq 3).[17a,18a]

Base-induced macrolactonization of a 19-hydroxy 2,3-alkenoic acid leads to extensive isomerization of the 2,3-(*Z*)-enoate (Figure 2, eq 2).[17b,c,18c] However, no *E*/*Z*-isomerization is observed during partial hydrogenation of a 2,3-alkynoate macrocycle[17b] or during Mitsunobu-type macrolactonization of a *seco* acid with (19*R*) hydroxy group.[19]

The sensitive epoxide can introduce regio- and stereoselectively in the last step by Sharpless epoxidation of 16,17-allylic alcohol of the unprotected macrocycle (Figure 2, eq 4).[18a,19]

This knowledge proved helpful in the total syntheses by Wender,[20] Crimmins,[21] Williams,[22] and Nelson,[23] which followed in 2002.

III. Early Synthetic Work

A. First Laulimalide Fragment (Ghosh)

In the first laulimalide-directed communication,[11a] Ghosh's group reported the enantioselective synthesis of methyl ketone **5** as a C_3-C_{14} segment of **1** which, following the retrosynthetic concept in Figure 3, was to be assembled with an appropriately functionalized $C_{15}-C_{20}$ epoxyaldehyde **4** by an aldol-type reaction.

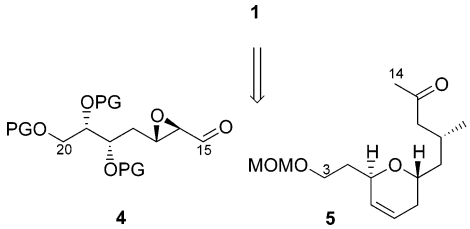


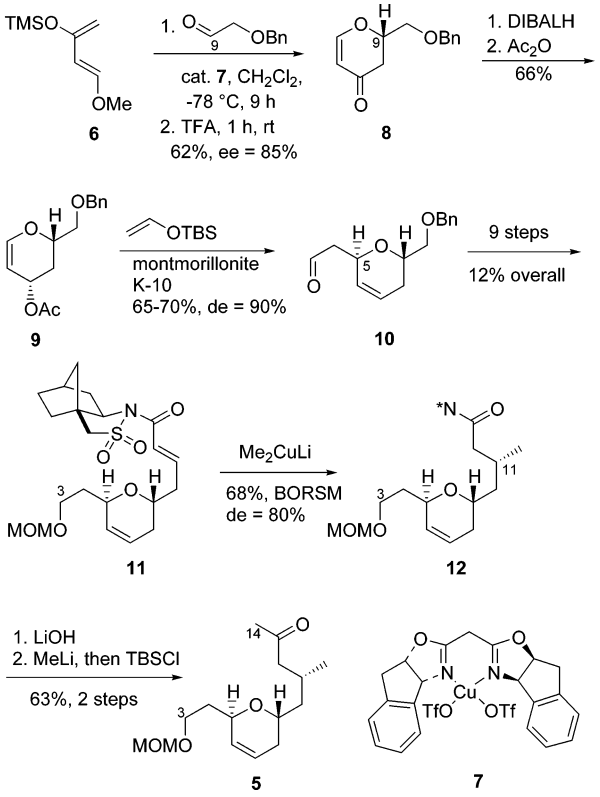
Figure 3. Ghosh's first retrosynthetic plan: fragment connection between C_{14} and C_{15}.

In the event, a hetero Diels−Alder reaction of benzyloxy acetaldehyde and Danishefsky's diene **6** catalyzed by the chiral Cu(II)−bisoxazoline complex **7**[25] was used to construct dihydropyranone **8** enantioselectively (62% yield, ee = 85%). After conversion of **8** to acetate **9**, the C_3-C_4 side chain was *trans*-stereoselectively appended by a Ferrier-type reaction with vinyl−OTBS using montmorillonite K10 clay as a Lewis acid.[26] To install the C_{11} methyl group, aldehyde **10** was converted in nine steps to *N*-enoylsultam **11**, which by reaction with Me_2CuLi afforded diastereoselectively conjugate addition product **12**, albeit with low conversion and in unsatisfactory yield. Alkylation product **12** was then transformed to methyl ketone **5** via the corresponding acid[27] (Scheme 1).

B. Fragment Syntheses by Nishiyama

The synthetic efforts of Nishiyama and Shimizu[12] did not, until now, lead to a total synthesis of **1**. In their retrosynthetic analysis (Figure 4), the Japanese group planned the convergent assembly of the laulimalide skeleton by an allylation of the chiral amide **15** with allyl iodide **14**, controlling the stereochemistry at C_{11} by the Evans oxazolidinone protocol.[28] The

Scheme 1. Ghosh's First Laulimalide Fragment: Synthesis of Methyl Ketone 5



C_{12}–C_{27} fragment, in turn, was to be assembled from subunits **16**, **17**, and **18**.

In their first approach,[12a] the bond construction between C_{10} and C_{11} was tested successfully with a C_{12}–C_{16} model iodide and served to synthesize a C_1–C_{16} fragment of **1** (Schemes 2 and 3). The synthesis started from D-mannose pentaacetate (**19**), which was

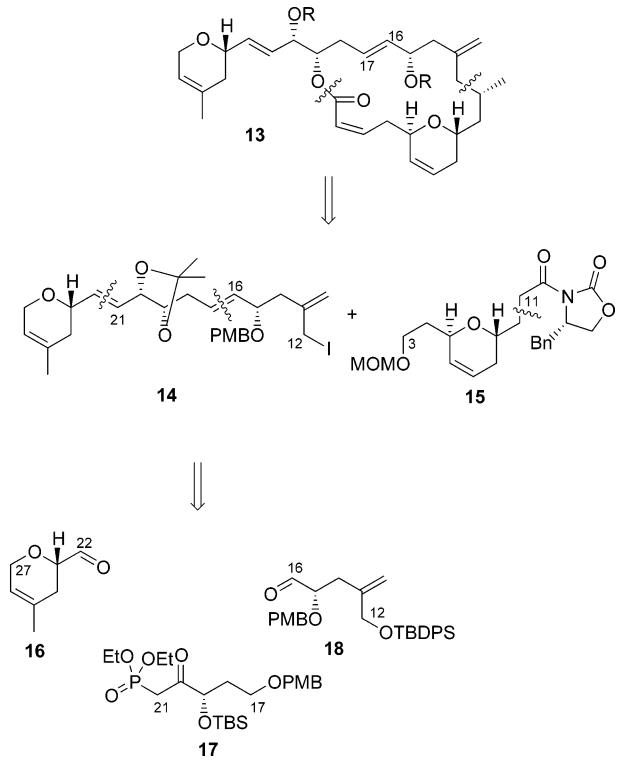
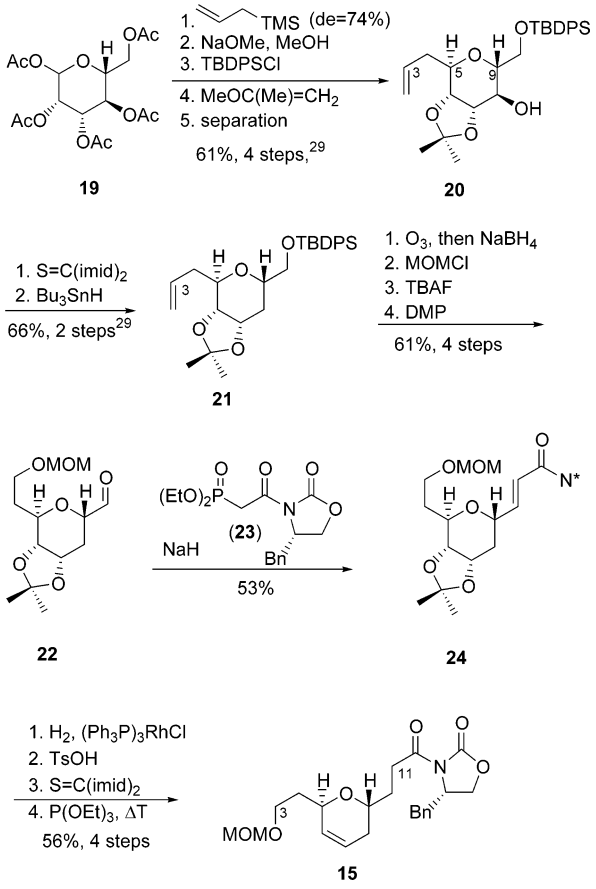
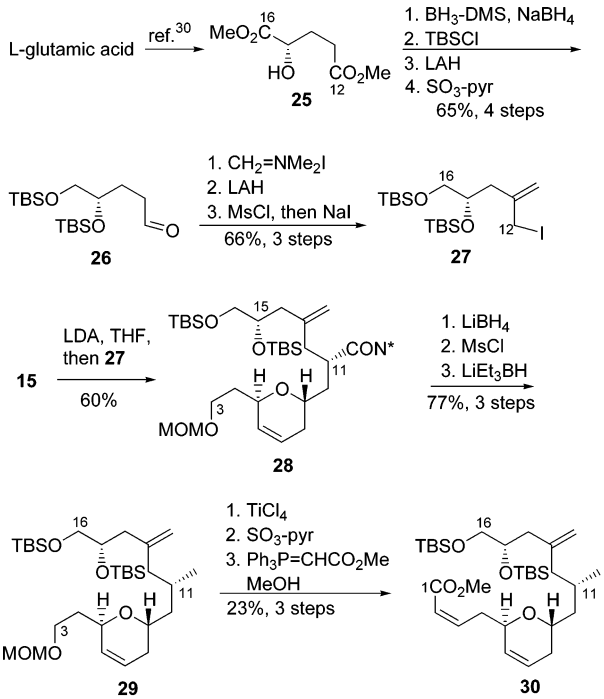


Figure 4. Nishiyama's retrosynthetic analysis.

Scheme 2. Nishiyama's Synthesis of C_3–C_{11} Fragment 15



Scheme 3. Syntheses of Allyl Iodide 27 and C_1–C_{16} Fragment 30 by Nishiyama and Shimizu



transformed to the known tetrahydropyran **21** by Nicolaou's six-step procedure.[29] Compound **21** was converted to aldehyde **22** by routine operations. Olefination of **22** with the chiral phosphonate **23** led selectively to (*E*)-enamide **24** in moderate yield. The

double bond in **24** was hydrogenated in the presence of a Wilkinson catalyst, and after selective removal of the isopropylidene group, the resulting diol was deoxygenated to key compound **15**.

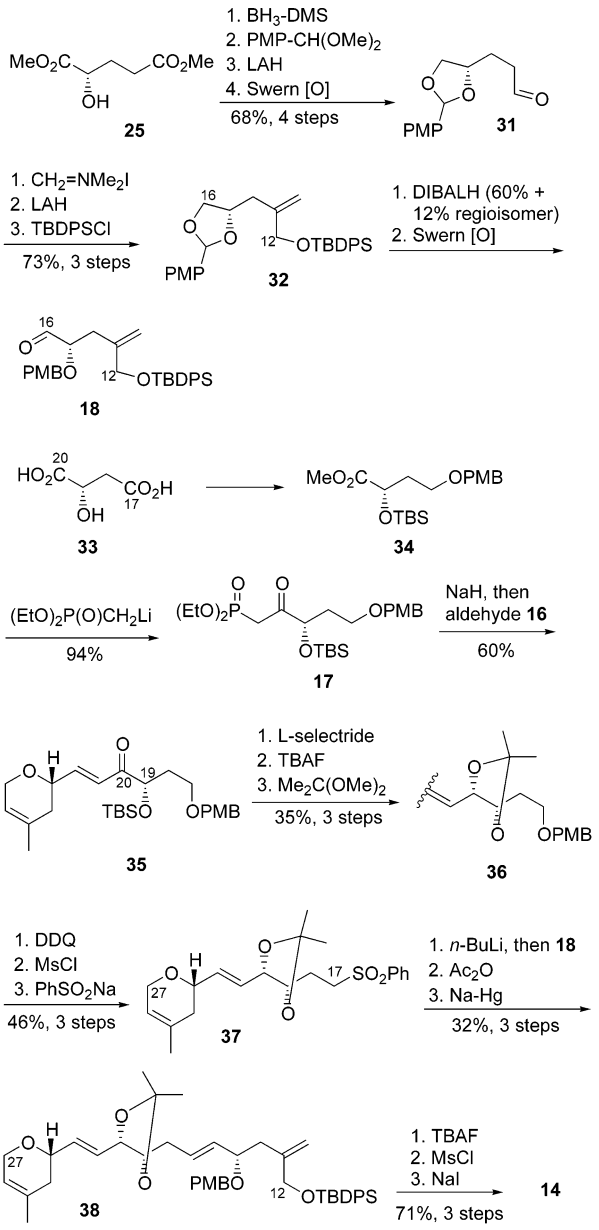
The synthesis of allyl iodide **27** (Scheme 3), serving as a model compound in the critical allylation step, began with the L-glutamic acid-derived diester **25**,[30] which was selectively reduced at the C_{16} position. After protection of the resulting diol, reduction of the C_{12} ester group followed by oxidation afforded aldehyde **26**. Eschenmoser methylenation[31] of aldehyde **26** led to an enal, which was smoothly converted to the desired iodide **27**. The lithium enolate of **15** was then alkylated with iodide **27** to provide amide **28** with the required configuration at C_{11}. Reduction of the carboxamide to the methyl group was accomplished in three steps and led to the 11-methyl derivative **29** in good yield. After selective cleavage of the MOM ether in **29** and Parikh–Doering oxidation of the alcohol,[32] the resulting aldehyde was subjected to a Wittig reaction under Mukaiyama–Suzuki conditions,[33] leading to 2,3-(*Z*)-enoate **30** in rather low yield.

Following the retrosynthetic plan in Figure 4, Nishiyama and Shimizu reported the synthesis of the extended allyl iodide **14** with the complete C_{12}–C_{27} moiety (Scheme 4).[12b] The *E* double bonds in **14** were to be generated by an HWE olefination of aldehyde **16** with *β*-oxophosphonate **17** (C_{21}=C_{22}) and by a classical Julia olefination between a C_{17} phenyl sulfone and aldehyde **18** (C_{16}=C_{17}), respectively. Aldehyde **18**, which represents the C_{12}–C_{16} part, was again prepared from diester **25**,[30] which was converted to PMP-acetal **31** in four steps. α-Methylenation[31] of aldehyde **31**, followed by reduction and silylation, led to intermediate **32**. Reductive cleavage of the cyclic acetal in **32** proceeded with moderate selectivity, leading to a 5:1 mixture of regioisomers. The primary alcohol was then oxidized to aldehyde **18**.

The exocyclic dihydropyran fragment **16** was prepared according to the Jørgensen protocol,[34] by asymmetric hetero-Diels–Alder (HDA) reaction of isoprene and ethyl glyoxylate in the presence of (*R*)-(+)-BINOL-Al-Me as catalyst and ensuing ester to aldehyde interconversion (no further details were given in the communication). This cycloaddition is known to proceed with high enantiocontrol (up to 97% ee), but the HDA adduct is formed as a 2:1 mixture with the corresponding ene product.[34] (Later on, the HDA reaction between isoprene and methyl glyoxylate reappeared in the total synthesis of Wender,[20] who utilized Mikami's catalyst[35] instead; see Scheme 31.)

The synthesis of the C_{17}–C_{20} subunit (Scheme 4) started with natural (*S*)-malic acid (**33**), which was transformed to methyl ester **34** (no preparation given). Acylation of dimethyl (lithiomethyl)phosphonate with ester **34** afforded *β*-oxophosphonate **17**, which was connected with aldehyde **16** to provide selectively (*E*)-enone **35** in moderate yield. Diastereoselective carbonyl reduction of **35** with L-selectride furnished the desired 20*S*-configuration but evidently led to extensive silyl migration. This would explain the following transformations leading to isopropylidene acetal **36**, which resulted in the loss of orthogonal protective groups at the vicinal C_{19} and C_{20} hydroxy groups. Deprotection of the PMB ether in **36** and phenylsulfonylation of the resulting primary alcohol via the mesylate provided sulfone **37**. The subsequent three-step Julia olefination between **37** and aldehyde **18** led to (*E*)-olefin **38** as the sole product; however, the overall yield of the coupling was unsatisfactory (32% for three steps).[36] To complete the synthesis of key fragment **14**, the silyl ether in coupling product **38** was cleaved and the resulting primary alcohol halogenated via the mesylate.

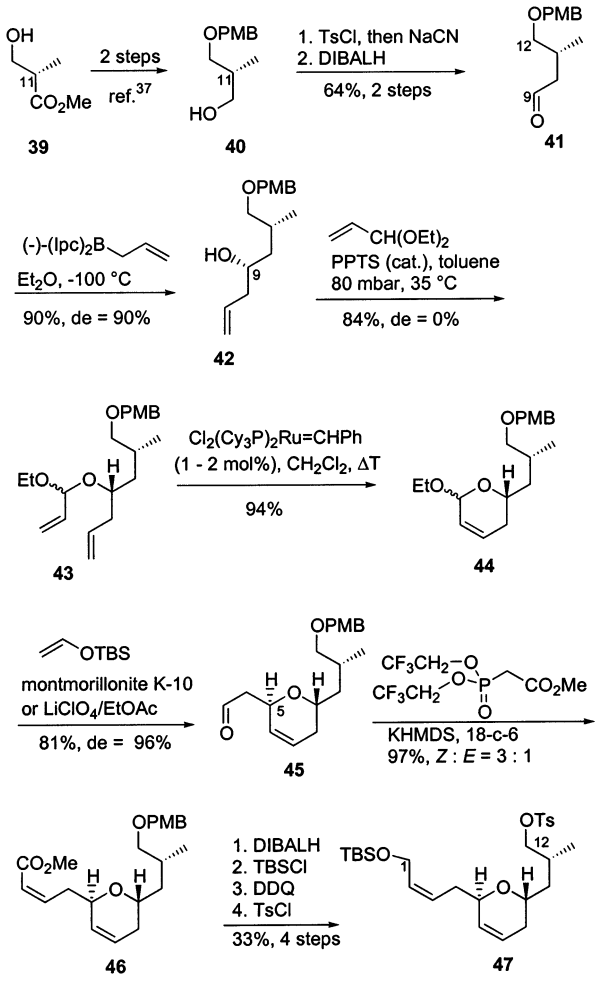
Scheme 4. Nishiyama's Synthesis of C_{12}–C_{27} Allyl Iodide 14



C. First RCM-Based Fragment Syntheses (Mulzer and Ghosh)

In September 1999, Mulzer and Hanbauer reported the first ring-closing metathesis (RCM)[24] approach to the crucial dihydropyran ring in a C_1–C_{12} fragment of laulimalide (Scheme 5).[13a] The synthesis

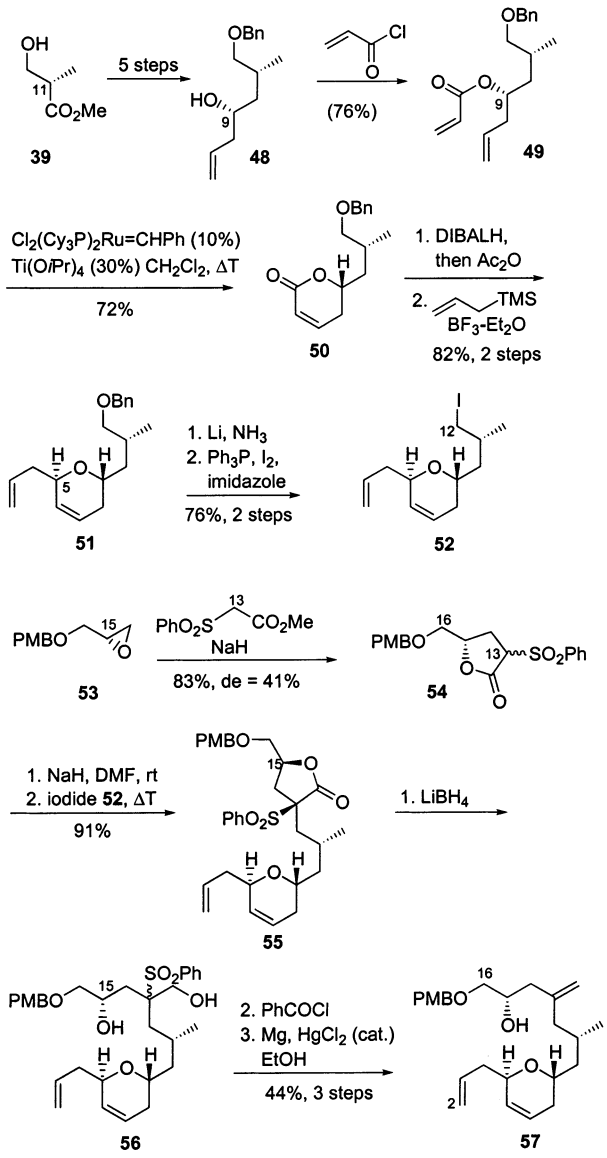
Scheme 5. Mulzer's RCM-Based Route to a C_1−C_{12} Fragment



started from commercially available methyl (*S*)-2-methyl-3-hydroxypropionate (**39**), which was converted to the known alcohol **40**[37] and then homologated to aldehyde **41** via the corresponding cyanide. The C_9 stereocenter was efficiently installed by asymmetric Brown allylation[38a] under "salt-free conditions" at −100 °C,[38b] which led to the homoallylic alcohol **42** in excellent yield. Transacetalization of **42** with acrolein diethylacetal furnished the mixed acetals **43** in 84% yield. This reaction was carried out under azeotropical removal of ethanol by an improved modification of Crimmins' protocol.[39] RCM of dienes **43** with Grubbs' first-generation Ru catalyst proceeded smoothly to give an anomeric mixture of ethyl glycosides **44** in 94% yield.[40] The C_5 stereocenter was generated by Lewis acid-mediated *C*-glycosidation of **44** with vinyl−OTBS in the presence of montmorillonite K-10[26] or lithium perchlorate in ethyl acetate[41] to afford aldehyde **45** as a single isomer. Still−Gennari olefination[42] of **45** led to *Z*-enoate **46**, which was converted to tosylate **47** in four steps. In the end, tosylate **47** was not used in Mulzer's subsequent total syntheses, in contrast to aldehyde **45** (cf. Schemes 12 and 27).

Independently, Ghosh and Wang reported the synthesis of an advanced C_2−C_{16} intermediate of **1**, which features a slightly different RCM strategy to elaborate the dihydropyran ring and a Julia olefination sequence for introduction of the C_{13} *exo*-methylene unit (Scheme 6).[11b] The synthesis began with the conversion of methyl (*S*)-2-methyl-3-hydroxypropionate (**39**) to homoallylic alcohol **48**, which is the benzyl-protected analogue of Mulzer's intermediate **42**. Alcohol **48** was acylated with acryloyl chloride, and acrylate **49** was exposed to Grubbs' first-generation Ru catalyst (10 mol %) in the presence of Ti(OiPr)$_4$ (30 mol %) to provide lactone **50**.[43] To introduce the side chain at C_5, lactone **50** was reduced and the lactol acetylated in situ. Exposure of the resulting acetate to allyltrimethylsilane in the presence of BF_3·OEt_2 furnished product **51** as a single isomer, which was transformed into iodide **52** in two steps. For the simultaneous installation of the C_{13} methylene unit and the C_{15} hydroxyl group, the (*R*)-glycidol-derived PMB ether **53** was treated with the sodium enolate of methyl phenylsulfonyl acetate to generate a 2.4:1 mixture of α-phenylsulfonyllactones **54**, which was deprotonated and alkylated with iodide **52**. Alkylation product **55**, obtained as a single diastereomer in 91% yield, was reduced with $LiBH_4$ to provide 1,4-

Scheme 6. Ghosh's Synthesis of C_2−C_{16} Fragment 57



diol **56**. Perbenzoylation of **56**, followed by treatment of the resulting dibenzoate with magnesium amalgam in ethanol,[44] led to the C_{13}-methylene derivative **57** with concomitant loss of the C_{15} benzoate.

In subsequent work, a C_{16}-aldehyde derived from **57** was connected with a $C_{17}-C_{27}$ phenyl sulfone by standard Julia coupling and served to investigate RCM methodology as the macrocyclization step in the total synthesis of **1**. However, this strategy was not successful (see Figure 2, eq 3).[17c] A slightly modified analogue of **57**, however, was used in the first total synthesis of laulimalide.[17a]

IV. Total Syntheses of Laulimalide and Analogues

A. First Total Synthesis of Laulimalide (Ghosh and Wang)

Ghosh's alternative and finally successful retrosynthetic plan (Figure 5)[17a,c] involved a convergent

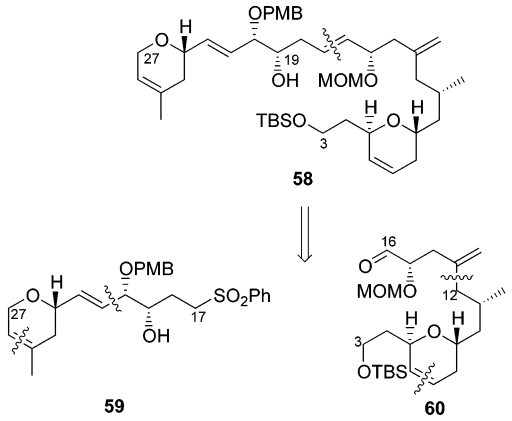
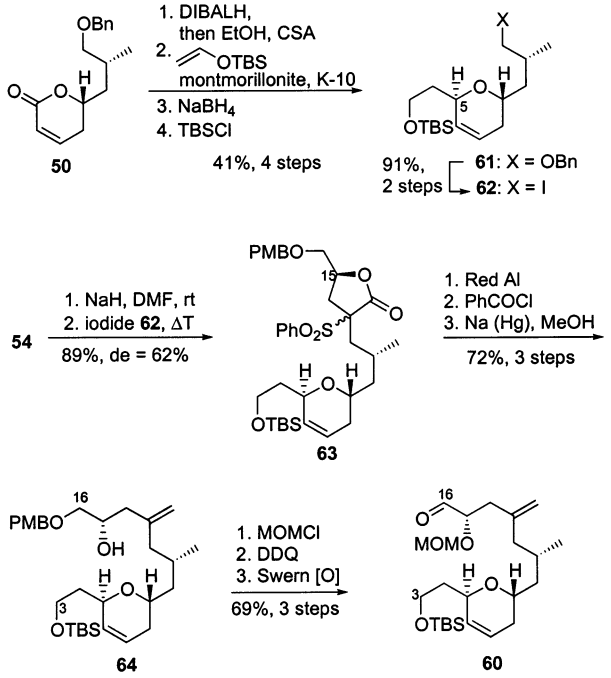


Figure 5. Ghosh's improved retrosynthetic analysis: Fragment assembly by Julia olefination.

assembly of the C_3-C_{16} aldehyde **60** and the $C_{17}-C_{27}$ phenyl sulfone **59** by Julia olefination. The macrocycle was to be obtained either by macrolactonization of a 2,3-*Z seco* acid (Figure 2, eq 3) or by an intramolecular HWE reaction between a C_{19} phosphonoacetate and a C_3 aldehyde (Figure 2, eq 2), derived from main fragment **58**. The sensitive epoxide would be introduced in the penultimate step by applying the Sharpless protocol[45] to the $C_{20}-$OPMB-protected macrocycle. Fragment **60** was to be prepared by slight modification of the sequence outlined in Scheme 6, while coupling partner **59** should come from the addition of an alkynyl anion to a C_{20} aldehyde. The dihydropyran units of both key fragments should be generated by ring-closing olefin metathesis.[24]

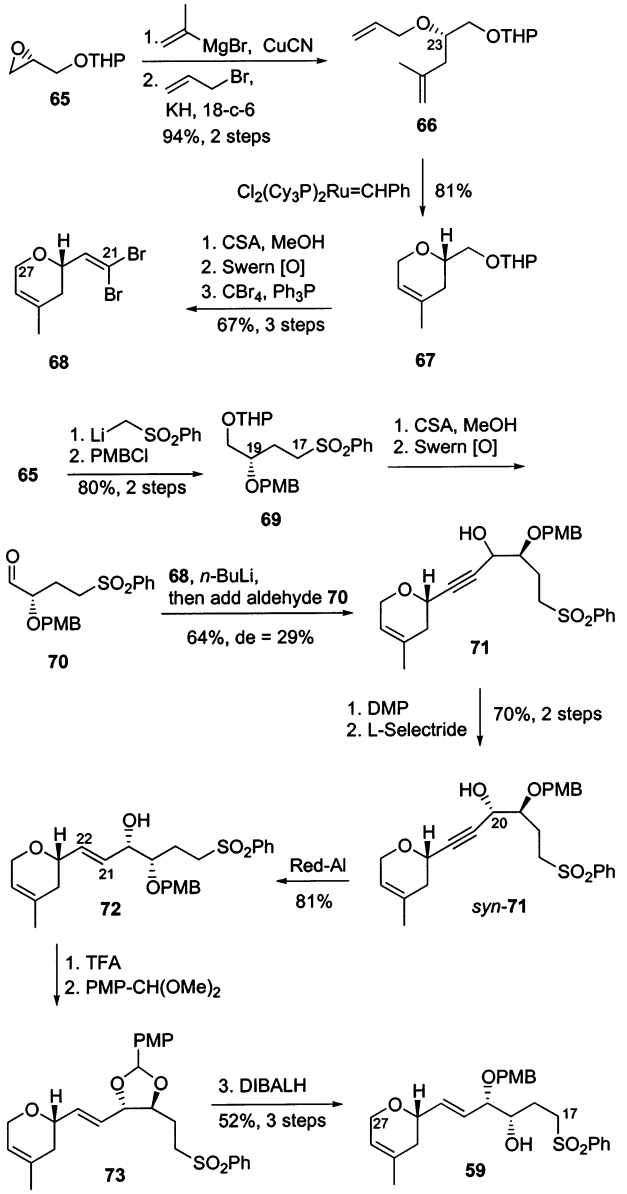
Synthesis of the C3−C16 Fragment. In modification of the sequence in Scheme 6, lactone **50** was converted to iodide **62** in six steps (Scheme 7). Alkylation of α-phenylsulfonyl-lactone **54** with iodide **62** led to intermediate **63** as a 4.2:1 mixture of diastereomers. The C_{13} *exo*-methylene group was elaborated by a slightly modified three-step sequence leading to intermediate **64** in 72% overall yield. Protective group manipulations and Swern oxidation completed the synthesis of key aldehyde **60**.

Scheme 7. Synthesis of C_3-C_{16} Aldehyde 60 via Sulfone Alkylation and Julia Olefination



Synthesis of the C27−C17 Sulfone 59. To obtain the external dihydropyran subunit, Ghosh and Wang relied again on a RCM strategy (Scheme 8).[11c,46] Thus, copper(I)-catalyzed opening of glycidyl ether **65** with isopropenylmagnesium bromide followed by allylation of the resulting homoallylic alcohol provided diene **66** in excellent yield. The trisubstituted double bond was smoothly formed with Grubbs' first-generation Ru catalyst in dichloromethane at room temperature to give dihydropyran **67**. Deprotection, followed by Swern oxidation and Corey−Fuchs homologation,[47] led to dibromo olefin **68**. To complete the synthesis of key fragment **59**, glycidyl ether **65** which had already served to obtain enantiopure subunit **68**, was also used to install the C_{19} stereocenter. Thus, treatment of the lithium salt derived from methyl phenyl sulfone with epoxide **65** furnished an alcohol that was protected as PMB ether **69** and was then converted to aldehyde **70** by deprotection and Swern oxidation. Now the stage was set for coupling **70** with the alkynyl anion derived from precursor **68**. Treatment of dibromo olefin **68** with *n*-BuLi followed by reaction of the resulting alkynyl anion with aldehyde **70** proceeded with low stereoselectivity (syn:anti = 1.8:1) in 64% yield. The mixture of the C_{20} epimeric alcohols **71** was oxidized with Dess−Martin periodinane (DMP) to give an alkynyl ketone, which was reduced with L-selectride to deliver *syn*-**71** as a single diastereomer. Selective reduction of the triple bond in *syn*-**71** with Red-Al secured the $C_{21}-C_{22}$ *E* geometry and furnished allylic alcohol **72**—a regioisomer of target compound **59**—in 81% yield. To shift the $C_{19}-$OPMB group to the vicinal hydroxy group, the PMB ether in **72** was removed with TFA and the resulting diol was transformed to 4-methoxybenzylidene acetal **73**, which was regioselectively reduced with DIBALH to the desired $C_{20}-$OPMB ether **59** in 52% overall yield from regioisomer **72**. The observed

Scheme 8. Synthesis of $C_{17}-C_{27}$ Phenyl Sulfone 59

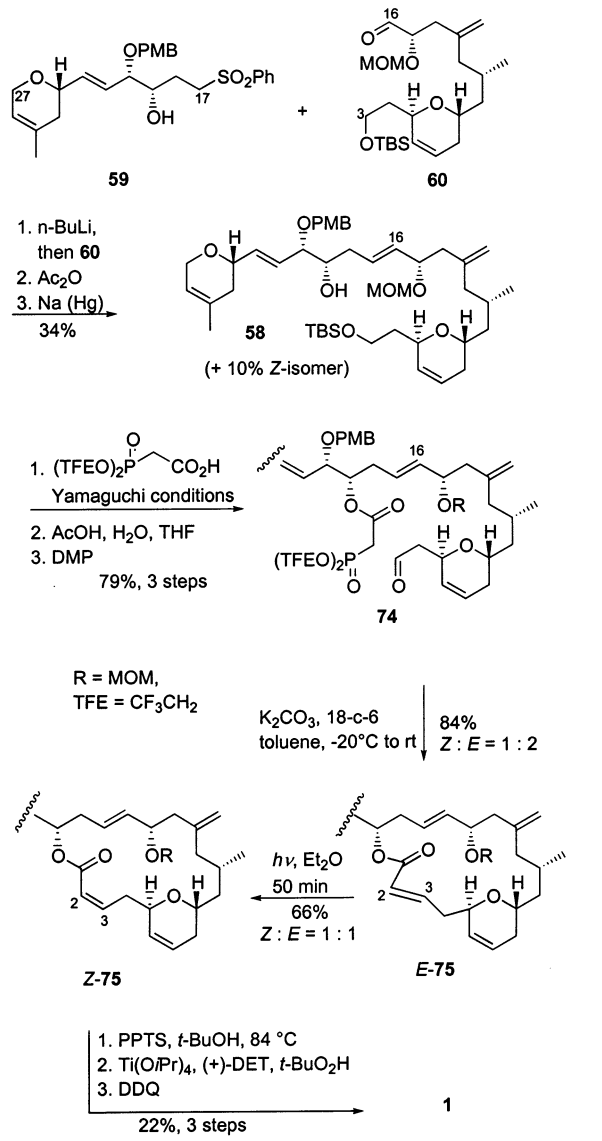


regioselectivity of this reduction is postulated to arise from stabilization of Al chelation by the sulfone oxygens.

Fragment Coupling and Completion of the Synthesis of 1. For the crucial Julia coupling, γ-hydroxy-sulfone **59** was lithiated and the resulting dianion treated with aldehyde **60**. Peracetylation of the intermediate β,γ-dihydroxysulfones followed by exposure to sodium amalgam furnished a 3.4:1 mixture of olefination products, from which the desired isomer **58** was separated in 34% yield (Scheme 9).

Starting from **58** and several close analogues, attempts were made to construct the macrocycle with C_2-C_3 *Z* geometry: RCM of a $C_{19}-O$-acryloyl 5-allyl-substituted analogue led to decomposition (Figure 2, eq 1),[17c] and Yamaguchi macrocyclization of a 2,3-*Z*-19-hydroxy *seco* acid was accompanied by extensive *Z*/*E* isomerization (*Z*:*E* ≈ 1:2).[17b,48] Finally, encouraged by the successful installation of a 2,3-*Z*-enoate in the macrolactone moiety of phorboxazole,[50] an

Scheme 9. Fragment Coupling and Completion of Ghosh's First Synthesis of 1



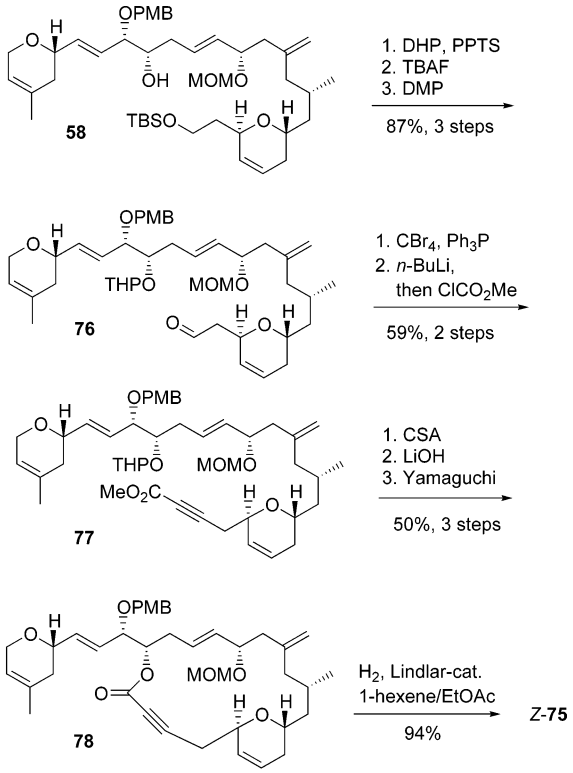
intramolecular HWE olefination by Still–Gennari's protocol[42] was carried out to close the 2,3-double bond. Toward this aim (Scheme 9), **58** was acylated with bis(2,2,2-trifluoroethyl)phosphonoacetic acid under Yamaguchi conditions.[51] Selective removal of the TBS group with aqueous acetic acid in THF and oxidation with Dess–Martin periodinane furnished cyclization precursor **74** in 79% overall yield. However, treatment of **74** with K_2CO_3 in the presence of 18-crown-6 in toluene at −20 to 0 °C afforded an unfavorable 1:2 mixture of *Z*-**75** and *E*-**75** in 84% combined yields. Attempts to improve the amount of *Z* isomer by changing the protecting group at $C_{20}-O$ or by using Ando's variant[52] of the HWE reaction were not successful. Finally, the overall yield of *Z*-**75** was improved from 28% to 47% by UV irradiation of *E*-**75** in Et_2O for 50 min. This procedure, however, led to partial decomposition and produced a 1:1 mixture of isomers **75** in 66% yield. The fully protected macrolactone *Z*-**75** was then converted to **1** in three steps. Thus, selective cleavage of the $C_{15}-O-$MOM group with PPTS in *tert*-butyl alcohol at 84 °C (45% yield), followed by SAE with (+)-diethyl tar-

trate,[45] and removal of the remaining allylic C_{20}−OPMB ether with DDQ (48% yield, two steps) finally provided the first synthetic sample of (−)-laulimalide in 22% overall yield from *Z*-**75**.

B. Stereocontrolled Introduction of the 2,3-*Z*-Enoate (Ghosh)

Some months later, Ghosh and Wang[17b,c] came up with a stereocontrolled installation of the 2,3-*Z*-enoate (Scheme 10). Thus, key fragment **58** was converted to aldehyde **76** by protective group manipulation and oxidation with Dess−Martin periodinane. Aldehyde **76** was transformed to alkynoate **77** via Corey−Fuchs homologation.[47] Removal of C_{19}-THP group followed by ester hydrolysis afforded the *seco* hydroxy acid, which was cyclized to macrolide **78** under Yamaguchi's conditions.[51] Lindlar hydrogenation of the triple bond[53] provided macrolactone *Z*-**75** as a single isomer in 94% yield.

Scheme 10. Ghosh's Improved Synthesis of *Z*-75 by Stereoselective Introduction of the 2,3-*Z*-Enoate



C. Last Step Introduction of the Epoxide

Mulzer[18a] and Paterson[19] disclosed two total syntheses of **1** which featured the same endgame. In view of the easy isomerization of **1** to **2**, both authors avoided protective group manipulations at the C_{20}-OH function after the introduction of the C_{16}−C_{17} epoxide and applied regio- and stereoselective Sharpless asymmetric epoxidation (SAE)[45] of the unprotected macrocycle **79** as the last step. This strategy was also used in Mulzer's following syntheses[18b,c] and in the syntheses by Wender[20] and Nelson.[23]

1. Mulzer's First Approach

With respect to the retrosynthetic bond disconnections, the approach of Mulzer and Öhler (Figure 6) is similar to that of Ghosh. An intramolecular Still−Gennari olefination[42] of phosphonate aldehyde **80** (an analogue of Ghosh's advanced synthetic intermediate **74**) was intended for macrocyclization and introduction of the C_2−C_3-*Z*-enoate. An *E*-selective one-step Julia−Kocienski olefination[54] was envisioned for connecting main fragments **60** and **81**, and to simplify the preparation of the deprotected macrocycle **79**, C_{17}−C_{27} sulfone **81** and C_3−C_{16} aldehyde **60** were MOM-protected at the C_{20} and C_{15} allylic alcohols. Both dihydropyran rings of **1** were prepared not only by RCM, but also by other methods. Inexpensive compounds from the chiral carbon pool, derived from D-mannitol, D-glucose, and *S*-malic acid, served to procure the subunits **16**, **82**, and **83**.

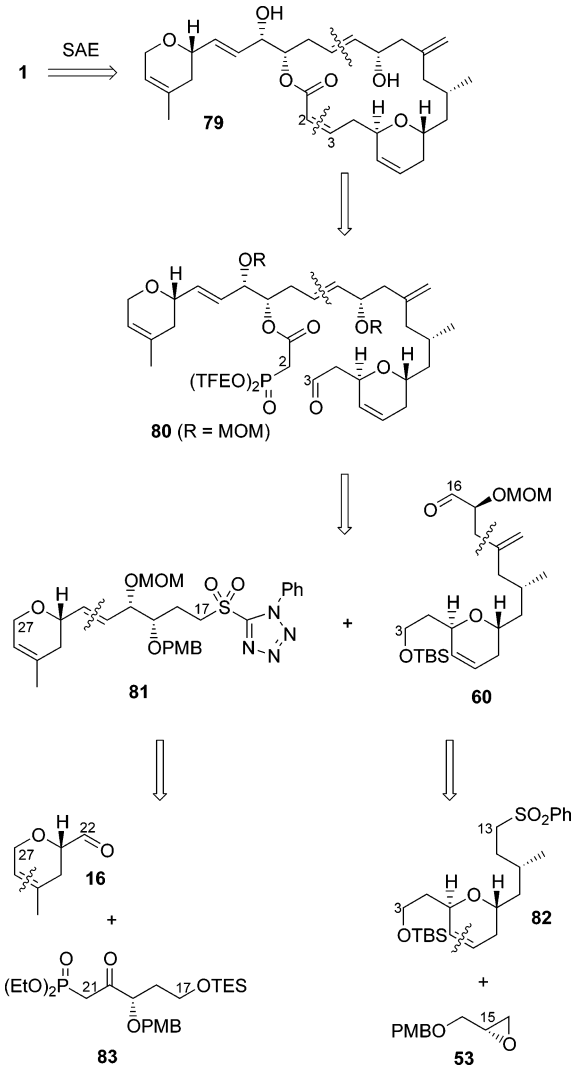
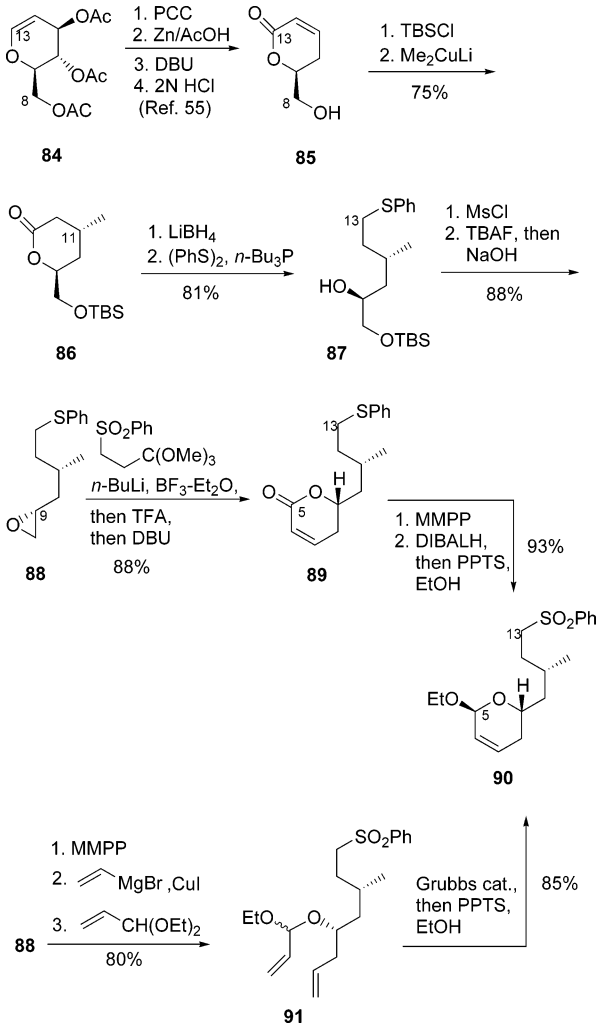


Figure 6. Retrosynthetic analysis of Mulzer and Öhler.

Synthesis of the C3−C16 Fragment. The synthesis of the C_3−C_{16} aldehyde **60**, which also served as a key intermediate in Ghosh's synthesis of **1**, started from the known α,β-unsaturated lactone **85** (Scheme 11), available from tri-*O*-acetyl-D-glucal (**84**) in four high-yielding steps[55] and providing carbons C_8−C_{13} of the laulimalide skeleton. After TBS protection, conjugate *trans*-addition of Me_2CuLi led to methyl derivative **86** as a single diastereomer with correct configuration at C_{11}. To allow inversion at C_9 and introduction of the C_{13}-phenylsulfonyl group

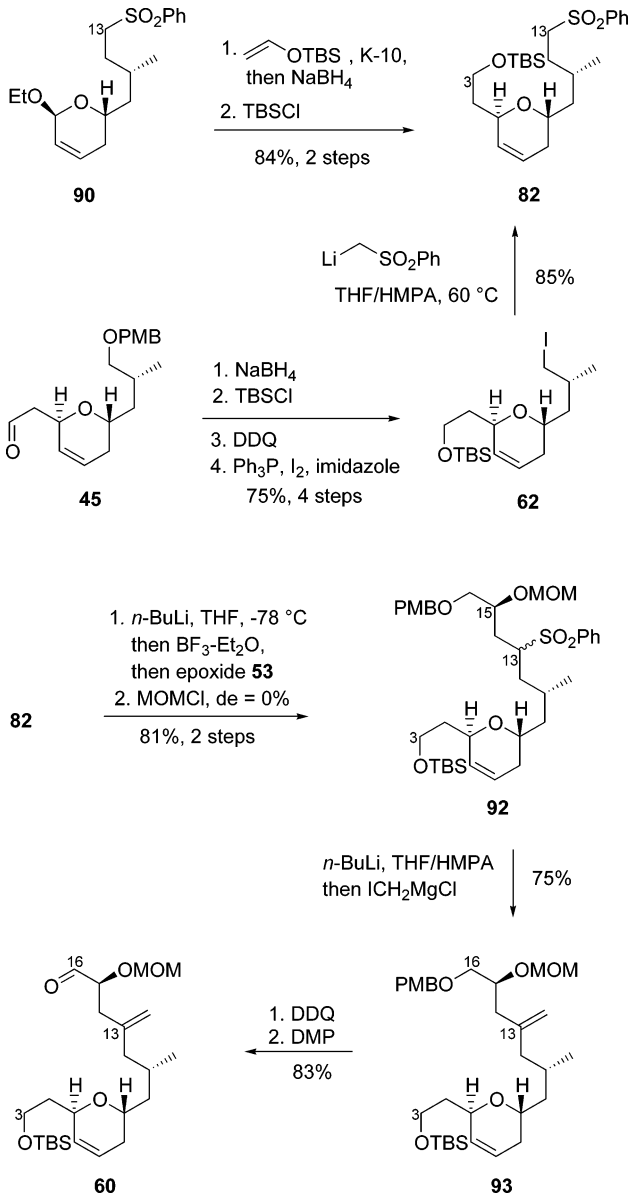
Scheme 11. Two Syntheses of Ethyl Glycoside 90



lactone, **86** was reduced and the primary hydroxy group of the resulting 1,5-diol selectively protected as the phenylsulfide **87**. Mesylation followed by desilylation and ring closure under inversion at C_9 furnished epoxide **88**, from which the dihydropyran ring was elaborated in comparable overall yields either by Ghosez's one-pot lactonization[56] or by the well-proven RCM protocol[13a] (cf. Scheme 5). Thus, borontrifluoride etherate-mediated addition of the lithium salt derived from methyl 3-phenylsulfonyl-orthopropionate[57] to epoxide **88** followed by acid-catalyzed cyclization and base-induced elimination of phenylsulfinic acid led to lactone **89**, which was converted to ethyl glycoside **90**. Alternatively, epoxide **88** was also smoothly converted into the RCM precursor **91** and then to dihydropyran **90** by the four-step sequence shown in Scheme 11.

The conversion of intermediate **90** to key aldehyde **60** is outlined in Scheme 12. Stereoselective *C*-glycosidation of **90** with vinyl-OTBS, followed by reduction and TBS protection, provided C_3-C_{13} subunit **82** in 84% overall yield from **90**. Later,[18d] sulfone **82** was also conveniently prepared from previous intermediate **45** (cf. Scheme 5). Toward this end, aldehyde **45** was converted to iodide **62** in four conventional steps. Treatment of **62** with the anion derived from methyl phenyl sulfone and *n*-BuLi led to sulfone **82** in 85% yield.

Scheme 12. Two Syntheses of Phenyl Sulfone 82 and Completion of Key Aldehyde 60



Further elaboration of the C_3-C_{16} fragment involved deprotonation of sulfone **82**, followed by $BF_3 \cdot Et_2O$-mediated addition to (*S*)-4-methoxybenzyl glycidyl ether (**53**), and MOM protection, which led to a 1:1 mixture of C_{13} epimeric sulfones **92**. The C_{13} *exo*-methylene group was introduced by treating the lithium salt from sulfones **92** with the carbenoid intermediate prepared in situ from isopropylmagnesium chloride and diiodomethane following a slight modification of Julia's procedure.[58] Methylenation product **93**, obtained in 75% yield, was then transformed to key aldehyde **60** in two steps.

Novel Synthesis of the C3−C16 Fragment via Chirally Catalyzed Ene Reaction. Very recently, Mulzer and Pitts disclosed a highly efficient route to C_3-C_{16} fragment **60**.[13e] In the novel approach, the C_{15} stereocenter was created by a chirally catalyzed ene reaction[59] between olefin **95** and ethyl glyoxylate **94** (Figure 7).

The synthesis (Scheme 13) began with the allylation of oxazolidinone **96** with 3-bromo-2-methyl-

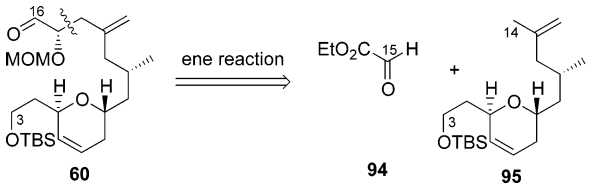
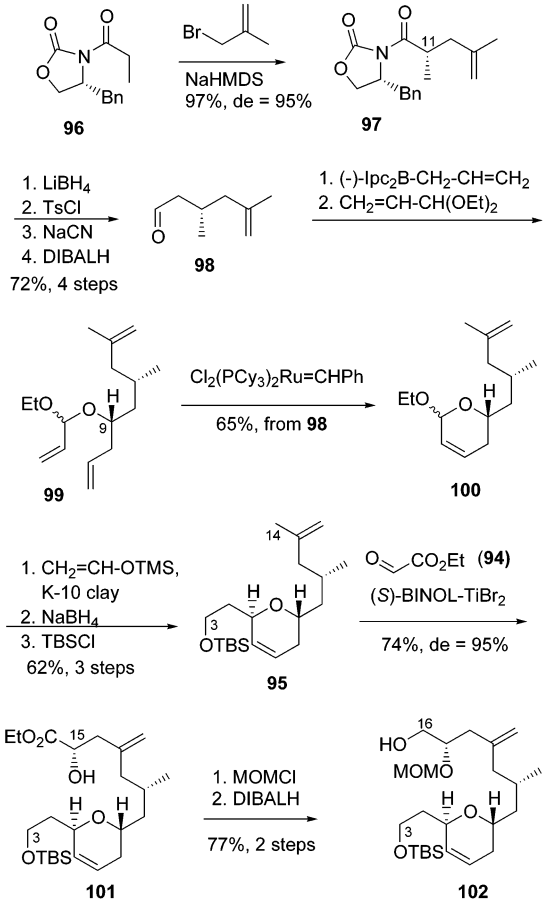


Figure 7. Improved construction of C_3-C_{16} fragment **60** via ene reaction.

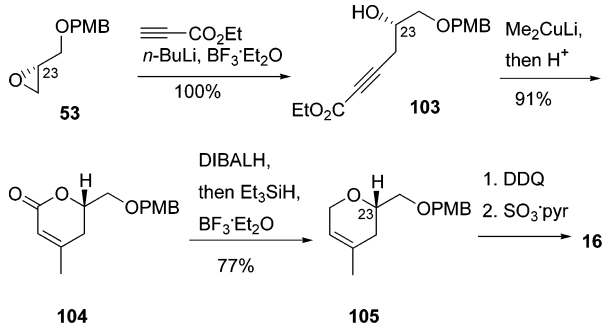
propene to provide adduct **97** selectively (97%, de = 95%). After reductive removal of the auxiliary, the resulting alcohol was homologated to aldehyde **98** via the nitrile. Brown allylation[38] of **98** generated a homoallylic alcohol with the desired stereochemistry at C_9, which was elaborated to key intermediate **95** via the previous protocol.[13a] Interestingly, RCM of triene **99** proceeded to the desired dihydropyran **100** without interference from the C_{13} methylene group. Stereoselective *C*-glycosidation of **100** was performed using commercially available trimethyl vinyloxysilane as the nucleophile and montmorillonite K 10 as the Lewis acid activator.[26] The resulting aldehyde was then converted to key compound **95** in two steps. Treatment of **95** with ethyl glyoxylate in the presence of a catalytic amount of (*S*)-BINOL−$TiBr_2$[59a] provided the ene product **101** in 74% yield with excellent stereocontrol (de = 95%). MOM protection and ester reduction furnished alcohol **102**.

Scheme 13. Novel Synthesis of C_3-C_{16} Fragment 102



Synthesis of the C17−C27 Sulfone 81. Following the retrosynthetic plan in Figure 6, the carbon skeleton of $C_{17}-C_{27}$ fragment **81** was assembled by an *E*-selective HWE olefination of aldehyde **16** with the chiral *β*-oxophosphonate **83** derived from inexpensive (*S*)-malic acid. Altogether, three approaches to aldehyde **16** were elaborated by Mulzer's team,[13b,d] two of which were based on RCM. In the first approach (Scheme 14), glycidyl ether **53** was opened

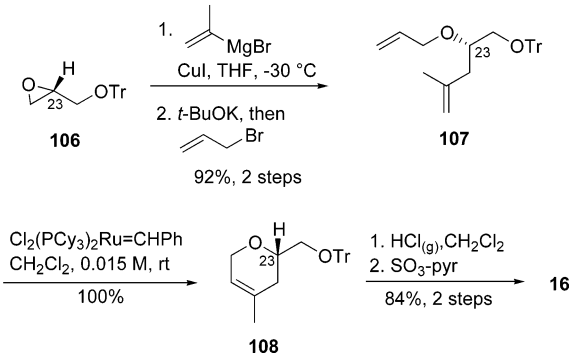
Scheme 14. Synthesis of Aldehyde 16 by a Non-RCM Strategy



with the Li salt of ethyl propiolate in the presence of $BF_3{\cdot}Et_2O$ to give alcohol **103**. Stereoselective conjugate addition of Me_2CuLi and in situ cyclization of the hydroxy ester furnished lactone **104**. Reduction of **104** to the lactol and in situ removal of the anomeric hydroxy group provided dihydropyran **105**, which was transformed to aldehyde **16** in two steps.

The second, more convenient approach to aldehyde **16** (Scheme 15)[13b] started from glycidyl trityl ether

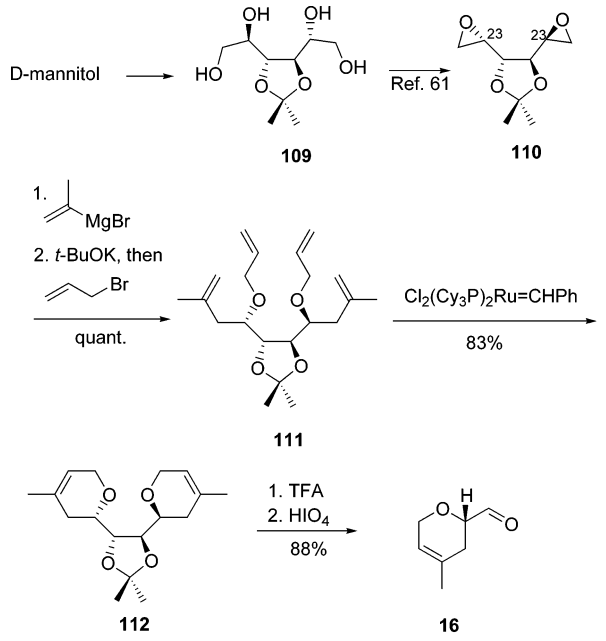
Scheme 15. Mulzer's First RCM Approach to Aldehyde 16



106, which was opened with isopropenylmagnesium bromide under copper(I) catalysis. The resulting alcohol was allylated to diene **107** in high overall yield. Despite the presence of a *gem*-disubstituted double bond, diene **107** furnished dihydropyran **108** quantitatively on exposure to 2−3 mol % of Grubbs' first-generation Ru catalyst under high dilution at room temperature. Deprotection of **108** under nonaqueous conditions and ensuing oxidation led to aldehyde **16**.[46]

In Mulzer's third approach to aldehyde **16** (Scheme 16),[13d] a two-directional synthesis[60] was applied to the known diepoxide **110**,[61] readily available from the D-mannitol-derived tetraol **109**. Compound **110** was transformed into tetraene **111**, which on RCM under high dilution gave bis-dihydropyran **112** in 83% yield. No medium-ring-sized cycloolefins were formed across the central acetonide ring, which under these condi-

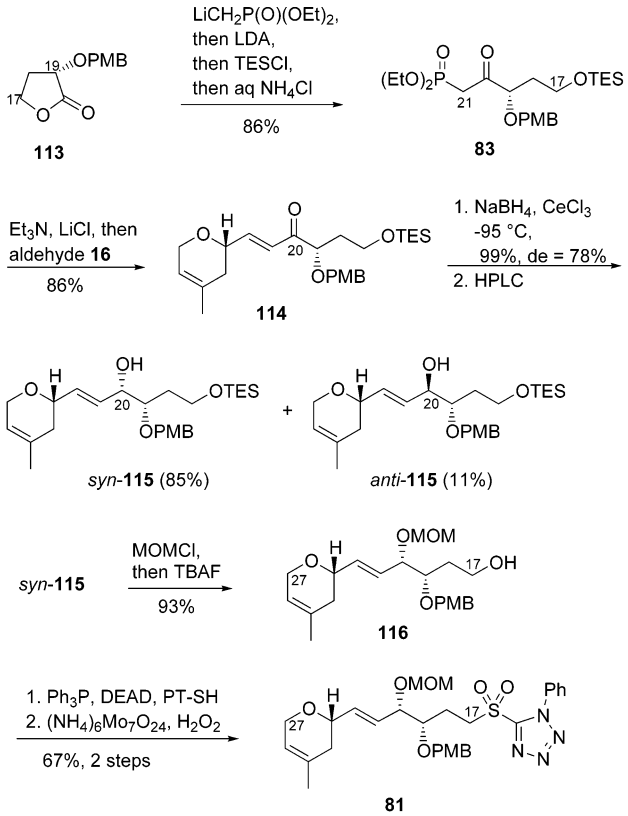
Scheme 16. Synthesis of Aldehyde 16 by Two-Directional RCM Strategy



tions served as a barrier to crossover metathesis.[62] Deprotection and cleavage of the resulting vicinal diol in low-boiling solvents furnished the volatile aldehyde **16** in high yield and purity.

The orthogonally protected phosphonate **83**, which provided the C_{19} stereocenter of **1**, was prepared in 86% yield from the (*S*)-malic acid-derived lactone **113**[63] and diethyl methanephosphonate in one pot (Scheme 17).[64] Subsequent olefination[65] of **83** with aldehyde **16** afforded enone **114** *E*-selectively in high

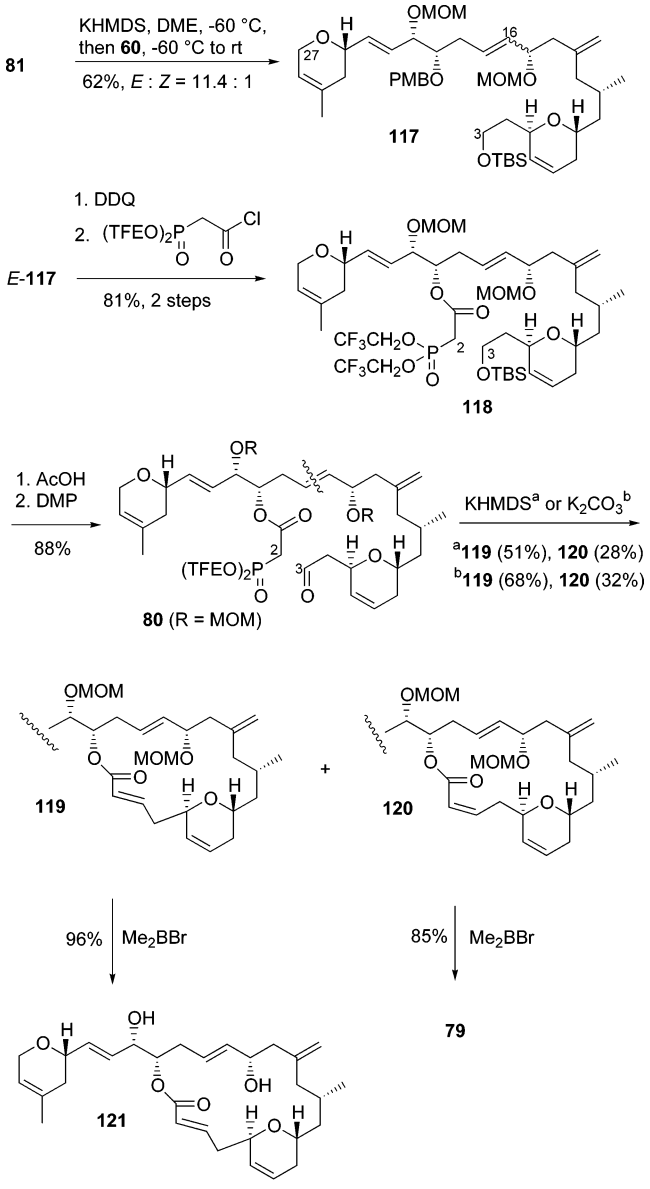
Scheme 17. Synthesis of C_{27}−C_{17} Sulfone 81



yield. Luche reduction[66] of the C_{20} carbonyl group in **114** at −95 °C led to an 8:1 mixture of C_{20} epimeric alcohols in favor of the required epimer *syn*-**115** in 99% combined yields. After separation by HPLC, *anti*-**115** was recycled by oxidation and *syn*-**115** was converted to the primary alcohol **116**. Treatment of **116** with 1-phenyl-1*H*-tetrazole-5-thiol (PT-SH) under Mitsunobu conditions[67] followed by oxidation of the thioether led to key fragment **81**, ready for connection to C_3−C_{16} fragment **60**.

Fragment Assembly and Completion of the Synthesis. The crucial fragment assembly (Scheme 18) was performed via a one-step Julia−Kocienski

Scheme 18. Fragment Union by Julia−Kocienski Olefination and Macrocyclization by Intramolecular Still−Gennari Olefination



olefination.[54] The potassium salt of sulfone **81** was treated with aldehyde **60** to provide olefins *E*-**117** and *Z*-**117** in 62% combined yields as an 11.4:1 mixture, from which the *E* isomer was isolated in 57% yield. When the reaction was performed in THF, the overall yield rose to 71% but the *E*/*Z* ratio dropped to

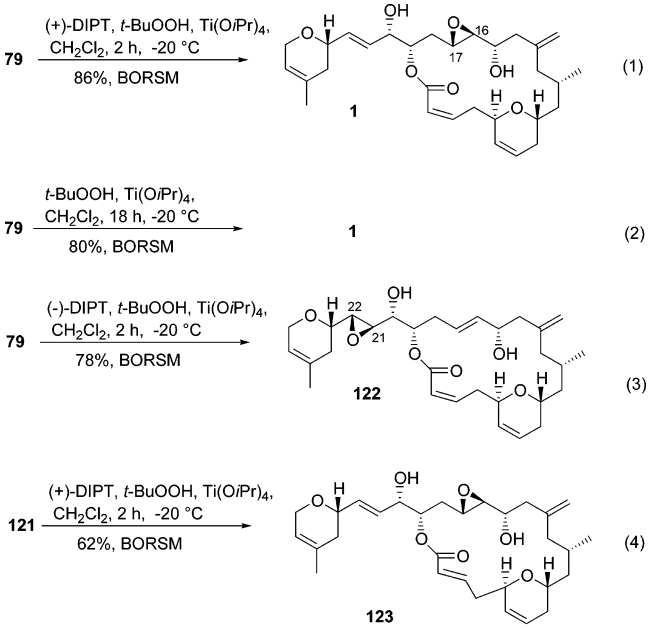
2.8:1.[18d] The PMB ether in *E*-**117** was cleaved, and the resulting alcohol was acylated with bis(2,2,2-trifluoroethoxy)phosphonoacetyl chloride[68] to provide phosphonate **118**, which was converted to the cyclization precursor **80** by acid-promoted cleavage of the silyl ether and oxidation with Dess−Martin periodinane (Scheme 18). The crucial intramolecular HWE olefination of phosphonate aldehyde **80**, performed under Still's optimized conditions[42] and avoiding an excess of base (0.95 equiv of KHMDS, 6 equiv of 18-crown-6, THF, 50 min, −78 °C), disappointingly led to a mixture (*Z*:*E* = 1:1.8) of macrocycles **119** and **120** in 80% combined yield. Later,[18d] the olefination was performed with K_2CO_3/18-crown-6 in toluene *at room temperature*, conditions that improved the *Z*-selectivity during phorboxazole ring closure.[50c] This procedure provided the olefination products quantitatively but did not improve the isomer ratio (*Z*:*E* = 1:2.1). Separation of **119** and **120**, followed by simultaneous removal of both MOM groups with dimethylboron bromide,[69] generated the 16,17-deoxylaulimalides **79** and **121** in 96% and 85% yield, respectively.

Exposure of 2,3-*Z*-isomer **79** to Sharpless' asymmetric epoxidation (SAE)[45] with natural (+)-diisopropyl tartrate (DIPT) for 2 h at −20 °C proceeded with clean epoxidation at the "matched" allylic site to give a 2:1 mixture of (−)-**1** and unreacted compound **79**, from which **1** was isolated in 86% yield, based on recovered starting material (Scheme 19, eq 1).

2. Synthesis of Laulimalide Analogues (Mulzer)

In subsequent work,[18d] Mulzer's group disclosed the results of additional epoxidation experiments with the deoxylaulimalides **79** and **121** (Scheme 19, eqs 2−4). When the epoxidation of **79** was repeated under the same conditions, however, without the tartrate additive (Scheme 19, eq 2), **1** was formed selectively, albeit in a distinctly slower reaction. This result underscores that there is an intrinsic preference for the 16,17-epoxidation, which means that epoxidation with natural tartrate represents the case in which substrate and reagent control are "matched" to each other. To test the "mismatched" case also, SAE of **79** with (−)-DIPT was also investigated (Scheme 19, eq 3). This reaction led to the "unnatural" 21,22-epoxide **122** regio- and stereoselectively, underlining the power of the SAE reaction. Epoxidation of *E*-isomer **121** in the presence of (+)-DIPT under the same conditions furnished the expected 16,17-epoxide **123**, however, in lower yield (Scheme 19, eq 4).

Scheme 19. Regio- and Stereoselective Epoxidation of Deoxylaulimalides 79 and 121



3. Ring Closure by Mitsunobu-Lactonization (Paterson's Approach)

In contrast to the previous syntheses, Paterson's plan (Figure 8)[19] aimed for fragment assembling by asymmetric aldol reaction of C_1-C_{14} methyl ketone **126**, already containing the *Z*-enoate, and $C_{27}-C_{15}$ aldehyde **125**. The C_{19} stereocenter in *seco* acid **124** was to be inverted by a Mitsunobu-type[67] macrolactonization. This protocol had been applied successfully in Paterson's previous synthesis of the macrocyclic core of **1**[15] and has served to install the sensitive (*Z*)-enoate without *Z*/*E* isomerization. Aldehyde **125**, in turn, was to be prepared by aldol reaction of aldehyde **16** with C_{20} methyl ketone **127**.

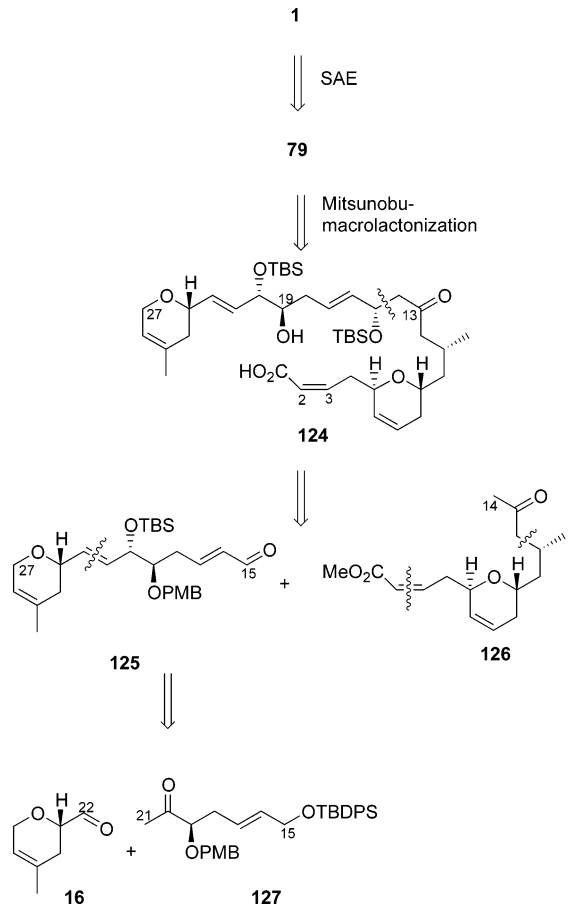
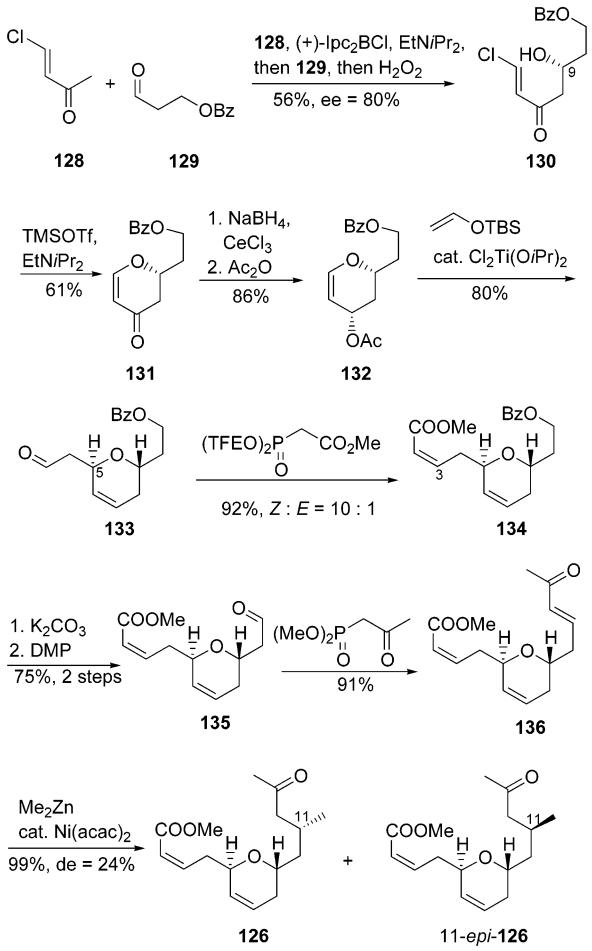


Figure 8. Retrosynthetic analysis of Paterson et al.

Synthesis of the C1−C14 Fragment 126. The synthesis of key fragment **126** (Scheme 20) started with the construction of the *trans*-disubstituted dihydropyran unit of **1** by asymmetric boron aldol

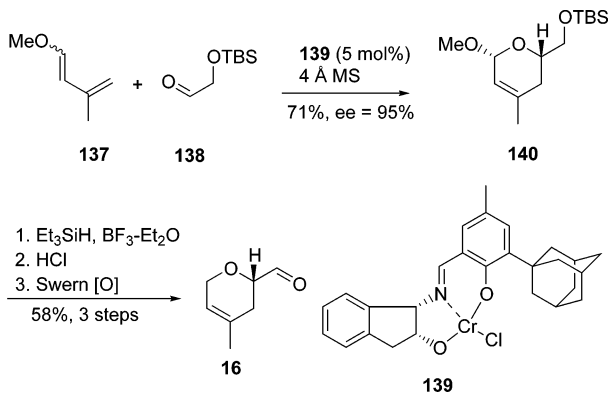
Scheme 20. Synthesis of C_1-C_{14} Methyl Ketone 126



methodology. Thus, reaction of the boron enolate derived from β-chlorovinyl methyl ketone (**128**) with aldehyde **129** provided intermediate **130** in 56% yield, installing the C_9 stereocenter with 80% ee. Alcohol **130** was cyclized to the vinylogous lactone **131** in 61% yield. After conversion to acetate **132**, the C_5 stereocenter was introduced by a Ferrier-type reaction with vinyl-OTBS to provide aldehyde **133** in 80% yield. The aldehyde, which had already been used for the syntheses of swinholide A[70a,b] and scyptophycin,[70c] was then converted into *Z*-enoate **134** by Still–Gennari olefination[42] under careful control of the reaction conditions. Homologation of aldehyde **135**, obtained in two steps from **134**, in a further HWE reaction provided *E*-enone **136** stereoselectively. 1,4-Addition of Me_2Zn to **136** in the presence of catalytic $Ni(acac)_2$[71] generated a separable mixture of adducts **126** and 11-*epi*-**126** with only a slight excess of the desired 11*R*-isomer **126** (**126**:11-*epi*-**126** = 1.6:1).

Synthesis of the C15–C27 Fragment 125. In contrast to the previous syntheses of Ghosh and Mulzer, Jacobsen's hetero-Diels–Alder (HDA) reaction[72] was used for the enantioselective construction of the exocyclic dihydropyran subunit (Scheme 21). Thus, exposure of a neat mixture of diene **137** and aldehyde **138** in the presence of molecular sieves to preformed chromium(III) Lewis acid catalyst **139** (5 mol %) gave HDA adduct **140** in 91% yield and with 95% ee. Reductive removal of the anomeric methoxy group followed by deprotection and Swern oxidation

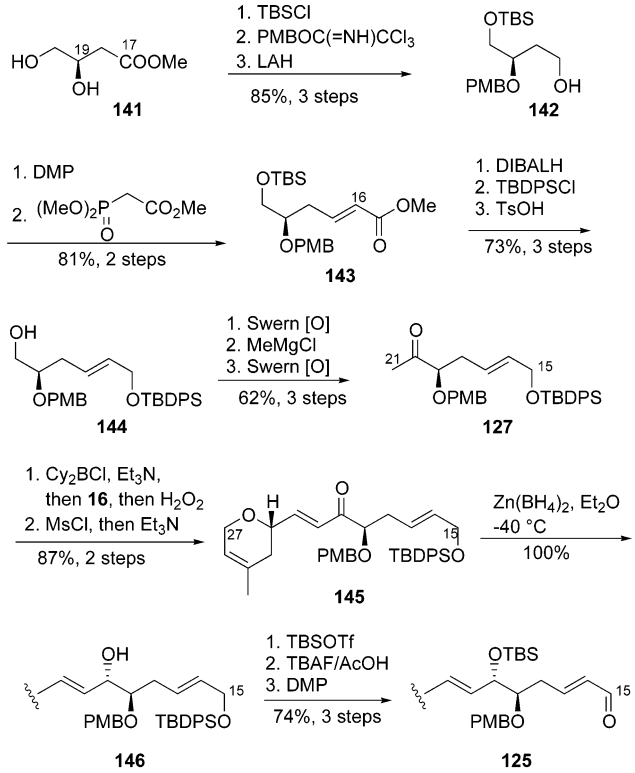
Scheme 21. Synthesis of Aldehyde 16 by HDA Chemistry



furnished aldehyde **16**, which was to be connected with methyl ketone **127** according to the retrosynthetic plan.

The synthesis of methyl ketone **127** (Scheme 22) started from unnatural dimethyl (*R*)-malate, which

Scheme 22. Synthesis of Methyl Ketone 127 and Completion of $C_{27}-C_{15}$ Fragment 125

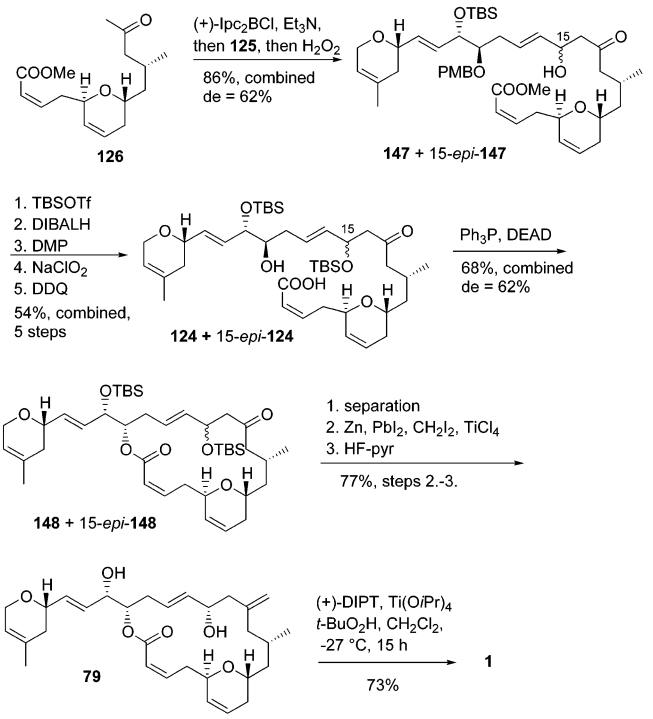


was converted to alcohol **142** via diol **141**.[73] The $C_{16}-C_{17}$ double bond was efficiently introduced by HWE olefination of the aldehyde derived from **142** with trimethyl phosphonoacetate, and (*E*)-enoate **143** was then transformed to methyl ketone **127** by a series of conventional steps. Boron-mediated aldol coupling of **127** with aldehyde **16** followed by base-induced elimination of the adduct via the corresponding mesylate provided (*E*)-enone **145** as a single stereoisomer. Chelation-controlled reduction of **145** with $Zn(BH_4)_2$ selectively produced *anti*-alcohol **146**. After TBS protection, the primary TBDPS ether was cleaved using TBAF buffered with acetic acid. Oxida-

tion of the resulting alcohol with Dess−Martin periodinane completed the synthesis of $C_{27}-C_{15}$ aldehyde **125**, ready for the connection to the C_1-C_{14} fragment **126**.

Fragment Assembly and Completion of the Total Synthesis. The aldol coupling of fragments **125** and **126**, mediated by (+)-Ipc_2BCl/Et_3N,[74] furnished an inseparable 4:1 mixture of alcohols **147** and 15-*epi*-**147** (for an approach with improved stereocontrol, see Scheme 44).[23] Without separation, this mixture was converted in five steps to a mixture of *seco* acid **124** and its C_{15} epimer. As the direct hydrolysis of the methyl ester resulted in 2,3-*Z*/*E*-isomerization, the three-step reduction/oxidation sequence shown in Scheme 23 was performed to

Scheme 23. Fragment Connection and Completion of the Total Synthesis of 1



produce acids **124** and 15-*epi*-**124**. Mitsunobu-type[67] macrolactonization of this mixture of hydroxy acids provided macrolide **148** without isomerization of the (*Z*)-enoate, along with the now separable C_{15} epimer. Introduction of the C_{13} *exo*-methylene via the Takai reagent[75] followed by deprotection of the two allylic TBS ethers led to deoxylaulimalide **79**, which was epoxidized selectively to (−)-**1** by SAE[45] in the presence of (+)-DIPT.

D. Chiral Allylsilane Addition

1. For Macrocyclization (Mulzer and Enev)

Soon after, a fully stereocontrolled route to laulimalide was reported by Mulzer and Enev.[18b] Retrosynthetically (Figure 9), the carbon skeleton of deoxylaulimalide **79** was to be assembled from phosphonoacetate **150** and aldehyde **151**, generating the sensitive 2,3-*Z*-enoate now by an *intermolecular* Still−Gennari olefination.[42] In a hitherto unprecedented approach, macrocyclization was to be performed by closing *seco* compound **149** via an *intramolecular* allyl transfer, the stereochemistry at C_{15} being controlled by a chirally substituted acetal.[76−79]

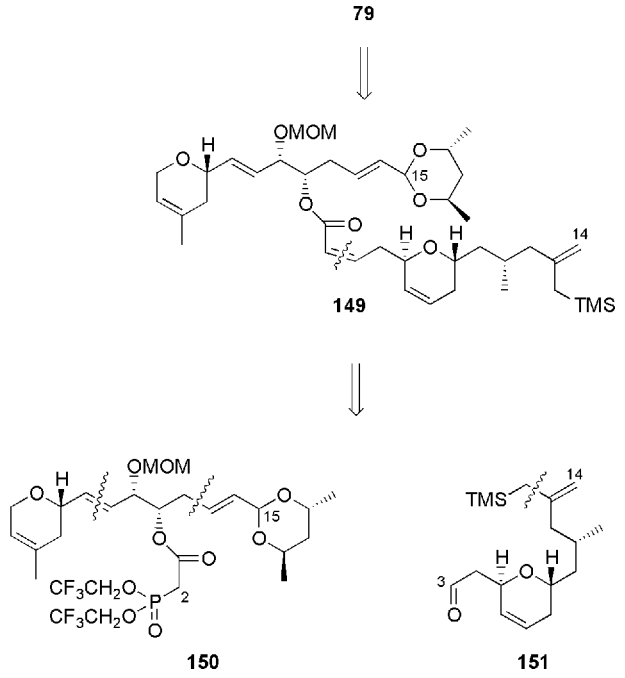
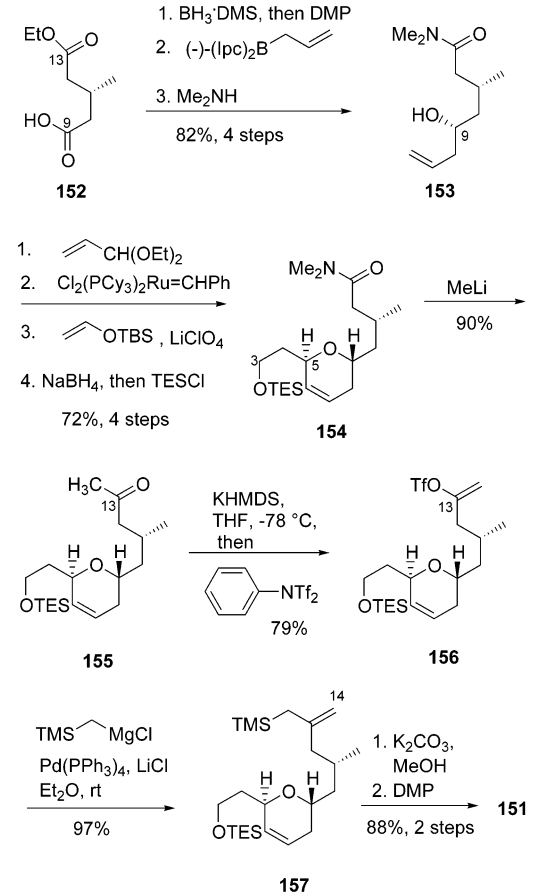


Figure 9. Retrosynthetic analysis of Mulzer and Enev.

Synthesis of Allylsilane 151. The synthesis of C_3-C_{14} fragment **151** started from commercially available ethyl hydrogen (*R*)-3-methylglutarate **152** (Scheme 24), which provided the C_9-C_{13} segment of

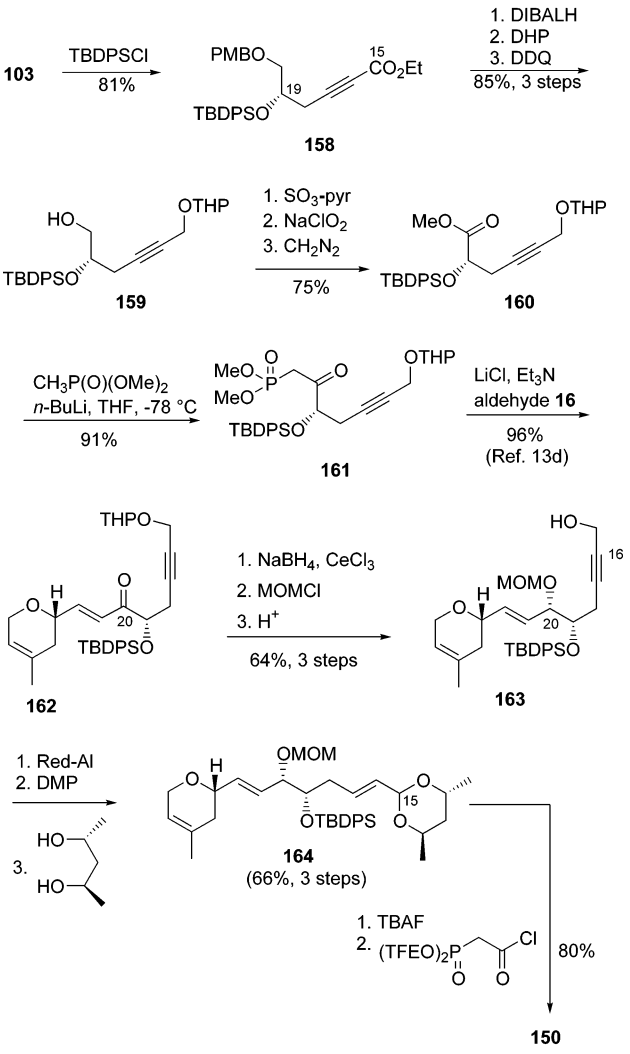
Scheme 24. Synthesis of C_3-C_{14} Allylsilane 151



1. Acid **152** was transformed to homoallylic alcohol **153** in four steps, the C_9 stereocenter being installed via Brown's asymmetric allylboration.[38] Elaboration of the dihydropyran ring via RCM strategy and stereoselective introduction of the two-carbon side chain at C_5 was performed as before,[13a] leading to amide **154**, which was transformed to methyl ketone **155** in high yield. For the introduction of the allylsilane moiety, methyl ketone **155** was converted to the enolate under kinetic control and treated with $PhNTf_2$[80] to provide enoltriflate **156** as a single regioisomer, which was coupled with trimethylsilylmagnesium chloride under Stille's conditions[81] to afford allylsilane **157** in excellent yield. Removal of the TES ether with K_2CO_3/MeOH followed by oxidation with Dess−Martin periodinane led to key aldehyde **151**.

Synthesis of Phosphonoacetate 150. Phosphonate **150** (Scheme 25) was easily derived from a

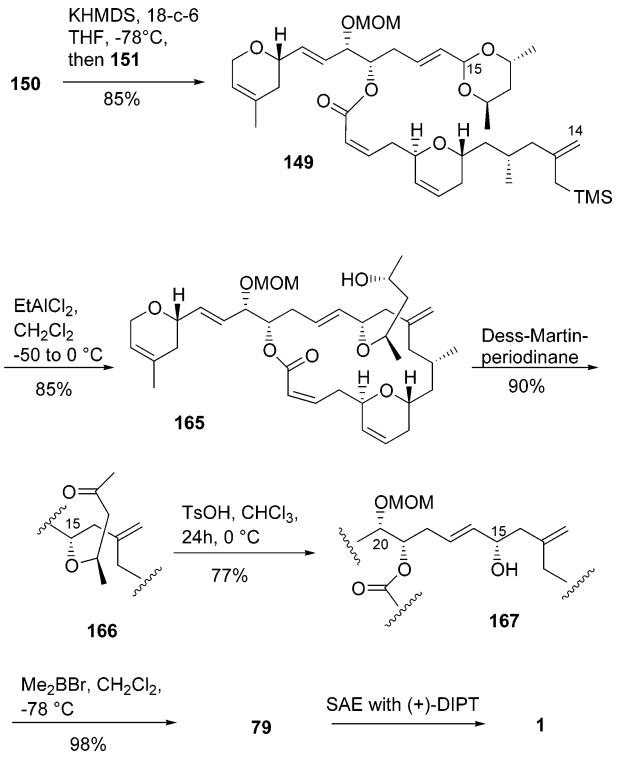
Scheme 25. Synthesis of Phosphonoacetate 150



previously reported C_{15}−C_{27} fragment.[13b] Thus, intermediate **103** (cf. Scheme 14) was protected as silyl ether **158** and transformed to alcohol **159** and ester **160** by routine functional group manipulations. Ester **160** was treated with the lithium salt derived from dimethyl methanephosphonate to give β-oxophosphonate **161**, which served to install the C_{21}−C_{22} double bond *E*-selectively by olefination with aldehyde **16**. Reduction of the C_{20} carbonyl group of enone **162** under Luche conditions[66] followed by MOM protection of the secondary and liberation of the primary alcohol led to propargylic alcohol **163** with the correct stereochemistry at C_{20}. Stereoselective reduction of the triple bond in **163** with Red-Al followed by oxidation of the resulting *E*-allylic alcohol with Dess−Martin periodinane and acetalization with commercially available (*R*,*R*)-(+)-pentane-2,4-diol led to intermediate **164**. Removal of the silyl ether in **164** followed by acylation with bis(2,2,2-trifluoroethoxy)-phosphinylacetyl chloride[68] completed the synthesis of key fragment **150**, which was needed for the olefination of aldehyde **151**.

Fragment Assembly and Completion of the Total Synthesis of 1. To connect fragments **150** and **151** (Scheme 26), phosphonate **150** was deprotonated

Scheme 26. Fragment Connection and Completion of the Total Synthesis of 1



with KHMDS in the presence of 18-crown-6 and treated with aldehyde **151** at −78 °C, carefully avoiding an excess of base. Under these conditions, *Z*-enoate **149** with the complete laulimalide skeleton was obtained as a single isomer in 85% yield. The macrocyclization was performed by adding *seco* compound **149** slowly at −50 °C to a highly diluted solution of $EtAlCl_2$ in dichloromethane, providing cyclization product **165** with 15*S*-configuration in 85% yield. The γ-hydroxy ether remaining at C_{15}−O was removed by oxidation to ketone **166** and subsequent β-elimination with TsOH in chloroform. The remaining MOM ether in intermediate **167** was cleaved with dimethylboron bromide at −78 °C[69] to provide deoxylaulimalide **79** in high yield. The conversion of **79** to **1** via reagent matched SAE was then performed according to Mulzer's first synthesis.

2. For Fragment Union (Mulzer and Hanbauer)

With respect to the bond formation between C_{14} and C_{15}, the synthesis disclosed by Mulzer and Hanbauer[18c] is closely related to that of Mulzer and Enev (Figure 9).[18b] In this approach, a macrolactonization of *seco* acid **168** was planned as the ring-closing step, whereas an *intermolecular* diastereoselective addition of allyl silane **169** to the chiral acetal **164**[76−79] was envisioned to connect the main fragments (Figure 10).

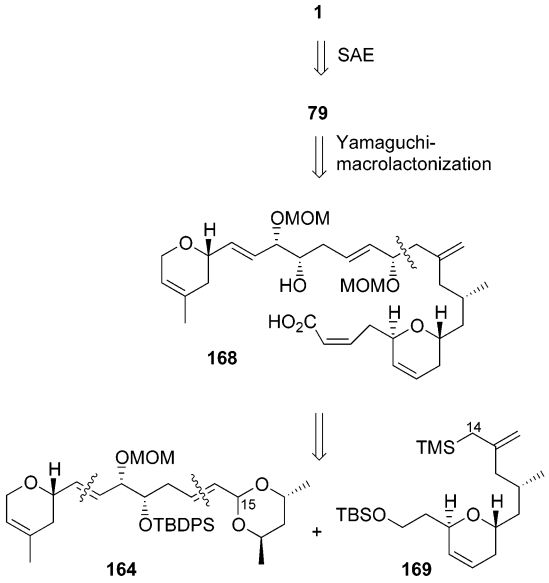
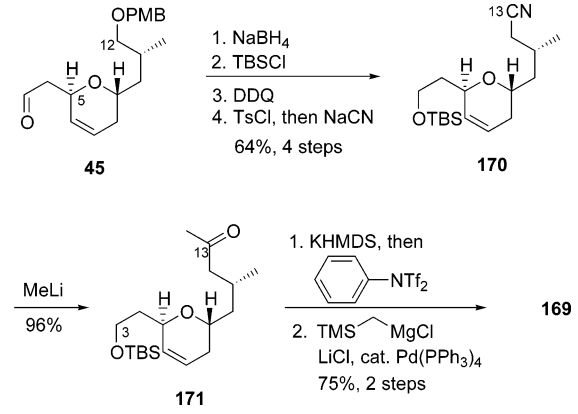


Figure 10. Retrosynthetic analysis of Mulzer and Hanbauer.

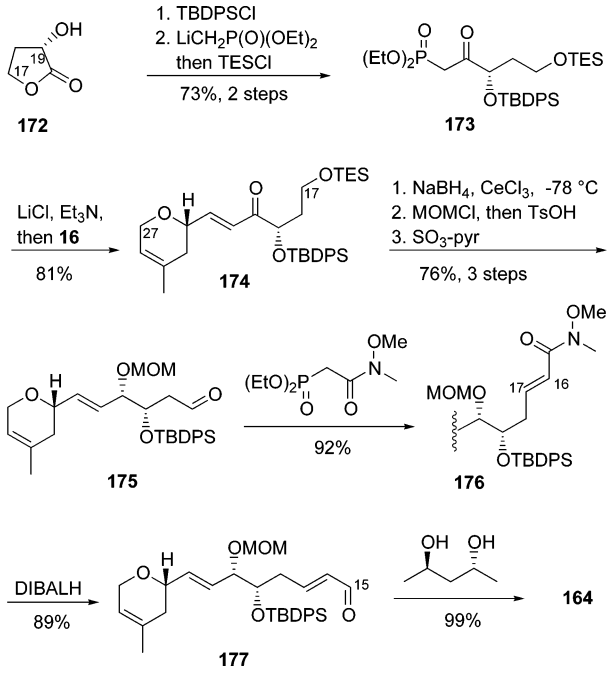
Synthesis of Allylsilane 169. For the synthesis of allylsilane **169** (Scheme 27), the previous intermediate **45** (cf. Scheme 5) was elaborated to cyanide **170** in four high-yielding steps. Treatment of **170** with methyllithium led to methyl ketone **171**, which was converted to allylsilane **169** by analogy to the procedure shown in Scheme 24.

Scheme 27. Synthesis of the Allylsilane 169



Synthesis of the C15−C27 Fragment 164. Acetal **164**, which had also been an advanced intermediate in the synthesis of Enev and Mulzer[18b] (cf. Scheme 25), was now prepared along an improved route, which also compares favorably with other syntheses of $C_{15}-C_{27}$ fragments (cf. Schemes 22, 32, 36, 40, 43, 46, and 47). The synthesis (Scheme 28) started from commercially available α-hydroxybutyrolactone **172**, easily derived from natural (*S*)-malic acid.[82] After TBDPS protection, the lactone was converted to the chiral *β*-oxophosphonate **173** by an one-pot procedure.[64] Olefination of **173** with aldehyde **16** under Masamune−Roush conditions[65] led to (*E*)-enone **174** as a single isomer. Reduction of the carbonyl group in **174** under Luche conditions[66] followed by functional group manipulations led to aldehyde **175** in high overall yield. Notably, in contrast to the C_{19}−OPMB-protected analogue **114** (cf. Scheme 17), 1,2-reduction of **174** at −78 °C furnished the desired *syn*-alcohol exclusively. Aldehyde **175** was homologated by another *E*-selective HWE reaction to afford Weinreb-amide **176**, which was smoothly converted to key fragment **164** in two steps.

Scheme 28. Improved Synthesis of $C_{15}-C_{27}$ Fragment 164



Fragment Union and Completion of the Synthesis. The crucial coupling of acetal **164** with allylsilane **169**, performed in the presence of $TiCl_4$, pretreated with a trace of triethylamine, led to adduct **178** stereoselectively in 65% yield. The *β*-hydroxy ether at the newly created C_{15} stereogenic center in **178** was removed by Dess−Martin oxidation to methyl ketone **179** and subsequent base-induced *β*-elimination to C_{15} alcohol **180**, which was converted to the fully protected intermediate **182** by protective group manipulations. Selective Swern oxidation of the primary TES ether[83] in **182** led to C_3 aldehyde **183,** which was subjected to a *Z*-selective Ando−Horner−Emmons olefination.[52,84] Treatment of the resulting *Z*-enoate **184** with TBAF led to the desired *seco* acid **168**. However, Yamaguchi macrocyclization[51] of **168** was accompanied by extensive *Z*/*E* isomerization of the 2,3-double bond and led to the MOM-protected macrolides **119** and **120** as an isomeric mixture (*E*:*Z* = 2.7:1).[85]

E. Regioselective Macrolactonization with Unprotected Diol (Wender)

In 2002, a series of laulimalide total syntheses appeared, the first of which was submitted by the group of Wender at Stanford.[20] The retrosynthetic strategy outlined in Figure 11 envisioned the con-

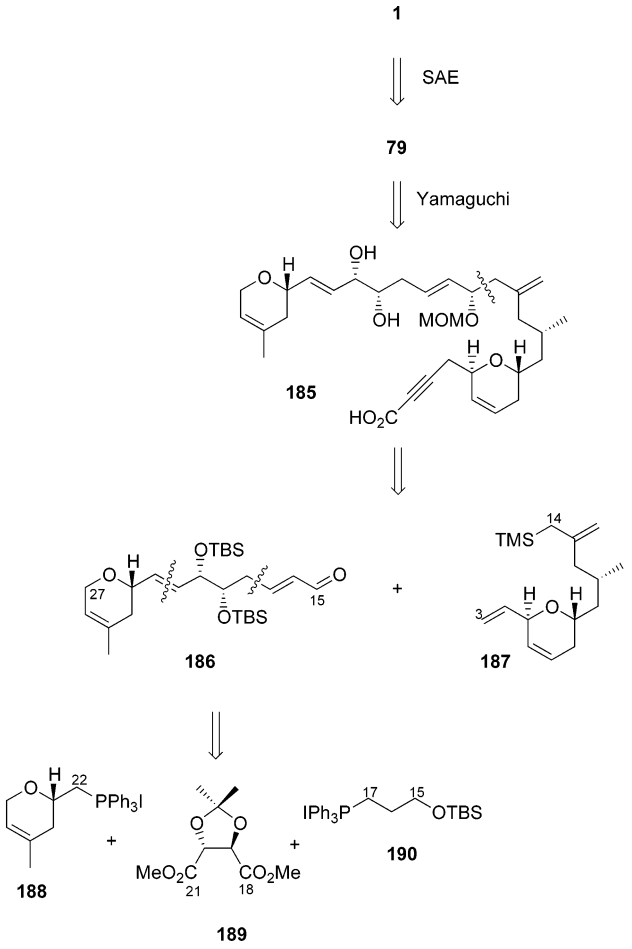
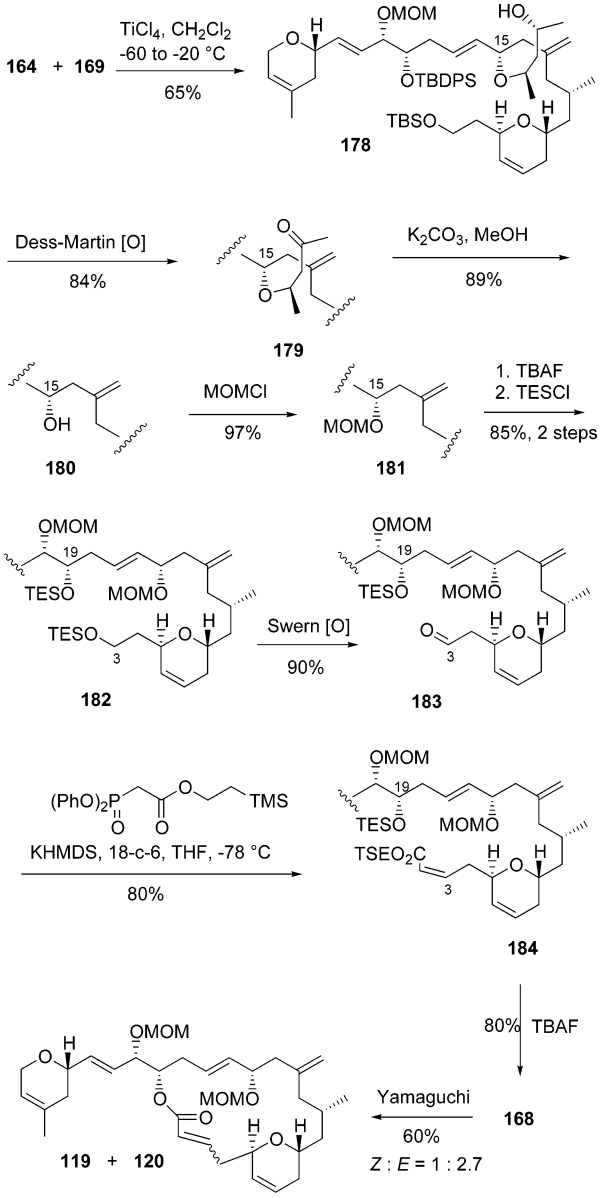


Figure 11. Retrosynthetic plan by Wender et al.

junction of the 5-vinyl-substituted allylsilane **187** with C_{15}-enal **186** by means of an asymmetric Sakurai reaction,[86] followed by C_3 homologation and macrolactonization. The presence of two identical protective groups in fragment **186** called for regioselective macrolactonization of an alkynoic acid with unprotected hydroxy groups at C_{19} and C_{20}, and alkynoic acid **185** was expected to provide the 18-membered ring of **1** and not the 19-membered one of its regioisomer neolaulimalide (**3**).[1d] Commercially available isopropylidene tartrate **189** was envisioned to provide the *syn*-diol unit in key fragment **186**. This four-carbon synthon comprising $C_{18}-C_{21}$ of the laulimalide skeleton was to be extended at both ends by two consecutive Wittig olefinations with phosphonium salts **188** and **190**, respectively. With respect to the final steps (selective semi-hydrogenation of a highly unsaturated alkynoic macrolide to generate the sensitive *Z*-enoate[17b] and asymmetric epoxidation of the reagent matched allylic alcohol in deoxylaulimalide **79**),[18a,19] Wender's approach followed the precedence of previous syntheses.

Synthesis of Allylsilane 187. The stereogenic center at C_{11} of fragment **187** (Scheme 30) was

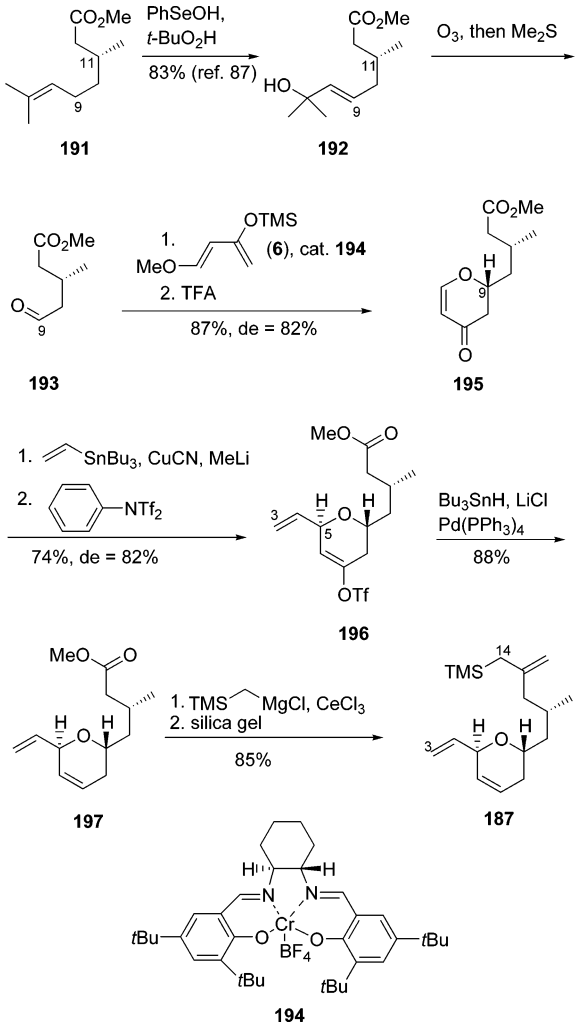
Scheme 29. Assembly of Fragments 164 and 169 and Nonstereoselective Ring Closure



derived from commercial methyl (*R*)-citronellate (**191**), which was converted to aldehyde **193** by a known three-step procedure.[87] HDA of aldehyde **193** with Danishefsky's diene **6**, catalyzed by Jacobsen's (*S*,*S*)-Cr−Salen catalyst **194**,[88] "under non standard conditions" yielded, after treatment with acid, pyranone **195** in 87% yield and with satisfactory diastereoselectivity. Conjugate cuprate addition to **195** using Lipshutz's procedure,[89] followed by trapping of the resulting enolate with Comins reagent,[80b] afforded enol triflate **196** (74%, de = 82%), which was reduced under Stille's conditions[90] to yield intermediate **197**. Treatment of C_{13} ester **197** with excess $TMSCH_2MgCl$ in the presence of rigorously dried $CeCl_3$,[91] followed by silica gel induced Peterson elimination of the intermediate bis-silylmethyl carbinol-generated allylsilane **187**.

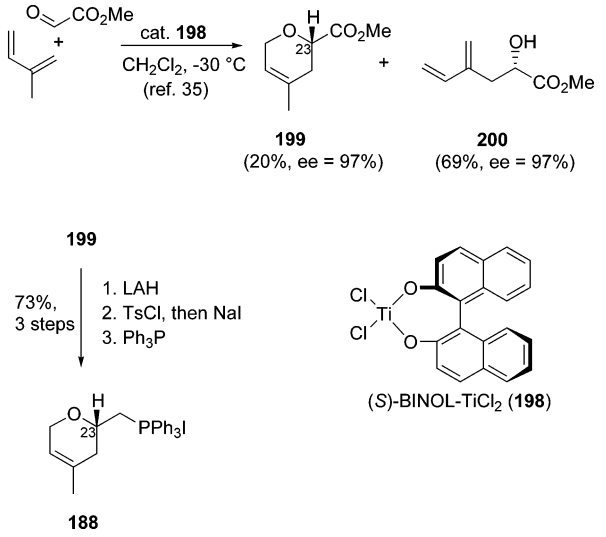
Synthesis of C15−C27 Aldehyde 186. The synthesis of **186** started with the construction of the exocyclic dihydropyran fragment **188**, which was produced according to Mikami's procedure,[35] by asym-

Scheme 30. Synthesis of Allylsilane 187



metric hetero Diels−Alder reaction of isoprene and methyl glyoxylate in the presence of the chiral titanium complex **198** (Scheme 31). This reaction was

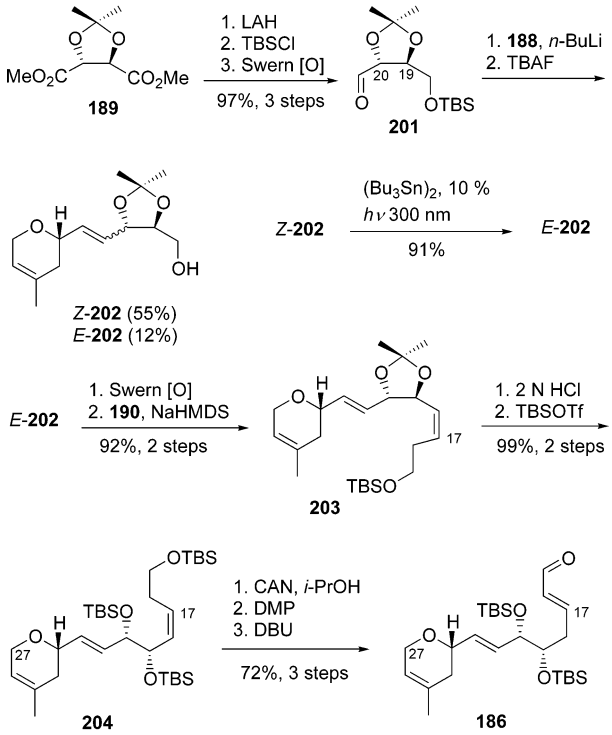
Scheme 31. Synthesis of Phosphonium Salt 188



reported to produce HDA product **199** enantioselectively (ee = 97%) but in very low yield due to the preferred formation of ene product **200**. Ester **199** was reduced and converted to phosphonium salt **188** by the three-step sequence depicted in Scheme 31.

The Wittig reaction of **188** with aldehyde **201**, derived from tartrate **189** in three steps (Scheme 32),[92] resulted, after deprotection with TBAF, in the

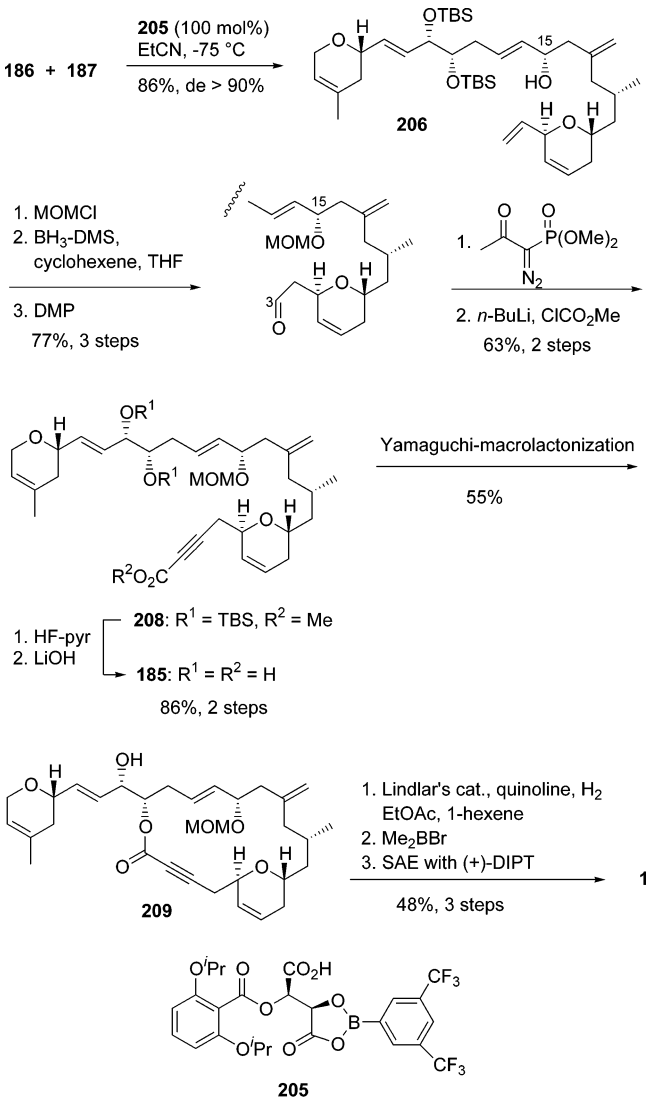
Scheme 32. Synthesis of Key Aldehyde 186



formation of a 4.5:1 mixture of isomers **202** in favor of the undesired *Z* isomer in 67% combined yield. After separation, *Z*-**202** was isomerized using a novel procedure by irradiation of a benzene solution in the presence of hexabutyl distannane to provide an 11.4:1 mixture in favor of the *E*-isomer. *E*-**202** was oxidized and the resulting aldehyde homologated by another *Z*-selective Wittig reaction with the known phosphonium salt **190**[93] to intermediate **203** with a double bond between C_{17} and C_{18}. Global deprotection of **203** and subsequent silylation afforded the tris-silylated compound **204**, from which selective removal of the primary TBS ether was finally achieved using cerium ammonium nitrate.[94] Oxidation of the resulting homoallylic alcohol with Dess−Martin periodinane followed by transposition and concomitant isomerization of the double bond completed the synthesis of enal **186**, ready for the union with allylsilane **187**.

Fragment Assembly and Completion of the Total Synthesis of 1. The uniquely complex Sakurai reaction between aldehyde **186** and allylsilane **187**, mediated by Yamamoto's acyloxyborane **205**[95] (Scheme 33), resulted in the formation of alcohol **206** with complete control of the C_{15} stereocenter in excellent 86% yield. After MOM protection, chemo- and regioselective hydroboration of the C_5-vinyl group in the highly unsaturated substrate, performed in the presence of cyclohexene,[96] followed by oxidation led to C_3-aldehyde **207** in high yield. Homologation of **207** using the Bestmann modification of the Gilbert−Seyferth reaction[97] and acylation of the resultant alkyne afforded alkynoate **208**. Desilylation and ester

Scheme 33. Fragment Conjunction and Completion of the Total Synthesis of 1



hydrolysis led to the desired 19,20-dihydroxy alkynoic acid **185**, which under Yamaguchi's conditions[51] afforded the 18-membered macrolide **209** regioselectively in 55% yield. Lindlar hydrogenation in the presence of 1-hexene,[53] as previously performed by Ghosh with a close analogue of **209**,[17b] followed by MOM deprotection with dimethylboron bromide[69] provided deoxylaulimalide **79**, which was selectively epoxidized to **1**.

F. Early Incorporation of the Epoxide

1. Crimmins' Approach

Crimmins' laboratory disclosed a highly concise total synthesis of **1** that demonstrated for the first time that the sensitive epoxide could be introduced at an early stage.[21] The retrosynthetic design focused on a (19*R*)-hydroxy acid **210** with preformed epoxide moiety, which should serve as the substrate in a Mitsunobu-type[67] macrolactonization (Figure 12). A diastereoselective addition of a C_1-C_{14} allylstannane **212** to a $C_{15}-C_{27}$ α,β-epoxyaldehyde **211** was envisioned to join the major fragments. The presence of homoallylic (or latent homoallylic) C−O bonds at C_5, C_{19}, and C_{23} in **1** led to the strategic decision to rely on the glycolate variant[98] of the Evans asymmetric alkylation[28] to construct both subunits. Additionally and in contrast to previous syntheses of **1**, removal of the two TBS protective groups from the C_{15} and C_{20} hydroxyls should be attempted as the final step without affecting the *Z*-enoate *and* the epoxide.

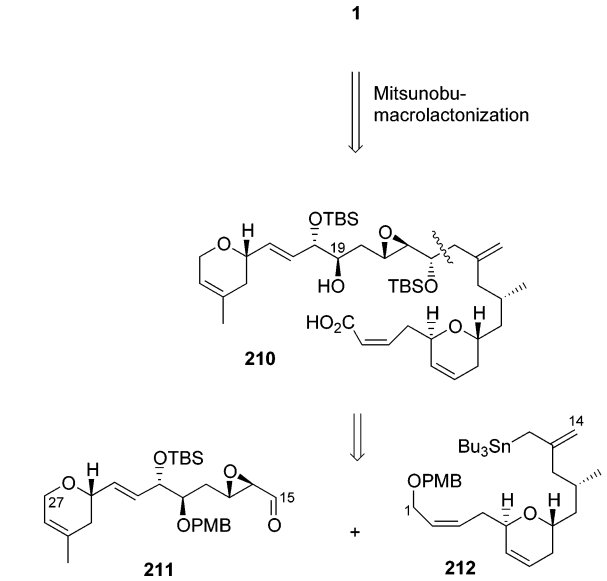


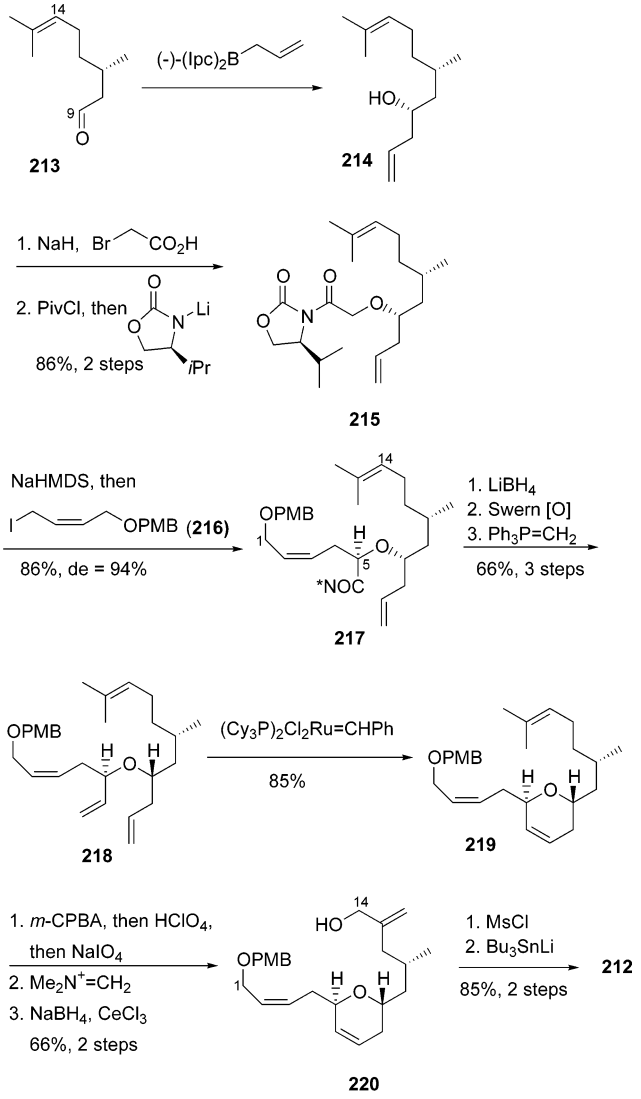
Figure 12. Crimmins' retrosynthetic analysis.

Synthesis of the C1−C14 Fragment 212. The synthesis displayed in Scheme 34 started from (*S*)-citronellal (**213**),[99] which provided the C_9-C_{14} part of the laulimalide skeleton. Treatment of **213** with Brown's chiral borane[38] produced homoallylic alcohol **214**, which was transformed into acyl oxazolidinone **215** by alkylation with bromoacetic acid followed by acylation of the D-valine-derived oxazolidinone. Alkylation of intermediate **215** with the *Z*-allylic iodide **216** proceeded with high diastereoselectivity (de = 94%) to generate intermediate **217** with the required C_5 stereochemistry. The chiral auxiliary in **217** was removed with $LiBH_4$[100] to provide a primary alcohol, which was converted to tetraene **218** by Swern oxidation and Wittig methylenation. RCM of **218** with Grubbs' first-generation ruthenium catalyst led to dihydropyran **219** in high yield without affecting the other double bonds. Selective cleavage of the trisubstituted double bond in **219**, followed by α-methylenation of the intermediate aldehyde,[31] and 1,2-reduction of the resulting enal led to allylic alcohol **220**, which was transformed to allylstannane **212** via the mesylate.

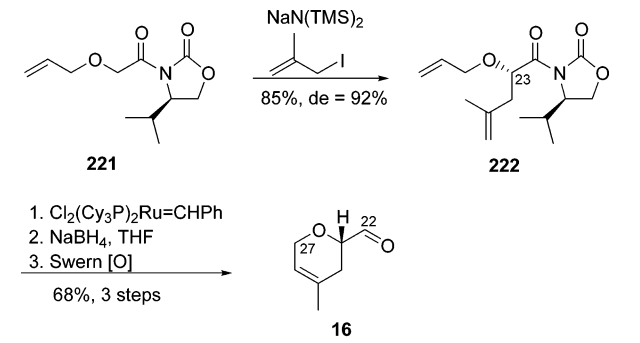
Synthesis of the C15−C27 Fragment 211. The $C_{22}-C_{27}$ subunit of **1** was also prepared by taking advantage of the asymmetric glycolate alkylation (Scheme 35). Thus, oxazolidinone **221** was alkylated with 2-methylallyl iodide to install the C_{23} stereocenter in diene **222** (de = 92%). RCM of **222**, followed by reductive removal of the auxiliary, and Swern oxidation of the resulting alcohol provided aldehyde **16**.[101]

Asymmetric glycolate alkylation was also utilized to establish the C_{19} stereocenter (Scheme 36). Alkylation of glycolate **223** with (*E*)-allyl iodide **224** produced intermediate **225** (de = 96%), which was

Scheme 34. Synthesis of C_1−C_{14} Allylstannane 212

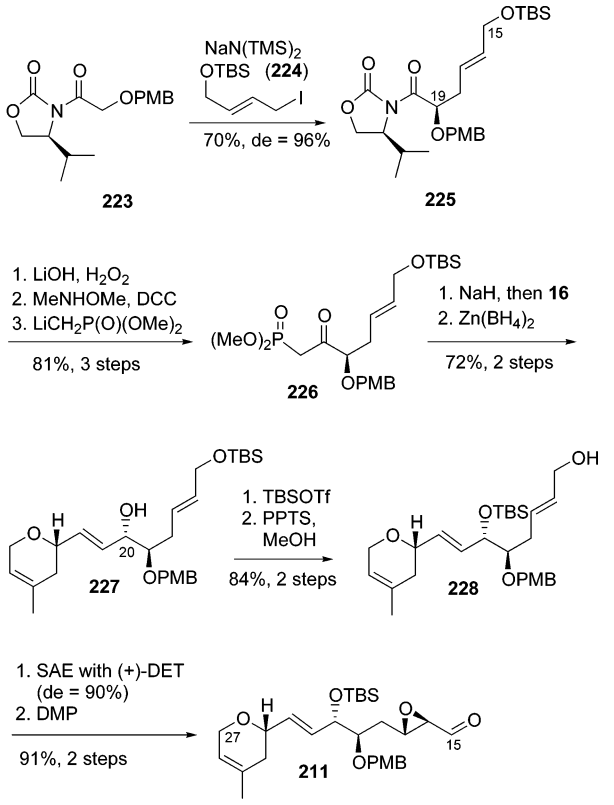


Scheme 35. Synthesis of Aldehyde 16 via Glycolate Alkylation/RCM Sequence



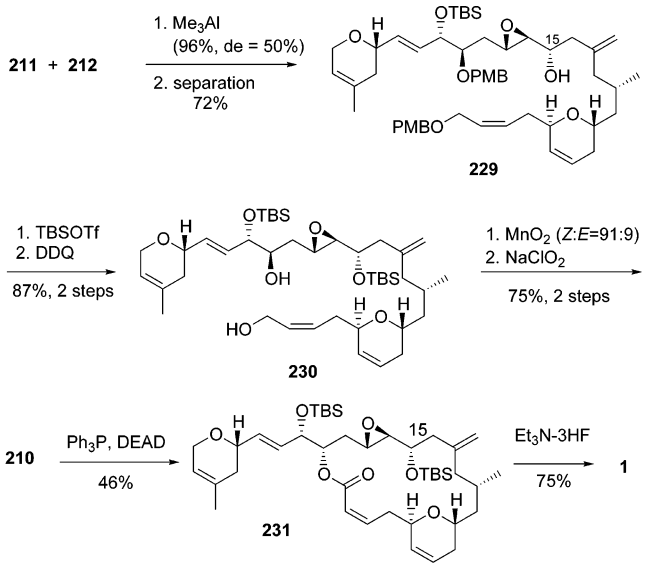
converted to the chiral β-oxophosphonate **226** via an intermediate Weinreb amide. The C_{21}−C_{22} double bond and the C_{20} stereocenter were then selectively elaborated by HWE olefination of phosphonate **226** with aldehyde **16**, followed by chelation-controlled 1,2-reduction[102] of the resulting (*E*)-enone. Sequential TBS protection of the secondary hydroxy group in **227** and deprotection of the primary one generated allylic alcohol **228**. SAE of **228** (de = 90%) and Dess−Martin oxidation of the intermediate epoxy alcohol generated key fragment **211** in high yield.

Scheme 36. Synthesis of the C_{15}−C_{27} Fragment 211



Fragment Assembly and Completion of the Synthesis of 1. Trimethylaluminum-mediated addition of allylstannane **212** to epoxy aldehyde **211** (Scheme 37) resulted in a 3:1 mixture of C_{15} alcohols,

Scheme 37. Fragment Assembly and Completion of the Total Synthesis of 1



from which the major Felkin−Anh diastereomer **229** with laulimalide stereochemistry at C_{15} was isolated in 72% yield. TBS protection of **229**, followed by removal of both PMB groups, led to diol **230**. Selective oxidation of the C_1 allylic alcohol in **230** with MnO_2 led to partial isomerization of the *Z*-enal (*Z*:*E* = 91:9), which was immediately oxidized to *seco* acid **210**. Macrolactonization under Mitsunobu's condi-

tions[67] generated the TBS-protected macrolide **231** in 46% yield, which upon careful exposure to Et_3N-HF[103] furnished **1** without affecting the *Z*-enoate and without concomitant isomerization to isolaulimalide (**2**).

2. Williams' Approach

A synthesis of the TBS-protected laulimalide macrocycle **231** was also achieved by the team of D. R. Williams.[22] As outlined in Figure 13, the retrosyn-

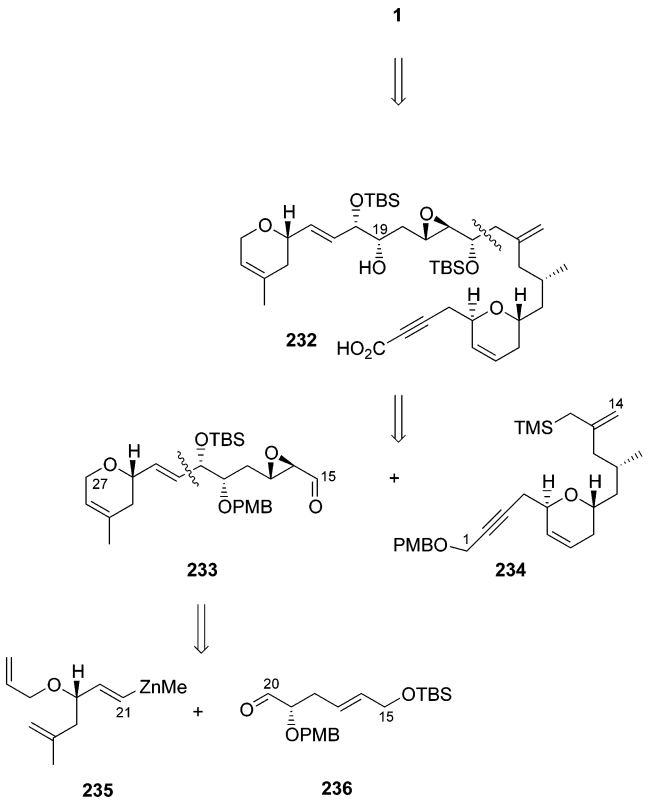
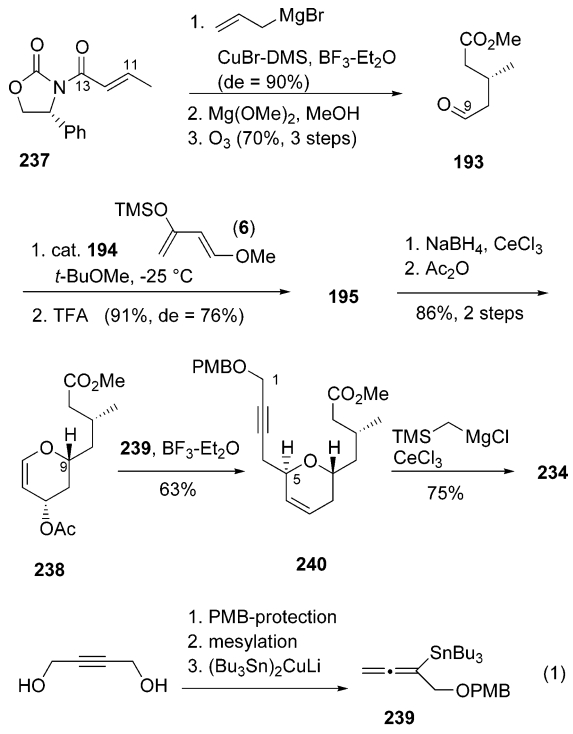


Figure 13. Retrosynthetic analysis by D. R. Williams et al.

thetic disconnections and also the main fragments are closely related to Crimmins' synthesis. Key fragments **233** and **234** were to be coupled diastereoselectively. In contrast to the work of Crimmins, the crucial allylation of α,*β*-epoxyaldehyde **233** (C_{19} epimer of Crimmins' main fragment **211**) was to be performed with allyl*silane* **234**. In a novel approach, the $C_{19}-C_{20}$ *syn*-diol unit in main fragment **233** should arise from a chelation-controlled addition of alkenylzincate **235** to the (*S*)-malic acid-derived aldehyde **236**. This implied that the subsequent RCM step for generation of the exocyclic dihydropyran moiety was to be performed with a highly unsaturated intermediate. The acetylenic C_1-C_4 unit in allylsilane **234** was introduced in one step by a novel allenylstannane Ferrier reaction and allowed the introduction of the sensitive *Z*-enoate through macrolactonization of 2,3-alkynoic acid **232** and subsequent partial hydrogenation.

Synthesis of the C1−C14 Fragment 234. The synthesis of allylsilane **234** began with the introduction of the C_{11} stereocenter by asymmetric conjugate addition of an allylcopper reagent, formed under Yamamoto's conditions,[104] to *N*-enoyloxazolidinone **237** (Scheme 38). Subsequent removal of the chiral

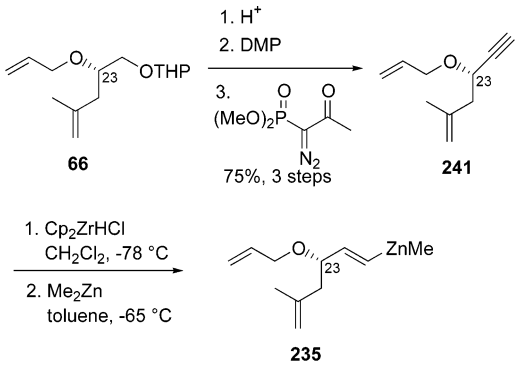
Scheme 38. Synthesis of Allylsilane 234



auxiliary and ozonolysis led to aldehyde **193**, which as in the work of Wender (cf. Scheme 30) was elaborated to dihydropyranone **195** by asymmetric HDA with diene **6** in the presence of Jacobsen's (*S*,*S*)-Cr−salen catalyst **194**.[88] The cycloaddition performed in *t*-BuOMe at −25 °C led, after treatment with acid, to an inseparable mixture of C_9 diastereomers (7.5:1) in 91% combined yield, which was used in the ensuing steps. 1,2-Reduction under Luche's conditions[66] and acetylation provided acetate **238**, which was treated with allenylstannane **239** in the presence of $BF_3 \cdot Et_2O$ to generate the propargylated compound **240** with the required configuration at C_5. Allenylstannane **239** was prepared from 2-butyn-1,4-diol by PMB monoprotection followed by mesylation and S_N2' displacement with $(Bu_3Sn)_2CuLi$ (eq 1 in Scheme 38, no further details were given in the paper).[105] The preparation of C_1-C_{14} fragment **234** was then completed as in Wender's work through cerium chloride-mediated double addition of $TMSCH_2MgCl$,[91] which resulted in spontaneous elimination to generate the allylsilane moiety.

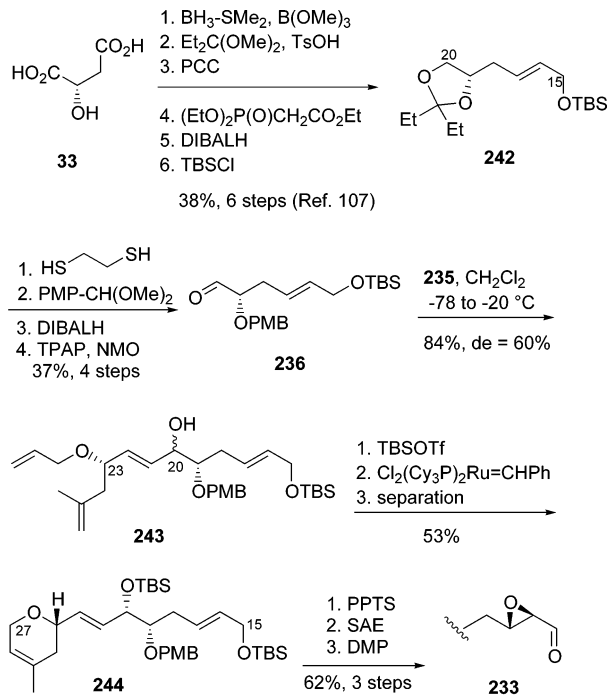
Synthesis of Epoxyaldehyde 233. The synthesis of epoxyaldehyde **233** started with the preparation of alkenylzincate **235** (Scheme 39). Diene **66** (cf. Scheme 8), available in two steps from THP-protected (*R*)-glycidol, was transformed to alkyne **241** by conversion to the corresponding aldehyde and homologation via Bestmann's modification of the Gilbert−Seyferth reaction.[97] Hydrozirconation of alkyne **241** and in situ transmetalation with dimethylzinc, as described by Wipf,[106] yielded the (*E*)-alkenyl derivative **235**, ready for the *syn*-selective coupling with the $C_{15}-C_{20}$ subunit.

Scheme 39. Synthesis of the Alkenylzincate 235



The synthesis of the coupling partner **236** started from natural (*S*)-malic acid (**33**), which was transformed via a known six-step sequence[107] to acetal **242** and then to the C_{19}−OPMB-protected aldehyde **236** by a series of protective group manipulations (Scheme 40). Aldehyde **236** was treated with alkenylzinc

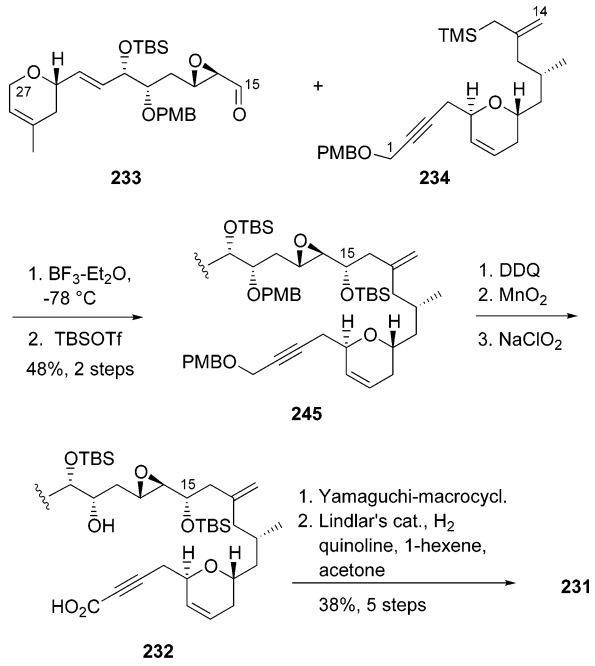
Scheme 40. Synthesis of Epoxyaldehyde 233



species **235** to provide a 4:1 mixture of C_{20} diastereomers in favor of the required (20*S*)-alcohol **243**. After TBS protection, a late-stage RCM with Grubbs' first-generation ruthenium catalyst led to the selective formation of the dihydropyran ring, without affecting the other double bonds, albeit in low yield. At this point, the C_{20} epimers were separated and intermediate **244** converted to epoxyaldehyde **233** by selective cleavage of the primary silyl ether followed by SAE[25] and oxidation with Dess−Martin periodinane.

Fragment Assembly and Completion of the Synthesis. The final steps of the synthesis are shown in Scheme 41. Borontrifluoride etherate-mediated allylation of epoxyaldehyde **233** with allylsilane **234** led to the desired Felkin−Anh adduct with 15*S*-configuration in 53% yield, which was protected as the TBS ether **245**. Removal of the PMB groups at

Scheme 41. Fragment Assembly and Synthesis of the TBS-Protected Laulimalide 231



C_1 and C_{19} led to a diol that was selectively oxidized to *seco* acid **232**. Yamaguchi macrocyclization, followed by selective Lindlar hydrogenation of the resulting 2,3-alkynoic lactone in the presence of 1-hexene,[53] generated the TBS-protected macrolide **231**. Attempts to remove the silyl groups under standard conditions led to *Z*/*E* isomerization and other side reactions. However, the successful conversion of **231** to laulimalide had previously been reported by Crimmins.[21]

G. Asymmetric Acyl Halide−Aldehyde Cyclocondensation (Nelson)

A remarkable sequence leading from acetaldehyde to (−)-laulimalide in only 23 steps along the longest linear route has been presented by the team of S. G. Nelson.[23] They were mainly interested in **1** as a platform for evaluating their recently developed asymmetric acyl halide−aldehyde cyclocondensation (AAC) methodology[108] and ensuing transformations of the resulting chiral β-lactones for the synthesis of major fragments of **1**. AAC-based bond constructions catalyzed by the chiral Al(III)−triamine complex **251** were used to generate the C_{19} and C_9,C_{11} stereocenters in main fragments **247** and **248** (Figure 14) and served also to construct the dihydropyran moiety in fragment **248** by a novel one-pot β-lactone to dihydropyrone interconversion.[109] Similar to Williams' synthesis,[22] the *syn*-diol arrangement in fragment **247** was to be generated by chelate-controlled addition of an alkenyl−metal intermediate **249** to a C_{15}−C_{20} aldehyde **250**. With respect to the asymmetric aldol reaction between C_{15}−C_{27} enal **247** and C_1−C_{14} methyl ketone **248** and the late-stage introduction of the C_{13} *exo*-methylene group, the synthesis follows (and improves) Paterson's approach.[19] The stereoselective attachment of the entire C_1−C_4 moiety by Lewis acid-mediated allenylstannane addition to

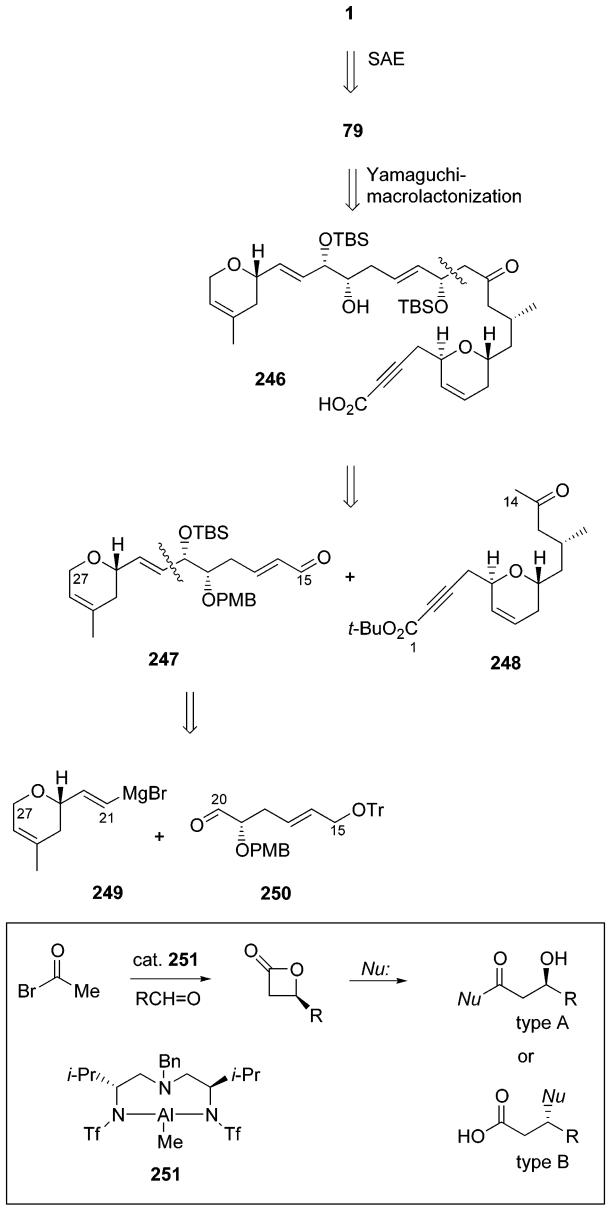
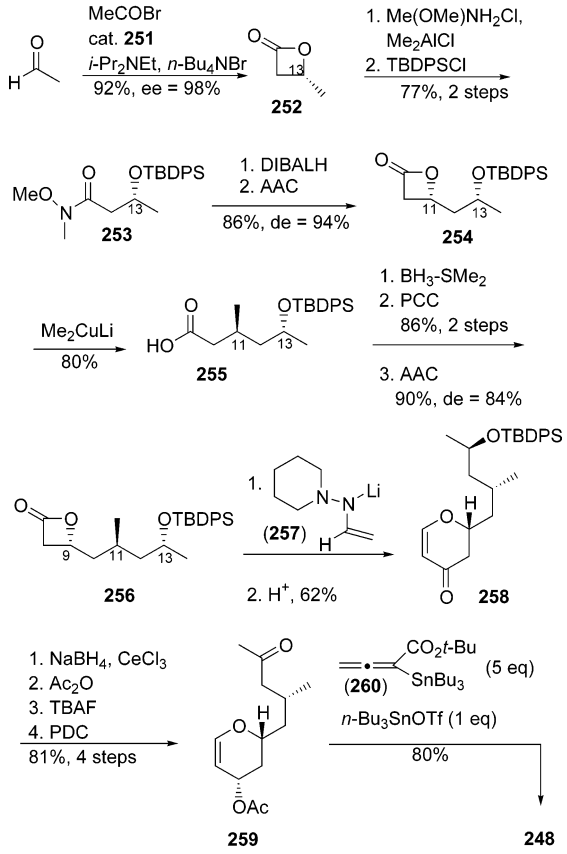


Figure 14. Nelson's retrosynthetic analysis.

a glycal intermediate, also performed by Williams,[22] allows a straightforward access to the 2,3-*Z*-enoate. The last-step epoxidation of deprotected deoxylaulimalide **79**, in turn, was to be performed following procedures described by Mulzer[18] and Paterson.[19]

Synthesis of C1−C14 Fragment 248. The construction of methyl ketone **248** (Scheme 42) commenced with (*R*)-propiolactone **252**, derived from asymmetric AAC between acetaldehyde and acetyl bromide. Type A lactone opening with aluminum *N*,*O*-dimethylhydroxylamide[110] and ensuing silyl protection led to Weinreb amide **253**, which was transformed to 1,3-*syn*-β-lactone **254** by sequential amide to aldehyde interconversion and asymmetric AAC homologation (86% yield, de = 94%). The C_{11} stereocenter was then installed by cuprate-mediated S_N2 (type B) opening of lactone **254** to provide carboxylic acid **255**.[111] After acid to aldehyde interconversion, the configuration at C_9 was established also by asymmetric AAC methodology, leading to *anti*,*anti*-β-lactone **256** (90% yield, de = 84%). According to a previously developed procedure,[109] β-lactone **256** was

Scheme 42. Synthesis of C_1−C_{14} Methyl Ketone 248

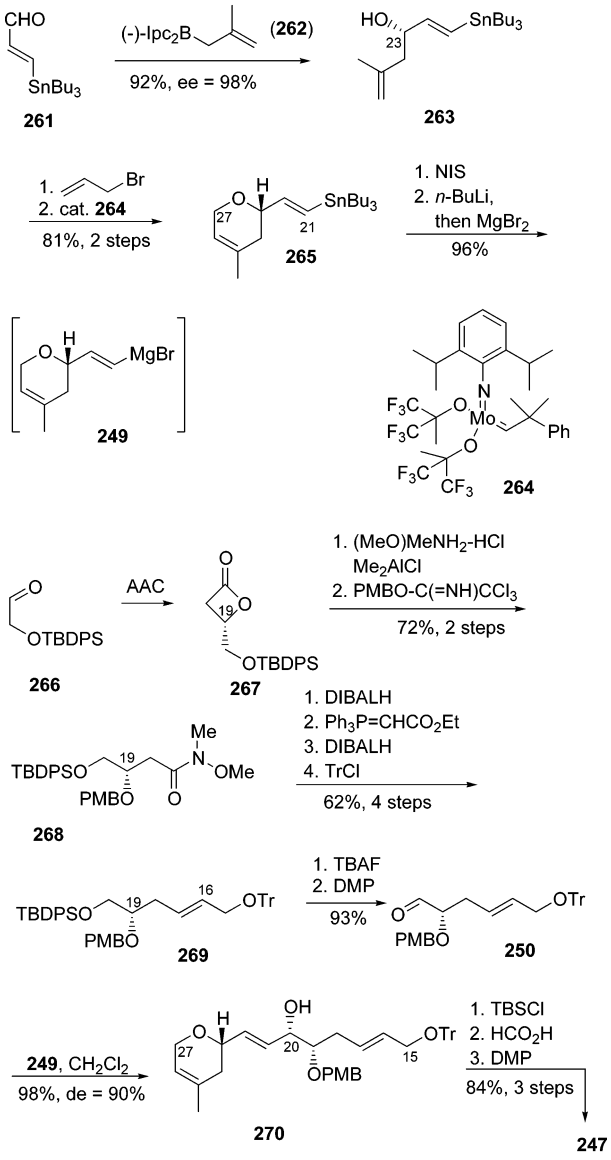


transformed to dihydropyrone **258** by reaction with acetaldehyde equivalent **257** (type A lactone opening) and ensuing acid-mediated cyclization−dehydroamination of the intermediate β-ketohydrazone. Diastereoselective carbonyl reduction, followed by acetylation, and installation of the C_{13} carbonyl group led to glycal acetate **259**, ready for the introduction of the C_1−C_4 moiety. Treatment of **259** with allenylstannane **260** (no preparation was given for this compound)[105] in the presence of *n*-Bu_3SnOTf as the Lewis acid activator completed the synthesis of main fragment **248**.[112]

Synthesis of C15−C27 Aldehyde 247. The synthesis of vinyl anion equivalent **249** (Scheme 43) began with Brown allylation[38] of β-tributylstannyl acrolein **261** using the chiral borane **262** to produce homoallylic alcohol **263** in high yield. Alcohol **263** was *O*-allylated, and the resulting triene was subjected to RCM with Schrock's highly sensitive Mo(VI) catalyst **264**.[113] This reaction did not affect the stannyl-substituted double bond and led cleanly to dihydropyran **265**. Conversion of stannane **265** to the iodide and subsequent transmetalation to the Grignard reagent furnished the desired vinyl anion equivalent **249**.

The preparation of coupling partner **250** was initiated by asymmetric AAC of aldehyde **266** to provide propiolactone **267** with the desired configuration at C_{19}. Amine-mediated (type A) opening of lactone **267** and hydroxyl group protection delivered Weinreb amide **268**, which was homologated to aldehyde **250** via the orthogonally protected triol **269** by routine functional group manipulation. Coupling of aldehyde

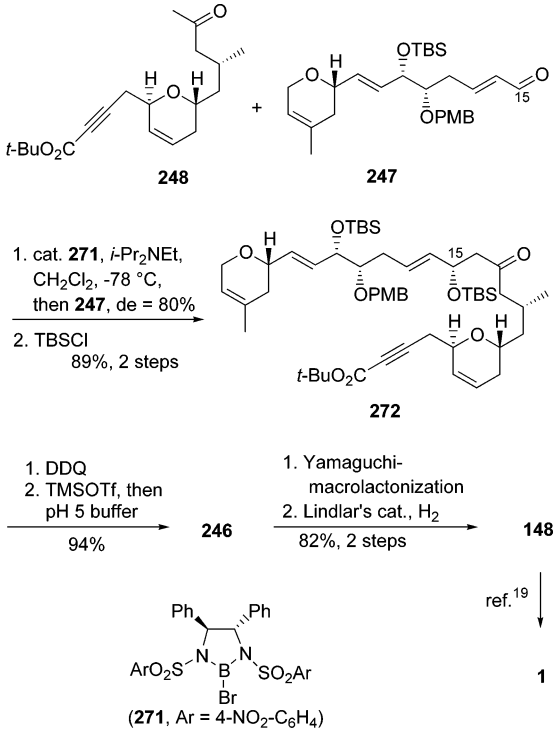
Scheme 43. Synthesis of Aldehyde 247



250 with Grignard reagent **249** proceeded with complete chelate control to alcohol **270** with the desired configuration at C_{20}, which was converted to key aldehyde **247** in three steps.

Fragment Coupling and Completion of the Synthesis. The diastereoselective coupling of key fragments **247** and **248** (Scheme 44) was performed by first converting methyl ketone **248** to the chiral boron enolate derived from bromo borane **271**,[114] followed by treatment with aldehyde **247**. As a major improvement of the analogous step in Paterson's synthesis (cf. Scheme 23), which was performed with (+)-Ipc$_2$BCl and furnished an inseparable 4:1 mixture of C_{15} epimers,[19] the aldol addition was now mediated with Corey's reagent **271** and led to a 9:1 mixture of alcohol diastereomers, which after TBS protection gave intermediate **272** in 89% yield. Successive deprotection of the PMB ether and the *tert*-butyl ester in **272** produced *seco* acid **246**. Modified Yamaguchi macrolactonization and Lindlar hydrogenation led to macrolactone **148**, which had been an intermediate in Paterson's synthesis (cf. Scheme 23).[19] Therefore, the synthesis was completed accordingly by Takai

Scheme 44. Fragment Connection and Completion of the Synthesis via Paterson's Intermediate 148



methylenation at C_{13},[75] global deprotection, and selective SAE[18,19] of the resulting desepoxylaulimalide **79**.

V. Syntheses of Laulimalide Fragments

A. Davidson's Contributions

To date, the Davidson group, who identified laulimalide as a member of the MSAA family,[2a] has presented three syntheses of main fragments of **1**.[14] Originally, Davidson suggested the connection of (19*S*)-aldehyde **273** with C_1-C_{14} fragment **274** via asymmetric allyl transfer (Figure 15).[14a,b] Anticipating Crimmins' approach (Figure 12, Scheme 37),[21] this concept was later modified,[14c] and (19*R*)-epoxyaldehyde **275** was to be combined with allylstannane **274**.

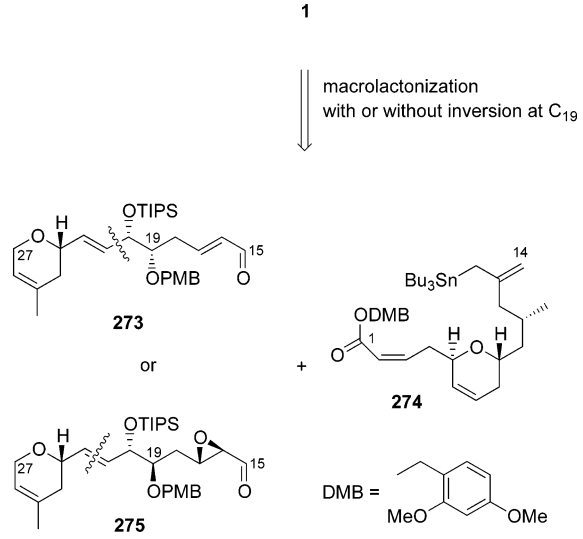


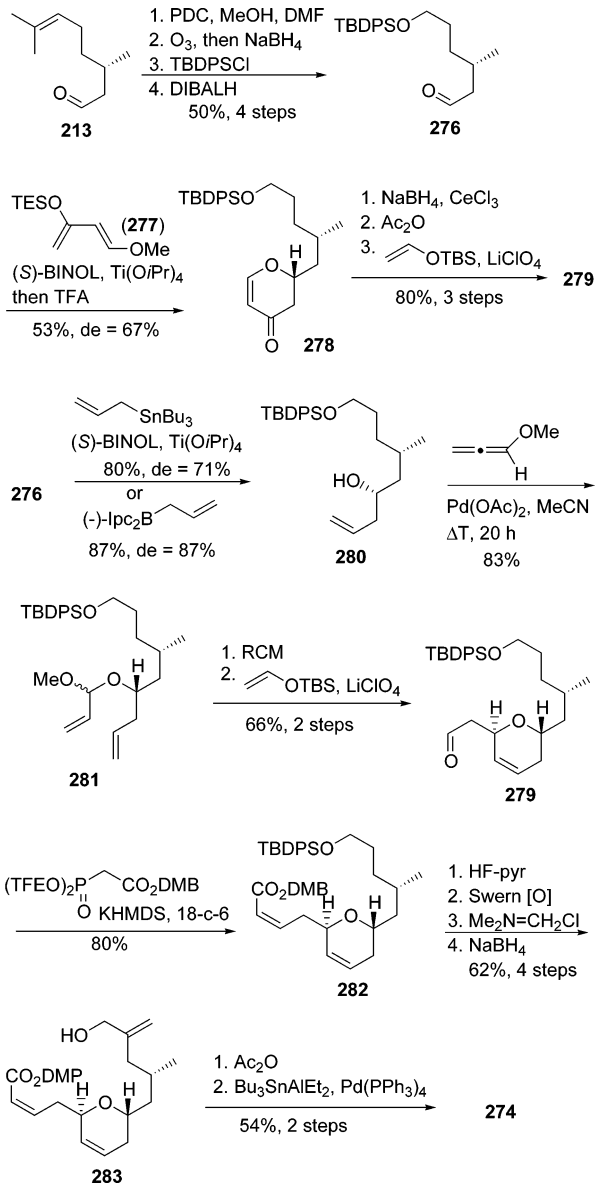
Figure 15. Davidson's retrosynthetic analyses.

In the first communication,[14a] (*S*)-citronellal (**213**) was used to provide the C_9-C_{14} segment of laulimalide (Scheme 45).[115] To this end, **213** was converted to aldehyde **276** in four steps. Aldehyde **276** was subjected to the conditions of Keck's asymmetric HDA reaction[116] with the Danishefsky-type diene **277** to provide dihydropyranone **278** in moderate yield and with low diastereocontrol. Reduction of the carbonyl group in **278** followed by acetylation and Ferrier-type *C*-glycosidation with vinyl-OTBS produced the *trans*-disubstituted dihydropyran **279**. In an improved approach, aldehyde **276** was allylated using Keck's protocol[117] or with better diastereoselection Brown allylation[38] to give homoallylic alcohol **280**. Treatment of **280** with methoxyallene in the presence of $Pd(OAc)_2$ provided diene **281**,[40b] which was subjected to RCM. *C*-Glycosidation of the resulting methyl glycoside provided aldehyde **279**. The sensitive 2,3-*Z*-enoate was then introduced by Still–Gennari olefination[42] of **279** with 2,4-dimethoxybenzyl (DMB) bis(2,2,2-trifluoroethylphosphono)acetate to afford **282**. Removal of the silyl ether present in **282** followed by Swern oxidation and Eschenmoser methylenation[31] produced an enal, which was reduced to alcohol **283**. The allylic alcohol **283** was acetylated and treated with $Bu_3SnAlEt_2$ applying Trost's methodology[118] to generate the desired allylstannane **274** in moderate yield.

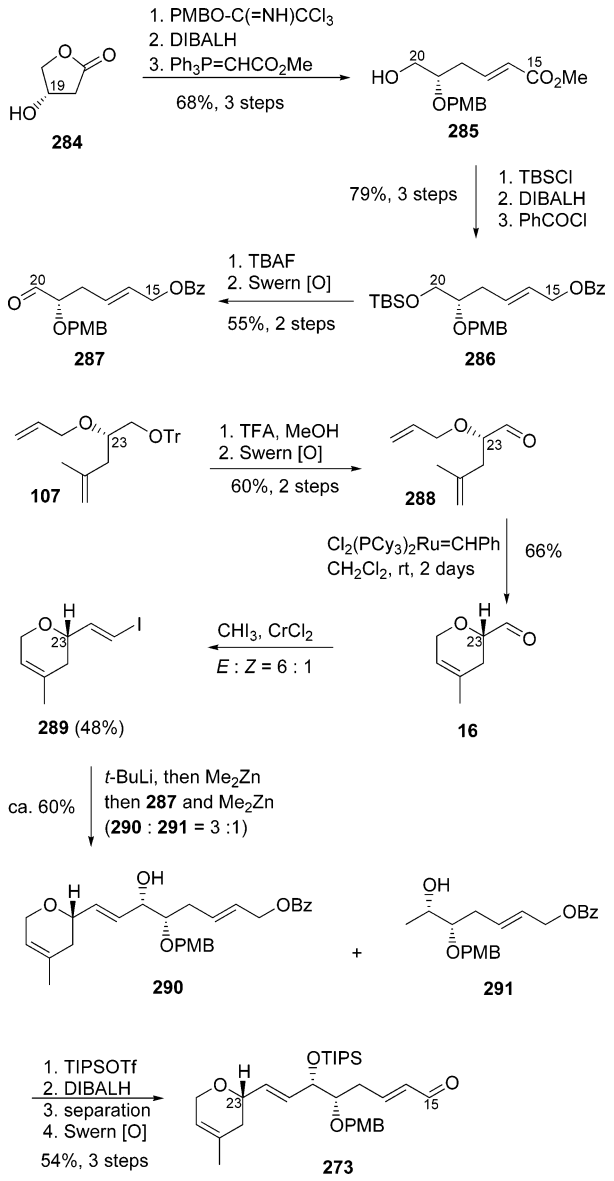
In an adjoining paper,[14b] the $C_{15}-C_{27}$ aldehyde **273** was prepared starting from commercially available β-hydroxy-lactone **284** (Scheme 46). After PMB protection, the lactone was reduced to the lactol, which was directly olefinated to (*E*)-enoate **285**. Protective group manipulations and a Swern oxidation led to $C_{15}-C_{20}$ aldehyde **287**, which was to be connected with the exocyclic dihydropyran fragment by means of chelation-controlled addition of a vinyl anion.[119,120]

To obtain the required $C_{22}-C_{27}$ subunit (Scheme 46), diene **107**, prepared from trityl (*S*)-glycidyl ether according to Scheme 15,[13b] was deprotected and oxidized to aldehyde **288**, which on RCM with Grubbs' first-generation ruthenium catalyst furnished dihydropyran aldehyde **16** in moderate yield. Takai iodoolefination[121] of **16** led to a 6:1 mixture of isomers,

Scheme 45. Synthesis of C_1-C_{14} Allylstannane 274



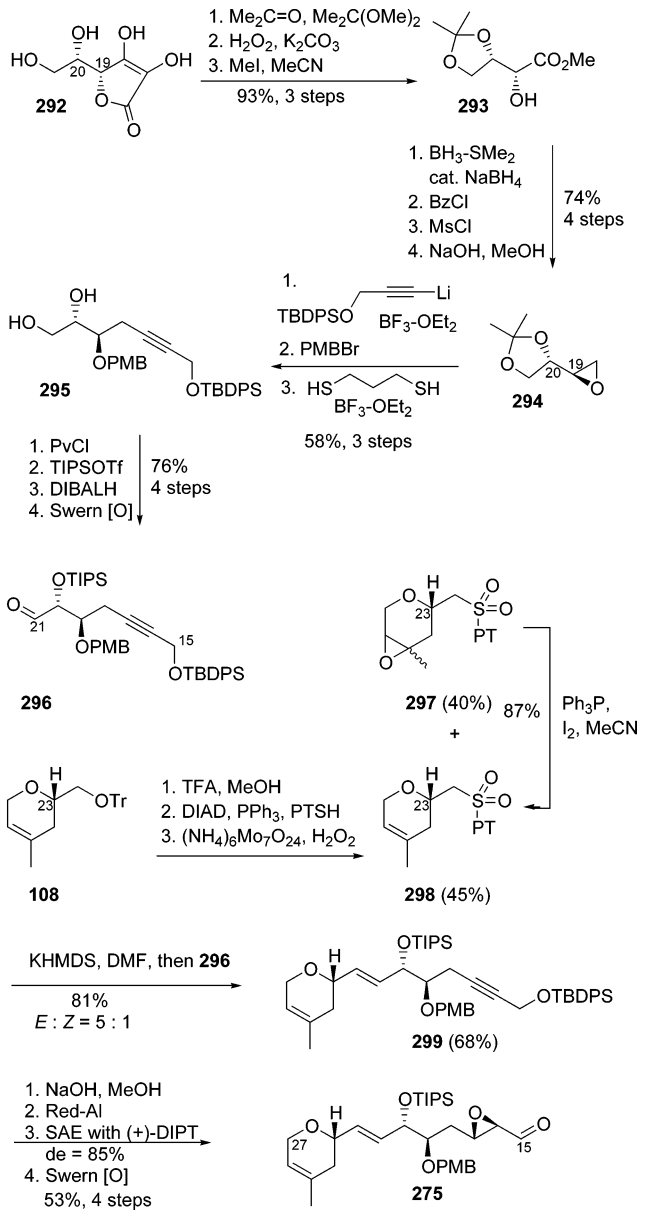
Scheme 46. Synthesis of the $C_{15}-C_{27}$ Fragment 273



from which (*E*)-vinyl iodide **289** was isolated in 48% yield. Lithiation of **289** followed by transmetalation with Me_2Zn and coupling with **287** stereoselectively led to (20*S*)-alcohol **290**. However, substantial amounts of methylation product **291** were also formed, which could not be separated at this point. After TIPS protection and reductive removal of the benzoyl protecting group, the mixture of primary alcohols was separated and the desired alcohol oxidized to key aldehyde **273**.

In a second-generation synthesis (Scheme 47),[14c] Davidson's group prepared the (19*R*)-epoxyaldehyde

Scheme 47. Synthesis of Epoxy Aldehyde 275



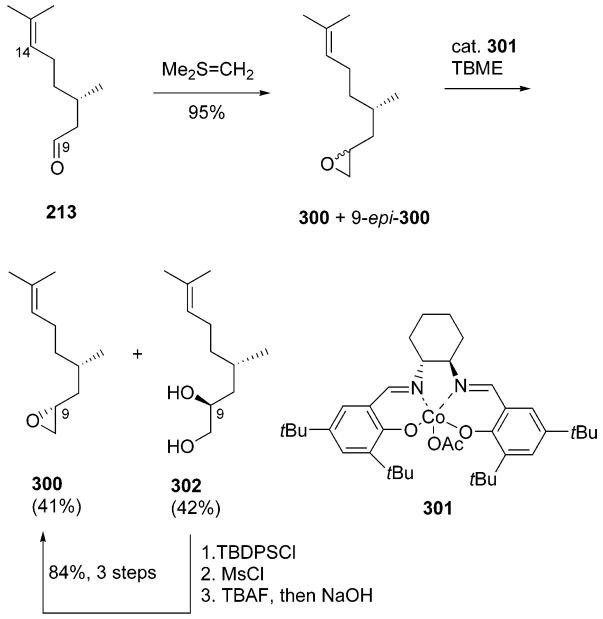
275 which was required for a final Mitsunobu-macrolactonization.[67] The $C_{21}-C_{22}$ double bond was to be formed via a Julia–Kocienski coupling reaction.[54] The $C_{19}-C_{20}$ *syn*-diol unit was now prepared from L-ascorbic acid (**292**), which was converted to known epoxide **294** in seven steps by slight modifications of the known procedure.[122] The epoxide was opened with the lithium salt generated from TBDPS propargyl ether, and the resulting alcohol was converted to C_{21}-aldehyde **296** by a series of protective group manipulations.

The desired coupling partner was now obtained from trityl ether **108**, prepared by the RCM strategy outlined in Scheme 15.[13b] Removal of the trityl group followed by reaction with 1-phenyl-1*H*-tetrazol-5-thiol (PT-SH) under Mitsunobu conditions[67] furnished the thioether, which was oxidized with ammonium molybdate/H_2O_2 to provide a 1:1 mixture of the desired sulfone **298** along with epoxide **297**, which resulted from additional attack on the double bond. Epoxy derivative **297** was recycled to the desired dihydropyran **298** by treatment with iodine/Ph_3P. The one-step olefination[54] between the anion derived from sulfone **298** and aldehyde **296** in DME led to an unfavorable 1:1.3 mixture in favor of the undesired *Z* isomer. When DME was replaced by DMF, the isomeric ratio was improved to 5:1, and after separation, (*E*)-isomer **299** was obtained in 68% yield. Selective removal of the TBDPS ether in **299** and reduction of the resulting propargylic alcohol with Red-Al led to an allylic alcohol, which was transformed to epoxy aldehyde **275** by SAE and ensuing Swern oxidation.

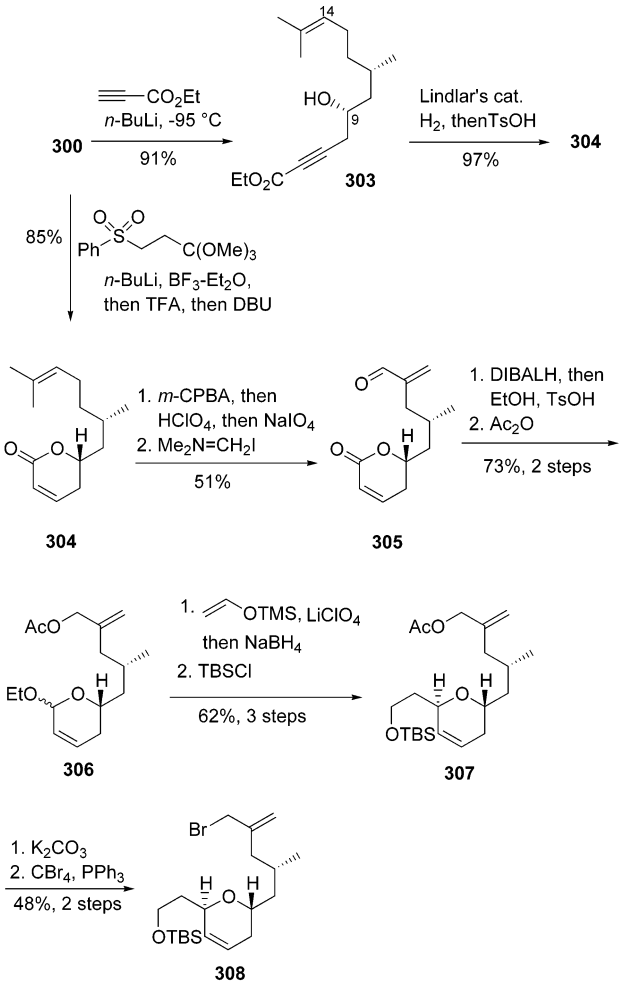
B. Mulzer's (*S*)-Citronellal Based Route to a C_3-C_{14} Fragment

In contrast to Davidson's (*S*)-citronellal-based route to a C_1-C_{14} fragment of **1** (cf. Scheme 45), Mulzer (Schemes 48 and 49)[13c] and later also Crimmins (Scheme 34)[21] utilized the isopropylidene group in **213** as a protective group by starting their synthesis of allylic laulimalide fragments with the introduction of stereocenter C_9. In Mulzer's approach, aldehyde **213** was converted to a 1:1 mixture of epoxide diastereomers **300** and 9-*epi*-**300** via Corey's sulfonium ylide addition.[123] Subsequent Jacobsen's HKR in the presence of catalyst **301**[124] led to the formation of diol **302** along with the desired epoxide **300**. Diol **302** was transformed to **300** by a dehydrative cy-

Scheme 48. Synthesis of Epoxide 300



Scheme 49. Mulzer's Synthesis of Allyl Bromide 308



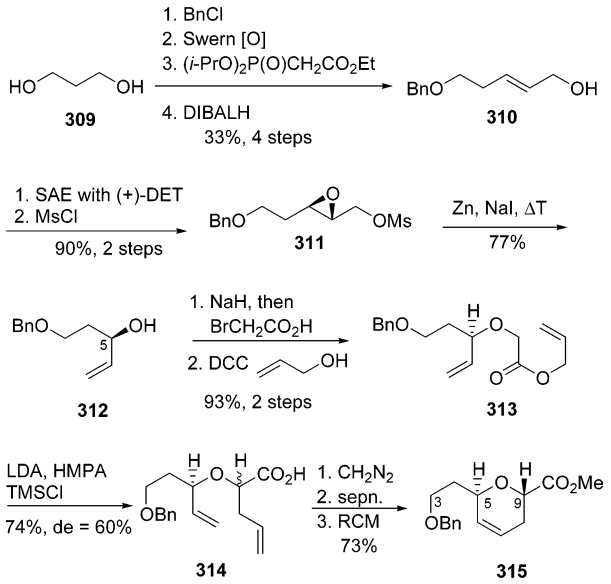
clization under inversion at C_9 providing epoxide **300** in 76% overall yield from **213**.

The conversion of epoxide **300** to dihydropyrone **304** was effected either by Ghosez's sulfone-based procedure[56] or by addition of the anion generated from ethyl propiolate and *n*-BuLi at −95 °C, followed by partial hydrogenation and cyclization (Scheme 49).[125] The electron-rich double bond in **304** was then selectively cleaved to provide the C_{14} aldehyde, which was subjected to Eschenmoser methylenation[31] to generate enal **305**. Reduction of both carbonyl groups in **305** with DIBALH and sequential treatment with EtOH/TsOH and acetylation led to intermediate **306**, ready for the stereoselective introduction of the C_2C_3 appendage. The *C*-glycosidation, performed with commercially available vinyl-OTMS, led to the corresponding C_3 aldehyde, which was converted to allyl bromide **308** via acetate **307**.

C. Syntheses of Laulimalide Subunits by Lee et al.

In 2001, a Korean group reported several RCM-based approaches to the dihydropyran subunits of **1**.[16] The *trans*-disubstituted C_3-C_{10} dihydropyran moiety was to be prepared by Burke's tandem glycolate Claisen rearrangement−RCM strategy.[126] Toward this end (Scheme 50), propane-1,3-diol (**309**) was

Scheme 50. Synthesis of *trans*-Disubstituted Dihydropyran 315

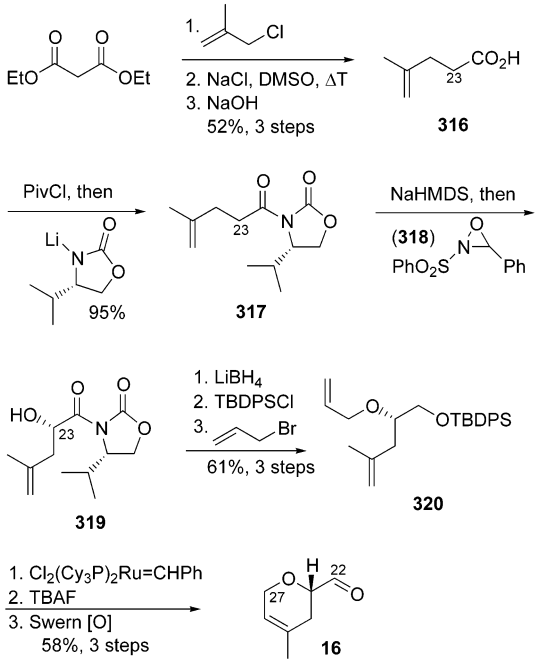


converted to allylic alcohol **310** in four conventional steps. SAE of **310** and ensuing mesylation led to intermediate **311**, which on treatment with Zn/NaI provided secondary alcohol **312** with the required C_5 stereochemistry. The alcohol was etherified with sodium bromoacetate, and the resulting acid was converted into the allyl ester **313**. Rearrangement of **313** via the corresponding TMS−enol ether led to acids **314** as a 4:1 mixture of C_9 epimers, which were separated after esterification with diazomethane. The major isomer was then subjected to RCM with Grubbs' first-generation ruthenium catalyst to provide ester **315** as a C_3-C_{10} fragment of **1**.

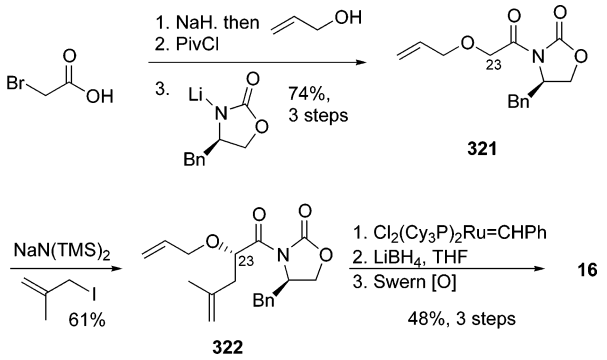
Three different RCM routes to the exocyclic dihydropyran fragment **16** were also presented by Lee's group. The first one[16a] utilized Evans' asymmetric hydroxylation[127] to generate the C_{23} stereocenter (Scheme 51). Thus, alkenyl carboxylic acid **316**, prepared from diethyl malonate by standard chemistry, was connected with the L-valine-derived oxazolidinone to provide intermediate **317**. Hydroxylation of **317** with oxaziridine **318** generated α-hydroxyamide **319** stereoselectively. Reductive removal of the auxiliary led to a diol, which was silylated at the primary and allylated at the secondary hydroxyl group to provide cyclization precursor **320**. RCM of diene **320** followed by deprotection led, after 11 steps, to aldehyde **16**.

"To circumvent the cumbersome use of the oxaziridine reagent", two improved approaches to aldehyde **16** were disclosed in the following communication,[16b] which appeared 6 months later. The first one (Scheme 52) utilized Crimmins' glycolate variation of Evans' methodology.[98] Sodium bromoacetate was converted to allyloxyacetic acid, which was connected with the D-phenylalanine-derived oxazolidinone via the mixed pivaloyl anhydride to furnish intermediate **321**. Alkylation of glycolate **321** with methallyliodide led to a diene with the required C_{23} stereocenter, which was cyclized by RCM to provide the dihydropyran in moderate yield. Reductive removal of the auxiliary followed by Swern oxidation led to aldehyde **16**.[128]

Scheme 51. Synthesis of Aldehyde 16 by Asymmetric a-Hydroxylation-RCM-Strategy

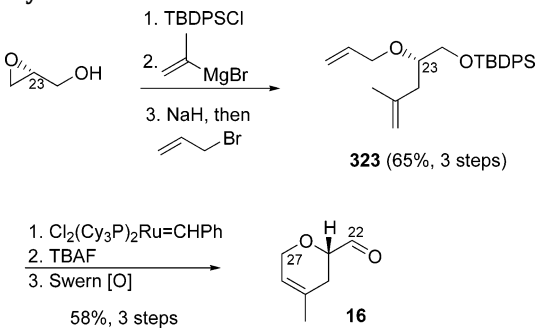


Scheme 52. Synthesis of Aldehyde 16 by Asymmetric Glycolate Alkylation



Eliminating the need of a chiral auxiliary, Lee et al. reported a third approach to aldehyde **16**,[16b] which parallels previous work of Ghosh (Scheme 8) and Mulzer (Scheme 15), by using (*R*)-glycidol for the introduction of the C_{23} stereocenter (Scheme 53). In this route, the TBDPS-protected glycidyl ether was subjected to the same reaction sequence. Interestingly, the epoxide was regioselectively opened without the use of copper salts, and no silyl shifts during epoxide opening and allylation were observed.

Scheme 53. Synthesis of Aldehyde 16 from (*R*)-Glycidol



VI. General Evaluation

After presentation of the complete synthetic work directed to laulimalide, the following short discussion tries to underscore the basic aspects of laulimalide chemistry and also to highlight some of the novel methodology involved.

A. Construction of DHP Fragments

RCM seems to be the most favorable route to construct the exocyclic dihydropyran fragment of **1** (Schemes 8, 15, 16, 35,46, and 53), and it was shown that the ring closure can also be performed regioselectively with advanced intermediates already containing the $C_{21}-C_{22}$ (Scheme 43) and moreover also a $C_{16}-C_{17}$ double bond (Scheme 40). Enantioselective HDA reaction between isoprene and glyoxylates catalyzed by chiral Lewis acids (Scheme 31)[34,35] is, due to concomitant formation of ene products, less efficient. However, HDA methodology was successfully applied by using an 1-alkoxy-substituted diene and Jacobsen's chiral Cr(III) catalyst, followed by reductive displacement of the resulting anomeric alkoxy substituent (Scheme 21).

Starting from chiral C_9 homoallylic alcohols, which were converted to acrylates (Scheme 6) or more favorable to mixed acrolein acetals (Schemes 5, 11, 13, 24, and 45) also, the endocyclic dihydropyran fragment was mostly constructed by RCM. In the approach presented by Crimmins, an advanced tetraene intermediate was utilized for regioselective cyclization (Scheme 34). Alternatively, a propiolate addition−hydrogenation−lactonization sequence (Scheme 49) or Ghosez's sulfone-based method (Schemes 11 and 49) were applied with comparable success. Asymmetric HDA reaction between an aldehyde and a Danishefsky diene in the presence of chiral catalysts (Schemes 1, 30, 38, and 45) leading to chiral dihydropyrones apparently requires extensive screening of catalysts and reaction conditions to obtain satisfactory stereoselectivities. As a novel strategy, chiral β-lactone to dihydropyrone interconversion was applied in Nelson's total synthesis (Scheme 42). The stereocenter in the β-lactone was created by novel asymmetric acyl halide−aldehyde cyclocondensation (AAC) chemistry, which was amply used in Nelson's approach to **1**.

The 5,9-*trans*-disubstitution of the C_5-C_9 dihydropyran fragment was generated commonly by Lewis acid-mediated reaction of ethyl glycosides (without rearrangement) or glycal acetates (via Ferrier rearrangement) with vinyl silyl ethers or more recently by a novel *C*-propargylation with Marshall-type[105] allenyl stannanes (Schemes 38 and 42), which allows the early introduction of the complete C_1-C_4 moiety. Different approaches were presented by Crimmins, who generated first the C_5 stereocenter by asymmetric glycolate allylation and applied RCM to an advanced intermediate (Scheme 34), and also by Wender, who generated the C_5 stereocenter by conjugate addition of vinyl cuprate to a dihydropyrone, followed by reductive removal of the carbonyl group via the corresponding enol triflate (Scheme 30).

Table 1. Antiproliferative Effects of 1, 2, and Paclitaxel in Drug-Sensitive and -Resistant Cells[2a]

compound	IC_{50} [nM]			
	MDA-MB-435[a]	SK-OV-3[b]	SKVLB-1[c]	resistance factor[d]
laulimalide (**1**)	5.74 ± 0.58	11.53 ± 0.53	1.210 ± 490	105
isolaulimalide (**2**)	1.970 ± 97	2.570 ± 290	2.650 ± 1.384	1.03
paclitaxel	1.02 ± 0.25	1.71 ± 1.07	>100.000	>58.480

[a] Human breast adenocarcinoma cell line. [b] Human ovarian carcinoma cell line. [c] Multidrug-resistant subline of SK-OV-3. [d] The IC_{50} value of the resistant line SKVLB-1 divided by the IC_{50} value of the parental line SK−OV-3.

B. Connection of Main Fragments

In the early syntheses, the union of major fragments was achieved by formation of a $C_{16}-C_{17}$ double bond. While the classical three-step variant of the Julia olefination provided poor results (Schemes 4 and 9), Kocienski's one-step modification led to higher yield and improved *E*-selectivity (Scheme 18). With one exception, the ensuing syntheses uniformly utilized bond construction between C_{14} and C_{15} with concomitant creation of the C_{15} stereocenter to connect the main fragments. This was achieved either by asymmetric boron−aldol reaction (Schemes 23 and 44) or by allylsilane (stannane) chemistry (Schemes 29, 33, 37, and 41). Only in the approach of Mulzer and Enev, the major fragments were connected by a highly stereoselective formation of the 2,3-*Z*-enoate through Still−Gennari olefination (Scheme 26).

C. Macrocyclization

In the early approaches to **1**, construction of the laulimalide macrocycle by intramolecular HWE olefination using Still−Gennari's or Ando's method (Schemes 9 and 18) as well as base-induced macrolactonization (Scheme 29) led to extensive loss of 2,3-*Z*-geometry. In the subsequent syntheses, the ring closure was therefore performed according to Ghosh's precedence, by macrocyclization of a 2,3-ynoic acid and subsequent Lindlar hydrogenation in the presence of 1-hexene (Schemes 41 and 43). In the synthesis of Wender it was additionally shown that this ring closure proceeds regioselectively in the presence of an unprotected 20-hydroxy group (Scheme 33). Alternatively, macrocyclization with retention of 2,3-*Z* geometry was also achieved under inversion at C_{19} by Mitsunobu's protocol (Scheme 23), and it was shown that this reaction can also be performed in the presence of the 16,17-epoxide (Scheme 37). A totally different macrocyclization strategy was applied in the total synthesis of Mulzer and Enev, who achieved the macrocyclization by acetal-directed allyl transfer (Scheme 26).

D. The Endgame

In Ghosh's early syntheses, the epoxidation was performed on a 20-OPMB-protected macrocycle and final removal of the PMB ether provided laulimalide in moderate yield. To avoid isomerization to the isolaulimalide skeleton and/or loss of 2,3-*Z* geometry during a final deprotection step, reagent-matched regio- and stereoselective SAE of the unprotected macrocycle was mostly applied (Schemes 19, 23, 26, 33, and 47). Attempts to remove two TBS ethers from the complete laulimalide skeleton by conventional deprotection methods led indeed to decomposition.[22] However, this deprotection was successfully achieved without isomerization by careful exposure to HF−triethylamine (Scheme 37).

VII. Antitumor Activity of Laulimalides and Analogues

In the first cytotoxicity tests with laulimalide (**1**) and isolaulimalide (**2**), it was shown that **1** is significantly more active against the KB cell line (5 ng/mL) than **2** (>200 ng/mL).[1a] In the adjoining communication,[1b] the inhibition of cell growth was investigated with synthetic laulimalide diacetate and isolaulimalide, using HT-29 (human colon tumor), P388 (murine lymphoma), A549 (human lung tumor), and HL-60 (human promyelocytic leucemia) cells. IC_{50} values in the low micromolecular range, 9−14 and 0.5−6 μM, were obtained for $C_{15}-O$,$C_{20}-O$-diacetyl-**1** and **2**, respectively. In Higa's more recent study,[1d] the same cell lines and additionally the MEL28 line were used to determine the activity of unprotected **1** and its minor congener neolaulimalide (**3**). Very high activity ($IC_{50} = 0.01-0.05$ μM) was observed for both compounds in the same assay.

In February 1999, a mechanism-based screening program, aiming for the discovery of new antimicrotubule agents from natural products, identified **1** and **2** as compounds with microtubule-stabilizing activity.[2a] Treatment of A-10 cells (rat aortic smooth muscle cell line, a nontransformed line) with **1** resulted in a dose-dependent reorganization of the microtubule network in the cells and in the formation of microtubule bundles and abnormal mitotic spindles. Coincidentally, **1** and **2** induced nuclear convolution and the formation of multiple micronuclei. Incubation of MDA-MB-435 cells with **1** resulted in mitotic arrest and activation of the proteolytic enzymes that accompany apoptotic cell death.

Like paclitaxel, **1** inhibited the cell proliferation of the drug-sensitive cell lines SK-OV-3 (ovarian carcinoma) and MDA-MB-435 (human breast adenocarcinoma), the IC_{50} values being between 5 and 12 nM. Isolaulimalide (**2**) was less potent with values in the low μM range (Table 1). Most importantly, both **1** and **2** also inhibited the proliferation of the multidrug-resistant SKVLB-1 cell line (a subline of SK-OV-3) that overexpresses the drug efflux pump P-glycoprotein, whereby laulimalide was as much as 100-fold more potent than paclitaxel in the same assay. These data confirm that **1** and **2** are poor substrates for transport by P-glycoprotein, a property that may provide advantages over the taxanes.

Further exciting data were recently communicated by Hamel et al.[2b] It was shown that **1**, while as active

Table 2. Human Ovarian Carcinoma Cells Resistant to Paclitaxel and Epothilones Remain Sensitive to Laulimalide (1)[2b]

	IC50 [nM] (resistance factor)[a]					
compound	1A9[b]	PTX10[c]	PTX22[c]	A8[d]	B10[e]	A2780/AD10[f]
laulimalide (**1**)	3.9 ± 0.4	6.0 ± 1 (1.5)	6.3 ± 1 (1.6)	9.2 ± 2 (2.4)	15 ± (0.2) (3.8)	31 ± 0.6 (7.9)
epothilone A	1.7 ± 0.3	18 ± 7 (11)	4.3 ± 1 (2.5)	93 ± 30 (55)	125 ± 25 (74)	16 ± 0.6 (9.4)
epothilone B	0.17 ± 0.08	0.70 ± 0.4 (4.1)	0.32 ± 0.2 (1.9)	6.4 ± 4 (38)	9.0 ±5 (53)	2.6 ± 2 (15)
paclitaxel	1.7 ± 0.3	50 ± 11 (29)	34 ± 3 (20)	13 ± 2 (7.6)	16 ±4 (9.4)	4000 ± 900 (2400)

[a] IC_{50} value of the resistant line divided by the IC_{50} value of the parental line 1A9. [b] Parental cell line, a clone of line A2780. [c] Paclitaxel-resistant cell lines selected from 1A9. [d] Epothilone A-resistant cell line selected from 1A9. [e] Epothilone B-resistant cell line selected from 1A9. [f] Multidrug-resistant, P-glycoprotein overexpressing cell line, derived from line A2780, selected in the presence of adriamycin.

as paclitaxel, epothilone A, and eleutherobin in promoting the assembly of cold-stable microtubules, was unable to inhibit the binding of [^{3}H]-paclitaxel or a fluorescent paclitaxel derivative to tubulin. Moreover, microtubules formed in the presence of **1** and paclitaxel contained approximately equivalent quantities of both drugs. These findings strongly suggest the existence of a drug binding site on microtubules distinct from that occupied by taxoids. (However, to date, it cannot be excluded that **1** binds already to unpolymerized tubulin or to structurally aberrant polymers). Results obtained with paclitaxel- and epothilone-resistant cell lines bearing mutated β-tubulin genes further support this conclusion and underline the high biological potential of **1**. Although the paclitaxel-resistant mutants (PTX10, PTX22) remain sensitive to the epothilones and the epothilone-resistant mutants (A8 for epothilone A, B1 for epothilone B) remained partially sensitive to paclitaxel, the relative resistance values (i.e., the IC_{50} value of the resistant line divided by the IC_{50} value of the parental line) for laulimalide (**1**) were the lowest observed in all cases (Table 2).

To date, only two initial studies exist concerning the effect of synthetic laulimalide derivatives on cell growth.[2b,18d] In Hamel's recent article,[2b] deoxylaulimalide (**79**) and synthetic **1**[17c] were compared to paclitaxel for their effects on the growth of human MCF-7 breast cancer cells. In fact, compound **79**, missing the C_{16},C_{17}-epoxide, exhibited reduced potency (1/50 of **1**), as demonstrated by the IC_{50} values of 360, 7.0, and 2.4 nM for **79**, **1**, and paclitaxel, respectively.

In the recent full account on Mulzer's laulimalide-related work,[18d] laulimalide (**1**), deoxylaulimalide (**79**), and the corresponding analogues with 2,3-*E*-enoate (desepoxy compound **121** and its 16,17-epoxide **123**) were tested for their effects on the proliferation of two drug-sensitive human breast cancer cell lines (MCF-7, MaTu) and two multidrug-resistant human breast tumor lines (NCI/ADR, MaTu/ADR), along with paclitaxel and epothilone B as standards (Table 3). It turned out that **1** is about as active as paclitaxel against the drug-sensitive cells. Unlike paclitaxel, **1** retained its activity against the drug-resistant cell lines, but in all cases it was significantly less active than epothilone B. Compound **121** (2,3-*E*-enoate, no epoxide) exhibited no activity at all. Deoxylaulimalide (**79**) and compound **123** (the 16,17-epoxide derived from 2,3-*E*-macrolide **121**) displayed diminished activity (Table 3).

Table 3. Antiproliferative Effects of Laulimalides 1, 79, 121, and 123, Compared with Paclitaxel and Epothilone B[18d]

	IC_{50} [nM]			
compound	MCF-7[a]	NCI/ADR[b]	MaTu[a]	MaTu/ADR[b]
121[c]	ni[f]	ni	ni	ni
79[d]	89	ni	43	170
123[e]	54	ni	38	250
laulimalide (1)	3.8	36	3.8	6.0
epothilone B	0.59	3.5	0.46	1.2
paclitaxel	3.2	>1000	3.3	600

[a] Human breast tumor cell line. [b] Human multidrug-resistant breast tumor cell line. [c] 2,3-*E*-16,17-Deoxylaulimalide. [d] 2,3-*Z*-16,17-Deoxylaulimalide. [e] 2,3-*E*-Laulimalide. [f] No inhibition measured up to 100 nM.

VIII. Conclusion and Prospects

Laulimalide, a new member of the growing family of nontaxane natural compounds with microtubule-stabilizing activity that displays antimitotic activity also against paclitaxel- and epothilone-resistant tumor cell lines, has attracted significant attention in both the synthetic organic and the medicinal communities. A variety of total syntheses was accomplished within the last 3 years. Problems arising from the presence of the (*Z*)-enoate and the epoxide, which are both highly sensitive to isomerization, have been overcome by novel macrocyclization strategies and by stereoselective last-step epoxidation. Due to lack of material, the in vivo evaluation of laulimalide and of the few analogues which have been synthesized to date has yet not been possible. However, as short and economical solutions for the construction of main fragments and their conjunction have been developed, it will be possible to design and synthesize further analogues that might be helpful to identify the critical structural features necessary for improved stability and biological activity.

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