Grubbs' RCM in the Total Synthesis of the Microtubule Stabilizing Drug Laulimalide

Johann Mulzer,* Elisabeth Öhler, Valentin S. Enev, Martin Hanbauer

Institut für Organische Chemie der Universität Wien, Währinger Strasse 38, 1090 Vienna, Austria
Fax: (+43)-1-4277-52190, e-mail: johann.mulzer@univie.ac.at

Received: January 30, 2002; Accepted: March 12, 2002
Dedicated to Professor Lutz-F. Tietze on the occasion of his 60th birthday

Abstract: Two independent syntheses of the microtubule stabilizing antitumor agent laulimalide are described, which mainly differ with respect to the macrocyclization step. The first synthesis employs a Still–Gennari olefination and the second one an Alexakis-type, allylsilane/acetal addition to close the final ring. For the construction of the dihydropyran subunits, RCM methodology and alternative strategies are presented in comparison.

1 Introduction
2 Still–Gennari Macrocyclization Route
3 Allylsilane/Acetal Macrocyclization Route
4 Conclusion

Keywords: allyl transfer; antitumor compounds; marine organisms; microtubule stabilization; ring-closing metathesis; Still–Gennari macrocyclization, total synthesis

1 Introduction

Laulimalide (**1**), also known as fijianolide B, was isolated from the marine sponges *Cacospongia mycofijiensis* and *Hyatella* sp., respectively, by the groups of Moore[1a] and Crews.[1b] Later Higa and his group isolated **1** from the Okinawan sponge *Fasciospongia rimosa*[2a] and determined the structure by X-ray analysis. Very recently, **1** (along with isolaulimalide, **2**) has also been isolated from *Dactylospongia* sp., a sponge from Vanuatu islands.[2b] Compound **1** exhibits antitumor activity against numerous tumor cell lines at the ng/mL level, and maintains a high toxicity even against the multi-drug-resistant cell line SKVLB-1. It has been shown by Mooberry and coworkers[3] that **1** shows the same mechanism of action (i.e., microtubule stabilization) as the extremely successful drug taxol (paclitaxel)[4] and its potential successors epothilone,[5] discodermolide,[6] eleutherobin,[7] and FR182877.[8] A major advantage of **1** may be seen in the fact that it inhibits the P-glycoprotein which is responsible for multi-drug resistance in tumor cells. This underscores the potential that **1** has as a forthcoming anticancer drug.

So far, altogether five total syntheses of **1** have been reported,[9] along with several approaches to major fragments thereof.[10] As in the total synthesis of the epothilones, Grubbs ring-closing olefin metathesis (RCM)[11] reactions have been used abundantly in many approaches to **1**, in particular when preparing the two dihydropyran rings.[9a, c,d, e,10b, c,f, g,i-l, n,o] Remarkably, an attempted RCM macrocyclization connecting C2-C3 has been unsuccessful so far.[9c] In this review we highlight our two recent total syntheses of **1**.[9d, e] Specifically, we will focus on the two dihydropyran fragments, which have been prepared by RCM and other methodology, so that a comparison can be made of the alternative approaches.

The total synthesis of **1** is complicated by the sensitivity of the compound towards dilute acid. Even 0.01 N HCl[1a] (or camphorsulfonic acid in dichloromethane[9f]) causes rapid destruction of the epoxide by ring closure to the tetrahydrofuran derivative isolaulimalide (**2**) which shows a drastically reduced antitumor activity (Scheme 1). This fact makes the endgame of a total synthesis extremely challenging, in particular with respect to potential *O*-protective groups on the C20-hydroxy function. At any rate, *O*-protected deoxylaulimalide **3** emerged as a logical retrosynthetic precursor of **1**, the imminent formation of **2** during protective group removal notwithstanding.

2 Still–Gennari Macrocyclization Route

For the formation of **3** two possible ring-closing processes could be envisaged (Scheme 2): a Still–Gennari macrocyclization[12] of phosphonate aldehyde **4**, hopefully to generate an excess of the 2,3-*Z*-olefin, or alternatively a Yamaguchi-type macrolactonization[13] of *seco*-acid **5**. The latter possibility was soon discarded, as at the stage of the activated ester a rapid *E/Z*-equilibration of the 2,3-enoate had to be expected. So we concentrated on precursor **4** (Scheme 3).

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Johann Mulzer was born in 1944 at Prien in Upper Bavaria. In 1974 he received his PhD under the supervision of Rolf Huisgen at the Ludwigs-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 is 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, among others, morphine, tartrolone B, epothilones, cobyric acid, and laulimalide.

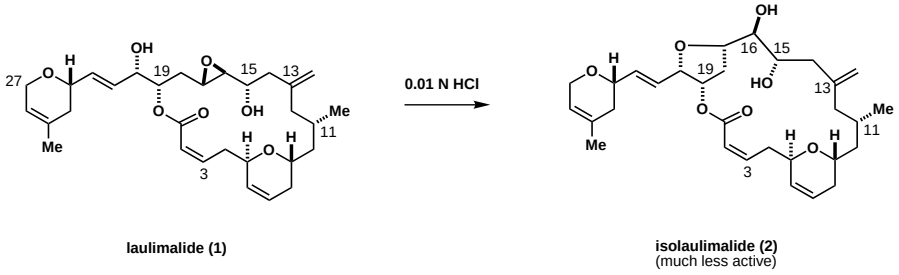
Elisabeth Öhler was born in Vienna and received her PhD in organic chemistry at the University of Vienna in 1968 for work on Reformatsky-type reactions under the guidance of Ulrich Schmidt. Afterwards she joined Erich Zbiral to explore phosphorous chemistry. Since 1996 she is a senior research fellow in the Mulzer group. Apart from laulimalide she has greatly contributed to epothilone syntheses.

Valentin Enev was born in 1957 in Sofia, Bulgaria and received his PhD at the Bulgarian Academy of Science. From 1986 – 1992 he was an Assistant Professor at Bulgarian Academy of Science. In 1992 he moved to the University of Zürich with a postdoctoral fellowship into the group of Doz. Dr. S. Bienz, and from 1993 – 1997 he was a Senior Researcher at Schering AG/Berlin. In 1998 he joined the Mulzer group as a postdoctoral research fellow, and since 2002 he is a Vertragsassistent at the University of Vienna.

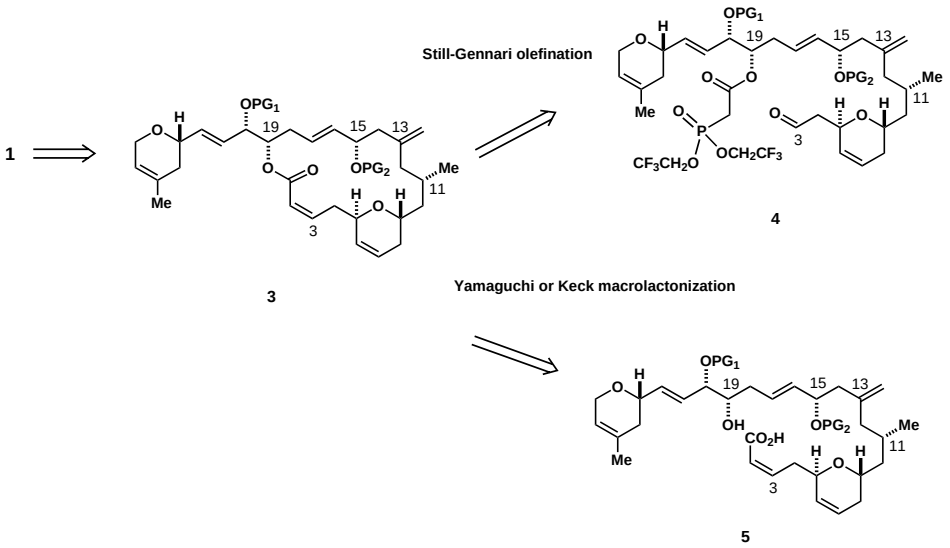
Martin Hanbauer was born 1975 in Waidhofen/Ybbs; Lower Austria and received his diploma in 1998 under the supervision of Prof. F. Hammerschmidt at the University of Vienna. Since 1999 he is working in the Mulzer group on the total synthesis of laulimalide within the context of his PhD thesis.

The C16,17-*E*-olefinic bond of **4** was to be generated from fragments **6** and **7** by a Julia–Kocienski olefination.[14] Concerning the protective group strategy in our synthesis, we decided to use the same protective groups (i.e., MOM) for the C20- and the C15-alcohol and orthogonal protective groups (TBS and PMB, respectively) for the C3- and the C19-hydroxy functions.

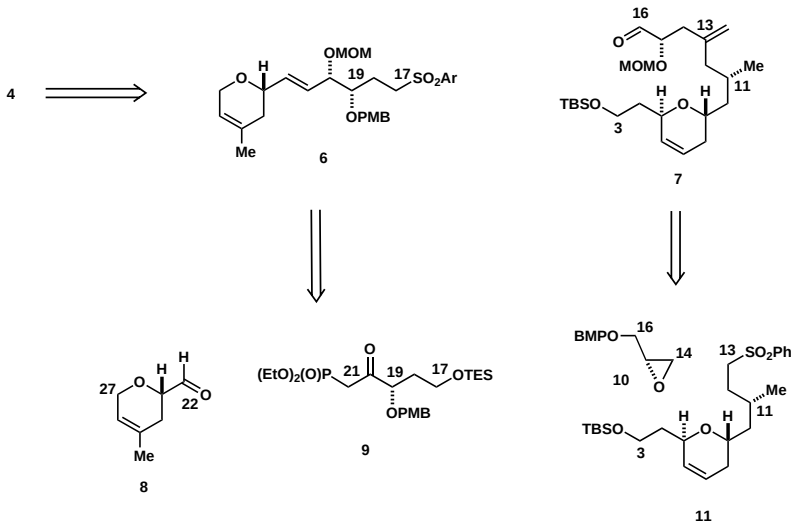
Furthermore, we planned to synthesize sulfone **6** and aldehyde **7** from inexpensive chiral carbon pool compounds, such as D-mannitol, *S*-malic acid, and D-glucose, respectively. Intermediates **6** and **7** were to be assembled from the smaller fragments **8**, **9** and **10**, **11**, respectively, and it was decided to prepare the dihydropyrans **8** and **11** not only by the relatively obvious RCM,[15] but also by other competing methodology. The C27-C17 sulfone **6** was to be assembled via Horner–Wadsworth–Emmons olefination of aldehyde **8** and ketophosphonate **9**, whereas aldehyde **7** should be prepared by addition of C13-metallated sulfone **11** to epoxide **10** and subsequent introduction of the C13 methylene group.



Scheme 1. Acid-catalyzed rearrangement of laulimalide to isolaulimalide.



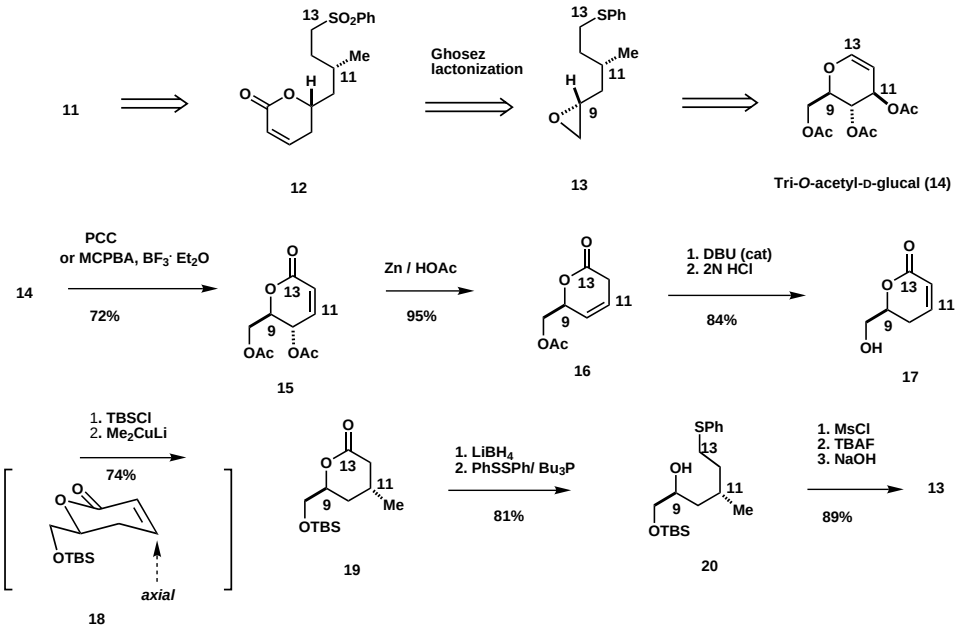
Scheme 2. Macrocyclization strategies for laulimalide.



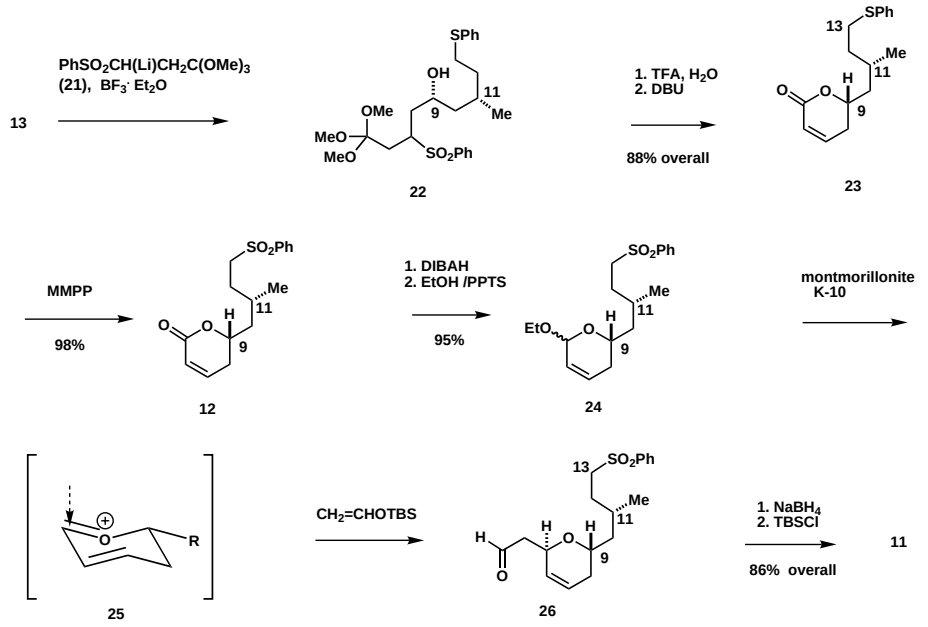
Scheme 3. Retrosynthetic considerations.

Our first approach[9d] to sulfone **11** was based on a Ghosez lactonization[16] of epoxide **13** which should be available from inexpensive tri-*O*-acetyl-D-glucal (**14**) (Scheme 4). Thus, the synthesis started from the known α,β-unsaturated lactone **17**, readily available from **14** in four steps.[17] After conversion to the OTBS-derivative, axial addition of dimethylcopper lithium to conformer **18** smoothly provided the desired 9,11-*trans* disubstituted lactone **19** as a single diastereomer.[18] The formation of epoxide **13** required an inversion of configuration at C9. Therefore, **19** was reduced to the 1,5-diol, and the primary alcohol at C13 was selectively transformed to the corresponding phenyl sulfide **20** by treatment with tributylphosphine/diphenyl disulfide.[19] Mesylation of the C9-hydroxy group, desilylation, and ring closure with sodium hydroxide delivered epoxide **13**. Elaboration into the dihydropyran **11** was accomplished via reagent **21** which gave adduct **22** and, after two more work-up steps, lactone **23** in 88% overall yield (Scheme 5). Oxidation of the sulfide gave sulfone **12** which was converted to the ethyl glycoside **24**. The C3-C4 unit was stereoselectively introduced (Scheme 3) by generating oxonium ion **25** from **24** which underwent axial addition[10a,20] of *t*-butyldimethylsilyl vinyl ether to form aldehyde **26**. Sodium borohydride reduction and TBS protection gave the C3-C13 fragment **11**.

Alternatively, **24** was prepared via RCM of diene **28** with Grubbs' catalyst **29**[21] in 89% yield. Diene **28** was obtained from epoxide **13** via sulfone **27** (Scheme 6). Additionally, intermediate **11** was prepared along another route also employing Grubbs RCM.[10f] Specifically, known alcohol **30**[22] was converted into aldehyde



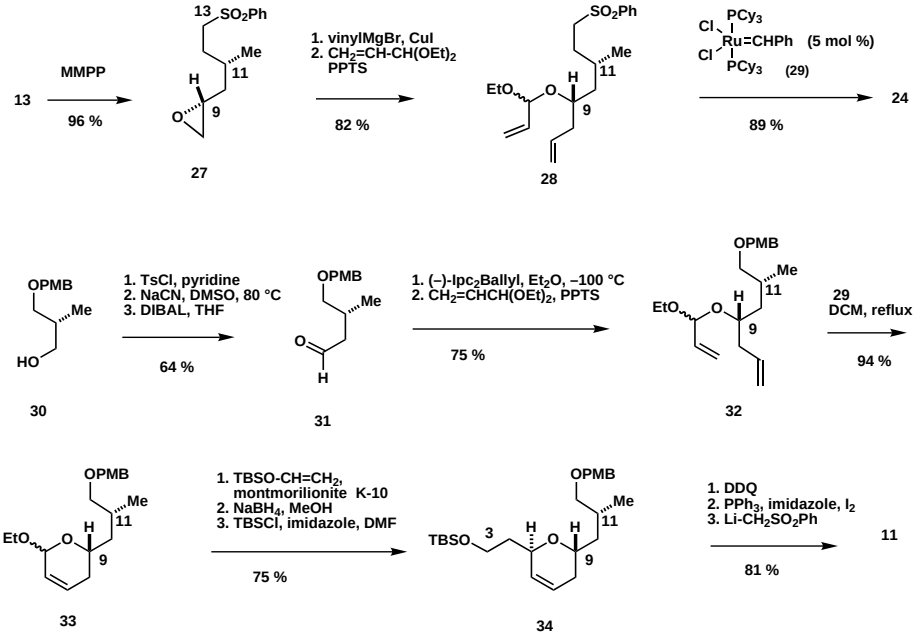
Scheme 4. Synthesis of epoxide **13**.



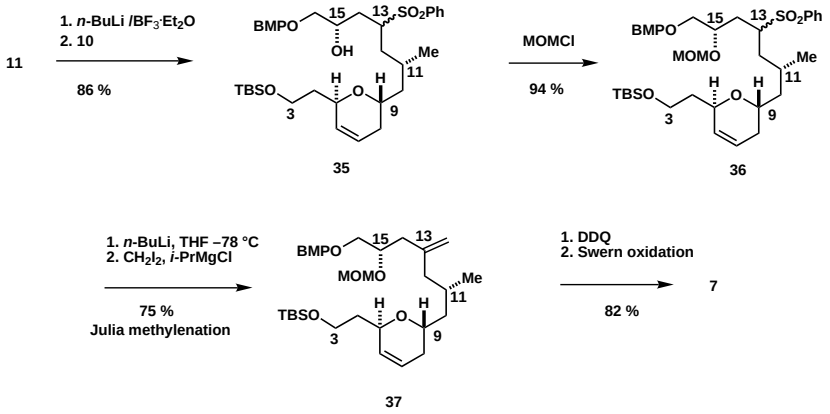
Scheme 5. Synthesis of dihydropyran **11** by Ghosez lactonization.

31, which was elaborated into diene **32** via Brown allylation[23] (de 92%) and transketalization with acrolein diethyl acetal. The anomeric mixture of acetals **32** was treated as before to form **34**, which was converted into intermediate **11** in three steps. On comparing the three alternative routes to key intermediate **11**, the Ghosez lactonization pathway appears the best one with respect to overall yield and ease of preparation. The RCM routes (which have been used in modified forms also by Ghosh[9a,10b] and Davidson[10j]) perform well with respect to the yield, however, in our synthesis, they are handicapped by the tricky transketalizations required to form the dienes **28** and **32**, respectively.

Next (Scheme 7) sulfone **11** was converted into a 1:1 mixture of the C13-epimeric sulfones **35** by deprotonation and subsequent treatment with glycidyl ether **10**.[24] After formation of the 15-OMOM ether **36** the C13-methylene moiety was introduced via a Julia methylenation[25] to give **37**. Deprotection of the 16-PMB ether followed by Swern oxidation completed the synthesis of aldehyde **7**,[9d] which is also a key fragment in the Ghosh synthesis.[9a, c]



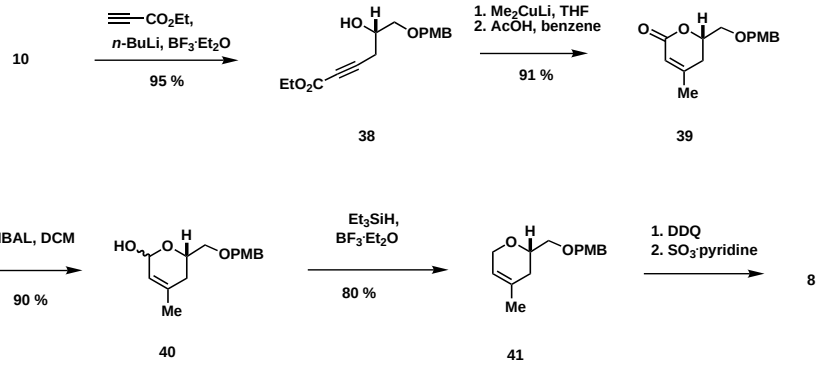
Scheme 6. Synthesis of dihydropyran **11** by RCM.



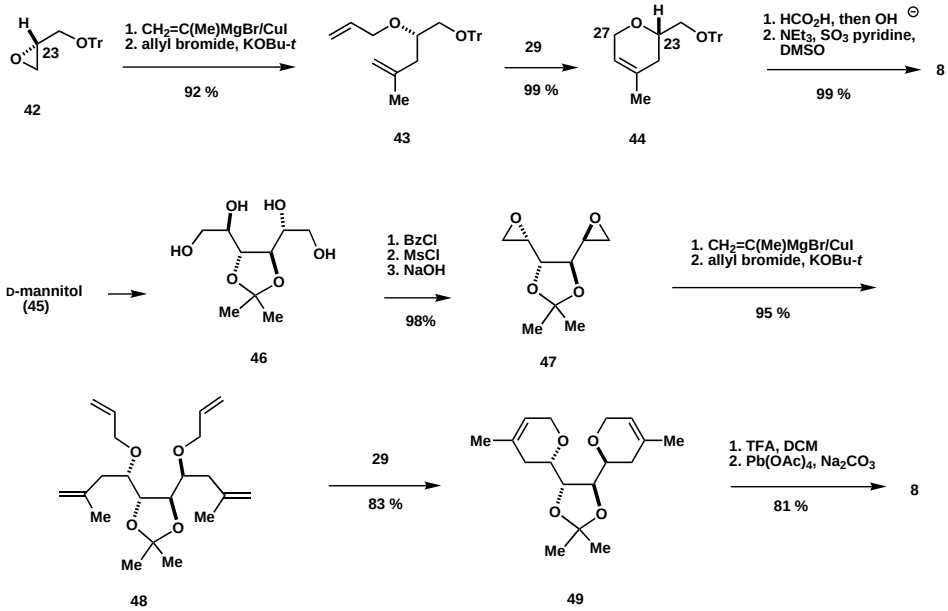
Scheme 7. Synthesis of the C3-C16 fragment.

We next turned to the synthesis of dihydropyran aldehyde **8**. Altogether three approaches were tested, two of which were based on RCM. In the first one (Scheme 8),[10g] we used non-RCM chemistry by starting from glycidyl ether **10**, which was opened at the least hindered side with the anion of ethyl propiolate to give alcohol **38**. Stereoselective cuprate addition and cyclization with acetic acid led to lactone **39**, which was reduced with DIBAL to give lactol **40**. Reduction of the hemiacetal with triethylsilane furnished dihydropyran **41** which was deprotected and oxidized to aldehyde **8**. The first RCM route[10g] (Scheme 9) started with glycidyl ether **42** which was opened with isopropenylmagnesium bromide under copper(I) catalysis. Allylation of the resulting alcohol furnished diene **43**, which gave dihydropyran **44** under modified[26] Grubbs RCM conditions. Deprotection and oxidation furnished aldehyde **8**.

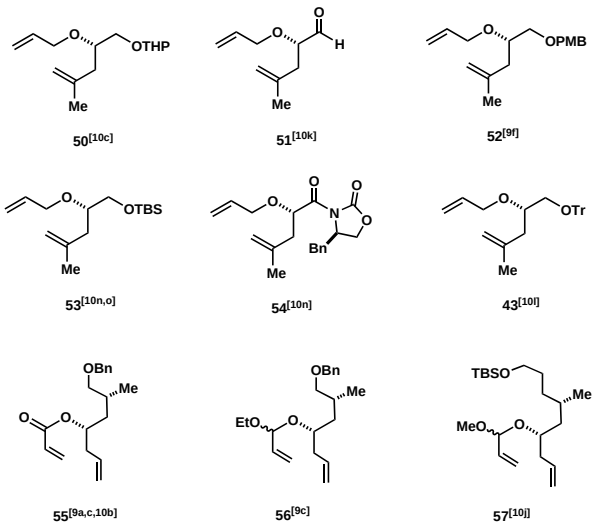
In a more sophisticated approach,[10i] two-directional synthesis[27] was applied by starting from mannitol-derived acetonide **46**, which was converted into bis-epoxide **47**[28] under two-fold inversion of configuration. Further transformation as described above gave tetraene **48** which was subjected to Grubbs RCM. No medium ring-sized cycloolefins were formed across the central acetonide ring which served as a barrier to cross-over metathesis.[29] In this way the bis-dihydropyran **49** was obtained which was converted into **8** via hydrolysis of the central acetonide and glycol cleavage. This approach had the advantage of generating the highly volatile and sensitive aldehyde **8** in high purity under neutral conditions, which were not so easily achieved when preparing **8** from the corresponding alcohol. In the meantime, a series of close analogues (**50 – 57**) of dienes **28**, **32**, and **43** have been subjected to RCM by other



Scheme 8. Synthesis of aldehyde **8** via acetylide addition.



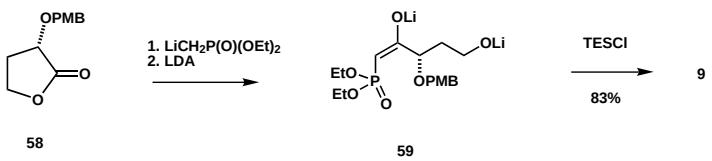
Scheme 9. Synthesis of aldehyde **8** by RCM.



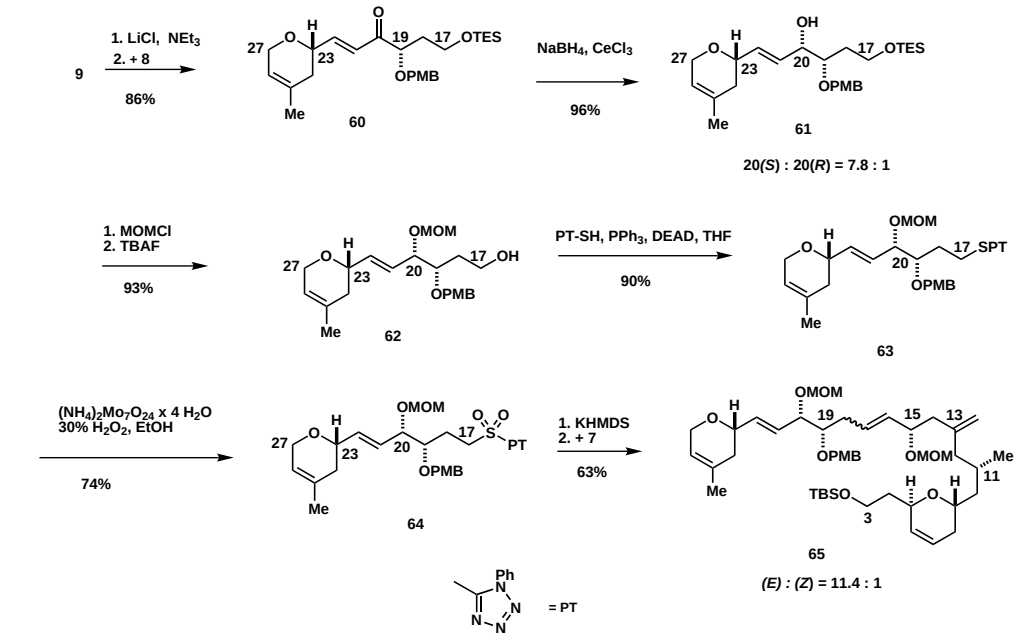
Scheme 10. Literature substrates for RCM preparation of laulimalide dihydropyran subunits.

authors to prepare the C5-C9- and C27-C23-dihydropyrans of **1** (Scheme 10). Aldehyde **51** and acrylate **55** exhibit a relatively low RCM yield, whereas the yields of the other examples are close to ours.

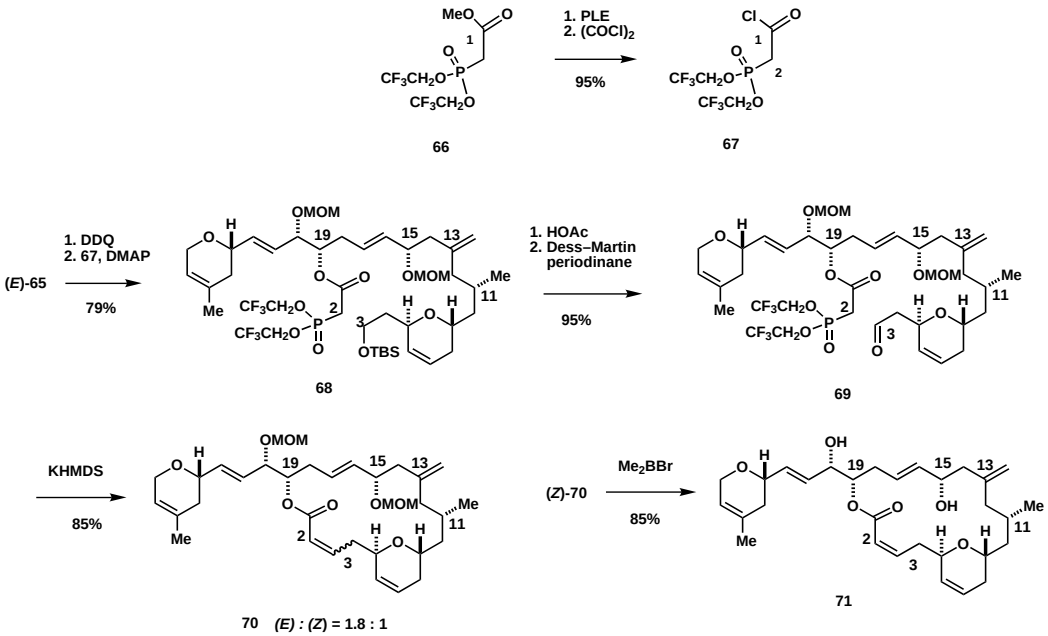
The synthesis[9d] of β-oxophosphonate **9** (Scheme 11) started from the known butyrolactone **58**,[30] easily obtained from natural *S*-malic acid. Reaction of **58** with the lithium salt of diethyl methanephosphonate and subsequent addition of one equivalent of lithium diisopropylamide[31] provided enolate **59** which was silylated to give **9** after hydrolytic work-up.



Scheme 11. Synthesis of phosphonate **9**.



Scheme 12. Synthesis of fragment **65**.



Scheme 13. Still–Gennari macrocyclization in the synthesis of deoxylaulimalide **71**.

Olefination[32] of **9** with aldehyde **8** afforded enone **60** stereoselectively in 87% yield (Scheme 12). Luche reduction[33] at –95 °C produced a 7.8:1 C20-epimeric mixture in favor of the desired (20*S*)-epimer **61**. After separation by HPLC, the (20*R*)-epimer was recycled by Parikh–Doering oxidation.[34]

Alcohol **62** was obtained from **61** by MOM-protection and desilylation and treated with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions[35] to give sulfide **63**. Oxidation[36] of **63** furnished the crystalline sulfone **64**, which was connected with aldehyde **7** by a one-pot Julia–Kocienski olefination[14] to give an 11.4:1 *E,Z*-mixture of olefins, from which (*E*)-**65** was isolated by chromatography. For the completion of the synthesis (Scheme 13) bis(2,2,2-trifluoroethyl)phosphonoacetyl chloride **67** was prepared from commercially available methyl ester **66** by PLE-catalyzed ester hydrolysis and subsequent treatment with oxalyl chloride. The C19 hydroxy group in (*E*)-**65** was deprotected and acylated with **67** to form ketophosphonate **68**. 3-*O*-Desilylation

was achieved smoothly with acetic acid (attempted desilylation with tetra-*n*-butylammonium fluoride resulted in decomposition of the phosphonate moiety) and the resulting alcohol was converted into aldehyde **69** by Dess–Martin oxidation.[37] Macrocyclization under Still–Gennari conditions (KHMDS, 18-crown-6, THF, 50 min, –78 °C) led to a 1.8:1 *E,Z*-mixture of the olefins **70**, which could be separated by chromatography. (*Z*)-**70** was *O*-deprotected with dimethylboron bromide[38] to generate 16,17-deoxy-laulimalide **71**.

3 Allylsilane/Acetal Macrocyclization Route

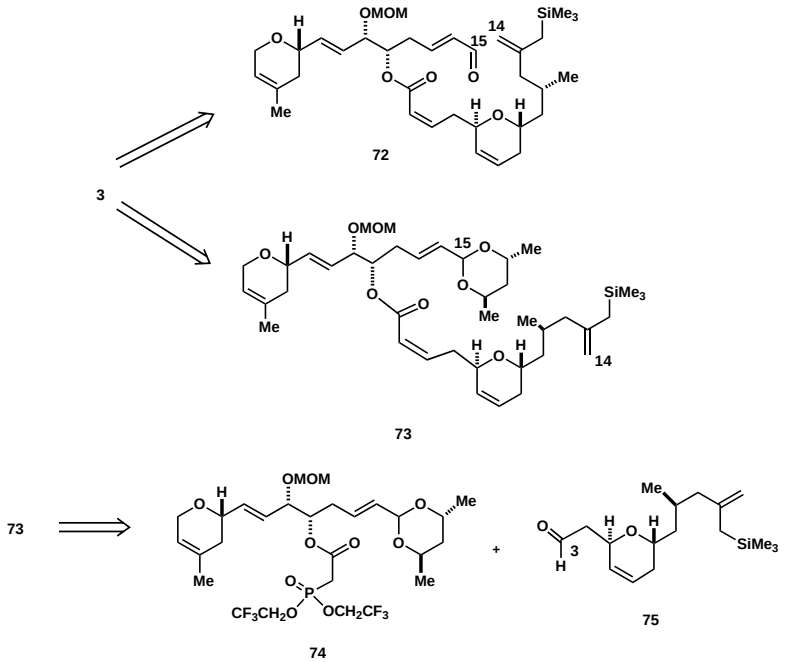
To avoid the formation of 2,3-*E,Z*-mixtures, an alternative approach to **71** was envisaged. Instead of forming the macrocyclic ring by olefination, it appeared more appropriate to use an allylic transfer reaction[39] for closing the C14-C15-bond (Scheme 14).

For instance, the cyclization of *seco*-precursor **72** should occur under very mild conditions, so that a (*Z*)-enoate in the C2-C3-position could easily survive. For obtaining stereocontrol over center C15 it was advisable to convert aldehyde **72** into the chiral acetal[40] **73** which would be opened by the allylsilane in a stereodefined manner. Retrosynthetically, **73** was to be generated by combining fragments **74** and **75** via Still–Gennari olefination.

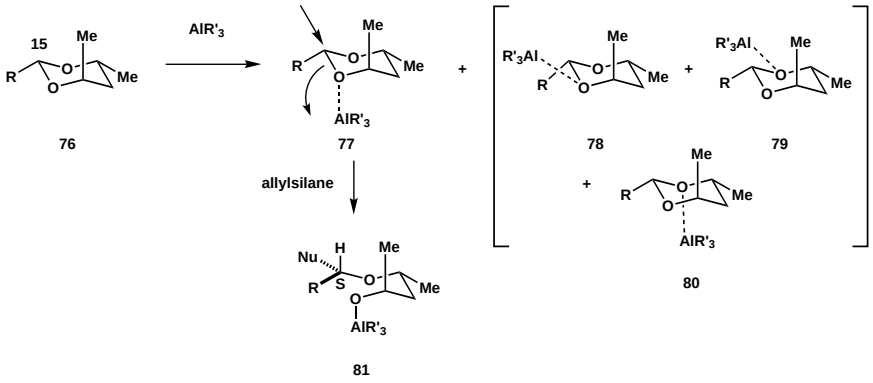
Acetals of type **76** contain a non-stereogenic chirotopic acetal center, so that no stereounambiguity can arise in the formation of center C15 (Scheme 15). The diastereotopic differentiation of the two oxygens occurs during activation with Lewis acids, e.g., $EtAlCl_2$.[40c,41] Altogether, four diastereomeric complexes (**77 – 80**) can be formed, among which **77** is energetically favored, because AlR'_3 has only one *syn*-interaction with a vicinal substituent. In contrast, **78 – 80** all have two such vicinal interactions. Thus, the allylsilane selectively reacts with **77** to generate **81** under inversion of configuration at C15.[40c]

The synthesis of the allylsilane **75** was started from commercially available (*R*) ethyl hydrogen 3-methylglutarate **82** (Scheme 16), which was elaborated into the diene **84** via homoallylic alcohol **83**. The transketalization from acrolein diethyl acetal was facilitated by the stability of the amide; subjecting ester **83** to the same conditions led to the formation of the δ-lactone.

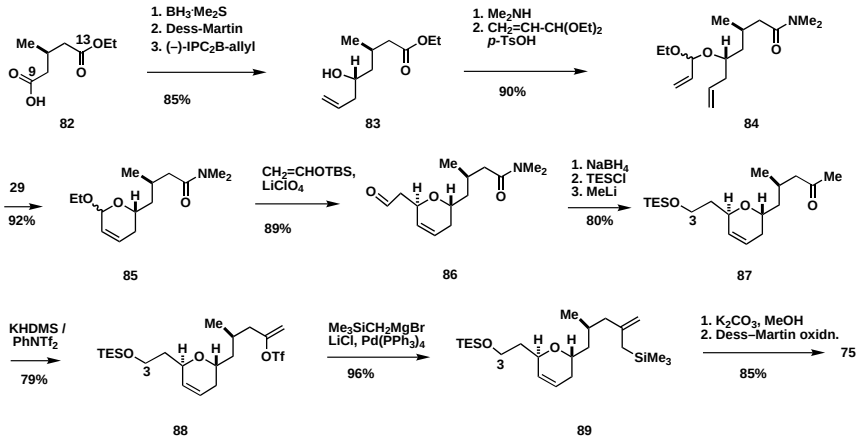
Grubbs RCM worked perfectly to convert **84** into dihydropyran **85**, and the introduction of the C3-C4 side-chain was performed as before to generate aldehyde **86**. Three additional steps were required to prepare ketone **87**. Under kinetically controlled deprotonation (KHMDS, 1.5 equiv.), and subsequent treatment with $PhNTf_2$ enol triflate **88** was obtained as a single regioisomer, which was – following Kuwajima's protocol[42] – treated with $TMSCH_2MgBr$ (6 equiv.) in the presence of $Pd(PPh_3)_4$ (30 mol %) to give, after 1 h, an inseparable 1:1 mixture of allylsilane **89** and its $\Delta^{12,13}$-isomers. Quite obviously, the large amount of the catalyst and the long reaction time have led to isomerization. The similarity of the described protocol and the Stille coupling[43] prompted us to perform the reaction in the presence of 5 equiv. LiCl and 5 mol % $Pd(PPh_3)_4$.



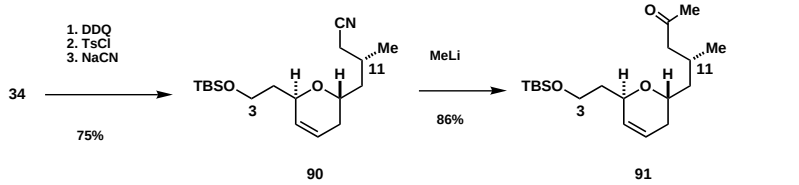
Scheme 14. Allylsilane cyclization strategies for the synthesis of protected deoxylaulimalide **3**.



Scheme 15. Stereochemical course of acetal/allylsilane addition.



Scheme 16. Synthesis of aldehyde **75**.



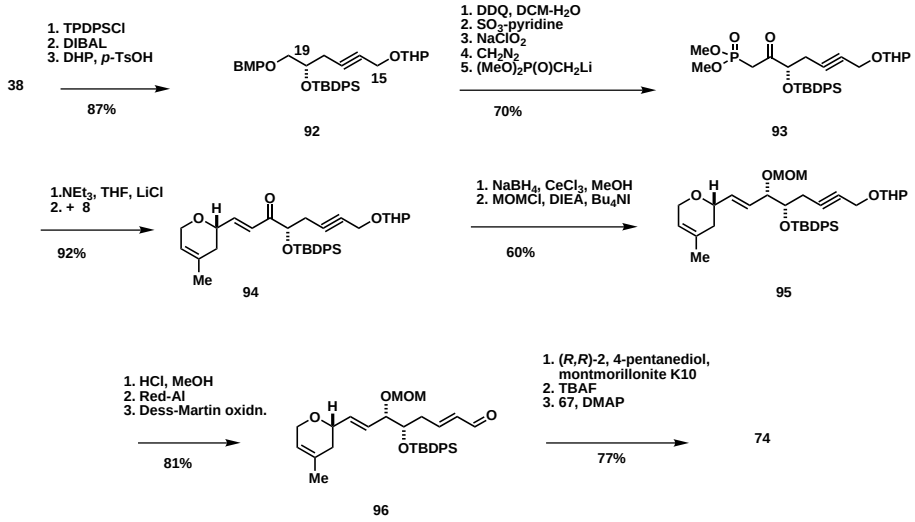
Scheme 17. Simplified synthesis of methyl ketone **91**.

Under these conditions, **88** reacted with $TMSCH_2MgBr$ (2 equiv.) to give, after 10 min, allylsilane **89** in 96% yield. Removal of the TES group (K_2CO_3-MeOH) followed by Dess–Martin oxidation afforded aldehyde **75** which was thus available from **82** in 14 steps and 31% overall yield. An alternative approach to ketone **87** in form of the 3-OTBS-derivative **91** utilizes our previous[10f] intermediate **34** (Scheme 17).

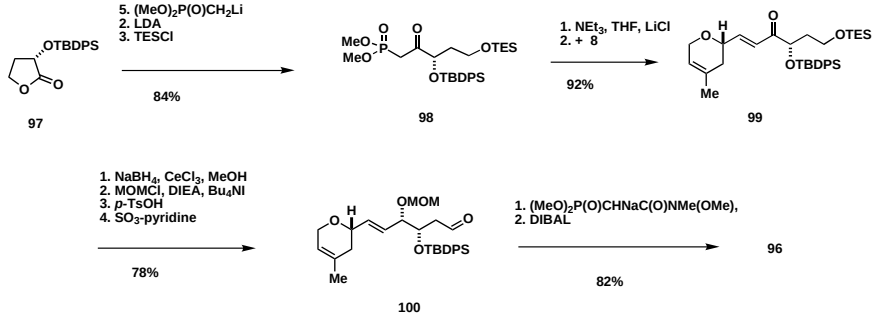
For the synthesis of the C27-C15 component **74** (Scheme 18), our previous[10g] intermediate **38** was converted into protected triol **92**, from which the phosphonate **93** was prepared via deprotection, oxidation, and chain elongation. Horner–Wadsworth–Emmons olefination with aldehyde **8** furnished enone **94** (*E*)-selectively. Luche reduction of the ketone led to the exclusive formation of the desired (20*S*)-alcohol which was protected with MOM chloride to give **95**. Removal of the THP group and reduction of the propargylic alcohol furnished the corresponding allyl alcohol (*E*)-selectively which was oxidized to aldehyde **96** with Dess–Martin periodinane.

Acetalization of aldehyde **96** with (*R,R*)-(+)-2,4-pentanediol, removal of the TBDPS group, and acylation of the corresponding alcohol with phosphonoacetyl chloride **67** provided C15-C27 fragment **74**. Quite recently, we developed a more efficient synthesis of aldehyde **96** by starting from lactone **97** (Scheme 19); in particular, the Luche reduction of enone **99** proceeded with complete stereoselectivity.

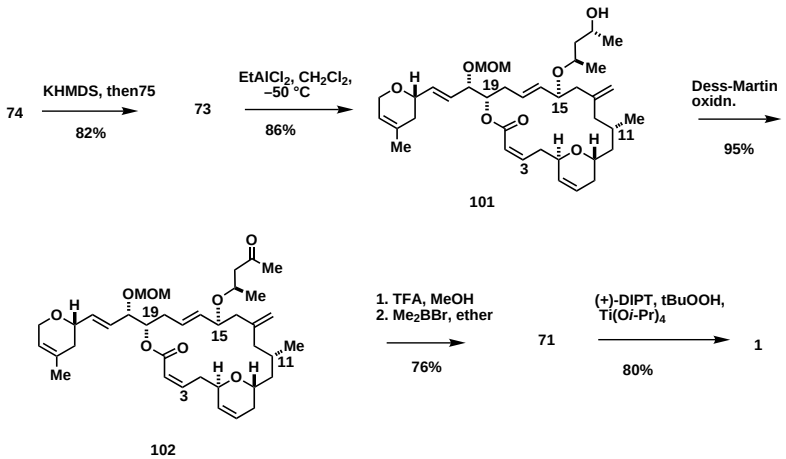
Starting the next set of operations, phosphonate **74** was deprotonated (KHMDS, THF) and treated with



Scheme 18. Synthesis of acetal **74**.



Scheme 19. Alternative synthesis of aldehyde **96**.



Scheme 20. Synthesis of deoxylaulimalide **71** by allyl transfer cyclization. Completion of the synthesis by SAE.

aldehyde **75** to give pure *Z*-enoate **73** in 82% yield (Scheme 20).

The cyclization of **73** was performed in $4 \cdot 10^{-4}$ M CH_2Cl_2 solution with 2 equiv. of $EtAlCl_2$ and provided macrolide **101** as a single isomer in 86% yield. As expected, these conditions were so mild that they did not induce the 2,3-*Z*-*E*-isomerization which has been so painfully experienced in previous syntheses. After oxidation of **101** to ketone **102**, both protective groups were removed in succession to generate 16,17-deoxylaulimalide **71**, which was identical (TLC and spectral data) with the compound obtained previously. The

epoxidation of **71**[9d] was performed via SAE [(+)-DIPT, *t*-BuOOH, Ti(O*i*-Pr)$_4$, CH_2Cl_2, –20 °C][44] which gave **1** as the only product.

4 Conclusion

In conclusion, we have presented two total syntheses of 16,17-deoxy-laulimalide (**71**), which was epoxidized to **1** by regio- and stereoselective SAE. RCM played a central role for preparing the two dihydropyran subunits, although alternative methods were shown to provide acceptable results as well.

Acknowledgements

Financial support by the FWF (project 13941-CHE) is greatfully acknowledged.

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