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Total Synthesis of Laulimalide: Synthesis of the Northern and Southern Fragments

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Abstract: The first stage in the development of a synthetic route for the total synthesis of laulimalide (**1**) is described. Our retrosynthetic analysis envisioned a novel macrocyclization route to the natural product by using a Ru-catalyzed alkene–alkyne coupling. This would be preceded by an esterification of the C19 hydroxyl group, joining together two equally sized synthons, the northern fragment **7** and the southern fragment **8**. Our first generation approach to the northern fragment entailed a key sequential Ru/Pd coupling sequence to assemble the dihydropyran. The key reactions proceeded smoothly, but the inability to achieve a key olefin migration led to the development of an alternative route based on an asymmetric dinuclear Zn-catalyzed aldol reaction of a hydroxyl acylpyrrole. This key reaction led to the desired diol adduct **66** with excellent *syn*/*anti* selectivity (10:1), and allowed for the successful completion of the northern fragment **7**. The key step for the synthesis of the southern fragment was a chemoselective Rh-catalyzed cycloisomerization reaction to form the dihydropyran ring from a diyne precursor. This reaction proved to be selective for the formation of a six-membered ring, over a seven. The use of an electron-deficient bidentate phosphine allowed for the reaction to proceed with a reduced catalyst loading.

Keywords: aldol reaction · asymmetric synthesis · chemoselectivity · macrocycles · total synthesis

Introduction

The focus of work in our laboratories has been the discovery of new and efficient methodologies for the synthesis of complex natural products. The development of these new techniques within the context of total synthesis presents a unique challenge and allows for in depth exploration of the scope and limitations of the methodology. Our ultimate goal is overcoming these limitations by using complex natural product intermediates as substrates. In this and the following article, we wish to report a full account of our efforts that culminated in the successful total synthesis of the natural product laulimalide (**1**) and a biologically active analogue. A portion of this work has appeared in a communication.[1]

Laulimalide (**1**), also known as fijianolide B, is a structurally unique 20-membered marine macrolide that was isolated from two different marine sponges,[2] *Cacospongia mycofijiensis* and *Hyattella sp*, simultaneously and independently by the Crews[2a] and Moore and Scheuer[2b] research groups. Two closely related analogues have also been identified (Figure 1). Isolaulimalide (**2**; fijianolide A) is an isomer of laulimalide in which the C20 hydroxyl has opened the C16–C17 epoxide, resulting in a new tetrahydrofuran ring. This transformation readily occurs under mild acidic conditions.[2a] A second regioisomer of laulimalide is neolaulimalide (**3**), which possesses an ester linkage at the C20 hydroxyl, leading to a macrocycle that has been enlarged by one carbon (versus laulimalide).

The structure and absolute stereochemical configuration of laulimalide was determined through X-ray crystallography.[3] Initially, it was shown that laulimalide displays potent cytotoxicity towards numerous National Cancer Institute (NCI) cell lines,[2b] however, it did not attract the attention of synthetic chemists until Mooberry and co-workers discovered that laulimalide displays microtubule stabilizing activity similar to that of paclitaxel and the epothilones.[4] Addition-

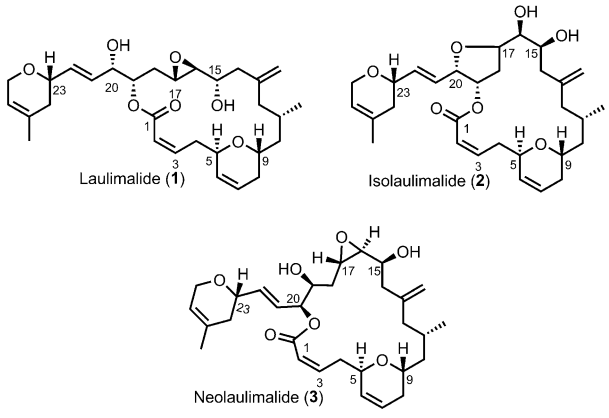

Figure 1. Laulimalide and two naturally occurring analogues.

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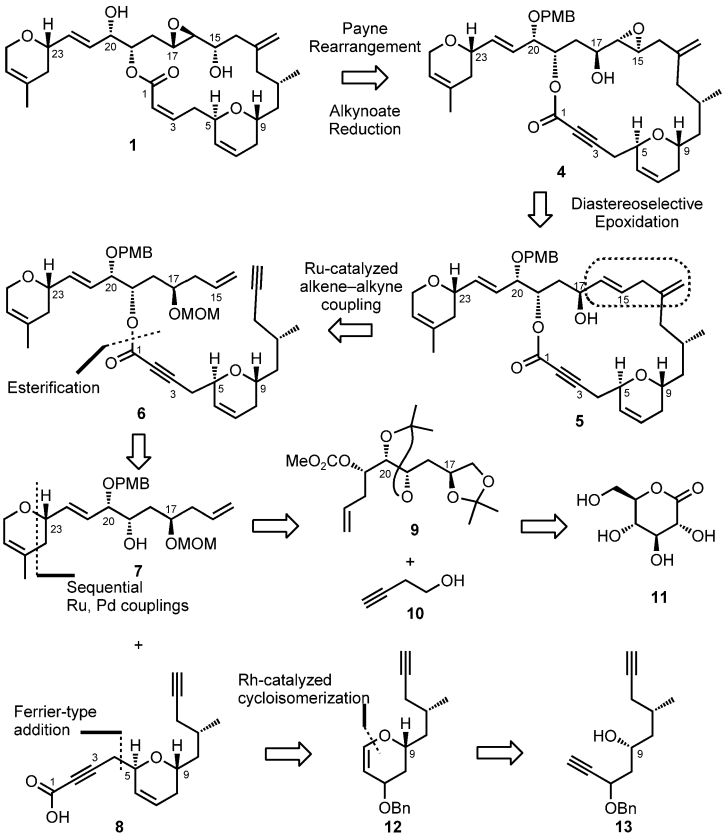
ally, laulimalide was found to bind to tubulin at a different site from paclitaxel, and was found to be active against multidrug-resistant cancer cell lines.[5] Recently, a distinct laulimalide microtubule-binding site has been identified by using mass-shift perturbation mapping.[6] This discovery has the potential to help direct the synthesis of novel antimitotic laulimalide analogues.

Due to both its unique pharmaceutical profile and challenging chemical architecture, laulimalide has attracted considerable interest from the synthetic chemistry community, leading to numerous attempts and several successful syntheses of both the naturally occurring compound and some analogues.[7] These approaches have underscored several unique structural features that can be addressed through the development of new, efficient, and atom economical transformations. The key features of laulimalide include nine stereogenic centers, two dihydropyran rings, and a *trans*-disubstituted epoxide, which is susceptible to nucleophilic attack from the C20 hydroxyl group under mild acidic conditions to form a tetrahydrofuran regioisomer (isolaulimalide, **2**) that is more stable but significantly less biologically active than the parent compound.

Synthetic planning: Our main goal when designing a synthesis of laulimalide was to develop an efficient synthesis of this structurally challenging natural product that would serve as a springboard for the development of new synthetic methodologies. We were drawn to the use of the alkyne moiety as a synthetic handle for our key macrocyclization step. As such, our retrosynthetic analysis for laulimalide was based on the assumption that the natural product could be formed from the 1,4-diene **5**, which could be accessed through a key intramolecular ruthenium-catalyzed alkene–alkyne coupling of enyne **6** (Scheme 1). The resulting 1,4-diene **5** could be converted into compound **4** through a diastereoselective epoxidation of allylic alcohol **5**, followed by an epoxide transposition (Payne rearrangement)[8] to give the correct oxidation pattern found in laulimalide. The enyne substrate **6** for the key macrocyclization would be accessed from an esterification between two dihydropyran-containing fragments of similar size and complexity: alcohol **7** (northern fragment) and acid **8** (southern fragment). Further retrosynthetic analysis revealed that the six-membered ring of the northern fragment **7** could be generated through sequential ruthenium and palladium catalysis between alkene **9** and alkyne **10**.[9] We envisioned that alkene **9** could in turn be derived stereoselectively from the chiral pool by using δ-gluconolactone **11**. The dihydropyran of the southern fragment **8** was envisioned to be assembled in two key steps; a rhodium-catalyzed cycloisomerization of diyne **13** would provide dihydropyran **12**,[10] and a Ferrier-type addition of an allenyl stannane to the resulting dihydropyran would complete the synthesis of the southern fragment **8**.[11]

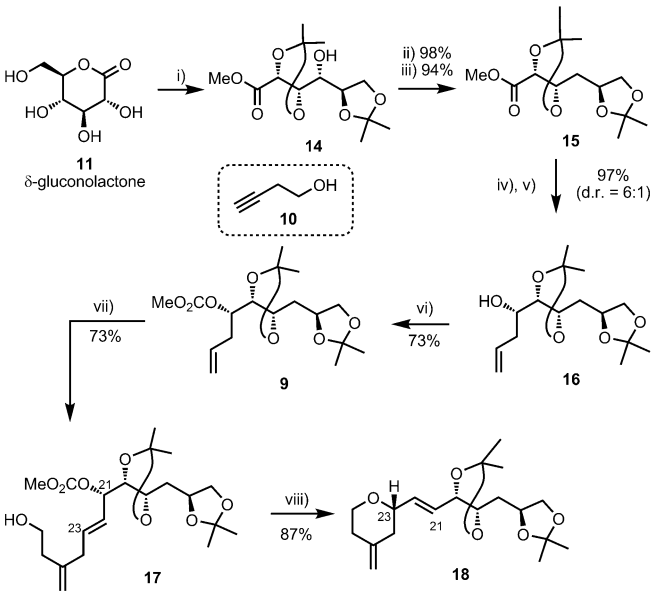
A Ru/Pd coupling sequence for the synthesis of the northern fragment: The preparation of the northern fragment began with commercially available δ-gluconolactone **11**



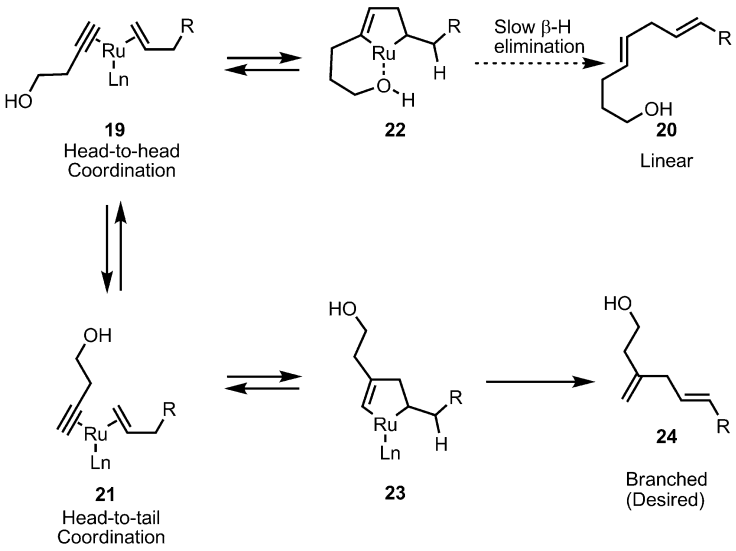
Scheme 1. First generation retrosynthetic analysis (PMB = *para*-methoxybenzyl, MOM = methoxymethyl, Bn = benzyl).

(Scheme 2). Following literature precedent, compound **11** was treated with 2,2-dimethoxypropane to form bis(acetonide) **14**,[12] which in turn was subjected to a Barton–McCombie deoxygenation, affording the methyl ester **15** in high yield (94%). Next, methyl ester **15** was derivatized to give alcohol **16** by reduction of the ester moiety followed by diastereoselective Barbier-type allylation of the resulting aldehyde,[13] giving an inseparable mixture of diastereoisomers favoring the desired *anti* product **16** derived from the Felkin–Anh mode of addition (d.r. = 6:1). Fortunately, the desired isomer was separable by flash column chromatography on silica gel after transforming the hydroxyl group of alcohol **16** into methyl carbonate **9**.

Having completed the preparation of the alkene partner **9**, we began to explore the key Ru-catalyzed transformation.[14] Our group has previously demonstrated that Ru-catalyzed alkene–alkyne coupling provides an atom-economical and highly functional-group tolerant route to 1,4-dienes. Additionally, depending on the relative orientation of the alkene and alkyne for the initial ruthenacycle formation, either "branched" or "linear" 1,4-diene products could arise. Earlier studies in our group have shown that the branched/linear selectivity is influenced by steric modification on either substrate. In particular, silylation of the alkyne coupling partner has proven to be a reliable method to drive the reaction to afford high selectivity for the branched prod-



Scheme 2. A Ru/Pd coupling sequence. i) See reference [12]; ii) S=C(Im)$_2$ (Im = imidazole), pyridine, CH_2Cl_2; iii) nBu$_3$SnH, azobisisobutyronitrile (AIBN), toluene, 100 °C; iv) diisobutylaluminum hydride (DIBAL-H), CH_2Cl_2; v) Zn, allylbromide, THF; vi) $ClCO_2CH_3$, pyridine, CH_2Cl_2; vii) **10**, [CpRu(CH$_3$CN)$_3$][PF$_6$], acetone; viii) [Pd$_2$(dba)$_3$]·CHCl$_3$ (dba = dibenzylideneacetone), 1,1′-bis(diphenylphosphino)ferrocene (dppf), dichloroethane (DCE).



Scheme 3. Mechanistic rationale for the formation of the branched diene.

uct.[15] Based on these observations, we initiated the study of this reaction with a trimethylsilyl (TMS)-substituted alkyne as our substrate to attain high selectivity for the branched product. However, we soon discovered that the unsubstituted terminal alkyne 3-butyn-1-ol **10** also gave the desired regioselectivity. Thus, when alkene **9** and alkyne **10** were exposed to the cationic ruthenium complex [CpRu(CH$_3$CN)$_3$][PF$_6$] (10 mol %; Cp = cyclopentadienyl) in acetone,[16] the desired branched diene **17** was obtained in good yield with no apparent formation of the undesired linear isomer, as judged by ^{1}H NMR spectroscopy. An optimization study revealed that high yields were obtained if an excess of the alkene coupling partner **9** was employed. Most (>85 %) of the unreacted alkene could be recovered through column chromatography. The requirement for excess alkene was presumably due to the stronger coordination ability of the alkyne to the metal, resulting in a catalytically inactive, coordinatively saturated ruthenium–alkyne complex. Slow addition of the alkyne substrate to the reaction mixture was moderately effective in reducing the amount of alkene required. However, consistently better yields were obtained by simply using an excess of the alkene.

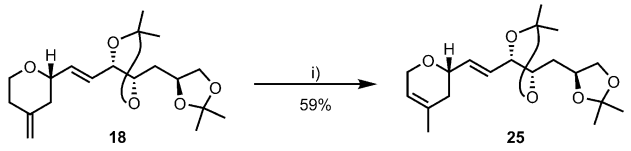
In the key ruthenium-catalyzed alkene–alkyne coupling step, the exclusive formation of a branched 1,4-diene in the absence of the high molecular weight TMS group on the alkyne renders our approach to the northern fragment more atom economical. Although the exact mechanism awaits further study, we believe the presence of a hydroxyl functionality at the homopropargylic position may play a role, as illustrated in Scheme 3. In the initial complexation step, the head-to-head complexation (compound **19**), which will ultimately lead to the linear 1,4-diene product **20**, is thought to be favored to avoid steric encumbrance (compound **21**) near the newly formed carbon–carbon bond. However, in the resulting ruthenacyclopentene **22**, the pendant hydroxyl group is well positioned to provide ligation to the electrophilic Ru^{III} metal center. It is expected that coordination of the hydroxyl group will slow the subsequent β-hydride-elimination process by making the additional coordination site unavailable for the β-hydrogen atom.[17] This coordination has the overall effect of favoring the formation of the desired branched product (leading to compound **24**), despite the greater hindrance of the head to tail coordination.

With the desired 1,4-diene in hand, we could now form the six-membered ring through a palladium-catalyzed cyclization. When carbonate **17** was exposed to [Pd$_2$(dba)$_3$]·CHCl$_3$ in the presence of diphenylphosphinoferrocene (dppf), clean cyclization occurred, giving tetrahydropyran **18** as a single diastereomer in 87 % isolated yield. This cyclization reaction is stereospecific because the stereochemistry at the C21 position (laulimalide numbering) of carbonate **17** was completely transferred to the C23 position (laulimalide numbering) of tetrahydropyran **18**, in accordance with the well-known π-allylpalladium mechanism.[18]

With compound **18** in hand, an *exo* to *endo* olefin isomerization was necessary to provide the correct olefin regioisomer present in laulimalide (see above). It was initially expected that the propensity of the olefin to migrate to form a more stable isomer (*exo* to *endo*) and the steric bias from the C23 substituent (laulimalide numbering) would help to provide the correct regioselectivity; however, extensive ex-

perimentation utilizing various acids, bases, and transition metals led to either poor selectivity or low conversion.[19]

After screening a substantial set of conditions[20] to achieve the double-bond migration, the most promising proved to be the utilization of $Pd(OAc)_2$ (20 mol%), in the presence of camphorsulfonic acid (CSA; 1.0 equiv) in MeCN at room temperature, which provided the desired double-bond isomer as the only product, albeit in poor yield (15%). However, satisfactory yields were obtained if a stoichiometric amount of palladium was used (Scheme 4). Efforts to develop a catalytic system were unsuccessful.



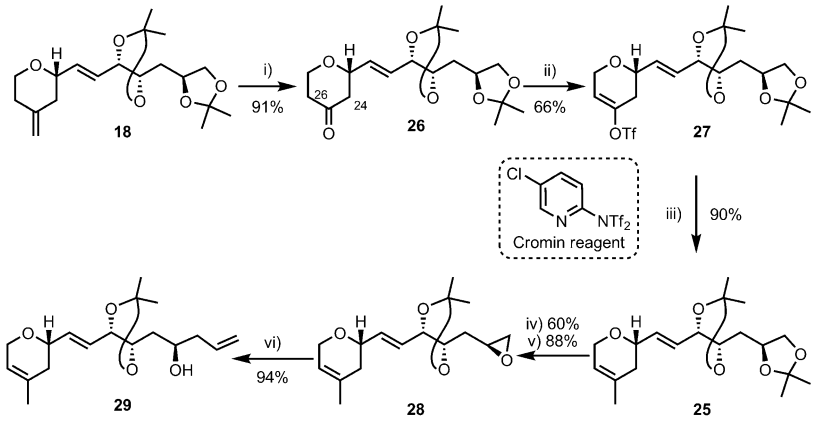
Scheme 4. Stoichiometric Pd isomerization. i) $Pd(OAc)_2$ (1.0 equiv), camphor sulfonic acid (CSA), MeCN, RT.

The difficulty in achieving a direct, catalytic olefin migration led us to consider indirect methods. Ultimately, a successful route was developed that utilized a three-step sequence: 1) oxidative cleavage of the exocyclic double bond, 2) regioselective vinyltriflate formation, and 3) a cross-coupling reaction with a methyl donor (Scheme 5). The transformation of the exocyclic methylene group in compound **18** into ketone **26** could be achieved chemoselectively by an osmium tetroxide catalyzed dihydroxylation, with the internal olefin remaining intact. This oxidation could be carried out either by using a two-step (OsO_4, *N*-methylmorpholine-*N*-oxide (NMO) then $NaIO_4$) or a one-step protocol (OsO_4, $NaIO_4$).[21] Although more convenient, the latter conditions gave a somewhat lower yield than the stepwise procedure (70 vs. 91%). Regioselective enolate formation was achieved distal to C23 (laulimalide numbering) with good selectivity (9:1) by using bulky TrLi, furnishing enol triflate **27**, with the Comins reagent as the triflating agent, in 66% yield.[22] More commonly used bulky amide bases, such as lithium diisopropylamide (LDA) or lithium 2,2,6,6,-tetramethylpiperidide (LTMP) proved ineffective, giving very poor regioselectivity even at −100 °C (<2:1).

The conversion of **27** to the complete carbon skeleton of the northern fragment was achieved in four steps, initiated by a Negishi coupling with dimethylzinc to provide dihydropyran **25**.[23] A selective terminal acetonide deprotection, epoxide formation by using catalytic tin oxide,[24] and finally a copper-catalyzed vinyl Grignard addition furnished dihydropyran **29** (Scheme 5).[25]

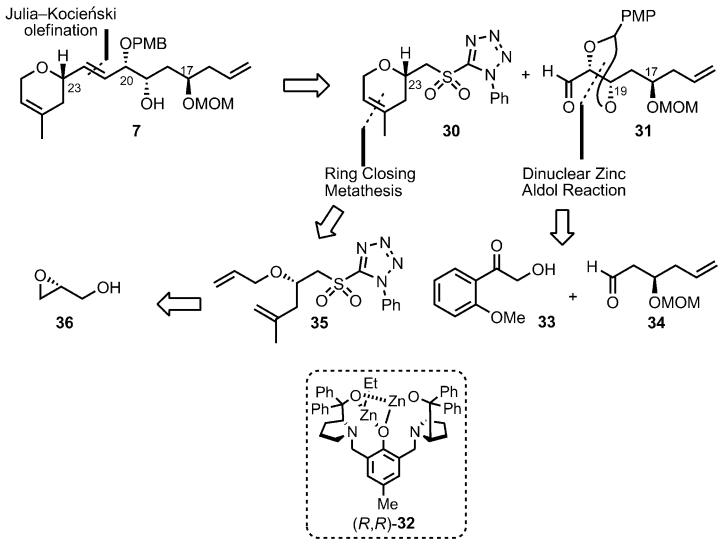
Although the route described above provided an excellent example of the novel use of a Ru/Pd sequence for the construction of the enantiopure dihydropyran of the C14–C27 fragment of laulimalide, the lack of an efficient solution to the double-bond migration prompted us to re-evaluate our synthetic strategy. In designing a second generation synthesis, our focus was on the potential implementation of a key zinc-catalyzed direct aldol addition to install the *cis*-diol at C19–C20 (laulimalide numbering).

A dinuclear zinc aldol reaction for the synthesis of the northern fragment: Our new retrosynthetic approach envisioned a Julia–Kocieński olefination[26] to construct fragment **7** from phenyl tetrazole sulfone **30** and aldehyde **31** (Scheme 6). Aldehyde **31** would be assembled by using a dinuclear zinc-catalyzed aldol reaction employing (*R*,*R*)-ProPhenol[27] ((*R*,*R*)-**32**) as the catalyst with an aryl hydroxymethyl ketone **33** as the donor and aldehyde **34** as the acceptor. To assemble the dihydropyran of sulfone **30**, we planned to utilize a ring-closing metathesis (RCM) approach by using diene **35**, which would be derived from (*R*)-glycidol (**36**). Several groups have used an RCM sequence for the construction of the exocyclic dihydropyran of laulimalide;[7o] however, we envisioned that we could improve upon these routes by utilizing a novel protecting group-free approach.



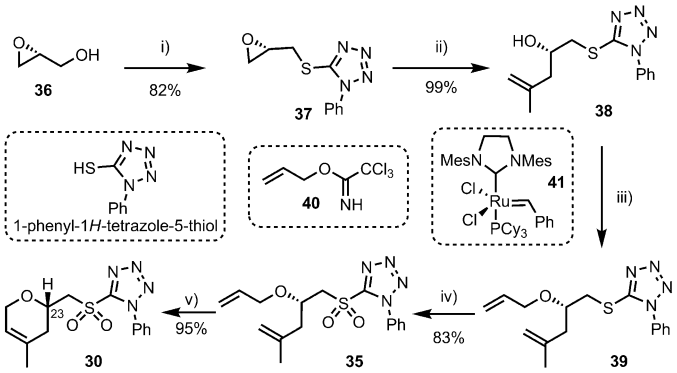
Scheme 5. Synthesis of the carbon skeleton of the northern fragment. i) OsO_4, *N*-methylmorpholine-*N*-oxide (NMO) then $NaIO_4$; ii) triphenylmethyllithium (TrLi), THF, Comins' reagent, −78 to −40 °C; iii) $[Pd(PPh_3)_4]$, Me_2Zn, THF, 0 °C to RT; iv) aqueous AcOH; v) nBu_2SnO, tosylchloride (TsCl), Et_3N, CH_2Cl_2, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); vi) $CH_2CHMgBr$, CuI, THF.

We began the synthesis of the sulfone coupling partner **30** through Mitsunobu coupling of (*R*)-glycidol **36** with 1-phenyl-1*H*-tetrazole-5-thiol to provide epoxysulfide **37** in good yield (Table 1). The epoxide underwent regioselective opening with isopropenylmagnesium bromide in the presence of a catalytic amount of copper iodide to provide alcohol **38** in near quantitative yield.[25] Allylation of alcohol **38** to provide diene **39** proved to be less straightforward than it initially appeared (see Table 1). Simple alkylations under acidic conditions by using the trichloroimi-



Scheme 6. Second generation approach to the northern fragment (PMP = *para*-methoxyphenyl).

Table 1. Synthesis of the sulfone coupling partner.[a]



	Conditions	Result
1	**40**, TfOH (50 mol %), CH_2Cl_2	decomposition
2	**40**, TfOH (5 mol %), CH_2Cl_2/hexane	decomposition
3	**40**, Cu(OTf)$_2$, PhMe	no reaction
4	**40**, BF_3·OEt_2	decomposition
5	allyl bromide, Ag_2O, $CaSO_4$, PhH	no reaction
6	Et_2Zn, Pd(OAc)$_2$, PPh_3, allyl acetate, THF	**39** (61 %)

[a] Reaction conditions: i) 1-phenyl-1*H*-tetrazole-5-thiol, diethyl azodicarboxylate (DEAD), PPh_3, THF; ii) isopropenylmagnesium bromide, CuI, THF, 0 °C; iii) see the table, Tf = triflate; iv) $[Mo_7O_{24}(NH_4)_6]$·$4H_2O$, H_2O_2, EtOH; v) **41**, CH_2Cl_2, RT; Mes = mesityl, Cy = cyclohexyl.

date **40**[28,29] or under basic conditions with allyl bromide[30] failed.

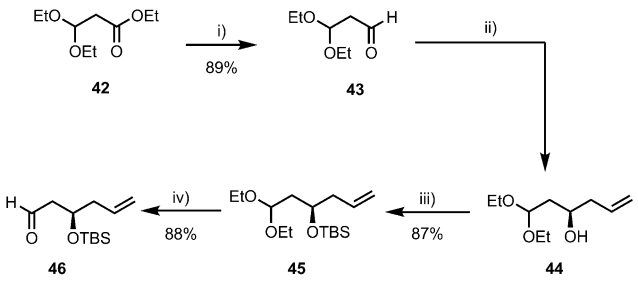
Having been unsuccessful with several sets of traditional allylation conditions, we investigated the possibility of a transition-metal-catalyzed allylation reaction.[31] Aliphatic alcohols are poor nucleophiles and the corresponding alkoxide anions are hard nucleophiles, making them unsuitable substrates for a metal-catalyzed reaction.[32] In order to overcome the reactivity mismatch between hard alkoxide anions and soft η^3-allylmetal cations, Lee et al. have shown that the formation of a zinc alkoxide has the beneficial effect of softening the alkoxide anion (through the Zn^{II} center), resulting in an attenuated basicity while retaining sufficient nucleophilicity toward a metal-bound allylic cation.[31]

Thus, addition of the zinc alkoxide of alcohol **38** to an in situ generated π-allylpalladium complex (Pd(OAc)$_2$, PPh_3, allylacetate) successfully resulted in the formation of the desired allylated compound **39** in 61 % yield. Molybdenum-catalyzed oxidation of the sulfide into the corresponding sulfone **35**, followed by a ring-closing metathesis by using the second generation Grubbs catalyst (**41**) provided the dihydropyran **30** in excellent yield.[33]

With sulfone **30** in hand, our efforts shifted to the construction of the aldehyde partner for the Julia–Kocieński olefination. This piece was to be assembled by using a dinuclear zinc aldol reaction employing (*R*,*R*)-**32** to couple α-hydroxyacetophenone with a suitable aldehyde donor. The catalytic asymmetric aldol reaction is a powerful tool for the enantioselective generation of carbon–carbon bonds.[34] Previous studies in our group have demonstrated the feasibility of using dinuclear zinc catalyst (*R*,*R*)-**32** with α-hydroxyacetophenone as the donor to produce *syn* diols in up to 30:1 d.r. and 92 % *ee*.[35] Shibasaki et al. have reported a similar reaction by using α-hydroxyacetophenone donors with a dinuclear zinc 1,1′-bi-2-naphthol (BINOL)-type catalyst.[36] However, the phenyl ketone product would not be synthetically useful in our synthesis of laulimalide. To overcome this obstacle, we looked into a strategy that Shibasaki et al. had used for further functionalization of aryl ketone aldol products: a methoxy-substituted α-hydroxyacetophenone donor.[36b–d] It was shown that these electron-rich aryl ketone products could be either oxidized through a Baeyer–Villiger oxidation[37] to the corresponding phenyl ester, or subjected to a Beckmann rearrangement[38] to provide an aryl amide product. These precedents provided an attractive route to utilize the α-hydroxyacetophenone donor in our synthesis.

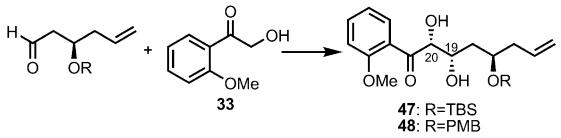
The synthesis of the aldehyde acceptor for the aldol reaction began with reduction of the commercially available ester **42** to aldehyde **43** in excellent yield (Scheme 7). The Brown allylation reaction provided alcohol **44** in good yield and excellent stereoselectivity.[39] *tert*-Butyldimethylsilyl (TBS)-protection of the hydroxyl moiety and careful deprotection[40] of the diethyl acetal gave aldehyde **46**. With a reliable and scalable route to the desired aldehyde **46** in hand, optimization studies of the aldol reaction were undertaken.

In the event, aldehyde **46** was coupled with α-hydroxyacetophenone (**33**) by using (*R*,*R*)-**32** (2.5 mol %) and Et_2Zn (5 mol %) in THF at room temperature to produce the desired aldol adduct **47** with a 4.8:1 *syn*/*anti* diol ratio (Table 2, entry 1). The desired diastereomer was separated through flash column chromatography on silica gel and obtained in a 52 % isolated yield. It was found that switching the protecting group on the hydroxyl moiety of the aldehyde from a TBS to a *para*-methoxybenzyl (PMB) group did not significantly alter the *syn*/*anti* diol ratio, but the isolated yield of



Scheme 7. Route to the aldehyde substrate for the aldol reaction. i) DIBAL-H, CH_2Cl_2; ii) (+)-*B*-Methoxydiisopinocampheylborane ((+)-IPC$_2$BOMe), allylmagnesium bromide then $NaBO_3$, H_2O; iii) tributylsilyl chloride (TBSCl), imidazole, THF; iv) trifluoroacetic acid (TFA)/ H_2O (50%), $CHCl_3$, 0°C.

Table 2. Optimization of the α-hydroxyl acetophenone aldol reaction.[a]



	R	Solvent	*syn*/*anti*	d.e. of *syn* [%]	Isolated yield [%] (compound)
1	TBS	THF	4.8:1	91	52 (**47**)
2	PMB	THF	5:1	92	69 (**48**)
3	PMB	toluene	9:1	94	83 (**48**)
4	PMB	MeCN	7.5:1	90	70 (**48**)
5	PMB	CH_2Cl_2	6:1	88	51 (**48**)

[a] Reaction conditions: (*R*,*R*)-**32** (2.5 mol%), molecular sieves (4 Å), solvent.

the desired diastereomer **48** increased. The *syn* configuration of the major product was confirmed through coupling constants of the C20−C19 hydrogen atoms (laulimalide numbering) after conversion to the corresponding carbonate **49** (see below; $J = 3.8$ Hz for the *syn* diol carbonate, $J = 6.1$ Hz for *anti* diol carbonate). Switching the solvent from THF to toluene, acetonitrile, or dichloromethane led to dramatic improvements in the selectivity of the reaction, with toluene proving to be optimal, providing the desired product with a 9:1 *syn*/*anti* selectivity and an 83% isolated yield (Table 2, entry 3). In addition to a less favorable *syn*/*anti* ratio, the use of acetonitrile and dichloromethane led to a decrease in the isolated yield of the desired product when compared to toluene.

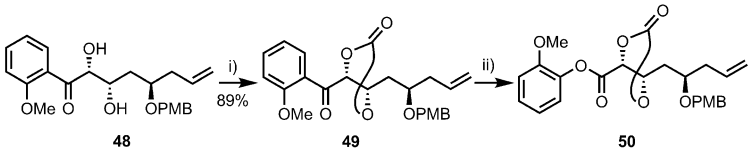
After optimization of the aldol reaction, the next step was a Baeyer–Villiger oxidation to convert the ketone moiety to the corresponding phenyl ester to complete the synthesis of fragment **50** (Table 3).[36b–d] Carbonate formation proceeded smoothly to give the protected triol **49**. However, several difficulties were encountered during the course of the oxidation (Table 3).

The use of bis(trimethylsilyl)peroxide and $SnCl_4$ as the Lewis acid for the oxidation led only to deprotection of the PMB group (Table 3, entry 1).[36c] Switching the PMB group to a silyl ether (TBS) led to no reaction. The use of different additives (Table 3, entries 2 and 3) was ineffective. *meta*-Chloroperoxybenzoic acid (*m*CPBA) was an effective oxidant for the substrates employed by Shibasaki et al.[36b–d] In our example it proved to be a poor oxidant for the reaction, either leading to no reaction at low temperature or undesired epoxidation of the terminal olefin (Table 3, entries 4 and 5). The use of other peroxyacids (Table 3, entries 6–8) led to extensive epimerization of the C20 hydroxyl group (laulimalide numbering) with no detectable oxidation product. Several additional reaction conditions were tested, including different oxidants and solvents, to no avail (data not shown). At this point, it was decided that even though the dinuclear zinc aldol reaction had proceeded smoothly, we had hit an impassable roadblock in the inability to achieve a Baeyer–Villiger-type process with our substrate. We therefore decided to change the donor for the aldol reaction from α-hydroxyacetophenone to α-hydroxyacylpyrrole.

In contrast to the use of α-hydroxyacetophenone as the donor for the aldol reaction, the use of α-hydroxyacylpyrrole should lead to aldol products that can readily be transformed without having to resort to oxidative rearrangements because the products are already at the carboxylic acid oxidation state.[41] Acylpyrroles have previously been used in several types of asymmetric transformations. For example, *N*-acylpyrroles have been utilized as ester surrogates in asymmetric conjugate addition reactions.[42] Additionally, acylpyrrole enolsilanes have been employed in enantioselective aminations,[43] and diastereoselective Mukaiyama–Michael reactions.[44] α-Hydroxyacylpyrrole itself has been employed in asymmetric Mannich-type reactions.[45]

Our initial investigations by using a TBS-protected β-hydroxyaldehyde revealed that the reaction proceeds in high

Table 3. Attempted Baeyer–Villiger Reaction.[a]

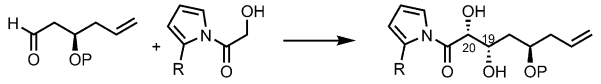


	Oxidant	Additive	Temperature [°C]	Solvent	Result
1	TMSO−OTMS	$SnCl_4$	−20	CH_2Cl_2	80% PMB deprotection
2	TMSO−OTMS	$CeCl_3$	−20 to RT	CH_2Cl_2	no reaction
3	TMSO−OTMS	toluene	−20 to RT	CH_2Cl_2	no reaction
4	*m*CPBA	TBAF	0	CH_2Cl_2	no reaction
5	*m*CPBA	none	RT	CH_2Cl_2	70% epoxidation
6	peroxyacetic acid	none	0	$CHCl_3$	78% epimerization
7	peroxytrifluoroacetic acid	none	0	$CHCl_3$	62% epimerization
8	mono peroxyphthalate (Mg salt)	none	RT	$CHCl_3$	30% epimerization

[a] Reaction conditions: i) triphosgene, pyridine, CH_2Cl_2; ii) see table.

yield, but with low diastereoselectivity (diol *syn*/*anti* = 1.5:1; Table 4, entry 1). The focus of the reaction optimization was on the improvement of the *syn*/*anti* ratio. Additional experiments indicated that the *syn*/*anti* d.r. for the newly formed 1,2-diol was somewhat dependent on the nature of the protecting group (P) of the β-hydroxyaldehyde (Table 4, entries 1–4). The largest affect arose by the use of a strong zinc-chelating group, methylthiomethyl (MTM, Table 4, entry 4), which resulted in a slight improvement in the *syn*/*anti* ratio, but a drastic reduction in the yield. Turning to modification of the donor, it was thought that increasing the steric bulk at the 2-position of the acylpyrrole might improve the observed diastereoselectivity. Gratifyingly, 2-ethyl-*N*-acylpyrrole significantly improved the *syn*/*anti* ratio to 4:1 when P was a TBS group (Table 4, entry 5).

Table 4. Initial optimization of the acyl pyrrole aldol reaction.[a]



syn 1,2-diol ((*R*)-C^{20}, (*S*)-C^{19})

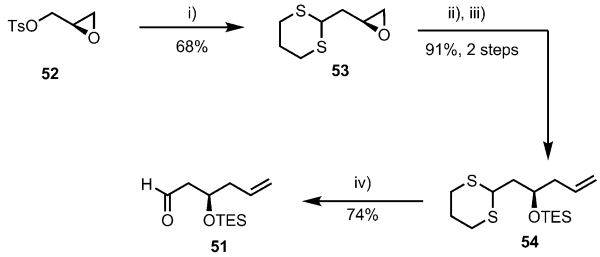
	P	R	Yield [%]	*syn*/*anti*	*de* (*syn*)
1	TBS	H	80	1.5:1	86
2	TBDPS	H	85	1.1:1	68
3	PMB	H	70	1.1:1	41
4	MTM	H	25	1.9:1	60
5	TBS	Et	80	4:1	n.d.

[a] Reaction conditions: (*R*,*R*)-**32**, THF. n.d. = not determined.

At this point, we wanted to demonstrate that the observed selectivity of the aldol reaction was due to catalyst control and not substrate control (due to the presence of the existing stereocenter). To this end, the opposite enantiomer of the catalyst (*S*,*S*)-**32** was used in place of the (*R*,*R*)-**32** that had provided the aldol products with the desired configuration. When the reaction was conducted with the (*S*,*S*) catalyst, the opposite configuration of the diol was achieved ((*S*)-C20, (*R*)-C19) in a similar *syn*/*anti* ratio (2:1) to that of the desired configuration ((*R*)-C20, (*S*)-C19) shown in Table 4. This result confirmed that it was indeed catalyst and not substrate control of the stereoselectivity that provided the desired aldol products.

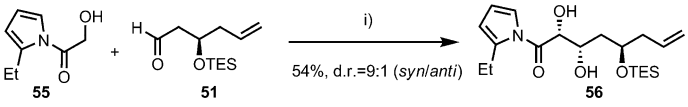
Considering the results in Table 4, it appeared that the use of a nonchelating protecting group was necessary to achieve good chemical yield and an acceptable *syn*/*anti* ratio, and the size of the hydroxyl protecting group should ideally be as small as possible. In addition, the use of 2-ethylpyrrole instead of pyrrole led to a significant improvement in the *syn*/*anti* ratio. With this information in hand, we envisioned that switching from a TBS group to the smaller triethylsilyl (TES) protecting group may furnish the desired product with improved diastereoselectivity. The synthesis of this new substrate also provided an opportunity to revisit our synthetic route to the β-hydroxyaldehyde.

To circumvent the use of a stoichiometric amount of a chiral reagent (Brown allylation) and the large amount of waste generated in that reaction, a new route to the aldehyde acceptor was adopted (Scheme 8).[46] The required β-triethylsiloxyaldehyde **51** was prepared from the commercially available (*S*)-glycidyl tosylate **52**, which was treated with lithiated 1,3-dithiane to give dithiane **53**. Subsequent copper-catalyzed vinyl Grignard addition, followed by protection of the resulting homoallylic alcohol as its TES ether gave compound **54**. The desired aldehyde **51** was ultimately obtained upon treatment of dithiane **54** with MeI in the presence of $CaCO_3$ (74% yield).



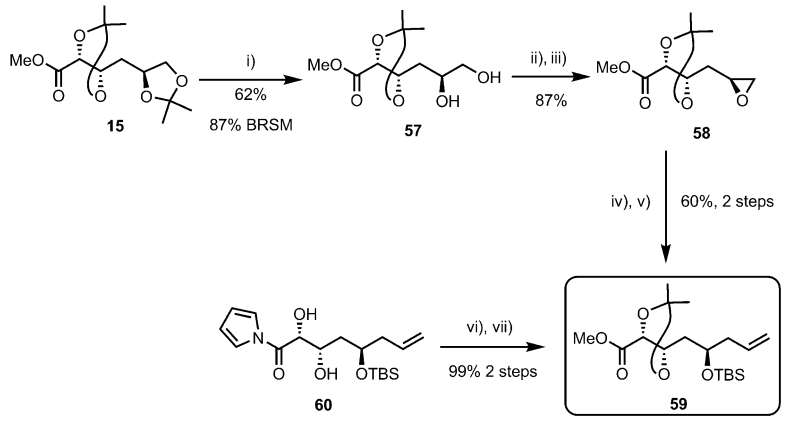
Scheme 8. Modified route to the aldehyde substrate for the aldol reaction. i) *n*BuLi, 1,3-dithiane, THF, −78 °C; ii) CuI, vinylmagnesium bromide, THF; iii) triethylsilyl chloride (TESCl), imidazole, 4-dimethylaminopyridine; DMF; iv) MeI, $CaCO_3$, $MeCN/H_2O$, 45 °C.

We now had the required intermediates for the crucial zinc aldol reaction. The reaction proceeded as anticipated by using (*R*,*R*)-**32** (15 mol%) and 2-ethyl acylpyrrole **55** as the donor, giving the desired *syn* 1,2-diol **56** in 9:1 d.r. and 54% isolated yield (Scheme 9).



Scheme 9. Aldol reaction by using a TES protecting group and 2-ethyl acylpyrrole. i) (*R*,*R*)-**32** (15 mol%), molecular sieves (4 Å), THF, 12 h, RT.

To unequivocally prove the absolute stereochemistry of the *N*-acylpyrrole aldol product, it was converted into a substrate that could be formed through our previous synthetic route that involved the use of gluconolactone **11** (Scheme 2). Deprotection of the terminal acetonide of ester **15** gave diol **57** in good yield (Scheme 10). Tosylate formation mediated by dibutyltin oxide and base-induced[47] cyclization led to epoxide **58** in good yield. Epoxide opening with higher order lithium divinyl cyanocuprate in the presence of $BF_3{\cdot}OEt_2$ led to the formation of the corresponding homoallylic alcohol, which was subsequently protected with a TBS group to provide ester **59**. This intermediate was intercepted by the acyl pyrrole aldol adduct **60** (from Table 4, entry 1) by installation of the acetonide, followed by methanolysis of the pyrrole. Both the sugar-derived ester **59** and the aldol-derived adduct were identical by ^1H and ^{13}C NMR



Scheme 10. Confirmation of the absolute stereochemistry for the aldol reaction product. i) H_2SO_4, HOAc; ii) Bu_2SnO, TsCl; iii) K_2CO_3, MeOH; iv) $LiCu(vinyl)_2$, $BF_3{\cdot}OEt_2$, THF, −78 °C; v) TBSCl, imidazole, DMF; vi) 2,2-dimethoxypropane, TsOH, CH_2Cl_2; vii) NaOMe, MeOH.

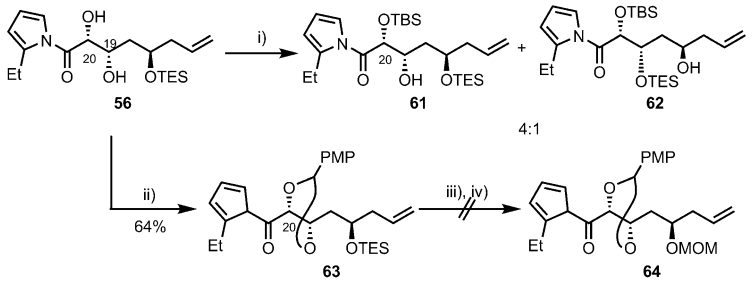
spectroscopy and optical rotation, thus, confirming our stereochemical assignment.

Having the desired *syn* 1,2-diol **56** in hand, we needed to orthogonally protect the two hydroxyl groups, since the northern fragment will later need to be selectively attached to the southern fragment through an esterification of the alcohol at the β position (C19; laulimalide numbering) of the carbonyl group (see above). Taking advantage of the enhanced acidity of the alcohol α to the carbonyl group of diol **56** (C20; laulimalide numbering), we intended to protect it selectively as a TBS ether (Scheme 11). To this end, diol **56** was treated with TBSCl, in the presence of imidazole in DMF, which furnished the desired protected alcohol **61** along with compound **62** (inseparable from **61**), resulting from migration of the TES group.

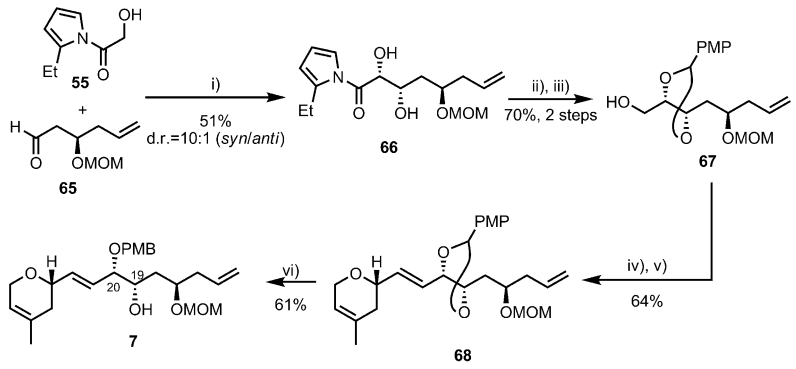
To circumvent this silyl migration issue, we planned to protect the 1,2-diol of compound **56** as its *para*-methoxyphenyl (PMP) acetal and then replace the TES ether with an MOM ether. Additionally, replacement of the TES protecting group with a chelating MOM group should, in principle, allow for selective opening of the PMP acetal with diisobutylaluminum hydride (DIBAL-H) through chelation, to afford the desired C20 PMB ether (laulimalide numbering). It was found that the protection of 1,2-diol **56** as a PMP acetal was best performed by employing a large excess of the dimethylacetal of *para*-anisaldehyde (10 equiv) in the presence of CSA (64% yield). Indeed, when only one equivalent is used the reaction is slow and significant deprotection of the secondary TES ether occurs. The excess of *para*-anisaldehyde dimethylacetal can be separated from the desired product **63** by simply stirring the crude residue with silica in chloroform. These mild acidic conditions allowed the conversion of *para*-anisaldehyde dimethylacetal into *para*-anisaldehyde, which is easily separable from **63** by flash column chromatography on silica gel. We then needed to convert the TES ether into an MOM protecting group, as suggested above. Accordingly, TES ether **63** was treated with TBAF, which resulted in complete decomposition of the starting material. It seemed that the 2-ethyl-*N*-acylpyrrole moiety was not stable to the basic reaction conditions, based on the TLC of the reaction mixture that indicated the release of 2-ethylpyrrole. Even though the use of milder conditions could certainly circumvent this issue, we decided to investigate the dinuclear zinc aldol chemistry applied directly to a β-OMOM aldehyde, thus avoiding this impractical and inelegant change of protecting groups.

Utilizing a similar route to that outlined in Scheme 8, the required β-methoxymethyloxy aldehyde **65** was obtained in 63% yield from tosyl glycidol **52**. Remarkably, the use of (*R*,*R*)-**32** (15 mol%) and 2-ethyl acylpyrrole **55** as the donor provided the desired *syn* 1,2-diol **66** with a 10:1 d.r. in 51% isolated yield (Scheme 12). Surprisingly, and to our delight, the chelation properties of the MOM protecting group did not seem to affect the diastereoselectivity of the reaction with the ethyl pyrrole. This was not true in the case of the parent acylpyrrole (e.g., Table 4, entry 3); evidently the additional steric bulk associated with the ethyl group overcomes any stereochemical bias of the chelating protecting group.

After protection of the resulting 1,2-diol as a PMP acetal and cleavage of the acylpyrrole upon exposure to sodium borohydride in THF, alcohol **67** could be isolated in 70% yield (over 2 steps). Oxidation of **67** with the Dess–Martin periodinane gave rise to the corresponding aldehyde, which was treated with the lithium salt of sulfone **30** in a THF/hexamethylphosphoramide (HMPA)



Scheme 11. Attempted protection strategy for the *syn* diol. i) TBSCl, imidazole, DMF; ii) *para*-methoxyphenyl acetal, CSA, CH_2Cl_2; iii) TBAF, THF; iv) MOMCl.

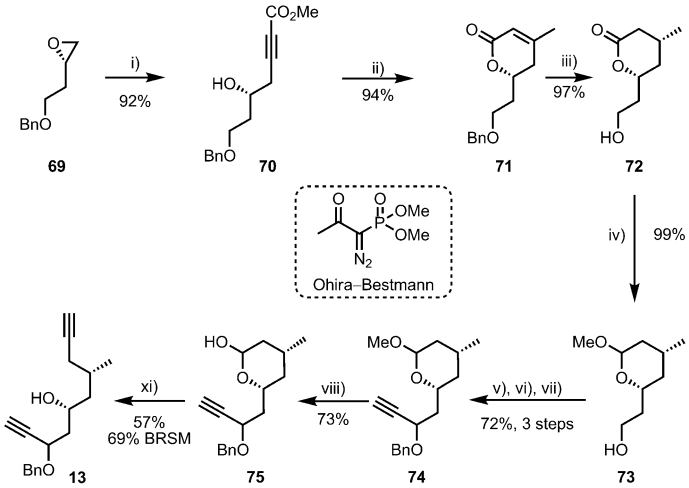


Scheme 12. Completion of the synthesis of the northern fragment. i) (*R*,*R*)-**32**, molecular sieves (4 Å), THF, 12 h, RT; ii) PMP acetal, CSA, CH_2Cl_2; iii) $NaBH_4$, THF; iv) Dess–Martin periodinane, CH_2Cl_2; v) Lithium hexamethyldisilazide (LiHMDS), **30**, DMF/hexamethylphosphoramide (HMPA), −35 °C to RT; vi) DIBAL-H, CH_2Cl_2, −78 to 0 °C.

mixture to give alkene **68** in 64% yield and as a single (*E*) geometric isomer. Taking advantage of the presence of the MOM chelating group, the PMP acetal **68** could be opened in a regioselective fashion (3:1, C20/C19 laulimalide numbering) upon treatment with DIBAL-H in dichloromethane at −78 °C, to give the desired fragment **7** as a single *E*-configured geometric isomer, completing the synthesis of the northern fragment. The PMB regioisomers were separable by column chromatography, and the undesired C19-PMB ether could be recycled by exposure to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), giving back the starting acetal **68** and increasing the overall synthetic efficiency.

Rh^{I} cycloisomerization for the synthesis of the southern fragment: As noted in the introduction, our retrosynthetic analysis for the southern fragment is based upon the notion that a Ferrier-type reaction would install the C1–C4 side chain (laulimalide numbering) of dihydropyran **8** stereoselectively through an axial delivery of a nucleophile onto the oxocarbenium ion generated from vinylogous acetal **12**. The vinylogous acetal **12** was, in turn, envisioned to come from a key rhodium-catalyzed cycloisomerization reaction. Cycloisomerization reactions are efficient and atom-economical[48] transformations because all of the atoms in the starting material are present in the product.[49] Previous work in our group had demonstrated the feasibility of Ru- and Rh-catalyzed cycloisomerization reactions to form dihydropyran rings.[10,50] For the synthesis of laulimalide, we chose to implement the Rh-catalyzed reaction to take advantage of its broader functional-group tolerance. In particular, the Rh-catalyzed reaction is more tolerant of substituents at the propargylic position (such as the OBn group in diyne **13**). Recently, Morris and Shair demonstrated the utility of the Rh-catalyzed cycloisomerization in the formation of an intermediate glycal for the synthesis of lomaiviticin A and B.[51] In our synthesis of laulimalide, we were interested in exploring the scope of the reaction by employing a challenging diyne substrate **13**. The success of this cycloisomerization step would rely on the reversibility of the Rh–vinylidene formation and the kinetically more facile production of the six-membered cyclic glycal product over a seven-membered ring.[52]

The synthesis of the key diyne substrate **13** is shown in Scheme 13. Starting with oxirane **69**, which is readily prepared from D-aspartic acid,[53] alkylation with the lithium salt of methyl propiolate provided alcohol **70**. Conjugate addition of dimethylcuprate, followed by acid-catalyzed lactonization, gave lactone **71** in excellent yield for the two-step procedure. Diastereoselective hydrogenation and concomitant benzyl deprotection furnished saturated lactone **72** as a single stereoisomer. Reduction of lactone **72** with DIBAL-H to the lactol, followed by protection as the mixed acetal gave alcohol **73**. Dess–Martin periodinane oxidation to the aldehyde, followed by a Grignard reaction with ethynylmagnesium bromide and then protection of the resulting alcohol as a benzyl ether proceeded in good yield (73%) for the three-step procedure, providing ether **74**. Hydrolysis of the acetal gave lactol **75**, which provided, upon treatment with the Ohira–Bestmann reagent,[54] diyne **13** in moderate yield.

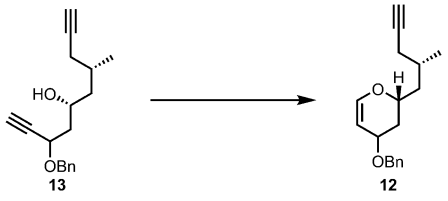


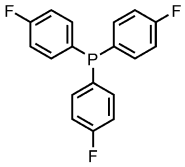
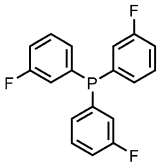
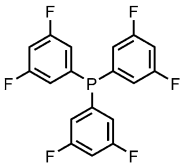
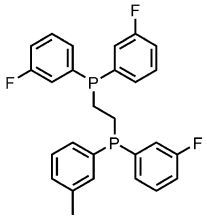
Scheme 13. Synthesis of the diyne cycloisomerization substrate. i) Methylpropyolate, *n*BuLi, $BF_3{\cdot}OEt_2$; ii) CuI, MeLi, THF then AcOH, PhH; iii) $Pd(OH)_2$, H_2, EtOAc; iv) DIBAL-H, CH_2Cl_2 then Dowex 50W×8, MeOH; v) Dess–Martin Periodinane, CH_2Cl_2; vi) ethynylmagnesium bromide, THF; vii) NaH, BnBr; viii) HOAc, H_2SO_4; ix) Ohira–Bestmann reagent, K_2CO_3, MeOH.

With the diyne substrate **13** in hand, we explored the key cycloisomerization reaction. Employing the chloro(1,5-cyclooctadiene)rhodium dimer as the precatalyst, we examined a series of electron-poor triarylphosphine ligands (**76**–**79**). To our delight, the desired dihydropyran was obtained in mod-

erate yield, with no noticeable 7-membered-ring formation (Table 5). However, when the reaction time was too long, there was significant decomposition (Table 5, entry 3). Although tri(3-fluorophenyl)phosphine **76** was most effective in this series, the cyclization required up to 1.1 equivalents of ligand for acceptable reactivity.

Table 5. Optimization of the Key Rh-Catalyzed Cycloisomerization.[a]



	Phosphine ([equiv])	Time [h]	Yield [%][b]
1	 **76** (1.1)	2	40
2	 **77** (1.1)	2	50
3	**77** (1.1)	18	decomposed
4	 **78** (1.1)	2	48
5	 **79** (1.1)	18	no reaction
6	**79** (0.2)	5	60
7	**79** (0.1)	5	55
8	**79** (0.1)	5	15[c]

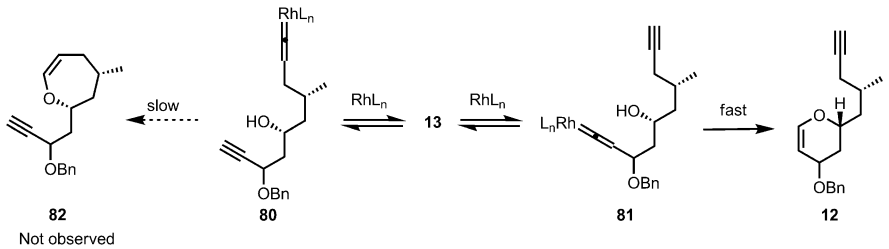
[a] Reaction conditions: [{Rh(cod)Cl}$_2$] (5 mol%), phosphine, DMF, 85°C; [b] Isolated yield; [c] CSA (1 equiv) was used.

It is proposed that the use of an excess of the phosphine ligand is essential to suppress the coordination of the second alkyne to the metal center after vinylidene formation, which would serve as a route to an undesired alkyne–alkyne coupling reaction, leading to dimeric and oligomeric mixtures.[55] In our case, it was hypothesized that if a bidentate phosphine, such as **79**, was used, this would overcome the need for large excesses of phosphine ligands because it would require less phosphine to maintain a coordinatively saturated rhodium. Indeed, the use of the bidentate phosphine **79** allowed for a lower ligand loading, and at the same time, provided a higher yield of the cyclized product (Table 5, entries 6 and 7). Surprisingly, the use of a large excess of the bidentate phosphine **79** (Table 5, entry 5) led to almost complete suppression of the reaction, presumably due to full saturation of the rhodium and the lack of any available coordination sites to bind the alkyne. However, when the bidentate phosphine ligand was used at significantly lower loadings (Table 5, entries 6 and 7), a good yield of the product could be obtained. Under the optimized conditions, only 5 mol% of the pre-catalyst and as low as 10 mol% of the bidentate phosphine was required for moderate to good reactivity (Table 5, entry 7).

Electron-poor ligands are crucial for the success of the cycloisomerization, and are thought to facilitate the rate-determining cyclization event in the catalytic cycle by stabilizing the ensuing Rh^{III} to Rh^{I} reduction step. The subsequent proto-derhodation would then regenerate the catalyst. We attempted to further optimize the reaction by facilitating the protonation step with an exogenous acid to no avail. For instance, the addition of CSA was detrimental, lowering the yield significantly (Table 5, entry 8). As with the reaction with monodentate ligands, it was important to stop the reaction after about 5 h to prevent decomposition of the product, presumably through intermolecular alkyne dimerization. We also explored the use of alternative solvents. For instance, acetonitrile provided a 43% yield of the product at 100% conversion, whereas dioxane gave only a 21% yield. In both cases, a significant number of side products were obtained.

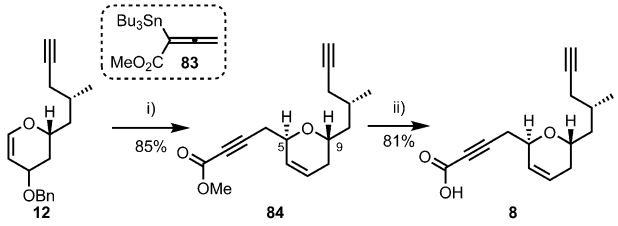
It is noteworthy that the reaction was completely chemoselective toward six-membered ring formation. In addition, the fact that the alkyne at C13 (laulimalide numbering) remained intact appears to indicate that the vinylidene–rhodium complex-formation step was reversible. Although the elucidation of the exact mechanism awaits further study, the initial vinylidene–rhodium complex formation (**80** and **81**, Scheme 14) is likely to be indiscriminate and reversible, and only the kinetically viable complex **81** undergoes subsequent cyclization to form the desired dihydropyran **12**. The 7-membered ring cycloisomerization product **82**, arising from vinylidene–rhodium complex **80**, was not observed.

To complete the synthesis of the southern fragment, the obtained glycal **12** was activated with $BF_3{\cdot}Et_2O$ and under-



Scheme 14. Rationale for the selective formation of a six-membered ring.

went a highly diastereoselective Ferrier addition of a Marshall-type[56] with allenylstannane **83** at low temperature to furnish exclusively the *trans*-disubstituted dihydropyran **84** in 85% yield, as confirmed by the absence of a nOe between the C5 and C9 hydrogen atoms (Scheme 15). This



Scheme 15. Completion of the southern fragment. i) **83**, $BF_3{\cdot}OEt_3$, CH_2Cl_2, −78 to −40 °C; ii) LiOH, THF/H_2O.

transformation allowed for the installation of the desired propargylic ester in one step from glycal **12**. The groups of Williams[7h] and Nelson[7i] both successfully employed similar allenyl stannanes in their syntheses of laulimalide. Finally, saponification of the propargylic methyl ester **84** with lithium hydroxide (2 equiv) resulted in the formation of the desired acid **8** in 81% yield, completing the synthesis of the southern fragment.

Conclusion

We have developed a novel synthesis of two similarly sized fragments of laulimalide. The northern fragment was completed by using a diastereoselective dinuclear zinc aldol reaction of a novel acylpyrrole aldol donor, followed by a Julia–Kocieński olefination reaction. The southern fragment was assembled through a key Rh^I-catalyzed cycloisomerization reaction applied to a challenging diyne substrate. In the following paper, we detail the union of the two fragments and the completion of the total synthesis of laulimalide.

Experimental Section

(*S*,*E*)-1-((4*R*,5*S*)-5-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl)-7-hydroxy-5-methylenehept-2-enyl methyl carbonate (17): A solution of 3-butyn-1-ol (**10**; 291 μL, 3.85 mmol) and alkene **9** (3.978 g, 11.55 mmol) in dry, degassed acetone (15 mL) was cooled to 0 °C, and $[CpRu(CH_3CN)_3][PF_6]$ (139 mg, 0.39 mmol) was added in one portion. The resulting orange mixture was stirred at 0 °C for 10 min, and at RT for 18 h. The mixture was then concentrated in vacuo, and the residue was purified by column chromatography (petroleum ether/EtOAc = 4:1 to 2:1) to give the compound **17** (1.165 g, 2.811 mmol, 73%) as a pale yellow oil. $[\alpha]_D^{23} = -1.9$ ($c = 1.06$ in CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 3496, 2987, 1752, 1443, 1380, 1269, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.86 (ddd, J = 15.5, 7.1, 6.2 Hz, 1H), 5.59 (dd, J = 15.5, 7.4 Hz, 1H), 5.20 (dd, J = 7.0, 4.9 Hz, 1H), 4.90 (s, 1H), 4.89 (s, 1H), 4.26–4.21 (m, 1H), 4.11–4.08 (m, 1H), 4.06–4.02 (m, 1H), 3.81 (dd, J = 8.1, 4.5 Hz, 1H), 3.78 (s, 3H), 3.70 (t, J = 6.5 Hz, 2H), 3.60–3.57 (m, 1H), 2.83 (d, J = 6.8 Hz, 2H), 2.29 (t, J = 6.5 Hz, 2H), 1.94 (ddd, J = 13.8, 7.7, 1.7 Hz, 1H), 1.72 (ddd, J = 13.8, 9.9, 5.4 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.36 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 143.7, 134.5, 125.5, 113.2, 109.6, 108.7, 81.7, 77.7, 75.0, 73.6, 69.7, 60.3, 54.8, 39.1, 39.0, 38.6, 27.6, 27.3, 26.9, 26.6, 25.6 ppm; HRMS: m/z calcd for $C_{20}H_{31}O_8$: 399.2020 $[M-CH_3]^+$; found: 399.2023.

(*S*)-2-[(*E*)-2-((4*S*,5*S*)-5-{[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl}-2,2-dimethyl-1,3-dioxolan-4-yl)vinyl]-4-methylenetetrahydro-2*H*-pyran (18): A mixture of $[Pd_2(dba)_3]{\cdot}CHCl_3$ (0.175 g, 0.169 mmol) and dppf (0.187 g, 0.338 mmol) in dry, degassed dichloroethane (10 mL) was stirred under a N_2 atmosphere at RT for 15 min, during which time it formed a clear deep-red solution. This solution was transferred into a flask that contained a solution of **17** (2.800 g, 6.755 mmol) in dry, degassed dichloroethane (120 mL), rinsing with dichloroethane (5 mL) to ensure complete transfer. The resulting mixture was placed in an oil bath, which was preheated to 70 °C, and stirred for 12 h. After cooling to room temperature, the mixture was concentrated in vacuo, and the residue was purified by column chromatography (petroleum ether/EtOAc = 15:1 to 10:1) to give **18** (1.999 g, 5.907 mmol, 87%) as a pale yellow oil. $[\alpha]_D^{23} = +15.9$ ($c = 1.01$ in CH_2Cl_2); IR (neat): $\tilde{\nu}$ = 2986, 1380, 1370, 1244, 1090, 1059, 890 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.84 (ddd, J = 15.5, 5.5, 0.6 Hz, 1H), 5.70 (ddd, J = 15.5, 7.4, 1.3 Hz, 1H), 4.77–4.74 (m, 2H), 4.22 (ddd, J = 13.0, 7.1, 6.0 Hz, 1H), 4.00 (t, J = 7.9 Hz, 1H), 3.83–3.79 (m, 2H), 3.58 (dd, J = 8.2, 7.2 Hz, 1H), 3.42 (ddd, J = 12.1, 11.0, 2.8 Hz, 1H), 2.34–2.27 (m, 2H), 2.17–2.14 (m, 1H), 2.10–2.05 (m, 1H), 1.92 (ddd, J = 13.8, 7.1, 2.6 Hz, 1H), 1.65 (ddd, J = 13.8, 9.9, 5.8 Hz, 1H), 1.40 (s, 9H), 1.35 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.7, 135.5, 127.2, 109.0, 108.9, 108.6, 82.1, 78.0, 77.7, 73.7, 69.8, 68.4, 41.0, 36.2, 34.8, 27.2, 27.0, 25.7 ppm; HRMS: m/z calcd for $C_{19}H_{30}O_5$: 338.2093; found: 333.2087.

(2*R*,3*S*,5*R*)-2,3-Dihydroxy-5-(4-methoxybenzylhydroxy)(2-methoxyphenyl)oct-7-en-1-one (48): (*R*,*R*)-**32** (4.0 mg, 0.00625 mmol) was placed under a nitrogen atmosphere and THF (320 μL) was added. Diethylzinc (13 μL, 0.0125 mmol, 1.0 M in THF) was added dropwise and stirred for 15 min. Separately, powdered molecular sieves (4 Å, 50 mg) and 2-hydroxy-2′-methoxyacetophenone (**33**; 54.0 mg, 0.325 mmol) were placed into a vial and placed under a nitrogen atmosphere. (*R*)-3-((4-methoxybenzyl)oxy)hex-5-enal (57.0 mg, 0.250 mmol) in THF (320 μL) was added in one portion. The mixture was cooled to 0 °C and the catalyst solution was added through a syringe. The reaction mixture was then stirred at room temperature for 12 h. HCl (1 M) was added, and the mixture was extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Column chromatography (petroleum ether/EtOAc = 4:1 to 2:1) provided **32** (53 mg, 52%) as a white solid. M.p. 70–71 °C; $[\alpha]_D^{23} = 7.0$ ($c = 1.0$ $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3452, 3075, 3008, 2936, 2915, 2839, 1667, 1599, 1533, 1514, 1487, 1465, 1438, 1395, 1293, 1246, 1179, 1076, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (dd, J = 1.8, 5.9 Hz, 1H), 7.53–7.58 (m, 1H), 7.06–7.10 (m, 3H), 6.91 (d, J = 7.9 Hz, 1H), 5.79–5.89 (m, 2H), 5.07–5.14 (m, 2H), 4.96 (d, J = 1.8 Hz, 1H), 4.53 (d, J = 10.8 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 4.20 (m, 1H), 4.09–4.13 (m, 1H), 3.89 (d, J = 8.7 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 2.29–2.45 (m, 2H), 2.06 (d, J = 9.8 Hz, 1H), 1.73 (dddd, J = 1.7, 2.5, 2.5, 7.2 Hz, 1H), 1.25 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 158.7, 134.5, 131.5, 130.7, 129.4, 123.8, 121.2, 117.4, 113.6, 111.6, 79.9, 75.5, 71.3, 68.4, 55.6, 55.2, 40.3, 38.7 ppm; HRMS (EI): m/z calcd for $C_{23}H_{28}O_6$: 423.1784 $[M+Na]^+$; found: 423.1780; elemental analysis calcd (%) for $C_{23}H_{28}O_6$: C 68.98, H 7.05; found: C 68.90, H 7.08.

(2*R*,3*S*,5*R*)-1-(2-Ethyl-1*H*-pyrrol-1-yl)-2,3-dihydroxy-5-(methoxymethoxy)oct-7-en-1-one (66): (*R*,*R*)-**32** (30 mg, 0.047 mmol) was placed under an argon atmosphere and THF (500 μL) was added. Diethylzinc (1.0 M in hexanes, 95 μL, 0.095 mmol) was added dropwise at RT and the reaction mixture was stirred for 20 min to give the dinuclear zinc catalyst as a yellow solution. Powdered molecular sieves (4 Å, 50 mg) were placed into a flame-dried flask, followed by acyl pyrrole **55** (63 mg, 0.411 mmol) and the flask was placed under an argon atmosphere. Aldehyde **65** (50 mg, 0.316 mmol) in THF (500 μL) was then added to the acyl pyrrole/molecular sieves mixture in one portion. The resulting mixture was stirred vigorously and the catalyst was added dropwise through a syringe. After stirring at RT for 12 h, the reaction mixture was hydrolyzed by adding aqueous HCl (1 M, 2 mL) and the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine,

dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (petroleum ether/EtOAc = 9:1 to 7:3) provided 1,2-diol **66** as a brown solid, consisting of a mixture of two inseparable diastereoisomers (52.1 mg, 51%) in a 10:1 ratio, as determined by the ratio of the NMR peaks at $\delta = 6.97$ and 7.06 ppm. M.p. = 54 °C; $[\alpha]_D^{23} = -25.7$ ($c = 0.75$ in $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3375, 2928, 1726, 1641, 1502, 1450, 1420, 1377, 1322, 1252, 1147, 1125, 1094, 1040, 914, 872, 813, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.97$ (dd, $J = 3.6$, 1.6 Hz, 1H), 6.20 (t, $J = 3.6$ Hz, 1H), 6.04 (m, 1H), 5.76 (ddt, $J = 16.8$, 10.4, 7.2 Hz, 1H), 5.12–5.06 (m, 2H), 4.66 (dd, $J = 7.6$, 1.6 Hz, 1H), 4.63 (d, $J = 6.8$ Hz, 1H), 4.61 (d, $J = 6.8$ Hz, 1H), 4.23 (m, 1H), 3.85 (m, 1H), 3.69 (d, $J = 7.6$ Hz, OH), 3.27 (s, 3H), 2.97–2.90 (m, 2H + OH), 2.41–2.27 (m, 2H), 1.97 (ddd, $J = 14.8$, 10.8, 2.8 Hz, 1H), 1.70 (ddd, $J = 14.8$, 9.6, 2.8 Hz, 1H), 1.20 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.5$, 140.1, 134.1, 119.1, 118.2, 112.9, 111.4, 96.8, 75.3, 74.0, 69.4, 56.0, 39.8, 38.5, 22.8, 13.1 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{25}NO_5Na$: 334.1620 $[M+Na]^+$; found: 334.1630.

(*R*)-4-(Benzyloxy)-2-[(*S*)-2-methylpent-4-ynyl]-3,4-dihydro-2*H*-pyran (12): A mixture of $[Rh(cod)Cl]_2$ (64 mg, 0.081 mmol) and bidentate phosphine **79** (142 mg, 0.324 mmol) was added to a solution of **13** (438 mg, 1.62 mmol) in dry, degassed DMF (15 mL) in a Schlenk flask. The Schlenk flask was then purged with argon, closed, and immersed in a preheated oil bath (85 °C). After 5 h, the reaction mixture was cooled to RT, diluted with diethyl ether, and washed with water. The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried over $MgSO_4$. After filtration, the filtrate was concentrated under vacuum, and the residue was purified by flash column chromatography on deactivated silica (petroleum ether/EtOAc = 30:1) to give **12** (243 mg, 55%) as a colorless oil. IR (neat): $\tilde{\nu}$ = 3301, 2926, 1640, 1243, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.27 (m, 5H), 6.54 (d, $J = 6.1$ Hz, 0.9H), 6.39 (d, $J = 6.3$ Hz, 0.1H), 4.99 (ddd, $J = 6.1$, 5.3, 2.0 Hz, 0.9H), 4.86 (dt, $J = 6.3$, 1.9 Hz, 0.1H), 4.76 (ABq, $J = 11.7$, $\Delta\nu = 41.8$ Hz, 0.2H), 4.57 (ABq, $J = 11.9$, $\Delta\nu = 31.3$ Hz, 1.8H), 4.09–4.02 (m, 1H), 3.85 (deformed ddd, $J = 5.3$, 4.1, 1.8 Hz, 1.8H), 2.22 (ddd, $J = 16.6$, 6.1. 2.7 Hz, 0.9H), 2.16 (ddd, $J = 16.6$, 6.3, 2.7 Hz, 0.9H), 2.07–2.00 (m, 1H), 1.98 (t, $J = 2.7$ Hz, 0.9H), 1.95 (ddd, $J = 14.3$, 3.7, 1.8 Hz, 0.9H), 1.79 (ddd, $J = 14.0$, 9.8, 4.7 Hz, 0.9H), 1.58 (ddd, $J = 14.3$, 12.0, 4.1 Hz, 0.9H), 1.36 (ddd, $J = 14.0$, 9.5, 3.5 Hz, 0.9H), 1.05 (d, $J = 6.6$ Hz, 2.7H), 1.02 ppm (d, $J = 6.7$ Hz, 0.3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.3$, 138.8, 128.4, 127.7, 127.6, 127.5, 100.2, 82.9, 69.4, 69.4, 66.4, 41.3, 34.8, 28.6, 26.5, 18.9 ppm; HRMS (ESI): m/z calcd for $C_{11}H_{15}O_2$: 179.1072 $[M-PhCH_2]^+$; found: 179.1071.

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