

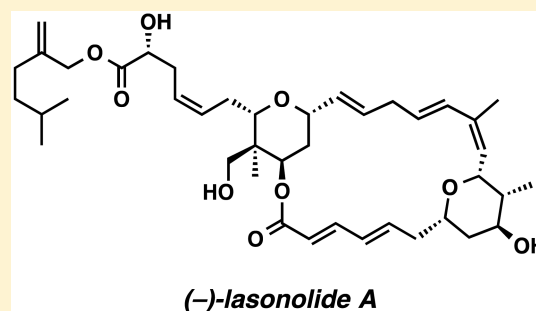
Total Synthesis of (–)-Lasonolide A

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S Supporting Information

ABSTRACT: The lasonolides are novel polyketides that have displayed remarkable biological activity in vitro against a variety of cancer cell lines. Herein we describe our first-generation approach to the formal synthesis of lasonolide A. The key findings from these studies ultimately allowed us to go on and complete a total synthesis of lasonolide A. The convergent approach unites two highly complex fragments utilizing a Ru-catalyzed alkene–alkyne coupling. This type of coupling typically generates branched products; however, through a detailed investigation, we are now able to demonstrate that subtle structural changes to the substrates can alter the selectivity to favor the formation of the linear product. The synthesis of the fragments features a number of atom-economical transformations which are highlighted by the discovery of an engineered enzyme to perform a dynamic kinetic reduction of a β -ketoester to establish the absolute stereochemistry of the southern tetrahydropyran ring with high levels of enantioselectivity.



INTRODUCTION

Lasonolide A was discovered in 1994 by McConnell and co-workers in an effort to identify new and diverse antitumor agents from marine organisms.¹ The connectivity of the lasonolides and relative stereochemistry of each tetrahydropyran were determined by NMR correlation spectroscopy from isolated materials. In 2002, the correct fully elucidated structure of lasonolide A was disclosed in Lee's total synthesis.² This seminal work established the unknown relative stereochemistry of the C28 stereocenter and corrected the C17–C18 and C25–C26 olefin geometries, which had been incorrectly assigned (Figure 1). Importantly, the synthesis also established the absolute stereochemistry of the natural product and revealed that the levorotatory or (–)-lasonolide A was the biologically active enantiomer, contrary to what had been reported in the isolation paper. Despite the remarkable activity lasonolide A displayed in the NCI's 60-cell-line screen,³ very few analogues have been prepared.^{4,5}

RESULTS AND DISCUSSION

Our pursuit of the target molecule was inspired by not only its unique biological activity but also its novel molecular architecture that presented us with the opportunity to execute and expand on many of the organic transformations that had previously been developed in our laboratory. We aimed at developing a more concise and efficient synthesis compared to those previously known.^{2,6,7} A preliminary report of our efforts has been communicated.^{7a}

We recognized that the main point of diversification between lasonolides A–F occurred at the C28 and C30 positions (Figure 1. Subtle structural differences had dramatic effects on the

biological profiles between each of the six natural analogues. While a comprehensive understanding of the structure activity relationships remains unclear, we felt that it was important to devise a synthesis plan (Scheme 1) that could allow for the installation of a range of diverse structural elements at these positions. A late-stage Wittig olefination could install the required *Z*-olefin geometry present in all lasonolides and enable a flexible strategy for analogue synthesis. The macrocycle can then be disconnected into two equally complex tetrahydropyrans, which could be joined together by an esterification/macrolactonization and a Ru-catalyzed alkene–alkyne coupling. These disconnections of the lasonopyran skeleton allowed us to identify three subtargets, **9**, **10**, and **11**, for synthesis.

The hallmark of our synthetic plan, the Ru-catalyzed alkene–alkyne coupling, was unique in the fact that we aimed to obtain a linear 1,4-diene product. Previously we demonstrated that branched selectivity is generally observed, as shown in eq 1 at the top of Figure 2.⁸ However, in a few cases, the linear product dominated (eq 2). We have put forth a mechanistic rationale to understand this behavior. The proposed mechanism for the transformation, via ruthenacyclopentene formation, is depicted in the bottom part of Figure 2. The initial oxidative cycloisomerization with the Ru catalyst is believed to be reversible and can form one of two possible regioisomers, **A** or **B**. A subsequent β -hydride and reductive elimination, from the metallacycles, can afford the linear or branched isomers. Steric factors suggest that intermediate **B** is more stable than intermediate **A** which accounts for the preferential formation of the branched product. However, the tautomerization of the

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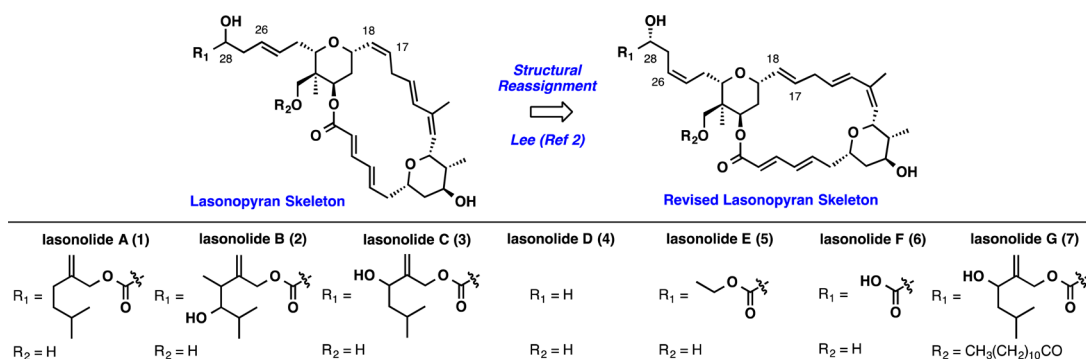
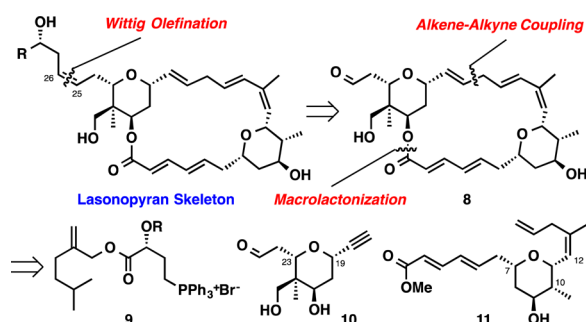


Figure 1. Reassigned lasonopyran skeleton: lasonolides A–G.

Scheme 1. Synthesis Plan for (–)-Lasonolide A

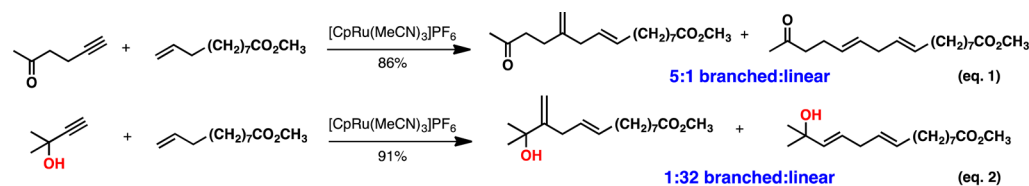


initial alkene–alkyne complex C is thought to be faster than that of complex D then forms the new C–C bond between the sterically less-hindered terminus of each unsaturated partner. If the rate of β -hydride elimination of complex A can outcompete its cycloreversion to complex C, a linear product would result. Indeed, introduction of a tetrasubstituted propargylic center inhibits cycloisomerization of complex D to the point that the reaction is now favored via complex A.

In all our prior total syntheses involving terminal alkyne partners, only branched products have been formed: alternaric acid,⁹ amphidinolides A¹⁰ and P,¹¹ and laulimalide.¹² The

particular efficiency of the Ru-catalyzed macrocyclization in the laulimalide synthesis stimulates exploration of the Ru-catalyzed process making linear rather than branched products. To be applied to the total synthesis of lasonolide A, there are two possible approaches that could afford the desired product (Scheme 2). The first would feature an intramolecular reaction to generate the macrocycle (14) of lasonolide A. The second would be an intermolecular approach to form 19. Theoretically, in each scenario the linear isomer can be formed using either functional group orientation (i.e., 12 vs 13 and 15/16 vs 17/18).

We, therefore, initiated studies on representative model systems. Tetrahydropyrans **20**¹³ and **21** were subjected to several reaction conditions to test the feasibility of the intermolecular coupling and to gain insight concerning the levels of linear:branched selectivity. We screened several solvents that have been previously utilized in alkene–alkyne couplings. No reaction was observed in non-coordinating solvents such as CH_2Cl_2 and DCE (Table 1, entries 1 and 2), likely due to catalyst decomposition. Next we screened coordinating solvents (acetone and DMF) (Table 1, entries 3–5) in an effort to stabilize the coordinatively unsaturated Ru catalyst. To our delight, reactions run in DMF and acetone delivered the desired coupled products. The linear:branched



Proposed Catalytic Cycle

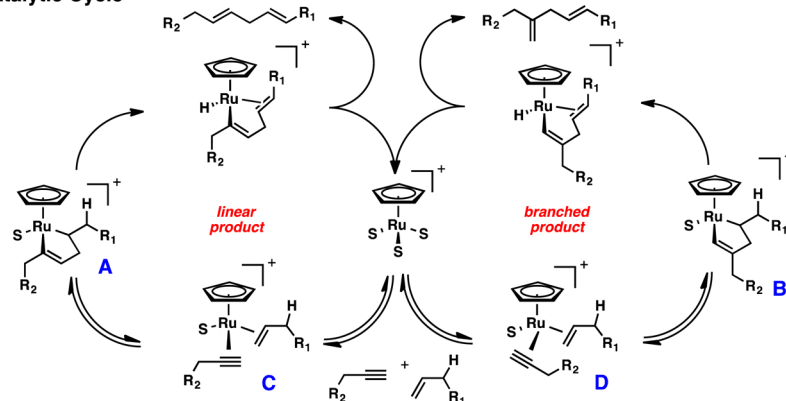


Figure 2. Known Ru-catalyzed alkene–alkyne couplings favoring linear and branched products: proposed catalytic cycle.

Scheme 2. Proposed Ru-Catalyzed Alkene–Alkyne Couplings

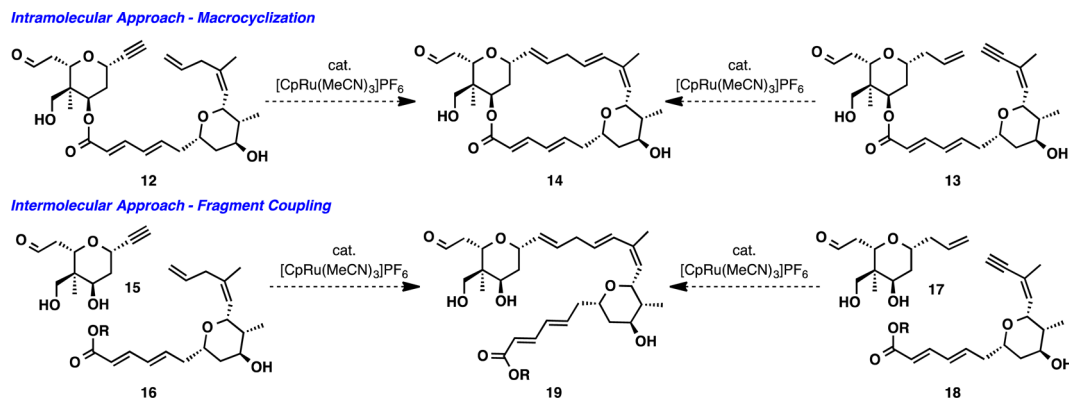


Table 1. Model Studies for Alkene–Alkyne Coupling

entry ^a	solvent (concn)	21 (equiv) ^b	conv (%) ^c	22:23 ^c
1	CH ₂ Cl ₂ (5 M)	1.2	0	
2	DCE (5 M)	1.2	0	
3	DMF (5 M)	1.2	33	1:1
4	acetone (5 M)	1.2	37	3.5:1
5	acetone (1 M)	5.0	56 ^d	4.0:1

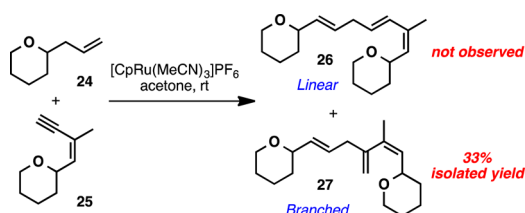
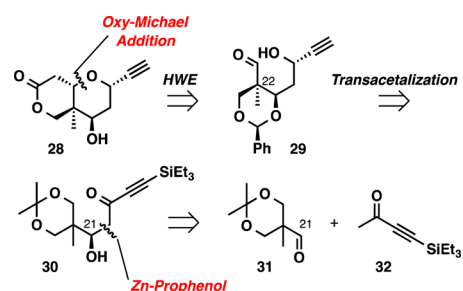
^aAll reactions were run using 0.1 mmol (**20**) and 10 mol% [CpRu(MeCN)₃]PF₆ at rt for 14 h. ^b**21** was added as a solution dropwise over 1 h using a syringe pump. ^cDetermined by ¹H NMR. ^dIsolated yield.

ratios were much higher in acetone (3.5:1) than in DMF (1:1), suggesting that DMF promotes a reversible cycloisomerization and therefore Curtin–Hammett conditions. Increasing the amount of alkene **21** (5 equiv) delivered the desired 1,4-diene (**22**) as a 4:1 mixture of linear:branched isomers in 56% yield.¹⁴ Importantly, 74% of the excess alkene was recovered at the end of the reaction.

The alternative substitution pattern was also explored on a similar model system using the optimal conditions discovered in Table 1, entry 5 (Scheme 3). In this case, the branched isomer (**27**) was exclusively formed in 33% yield.

The synthesis plan for alkyne **28** is presented in Scheme 4. A dinuclear Zn-catalyzed aldol reaction between ynone **32** and aldehyde **31** is envisioned to establish the absolute stereochemistry of fragment **30**. It is important that high enantio-

Scheme 3. Additional Model Studies for Alkene–Alkyne Coupling

Scheme 4. Synthesis Plan for Alkyne **28**

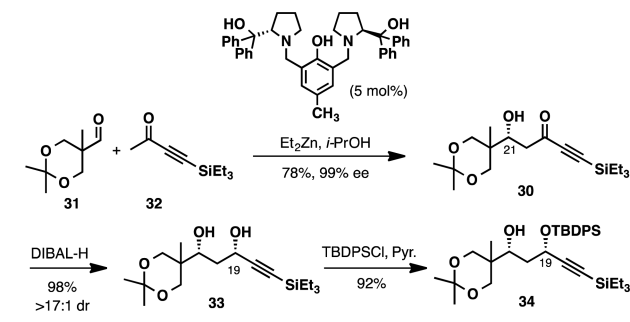
selectivity is attained, since the C21 hydroxyl group will dictate the formation of each subsequent stereocenter. The C22 quaternary stereocenter will be created from the thermodynamic formation of benzylidene acetal **29** via transacetalization. An analogous approach was previously reported by the Kang group in their total synthesis of (+)-lasonolide A.^{7d} Finally, Horner–Wadsworth–Emmons (HWE) olefination with subsequent oxy-Michael addition should favor formation of the desired equatorial C23 stereocenter to complete the synthesis of alkyne **28**.

The synthesis of alkyne **28** commenced with an asymmetric aldol reaction between ynone **32** and aldehyde **31**.¹⁵ Under our standard set of conditions significant elimination was observed when reactions were run at room temperature (Table S2, entry 1), and at 4 °C (Table S2, entry 2).¹⁶ The elimination could be suppressed by running the reaction at –20 °C (Table S2, entry 3) for 72 h. This affords the desired β -hydroxy ketone (**30**) in a moderate 54% yield but with high levels of enantioselectivity (99% ee). Elimination of the β -hydroxy group could be entirely suppressed by modifying the workup procedure. Switching from an aqueous workup to a direct filtration through Celite improved the isolated yield of **30** to 78% (Table S2, entry 4).

With an optimized protocol in hand, we then investigated a 1,3-*syn* reduction of β -hydroxy ketone **30** (Scheme 5). Under standard conditions (Et₂BOME and NaBH₄)¹⁷ the reduction of **30** only afforded a ~4:1 mixture of diastereomers favoring the *syn*-diol. Switching to Kiyooka's conditions (DIBAL-H, –78 °C) increased the diastereoselectivity to 17:1 and the desired diol (**33**) was isolated in 98% yield.¹⁸ Selective protection of the less sterically hindered secondary propargyl alcohol with TBDPSCl gave **34**.

We then aimed to establish the C22 quaternary stereocenter via transacetalization of **34** to form a thermodynamically favored benzylidene acetal.^{7d} Utilization of Kang's conditions (PhCHO, TFA, PhMe –20 °C to rt, 3.5 h), led primarily to the

Scheme 5. Preparation of 34

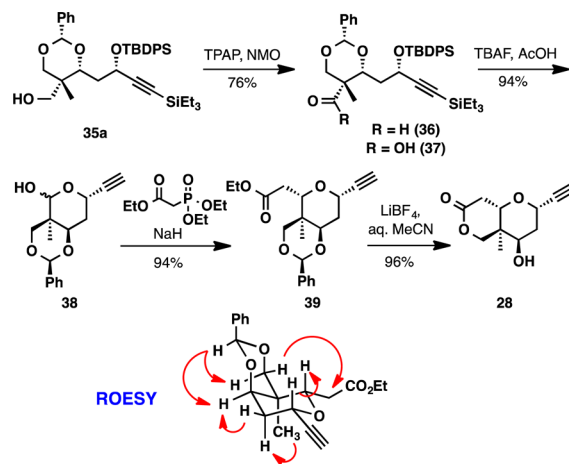


formation of isomers **35c** and **35d** (Figure 3). Only trace amounts of **35a** and **35b** were detected in the crude ^1H NMR spectrum. Although the cyclization favored the incorrect isomer, we were encouraged that these products were isolated in near quantitative yield with little evidence of decomposition that may have arisen from the acidic conditions. Assuming that the observed products were not the thermodynamically preferred ones, we decided to conduct the acetal formation in a more polar solvent (CHCl_3) for an extended period of time. Under these new conditions the desired acetal (**35a**) was strongly favored in good yield, 5:1 chemoselectivity, and 10:1 diastereoselectivity. Importantly, the undesired isomers (**35b**, **35c**, and **35d**) could be separated from the predominant diastereomer (**35a**) by silica gel chromatography and re-subjected to the reaction conditions. After 2 rounds of recycling the undesired diastereomers, acetal **35a**, containing the newly formed C22 quaternary stereocenter, was isolated in 93% yield.

With **35a** in hand we pushed forward toward the completion of the alkyne **28** (Scheme 6). The sequence began with exploring an oxidation of the primary neopentyl alcohol. Surprisingly, **35a** was resistant to oxidation using Dess–Martin periodinane, PDC, TEMPO, and under Moffatt–Swern conditions. Fortunately, Ley's catalytic TPAP/NMO oxidation reliably delivered aldehyde **36** in 76% yield.¹⁹ TBAF-mediated deprotection of the TBDPS and TES protecting groups followed by concomitant cyclization produced lactol **38** in 59% yield. In addition to lactol **38**, carboxylic acid **37** was also isolated in 20% yield. We postulated the undesired side product was arising from a Cannizzaro reaction promoted by the hydroxide typically present in TBAF solutions. Buffering the reaction with acetic acid²⁰ suppressed formation of the carboxylic acid and improved the isolated yield to 94%.

HWE olefination and concomitant intramolecular oxy-Michael addition generated tetrahydropyran **39** as a single diastereomer detectable by ^1H NMR in 94% isolated yield.²¹

Scheme 6. Synthesis of Alkyne 28

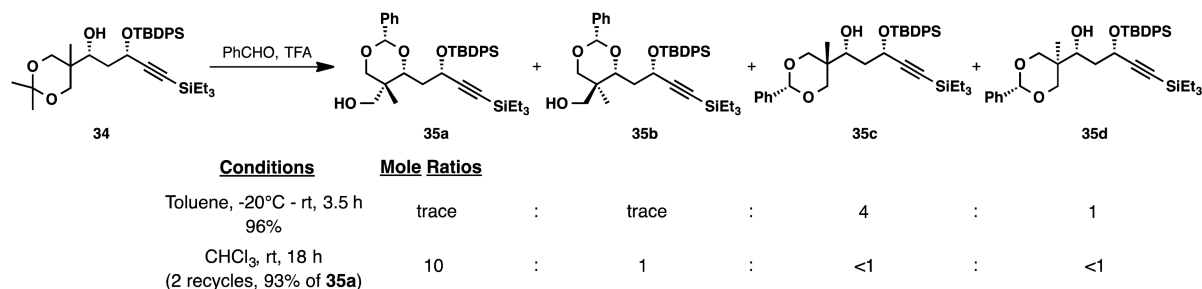


The stereochemistry of the tetrahydropyran was assigned by ROESY correlation.

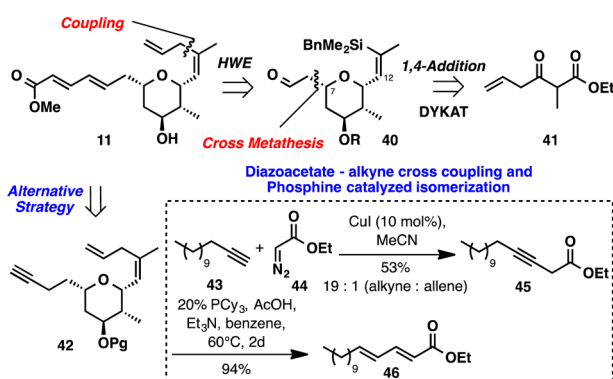
The completion of the alkyne **28** involved hydrolysis of the benzylidene acetal and cyclization of the resulting primary alcohol. Toward this end, a variety of acids were screened to effect the desired hydrolysis/cyclization sequence. The use of *p*-toluenesulfonic acid (MeOH)²² or acetic acid (THF , $50\text{ }^\circ\text{C}$)²³ gave only recovered starting material. Reactions involving BCl_3 (DCM , $-78\text{ }^\circ\text{C}$ to rt),²⁴ 2 M HCl (MeOH , $65\text{ }^\circ\text{C}$),²⁵ or Amberlyst A-15 (4 Å MS, MeCN)²⁶ led to complicated mixtures of partially hydrolyzed products and alkyne **28** in <40% isolated yield. This partial conversion to the lactone was not unexpected since the equilibrium to remove the benzylidene requires the presence of both acid and water, whereas the equilibrium to form the lactone requires the presence of acid, but the exclusion of water/alcohol. Along these lines, we discovered that the desired lactol could be obtained in 53–82% isolated yield by utilizing a two-step procedure, which involved hydrolysis of the acetal with HCl in THF at $80\text{ }^\circ\text{C}$ and then ring closure using catalytic *p*- TsOH in refluxing toluene.²⁷ We later discovered that formation of alkyne **28** could be accomplished in a single step using LiBF_4 in aqueous MeCN in 96% yield.²⁸

The synthesis plan for alkene **11** is presented in Scheme 7. A dynamic kinetic asymmetric reduction of β -ketoester **41** was envisioned to establish the absolute stereochemistry. The C7 stereocenter would be formed through a Michael addition, which could occur after the installation of an appropriate acceptor. Several possible routes were considered for the formation of the dienolate fragment. Our first tier of

Transacetalization Results:

Figure 3. Selective formation of benzylidene acetal **35a**.

Scheme 7. Synthesis Plans for Alkene 11

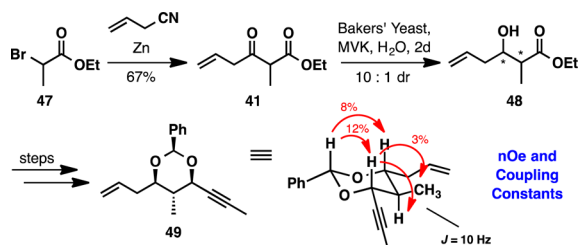


experiments would focus on incorporating this side chain via HWE olefination. Alternatively, if complications arose from the proposed HWE reaction, we also developed a convenient new strategy to form 2,4-dienoates that evolved from the reaction of terminal alkynes with ethyl diazoacetate²⁹ followed by subsequent phosphine-catalyzed isomerization.³⁰ A series of model studies, as illustrated in the conversion of alkyne **43** to dienoate **46** via intermediate **45**, validated this latter approach (see Scheme 7).¹⁶

Initially, we were intrigued by the prospect of utilizing a transition-metal-catalyzed hydrogenation reaction to establish the absolute stereochemistry of fragment **11**.³¹ Although these highly atom economical³² methods proceed with high enantio- and diastereoselectivities for a range of substrates, the chiral catalysts developed so far exhibit poor diastereoselectivities for methyl substituted β -ketoesters such as **41**.³³ As a result, we believed it would be worthwhile to investigate a microbial transformation that could establish the necessary absolute and relative stereochemistry via dynamic reduction of a racemic β -ketoester. After surveying the literature, we discovered that Baker's yeast reductions of methyl-substituted β -ketoesters could provide the requisite products.^{16,34}

Encouraged by this precedent, we embarked on our synthesis of fragment **11** first by preparing the necessary starting material (Scheme 8). β -ketoester **41** was generated through a Blaise

Scheme 8. Relative Stereochemical Assignment of 49



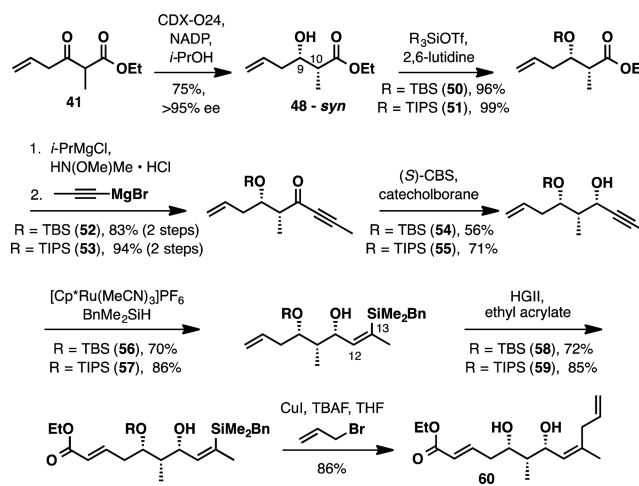
reaction with commercially available α -bromoester **47** and allyl cyanide.³⁵ Interestingly, when we investigated the reduction of β -ketoester **41** with Baker's yeast (Sigma-Aldrich, YSC2, batch 035K0169), the undesired *anti* product was formed with 10:1 diastereoselectivity (30% ee). Without heat treatment or additives, the diastereoselectivity for the reduction decreased to 4:1. The relative stereochemistry was further confirmed by NOE and *J*-coupling analysis on an advanced intermediate.³⁶ These results were in direct contrast to the trends observed from the literature, therefore we decided to screen a number of isolated enzymes,³⁷ generously donated to us by Codexis Inc.,

to determine their performance in the dynamic kinetic asymmetric reduction of β -ketoester **41**. Two types of enzymes were examined in the reaction; the first was derived from Baker's yeast and utilized GDH (glucose dehydrogenase) and NADP with glucose as the stoichiometric reductant.¹⁶ The pH of these reactions must be carefully controlled due to the accumulation of gluconic acid. The second type of enzyme utilizes NADPH as the cofactor and 2-propanol as the reductant. Table S5 of the SI provides a comprehensive screening of enzymatic methods.

NADP dependent ketoreductases, in general, showed enhanced selectivity for the *syn* product. However, under the standard conditions (Conditions A) using triethanolamine as a buffer, significant olefin isomerization of β -ketoester **41** was observed. After an exhaustive investigation of various buffers (pH 4.5–10 screened), we found that a pH 4.5 phosphate buffer completely suppressed the isomerization. CDX-024 demonstrated the highest diastereoselectivity favoring the *syn*-diastereomer (**48**) with high levels of enantioselectivity (see SI, Table S5, entries 7 and 8). Using this enzyme we were able to obtain the desired *syn* product (**48**) in 75% yield, with a 4:1 diastereoselectivity and greater than 95% ee (Table S5, entry 8).³⁸

The synthesis of fragment **11** was advanced using the synthetic sequence depicted in Scheme 9. It began with the silyl

Scheme 9. Synthesis of Diol 60



protection of the C9 alcohol, which was subsequently followed by a 2-step Weinreb amide synthesis and Grignard addition to obtain ynone **52/53** in excellent yield.³⁹ (*S*)-CBS reduction under standard conditions ((*S*)-CBS, $\text{BH}_3 \cdot \text{DMS}$, THF) delivered the desired propargyl alcohols (**54/55**) in good yields (50–70%) as a 6.7:1 mixture of diastereomers. Yu has reported that the use of nitroethane as solvent has a profound effect on both reaction rate and stereoselectivity.⁴⁰ Pleasingly, we found that when we made this switch and used freshly distilled catechol borane the diastereoselectivity improved to >20:1.

Propargyl alcohol **54/55** was then subjected to a Ru-catalyzed hydrosilylation to generate trisubstituted (*Z*)-vinylsilane **56/57**.⁴¹ In each case (R = TBS, or R = TIPS) high selectivities for a single geometric isomer (>15:1) were obtained. In preparation for tetrahydropyran formation via oxy-Michael addition, the enoate acceptor was installed through cross-metathesis with ethyl acrylate.⁴² Finally, the C13 allyl

moiety was introduced by a copper-mediated cross-coupling to form diol **60**.⁴³

Deprotonation of diol **60** with sodium hydride generated tetrahydropyrans **61a/61b** as a 1:1 mixture of diastereomers (Figure 4). Unfortunately, no improvement in diastereo-

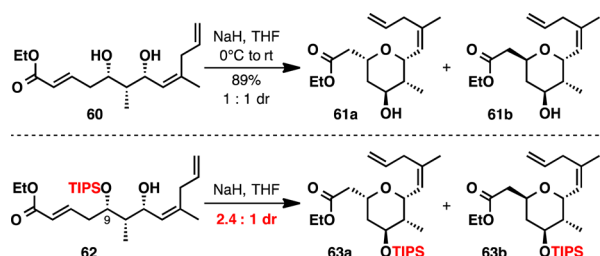
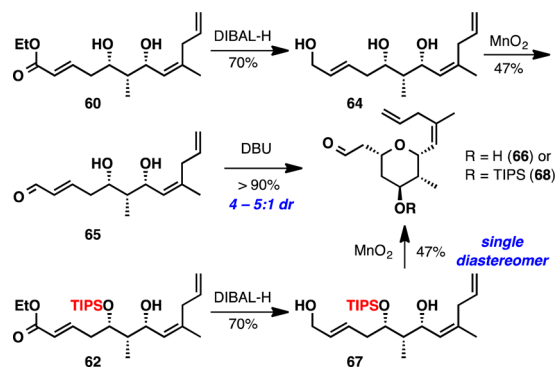


Figure 4. THP cyclizations of **60** and **62**.

selectivity was observed after screening various bases (*t*-BuOK and EtONa), solvents (DMF, THF, and DMSO) and reaction temperatures (-78 °C, 0 °C, rt and 60 °C). Furthermore, equilibration of the diastereomeric mixture under basic conditions did not improve diastereoselectivity. We were aware that a similar approach to the southern tetrahydropyran ring was utilized in Kang's total synthesis of (+)-lasonolide A;^{7d} during their studies, an enhancement in diastereoselectivity was observed upon switching the protecting group on the C9 hydroxyl from TBS to TIPS. Likewise, we observed a modest increase in diastereoselectivity (1:1 to 2.4:1) for the cyclization when a TIPS protecting group was incorporated (**62**). This experiment supported the notion that this structural feature was important for improving selectivity in the cyclization.

Several reports in the literature have indicated that cyclizations of secondary alcohols onto a proximal α,β -unsaturated aldehyde could enhance diastereoselectivity.⁴⁴ It is conceivable that the lower pK_a of the proton adjacent to the aldehyde would render the reaction more reversible, and thereby favor the formation of the thermodynamically preferred 2,6-*cis*-tetrahydropyran ring. To test this hypothesis, α,β -unsaturated aldehyde **65** was prepared (Scheme 10) in two

Scheme 10. Further Studies Investigating THP Cyclizations

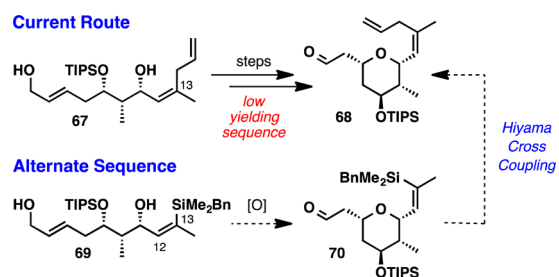


steps from ester **60** and subjected to cyclization using DBU. We found that the diastereoselectivity was improved to ~ 4 – 5 :1. Recalling our previous experience, we suspected that the incorporation of a protecting group at C9 could further enhance diastereoselectivity. Upon preparing the TIPS protected substrate, spontaneous cyclization was observed upon oxidizing allylic alcohol **67** with MnO_2 , and the desired tetrahydropyran

(**68**) was isolated as a single diastereomer in an un-optimized 47% yield.

While encouraged by these results, access to allylic alcohol **67** was problematic due to several low yielding steps that were not amenable to scale-up. To circumvent these issues we decided to pursue an alternative reaction sequence that would feature a THP cyclization, bearing the necessary TIPS protection on the C9 hydroxyl, before installation of the C13 allyl segment (Scheme 11). However, in this alternate sequence, the alcohol

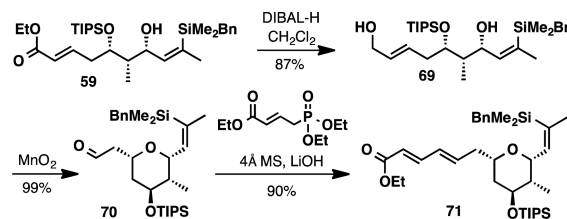
Scheme 11. Revised Synthetic Approach to Access THP **68**



required for the copper-mediated cross-coupling reaction would no longer be available. Therefore, we decided to investigate a Hiyama cross-coupling⁴⁵ for the late-stage installation of the allyl moiety. At the time this work was executed, the use of allyl acetate in the Hiyama cross-coupling had not been described.

The revised synthesis of fragment **11** began with the DIBAL-H reduction of ester **59** (Scheme 12). Allylic oxidation of

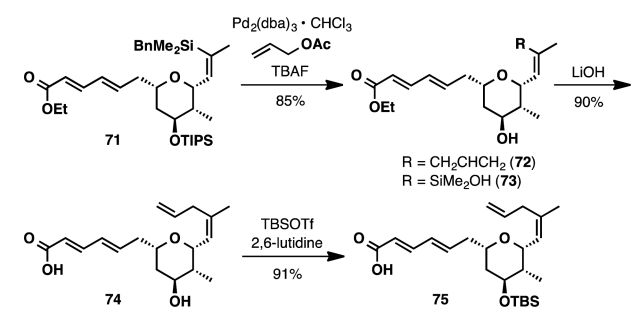
Scheme 12. Synthesis of Vinyl Silane **71**



alcohol **69** with MnO_2 afforded tetrahydropyran **70** directly in nearly quantitative yield as a single diastereomer.⁴⁶ Attempts to perform the Hiyama cross-coupling with aldehyde **70** and allyl acetate were unsuccessful, presumably due to the insufficient stability of the starting aldehyde. To eliminate this problematic functionality, we first installed the dienolate moiety, before re-exploring the Hiyama coupling. Elaboration of the aldehyde into *E,E*-dienolate **71** was accomplished via HWE olefination using 4 \AA MS and LiOH.

Our investigation of the Hiyama coupling¹⁶ between allyl acetate⁴⁷ and vinyl silane **71** began with utilizing 2 mol% $Pd_2dba_3 \cdot CHCl_3$ and 4.2 equiv of TBAF in a solution of THF (see Scheme 13 and SI Table S6). After 19 h, a mixture of the desired product (**72**) along with an equimolar amount of silanol **73** (entry 1) was obtained in 75% combined yield. Extending the reaction time from 19 h to 3 days also generated a 1:1 mixture of **72**:**73** but diminished the yield to 44% (entry 2). Increasing both the catalyst loading (10 mol%) and amount of TBAF (6.4 equiv) was found to decrease the proportion of the remaining intermediate silanol **73**, and alkene **72** could be isolated in 78% yield (entry 3). It is important to note that, when we repeated the experiment, we noticed that the highest yields for this reaction (85%) were obtained when fresh TBAF

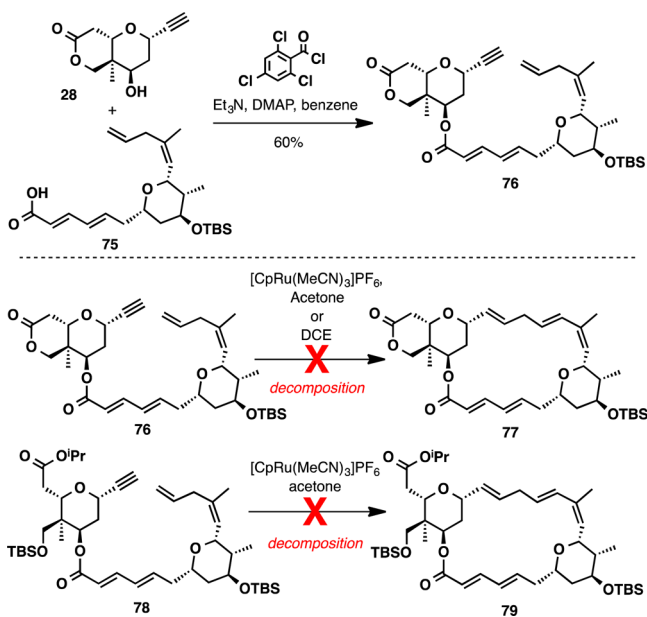
Scheme 13. Synthesis of Alkene 75



solutions were used (entry 4). This modest increase in yield may be related to the water concentration present in TBAF solutions.⁴⁸ Alkene 75 was completed in two steps from 72; saponification using lithium hydroxide, followed by TBS protection and *in situ* hydrolysis of the resulting silyl ester (Scheme 13).

Having achieved a synthesis of both fragments, we were poised to examine our key Ru-catalyzed alkene–alkyne coupling. Initial efforts were dedicated to exploring an intramolecular reaction to forge the macrocycle, since to date only three examples of intramolecular Ru-catalyzed alkene–alkyne couplings have been reported. These have appeared in the total syntheses of (+)-amphidinolide A, (+)-pinnatoin A,⁴⁹ and laulimalide. However, in each of these examples only branched products were generated. Figuring we possessed the necessary coordinating groups to favor the generation of a linear isomer, we were excited by the prospect of investigating a linear selective macrocyclization. Two substrates were examined in the macrocyclization reaction (76 and 78), each of which could easily be accessed using a Yamaguchi esterification.⁵⁰ Unfortunately, after extensive investigation we were never able to form the desired macrocycle as rapid decomposition was observed in all experiments that were attempted (Scheme 14).

Scheme 14. Attempted Macrocyclization via Ru-Catalyzed Alkene–Alkyne Coupling



We then decided to turn our attention to the exploration of an intermolecular alkene–alkyne coupling (Figure 5, eq 3).¹⁶ We were concerned that the π systems of electron deficient ester, present in alkene 11, could be coordinating to the ruthenium catalyst and inhibiting the coupling. As a result, we chose to use alkyne 28 in excess in an attempt to diminish this potential interaction (Table S7, entries 1–6). We observed 50% conversion of the alkene to the desired coupled products (80a and 80b) as an inseparable 2:1 mixture of linear:branched isomers (entry 1). Unfortunately, the excess alkyne that was used could not be recovered as it seems to decompose over the course of the reaction, likely to the hydrated dimer.⁹ Heating the reaction to 50 °C had little effect on the overall conversion (entry 2). However, when the alkyne was added to the reaction dropwise over 15 min and then heated at 50 °C we noticed an increase in conversion to 70% (entry 3). Increasing the concentration from 0.02 to 0.04 M (entry 4) also had no effect on conversion.

Content with our reaction conditions (entry 3), we increased the scale of the reaction from 5 to 60 μ mol in an attempt to obtain an isolated yield for the coupling. To our surprise, this seemingly minor modification was not tolerated and the conversion diminished significantly to \sim 20%. In this case, increasing the concentration to 0.12 M (entry 5) rescued the conversion slightly (35%) but not to the levels that were seen previously. Increasing both the catalyst loading and concentration had a deleterious effect on the overall conversion (entry 6).

Based on the experimental evidence presented in Table S7, entries 1–5 (see SI), we realized that our initial concerns related to catalyst deactivation via coordination to alkene 11 were largely attenuated due to the fact that in each of these entries, which successfully generated product, a 5-fold excess of alkene 11 to catalyst was present. Therefore, we decided to screen reactions that used the alkene in excess. This change resulted in the complete consumption of alkyne 28 on a 68 μ mol scale (Table S7, entry 7). Furthermore, after brief optimization, we determined that only 3 equiv of alkene 11 were needed (using 10 mol% catalyst, in a 0.094 M solution of acetone) to achieve a 66% yield (entry 8).

With a reliable synthetic route, we advanced our synthesis adhering to the current synthesis plan (Scheme 15). Saponification of the ester and lactone, followed by re-lactonization, delivered seco acid 81. Macrolactonization was attempted with a variety of reagents including 2,4,6-trichlorobenzoyl chloride, 2-methyl-6-nitrobenzoic anhydride,⁵¹ and dibutyltin oxide.⁵² Unfortunately, in all cases the macrocycle was never observed and the substrate decomposed under each of the reaction conditions. We speculated that the restricted conformational mobility of the C21 alcohol could be unable to access its optimal conformation for macrolactonization. Therefore, opening the lactone could enable further flexibility of the C21 alcohol and could allow for the desired cyclization to occur. As a result we decided to incorporate this idea into two modified substrates, 83 and 84.

We had hoped to access the elaborated seco acid (83) from lactone 80a via reduction to the lactol, subsequent Wittig olefination, and saponification. Disappointingly, after completing the synthesis of Wittig salt 90, the proposed reaction sequence was unsuccessful in our model system (Scheme 16). Warming the reaction above -15 °C decomposed the unstabilized Wittig reagent rapidly.

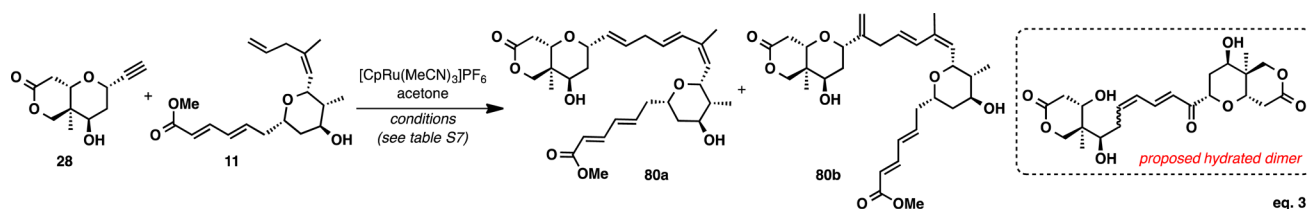
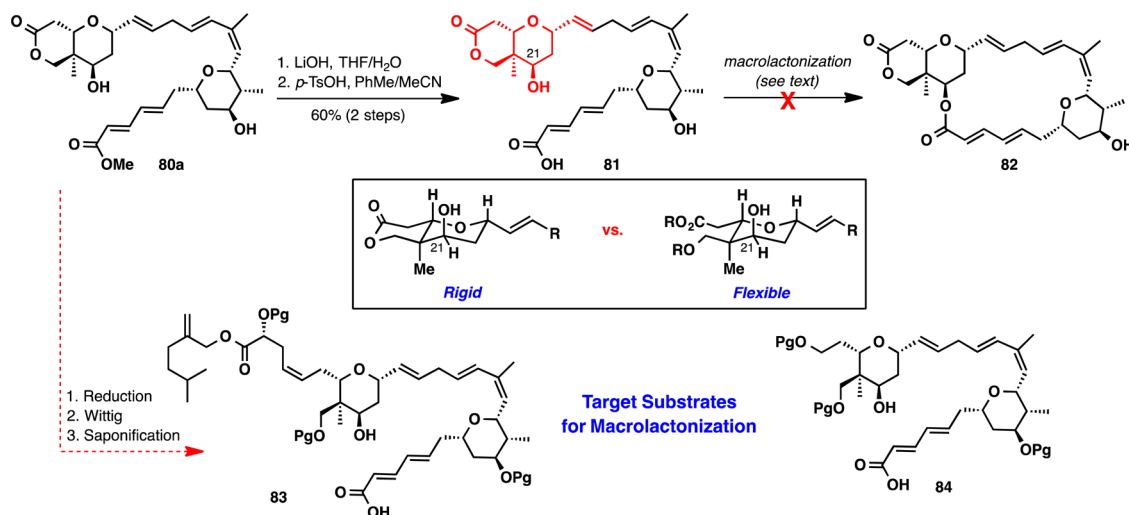
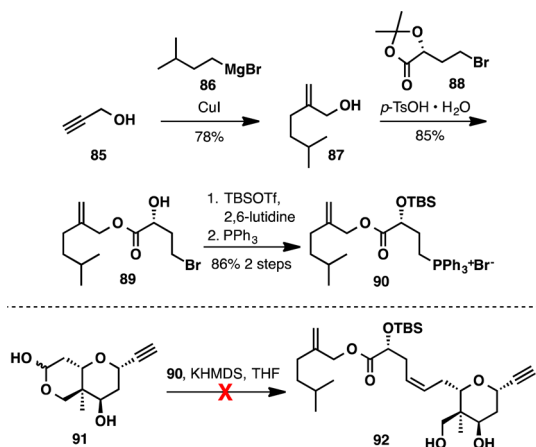


Figure 5. Intermolecular Ru-catalyzed alkene-alkyne coupling.

Scheme 15. Attempted Macrolactonization and Revised Synthetic Strategy



Scheme 16. Preparation of Wittig Salt 90 and Attempted Olefination with Lactol 91



At this point, we decided to take a step back and, in turn, we began investigating a synthesis of seco acid **84**. Ideally, an alkene-alkyne coupling between triol **93** and alkene **94** could provide rapid access to seco acid **84**. Accordingly, we began screening conditions similar to those found to be optimal previously (Table S7). When acetone was used as solvent, we were able to obtain the desired products as their acetonides in 32% yield, as a 3.2:1 mixture of linear:branched isomers (Table 2, entry 1). Upon switching the solvent to cyclopentanone, the product ratio was enhanced to 3.8:1 (entry 2)—this was the highest ratio we had ever observed in our studies. We speculate that the enhanced selectivity could be related to several factors. Because the ruthenium catalyst has one open coordination site, the size of the solvent could have an effect on the product

Table 2. Probing at Structure and Solvent Effects in Ru-Catalyzed Alkene-Alkyne Coupling

Entry ^a	R ₁	R ₂	R ₃	Solvent	Yield ^b	95a:95b ^c
1	H	H		acetone	32%	3.2 : 1
2	H	H		cyclopentanone	39%	3.8 : 1
3	H			acetone	41%	3.7 : 1
4	H			cyclopentanone	62%	3 : 1
5	TBS			cyclopentanone	36%	3.7 : 1

^aAll reactions were run using 3.0 equiv of **94** and 15 mol% $[\text{CpRu}(\text{MeCN})_3]\text{PF}_6$ in 0.047 M solvent, at 55 °C for 2 h 10 min. ^bMixture of **95a**:**95b**. ^cDetermined by ¹H NMR.

ratios. Alternatively, triol **93** might have been protected as its acetonide or cyclopentanone ketal before coupling occurs and

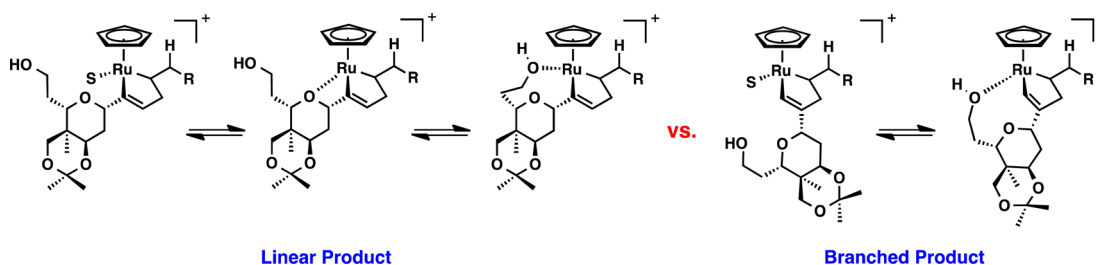


Figure 6. Possible ruthenacyclopentene intermediates for linear and branched products.

the linear to branched ratios may be substrate specific. Finally, it is known that coordinating substituents in the substrates have dramatic effects on product distributions,⁵³ and the presence of the C25 primary alcohol may be contributing to selectivity.

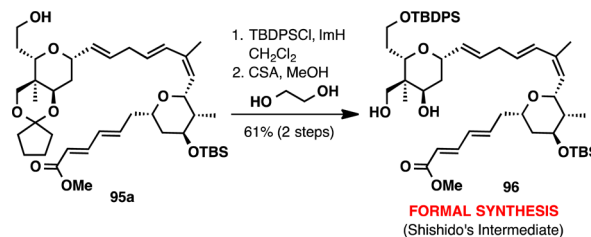
We designed a series of experiments to probe these hypotheses. To determine the extent of contribution from solvent, we tested the cyclopentanone-protected substrate (Table 2, entry 3) in the coupling reaction using acetone as solvent. Only a slight decrease in the linear:branched ratio from 3.8:1 to 3.7:1 was observed. When the acetonide-protected substrate (entry 4) was tested, this time using cyclopentanone as solvent, we saw a decrease in linear:branched ratio to from 3.8:1 to 3:1. Finally, to probe the role of the C25 alcohol, we incorporated a TBS protecting group onto the cyclopentanone protected substrate (entry 5), expecting the linear:branched ratios to decrease if coordination was no longer possible. An identical 3.7:1 ratio of linear:branched isomers was obtained. The fact that the TBS protecting group was cleaved during the reaction invalidates any conclusions about the role of the hydroxyl group since the desilylation could have occurred prior to or after the alkene–alkyne coupling.

Several proposed ruthenacyclopentene intermediates for both the linear and branched products are depicted in Figure 5. After oxidative coupling, ruthenium has one open coordination site and can be occupied by solvent (S) or by a coordinating atom present in the substrate. For the linear isomer, the oxygen in the tetrahydropyran ring or the primary alcohol could occupy this site. For the branched isomer only coordination of the primary alcohol may be possible but, as depicted in Figure 6, seems to be rather unfavorable. The facile desilylation that was observed in the reaction (Table 2, entry 5) suggests that the alcohol may be coordinated to the Lewis acidic ruthenium rendering it more susceptible toward desilylation. Taken together, these results begin to provide evidence that the product ratio is *highly* dependent on the identity of the substrate and is less influenced by the solvent (i.e., cyclopentanone vs acetone).

From diene **95a**, protection of the primary alcohol as its TBDPS ether and hydrolysis of the cyclopentanone ketal provided diol **96**, an intermediate that was used in Shishido's total synthesis of (+)-lasonolide A (Scheme 17).^{7e} The physical data for diol **96** was in complete agreement with the reported data. The optical rotation of **96** was +11.4 (*c* 0.75, CHCl₃), opposite to that reported in the Shishido synthesis ($[\alpha]_D^{23}$ -19.3 (*c* 1.04, CHCl₃), and consistent with our absolute stereochemical assignment for (-)-lasonolide A.

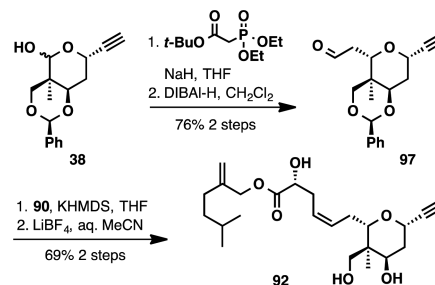
At this point, we decided to further streamline our synthesis of lasonolide A to help fulfill the need for material that will help advance biological investigations. We turned our attention back to the Ru-catalyzed coupling reaction and questioned if a more elaborated coupling partner could be tolerated under the

Scheme 17. Formal Synthesis of (-)-Lasonolide A



reaction conditions. Alkyne **92**, which contains the fully elaborated side chain could be obtained in four steps from lactol **38** (Scheme 18). Although alkyne **92** contains two alkenes, disubstituted olefins are typically unreactive in the Ru-catalyzed coupling.⁵³

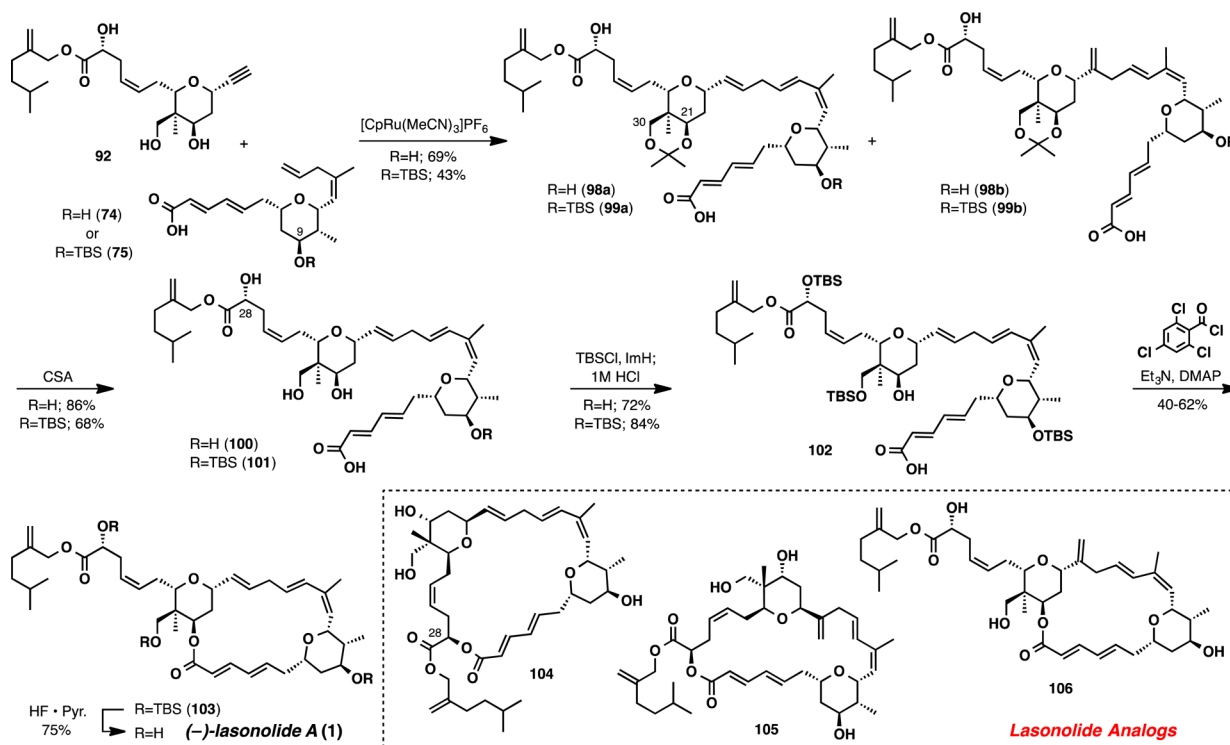
Scheme 18. Synthesis of Alkyne 92



The alkene–alkyne coupling between **92** and **75** (Scheme 19), run under our standard set of conditions, took place in 43% yield with a linear:branched ratio of 3:1. The coupling between **92** and **74** also successfully occurred albeit with diminished linear:branched ratios (2:1) but in 69% yield. Reactions run in cyclopentanone led to poor conversion and slightly diminished linear:branched ratios in each case. Additionally, for the coupling between **92** and **74**, decreasing the amount of catalyst (from 15 to 5 mol%) while also increasing the concentration (from 0.047 M to 0.14 M) decreased the yield to 28% (51% of **92** as its acetonide was recovered) without affecting the linear:branched ratio. It is also important to note that in each of the examples described above, >80% of the alkene **74/75** was recovered.

Completion of the synthesis was accomplished from both intermediates **98a** and **99a**.⁵⁴ Removal of the acetonide with CSA followed by protection of the most accessible alcohols in both **100** and **101** provided seco acid **102**, a common intermediate in both routes. Macrolactonization using the Yamaguchi reagent occurred without incident to provide the TBS protected lasonolide (**103**) in yields ranging from 40 to 62%. At this point, the undesired branched isomer that was

Scheme 19. Final Reaction Sequence Completing the Synthesis of (–)-Lasonolide A and Lasonolide Analogues



generated during the coupling could be separated from the linear isomer. A final desilylation, using HF·Pyr, provided the target molecule, (–)-lasonolide A in 75% yield.

In addition to synthesizing the natural product we have also generated three analogues (Scheme 19). Compound 104 came from macrolactonization of the fully deprotected precursor hydroxyl acid. Compounds 105 and 106 were straightforwardly derived from the branched byproducts of the alkene–alkyne couplings. The synthetic lasonolide A and the three analogues were submitted to *in vitro* testing in an attempt to explore their activity against various cell lines.¹⁶ Each analogue tested was essentially inactive compared to the synthetic (–)-lasonolide A in all assays except for the HCT116.

SUMMARY

In conclusion, a synthesis of (–)-lasonolide A has been described. The synthesis has been accomplished in 16 linear steps and 34 total steps from commercially available starting materials. A formal intermediate was also prepared and matches the physical data that were reported in Shishido's synthesis of (+)-lasonolide A. Biological studies, utilizing the synthetic material generated from this work, are currently underway in an effort to further understand the mechanism of action. Importantly, these studies verify that the Ru-catalyzed alkene–alkyne coupling is amenable for making linear as well as branched 1,4-diene motifs en route to natural products, notably biologically active macrocycles. This success of the intermolecular coupling between fully unprotected polyhydroxy diene-yne 92 and tetraene 74/75 demonstrates a remarkable chemoselectivity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05127. Data

for the compounds reported in the preliminary communication appear in the Supporting Information of the communication.^{7a}

Experimental procedures, analytical data (¹H NMR, ¹³C NMR, MS, IR, and [α]_D) for all new compounds, additional reaction optimization tables (PDF)

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Notes

The authors declare no competing financial interest.

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