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Total Synthesis and Stereochemical Assignment of (−)-Ushikulide A

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Abstract: We report the determination of the full stereostructure of (−)-ushikulide A (**1**), a spiroketal containing macrolide by total synthesis. Ushikulide A (**1**) was isolated from a culture broth of *Streptomyces* sp. IUK-102 and exhibits potent immunosuppressant activity ($IC_{50} = 70$ nM). To embark upon an ushikulide A synthesis, a tentative assignment was made based on analogy to cytovaricin (**2**), a related macrolide isolated from a culture of *Streptomyces diastatochromogenes* whose full structure was previously established via synthesis and X-ray crystallography. This report delineates studies on several key steps, namely a direct aldol reaction catalyzed by the dinuclear zinc ProPhenol complex, a metal catalyzed spiroketalization, as well as application of an unprecedented asymmetric alkynylation of a simple saturated aldehyde with methyl propiolate to prepare the nucleophilic partner for a Marshall−Tamaru propargylation. These studies culminated in the first total synthesis and stereochemical assignment of (−)-ushikulide A and significantly extended the scope of the above-mentioned methodologies.

Introduction

In spite of the tremendous advances in modern spectroscopic methods, organic synthesis continues to play a pivotal role in elucidating the full structure of complex natural products.[1] This method has the advantage that, even in the absence of a firm structural assignment, a combination of logic and spectroscopic comparison can arrive at the correct structure. Previous work in our group led to the assignment of amphidinolide A after a total of 11 diastereomers were prepared synthetically.[2] Thus, we were encouraged to consider the synthesis of other natural products of uncertain stereochemistry.

Ushikulide A (**1**), a newly isolated[3] and stereochemically undefined member of the oligomycin-rutamycin family, was chosen out of many possible synthetic targets based on several considerations. Due to the stereochemical complexity of such natural products, randomly preparing diastereomers would lead to an exceedingly tedious task (ushikulide A contains 14 stereogenic centers, leading to $2^{14} = 16384$ stereoisomers). Therefore, a reasonable amount of likely stereochemical information was required before synthetic studies could be initiated. **1** has a remarkable resemblance to cytovaricin (**2**), a natural product isolated from the same species of bacteria, whose full structure was established through X-ray crystallography[4] and confirmed via synthesis.[5] Furthermore, careful comparison of the NMR spectra of these structures revealed close similarity between the spiroketal regions of **1** and **2** (Figure 2). While this was clearly insufficient evidence to firmly assign the structure of ushikulide, it appeared at the outset that eight of the stereocenters (carbons 16, 19, 20, 21, 23, 26, 27, and 29) were either clearly analogous to cytovaricin or their configuration should be apparent after the first synthetic diastereomer was prepared. Specifically, stereochemistry at C_{16} could be lost through base catalyzed isomerization of the β,γ-unsaturated ketone yielding ushikulide B (which contains an *E* olefin between C_{15} and C_{16}), while the stereochemistry at C_{29} (which is isolated from the macrolactone) could be assigned as long as the spiroketal portion of the synthetic material had the correct configuration. Only six centers remained, a task roughly comparable to our successful synthesis of amphidinolide A.[2] In the absence of significant quantities of a natural product for degradation studies, synthesis is the only method to reliably assign a structure in the event that X-ray crystallography proves untenable, as was the case for **1**.[6] We hope that this full account[7] will provide a deeper understanding of the chemistry employed in this study while also outlining the power of synthesis for the determination of structure.

Synthetic Planning. A flexible approach that could be amended to prepare any diastereomer of **1** was envisioned (Scheme 1). As the stereochemistry of the spiroketal was pivotal, it seemed well advised to split the spiroketal (**3**) away from the aliphatic portion (**4**) via Suzuki coupling and esterification. While sp^2-sp^2 Suzuki coupling is a well-established disconnection for diene-containing members of this family,[8] our retrosynthesis relied on a less common sp^2-sp^3 Suzuki reaction[9] to access the $C_{14}-C_{15}$ olefin of ushikulide A. For spiroketal fragment **3**, a Marshall−Tamaru propargylation would provide the homopropargylic alcohol that could be elaborated to the

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10.1021/ja906056v CCC: $40.75

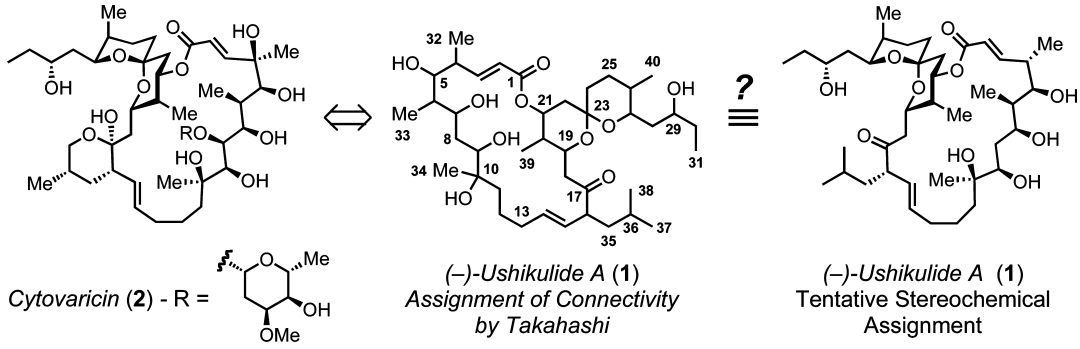

Figure 1. Tentative Stereochemical Assignment of (−)-Ushikulide A.

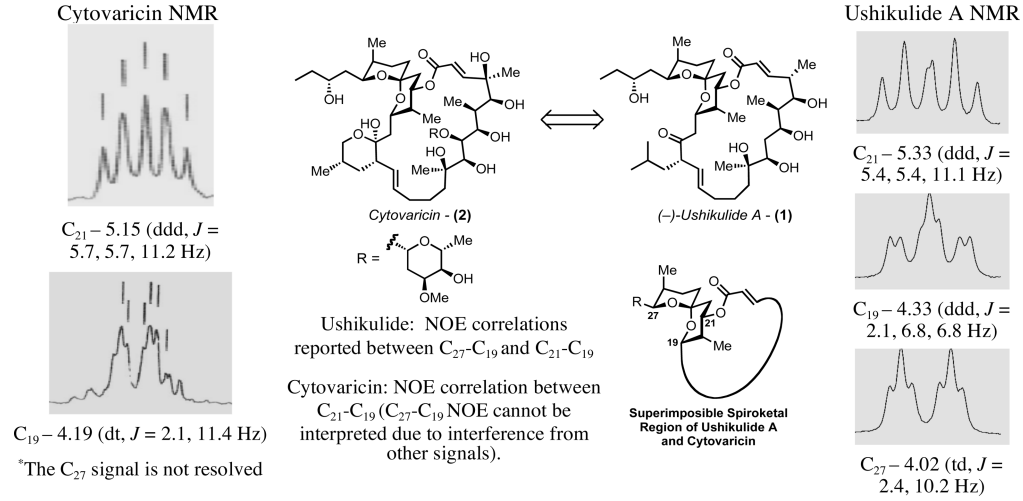

Figure 2. Comparison of Cytovaricin and Ushikulide A.

C_{15}−C_{14} olefin. The metal catalyzed spiroketalization, pioneered by Utimoto,[10] represents a highly atom-economical and redox-neutral[11] approach to the desired spiroketal ring system. Utilization of an alkyne as an orthogonally reactive surrogate[12] for the desired spiroketal is strategically advantageous as it enables two carbon−carbon bond forming reactions without requiring the use of additional protecting group manipulations or activating groups, which certainly would have been required if more conventional carbonyl chemistry had been employed. Either **5** or **6** could potentially lead to the desired spiroketal; however, only the former case appeared likely to give the desired regioselectivity (see **6** to **7**, Scheme 1). Application of our dinuclear zinc aldol methodology[13] was expected to simplify the aliphatic fragment into ketone **9** and aldehyde **10**. Due to the similar steric bulk of the methyl and allyl groups at C_{10}, conventional aldol methodologies would not be expected to give acceptable diastereoselectivity for this reaction. However, we envisioned that through catalyst control this highly convergent strategy would become tenable.

Synthesis of the Spiroketal Fragment. Our studies began with the preparation of several aldehydes to fulfill the role of synthon **8** (**16a**−**d**, Scheme 2). To accomplish this, a Crimmins[14] aldol reaction between thiazolidinethione **14** and three known aldehydes (**13a**−**c**)[15] was employed. Reaction of the (*Z*)-titanium enolate derived from **14** with aldehydes **13a**−**c** resulted in essentially complete diastereoselectivity and quantitative yield for each case. Reduction of aldol adduct **15a** to the β-hydroxy aldehyde was complicated by facile epimerization of the α-stereogenic center on silica gel (not shown). However, after protection of the secondary alcohol, monoreduction proceeded

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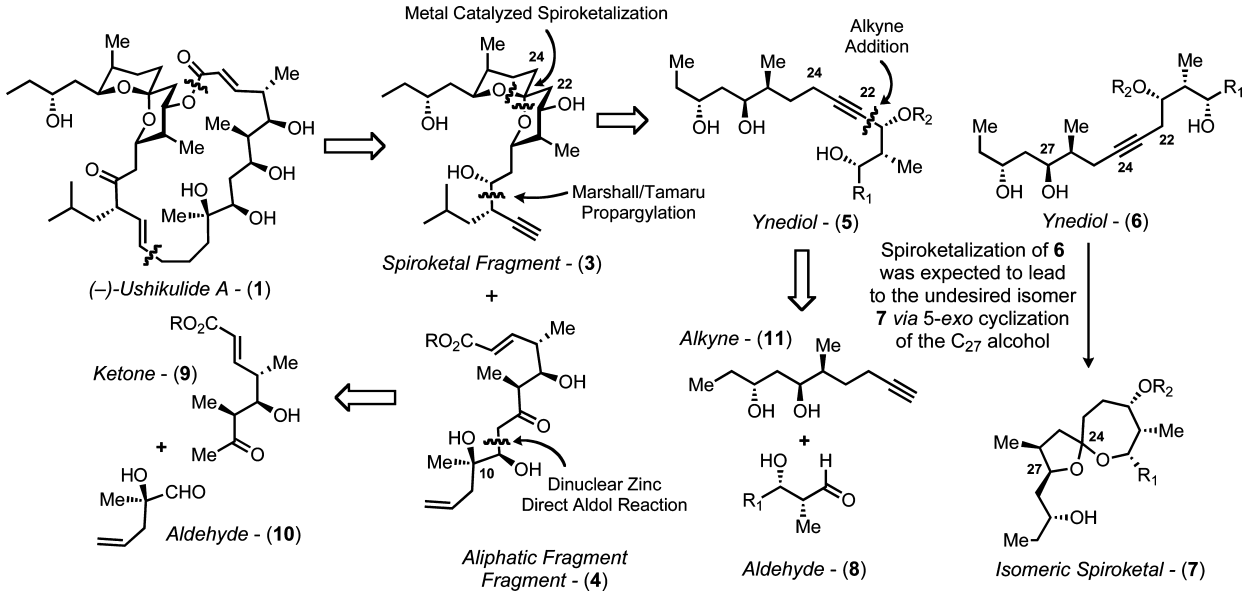
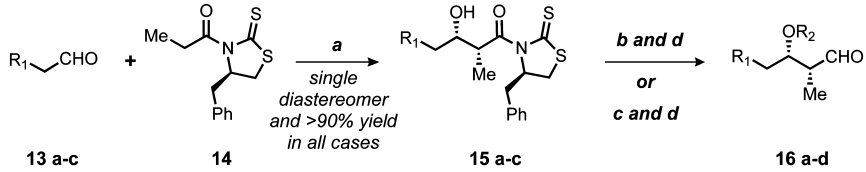
Scheme 1. Retrosynthetic Analysis of Ushikulide A



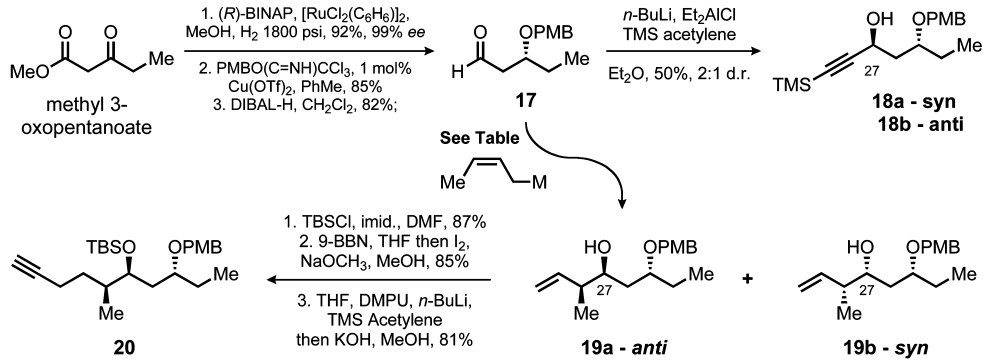
Scheme 2. Preparation of Several Aldehyde Partners through a Crimmins Aldol Reaction



a. $TiCl_4$, NMP, (–)-sparteine, CH_2Cl_2
b. TBSOTf, 2,6-lutidine, CH_2Cl_2
c. MOMCl, *n*-Bu_4NI, EtN(*i*-$Pr)_2$, DMF
d. DIBAL-H, CH_2Cl_2, -78 ºC

16a - $R_1 = CH_2OTBDPS$, R_2 = TBS, 80% over 3 steps
16b - $R_1 = CH_2OBn$, R_2 = TBS, 80% over 3 steps
16c - R_1 =  , R_2 = TBS, 74% over 3 steps
16d - R_1 = , R_2 = MOM, 56% over 3 steps

Scheme 3. Preparation of the Alkyne Fragment



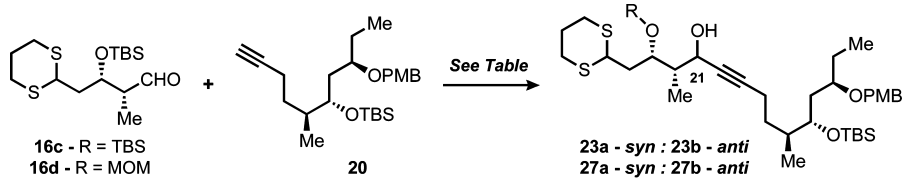
Entry	M =	Conditions	Yield (**19a:19b**)*
1	Bu_3Sn	CH_2Cl_2, BF_3•OEt_2	64% (2:1)
2	Bu_3Sn	CH_2Cl_2, $SnCl_4$	57% (7:3)
3	(+)-Ipc_2B	*i. cis*-2-butene, *t*-BuOK, *n*-BuLi, THF *ii.* (+)-Ipc_2BOMe *iii.* **17**, BF_3•OEt_2	80% (20:1)
4	(–)-Ipc_2B	*i. cis*-2-butene, *t*-BuOK, *n*-BuLi, THF *ii.* (–)-Ipc_2BOMe *iii.* **17**, BF_3•OEt_2	75% (1:20)

* Isolated yields after purification by flash column chromatography. Diastereomeric ratios were determined by ^1H NMR analysis of the crude reaction mixture prior to purification.

uneventfully to yield the desired aldehydes (**16a**−**d**) in good yield over three steps.

Preparation of an alkyne fragment to fulfill the role of synthon **11** began with a known Noyori reduction of methyl-3-oxopen-

Scheme 4. Attempted Diastereoselective Alkyne Addition

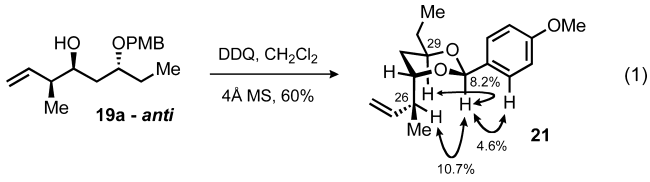


Entry	R =	Conditions	Yield (*anti:syn*)*
1	TBS	*n*-BuLi, THF	90% (2:3)
2	TBS	*n*-BuLi, LiBr, 4Å M.S., THF	77% (1:6)
3	TBS	*n*-BuLi, Et_2AlCl, toluene	38% (1:2.5)
4	MOM	$LiN(i\text{-}Pr)_2$, THF	43% (4:1)

* Isolated yields after purification by flash column chromatography. Diastereomeric ratios were determined by ^1H NMR analysis of the crude reaction mixture prior to purification.

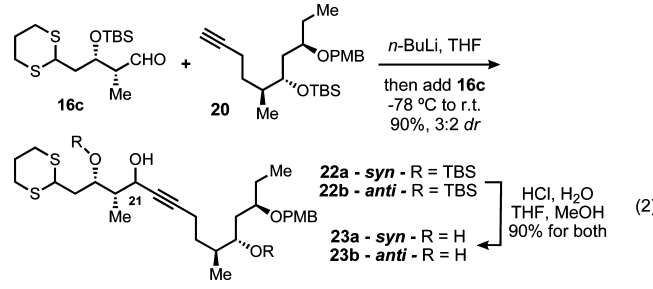
tanoate (Scheme 3).[16] Formation of the *p*-methoxybenzyl ether and monoreduction with diisobutylaluminum hydride gave aldehyde **17** in good yield. Addition of the lithium anion of TMS acetylene in the presence of a chelating Lewis acid (Et_2AlCl) gave a mixture of propargyl alcohols **18a** and **18b** in low diastereoselectivity and yield (~2:1 at C_{27}, Scheme 3). Separation of these epimers on a preparative scale was prohibitively difficult, particularly at this early stage in the synthesis. As an alternative, a number of crotylations were surveyed, starting with the conditions of Keck,[17] which afforded a mixture of predominantly two diastereomers (2:1, **19a:19b**) that were also inseparable by flash chromatography on silica gel. Varying the Lewis acid ($SnCl_4$, CH_2Cl_2, Entry 2) led to only a negligible increase in diastereoselectivity. Fortunately, ample precedent suggested that this problem could be overcome by reagent control.[18] In our case, using either antipode of Brown's[19] (*Z*)-crotyl-B(Ipc)$_2$ reagent led to excellent control of stereochemistry for the preparation of **19a** or **19b** in >20:1 d.r. by ^1H NMR analysis for both cases. Preparation of alkyne **20** was completed in three additional steps (silylation, hydroboration−iodination, and nucleophilic substitution). Because no chromatographic separation of diastereomers was required, this route proved to be highly scalable and more than 10 g of **20** were ultimately prepared.

The stereochemistry of **19a** was also confirmed via formation of a cyclic para-mehoxybenzyl acetal (eq 1). Exposure of **19a** to DDQ in the presence of molecular sieves[20] furnished acetal **21**, which could be cleanly separated from an initial mixture of diastereomers in 60% isolated yield. NOE irradiation of the benzylic acetal proton showed strong enhancements at C_{26} and C_{29}, consistent with the indicated chair form and demonstrating the 1,3 diol to be of an anti stereochemical relationship.



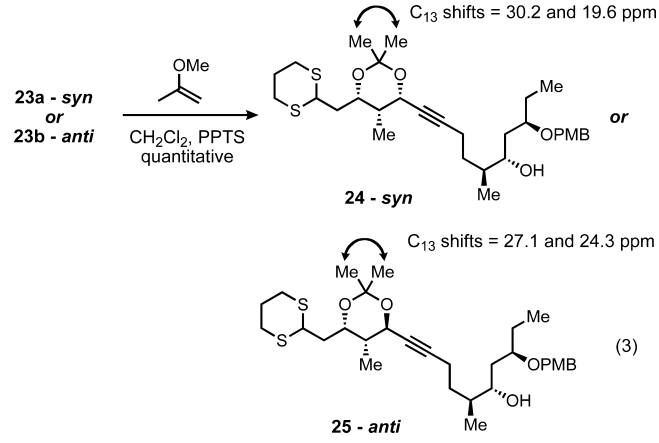
(1)

With the two fragments in hand, our attention turned to nucleophilic addition of alkyne **20** to the aldehyde fragment **16c** (eq 2). The addition proceeded with low diastereoselectivity; however, separation of the C_{21} epimers was readily accomplished by silica gel chromatography. Desilylation with fluoride (HF•pyridine or *n*-Bu_4NF) proceeded only very slowly at one of the two silyl groups, but exposure of either **22a** or **22b** to hydrochloric acid yielded either epimeric diol in good yield (**23a** or **23b**).



(2)

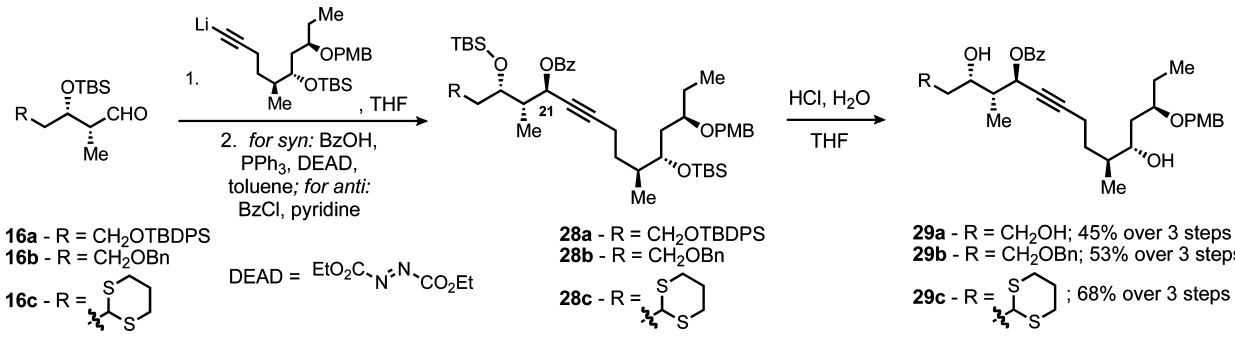
The stereochemistry of each triol was assigned by the method of Rychnovsky (eq 3).[21] Protection of 1,3-diols **23a** and **23b** was accomplished with 2-methoxypropene and PPTS, yielding acetonides **24** and **25**. *g*HSQC analysis of either acetonide confirmed the relative stereochemistry with syn acetonide **24** displaying large differences in the acetonide ^{13}C NMR shifts, consistent with a chair conformation, while anti acetonide **25** displayed nearly equivalent ^{13}C NMR shifts consistent with a half-chair conformation.



(3)

Attempts were also made to improve the diastereoselectivity of the alkyne addition reaction (Scheme 4). Moderate Felkin−Anh selectivity could be obtained in the presence of lithium bromide and molecular sieves (6:1 d.r., Entry 2). However, obtaining the chelation controlled product (**22b**) proved not to be feasible

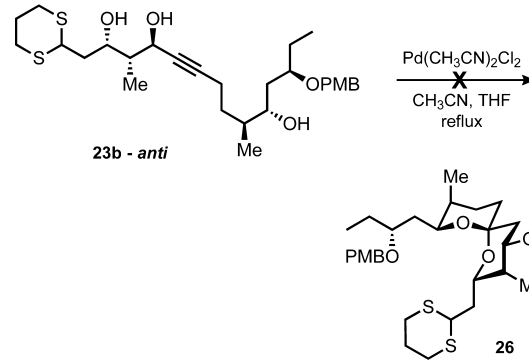
Scheme 5. Modification of the Spiroketalization Substrate



under the reaction conditions examined. Switching the C_{19} *tert*-butyldimethylsilyl group to a methoxymethyl ether (**16d**, Entry 4) gave some improvement of the diastereoselectivity; unfortunately, the resulting epimers (**27a** and **27b**) were very recalcitrant to chromatographic separation, causing this route to be impractical.

The low selectivity of the alkynylation led us to consider two possible alternatives. The first would be addition of the alkyne to a Weinreb amide, followed by diastereoselective Noyori reduction,[22] while the second would be inversion of the syn 1,3-diol to converge both epimers to the anti stereochemistry. Because of the ease of chromatographic separation, we ultimately elected to pursue the latter course (Scheme 5). Alternatives to the 1,3-dithiane protecting group were also examined as the sulfur atoms it contained might cause catalyst poisoning during the key spiroketalization reaction. Three aldehydes (**16a**−**c**) were subjected to alkyne addition with the lithium acetylene derived from **20**. After separation of the resulting epimers, the anti product was esterified with retention (BzCl, pyridine), while the syn product was esterified under conditions leading to inversion (PPh_3, DEAD, BzOH, toluene). All three pairs of epimers converged, yielding propargyl benzoates **28a**−**c**. The TBDPS group (**28a**) proved too acid-labile and yielded predominantly triol **29a** when subjected to the deprotection conditions developed previously (HCl, H_2O, THF). Fortunately, both **28b** and **28c** could be cleanly desilylated yielding diols **29b** and **29c** respectively.

With the triol **23b** in hand, we examined application of a metal catalyzed spiroketalization for the preparation of spiroketal **26**. Coordination of a carbophilic Lewis acid (Pd^{II}) to the alkyne present in the starting material should lead to oxypalladation, generating an enol-ether and ultimately producing the desired spiroketal. Unfortunately, Utimoto's conditions ($Pd[CH_3CN]_2Cl_2$, THF, CH_3CN, reflux)[10] failed entirely for the preparation of **26** (eq 4). When acetone was substituted as solvent with the same catalyst, a mixture of acetonide **25** along with an unidentified product was obtained. All other Pd^{II} catalyzed conditions that were examined afforded only decomposition after prolonged heating.



(4)

Further investigation of the spiroketalization reaction focused on triol **30b** and propargyl benzoate **29b** as precursors to spiroketal **31a** (Scheme 6). Palladium catalysis again provided only limited reactivity (Entry 1), prompting us to examine platinum[23] and gold.[24] While platinum also failed (Entry 2), gold(I)-chloride gave complete conversion at room temperature, but almost none of the desired spiroketal (**31a**) was observed. Instead elimination product **32** was isolated in 61% yield (Entry 3). Examination of other gold catalysts (such as $AuClPPh_3$ with or without added silver salts) failed to resolve this difficulty. Under nearly identical conditions, propargyl benzoate **29b** gave a 17% yield of spiroketal **31b** along with 47% of elimination product **32** (Entry 4). Examination of several Brønsted acid additives showed that the distribution of products could be biased toward the formation of **31b** in the presence of PPTS (Entry 5). In the presence of stronger acid (CSA, Entry 6), the elimination problem was significantly exacerbated and the overall yield decreased significantly. Variation of the solvent caused significant perturbation to the ratio of products. Moving from MTBE to THF (Entry 7) significantly improved the yield of **31b**, but continuing to an even more polar solvent, such as methanol, increased the elimination problem relative to THF. Out of the conditions surveyed, the best were those outlined in Entry 7, and these were used for all further spiroketalization reactions.

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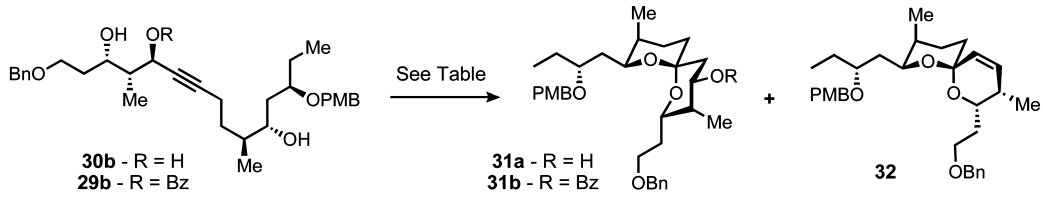
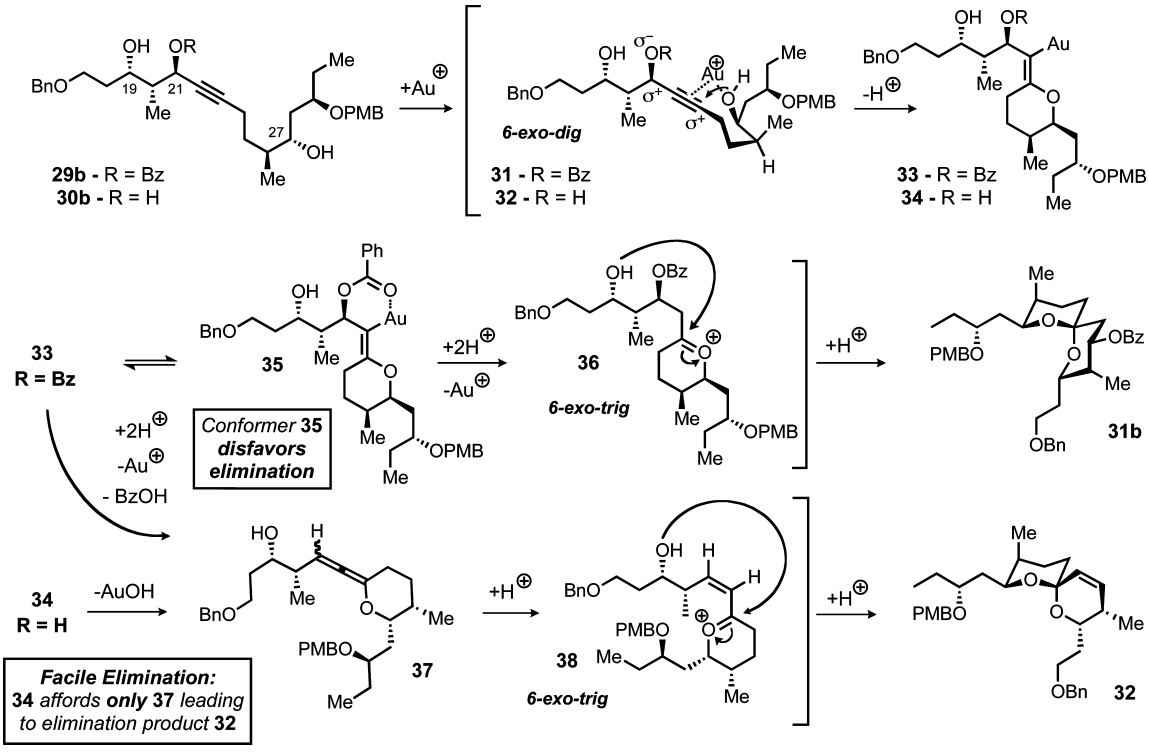
Scheme 6. Optimization of the Spiroketalization Reaction



Entry	R =	Conditions	Yield (**31:32**)*
1	H	10 mol% $PdCl_2(CH_3CN)_2$, PPTS, MeOH, 50 °C	No Pdt. observed
2	H	10 mol% $Pt(COD)Cl_2$, *i*-Pr_2O, PPTS, 60 °C	No Pdt. observed
3	H	5 mol% AuCl, MeOH, PPTS, r.t.	Trace : 61%
4	Bz	5 mol% AuCl, MTBE, r.t.	17% : 47%
5	Bz	5 mol% AuCl, PPTS, MTBE, r.t.	41% : 41%
6	Bz	5 mol% AuCl, CSA, MTBE, r.t.	24% : 34%
7	**Bz**	**5 mol% AuCl, PPTS, THF, r.t.**	**69% : 15%**

* Yields for Entries 1−6 were determined through ^{1}H NMR analysis of the crude reaction mixture using benzyl benzoate as an internal standard. Entry 7 is the average isolated yield of two reactions, after separation of **31b** and **32** by column chromatography. Both reactions were performed on greater than 150 mg scale.

Scheme 7. Mechanism of the Spiroketalization Reaction

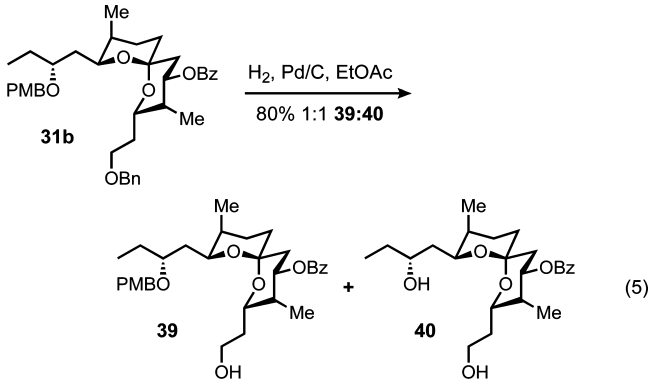


Aponick[25] reported the preparation of unsaturated 1,7-dioxaspiro[5.5]undec-4-ene spiroketals via a gold catalyzed dehydrative cyclization of monopropargylic triols. Thus, in retrospect, it is not surprising that triol **30b** was so prone to elimination. However, the leaving group ability of benzoate appears to be greater than a hydroxyl group, at least in a thermodynamic sense (pK_a 15.7 vs 4.3 in water).[26] At first, we were somewhat puzzled by this counterintuitive observation. This issue is also convoluted by the fact that it is unclear whether the gold cation is lost via protonaton prior to or following the elimination. The mechanism below (Scheme 7) assumes loss of gold cation prior to formation of the spiroketal. While we cannot rule out that enol ether **33** or **34** could induce elimination directly after protonolysis of the gold cation, the heightened propensity of the hydroxy group to eliminate suggests that gold is involved in the elimination step prior to protonolysis. This premise is consistent with the fact that weak acid disfavors elimination, as acid should favor protonolysis of the gold cation before elimination can occur. The length of the reaction time

(25) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121.
(26) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Harned, H. S.; Robinson, R. A. *Trans. Faraday Soc.* **1940**, *36*, 973.

did not alter the ratio of **31b** and **32**, implying that **31b** does not convert to **32** directly via reionization and solvolysis. The first report of a gold catalyzed spiroketalization[24] presented several reactions in which 5-*exo*-dig cyclization dominated over a possible 6-*endo*-dig pathway. Therefore, it seems more likely that the C_{27} hydroxyl group attacks first via a 6-*exo* dig pathway to form intermediate **33** or **34**, although we cannot rule out a 6-*endo* cyclization of the C_{19} hydroxyl group, as it would lead to the same product. Nucleophilic addition to C_{23} in preference to C_{22} is enforced by the benzoyloxy or hydroxy group at C_{21}, which through its inductive electron withdrawing nature disfavors a cationic intermediate at C_{22}.[27] Calculations have indicated that this oxy-metalation consists of a syn addition across the alkyne, resulting from prior coordination of the hydroxy group to the gold Lewis acid (see intermediates **33** and **34**).[28] One possible rationalization for the benzoyl groups lessened propensity toward elimination would be formation of a 6-membered chelate (**35**), in which the σ^* orbital of the C_{21}−O bond is orthogonal to both the π-system and the Au−C σ bond, leading to a kinetically inert conformation. Intermediate **34** instead encourages elimination through coordination of the hydroxyl group to the gold center, resulting in formation allenyl enol ether **37**, which could undergo reversible protonation to form oxonium **38**, explaining the formation of the cis olefin geometry required for **32**.

Because we had assumed that triol **30b** would be a superior spiroketalization substrate, it had not been anticipated that the benzoyl group would be present in the product. This led to unexpected protecting group difficulties as the benzoyl group was not compatible with conditions known to selectively cleave benzyl groups in the presence of *p*-methoxybenzyl groups (lithium 4,4′-di-*tert*-butylbiphenyl, THF, −78 °C).[29] Hydrogenolysis was unsatisfactory, and after surveying a fair number of conditions, only a 40% yield of the desired alcohol (**39**) could be isolated (eq 5).



As a result, the 1,3-dithiane group was reinvestigated, and to our delight, it proved to be an effective substrate for the spiroketalization (Scheme 8). In analogy to the spiroketalization with the benzyl ether, employing triol **30c** in the spiroketalization led almost exclusively to elimination product **42**. In contrast, benzoate **29c** led, at slightly elevated temperature and increased catalyst loading (50 °C, 10 mol % AuCl, THF), to spiroketal **41** in 63% isolated yield. Discrimination of the protecting groups was now trivial and methyl iodide in buffered aqueous acetonitrile gave aldehyde **45** directly.

Our need to access mesylate **44** prompted us to examine the asymmetric alkynylation of isovaleraldehyde with methyl propiolate, a very challenging transformation[30] that was unprecedented before our communication.[7] Implementation of our zinc alkynylation method[31] led to the isolation of **43** in high yield and excellent enantioselectivity, the first such transformation reported for a simple aliphatic aldehyde. Under identical conditions, TMS acetylene fails entirely due to its increased basicity, which causes destructive polymerization of the aldehyde by a competing aldol pathway. Methyl propiolate serves as a very effective acetylene equivalent as saponification and decarboxylation were easily accomplished,[32] yielding **44** after mesylation. Propargylation of **45** with **44** under the conditions of Marshall[33] afforded a 3.7:1 mixture of separable propargyl epimers (C_{17}) in a combined 90% yield. The stereochemistry of **46a** is assigned by Marshall's model in which propargyl mesylate **44** undergoes oxidative addition with palladium(0) with inversion, followed by transmetalation to diethyl zinc with retention. The resulting allenylzinc undergoes nucleophilic addition to aldehyde **45** via coordination of the aldehyde to zinc. Thus, stereochemistry at C_{16} is completely controlled, whereas C_{17} is formed as a mixture favoring **46a** through a Zimmerman−Traxler transition state in which the aldehyde group occupies a pseudoequatorial position. Both epimers were independently carried forward to the complete spiroketal fragment, as the C_{17} stereochemistry is ultimately irrelevant and will be removed by oxidation later in the synthesis. After some experimentation, it proved best to incorporate the sensitive vinyl iodide last, giving the completed spiroketal fragment (**47**) in 16 linear steps from methyl 3-oxopentanoate.

Spiroketal product **41** was examined extensively by various NMR experiments (*g*COSY, *g*HSQC, *g*HMBC, ROESY, Figure 3). The expected NOE correlations (H_{19} to H_{27} and H_{19} to H_{21}) and coupling constants ($J_{C26-C27}$ = 2.5 Hz [equatorial−axial], $J_{C21-C22}$ = 4.5 Hz [axial−equatorial] 12.0 Hz [axial−axial], $J_{C19-C20}$ = 2.5 Hz [axial−equatorial]) were observed within the bicyclic framework of spiroketal **41** consistent with the indicated structure. The strong resemblance of these data to the NMR spectrum of authentic ushikulide A (Figure 2) was taken to be a very positive sign and improved the likelihood that our synthetic spiroketal had the same relative stereochemistry as the natural product.

Synthesis of the Aliphatic Fragment. A first generation approach toward an aliphatic fragment to fulfill the role of synthon **4** began from the known dibromide **48** (available in three steps from the (*S*)-Roche ester, Scheme 9).[20,34] Exposing

(27) This electronic bias has been observed in the mechanistically related Wacker oxidation of terminal alkenes with allylic alkoxy substituents: (a) Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678.

(28) Evidence for syn oxymetalation in gold-catalyzed hydration: (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415. And in a related palladium-catalyzed Wacker-type cyclization: (b) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036.

(29) Crimmins, M. T.; McDougall, P. J.; Ellis, J. M. *Org. Lett.* **2006**, *8*, 4079.

(30) The method of Carreira is the most general, however, its catalytic implementation, particularly for α-mono-substituted or acidic aldehydes is somewhat unreliable: (a) Anand, N. K.; Carreria, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. At the time of our communication, **43** was the first report of enantioselective methyl propiolate addition to an α-mono-substituted aldehyde in >90% ee. Since then additional examples have been disclosed: (b) Tulington, M.; DeBerardinis, A. M.; Pu, L. *Org. Lett.* **2009**, *11*, 2441.

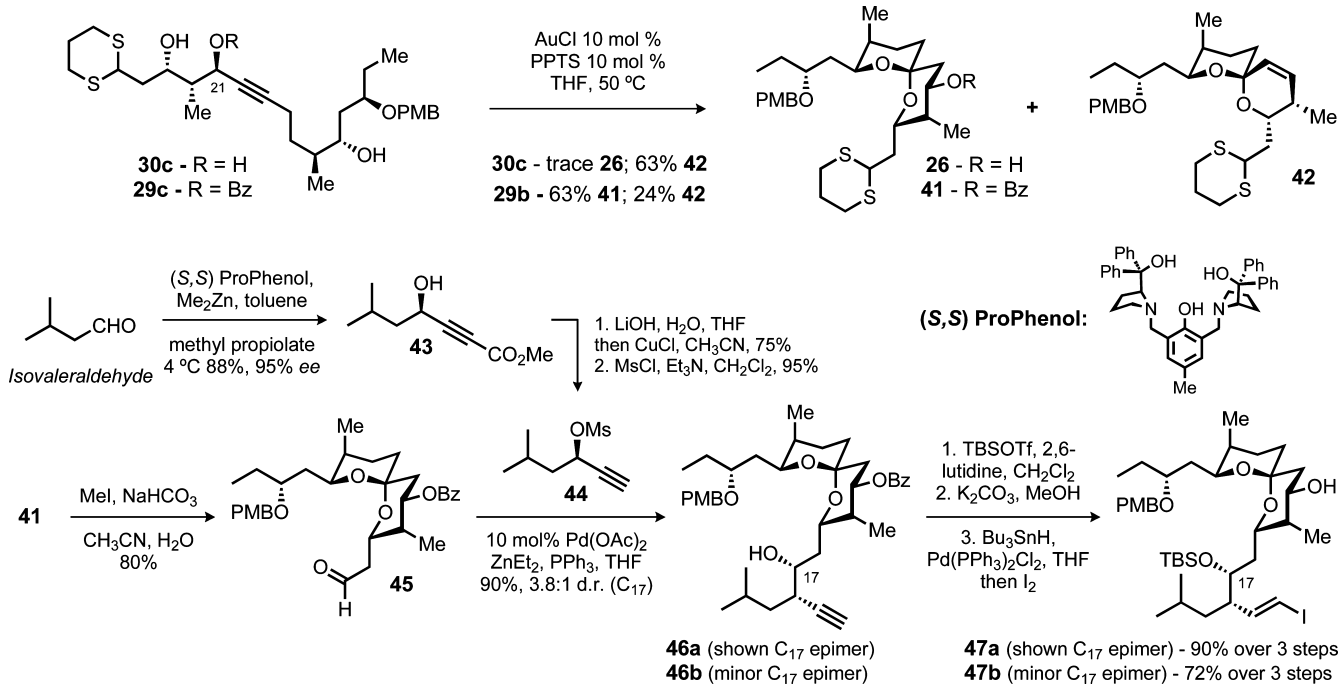
(31) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8.

(32) Trost, B. M.; Weiss, A. H. *Org. Lett.* **2006**, *8*, 4461.

(33) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825.

(34) Mulzer, J.; Berger, M. *J. Org. Chem.* **2004**, *69*, 891.

Scheme 8. Completion of the Spiroketal Fragment



dibromide **48** to *n*-BuLi led to the expected Fritsch−Buttenberg−Wiechell rearrangement,[35] and the resulting lithium acetylide was quenched with *N*-methoxy-*N*-methylacetamide to yield ynone **49** in 76% yield. This ketone gave good reactivity in the direct zinc aldol reaction[13] with aldehyde **50**[13d] to yield aldol adduct **51** as a single diastereomer by ^{1}H NMR analysis. Unfortunately, hydrosilylation[36] of this product under the standard conditions (Cp*Ru(CH$_3$CN)$_3$PF$_6$, BDMSH, acetone) caused deprotection of the diethoxyketal. Changing the solvent to dichloromethane failed to remedy the problem. Therefore, aldehyde **53** was prepared in enantiopure form via an allylation reported by Mukaiyama.[37] This aldehyde also gave good yield and diastereoselectivity in the zinc aldol reaction to afford aldol adduct **54**, again as a single diastereomer. The alkyne moiety of **54** was reduced in a syn fashion via a palladium-catalyzed reduction,[38] yielding enone **55**. Lindlar reduction was also attempted on ynone **54** or the corresponding syn 1,3-diol after reduction of the ketone function. Both substrates gave preferential reduction of the terminal double bond, demonstrating the superior selectivity of homogeneous palladium catalysis in this case. Enone **55** was then reduced to the syn diol and protected as a cyclic acetonide (syn stereochemistry of **56** and **64** was consistent with Rychnovsky's ^{13}C shift analysis).[21] Epoxidation of **56** gave no diastereoselectivity and modest chemoselectivity for the more substituted olefin to yield epoxides **57** and **58** as a separable but unassigned mixture of diastereomers. Before any attempt was made to remedy this diastereoselectivity issue, the epoxide opening had to be demonstrated. Unfortunately, several attempts to accomplish this transformation failed to yield **59**, instead cleaving the *p*-methoxybenzyl group. While this general strategy still might have provided the completed aliphatic fragment,[39] a more direct strategy was already showing promise (*vide infra*).

One potential method to prepare the aliphatic fragment would be to couple a fully saturated aldehyde and ketone through the direct aldol methodology. Utilization of such an unstabilized ketone enolate with nearly 1:1 stoichiometry had not previously been demonstrated in this reaction (acetone and acetophenone are commonly employed as solvent or in excess [5−10 equivalents]). The requisite methyl ketone **61** was prepared easily via Wacker oxidation[40] of the known[41] homoallylic alcohol **60** (Scheme 10). By using a preformed lithium enolate of ketone **61** with aldehyde **53**, the expected aldol product could be generated, but low stereoselectivity was observed as expected

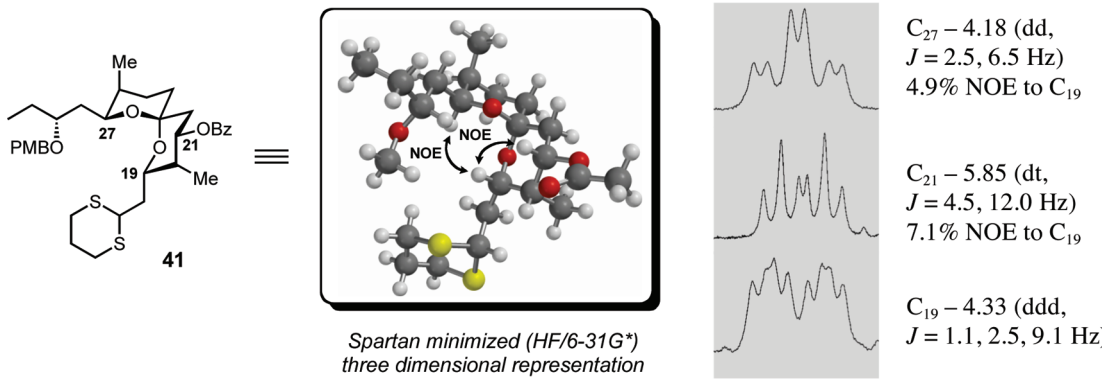
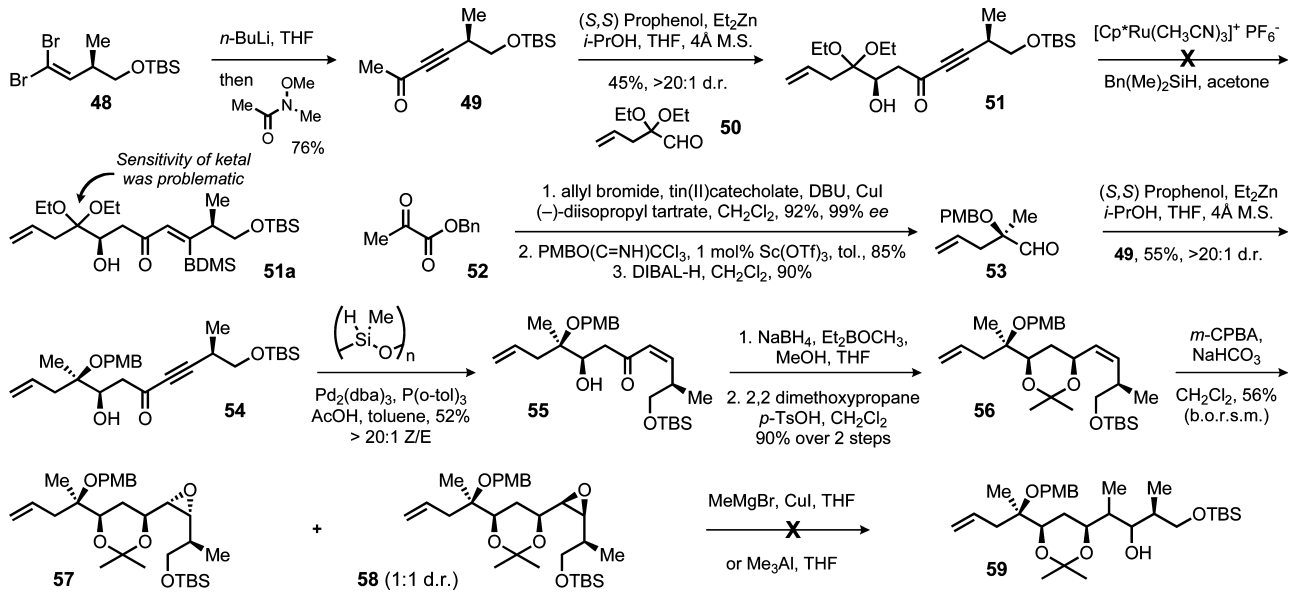
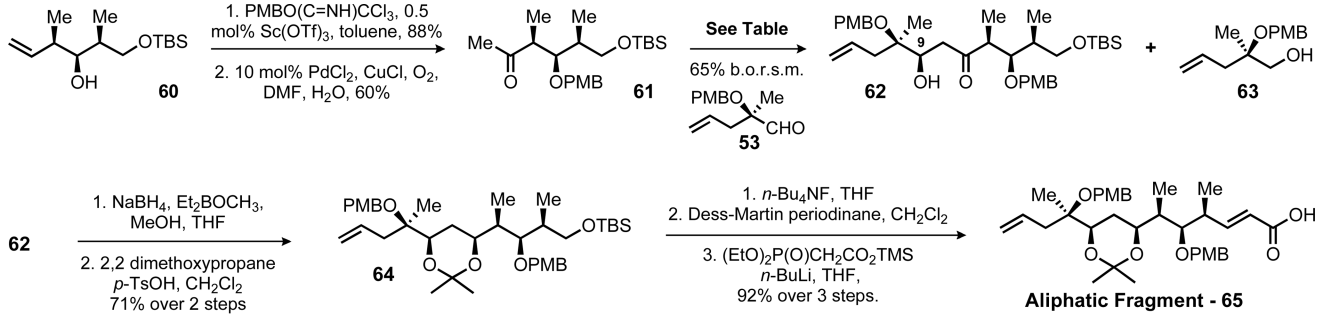


Figure 3. NOE and Coupling Constant Analysis of the Spiroketal.

Scheme 9. First Approach Toward the Aliphatic Fragment



Scheme 10. Second Generation and Completion of the Aliphatic Fragment



Entry	Conditions	Yield (d.r.)*
1	LiN(*i*-Pr)$_2$, THF, then add **53**	60% (~1:1)
2	10 mol% (*S,S*)-ProPhenol, 20 mol% Et$_2$Zn, *i*-PrOH, THF	no pdt; **63** isolated
3	10 mol% (*S,S*)-ProPhenol, 20 mol% Et$_2$Zn, *t*-BuOH, THF	~10% (>20:1)
4	30 mol% (*S,S*)-ProPhenol, 60 mol% Et$_2$Zn, *t*-BuOH, 1,4-dioxane	35% (>20:1)
5	1.1 eq. (*S,S*)-ProPhenol, 2.2 eq. Et$_2$Zn, *t*-BuOH, 1,4-dioxane	not clean
6	Same as Entry 4, three total runs with recovered starting material	65% (>20:1)

* Isolated yields after purification by flash column chromatography. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture prior to purification. Entry 6 is based on recovered starting material (b.o.r.s.m.) after three total reactions.

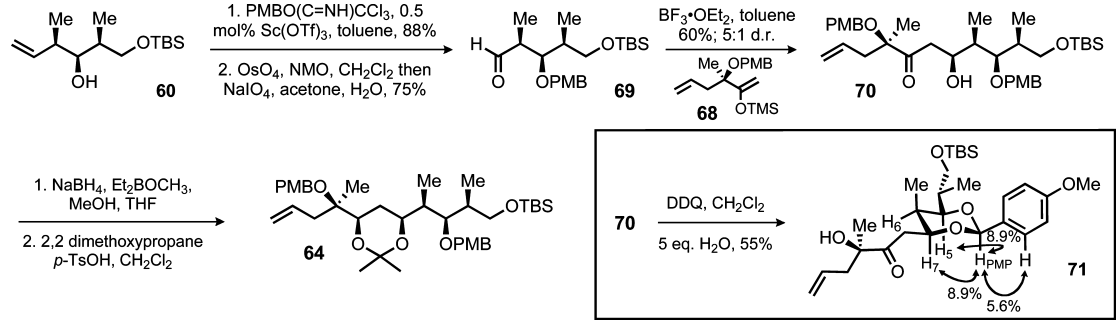
(~1:1 d.r., Entry 1). The standard zinc aldol conditions failed entirely to give the desired product and only the reduced primary alcohol (**63**) and recovered ketone (**61**) were observed (Entry 2). Presumably this reduction must proceed via a Meerwein−Ponndorf−Verley pathway. Employing *t*-BuOH instead of *i*-PrOH resulted in some yield of the desired product (**62**, Entry 3), while switching the solvent to 1,4-dioxane and increasing the catalyst loading gave an improved yield of aldol **62** in excellent stereoselectivity (Entry 4). Stoichiometric ProPhenol and diethylzinc failed to increase this yield and instead led to contamination of the product with various side products (Entry 5). Fortunately, the aldehyde and ketone could be recovered and resubjected to the reaction conditions, leading to an acceptable yield (65%) after three total runs. With ketone **62** in hand syn reduction and acetonide formation gave **64**, which was converted to aliphatic fragment **65** in three additional steps including a Horner−Wadsworth−Emmons olefination.

Further attempts to optimize the aldol reaction were fruitless, and short of modifying the ligand, there seemed little hope for

(35) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769. (b) Orita, A.; Otera, J. *Chem. Rev.* **2006**, *106*, 5387.

(36) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644.
(37) Yamada, K.; Tozawa, T.; Nishida, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2301.
(38) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657.
(39) Torres, W.; Rodriguez, R. R.; Prieto, J. A. *J. Org. Chem.* **2009**, *74*, 2447.

Scheme 11. Alternative Aldol Disconnection in the Synthesis of the Aliphatic Fragment



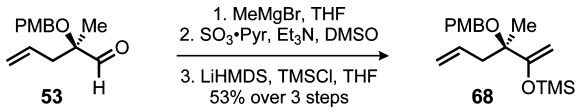
solving the problem of catalyst turnover that required several recycling iterations. To this end, we considered another aldol disconnection, wherein the C_7-C_8 bond instead of the C_8-C_9 would be formed in the aldol reaction. To attempt this, preparation of methyl ketone **67** was required rather than aldehyde **53**. The ideal method to accomplish this would be a stereoselective allylation of 2,3-butanedione (eq 6). This reaction was unknown in the literature, and a number of attempts were made to accomplish it, which are outlined below. Unfortunately, the best enantioselectivity obtained was 45% *ee*, (Entry 5) too low to carry forward with the desired route.

(6)

Entry	M =	Conditions	Yield (*ee*)*
1	(+)-Ipc$_2$B	AllylMgBr, (+)-Ipc$_2$OMe, Et$_2$O	>10% (9%)
2	Br	(+)-DIPT, CuI, DBU, Sn^{II}(catecholate), CH$_2$Cl$_2$	20% (7%)
3	PinB	20 mol% In(OTf)$_3$, 10 mol% (*S,S*)-ProPhenol, THF, 4 °C	60% (0%)
4	PinB	20 mol% Et$_2$Zn, 10 mol% (*S,S*)-ProPhenol, THF, 4 °C	25% (45%)
5	PinB	20 mol% Et$_2$Zn, 10 mol% (*S,S*)-ProPhenol, THF, *i*-PrOH, 4 °C	52% (44%)

* Yield and *ee* were determined by achiral and chiral GC respectively. For achiral GC naphthalene was employed as an internal standard.

Alternatively, aldehyde **53** was transformed to silyl ether **68** in three steps. Addition of methyl magnesium bromide gave a mixture of secondary alcohols, which were oxidized without further purification. Finally, formation of the lithium enolate and silylation afforded the desired silyl enol ether.



(7)

Aldehyde partner **69** was prepared via oxidative cleavage of **60**. Moderate yield and diastereoselectivity were obtained in the Mukaiyama, aldol reaction[42] using a slight excess of **68** in toluene with boron trifluoride diethyl etherate to yield the Felkin−Anh aldol product (**70**).[43] Reduction of this hydroxy ketone afforded the syn-diol, which was converted to an acetonide (**64**) identical to that prepared in our previous strategy. Alternatively, the PMB group was cyclized to the *p*-methoxyphenyl acetal (**71**). Upon irradiation of the benzylic proton, strong NOE correlations were observed to H_5 and H_7. Coupling constant analysis ($J_{H5-H6} = 2.0$ Hz [axial−equatorial] and $J_{H6-H7} = 2.0$ Hz [axial− equatorial]) was also consistent with the chair form indicated, further supporting that the expected stereochemistry had been observed in both aldol reactions.

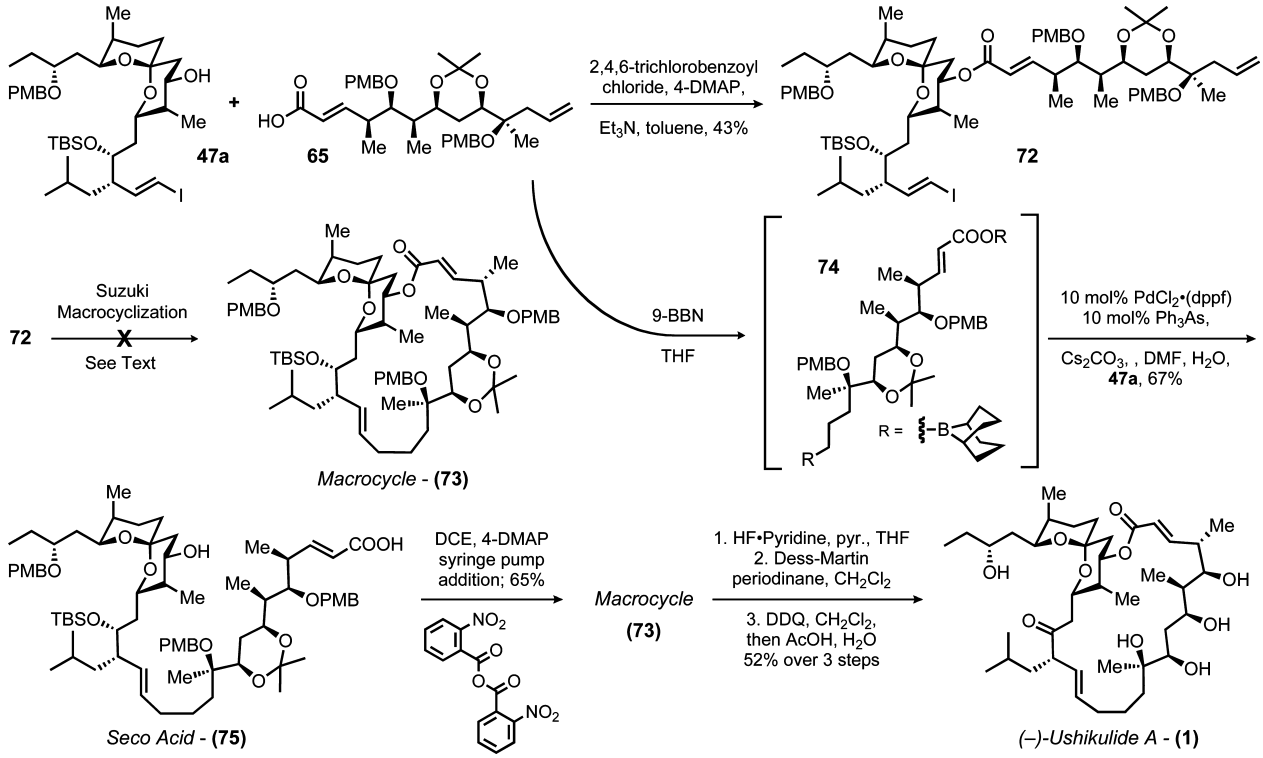
Completion of the Synthesis. Completion of the synthesis rested on two key bond-forming reactions—an sp^3-sp^2 Suzuki coupling[44] and an esterification. While a great many syntheses have relied on macrolactonization,[45] only a few have utilized Suzuki coupling (particularly an sp^3-sp^2 coupling) for the formation of macrocycles.[46] We therefore elected to attempt the Suzuki macrocyclization first to explore its potential in this arena (Scheme 12). Yamaguchi esterification[47] allowed for the direct coupling of **47a** and **65** to yield ester **72**. Hydroboration of **72** (9-BBN, THF) gave the expected preference for reaction of the terminal olefin as observed by ^{1}H NMR analysis. However, under a variety of conditions, which were later shown to be viable in an intermolecular reaction, macrocycle **73** could not be detected or isolated. The borate described above was injected via syringe pump to a solution containing palladium catalyst, base, and solvent (palladium sources: Pd[PPh$_3$]$_4$, PdCl$_2$•(dppf), and Pd$_2$(dba)$_3$•CHCl$_3$; bases: Cs$_2$CO$_3$, TlOEt; solvents: dioxane, THF, DMF, each with cosolvent of water). In many of these attempts the vinyl iodide was clearly consumed, unfortunately a number of products were formed, none of which corresponded to the macrocycle **73**, which was successfully isolated later on.

The alternative pathway (Suzuki coupling then macrolactonization) was attempted. From the unsaturated acid (**65**), hydroboration was feasible with 2.5 equiv of 9-BBN. Immediate gas evolution gave evidence that the carboxylic acid was reacting with 1 equiv of 9-BBN; however, this fast reaction was followed by consumption of the terminal olefin. The crude borate (**74**) was added along with vinyl iodide **47a** to a flask containing PdCl$_2$•(dppf), triphenylarsine, and cesium carbonate.[48] At room temperature, this gave *seco*-acid **75** directly.

Several conditions were applied to the *seco*-acid (**75**) to effect macrolactonization. Yonemitsu's modification of the Yamaguchi esterification protocol[8b] failed to give any product (2,4,6-

(40) Tsuji, J. *Synthesis* **1984**, 369.
(41) (a) Keck, G. C. Abbott, D. E. Boden, E. P. Enhom, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927. For detailed experimental conditions see ref 10.
(42) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095.
(43) Mitchell, I. S.; Pattenden, G.; Stonehouse, J. *Org. Biomol. Chem.* **2005**, *3*, 4412.
(44) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.
(45) Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911.
(46) (a) White, J. D.; Tiller, T.; Ohba, Y.; Porter, W. J.; Jackson, R. W.; Wang, S.; Hanselmann, R. *Chem. Commun.* **1998**, 79. (b) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695. (c) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687. (e) Mohr, P. J.; Halcomb, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 1712. Williams, D. R.; Walsh, M. J.; Miller, N. A. *J. Am. Chem. Soc.* **2009**, *131*, 9038.
(47) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc.* **2006**, *128*, 9194.

Scheme 12. Completion of the Synthesis



trichlorobenzoyl chloride, Et_3N, 4-DMAP, benzene). Applying the Wasserman−Kita esterification to macrolaconization[49] gave the first successful isolation of macrocycle **73** in ∼30% yield, but attempts to improve the yield were unsuccessful (ethoxy acetylene, 2 mol % $[RuCl_2(p\text{-cymene})]_2$, toluene, then 10 mol % CSA). The conditions of Shiina[50] gave the best result (65%) for preparation of macrolactone **73**. Following cyclization, the secondary *tert*-butyldimethylsilyl ether was cleaved employing buffered HF•pyridine and the resulting alcohol was oxidized with Dess−Martin periodinane. The final deprotection required DDQ to oxidatively cleave the *p*-methoxybenzyl ethers and then acid to hydrolyze the cyclic acetonide. It proved to be essential to perform the oxidative deprotection first, as prior deprotection of the acetonide led to undesired cyclization during oxidative removal of the PMB group (PMP acetal or *p*-methoxybenzoate formation). When the PMB groups were removed first, the resulting triol could be cleanly isolated without interference from neighboring groups. In the final acid catalyzed deprotection, the starting acetonide triol quickly interconverted to two other compounds of similar polarity as evidenced by TLC analysis (presumably these were migration of the acetonide to the C_5 or C_{10} oxygens, respectively); however, on prolonged stirring at room temperature (∼4 h), these three compounds converged to a single spot of indistinguishable R_f when compared to an authentic sample of ushikulide A. Upon isolation, this compound exhibited identical ^1H, ^{13}C, IR, HRMS, and HPLC properties when compared to the same authentic sample. Measurement of the optical rotation $\{[\alpha]_D$ (24 °C): −12° (*c* 0.28, MeOH)$\}$ confirmed that the absolute stereochemistry was the same as that of natural ushikulide A $\{[\alpha]_D$ (24 °C): −13° (*c* 0.50, MeOH)$\}$. In total, these data confirmed our tentative assignment and led us to assign the complete structure of (−)-ushikulide A as depicted in Scheme 12.

Summary

We have developed a flexible synthetic route, which establishes the full structure of (−)-ushikulide A for the first time. This route, which requires 21 linear and 40 total steps, provides the natural product in 2.2% yield over the longest linear sequence, a significant accomplishment given the complexity of **1**. The key gold-catalyzed spiroketalization to yield **41** is the first example of a metal-catalyzed spiroketalization in which regioselectivity is controlled by the electronic bias of the alkyne. This implementation extends the methodology to 1,7-dioxaspiro[5.5]undecane ring systems, a motif found in many natural products. Application of our zinc aldol methodology to aldehyde **53** and ketone **61** gave excellent control of diastereoselectivity, although catalyst turnover still needs to be improved. Control of diastereoselectivity in this manner allowed for an otherwise unavailable synthetic disconnection resulting in the preparation of aliphatic fragment **65** in only 11 linear steps. Finally, effective use of Suzuki coupling, Shiina macrolactonization, and the Marshall−Tamaru propargylation all contributed to the overall success of this synthetic endeavor.

This synthesis confirmed the "educated guess" that was made when we began our synthesis; however, it is likely that almost any diastereomer of ushikulide might have been prepared via this general strategy. Furthermore, a large number of unassigned natural products could be targeted by this method. In total, there are at least 12 natural products as close in similarity to ushikulide as cytovaricin,[51] and many other unknown natural products could be approached in such a manner. Each specific case would lead to a slightly different implementation of this method. For example, access to greater amounts of material would allow for degradation studies, whereas a less conformational flexible

(48) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Kapur, M.; Khartulyari, A.; Maier, M. E. *Org. Lett.* **2006**, *8*, 1629.
(49) Trost, B. M.; Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743.
(50) (a) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822. (b) Shiina, I. *Chem. Rev.* **2007**, *107*, 239.

target would allow for more computational analysis than was possible here. The success of this project is a testament to the power of organic synthesis in the structural elucidation of complex natural products. Further studies to apply and improve upon this strategy in the synthesis of other members of the oligomycin-rutamycin family are underway and will be reported in due course.

Experimental Section

(2*S*,3*S*,4*S*,6*R*,8*S*)-2-((1,3-Dithian-2-yl)methyl)-8-((*R*)-2-(4-methoxybenzyloxy)butyl)-3,9-dimethyl-1,7-dioxaspiro[5.5]undecan-4-yl Benzoate (41). A solution of diol **29c** (1.1492 g, 1.82 mmol) in dry THF (0.05M, 36 mL) is degassed (2× freeze/pump/thaw) and allowed to warm under argon. Gold(I) chloride (42.3 mg, 0.18 mmol) and PPTS (45.7 mg, 0.18 mmol) are added, and degassing is repeated for 2 additional cycles. The reaction is then warmed to 50 °C for a period of 22 h. After this time, the solvent is removed under reduced pressure, a drop of triethyl amine is added, and the residue is purified by flash chromatography (9:1 hexane/THF) yielding unsaturated spiroketal **41** (325.6 mg, 28%) followed by the desired spiroketal product **42** (729.6 mg, 63%).

Data for 41. $R_f = 0.23$ (9:1 Hexane/THF); $[\alpha]_D$ (23 °C): −5.2° ($c = 0.71$, $CHCl_3$); IR (neat): 2936, 1719 (sharp) cm^{-1};^{1}H NMR (500 MHz, C_6D_6): δ 8.17−8.16 (m, 2H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.16−7.07 (m, 3H), 6.85 (d, $J = 8.5$ Hz, 2H), 5.83 (dt, 1H, $J = 4.7$, 12.1 Hz), 4.56 (d, $J = 11.4$ Hz, 1H), 4.50 (d, $J = 11.4$ Hz, 1H), 4.34 (ddd, 1H, $J = 3.4$, 3.6, 11.4 Hz), 4.26 (dd, 1H, $J = 5.9$, 8.5 Hz), 4.19 (dt, $J = 2.4$, 6.8 Hz, 1H), 3.71−3.68 (m, 1H), 3.31 (s, 3H), 2.43−2.24 (m, 4H), 2.09 (t, $J = 7.0$ Hz, 1H), 1.92−1.84 (m, 3H), 1.73−1.58 (m, 4H), 1.50−1.20 (m, 8H), 1.14 (t, $J = 7.4$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 165.3, 159.4, 132.8, 132.1, 129.8, 129.1, 113.9, 97.7, 78.3, 71.0, 69.9, 67.4, 54.7, 44.4, 39.3, 37.5, 36.0, 35.8, 30.5, 30.3, 30.2, 29.9, 29.9, 27.4, 26.8, 25.9, 11.4, 9.6, 5.4 ppm; HRMS (ESI+) calcd for $C_{35}H_{48}NaO_6S_2$ $(M + Na)^+$ 651.2790, found 651.3694.

(*R*)-Methyl 4-Hydroxy-6-methylhept-2-ynoate (43). A flask containing *(S,S)* ProPhenol (479.1 mg, 0.75 mmol) dissolved in dry toluene (50 mL) is sequentially treated with methyl propiolate (1.87 mL, 21.0 mmol) followed by dimethyl zinc (1.2 M in hexane, 17.5 mL, 21.0 mmol). After 30 min, isovaleraldehyde is injected (804 μL, 7.5 mmol). The reaction is transferred to the cold room (ca. 4 °C) and stirred for a period of 60 h. Concentrated aqueous ammonium chloride (50 mL) and diethyl ether (50 mL) are added, and the reaction is transferred to a separatory funnel. The organic phase is dried over magnesium sulfate, filtered, and concentrated under reduced pressure (ca. 100 Torr). The resulting solution is purified by flash chromatography (4:1 PE/Et_2O) and concentrated under reduced pressure (∼100 Torr) to yield propargyl alcohol **44a** as a clear oil (1.1193 g, 88%).

Data for 43.[52] Enantiomeric excess is determined to be 95% on Chiracel OD column; 98:2 heptane/isopropanol; Flow rate = 0.8 mL/min; Detector set to 220 nm; R_t(major S): 21.6 min, R_t(minor R): 23.67 min; $R_f = 0.30$ (2:1 Hexanes/Et_2O); $[\alpha]_D$ (23 °C): 13.8° ($c = 0.93$, $CHCl_3$); IR (neat): 3419, 2959, 2237, 1719, 1436, 1254, 1070 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$): δ 4.52 (t, 1H, $J = 7.0$ Hz), 3.77 (s, 3H), 2.70 (s, broad, 1H), 1.89−1.81 (m, 1H), 1.70 (ddd, $J = 7.0$, 7.5, 13.5 Hz, 1H), 1.60 (ddd, $J = 7.0$, 7.0, 14.0 Hz, 1H), 0.94 (d, $J = 7.0$ Hz, 3H), 0.94 (d, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 88.8, 75.9, 60.5, 52.8, 45.6, 24.4, 22.4, 22.1 ppm.

(2*S*,3*S*,4*R*,6*R*,8*S*)-2-((2*R*,3*S*)-3-Ethynyl-2-hydroxy-5-methylhexyl)-8-((*R*)-2-(4-methoxybenzyloxy)butyl)-3,9-dimethyl-1,7-dioxaspiro-[5.5]undecan-4-yl Benzoate (46). Aldehyde **45** (132.9 mg, 0.25 mmol) and propargyl mesylate **44** (71.5 mg, 0.38 mmol) are dissolved in dry THF (1.7 mL) and cooled to −78 °C. A solution of palladium acetate (5.6 mg, 25.1 μmol) and triphenylphosphine (6.6 mg, 25.1 μmol) in THF (1 mL) is transferred into the reaction flask via syringe, followed by a solution of diethyl zinc in hexanes (0.75 mL, 1M, 0.75 mmol). The reaction is allowed to warm to −20 °C for a period of 14 h, after which time it is poured into a saturated solution of ammonium chloride. The organic phase is diluted with ethyl acetate, separated and dried over sodium sulfate. Following filtration and concentration, the crude residue is purified by flash chromatography (19:1 toluene/EtOAc) yielding the major diastereomer **46a** (113.2 mg, 71%) followed by its C-17 epimer **46b** (30.0 mg, 19%).

Data for 46a. $R_f = 0.20$ (19:1 Toluene/EtOAc); $[\alpha]_D$ (23 °C): −69° ($c = 0.93$, $CHCl_3$); IR (neat): 3505 (broad), 3305, 2955, 1718 (sharp), 1514 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, $J = 7.2$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.29 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.54 (td, $J = 12.0$, 4.8 Hz, 1H), 4.50 (d, $J = 11.4$ Hz, 1H), 4.45 (d, $J = 11.2$ Hz, 1H), 4.17 (m, 1H), 4.02−3.95 (m, 1H), 3.87 (s, 1H), 3.78 (s, 3H), 3.73 (dd, $J = 9.7$, 3.0 Hz, 1H), 3.64 (dt, $J = 10.0$, 5.4 Hz, 1H), 2.34−2.22 (m, 1H), 2.17−2.10 (m, 1H), 2.04 (d, $J = 2.3$ Hz, 1H), 1.99−1.90 (m, 3H), 1.84−1.73 (m, 2H), 1.73−1.41 (m, 9H), 1.38 (dd, $J = 14.36$, 1.78 Hz, 1H), 1.17−1.05 (m, 1H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 7.3$ Hz, 3H), 0.95−0.90 (m, 6H), 0.84 (d, $J = 6.6$ Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7, 158.8, 132.9, 131.3, 130.5, 129.5, 128.7, 128.4, 113.7, 98.2, 84.6, 76.9, 73.0, 71.6, 70.8, 70.6, 69.3, 68.2, 55.2, 39.0, 37.0, 36.6, 36.2, 35.7, 30.1, 29.1, 26.6, 26.2, 25.8, 23.6, 21.1, 11.2, 9.2, 5.6 ppm; HRMS (ESI+) calcd for $C_{39}H_{54}O_7Na$ $(M + Na)^+$ 657.3766 found 657.3767.

(2*S*,3*R*,4*S*,7*R*,8*R*)-1-(Tert-butyldimethylsilyloxy)-7-hydroxy-3,8-bis(4-methoxybenzyloxy)-2,4,8-trimethylundec-10-en-5-one (62). A solution of *(S,S)* ProPhenol (590.2 mg, 0.92 mmol) in dioxane (8 mL) is treated with diethyl zinc (1 M in hexanes, 1.84 mL) at ambient temperature. A separate flask is charged with ketone **61** (913.6 mg, 2.31 mmol), aldehyde **53** (759.5 mg, 3.24 mmol) and activated 4 Å powdered molecular sieves (500 mg). After 30 min, the catalyst solution is transferred into the reaction flask at ambient temperature. The reaction is stirred for 45 h and quenched with 0.1 N HCl (50 mL) and diluted with ethyl acetate (100 mL). The solution is filtered and the organic phase is washed with an addition portion of 0.1 N HCl followed by sodium bicarbonate (25 mL portions). The organic phase is dried over sodium sulfate, filtered and concentrated. Flash chromatography (85:15 Hexane/EtOAc) gives aldol adduct **62** (518.5 mg, 35%) as a single diastereomer along with a 1.4:1 mixture of the aldehyde and ketone (1.026 g, 60%). Repetition of the procedure above 2 additional times (identical relative stoichiometry) with recovered starting material gives a total of 65% yield based on recovered starting material.

Data for 62. $R_f = 0.33$ (4:1 Hexane/EtOAc); $[\alpha]_D$ (23 °C): +28° ($c = 0.28$, CH_2Cl_2); IR (neat): 3525 (broad), 2931, 1703 (sharp), 1514 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, $J = 9.3$ Hz, 4H), 6.84 (d, $J = 8.7$ Hz, 4H), 5.94−5.82 (m, 1H), 5.20−5.05 (m, 2H), 4.43−4.39 (m, 4H), 4.19−4.06 (m, 1H), 3.88−3.71 (m, 7H), 3.54−3.40 (m, 2H), 3.04−2.82 (m, 2H), 2.63−2.48 (m, 2H), 2.45−2.32 (m, 1H), 1.73−1.69 (m, 1H), 1.21 (s, 3H), 1.14 (d, $J = 6.7$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H), 0.90 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.9, 159.1,

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133.7, 131.2, 130.8, 129.3, 128.8, 117.9, 113.8, 113.7, 79.7, 78.5, 73.9, 71.7, 65.5, 63.8, 55.3, 50.0, 43.5, 39.0, 38.8, 29.7, 25.9, 19.6, 18.2, 12.6, 11.5, −5.4, −5.5; HRMS (ESI+) calcd for $C_{36}H_{56}O_7NaSi$ $(M + Na)^+$ 651.3693 found 651.3694.

Seco Acid (75). Carboxylic acid **65** (64.8 mg, 0.109 mmol) and 9-BBN (33.1 mg, 0.271 mmol) are dissolved in THF (1 mL) and stirred under a nitrogen atmosphere for a period of 14 h. The solvent is removed under reduced pressure and water is injected (60 μL). In a separate flask vinyl iodide **47** (109.5 mg, 0.141 mmol) is dissolved in DMF (2 mL) and the solvent is degassed (2× freeze/pump/thaw). $PdCl_2$(dppf) (7.9 mg, 10.9 μmol), cesium carbonate (106.5 mg, 0.327 mmol) and triphenyl arsine (3.3 mg, 11.0 μmol) are added to the flask containing **74**. The DMF solution of **47** is transferred into the reaction flask and the reaction is stirred at ambient temperature under argon for 21 h. The reaction is then cooled in an ice bath, and 30% aqueous peroxide (2 mL) is injected dropwise. After warming to ambient temperature for 30 min, the reaction is poured into sodium thiosulfate (5 mL) acidified with 1 M sodium bisulfate (pH = 2, ∼15 mL) and further diluted with water (30 mL). The aqueous solution is washed with ethyl acetate (3 × 25 mL), and the combined organic extracts are dried over sodium sulfate, filtered, and concentrated. Flash chromatography (gradient 10 to 20 to 35% chloroform/EtOAc with 1% methanol) gives *seco*-acid **75** as a white foam (89.1 mg, 67%).

Data for 75. R_f = 0.35 (2:1 chloroform/EtOAc with 1% methanol); $[\alpha]_D$ (23 °C): −16° (c = 0.26, benzene); IR (neat): 3419 (broad), 2956, 1697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37−7.18 (m, 6H), 7.10 (dd, J = 15.7, 7.9 Hz, 1H), 6.91−6.85 (m, 6H), 5.83 (d, J = 15.8 Hz, 1H), 5.40 (dd, J = 14.3, 7.5 Hz, 1H), 5.19 (dd, J = 15.2, 8.9 Hz, 1H), 4.63−4.34 (m, 7H), 4.25−4.13 (m, 1H), 3.88−3.76 (m, 12H), 3.71−3.63 (m, 1H), 3.51−3.38 (m, 2H), 2.82−2.68 (m, 1H), 2.27−2.15 (m, 1H), 2.12−2.00 (m, 2H), 1.95−1.81 (m, 2H), 1.82−1.44 (m, 17H), 1.39 (s, 1H), 1.36 (s, 3H), 1.20−1.30 (m, 2H), 1.14 (s, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.98−0.93 (m, 9H), 0.88 (s, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.81−0.77 (m, 6H), 0.07 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ; 170.2, 159.1, 159.0, 158.7, 154.4, 132.4, 132.0, 131.1, 130.8, 129.2, 128.8, 128.3, 119.9, 113.7, 113.7, 113.7, 98.4, 97.5, 82.5, 77.9, 74.1, 73.7, 73.7, 73.5, 70.7, 69.6, 68.2, 67.3, 64.3, 55.2 (3C), 47.1, 41.1, 40.0, 39.4, 37.4, 36.4, 34.6, 30.3, 30.1, 29.8, 28.3, 27.8, 27.4, 27.0, 26.8, 26.5, 26.0, 25.6, 24.3, 22.6, 20.6, 19.3, 18.1, 17.5, 14.9, 13.6, 10.9, 9.8, 9.3, −4.1, −4.3 ppm; HRMS (ESI+) calcd for $C_{73}H_{114}O_{14}NaSi$ $(M + Na)^+$ 1265.7876 found 1265.7885.

Macrocycle (73). A solution of *seco*-acid **75** (84.3 mg, 68.8 μmol) in dry DCE (5 mL) is transferred to a gastight syringe and injected into a flask containing 2-nitrobenzoic anhydride (freshly recrystallized, 38.6 mg, 0.105 mmol) and 4-DMAP (18.0 mg, 0.126 mmol) in additional DCE (55 mL) over a period of 18 h. After an additional 2 h, the reaction is poured into a separatory funnel containing saturated sodium bicarbonate (30 mL) and ethyl acetate (90 mL). The aqueous phase is separated, and the organic phase is washed with ammonium chloride and sodium bicarbonate (30 mL portions). The organic phase is then dried over sodium sulfate, filtered, and concentrated. Flash chromatography (95:5 toluene/ethyl acetate) gives the macrocycle as a white foam (55.4 mg, 65%).

Data for 73. R_f = 0.54 (9:1 toluene/EtOAc); $[\alpha]_D$ (23 °C): −20° (c = 0.10, chloroform); IR (neat): 2926, 1718, 1514 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29−7.21 (m, 6H), 6.88−6.82 (m, 6H), 6.83 (dd, J = 15.6, 7.9 Hz, 1H), 5.83 (d, J = 15.8 Hz, 1H), 5.54−5.28 (m, 2H), 5.19 (dd, J = 15.2, 9.3 Hz, 1H), 4.58−4.35 (m, 6H), 4.00−3.95 (m, 1H), 3.85−3.83 (m, 1H), 3.82−3.75 (m, 10H), 3.67−3.61 (m, 1H), 3.48−3.34 (m, 2H), 3.18 (d, J = 7.0 Hz, 1H), 2.78−2.61 (m, 1H), 2.12−1.91 (m, 4H), 1.90−1.77 (m, 2H), 1.79−1.42 (m, 19H), 1.39 (s, 3H), 1.36 (s, 3H), 1.28−1.22 (m, 2H), 1.14 (s, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.96−0.90 (m, 6H), 0.88 (s, 9H), 0.85−0.79 (m, 3H), 0.78−0.74 (m, 6H), 0.07 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.5, 159.1, 158.9, 158.7, 150.6, 132.5, 131.2, 130.9, 129.4, 129.2, 128.6, 128.2, 122.2, 113.7, 113.7, 113.6, 98.4, 97.4, 84.4, 78.2, 77.9, 74.2, 73.9, 73.4, 70.7, 69.7 (3C), 67.4, 63.7, 55.2 (3C), 47.1, 42.3, 42.1, 37.5, 36.0, 34.3, 33.7, 33.0, 30.2, 30.1, 29.9, 29.7, 26.9, 26.4, 26.0, 25.5, 24.3, 22.6, 21.3, 20.3, 19.5, 18.1, 17.7, 10.9, 9.1, 7.8, 4.7, −4.2, −4.4 ppm; HRMS (ESI+) calcd for $C_{73}H_{112}O_{13}NaSi$ $(M + Na)^+$ 1247.7770 found 1247.7766.

(−)-Ushikulide A (1). A plastic vial is charged with THF (10 mL), pyridine (5.7 mL), and HF•pyridine (Aldrich, 3.0 mL). To a second plastic vial containing macrocycle **73** (10.6 mg, 8.7 μmol) is added the stock solution prepared above (5 mL). The reaction is stirred under nitrogen for 26 h and diluted with ethyl acetate (100 mL) and diluted with water (25 mL). Finally, the biphasic mixture is neutralized with saturated sodium bicarbonate (∼20 mL). The organic phase is then washed with copper sulfate, water, and brine (30 mL portions). The organic phase is then dried over sodium sulfate, filtered, and concentrated. Flash chromagraphy (9:1 toluene/EtOAc) gives the alcohol as a white foam.

The alcohol prepared above is immediately dissolved in dichloromethane (1 mL) and Dess−Martin reagent is added (15.0 mg). The milky white solution is stirred for 4 h and quenched with sodium thiosulfate (5 mL) and diluted with diethyl ether (40 mL). The organic phase is washed with sodium bicarbonate (2 × 15 mL), dried over sodium sulfate, concentrated, and used directly in the next step without further purification.

The crude ketone is dissolved in dichloromethane (3 mL) and water (0.5 mL). DDQ (10.2 mg) is added at ambient temperature, and the red solution is stirred vigorously for 45 min. Silica gel (300 mg) is added along with additional dichloromethane (10 mL). The solution is concentrated to dryness and the residual solid is loaded onto a short column of silica gel. The product elutes (single fraction collected, 9:1 DCM/EtOAc) separating easily from the red catechol byproduct. After concentration, the crude triol is suspended in a 3:2 mixture of glacial acetic acid and water (3 mL), and the reaction is stirred vigorously under nitrogen for 5 h. The solvent is removed *in vacuo,* and the residue is dissolved three times in toluene and concentrated to dryness (for the first cycle a minimum amount of methanol is added to give a homogeneous solution). The resulting oil is purified by flash chromatography (10:1 chloroform/methanol) yielding **1** as a white powder (3.3 mg, 52% over 3 steps).

Data for Synthetic (−)-Ushikulide A:[53] R_f = 0.30 (9:1 chloroform/methanol); $[\alpha]_D$ (23 °C): −12° (c = 0.28, CH_3OH); IR (neat): 3440 (broad), 1711 (sharp), 1463, 1276, 985 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ 6.76 (dd, J = 15.7, 10.1 Hz, 1H), 5.81 (d, J = 15.7 Hz, 1H), 5.60 (ddd, J = 15.0, 9.4, 4.2 Hz, 1H), 5.44 (dd, J = 15.4, 8.8 Hz, 1H), 5.30 (ddd, J = 11.6, 5.0, 5.0 Hz, 1H), 4.33 (t, broad, J=8.2 Hz, 1H), 4.09 (m, 1H), 4.02 (m, 1H), 3.78 (m, 1H), 3.62 (J = dd, 9.5, 1.5 Hz, 1H), 3.18 (J = dd, 11.0, 2.0 Hz, 1H), 3.07 (ddd, J = 15.1, 9.0, 8.0 Hz, 1H), 2.78 (dd, J = 17.6, 6.6 Hz, 1H), 2.73 (J = dd, 17.4, 8.1 Hz, 1H), 2.46 (m, 1H), 2.23 (m, 1H), 2.19 (m, 1H), 2.15−2.00 (m, 3H), 1.80−1.40 (m, 18H), 1.28 (m, 1H), 1.14 (d, J = 6.6 Hz, 3H), 1.06 (s, 3H), 0.98 (t, J = 7.3 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz): δ 212.5, 166.5, 152.1, 136.6, 129.5, 122.7, 98.8, 81.3, 75.9, 75.4, 74.9, 71.2, 70.5, 69.0, 67.1, 57.8, 42.9, 41.6, 41.9, 41.3, 39.7, 38.4, 36.3, 36.3, 34.6, 34.5, 33.0, 32.0, 30.6, 27.5, 26.6, 24.1, 23.2, 22.7, 22.3, 17.9, 11.4, 10.2, 6.1, 4.2 ppm; HRMS (ESI+) calcd for $C_{40}H_{68}NaO_{10}$ $(M + Na)^+$ 731.4710, found 731.4700.

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(53) The ^1H NMR of synthetic ushikulide A was compared to an authentic sample generously provided by K. Takahashi. The authentic spectrum was obtained on the same instrument (600 MHz) and at the same concentration (∼2 mg/mL) as our synthetic sample. All protons are within 0.01 ppm, and the coupling constants for all peaks also match. The ^{13}C spectra from the literature is in excellent agreement (within 0.1 ppm) with our synthetic sample. See Supporting Information for further details and spectral data. For published data see ref 5.

Evans for providing spectra of cytovaricin. We also acknowledge S. Lynch for his invaluable help in the acquisition of 2-D NMR data. We thank the Stanford Graduate Fellowship Program and NIH (GM 13598) for their financial support of our program, Johnson Matthey for their supply of precious metal salts, and Aldrich for ProPhenol.

Supporting Information Available: Detailed experimental procedures, full characterization of all products, and comparison NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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