Communication

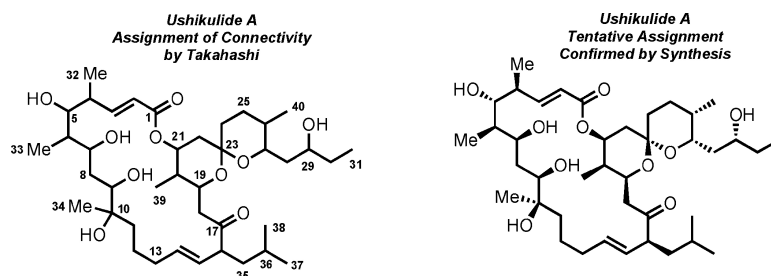# Exploiting Orthogonally Reactive Functionality: Synthesis and Stereochemical Assignment of (#)-Ushikulide A

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Exploiting Orthogonally Reactive Functionality: Synthesis and Stereochemical Assignment of (−)-Ushikulide A

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In 2005, Takahashi and co-workers reported the isolation of ushikulide A (**1**) from a culture broth of *Streptomyces* sp. IUK-102 (Figure 1).[1] This compound exhibits potent activity against murine splenic lymphocyte proliferation ($IC_{50} = 70$ nM), rivaling that of the well-known cyclosporin A[2] and FK506,[3] which revolutionized organ transplant therapy by suppressing rejection. Takahashi's structural assignment dealt with connectivity, not stereochemistry, as analysis of **1** by X-ray diffraction proved untenable in this particular case.[4] Thus the complete structure remains unknown, along with several other members of this family.[5,6] Interestingly, while some family members have potent antibiotic activity (cytovaricin), others exhibit immunosuppressant activity (ushikulide A, dunaimycin D2S). The exact cause of this divergent activity and in some cases the full structure of the bioactive natural product (e.g. dunaimycin D2S, Figure 1) remains unknown. Therefore, development of an effective and versatile synthetic strategy to such compounds would have the dual objective of establishing the full three-dimensional structures of these natural products, while also providing a mechanism to explore the relationship of structure and function. To embark upon an ushikulide A synthesis, we made a tentative assignment based on analogy to cytovaricin,[6] a structurally similar compound whose full structure is well established.
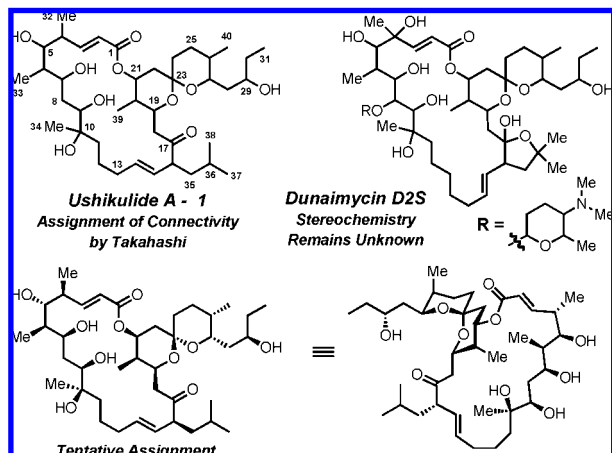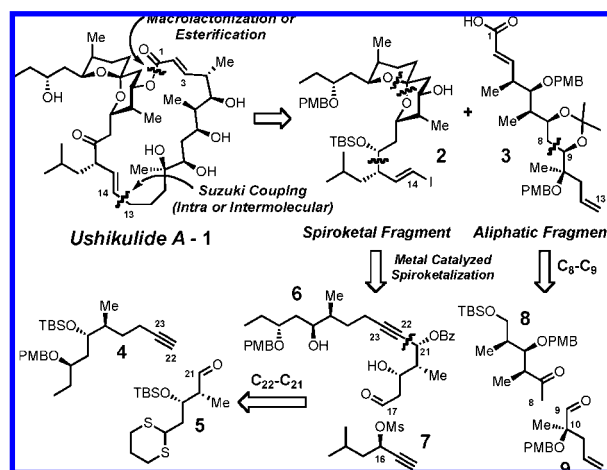
Figure 1. Tentative assignment of ushikulide A.

While sp^2-sp^2 Suzuki coupling and esterification are well-established in several related natural product syntheses,[7,8] we envisioned a less common sp^3-sp^2 Suzuki coupling[9] and esterification to be an attractive alternative to access the C-14, C-15 olefin with geometric control (Scheme 1), thereby simplifying the synthetic problem to preparation of a spiroketal fragment (**2**) and an aliphatic fragment (**3**). By utilizing the reactivity of a carboxyl group in the former step, and then the reactivities of two C—C π-systems, we sequentially utilize more common carbonyl and hydroxyl discon-

nections with less utilized but orthogonally reactive alkene and alkyne chemistry. Furthermore, these operations appear feasible in either order, allowing either the Suzuki coupling or a macrolactonization to close the 22-membered ring.

The desired spiroketal fragment (**2**) is rapidly assembled by utilizing two alkynes, which serve as functional equivalents to groups typically accessed via alcohols or ketones (e.g., the spiroketal and C-14, C-15 olefin, Scheme 1). Specifically, the alkyne **4** serves as a stabilized anion, which undergoes addition to aldehyde **5**. The alkyne contained in **6** then functions as an electrophile in a metal catalyzed spiroketalization reaction. Utilization of the alkyne in this manner achieves efficiency by functioning as a carbonyl surrogate, which chemoselectively unveils the desired spiroketal (**2**). A novel aspect of this strategy is the recognition that the inherent polarization of the alkyne (**6**) would lead to the desired regioselectivity in the spirocyclization. By having an inductively electron-withdrawing benzoyloxy group at C-21, a positive charge at the neighboring acetylenic carbon (C-22) should be destabilized, directing the initial cyclization onto C-23 and leading to the desired spiroketal.[10] A second alkyne building block (**7**) serves as a propargyl nucleophile under conditions developed by Tamaru[11] and extended by Marshall,[12] thus completing the spiroketal fragment (**2**).

Scheme 1. Retrosynthesis of Ushikulide A

We envision that the aliphatic fragment (**3**) could be accessed in a convergent manner via disconnection of the C-8, C-9 bond, furnishing an aldol donor (**8**) and an acceptor (**9**). Given the similar size of the methyl and allyl groups at C-10, such a process is not expected to give acceptable diastereoselectivity. However, recent advances in our zinc aldol methodology[13] cause us to envision that such a reaction could be made diastereoselective through catalyst control.

Preparation of the spiroketal (**2**) begins with the known reduction of methyl 3-oxopentanoate,[14] followed by protection of the second-

ary alcohol as a *p*-methoxybenzyl ether and monoreduction with DIBAL-H to yield aldehyde **10** in good yield and excellent optical activity (Scheme 2). A brief survey of crotylations led us to the method of Brown,[15] which after TBS protection provides the alkene **11** as a pure diastereomer (d.r. > 20:1). Hydroboration/iodination is followed by nucleophilic substitution yielding the desired alkyne **4** in seven linear steps.

Scheme 2. Toward the Synthesis of the Spiroketal Fragment[a]
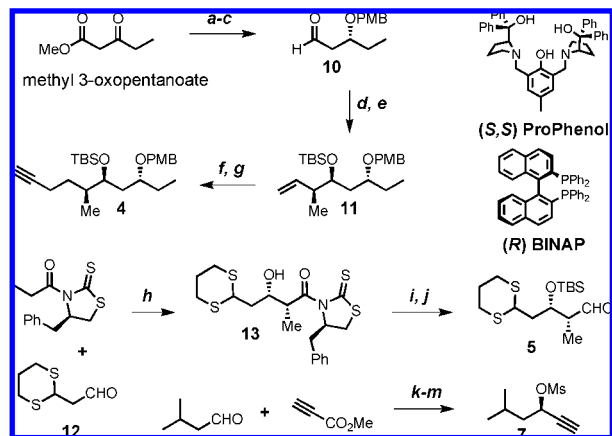
[a] Conditions: (a) 0.1 mol% (*R*)-BINAP, 0.05 mol% [RuCl₂(C₆H₆)]₂, MeOH, H₂ 1800 psi, 92%, 99% *ee*; (b) PMBO(C=NH)CCl₃, 1 mol% Cu(OTf)₂, toluene, 85%; (c) DIBAL-H, CH₂Cl₂, 82%; (d) (i) *cis*-2-butene, *n*-BuLi, KO*t*-Bu, THF, (ii) (+) Ipc₂BOMe, (iii) BF₃·OEt₂ then **10**, >20:1 d.r.; (e) TBSCl, imid., DMF, 87% over 2 steps; (f) 9-BBN, THF then I₂, NaOCH₃, MeOH, 85%; (g) THF, DMPU, LiCCTMS, then KOH, MeOH, 81%; (h) TiCl₄, EtN(*i*-Pr)₂, NMP, CH₂Cl₂, single diastereomer, 90%; (i) TBSOTf, 2,6-lutidine, CH₂Cl₂, 96%; (j) DIBAL-H, CH₂Cl₂, 87%; (k) 10 mol% (*S*,*S*) ProPhenol, Me₂Zn, toluene, 88%, 95% *ee*; (l) LiOH, THF, H₂O then CuCl, CH₃CN, 75%; (m) MsCl, Et₃N, CH₂Cl₂, 95%.

The known aldehyde **12**[16] participates in an aldol reaction under the conditions of Crimmins[17] yielding the aldol adduct **13** in excellent yield as a single diastereomer. Protection and DIBAL-H reduction affords the aldehyde **5**.

For synthesis of propargyl mesylate **7**, we turned to our ProPhenol zinc alkynylation methodology,[18] which affords the adduct of isovaleraldehyde and methyl propiolate in good yield and excellent stereoselectivity (Scheme 2). Following saponification of the methyl ester, exposure of the crude acid to cuprous chloride induces decarboxylation,[19] leaving only mesylation of the secondary propargyl alcohol to complete the propargyl mesylate (**7**).

Union of aldehyde **5** and alkyne **4** (Scheme 3) by metalation of alkyne (*n*-BuLi, −78 °C), followed by addition of the aldehyde, affords a mixture of diastereomers at C-21 (∼1.5:1 d.r.). Addition of bidentate Lewis acids (Et₂AlCl, MgBr₂·OEt₂, or Ti(O*i*-Pr)₃) to favor the desired *anti* 1,3 diol is unsuccessful due to low conversion and modest stereoselectivity. However, these epimers (not shown) are easily separable on silica gel, and both epimers converge to the desired diol **14**, one via ester formation by Mitsunobu inversion and the other via standard esterification (BzCl, pyridine). Utilization of a Pd^II catalyzed spiroketalization[20−22] results in low conversion in this case. On the other hand, warming a THF solution containing diol **14**, gold(I) chloride, and PPTS[23,24] proceeds smoothly to yield spiroketal **15**. Hydrolysis of the 1,3 dithiane in the presence of methyl iodide yields the aldehyde **16**, which is successfully propargylated under the conditions of Marshall[12] furnishing a 3.8:1 distribution of separable C-17 epimers. As this center will be oxidized, both epimers are of equal value in our synthesis; however for practical reasons, we continue forward with the major compound **17**. Three additional steps produce the

desired spiroketal fragment (**2**) in a total of 16 linear steps from methyl 3-oxopentanoate.

Scheme 3. Completion of the Spiroketal Fragment[a]
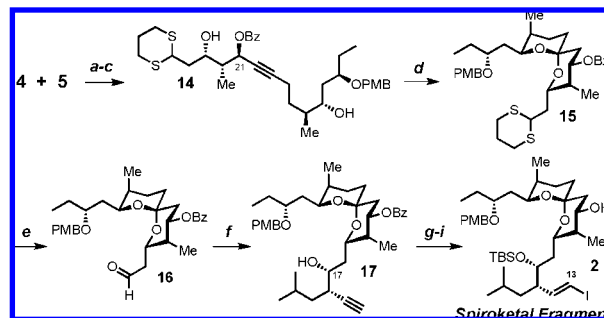
[a] Conditions: (a) *n*-BuLi, THF, 90%, 1.5:1 *syn/anti*; (b) for *syn*: DEAD, PhCOOH, PPh₃, toluene, 92%, for *anti*: BzCl, pyridine, 95%; (c) HCl, H₂O, THF; (d) 10 mol % AuCl, PPTS, THF, 63%; (e) MeI, NaHCO₃, CH₃CN, H₂O, 80%; (f) 10 mol% Pd(OAc)₂, ZnEt₂, PPh₃, THF, **7**, 90%, 3.8:1 d.r.; (g) TBSOTf, 2,6-lutidine, CH₂Cl₂ (h) K₂CO₃, MeOH (i) Bu₃SnH, 5 mol% PdCl₂(PPh₃)₂, THF, then I₂, 90% over 3 steps.

Our approach toward the aliphatic fragment (**3**) begins with the known homoallyl alcohol **18** (Scheme 4).[25] Wacker oxidation[10] unveils the desired ketone **19**. Preparation of the aldehyde partner **9** utilizes a tartrate modified Sn^II mediated addition of allyl bromide to benzyl pyruvate, as described by Mukaiyama,[26] to give tertiary alcohol **20** in excellent chemical yield and optical purity. Protection and DIBAL-H reduction affords the aldehyde **9**.

**Scheme 4.** Synthesis of the Aliphatic Fragment[a]
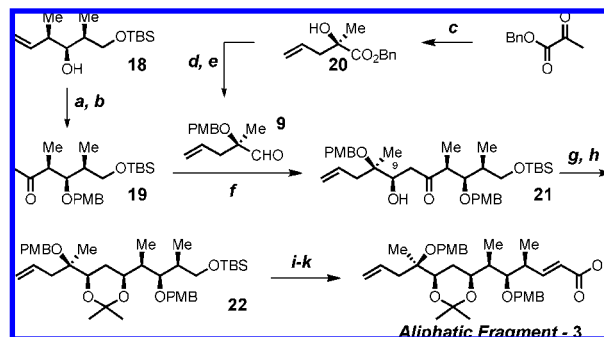
[a] Conditions: (a) PMBO(C=NH)CCl₃, 0.5 mol% Sc(OTf)₃, toluene, 88%; (b) 10 mol% PdCl₂, CuCl, O₂, DMF, H₂O, 60%; (c) allyl bromide, tin(II) catecholate, DBU, CuI, (−)-diisopropyl tartrate, CH₂Cl₂, 92%, 99% *ee*; (d) PMBO(C=NH)CCl₃, 1 mol% Sc(OTf)₃, toluene, 85%; (e) DIBAL-H, CH₂Cl₂, 90%; (f) 60 mol% Et₂Zn, *t*-BuOH, dioxane, 30 mol% (*S*,*S*) ProPhenol, 65% b.r.s.m.; (g) NaBH₄, MeOBEt₂, MeOH, THF; (h) *p*-TsOH, CH₂Cl₂, 2,2-dimethoxypropane, 71% over 2 steps; (i) *n*-Bu₄NF, THF; (j) Dess−Martin reagent, CH₂Cl₂; (k) *n*-BuLi, (EtO)₂P(O)CH₂CO₂TMS, THF, 92% over 3 steps.

Enolate formation (**19**, LiN(*i*-Pr)₂, −78 °C) prior to addition of aldehyde **9** reveals the expected low stereoselectivity (∼1:1 d.r.) for the direct aldol reaction. Addition of chelating Lewis acids (e.g., ZnCl₂) failed to increase this selectivity. Worse, separation of the resulting C-9 aldol epimers is prohibitively difficult on a preparative scale. An attempted Mukaiyama aldol reaction after formation of the silyl enol ether (**19**, LiN(*i*-Pr)₂, Me₃SiCl, −78 °C) with several bidentate Lewis acids (ZnCl₂, MgBr₂·OEt₂, GaCl₃ TiCl₄, or Ti(O*i*-Pr)₂Cl₂) results in only slow hydrolysis of the silyl enol ether. Therefore, our attention turned to catalyst control as a means to overcome this stereochemical quandary. Gratifyingly, the (*S*,*S*) ProPhenol dinuclear zinc complex promotes the aldol process, wherein the desired diastereomer is formed with >20:1 d.r.[13] A

syn reduction of the aldol **21** is followed by formation of acetonide **22**. The aliphatic fragment (**3**) is completed in three additional steps and a total of 11 linear steps from the (*S*)-Roche ester.

Suzuki coupling[9] unites the spiroketal and aliphatic fragments yielding *seco*-acid **23** directly (Scheme 5). Yonemitsu's modification of the Yamaguchi esterification[7] fails to give any product when applied to *seco*-acid **23**. Applying the Wasserman−Kita esterification to macrolaconization[27] affords the desired macrocycle **24** in ~30% yield. However, the method of Shiina[28] improves this yield to 65%.

Scheme 5. Completion of the Synthesis[a]
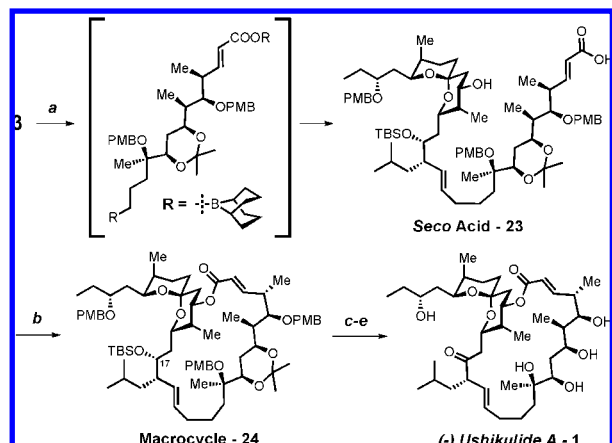
[a] Conditions: (a) **3**, 9-BBN, THF; then **2**, DMF, H₂O, 10 mol% PdCl₂(dppf), 10 mol% Ph₃As, Cs₂CO₃, 67%; (b) 2-methyl-6-nitrobenzoic anhydride, 4-DMAP, DCE, 65%; (c) HF·pyridine, pyridine, THF; (d) Dess−Martin reagent, CH₂Cl₂; (e) DDQ, H₂O, CH₂Cl₂ then dilute with 3:2 AcOH/H₂O, 52% over 3 steps.

Deprotection of the C-17 TBS group of **24** is accomplished under buffered HF·pyridine conditions (Scheme 5). Dess−Martin oxidation unveils the sensitive β,γ unsaturated ketone, which is cleanly deprotected of its three *p*-methoxybenzyl ethers upon exposure to DDQ. The resulting triol (not shown) is dissolved in a 3:2 mixture of acetic acid and water to remove the acetonide. As the reaction progresses, TLC analysis shows the formation of a more polar spot of indistinguishable R_f compared to an authentic sample of ushikulide A. Upon isolation, this compound exhibits identical ¹H, ¹³C, IR, HRMS, and HPLC properties when compared to the same authentic sample. Measurement of the optical rotation {$[\alpha]^{24}_D = -12°$ (*c* 0.28, MeOH)} confirms that the absolute stereochemistry also matches that of natural ushikulide A[1] {$[\alpha]^{25}_D = -13°$ (*c* 0.50, MeOH)}. In total, these data prove our tentative assignment to be correct and lead us to assign the complete structure of (−)-ushikulide A as depicted below.

In summary, we report the first synthesis of (−)-ushikulide A which establishes its relative and absolute stereochemistry. Our route requires 21 linear and 41 total steps (2.2% yield over the linear sequence), which is gratifying given the complexity of our target (40 carbon atoms and 14 stereogenic centers). The efficiency of this strategy is in no small measure due to the utilization of alkenes and alkynes as orthogonally reactive surrogates for hydroxyl and carbonyl functionalities. Further novel features of this synthesis include a new and highly regioselective gold catalyzed spiroketalization reaction, utilization of (*S*,*S*) ProPhenol in enantio- and diastereoselective alkynylation and aldol reactions, and establishment of the full structure of ushikulide A via total synthesis. Further efforts to optimize this route and apply it to other members of the family are underway and will be reported in due course.

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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