

Published in final edited form as:

J Am Chem Soc. 2008 December 3; 130(48): 16190–16192. doi:10.1021/ja807127s.

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

Barry M. Trost* and Brendan M. O’Boyle

Department of Chemistry, Stanford University, Stanford, California, 94305-5080

Abstract

In spite of the tremendous advances in modern spectroscopic methods, organic synthesis continues to play a pivotal role in elucidating the full structures of complex natural products. 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. Herein, we report execution of this strategy with respect to ushikulide A, a newly isolated and previously stereochemically-undefined member of the oligomycin-rutamycin family. To maximize synthetic efficiency, we envisioned chemoselective manipulation of orthogonally reactive functional groups, notably alkenes and alkynes as surrogates for certain carbonyl and hydroxyl functionalities. This approach has the dual effect of minimizing the number of steps and protecting groups required for our synthetic route. This strategy culminated in the efficient synthesis and stereochemical assignment of ushikulide A.

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 (IC₅₀ = 70 nM), rivaling that of the well-known cyclosporin A² 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 3-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.

While sp²-sp² Suzuki coupling and esterification are well-established in several related natural product syntheses,^{7,8} we envisioned a less common sp³-sp² Suzuki coupling⁹ and esterification to be an attractive alternative to access the C-14, C-15 olefin with geometric control (Figure 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 disconnections 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.

bmtrost@stanford.edu.

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 Tamaru¹¹ and extended by Marshall,¹² thus completing the spiroketal fragment (**2**).

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 methodology¹³ 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 secondary alcohol as a *p*-methoxybenzyl ether and mono-reduction 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 Brown¹⁵, 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.

The known aldehyde **12**¹⁶ participates in an aldol reaction under the conditions of Crimmins¹⁷ 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(Oi-Pr)Cl₃) to favor the desired *anti* 1,3 diol are 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^{20,21,22} 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 Marshall¹² 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.

Our approach toward the aliphatic fragment (**3**) begins with the known homoallyl alcohol **18** (Scheme 4).²⁵ Wacker oxidation¹⁰ 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**.

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 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 coupling⁹ 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 macrolaconization²⁷ affords the desired macrocycle **24** in ~30% yield. However, the method of Shiina²⁸ improves this yield to 65%.

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 & HPLC properties when compared to the same authentic sample. Measurement of the optical rotation {[α]²⁴_D = -12° (c 0.28, MeOH)} confirms that the absolute stereochemistry also matches that of natural ushikulide A¹ {[α]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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We gratefully acknowledge K. Takahashi for providing an authentic sample of ushikulide A. 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.

References

1. Takahashi K, Yoshihara T, Kurosawa K. *J. Antibiot* 2005;58:420. [PubMed: 16156521]
2. Dreyfuss M, Harri E, Hoffmann H, Kobel H, Pache W, Tscherter H. *Eur. J. Appl. Microbiol* 1976;3:125.
3. Kino T, Hatanaka H, Hashimoto M, Nishiyama M, Goto T, Okuhara M, Kohsaka M, Aoki H, Imanaka H. *J. Antibiot* 1987;40:1249. [PubMed: 2445721]
4. Attempts to prepare crystals of ushikulide A suitable for X-ray diffraction were unsuccessful in this case. Takahashi K. 2008 July 22;personal communication
5. Kirst HA, Mynderse JS, Martin JW, Baker PJ, Paschal JW, Steiner JL, Lobkovsky E, Clardy J. *J. Antibiot* 1996;49:162. [PubMed: 8621357]
6. Evans DA, Kaldor SW, Jones TK, Clardy J, Stout TJ. *J. Am. Chem. Soc* 1990;112:7001.
7. Evans DA, Ng HP, Rieger DL. *J. Am. Chem. Soc* 1993;115:11446.
8. White JD, Hanselmann R, Jackson RW, Porter WJ, Ohba Y, Tiller T, Wang S. *J. Org. Chem* 2001;66:5217. [PubMed: 11463276]
9. Chemler SR, Trauner D, Danishefsky SJ. *Angew. Chem. Int. Ed* 2001;40:4544.
10. Kang SK, Jung KY, Chung JU, Namkoong EY, Kim TH. *J. Org. Chem* 1995;60:4678.
11. Tamaru Y. Activation of allyl alcohols as allyl cations, allyl anions, and amphiphilic allylic species by palladium. *Eur. J. Org. Chem* 2005;13:2647–2656.
12. Marshall JA, Schaaf GM. *J. Org. Chem* 2001;66:7825. [PubMed: 11701042]
13. Trost BM, Silcoff ER, Ito H. *Org. Lett* 2001;3:2497. [PubMed: 11483044]
14. Kitamura M, Tokunaga M, Ohkuma T, Noyori R. *Org. Syn* 1998;71:589.
15. Brown HC, Bhat KS. *J. Am. Chem. Soc* 1986;108:5919.
16. Hatakeyama S, Kawamura M, Shimanuki E, Saijo K, Takano S. *Synlett* 1992;2:114.
17. Crimmins MT, She J. *Synlett* 2004;8:1371.
18. Trost BM, Weiss AH, von Wangelin AJ. *J. Am. Chem. Soc* 2006;128:8. [PubMed: 16390095]
19. Trost BM, Weiss AH. *Org. Lett* 2006;8:4461. [PubMed: 16986925]
20. Utimoto K. *Pure & Appl. Chem* 1983;55:1845.
21. Trost BM, Weiss AH. *Angew. Chem. Int. Ed* 2007;46:7664.
22. Trost BM, Horne DB, Woltering MJ. *Chem. Eur. J* 2006;12:6607.
23. Antoniotti S, Genin E, Michelet V, Genet JP. *J. Am. Chem. Soc* 2005;127:9976. [PubMed: 16011342]
24. Li Y, Zhou F, Forsyth C. *J. Angew. Chem. Int. Ed* 2007;46:279.
25. Keck GE, Abbott DE, Boden EP, Enholm EJ. *Tetrahedron Lett* 1984;25:3927.
26. Yamada K, Tozawa T, Nishida M, Mukaiyama T. *Bull. Chem. Soc. Jpn* 1997;70:2301.
27. Trost BM, Chisholm JD. *Org. Lett* 2002;4:3743. [PubMed: 12375933]
28. Shiina I, Kubota M, Oshiumi H, Hashizume M. *J. Org. Chem* 2004;69:1822. [PubMed: 15058924]

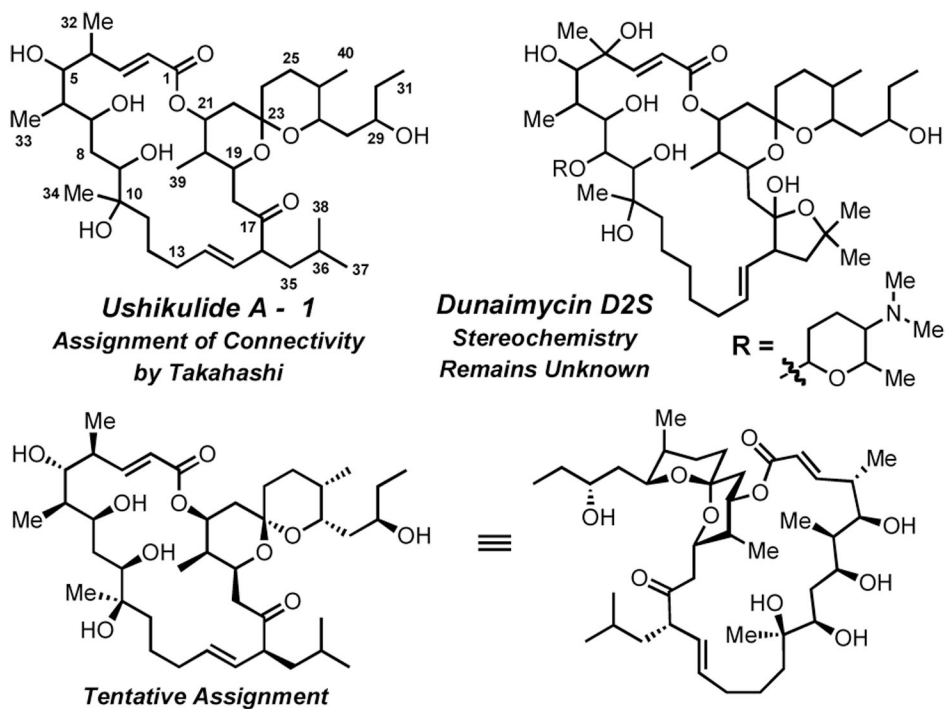
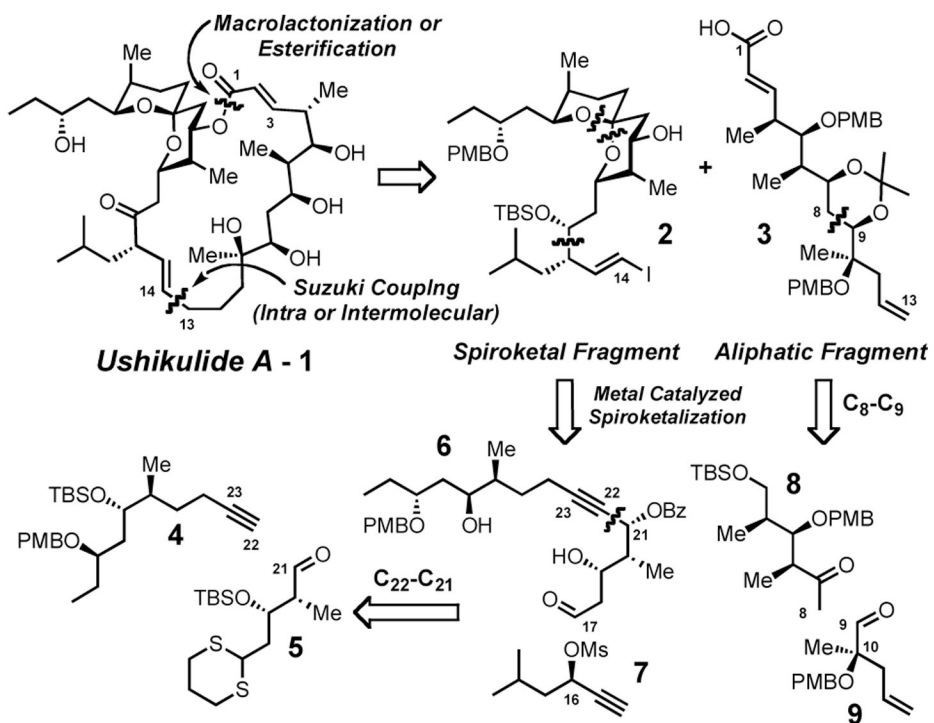
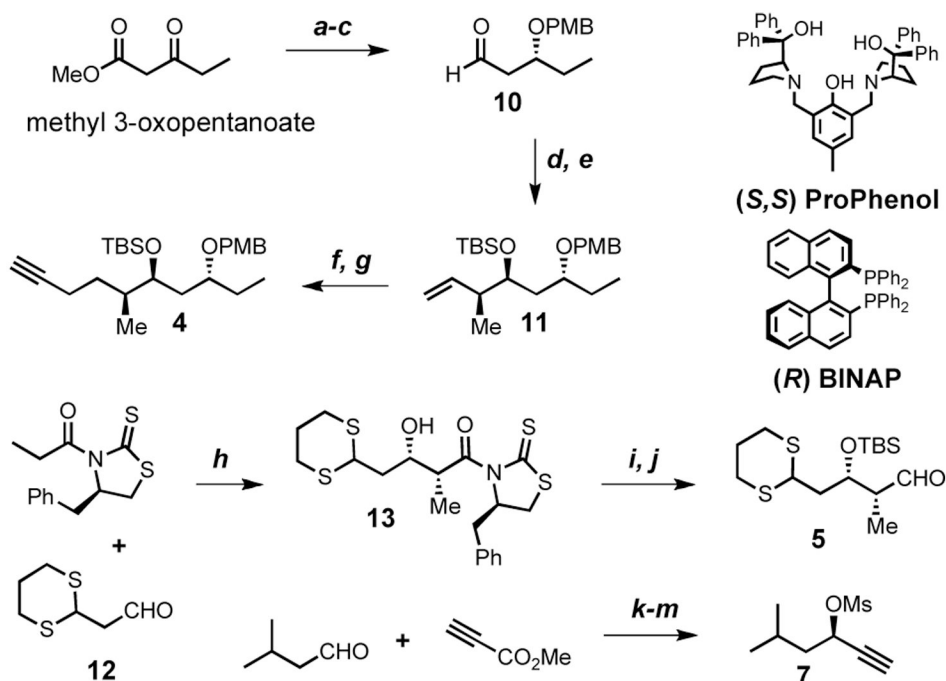


Figure 1. Tentative Assignment of Ushikulide A

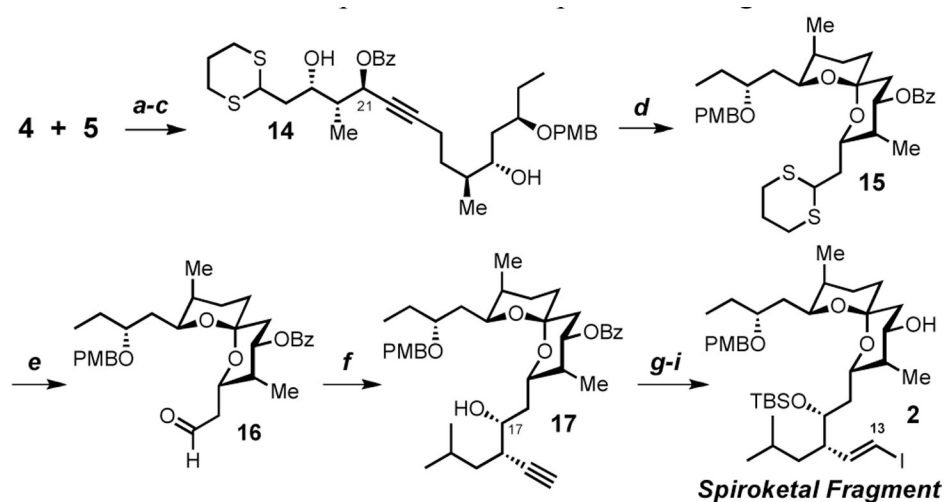


Scheme 1. Retrosynthesis of Ushikulide A



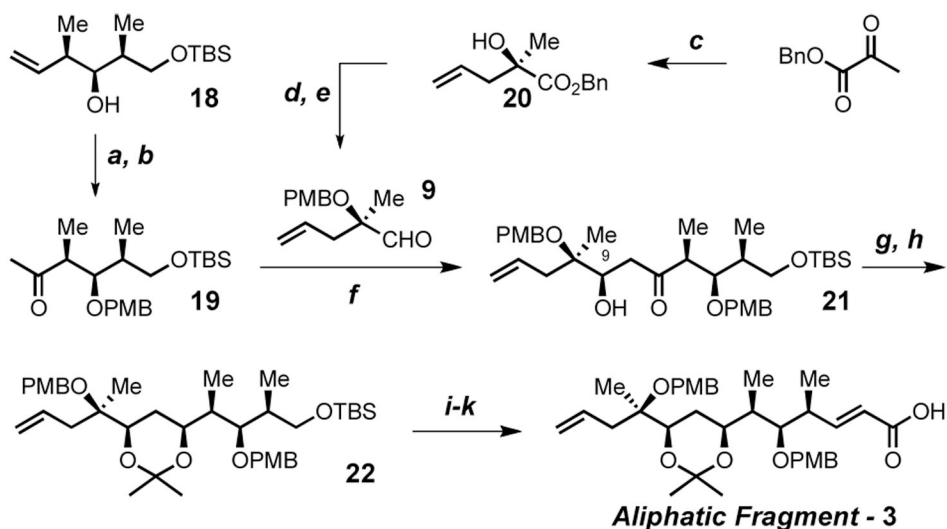
Scheme 2. Toward the Synthesis of the Spiroketal Fragment^a

^aConditions: (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%.



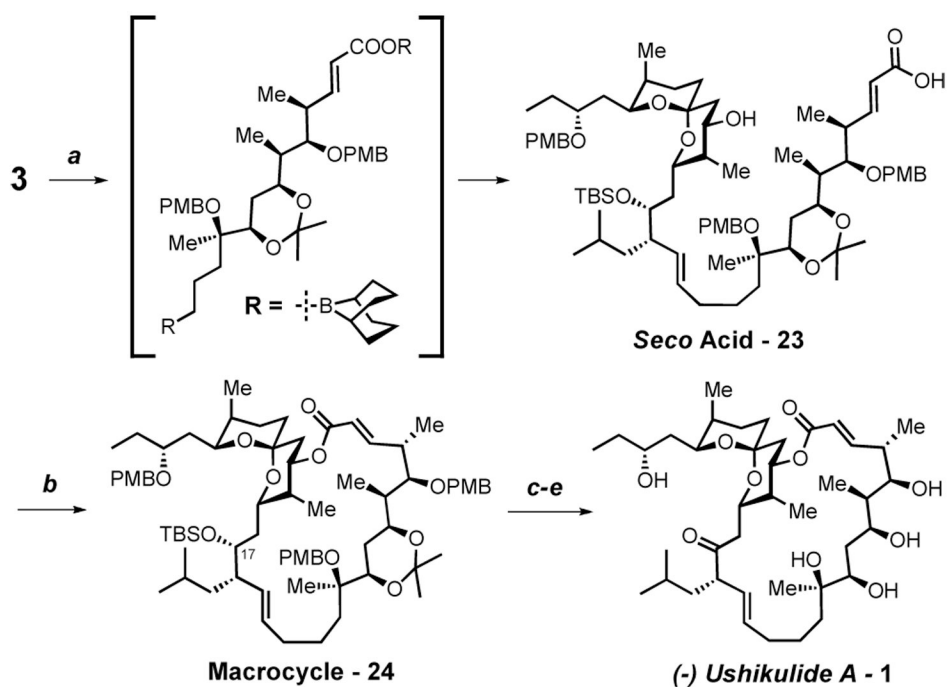
Scheme 3. Completion of the Spiroketal Fragment^a

^aConditions: (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.



Scheme 4. Synthesis of the Aliphatic Fragment^a

^aConditions: (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, MeOEt, 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.

**Scheme 5. Completion of the Synthesis^a**

^aConditions: (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.