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Total Synthesis of Ascospiroketal A Through a Ag^I-Promoted Cyclization Cascade**

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Abstract: *The total synthesis of four candidate stereostructures for the marine octaketide ascospiroketal A have been achieved. These concise and highly stereocontrolled syntheses feature a unique Ag^I-promoted cyclization cascade involving an oxetanyl ketochlorohydrin to access the entire tricyclic core of the natural product in one step. These syntheses also establish the full stereochemistry for the ascospiroketal natural products.*

In 2007, König reported the isolation of ascospiroketals A (**1**) and B (**2**) (Figure 1) as single spiroacetal epimers from the marine-derived fungus *Ascochyta salicorniae.*[1] Following extensive analysis of 1D and 2D NMR spectra, it was proposed that **1** and **2** possess a rare octaketide tricyclic core, in which the terminal ring is cyclized through an ether or ester linkage and includes a quaternary stereogenic center at C2 installed through geminal SAM methylation.[1] The relative stereochemistry within the tricyclic core of the ascospiroketals was established from analysis of NOESY experiments and confirmed that these compounds are anomeric spiroacetals. Unfortunately, no information could be obtained regarding their absolute stereochemistry, the configurational relationship between the tricyclic core and side chain, or within the side chain itself. Thus, the relative stereochemistry of the three remote stereocenters remained undefined. Structurally, these compounds represent the most complex members of a small family of tricyclic 5,5-spiroacetals[2] that includes the cephalosporolides,[3] penisporolides,[4] and opaliferin,[5] for which several potentially useful biological activities have been ascribed.[3–5] Herein we describe the first total synthesis and full stereochemical assignment of ascospiroketal A (**1**)[6] through a highly efficient Ag^I-promoted cyclization cascade that assembles the entire tricyclic core in one step from an acyclic precursor.

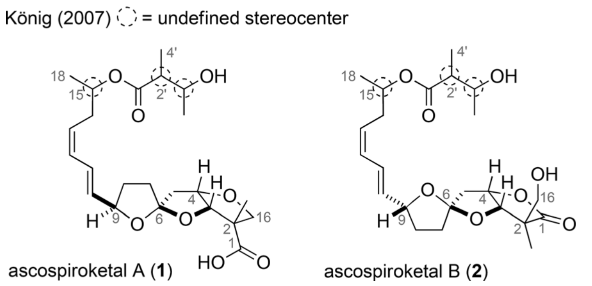
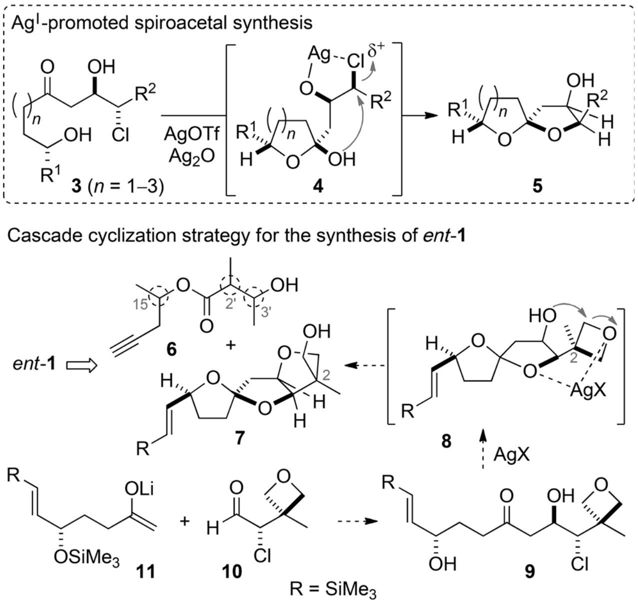


Figure 1. Naturally occurring octaketides ascospiroketals A and B.



Scheme 1. A silver(I)-promoted spirocyclization strategy to access ascospiroketal A.

We have recently reported that aldol adducts of α-chloroaldehydes **3** (Scheme 1) undergo Ag^I-promoted cyclization to afford various spiroacetals **5**,[7] including 5,5-spiroacetals such as those embedded in the tricyclic core of the ascospiroketals. This unique spirocyclization strategy involves intramolecular alkylation of a hemiacetal by a Ag^I-activated chloromethine (e.g., **4**). In contemplating a total synthesis of the ascospiroketals, we envisaged that ultimately the side chain **6** (Scheme 1) would be appended to the fully functionalized core **7** through a Sonogashira coupling.[8] Importantly, this late-stage coupling would allow for the rapid production of configurational isomers at the undefined stereocenters C15, C2′, and C3′. In turn, a Ag^I-promoted spirocyclization of the ketochlorohydrin **9** would provide the spiroacetal **8** and the terminal ring would be accessed through

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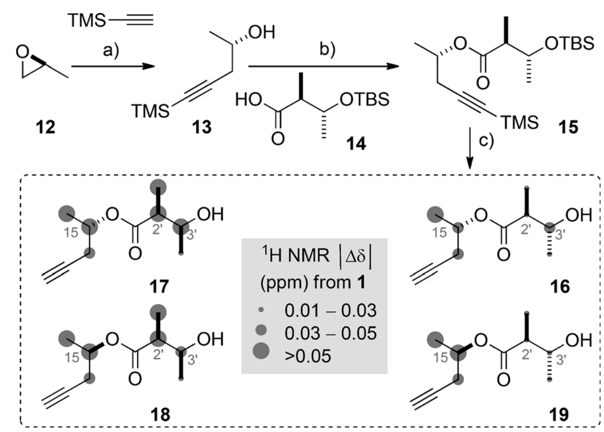
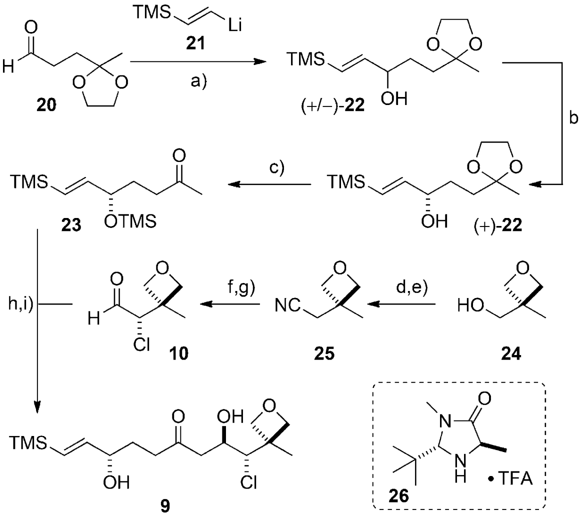
rearrangement of the hydroxy oxetane function (i.e., **8**→**7**).[9] Molecular models suggested that Lewis acid activation of the oxetane function in **8** could involve a secondary coordination to the central ring oxygen (Scheme 1). Importantly, this bidentate chelate structure would enforce the desired sense of diastereoselectivity on this critical rearrangement and secure the correct configuration at the all-carbon quaternary center C2. While without precedent, the potential for these two distinct cyclization reactions to be promoted in tandem by a Ag^I salt was a particularly appealing aspect of this route. Building on our experiences in aldol reactions of α-chloroaldehydes,[10] we expected the ketochlorohydrin **9** to be readily available from the union of suitably functionalized aldol coupling partners **10** and **11**.

In an attempt to address stereochemical uncertainties regarding the ascospiroketal A side chain,[1] we first targeted the four potential diastereomeric truncated side chains **16**–**19** (Scheme 2). Thus, readily available TBS-protected (2*S*,3*R*)-3-hydroxy-2-methylbutyric acid **14**[11] was coupled with the homopropargyl alcohol **13** derived from TMS-acetylene addition to (−)-propylene oxide (**12**).[12] Deprotection of the resulting silyloxy ester **15** gave the hydroxy ester **16**. Repeating this sequence of reactions separately with (+)-propylene oxide and/or (2*S*,3*S*)-3-hydroxy-2-methylbutyric acid[13] (see the Supporting Information (SI) for full details) afforded the corresponding esters **17**–**19**. With these materials in hand, comparison of their ^1H and ^{13}C NMR spectral data (Scheme 2 and SI) with that reported for the equivalent portion of ascospiroketal A[1] suggested that the natural products possess a (2′*S**,3′*R**) relative configuration as depicted for esters **16** and **19**. Unfortunately, we were not able to confidently assign the relative configuration at C15 using these model compounds. Considering this uncertainty, the complete stereochemical assignment of ascospiroketal A would ultimately require the synthesis of four candidate stereostructures using the side-chain precursors **16**, **19**, and *ent*-**16**, *ent*-**19**, and comparison of their spectral data to that reported for the natural product.



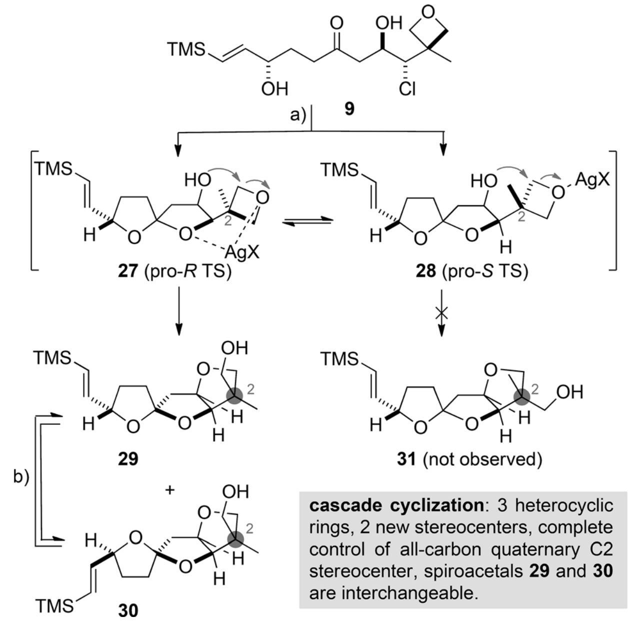
Scheme 2. Synthesis of diastereomeric ascospiroketal A side chains and comparison of their ^1H NMR spectral data to **1**. a) TMS-acetylene, *n*BuLi, then **12**, $BF_3{\cdot}OEt_2$, Et_2O, −78 °C, 69 %; b) DIC, DMAP, CH_2Cl_2, 20 h, 96 %; c) TBAF, THF, 83 %. DIC = *N*,*N*′-diisopropylcarbodiimide, DMAP = 4-(dimethylamino)pyridine, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.



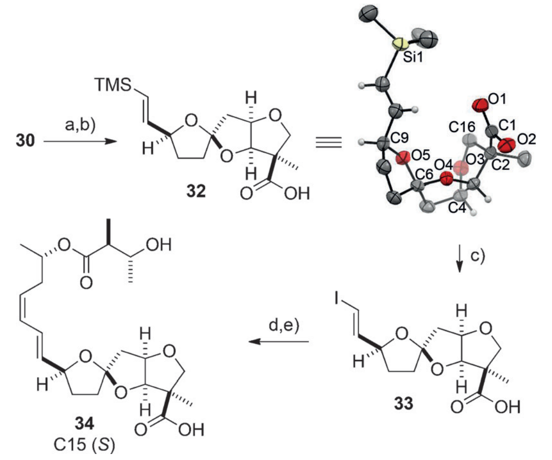
Scheme 3. Synthesis of the oxetanyl ketochlorohydrin **9**. a) Et_2O, −40 °C, 1.5 h, 80 %; b) $Ti(O{\it i}Pr)_4$, (−)-DIPT, TBHP, CH_2Cl_2, −20 °C, 38 h, 40 % (*ee* 98 %); c) 1) PTSA, H_2O/acetone, 65 °C, 2.5 h; 2) Et_3N, TMSCl, THF, 0 °C to RT, 91 % over two steps; d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; e) KCN, DMF, 80 °C, 16 h, 76 % over two steps; f) DIBAL, CH_2Cl_2, −5 °C, 1 h; g) NCS, **26** (20 mol %), CH_2Cl_2, 5 °C, 24 h, 64 % over two steps; h) **23**, LDA, then **10**, THF, −78 °C, 46 % (72 % based on recovered **23**, d.r. = 12:1); i) PTSA, H_2O/acetone, 5 min, 83 %. (−)-DIPT = (−)-diisopropyl D-tartrate, TBHP = *tert*-butyl hydroperoxide, PTSA = *p*-toluenesulfonic acid, TMSCl = chlorotrimethylsilane, DMF = *N*,*N*-dimethylformamide, DIBAL = diisobutylaluminum hydride, NCS = *N*-chlorosuccinimide, LDA = lithium diisopropylamide.

Synthesis of the tricyclic core of ascospiroketal A was initiated with the addition of vinyl lithium reagent **21** to the known aldehyde **20** (Scheme 3).[14] Sharpless asymmetric epoxidation[15] of **22** afforded the corresponding epoxide (not shown) along with recovered alcohol (+)-**22** in high enantiomeric purity (98 % *ee*) at 60 % conversion. Removal of the acetal protecting group and protection of the secondary alcohol function in (+)-**22** then yielded the methyl ketone **23**. The preparation of α-chloroaldehyde **10** involved a one-carbon homologation of commercially available alcohol **24** by displacement of the corresponding mesylate with cyanide and subsequent reduction. The organocatalytic asymmetric α-chlorination[10a] was explored using the conditions reported by MacMillan,[16] Jørgensen,[17] and Christmann.[18] After some experimentation with this unusual substrate, we found that a combination of MacMillan's catalyst **26**[16] and NCS[18] gave α-chloroaldehyde **10** in optimal enantiomeric purity (85 % *ee*). Finally, coupling of the lithium enolate derived from methyl ketone **23** with the α-chloroaldehyde **10** provided the aldol adduct **9** in good yield and excellent diastereoselectivity (d.r. = 12:1).[10f]

Having established a concise, 6-step synthesis of ketochlorohydrin **9** we next explored the key spirocyclization reaction. Using our optimized conditions[7] for the formation of simple spiroacetals, we were delighted to find that overnight reaction of **9** with AgOTf and Ag_2O proceeded smoothly to afford the anomeric spiroacetals **27** in good combined yield. Pleasingly, the only by-products produced in



Scheme 4. Ag^I-promoted cascade cyclization of **9**. a) Ag_2O, $AgBF_4$, THF, 20 °C to 50 °C, 82 % (**29**/**30** ~1:1); b) $ZnCl_2$, MgO, CH_2Cl_2, 6.5 h, **29**/**30** (2:1).



Scheme 5. Synthesis of candidate stereostructure **34** and ORTEP representation of **32**. a) DMP, $NaHCO_3$, CH_2Cl_2, 1 h, 79 %; b) $NaClO_2$, $NaH_2PO_4\cdot H_2O$, 2-methyl-2-butene, H_2O:*t*BuOH, 45 min, 87 %; c) NIS, HFIP, 0 °C, 30 min, 67 %; d) **16**, $PdCl_2(PPh_3)_2$, CuI, DIPA, THF, 14 h; e) H_2 (balloon), Lindlar catalyst, quinoline, EtOH, 46 % over two steps. DMP = Dess–Martin periodinane, NIS = *N*-iodosuccinimide, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, DIPA = diisopropylamine. Ellipsoids are given at 50 % probability.

any appreciable quantity were the tricycles **29** and **30**. Further optimization of the formation of these tricycles involved a brief screen of Ag^I salts, whereupon a combination of $AgBF_4$ and Ag_2O[7] was identified as optimal, delivering **29** and **30** in a combined isolated yield of 82 %. As highlighted in Scheme 4, the complete diastereoselectivity observed in the opening of the prochiral oxetane may be attributed to chelation of the central ring oxygen and that of the oxetane to the Ag^I salt (see **27**). This bidentate chelation[19] is not possible in the pro-*S* transition structure **28**. It is notable that the Ag^I-promoted cyclization cascade effects the formation of three heterocyclic rings and a spiroacetal center, and secures the relative stereochemistry at the all-carbon quaternary center required for ascospiroketal A. To improve the overall efficiency of this reaction, the undesired spiroactetal **29** was readily epimerized using Dudley's conditions ($ZnCl_2$, MgO)[3a,20] to provide a mixture of the anomeric spiroacetals **29** and **30** and a means to recycle the former material.

Completion of the total synthesis of the candidate stereostructures for ascospiroketal A is depicted in Scheme 5. A two-step oxidation[21,22] of the primary alcohol function in tricycle **30** provided the carboxylic acid **32** without epimerization of the spiroacetal center. At this point, suitable crystals were obtained for X-ray crystallographic analysis (see ORTEP, Scheme 5), which confirmed our stereochemical assignment of the tricyclic core. Moreover, the spectral data (^{1}H and ^{13}C NMR) derived from **32** were in close agreement with that reported for the same region of ascospiroketal A, supporting the assigned stereochemistry for the natural product. Following silicon to iodine exchange (**32**→**33**),[23] Sonogashira coupling[8] of the side chain **16** with vinyl iodide **33** provided the full carbon skeleton of ascospiroketal A. Lindlar reduction[24] of the resulting enyne completed the total synthesis of candidate stereostructure **34**, which required only 12 steps from the readily available aldehyde **20**. Repetition of the final two reactions using the stereochemically unique side chains **19**, *ent*-**16**, and *ent*-**19** gave the candidate stereostructures **35**, **36**, and **37**, respectively (Figure 2). Whereas the ^{1}H NMR spectra derived from these synthetic materials were similar, the resonances for the diastereotopic protons at C14 proved to be diagnostic for the C15-(*S*) and C15-(*R*) series. Notably, only the spectra derived from the C15-(*S*) diastereomers **34** and **37** contained H14a/H14b resonances characteristic of ascospiroketal A (see truncated spectra, Figure 2).[25] Furthermore, whereas the ^{1}H NMR spectrum of **37** acquired at 500 MHz closely matched that of the natural product, several subtle differences in the chemical shift ($\Delta\delta > 0.01$ ppm) and/or shape of resonances for H10, H13, H14, and H3′ existed between the spectra of **34** and ascospiroketal A.[25] Thus, based on the distinct ^{1}H NMR spectra of the candidate stereostructures **34**–**37**, the relative configuration for ascospiroketal A was confidently assigned as that depicted for **37**. The specific rotation for **37** ($[\alpha]_D^{20} = +5$ (*c* 0.20 in MeOH)) was also consistent in sign with that reported for the natural product ($[\alpha]_D^{20} + 20$ (*c* 0.45 in MeOH)),[1] confirming the absolute stereochemistry of ascospiroketal A as shown for **37**. Interestingly, the structurally related octaketide cephalosporolide H,[2c] also isolated from a marine-derived fungus, possesses the same absolute stereochemistry within its tricyclic spiroacetal core.

In summary, exploiting a Ag^I-promoted cyclization cascade, concise (14-step) syntheses of four candidate stereostructures of the naturally occurring polyketide ascospiroketal A were realized. Comparison of their spectral data with that reported for **1** allowed for the confident assignment of the relative and absolute stereochemistry for the natural product as (2*R*, 3*R*, 4*R*, 6*R*, 9*S*, 15*S*, 2′*R*, 3′*S*). Considering the similarities in structure between the ascospiroketals A (**1**) and

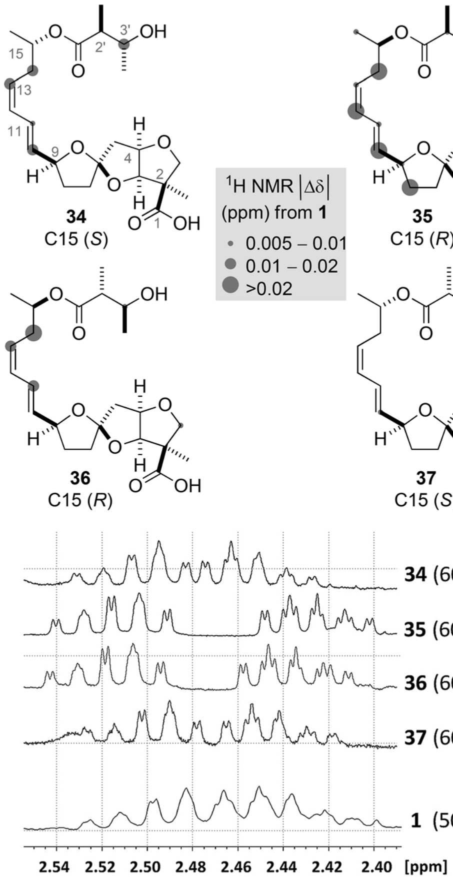


Figure 2. Comparison of the ^{1}H NMR spectra ([D$_6$]acetone) of candidate stereostructures **34–37** to **1** and enlargement of the H14 resonances from the ^{1}H NMR spectra of **1**[25] and **34–37**.

B (**2**), the relative and absolute stereochemistry of ascospiroketal B should also be revised accordingly.

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[25] The authors thank Professor Gabrielle König for providing a data file of the 500 MHz ^{1}H NMR spectrum of ascospiroketal A (500 MHz, [D$_6$]acetone).