Total Synthesis and Stereochemical Assignment of (±)-Sorbiterrin A

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Ⓢ *Supporting Information*

ABSTRACT: A concise, biomimetic approach to sorbiterrin A has been developed employing consecutive Michael additions of a 4-hydroxypyrone to a sorbicillinol derivative and silver nanoparticle-mediated bridged aldol/dehydration to construct the [3.3.1] ring system. The relative stereochemistry of sorbiterrin A was unambiguously confirmed by X-ray crystallographic analysis.

S orbicillinoids are a class of polyketides with high structural diversity and bioactivity.[1] The recently isolated sorbiterrin A (1) is a novel sorbicillin derivative featuring an intriguing bridged [3.3.1] ring system and acetylcholinesterase inhibitory activity.[2] The relative stereochemistries at C-2 and C-3 (Scheme 1) were

Scheme 1. Biosynthetic *vs* Biomimetic Pathways
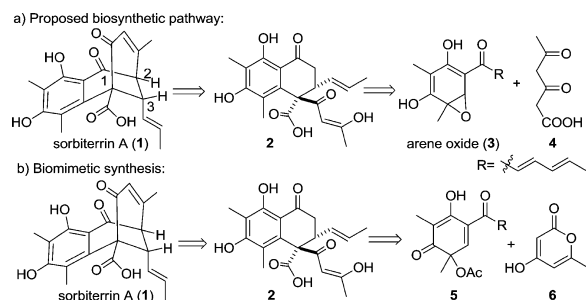
proposed based on coupling constant analysis ($^3J_{2,3} = 2.8$ Hz).[2] Herein, we describe a concise approach to sorbiterrin A along with studies to confirm relative stereochemistry. The synthesis employs a biomimetic process involving consecutive Michael additions of a 4-hydroxypyrone to a protected sorbicillinol derivative followed by silver nanoparticle-mediated bridged aldol/dehydration to access the [3.3.1] framework.

Biosynthetically, sorbiterrin A (1) was proposed to originate from vinylogous acid 2 through an intramolecular aldol/dehydration reaction. Precursor 2 may be obtained from addition of 4 to arene oxide 3. Inspired by previous syntheses of sorbicillinoids,[1] we envisioned that the quaternary center of 2 may be derived from consecutive Michael additions of the commercially available 4-hydroxypyrone 6 to the known sorbicillinol acetate derivative 5 followed by pyrone opening (Scheme 1). The overall synthetic strategy would allow very concise syntheses of sorbiterrin A and analogues.

We initiated our study with the preparation of acetoxy sorbicillinol 5 (Scheme 2).[3] Acetylation of sorbicillin (7) was

Scheme 2. Synthesis of Acetoxy Sorbicillinol 5
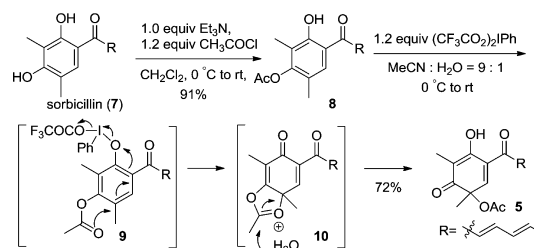
achieved under basic conditions with acetyl chloride to afford 8 in 91% yield. Treatment of 8 with [bis(trifluoroacetoxy)iodo]-benzene (PIFA)[4] in acetonitrile/water (9:1) afforded acetoxy sorbicillinol 5 in 72% yield. One mechanism for this process involves activation of 8 with PIFA to afford intermediate 9, ester trapping[5] to generate acetoxonium ion intermediate 10,[6] and hydrolysis. Alternatively, nucleophilic addition of water to 9,[7] followed by acyl migration, may also generate 5.

To probe the feasibility for the Michael addition cascade to construct the quaternary center in 2 using a 4-hydroxypyrone,[8] we examined a number of basic and Lewis acid mediated conditions. Unfortunately, we found that substrate 5 was highly unstable under basic conditions which resulted in significant degradation or dimerization.[3] We also found that several Lewis acid conditions (e.g., Yb(OTf)$_3$, In(OTf)$_3$, and Sc(OTf)$_3$) afforded trace amounts of 3-aryl-4-hydroxypyrone product 11. Reaction partners 5 and 6 were further treated with Lewis acid promoters under thermal conditions in which case only decomposition was observed. Gratifyingly, thermolysis of 5 and 6 in the presence of silica gel (130 °C) produced the spiro compounds 12 and 13 in 80% yield (d.r. = 1.5:1) (Scheme 3). By lowering the reaction temperature to 90 °C, we were able to isolate compound 11 in 28% yield along with the spiro compounds 12 and 13 (50%). We found that 11 could also be converted to 12 and 13 in 94% yield at 130 °C using silica gel as a catalyst.

The similarities in ^{1}H NMR spectra, NOE correlations, and the noncrystalline properties[9] of 12 and 13 caused significant difficulty with their stereochemical assignments. Accordingly, we considered further derivatization to elucidate their structures. Examination of the π-orbital alignments for compounds 12 and 13[9] suggested that they may have different reactivities under photocycloaddition conditions. The parallel arrangement of the
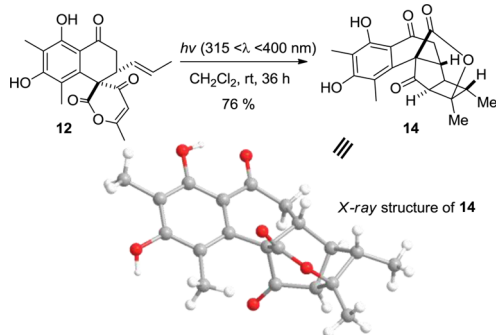
Scheme 3. Michael Additions of 4-Hydroxypyrone 6 to 5
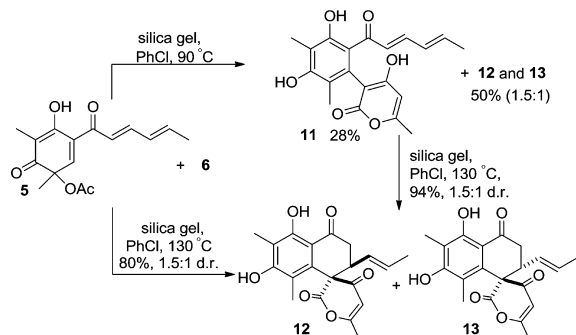
two double bonds in **12** should allow for [2 + 2] photocycloaddition[10] which may not occur with compound **13** as substrate. Upon photoirradiation, only diastereomer **12** was converted to [4.2.1.0$^{3.8}$] tricyclic structure[11] **14** as confirmed by X-ray crystallographic analysis (Scheme 4).[9]

Scheme 4. Tricyclo [4.2.1.0$^{3.8}$] Derivative 14

In order to prepare intramolecular aldol substrate **2**, spiro compound **13** was treated with various acidic (e.g. HCl, H$_2$NTf, *p*-TsOH) and basic (e.g. NaOH, NaOMe, pyrrolidine) conditions. Unfortunately, all conditions led to degradation or decarboxylation products. Accordingly, we targeted the synthesis of the corresponding methyl ester **15** through transesterification. A number of Lewis acids including Cu(OTf)$_2$, Mg(OTf)$_2$, Ti(OEt)$_4$, and Zn(OTf)$_2$[12] were evaluated on substrate **13** using methanol as solvent. We were pleased to observe that Zn(OTf)$_2$ (80 °C, MeOH) efficiently catalyzed the desired transesterification in the presence of 4 Å molecular sieves. However, we also observed epimerization in this reaction; a 1:1 mixture of methyl esters **15** and **16** was observed using either **12** or **13** as starting material. No reaction was observed after treatment of **12** or **13** with Zn(OTf)$_2$ in 1,2-dichloroethane (80 °C) which indicates the epimerization likely occurs on products **15** and **16**. Accordingly, a mixture of **12** and **13** was submitted to the Zn(OTf)$_2$ conditions to prepare **15** and **16** in 74% yield and in a 1:1 ratio (Scheme 5). The relative stereochemistries of **15** and **16** were determined by correlation to sorbiterrin A (*vide infra*).

Scheme 5. Spirocyclic Ring-Opening *via* Transesterification
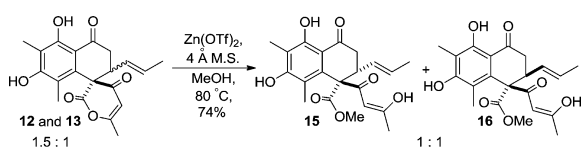
With advanced intermediates **15**/**16** in hand, we attempted the key intramolecular bridged aldol/dehydration step to construct the [3.3.1] ring system of sorbiterrin A. The base sensitivity[13] of both **15** and **16** prompted us to focus on examination of acidic conditions. We initiated our study by screening various Brønsted and Lewis acid catalysts including HCl in dioxane,[14] trifluoroacetic acid, *p*-toluenesulfonic acid,[15] and BF$_3$·Et$_2$O[16] for cyclization of **15**. Based on our previous studies employing silica-supported silver nanoparticles (AgNP's) as catalysts for activation of 2′-hydroxychalcones toward [4 + 2] cycloadditions,[17] this catalyst system was also evaluated. To our surprise, only conditions employing silver nanoparticles afforded the desired product; other conditions either degraded the starting materials or gave no reactivity.[9] After optimization, best results involved treatment of **15** with 0.25 mol % AgNP's at 135 °C in chlorobenzene which afforded a 72% yield of the cyclized product **17** (Scheme 6). Compound **17** was further treated with

Scheme 6. Synthesis of Sorbiterrin A
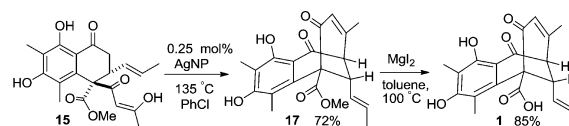
MgI$_2$ in toluene to effect demethylation which afforded sorbiterrin A in 85% yield after acidic workup. Treatment of the diastereomeric substrate **16** under similar conditions (0.25 mol % AgNP's, 135 °C, chlorobenzene) afforded a mixture of diastereomers **17** and **18** in a 1:2 ratio and 50% combined yield (Scheme 7). The inseparable mixture of **17** and **18** was demethylated using MgI$_2$ to provide sorbiterrin A (**1**) and 3-*epi*-sorbiterrin A (**20**) in a 1:2 ratio and 88% combined yield.

Scheme 7. Synthesis of 3-*epi*-Sorbiterrin A
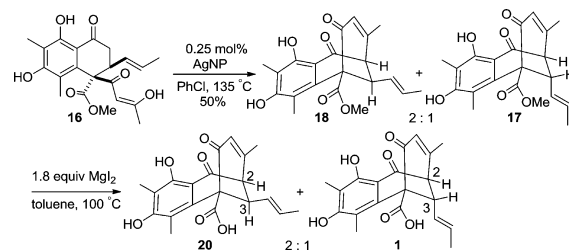
Sorbiterrin A (**1**) and 3-*epi*-sorbiterrin A (**20**) were found to have very similar ^{1}H NMR coupling constants between H-2 and H-3;[9] in particular **20** has a $^3J_{2,3}$ = 2.3 Hz in comparison to $^3J_{2,3}$ = 2.8 Hz for **1** (cf. Scheme 1). These similar coupling constant values called into question the assignment of the relative stereochemistry at H-2 and H-3 for **1**. Numerous modes of derivatization were attempted on both **1** and **20**. Luckily, both **1** and **20** were found to form the corresponding iodolactonization products.[18] However, only compound **22** was found to be crystalline (Scheme 8).[9] X-ray crystallographic analysis revealed a *cis* configuration between C-2 and C-3 in **22** which confirmed the proposed[2] *trans* configuration between H-2 and H-3 in **1**.

We next performed a series of mechanistic studies of the AgNP-mediated aldol condensation. We initiated these studies by conducting control experiments with substrate **15** using several silver salts as Lewis acids including AgBF$_4$, Ag$_2$O, and AgOTf which in all cases did not afford the desired products.[9] Intermolecular aldol condensation between 2′,4′-dihydroxy-

Scheme 8. Synthesis of Iodolactone 22
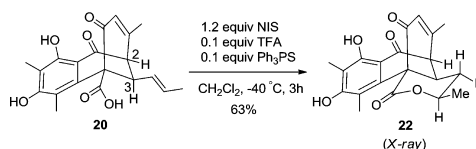
acetophenone **23**[19] and **24** was also found to be efficiently catalyzed by AgNP's affording chalcone **25**[3c] (Scheme 9). In

Scheme 9. Model Aldol Condensation Reactions
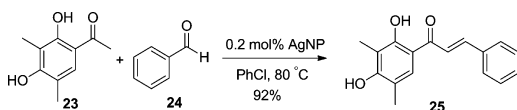
addition, no aldol condensation was observed when the corresponding 2′,4′-methoxyacetophenone was used as the substrate.[9] In our previous studies, AgNP's were employed as a catalyst for Diels−Alder cycloadditions of 2′-hydroxychalcones through a proposed radical cation intermediate. In line with our previous mechanistic studies, we hypothesized that the aldol condensation could also be catalyzed by the AgNP's through an electron transfer mechanism. To probe the involvement of possible radical intermediates, 5,5-dimethyl-1-pyrroline N-oxide (DMPO) was used as a spin trap[20] to access long lifetime radicals. Electron paramagnetic resonance (EPR) measurements were conducted on a mixture of the silica-supported AgNP catalyst, DMPO, and compound **16** in which case a strong radical signal was evident in the EPR spectrum (Figure 1a). Similar
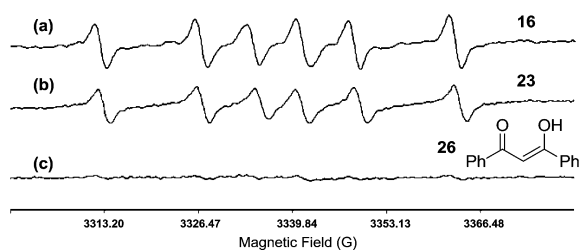

Figure 1. EPR spectra of spin trapping. (a) Experimental EPR spectrum obtained from a mixture of silica-supported AgNP catalyst (150 mg), **16** (19.4 mg, 0.05 mmol), and DMPO (20 μL, 0.18 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 25 °C. a_N = 14.4 G, $a_{H\beta}$ = 21.7 G. (b) Experimental EPR spectrum obtained from a mixture of silica-supported AgNP catalyst (150 mg), **23** (9.2 mg, 0.05 mmol), and DMPO (20 μL, 0.18 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 25 °C. a_N = 14.1 G, $a_{H\beta}$ = 22.4 G. (c) Experimental EPR spectrum obtained from a mixture of silica-supported AgNP catalyst (150 mg), **26** (11.0 mg, 0.05 mmol), and DMPO (20 μL, 0.18 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 25 °C.

experiments were conducted using both compound **23** and vinylogous acid **26**. A similar EPR signal was detected using **23** but not with **26** which supports the unique property of the 2′-hydroxyacetophenone moiety to generate a radical species under AgNP-catalyzed conditions.

Based on our experimental results, we propose a mechanism for the AgNP-mediated intramolecular aldol reaction of substrate **15** as shown in Scheme 10. Absorption of **15** to the AgNP surface may lead to proton removal and single electron transfer (SET)[17,21−23] from **15** to provide phenoxyl radical **27** (Scheme 10a) which is in resonance with the carbon-centered radical **28**. We hypothesize that the electron deficient character of radical

Scheme 10. Proposed Mechanisms for the AgNP-Mediated Aldol Reaction
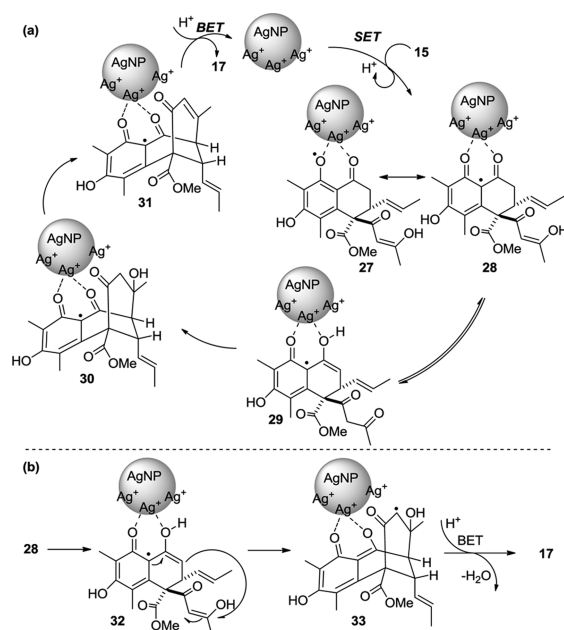
cation intermediate **28** may facilitate enolization of the ketone by increasing the kinetic acidity of the α-hydrogen atoms to afford enol tautomer **29**. Intramolecular aldol reaction of **29** to **30** may be followed by dehydration to intermediate **31** followed by back electron transfer (BET) and protonation to product **17**. Alternatively, enol tautomer **32** (Scheme 10b) may undergo radical cyclization[24] to intermediate **33**, which may be followed by back electron transfer, protonation, and dehydration to obtain product **17**.

Analysis of molecular models of the two proposed aldol transition states (Figure 2A and B, respectively, leading to **18** and
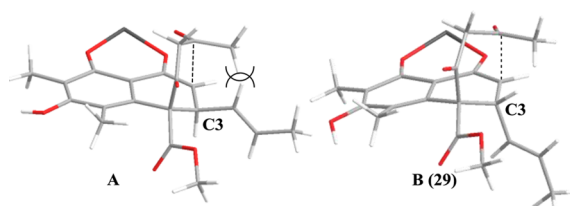
Figure 2. Molecular models of two proposed aldol transition states.

17) provides a plausible explanation for the C3 epimerization observed for substrate **16** (Scheme 7). By comparing the two models, we hypothesize that the equatorially positioned propenyl substituent at C3 in transition state **A** may interact with the methyl ketone (1,3-diaxial interaction) which should increase the energy barrier for the intramolecular aldol reaction. This steric repulsion is not observed in the corresponding transition state **B**. Due to the higher projected energy barrier of **A**, C3-epimerization may subsequentially occur by retro-Michael/Michael addition.

In summary, we have developed a biomimetic synthesis of the bicyclo [3.3.1] natural product sorbiterrin A. The quaternary carbon center was established *via* consecutive Michael additions of a 4-hydroxypyrone to acetoxy sorbicillinol. The [3.3.1] ring system was constructed using a unique AgNP-catalyzed bridged aldol condensation. Mechanistic studies including EPR experi-

ments support the involvement of radical intermediates in the aldol process. Further studies including the asymmetric synthesis of sorbiterrin A and development of AgNP-catalyzed reactions are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds described herein, including CIF files for compounds **14** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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