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Total synthesis and stereochemical assignment of (±)-sorbiterrin A.

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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 aldol/dehydration to construct the [3.3.1] ring system. The relative stereochemistry of sorbiterrin A was unambiguously confirmed by X-ray crystallographic analysis.

Sorbicillinoids are a class of polyketides with high structural diversity and bioactivity. The recently isolated sorbiterrin A (1) is a novel sorbicillin derivative featuring an intriguing bridged [3.3.1] ring system and acetylcholinesterase inhibitory activity. The relative stereochemistries at C-2 and C-3 (Scheme 1) were proposed based on coupling constant analysis ($J_{1,3} = 2.8$ Hz). Herein, we describe a concise approach to sorbiterrin A along with studies to confirm relative stereochemistry. The synthesis employs a biomimetic process featuring 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 vinlylogous 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, 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 sorbicillin 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). Acetylation of sorbicillin (7) was 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 trapping4 to generate acetoxy ion intermediate 10, and hydrolysis. Alternatively, nucleophilic addition of water to 9, 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, 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. 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 1H NMR spectra, NOE correlations, and the noncrystalline properties 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 suggested that they may have different reactivities under photocycloaddition conditions. The parallel arrangement of the
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 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, trifluoroacetic acid, p-toluenesulfonic acid, and BF₃·Et₂O 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, 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. 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 MgI₂ 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 MgI₂ to provide sorbiterrin A (1) and 3-epi-sorbiterrin A (20) in a 1:2 ratio and 88% combined yield.

In order to prepare intramolecular aldol substrate 2, spiro compound 13 was treated with various acidic (e.g. HCl, H₃NTf, 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 were evaluated on substrate 13 using methanol as solvent. We were pleased to observe that Zn(OTf)₂ in 1,2-dichloroethane (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).

Sorbitterrin A (1) and 3-epi-sorbiterrin A (20) were found to have very similar ¹H NMR coupling constants between H-2 and H-3; in particular 20 has a J₂,₃ = 2.3 Hz in comparison to J₂,₃ = 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. However, only compound 22 was found to be crystalline (Scheme 8). X-ray crystallographic analysis revealed a cis configuration between C-2 and C-3 in 22 which confirmed the proposed 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 AgBF₄, Ag₂O, and AgOTf which in all cases did not afford the desired products. Intermolecular aldol condensation between 2',4',5'-dihydroxy-
acetophenone 23 and 24 was also found to be efficiently catalyzed by AgNP’s affording chalcone 25 (Scheme 9). In addition, no aldol condensation was observed when the corresponding 2’,4’-methoxyacetophenone was used as the substrate. 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 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 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’-hydroxacetophenone 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) 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 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 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 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 subsequently 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

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.

■ ACKNOWLEDGMENTS

The authors declare no competing financial interest.

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