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Bypassing Biocatalytic Substrate Limitations in Oxidative Dearomatization Reactions by Transient Substrate Mimicking

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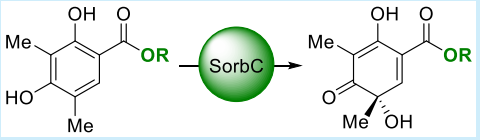
Supporting Information

ABSTRACT: Enzymatic oxidative dearomatization is an efficient way to generate chiral molecules from simple arenes. One example is the flavin-dependent monooxygenase SorbC involved in sorbicillinoid biosynthesis. However, SorbC requires a long-chain keto substituent at its phenolic substrate, thus preventing its application beyond the synthesis of natural sorbicillinoids or close structural analogues. This work describes an approach to broaden the accessible product spectrum of SorbC by employing an ester functionality mimicking the natural substrate structure during enzymatic oxidation.



The ability to generate molecular complexity from readily available, simple starting materials is key to the efficient synthesis of structurally demanding small molecules, such as natural products. Dearomatization reactions are a synthetic tool for the rapid functionalization of arenes to give such valuable synthetic building blocks. It is thus not surprising that the development of new dearomative transformations has received significant attention, in particular, over the last two decades. This has led to a broad repertoire of methods, including nucleophilic,[1] photochemical,[2] transition-metal catalyzed,[3] and enantioselective dearomatization reactions,[4] also for nonactivated aromatics.[5] These techniques have also significantly contributed to the development of streamlined routes to complex natural products of diverse biosynthetic origin.[6]

Nature has also developed a broad range of oxidative dearomatization reactions that can be harnessed as complementary biocatalytic alternatives to chemical methods. Impressive examples include aromatic dioxygenases that catalyze the *cis*-1,2-addition of both oxygen atoms of molecular oxygen onto their aromatic substrates, yielding the corresponding 3,5-diene-1,2-diols.[7] This enzymatic transformation was discovered by Gibson et al.[8] who also developed a first recombinant *Escherichia coli* whole-cell system for its application in synthetic chemistry.[9] The product 3,5-diene-1,2-diol structural portion can be further modified at the diol (e.g., by Claisen rearrangements) and the diene (e.g., by oxidative cleavage and (cyclo-)addition reactions), thus providing versatile precursors for natural product synthesis. Because of this synthetic value of dioxygenase products, these enzymes have since been exploited in many total syntheses.[10,11] Another important biosynthetic dearomative reaction is the oxidative dearomatization of phenols catalyzed by monooxygenases. Pioneering work by the Cox and Tang groups revealed this transformation as the key step in the biosyntheses of a variety of fungal natural products (Figure 1):

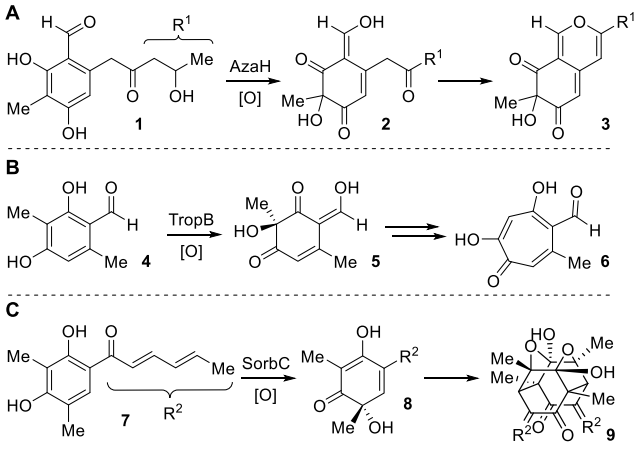


Figure 1. Oxidative dearomatization of phenolic precursors as a key step in the biosynthesis of the azaphilone (A), tropolone (B), and sorbicillinoid (C) natural product families.

for example, aldehyde **1** gets oxidatively dearomatized by AzaH to give **2**, which upon cyclization delivers the azaphilone derivative azanigerone E (**3**).[12] In tropolone biosynthesis, TropB transforms aldehyde **4** into **5**, which gets further elaborated to stipidaldehyde (**6**).[13] Sorbicillin (**7**) is oxidized by SorbC to the highly reactive sorbicillinol (**8**), which is

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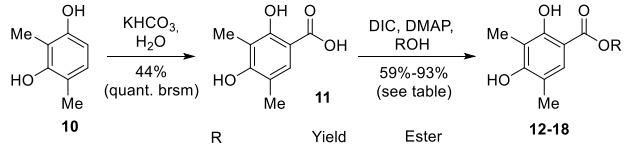
further diversified into the large sorbicillinoid natural product family, for example, by dimerization to yield trichodimerol (**9**).[14]

We recently showed that SorbC can also be used as a tool for the in vitro assembly of sorbicillinoids. This led to the first biocatalytic total syntheses of dimeric[15] and further functionalized sorbicillinoid natural products[16] with complex molecular architectures from synthetically readily available sorbicillin, thereby significantly improving previous synthetic strategies to access these compounds and developing first synthetic routes to some congeners. However, our work and an additional study evaluating the substrate scope by Narayan et al.[17] that also included AzaH and TropB revealed rather low substrate promiscuity of these oxidative enzymes. While many alterations of the substitution pattern at the aromatic portion of sorbicillin are permitted for SorbC, the sorbyl side-chain (R^2 in Figure 1) or a similar long alkyl- or alkenyl ketone substituent is required to retain high catalytic efficiency and stereoselectivity.[15−17] To enable a more flexible variation of the sorbicillinoid natural product structures at this position, for example, for structure-activity relationship studies on this biomedically rewarding natural product family,[18] the availability of an approach to freely alter this side chain is highly desirable. In addition, circumventing the need for a long-chain keto substituent in the substrate would also permit the application of SorbC in the total synthesis of other compounds of the many examples of natural products accessible by oxidative dearomatization.[6] While the goal of broadening the substrate scope might be achieved by protein engineering approaches, we were interested in developing a straightforward, simple, alternative approach that exclusively relies on suitable modifications of the substrate structure.

Given the apparent need of an alk(en)yl ketone substituent at the substrate of SorbC to permit efficient and stereoselective conversion to the oxidatively dearomatized product,[15−17] we anticipated that introduction of a moiety mimicking the natural sorbyl side chain would permit the biocatalytic reaction to proceed. Potential alternatives resembling the alk(en)yl ketone could be based on a carboxylic acid, condensed with an alk(en)ylamine to give the corresponding amide, an alk(en)ylthiol leading to the respective thioesters, or an alcohol to give the corresponding oxoester. The latter was considered the best option, as oxoesters can be saponified under mild conditions for further downstream processing when compared to the amide and in addition should be more easily accommodated within the active site of the enzyme when compared to the thioester. To comprehensively assess the substrate promiscuity of SorbC, the synthesis of substrates with saturated ester functions ranging from C1 to C6 as well as the ester of crotyl alcohol bearing a double bond more closely resembling the sorbyl side chain of the natural substrate was projected. The precursor to these substrates, 2,4-dimethylresorcinol (**10**), was obtained in two steps from methylresorcinol following a published procedure.[15] Carboxylation of **10** was conducted with $KHCO_3$[19] to yield 2,4-dihydroxy-3,5-dimethylbenzoic acid (**11**) in 44% yield (quantitative yield based on re-isolated starting material (brsm), Scheme 1). The desired esters **12**−**18** were obtained by coupling of **11** to the respective alcohols using *N*,*N*′-diisopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (DMAP) in yields of 63% (**12**, methyl ester), 83% (**13**, ethyl ester), 93% (**14**, propyl ester), 61% (**15**, butyl ester), 73% (**16**, pentyl ester), 71% (**17**, hexyl ester), and 59% (**18**, crotyl ester).

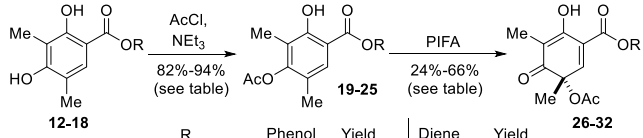
Scheme 1. Synthesis of the Ester Substrates 12−18 for SorbC Substrate Screening



R	Yield	Ester
Me	63%	**12**
Et	83%	**13**
n-Pr	93%	**14**
n-Bu	61%	**15**
n-Pentyl	73%	**16**
n-Hexyl	71%	**17**
trans-Crotyl	59%	**18**

To facilitate the evaluation of the enantioselectivity of the SorbC-catalyzed oxidative dearomatization reaction, the expected oxidation products **26**−**32** were next chemically synthesized in racemic, *O*-acetylated (and thus chemically stable) form as standards for analysis by high-performance liquid chromatography (HPLC) on a chiral phase (Scheme 2).

Scheme 2. Chemical Synthesis of Racemic Acetates 26−32 using PIFA as the Oxidant



R	Phenol	Yield	Diene	Yield
Me	**19**	92%	**26**	35%
Et	**20**	94%	**27**	66%
n-Pr	**21**	92%	**28**	24%
n-Bu	**22**	92%	**29**	50%
n-Pentyl	**23**	92%	**30**	34%
n-Hexyl	**24**	86%	**31**	41%
trans-Crotyl	**25**	82%	**32**	36%

Hence, esters **12**−**18** were *O*-acetylated with acetyl chloride to give compounds **19**−**25** in 82−94% yield. Oxidative dearomatization of **19**−**25** to the corresponding dienes **26**−**32** was achieved with phenyliodine bis(trifluoroacetate) (PIFA)[20] in 24−66% yield.

Next, the ester substrate mimics **12**−**18** were dissolved in dimethylformamide (DMF) and submitted to enzymatic oxidation with SorbC (2 μmol substrate, 2.5 mol % enzyme; see Supporting Information for experimental details), with an additional control experiment with sorbicillin (**7**), prepared by acylation of **10** with sorbic acid chloride,[15] as benchmark substrate. Substrate conversion was assessed based on consumption of **7** or **12**−**18** and quantified over a reaction time of 120 min using individual calibration curves of the respective pure substrates (see Supporting Information, Figures S1−S7 and S10). The natural substrate **7** was fully consumed within 60 min (Figure S20). While the methyl (**12**) and ethyl (**13**) ester derivatives did not show any significant conversion to **33** and **34** (Figures S11 and S12), the propyl ester (**14**) was selectively oxidized to the desired product **35** with 39% conversion after 120 min (Figure S13). To our delight, both the butyl (**15**) and pentyl (**16**) esters were efficiently transformed to products **36** and **37** by SorbC in 79% and 83% yields, respectively, after 120 min (Figures S14 and S15). The hexyl ester **17** was a less suitable substrate with reduced 48% consumption after 120 min (Figure S16). Surprisingly, the crotyl ester derivative **18** was likewise an

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inferior substrate when compared to **15** and **16**, with 51% conversion after 120 min (Figure S17).

The stereochemical outcome of the SorbC-catalyzed oxidative dearomatization of substrates **14**−**18**, all showing significant conversion, was further evaluated by HPLC analysis on a chiral phase (Chiralcel OD-RH). To facilitate these investigations, the biocatalytically formed sorbicillinol intermediates **35**−**39** of these compounds were *O*-acetylated using acetic acid anhydride to give (*S*)-**28** to (*S*)-**32**, purified by semipreparative HPLC, and analyzed in comparison with the respective synthetic racemic material. For all compounds, the biocatalytic oxidative dearomatization proceeded with excellent stereocontrol (no enantiomeric product detectable), exclusively delivering the desired (*S*)-configured oxidized products, as exemplarily shown for (*S*)-**29** and (*S*)-**30** in Figure 2 (see also Figures S21 and S22, Table S1). The activity of SorbC toward the respective precursors **15** and **16** (of **29** and **30**, respectively) was assayed in comparison with the native substrate sorbicillin (**7**) by monitoring nicotinamide adenine dinucleotide (NADH) consumption. The preferred substrate was **7** (107 U/mg enzyme), with an approximately fourfold reduced activity for both **15** (27.5 U/mg) and **16** (23.3 U/mg).

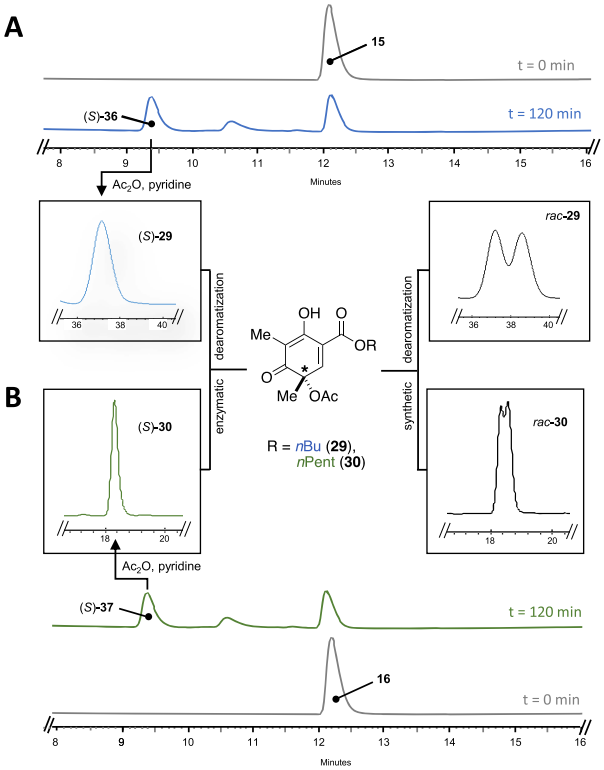
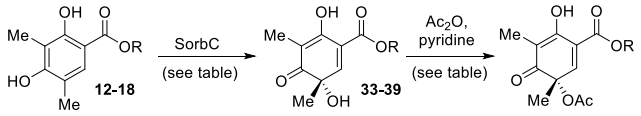


Figure 2. Analysis of the stereochemical outcome of oxidative dearomatization reactions employing SorbC and ester analogues **15** (A) and **16** (B).

The acetylated sorbicillinol analogues (*S*)-**28** to (*S*)-**32** were primarily produced to facilitate their stereochemical analysis, as typical downstream-processing for the total synthesis of sorbicillinoid natural products directly utilizes unprotected sorbicillinol.[15,16] Although acetylation yields were thus not optimized, the overall yields of the biocatalytic procedure to enantiopure products delivered similar to increased yields when compared to the purely chemical, racemic acetylation/PIFA oxidation sequence (cf. Scheme 3, table columns Y1 and Y2; Table S1).

Scheme 3. Biocatalytic Oxidative Dearomatization of Substrates 12−18 to 33−39 using SorbC and Subsequent *O*-Acetylation to Enantiopure (*S*)-Configured Products 28−32[a]

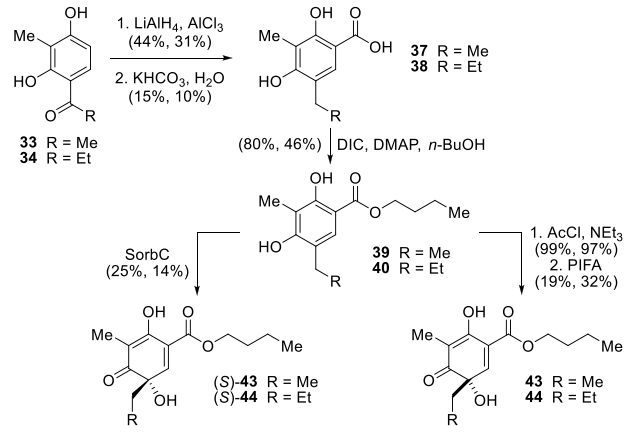


R	Phenol	Conversion	Diene	(S)-acetate	Y1	Y2
Me	**12**	<5%	**33**	**26**	-	35%
Et	**13**	<5%	**34**	**27**	-	62%
n-Pr	**14**	39%	**35**	**28**	20%	22%
n-Bu	**15**	79%	**36**	**29**	55%	46%
n-Pentyl	**16**	83%	**37**	**30**	36%	31%
n-Hexyl	**17**	48%	**38**	**31**	15%	35%
trans-Crotyl	**18**	51%	**39**	**32**	37%	29%

[a]Conversion is given after 120 min. Y1: isolated yields of enantiopure (*S*)-product. Y2: isolated yields of *rac*-product by chemical acetylation/PIFA oxidation.

For an initial evaluation of the applicability of the ester substrate mimicking approach, two substrates with altered substitution at the aromatic core were synthesized. 2-Methylresorcinol was therefore acetylated at C-4 using acetic or propionic acid anhydride to give **33** and **34**, respectively, which were reduced to the ethyl- and propyl-substituted phenols **35** and **36**, carboxylated (**37** and **38**), and esterified with *n*-butanol to deliver sorbicillin analogues **39** and **40** analogously to the procedures described above (see Supporting Information for experimental details). The corresponding oxidized products were likewise synthetically prepared by *O*-acetylation of **39** and **40** to give **41** and **42**, followed by PIFA-mediated oxidation to **43** and **44**. Enzymatic oxidative dearomatization proceeded with 62% and 37% conversion of **39** and **40**, respectively, again exclusively producing (*S*)-**43** and (*S*)-**44** in 25% and 14% isolated yield (Scheme 4; calibration curves, Figures S8 and S9; substrate conversion analyses, Figures S18 and S19; yields, Table S1).

Scheme 4. Synthesis of Ethyl- and Propyl-Substituted Substrate Analogues 41 and 42 and Their Chemical and Biocatalytic Oxidation to Sorbicillinol Analogues 43 and 44



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Irrespective of the substrate employed, HPLC analyses of all biocatalytic oxidation reactions revealed the presence of an additional product peak with a retention time between oxidized product and substrate, exemplarily depicted for the synthesis of (*S*)-**36** in Figure 3. The relative amount of this

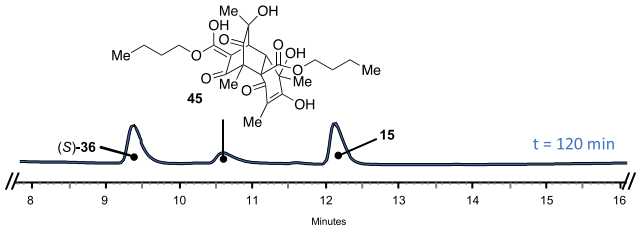

Figure 3. Characterization of the additional product peak observed in biocatalytic oxidation reactions, exemplarily for the conversion of **15** to (*S*)-**36**: identification of a new bisorbicillinol analogue **45**.

product increased with prolonged reaction times. On the basis of our experience with the synthesis of dimeric sorbicillinoid natural products[15,16] we thus suspected these compounds to correspond to the respective bisorbicillinol analogues. Optimization of the turnover to this compound by switching the employed cosolvent from DMF to acetone and extended stirring for 6 h facilitated the isolation and in-depth structural characterization of this product, indeed validating it to be bisorbicillinol analogue **45**, derived of Diels-Alder cycloaddition reaction of 2 equiv of (*S*)-**36**. The enzymatic oxidative dearomatization reaction with ester substrate mimics is thus not only a clean transformation but additionally permits typical downstream dimerization processing toward the sorbicillin natural product family.

In conclusion, we herein developed a methodology to circumvent the inherent structural requirements of SorbC toward its substrate to broaden the substrate scope of biocatalytic oxidative dearomatization. Our work revealed that the enzyme accepts ester analogues of its natural substrate sorbicillin (**7**), while retaining catalytic efficiency and stereocontrol. This work constitutes an important breakthrough in overcoming substrate specificity and limitations in such biocatalytic transformations and will thus facilitate its broader application in synthetic organic chemistry. In particular, it sets the stage for the preparation of unnaturally functionalized sorbicillinoid natural products with flexible alterations at the sorbyl side chain. This will permit future biomedical evaluation of sorbicillinoid analogues with diverse substituents at this position that can readily be introduced after biocatalytic synthesis of the respective reactive sorbicillinol derivatives. In addition, this work paves the way for the utilization of SorbC as a catalyst for the synthesis of natural products beyond the sorbicillinoid family.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01398.

Experimental procedures, supplementary figures, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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