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A Concise Synthetic Approach to the Sorbicillactones: Total Synthesis of Sorbicillactone A and 9-*epi*-Sorbicillactone A

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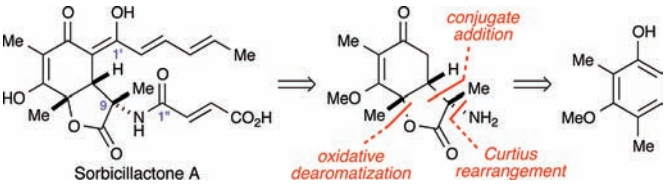
ABSTRACT



A concise (12 step) total synthesis of sorbicillactone A and 9-*epi*-sorbicillactone A is reported. Unlike typical routes to the sorbicillinoids, this strategy does not start from sorbicillin and allows for the production of the bicyclic core on a multigram scale. The intramolecular conjugate addition of a tethered malonate serves as an effective means of introducing the lactone ring and provides a synthetic handle for installing the amide nitrogen.

The sorbicillinoid natural products are a family of bioactive molecules that have been isolated from fungal species found in both terrestrial and marine environments.[1] Various members of the family have demonstrated activity in radical scavenging, anticancer, and tumor necrosis factor-α inhibition screens, among others. Synthetic efforts toward these natural products have typically involved an initial oxidative dearomatization of sorbicillin or a close derivative.[2,3] This generates an intermediate similar to sorbicillinol (**1**, Scheme 1) that is poised for dimerization, conjugate addition, and other diversification reactions.[1] While these studies have confirmed many of the biosynthetic hypotheses[4] concerning these compounds, their reliance on sorbicillin as a starting material limits the number of analogs that can be generated for further structure–activity relationship studies.

In 2003, Bringmann and co-workers reported the isolation of sorbicillactones A (**2**) and B (**3**).[5] Structurally, these compounds are interesting as they are the first, and to date only, sorbicillinoids containing an amino acid residue (Scheme 1). This introduces synthetic challenges that are not present in other members of the family. The biological activity of these compounds is also quite interesting: while **2** demonstrated selective antileukemia activity, the

(1) Review: Harned, A. M.; Volp, K. A. Manuscript submitted.

(2) (a) Barnes-Seeman, D.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1503–1504. (b) Pettus, L. H.; Van de Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2001**, *3*, 905–908. (c) Nicolaou, K. C.; Jautelat, R.; Vassilikogiannakis, G.; Baran, P. S.; Simonsen, K. B. *Chem.—Eur. J.* **1999**, *5*, 3651–3665. (d) Nicolaou, K. C.; Vassilikogiannakis, G.; Simonsen, K. B.; Baran, P. S.; Zhong, Y.-L.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 3071–3079. (e) Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3555–3559. (f) Hong, R.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3478–3481.

(3) For an alternative approach, see: Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097–2098.

(4) (a) Abe, N.; Sugimoto, O.; Tanji, K.-i.; Hirota, A. *J. Am. Chem. Soc.* **2000**, *122*, 12606–12607. (b) Abe, N.; Arakawa, T.; Yamamoto, K.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 2090–2099.

(5) (a) Bringmann, G.; Lang, G.; Mühlbacher, J.; Schaumann, K.; Steffens, S.; Rytik, P. G.; Hentschel, U.; Morschhäuser, J.; Müller, W. E. G. Sorbicillactone A: A Structurally Unprecedented Bioactive Novel-Type Alkaloid from a Sponge-Derived Fungus. In *Sponges (Porifera)*; Müller, W. E. G., Ed.; Springer Verlag: Berlin, 2003; pp 231–253. (b) Bringmann, G.; Lang, G.; Gulder, T. A. M.; Tsuruta, H.; Mühlbacher, J.; Maksimenka, K.; Steffens, S.; Schaumann, K.; Stöhr, R.; Wiese, J.; Imhoff, J. F.; Perovic-Ottstadt, S.; Boreiko, O.; Müller, W. E. G. *Tetrahedron* **2005**, *61*, 7252–7265.

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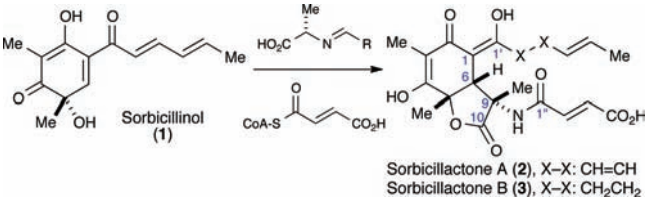
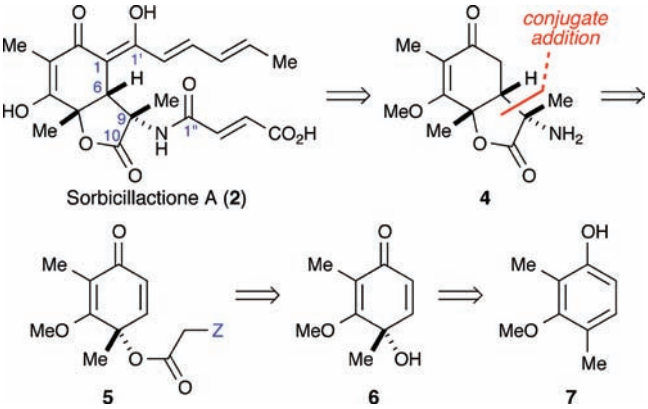
seemingly minor change of removing the 2′−3′ double bond was enough to render **3** inactive. Further investigations revealed that **2** also displayed activity in anti-HIV and neuroprotection assays.[5] We were intrigued by the biological properties displayed by **2** and set out to develop a synthesis of this molecule that would allow for the facile generation of analogs. In particular, we were interested in further exploring the influence of the C1′ and C1″ side chain structure on the biological activity. Herein, we report our work on the total synthesis of sorbicillactone A. As will be seen, this remarkably concise route can generate multigram quantities of a key intermediate that will prove useful for generating unnatural analogs for further biological studies.[6]

Scheme 1. Bringmann's Proposed Biosynthetic Origin of the Sorbicillactones[5]



In order to accomplish our goal, a route needed to be devised that was not dependent on sorbicillin (Scheme 2). Our plan was to install the C1′ and C1″ side chains at a late stage through the use of a bicyclic intermediate similar to **4**. We envisioned forging the C6−C9 bond through an intramolecular conjugate addition of dienone **5**. Because of the sensitivity of quinol derivatives to strong bases, the Michael donor in **5** would need to be substituted in such a way as to greatly increase the acidity of the α-carbon. Furthermore, the activating substituent ("Z-group") would also have to function as a synthetic equivalent of an NH_2 group. Based on this strategy, phenol **7** was chosen as the starting material.

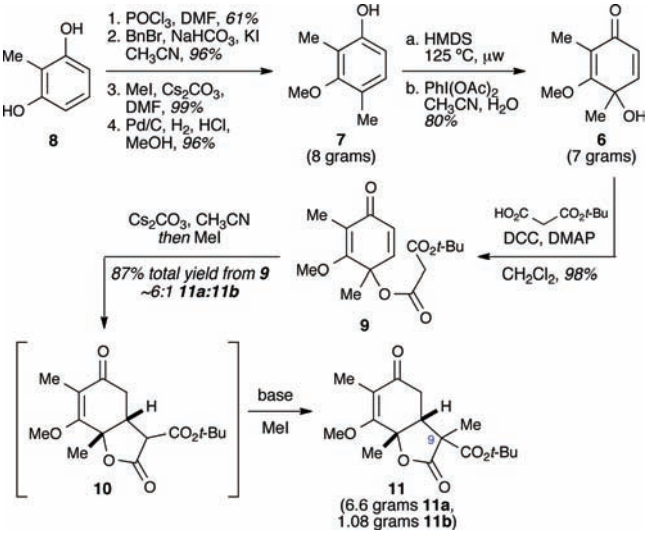
Scheme 2. Our Synthetic Strategy to Sorbicillactone A



(6) For a large scale fermentation of sorbicillactone A, see: Bringmann, G.; Gulder, T. A. M.; Lang, G.; Schmitt, S.; Stöhr, R.; Wiese, J.; Nagel, K.; Imhoff, J. F. *Mar. Drugs* **2007**, *5*, 23–30.

The synthesis of phenol **7** began with the formylation of 2-methylresorcinol (**8**, Scheme 3). Sequential selective benzylation and methylation of the two hydroxyl groups was followed by exhaustive hydrogenolysis to afford phenol **7**. Oxidative dearomatization proceeded smoothly to give quinol **6**. While the direct treatment of the phenol with $PhI(OAc)_2$ in aqueous acetonitrile could be used to form the quinol, higher yields were realized by first converting the phenol into the corresponding trimethylsilyl ether.[7]

Scheme 3. Building the Sorbicillactone Core[a]



[a] For more details, see Supporting Information.

After investigating several options for acylating quinol **6**, we determined that malonic acid monoesters were uniquely suited to this task. A malonate side chain would not only facilitate the construction of the C6−C9 bond and the installation of the C9 methyl group but also serve as a masked amine that could be revealed through a Curtius rearrangement sequence.

To this end, the coupling of quinol **6** with mono-*tert*-butyl malonate produced dienone **9**. Initial work employed conditions reported by Stork[8] for coupling a tertiary alcohol to a malonic ester using TFAA; however, we found DCC/DMAP to be more practical for larger scale work. Malonate **9** was then cyclized to bicyclic lactone **10** in the presence of Cs_2CO_3.[9] Although intermediate **10** could be isolated, it was more convenient to add MeI to the reaction mixture once the cyclization was complete. Initial work with this sequence allowed us to isolate lactone **11a** as a single diastereomer directly from quinol **6** with only a single purification.

(7) Felpin, F.-X. *Tetrahedron Lett.* **2007**, *48*, 409–412.
(8) Stork, G.; La Clair, J. J.; Spargo, P.; Nargund, R. P.; Totah, N. *J. Am. Chem. Soc.* **1996**, *118*, 5304–5305.
(9) Nicolaou has reported a similar cyclization of an acetate with the sorbyl chain present. See ref 2d.

Performing an NOE experiment allowed us to confirm the *cis*-fused ring system. Unfortunately, we did not observe an NOE between the C9 methyl group and the C5 methyl or C6 proton, which would be expected with the desired diastereomer (Figure 1). We then converted compound **11a** into amide **12**,[10] which afforded crystals suitable for X-ray analysis. This confirmed our suspicions that the C9 stereocenter in **11a** was indeed epimeric to the natural material.

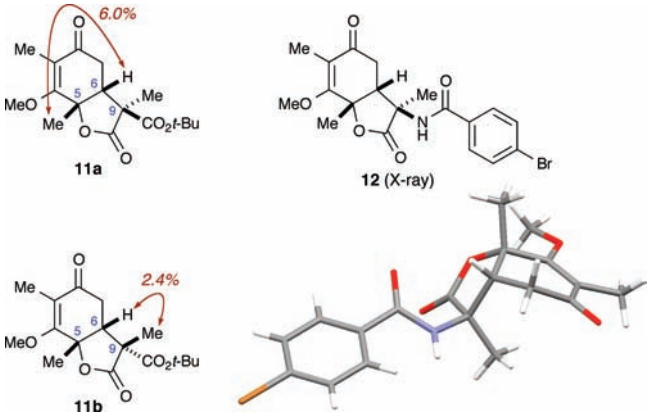
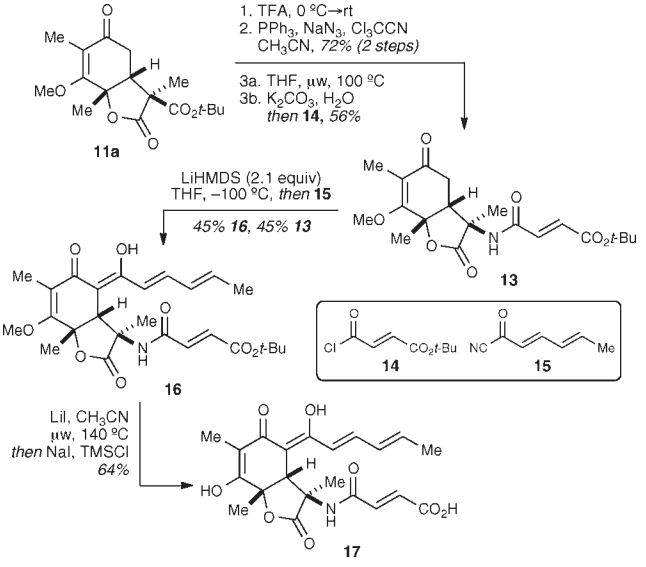


Figure 1. Observed NOEs (red lines) for the two diastereomers of **11** and X-ray of **12**.

Fortunately, when the conversion of **6** to **11** was run on a larger scale, we were able to isolate a minor component that we identified as diastereomer **11b**.[11] Gratifyingly, this compound did reveal an NOE interaction between the C9 methyl and the C6 proton. Although the diastereomeric ratio is unfavorable,[12] the concise and high-yielding route to this key intermediate has allowed us to perform the conversion of **6** to **11** on a multigram scale. In doing so, we have been able to isolate over 1 g of **11b**. Additionally, diastereomer **11a** proved to be a useful intermediate for developing the remaining synthetic steps and will provide access to 9-*epi*-sorbicillactone analogs, allowing us to compare their biological activity to the natural diastereomers.

The *tert*-butyl ester in **11a** was cleaved with TFA (Scheme 4), and the resulting carboxylic acid was converted directly to the corresponding acyl azide.[13] After experimenting with several methods for effecting the Curtius rearrangement, we determined that the optimal conditions were to simply heat a THF solution of the azide in a microwave reactor. Monitoring the reaction progress by IR spectroscopy confirmed the disappearance of the azide and the formation of the isocyanate. Hydrolysis was then followed by in situ acylation with fumarate **14** to provide amide **13**.

Scheme 4. Synthesis of 9-*epi*-Sorbicillactone A[a]



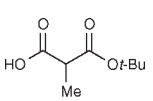
[a] For more details, see Supporting Information.

With amide **13** in hand, the remaining hurdle was the installation of the C1′ side chain. This task proved to be more challenging than initially anticipated. Unfortunately, employing standard reaction conditions (e.g., LDA or LiHMDS, −78 °C; acid chloride, aldehyde, or cyanoacetate) afforded only trace quantities of the desired product and decomposition of the starting material. We were able to remedy this problem by forming and reacting the enolate at −100 °C.[14] To our delight, this approach worked well and product **16** could be produced in an acceptable 45% yield along with 45% of recovered starting material.

With both side chains in place, all that remained was the cleavage of the methyl ether and the *tert*-butyl ester. Although treating **16** with NaI/TMSCl efficiently removed the *tert*-butyl ester, the methyl ether proved to be quite resistant to these conditions.[15] Various other acidic, basic, and nucleophilic conditions were attempted in order to realize this deprotection. Ultimately, we found that heating

(10) See Supporting Information for details.

(11) We also tried to alkylate malonate **10** by using NaH and MeI. Once again, diastereomer **11a** was isolated as the major product along with minor amounts of **11b**. Likewise, performing a similar acylation/cyclization with **A** also did not improve the diastereoselectivity.



A

(12) Myers and co-workers have observed a similar *endo* preference during the alkylation of bicyclic lactams. This was rationalized on stereoelectronic grounds and may involve an interaction between the developing σ^* orbital of the newly formed C−C bond and the lone pair of the lactam (in this case the lactone) in the transition state. See: (a) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509–2510. (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7429–7438 and references therein.

(13) Kim, J.-G.; Jang, D. O. *Synthesis* **2008**, 2072–2074.

(14) Franck, G.; Brödner, K.; Helmchen, G. *Org. Lett.* **2010**, *12*, 3886–3889.

(15) When **13** was treated with 4 equiv of TMSI, both the *tert*-butyl ester and the methyl ether were cleaved.

(16) (a) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840–8844. (b) Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc.* **2003**, *125*, 13022–13023.

a mixture of **16** and LiI in a microwave reactor cleanly effected the cleavage of the vinylogous methyl ester.[16] A one-pot deprotection of the *tert*-butyl ester was achieved by adding NaI and TMSCl. This afforded 9-*epi*-sorbicillactione A (**17**) in 12 overall steps from 2-methylresorcinol.[17]

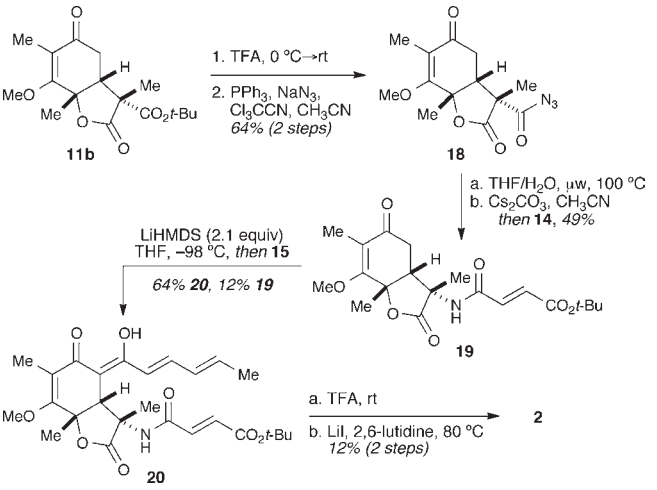
With a viable route to the complete sorbicillactone skeleton, we turned our attention to the conversion of lactone **11b** into the original synthetic target, sorbicillactone A (Scheme 5). Using similar conditions as those described above, we were able to convert the *tert*-butyl ester in **11b** into the acyl azide **18**. Curiously, attempts at using the above Curtius rearrangement conditions (THF, 100 °C, μw) with **18** were unreliable and produced unidentified polar reaction products that failed to react with fumarate **14**. Contrary to the *exo* isocyanate formed from **11a**, the *endo* isocyanate formed from **18** would likely be in close proximity to the vinylogous ester moiety. This may allow undesired side reactions to occur at high temperature in the absence of a suitable trap. To circumvent this problem, we used modified conditions in which acyl azide **18** was heated in a THF/H_2O mixture. This succeeded in producing the desired amine. The acylation of this amine to give amide **19** also proved to be much more sluggish than with the epimeric substrate. We were able to overcome this reactivity difference by extending the reaction times and using multiple additions of fumarate **14**.

The *C*-acylation of amide **19** proceeded smoothly to give **20**. We experienced considerable difficulties when attempting to deprotect compound **20**. Treating this compound with TFA or NaI/TMSCl cleanly revealed the carboxylic acid,[10] but all attempts at cleaving the methoxy group were accompanied by significant amounts of decomposition to as yet unidentified compounds. We made repeated attempts at purifying the product with both Sephadex LH-20 and reverse-phase chromatography but were unable to attain synthetic sorbicillactone A (**2**) in our usual standards of purity.[17] In contrast, 9-*epi*-sorbicillactone A (**17**) and the two protected compounds **16** and **20** proved to be stable and survived chromatographic purification. At this time, it is not clear why **2** is unstable to removing the methoxy group, but it may be related to the reactivity of the vinylogous acid and the close proximity of the endocyclic amide.

In conclusion, we have completed the first total synthesis of sorbicillactone A and 9-*epi*-sorbicillactone A. This concise 12-step route can produce gram quantities of the key intermediate **11** and is highly amenable to the synthesis of other analogs. We plan to use this strategy to further explore the structure–activity relationships of the sorbicillactones and to probe their mechanism of action. In addition to devising a solution to the diastereoselectivity observed during installation of the C9 stereocenter, we are also exploring methods to access enantiopure material. These results will be reported in due course.

(17) See Supporting Information for a comparison of the ^{1}H NMR spectra of natural sorbicillactone A (**2**), synthetic **2**, and 9-*epi*-sorbicillactone A (**17**).

Scheme 5. Synthesis of Sorbicillactone A[a]



[a] For more details, see Supporting Information.

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Supporting Information Available. Experimental procedures and spectral information are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. This article was published ASAP on July 29, 2011. A correction has been made to the text in paragraph three. The corrected version was posted on August 2, 2011.