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First Total Synthesis of Epicoccarine A via *O*- to *C*-Acyl Rearrangement Strategy

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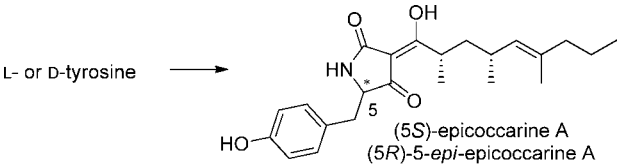
ABSTRACT



The first total synthesis of antibacterial epicoccarine A isolated from a fungus *Epicoccum* sp. has been accomplished in 10 steps along with synthetic elaboration of its C5-epimer, highlighting the utility of *O*- to *C*-acyl rearrangement of a 4-*O*-acyltetramic acid derivative. Comparison of spectroscopic properties and specific optical rotations of the synthetic samples with those reported for authentic material has clearly indicated the unspecified absolute stereochemistry of this natural product to be 5*S*.

Microorganisms associated with other organisms are a rich source of novel metabolites with unique and potent biological activities.[1] *Epicoccum* species are well-known widespread fungi of symbiotic microorganisms, and one constituent member of this family growing within the fruit body of the tree fungus *Pholiota squarrosa* has shown to produce structurally diverse compounds with intriguing biological activities, as exemplified in Figure 1 by epipyridone (antibacterial activity),[2a] epicoccalone (chymotrypsin inhibitory activity),[2b] epicoccamides A–D (cytotoxicity),[2c,d] and two types of epicoccarines. Epicoccarine A has been reported as a minor component of the metabolites isolated from this fungus and proved to be a more potent and selective antibacterial agent against Gram positive bacteria (*Mycobacterium vaccae*, MIC = 6.25 μg/mL) than epicoccarine B, making it a potential candidate as a new lead antibacterial agent. These two epicoccarines consist of a tyrosine-derived 3-acyltetramic acid core and a stereodefined alkenyl side chain, whose relative stereochemistry at the two stereogenic centers (C8 and C10) has been established as depicted in Figure 1.[2a]

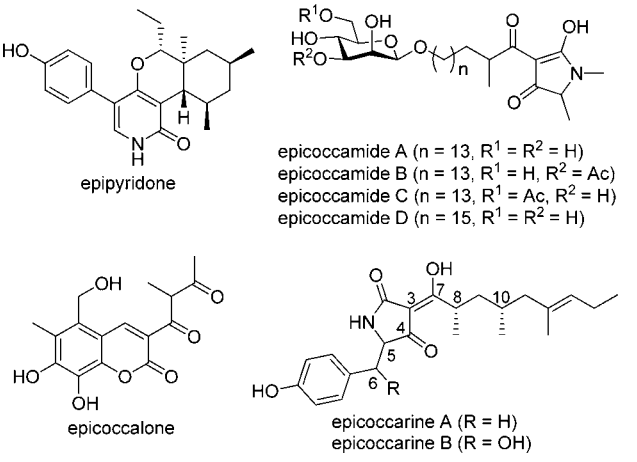


Figure 1. Structures of medicinally important isolates from *Epicoccum* sp.

Despite the simple structure and promising biological properties of epicoccarine A, synthetic elaboration of this natural product remains a significant challenge and, to our knowledge, no reports have appeared previously

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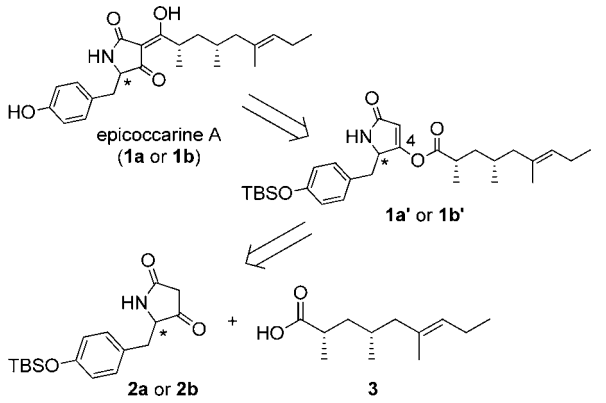
describing success in the completion of a total synthesis, possibly due to the fact that mild and efficient methods for manipulating chiral tetramate elements, without erosion of their optical quality, are limited. In this regard, a modified *O*- to *C*-acyl rearrangement of 4-*O*-acyl tetramates, in which metal salts such as calcium chloride are used to improve the reaction yield,[3] was developed to extend the carbon skeleta of C3-unsubstituted tetramic acids without loss of stereochemical integrity of the chiral tetramate systems. In addition to successful implementation of this method for the synthesis of two natural products,[3,4] the accumulated results from our experiments suggested that this approach would provide synthetic versatility for introduction of more chemically sensitive chiral segments into the tetramate systems. Thus, to test this possibility and demonstrate more general utility of our synthetic methodology, we set out to develop a stereocontrolled synthesis of epicoccarine A through a strategy involving a modified *O*- to *C*-acyl rearrangement. However, the target-directed synthesis was complicated by the lack of stereochemical knowledge of the C5 center on the tetramic acid core. Accordingly, the objective of this work was to synthesize the two possible candidates **1a** and **1b** from L- and D-tyrosine, respectively, employing an *O*- to *C*-acyl rearrangement strategy and to determine which C5-stereoisomer could be assigned to this natural product on the basis of spectroscopic evidence.

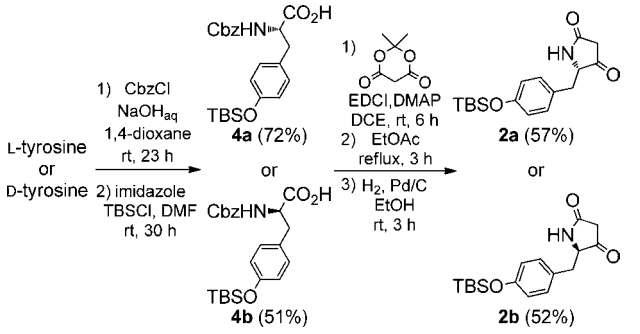
For the construction of **1a** and **1b**, we planned to use the retrosynthetic strategy outlined in Scheme 1, which would involve the modified *O*- to *C*-acyl rearrangement of **1a**′ and **1b**′ as key steps, respectively. We envisaged that these compounds could be prepared by introducing the alkenyl side chain onto the enolic oxygen at C4 positions of **2a** and **2b** through dehydration with the relevant chiral carboxylic acid **3**. The synthesis started with functional group protection of L- and D-tyrosines through sequential treatment with CbzCl and TBSCl (Scheme 2).[5] The reactions proceeded smoothly to furnish **4a** and **4b** in 72 and 51% yields respectively, which were then subjected to EDCI coupling with Meldrum's acid followed by thermal decarboxylation and concomitant cyclization to generate the corresponding Cbz-protected tetramic acids.[6] The Cbz groups of these substrates underwent facile deprotection upon hydrogenolysis in EtOH, using catalytic Pd/C, and both tetramic acids **2a** and **2b** were obtained in enantiomerically pure form in 57 and 52% yields over three steps, respectively.

Our next task was to perform an asymmetric synthesis of **3**, which would be achieved using Oppolzer's *N*-propionylsultam **5** as a chiral source (Scheme 3).[7] Indeed,

Scheme 1. Retrosynthetic Analysis of Epicoccarine A



Scheme 2. Synthesis of **2a** and **2b**



alkylation of **5** with (*E*)-1-bromo-2-methyl-2-pentene[8] using NaHMDS and HMPA led to extremely high stereochemical control, giving rise to **6** in 69% yield as a single stereoisomer. The chiral substituent of this product was removed by treatment with $LiEt_3BH$ in THF to provide the alkenyl alcohol, which was then converted via the Appel reaction[9] to the corresponding iodide **7** in 81% yield in two steps. Next, we attempted carbon chain elongation of **7** by the Evans protocol[10] to obtain alkenyl amide **8**, in which the absolute configuration at the C2 stereocenter should be *S*. Accordingly, the alkenyl chain end of **7** was elongated with D-prolinol *N*-propionamide using LDA and HMPA at elevated temperatures (from −100 to −40 °C) to afford **8** in 45% yield, in diastereomerically enriched form, as a 94:6 mixture of 2*S*- and 2*R*-diastereomers as determined by the ^1H NMR. Then, we examined acidic hydrolysis of this product to gain direct access to **3**. Exposure to 1 N aqueous HCl at 80 °C in 1,4-dioxane solution was problematic, with carbon−carbon double bond isomerization occurring during the conversion, resulting in the formation of complex mixtures of olefinic

(3) For a detailed investigation on the modified *O*- to *C*-acyl rearrangement and total synthesis of penicillenol A_2, see: Sengoku, T.; Nagae, Y.; Ujihara, Y.; Takahashi, M.; Yoda, H. *J. Org. Chem.* **2012**, *77*, 4391.

(4) For a total synthesis of penicillenol A_1, see: Sengoku, T.; Wierzejska, J.; Takahashi, M.; Yoda, H. *Synlett* **2010**, 2944.

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(9) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.

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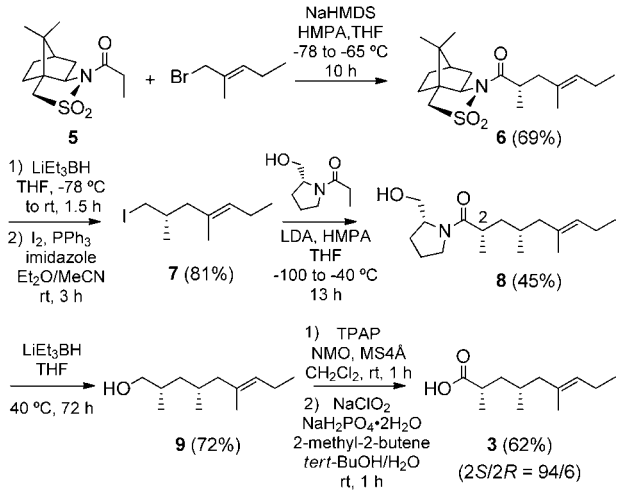
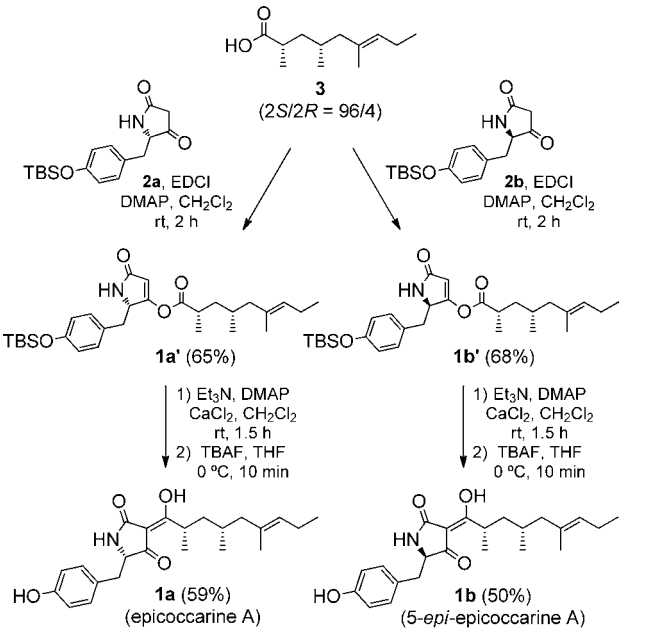
isomers. Due to the loss of structural integrity, we next explored a different route to **3**. As in the case of **6**, the chiral substituent of **8** underwent slow reduction upon treatment with 7.5 equiv of $LiEt_3BH$ at 40 °C for 3 days to afford the desired alkenyl alcohol **9** in 72% yield as a regiochemically and geometrically single isomer.[11] Conversion of **9** to **3** was achieved via two sequential oxidation processes using TPAP[12] and $NaClO_2$,[13] which provided the desired carboxylic acid in 62% yield in two steps without loss of stereochemistry.

Scheme 3. Synthesis of **3**



Having succeeded in the efficient stereocontrolled syntheses of **2** and **3**, we turned our attention to their condensation and subsequent elaboration into epicoccarine A and its C5-epimer (Scheme 4). The initial esterification of **3** of a 94:6 mixture of 2*S*- and 2*R*-diastereomers was conducted individually with **2a** and **2b** using EDCI and DMAP to afford the respective *O*-acyl tetramates. Fortunately, both products could be purified by means of silica gel column chromatography to yield **1a**′ and **1b**′ as enantiomerically pure materials in 65 and 68% yields, respectively. In the final stages of the total synthesis, **1a**′ and **1b**′ were subjected to the *O*- to *C*-acyl rearrangement reactions, which can be facilitated by addition of metal salts.[3] We found that calcium chloride markedly effected the reactions of these substrates in CH_2Cl_2 at room temperature, in the presence of Et_3N and DMAP, to form the respective 3-acyltetramic acids without epimerization of the C5 stereogenic center.[3,4] Finally, the TBS protective groups of these products could be removed by treatment with TBAF to accomplish the

Scheme 4. Completion of Total Synthesis of **1a** and **1b**



first synthesis of L- and D-tyrosine-derived epicoccarines **1a** and **1b** in 59 and 50% yields in two steps, respectively. The purity of these products was established by elemental analysis and other characterization means, which proved to be in good agreement with the expectations.

Figure 2 depicts the δ 2.5−3.4 ppm region of the 300 MHz ^{1}H NMR spectra for **1a** and **1b** in $CDCl_3$. As anticipated from earlier observations, where various types of 3-acyltetramic acids spontaneously equilibrate to mixtures of the keto and enol tautomers on the time scale of NMR experiments,[14] these materials underwent valence tautomerization at room temperature in $CDCl_3$ to result in geometric isomerization at the C3,7-double bonds to 82:18 mixtures of *Z*- and *E*-enol tautomers (Figure 3). Remarkably, the spectral shape observed for **1a** perfectly matched that given in the literature,[2a] where relative signal intensities of each enol tautomer are entirely consistent with the reported data. On the other hand, **1b** showed noticeable differences in chemical shift values for the protons at the C6 position (H6 and H6′) of the *Z*-enol tautomer. Indeed, the H6 resonances were significantly shifted upfield from δ 3.19 to 3.17 ppm, while the H6′ proton exhibited a pronounced downfield shift from δ 2.66 to 2.68 ppm.[15] From these observations, it is evident that **1a** can be assigned as natural epicoccarine A and **1b**

(11) In this case, carbon−carbon double bond isomerization did not occur as indicated by a simple ^{1}H NMR spectrum of **9**. Additionally, the 1,3-*cis* configuration of **9** was confirmed by the ^{1}H NMR analysis, revealing that the chemical shifts for the methine protons at the C2 and C4 positions closely resemble those of a related molecular system; see: Boeckman, R. K., Jr.; Pero, J. E.; Boehmler, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 11032.

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(15) Larger differences in the chemical shift values were observed for the *E*-enol tautomer of **1b**, where the resonances attributed to H6 and H6′ protons were shifted from δ 3.16 to 3.20 ppm and from δ 2.75 to 2.67 ppm, respectively.

(16) In the ^{13}C NMR spectra, no significant difference that allowed us to distinguish between **1a** and **1b** was observed.

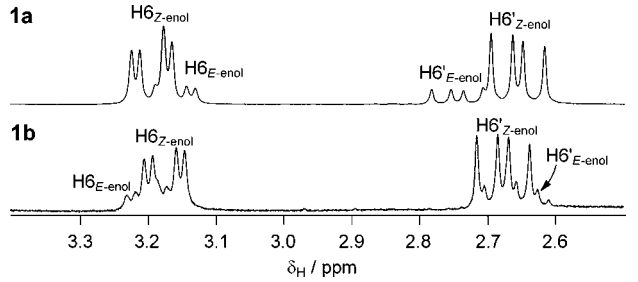

Figure 2. Comparison of ^{1}H NMR spectra on H6 and H6′ of **1a** and **1b** (300 MHz, $CDCl_3$, rt).

should be its C5-epimer.[16] The above structural assignments to the synthetic samples were further secured by comparable analyses of specific optical rotations measured in MeOH solution according to the reference ($[\alpha]_D^{25}$ −45.8 for natural epicoccarine A, *c* 0.15).[2a] In fact, **1a** was found to exhibit an optical rotation of $[\alpha]_D^{26}$ −161.8 (*c* 0.15, MeOH). Although it was of the same sign, it had an unexpectedly large magnitude in comparison to the reported value, whereas **1b** showed an opposite optical rotation of $[\alpha]_D^{21}$ +97.5 (*c* 0.15, MeOH). Considering the chemical integrity of the synthetic products, ensured by a range of analytical experiments, the observed difference in absolute values between the optical rotation of **1a** and that reported in the literature may be possibly due to low purity of the extracted sample obtained from the natural source, which would cause significant underestimation of its own chiral properties.[17,18] Nevertheless, it was advisable at this stage to determine the absolute stereochemistry on the basis of comparison of the signs of the measured optical rotations, since the signs for **1a** and **1b** were distinguishable from each other. The agreement of the sign for **1a** with that for the naturally occurring material provides definitive support for the assignments mentioned above.

(17) In view of the ^{1}H NMR spectrum reported in the literature, we found unassignable signals that would be attributed to residual impurities included in the extractive sample; see ref 2a.

(18) The difference in optical rotation might be due to the conditions of the samples, such as sodium salt, in strong acids as in the case of tetramic acids. The synthetic samples are sure to be free acids from the elemental analysis. However, that of the natural product was not reported.

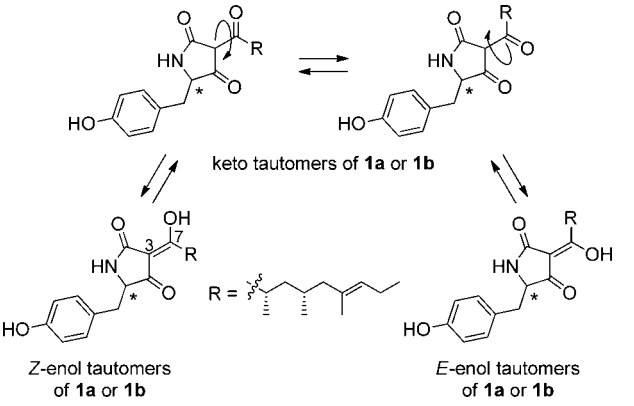

Figure 3. Geometric isomerization of **1a** and **1b**.

In conclusion, we have successfully achieved the first total synthesis of antibacterial epicoccarine A and its C5-epimer through a longest linear sequence of 10 steps. The syntheses proceed in 4.3 and 3.8% overall yields from **5**, respectively. The work allowed the unspecified absolute stereochemistry of this natural product to be assigned as 5*S*, with convincing evidence furnished by comparison of the spectroscopic properties and the specific optical rotations. The strategy used an *O*- to *C*-acyl rearrangement to complete the total synthesis. This serves as a mild and efficient method for preparing 3-acyltetramic acids with highly labile alkenyl side chains, without loss of structural and stereochemical quality. Further extension of this *O*- to *C*-acyl rearrangement strategy in the synthesis of various other 3-acyltetramic acid-type of natural products will be the subject of future work.

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Supporting Information Available. Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.