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Stereoselective Synthesis of the Epicoccin Core

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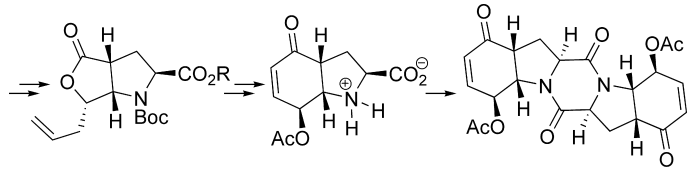
ABSTRACT



A short, convergent, and asymmetric synthesis of the epicoccin core was achieved using a phosphite-promoted one-step condensation of a complex proline-type amino acid. Key features of the assembly of this amino acid were a double-bond isomerization/vinylation/ring-closing metathesis strategy as well as an efficient, highly diastereoselective [2 + 2] cycloaddition of a ketene to an enecarbamate, derived from L-pyroglutamic acid.

The epicoccins are members of a large group of structurally complex fungal metabolites containing thiodiketopiperazine subunits, all exhibiting interesting biological activities. Within this group, epicoccins A−D (**1**) have been isolated in 2007 from a cordyceps-colonizing isolate of epicoccum nigrum by Liu et al. (Figure 1).[1,2] After preliminary studies, epicoccin A (**1a**) showed modest antimicrobial activities.[1]

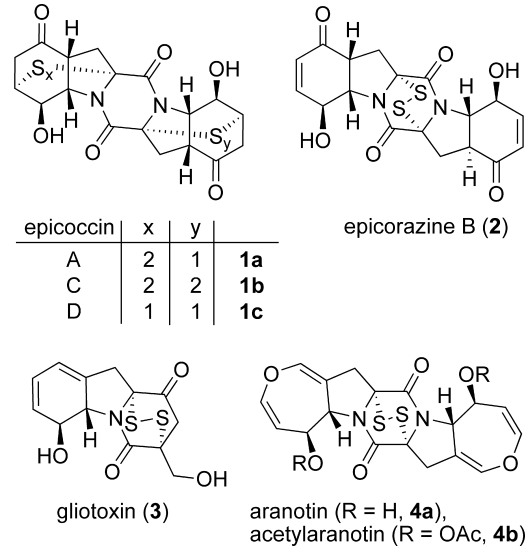


Figure 1. Some polycyclic thiodiketopiperazines.

Other members of this group of very closely related compounds include the well-known gliotoxin (**3**),[3] the

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(3) (a) Weindling, R.; Emerson, O. *Phytopath.* **1936**, *26*, 1068–1070. (b) Johnson, J. R.; Bruce, F. W.; Dutcher, J. D. *J. Am. Chem. Soc.* **1943**, *65*, 2005–2009. (c) Miller, P. A.; Milstrey, K. P.; Trown, P. W. *Science* **1968**, *159*, 431–432. (d) Rightsel, W. A.; Schneider, H. G.; Sloan, B. L.; Graf, P. R.; Miller, F. A.; Bartz, Q. R.; Ehrlich, J.; Dixon, G. J. *Nature* **1964**, *204*, 1333–1334.
(4) (a) Neuss, N.; Boeck, L. D.; Brannon, D. R.; Cline, J. C.; DeLong, D. C.; Gorman, M.; Huckstep, L. L.; Lively, D. H.; Mabe, J.; Marsh, M. M.; Molloy, B. B.; Bagarajan, R.; Nelson, J. D.; Stark, W. M. *Antimicrob. Agents Chemother.* **1968**, *8*, 213–219. (b) Delong, D. C.; Lively, D. H.; Neuss, N. U.S. Patent 3 907 988, 23. sept. 1975. (c) Miller, P. A.; Nyack, W.; Trown, P. W. U.S. Patent 3 701 774, 31. oct. 1972. (d) Trown, P. W.; Lindh, H. F.; Milstrey, K. P.; Gallo, V. M.; Mayberry, B. R.; Lindsay, H. L.; Miller, P. A. *Antimicrob. Agents Chemother.* **1986**, *8*, 225–228. (e) Murdock, K. C. *J. Med. Chem.* **1974**, *17*, 827–835.
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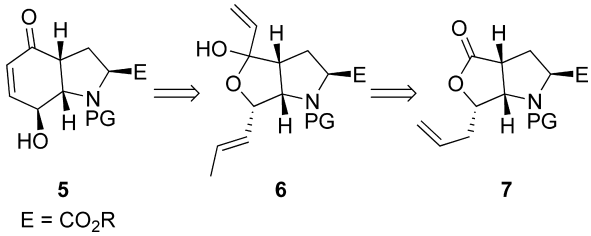
aranotin family (**4**),[4] as well as epicorazine B (**2**).[5] They bear the same absolute configuration in their monomer structure. All of these substances are mycotoxins, exhibiting important biological characteristics such as activities against viruses,[3,4] fungi,[3] and bacteria.[3,5] Their complex structures and important biological activities clearly mark them as important synthetic targets. However, to the best of our knowledge, within the large class of thiodiketopiperazine natural products, only gliotoxin (**3**)[6] and (+)-11,11′-dideoxyverticillin A[7] have been reached by total synthesis so far.

We report here the synthesis of the epicoccin scaffold, in which we use a new stereoselective approach to azabicyclic cyclohexenones. Our route to the cyclohexenone structure involves a ring-closing metathesis reaction of an intermediate lactol **6**, generated by isomerization of a terminal double bond in lactone **7** and subsequent vinylation (Scheme 1).

Scheme 1. Retrosynthetic Analysis of the Bicyclic System **5**

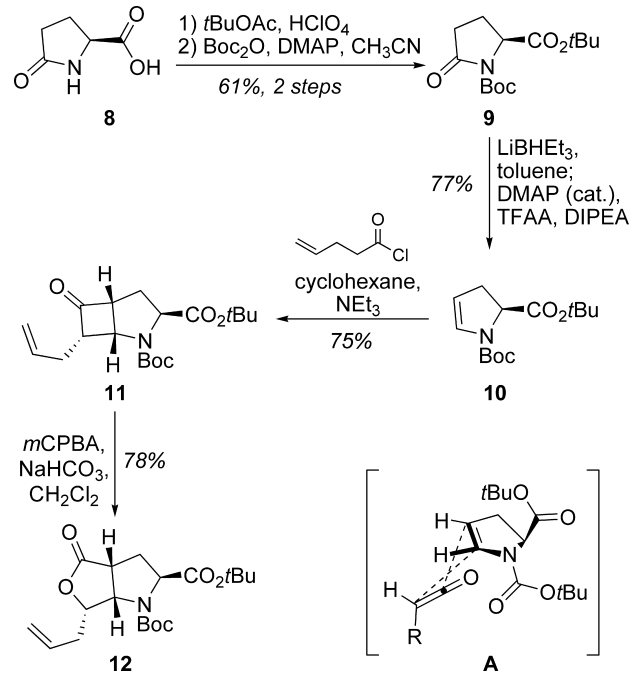


The final diketopiperazine unit was built through a one-step phosphite-promoted coupling of two identical proline-type amino acids. This methodology, previously elaborated in our group,[8] has proved to be ideal for the synthesis of C_2-symmetrical and unsymmetrical diketopiperazines, thus enabling us to apply our results reported herein to the syntheses of gliotoxin (**3**) and epicorazine B (**2**) in the future.

As starting material for the synthesis of epicoccin, we used the inexpensive L-pyroglutamic acid (**8**), which was converted by conventional methods into the protected amino acid derivative **9** (Scheme 2).[9] The required enecarbamate **10**[10] was generated by reduction of the lactam carbamate **9** with Super-Hydride, followed by dehydration with TFAA (trifluoroacetic anhydride), Hünig base, and DMAP as catalyst.

It is noteworthy that by performing this sequence as a one-step procedure, instead of isolating the intermediate

Scheme 2. Synthesis of the Precursor **12**



aminal,[10b,11] the dehydration proceeds smoothly at room temperature and gave the enecarbamate **10** reliably in good yield.[12]

To build up the azabicyclic cyclobutanone scaffold **11**, we used a method previously reported by Valle et al.[13,10b]

The enecarbamate **10** was submitted to a [2 + 2] cycloaddition with an allylketene, in situ generated from the corresponding pent-4-enoyl chloride and triethylamine. The *endo*-cycloadduct **11** was isolated as single diastereoisomer in 75% yield. The relative configuration could be proven by NOESY experiments and was consistent with observations reported by Valle et al. for similar substrates. The obtained stereoselectivity can be explained by a preferred *endo*-approach of the ketene from the less hindered side of the enecarbamate **10** and pointing its substituent in the opposite direction of the ring (**A**, Scheme 2).[13]

The intermediate cyclobutanone **11** was subsequently converted into lactone **12** by a completely regioselective Baeyer−Villiger oxidation.[10b,13] It is noteworthy that the terminal double bond is not oxidized under these conditions.

The allylic side chain of lactone **12** was then successfully isomerized (Scheme 3) under ruthenium hydride catalysis, the active species being generated from Grubbs II catalyst[14]

(6) Fukuyama, T.; Nakatsuka, S.-I.; Kishi, Y. *Tetrahedron* **1981**, *37*, 2045–2078.
(7) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238–241.
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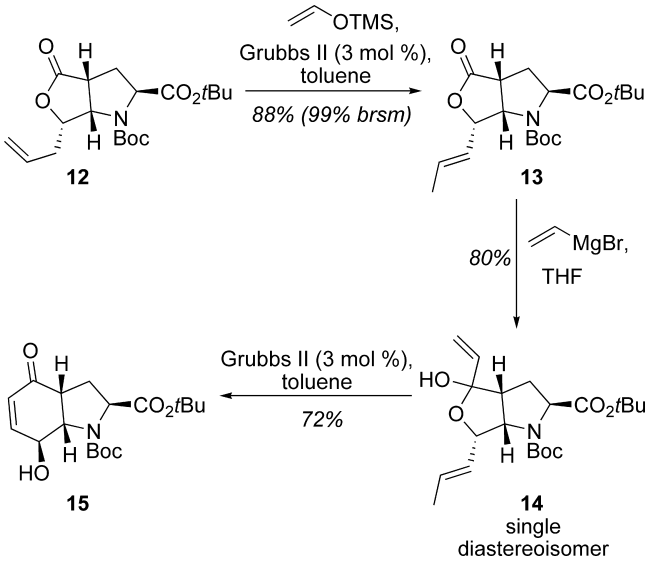
Scheme 3. Metathesis Sequence to Yield **15**



and stoichiometric amounts of vinyloxytrimethylsilane.[15] The desired product **13** was isolated in 85% yield, exclusively in (*E*)-configuration. Addition of vinyl-Grignard reagent gave lactol **14** in good yield as one diastereoisomer (with unknown configuration at the lactol center). Gratifyingly, subsequent ring-closing metathesis[16] underwent smoothly with Grubbs II catalyst to the corresponding azabicyclic cyclohexenone **15** in good yield. The absolute configuration of the cyclohexenone **15** could be proven by crystal structure (Figure 2).[17]

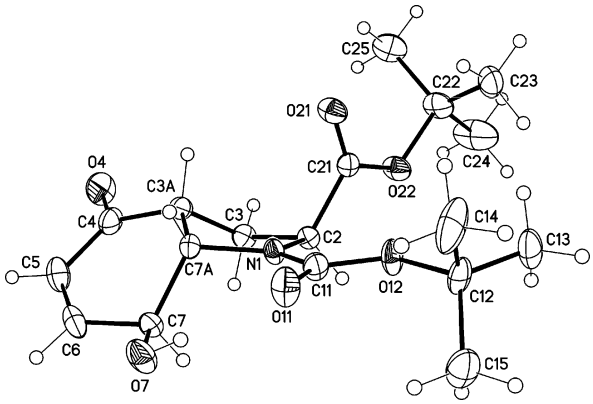
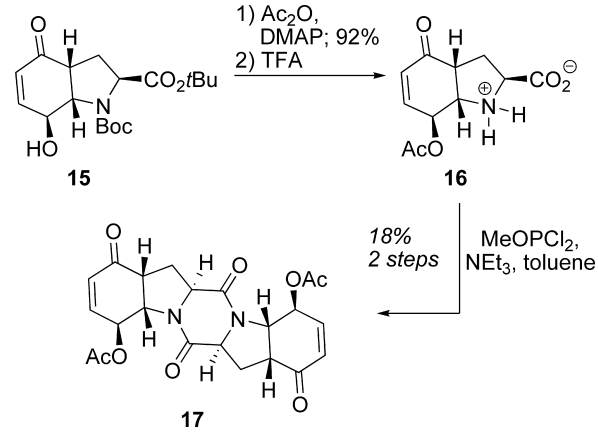


Figure 2. Molecular structure of **15** (displacement parameters are drawn at 50% probability level).

This vinylation/RCM-sequence represents — to the best of our knowledge — a new methodology to generate highly substituted annelated cyclohexenones.[16]

The hydroxy function was protected as acetate in almost quantitative yield, and the free amino acid as betain **16** was generated in neat TFA (Scheme 4). The crude material was

Scheme 4. Final Assembly of the Epicoccin Core **17**



then submitted to our dimerization conditions.[8] With triethylamine and the phosphite reagent in refluxing toluene, the desired diketopiperazine **17** could be isolated in 18% yield[18] over two steps as a single diastereoisomer **17**, representing a dethio-analogue of the epicoccin family **1**. Thus, these results showed for the first time that the reported dimerization method is also suitable for highly complex proline-type amino acids.

In summary, we have developed a short and stereoselective route to the core of epicoccin that involves a new method to generate highly substituted cyclohexenones. The scaffold was synthesized by a diastereoselective [2 + 2] cycloaddition of an allylketene to an enecarbamate, itself deriving from the chiral pool. Lactone **12** also represents a key intermediate in our synthetic strategy to aranotin (**4a**) and the epicorazines such as **2** which will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral characterization for compounds **8**−**17**, and crystallographic data for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For related RCM to generate cyclohexenones: Boiteau, J.-G.; Van de Weghe, P.; Eustache, J. *Org. Lett* **2001**, *3*, 2737–2740. (b) Rodeschini, V.; Boiteau, J.-G.; Van de Weghe, P.; Tarnus, C.; Eustache, J. *J. Org. Chem.* **2004**, *69*, 357–373.

(17) Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 743718 (**15**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (Fax: int.code+(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

(18) The low yield in the dimerization reaction can probably be attributed to a low conversion of the starting material, whose reisolation is impossible due to the high polarity of the free amino acid. Filtration of the crude reaction mixture through a pad of silica furnishes the diketopiperazine as essentially pure product; no byproducts can be observed.