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COMMUNICATION

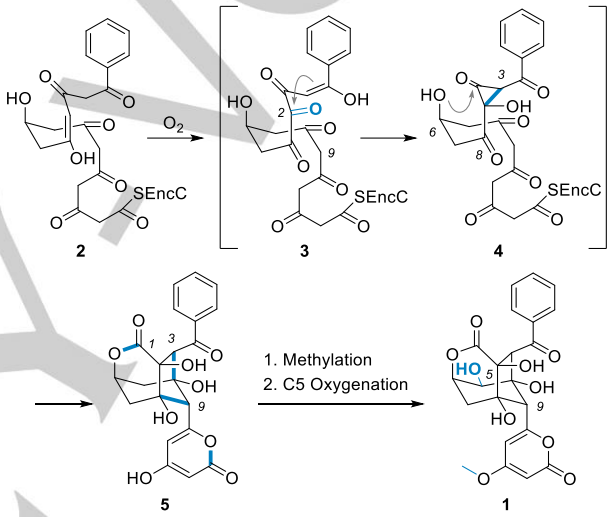
Biomimetic Total Synthesis of Enterocin

Lilla Koser, Vivian Miles Lechner, and Thorsten Bach*

In memory of Klaus Hafner

Abstract: The first chemical total synthesis of the highly oxygenated polyketide enterocin has been accomplished. The key step of the synthesis was a late-stage biomimetic reaction cascade involving two intramolecular aldol reactions in which each step proceeded in 52% yield (averaged) and which established four of the seven stereogenic centers. The pivotal precursor for the cascade reaction was assembled from three readily available building blocks. A chiral dithioacetal with two stereogenic centers originating from L-arabinose represented the core fragment to both ends of which the other building blocks were attached by aldol reactions. The remaining stereogenic center was installed by Davis oxygenation immediately prior to the key step.

Enterocin (**1**, Scheme 1) is a polyketide natural product, the structure of which was first described in independent reports by the groups of Miyairi[1] and Seto.[2] The former group isolated the compound from *Streptomyces candidus* var. *enterostaticus* WS-8096 and from variant M-127 of *Streptomyces viridochromogenes.* The latter group, who originally named the natural product vulgamycin, reported its production by *Streptomyces hygroscopicus* No A-5294. Subsequently, the metabolite was isolated from other biological sources, including several marine-derived *Streptomyces* strains[3] and a marine ascidian of the genus *Didemnum*.[4] While the biological activity of enterocin remains to be comprehensively studied,[2,3a,3e] the biosynthesis of enterocin has been successfully unraveled. Moore and co-workers cloned and sequenced the gene cluster that is responsible for the production of not only enterocin, but also related natural products, including the wailupemycins.[5] The biosynthesis commences with the assembly of an octaketide by a type II polyketide synthase (PKS).[6] In this instance, benzoic acid serves as the bacterial PKS starter unit,[7] to which seven acetyl units stemming from malonyl-CoA (CoA = coenzyme A) are successively attached. Selective reduction of one keto group by a ketoreductase (EncD) during elongation[8] generates dihydrooctaketide **2**. The most notable feature of the biosynthesis is a Favorskii-type rearrangement, which leads to a disruption of the typical 1,3-difunctionality present in polyketides.[2,9] Oxygenation of one methylene group by the bacterial flavoenzyme EncM[10] generates triketone **3**, which undergoes the rearrangement *via* intermediate cyclopropanone **4**. The latter is trapped by the oxygen atom of the C6 alcohol to a δ-lactone with subsequent formation of two C–C single bonds (C3–C4 and C8–C9) by aldol reactions and of the α-pyrone ring by lactonization. Methylation of the free pyrone hydroxy group in intermediate **5** generates 5-deoxyenterocin, which has been isolated as a minor metabolite from typical producers of enterocin.[3b,3c,4] The biosynthesis is concluded by selective oxygenation at C5 mediated by a cytochrome P-450 hydroxylase (EncR).



Scheme 1. Biosynthetic pathway from dihydrooctaketide **2** (EncC = enoyl-CoA carrier protein) to enterocin (**1**).[5-11] Oxygenation at position C2 (enterocin numbering) initiates a Favorskii-type rearrangement which proceeds *via* cyclopropanone **4** to precursor **5** of the natural product: Two aldol reactions establish the key bonds C3–C4 and C8–C9 of the tricyclic skeleton.

Despite the elegance and brevity of its biosynthesis, enterocin has not yet surrendered to chemical total synthesis.[11] The highly oxygenated tricyclic core structure poses an extraordinary challenge regarding the selective, sequential introduction of functional groups and their compatibility. A few synthetic studies exist: Flores-Parra and Khuong-Huu showed that an early precursor with the 2-oxabicyclo[3.3.1]nonane core of enterocin could be prepared from quinic acid, but further steps towards the natural product were not reported.[12] Hong and Chin probed, with limited success, a McMurry-type coupling to construct the bridgehead dihydroxybicyclo[3.2.1]octane skeleton.[13] The Trauner group synthesized an intermediate with the required 2-oxabicyclo-[3.3.1]nonane skeleton of the natural product. However, the compound lacked the benzoyl and lactone carbonyl groups and displayed the α-pyrone part as the undesired epimer at C9.[14] In an alternative approach, they successfully prepared an acyclic precursor to 5-deoxyenterocin, but the envisaged biomimetic lactonization and aldol reactions remained futile.[15] Based on our earlier work on the total synthesis of wailupemycin B,[16] we have been interested in the total synthesis of enterocin for some

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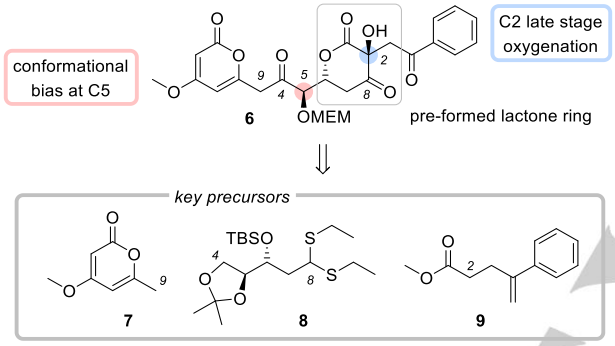
time.[17] One strategy we have pursued revolves around biomimetic aldol reactions, particularly in view of the fact that bond formation at C3–C4 and C8–C9 allows for immediate access to the highly oxygenated natural product. We now report the successful implementation of this concept, which culminated in the first total synthesis of enterocin.

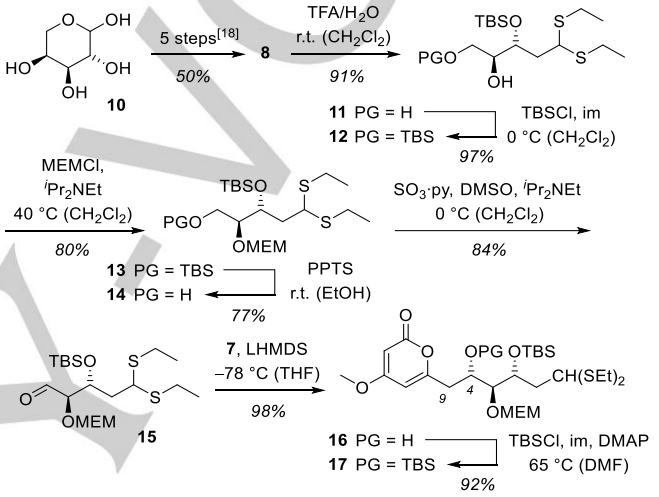
Although Nature beautifully masters the combination of lactonization to the δ-lactone ring with the pivotal aldol reactions, we hypothesized that this process might be too challenging entropically and we rather focused on the synthesis of a precursor with an intact δ-lactone ring. In this precursor, we additionally intended to install a protected hydroxy group at position C5 with the correct relative configuration, reasoning that, by adopting an equatorial position, this would favor the necessary pre-orientation in the six-membered transition state required to form the C8–C9 bond. Compound **6** evolved from these considerations as an ideal precursor for the aldol cascade (Scheme 2).



Scheme 2. Retrosynthetic disconnection and key features of the pivotal intermediate **6** (numbering as for enterocin) for a two-fold biomimetic aldol reaction (MEM = 2-methoxyethoxymethyl, TBS = *tert*-butyldimethylsilyl). Top: The pre-formed lactone ring and the conformational bias invoked by the stereogenic center at C5 should favor the cyclization (C8–C9 bond formation). The correct oxidation states at carbon atoms C2 and C4 were envisaged to be generated in the final steps in the synthesis of compound **6**. Bottom: Three components **7**-**9** comprise all carbon atoms required for the assembly of enterocin.

The 2-methoxyethoxymethyl (MEM) group was chosen as a protecting group at the C5 alcohol, which was to be removed after the projected aldol reactions. Since the highly oxygenated lactone fragment had previously been found to be capricious,[17b] we planned to install the hydroxy group at C2 in a late stage of the synthesis before establishing the required ketone functionality at C4. Further retrosynthetic analysis led to three key precursors **7**-**9**, which would combine the 22 carbon atoms of enterocin in a convergent fashion. The core fragment **8** is a known compound[18] which is readily accessible from L-arabinose (*vide infra*) and displays the two stereogenic centers at carbon atom C5 and C6 with the required relative configuration. Similarly, the other two building blocks **7**[19] and **9**[20] are also known and readily prepared in a few steps.

Following the plan outlined above, the synthesis of enterocin commenced with the preparation of dithioacetal **8** from L-arabinose (**10**, Scheme 3). The reported procedure[18] was optimized so that only a single chromatographic purification was required after the final step of the sequence. Initial attempts to retain the acetonide protecting group and install the oxygenated lactone moiety of compound **6** were not successful. Instead, we decided to cleave the acetonide under mild conditions,[21] which furnished 1,2-diol **11**. The primary alcohol was temporarily TBS-protected and the secondary alcohol **12** was converted into its MEM ether **13**.[22] Selective deprotection of the primary silyl ether was achieved by treatment with pyridinium *para*-toluenesulfonate (PPTS) in ethanol.[23] Careful product monitoring was required to avoid two-fold deprotection to the undesired 1,3-diol. Oxidation of primary alcohol **14** to aldehyde **15** was performed under Parikh-Doering conditions,[24] thus avoiding any undesired oxidation of the dithioacetal.



Scheme 3. Synthesis of the left-hand fragment **17** of enterocin from L-arabinose (**10**): An aldol addition of methoxypyrone **7** to aldehyde **15** establishes the C–C bond at positions C4 and C9 [TFA = trifluoroacetic acid, PG = protecting group, im = imidazole, PPTS = pyridinium *para*-toluenesulfonate, py = pyridine, LHDMS = lithium hexamethyldisilazide, DMAP = 4-(*N*,*N*-dimethylamino)pyridine].

The aldol-type addition of deprotonated methyl pyrone **7** to aldehyde **15** proceeded with remarkable diastereoselectivity, delivering the desired alcohol **16** essentially as a single diastereoisomer (diastereomeric ratio = d.r. = 95/5) at the newly generated stereogenic center C4. Although its configuration was inconsequential for the further course of the synthesis, the alcohol was shown to be (*S*)-configured by Mosher analysis.[25] The facial diastereoselectivity is thus governed by a Felkin-Anh- or Cornforth-controlled addition of the carbon nucleophile to the carbonyl carbon atom.[26] The steric hindrance around the newly formed secondary alcohol was reflected in the relatively harsh conditions required for its TBS protection. Strategically, the presence of two TBS protecting groups was considered ideal because in the diol resulting from their simultaneous removal, only the C6 hydroxy group would be competent to form the desired δ-lactone; we would thus eschew a separate deprotection step for the C4 alcohol.

Having withstood a remarkable array of reactions, the dithioacetal group in compound **17** was to be removed to liberate an aldehyde group at the future carbon atom C8. Iodine-mediated oxidative cleavage[18c] transpired to be a fortuitous choice, delivering the unstable aldehyde **18** in high yield (Scheme 4). The ensuing aldol addition to aldehyde **18** involved ester **9** as the nucleophile, which

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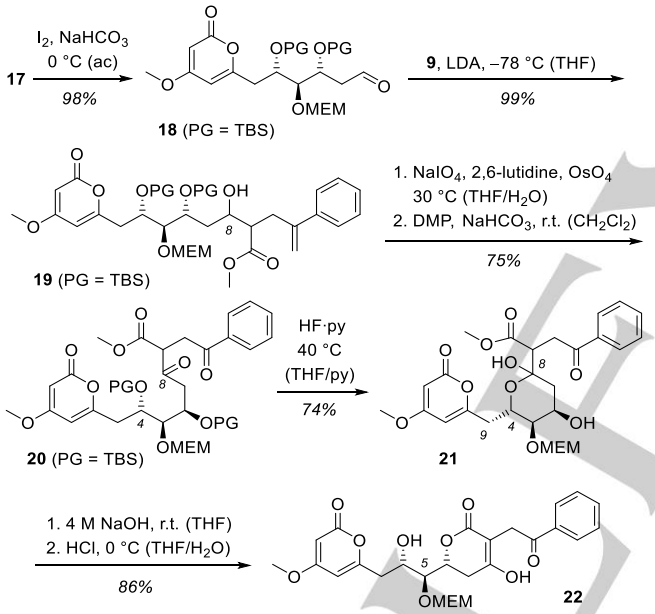
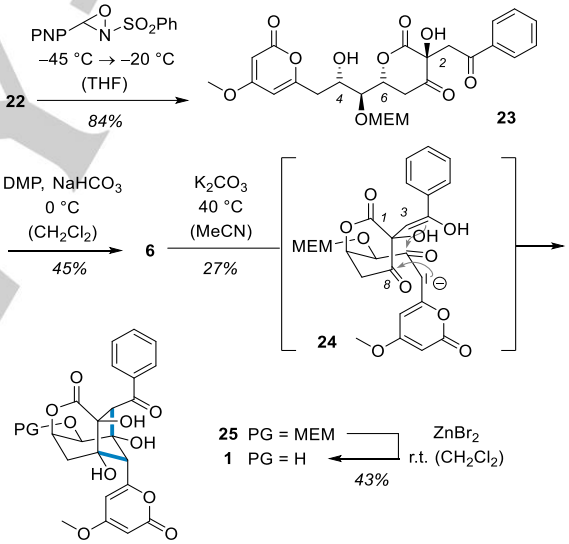
was preferably deprotonated with lithium diisopropylamide (LDA) but not with LHMDS. In the former case, the reaction proceeded in near quantitative yield while in the latter case an unidentified side product precluded the isolation of aldol product **19** in pure form. Expectedly, there was no significant facial or simple diastereoselectivity, which is why all four diastereoisomers of product **19** were formed (d.r. = 38/36/14/12). Since both stereogenic centers are irrelevant for the further course of the synthesis, no attempts were made to investigate the selectivity more closely. From compound **19**, oxidative cleavage of the terminal double bond was performed under Lemieux-Johnson conditions[27] and the alcohol at position C8 was oxidized to ketone **20** with Dess-Martin periodinane.[28] To our surprise, deprotection of the two silyl ethers at C4 and C6 did not lead to the desired δ-lactone but rather to hemiacetal **21**. Closer inspection of this compound revealed that acetal formation had occurred by O–C bond formation between the oxygen atom at C4 and the C8 carbonyl carbon atom. The facile ring closure corroborated our expectation that a substituent adjacent to carbon C4 can cyclize to a six-membered ring by attack at the carbonyl group (*vide supra*).



Scheme 4. Assembly of the lactone precursor **21** of enterocin by an aldol reaction of ester **9** to aldehyde **18** and subsequent functional group manipulations (DMP = Dess-Martin periodinane). Formation of hemiacetal **21** was a first indication that the substituent at carbon atom C4 can intramolecularly attack the C8 carbonyl group.

required to be compatible with the existing functional groups. Attempts to introduce the desired hydroxy group at position C2 of ketolactone **22** commenced with the standard Davis protocol[29] employing a base and 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine as the oxygen donor. Yields remained mediocre (ca. 50%) even when the more reactive 2-*para*-nitrophenyl (PNP) derivative[30] was used. Eventually, it turned out that the reaction was most efficient in the absence of base, delivering the desired product **23** in high yield with perfect diastereoselectivity. The configuration of the newly generated stereogenic center at C2 was corroborated by NOESY studies (DMSO-d_6, 300 K): The compound exists in a boat conformation[17b] and there is an NOE contact between the hydroxy proton at C2 and the proton at C6. The subsequent oxidation of the alcohol at C4 to the desired cyclization precursor proved to be even more challenging than the oxygenation. Only Dess-Martin conditions[28] enabled oxidation to the ketone; careful monitoring of the reaction conditions led us to use a slight excess of oxidant and to terminate the reaction after 2.5 hours. Product **6** initially escaped isolation due to its lability under even slightly acidic conditions, e.g. on silica gel, but eventually purification by semi-preparative, reversed-phase HPLC proved suitable. Ketone **6** was thus obtained in 45% yield, together with 5% of re-isolated substrate **23**.



Scheme 5. Conclusion of the total synthesis of enterocin (**1**). Oxidation at C2 occurs presumably via the enol of ketolactone **22**. After oxidation of alcohol **23**, the formation of product **25** was observed when storing a solution of ketone **6** at room temperature. The reaction was accelerated by treatment of ketone **6** with a mild base. For further details, see the narrative.

The undesired hemiacetal formation was smoothly corrected by saponification of the methyl ester at carbon atom C1. Upon acidification of the solution to pH 4, ring closure to the desired δ-lactone **22** occurred. The compound exists as a mixture of the depicted enol form and the respective ketone in $CDCl_3$ solution. In DMSO-d_6 at 300 K, only the enol form was detected by NMR spectroscopy.

Until this stage, the isolation of all compounds had been unproblematic but with the increasing density of oxygen functionalities, handling the products required greater care and optimization. Equally, any ensuing oxidative transformations were

The limited quantities obtained of ketone **6** have not yet allowed to screen a wide range of conditions for the projected cyclization. Gratifyingly, though, the desired cascade reaction was found to occur in acetonitrile as the solvent and was accelerated by a mild base. The best result thus far was achieved using potassium carbonate as the base, delivering the two-fold aldol addition product **25** in 27% yield. This seemingly low yield must be put into perspective, given that (a) the two sequential reactions are highly complex and (b) on average, each C–C bond formation occurs with a yield of 52%. It is likely that the base facilitates formation of anion **24** which initiates the first cyclization followed by the second aldol

reaction. An orange-colored side product was isolated in 21% yield, which was tentatively assigned as the product of oxidative degradation and condensation (see the SI for further details). In the final step, the removal of the MEM protective group was favorably performed in dichloromethane as the solvent, in which enterocin is not soluble. The compound thus precipitated during the deprotection reaction and could be isolated in pure form after semi-preparative, reversed phase HPLC purification. As some starting material was still detectable in the crude product, further optimization of the deprotection conditions is warranted. Synthetic enterocin (**1**) was shown by HPLC and NMR analysis to be, in all scalar properties, fully identical with the natural product.[31]

In summary, we have achieved the first chemical total synthesis of enterocin. The longest linear sequence starting from L-arabinose (**10**) comprises a total number of 22 steps (0.4% overall yield). The final three steps of the synthesis require further optimization, which should lead to an improved overall yield. Due to its modular synthetic scheme, substituent modification around the enterocin core should be readily possible and will be employed as a tool to study the biological relevance of this intriguing molecule in more detail.

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Keywords: aldol reaction · biomimetic synthesis · oxygenation · polyketides · total synthesis

[1] a) N. Miyairi, H. Sakai, T. Konomi, H. Imanaka, *J. Antibiot.* **1976**, *29*, 227-235; b) Y. Tokuma, N. Miyairi, Y. Morimoto, *J. Antibiot.* **1976**, *29*, 1114-1116.

[2] H. Seto, T. Sato, S. Urano, J. Uzawa, H. Yonehara, *Tetrahedron Lett.* **1976**, *17*, 4367-4370.

[3] a) P. Babczinski, M. Dorgerloh, A. Löbberding, H.-J. Santel, R. R. Schmidt, P. Schmitt, C. Wünsche, *Pestic. Sci.* **1991**, *33*, 439-446; b) N. Sitachitta, M. Gadepalli, B. S. Davidson, *Tetrahedron* **1996**, 52, 8073-8080; c) H. Liu, Z. Chen, G. Zhu, L. Wang, Y. Du, Y. Wang, W. Zhu, *Tetrahedron* **2017**, *73*, 5451-5455; d) L. Zheng, X. Jiang, Q. Zhang, Y. Zhu, H. Zhang, W. Zhang, K. Saurav, J. Liu, C. Zhang, *Org. Lett.* **2019**, *21*, 9066-9070; e) A. A. Salim, K. Samarasekera, Z. G. Khalil, R. J. Capon, *Org. Lett.* **2020**, *22*, 4828-4832; f) M. S. Cowled, D. Vuong, A. Crombie, E. Lacey, P. Karuso, A. M. Piggott, *Org. Biomol. Chem.* **2020**, *18*, 5879-5890; g) M. S. Cowled, E. Lacey, P. Karuso, A. M. Piggott, *Org. Lett.* **2020**, *22*, 9688-9692.

[4] H. Kang, P. R. Jensen, W. Fenical, *J. Org. Chem.* **1996**, *61*, 1543-1546.

[5] a) J. Piel, K. Hoang, B. S. Moore, *J. Am. Chem. Soc.* **2000**, *122*, 5415-5416; b) J. Piel, C. Hertweck, P. R. Shipley, D. M. Hunt, M. S. Newman, B. S. Moore, *Chem. Biol.* **2000**, *7*, 943-955; c) J. A. Kalaitzis, M. Izumikawa, L. Xiang, C. Hertweck, B. S. Moore, *J. Am. Chem. Soc.* **2003**, *125*, 9290-9291.

[6] Reviews: a) C. Hertweck, A. Luzhetskyy, Y. Rebets, A. Bechthold, *Nat. Prod. Rep.* **2007**, *24*, 162-190; b) C. Hertweck, *Angew. Chem.* **2009**, *121,* 4782-4811; *Angew. Chem. Int. Ed.* **2009**, *48*, 4688-4716; c) M. Claus, M. Grininger, *Nat. Prod. Rep*. **2018**, *35*, 1070-1081.

[7] a) C. Hertweck, B. S. Moore, *Tetrahedron* **2000**, *56*, 9115–9120; b) J. A. Kalaitzis, Q. Cheng, D. Meluzzi, L. Xiang, M. Izumikawa, P. C. Dorrestein, B. S. Moore, *Biorg. Med. Chem.* **2011**, *19*, 6633-6638; b) B. S. Moore, C. Hertweck, J. N. Hopke, M. Izumikawa, J. A. Kalaitzis, G. Nilsen, T. O'Hare, J. Piel, P. R. Shipley, L, Xiang, M, B. Austin, J, P. Noel *J. Nat. Prod.* **2002**, *65*, 1956-1962.

[8] C. Hertweck, L. Xiang, J. A. Kalaitzis, Q. Cheng, M. Palzer, B. S. Moore, *Chem. Biol.* **2004**, *11*, 461-468.

[9] a) L. Xiang, J. A. Kalaitzis, G. Nilsen, L. Chen, B. S. Moore, *Org. Lett.* **2002**, *4*, 957-960; b) L. Xiang, J. A. Kalaitzis, B. S. Moore, *Proc. Natl. Acad. Sci.* **2004***, 101*, 15609-15614; c) R. Teufel, A. Miyanaga, Q. Michaudel, F. Stull, G. Louie, J. P. Noel, P. S. Baran, B. Palfey, B. S. Moore, *Nature* **2013**, *503*, 552-556.

[10] R. Teufel, F. Stull, M. J. Meehan, Q. Michaudel, P. C. Dorrestein, B. Palfey, B. S. Moore, *J. Am. Chem. Soc.* **2015**, *137*, 8078-8085.

[11] For an enzymatic total synthesis, see: Q. Cheng, L. Xiang, M. Izumikawa, D. Meluzzi, B. S. Moore, *Nat. Chem. Biol.* **2007**, *3*, 557-558.

[12] A. Flores-Parra, F. Khuong-Huu, *Tetrahedron* **1986**, *42*, 5925-5930.

[13] B.-C. Hong, S.-F. Chin, *Synth. Commun.* **1999**, *29*, 3097-3106.

[14] A. Rizzo, D. Trauner, *Org. Lett.* **2018**, *20*, 1841-1844.

[15] A. Rizzo, R. J. Mayer, D. Trauner, *J. Org. Chem.* **2019**, *84*, 1162-1175.

[16] a) S. Kirsch, T. Bach, *Angew. Chem.* **2003**, *115*, 4833-4835; *Angew. Chem. Int. Ed.* **2003**, *42*, 4685-4687; b) S. F. Kirsch, T. Bach, *Chem. Eur. J.* **2005**, *11*, 7007-7023.

[17] a) M. Wegmann, T. Bach, *J. Org. Chem.* **2015**, *80*, 2017-2023; b) M. Wegmann, T. Bach, *Synthesis* **2017**, *49*, 209-217.

[18] a) M. Y. H. Wong, G. R. Gray, *J. Am. Chem. Soc.* **1978**, *100*, 3548-3553; b) J. D. White, M. S. Jensen, *J. Am. Chem. Soc.* **1995**, *117*, 6224-6233; c) B. Wang, T. M. Hansen, T. Wang, D. Wu, L. Weyer, L. Ying, M. M. Engler, M. Sanville, C. Leitheiser, M. Christmann, Y. Lu, J. Chen, N. Zunker, R. D. Cink, F. Ahmed, C. S. Lee, C. J. Forsyth, *J. Am. Chem. Soc.* **2011**, *133*, 1484-1505.

[19] H. Oikawa, T. Kobayashi, K. Katayama, Y. Suzuki, A. Ichihara, *J. Org. Chem.* **1998**, *63*, 8748-8756.

[20] Prepared from known 3-hydroxy-2-phenylpropene[17b] by the Johnson variant of the Claisen rearrangement: L. Werthemann, W. S. Johnson, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, M. R. Peterson, *J. Am. Chem. Soc.* **1970**, *92*, 741-743.

[21] D. V. Reddy, G. Sabitha, J. S. Yadav, *Tetrahedron Lett.* **2015**, *56*, 4112-4114.

[22] A. G. M. Barrett, B. C. B. Bezuidenhoudt, D. Dhanak, A. F. Gasiecki, A. R. Howell, A. C. Lee, M. A. Russell, *J. Org. Chem.* **1989**, *54*, 3321-3324.

[23] P. G. M. Wuts, *Greene's Protective Groups in Organic Synthesis*, 5th ed., Wiley, Hoboken, 2014.

[24] a) J. R. Parikh, W. v. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507; b) A. Adibekian, P. Bindschädler, M. S. M. Timmer, C. Noti, N. Schützenmeister, P. H. Seeberger, *Chem. Eur. J.* **2007**, *13*, 4510-4522.

[25] a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512-519; b) T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451-2458.

[26] a) M. Braun, H. Mahler, *Liebigs Ann. Chem.* **1995**, 29-40; b) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191-1223; c) D. A. Evans, V. J. Cee, S. J. Siska, *J. Am. Chem. Soc.* **2006**, *128*, 9433-9441.

[27] R. Pappo, J. D. S. Allen, R. U. Lemieux, W. S. Johnson, *J. Org. Chem.* **1956**, *21*, 478-479.

[28] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

[29] a) F. A. Davis, L. C. Vishwakarma, J. G. Billmers, J. Finn, *J. Org. Chem.* **1984**, *49*, 3241-3243; b) F. A. Davis, A. C. Sheppard, *Tetrahedron* **1989**, *45*, 5703-5742.

[30] Initially described for the oxidation of sulfides and selenides: a) F. A. Davis, O. D. Stringer, *J. Org. Chem.* **1982**, *47*, 1774-1775; b) F. A. Davis, O. D. Stringer, J. M. Billmers, *Tetrahedron Lett.* **1983**, *24*,1213-1216.

[31] The limited quantities did not allow us to reliably determine the specific rotation of the synthetic material, which was exacerbated by the fact that the reported value ($[\alpha]_D^{20} = -10.5$) is relatively low. Based on biosynthetic studies[9c] and on the crystal structure of neoenterocin A,[3d] it is very likely that the absolute configuration of the natural product is identical to synthetic enterocin.

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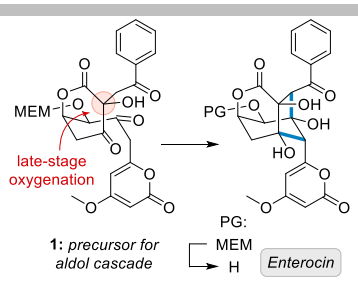
Entering Nature's Design Office: The highly oxygenated natural product enterocin, that has to far resisted total synthetic attempts, was obtained in a biomimetic key step from triketone **1**, which in turn was assembled from a L-arabinose-derived core fragment with a defined absolute configuration.



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