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Total Synthesis of (−)-5-Deoxyenterocin and Attempted Late-Stage Functionalization Reactions

Lilla Koser[a] and Thorsten Bach*[a]

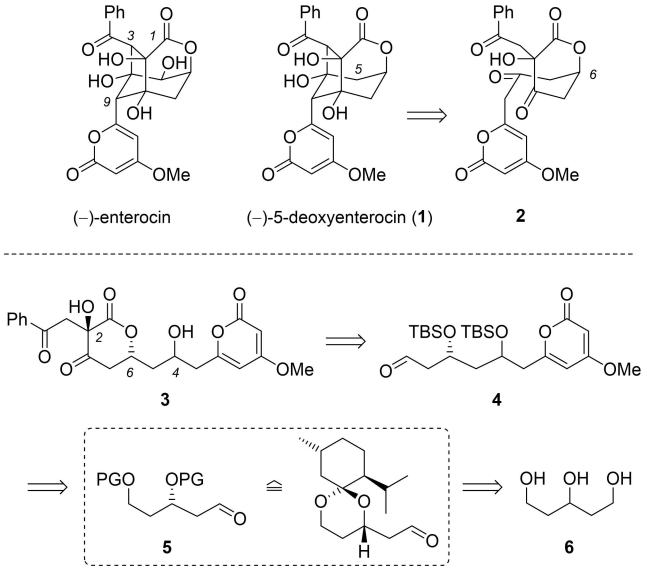
The first total synthesis of (−)-5-deoxyenterocin has been accomplished starting from pentane-1,3,5-triol (16 steps in the longest linear sequence, 0.2% overall yield). (−)-Menthone served as the source of chirality to distinguish the enantiotopic hydroxymethyl groups of the substrate. Key steps of the synthesis include two aldol reactions to either end of the C_5-skeleton, a diastereoselective hydroxylation reaction and a biomimetic twofold intramolecular aldol reaction as the final step. Although this step suffered from geometrical constraints and was low yielding (10%), enough synthetic material could be secured to substantiate the relative and absolute configuration of the natural product. Additional experiments were directed toward a C–H functionalization at carbon atom C5. Despite the fact that several protocols could be successfully applied to (3a*R*)-(+)-sclareolide as model substrate, (−)-5-deoxyenterocin withstood any selective functionalization.

Introduction

Due to their diverse biological activity, polyketide natural products continue to be one of the most important target classes for contemporary total synthesis.[1] In addition, their biosynthesis has been intensively studied revealing that, beyond the decisive C–C bond forming steps, a suite of other reactions accounts for their structural diversity.[2] The Favorskii-type rearrangement discovered in the biosynthesis of (−)-enterocin serves as excellent example how an originally assembled octaketide is structurally modified in consecutive steps. Herein, the regular pattern with functional groups in a 1,3-relationship is transformed by the flavoenzyme EncM into a lactone ring oxygenated in α- and β-position.[3] The carbocyclic bicyclo[3.2.1]octane core of the molecule is formed by a twofold aldol reaction with (−)-5-deoxyenterocin being the immediate precursor to the natural product. Despite the large attention which (−)-enterocin has received ever since it was discovered[4] in 1976, it withstood until very recently all total synthetic attempts.[5,6] It was eventually a biomimetic approach that enabled the assembly of enterocin starting from L-arabinose.[7] The synthetic material turned out to be (+)-enterocin, the enantiomer of the natural product, and the synthesis allowed to assign the absolute configuration of the polyketide.[8]

Inspired by the fact that the biosynthesis of (−)-enterocin involves a late-stage oxygenation of (−)-5-deoxyenterocin (**1**), we considered to use the latter compound to access non-natural derivatives of enterocin.[9] Since antiviral and antibacterial (−)-5-deoxyenterocin has also been isolated from different natural sources,[9b,10] its total synthesis was meant to additionally substantiate the assignment of the absolute configuration. A chemical total synthesis of (−)-5-deoxyenterocin (**1**) has not been previously accomplished.[5f,6,9]

Our retrosynthetic disconnection (Scheme 1) aimed to construct the carbon skeleton of the molecule by a twofold intramolecular aldol reaction of the enantiomerically pure triketone **2**. The keto group at C4 (enterocin numbering) was



Scheme 1. Structure and configuration of (−)-enterocin and its biosynthetic precursor (−)-5-deoxyenterocin (**1**). The synthesis of the latter was envisioned by a biomimetic twofold-aldol reaction of triketone **2** (top). Further retrosynthetic disconnection led to alcohol **3** and via pyrone **4** to enantiomerically pure aldehyde **5**, the synthesis of which seemed possible from triol **6** (bottom). TBS = *tert*-butyldimethylsilyl; PG = protecting group.

[a] *Dr. L. Koser, Prof. Dr. T. Bach*
Department Chemie and Catalysis Research Center (CRC)
School of Natural Sciences, Technische Universität München
Lichtenbergstraße 4, 85747 Garching (Germany)
E-mail: thorsten.bach@ch.tum.de
Homepage: http://www.ch.nat.tum.de/en/oc1/home/

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envisioned to stem from alcohol **3**, which in turn meant that the relative configuration at this stereogenic center was later erased and irrelevant for the further course of the synthesis. Installation of the lactone ring at aldehyde **4** was planned to occur by an aldol addition and an oxygenation at carbon atom C2 as key steps. The stereogenic center at C6 was expected to provide a high degree of facial diastereoselectivity for this transformation. Retrosynthetic removal of the α-pyrone fragment resulted in a linear *O*-protected dihydroxypentanal **5** with a single defined stereogenic center. Literature precedence[11] suggested an enantioselective approach to this aldehyde to be possible from achiral triol **6** and (−)-menthone.

Despite the fact that the final steps of the planned route parallel our previous approach to enterocin,[7] it was uncertain whether the cyclization **2**→**1** would be successful given that a substituent at C5 was lacking which provides a conformational preference for the required folding.

In this research article we report full details of our total synthesis studies towards 5-deoxyenterocin and we also present our work on the attempted late-stage functionalization with (3a*R*)-(+)-sclareolide serving as a model substrate. While the former efforts culminated in a completed total synthesis of (−)-5-deoxyenterocin (**1**), the latter experiments did not result in a notable reaction at the desired position C5.

Results and Discussion

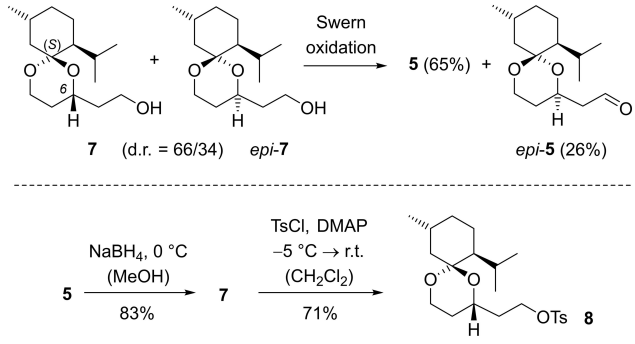
Total Synthesis of (−)-5-deoxyenterocin

The synthesis commenced with the preparation of known[12] alcohols **7** and *epi*-**7** obtained from (−)-menthone and 1,3,5-pentantriol (**6**). Without separation, the mixture of both diastereoisomers was oxidized to aldehydes **5** and *epi*-**5** by a Swern oxidation[13] (Scheme 2). Particularly on large scale the Swern protocol was superior to the Parikh–Doering oxidation which led to the formation of by-products (see the Supporting Information for experimental details on the optimization of the individual reaction steps). When applying the described ketalization-oxidation sequence, the desired stereoisomer at carbon atom C6 formed exclusively the (*S*)-configured ketal and the resulting major diastereoisomer **5** was isolated by column chromatography.

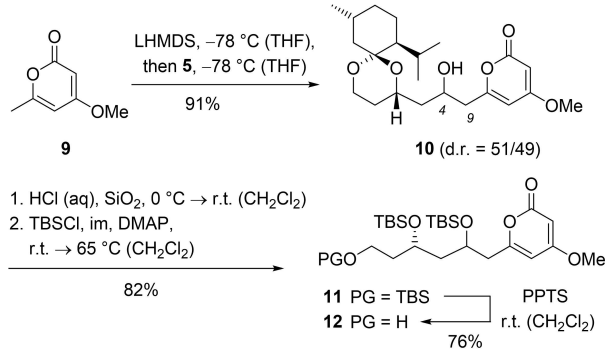
To further support the relative configuration at carbon atom C6, the separated aldehyde **5** was converted to known tosylate **8**[11a,12] by reduction and subsequent tosylation of alcohol **7**. Both ^{1}H NMR and ^{13}C NMR signals as well as the specific rotation of tosylate **8** matched the reported values and corroborated the depicted relative configuration of intermediate **5**.

After the described stereoselective ketalization and subsequent oxidation allowed to set the required configuration at carbon atom C6 of aldehyde **5**, pyrone **9** was connected to the core fragment (Scheme 3). The formation of the C–C bond between carbon atom C4 and C9 yielding alcohol **10** was accomplished by an aldol-type addition.[14] As expected, no facial diastereoselectivity was observed and the product was obtained as a mixture of two diastereoisomers. Since the stereogenic center in carbon atom C4 was lost by an oxidation in a later step (see above), it was not assigned. The subsequently prepared compounds **11**, **12**, and **4** were also mixtures of two diastereoisomers. Deprotection under acidic conditions allowed for the removal of the menthone-derived ketal, and subsequent *tert*-butyldimethylsilyl(TBS)-protection of unpurified triol yielded the comprehensively silylated product **11**. The silyl ether protecting groups at carbon atoms C6 and C4 seemed advantageous for the further course of the total synthesis allowing us to obviate an additional deprotection step. To access primary alcohol **12**, the silyl group at this position was selectively removed with pyridinium *para*-toluenesulfonate (PPTS). The conditions were carefully optimized to prevent additional deprotection of a secondary silyl ether. To complete the synthesis of advanced intermediate **4**, alcohol **12** was oxidized under Swern conditions[13] to obtain aldehyde **4** (d.r. = 50/50) in high yield (95 %).

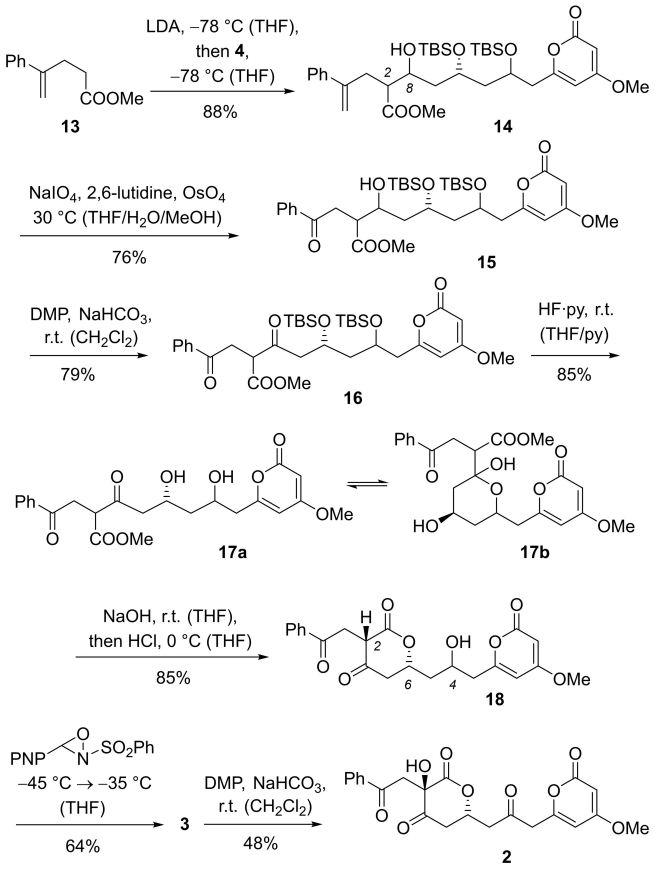
According to the illustrated retrosynthesis (Scheme 1), the construction of polyketide **1** was pursued by connecting ester **13** as a C_{11}-building block to aldehyde **4** (Scheme 4). In order to avoid regioselectivity issues in the deprotonation step, the benzoyl group was masked as an olefin. An intermolecular aldol addition was applied to connect carbon atoms C8 and C2 to



Scheme 2. Aldehydes **5** and *epi*-**5** can be separated by column chromatography and were obtained from a mixture of (−)-menthone-derived alcohols **7** and *epi*-**7**. Their relative configuration had been previously assigned (top). The assignment was further corroborated by conversion of aldehyde **5** to tosylate **8**, the absolute and relative configuration of which is known.



Scheme 3. Aldol reaction of γ-pyrone **9** with aldehyde **5** and subsequent transformation into primary alcohol **12** (d.r. = 50/50). LHMDS = lithium hexamethyldisilazide; im = imidazole; DMAP = 4-(*N*,*N*-dimethylamino)pyridine.

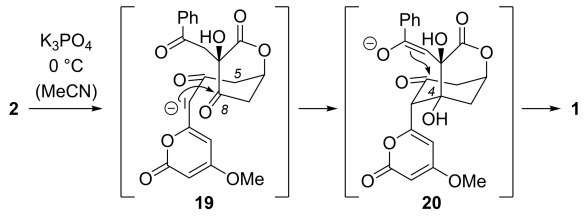


Scheme 4. Synthesis of triketone **2** from γ,δ-unsaturated ester **13** and chiral aldehyde **4**. Stereogenic centers which were irrelevant for the synthesis of ketone **2** were not assigned and intermediates **14–17** were mixtures of several diastereoisomers. Like aldehyde **4**, alcohol **18** was a mixture of two diastereoisomers (d.r. = 52/48). DMP = Dess–Martin periodinane (1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-one); py = pyridine.

obtain product **14**. To reach full conversion of aldehyde **4**, treatment with a high excess of the strong base lithium diisopropylamide (LDA) and of ester **13** was crucial. As anticipated, no simple or facial diastereoselectivity was observed and a total of eight diastereoisomers was formed during the reaction. With the carbon skeleton in place, the benzoyl moiety in intermediate **15** was liberated by a Lemieux-Johnson oxidation[15] of the terminal olefin. The yield of the one-pot sequence comprising a dihydroxylation and oxidative cleavage suffered from an undesired lactonization of the respective diol intermediate. Higher amounts of the oxidative cleavage reagent, sodium periodate, reduced the side product formation and increased the yields of ketone **15**. The ensuing oxidation to ketone **16** by the Dess–Martin reagent[16] required short reaction times to avoid the formation of an unidentified side product. Upon deprotection with Olah's reagent,[17] a mixture of the expected diol **17a** and hemiketal **17b** (with **17a**/**17b** = 70/30 in MeCN-d_3) was isolated. Under basic conditions, the hemiketal formation was reversed and lactonization to β-keto lactone **18** occurred smoothly. The relative configuration at carbon atom C2 is likely a result of thermodynamic control and was corroborated by NOESY-studies (MeCN-d_3, 298 K). Compound **18** adopts a boat conformation (in accordance with a related intermediate in the enterocin total synthesis)[7] and a NOE contact between the protons at carbon atoms C6 and C2 was clearly visible. A modified Davis reagent (PNP = 2-*para*-nitrophenyl)[18] enabled the diastereoselective α-hydroxylation of β-keto lactone **18** in moderate yields (64%) to obtain α-hydroxy-β-keto lactone **3**. A Dess–Martin oxidation to diastereomerically pure ketone **2** completed the assembly of the skeleton and the adjustmentof the oxidation states.

The final step of the synthesis (Scheme 5) attempted to mimic the biosynthetic key step[3] of (−)-5-deoxyenterocin and aimed at a formation of the rigid tricyclic core of natural product **1**. It is proposed that the reaction proceeds via the deprotonated triketone **19** to first form the six-membered ring of bicyclic intermediate **20** which subsequently cyclizes to yield natural product **1**. Contrary to the previous total synthesis of (+)-enterocin,[7] precursor **2** does not possess a conformational bias at carbon atom C5 facilitating the C8–C9 bond formation. While nature provides a suitable pocket to enforce the proximity of the reactive centers,[3] the situation in solution is different and conformation **19** requires an enthalpic barrier to be overcome. As anticipated, even at low temperatures of 0 °C the cyclization towards natural product **1** occurred less selectively than in the enterocin case and with more decomposition to unidentified side products. Altering the mild base (Cs_2CO_3 with 7% yield, K_2CO_3 with 8% yield, and K_3PO_4 with 10% yield) did not significantly affect the yield. An attempted organocatalytic reaction with racemic proline led to the decomposition of the starting material at temperatures greater than 0 °C. Purification by reversed-phase semipreparative HPLC resulted in the first-time isolation of synthetic 5-deoxyenterocin (**1**).

Synthetic (−)-5-deoxyenterocin (**1**) was identical to the natural product by all scalar properties, i.e. by HRMS (high resolution mass spectrometry), HPLC (achiral stationary phase), and by ^{1}H and ^{13}C NMR spectra.[10c] Furthermore, the measured specific rotation $[\alpha]_D^{30}$ of −24.9 (c = 1.0, MeOH) was in accordance with the literature-reported values regarding its direction (levorotatory). Although there was no indication for a racemization in the course of our synthesis, the literature values of −31.5[10b] (c = 1.0, MeOH), and −38.8[10c] (c = 4.7) are more negative. When subjecting a mixture of natural and synthetic material of (−)-5-deoxyenterocin (**1**) to HPLC on a chiral stationary phase, no separation was observed. The results

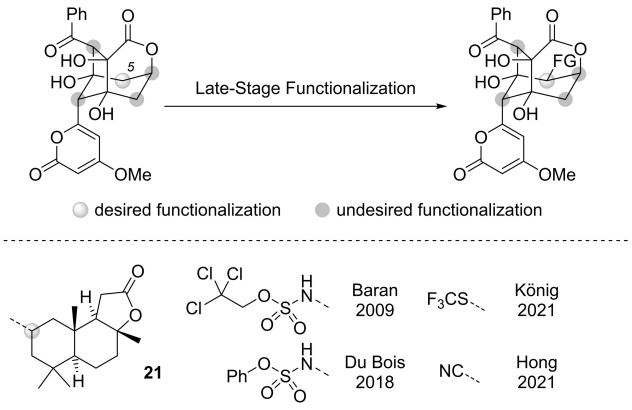


Scheme 5. Suggested formation of (−)-5-deoxyenterocin (**1**) from triketone **2**. For the first bond formation via enolate **19**, the carbon chain needs to fold in the direction of carbonyl carbon atom C8. The folding is favored in the enterocin synthesis by the protected, equatorial hydroxy group at C5. For details and yields, see the narrative.

suggest that synthetic and naturally occurring deoxyenterocin are identical both in their relative and absolute configuration. Since the absolute configuration of the synthetic material is known from the established chirality at the initial carbon atom C6 (aldehyde **5**), the synthesis corroborates the absolute configuration of the natural product. It further supports our configuration assignment of (−)-enterocin which was based on the total synthesis and on a vibrational circular dichroism (VCD) study.[7,8]

Late-Stage Functionalization Experiments

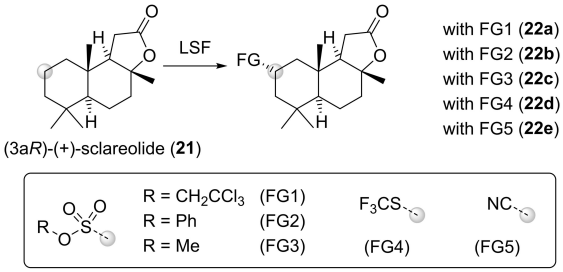
After having successfully established a concise total synthetic route towards 5-deoxyenterocin (**1**), we turned our attention to the possibility of its late-stage functionalization (LSF) at position C5 (Scheme 6). Transition metal-,[19] radical-,[20] and photoredox-mediated[21] C–H functionalization strategies represent versatile tools for the derivatization of natural products.[22] However, many of the transformations were reported with the reagent instead of the substrate being the limiting component. Additional challenges associated with 5-deoxyenterocin are its instability at elevated temperature,[23] the limited availability (low substrate concentration), and several additional reactive positions (highlighted as gray spheres) apart from the desired, sp^3-hybridized C5 position. We chose (3a*R*)-(+)-sclareolide (**21**) as a substrate for initial optimization studies since this commercially available sesquiterpene had already been successfully applied in different late-stage functionalizations at the secondary, sp^3-hybridized carbon center, including halogenation, azidation, alkylation, oxidation, amination, trifluoromethyl(thiol)ation, and cyanation reactions. A first series of preliminary experiments revealed some methods to be better suited to our needs than others, particularly based on the criteria outlined above.



Scheme 6. Strategy for the late-stage functionalization of 5-deoxyenterocin (**1**). The desired derivatization at carbon position C5 is hampered by the presence of multiple reactive positions (top). Literature-known protocols (amination,[19a,i] trifluoromethylthiolation,[20e] cyanation[20d]) for the functionalization of the secondary sp^3-hybridized carbon atoms as applied to (3a*R*)-(+)-sclareolide (**21**). Only the method by Du Bois and co-workers[19i] described the use of the substrate as limiting component.

We moved forward with C–H functionalization methods described by Baran,[19a] Du Bois,[19i] König,[20e] and Hong,[20d] and continued to optimize the conversion of sclareolide (**21**) as limiting reagent (Table 1). In all experiments, we employed temperatures lower than room temperature to avoid decomposition[23] in the case of 5-deoxyenterocin (**1**). Also, low concentrations were applied since only small amounts of natural product **1** were available. In principle, all four C–H functionalizations were successful and we observed an amination, a trifluoromethylthiolation, and a cyanation of sesquiterpene **21** to the corresponding products **22a**–**22e**. When applying substrate **21** as the limiting component the yield was diminished in the case of the amination products from a quantitative yield for the functional group (FG) FG1 = $Cl_3CCH_2OSO_2NH$, 88% for FG2 = $PhOSO_2NH$, and 75% for FG3 = $MeOSO_2NH$ to 24% for FG1 (Table 1, entry 1), and to 57% for FG2 (Table 1, entry 2). In the case of FG2 the reaction was

Table 1. Late-stage functionalization of model substrate (3a*R*)-(+)-sclareolide (**21**). Literature-reported methods enabling a C–H functionalization of the marked (gray shaded circle) secondary carbon atom position in substrate **21** were optimized to apply substrate **21** as a limiting component, at low concentrations, and at temperatures T ≤ r.t.



Entry	FG	Reagent	*c* [mol/L]	Yield[a] (yield)[b] [%]
1	FG1[c]	$Cl_3CCH_2OSO_2NH_2$	1.00	24 (quant.)[b]
2	FG2[c]	$PhOSO_2NH_2$	1.00	57 (88)[b]
3	FG2[d]	$PhOSO_2NH_2$	0.10	44
4	FG3[c]	$MeOSO_2NH_2$	1.00	0 (75)[b]
5	FG4[e]	NPhth-SCF_3	0.20	24 (lit.: 55)[20e]
6	FG4[f]	$AgSCF_3$	0.11	57 (lit.: 42)[20c]
7	FG5[g]	TosCN	0.05	40 (lit.: 81)[20d]

[a] The yield was referenced to substrate **21** [b] Yield was calculated based on the reagent (lit. = yield provided in the literature). Analogous to Baran's[19a] and Du Bois's[19e] procedure: Rh_2esp_2 (1.0 mol%), $PhI(OAc)_2$ (2.00 equiv.), sulfamate (1.00 equiv.), substrate **21** (6.67 equiv.), r.t., o/n (^{i}PrOAc). [c] According to Du Bois's[19i] procedure: Rh_2esp_2 (1.0 mol%), $PhI(OPiv)_2$ (1.50 equiv.), Al_2O_3 (neutral, 4.00 equiv.), sulfamate (1.30 equiv.), substrate **21** (1.00 equiv.), r.t., o/n (^{t}BuCN). [d] Deviation from reaction conditions in entry 2: $PhI(OPiv)_2$ (3×0.50 equiv. every two hours), sulfamate (3×0.50 equiv. every two hours). [e] Modification of König's[20e] procedure: substrate **21** (1.00 equiv.), NPhth-SCF_3 (1.20 equiv.), TBADT (3.0 mol%), λ_{max} = 365 nm (1 W, LED parallel reactor), 20 °C, 16 h (MeCN). [f] Modification of Tang's[20c] procedure: substrate **21** (1.00 equiv.), $AgSCF_3$ (2.50 equiv.), $Na_2S_2O_8$ (4.00 equiv.), 35 °C, 16 h (MeCN/H_2O/DCE). [g] Modification of Hong's[20d] procedure: substrate **21** (1.00 equiv.), TosCN (1.10 equiv.), TBADT (2.0 mol%), λ_{max} = 365 nm (1 W, LED parallel reactor), 20 °C, 24 h (MeCN/H_2O). Rh_2esp_2 = bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid; TBADT = tetra-*n*-butylammonium decatungstate.

carried out at a lower concentration of 0.1 M, and a yield of 44% for the amination product (Table 1, entry 3) was achieved after modification of the original procedure.[19i] Unfortunately, with FG3 no amination product was observed when applying substrate **21** as the limiting component (Table 1, entry 4). A similar pattern could be observed when comparing the literature-reported yield of 55%[20e] for the SCF_3-functionalization catalyzed by TBADT (tetra-*n*-butylammonium decatungstate). When substrate **21** was applied as the limiting component a yield of 24% (Table 1, entry 5) was reached. When applying the $AgSCF_3$ reagent[20c] (Table 1, entry 6) in the trifluoromethylthiolation instead, a reaction temperature of at least 35 °C was required, since no product formation was observed at room temperature. Thus, this reaction was not further optimized since the increased reaction temperature would very likely lead to epimerization[23b] and decomposition[23a] of polyketide **1**. In a final set of experiments, the cyanation exhibited a similar trend as the other C–H functionalization methods. The yield of 81% reported in the literature[20d] was reduced to 40% (Table 1, entry 7) when applying substrate **21** as the limiting component. Still, even though several of the methods had not been previously performed with substrate **21** as the limiting component, they clearly delivered the desired functionalization product as a single isolable compound which was adequately characterized.

The functionalization of 5-deoxyenterocin (**1**) was attempted under the two most promising C–H functionalization procedures, the amination with FG2 (Table 1, entry 3) and the cyanation (Table 1, entry 7). Disappointingly, both conditions did not give access to a new derivative. In the former case, no conversion of natural product **1** was detected and in the latter case only conversion to unidentified side products was observed. Our experiments underline the importance of embedding 5-deoxyenterocin (**1**) in a defined enzymatic cavity for the crucial C–H functionalization (oxygenation) during the enterocin biosynthesis.[3] Unless properly positioned, it appears as if 5-deoxyenterocin (**1**) is characterized by a significant resistance towards a C–H functionalization reaction at position C5. Further experiments were not possible due to the limited amount of material we had in hand.

Conclusions

The polyketide natural product (−)-5-deoxyenterocin has been prepared for the first time by a chemical total synthesis. The synthesis commenced with a starting material with defined stereogenic centers, which in turn allows to assign the absolute configuration of the natural product. Because (−)-5-deoxyenterocin is the biogenetic precursor to (−)-enterocin, its synthesis also validates a previous configuration assignment for the latter compound. No attempt has been made to assign the relative configuration of intermediates with stereogenic centers which would vanish or equilibrate due to ensuing oxidation reactions or due to an epimerization. Low yields in the final two steps of the synthesis indicate the high instability of the compound and its immediate precursor. The oxygen substituent at position C5 within (−)-enterocin appears to mitigate the instability and provides the biomimetic aldol reactions with an improved conformational bias as opposed to (−)-5-deoxyenterocin.

The selection of C–H activation reactions that were screened with (3a*R*)-(+)-sclareolide as model substrate gave promising results even if conditions were chosen which deviate from typical conditions (substrate as limiting component, low concentration, low reaction temperature). Still, it was not possible to apply the optimized conditions to a successful, selective functionalization of (−)-5-deoxyenterocin. Thereby, it becomes apparent that an enzymatic environment, as provided by the cytochrome P450 hydroxylase in the enterocin biosynthesis, is crucial for the activation of the secondary sp^3-hybridized carbon atom in position C5 enabling its oxygenation.

Experimental Section

For all experimental details see the Supporting Information. Additional references are cited within the Supporting Information.[24–33]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article. Original NMR datasets (FIDs), HRMS, IR, and HPLC data are available at Open Science Framework at https://osf.io/jbgdv/?view only=e9dd8a60f7bf4cd3bf26c0a55f7c9b4a (DOI 10.17605/OSF.IO/JBGDV).

Keywords: aldol reactions · biomimetic synthesis · C–H activation · polyketides · total synthesis

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