Total Synthesis

How to cite:
International Edition: doi.org/10.1002/anie.202002328
German Editon:: doi.org/10.1002/ange.202002328

Total Synthesis of the Cyclic Depsipeptide Vioprolide D via its (*Z*)-Diastereoisomer

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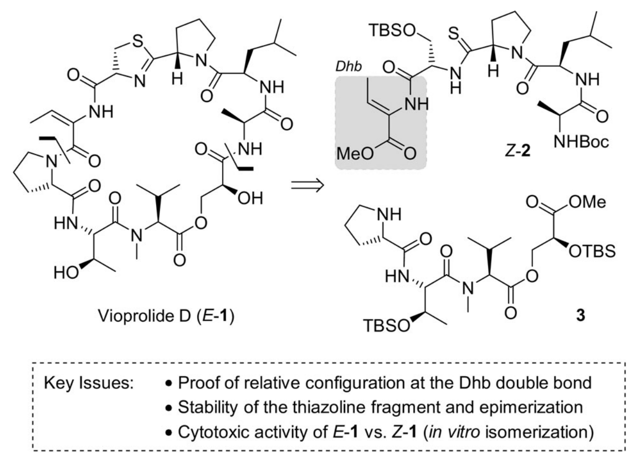
In memory of Rolf Huisgen

Abstract: *The first total synthesis of vioprolide D was accomplished in an overall yield of 2.0% starting from methyl (2S)-3-benzyloxy-2-hydroxypropanoate (16 steps in the longest linear sequence). The cyclic depsipeptide was assembled from two building blocks of similar size and complexity in a modular, highly convergent approach. Peptide bond formation at the C-terminal dehydrobutyrine amino acid of the northern fragment was possible via its (Z)-diastereoisomer. After macrolactamization and formation of the thiazoline ring, the (Z)-double bond of the dehydrobutyrine unit was isomerized to the (E)-double bond of the natural product. The cytotoxicity of vioprolide D is significantly higher than that of its (Z)-diastereoisomer.*

The vioprolides were first isolated by Schummer et al. from the myxobacterium *Cystobacter violaceus* Cb vi35.[1] Four members of the compound class were reported and were denominated as vioprolides A–D. The compounds were found to be cyclic depsipeptides[2] containing a sequence of eight amino acids or amino acid derived building blocks and L-glyceric acid (L-Gla). Starting from the N-terminal site, the amino acid sequence of vioprolide D (*E*-**1**, Scheme 1) can be identified as: L-Ala, D-Leu, L-Pro, L-Cys, L-Thr, L-Pro, L-Thr, L-Me-Val. In vioprolides A and C the L-Pro unit in the northern part of the molecule is replaced by (2*S*,4*R*)-4-methylazetidine carboxylic acid (L-Maz). In vioprolides A and B, pipecolic acid (L-Pip) is incorporated in the western hemisphere of the molecule instead of L-Pro. The vioprolides are nonribosomal peptides and their assembly commences presumably with the generation of an *O*-acyl L-Gla building block, which is linked to L-Ala.[3] The acyl group is located at the secondary hydroxy group of the glycerate. The (*E*)-dehydrobutyrine (*E*-Dhb) unit is likely formed by dehydration of L-Thr[4] and the assignment of its relative configuration was based on NOESY spectra.[1] Dehydration of the L-Pro-L-Cys dipeptide leads biosynthetically to the formation of the thiazoline ring. All other amino acid fragments remain unaltered and the cyclization occurs as a macrolactonization between the terminal primary hydroxy group of the *O*-acyl glyceric acid amide and the carboxylic acid residue of L-Me-Val.[3]

Synthetically, the vioprolides represent a significant challenge[5] mainly due to the sensitivity of the thiazoline fragment[6] and due to the difficult—if not impossible—bond formation between *E*-Dhb and L-Pro.[7] The Thomas group has extensively studied[5b,c] the synthesis of macrocyclic precursors to the vioprolides but did not succeed in establishing the required *E*-Dhb double bond by elimination.[8] Our synthetic interest in the vioprolides was kindled by the biological activity of the compounds both against fungi and against human cancer cell lines.[1,9] In the latter context, it was recently reported that vioprolide A targets nucleolar protein 14 which is essential for ribosome biogenesis.[9] Despite the higher activity of vioprolide A, we focused our synthetic attention on vioprolide D, mainly because the individual building blocks (L-Pro) are more readily available than L-Maz and/or L-Pip. Our synthetic strategy aimed at the preparation of the (*Z*)-isomer (*Z*-**1**) of vioprolide D and its late-stage conversion into the natural product.

Apart from the fact that the strategy avoided the formation of the congested bond between *E*-Dhb and L-Pro



Scheme 1. Retrosynthetic disconnection of vioprolide D (*E*-**1**) into northern fragment *Z*-**2** with a C-terminal (*Z*)-dehydrobutyrine (*Z*-Dhb) and into southern fragment **3** composed of L-Pro, L-Thr, L-Me-Val, and a C-terminal L-glyceric acid (L-Gla).

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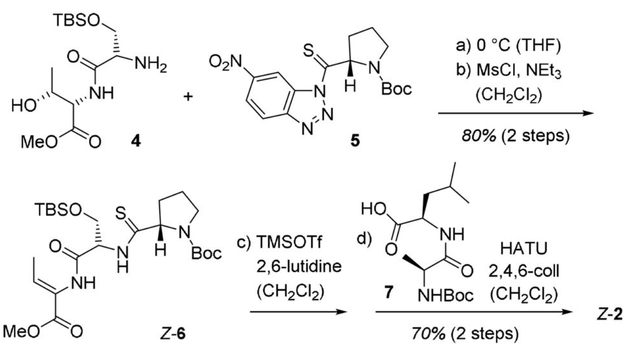
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202002328.

it was also desirable to access the (Z)-isomer of vioprolide D for its own sake. Although the assignment of the double bond configuration rested on solid NOESY data, a synthetic proof of the assignment was warranted. This was even more true since most dehydrobutyrines occurring in natural products[10,11] exhibit the thermodynamically preferred (Z)-configuration. In addition, it was to be explored whether the biological activities of Z-**1** and E-**1** were different or identical. Herein we address these questions and report the total synthesis of vioprolide D (E-**1**) via its (Z)-isomer Z-**1**.

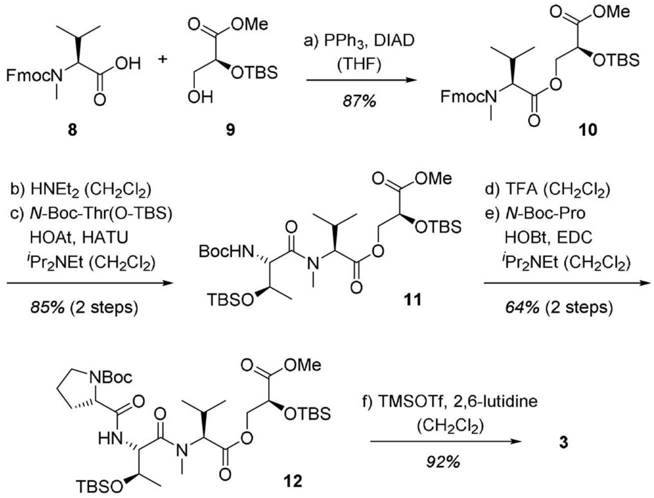
In agreement with the findings of Thomas and co-workers,[5c] we had in simultaneous experiments discovered that the biomimetic macrolactonization[3] was not suited for ring closure to a vioprolide D precursor. Instead, we dissected the molecule retrosynthetically between L-Gla and L-Ala which led after another retrosynthetic disconnection between L-Pro and Z-Dhb to pentapeptide Z-**2** and tripeptidyl glycerate **3** as potential building blocks. The synthesis of the northern fragment Z-**2** (Scheme 2) commenced with thioamide formation between the known amino dipeptide **4**[12] and triazole **5**. The latter compound serves to transfer a N-Boc-protected thioproline unit,[13] which in turn was required to create the thiazoline ring at a more advanced stage of the total synthesis. After tripeptide formation, dehydration at the C-terminal L-Thr was initiated with methanesulfonyl chloride and triethylamine.[14] The elimination led exclusively to the expected Z-Dhb diastereoisomer without formation of the other diastereoisomer. The N-terminal Boc group of tripeptide Z-**6** was removed[15] to enable in the next step peptide coupling between the proline nitrogen atom and the carboxylic acid of known dipeptide **7**.[5c] Coupling with HATU and 2,4,6-collidine[16] delivered diastereomerically pure product Z-**2** successfully, avoiding any epimerization by oxazolone formation within the activated dipeptide.

The assembly of the southern fragment **3** (Scheme 3) was initiated by Mitsunobu esterification of Fmoc-protected N-methyl valine (**8**)[17] with alcohol **9**. The latter substrate was prepared from a known glycerate precursor,[18] which in turn was synthesized from L-serine. The chosen procedure avoided carboxyl activation of the sterically encumbered, racemization-prone amino acid. Basic removal of the Fmoc group liberated the secondary amine at the N-terminal site of **10** that was required for peptide coupling with an appropriately protected threonine acid.[19] The final proline entity was installed by another peptide coupling step after release of the N-terminal Boc protecting group in **11** under acidic conditions. The ammonium salt was directly taken[20] into the coupling with commercially available N-Boc-protected proline and delivered the desired depsipeptide **12**. Preliminary experiments had shown that deprotonation of the ammonium salt prior to coupling leads to extensive formation of diketopiperazines.[21] Boc deprotection of fragment **12** delivered the southern part of vioprolide D (**3**), which required ligation to the northern part by peptide bond formation between L-Pro and Z-Dhb. The desired transformation was achieved after saponification of ester Z-**2** by peptide coupling to fragment **3** (Scheme 4).

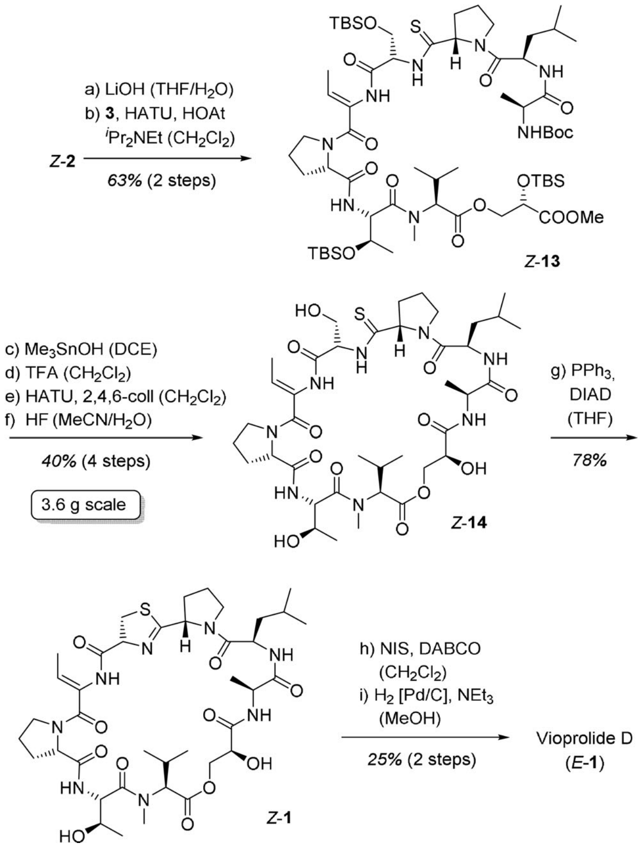
The selective hydrolysis of the methyl ester Z-**13** was successfully performed with trimethyltin hydroxide, generating a free carboxylic acid at the C-terminal site. Under the chosen conditions,[22] the valine-glycerate ester bond remained intact. However, the cleavage of a single TBS protecting group was recorded after acidic workup and purification. Removal of the Boc protecting group at the N-terminal site of the depsipeptide set the stage for the macrolactamization.[16] In this step, the partial loss of additional TBS groups was observed. Without further purification



Scheme 2. Synthesis of northern fragment Z-**2**. Exact conditions and yields: (a) (THF), 0°C, 5 min, 85%; (b) MsCl (1.54 equiv.), NEt_3 (3.07 equiv.), (CH_2Cl_2), 0°C→r.t., 94%; (c) TMSOTf (6.00 equiv.), 2,6-lutidine (8.00 equiv.), (CH_2Cl_2), 0°C, 3 h; (d) **7** (1.05 equiv.), HATU (1.10 equiv.), 2,4,6-collidine (1.00 equiv.), (CH_2Cl_2), 0°C→r.t., 14.5 h, 70% over two steps; Boc = *tert*-butyloxycarbonyl, coll = collidine, HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.



Scheme 3. Synthesis of southern fragment **3**. Exact conditions and yields: (a) **8** (1.10 equiv.), PPh_3 (1.00 equiv.), DIAD (1.05 equiv.), (THF), r.t., 18 h, 87%; (b) $HNEt_2$ (46.0 equiv.), (CH_2Cl_2), 0°C, 5 h, 98%; (c) N-Boc-Thr(O-TBS) (1.40 equiv.), HOAt (0.50 equiv.), HATU (1.40 equiv.), $^iPr_2NEt$ (2.00 equiv.), (CH_2Cl_2), 0°C→r.t., 18.5 h, 87%; (d) TFA (14.6 equiv.), (CH_2Cl_2), 0°C; 70 min; (e) N-Boc-Pro (1.76 equiv.), HOBt·H_2O (1.76 equiv.), EDC·HCl (3.56 equiv.), $^iPr_2NEt$ (2.67 equiv.), (CH_2Cl_2), 0°C→r.t., 19.5 h, 64% over two steps; (f) TMSOTf (6.00 equiv.), 2,6-lutidine (8.00 equiv.), (CH_2Cl_2), 0°C, 3.5 h, 92%; DIAD = diisopropyl azodicarboxylate, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, Fmoc = fluorenylmethoxycarbonyl, HOAt = 1-hydroxy-7-azabenzotriazole, HOBt = 1-hydroxybenzotriazole, Pro = L-proline, TFA = trifluoroacetic acid, Thr = L-threonine.



Scheme 4. Synthesis of vioprolide D (*E*-**1**) via its (*Z*)-diastereomer *Z*-**1**. Exact conditions and yields: (a) LiOH·H_2O (2.50 equiv.), (H_2O/THF), 0°C, 6 h; (b) **3** (1.00 equiv.), HOAt (1.20 equiv.), HATU (1.20 equiv.), $^{i}Pr_2NEt$ (2.00 equiv.), (CH_2Cl_2), 0°C→r.t., 15 h, 63% over two steps; (c) Me_3SnOH (8.00 equiv.), (DCE), 80°C, 47.5 h; (d) (TFA/CH_2Cl_2), 0°C, 1 h; (e) HATU (2.12 equiv.), 2,4,6-collidine (3.39 equiv.), (CH_2Cl_2), r.t., 14.5 h; (f) HF (195 equiv.), (H_2O/MeCN), r.t., 24 h, 40% over four steps; g) PPh_3 (1.50 equiv.), DIAD (1.50 equiv.), (THF), r.t., 22 h, 78%; h) NIS (0.95 equiv.), DABCO (1.10 equiv.), (CH_2Cl_2), r.t., 5 h; i) 5% Pd/C, NEt_3 (1.20 equiv.), H_2 (1 atm), (MeOH), r.t., 3 h, 25% *E*-**1**, 24% *Z*-**1** (two steps); DCE = dichloroethane, NIS = *N*-iodosuccinimide, DABCO = 1,4-diazabicyclo[2.2.2]octane.

the macrolactamization product was globally deprotected with hydrofluoric acid. The complete four-step reaction sequence was performed on a scale of up to 3.6 g and the final product *Z*-**14** was obtained by column chromatography. The compound was not diastereomerically pure but was contaminated by two other diastereoisomers (diastereomeric ratio d.r. = 88/6/6). One of the minor diastereoisomers turned out to be the *E*-Dhb depsipeptide *E*-**14** and seems to be formed during ester cleavage. The constitution and configuration assignment was substantiated by NOESY experiments and by conversion (see the Supporting Information for further details) of this diastereoisomer into vioprolide D (*E*-**1**). The second minor diastereoisomer is likely the epimeric D-Gla depsipeptide which is formed in the macrolactamization step. The separation of the three mentioned diastereoisomers was possible by semipreparative HPLC and the diastereomerically pure compound *Z*-**14** was obtained in an overall yield of 40% (over four steps). Cyclization of the thiazoline ring under Mitsunobu conditions[23] led to the initial target *Z*-**1**. Like vioprolide D (*E*-**1**),[1] the compound also exists as a mixture of two rotamers, presumably due to rotation around the Thr-Me-Val peptide bond.

The NMR signals of *Z*-**1** were clearly different from the signals reported for the natural product and its cytotoxicity was much less pronounced (see below). While this result supported the previous configuration assignment of the natural product,[1] the completion of the total synthesis now rested on the challenging inversion of the olefin configuration. Indeed, access to the (*E*)-diastereoisomer by isomerization of the double bond of *Z*-**1** required extensive optimization (see the Supporting Information for details). Eventually, it was found that a sequence of iodination and hydro-deiodination was viable when reported methods were properly adjusted. The first step, the iodination of the dehydrobutyrine, was adapted from an inversion procedure that had previously been used only for less complex substrates.[24] Simultaneous treatment of compound *Z*-**1** with NIS and DABCO evolved as the preferred procedure for initial iodination and guaranteed high reproducibility and almost quantitative conversion. The reaction commences presumably with the formation of an α-iodinated imine which tautomerizes to an inseparable mixture of (*E*)- and (*Z*)-iodovioprolide D.[25] The subsequent hydro-deiodination protocol relied on the reductive power of hydrogen and NEt_3 in the presence of palladium on carbon.[26] The reaction is expected to be stereospecific and led consequently to a mixture of *E*-**1** and *Z*-**1**. Fortunately, the separation of the two diastereoisomeric depsipeptides could be achieved by semipreparative HPLC and allowed the isolation of the pure natural product vioprolide D (*E*-**1**, 25% over two steps) and the re-isolation of its diastereoisomer *Z*-**1** (24% over two steps). Despite the relatively low yield for the final two-step sequence, it was possible to isolate significant amounts (25 mg) of vioprolide D from this transformation. The synthetic material was identical in all its physical properties (IR, ^{1}H and ^{13}C NMR spectra, MS, specific rotation) with the natural product (see the Supporting Information for details).[1] The longest linear sequence towards vioprolide D commences with a literature-known glycerate, methyl (2*S*)-3-benzyloxy-2-hydroxypropanoate,[18] and includes a total of 16 steps with an overall yield of 2.0%.

The impact of the configuration of the dehydrobutyrine moiety on the biological potency of vioprolide D was evaluated in a MTT assay [MTT = 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide] (Figure 1).[27] To this end, cells of the acute lymphoblastic leukemia (ALL) cell line Jurkat were treated with vioprolide D (*E*-**1**) and (*Z*)-vioprolide D (*Z*-**1**) in various concentrations for 72 h. Whereas synthetic vioprolide D exhibited cytotoxic activity with a half-maximal inhibitory concentration (IC_{50}) of 679 nM, its diastereoisomer *Z*-**1** (48.2 μM) showed a significantly reduced bioactivity. Since the IC_{50} of the latter compound is approximately 70-fold higher than that of vioprolide D, it can be concluded that the configuration of the double bond is crucial for the biological activity of the natural product. The observation also rules out an in vitro epimerization of the two diastereoisomers. The determined cytotoxicity of synthetic *E*-

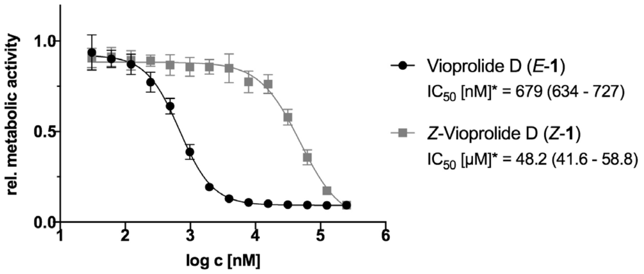


Figure 1. Dose–response curves and corresponding IC_{50} values from Jurkat cells treated with vioprolide D (*E*-**1**) and (*Z*)-vioprolide D (*Z*-**1**) as determined by MTT assay after 72 h incubation time. Data points represent the mean ± SEM (standard error of the mean) of three independent replicates performed in triplicate; rel. = relative; *IC_{50} values were determined with 95 % confidence interval as calculated using GraphPad Prism 8.

1 compares well with the previously established cytotoxicity of vioprolide D extracted from the natural producer.[9]

In summary, we have successfully completed the first total synthesis of a vioprolide in a concise and convergent approach. The hitherto unsolved challenge to access a natural product with a peptide bond between the C-terminal end of *E*-Dhb and the L-Pro nitrogen atom has been overcome by a late-stage double bond isomerization. In addition, the reaction conditions avoid any significant epimerization at stereogenic centers and suppress the oxidation of the sensitive thiazoline ring. The chosen route should be applicable to vioprolides A–C by altering the individual northern and southern fragments. In addition, we hope to aid target identification and to further interrogate the mode of action by the preparation of synthetic vioprolide analogues.

Acknowledgements

We are grateful to Prof. Dr. R. Müller for providing reference NMR spectra of vioprolide D. We kindly thank Dr. G. Gemmecker, C. Schwarz, and T. Steiner for measuring high- and low-temperature NMR spectra. O. Ackermann is acknowledged for his help with HPLC purification.

Conflict of interest

The authors declare no conflict of interest.

Keywords: antitumor agents · isomerization · macrocycles · peptides · total synthesis

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Manuscript received: February 14, 2020
Accepted manuscript online: March 3, 2020
Version of record online: ■■ ■■, ■■■■

Communications

Total Synthesis

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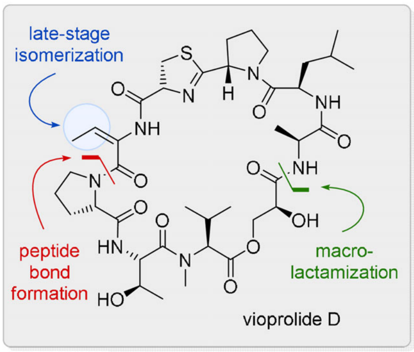
Total Synthesis of the Cyclic Depsipeptide Vioprolide D via its (*Z*)-Diastereoisomer



Better late than never: The key linkage between a proline and an (*E*)-dehydrobutyrine in vioprolide D was successfully tackled by a late-stage double-bond isomerization. The first member of this class of biologically potent depsipeptides has thus been efficiently synthesized (16 linear steps, 2.0% overall yield).