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Cyclodepsipeptide alveolaride C: total synthesis and structural assignment†

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First stereoselective total synthesis of naturally occurring bioactive cyclodepsipeptide alveolaride C has been achieved using a convergent approach. This synthetic study enabled us to establish unambiguously the stereochemistry of three unassigned chiral centres embedded in the nonpeptidic segment as well as revised the stereochemistry of the proposed β-phenylalanine counterpart of the molecule. The key strategic features of this synthesis include Sharpless asymmetric dihydroxylation for installing the vicinal diol moiety, Julia–Kocienski olefination for constructing the aliphatic side chain, the Shiina protocol for intermolecular esterification, amide coupling and macrolactamization for the ring formation.

Introduction

Microorganisms are known as the rich sources of structurally novel secondary metabolites. Many of them possess a broad range of biological activities.[1] Chemical synthesis of these metabolites is, thus, crucial for their unambiguous structural confirmation and to ensure adequate supply for exploring their biological importance.[2] During the search for naturally occurring environmentally benign pesticides from microorganisms Dow Agro Sciences, in 2018, first identified and isolated a family of novel cyclodepsipeptide alveolarides A–C (**1–3**, Fig. 1) from the culture broth of *Microascus alveolaris* strain PF1466.[3] Invitro inhibition studies against different harmful plant pathogens *Pyricularia oryzae*, *Zymoseptoria tritici*, *Ustilago maydis*, *Puccinia triticina*, and *Phakopsora pachyrhizi* revealed that these cyclodepsipeptides exhibited excellent to moderate activities.[3] The structures of these molecules were determined partially using NMR, mass spectroscopic analysis and chemical modification techniques. Architecturally, alveolarides are 17-membered macrocycles bearing rarely found 2,3-dihydroxy-4-methyltetradecanoic acid (DHMTDA) as the nonpeptide unit in which the configurations of all three stereocentres remained undetermined. The DHMTDA segment of alveolaride B was found to be slightly different from that of alveolarides A and C in which an olefin between C39–C40 is present. D-β-Phenylalanine, L-glutamine and D-serine are the residues common to all the members of this family of cyclodepsipeptides. An L-Glutamic acid derivative bearing two additional unassigned stereocentres in alveolarides A & B and L-tryptophan in alveolaride C were observed as the other amino acid counterparts, respectively.[3] The

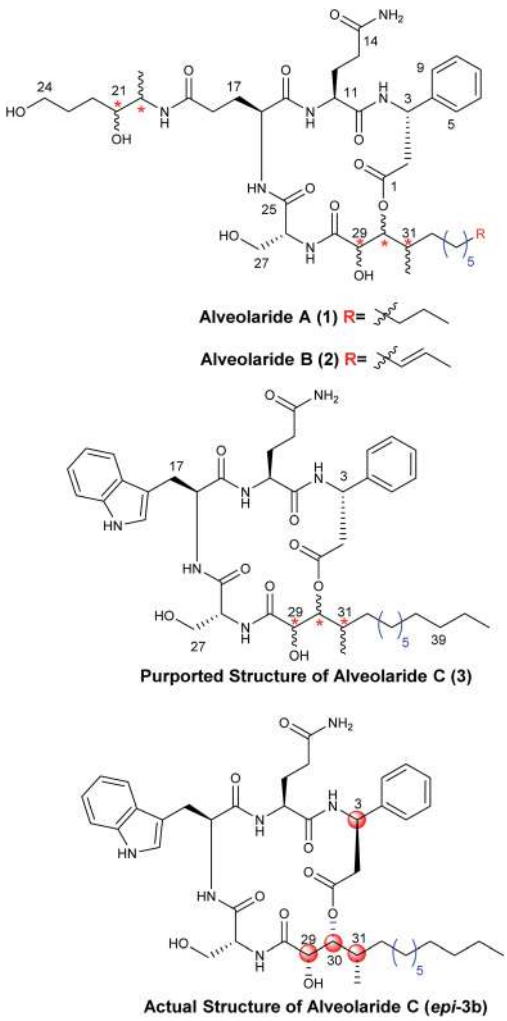

Fig. 1 Chemical structures of alveolarides.

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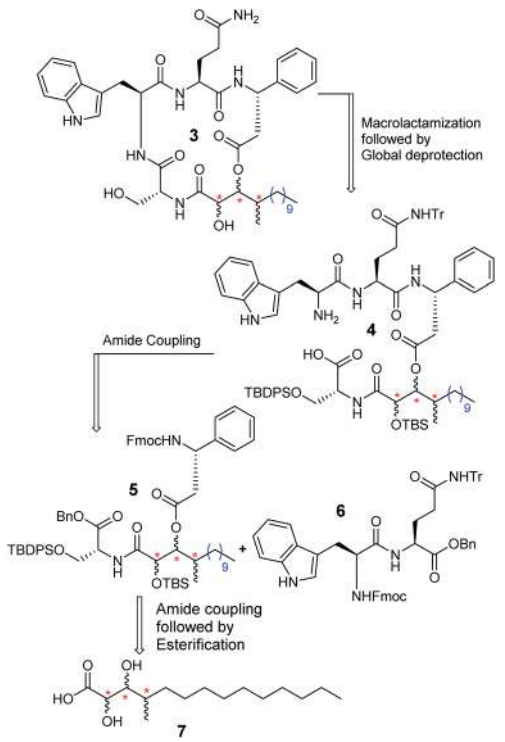
chemical structure of alveolaride C was proposed based on the similarities in the ^{1}H and ^{13}C NMR data of alveolarides A and B but no degradation study was performed due to the scarcity of the compound. Our continual interest in synthesis of natural products and their structural assignment[4] prompted us to envisage initially the total synthesis of structurally unique alveolaride C (**3**). The establishment of the stereochemistry of the unassigned centres in the common nonpeptide segment of this family of molecules is very crucial and essential to synthesize the other members including the more active alveolaride A. There are three undetermined stereocentres in the molecule providing the possibility of eight configurational isomers among which one could be expected to be the actual structure of alveolaride C. To narrow down these possibilities, we depended on the reported NMR spectral data of the DHMTDA counterpart of alveolaride C.[3] Two diastereomers of the purported structure of alveolaride C (**3**) having the stereochemistry 29-(*R*)/30-(*S*)/31-(*R*) and 29-(*S*)/30-(*R*)/31-(*S*) were synthesized initially as the specific rotation value of DHMTDA was not reported.[3] Comparison of their NMR data with those of the isolated alveolaride C (**3**) revealed that the latter isomer was a better match with some discrepancies originating from the β-phenylalanine counterpart. Herein, we described a convergent and flexible route for the first stereoselective total synthesis of the actual structure of alveolaride C (***epi*-3b**, Fig. 1) which enabled us to assign the undetermined stereocentres (C-29, C-30, and C-31) successfully and also revise the proposed configuration of the β-phenylalanine (C-3) counterpart of the molecule.

The retrosynthetic analysis of alveolaride C (**3**) is delineated in Scheme 1. There are a few possible sites in the molecule that



Scheme 1 Retrosynthesis of alveolaride C (**3**).

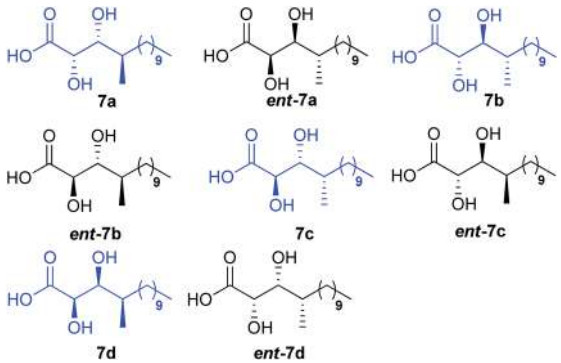


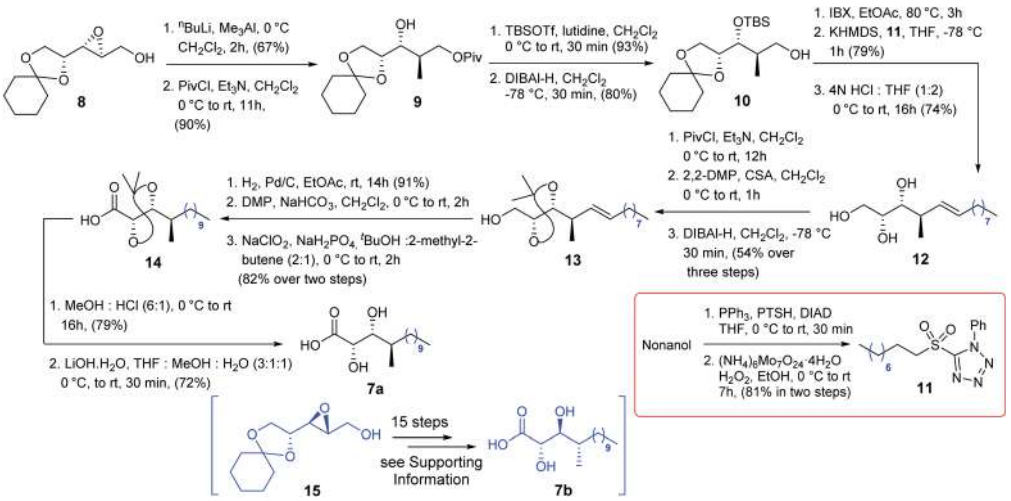
Fig. 2 Possible stereoisomers of 2,3-dihydroxy-4-methyl-tetradecanoic (DHMTDA) [**7(a–d)** and ***ent*-7(a–d)**].

are suitable for macrocyclization. We relied on the macrolactamization approach and planned to synthesize the target molecule from precursor **4** which further could be prepared from suitably protected compounds **5** and **6** by amide coupling. Compound **5** could be synthesized from acid **7** by amide coupling with the D-serine residue followed by intermolecular esterification with the N-protected D-β-phenylalanine counterpart.

There are three stereocentres in the DHMTDA counterpart of alveolaride C which remained unassigned during its discovery. Thus, it could be conceived that the structure of DHMTDA would match with one out of eight possible stereoisomers [**7(a–d)** and ***ent*-7(a–d)**, Fig. 2]. To solve this structural riddle, we initially planned to synthesize four of them **7(a–d)** with an intension to compare their spectroscopic data with the reported data of the DHMTDA segment. The initial trial of the isolation group to confirm the absolute configurations of these stereocentres using Mosher's ester method was not successful as the required ester did not form.[3]

Results and discussion

The synthesis of acid **7a** commenced with the known epoxide **8** [5a] (Scheme 2) which was treated with ^{n}BuLi/Me_3Al[6] followed by treatment with $NaIO_4$ to obtain the corresponding 1,3-diol which was further reacted with PivCl/Et_3N to obtain compound **9**. The secondary hydroxy centre of compound **9** was protected as TBS ether and subsequently treated with DIBAL-H to access alcohol **10** which was oxidized further using IBX. The resultant aldehyde was then subjected to Julia–Kocienski olefination[7] with sulfone **11**, prepared from nonanol in two steps (Scheme 2), in the presence of KHMDS to produce the corresponding olefin with complete *E*-selectivity and treated further with 4N HCl/THF to obtain triol **12**. Next, triol **12** was treated with PivCl/Et_3N followed by 2,2-DMP/CSA and finally with DIBAL-H to yield compound **13** efficiently. It was then hydrogenated and subsequently oxidized to acid **14** following a two-step protocol, and DMP oxidation followed by Pinnick oxidation. Many conditions (HCl/THF, AcOH/H_2O, HF/Py, CSA/MeOH, and HCl/MeOH) at different temperatures were screened to deprotect the acetonide of acid **14**. CSA/MeOH for 23 h as well as HCl/MeOH for 16 h

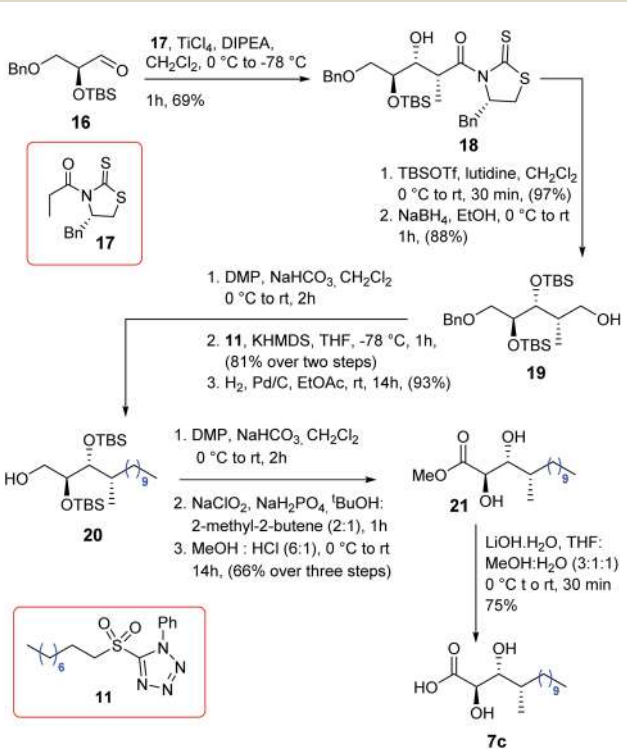


Scheme 2 Synthesis of acids **7a** and **7b**.

provided the corresponding acetonide deprotected product in satisfactory yield. However, the acid functionality concomitantly transformed into its corresponding methyl ester which was later hydrolyzed using $LiOH \cdot H_2O$ to acid **7a**.

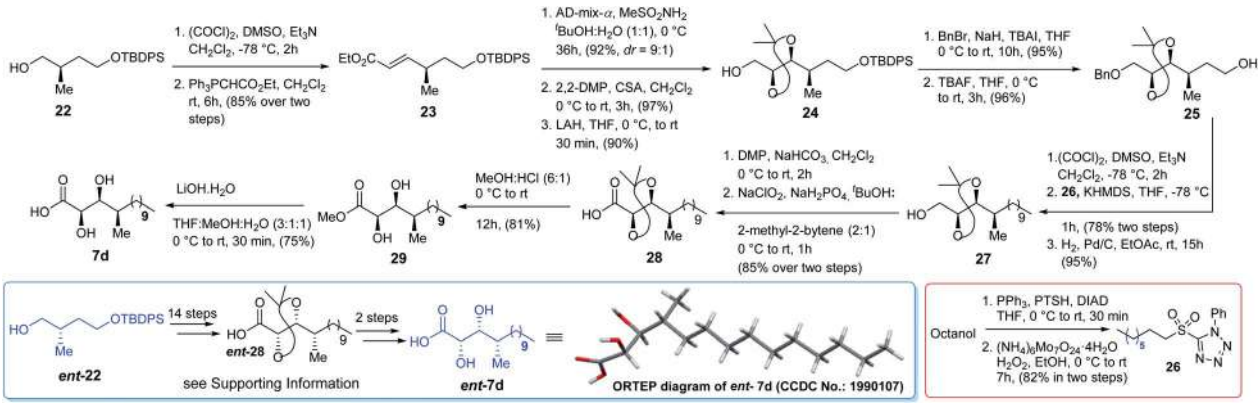
Acid **7b** was also synthesized from the known compound **15** [5] following exactly the same chemistry of acid **7a** [see Scheme S2 (page-S28) in the ESI†].

The synthesis of acid **7c** is described in Scheme 3. The known aldehyde **16** [8] was subjected to Crimmins aldol[9] using the thiazolidinethione **17** [9a] in the presence of $TiCl_4$/DIPEA to obtain compound **18** as a single isomer which was further treated using TBSOTf/2,6-lutidine followed by $NaBH_4$/EtOH to alcohol **19**. Next, alcohol **19** was oxidized to the corresponding aldehyde using DMP and subsequently subjected to Julia–Kocienski olefination[7] using sulfone **11** in the presence of KHMDS to yield the corresponding olefin with complete *E*-selectivity. The resultant olefin was hydrogenated further to provide compound **20** which was then oxidized to the corresponding acid using DMP following Pinnick oxidations. The acid was treated further with HCl/MeOH to yield compound **21** which finally was hydrolyzed to obtain acid **7c** in good overall yield.



Scheme 3 Synthesis of acid **7c**.

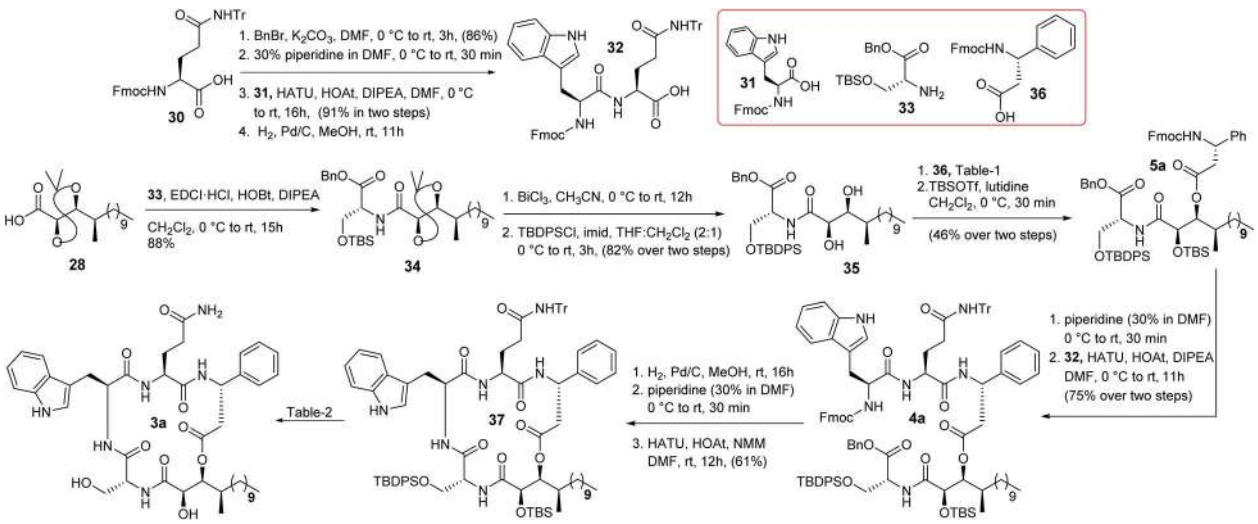
Initially we planned to introduce the *syn* C-2 and C-3 hydroxy centre of acid **7d** adopting the same approach as for the synthesis of acid **7c** using auxiliary ***ent*-17** but the required isomer was obtained as a minor product. Moreover, the use of glycolate aldol to install the same chiral centres of acid **7d** from compound **22** [10] was also not fruitful. Thus, compound **22** (Scheme 4) was oxidized using Swern conditions and the resultant aldehyde was subjected to Wittig olefination using Ph_3PCHCO_2Et to obtain olefin **23** exclusively. Next, olefin **23** was subjected to Sharpless asymmetric dihydroxylation[11] using AD-mix-α/$MeSO_2NH_2$ to obtain the corresponding diol ($d : r = 9 : 1$) which was further treated with 2,2-DMP followed by LAH to alcohol **24**. It was then benzylated and treated with TBAF to obtain alcohol **25** which was oxidized further. The resultant aldehyde was subjected to Julia–Kocienski olefination[7] using sulfone **26**, prepared from octanol in two steps (Scheme 4), to access the corresponding *E*-olefin exclusively. The resultant olefin finally was hydrogenated to obtain alcohol **27** which was oxidized further to acid **28** in two steps. Treatment of acid **28** with HCl/MeOH provided methyl ester **29** which was hydrolyzed to acid **7d**. Comparison of both ^1H and ^{13}C NMR data [see Tables ST1 to ST4 (page-S3 to S6) in the ESI†] with the reported data[3] revealed that acid **7d** was the best match among the four isomers synthesized. The optical rotation of the DHMTDA unit was not reported by the isolation group. Thus, one needs to consider the possibility of its enantiomer ***ent*-7d** also as the



Scheme 4 Synthesis of acids **7d** and ***ent*-7d**.

absolute configurations of those centres were not known. Thus, ***ent*-7d** (Scheme 4) was also synthesized from the known compound ***ent*-22** [10] following exactly an identical approach to acid **7d** [see Scheme S5 (page-S49) in the ESI†]. Fortunately, acid ***ent*-7d** crystallized and the structure was confirmed unambiguously using X-ray crystallographic analysis [see Fig. SF1 (page-S7) and Table ST5 (page-S7) in the ESI†]. We planned initially to synthesize both the macrocycles bearing acid **7d** and ***ent*-7d** as the DHMTDA unit to compare their NMR data with the reported data of the isolated alveolaride C.

The synthesis of compound **3a** is depicted in Scheme 5. N-protected L-glutamine was treated with $BnBr/K_2CO_3$ followed by 30% piperidine to obtain the corresponding Fmoc deprotected product that was further coupled with N-protected L-tryptophan in the presence of HATU/HOAt/DIPEA[12] to obtain the corresponding amide which was hydrogenated to produce the required dipeptide unit **32**. On the other hand, the previously synthesized compound **28** was coupled with the known D-serine counterpart **33** [13] to access compound **34** which was then treated with $BiCl_3$ to yield the corresponding acetonide and TBS deprotected triol. The primary hydroxy group of the corresponding triol was protected as TBDPS ether to obtain diol **35**. Next, different conditions for the selective esterification of diol **35** with protected D-β-phenylalanine (**36**)[14] were screened (Table 1). The Yamaguchi conditions were not tested because the isolation group was unable to obtain the required Mosher's ester under these conditions.[3] EDCI based esterification[15a,b] was found to be ineffective (entry 1). However, the Shiina esterification protocol[15c] produced (entry 2) the corresponding C-3 esterified product in moderate yield (52%), which was protected further as TBS ether to obtain compound **5a**. The change of solvent polarity in the Shiina protocol did not offer any encouraging result (entry 3 & 4). It was observed that the esterification reaction was highly sensitive to moisture and impurity. It is noteworthy that we were unable to detect the formation of any C-2 or bis(C-2/C-3) esterified products during this esterification reaction likely due to the engagement of the C-2 hydroxy group in strong hydrogen bonding[16] with the adjacent amide carbonyl. The formation of compound **5a** was confirmed by detailed 2D NMR analysis [see Fig. SF2 (page-S8),



Scheme 5 Completion of total synthesis of compound **3a**.

Table 1 Optimization for esterification

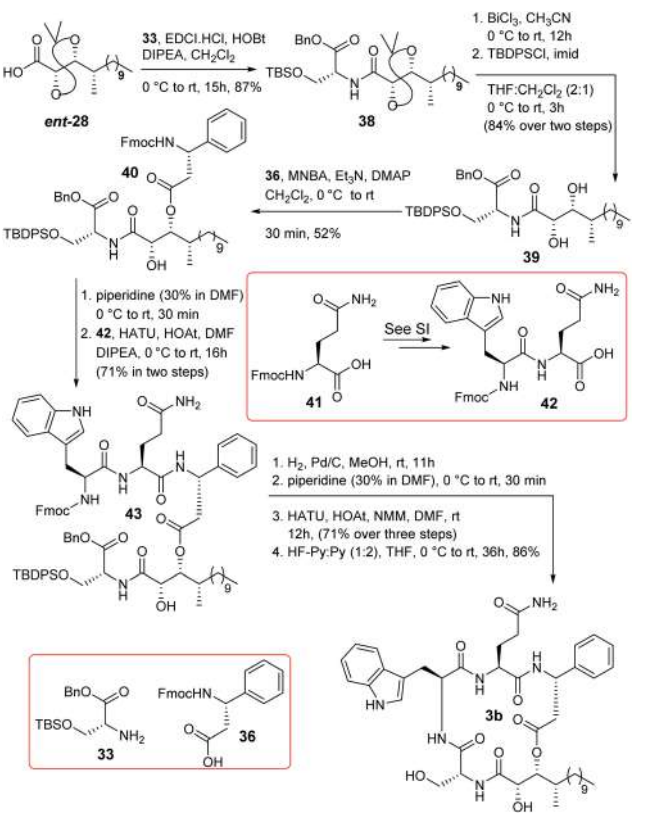
Entry	Conditions	Yield (%)
1	EDCI, HCl, CH_2Cl_2, 0 °C to rt, 6 h	No reaction
2	MNBA, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 30 min	52
3	MNBA, Et_3N, DMAP, DMF, 0 °C to rt, 30 min	Unidentified product
4	MNBA, Et_3N, DMAP, toluene, 0 °C to rt, 30 min	47

Table 2 Optimization for global deprotection

Entry	Conditions	Result
1	CSA in MeOH, 0 °C, 2 h	Decomposition
2	HCl (2N) : THF (1 : 2), 0 °C, 1 h	Decomposition
3	AcOH : H_2O (8 : 2), 0 °C, 4 h	Decomposition
4	TBAF in THF, 0 °C, 1 h	Decomposition
5	TBAF : AcOH (1 : 1), in THF, 0 °C to rt, 24 h	Partial deprotection of TBDPS and TBS
6	HF-Py in THF, 0 °C to rt, 24 h	Partial deprotection TBDPS and TBS with some unidentified spot
7	HF-Py : Py (1 : 2) in THF, 0 °C to rt, 36 h	Only silyls were deprotected
8	15% TFA in DCM, 0 °C to rt, 30 min	Only trityl was deprotected

COSY (page-S110) and HSQC (page-S110) in the ESI†]. Next, compound **5a** was treated with 30% piperidine/DMF and the resultant compound was coupled with dipeptide **32** to furnish compound **4a** in good overall yield. Hydrogenation followed by treatment with 30% piperidine/DMF resulted in the corresponding precursor of macrolactamization from compound **4a** in good yield. Quite a few reaction conditions were screened at this stage for macrocyclization. EDCI/DIPEA/DMF did not function whereas PyBOP/DIPEA/DMF,[17a] HATU/HOAt/DIPEA/DMF[17b] and HATU/HOAt/NMM/DMF [17c] provided the cyclized product **37** in 38%, 51% and 61% yield, respectively. Next, a detailed optimization (Table 2) for the global deprotection was performed. It was observed that compound **37** decomposed completely in the presence of CSA/MeOH (entry 1), HCl/THF (entry 2), AcOH/H_2O (entry 3) and TBAF/THF (entry 4). TBAF/AcOH (1 : 1) (entry 5), HF-Py (entry 6), and HF-Py/Py (1 : 2) (entry 7) provided only the corresponding desilylated product at different extents. HF-Py/Py was found to be the best desilylation condition compared to others in our case. It was observed that 15% TFA in CH_2Cl_2 (entry 8) deprotected only the trityl of compound **37** where the silyl ethers remained unaffected. Thus, a two-step protocol was adopted for the global deprotection where compound **37** was first subjected to trityl deprotection (entry 8) and subsequently silyl deprotection (entry 7) to access compound **3a** in good overall yield (68% in two steps).

Some changes in the protection group strategy with respect to the route of compound **3a** were adopted during the synthesis of compound **3b** (Scheme 6) as the global deprotection of compound **37** was challenging. ***ent*-28** was coupled with compound **33** to obtain compound **38** which was then converted to compound **39** by functional group manipulation. Compound **39** was then esterified with acid **36** following the Shiina protocol to obtain compound **40**. Next, the Fmoc group of compound **40** was deprotected and the resultant compound was coupled with dipeptide **42** to access compound **43**. It is noteworthy that dipeptide **42** was prepared directly from Fmoc protected L-glutamine (**41**) [see Scheme S8 (page-S65) in the ESI†] to avoid the trityl deprotection step in the final stage of the synthesis. Next, compound **43** was hydrogenated and subsequently reacted with piperidine to furnish the corresponding precursor of macrolactamization. Cyclization using HATU/HOAt/NMM resulted in the corresponding product which finally was

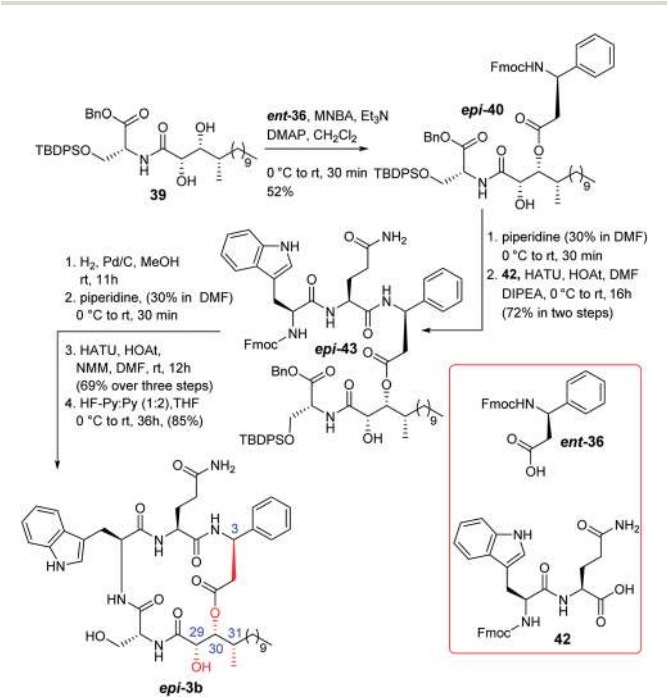


Scheme 6 Completion of total synthesis of compound **3b**.

treated with HF-Py/Py (1 : 2) in THF to obtain compound **3b** in good overall yield.

The ^{1}H and ^{13}C NMR data of both compounds **3a** and **3b** were compared with the reported data of the isolated natural product [see Tables ST6 (pages S9 and S10), and ST7 (pages S11 and S12), Fig. SF3 (page-S15), SF4 (page-S15), SF5 (page-S16) and SF6 (page-S16) in the ESI†]. Major mismatches were observed for compound **3a** in both ^{1}H and ^{13}C NMR data whereas the ^{1}H NMR data of compound **3b** seemed promising even though some anomalies were observed in its ^{13}C NMR data. However, few noticeable discrepancies in the ^{1}H NMR data of compound **3b** were observed for the protons near the β-phenylalanine and DHMTDA counterparts. The H-2 of β-phenylalanine was reported at 2.87 and 3.15 ppm whereas the same protons for the synthesized compound **3b** were observed at 2.83 ppm. Moreover, anomalies in H-3 and aromatic protons (H-5, H-6, H-8 and H-9) of the phenyl ring of β-phenylalanine were also observed where the difference in the chemical shift was more than 0.3 ppm. The difference of ∼0.2 ppm in the chemical shift was also noted for H-29, H-30 and H-31. These observations clearly indicated that the stereochemistry of either C-3 or C-29 or C-30 or C-31 or all might not be accurate. However, the stereochemistry of all the centres (C-29, C-30, and C-31) of the DHMTDA counterpart was confirmed by NMR and X-ray crystallographic analysis but the absolute stereochemistry of amino acids of alveolaride C (**3**) was proposed by comparing the NMR data with those of alveolaride A (**1**) without performing degradation chemistry due to the lack of compound.[3] Therefore, we decided to synthesize the C-3 epimer of compound **3b**.

The completion of total synthesis of the actual structure of alveolaride C (***epi*-3b**) is shown in Scheme 7. The chemistry adopted was exactly the same as that of compound **3b**. Compound **39** was esterified with Fmoc protected L-β-phenylalanine (***ent*-36**)[14] to access compound ***epi*-40** which was then coupled with dipeptide **42** to obtain compound ***epi*-43**. It was then hydrogenated and subjected further to Fmoc deprotection. The resultant compound was then cyclized to obtain the corresponding macrocyclic compound. Finally, the TBDPS ether was deprotected to provide compound ***epi*-3b** in good overall yield (59% over four steps). The ^{1}H and ^{13}C NMR data were recorded. We were quite delighted to observe that the NMR and optical rotation {observed $[\alpha]_{D}^{25} = -15.8$ (*c* 0.21, MeOH); reported $[\alpha]_{D}^{25} = -10.2$ (*c* 0.12, MeOH)} data of our synthesized compound ***epi*-3b** were in accordance [see comparison Table ST8 (page-S13, S-14) and Fig. SF7 (page-S16) in the ESI†] with the reported data of the isolated natural product which clearly established the actual structure of alveolaride C. It is noteworthy that the ^{13}C signals of C-6 and C-8 of the phenyl ring of β-phenyl alanine were reported at δ 126.4 ppm whereas the same carbons of very similar alveolarides A (**1**) and B (**2**) were reported at δ 128.2 ppm by the isolation group. We observed the ^{13}C NMR signals of those carbons at δ 128.27 ppm for the synthesized alveolaride C (***epi*-3b**).[18]



Scheme 7 Completion of total synthesis of the actual structure of alveolaride C (***epi*-3b**).

Conclusions

In summary, a flexible and convergent route for the first total synthesis of structurally attractive alveolaride C was accomplished. The target natural product was prepared in 22 linear steps with 6.05% overall yield from the known compound ***ent*-22**. The structural riddle of alveolaride C was solved successfully. The absolute stereochemistry of three undetermined centres on the DHMTDA segment was established unambiguously as 29-(*S*), 30-(*R*) and 31-(*S*). The stereochemistry of β-phenylalanine was revised from *S* to *R*. This synthetic study will be immensely useful for establishing the structure of other members of the alveolaride family. The synthesis of other members of this family is under progress in our laboratory which will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 The crystal structure of ***ent*-7d** revealed a possible hydrogen bonding between the C-2 hydroxy and carbonyl oxygen of the acid moiety. A similar interaction could be expected between the C-2 hydroxy and carbonyl oxygen of the amide of compound **35**.

17 (*a*) N. K. Lim, X. Linghu, N. Wong, H. Zhang and C. G. Sowell, *Org. Lett.*, 2019, **21**, 147–151; (*b*) E. Y. Melikhova, R. D. C. Pullin, C. Winter and T. J. Donohoe, *Angew. Chem., Int. Ed.*, 2016, **55**, 9753–9757; (*c*) N. K. Lim, X. Linghu, N. Wong, H. Zhang, C. G. Sowell and F. Gosselin, *Org. Lett.*, 2019, **21**, 147–151.

18 This anomaly is most likely due to typographic mistakes. No spectra of alveolaride C were made available by the isolation group.

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Late-Stage Functionalization: Total Synthesis of Beauveamide A and Its Congeners and Their Anticancer Activities

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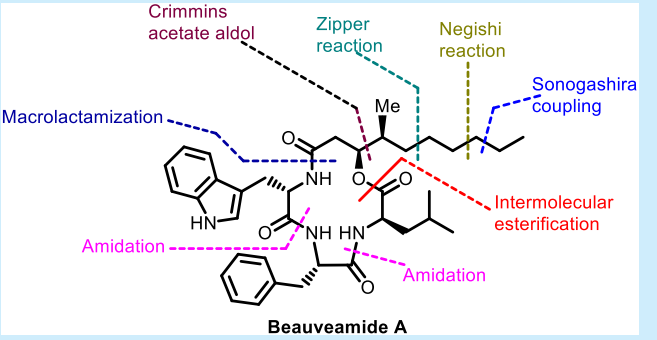
ABSTRACT: Asymmetric total synthesis of cyclotetradepsipeptide beauveamide A has been achieved for the first time. A macrolactamization strategy involving two possible sites has been explored to find the most effective route for cyclization. A late-stage functionalization approach has been adopted for easy access of non-natural analogues of beauveamide A for further biological evaluation. Interestingly, the anticancer activity of one of the synthesized analogues was better than that of the parent natural product.



Cyclodepsipeptides make up a large family of natural products having diverse architectural features. Many of them possess potential pharmaceutical and agrochemical value, which has attracted researchers worldwide to envisage their chemical synthesis.[1] During the search for novel secondary metabolites from endolichenic fungi, Puno and co-workers in 2021 discovered a family of seven new cyclotetradepsipeptides beauveamides A–G (**1**–**7**, respectively) along with the known cyclodepsipeptide beauverolide Ka (**8**) (Figure 1) using the cultures of endolichenic *Beauveria* sp. isolated from *Gypsoplaca macrophylla* (Zahlbr.) Timdal.[2] The structures of these natural products were determined using detailed spectroscopic analysis as well as Marfey's and NMR computational methods.[2] Structurally, beauveamides A–G **1**–**7** are 13-membered macrocycles bearing a common fatty acid moiety, 3-hydroxy-4-methyldecanoic acid (HMDA). There are three amino acids in the peptide segment that varies among the members. Beauveamides A (**1**) and B (**2**) exhibited protective effects on a mouse auditory cell line (HEI-OC1) at micromolar concentrations, whereas beauveamides A (**1**), D (**4**), and E (**5**) stimulated glucose uptake in cultured rat L6 myoblasts. Bioactivities, natural scarcity, and interesting structural features together with our[3] interest in natural product chemistry prompted us to embark on the chemical synthesis of beauveamide A (**1**), the most active member of this family, where the peptide part comprises D-leucine, L-phenylalanine, and L-tryptophan. Herein, we report the first total synthesis of beauveamide A (**1**) following a late-stage functionalization approach.[4] A common intermediate that could provide a diverse set of analogues having modification in the HMDA unit suitable to drive biological study has been designed. The anticancer activities of beauveamide A and two of its non-natural variants have been evaluated against human metastatic breast adenocarcinoma (MDA-MB-231) and cervical cancer (HeLa) cell lines in which one of analogues was found to be more effective than the parent natural product.

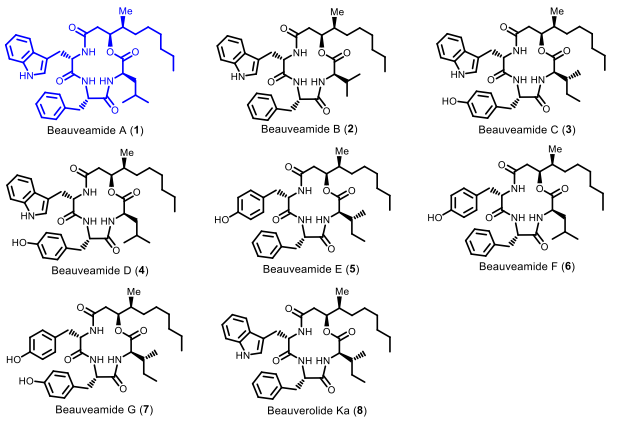


Figure 1. Chemical structures of beauveamides A–G (**1**–**7**) and beauverolide Ka (**8**).

The retrosynthetic analysis of beauveamide A (**1**) is depicted in Scheme 1, in which a late-stage functionalization approach has been adopted to diversify the synthetic route. The target

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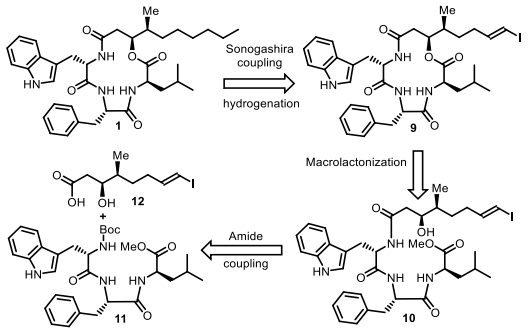
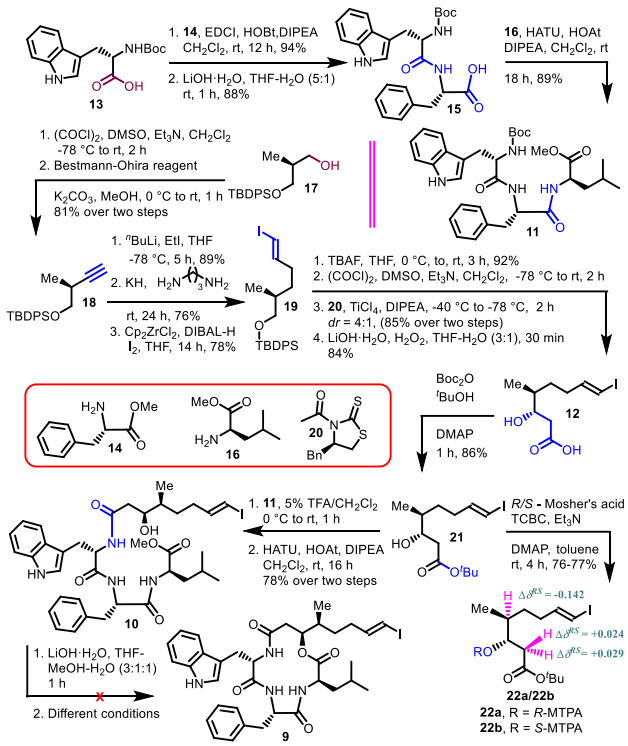
Scheme 1. Retrosynthesis of Beauveamide A (1)



natural product could be synthesized from key precursor **9** following Sonogashira coupling followed by hydrogenation. Notably, the introduction of vinyl iodide **9** would enable us to test the efficacy of the metal-mediated cross coupling in a peptide context. Moreover, designing this intermediate could provide biologically active unnatural analogues having unsaturation in the HMDA unit as it is known[5] that saturated lipidic amino acid is not very important to show activity. A macrolactonization approach could be planned to access compound **9** from the corresponding seco acid derived from compound **10**, which in turn could be prepared from tripeptide **11** and acid **12** using amidation chemistry.

The effort toward the synthesis of vinyl iodide **9** adopting a macrolactonization approach is depicted in Scheme 2. Commercially available Boc-protected tryptophan **13** was subjected to amidation with the known methyl ester of L-phenylalanine **14**[6] using EDCI/HOBt/DIPEA to obtain the corresponding coupled product, which was then hydrolyzed in the presence of $LiOH·H_2O$ to obtain dipeptide **15**. It was then

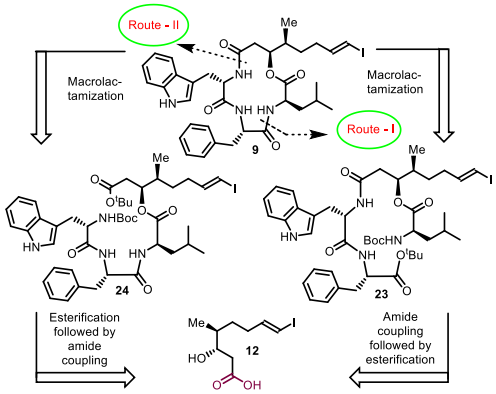
Scheme 2. Effort toward the Synthesis of Vinyl Iodide 9 following a Macrolactonization Approach



coupled with methyl D-leucinate **16**[7] using HATU/HOAt/DIPEA to access tripeptide **11** in very good overall yield. We then concentrated on the synthesis of the β-hydroxy γ-methyl aliphatic acid part following a route other than the existing approach.[8] The known alcohol **17**[9] was oxidized under Swern conditions and subjected further to Bestmann−Ohira reaction[10] to yield alkyne **18**. This was reacted with *n*-BuLi/EtI to obtain the corresponding ethylated product and subsequently exposed to zipper reaction conditions[11] to transform it into the corresponding terminal alkyne, which was finally reacted with Cp_2ZrCl/DIBAL-H/I_2 following the Negishi protocol[12] to access vinyl iodide **19** in 59% overall yield. The TBDPS ether of vinyl iodide **19** was then cleaved, and the resultant alcohol was oxidized using Swern conditions and concomitantly subjected to Crimmins acetate aldol[13] using the known *N*-acetylthiazolidinethione **20**[13a] to obtain the corresponding required aldol product (dr = 4:1). The major aldol isomer was separated from its minor counterpart and hydrolyzed using $LiOH·H_2O/H_2O_2$ to afford acid **12**, which was treated further with Boc_2O/*t*-BuOH to provide *tert*-butyl ester **21**. The absolute stereochemistry of the hydroxy center generated in the acetate aldol reaction was confirmed further as *R* by NMR analysis of synthesized Mosher's esters **22a** and **22b**.[14] Next, tripeptide **11** was treated with 5% TFA/CH_2Cl_2 and subsequently subjected to amidation with acid **12** in the presence of HATU/HOAt/DIPEA to obtain compound **10** in 78% yield (over two steps). The methyl ester of compound **10** was hydrolyzed to the corresponding seco acid, which was subjected to macrolactonization.[15] A number of conditions, including Steglich (DIPC/DMAP),[15a] modified Steglich (EDCI·HCl/collidine/DMAP),[15b] Shiina (2-methyl-6-nitrobenzoic anhydride/Et_3N/DMAP),[15c] and Yamaguchi (2,4,6-trichlorobenzoyl chloride/Et_3N/DMAP)[15d] protocols, have been screened under different conditions. Unfortunately, none of these conditions provided the required key intermediate **9**, which compelled us to search for a different strategy.

An alternative strategy for the synthesis of key intermediate **9** is depicted in Scheme 3, in which we relied on a macrolactamization approach. There are three sites for macrolactamization. To search for the shortest synthetic path, we planned to test the feasibility of this strategy in two possible sites using intermediates **23** (route I) and **24** (route II), which could be synthesized from acid **12** and the dipeptide

Scheme 3. Alternative Retrosynthetic Approach for Vinyl Iodide 9



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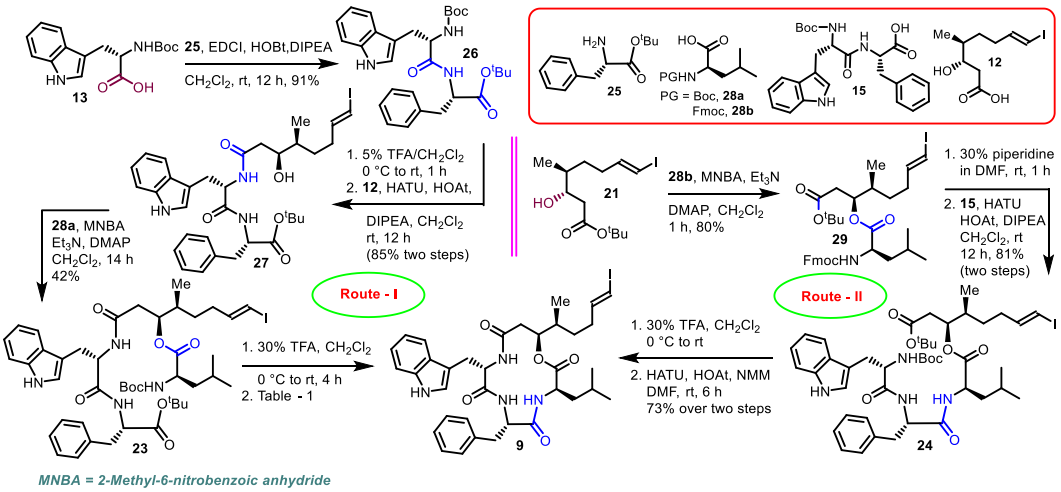
Scheme 4. Synthesis of Vinyl Iodide 9 Using a Macrolactamization Approach



of L-tryptophan-L-phenylalanine and D-leucine using amidation and esterification chemistry, respectively.

The synthesis of vinyl iodide **9** is depicted in Scheme 4. Suitably protected dipeptide **26** was prepared from commercially available Boc-protected L-tryptophan (**13**) and the known *tert*-butyl-L-phenyl alaninate (**25**)[16] in the presence of EDCI/HOBt/DIPEA, which was treated with 5%TFA/CH_2Cl_2 and subsequently coupled with acid **12** in the presence of HATU/HOAt/DIPEA to access compound **27** in 85% overall yield. The free hydroxy of compound **27** was then subjected to esterification using commercially available Boc-D-leucine (**28a**). Different protocols involving modified Steglich,[17] Yamaguchi,[18] and Shiina[19] conditions have been tested to obtain compound **23** in trace amounts, in 36% and 42% yields. Disappointingly, none of these conditions enhanced the yield of the esterification to a satisfactory level. Starting material **27** was recovered to different extents in all of the cases mentioned above. Next, the Boc and *tert*-butyl groups of compound **23** were deprotected using 30% TFA/CH_2Cl_2, and the resultant compound was subjected to macrolactamization. Different conditions have been screened (Table 1). HATU/HOAt/NMM conditions (entry 3) were found to be the best for producing vinyl iodide **9**. On the contrary, previously synthesized compound **21** was esterified with commercially available Fmoc-protected D-leucine (**28b**) following the Shiina conditions (MNBA/Et_3N/DMAP)[19] to produce compound **29** in 80% yield. It was then treated with 30% piperidine, and the resultant Fmoc-deprotected counterpart was coupled with dipeptide **15** in the presence of HATU/HOAt/DIPEA to obtain compound **24**. The Boc and *tert*-butyl groups of compound **24** were deprotected using 30% TFA/CH_2Cl_2 and subsequently subjected to macrolactamization in the presence of HATU/HOAt/NMM to afford vinyl iodide **9** in 73% yield.

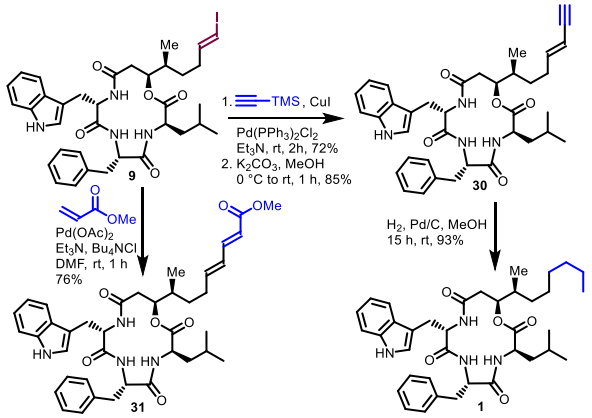
Table 1. Optimization of the Macrolactamization of Compound 23

entry	reagents and conditions	yield (%)
1	EDCI/HOBt/DIPEA, CH_2Cl_2, 0 °C to rt, 14 h	48
2	HATU/HOAt/DIPEA, DMF, 0 °C to rt, 10 h	72
3	HATU/HOAt/NMM, DMF, 0 °C to rt, 6 h	78
4	PyBOP/DIPEA, DMF, 0 °C to rt	65
5	COMU/DIPEA, DMF 0 °C to rt	59

Notably, the macrolactamization via intermediate **24** (route II) was found to be much more efficient than that via intermediate **23** (route I) as the esterification was found to be the determining step.

The completion of the total synthesis of beauveamide A (**1**) is shown in Scheme 5. A late-stage functionalization approach

Scheme 5. Completion of the Total Synthesis of Beauveamide A (1) and Its Congeners



was adopted in which vinyl iodide **9** was subjected to Sonogashira coupling[20] using TMS-acetylene in the presence of $Pd(Ph_3P)_2Cl_2/Et_3N$, and the coupled product was treated with K_2CO_3 in MeOH to furnish compound **30**, which was finally hydrogenated to compound **1** in 57% yield over three steps. The spectroscopic data of compound **1** were recorded and compared with the literature data. The ^1H and ^{13}C NMR data (see the comparison in Table S1 and Figures S2−S4) and specific rotation $[[\alpha]_D^{25} = -14.66$ (c 0.27, MeOH); reported $[\alpha]_D^{22} = -15.81$ (c 0.04, MeOH)] of synthesized compound **1** were in good agreement with the data of isolated beauveamide A, which unambiguously established the first total synthesis of the title natural product. The initial success in the diversification of vinyl iodide **9** following Sonogashira coupling prompted us to test the feasibility of the Heck coupling.[21] Thus, vinyl iodide **9** was treated with methyl acrylate in the presence of $Pd(Ph_3P)_2Cl_2/Et_3N/Bu_4NCl$ to access compound **31** in very good yield. Cyclodepsipeptide-based natural products are known to exhibit anticancer activities,[1,22] which

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made us curious to evaluate the anticancer efficacies of beauveamide A and its analogues **30** and **31** as no such literature precedents were available in this direction for this family of cyclodepsipeptides. The *in vitro* cytotoxic effects of synthesized compound **1** and its congeners **30** and **31** were determined by the MTT assay using HeLa and MDA-MB-231 cancer cell lines. The results suggested (Table 2) that the cytotoxicity of compound **31** was better than that of beauveamide A (**1**), whereas compound **30** was found to be the least active. Next, the mode of killing of cancer cells by all of the synthesized compounds was evaluated using flow cytometric analysis (Figure 2). The cell cycle of the MDA-MB-231 cells was measured. All of the synthesized compounds have shown a significant increase in DNA content at the sub-G0/G1 position, which is considered the signature peak for apoptosis. The untreated control set has very insignificant (5.6%) DNA content at the sub-G0/G1 position, whereas DNA contents of 45.6%, 33.5%, 53.7%, and 60.5% were observed with a distinct apoptotic peak for beauveamide A (**1**), compound **30**, compound **31**, and doxorubicin, respectively. FACS analysis was found to be consistent with the MTT assay in which the extent of inducing apoptosis of compound **31** was comparable to that of the known chemotherapeutic drug doxorubicin.

Table 2. Estimation of Cytotoxic Potentials of Beauveamide A (1) and Its Congeners (30 and 31) against Cancer Cell Lines

	IC_{50} (μM)	
compound	HeLa	MDA-MB-231
beauveamide A (**1**)	13.6	16.2
30	21.2	25.7
31	7.6	9.6
doxorubicin	5.5	8.0

In summary, we have achieved the first total synthesis of beauveamide A from known compound **17** in 18 linear steps with a 5.2% overall yield in which the applicability of both macrolactamization and macrolactonization approaches has been studied. The adopted late-stage functionalization approach diversified the synthesis, which has provided initially two analogues of the parent natural product quite efficiently. The anticancer activities of beauveamide A and two of its analogues have been evaluated for the first time. Interestingly, the effect of modification in the HMDA part of the target natural product is reflected in its bioactivity. The analogue having an enyne moiety (**30**), however, was found to be less active than the parent molecule, whereas analogues embedded with a conjugated ester (**31**) exhibited the best apoptotic results. It could be possible that the presence of a Michael acceptor in the HMDA part is responsible for the difference. This study left an opportunity to explore different beauveamide A variants by coupling a variety of suitable partners with key vinyl intermediate **9** to understand their structure−activity relationships. A related study is in progress in our laboratory and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02699.

Experimental section (chemistry and biology), NMR comparison (Table S1 and Figures S2−S4), two-dimensional (2D) NMR correlation (Figure S1), copies of NMR spectra (^{1}H, ^{13}C, and 2D), and HRMS spectra of representative compounds (PDF)

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Notes

The authors declare no competing financial interest.

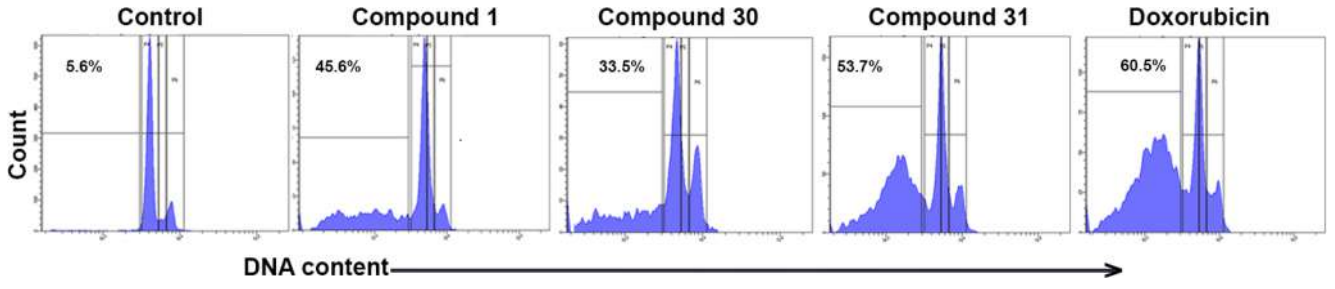

Figure 2. Compounds reduce cancer cell viability by triggering apoptosis. The apoptotic cell population was measured by flow cytometry analysis. MDA-MB-231 cells were treated with compounds **1**, **30**, and **31** at 25 μM for 48 h and stained with PI, and cell cycle analysis was performed in the flow cytometer. The percentages of apoptotic cells are given.

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