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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  $\beta$ -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.<sup>1</sup> Chemical synthesis of these metabolites is, thus, crucial for their unambiguous structural confirmation and to ensure adequate supply for exploring their biological importance.<sup>2</sup> 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.<sup>3</sup> 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.<sup>3</sup> 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- $\beta$ -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.<sup>3</sup> The

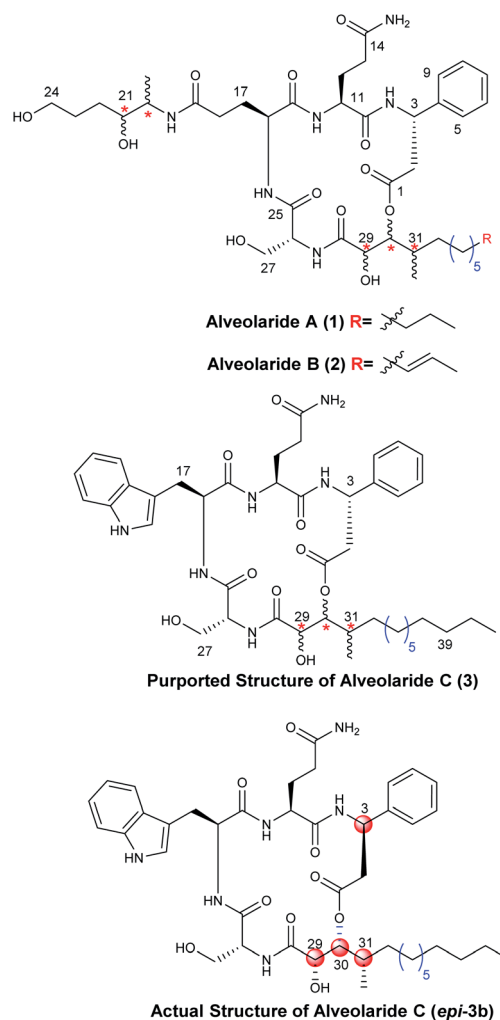


Fig. 1 Chemical structures of alveolarides.

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chemical structure of alveolaride C was proposed based on the similarities in the  $^1\text{H}$  and  $^{13}\text{C}$  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<sup>4</sup> 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.<sup>3</sup> 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.<sup>3</sup> 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  $\beta$ -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  $\beta$ -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

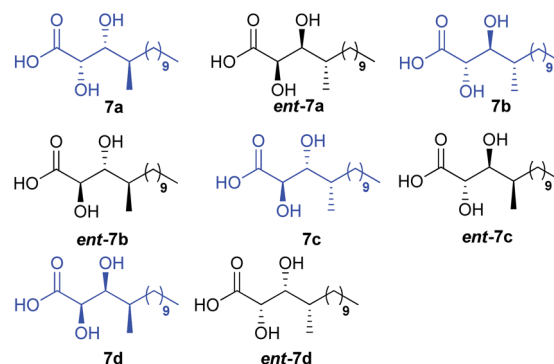


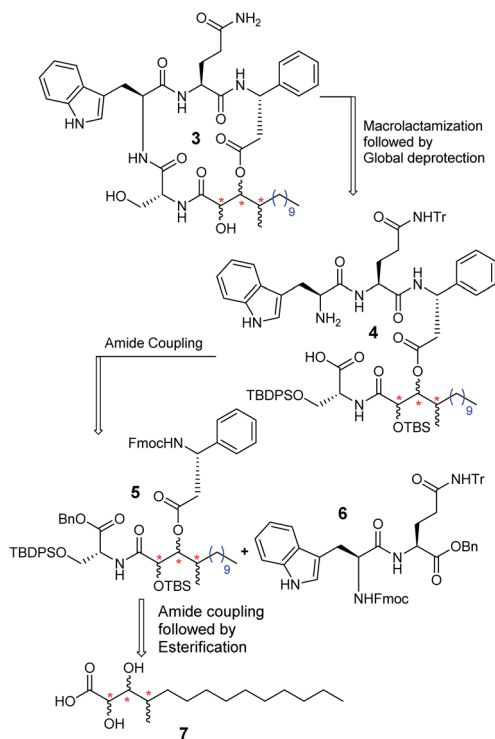
Fig. 2 Possible stereoisomers of 2,3-dihydroxy-4-methyl-tetradecanoic (DHMTDA) [7(a–d) and *ent*-7(a–d)].

are suitable for macrocyclization. We relied on the macro-lactamization 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*- $\beta$ -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 intention 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.<sup>3</sup>

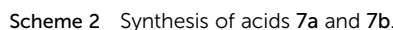
## Results and discussion

The synthesis of acid 7a commenced with the known epoxide 8<sup>5a</sup> (Scheme 2) which was treated with  $n\text{BuLi}/\text{Me}_3\text{Al}$ <sup>6</sup> followed by treatment with  $\text{NaIO}_4$  to obtain the corresponding 1,3-diol which was further reacted with  $\text{PivCl}/\text{Et}_3\text{N}$  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<sup>7</sup> 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 4*N*  $\text{HCl}/\text{THF}$  to obtain triol 12. Next, triol 12 was treated with  $\text{PivCl}/\text{Et}_3\text{N}$  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 ( $\text{HCl}/\text{THF}$ ,  $\text{AcOH}/\text{H}_2\text{O}$ ,  $\text{HF}/\text{Py}$ , CSA/MeOH, and  $\text{HCl}/\text{MeOH}$ ) at different temperatures were screened to deprotect the acetonide of acid 14. CSA/MeOH for 23 h as well as  $\text{HCl}/\text{MeOH}$  for 16 h



Scheme 1 Retrosynthesis of alveolaride C (3).

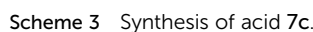


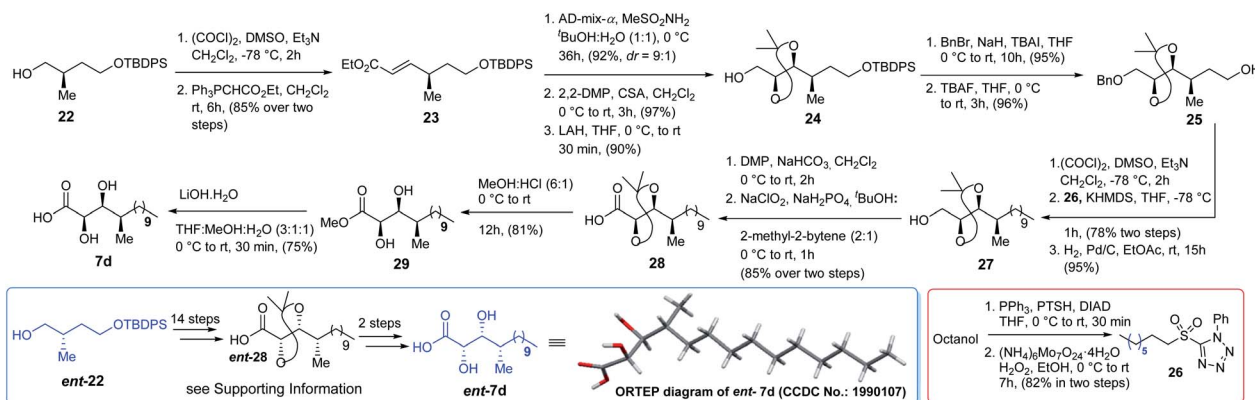


The synthesis of acid **7c** is described in Scheme 3. The known aldehyde **16**<sup>8</sup> was subjected to Crimmins aldol<sup>9</sup> using the thiazolidinethione **17**<sup>9a</sup> in the presence of TiCl<sub>4</sub>/DIPEA to obtain compound **18** as a single isomer which was further

treated using TBSOTf/2,6-lutidine followed by NaBH<sub>4</sub>/EtOH to alcohol **19**. Next, alcohol **19** was oxidized to the corresponding aldehyde using DMP and subsequently subjected to Julia-Kocienski olefination<sup>7</sup> 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.

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**<sup>10</sup> 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<sub>3</sub>PCHCO<sub>2</sub>Et to obtain olefin **23** exclusively. Next, olefin **23** was subjected to Sharpless asymmetric dihydroxylation<sup>11</sup> using AD-mix- $\alpha$ /MeSO<sub>2</sub>NH<sub>2</sub> 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<sup>7</sup> 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 <sup>1</sup>H and <sup>13</sup>C NMR data [see Tables ST1 to ST4 (page-S3 to S6) in the ESI†] with the reported data<sup>3</sup> 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

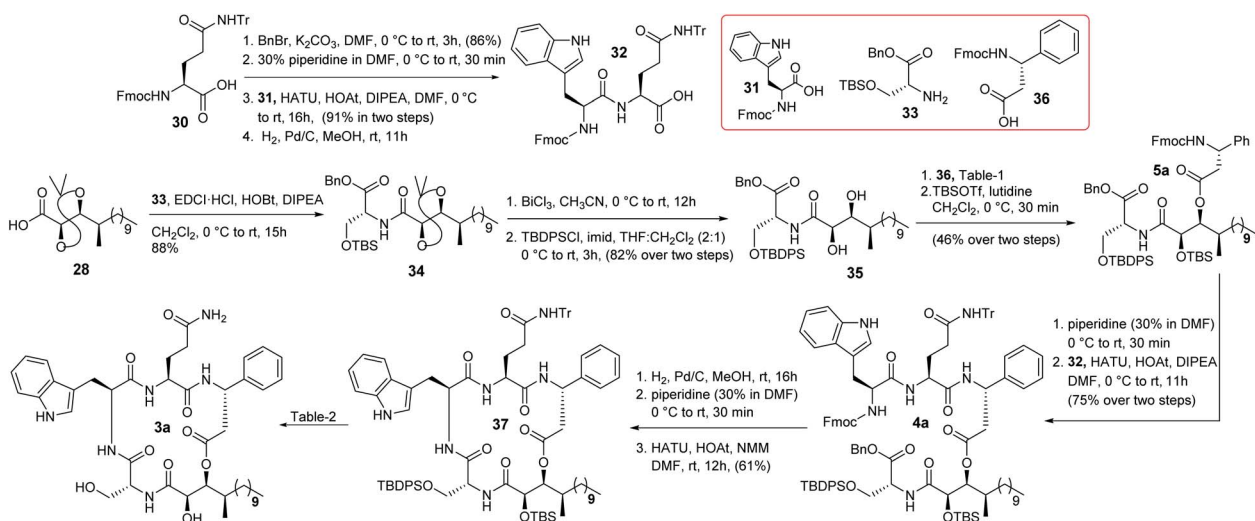


Scheme 4 Synthesis of acids 7d and *ent*-7d.

absolute configurations of those centres were not known. Thus, *ent*-7d (Scheme 4) was also synthesized from the known compound *ent*-22<sup>10</sup> 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<sub>2</sub>CO<sub>3</sub> 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<sup>12</sup> 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<sup>13</sup> to access compound 34 which was then treated with BiCl<sub>3</sub> 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)<sup>14</sup> 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.<sup>3</sup> EDCI based esterification<sup>15a,b</sup> was found to be ineffective (entry 1). However, the Shiina esterification protocol<sup>15c</sup> 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<sup>16</sup> 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 <sub>2</sub> Cl <sub>2</sub> , 0 °C to rt, 6 h	No reaction
2	MNBA, Et <sub>3</sub> N, DMAP, CH <sub>2</sub> Cl <sub>2</sub> , 0 °C to rt, 30 min	52
3	MNBA, Et <sub>3</sub> N, DMAP, DMF, 0 °C to rt, 30 min	Unidentified product
4	MNBA, Et <sub>3</sub> N, DMAP, toluene, 0 °C to rt, 30 min	47

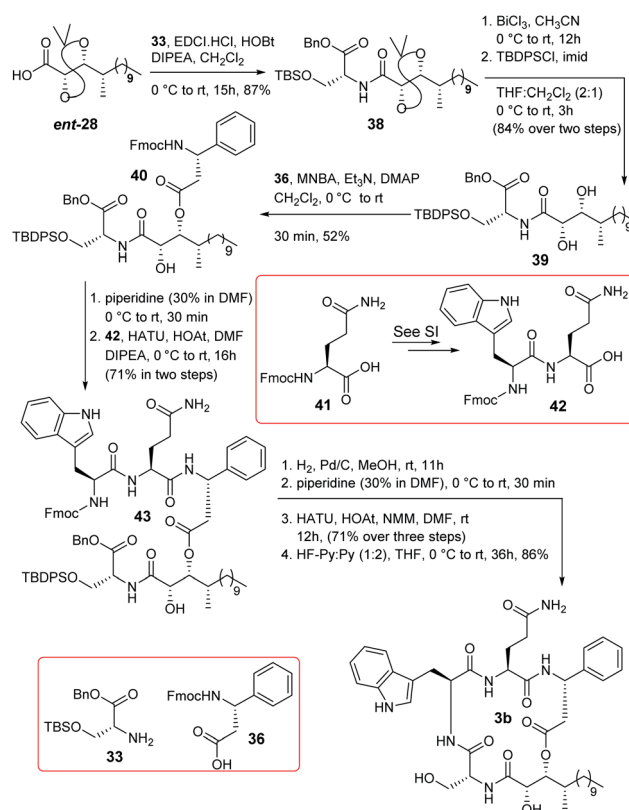
Table 2 Optimization for global deprotection

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 <sub>2</sub> O (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<sup>+</sup>. 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,<sup>17a</sup> HATU/HOAt/DIPEA/DMF<sup>17b</sup> and HATU/HOAt/MM/DMF<sup>17c</sup> 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<sub>2</sub>O (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<sub>2</sub>Cl<sub>2</sub> (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<sup>+</sup>] 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/MM 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  $^1\text{H}$  and  $^{13}\text{C}$  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  $^1\text{H}$  and  $^{13}\text{C}$  NMR data whereas the  $^1\text{H}$  NMR data of compound **3b** seemed promising even though some anomalies were observed in its  $^{13}\text{C}$  NMR data. However, few noticeable discrepancies in the  $^1\text{H}$  NMR data of compound **3b** were observed for the protons near the  $\beta$ -phenylalanine and DHMTDA counterparts. The H-2 of  $\beta$ -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  $\beta$ -phenylalanine were also observed where the difference in the chemical shift was more than 0.3 ppm. The difference of  $\sim 0.2$  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- $\beta$ -phenylalanine (**ent-36**)<sup>14</sup> 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  $^1\text{H}$  and  $^{13}\text{C}$  NMR data were recorded. We were quite delighted to observe that the NMR and optical rotation {observed  $[\alpha]_{\text{D}}^{25} = -15.8$  ( $c$  0.21, MeOH); reported  $[\alpha]_{\text{D}}^{25} = -10.2$  ( $c$  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  $^{13}\text{C}$  signals of C-6 and C-8 of the phenyl ring of  $\beta$ -phenylalanine were reported at  $\delta$  126.4 ppm whereas the same carbons of very similar alveolarides A (**1**) and B (**2**) were reported at  $\delta$  128.2 ppm by the isolation group. We observed the  $^{13}\text{C}$  NMR signals of those carbons at  $\delta$  128.27 ppm for the synthesized alveolaride C (**epi-3b**).<sup>18</sup>

## 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  $\beta$ -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

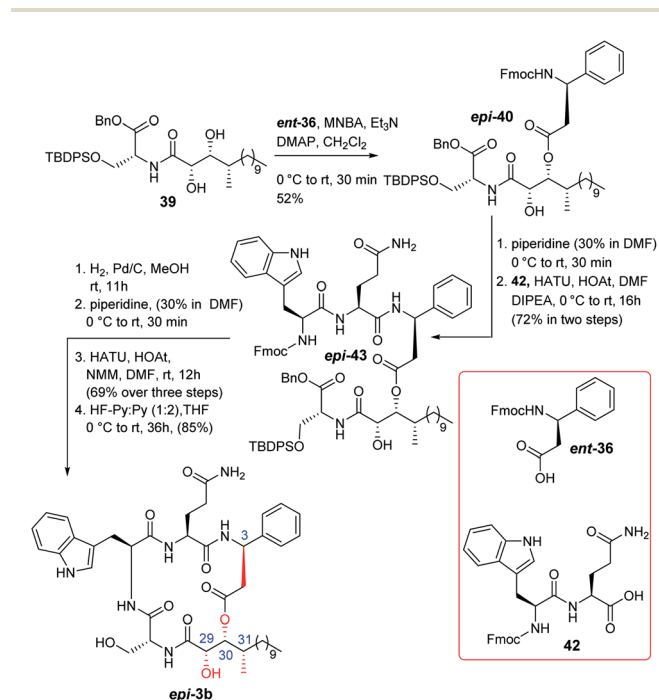
There are no conflicts to declare.

## Acknowledgements

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



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

