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First stereoselective total synthesis of triumfettamide

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ABSTRACT

The first total synthesis of triumfettamide (**1**) is described. The asymmetric syntheses of two highly functionalized units—α-hydroxylated C17 monounsaturated fatty acid unit (**2**) and C26 phytosphingosine (**3**) have been accomplished involving Sharpless asymmetric dihydroxylation, Sharpless kinetic resolution, regioselective epoxide opening, regioselective DIBAL-H reduction of acetal, Wittig olefination as the key steps. Finally N-acylation of phytosphingosine **3** with (2*R*,6*Z*)-2-hydroxy-6-heptadecenoic acid **2** followed by DDQ deprotection of PMB, provided target compound **1**.

1. Introduction

Phytoceramides (Fig. 1) are a unique class of secondary metabolites, which play essential roles in cell growth, survival and cell death. This class of compounds is composed of phytosphingosine base[1] and fatty acid linked by an amide bond. These are abundant in yeast, plants[2] and also in mammals.[3] They exhibit a wide spectrum of biological activities.[4] One important application of phytoceramides is in cosmetic industries as they play important roles in human stratum corneum.[5] They are involved in skin permeability and antimicrobial barrier homeostatic functions.[6]

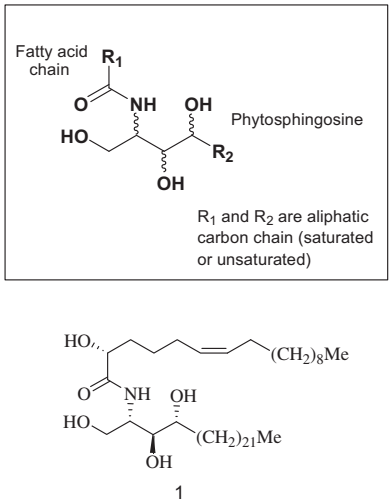

Fig. 1. Structure of phytoceramide and triumfettamide (**1**).

Triumfettamide **1** (Fig. 1), is a phytoceramide, which was isolated from *Triumfetta cordofolia A.* RICH,[7] a wild shrub, which is localized in the tropical Africa. This species is used as folk medicine for the treatment of diahorrea, dysentery and cholera. Its crushed stems are used to treat wounds and aqueous extracts of its stems and leaves are also employed as laxative, dystocia etc. We have long been engaged in the synthesis of bioactive natural products[8] having chiral 2-amino alcohol moiety and in continuation of our research work on synthesis of naturally occurring bioactive sphingolipids,[9] we report herein a concise and convergent synthesis of triumfettamide **1** involving Sharpless asymmetric dihydroxylation,[10] Sharpless kinetic resolution,[11] regioselective DIBAL-H reduction of acetal,[12] regioselective epoxide opening[13] and Wittig olefination[14] as the key steps. To the best of our knowledge, no total synthesis of **1** has been reported till date.

2. Results and discussion

2.1. Synthetic approach

Retrosynthetic analysis of triumfettamide **1** is depicted in Scheme 1. We envisioned completion of the synthesis of

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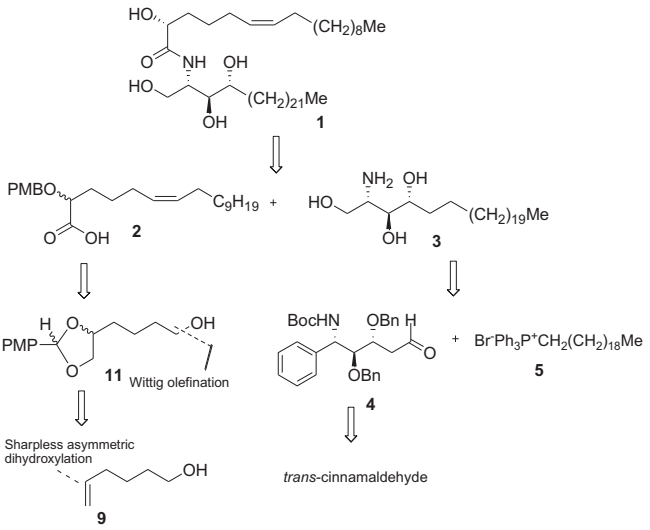
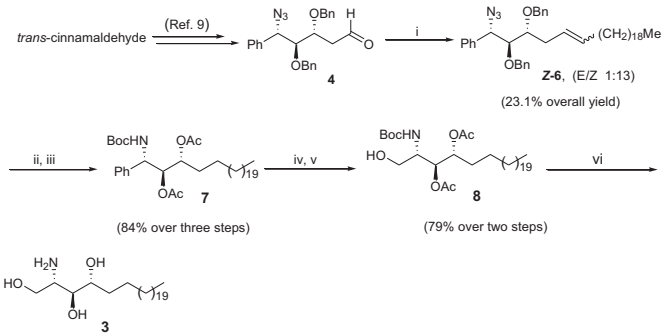


Scheme 1. Retrosynthesis of triumfettamide.

triumfettamide **1** occurring through N-acylation between C26 phytosphingosine **3** and (2*R*,6*Z*)-2-hydroxy-6-heptadecenoic acid **2**. The synthesis was designed with several key principles in mind, first we planned creation of chiral hydroxyl group at α-position of fatty acid **2** occurring through Sharpless asymmetric dihydroxylation[10] reaction of commercially available hex-5-en-1-ol **9**. The C-1 carbonyl groups of oxidized products of **11a** and **11b** would be elongated through Wittig olefination resulting *Z*-olefin of the required hydrocarbon chain. Reductive opening of acetal **12a**–**b** with DIBAL-H could be used for the formation of terminal primary alcohol, which in turn would be converted to carboxylic acid (Scheme 1). The C26 phytosphingosine part could be synthesized from aldehyde **4** through Wittig olefination with phosphonium salt **5**. Finally aldehyde **4** could be obtained from *trans*-cinnamaldehyde.

2.2. Synthesis of C26 D-*ribo*-phytosphingosine

Recently we have reported a stereoselective synthetic route to C18 D-*ribo*-phytospingosine starting from a cheap and commercially available *trans*-cinnamaldehyde.[9] Using the same synthetic route we synthesized the important intermediate aldehyde **4** from *trans*-cinnamaldehyde (Scheme 2). At this step different alkyl chains of varied length can be linked to construct phytosphingosines of different alkyl chain backbones. Here we used C20 phosphonium salt to get C26 phytosphingosine **3**.

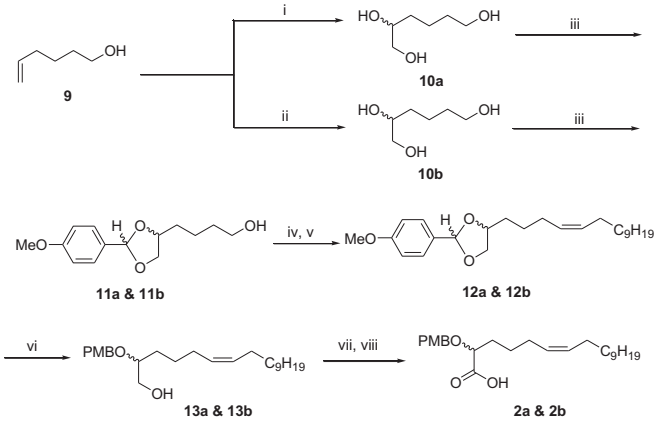


Scheme 2. Synthesis of C20 D-*ribo*-phytosphingosine. Reagents and conditions: (i) $Br^{-}Ph_3P^{+}CH_2(CH_2)_{18}Me$ (**5**), *n*-BuLi, THF, −40 °C to rt, 5 h; (ii) 10% Pd/C, H_2, EtOAc, rt; $(Boc)_2O$, Et_3N, DCM, rt; (iii) Ac_2O, pyridine, DMAP, 2 h,; (iv) $NaIO_4$, $RuCl_3\cdot H_2O$, CCl_4/CH_3CN/H_2O (2:2:3), 0 °C to rt, 8 h; (v) $BH_3\cdot Me_2S$, THF, −78 °C to rt, 6 h; (vi) pyridine, MeOH, rt, 4 h; TFA, rt, 2.5 h, 95% yield, 98% ee.

Wittig olefination of the aldehyde **4** with Wittig salt ($Br^{-}Ph_3P^{+}CH_2C_{19}H_{39}$) **5** using *n*-BuLi as base in dry THF at low temperature furnished the *Z*-olefin **6** contaminated with its *E*-isomer in the ratio of 13:1 in 23% overall yield starting from *trans*-cinnamaldehyde. Catalytic hydrogenation of compound **6** with 10% Pd/C in EtOAc[15] at room temperature reduced the azide and double bond as well as deprotected the benzyl groups. This on *N*-Boc protection with $(Boc)_2O$, Et_3N in DCM[16] followed by acetylation of the diol with Ac_2O in pyridine using DMAP[17] as catalyst gave the protected amino diol **7**. Phenyl ring cleavage to carboxylic group on treatment with $RuCl_3\cdot 3H_2O$, $NaIO_4$, in CH_3CN/CCl_4/H_2O solvent system[18] followed by $BH_3\cdot Me_2S$ reduction in dry THF[19] at room temperature provided the aminotriol **8**. Finally base catalysed deprotection of two O-Ac of **8** using Et_3N in MeOH[20] at room temperature followed by acid catalysed *N*-Boc deprotection (TFA/DCM at room temperature)[16] furnished the phytosphingosine **3**.

2.3. Synthesis of (2*R*,6*Z*)-2-hydroxy-6-heptadecenoic acid

As illustrated in Scheme 3, we began the synthesis of (2*R*,6*Z*)-2-hydroxy-6-heptadecenoic acid by subjecting hex-5-en-1-ol **9** to Sharpless asymmetric dihydroxylation[13] using AD-mix-α (and AD-mix-β) to provide the triols **10a**–**b** in 96% yield with 99% ee (as determined by chiral column HPLC) as colourless gum. The triol **10a**–**b** was protected as benzylidene acetals by reaction with dimethoxy acetal *p*-anisaldehyde and catalytic CSA giving compounds **11a**–**b** as a mixture of two diastereomers (1:1) in 96% yield.[21]



Scheme 3. Synthesis of (2*R*,6*Z*)-2-hydroxy-6-heptadecenoic acid. Reagents and conditions: (i) AD-mix-α, *t*-BuOH/H_2O (1:1), 0 °C, 96%; (ii) AD-mix-β, *t*-BuOH/H_2O (1:1), 0 °C, 96%; (iii) *p*-methoxybenzyl-dimethyl acetal, CSA, DCM, rt, 91%; (iv) Dess–Martin periodinane, $NaHCO_3$, DCM, rt; (v) $Br^{-}Ph_3P^{+}CH_2(CH_2)_9Me$, *n*-BuLi, THF, −45 °C to rt, 89% over two steps; (vi) DIBAL-H, DCM, −78 °C, 96%; (vii) Dess–Martin periodinane, $NaHCO_3$, DCM, rt; (viii) $NaClO_2$, $NaHPO_4$, *t*-BuOH, H_2O, H_2O_2, 87% over two steps.

Dess–Martin periodinane oxidation[22] of the terminal hydroxyl group of diastereomers **11a**–**b** provided the corresponding aldehydes, which were subjected to Wittig olefination using $Br^{-}Ph_3PCH_2(CH_2)_9Me$ in the presence of *n*-BuLi at −45 °C to furnish **12a**–**b** in 89% yield with major *Z*-olefin contaminated with its *E*-isomers in the ratio of 12.3:1. Regioselective reduction of acetal **12a**–**b** with DIBAL-H in DCM[12] at −78 °C provided the compound **13a**–**b** in 96% yield. Finally the terminal hydroxyl group of **13a**–**b** were oxidised to aldehyde using Dess–Martin periodinane followed by Pinnick oxidation[23] ($NaClO_2$, $NaHPO_4$, H_2O_2, *t*-BuOH/H_2O) to provide the PMB protected α-hydroxyl fatty acids **2a**–**b**.

2.4. Synthesis of triumfettamide

With phytosphingosine **3**, and fatty acids **2a**–**b** in hand, we performed the N-acylation by first converting the fatty acids **2a**–**b**