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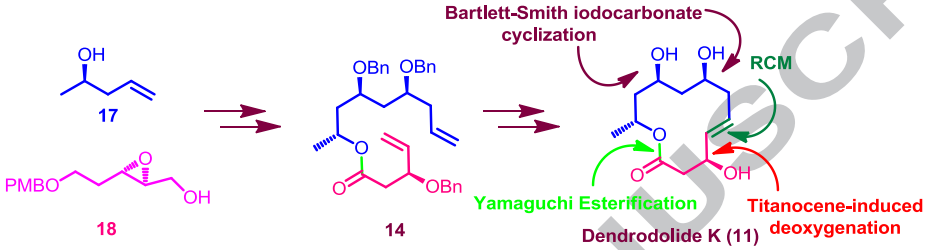

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13-Step total synthesis of Dendrodolide K following iterative Bartlett-Smith iodocarbonate cyclization

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ABSTRACT

A convergent total synthesis of Dendrodolide K has been achieved starting from commercially available homoallyl alcohol **17** in 13 longest linear sequence with 18.2% overall yield. The key features of this synthesis are Bartlett–Smith iodocarbonate cyclization reaction for the construction of 1,3-*syn* centers of the polyol system, Sharpless epoxidation followed by titanocene induced deoxygenation of 2,3-epoxy alcohol to fix stereogenic center at C-3 position, Yamaguchi esterification followed by ring-closing metathesis (RCM) reaction to form the macrolactone.

Naturally occurring 12-membered lactones isolated from fungal metabolites play an important role in the biochemical community due to their potent medicinal properties.[1] Many important 12-membered lactones such as recifeiolide,[2] Cladospolides,[3] and Patulolides[4] have phototoxic,[5] antibacterial,[6] antiviral,[7] antifungal and cytotoxic[8] activities. Recently, Zhang and co-workers reported the isolation of thirteen new 12-membered macrolides Dendrodolides A-M (**1-13**) from *Dendrodochium* sp.,[9] a fungus associated with the sea cucumber *Holothuria obilis* Selenka, which was collected from the South China Sea. These were the first group of 12-membered macrolides from the fungus of the genus *Dendrodochium*. The structures of the Dendrodolides were elucidated by means of

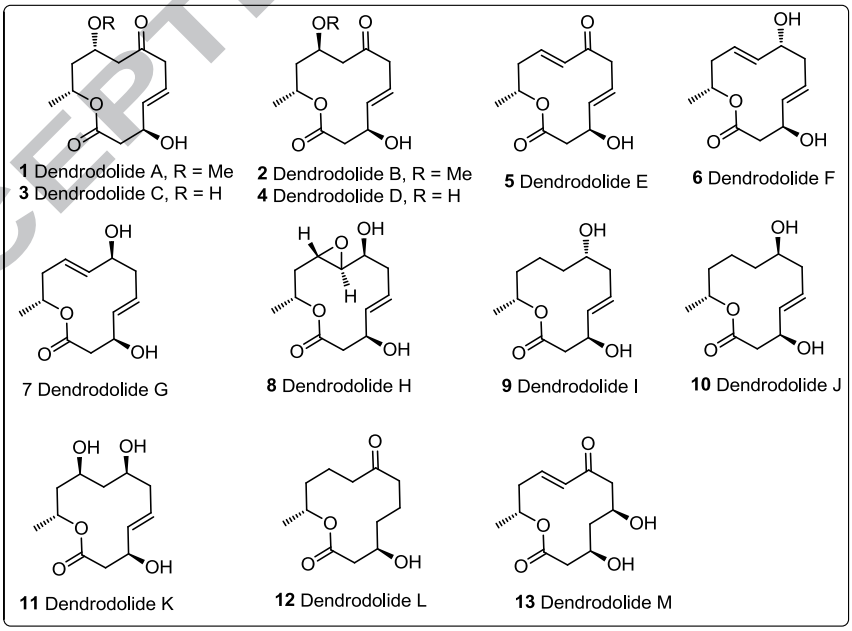

Figure 1: Structures of Dendrodolides.

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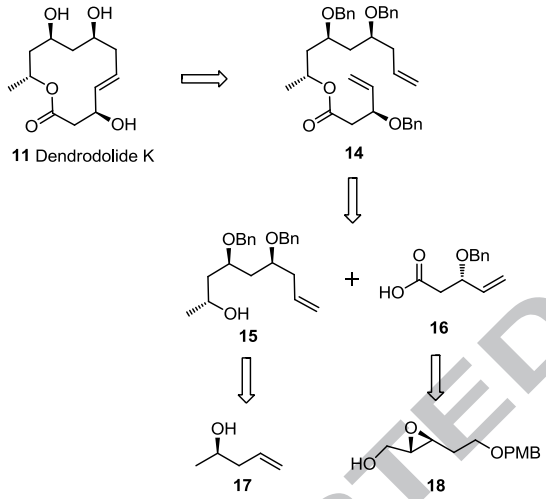
detailed spectroscopic analysis and X-ray single crystal diffraction studies. The absolute configurations were assigned using the modified Mosher's method, exciton-coupled circular dichroism (ECCD), electronic solution and solid-state circular dichroism (ECD) and X-ray analysis. In an in vitro bioassay, Dendrodolides exhibited different levels of growth inhibitory activity against SMMC-7721 and HCT116 Cells. The distinctive biological activities, fascinating structural architecture, and scarcity of natural products have attracted our attention to develop a general synthetic strategy to prepare majority or all thirteen Dendrodolides. We have already reported the synthesis of majority of macrolides of this group.[11a,b] Herein, we report the first stereoselective total synthesis of Dendrodolide K.

As part of our ongoing program in exploring the use of di-*tert*-butyl dicarbonate (Bocanhydride, Boc_2O) in the area of total synthesis particularly for creating 1,3-*syn* centers[10] and also ring-closing metathesis for macrolide syntheses,[11] we demonstrated the use of both strategies for the total synthesis of Dendrodolides K. The retrosynthetic analysis of Dendrodolide K is depicted in Scheme 1. The macrolactone **11** could be synthesized from bis-

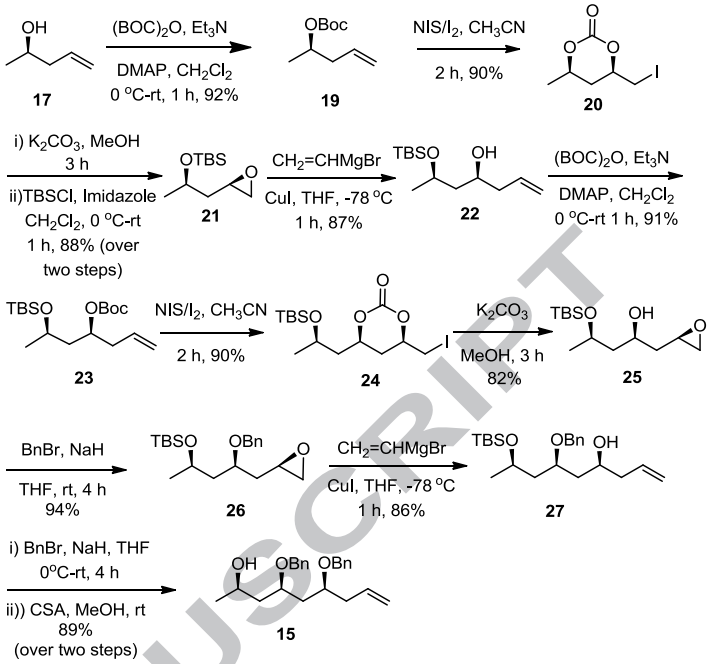


Scheme 1. Retrosynthetic analysis.

alkene **14** by utilizing ring-closing metathesis[12] reaction. Bis-alkene **14** would be synthesized by coupling alcohol **15** and acid **16** under Yamaguchi esterification conditions. Fragment **15** and **16** could be prepared from commercially available homoallyl alcohol **17** and known epoxy alcohol **18**, respectively.

Results and Discussion

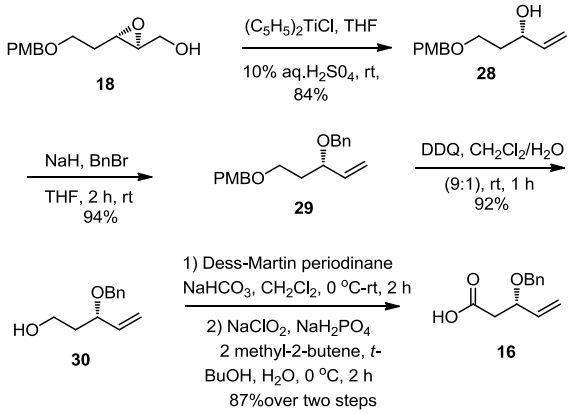
The synthesis of alcohol fragment **15** began with the commercially available (*R*)-pent-4-en-2-ol (**17**). Compound **17** was treated with di-*tert*-butyl dicarbonate in the presence of triethylamine and 4-(dimethylamino)pyridine (DMAP) to form homoallylic *tert*-butyl carbonate **19** in 92% yield.[13] The next stereogenic center of the triol system was achieved through Bartlett–Smith iodocarbonate cyclization reaction.[14] Accordingly, treatment of compound **19** with *N*-iodosuccinimide (NIS) or iodine in CH_3CN at 0 °C produced the desired iodocarbonate derivative **20** in 90% yield as the only product. Iodocarbonate **20** was treated with K_2CO_3 in MeOH that rapidly underwent hydrolysis to give in situ epoxy alcohol and was protected as its TBS ether with TBSCl in the presence of imidazol in CH_2Cl_2 at 0 °C to afford epoxide **21** in 88% yield. Treatment of **21** with vinyl magnesium bromide in the presence of a catalytic amount of copper(I) iodide at 0 °C furnished homoallyl alcohol **22** in 87% yield (Scheme 3).[15] compound **22** was treated with di-*tert*-butyl dicarbonate in the presence of triethylamine and 4-(dimethylamino) pyridine to afford homoallylic *tert*-butyl carbonate **23** in 91% yield.



Scheme 2. Synthesis of the fragment **15**.

Here, the Bartlett–Smith iodocarbonate cyclization reaction was repeated for generating the next sereogenic center of polyol system in an iterative mode to afford epoxy alcohol **25** in 86% yield. The secondary hydroxyl group was protected as its benzyl ether with BnBr in the presence of NaH in THF at 0 °C to afford epoxide **26** in 94% yield. Treatment of **26** with vinylmagnesium bromide in the presence of a catalytic amount of copper(I) iodide at 0 °C afforded homoallyl alcohol **27** in 86% yield (Scheme 2). The resulting hydroxyl group was then protected as its benzyl ether by using benzyl bromide in the presence of NaH in anhydrous THF followed by deprotection of silyl group under acidic conditions (CSA, MeOH) afforded the required fragment **15** in 89% yield over two steps.

Next, our focus was shifted towards the synthesis of acid fragment **16** which was started from known epoxy alcohol **18**.[16] Conversion of epoxy alcohol to allyl alcohol was achieved by applying titanium(III)-mediated $[(C_5H_5)_2TiCl]$ deoxygenation of 2,3-epoxy alcohol to opically pure allyl alcohol **28** in a single step with 84% yield.[17] The hydroxyl functionality present in **28** was protected as its benzyl ether with benzyl bromide in presence of NaH

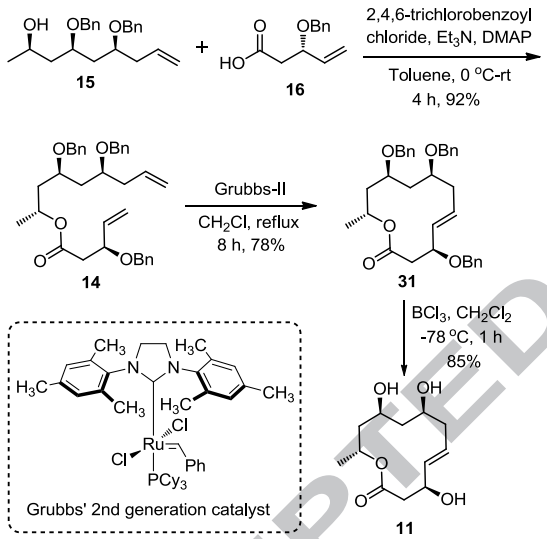


Scheme 3. Synthesis of the fragment **16**.

to achieve **29** in 94% yield. The PMB group was deprotected using DDQ under standard reaction conditions to afford the primary alcohol **30** in 92% yield. The primary alcohol **30** was converted to acid by following a two-step sequence; oxidation of primary alcohol to aldehyde by Dess-Martin periodinane[18] followed by further

oxidation under Pinnick conditions[19] to afford acid **16** in 87% yield over two steps (Scheme 3).

With the requisite fragments in hand, the coupling reaction between **15** and **16** was carried out to verify the output of RCM reaction. Accordingly, alcohol **15** and acid **16** were coupled under Yamaguchi conditions[20] using 2,4,6-trichlorobenzoyl chloride to furnish the required bis-alkene **14** in 92% yield. Pleasingly, 12-membered macrolactone formation under ring closing metathesis condition proceeded smoothly with Grubbs second generation catalyst in high dilution (0.01M) under refluxing conditions to afford **31** as a major isomer (*E*/*Z* = 9:1) in 78% yield. After formation of macrolactone core **31,** it was a crucial task to deprotect three benzyl groups in one pot. Different conditions like Li/Naphthalene[21] in THF, $TiCl_4$[22] in CH_2Cl_2 and DDQ[23] in aqueous CH_2Cl_2 were tried. Unfortunately, the product did not form and in all cases ended up with intractable mixture of compounds. Finally, treatment of compound **31** with BCl_3 in CH_2Cl_2 at –78 °C afforded **11** in 85% yield (Scheme 4).[24] The spectral and analytical data of **11** (^{1}H NMR, ^{13}C NMR and MS) were identical to those of reported for the natural product. The optical rotation of synthetic **11** {$[\alpha]_D^{27}$ +16.4 (*c* 0.43, $CHCl_3$)} was in good agreement with that of natural **11** {ref.[9] $[\alpha]_D^{27}$ +11.7 (*c* 0.285, $CHCl_3$)}.



Scheme 4. Synthesis of the Dendrodolide K

In summary, we have demonstrated an efficient and highly stereoselective approach to accomplish Dendrodolide K starting from commercial available homo allyl alcohol **17** following Bartlett-Smith iodocarbonate cyclization strategy and ring-closing metathesis reaction as key steps.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/xxxxx/xxxxxxxx.