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PAPER

A convergent stereocontrolled total synthesis of (−)-terpestacin†

Yehua Jin and Fayang G. Qiu*

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A stereocontrolled total synthesis of (−)-terpestacin has been achieved starting from (*R*)-(−)-carvone as a chiral pool and (*E*,*E*)-farnesol *via* a highly convergent approach. Thus, (*R*)-(−)-carvone was transformed into the cyclopentanone segment through a series of high yielding operations with the proper setup of all the stereochemical centers while (*E*,*E*)-farnesol was converted into the other requisite building block *via* a series of high yielding reactions. The cyclopentanone intermediate was both selectively enolized and alkylated at room temperature to yield the desired coupling product, which provided the natural product upon further transformations.

Introduction

Terpestacin (**1a**), (Fig. 1) a sesterterpene natural product, was first isolated from *Arthrinium*[1] in 1993 and then from *Ulocladium*[2] in 2001, though the enantiomeric structure was assigned in the latter case. Soon siccanol from *Bipolaris sorokiniana* was reported in 2002 to have the 11-*epi*-terpestacin structure.[3] Subsequently, Jamison demonstrated that siccanol was terpestacin through the total synthesis of (−)-terpestacin.[4] Fusaproliferin (**1b**), (Fig. 1) the C-24 acetate of terpestacin, was isolated from *Fusarium proliferatum* in 1993.[5] However, the correct absolute configurations of both (−)-terpestacin and (−)-fusaproliferin were defined only after Myers' total syntheses of both natural products.[6]

After its isolation, terpestacin was reported to be a potent inhibitor (ID_{50} 0.46 μg mL^{-1}) of the formation of syncytia,[1,2] which are multinucleated cells that account in part for the pathology of HIV infection, and to be an angiogenesis inhibitor both in bovine aortic endothelial cells and in chorioallantoic membrane from chick embryos.[1d] It was also shown that terpestacin had only weak antimicrobial activity,[1a] suggesting that the activity of terpestacin was selective and thus would potentially be valuable for the development of anticancer as well as anti-AIDS therapeutics.

Apart from the impressive biological activities, terpestacin possesses four chiral centers, three *E*-carbon–carbon double bonds, two vicinal ketone carbonyl groups and a structural feature of a five-membered ring fused to a fifteen-membered ring. These combined structural elements have imposed significant challenges to synthetic chemists. Consequently, terpestacin became an important target of total synthesis shortly after its discovery. So far, four total syntheses of (−)-terpestacin by Tatsuta and Masuda (1998),[7a] Myers *et al.* (2002),[6a] Jamison and Chan (2003),[4a] and more recently by Trost *et al.* (2007),[8] and two for the racemate by Tatsuta *et al.* (1998)[7b] and Tius and Berger (2007),[9a] respectively, have been reported, together with three approaches to the fused ring system independently described by Takeda *et al.* (1995),[10] Heissler and co-workers (1999),[11] and Tius and Berger (2005),[9b] respectively.

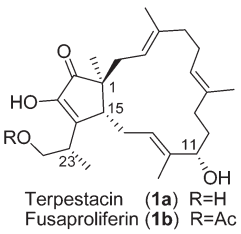

Fig. 1 Structures of terpestacin and fusaproliferin.

Results and discussion

We are interested in the development of a therapeutic material based on (−)-terpestacin. From a practical point of view, the starting materials and the reagents must be either commercially available or readily accessible and conventional reaction conditions are desired. Based on such considerations and the previous synthetic accomplishments in this area, our synthetic strategy was designed to utilize high yielding reactions throughout the synthesis and to involve the least number of chromatographic separations. Herein we wish to disclose a convergent stereocontrolled total synthesis of (−)-terpestacin starting from

Laboratory of Molecular Engineering, and Laboratory of Natural Product Synthesis, Guangzhou Institutes of Biomedicine and Health, The Chinese Academy of Sciences, 190 Kaiyuan Avenue, Guangzhou 510530, China. E-mail: qiu_fayang@gibh.ac.cn

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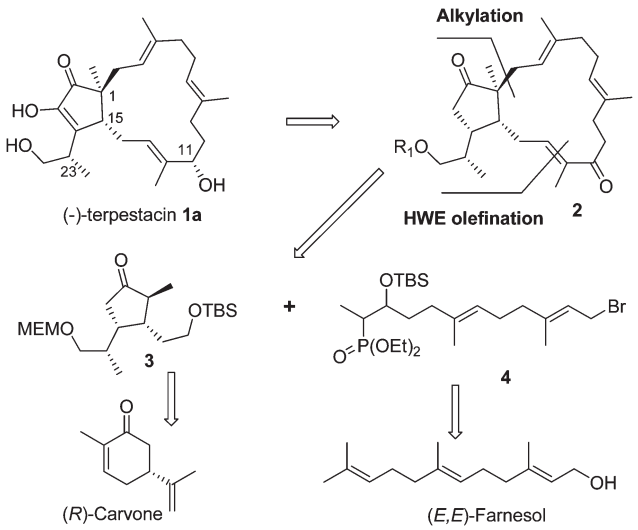
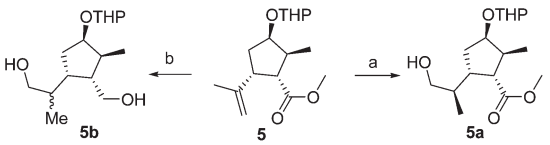
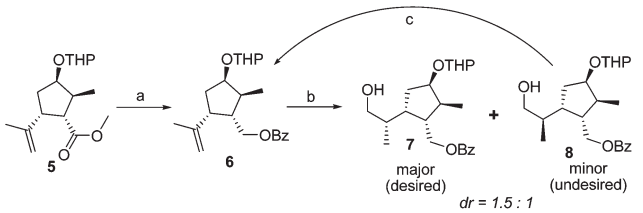


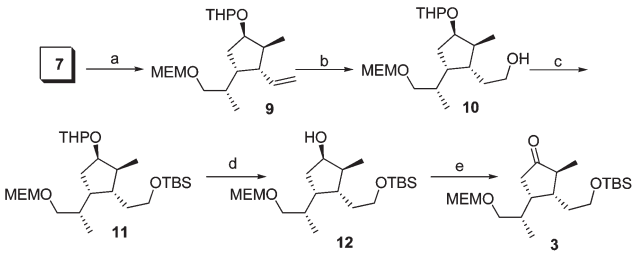
Scheme 1 The retrosynthetic analysis of (−)-terpestacin.



Scheme 2 Hydroboration of intermediate **5**. (a) Disiamylborane, THF, 0 °C, then NaOH, H_2O_2, 0 °C; (b) BH_3·DMS, THF, 0 °C, then NaOH, H_2O_2, 0 °C.



Scheme 3 Synthesis of intermediate **7**. (a) (i) LAH, THF, RT; (ii) BzCl, Et_3N, CH_2Cl_2, RT, 92% over two steps; (b) BH_3·DMS, THF, 0 °C, then $NaBO_3(H_2O)_4$, **7**/**8** = 53/35, 88%; (c) MsCl, Et_3N, LiBr–Li_2CO_3, 70%.



Scheme 4 Synthesis of the intermediate **3**. (a) (i) MEMCl, DIPEA, CH_2Cl_2, RT, 92%; (ii) 1% NaOH in MeOH, 90%; (iii) TEMPO, bis-(acetoxy)iodobenzene (BAIB), CH_2Cl_2, RT, 98%; (iv) Ph_3PCH_3Br, NaHMDS, THF, 0 °C, 91%, (74% over 4 steps); (b) BH_3·THF, THF, 0 °C, then NaOH, H_2O_2, 0 °C, 88%; (c) TBSCl, Et_3N, DMAP, CH_2Cl_2, RT, 98%; (d) $MgBr_2$, Et_2O, RT, 94%; (e) TEMPO, BAIB, CH_2Cl_2, RT, 96%.

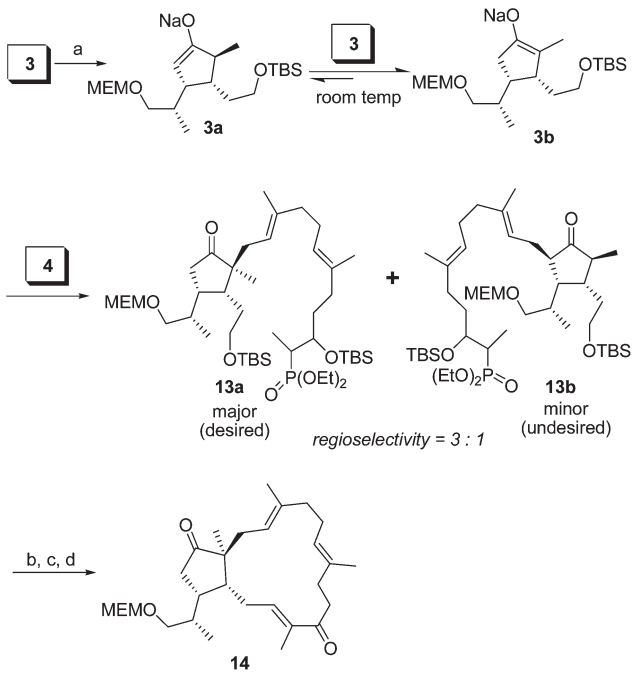
(*R*)-(−)-carvone and (*E*,*E*)-farnesol. The retrosynthetic analysis of terpestacin is outlined in Scheme 1. The vicinal diketone functionality in the five-membered ring may be introduced through oxidation of the ketone carbonyl of the bicyclic intermediate **2**, which may be derived from the cyclopentanone intermediate **3** and phosphonate **4**. While intermediate **3** may be derived from (*R*)-(−)-carvone, the phosphonate may be obtained from (*E*,*E*)-farnesol according to a similar known procedure.[7,9a]

Intermediate **5** was obtained from (*R*)-(−)-carvone as a single diastereomer (dr > 19 : 1) according to the procedure developed by Ley *et al.*[12] Hydroboration of **5** with disiamylborane afforded the undesired **5a** in 85% yield, in line with the observations of Yoon and Lee on a similar system.[13] Hydroboration with BH_3·Me_2S produced a mixture of the diol **5b**, in which both the carbon–carbon double bond and the ester functionality were hydroborated (Scheme 2). Thus, the ester functionality was reduced with LAH to the alcohol. After protecting the hydroxyl group with benzoyl chloride to form benzoate **6**, compound **7** and **8** were obtained when BH_3·Me_2S was used (Scheme 3). Compound **8** was dehydrated to recover the starting material (70%) according to a similar procedure.[14] Thus, the yield of the desired product **7** was promoted to 69% based on the recovered starting material. We believe that the ester functionality may have mainly displayed steric hindrance instead of coordination to the boron atom of the incoming hydroborating agent.

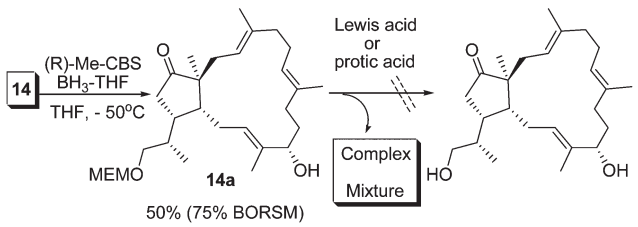
The hydroxyl group in **7** was protected with MEMCl and the benzoate was hydrolyzed with sodium hydroxide in methanol. After an extraction work-up, the newly formed alcohol was oxidized with TEMPO–BAIB to the aldehyde, which was, after a brief work-up, treated with the methyl ylide to provide the desired alkene **9** (74% for the combined 4 steps). Hydroboration of the olefin with the borane–THF complex followed by treatment with basic hydrogen peroxide afforded the desired alcohol **10** (88%). Subsequent conversion of **10** into the key intermediate **3** was achieved as a single diastereomer determined on the basis of ^{1}HNMR and ^{13}CNMR data analysis through a sequence of protection of the hydroxyl group with TBSCl–Et_3N, selective removal of the THP protective group with magnesium bromide in dry diethyl ether and oxidation of the secondary alcohol with TEMPO–BAIB (88% for the combined 3 steps) (Scheme 4).

On the other hand, (*E*,*E*)-farnesol was transformed into the desired phosphonate **4** through 8 reactions following a modified procedure initially developed by Tatsuta[7] and modified by Tius and Berger[9a] in 42% overall yield.

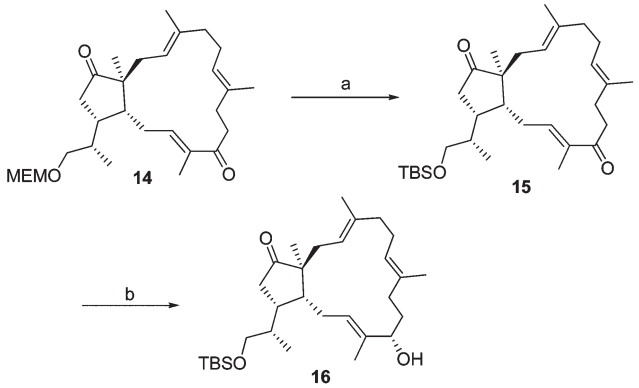
With both key intermediates in hand, we started to assemble the entire molecule. A highly selective deprotonation method was in need. However, the selectivity for the formation of a variety of thermodynamic silyl enol ethers was found to be poor, while the use of LHMDS or the Yamamoto *et al.* method,[15] which utilized the precoordination of the starting ketone with an aluminum complex before treatment with LDA, was unsuccessful in this case, either. Upon treatment with NaHMDS at −20 °C, intermediate **3** was deprotonated to give **3a**, the less highly substituted enolate, as a major product. The latter was treated with allyl bromide to afford the corresponding alkylation product in 95% yield. After these unsuccessful efforts, potassium *tert*-butoxide, sodium hydride, and a magnesium reagent[16] that were reported to be effective for this purpose were all tested, but



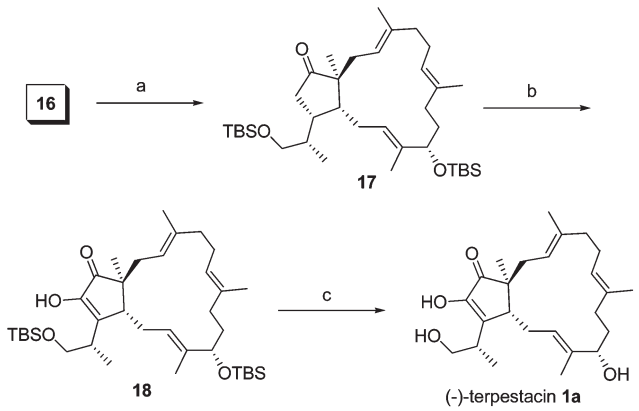
Scheme 5 Regioselective enolate formation from **3** and the synthesis of intermediate **14**. (a) NaHMDS (0.95 equiv), 2 h, then phosphonate **4**, 93%; (b) TBAF, THF, RT, 93%; (c) IBX, DMSO, RT, 80%; (d) DIPEA, LiCl, CH_3CN, RT, C = 0.005 M, 65%. (45% over 4 steps).



Scheme 6 Unsuccessful deprotection of the MEM group from **14a**.



Scheme 7 Synthesis of intermediate **16**. (a) (i) PPTS, *t*-BuOH, reflux; (ii) TBSCl, Et_3N, DMAP, CH_2Cl_2, RT, 70% over 2 steps; (b) (*R*)-Me-CBS, BH_3·THF, THF, −50 °C, 50%. (75% based on recovered starting material).



Scheme 8 Completion of the total synthesis of (−)-terpestacin. (a) TBSOTf, 2.6-lutidine, CH_2Cl_2, −78 °C, 97%; (b) (i) NaHMDS, *N*-sulfonyloxaziridines, THF, −78 °C; (ii) $Cu(OAc)_2$ in MeOH, RT, 79%; (c) HF, THF, RT, 90%.

none provided satisfactory selectivity. Fortunately, slow addition of NaHMDS (0.95 equiv) during 1 h at room temperature to the ketone moiety **3** and then stirring the mixture for an additional hour before the addition of phosphonate **4** provides a 3 : 1 ratio of regioisomers **13a**/**13b** in 93% combined yield, though the separation of the two isomers was difficult. The enolate equilibration was in favor of the formation of the more highly substituted enolate. This room temperature enolate alkylation result is of practical importance since the conventional methods of enolate alkylation are usually done at low temperatures. The mixture of **13a** and **13b** was then treated with TBAF to remove the TBS protective groups and the hydroxyl groups were oxidized with IBX to the corresponding carbonyl functionalities. Following a brief work-up, the product mixture was treated with DIPEA and lithium chloride under high dilution conditions at room temperature and only the desired isomer provided the macrocyclization product **14** as a single isomer with correct stereochemistry and double bond geometry (Scheme 5). Obviously, the undesired macrocyclization from the other isomer was slow compared with the desired one. The net overall yield of the desired product for the combined four-step operations was 45%.

Hydroboration of **14** with the borane–THF complex in the presence of CBS led to the isolation of **14a** as a single diastereomer determined on the basis of ^{1}HNMR and ^{13}CNMR data analysis. However, the subsequent removal of the MEM protection was problematic. Compound **14a** was unstable under strongly acidic conditions that can be used to remove the MEM protective group due to the presence of the allylic alcohol at C11, while the MEM protection can survive the weakly acidic conditions (Scheme 6).

Obviously, the MEM protective group has to be replaced by a different protective group before the reduction of the diketone intermediate. Thus, treatment of intermediate **14** with PPTS in refluxing *t*-BuOH and then with TBSCl in DCM at room temperature afforded compound **15** in 70% overall yield. Chemoselective reduction of the C11 carbonyl group afforded the spectroscopically pure product **16** in 50% yield (75% based on recovered starting material) after treatment with (*R*)-Me-CBS-borane in THF at −50 °C accompanied by the recovery of some starting materials (Scheme 7).

The C11-hydroxyl group was silylated with TBSOTf at −78 °C in essentially quantitative yield and the product was

subjected to the Davis' oxidation at −78 °C. After a brief work-up, cupric acetate was added to the methanol solution of the crude product to introduce the desired ketone carbonyl group (79%), which automatically enolized to arrive at product **18** as a single diastereomer determined on the basis of ^{1}HNMR and ^{13}CNMR data analysis. Finally, removal of the TBS groups with aqueous HF afforded the desired product in 90% yield (Scheme 8), which showed identical characteristic patterns in both the NMR spectra (proton and carbon-13) and the sign and magnitude of the optical rotation with the natural product reported[2] (see ESI†).

Conclusions

A total synthesis of (−)-terpestacin starting from a chiral pool was achieved in 22 steps (3% overall yield from intermediate **5**). There are several features in this synthetic strategy: (1) controlled introduction of the C23 chiral center; (2) the formation of the more highly substituted enolate of intermediate **3** through enolate equilibration and the alkylation of the resulting enolate at room temperature; and (3) the stereoselective CBS-borane reduction at C11 carbonyl of the diketone intermediate **15**. All these effective elements combined with mild reaction conditions will make this synthesis practically feasible.

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