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Terpestacin Core Structure. Control of Stereochemistry

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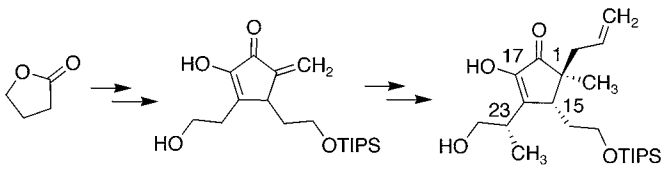
ABSTRACT



The α-hydroxycyclopentenone core structure of terpestacin has been prepared in a model system through an allene ether Nazarov cyclization of an alkylidene-γ-butyrolactone followed by regio- and stereoselective alkylation reactions. The stereochemistry at C15 (terpestacin numbering) has been used to control stereochemistry at C1 and at C23. The use of *E*-alkylidene-γ-butyrolactones extends the scope of the cationic cyclopentannelation reaction.

The isolation and structure elucidation in 1993 by Oka and co-workers of terpestacin, a fungal natural product from *Arthrinium* sp. FA 1744,[1] was followed by the first report of its total synthesis by Tatsuta in 1998.[2] The interest in this compound was presumably due both to the novel carbon skeleton and the pharmacological activity. Terpestacin inhibits the formation of syncytia, large multinucleated cells that are associated with HIV infection, with very good activity ($ID_{50} = 0.46\ \mu g/mL$), and is therefore of great interest as an antiviral agent in the treatment of AIDS. More recently antiangiogenic activity has been associated with terpestacin,[3] suggesting that it may also be useful as a lead for anticancer chemotherapeutics. The modest antimicrobial activity that has been reported for the natural product is encouraging, as it suggests that terpestacin is not an indiscriminate cytotoxin.

Fusaproliferin, the primary acetate derived from terpestacin, was isolated in 1993 by Randazzo and co-workers from *Fusarium proliferatum*, a fungal pathogen of maize.[4] Some confusion regarding the stereochemical assignment of fusaproliferin was laid to rest by Myers' synthesis in 2002 of (natural) (−)-terpestacin and (−)-fusaproliferin.[5] Jamison's total synthesis of (−)-terpestacin[6,7] revealed that siccanol, a natural product that had been isolated by Miyagawa in 2002,[8] is in fact identical with terpestacin, and not 11-*epi*-terpestacin, as had been reported initially. A very clear discussion and chronology of all the isolation and synthesis efforts through the middle of 2004 can be found in Jamison's paper.[6]

In addition to the syntheses of (−)-terpestacin by the Tatsuta,[2] Jamison,[6,7] and Myers[5,9] groups, synthetic approaches to the terpestacin ring system have been disclosed by Takeda[10] and by Heissler[11] and co-workers. We were drawn to the synthesis by the very close structural homology

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between the α-hydroxy cyclopentenone portion of the natural product and the fundamental structure **1** that is accessible through the allene ether cyclopentannelation reaction (Figure 1).[12] This suggested a very straightforward approach to the

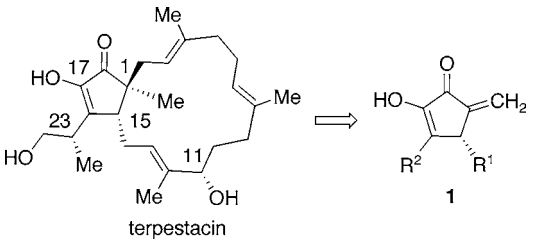
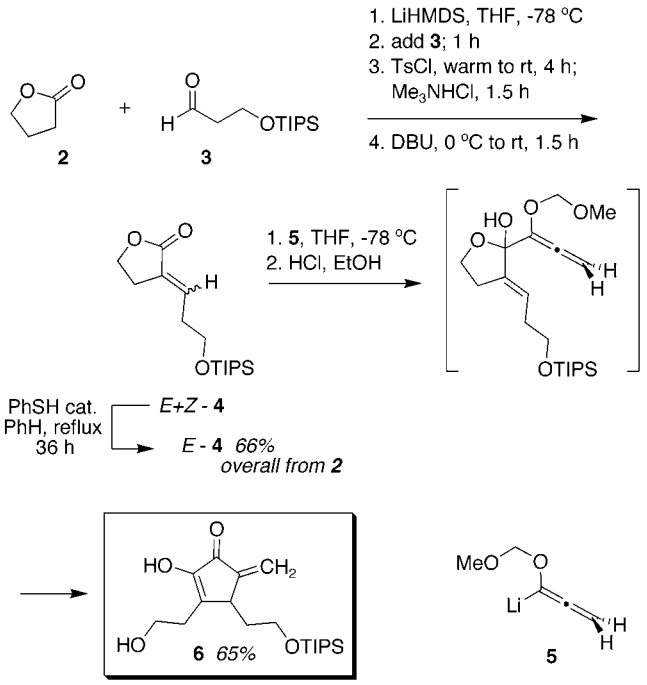


Figure 1. Terpestacin and core structure.

total synthesis. In addition, we hypothesized that the hydroxylated cyclopentenone portion of terpestacin was important for both activities, syncytium inhibition and angiogenesis suppression, and that the cyclopentannelation reaction would be ideal for the synthesis of truncated terpestacin analogues. In this Letter we describe the assembly of the cyclopentenone core and the control of relative stereochemistry at C1, C15, and C23.

Our strategy was to use the C15 appendage to direct stereochemistry at C1 and C23 while controlling the stereochemistry at C11 independently. Since we have demonstrated the asymmetric version of the cyclopentannelation, this strategy is applicable to the enantioselective synthesis of terpestacin. Scheme 1 summarizes the early steps in the

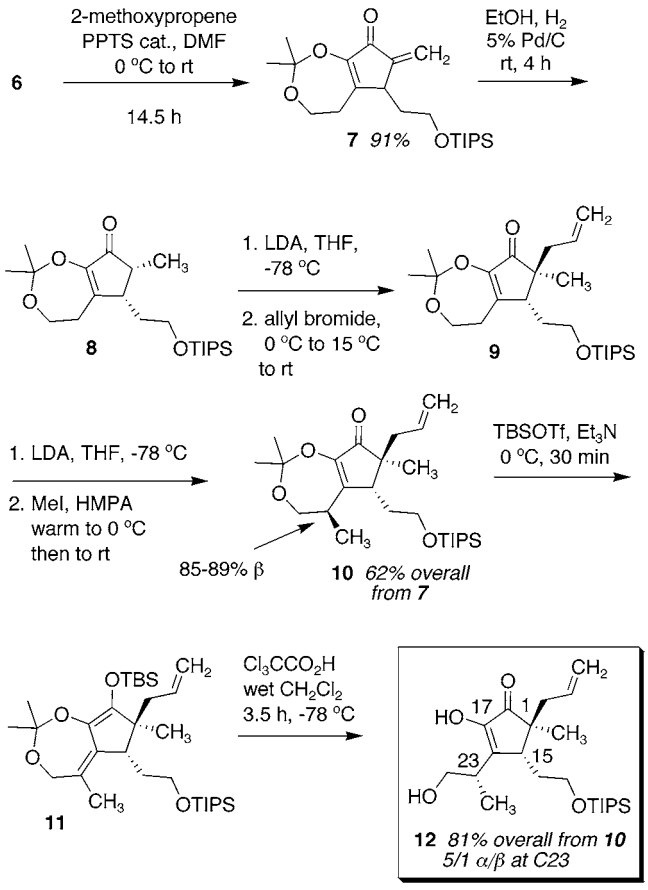
Scheme 1



synthesis of **12**, a racemic model for the cyclopentenone core of terpestacin. γ-Butyrolactone **2** was combined with aldehyde **3**[13] in a one-pot aldol/dehydration process to give **4** as a mixture of geometrical isomers.[14] Exposure of **4** to catalytic thiophenol in refluxing benzene[15] led to *E*-**4** in 66% overall yield from **2**. Addition of lithioallene **5** to *E*-**4** at −78 °C followed by rapid transfer via cannula of ethanolic HCl at −78 °C gave cyclopentenone **6** in 65% yield. The Nazarov cyclization presumably takes place through the tetrahedral intermediate shown in Scheme 1. It is important to neutralize the reaction mixture after 1 min. Under these conditions the reaction was completely reproducible and scaled well (3.3 g of **6**).

The diol function in **6** was converted to the acetonide (**7** in Scheme 2). Elimination of the primary hydroxyl group

Scheme 2



from **6** took place under a variety of conditions to produce a conjugated diene. This undesired reactivity was completely

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suppressed in the acetonide, possibly for stereoelectronic reasons. Selective hydrogenation of the exocyclic alkene gave **8**, which was exposed to LDA followed by allyl bromide to give **9**, in which the facial approach of the electrophile is controlled by the C15 2-silyloxyethyl substituent. None of the C1 diastereomer could be detected by ^{1}H NMR or ^{13}C NMR.

The final task in this study was introduction of the methyl group at C23. Deprotonation of **9** with LDA, followed by exposure to iodomethane and HMPA at 0 °C, then at room temperature led to **10** in 62% overall yield from **7**. Deprotonation took place at C23 rather than C15 with complete selectivity, presumably for steric reasons (methylene vs methine). The stereochemical preference of the second alkylation step as well as the first was determined by the C15 appendage, and is predominantly (85−89% β) *opposite* of the one desired (vide infra). It is worth noting that the alkylation was slow, and did not take place readily at 0 °C. Furthermore, it appears that competing alkylation (deconjugative) at C17 did not take place. The sequence of operations leading to **10** is also important, since all attempts to alkylate at C23 in **7** failed. The presence of the reactive exocyclic methylene group appears to be incompatible with the conditions for the alkylation.

We have noted unusual reactivity for the enolates derived from **9** and **10** and dienol ether **11**: all undergo extremely facile autoxidation at C23. For example, a neat sample of **11** was converted in ca. 50% yield to a diastereomeric mixture of C23 alcohols upon storage at −4 °C overnight in the freezer. These processes may be driven by release of strain.[16] If **11** was stored in frozen, degassed benzene it was stable for at least one month.

Since alkylation had led primarily to the wrong stereoisomer at C23 under the influence of the C15 group, the same effect was exploited to correct the problem. This was done in a straightforward way, by first converting **10** to silyl dienol ether **11** with *tert*-butyldimethylsilyl triflate and triethylamine, then hydrolyzing the enol ether with wet trichloroacetic acid in dichloromethane at −78 °C to give **12** in 81% yield as a 5/1 mixture of C23 diasteroisomers (major diastereomer shown).[17]

Stereochemistry was assigned in **10** on the basis of nOe correlations (Figure 2). Irradiation of the C15 methine led to enhancement of the signals for the C23 methyl group as well as the C2 allylic methylene signal indicating that allyl, C23 methyl, and C15 methine are all β. The stereochemical assignment was confirmed by irradiating each of the C14 methylene protons. Irradiation of one of the diastereotopic C14 methylene protons (H_a) led to enhancement of the signal for the C1 methyl group, whereas irradiation of the other C14 methylene proton (H_b) led to enhancement of the resonance for the C23 methine proton.

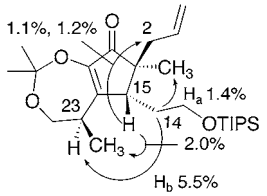

Figure 2. nOe correlations in **10**.

That the stereochemistry of **12** and **10** differs at C23 was shown by hydrolyzing **10** (Cl_3CCO_2H, aq CH_2Cl_2, 0 °C, 5 min) to the C23 epimer of **12**. The minor product of the hydrolysis of **10** was identical with **12**.

In summary, Schemes 1 and 2 demonstrate that the allene ether cyclopentannelation reaction can be employed efficiently for assembly of the core structure of terpestacin. There are several noteworthy features of this work. This is the first demonstration of the use of a lactone such as **4** as the carbonyl electrophile in the cyclopentannelation. Heretofore morpholino or Weinreb enamides had been used exclusively. The option of using lactones in the reaction broadens its scope considerably. The ease with which **6** underwent dehydration, while an undesired process in the context of the terpestacin synthesis, suggests an easy means to access the β-vinyl series of hydroxycyclopentenones (**1**, R^2 = vinyl). Work is underway to apply the strategy of Scheme 2 to the asymmetric synthesis of (−)-terpestacin.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR data for **6**−**12**; reproductions of ^{1}H and ^{13}C NMR spectra for **6**, **9**, **10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) We are indebted to Professor Joseph Konopelski for making this suggestion.

(17) The ratio of the diastereomers of **12** was determined by integration of the C23 methyl signals in the 500 MHz ^{1}H NMR spectrum in acetone-d_6.