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A Diosphenol-Based Strategy for the Total Synthesis of (−)-Terpestacin

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Terpestacin (**1**), originally isolated from *Arthrinium* sp. FA1744, inhibits the formation of syncytia (IC_{50} = 0.46 μg/mL) by HIV-infected T cells.[1] It also inhibits angiogenesis, which suggests that **1** could be a potential drug lead for anticancer chemotherapeutics.[1] The presence of the enol form of an α-diketone combined with the 15-membered macrocycle containing three geometrically defined trisubstituted olefins constitutes significant synthetic challenges. In 1998, Tatsuta described the first total synthesis,[2a] and later that year, he reported the first enantiospecific synthesis of terpestacin.[2b] Myers's enantioselective synthesis in 2002 conclusively established the absolute configuration of this natural product.[3] In 2003, Jamison reported the third enantioselective synthesis, in which they discovered that siccanol is not 11-*epi*-terpestacin, but terpestacin itself.[4]

The presence of the cyclic 1,2-diketone (as its enol form) offers the prospect of serving as a pivotal core onto which can be installed all of the carbon chains (save the methyl group) due to the unique reactivity of such building blocks as outlined in Figure 1. The sequence of O-allylation−Claisen rearrangement (Figure 1A) provides a chemo- and regioselective enolate allylation, which can be performed asymmetrically with respect to the enolate or allyl fragment or both.[5] In this way, the carbon chains at C1 and C16 of terpestacin may be introduced with catalyst control of absolute stereochemistry. In addition, conversion of a 3,3-disubstituted cyclopentane-1,2-dione to the corresponding enedione (Figure 1B) creates a highly reactive but relatively unknown Michael acceptor to allow installation of the third carbon chain at C15 of terpestacin. In this paper, we realize the use of these concepts that culminated in a successful asymmetric synthesis of terpestacin.

Scheme 1 summarizes our retrosynthetic analysis. The side chain along with the C23 stereocenter would be accessed via "Pd AAA−Claisen" protocol followed by oxidative cleavage. A highly selective ring-closing metathesis (RCM) to form the C12−C13 olefin would be employed to generate the 15-membered macrocycle, while the C5−C6 bond would be constructed by sulfone-mediated alkylation between sulfone **3** and allyl bromide **4**. The stereocenter at C15 in **4** could be generated via a stereoselective Sakurai allylation, and the C1 quaternary center would arise from another Pd AAA−Claisen of the inexpensive and commercially available 3-methyl-1,2-cyclopentanedione.

The Pd-catalyzed AAA between 3-methyl-1,2-cyclopentanedione (nucleophile) and isoprene monoepoxide (electrophile) was quite successful. When 50 mol % of Bu_4NCl was included and the nucleophile was added slowly, excellent yield and enantiomeric excess were obtained, and the adduct was silylated in the same pot to provide **5** (Scheme 2). Claisen rearrangement of **5** in $CHCl_3$ under microwave conditions gave *C*-alkylation product **6** with complete chirality transfer. A Saegusa oxidation of **6** to enedione **7** proved crucial and, to our knowledge, has not been previously reported for diosphenols. Conjugated cyclopenten-1,2-diones containing no substituents at C3 and C4, such as **7**, are rare and underutilized species.[6] Reaction of **7** with $MgBr_2$ and allyltrimethylsilane gave a stereoselective conjugate *C*-allyl addition (dr 5.7:1), which to our knowledge is the first example of an intermolecular *C*-1,4-addition

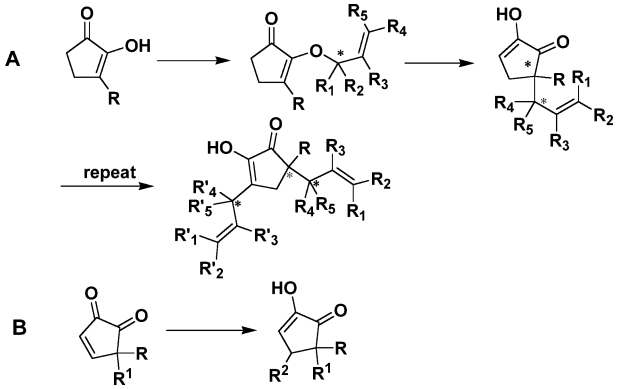
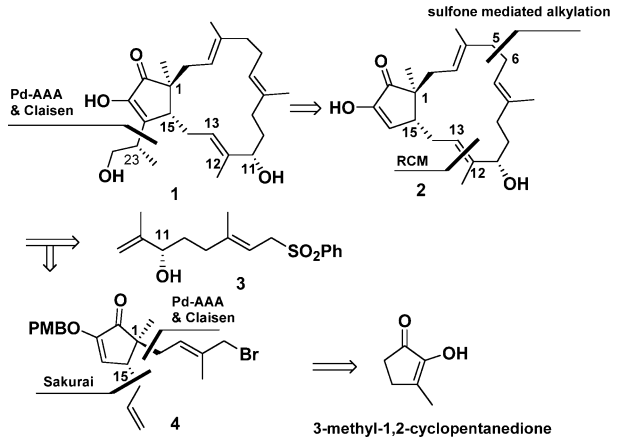


Figure 1. Key reactions of 3-substituted-1,2-dione.

Scheme 1



into these enedione species.[7] Subsequent protection of **8** as a PMB ether, removal of the TIPS group, and treatment of the allylic alcohol with CBr_4 and PPh_3 provided the allyl bromide segment **4**.

The sulfone segment **3** was accessed via two steps (Sharpless asymmetric epoxidation and reductive epoxide rearrangement) from known compound **9**, which was prepared in two steps from commercially available geranyl bromide.[8] Treatment of **3** and **4** with 2 equiv of LiHMDS gave the dianion coupling product in 74−85% yield. The following Pd-catalyzed reductive desulfonation gave **10** in 77% yield, which served as precursor in the subsequent macrocyclization. Since compound **10** contains five olefins, many outcomes are possible for the RCM, for example, C13 and C3 could close to form a six-membered ring; C8 and C12 could close to form a five-membered ring, etc. After careful screening, we found that treatment of **10** with 10 mol % of Grubbs second generation catalyst in benzene at room temperature produced the desired 15-membered carbocycle with a reasonable yield (35−44% on the *E* isomer), in which a low reaction temperature and the allylic alcohol moiety are critical for the success of this highly chemoselective RCM.[9] The PMB group was removed using $MgBr_2$ and dimethyl sulfide[10] when conventional methods for PMB deprotection failed.

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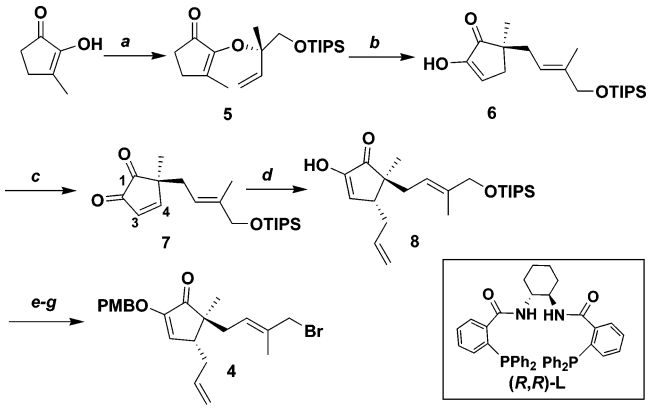
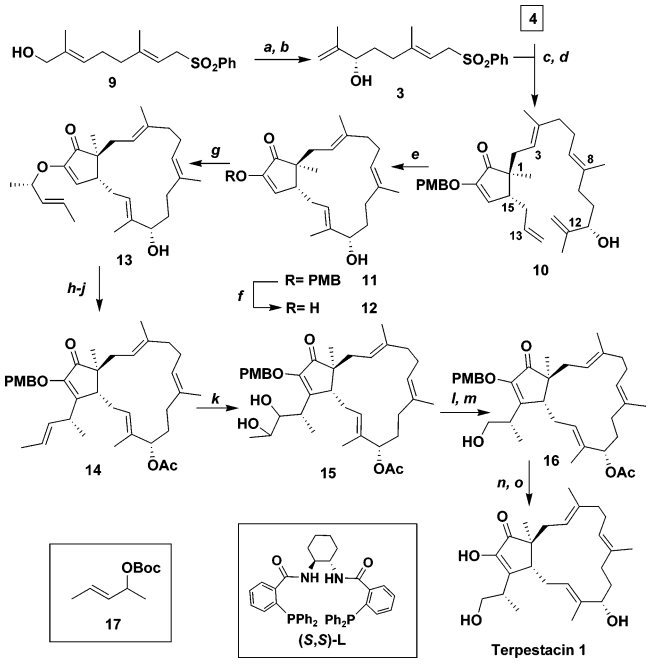
Scheme 2 [a]



[a] Reaction conditions: (a) isoprene monoepoxide, $Pd_2dba_3{\cdot}CHCl_3$ (1 mol %), (*R*,*R*)-**L** (2.6 mol %), Bu_4NCl (50 mol %), DCM; TIPSOTf, 2,6-lutidine, 95%, 88−96% ee; (b) $CHCl_3$, microwave, 100 °C, 15 min; 120 °C, 15 min; (c) $Pd(OAc)_2$, Cs_2CO_3, CH_3CN, rt, 78% over two steps, *E*/*Z* 4:1; (d) $MgBr_2{\cdot}Et_2O$, allyltrimethylsilane, DCM, −78 °C to rt, 86%, dr 5.7:1; (e) PMBCl, Cs_2CO_3, cat. Bu_4NI, DMF, 79%; (f) TBAF, THF, 86%; (g) CBr_4, PPh_3, CH_3CN, 88%.

Scheme 3 [a]



[a] Reaction conditions: (a) $Ti(O^iPr)_4$, TBHP, L-DET, DCM, −20 °C, 80%, 98% ee; (b) Py, I_2, PPh_3, CH_3CN/ether (3:5), 0 °C; H_2O, 38 °C, 74%; (c) **17**, LiHMDS (2 equiv), THF/HMPA (3:1), −40 °C, 74−85%; (d) $Pd(OAc)_2$ (20 mol %), DPPP (25 mol %), $NaBH_4$, DMSO, 77%; (e) Grubbs second generation catalyst (10 mol %), benzene, rt, c = 0.001 M, 35%-44% *E* isomer; (f) $MgBr_2{\cdot}Et_2O$, DMS, DCM, −78 to 0 °C, 93%; (g) **17** (2.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), (*S*,*S*)-**L** (7.5 mol %), DCM, rt, 89%, dr >15: 1; (h) microwave, DME, 150 °C; (i) PMBCl, Cs_2CO_3, cat. Bu_4NI, DMF; (j) Ac_2O, Py, 69% over three steps; (k) $K_2OsO_2(OH)_4$ (1 mol %), $(DHQ)_2PHAL$ (5 mol %), $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0 °C, 65% (∼80% brsm); (l) $NaIO_4$, THF/H_2O (4:1); (m) $NaBH_4$, DCM/MeOH, −78 °C, 78% over two steps; (n) LiOH, THF/MeOH/H_2O (3:1:1), 89%; (o) $MgBr_2{\cdot}Et_2O$, DMS, DCM, −78 to 0 °C, 74%.

The resulting enol in **12** could chemoselectively serve as a nucleophile (vs the secondary alcohol) in the second Pd AAA reaction to give **13** in high yield and high diastereoselectivity. Subsequently, Claisen rearrangement of **13** resulted in the C-alkylated product and established the requisite chirality of the side chain. At this stage, all of the stereocenters and the carbon skeleton were constructed. The remaining challenge was to oxidatively cleave the 1,2-disubstituted olefin in the presence of three trisubstituted olefins that are typically more susceptible toward oxidation. We hypothesized that the endocyclic trisubstituted olefins would have a facial bias owing to their restricted rotation, whereas the disubstituted olefin is more conformationally flexible. By using an asymmetric oxidation that is mismatched for the trisubstituted alkenes, oxidation of the disubstituted olefin should be kinetically favored. Indeed, Sharpless asymmetric dihydroxylation (AD-mix $\alpha/CH_3SO_2NH_2$) was ultimately found to provide a satisfactory chemoselectivity,[11] giving the desired diol **15** in 65% (brsm ∼80%) yield. Subsequent periodate cleavage of the diol and chemoselective reduction of the aldehyde in the presence of the ketone with $NaBH_4$ at −78 °C in DCM/MeOH completed the construction of the side chain. The final deprotections (hydrolysis and PMB-ether cleavage) afforded (−)-terpestacin (**1**), which is spectroscopically identical to those previously reported.[3,4]

In summary, we have designed a novel and concise strategy for the total synthesis of terpestacin by multiple usage of the α-diketone functionality, first in the Pd AAA−Claisen protocol, and second by the employment of its oxidized form, the ene-1,2-dione, as an excellent Michael acceptor, which is quite distinct from other previous syntheses. Many interesting chemoselectivity issues have been addressed in this synthesis, including a highly selective RCM and a dihydroxylation, which may have implications beyond this work.

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Note Added after ASAP Publication. Scheme 3 was replaced March 13, 2007, and Scheme 2 was replaced and Supporting Information updated March 23, 2007.

Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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