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Synthesis of (−)-Terpestacin via Catalytic, Stereoselective Fragment Coupling: Siccanol Is Terpestacin, Not 11-*epi*-Terpestacin

Johann Chan and Timothy F. Jamison*

Massachusetts Institute of Technology, Department of Chemistry, Cambridge, Massachusetts 02139

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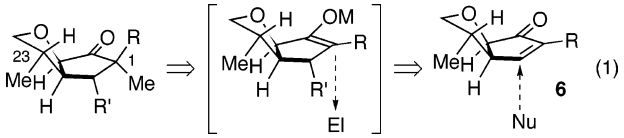
The sesterterpene terpestacin (**1a**) and structurally related compounds (Scheme 1) have attracted considerable attention from several scientific communities. Originally isolated in a search for inhibitors of the formation of syncytia by HIV-infected T cells, terpestacin also inhibits angiogenesis.[1] In 1993 Oka disclosed the solid-state structure and absolute stereochemistry of terpestacin.[2] Fusaproliferin (**2**), an acetate ester of terpestacin, was isolated shortly thereafter.[3] In 1998 Tatsuta described an enantiospecific synthesis of terpestacin,[4] and Myers recently reported enantioselective total syntheses of both natural products.[5] In a thorough series of investigations, Myers also conclusively established the absolute configurations of both terpestacin and fusaproliferin. At approximately the same time, Miyagawa reported that another natural product, siccanol, is diastereomeric to terpestacin at the allylic carbinol in the 15-membered ring (C11) and renamed it accordingly: 11-*epi*-terpestacin (**1b**).[6]

Herein we report enantiospecific syntheses of both (−)-terpestacin (**1a**, naturally occurring enantiomer[5]) and (+)-11-*epi*-terpestacin (**1b**) using catalyst-controlled, stereoselective intermolecular reductive couplings of alkyne **4** and aldehyde **5**. Related to enantioselective methods developed in our laboratory,[7] these stereoselective fragment couplings were instrumental in confirming that "siccanol" is *not* 11-*epi*-terpestacin, but in fact is (−)-terpestacin itself.

The remaining three stereogenic centers in **1a** and **1b** are of the same absolute configuration and were created by relaying the configuration of C23 to a quaternary carbon stereogenic center (C1) and its neighbor (C15), which together also comprise the junction of the 5- and 15-membered rings (eq 1). Conjugate addition to

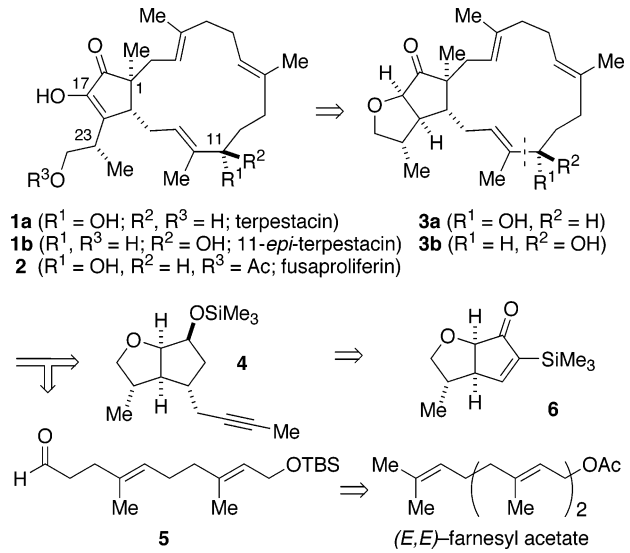


(1)

oxabicyclo[3.3.0]octenone **6** was expected to occur on the convex face, but prediction of the major diastereomer in a subsequent enolate alkylation was less clear (desired approach shown; El = MeI) since a substituent on this face, adjacent to the site of alkylation, might strongly influence the stereochemical course of the reaction. Moreover, since the net stereochemical impact of a fused 15-membered ring was unclear a priori, we allowed for flexibility in the order of installation of the C1 Me group (C19) and the rest of the carbon framework.[4] Another benefit of lowering the oxidation state of C17 and connecting it to the C24 oxygen to form a tetrahydrofuran ring (e.g., **3a**−**b**, Scheme 1) was concomitant protection of two otherwise interfering functional groups, the latent 1,2-diketone and the primary hydroxyl group.

An NMO-promoted,[8] intermolecular Pauson−Khand reaction between dihydrofuran **7**[9] and the hexacarbonyldicobalt complex of trimethylsilylacetylene (**8**) afforded **6**, the oxabicyclo[3.3.0]octenone discussed above, in 51% yield (Scheme 2). Notably, no other

Scheme 1



1a (R^1 = OH; R^2, R^3 = H; terpestacin)
1b (R^1, R^3 = H; R^2 = OH; 11-*epi*-terpestacin)
2 (R^1 = OH, R^2 = H, R^3 = Ac; fusaproliferin)
3a (R^1 = OH, R^2 = H)
3b (R^1 = H, R^2 = OH)

diastereomers nor any of three other possible regioisomers could be detected (^{1}H NMR).[10]

Conjugate addition of a lithium cuprate reagent derived from iodide **9** occurred with complete diastereoselectivity in the manner predicted above. To place the triple bond in the position required[11] for the catalytic reductive couplings, terminal acetylene **10** was isomerized with KO*t*-Bu in DMSO[12] in 90−95% yield. The other coupling partner (aldehyde **5**) was prepared from diol **12** (52% yield, three steps), itself obtained by a site-selective (and enantioselective) catalytic dihydroxylation of *(E,E)*-farnesyl acetate.[13]

Reductive, nickel-catalyzed fragment coupling of alkyne **4** and aldehyde **5** using Bu_3P as a ligand was completely nondiastereoselective (1:1). A further challenge presented by this coupling is that catalytic additions to internal acetylenes of the type RCH_2−C≡C−Me, i.e. with substitutents nearly identical in electronic nature and steric demand, are typically nonregioselective.[14] We were therefore pleased to discover that a catalyst incorporating the *P*-chiral ferrocenylphosphine ligand *(R)*-**14**[7a] favored the diastereomer (3:1) and regioisomer (2:1) corresponding to (−)-terpestacin in a combined yield of 70%.[15] The diastereomer corresponding to 11-*epi*-terpestacin (11-*epi*-**13**, terpestacin numbering) was obtained with *equal* regioselectivity and *equal and opposite* diastereoselectivity simply by using *(S)*-**14**, the enantiomer of the ligand used in the terpestacin-series coupling.

After suitable functional group manipulation, an intramolecular allylation constructed the 15-membered ring. Overall, farnesyl acetate served as a convenient source of an allylic electrophile, 12 carbon atoms and two *E* alkenes in the 15-membered ring.

Installation of the critical quaternary methyl group (C19) at C1 was best accomplished under rather unusual conditions. Treatment of **15** with NaH and MeI in toluene gave only recovered starting

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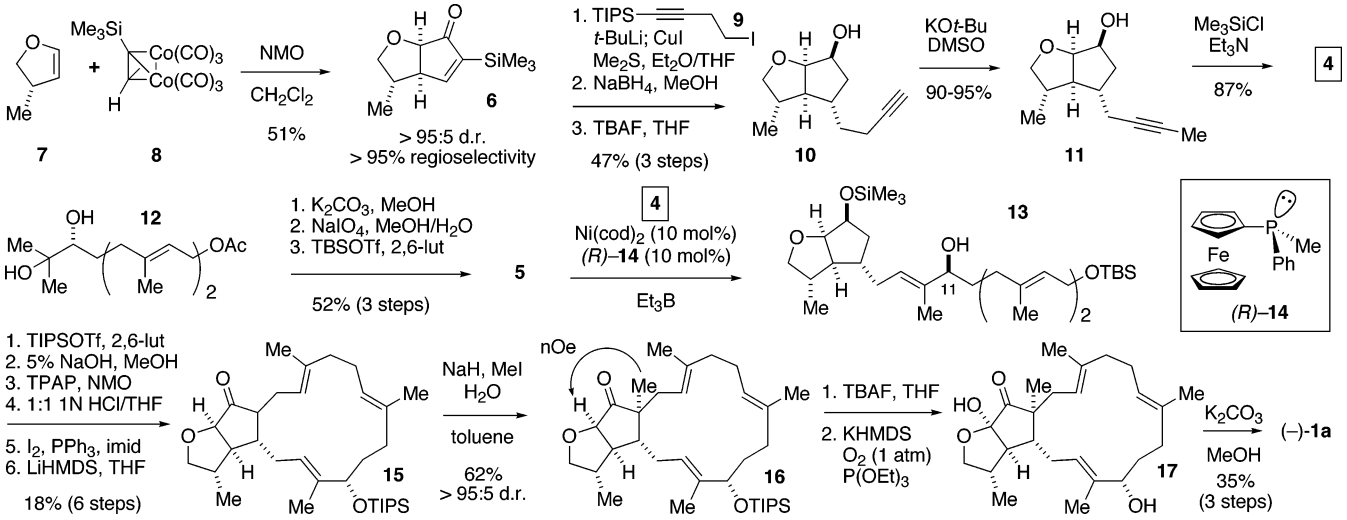
Scheme 2



material, but added H_2O[16] (200 mol % relative to **15**) afforded the desired product (**16**) in >95:5 dr (nOe).

Completion of the synthesis of (−)-terpestacin required three further transformations, TBAF-mediated removal of the TIPS protective group and oxidative ring opening of **3a** by way of enolate hydroxylation[17] and isomerization of the resulting hemiketal (**17**) under mild, basic conditions. Overall, preparation of **1a** and **1b** each required 17 steps from **7** (longest linear sequence).[18]

The spectroscopic data we obtained for our synthetic (−)-terpestacin are identical in all respects to those previously reported for natural and synthetic material.[19] However, "siccanol" differs strikingly from our synthetic 11-*epi*-terpestacin and in fact is *indistinguishable* from (−)-*terpestacin*. A sample of natural material kindly provided to us by Professor Miyagawa confirmed the structural reassignment—"siccanol" is (−)-terpestacin, not 11-*epi*-terpestacin (see Supporting Information). Our hypothesis is that the Mosher ester analysis used in the original assignment of the C11 configuration of siccanol is ultimately the origin of this discrepancy. A detailed analysis of the data in the literature relevant to this issue, and a full account of the syntheses summarized above will be reported in due course.

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Supporting Information Available: Experimental procedures and data; tabulated NMR data and spectra of natural and synthetic **1a** and of **1b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) *R*)-*P*-phenyl-*P*-(*p*-xylyl)-ferrocenylphosphine provided a higher overall yield (85%; 2.1:1 dr, 2.6:1 regioselectivity); see Supporting Information.

(16) Sodium hydroxide, finely dispersed in toluene, is likely the operative base, and it should be noted that the use of solvents other than toluene led to nearly exclusive *O*-alkylation of the enolate.

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(18) *epi*-Terpestacin (**1b**) was prepared by the same sequence from 11-*epi*-**13**. The same nOe shown for **16** (Scheme 2) was observed in 11-*epi*-**16**.

(19) That is, refs 2c and 5, and all data in refs 1a, 2a,b, and 4, except $[\alpha]_D$, which Myers demonstrated to be artifactual (see ref 5).

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