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# Enantioselective Synthesis of (−)-Terpestacin and (−)-Fusaproliferin: Clarification of Optical Rotational Measurements and Absolute Configurational Assignments Establishes a Homochiral Structural Series

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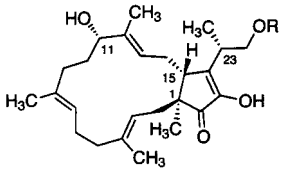
Terpestacin (**1**) is a fungal metabolite that inhibits the formation of syncytia ($IC_{50}$ = 0.46 mg/mL),[1] multinucleated cell bodies that are part of the pathology of AIDS infection.[2] Relative stereochemical assignments within terpestacin (**1**) were determined by X-ray crystallographic analysis; absolute stereochemistry was assigned by two different methods (exciton chirality method, $^1$H NMR analysis of diastereomeric *O*-methylmandelate ester derivatives).[1] Subsequently, an enantioselective synthesis of **1** proceeding in ∼38 steps from tri-*O*-acetyl-D-galactal was described, apparently confirming the absolute stereochemical assignment (synthetic: $[\alpha]_D$ = +27, *c* 0.22, $CHCl_3$, natural: $[\alpha]_D^{22}$ = +26, *c* 0.5, $CHCl_3$).[3] Contemporaneous with reports of the isolation of **1**, the natural product fusaproliferin, an acetic acid ester of **1**, was identified in the fermentation broth of the maize pathogen *Fusarium proliferatum*.[4a] A tentative assignment of its structure was made and later twice redefined to include the assignment of absolute stereochemistry.[4b,c] The structure finally proposed was enantiomeric with structure **2** shown below. Most recently, a third natural product was isolated from cultures of *Ulocladium* that inhibited syncytium formation in cells infected with respiratory syncytial virus.[5] This natural product was spectroscopically identical with terpestacin (**1**) but differed in the sign (and magnitude) of its optical rotation, ($[\alpha]_D^{25}$ = −16.5, *c* 0.29, $CDCl_3$), on which basis it was assigned as the enantiomer of terpestacin.[5]




Terpestacin (**1**) R = H
Fusaproliferin (**2**) R = Ac

Here, we describe an enantioselective synthesis of terpestacin (**1**, 19 steps, 5.8% yield from the pseudoephedrine amide **3**) and fusaproliferin (**2**, 21 steps, 5.3% yield from **3**) in their natural configurations, by a route that employs a series of stereoselective enolate alkylation reactions to establish the initial stereogenic center, set the quaternary carbon configuration, close the 15-membered ring, and introduce the side-chain residue with proper stereochemistry. Careful analysis of our synthetic materials alongside natural samples has revealed that several errors were made in the earlier measurements of optical rotation or in the absolute stereochemical assignments of these natural products. Clarifying all discrepancies, we show here that natural terpestacin (**1**) is levorotatory, not dextrorotatory as originally described, but was correctly assigned as the (1*S*,11*S*,15*R*,23*S*)-enantiomer. Fusaproliferin (**2**) is levorotatory, as reported, but is in fact the (1*S*,11*S*,-15*R*,23*S*)-enantiomer,[6] not the antipodal configuration originally assigned.

Our synthetic route to **1** and **2** begins with the allylation product **3** (Scheme 1), formed from (*R*,*R*)-pseudoephedrine propionamide in 93% yield and 99% de (25-g scale).[7] Iodolactonization of **3** afforded the *trans*-iodolactone **4** selectively (*trans*:*cis*, 12:1, 86% yield of pure *trans*-isomer after flash column chromatography).[8] The iodolactonization reaction served to cleave the pseudoephedrine amide bond[8b,9] and also as a device to control the configuration of the quaternary center of terpestacin (vide infra). Toward this end, the iodide **4** was transformed into the triisopropylsilyl ether **5**, in an efficient two-step sequence, via an alcohol of previously proven absolute configuration ($[\alpha]_D^{26}$ = −38.6, *c* 0.32, EtOH, lit.[10] $[\alpha]_D^{20}$ = −35.7, *c* 0.3, EtOH). For alkylative coupling with **5**, the biselectrophile **7** was prepared from the known epoxy alcohol **6**,[11] as shown in Scheme 1. Coupling of the components **5** and **7** and formation of the quaternary carbon center of **1** was achieved diastereoselectively (8.8:1) by the addition of **7** (1 equiv) to the potassium enolate derived from **5** (1.5 equiv) at −78 °C. The *trans*-diastereomer (**8**) was obtained in pure form by flash column chromatography (86% yield, two steps). Alkaline hydrolysis of the lactone **8** followed by acidification (pH = 5), immediate esterification of the resulting hydroxy acid, and oxidation with the Dess−Martin periodinane[12] furnished the keto ester **9** in 82% yield. Dieckmann-like cyclization then occurred upon slow addition of **9** to a suspension of sodium hydride in *N*,*N*-dimethylformamide at 24 °C. Subsequent addition of triethylamine, *N*,*N*-dimethylcarbamoyl chloride, and 4-(dimethylamino)pyridine to the cyclization reaction at 0 °C led to the exclusive acylation of the cyclization product to form the enol carbamate **10** in 81% yield from **9**. Reduction of **10** with diisobutylaluminum hydride in tetrahydrofuran (THF) at −78 °C formed a 1:1 mixture of diastereomeric allylic alcohols (85% yield); addition of methyllithium (−78→0 °C) to this mixture led to cleavage of the enol carbamate group of both isomers and, upon workup, elimination of water to give a single product, the cyclopentenone **11** (88% yield). To establish the stereochemistry of the remaining trisubstituted olefin of terpestacin (C12−C13) and, at the same time, provide a suitable substrate for macrocyclization, the allylic epoxide **11** was transformed stereoselectively into the allylic iodide **12**. In the optimized procedure, treatment of **11** with lithium iodide (5 equiv) in the presence of scandium trifluoromethanesulfonate (1 equiv, hydrate) in THF (−78→−25 °C) followed by hydroxyl protection with *tert*-butyldimethylsilyl triflate gave **12** in 89% yield. Deprotonation and macrocyclization occurred upon treatment of a dilute solution of **12** (0.002 M, THF, 0 °C) with Masamune's base (lithium bis(dimethylphenylsilyl)amide) to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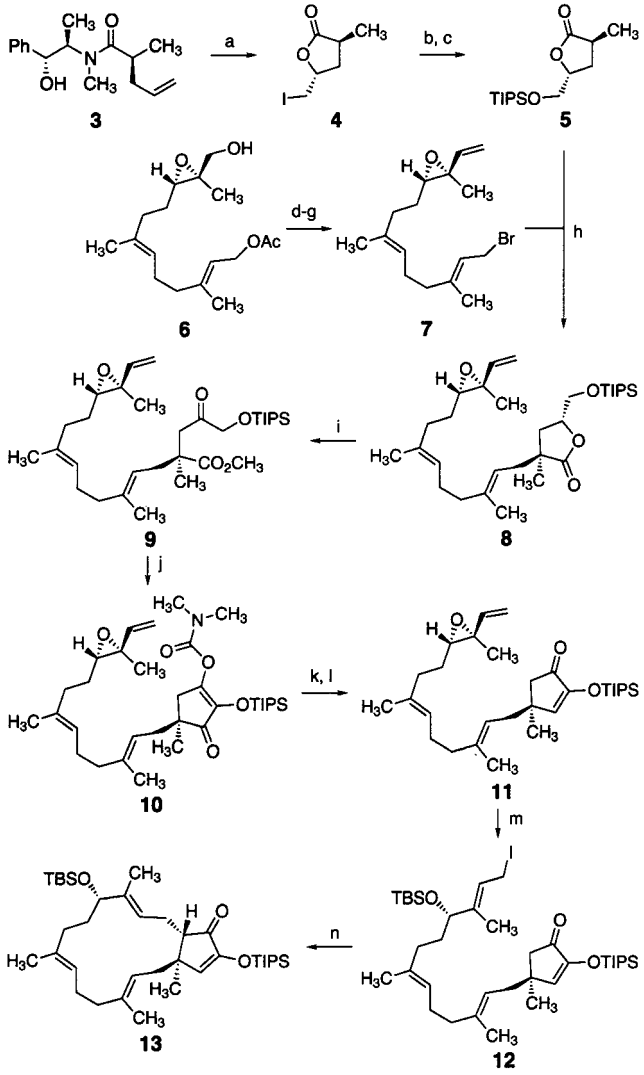
***Scheme 1***[a]

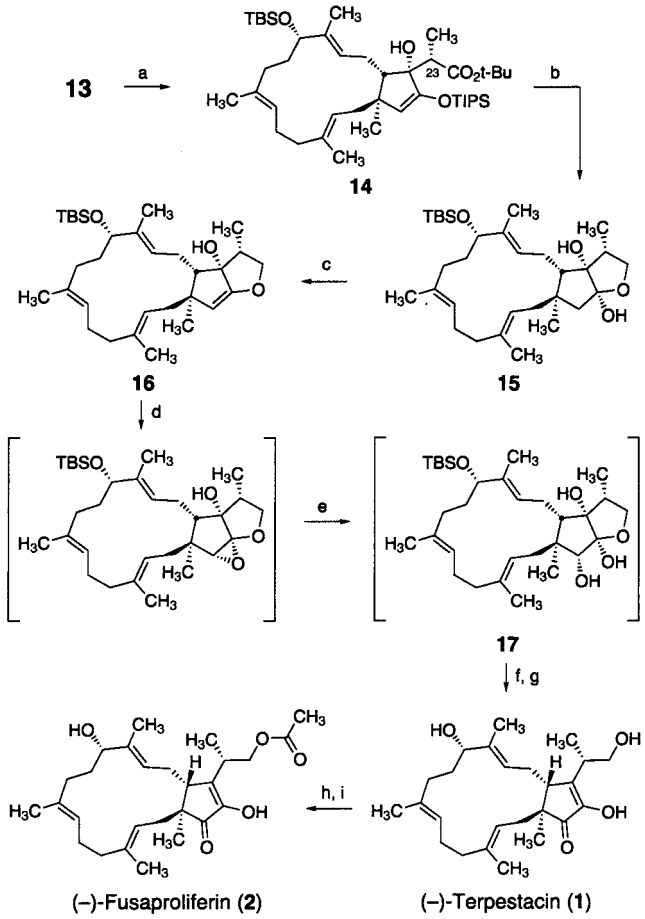



[a] Reaction conditions: (a) $I_2$, THF, $H_2O$, 96% (*trans*:*cis* 12:1); (b) $CsO_2CCF_3$, DMF, 90 °C; $Et_2NH$, 95%; (c) TIPSCl, imidazole, DMF, 98%; (d) $(COCl)_2$, DMSO, $CH_2Cl_2$; $Et_3N$, −78→0 °C; (e) NaHMDS, $Ph_3PCH_3Br$, THF, 93% (2 steps); (f) $K_2CO_3$, MeOH, 99%; (g) MsCl, $Et_3N$, THF, −45 °C; LiBr, 0 °C; (h) KHMDS, THF, −78 °C; 86% (2 steps); (i) KOH, EtOH; $CH_2N_2$; Dess−Martin periodinane, pyridine, $CH_2Cl_2$, 82%; (j) NaH, DMF; $(CH_3)_2NCOCl$, DMAP, $Et_3N$, 81%; (k) DIBAL, THF, −78 °C, 85%; (l) $CH_3Li$, $Et_2O$, −78→0 °C, 88%; (m) LiI, $Sc(OTf)_3$, THF, −25 °C, 92%; TBSOTf, 2,6-lutidine, THF, −78 °C, 97%; (n) $LiN(Si(CH_3)_2Ph)_2$, THF, 0 °C, 53% (*trans*:*cis* 4.8:1).

afford the *trans*-fused alkylation product **13** selectively (53%, diastereomeric ratio: 4.8:1).

With successful construction of the *trans*-fused [13.3.0]-bicyclic ring system of terpestacin, all that remained to complete the synthesis of **1** and **2** was to introduce the three-carbon side-chain residue with proper stereochemistry, followed by formal oxidative 1,3-transposition within the five-membered ring. The first objective was readily attained by 1,2-addition of the (*Z*)-enolate derived from *tert*-butyl propionate and lithium diisopropylamide to the enone **13**, giving rise to a single aldol addition product, the hydroxy ester **14**, in 94% yield (Scheme 2). *β*-Face addition, as indicated in structure **14**, was presumed on the basis of steric considerations and was supported by nOe data for **15** (vide infra); the more important issue of the stereochemistry of the C23 center was proven conclusively by the ultimate conversion of **14** to **1** (confirmed by independent X-ray analysis). Two-step reduction of the *tert*-butyl

***Scheme 2***[a]




[a] Reaction conditions: (a) $CH_3CH_2CO_2t$-Bu, LDA, THF, −78 °C, 94%; (b) *i.* Red-Al, THF, −78→0 °C; HOAc; *ii.* Red-Al, toluene, −78→24 °C, 75%; (c) Martin sulfurane, $CH_2Cl_2$, −78 °C, 89%; (d) DMDO, acetone, −24 °C; (e) $CF_3CO_2H$, $Et_2O$; $Et_2NH$; (f) $K_2CO_3$, MeOH, 73%; (g) 1 N HCl, THF, 94%; (h) AcCl, *i*-$Pr_2NEt$, $CH_2Cl_2$, −78 °C, 95%; (i) *n*-$PrNH_2$, toluene, 0 °C, 96%.

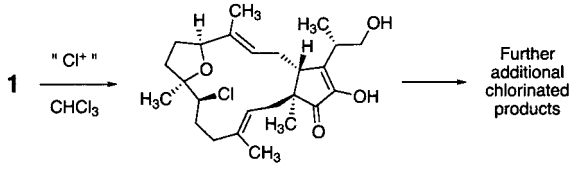
ester group of **14** proceeded with concomitant cleavage of the triisopropylsilyl enol ether, providing the tricyclic hemiketal **15** (75% yield). Completion of the synthesis of **1** was then accomplished by the following sequence, developed after extensive experimentation. Treatment of the hemiketal **15** with the Martin sulfurane produced the cyclic enol ether **16** in 89% yield. Epoxidation of **16** with dimethyldioxirane in acetone at 0 °C then produced an unstable epoxide intermediate; epoxide opening with trifluoroacetic acid at 0 °C, followed by treatment of the resulting trifluoroacetate with excess diethylamine gave the presumed intermediate **17**. Base-mediated isomerization−dehydration of **17** (potassium carbonate, MeOH, 24 °C, 36 h) followed by acidic cleavage of the *tert*-butyldimethylsilyl group then gave synthetic **1** in 69% yield from **16**, as a white amorphous powder. Crystallization from methanol provided a single-crystal suitable for X-ray analysis, confirming all relative stereochemical assignments. Surprisingly, however, the specific rotation of our synthetic sample deviated both in sign and magnitude from values reported in both the initial isolation study[1] and the prior synthetic route[3b] (Table 1) but closely matched data from the second isolation report[5] of an "enantiomeric" terpestacin. Analysis of an authentic sample of terpestacin obtained from *Arthrinium* sp. FA1744 (original source) showed that, in fact, the natural material was levorotatory, not dextrorotatory as originally reported (the small sample size precluded accurate determination of the magnitude of the rotation). Furthermore, synthetic and natural

***Table 1.*** Optical Rotational Measurements of Terpestacin and Fusaproliferin

| | | |
|---|---|---|
| **Terpestacin** | **Specific Rotation ($[\alpha]_D$)** | |
| 1993 Isolation (*Arthrinium*)[1] | +26 | (*c* 0.5, $CHCl_3$, 22 °C) |
| 1998 Synthesis[3b] | +27 | (*c* 0.22, $CHCl_3$) |
| 2001 Isolation (*Ulocladium*)[5] | −16.5 | (*c* 0.29, $CDCl_3$, 25 °C) |
| | −21.5 | (*c* 0.32, MeOH, 25 °C) |
| 2002 Synthesis (this work) | −17 | (*c* 0.58, $CHCl_3$, 28 °C) |
| | −18 | (*c* 0.06, MeOH, 29 °C) |
| **Fusaproliferin** | | |
| 1993 Isolation[4a] | −35 | (*c* 0.255, MeOH) |
| 1996 X-ray report[4c] | −35 | (*c* 0.7, $CHCl_3$, 25 °C) |
| 2002 Synthesis (this work) | −37 | (*c* 0.22, MeOH, 29 °C) |
| | −35 | (*c* 0.093, $CHCl_3$, 27 °C) |

terpestacin were found to provide identical circular dichroism spectra (and were identical by all other spectroscopic and chromatographic comparisons). A sample of terpestacin from *Ulocladium* was also found to provide an identical CD spectrum. It is thus clear that our synthetic **1** and **1** derived from both natural sources are identical in all respects, including absolute stereochemistry.

A plausible explanation for what must be erroneous optical rotational measurements reported in the original isolation work[1] and the earlier synthesis[3b] was suggested when we discovered that exposure of synthetic or natural **1** to certain lots of laboratory chloroform (the solvent used for optical rotational measurements) led to the formation of a chlorine-containing byproduct, tentatively assigned as the tetrahydrofuran derivative **18** (further chlorination of **18** occurred upon extended exposure).[13] It was noted that chloroform solutions producing **18** had been stored over granular potassium carbonate. These solutions also tested positive for chlorine in a semiquantitative spot test. Interestingly, identical lots of chloroform that had been stored instead over 4 Å molecular sieves did not test positive for chlorine, and gave stable solutions of **1**. Solutions of the pure chlorination product **18** in chloroform were found to be dextrorotatory and the magnitude of the rotation was found to exceed that of pure terpestacin (Table 1).




**18**
$[\alpha]_D^{29}$ = +33 (c 0.03, $CHCl_3$)

Acetylation of terpestacin (**1**) to form fusaproliferin (**2**) could not be achieved directly but was accomplished by bisacetylation followed by selective (enol) acetate cleavage (Scheme 2). Synthetic **2** was found to be identical in all respects to a sample of authentic fusaproliferin, including circular dichroism measurements. Thus, the absolute configuration of fusaproliferin must be revised as shown in structure **2**. Like **1**, **2** was observed to undergo chlorinative cyclization in chlorine-positive chloroform solutions, forming the acetate ester corresponding to **18**.

On the basis of the unambiguous stereo- and enantioselective synthesis of terpestacin and fusaproliferin described herein and comparisons of synthetic and natural materials, it is clear that these natural products form a homochiral structural series. The terpestacins isolated from *Arthrinium* and *Ulocladium* fungal sources are thus shown to be the same, and the absolute configuration of fusaproliferin is revised as shown in structure **2**.

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**Supporting Information Available:** Listings of spectral data (PDF) and X-ray crystallographic file (CIF) for synthetic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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