Total Synthesis and Absolute Configuration of Laurenditerpenol: A Hypoxia Inducible Factor-1 Activation Inhibitor

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Abstract: The absolute stereo structure of the natural product laurenditerpenol (1*S*, 6*R*, 7*S*, 10*R*, 11*R*, 14*S*, 15*R*) has been accomplished from eight plausible stereoisomers by its first asymmetric total synthesis in a highly convergent and flexible synthetic pathway. Six stereoisomers of laurenditerpenol were synthesized and evaluated for their biological activity.

The rapid proliferation of cells within a tumor mass quickly outpaces the capability of existing vasculature to supply oxygen and nutrients. In cancer patients, the extent of tumor hypoxia correlates with advanced disease stages and an overall poor prognosis.[1] Presently, there is no drug that specifically targets hypoxic tumor cells. The transcription factor hypoxia-inducible factor 1 (HIF-1[a]), a heterodimer of the bHLH-PAS proteins HIF-1α and HIF-1β/ARNT, functions as a master regulator of hypoxia-induced gene expression when mammalian cells are subjected to oxygen-deprived conditions.[2] Inhibition of HIF-1 production/function in animal models significantly reduces tumor growth,[3] and small molecule HIF-1 inhibitors represent potential tumor hypoxia-selective anticancer drug leads.[4]

Bioassay-guided fractionation of the lipid extract of the red alga *Laurencia intricata* yielded a structurally novel bicyclic diterpene, laurenditerpenol **1**.[5] Laurenditerpenol was the first marine natural product found to inhibit hypoxia (1% O_2)-induced HIF-1 activation and potently inhibited HIF-1 activation in T47D breast tumor cells by hypoxia with an IC_{50} value of 0.4 μM.[5] Mitochondrial respiration studies suggest that laurenditerpenol is the first member of a structurally novel class of marine natural product-based mitochondrial inhibitors that block mitochondrial oxygen consumption and promote the degradation of HIF-1α protein under hypoxic conditions.[5]

The intriguing biological properties of laurenditerpenol with the structural complexity of the molecule, including an unprecedented 7-oxabicyclo[2.2.1]heptane ring system and contiguous stereogenic centers at C1, C6, and C7, pose a significant synthetic challenge. Although previous spectroscopic studies permitted the identification of the structure of the natural product, including the absolute configuration at C1 and the relative *syn*-configuration of the 7-oxabicyclo[2.2.1]heptane ring methyl chiral centers at C11, C14, and C15, as well as their *trans* relationship to C10, the configurations of the stereocenters at C6 and C7, including the issue of absolute stereochemistry at C10, C11, C14, and C15, remained unknown. These uncertainties prompted us to initiate a total synthesis of laurenditerpenol to determine its absolute stereochemistry. We describe herein an inaugural total assignment of the absolute configuration of laurenditerpenol from one of eight possible stereoisomers of **1** (Figure 1) through the first asymmetric total synthesis.

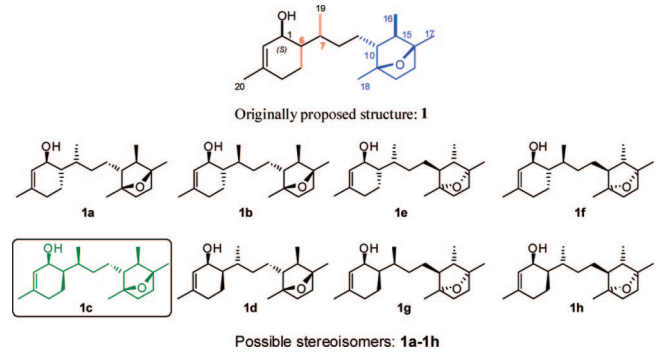
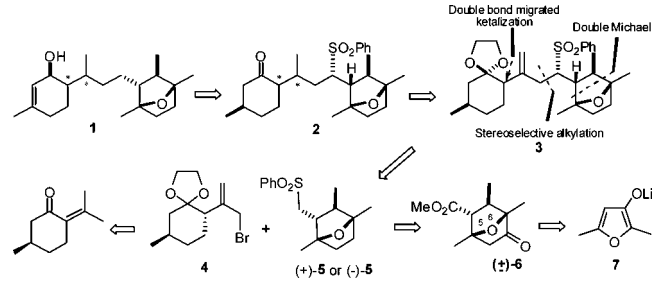


Figure 1. Originally proposed (**1**) and absolute stereochemical assignment (**1c**) of laurenditerpenol from eight possible stereoisomers.

Scheme 1. Retrosynthetic Analysis of Laurenditerpenol



Our retrosynthetic analysis of the basic skeleton of laurenditerpenol is depicted in Scheme 1. This envisioned analysis is a result of preliminary studies with racemic materials that have eliminated many obvious construction strategies, leading to a rather straightforward sulfone-mediated C−C bond formation between bromide **4** and hindered bicyclic sulfone **5**. This disconnection approach provides a flexible strategy to incorporate either enantiomer of sulfone **5**, and the C7 configuration could be introduced by adopting appropriate stereoselective transformations. The double Michael/Diels–Alder addition of methyl crotonate to the furanone enolate can provide adduct (±)-**6** and could be converted into olefin **3** with all the essential substituents and the correct relative configuration, including a *trans* relationship between the methyl and carboxylic acid substituents.

The synthetic venture commenced with an "anion-assisted" Diels–Alder reaction/sequential Michael addition of lithium enolate **7** with methyl crotonate, which remarkably produced 6-*exo*-ketoester (±)-**6** as a single diastereomer (Scheme 2).[6] The assignment of the 6-*exo* configuration was made based on NMR experiments, as shown in the Scheme 2. Racemic ketoester (±)-**6** was protected as the thioketal and hydrolyzed into acid (±)-**9**.

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[a] Abbreviations: HIF-1, hypoxia inducible factor 1; bHLH, basic-helix–loop–helix; PAS, Per-Arnt-Sim; Arnt, AhR nuclear translocator; AhR, aryl hydrocarbon receptor; pHRE, putative hypoxia response element; TK-luc, thymidine kinase-luciferase.

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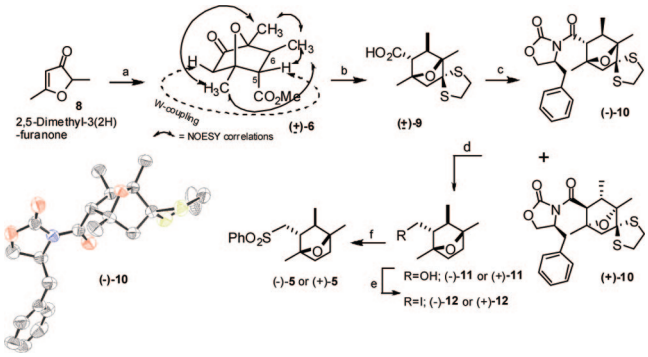
Scheme 2. Synthesis of Chiral 7-Oxabicyclo[2.2.1]-heptane Ring System[a]

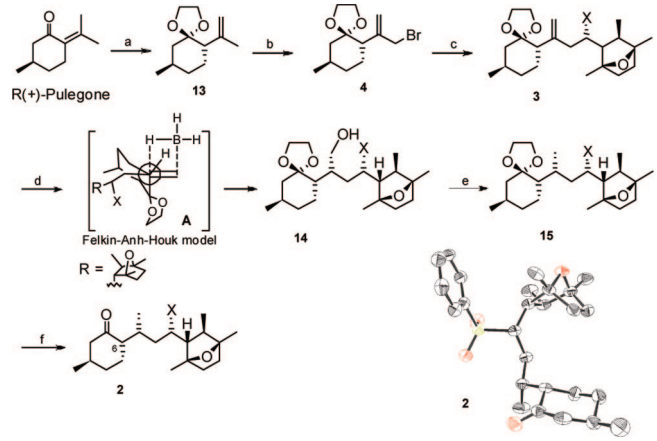


[a] Reagents and conditions: (a) LDA, Et_2O/cyclohexane, –78 °C, then methyl crotonate, 69%; (b) (i) ethanedithiol, *p*-TsOH, benzene, reflux; (ii) LiOH, aq MeOH, 92%, two steps; (c) TEA, trimethylacetyl chloride, LiCl, (*S*)-(–)-4-benzyl-2-oxazolidinone, CH_2Cl_2, rt, separation of diastereomers by silica gel chromatography: (–)-**10**, 40%, (+)-**10**, 42%; (d) (i) Raney Ni, EtOH, reflux, 98%; (ii) $LiBH_4$, THF, 0 °C, (−)-**11**, 95%, (+)-**11** 96%; (e) Ph_3P, I_2, imidazole, CH_2Cl_2, rt, (−)-**12**, 94%, (+)-**12**, 92%; (f) $PhSO_2Na$, DMF, 60 °C, (–)-**5**, 90%, (+)-**5**, 91%. ORTEP representation of the *N*-acyloxazolidinone (−)-**10** (H atoms are omitted for clarity).

With the ambiguity in the relative configuration of the bicyclic moiety, we decided to alter our synthesis to obtain both the (+)- and (−)-bicyclic intermediates of **5**. Seeking a higher level of convergence, the best resolution of racemic acid (±)-**9** has been achieved by converting it into *N*-acyloxazolidinone diastereomers (−)-**10** and (+)-**10** employing standard coupling conditions PivCl/Et_3N/LiCl in 82% yield.[7] The crystal structure of oxazolidinone (−)-**10**[8] confirmed the soundness of NMR experiments analysis on ketoester (±)-**6** and established the absolute configuration of the 7-oxabicyclo[2.2.1]heptane ring system. With completely characterized diastereomers (−)-**10** and (+)-**10** in hand, each isomer was separately converted into its corresponding enantiomeric sulfone in a four-step reaction sequence. Thus, reductive elimination of the thioketal functionality followed by reductive removal of the chiral auxiliary with $LiBH_4$ provided alcohol (−)-**11**. Direct iodination of alcohol (–)-**11** with TPP/I_2/imidazole[9] followed by sulfonylation with $PhSO_2Na$ produced sulfone (−)-**5**. Following the same reaction sequence sulfone (+)-**5** was also prepared from oxazolidinone (+)-**10**.

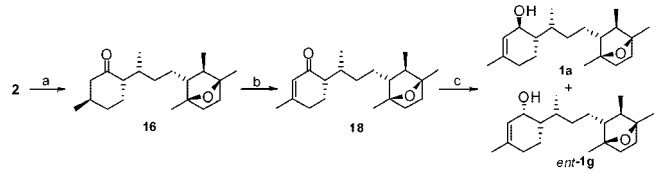
Following the synthetic strategy, an acid-catalyzed ketalization of *R*-(+)-pulegone accompanied by double bond migration introduced the C6 stereogenic center to produce diequatorial ketal **13** in high diastereoselectivity.[10] Regioselective allylic bromination of ketal **13** with NBS employing Yamanaka conditions[11] afforded bromide **4** in moderate yields, while classical radical bromination disappointingly produced an inseparable plethora of products. Stereoselective alkylation of allyl bromide **4** with sulfone (−)-**5** was successfully achieved in 98% yield with high diastereoselectivity (*dr* 95:5). Direct hydrogenation[12] of olefin **3** proved to be unsuccessful in our hands, while stereoselective hydroxylation of the olefin moiety occurred under routine conditions employing a hydroboration/oxidation[13] sequence. The resultant *anti*-Markovnikov alcohol **14** was formed as expected while introducing the C7 methyl stereocenter. As anticipated, the hydroxy sulfone **14** was produced with excellent regio- and stereoselectivity, which could be explained in terms of electrophilic borane addition by the Felkin-Anh-Houk paradigm (Figure A).[14] Sulfinylation of **14** with PhSSPh/Bu_3P[15] followed by reductive elimination afforded methyl sulfone **15** in excellent yield. Deketalization of **15** with $PdCl_2(CH_3CN)_2$/acetone[16] efficiently produced ketosulfone **2** in

Scheme 3. Fragment Coupling and Synthesis of Keto-sulfone **2** (X = SO_2Ph)[a]



[a] Reagents and conditions: (a) $(CH_2OH)_2$, CSA, benzene, reflux, 24 h, 73% (*dr* 92:8); (b) NBS, Yb(OTf)$_3$, TMSCl, CH_2Cl_2, 0 °C, 15 min, 48%; (c) (−)-**5**, *n*-BuLi, HMPA, THF, –40 °C, 40 min, then **4**, 2 h, 98% (*dr* 95:5); (d) (i) $BH_3.S(CH_3)_2$, THF, 10 h; (ii) H_2O_2, NaOH, 0 °C, 87%; (e) (i) PhSSPh, (n-Bu_3)P, toluene, rt, 94%; (ii) Raney Ni, EtOH, reflux, 90%; (f) $PdCl_2(CH_3CN)_2$, acetone, rt, 30 min, 92%. In ORTEP representation of one of the two crystallographically independent molecules of **2** (H atoms and cocrystallized ether molecules are omitted for clarity).

Scheme 4. Synthesis and Absolute Configuration of Stereoisomers of Laurenditerpenol **1a** and *ent*-**1g**[a]



[a] Reagents and conditions: (a) Na-Hg (10%), MeOH, rt, 68%; (b) (i) LDA, PhSeCl, THF, −78 °C; (ii) Py, H_2O_2, CH_2Cl_2, H_2O, 0 °C, 78%; (c) $CeCl_3$, $NaBH_4$, MeOH, 0 °C, 72%.

92% yield with no epimerization at C6 (Scheme 3), whereas longer reaction times under the same conditions or other acid-catalyzed deketalization conditions[17] resulted in C6 epimerization in minor quantities. X-ray crystallographic analysis[18] of ketosulfone **2** revealed 7*R*-configuration at the C7 methyl center and supported the evolution of C7 configuration as anticipated by the Felkin-Anh-Houk model of electrophilic hydroboration.

Having established the absolute configuration of ketosulfone **2**, reductive desulfonylation[19] as originally planned was accomplished using Na-Hg in MeOH to produce ketone **16** with traces of the C6 epimerized product.[20]

Regioselective enolization of **2** with lithium diisopropylamide at –78 °C followed by addition of PhSeCl produced a mixture of diastereomers,[20] which was further subjected to oxidative elimination to afford α,β-unsaturated ketone **18**.[21] Regioselective reduction of the α,β-unsaturated ketone with $CeCl_3$-$NaBH_4$[22] produced chromatographically separable C1 epimers, *ent*-**1g** and **1a** in a 2:3 ratio. Thus, we have synthesized two stereoisomers of laurenditerpenol in a single pot (Scheme 4), one with the desired 1*S*-configuration and one is the enantiomer of the probable eight isomers (Figure 1).

The ^1H NMR spectroscopic data and the physical parameters (TLC and specific rotation) of the stereoisomer **1a** did not match with an authentic sample of natural product **1**, whereas the *ent*-**1g** ^1H NMR spectrum was closely similar. ^1H NMR spectral data analyses of these C-1 epimers were clearly characteristic of the natural product, which in turn reduced the synthetic

maneuver required to identify the correct stereoisomer of laurenditerpenol. The ^{1}H NMR spectrum of **1a** showed the H2 proton resonance at δ 5.39 ppm as a broad singlet, and the H1 proton appeared at 4.03 ppm as a broad multiplet, whereas the ^{1}H NMR spectrum of *ent*-**1g** showed the H2 resonance at 5.64 ppm as a doublet (J = 4.0 Hz) and H1 at 4.11 ppm as a broad singlet. When a comparison was made of this spectral data with reported spectral data of similar systems,[23] we concluded that 1,6-*syn*-cyclohex-2-en-1-ol and 1,6-*anti*-cyclohex-2-en-1-ol systems exhibit this characteristic ^{1}H NMR signal difference in chemical shift values.[24] Based on this characterization and comparison of the H2 and H1 proton chemical shift values of natural product **1** with *ent*-**1g**, it is clear that laurenditerpenol must possess a 1,6-*syn*-cyclohex-2-en-1-ol system within its structure. This analysis eliminates all of the remaining 1,6-*anti*-cyclohex-2-en-1-ol isomers **1b**,**1e**, **1f** and leaves 1,6-*syn*-cyclohex-2-en-1-ol isomers.

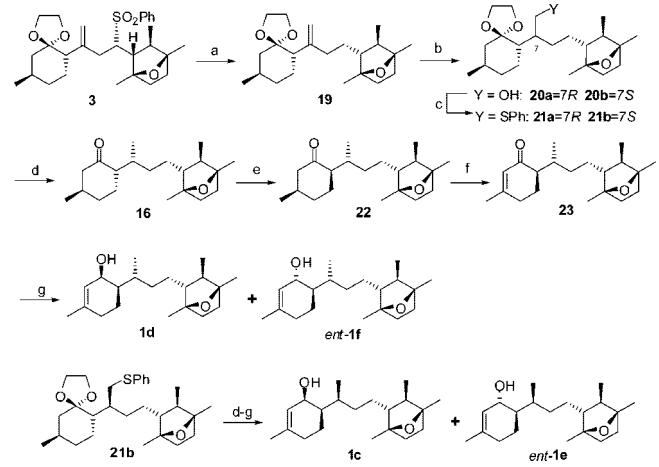
Thus, the first successful synthesis of stereoisomers of laurenditerpenol **1a** and *ent*-**1g** has limited the possibility of the natural product from its eight stereoisomers **1a**−**1h** to three stereoisomers **1c**, **1d**, and **1h** (Figure 1).

At this stage, we advanced to synthesize the remaining target stereoisomers with sulfone (–)-**5**. Following the developed synthetic technology, we altered the reaction sequence to maneuver the synthesis of both the C7 stereoisomers. Thus, sulfone **3** was desulfonylated to culminate the observed stereoinduction in the hydroboration reaction due to phenylsulfone functionality, which in turn facilitates access to both the 7*R*- and 7*S*-hydroxy compounds **20a** and **20b**, respectively. Because these diastereomers are chromatographically difficult to separate, the mixture was further subjected to sulfinylation to provide the corresponding phenylsulfides **21a** and **21b** as a chromatographically separable mixture of diastereomers. Reductive elimination of phenylsulfide **21a** followed by deketalization afforded ketone **16**.

The desired C1−C6 *syn* stereoselectivity was achieved by epimerization of ketone **16** to **22**, and the diastereomers were separated by silica gel flash chromatography.[25] Dehydrogenation of ketone **22** to enone **23** using a two-step protocol, followed by regioselective reduction under Luche conditions, produced stereoisomers of laurenditerpenol **1d** and *ent*-**1f** in a 2:3 ratio as a chromatographically separable mixture of isomers (Scheme 5). As anticipated, stereoisomer **1d** closely matched the ^{1}H NMR spectral data of the natural product, but the carbon values varied moderately, and the TLC R_f did not match with an authentic sample of the natural product. Following the same synthetic transformations, stereoisomer **1c** also synthesized from phenylsulfide **21b**. The ^{1}H and ^{13}C NMR spectra of synthetic **1c** were identical with natural product **1**. Moreover, synthetic **1c** and authentic natural product **1** exhibited identical behavior on TLC, confirming the absolute configuration as drawn.[26]

The synthetically produced isomers of laurenditerpenol were evaluated for their ability to inhibit hypoxia-induced HIF-1 activation in T47D breast tumor cells.[27] Synthetic laurenditerpenol **1c** is very similar in potency (IC_{50} 0.82 μM) to the original compound isolated from *L. intricata* (Table 1).[28] At concentrations as high as 30 μM, compound **1c** neither inhibited luciferase expression from the pGL3-control reporter, nor inhibited T47D cell proliferation/viability under assay conditions. Therefore, the inhibition of hypoxia-induced HIF-1 activation (pHRE3-TK-luc) by **1c** was selective and independent of any effect on T47D cell viability. Inversion of configuration at C7 **1d** was associated with a 76% drop in potency, relative to synthetic laurenditerpenol **1c**. Inversion of configuration at C1, C6, and C7 essentially deactivated *ent*-**1g**.

Scheme 5. Total Synthesis of Laurenditerpenol[a]



[a] Reagents and conditions: (a) Na-Hg, MeOH, rt, 6 h, 78%; (b) (i) BH_3·DMS, THF followed by H_2O_2, NaOH, 0 °C, 86%; (c) $(PhS)_2$, n-Bu_3P, toluene, rt, 90% (**21a/21b** 3:1); (d) (i) Raney Ni, EtOH, reflux, 94%, *92%*; (ii) $PdCl_2(CH_3CN)_2$, acetone, rt, 30 min, 92%, *90%*; (e) KOH, MeOH, rt, 12 h, 30% epimerization, *35%* epimerization; f) (i) **21a/21b**, LDA, –78°C, HMPA, THF, 1 h, PhSeCl, 2 h; (ii) H_2O_2, THF, 30 min, 72%, *68%*; (g) $CeCl_3$, $NaBH_4$, MeOH, 0 °C, 84% (2:3 **1d**/*ent*-**1f**), *80%* (2:3 **1c**/*ent*-**1e**). The representative yields in italics are corresponds to the 7*S*-isomer.

Table 1. IC_{50} Values of Synthetic Stereoisomers of Laurenditerpenol

isomer	hypoxia (16 h) pHRE3-TK-luc[a]
1c	0.82 μM
1d	3.4 μM
ent-**1g**	>30 μM

[a] Values were obtained from the T47D cell-based reporter assay.

In summary, the goal of assigning the absolute configuration of laurenditerpenol has been accomplished from eight plausible stereoisomers by its first asymmetric total synthesis in a highly convergent manner. The flexibility of the current strategy to deliver either configuration at each stereocenter allows construction of all stereoisomers of this valuable natural product for further biological evaluation. An asymmetric variant of the current total synthesis and the structure–activity relationships of all the isomers and the rational design of other novel HIF-1 analogues for chemical biology studies are in progress and the results will be reported in due course.

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Supporting Information Available: Spectral characterization data of selected compounds (^{1}H, ^{13}C NMR, HRMS). This material is available free of charge via Internet at http://pubs.acs.org.

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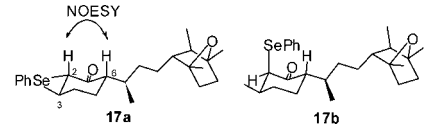
(20) Ketone **16** was separated from traces of epimerized diastereomers by column chromatography. To confirm the configuration of **16** at the C6 stereocenter, a diastereomeric mixture of selenides were separated by silica gel flash column chromatography to afford the 2,3-*anti*-isomer **17a** and the 2,3-*syn*-isomer **17b** in 2:3 ratio. Observation of NOESY correlations between H2 and H6 in the 2,3-*anti*-isomer **17a** confirmed its 6*S* configuration.



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(24) Spectroscopic analysis and mechanistic implications of these kind of systems are under progress, and the detailed results will be explored elsewhere in the future.

(25) To improve the epimerized product yield, several basic conditions were attempted. Either similar yield or decomposed product(s) especially with metal hydrides in aprotic solvents was obtained. It was determined at this stage to use this quick and processible reaction, albeit to provide the material for exploration.

(26) See Supporting Information for a complete set of spectral data. Regarding the rotation value, variation in rotation value from reported **1** and synthesized **1c** may be due to nonidentical experimental conditions. When we recorded the rotation of our authentic sample and synthetic sample under identical experimental conditions, the rotation value is identical.

(27) For experimental details, see Supporting Information.

(28) It is critical to note that due to the poor solubility of laurenditerpenol in the formulation for biological evaluation, the original IC_{50} values varied between separate concentration−response studies, and the average IC_{50} value (0.4 μM) from a series of independent experiments was ultimately reported. This variation in potency is within the range of values observed in the original studies.

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