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Convergent total synthesis of the racemic HIF-1 inhibitor laurenditerpenol

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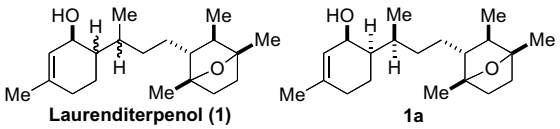
ABSTRACT

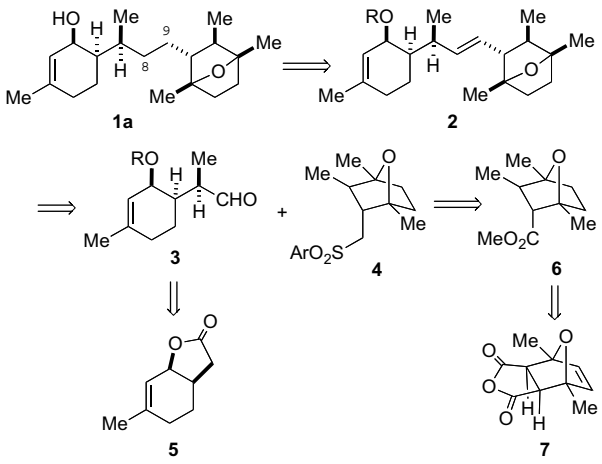
The convergent total synthesis of the HIF-1 inhibitor laurenditerpenol **1a** is reported. The key step is the Julia olefination–reduction process between the two components, the sulfone **4** (prepared from the dimethylfuran-maleic anhydride Diels–Alder adduct) and the aldehyde **3** (prepared from 3-methylcyclohexenone).

Laurenditerpenol **1**, a secondary metabolite isolated from the Jamaican red alga *Laurencia intricata* in 2004 by Zhou and Nagel,[1] was shown to inhibit activation of the hypoxia inducible factor-1 (HIF-1) under hypoxia using a T47D human breast tumor cell-based reporter assay with an IC_{50} of 0.4 μM. Upregulation of HIF-1 in late-stage tumors activates oxygen sensitive genes leading to angiogenesis and results in the survival and further proliferation of the tumor.[2] Inhibition of HIF-1 represents an alternate strategy in late-stage cancer therapy.[3] In the original isolation paper, the stereochemistry at C6 and C7 was not determined, nor was the relative stereochemistry of the oxabicycloheptane unit versus the cyclohexenol. Very recently, Avery and coworkers published a synthesis of laurenditerpenol and many of its diastereomers, which proved the relative and absolute structure to be that shown in **1a** (Scheme 1).[4] This publication prompts us to report our synthesis of laurenditerpenol **1a** and its stereoisomers in racemic form by a completely different route to the one used by Avery. Our convergent synthetic route allowed for the easy installation of the C6 and C7 stereocenters and a late-stage coupling of the two major subunits.

The retrosynthetic strategy involved a disconnection at C8 and C9 to give two key intermediates, the aldehyde **3** and the sulfone **4**, which would be coupled via a modified Julia olefination procedure to give the alkene **2** and thence **1a** (Scheme 2). The aldehyde **3** would be prepared from the lactone **5** while the sulfone **4** would



Scheme 1.



Scheme 2.

be obtained from the ester **6**, which would be prepared from the known cyclic anhydride **7**.

The synthesis of the aldehyde **3** (Scheme 3) began with the reduction of the known ester enone **8** (prepared by alkylation of the 3-methylcyclohexenone)[5] to give a diastereomeric mixture of the allylic alcohols **9** in 86% yield.[6] Saponification to the hydroxy acid and lactonization using DCC yielded the two lactones **10** and **11** as a separable 2:1 mixture. Methylation of the enolate of the major lactone **10** occurred from the less hindered face to generate in 85% yield the methyl lactone **12**, which on DIBAL reduction gave the lactol **13**. Similarly, methylation of the trans lactone **11** occurred cis to the allylic hydrogen to generate the methylated product **14** in modest yield.

The oxanorbornane sulfone **4** was synthesized starting from the known exo Diels–Alder adduct of 2,5-dimethylfuran and maleic anhydride **7**, which had been originally prepared by Diels and Alder in 1928[7] (Scheme 4). Hydrogenation gave the anhydride,

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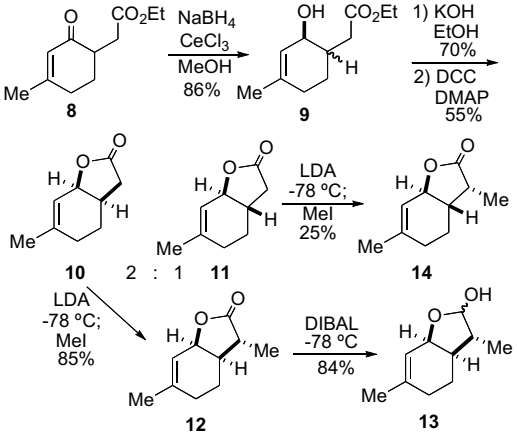
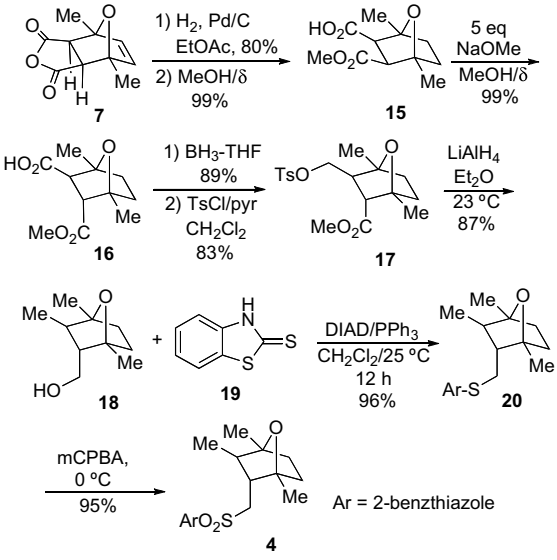
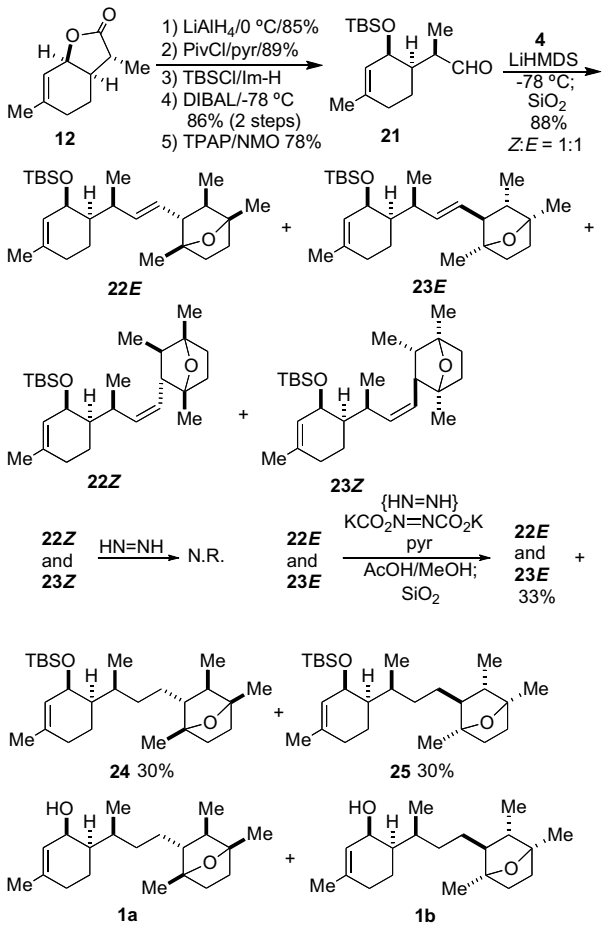


Scheme 3.



Scheme 4.

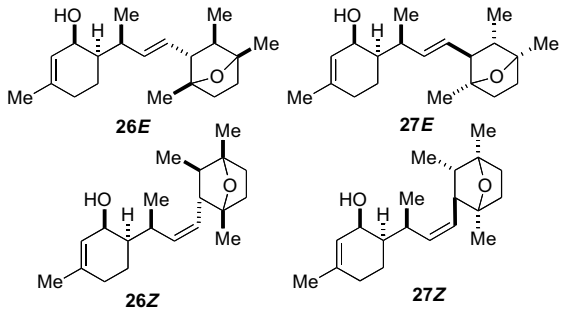


Scheme 5.

which was opened to the known carboxylic acid ester **15**[7c] via methanolysis. Treatment of **15** with sodium methoxide in methanol took advantage of the difference in pK_a for protons α to an ester versus those α to a carboxylate salt, a principle we had used before in the synthesis of cyclobut-A analogues,[8] to give cleanly the epimerized ester **16**. Selective reduction of the carboxylic acid with borane furnished in 89% yield the alcohol, which was converted to the tosylate **17** in 83% yield. Reduction of both the ester and the tosylate with lithium aluminum hydride unveiled the third methyl group to afford the trimethyl oxanorbornane alcohol **18** in 87% yield. The alcohol was converted to the sulfide **20** (96%) via treatment with 2-mercaptobenzothiazole **19** under Mitsunobu conditions, for example, diisopropyl azodicarboxylate (DIAD) and triphenylphosphine, which was then oxidized with *m*-CPBA to yield the desired sulfone **4** in 95% yield.

Unfortunately, the key Julia–Kocienski olefination[9] between the lactol **13** and the sulfone **4** was unsuccessful presumably due to the fact that the lactol exists predominately in the cyclic isomer with little or none of the hydroxyaldehyde being present. The required free aldehyde **21** was therefore prepared via the 5-step protecting group manipulation starting from the lactone **12**, that is, reduction to the diol (85%), monoprotection as the pivalate (89%), silylation and reductive removal of the pivalate (86%), and final oxidation to give the aldehyde **21** in 78% yield (Scheme 5).[10] The modified Julia olefination of the protected hydroxyaldehyde **21** and the sulfone **4** yielded the desired set of racemic trans products **22*E*** and **23*E***, along with the racemic cis products **22*Z*** and **23*Z*** in 88% yield as a 1:1 mixture of the *Z* and *E* isomers.[11] The *E* isomers could be separated from the *Z* isomers by flash chromatography. We planned to carry out selective reduction of the disubstituted alkene in the presence of the cyclic trisubstituted alkene via reduction with diimide[12] (prepared by protonation of dipotassium azodicarboxylate by acetic acid in a solution of pyridine and methanol). The hindered *Z* isomers—**22*Z*** and **23*Z***—did not react with diimide and the starting alkenes were recovered unchanged. However, the mixture of the *E* isomers, **22*E*** and **23*E***, underwent diimide reduction to afford, in addition to 15% starting material, a 1:1 mixture of the desired reduced products **24** and **25** in 80% yield, as observed in the NMR. Unfortunately, the unreduced olefin and the desired alkane diastereomers were difficult to separate via column chromatography, and only the diastereomer **25** was isolated in small quantities. Desilylation of the TBS ether of **25** with TBAF afforded the laurenditerpenol diastereomer **1b** in 72% yield. TBAF deprotection of the TBS ethers of the mixture of the alkenes and alkanes gave both laurenditerpenol diastereomers **1a** and **1b**, which were partially separated by careful chromatography. The proton, and especially the carbon, NMRs of these isolated diastereomers matched those reported by Avery and coworkers (which were numbered **1c** and *ent*-**1g** in their paper).[1]

We have also prepared several analogues of laurenditerpenol and are submitting them for biological evaluation as potential



Scheme 6.

HIF-1 inhibitors (Scheme 6). Thus hydrolysis of the silyl ethers of the four alkene stereoisomers—**22*E*/23*E*** and **22*Z*/23*Z***—with TBAF in THF afforded the dienols **26*E*/27*E*** and **26*Z*/27*Z***, which were separated by careful flash column chromatography.[13] The results of the biological assays of these compounds will be reported in due course.

Finally, we were able to prepare the correct (*S*)-enantiomer of the allylic alcohol **9** using the Corey–Bakshi–Shibata (CBS) reduction[14] of the cyclohexenone **8**, even though **8** has a stereocenter α to the ketone. This reduction gave a diastereomeric mixture of the allylic alcohols **9** in 60% yield and 85% de.[15] We are currently investigating a chiral synthesis of the oxabicyclo[2.2.1]heptane sulfone **4** (via a chemical or enzymatic resolution of the anhydride **7**) with the idea of carrying out a more efficient chiral synthesis of the correct enantiomer. Our results will be reported in due course.

In summary, we have described a convergent synthesis of racemic laurenditerpenol **1a** and its diastereomer **1b**, in 13 steps from 3-methyl-2-cyclohexen-1-one. The methylated oxanorbornane fragment **4** was successfully synthesized from 2,5-dimethylfuran and coupled to the aldehyde **21** via a high-yielding modified Julia olefination procedure. A more detailed account of the synthesis, along with efforts toward the synthesis of analogues, will be forthcoming.

Acknowledgments

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