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Enantioselective Total Synthesis of (−)-Laurenditerpenol

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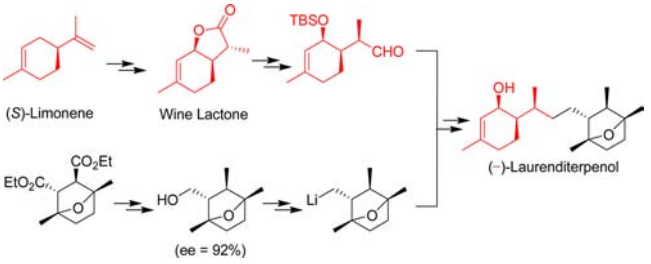
ABSTRACT



A highly convergent total synthesis of (−)-laurenditerpenol has been accomplished through an organolithium to aldehyde nucleophilic addition. Preparation of the prerequisite key intermediates in optically pure form was based on an improved, short, and efficient synthesis of "*wine lactone*" from (*S*)-limonene and Corey's catalytic enantioselective Diels–Alder reaction of 2,5-dimethyl furan with diethyl fumarate.

Hypoxia-inducible factor-1 (HIF-1) small molecule inhibitors are considered potential new anticancer drug leads that could exploit the hypoxic microenvironment of developing solid tumors.[1] Laurenditerpenol (**1**, Figure 1) was isolated from the marine alga *Laurencia intricata* as a potent and selective inhibitor of HIF-1 in breast tumor cells (IC_{50} 0.4 μM). However, only the absolute configuration at C(1) and the relative configuration of the 7-oxabicylco[2.1.1]heptane ring could be established through spectroscopic studies.[2] Full elucidation of the absolute stereostructure relied on the stereocontrolled synthesis of several diastereomeric pairs and comparison of spectroscopic data, as well as biological activities, of the purified diastereomers with those of the natural product.[3]

The total synthesis of racemic laurenditerpenol has been accomplished,[4] and two key intermediates invoked by this route have been prepared in a stereocontrolled manner.[5] We report herein an enantioselective total synthesis of laurenditerpenol.[6]

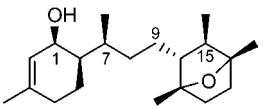


Figure 1. (−)-Laurenditerpenol, **1**.

The presence of two isolated ring systems invites the retrosynthetic disconnection of the C(8)–C(9) bond to dissect the molecule in two precursors of similar size and complexity (Scheme 1). In previous synthetic efforts retrosynthetic addition of either a double bond or activating group(s) at this locality was required before this structurally simplifying retrosynthetic transform could be applied. Thus, the former approach has been adopted for the preparation of simplified analogues (through an olefin cross-metathesis),[6] as well as for the total synthesis of **1** in racemic form (*via* **2** through a Julia–Kocienski olefination).[4] However as this synthesis has illustrated, the

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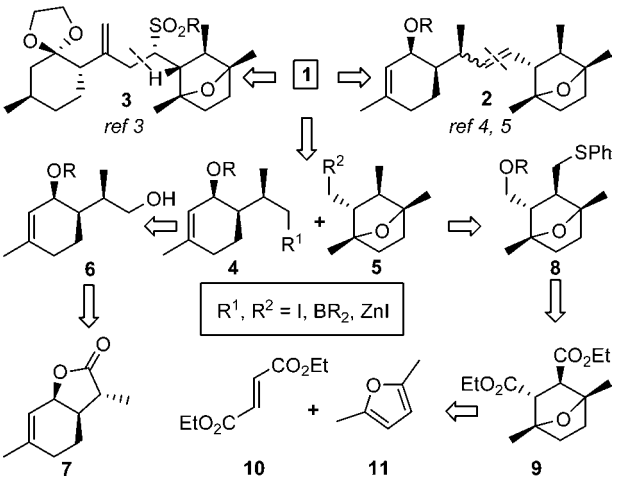
Scheme 1. Retrosynthetic Plan for (−)-Laurenditerpenol **1**

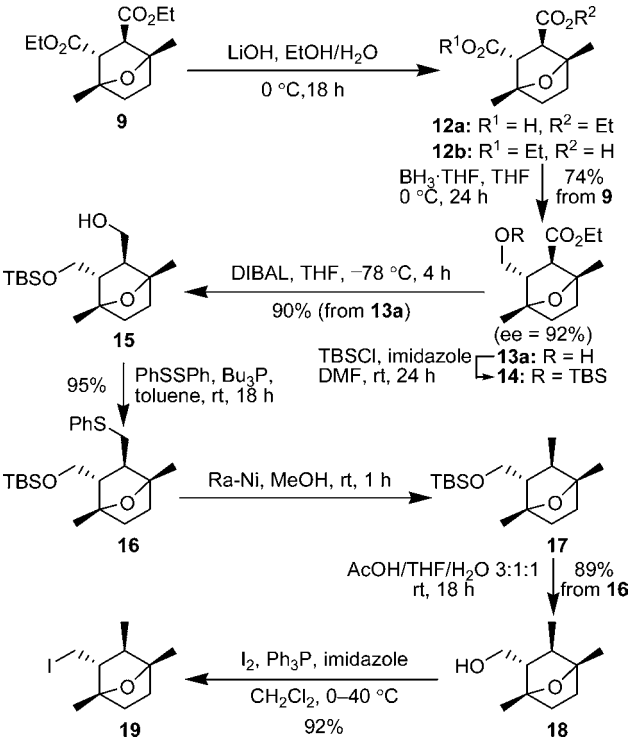


lack of stereocontrol in the olefination step diminishes overall efficiency. On the other hand, the latter approach, in the form of alkylation of a sulfone with an allylic bromide to provide **3**, has been exploited for the establishment of the absolute stereostructure of **1**.[3] Unfortunately, this route forfeits stereocontrol at C(7).

In order to overcome the above-mentioned drawbacks we aimed to establish the complete carbon framework of **1** through either a Suzuki−Miyaura or Negishi-type alkyl−alkyl cross-coupling[7] between coupling partners **4** and **5**. Alcohol **6** could serve as the source of the left-part coupling partner. This alcohol was anticipated to be derived from "*wine lactone*" **7** that, in turn, is known to be accessible from (*S*)-limonene.[8] Preparation of the right-part coupling partner **5** would exploit the anticipated *exo*-facial selectivity[9] in monohydrolysis of the known dicarboxylate **9**.[10]

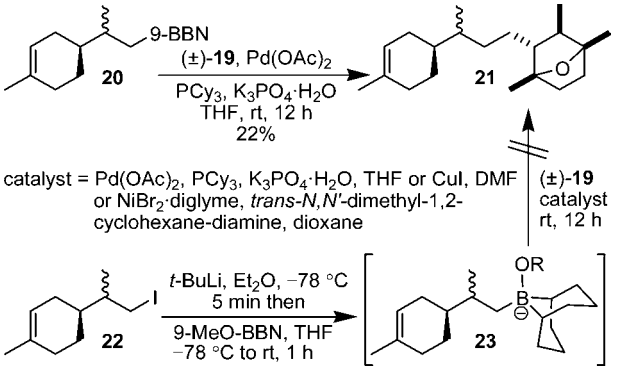
Indeed, this dicarboxylate was prepared as previously described through a catalytic enantioselective Diels−Alder reaction of diethyl fumarate (**10**) and 2,5-dimethyl-furan (**11**) and subsequent hydrogenation of the cycloadduct.[10] Upon hydrolysis with LiOH in aqueous ethanol, an inseparable mixture of the two monoacids **12a** and **12b** was obtained (Scheme 2). Subsequent reduction with $BH_3 \cdot THF$ led to isolation of the corresponding alcohols in 74% and 13% yield respectively from **9**. The major product was alcohol **13a**. Thus it was revealed that, in the case of 7-oxabicylco[2.1.1]heptane diester **9**, monohydrolysis had proceeded with *endo*-selectivity instead of the *exo*-one previously observed in related bicylco[2.1.1]heptanes.[9] The only consequence of this observed reversal of selectivity, be it unexpected and intriguing, was a reversal in the

Scheme 2. Synthesis of the C(9)−C(15) Fragment



timing of subsequent planned transformations. Thus, alcohol **13a** (ee = 92% based on HPLC analysis using a chiral column) was protected as the corresponding TBS-ether (**14**), and the remaining carboxylate was reduced with DIBAL-H at −78 °C to provide in 90% overall yield the monoprotected diol **15**. Subsequent treatment with diphenyl disulfide in the presence of tri-*n*-butylphosphine[11] furnished thioether **16** in 95% yield. Then, reduction with Raney-Ni followed by acidic hydrolysis of the silylether provided alcohol **18**, which was converted to the corresponding iodide **19** (ee = 92%; 10 steps, 37% overall yield from diethyl fumarate).

Scheme 3. Alkyl−Alkyl Cross-Coupling Studies



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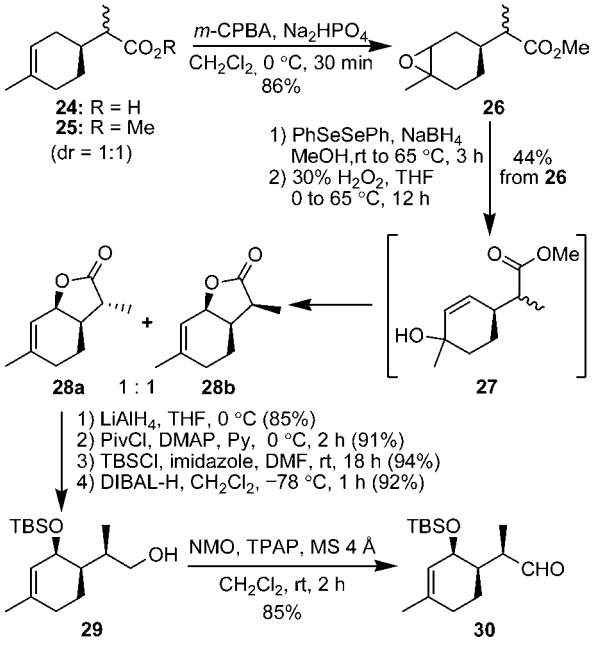
With iodide **19** in hand, we proceeded to investigate the feasibility of the planned alkyl–alkyl cross-coupling employing the conditions that Fu et al. have developed for the efficient palladium-catalyzed Suzuki–Miyaura cross-coupling of alkyl bromides with alkyl boranes.[12] Thus, when the readily available[8] borane **20** was used as the alkylating agent, the expected mixture of diastereomeric cross-coupling products **21** with racemic iodide[13] **19** was obtained albeit in low yield (Scheme 3). Borate **23** (R = H) is presumed to be the actual alkylating species in this transformation,[12] and alkyl borates have been employed successfully in palladium-catalyzed cross-coupling reactions with alkenyl halides.[14] Since generation of an alkylborane more relevant to our plans (**4**, $R^1 = BR_2$; Scheme 1), through hydroboration, was anticipated to provide a mixture of C(7) epimers,[8] use of borate **23** (R = Me) was attempted as an alternative to borane **20**. However, this exchange failed to furnish any of the desired cross-coupling products with iodide **19** under otherwise identical conditions. Equally disappointing were the results obtained using borate **23** (R = Me), iodide **19**, and nickel[15] or copper[16] based catalysts. Moreover, Fu's conditions did not promote the coupling of iodide **22**[17] with the borate derived from **19** upon lithiation and quenching with 9-MeO-BBN.

In parallel to the above-mentioned cross-coupling studies, preparation of the C(1)–C(8) fragment had begun (Scheme 4). It is known[8] that treatment of acid **24** with PDC and *t*-BuOOH in benzene provides in one step and 25% yield a 1:1 mixture of lactones **28a** and **28b**. This procedure however was deemed inappropriate for the large scale preparation of lactone **28a**. Thus, an alternative, more reliable, and efficient procedure was sought.[18] To this end, methyl ester **25**, that was obtained in three steps as a 1:1 mixture of diastereomers from (*S*)-limonene,[8] was converted to a mixture of diastereomeric epoxides **26**. The aim was to exploit the organoselenium based method developed by Sharpless and Lauer[19] for their conversion to allylic alcohols **27**. However, upon nucleophilic opening of the mixture of epoxides **26** by the phenylselenide anion prepared *in situ* from diphenyldiselenide/sodium borohydride in methanol and subsequent treatment with hydrogen peroxide, direct formation of lactones **28a** and **28b** as a 1:1 mixture was observed. This mixture could be chromatographically separated and the undesired epimer (**28b**) gave a new mixture of **28a**/**28b** (> 4:1) upon treatment with *t*-BuOK in *t*-BuOH/THF.[18c] Thus, all material could be converted to the desired epimer **28a**.

Conversion of (±)-**28a** to alcohol (±)-**29** through a four-step sequence has been described for the synthesis of racemic laurenditerpenol[4] and was used for the preparation of (−)-**29** from (+)-**28a**. However, efficient conversion of this alcohol or its mesylate derivative to the corresponding iodide could not be achieved. Thus, further explorations along the alkyl–alkyl cross-coupling approach (i.e., evaluation of Negishi-type cross-coupling conditions[7b]) were discouraged, and in conjunction with the disappointing results of the Suzuki–Miyaura alkyl–alkyl cross-coupling studies (*vide supra*), we were forced to reconsider how to join the fully functionalized C(1)–C(8) and C(9)–C(15) fragments.

Addition of an organometal species derived from iodide **19** to aldehyde **30**, which is readily available from alcohol **29** upon oxidation of the latter with TPAP/NMO,[4] appeared as an attractive alternative coupling method toward the fully functionalized carbon framework of **1**. Such an approach, if successful, would fulfill the key requirements set forth in our original retrosynthetic analysis: (a) to circumvent the drawbacks associated with the formation of a C(8)–C(9) double bond and (b) to maintain control of the C(7) stereocenter. With both iodide **19** and aldehyde **30** in hand, temptation to test this approach overruled the alarming report that lithiation of iodide **19** and quenching

Scheme 4. Synthesis of the C(1)–C(8) Fragment



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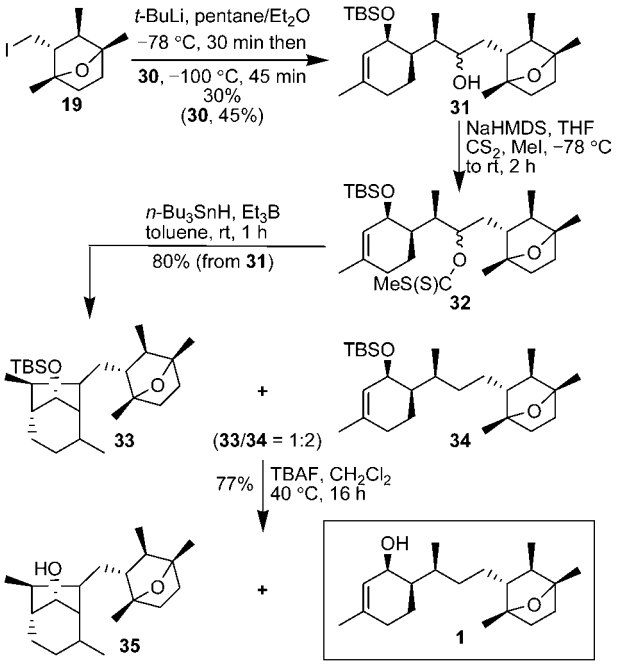
Scheme 5



with a one-carbon electrophile had failed to yield any of the desired product.[4b]

Without any optimization, lithiation of **19** followed by slow addition at −100 °C of a solution of aldehyde **30** in diethyl ether led to the formation of alcohols **31** in 30% yield as a 3:1 mixture of C(8) epimers, along with 45% of recovered aldehyde **30** (Scheme 5). Subsequent removal of the redundant hydroxyl group proved to be a nontrivial transformation. Thus, attempted reductive cleavage of the mesylate derivatives of alcohols **31** with lithium aluminum hydride or lithium triethylborohydride led to recovery of the original alcohols while formation of complex product mixtures was observed upon treatment of the corresponding 2-propanesulfonates with lithium triethylborohydride.[20] Initial attempts to reduce the corresponding xanthates **32** with Bu_3SnH/AIBN at 110 °C led to the formation of an inseparable 4:1 mixture of a byproduct that was tentatively assigned structure **33** and **34**. Running the reaction at lower temperature (80 °C) improved the ratio to 2:1, but the desired deoxygenated product **34** still remained the minor component. Finally, replacement of AIBN with Et_3B as a radical initiator allowed the reaction to proceed at ambient temperature[21] leading to preferential formation of the radical reduction product **34** over the radical intramolecular cyclization one **33** (**33:34** = 1:2). Subsequent treatment of this mixture with TBAF cleaved the silyl protective groups allowing, after careful chromatography, isolation of (−)-laurenditerpenol (**1**) and alcohol **35**.

In summary, an improved, short, and more efficient preparation of (3*R*,3a*R*,7a*S*)-"*wine lactone*" from readily available (*S*)-limonene secured in optically pure form aldehyde **30** (fully functionalized C(1)−C(8) segment; 11 steps, 5% overall yield) while a previously reported catalytic asymmetric Diels−Alder reaction between diethyl fumarate and 2,5-dimethyl furan was exploited for the efficient preparation of iodide **19** in 92% ee (fully functionalized C(9)−C(15) segment; 10 steps, 37% overall yield). The feasibility of an alternative coupling of these two key intermediates was demonstrated allowing (in 31% yield, in four steps) the total synthesis of (−)-laurenditerpenol (**1**).

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Supporting Information Available. Spectral data and experimental procedures for compounds **13**, **15**, **16**, **18**, **19**, **21**, **26**, **28**−**31**, **33**−**35**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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